Electronic Health Records used to derive Control Arms for Single-Arm oncology trials: Proof of concept using RCT's in lung cancer

Gonzalo Duran-Pacheco on behalf of: Gillis Carrigan, Samuel Whipple, William B. Capra, Michael D. Taylor, Michael Lu, Brandon Arnieri, Jeffrey S. Brown, Amy Abernethy, Ryan Copping and Kenneth J. Rothman

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Disclaimer

- *I'll present this work on behalf of those who actually conducted this study*
- *I might not be able to answer some questions, I'll do my very best*
- *EC instead of SC*

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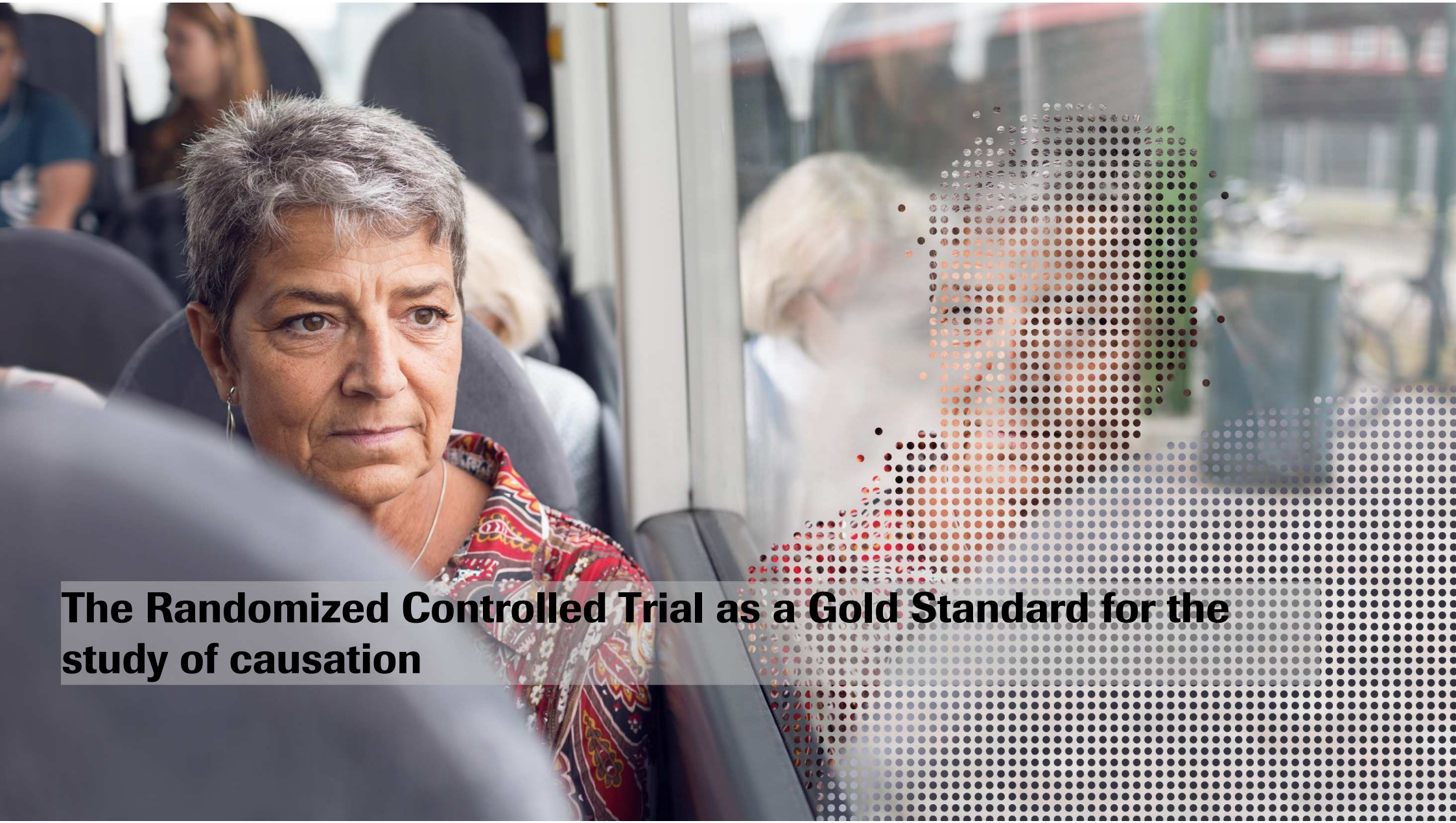


The Randomized Controlled Trial as a Gold Standard for the study of causation

Causal Effects of Treatment A

- Counterfactuals and observed outcomes. Be:
  - Y the observed outcome under treatment A (A = 0, 1)
  - $Y_{a=0}$ the potential outcome had A = 0
  - $Y_{a=1}$ the potential outcome had A = 1

