AUTOLOGOUS CAR-T ARE SUPERIOR TO ALLOGENEIC CAR-T

Mini-Debate 2. June 27, 2025

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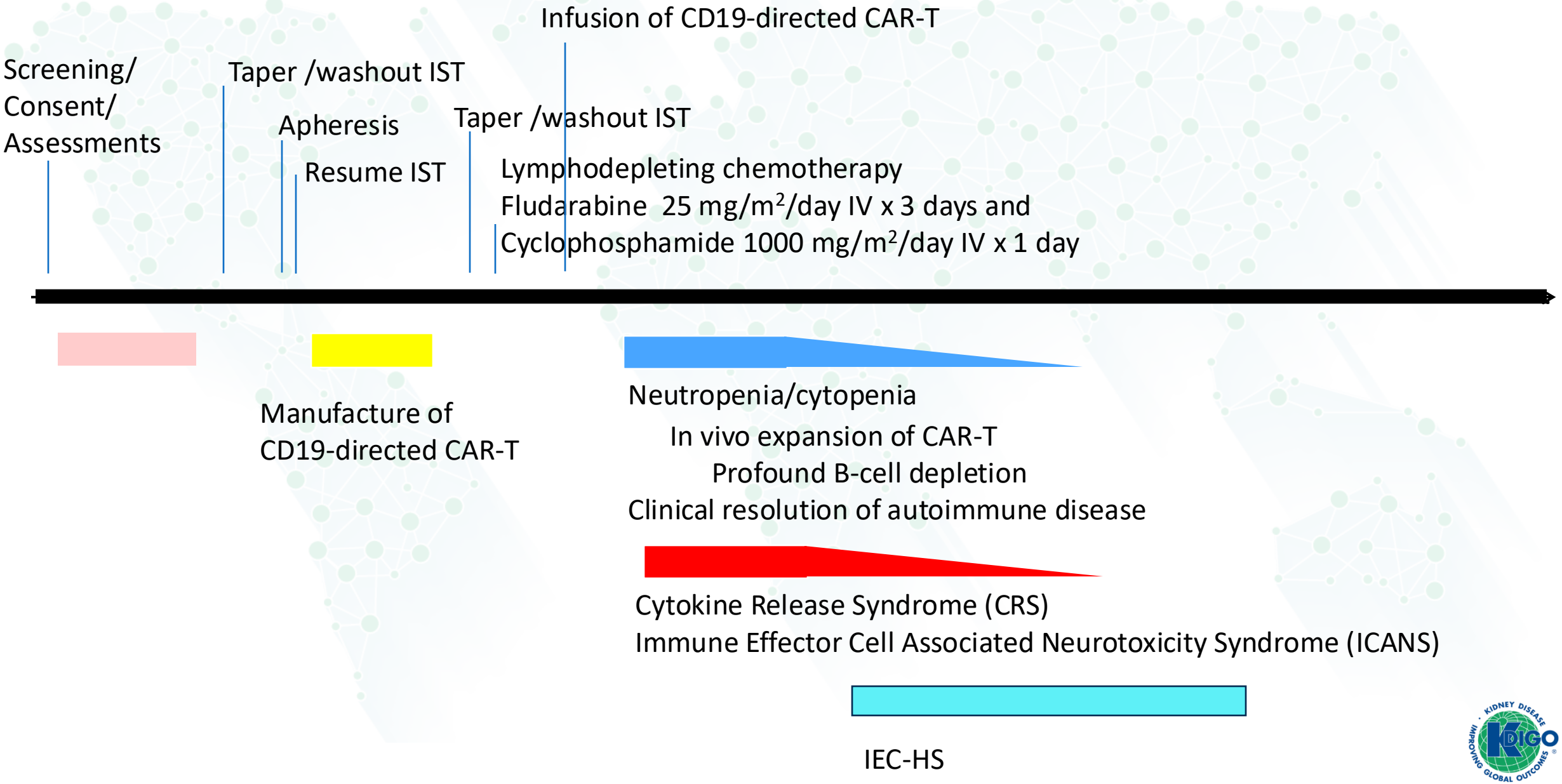
DISCLOSURES

- Research Funding/ Consulting Fees:
- Novartis
- Bristol Myers Squibb
- Cabaletta

