THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center
Making Cancer History®

# *UPDATES ON GRAFT-VS-HOST DISEASE (GVHD) THERAPIES: ACUTE & CHRONIC GVHD*


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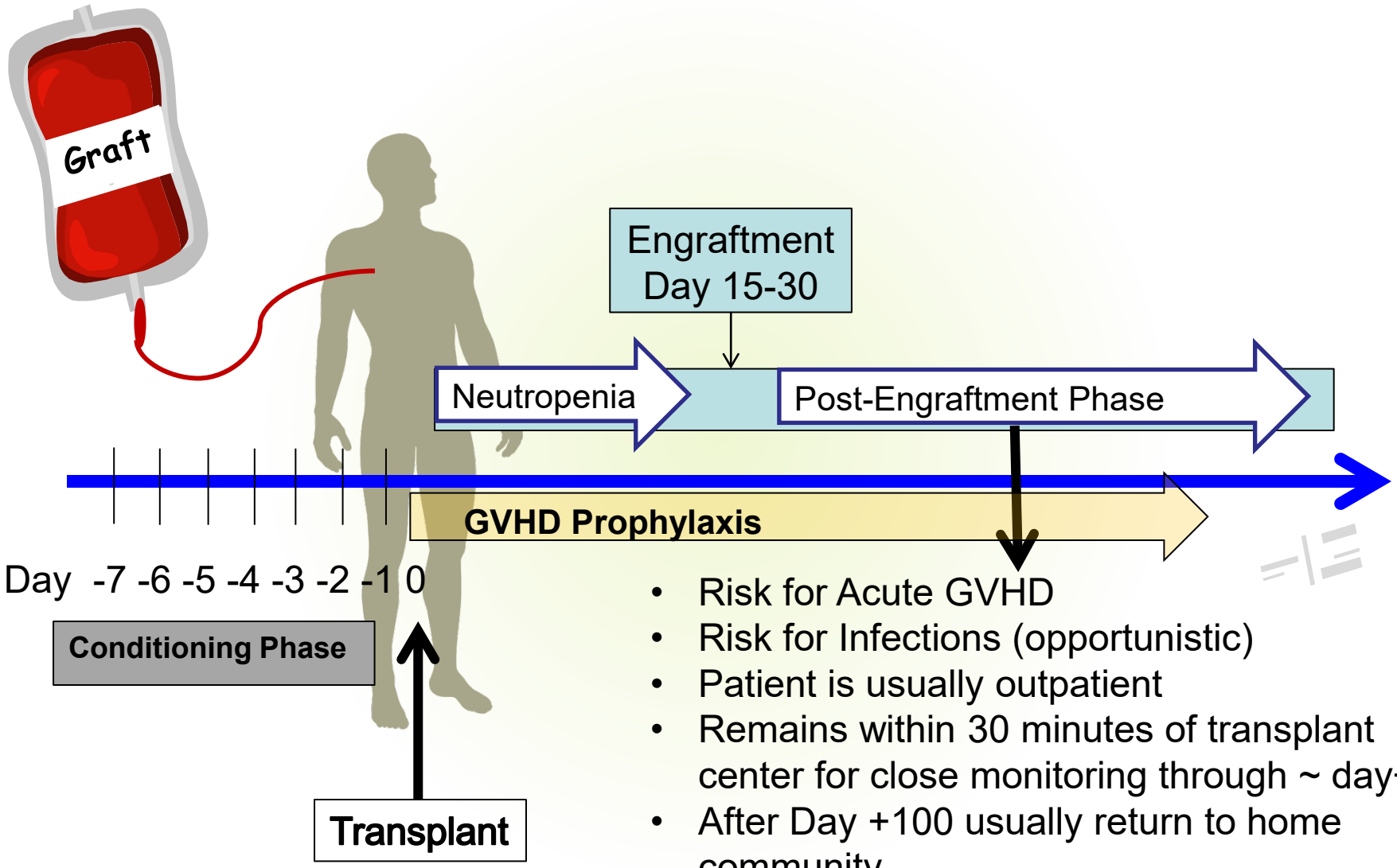
~~GVHD~~

# Disclosures

- Research Support: Therakos / Mallinkrodt, Incyte
- Consultant: Prolacta
- Advisory Board:  Kadmon, Syndax
- Paid Speaker:  Therakos / Mallinkrodt

# Allogeneic Hematopoietic Stem Cell Transplant




- Risk for Acute GVHD
- Risk for Infections (opportunistic)
- Patient is usually outpatient
- Remains within 30 minutes of transplant center for close monitoring through ~ day+100.
- After Day +100 usually return to home community.

# CLINICAL VIGNETTE

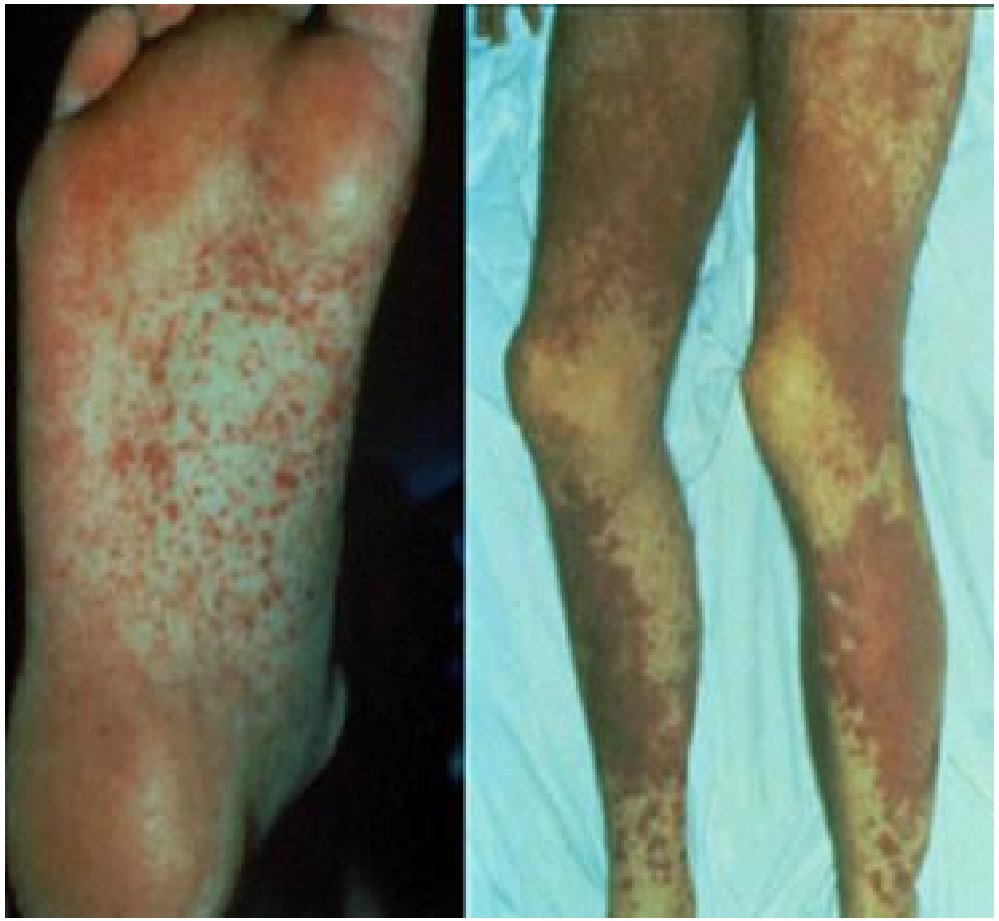
- 54 y/o woman with AML underwent a Peripheral Blood HCT from a Matched Unrelated Donor (MUD) following conditioning chemotherapy of Busulfan and Fludarabine.
- GVHD Prophylaxis was Tacrolimus and Short-course Methotrexate.
- She engrafted on day 15 and was d/c'ed on day 18.
- She is now Day 28 and presents with acute onset non-pruritic rash, 2 day history of crampy abdominal pain and 8-10 watery stools, non-bloody, and nausea and vomiting.

# Acute GVHD

- GVHD occurs when immune cells transplanted from a non-identical donor (the graft) recognize the transplant recipient (the host) as foreign → immune reaction → tissue injury.
- Occurs in 10-65% of patients depending on the number of risk factors.
- Typically occurs early post-engraftment period but can later ("Late Acute GVHD").
- Manifestations / Target Organs:
  - Skin (morbilloform rash)
  - Upper GI Tract (Nausea, Vomiting and Failure-to-Thrive)
  - Lower GI Tract (secretory diarrhea)
  - Liver (cholestatic jaundice)

# CLINICAL VIGNETTE: ORGAN STAGING

Skin: >50% Rash, no Bullous Lesions



Upper GI

+ Nausea/ Vomiting

Lower GI

+ 8-10 watery Stools per Day

Liver

Normal Total Bili (alk phos, LFT's)

# GRADING OF ACUTE GVHD



**Table 1**
GVHD Target Organ Staging

| Stage | Skin (Active Erythema Only) | Liver (Bilirubin) | Upper GI | Lower GI (stool output/day) |
|---|---|---|---|---|
| 0 | No active (erythematous) GVHD rash | <2 mg/dL | No or intermittent nausea, vomiting, or anorexia | Adult: <500 mL/day or <3 episodes/day<br>Child: <10 mL/kg/day or <4 episodes/day |
| 1 | Maculopapular rash <25% BSA | 2-3 mg/dL | Persistent nausea, vomiting or anorexia | Adult: 500-999 mL/day or 3-4 episodes/day<br>Child: 10-19.9 mL/kg/day or 4-6 episodes/day |
| 2 | Maculopapular rash 25-50% BSA | 3.1-6 mg/dL | | Adult: 1000-1500 mL/day or 5-7 episodes/day<br>Child: 20-30 mL/kg/day or 7-10 episodes/day |
| 3 | Maculopapular rash >50% BSA | 6.1-15 mg/dL | | Adult: >1500 mL/day or >7 episodes/day<br>Child: >30 mL/kg/day or >10 episodes/day |
| 4 | Generalized erythroderma (>50% BSA) *plus* bullous formation and desquamation >5% BSA | >15 mg/dL | | Severe abdominal pain with or without ileus or grossly bloody stool (regardless of stool volume). |

Overall clinical grade (based on most severe target organ involvement):
Grade 0: No stage 1-4 of any organ.
Grade I: Stage 1-2 skin without liver, upper GI, or lower GI involvement.
Grade II: Stage 3 rash and/or stage 1 liver and/or stage 1 upper GI and/or stage 1 lower GI.
Grade III: Stage 2-3 liver and/or stage 2-3 lower GI, with stage 0-3 skin and/or stage 0-1 upper GI.
Grade IV: Stage 4 skin, liver, or lower GI involvement, with stage 0-1 upper GI.

**Non-Relapse Mortality**
Grade III/ IV > Grade II > 0/ I

Harris AC, et al. Biol Blood Marrow Transplant 2016;22:4-10

# ACUTE GVHD: TREATMENT

- Grades II-IV AGVHD: Prednisone / Methylprednisone at 1-2 mg/kg/day followed by (slow) taper
- Response Rate varies from 40-75%.
- Steroids result in numerous side effects.
  - Diabetes
  - Infections
  - Myopathy
  - Psychosis
  - Osteoporosis
  - Avascular Necrosis of Joints
  - Weight Gain
  - Adrenal Insufficiency
- Steroid-refractory Acute GVHD has High Mortality (70% or >).

# STUDY POPULATIONS FOR ACUTE GVHD TRIALS

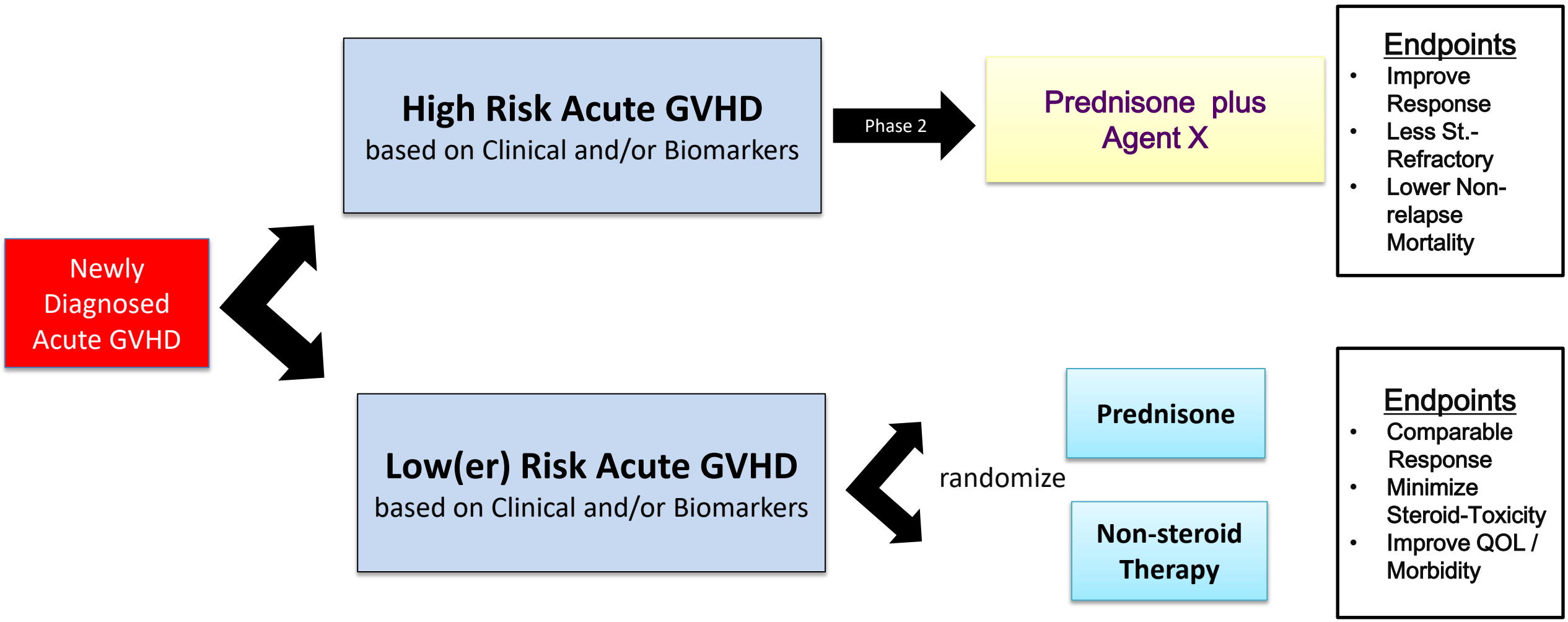
- Newly-Diagnosed ("Upfront") Acute GVHD Population
- Steroid-Refractory Acute GVHD Population
  - Generally defined as No response or Progression on steroids or Flare in Acute GVHD while on high-doses of steroids (>0.5-1mg per kg).
  - Difficult patient to study (or positively impact)
  - Even when GVHD responds; NRM remains high from infection and organ toxicity.