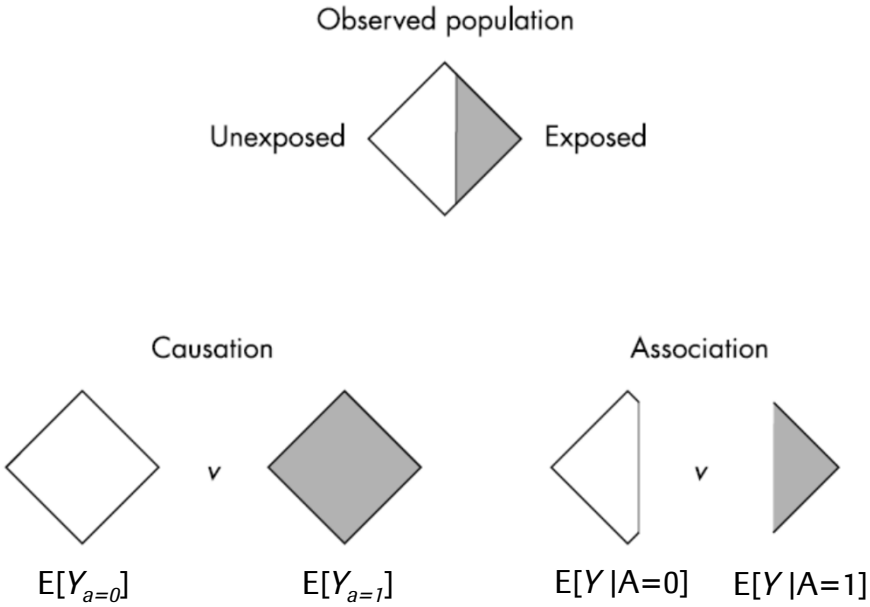
The **individual causal effect** : $ICE = Y_{a=1} - Y_{a=0}$

The **population causal effect** : $PCE = E[Y_{a=1}] - E[Y_{a=0}]$

  - Causation and Correlation

$E[Y_{a=1}] - E[Y_{a=0}] \neq E[Y|A=1] - E[Y|A=0]$

Fundamental problem: Estimate PCE when only one counterfactual is observed



Hernan & Robins, 2018

Causal Effects and RCT

- Under which conditions is $E[Y_{a=1}] - E[Y_{a=0}] = E[Y|A=1] - E[Y|A=0]$?
  - Exchangeability: $Y_a \perp A$
  - Consistency: $Y_a = Y$ when a subject received treatment A = a
  - Positivity: $f_{A|L}(a|l) > 0$ if $f_L(l) \neq 0$ (with confounding factors L)
- Under ideal RCT conditions (i.e. full compliance, no loss to-follow-up, blind assignment)
  - $E[Y|A=1] = E[Y_a \mid A=1]$ a for given *a*

    $= E[Y_a \mid A=0]$

    $= E[Y_a]$

    $E[Y_a] \perp A \ \forall\ a\ (0, 1)$

    $\therefore$ Equation above holds

Conditional exchangeability

- Same as above but $E[Y_a] \perp A \mid \mathbf{L}$

  where **L** is a vector of covariates

  $$E[Y_{a=1}] - E[Y_{a=0}] \mid \mathbf{L} = E[Y \mid A=1] - E[Y \mid A=0] \mid \mathbf{L}$$

- Example:
  - The Propensity Scores Theorem:
    - Be treatment A wit values 0 and 1
    - The propensity of "choosing" treatment given covariates **L**: $PS(\mathbf{L}) = P(A=a \mid \mathbf{L})$

      If $Y_a \perp A \mid \mathbf{L}$ (Conditional Independence Assumption)

      then $Y_a \perp A \mid PS(\mathbf{L})$ (PST)

