Avanserte Terapier- Regulatoriske utfordringer

Rune Kjeken

Norwegian Medicines Agency

INNFØRES: Etter tirsdagens møte i Beslutningsforum innføres ni metoder. Helse Vest-direktør Inger Cathrine Bryne forteller at CAR-T-behandling blant de som fikk ja.
Foto: Vidar Sandnes

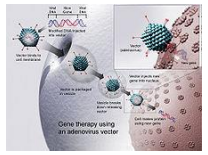
Innfører CAR-T-behandling for pasienter med lymfekreft

Dagens Medisin
18-10-22

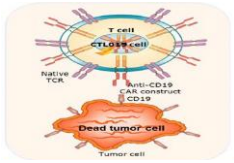
What are ATMP‘s ?

Gene therapy

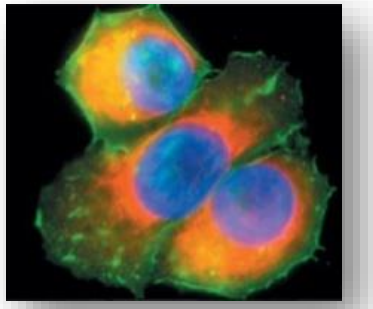
In vivo



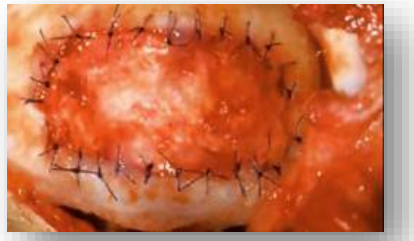
Ex vivo



Somatic cell therapy

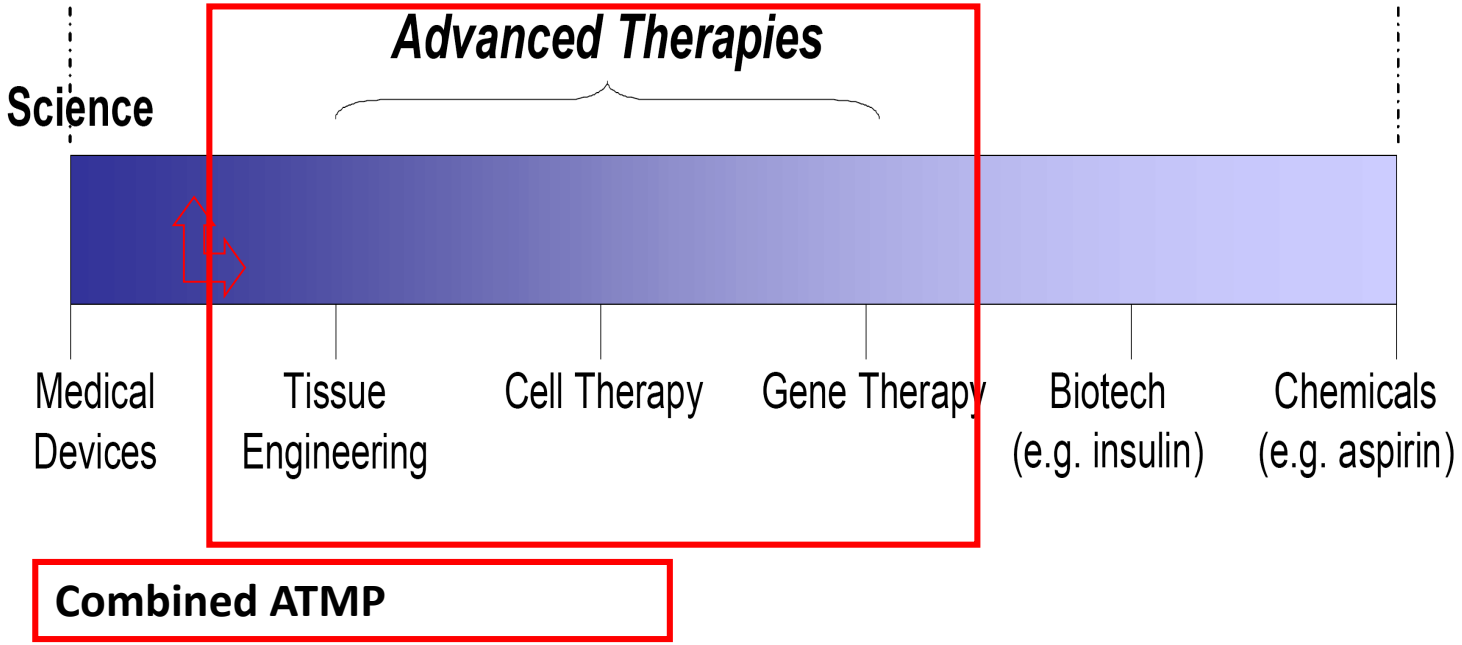


Tissue engineered product

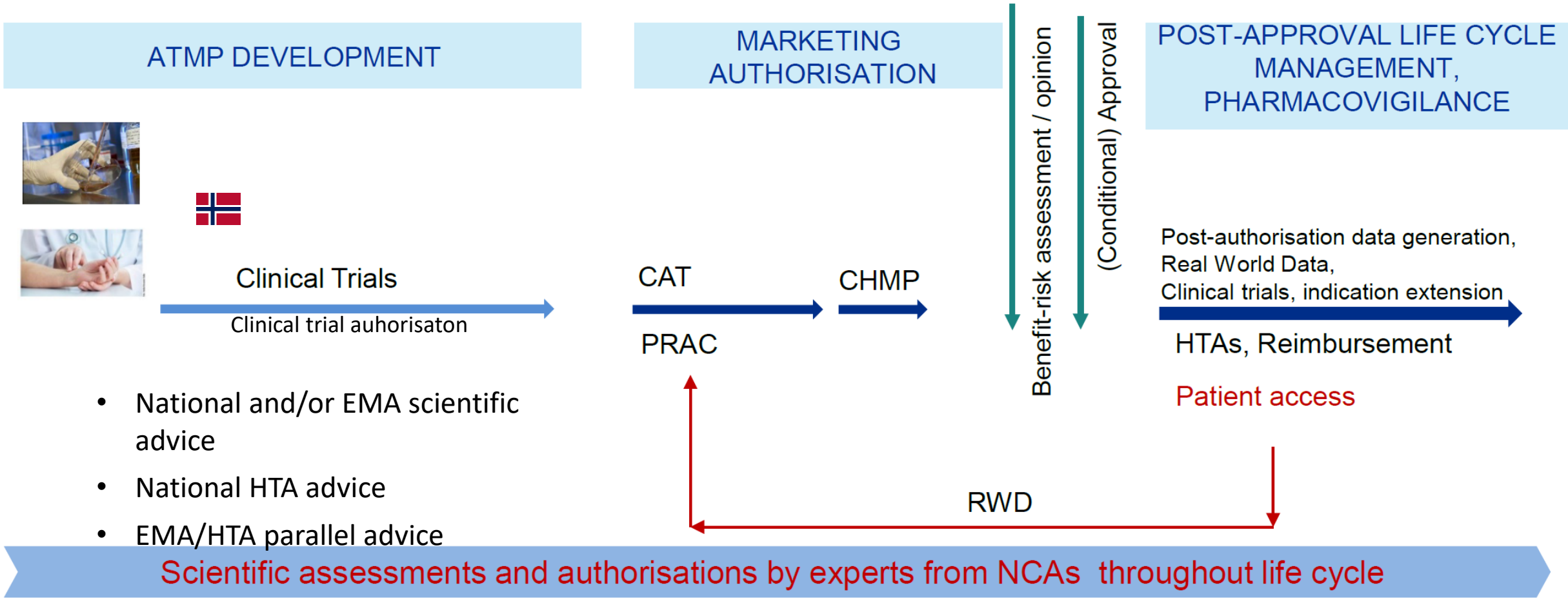


Advanced Therapy Medicinal Products Regulation (EC) 1394/2007

- Defines 3 product classes
- Stipulates EU authorization via the centralized procedure, coordinated by European Medicines Agency EMA
- Assessment by national experts in the specialized Committee for Advanced Therapies (CAT)
- Principles of existing legislation apply: quality, safety, efficacy, pharmacovigilance, post-authorisation patient follow-up

