

Clonal evolution and the risk of secondary myeloid neoplasia following chimeric antigen receptor T-cell therapy

Authors

Francesca Sillito,¹ Alexandros Rampotas,^{1,2} Kathleen Cheok,¹ Sabine Pomplun,¹ Robert Baker,³ Teresa Marafioti,^{1,2} Maeve O'Reilly,¹ Rajeev Gupta,¹⁻³ Amy A. Kirkwood^{2,4} and Claire Roddie^{1,2}

¹University College London Hospitals; ²University College London (UCL) Cancer Institute, UCL; ³Molecular Haematology, Health Services Laboratories and ⁴CRUK and UCL Cancer Trials Centre, UCL Cancer Institute, UCL, London, UK

Correspondence:

C. RODDIE - c.roddie@ucl.ac.uk

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Flow chart

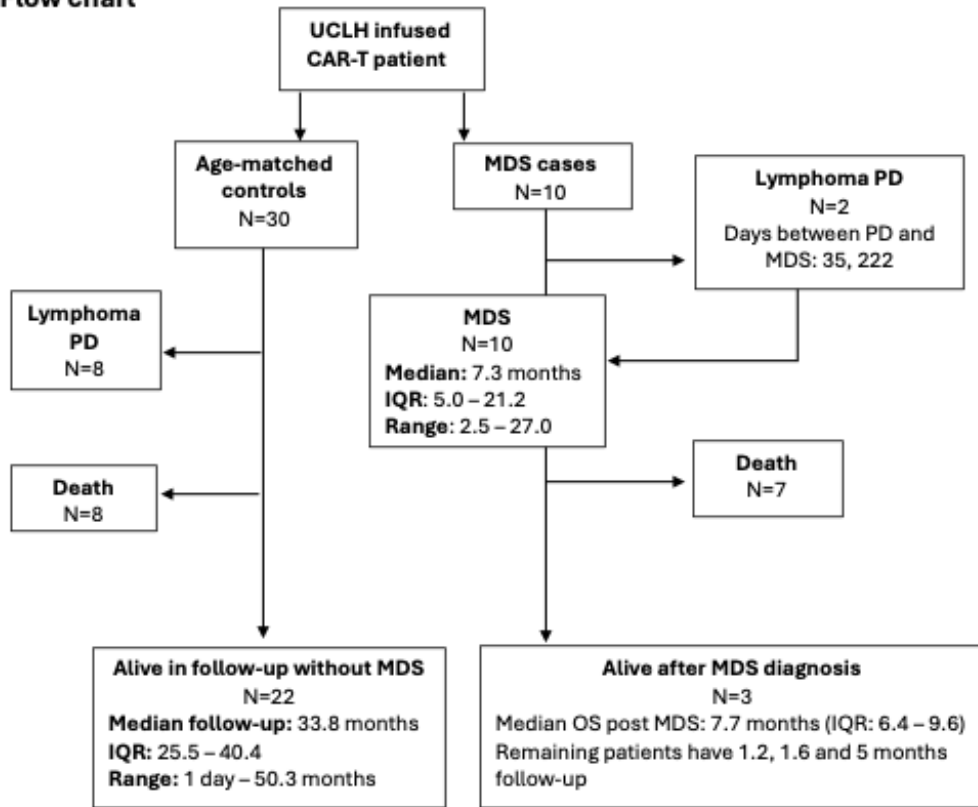


Figure S1: Consort diagram showing clinical outcomes for CAR-T patients diagnosed with tMN compared with an age-matched control cohort.

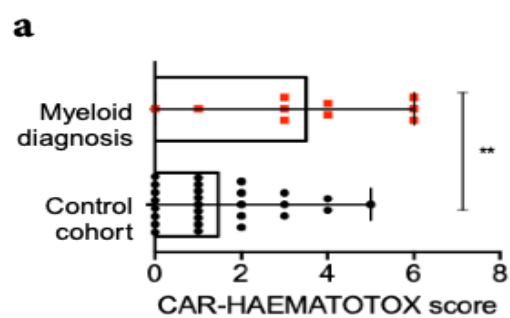


Figure S2 **(a)** HT score Myeloid diagnosis 'MN' cohort vs control cohort, statistics are mann-whitney test, two tailed p value 0.003, median with range

	Age at tMN diagnosis	Primary diagnosis	CAR-T product and conditioning used	Prior lines of therapy	Best response to CAR-T	Lymphoma Relapse post CAR-T	Peak Ferritin (ug/L)	Myeloid malignancy	Myeloid mutations (VAF%)	Treatment for MDS	Survival (months)	Cause of death
1	36	DLBCL (progression from Follicular lymphoma)	Axi-cel (Flu/Cy)	CVP, CHOP, Ofatumumab, ESHAP, IVE, LEAM Auto, Idelalisib, Bendamustine, Obinutuzamb, RT, TBI RIC haplo 2021	CR	Yes	2312	Therapy related AML	ASXL1 truncation (5%)	Ven-Aza	24	AML
2	62	DLBCL (progression from Follicular lymphoma)	Axi-cel (Flu/Cy)	Chlorambucil, Rituximab, R-CHOPx4, BEAM Auto, R-DHAP	CR	No	751	Myelodysplastic Syndrome IPSS 1.5	PPM1D (6.7%), TP53 (3 variants 22.1%, 35.8%, 13.9%), Pathogenic splice variant DNMT3A (46.1%), ZRSR2 (99.6%)	Azacytidine	8	MDS
3	49	Follicular Lymphoma	Axi-cel (Flu/Cy)	RCHOPx6, R-ICEx2, DHAPx2, BEAM Auto, R-GDP, R-Bendax2, Lenalidomide, Pola-BR	CR	No	1051	Therapy Related MDS IPSS 2 R-IPSS 5	TP53 mutation (C176S 85%), CNV pattern gain Chr 21	Azacytidine	12	MDS
4	67	Transformed LPL	Axi-cel (Flu/Cy)	Fludarabine x5, R-CPx8, R-CHOPx4, ESHAPx1, R-GDPxx3, BEAM Auto, RT	CR	No	1344	Myelodysplastic Syndrome IPSS 2 R-IPSS 5		Azacytidine	6	MDS

