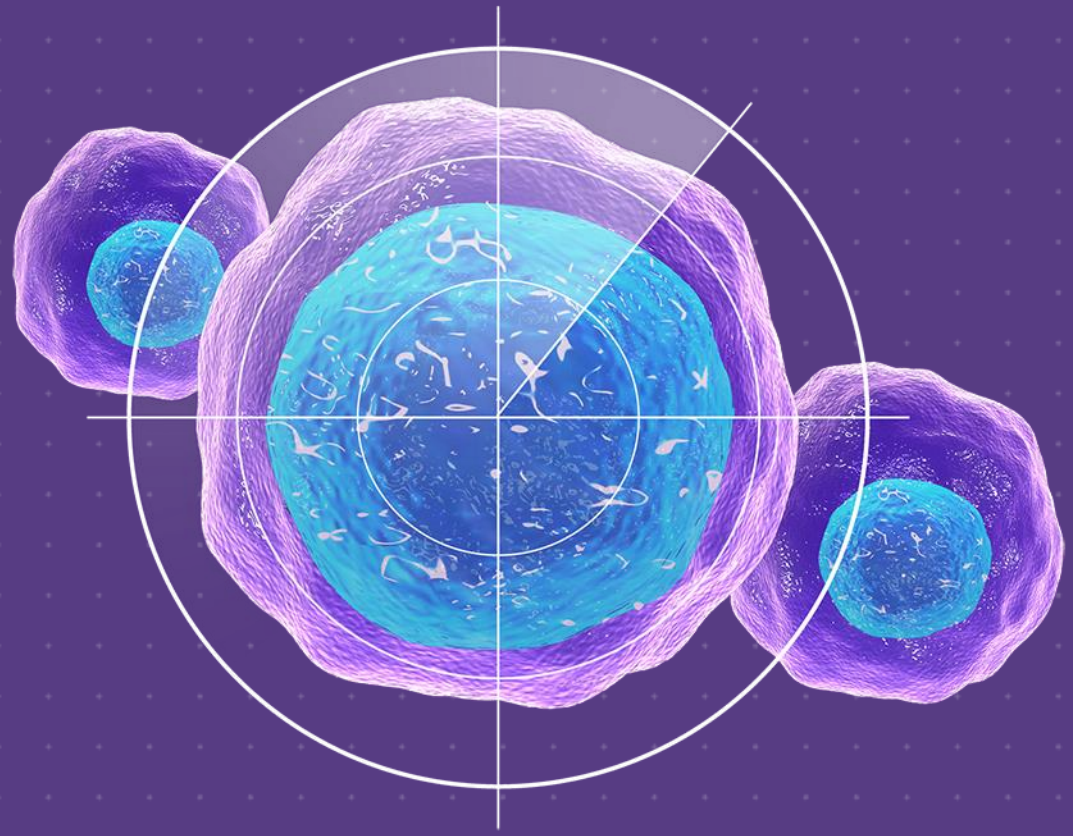
LymphomaHub

VIRTUAL SATELLITE SYMPOSIUM

How I treat relapsed/refractory disease – DLBCL and CLL

November 8, 2020



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Case 1:
Patient with R/R DLBCL – European perspective