# STUDY POPULATIONS FOR ACUTE GVHD TRIALS

- Upfront Treatment Trials
  - Patients with newly diagnosed Acute GVHD defined as having received 1-2mg/kg/ day for < 72 hours.
  - Investigational Agent X is added to steroids with goal of improving day 28 GVHD response.
  - No improvement in response rate or outcome by addition of 2nd agent.
    - ATG [1]
    - Anti-interleukin-2 Receptor Antibodies [2]
    - Anti-TNF alpha agent (infliximab) [3]


1 Cragg et al. *BBMT*. 2000.
2 Lee et al. *Blood.* 2004.
3 Couriel / Alousi. *BBMT*. 2009.

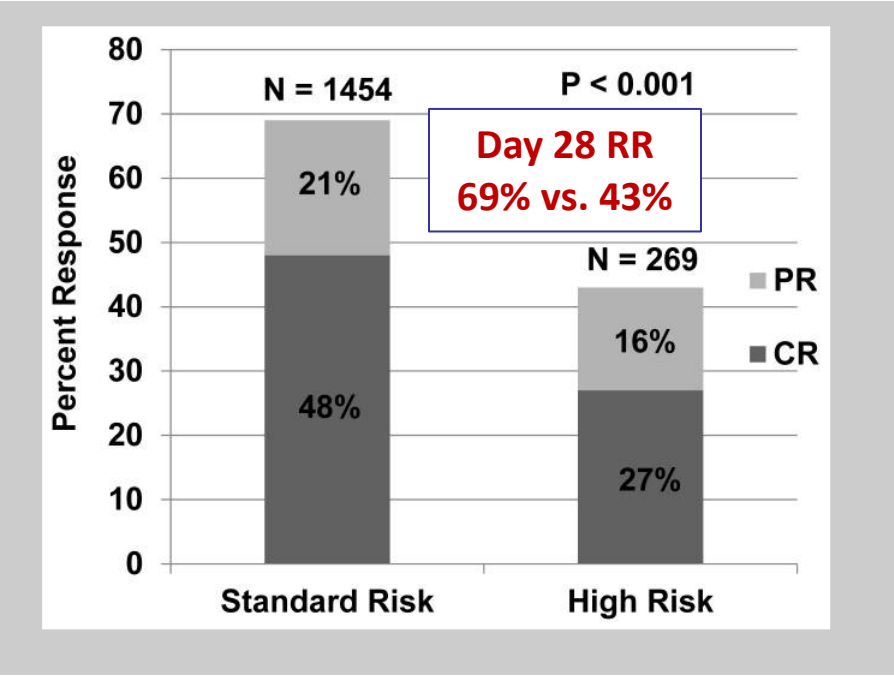
# Upfront Trials: New Paradigm of Risk Stratification

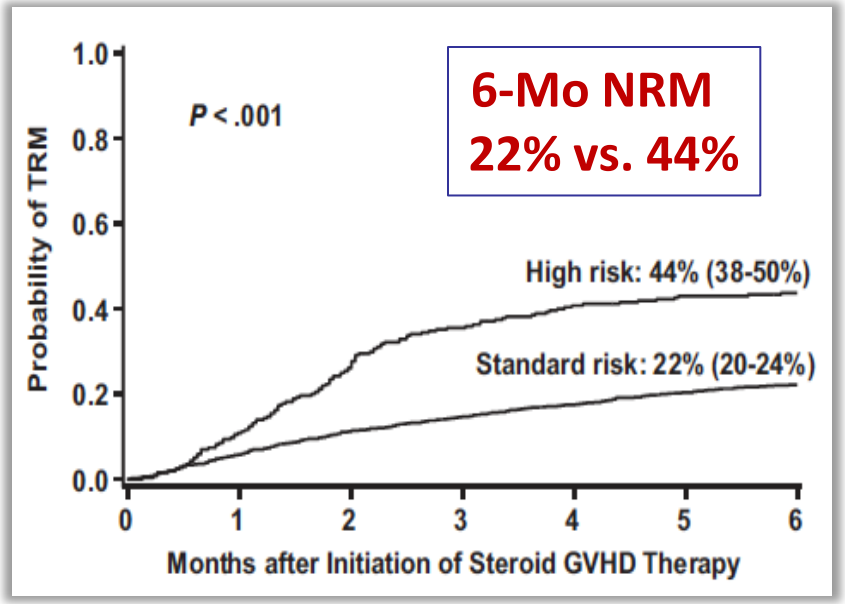


# RISK STRATIFYING BASED ON CLINICALGRADING: MINNESOTA REVISED GRADING✦

- Clinical Grading System Based on Glucksberg Individual Organ Stages.

- Categorizes patients as “Standard Risk” and “High-Risk”.




✧ MacMillan et al. *BBMT*. 2015.

# REVISED MINNESOTA GRADING: "HIGH-RISK" IS ROUGHLY 15% OF ALL CASES (AT LEAST IN MINNESOTA)

✧ MacMillan et al. *BBMT*. 2015.

**Table 4**
GVHD Risk Definition by Organ Stage at Onset

| GVHD Risk Score | One Organ (n) | Two Organs (n) | Three Organs (n) |
|---|---|---|---|
| SR (n = 1454, 84%) | Stage 1-3 Skin (901)<br>Stage 1-2 GI (279)† | Stage 1-3 skin plus stage 1 GI (223)*<br>Stage 1-3 skin plus stage 1-4 liver (51) | –<br>– |
| HR‡ (n = 269, 16%) | Stage 4 Skin (13)<br>Stage 3-4 GI (74)§<br>Stage 1-4 Liver (25)‖ | Stage 1-3 skin plus stage 2 GI (54)<br>Stage 1-2 lower GI plus stage 1-3 liver (12)<br>Stage 3-4 GI plus stage 1-3 skin (45)<br>Stage 3-4 GI plus stage 1-4 liver (10) | Stage 1-3 skin plus stage 1-2 GI plus stage 1-3 liver (23)<br>Stage 1-3 skin plus stage 3-4 GI plus stage 1-4 liver (13) |

UGI plus lower GI considered as single-organ disease.

* Stage 1-3 skin plus stage 1 GI includes stage 1-3 skin plus UGI (n = 90), stage 1-3 skin plus stage 1 lower GI (n = 71), or stage 1-3 skin plus UGI plus stage 1 lower GI (n = 62).

† Stage 1-2 GI includes UGI alone (n = 115), stage 1-2 lower GI alone (n = 100), or UGI or stage 1 lower GI (n = 64).

‡ For HR disease, the degree of organ involvement is the minimum necessary to be deemed HR. Patients with higher stage of GVHD than observed in the HR group should also be considered HR.

§ Stage 3-4 GI includes stage 3 lower GI alone (n = 65), or stage 4 lower GI alone (n = 9).

‖ Stage 1-4 liver includes Stage 1 liver alone (n = 7), stage 2 liver alone (n = 10), stage 3 liver alone (n = 5), or stage 4 liver alone (n = 3).

**One Organ**
- Stage 4 Skin
- Stage 3 /4 Lower GI GVHD (>1500 cc stool)
- Any Isolated Liver (Bili >2 mg/dl)

**Two Organs**
- Any Skin with Lower GI Stage ≥ 2
- Any Lower GI + Any Liver

**Three Organs**
- Always

# Incorporation of Biomarkers to Identify High-Risk Patients with New Onset GVHD

# ANN ARBOR SCORES
# BIOMARKERS AND GI GVHD

- TNFR1: TNFα amplifies GI injury
  *Schmaltz Blood 2003*
- ST2 and its ligand IL33 regulate inflammatory bowel disease activity
  *Pastorelli PNAS 2010*
- REG3α protects intestinal epithelial cells from damage
  *Ogawa Inflamm Bowel Disease 2003*

✧ Levine et al. *Lancet Oncology*. 2015.

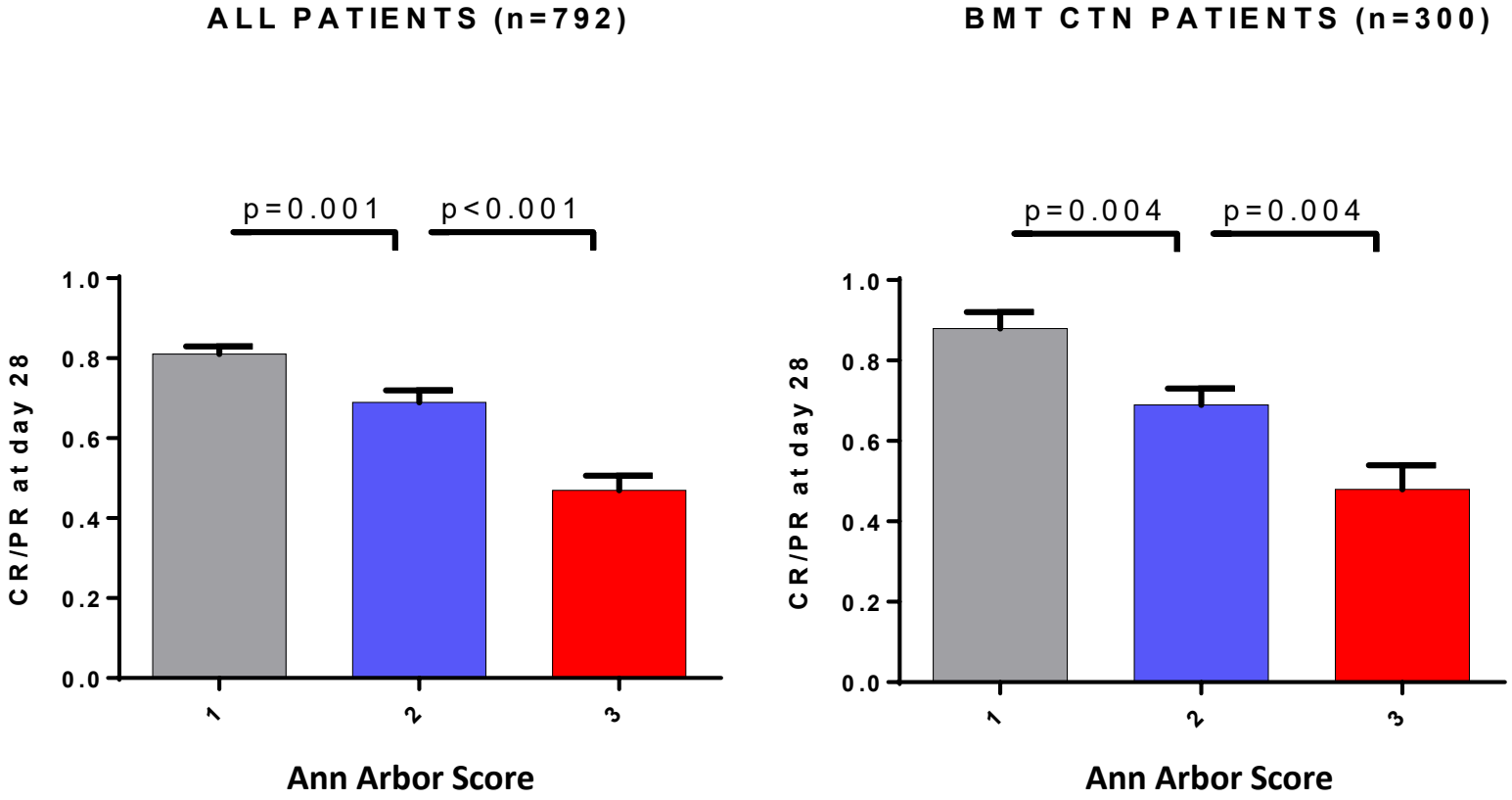
# ACUTE GVHD CLINICAL GRADE AND BIOMARKER GRADE (CALLED ANN ARBOR) at GVHD ONSET

| Acute GVHD Clinical Grade (Glucksberg Grading) | Ann Arbor I (Biomarker Grade) | Ann Arbor II (Biomarker Grade) | Ann Arbor III (Biomarker Grade) |
|---|---|---|---|
| Grade I (n=51) | 23% | 59% | 18% |
| Grade II (n=183) | 25% | 56% | 19% |
| Grade III/IV (n=69) | 26% | 49% | 25% |
| Total: 303 patients | 25% | 55% | 20% |

Biomarker Grading Can Outperform Clinical Grading by Identifying Seemingly Low-Risk Patients who are Actually High-Risk and vice-versa

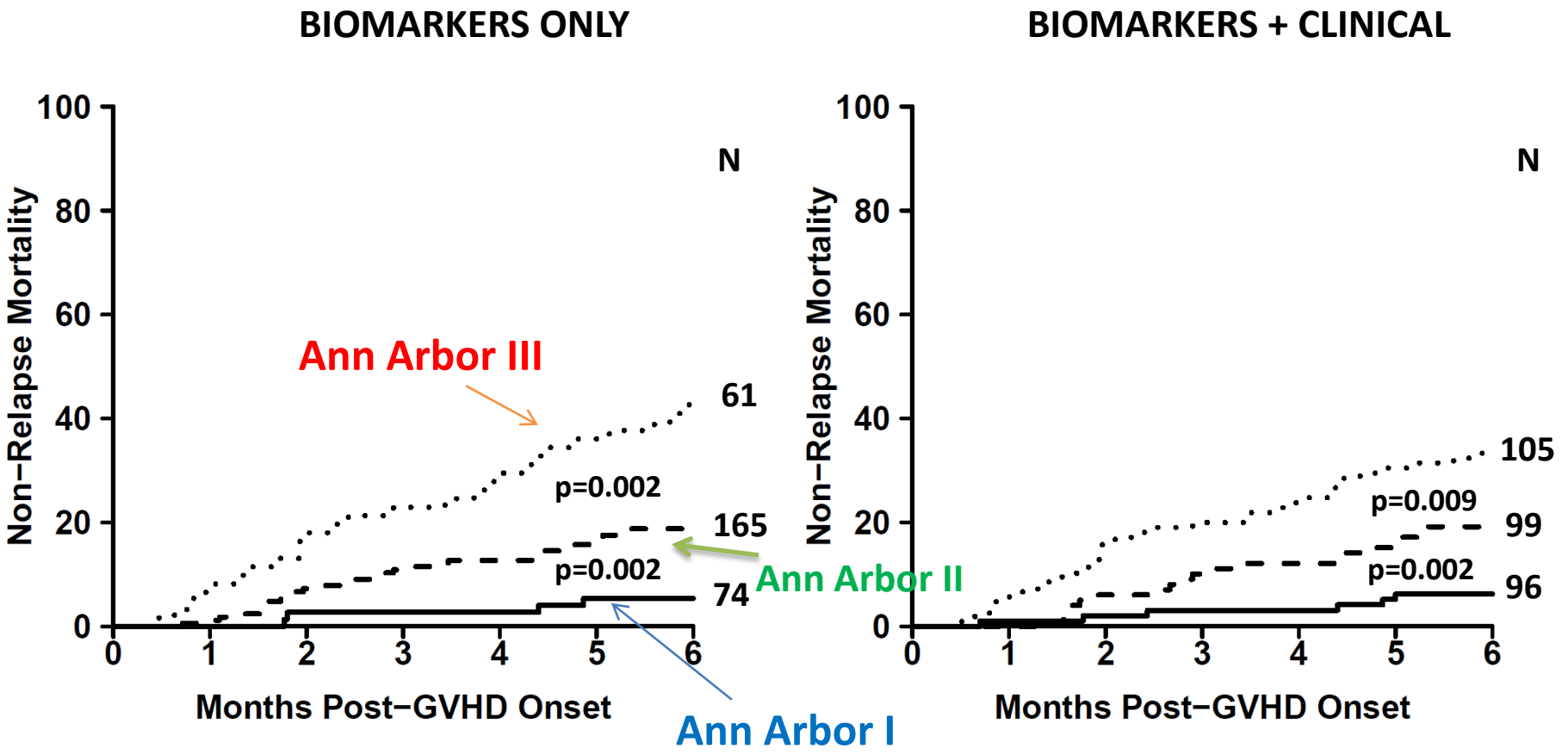
✧ Levine et al. *Lancet Oncology*. 2015.

