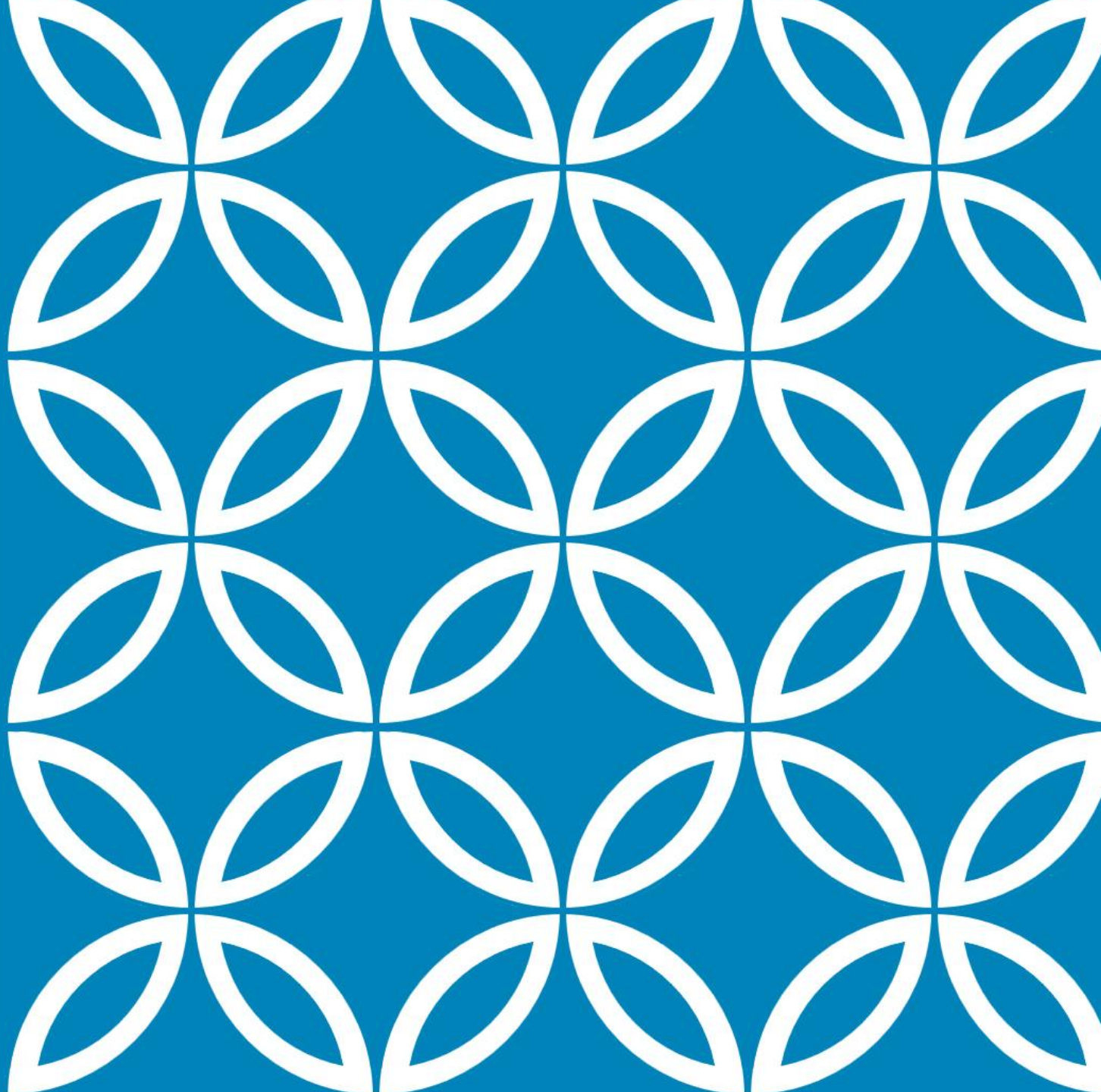
THE POWER WITHIN: IMMUNOTHERAPY FOR LYMPHOMA

June 3, 2025

David Macdonald, MD, FRCPC
Hematologist, The Ottawa Hospital

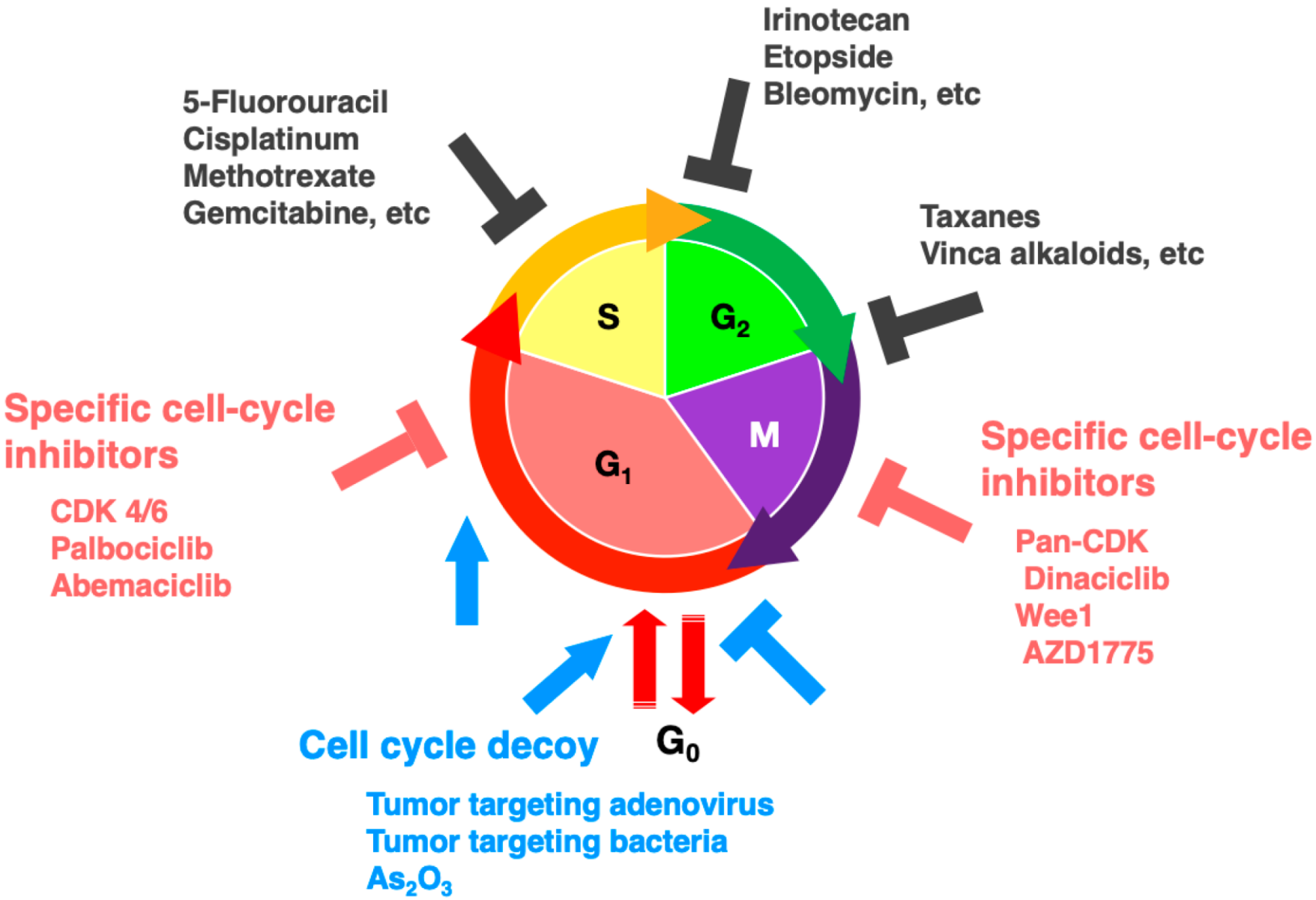
OUTLINE

1. What is Immunotherapy?
2. The proof that it works (and the unique side effects)
3. When is it available to you (or when will it be)?



