國立臺灣大學醫學院臨床醫學研究所

碩士論文

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Master Thesis

比較第三代與上一代表皮生長因子接受器抑制劑用在第一線治療轉移性表皮生長因子接受器突變非小細胞肺癌之系統性回顧、統合分析及臨床試驗計畫書

Third generation EGFR inhibitors vs. prior generation EGFR inhibitors as the first-line therapy in metastatic *EGFR* mutant non-small cell lung cancer: A systematic review and meta-analysis as well as a clinical trial protocol

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國立臺灣大學碩士學位論文
口試委員會審定書

比較第三代與上一代表皮生長因子接受器抑制劑用在第一線治療轉移性表皮生長因子接受器突變非小細胞肺癌之系統性回顧、統合分析及臨床試驗計畫書

Third generation EGFR inhibitors vs. prior generation EGFR inhibitors as the first-line therapy in metastatic *EGFR* mutant non-small cell lung cancer: A systematic review and meta-analysis as well as a clinical trial protocol

本論文係 詹巧雯（P10421413）在國立臺灣大學醫學院臨床醫學研究所完成之碩士學位論文，於民國 112 年 07 月 08 日承下列考試委員審查通過及口試及格，特此證明。

口試委員：

_____（簽名）

（指導教授）

_____

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系主任、所長 _____（簽名）

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中文摘要

背景

肺癌是全球癌症死亡原因之首。依據病理分類，其中 80−85% 屬於非小細胞肺癌（NSCLC），當中肺腺癌和鱗狀上皮細胞肺癌為主要形態。精準醫療是現今非小細胞肺癌治療的主流，病人在接受治療前須檢測有無標靶藥物相對應的致癌驅動基因。在東亞大多數的非小細胞肺癌，至少一半以上的肺腺癌病人會帶有一個致癌驅動基因突變（oncogenic driver mutation）。而在亞洲群族中最常發生的致癌驅動基因是表皮生長因子接受器突變（*EGFR* mutation），肺腺癌當中有 50−60% 帶此突變。目前針對晚期 NSCLC 而且帶有表皮生長因子接受器突變的病人，首選用藥是使用表皮生長因子接受器-酪胺酸酶抑制劑（EGFR-TKIs）。目前雖已有臨床試驗去比較不同世代藥物之間對病人療效的差異，但是單一臨床試驗所納入的病人是有限的，本篇研究最主要的目的是希望經由系統性回顧及統合分析比較晚期非小細胞肺癌病人在第一線治療使用不同世代的 EGFR-TKIs 在臨床上之療效及藥物安全性。

方法

通過系統性回顧及統合分析，使用 NSCLC、第三代 EGFR-TKIs、第一線治療做為關鍵字，透過 PubMed、Embase、Cochrane 資料庫及 ASCO、WCLC、ESMO 摘要中進行檢索，篩選過去十年間發表的臨床試驗，比較第三代和上一代 EGFR-TKIs 使用在第一線治療帶有表皮生長因子接受器突變晚期非小細胞肺癌的療效和藥物安全性。主要對無惡化存活期（PFS）、藥物毒性（AE）和次組群包括性別、吸菸狀態、表皮生長因子接受器突變分型及有無腦轉移進行分析。

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結果

透過系統回顧共有五個第三代相較於上一代 EGFR-TKIs 之臨床試驗可進行統合分析。PFS 整體而言第三代（除了 naquotinib）優於上一代，其 PFS (hazard ratio [HR] = 0.57; 95% CI: 0.39−0.81, p = 0.002)。在次組群包括性別、吸菸狀態、表皮生長因子接受器突變分型 (exon19 deletion 及 L858R）及有無腦轉移進行分析，使用第三代（除 naquotinib）其 PFS 都相對於上一代有較好的表現。而針對藥物毒性部分，使用第三代則與上一代類似，AEs grade 3−5 (relative risk [RR] = 1.00; 95% CI: 0.81−1.26, p = 0.99)，統計上無顯著差異。除了 osimertinib 外，由於多數臨床試驗的總存活率尚未有成熟的資料，因此在本次統合分析總存活率部分沒有做分析。

關鍵詞：非小細胞肺癌、表皮生長因子接受器突變、表皮生長因子接受器−酪胺酸酶抑制劑、第三代、系統性回顧、統合分析

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Abstract

Background

Lung cancer is the leading cause of cancer-related death worldwide. Of them, non-small cell lung cancer (NSCLC) represents about 80 to 85%, including majorly adenocarcinoma and squamous cell carcinoma. At present, precision medicine is the mainstream for NSCLC treatment. Oncogenic driver gene tests are important before the treatment. In East Asia, NSCLC, especially adenocarcinoma, more than half of the patients will harbor the driver gene mutation. *Epidermal growth factor receptor (EGFR)* mutation is the major one, 50−60% in lung adenocarcinoma patients in East Asia. Nowadays, EGFR-tyrosine kinase inhibitors (TKIs) are the first-line treatment for advanced *EGFR* mutant NSCLC patients. Although previous clinical trials had demonstrated the clinical efficacies in different generations of EGFR-TKIs, but the patients enrolled in any single trial were limited. Therefore, we conducted this study to compare the treatment outcomes and side effects between different generation EGFR-TKIs through systematic review and meta-analysis.

Methods

To compare the efficacy and safety of the third-generation with prior generation EGFR-TKIs, we performed meta-analysis EGFR-TKIs use as first-line treatment for advanced *EGFR* mutant NSCLC patients in literature search of Pubmed, Embase, Cochrane databank, ASCO, WCLC, and ESMO meeting abstracts with keywords of third-generation EGFR inhibitors, osimertinib, aumolertinib, furmonertinib, naquotinib, lazertinib, first-line, and non-small cell lung cancer, NSCLC.

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Results

Five eligible randomized controlled trials (RCTs) were included and analysis was performed by ReviewManager version 5.4. The third-generation (except naquotinib) had better progression-free survival (PFS) than prior generation EGFR-TKIs (hazard ratio [HR] = 0.57; 95% CI: 0.39−0.81, p = 0.002). In the subgroup analysis of PFS, third-generation (excluding naquotinib) had better performance than prior generation EGFR-TKIs regardless of sex, smoking status, *EGFR* mutation subtypes or central nervous system (CNS) metastasis status. As for the grade 3−5 adverse events (AEs), there were no differences between third-generation and first-generation EGFR-TKIs (relative risk [RR] = 1.00; 95% CI: 0.81−1.26, p = 0.99). Overall survival (OS) analysis was not performed as most studies (except osimertinib) did not have mature OS data.

Keywords: *Epidermal growth factor receptor (EGFR)* mutation, third-generation, EGFR-tyrosine kinase inhibitors, non-small cell lung cancer, systematic review, meta-analysis

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1. Introduction

Lung cancer is the leading cause of cancer-related death worldwide (Siegel et al., 2020). Histologically, lung cancer was composed of small-cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC). Approximate 85% of all lung cancers are NSCLC, majorly including squamous cell carcinoma and adenocarcinoma (Miller et al., 2019). Treatment is currently personalized on the basis of histological type and molecular test results. Patients with specific oncogenic mutations that can be targeted by drugs have shown improved survival rates when receiving appropriate targeted therapies (Kris et al., 2014). In NSCLC, particularly adenocarcinoma, crucial genetic drivers include epidermal growth factor receptor *(EGFR)* mutations, Kirsten rat sarcoma viral oncogene homolog variants, and anaplastic lymphoma kinase fusion (Bronte et al., 2010). Among patients in East Asia, *EGFR* mutations are the most common genetic drivers of advanced NSCLC (Shi et al., 2014), accounting for 50% – 60% of patients (Hsu et al., 2015), whereas among patients in Western countries, *EGFR* mutations account for only 10% – 20% of NSCLC patients (Jordan et al., 2017; Kris et al., 2014).

