# A Phase 1, Open-Label Study of MGD013 (Tebotelimab), a Bispecific DART® Molecule Binding PD-1 and LAG-3, in Patients with Relapsed or Refractory Diffuse Large B-Cell Lymphoma

Wang J[1], Asch AS[2], Hamad N[3], Weickhardt[4], Tomaszewska-Kienca M[5], Dlugosz-Danecka M[6], Pylypenko H[7], Bahadur S[8], Ulahannan S[2], Koucheki J[9], Sun J[9], Li H[9], Chen F[9], Zhang X[9], Muth J[9], Kaminker P[9], Moore PA[9], Sumrow BJ[9]

[1]Duke University Medical Center; Durham, NC. [2]OUHSC Oklahoma City, OK/SCRI, Nashville, TN. [3]St Vincent's Health Network; Kinghorn Cancer Centre; Sydney, Australia. [4]Austin Health, Olivia Newton-John Cancer Research Institute, Heidelberg, Victoria, Australia. [5]BioVirtus Research Site Sp. Z o.o.; Jozefow, Poland. [6]Pratia MCM Krakow; Krakow, Poland. [7]Cherkasy Regional Oncology; Cherkasy, Ukraine. [8]Banner MD Anderson Cancer Center, Gilbert, AZ. [9]MacroGenics, Inc., Rockville, MD

# Disclosure Information

**Speaker**:

Jie Wang , MD
Duke Cancer Institute
Durham, NC

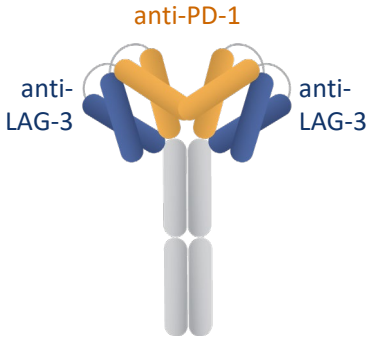
**Industry Relationships**:

Advisory Boards:  Verastem, Kyowa Kirin

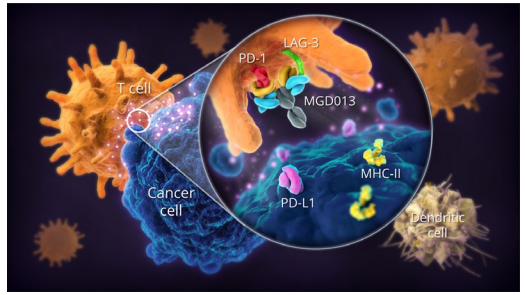
# Background

- PD-1 and LAG-3 receptors are expressed on “exhausted” T cells
  - Interactions with corresponding ligands negate anti-tumor T-cell activity
- Unmet need remains for relapsed/refractory DLBCL patients
  - LAG-3 highly expressed in DLBCL[1], and has emerged as therapeutic target of interest in this population
  - PD-1-targeted therapy (e.g., nivolumab) has yielded modest efficacy [2]
- Tebotelimab, an investigational DART protein, targets PD-1 and LAG-3 with a single molecule
  - Tetravalent (bivalent for each target) structure with IgG4 Fc
  - Greater synergistic T-cell activation (IFN-γ) in vitro with tebotelimab compared with combination of individual constituents
- Ongoing phase 1 study demonstrated safety up to 1200 mg Q2W, with evidence of antitumor activity as monotherapy and in combination with margetuximab in various advanced solid tumor populations
  - Monotherapy objective responses associated with increased baseline LAG-3 expression (IHC) and IFN-γ gene signature[3]
  - Combination (margetuximab) antitumor activity associated with baseline mRNA expression of LAG-3 and PD-1[4]
  - RP2D defined as 600 mg