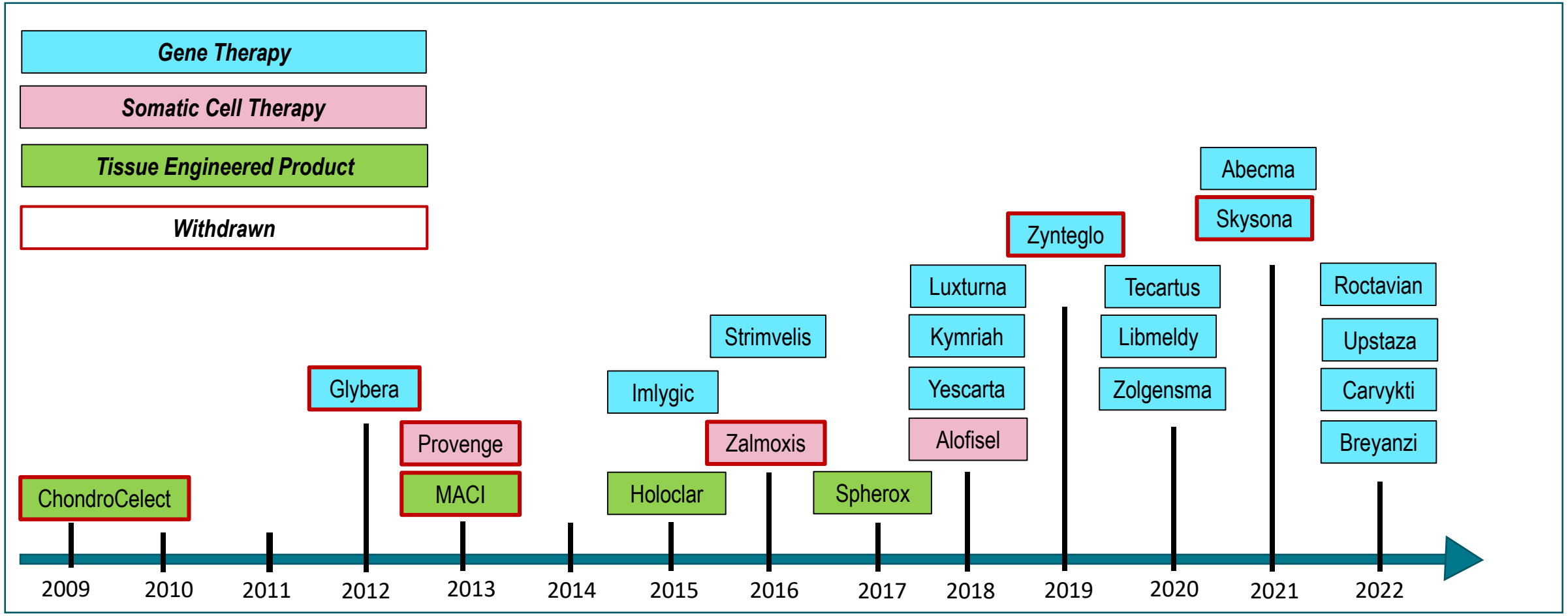


The ATMP life cycle



M. Schüßler-Lenz

Approved ATMP‘s in EU 2022



M. Schüßler-Lenz et al; Pharmakon 8.2022

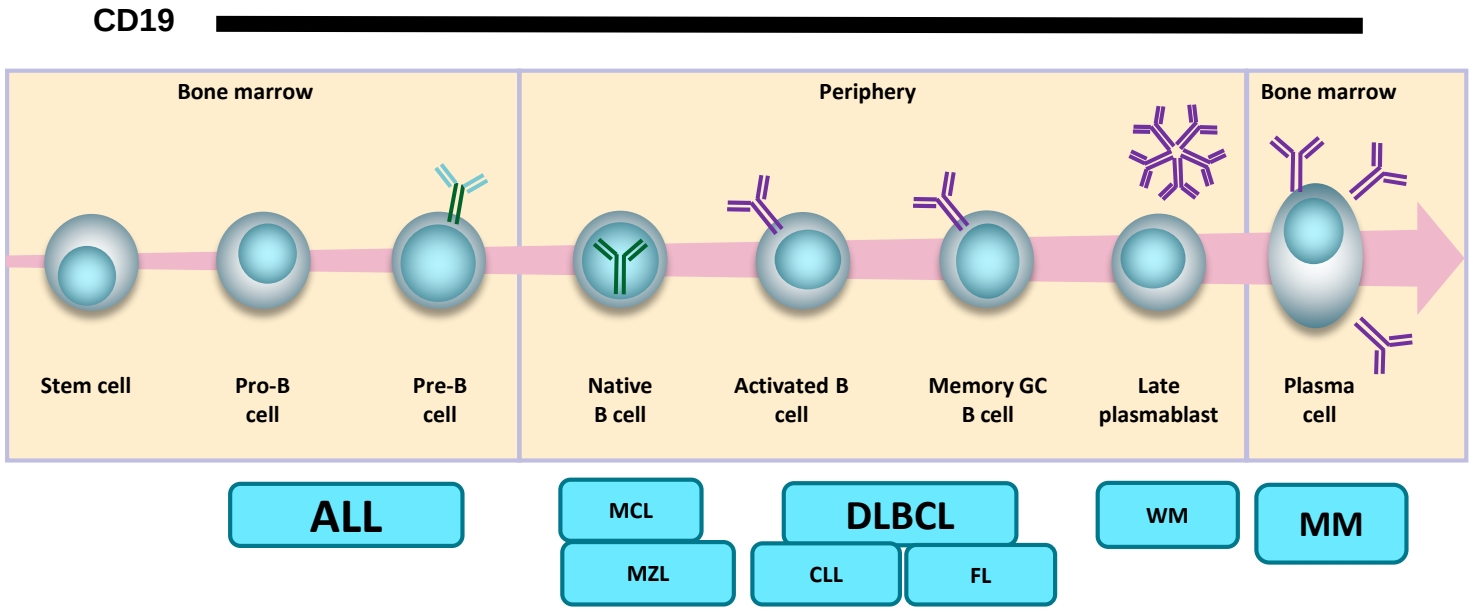
CART‘s in EU

Name	Target	Indication
Kymriah	CD19	pALL, DLBCL, FL
Yescarta	CD19	DLBCL, FL
Breyanzi	CD19	DLBCL
Tecartus	CD19	MCL, ALL
Abecma	BCMA	MM
Carvikty	BCMA	MM

pALL; paediatric Acute lymphoblastic leukaemia
