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Estimand Framework and its Impact on Oncology Drug Development:

- *Findings From An Industry-Wide Working Group*

Yi Liu

on behalf of the Oncology Estimand Working Group

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ICH E9 Estimand framework

- A structured **framework** requiring a precise definition of the scientific question of interest and ensuring alignment between trial objectives and analysis
- It aims to **facilitate the dialogue** between *sponsors, regulators, payers, physicians, and patients* regarding the key questions of interest that a clinical trial should address

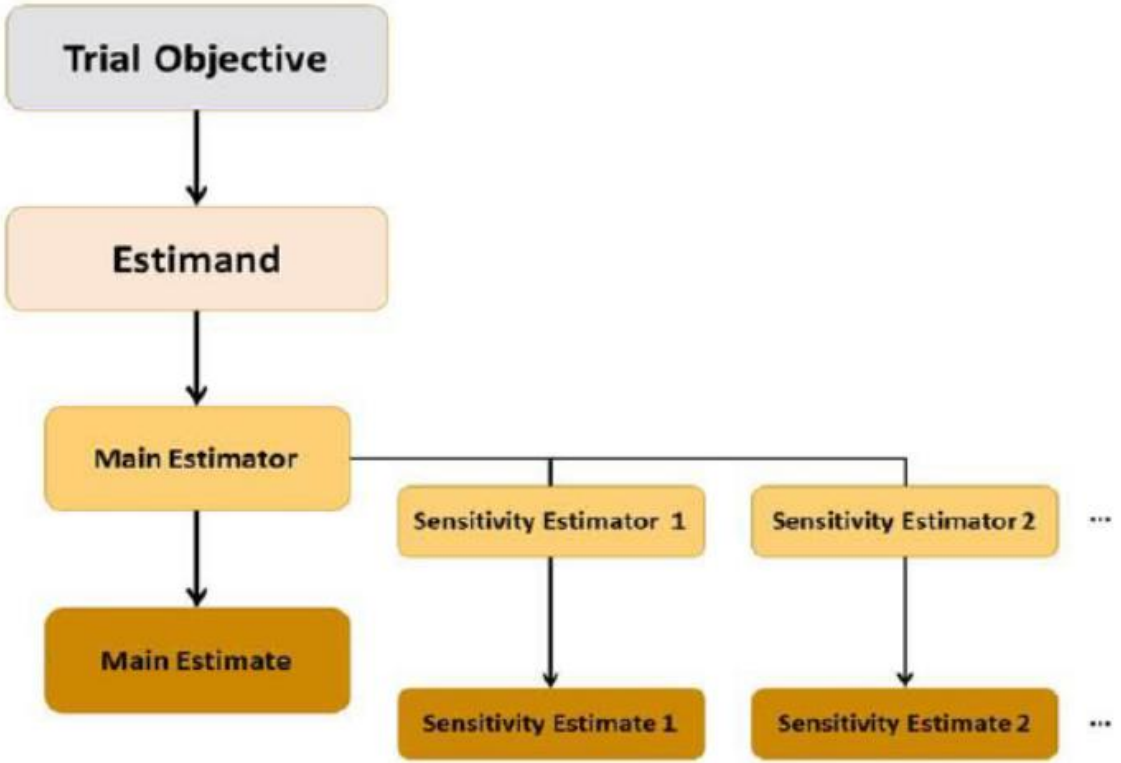


Figure 1: Aligning target of estimation, method of estimation, and sensitivity analysis, for a given trial objective

ICH E9 Addendum

Motivational Example 1
Checkmate-37 trial

Primary Objectives:

- To estimate Objective Response Rate (ORR) in the nivolumab treatment group (noncomparative assessment)
- To compare Overall Survival of nivolumab to chemo (All randomized population)

Checkmate-37

Primary analysis for Objective Response Rate

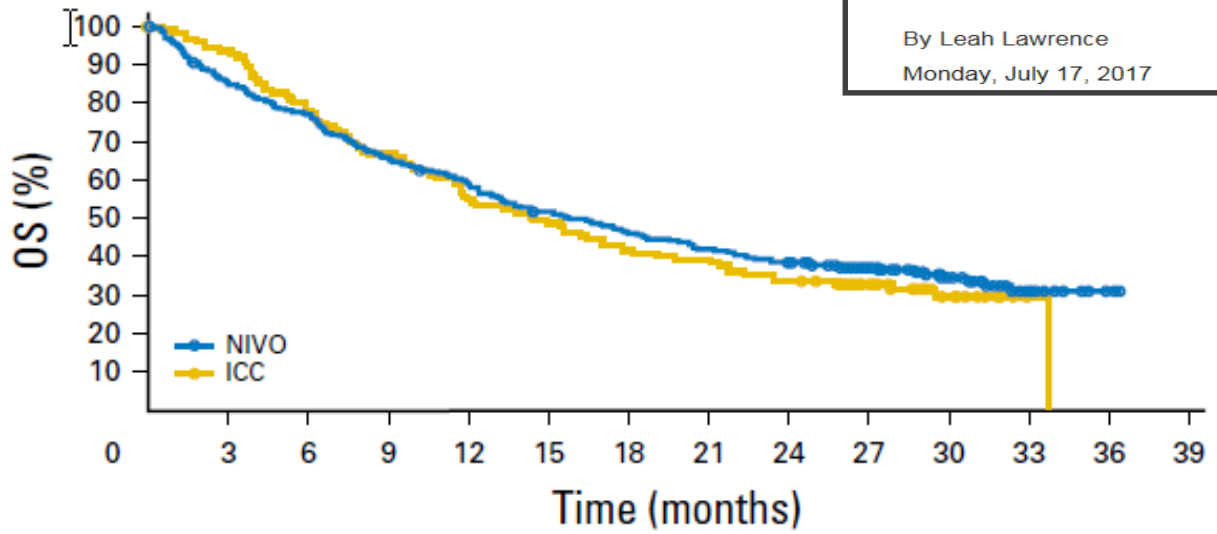
- 31.7% ORR in Nivolumab group
  - 95% CI: (23.5,40.8) exclude pre-defined 15% threshold
- Accelerated approval granted by FDA based on ORR data
- Confirmatory evidence expected either through mature data from this study or other ongoing trials
- Study continued until primary analysis of the other primary endpoint OS
- Nivolumab received approvals in US, EU and Japan in 1L&2L melanoma based on the data of this and two other trials prior to OS readout

