Comparison of Naïve versus Delayed-Entry Adjustment Methods in Real-World Survival Analysis of First-Line Metastatic NSCLC with PD-L1 TPS ≥50%

Poster #MSR29

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Conclusions

- Median and landmark OS and PFS estimates were generally similar between naïve and delayed-entry adjusted approaches
- PFS estimates and associated predictors remained largely unchanged after risk-set adjustment (RSA), suggesting limited influence of sequencing-related delayed entry on PFS
- OS results were more sensitive to adjustment, particularly in the multivariable Cox analysis, where several predictors identified in the naïve model were no longer statistically significant after applying the prospective approach
- These findings support evaluating delayed entry in studies that rely on real-world data and applying outcome-specific adjustment methods when warranted

Plain Language Summary

- In real-world studies requiring genetic testing of tumors, patients may start treatment before testing but must survive until testing to be included. Not accounting for this may bias survival analysis
- We compared traditional analysis with methods that account for when sequencing occurred among patients receiving first-line treatment for advanced lung cancer
- The methods produced similar estimates of overall survival and survival without progression. However, adjusting the overall survival analysis changed which patient and treatment factors were linked to the risk of death
- Researchers should assess delayed entry separately for each outcome and apply an adjustment method when needed to reduce potential bias

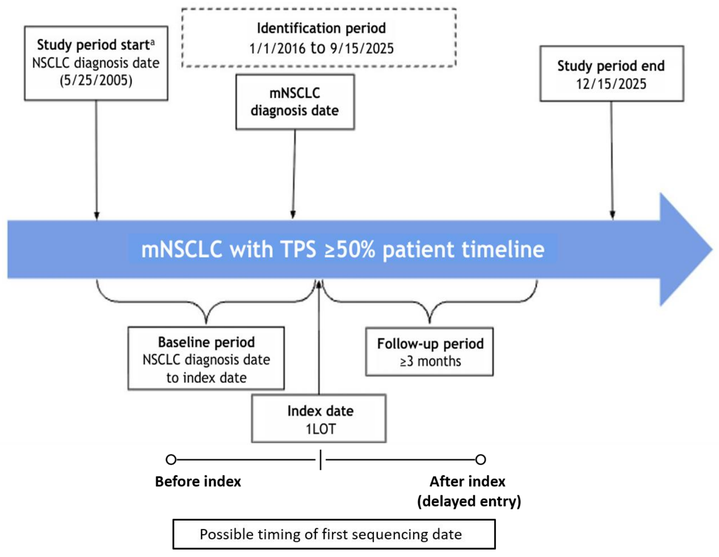
Introduction

- For patients with metastatic non-small cell lung cancer (mNSCLC) programmed death ligand 1 (PD-[L]1) tumor proportion score (TPS) ≥50%, and no actionable genomic aberrations, first-line (1L) treatment commonly includes a PD-[L]1 inhibitor alone or in combination with chemotherapy[1,2,3]
- Real-world clinico-genomic databases support outcomes research in biomarker-defined populations by linking longitudinal clinical information with tumor sequencing data
- However, tumor sequencing may occur after treatment initiation. When follow-up begins at treatment initiation, patients sequenced later must survive long enough to enter the database, creating delayed entry, also called left truncation, that may preferentially select longer-surviving patients and bias time-to-event estimates[4,5]
- Naïve Kaplan–Meier and Cox models that begin follow-up at treatment initiation without accounting for delayed entry may therefore produce biased survival estimates. Delayed-entry adjustment methods can be used to address this potential bias in time-to-event analyses[4,5]
- **Objective:** The aim of this study was to evaluate how naïve and delayed-entry adjusted approaches influence overall survival (OS), progression-free survival (PFS), and associated prognostic factors among patients receiving 1L treatment for mNSCLC with PD-L1 TPS ≥50% and no actionable genomic aberrations

Methods

- This retrospective observational study used the de-identified Tempus Multimodal database (Tempus AI, Inc., Chicago, IL, USA) from 2016 to 2025
- **Inclusion criteria:**
  - Patients aged 18–89 years with mNSCLC
  - Initiation of ≥1 systemic therapy in the 1L metastatic setting
  - PD-L1 TPS ≥50%
  - Confirmed absence of actionable genomic aberrations in EGFR, ALK, and ROS1, and
  - First clinical activity within 90 days after mNSCLC diagnosis
- **Exclusion criteria:**
  - Enrollment in a clinical trial during the study period or
  - Another prior primary cancer, except nonmelanoma skin cancer
- The index date was initiation of 1L therapy in the metastatic setting, and the follow-up period was ≥3 months from the index date until death, loss to follow-up, or study end **(Figure 1)**. Database entry was defined as the first sequencing date
- Study outcomes of OS and PFS were measured as follows:
  - OS was measured from the index date to death from any cause. PFS was measured from the index date to the earliest documented disease progression or death
  - Kaplan–Meier methods estimated OS and PFS. Multivariable Cox proportional hazards models evaluated prognostic factors after adjustment for prespecified demographic and clinical characteristics

