



COVID-19: acute leukaemia, transplant, cellular/CAR-T therapies

COVID-19 vaccination and immune
challenges for leukemia

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Lead for Cellular/CAR-T therapies

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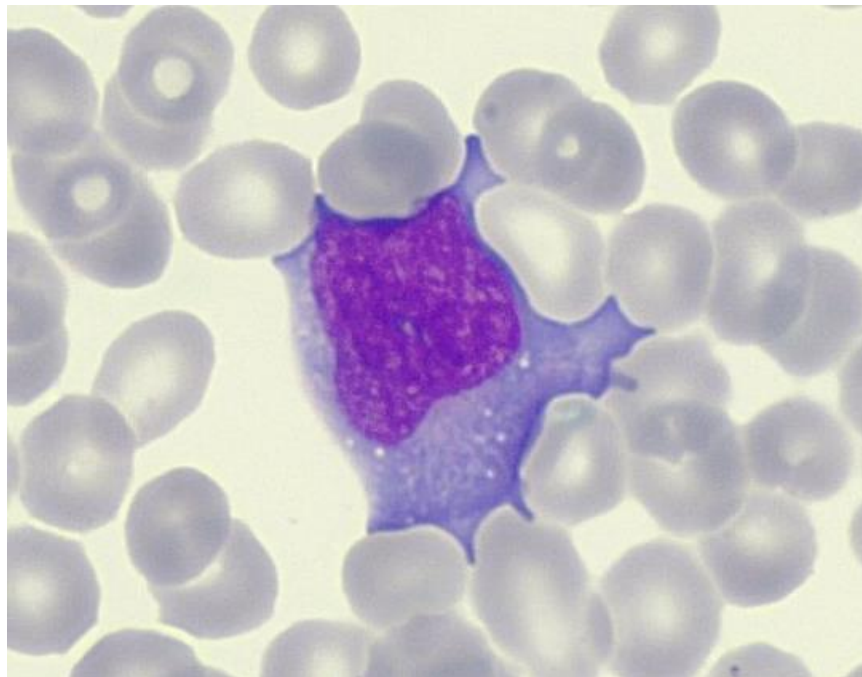
11th February 2021

The Christie NHS Foundation Trust, Manchester, UK

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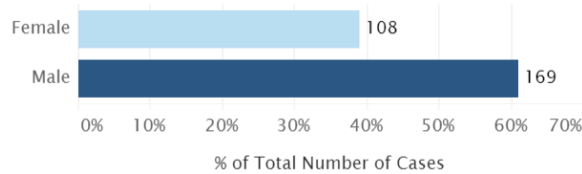
Disclosures

- The Christie Private Clinic, HCA UK, Manchester
- Novartis
- Kite Gilead
- Janssen
- BMS/Celgene