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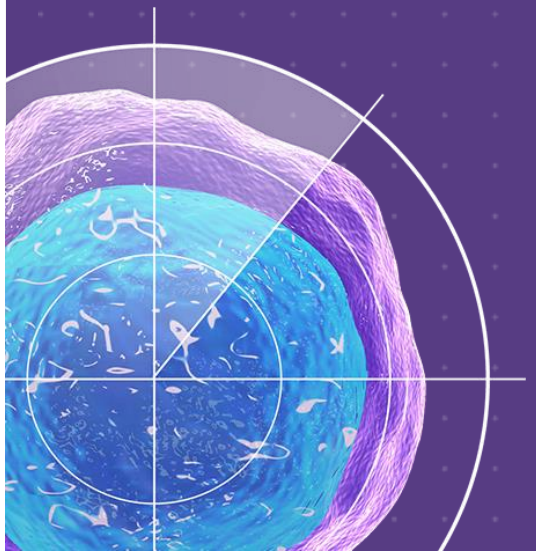
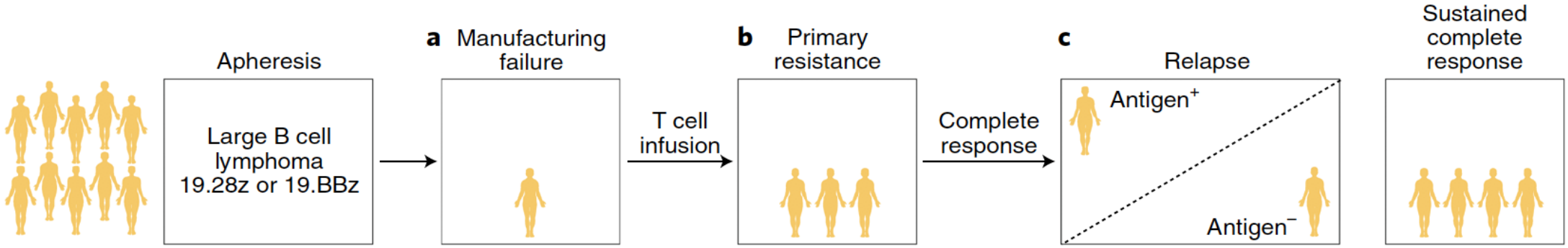
Amsterdam, NL



CAR T-cell treatment in R/R DLBCL: Pivotal phase II trials

Study/ Sponsor	Product	N	Best ORR	Best CR rate	Median FU, months	Median DOR, months	Progression-free at median FU	Ref.
ZUMA-1	CD19/ CD28	101	83%	58%	27	11.1	39%	Locke, *Lancet Oncol.* 2018; Neelapu, *NEJM.* 2017
JULIET	CD19/ 4-1BB	111	52%	40%	19	NR	32%	Schuster, *NEJM.* 2018
TRANSCEND	CD19/ 4-1BB	256	73%	53%	12	NR	44%	Abramson, *Lancet.* 2020