In 2004, *EGFR* mutations were found to be associated with response to EGFR-tyrosine kinase inhibitors (TKIs) (Lynch et al., 2004). In clinical trials, such as IPASS and EURTAC, the use of EGFR-TKIs as first-line therapy in *EGFR*-mutated NSCLC patients has resulted in a significantly greater progression-free survival (PFS) compared to chemotherapy. EGFR-TKIs achieved a median PFS of 9-11 months, whereas the mean PFS with chemotherapy was only 5-6 months. Additionally, EGFR-TKIs have demonstrated higher response rates and better quality of life outcomes than chemotherapy. Most patients with *EGFR* mutation develop resistance after receiving first-generation EGFR-TKIs (Wang et al., 2016). The second-generation EGFR-TKI, afatinib, was

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initially designed to overcome resistance to first-generation EGFR-TKIs but did not achieve the desired outcome. In the previous studies, majority of patients with *EGFR* mutation developed resistance after receiving therapy with first and second-generation EGFR-TKIs usually in 9 - 13 months (He et al. 2021; Wang et al., 2016), primarily due to the T790M mutation, which is present in 50% – 60% of patients (Stewart al., 2015; Yun et al., 2008). However, both gefitinib/erlotinib (1st EGFR-TKIs) and afatinib/dacomitinib (2nd generation EGFR-TKIs) have demonstrated longer PFS compared with platinum doublet chemotherapy in late-stage NSCLC with *EGFR* mutations (Mok et al., 2009; Maemondo et al., 2010; Mitsudomi et al., 2010; Zhou et al., 2011; Rosell et al., 2012; Sequist et al., 2013; Mok et al., 2018). Third-generation EGFR-TKIs have since been developed as a second-line therapy to target *EGFR* mutations associated with treatment resistance.

In the FLAURA study, osimertinib, a third-generation EGFR-TKI, demonstrated superior overall survival and PFS compared with first-generation EGFR-TKIs in treatment naïve advanced *EGFR* mutant NSCLC patients (Ramalingam et al., 2020; Soria et al., 2018). In addition to osimertinib, clinical trials comparing third- generation EGFR-TKIs such as aumolertinib, furmonertinib, naquotinib, and lazertinib to prior generation EGFR-TKIs had been conducted (Cho et.al., 2022; Kelly et.al.,2019; Lu et al., 2022; Shi et al., 2014). Given the limited number of patients in each trial, we sought to investigate the differences in outcomes (including PFS, response, and safety) between the third-generation and prior generation EGFR-TKIs through systematic reviews and meta-analysis.

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2. Methods

2.1 Literature search strategy

This study was conducted in accordance with the reporting items of the Systematic Reviews and Meta-Analyses 2020 (PRISMA2020) statement. The search was conducted on December 16, 2022, using PubMed, Cochrane Library, Embase, and Clinical Trials databases, without language limitations. We included the terms “osimertinib,” “aumolertinib,” “furmonertinib,” “naquotinib,” “lazertinib,” “first-line,” and “non-small cell lung cancer, NSCLC” in the search. Abstracts that mentioned the American Society of Clinical Oncology (ASCO), World Conference on Lung Cancer (WCLC), or European Society of Medical Oncology (ESMO) were also reviewed.

The characteristics of the studies which were included were, (1) randomized controlled trials, (2) enrolling metastatic *EGFR* mutant NSCLC patients, (3) the first-line therapy setting, (4) comparing third-generation EGFR-TKIs versus prior generation EGFR-TKIs, and (5) reporting at least one of the outcomes, such as PFS, OS, incidence of severe adverse events (AEs) (as defined by Common Terminology Criteria for Adverse Events [CTCAE] version 4 or 5).

The exclusion criteria encompassed case reports, retrospective clinical analyses, review articles, duplicative information, systematic reviews and meta-analyses.

2.2 Data extraction

For each eligible trial, we gathered the following information: title, publication year, study design, trial phase, number of treatment arms, participant count, sex, smoking status, *EGFR* mutation status, central nervous system metastasis (CNS) status, and primary and secondary endpoints.

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2.3 Statistical analysis

The primary endpoint was PFS, while the secondary endpoint was grade 3 or higher adverse events. We conducted subgroup analyses based on sex, smoking status, *EGFR* mutation subtype, and CNS metastasis status. The time-to-event variable (PFS) was evaluated using the hazard ratio (HR) with 95% CIs. Dichotomous adverse events were assessed using relative risks and 95% CIs. We evaluated heterogeneity using the I^2 statistic and forest plots, assuming significant heterogeneity if I^2 exceeded 50%, at which point a random-effects model was used for meta-analysis. The analysis was conducted using Review Manager 5.4 (Cochrane Collaboration, 2020).

3. Results

3.1 Study characteristics

Figure 1 depicts a flowchart detailing the process of literature search. Following the removal of irrelevant titles and abstracts, five randomized controlled trials (RCTs) comprising 2266 patients were eligible for meta-analysis (Cho et al., 2022; Kelly et al., 2019; Lu et al., 2022; Shi et al., 2022; Soria et al., 2018). The characteristics of the included trials are summarized in Table 1.

3.2 Quality assessments and publication bias

The majority of trials demonstrated a low risk of bias. The SOLAR study, however, was prematurely terminated, resulting in missing data and leading to an unclear risk of selective reporting bias. As the SOLAR study was an open-label study, it also presented an unclear risk of performance bias. Additionally, the results from the LASER301 study

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were derived from a presentation at ESMO.

3.3 Progress-free survival

The forest plot of PFS was shown in Figure 3. PFS was significantly better in third-generation EGFR-TKIs than in prior generation EGFR-TKIs (HR = 0.57, 95% CI 0.39−0.81, p = 0.0002; heterogeneity: $I^2 = 89\%$).

3.4 Subgroup meta-analyses

Subgroup-based PFS data considering sex, smoking status, *EGFR* mutation types, and CNS metastasis status were available from four trials.

3.4.1 Sex

Among Female patients, third-generation EGFR-TKIs was associated with significantly longer PFS than did prior-generation EGFR-TKIs (HR = 0.45, 95% CI: 0.40−0.51, p < 0.001). PFS was also significantly longer for third-generation EGFR-TKIs than for prior generation EGFR-TKIs among male patients (HR= 0.50, 95% CI: 0.40−0.51, p < 0.001) (Figure 4).

3.4.2 Smoking status

Third-generation EGFR-TKIs were significantly associated with longer PFS in both smokers and nonsmokers, demonstrating HR of 0.50 (95% CI: 0.41−0.63, p < 0.001) and 0.43 (95% CI: 0.37−0.50, p < 0.001), respectively (Figure 5).

3.4.3 *EGFR* mutation subtypes

In patients exhibiting the *EGFR* exon 19 deletion, PFS was longer when treated with

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third-generation EGFR-TKIs compared to prior generation therapies, with an HR of 0.41 (95% CI 0.35−0.49, $p < 0.0001$). Similar improvements were seen in patients with the *EGFR* L858R mutation, exhibiting an HR of 0.45 (95% CI 0.40−0.52, $p < 0.001$) (Figure 6).

3.4.4 CNS status

PFS significantly improved in patients treated with third-generation EGFR-TKIs, regardless of CNS metastasis status. The HR was 0.44 (95% CI: 0.35−0.56, $p < 0.001$) for patients with CNS metastasis, and 0.46 (95% CI: 0.40−0.53, $p < 0.001$) for those without (Figure 7).

3.5 Adverse events in grade 3−5

A forest plot of adverse events is shown in Figure 8. No significant differences in the incidence of adverse events of grade 3 or higher were observed between the third-generation and prior-generation EGFR-TKIs (RR = 1.00, 95% CI: 0.84−1.19, $p = 0.99$, heterogeneity: $I^2 = 66\%$).

4. Discussion

Except for naquotinib, the third-generation EGFR-TKIs showed better outcome in terms of PFS and similar side effects compared with the prior generation EGFR-TKIs this meta-analysis. Subgroup analysis also showed improved PFS regardless of sex, smoking status, *EGFR* exon 19 deletion or L858R mutation, and CNS metastasis status in the third generation (except naquotinib) compared with the prior generation EGFR-TKIs. Due to

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the significant heterogeneity observed in the PFS and AE analysis, a random-effects model was selected for data analysis.

No statistical significance was observed in the proportion of grade 3 or higher adverse effects between prior and third-generation EGFR-TKIs in this analysis. In the incidence rate of adverse effects, the incidence of adverse events was lower with osimertinib and higher with naquotinib than it was with prior generation EGFR-TKIs. Also, an increased incidence rate of paresthesia was particularly observed with naquotinib and lazertinib. However, common adverse effects, including diarrhea, skin rash, paronychia, and elevated levels of alanine transaminase and aspartate aminotransferase, showed no notable differences in incidence rates.