COVID-19 in acute leukaemia/MDS

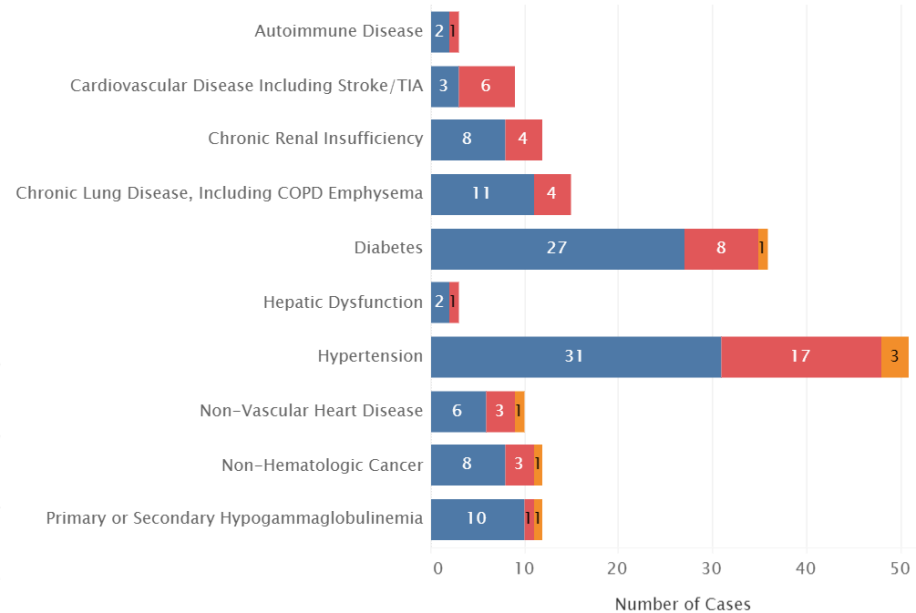
Sex



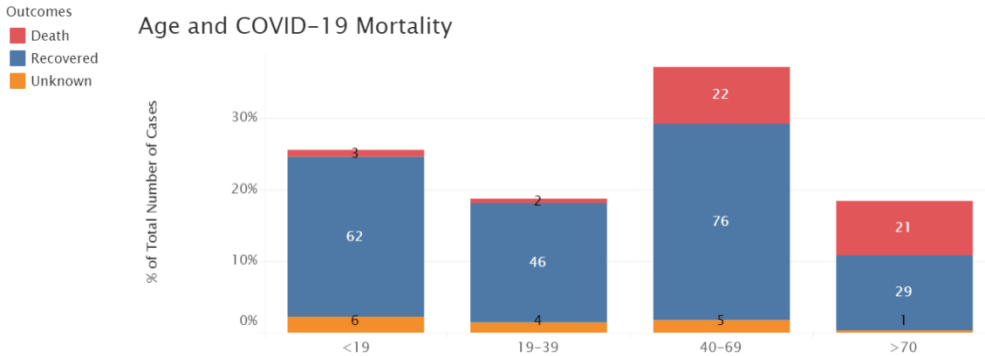
Outcomes



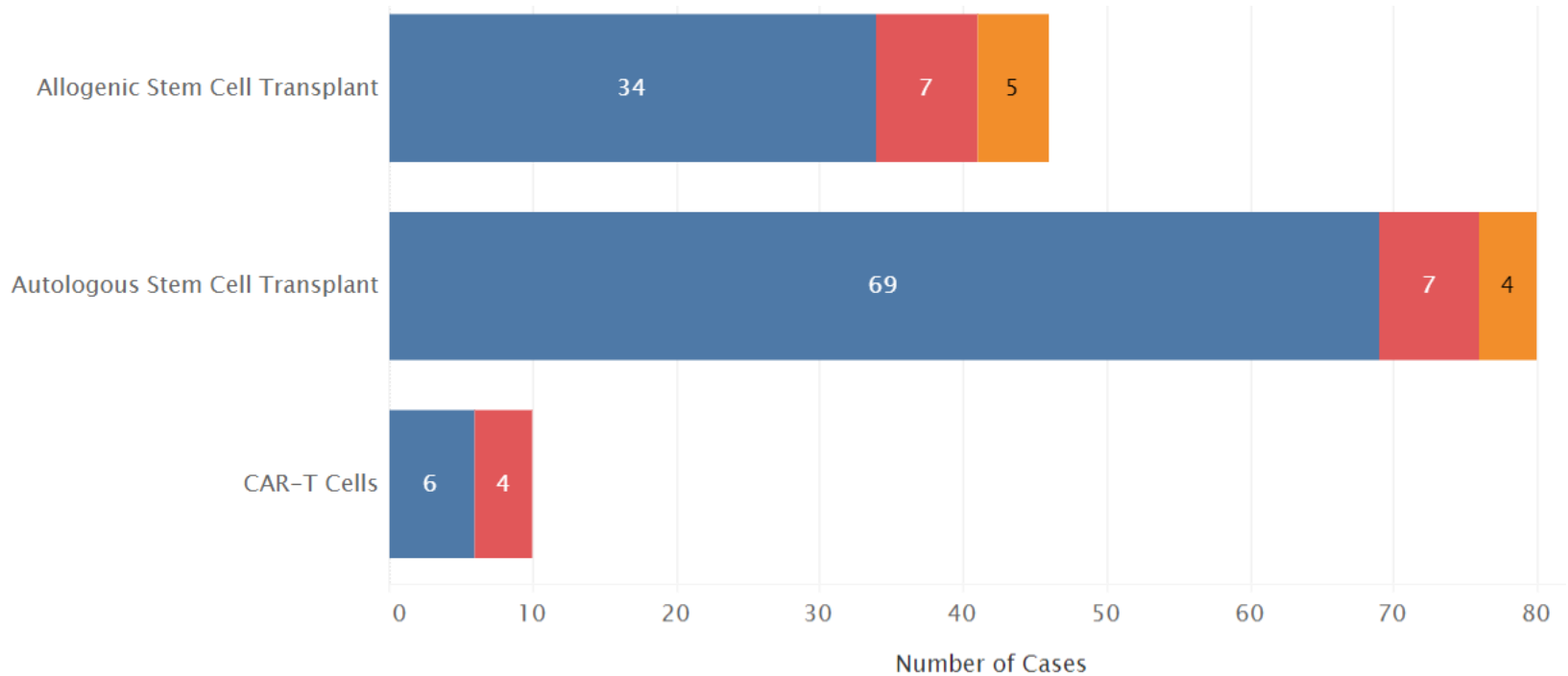
Comorbidities



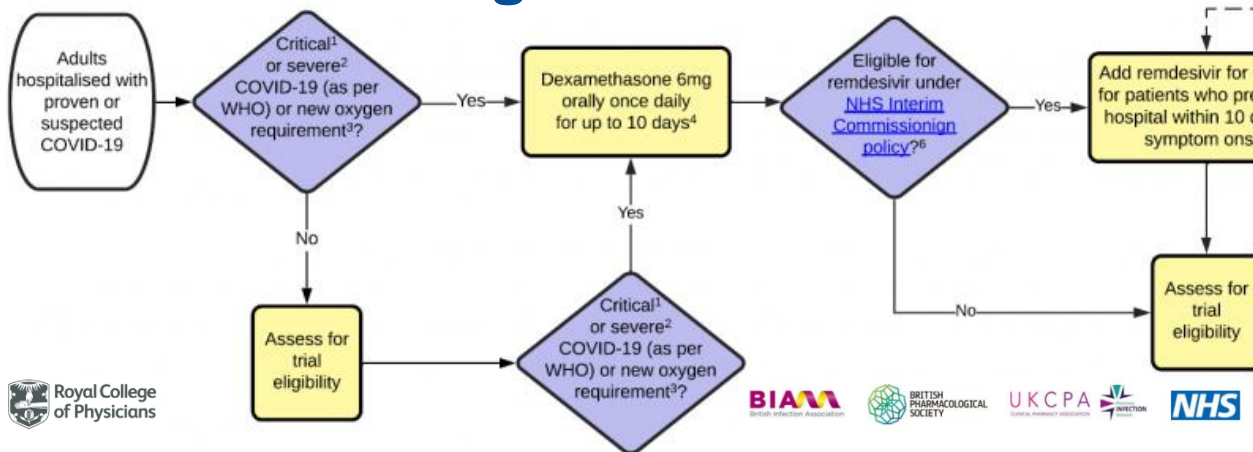
Age and COVID-19 Mortality



COVID-19 after Transplantation and Cellular Therapies



Management of COVID-19 in the UK



Tocilizumab in <24 hours of organ support commencement in critical care area



Overarching term	Hyperinflammation (aka Cytokine Storm Syndrome)						
Syndrome name	Primary or Familial haemophagocytic lymphohistiocytosis (FHLH)	Secondary haemophagocytic lymphohistiocytosis (SHLH)			COVID-19 associated hyper-inflammation	Cytokine release syndrome (CRS)	
Underlying cause	Genetic abnormalities	Infection (inc. SARS-Cov-2) and sepsis	Rheumatic disease	Malignancy	Immuno-deficiency (inc. transplant)	SARS-Cov-2	CAR-T therapy, therapeutic antibodies, allogeneic stem cell transplant