External Controls for Lung Cancer RCTs using EHR: Background

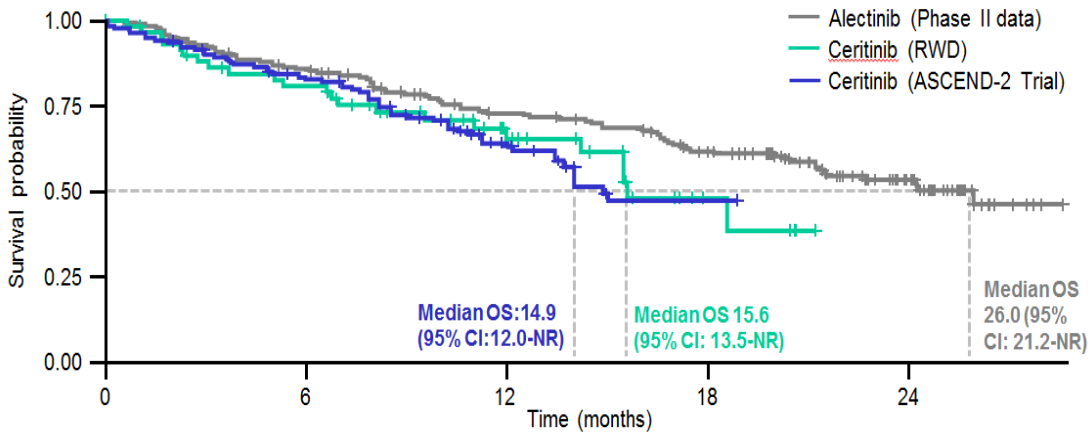
Background

- Accelerated or breakthrough regulatory approval based on single-arm trials often
  - standard-of-care control arm is not included, challenges in interpretation of efficacy
- External controls (EC) derived from electronic health record (EHR) databases may provide an additional context for interpretation

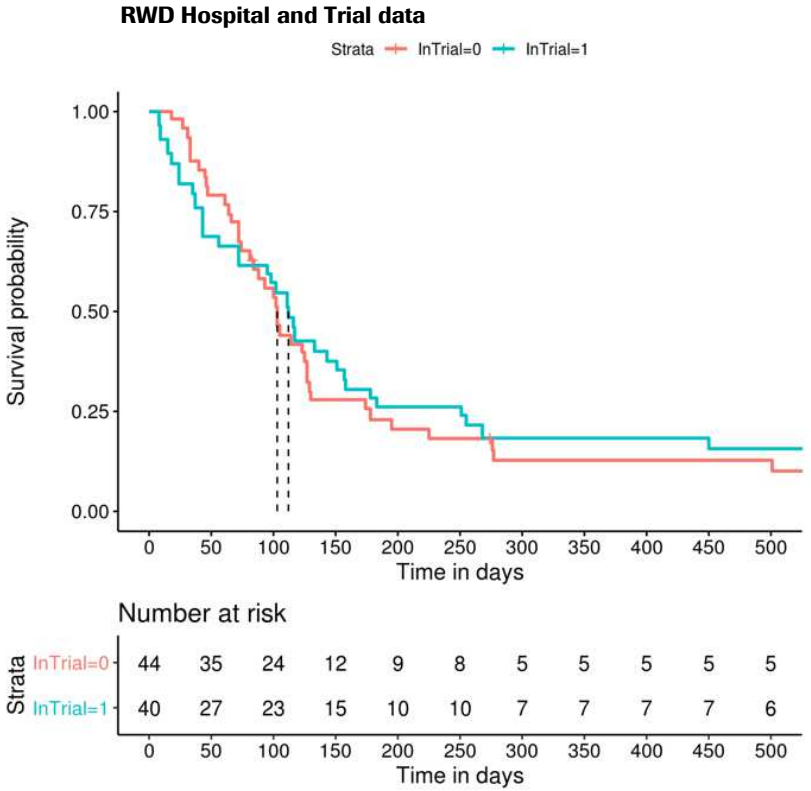
- Curated EHR datasets are now large enough, with sufficient clinical detail, to create contemporaneous EC groups
- The Flatiron Health database is a longitudinal, demographically and geographically diverse database derived from EHR data
  - 260 community-based cancer treatment clinics and 3 academic networks, > 2 million active cancer patients in the US
  - High quality mortality data for lung cancer benchmarked against the US National Death Index

Background

- Efforts towards EC



CI, confidence interval; HR, hazard ratio; NR, not reached; OS, overall survival; RWD, real-world data.



Objective

- To assess how closely results from RCTs on aNSCLC could be replicated by substituting EHR-based EC groups as the comparator

External Controls for Lung Cancer RCTs using EHR: Cohorts creation and Analysis

Trials selection

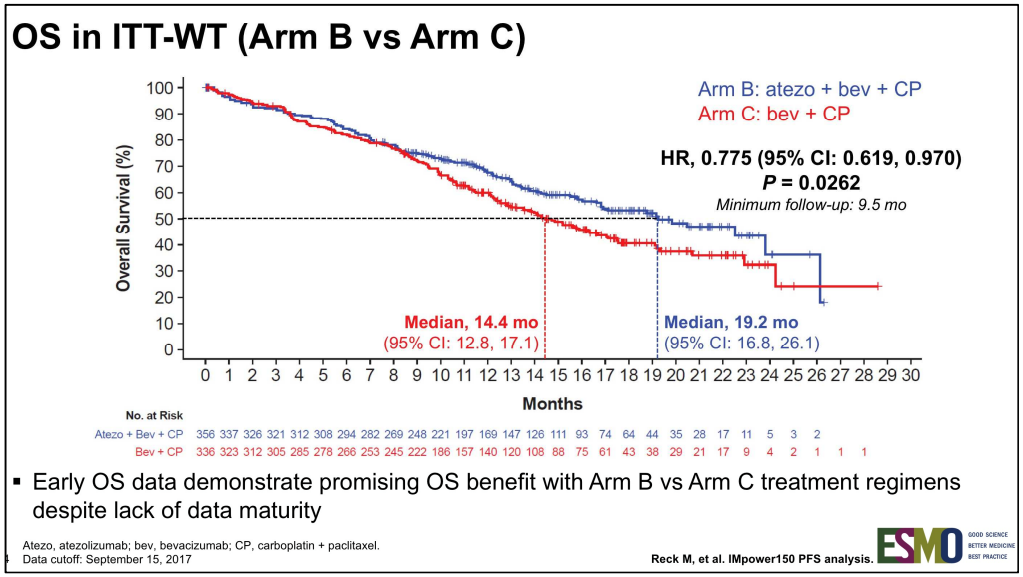
- Study on all Roche-sponsored aNSCLC RCT meeting the following:

