

**UNIVERSITY OF PUERTO RICO SCHOOL OF MEDICINE  
HEMATOLOGY AND MEDICAL ONCOLOGY SECTION**

# **CAR-T CELLS THERAPY: A LIVING DRUG.**

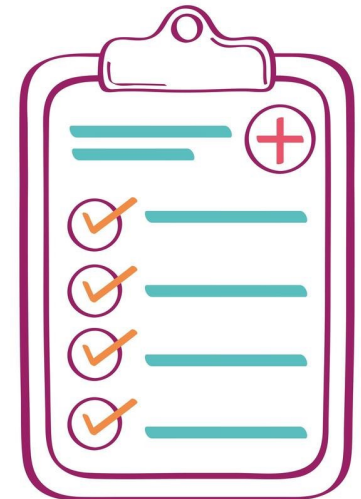
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**ACKNOWLEDGMENT TO DR. CHRISTIAN RODRIGUEZ-AROCHO, BMT-CI SPECIALIST**

## CASE PRESENTATION

- A 63 year-old woman was refer 4 years ago to the *Auxilio Blood and Marrow Transplant and Cellular Therapy Center* for evaluation after being diagnose with a Relapse/Refractory Follicular Lymphoma.
- The patient presented with one-year of back pain and unspecified GI discomfort.
- She was treated for Gastritis, with no resolution of symptoms.
- Symptoms progressed to early satiety and chills.
- Associated with a 25-pounds weight loss in 3 months.
- Denies fever or night sweats.



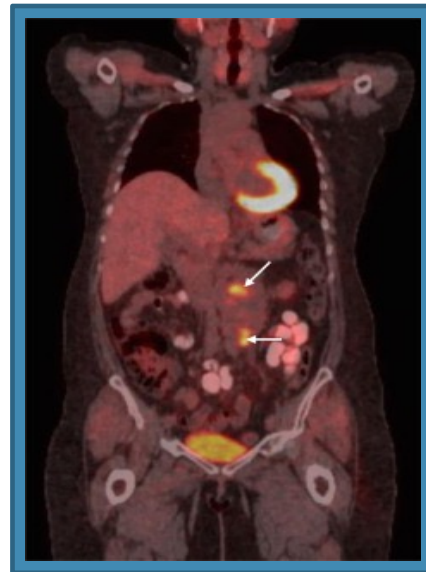
## CASE PRESENTATION

- **Past Medical History:** Hyperlipidemia, Mitral valve prolapse, Major Depressive Disorder, and Generalized Anxiety Disorder
- **Medications:** Duloxetine 60mg daily, metoprolol 25mg, buspirone 5mg BID, Clonazepam 2mg, Temazepam 15mg
- **Allergies:** None reported
- **Family Medical History:** Mother suffers from BA and RA, Father suffers from AHTN and DMII, both brothers suffers from DMII.
- **Past Surgical History:** Laminectomy with fusion and instrumentation, Appendectomy, Cholecystectomy
- **Social:** Former smoker, quit 2 years prior to diagnosis of lymphoma. Drink alcohol on special occasions, 1 to 2 drink per month.

# INITIAL DIAGNOSTIC EVALUATION

## Abd/Pelvic CT Scan W Contrast:

- 12.2 x 8.8 x 21.5cm (transverse x AP x CC) retroperitoneal mass suspicious for large lymph node conglomerate.
- The mass completely encases abdominal aorta, bilateral renal arteries and common iliac arteries.
- Retroperitoneal, peripancreatic and pelvic lymphadenopathy.



## Whole-Body PET/CT Scan:

- Infraclavicular nodes 2.73 x 2.67cm; SUV 16.9
- Anterior and superior mediastinal nodes 2.45 x 6.6cm, and 2.5 x 2.5 cm; SUV 22.4 and 22.1
- Mid-abdominal mass **12.3 x 6.0 cm; SUV 95.2**
- Anterior diaphragmatic nodes 1.92 x 2.1 cm; SUV 10.3
- Right external iliac nodes 3.0 x 2.7 cm; SUV 16.0
- Left external iliac node 3.9 x 5.5 cm; SUV 26.39
- Enlarge liver 22.3 x 14.2 cm
- Spleen 7.6 x 3.9 cm. Spleen/hilum SUV 20.0
- FDG avid accumulation in pancreas; SUV 26.7cm
- Thoracic vertebra (T11/T12) SUV 18.7
- Lumbar vertebra (L1/L4) SUV 19.0

# INITIAL DIAGNOSTIC EVALUATION

## ➤ Retroperitoneal mass CT-guided biopsy:

➤ Small to medium sized cleaved B-cells with scattered large cells.

