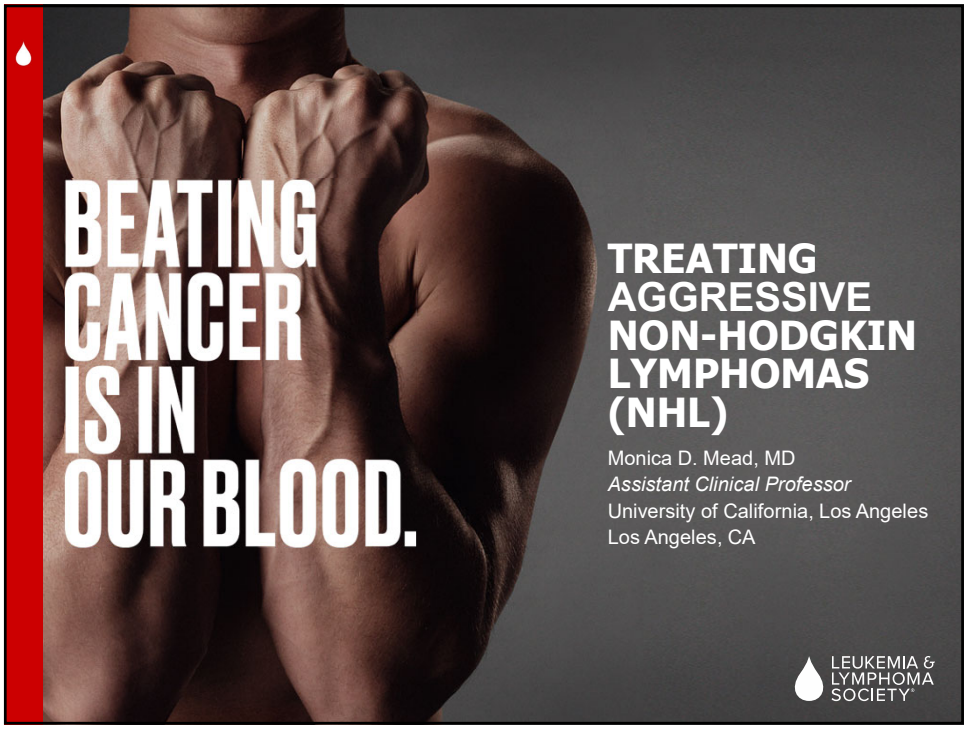

TREATING AGGRESSIVE NON-HODGKIN LYMPHOMAS (NHL)

Monica D. Mead, MD
Assistant Clinical Professor
University of California, Los Angeles
Los Angeles, CA

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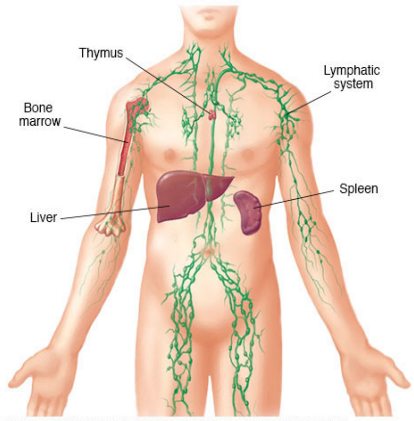
OBJECTIVES

- Define aggressive Non-Hodgkin Lymphomas (NHL)
- Treatment advances
- Importance of communication
- Side effect management

THE IMMUNE SYSTEM

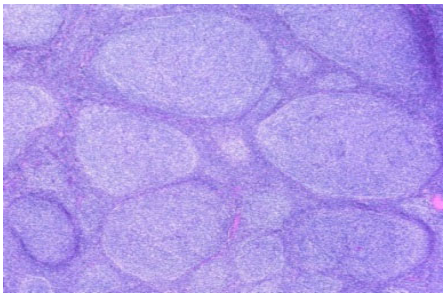


- Marrow
- Lymphocytes
- Lymph nodes
- Spleen

WHAT IS LYMPHOMA?

American Cancer Society:

- Non-Hodgkin lymphoma (also known as non-Hodgkin's lymphoma, NHL, or sometimes just lymphoma) is a cancer that starts in white blood cells called lymphocytes, which are part of the body's immune system.



NHL CLASSIFICATION

- Indolent
- Aggressive
- Very Aggressive

NHL CLASSIFICATION

Indolent

- CLL/SLL
- Waldenstrom's macroglobulinemia
- Marginal zone lymphoma
- Splenic marginal zone lymphoma
- Follicular lymphoma
- Cutaneous T cell lymphoma

Aggressive

- Multiple myeloma
- Mantle cell lymphoma
- DLBCL
- Histologic transformation of follicular lymphoma
- High grade BCL with MYC and BCL2 and/or BCL6 rearrangements
- Richter's transformation
- Primary mediastinal large cell lymphoma
- Burkitt's-like lymphoma
- Peripheral TCL

Very Aggressive

- Lymphoblastic lymphoma/leukemia
- Burkitt's lymphoma
- Plasma cell leukemia

NHL CLASSIFICATION

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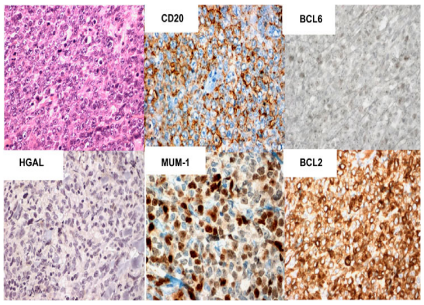
Very Aggressive

- Lymphoblastic lymphoma/leukemia
- Burkitt's lymphoma
- Plasma cell leukemia

HOW DO YOU DISTINGUISH BETWEEN DIFFERENT TYPES OF AGGRESSIVE NHL?

