Applying the Estimand and Target Trial frameworks to external control analyses using observational data: a case study in the solid tumor setting

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Background

- Randomized Clinical Trials (RCTs) are the gold standard to answer causal questions about efficacy and safety of health-related interventions.

- When RCTs are not feasible, high quality Real-World Data (RWD) could be considered to answer causal questions[1]
  - At the cost of introducing further assumptions.
  - Require transparency on the observational study design that emulates the target trial[2].

1ESMO debate session by Prof. S. Peters at ESMO Virtual Plenary April 2021
2Hernán MA et al. Observational studies analyzed like randomized experiments: an application to postmenopausal hormone therapy and coronary heart disease. Epidemiology. 2008;19(6):766.

Estimand & Target trial frameworks combined

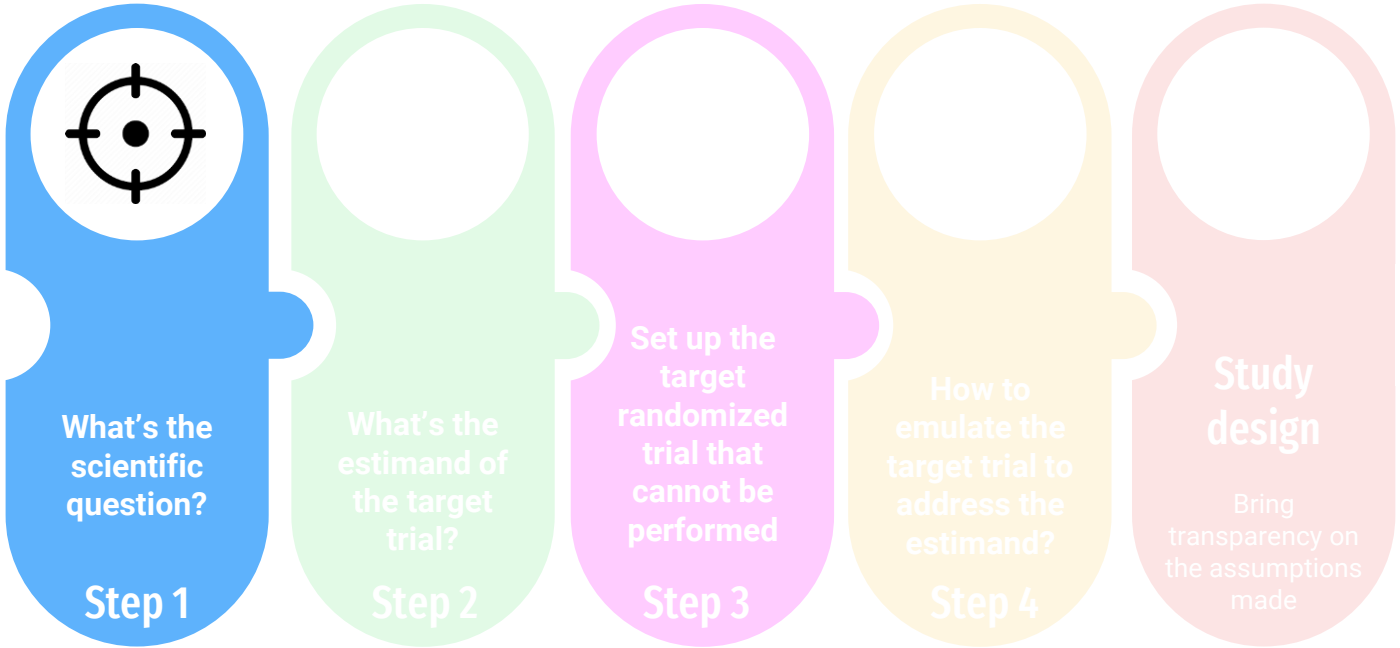
Use case: study objective

- **Study objective:** determine whether there is a difference in overall survival (OS) between patients with metastatic non-small cell lung (NSCLC)[1] receiving front-line chemotherapy in pivotal trials vs patients with metastatic NSCLC who received front-line chemotherapy as part of routine care.

- **Broader context:** assess the utility of RWD for use as external control in drug development

[1]Non-small cell lung cancer (NSCLC) is the most common type of lung cancer. Metastatic NSCLC refers to later stages of the cancer where it has spread to distant parts of the body.