Sub-category syndrome name		Macrophage activation-like syndrome (MALS)	Macrophage activation syndrome (MAS)	No specific term			



COVID-19 vaccines for leukaemia, HSCT, CAR-T patients in the UK

Vaccine	Technology	Trial design, blood cancer and CAR-T patient inclusion				
		Age, years	Blood cancer patients	HSCT / CAR-T patients	Post 1 dose efficacy	Post 2 dose efficacy
Pfizer/BioNTech; BNT162b2	mRNA	≥16	76 with leukaemia and lymphoma	Nil / unknown	52%	95%
AstraZeneca/Oxford; ChAdOx1 nCOV-19	chimpanzee adenoviral vector	≥18	Nil / unknown	Nil / unknown	73.4%	70.4% (pooled data)
Moderna/NIH; mRNA-1273	mRNA	≥18	Nil / unknown	Nil / unknown	?	94.1%

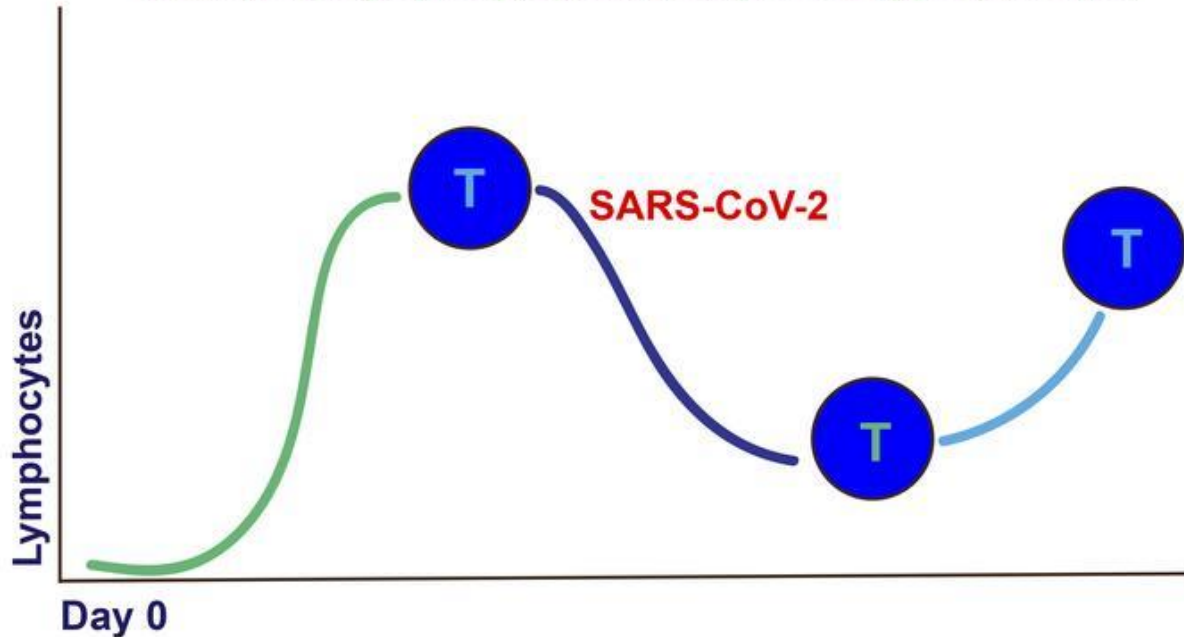
SARS-CoV-2 vaccination following haematopoietic stem cell transplant (HSCT) and chimeric antigen receptor T-cell (CAR-T) therapy. Prepared by the British Society of Blood and Marrow Transplantation and Cellular Therapy Vaccination Sub-Committee (BSBMTCT-VSC); updated 12 January 2021