Naquotinib is a third-generation EGFR-TKI. The efficacy of naquotinib was demonstrated in vitro and in vivo in a preclinical study to be similar to that of osimertinib (Hirano et al., 2018). Naquotinib is a pyrazine carboxamide–based compound with a reactive acrylamide moiety, whereas osimertinib has a pyrimidine-based structure (Cross et al., 2014; Walter et al., 2013). The structures of these compounds may influence their efficacy and side effects (Figure 3 and Figure 8). However, the safety profile and clinical efficacy of naquotinib have not been demonstrated in the SOALR study. Furthermore, the response of the control group in the study was inferior compared to other studies. The observed difference in outcomes may be attributed to potential disparities, such as a lower proportion of *EGFR* exon 19 deletions (66% versus 50%) and a higher proportion of *EGFR* L858R mutations (34% versus 41%), when compared with the patient population in the EURTAC study evaluating the efficacy of erlotinib in NSCLC patients (Kelly et al., 2019; Rosell et al., 2012).

The third-generation generation EGFR-TKIs were developed based on pyrimidine-containing molecules, which were different from the quinazoline-containing molecules

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of first and second-generation TKIs (Yadav et al., 2022). The differences of molecular structures make the third-generation TKIs more potent against the *EGFR* T790M mutation, and may contribute superior clinical outcomes than first and second-generation TKIs (Nagasaka et al., 2020). After the drug resistance of third-generation EGFR-TKIs, there are several possible pathways known, including C797S, mesenchymal-epithelial transition factor (MET) amplifications, human epidermal growth factor receptor 2 (HER2) amplification, fusion genes, or small cell transformation. Several methods have been proposed to improve OS, including combining chemotherapy with EGFR-TKIs (Planchard et al., 2021), MET-TKIs (Smit et al., 2022) and combining bispecific antibodies, such as amivantamab, with EGFR-TKIs (Cho et al., 2022). In the FLAURA study, overall survival was prolonged by first-line treatment with third-generation EGFR-TKIs. The other trials in the present review lacked overall survival data due to their limited follow-up periods. Several clinical trials of novel third-generation EGFR-TIKs are ongoing (e.g., SH-1028, NCT04239833 and BPI-7711, NCT03866499); therefore, we expect their results in the near future.

5. Conclusion

This meta-analysis and systematic review analyzed trials comparing the survival outcomes and safety characteristics of third-generation and prior generation EGFR-TKIs as first-line treatment for NSCLC. The findings were consistent with those of other studies: Compared with prior generation EGFR-TKI third-generation EGFR-TKIs (except naquotinib) had greater efficacy in improving PFS, both overall and in major subgroups, and similar side effects. However, in this meta-analysis, all referenced prior generation EGFR-TKIs were from the first-generation. At present, there are no head-to-

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head clinical trials to compare the efficacy between third-generation and second-generation EGFR-TKIs in advanced *EGFR* mutant NSCLC. We try to design the clinical trial investigating if there were differences in outcomes of first-line treatment with third-generation versus second-generation EGFR-TKIs, including PFS, OS, and safety measures.

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Table 1 Study Characteristics

Study	Year	Treatment Control	Sample size	Efficacy ORR(%)	 mPFS(mo)	 mOS(mo)	EGFR mutation ex19 del (n)	 L858R(n)	CNS metastases (n)	 (%)	AE grade≥3(%)
FLAURA	2018	Osimertinib Erlotinib/Gefitinib	279 277	80 76	18.9 10.2	38.6 31.8	175 174	104 103	53 63	23 29	42 47
SOLAR	2019	Naquotinib Erlotinib/Gefitinib	267 263	33 47.9	09.3 09.6	NA NA	134 111	129 108	NA		54.7 43.5
AENEAS	2022	Aumolertinib Gefitinib	214 215	73.8 72.1	19.3 09.9	NA NA	140 141	74 74	56 59	35 38	36.4 35.8
FURLONG	2022	Furmonertinib Gefitinib	178 179	89 84	20.8 11.1	NA NA	91 92	87 87	63 58	55 48	35 34
LASER301	2022	Lazertinib Gefitinib	196 197	76 76	20.6 09.7	NA NA	122 122	74 75	51 47	35 31	41 43

AE, adverse event; CNS, central nervous system; *EGFR*, *Epidermal growth factor receptor*; mPFS, medium progression-free survival; mOS, medium overall-survival; mo, months; NA, not applicable; ORR, objective response rate.

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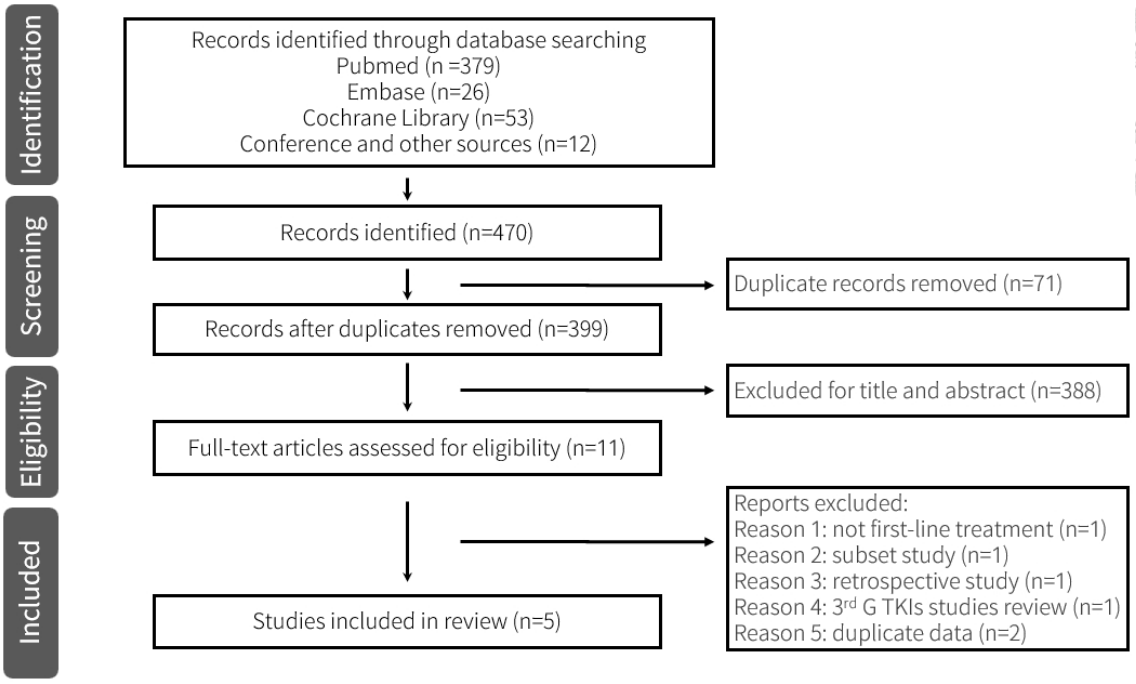

Figure 1 PRISMA2020 flow diagram

3rd G TKIs, third-generation tyrosine kinase inhibitors; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

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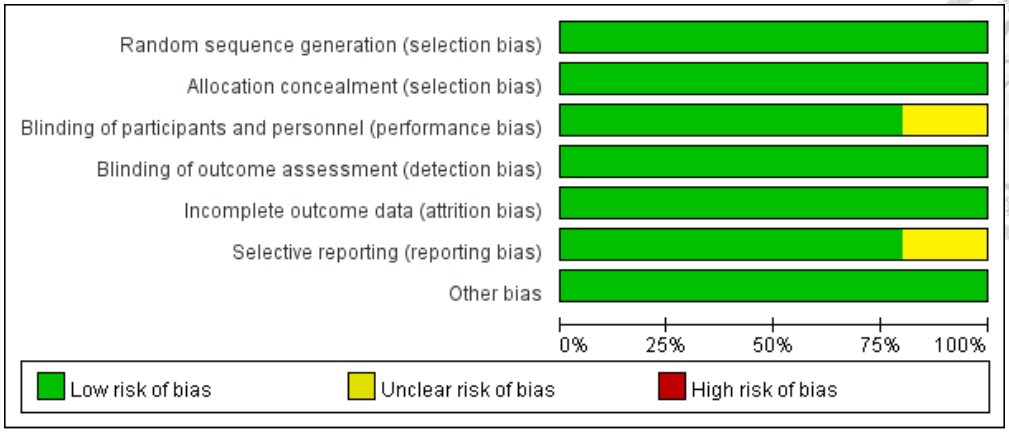