DLBCL; diffuse large B-cell lymphoma
FL; Follicular Lymphoma
MCL; mantel cell lymphoma
MM; multiple myeloma

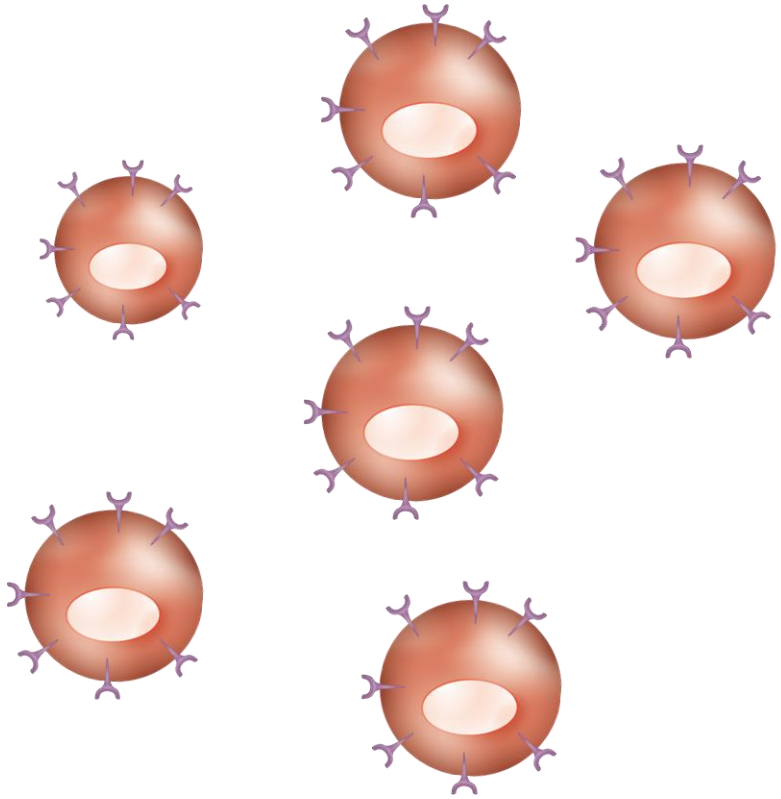
CD19: important target for CAR T-cell therapy in treating B-cell malignancies

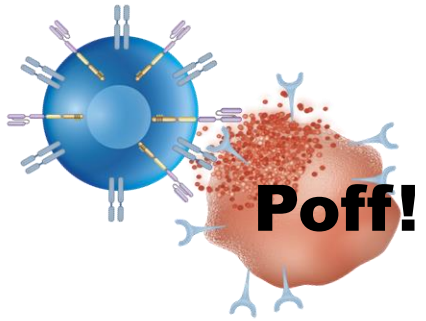
- CD19 is expressed on B cells and B-cell precursors and is not expressed on bone marrow stem cells or other tissues



