Fred Hutch Cancer Center

Relapsed/refractory myeloma and other plasma cell disorders

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UW Medicine

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Disclosures

- Consulting:
  - Abbvie, Adaptive Biotech, BMS, Caribou Biosciences, Genentech/Roche, Gilead/Kite, GSK, Karyopharm, Legend Biotech, JNJ, Pfizer, Poseida Therapeutics, Sanofi Pasteur, SparkCures

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Today's agenda

- 15 min: CAR-T therapy and bispecific antibodies
- 5 min: Other RRMM therapies
- 10 min: AL amyloidosis and other plasma cell disorders

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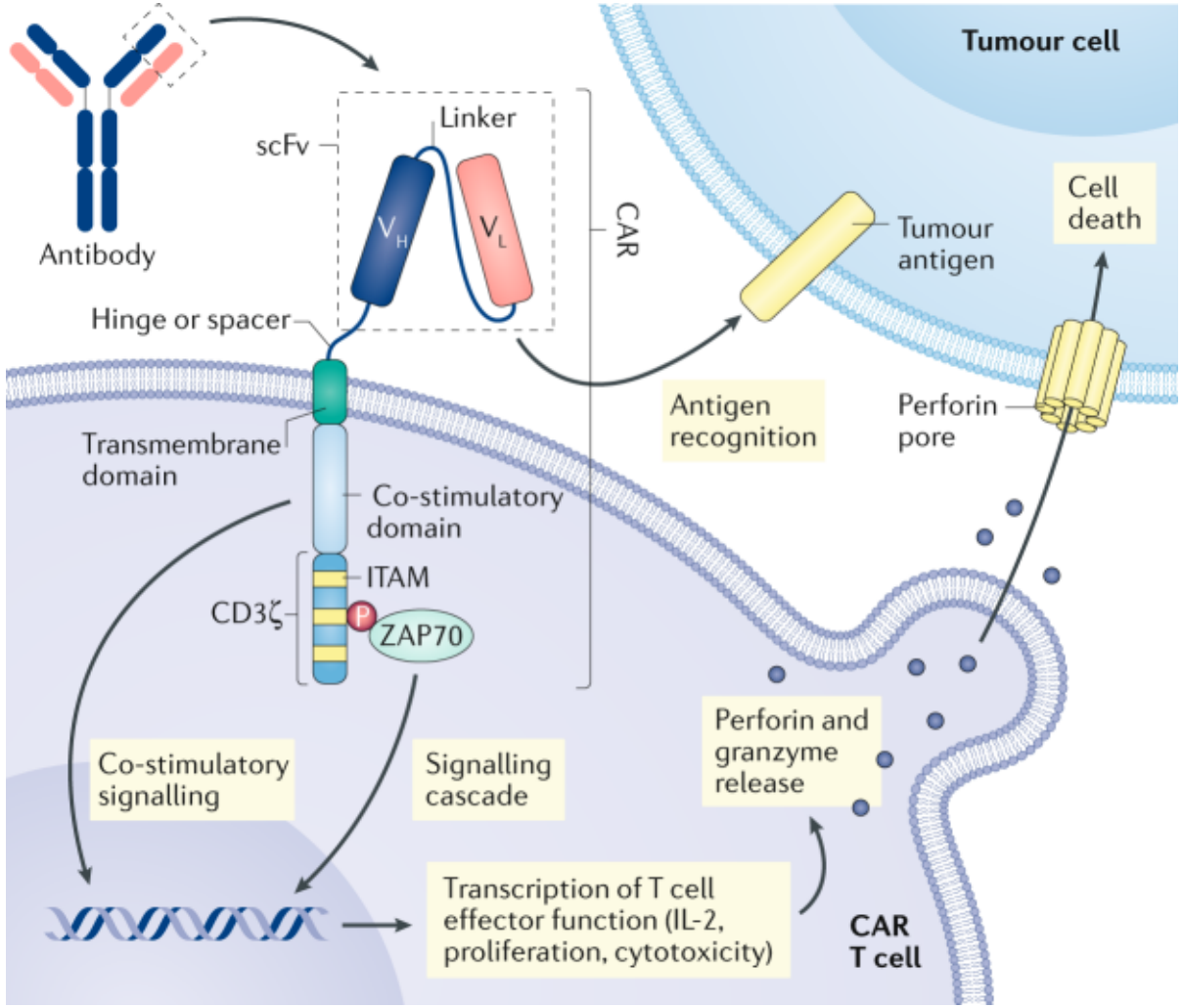
What is CAR-T therapy (simplified)?