## ➤ IHC:

➤ Positive for CD 20, CD 10, BCL6, and BCL 2

➤ Ki 67: 5-10%



A calendar for November 2018. The days of the week are listed at the top: S, M, T, W, T, F, S. The dates are arranged in a grid. The date 27 is circled in blue.

November 2018						
S	M	T	W	T	F	S
				1	2	3
4	5	6	7	8	9	10
11	12	13	14	15	16	17
18	19	20	21	22	23	24
25	26	27	28	29	30	

➤ **Note from Pathologist:** Due to diffuse nature of the infiltrate and the presence of what appear to be small to medium cells with low proliferation rate, a **low grade follicular lymphoma** is favored at this time.

# DIAGNOSIS

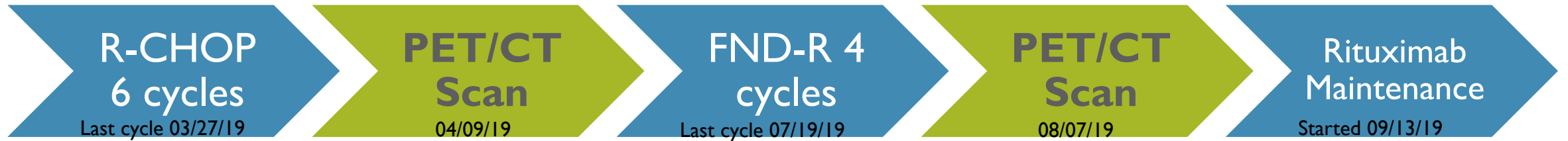
## ➤ **Follicular Lymphoma:**

- Grade at diagnosis: 2
- Stage IVB
  - Disease above and below the diaphragm
  - Bone involvement
- Bulky disease
- Clinically Discordant Indolent Histology
  - Elevated SUV's on PET/CT Scan

- FLIPI score: At least Intermediate Risk.
  - LDH at diagnosis not available
- Bone marrow aspiration and biopsy negative for lymphoma involvement.



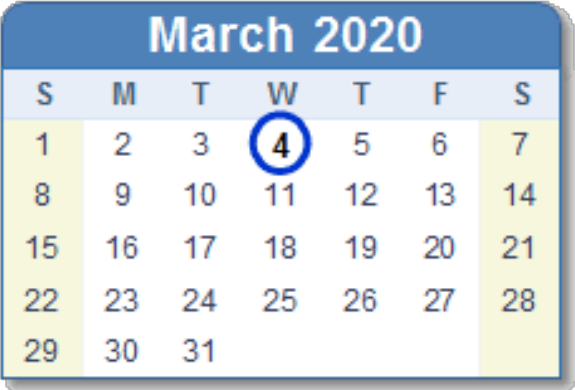
# FIRST LINE THERAPY



- The retroperitoneal mass decrease >70%, was less than 2 cm in size, with an SUV of 4.1.
- No evidence of FDG-avid lesions elsewhere.
- **Partial Response I.**
- Small para-aortic node measuring 1.0 x 0.9cm, non-FDG avid.
- No evidence of FDG-avid lesions elsewhere.
- **Complete Response I.**

## INTERVAL HISTORY

- By February 2020, the patient developed back pain, as well as night sweats.
- **Whole-body PET/CT Scan:**
  - Retroperitoneal mass of 2.7 x 5.33 cm; SUV 16.19
  - Internal iliac node 1.46 x 1.99; SUV 6.89.
- **CT-guided core biopsy of the mass:**
  - Follicular Lymphoma, Grade 3a
  - IHC positive for: CD10, CD20, BCL6
  - IHC negative for: CD5, CD23, BCL2
  - Ki 67: 75-80%
  - FISH negative for BCL2, BCL6, Myc rearrangement
  - Mutations in EHZ2, CREBBP, APC, KMT2D, PRKDC genes detected.



