



# Advances in the Treatment of Graft-versus-Host Disease (GVHD)

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# Learning Objectives

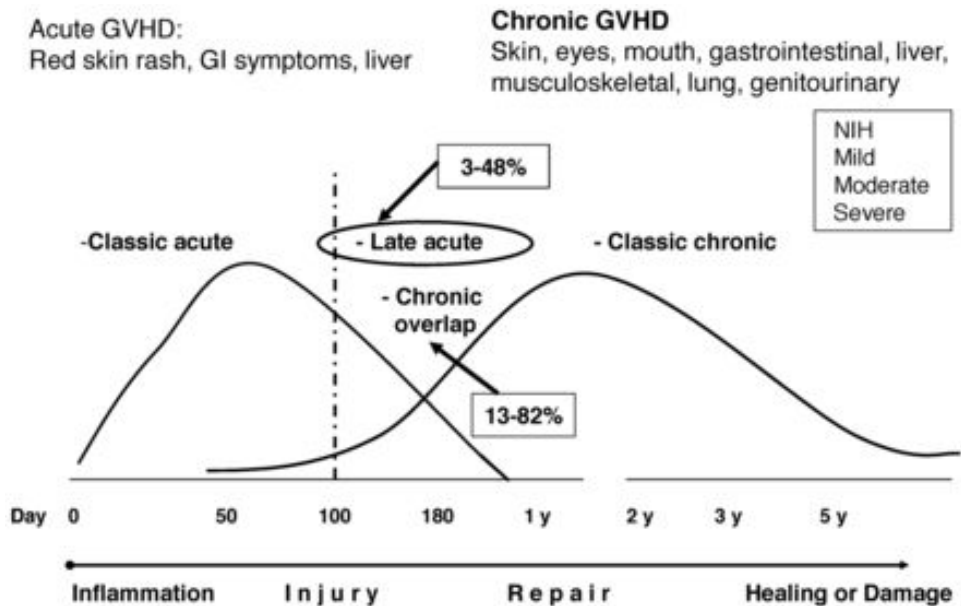
- There are 3 FDA-approved agents for chronic GVHD
- Many clinical trials are ongoing evaluating additional treatments and clinical settings
- Talk with your physician about opportunities for clinical trials

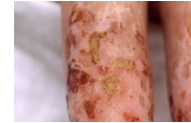
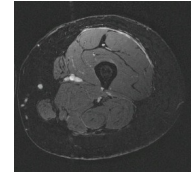
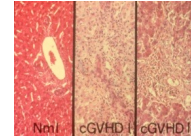
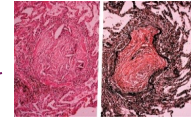
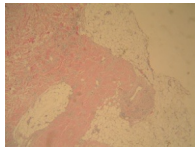
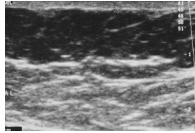
# Chronic GVHD

- Multi-organ disorder with immune dysregulation, inflammation and fibrosis, immunodeficiency, and impaired organ function
- Incidence of chronic GVHD is 30-70%
- Symptoms usually present within 1-3 years after HCT (median 4-6 months)

# Chronic GVHD

- Clinical manifestations (vs time after transplant) determine whether clinical GVHD is acute, chronic, or both (overlap)

