CLL SOCIETY

Smart Patients Get Smart Care™

NEXT GENERATION CLL TREATMENTS: UNDERSTANDING CLINICAL TRIALS AND FUTURE THERAPEUTIC STRATEGIES

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Worthington and Margaret Collette Professor of Medicine;
Dana-Farber Cancer Institute
and Harvard Medical School

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WHAT IS A CLINICAL TRIAL?

- **Formal investigation of a therapy that is (relatively) new to the disease being studied:**
  - A brand new drug never used in humans before
  - A drug previously studied or FDA approved in a different disease, now being studied in a new disease
  - A new combination of drugs
  - A drug or combination previously studied in this disease for which more data are required

- **Outcomes include establishing a dose, safety, effectiveness (measured by response rate or duration of response), and patient-reported outcomes (PROs)**
  - Patient-reported outcomes come from questionnaires that the participants fill out about how they are feeling, side effects, etc.

CLINICAL TRIAL (PHASES)

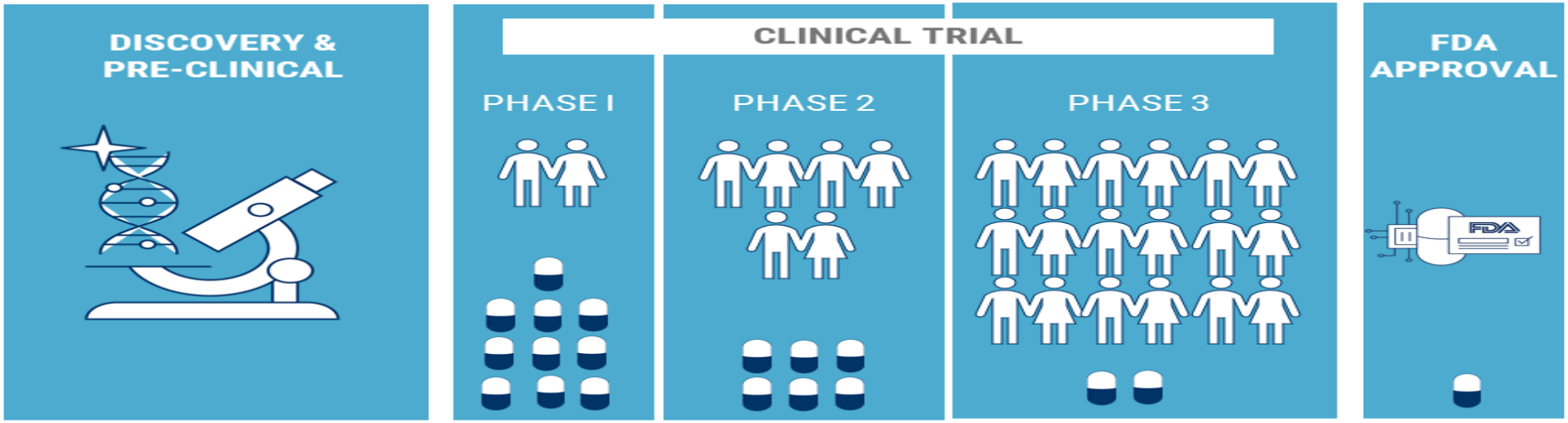
- **Phase 0 trials** are often first in human trials with 10 -15 people to see how a drug in processed by the body and its effects.

- **Phase I trials** find the best dose of a new drug with the fewest side effects. The drug will be tested in a small group of 15 to 30 patients. Phase I trials are to test a drug's safety.

- **Phase II trials** further assess safety as well as whether a drug works. The drug is often tested among patients with a specific type of cancer. Phase II trials are done in larger groups of patients. Often, new combinations of drugs are tested.

CLINICAL TRIALS (PHASES CONTINUED)

- **Phase III trials** compare a new drug to the standard-of-care (SOC) drug enrolling 100 or more patients. There can be more than two treatment groups in phase III trials. Often, these trials are randomized. Phase III clinical trials are usually needed for FDA approval of a new drug.
- **Phase IV trials** test drugs approved by the FDA. The drug is tested in several hundreds or thousands of patients.



Source: cbinsights.com

CLINICAL TRIALS (Clinicaltrials.gov)

www.clinicaltrials.gov

- Clinicaltrials.gov is a US-based website that requires companies and investigators to post information about clinical trials in a public forum.
- All US trials should be posted within about 3 weeks of when the sponsor (company) or investigator plans to start dosing (giving the test medication) to the first patient or subject.
- The site is organized by a simple listing, by topic, by geographic map, or specific search details or search terms.
- You can search by topics, such as disease type (previously treated or untreated), drug or drugs being studied (also known as interventions) and phase of clinical trials.

PROS AND CONS OF A CLINICAL TRIAL

- **PROs:**
  - Access to new therapies or combinations in development
  - Extra attention (staff dedicated to trial participants)
  - Drug may be provided free of charge
  - Patients do better when in trials (more expert care, closer supervision)
  - Contribute to new knowledge
- **CONs:**
  - More visits (most likely)
  - Treatment is not as established
  - Possibility of extra costs for travel or visits
  - CT scans are often more frequent than in standard of care
  - Some phase 3 trials have a less strong control arm, and may not allow crossover to the new therapy (equipoise)

WHAT TO ASK IF YOU ARE CONSIDERING A CLINICAL TRIAL

- What are the drugs being studied and why is this trial being done?
- What is the treatment / visit schedule?
- How many scans and bone marrow biopsies are required?
- Would the drugs be supplied by the trial?
- Will my insurance cover the treatment and other related costs?
- How long is the trial?
- How well has it been working and what are the side effects so far?
- Will I know the results of the trial once completed?
- What treatment would you suggest if I did not go on this trial?