# TREATMENT RESPONSE AT DAY 28



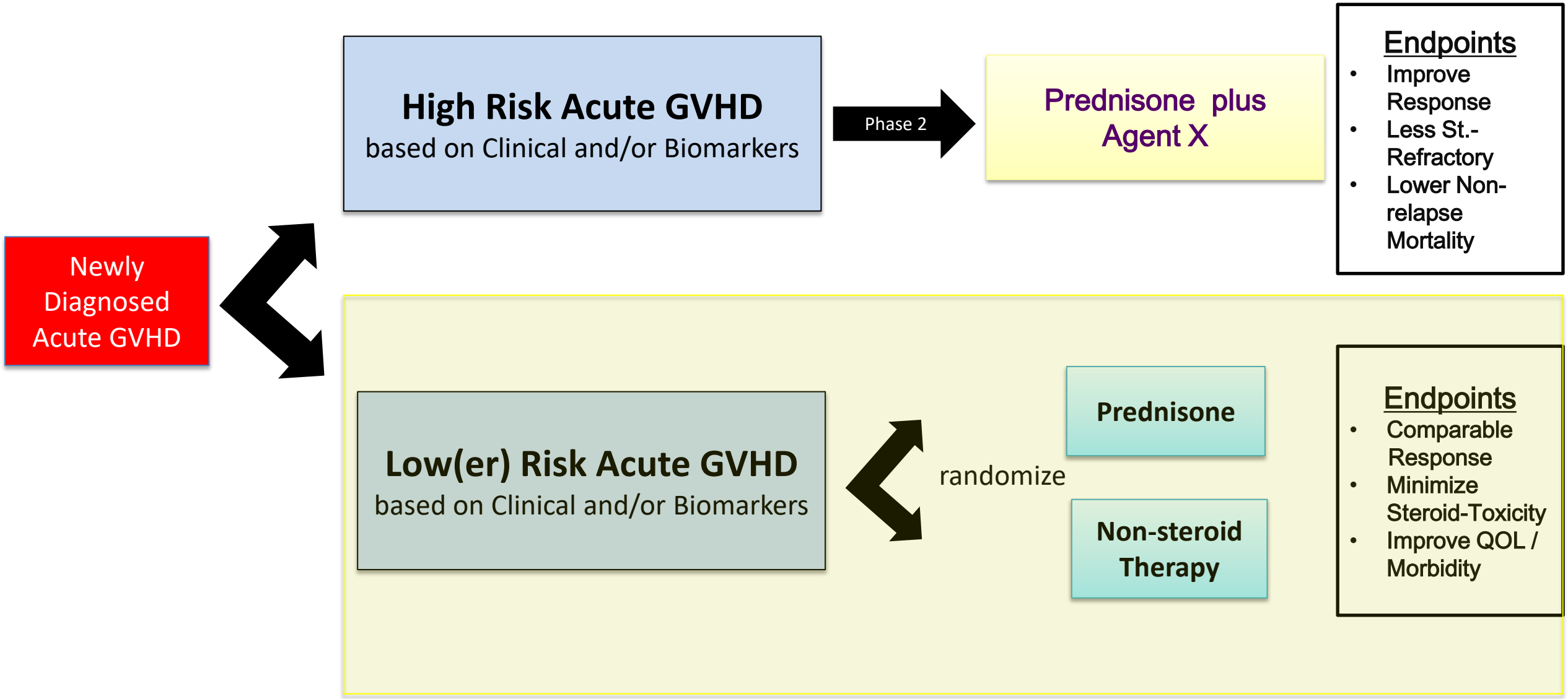

✧ Levine et al. *Lancet Oncology*. 2015.

# BMT CTN (N=300): 6-MONTH NRM BASED ON BIOMARKER PANEL




✧ Levine et al. *Lancet Oncology*. 2015.

# Upfront Trials: New Paradigm of Risk Stratification



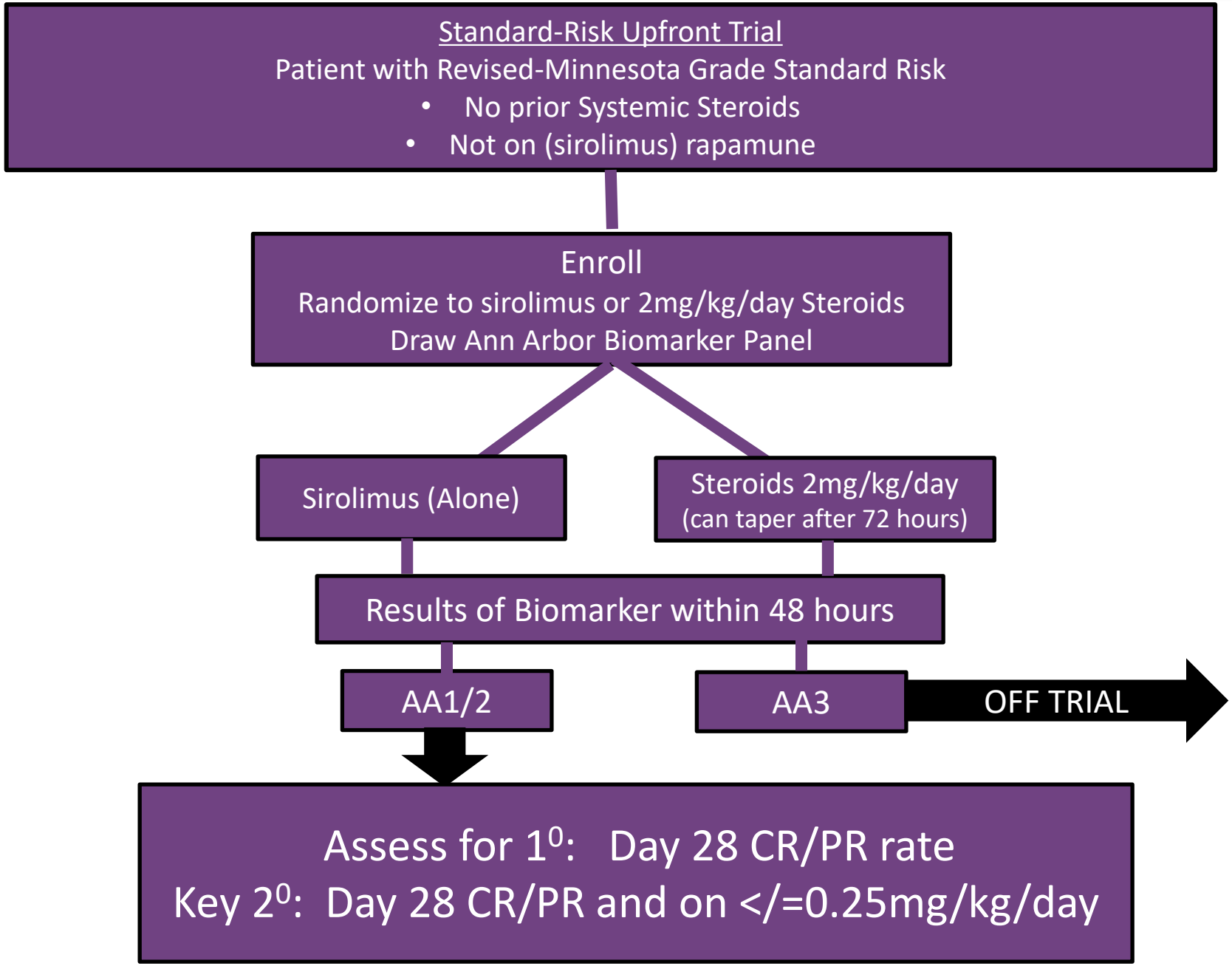
# BMTCTN 1501

# *CAN ONE USE ANYTHING OTHER THAN STEROIDS FOR NEWLY DIAGNOSED ACUTE GVHD?*

Results of BMTCTN 1501: Sirolimus vs. Prednisone for Patients with Minnesota Standard Risk Acute GVHD

- Pidala et al. 2020. *Blood*;135:97-107

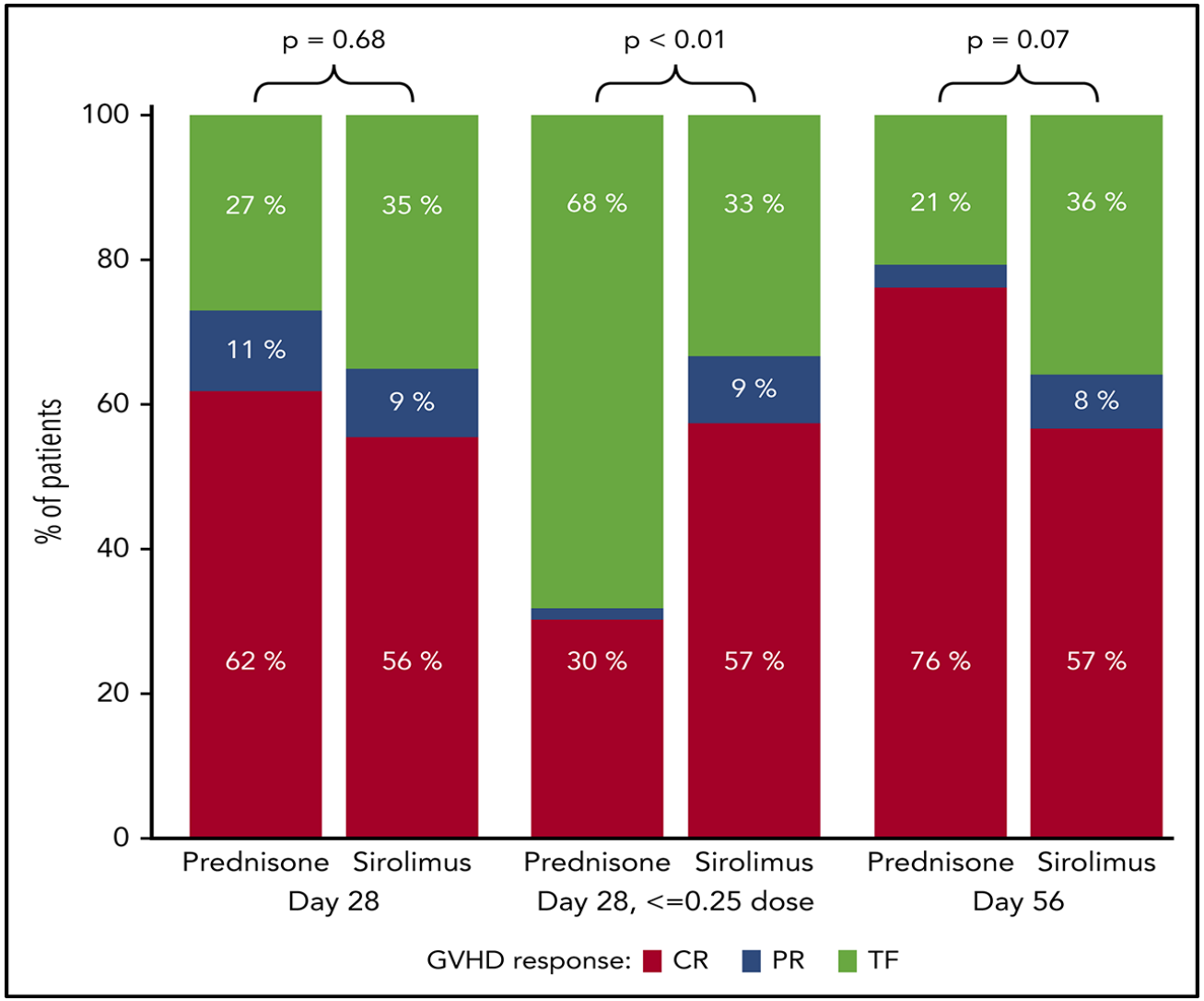
# TREATMENT SCHEMA BMTCTN 1501



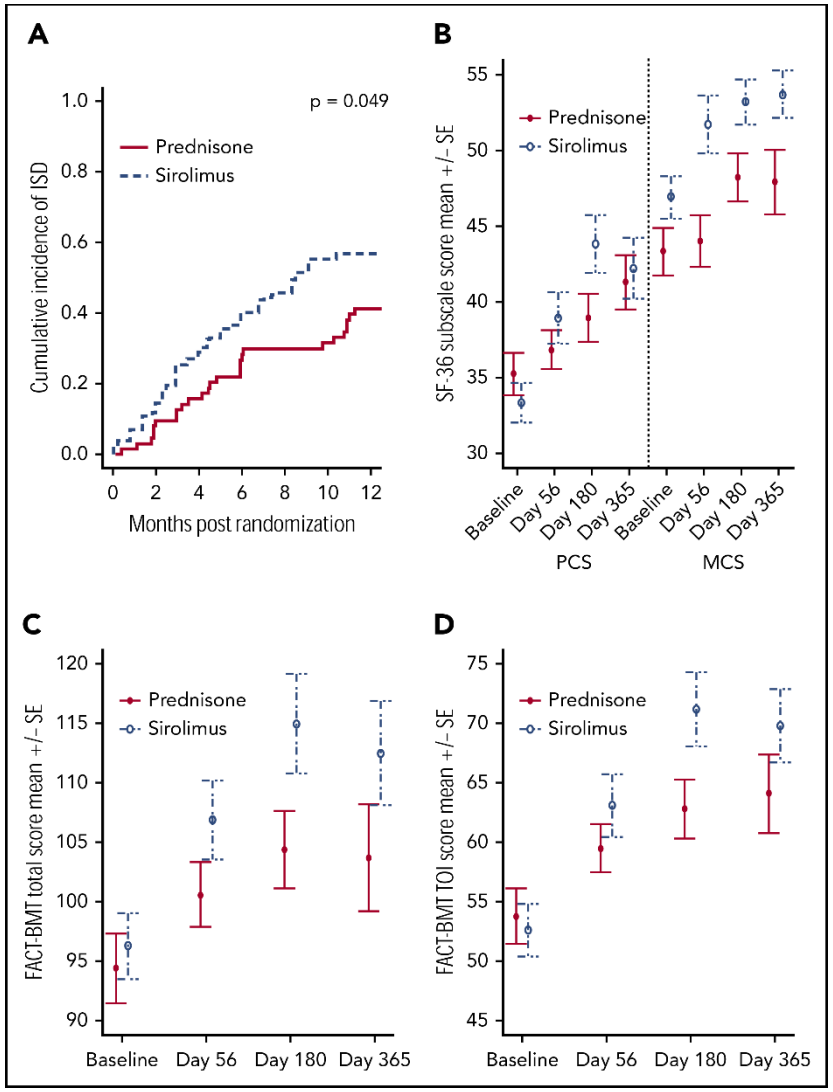
| | Prednisone (N=64) N (%) | Sirolimus (N=58) N (%) | Total (N=122) N (%) |
|---|---|---|---|
| Skin GVHD Stage | | | |
| 0 | 19 (29.7%) | 20 (34.5%) | 39 (32.0%) |
| 1 | 11 (17.2%) | 8 (13.8%) | 19 (15.6%) |
| 2 | 13 (20.3%) | 14 (24.1%) | 27 (22.1%) |
| 3 | 21 (32.8%) | 16 (27.6%) | 37 (30.3%) |
| Upper GI GVHD | | | |
| 0 | 36 (56.3%) | 32 (55.2%) | 68 (55.7%) |
| 1 | 28 (43.8%) | 26 (44.8%) | 54 (44.3%) |
| Lower GI GVHD Stage | | | |
| 0 | 56 (87.5%) | 56 (96.6%) | 112 (91.8%) |
| 1 | 7 (10.9%) | 2 (3.4%) | 9 (7.4%) |
| 2 | 1 (1.6%) | 0 (0.0%) | 1 (0.8%) |
| Liver GVHD Stage | | | |
| 0 | 63 (98.4%) | 58 (100.0%) | 121 (99.2%) |
| 1 | 1 (1.6%) | 0 (0.0%) | 1 (0.8%) |

# COMPARISON OF TREATMENT RESPONSES AT DAY 28 AND 56 FOR PREDNISONE VS. SIROLIMUS

- Day 28 Response was comparable
- Day 28 Response and being on low doses of steroids better for sirolimus (66 vs. 32%%)
- Response (on day 56) more durable for steroids



