Estimand and analysis considerations of phase 3 clinical trials involving CAR-T – A case study in lymphoma

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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

Oncology / CAR-T Program

Business Use Only
CAR-T Cell Manufacturing process

1. LEUKAPHESIS

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

CR: Complete response

Screening, apheresis, and cryopreservation

Bridging chemotherapy

Enrollment

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)
Polling Question:
Which study population would you propose for the primary efficacy analysis?

1. Enrolled set
2. Infused 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 CAR-T 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
Questions to be addressed in the Phase 3 design

• What is the scientific objective?
• What is the treatment effect of interest?
  – Entire strategy or only CAR-T 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?
CAR-T Phase III study design

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

**CAR-T infusion ~ week 6**
- Bridging chemo as needed
- Lympho-depleting chemotherapy

- **6 wk CT**
  - Week 6 for treatment decision
  - Week 12 +/-1w for disease assessment

- **12 wk PET /CT**
  - Crossover allowed, if no response ≥ 11 weeks by BIRC

**Follow-up**
- Bridging chemo as needed
- Lympho-depleting chemotherapy

**Standard of Care (SOC)**
- CR
- PR
- SD/PD by BIRC
- High dose chemo + ASCT
- SOC 2 – 6w

**Follow-up**
- Manufacturing
- Start CAR-T manufacturing if PD/SD at week 6

**1° Endpoint: Event Free Survival**
- EFS event:
  - SD/PD by BIRC at/after wk 11
  - Death at any time

**Oncology / CAR-T Program**

Business Use Only
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:
  – Kymriah 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
  1) disease progression / stable disease at or after 11 weeks post randomization; or
  2) death at any time
- Disease progression prior to week 11 is not the final outcome of the treatment strategy
  - Used for treatment decision only for SOC strategy
  - Not used for CAR-T 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

Population

Variable

Treatment Strategy

Summary measure

Intercurrent Event

• ???

• ???

• ???
## Intercurrent events

<table>
<thead>
<tr>
<th>Intercurrent event</th>
<th>Handling strategy</th>
<th>Justification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Manufacturing failure in Kymriah 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 Kymriah arm.</td>
</tr>
</tbody>
</table>
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

All randomized patients defined by I/E criteria

Summary measure

Intercurrent Event

Population

Variable
**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
- Generalized piecewise weighted log-rank test

**Both can be of interest!!**
Estimand

Population

• All randomized patients defined by I/E criteria

Variable

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

Treatment Strategy

Summary measure

• Cox HR
• Weighted HR
• Piecewise HR
• Etc.

Intercurrent Event

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