- **Extracellular domain:** Bind a target antigen like BCMA (in myeloma) or CD19 (in NHL & B-ALL)
- **Intracellular domain**: Co-stimulatory domain for ‘second signal’ and downstream activation



Larson RC et al, Nature Reviews Cancer 2021. PMID: 33483715.

Abbreviations: B-ALL, B-cell acute lymphoblastic leukemia; BCMA, B-cell maturation antigen; CAR-T, chimeric antigen receptor T-cell therapy; NHL, non-Hodgkin lymphoma.

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CAR-T therapy in MM: A brief history

Ide-cel in 4+ prior lines

March 2021: Required PI, IMiD, and CD38 exposure

Cilta-cel in 4+ prior lines

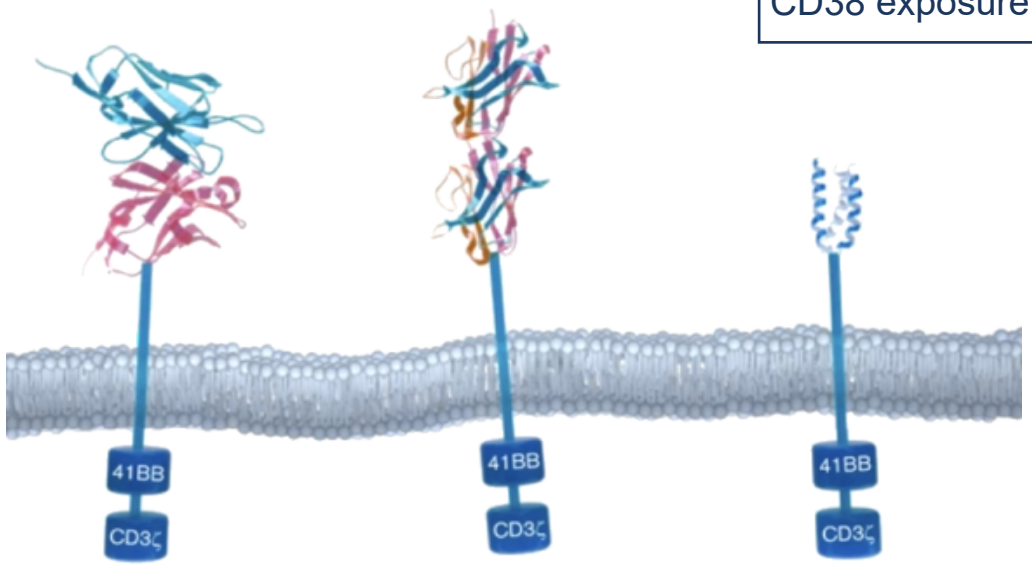
February 2022: Required PI, IMiD, and CD38 exposure

Ide-cel in 2+ prior lines

April 2024: Requires PI, IMiD, and CD38 exposure

Cilta-cel in 1+ prior line

April 2024: Requires PI exposure & len refract-oriness (CD38 agnostic)



Ide-cel **Cilta-cel** **Anito-cel (not approved yet)**

In real life: feel free to refer patients to us as early as possible! 1 prior line doesn't require refractoriness *per se.*

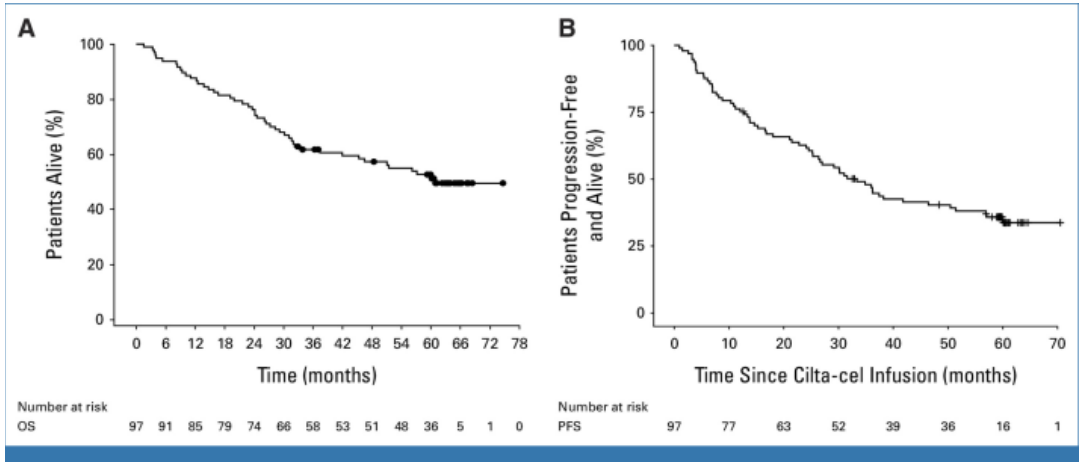
Frigault MJ et al, Blood Adv 2023. PMID: 35468618

Abbreviations: Anito-cel, anitocabtagene autoleucel; Cilta-cel, ciltacabtagene autoleucel; ide-cel, idecabtagene vicleucel; IMiDs, immunomodulatory drugs; mAbs, monoclonal antibodies; PIs, proteasome inhibitors.