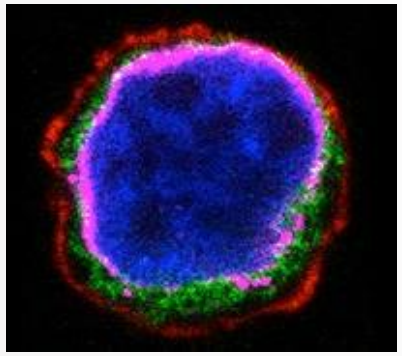


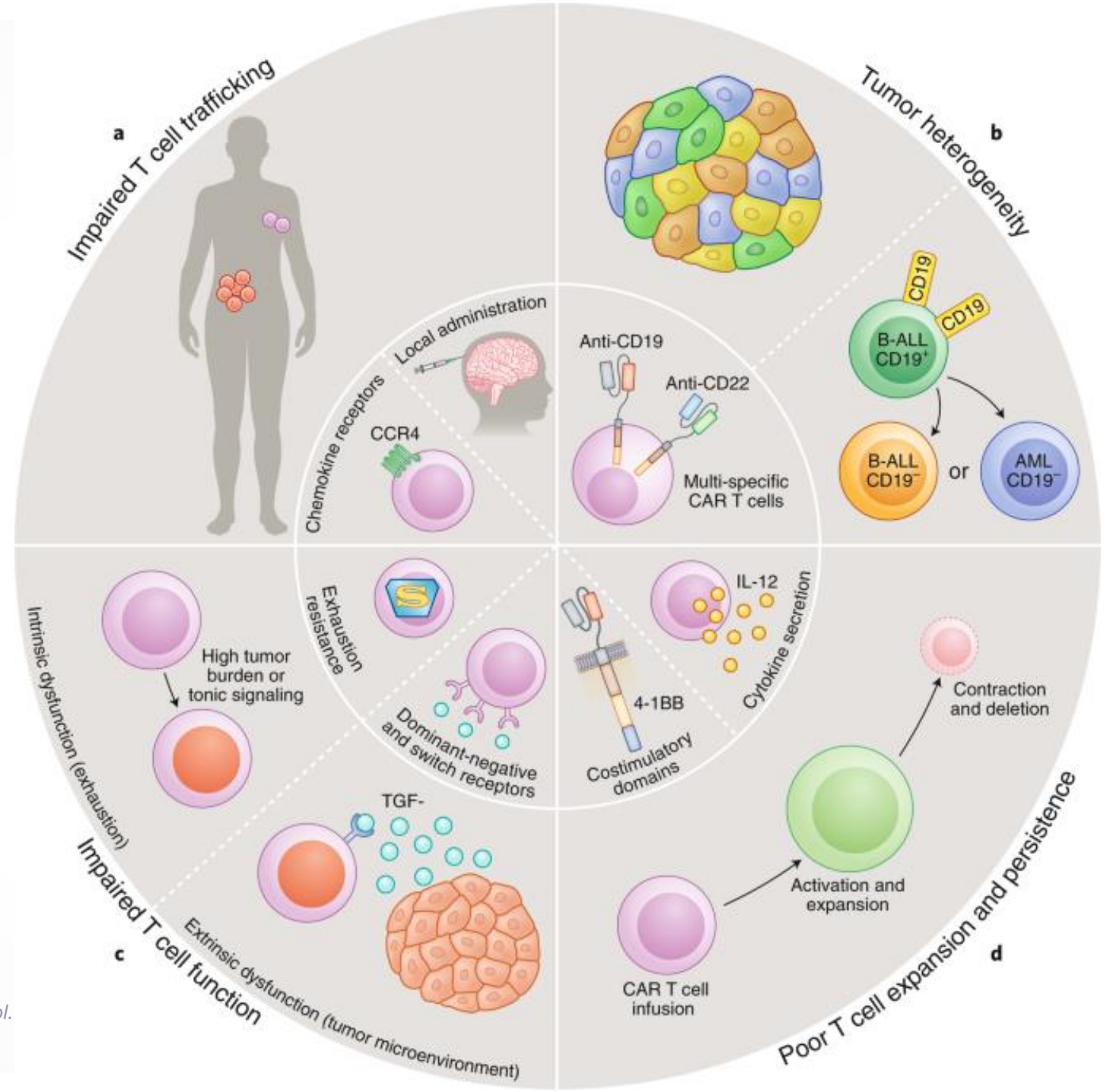
Locke FL, et al. *Lancet Oncol.* 2019;20:31-42; Majzner RG, et al. *Nat Med.* 2019 Sep;25(9):1341-1355; Neelapu et al. *N Engl J Med.* 2017;377:2531-2544; Schuster SJ, et al. *N Engl J Med.* 2019;380:45-56; Abramson JS, et al. *Lancet*. 2020;396(10254):839-852.

CR, complete response; DOR, duration of response; FU, follow-up; NR, not reached; ORR, overall response rate.