**Tebotelimab**




**PD-1 × LAG-3**
Tetravalent Bispecific
DART Molecule

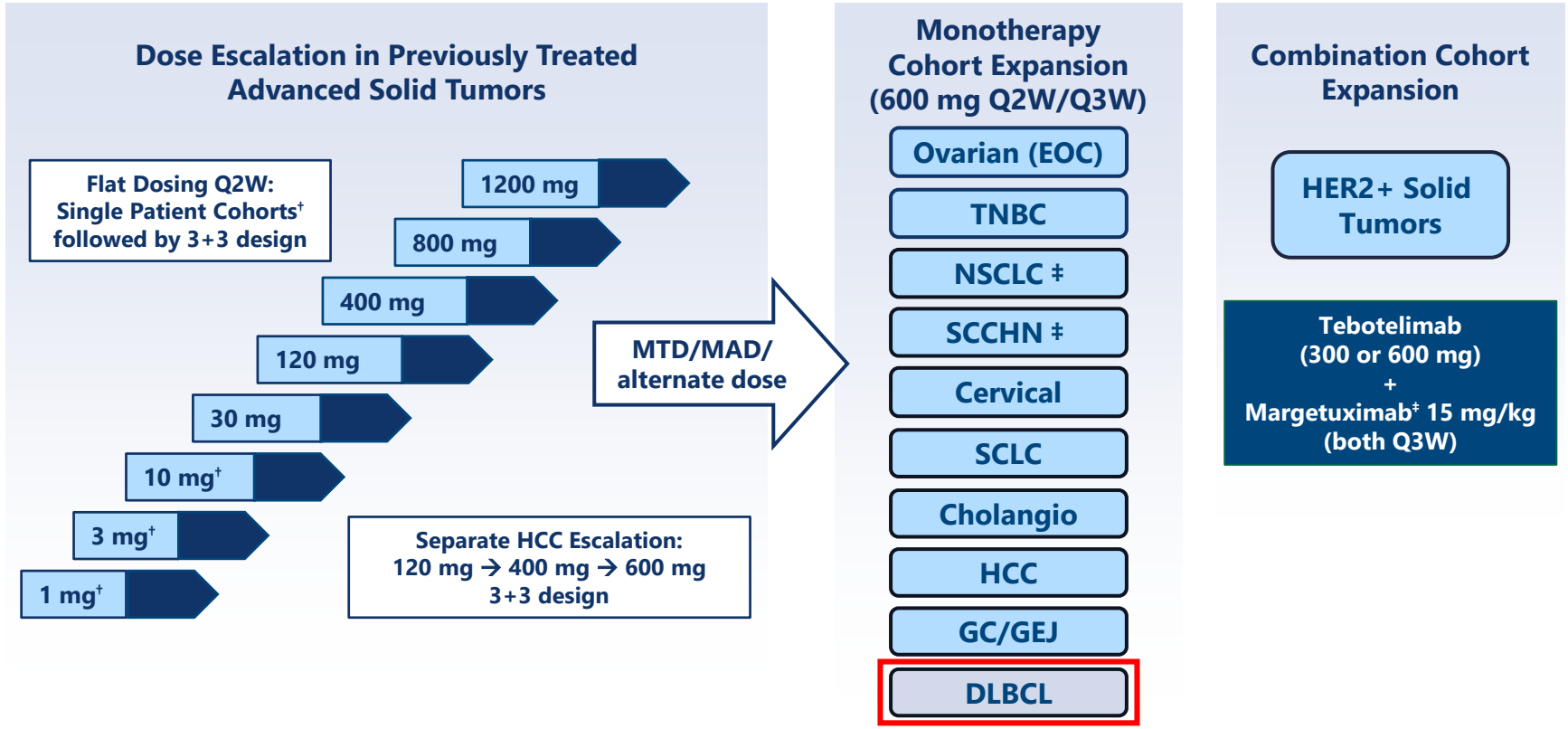




1. Ansell SM, et al. *J Clin Oncol*, 2019. 37(6): p. 481-489.
2. Keane C, et al. *Blood Adv*. 2020;4(7):1367-1377. doi:10.1182/bloodadvances.2019001390.
3. Luke JJ, et al. *ASCO 2020*.
4. Patel MR, et al. *SITC 2020*.

# Tebotelimab Phase 1 Trial Design

- **Primary objectives:**
  - Safety, tolerability
  - DLTs, MTD, MAD
  - Alternate dose
- **Secondary objectives:**
  - Pharmacokinetics
  - Immunogenicity
  - Preliminary activity
- **Exploratory PD objectives:**
  - Receptor/ligand expression
  - Serum biomarkers
  - Gene expression profiling




‡ separate CPI-naïve and post-PD-1 cohorts

**Trial Registration**: NCT03219268

# DLBCL Entry Criteria & Patient Demographics

## Key Entry Criteria

- Relapsed or refractory (R/R) DLBCL treated with at least one chemo combination, including therapeutic anti-CD20 Ab and autologous SCT, if indicated
  - Patients ineligible for, or who decline SCT, are eligible
  - Patients with primary CNS lymphoma or uncontrolled brain metastasis are not eligible
  - Minimum of 10 patients must have previously received prior CD19-directed CAR T cell therapy
- Age ≥18 years
- ECOG performance status 0 or 1
- Life expectancy ≥12 weeks
- ≥1 Measurable lesion >1.5 cm as defined by Lugano classification
- Acceptable laboratory parameters

