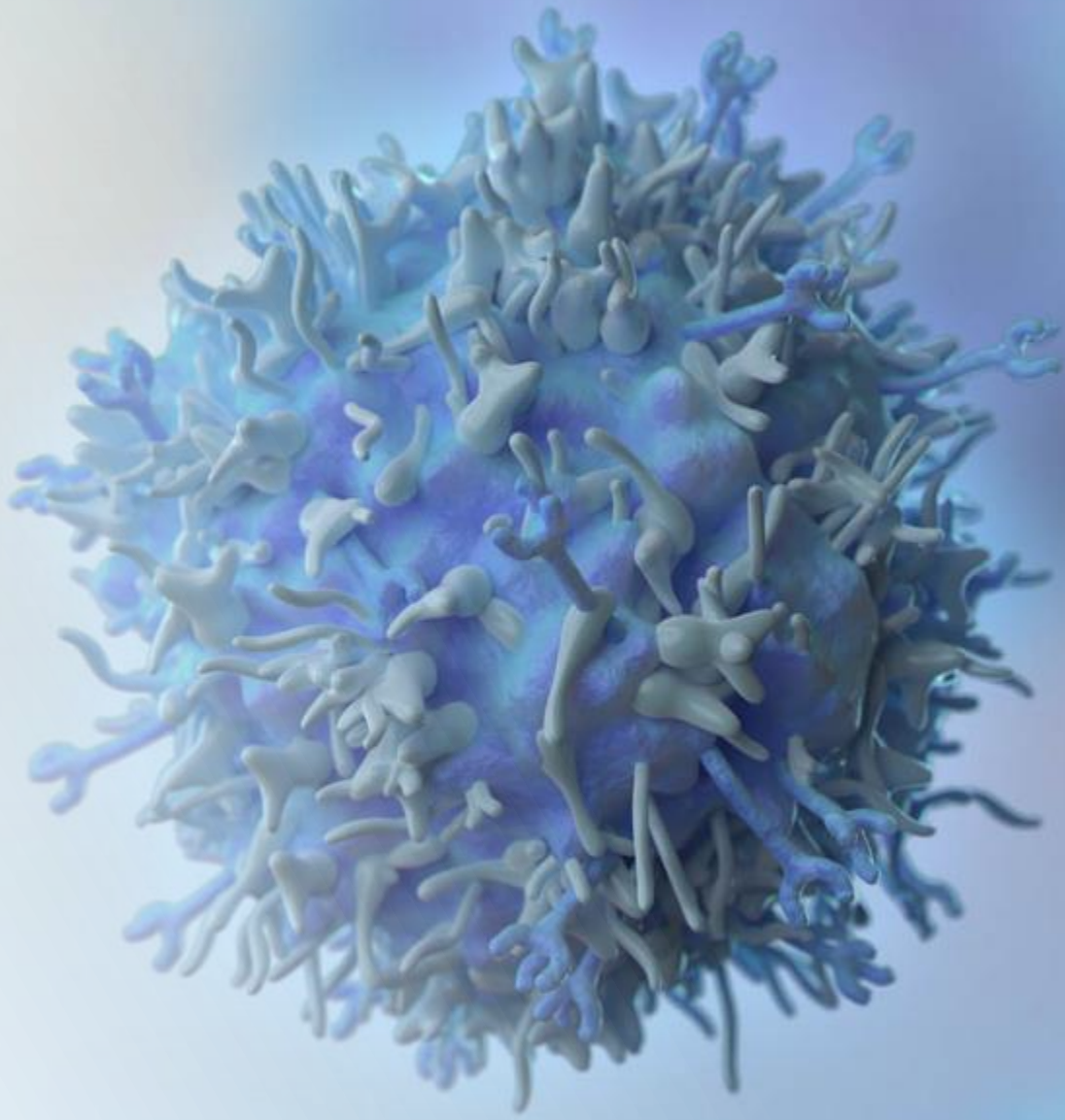
Current and Potential Future Considerations of Single Arm Clinical Trial



Nov 2025

A. Scott Jung MD
Vice President, Clinical Development
Head of Early Development
Kite Pharma, a Gilead company

Background: Utility of Surrogate Endpoints in Oncology Trials

- Surrogate endpoints (endpt) can be measured earlier or more easily, serving as a substitute for clinical outcomes (e.g., survival or quality of life)
  - Relationship to a clinical benefit must be well-understood and ideally be validated
- The FDA may grant accelerated approval (AA) based on a clinical endpt that can be measured earlier than “irreversible morbidity or mortality,” and which is reasonably likely to predict clinical benefit (draft guidance FDA 2024)
  - Whether tumor measures such as overall response rate (ORR) or progression free survival (PFS) are used as an AA or traditional approval endpt depends on the context of the disease, magnitude of benefit, and other factors
- In EU, pivotal trials supporting marketing authorization recommendations through Conditional Marketing Approval (CMA) use both clinical and surrogate endpoints.
  - To be granted CMA, product must be intended to be used in seriously debilitating or life-threatening disease, an orphan medicinal product, or a public health emergencies
- AA and CMA come with post-marketed obligations

Factors for consideration in single arm trials

- Presence of unmet need
  - Limited number of therapies or when available therapies that are used provide little or modest benefit
- Potential use of existing protocol(s)
  - Operational feasibility when First-in-Human studies are focused in patient segments of unmet need
- Opportunity to provide medicine in a timely manner
  - Typically requires fewer number of patients than randomized trials
  - Rare diseases may be difficult in recruitment
- Patient centricity
  - Lack of placebo or standard of care with modest benefit
- Global regulatory considerations for acceptability of various clinical trial designs

Kite
A GILEAD Company

Limitations in single arm trials

- Lack of control group
  - May lead to patient selection bias (investigator bias as well) which may make it difficult to contextualize historical data
- Safety/efficacy profile
  - Especially in the setting of combination therapies, it may be challenging how to attribute particular safety and efficacy profiles to an individual therapeutic agent
- Some key endpoints may be challenging to interpret
  - Endpts such as overall survival may be difficult to compare without direct comparison even with robust historical control due to evolving use and impact of subsequent therapies
  - Censoring methods and visit timing for PFS may differ from historical trial(s)

Challenges of Randomized Control Trials (RCT)

- Transformational Efficacy
  - Clinical equipoise is challenged when investigational therapies induce high and durable responses
  - Risk of drop off may be increased
- Limited therapeutic options
  - Disease or segments where available therapies are few and sub-optimal
- Rare diseases
  - Recruitment may be challenging
- Difficult to implement placebo: e.g. invasive procedures/interventions for delivery of product
- Diseases with long natural histories
  - Impact of subsequent therapies
  - Duration of the study may challenge feasibility

Agrawal et al. *JAMA Oncol*. 2023;9(2):266-272

Trends and Opportunities

- Optimal manner of leveraging real world data
- Novel approach of synthetic control (mixture of data sets)
- Artificial Intelligence Implementation (eg, “digital twins”)
- More data regarding disease biology over time are available
  - Some diseases may have “consistent” outcomes over time

Conclusions

- Multiple factors impact single arm trials and continue to be a considered as a label enabling study design
- Single arm trials have both advantages and limitations
- With increase in amount of potentially accessible data, there may be opportunities to leverage single arm trials in different ways

Acknowledgement

- Special Thanks to
  - Jim Whitmore, Head of Biostats at Kite
  - Lana Shiu, Head of Regulatory Affairs at Kite