Graft-versus-Host Disease: Advances and Challenges in Prevention and Treatment

Celebrating a Second Chance at Life Survivorship Symposium

April 27 – May 3, 2024

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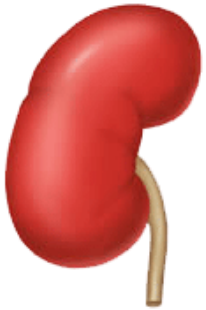
Learning Objectives:

- Strategies to **prevent** acute and chronic GVHD
- **Treatments** for acute and chronic GVHD
  - Available new drugs
  - Drugs in clinical trials
  - Side effects of therapies used to treat GVHD
  - Ancillary GVHD therapies

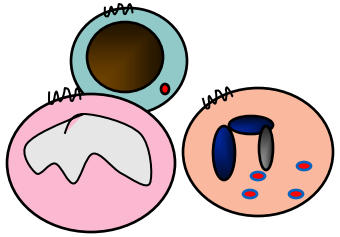
GVHD

Caused by the interaction between the transplanted stem cells (graft) and recipient/patient tissues (host)

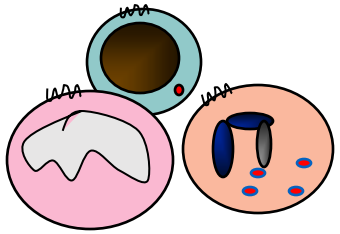


Transplanted organ

Rejection

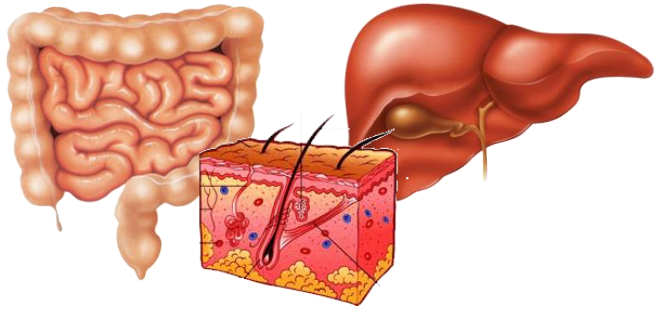


Host Immune system



Transplanted stem cell graft

GVHD



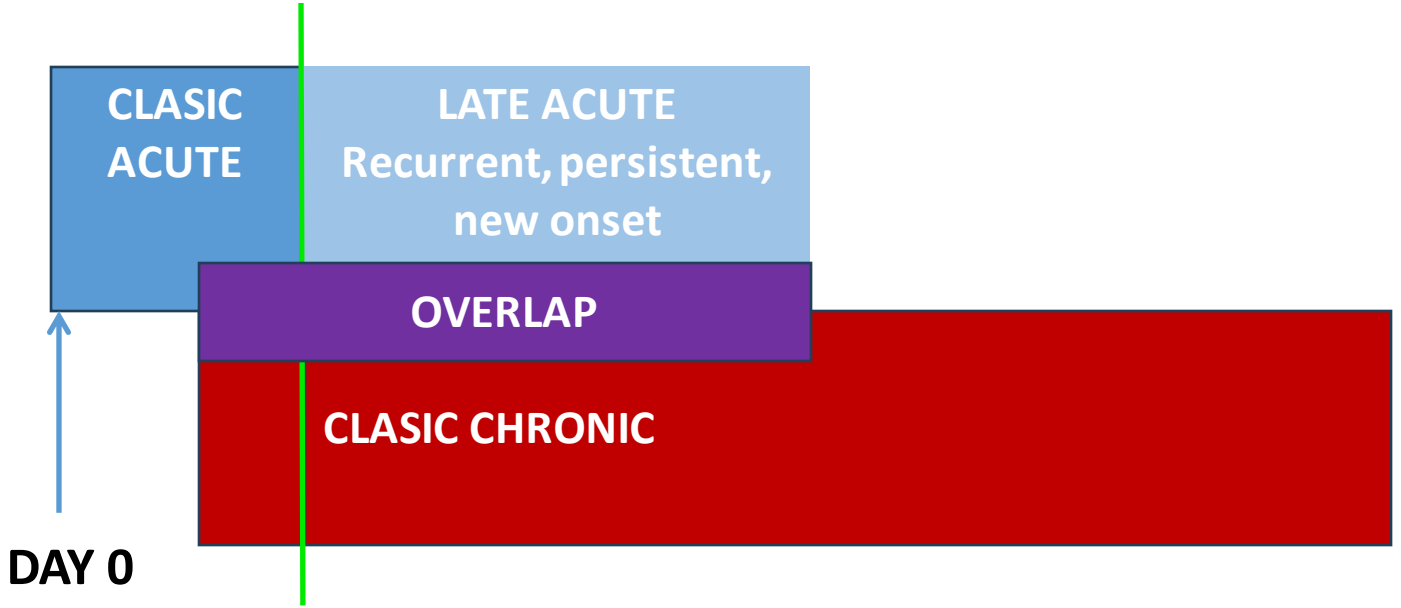
Host Target tissues

Courtesy of Dr. John DiPersio

Acute and Chronic GVHD

Acute GVHD

- Occurs early after transplant (4-8 weeks)
- Incidence ~30-50%
- Primarily affects: skin, gastro-intestinal system and liver
- Inflammatory process



Chronic GVHD

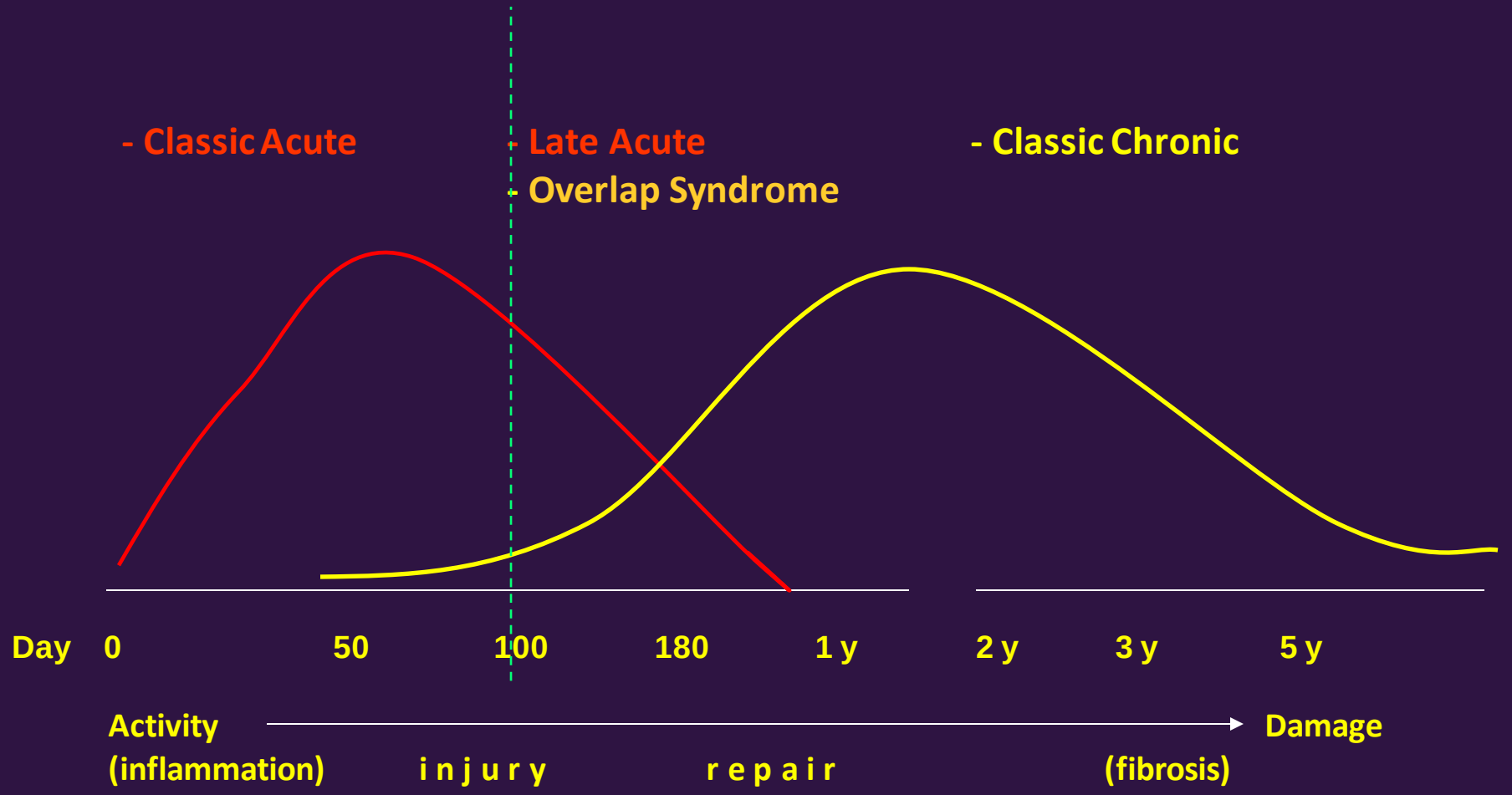
- Typically occurs 3+ months after transplant
- Incidence ~40-50%
- Can affect essentially any part of the body
- Systemic disease, resembles autoimmune disease, fibrosis/sclerosis

