CELLULAR THERAPIES – DELIVERY OF THEM: LEARNING FROM CAR-T CELLS

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DISCLOSURES DR MENNE

- Travel grants: Amgen, Jazz, Pfizer, Bayer, Kyowa Kirin, Celgene/BMS, Kite/Gilead, Janssen, Takeda
- Honoraria for advisory board meetings: Kite/Gilead, Amgen, Novartis, Pfizer, Celgene/BMS, Daiichi Sankyo, Atara, Roche, Janssen
- Honoraria for lectures: Kite/Gilead, Takeda, Janssen, Roche, Servier, Novartis, Celgene/BMS, Pfizer, Incyte
- Research funding: Janssen, AstraZeneca, Novartis

UK EXPERIENCE

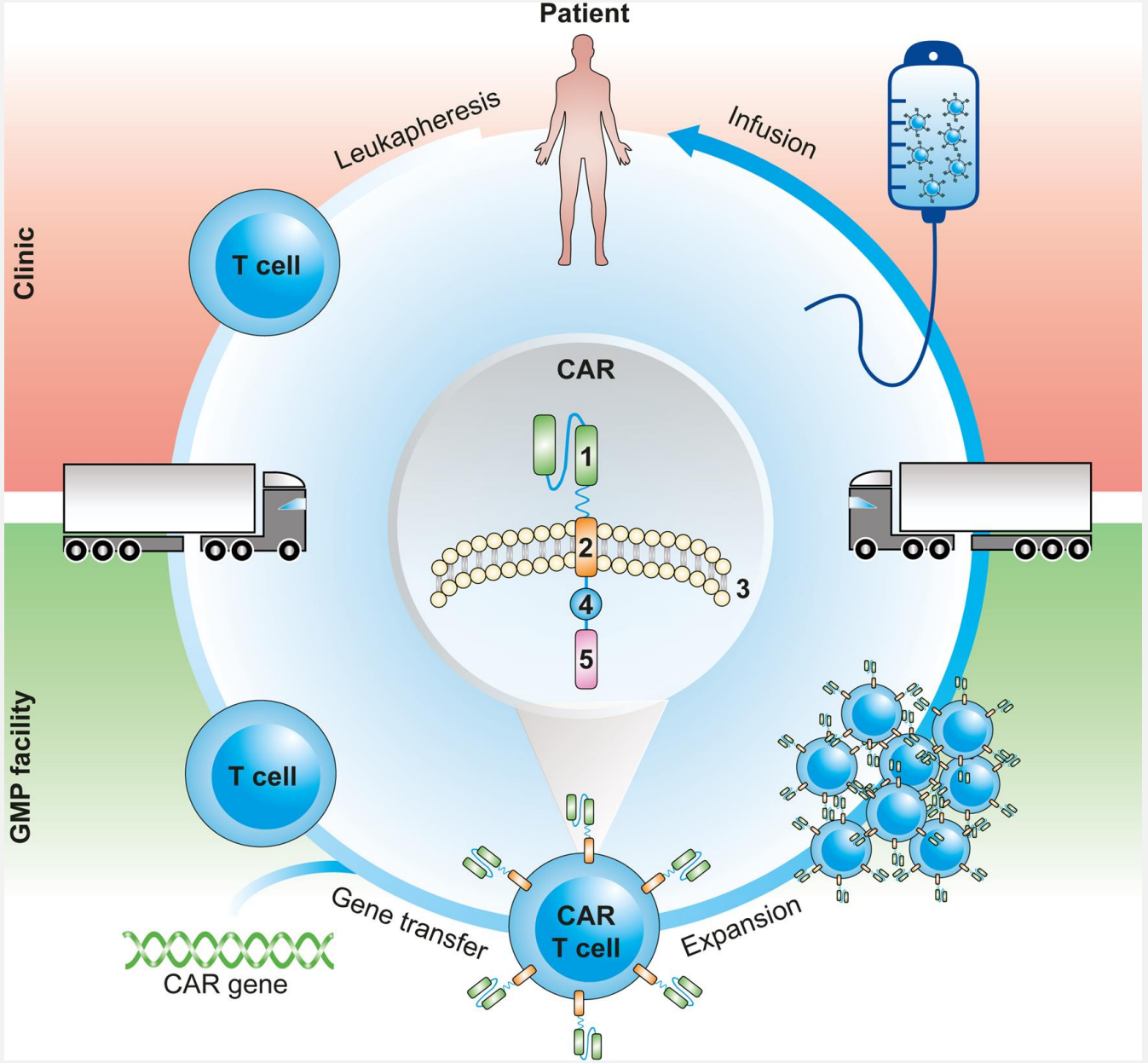
NICE recommendations

- Oct 18 — Axicel for 3L+ HGBCL
- Nov 18 — Tisagen for R/R-B-ALL up to age 25 years
- Nov 18 — Tisagen for 3L+ HGBCL
- Feb 21 — Brexu-cel for R/R MCL
- June 23 — Brexucel for RR B-ALL 26+ years
- June 23 — Axicel for 2nd line HGBCL
- Mar 25 — Lisocel for 2nd line HGBCL
- Summer 25 — Obecel for RR B-ALL (Expected)

