Treatment of Lymphoma
New Therapies and Clinical Trials

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- General things about lymphoma
- Some information about clinical trials
- Immunotherapy: the new hot thing

- Questions and hopefully answers

Lymphoma – more than 50 different types

Treatment depends on:

- type of lymphoma
- where it is
- age, general health

Lymphoma Subtypes

Indolent
- long natural history (12-15+ years)
- remissions + relapses
- respond to many treatments
- responses/remissions less often complete, shorter with passage of time

Lymphoma Subtypes

Aggressive

- shorter period of symptoms before diagnosis
- may present in a place that is not a lymph node (stomach, sinuses, thyroid)
- treatment intent is usually “cure”—chemotherapy with or without radiation

Many B cell, most T cell lymphomas

What Determines the Outcome of Treatment for Lymphoma?

- type of lymphoma
- age
- performance status
- stage
- bulk of disease (size of lumps)
- extranodal disease
- treatment

Remission ≠ **Cure**

a state of being

requires decades of followup

Completed randomized trials, data awaited:

- DLBCL:
  - RCHOP → lenalidomide vs no further Rx
  - RCHOP + ibrutinib BTK inhibitor or placebo
  - RCHOP v dose adjusted R-EPOCH
    - Infusional chemotherapy
- Follicular:
  - R-chemotherapy v lenalidomide -rituximab

Lymphoma Clinical Trials

1) Kinds of clinical research
2) Reasons for clinical trials
3) Types of clinical trials
4) Are clinical trials right for you?

Levels of Evidence

3) Clinical Trials

Phase I

Phase II

Phase III

(Phase IV)

Phase I

Question: "what happens if we give…."

- test new drugs in humans that seem promising in laboratory testing
  - *how much can be given?*
  - *what are the side effects?*
- explore mechanisms: correlative science eg. pre- and post-treatment biopsies, blood evaluation of circulating tumor DNA….

Does treatment do in people what it did in the laboratory/animal models?

Phase II

Question: "Does this treatment 'work'"?

- What is the response rate to the new drug (% of patients whose cancer shrinks > 50%)

- What are the side effects when a larger number of patients are treated (vs small number in Phase I)
- Opportunity for correlative studies**

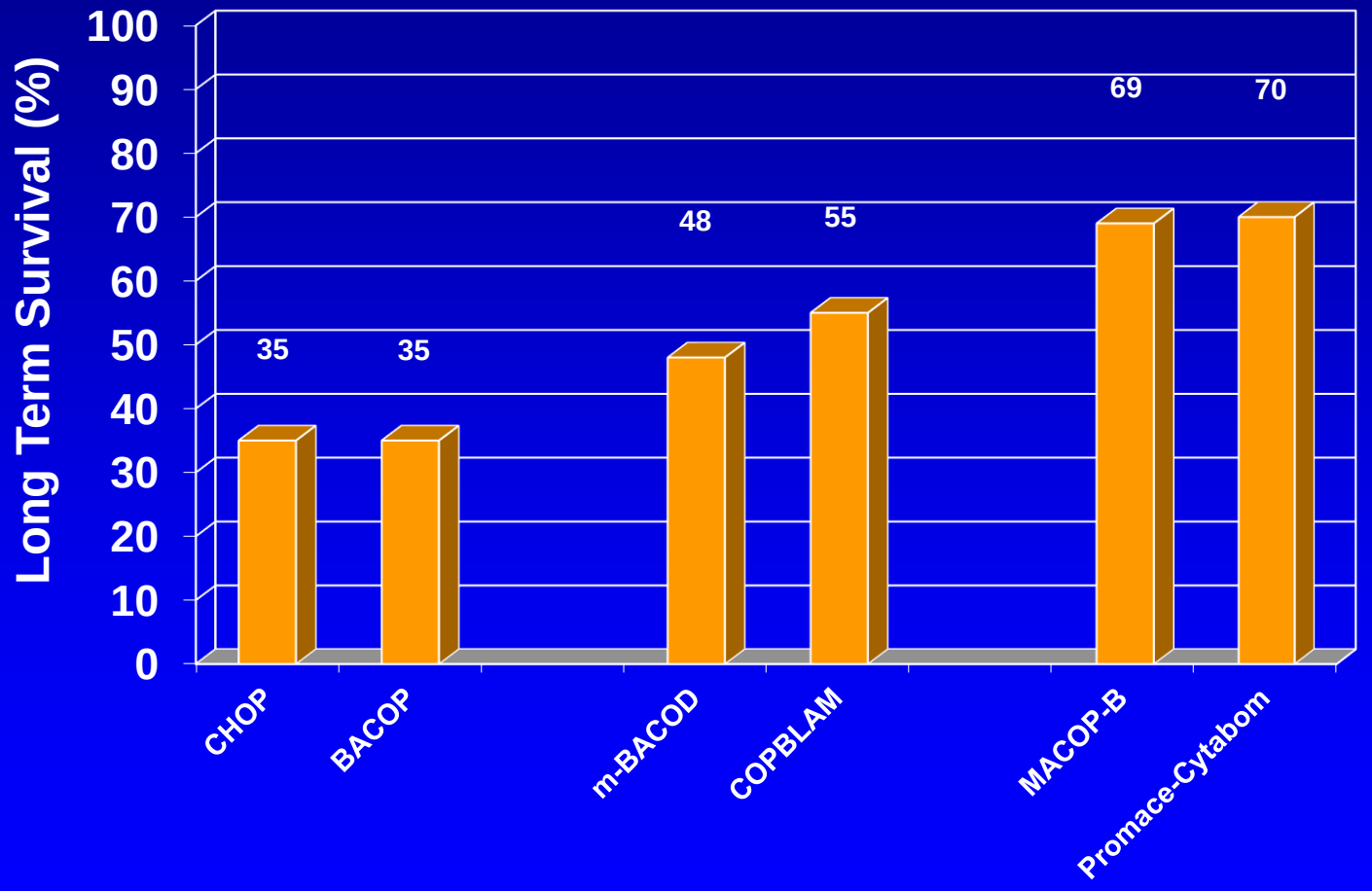
Phase II

How do we use Phase II information?

