2023 Midwest Radiation Oncology Symposium

CAR-T Cell Therapy for B-Cell Lymphoma: Does Radiation Therapy Have a Role?

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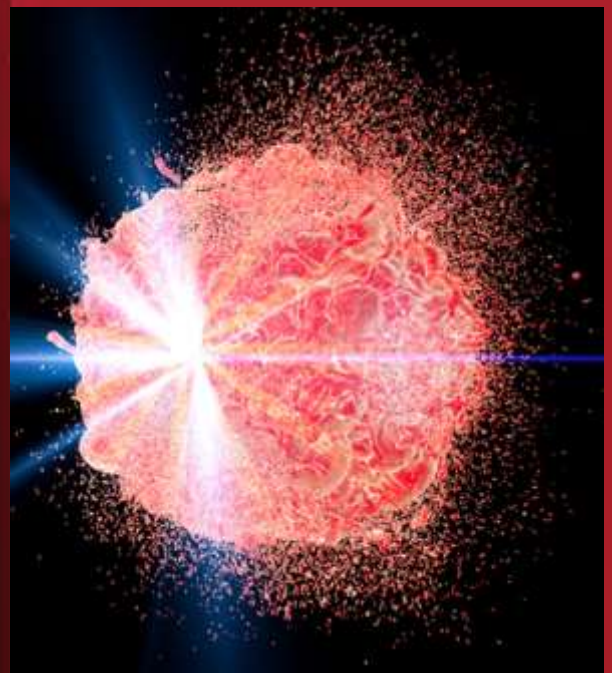


University of Nebraska Medical Center

Nebraska Medicine

Conflict of Interest Attestation

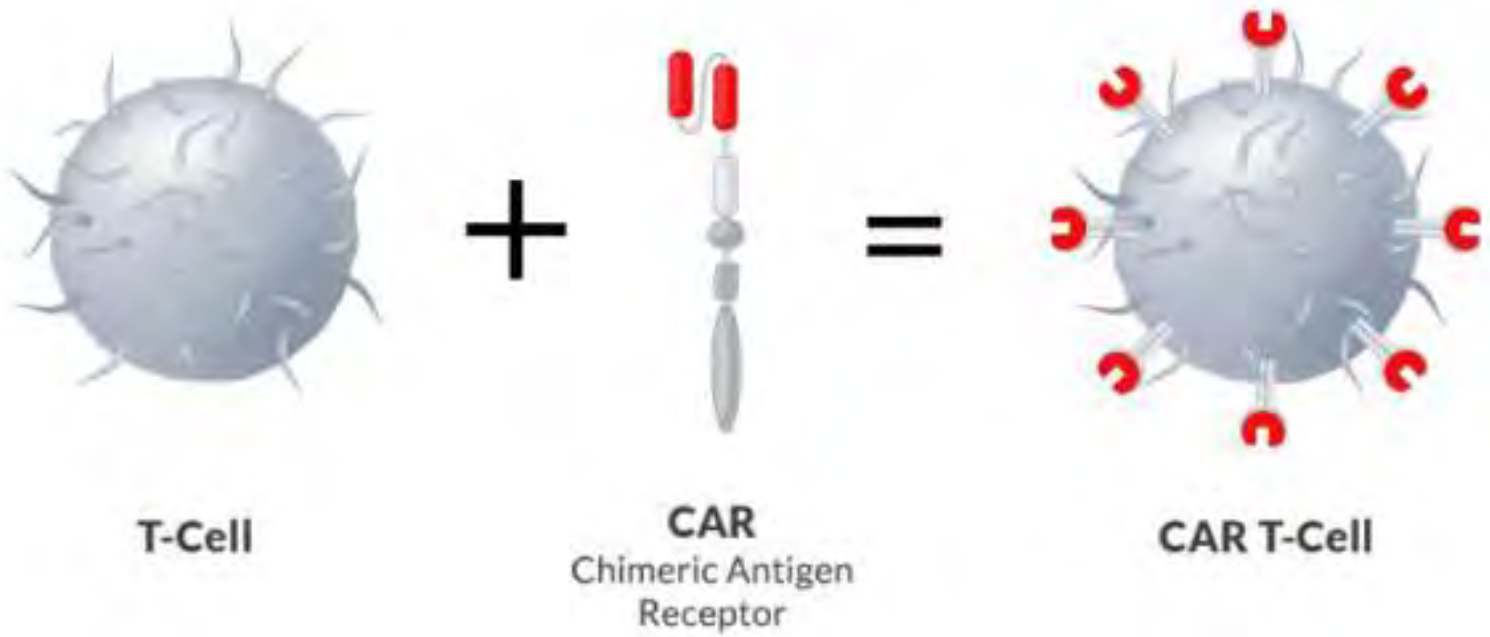
I have no COI to declare/report. CA Enke

