SEMINAR ON ADAPTIVE TRIAL DESIGN: CAR T-CELL AND OTHER ONCOLOGIC EXAMPLES

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OBJECTIVES

• Local example of adaptive clinical trial: CAR T-cells
• Other design examples in oncology
DISCLOSURE

• Research support: Bristol Myers Squibb, Celgene,
IMMUNOLOGY PRIMER
Mutations – alteration of antigens

Reduction/lack of antigens

Checkpoint inhibition

Alteration of microenvironment

Alteration of micro-environment

Recruitment of suppressor cells (Treg, MDSC, etc)
T-CELLS IN CANCER IMMUNOLOGY

• Part of Adaptive system and felt to be the most active/important in providing anti-tumoral response
  • Support for importance of T-cells supported by landmark checkpoint inhibitor trials; Ex: ipilimumab, nivolumab, pembrolizumab
CAR T-CELLS
NEXT GENERATIONS

C Pooled CAR T cell product
Multi-CAR T cell
Tandem CAR T cell
Conditional CAR T cell
Split CARs
iCARs
Suicide switch

T CELL

Small molecule
Activation
Inactivation
Small molecule

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PRODUCTION

Apheresis product wash/fractionation
- COBE 2991, Cell Saver 5, LOVO, Elutra, Sepax, Prodigy
- Dynabeads & MPC, ClinMACS, Prodigy

T-cell selection
- AAPCs, Dynabeads, ExpAct Treg beads, TransAct beads, Expamer

T-cell activation
- Retroviral and lentiviral vectors
  - Transposon/transposase
  - mRNA electroporation

Gene transfer
- WAVE, G-Rex, Cell culture bag, Prodigy

CAR-T cell manufacturing

T-cell expansion
- COBE 2991, Cell Saver 5, LOVO, Sepax, Prodigy

T-cell formulation
- Controlled-rate freezer

T-cell cryopreservation

infusion

Patient
T-CELL EXPANSION
PHASE 1B/2 LOCALLY PRODUCED CD19 CAR T-CELLS

**Adult r/r ALL or aggressive NHL**
- Dose Level 1: $1 \times 10^6$/kg.
- Dose Level 2: $2 \times 10^6$/kg.
- Dose Level 3: $4 \times 10^6$/kg.
- Dose Level 4: $8 \times 10^5$/kg.

**Pediatric r/r ALL**
- Dose Level 1: $1 \times 10^6$/kg.
- Dose Level 2: $2 \times 10^6$/kg.
- Dose Level 3: $4 \times 10^6$/kg.
- Dose Level 4: $8 \times 10^5$/kg.

**RP2D selection**

- Adult r/r ALL
- Adult r/r aggressive NHL
- Pediatric r/r ALL
PHASE 2: SIMON 2-STEP

- Step 1: Recruit 4 patients per cohort
  - Provided 1 responder, then continue to accrue; otherwise stop
- Step 2: Recruit additional 9 patients (total n=13)
  - Goal is to find 6 or more responders to reject null hypothesis
  - Assuming 50% response rate, 80% power to identify this
SIMON 2 STEP

• Built in futility analysis allows for stopping study; for IIT studies this allows for early analysis, built-in statistically relevant reporting, but also budget savings and safety if likely heading toward negative outcome
OTHER OPTIONS: SARGENT 3-STEP

• Subsequent design to build in not only futility but also interim efficacy assessment

• More complicated design but useful when endpoint is firmly defined (Ex: in oncology, partial response which is defined as at least 50% shrinkage in lymphoma [Lugano] or 20% in solid tumors [RECIST])
SARGENT EXAMPLE

• Checkpoint inhibitor study, CPI-444 phase 2 with primary endpoint = objective response in solid tumor patients
  • Stage 1 = initial enrollment of 14 patients
  • Stage 2 = expansion for an additional 12 patients (n=26 total)
  • Stage 3 = 2\textsuperscript{nd} expansion for an additional 22 patients (n=48)
SARGENT EXAMPLE

- **Stage 1 = futility assessment**
  - 0 responses, futility met with 95% confidence true response rate is <20%
  - 1 response, triggers 2-stage, 3-outcome minimax design

- **Stage 2 = interim efficacy assessment**
  - If >/= 5 responders out of total 26, then proceed to Stage 3

- **Stage 3 = final assessment**
  - If >/= 12 responders, then null hypothesis rejected
  - If 10 or 11 responders, then inconclusive results
  - <10 responders, then cannot reject null hypothesis
SARGENT EXAMPLE

• 10% probability of rejecting drug if true response is at least 30%
• 5% probability accepting drug if true response is \(\leq 15\%\)
• 80% probability of accepting drug if true response is at least 30\%
MODERN EXAMPLES: BASKET TRIAL

• Product of increased knowledge regarding particular mutations/expressions/deletions and our ability to target them

• Idea is to have one disease but differing groups based on single mutation/change that makes them prone to a particular drug
CONCLUSION

• In oncology, most adaptive designs typically surround futility or interim efficacy analysis
  • Safety
  • Cost

• Multiple adaptive designs exist and appropriate selection is based on refining to clear, easy to answer clinical question
Generating super-soldiers
the production of CAR-T cells

T-cell

CAR-T cell

retroviral vector

Chimeric Antigen Receptor