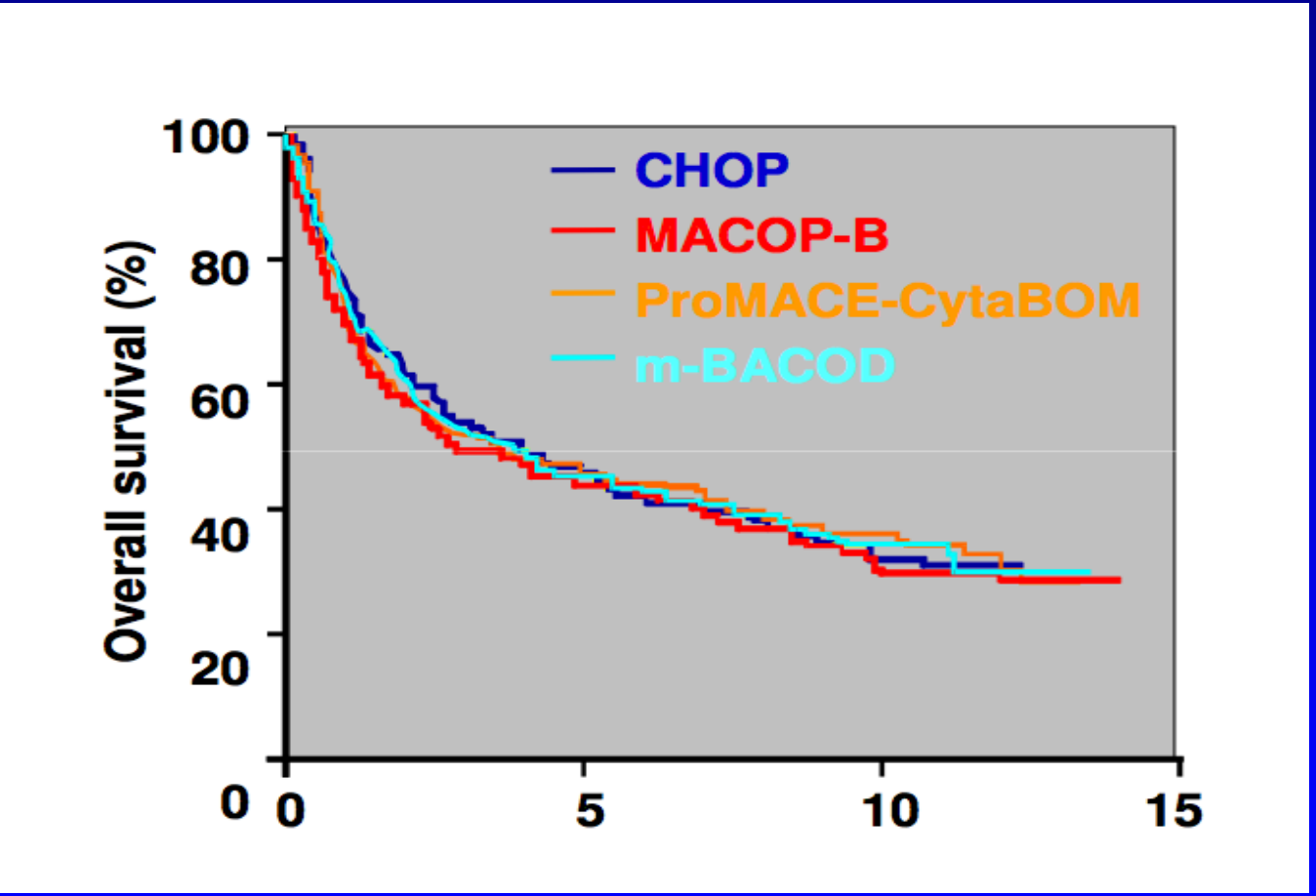
- Adopt as new treatment
- Add drug x to standard treatment (repeat phase I or II)
- Compare new treatment to standard of care

* Do phase II trials change practice?: only sometimes!

Doxorubicin-Based Chemotherapy Regimens Reported in phase II clinical trials



Direct Comparison of 4 Chemotherapy regimens in DLBCL



Fisher, NEJM, 1993

Phase III

- compare the standard of care to something new that is potentially better *or* has less toxicity
- used to determine if the standard of care should change
- "controlled": half of the patients get standard therapy
- "randomized": participants don't choose which
  - reduces bias
  - ensures 2 groups only differ by treatment and not stage, etc.

"Can I Be In This Clinical Trial?"

- Eligibility Criteria are the key
- list of "exclusions" and "inclusions"

Purpose - to be sure that the patients in the study are all "the same"
- to reduce risks to the participants
- allow accurate assessment of whether treatment works

Why Don't All Hospitals/Doctors Study … Immunotherapy?

Clinical Trials are:

- expensive
- time consuming
- require resources
  - nurses
  - pharmacists
  - MD's
- require scientific back-up
  -translational research

When Does a New Treatment Become Standard?

- usually requires randomized phase III trial showing "significant" improvement in an important measure: survival, time to progression, reduced toxicity

- sometimes from Phase II (non-comparative) study: eg. Brentuximab vedotin in Hodgkin lymphoma
  - 70% response rate, relatively side effects, duration of remission 6-9 months, no other approved drug in refractory HL post-transplant

There are a few more steps though….

- Health Canada approval (pharma application)
- Pan-Canadian Oncology Drug Review (pCODR)
- Cancer Care Ontario evaluation (costs)
- Regional cancer centre implementation

Immunotherapy in Lymphoma

- Monoclonal antibodies + chemo (immunoconjugates)
- Checkpoint inhibitors – nivolumab, pembrolizumab
- Bi-specific antibodies
- CAR-T cells

B cells

- Make antibodies in response to foreign material (viruses, bacteria, etc)
- Requires exposure (vaccination)
- Requires co-operation with other cells (eg. T cells)

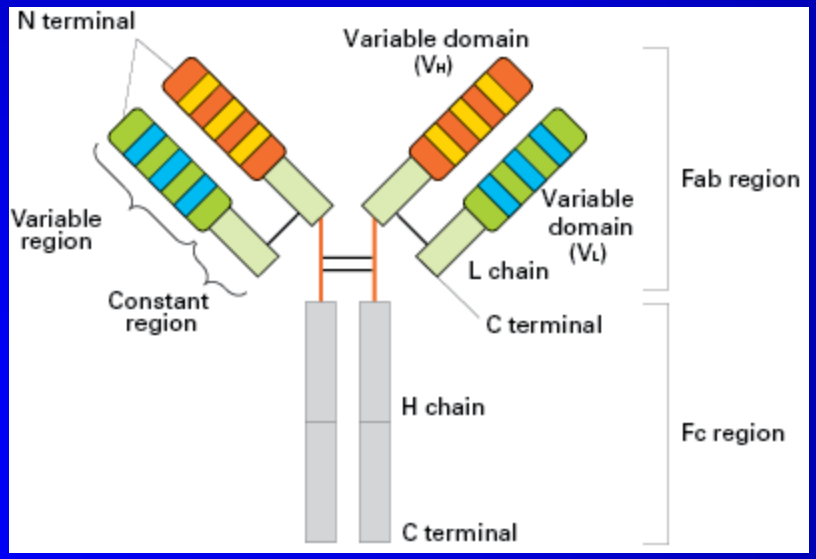
T cells (NK cells)

- ‘cellular’ immunity – recognize foreign cells (bacteria, viruses)

- Both types have ‘memory’ – ready to act when exposure repeated

Obinutuzimab (Gazyva)

- Anti CD20 antibody
- Same target as rituximab but with different properties
- Better ability to recruit cells of immune system to attack lymphoma