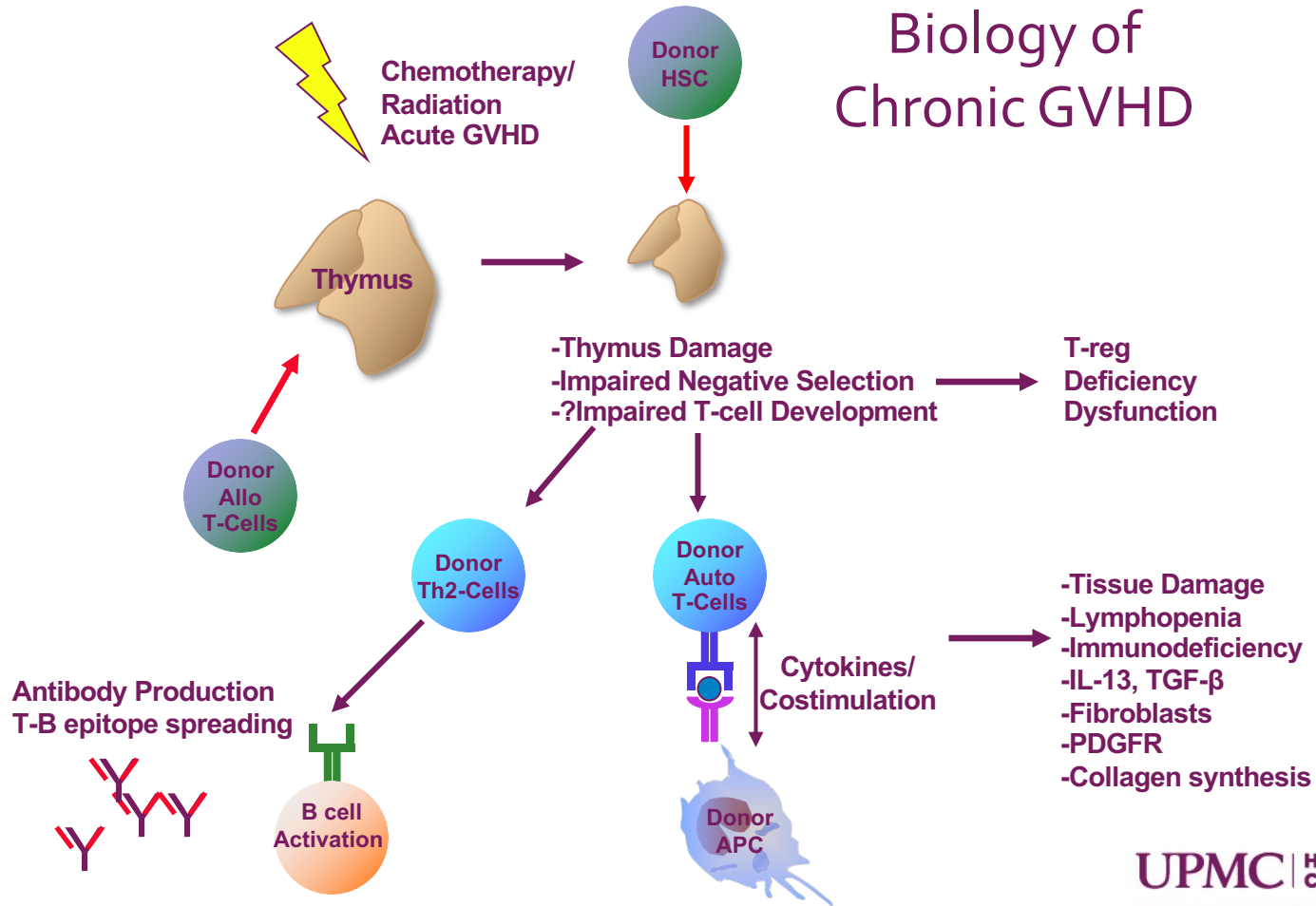




## Spectrum of manifestations In cGVHD

- 50% Incidence
- 15% Life Threatening

# Biology of Chronic GVHD



## NIH Consensus Development Project 2005, 2014

- Goal: To develop standardized criteria and guidelines for
  - I. Diagnosis and staging
  - II. Pathology
  - III. Biomarkers
  - IV. Response criteria
  - V. Ancillary therapy/supportive care
  - VI. Clinical trial design
- Standardized how we define and approach chronic GVHD



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## Biology of Blood and Marrow Transplantation

journal homepage: [www.bbmt.org](http://www.bbmt.org)