Adapted from: Lee S. Blood 2017;129(1):30-7.

Acute and Chronic GVHD

Acute GVHD: rash, GI, liver

Chronic GVHD: skin, eyes, mouth, GI, liver, musculoskeletal, lungs, genital

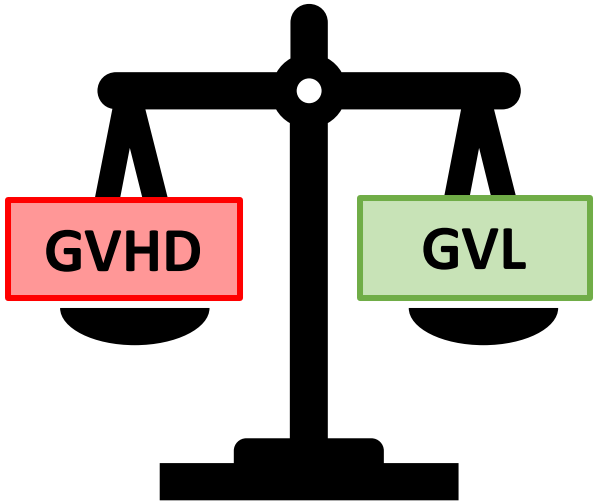


NCI Chronic GVHD Consortium

Acute GVHD	Chronic GVHD	
Skin	**Skin (+ Nails, Hair)**	**Joints and muscles**
• Sunburn-like rash • Blisters • Mouth sores, gingivitis	• Skin thickening • Rash • Itchy skin • Nail changes, Hair loss	• Pain, stiffness • Decreased range of motion • Cramps
Gastro-intestinal (GI) system	**Eyes**	**GI system**
• Loss of appetite • Persistent nausea • Vomiting • Diarrhea • Persistent belly pain • Blood in the stool	• Dry or teary eyes • Irritation, redness • Pain • Blurry vision	• Difficulty swallowing • Diarrhea • “Food gets stuck”
Liver	**Mouth**	**Genitals**
• Yellow tinge of eyes or skin • Dark, tea-colored urine • Belly pain • Swelling	• Redness, white streaks • Dry mouth • Sores, pain, sensitivity • Trouble opening mouth	• Irritation, dryness • Rash • Painful intercourse
	Lung	
	• Shortness of breath • Cough • Frequent infections	

GVHD

- **<u>Immune cells in the graft:</u>**
  - They can attack the recipient (host) → **GVHD**
  - They can destroy cancer cells → **graft-versus-leukemia (GVL) effect**
- GVHD can be eliminated by removing immune cells from the donor collection
- If you completely remove donor immune cells → increased risk of relapse



Chapter 1:

Prevention (Prophylaxis)

GVHD Prevention Strategies

Prevention starts before GVHD develops (around the time of transplant) !!

GVHD Prevention Strategies: Graft Manipulation

- **Selective removal of immune cells that are capable of causing GVHD (Naïve T-cells)**
- **Enhancing the graft with cells that might be of benefit (Regulatory T-cells)**

  - Naïve T-cell depletion
  - αβ T-cell depletion
  - CD34 cell selection
  - Graft engineering (ORCA-T, VOR33,…)

Bleakly M et al. JCO 2022;40(11):1174-85.
De Witte M et al. Blood Adv 2021.;5(1):240-248.
Oliai C et al. Blood 2023, Vol 142.

GVHD Prevention Strategies: Medications

- **Tacrolimus (Tacro) or Cyclosporine + Methotrexate (MTX); Tacro+MTX**
  - ± Mycophenolate Mofetil (MMF, CellCept®)
  - ± Anti-thymocyte Globulin (ATG)
  - Sirolimus

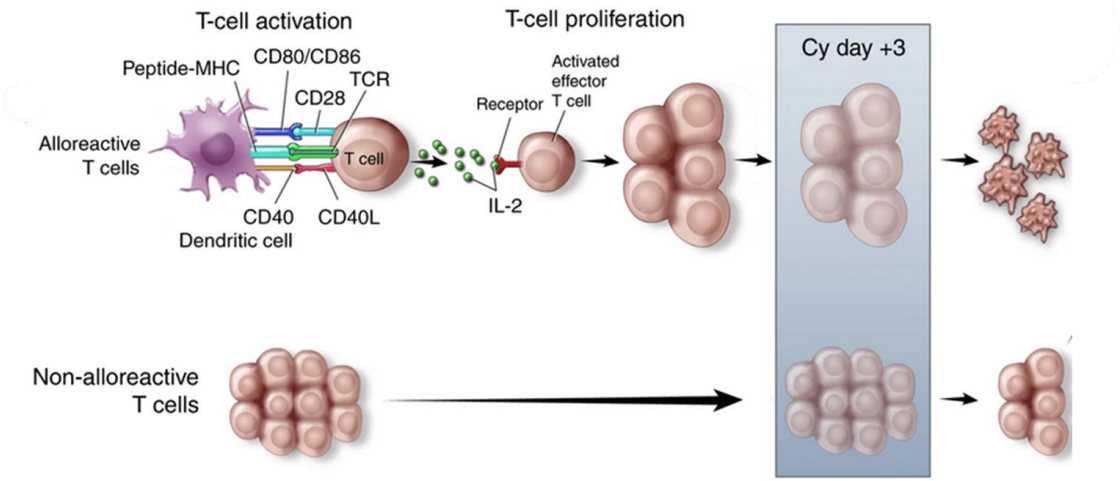
→ **Good immunosuppressive drugs**

→ **Side effects: hypertension, renal dysfunction, cardiovascular, abnormal hair growth, risk of infections, high cholesterol, …**

→ **Do not induce immune tolerance !**

GVHD Prevention Strategies: Medications

- **Post-transplant cyclophosphamide (PtCy) –** chemo, immunosuppressive
  - Initially used for haplo-identical transplants ("Haplo"= half-matched related)



