Duration of and time to response in the estimands framework

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on behalf of the DOR-TTR subteam

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DOR-TTR subteam

- The *Estimands in Oncology* working group founded a subteam on duration of response (**DOR**) and time to response (**TTR**)
- Members:
  - Hans-Jochen Weber (Novartis)
  - Francois Mercier (Roche)
  - Jiang Li (Beigene)
  - Alexander Todd (AstraZeneca)
  - Oliver Sailer (BI)
  - Steven Sun (Johnson&Johnson)
  - Satrajit Roychoudhury (Pfizer)
  - Godwin Yung (Genentech)
  - Stephen Corson (Phastar)

- This presentation summarizes the views of the subteam on how to embed DOR and TTR into the estimands framework

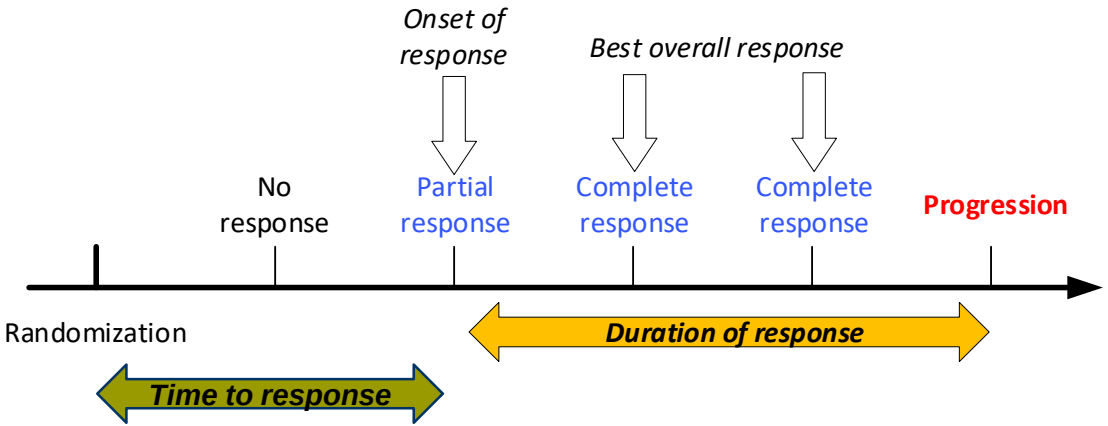
Background

- DOR and TTR are supportive / descriptive endpoints
- Add to response analysis in Oncology
- Historically, analysis defined without explicit consideration of clinical research question or underlying assumptions
  – E.g. censoring rules for DOR simply copied from Progression-free survival (PFS)

- Subteam explores how to embed DOR and TTR into estimands framework
- White paper draft

Response related endpoints

- Most important in single arm setting, also used in RCT
- In Oncology, typically no spontaneous response
  – Response in single arm trial attributed to experimental therapy
- Further description of response by DOR and TTR



Duration of response*

- Time from onset of response to progression or death, whichever occurs earlier (Eisenhauer et al. 2009 Eur J Cancer 45:228-247)
- If response ongoing at end of study, last assessment that indicates absence of progression is considered
- Analysed in conjunction with objective response (ORR)
- Used as characterization of **quality of responses** as **non-transient**
- **Conditional** on being a responder (conditional DOR, cDOR)
- “Not only does the new treatment have an ORR of 40% but the responses are also long-lasting. The median DOR among responders was 7 months”

*here: Duration of overall response per RECIST 1.1

DOR estimand

Attribute/ Question	Estimand reconstructed from traditional analysis
Question	Among responders from population P treated with T, what is the median time from response to progression or death, regardless of treatment discontinuation but assuming absence of subsequent therapy?
Treatment	Treatment condition of interest (and comparator where applicable)
Population	Patients who meet the I/E criteria and who respond to treatment
Endpoint	Time from response to progression or death
Summary measure	Median
Intercurrent events	• Treatment discontinuation: treatment policy • Subsequent therapy: **hypothetical strategy**

DOR estimand: intercurrent event

Attribute/ Question	Traditional estimand	Alternative estimand copying over censoring rule from „EMA“ PFS analysis
Question	Among responders, median time from response to PD/death, regardless of treatment disc. but assuming absence of subseq. therapy?	Among responders, median time from response to PD/death, regardless of treatment discontinuation or subsequent therapy?
Treatment	Treatment condition of interest / comparator	Treatment condition of interest / comparator
Population	Patients who meet the I/E criteria and who respond to treatment	Patients who meet the I/E criteria and who respond to treatment
Endpoint	Time from response to progression or death	Time from response to progression or death
Summary	Median	Median
Intercurrent events	• Treatment disc.: treatment policy • Subseq. therapy: **hypothetical strategy**	• Treatment disc.: treatment policy • Subseq. therapy: **treatment policy**