## Baseline Demographics

| | DLBCL Expansion (n=20) |
|---|---|
| **Median age (range), years** | 63 (27, 75) |
| **Gender, n (%)** | |
| Male | 15 (75) |
| Female | 5 (25) |
| **ECOG PS, n (%)** | |
| 0 | 6 (30) |
| 1 | 14 (70) |
| **Median prior lines of therapy (range)** | 3 (1, 6) |
| **Disease Subtype, n (%)** | |
| GCB | 5 (25) |
| non-GCB (i.e. ABC) | 3 (15) |
| Double-hit (MYC/BCL2) | 2 (10) |
| Other/Unknown | 10 (50) |
| **Prior CAR T, n (%)** | |
| Yes | 10 (50) |
| No | 10 (50) |

# Preliminary Results*

## Safety Overview

| Overall AE Totals | No. (%) of Patients | |
|---|---|---|
| | All Grades (N=20) | ≥ Grade 3 (N=20) |
| AE (irrespective of causality) | 16 (80) | 9 (45) |
| Treatment-related AE | 13 (65) | 2 (10) |
| SAE (irrespective of causality) | 6 (30) | 4 (20) |
| Treatment-related SAE | 3 (15) | 0 (0) |
| AE leading to tx discontinuation | 1 (5) | 1 (5) |
| **Treatment-Related Adverse Events in > 1 Patient** | | |
| Pyrexia | 3 (15) | 0 (0) |
| IRR/CRS | 2 (10) | 0 (0) |
| Fatigue | 2 (10) | 0 (0) |
| Anemia | 2 (10) | 1 (5) |
| Hyperthyroidism/thyroiditis | 2 (10) | 0 (0) |

- Generally well-tolerated with safety profile consistent with anti-PD-(L)1 therapy
- Infusion-related reactions (n=2) have been Grade 2 and reversible with supportive treatment
- No evidence of tumor lysis syndrome observed

## End of Treatment Disposition

| | DLBCL Expansion: Tebotelimab 600 mg Q2W |
|---|---|
| Patients Treated | 20 |
| Response-Evaluable Patients, n (%) | 13 (65) |
| Median duration of therapy, weeks (min, max) | 8.3 (0.6, 42.6) |
| Continuing treatment, n (%) | 8 (40) |
| Treatment discontinuation, n (%) | 12 (60) |
| **Reasons for discontinuation, n (%)** | |
| Disease Progression (Radiographic) | 5 (25) |
| Disease Progression (Clinical) | 3 (15) |
| Death | 2 (10) |
| Complete Response (→ allo-SCT) | 1 (5) |
| Adverse Event† | 1 (5) |

†Grade 5 event of gastrointestinal hemorrhage related to underlying disease (not related to tebotelimab)

