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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Affiliations at the time the study was conducted:
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Disclosure: this presentation reflects the views of the authors and not necessarily those of Hoffman-La Roche and Flatiron Health

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Introduction

- 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].
- One important application in pharmacoepidemiology is the use of of RWD to generate external control arms for estimating comparative treatment effect. There are several efforts to replicate trial control arms using RWD.
- **Case study:** Applying the Estimand[3] and Target Trial[2] frameworks to replicate trial control arms from pivotal trials in non-small cell lung cancer (NSCLC) first-line setting using RWD

1ESMO debate session by Prof. S. Peters at ESMO Virtual Plenary April 2021; 2Hernan MA, Robins JM. American Journal of Epidemiology;183(8) 2016, 3ICH E9 (R1) addendum

Estimand & Target trial frameworks combined

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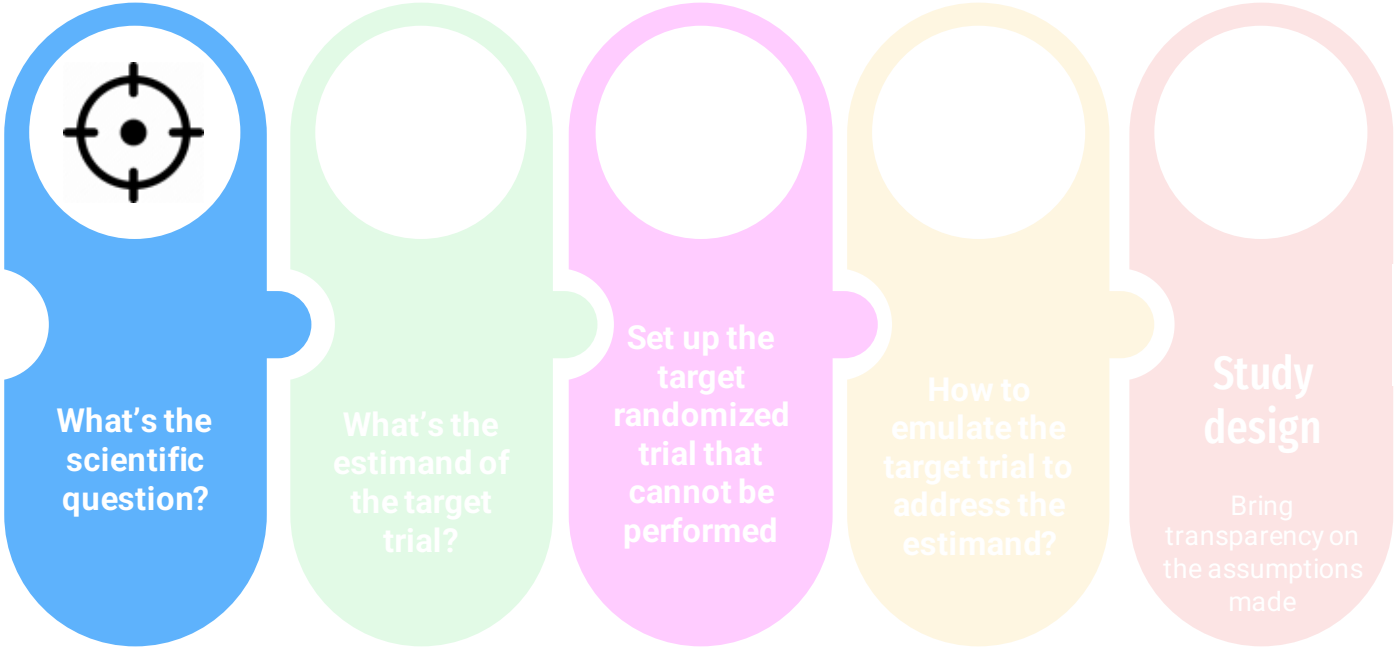


