Disclosure Information

Relationships with Companies

Ramakrishnan, Aravind

-Speaking and Advisory Boards-Millenium/Takeda

-Advisory Boards-Amgen

-Honoraria-Cigna

Phase 1/2 study of AUTO3, the first bicistronic chimeric antigen receptor (CAR) targeting CD19 and CD22, followed by an anti-PD1 in patients with relapsed/refractory (r/r) Diffuse Large B Cell Lymphoma (DLBCL): Results of Safety Cohorts of the ALEXANDER study

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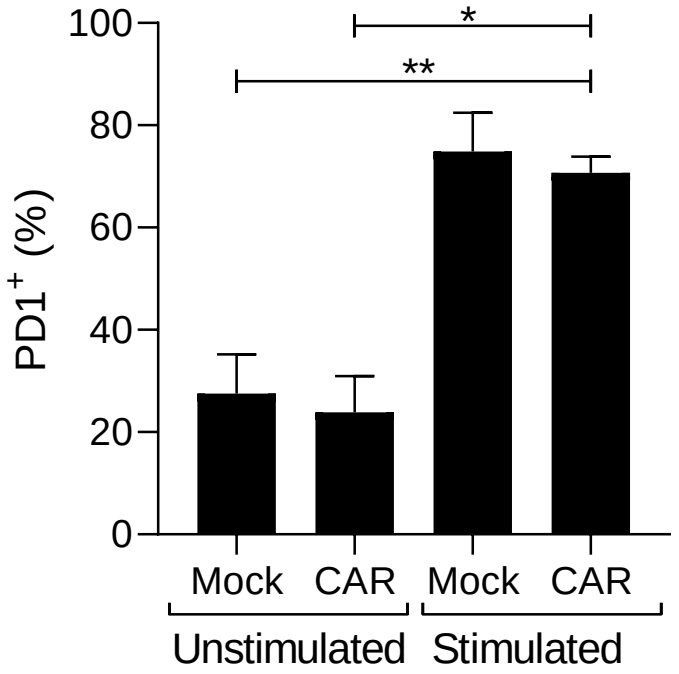
Improving CAR T Cell Immunotherapy In DLBCL

Dual Targeting CAR & Prevention of Early CAR T Exhaustion

- CD19 CARs are active in r/r DLBCL
- However unmet need remains with CD19 CAR T cell therapy
  - 29-37% durable CRR in DLBCL[1,2]
  - The potential causes for relapse include:
    - PD-L1 upregulation[3] which contributes to CAR T exhaustion
    - CD19 antigen loss[4]
  - Rate of severe (grade ≥3) cytokine release syndrome (CRS 13-22%) and neurotoxicity (NT 12-28%)[2,4]
- Simultaneous targeting of CD19 and CD22 may reduce the probability of relapse due to antigen loss
- PD1/PDL1 mediated CAR T cell exhaustion may be prevented by adding pembrolizumab to the preconditioning regimen