What does CAR-T therapy offer in RRMM?

- Probably cure for some patients with myeloma, but we can't tell whom and thus can't comfortably use the word yet

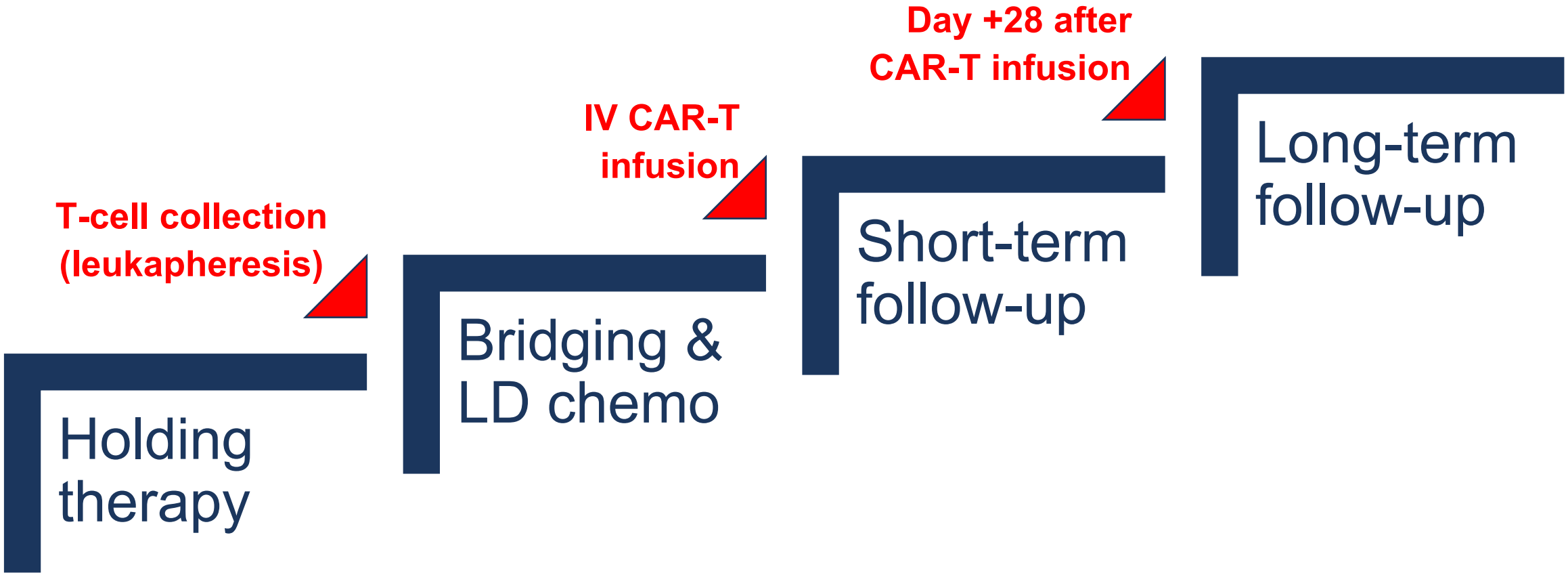
	≥5 years progression-free (n=32)
Age, years, median (range)	60.0 (43–78)
High-risk cytogenetics,[a] n/N (%)	**7/30 (23.3)[b]**
Extramedullary plasmacytomas, n (%)	**4 (12.5)[c]**
Time to progression on last prior LOT, months, median (range)	3.98 (0.7–48.6)[d]
Prior LOT, median (range)	6.5 (3–14)
Triple-class[f] refractory, n (%)	29 (90.6)
Penta-drug[g] refractory, n (%)	15 (46.9)
Bone marrow plasma cells, %, median (range)	**5.0 (0.8–80.0)**
Soluble BCMA, µg/L, median (range)	**36.0 (3.7–864.6)**
High baseline tumor burden,[h] n (%)	2 (6.3)



With CARTITUDE-1, likely 100% of patients would have died ≤6 months without CAR-T therapy. Instead, 33% are alive and disease-free >5 years later!

Jagannath et al, JCO 2025. PMID: 40459151.
Abbreviations: LOT, line of therapy; PFS, progression-free survival; OS, overall survival.

CAR-T therapy: A play in 4 parts



Abbreviations: IV, intravenous; LD, lymphodepletion.