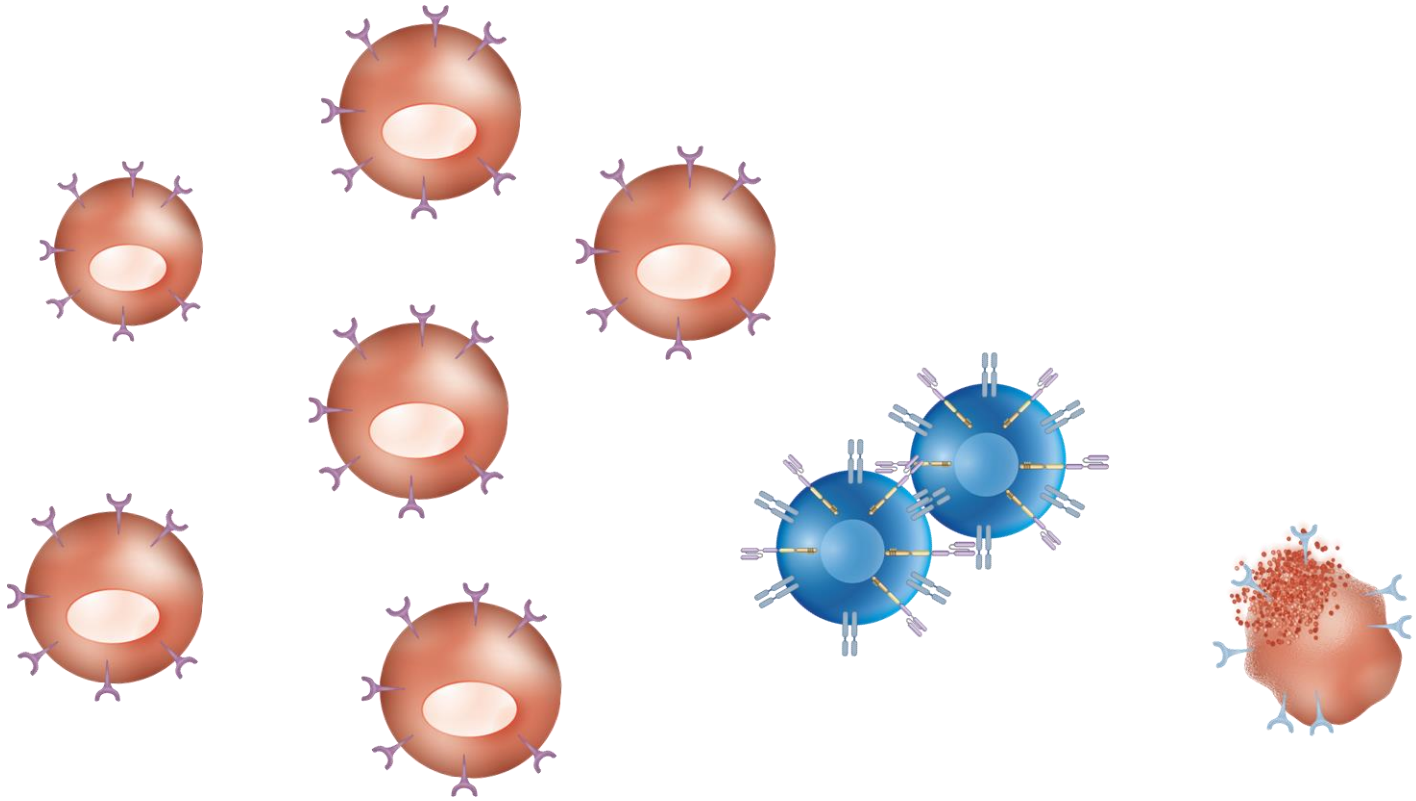
Adapted from Blanc V et al, Clin Cancer Res; 2011; 17(20); 6448–58