Figure 2 (a) Risk of bias graph

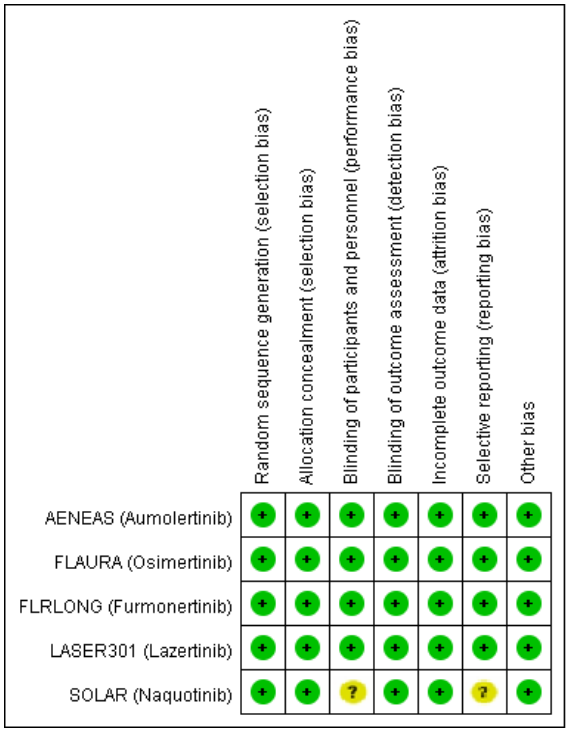

Figure 2 (b) Risk of bias summary

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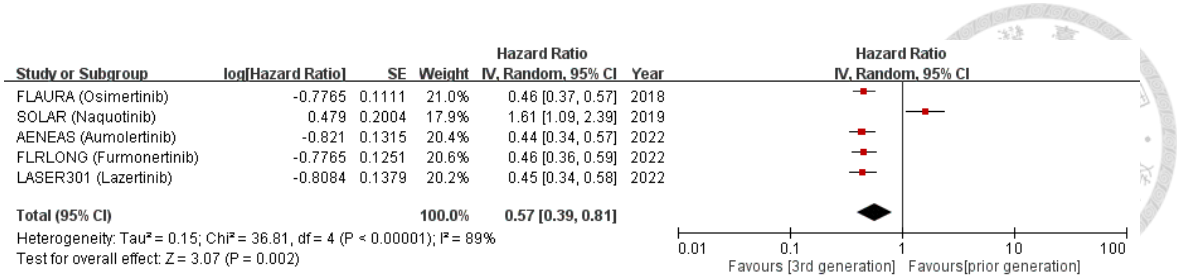

Figure 3 Progression-free survival

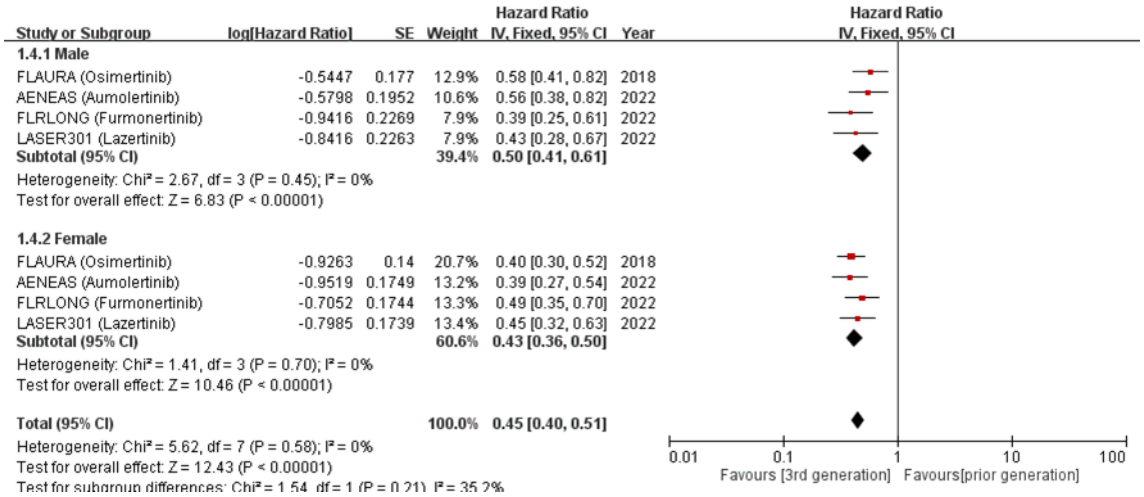

Figure 4 Progression-free survival based on the sex

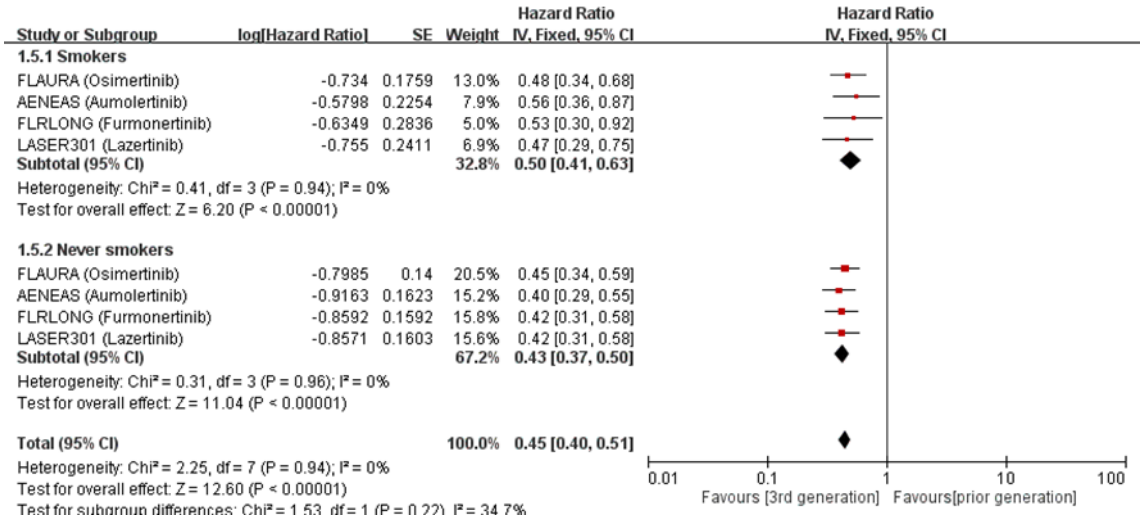

Figure 5 Progression-free survival based on the smoking status

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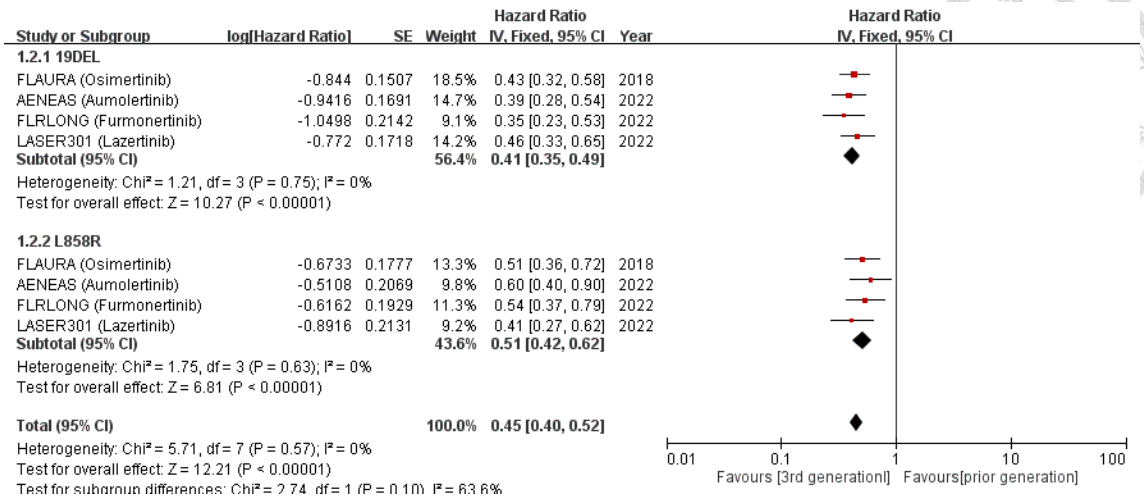

Figure 6 Progression-free survival based on the *Epidermal growth factor receptor (EGFR)* mutation subtypes