TOWARDS A "CHEMO-FREE FUTURE"

- Conventional Chemotherapy
  - Medication that targets cells at various phases of the cell cycle, preventing their division and growth
    - Cancer arises from uncontrolled cell growth and division, with cancer cells often dividing more rapidly than healthy cells
    - While chemotherapy affects cancer cells, it can also impact rapidly dividing healthy cells in the bone marrow, skin, hair, and intestines, leading to side effects



Yano et al, *Cancers* **2020**, *12*(9), 2655

CONVENTIONAL CHEMOTHERAPY

A driamycin – anthracycline antibiotic
B leomycin – non-anthracycline antibiotic
V inblastine – vinka alkyloid
D acarbazine - alkylator

R ituximab
C yclophosphamide – alkylator
H (ydroxyadriamycin) – anthracycline
O ncovin (Vincristine) – vinka alkaloid
P rednisone – corticosteroid

F ludarabine – purine analog
C yclophosphamide – alkylator
R ituximab

B endamustine – alkylator with purine analog ring
R ituximab

"Chemoimmunotherapy" = chemotherapy + monoclonal antibody

"TARGETED THERAPY"

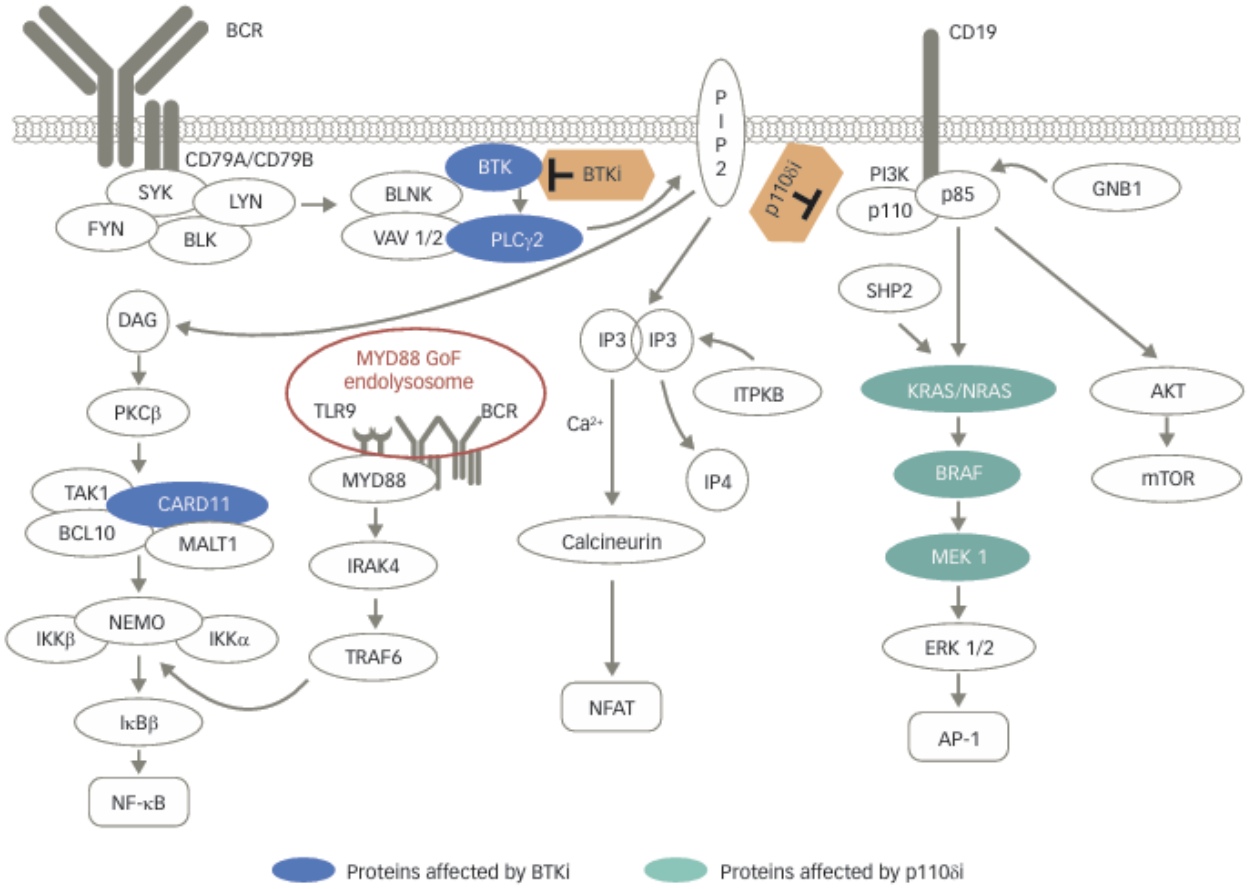
This usually refers to medications (often oral) that work to inhibit specific pathways that are overly active within specific cancer cells

Examples:

Proteasome inhibitors – bortezomib

BTK inhibitors – ibrutinib, acalabrutinib, Zanubrutinib

BCL2 inhibitors – venetoclax



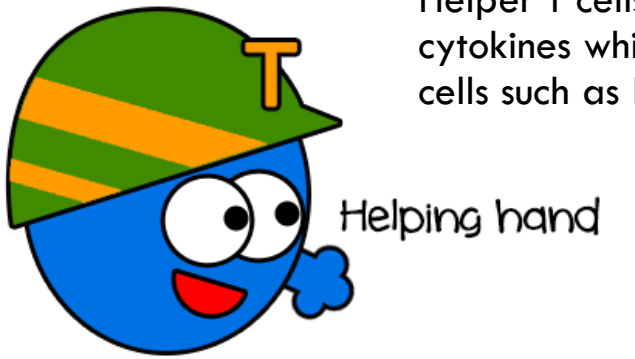
Rosenthal and Munoz, touchREVIEWS in Oncology & Haematology. 2022;18(1):44–52

IMMUNOTHERAPY

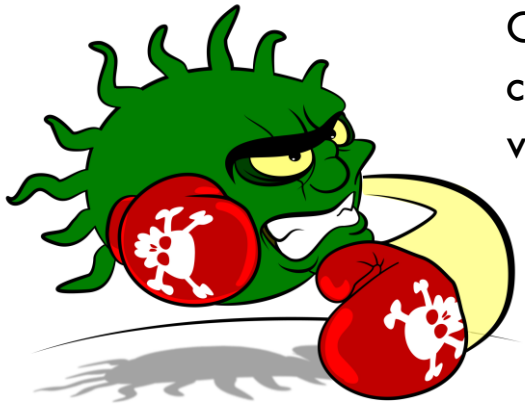
Recruiting the immune system to attack cancer cells

IMMUNOSURVEILLANCE: How T-lymphocytes participate in fighting cancer

- **Patrolling the body** – T cells act like security guards, constantly scanning your body for suspicious or harmful cells, including cancer cells.
- **Recognizing threats** – When they spot abnormal cells that don't belong (like cancer cells), they send signals to alert the immune system and prepare for attack.
- **Eliminating the danger** – Some T cells directly destroy cancer cells, while others help coordinate the immune response to clear out threats before they grow into a serious problem.



Helper T cells (CD4 +) produce chemical messages called cytokines which boost immune responses by other immune cells such as B cells and macrophages



Killer T-Cell

Cytotoxic T cells (CD 8+) patrol the body checking our own cells for invaders such as viruses

http://commonconstitutionalist.com

Proof of Immunosurveillance

Increased incidence of lymphoma in pts with autoimmune disease

Post-transplant lymphoproliferative disorder (PTLD)

Cancer Cell Evasion of Immunosurveillance

AACR – American Association for Cancer Research Annual meeting, April 25-30 2025, Chicago

TIME

APR 28, 2025 3:09 PM ET

A New Immune Treatment May Work Against Several Cancer Types

HEALTH | CANCER

by Alice Park
SENIOR CORRESPONDENT

The NEW ENGLAND JOURNAL of MEDICINE

CURRENT ISSUE | SPECIALTIES | TOPICS | MULTIMEI

ORIGINAL ARTICLE

Nonoperative Management of Mismatch Repair–Deficient Tumors

Authors: Andrea Cercek, M.D., Michael B. Foote, M.D., Benoit Rousseau, M.D., Ph.D., J. Joshua Smith, M.D., Ph.D., Jinru Shia, M.D., Jenna Sinopoli, N.P., Jill Weiss, B.S., +40 , and Luis A. Diaz, Jr., M.D. Author Info & Affiliations

Published April 27, 2025 | DOI: 10.1056/NEJMoa2404512 | Copyright © 2025

IMMUNOTHERAPY IN METASTATIC MELANOMA

what has been the impact of immune checkpoint inhibitors on the outcome of metastatic melanoma?