Checkmate-37

Primary analysis for Overall Survival

OS in all randomized patients: HR=0.95, mOS 15.7m vs 14.4m

> **CheckMate 037: Nivolumab Improved Responses, Not Survival in Advanced Melanoma**
>
> By Leah Lawrence
>
> Monday, July 17, 2017

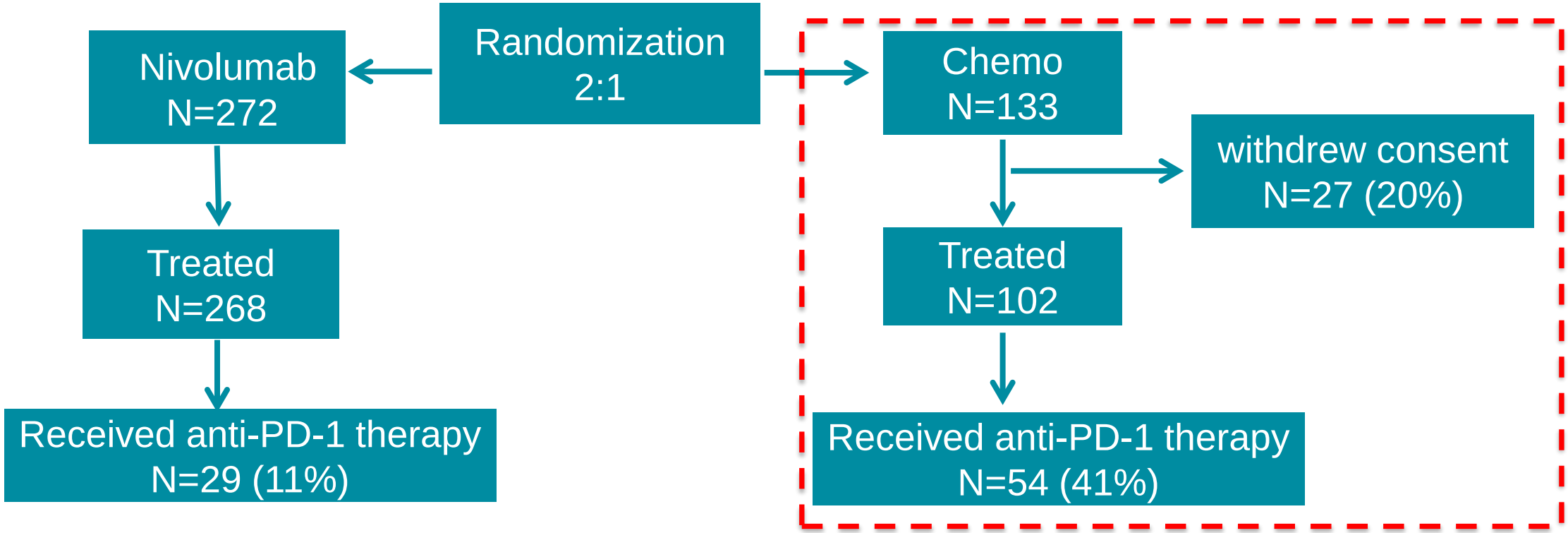


No. of patients at risk

NIVO	272	230	208	178	158	138	123	112	103	71	44	16	3	0
ICC	133	119	99	85	70	62	53	49	43	28	14	2	0	0

Checkmate-37
What happened?

- Checkmate-037 was open-label and several competing studies with other checkpoint inhibitors were ongoing at the time of enrollment
- 20% in chemo-arm withdrew consent immediately after randomization and before starting treatment
- Post-discontinuation data suggests that 41% of patients in chemo-arm received other checkpoint inhibitors vs 11% in the nivolumab arm