Activated T-cells Upregulate PD1

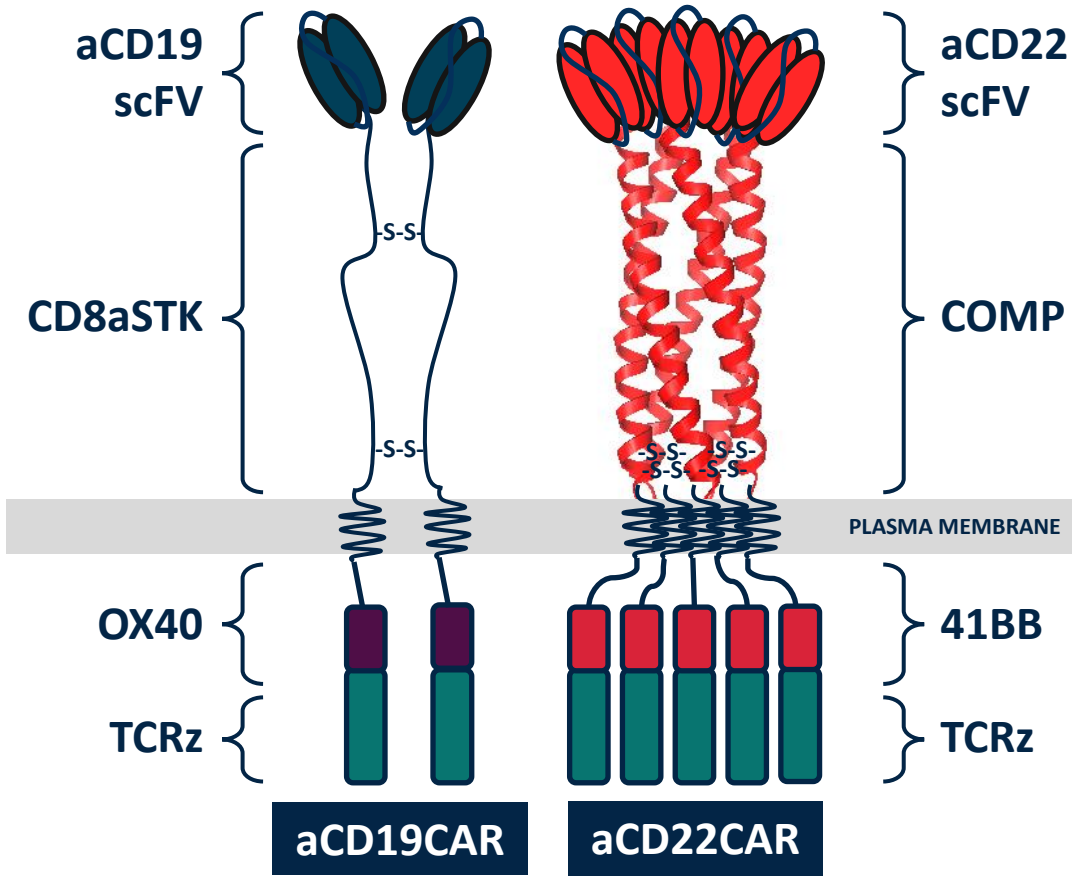


[1] Locke F et al Lancet Oncol 2019
[2] Schuster S et al NEJM 2019
[3] Neelapu S et al ASCO 2018
[4] Neelapu S et al NEJM 2017

AUTO3: First CD19 and CD22 Targeting Bicistronic CAR

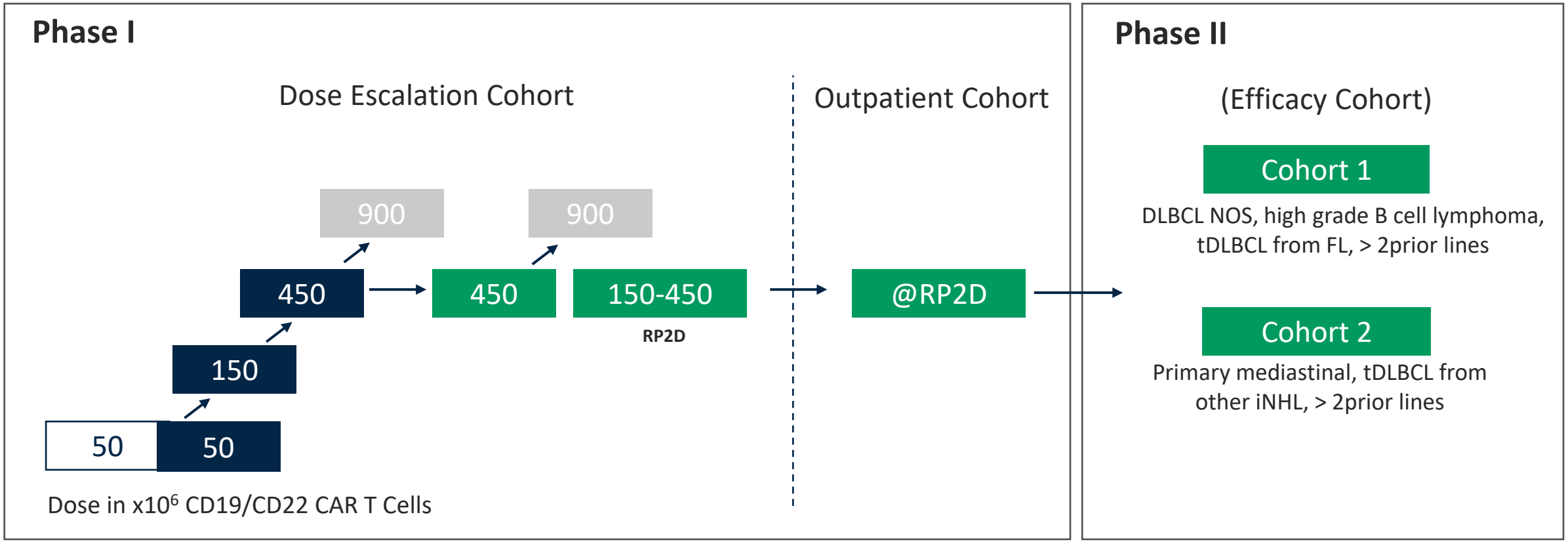
Gamma Retroviral-Based Vector with RD114 Pseudotype