# BMTCTN 1501: SIROLIMUS RESULTED IN IMPROVED QOL

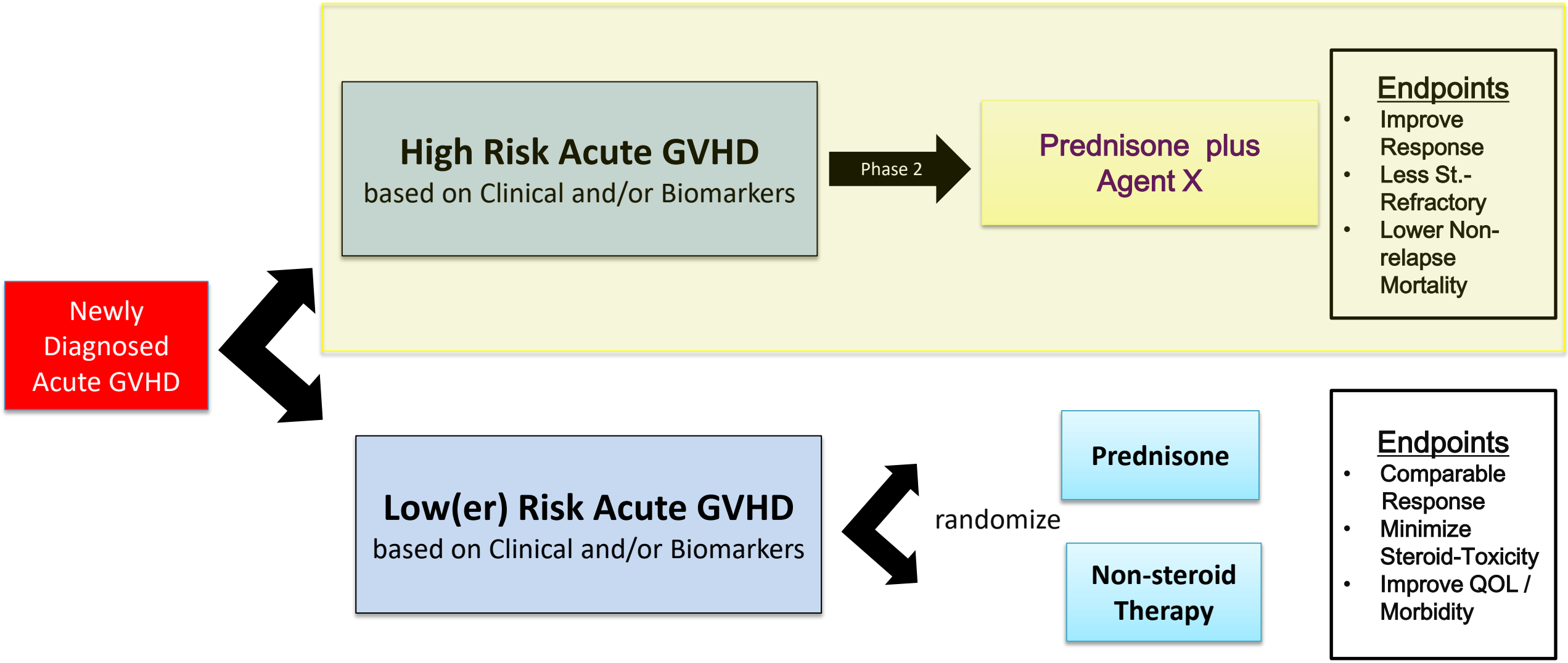


# BMT CTN 1501: CONCLUSIONS

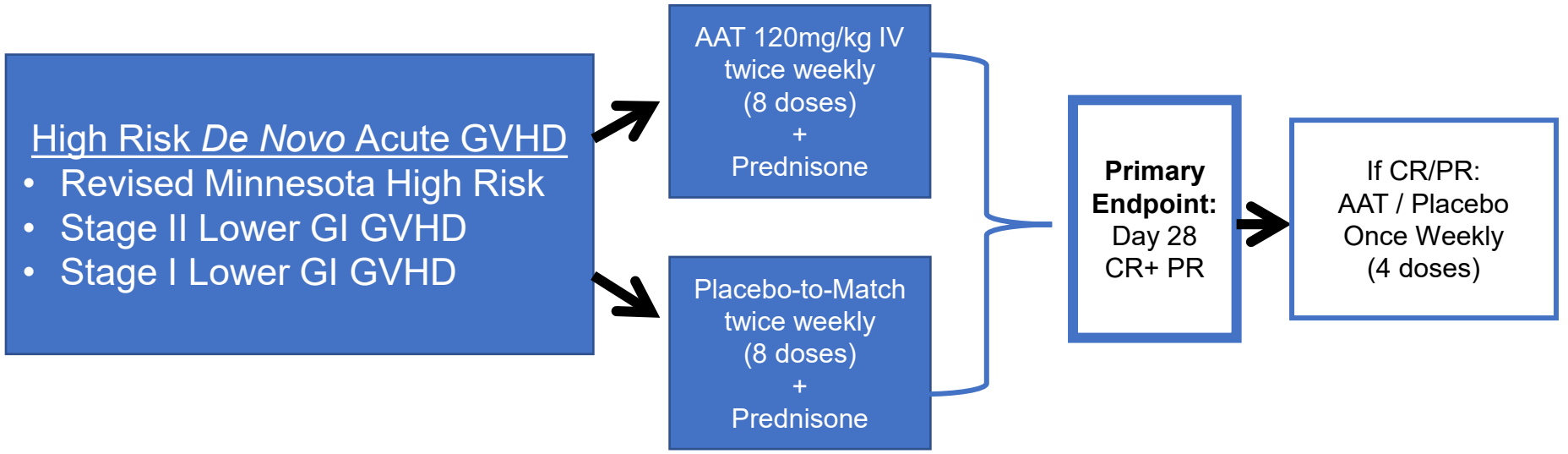
- Sirolimus may serve as alternative to steroids in selected patients with newly diagnosed acute GVHD.
- Comparable Day 28 Response.
- Translated into less steroid exposure, higher likelihood of Discontinuation of Immunosuppressive, less hyperglycemia, improved QOL.
- Primarily tested in Upper GI GVHD, Limited Skin GVHD, **No Data for patients with lower GI GVHD**

❖ Pidala et al. 2020. *Blood*;135:97-107

# Upfront Trials: New Paradigm of Risk Stratification



# Treatment Schema: BMT CTN1705
# AAT in Patients with High-Risk Acute GVHD




National Protocol Chairs
John Magenau
Amin Alousi

# STUDY POPULATIONS FOR ACUTE GVHD TRIALS

- Newly-Diagnosed ("Upfront") Acute GVHD Population

- **Steroid-Refractory Acute GVHD Population**
  - Generally defined as No response or Progression on steroids or Flare in Acute GVHD while on high-doses of steroids (>0.5-1mg per kg).
  - Difficult patient to study (or positively impact)
  - Even when GVHD responds; NRM remains high from infection and organ toxicity.

# JAK (JANUS ASSOCIATED KINASE) INHIBITION

- JAK1 and JAK2 mediate signaling of cytokine and growth factors responsible for hematopoiesis and immune function.
- JAK mediated signaling involves recruitment of STATs (signal transducers and activators of transcription) to cytokine receptors which modulate gene expression.
- Janus kinases serve to transduce extracellular signals from a number of cytokines and growth factors that are upregulated and thought to be involved in the pathogenesis of various inflammatory disease states.
- **Ruxolitinib** is a kinase inhibitor which selectively inhibits JAK1 and JAK2 originally approved for the treatment of patients with myelofibrosis.

# PRE-CLINICAL GVHD MODELS

- Ruxolitinib treatment in mice resulted in less CXCR3 expression, reduced GVHD and improved survival after strain mismatch alloHCT.
- Effect was shown to be mediated by altered trafficking of T-cell to GVHD target organs.
- Other models suggested ruxolitinib impaired differentiation of CD4+T cells into interferon-ϒ and IL-17A-producing cells which are critical to GVHD pathophysiology.
- Ruxolitinib treatment is also believed to increase FoxP3+ T regs in periphery and target tissues.


❖ Choi J, et al. PLoS ONE 2014;9:e109799
❖ Carniti C, et al. Clin Cancer Res 2015;21:3740-49
❖ Spoerl S, et al. Blood 2014;124:3934

# RUXOLITINIB

- FDA Granted Ruxolitinib Breakthrough Designation for Acute GVHD based on retrospective case survey by Zeiser et al.

- In the United States: **REACH1**: A Single-Cohort, Phase 2 Study of Ruxolitinib in Combination With Corticosteroids for the Treatment of Steroid-Refractory Acute Graft-Versus-Host Disease

- International (Non-U.S.A.) : **REACH 2**: Randomized Trial of Ruxolitinib vs. Best Available Therapy (BAT) in patients with steroid-refractory acute GVHD.

# REACH1 STUDY DESIGN:
# OPEN-LABEL, MULTICENTER, PHASE 2 TRIAL

- Eligibility: ≥12 years, first alloHCT, myeloid engraftment, SR-aGVHD who received ≤ 1 line of therapy beyond steroids.

- Treatment Scheme:


- Endpoints
  - Primary: Day 28 Overall Response Rate (CR, VGPR, PR).
  - Key Secondary: Duration of Response at 6 months.
  - Other Secondary: NRM, Safety, Relapse Rate, OS

❖ Jagasia M, et al. Blood 2018:132-601

# OVERALL RESPONSE AT DAY 28 AND 6-MONTH SURVIVAL

| Response at Day 28, N (%) | Grade II (N=23) | Grade III (N=34) | Grade IV (N=14) | TOTAL (N=71) |
|---|---|---|---|---|
| CR | 11 (28%) | 7 (21%) | 1 (7%) | 19 (27%) |
| VGPR | 4 (17%) | 2 (6) | 1 (7%) | 7 (10%) |
| PR | 4 (17%) | 5 (15%) | 4 (29%) | 13 (18%) |
| Overall Response Rate | 19 (83%) | 14 (42%) | 6 (43%) | 29 (55%) |

* 52 patients (73%) had a response at any time during treatment (including CR, 56%)

| | Day 28 Responders (N=39) | Responders Any Time (N=13) | Non-Responders (N=19) |
|---|---|---|---|
| 6-Month OS (95% Confidence Interval) | 73% (56-85) | 36% (12-61) | 16% (4-35) |

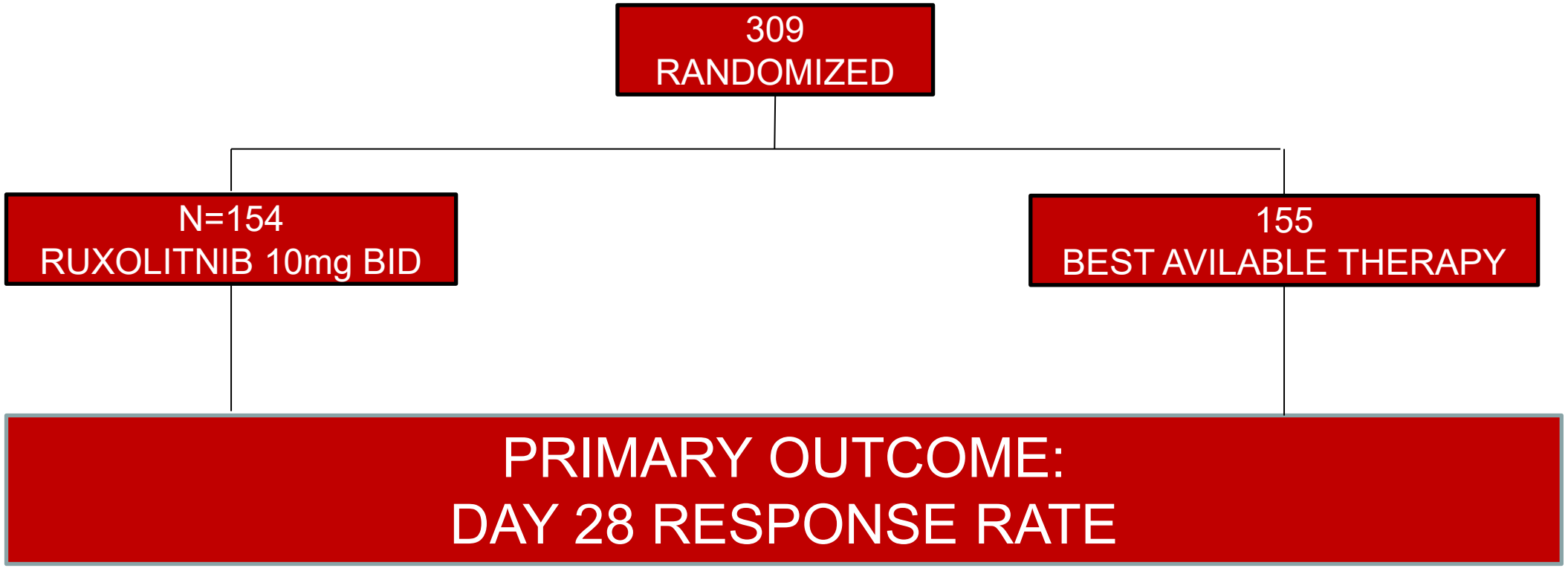
❖ Jagasia M, et al. Blood 2018:132-601

# OVERALL RESPONSE RATE: BASED ON ORGAN INVOLVED AND NUMBER OF ORGANS

| Acute GVHD Characteristic (N) | Overall Response Rate | 95% Confidence Interval |
|---|---|---|
| Skin (N=36) | 61% | (44-77) |
| Lower GI (N=50) | 46% | (32-61) |
| Liver (N=15) | 27% | (8-55) |
| Number of Organs<br>1 organ (N=36)<br>2 or > organs (N=35) | <br>63%<br>47% | |

❖ Jagasia M, et al. Blood 2018:132-601

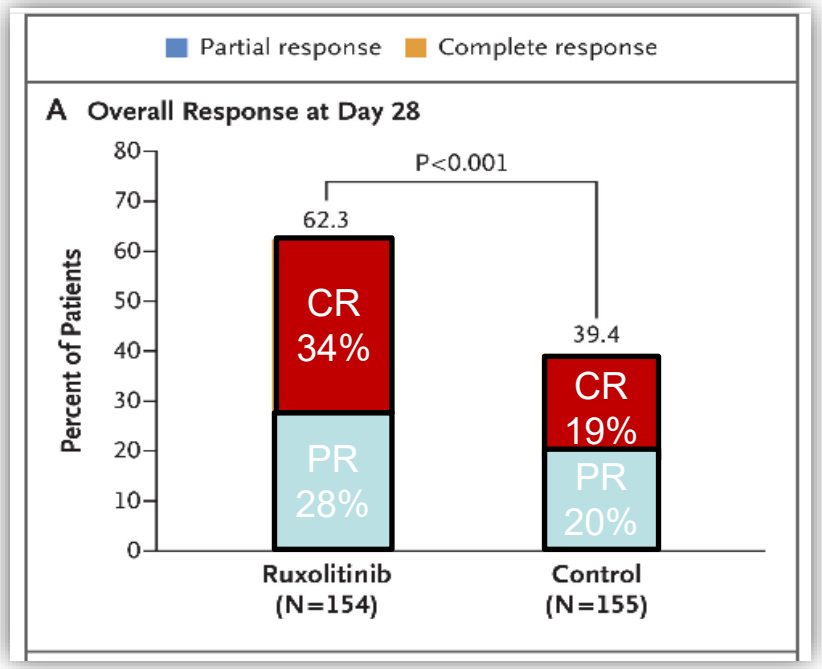
# REACH 2: RANDOMIZED TRIAL OF RUXOLITNIB VS. BAT