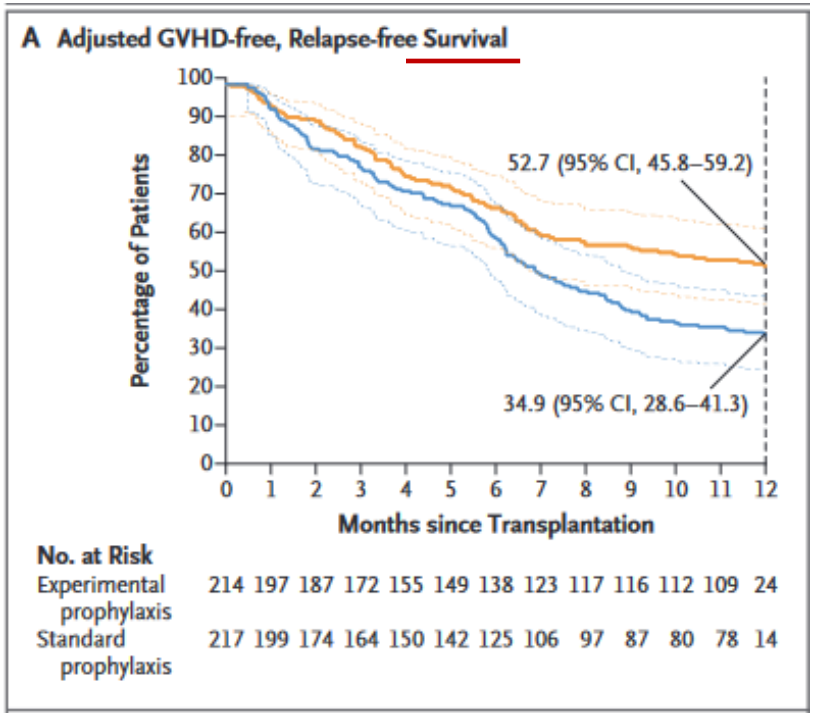
Alloreactive T-cells expand and are destroyed by PtCy

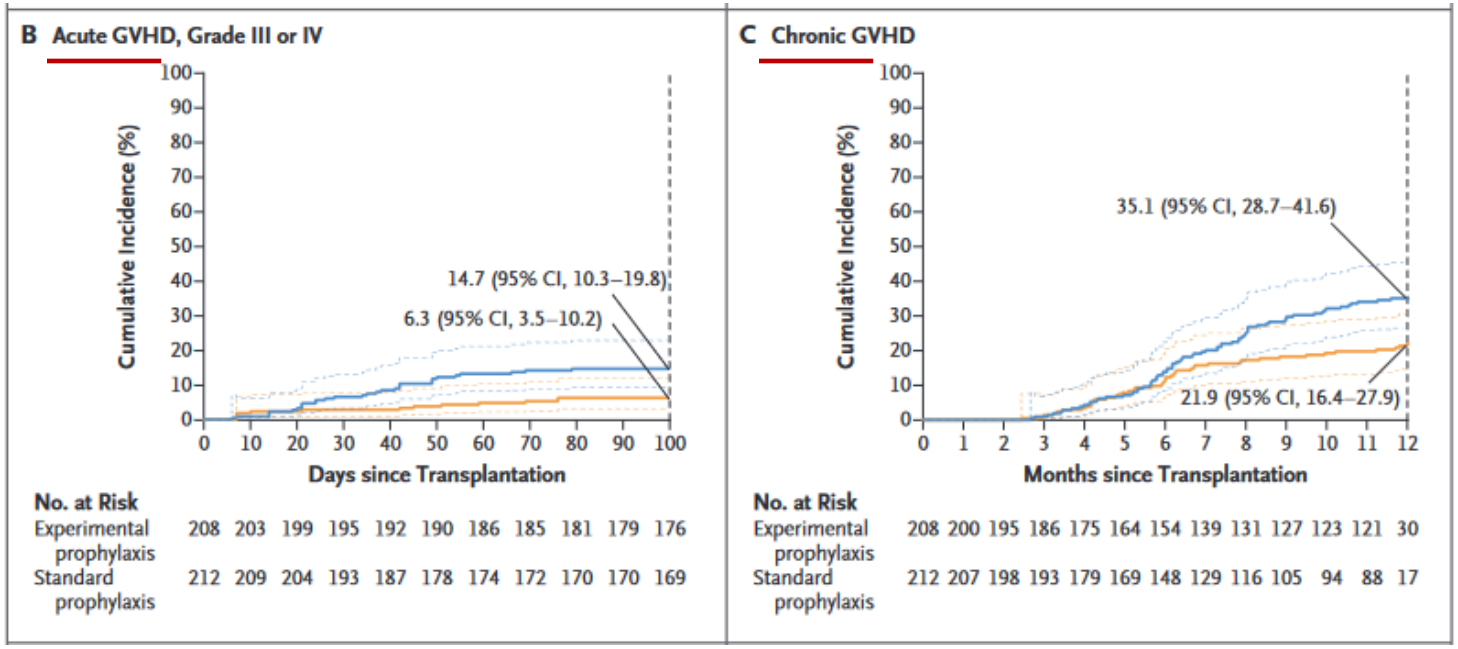
- **delayed immune reconstitution**
- **delayed count recovery**
- **cardiac toxicity**

GVHD Prevention Strategies: Medications

- **Post-transplant cyclophosphamide (PtCy) –** chemo, immunosuppressive

- **BMT CTN 1703** trial: reduced-intensity conditioning transplants from unrelated donors comparing **Tacro + MTX** with **PtCy + Tacro + MMF**





- **PtCy + Tacro + MMF is now part of the GVHD prophylaxis for unrelated donor transplants**

Experimental prophylaxis
Standard prophylaxis

Bolanos-Meade et al. NEJM 2023;388:2338-48.

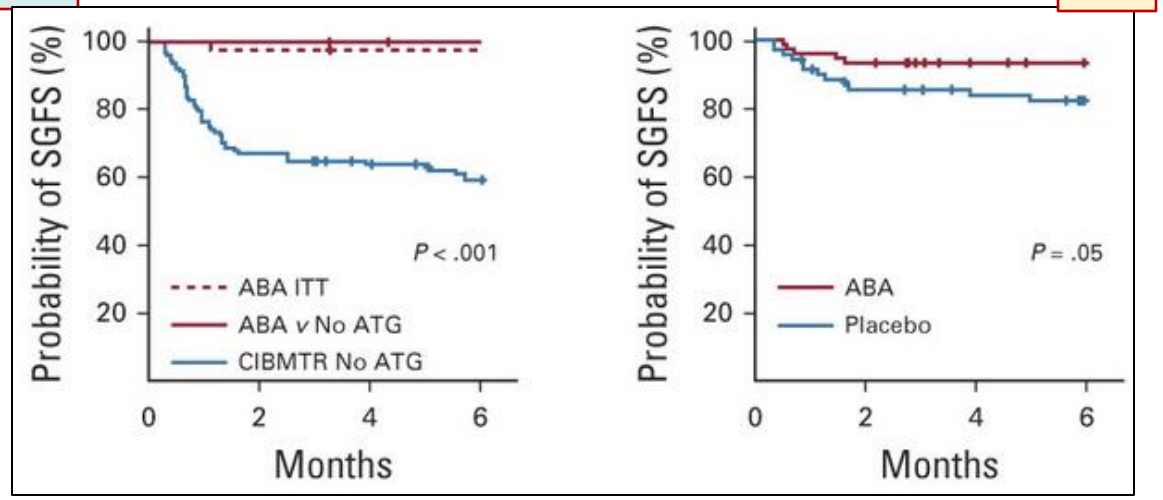
GVHD Prevention Strategies: Medications

- **Abatacept –** T-cell costimulation blocker
  - **Abatacept + Tacro + MTX**; in 7/8 and 8/8 matched unrelated donor transplants