CAR-T Part 1: Holding the line until collection

- **Goals of this phase:**
  - Initial referral to CAR-T center, insurance logistics, etc.
  - Successfully collecting autologous T cells for processing
- **Things to know for boards:**
  - **Avoid bendamustine**! Long-term deleterious effects on T cells
  - Ideally ≥4 weeks since bispecific antibodies (T-cell exhaustion)

CAR-T Part 2: Bridging the patient to CAR-T

- **Goals of this phase:**
  - **Bridging therapy:** Systemic therapy or radiation to prevent death or horrible disease-related morbidity during 4-6 week manufacturing
  - **Lymphodepletion (LD)**: Typically 3 days of fludarabine & cyclophosphamide to create 'T-cell void' that promotes CAR-T expansion 2 days later
- **Things to know for boards**:
  - Okay if bridging therapy only results in SD or even biochemical PD. Hitting too hard with alkylators puts patients at risk of ICAHT (hematotoxicity) later.
  - Fludarabine is renally dosed. For patients on dialysis, you can use bendamustine monotherapy as LD instead. *[Of course never use benda for 'holding' therapy!]*

Abbreviations: ICAHT, immune effector-cell associated hematotoxicity syndrome; PD, progressive disease; SD, stable disease.

CAR-T Part 3: Day 0 to Day +28

- **Goals of this phase:**
  - Monitoring for toxicities, most notably CRS and ICANS
- **Things to know for boards**:
  - **CRS:** Look for fevers. Management: full infectious workup, tocilizumab (IL-6 receptor antagonist), dexamethasone.
  - **ICANS**: Look for confusion or aphasia. Management: full delirium workup, dexamethasone preferred over tocilizumab.

Abbreviations: CRS, cytokine release syndrome; ICANS, immune effector cell-associated neurotoxicity syndrome.

CAR-T Part 4: Long-term follow-up

- **Goals of this phase:**
  - Supportive care alone; no role for MM maintenance therapy currently
- **Things to know for boards:**
  - Risk #1: MM relapse – Can re-use old therapies or go to bispecifics.
  - Risk #2: Infections – IVIG liberally, PJP PPx x6 mo, VZV PPx x12mo
  - Risk #3: Weird things, more likely on boards than in real life

Abbreviations: IVIG, intravenous immunoglobulin; PJP, Pneumocystis jirovecii; PPx, prophylaxis; VZV, varicella zoster virus.

