Safety, Efficiency and Long-Term Follow-up of AUTO1, a Fast-Off Rate CD19 CAR in Relapsed/Refractory B-Cell Acute Lymphoblastic Leukaemia and Other B-Cell Malignancies

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INTRODUCTION

- AUTO1 (obecabtagene autoleucel) is a fast off-rate CD19 binding domain autologous CAR, designed to reduce immune toxicity and improve engraftment. Its clinical activity has been tested in r/r paediatric and adult B-ALL (Ghorashian S et al., Nat Med 2019; Roddie C et al., JCO 2021) and now in adult B-NHL and CLL/SLL (NCT02935257).
- Here we present data from adult B-NHL and CLL cohorts treated with AUTO1, and report on long-term follow-up of adult B-ALL patients post-AUTO1.

METHODS

- **ALLCAR19 (NCT02935257) is a multi-centre, non-randomised, open-label Phase I/II study recruiting a total of 60 patients with r/r B-ALL, FL, MCL, DLBCL or CLL/SLL.**
  - B-ALL: r/r following ≥2 prior lines
  - DLBCL (incl. transformed FL but not Richter's): following ≥2 prior lines (incl. Rituximab and anthracycline)
  - FL/MCL: r/r following ≥2 prior lines
  - CLL/SLL: following ≥2 prior lines (incl. Ibrutinib/other BTKi)
- AUTO1 is manufactured with non-mobilised autologous leukapheresate on the semi-automated Miltenyi CliniMACS Prodigy®.
- All patients receive Cyclophosphamide (Cy) (60mg/kg) and Fludarabine (Flu) (3x30 mg/m^2) lymphodepletion. DLBCL patients also receive a single dose of Pembrolizumab (200mg i.v.) as part of pre-conditioning.
- In B-ALL, patients received split dose AUTO1 (day 0: ≥20% Bone Marrow (BM) blasts, AUTO1 dose=10 million CART; <20% BM blasts, AUTO1 dose=100 million. At day+9: if no grade 3-5 CRS/ICANS, dose 2 is administered to a total AUTO1 dose of 410 million CART*. Split dosing is employed in the CLL cohort (day 0 AUTO1 dose= 30 million; day 9 AUTO1 dose= 200 million). B-NHL patients receive a single AUTO1 dose of 200 million.
- Study endpoints include manufacture feasibility, grade 3-5 toxicity and remission rates at 1 and 3 months.
- Disease assessment was by ^{18}FDG PET-CT imaging as per Lugano criteria (Cheson et al.) for FL, MCL and DLBCL, and by CT and BM biopsy assessment for B-ALL and CLL/SLL.

Indication	LD	Day 0 Dose 1 (x10^6 CAR T-cells)	Day 9 Dose 2 (x10^6 CAR T-cells)
DLBCL	Cy / Flu Pembro (D-1)	200	-
B-CLL/SLL	Cy / Flu	30	200
FL	Cy / Flu	200	-
MCL	Cy / Flu	200	-
B-ALL	Cy / Flu	10/100*	400/310*

Table 1. ALLCAR19 treatment schedule

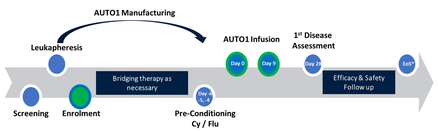
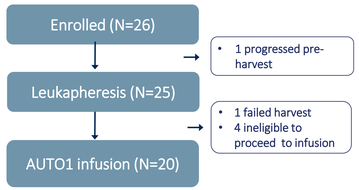