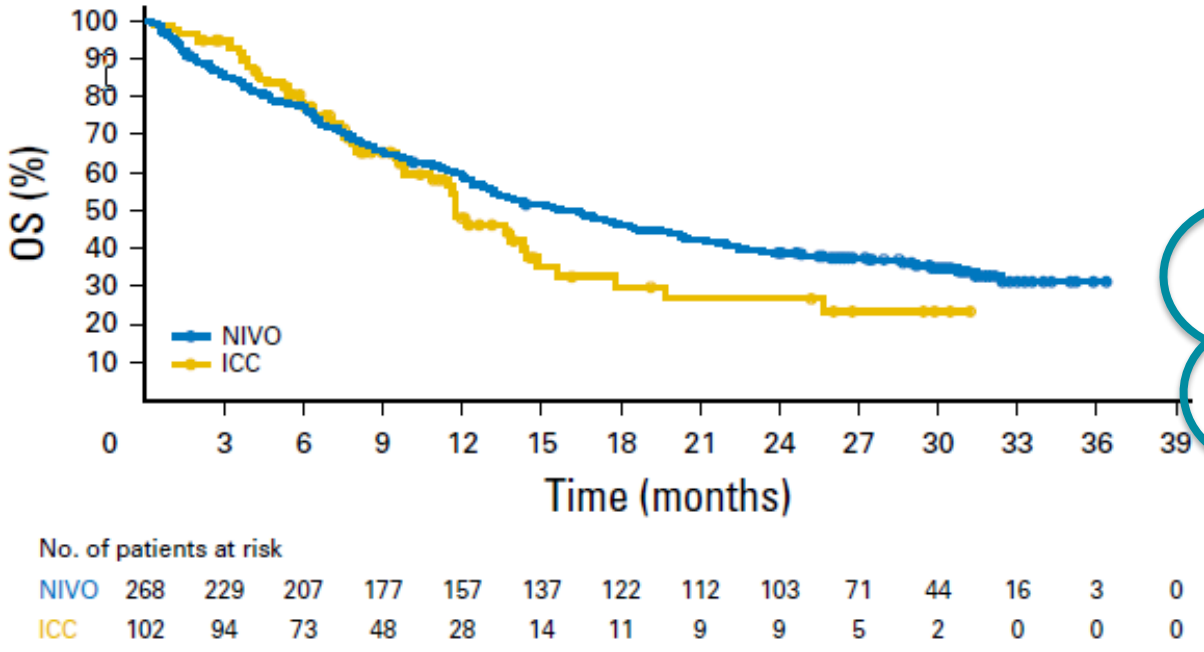


Checkmate-37

Published post-hoc analysis for Overall Survival

OS in treated patients and censoring in chemo-arm at the start of PD-1 or PD-L1 agent: HR=0.81, mOS: 16.4m vs 11.8m

Recall: OS in all randomized patients: HR=0.95, mOS 15.7m vs 14.4m

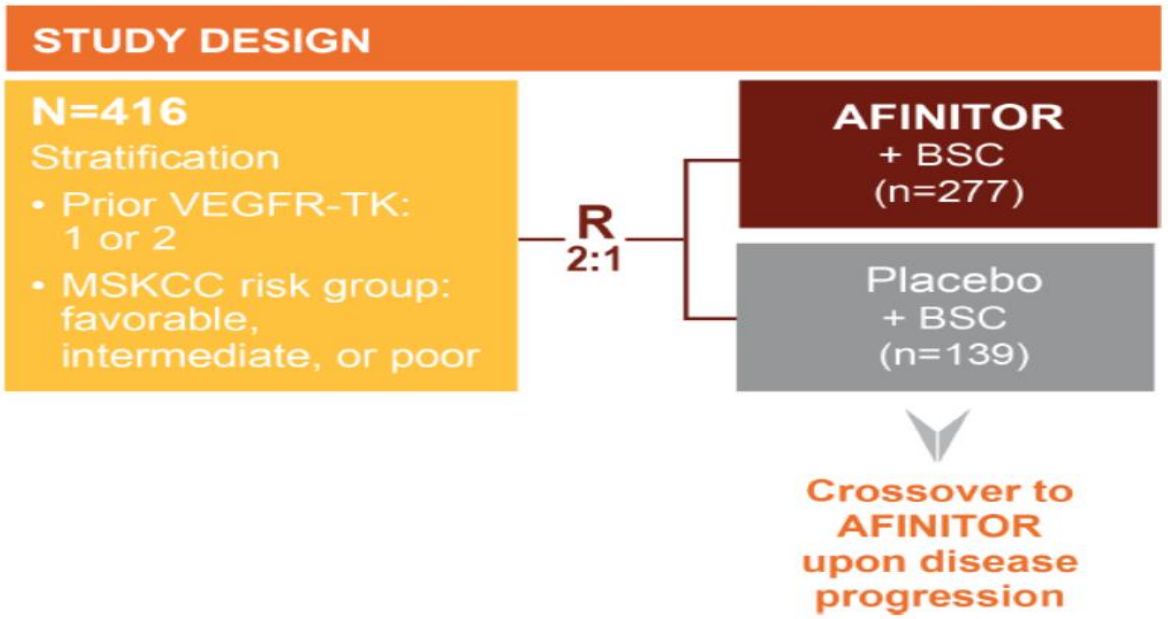


Which OS analysis is more relevant to regulators, payers, physicians and patients despite the post-hoc nature of this analysis?

Larkin et al. (2018), Overall Survival in Patients with Advanced Melanoma Who Received Nivolumab Versus Investigator's Choice Chemotherapy in Checkmate 037: A Randomized, Open-Label Phase III Trial, Journal of Clinical Oncology 2018 36:4, 383-390