7/8

Survival without severe acute GVHD

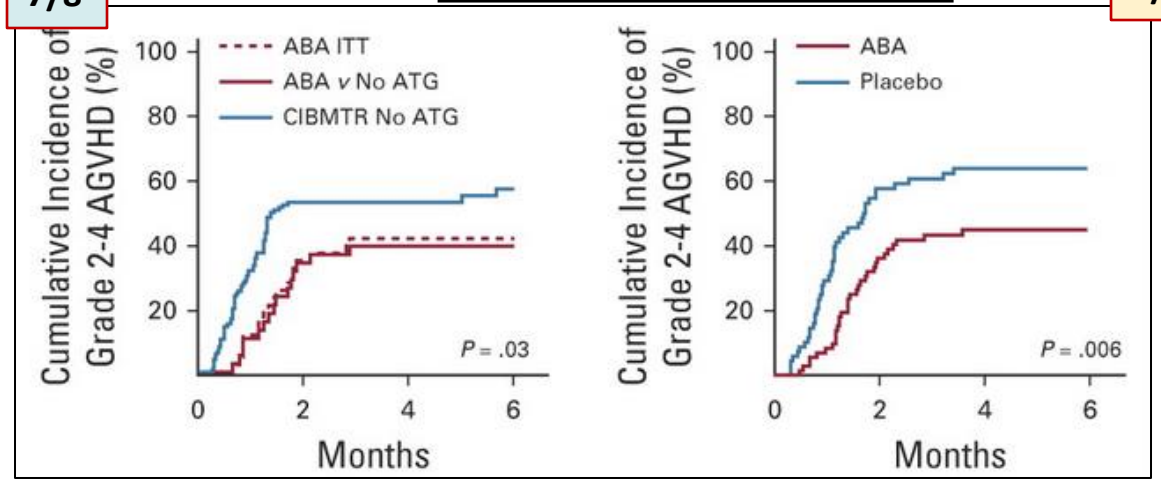
8/8



7/8

Grade II-IV acute GVHD

8/8



- **FDA approved Abatacept + Tacro + MTX for GVHD prophylaxis in 2021**

Watkins B et al. JCO 2021;39:1865-77.

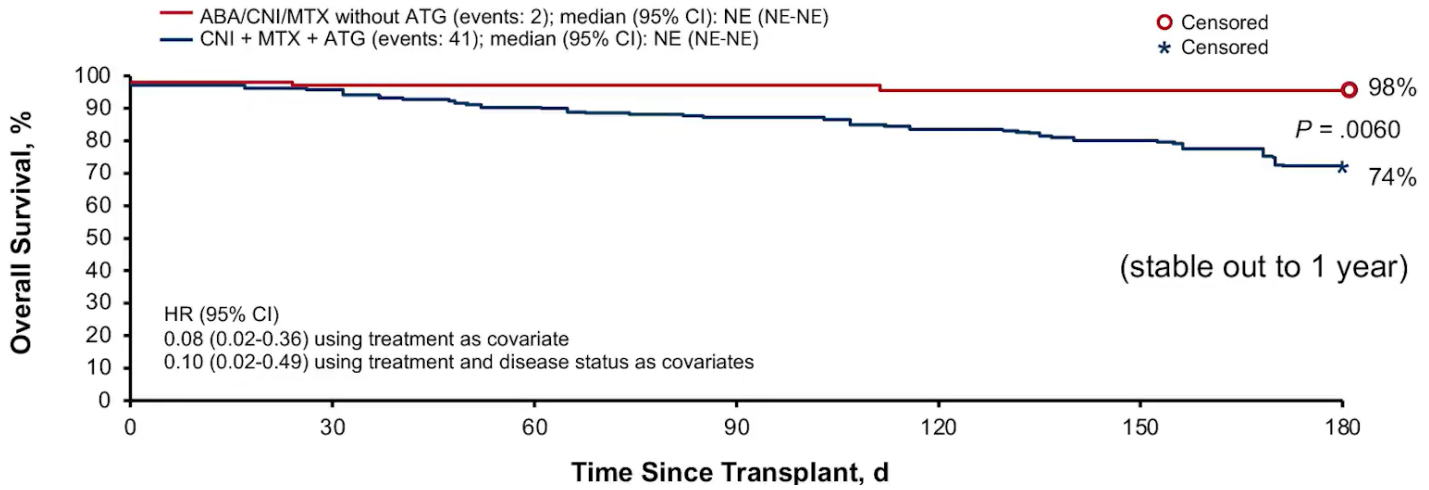
GVHD Prevention Strategies: Medications

~~ATG?~~

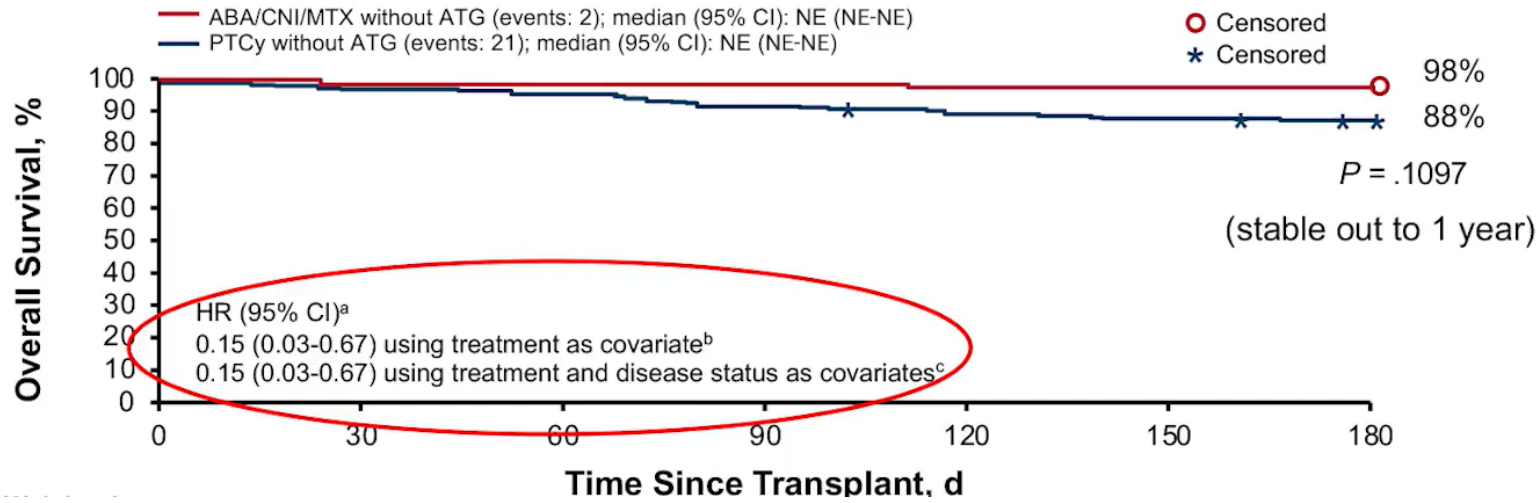
PtCy? ✓

Abatacept? ✓

7/8 Matched Unrelated Donors



More data still needed !



Kean L et al. ASH 2021; Abstract 3912.

GVHD Prevention Strategies

➢Clinical Trials

- Many ongoing trials testing various approaches and novel agents
- If your transplant institution has a clinical trial on GVHD prevention, consider participating !