- **Note**

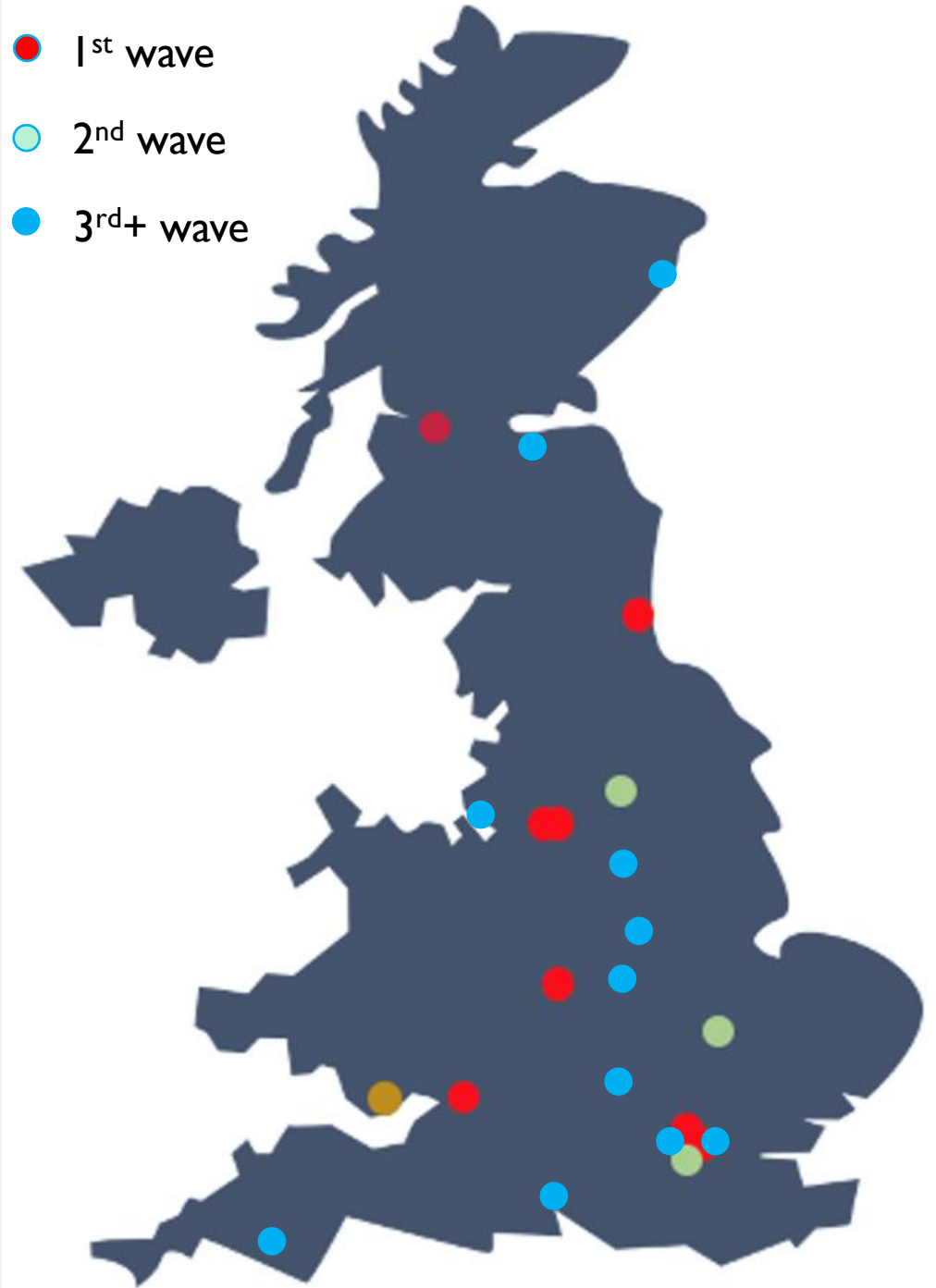
  So far no Myeloma CAR-T cell therapy has been approved by NICE due to cost implications

VERY COMPLEX PROCESS TO DELIVER CAR-T CELLS



TOPICS TO COVER

- Apheresis phase
- Manufacturing CAR-T cell phase
- Lymphodepletion and CAR-T treatment phase
- Post CAR-T therapy phase

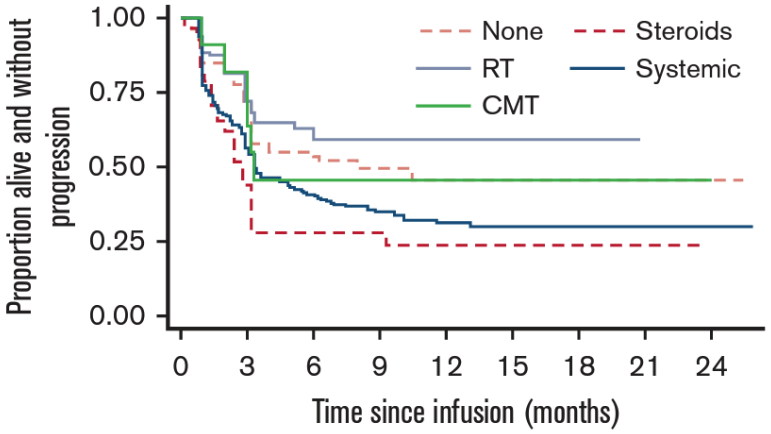


APHERESIS PHASE

- Identify patients
  - Does the patient meet the NICE approved indication
  - ECOG performance status 0 or 1
  - Disease that is stable enough to allow collection of T-cells and manufacture of CAR-T cells
  - “Adequate organ function”
- Discuss at national CAR-T panel
- Apherese as quickly as possible

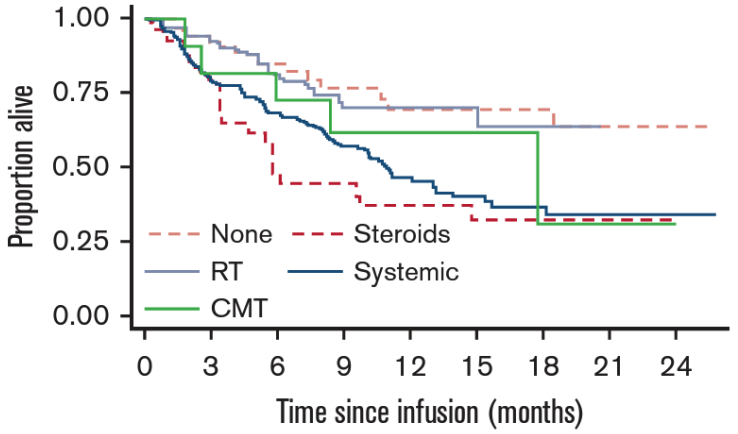
MANUFACTURING CAR-T CELL PHASE

- Typically takes 3-4 weeks from apheresis to start lymphodepletion
- Often Bridging therapy is given
  - Chemotherapy
  - Radiotherapy
- Risk of progression with deteriorating ECOG performance score
- Low chance of CAR-T production failure or OOS - Out of Specification product



