Oncology Biostatistics

Estimand framework in Oncology drug development – impact and opportunities

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on behalf of Estimands in Oncology Working Group

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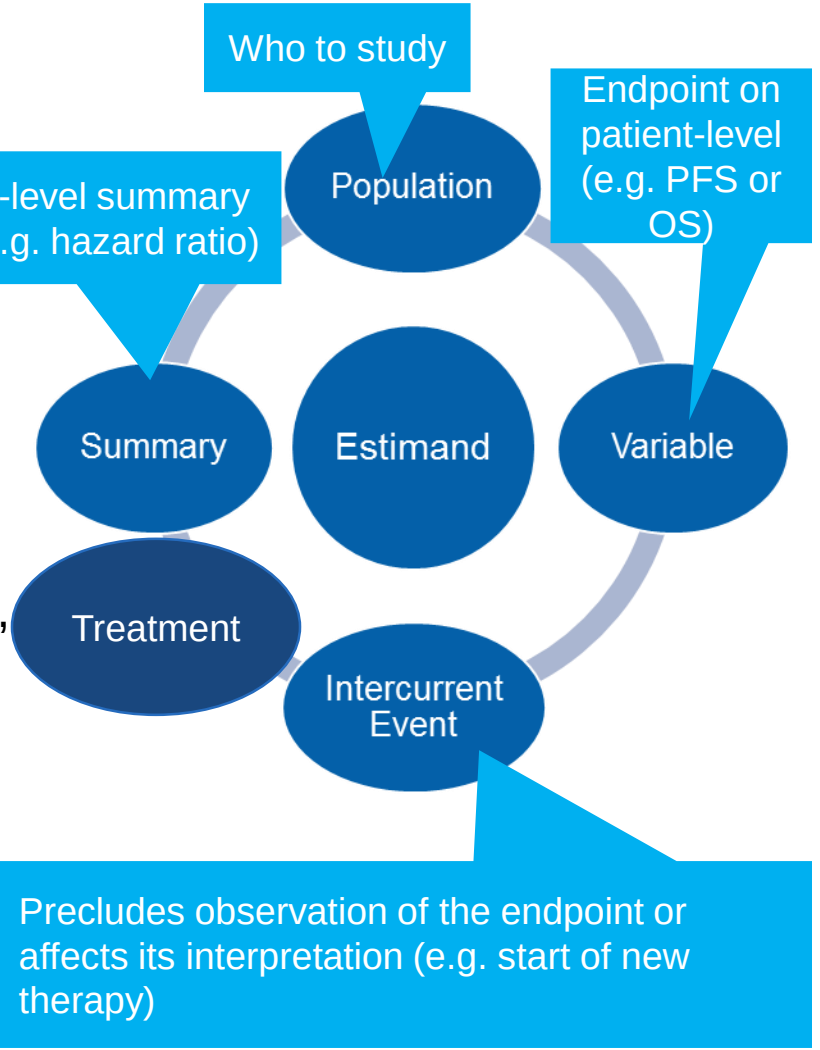
Estimand framework

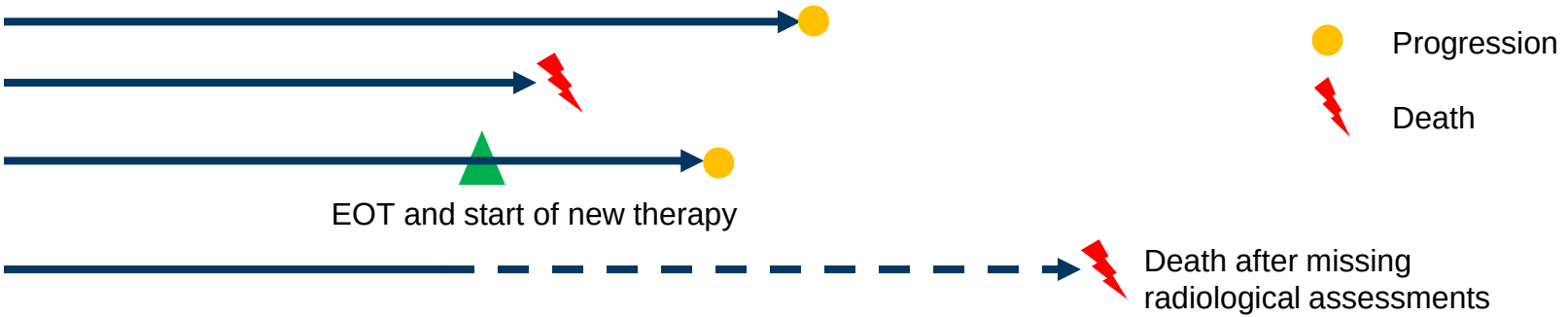
ICH E9 addendum

- 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



PFS: Progression-free Survival, time from randomization to progression or death
OS: Overall Survival, time from randomization to death

Oncology clinical trials today
Routinely performed analyses



- High number of analyses routinely performed for PFS
  - various rules to handle new therapies and events occurring after missing assessments
  - driven by the desire to see consistent results
  - same analyses inconsistently described as «sensitivity» or «supportive» across industry
  - underlying questions clinically relevant? true meaning of sensitivity and supportive?