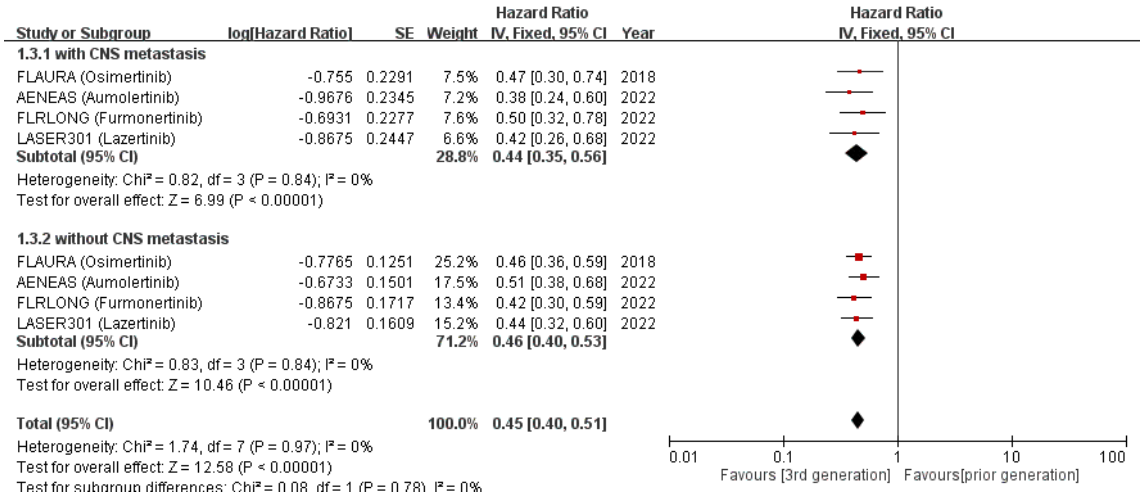

Figure 7 Progression-free survival based on the Central Nervous System metastasis status

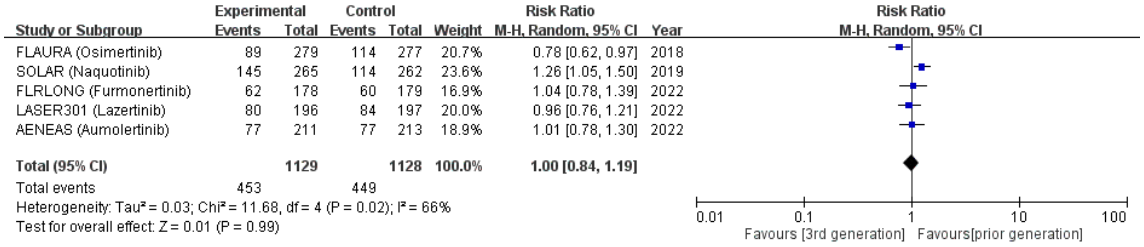

Figure 8 Adverse events in grade 3−5

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APPENDIX A. Protocol

A Randomized, Open-label Phase 3 Study to assess the Safety and Efficacy of Osimertinib Versus Dacomitinib as First-line Treatment in Patients with *EGFR* mutant, Locally Advanced or Metastatic Non-Small Cell Lung Cancer

Study Number:

Study Phase: Phase III

Version / Date: 1.0 /20 May 2023

Author: Chiao-Wen Chan

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Synopsis

Title: A Randomized, Open-label Phase 3 Study to assess the Safety and Efficacy of Osimertinib Versus Dacomitinib as First-line Treatment in Patients with *EGFR* mutant, Locally Advanced or Metastatic Non-Small Cell Lung Cancer
Protocol Number:
Trial Type: Intervention study
Study Design: The trial is a Phase III randomized controlled trial with open-label to compare the efficacy and safety of osimertinib versus dacomitinib in previously untreated patients with *EGFR* mutant advanced NSCLC as first-line therapy. Approximately 734 eligible subjects will be randomized in a 1:1 ratio as indicated below: Arm A: osimertinib 80mg once daily in 28-day cycles Arm B: dacomitinib 45 mg once daily in 28-day cycles
Hypotheses: The primary hypothesis of this study is that osimertinib is superior to with dacomitinib with respect to Progression-Free Survival (PFS).
Study Period: Approximately 48 months
Primary Objective: Progression-free survival (PFS), by independent review (defined as the time from randomization to the date of disease progression according to RECIST version 1.1 per independent review or death due to any cause, whichever occurred first) in the intention-to-treat population (all randomised patients). **Secondary Objectives:** Overall survival (OS), defined as the time from random assignment to the date of death. Safety, Safety will be evaluated based on reported adverse events (AEs), vital signs, physical examinations and clinical laboratory assessments. Adverse events will be reported and graded using the Common Terminology Criteria Version 5.0 (CTCAE v5.0). Patient-Reported Outcomes, all patients will undergo assessment for symptoms, quality of life and health status using the EQ-5D-5L, EORTC-QLQ-C30 and EORTC-QLQ-LC13. Participants will complete the instruments at baseline, at Cycle 1, thereafter at every other cycle and at the end of treatment visit.

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1 INTRODUCTION

1.1 Background

Lung cancer is the leading cause of cancer-related mortality worldwide (Siegel et al., 2020). Histologically, lung cancer was composed of small-cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC). Approximate 85% of all lung cancers are NSCLC, majorly including squamous cell carcinoma and adenocarcinoma (Miller et al., 2019). The treatment choice nowadays is personalized and grounded largely on the different histology and molecular test results. Patients with druggable driver mutation will have improved survival if they took proper targeted agents. (Kris et al., 2014). For patients with NSCLC, particularly adenocarcinoma, several important driver genes are well known including Kirsten rat sarcoma viral oncogene homolog (*KRAS*), epidermal growth factor receptor (*EGFR*), anaplastic lymphoma kinase (*ALK*) fusion and c-ros oncogene 1 (*ROS1*) fusion (Bronte et al., 2010). Among East Asian patients, the most common oncogenic mutation gene in advanced NSCLC is *EGFR* mutation (Shi et al., 2014), which accounts for 50−60% of NSCLC patients (Hsu et al., 2015), while the rate is only 10−20% of patients in the western countries (Jordan et al.,2017; Kris et al., 2014). In 2004, several *EGFR* mutations were found with benefits to EGFR-Tyrosine Kinase Inhibitors (TKIs) (Lynch et al., 2004). Since then, either gefitinib/erlotinib (1st generation) or afatinib/dacomitinib (2nd generation) EGFR-TKI therapy have proved much better progression-free survival (PFS) and less side effects as compared with platinum-based chemotherapy in advanced *EGFR*-mutant NSCLC patients (Maemond et al., 2010; Rosell et al., 2012; Sequist et al., 2013). Additionally, the FLAURA study presented the third-generation EGFR-TKI, osimertinib, which displayed better PFS and overall survival (OS) than first-generation EGFR-TKIs in NSCLC patients with *EGFR* mutation (Ramalingam et al., 2020; Soria et al., 2018). Even with better PFS and OS in *EGFR* mutant NSCLC, there are different effects on *EGFR* exon 19 deletion and L858R mutant patients. Asian patients with gefitinib treatment have non-inferior OS compared with osimertinb, especially in L858R patients (Cho et al., 2019; Ohe et al., 2019; Tsukita & Inoue, 2022).

1.2 Rationale

Dacomitinib, the second-generation EGFR-TKI, has better PFS and OS when compared with gefitinib. The median PFS in *EGFR* exon 19 deletion and L858R patients with dacomitinib use were 16.5 and 12.3 months, respectively (Mok et al., 2018; Wu et al.,2017). In ARCHER1050 Japanese subset data, dacomitinib had a median PFS of 18.2 months, which were quite similar to osimertinib treatment in Japanese subset data, 19.1 months (Nishio et al., 2020; Tsukita & Inoue, 2022).

As there are no clinical trials to compare the efficacy between third-generation and second-generation EGFR-TKIs in advanced *EGFR*- mutant NSCLC, we try to design the clinical trial investigating if there were differences in outcomes of first-line treatment with osimertinib versus dacomitinb, including PFS, OS, and safety with subgroup

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analysis, especially the brain metastasis status as dacomitinib trial ARCHER1050 excluding brain metastasis patients.

2 OBJECTIVES AND ENDPOINTS

Objectives and corresponding endpoints of this study are presented in Table 1.