*Data cut: 23-October-2020

# Encouraging Evidence of Antitumor Activity*

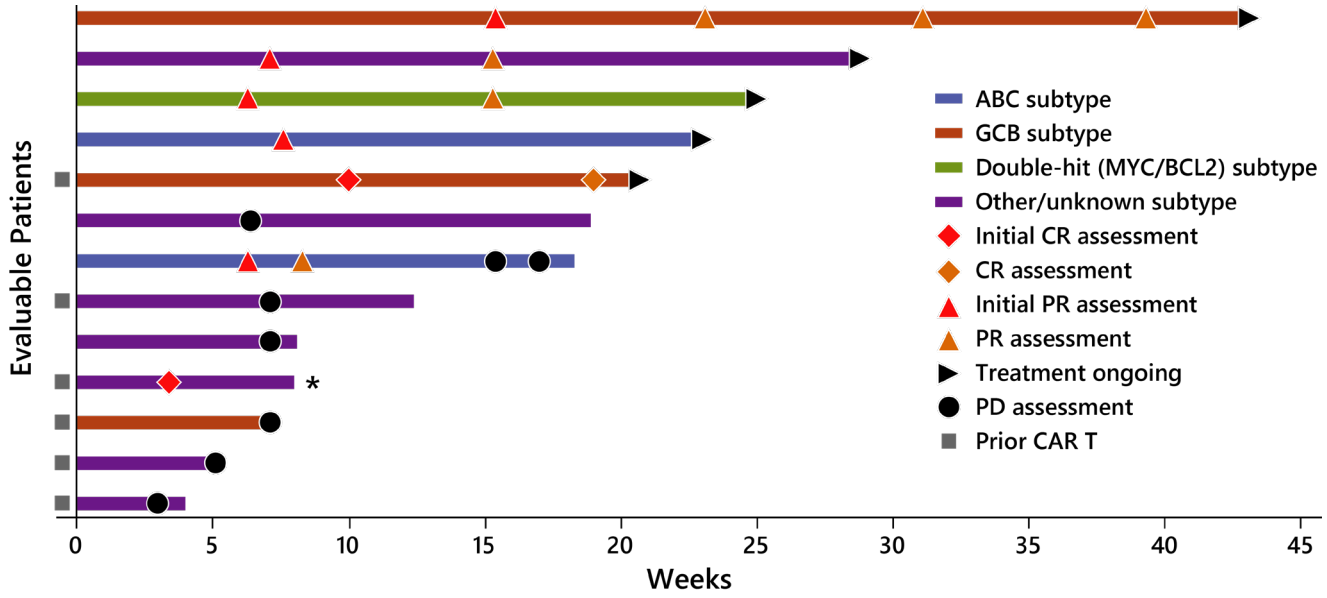
- Preliminary ORR of 53.8%
  - 71.4% (5/7) for CAR T naïve patients
  - 33.3% (2/6) for CAR T experienced patients
- Responding patients (n=7) encompass activated B-cell (ABC), germinal center B-cell (GCB), and double-hit (MYC/BCL2) molecular subtypes
- Duration of Response ranges from 1 (2nd scan data pending) to 168 days, with 6 of 7 responders remaining in response

| | No. (%) of Response-Evaluable Patients† | | |
|---|---|---|---|
| | Post CAR T (N=6) | CAR T Naive (N=7) | Total (N=13) |
| Best Overall Response‡ | | | |
| CR | 2 (33.3) | 0 (0) | 2 (15.4) |
| PR | 0 (0) | 5 (71.4) | 5 (38.5) |
| Stable disease | 0 (0) | 0 (0) | 0 (0) |
| Progressive Disease | 4 (66.7) | 2 (28.6) | 6 (46.2) |
| ORR, *n* (%) | 2 (33.3) | 5 (71.4) | 7 (53.8) |
| DCR, *n* (%) | 2 (33.3) | 5 (71.4) | 7 (53.8) |

† patients treated with at least one post-baseline tumor assessment, and excludes 3 patients who discontinued treatment prior to first scan due to death (n=2) and adverse event (n=1)