- Targets treatment sequence: Mixing effect of treatment of interest with effect of subseq. therapy
- Don’t simply copy over censoring rules from PFS, focus on scientific question

DOR estimand: intercurrent event

Attribute/ Question	Traditional estimand	Alternative estimand targeting treatment failure / clinical progression
Question	Among responders, median time from response to PD/death, regardless of treatment disc. but assuming absence of subseq. therapy?	Among responders, median time from response to PD/death or subsequent therapy, regardless of treatment discontinuation?
Treatment	Treatment condition of interest / comparator	Treatment condition of interest / comparator
Population	Patients who meet the I/E criteria and who respond to treatment	Patients who meet the I/E criteria and who respond to treatment
Endpoint	Time from response to progression or death	Time from response to progression, death or start of subsequent therapy
Summary	Median	Median
Intercurrent events	• Treatment disc.: treatment policy • Subseq. therapy: **hypothetical strategy**	• Treatment disc.: treatment policy • Subseq. therapy: **composite strategy**

- Start of subsequent therapy as negative event for treatment of interest becomes part of endpoint

DOR to characterize responses

Patient level preference

- Between two drugs to which patient responds, prefers that with longer DOR (all other things being equal)

Population level preference

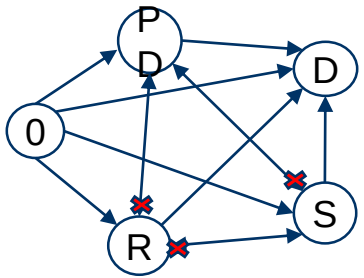
- For drugs with different ORR, trade-off between response rate & cDOR not apparent
- Even if ORR & median cDOR same for two drugs, efficacy might be different
  - E.g. treatments A, B both have ORR=40% but responders are in different subgroups of patients

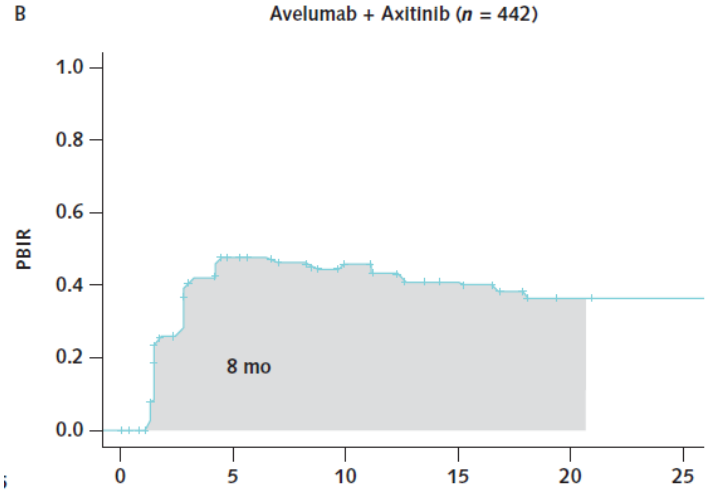
Alternative characterizations: EDOR

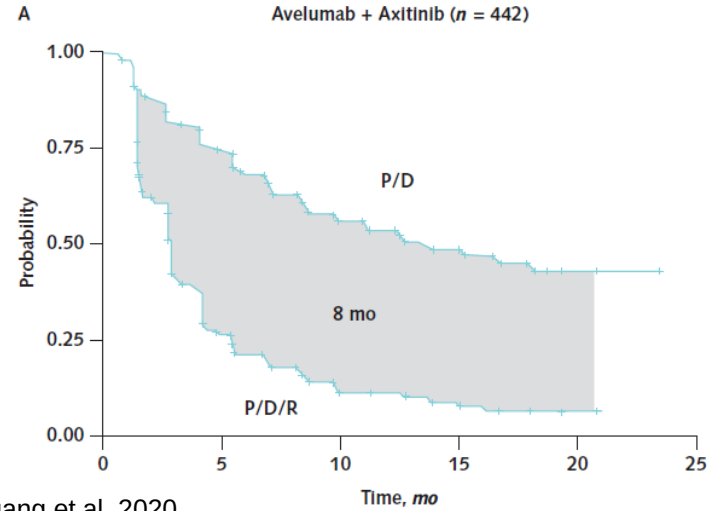
- Since conditional on response, comparison of cDOR between arms not meaningful
- Combine ORR and cDOR in a single **unconditional mean DOR** (expected DOR, **EDOR**)
- Analyse via **probability of being in response function (PBRF)** (Ellis 2008 CCT 29 456-465)
  - Area under PBRF = EDOR
  - Comparison via ratio of EDORs
- Patient level: unconditional DOR=0 if non-responder, else =cDOR
- EDOR more informative than ORR + cDOR? (Huang et al. 2020 Ann Intern Med 173: 368-374)