Biopsy of enlarged lymph node, mass or bone marrow

- Morphology
- Immunophenotype (stains)
- Flow cytometry
- DNA tests
  - Cytogenetics
  - PCR



YOU HAVE YOUR DIAGNOSIS, NOW WHAT?

TREATMENT PLANNING

TREATMENT OF AGGRESSIVE NHL

1. Anti-CD20 monoclonal antibodies

2. Chemotherapy

3. Autologous stem cell transplant

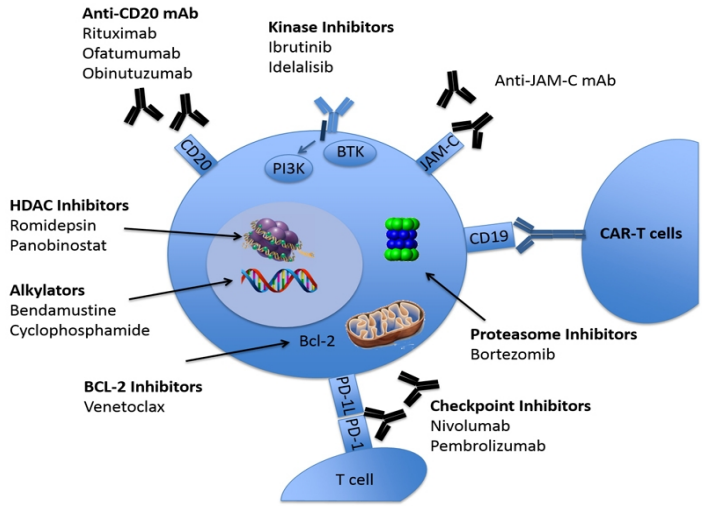
4. Antibody-drug conjugates

5. Chimeric antigen receptor T cells (CAR-T)

6. Checkpoint Inhibitors (“Immunotherapy”)

7. Promising clinical trials

TREATMENT



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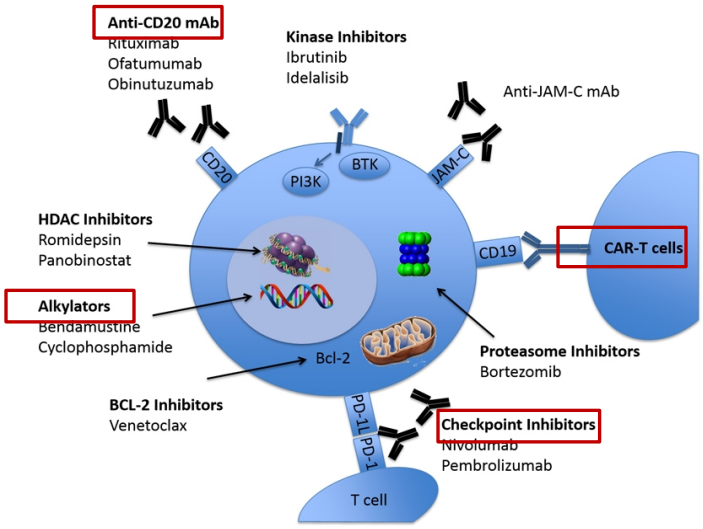
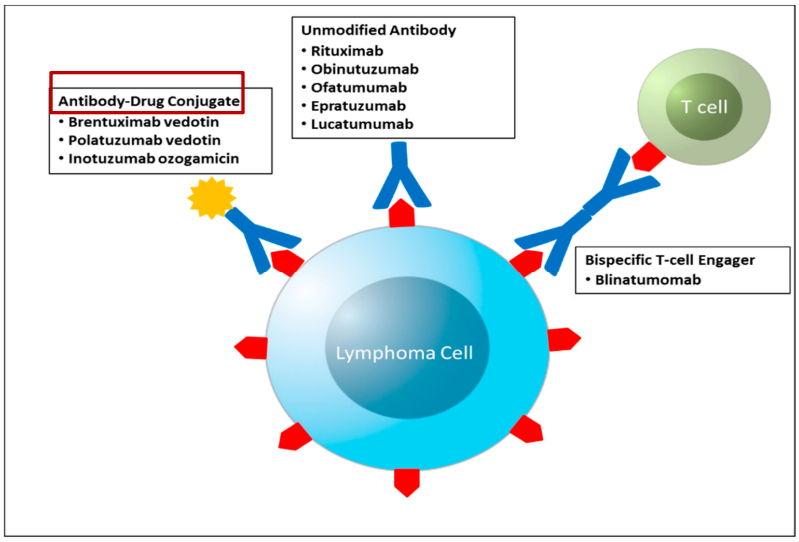


TREATMENT



TREATMENT OF AGGRESSIVE NHL

1. Anti-CD20 monoclonal antibodies
Rituximab
2. Chemotherapy
R-CHOP
EPOCH-R
Common 2nd line regimens
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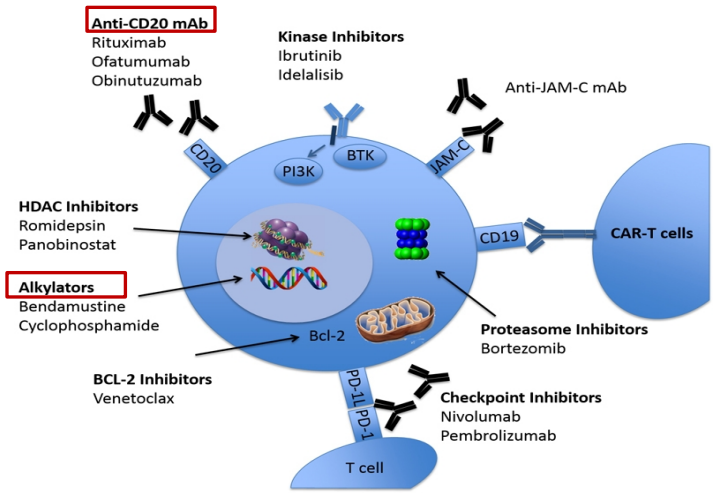
7. Promising clinical trials