‡ tumor assessments per the Lugano classification

## Durable Responses Observed in Multiple Patients



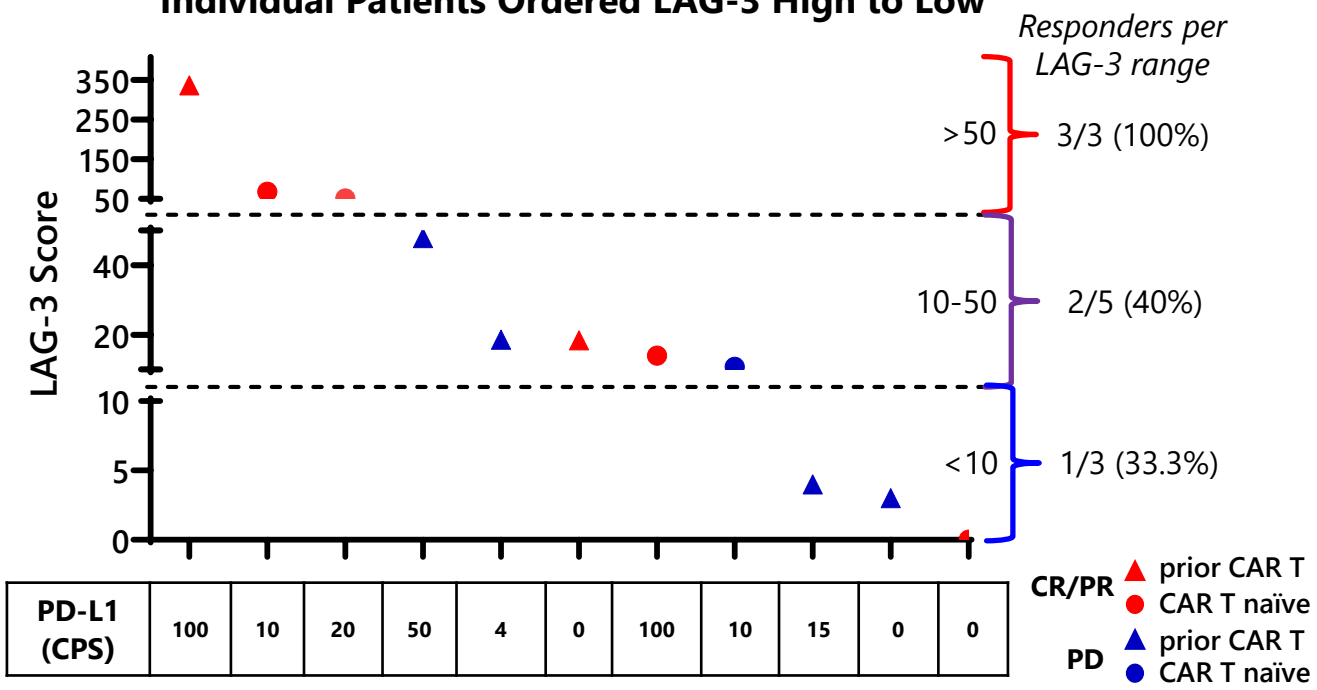

*Allogeneic stem cell transplant (allo-SCT) performed after CR and end of treatment. Patient remains in remission approx. 16 months post-allo-SCT.

*Data cut: 23-October-2020

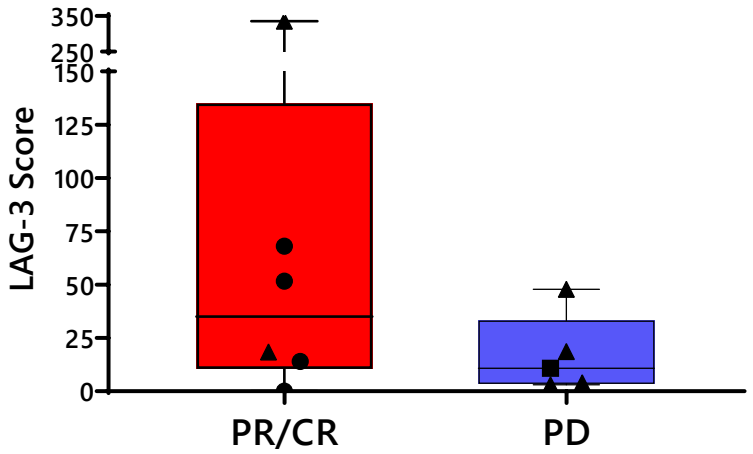
# Association of Objective Responses with Baseline LAG-3 Expression

*Retrospective IHC Analyses Performed on Preliminary Set of Patients Treated with Tebotelimab*

**Individual Patients Ordered LAG-3 High to Low**




**LAG-3 Expression by Objective Response**




**Patients displaying higher baseline levels of LAG-3 appear to show improved response**

Pre-treatment biopsies available from the DLBCL expansion cohort for IHC analyses (N = 11) were analyzed for LAG-3 and PD-L1 expression, including patients with (▲ N= 6) or without (● N = 5) prior CAR T therapy. LAG-3 expression was determined by calculating mean value of LAG-3+ cells per 40x field across 5 LAG-3+ hot spots (Chen et al., e15086 ASCO 2020). PD-L1 expression was determined per Agilent PD-L1 (22C3) pharmDx kit; CPS was calculated as follows: number of PD-L1 + cells (tumor and immune)/total number of viable tumor cells x 100.

