Oncology Biostatistics

Estimands in Oncology

Evgeny Degtyarev, on behalf of EFSPI SIG Estimands in Oncology

Latest Trends on Health Technology Assessments (HTA)
Berlin, February 15, 2019

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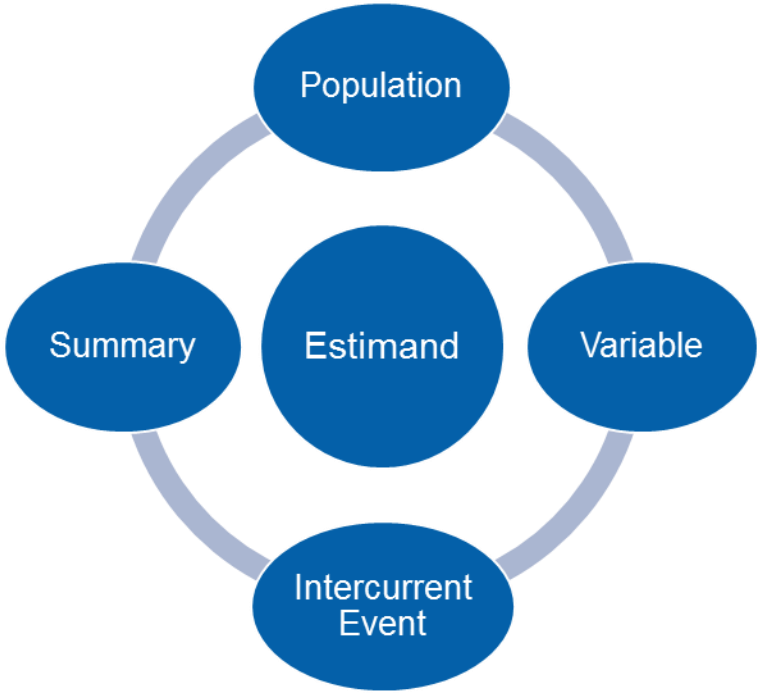
Estimand framework

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



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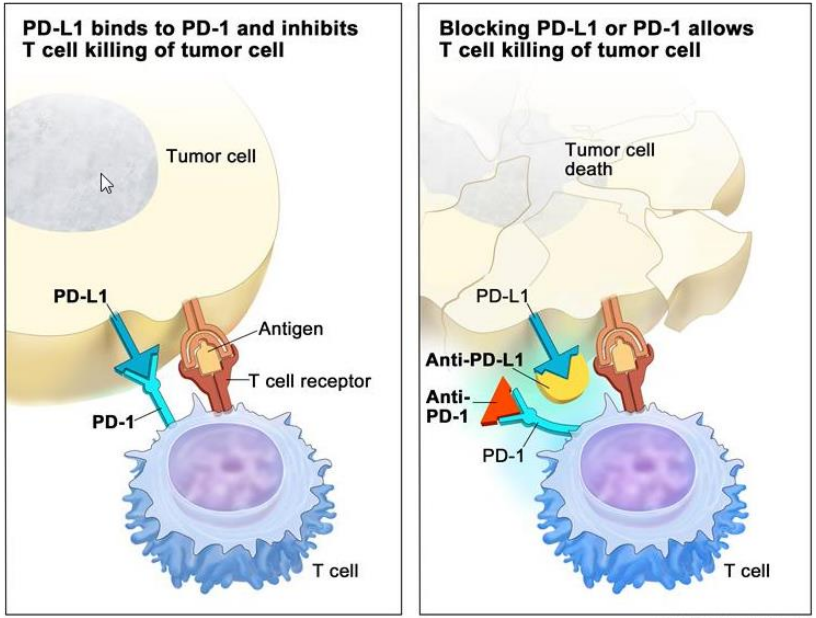
Motivational Example

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[1]
- 6 drugs targeting PD1/PDL1 approved by FDA for 14 cancer types and one histology-agnostic indication



1. Tang et al. (2018) The clinical trial landscape for PD1/PDL1 immune checkpoint inhibitors. Nature Reviews Drug Discovery volume 17, pages 854–855 (2018)