March 2020

S	M	T	W	T	F	S
1	2	3	4	5	6	7
8	9	10	11	12	13	14
15	16	17	18	19	20	21
22	23	24	25	26	27	28
29	30	31				



## SECOND LINE THERAPY

GROC-R-Rev  
5 cycles

CAP CT Scan

BMT  
Evaluation

- Extensive retroperitoneal and bilateral iliac station confluent mass-like process surrounding the aorta and extending to the pelvis.
- Slightly decrease in size.
- **Stable disease** by RECIST criteria.
- Allogeneic HSCT evaluation.
- HLA testing.
- PET/CT Scan.
- Bone marrow aspiration and biopsy.

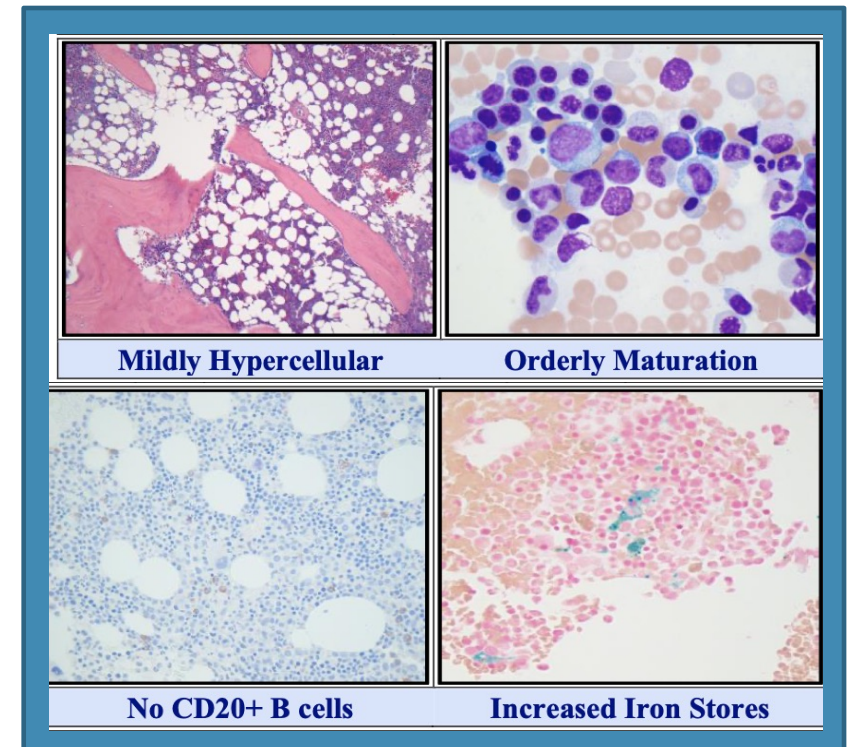
# INTERVAL HISTORY

## ➤ **Whole-body PET/CT Scan:**

- Increase FDG accumulation involving the retroperitoneal mass close to the aorta, inferior vena cava and iliac. SUV 8.03.
- Increase FDG accumulation involving the internal iliac nodes. SUV 5.99.
- Deauville score of 4.

## ➤ **Bone marrow aspiration and biopsy:**

- Hypercellular marrow with no lymphoma.
- Normal karyotype.



# THIRD LINE THERAPY

## CARTs protocol?

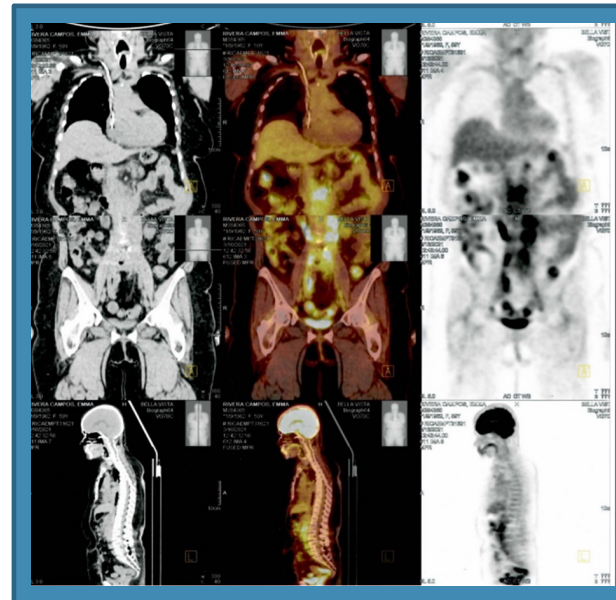
- By August 2020, Allo-CART clinical trial at Moffitt Cancer Center (MCC) open a slot for R/R Follicular Lymphoma.
- It closes prior to this patient evaluation at MCC.