Table S1 Study Objectives and Endpoints

Primary Objective	**Endpoint**
To compare the efficacy, as demonstrated by PFS, in participants treated with osimertinib versus dacomitinib	· PFS, using RECIST v1.1 based on independent imaging review
Secondary Objective	**Endpoint**
To further assess the clinical benefit achieved with osimertinib versus dacomitinib	· Overall survival (OS)
To assess the safety and tolerability profile in participants treated with osimertinib versus dacomitinib	· Adverse events (AEs), grade by Common Terminology Criteria for Adverse Events (CTCAE) v5.0 · Laboratory abnormalities · Vital signs, physical examination · Electrocardiogram · Left ventricular ejection fraction (LVEF)
Patient-Reported Outcomes	· EQ-5D-5L · EORTC-QLQ-LC13 · EORTC-QLQ C30

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Table S2 Schedule of Activities

Procedure	Pre-treatment (Baseline)	Treatment Period (28 days/Cycle)						Unscheduled visit[1]	End of treatment	Follow up phase	
Cycle/Day	-28	C1D1	C1D8	C1D15	C2D1	C3D1	C4 +	NA	NA	30 day safety follow-up	Long-Term survival follow-up (every 12 weeks)[2]
Windows (days)	NA	0	±2	±2	±7	±7	±7	NA	NA	±7	±14
Background											
Informed consent[3]	x										
Inclusion/Exclusion criteria	x										
Medical history	x										
EGFR status[4]	x										
Prior/Concomitant medication	x	←								→	
Physical examination											
Height	x										
Vital signs[5]	x	x	x	x	x	x	x	(x)	x	x	
ECOG Performance status	x	x			x	x	x	(x)	x	x	
Physical examination including weight	x	x			x	x	x	(x)	x	x	
12-lead ECG	x	x	x	x	x	x	x	(x)	x		
Echocardiogram/MUGA (for LVEF)	x	every 12 weeks relative to randomization and as clinically required						(x)	x		
Ophthalmologic assessment	x	as clinically indicated									
AE/SAE assessment	x	←								→	

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Procedure	Pre-treatment (Baseline)	Treatment Period (28 days/Cycle)						Unscheduled visit[1]	End of treatment	Follow up phase	
Cycle/Day	-28	C1D1	C1D8	C1D15	C2D1	C3D1	C4 +	NA	NA	30 day safety follow-up	Long-Term survival follow-up (every 12 weeks)[2]
Windows (days)	NA	0	±2	±2	±7	±7	±7	NA	NA	±7	±14
Laboratory assessments[6]											
Hematology	x	x	x	x	x	x	x	(x)	x	x	
Chemistry	x	x	x	x	x	x	x	(x)	x	x	
Coagulation	x	x			x	x	x	(x)	x		
Urinalysis	x	x			x	x	x	(x)	x		
Urine pregnancy test	x	x									
Hepatitis B and C	x										
Efficacy Measurement											
Tumor assessments (RECIST v1.1)	x	Every 8 weeks (±7 days) after the start of treatment for the first 6 cycles then every 12 weeks (±7 days) until objective disease progression.									
Brain MRI	x										
Survival and anti-cancer therapy survey										x	x
IP administration											
Randomization[7]		x									
Dose with study drug		daily dosing									
Patient-Reported outcomes[8]											
EQ-5D-5L, EORTC-QLQ-C30 EORTC-QLQ-LC13	x	x			x	x	x		x	x	

1. Unscheduled visits can be arranged if necessary. Study procedures will be performed at the discretion of the investigator.
2. All participants will be followed for survival, disease progression (per local standard practice) and any post-study anticancer treatment via at least a telephone contact every 12 weeks following discontinuation of study treatment, until lost to follow up, the withdrawal of consent, or death (whichever is earlier). However, the participants

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who discontinue study treatment for reasons other than objective disease progression will conduct survival follow-up following confirmation of objective disease progression.

3. Signed informed consent must be obtained before the participant undergoes any study-specific procedures.
4. Tumor samples for screening *EGFR* mutations test should be assessed by an accredited local laboratory.
5. Vital signs (heart rate, blood pressure and body temperature) will be obtained after the participant has rested for 1 0 minutes. The date and time of the assessment should be recorded.
6. Clinical laboratory tests are not required at Cycle 1 Day 1 if acceptable screening is performed within 7 days prior to randomization, unless the participant 's clinical condition has changed significantly. If needed, any clinical laboratory tests may also be performed for safety evaluation of participants.
7. Randomization procedures should be performed following completion of all eligibility assessments and determination of patient eligibility prior to the initiation of assigned study treatment.
8. Questionnaires should be completed prior to any visit-specific procedures.

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3 STUDY DESIGN

3.1 Schema

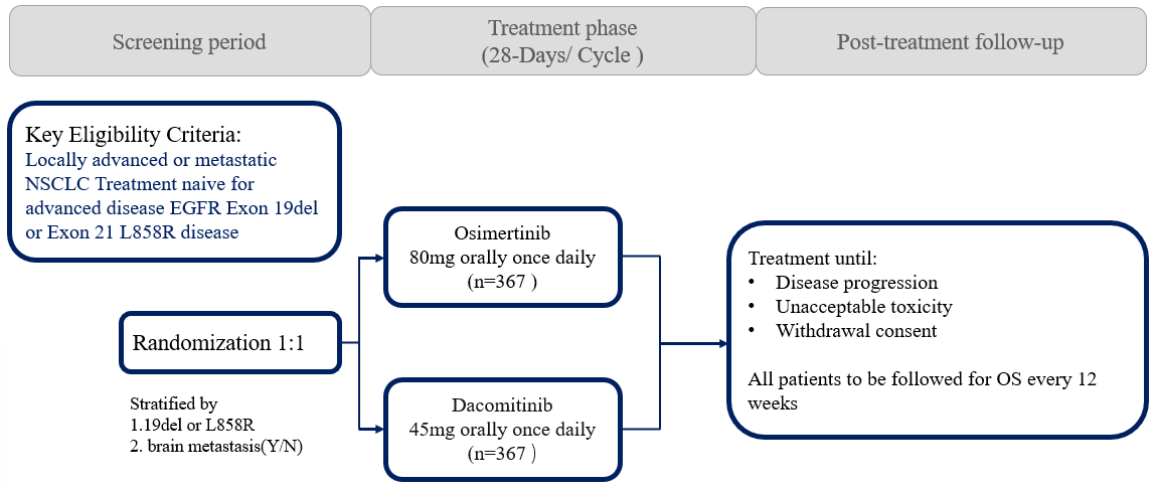

Figure S1 Schematic Overview of Study Design

3.2 Design Overview

The study will encompass three phases: a screening phase, a treatment phase, and a post-treatment follow-up phase. Participants are required to undergo screening procedures within a 28-day timeframe before the randomization process. To be eligible for randomization, participants must have been previously diagnosed with NSCLC, a condition characterized by the deletion of exon 19 and L858R *EGFR* mutations. The Treatment Phase for participants will begin on Cycle 1 Day 1 and continue as 28-day cycles until the end of treatment visit, approximately 30 days after the discontinuation of the experimental treatment. The Follow-up Phase commences immediately after the end of the treatment visit and continues until whichever of the following first occurs: the conclusion of the study, an occurrence of death, the patient can no longer be monitored, or withdrawal of consent. Approximately 734 eligible participants will be randomly assigned to two groups in the study treatment in a 1:1 ratio (Arm A and Arm B). Randomization will be stratified by *EGFR* mutation subtypes (Exon 19del vs. Exon 21 L858R) and history of brain metastasis (present vs absent).

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4 STUDY POPULATION

4.1 Inclusion Criteria

1. Signed Informed Consent Form.
2. Male or female, aged at least 18 years.
3. Participant must have histologically or cytologically confirmed adenocarcinoma of the lung, locally advanced or metastatic NSCLC not amenable to curative surgery or radiotherapy.
4. The tumor harbors one of the 2 common *EGFR* mutations known to be associated with EGFR-TKI sensitivity (Ex19del, L858R), assessed by an FDA-approved or an accredited local laboratory.
5. Participant must have ECOG performance status 0 or 1.
6. Participant must be treatment- naive for locally advanced or metastatic NSCLC.
7. Participant must have at least 1 measurable lesion, according to RECIST v1.1 that has not been previously irradiated. If only one measurable lesion exists, it is acceptable to be used (as a target lesion) as long as it has not been previously irradiated and baseline tumor assessment scans are done at least 14 days after the screening biopsy is performed.
8. Screening laboratory values must meet the following criteria and should be obtained within 14 days prior to randomization:
   - Hemoglobin ≥10 g/dL
   - Absolute neutrophil count ≥1.5 x10^9 /L, without any prior use of G-CSF
   - Platelets ≥75 x 10^9 /L
   - Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤3 x upper limit of normal (ULN)
   - Total bilirubin ≤1.5 x ULN
   - Serum creatinine ≤1.5 x ULN
   - Participant must have adequate organ and bone marrow function as follows, without history of red blood cell transfusion, platelet transfusion, or granulocyte colony-stimulating factor (G-CSF) within 7 days prior to the date of the test.
9. Female participants should be using adequate contraceptive measures, should not be breast feeding, and must have a negative pregnancy test within 72 hours of the first dose of study; or female participants must have evidence of non-child-bearing potential by fulfilling one of the following criteria at:
   - Women under 50 years old would be consider postmenopausal if they have been amenorrheic for 12 months or more following cessation of exogenous hormonal treatments and with luteinizing hormone (LH) and follicle-stimulating hormone (FSH) levels in the post-menopausal range for the institution.

