Current State and Advances in Chronic GVHD

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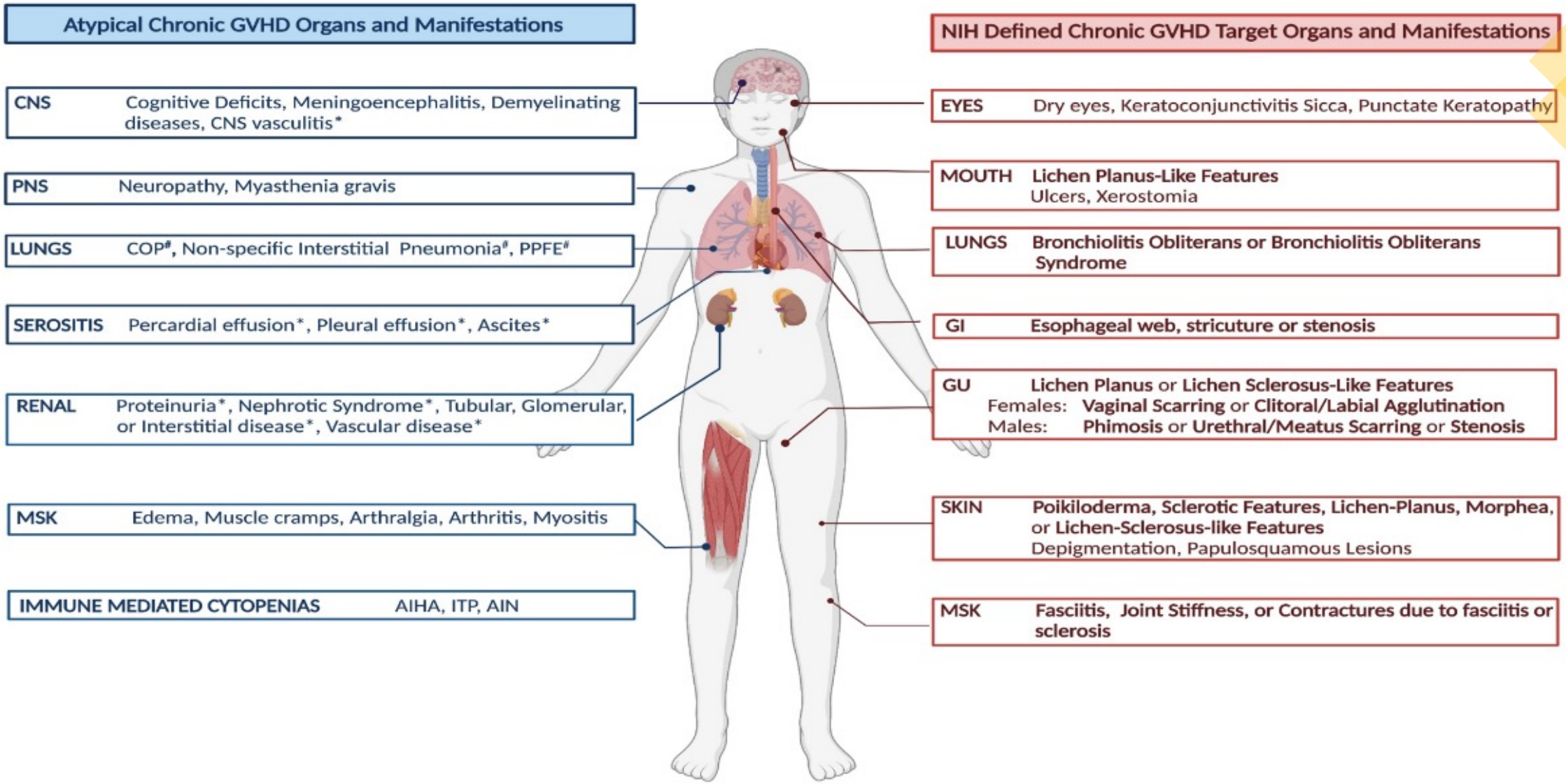
Overview

- Current status:
  - Primary treatment
  - Second line agents
- What drug and when?
- Long-term Impact of chronic GVHD

Chronic GVHD incidence and limited treatment options

- Chronic GVHD commonly affects 30-50% of allogeneic HCT recipients
- Less than 20% will achieve a CR or PR without requiring secondary therapy within 1 YR of diagnosis
- Most patients will require years of treatment; average 2-3 years
- 3 FDA approved agents available for second line treatment of chronic GVHD
  - Ibrutinib, Ruxolitinib, Belumosudil
- Morbidity and mortality in patients needing second or further lines of therapy remains high
- Patients with with sclerosis and lung involvement are difficult to treat and associated with worse outcomes
- Development of novel agents to treat chronic GVHD remains an unmet medical need



Cuvelier GDE et al. *Transplant Cell Ther.* 2022.

Goals of Treatment for Chronic GVHD

Goal	Clinical considerations
1. Control current signs and symptoms	How bothersome are symptoms?