Estimand & Target trial frameworks combined



Scientific question

“Is there a difference in overall survival (OS) between patients with metastatic NSCLC receiving front-line platinum-based chemotherapy in pivotal trials vs patients with metastatic NSCLC who received front-line platinum-based chemotherapy as part of routine care?”

What do we actually measure?

Scientific question: traditional approach

"Is there a difference in overall survival (OS) between patients with metastatic NSCLC receiving front-line platinum-based chemotherapy in pivotal trials vs patients with metastatic NSCLC who received front-line platinum-based chemotherapy as part of routine care, **regardless of whether a patient received another therapy**?"

Assumption: subsequent treatments reflect routine clinical practice for both clinical trial and observational arms

Scientific question: hypothetical scenario

“Is there a difference in overall survival (OS) between patients with metastatic NSCLC receiving front-line platinum-based chemotherapy in pivotal trials vs patients with metastatic NSCLC who received front-line platinum-based chemotherapy as part of routine care, **had patients not received a subsequent therapy**?”.

Estimand & Target trial frameworks combined

Attributes of the estimand of the target trial

Target population	Metastatic squamous and non-squamous NSCLC patients, 18 years of age or older, with ECOG PS 0,1 and with adequate hematological and end-organ function.
Treatment	Trial control arm and comparator observational arm (will) receive platinum-based chemotherapies. The “experimental group” receives care according to the trial protocol, whereas the “comparator” group receives care according to real-world practice.
Primary Endpoint	Overall Survival
Intercurrent events	Receipt of a subsequent treatment; Strategy: hypothetical strategy
Population-level summary	HR with confidence interval (CI); K-M estimator

Estimand & Target trial frameworks combined

What's the scientific question?

Step 1

What's the estimand of the target trial?

Step 2

Set up the target randomized trial that cannot be performed

Step 3

How to emulate the target trial to address the estimand?

Step 4

Study design

Bring transparency on the assumptions made

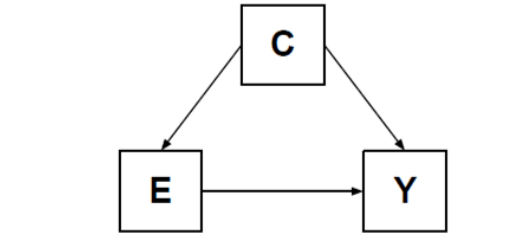
Assumptions to emulate the target trial

EF/TTF Attributes	Target trial	Emulation of the target trial	Assumptions
Target population/Eligibility criteria	Metastatic squamous and non-squamous NSCLC patients, 18 years of age or older, with ECOG PS 0,1 and with adequate hematological and end-organ function.	Same as the target trial for the RCT arm, with some assumptions for the OC arm.	Observational data does not perfectly emulate the trial I/E criteria. We attempt to define the study cohort that best approximates the target population by including additional rules. • Time window for the eligibility assessment (ECOG PS, lab values, biomarker)

Full table <Table 1> https://arxiv.org/ftp/arxiv/papers/2208/2208.06707.pdf

Key methodological considerations

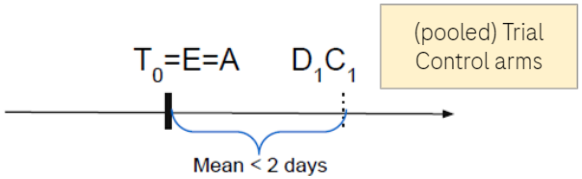
Assignment strategy

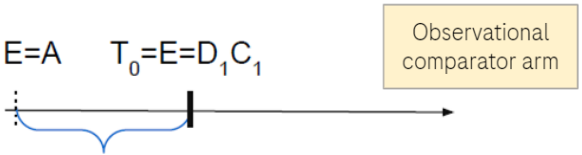


C, baseline confounder; E, Exposure (setting); Y, Outcome

- ~~Analytical solution:~~ IPTW-ATT
- **Measured confounding variables:** age group, gender, race, metastatic tumor type, time from initial diagnosis to index date, smoking history, histology, treatment type.