Cellular Therapies & COVID-19

Outcomes of 77 CAR-T, autologous, or allogeneic hematopoietic cellular transplant recipients with COVID-19

Favorable clinical outcomes for patients without active malignancy
Nearly half of patients remained outpatient
Detection of SARS-CoV-2 antibodies, at times with low B cell counts
Reduction of lymphocytes followed by recovery post-infection

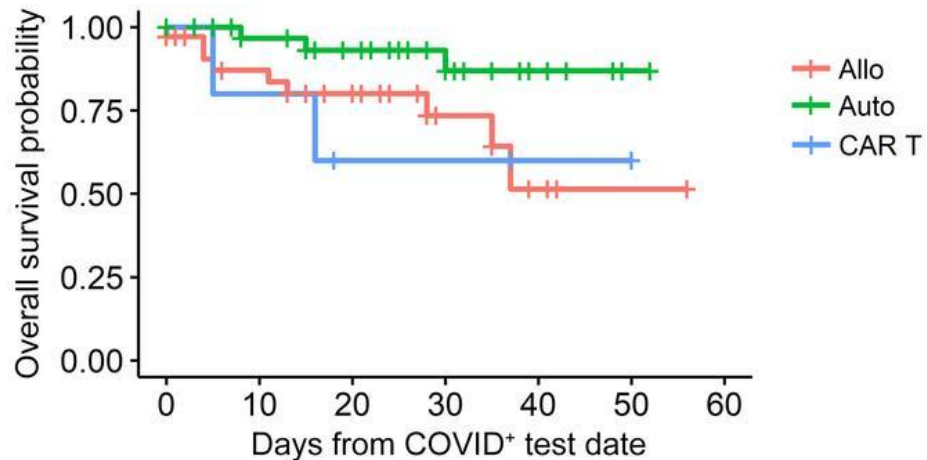
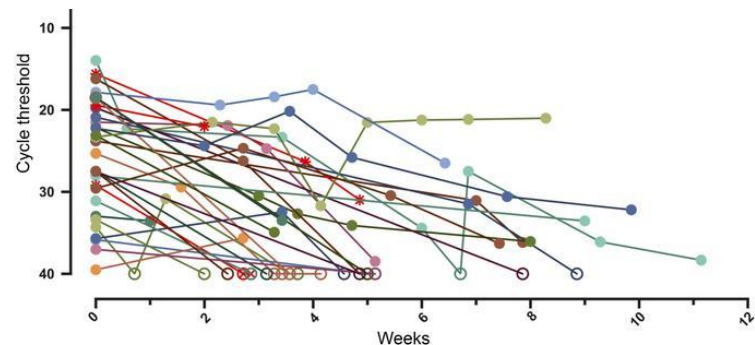


Immune profiles and outcomes post CVOID-19 in HSCT and CAR-T patients

Table 3. Immune profiling correlates of patients with COVID-19

Characteristic	Overall		Allo		Auto		CART	
	N	Median (IQR)	N	Median (IQR)	N	Median (IQR)	N	Median (IQR)
Absolute CD3*	25	354 (119–636)	12	365.5 (54.5–526)	10	376.5 (212.8–804)	3	354 (216–611.5)
Absolute CD4*	25	140 (51–194)	12	146.5 (28.8–202.8)	10	154 (119–199.2)	3	51 (39–73.5)
Absolute CD8*	25	221 (35–327)	12	180 (26–283.5)	10	212.5 (48.5–614.5)	3	254 (140–507)
Absolute CD19*	25	11 (0–50)	12	9 (0.8–26.8)	10	49.5 (5.2–80)	3	0 (0–0)
Absolute NK	25	100 (52–151)	12	115.5 (92.2–252.2)	10	56 (38.5–116.5)	3	72 (54–98.5)
CD4/CD8 ratio	25	0.9 (0.5–1.6)	12	1 (0.6–2.1)	10	0.7 (0.4–1.4)	3	0.4 (0.2–1.2)