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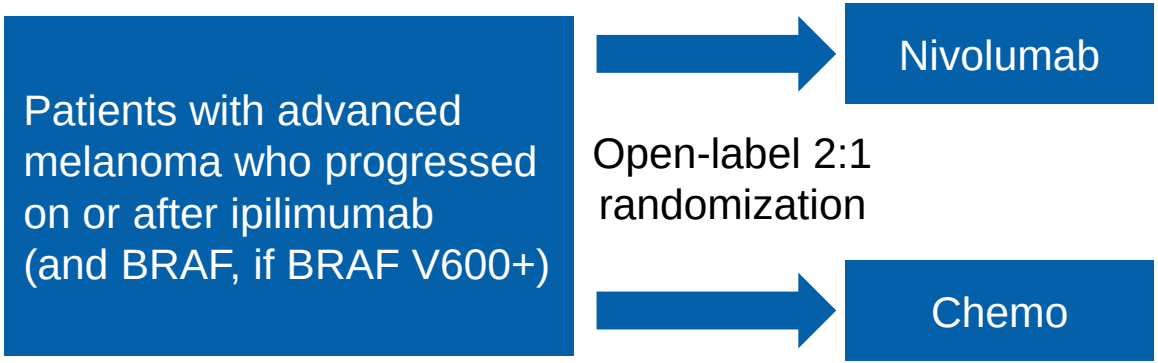
Motivational Example

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)

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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

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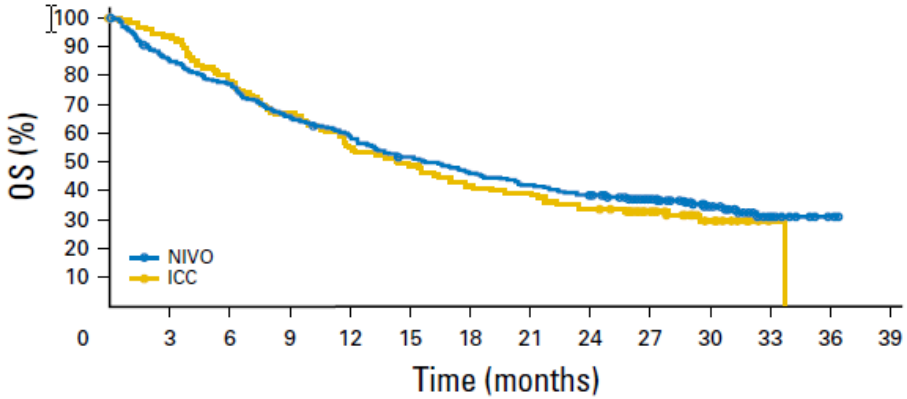
Checkmate-37

Primary analysis for Overall Survival

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



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 037: Nivolumab Improved Responses, Not Survival in Advanced Melanoma

By Leah Lawrence

Monday, July 17, 2017

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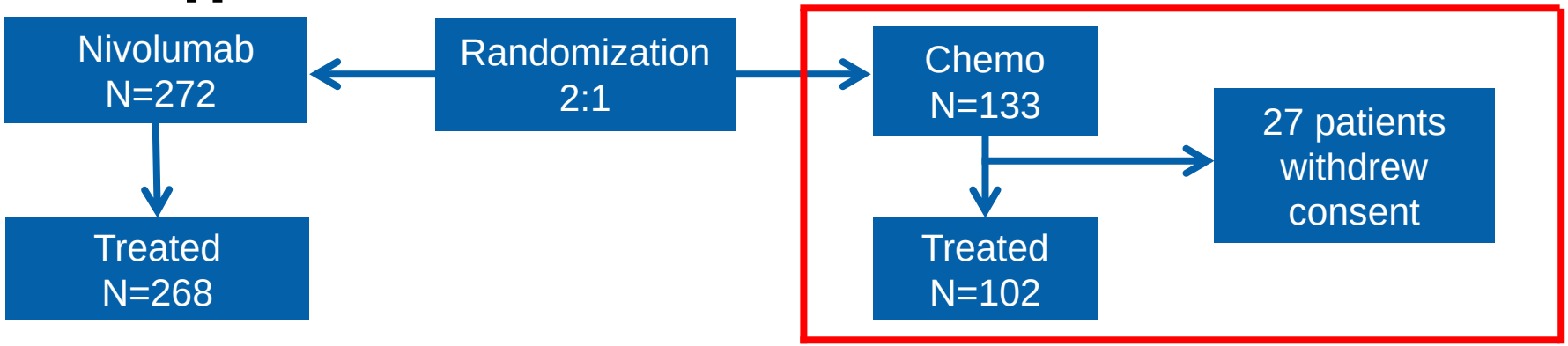
Checkmate-37

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)

