Need for Treatment strategy as an estimand attribute – A case study of CAR-T in lymphoma

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on behalf of Novartis Team
What is the Estimand framework

*ICH E9 Addendum*

- A structured **framework** that translates the **trial objective** into a precise definition of the **treatment effect** that is to be estimated.

- It aims to **facilitate the dialogue** between disciplines involved in clinical trial planning, conduct, analysis and interpretation, as well as **between sponsor and regulator**, regarding the treatment effects of interest that a clinical trial should address.
Kymriah (CTL019) – Chimeric antigen receptor T cell (CAR-T) therapy

A living drug designed to target CD19+ B cells

Patient’s T cell

CTL019 cell

Anti-CD19 CAR construct

Native TCR

Lentiviral vector

Tumor cell

Dead tumor cell

CD19

Cytokine release

CTL019 proliferation
CAR-T Cell Manufacturing process

1. Leukapheresis
2. Enrichment & Activation
3. Transduction
4. Expansion
5. Formulation & Quality Assessment
6. Administration
Motivating example: Pivotal Phase II Single Arm Study

- Adult relapse or refractory diffuse large B cell lymphoma (DLBCL) patients after 2 systematic therapies
- Primary endpoint: Overall Response Rate (ORR) in All Infused Patients

Screening, apheresis, and cryopreservation

Enrollment

Bridging chemotherapy

CAR-T manufacturing

Restaging, lymphodepletion

CAR-T infusion

Safety and efficacy follow-up

Imaging at months 1, 3, 6, 9, 12...

Dropped out

Achieved CR

CR: Complete response
What is the treatment effect of interest?

- CAR-T infusion? (Infused set)
- Bridging chemo followed by CAR-T infusion? (Enrolled set)
What is the proper baseline?

• Timing of baseline?
• Evidence of disease at baseline?
  – At enrollment, all patients had disease
  – Some patients may have transient response to bridging chemotherapy prior to CTL019 infusion
Regulatory feedback during Kymriah approval process

• EMA: Focused on enrolled patients with evidence of disease at enrollment
  – Sensitivity analyses performed using all enrolled patients regardless of disease status prior to CAR-T infusion for all relevant endpoints

• FDA: Focused on infused patients with evidence of disease prior to infusion
  – Retrospectively identified sub-group among infused patients
    – Excluded patients without documented disease after bridging and prior to CAR-T infusion
CAR-T Phase III study design

Earlier line; patients eligible for allo stem cell transplant (ASCT)

- CAR-T infusion ~ week 6
  - Week 6 for treatment decision
  - Week 12 +/-1w for disease assessment

- High dose chemo + ASCT
- SD/PD by BIRC
- Start CAR-T manufacturing if PD/SD at week 6
- Crossover allowed, if no response ≥ 11 weeks by BIRC
- Bridging chemo as needed
- Lympho-depleting chemotherapy

Follow-up

- SD/PD by BIRC at/after week 11
- Death at any time

1° Endpoint: EFS

Standard of Care (SOC) 1 – 6w
- CR
- PR
- SD/PD by BIRC

SOC 2 – 6w

Manufacturing

Follow-up
Questions to be addressed

• What is the scientific objective?

• What is the treatment effect of interest?
  – Entire strategy or only CTL infusion?
  – What is the right timing of randomization?

• What are the intercurrent events and how to handle them?

• How to test for the presence of a treatment effect and measure its size?
Challenges in defining the treatment effect

• CAR-T treatment not readily available at randomization:
  – Patients in CAR-T arm need to wait, and may take bridging therapy
  – Tumor may progress or respond to bridging therapy, before receiving CAR-T
  – Manufacturing process may fail and patients may not receive CAR-T
  – Delayed treatment effect and possible curative effect are expected: highly non-proportional hazards

• SOC is a complex treatment algorithm:
  – Possibly involving several lines of treatment, including ASCT or not
  – Decisions made based on tumor response to different treatment courses
  – In contrast, CAR-T is a single infusion, regardless of response to bridging therapy

• Crossover needs to be allowed:
  – CAR-T approved in US & EU in patients after 2 or more lines of treatment
  – No other available option for patients failing SOC
Estimand

Defining treatment strategy is a critical step to define other estimand attributes!
Complex treatment strategies

• CAR-T strategy:
  – CTL019 after optional bridging chemotherapy and lymphodepleting chemotherapy

• SOC strategy:
  – Standard of care chemotherapy followed by transplant (ASCT) if eligible

• Patients may not receive final treatment in both arms!!