## Tazemetostat 4 months

- Inhibitor of EZH2 enzymatic activity.
- October 2020 to January 2021.

## PET/CT Scan

- January 2021.
- **Stable disease.**



## Allo-HSCT

- Three potential haploidentical donors identified.
- TBI Based Conditioning Regimen
  - 5-year-OS: 61%
  - PFS: 52%
- Persisted with active disease.

# ZUMA-5 TRIAL

Phase 2 (N=151 enrolled)

R/R  
iNHL N=146 Treated  
(124 FL, 22 MZL)

### Key Eligibility Criteria

- R/R FL (Grades 1–3a) or MZL (nodal or extranodal)<sup>a</sup>
- ≥2 Prior lines of therapy—must have included an anti-CD20 mAb combined with an alkylating agent<sup>b</sup>

### Conditioning Regimen

- Fludarabine 30 mg/m<sup>2</sup> IV and cyclophosphamide 500 mg/m<sup>2</sup> IV on Days -5, -4, -3

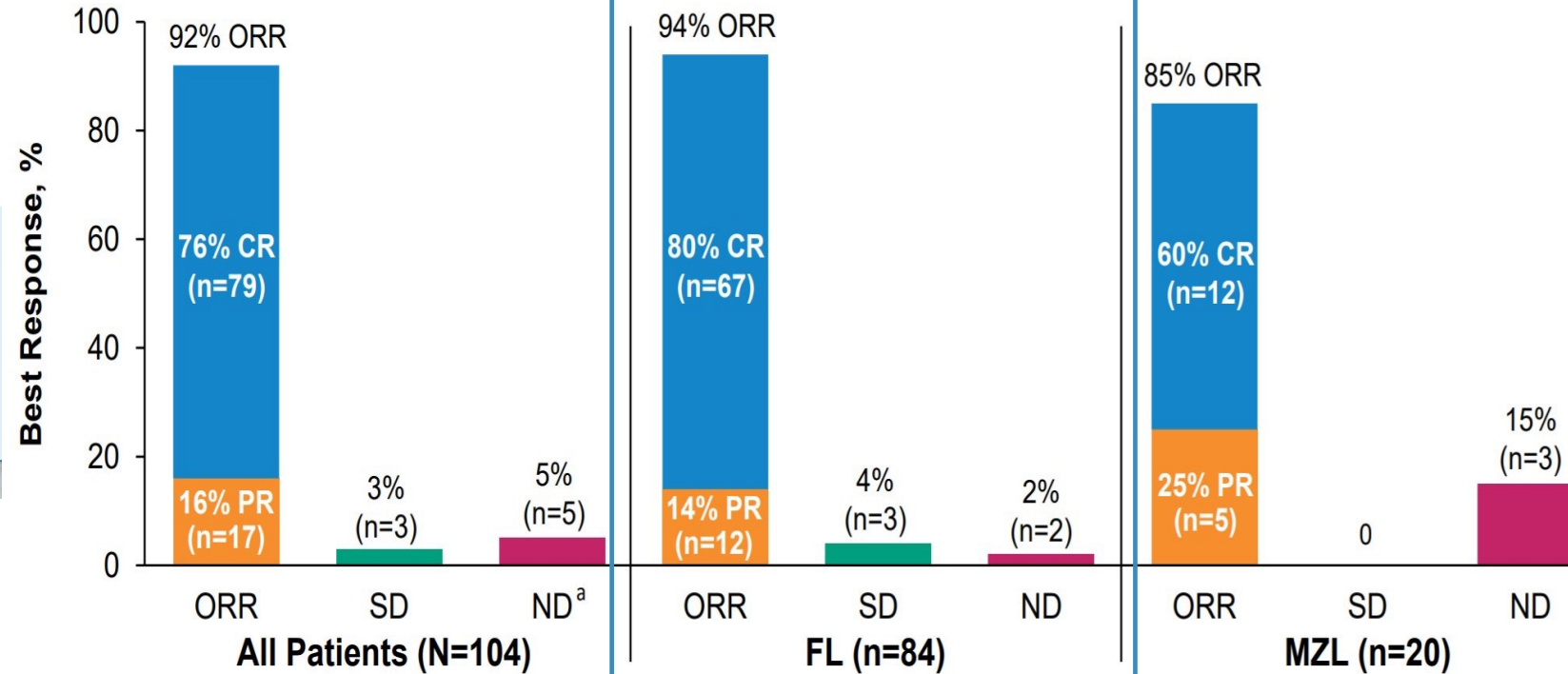
Axi-Cel: 2×10<sup>6</sup> CAR+ cells/kg

### Primary Endpoint

- ORR (IRRC-assessed per the Lugano classification<sup>1</sup>)