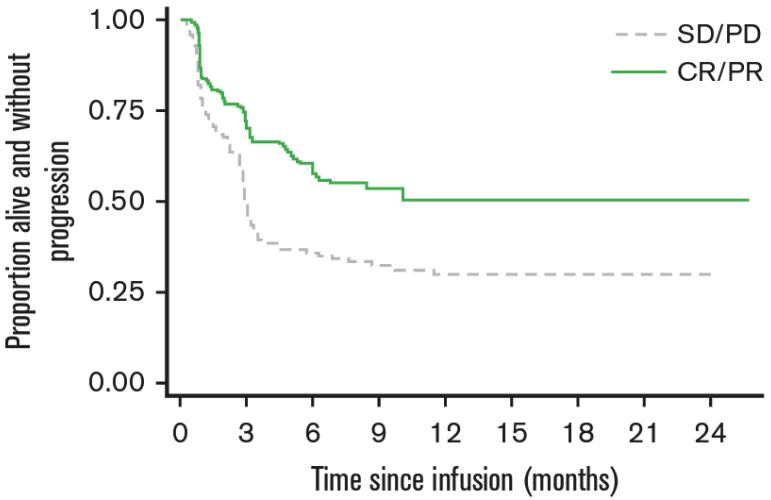
Number at risk

None	40	26	21	14	12	10	9	4	2
Steroids	29	13	8	7	6	6	6	5	0
RT	54	39	33	26	14	10	8	0	0
Systemic	166	90	65	40	27	15	10	4	1
CMT	11	8	5	4	4	3	1	1	1



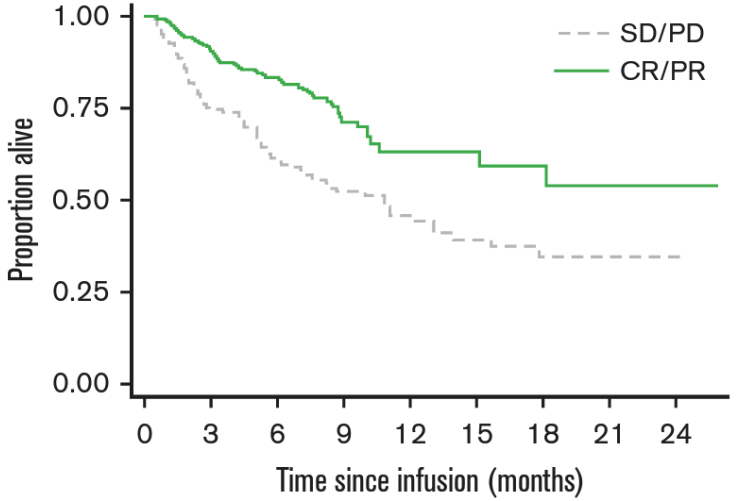
Number at risk

None	40	37	34	23	18	15	13	5	3
Steroids	29	23	14	12	10	7	7	6	0
RT	54	50	42	30	17	13	8	0	0
Systemic	166	132	111	71	42	24	14	6	2
CMT	11	9	8	6	5	4	1	1	1



Number at risk

SD/PD	115	58	38	28	19	13	9	2	1
CR/PR	104	74	62	39	24	14	10	3	1



Number at risk

SD/PD	115	86	66	49	31	20	12	4	2
CR/PR	104	94	86	52	30	19	11	3	1

EFFECTIVE BRIDGING CAN IMPROVE CAR-T OUTCOMES

Multivariate analysis of baseline factors

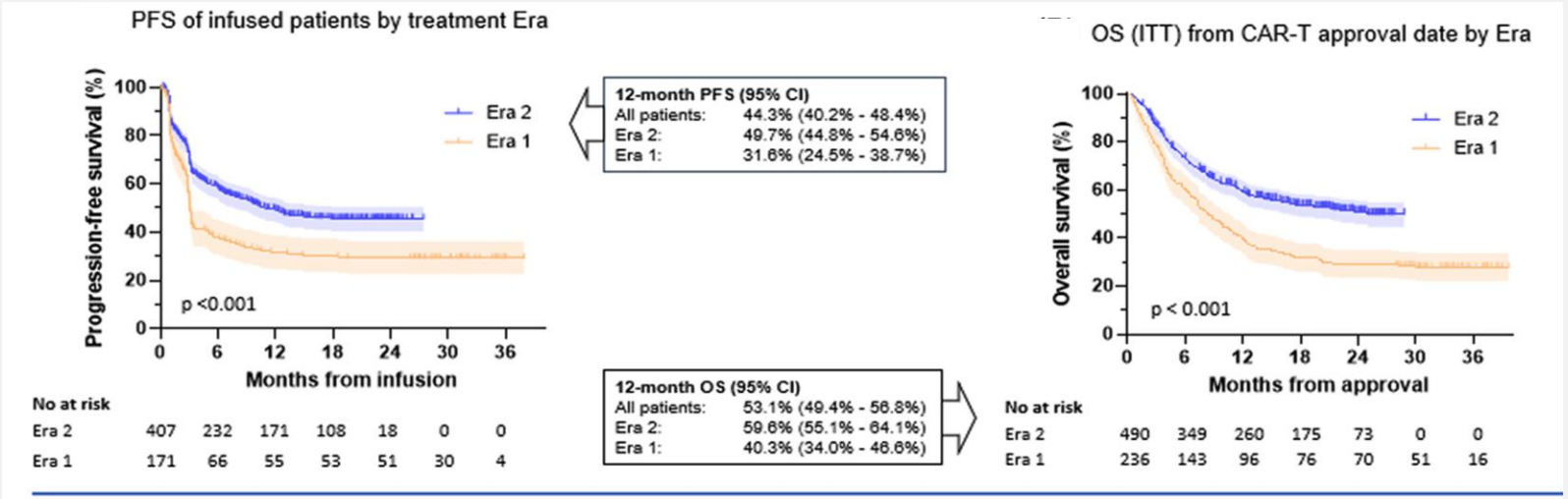
Factors affecting response to BT	Responder/N	OR (95% CI)	*P*-value
RBP bridging			
No	34/134	1.00	.010
Yes	35/83	2.21 (1.21-4.05)	
Response last line			
SD/PD	45/165	1.00	.023
CR/PR	24/52	2.16 (1.11-4.22)	
Bulky disease			
No	55/149	1.00	.045
Yes	14/68	0.49 (0.25-0.98)	
Factors affecting response to CAR-T	**Events/N**	**HR (95% CI)**	***P*-value**
LDH at LD			
≤2ULN	74/141	1.00	.001
>2ULN	34/41	2.06 (1.34-3.16)	
Extra nodal sites			
<3	91.160	1.00	.001
≥3	17/22	2.51 (1.46-4.32)	
BT response			
SD/PD	68/100	1.00	.012
CR/PR	40/82	0.58 (0.38-0.89)	