  a) First patient enrolled on or after January 1, 2011
  b) mOS attained, findings presented in a journal or at a congress, by March 31, 2018
  c) including at least one US study site
  d) in the case of a biomarker-defined study population, availability of the biomarker within the curated EHR dataset

Retrieve patient level data and verify trial results

- Verify RCT results published in public forums
  - BL and demographics (Table 1)
  - Main results

OS results for IMpower150 presented at ESMO

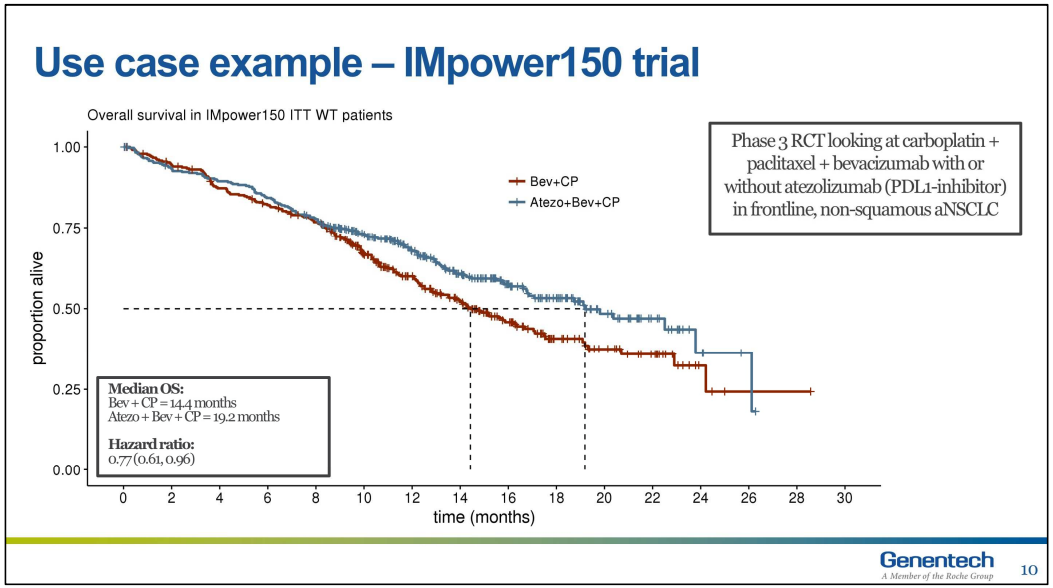


- Early OS data demonstrate promising OS benefit with Arm B vs Arm C treatment regimens despite lack of data maturity

Atezo, atezolizumab; bev, bevacizumab; CP, carboplatin + paclitaxel.
Data cutoff: September 15, 2017

Reck M, et al. IMpower150 PFS analysis. ESMO

Reproduced results with received data cut



Review trial protocol and identify criteria to apply

- Done cross-functionally with the study team
- Go through the I/E criteria one by one, flagging those criteria which can be applied to the EC cohort
    - Not everything will be able to be applied
        - e.g. life expectancy, comorbidities, other medications, pregnancy, etc..
    - For transparency, those criteria that are unable to be applied should be called out

- We found it especially beneficial to sit down with clinical scientists to review certain criteria and decide how best to apply to Flatiron
    - Often some “translation” needs to occur between protocol and Flatiron (e.g. staging)

Build EC cohort

- Select patients from the EHR cohort that received standard-of-care treatment as in the trial
- Apply RCT I/E criteria available in the EHR to select EHR-based controls comparable in terms of demographic and clinical characteristics with RCT patients
  - Attrition rates displayed at each step
    - Alternatively, make each criteria a flag in your dataset so that you can easily turn them on/off in different orders
  - Some criteria will be straightforward
    - Therapy of interest, Histology, Age
  - For others (ECOG and lab values), we've developed some business rules to alleviate issues like high levels of missingness

