Controlling For What Comes Next: Estimating Generalized Direct Effects of First-Line Therapy on Real-World Overall Survival Using Counterfactual Second-Line Distributions in Advanced Non-Small Cell Lung Cancer

MSR200

Scan to learn more

Kenneth A. Taylor[1]; **Philani Mpofu**[2]; **Lockwood Taylor**[2]; **Raina Mathur**[2]
[1]Flatiron Health, Durham, NC, USA; [2]Flatiron Health, New York, NY, USA

Introduction

- First-line (1L) therapy's effect on real-world overall survival (rwOS) operates partly through second-line (2L) therapy
- When 2L practice differs across populations or over time, the estimated 1L effect on rwOS can differ
- Standard adjustment does not isolate the 1L effect under a specified 2L distribution

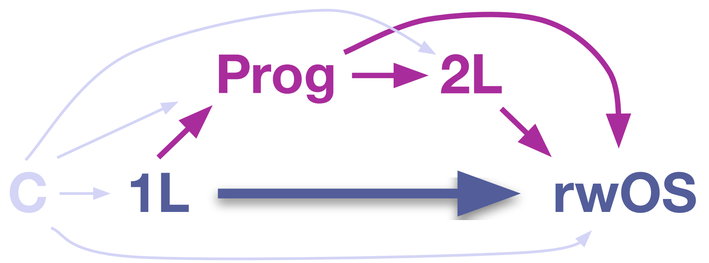
Objective

To demonstrate estimation of a generalized direct effect (GDE) of 1L therapy on rwOS under three pre-specified counterfactual 2L distributions

Methods

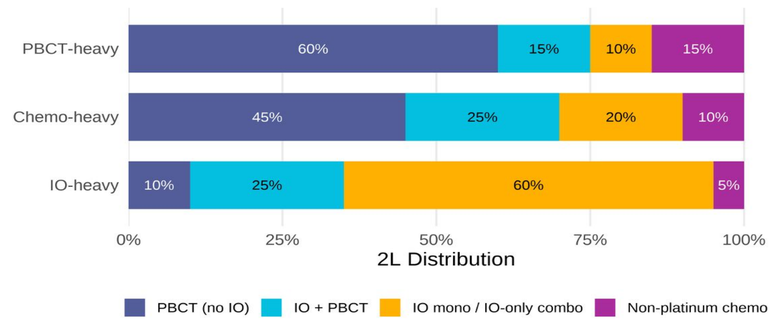
- **Data source:** Retrospective, de-identified electronic health record (EHR) data from the US Flatiron Health Research Database, originating from >220 cancer clinics (>1600 sites of care; primarily community oncology settings) and curated via technology-enabled extraction[1]
- **Setting:** This study included patients diagnosed with stage IV non-small cell lung cancer (NSCLC) between January 01, 2017, and February 28, 2026, who initiated 1L immunotherapy (IO) or platinum-based chemotherapy (PBCT), with no targetable biomarker alterations on or before 1L initiation (index). We excluded patients with a mid-month imputed death date falling before the index date
- **Main outcome/estimand:** GDE of the rwOS probability difference between 1L IO and 1L PBCT up to 36 months with a specified 2L therapy (mediator) distribution (**Figure 1**)
- **Statistical analysis:**
  - Discrete-time pooled logistic regression models (14-day intervals; time as natural cubic spline, 1L x time interaction), adjusted for baseline demographic, clinical (PD-L1, ECOG, metastatic burden, histology, smoking history), and treatment-setting confounders
  - Naive adjusted 1L effect (reference, non-GDE): g-computation over baseline confounders; 2L and progression left as observed
  - GDE*:* parametric mediational g-computation (Monte Carlo)[2] under three pre-specified 2L regimen distributions among 2L initiators, limited to classes with adequate positivity (**Figure 2**)
    - Same distribution applied to both 1L groups; timing of progression and 2L start left as observed; added time-varying progression (intermediate confounder) and 1L x 2L interaction in rwOS model
  - 95% CIs: percentile bootstrap (499 patient-level resamples, all models refit)

Figure 1. Simplified directed acyclic graph for the generalized direct effect of 1L therapy on rwOS



Abbreviations: 1L, first-line therapy; 2L, second-line therapy (mediator); C, baseline confounders; Prog, disease progression after 1L start (intermediate mediator-outcome confounder affected by 1L); rwOS, real-world overall survival.

Figure 2. Pre-specified counterfactual 2L distributions



Abbreviations: Chemo, chemotherapy; combo, combination; IO, immunotherapy; mono, monotherapy; PBCT, platinum-based chemotherapy.