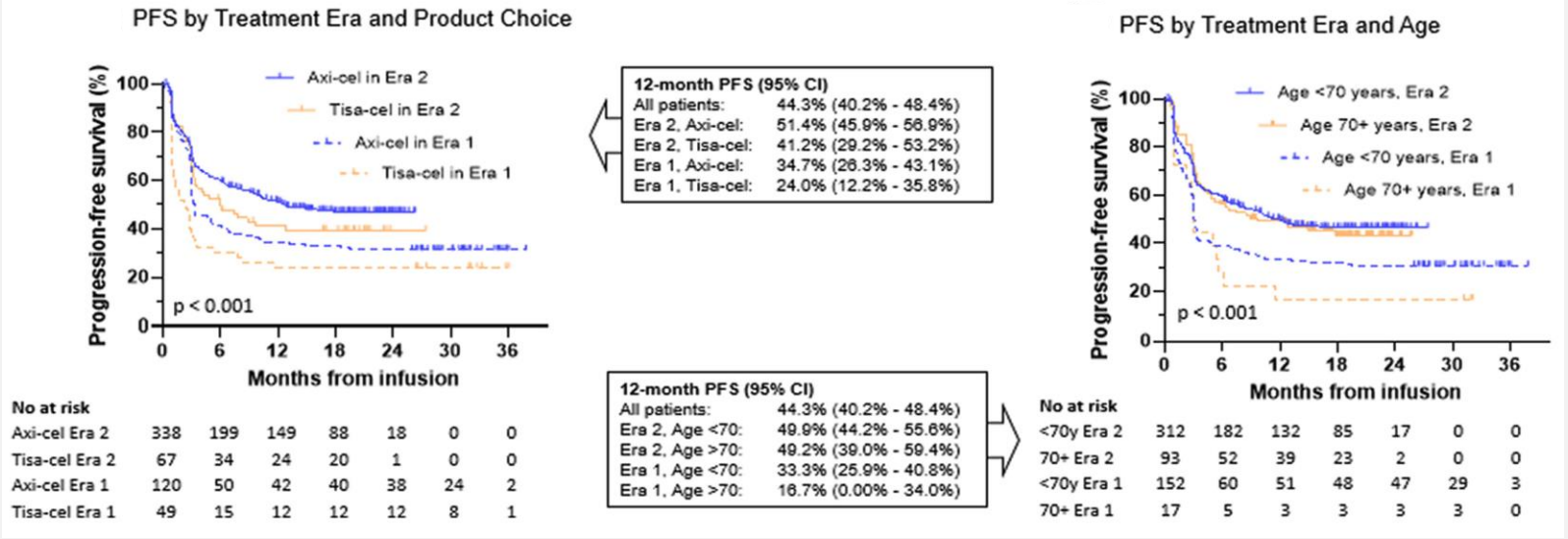
Roddie C et al (2023) Blood Advances 7: 2872-2883

LYMPHODEPLETION AND CAR-T TREATMENT PHASE

- Lymphodepletion phase 5-6 days followed by CAR-T infusion
- CAR-T treatment phase typically 28 days with most patients being an inpatient for 10-14 days post CAR-T infusion
- High chance of developing CRS and ICANS
- TRM rates of 3-5%
- Response assessment at 28-30 days post CAR-T cells important predicter for PFS

LARGE B-CELL LYMPHOMA PATIENTS TREATED WITH CD19 CAR T IN THE UK OVER TIME





2nd line Axi-cel

UK RWD data

N=195 patients
Median FU 9.1 months

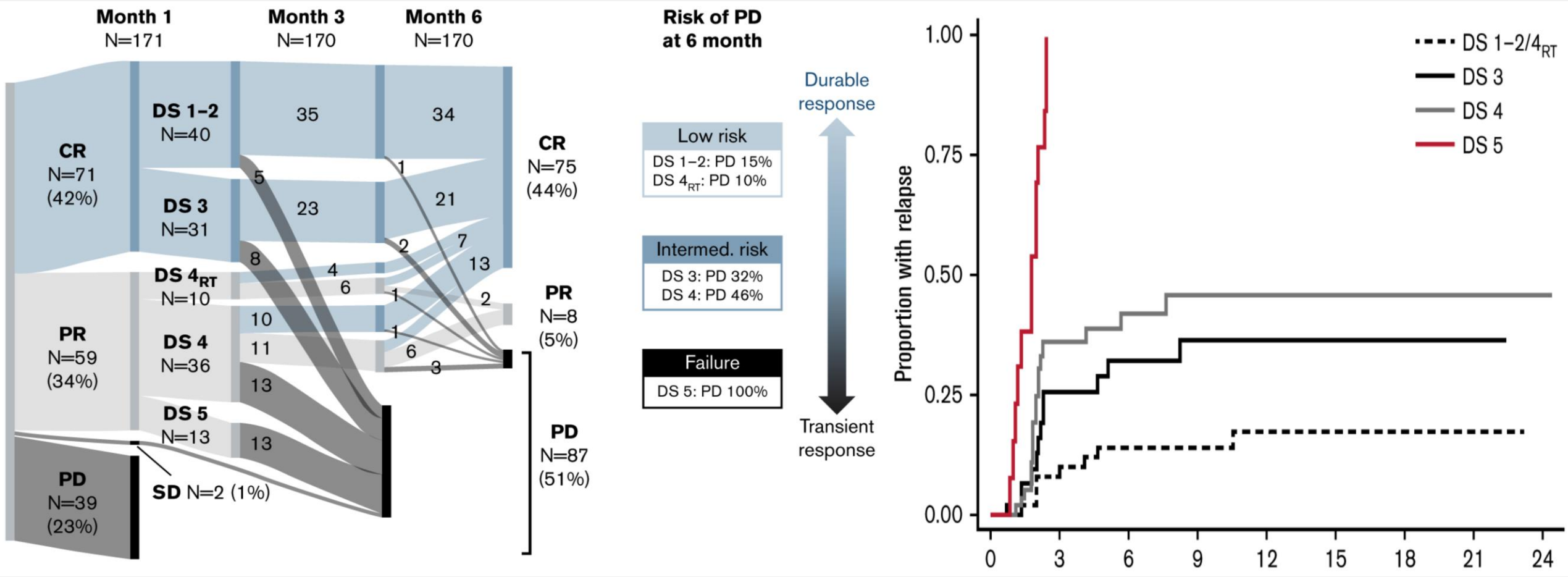
ORR: 88%
CMR: 61%

Patients – Axi-cel infused
- 9-month PFS: 47.6%
- 9-month OS: 77%

Patients – not infused
- 9-month OS: 19.7

Boyle S et al (2023) Br J Haematol, DOI: (10.1111/bjh.19157); Kuhnl A et al (2024) ASH abstract 2342