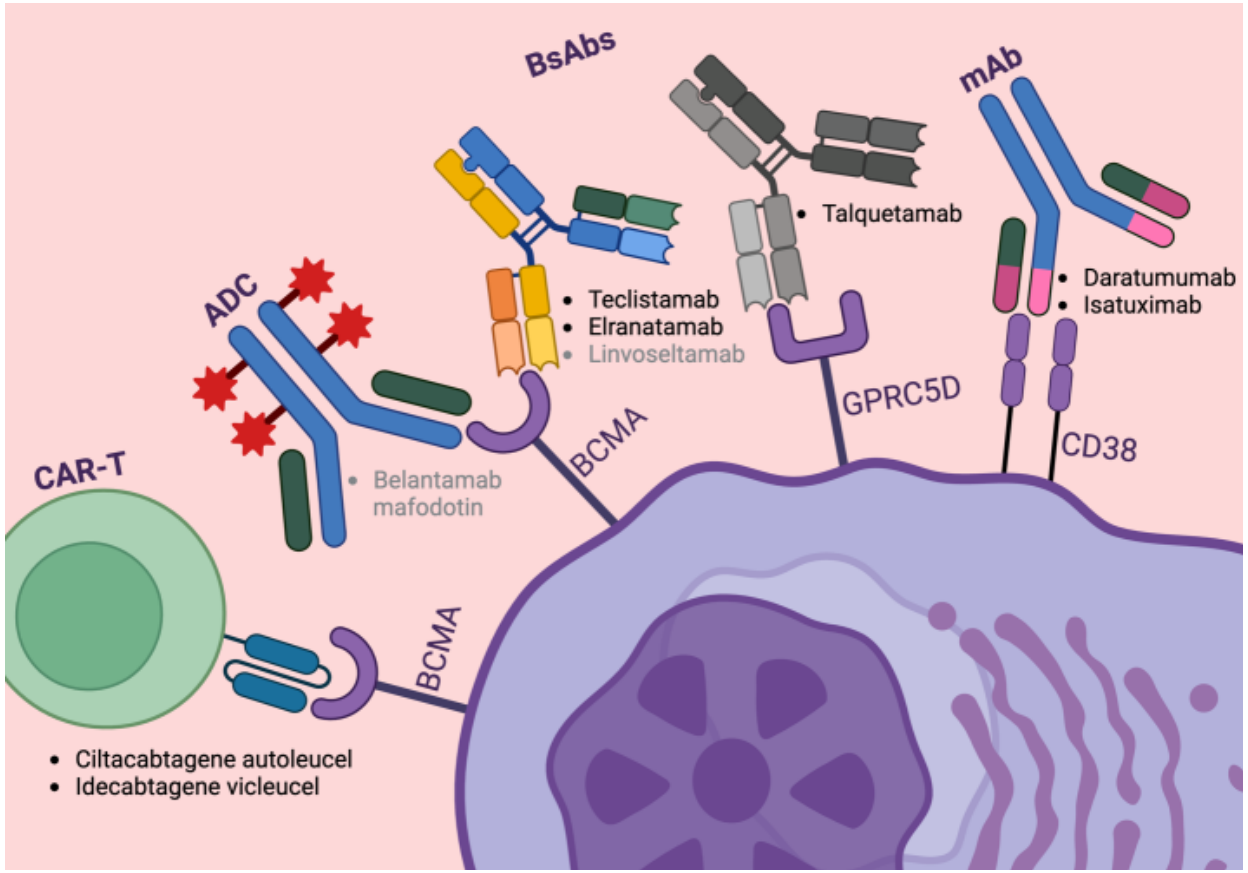
Delayed complications of CAR-T in MM

- **Weird complication #1:**
  - **Delayed neurocognitive toxicities**, including Bell's palsy and Parkinsonism. Corticosteroids if Bell's palsy, high-dose chemo (kill CAR-T cells) if Parkinsonism.
- **Weird complication #2**:
  - **IEC-associated enterocolitis** (bloody diarrhea). Not completely understood yet. Treat like ICI-associated colitis (e.g. infliximab) and not like GVHD with steroids alone.
- **Weird complication #3:**
  - **T-cell lymphomas**, ± CAR positivity in the cells. Low threshold to biopsy any suspicious lesions after CAR-T therapy, and work closely with us if so.

Abbreviations: GVHD, graft-versus-host disease; ICI, immune checkpoint inhibitor.

What about bispecific antibodies?

- Goal: Replicate CAR-T effector function an ‘off-the-shelf’ antibody
- **Versus CAR-T:**
  - Easier to operationalize
  - Lower CRS & ICANS
  - Higher infections if BCMA -targeting
  - More ‘time toxicity’



Portuguese A et al, JCO OP 2025. PMID: 39772633.

What to know for boards re: bispecifics

- **How to lower the risk of CRS:**
  - Step-up dosing (phased ramp-up of initial dosing) is required for most products across malignancies. Can be done in inpatient settings.
  - Prophylactic tocilizumab is now recommended in NCCN guidelines
- **How to lower infections (higher risk than BCMA CAR-T!):**
  - Primary IVIG prophylaxis (monthly repletion regardless of IgG levels) preferred over preemptive IgG repletion (waiting until IgG < 400)
  - Whatever you do, do not wait until a Grade 4 infection to start IVIG

Abbreviations: IVIG, intravenous immunoglobulin; NCCN, National Comprehensive Cancer Network.

What to know for boards re: GPRC5D

- Most approved bispecific antibodies target BCMA. However, talquetamab is the only approved drug targeting GPRC5D.
- **Good news:** It's not BCMA!
  - Works quite well both before and after BCMA CAR-T therapy
  - Lower risk of infections than with BCMA bispecifics
- **Bad news**: GPRC5D on skin, nail, and tongue cells
  - Over half of patients will get dysgeusia ± weight loss. Skin changes (especially on palms) also common. Supportive care is important.

Questions about CAR-T or bispecifics?

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- **5 min: Other RRMM therapies**
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What other RRMM therapies are there?

- Various combinations of drugs with all sorts of dosing schemas – we are happy to help since this is honestly a mess!
- A few options for classes:
  - **mAbs:** daratumumab (CD38), isatuximab (CD38), elotuzumab (SLAMF7)
  - **PIs:** bortezomib (think neuropathy), carfilzomib (think hypertension)
  - **IMiDs:** Pomalidomide (same dosing regardless of renal function)
  - **Others**: Selinexor (think N/V), venetoclax if t(11;14)

Abbreviations: IMiD, immunomodulatory imide drugs; mAb, monoclonal antibodies; N/V, nausea / vomiting; PI, proteasome inhibitors.