CAR-T Mechanism of Action

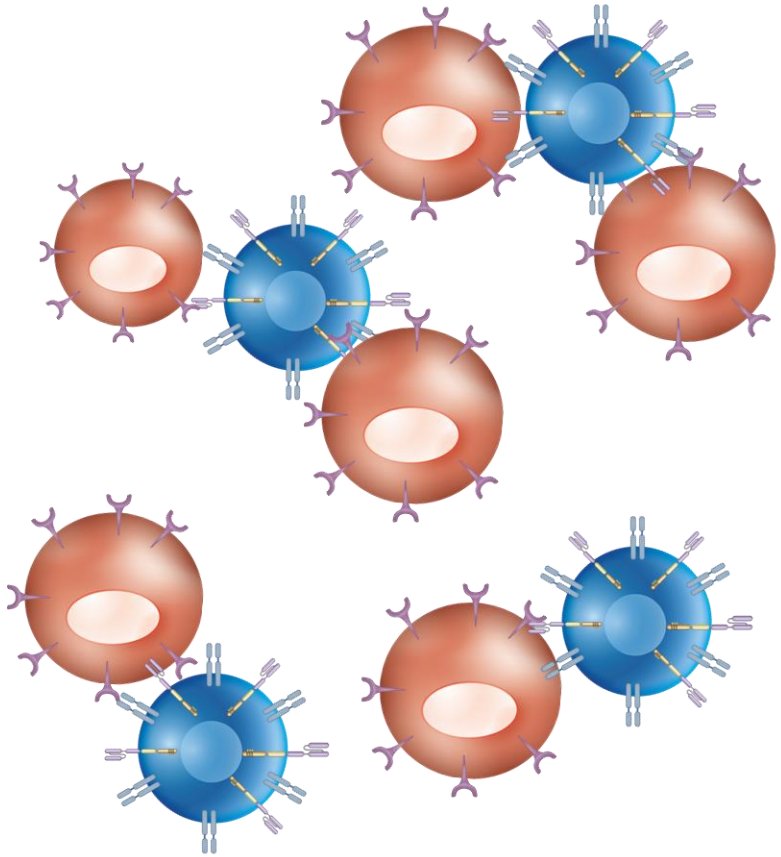


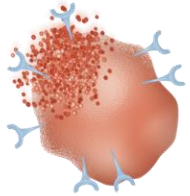


CAR-T Mechanism of Action

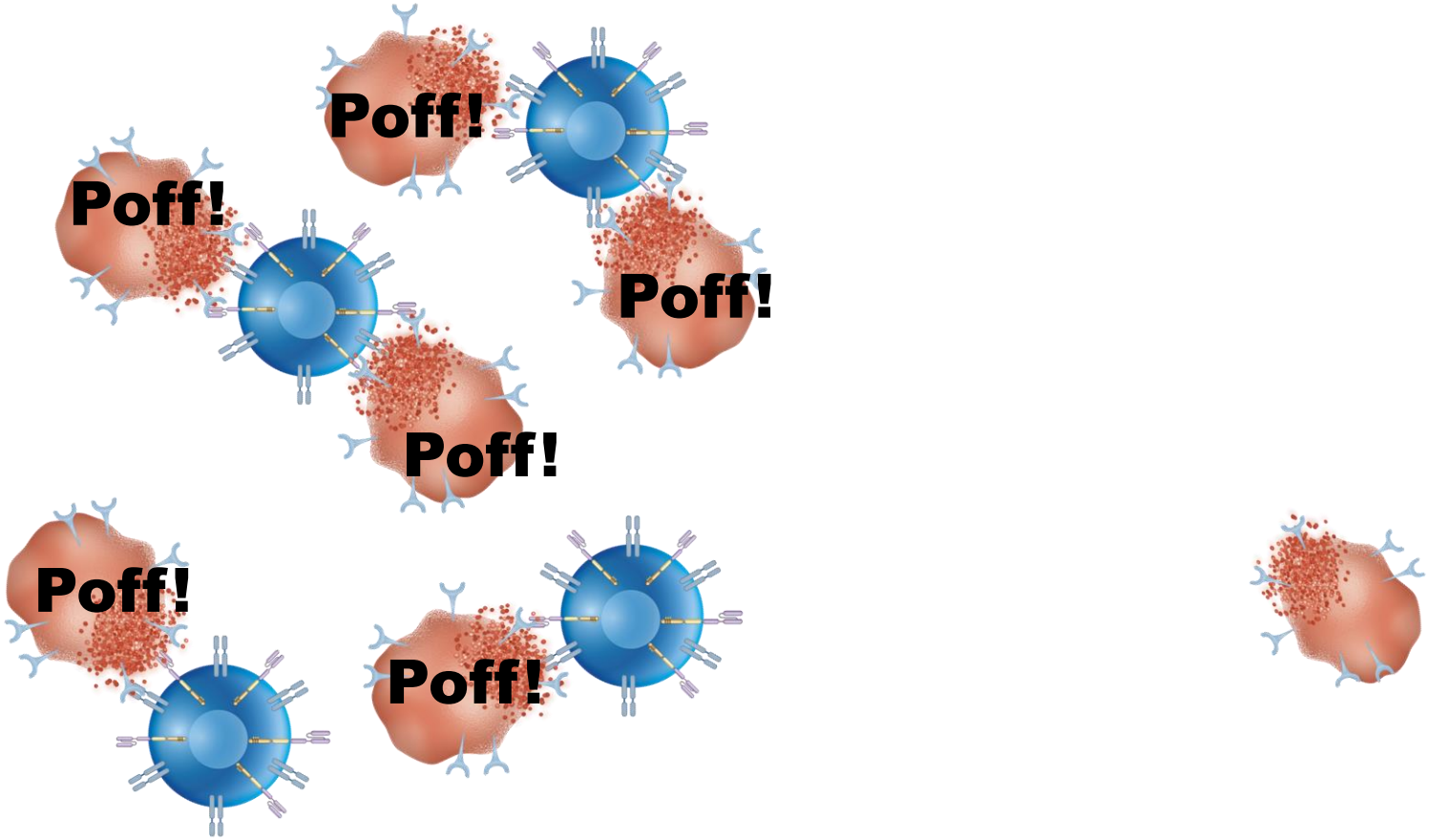


CAR-T Mechanism of Action



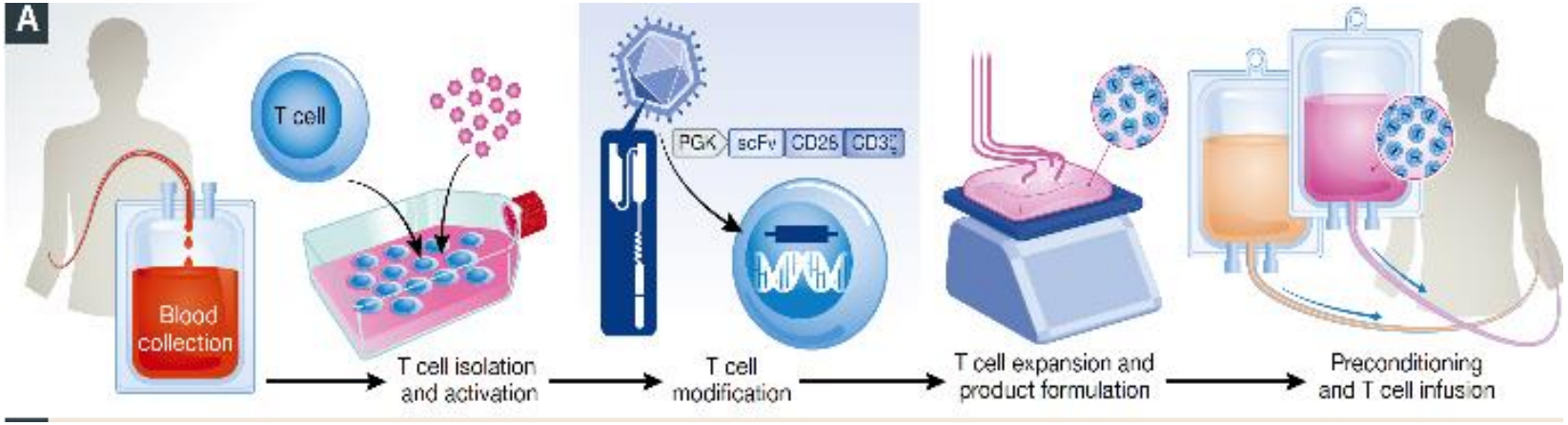


CAR-T Mechanism of Action



Regulatory particularities for CARTs: Quality aspects

- complex products with complex manufacturing
- Individualised “person specific” therapies
- strict requirements for chain of custody: one patient = one batch
- Sterility
- Consistency
- Routines to be in place for release of “Out of spec (OOS) batches” for person specific cell therapies
- Strict requirement for long term safety follow up for integrating vectors due potential/hypothetical risk of insertional mutagenesis/cancer



CAR-T: Over halvparten av pasientene hadde ikke tegn til kreft

66 prosent av pasientene i ELARA-studien fikk komplett remisjon etter å ha gjennomgått CAR-T-behandling.