Follow-up period





Assumptions:
-time from assignment and start of therapy is short in the RWD,
-disease with relatively no rapid course in 1L

E = eligibility, A = treatment assignment, T_0 = index date, D_1C_1 dose 1 cycle 1

Intercurrent events

- **Risk**: Not accounting for informative censoring introduce bias.
- **Analytical solution**: IPCW(t) including confounders that predict both treatment switch and outcome OS
- **Measured confounding variables:** age group, histology/treatment, progression after treatment initiation

Baseline characteristics

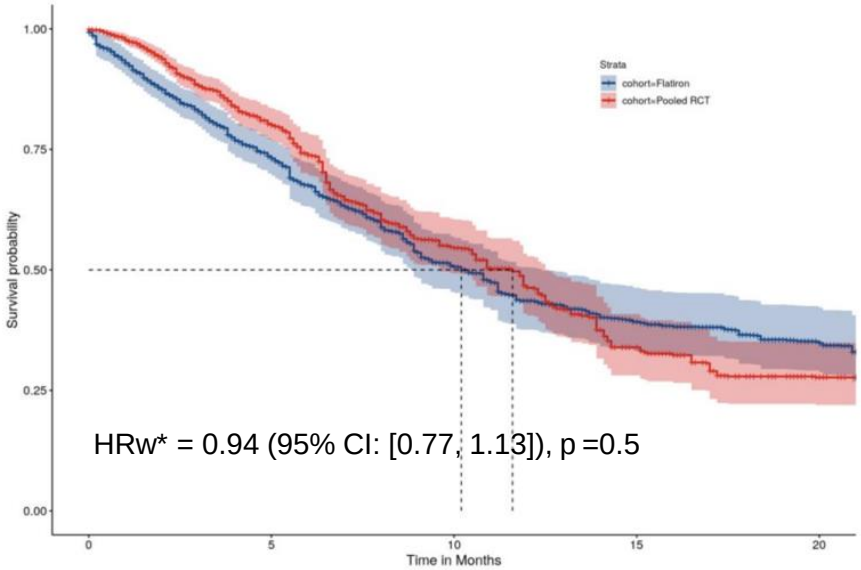
- Pts were on average younger, …

Variable	Categories	pooled_RCT N=849	Flatiron_RWD N=3340	SMD Pre-IPTW	SMD Post-IPTW
Age group (years), n(%)	< 65	435 (51.2)	1222 (36.6)	**0.42**	0.03
	≥65 and <75	322 (37.9)	1268 (38.0)		
	≥75	92 (10.8)	850 (25.4)		
Gender, n(%)	Female	248 (29.2)	1457 (43.6)	**0.3**	0.04
Race, n(%)	Asian	105 (12.4)	46 (1.4)	**0.75**	0.06
	Other	45 (5.3)	921 (27.6)		
	White	699 (82.3)	2373 (71.0)		
ECOG-PS, n(%)	0	314 (37.0)	714 (21.4)	0.05*	
	1	532 (62.7)	1179 (35.3)		
	NA	2 (0.2)	1447 (43.3)		
Metastatic diagnosis, n(%)	De novo Stage IV	706 (83.2)	2118 (63.4)	**0.46**	0.03
	Recurrent disease	143 (16.8)	1221 (36.6)		
Smoking history, n(%)	No	69 (8.1)	257 (7.7)	0.02	0.06
	Yes	780 (91.9)	3070 (91.9)		
	NA	0 (0.0)	13 (0.4)		
Histology, n(%)	Non-squamous	509 (60.0)	2278 (68.2)	**0.17**	0.01
	Squamous	340 (40.0)	1062 (31.8)		
Time from initial diagnosis to index date (months), (median [IQR])		1.41 [0.92, 2.89]	1.25 [0.79, 2.27]	**0.15**	0.01
Treatment, n(%)	Carboplatin+Pacli/Nab-pacli	568 (66.9)	1877 (56.2)	**0.22**	0.04
	Platinum+Pemetrexed	281 (33.1)	1463 (43.8)		

**ECOG-PS variable was not included in the propensity score model because of the high proportion of missing ECOG-PS. Developing an Imputation model to differentiate score 0 vs 1 was considered out of scope for the goal of this presentation.*

Trial pts were on average younger, more frequently were males, diagnosed as de novo stage IV and with squamous histology

Estimation method aligned with the estimand



*Model with Stabilized weights

Scientific question: Is there a difference in overall survival (OS) between patients with metastatic NSCLC receiving front-line chemotherapy vs patients with metastatic NSCLC who received front-line chemotherapy as part of routine care, had patients not received a subsequent therapy?