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Oncology clinical trials today
Inconsistent endpoint definitions

- inconsistent definitions in particular for DFS in adjuvant trials

Trial	Local/Regional Recurrence	Distant Metastasis	Death From Any Cause	Invasive Contralateral Breast Cancer	Second Primary Invasive Cancer (nonbreast)	Ipsilateral DCIS	Contralateral DCIS	Ipsilateral LCIS	Contralateral LCIS
BIG 1-98[4]	X	X	X	X	X				
MA-17[1]	X	X		X		X	X	X	X
ATAC[2]	X	X	X	X		X	X		
IES[3]	X	X	X	X					
ARNO[5]	X	X		X					

NOTE: Event-free survival used by ARNO.
Abbreviations: DCIS, ductal carcinoma in situ; LCIS, lobular carcinoma in situ; BIG, Breast International Group; MA, National Cancer Institute of Canada Clinical Trials Group MA-17; ATAC, Arimidex, Tamoxifen Alone, or in Combination; IES, Intergroup Exemestane 031; ARNO, Arimidex, Nolvadex 95 Study.

- meta-analyses and use of historical data:
  risk of comparing apples vs oranges

DFS: Disease-free survival; Hudis (2007)

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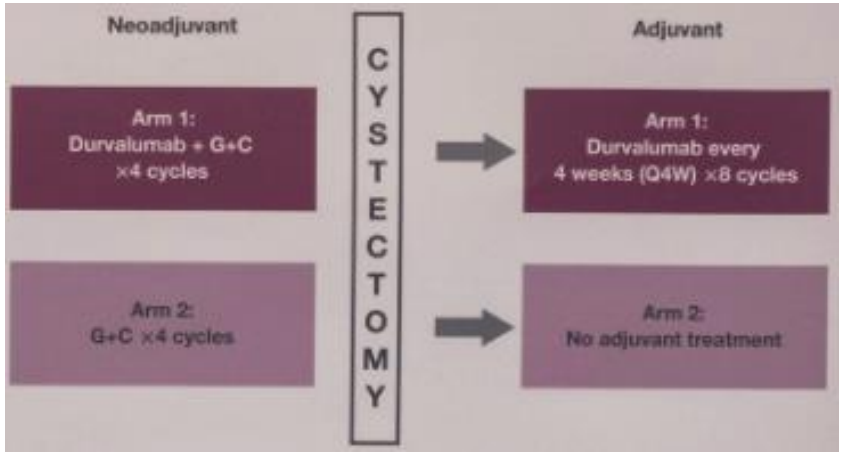
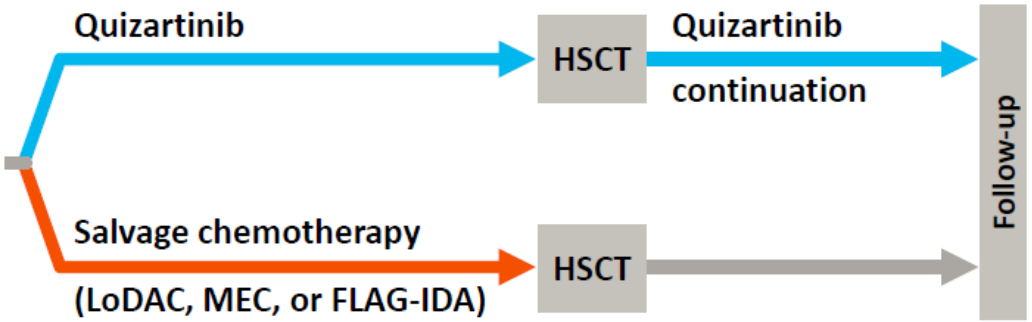
Oncology clinical trials today
Treatment as sequence of interventions

- Studying effect of each part vs whole sequence?