Business end: effector cells bind here

Obinutuzimab

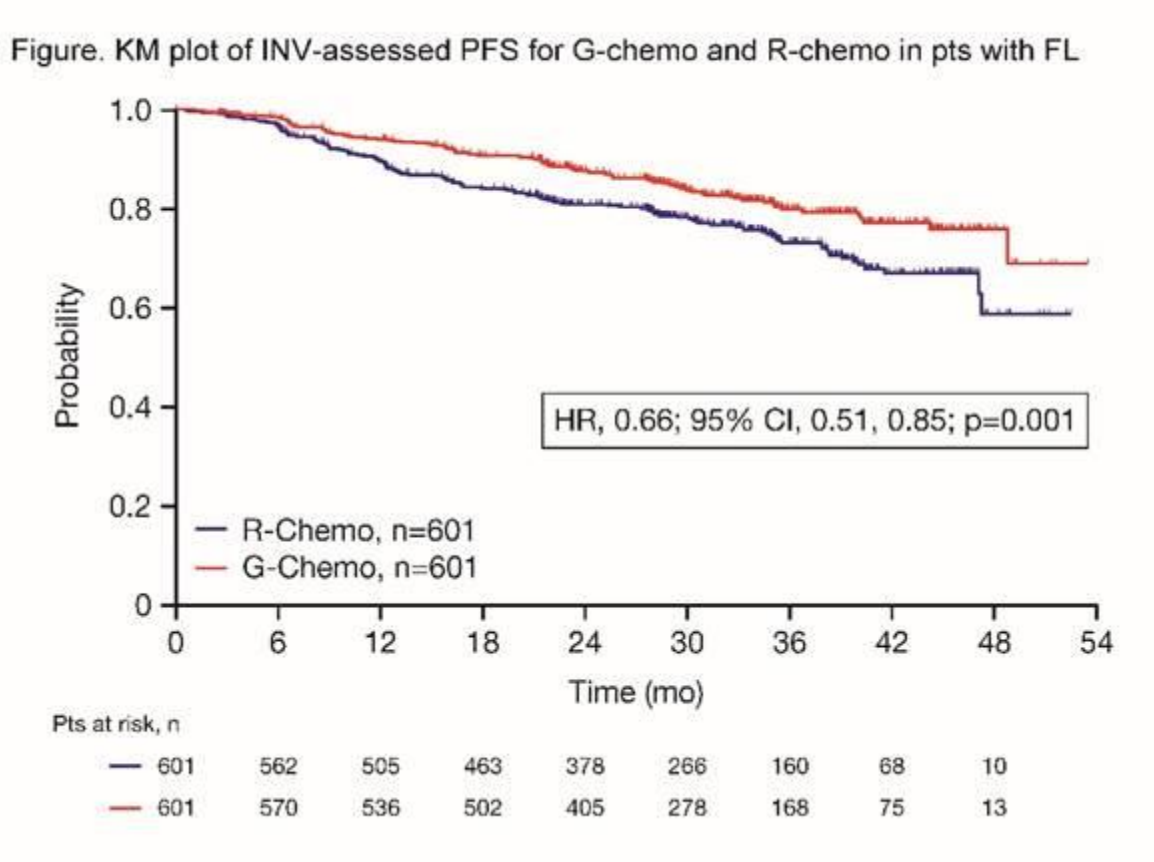
Chronic lymphocytic leukemia + chlorambucil

- better response, disease control vs rituximab
- new approved in Ontario

Indolent (follicular) lymphoma

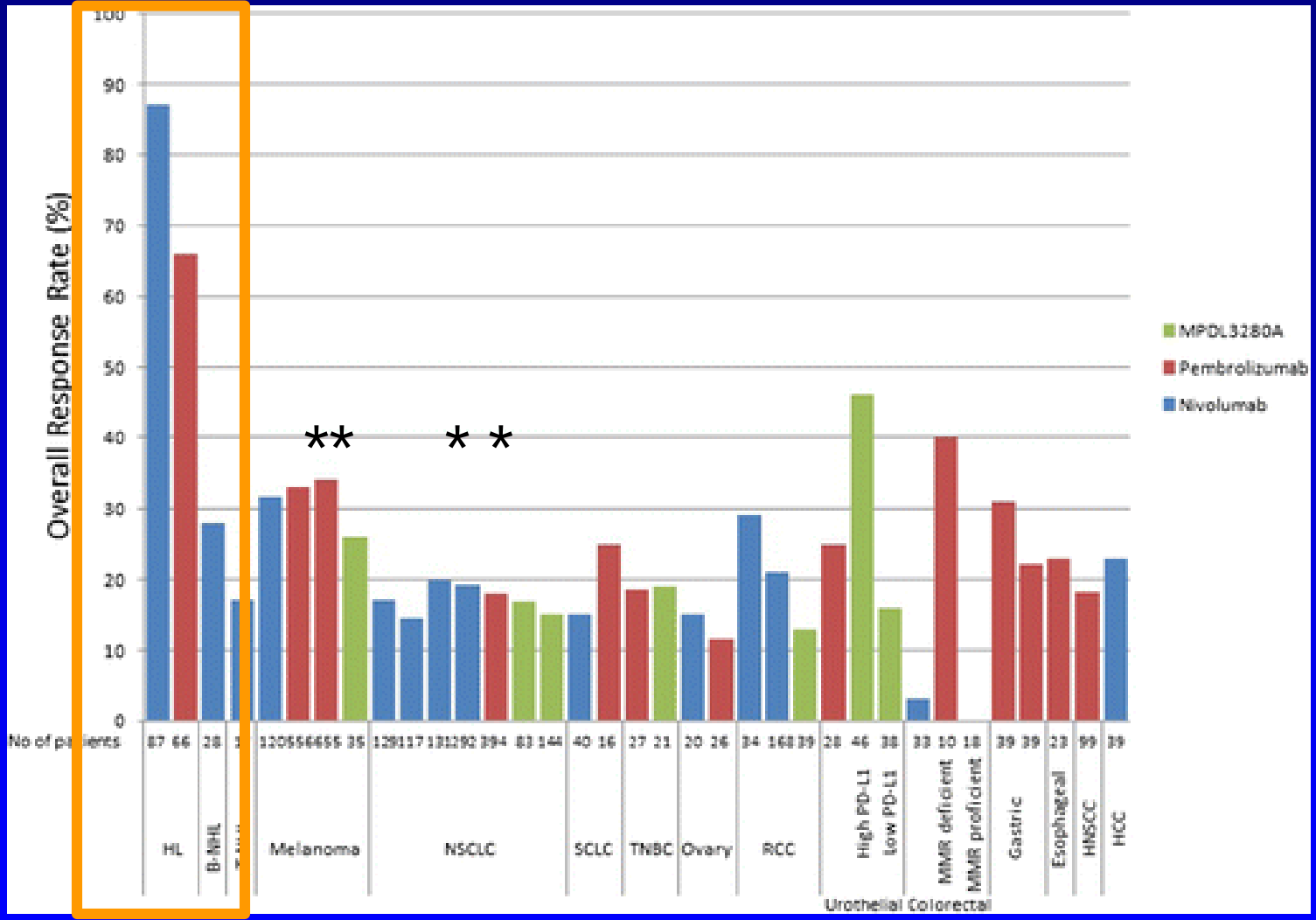
- longer response duration after chemo + maintenance therapy than rituximab
- better response duration in patients who progressed on rituximab

Obinutuzumab vs Rituximab with chemotherapy in follicular lymphoma



Checkpoint inhibitors: something really new!