Chapter 2:

Acute GVHD Treatment

Acute GVHD Treatment: 1st line therapy

➢Determined by the severity of acute GVHD

- **Mild skin GVHD (<50% body surface area involvement)**
  - Continue (adjusted for level) *or restart* prophylactic medications
  - Topical steroids for skin GVHD

Acute GVHD Treatment: 1st line therapy

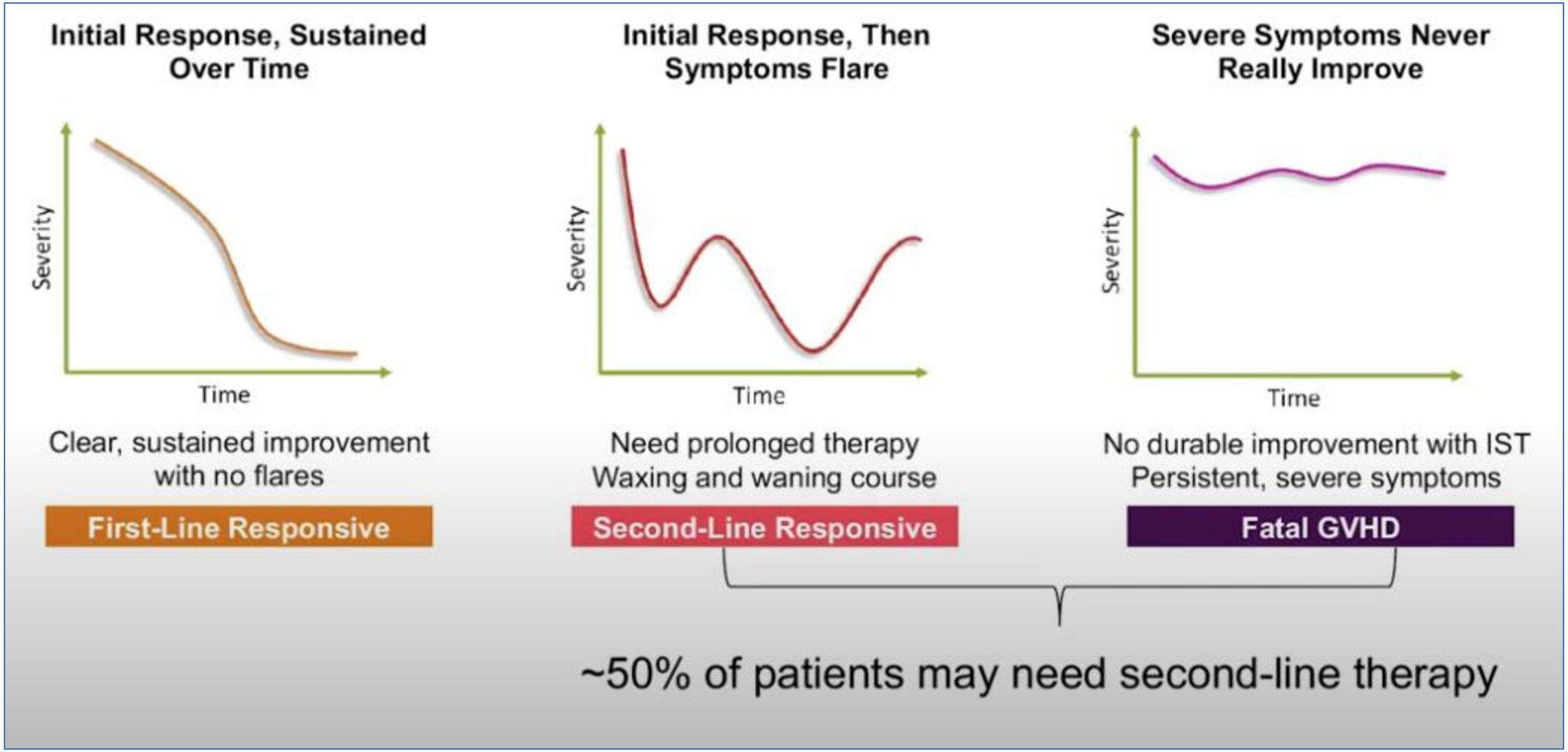
- **More severe skin acute GVHD ± gastrointestinal (GI) and/or liver acute GVHD**
  - Steroids (+ restart Tacrolimus/Cyclosporine)
  - Steroids + Sirolimus
  - Steroid-free approach (Sirolimus)
  - **Clinical trial (adding medications to steroids or without steroids)**

+ topical steroids
+ "non-absorbable" oral steroids beclomethasone/budesonide for GI GVHD

❖ Steroids

- Dose: 1-2 mg/kg/day, divided in 2 doses (higher doses not more effective but more toxic)
- If GVHD improving, decrease (taper) the dose
- **Side effects**:
  - Weight gain
  - Risk of infections
  - High blood sugar
  - High blood pressure
  - Mood swings
  - Cataracts
  - Osteoporosis, avascular necrosis

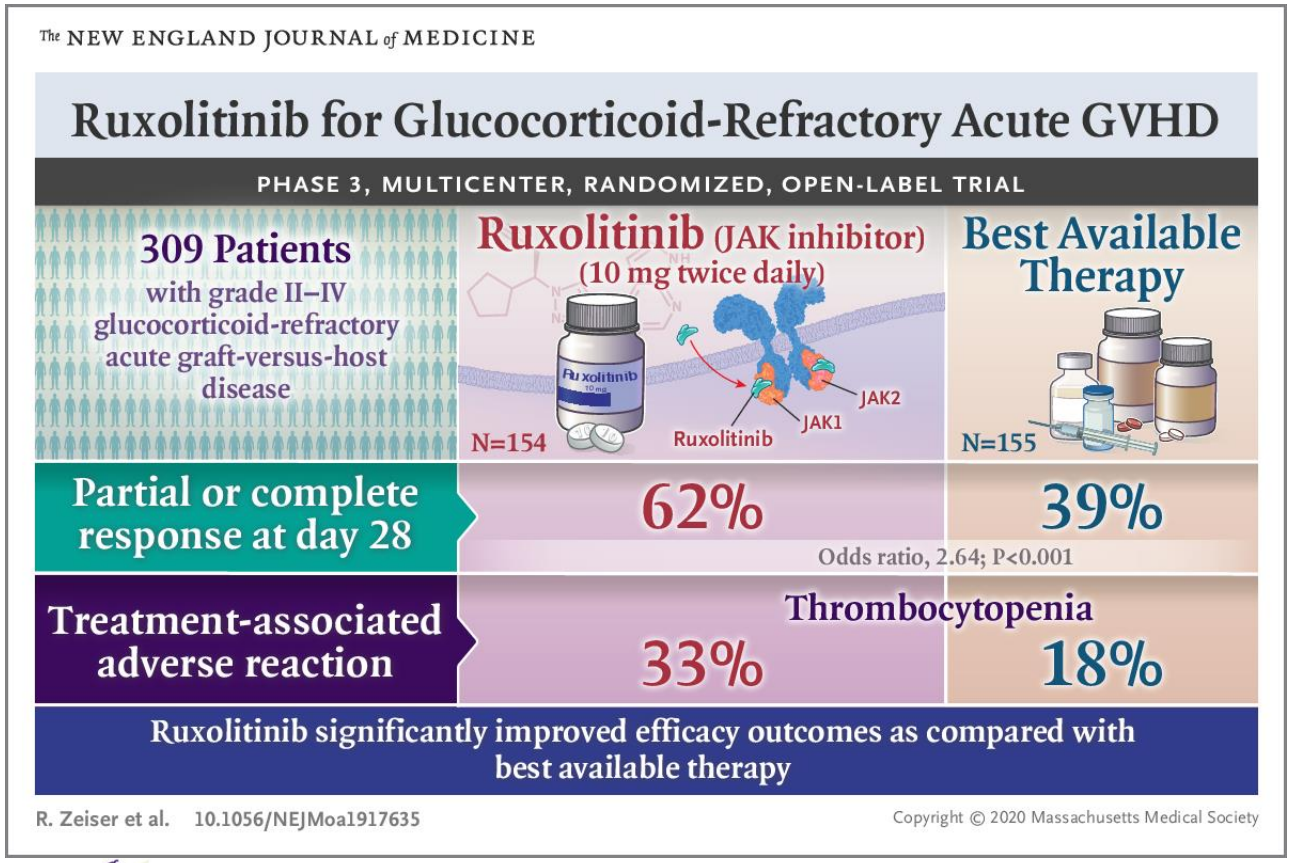
Acute GVHD Treatment: 1st line therapy



Newell LF, Holtan SG. Hem Am Soc Education Program 2021:642-47.