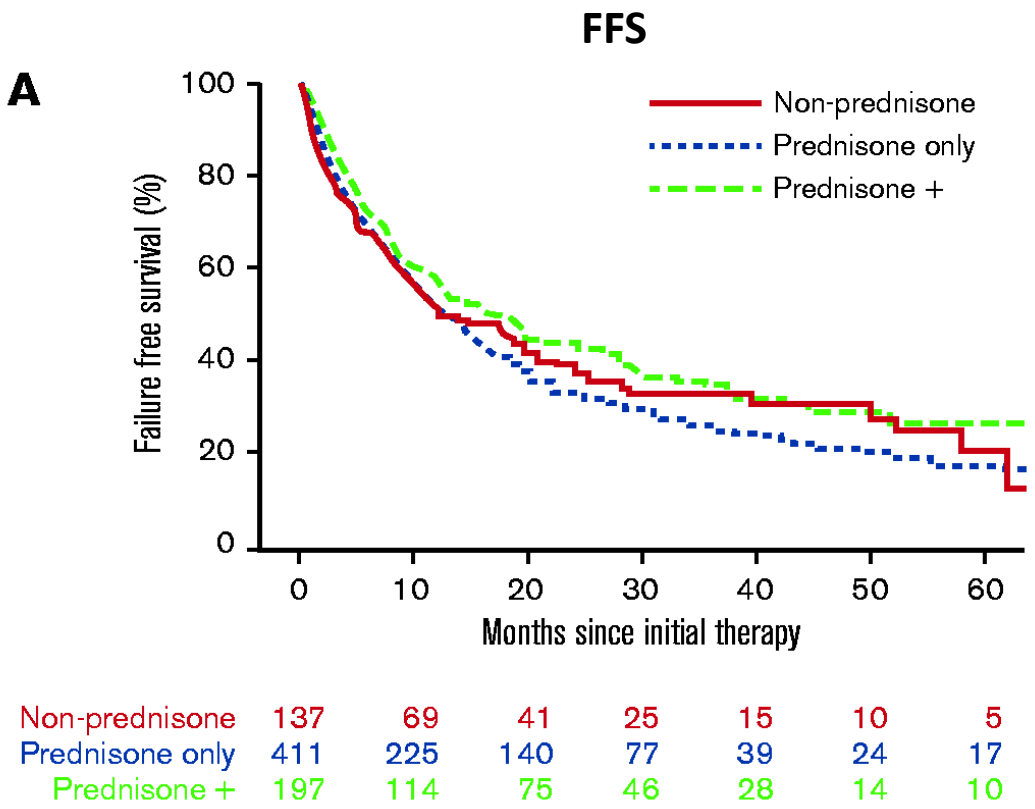
tox = toxicity; Rx = Treatment.

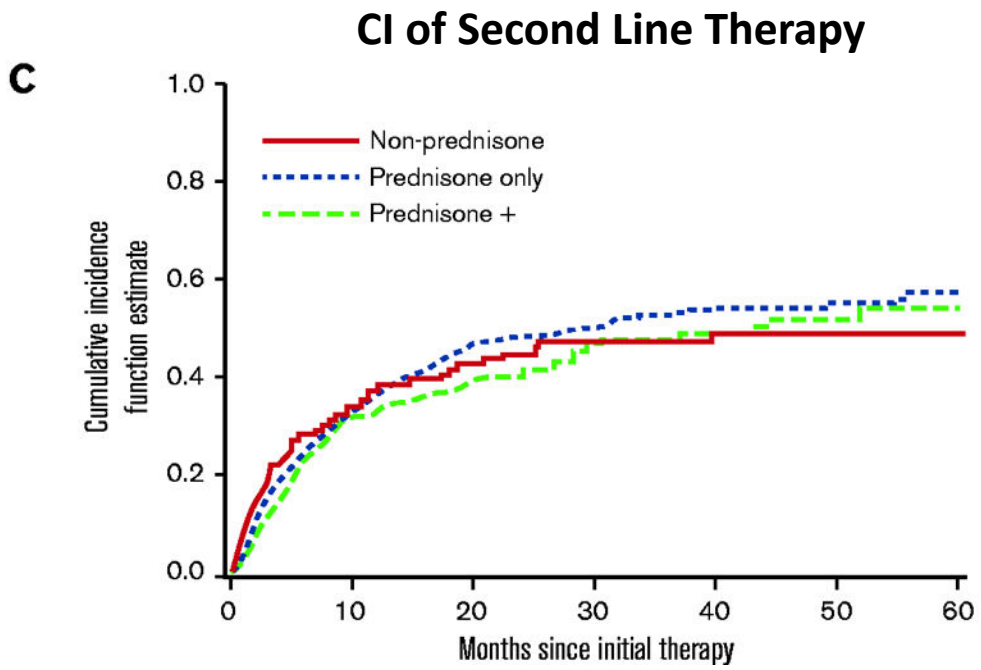
First Line Treatment

Corticosteroids

- Textbook starting dose 1 mg/kg/day
- No significant benefit to add additional agents up front
- Only 40-50% response rate
- > 50% require second-line therapy within 2 years
- Broadly immunosuppressive
- Abundant side effects: Infection, myopathy, edema, cataracts, hyperglycemia, bone density loss, avascular necrosis, sleep/mood disturbances

Real Life Data: Pidala et al. Blood Adv. 2021





- Prednisone only – 411 (55%)
- Prednisone + other – 194 (27%)
  - Of those on prednisone ~55% on doses > 0.74 mg/kg/d
- Non-prednisone – 137 (18%)

NCCN Guidelines: Steroid-Refractory Chronic GVHD

Those in **bold** are FDA approved for ages ≥12

Ruxolitinib (category 1)	**Ibrutinib [approved ages ≥1]**
Abatacept	Imatinib
Alemtuzumab	Interleukin-2 (IL-2)
Belumosudil	Low-dose methotrexate
Calcineurin inhibitors (eg, tacrolimus, cyclosporine)	mTOR inhibitors (eg, sirolimus)
Etanercept	Mycophenolate mofetil
Extracorporeal Photopheresis (ECP)	Pentostatin
Hydroxychloroquine	Rituximab

All recommendations cat 2A unless indicated otherwise.
NCCN. HCT. Version 1.2022.