RRMM: Focus on antibodies

- **CD38-targeted mAbs: SC daratumumab, IV isatuximab**
  - Often combined with carfilzomib or pomalidomide. VZV PPx required.
  - In real life, can re-use these if ≥12 months since last CD38 exposure.
- **SLAMF7-targeted mAbs: Elotuzumab**
  - 0% ORR unless you combine it with an IMiD, e.g., pom
- ***[BCMA ADC: Belantamab mafodotin]*** *Was pulled from the US market but returning in 2025… too new to be on boards*
  - But if it is: Blurry vision / keratopathy common. Space out doses early.

Abbreviations: ADC, antibody-drug conjugate; IV, intravenous; SC, subcutaneous.

RRMM: Focus on carfilzomib

- Carfilzomib has been shown to outperform bortezomib in RRMM, versus in newly diagnosed MM where it's complicated
- Things to remember with carfilzomib for boards:
  - 4% incidence of heart failure in trials largely driven by overdosing & overhydrating. Use lower doses and once-weekly dosing.
  - Rare toxicities can still occur, most notably TMA with renal injury and thrombocytopenia. Permanent discontinuation if so.

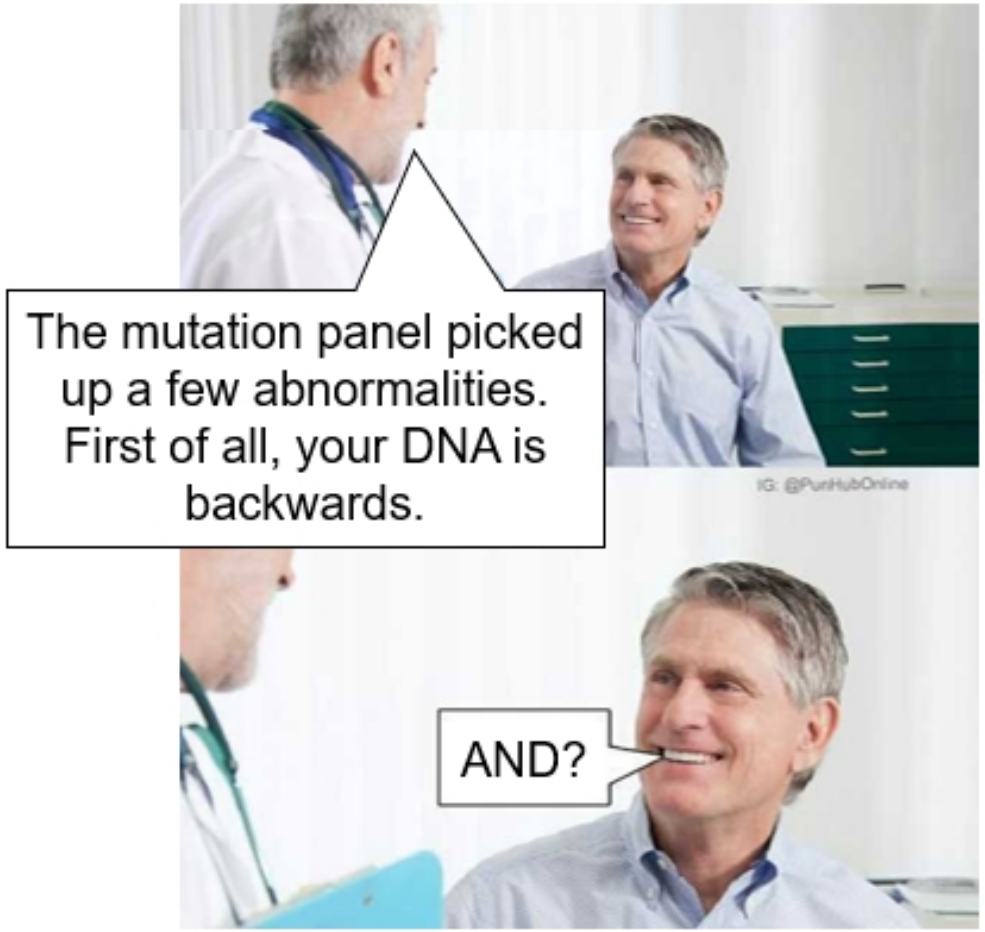
Abbreviations: TMA, thrombotic microangiopathy

RRMM: Focus on oral agents

- **Pomalidomide**: Great activity even in lenalidomide-refractory disease, and overall is tolerated quite well
  - Pom 2mg seems to perform similarly to pom 4mg in trials
- **Selinexor**: Novel exportin inhibitor, namely that it sequesters p53 protein and its tumor-suppressor friends in the nucleus
  - Start low and use anti-emetics & TPO agonists quite liberally
- **Venetoclax:** Works quite well in MM with t(11;14), but will never be approved for this indication (long story)
  - If you're asked: Don't worry about TLS, but yes worry about infections

Abbreviations: TLS, tumor lysis syndrome; TPO, thrombopoietin

Questions about other RRMM treatments?