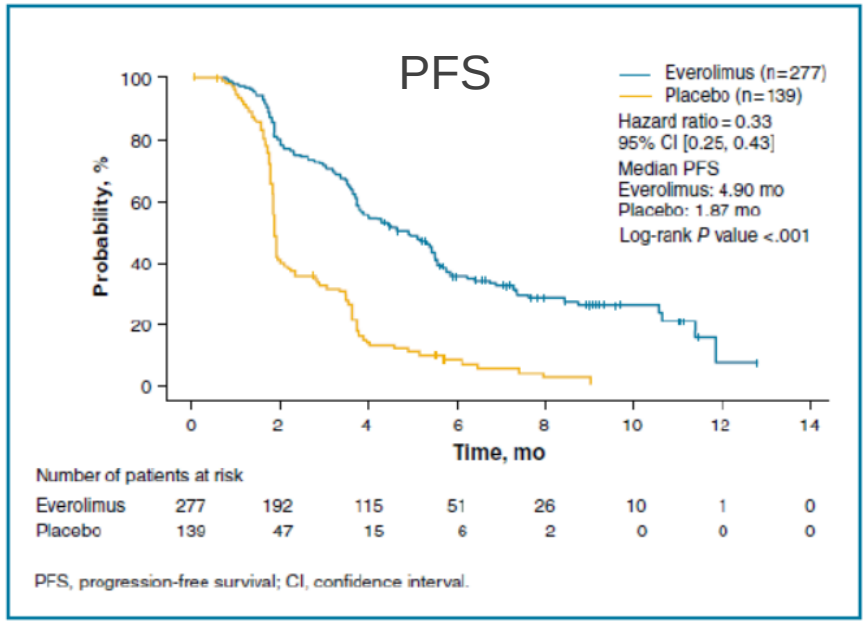
Motivational Example 2
RECORD - 1

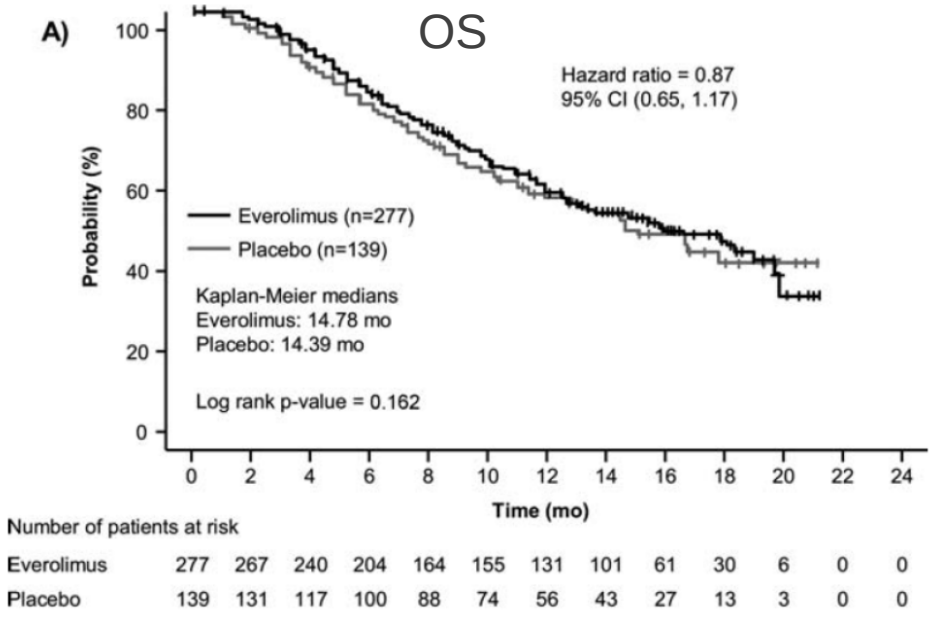
- Phase III study of everolimus in metastatic renal cell carcinoma Motzer et al (2008, 2010)
- Double-blind, multicenter study with patients randomized to receive either everolimus (n=277) or placebo (n=139)
- Primary endpoint – progression-free survival defined as time from randomization until disease progression or death



RECORD - 1
PFS and OS results

- Positive study with clinically meaningful improvement in PFS (HR=0.33, 95% CI: 0.25, 0.43, p < 0.001)
- Protocol allowed crossover from placebo to Everolimus upon progression (106 out of 139 pts, 76%)
- ITT analysis of OS showed trend in OS benefit (HR=0.87, 95% CI: 0.65-1.17, p=0.162)





RECORD - 1

Reconstructing Placebo OS data if patients had not crossed over

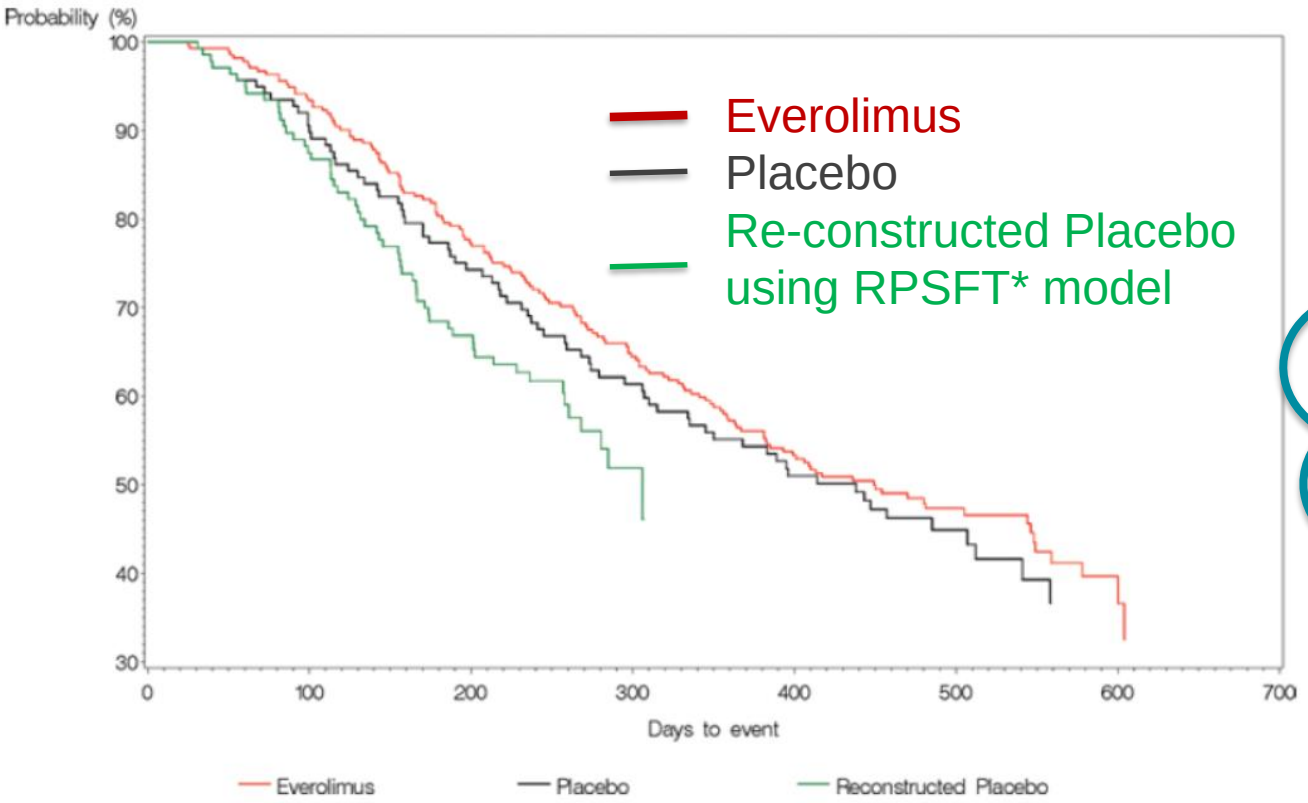


Figure 5 Kaplan–Meier survival curves by randomization arm (everolimus in red, placebo in black) plus the reconstructed treatment-free Kaplan–Meier survival curve for the placebo arm using $\widehat{\psi} = -0.66$ (reconstructed placebo, in green). (Color figure available online.)

