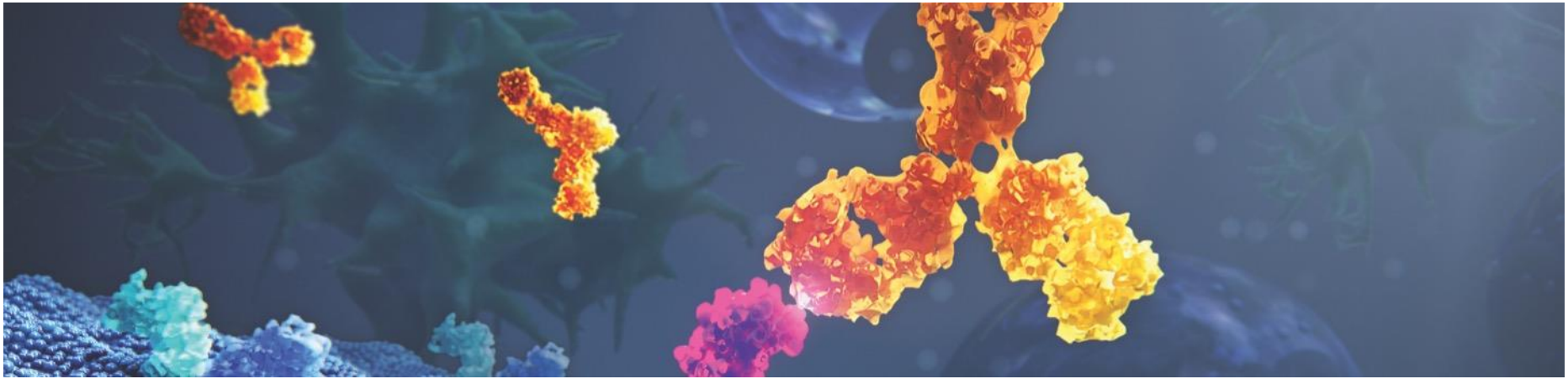
Developing Estimands in Oncology Trials: Understand Scientific Questions of Interest

Feng Liu, PhD, Oncology Estimand Working Group

Lifetime Data Science Conference 2019



Outline

- Introduction to ICH E9 R1
- Motivating Example Illustrating handling of Intercurrent Events (Published data from CM37)
- Estimand of Neo-adjuvant / Adjuvant

- Acknowledgement: Oncology Estimands Working Group

Background

- 3-4Q 2017: ICH E9/R1 draft was released for public comment across all the ICH regions

- E9/R1: Why was it deemed necessary?

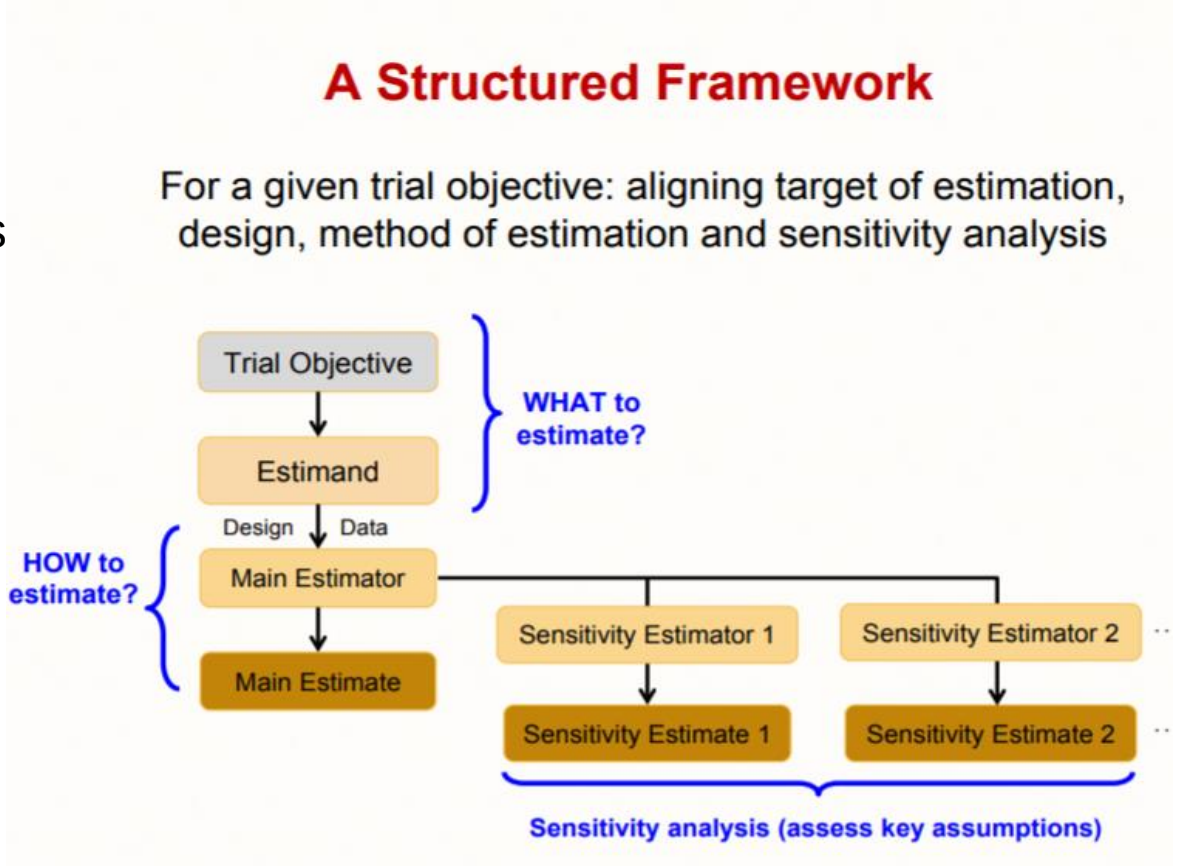
1. Insufficient clarity in objectives and related treatment effect parameters (i.e., estimands) of interest
2. Lack of logical connectivity between trial objectives, design, conduct, analysis and interpretation
3. Misalignment between “missing data” analysis methods and estimands of interest – Misunderstanding of the term “sensitivity analysis”

