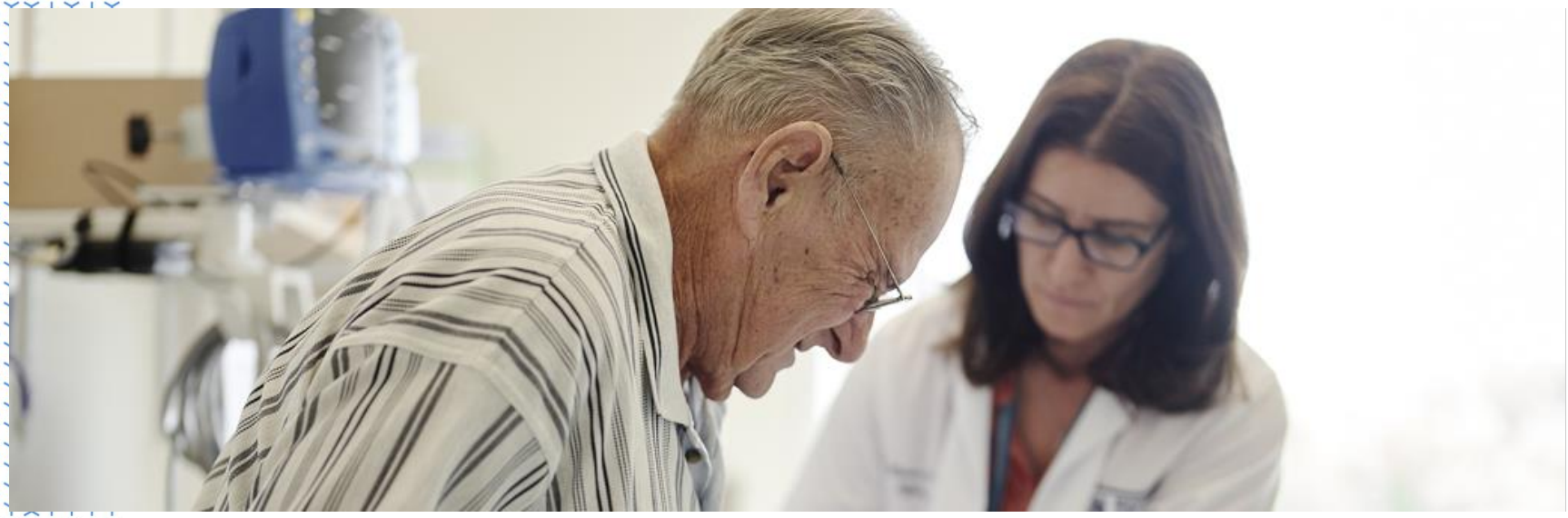

Event Free Survival in the light of the patient journey: what do we really want to measure ?

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ASA NJ Estimand non-standard endpoints webinar

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NOVARTIS | Reimagining Medicine

Overview

- Event Free Survival (EFS) definition(s) in second line (2L) treatment of Lymphoma
- A clinical rationale for treatment failure in EFS
- Challenges from patient journeys
- Need for estimand clarity for trial interpretability

Event Free Survival (EFS) in 2L Lymphoma

- EFS commonly used in second line (2L) Diffuse Large B Cell Lymphoma (DLBCL)
- EFS : time from randomization to event generally defined as first of
  - Death whatever the cause
  - Tumor relapse / evidence of disease progression
  - Treatment failure
- Death and Tumor relapse/progression : clear clinical detriment, objective date
- Treatment failure:
  - How defined, at which date ?
  - Can it be delayed by treatment ?
  - What clinical relevance ?

Treatment failure in EFS in 2L Lymphoma

- How defined, at which date ?