FDA Approved Agents

All approved for steroid refractory cGVHD

- Ibrutinib
- Ruxolitinib
- Belumosudil

Ibrutinib for SR-cGvHD: *Phase 1b/2 Design*

Patients with steroid-dependent/refractory cGvHD

- **> 25% BSA "erythematous rash" or**
- **> 4 total mouth score**
- **N = 42**

Ibrutinib 420 mg until cGvHD progression or unacceptable toxicity

Primary Endpoint:

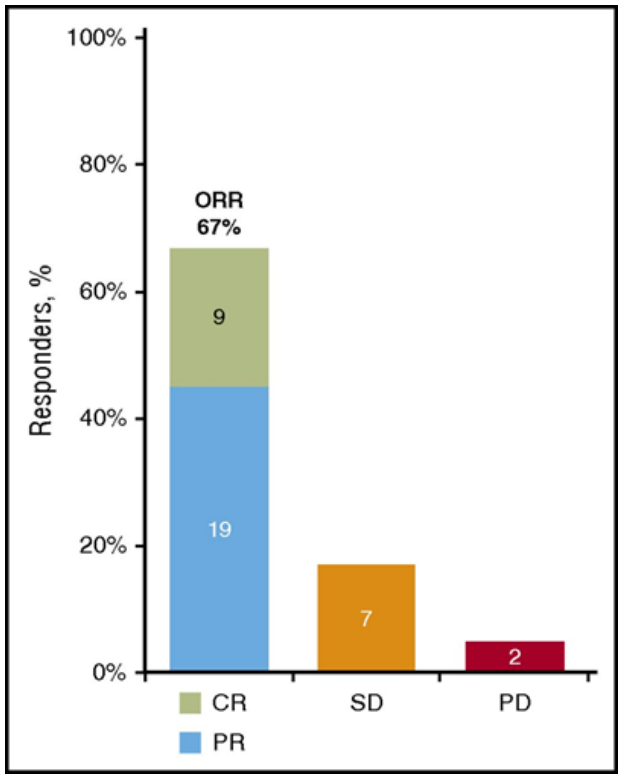
cGvHD Response per NIH 2005 Consensus Response Criteria

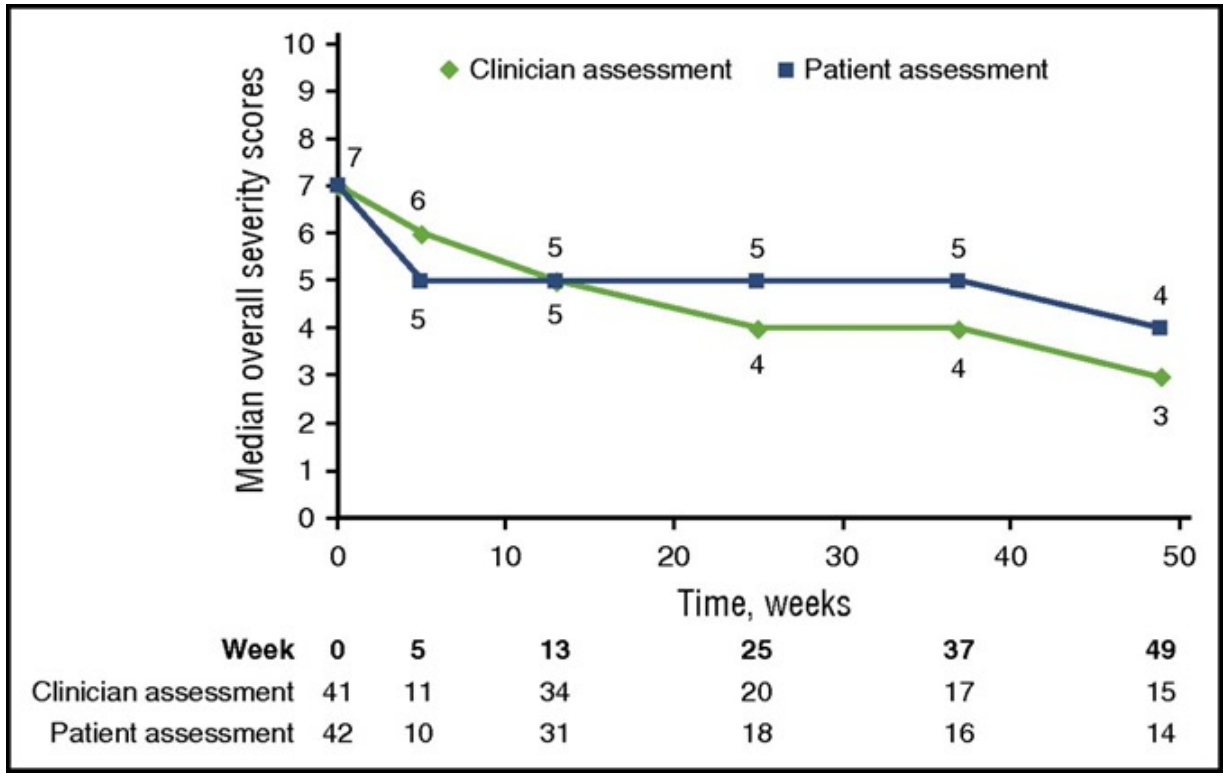
BSA, body surface area.