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Qualitative issues with paraproteins

- Whereas the MGUS → SMM → MM distinction is a *quantitative* issue, paraproteins can have *qualitative* issues too. E.g.:

  - **AL amyloidosis**: Paraprotein (typically lambda light chain) forms fibril clumps in heart, kidneys, nerves, etc.

  - **MGRS**: Quantitatively still MGUS, but light chains attacking kidneys. AL amyloidosis as above, light chain deposition disease, PGNMID, and other rare conditions.

  - **POEMS**: Paraprotein triggers production of VEGF, IL-6, and other cytokines that lead to neuropathy, skin changes, et al

PGNMID: Proliferative glomerulonephritis with monoclonal IgG deposits; POEMS, Polyneuropathy organomegaly endocrinopathy monoclonal plasma cell disorder skin changes; VEGF, vascular endothelial growth factor.

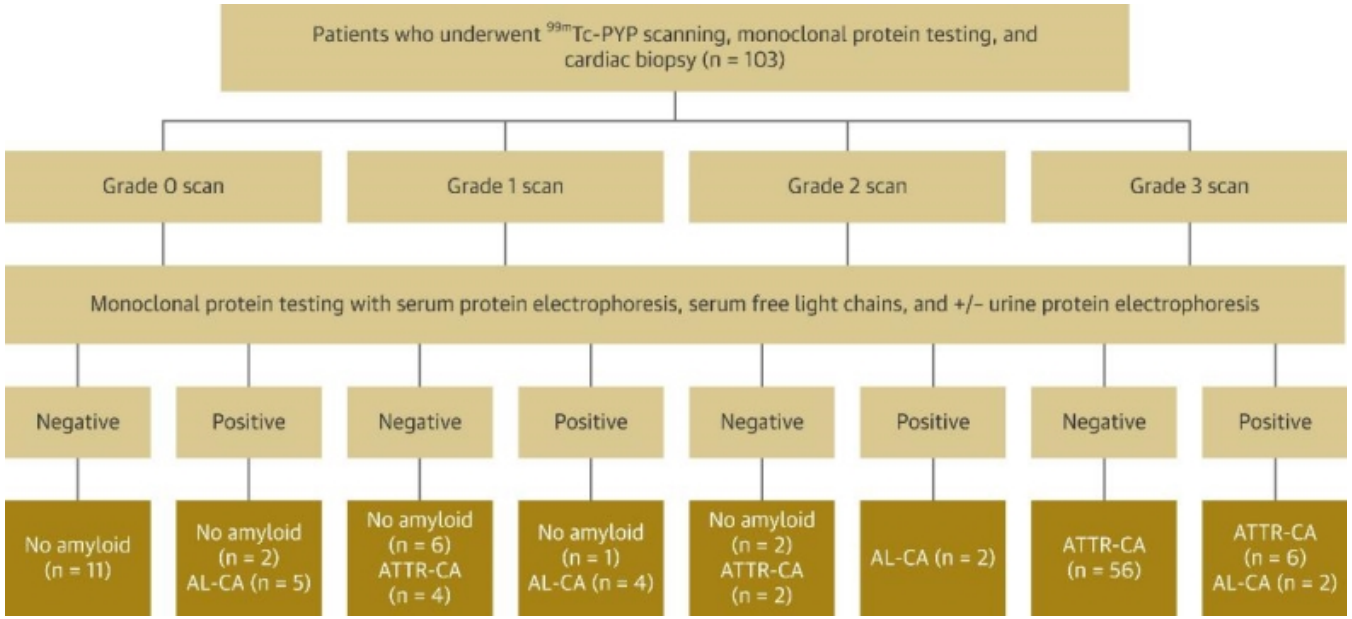
So what does AL amyloidosis look like?

- **MGUS plus any of the following:**
  - **Cardiac involvement**: Heart failure with preserved ejection fraction. Thickened LV posterior wall & septal thickening during diastole.
  - **Renal involvement**: Unexplained proteinuria, typically albuminuria and not Bence-Jones proteinuria. Serum creatinine often preserved.
  - **Nerve involvement**: Typically painless neuropathy in bilateral Les
  - **GI involvement:** Macroglossia, worsening constipation
  - **Soft tissue involvement**: Bilateral carpal tunnel syndrome

Abbreviations: GI, gastrointestinal; LE, lower extremity.

AL versus ATTR amyloidosis

- **ATTR amyloidosis**: Abnormal transthyretin produced by the liver, typically with cardiac and/or neurological manifestations
- PYP scan can help, but it's not perfect.
- We **must** run mass spectrometry off Congo Red positive deposits to confirm what type of amyloidosis a patient has!