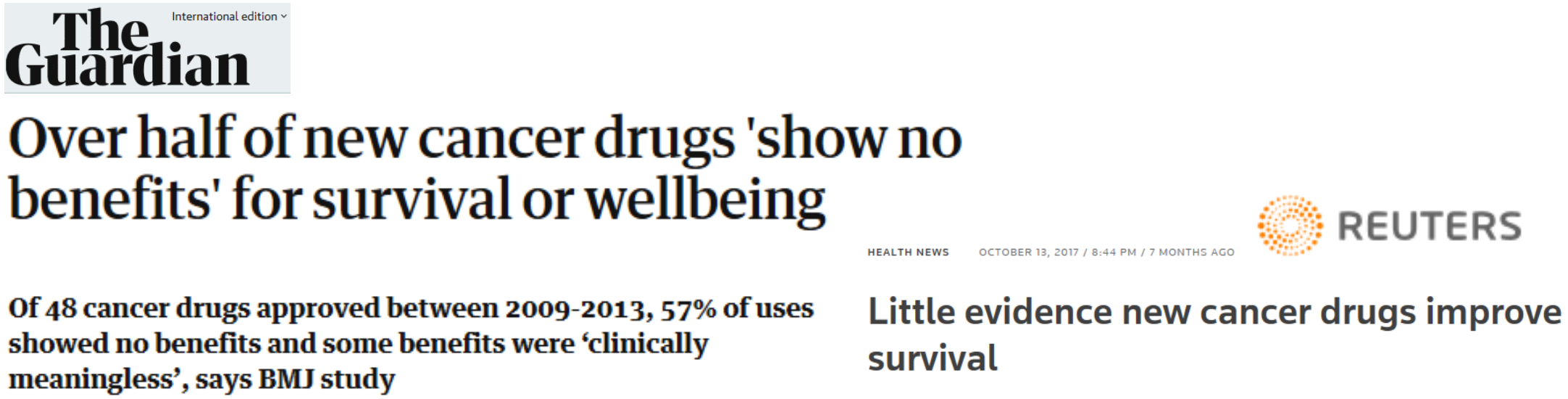
Is it more relevant to compare Everolimus to observed or re-constructed Placebo for regulators, payers, physicians and patients?

* RPSFT: Rank-Preserving Structural Failure Time

Korhonen et al. (2013) *Journal of Biopharmaceutical Statistics*

Estimands in Oncology
Implications beyond clinical trials

- Cancer drugs often perceived as expensive and not improving survival
- Davis et al. in BMJ 2017: most oncology drugs approved without showing survival benefit and without conclusive evidence years later



Estimands in Oncology
Implications beyond clinical trials

- All stakeholders in the industry criticized for approvals and pricing
- Negative perception driven by the main reported OS result targeting the *estimand* assessing treatment effect regardless of whether patients take assigned treatment or receive other therapy

But is this the estimand always of greatest relevance to regulators, payers, physicians or patients?

- Estimand framework provides us the opportunity to clarify the interpretation of the results and added value of the drugs

Estimands in Oncology
Need for the Industry Working Group

- Increased transparency on treatment effect of interest important goal of the ICH E9 addendum
- But what if the same estimand is described differently by sponsors in protocols and publications?
  - confusion for HA, payers, physicians and patients
  - possibly inconsistent labels
  - more HA questions on estimands creating perception of estimand topic being rather a burden
- Main purpose of the Working Group:
  - ensure common understanding and consistent definitions for key estimands in Oncology across industry
  - share experience and discuss estimands, intercurrent events and the used sensitivity analyses in Oncology

Estimands in Oncology Working Group (WG)

What is it?

- Initiated in 2018 and led by Evgeny Degtyarev (Novartis) and Kaspar Rufibach (Roche)
- Main purpose: ensure common understanding and consistent definitions for key estimands in Oncology across industry
- 31 members (14 from Europe and 18 from US) representing 20 companies
  - 5 subteams: causal, treatment switching, censoring mechanisms, case studies in solid tumors, case studies in hematology
- established as EFSPI SIG (Nov 2018) and ASA Biopharm Section SWG (Apr 2019)
- In dialogue with regulators from EMA, FDA, China, Taiwan, Japan and Canada

Back to the Estimand framework

Description of Estimand

ICH E9 Addendum, Section A.3.1:

"How the outcome of treatment compares to what would have happened to the same subjects under different treatment conditions…"