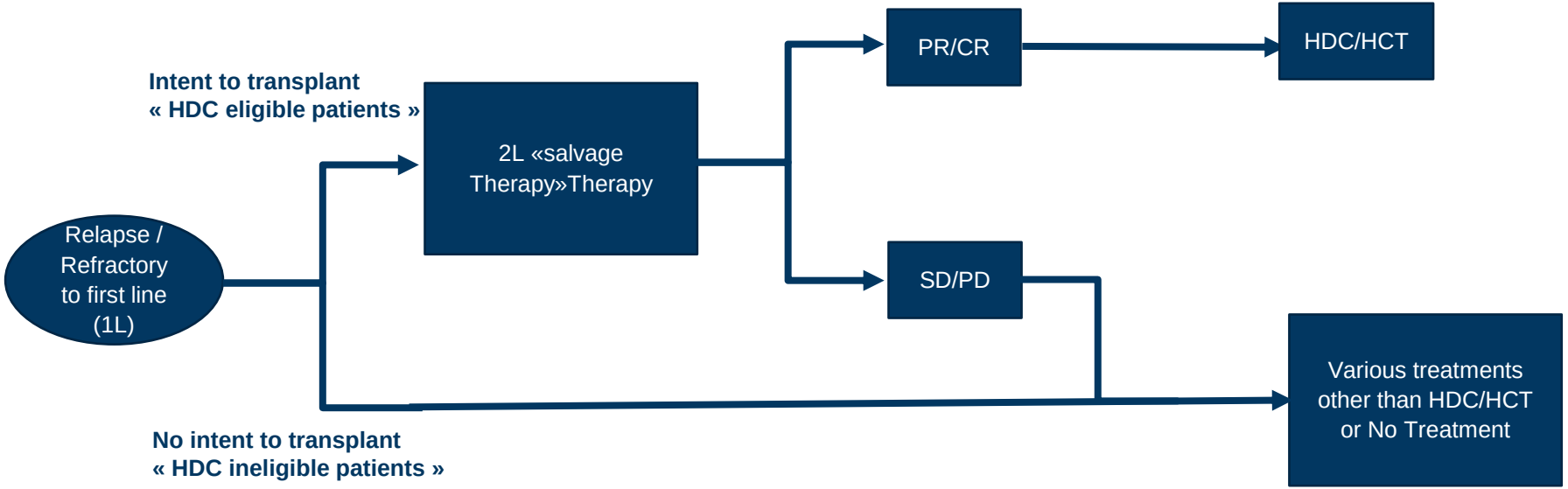
Possible treatment failure event definition	Possible date of event
Starting new therapy for any reason (safety or efficacy)	Date of last adequate assessment / start of new therapy Date of randomization
Starting new therapy for efficacy related reasons only	Date of last adequate assessment / Date of start of new therapy Date of “efficacy related reason” (progression/lack of response) Date of randomization
No complete or partial response after 2 cycle of salvage or by a given time after start of salvage	Date of assessment after 2 cycles (or date of time limit) Date of randomization

- Can it be delayed by treatment ?

  When date of event is set by convention (date of randomization or limit date or 2 treatment cycles): it is a yes/no contribution to time to event, it cannot be delayed by treatment

Clinical rationale for treatment failure in 2L EFS

- Second line (2L) patient journeys (simplified from NCCN Guidelines v 4., 2021)