Single agent activity of CI's in cancer

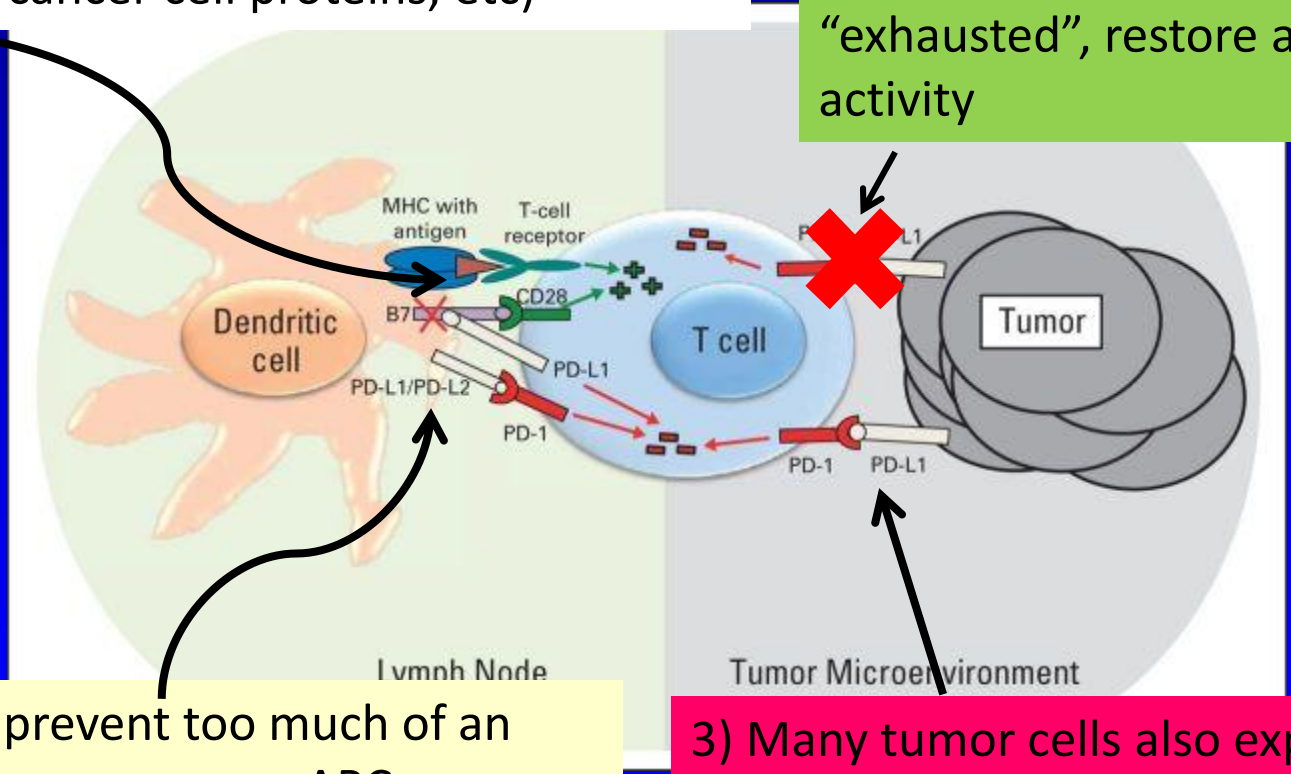


Matsuki, Younes, Current treatment options in Oncology, 2016,17:31

How does this work?

1) antigen presenting cells show bits of foreign protein to T cells to get them going (bacteria, cancer cell proteins, etc)

4) Antibodies to PD1 or PDL1 prevent T cells from being "exhausted", restore anti-tumor activity



2) to prevent too much of an immune response, APCs express PDL1/2 to slow down the T cells

3) Many tumor cells also express PDL1/2 to prevent T cells from attacking them (immune evasion)

Good things about checkpoint inhibitors

- long-lasting responses seen in some patients with little toxicity
- no (rare) infusion-related side effects
- delayed response (5-10%)

Difficulties with checkpoint inhibitors

- Not all lymphomas respond
  (Hodgkin 70%; DLBCL 20-30%; FL ?)

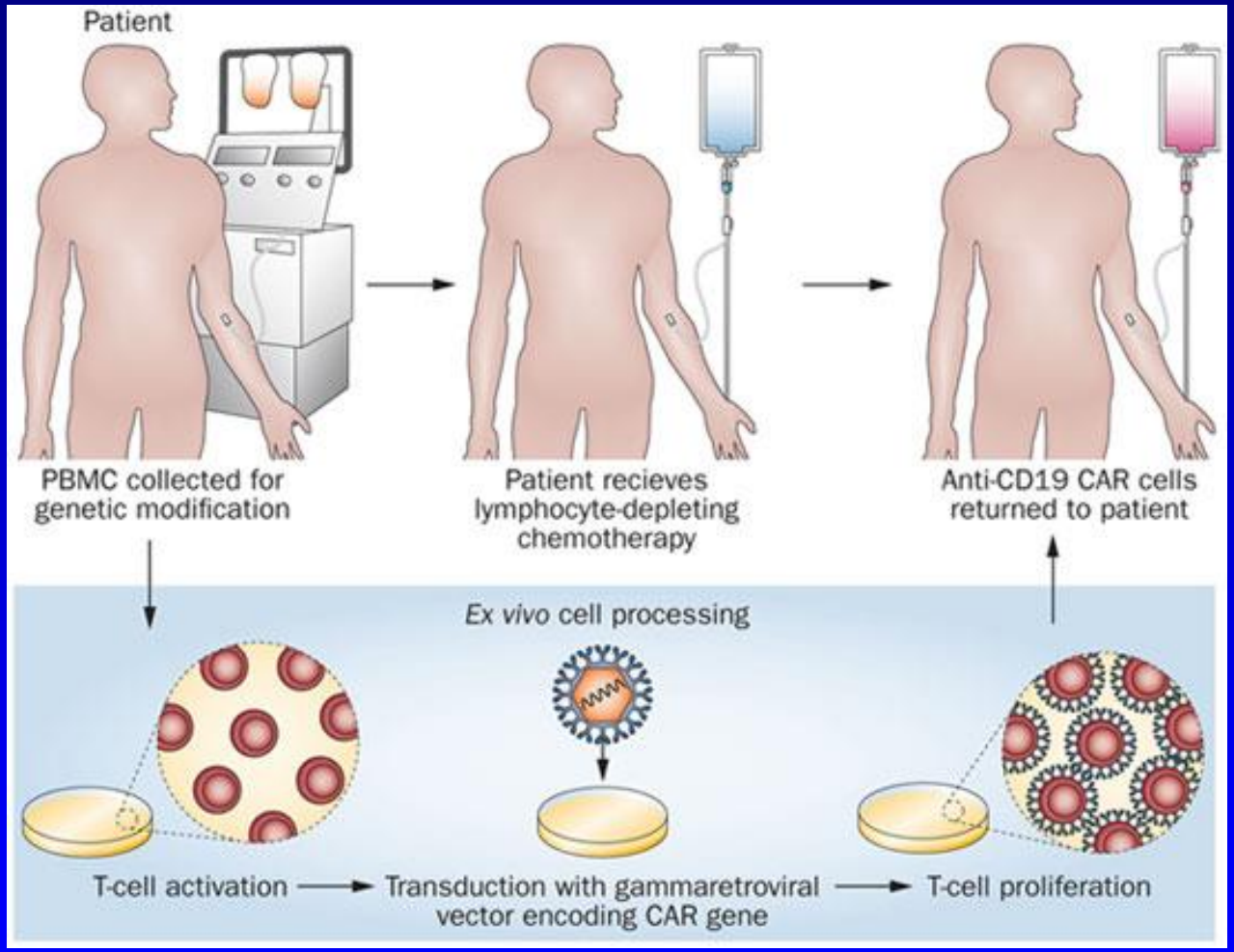
- Immune-related site effects: autoimmunity
  - bowel inflammation
  - thyroiditis
  - skin, liver, lung, nervous system – rare

- ? indefinite treatment (cost!)

T Cells

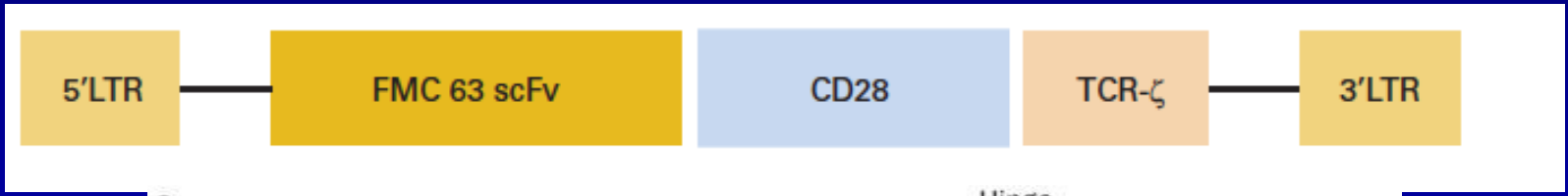
- **T cells** are lymphocytes that play a number of roles within the immune system. **After engineering, CAR-T cells have a mixture of these types.**
  - **Cytotoxic T Lymphocytes (CTLs)** – directly kill cells through the release of granzymes and perforin (perforin allows granzymes to enter the targeted cell, which then activates programmed cell death: apoptosis).
  - Helper T Cells – act as antigen presenting cells and release modulatory cytokines
  - Memory T Cells – long lived cells that recall past vaccinations and infections and activate on re-infection.
  - Regulatory T Cells – act as T cell suppressors and prevent autoimmunity