Figure 1. Overall ALLCAR19 - Study Design

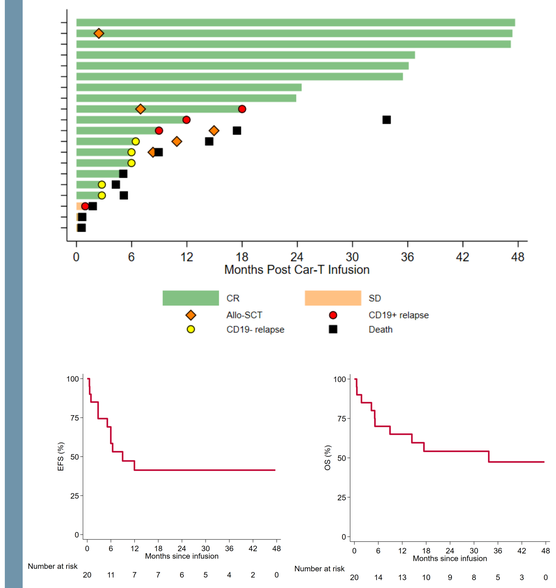
RESULTS: B-ALL

Figure 2. CONSORT Diagram & Manufacturing Feasibility B-ALL



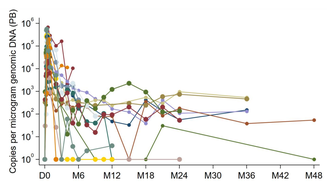
Data cut: 2-NOV-2022

Figure 3. Swimmers plot, EFS and OS plots



- Of the 20 infused B-ALL patients, 8/20 (40%) are in ongoing CR at a median FU of 36 months (IQR 24-47) post-AUTO1
- 7/8 maintain remission without any further therapy (including TKI)
- Long-term remission is associated with CAR-T persistence in 7/8 (88%) at last follow-up (data cut-off 02/11/22)

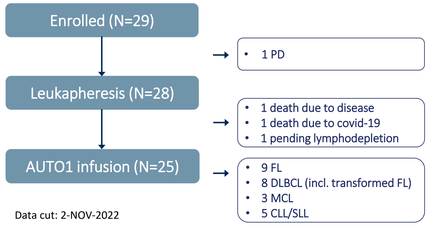
Figure 4. Post-Infusion Kinetics of CAR T-Cells in the Blood (qPCR) in n=20 infused B-ALL patients



Cmax (CAR transgene per ug gDNA)	
n	20
Mean	204249
CV%	91.6%
Time to Cmax (Days)	
n	20
Median	12.5
Range	7-21
Time last measurable in Blood (Days)	
n	20
Median	320
Range	14-1461

RESULTS: NHL/CLL

Figure 5. CONSORT Diagram & Manufacturing Feasibility NHL/CLL



Data cut: 2-NOV-2022

Table 2. Baseline Characteristics NHL & CLL cohorts

Baseline Characteristics	N=25
Median age, years (range)	60 (39 - 79)
Gender	7F / 18M
Disease	
• Follicular Lymphoma (FL)	9(36%)
• DLBCL (incl. transformed FL)	8(32%)
• Mantle Cell Lymphoma (MCL)	3 (12%)
• CLL/ SLL	5 (20%)
Lines of treatment	
• Median (range)	3 (2-8)
• Prior autograft	6(24%)
• Prior allo-HSCT	2 (8%)
Stage of disease at screening	
Ann Arbor (B-NHL)	20 Patients
• Stage II	3 (15%)
• Stage III	1 (5%)
• Stage IV	15 (75%)
• Unknown	1 (5%)
Rai/BINET (B-CLL)	5 Patients
• I/A	2 (40%)
• I/B	1 (20%)
• II/B	1 (20%)
• Unknown	1 (20%)
Bridging therapy	
• Chemoimmunotherapy	14 (56%)
• Chemoimmunotherapy + radiotherapy	1 (4%)
• Radiotherapy only	2 (8%)
• Chemotherapy only	2 (8%)
• Immunotherapy only	4 (16%)
• Nil	2 (8%)

Table 3. Treatment-Emergent Adverse Events ≥ 25% (n=25)

TEAEs (N=25)	Any grade	Grade 3 & 4
Any event	23 (92%)	20 (80%)
Neutrophil count decreased	18 (72%)	17 (68%)
Fever	17 (68%)	1 (4%)
Anaemia	14 (56%)	12 (48%)
Diarrhoea	14 (56%)	1 (4%)
Platelet count decreased	13 (52%)	10 (40%)
Fatigue	13 (52%)	1 (4%)
Hypokalaemia	13 (52%)	3 (12%)
Nausea	11 (44%)	0
Hypophosphataemia	9(36%)	5(20%)
Anorexia	9 (36%)	1 (4%)
Febrile neutropenia	9 (36%)	9 (36%)
Hypotension	8 (32%)	20 (80%)
White blood cell decreased	8 (32%)	8 (32%)
Chills	8 (32%)	0
Headache	7 (28%)	0