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- Documentation of irreversible surgical sterilisation by hysterectomy, bilateral oophorectomy, or bilateral salpingectomy but not tubal ligation.

10. Male participants should be willing to use barrier contraception, i.e., condoms.

4.2 Exclusion Criteria

1. Participant has received any prior systemic treatment for locally advanced or metastatic disease. (Adjuvant or neoadjuvant therapy is allowed, if administered more than 12 months prior to the development of locally advanced or metastatic disease).
2. Treatment with any of the following:
   - Prior treatment with an EGFR-TKI.
   - Major surgery (excluding placement of vascular access) within 4 weeks of the first dose of study drug.
   - Radiotherapy treatment with a wide field of radiation within 4 weeks of the first dose of study drug.
3. Spinal cord compression, symptomatic and unstable brain metastases, except for those participants who have completed definitive therapy, are not on steroids, have a stable neurologic status for at least 2 weeks after completion of the definitive therapy and steroids.
4. Participant has an active or past medical history of interstitial lung disease (ILD)/pneumonitis, including drug-induced or radiation ILD/pneumonitis.
5. Any of the following cardiovascular disease criteria:
   - Mean resting corrected QT interval (QTc) > 470 msec, obtained from 3 ECGs, using the screening clinic ECG machine-derived QTcF value.
   - Any clinically important abnormalities in rhythm, conduction, or morphology of resting ECG, e.g., complete left bundle branch block, third-degree heart block, second-degree heart block, PR interval >250 msec.
   - Any factors that increase the risk of QTc prolongation or risk of arrhythmic events such as heart failure, hypokalaemia, congenital long QT syndrome, or any concomitant medication known to prolong the QT interval.
   - Baseline LVEF below the lower limit of normal (LLN) as assessed by screening echocardiogram (ECHO) or multigated acquisition (MUGA) scan.
   - Uncontrolled (persistent) hypertension: systolic blood pressure >160 mm Hg; diastolic blood pressure >100 mm Hg.
6. History of hepatitis B (defined as HBsAg reactive) or known active hepatitis C virus (defined as detectable HCV RNA [qualitative]) infection.
7. Has history of HIV infection. HIV testing is not required unless mandated by local health authority.

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8. Other malignancies within the past five years requiring treatment except basal or squamous skin carcinomas or carcinoma in situ of the cervix.
9. Judgment by the Investigator that the participant should not participate in the study if the participant is unlikely to comply with study procedures, restrictions, and requirements.

4.3 Discontinuation from Investigational Product

- Participant decision. The participant is at any time free to discontinue his/her participation in the study, without prejudice.
- Adverse event
- Pregnancy
- Severe non-compliance with the study protocol as judged by the Investigator.
- Participants who are incorrectly initiated on IP
- Objective disease progression as per RECIST v1.1 or Participant is no longer receiving clinical benefit
- Participants experiencing corneal ulceration or ILD will not be permitted to restart study treatment

4.4 Withdrawal from the Study

At any time, participants are free to discontinue the experimental treatment or withdraw from the study without any impact on their subsequent treatment. The Investigator will conduct follow-up assessments on any AEs that remain unresolved during the 30-day safety (F/U) visit. The participant or his/her representative will return all unused study drugs.

For any participant who discontinues study treatment for reasons other than objective disease progression, unless the participant withdraws consent, tumor assessments should be performed as outlined in the protocol until objective disease progression as per RECIST v1.1.

4.5 Lost to Follow-Up from the Study

In the event that a participant repeatedly misses scheduled visits and cannot be reached by the research group through various means of communication, they will be classified as “lost to follow-up.” The research group is responsible for attempting to contact the participant and rescheduling the missed visit as soon as possible (and within the visit window, where one is defined), counseling the participant on the importance of adhering to the assigned visit schedule, and ascertaining whether or not the participant wishes to and/or should continue in the study. Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

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4.6 Treatment Compliance

Participants must return any unused study treatment tablets at the beginning of their next treatment cycle. The research group will count and document the unused tablets to evaluate the participant's compliance with the study treatment. Any instances of dose interruption, reduction, or omission will also be documented in the electronic case report form (eCRF), along with the reasons for such actions.

5 STUDY PLAN AND TREATMENT

5.1 Study Plan

Detailed study treatment schedule is shown in the SoA (See Table 2).

5.2 Dosage and Administration of Study Treatment

In this study, the experimental drugs are osimertinib and dacomitinib. Cycle 1, Day 1 should take place on the day of randomization or within a maximum of 3 days following randomization. All doses prescribed and dispensed to the participant, as well as changes to the dosage during the study, along with the reasons for the modification, must all be documented on the corresponding eCRF.

The experimental drug should be taken at a similar time each day, approximately 24 hours apart, and participants should ensure that doses are not missed. If a participant misses taking a scheduled dose, it is acceptable for them to take the dose within the next 12 hours of the missed scheduled dose. If more than 12 hours have elapsed since the scheduled dose, the missed dose should not be taken, and the participant should be instructed to forgo the missed dose and take the next dose at the next scheduled time. If a participant vomits after ingesting the experimental drug, they should not retake another dose, and instead take the next dose at the next scheduled time.

5.3 Guidelines for Dose Modification

Dose reductions are allowed for osimertinib and dacomitinib and should follow the steps for dose reduction described in Table 3. For each participant, a maximum of two consecutive dose level reductions is allowed for dacomitinib and one dose level reduction is allowed for osimertinib, after which, should the participant remain intolerant of the reduced dose, said participant should be removed from the study.

Participants who can not tolerate the protocol specified dosing schedule, dose interruptions, and/or dose reductions must temporarily pause their treatment or reduce their dose, and wait until they have recovered before continuing their treatment.

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All dose modifications, interruptions, or discontinuations must be made according to the toxicity grade by CTCAE version 5.0 and any dosage changes must be recorded on the administration eCRF.

Table S3 Dose Modification Level

Dose level	Osimertinib	Dacomitinib
Starting dose	80mg once daily	45mg once daily
First dose reduction	40 mg once daily	30mg once daily
Second dose reduction	X	15mg once daily

5.4 General Dose Adjustments for Adverse Events

All participants are to commence treatment at the starting dose level as shown in Table S3. Participants who are unable to tolerate the dosing schedule specified by the protocol due to a toxicity grade of CTCAE grade 3 or higher and/or unacceptable toxicity (of any grade) are advised to undergo dose interruptions and/or reductions to enable them to continue with the treatment.

If the toxicity level is alleviated or reverts to a CTCAE grade 1 or lower within 3 weeks of its original onset, the study treatment may be resumed, starting at the same dose (starting dose) or a reduced dose based on the reduction levels in Table S3. If a participant is restarting at the same dose level, the participant should be closely monitored for 3 days following the restart of the treatment. If there is a recurrence of elevated toxicity within 3 days, a dose reduction should be considered at the researcher's discretion. If the toxicity does not resolve itself to a CTCAE grade 1 or lower within 3 weeks, the participant should be withdrawn from the study treatment and the toxicity should be further monitored.

5.5 Concomitant and Non-drug treatments

Information pertaining to any treatment within 4 weeks prior to the initiation of the study drug, and all concomitant treatments given up to 30 days after the discontinuation of the study treatment will be recorded in the eCRF. Thereafter, only subsequent anti-cancer therapy regimens will be recorded in eCRF.