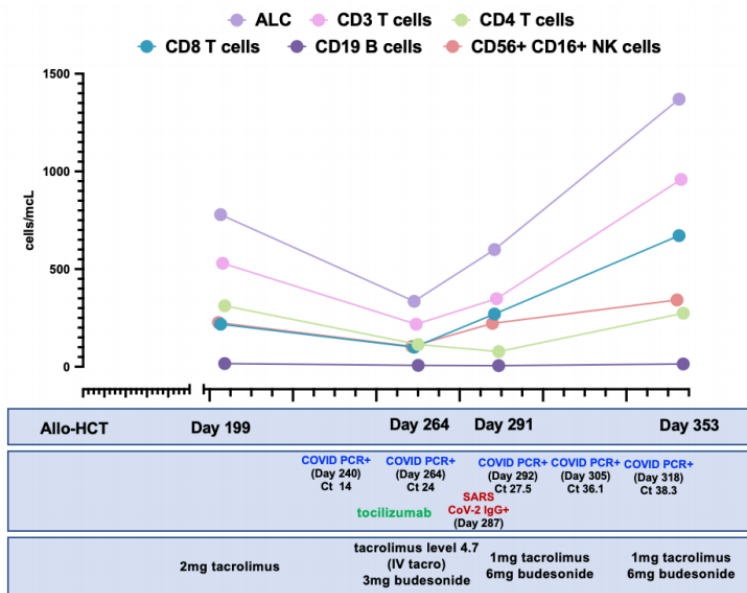
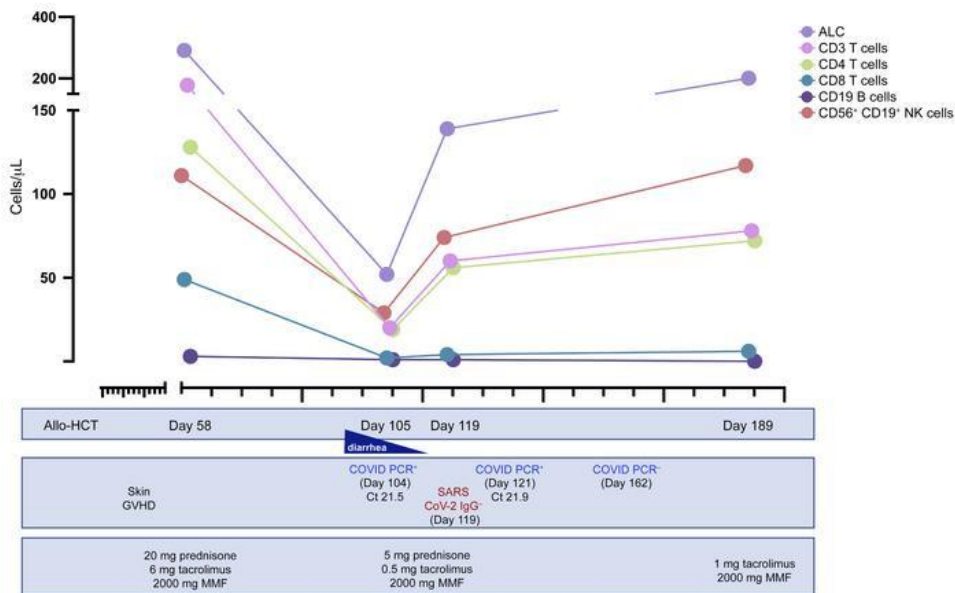
Allo, allogeneic hematopoietic stem cell transplantation; Auto, autologous hematopoietic stem cell transplantation; CART, CD19-directed chimeric antigen receptor T cell therapy.



	Number at risk						
	0	10	20	30	40	50	60
Allo	35	25	20	8	3	1	0
Auto	37	28	22	15	5	1	0
CAR T	5	4	2	2	1	1	0

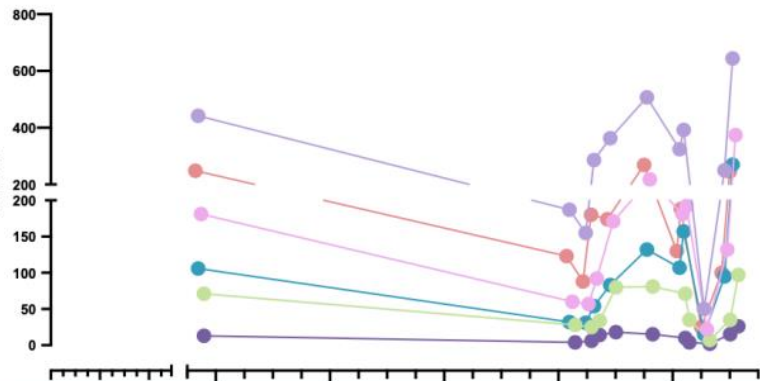


Multiple patterns of immune response and viral clearance post allogeneic stem cell transplant



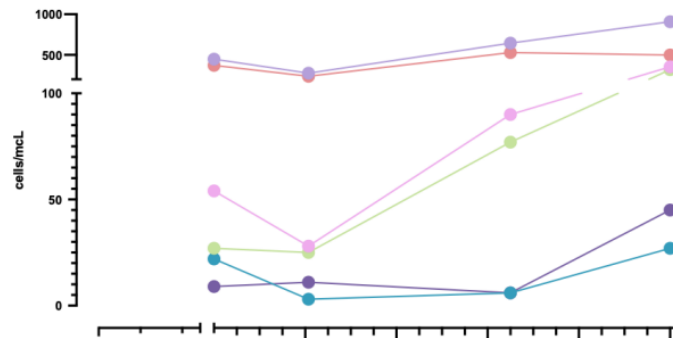
Multiple patterns of immune response and viral clearance post allogeneic stem cell transplant