Estimation method: Weighted Cox regression model (PH), weighted Kaplan-Meier curves
Weights: **IPTW-ATT*IPCW(t)**

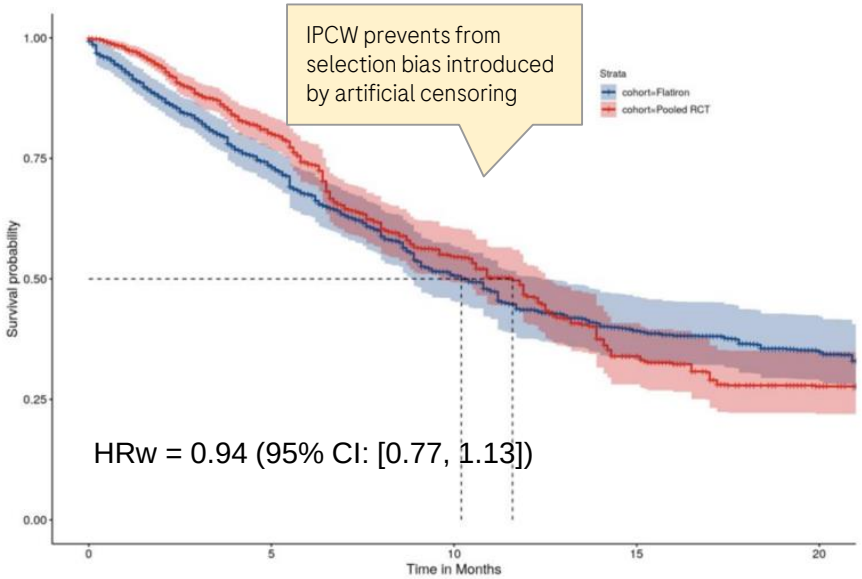
Confounding variables: age group, histology/treatment, progression after treatment initiation

Positivity assumption => there are both exposed and unexposed individuals at every level of the confounder (including time-varying confounders)

Accounting for censoring confounding variables

Hypothetical strategy
IPTW-ATT*IPCW(t)

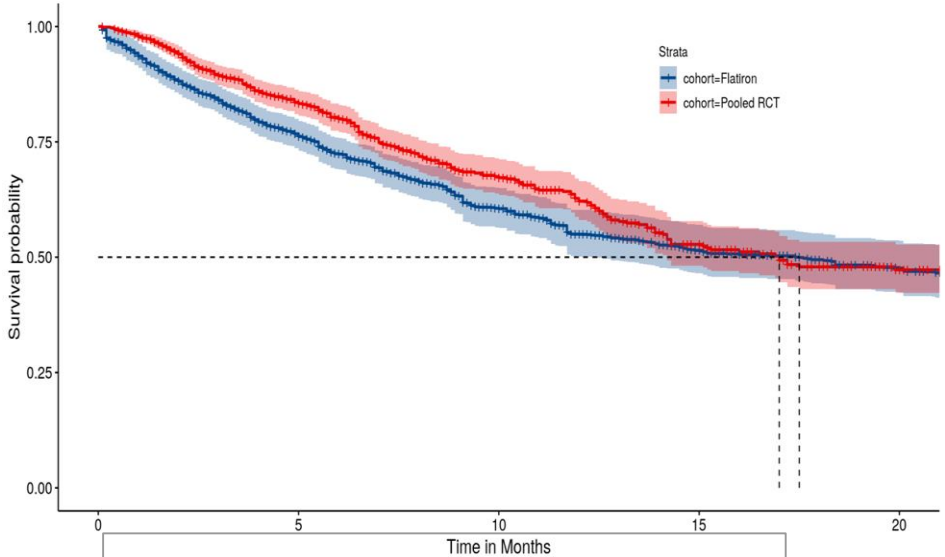
Primary analysis



HRw = 0.94 (95% CI: [0.77, 1.13])

Hypothetical strategy
IPTW-ATT without IPCW(t)