SEQUENCING OF STANDARD THERAPIES

- Key therapies right now:
  - **Covalent BTK inhibitors** (acalabrutinib, zanubrutinib, (ibrutinib))
  - **BCL-2 inhibitors (venetoclax),** usually given with obinutuzumab

- BTK inhibitors are typically given continuously, indefinitely
  - With disease progression – go to venetoclax based treatment

- Venetoclax-obinutuzumab is one year of therapy
  - Can potentially do the same treatment again after a long remission, before switching to BTK inhibitor based treatment

COMBINATIONS EMERGING FROM CLINICAL TRIALS

- **Increasing interest in BTK inhibitor – BCL-2 inhibitor combinations, and emerging evidence that 3 drugs may sometimes be more effective than 2 drugs, particularly in patients with higher risk disease – albeit usually with more side effects**

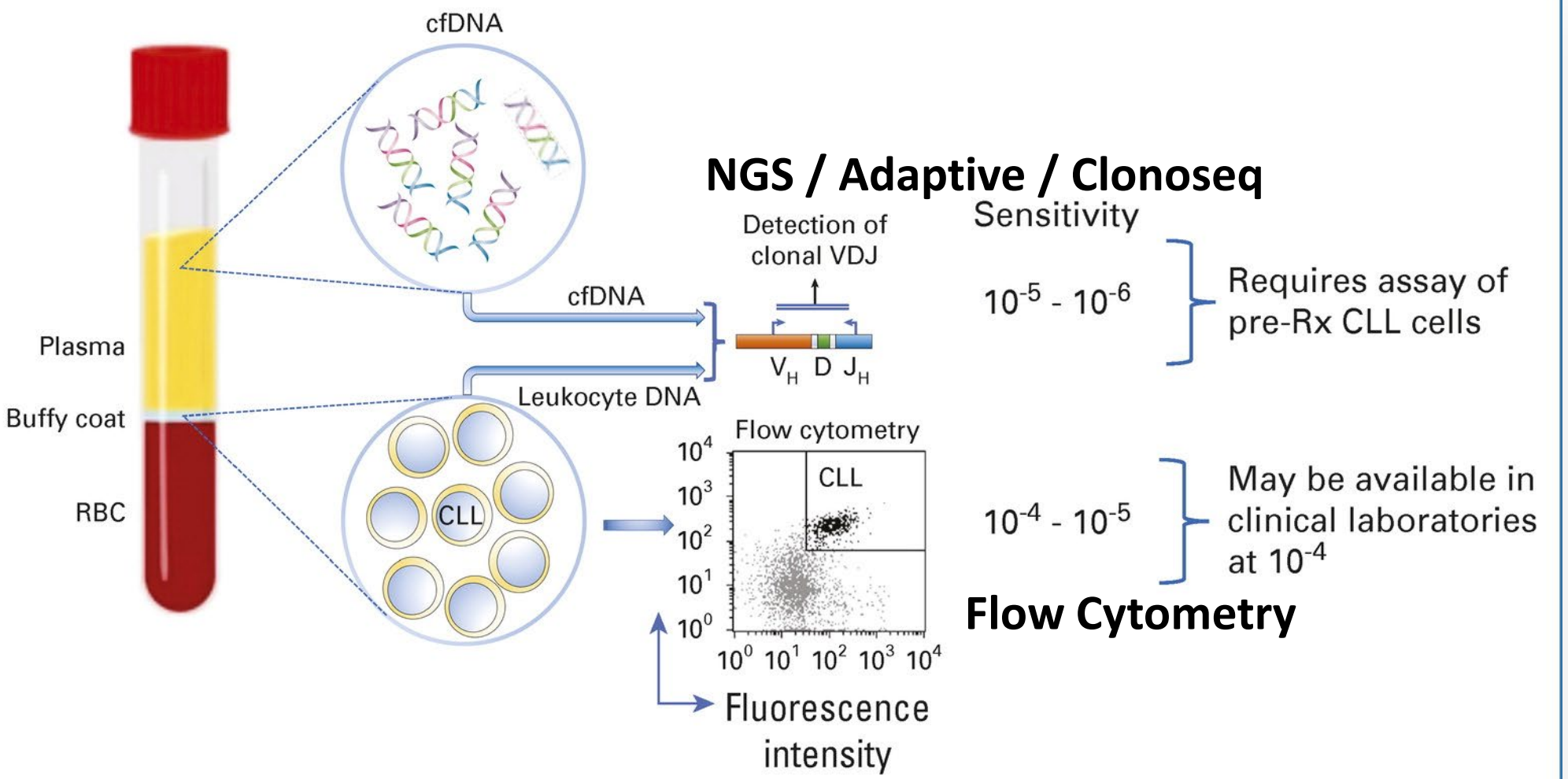
- Recent study found effectiveness of acalabrutinib venetoclax +/- obinutuzumab
  - Three drugs appeared better than 2 drugs in HIGHER RISK patients
  - Hoping for FDA approval soon

- Zanubrutinib with novel BCL-2 inhibitor sonrotoclax has completed accrual to a registration trial