Amy

Experimental (E) → Death from any cause

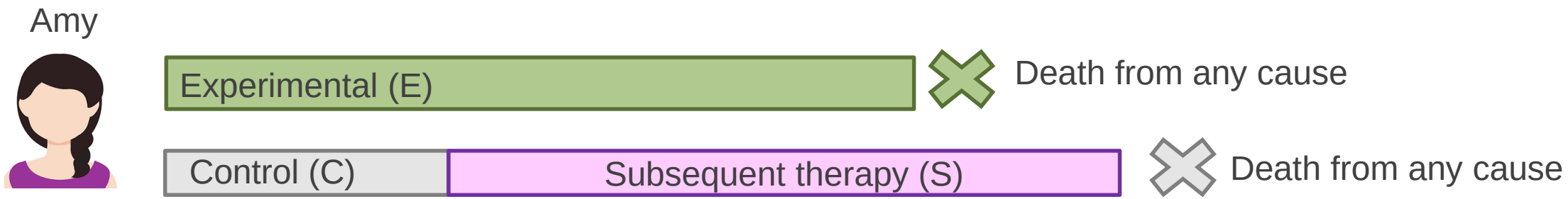
Control (C) → Death from any cause

- What type of pt is Amy? **– *Population***
- What to measure once Amy takes the drug? **– *Variable***
- How to summarize the treatment effect (E vs C) once data on many pts like Amy is collected? **– *Summary***

Back to the Estimand framework

Description of Estimand

"What if when Amy was taking drug C and experienced progressive disease, and she switched to another therapy that doctors thought may benefit her?"



- What type of pt is Amy? – *Population*
- What to measure once Amy takes the drug? – *Variable*
- How to summarize the treatment effect (E vs C) once data on many pts like Amy is collected? – *Summary*
- Is there any event that could complicate the description and interpretation of treatment effect (E vs C)? – ***intercurrent event***

Subsequent therapy in this case

Back to the Estimand framework

Four key attributes of Estimand

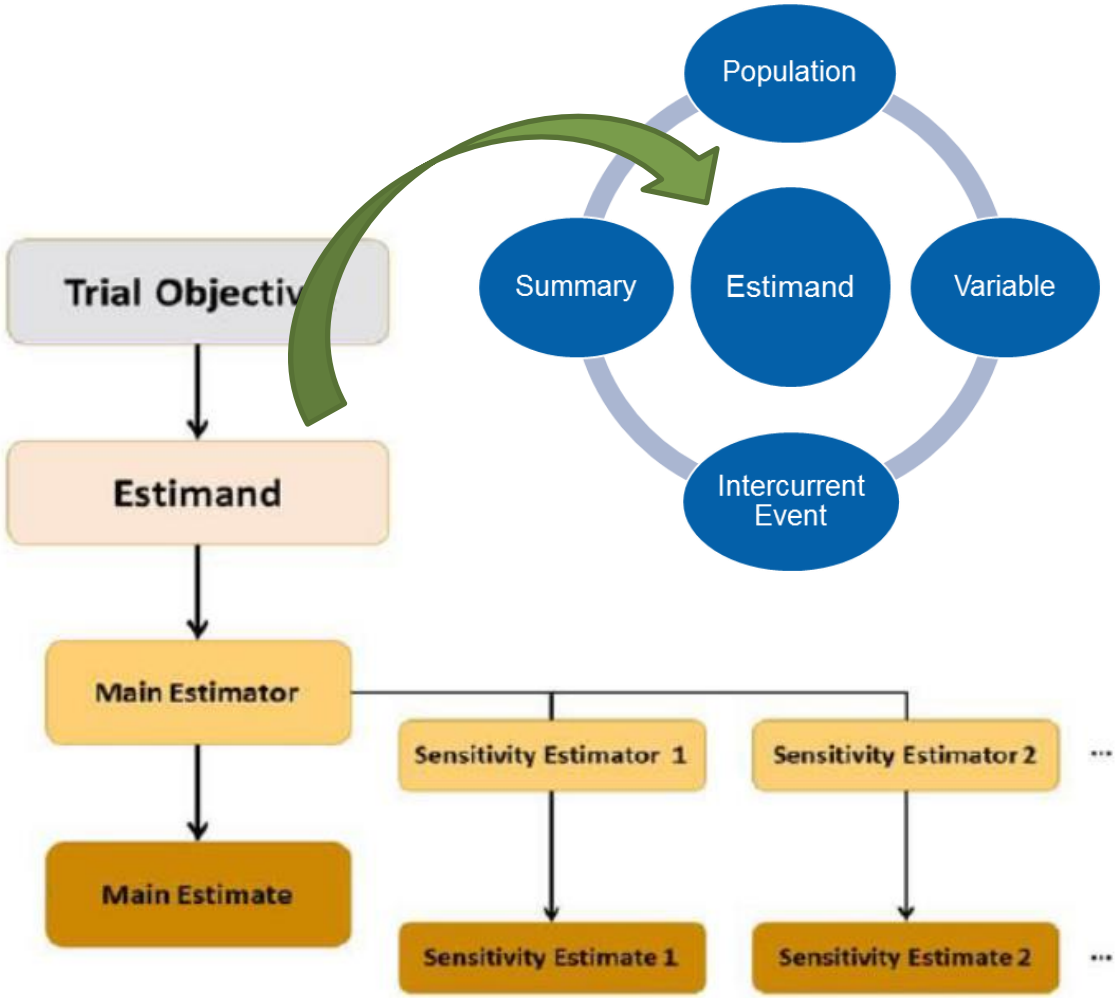
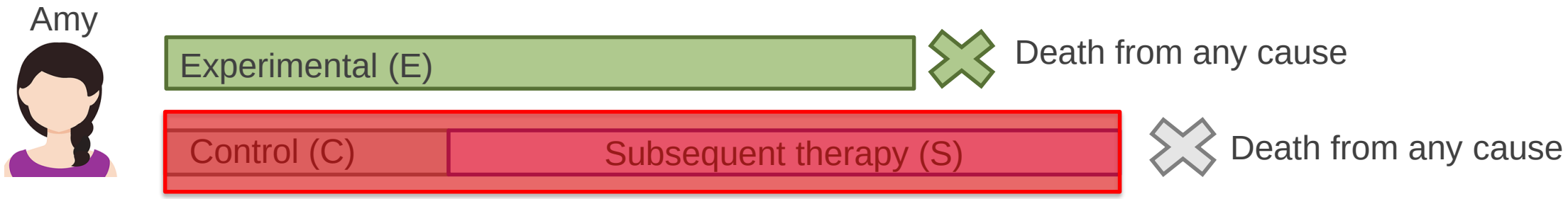