### Key Secondary Endpoints

- CR rate (IRRC-assessed)
- Investigator-assessed ORR<sup>1</sup>
- DOR, PFS, OS
- AEs
- CAR T cell and cytokine levels



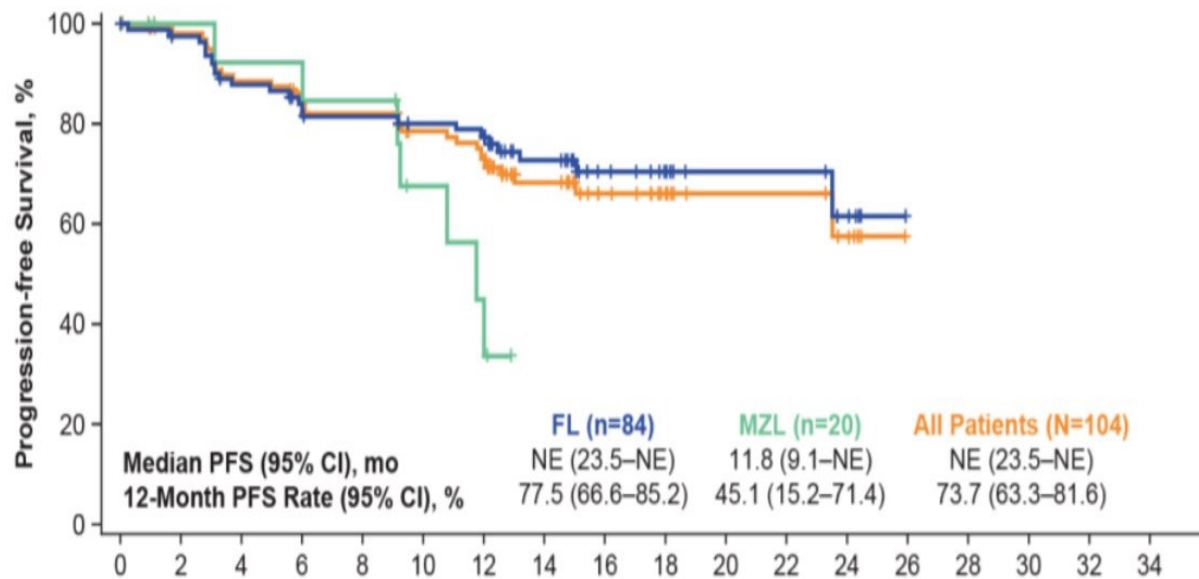
March 2021						
S	M	T	W	T	F	S
	1	2	3	4	5	6
7	8	9	10	11	12	13
14	15	16	17	18	19	20
21	22	23	24	25	26	27
28	29	30	31			

The median time to first response was 1 month (range, 0.8–3.1)

Among the 25 patients with FL who initially had a PR, 13 (52%) subsequently converted to a CR after a median of 2.2 months (range, 1.9–11.2)