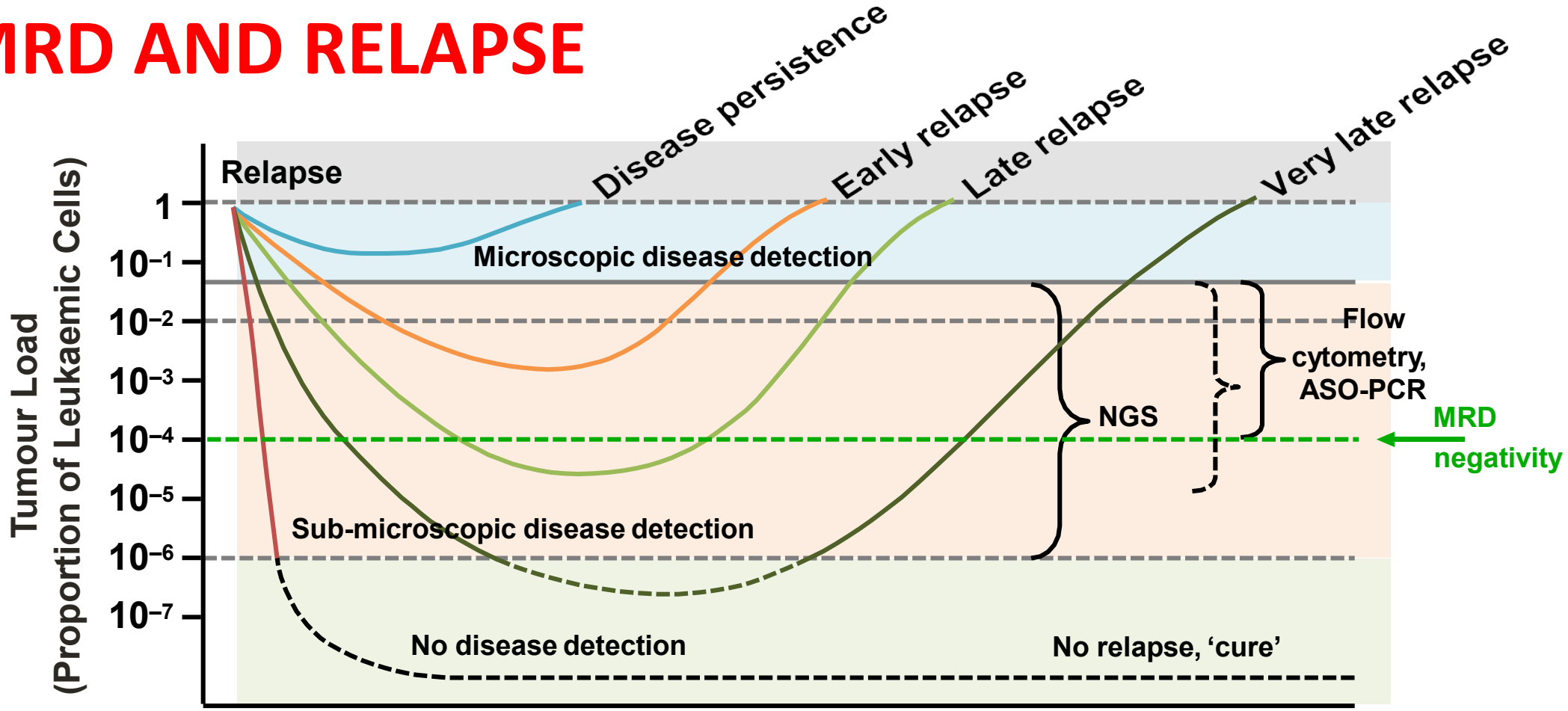
- Ibrutinib venetoclax has shown efficacy (better than ibrutinib alone) especially when the duration of therapy is guided by measurements of residual disease

- A German trial showed that ibrutinib venetoclax obinutuzumab (3 drugs) are more effective than venetoclax obinutuzumab (2 drugs) in HIGHER RISK patients

MEASURABLE RESIDUAL DISEASE (MRD)



