Implementation of the ICH E9 addendum: RATIFY - A case study in hematology

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On behalf of the Hematology Subteam of the Oncology Estimand Working Group.

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Estimands in Oncology WG

- initiated and led by Evgeny Degtyarev (Novartis) and Kaspar Rufibach (Roche), first TC Feb 2018
- main purpose: ensure common understanding and consistent definitions for key estimands in Oncology across industry
- 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

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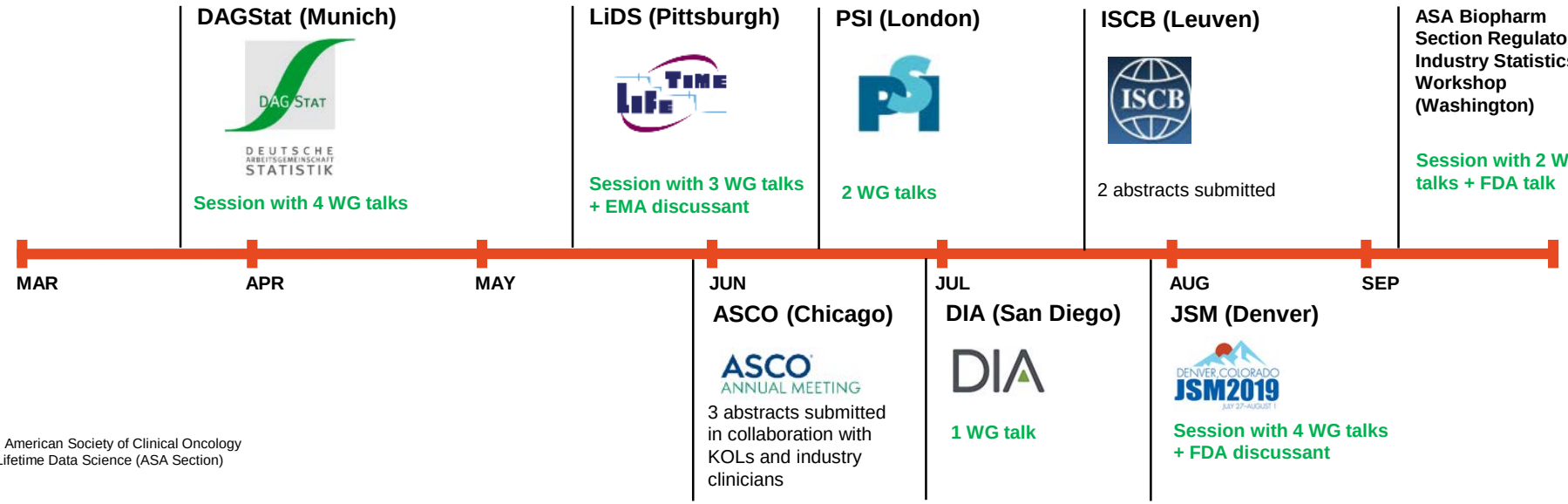
Estimands in Oncology WG

Communication plan for 2019

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



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

Why a dedicated estimand subteam for hematology?

- In hematologic malignancies, treatments are often given in a **sequence** based on a certain **algorithm** (e.g. AML: induction, consolidation, maintenance)
- **Stem cell transplantation** (SCT) as option for cure
- Response to treatment is usually assessed using **composite endpoints**
  - Consisting of blood counts, bone marrow aspirate and other components
- Multiple **new classes of drugs** available recently providing new options after treatment failure/ relapse

⇒ **Specific topics requiring dedicated considerations in the estimand framework**