- Dual antigen targeting
- Two independent CARs delivered in single retroviral vector
- Humanized binders
- CD22 CAR with novel pentameric spacer
- OX40/41BB costimulatory domains designed to improve persistence
- Independently target CD19 and CD22



Alexander Study Design

AUTO3-DB1, Single-Arm, Open-Label, Multi-Center, Phase 1/2 Study



Preconditioning: Flu/Cy	Flu/Cy + Pembro day 14 x 3 doses	Flu/Cy + Pembro day -1 x 1 dose

Key Eligibility Criteria

Inclusion criteria

- ≥ 18 years
- Chemo-refractory disease, or relapse after at least two lines of therapy, or after ASCT
- DLBCL not otherwise specified (NOS), and DLBCL with MYC and BCL2 and/or BCL6 rearrangements (double/triple hit)
- Transformed DLBCL from follicular lymphoma
- Transformed DBCL from other indolent lymphomas (excluding Richter's transformation)
- High-grade B cell lymphoma with MYC expression (excluding Burkitt's lymphoma)
- Primary mediastinal large B cell lymphoma

Exclusion criteria

- Pre-existing significant neurological disorder
- Prior allogenic haematopoietic stem cell transplant
- Prior CD19 or CD22 targeted therapy
- Contraindication to receiving pembrolizumab

Study End Points

Primary

Phase I

- Incidence of Grade 3–5 toxicity occurring within 75 days of AUTO3 infusion
- Frequency of dose limiting toxicities of AUTO3

Phase II

- Best overall response post-AUTO3 infusion
- Incidence of Grade 3–5 toxicity occurring within 75 days of AUTO3 infusion

Secondary

Phase I and Phase II

- Safety
- Feasibility of AUTO3 product generation
- Cellular kinetics
- Efficacy: CR, DFS, PFS, OS
- B-cell aplasia

Patient Characteristics

Baseline Patient Characteristics		N=23
Age, median (min-max)		57 (28-83)
Gender, n	Male, Female	14, 9
Current Histology, n	**DLBCL** - GCB - Non-GCB **tDLBCL** - FL - MZL	 10 7 5 1
Disease Stage, n	II III IV	2 5 16
Relapsed/Refractory, n	Refractory Relapsed Relapsed and Refractory	5 3 15
IPI, n	0-1 2 3-4	4 7 12
No. Prior Therapies, median (min-max)		3 (2-10)
Prior ASCT, n		4
SPD, median (min-max)		22.3 cm (2.08 – 260.84)

ASCT: Autologous Stem Cell Transplant; tDLBCL: transformed DLBCL; IPI: International Prognostic Index; ABC: Activated B-Cell like; GCB: Germinal Center B Cell-like; FL: Follicular Lymphoma; MZL: Marginal Zone Lymphoma; No.: Number

Treatment Emergent Adverse Events (≥ 25%)

AEs (Total N = 23)	All Grades N (%)	Grades 3 & 4 N (%)
Neutropenia	20 (87%)	20 (87%)
Thrombocytopenia	15 (65%)	13 (57%)
Anaemia	13 (57%)	11 (48%)
Cytokine release syndrome	9 (39%)	0
Fever	9 (39%)	0
Constipation	7 (30%)	0
Fatigue	6 (26%)	0

- Majority of > Grade 3 AEs are haematological
- No dose limiting toxicities
- No AUTO3-related deaths or Grade 5 adverse events

SAE = Majority hematological including febrile neutropenias. Others include 1 case of gallbladder abscess, 1 case of grade 4 pneumonia due to parainfluenza, 1 case of subdural hemorrhage due to thrombocytopenia and fall, and 1 case of grade 3 NT which all resolved.