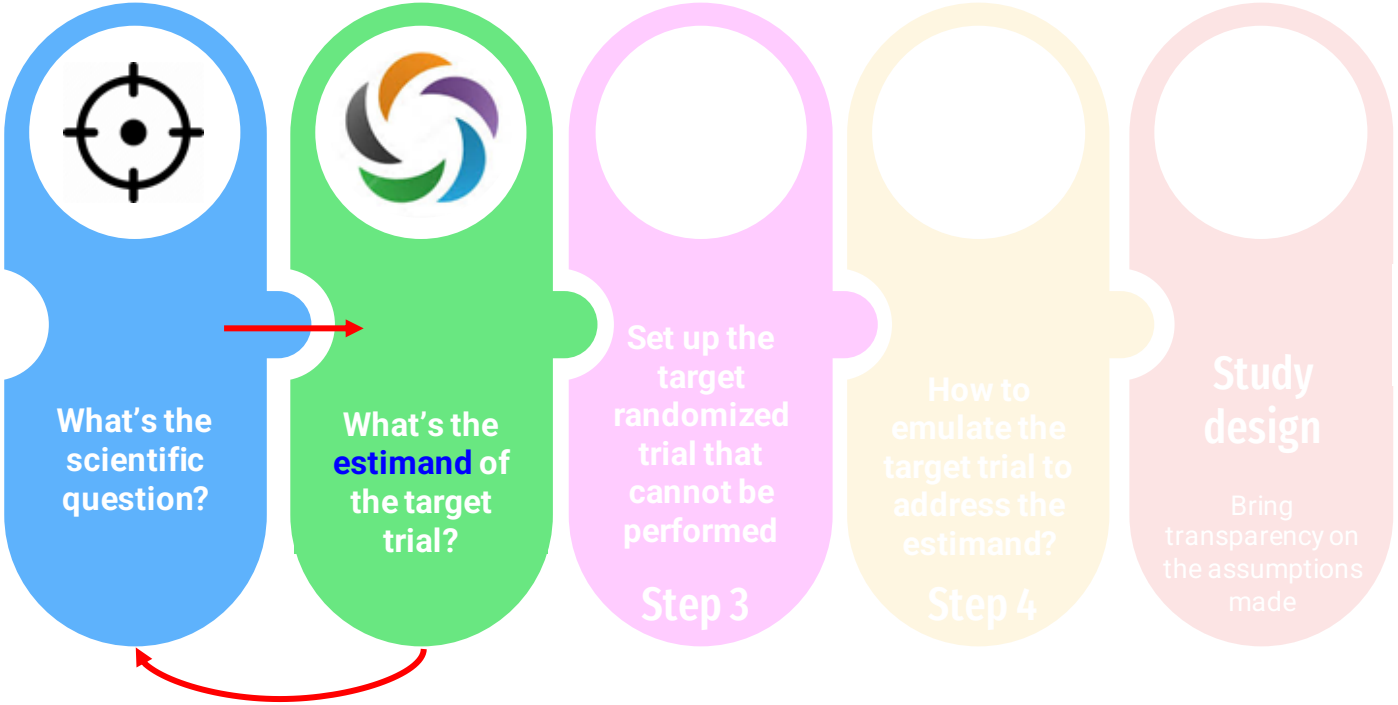
Case study: scientific question

- **Scientific question:** Is there a difference in overall survival (OS) between patients with metastatic NSCLC[1] 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?

Is this question clear enough to leave no ambiguity about the estimand?

[1]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: 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

Risk: differences in subsequent therapies across treatment settings may introduce complexities in estimating causal treatment effects for long-term outcomes such as OS and ultimately complicate interpretation.

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**?".

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 to handle IE: hypothetical strategy
Population-level summary	Hazard ratio (HR) with confidence interval (CI); Kaplan-Meier 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

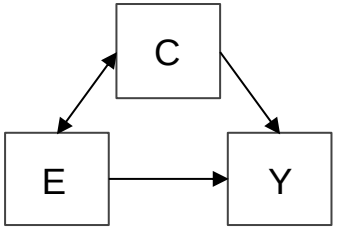
Assumptions to emulate the target trial

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> Polito et al. 2022 https://arxiv.org/ftp/arxiv/papers/2208/2208.06707.pdf

Key methodological considerations

Assignment strategy



C, baseline confounder; E, exposure; Y, Outcome

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

Key methodological considerations

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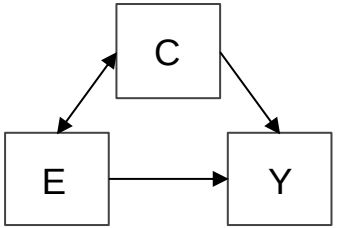

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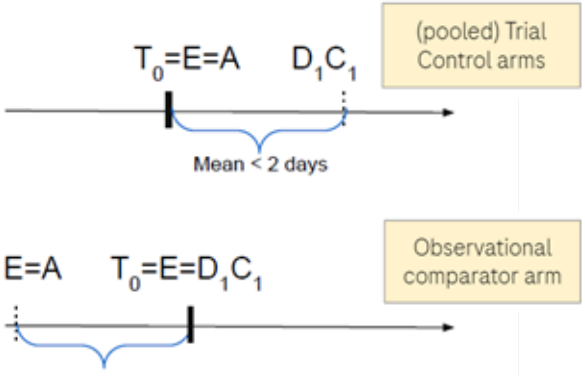
Follow-up period

