Principal stratum strategy to investigate anti-drug antibody impact on outcome in randomized controlled trials

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Disclosures

- Dominik Heinzmann & Shengchun Kong are full time employees of Roche/Genentech and own non-voting shares from Roche
- Any opinions, findings, and conclusions expressed in this work are those of the presenters and do not necessarily reflect those of Roche/Genentech

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(i) Scientific question of interest

(ii) Weighted approach for Principal Stratum Incorporating Missing Data

(iii) Application

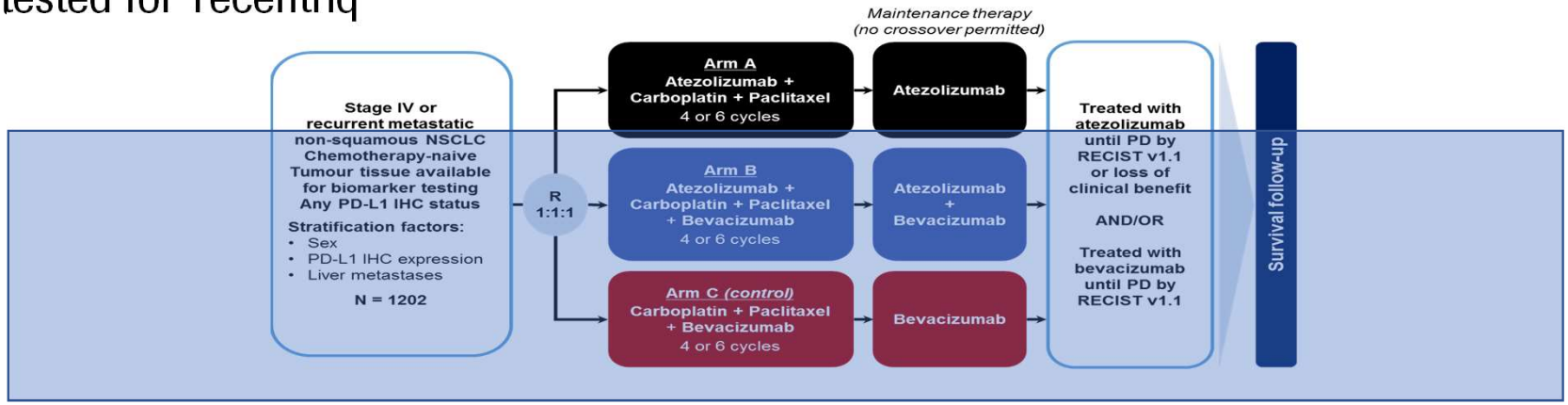
Anti-drug antibodies (ADA) = Intercurrent Event

- Development of novel biologic treatments may be associated with immunogenicity, i.e. ability of a biologic to provoke an unwanted immune response with the formation of ADA
- Stimulation of such an immune response and the formation of ADA can negatively impact safety, PK, PD and/or efficacy of such a biologic treatment
- **Here, we focus on RCTs**
- In RCTs, in general ADA tested only in experimental arm (where new biologic is tested) and no ADA testing done for control arm patients (as ADA assay is specific to molecule)

- Patient is **treatment-emergent ADA-positive for experimental treatment** if either
  - ADA-negative at baseline and ADA-positive after baseline (=newly arise)
  - ADA-positive at baseline and significant increase of ADA titer post-baseline due to treatment initiation (= pre-existing host antibodies that are cross-reactive with the treatment)
- Based on this definition, ADA = **Intercurrent event** in the language of ICH E9 addendum
  - ADA is a post-randomization variable induced / influenced by treatment
  - ADA has potential impact on the interpretation of the clinical outcome