Data Analysis

- **Primary endpoint:** time from randomization or treatment initiation (EHR) to death (OS)
- **Statistical Analysis:**
  - Proportional hazards cox model used to estimate treatment effects (HR) comparing the experimental trial arms with EC
  - PS obtained: Probability of being in the trial treatment arm rather than in the EC given **L**
    - **L** = age, gender, race, smoking history, histology, disease stage at initial diagnosis, time from initial diagnosis to either the start of treatment (EHR data) or randomization (trial data)
    - **L** derived from discussions with subject matter experts

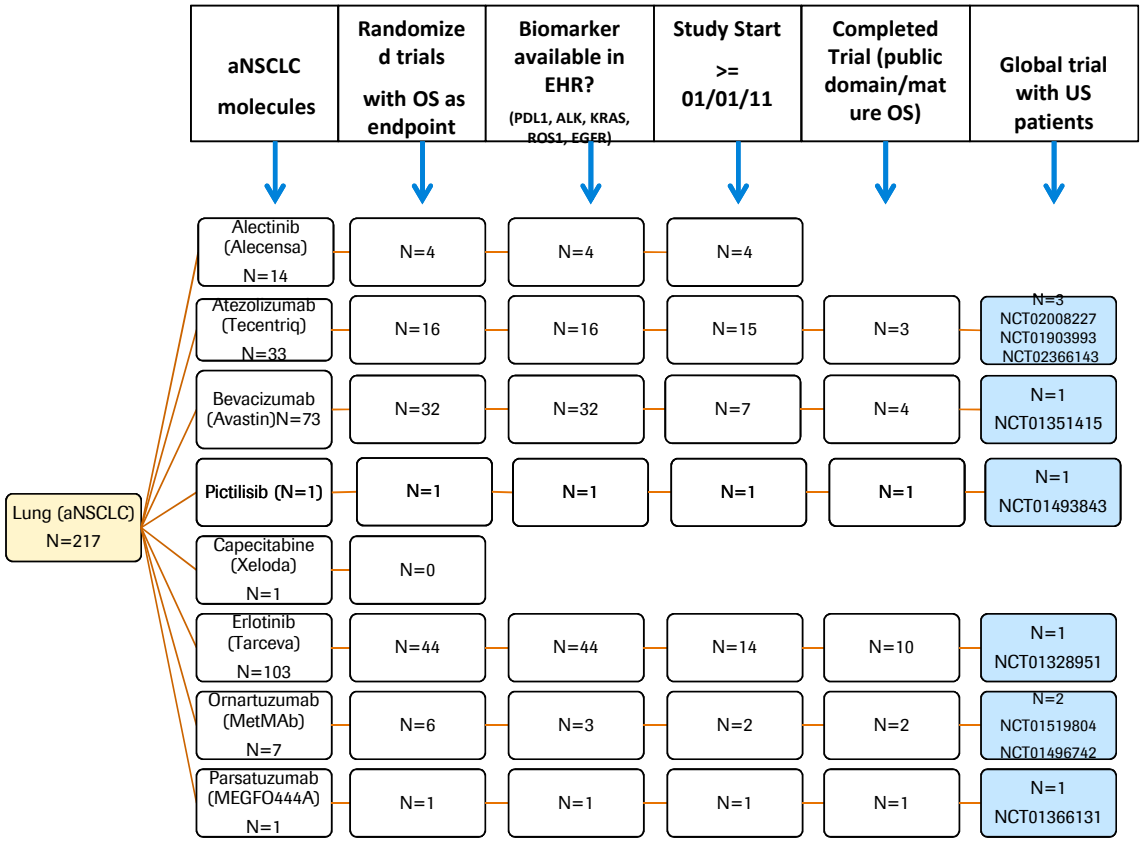
Data Analysis

- **PS Methods applied:**
  - PS stratification
  - IPTW (ATE, ATT)
  - Cox PH adjusting directly for **L**
  - Weights stabilization: trimming/truncation
- Sensitivity Analysis