● ALC ● CD3 T cells ● CD4 T cells
● CD8 T cells ● CD19 B cells ● CD56+ CD16+ NK cells



Allo-HCT	Day 107	Day 198	Day 217	Day 238
		COVID PCR+ (Day 180) Ct 17.85	COVID PCR+ (Days 196, 203, 298, 225) Ct 19.4, 18.4, 17.49, 26.48	COVID PCR- (Day 239)
			NAC Tocilizumab Dexamethasone	SARS CoV-2 IgG+ CoV-2 IgG- (Day 240)
	2mg tacrolimus budesonide 6mg MMF 2000mg	1.5mg tacrolimus budesonide 9mg 1440 mycophenolic acid	1.5mg tacrolimus budesonide 9mg (mycophenolic acid stopped for day 226)	

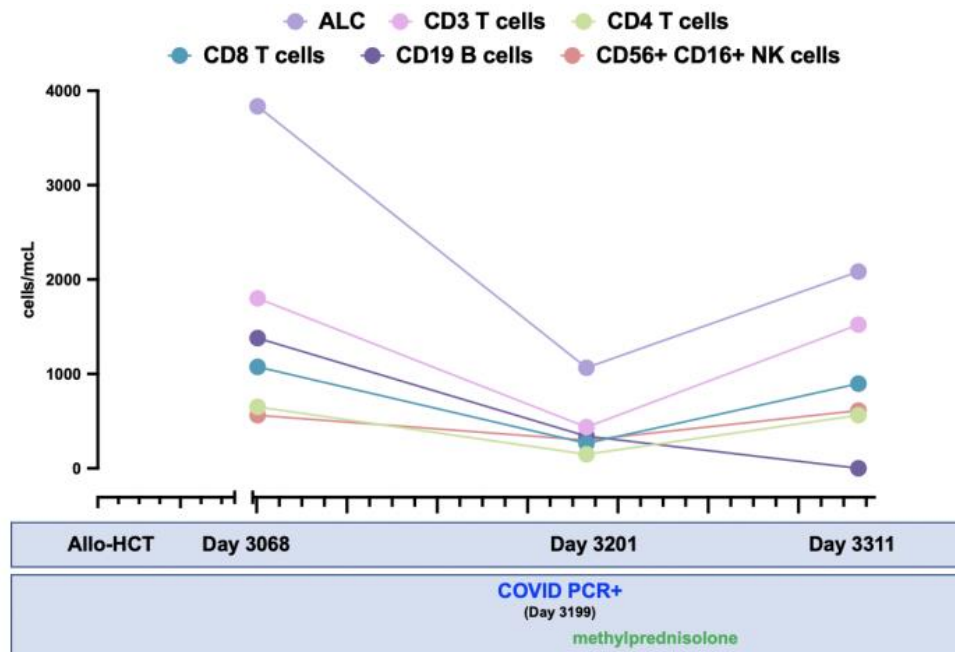
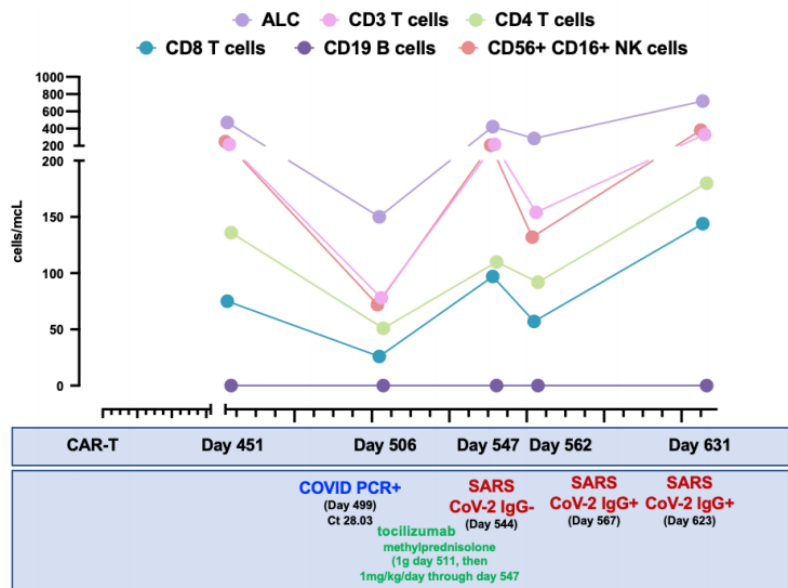
● ALC ● CD3 T cells ● CD4 T cells
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Allo-HCT	Day 28	Day 57	Day 119	Day 168	
		COVID PCR+ (Day 54) Ct 23.79	COVID PCR- (Day 103) Ct 31.05	COVID PCR+ (Day 109) Ct 36.17	COVID PCR- (Day 119)
		Skin GVHD	SARS CoV-2 IgG- (Day 84)		
	cyclosporine 250 mg mycophenolate mofetil 2000 mg	prednisone 35 mg cyclosporine 225 mg mycophenolate mofetil 3000 mg	prednisone 20 mg/10mg alternating days cyclosporine 150 mg mycophenolate mofetil 1000 mg	prednisone 15 mg every other day cyclosporine 150 mg	