E9/R1 is intended to address these gaps, with a goal of improving clinical trial design/analysis/interpretation, NDA submissions and (ultimately) product labels

Estimand framework

ICH E9 addendum

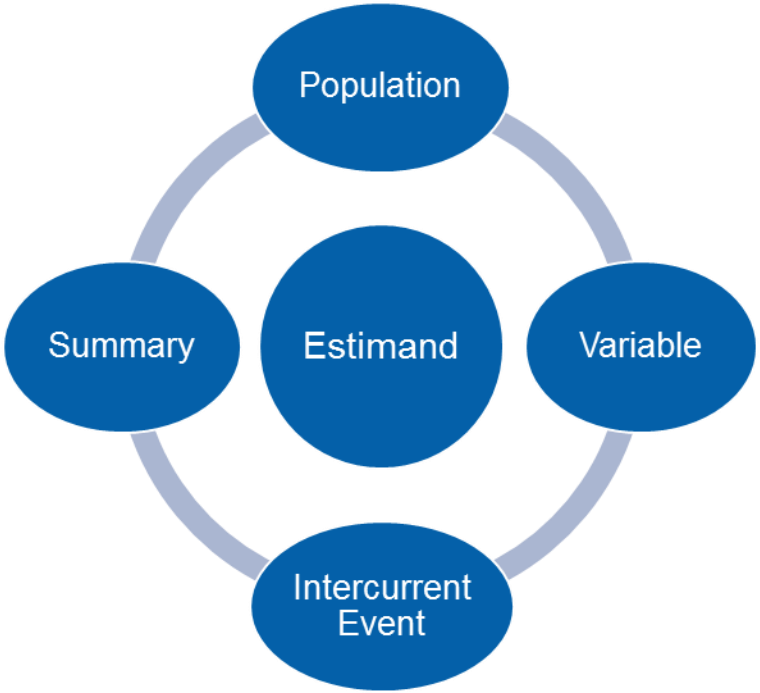
- Precise definition of the scientific question of interes
- Alignment between trial objectives and analysis
- **Dialogue** between sponsors, regulators, payers, physicians, and patients regarding the key questions of interest in clinical trials



ICH E9(R1) Addendum Content

Estimand description

A. Population – Patients targeted by scientific question
B. Variable – Endpoint(s) to be obtained for each patient to address the scientific question
C. Intercurrent events - Specification of how to account for these to reflect the scientific question
D. Summary - Population-level summary for the variable which provides a basis for a comparison between treatments