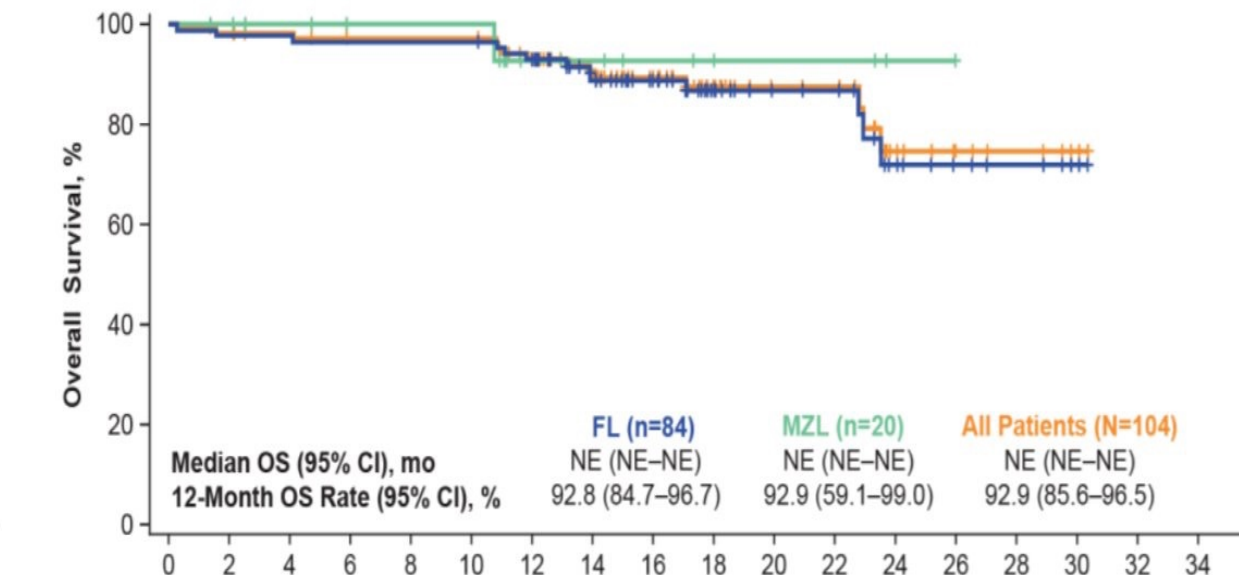
# ZUMA-5 TRIAL

## Progression-Free Survival



No. at Risk	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34
FL	84	80	71	65	62	59	57	40	27	21	9	9	6	0				
MZL	20	13	12	12	11	6	4	0										
All Patients	104	93	83	77	73	65	61	40	27	21	9	9	6	0				

## Overall Survival



No. at Risk	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34
FL	84	82	82	81	81	81	77	63	52	35	21	20	11	7	5	2	0	
MZL	20	19	16	14	14	14	9	7	5	4	3	3	1	0				
All Patients	104	101	98	95	95	95	86	70	57	39	24	23	12	7	5	2	0	

# FOURTH LINE THERAPY

R-CHOP 6  
cycles

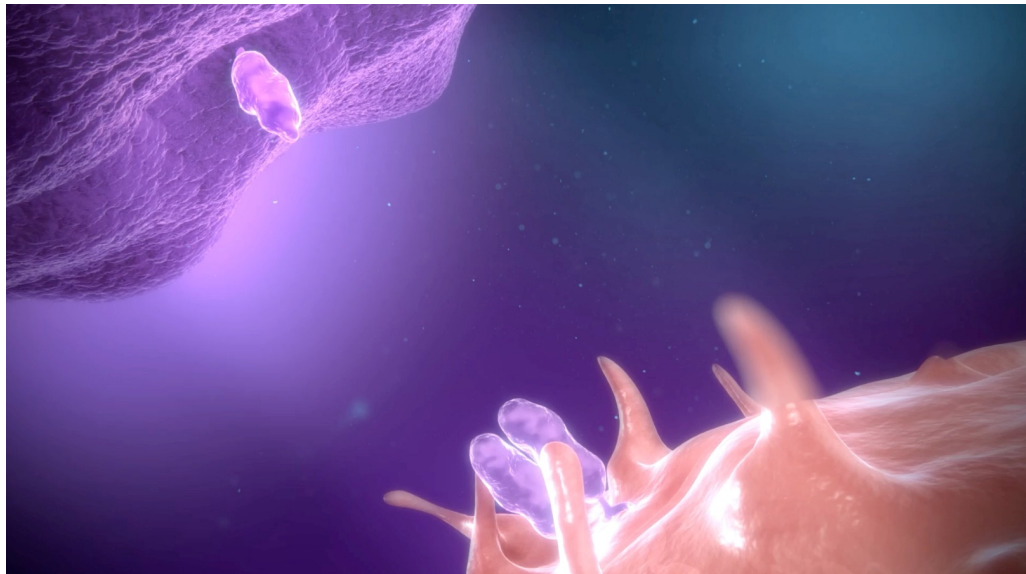
FND-R 4  
cycles

GROC-Rev 5  
cycles

Tazemetostat

**Axicabtagene  
ciloleucel**

- CART infusion on 07/15/2021 at MCC.
- Patient achieved CR 2.





## TWO YEARS LATER

- **Whole-body PET/CT Scan:**
  - Soft tissue density with ill-defined borders at the retroperitoneum from the renal hilum level downward, showing no significant FDG uptake.
    - SUV Max of 2.2
    - Deauville score 2
- The patient persists in complete remission.