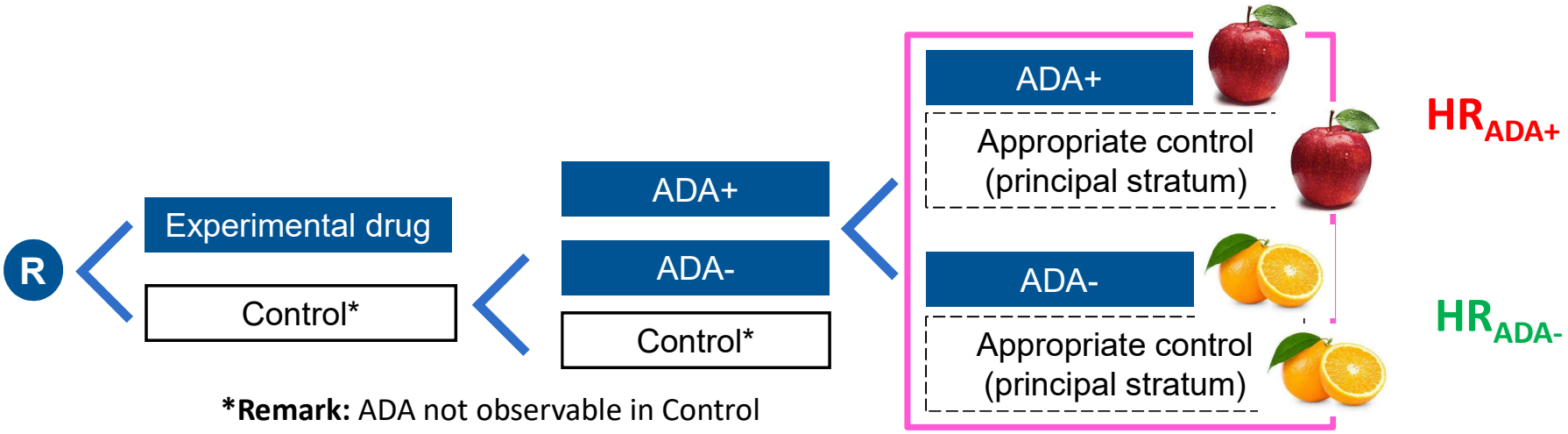
Application: RCT IMpower150

- IMpower150 trial comparison B versus C: Tecentriq+Avastin+chemo versus Avastin+chemo
- ADA tested for Tecentriq



- ADA incidence proportion **Arm B**: 36.4%
- Median OS:
  - ADA-positive 18.7 mo (95%CI: 13.8-25.2)
  - ADA-negative 24.0 mo (19.5-NE)
  - Control (ITT): 14.7 mo (13.3-16.9)
- **Comparison of these medians in terms of treatment effect are likely misleading** as difference is influenced by difference in important baseline prognostic variables

Scientific questions of interest



***Remark:** ADA not observable in Control

- A comparison of treatment effects between each ADA subgroup compared to corresponding control, i.e. compare **HR_{ADA+}** with **HR_{ADA-}**
- An assessment of whether the ADA-positive subgroup derives benefit from treatment with atezolizumab, i.e. assess **HR_{ADA+}**

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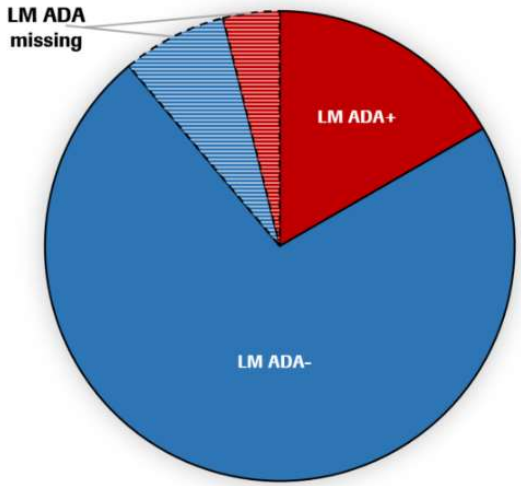
Different Approaches for Handling Missing ADA Data at Landmark (LM)[a]

- Landmark (LM) approach needed as ADA measures only in experimental treatment and hence experimental arm patients needs to live long enough to have an ADA assessment (not applicable to control)
- Across multiple studies investigated, 4%–18% of patients had missing ADA status at the early LM

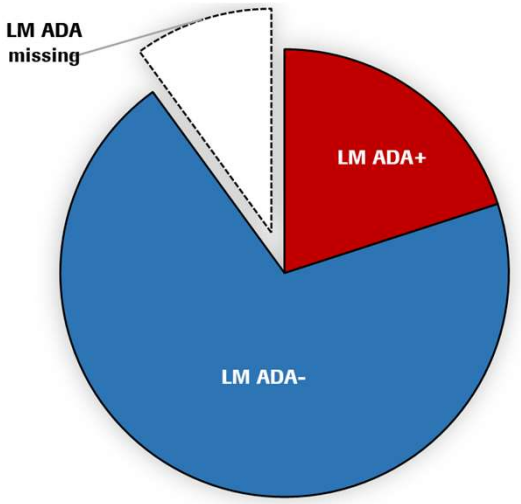
LM definition "All"