Principles of High Dose Chemotherapy and Stem Cell Transplant (HDC / SCT) in 2L

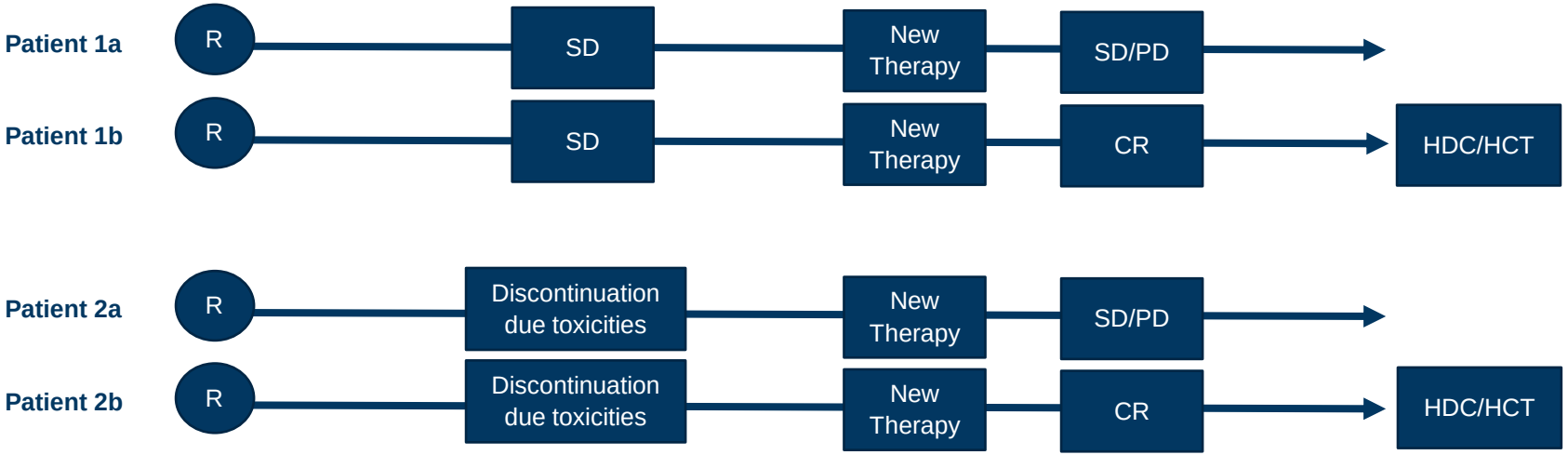
- HDC is the component of 2L therapy that results in patient benefit
  - possibility of cure
  - SCT is administered to address severe toxicity of HDC
- Salvage therapy selects patients who may benefit from HDC/SCT
  - Select for patients who have complete or partial response (CR/PR) to standard doses of chemotherapy
- Lack of administration of HDC/SCT = clinically significant detrimental event
  - Efficacy reason (Not achieving CR or PR)
  - Safety reason:
    - No further therapy is administered, or
    - No HDC/SCT is administered even if other standard chemotherapy are administered

“Treatment failure” : proxy for “no HDC/SCT”

- “Treatment failure” reflects inability to enable HDC/SCT administration
  - Decision/triggering situation, rather than its consequence of “No HDC/SCT”
  - Focus on easily measurable reasons for “objectivity”, yet not standardized
- Very heterogenous across studies
  - Multiple combinations of possible definitions of treatment failure
  - Clinical significance of dates of event (e.g., baseline vs. date of new Therapy vs. date of SD) ?
- Treatment failure is a questionable predictor of “no HDC/SCT”
  - Meant as (post-baseline) indicator of population not likely to receive benefit-driving intervention
  - It is questionable as a predictor, considering the diversity of possible patient journeys