Figure 1: Aligning target of estimation, method of estimation, and sensitivity analysis, for a given trial objective

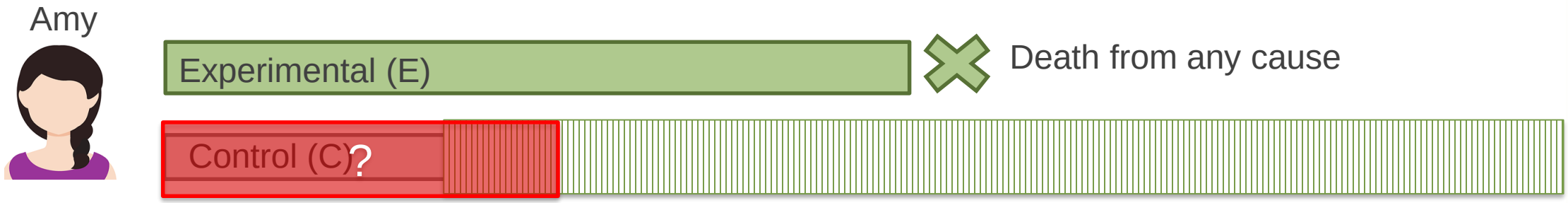
- Population – pts targeted by the scientfic question
- Variable (or endpoint) to be obtained for each pt, that is required to address the scientific question
- The population level summary for the variable which provides, as required, a basis for comparison between treatment conditions.
- The specification of how to account for intercurrent events to reflect the scientific question of interest

Estimand framework
How to handle intercurrent events

- Strategies for addressing intercurrent events
  - ***Treatment Policy***: occurrence of intercurrent event is irrelevant



  - ***Hypothetical***: a hypothetical scenario is envisaged in which the intercurrent event would not occur



Different analysis methods can be utilized to “uncover” the OS for Amy under C without intercurrent event

Revisiting Checkmate-37

Precise definition of the question of interest

Primary objective: “To compare OS of nivolumab to chemo”

– But what exactly does this mean?

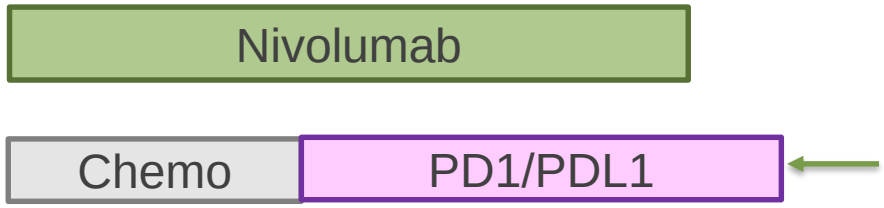
	Primary analysis	**Post-hoc analysis**
Question of interest	Survival benefit after prescription of Nivolumab vs Chemo regardless of whether patients take assigned treatment or receive other therapy	Survival benefit after treatment with Nivolumab vs Chemo if patients in chemo-arm never receiving PD1/PDL1 agent
Intercurrent event: *PD1 therapy received in chemo-arm*	Treatment policy	Hypothetical

- Different questions with different answers: HR: 0.95 vs 0.81; ΔmOS: 1.3m vs 4.6m
  - Performed post-hoc analysis not the only way to address the hypothetical estimand, e.g. IPCW
  - Performed Post-hoc analysis requires the assumption that those who get PD1 have same risk as those who continue on randomized treatment
  - Choice of estimand and analysis method impacts data collection, e.g. information needed to model the switch

Revisiting Checkmate-37

- Primary analysis for OS targeted treatment policy estimand
  - assumes whatever happens after randomization reflects clinical practice
  - not always yields a clinically meaningful comparison of treatments if this assumption is violated
    - Checkpoint inhibors not yet widely available and not part of clinical practice
    - After approvals PD1/PDL1 drugs used in lieu of chemo and not after chemo
- Comparison Nivolumab vs Chemo followed by PD1/PDL1 drug relevant?

Patients with advanced melanoma who progressed on or after ipilimumab (and BRAF, if BRAF V600+)



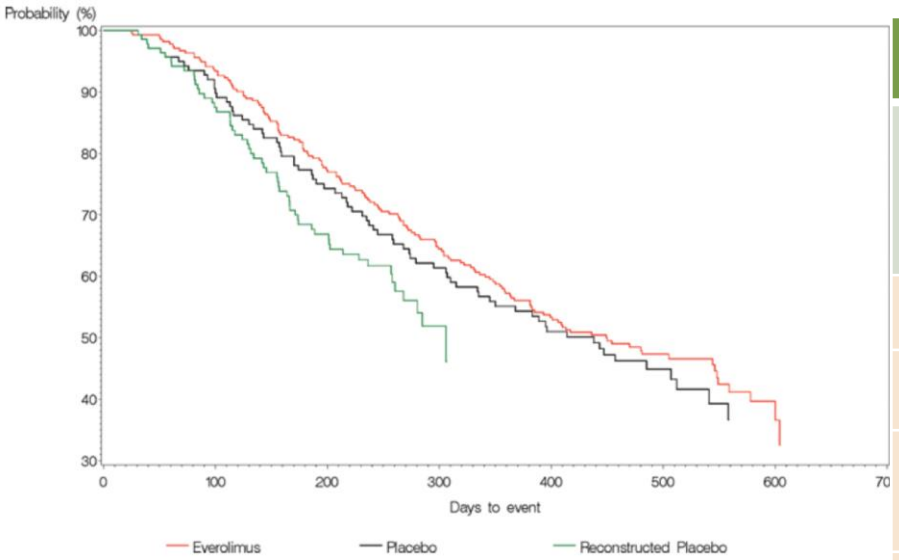
This was not the SOC in clinical practice at that time