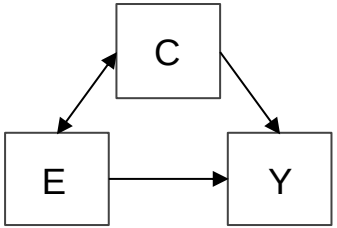


E, eligibility; A, treatment assignment; T0, index date; D1C1, dose 1 cycle 1

- **Assumptions:**
  - Time from assignment to start of therapy is short in the RWD
  - Disease with relatively no rapid course in first-line

Key methodological considerations

Assignment strategy



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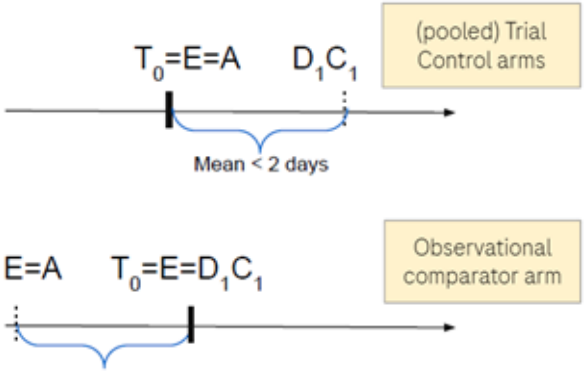

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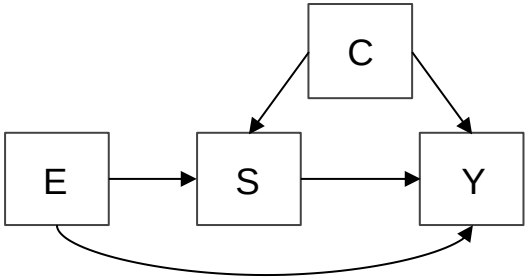
Intercurrent events



C, time-fixed confounder; E, exposure; S, intercurrent event; Y, Outcome

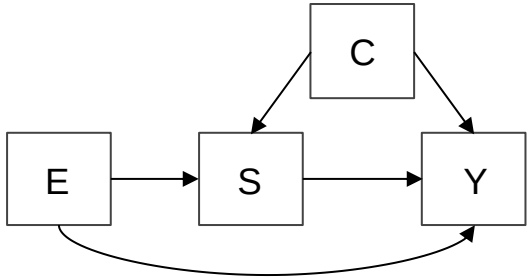
- **Analytical strategy:** IPCW(t)
- **Measured confounding variables:** age group, histology/treatment. progression after treatment initiation

Key methodological considerations

- Good alignment between progression in the real world and in clinical trials [Griffith et al. 2019]
- Progression is not an exact proxy of treatment switch

Positivity assumption => there are both switchers and non-switcher at every level of the confounder (including time-varying confounders)

Intercurrent events



C, time-fixed confounder; E, exposure; S, intercurrent event; Y, Outcome

- **Analytical strategy:** IPCW
- **Measured confounding variables:** age group, histology/treatment, progression after treatment initiation