# DISCUSSION

- Follicular lymphoma (FL) is the most common indolent lymphoma in the western world.
- Near 20% of the patients experienced rapid progression of disease after first line therapy.
- Progression of disease within 24 months (POD24) of first line treatment is a predictor of inferior OS in patients who were treated at diagnosis with alkylator or bendamustine based regimens.
- CARTs may be the prefer treatment modality for those patients with PO24.
  - ORR with EZH inhibitors 69%; yet CR rates remains very low, 13%.

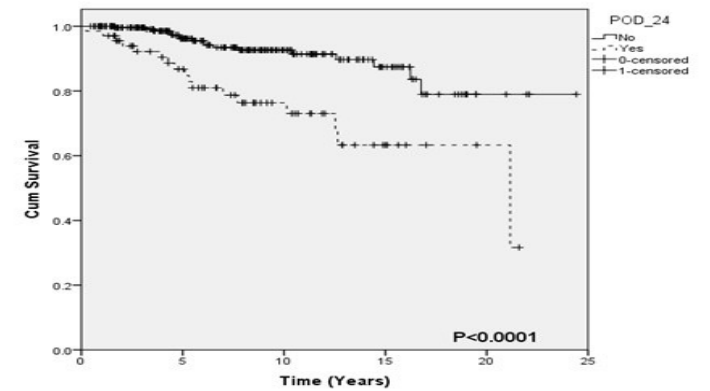


Figure 1A: OS by POD24 for the entire cohort

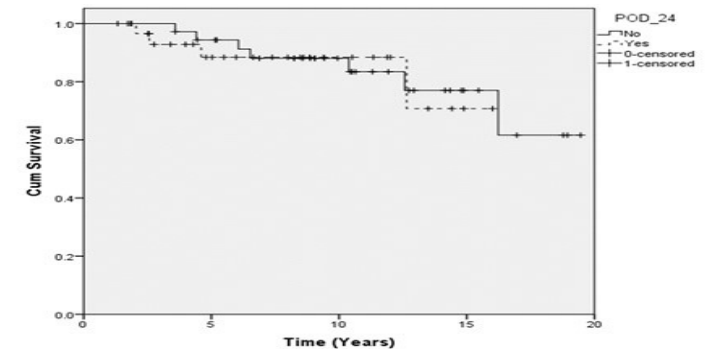
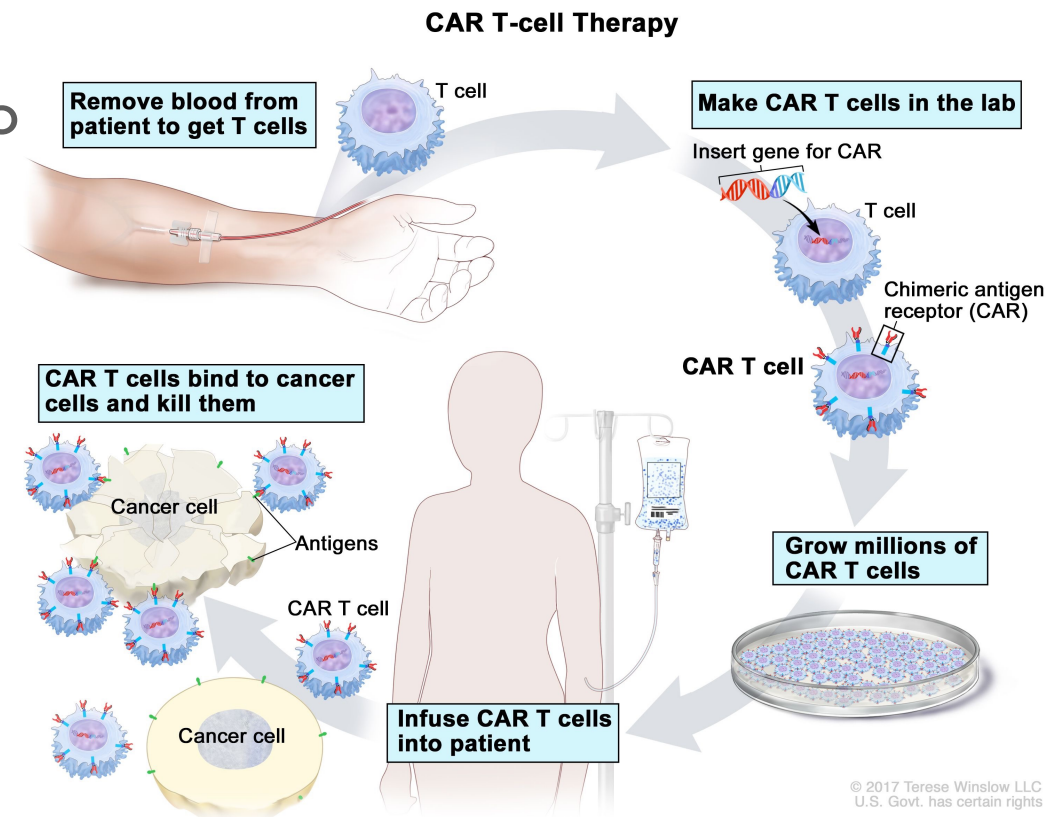