Mechanisms of resistance to CD19 CAR T-cell therapy

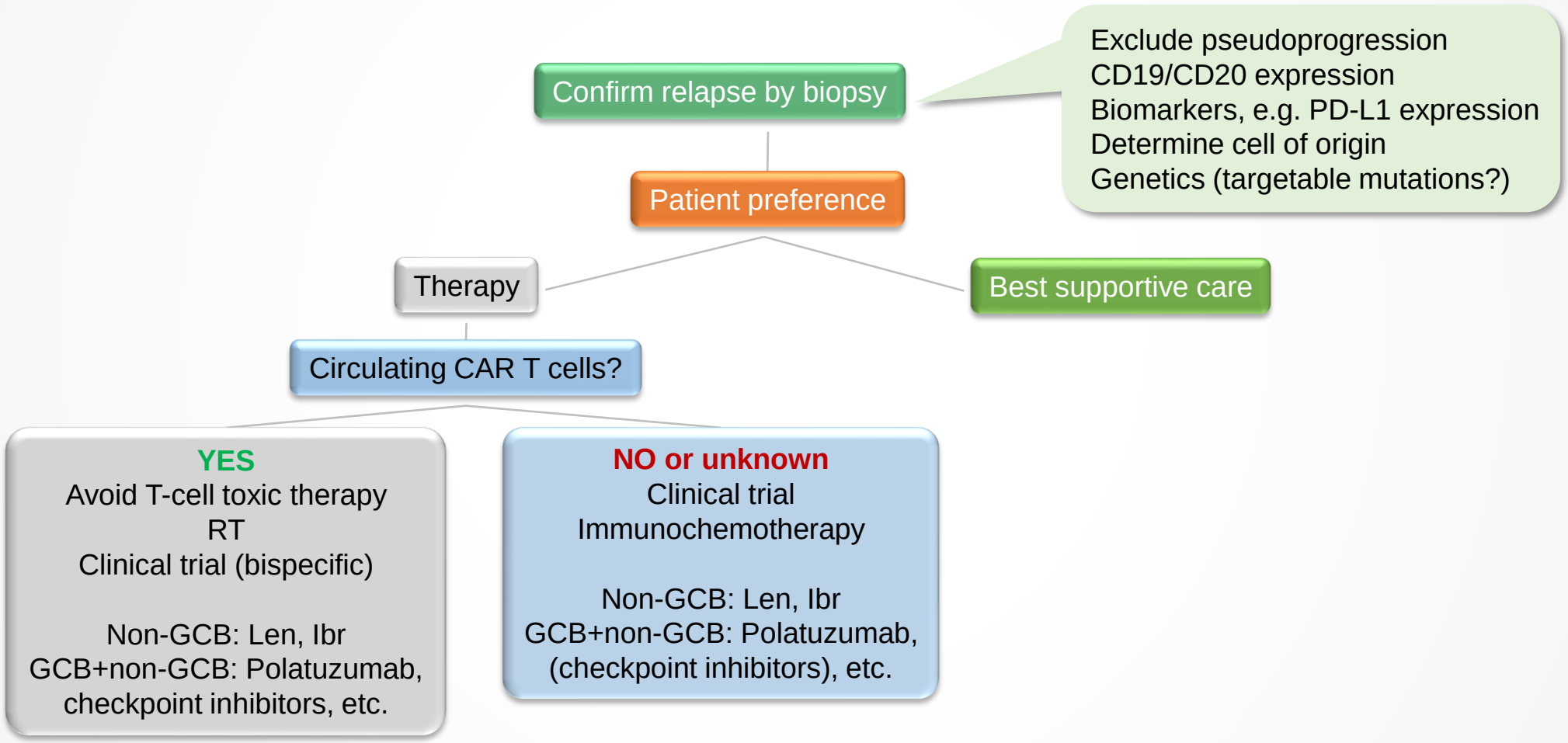
- Lack of persistence
- Exhaustion of T cells
- Loss of target antigen
- Defects in death receptor signaling pathways
- Upregulation of checkpoints
- Hostile microenvironment





Majzner RG, et al. *Nat Med.* 2019 Sep;25(9):1341-1355; Bagashev A, et al. *Mol Cell Biol.* 2018;38(21):e00383-18; Singh N, et al. *Cancer Discov*. 2020;10(4):552-567.

Relapse after CD19 CAR T-cell therapy



Slide courtesy of U. Jaeger.

CAR, chimeric antigen receptor; GCB, germinal-center B-cell–like; Ibr, ibrutinib; Len, lenalidomide; PD-L1, programmed death-ligand 1.

Second infusion of CAR T cells

Study design

- 14 patients treated in ZUMA-1 (axi-cel) received a second infusion
- Eligibility: progressive disease after remission; no loss of CD19
- Retreatment source:
  - second bag (n = 4), manufactured from cryopreserved PBMC (n = 9), new apheresis (n = 1)

Results

- Median interval to retreatment, 9 months
- ORR, 57% (5 CR, 3 PR)
- Response to retreatment more often after CR at 1st treatment (86% *vs* 33%)
- Median duration of response after retreatment was 9.4 months (range, 0.03–18.2+)
- 2 patients still in remission at 11+ and 18+ months
- Comparable rates of CRS and fewer Grade ≥ 3 NT were observed
- Peak CAR T-cell expansion was lower upon retreatment *vs* 1st treatment

Conclusions

- Retreatment is feasible but responses are often not durable → use as bridge to allogeneic transplant?
- Currently not registered and not reimbursed

Locke F, et al. Abstract #8012. ASCO 2020.

axi-cel, axicabtagene ciloleucel; CAR, chimeric antigen receptor; CR, complete response; CRS, cytokine release syndrome; NT, neurotoxicity; ORR, objective response rate; PBMC, peripheral blood mononuclear cell; PR, partial response.