CHEMOIMMUNOTHERAPY



CHEMOIMMUNOTHERAPY

R-CHOP

Rituximab, cyclophosphamide, hydroxydaunorubicin, oncovin, prednisone

Given as an IV, once daily, every 21 days

3-6 cycles

LNH-98.5 trial (2002)

- 399 DLBCL pts
- CHOP vs R-CHOP
- Complete remission rate: 63% (CHOP) vs 76% (RCHOP)
- Rituxan did not add toxicity

N Engl J Med, Vol. 346, No. 4 · January 24, 2002

R-CHOP

PAGE 17

- **DLBCL**
- **Histologic transformation of follicular lymphoma**
- **Richter's transformation**

BEATING CANCER IS IN OUR BLOOD.

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CAN WE MAKE R-CHOP BETTER?

PAGE 18

More chemotherapy

- 8 cycles not better than 6
- Dose-dense not better than standard dosing
- Infusional chemotherapy not better*
- Adding a "bone marrow transplant" not better

R-CHOP + new drug

- Velcade
- Ibrutinib

Different CD20 antibody better rituxan

- Gazyva
- Ofatumumab

Maintenance does not help

- Rituxan
- Lenalidomide

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INFUSIONAL CHEMOIMMUNOTHERAPY

EPOCH-R

Etoposide, prednisone, oncovin, cyclophosphamide, hydroxydaunorubicin

Given IV slowly over 96 hours, every 21 days for 6 cycles

Labs on specific days are obtained to guide dosing for subsequent cycles

EPOCH-R

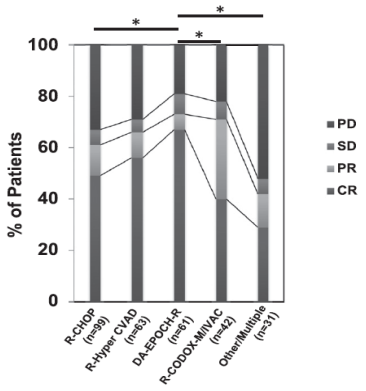
High grade B cell lymphoma with CMYC, BCL2 and/or BCL6 rearrangements

"double hit" lymphoma

Primary mediastinal B cell lymphoma

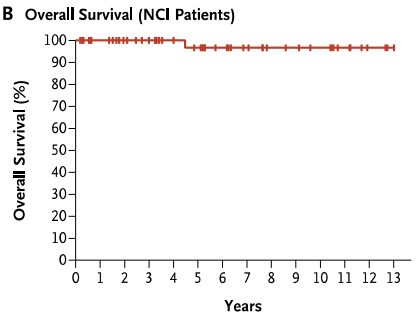
EPOCH-R

High grade B cell lymphoma with MYC and BCL2 and/or BCL6 rearrangements



* p<0,05 for CR rate by Fisher's exact test, two-tailed.

Primary mediastinal B cell lymphoma



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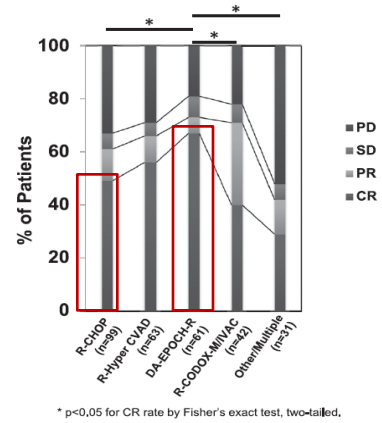
EPOCH-R

High grade B cell lymphoma with MYC and BCL2 and/or BCL6 rearrangements



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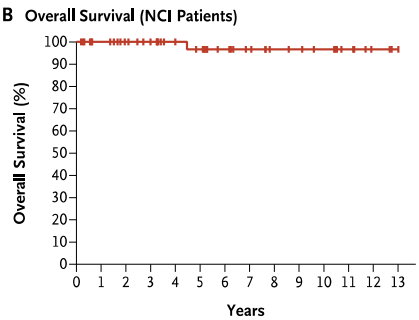
Primary mediastinal B cell lymphoma



N Engl J Med 2013; 368:1408-1416

BEATING CANCER IS IN OUR BLOOD.

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WHAT IF MY 1ST CHEMOTHERAPY DOES NOT WORK?

PAGE 23

R-ICE
R-DHAP
R-ESHAP
R-GemOx

These regimens may induce remission but response is generally short-lived due to lymphoma stem cells that are resistant to "standard doses" of chemotherapy

TREATMENT OF AGGRESSIVE NHL

PAGE 24

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6. Checkpoint Inhibitors
7. Promising clinical trials

AUTOLOGOUS STEM CELL TRANSPLANT "BONE MARROW TRANSPLANT"

- If a patient's lymphoma goes into remission with 2nd line treatment, ASCT is used to **maintain** the remission.
- During 2nd line treatment, a patient's healthy blood-producing cells are obtained and frozen.
- After completing 2nd line chemotherapy, patient receives a "high dose chemotherapy" regimen, followed by infusion of their own healthy blood-producing cells.

  -This helps prevent toxicity of the "high dose chemotherapy."

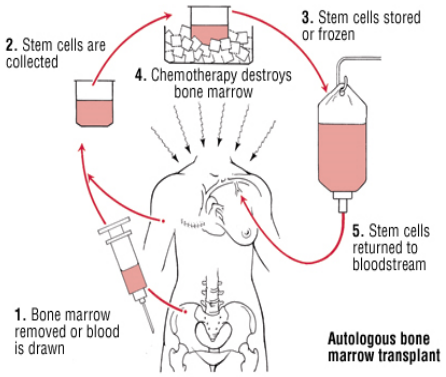
AUTOLOGOUS STEM CELL TRANSPLANT

How is this "high dose chemotherapy" going to help me?