Acute GVHD Treatment: 2nd line therapy

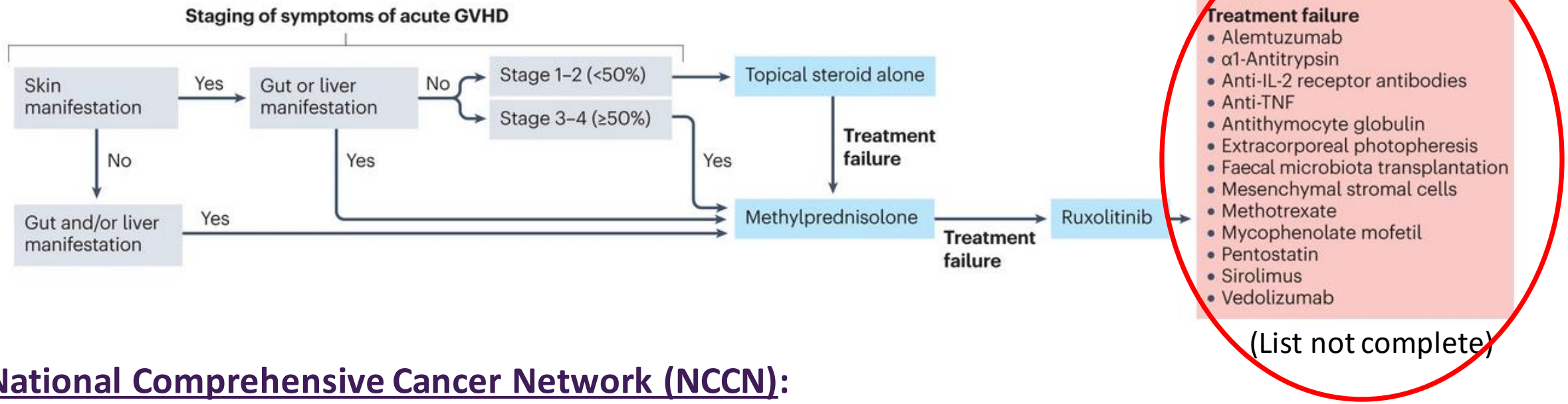
- **No response to steroids after 5-7 days or progression after 3 days**
- **Ruxolitinib (Jakafi®)** -- Oral, well-tolerated



FDA-approved in 2019

Zeiser R et al. NEJM 2020;385:1800-10.

Acute GVHD Treatment



(List not complete)

National Comprehensive Cancer Network (NCCN):
insufficient evidence to recommend one agent over another

Clinical trial:
clinicaltrials.gov

- Targeting cells involved in GVHD development
- Enhance tissue repair
- Avoid broad immunosuppression

Malard F et al. Nature Rev,2023,27:1-18.

Chapter 2:

Chronic GVHD Prevention

Chronic GvHD Prevention

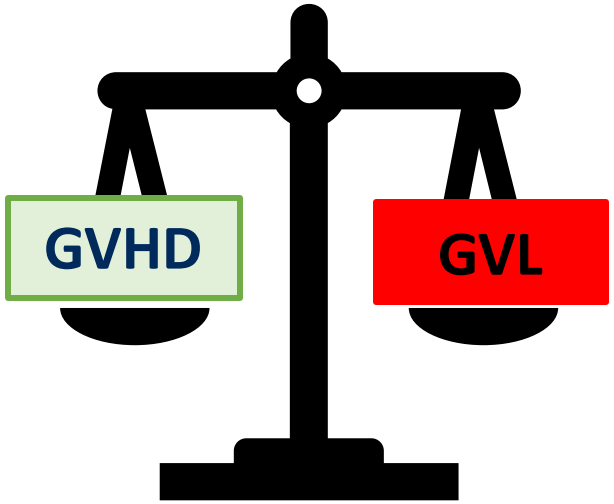
- **Process leading to chronic GVHD begins long before clinical manifestations of chronic GvHD develop**

  → Risk stratification to identify people at risk for developing chronic GvHD and intervene early

- **Balance the risks of chronic GvHD with risk of graft rejection, delayed recovery of immune system**

  → Develop targeted therapies that could prevent chronic GvHD without impairing immune recovery

➢ **An agent that could both prevent chronic GvHD and target tumor cells to decrease risk of relapse (GvL)**



Chapter 2:

Chronic GVHD Treatment

Chronic GvHD Treatment Goals

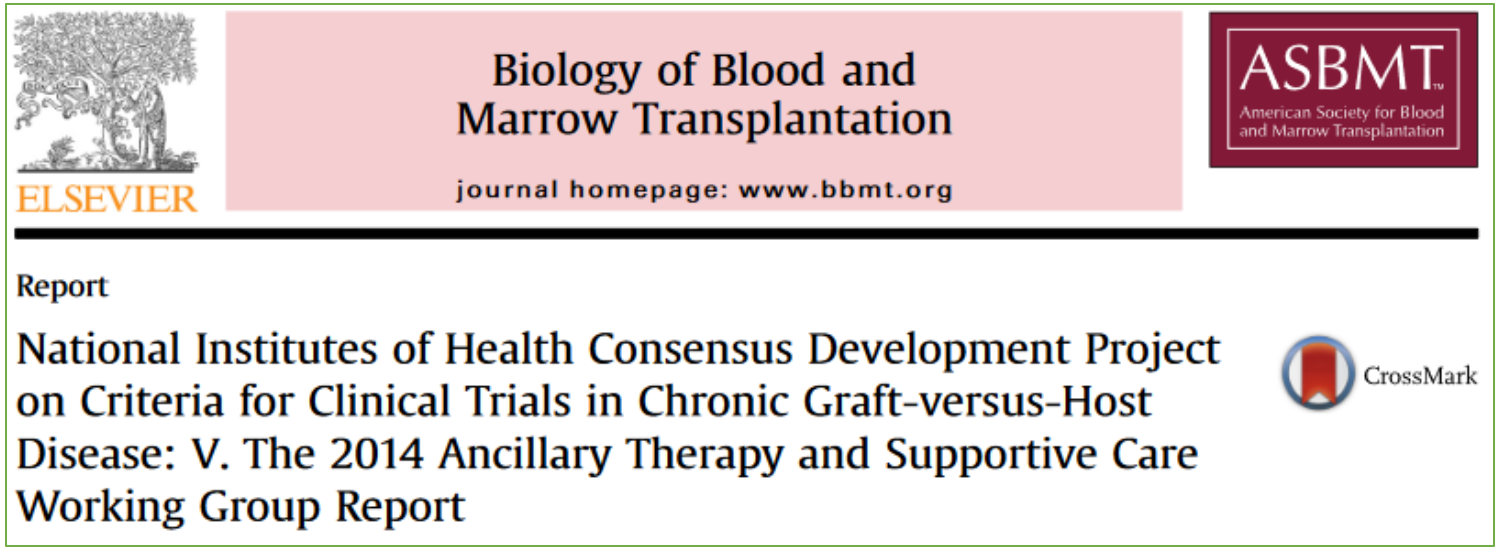
- Control signs and symptoms
- Prevent further progression and additional tissue/organ damage
- Maintain anti-leukemia/ anti-tumor effect (GVL)
- Achieve tolerance, stop immunosuppression
- Minimize treatment toxicity
- Decrease mortality and improve quality of life and survival

Chronic GVHD: 10 Questions

1. Does your **skin** feel tight or hard, new rash, increased dryness, pruritus, scaly?
2. Inability to **sweat** or keep body warm?
3. Loss of **hair** or **nail** changes?
4. Stiffness or pain in **joints** or limited range of motion, muscle cramps or pains?
5. **Eye** dryness, excessive tearing, do you use artificial tears, pain, punctate plugs?
6. **Oral** dryness, taste alterations, food sensitivity, ulcers, difficulty opening mouth?
7. Food or pills get stuck upon **swallowing**?
8. Cough, **shortness of breath** or wheezing?
9. **Vaginal** dryness, painful intercourse, itching, painful urination?
10. Unexplained **weight loss** or inability to gain weight, nausea, vomiting diarrhea, poor appetite?