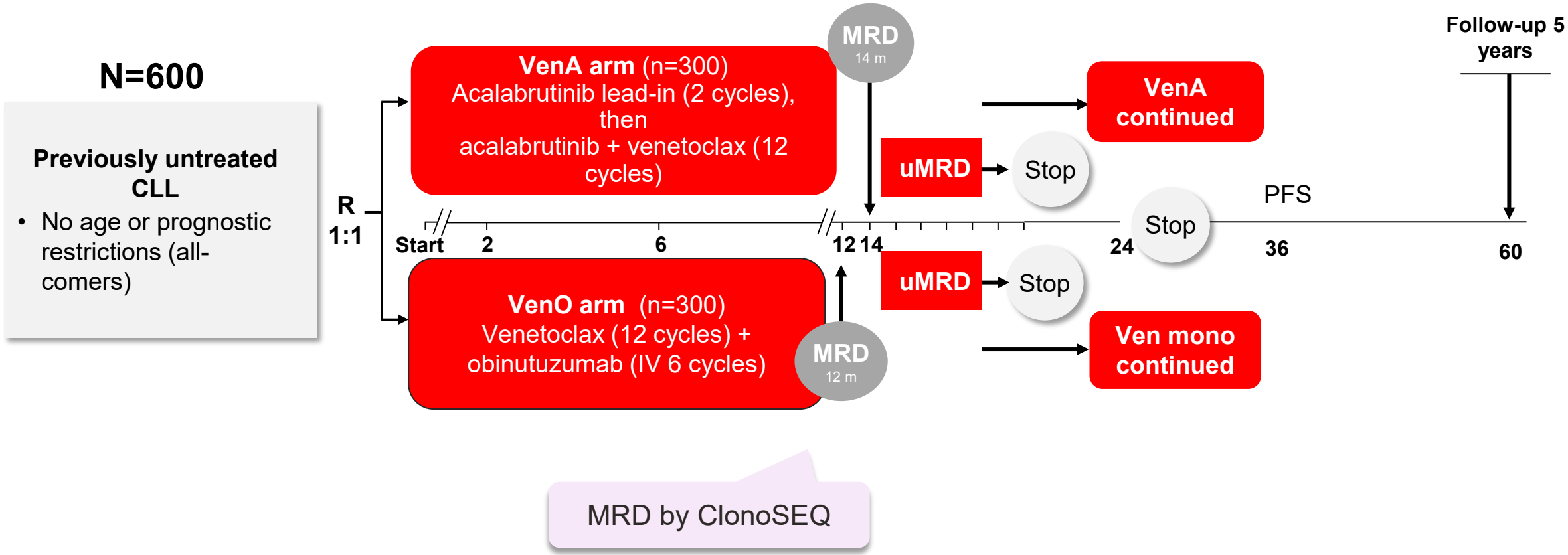
PREDICTED CORRELATION OF UNDETECTABLE MRD AND RELAPSE



Lower level of residual disease, generally associated with longer time to progression (i.e. less likely to relapse)

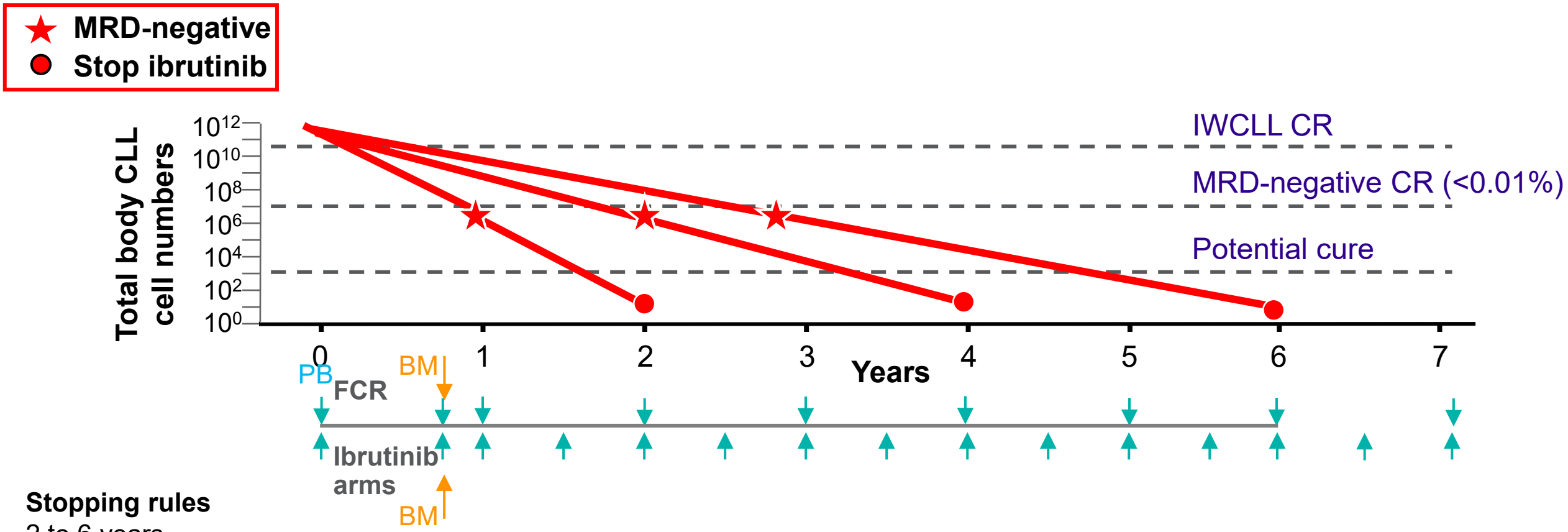
Adapted from: Buckley SA, et al. Bone Marrow Transplant 2013; 48:630–641.

HOW DOES A MRD GUIDED TRIAL WORK?
MAJIC: MRD-GUIDED VENETOCLAX + ACALABRUTINIB vs VENETOCLAX + OBINUTUMAB



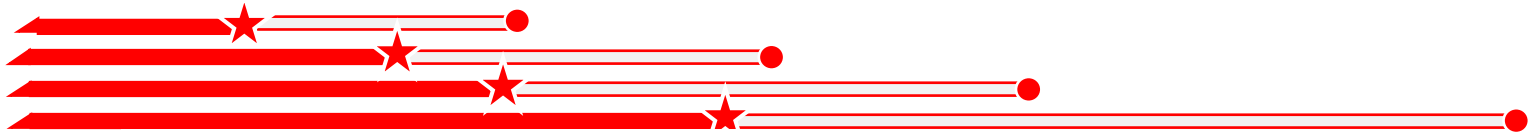
Ryan et al. *Future Oncol.* 2022 Oct;18(33):3689-3699. doi: 10.2217/fon-2022-0456.