(Neo)adjuvant setting



Transplant setting



- not always consistent thinking and interpretation

Niagara trial: Powles T. , ASCO poster 2019, NCT03732677
Quantum-R trial: from ODAC presentation in May 2019 by Daiichi Sankyo

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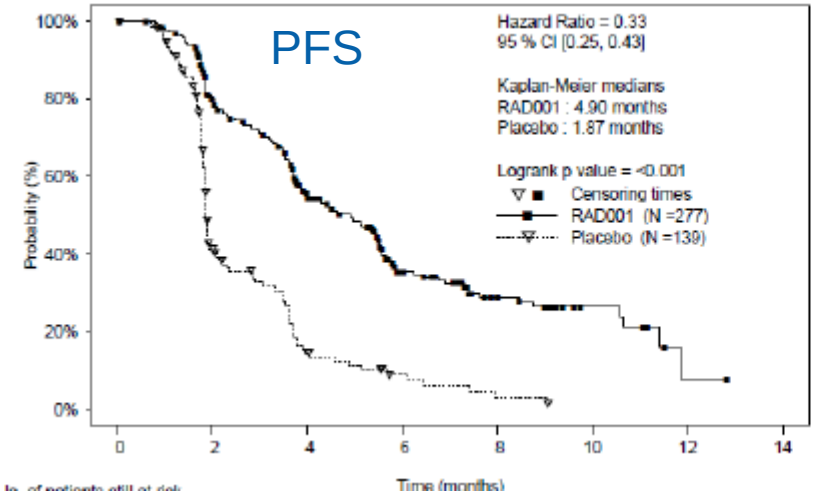
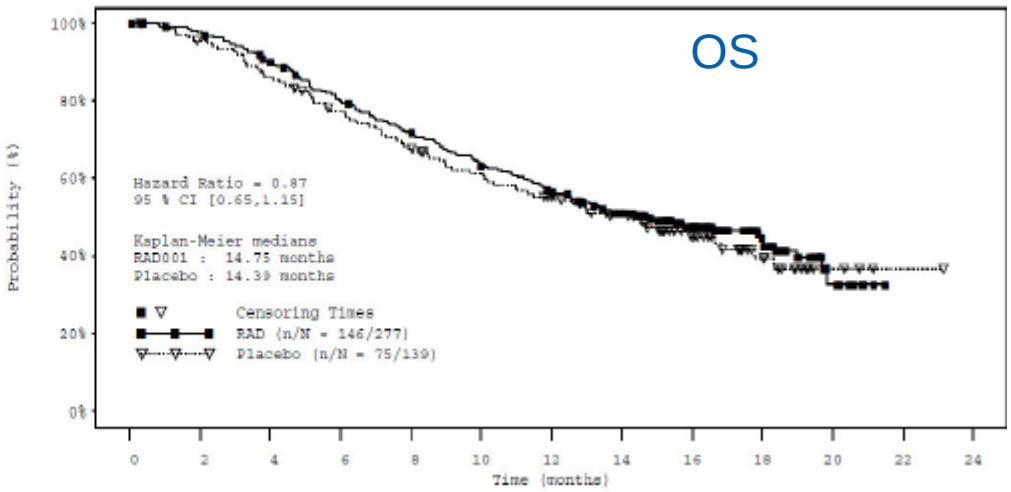
Oncology clinical trials today
OS and treatment switching





- Some protocols allow crossover from control to investigational arm upon progression
- Treatment switching from control to drugs with the same mechanism of action as investigational treatment outside of the study observed frequently with e.g. immunotherapies
- challenging interpretation of study results

RECORD-1 study: Everolimus vs Placebo in Renal Cell Carcinoma

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Oncology clinical trials today
Patients randomized, but not treated

- Blinding often not feasible, in particular versus chemotherapy
- Highly competitive environment with many ongoing studies with novel compounds
  → patients not interested to receive chemo and withdraw consent after randomization
- Several examples with many patients randomized to control, but not treated
  - Quantum-R trial (2019): 23% (vs 1.6% on investigational arm)
  - Checkmate-37 trial (2015): 20% (vs 1.5% on investigational arm)
- R.Pazdur, director of FDA Oncology Center of Excellence, on Quantum-R:
  "That is quite bothersome, I've been here 20 years. I haven't seen this discrepancy of randomized-but-not-treated to this extent."
- this issue can be anticipated - new challenge due to higher competition requiring new approaches?