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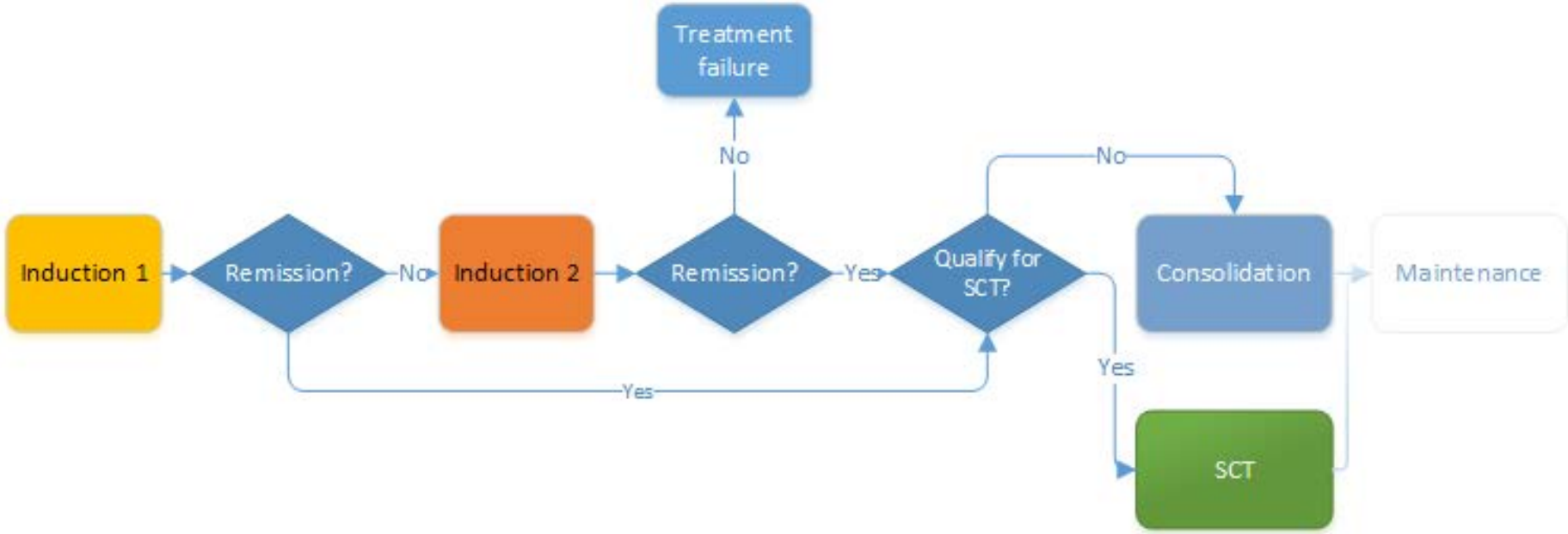
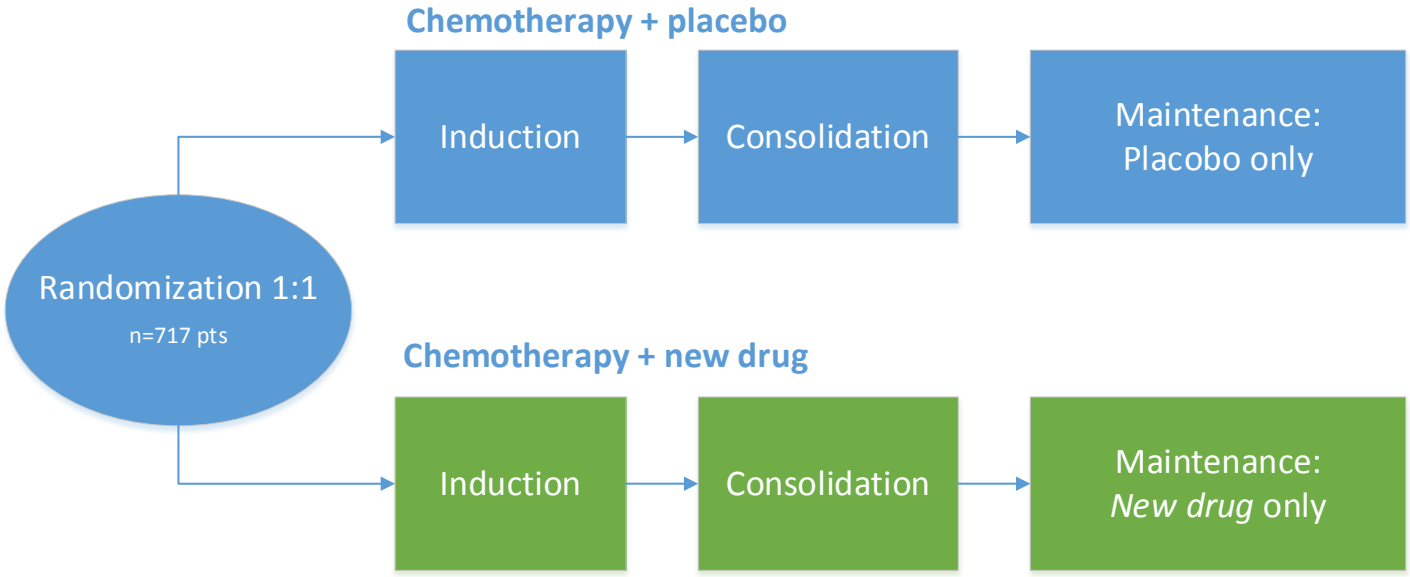
Treatment strategy in newly diagnosed AML patients[1]