Objectives

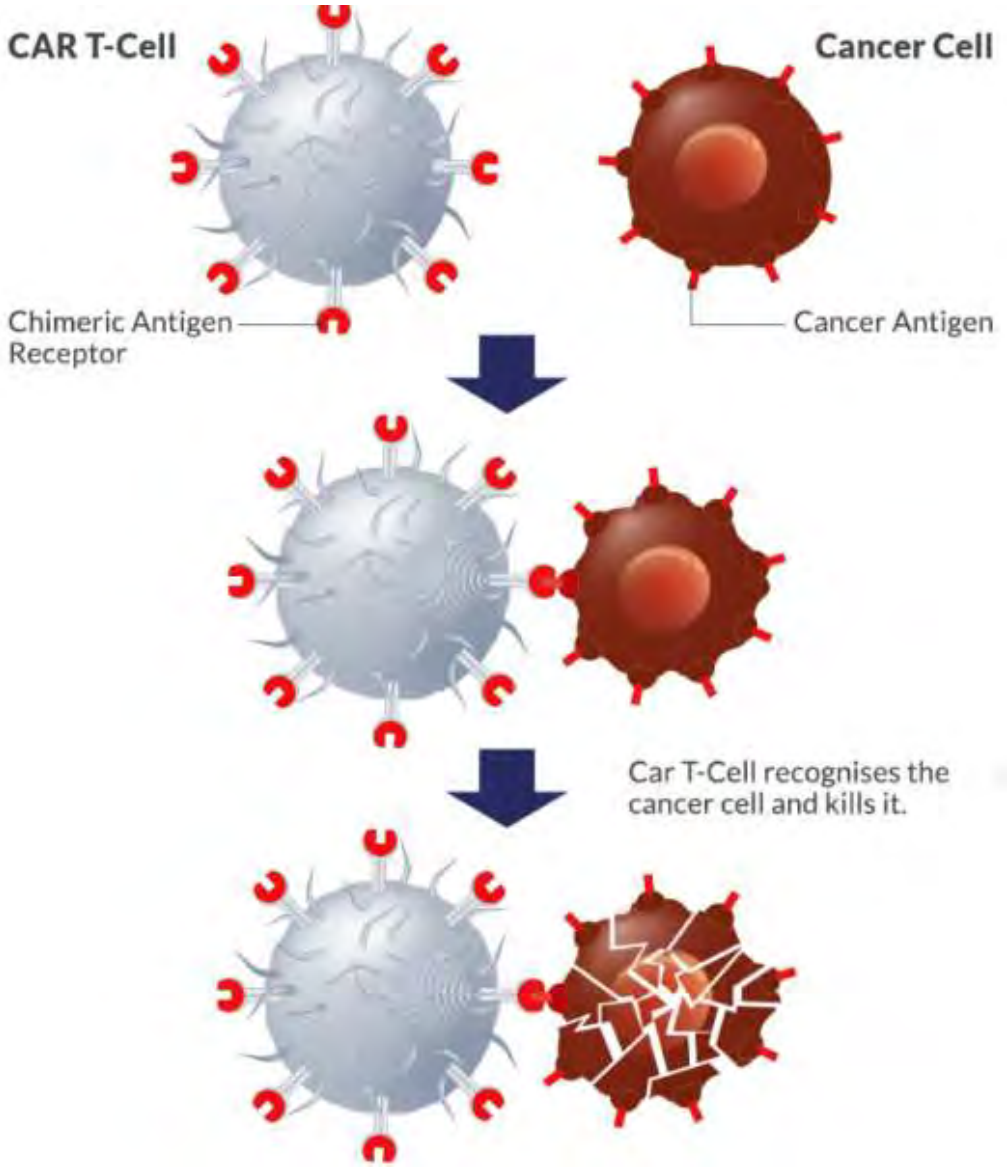
1. Describe the lymphoma features that predict a poor outcome with current CAR-T Cell therapy
2. Discuss the potential benefits and risks associated with Radiation Therapy and CAR-T Cell Therapy
3. Discuss the current role of Radiation Therapy with CAR-T Cell Rx: When Where and How Much

Look for the star associated with the slide that addresses the objective 

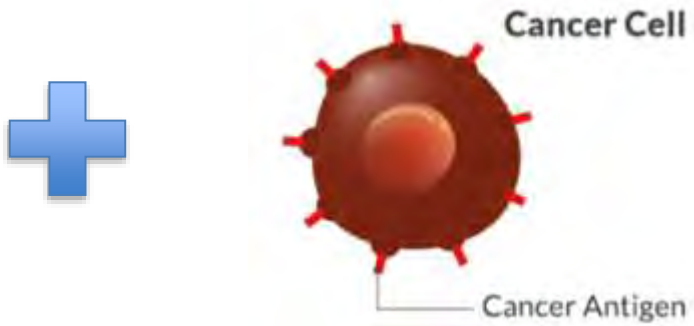
CAR-T Cell



CAR-T Cell Therapy



CAR-T Cell Rx + Radiation Rx
Should We Combine Them Like This?

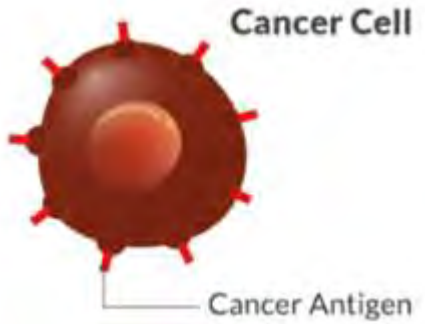


CAR T-Cell

TIME

or This??
CAR-T Cell Rx Radiation RX

CAR T-Cell



TIME

To Get This!!!

Dead Lymphoma Cell

What Features in Lymphoma Predict a Higher Risk of Persistence or Relapse Following CAR-T Cell Therapy?