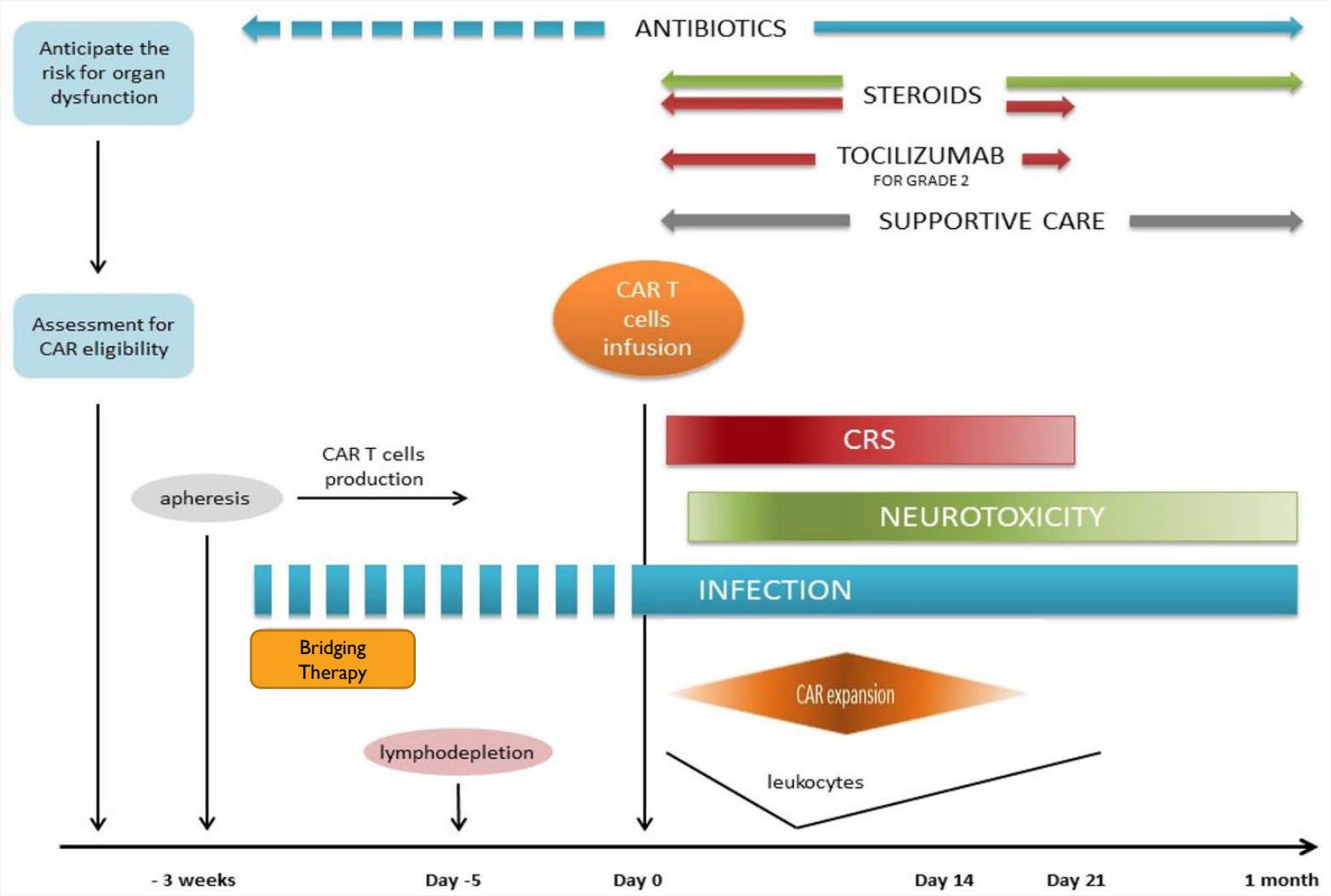
EARLY FDG-PET RESPONSE PREDICTS CAR-T FAILURE IN LARGE B-CELL LYMPHOMA



Kuhnl A et al (2022) Blood Advances 6: 321-326

MANAGEMENT OF TOXICITIES EARLY AND LATE

TIMING OF LIFE THREATENING COMPLICATIONS FOLLOWING CAR-T CELLS INFUSION



Azoulay E et al (2020) Intensive Care Med 46:1723-1726

ACUTE CAR-T TOXICITY OUTCOMES IN THE UK OVER TIME

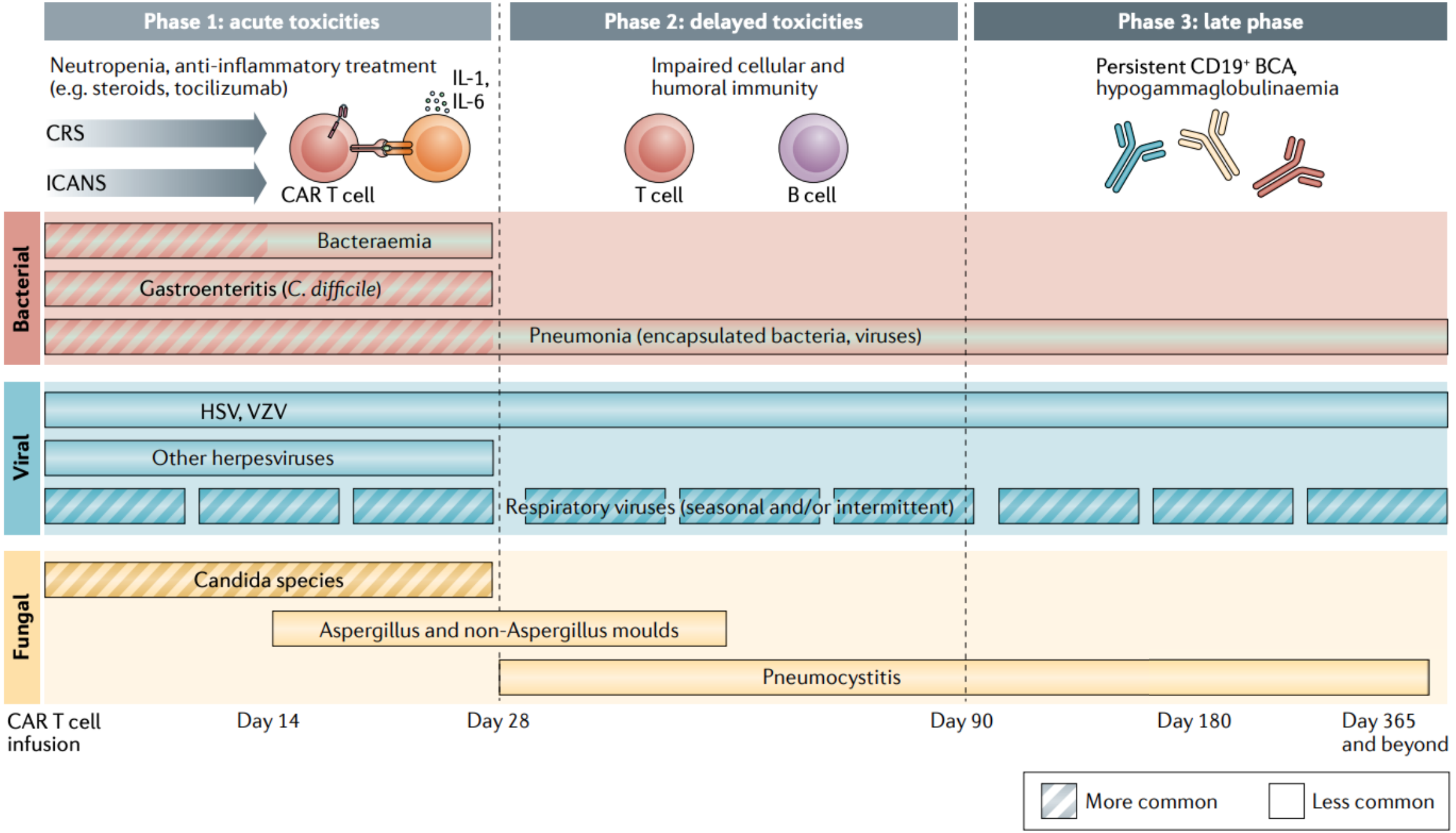
	Era 1 2019 *n* (available)	%	Era 2 2020-2022 *n* (available)	%	*p* Value
Of those who received CAR T					
Axi-cel infused	121 (171)	71	339 (407)	83	**<0.001**
CRS grade 3+	16 (171)	9	16 (405)	4	**0.01**
ICANS grade 3+	27 (171)	16	63 (405)	16	0.94
Tocilizumab use	104 (171)	61	141 (185)	76	**0.002**
Corticosteroid use	59 (171)	35	84 (184)	46	**0.03**
ICU admission	55 (171)	32	79 (405)	20	**0.001**