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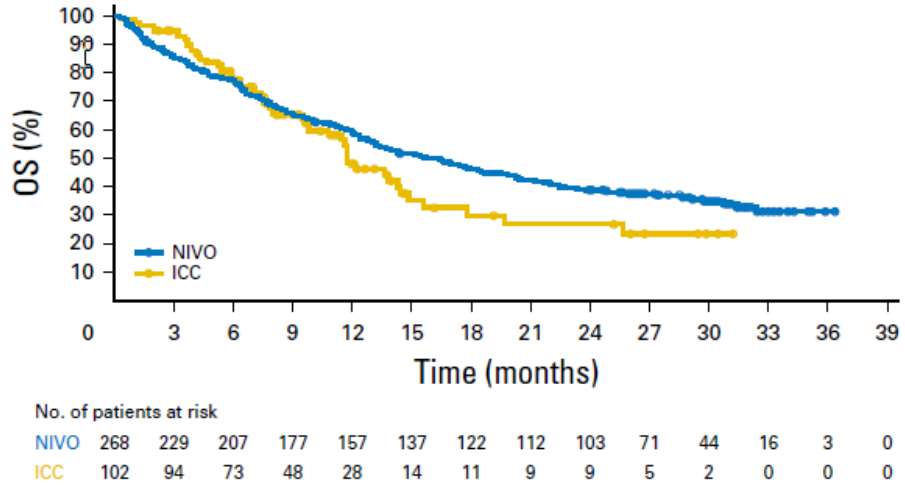
Checkmate-37

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



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

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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/PDL1 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
  - performed post-hoc analysis not the only way to address the hypothetical estimand, e.g. IPCW
  - choice of the estimand impacts data collection

IPCW: Inverse Probability of Censoring Weighting

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?

- 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

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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

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

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

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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

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 treatment switching and its impact

underlying OS estimands targeted by frequently used approaches: censor at switch, IPCW, RPSFT etc.

PFS2 estimand

Estimands in Oncology WG

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

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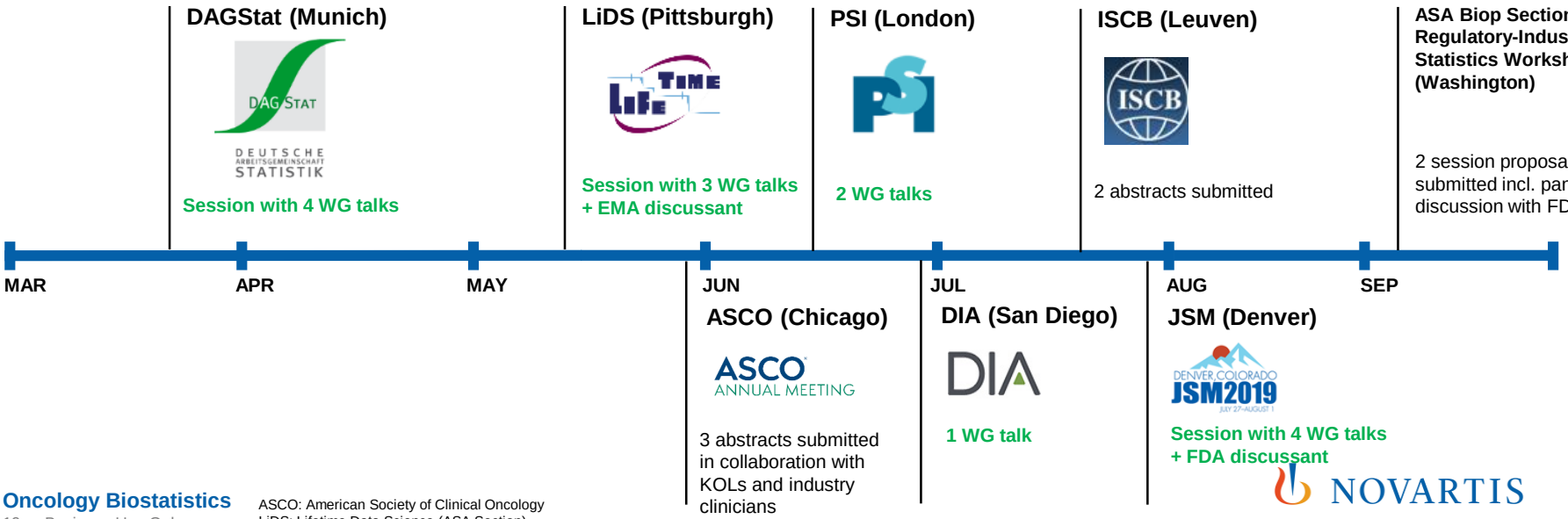
Estimands in Oncology WG

Communication plan for 2019

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



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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
- EFSPI 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!