- Lymphoma stem cells resistant to standard dose chemotherapy may lead to relapse
- High dose chemotherapy overcomes this resistance but is too toxic to patient's healthy blood-producing cells
- Saving a patient's blood-producing cells **before** giving high dose chemotherapy allows safe delivery of high dose chemotherapy, followed by an infusion of the patient's blood-producing cells

AUTOLOGOUS STEM CELL TRANSPLANT

- Must be in remission
- Stem cells derived from patient
- High dose chemotherapy
- Stem cell infusion
- Bone marrow recovers in 1.5-3 weeks
- Adverse effects in ~ 3-7%



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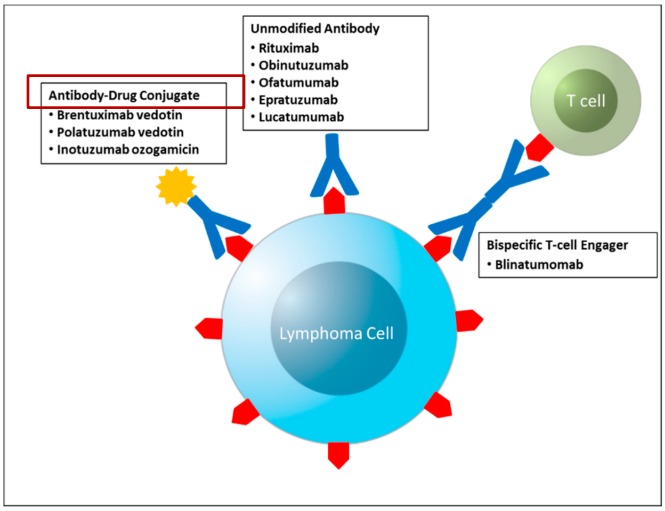
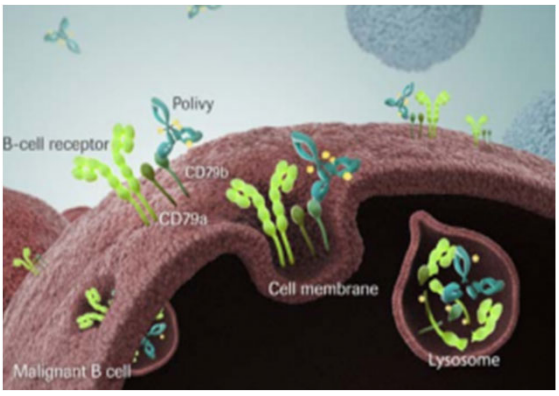


ANTIBODY DRUG CONJUGATE (ADC): POLATUZUMAB VEDOTIN

ADC:
1. Binding site for tumor protein

2. Potent chemotherapy molecule

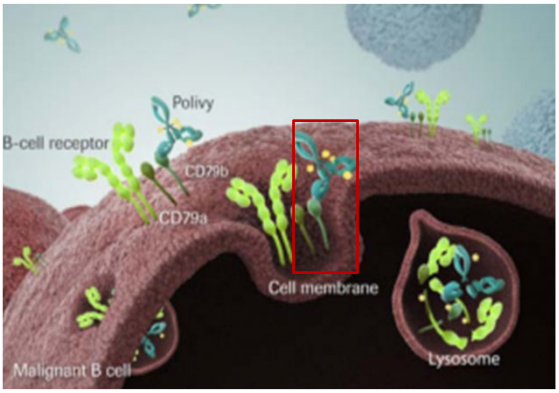


ANTIBODY DRUG CONJUGATE (ADC): POLATUZUMAB VEDOTIN

1. ADC binds to tumor protein

2. ADC is brought inside tumor cell

3. ADC releases potent chemotherapy molecule inside tumor cell.



ANTIBODY DRUG CONJUGATE (ADC): POLATUZUMAB VEDOTIN

Randomized trial

Bendamustine + rituxan

or

Bendamustine + rituxan + polatuzumab vedotin

Addition of polatuzumab vedotin

More patients achieved a complete remission

Patients lived longer

FDA approved for relapsed/refractory DLBCL

Journal of Clinical Oncology 36, no. 15_suppl (May 20, 2018) 7507-7507.

- **What if my lymphoma comes back after an autologous stem cell transplant?**
- **What if my lymphoma will not go into remission in order to proceed to an autologous stem cell transplant?**

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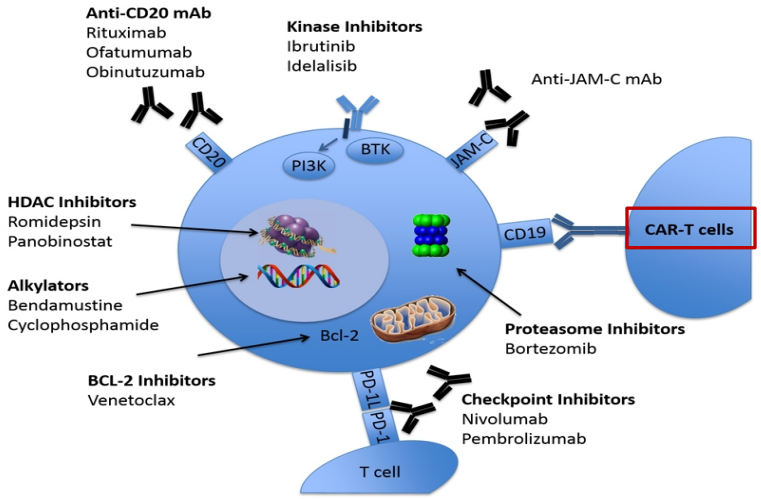
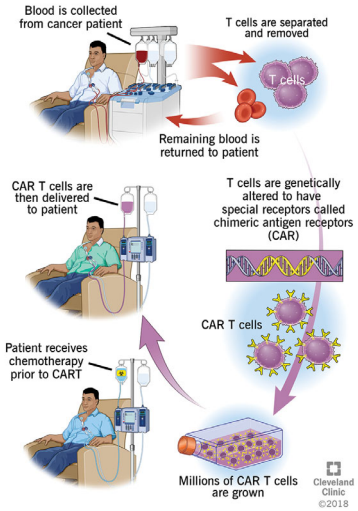
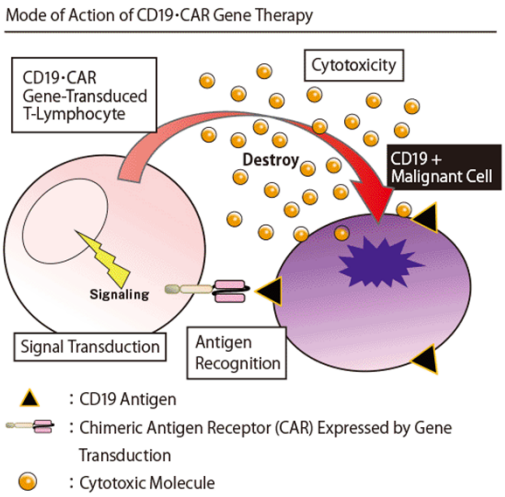