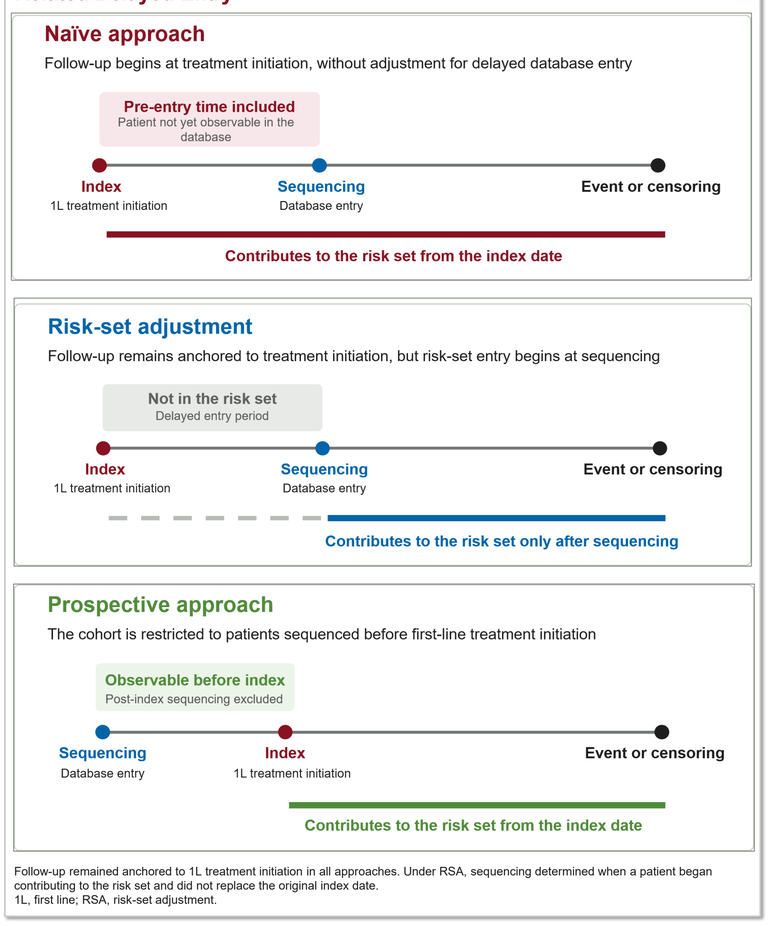
Figure 1. Study Design



[a]The study period start date was the earliest date at which the patient was defined as having a primary lung cancer diagnosis in the Tempus AI database based on the pathology diagnosis; the date could occur any time on or before the mNSCLC diagnosis date and is not bound by the identification period.
1LOT, first line of therapy; mNSCLC, metastatic non-small cell lung cancer; NSCLC, non-small cell lung cancer

- The independent delayed-entry assumption was evaluated before selecting the adjusted analysis approach
  - **Independent delayed entry:** Risk-set adjustment (RSA) assumes that the timing of sequencing is independent of the patient's subsequent risk of the outcome. If this assumption is violated, RSA may not adequately address the overrepresentation of patients who survive long enough to undergo sequencing[4,5]
- The following approaches were evaluated **(Figure 2)**:
  - **Naïve approach:** Included eligible patients from the 1L treatment index date to the outcome or censoring date, without adjustment for delayed database entry
  - **Risk-set adjustment:** Retained the original index date but allowed patients to contribute to the risk set only after sequencing. This approach requires the independent delayed-entry assumption[4,5]
  - **Prospective approach:** Restricted the analysis to patients sequenced before 1L treatment initiation, ensuring that all included patients were observable at the index date

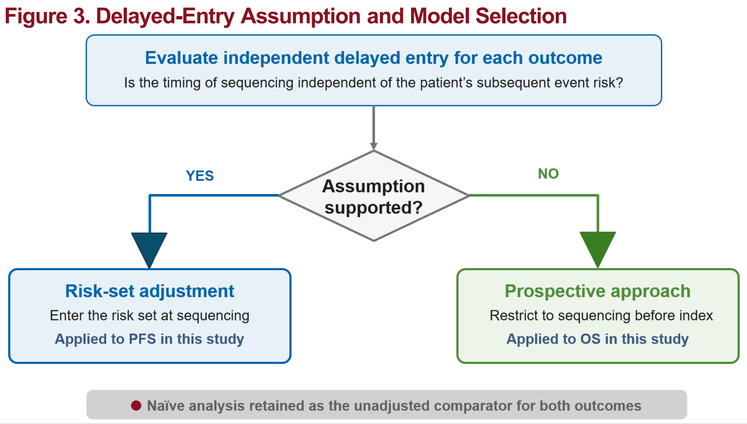
Figure 2. Comparison of Survival Analysis Approaches for Sequencing-Related Delayed Entry



Follow-up remained anchored to 1L treatment initiation in all approaches. Under RSA, sequencing determined when a patient began contributing to the risk set and did not replace the original index date.
1L, first line; RSA, risk-set adjustment.