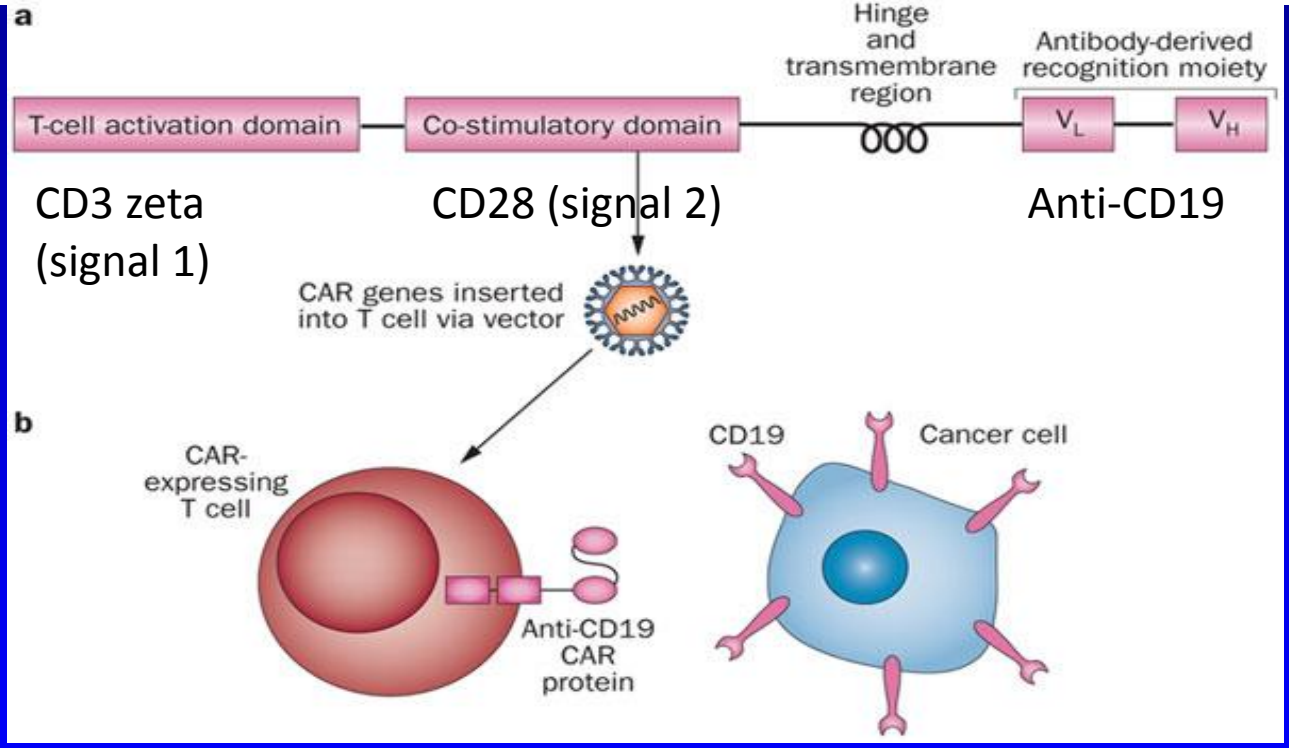
How to program a patient's immune cells and reinfuse them



Kochenderfer and Rosenberg Nat. Rev. Clin. Oncol. 2013

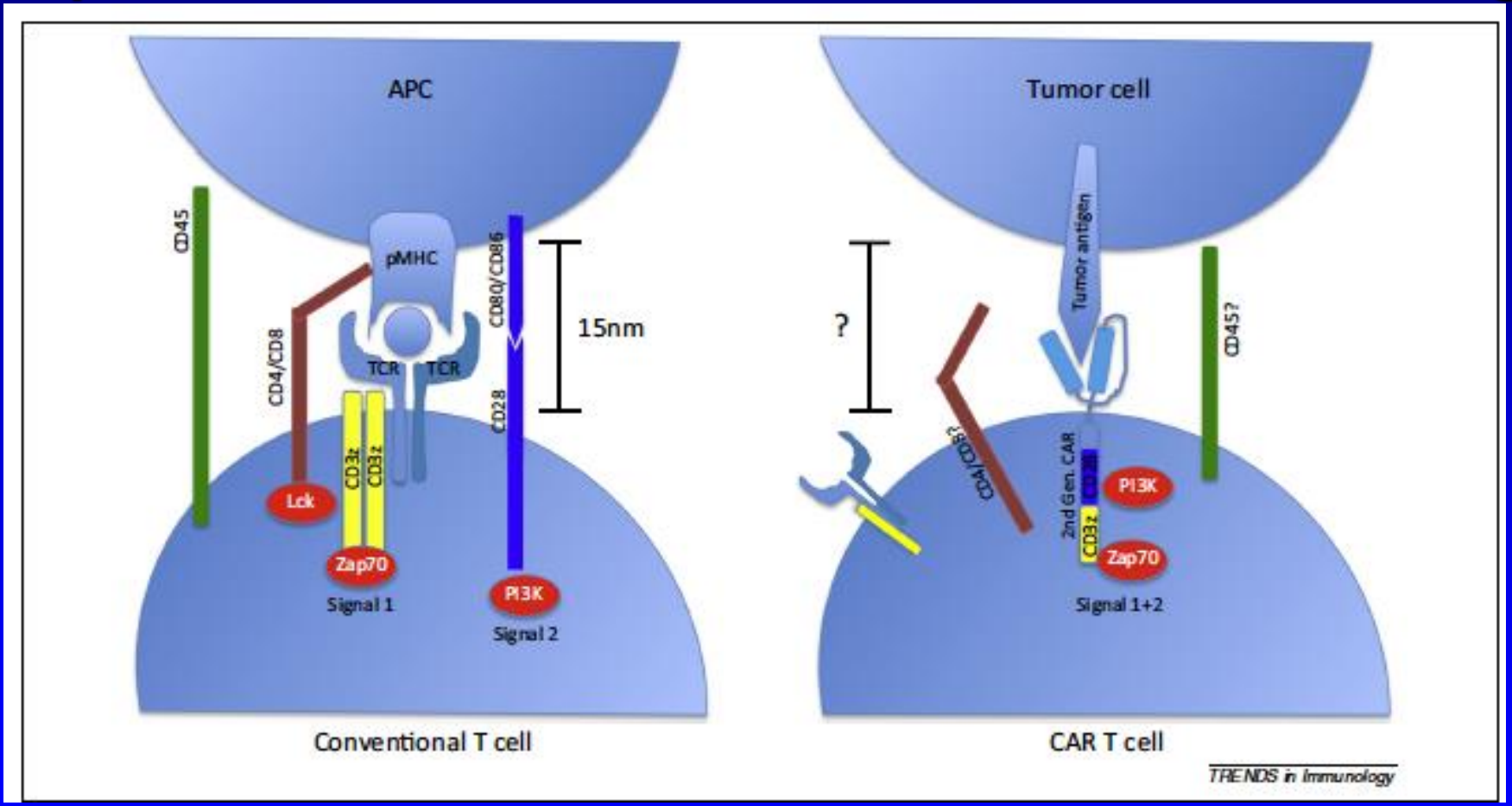
Chimeric antigen receptor (CAR) anti-CD19 gene is inserted to generate a CAR T cell





Kochenderfer and Rosenberg *Nat. Rev. Clin. Oncol*. 2013.
Kochenderfer et al. *J. Clin. Oncol.* 2014.

CARs are engineered to provide the normal signals required for T cell stimulation and cancer cell killing



Srivastava and Riddell *Trends Immunol*. 2015.