Report

### National Institutes of Health Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-versus-Host Disease:



#### I. The 2014 Diagnosis and Staging Working Group Report

Madan H. Jagasia<sup>1</sup>, Hildegard T. Greinix<sup>2</sup>, Mukta Arora<sup>3</sup>, Kirsten M. Williams<sup>4,5</sup>, Daniel Wolff<sup>6</sup>, Edward W. Cowen<sup>4</sup>, Jeanne Palmer<sup>7</sup>, Daniel Weisdorf<sup>3</sup>, Nathaniel S. Treister<sup>8</sup>, Guang-Shing Cheng<sup>9</sup>, Holly Kerr<sup>10</sup>, Pamela Stratton<sup>11</sup>, Rafael F. Duarte<sup>12</sup>, George B. McDonald<sup>9</sup>, Yoshihiro Inamoto<sup>13</sup>, Afonso Vigorito<sup>14</sup>, Sally Arai<sup>15</sup>, Manuel B. Datile<sup>16</sup>, David Jacobsohn<sup>5</sup>, Theo Heller<sup>17</sup>, Carrie L. Kitko<sup>18</sup>, Sandra A. Mitchell<sup>19</sup>, Paul J. Martin<sup>9</sup>, Howard Shulman<sup>9</sup>, Roy S. Wu<sup>20</sup>, Corey S. Cutler<sup>21</sup>, Georgia B. Vogelsang<sup>22</sup>, Stephanie J. Lee<sup>9</sup>, Steven Z. Pavletic<sup>4</sup>, Mary E.D. Flowers<sup>9,\*</sup>



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Report

### National Institutes of Health Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-versus-Host Disease:



#### V. The 2014 Ancillary Therapy and Supportive Care Working Group Report

Paul A. Carpenter<sup>1,\*</sup>, Carrie L. Kitko<sup>2</sup>, Sharon Elad<sup>3</sup>, Mary E.D. Flowers<sup>1</sup>, Juan C. Gea-Banadoche<sup>4</sup>, Jörg P. Halter<sup>5</sup>, Flora Hoodin<sup>6</sup>, Laura Johnston<sup>7</sup>, Anita Lawitschka<sup>8</sup>, George B. McDonald<sup>1</sup>, Anthony W. Opipari<sup>9</sup>, Bipin N. Savani<sup>10</sup>, Kirk R. Schultz<sup>11</sup>, Sean R. Smith<sup>12</sup>, Karen L. Syrjala<sup>1</sup>, Nathaniel Treister<sup>13</sup>, Georgia B. Vogelsang<sup>14</sup>, Kirsten M. Williams<sup>4</sup>, Steven Z. Pavletic<sup>4</sup>, Paul J. Martin<sup>1</sup>, Stephanie J. Lee<sup>1</sup>, Daniel R. Couriel<sup>2</sup>

# NIH Chronic GVHD Consensus Project 2020

- Focus on next steps in the field
  - I. Prevention
  - II. Early diagnosis
  - III. Treatment
  - IV. Highly morbid forms

# Treatment goals in chronic GVHD

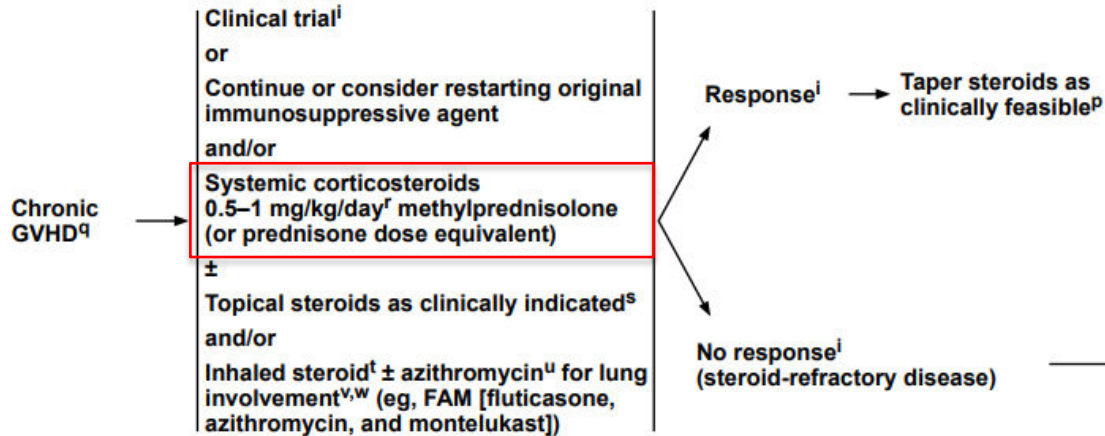
- Improve survival
- Improvement or stabilization of organ manifestations
- Reduce symptom burden and improve quality of life
- Limit long term treatment-related toxicities