# Complete Response after Single Tebotelimab Administration

*28-year-old male with DLBCL progressive disease after CAR T cell therapy*

***DA-R-EPOCH*** → *Relapse*

***JCAR017*** → *Relapse*

**Screening**

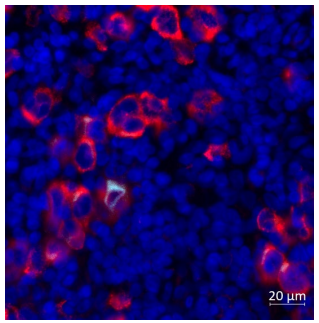
***Tebotelimab*** *600 mg x1*

*Grade 2 CRS*

**Study Day 24**
**Complete Response**

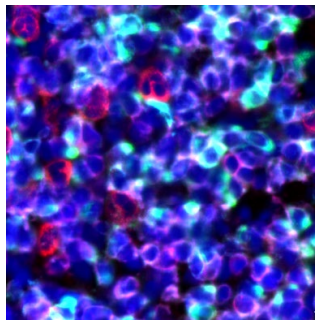
***Allo-SCT***

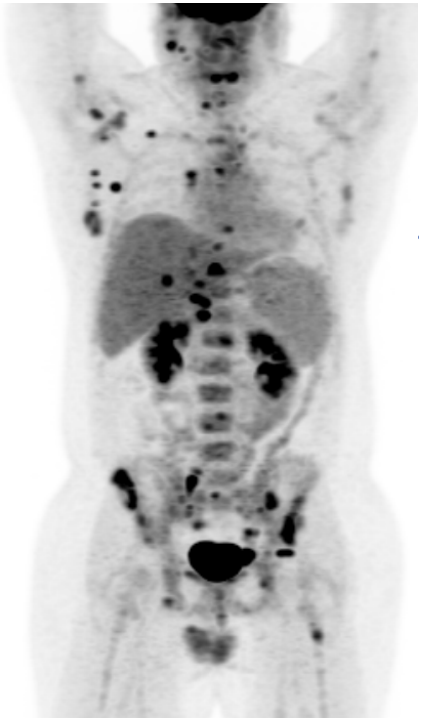
**Pre-CAR T**



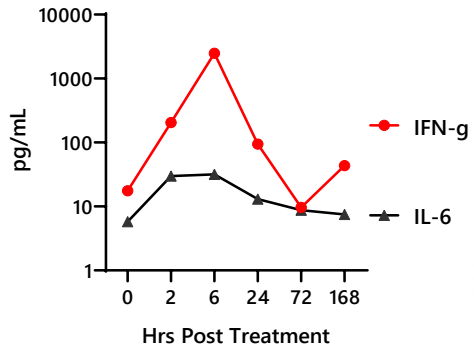

CD3 (2GV6)
CD79a (SP18)
PD-1 (NAT105)
LAG-3 (EPR4392(2))
DAPI

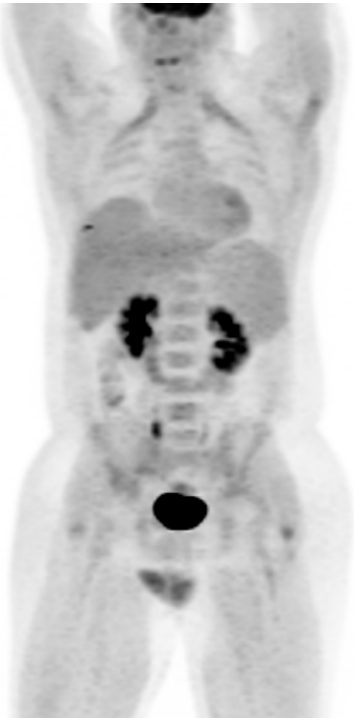
**Post-CAR T**
**(Pre-tebotelimab)**





**Serum Cytokine Kinetics**



- Dynamic changes observed in the TME after CAR T therapy, with increased expression of LAG-3, PD-1, PD-L1, and MHC-II evident
- Malignant cells CD19-negative, consistent with antigen loss relapse

- After Grade 2 CRS, early scan demonstrated Complete Response at Day 24
- JCAR017's EGFR epitope not detected pre- or post-tebotelimab
- The patient remains in remission approximately 18 months post-tebotelimab and 16 months post-allo-SCT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# Conclusions

- Tebotelimab monotherapy generally well-tolerated among heavily pre-treated R/R DLBCL patients
  - Infusion related reactions manageable and no evidence of tumor lysis syndrome
- Encouraging preliminary evidence of antitumor activity observed among CAR T-experienced and -naive R/R DLBCL patients, representing various molecular subtypes
  - Preliminary ORR:  53.8%
  - Baseline LAG-3 expression appears to associate with clinical response
- A complete response observed in a post-CAR T patient after single tebotelimab administration
  - Pre-tebotelimab tumor tissue demonstrated increased expression of LAG-3, PD-1, and respective ligands
  - Marked enhancement of circulating IFN-γ, with only modest IL-6
  - No evidence of CAR T or CAR T expansion by flow cytometry for EGFR marker
  - Remission ongoing 15 months after allo-SCT
- Further DLBCL enrollment and additional correlative translational analyses ongoing