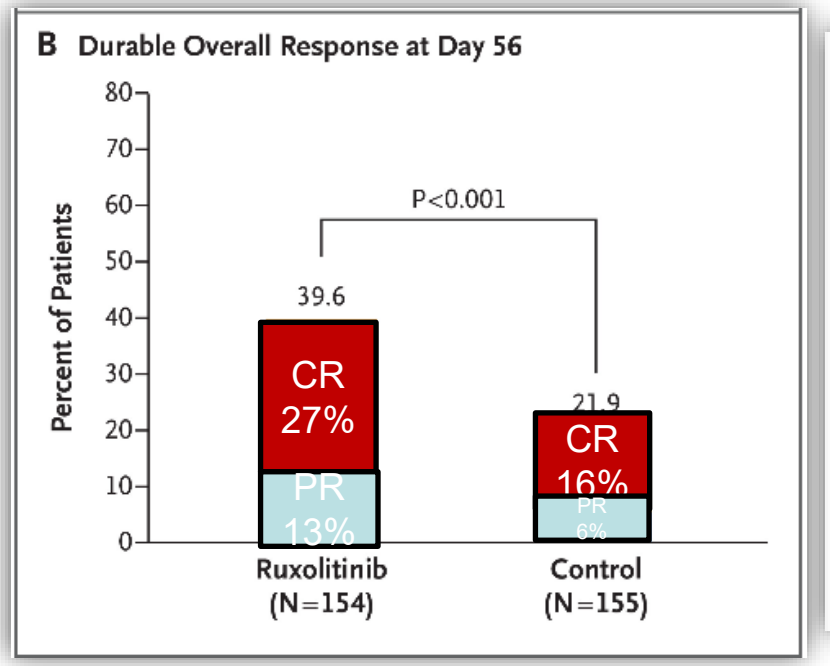

**Zeiser et al. NEJM 2020; 382: 1800-1810**

# REACH 2: RANDOMIZED TRIAL OF RUXOLITNIB VS. BAT
# RUXO CAN BE CONSIDERED THE STANDARD OF CARE

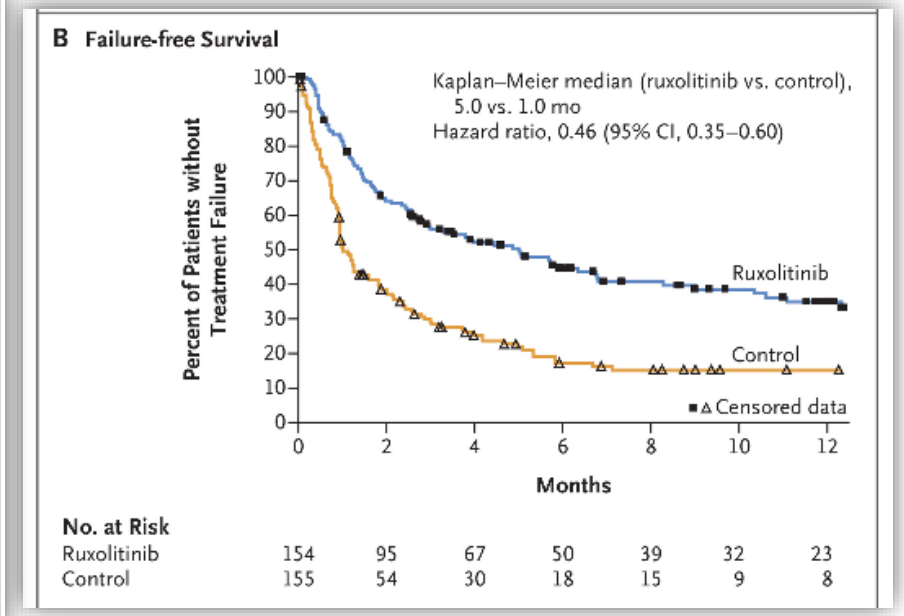
Day 28 RR: 62 vs. 39%




Day 56 RR: 40 vs. 22%




FFS @ 6 months: ~50 vs. 20%




❖ **Zeiser et al. NEJM 2020; 382: 1800-1810**

# EFFICACY RESULTS RUXO VS. BAT IN ST-REFRACTORY ACUTE GVHD

| | Ruxolitinib | BAT |
|---|---|---|
| Response Rate<br>▪ Grade II<br>▪ Grade III<br>▪ Grade IV | <br>75%<br>56%<br>53% | <br>51%<br>38%<br>23% |
| Loss of Response @ 6 months | 10% | 39% |
| NRM @ 18 months | 49% | 51% |

❖ **Zeiser et al. NEJM 2020; 382: 1800-1810**

# REACH 2: RANDOMIZED TRIAL OF RUXOLITNIB VS. BAT RUXO CAN BE CONSIDERED THE STANDARD OF CARE

- In randomized trial, Ruxolitinib resulted in higher response rates for patients with steroid-refractory acute GVHD.
- Responses were more durable with Ruxolitinib.
- Overall Survival was nearly double BAT (11.1 vs. 6.5 months, but did not reach statistical significance).
- Overall well tolerated with cytopenias most common side effect.

❖ **Zeiser et al. NEJM 2020; 382: 1800-1810**

# RUXO CAN BE CONSIDERED THE STANDARD OF CARE FOR ST.-REFRACTORY AGVHD HOWEVER BETTER TREATMENT IS STILL NEEDED

- Day 56 durable response rate was only 40%.
- Roughly 50% patients still died of non-relapse causes.

**Zeiser et al. NEJM 2020; 382: 1800-1810**

# *Next Generation Therapies: Targeting High-risk GVHD Organ(s)*

## THERAPIES DIRECTED AT THE GASTROINTESTINAL TRACT

Fecal Microbiota Transplant

Anti-complement Therapy

Alpha-1-antitrypsin (AAT)

Recombinant IL-22

Anti-integrins


- Kakihana K, et al. Blood 2016; 128: 2083-88
- DeFlipp Z, et al. Blood Adv 2018; 7: 745-53
- Kwan WH, et al. J Clin Invest.2012; 6: 2234-8.
- Magenau JM, et al. Blood 2018;131:1372-79
- Marondes AM, et al. Biol Blood Marrow Transplant 2016;22:1596-160
- Hanash AM, et al. Immunity 2012; 2: 339-50
- Lindemans CA, et al. Nature 2015; 528: 560-64
- Kekre N, et al. Blood 2017;130:3252
- Floisand Y, et al. Biol Blood Marrow Transplant 2017; 1: 172-75

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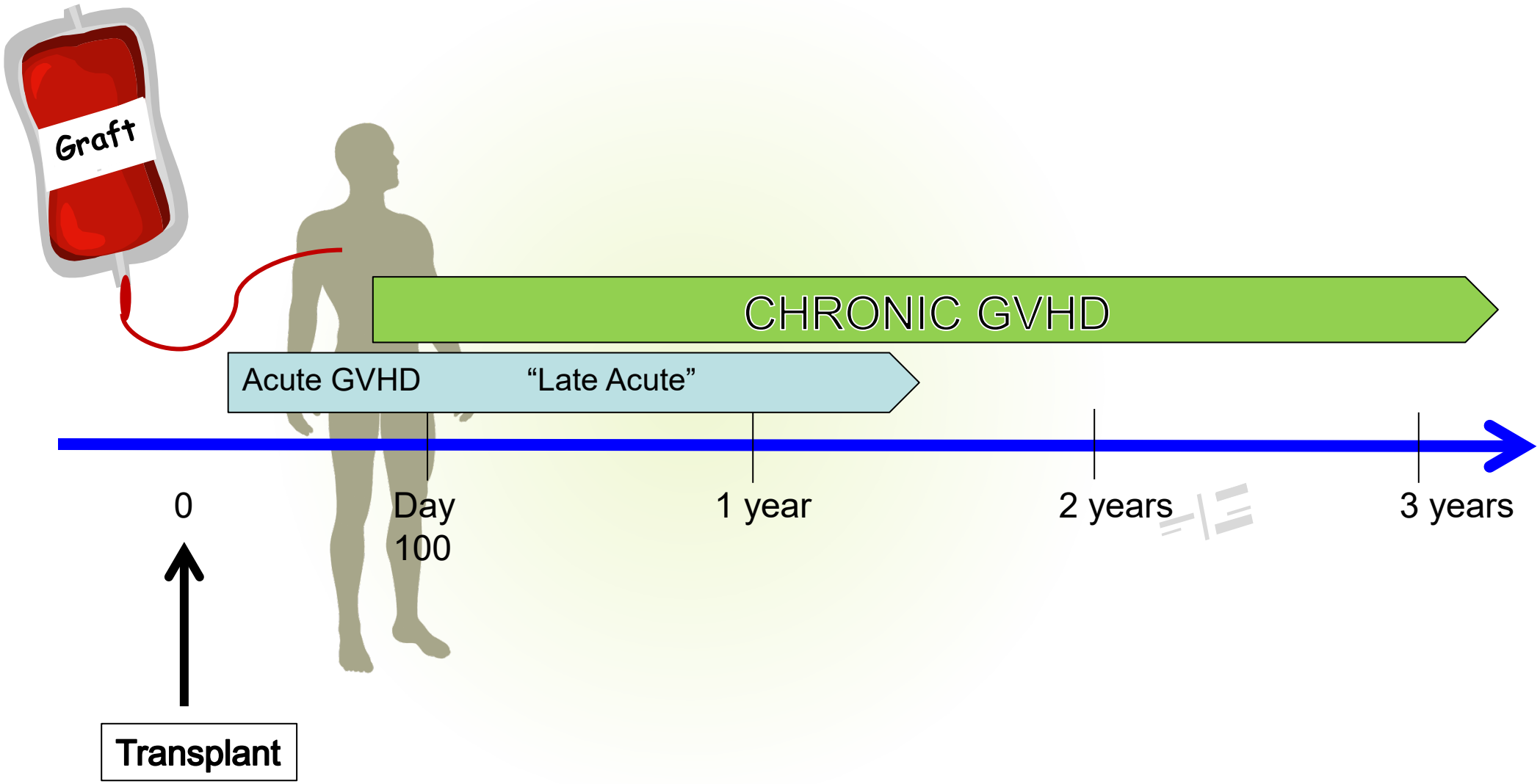

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- 54 y/o woman with AML underwent a Peripheral Blood HCT from a Matched Unrelated Donor (MUD) following conditioning chemotherapy of Busulfan and Fludarabine.
- GVHD Prophylaxis was Tacrolimus and Short-course Methotrexate.
- At Day +35 she developed Grade III Acute GVHD of the Skin and Lower GI tract for which she received treatment with systemic steroids and Ruxolitinib as second-line therapy.
- Her AGVHD improved and at day +125 she returns to her home community on low dose steroids and tacrolimus.
- She now presents for her 9 month visit follow-up and reports significant dry eyes with impaired vision, oral pain with ulcerations, skin “thickening”, stiff joints and dyspareunia.

# Chronic GVHD

- Major Contributor to late mortality and QOL.
- Median Onset 4-6 months; majority of cases (90%) by 2 years.
- Incidence 30-60%
- Protean Manifestations:
  - Skin
  - Eyes
  - Mouth
  - Fascia/ Joints
  - Genital Tract
  - Lungs
  - Liver
  - G.I. Tract
  - Kidneys

# IMPLICATION OF CHRONIC GVHD:
# *DURATION OF IMMUNOSUPPRESIVE THERAPY (IST)*

- Median Duration of IST = **2 years**
- % of Pts @ 7 yrs who are alive, w/o relapse needing IST = **15%**
- Risk Factors for Longer Duration of IST
  - Receipt of Peripheral Blood
  - Female Donor for Male Patient
  - Receipt of HLA Mismatch Unrelated
  - Elevated Bilirubin
  - Multiple organs

* Stewart, Storer, Storek et al. *Blood*. 2004

# GOALS OF TREATMENT IN PATIENTS WITH CHRONIC GVHD

- Improvement or Stabilization of Organ Manifestations
- Improvement in Patient's Functional Capacity and QOL
- Improvement in Overall Survival
- All while limiting short-term (infections, diarrhea, cytopenias, etc.) and long-term toxicities (Avascular Necrosis, CV Risk, Diabetes, Osteoporosis, etc).

# TREATMENT OF CHRONIC GVHD

- Steroids @ 0.5-1mg/kg  with or without Calcineurin Inhibitor
- Previous Randomized Study of MMF closed early due to higher death (and trend for higher relapse) in MMF arm compared to steroids alone
  - **Martin et. al. *Blood*. 113: 5074-82. 2009.**
- Ibrutinib is the only FDA-approved therapy.
- Previously Tested:
  - Extracorporeal Phototherapy (ECP vs. BAT) in St.-Refractory
  - Sirolimus: BMTCTN 0801
  - Rituximab and Imatinib
  - Carfilzomib / Ixazomib
- Recent Interest / Drug's for which FDA approval is pending:
  - Ruxolitinib: REACH 3 Trial: Phase 3, open-label trial of Ruxo vs. BAT in st.-refractory
  - KD025 (*Belumosudil)*: ROCKstar Trial: Phase 2 trial

# IBRUTINIB INHIBITS BTK AND ITK

- Both B and T-cells play critical role in the pathogenesis of chronic GVHD.
- Activation of B-cell receptor triggers the Bruton-tyrosine kinase (BTK) pathway which regulates B-cell survival.
- Interleukin-2 inducible kinase (ITK), mediated by phospholipase C gamma is involved in the selective activation of T-cell subsets that drive immune reactivity.
- Mice that are deficient in BTK or ITK don't develop chronic GVHD *.

❖ Dubovsky et al. *J Clin Invest*. 2014

# Design: Eligibility and Primary Endpoint

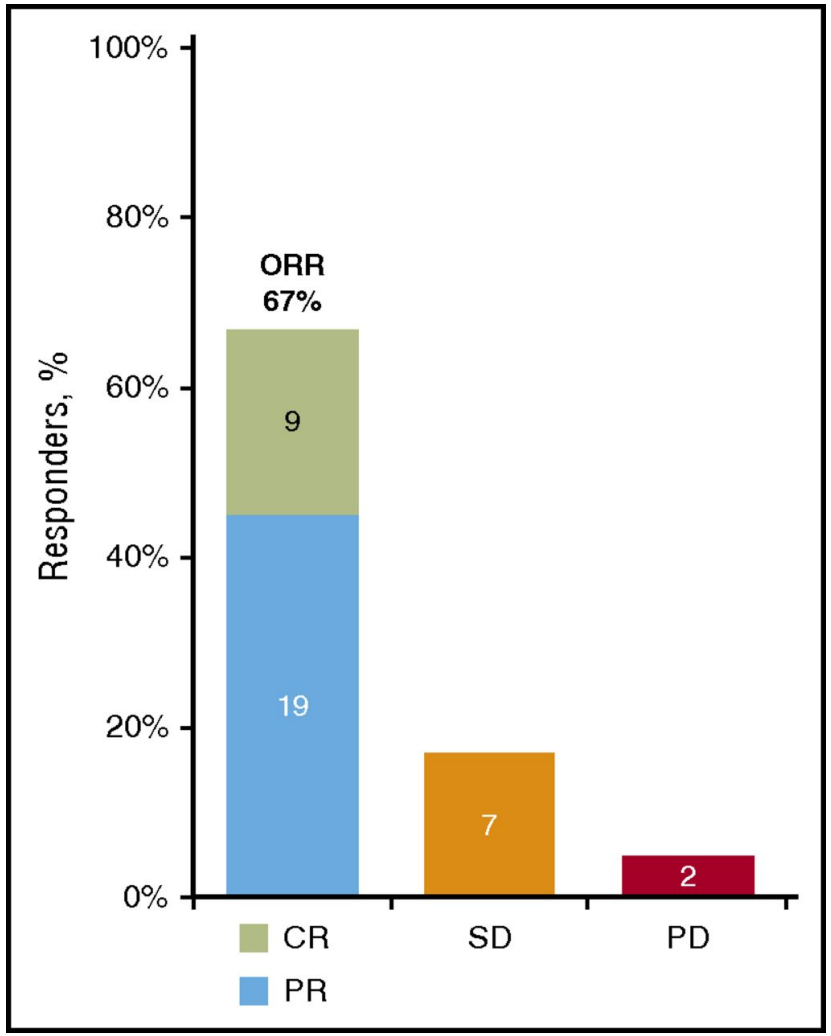
- Patients $\geq$ 18 years and had steroid refractory or dependent chronic GVHD.
- $\leq$ 3 lines of prior therapy for chronic GVHD.
- Active chronic GVHD was required defined as > 25% erythemic rash or NIH mouth score of >4.
- "These manifestations were selected b/c they were expected to respond rapidly to an effective therapy . . . "
- Phase 1b/2 design with starting dose of 420mg chosen in phase 1b portion.
- Phase 1b $1^0$ Endpoint was safety in first 28 days; phase 2 best overall RR.