→ Median duration of treatment is 2-3 years; 15% require long term immunosuppression

# NCCN recommendations for treatment of chronic GVHD

## MANAGEMENT OF CHRONIC GVHD

### FIRST-LINE THERAPY



### ADDITIONAL THERAPY

Clinical trial<sup>j</sup>  
or  
Addition of systemic agent to corticosteroids with steroid taper as clinically feasible<sup>p</sup>  
[See Suggested Systemic Agents for Steroid-Refractory GVHD \(GVHD-E\)](#)

# NCCN recommendations for treatment of chronic GVHD

## SUGGESTED SYSTEMIC AGENTS FOR STEROID-REFRACTORY GVHD

- Participation in clinical trials is encouraged.
- The following systemic agents are used in conjunction with corticosteroids for steroid-refractory GVHD. There is insufficient evidence to recommend one systemic agent as preferred over another. However, these are the most commonly used agents among the NCCN Member Institutions.
- The selection of systemic agent should be based on institutional preferences, physician experience, agent's toxicity profile, the effect of prior treatment, drug interactions, convenience/accessibility, and patient tolerability.

### Suggested Systemic Agents for Steroid-Refractory GVHD<sup>a</sup> (listed in alphabetical order, except for category 1)

#### Acute GVHD<sup>1</sup>

*The following agents are often used in conjunction with the original immunosuppressive agent.*

- Ruxolitinib (category 1)<sup>b,2</sup>
- Alemtuzumab<sup>3,4</sup>
- Alpha-1 antitrypsin<sup>5</sup>
- ATG<sup>6</sup>
- Basiliximab<sup>7</sup>
- CNIs (eg, tacrolimus, cyclosporine)
- Etanercept<sup>8</sup>
- Extracorporeal photopheresis (ECP)<sup>c,9</sup>
- Infliximab<sup>10</sup>
- mTOR inhibitors (eg, sirolimus)<sup>11,12</sup>
- Mycophenolate mofetil<sup>13,14</sup>
- Pentostatin<sup>15-17</sup>
- Tocilizumab<sup>d,18-21</sup>

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

# FDA-approved drugs for chronic GVHD (all since 2017!)

## Ruxolitinib

- chronic GVHD after failure of **1 or 2 lines** of therapy
- age 12 and above

## Ibrutinib

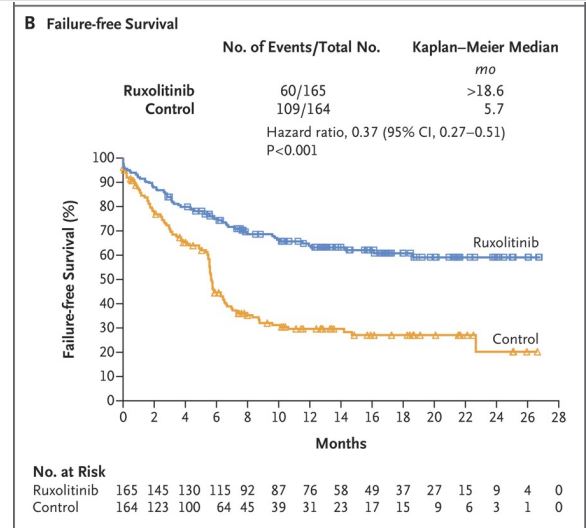
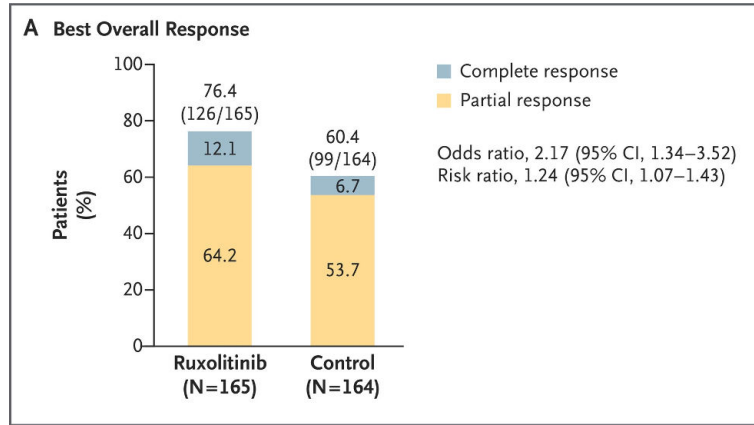
- chronic GVHD after failure of **1 or more lines** of therapy
- age 1 and above