CHIMERIC ANTIGEN RECEPTOR T CELL THERAPY (CAR-T)



HOW DO CAR-T CELLS WORK?



CAR-T

Side effects

- Cytokine release syndrome
- Neurologic toxicity
- Low blood counts
- Infection

TREATMENT OF AGGRESSIVE NHL

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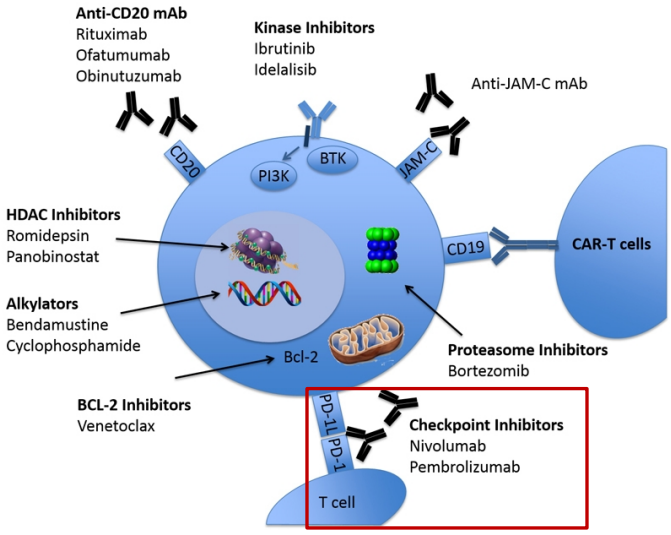
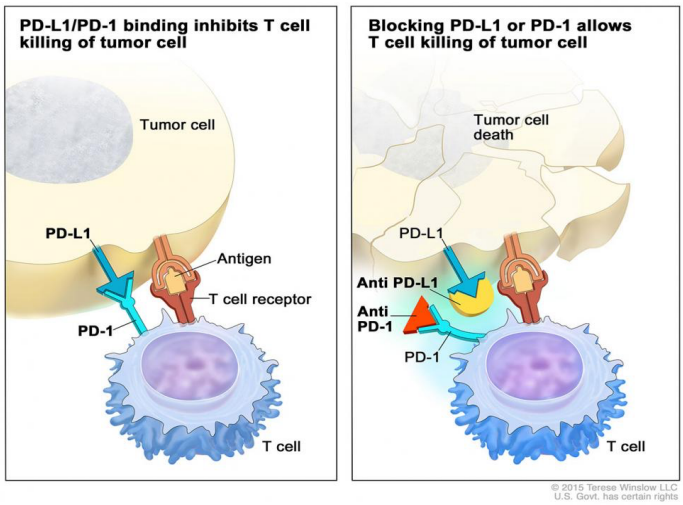
6. **Checkpoint Inhibitors: "Immunotherapy"**
7. Promising clinical trials

TREATMENT



CHECKPOINT INHIBITORS AKA "IMMUNOTHERAPY"



CHECKPOINT INHIBITORS

- **Largely disappointing in aggressive NHL**
- **Exception: relapsed/refractory primary mediastinal B cell lymphoma**
- **Pembrolizumab, nivolimab**

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6. Checkpoint Inhibitors: “Immunotherapy”
7. Promising clinical trials / emerging therapies

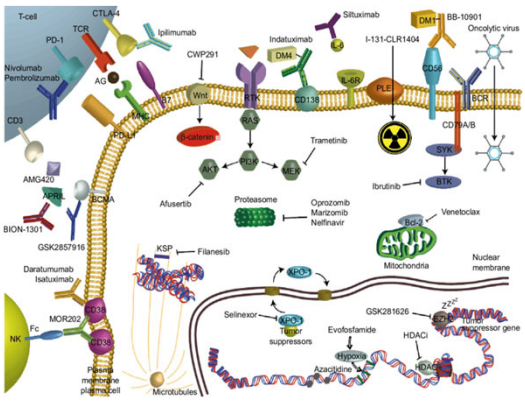
EMERGING THERAPIES

1. Immunotherapies

2. Antibody-drug conjugates

3. Epigenetic modifiers

4. Small molecule inhibitors



EMERGING THERAPIES

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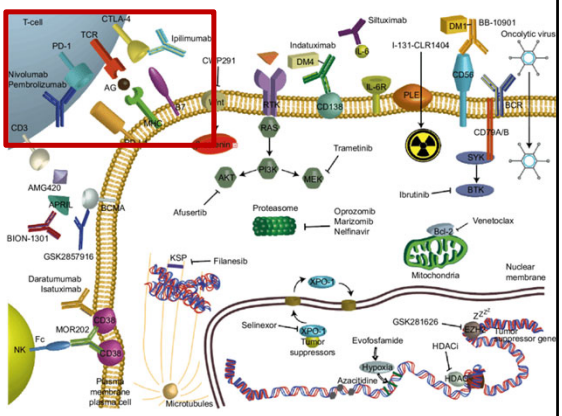

BEATING CANCER IS IN OUR BLOOD.

