Using Regression Discontinuity in Time Design to Study Real-World Comparative Effectiveness: A Case Study of Advanced Non-Small Cell Lung Cancer

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Background

- Real-world data (RWD) is increasingly being used to address real-world effectiveness where randomized controlled trials fall short. However, non-randomized RWD is susceptible to bias, unobserved confounders, and missing data not at random.[1-3]
- The introduction of innovative treatments (e.g., immune checkpoint inhibitors) with advancements in disease diagnosis (e.g., PD-L1) has complicated real-world outcome assessments, primarily due to the lack of comparable historical controls and insufficient sample sizes of concurrent controls.[4-6]
- Regression discontinuity in time (RDiT), an extension of regression discontinuity design, leverages "time" as a running variable to create a "jump" in treatment likelihood. By assuming a local randomization-like time interval around the "jump", this quasi-experimental method can obtain less biased causal effects.[7]

Objective

- To demonstrate the RDiT method application in a case study of 2nd-line use of pembrolizumab versus docetaxel in advanced non-small cell lung cancer (aNSCLC).
- To compare the RDiT's performance with the time-stratified inverse probabilities treatment weighting (ts-IPTW) and the reconstructed target trial.

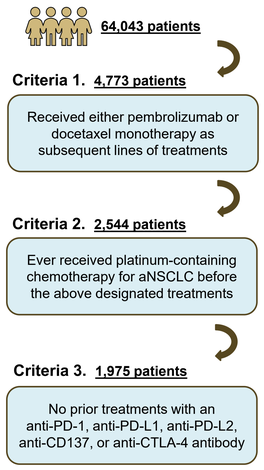
Methods

- This was a retrospective cohort study for patients with aNSCLC who received either pembrolizumab monotherapy or docetaxel monotherapy after disease progression on or after following platinum-containing chemotherapy.
- This study used the nationwide Flatiron Health electronic health record (EHR)-derived de-identified database.* The study included 64,043 patients diagnosed with aNSCLC cohort data from January 1, 2011 to June 30, 2023.**
- Treatment probabilities were estimated with the RDiT and ts-IPTW.
- We applied the RDiT method using a fuzzy approach:
  - **1st-stage model**: A logistic regression was used to calculate the treatment probabilities over time.
  - **2nd-stage model**: Survival analyses were applied using the expected treatment probabilities from the 1st-stage model.
- The ts-IPTW method was performed through two logistic regression models to obtain treatment probabilities, using the year 2016 as the cut-off time point:
  - **Entire period (2011 – 2023)**: Commonly known factors were adjusted, except for the PD-L1 expression level.
  - **Recent period (2016 – 2023)**: PD-L1 expression level was adjusted.
- A reconstructed individual patient-level data from the 5-year follow-up KEYNOTE-010 was performed for performance assessment.[8]
- Survival analyses based on the estimated over-time treatment probabilities were evaluated against the 5-year reconstructed targeted-trial data. Outcome included hazard ratios (HR), median survival, 1-year and 5-year survival rate, and restricted mean survival time (RMST).

Results

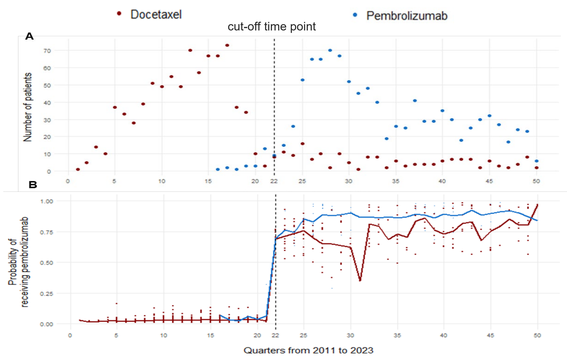
- A total of 1,975 patients met the enrollment criteria, with 1,014 patients receiving pembrolizumab and 961 patients receiving docetaxel monotherapy (**Figure 1**).
- Most enrolled patients had non-squamous histology, performance status (ECOG) of 0 to 2 and were current or former smokers. Patients in the pembrolizumab group (68.6 ± 9.3 y.o.) were older than patients in the docetaxel group (66.5 ± 9.5 y.o.) (**Table 1**).

Figure 1 Cohort Selection



- We chose the quarter 22 (April – June, 2016) as the cut-off time point in the RDiT method based on the FDA's accelerated approval for the indication, the treatment guideline updates, and real-world treatment transition to calculate the treatment probabilities over time (**Figure 2**).