## Belumosudil

- chronic GVHD after failure of **at least 2 prior lines** of therapy
- age 12 and above

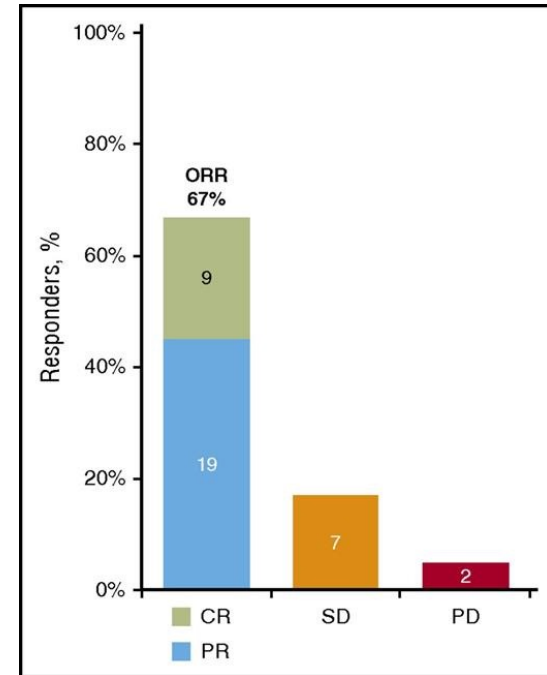
# Ruxolitinib: JAK<sub>1/2</sub> inhibitor

- REACH3 Trial: Randomized, controlled trial of rux vs. best available therapy in steroid-refractory/dependent chronic GVHD
- Overall response rate at 6 months: 50% vs 25%
- Responses across all organs
- Toxicities: thrombocytopenia, anemia



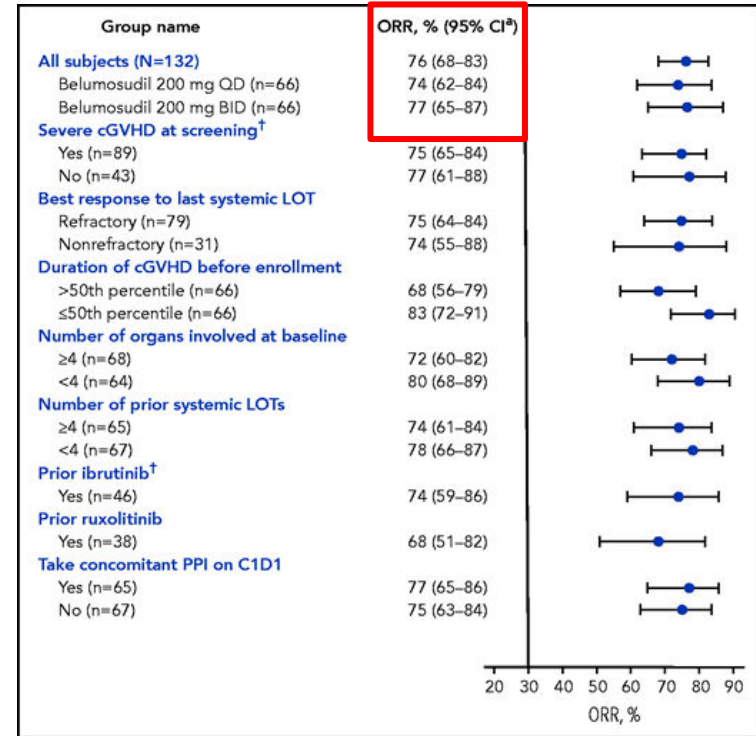
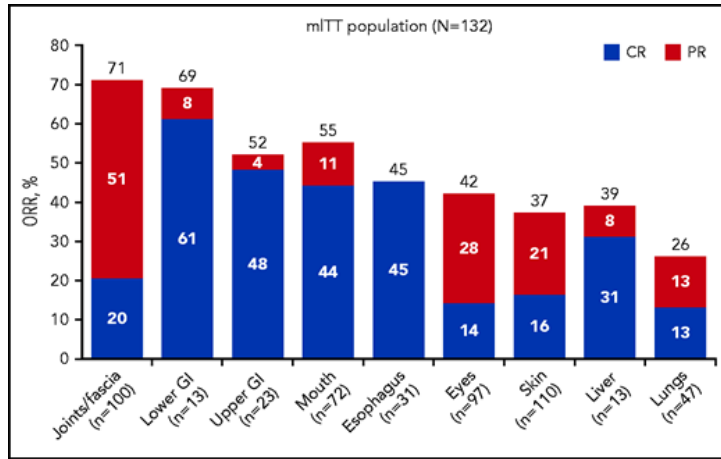
# Ibrutinib: BTK/ITK inhibitor