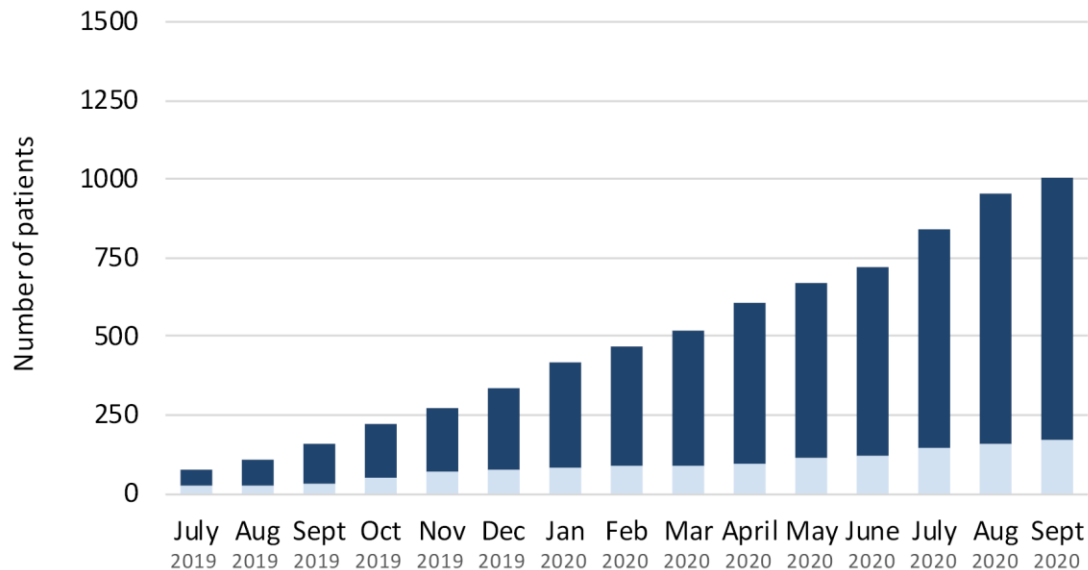


Multiple patterns of immune response and viral clearance post allogeneic stem cell transplant