Copilot

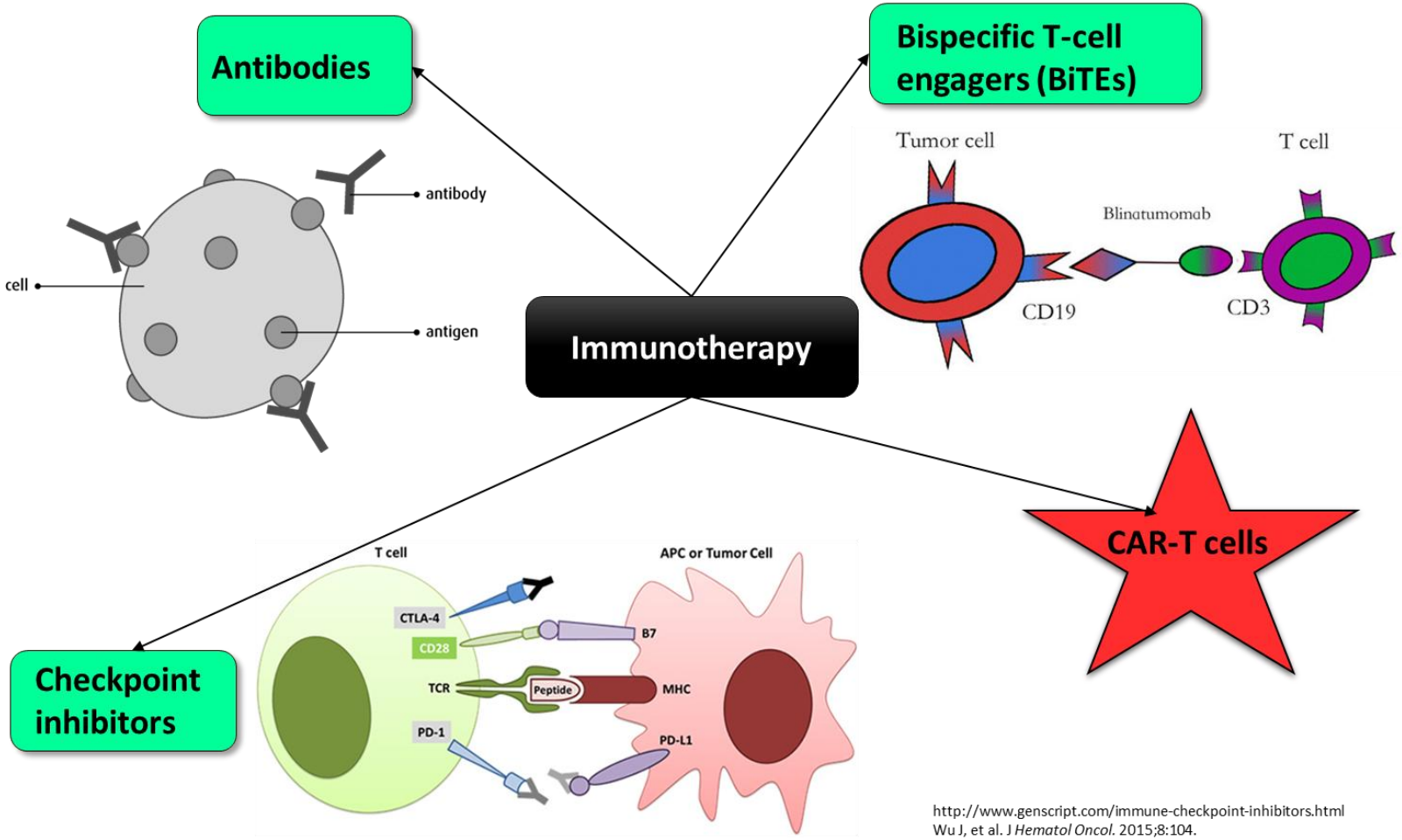
1. Dramatic Improvement in Survival

- Before ICIs, the median survival for metastatic melanoma was around **6.5 months**.
- With ICIs, particularly the combination of **nivolumab (anti-PD-1)** and **ipilimumab (anti-CTLA-4)**, **median survival has increased to over 6 years** [1].
- Long-term data from the **CheckMate 067 trial** show that **about 50% of patients** treated with this combination are **alive and cancer-free 10 years later**, a remarkable improvement [1].

4. Practice-Changing Implications

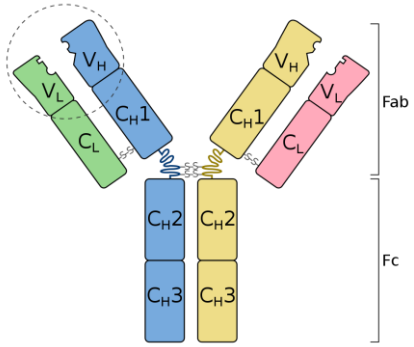
- These findings have **redefined the standard of care** for metastatic melanoma, shifting treatment paradigms from palliative to potentially curative in a significant subset of patients.

NEW CANCER THERAPIES TOUGHEN UP THE IMMUNE SYSTEM



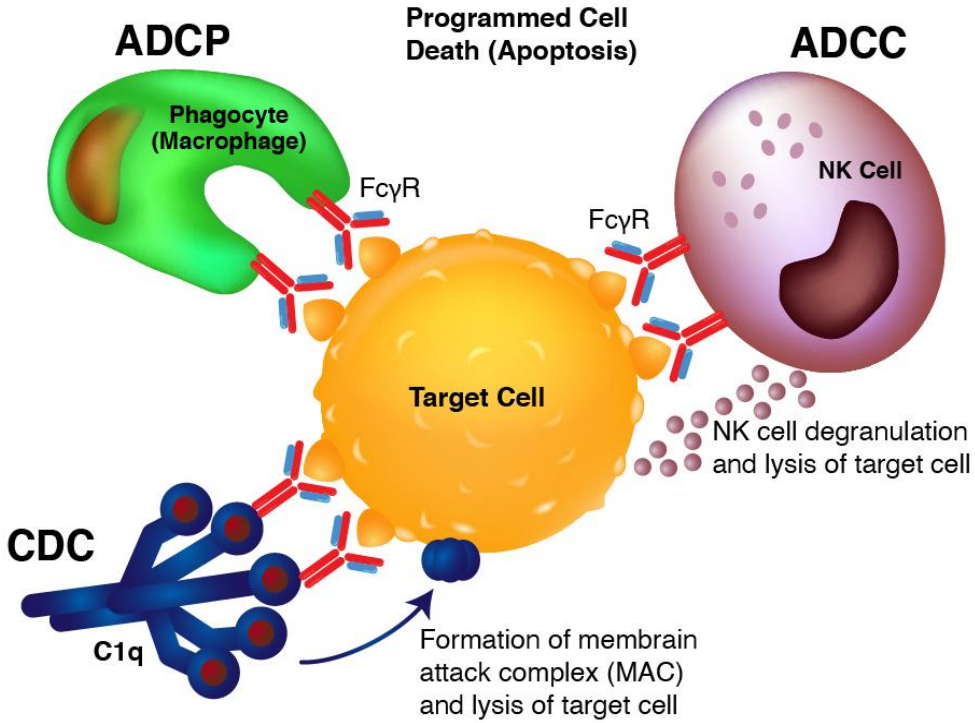
http://www.genscript.com/immune-checkpoint-inhibitors.html
Wu J, et al. J *Hematol Oncol.* 2015;8:104.