Julie Kalveland
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LANGT ETTER. – Vi har store forventninger nå ettersom vi ligger langt etter de fleste europeiske land når det gjelder godkjenning av denne typen behandling, sier overlege Arne Kolstad.
Foto: Vidar Sandnes

CAR-T-behandling blant 14 nye metoder til vurdering: – Vi har store forventninger

– Dette er pasienter som vi ikke har noen realistisk kurativ behandling tilgjengelig til i dag. Erfaringene med CAR-T-behandling tilsier at rundt 40 prosent vil kunne få en varig remisjon, sannsynligvis er de kurert, sier overlege Arne Kolstad.

Henriette Berthelsen Isachsen
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Publisert: 2022-10-14 — 06:00

Tirsdag skal direktørene i de fire regionale helseforetakene ta stilling til 14 metoder. Blant disse er CAR-T-behandling – en form for immunterapi basert på at celler høstes fra en kreftpasient, endres, og så settes tilbake i pasienten.

– I fagmiljøet har vi fått et inntrykk av at vi er veldig nær en godkjenning fra Beslutningsforum. Begge disse CAR-T-produktene har vært til behandling over veldig lang tid og vi har ventet på å få en godkjenning, i det minste av én av dem, sier Arne Kolstad, overlege på Sykehuset Innlandet Kreftavdelingen og professor ved NTNU.

Dagens Medisin har tidligere omtalt et ønske fra fagmiljøet om å få innført CAR-T-

Foto: Tonny Hoelig

CAR-T-terapi: – Sykdommen gikk kraftig tilbake hos mange av pasientene

Resultater fra en studie på CAR-T-behandling hvor norske pasienter har deltatt, skal presenteres på verdens største kreftkongress i juni.

Julie Kalveland
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DER HAKET I FOR PASIENTENE: Overlegene Alexander Fosså (t.v.) og Arne Kolstad er bekymret for at pasientene ikke har tilgang til ny behandling mot lymfekreft.
Foto: Vidar Sandnes

Vil ha «fast track» for ny behandling

Kreftlegene Arne Kolstad og Alexander Fosså mener at det bør innføres en betinget godkjenningsordning for å gi rask tilgang til nye, lovende kreftbehandlinger i Norge.

Julie Kalveland
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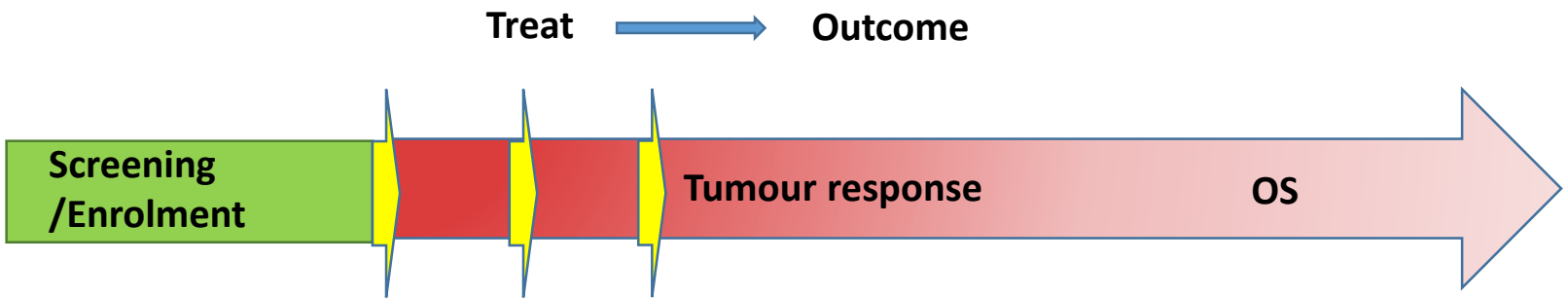
Publisert: 2021-06-18 — 06:00