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EMERGING IMMUNOTHERAPIES

Immunotherapies

Bispecific antibodies

Macrophage immune checkpoint inhibitor

PD1 inhibitors

Improving CAR-T

BEATING CANCER IS IN OUR BLOOD.

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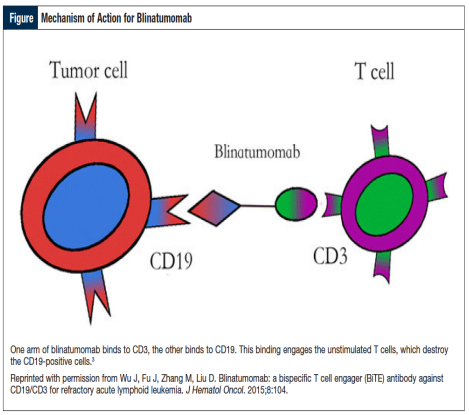
EMERGING IMMUNOTHERAPIES

Bispecific antibodies
- **Mosunetuzumab: CD20**
- **AMG562: CD19**

Macrophage immune checkpoint inhibitor

PD1 inhibitors

Improving CAR-T



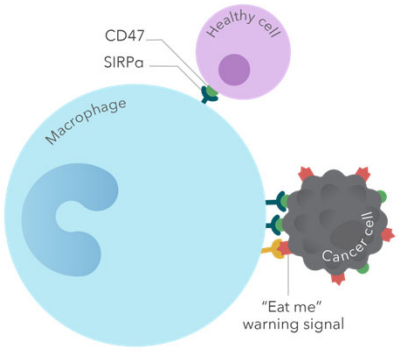
EMERGING IMMUNOTHERAPIES

Bispecific antibodies
- Mosunetuzumab: CD20
- AMG562: CD19

Macrophage immune checkpoint inhibitor
- **Hu5F9-G4: CD47**

PD1 inhibitors

CAR-T



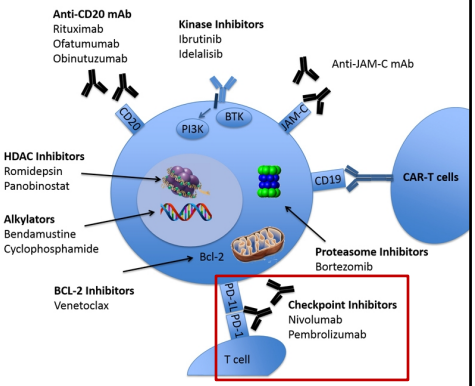
EMERGING IMMUNOTHERAPIES

Bispecific antibodies
- Mosunetuzumab: CD20
- AMG562: CD19

Macrophage immune checkpoint inhibitor
- Hu5F9-G4: CD47

PD1 inhibitors
- **Primary CNS lymphoma**

CAR-T



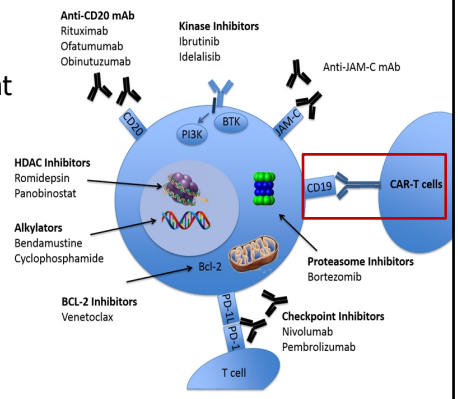
EMERGING IMMUNOTHERAPIES

– Bispecific antibodies
  - Mosunetuzumab: CD20
  - AMG562: CD19

– Macrophage immune checkpoint inhibitor
  - Hu5F9-G4: CD47

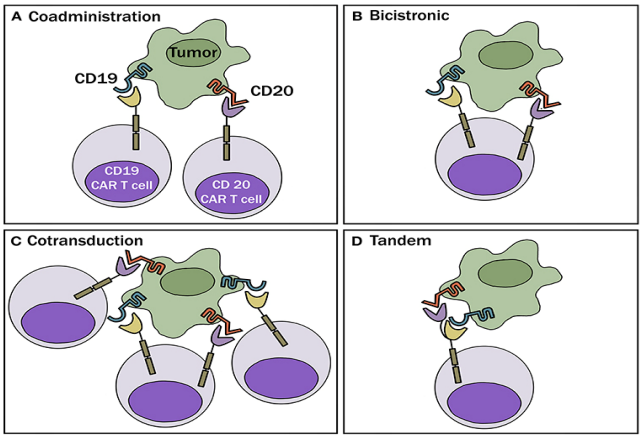
– PD1 inhibitors
  - Primary CNS lymphoma

– **CAR-T**
  - **Bispecific: targeting 2 tumor proteins**
  - **"Armored" CART**



BISPECIFIC CAR-T

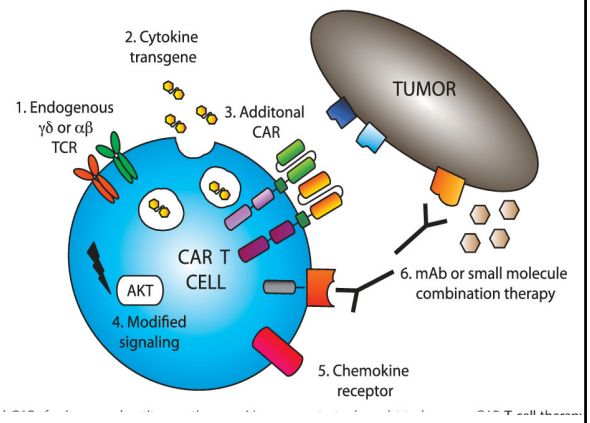
If binding to 1 lymphoma protein is good, is binding to 2 even better?