New CAR T-cell indications and constructs

Coming indications

- Multiple myeloma
- CLL
- Hodgkin lymphoma
- Acute myeloid leukemia
- Solid tumors

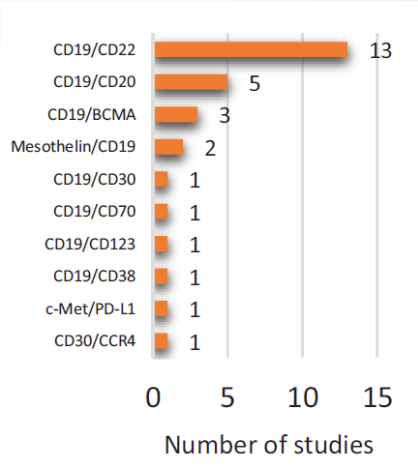
Combination with other agents

- Ibrutinib
- Immune checkpoint inhibitors

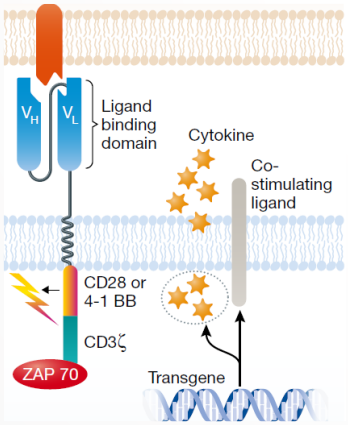
- Allogeneic CARs
- Third-party CARs
- NK-CARs

Gene editing

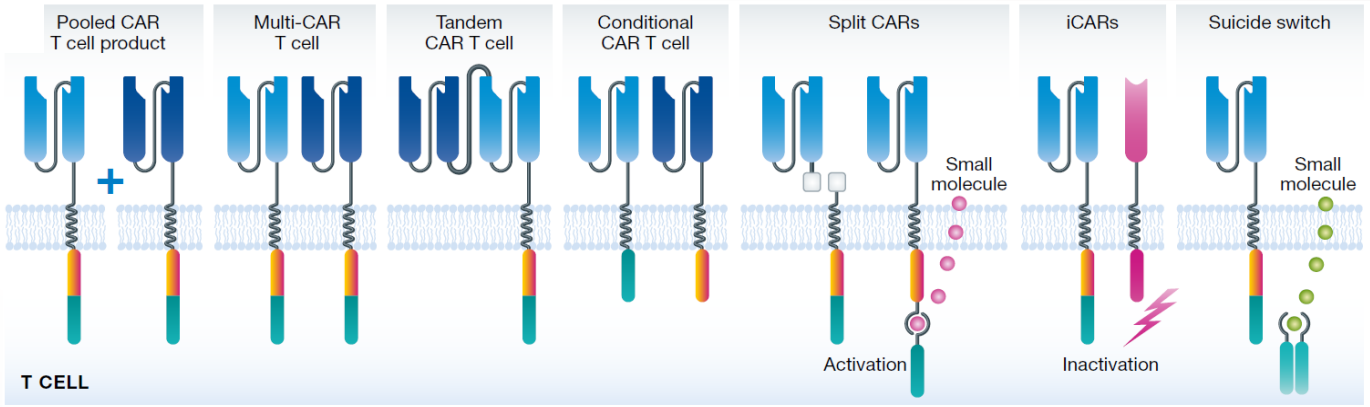
Combined/multiple targets[1]



4th generation (TRUCKs)



Novel CAR T-cell constructs[2]



1. Charrot S, Hallam S. *HemaSphere.* 2019;3(2):e188 **2.** Hartmann J, et al. *EMBO Mol Med.* 2017;9:1183-1197.

CAR, chimeric antigen receptor; CLL, chronic lymphocytic leukemia; NK, natural killer; TRUCK, T cells redirected for antigen-unrestricted cytokine-initiated killing.

So what's new in aggressive lymphoma other than CAR T?