Figure 2 Treatment Patterns and Treatment Probabilities (RDiT)



- Compared to the ts-IPTW method, the treatment assignment probabilities in the RDiT method had a broader range and a more distinct density contrast between the two groups (**Figure 3**).
- With a median follow-up 13.53 ± 17.53 months (range: 0 – 119.47), 721 of 1,014 patients in the pembrolizumab group and 882 out of 961 patients in the docetaxel group experienced death.
- Overall, pembrolizumab had better survival outcomes with respect to different specification of baseline hazard functions using either the RDiT method or the ts-IPTW method.

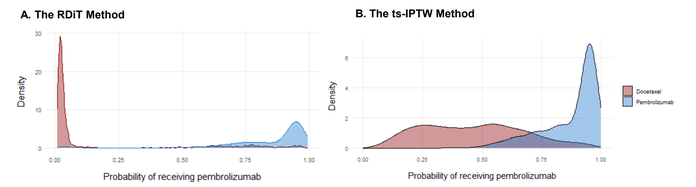
Table 2 Survival Estimates

	Cox PH model			Gompertz parametric model		
Median survival, mos (95% CI)	Pembrolizumab	Docetaxel	Difference	Pembrolizumab	Docetaxel	Difference
RDiT	11.52 (11.25, 11.79)	6.90 (6.72, 7.08)	-	12.21 (11.92, 12.49)	7.22 (7.03, 7.41)	-
ts-IPTW	13.56 (13.12, 13.99)	7.34 (7.15, 7.52)	-	14.17 (13.74, 14.59)	7.28 (7.10, 7.47)	-
KEYNOTE-010	11.8 (10.4, 13.1)	8.4 (7.6, 9.5)	-	-	-	-
1-year survival, %						
RDiT	46.03%	29.88%	16.15%	47.39%	31.11%	16.28%
ts-IPTW	48.91%	29.50%	19.41%	50.41%	31.16%	19.25%
KEYNOTE-010	47.76%	34.60%	13.16%	-	-	-
5-year survival, %						
RDiT	14.19%	5.30%	8.89%	12.95%	4.62%	8.33%
ts-IPTW	15.99%	4.72%	11.27%	14.41%	4.07%	10.34%
KEYNOTE-010	15.6%	6.5%	9.1%	-	-	-
RMST, mos (95% CI)						
RDiT	19.17 (19.06, 19.27)	12.12 (12.05, 12.12)	7.04 (6.97, 7.12)	19.21 (19.11, 19.31)	12.14 (12.07, 12.20)	7.07 (7.00, 7.14)
ts-IPTW	20.37 (20.23, 20.51)	11.79 (11.73, 11.86)	8.58 (8.49, 8.67)	20.56 (20.44, 20.68)	11.98 (11.93, 12.04)	8.58 (8.50, 8.66)
KEYNOTE-010	21.13 (19.57, 22.69)	14.78 (13.04, 16.52)	6.35 (4.01, 8.69)	-	-	-

- Among all Cox proportional hazard (PH) models and parametric survival models, the Cox PH and Gompertz parametric models provided the best fit.
- Compared to the ts-IPTW method, the adjusted survival estimates using the RDiT methods more closely aligned with the 5-year targeted trial results (**Table 2**).
- Sub-group analyses based on the key prognostic factors showed that the RDiT method had similar directions with the trial results.

Results

Figure 3 Treatment Assignment Probabilities Between Two Treatment Groups



Conclusion

- In the presence of unobservable confounders, in this case study, the RDiT method estimated smaller differences in absolute survival gains to the trial-based efficacy as compared to the ts-IPTW method.
- The RDiT method has the potential to be applied in real-world studies, particularly in cases where historical controls are used to study innovative treatments and when the overlap assumption is not met in propensity score approaches.

Discussion

- To our knowledge, this is the first study to introduce RDiT for assessing comparative effectiveness in RWD studies.
- The observed dual discontinuities in treatment assignment probabilities, with increasing trends for both treatment groups, may be attributed to the specific treatments included in this study. In real-world settings, however, other treatment combinations are frequently used in aNSCLC.

Limitations

- The RDiT design provided a local average treatment effect (LATE) instead of average treatment effect (ATE) over time, focusing on the individuals who were nearly above or below the cut-off time point. This may limit the generalizability of the treatment effect at different time points, despite the selection of the relatively recent time period in April – June 2016.
- The selection of the cut-off time point was based on the approval of indication, the guideline recommendations, and the treatment patterns observed in the dataset, which may be subject to the selection bias due to the variability of enrolled clinics over time.
- Larger confidence intervals observed in our results indicate reduced precision, potentially limiting the statistical power to detect smaller but clinically meaningful differences.

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*The Flatiron Health database is a longitudinal database, comprising de-identified patient-level structured and unstructured data, curated via technology-enabled abstraction. **During the study period, the de-identified data originated from approximately 800 cancer clinics enrolled.

Disclosure: The authors declare that (s)he has no relevant or material financial interests that relate to the research and data described in this study.