Cytokine Release Syndrome (CRS)

	50 x10^6 AUTO3 no pem (N=4)	50 x10^6 AUTO3 D14 pem (N=3)	150 x10^6 AUTO3 D14 pem (N=4)	450 x10^6 AUTO3 D14 pem (N=4)	450 x10^6 AUTO3 D -1 pem (N=4#)	150-450 x 10^6 AUTO3 D-1 pem RP2D (N=4)	Total (N=23)
Grade 1 CRS	1	0	1	1	2	1	6 (26.1%)
Grade 2 CRS	0	0	1	1	0	1	3 (13%)
≥ Grade 3 CRS	0	0*	0	0	0	0	0

* 1 patient who had no CRS with primary infusion, developed G3 CRS (severe hypoxia) with re-treatment 1 year later which happened in a setting of no CAR T expansion and significant disease burden in lung that had been treated with radiation

Includes one patient that received only 125 x 10^6

- No prophylactic measures of any kind
- Median time to CRS 7 days (1-36), median duration of CRS 5 days (1-19)
- No grade 3 or higher CRS* with primary infusion
- 4 patients (17%) received tocilizumab for CRS

Neurotoxicity (NT)

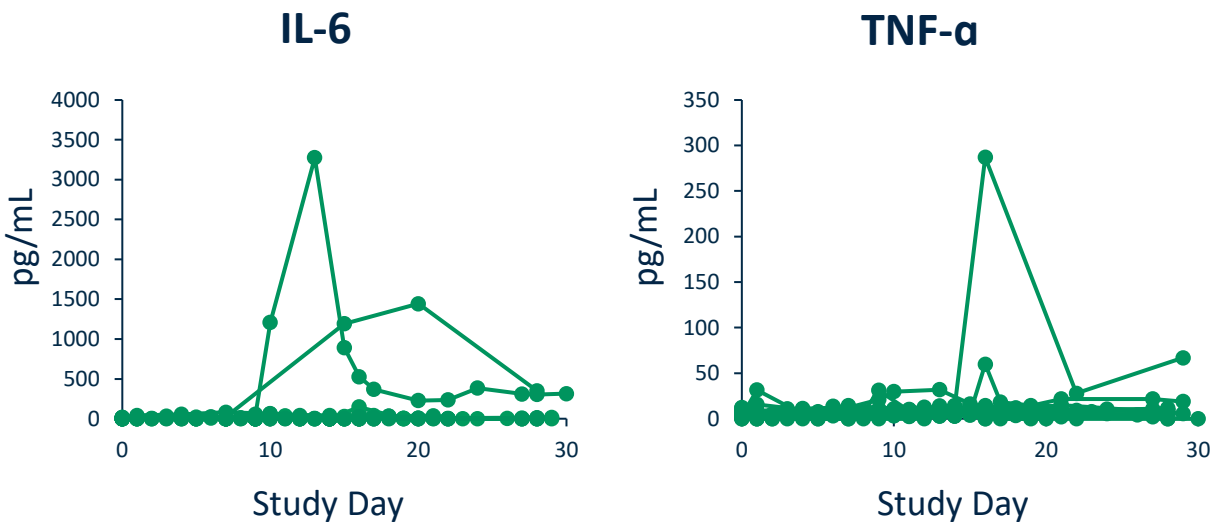
	50 x10^6 AUTO3 no pem (N=4)	50 x10^6 AUTO3 D14 pem (N=3)	150 x10^6 AUTO3 D14 pem (N=4)	450 x10^6 AUTO3 D14 pem (N=4)	450 x10^6 AUTO3 D -1 pem (N=4#)	150-450 x 10^6 AUTO3 D-1 pem RP2D (N=4)	Total (N=23)
All grades NT	1	0	0	0	0	0	1 (4.3%)
≥ Grade 3 NT	1	0	0	0	0	0	1 (4.3%)

Includes one patient that received only 125 x 10^6

- No prophylactic measures of any kind
- Only 1 case of NT (Grade 3) which resolved quickly with steroids
  - No CART expansion was seen at any time. Grade 3 NT occurred on day 53. Symptoms improved in 3 days. The same symptoms of facial/muscle weakness occurred > 10 years ago without specific diagnosis.
- No neurotoxicity of any grade in AUTO3 + pem