Immunotherapy

- Novel 'naked' CD20 antibodies: not (more) effective
- Tafasitamab (+ lenalidomide)
- Antibody–drug conjugates: brentuximab vedotin, polatuzumab vedotin
- Immunomodulatory drugs: lenalidomide, avadomide, iberdomide
- Antibody-based – T cell activating:
  - `Immune checkpoint inhibitors'
  - Bispecific antibodies/BiTE
  - CAR T cells

Precision medicine

- Targeting intracellular kinases
- Proteasome inhibitors

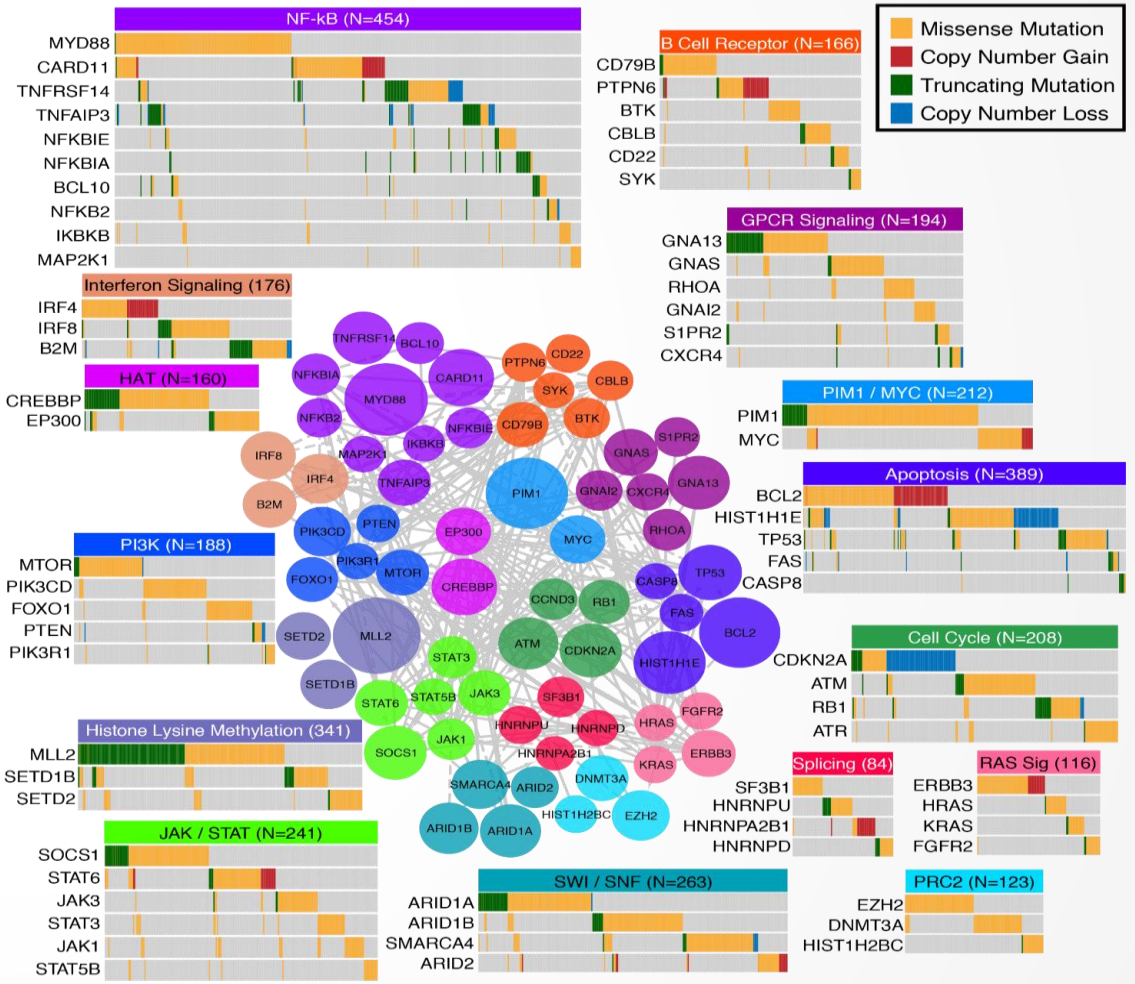
Induction of apoptosis

- BCL2 antagonists

BiTE, bispecific T-cell engager; CAR, chimeric antigen receptor.