Patterns and Predictors of Failure in Recurrent or Refractory Large B-Cell Lymphomas following CAR T-Cell Therapy (axi-cel) or (tisa-cel)

H. Lee Moffitt Cancer Center & Research Institute

- 469 Lesions seen on Imaging in 63 patients: 2015-2019

  (PET:<60 days before CAR T-Cell Rx, PET on Days: +30, +90, +180, then Q 90-180)

  (Patients with Bridging RT not included in analysis)

- Median Follow-Up 12.6 months (1.4 – 46.4 months)

- 57% Recurrence Rate

Nicholas B Figura, MD et al
PII: S0360-3016(21)00851-8
DOI: http://doi.org/10.1016/j.ijrobp.2021.06.038

Patterns and Predictors of Failure in Recurrent or Refractory Large B-Cell Lymphomas following CAR T-Cell Therapy (axi-cel) or (tisa-cel)

H. Lee Moffitt Cancer Center & Research Institute

Lesion-Specific Factors Predicting Local Failure

- Diameter ≥ 5cm p<0.001, 95% CI
- SUVmax ≥ 10 p<0.001, 95% CI
- Extra-nodal Disease p=0.01, 95% CI

Nicholas B Figura, MD et al
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Predictators of Persistent Disease or Relapse Following CAR-T Cell Rx

- **Primary Refractory Lymphoma**
- **Elevated max SUV ≥10 versus 20+**
- **Large Metabolic Tumor Volume**
- **Tumor Size >5-10+ cm**
- **Necrotic Tumor Volume**
- **Elevated LDH**
- **Multiple Relapses at the Same Location**

Potential Benefits of Radiation Therapy with CAR-T Cell Rx

Palliate Symptoms

Cytokine Release Syndrome

AGGRESSIVE Disease

RT Clean Up post CAR-T

Potential Risks of Radiation Therapy and CAR-T Cell Rx

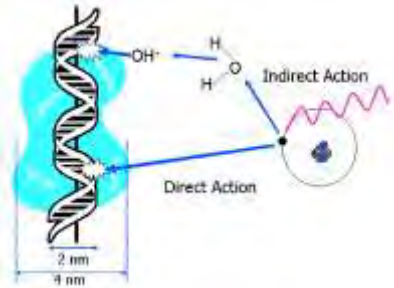
Prevent CAR-T Cell Expansion

Delay infusion of CAR-T Cells

The Role of Radiation Therapy with CAR-T Cell Rx 2023: When Where and How Much

Proposed Interactions of RT with CAR-T

Traditional Radiation Cell Death



Too many tumor cells could overwhelm available CAR-T cells

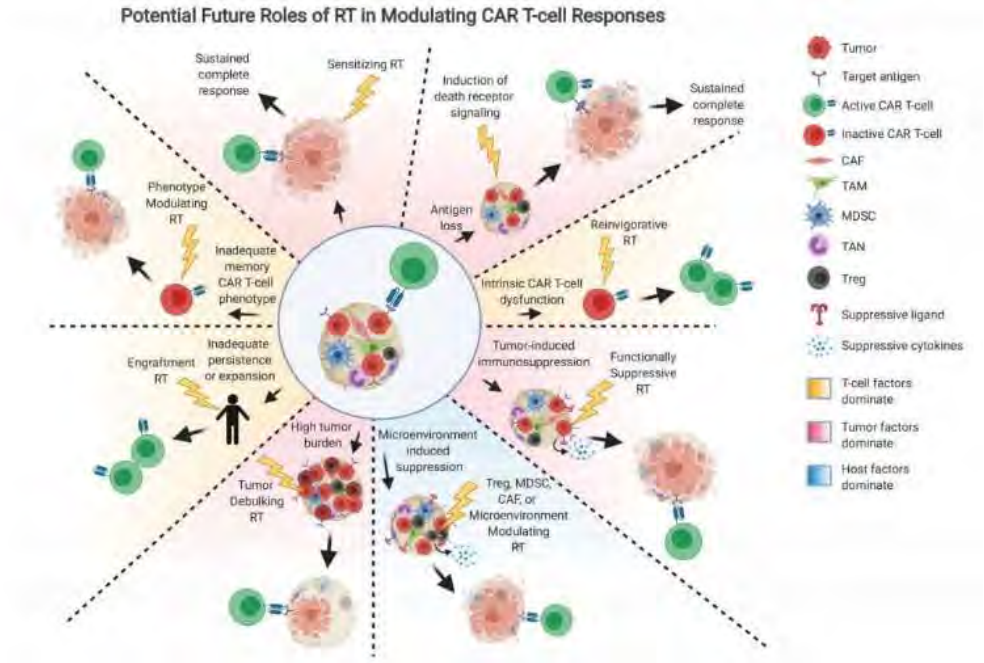
Use RT for “TUMOR DEBULKING”

Proposed Interactions of RT with CAR-T

Tumor Related Factors:
- Sensitizing RT
- Induction death receptor signaling
- Tumor induced immunosuppression
- Tumor Debulking RT

T-Cell Factors:
- Reinvigorative RT
- Engraftment RT
- Phenotype Modulating RT

Host Factors & CAR-T-Cell Resistance:
- Cancer Associated Fibroblasts
- Myeloid Derived Suppressive Cells
- Tumor Associated Macrophages
- Tumor Associated Neutrophils
- Regulatory T-Cells



Second- and third-generation CAR T cells, containing the CD3z domain with 1 or 2 cosignaling domains, Potential future roles of RT in modulating CAR T-cell outcomes. Beyond simple tumor debulking, RT may be utilized in the future at appropriate doses to address tumor-related factors (red background), T-cell factors (orange background), or host factors (blue background) that are operative in driving resistance to CAR T-cells. CAF, cancer associated fibroblasts; MDSC, myeloid derived suppressive cells; RT, radiation therapy; TAM, tumor associated macrophages; TAN, tumor associated neutrophils; Treg, regulatory T-cells. (DeSelm et al., BJR 2021).