Sensitivity analysis

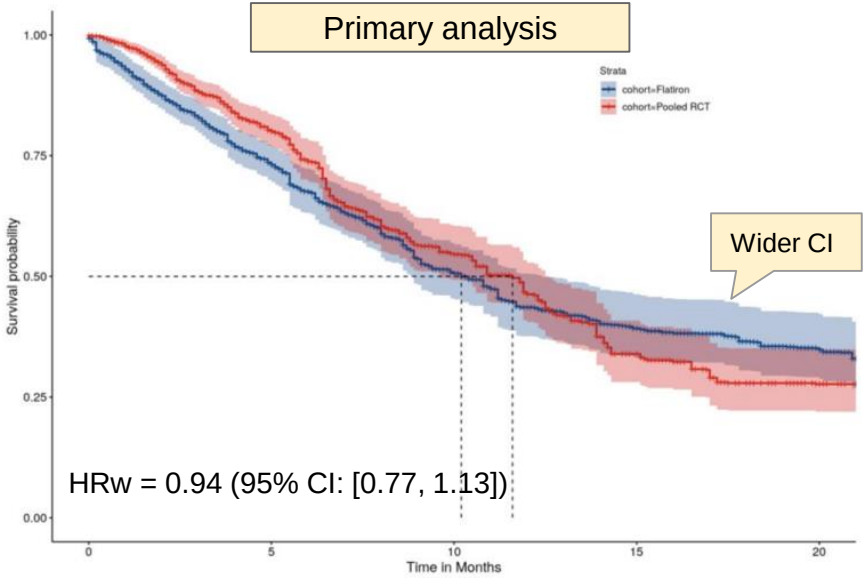


Assumption => Switcher and non-switchers have the same prognosis (i.e. no confounders)

Supplementary analysis - different strategies for IE

IPTW-ATT*IPCW(t)
Hypothetical strategy

Primary analysis

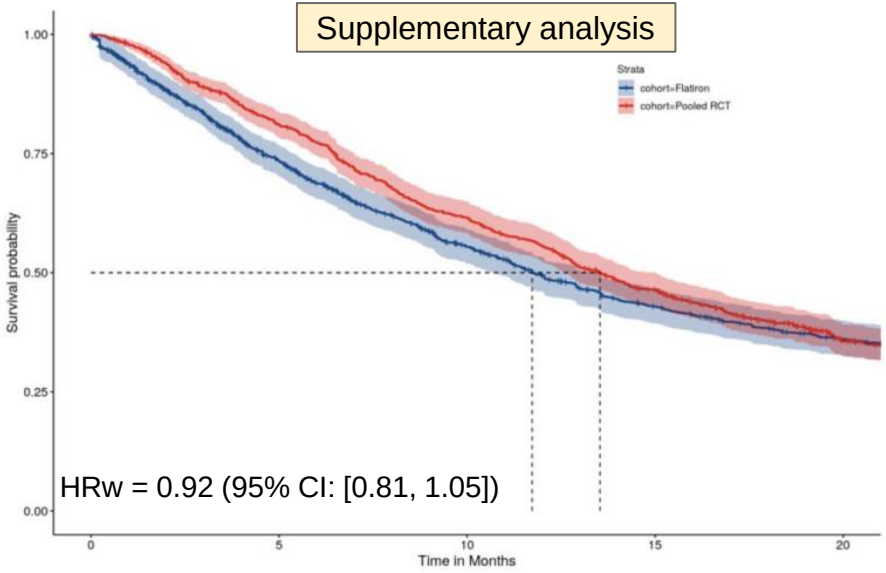


Wider CI

HRw = 0.94 (95% CI: [0.77, 1.13])

IPTW-ATT
Treatment policy strategy

Supplementary analysis



HRw = 0.92 (95% CI: [0.81, 1.05])

Study limitations

- We have pooled together different IMpower trials
  - IMpower130: non-squamous NSCLC treated with carboplatin plus nab-paclitaxel; IMpower131: squamous NSCLC treated with carboplatin plus nabpaclitaxel; IMpower132: non-squamous NSCLC treated with carboplatin or cisplatin plus pemetrexed
  - Mitigation strategy to account for heterogeneity between trials: Added trial indicator in the PS model: treatment x histology
- Patients in IMpower trials were global while patients in the observational arm were from the United States only
- Limited capture of potential confounders in the observational arm (e.g. comorbidities, sites of metastasis, and completeness of ECOG) - Assumption of IPTW and IPCW: no unmeasured confounding (at baseline and at time of switch)

Conclusions

- The estimand framework is increasingly used by regulators but also within the clinical teams.
  - Analysing RWD using the same framework as RCT avoids unneeded silos
    - Common terminology
    - Develop common analytical approaches
- The combined EF/TTF brings even more clarity on the study design of the “target trial”.
  - It brings transparency on the assumptions needed to emulate the target trial
  - Transparent description of potential limitations of the RWD source chosen (e.g. data quality)
  - Highlight the importance of variables not previously collected in the real world (e.g. intercurrent events)
- This requires a new mindset:
  - Become familiar with the strategies to address intercurrent events
  - As per ICH E9 addendum, think carefully on what constitutes sensitivity analyses vs supplementary analyses for the key estimand also in observational research