G3+ neutropenia at 3 months	26 (133)	20	16 (92)	17	0.68
G3+ thrombocytopenia at 3 months	25 (133)	19	18 (92)	20	0.88
NRM at 12 months	10 (167)	6	30 (402)	7.5	0.53

2nd line- UK 5/2023- 3/2024 N=195 %	
Axi-cel infused	91
CRS grade 3+	4
ICANS Grade 3+	17
Tocilizumab use	90
Corticosteroid use	60
ICU admission	20
Anakinra use	17
G3+ ICAHT at 1 month	29
NRM at 9 months	5.4

Boyle S et al (2023) Br J Haematol, DOI: (10.1111/bjh.19157) ; Kuhnl A et al (2024) ASH abstract 2342

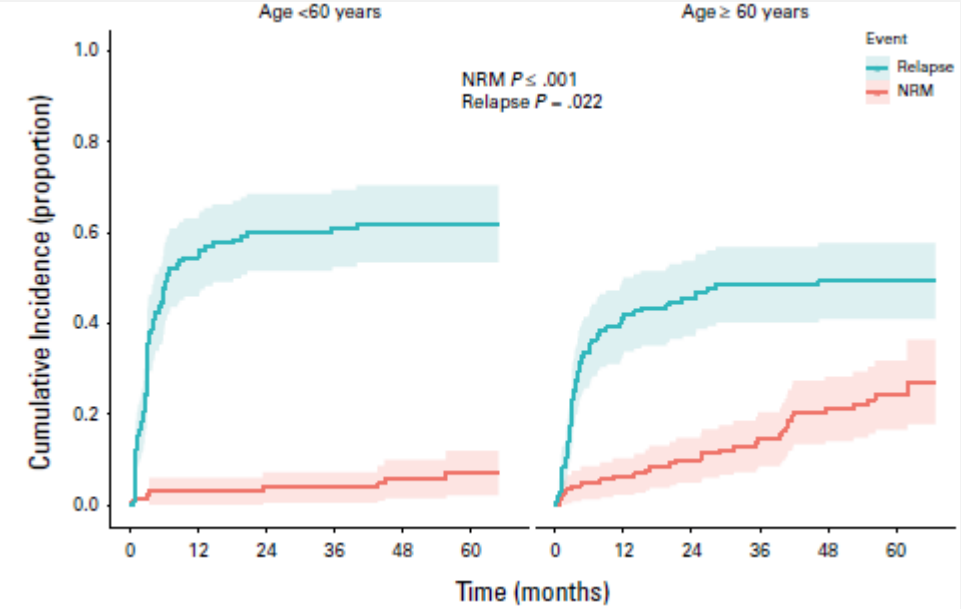
POST CAR-T THERAPY PHASE

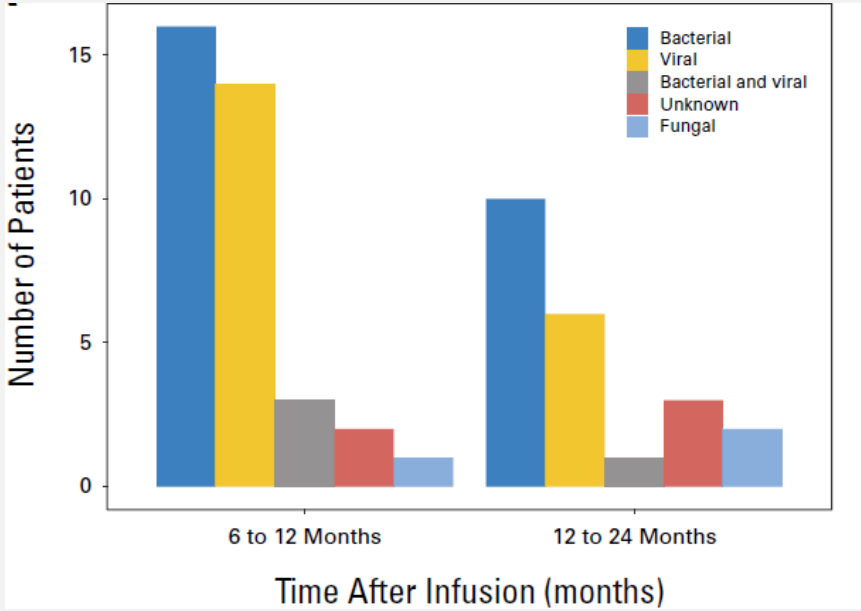
- From Day 28 onwards
- Shared care model is standard of care
- Ongoing infection, cytopenias and immunosuppression remains significant issue
- Many CAR-T centres have established nurse-led "late toxicity" clinics