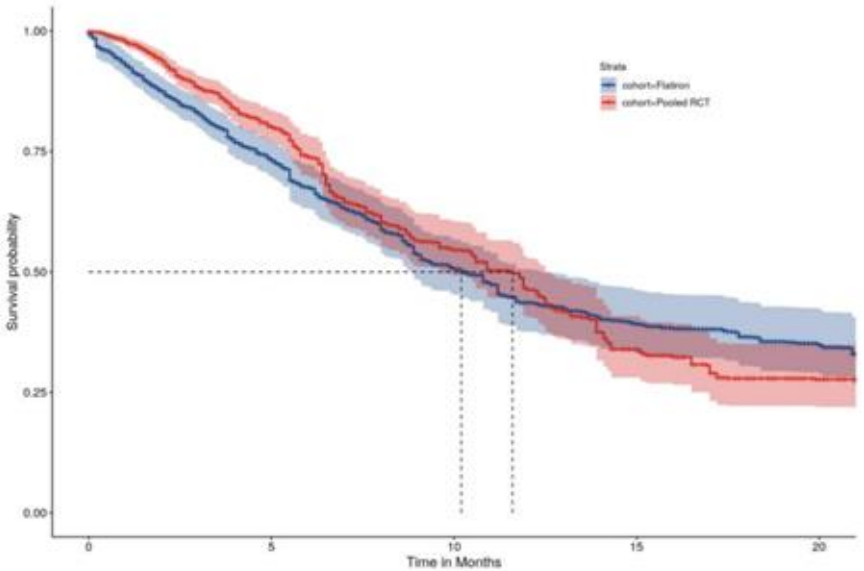
Baseline characteristics

- Patients enrolled in the trials were on average younger, more frequently were males, diagnosed as de novo stage IV and with squamous histology compared to patients in the real world

Variable	Categories	Pooled_trial control arms N=849	Observational control arm 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.*

Estimation method aligned with the estimand



	Pooled_trial control arms N=848	Observational control arm N=865
Events, n (%)	385 (45.4)	361 (41.7)
Censoring, n (%)	463 (54.6)	504 (58.3)
Median OS (95% CI), mo	11.6 (9.6-12.6)	10.2 (8.9-12.4)
IPTW-ATT*IPCW$_{(t)}$[§]-HR (95% CI)	0.94 (0.77-1.13), p=0.5	

[§]*Stabilized weight*

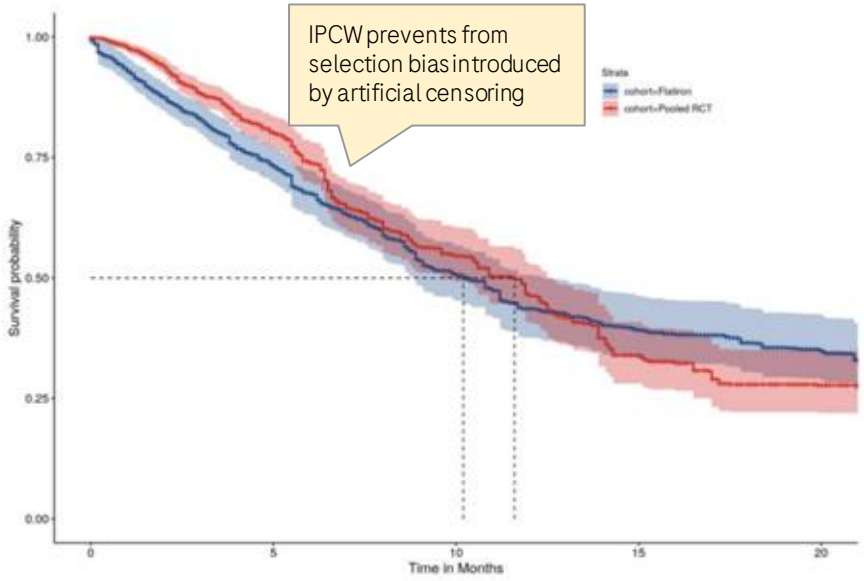
Scientific question: Would there be a difference in overall survival (OS) between patients with metastatic NSCLC receiving front-line chemotherapy vs patients with metastatic NSCLC who received front-line chemotherapy as part of routine care, had patients not received a subsequent therapy?

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

Accounting for censoring confounding variables

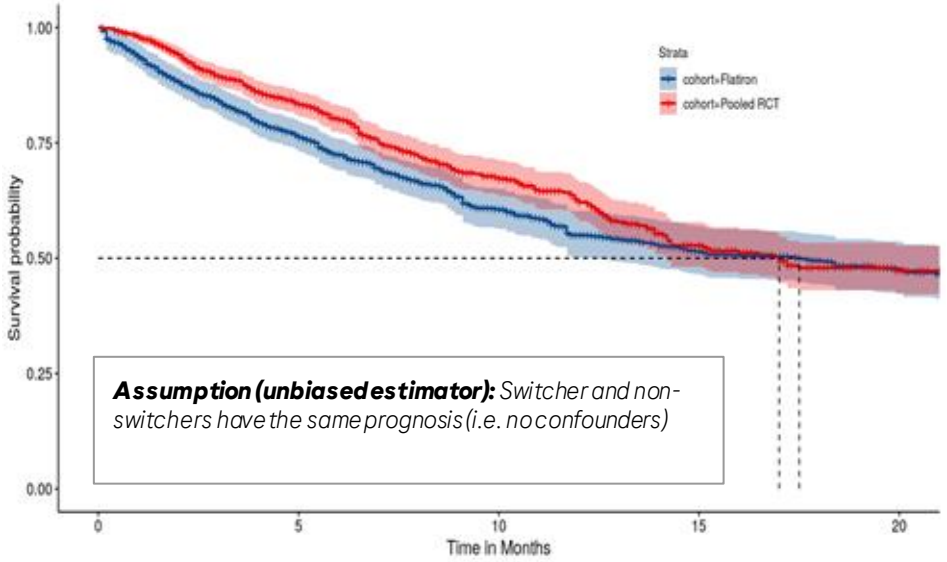
Primary analysis

Hypothetical strategy
IPTW-ATT*IPCW(t)