LM ADA missing modeled using next available ADA status and baseline covariates



LM definition "Drop"

LM ADA missing excluded



[a] Figures are provided for illustrative purposes only, and may not be reflective of actual proportions

[b] For weighted approaches, LM ADA missing and control arm patients are not assigned a determinate ADA status, but instead weighted according to their covariates

Different Approaches for Handling Missing ADA Data at Landmark (LM) - Resulting Estimands

	Non-missing landmark ADA status		Missing landmark ADA status	
	Landmark ADA+	Landmark ADA-	Underlying landmark ADA+	Underlying landmark ADA-
Treatment	T1	T2	**T3**	**T4**
Control	C1*	C2*	**C3***	**C4***

*Counterfactual outcomes of interest

Options	Short explanation	Target estimand
Landmark definition "All"	**RED** = Next status & baseline covariates	**ADA+: T1+T3 vs C1+C3** **ADA- : T2+T4 vs C2+C4**
Landmark definition "Drop"	DROP **RED** DROP **GREEN**	**ADA+: T1 vs C1** **ADA- : T2 vs C2** **MISS : T3+T4 vs C3+C4**

(i) Scientific question of interest

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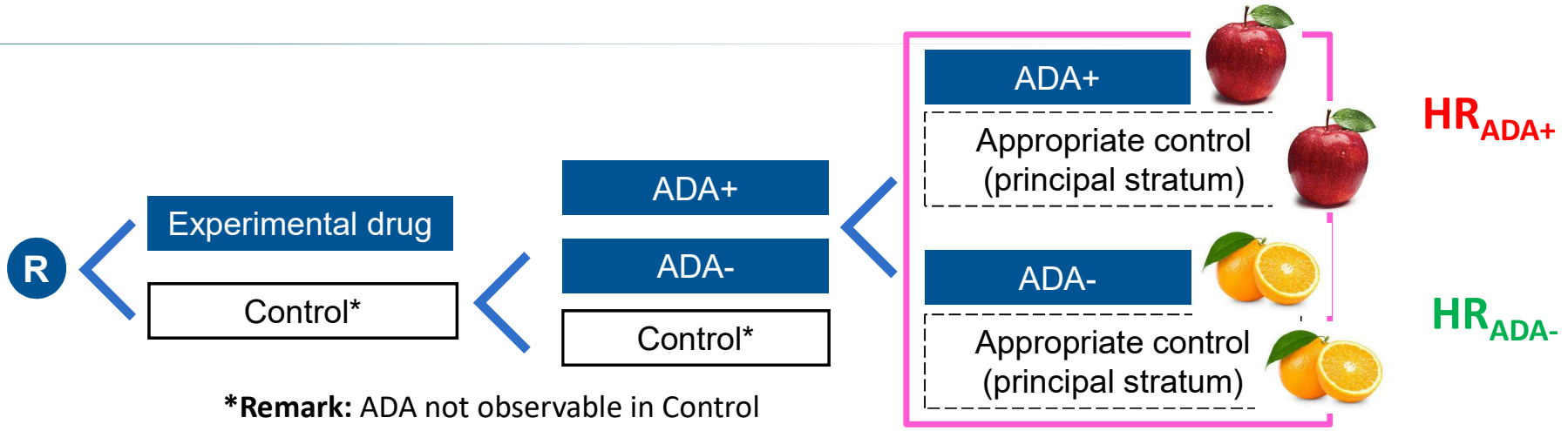
REMINDER: Scientific questions of interest