Miklos D, et al. Blood. 2017;130:2243-2250.

Ibrutinib for SR-cGVHD

- Ibrutinib: TKI targeting and impeding activation of B and T cells (binds and inhibits Btk and Itk)
- Phase 1b/2 open-label multi-center study of ibrutinib in steroid-refractory cGVHD who failed ≥1 therapy, leading to FDA approval of ibrutinib



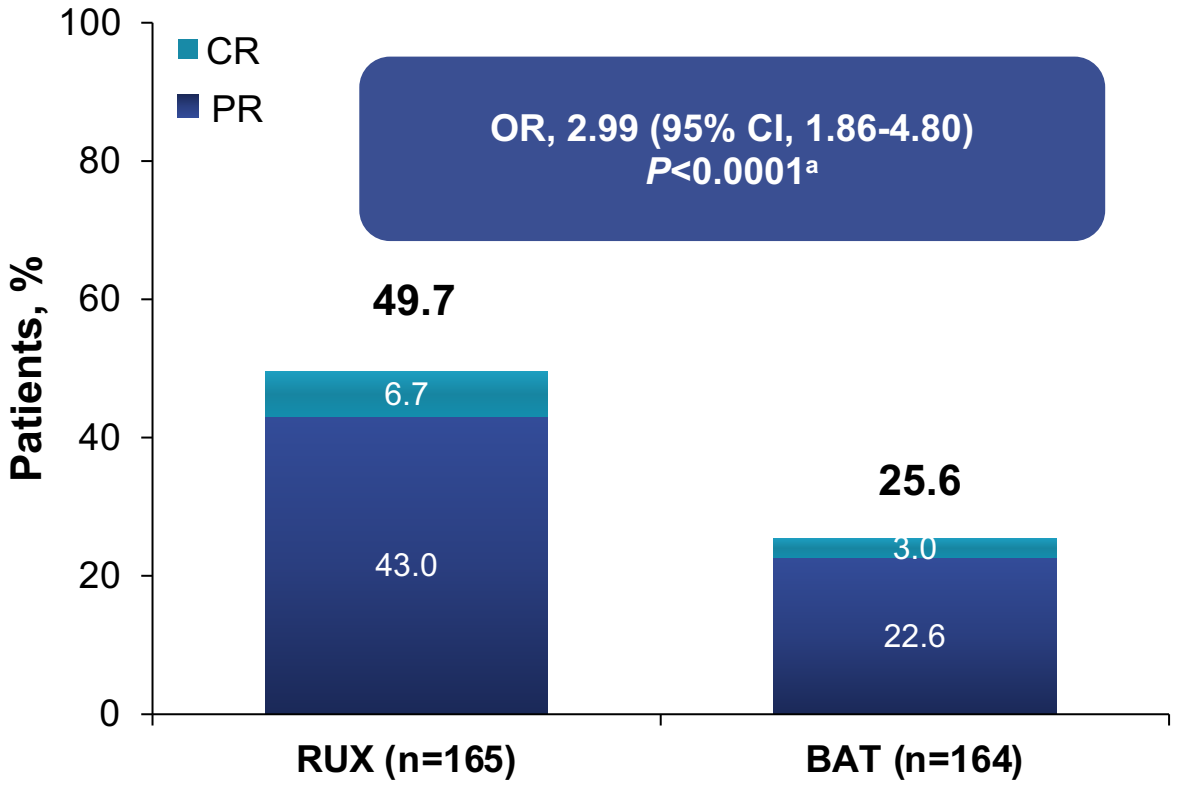


Miklos et al. Blood 2017; 130 (21): 2243-2250.