Results

Trial selection

- From 217 RCT (8 drugs) to 9 eligible RCT
- 11 experimental arms



Building EC cohorts

B=bevacizumab PE=pemetrexed

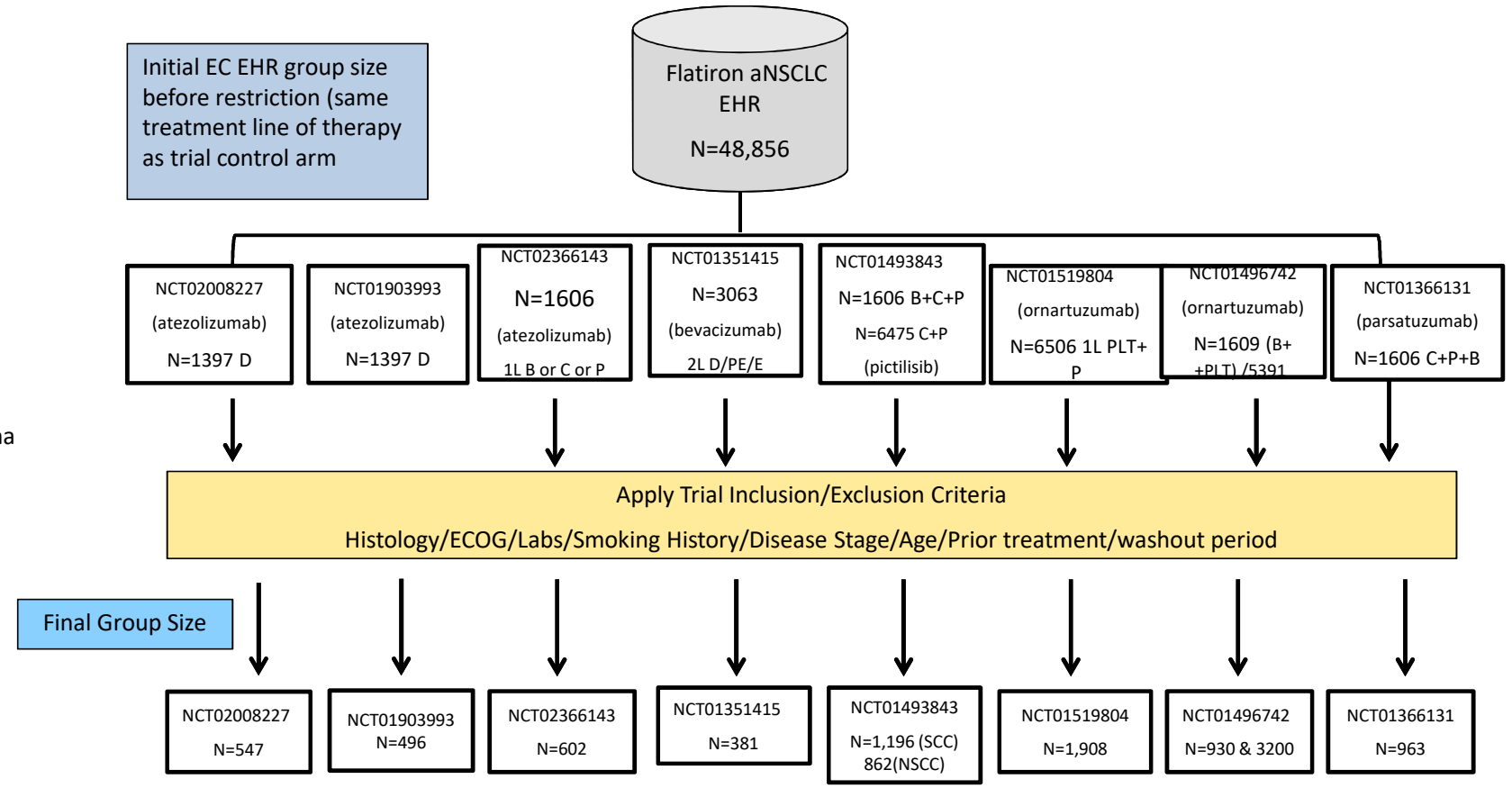
C=carboplatin PLT=platinum

D=docetaxel

P=paclitaxel

NSCC=non squamous cell carcinoma

SCC=squamous cell carcinoma



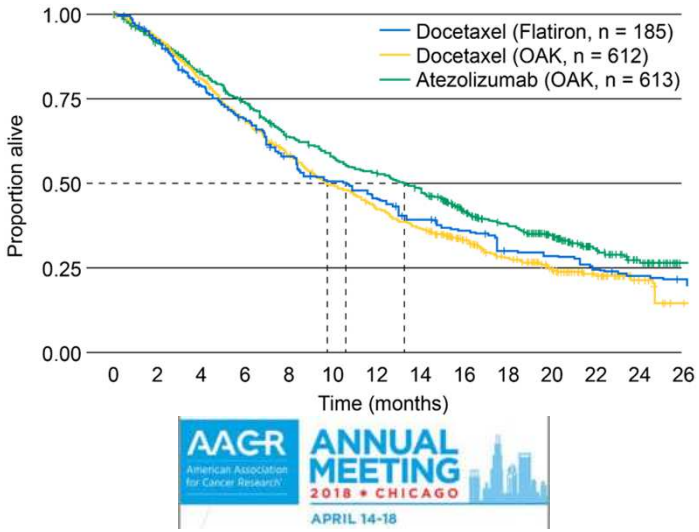
Trial Results

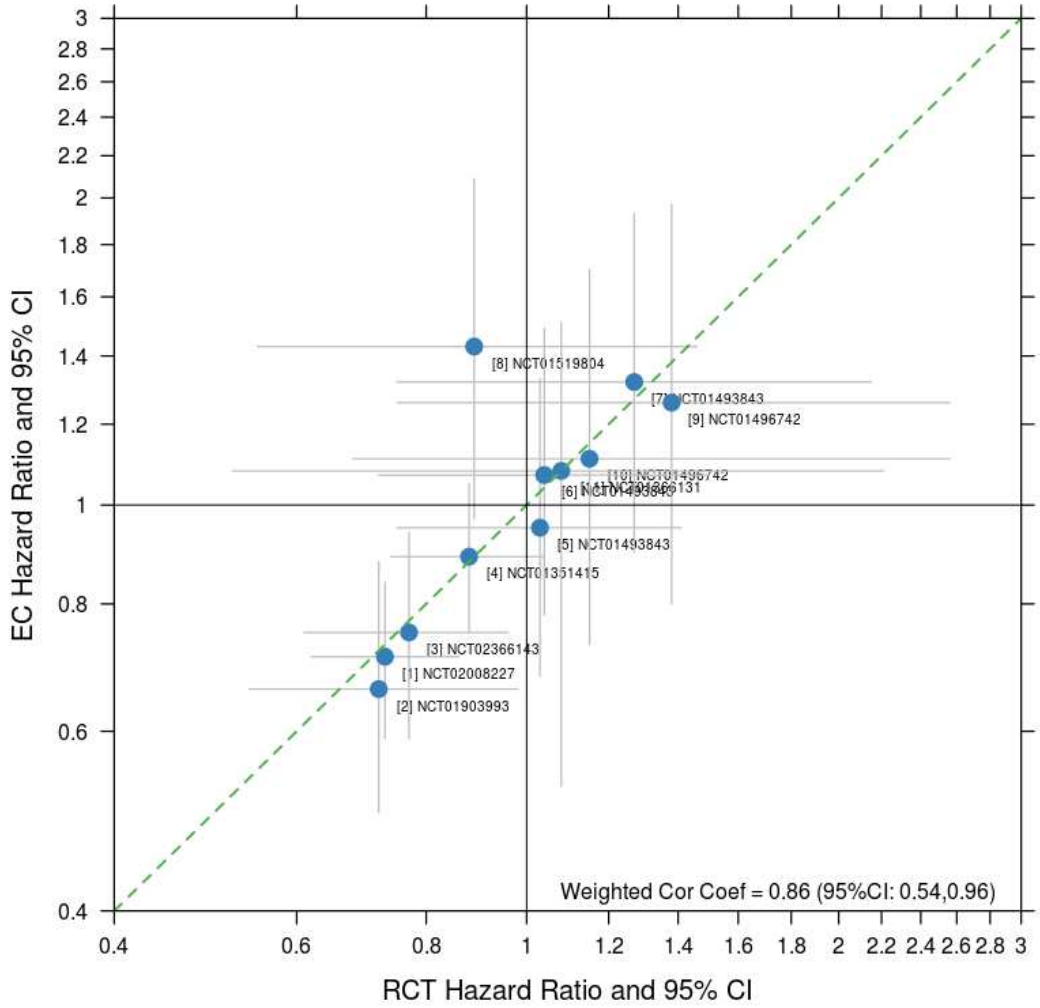
- Treatment effect estimates

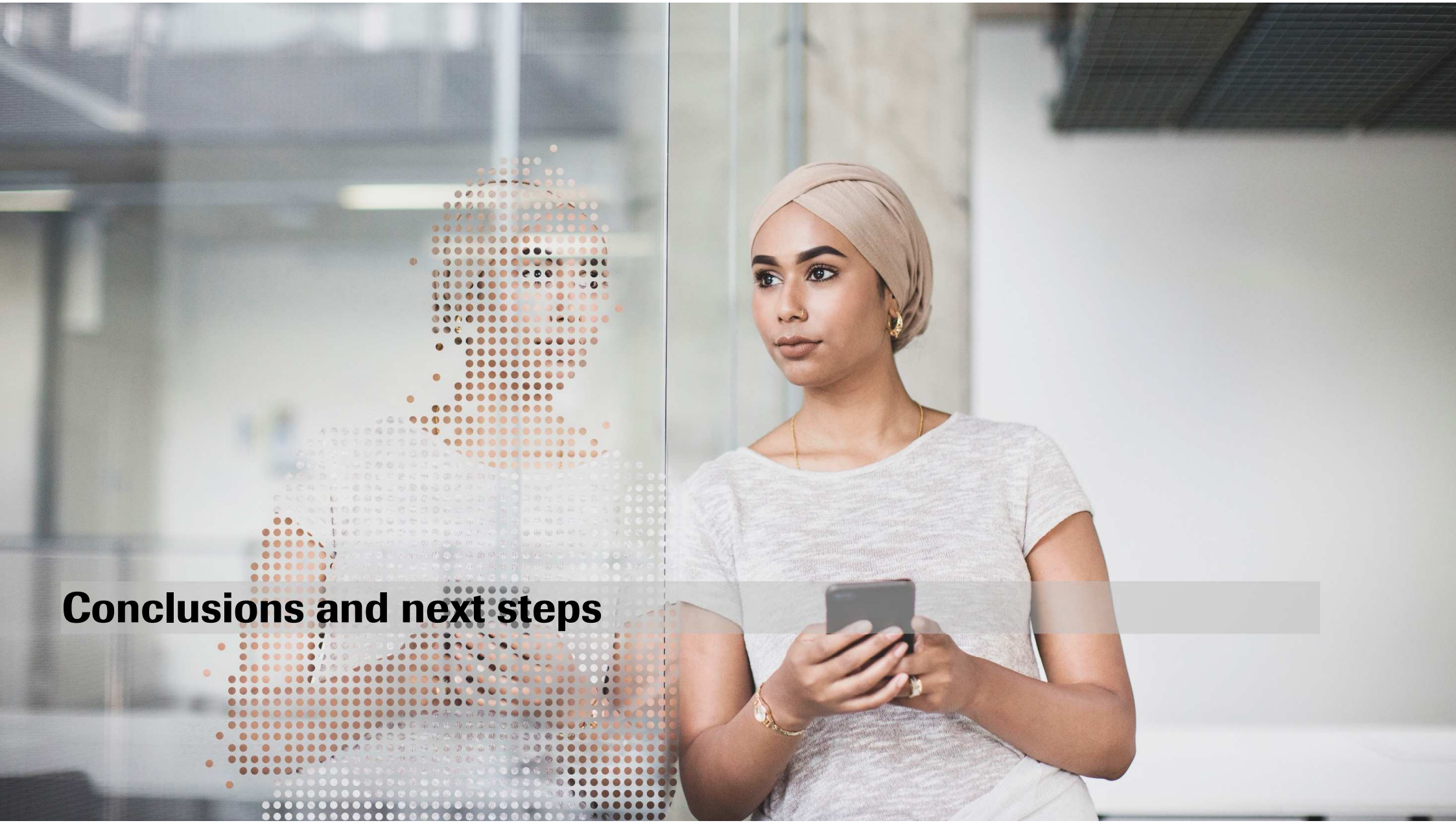
		RCT						
		Experimental		Control		RCT HR (95% CI)	EC adjusted HR (95% CI)	Difference
		N	Events	N	Events			
[1] NCT02008227		425	271	425	298	0.73 (0.62, 0.86)	0.71 (0.59, 0.84)	0.028 (-0.132, 0.188)
[2] NCT01903993		144	78	143	95	0.72 (0.54, 0.98)	0.66 (0.50, 0.88)	0.087 (-0.176, 0.350)