MONOCLONAL ANTIBODIES – THE VETERANS

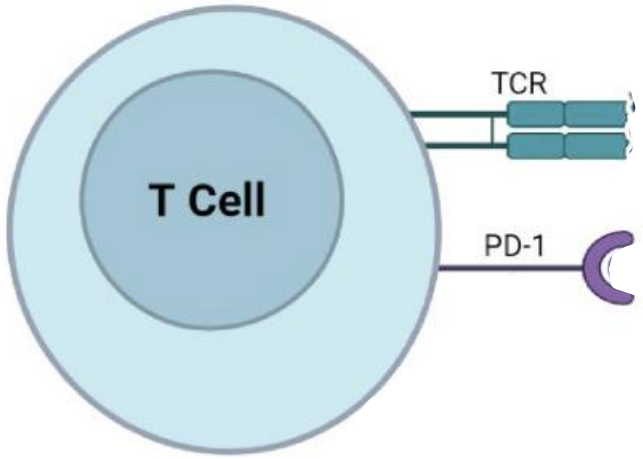


Rituximab
Obinutuzumab

Tafasitamab



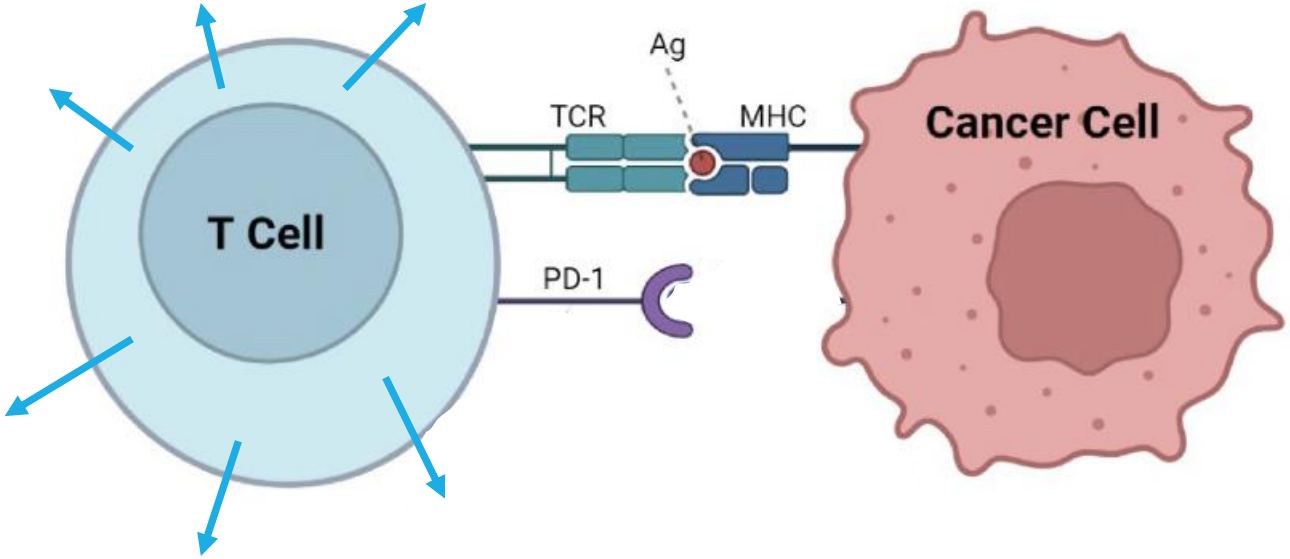
IMMUNE CHECKPOINT INHIBITORS



I. T cells roam around looking for invaders

Basudan, *Clin. Pract.* **2023**, *13*(1), 22-40

IMMUNE CHECKPOINT INHIBITORS

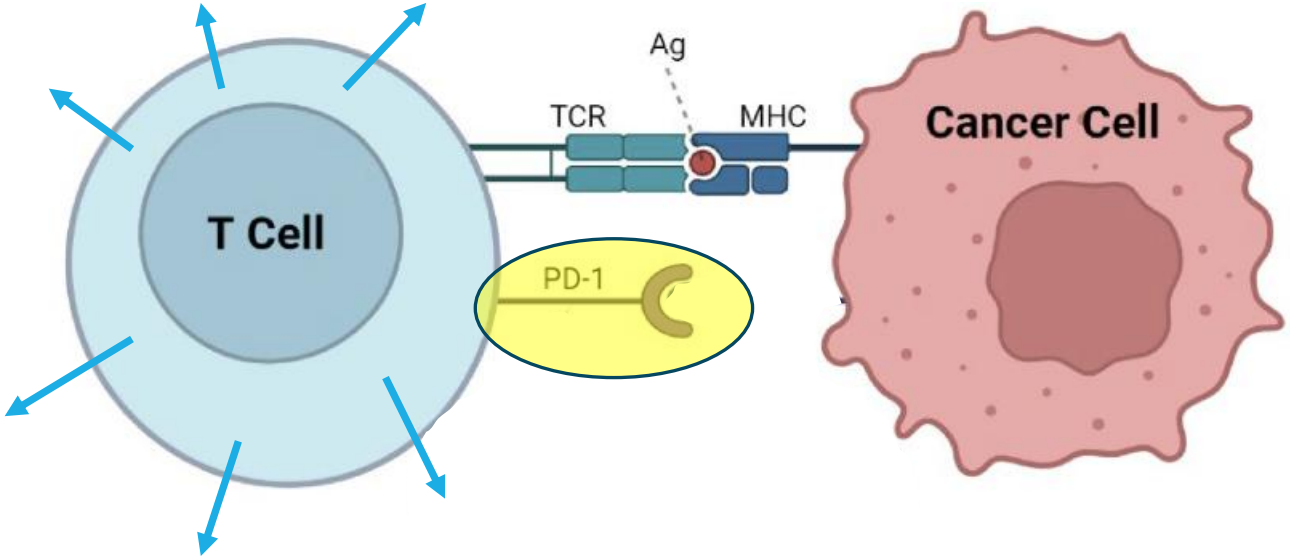


II. T cell comes into contact with cancer cell

III. T cell releases cytokines that trigger immune response

Basudan, *Clin. Pract.* **2023**, *13*(1), 22-40

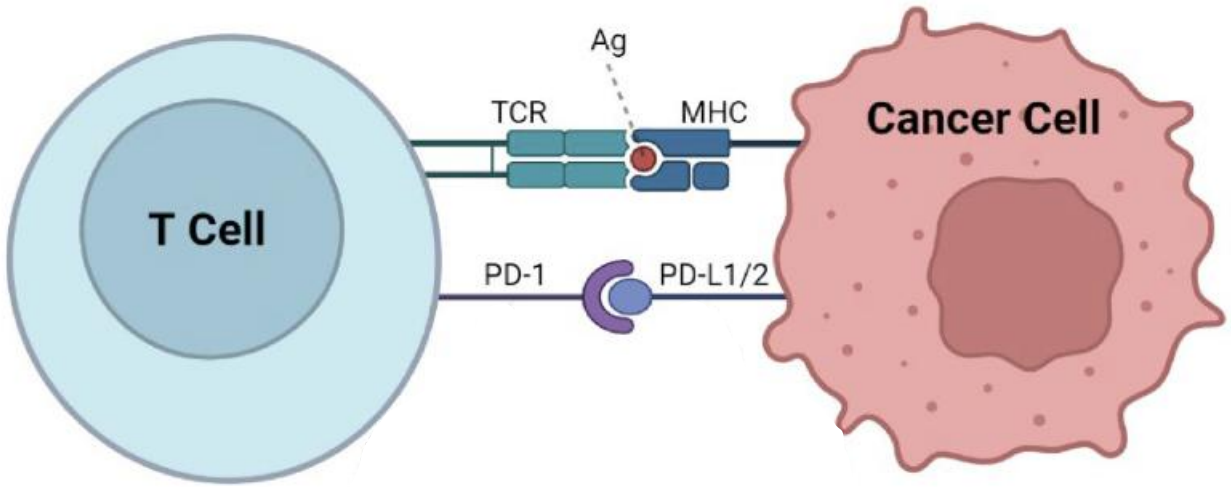
IMMUNE CHECKPOINT INHIBITORS



PD-1 is a checkpoint – it is like a switch that can turn off the cytokine release and hence dampen the immune response