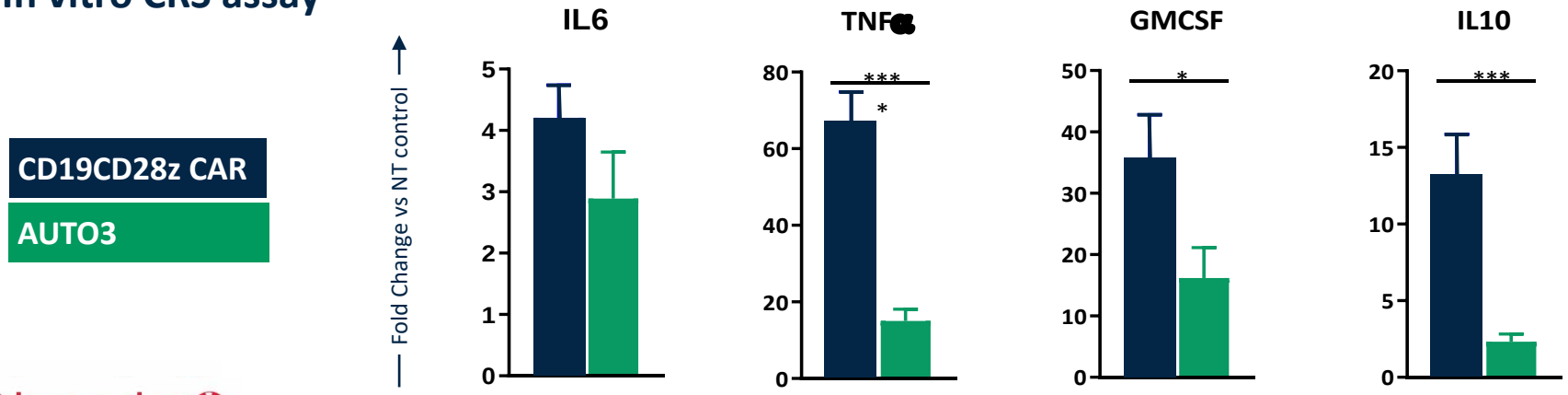
Low *in-vitro* and *in-vivo* Cytokines Consistent with Low Grade CRS

Clinical



CAR T Product	CRS Grade 0-2 Median IL-6 level pg/ml	CRS Grade ≥3 Median IL-6 level pg/ml
AUTO3	16.55 (0 – 3275)	NA
Yescarta	49.4 (3.5, 12109.7)	713.9 (152.5- 50705)

In vitro CRS assay



CRS-associated cytokines were produced at multi-fold higher levels by CD19CD28z CAR* versus AUTO3 in a trans well/ macrophages in vitro CRS model (Norelli et al 2018)

* CD19CD28z CAR is a FMC-63 based CAR similar to Yescarta

Preliminary Efficacy:

Dose level ≥ 150 x 10^6 day -1 pembro appears promising

	50 x 10^6 No pem (N=4)	50 x 10^6 D14 pem (N=3)	150 x 10^6 D14 pem (N=4)	450 x 10^6 D14 pem (N=4)	450 x 10^6 D-1 pem (N=4)	150-450 x 10^6 D-1 pem RP2D (N=4)
CR	1	1	2	2	2	3
PR	1	1	0	1	0	1
PD	2	0	2	1	2**	0
NE	0	1*	0	0	0	0