HOW DOES A MRD GUIDED TRIAL WORK?



Stopping rules
2 to 6 years
ibr+venetoclax
Double time after
MRD negative

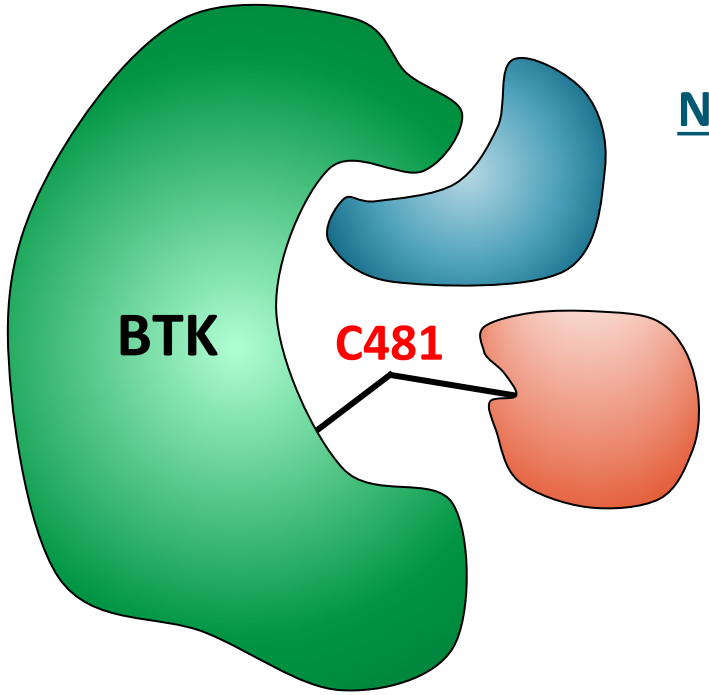
If PB MRD negative, repeat after 3 months and then PB and BM at 6 months
– if all MRD negative, then first PB MRD negative result is time to MRD negativity



Restart ibrutinib if becomes MRD positive prior to Year 6

Munir et al. *N Engl J Med* 2024;390:326-337DOI: 10.1056/NEJMoa231006

FDA APPROVED COVALENT AND NONCOVALENT BTK INHIBITORS



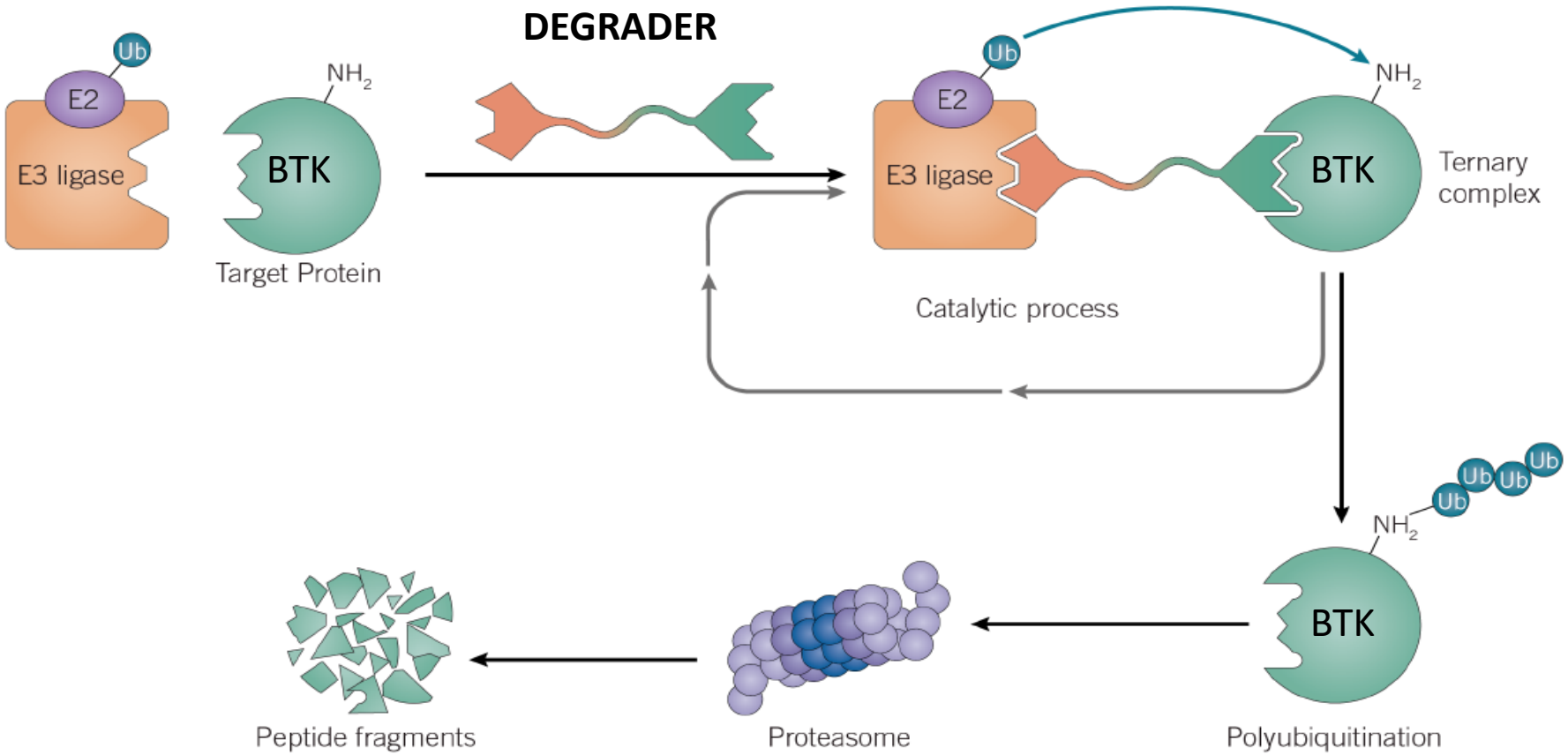
Noncovalent/reversible BTK inhibitors:
Pirtobrutinib