Basudan, *Clin. Pract.* **2023**, *13*(1), 22-40

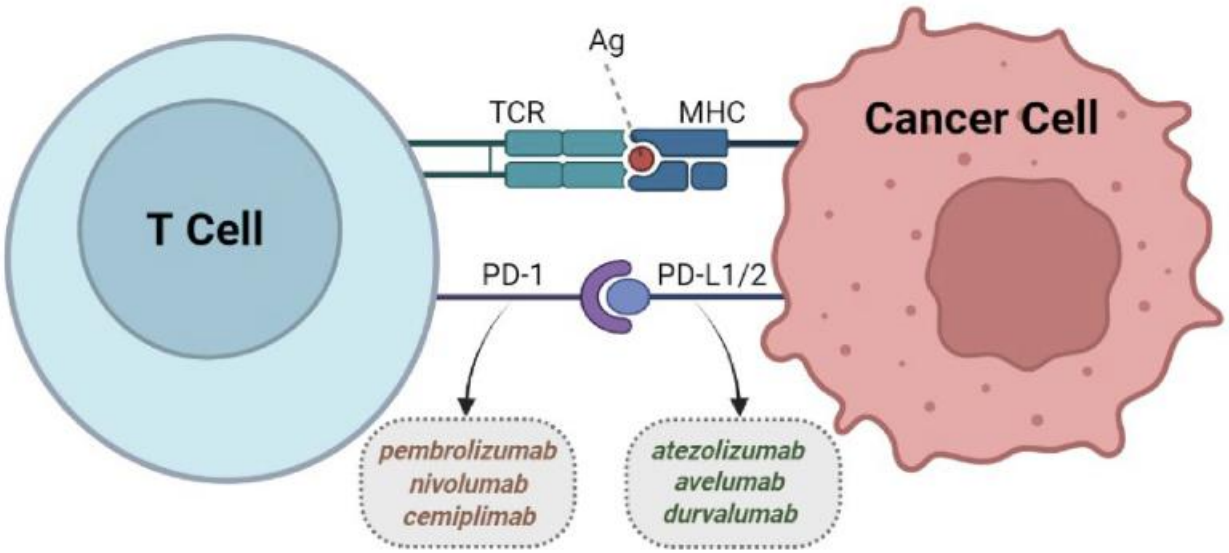
IMMUNE CHECKPOINT INHIBITORS



Cancer cells can have “PD1 Ligands” – these attach to PD-1, essentially activating the off switch, and allowing the cancer cell to avoid the immune system

Basudan, *Clin. Pract.* **2023**, *13*(1), 22-40

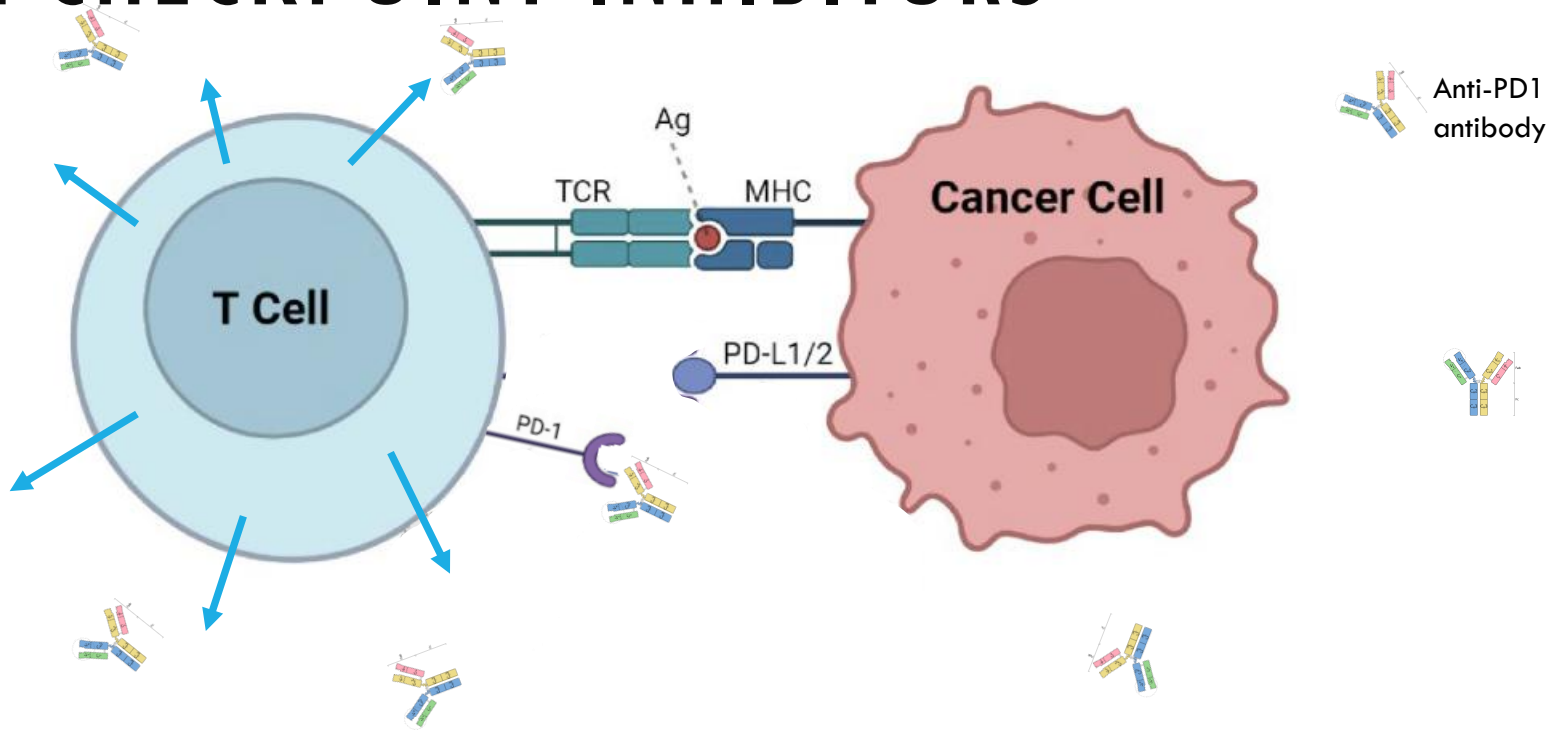
IMMUNE CHECKPOINT INHIBITORS



Cancer cells can have “PD1 Ligands” – these attach to PD-1, essentially activating the off switch, and allowing the cancer cell to avoid the immune system

Basudan, *Clin. Pract.* **2023**, *13*(1), 22-40

IMMUNE CHECKPOINT INHIBITORS



Checkpoint inhibitor prevents the cancer cell from activating the off-switch, so T cell can function normally and attack the cancer cell

Basudan, *Clin. Pract.* **2023**, *13*(1), 22-40

NIVOLUMAB IN RELAPSED HL

Previous treatment sequence for Hodgkin lymphoma:

- ABVD → GDP + auto transplant (ASCT) → Brentuximab vedotin → palliative care

CHECKMATE 039 – Phase 1 study in relapsed HL

- Overall response rate 87% (expect about 30%)
- Complete response rate 17% (expect <5%)

CHECKMATE 205 – Phase 2 study in HL that relapsed after ASCT and Brentuximab

- Overall Response Rate 69% (expect <20%)
- Complete Response Rate 16% (expect 0%)

PEMBROLIZUMAB IN RELAPSED HL

KEYNOTE-087 Trial – Phase 2 in HL relapsed after ASCT and BV

- Overall RR 69%, Complete RR rate 22.4%

CONCLUSION – Checkpoint inhibitors work remarkably well even after failure of brentuximab vedotin

LOGICAL QUESTION – are checkpoint inhibitors better than brentuximab?

KEYNOTE-204 – Phase 3 RCT of pembro vs Brentuximab in Relapsed HL

- Pembro showed significant improvement in Progression Free Survival – 13.2 mos versus 8.3 mos

NIVOLUMAB IN FRONT-LINE HL

Meanwhile, a trial of Brentuximab + AVD versus ABVD in front-line treatment of Stage 3 or 4 HL showed BV-AVD was better

SO next logical question – is a checkpoint inhibitor better than brentuximab when added to front-line chemotherapy?

SWOG S1826 Trial – Phase 3 RCT

Nivo-AVD vs BV-AVD in untreated advanced HL, 976 patients

- 2-year PFS 92% versus 83% in favour of Nivo-AVD
- Nivo-AVD caused fewer side effects than Brentuximab-AVD

IMMUNE CHECKPOINT INHIBITORS HAVE SIDE EFFECTS

Remember that the Checkpoint is the natural "off-switch" for the immune reacti
the T cell – if you block the off switch, expect inflammation to be worse!

Not exactly "chemo-free"

what are some common or important side effects of immune checkpoint inhibitors?