Table 4. Incidence of CRS/ICANS

Event N=25 patients	All Grades n (%)	G1 n (%)	G2 n (%)	G3 n (%)	G4 n (%)
CRS	14 (56%)	8 (32%)	6 (24%)	0	0
ICANS	0	1 (4%)	0	0	0

*CRS grading by ASTCT consensus criteria. Lee et al 2019; Data cut: 2-NOV-2022

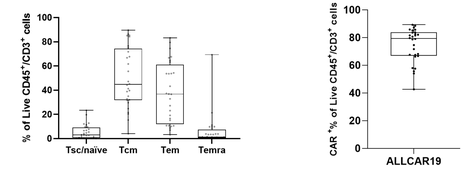
Table 5. Safety Summary

Safety, N=25 patients	n (%)
Number of subjects with at least one:	
-AE (any grade)	23 (92%)
-AE grade 3 & 4	20(80%)
-AE grade 5	1 (4%)*
-SAE	14 (56%)
Number of deaths of any causality	3 (12%)

* COVID-19; Data cut: 2-NOV-2022

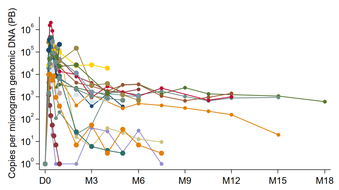
- **No patient required ICU admission due to CRS**
- **10 patients received tocilizumab for CRS**

Figure 5: Transduction Efficiency and Product Characteristics*



*for all patients who were leukapheresed

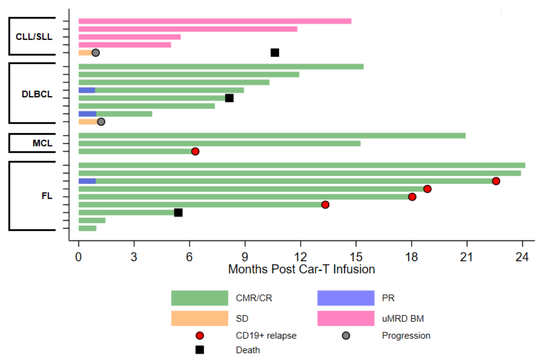
Figure 6. Post-Infusion Kinetics AUTO1 in the Blood (qPCR) in n=20 patients



Cmax (CAR transgene per ug gDNA)	
n	20
Mean	245101
CV%	185.7%
Time to Cmax (Days)	
n	20
Median	10
Range	7-21
Time last measurable in Blood (Days)	
n	20
Median	183
Range	21-548

Figure 7. Swimmers Plot, PFS plots CLL, DLBCL, MCL, FL

Median FU from infusion in NHL/CLL cohort is 12.9 months (IQR 7.4-18.0).
2 deaths in remission from COVID19; 1 death from PD.



CONCLUSIONS

B-ALL:

- 8/20 (40%) patients are in ongoing CR at median FU 36 months (IQR 24-47) post-AUTO1, 7/8 with no further therapy (including TKI).
- Ongoing long-term remissions appear to be associated with CAR-T persistence, which was also observed in 7/8 patients at last follow-up

B-NHL/CLL:

- AUTO1 manufacture successfully extended from B-ALL to patients with r/r FL, MCL, DLBCL, and CLL/SLL
- AUTO1 continues to display a favourable safety profile with no ICANS or Grade ≥ 3 CRS across different indications
- Of 25 patients with NHL/CLL evaluable for efficacy, best ORR was 23/25 (92%) and 18/23 (78%) are without disease progression at a median follow-up of 12.9 months (IQR 7.4-18.0)
- AUTO1 was well-tolerated and effective in DLBCL, with 7/8 patients in ongoing CR at last follow-up
- In CLL, 4/5 treated patients achieved undetectable MRD (uMRD) in the BM, ongoing at last follow-up
- Late CD19+ relapses were seen in FL, and ongoing CAR-T persistence appears to be important for ongoing response
- Longer follow-up and enrolment of additional MCL, DLBCL and CLL/SLL patients is ongoing

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