Covalent/irreversible BTK inhibitors:
Ibrutinib
Acalabrutinib
Zanubrutinib

Adapted from Woyach. NEJM 2014;370:2286.
Adapted from Gu. J Hematol Oncol. 2021;14:40.

Slide credit: clinicaloptions.com

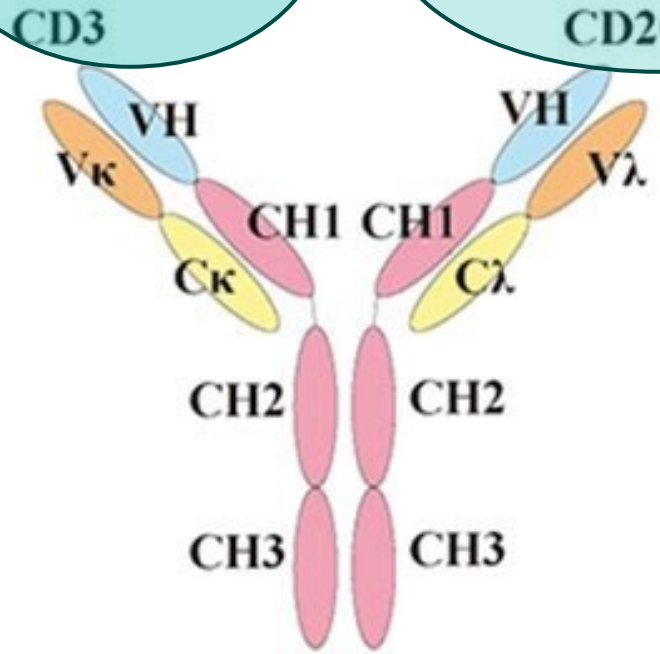
WHAT IS A DEGRADER?



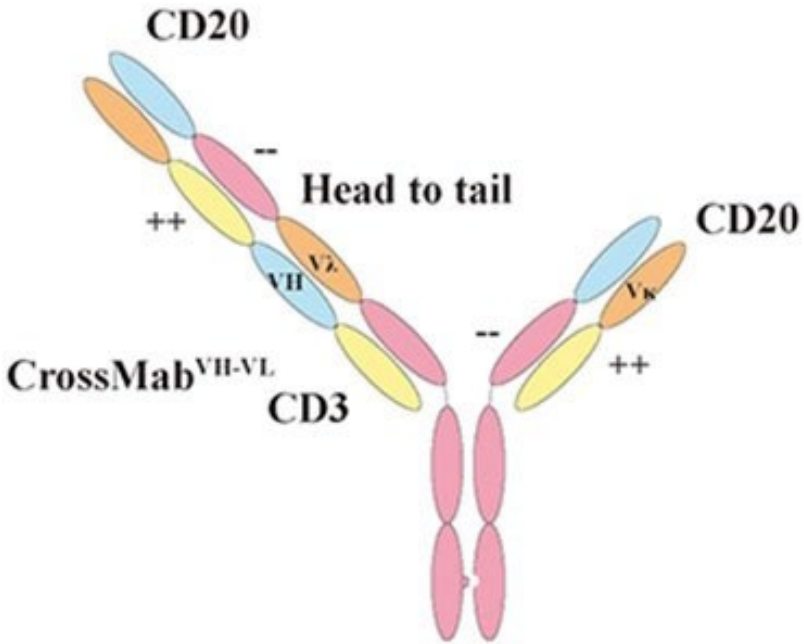
BISPECIFIC ANTIBODIES TESTED IN CLL

Pulls in T Cells!

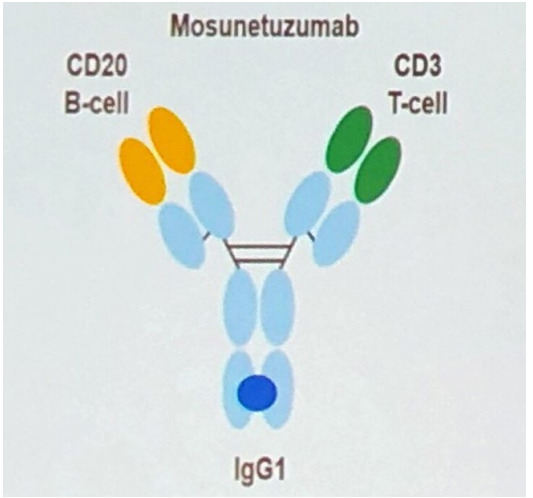
Attacks CLL Cells!