Generic single arm cancer trial with conventional drug



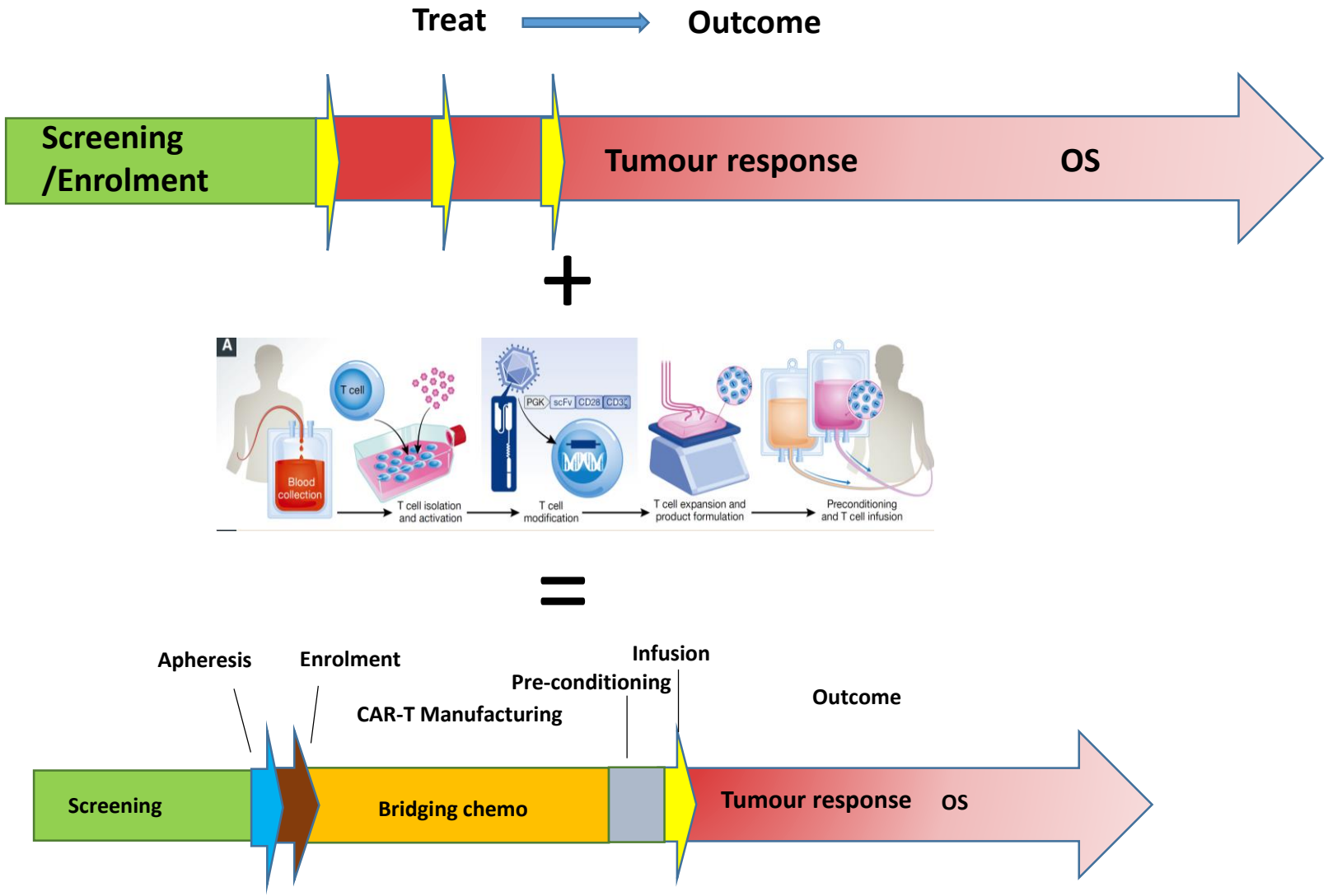
VS

Historical control as benchmark

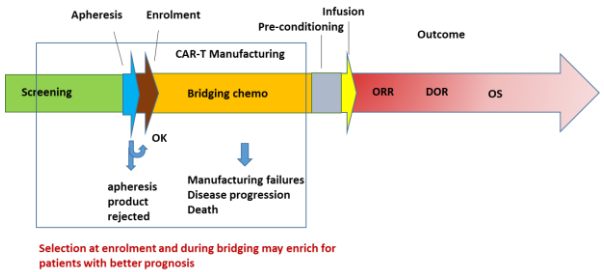
- Less robust data
- Surrogate endpoints- uncertainty regarding long term benefit
- Uncertainty regarding long term safety
- Uncertainty regarding historical comparison

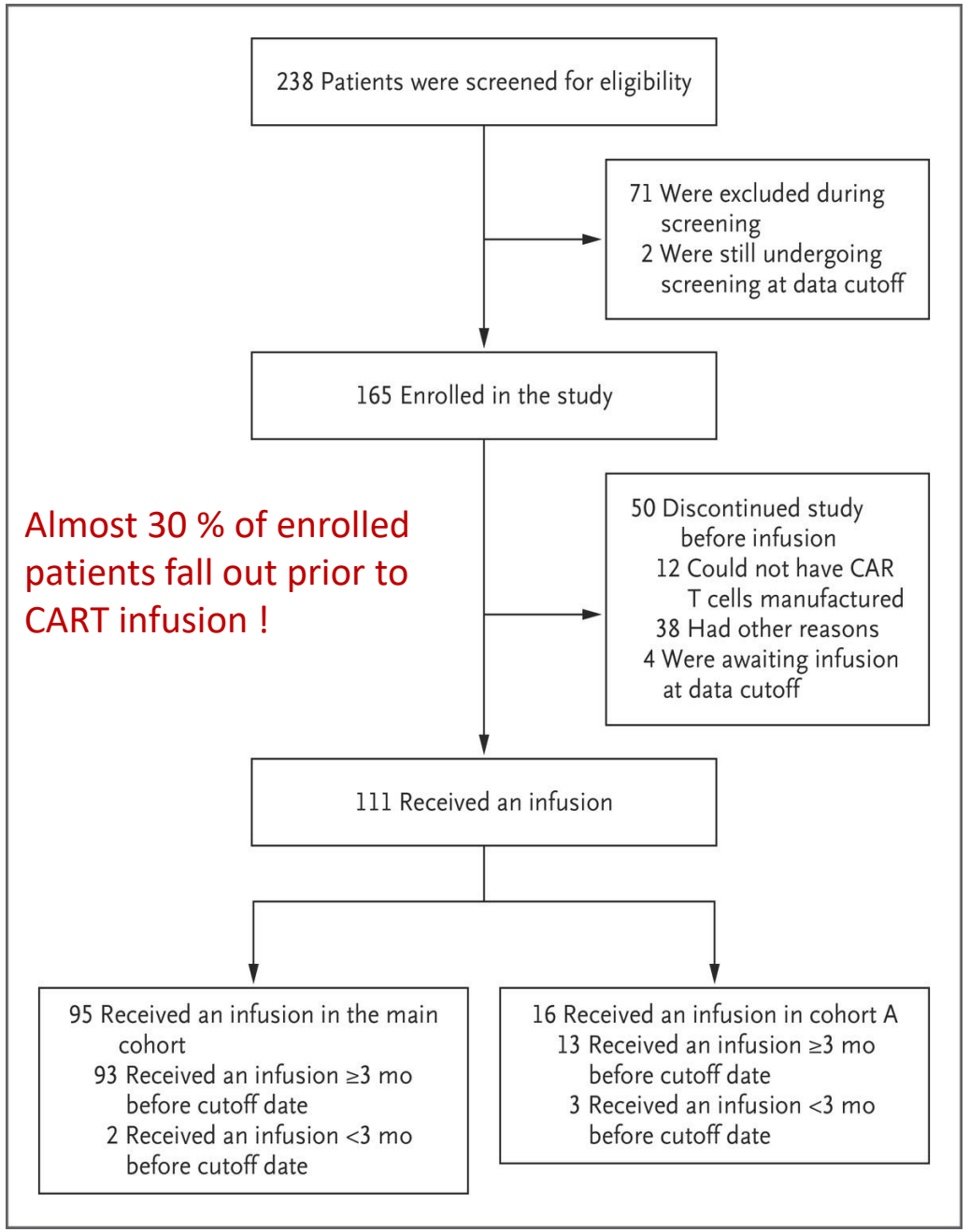
<u>Hard to justify a high price = delayed patient access</u>