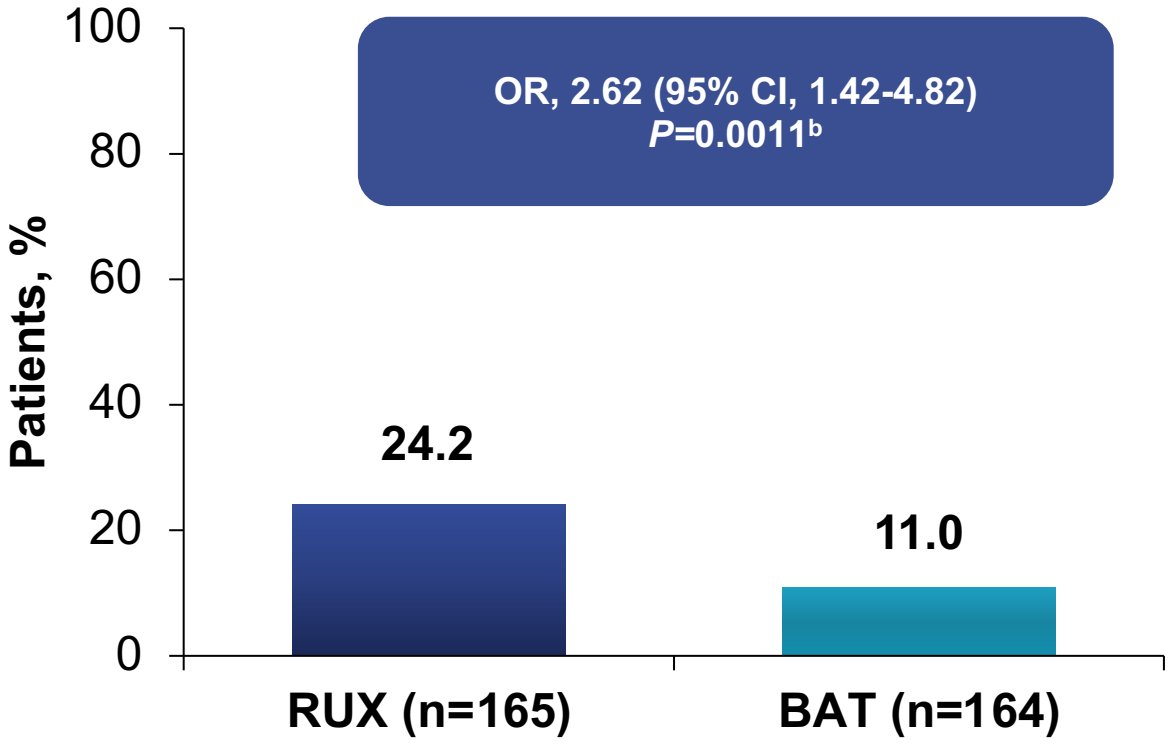
REACH 3: Ruxolitinib vs BAT

- Ruxolitinib: JAK1/2 inhibitor; JAK/STAT system is downstream of 50+ cytokine receptors
- Phase 3 open-label randomized trial, in steroid-refractory or dependent cGVHD who failed ≥1 therapy