CAR T cells are T cells

- Expand their numbers once inside the patient
- Change to mainly become CTLs once inside the patient
- Are affected by and affect cytokine levels (a high level of cytokine release)
- Travel throughout the body (can be collected from CSF)
- Decline to undetectable levels in about 3 - 4 weeks (? memory)
- Are killed by steroids such as prednisone
- Are subject to T cell exhaustion through the immune checkpoint

John et al. *Clin. Cancer Res.* 2013
Brentjens et al. *Sci. Transl. Med.* 2014
Kochenderfer et al. *J. Clin. Oncol.* 2014

Locke et al. ASH 2015
Rossi et al. ASH 2015
Bot et al. ASH 2015

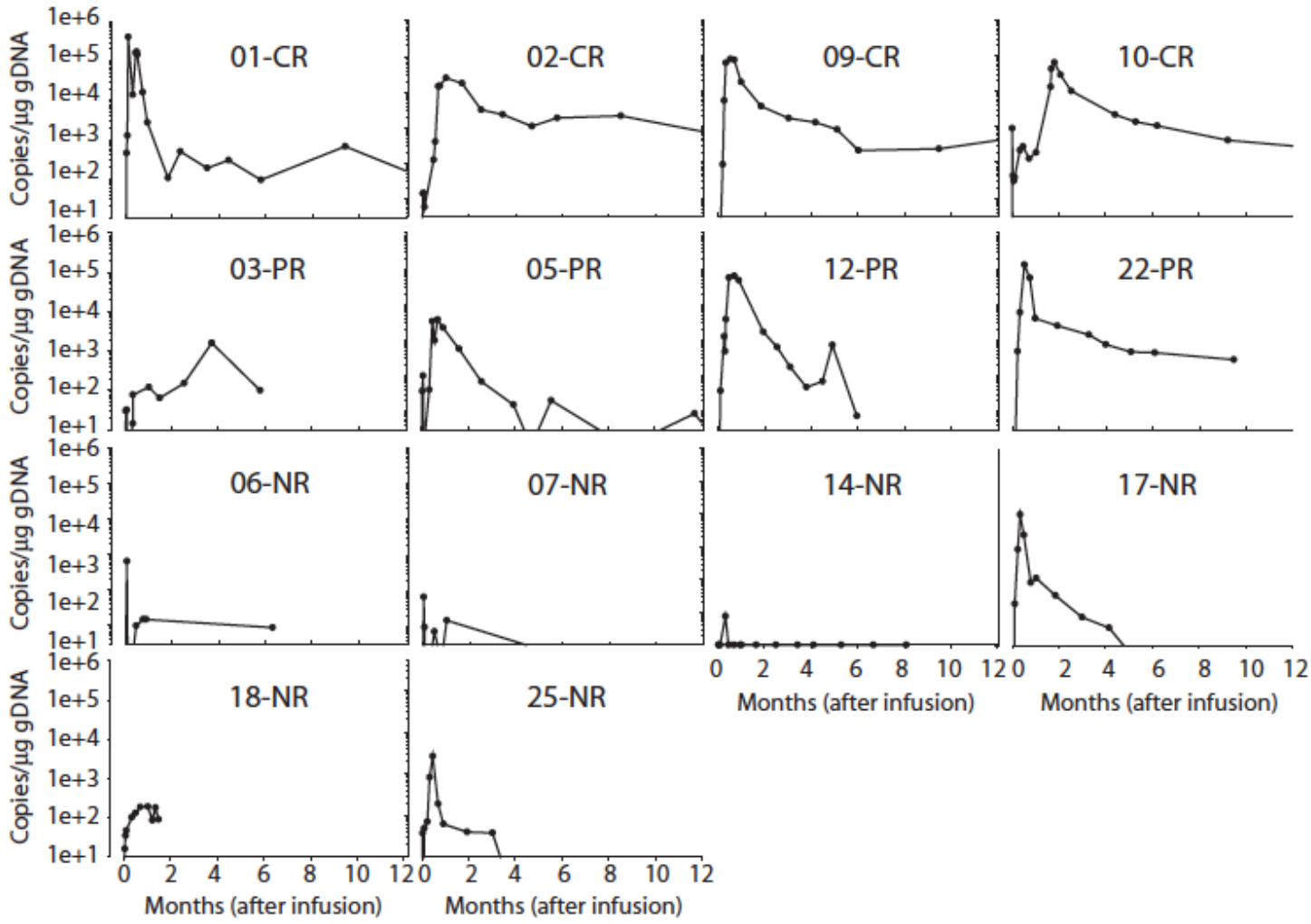


Fig. 2. CTL019 expansion by qPCR in the first 12 months. Peripheral blood CTL019 expansion was measured as copies per microgram of genomic DNA by qPCR in 14 subjects. Values below the quantitative limit of detection (<25 copies/µg DNA) are shown with open circles. (Source data, table S7).

- In CLL, CarT cells persisted much longer
- The peak of CarT cells corresponded to CRS, occuring at a median of 9.5 days after infusion
- 9/14 patients had CRS requiring intervention
- 4/14 patients required ICU admission (median ICU admission was 6 days)
- 4 patients received tocilizumab (2 patients also received steroids) which rapidly resolved symptoms.

Porter et al. Sci. Transl. Med. 2016

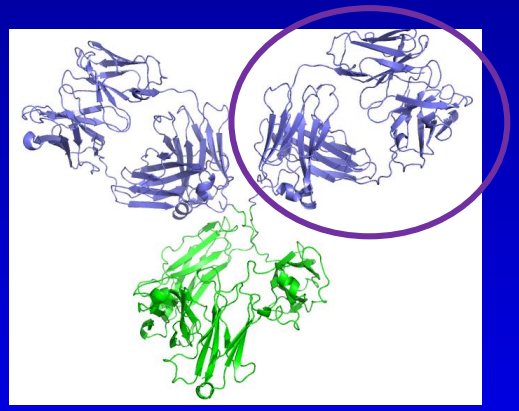
The Clinical Toxicities of CAR T Cells are Significant but Seemingly Transient

Cause a **cytokine release syndrome** (patients may need anti-IL-6 – tocilizumab - and/or steroids)

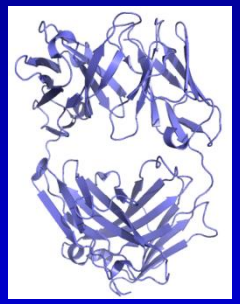
- Hypotension (patients can require medication for BP support)
- Fever (patients end up on antibiotics)
- Decreased cognition and/or level of consciousness (intubation in 1/6)

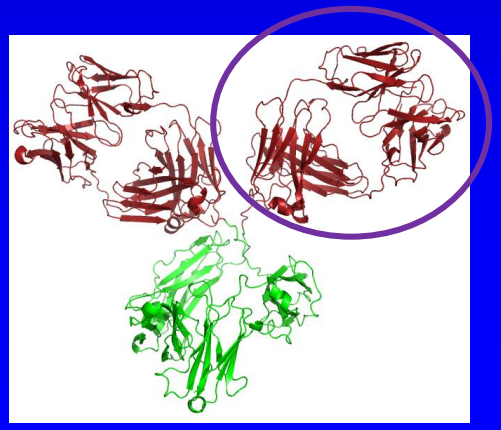
While harrowing, side effects seem to reverse rapidly when numbers of the CAR T cells fall (at 1 to 3 weeks) and seem to be fully reversible