Population:
All randomized patients regardless of receiving final treatment (CAR-T or ASCT)
Estimand

- All randomized patients defined by I/E criteria

Population

Variable

Treatment Strategy

Summary measure

Intercurrent Event

• ???

• ????

• ????

• ????
Primary endpoint

Event-free survival (EFS):

• Composite event of disease progression / stable disease at or after 11 weeks post randomization; or death at any time
  – Disease progression prior to week 11 is not the final outcome of the treatment strategy
Estimand

- All randomized patients defined by I/E criteria
- Event free survival with SD/PD at or after week 11 or death anytime as event
- Summary measure
- Intercurrent Event
- Treatment Strategy
- ???
- ???
# Intercurrent events

<table>
<thead>
<tr>
<th>Intercurrent event</th>
<th>Handling strategy</th>
<th>Justification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Manufacturing failure in CTL019 arm, or failing to receive SCT in SOC arm</td>
<td><strong>Treatment policy:</strong> Ignore, and follow patients until events or end of follow-up</td>
<td>Intrinsic to treatment strategy</td>
</tr>
<tr>
<td>New cancer therapy before observing event</td>
<td><strong>Hypothetical:</strong> Censor</td>
<td>Not part of treatment strategy</td>
</tr>
<tr>
<td>SD/PD at Week 6</td>
<td><strong>Treatment policy:</strong> Ignore, and follow patients until events or end of follow-up</td>
<td>Only used for treatment decision for SOC arm. Not used for CTL019 arm.</td>
</tr>
</tbody>
</table>
Estimand

- All randomized patients defined by I/E criteria
- Event free survival with SD/PD at or after week 11 or death anytime as event
- Failure/delay to reach final treatment
- SD/PD at week 6
- New therapy
- Event free survival with SD/PD at or after week 11 or death anytime as event
- All randomized patients defined by I/E criteria
- Event free survival with SD/PD at or after week 11 or death anytime as event
- Failure/delay to reach final treatment
- SD/PD at week 6
- New therapy
Summary measures

Challenge:
Non-proportional hazards
– Both arms are on a very similar treatment before CTL is available (in case of bridging therapy).
– Plateauing after ~9 month
Estimation of treatment effect

Which one (or which ones) should be of interest?

- Cox HR
- Weighted HR
- Piecewise HR
- Difference in restricted mean survival time
- Difference in milestone survival
- Difference in median survival
- Other?
Hypothesis testing

What is the primary focus?

Focus on the comparison during all periods after randomization

More focus on comparison during periods where differences are expected

- Regular log-rank test
- Weighted log-rank tests (e.g. Fleming-Harrington)
- Max combo tests
- Piecewise weighted log-rank test (e.g. assigning 0 weight during period there is no difference expected)

Both can be of interest!!
Estimand

- All randomized patients defined by I/E criteria

- Event free survival with SD/PD at or after week 11 or death anytime as event

- Failure/delay to receive final treatment
- SD/PD at week 6
- New therapy

Population

Variable

Summary measure

Intercurrent Event

Treatment Strategy

- Cox HR
- Weighted HR
- Piecewise HR
- Etc.
Acknowledgement

• Amy Racine
• Antonella Maniero
• Bjoern Bornkamp
• David Lebwohl
• Ekkehard Glimm
• Emmanuel Zuber
• Eric Bleickardt
• Evgeny Degtyarev
• Feng Tai
• Frank Bretz
• Jessie Gu
• Kalyanee Appanna
• Kapildeb Sen
• Lisa Hampson
• Mouna Akacha
• Oezlem Anak
• Yanqiu Weng
• Yiyun Zhang
Thank you