Copilot

Common Side Effects

These are generally mild to moderate and may include [1] [2]:

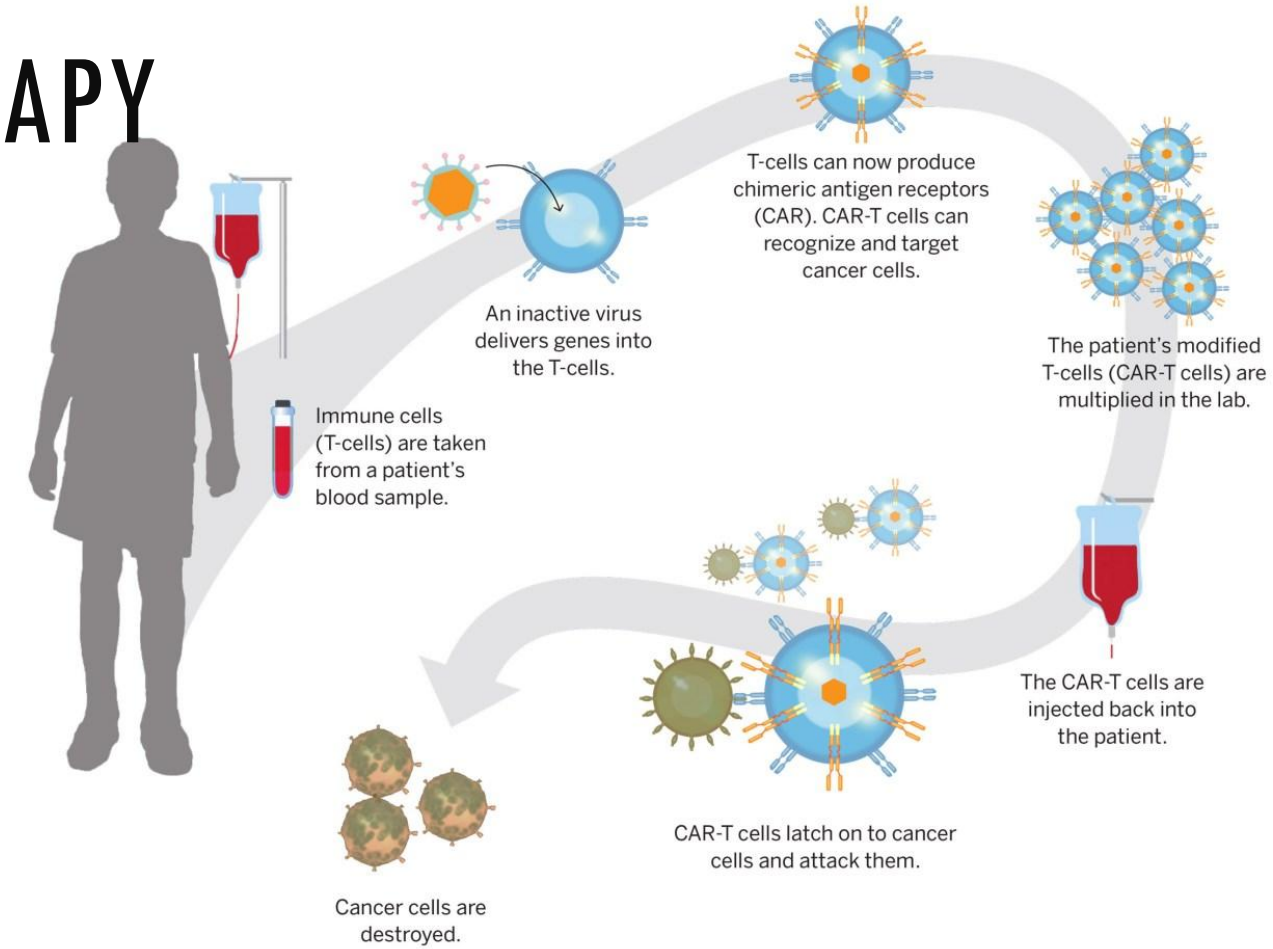
- Fatigue
- Skin rash or itching
- Diarrhea
- Nausea
- Cough
- Loss of appetite
- Constipation
- Muscle or joint pain

Serious (Immune-Related) Side Effects

These occur less frequently but can be severe or life-threatening if not managed promptly. They result from the immune system attacking normal tissues and may include [1] [2] [3]:

- **Pneumonitis** (inflammation of the lungs)
- **Colitis** (inflammation of the colon)
- **Hepatitis** (liver inflammation)
- **Endocrinopathies** (e.g., thyroiditis, adrenal insufficiency, hypophysitis)
- **Nephritis** (kidney inflammation)
- **Myocarditis** (heart inflammation)
- **Neurological effects** (e.g., peripheral neuropathy, encephalitis)

CAR-T THERAPY



Powell, *Harvard Gazette* Nov 25, 2019

CAR-T STUDIES IN DLBCL

Product	Trial Name	Setting
ZUMA-1	Axi-cel	Relapse after ASCT
JULIET	Tisa-cel	Relapse after ASCT
TRANSCEND	Liso-cel	Relapse after ASCT
ZUMA-7	Axi-cel	Second line
BELINDA	Tisa-cel	Second line
TRASNFORM	Liso-cel	Second line

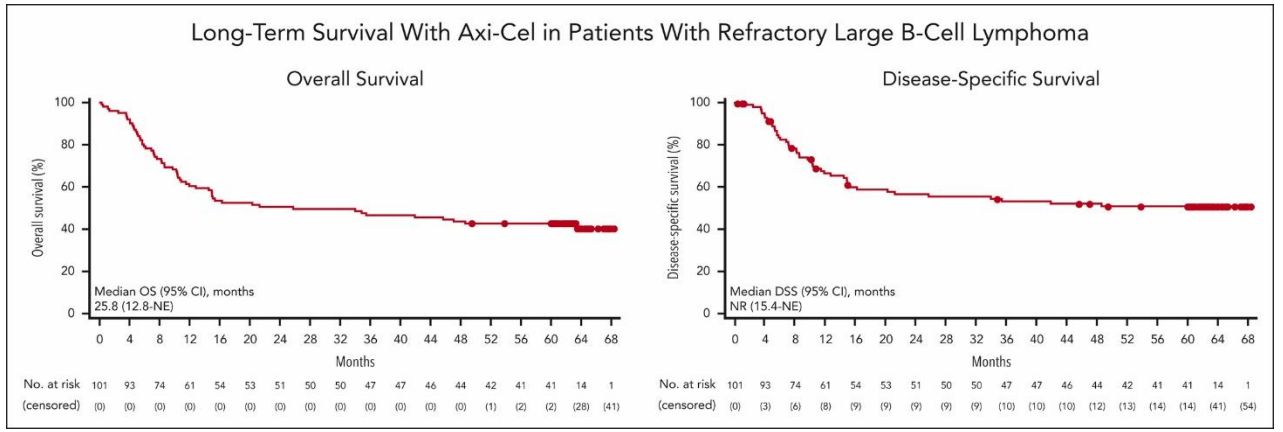
ZUMA-1

DLBCL patients who relapse after ASCT

Overall response rate 83%, CR 53% (expect ORR 40%, CR <10%)

42% of patients alive at 5 years

31% of responders were still in remission at 5 years



ZUMA-7

SO – if it works that well for patients who fail ASCT, would it be even better if used instead of ASCT?

