Safety and Effectiveness of EGFR-TKI Rechallenge after EGFR-TKI-Associated Interstitial Lung Disease in Advanced Non-Small Cell Lung Cancer: A Retrospective Cohort Study in Taiwan

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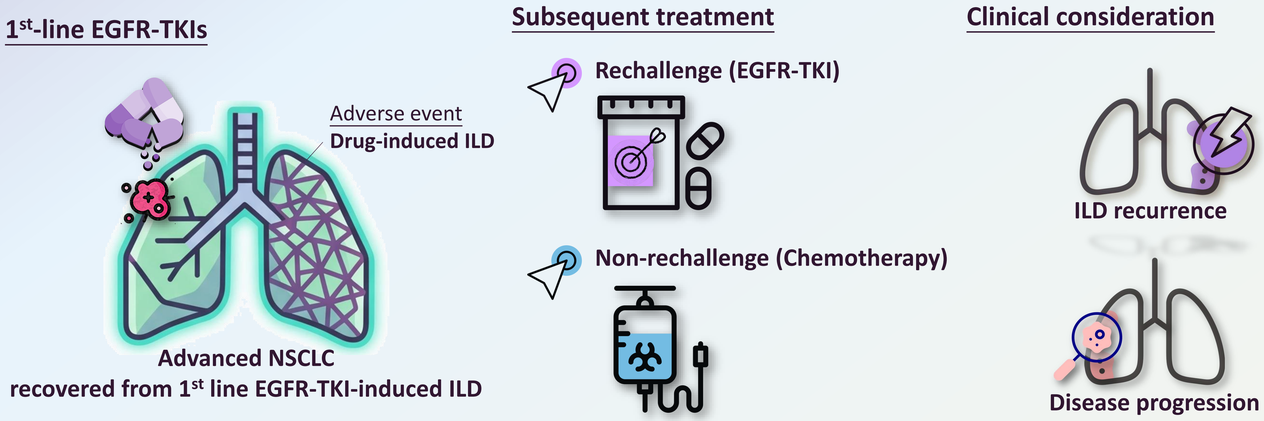
Background

- **Over 50%** of advanced NSCLC patients carry **EGFR mutations** in Taiwan.
- **EGFR-TKIs** are established as the standard care for first-line treatment in major international guidelines.
- **Drug-induced ILD** is considered one of the most serious adverse events associated with EGFR-TKIs.
- For advanced NSCLC patients after EGFR-TKI-induced ILD, **which decision offers the best balance of efficacy and safety?**

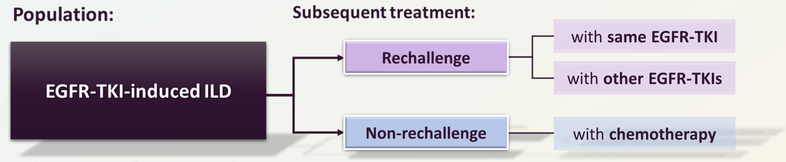


Objective

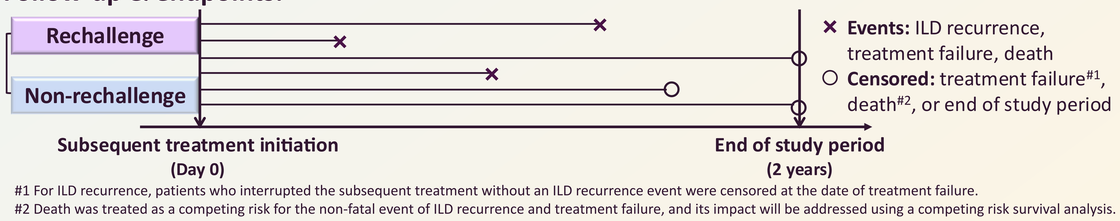
- **Study aim:** To compare the safety and effectiveness of two subsequent treatment strategies, **rechallenge (EGFR-TKI) vs. non-rechallenge (chemotherapy)**, for advanced NSCLC patients whose first-line EGFR-TKI treatment was interrupted by ILD.
- **Research questions:**
  1. Is rechallenge associated with a higher **risk of ILD recurrence** compared to non-rechallenge?
  2. Does rechallenge result in superior **effectiveness**, measured by time to **treatment failure (TTF)** and **overall survival (OS),** compared to non-rechallenge?

Methods

- **Study design:** Retrospective cohort study
- **Study period:** June 1, 2006 – December 31, 2022
- **Data source:** Taiwan's National Health Insurance Research Database (NHIRD)
- **Study population:** advanced NSCLC patients whose first-line EGFR-TKI treatment was interrupted due to TKI-related ILD between June 2006 and December 2020.