Results

- **Cohort:** 20,309 patients (**Figure 3**); for baseline characteristics see **QR Code**
  - Unadjusted median rwOS was 12.5 mo (95% CI, 11.9-13.1) for 1L IO vs 9.5 mo (95% CI, 9.2-9.8) for 1L PBCT
- **2L distributions and timing differed by 1L group** (**Figure 4**)
  - 2L initiation observed: 1L IO = 28.8%; 1L PBCT = 56.6%
    - Among 2L initiators, 69.2% 1L IO and 91.4% 1L PBCT started 2L ≤12 mo; median 7.3 mo (IO) vs 3.4 mo (PBCT)
- **Adjusted 1L IO benefit held across all 2L scenarios** (**Figure 5**)
  - ≤12 mo: GDE estimates favored 1L IO from month 3 (2.1-2.2 pp; 95% CIs excluding 0) vs month 5 for the naive estimate (1.6 pp)
  - >12 mo: GDE and naive estimates converged, fewer patients remained who were at-risk and had not yet initiated 2L

Figure 3. Study attrition flowchart

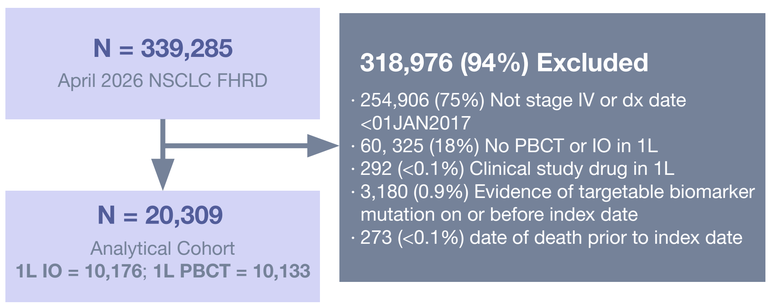
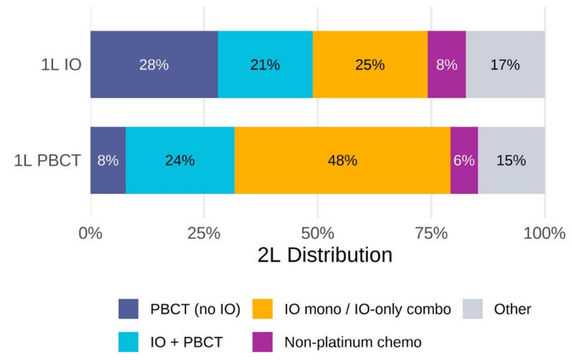
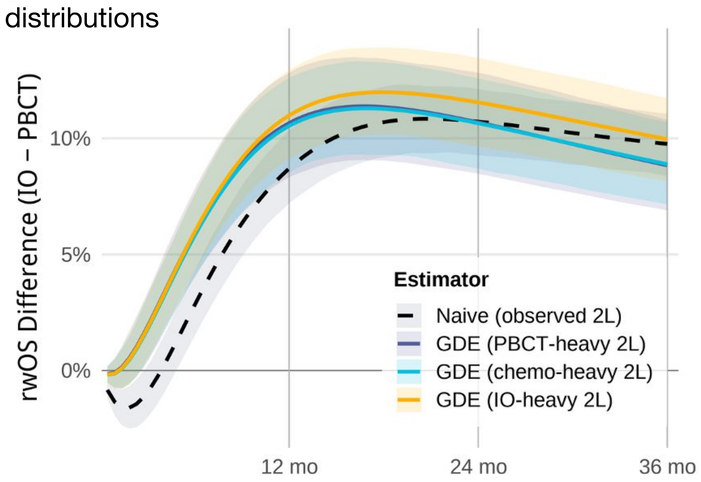


Figure 4. Observed 2L distributions



Abbreviations: 1L, first-line; chemo, chemotherapy; combo, combination; IO, immunotherapy; mono, monotherapy; PBCT, platinum-based chemotherapy.

Figure 5. Difference in rwOS over time: naive estimator vs generalized direct effect under three counterfactual 2L distributions



Absolute difference in rwOS (IO – PBCT) by month; positive favors IO. Naive estimator uses observed 2L; GDE estimators set 2L to counterfactual chemo-heavy, IO-heavy, and PBCT-heavy distributions.

Abbreviations: 2L, second-line; IO, immunotherapy; PBCT, platinum-based chemotherapy; rwOS, real-world overall survival.

Conclusion

- GDE estimation via parametric mediational g-computation is feasible with EHR-derived data, **enabling investigation of 1L effects in populations whose subsequent treatment distributions differ more substantially from those observed** (within the range of 2L regimens actually received)
- The discrete-time approach enables estimation of interpretable, collapsible measures that do not rely on proportional hazards (unlike the hazard ratio)

Limitations and Future Directions

- Analysis relied on parametric modeling assumptions and no unmeasured confounding of 1L-rwOS, 2L-rwOS, and 1L-2L associations; estimates >12 mo rest on fewer at-risk patients and modeled time trends
- Progression was ascertained through evidence available in the patient's EHR (real-world progression), which may misclassify some patients vs RECIST criteria
- GDE estimation requires positivity, limiting counterfactual 2L distributions to regimens received across patient subgroups; more extreme distributions could not be evaluated
- The estimated GDE has limited generalizability outside of the current study population
- Future work planned to assess GDE/interventional mediation analysis methods in combination with transportability methods

References: Scan **QR Code** for references and other supplemental content
Acknowledgments: Data first presented at ISPOR Europe in Vienna, Austria on November 8-11, 2026
Disclosures: This study was sponsored by Flatiron Health, Inc.—an independent member of the Roche Group. During the study period, KT, PM, LT, and RM reported employment with Flatiron Health, Inc. and stock ownership in Roche
Contact information: Kenneth Taylor, kenneth.taylor@flatiron.com