Estimands in Oncology

Evgeny Degtyarev, on behalf of EFSPN SIG Estimands in Oncology
Latest Trends on Health Technology Assessments (HTA)
Berlin, February 15, 2019
Estimand framework
ICH E9 addendum

- Precise definition of the scientific question of interest
- Alignment between trial objectives and analysis
- Dialogue between sponsors, regulators, payers, physicians, and patients regarding the key questions of interest in clinical trials
Motivational Example
Nivolumab - Immune Checkpoint Inhibitor

- Checkpoint proteins (PDL1 on tumor cells, PD1 on T cells) keep immune responses in check
- Clinical trials with anti-PD1/PDL1 agents:
  - 1 in 2006
  - 2,250 as of September 2018
- 6 drugs targeting PD1/PDL1 approved by FDA for 14 cancer types and one histology-agnostic indication

Motivational Example
Checkmate-37 trial

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

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
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 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-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

# Revisiting Checkmate-37

## Precise definition of the question of interest

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

<table>
<thead>
<tr>
<th>Intercurrent event</th>
<th>Primary analysis</th>
<th>Post-hoc analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomized treatment not received</td>
<td>Treatment policy</td>
<td>Hypothetical</td>
</tr>
<tr>
<td>PD1/PDL1 therapy received in chemo-arm</td>
<td>Treatment policy</td>
<td>Hypothetical</td>
</tr>
<tr>
<td>Question of interest</td>
<td>Survival benefit after prescription of Nivolumab vs Chemo regardless of whether patients take assigned treatment or receive other therapy</td>
<td>Survival benefit after treatment with Nivolumab vs Chemo if patients in chemo-arm never receiving PD1/PDL1 agent</td>
</tr>
</tbody>
</table>

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
  - performed post-hoc analysis not the only way to address the hypothetical estimand, e.g. IPCW
  - choice of the estimand impacts data collection
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 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?
- Additionally, many patients even did not receive chemo
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
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

- Negative perception driven by the main reported result targeting treatment-policy estimand for OS

→ All stakeholders in the industry criticized for approvals and pricing

- Opportunity to clarify the interpretation of the results and added value of the drugs
  - HTA key stakeholder in such discussions
Estimand issues in Oncology
Some examples

- Subsequent anticancer therapies as intercurrent event
  - different types of treatment switching and its impact
  - start of new anticancer therapy as negative outcome

- Treatment as sequence of interventions: effect of one part vs whole sequence?
  - different therapies during induction-consolidation-maintenance phases in hematology trials
  - neoadjuvant therapy followed by surgery followed by adjuvant therapy
  - additional complexities in studies with transplant and CAR-T therapies
Estimand issues in Oncology
Some examples

- Patient-reported outcomes
  - interested in quality of life on-treatment or including post-treatment period?
  - mixed models, time to definitive deterioration or time to first deterioration address different questions – careful interpretation required!

- High number of additional analyses usually performed for PFS
  - various rules for new therapies and events occurring after 2 missing assessments
  - questions addressed by such analyses clinically relevant?
  - sensitivity or supportive per ICH E9 addendum?
  - more meaningful ways to do sensitivity analyses?
  - focused on analysis in the past, but the question should drive the analysis!
  - opportunity to do less, but in a more meaningful way!
Estimands in Oncology

Need for the Industry Working Group

- Many specific estimand issues in Oncology
- Transparency on treatment effect of interest important goal of 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 WG

- initiated and led by Evgeny Degtyarev (Novartis) and Kaspar Rufibach (Roche), first TC Feb 2018
- 31 members (14 from Europe and 17 from US) representing 19 companies
- established as EFSPI SIG for Estimands in Oncology in Nov 2018
- close collaboration with regulators from EMA, FDA, China, Taiwan and Canada
### Causal Subteam
- causal estimands in T2E setting
- applications of principal stratification in Oncology

### Treatment Switching Subteam
- different types of treatment switching and its impact
- underlying OS estimands 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
- 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 for 2019

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

<table>
<thead>
<tr>
<th>Month</th>
<th>Event</th>
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<tbody>
<tr>
<td>MAR</td>
<td>DAGStat (Munich)</td>
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<tr>
<td></td>
<td>Session with 4 WG talks</td>
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<tr>
<td>APR</td>
<td>LiDS (Pittsburgh)</td>
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<td></td>
<td>Session with 3 WG talks + EMA discussant</td>
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<tr>
<td>MAY</td>
<td>PSI (London)</td>
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<tr>
<td></td>
<td>2 WG talks</td>
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<tr>
<td>JUN</td>
<td>ASCO (Chicago)</td>
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<td>3 abstracts submitted in collaboration with KOLs and industry clinicians</td>
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<tr>
<td>JUL</td>
<td>DIA (San Diego)</td>
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<td>1 WG talk</td>
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<tr>
<td>AUG</td>
<td>ISCB (Leuven)</td>
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<td>2 abstracts submitted</td>
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<tr>
<td>SEP</td>
<td>ASA Biop Section Regulatory-Industry Statistics Workshop (Washington)</td>
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<td>2 session proposals submitted incl. panel discussion with FDA</td>
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ASCO: American Society of Clinical Oncology
LiDS: Lifetime Data Science (ASA Section)
Conclusions

- More dialogue in future between all stakeholders including HTA ensuring:
  - key questions and needs are understood and addressed in the study design and study conduct (e.g. data collection)
  - 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

- EFSPIC SIG Oncology in Estimands active to ensure common understanding and consistent definitions in close collaboration with regulators
  - content will be shared throughout 2019 - stay tuned!
  - open to talk to HTAs!