❖ **David Miklos et al. Blood 2017;130:2243-2250**

# PATIENT POPULATION MORE *FAVORABLE* THAN RECENTLY TESTED DRUGS (RUXO/ KD025)

| Characteristics | Total (N=42) |
|---|---|
| Median age (range) | 56 years (19-74) |
| Median time from transplant (range) | 26 months (3-80) |
| Steroid refractory of cGVHD (%) | 14 (33%) |
| No of Involved Organs | |
| 1-2 | 30 (71%) |
| 3 | 9 (21%) |
| 4 or > | 3 (7%) |
| Involved Organs | |
| Mouth | 36 (86%) |
| Skin | 34 (81%) |
| GI Tract | 15 (36%) |
| Liver | 3 (7%) |
| Lungs | 2 (5%) |
| Median Prior Therapies (range) | 1 (1-3) |
| Median Prednisone Dose at Enrollment (range) | 0.31 mg/kg/ day (0.1-1.3) |

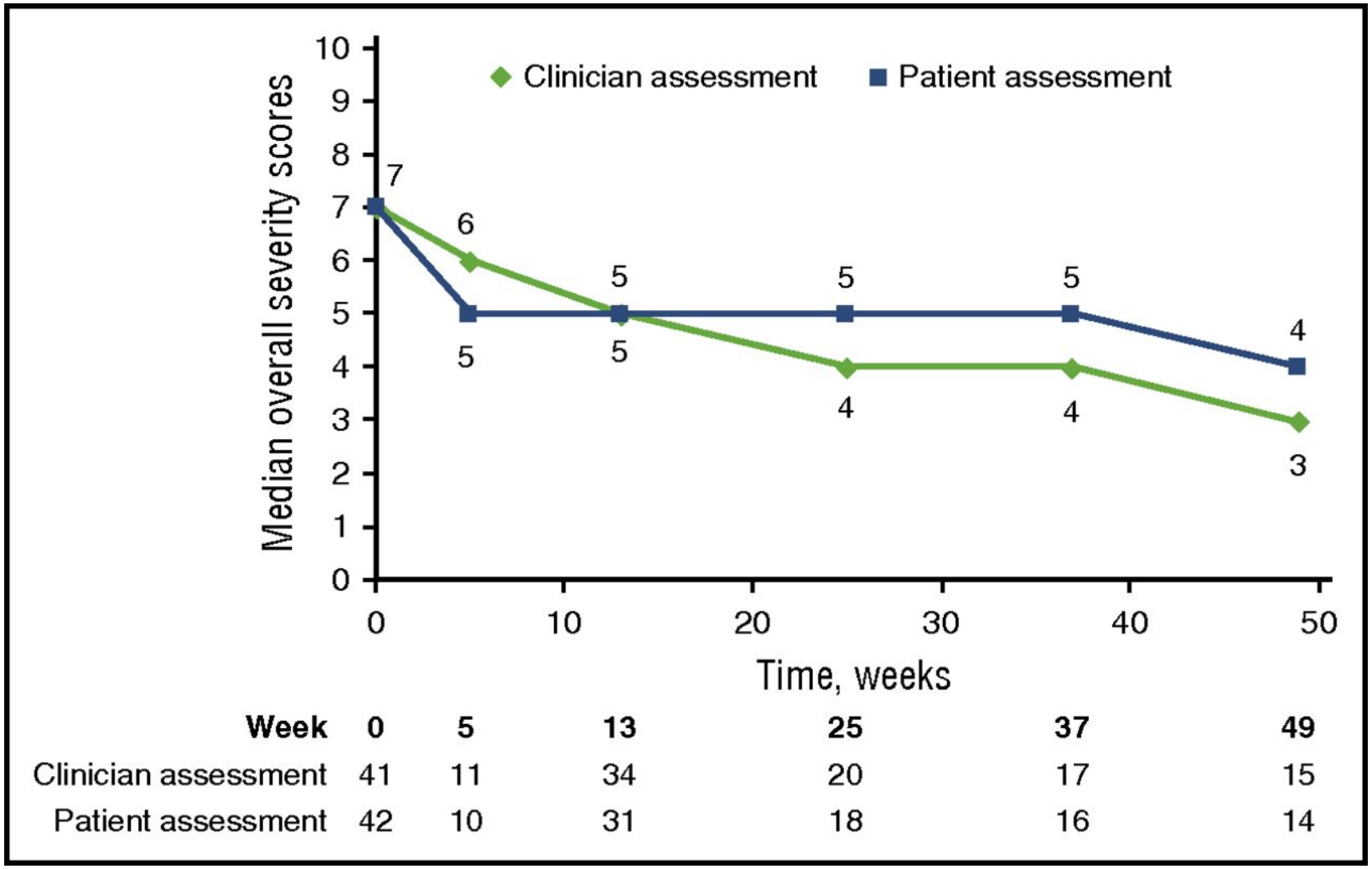
# BEST CHRONIC GVHD RESPONSE




CR= 21%
PR= 45%
Responses noted from 1- 3 months.
Lee Chronic GVHD Symptom Scale: 24% had clinically meaningful reduction.

**David Miklos et al. Blood 2017;130:2243-2250**

# IMPROVEMENT IN CGVHD SYMPTOMS AND SEVERITY




| Week | 0 | 5 | 13 | 25 | 37 | 49 |
|---|---|---|---|---|---|---|
| Clinician assessment | 41 | 11 | 34 | 20 | 17 | 15 |
| Patient assessment | 42 | 10 | 31 | 18 | 16 | 14 |

**David Miklos et al. Blood 2017;130:2243-2250**

**Table 2. Treatment-emergent adverse events reported in ≥10% of patients regardless of the cause**

| Adverse event (N = 42) | Grade 1 | Grade 2 | Grade 3 | Grade 4 | Grade 5 |
|---|---|---|---|---|---|
| Fatigue | 5 (12) | 14 (33) | 5 (12) | 0 | 0 |
| Diarrhea | 7 (17) | 4 (10) | 4 (10) | 0 | 0 |
| Muscle spasms | 8 (19) | 3 (7) | 1 (2) | 0 | 0 |
| Nausea | 8 (19) | 3 (7) | 0 | 0 | 0 |
| Bruising | 6 (14) | 4 (10) | 0 | 0 | 0 |
| Upper respiratory tract infection | 3 (7) | 5 (12) | 0 | 0 | 0 |
| Pneumonia | 1 (2) | 0 | 4 (10) | 1 (2) | 1 (2) |
| Pyrexia | 4 (10) | 1 (2) | 2 (5) | 0 | 0 |
| Headache | 3 (7) | 2 (5) | 2 (5) | 0 | 0 |
| Fall | 6 (14) | 1 (2) | 0 | 0 | 0 |
| Cough | 4 (10) | 2 (5) | 0 | 0 | 0 |
| Constipation | 3 (7) | 2 (5) | 0 | 0 | 0 |
| Dyspnea | 4 (10) | 0 | 1 (2) | 0 | 0 |
| Hyperglycemia | 1 (2) | 1 (2) | 3 (7) | 0 | 0 |
| Hypokalemia | 0 | 2 (5) | 3 (7) | 0 | 0 |
| Peripheral edema | 1 (2) | 4 (10) | 0 | 0 | 0 |

Data are presented as n (%).

- Infectious Complications: 69% including 36% grade 3 or >
- 2 AE's related deaths
- Dose Reductions from AE's occurred in 13 / 30 patients (31%).
- Most Common Reason for Dose Reduction= fatigue
- Most Common Reason for D/C= Fatigue

# Results:

- At median follow-up of 14 months, 12 patients (29%) were still receiving therapy with 70% stopping therapy.
- Reasons for D/C:
  - Adverse Events: 14/30 patients.
  - Chronic GVHD progression: 5/30 patients
  - Patient Decision: 6/30 patients
  - Resolution of GVHD: 2/30

❖ **David Miklos et al. Blood 2017;130:2243-2250**

# CONCLUSIONS: IBRUTINIB

- Ibrutinib demonstrated efficacy with 2/3 of patients experiencing an overall-response.
- 420mg dose determined to be R2PD based on 6 patients.
- Efficacy of lower doses not studied.
- Toxicity is not uncommon with fatigue, diarrhea, infections occurring in roughly 1/3 of patients.

# Prospective, Randomized Control Trial of ECP in Chronic GVHD

- Only published prospective, randomized control trial of ECP in chronic GVHD.
- This single-blind, multicenter study randomized 100 patients in a 1:1 ratio to ECP therapy in addition to conventional immunosuppression *versus* conventional immunosuppression alone.
- Eligible patients received at least 2 weeks of steroids and were considered steroid-refractory, dependent or intolerant.

❖ Flowers M E D et al. Blood 2008;112:2667-2674

# Prospective, Randomized Control Trial of ECP in Chronic GVHD

- ECP was administered on 3 days for the first week, and then twice weekly (on consecutive days) through 12 weeks.
- Patients in the ECP arm who responded were allowed to continue with 2 ECP sessions every 4 weeks until week 24.
- Control arm patients were allowed to cross-over to ECP if progressed or after completion of 12 weeks.

❖ Flowers M E D et al. Blood 2008;112:2667-2674

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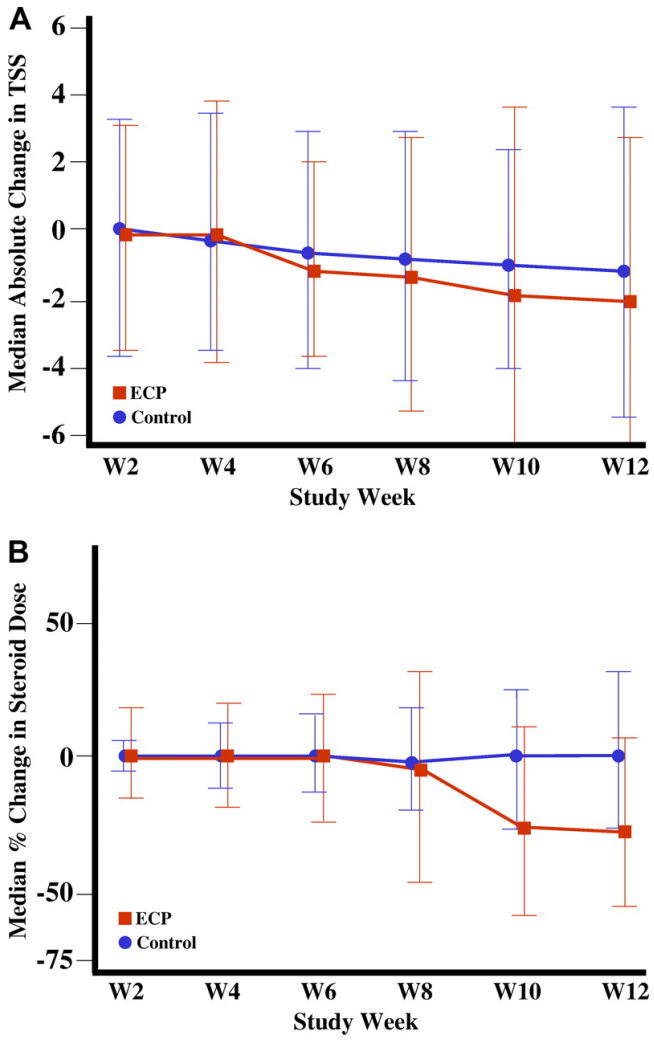
# Improvement in Total Skin Score (TSS) and reduction in steroid dose through week 12.




- Median changes in TSS from baseline until week 12: **ECP(14.5%)** and **control (8.5%)** arms were not statistically different (p=.48).
- **25.0% (n 12) of ECP-patients** and **12.8% (n 6) of control-patients** had a >/= 50% reduction in steroids (*P* .13).
- % of patients having both a 50% or > reduction in daily steroid dose and a 25% or > reduction in the TSS was higher in the ECP group than the control group (**8.3%; 4 patients** vs **0%; 0 patients**; *P* .04).
- **20.8% the ECP-patients** and **6.4% of the control-patients** had a 50% or > reduction in steroid dose and a daily dose of < 10 mg/day (*P* .04).



Flowers M E D et al. Blood 2008;112:2667-2674

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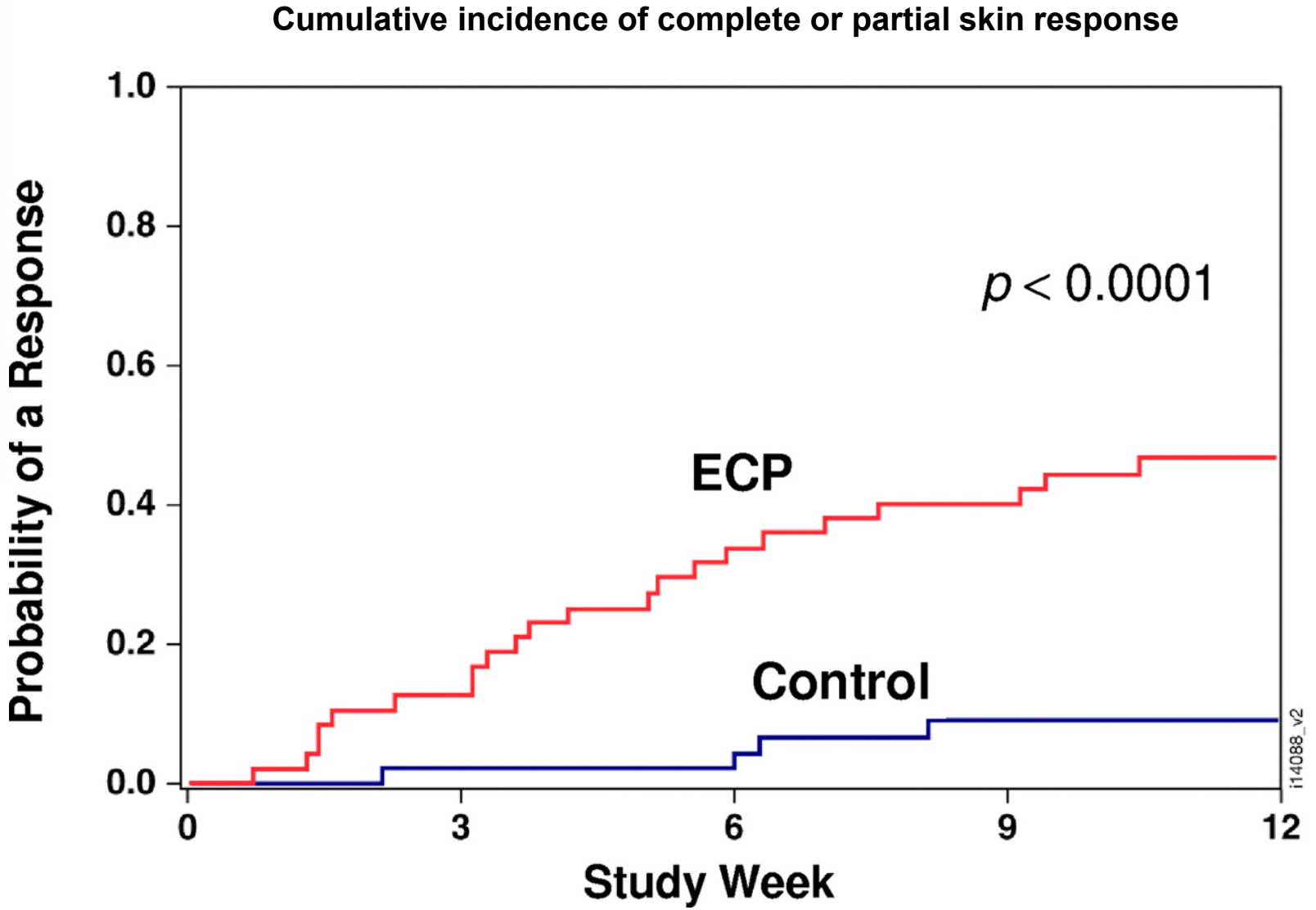
# Un-blinded assessment of Skin Involvement by an Experienced Clinical Investigator