CART's add complexity to clinical studies



Patient flow Juliet study (Kymriah)



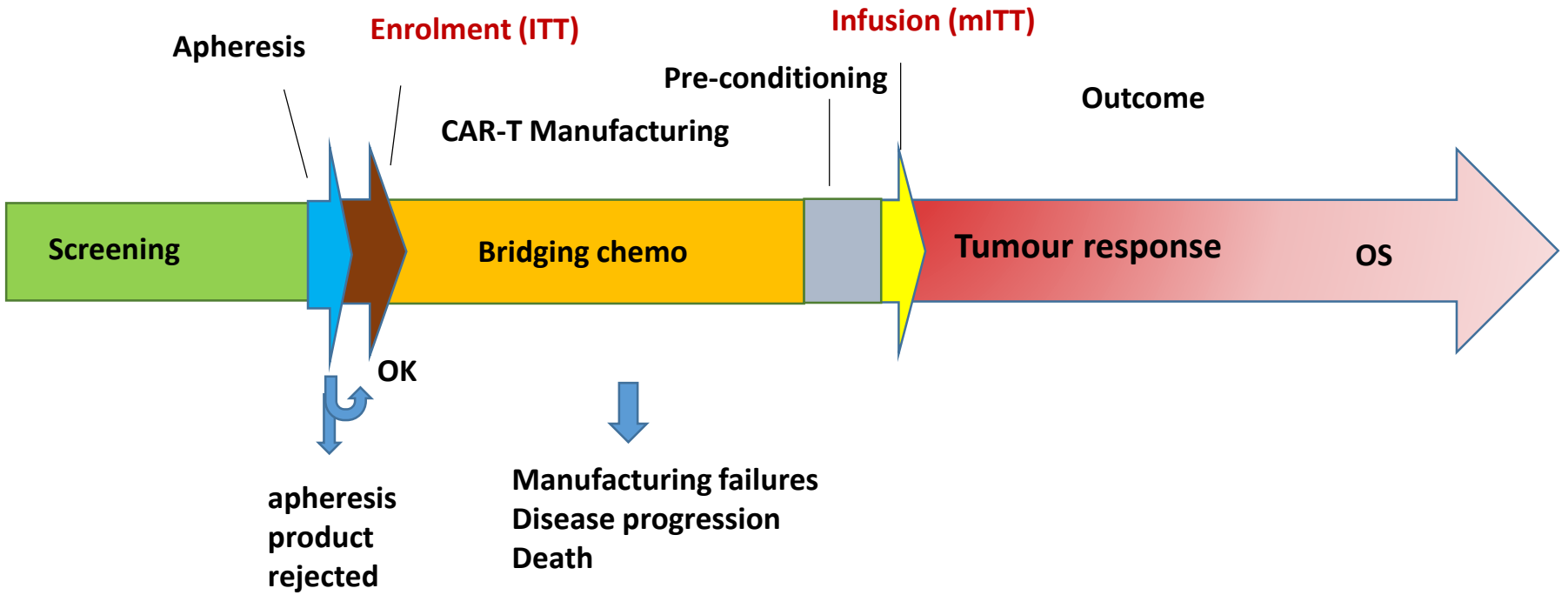


Almost 30 % of enrolled patients fall out prior to CART infusion !

Schuster et al. NEJM 2019

Single arm cancer trial CART

In what patient population to measure outcome?
Enrolled (ITT) or infused (mITT)?



Remedies to resolve remaining uncertainties when data is not considered «comprehensive» due to single arm trial design

1. Data from longer follow up for Pivotal study.
2. Prospective, observational study based on data from registry and matching patient characteristics and efficacy outcome measures in line with pivotal single arm study.
3. Conduct larger Randomized Controlled study in earlier treatment line to “confirm” data from later line.

CAR-T viste ikke bedre effekt i andrelinje for B-cellelymfom

CAR-T behandling hadde ikke bedre effekt enn kjemoterapi og stamcellebehandling i andrelinje for behandling av Diffust storcellet B-cellelymfom og Høygradig storcellet B-cellelymfom. – Overraskende, sier overlege Harald Holte ved OUS.

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Publisert: 2021-12-14 — 15.00

Summary

- Single arm clinical trials with CARTs suffer from a number of limitations
- Not All CART's are created equal
- Need more and better data (ultimately RCT)
  - Long term efficacy outcomes
  - Long term Safety
  - Quality of life
- New CART's should ideally be tested against approved in RCT's (in practice impossible, due to cost, logistical challenges etc)
- Market Access ≠ Patient Access (CARS are (too) expensive)

But

- **Many of the challenges above will ultimately be resolved.**
- **We are slowly getting more & better data,**
- **More efficient manufacturing (hopefully also cheaper)**
- **More competing products on the market**
- **Higher cost effectiveness will increase patient access**

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