For relapsed DLBCL, ASCT provides durable remissions in less than 40% of patients

ZUMA-7 randomized patients to ASCT or CAR-T for patients who relapsed within 12 months of initial chemotherapy

Axi-cel improved response rates, event free survival, and overall survival compared to ASCT

ZUMA-7

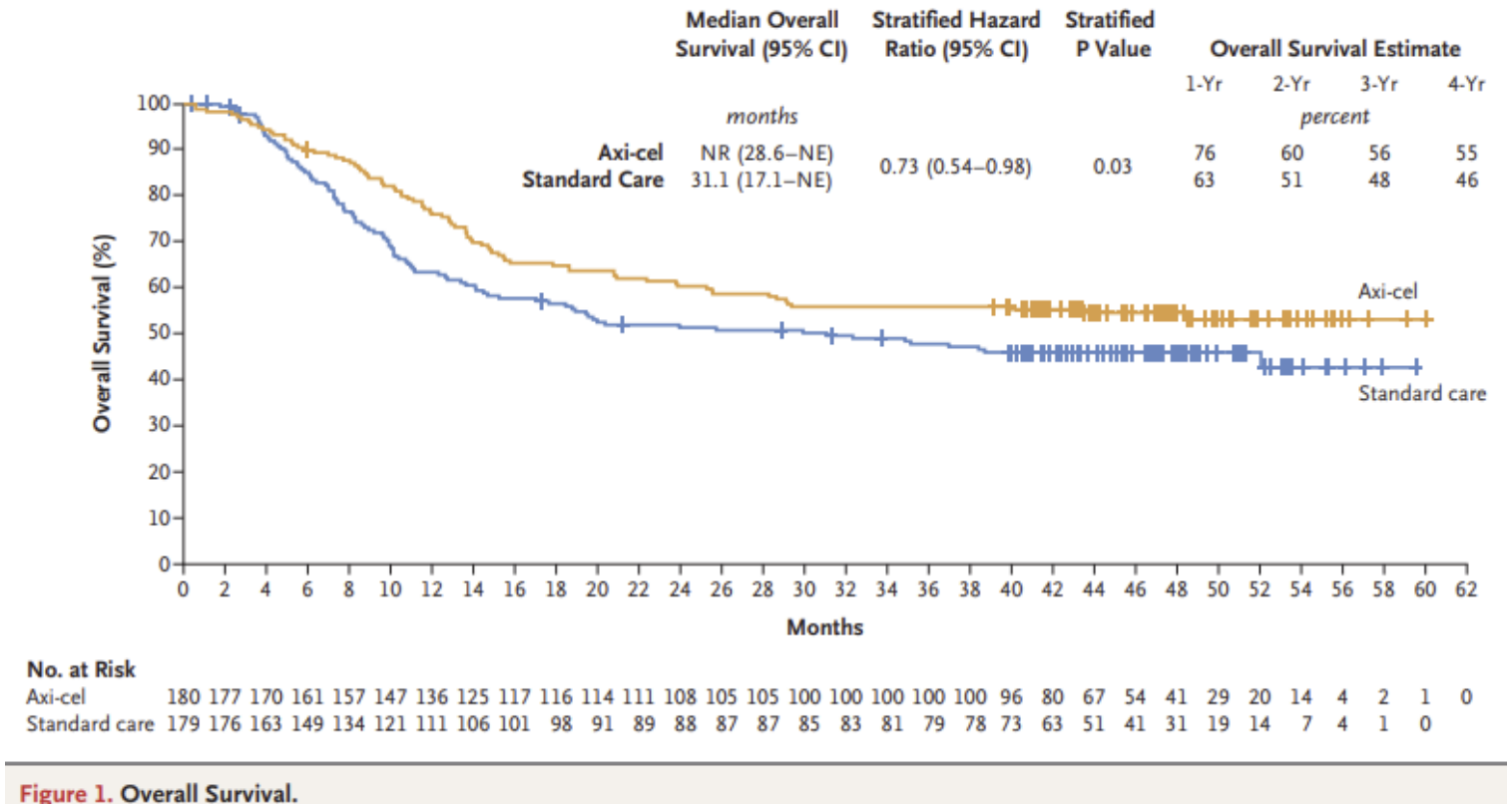


Figure 1. Overall Survival.

Westin, NEJM 2023

ZUMA-5

Axi-cel has also been studied in Relapsed Follicular and Marginal Zone Lymphoma in the ZUMA-5 study

- ORR 94%, CR 79% !!!
- Median duration of response 38 months
- POD24 patients did just as well as non-POD24

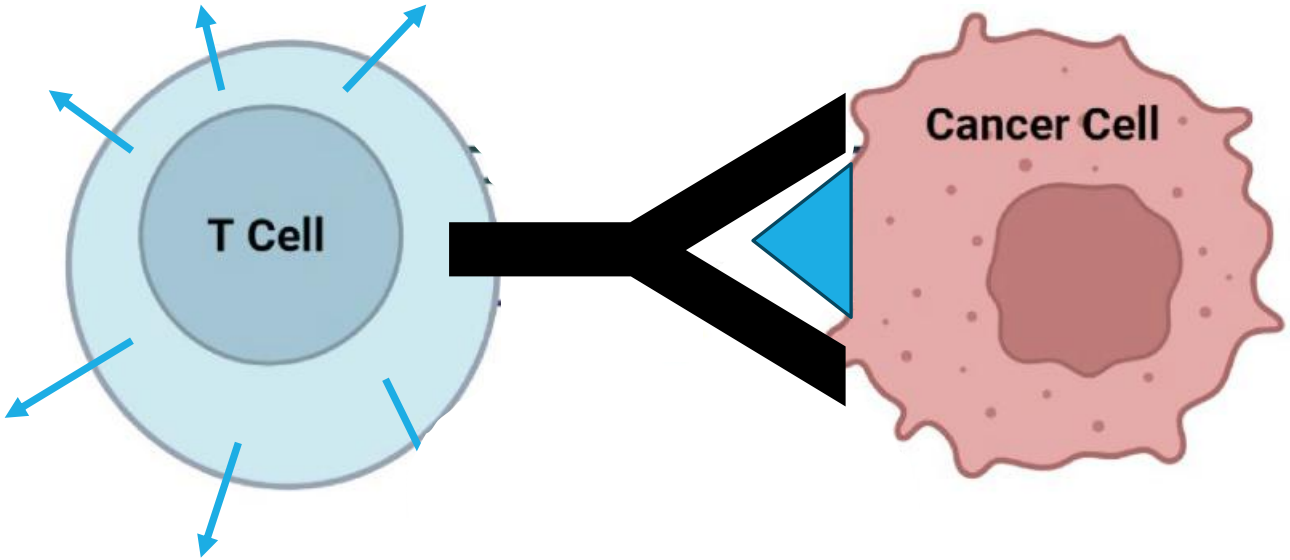
POD24 – patients who relapsed within 2 years of the end of their first treatment
- about 20% of all follicular lymphoma patients
- these patients historically did not respond well to second-line treatments

Neelapu, Blood 2021

CAR-T TOXICITIES

Cytokine Release Syndrome (CRS)

- Activation of the CAR-T cells causes massive release of cytokines resulting in fevers, hypotension, and potential for organ failure
- Severity ranges from mild flu-like illness to severe life-threatening conditions requiring ICU
- Managed with fluids, steroids and cytokine inhibitors like tocilizumab



CAR-T TOXICITIES

Immune effector-cell associated neurotoxicity syndrome (ICANS)

- A neuropsychiatric syndrome characterized by confusion, aphasia and seizures
- Can occur days to weeks after CAR-T infusion
- Usually reversible with appropriate management but symptoms can be severe and require ICU
- Management includes steroids and anti-seizure prophylaxis. Tocilizumab is less effective