ORR at 24 weeks

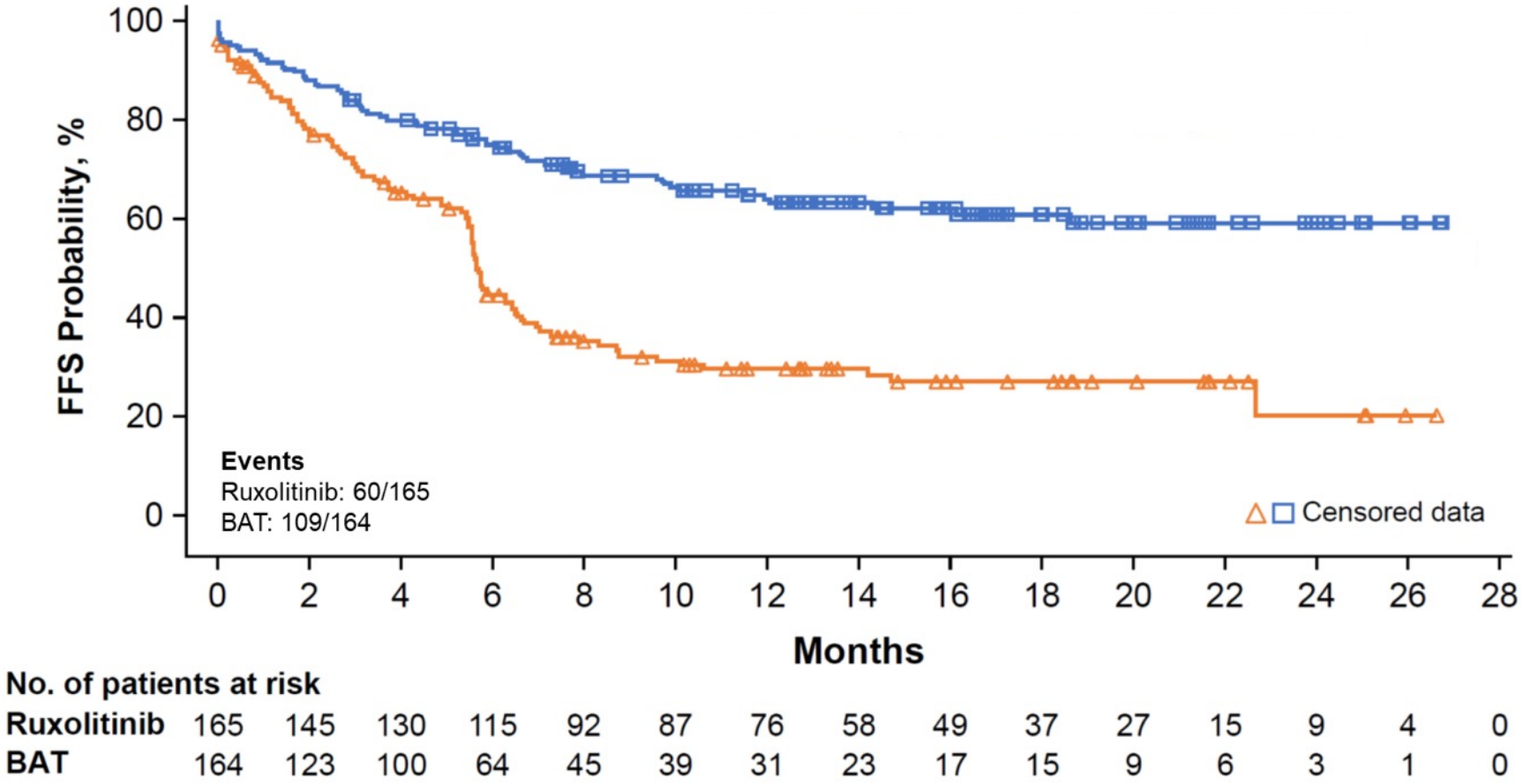


Improvement in Lee Symptom Scale



Zeiser R et al. NEJM. 2021

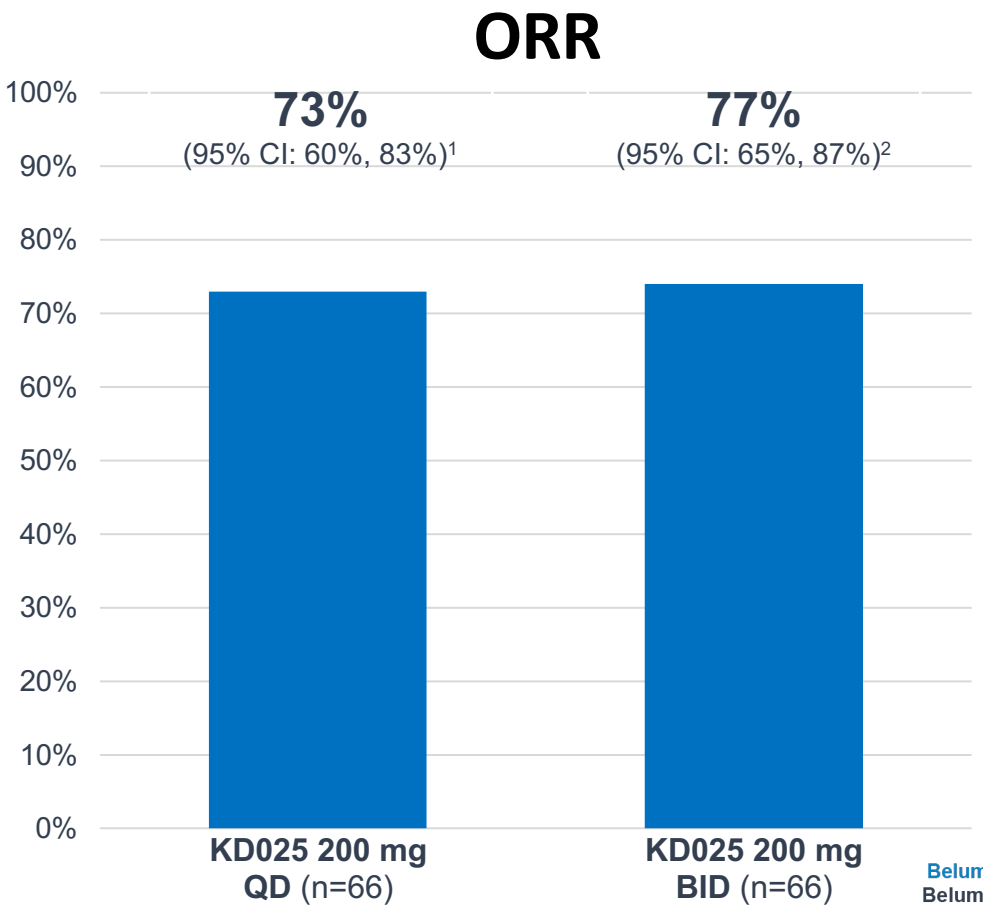
Rux vs BAT: Failure-free Survival

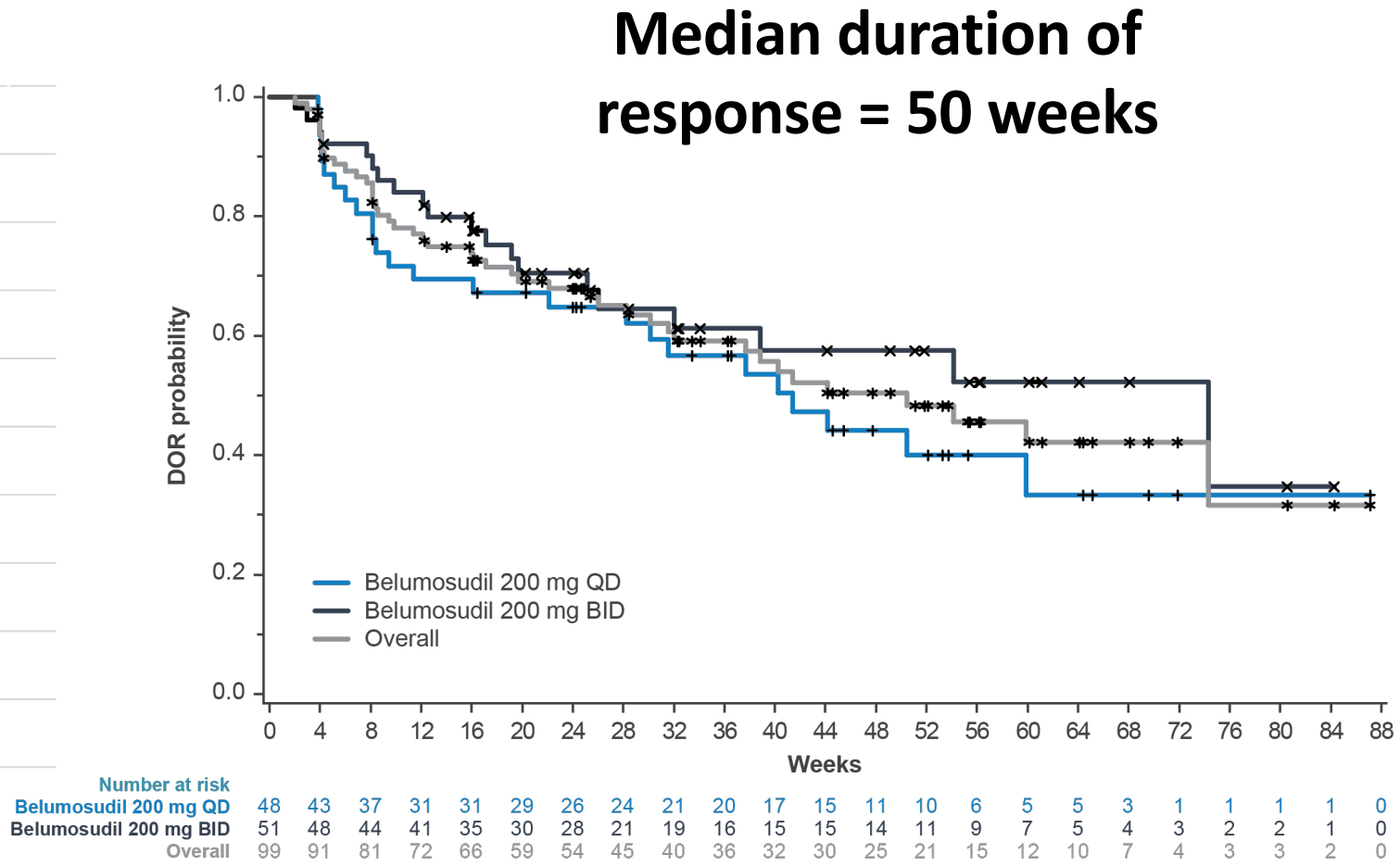