We should be capitalising on biological insights…. but it's complicated….

- 'Integrative genetic and clinical analysis through whole exome sequencing in 1001 diffuse large B cell lymphoma (DLBCL) patients reveals novel disease drivers and risk groups'.[1]
- 158 significantly mutated genes/CNAs/SVs identified by whole exome sequencing of 304 newly diagnosed DLBCL patients, several of which are targetable.[2]



Slide courtesy of Andrew Davies.

1. Zhang J, et al. *Blood.* 2016;128 (22):1087; **2.** Chapuy B, et al. *Blood.* 2017;130 (Supplement 1):38.
Figure: Reddy A, et al. *Cell.* 2020;171:481-494.
CNA, copy number alteration; SV, structural variant.

Access to novel drugs in Europe

- Approval by EMA → registration in Europe
- Reimbursement and access differ per country
- Some countries: direct access (e.g. Germany) or temporary access program (e.g. France)

Netherlands:

- Healthcare institute performs health technology assessment
  - Therapeutic value
  - Cost-effectiveness analysis/cost-utility analysis (societal perspective) → challenging if there is no SoC arm
  - Budget impact analysis
- New treatment can be placed in a 'lock' pending (secret) price negotiations MoH with company

→ For our patient: clinical trial is the best option

EMA, European Medicines Agency; MoH, Ministry of Health; SoC, standard of care.

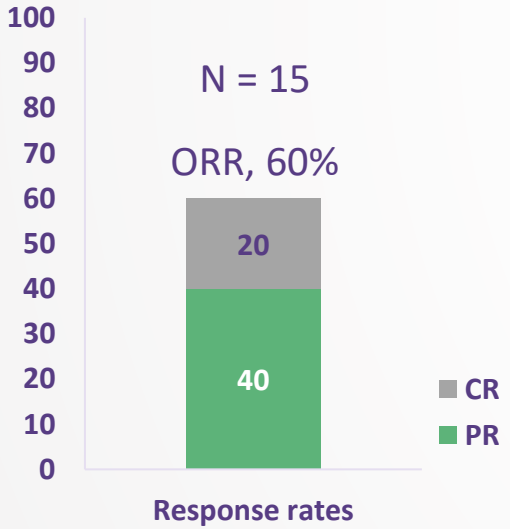
Clinical trial options for this patient: Bispecific antibodies

Epcoritamab (GEN 3013)

- An anti-CD3 + anti-CD20 bispecific antibody

GCT3013-01[1,2]

- Phase I/II open-label study of GEN3013, single agent
- Single SC injection in 28-day cycles until PD or toxicity



- No treatment-related deaths
- Most TEAEs were Grade 1–2
- 9/15 patients achieved a response, including 3 who failed prior CAR T-cell treatment

Blinatumomab

- An anti-CD19 + anti-CD3 BiTE
- ORR rates of 37% as single agent in R/R B-cell NHL[3]

KEYNOTE-348[4]

- Phase Ib open-label study of blinatumomab combined with pembrolizumab
- Up to 2 cycles blinatumomab IV (Cycle 1, 8 weeks; Cycle 2, 28 days)

Plus

- 1 cycle pembrolizumab IV every 3 weeks until PD

Primary outcome:

- Incidence of dose-limiting toxicities

1. ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT03625037. Updated, Oct 5, 2020. Accessed, Oct 15, 2020. **2.** Hutchings M, et al. Abstract #1218. EHA 2020. **3.** Coyle L, et al. *Leukemia & Lymphoma.* 2020;61(9):2103-2112; . **4.** ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT03340766. Updated Sep 3, 2020. Accessed Oct 15, 2020.

BiTE, bispecific T-cell engager; CAR, chimeric antigen receptor; CR, complete response; IV, intravenous; NHL, non-Hodgkin lymphoma; ORR, overall response rate; PD, progressive disease; PR, partial response; R/R, relapsed/refractory; SC, subcutaneous; TEAE, treatment-emergent adverse event.