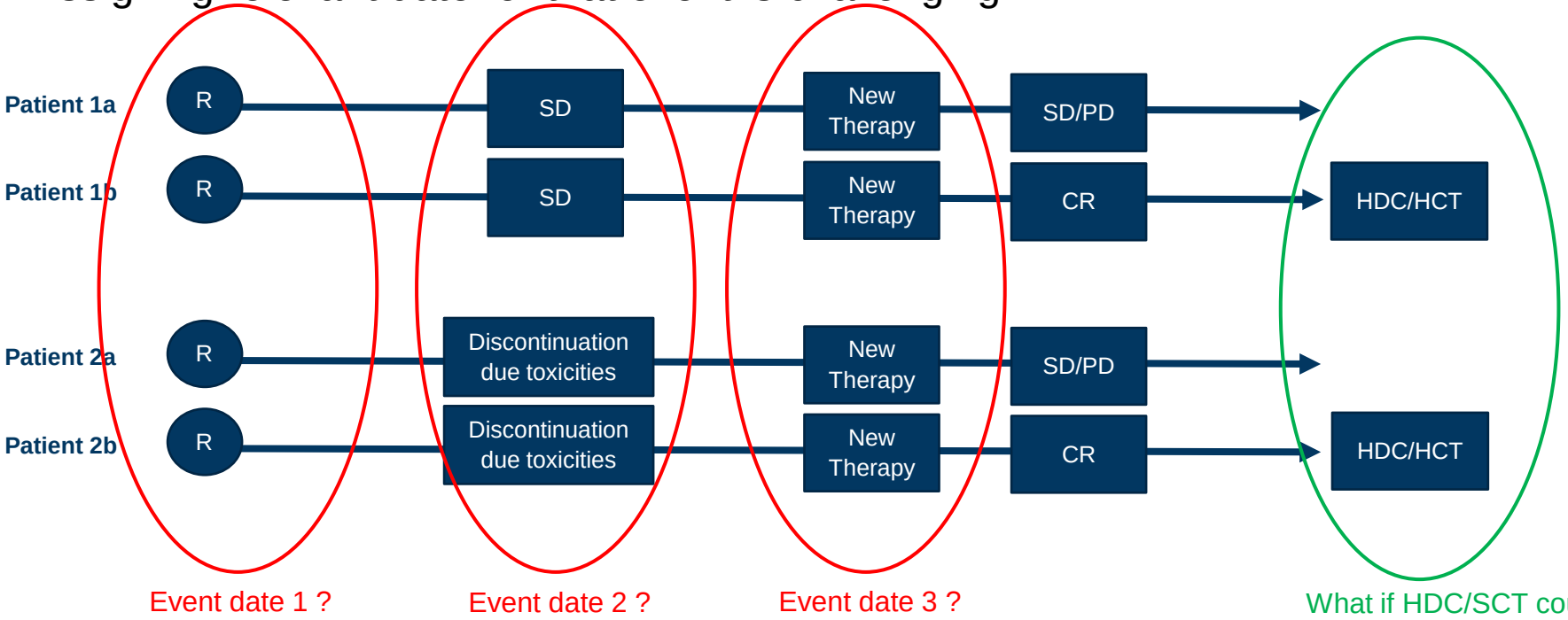
Challenges : 2L HDC eligible patient journeys

- Are “New Therapy”, “SD” or “lack of CR/PR”, or “Treatment Discontinuation” good proxies for “no HDC/SCT” in 2L HDC/SCT eligible patients?



Challenges : 2L HDC eligible patient journeys

- The real clinically relevant event is that HDC/SCT does not occur
- Assigning relevant date for that event is challenging



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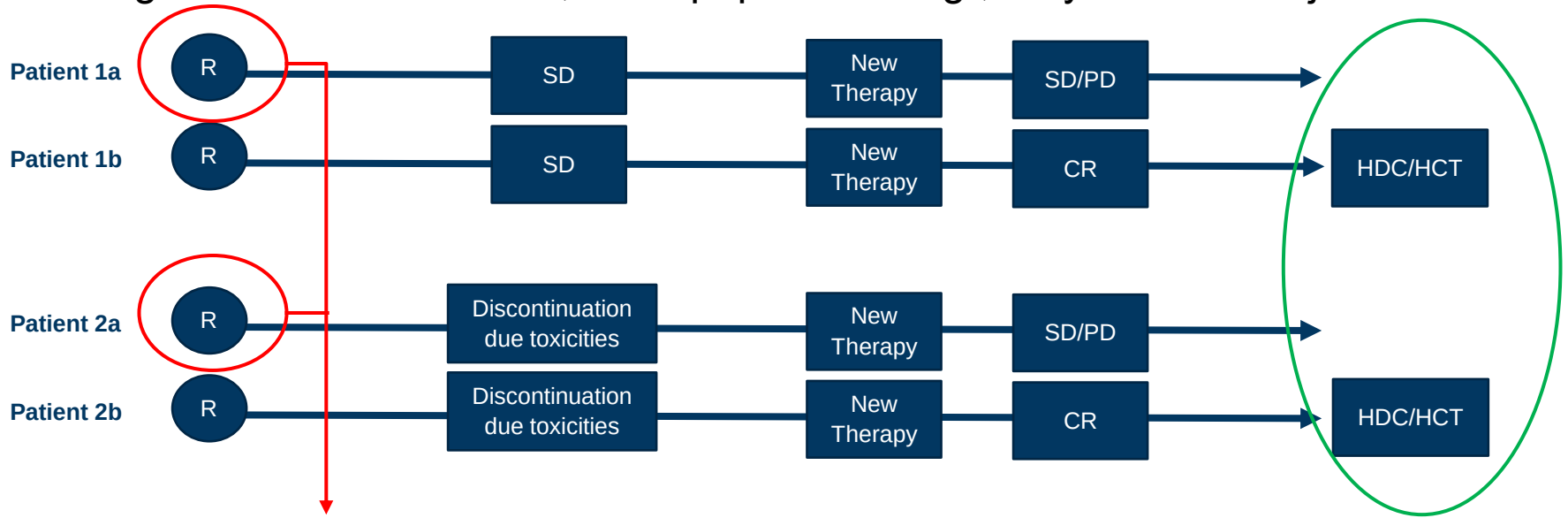
Proposal : 2L HDC eligible patient journeys