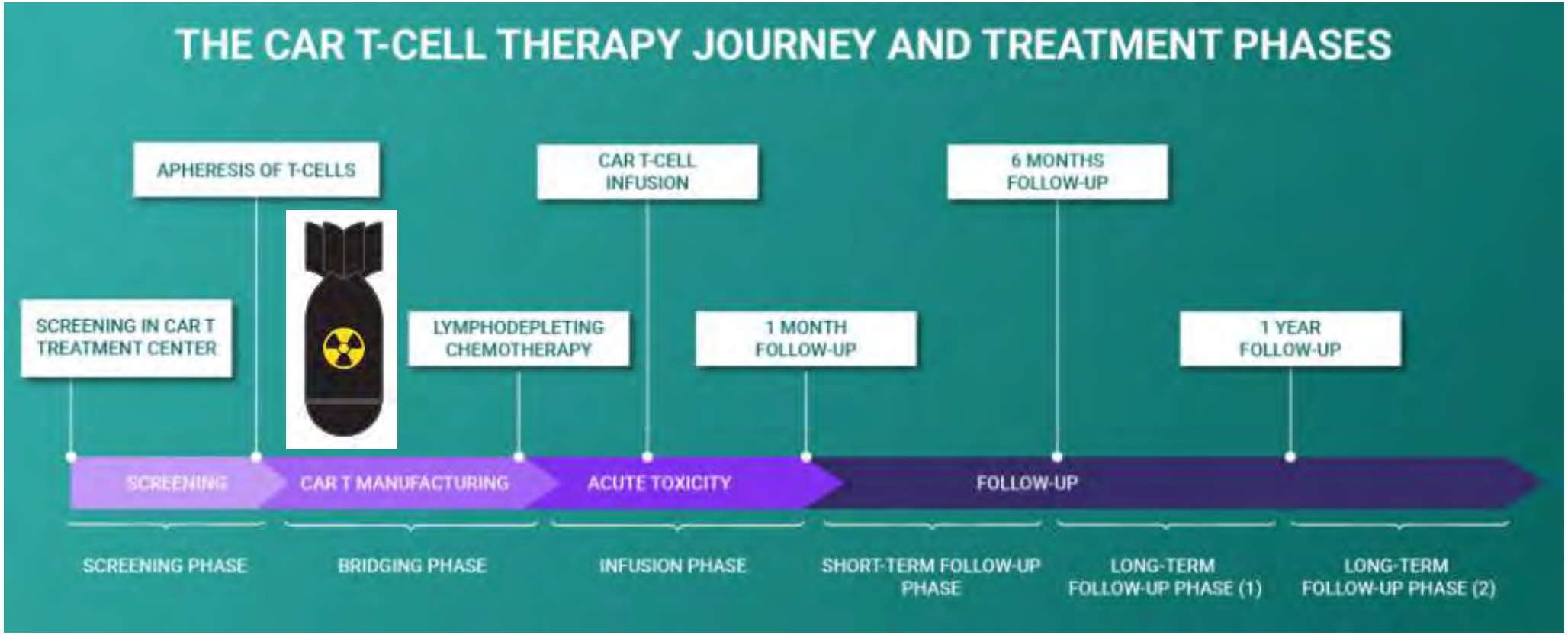
Reference: Carl DeSelm, The Current and Future Role of Radiation Therapy in the Era of CAR T-cell Salvage, *BJR*, 2021.

