Estimand Framework and its Impact on Oncology Drug Development:

- Findings From An Industry-Wide Working Group

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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
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)

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

Open-label 2:1 randomization

Nivolumab

Chemo
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-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.

**Flowchart:**

- Randomization 2:1
  - Nivolumab N=272
  - Treated N=268
  - Received anti-PD-1 therapy N=29 (11%)
  - Chemo N=133
  - Treated N=102
  - Received anti-PD-1 therapy N=27 (20%)
  - Withdrew consent N=27 (20%)
  - Received anti-PD-1 therapy N=54 (41%)
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

Motivational Example 2

**RECORD - 1**

- 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
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)
Reconstructing Placebo OS data if patients had not crossed over

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

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

The Guardian

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

Little evidence new cancer drugs improve survival
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
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
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
“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**
Back to the Estimand framework

Four key attributes of Estimand

- Population – pts targeted by the scientific 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
Strategies for addressing intercurrent events

- **Treatment Policy**: occurrence of intercurrent event is irrelevant

Amy

<table>
<thead>
<tr>
<th>Experimental (E)</th>
<th>×</th>
<th>Death from any cause</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control (C)</td>
<td></td>
<td>× Death from any cause</td>
</tr>
<tr>
<td>Subsequent therapy (S)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

Amy

<table>
<thead>
<tr>
<th>Experimental (E)</th>
<th>×</th>
<th>Death from any cause</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control (C)?</td>
<td></td>
<td>× Death from any cause</td>
</tr>
</tbody>
</table>

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?

<table>
<thead>
<tr>
<th>Primary analysis</th>
<th>Post-hoc analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Question of interest</strong></td>
<td>Survival benefit after prescription of Nivolumab vs Chemo regardless of whether patients take assigned treatment or receive other therapy</td>
</tr>
<tr>
<td><strong>Intercurrent event:</strong> PD1 therapy received in chemo-arm</td>
<td>Treatment policy</td>
</tr>
</tbody>
</table>

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
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 inhibitors 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

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

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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

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