Epcoritamab



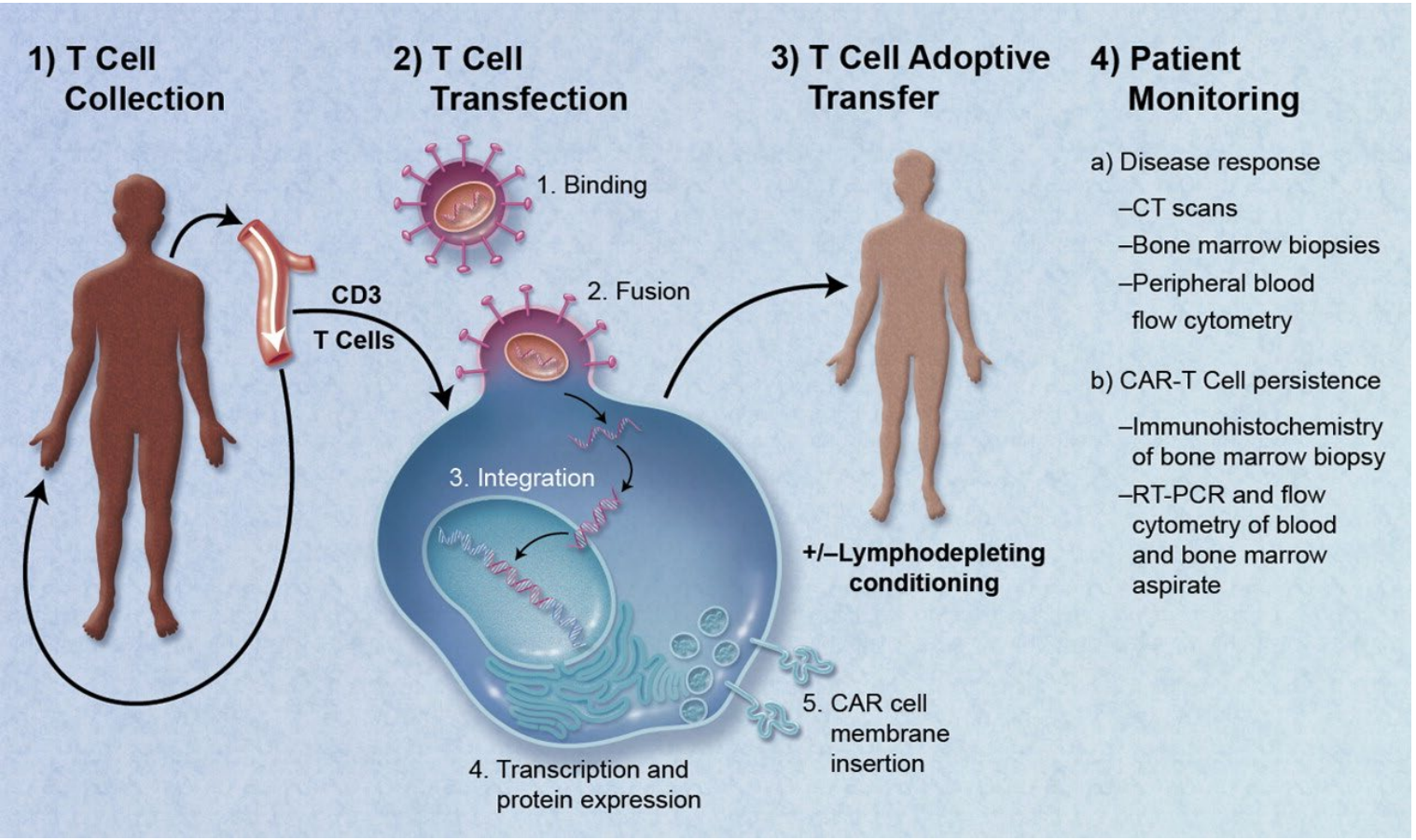
Glofitamab

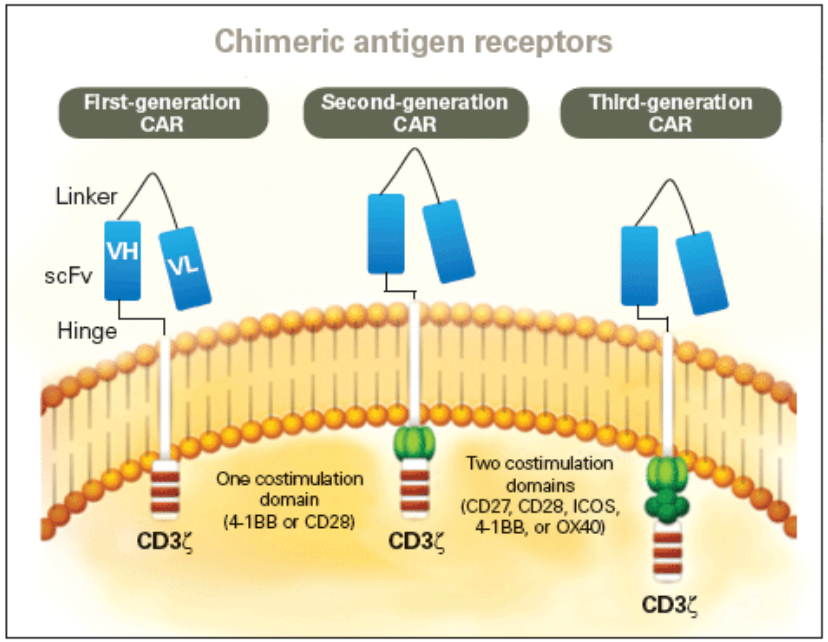


Mosunetuzumab

Ma J et al. *Front. Immunol.* 2021 12:626616.