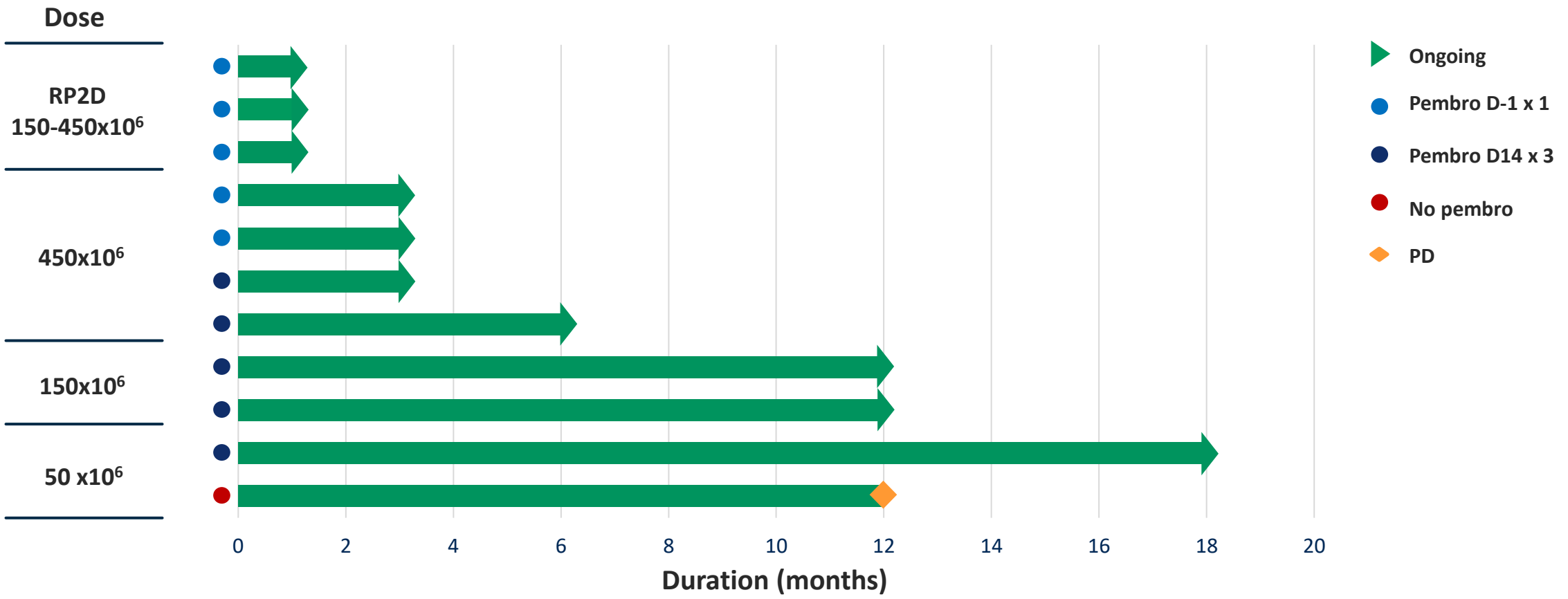
- All Dose Levels (N=23): ORR 65%, CRR 48%
  - ≥ 150 x 10^6 (N=16): ORR 69%, CRR 56%
  - ≥ 150 x 10^6, Day -1 pem (N=8): ORR 75%, CRR 63%

* NE because baseline PET negative disease, **Includes one patient that received only 125 x 10^6 and NE per protocol

* Per Lugano criteria; CR: complete response; PR: partial response; NE: not evaluable; PD: progressive disease
Data for patients with 4 weeks efficacy follow-up

Duration of Complete Responses

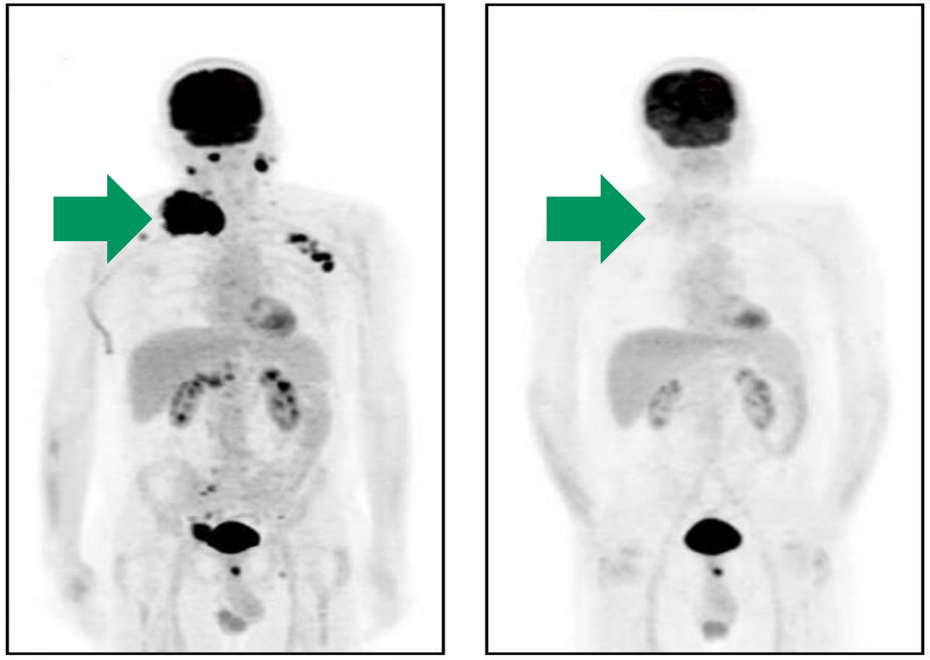
10 of 11 complete responses ongoing



At ≥ 150 x 10^6 dose all complete responses are ongoing with a median follow up 3 months (range 1-12m)