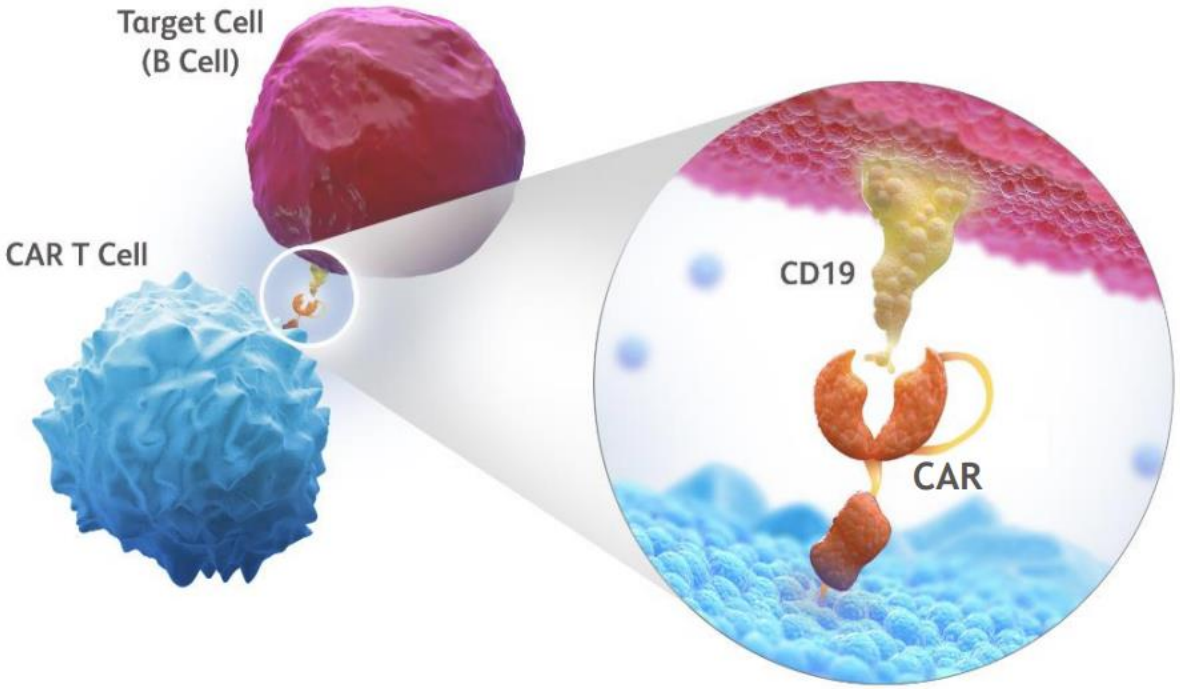
CAR-T for AID treatment timeline



AUTOLOGOUS VS. ALLOGENEIC CAR-T

- Manufacturing systems are well developed, safe, reproducible
- FDA approved licensed product available (CD19 and BCMA)
- Patient-specific therapy
- Manufacturing times are decreasing, less than 2 weeks
- Less immunogenic, simpler, less risk of off target gene mutations
- Lower dose of lymphodepleting chemotherapy
- Auto cells expand in vivo more and persist for longer duration compared to allogeneic
- Less risk of graft-versus-host disease
- Potentially lower risk of infections
- Potentially more efficacy in depleting target cells (deeper B-cell depletion)
- Auto more expensive manufacturing than allo, but ? may achieve longer disease remission/ disease control

Autologous CAR-T wins!