Increasing CAR-T activity in Europe during COVID-19 pandemic

Number of CAR-T cell treated patients registered in the EBMT Registry



Source: EBMT Registry, September 2020



COVID-19 in the UK

■ Patients treated with commercial CAR-T cells

■ Patients treated with investigational CAR-T cells

Countries reporting CAR-T cell treated patients to the EBMT Registry

■ Reporting countries



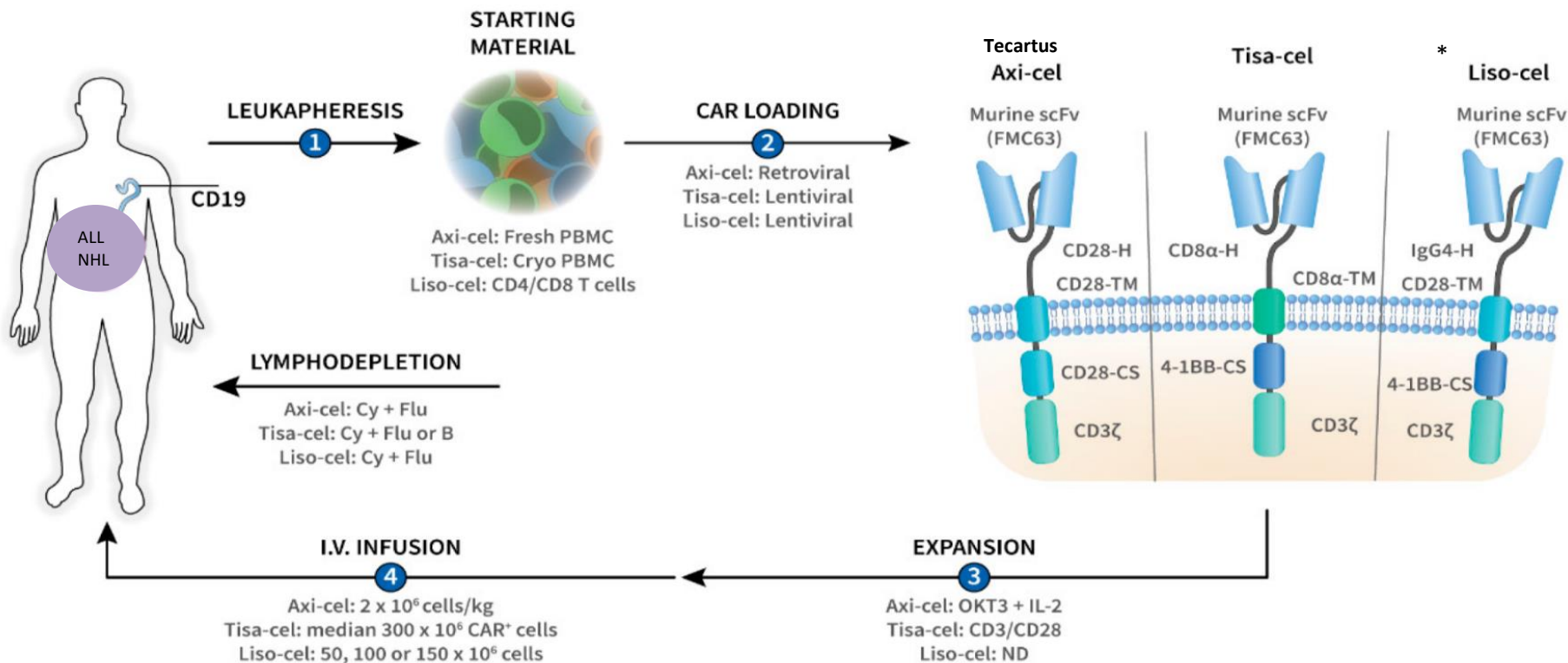
Source: EBMT Registry, March 2020



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CD19 directed autologous CAR-T therapy for ALL / NHL



*Lisocabtagene maraleucel is not currently licensed in the EU and has been investigated for CLL I clinical trials

**Dosing and lymphodepletion regimens differ for the 2 licensed products - refer to relevant SmPC

Van der Steegen S, et al. *Nat Rev Drug Discov.* 2015;14:499–509;

KYMRIAH (TISAGENLECLEUCEL) Summary of Product Characteristics, April 2020

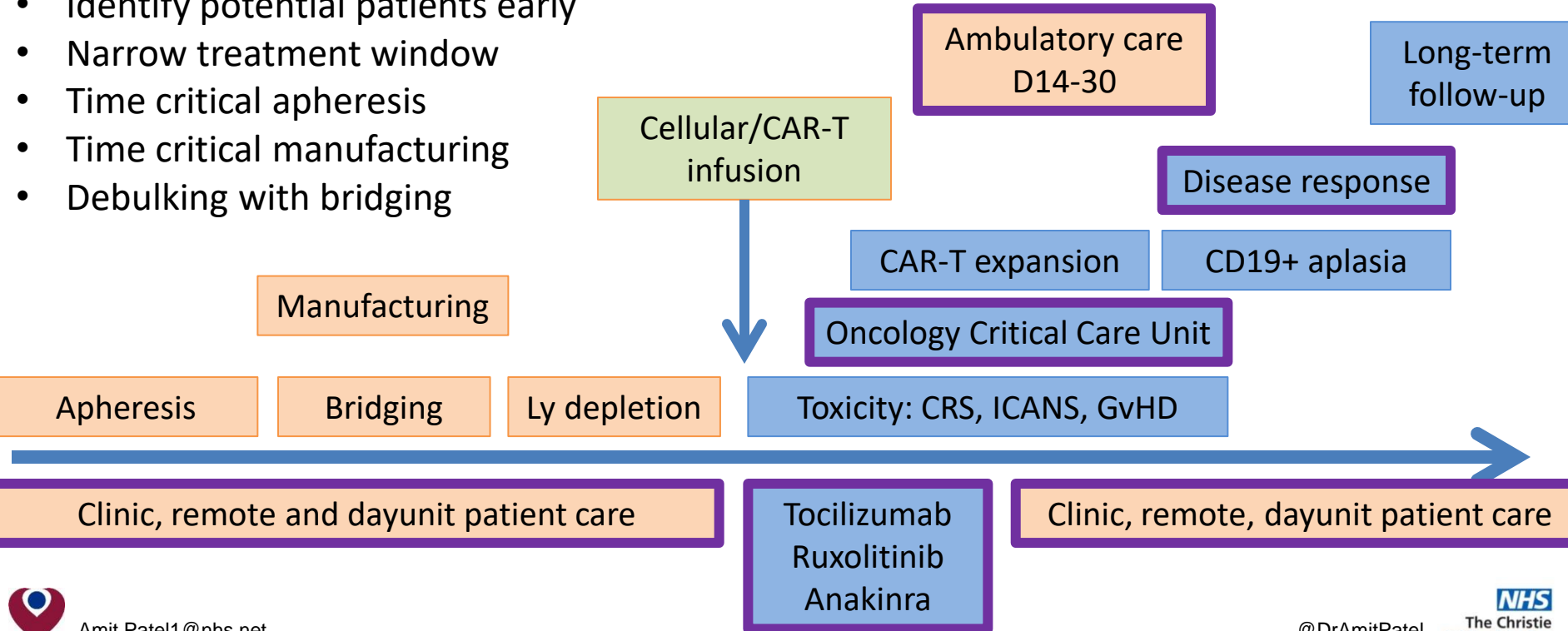
Axicabtagene ciloleucel Summary of Product Characteristics: <https://www.medicines.org.uk/emc/product/9439>

Pharmaceutics 2020, 12(2), 194; <https://doi.org/10.3390/pharmaceutics12020194>



Components of The Christie Cellular/CAR-T therapy pathway

- Identify potential patients early
- Narrow treatment window
- Time critical apheresis
- Time critical manufacturing
- Debulking with bridging





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