- A naïve approach was used as the unadjusted comparator. The selected adjusted approach depended on whether the independent delayed-entry assumption was supported for each outcome **(Figure 3)**

Figure 3. Delayed-Entry Assumption and Model Selection



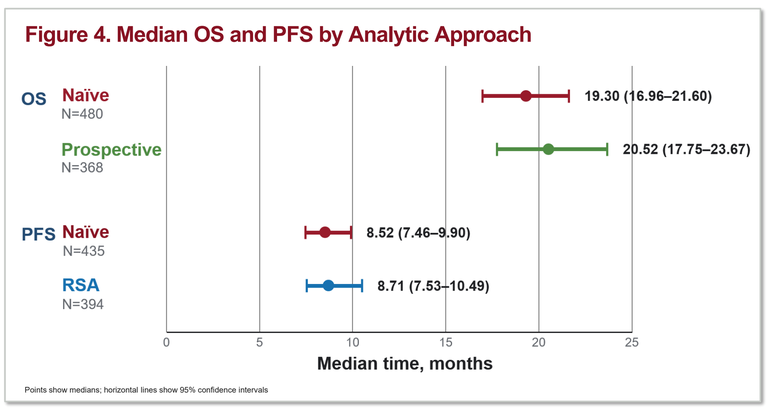
Application in this study

- Assumption violated for OS; therefore, a prospective approach was used
- Assumption holds for PFS; therefore, RSA was used

Results

- Naïve analyses included 480 patients for OS and 435 patients for PFS
- Adjusted analyses included 368 patients for OS (prospective approach) and 394 patients for PFS (RSA)
- Median OS was 19.30 months with the naïve approach and 20.52 months with the prospective approach **(Figure 4)**
- Median PFS was 8.52 months with the naïve approach and 8.71 months with RSA **(Figure 4)**

Figure 4. Median OS and PFS by Analytic Approach



Points show medians; horizontal lines show 95% confidence intervals

- At 6 months, OS was 80.36% with the naïve approach and 79.93% with the prospective approach; PFS was 60.22% with the naïve approach and 60.54% with RSA **(Table 1)**
- At 12 months, estimated OS was 64.59% with the naïve approach and 66.38% with the prospective approach; estimated PFS was 38.96% with the naïve approach and 40.03% with RSA **(Table 1)**

Table 1. Kaplan–Meier Landmark Estimates by Analytic Approach

Outcome/approach	6 months, % (95% CI)	12 months, % (95% CI)
OS, naïve	80.36 (76.48–83.67)	64.59 (59.90–68.89)
OS, prospective	79.93 (75.43–83.70)	66.38 (61.06–71.15)
PFS, naïve	60.22 (55.00–65.03)	38.96 (33.35–44.53)
PFS, RSA	60.54 (55.06–65.56)	40.03 (34.21–45.78)

Values are Kaplan–Meier estimates presented as % (95% CI). For PFS analyses, patients with progression or censoring within 14 days of the index date were excluded.
OS, overall survival; PFS, progression-free survival; RSA, risk-set adjustment.

- In OS-based Cox models, most factors significant in the naïve analysis were no longer significant after prospective adjustment; ECOG PS ≥2 remained significant **(Table 2)**
  - Associations observed for chemotherapy monotherapy, PD-[L]1 TPS >90%, and female sex in the naïve OS model were attenuated and no longer statistically significant after prospective adjustment
  - ECOG PS ≥2 remained associated with approximately twice the mortality hazard in both the naïve and prospective models
- In contrast, predictors identified as significant in the naïve PFS model remained significant under RSA

Table 2. Selected Multivariable Cox Model Results for OS by Analytic Approach

Variable	Naïve HR	95% CI	Prospective HR	95% CI
Chemotherapy monotherapy vs chemo + IO	1.97	**1.32–2.94**	1.40	0.80–2.43
PD-[L]1 TPS >90% vs 50%–90%	0.71	**0.53–0.96**	0.92	0.65–1.30
Female vs male	0.72	**0.55–0.93**	0.75	0.55–1.03
ECOG PS ≥2 vs 1	2.12	**1.48–3.04**	2.03	**1.34–3.07**

Bold values indicate 95% CIs that exclude 1.0
HRs were estimated using the full multivariable Cox proportional hazards models. HR, hazard ratio; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; IO, immuno-oncology; OS, overall survival; PD-L1 TPS, programmed death-ligand 1 tumor proportion score

Limitations

- Retrospective clinico-genomic data may be affected by missing information, misclassification, and residual confounding, and may not represent patients without genomic testing
- The proportional hazards assumption was violated in some Cox models; the corresponding HRs may not fully capture time-varying associations

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