[1] in patients tolerating chemotherapy (e.g. NCCN guidelines 2.2019)
AML – acute myeloid leukemia
SCT – stem cell transplantation

Motivating example: RATIFY study in AML
(Acute Myeloid Leukemia) Stone et al (2017)

- Population: newly diagnosed AML patients
- Primary Objective: to determine if the addition of *new drug* to induction, consolidation, and maintenance therapy improves Overall Survival (OS)
- Key-secondary endpoint: Event-free survival (EFS)
- Design: Phase 3, randomized, double-blinded, placebo-controlled



Stone (2017): Midostaurin plus chemotherapy for acute myeloid leukemia with a FLT3 mutation. N Engl J Med 377(5) 454-464

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RATIFY study: Scientific question

- Does the *new drug* improve overall survival in the study population when *added to induction, consolidation and maintenance*?
  - Primary objective describes a **treatment sequence** consisting of induction, consolidation and maintenance
  - There are different **treatment paths** like receiving stem cell transplant (SCT)
    - In case of SCT patients did not resume study treatment but have been followed for survival and disease assessments
  - Investigate the **treatment strategy** including the treatment sequence and optional treatment paths

  ⇒ Should we describe the treatment strategy in another attribute of an estimand?

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RATIFY study: Scientific question and Health Authory discussion

- **Treatment strategy**: Implications
  - Maintenance treatment is not part of a standard AML treatment strategy
  - Health authorities wanted to know the contribution of the maintenance treatment to the overall treatment effect
  - Understanding the contribution of maintenance treatment to the overall effect was not part of the underlying scientific question
    - Study was not designed to address the isolated maintenance effect
    - What would agencies expect in order to approve a drug in a modifed treatment sequence?

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RATIFY study: Intercurrent events

- **Example: Stem cell transplantation**
  - SCT is part of standard AML treatment strategy
  - Confounding?
  - RATIFY: Not detailed in objectives how to deal with SCT
    - Patients had to be followed for OS and EFS beyond SCT
  - Overall survival and EFS are assessed regardless of SCT (implicit)
    - SCT ignored as intercurrent event (treatment policy)

$\Rightarrow$ «ignoring SCT» is in line with approach to assess a treatment strategy having SCT as treatment option

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RATIFY study: Intercurrent events

- **Example: New antineoplastic therapies**
  - **Start of a new therapy** means failure of the treatment strategy or study treatment is not tolerated
    - Meaning of new therapies is different situation than SCT
  - Primary estimand overall survival was assessed **regardless of use of new therapies**
    - «Traditional» OS approach as per FDA guideline endpoints in oncology
    - Underlying question: Effect regardless of subsequent therapies
      - Treatment policy approach
      - What does this mean if new efficacious therapies are available or treatment switching?

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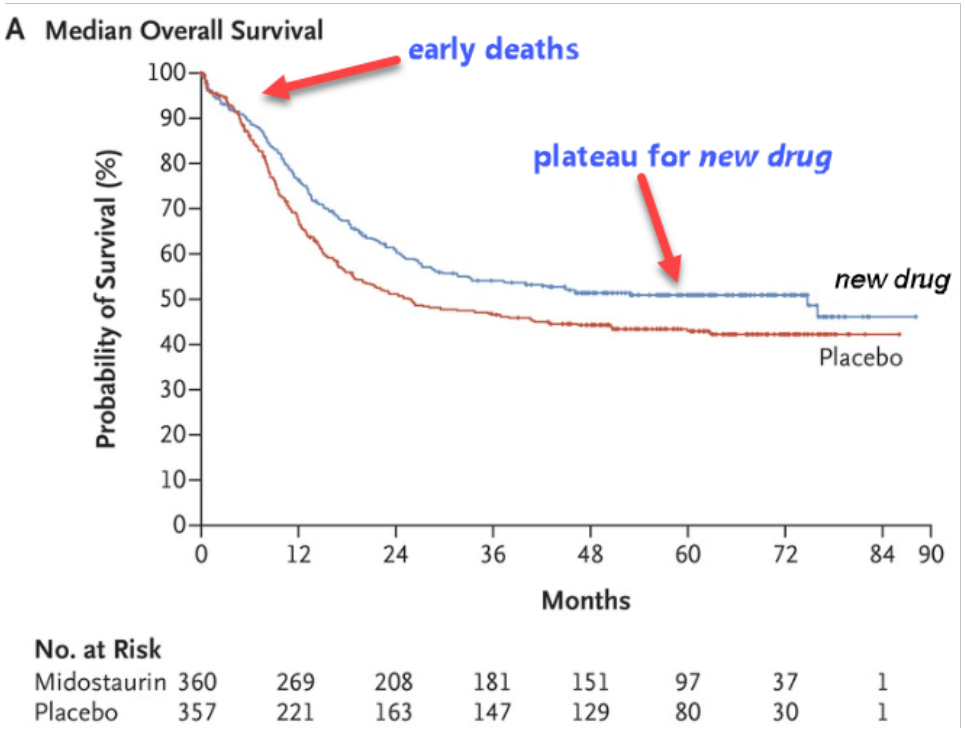
RATIFY study: OS analyses as per study protocol