Bispecific T-Cell Engagers: BiTEs



CD3 Monoclonal antibody
-binds to T-cells





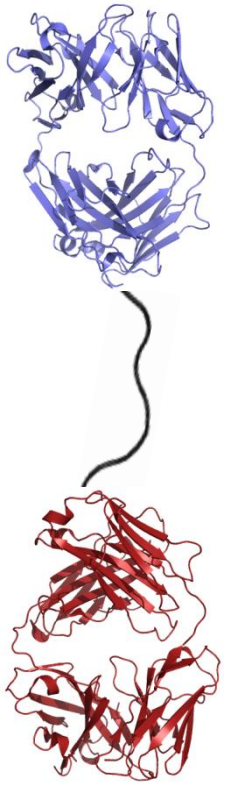
Monoclonal antibody against tumour antigen
-binds to cancer cell

Bispecific T-Cell Engagers: BiTEs

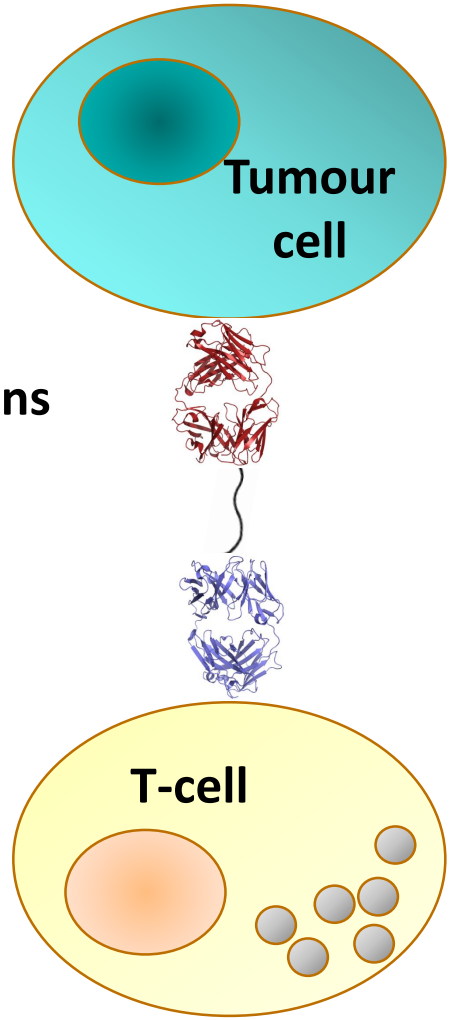
Fragment that binds to T-cells

Linker

Fragment that bind to tumour cell



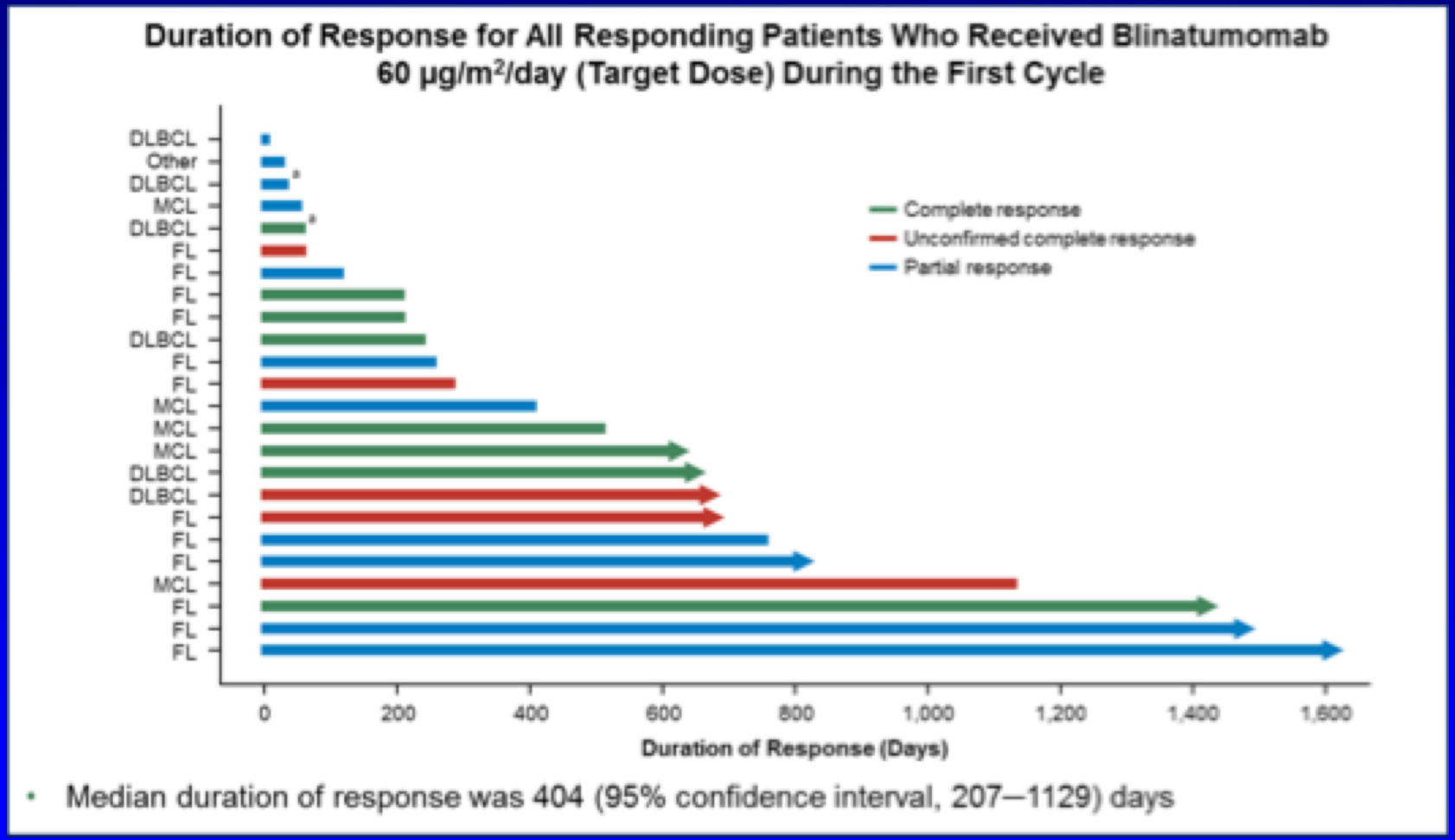
Bispecific T-Cell Engagers: BiTEs



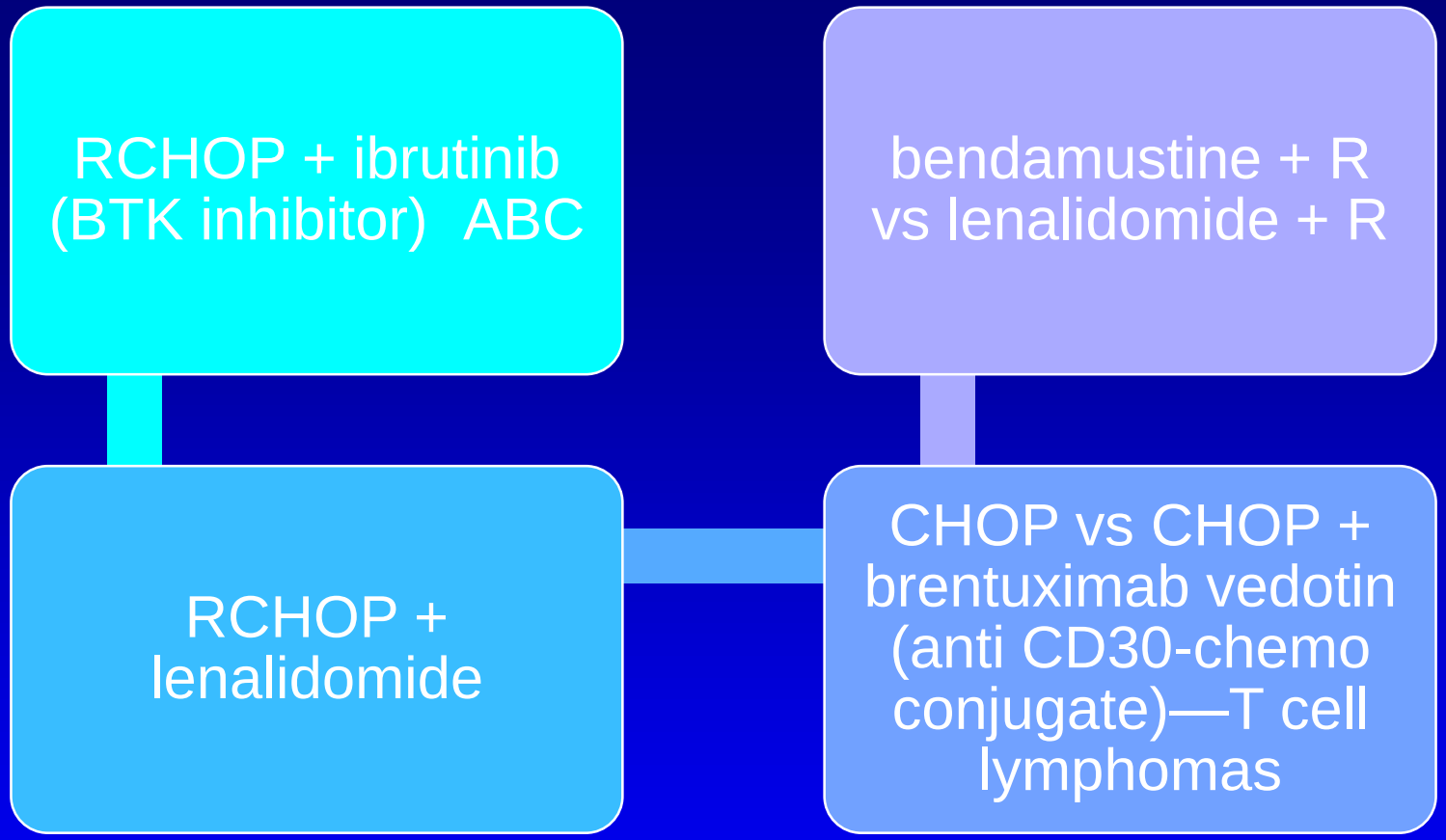
Immune synapse

BiTEs have been shown to cause cytokine storm, perhaps due to enhanced numbers of or through the artificial creation of the Immune synapse

Results with blinatumomab in relapsed lymphomas: response rate 69% (n=35)



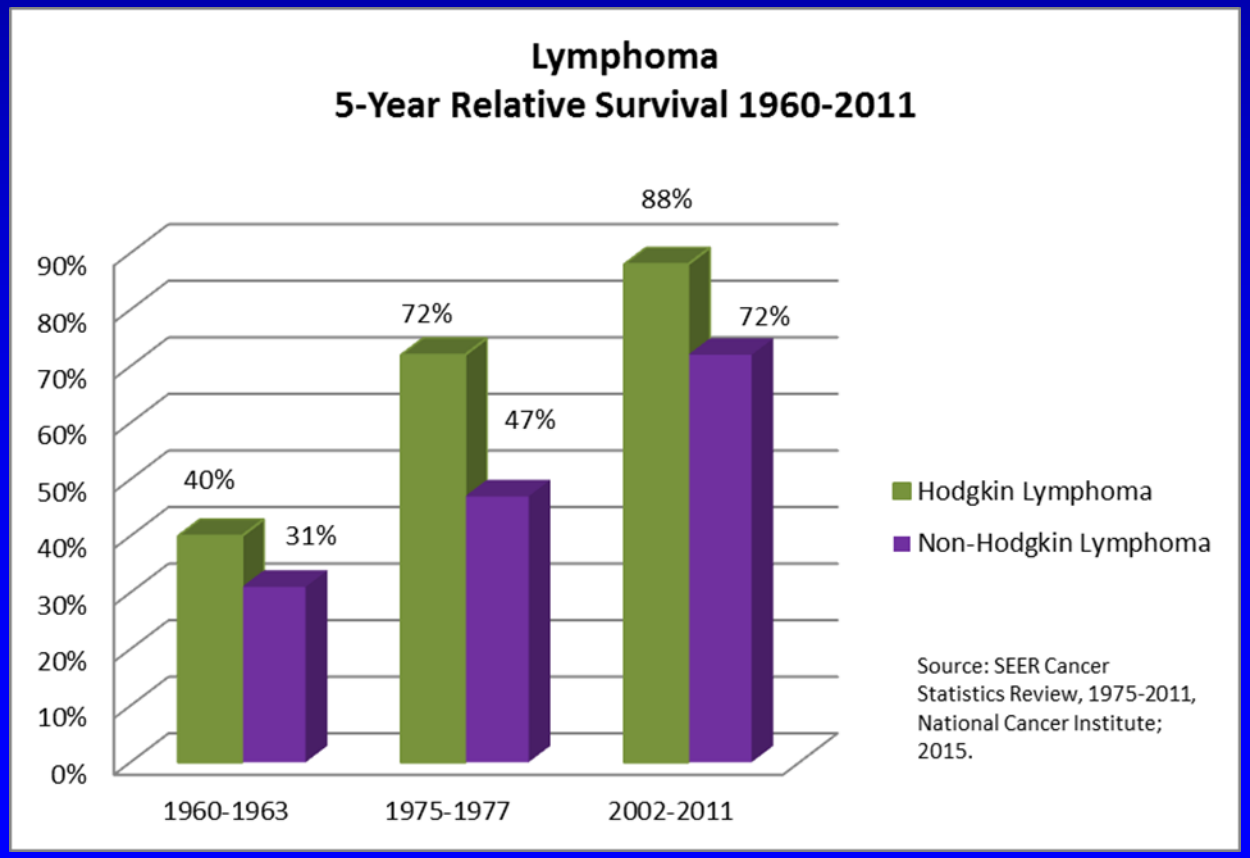
*patient received allogeneic stem cell transplant.
Arrows indicate ongoing response



Clinical trials that have recently been completed

conclusions

- Many new therapies for lymphomas!
- Research and clinical trials make a difference !
- Immunotherapy really is the next big thing!



Symptoms of CRS

- condition resulting from the release of cytokines from cells targeted by antibodies, immune effector cells recruited to the tumor area, and subject's immune cells activated.

Organ system	Symptoms
Constitutional	Fever ± rigors, malaise, fatigue, anorexia, myalgias, arthalgias, nausea, vomiting, headache
Skin	Rash
Gastrointestinal	Nausea, vomiting, diarrhea
Respiratory	Tachypnea, hypoxemia
Cardiovascular	Tachycardia, widened pulse pressure, hypotension, increased cardiac output (early), potentially diminished cardiac output (late)
Coagulation	Elevated D-dimer, hypofibrinogenemia ± bleeding
Renal	Azotemia
Hepatic	Transaminitis, hyperbilirubinemia
Neurologic	Headache, mental status changes, confusion, delirium, word finding difficulty or frank aphasia, hallucinations, tremor, dymetria, altered gait, seizures

Side Effects of Chemotherapy

nausea + vomiting

Early: < 24 hrs after: granisetron/ondansetron
Late: 1-5 days after: domperidone, dexamethasone

nausea hints:

- clear fluids on day of chemo
- avoid foods that are too hot or cold or too spicy
- smaller, more frequent meals

Fatigue

- common with all chemotherapy
- not only due to anemia (low hemoglobin)

Some solutions:

- exercise!
- stretching, range of motion
- walking
- stay active