When to Add Radiation Therapy

Option 1: During Bridge Interval

When to Add Radiation Therapy

Option 1: During Bridge Interval



★When/How Much Radiation Rx

Option 1: During Bridge Interval

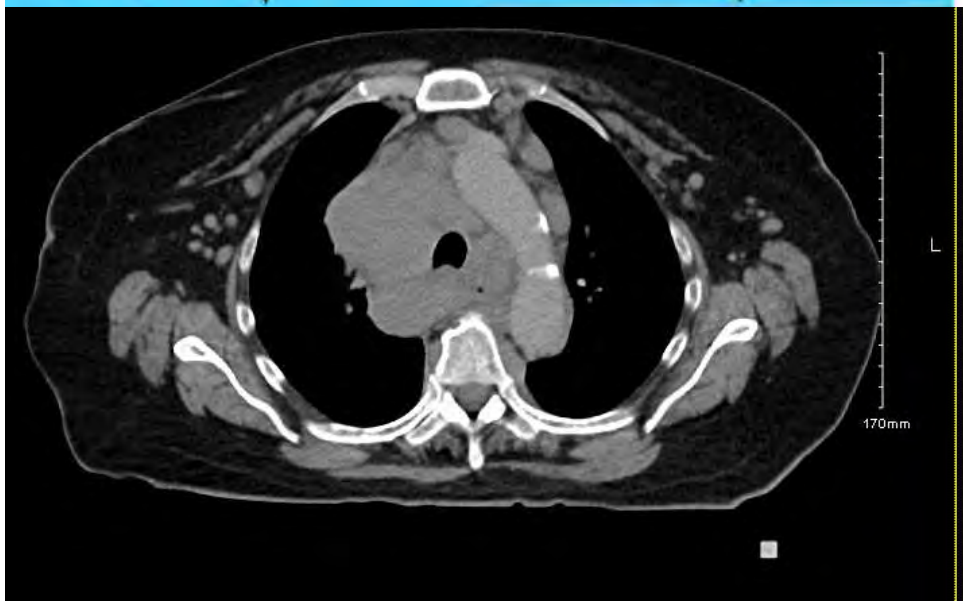
Palliate Symptoms — 20 Gy to 30 Gy in 5 versus 10 Treatments

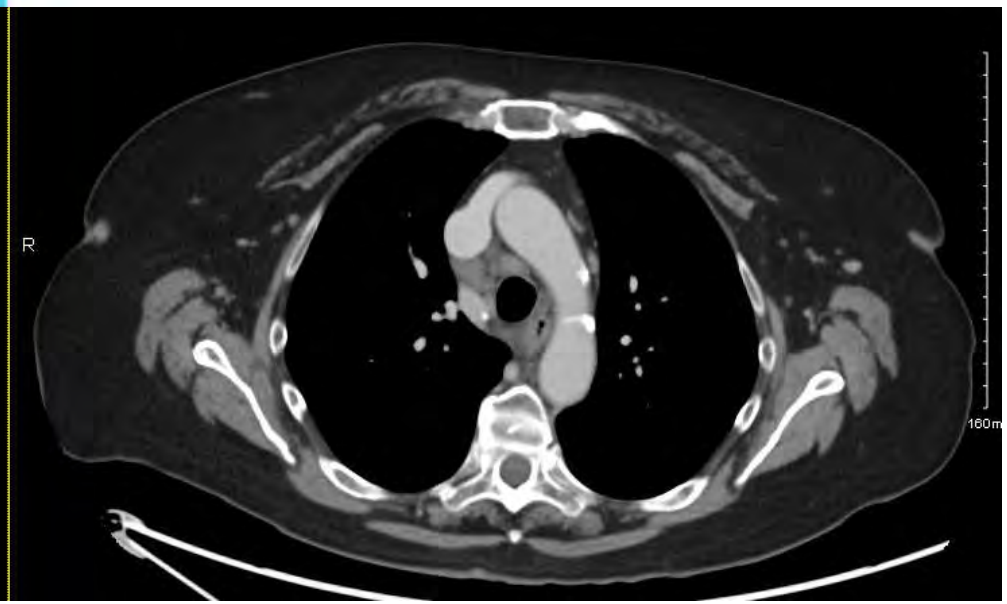
AGGRESSIVE Disease — 36 Gy in 20 **BID** Treatments in 10 Days

4 Gy in 2 Treatments

Boom Boom in Low Grade Lymphoma

4 Gy in 2 Treatments





Simulation CT Scan

9 Weeks Post Boom Boom

Patient-Level Disease Burden as a Predictor of In-Field Failures in Patients Undergoing Bridging Radiotherapy for CD19-Directed Chimeric Antigen Receptor (CAR) T-Cell Therapy for Recurrent/Refractory Large B-Cell Lymphomas

H. Lee Moffitt Cancer Center & Research Institute N.B. Figura et al

- Retrospective comparison of the original 63 unirradiated patients with 45 patients who did receive bRT
- Patients who received bRT had worse disease than unirradiated patients
- Median metabolic tumor volume (MTV): 463 vs 186cc
- Presence of any lesion > 5cm: 87 vs 67%
- Presence of any necrotic lesion: 50 vs 28%