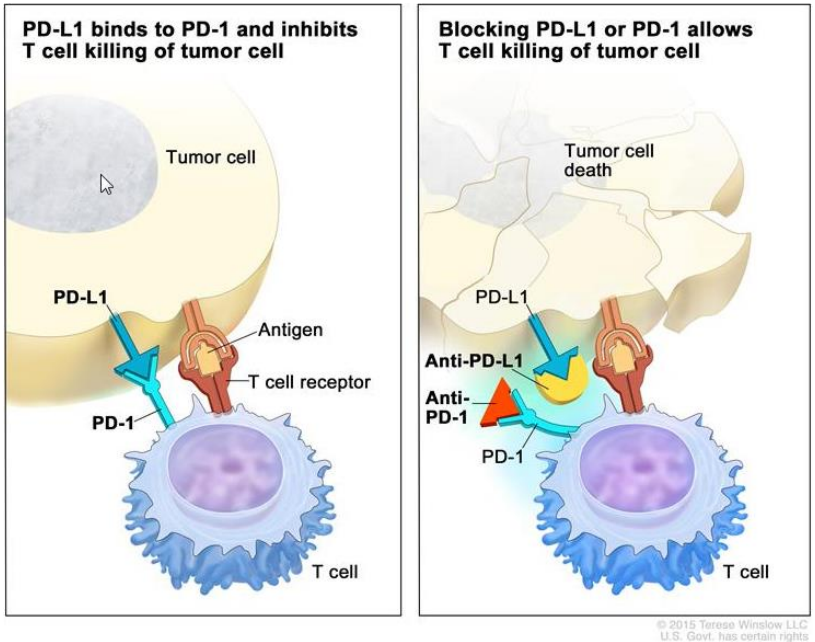


Five strategies for handling each intercurrent event

Treatment policy (ITT); Composite; Hypothetical
Principal stratum; While on treatment.

Motivational Example
Nivolumab - Immune Checkpoint Inhibitor

- Checkpoint proteins (PDL1 on tumor cells, PD1 on T cells)
- Clinical trials with anti-PD1/PDL1 agents:
  - 1 in 2006
  - 2,250 as of September 2018
- 6 drugs targeting PD1/PDL1 approved by FDA



Motivational Example

Checkmate-37 Trial

Primary objectives:

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

Checkmate-37

Co-primary Analysis for Objective Response Rate (ORR)

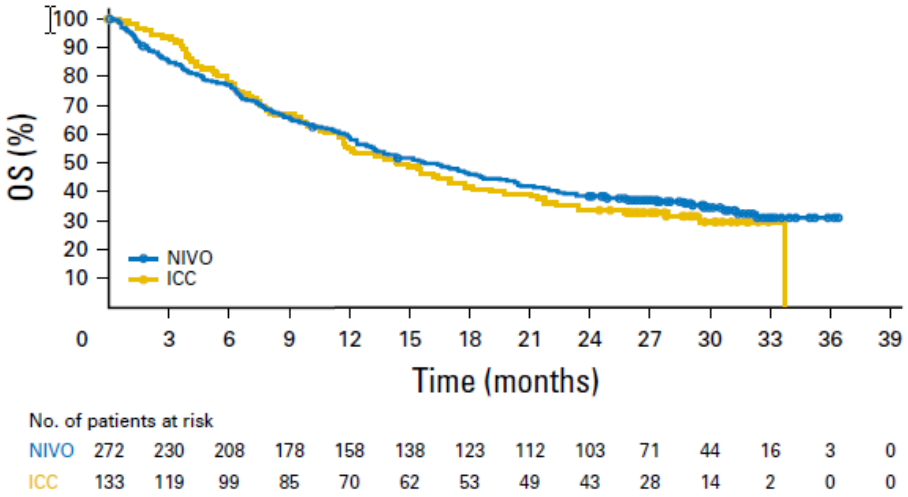
- Co-primary ORR = 31.7% in Nivolumab group
  - 95% CI: (23.5,40.8) exclude pre-defined 15% threshold

- Accelerated approval granted by FDA based on ORR data
  - Confirmatory evidence expected either through mature data from this or other trials
  - Study continued until primary analysis of co-primary endpoint OS
  - Full approvals granted in US, EU and Japan in 1L&2L melanoma based on the readouts from two other trials and this ORR data prior to OS analysis