Clinical trial options for this patient: CDK9 inhibition

AZD4573

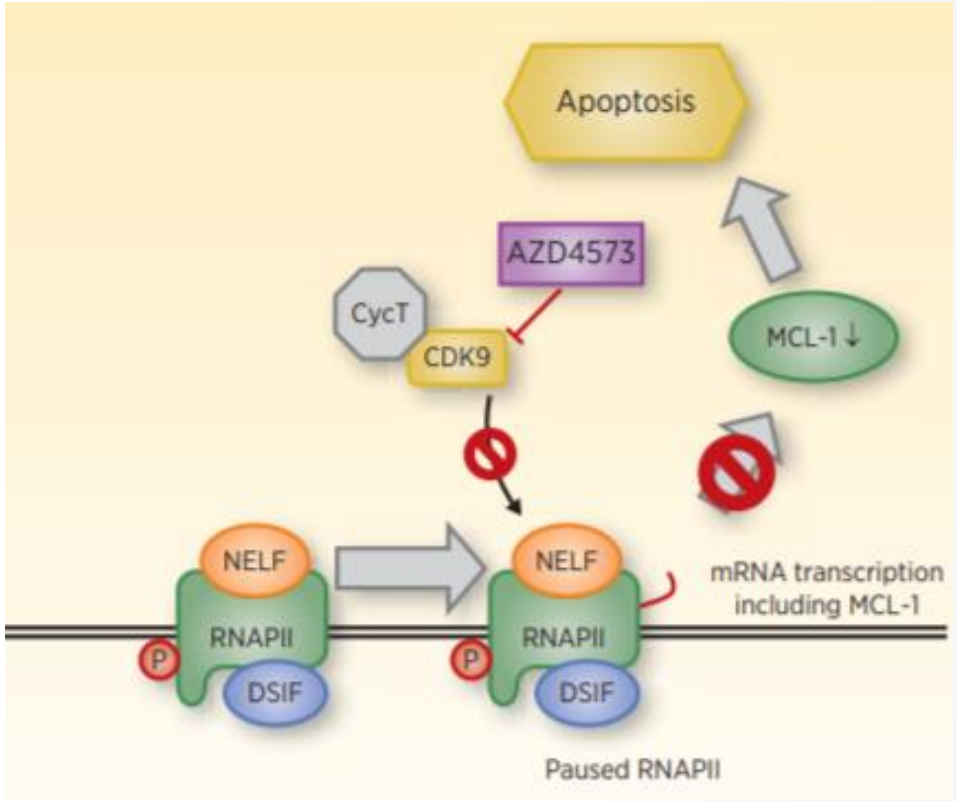
- A potent and highly selective CDK9 inhibitor that suppresses MCL-1 and induces apoptosis

NCT03263637

- A first-in-human, phase I, open-label, dose-escalation study of AZD4573 in R/R haematological malignancies
- IV infusion, 3 dose levels (for 8 weeks maximum)

Primary outcomes:

- Incidence of AEs
- Dose-limiting toxicities
- Maximum tolerated dose



Alcon C, et al. *Clin Cancer Res*. 2020;26(4):761-763; Cidado J, et al. *Clin Cancer Res.* 2020;26(4):922-934; ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT03263637. Accessed, 15 Oct 2020.
AE, adverse event; IV, intravenous; R/R, relapsed/refractory.

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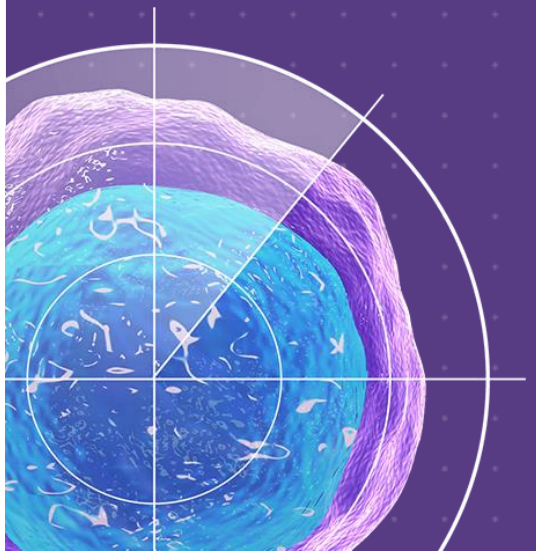
Thank you



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