Zeiser et al. NEJM. 2021

ROCKstar: Pivotal Trial of Belumosudil (KD025) in cGVHD

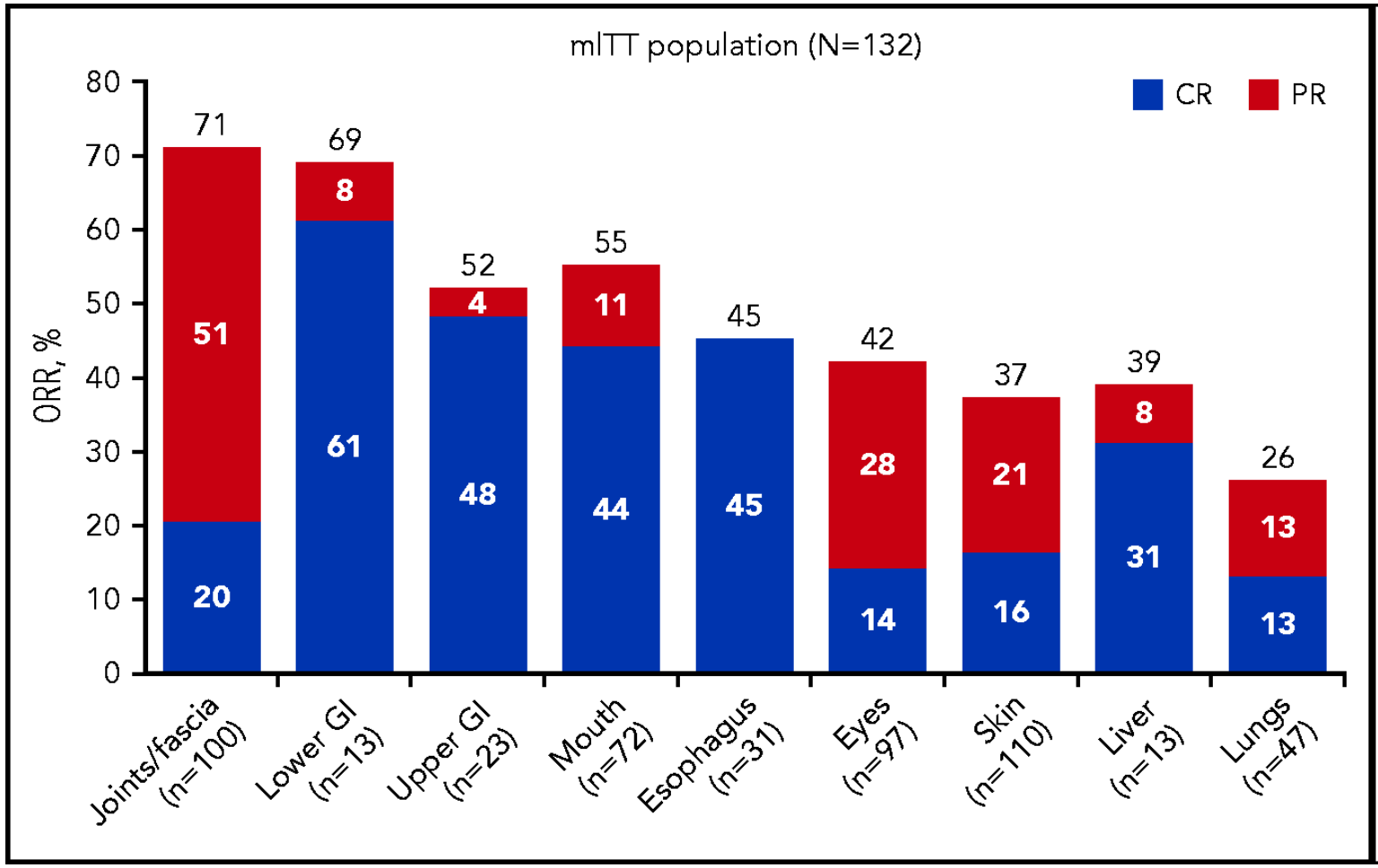
- Phase 2 open-label, in steroid-refractory or dependent cGVHD who failed 2-5 lines of therapy