Checkmate-37

Primary analysis for Overall Survival

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



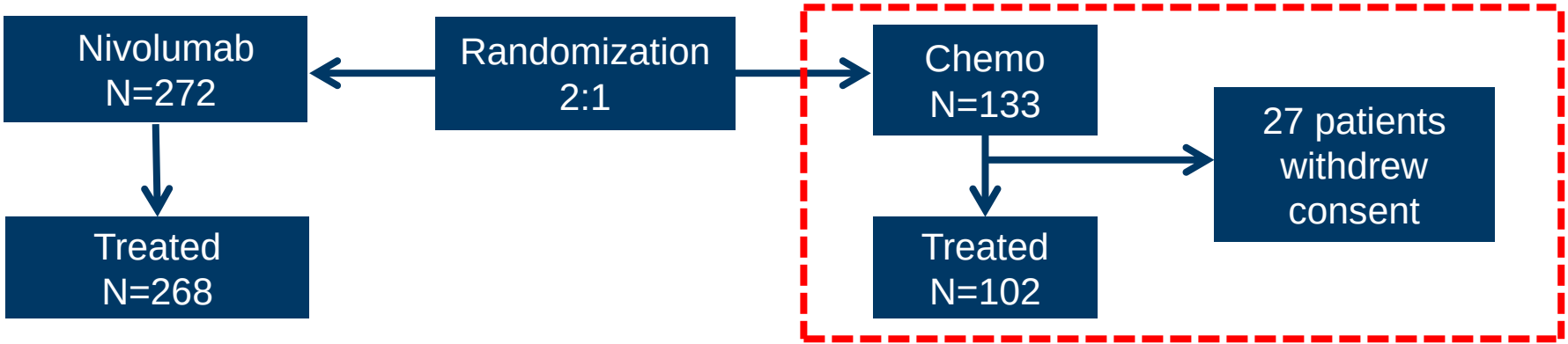
CheckMate 037: Nivolumab Improved Responses, Not Survival in Advanced Melanoma

By Leah Lawrence

Monday, July 17, 2017

Checkmate-37

What happened?

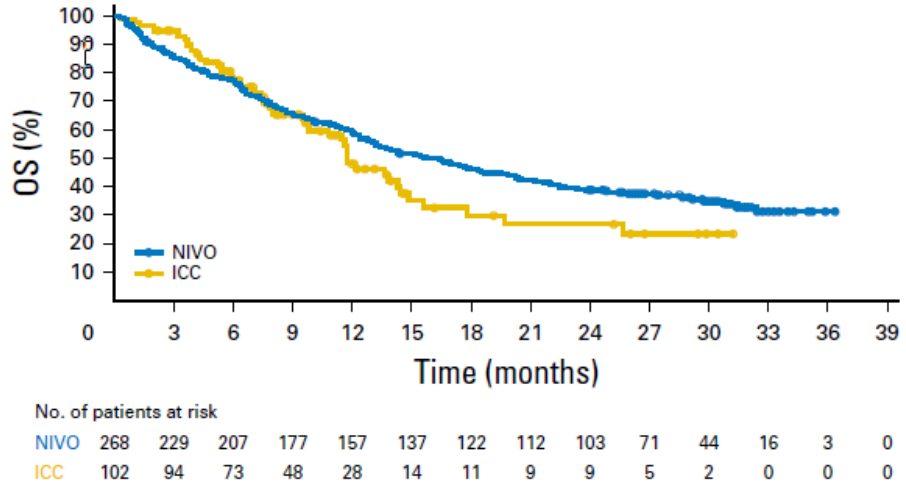


- Open-label trial and several competing studies with other checkpoint inhibitors ongoing at the time of enrollment
- 20% in chemo-arm withdrew consent immediately after randomization and before starting treatment
- Post-discontinuation data: 41% in chemo-arm received other checkpoint inhibitors (likely to be underestimation)

Checkmate-37

Published post-hoc analysis for Overall Survival

- OS in treated patients and censoring in chemo-arm at the start of PD1/PD-L1 agent: HR=0.81, mOS: 16.4m vs 11.8m



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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

Revisiting Checkmate-37

Precise definition of the question of interest

Primary objective: “To compare OS of nivolumab to chemo” – but what exactly is meant?

Intercurrent event	Primary analysis	Post-hoc analysis
Randomized treatment not received	Treatment policy	Hypothetical
PD1/PDL1 therapy received in chemo-arm	Treatment policy	Hypothetical
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/PD-L1 agent

Treatment policy: occurrence of the intercurrent event irrelevant
Hypothetical: interested in the effect if the intercurrent event would not occur

- Different questions with different answers: HR: 0.95 vs 0.81; ΔmOS: 1.3m vs 4.6m
  - Alternative post-hoc analysis to address the hypothetical estimand, e.g. IPCW
  - choice of the estimand impacts data collection
  - treatment switching to drugs with same mechanism of action could be anticipated due to competitive landscape and open-label feature of the study

IPCW: Inverse Probability of Censoring Weighting

Revisiting Checkmate-37

- In absence of estimand framework:
  - Treatment policy (ITT) → assumes whatever happens after randomization reflects clinical practice
  - Primary analysis based on treatment policy may not be informative
    - Checkpoint inhibors not yet widely available (at the time of study) and not part of clinical practice
    - not always yields a clinically meaningful comparison of treatments if this assumption is violated
- Using estimand framework:
  - Structured discussions with all stakeholders to align questions, objectives and estimators.
  - Trial design and primary analysis address the key question of interest
    - consider alternative approaches if appropriate
  - Trial results are informative and interpretation transparent