- The real clinically relevant event is that HDC/SCT does not occur
  - use this fact to identify the event instead of a proxy
- Dating the event at baseline, as a “population flag”, may be less subjective



Events at baseline: the patients 1a and 2a are not part of the benefiting population

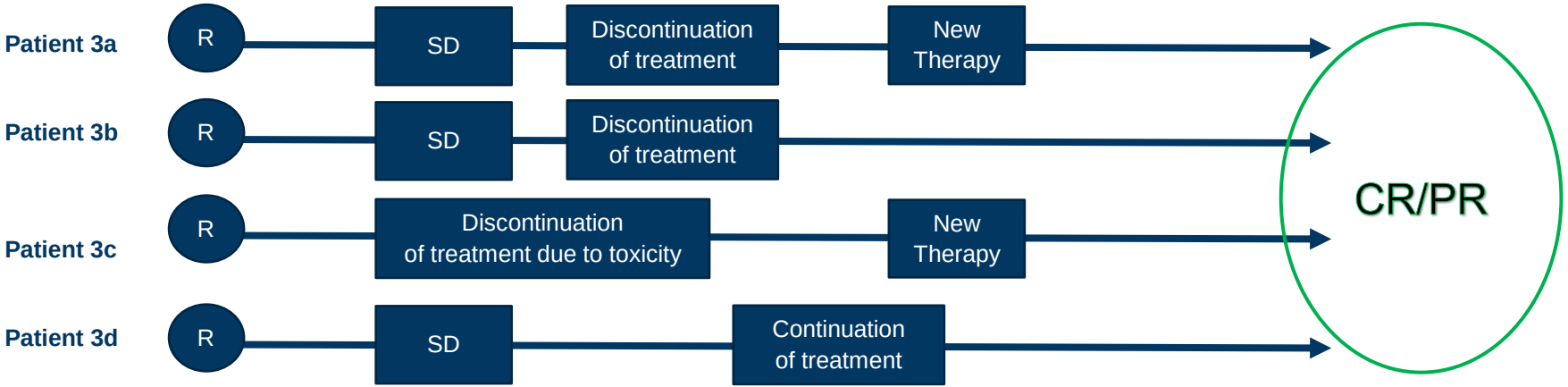
Patients 1b and 2b do receive the benefit driving intervention (HDC/SCT): it would be more consistent that they do not have an event