CAR-T TOXICITIES IN ZUMA-7

CRS

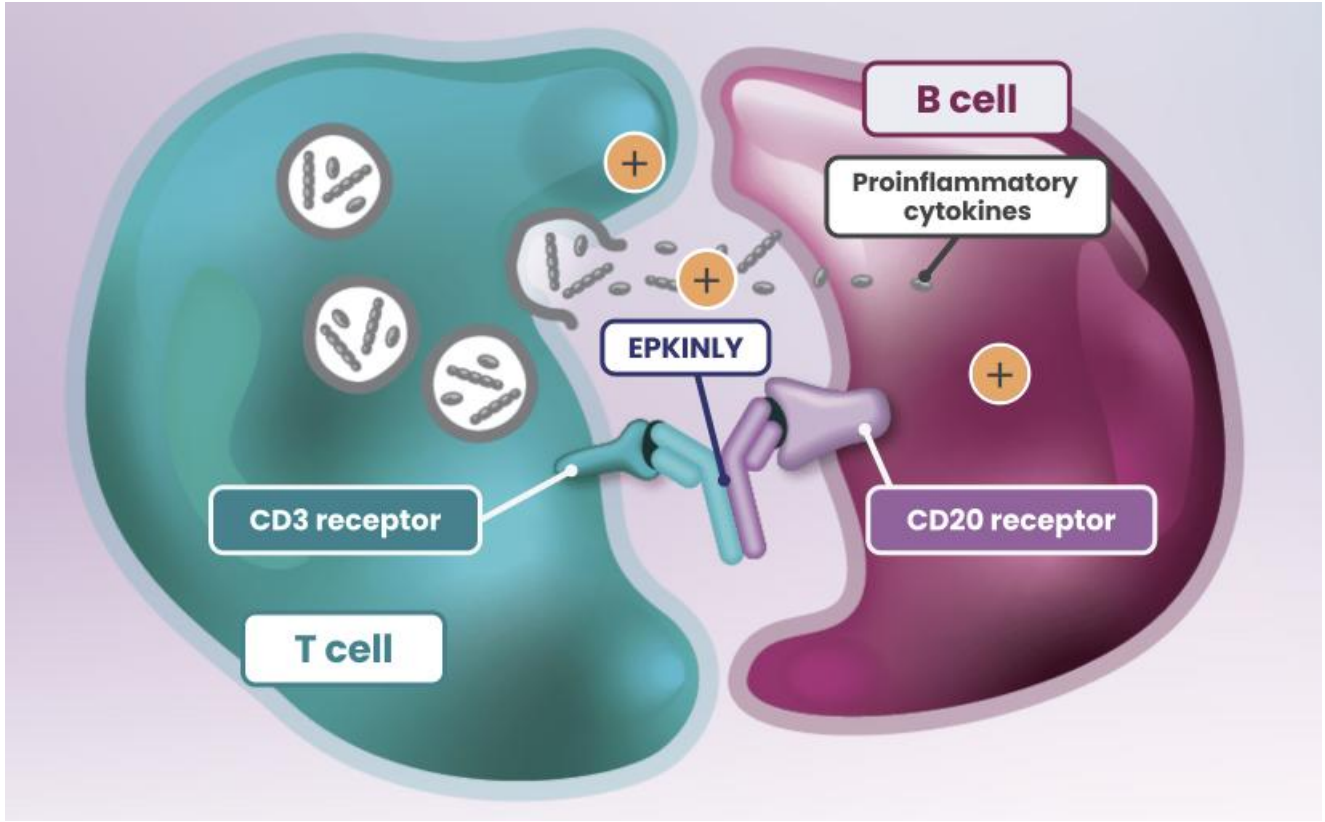
- Any grade 84% Serious (Grade 3 or higher) 6%

ICANS

- Any grade 40% Serious (Grade 3 or higher) 21%

“One in Five chance of having to go to the Intensive Care Unit”

BITE THERAPY



www.epkinlyhcp.com

BITE THERAPY IN DLBCL

Main drawbacks of CAR-T

- Requires treatment at specialized centre
- Process takes minimum 3-4 weeks

For both treatments:

- Overall Response Rate ~60%
- Complete Response Rate ~40%
- Patients who were in complete remission stayed in remission for average of 2 years

Bispecific products are off-the-shelf

epcoritamab and glofitamab are approved and funded in Canada

Epcoritamab is subcutaneous and indefinite

Glofitamab is intravenous, fixed duration, an requires a dose of Obinutuzumab 1 week before

Both have a ramp-up dosing schedule to reduce CRS and ICANS

ICI, CAR-T, AND BITE AVAILABLE NOW

Nivolumab in Hodgkin Lymphoma:

- Patients who relapse after ASCT and Brentuximab

Nivolumab in Primary Mediastinal B Cell Lymphoma

- Patients who relapse after ASCT or not eligible for ASCT

CAR-T in Diffuse Large B Cell Lymphoma

- Patients who relapse after 2 lines of treatment
- Patients who relapse within 12 months of their first line of treatment

CAR-T in Follicular and Marginal Zone Lymphoma

- Patients who relapse after 2 lines of treatment

BITE in Diffuse Large B Cell Lymphoma

- Patients who relapse after 2 lines of treatment and are not candidates for CAR-T

ICI, CAR-T, AND BITE ON CLINICAL TRIALS (TOH)

Nivolumab in Hodgkin Lymphoma

- Along with Brentuximab in relapsed patients proceeding to ASCT

CAR-T in Non Hodgkin Lymphoma

- New CD22-CART in relapsed aggressive B cell lymphoma, after 2 lines of therapy or after standard CD19-CART

Bispecific in Follicular Lymphoma

- Patients with no prior treatment – randomized to chemotherapy or bispecific with lenalidomide
- Patients relapsed after 2 prior therapies

Bispecific in Mantle Cell Lymphoma

- Patients with relapse after 2 prior treatments, one of which was a BTK inhibitor

WHERE DO I FIND A CLINICAL TRIAL FOR ME?

All clinical trials in North America have to be registered

The registration site for almost every trial is ClinicalTrials.gov

This site is searchable and accessible by anyone with a computer

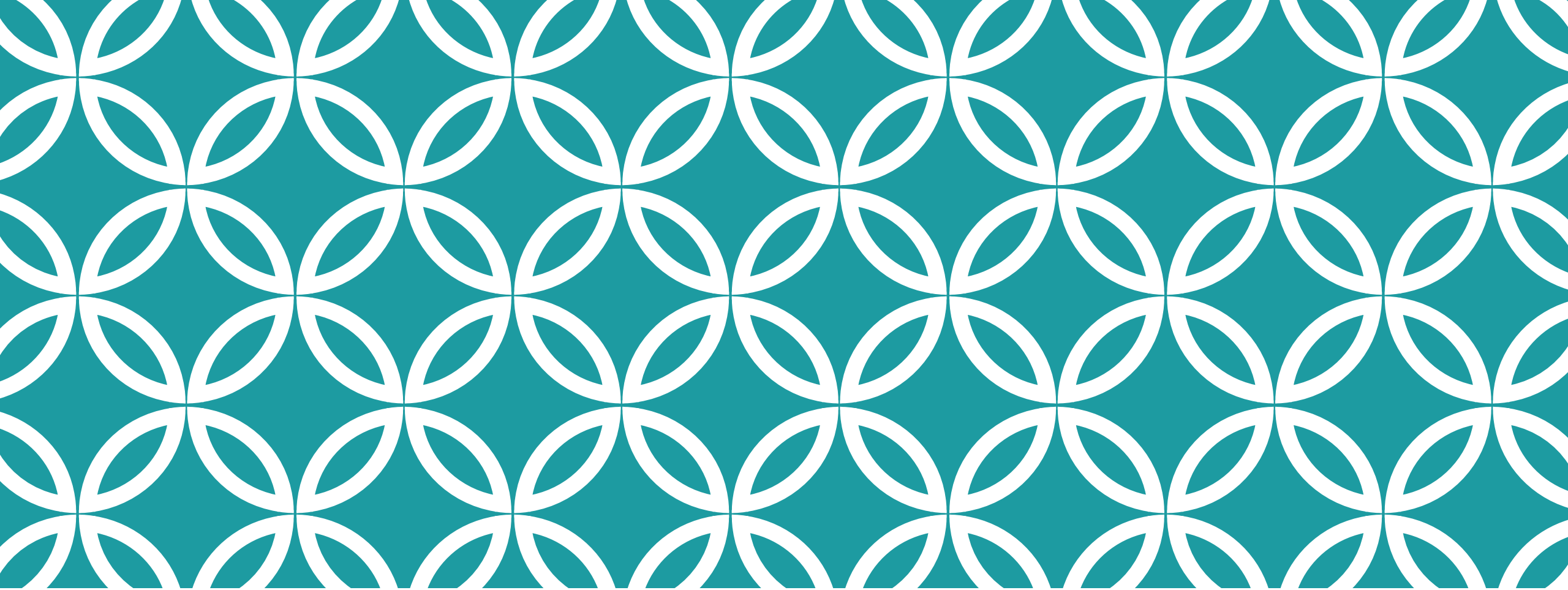
ClinicalTrials.gov

ICI, CAR-T AND BITE IN FUTURE

- Very likely we will be moving to Nivo-AVD for first-line treatment of Hodgkins
- Mosenutuzumab (bispecific) in relapsed follicular lymphoma (commercially available in ~1 year)
- CD19-CD3 bispecific in relapsed DLBCL relapsing after CAR-T and/or CD20-CD3 bite (clinical trial)
- CD19-CD3 bispecific plus dose reduced RCHOP as first treatment in elderly patients with DLBCL

SUMMARY

- The past 10 years has seen a movement away from conventional chemotherapy and toward a “chemo-free approach”, both with targeted therapies and with immunotherapy
- “chemo-free” is not “toxicity-free”
- Immune checkpoint inhibitors have changed the landscape across oncology, including in lymphoma
- CAR-T and Bispecific Therapy are giving new hope to lymphoma patients who previously had little or no effective options



QUESTIONS AND DISCUSSION