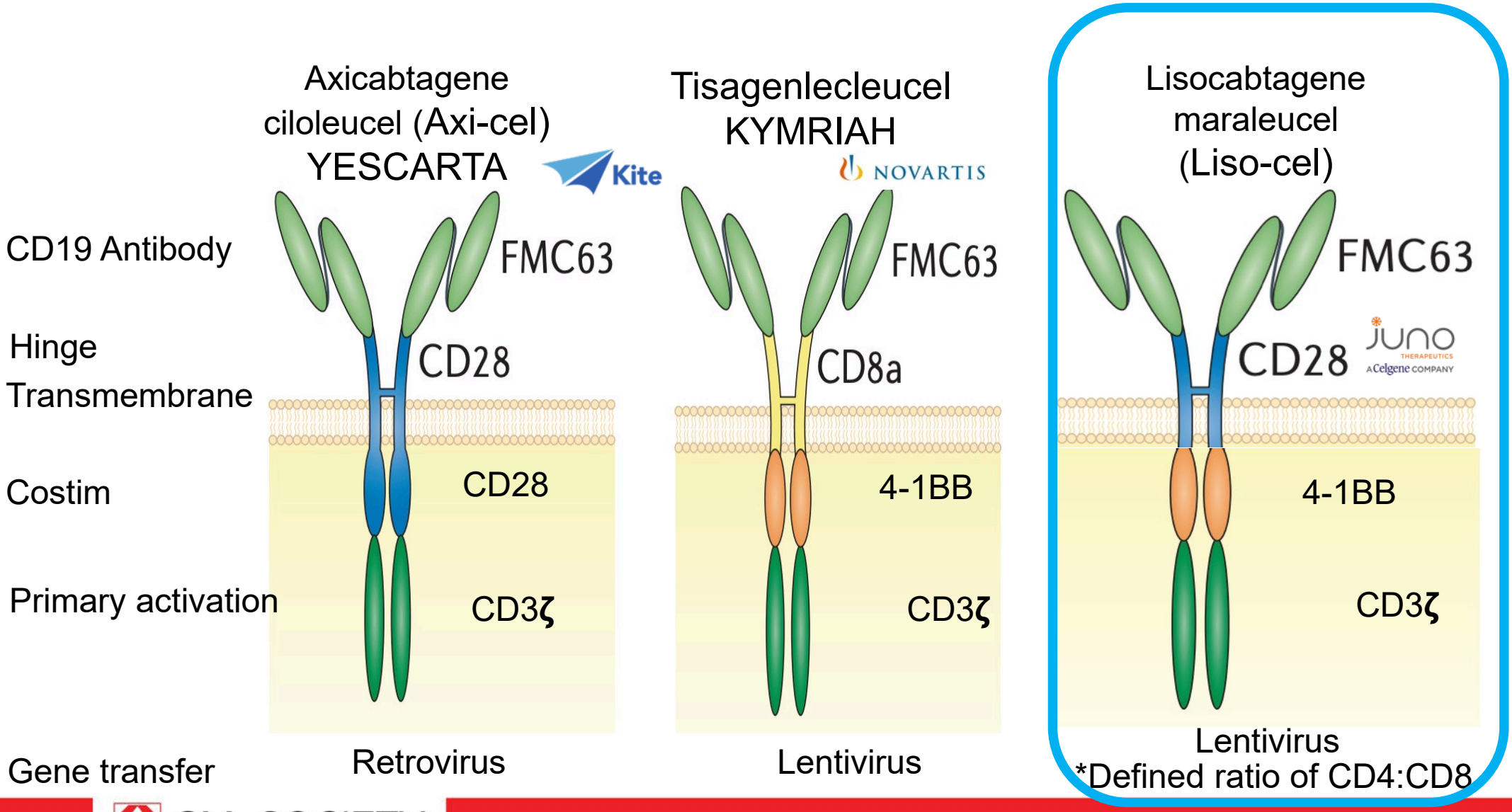
WHAT IS A CAR T-CELL AND HOW IS IT MADE?





- CAR = Chimeric antigen receptor
  - Chimera: part antibody molecule, part T-cell activating molecule

CD19 CHIMERIC ANTIGEN RECEPTOR-T CELLS IN THE CLINIC



Adapted from Nat Rev Drug Discov. 2015 Jul; 14(7): 499–509.

HOT TOPICS IN CLINICAL TRIALS

- **Combination therapy**
  - Often MRD guided
- **Time-limited BTK inhibitor therapy – usually based on either:**
  - A combination from the beginning
  - Adding in an additional therapy: BCL-2 inhibitor, bispecific antibody
- **Consolidation trials**
- **Novel drugs (new targets: MEK inhibitor, MALT1, PKCb)**
- **Infection control**
- **Early intervention : goals should include immune reconstitution**

SUMMARY

- **Clinical trials represent an excellent opportunity to access novel drugs or combinations that may soon become the standard of care**
  - Even if they don't become standard of care, they add to the armamentarium of treatments available for your individual care

- **Research and clinical care is trending toward time limited therapies and likely more individualized, MRD guided therapies**

- **New drugs on the horizon: BTK degraders, bispecific antibodies, novel CARs, novel targets**

- **Exciting times in CLL research! The advances continue rapidly**

AUDIENCE Q&A

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FROM SERVICE TO SUPPORT: MANAGING CLL/SLL IN THE VETERAN COMMUNITY

August 28th

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