Figure 1B: OS by POD24 status in patients diagnosed with progression by imaging



# DISCUSSION

- CAR T cells are genetically modified T cells that express synthetic receptors on the cell surface to detect and eradicate cancer cells by identifying specific tumor antigens.
- CAR T cells targeting CD19 have revolutionized the treatment of various B-cell lymphomas.
- Studies demonstrate impressive and durable responses.
- CAR-T therapy is associated with serious complications, including some fatal neurologic events and cytokine release syndrome.



Product	Target	Indications
Tisagenlecleucel Approved in 2017	CD 19	<ul style="list-style-type: none"> <li>• Patients up to 25 years of age with B-ALL that is refractory or in second or later relapse.</li> <li>• Adult patients with R/R large B-cell lymphoma after two or more lines of systemic therapy, including DLBCL-NOS, high grade B-cell lymphoma and DLBCL arising from FL.</li> <li>• Adult patients R/R FL after two or more lines of systemic therapy.</li> </ul>
Axicabtagene ciloleucel Approved in 2017	CD 19	<ul style="list-style-type: none"> <li>• Adult patients with large B-cell lymphoma that is refractory to first-line chemoimmunotherapy or that relapses within 12 months of first-line chemoimmunotherapy.</li> <li>• Adult patients with R/R large B-cell lymphoma after two or more lines of systemic therapy, including DLBCL-NOS, primary mediastinal large B-cell lymphoma, high grade B-cell lymphoma, and DLBCL arising from FL.</li> <li>• Adult patients with R/R FL after two or more lines of systemic therapy.</li> </ul>
Brexucabtagene autoleucel Approved in 2017	CD 19	<ul style="list-style-type: none"> <li>• Adult patients with R/R MCL.</li> <li>• Adult patients with R/R B-ALL.</li> </ul>
Lisocabtagene vicleucel Approved in 2021	CD 19	<p>Adult patients with LBCL, DLBCL –NOS, DLBCL arising from indolent lymphoma, high grade B-cell lymphoma, primary mediastinal large B-cell lymphoma, and FL grade 3B, who have:</p> <ul style="list-style-type: none"> <li>• refractory disease to first-line chemoimmunotherapy or relapse within 12 months of first-line chemoimmunotherapy; or</li> <li>• refractory disease to first-line chemoimmunotherapy or relapse after first-line chemoimmunotherapy and are not eligible for hematopoietic stem cell transplantation (HSCT) due to comorbidities or age; or</li> <li>• relapsed or refractory disease after two or more lines of systemic therapy.</li> </ul>
Idecabtagene vicleucel Approved in 2021	BCMA	Adult patients with relapsed or refractory multiple myeloma after four or more prior lines of therapy, including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 monoclonal antibody.
Ciltacabtagene autoleucel Approved in 2022	BCMA	Adult patients with relapsed or refractory multiple myeloma after four or more prior lines of therapy, including a proteasome inhibitor, an immunomodulatory agent, and an anti-CD38 monoclonal antibody.

## CONCLUSION

- CARTs therapy has significantly transformed the treatment of various R/R hematological malignancies that previously have not had many treatment options.
- However, high treatment prices impose a substantial burden on patients and payers, thus hindering its commercial success.
- Relapse after CARTs, tumor antigen escape, and severe treatment-related toxicities are unresolved concerns.
- The continuous development of CAR technology, novel CAR development and next-generation CARs, such as CAR-NKs and CAR-Ms, and CAR-based immunotherapy all have the potential to overcome the present restrictions and achieve a safer, more effective, and broader application in cancer treatment.



THANK YOU