Allogeneic CAR-T cells for Immune-Mediated Kidney Diseases

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Allogeneic CAR-T

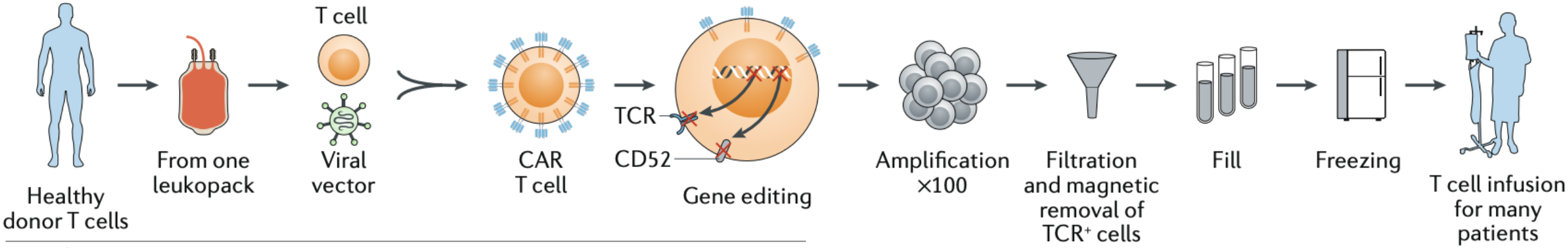


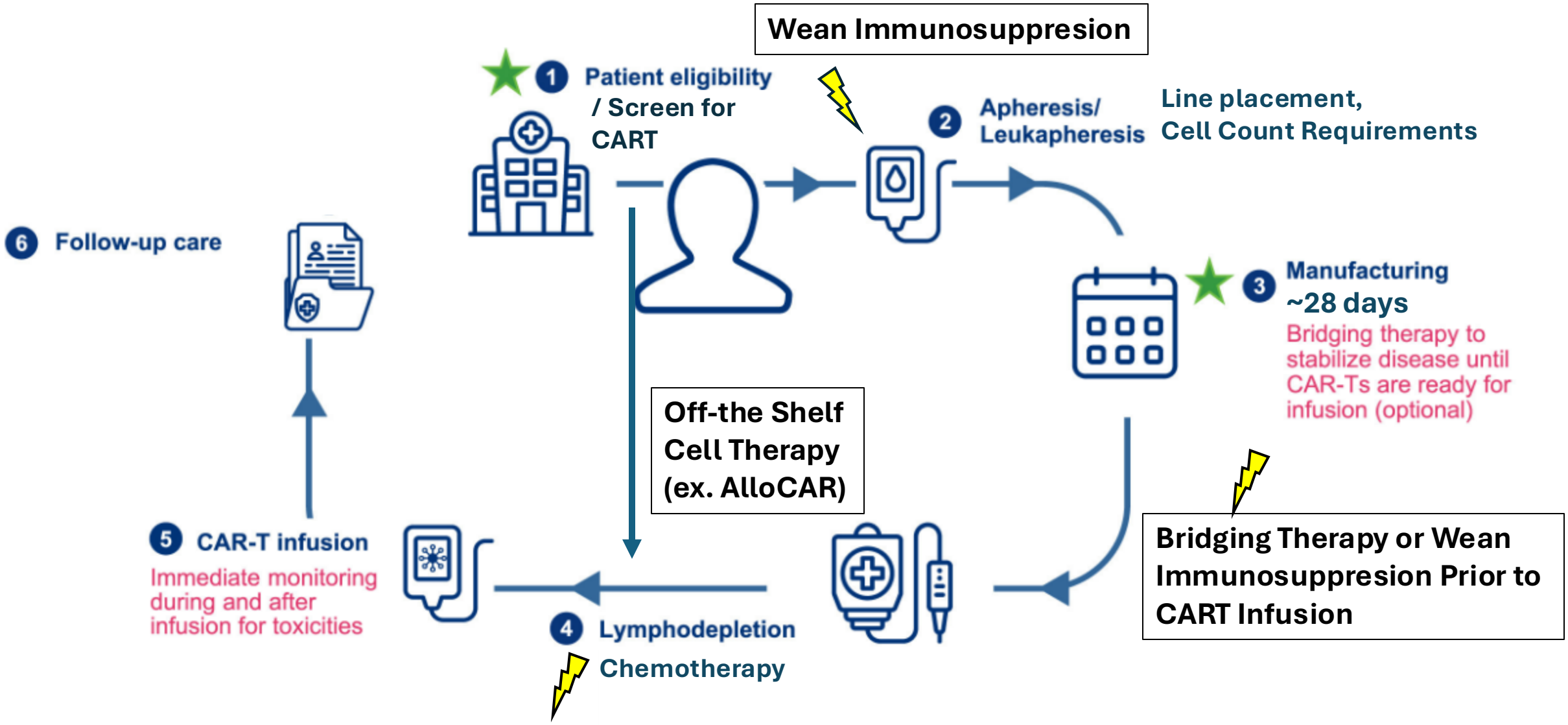
Table 1 | **Comparison between autologous and allogeneic CAR T cells**

Characteristic	Autologous CAR T cells	Allogeneic CAR T cells
Origin of the donor	Patient	Healthy donor
Production and manufacturing process	Complex logistics; delay from leukapheresis to CAR-T cell administration; variations of T-cell characteristics according to the patient's immune characteristics and influence of previous treatments	Scaled-up industrialized process in which a high number of CAR T cells can be produced and cryopreserved from a single donor; batches immediately available for patient treatment; possible standardization of T cell characteristics
Clinical indications	Haematological malignancies (demonstrated activity); solid tumours	Haematological malignancies (ongoing trials); solid tumours
Main issues/risks	Cytokine release syndrome; CAR-related gene modifications; potential long-term side effects (B cell aplasia for anti-CD19 CAR T cells)	Cytokine release syndrome; CAR and/or gene editing-related gene modifications; GVHD; rejection of allogeneic cells; toxicity in the case of intense lymphodepletion
Persistence	Intermediate to long (months to years)	Short to intermediate (weeks to months)
Redosing	Limited by the number of cells	Not limited by the number of cells but risk of alloimmunization
Cost	Currently high (may decrease in the future)	Expected to be moderate

Rafiq Nature Reviews Clinical Oncology *2020*

Pressure Points
(Potentially Modifiable)

Lifecycle of CART



Why Allogeneic CAR-T for autoimmune disease?

- Simplified manufacturing/distribution
- Significantly decreased costs
- Off the shelf (don't need to wait to manufacture for a patient requiring tx)
  - Speed – Screen, Wean, LD Chemo, Infuse
  - For autoimmune disease importantly, **less time and complication required for immunosuppression weaning.**
- Better availability for non-tertiary academic centers

Drawbacks to AlloCART?

- Clinical Trials in Cancer - Reduced efficacy of AlloCART
  - Less expansion; less persistence; host rejection

HOWEVER:

- Limited CAR-T cell expansion/persistence with deep B-cell depletion may all that is required in autoimmune dz
  - Quote "immune reset'
  - Decreased persistence = less immunosuppression
  - No large tumor burden, less expansion is adequate.
- Novel techniques:
  - CRISPR base editing - reduces risk of genotoxicity when T-cells undergo multiple DNA edits seen with CRISPR-Cas9
  - Immune cloaking (ex. HLA knockdown)