Treatment Strategies for Chronic GVHD

- **Mild chronic GVHD → Local therapy**
  - Topical immunosuppressive therapies
  - Supportive care



https://www.sciencedirect.com/science/article/pii/S1083879115002244?via%3Dihub

Treatment Strategies for Chronic GVHD

- **Moderate and severe chronic GvHD → Systemic Immunosuppression**
  - 3 or more involved organs with mild involvement
  - At least one organ with moderate-severe involvement
- **1st line treatment:** Prednisone at 0.5-1 mg/kg/d
  - Continue for 1-2 weeks, then slowly taper over 4-8 weeks
  - **To date, additional agents at onset of chronic GVHD: not shown to be beneficial**
  - Complete response rate: ~50%

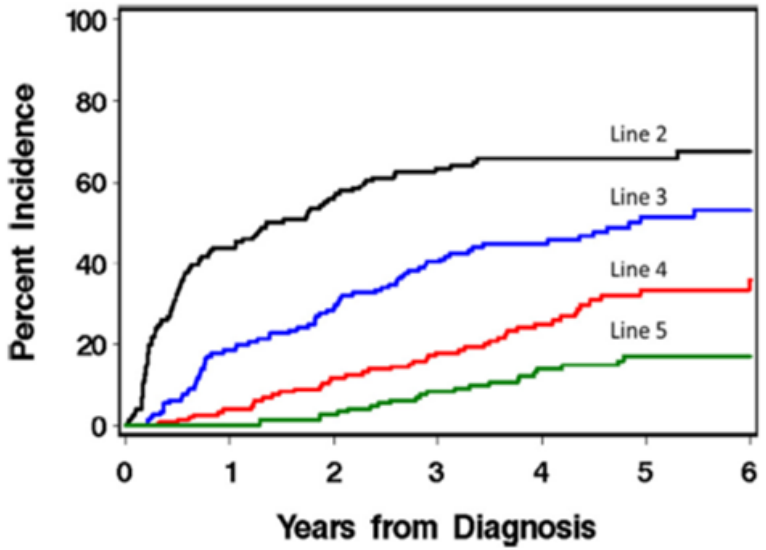
➢ Clinical Trials

- **Testing agents approved for refractory GVHD as a 1st line therapy**
  - Steroid-free approaches
  - Randomized trials comparing different therapies ± steroids

Carpenter PA et al. BBMT. 2015;21:1167-1187.
Sarantopoulos S et al. Blood. 2019;133:1191-1200.
Pidala J et al. Blood 2020;13592):97-107.

Indications for Secondary Therapies for Chronic GvHD

- Progression or no improvement on previous therapy
- Inability to taper prednisone below 1 mg/kg/day without worsening
- Toxicity
- Insurance issues
- New trial



- **The chance that a person starting 1st line systemic therapy will never need additional therapy was ~20%**
- **After stopping therapy for the first time, ~50% of people restarted therapy at a median 3.4 months**

Lee S. BBMT 2018,24(3):555-562.

➢ Management of chronic GVHD beyond initial therapy has been very much a trial and error !

➢ **Should I change therapy? How?**

- increase doses, add new agents, study??

➢ **How do we choose?**

➢ **No consensus**

- Physician/center experience
- Clinical efficacy
- Toxicity profile
- Mode of delivery, ease of use
- Patient compliance
- Cost
- Availability of a study

NCCN guidelines:

Chronic GVHD

While the following systemic agents may be used in any site, some agents are used more commonly in certain sites based on available data (see Discussion).

- **Ruxolitinib (category 1)[b,22-24]**
- **Abatacept[25]**
- **Alemtuzumab[26,27]**
- **Belumosudil[e,28]**
- **CNIs (eg, tacrolimus, cyclosporine)**
- **Etanercept[29]**
- **ECP[c,9]**
- **Hydroxychloroquine[30]**
- **Ibrutinib[f,31]**
- **Imatinib[32,33]**
- **Interleukin-2 (IL-2)[34]**
- **Low-dose methotrexate[35-37]**
- **mTOR inhibitors (eg, sirolimus)[38-40]**
- **Mycophenolate mofetil[41]**
- **Pentostatin[42-44]**
- **Rituximab[g,45]**

Secondary Therapies for Chronic GvHD in 2024

- **3 FDA-approved agents:**
  - **Ibrutinib (Feb 2017)**
    - **Second-line therapy**
  - **Belumosudil (July 2021)**
    - **Third-line therapy**
  - **Ruxolitinib (Sept 2021)**
    - **Second-line therapy**

Based on open label, non-blinded trials (only ruxolitinib had comparator arm)

Secondary Therapies for Chronic GvHD in 2024

	Ibrutinib	Ruxolitinib	Belumosudil	*Axatilimab*
Formulation	Pill, once a day	Pill, twice (once) a day	Pill, once - twice a day	*I.V., every 2-4 weeks*
Prior use ?	Yes; leukemia and lymphoma	Yes; myelofibrosis and Polycythemia Vera	New	*New*
How does it work ?	*BTK inhibitor*; Blocks B and T cell; Anti-inflammatory	*JAK inhibitor*; Modulates immune system	*ROCK2 inhibitor;* Modulates immune system; Anti-fibrosis	*CSF-1R blocker; Anti-macrophage*
Best overall response	**67 %**	**76 %**	**74-77 %**	***74 %***
		Compared with Best Available Therapy	Responses in people who progressed on ibrutinib and ruxolitinib	*Responses in people who progressed on ibrutinib, ruxolitinib and belumosudil*

➢ How do I choose or change therapy for chronic GvHD in the era of novel medications ?

- **Ibrutinib, belumosudil, ruxolitinib, (axatilimab) are FDA-approved → <u>What is standard of care?</u>**
- **Much more experience needed during post-approval phase**
  - Is one agent better than other for some specific GVHD manifestations?
    - Ibrutinib for oral and skin erythema (early cGvHD); ruxolitinib for fascia/joint; belumosudil for fibrosis
  - In what order we use them? (belumosudil approved as 3rd line)
  - How do we switch among them?
  - Can we combine them to maximize the likelihood of successful outcome (+/- steroids) ?
  - Tapering schedule and duration of therapy?
  - Rate of infections?
  - Cost !! (need for adequate Patient Assistance Programs)

➢ **Need to generate more evidence**

➢ **Clinical trials !**

How do I choose or change therapy for chronic GvHD in the era of novel medications ?

- **Chronic GvHD is <u>CHRONIC</u> immune disorder**
- **Should we strive to permanently taper off systemic immunosuppression? Is that the measure of "success"?**
  - Possible in only ~ 1/3 patients
- **Develop therapeutic approaches that will be well tolerated as a maintenance long-term**
  - **Success** = arrested progression of chronic GVHD, improve physical functioning and quality of life

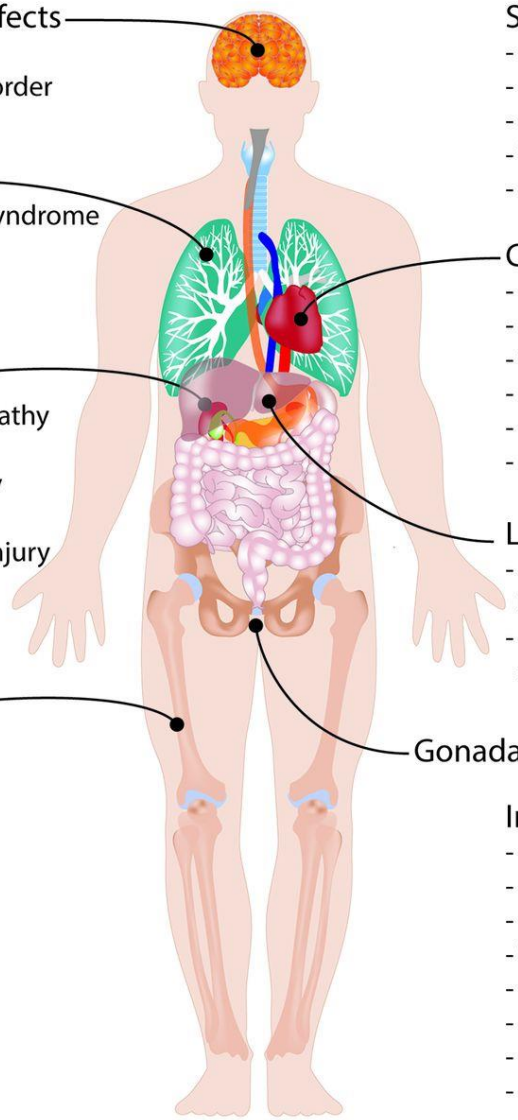
➢ **<u>Personalized and more biologically relevant</u> approaches (biomarkers!)**