Alternative characterizations: EDOR

- Multistate model for patient journey
- Model allows for analysis of TTR, unconditional DOR, cDOR, EDOR, PFS and conditional ORR (cORR) for every time point t
  - But not the unconditional ORR







Huang et al. 2020

EDOR estimand

Attribute/ Question	Traditional cDOR estimand	Alternative estimand targeting mean time in response
Question	Among responders, median time from response to PD/death, regardless of treatment disc. but assuming absence of subseq. therapy?	What is the expected time in response, regardless of treatment disc. but assuming absence of subseq. therapy?
Treatment	Treatment condition of interest / comparator	Treatment condition of interest / comparator
Population	Patients who meet the I/E criteria and who respond to treatment	Patients who meet the I/E criteria ~~and who respond to treatment~~
Endpoint	Time from response to progression or death	Time in response (0 for non-responders)
Summary	Median	Expected value
Intercurrent events	• Treatment disc.: treatment policy • Subseq. therapy: **hypothetical strategy**	• Treatment disc.: treatment policy • Subseq. therapy: **hypothetical strategy**

- Same analysis set in treatment comparisons

TTR estimand

Attribute/ Question	Traditional estimand (?)	Alternative estimand
Question	Among responders w/o subseq. therapy, what is the median time to response, regardless of treatment disc.	Median time to response regardless of treatment disc. but while patients have not yet suffered PD or death or switched to subseq. therapy,
Treatment	Treatment condition of interest / comparator	Treatment condition of interest / comparator
Population	Patients who meet the I/E criteria and who respond to treatment w/o subseq. Therapy	Patients who meet the I/E criteria ~~and who respond to treatment~~
Endpoint	Time from start of therapy to response	Time from start of therapy to response
Summary	Median	Median
Intercurrent events	• Treatment disc.: treatment policy • **PD, death, subseq. therapy: principal stratum**	• Treatment disc.: treatment policy • **PD, death, subseq. therapy: while-on-treatment**

- Response to current treatment only possible before PD/death
- Traditional descriptive subset analysis vs. PS model vs. time to event analysis on population level

TTR estimand

Attribute/ Question	Traditional estimand (?)	Alternative estimand
Question	Among responders w/o subseq. therapy, what is the median time to response, regardless of treatment disc.	Proportion of patients with response regardless of treatment disc. but while patients have not yet suffered PD or death or switched to subseq. therapy,
Treatment	Treatment condition of interest / comparator	Treatment condition of interest / comparator
Population	Patients who meet the I/E criteria and who respond to treatment w/o subseq. Therapy	Patients who meet the I/E criteria ~~and who respond to treatment~~
Endpoint	Time from start of therapy to response	Response within *t* months
Summary	Median	Proportion
Intercurrent events	• Treatment disc.: treatment policy • **PD, death, subseq. therapy: principal stratum**	• Treatment disc.: treatment policy • **PD, death, subseq. therapy: while-on-treatment**

- Response to current treatment only possible before PD/death

Summary

- DOR and TTR frequently reported
  - however protocols/ publications often do not describe the estimand (target of estimation)
- Different estimands can address very different clinical questions
  - Estimands should be described to facilitate proper interpretations
- We support the current practice of presenting ORR, DOR and TTR (among responders) together,
  - i.e. there is no clinically meaningful interpretation of (conditional) DOR and TTR if not presented together with ORR.
- Comparison of DOR between treatment groups should take ORR into account. Valid estimands available that integrate both aspects.
  - time in response (EMA, 2017), being in response at *t* months (Ellis, 2008; Garnett, 2013)

DOR-TTR subteam

Thank you!