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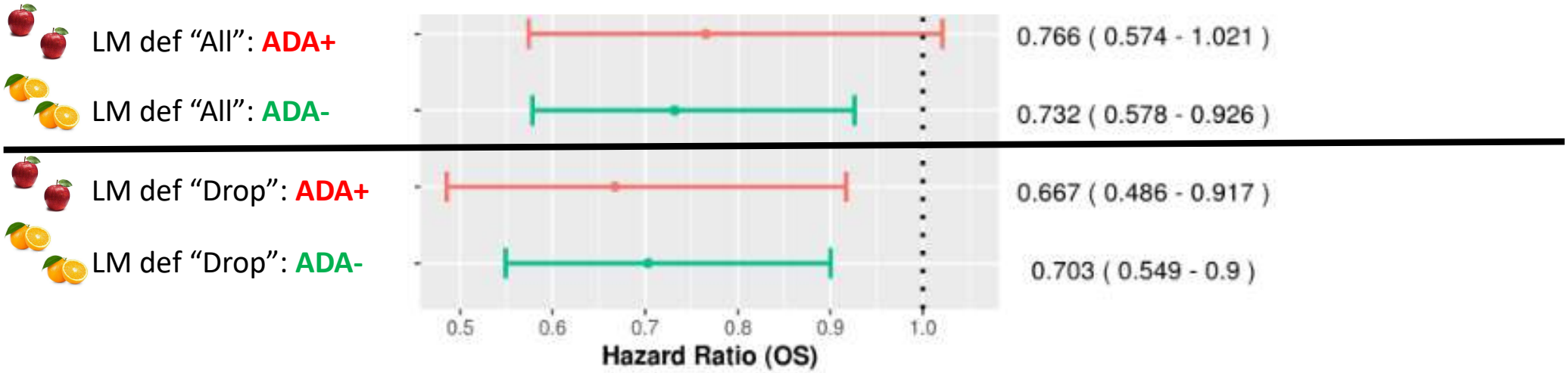
Weighted approach for Principal Stratum Incorporating Missing Data
Results: OS

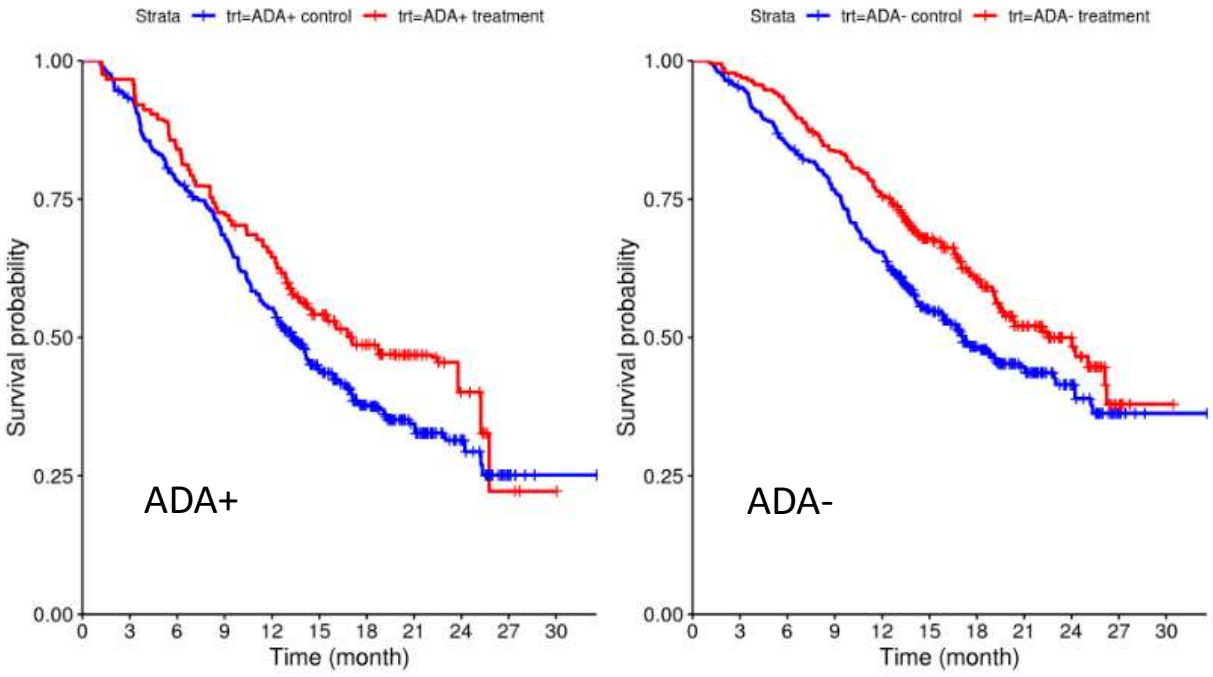
- **OS results:** Similar treatment effect size in ADA+ versus ADA- : I.e. similar hazard ratio and highly overlapping confidence interval



Remark: *15 confounding covariates included based on a holistic clinical and statistical assessment*

Weighted approach for Principal Stratum Incorporating Missing Data
Results: OS

- **Remark:** Landmark definition “All” is presented here, other LM show similar pattern
- **OS Results:** Clear treatment effect in both ADA stratum: I.e. KM curves between ADA group and appropriate control clearly separating