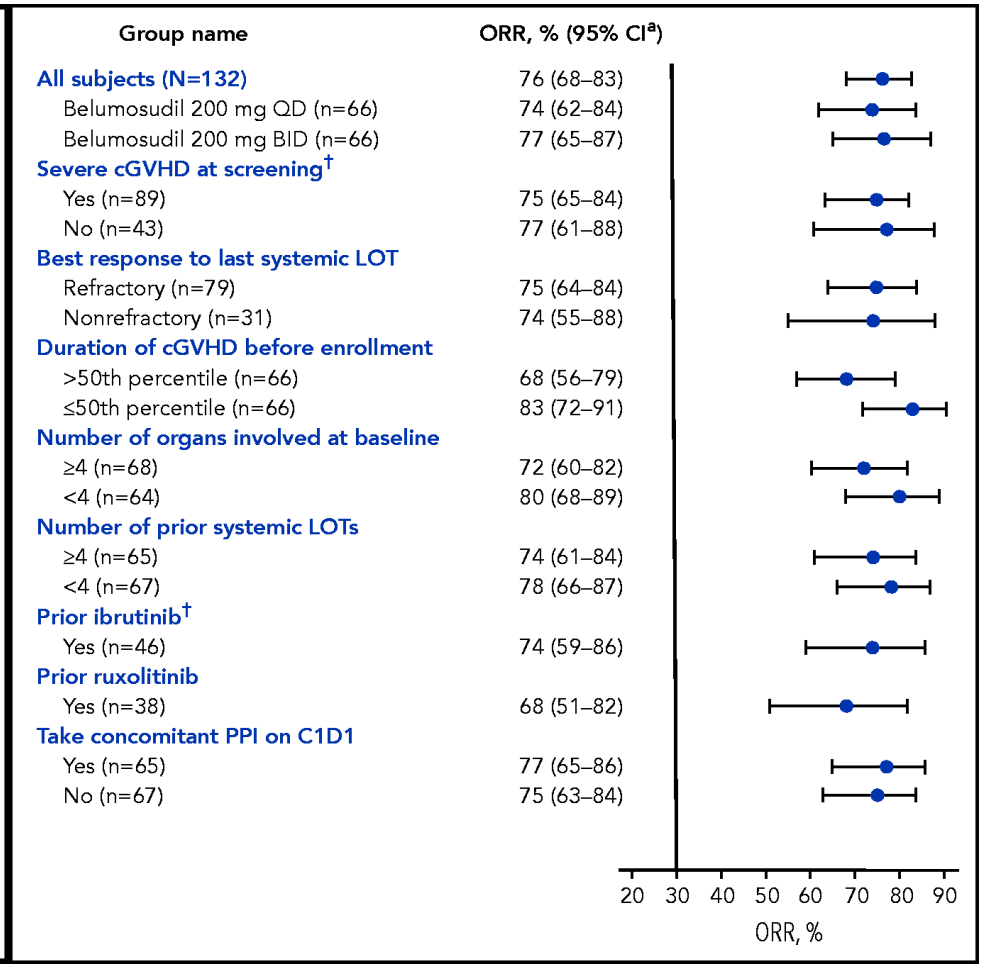


Cutler et al. Blood. 2021

Organ Specific Response



Subgroup Response



Cutler et al. Blood. 2021

What Drug and When?

- Current strategies typically rely on availability of clinical trials and physician preference (trial and error)
- All steroid refractory cGVHD is not the same
- Ideal state
  - Biologically driven selection
  - Consideration for toxicity profile
  - Biomarkers may help better define clinical and biologic phenotype

What else do I need to worry about when treating GVHD?

QOL and Function

- Physical health
- Functional status
- Social wellbeing
- GVHD specific symptoms
- Overall QOL

Psychological Distress

- Screening for psychological distress
- Depression
- Anxiety
- Post-traumatic stress
- Prognostic uncertainty
- Existential distress
- Demoralization

Maximal Supportive Care

- Multidisciplinary management
- Maximal topical therapy to alleviate GVHD symptoms
- Infection prophylaxis
- Vaccinations

El-Jawahri A. *Hematology Am Soc Hematol Educ Program*. 2021;2021(1):655–661.

GvHD Treatment-Induced Damage

- Immune deficiency
- Cataracts
- Chronic kidney injury
- Steroid-induced diabetes
- Dyslipidemia
- Steroid myopathy
- Adrenal insufficiency
- Osteoporosis
- Neuropathy
- Poor wound healing
- Second malignancies/PTLD

Flowers MED, et al. Long-term follow-up after HSCT: General guidelines for referring physicians. Jul 2019.

Questions?