Flowers M E D et al. Blood 2008;112:2667-2674

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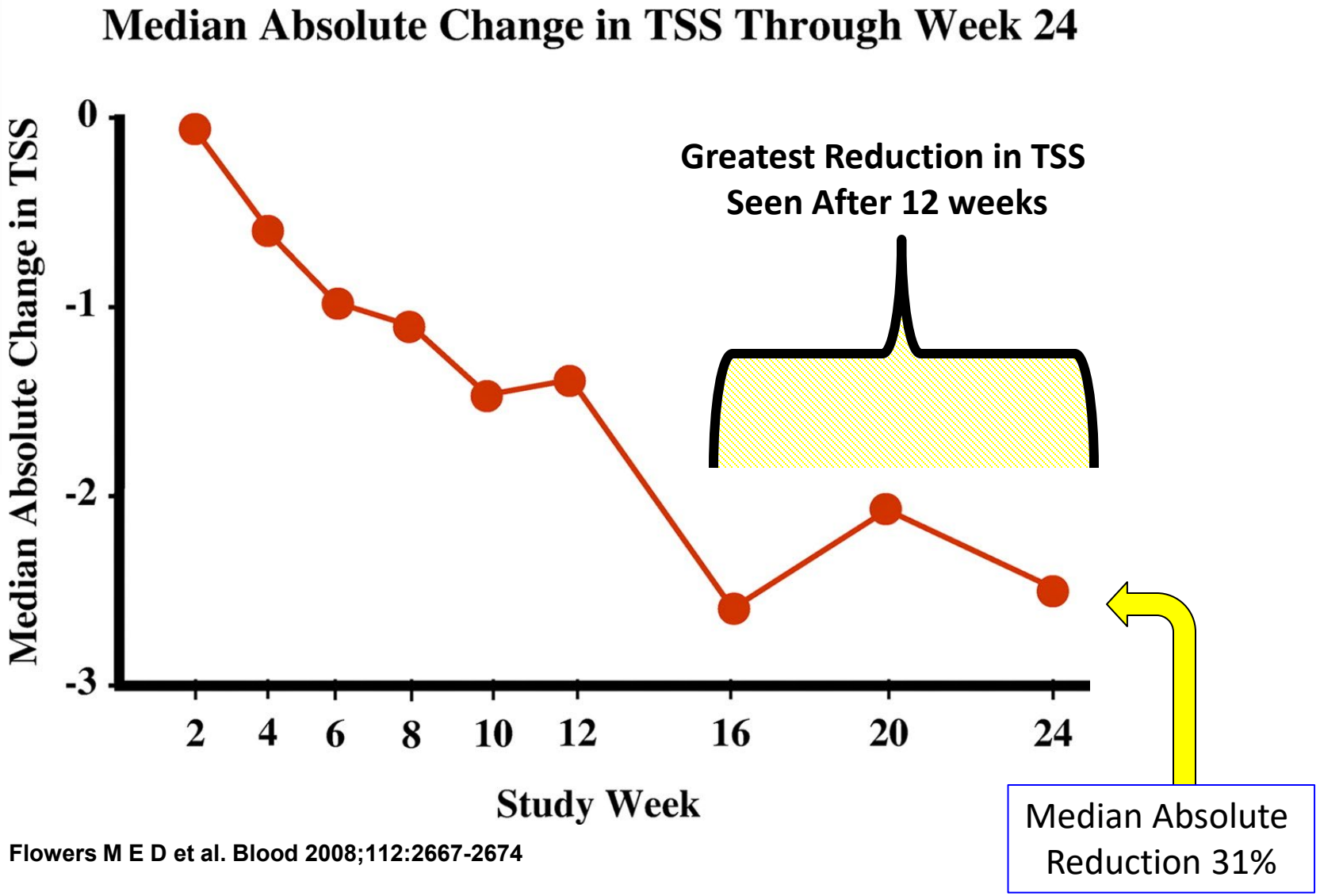
**Median absolute change in TSS through week 24 in ECP Patients.**

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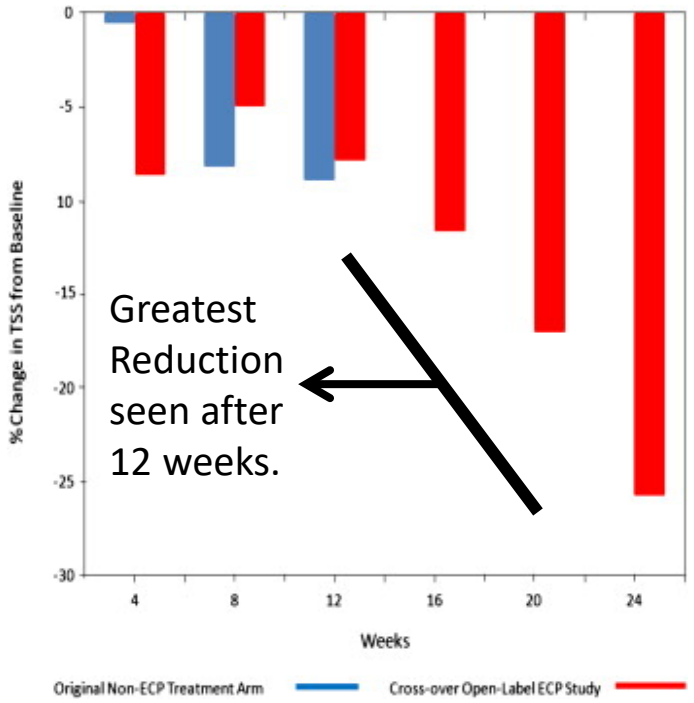



Figure 2 Comparison of percent decrease in total skin score (TSS) between patients of initial non-ECP standard therapy and crossover open-label ECP treatment.

Hildegard T. Greinix , Koen van Besien , Ahmet H. Elmaagacli , Uwe Hillen , Andrew Grigg , Robert Knobler , Dennis...

**Progressive Improvement in Cutaneous and Extracutaneous Chronic Graft-versus-Host Disease after a 24-Week Course of Extracorporeal Photopheresis—Results of a Crossover Randomized Study**

Biology of Blood and Marrow Transplantation, Volume 17, Issue 12, 2011, 1775 - 1782

http://dx.doi.org/10.1016/j.bbmt.2011.05.004

# RUXOLITINIB (JAK-STAT PATHWAY) AND CHRONIC GVHD

- Pathway is involved in signaling function of many inflammatory cytokines which impact differentiation of key effector cells
  - IFN-gamma
  - IL-2
  - IL-6
  - IL-12
  - IL-23
- Inhibits CXCR3 expression impairing effector cell trafficking
- Impairs T cell development via dampening inflammatory cytokines
- Impacts dendritic cell (APC's) development
- Increase in $T_{reg}/T_{effector}$ ratios
- Less Th17 cell differentiation

# RUXOLITINIB FOR CHRONIC GVHD: CASE SERIES FROM CITY OF HOPE (46 PATIENTS)

**Table 2**
Baseline Disease Severity

| Parameter | Score, % (n) | | | |
|---|---|---|---|---|
| | 3 (Severe) | 2 (Moderate) | 1 (Mild) | 0 |
| Skin | 63 (29) | 11 (5) | N/A | 26 (12) |
| Mouth | 4 (2) | 13 (6) | 15 (7) | 67 (31) |
| Eyes | 9 (4) | 13 (6) | 26 (12) | 52 (24) |
| Lungs | 4 (2) | 7 (3) | 11 (5) | 78 (36) |
| Joints/fascia | 9 (4) | 24 (11) | 15 (7) | 52 (24) |
| Global severity score | 76 (35) | 15 (7) | 9 (4) | 0 (0) |

N/A indicates not applicable.
Severity scores based on the 2014 NIH Consensus Project Report on Diagnosis and Staging of cGVHD [4].

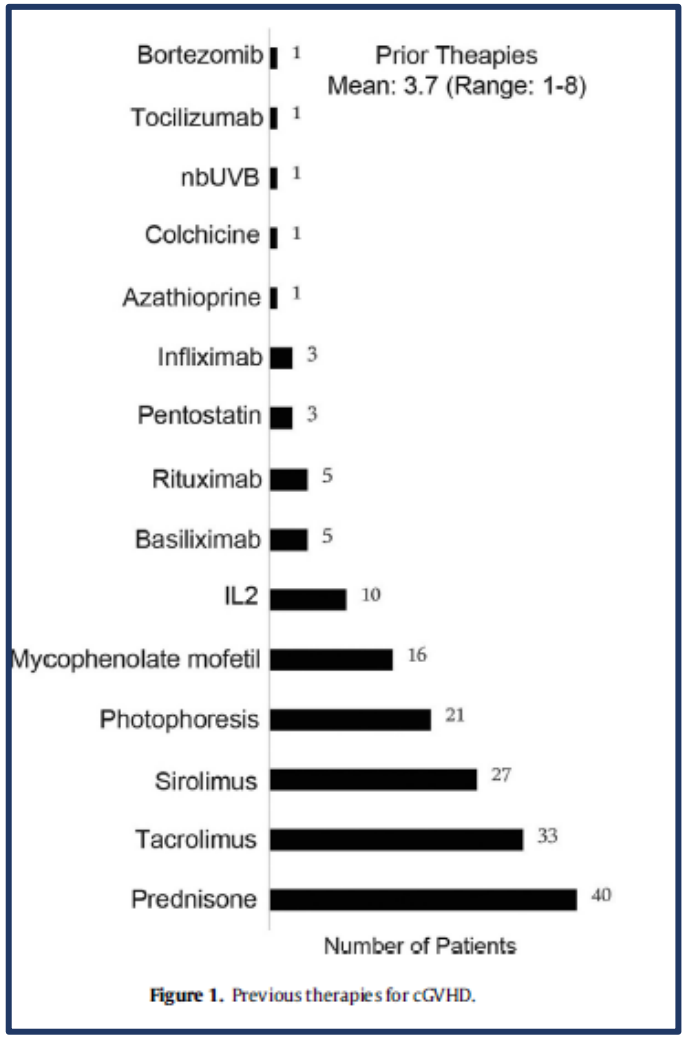


Figure 1. Previous therapies for cGVHD.

- Modil et al. Biol Blood Marrow Transplant (25) 2019.

# RUXOLITINIB FOR CHRONIC GVHD: CASE SERIES FROM CITY OF HOPE (46 PATIENTS)

**Table 3**
Global Response

| Response | 6 months, % (n) | 12 months |
|---|---|---|
| CR | 10 (5) | 13.0 (6) |
| PR | 37 (17) | 30.4 (14) |
| Stable disease | 15.2 (7) | 15 (5) |
| Overall response rate | 47.8 (22) | 43.4 (20) |

- **FFS at 1-year= 54%**
- **Treatment failure= 46%**
- **52% of patients developed infection in 1 year**
- **Cytopenias were rare and mild**

**Table 4**
Organ-Specific Response at 1 Year

| Response | Organ-Specific Response at 6 and 12 mo (n of Patients with Organ Involved at Baseline), % | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Skin (n = 39) | | Mouth (n = 15) | | Eyes (n = 23) | | Lungs (n = 10) | | Joints (n = 23) | |
| | 6 mo | 12 mo | 6 mo | 12 mo | 6 mo | 12 mo | 6 mo | 12 mo | 6 mo | 12 mo |
| CR | 12.5 | 15 | 40 | 60 | 0 | 4.3 | 10 | 10 | 9.1 | 9.1 |
| PR | 15 | 10 | 6.7 | 0 | 21.7 | 21.7 | 0 | 0 | 36.4 | 31.8 |
| No response/ failed | 72.5 | 75 | 53.3 | 40 | 78.2 | 73.9 | 90 | 90 | 54.5 | 59.1 |

❖ Modil et al. Biol Blood Marrow Transplant (25) 2019.

# *REACH 3 TRIAL*

A phase III randomized open-label multi-center study of ruxolitinib vs. best available therapy in patients with corticosteroid-refractory chronic graft vs host disease after allogeneic stem cell transplantation

- Primary Endpoint:

- Efficacy assessed by overall response rate (ORR) at 6 months

- Secondary Endpoints:

- Rate of failure-free survival (FFS)
- Best overall response (BOR)
- Cum incidence of (malignancy) relapse
- Changes in Functional Assessment of Cancer therapy - Bone Marrow Transplantation (FACT-BMT)
- Changes in EQ-5D.
- Incidence and severity of adverse events
- Change in the modified Lee cGvHD symptom scale score
- Overall survival (OS)

ASH MEETING 2020 !!!!!!

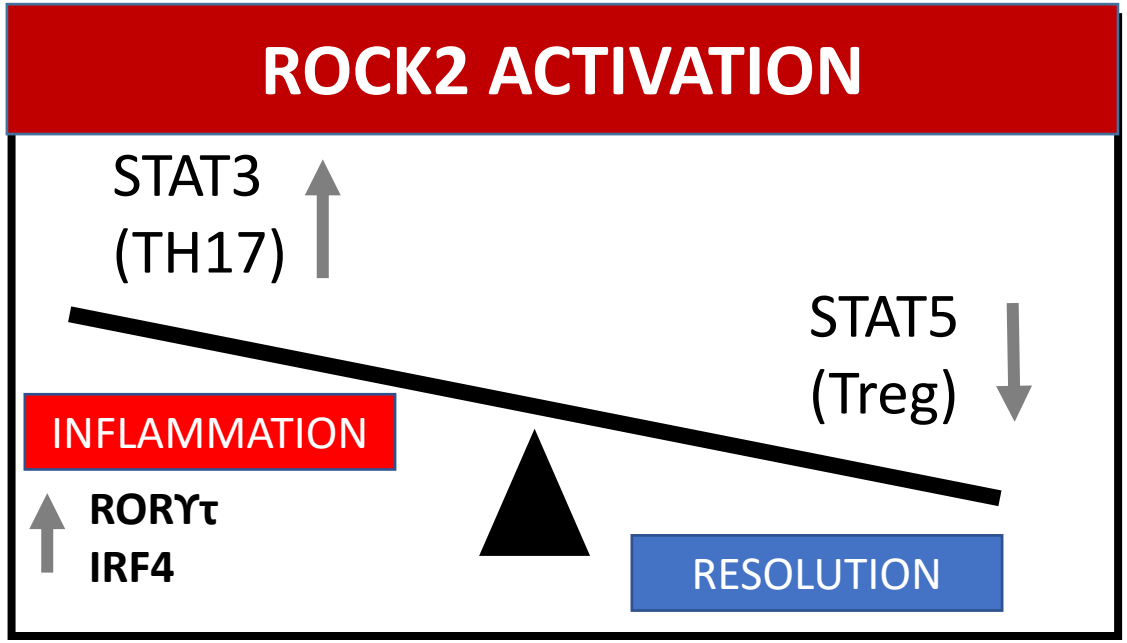
# *REACH 3 TRIAL*: ASH 2020

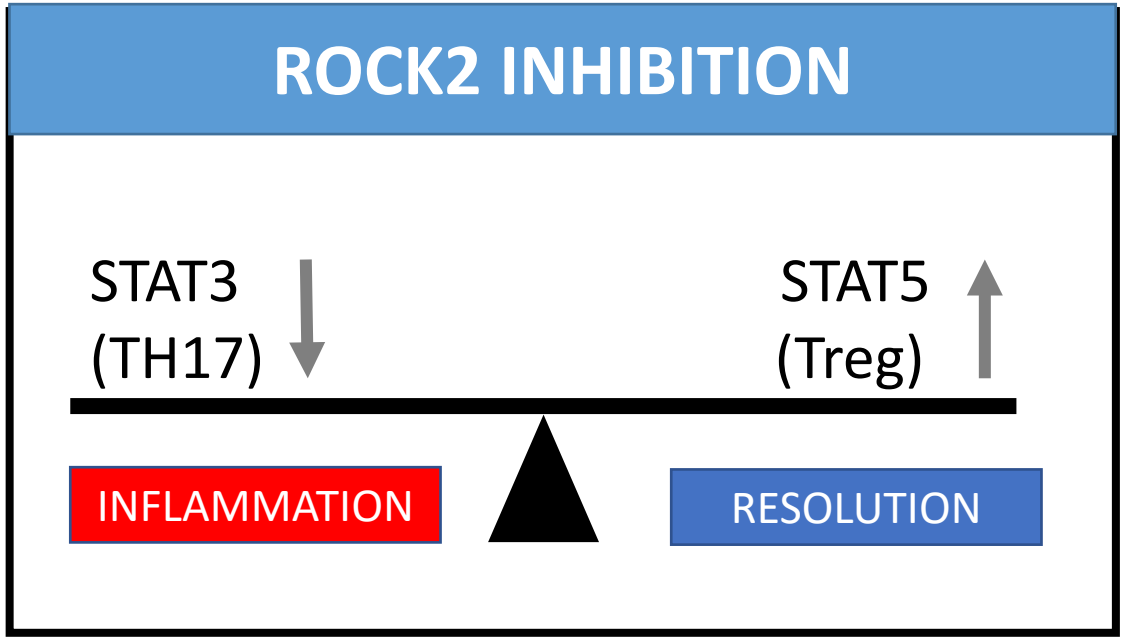
- N=329 patients (Rux=165 / BAT=164)
- NIH Moderate: 48% / Severe  GVHD: 52%
- Primary Endpoint:  ORR at completion of cycle 6: 50% vs. 26%, $p<0.0001$
- FFS: median not reached for Rx vs. 5.7 months BAT; HR: 0.370 (95% CI: 0.27-0.51)
- Rates of SAE's comparable in two arms (57% vs. 58%)
- Most common AE in RUX was anemia (29%) vs. 13% (BAT)
- Infection rates comparable