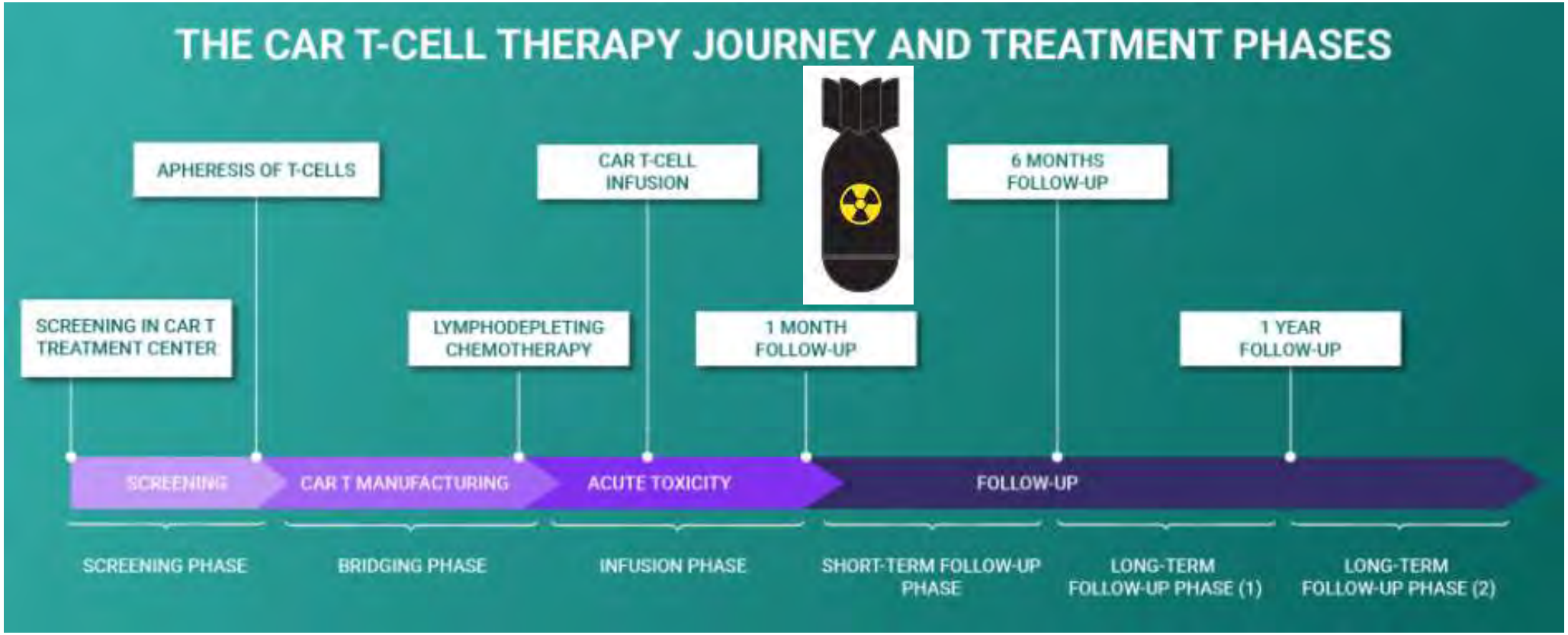
- 45 patients had 98 lesions treated with bRT: medin EQ2D (a/b=10) dose of 31.2 Gy

- Infield progression was: 28%(11/40) vs 24% (23/98)

- Conclusion: Patients receiving bRT prior to CAR T-Cell therapy for R/R LBCL with high MTV have similar outcomes to patients with far lower disease burden who did not receive bRT.
- Conclusion: In-field progression occurred in 25% of bRT patients and is strongly correlated with total disease burden.