Shalabi H et al (2021) Nat Rev Clin Onc 18:363-378

NON-RELAPSE MORTALITY AFTER STANDARD OF CARE AXI-CEL IN 3L INFECTIOUS COMPLICATIONS



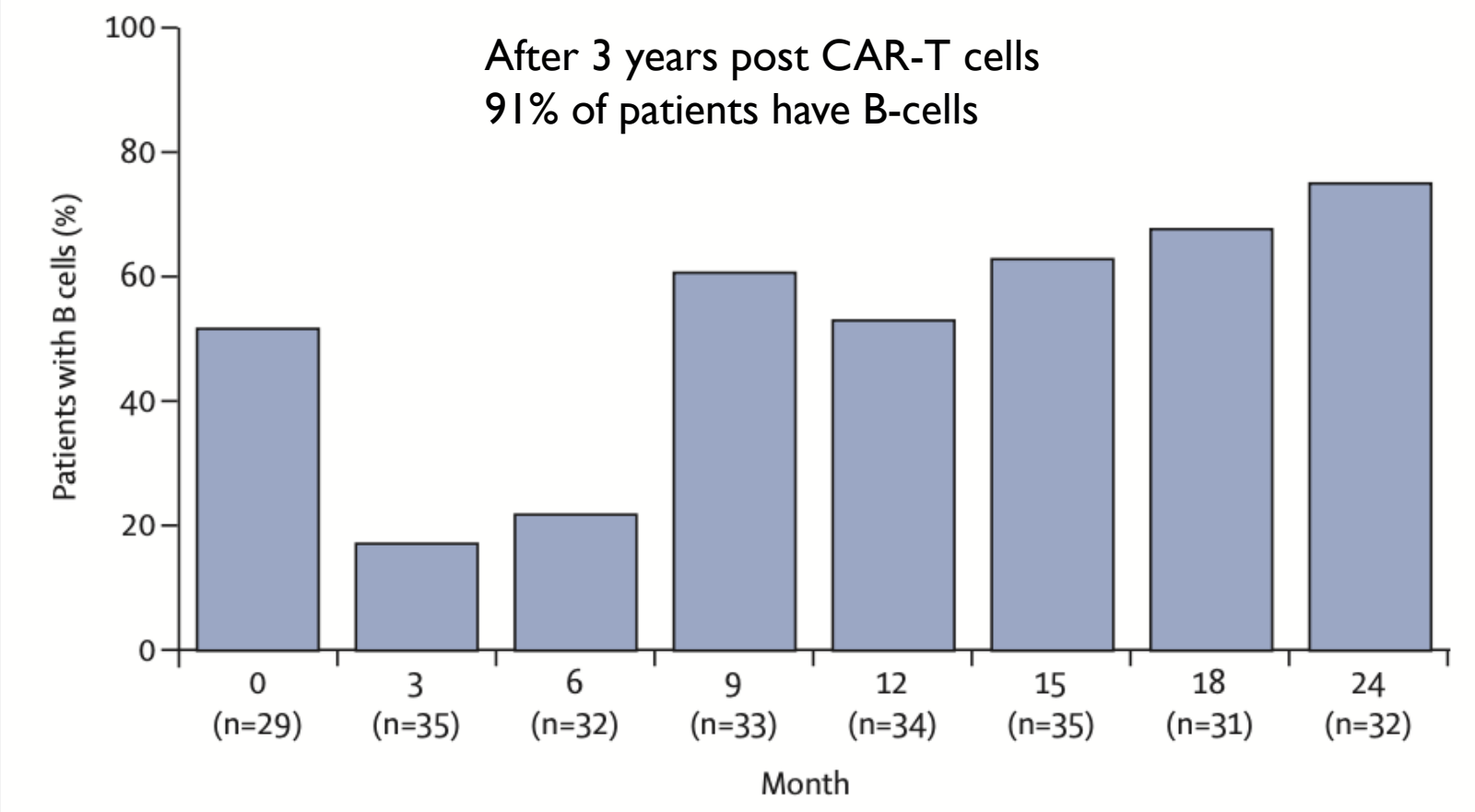


US Lymphoma CAR T Consortium - RWD dataset with 5 year follow up
275 patients treated with Axicel in 3L+
Death due to infections (majority respiratory): total 21/275 (7.7%)

- Age <60 years 4/132 (3%)
- Age >60 years 17/143 (11.8%)

Jain MD et al (2024) JCO 42:3581-3592

B-CELL RECOVERY AFTER CAR-T CELLS (AXICEL)