Revisiting Checkmate-37

- Primary analysis for OS considered confounded and not informative by regulators and HTAs
- Treatment switching to drugs with same mechanism of action could be anticipated due to competitive landscape and open-label feature of the study
- In absence of estimand framework:
  - applied treatment policy
  - primary analysis not informative
- Using estimand framework:
  - structured discussions with all stakeholders about key questions of interest
  - trial design and primary analysis address the key question of interest
    - consider alternative approaches if appropriate
  - trial results are informative and interpretation transparent

Revisiting RECORD – 1

Two different estimands for OS



- Everolimus
- Placebo
- Re-constructed Placebo using RPSFT* model

	Estimand 1	Estimand 2
Scientific question: Does experimental drug prolongs survival…	**… regardless of crossover**	**…had cross-over not occurred**
Population	Targeted population	Targeted population
variable	OS	OS
Intercurrent event: Cross-over to Everolimus	*Treatment Policy*	*Hypothetical*
Population-level summary	Hazard Ratio	Hazard Ratio
Analysis	Estimate HR using Cox model (**Red** vs **Black**)	Estimate HR from RPSFT model (**Red** vs **Green**)
Additional data collection	-	Date of crossover, information needed for the model

These are not different sensitivity analysis, but different estimands!

Conclusions

- Estimand framework facilitates dialogue at study design stage between all stakeholders including HTA:
  - To align on study objectives with specifications on how to handle intercurrent event
  - To ensure clarity in interpretation of results and discussions about added value of the drugs
- Many areas in Oncology can benefit from estimand discussions and the framework has the potential to change the way we design and analyze studies
- Oncology Estimand WG active to ensure common understanding and consistent definitions across stakeholders
  - whitepaper(s) and presentations at statistical and clinical conferences
  - plans to further engage with Clinical community beyond ASCO

Thank You

Yi Liu

Nektar Therapeutics

on behalf of the Oncology Estimand Working Group

Join the conversation #DIA2019

BACK UP SLIDES

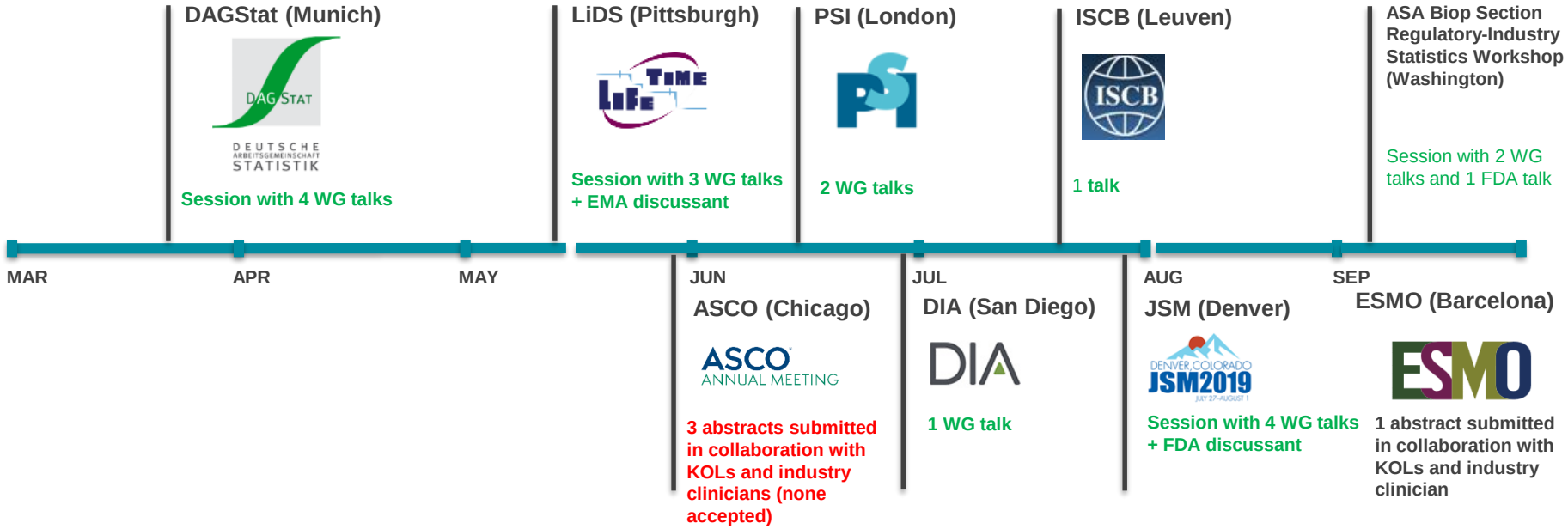
Estimands in Oncology WG

5 Subteams

- Causal subteam
  - causal estimands in T2E setting; applications of principal stratification in Oncology
- Treatment switching subteam
  - different types of switching and its impact on treatment-policy OS estimand
  - underlying OS estimands (incl. limitations/assumptions and sensitivity analyses) targeted by frequently used approaches: censor at switch, IPCW, RPSFT etc.
  - PFS2 estimand
- Censoring subteam
  - use of censoring in T2E setting to handle intercurrent events
  - sensitivity analyses for informative censoring / missing tumor assessments
- Hematology and Solid tumor case study subteams
  - discussion of relevant estimands, intercurrent events and sensitivity analyses based on case studies and HA guidelines; clarity on supplementary vs sensitivity analyses
  - recommendations for practical implementation

Estimands in Oncology WG
Communication plan 2019

- whitepaper(s) and presentations at statistical and clinical conferences
- plans to further engage with Clinical community beyond ASCO



ASCO: American Society of Clinical Oncology
LiDS: Lifetime Data Science (ASA Section)