When to Add Radiation Therapy

Option 2: Post CAR-T Cell Infusion



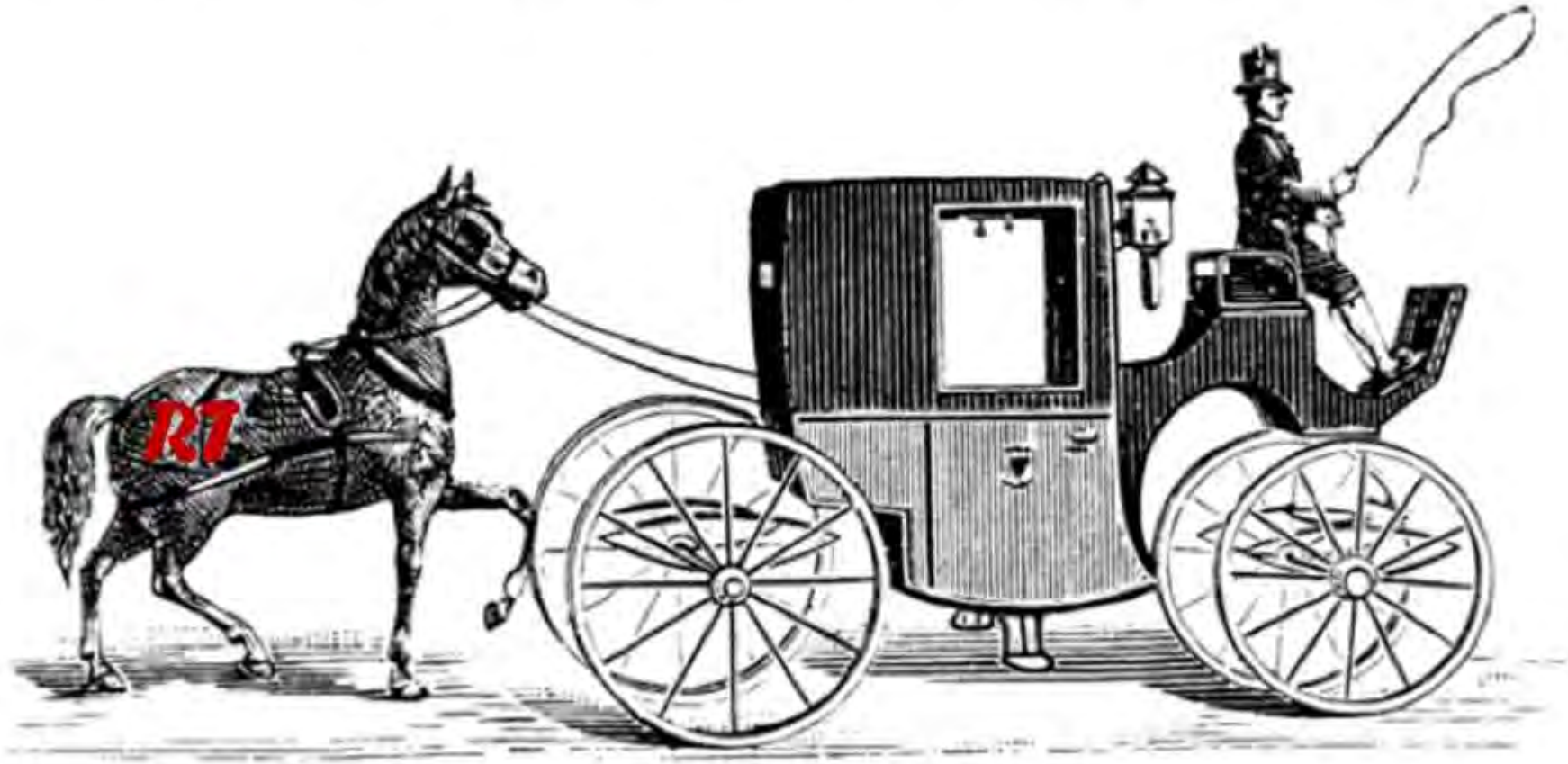
When/How Much Radiation Rx

Option 2: Post CAR-T Cell Infusion

20 Gy to 30-36 Gy in 5 versus 10-18 Fractions

AGGRESSIVE Disease 36 Gy in 20 BID Fractions in 10 Days

This isn't working at all... I should warn others not to put their CAR-T before the RT



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Don't Put the CART Before the Horse: The Role of Radiation Therapy in Peri-CAR T-cell Therapy for Aggressive B-cell Non-Hodgkin Lymphoma

Omran Saifi, MD • William G. Breen, MD • Scott C. Lester, MD • ... Mohamed A. Kharfan-Dabaja, MD, MBA • Bradford S. Hoppe, MD • Jennifer L. Peterson, MD • Show all authors

Published: December 20, 2022 • DOI: https://doi.org/10.1016/j.ijrobp.2022.12.017 •

Retrospective Review of 83 patients with r/r bNHL who received CAR-T and RT, either as Bridging RT (BRT N=35) versus Salvage RT (SRT N=48)

RT was either Comprehensive RT (treat all active disease-compRT) or Focal RT (focRT)

Limited Disease was amenable to compRT, involving <5 active disease sites

- BRT/CAR-T: **Bulkier Disease Sites** compared to CAR-T/SRT (median diameter, **8.7 vs 5.5 cm**; P= 0.01)
- BRT/CAR-T: **Received lower RT dose** compared to CAR-T/SRT (median 2 Gy dose, **23.3 vs 34.5** Gy; P=0.002)

RESULTS (124 total irradiated sites)

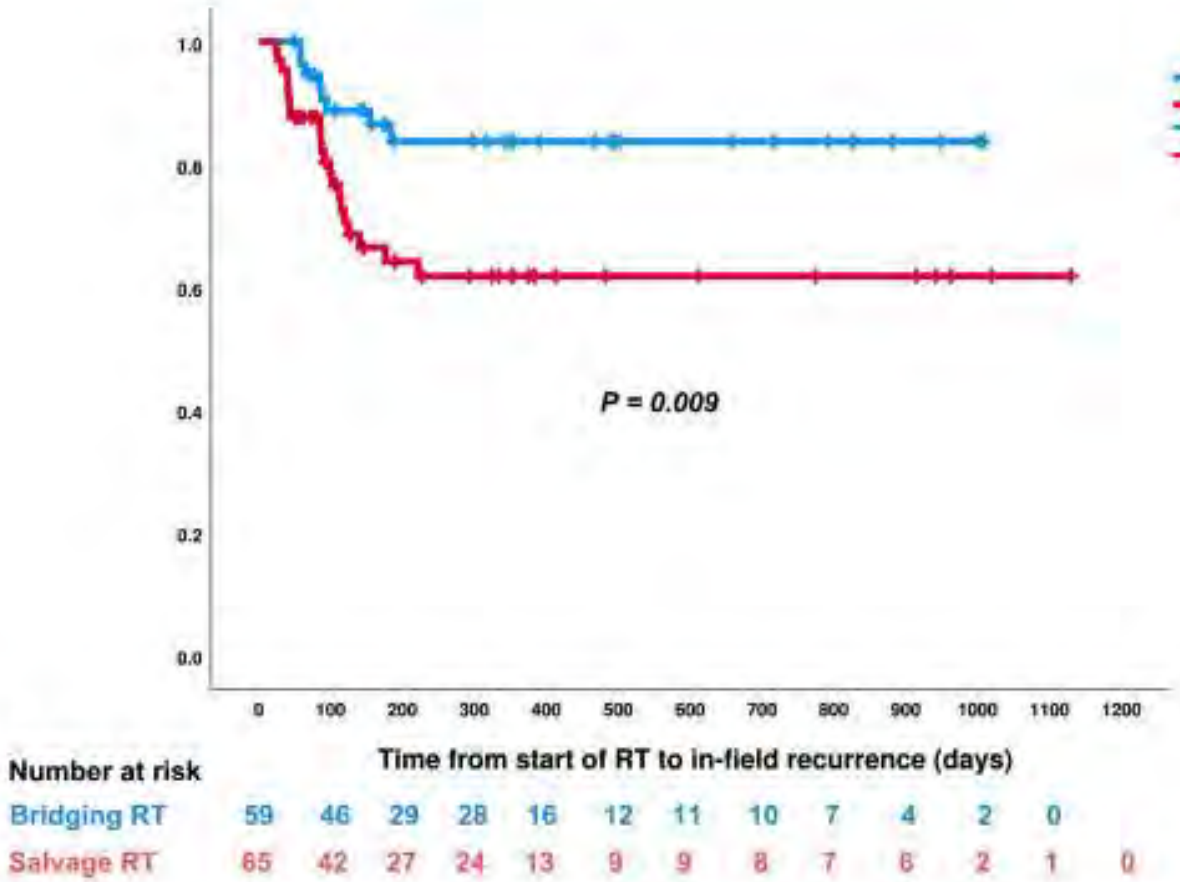
Infield Recurrence:

- **BRT**, preCAR-T: 8 of 59 (13%)
- **SRT**, postCAR-T: 21 of 65 (32%) **1-yr Local Control 84% vs 62% (P=0.009)**

Patients with limited postCAR-T Dz (n=37) receiving compSRT (n=26) vs focRT (n=11):

- **Overall Survival** (51% vs 12%; P=0.028)
- **Freedom from Progression** (31% vs 0%; P<0.001)
- **Freedom from Subsequent Event** (19% vs 0%; P=0.011)

Time to In-Field Recurrence



Number at risk													
Bridging RT	59	46	29	28	16	12	11	10	7	4	2	0	
Salvage RT	65	42	27	24	13	9	9	8	7	6	2	1	0

Fig. 1 Kaplan-Meier plot of local control by timing of radiation.

Time to Progression after Salvage RT

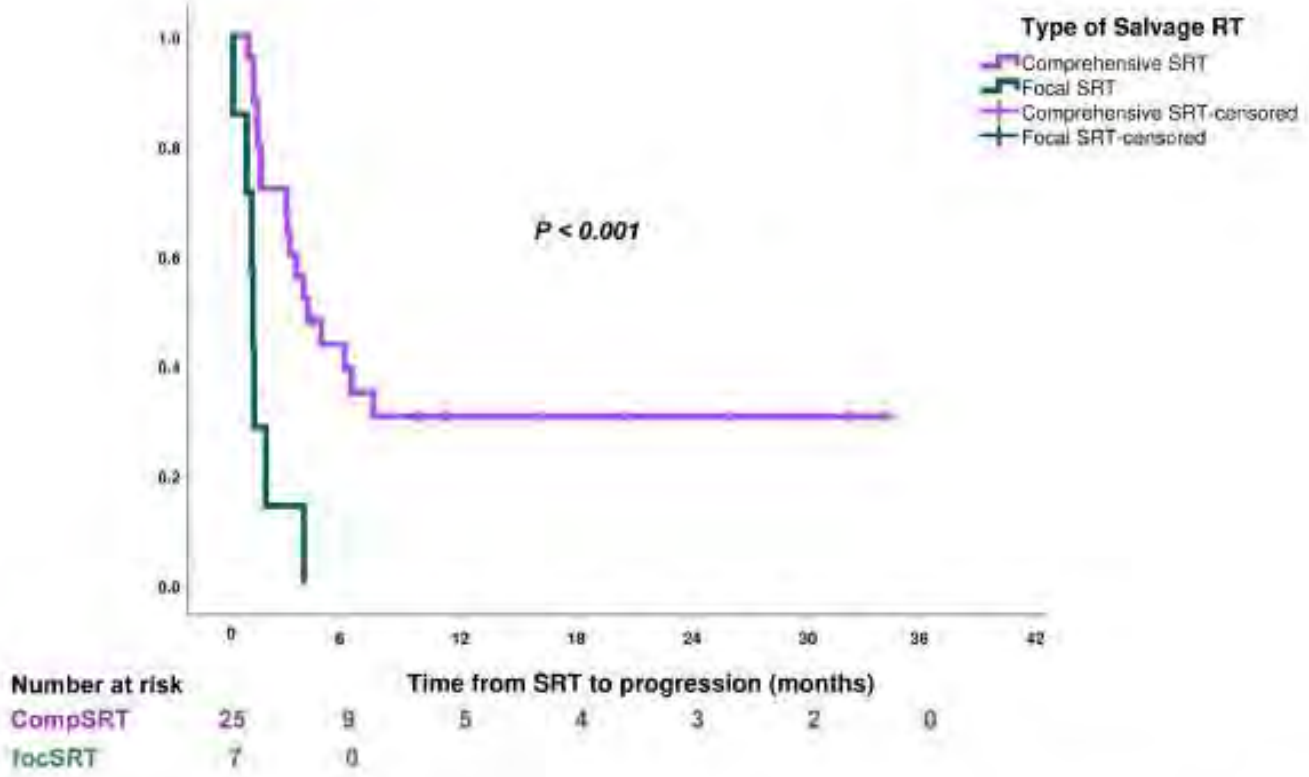


Fig. 2 Kaplan-Meier plot of freedom from subsequent progression by type of salvage radiation therapy (RT) in patients with limited disease.

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Thank You