# KD025 is an Oral Selective ROCK2 Inhibitor

## ROCK2 Inhibition Rebalances Immune Response to Treat Immune Dysfunction

- **Rho-associated coiled-coil kinase (ROCK) plays a central role in coordination and balancing of T-cell mediated immune responses**
  - Two isoforms exist: ROCK1 and ROCK2
- **ROCK2 inhibition**
  - Reduces STAT3 phosphorylation and increases STAT5 phosphorylation
  - Downregulates TH17 responses and increases Treg function, helping to resolve immune dysregulation



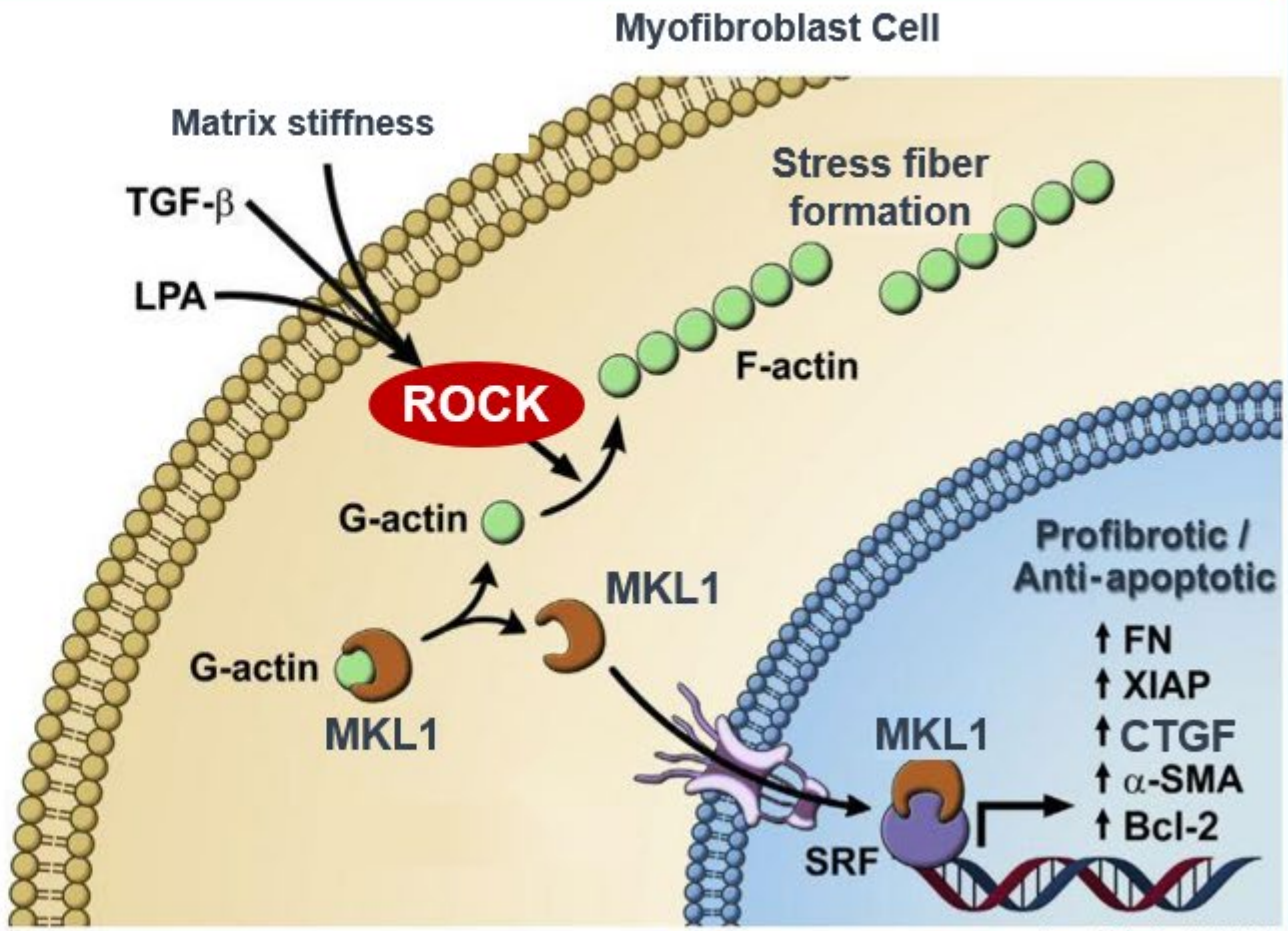


- Tybulewicz et al. *Nat Rev Immunol*. 2009
- Zanin-Zhorov et al. *Proc Natl Acad Sci*, 2014
- Flynn /Blazar. *Blood*. 2016

# ROCK is an Intercellular Integrator of Pro-Fibrotic Signals

## ROCK Regulates Multiple Profibrotic Processes, Including Myofibroblast Activation

- ROCK is downstream of major pro-fibrotic mediators
- ROCK regulates fibroblast differentiation to myofibroblasts, a pathological cell type in fibrosis
- ROCK mediates stress fiber formation
- ROCK regulates transcription of pro-fibrotic genes

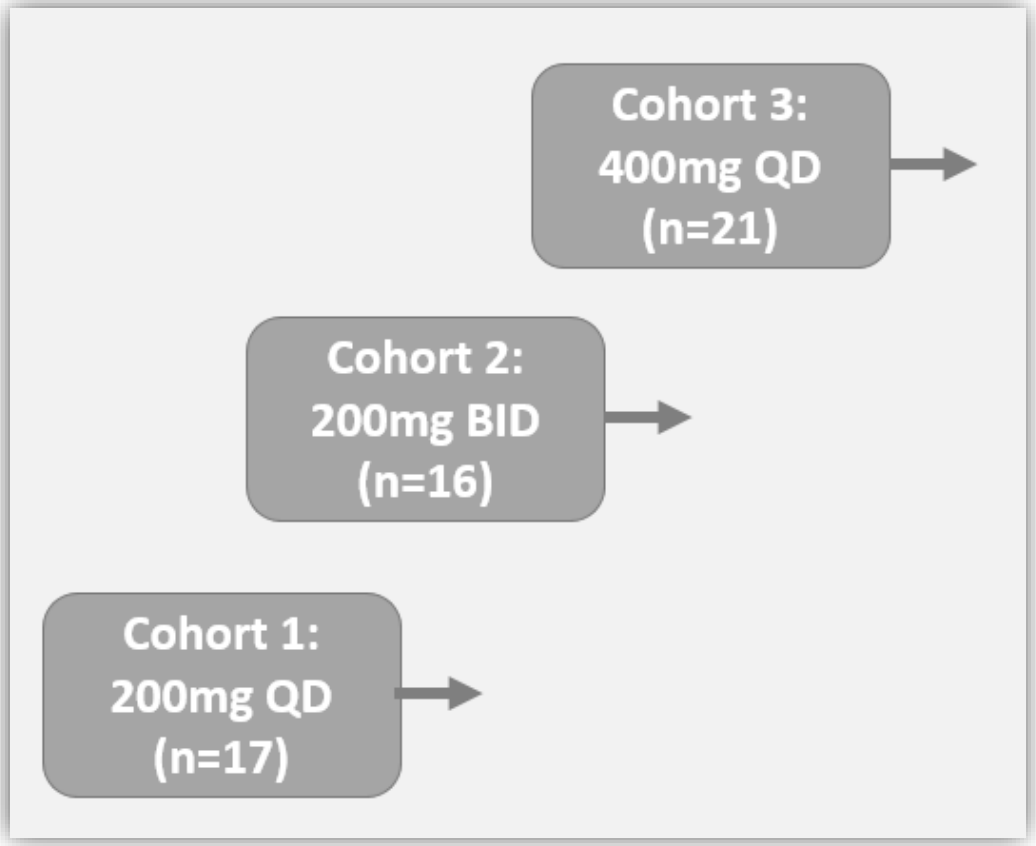



*Am J Pathol*, 2015

# KD025: PHASE 2a DESIGN

Key Eligibility Criteria

- Adults with steroid-dependent or refractory chronic GVHD
- Active Chronic GVHD after at least 2 months of steroids
- 1-3 lines of prior treatment
- Receiving steroids +/- CNI




*Three cohorts enrolled sequentially, following safety assessment of previous cohort*

Key Endpoints:

- ORR per NIH Criteria
- Safety and tolerability
- Duration of response
- Organ response
- Changes in steroid dose and CNI

# KD025 *(Belumosudil)*: Conclusions

**KD025 was Well Tolerated and Achieved Clinically Meaningful Responses**

- **KD025 was well tolerated:**
  - No treatment-related SAEs
  - No increased risk of infection observed
- **ORRs of ~60% across all three cohorts**
  - Responses observed in all affected organ systems, including in organs with fibrotic disease
- **Durable and clinically meaningful responses:**
  - 69% of patients were able to reduce or discontinue corticosteroids and other immunosuppressants
  - 72% of responders experienced clinically meaningful improvement (LSS score)
- **PD data showed a decrease in TH17 and an increase in Treg cells during treatment with KD025**

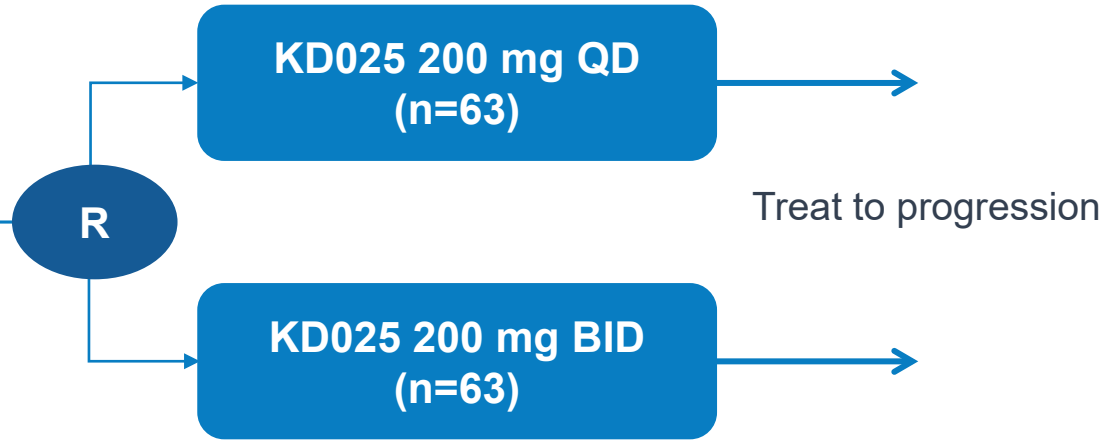
❖ Presented in Abstract: ASH 2019 and TCT: Jagasia et al., ASTCT Meeting: Vol 25, issue 3, Supplement, S28-S29, March 1, 2019

# KD025-213: PIVOTAL PHASE 2 TRIAL OF KD025 IN CGVHD

- **Objective: Demonstrate clinically meaningful responses with KD025 in cGVHD patients**
- **Primary endpoint: ORR (95% CI to exclude <30%)**
- **Open-label, two-arm trial with two doses of KD025 (200 mg QD and 200 mg BID)**
  - Either dose may be considered for registration
- **Enrollment completed in 2019**

**Key Eligibility Criteria:**

- Adults who have had allogeneic HCT
- Active cGVHD
- Received ≥2 prior lines of systemic therapy for cGVHD




**Primary Endpoint:**

- ORR, per 2014 NIH criteria

**Key Secondary Endpoints:**

- Safety
- Duration of response
- Response by organ system
- Lee Symptom Score
- Changes in corticosteroid and calcineurin inhibitor dose

❖ Cutler et al. ASH Oral Abstract. 2020

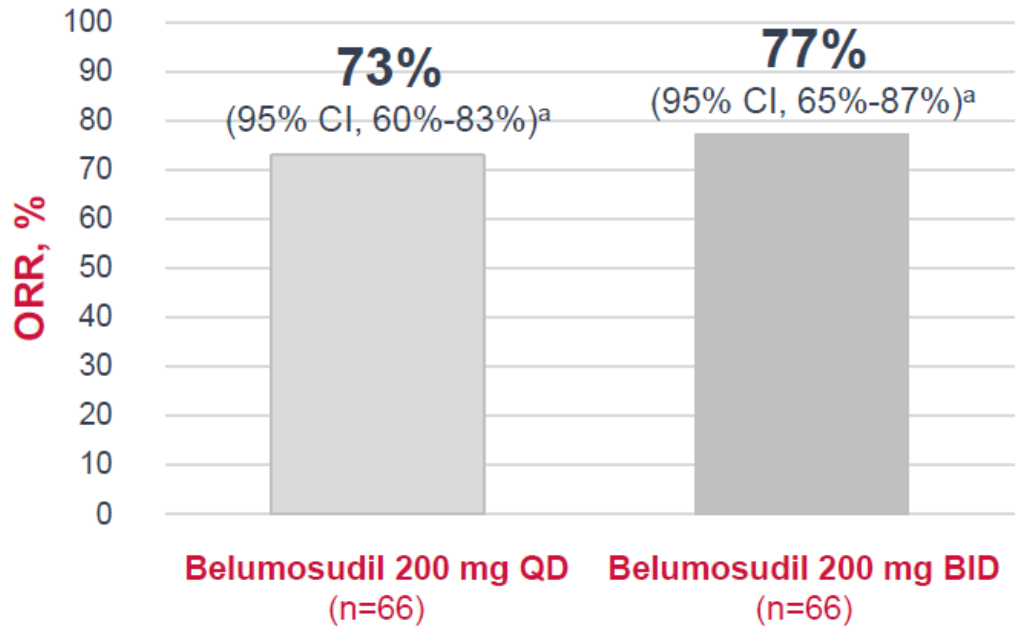
# KD025-213 (“ROCKstar Study”): PIVOTAL PHASE II TRIAL OF KD025 IN CGVHD

- Phase 2, open-label, randomized trial, MCT.
- Evaluated KD025 200mg Daily (N=66 pts) and BID (N=66 pts).
- High Risk Study Population:
  - 67% had NIH Severe CGVHD
  - 52% had 4 organs
  - 72% had ≥3 prior lines of therapy
  - 73% were refractory to their last line of therapy.

❖ Cutler et al. ASH Oral Abstract. 2020

# The ROCKstar Study: Primary End Point Met

## Belumosudil achieved clinically meaningful and statistically significant ORRs in both arms




- Follow-up analysis occurred 12 months after last patient was enrolled
- Seven patients achieved a CR in all affected organs
- Statistical significance is achieved if the lower bound of the 95% CI of ORR exceeds 30%

CR, complete response.

[a] $P<.0001$.

# KD025-213: OVERALL RESPONSE RATE

| Group Name | Overall Response Rate |
|---|---|
| All Patients (N=132) | 73% |
| • 200mg QD (N=66) | 73% |
| • 200mg BID (N=66) | 74% |
| Severe Chronic GVHD | |
| • Yes (N=89) | 72% |
| • No (N=43) | 77% |
| Refractory to Last TMT | |
| • Yes (N=79) | 73% |
| • No (N=30) | 67% |
| ≥4 lines of Prior TMT | |
| • Yes (N=68) | 69% |
| • No (N=63) | 79% |
| Prior Ibrutinib | |
| • Yes (N=46) | 72% |
| • No (N=86) | 74% |
| Prior Ruxolitinib | |
| • Yes (N=38) | 68% |
| • No (N=94) | 76% |

❖ Cutler et al. ASH Oral Abstract. 2020

# KD025-213: PIVOTAL TRIAL OF KD025 IN CGVHD: COMPLETED AND MET PRIMARY ENDPOINT

- 49% of patients had a duration of response $\geq$ 20 months
- Failure-Free Survival 77% at 6 months
- Drug appeared well tolerated with 10% of patients d/c'ing drug due to possible AE's.
- Most AE's were those expected for disease population.
- FDA review is expected this summer.

❖ Cutler et al. ASH Oral Abstract. 2020

# CONCLUSIONS

- Acute and Chronic GVHD remain significant contributors to morbidity and mortality in recipients of allogeneic HCT.
- A number of recent advances in acute and chronic GVHD leading to FDA approval of novel therapies which offer efficacy beyond steroids.
- However, better therapies are needed.
- Encourage Support for Clinical Trials.

❖ Cutler et al. ASH Oral Abstract. 2020

# *"It Takes a Whole Medical Center to Care for a BMT Patient"*

# *Thank you*

*questions:*

**aalousi@mdanderson.org**