[3] NCT02366143		356	144	336	166	0.77 (0.61, 0.96)	0.75 (0.59, 0.94)	0.026 (-0.179, 0.231)
[4] NCT01351415		245	194	240	193	0.88 (0.74, 1.04)	0.89 (0.75, 1.05)	-0.011 (-0.202, 0.179)
[5] NCT01493843:	Arm A vs. B	126	79	125	60	1.03 (0.75, 1.41)	0.95 (0.68, 1.33)	0.081 (-0.175, 0.337)
[6] NCT01493843:	Arm C vs. D	79	59	79	43	1.04 (0.72, 1.50)	1.07 (0.78, 1.49)	-0.028 (-0.319, 0.262)
[7] NCT01493843:	Arm E vs. F	62	42	30	13	1.27 (0.75, 2.15)	1.32 (0.90, 1.93)	-0.039 (-0.389, 0.312)
[8] NCT01519804		55	36	54	33	0.89 (0.55, 1.46)	1.43 (0.97, 2.09)	-0.474 (-0.835, -0.114)
[9] NCT01496742:	Cohort 1	69	32	70	29	1.38 (0.75, 2.56)	1.26 (0.80, 1.97)	0.091 (-0.310, 0.492)
[10] NCT01496742:	Cohort 2	59	37	61	36	1.15 (0.68, 2.56)	1.11 (0.73, 1.70)	0.035 (-0.332, 0.403)
[11] NCT01366131		52	24	52	18	1.08 (0.52,2.21)	0.90 (0.53, 1.51)	0.182 (-0.276, 0.640)

Treatment effects with EC

- Trials results replicated:
  - Treatment effect estimates, except for one trial
  - Conclusions from statistical tests (H0: logHR = 0)







Conclusions and next steps

Conclusions

- Properly selected and adjusted control arms from high quality contemporaneous EHR data could be used to replicate results from RCT in aNSCLC

Next steps

- Fully understand why and when EC don’t work
- Methods to optimize and validate EC for single arm trials
  - Estimands & PS methods
  - Unmeasured confounding
  - rwPFS and rwOS
  - Bayesian methods
- Understand data
- Apply learnings and do the same in other tumor types (Breast, mCRC)
- Hybrid Controls (HC)

Doing now what patients need next