5	60	Transformed WM	Axi-cel (Flu/Cy)	Rituximab, R-CHOPx4, RT, R-ESHAPx2	CR	No	12468	Therapy related MDS IPSS 1	ASXL1 mutation G646WfsTER12 (17%)	Planned for allo-SCT	9	N/A
6	61	DLBCL (progression from Follicular lymphoma)	Axi-cel (Flu/Cy)	Rituximab+Chlorambucil, 6xR-Benda, LEAM Auto, R-CHOPx6, R-ICE, RT	CR	No	1149	Secondary MDS IPSS 2 R-IPSS 4	Monosomy 7 (16%) Myeloid NGS PPM1D p.Ala481ProfsTer2 (28%)	Azacytidine	8	Mucormycosis MDS
7	51	Follicular Lymphoma	AUTO-1 (Flu/Cy)	RCHOPx6, R-GDP, Glofit+41BB ab (Trial P41072), R-Benda	CR	No	154	MDS IPSS 1 R-IPSS 3	DNMT3A (8%), LN: ASXL G646WfsTer12 variant LN NGS, FLIT3-ITD clone	Nil	1	Appendicitis MDS
8	58	Mantle Cell Lymphoma	Brexu-cel (Flu/Cy)	Nordic protocol, LEAM AUTO, Rituximab, Ibrutinib, Venetoclax	CR	Yes	1313	Therapy related MDS IPSS 1.5 R-IPSS 5	PPM1D p.Arg581Ter (9%), TP53 p.Arg273Leu (9%)	Nil	0	MDS
9	50	Diffuse Large B-cell Lymphoma	Axi-cel (Flu/Cy)	RCHOP, R-IVAC/RCODOX/M, R-GDP, LEAM ASCT, RBP	PR	No	1283	Therapy related AML	NUP98-NSD1 translocation; WT1 mutation; TET2 mutation	Ven-Aza And allo-SCT	8	N/A
10	52	Follicular	Axi-cel (Flu/Cy)	FL: Rbenda x6, Ritux maintenance, R-CHOP for relapse, LEAM Auto	CR	No	3554	Therapy related MDS	TET2 p.Ser714Ter (47%),	Nil	1	N/A

		Lymphoma		10/11/20; tFL: GDPx2, Epcoritimab x4				IPSS 1.5 R-IPSS 5.5	TET2 p.Arg544Ter (40%) and SRSF2 p.Pro95Leu DNMT3A p.Pro633Leu (18%), DNMT3A p.Asp658Ty r (10%), PPM1D p.Cys478Ter (7%) and DNMT3A c.2173_2173+1del splice donor and coding sequence (6%) variants.		
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Table S1. Detailed patient characteristics for patients who developed myeloid malignancy post CAR-T cells therapy. WM: Waldenstrom's Macroglobulinaemia. LPL: Lymphoplasmacytic Lymphoma. Axi-cel: Axicabtagene Ciloleucel. AUTO-1: CD19CAT-41BBζ. Flu/Cy: Fludarabine/Cyclophosphamide. CVP: cyclophosphamide, vincristine, and prednisolone. R-: Rituximab. CHOP: cyclophosphamide, doxorubicin hydrochloride (hydroxydaunomycin), vincristine sulfate (Oncovin) and prednisolone. ESHAP: Etoposide, Solumedrol, High-dose Ara-C, and Platinum. IVE: Ifosfamide, Etoposide, and Epirubicin. LEAM-Auto: Lomustine, Etoposide, Ara-C (cytarabine), and Melphalan autologous stem cell transplantation. RT: Radiotherapy. TBI: Total Body Irradiation. Haplo: Haploidentical stem cell transplantation. Benda: Bendamustine. GDP: Gemcitabine, Dexamethasone, and Cisplatin. ICE: Ifosfamide, Carboplatin, and Etoposide. Pola-BR: Polatuzumab Vedotin, Bendamustine, and Rituximab. IVAC: Ifosfamide, Etoposide, and high-dose Cytarabine. CODOX/M: Cyclophosphamide, Vincristine (Oncovin), Doxorubicin, high-dose Methotrexate, and cytarabine (Ara-C).(R)IPSS: (Revised) International Prognostic Scoring System. AML: Acute Myeloid Leukaemia. MDS: Myelodysplastic Syndrome.