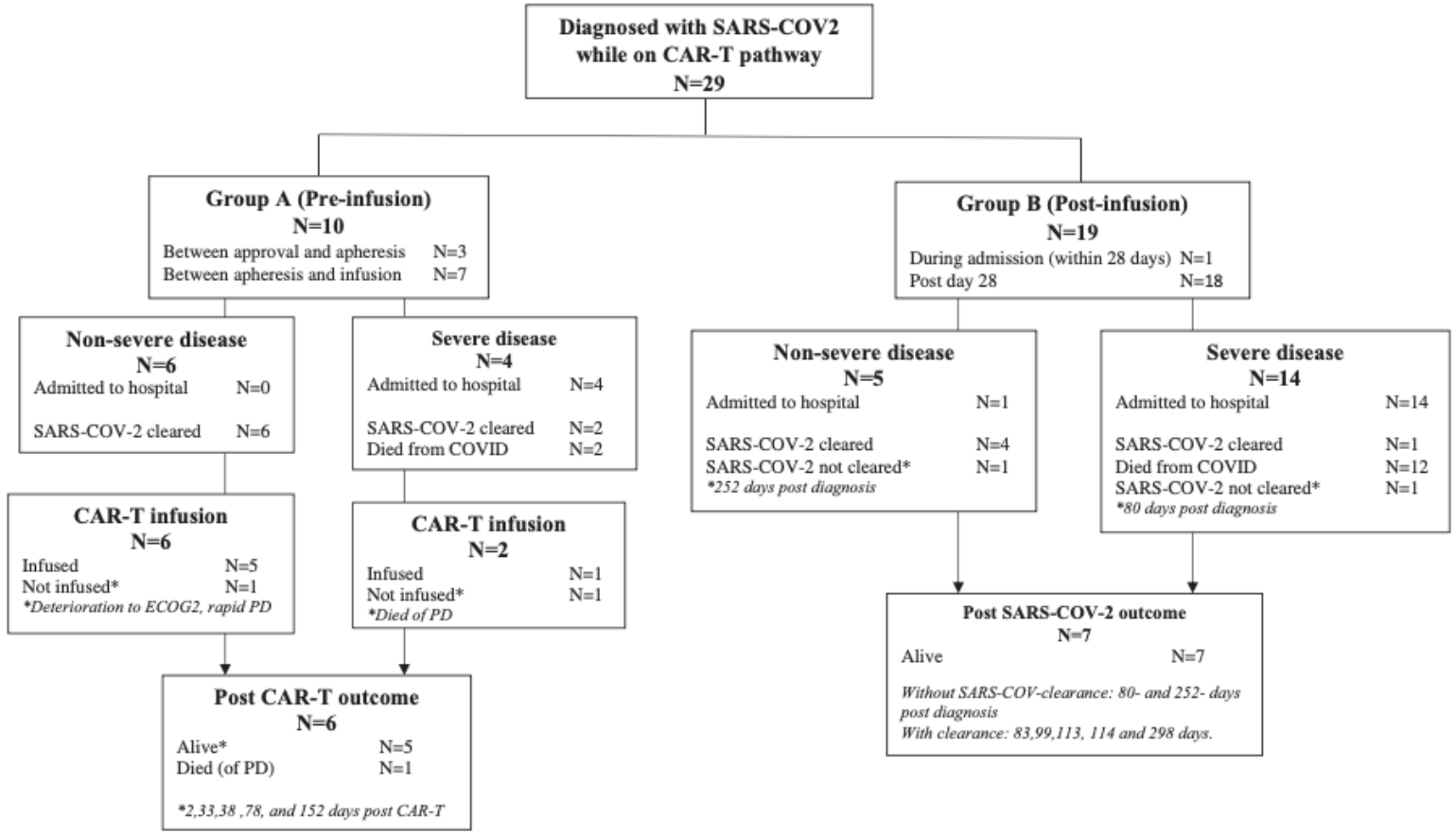


Locke FL, et al. *Lancet Oncol.* 2019;20:31–42; Jacobson et al (ASH (2020) Abstract 1187

Severe presentations and high mortality from SARS-CoV-2 in patients undergoing chimeric antigen receptor (CAR-T) therapy: a UK NCCP analysis

Kathleen P. L. Cheok[a,b], Amy A. Kirkwood[c], Tobias Menne[d], Eleni Tholouli[e], Sridhar Chaganti[f], Amrith Mathew[f], Ben Uttenthal[g], James Russell[g], David Irvine[h], Rod Johnson[i], Emma Nicholson[j], Jessica Bazin[j], William Townsend[b], Andrea Kuhnl[k], Maeve O'Reilly[b], Robin Sanderson[k], Amit Patel[l] and Claire Roddie[a,b]

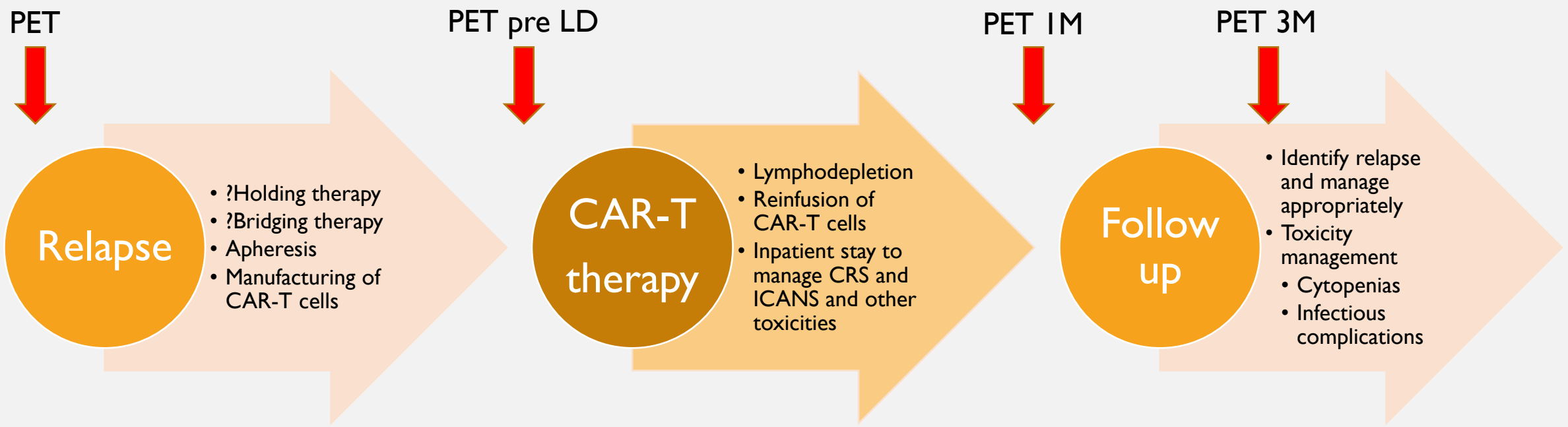
- Post CAR-T infusion
  - high mortality rate if patient develops severe COVID19
  - 12/14 died (86%)



Cheok KP et al, Leuk & Lymp (2022) https://doi.org/10.1080/10428194.2022.2057487

SHARED CARE MODEL

2L CAR-T TREATMENT PATHWAY



Referring and CAR-T centre (close collaboration)
- early MDT discussion
- Aim to apherese ASAP unless holding therapy
- Aim vein to vein time: 30 to 40 days

Mainly CAR-T centre
- Manage from D-6 to D+30
- Inpatient stay D0 to D10-14
  - Might be longer due to toxicities

Referring and CAR-T centre (close collaboration)
- Regular monitoring for relapse
- Manage cytopenias
- Management and prevention of infections

CONCLUSIONS

- Really interesting times for CAR-T cell therapies
- More indications becoming available and CAR-T cells move into earlier therapy lines
- Best sequencing between CAR-T cell and bispecific therapies needs to be established
- Allogenic CAR-T cell therapies are looking promising