- Phase 1b/2 trial of ibrutinib in steroid-refractory or dependent chronic GVHD, with skin erythema or severe oral involvement
- Skin, Mouth, GI ORR were ~90%
- Toxicities: fatigue, diarrhea, pneumonia

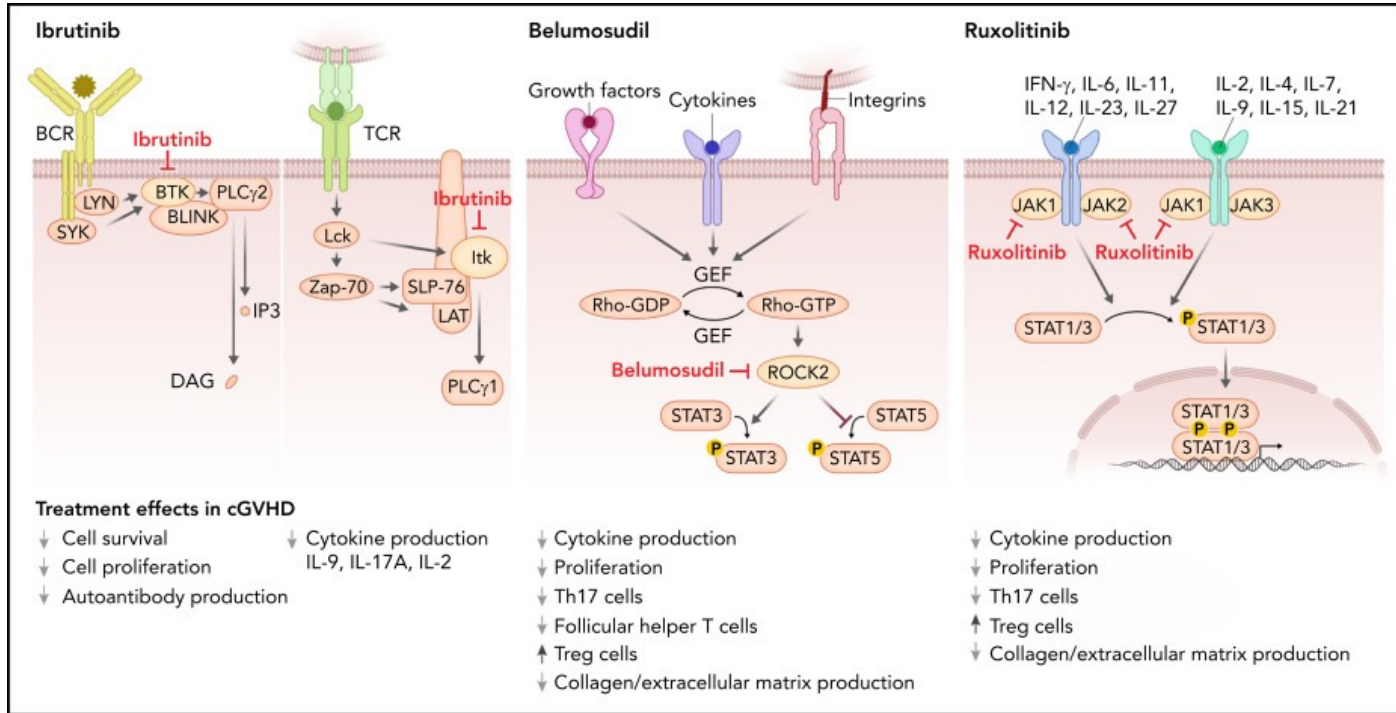


# Belumosudil: ROCK<sub>2</sub> inhibitor

- ROCKSTAR Study: Phase 2 trial of belumosudil in chronic GVHD after  $\geq 2$  prior lines of therapy
- Toxicities:  $\uparrow$ LFTs, HTN,  $\uparrow$ glucose, pneumonia