Poterucha TJ, Elias P, Bokhari S, et al. JACC Cardiovasc Imaging. 2021;14(6):1221-1231. PMID: 33221204.
PYP = pyrophosphate scan

So what does POEMS look like?

- Typically: middle-aged man with worsening symmetric neuropathy over several months.
- Often attributed to other causes before a neurologist suspects the diagnosis – OR – referred to hematology for MGUS, and we notice the neuropathy.

*Mandatory criteria	• Polyneuropathy • Monoclonal plasma cell disorder
**Major criteria	• Osteosclerotic lesion • Castleman disease • Elevated levels of vascular endothelial growth factor
***Minor criteria	• Organomegaly (splenomegaly, hepatomegaly, or lymphadenopathy) • Extravascular volume overload (edema, pleural effusion, or ascites) • Endocrinopathy (adrenal, thyroid, pituitary, gonadal, parathyroid, pancreatic) • Skin changes (hyperpigmentation, hypertrichosis, glomeruloid hemangiomata, plethora, acrocyanosis, flushing, white nails) • Papilledema • Thrombocytosis/polycythemia

Ali T et al. Eur J Hematol. 2021;106(1):14-18.

What to do when managing AL amyloidosis

- **Diagnostically:**
  - Confirm the diagnosis with typing as above
  - Assess thoroughly for cardiac involvement: nt-proBNP, troponin T, cardiac MRI (look for delayed gadolinium enhancement)
- **Therapeutically:**
  - Use Dara-CyBorD as per the ANDROMEDA trial. 6 months of weekly therapy (yes, even the bortezomib with its neuropathy risk), then 18 months of monthly daratumumab maintenance.

Abbreviations: Dara-CyBorD, daratumumab / cyclophosphamide / bortezomib / dexamethasone; nt-proBNP, n terminus pro--natriuretic peptide.

What not to do when managing AL amyloidosis

- **Go overboard with IMiDs or dexamethasone**
  - Lenalidomide can worsen cardiac and GI symptoms. I generally omit this entirely, e.g. with Dara-CyBorD which has no IMiDs
  - Dexamethasone: I use 10-20 mg once weekly for 1 cycle, then stop entirely. Risk of volume overload is too high otherwise.
- **Manage cardiac symptoms by yourself**
  - These patients need a cardiologist and ideally a cardio-oncologist. For example, slowing their heart rate with beta blockers is dangerous

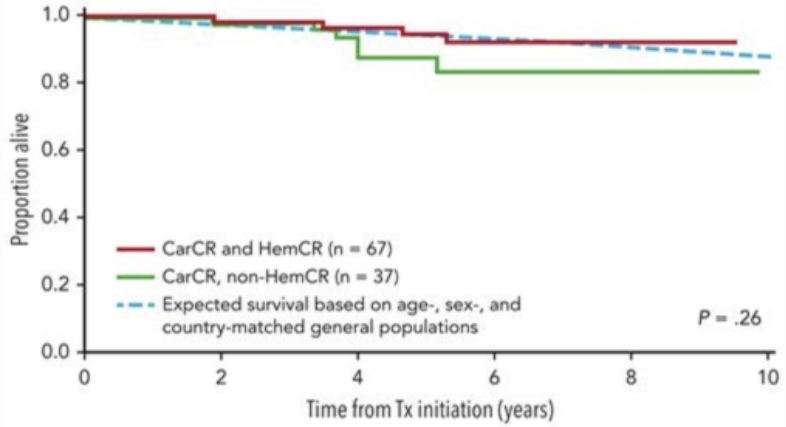
Last thing <u>not to do</u> with AL amyloidosis…

- Tell an ambulatory patient to go straight for hospice
- **AL amyloidosis is not the death sentence it once was!**
- First 6 months can be scary, but patients who achieve a cardiac response can do quite well in the long-term…

› Blood. 2024 Aug 15;144(7):790-793. doi: 10.1182/blood.2024024623.

Patients with a cardiac complete response in AL amyloidosis have survival rates similar to those of a matched general population

Eli Muchtar [1], Susan Geyer [2], Giampaolo Merlini [3 4], Morie A Gertz [1]



Muchtar et al, Blood 2024. PMID 3882059.
Abbreviations: CarCR, cardiac complete response; HemCR, hematologic complete response;

Questions about anything?

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Thank you!

> "In 2005, a man diagnosed with multiple myeloma asked me if he would be alive to watch his daughter graduate from high school in a few months. In 2009, bound to a wheelchair, he watched his daughter graduate from college. The wheelchair had nothing to do with his cancer. The man had fallen down while coaching his youngest son's baseball team."
>
> — Siddhartha Mukherjee, The Emperor of All Maladies: A Biography of Cancer

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