- OS primary analysis
  - Event: death due to any reason; ignore SCT and start of new therapies
- OS «sensitivity analysis»
  - **«Per-protocol analysis»:** excluding patients with a broad range of compliance issues (e.g., in-/exclusion criteria, treatment compliance, randomization issues)
    - Includes pre-randomization information but also intercurrent events (e.g., treatment compliance)
    - How to interpret?
- Secondary objective
  - **OS censored for SCT**: different estimand

RATIFY study: OS testing & estimation



- RATIFY
  - Testing: stratified log-rank test
  - Estimation: HR per stratified Cox PH
- Assumption of **proportional hazards**
  - Early deaths due to chemotherapy
  - Plateau at late phase (cure)
- Consistency of **testing** and **estimation**?

Rufibach (2019)

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RATIFY: Key OS estimands

	Primary estimand	Estimand 2 (supplementary)
Scientific question: Will adding new drug to newly diagnosed AML treatment strategy prolong the time to ...		
	... death regardless of new therapies and SCT	**... death regardless of new therapies if no SCT is given**
Population	All randomized patients	All randomized patients
Variable	OS	OS
Intercur. event: SCT	Treatment policy	Hypothetical
Intercur. event: Maintenance, new therapy	Treatment policy	Treatment policy
Summary measure	HR	HR
Analysis	Estimate HR using stratified Cox model and reported survival times, stratified log-rank test	Estimate HR using stratified Cox model and reported survival times, stratified log-rank test
Treatment strategy	Adding new drug to induction, consolidation and maintenance; patients in remission after induction may receive SCT	Adding new drug to induction, consolidation and maintenance; patients in remission after induction may receive SCT

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Conclusions

- Investigating a **treatment strategy** requires to make this explicit for the estimand definition
  - Consider treatment strategy as another estimand attribute?
- Specify also **intercurrent events that are ignored** for the treatment policy strategy like SCT and start of new therapies
- Be specific about what is assessed in **sensitvity analyses**
  - Move away from what is done always to what makes sense in your setting
- **Testing and estimating** the effect for time to event endpoints
  - Understand potential indication-specific deviations from PH assumption and whether the hazard ratio is the estimator of choice
- Great **opportunity** for **statisticians to guide estimand discussion!**

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References

- FDA guidance*: Clinical trial endpoints for the approval of cancer drugs and biologics* (2007, 2018)
- ICH E9 working group (2017). E9 (R1) *Addendum to Statistical Principles for Clinical Trials on Choosing Appropriate Estimands and Defining Sensitivity Analysis in Clinical Trials*
- NCCN Clinical Practice Guidelines in Oncology: *Acute Myeloid Leukemia*. Version 2.2019 (March 2019)
- Rufibach, K. (2019). *Treatment effect quantification for time-to-event endpoints -- estimands, analysis strategies, and beyond*. Pharmaceutical Statistics, to appear.
- Stone RM, Mandrekar SJ, Sanford BL, Laumann K, Geyer S, Bloomfield CD, Thiede C, Prior TW, Döhner K, Marcucci G, Lo-Coco F, Klisovic RB, Wei A, Sierra J, Sanz MA, Brandwein JM, de Witte T, Niederwieser D, Appelbaum FR, Medeiros BC, Tallman MS, Krauter J, Schlenk RF, Ganser A, Serve H, Ehninger G, Amadori S, Larson RA, Döhner H (2017): *Midostaurin plus chemotherapy for acute myeloid leukemia with a FLT3 mutation*. N Engl J Med 377(5) 454-464

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Thank you

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