"ARMORED CAR-T"

"ARMORED CAR-T"

- Secrete inflammatory cytokines to fight lymphoma
- Additional binding sites
- Help CART cells live longer



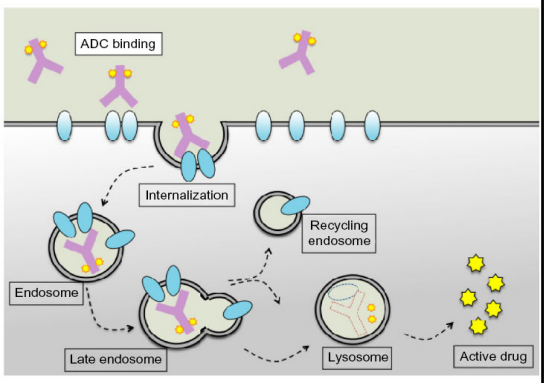
EMERGING THERAPIES

1. Immunotherapies

2. Antibody-drug conjugates

3. Epigenetic

4. Small molecule inhibitors



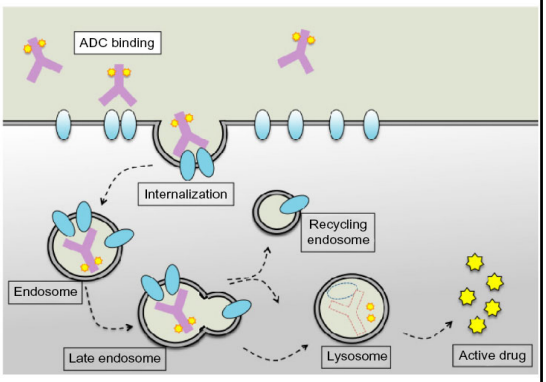
EMERGING THERAPIES

1. Immunotherapies

2. Antibody-drug conjugates
- Loncastuximab: CD19

3. Epigenetic

4. Small molecule inhibitors



EMERGING THERAPIES

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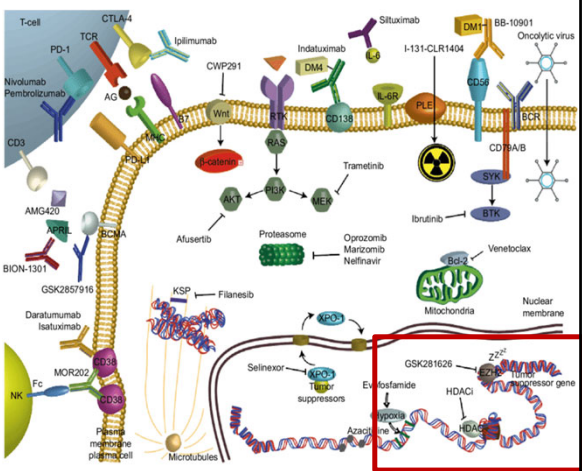
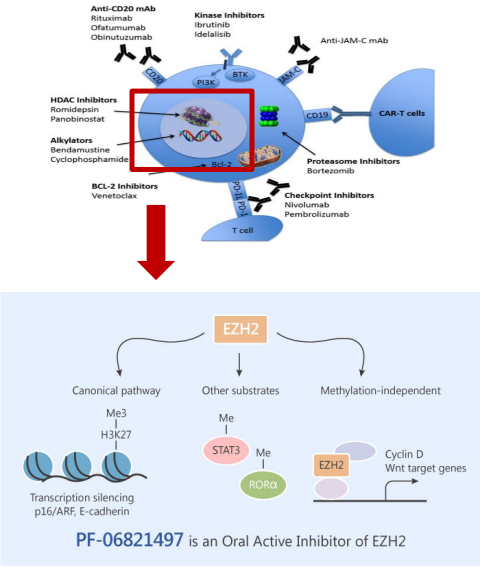


EMERGING THERAPIES

1. Immunotherapies
2. Antibody-drug conjugates
3. **Epigenetic**
   -EZH2 inhibitor: tazemetostat
   -HDAC inhibitor: mocetinostat
4. Small molecule inhibitors



EMERGING THERAPIES

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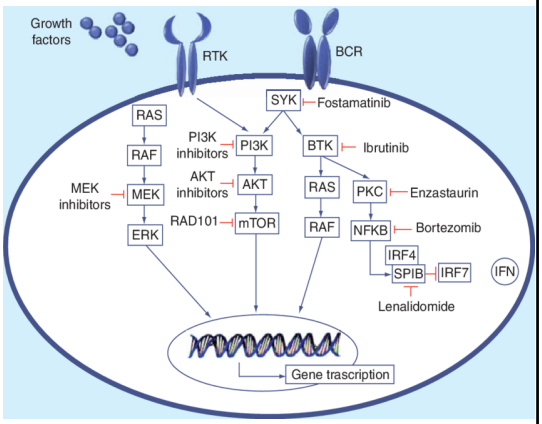
3. Epigenetic
4. **Small molecule inhibitors**



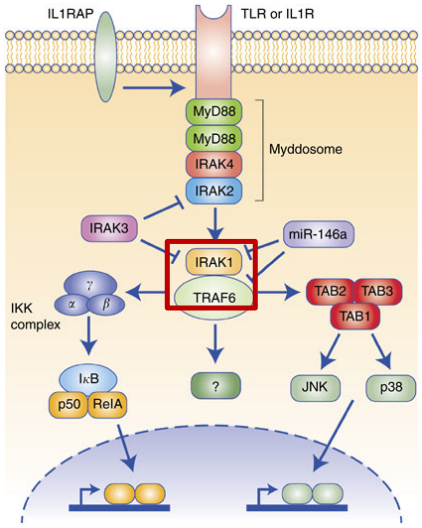
EMERGING THERAPIES

1. Immunotherapies

2. Antibody-drug conjugates

3. Epigenetic

4. Small molecule inhibitors
- IRAK inhibitor



MANAGING SIDE EFFECTS

COMMUNICATION WITH YOUR DOCTOR IS IMPORTANT

"The Doctor will see you now. Here's your medical jargon dictionary."