“Treatment failure” : intercurrent event in 2L HDC eligible patients

- In 2L HDC eligible patients, composite strategy: incorporated into EFS variable
  - Question of interest:
    “Does the treatment enable administration of HDC/SCT and prolong time to progression or death ?”
  - Clinical consistency between short term (enabling HDC/SCT) and long term outcomes is based on assumption that 2L treatment benefit hinges on HDC/SCT
  - “Treatment failure” event could be better defined as “no HDC/SCT delivered”, and dated at baseline, to indicate non-benefiting population more objectively
- EFS is a mixed endpoint in 2L HDC eligible patients, assessing the
  - Size of benefiting population (through treatment failure)
  - Duration of benefit (through time to relapse, progression, death)

Challenges : 2L HDC ineligible patient journeys

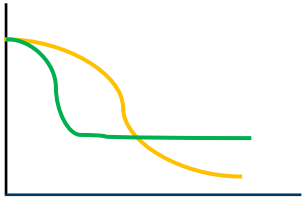
- "Treatment failure" also used in practice in 2L patients ineligible to HDC/SCT
  - Intent of treatment is no longer to receive benefit from HDC/SCT
- What is the clinical significance of SD, of treatment discontinuation or New therapy ?
  - Guidelines still recommend switch of treatment in case of SD
  - Practice likely to depend on SD ↑ or ↓ tumor dynamics
  - "Treatment failure" may need to be refined and depend on mode of action and question of interest



What if all those patients are in CR/PR thenafter ?

“Treatment failure” : intercurrent event in 2L HDC ineligible patients

- In 2L HDC ineligible patients, composite strategy: incorporated into EFS variable
  - Question(s) of interest:
    “Does the treatment enable the patient to remain in response on study treatment and prolong time to progression or death ?”
  - Clinical consistency between short term (treatment failure) and long term outcomes (PD/Death) less easy to identify
    - several clinically different situations may lead to an event
    - could be driven by treatment mode of action (e.g., is tumor response essential to benefit ?)
  - Possible challenging result interpretation:
    - High response rate with short duration, vs.
    - High treatment failure rate with cure of responders



"Treatment failure" : intercurrent event in 2L HDC ineligible patients

- In 2L HDC ineligible patients, treatment policy strategy: focus on PD/Death, as PFS
  - Question of interest:
    "Does the treatment prolong time to progression or death regardless of tumor response, treatment interruption, administration of new therapy ?"
  - Focus on long term clinical outcome of the patient, with "Treatment" defined as the study drug followed by any subsequent treatment received
- In 2L HDC ineligible patients, hypothetical (or "while on study treatment") strategy
  - Question of interest:
    "Does the treatment prolong time to progression or death, in scenario when new treatment would not be available ?"
  - "Treatment failure" = new therapy
    - hypothetical scenario of "if SD would not occur" clinically irrelevant
  - Greater focus on the "pure" pharmacodynamic effect of the treatment

Event Free Survival (EFS) in 2L Lymphoma

- Time for a systematic and thorough cross-functional estimand discussion
- What is the clinical question of interest
  - Is the treatment active on lymphoma (pharmacodynamic effect) , enabling curative intervention (in eligible patients), or providing long term benefit ?
- Intercurrent events
  - Greater granularity of “treatment failure” components
  - Impact may differ depending on disease/treatment setting
  - Could be better defined by observed clinical facts instead of proxies (e.g., no HDC/SCT administered, confirming interpretation of intercurrent event)
- Comparison of different complex treatment strategies: e.g., CAR-T vs. HDC/SCT, bispecific Ab vs. CAR-T...
  - Events & intercurrent events possibly defined by treatment
  - Based on clinical relevance vs. intent of treatment strategy, and type of comparison
  - Impact on possible bias, lack of equipoise, to be assessed

Conclusion

- Complex “historical” endpoints require a clinical understanding of their definition
  - Not to be used just “by tradition”
- Estimand thinking key to revisit definitions
  - Definitions possibly specific for each new drug development setting (population, type of treatment, intercurrent events, type of comparison)
- Clinical question of interest, estimand and clinical rationale need to be explicit
  - Articulate assumptions, justify conventions, clarify intended treatment effect
  - Clinical relevance to real patient journeys