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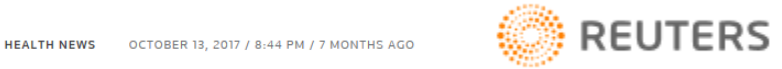
Oncology clinical trials today
Misinterpretation and negative perception

- 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



Little evidence new cancer drugs improve survival

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Oncology clinical trials today
Misinterpretation and negative perception

- Negative perception driven by the main reported result targeting treatment-policy estimand for OS
  - Davis lists e.g. RECORD-1 study (sl.6 example) as not showing benefit ignoring >70% cross-over from control after progression
- Misleading headlines for approved and efficacious drugs

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

By Leah Lawrence
Monday, July 17, 2017

Checkmate-37: 20% randomized to control, but not treated, 41% switched from control to a drug with the same mechanism of action as nivolumab

→ Sponsors, regulators, payers criticized for approvals and pricing

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Oncology clinical trials tomorrow? Estimand framework as a tool

- Less analyses for PFS, but more value for all stakeholders!
  - driven by clinical questions ensuring interpretability and relevance
  - meaningful sensitivity analyses
- Clarity on the effect of interest:
  - consistent and transparent endpoint definitions
  - clear treatment description in settings with sequence of interventions
- Open dialogue between all stakeholders using common language:
  - What if treatment switching and high number of patients randomized, but not treated anticipated?
  - Treatment policy estimand won't be informative – shouldn't we aim to ensure that research produces informative results?
  - Hypothetical estimand more informative and relevant? Other alternatives?
- Opportunity to clarify interpretation of study results and added value of the drugs

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Estimands in Oncology WG

- Purpose: common understanding and consistent definitions for key estimands in Oncology across industry
- initiated and led by Evgeny Degtyarev (Novartis) and Kaspar Rufibach (Roche), first TC Feb 2018
- 34 members (15 from Europe and 19 from US) representing 22 companies
- established as EFSPI SIG (Nov 2018) and ASA Biopharmaceutical Section SWG (Apr 2019)
- collaboration with regulators from EMA, FDA, Japan, 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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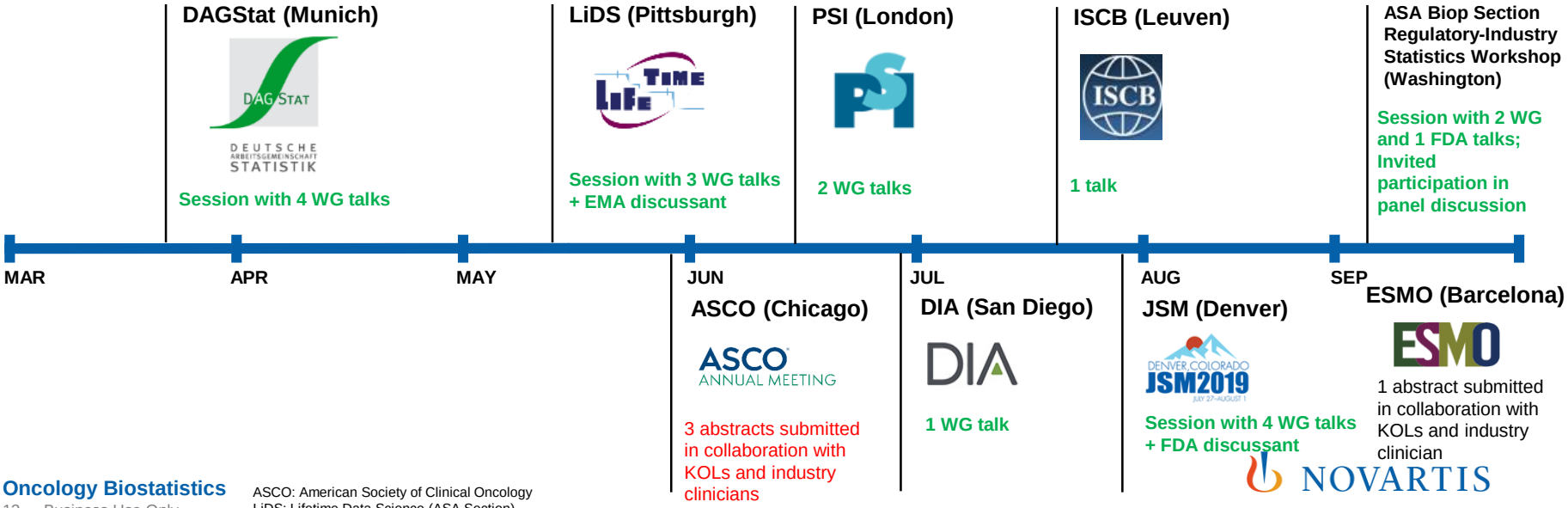
Estimands in Oncology WG

Communication plan for 2019

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



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

Conclusions

- More dialogue in future between all stakeholders 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
- Oncology in Estimands WG active to ensure common understanding and consistent definitions in close collaboration with regulators