Sensitivity analysis

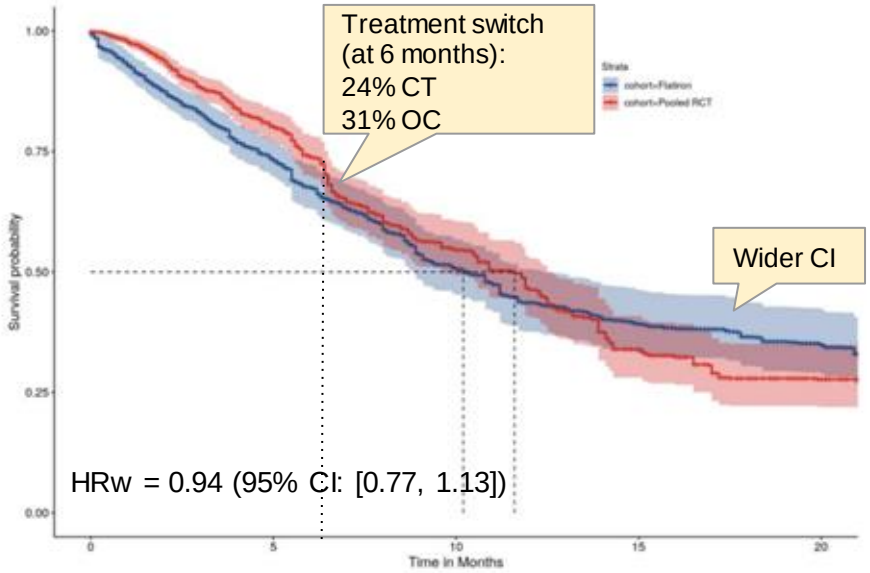
Hypothetical strategy
IPTW-ATT without IPCW(t)



Supplementary analysis - different strategies for IE

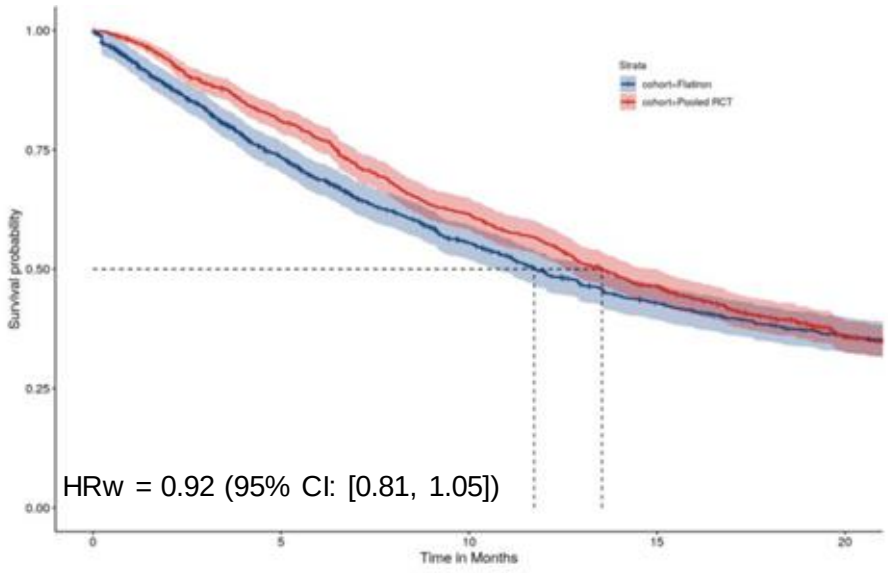
Primary analysis

IPTW-ATT*IPCW(t)
Hypothetical strategy



Supplementary analysis

IPTW-ATT
Treatment policy strategy



Study limitations

- 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)

- We have pooled together different IMpower 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

Conclusions/lessons learned

- 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

Thank you