Results: Progression-free survival (PFS)

- **PFS results confirm OS results**
  - Similar treatment effect size in ADA+ versus ADA- : I.e. similar HR and highly overlapping CIs *(Fig 1)*
  - Clear treatment effect in both ADA stratum: I.e. KM curves between ADA group and appropriate control clearly separating *(Fig 2)*

Figure 1: PFS HRs for LM defs "All" and "Drop"

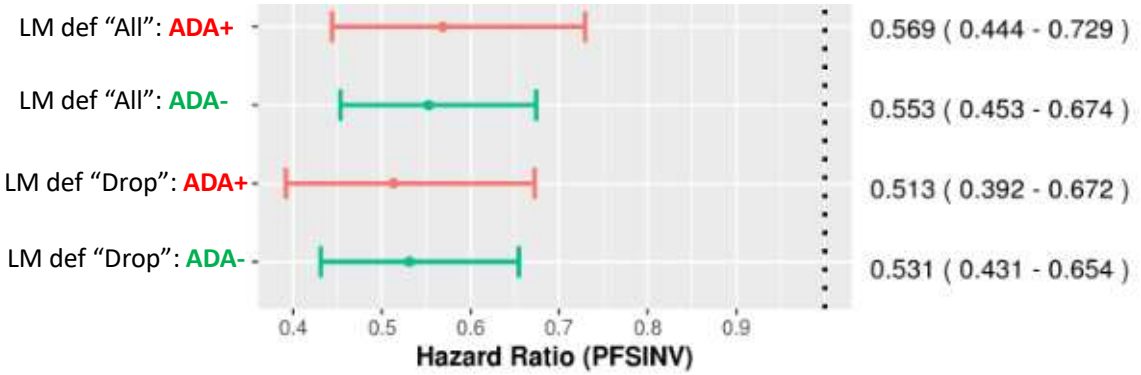
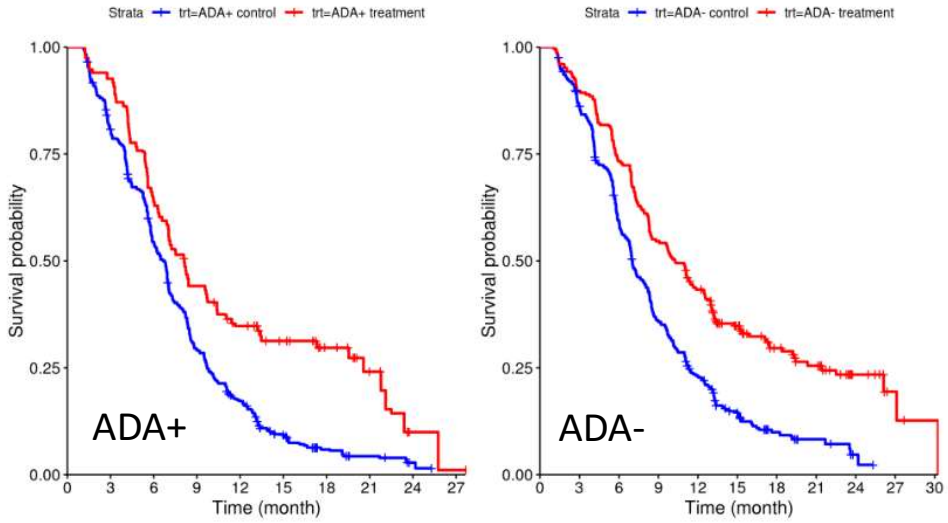


Figure 2: KM PFS plots for LM def "All"



Discussion

- **Investigations over many Tecentriq oncology studies indicates that baseline prognostic factors** generally appear imbalanced with poorer prognostics in ADA-positive stratum compared to ADA-negative stratum

- Naive analyses simply comparing ADA-positive (ADA-negative) patients to control are misleading as they do not account for those observed imbalances

- **A weighted approach for principal stratum** enables adjustment for imbalances in baseline prognostic factors, resulting in:
  - Overall no clinically relevant difference in efficacy between ADA strata for OS and PFS

Novelty

- As landmark approach used, missing data at LM possible (eg ADA only assessed after LM)
- Our approach incorporates this on the estimand level and it is proven that under specific assumptions (including no unmeasured confounders) it produces an **unbiased estimate of stratum treatment effect**

Doing now what patients need next