Estimands in Oncology
Implications beyond clinical trials

- Cancer drugs often perceived as expensive and not improving survival
- most oncology drugs approved without showing survival benefit and without conclusive evidence years later
- Negative perception driven by the main reported result targeting treatment-policy estimand for OS
- All stakeholders in the industry criticized for approvals and pricing

Over half of new cancer drugs 'show no benefits' for survival or wellbeing

Of 48 cancer drugs approved between 2009-2013, 57% of uses showed no benefits and some benefits were 'clinically meaningless', says BMJ study

HEALTH NEWS OCTOBER 13, 2017 / 8:44 PM / 7 MONTHS AGO

Little evidence new cancer drugs improve survival

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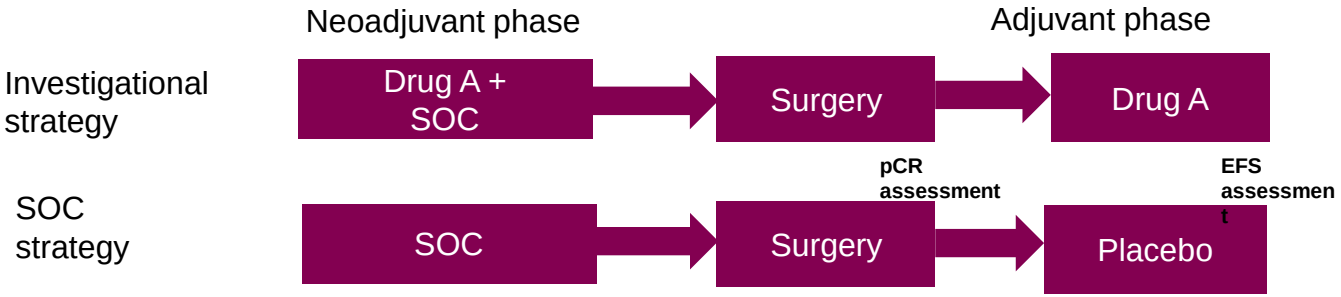
Revisiting Checkmate-37

- The estimand framework is NOT to save a failed study
  - The results were based on a post-doc analysis
  - Engaged discussion at design stage

To support submission, regulatory input is required.
Regulators favors treatment policy approach.

- **Estimand to start Dialogue** between sponsors, regulators, payers, physicians, and patients regarding the key questions of interest in clinical trials
- Pre-specified questions/objective/estimand/analysis

Study design combining Neoadjuvant and Adjuvant setting



Possible question of interest	Comment
What is the effect of Drug A + SOC vs SOC as neoadjuvant therapy?	• Primary endpoint as pCR, but not EFS • Sufficient evidence as neoadjuvant treatment for regulatory filing?
What is the effect of Drug A vs Placebo as adjuvant therapy?	• If benefit observed on EFS, but not on pCR, sufficient evidence for drug A as adjuvant treatment? • Systematic difference in neoadjuvant treatment impacts the extent of surgery and disease characteristics at the start of adjuvant phase. • Re-randomization after surgery required to ensure balance with regard to disease characteristics and neo-adjuvant therapy?
What is the effect of the treatment strategy Drug A + SOC followed by surgery followed by Drug A vs SOC followed by surgery followed by Placebo?	• Study design adequately compares the two strategies. Success on both pCR and EFS or just the final outcome EFS required for approval of the whole treatment strategy?

Estimand in Neoadjuvant and Adjuvant Setting

	Population	Variables	Intercurrent Events	Summary
Neoadjuvant Phase	Randomized population	pCR	Discontinuation of treatment due to AE, progression, other therapies	OR (ie Cochran-Mantel-Haenszel test)
Adjuvant Phase	Post-surgery (Resected set) or Re-randomized population	EFS/DFS	Radiotherapy (on treatment) crossover/treatment switching	HR (ie Stratified Cox PH)
Neoadjuvant and Adjuvant	Randomized population	EFS/OS	Radiotherapy/crossover/treatment switching	HR (ie Stratified Cox PH)

Summary: Estimands in Oncology

- Aligning research questions with study objectives
- Estimand framework seeks increased transparency in estimating treatment effect.
  - How to handle subsequent thereapy and different types of treatment switching and its impact
  - Increased clarify in complicated treatment regime. i.e. treatment as sequence of interventions
    - neoadjuvant therapy followed by surgery followed by adjuvant therapy
- Engaging HTA key stakeholders for transparent discussions (even with disagreement)

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