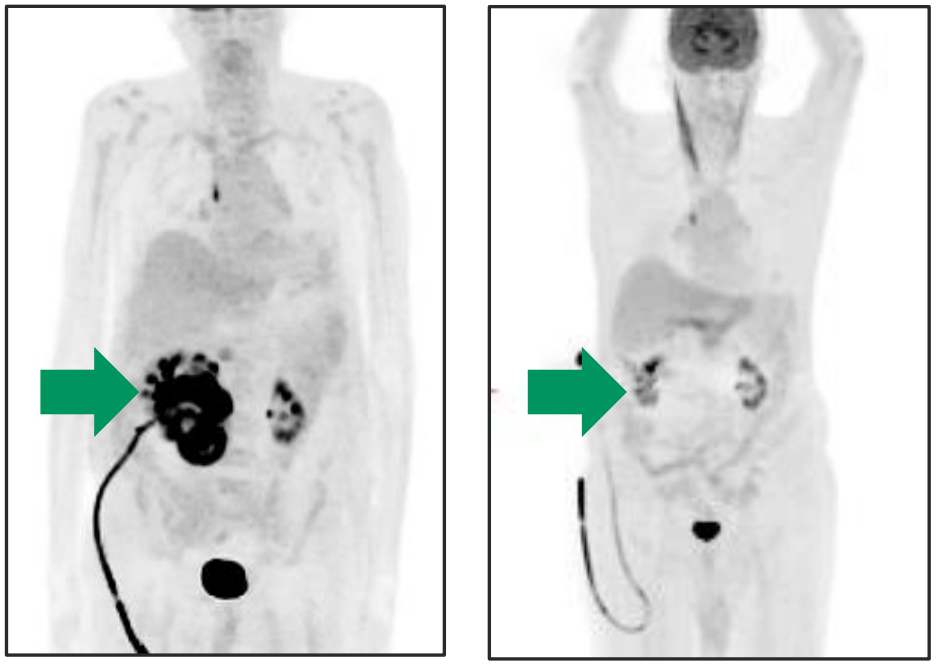
Complete Responses Seen in Bulky Tumors without sCRS or NT

Pre AUTO3 **Post AUTO3 Day 28**



60 yo male, Refractory DLBCL NOS, Bulky
Refractory to RCHOP/RICE/RESHAP
Dose: 50 x 10^6 D14 pem
No CRS or NT
CR duration 18 months+

Pre AUTO3 **Post AUTO3 Day 28**



83 yo male, Refractory DLBCL NOS, Bulky: SPD 125 cm^2
Refractory to RCHOP, RDHAX, Polatuzumab + R Bendamustine
Dose 450 x 10^6 D-1 pem
Grade 2 CRS, no NT

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Summary

Phase I Cohorts, ALEXANDER Study

- AUTO3 product was successfully manufactured for all patients
- Tolerable safety profile, 0% ≥ Grade 3 CRS and 4% (1/23) Grade 3 neurotoxicity with primary infusion
  - No neurotoxicity of any grade in patients treated ≥ 150 x 10^6
- RP2D range of 150 - 450 x 10^6 dose with pembrolizumab D-1 selected
  - CRR ≥ 150 x 10^6 with D-1 pembrolizumab is 63% (N=8)
- Complete responses achieved without severe CRS or neurotoxicity of any grade
- Complete responses are durable, 10/11 ongoing (median f/u 3 months)
- Outpatient expansion cohort will enroll shortly

Acknowledgments

Patients, Families and Caregivers

Study Site, Research Nurses and Staff

University College of London

Newcastle Freeman Hospital

Manchester Royal Infirmary

Glasgow Queen Elizabeth University

SCRI: Nashville TMC

SCRI: Austin St. Davids

SCRI: Denver CBCI

Washington University

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Nicola Courtenay and Project Team

Mei Mei Fung and Manufacturing Team

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Luise Weigand and Translational Team