COMMUNICATION WITH YOUR DOCTOR IS IMPORTANT

- **Side effects are common!**
- **Your doctor can help with management strategies aimed at improving quality of life**
- **Write down questions before your appointment.**
- **Bring someone with you, or put someone on speaker phone during the appointment**

COMMON SIDE EFFECTS

PAGE 63

- **Low blood counts**
- **Bleeding**
- **Fever**
- **Infection**
- **Rash**
- **Mucositis**
- **Diarrhea**
- **Nausea/vomiting**
- **Headache**
- **Fatigue**
- **Depression and/or anxiety**
- **Neuropathy**

BEATING CANCER IS IN OUR BLOOD.

LEUKEMIA & LYMPHOMA SOCIETY®

SIDE EFFECTS

PAGE 64

Low blood counts
Bleeding
Fever
Infection
Rash
Mucositis
Diarrhea
Nausea/vomiting
Headache
Fatigue

→ - Transfusional support
- Close monitoring
- No sick contacts

→ - Investigate for infection: Blood & urine cultures, chest x-ray
- **Promptly** start antibiotics with broad coverage
- IVF
- May need CT scans, MRIs, bronchoscopy, stool studies

BEATING CANCER IS IN OUR BLOOD.

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COMMON SIDE EFFECTS

Low blood counts
Bleeding
Fever
Infection
Rash
Mucositis →
- Evaluate for infection. Antivirals if needed
- Drug holiday and/or dose reduction
- Good oral care

Diarrhea →
Nausea/vomiting
Headache
Fatigue

- Evaluate for infection. Antibiotics if needed
- Anti-diarrheal agents (Imodium)
- Drug holiday and/or dose reduction

COMMON SIDE EFFECTS

Low blood counts
Bleeding
Fever
Infection
Rash
Mucositis
Diarrhea
Nausea/vomiting →
Headache
Fatigue

- Anti-nausea medications
- IV fluids

COMMON SIDE EFFECTS

Low blood counts
Bleeding
Fever
Infection
Rash
Mucositis
Diarrhea
Nausea/vomiting
Headache
Fatigue
Depression and/or anxiety ➡

- Support groups
- Therapy
- Medication

Q&A

Treating Aggressive Non-Hodgkin Lymphomas (NHL)

- **Ask a question by phone:**
  - Press star (*) then the number 1 on your keypad.
- **Ask a question by web:**
  - Click “Ask a question”
  - Type your question
  - Click “Submit”

Due to time constraints, we can only take one question per person. Once you’ve asked your question, the operator will transfer you back into the audience line.

LLS EDUCATION & SUPPORT RESOURCES

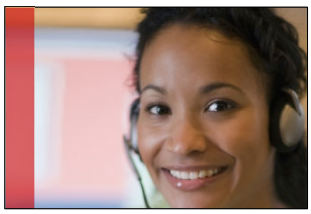
PAGE 69

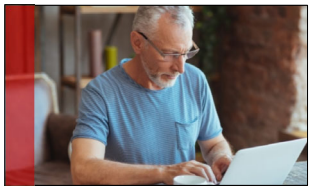
- **Information Specialists**

  Master's level oncology professionals, available to help cancer survivors navigate the best route from diagnosis through treatment, clinical trials and survivorship.

  - **EMAIL:** infocenter@LLS.org
  - **TOLL-FREE PHONE:** 1-800-955-4572

- **Caregiver Support:** www.LLS.org/caregiver
- **Free Education Booklets:** www.LLS.org/booklets
- **Free Telephone/Web Programs:** www.LLS.org/programs
- **Live, weekly Online Chats:** www.LLS.org/chat
- **LLS Community:** www.LLS.org/community
- **LLS COVID-19 Resources: www.LLS.org/coronavirus**





BEATING CANCER IS IN OUR BLOOD.

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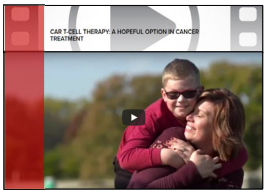
LLS EDUCATION & SUPPORT RESOURCES

PAGE 70



- **LLS Podcast, *The Bloodline with LLS***

  Listen in as experts and patients guide listeners in understanding diagnosis, treatment, and resources available to blood cancer patients: www.thebloodline.org

- **Education Videos**

  Free education videos about survivorship, treatment, disease updates and other topics: www.LLS.org/educationvideos

- **Patti Robinson Kaufmann First Connection Program**

  Peer-to-peer program that matches newly diagnosed patients and their families: www.LLS.org/firstconnection

- **Free Nutrition Consults**

  Telephone and email consultations with a Registered Dietitian: www.LLS.org/nutrition

- **What to Ask**

  Questions to ask the treatment team: www.LLS.org/whattoask

- **Other Support Resources**

  LLS Community, discussion boards, blogs, support groups, financial assistance and more: www.LLS.org/support

BEATING CANCER IS IN OUR BLOOD.

LEUKEMIA & LYMPHOMA SOCIETY®


THANK YOU
We have one goal: A world without blood cancers
LEUKEMIA & LYMPHOMA SOCIETY