5.5.1 Permitted and Prohibited treatments

- Other anti-cancer therapies, experimental agents, and radiotherapy should not be administered while the participant is on the study drug.
- Pre-medications will be allowed after, but not before the first dose of the study drug.
- Blood transfusions are allowed at any time during the study.
- Granulocyte-colony stimulating factors (G-CSF) should not be used prophylactically during Cycle 1. The use of prophylactic G-CSF may be considered after a discussion at the conclusion of Cycle 1.

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- Participants may receive treatment involving corticosteroids and/or bisphosphonates for the treatment of bone metastases. Participants may also receive palliative radiotherapy for painful bony metastases, as long as it will not affect the target and non-target lesions being assessed.

Table S4 Prohibited concomitant medication

	osimertinib	dacomitinib
Prolong QT interval	V	
CYP3A inducers	V	
CYP2D6 inhibitors		V
Proton pump inhibitor, PPI		V

Prohibited concomitant medication is shown in the Table S4.

There are specific medications that are prohibited from being used concurrently. Detailed information regarding such restrictions can be found in the approved package inserts in Taiwan.

6 EFFICACY MEASURES

6.1 Radiographic Tumor Assessments

The imaging modalities used for RECIST v1.1 assessments will be CT or MRI scans of the brain, chest and abdomen (including liver and adrenal glands). Baseline disease assessments should be performed no more than 28 days prior to randomization. Post-randomization disease assessments will occur every 8 weeks (±1 week) for the first 6 cycles, and then every 12 weeks (±1 week) until disease progression. Tumor assessments should continue as per protocol even if dosing is interrupted.

The objective tumor response criteria (complete response, partial response, stable disease, or progression of disease) are followed the RECIST v1.1 guideline.

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6.2 Safety Assessments

6.2.1 Adverse Events

An adverse event (AE) is any untoward medical occurrence (i.e., any unfavorable and unintended sign, including abnormal laboratory findings, symptoms or disease) in a clinical investigation participant after providing written informed consent for participation in the study. Adverse events will be assessed and graded according to the Common Terminology Criteria for Adverse Events (CTCAE V5.0).

6.2.2 Serious Adverse Events

An SAE is defined as any untoward medical occurrence that, at any dose:

- fatal
- life-threatening
- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization
- medically important

The Investigator must report any SAEs to Reach Ethics Committee/Institutional Review Board or regulatory authority within 24 hours of becoming aware of the event.

6.2.3 Laboratory Test Assessment

Refer to the SoA for the timing and frequency of all protocol-required laboratory assessments. (See Table S2).

The tests detailed in Table S5 will be performed by the local laboratory.

6.2.4 Vital Signs

Assessment and measurement of vital signs (seated systolic and diastolic blood pressure, heart rate, and body temperature) will be performed at the time points indicated in the SoA (See Table S2).

6.2.5 Physical Examinations

Height (at screening only) and weight will be measured and recorded. The physical examination includes an assessment of general appearance and a review of systems (e.g., dermatologic, head, eyes, ears, nose, mouth/throat/neck, thyroid, lymph nodes, respiratory, cardiovascular, gastrointestinal, extremities, musculoskeletal, neurologic, and psychiatric systems, etc.).

6.2.6 Performance status

ECOG Performance status scale will be used as described in Table S6.

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Table S5 Protocol-Required Safety Laboratory Assessments

Laboratory	Parameters	
Hematology	Hemoglobin	Absolute neutrophil count
	Platelet count	White blood cell (WBC) count with differential
Clinical Chemistry	Magnesium	Bilirubin (total, direct, and indirect)
	Potassium	Alanine aminotransferase (ALT)
	Albumin	Aspartate aminotransferase (AST)
	Sodium	Alkaline phosphatase
	Creatinine	Lactic acid dehydrogenase (LDH)
	Calcium	
Routine Urinalysis	Dipstick	
	Specific gravity	pH
	Glucose	Protein
	Ketones	Leukocyte esterase
	Nitrite	Urobilinogen
	Blood	
	Bilirubin	
Pregnancy Test	At screening a serum/urine pregnancy test is to be performed within 72 hr before the first dose	
Serology	HBsAg, hepatitis B surface antibody (HBsAb), and hepatitis B core antibody (HBcAb) (Participants with a history of HBV are also required to have HBV DNA quantification.)	
	Anti-HCV antibody (Participants with a history of HCV are required to have HCV RNA quantification	

Table S6 ECOG Performance Status

Grade	ECOG status
1	Fully active, able to carry on all pre-disease performance without restriction
2	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature e.g., light house work, office work
3	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
4	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
5	Dead

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6.2.7 12-lead Electrocardiograms

Twelve-lead ECGs will be obtained after the participant has been resting semi-supine for at least 10 minutes prior to times indicated. For each time point, the ECG should be taken three times at about 2 minutes-interval. Triplicate 12-lead ECG will be obtained using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT intervals and QTc.

6.2.8 Echocardiography

An echocardiogram or MUGA scan to assess left ventricular ejection fraction will be performed at screening, Cycle 1Day 1 prior to first dose of study drug, and at least every 12 weeks relative to randomization.

6.2.9 Ophthalmologic Assessment

An ophthalmic assessment, including slit lamp examination, fundoscopic examination, visual acuity test. If a participant experiences any visual symptoms (including blurring of vision), with additional tests.

6.2.10 Patient-Reported Outcomes

Patient-reported outcome (including EQ-5D-5L, EORTC-QLQ-C30, and EORTC-QLQ-LC13) measures should be administered prior to other assessments and collected at the specified times in the SoA (in Table S2). The PROs will be provided in the local language in accordance with local guidelines.

7 STATISICAL ANALYSES

7.1 Hypothesis

Osimertinib has the potential to deliver prolonged PFS versus Dacomitinib in the first-line setting

H0 (null hypothesis):

osimertinib is not superior to dacomitinib

H1 (alternative hypothesis):

osimertinib is superior to dacomitinib

7.2 Sample Size Estimate

To provide 80% power at a type 1 error of 5% (one-sided), approximately 243 progression-free survival events will be required to detect a hazard ratio of 0.78 (for median PFS of 18.9 months in osimertinib and 14.7 months in dacomitinib). We calculated that if 334 participants were enrolled for 24 months and followed for 24 months, the required number of events could be observed. An estimated 10% drop-out rate, with

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a target enrollment of 734 patients (367 in each group). Sample size estimates have been calculated using the web site of UCSF- Sample Size Calculators. (https://sample-size.net/sample-size-survival-analysis)

7.3 Populations for Analyses Sets

- The Full Analysis Set (FAS) will include all randomized subjects. Following the Intent-to-Treat principle, subjects will be analyzed according to the treatment and strata they have been assigned to during the randomization process
- The Safety Analysis Set (SAS) will include all subjects who received at least 1 dose of study drug. Subjects will be analyzed according to the study treatment received, where treatment received is the randomized study drug if the subject took at least 1 dose of the randomized study drug; otherwise, the first treatment received will be used.
- The Per-protocol Analysis Set will include all subjects in the FAS who did not have major protocol violations. Details about the major protocol deviations will be specified in the SAP.

7.4 Efficacy Analysis

- Progression free survival (PFS): The primary efficacy endpoint is PFS. PFS is defined as the time from randomization until the date of objective disease progression or death (by any cause in the absence of progression) whichever comes first based on investigator assessment using RECIST v1.1. PFS in the FAS will be analyzed using a log-rank test stratified by mutation type (Ex19del versus L858R) and history of brain metastasis (present vs absent). The number of events, medians, and 95% confidence intervals of the medians (calculated from the Kaplan-Meier estimate), and proportion of participants without an event at 12, 18, and 24 months will be summarized for each treatment group. The hazard ratio for PFS will be calculated, along with its 95% confidence intervals, from a stratified Cox model using the same stratification factors as for the log-rank test.
- Overall survival (OS): OS is defined as the time from the date of randomization to the date of death due to any cause. If a participant is alive at the date of the analysis cut-off or lost to follow-up, then OS will be censored at the last contact date prior to data cut-off date. OS will be summarized using the KM method, based on data from the FAS. The hazard ratio for OS will be calculated, along with its 95% confidence interval, from a stratified Cox model using the same stratification factors as for PFS analysis.

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8 INFORMED CONSENT PROCEDURES

Each participant must give their written consent to participate in the study. At the same time, the participant must be given sufficient time and opportunity to decide on their participation and to clarify any outstanding questions before the institution of any study procedures.

The declaration of consent is signed by the participant and the study doctor. The original declaration remains with the investigator and a copy must be given to the participant. The participant information sheet will be revised whenever important new information becomes available that may be relevant to the consent of participants.

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