➢ **Testing agents at earlier stages of chronic GVHD**

Gandelman J et al. Haemalologica. 2019;104(1):189-96
Pavletic, SZ and Schultz, KR. Haematologica. 2022;May 26; PMID: 35615928

Late Effects After Transplantation

Transplant survivors, particularly those with chronic GVHD, are 3x more likely to have 2 or more chronic health care conditions



Neuropsychological effects
- Depression, anxiety
- Post-traumatic stress disorder
- Neurocognitive deficits

Pulmonary diseases
- Bronchiolitis obliterans syndrome
- Cryptogenic organizing pneumonia
- Pulmonary hypertension

Kidney diseases
- Thrombotic microangiopathy
- Nephrotic syndrome
- Idiopathic chronic kidney disease
- Persistent acute kidney injury
- BK virus nephropathy

Iron overload

Bone diseases
- Osteopenia
- Osteoporosis
- Avascular necrosis

Endocrine diseases
- Thyroid dysfunction
- Gonadal dysfunction
- Diabetes
- Dyslipidemia
- Metabolic syndrome
- Adrenal insufficiency

Solid cancer
- Oral cavity
- Skin
- Breast
- Thyroid
- Other sites

Cardiovascular diseases
- Cardiomyopathy
- Congestive heart failure
- Valvar dysfunction
- Arrhythmia
- Pericarditis
- Coronary artery disease

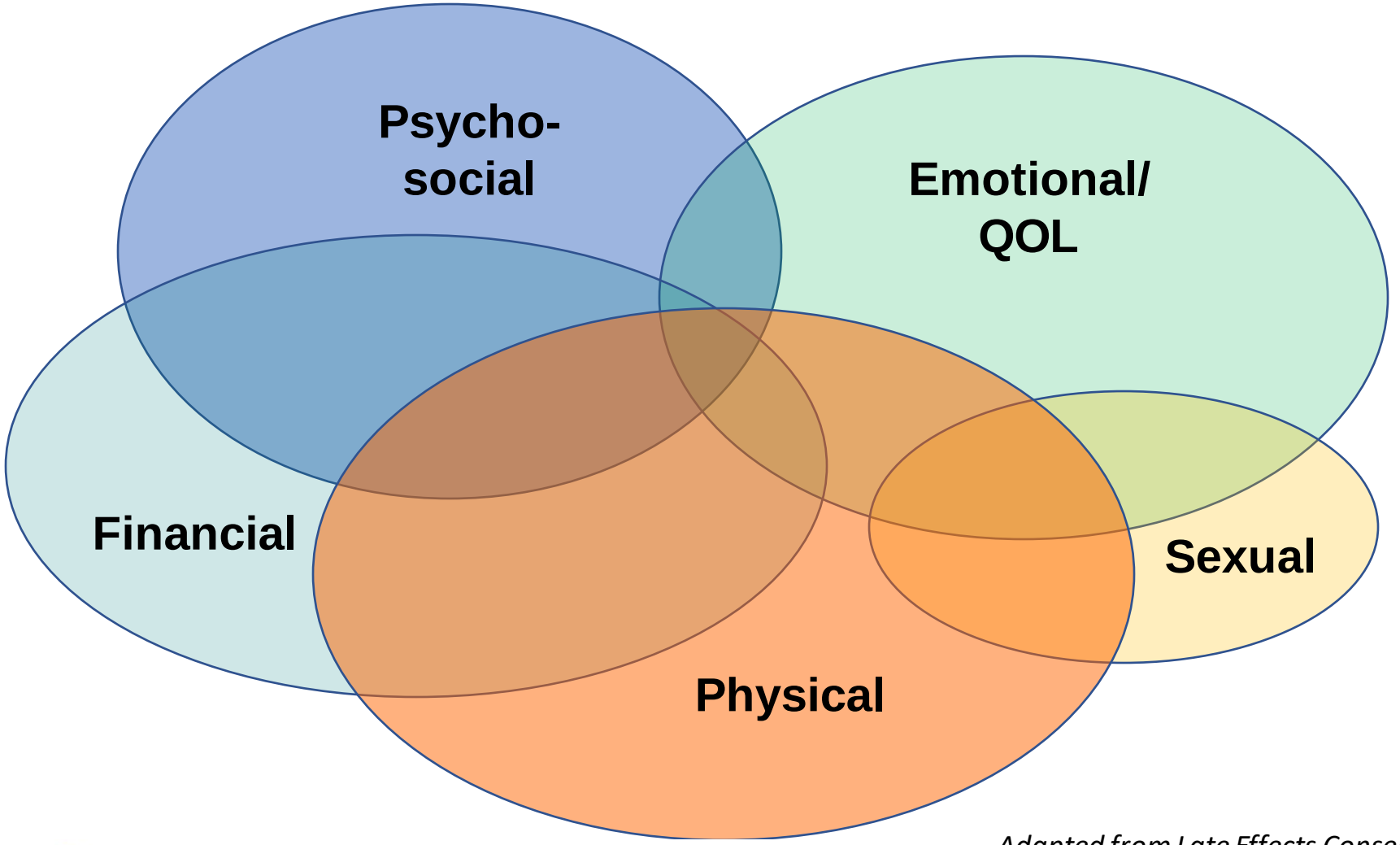
Liver diseases
- Hepatitis B, Hepatitis C, liver cirrhosis
- Nodular regenerative/focal nodular hyperplasia

Gonadal dysfunction/infertility

Infectious diseases
- *Pneumocystis jirovecci*
- Encapsulated bacteria
- Fungi
- Varicella-zoster virus
- Cytomegalovirus
- Respiratory syncytial virus
- Influenza virus
- Parainfluenza virus

Inamoto J et al. Haematologica 2017;102:614-625.
Arora M et al. Blod 2017;130 (Supplement 1)

Impact of chronic GvHD multiple domains of health



Adapted from Late Effects Consensus Conference 2014

Impact of chronic GvHD multiple domains of health

- **Management of chronic GVHD requires multidisciplinary team**
  - **Assessment and treat**

- Cardiovas
- Pulmon
- Derma
- Musc
- Opht
- Oral/
- Endoc
- Renal

- Vaccinatio
- Screening for s
- Assessment for recurre

cial worker
Financial team

Empower people to actively participate in their care

Conclusions

- With our improved understanding of how GvHD happen, it is now possible to develop new approaches for GvHD prophylaxis and treatment
  - **We still need**:
    - Pre-clinical research (better animal models)
    - Clinical trials (+ testing biomarkers)
- Aim is to develop **more effective, less toxic and more targeted** medications for GvHD
- Safer strategies to prevent and treat GvHD will expand applicability of allogeneic transplantation to older people

Stakeholders

- **Patient and caregivers**
- **Physicians** (academic medical center, community)
- **Research**
- **Industry**
- **Regulatory agencies** (drug approval)
- **Payer** (financial resources; lack of optimal payment models)

➢ **Effective partnership is needed for progress in developing new GvHD therapies !!**

Questions?

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Washington University School of Medicine

Let Us Know How We Can Help You

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