- **Follow-up & endpoints:**

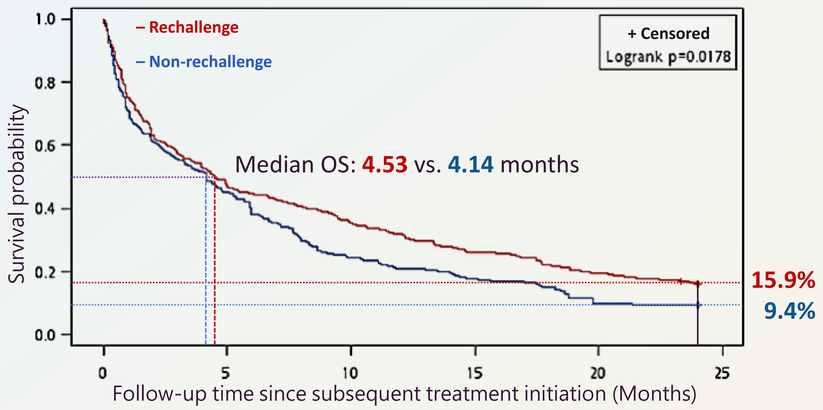


#1 For ILD recurrence, patients who interrupted the subsequent treatment without an ILD recurrence event were censored at the date of treatment failure.
#2 Death was treated as a competing risk for the non-fatal event of ILD recurrence and treatment failure, and its impact will be addressed using a competing risk survival analysis.

- **Statistical Analysis**
  - **Stabilized inverse probability treatment weighting (SIPTW)**: Employed to balance baseline characteristics between the groups, minimizing potential selection bias from the non-randomized design.
  - **Fine-Gray sub-distribution hazards model:** Utilized for ILD recurrence and piecewise TTF analysis, accounting for the competing risk of mortality.
  - **Weighted Cox regression model**: Accounted for non-proportional hazards in overall TTF analysis.
  - **Cox proportional hazards model:** Evaluated predictors and treatment effects on overall survival (OS).

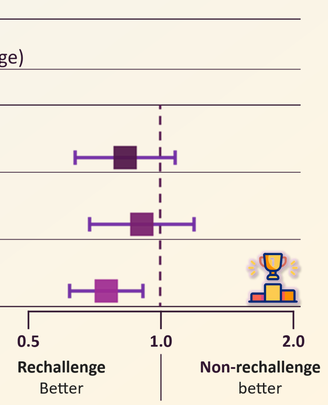
Results

- **Kaplan-Meier curves of overall survival (OS)**



- **Multivariable analysis of clinical outcomes**

Endpoints (Statistical models*)	Subsequent treatment strategy: Rechallenge (ref. = non-rechallenge) Adjusted SHR (95% CI)
Recurrent ILD (Fine-Gray sub-distribution hazards model)	0.84 (0.65-1.08)
Treatment failure (Weighted Cox regression model)	0.91 (0.70-1.19)
Overall survival (Cox proportional hazard model)	**0.76 (0.63-0.92)**



Abbreviations: SHR, sub-distribution hazard ratio; AHR, average hazard ratio; CI, confidence interval.
* The models were applied to the Stabilized IPTW weighted sample. Multivariable analysis was adjusted for sex, age, smoking status, CCI, COPD, cancer, initial EGFR-TKI, ILD severity, interruption duration, and index year. *p*-values less than 0.05 were considered statistically significant; significant values are highlighted in bold.

Higher risk, HR > 1
Lower risk, HR < 1

Significant predictors

Safety
- **Initial grade IV ILD severity** (aSHR: 1.94, 95% CI: 1.25-2.99)
- **Interruption duration >30 days** (aSHR: 0.57, 95% CI: 0.40-0.81)

Effectiveness
- **Males** (aAHR: 0.70, 95% CI: 0.53-0.94)
- **Age > 80** (aHR: 1.70, 95% CI: 1.25-2.30)
- **higher initial ILD severity** (aHR: 2.65, 95% CI: 1.85-3.79)
- **Initial Afatinib use** (aHR: 0.76, 95% CI: 0.58-0.98)
- **Longer Interruption duration** (aHR: 0.56, 95% CI: 0.42-0.75)

Conclusion

EGFR-TKI rechallenge is a better survival strategy with a safety profile similar to chemotherapy, making it a viable option for advanced NSCLC patients recovering from ILD.

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The authors have no conflicts of interest to declare.
The current study has been approved by the Institutional Review Board (IRB) of the National Yang Ming Chiao Tung University, No. NYCU114211AE.