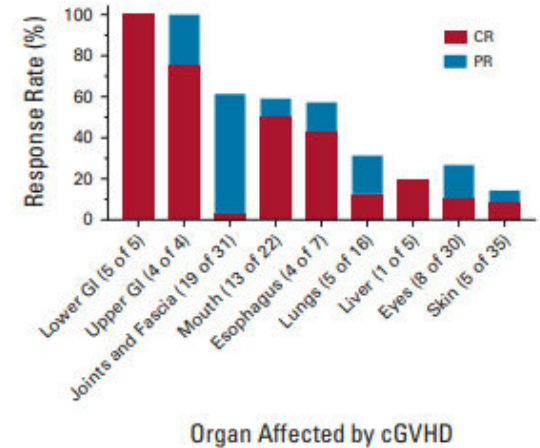


# Mechanism of action of 3 approved drugs

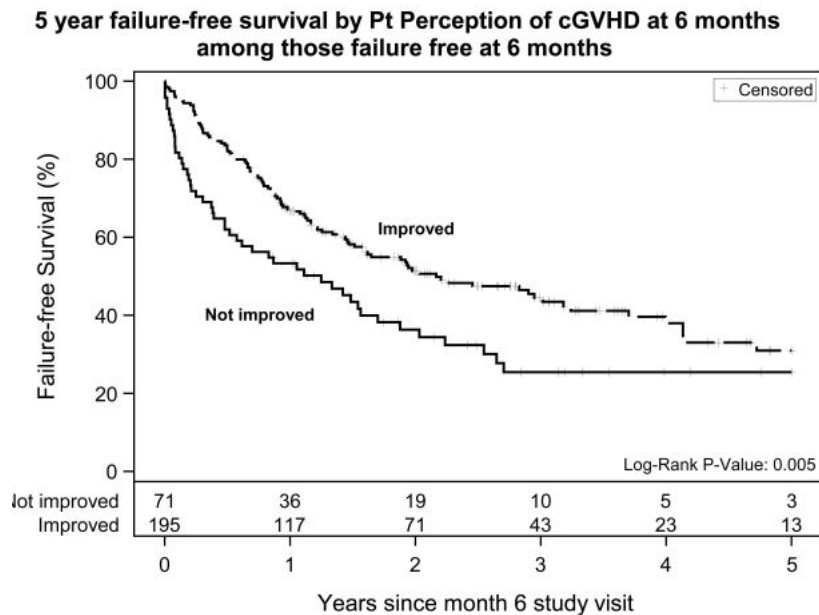


# Clinical trials: Axatilimab

- Anti-CSF1 receptor monoclonal antibody, targets macrophages
- Phase 1/2 trial in chronic GVHD after  $\geq 2$  prior therapies
- Overall response at 6 months: 50%
- Best overall response: 69%
- Toxicities:  $\uparrow$ LFTs,  $\uparrow$ CPK, fatigue, nausea, edema



# Patient-reported response is associated with failure-free survival



# NIH Chronic GVHD Consensus Guidelines 2020:

## III. Treatment of Chronic GVHD

*“...Initiation of systemic monotherapy of chronic GVHD without glucocorticoids is the optimal setting in which to investigate the clinical and biological impacts of an individual therapeutic agent. Furthermore, successful minimization or elimination of glucocorticoid use for initial treatment of chronic GVHD would constitute a major accomplishment for the field.”*

# The best form of treatment is prevention

- GVHD prophylaxis: Post-transplant cyclophosphamide
- Graft engineering: Naïve T-cell depletion

# Learning Objectives

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