- The information contained in this presentation is for educational purposes only. It does not constitute any advice or recommendation for medical decision making.
- For additional details governing the activities of the website visitors, please refer to the TERMS AND CONDITIONS webpage.

1

ACUTE GVHD: WHAT HAVE WE LEARNED?

Daniel R Couriel, MD, MS

Indus BMT Meeting 2020

New Delhi, India (Wish we were there!)

2

TOPICS (IN 25 MIN)

- Risk Factors
- Acute GVHD in the era of new prophylaxis
- Classification and scoring: new strategies
- Biomarkers and AI in risk stratification
- Front-Line Treatment: How much prednisone?
- What Second Line…? Wait, we do have an FDA-approved option
- Conclusions

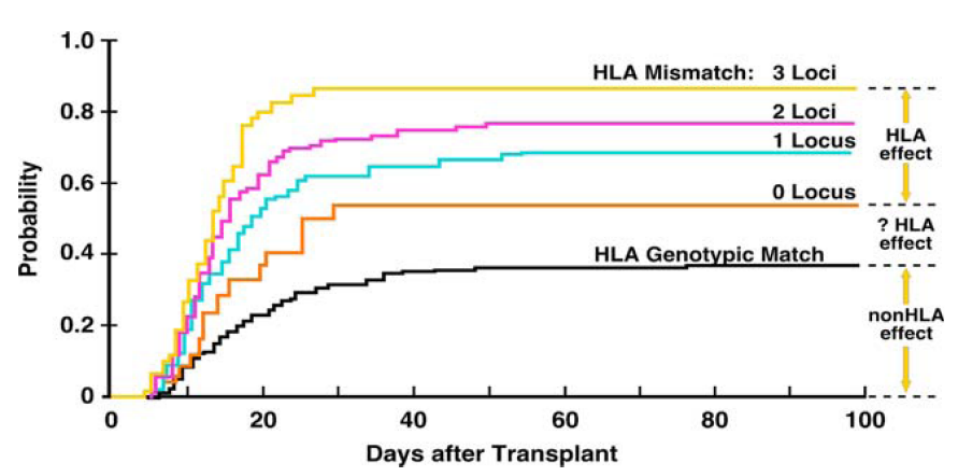
3

RISK FACTORS

Factor	Condition that ↑ risk of aGVHD
Donor-recipient factors	
Major HLA disparity (HLA class I, II)	HLA mismatched donor > matched donor
Minor HLA disparity (mHA)	Unrelated donor > related donor
Sex matching	Mismatch > match
Donor parity	Multiparity > nulliparity
Donor age	Older donor > younger donor
ABO type	ABO mismatch > ABO match
Donor CMV serostatus	CMV positive > CMV negative
Cytokine gene polymorphisms	Numerous associated with acute GVHD
Stem cell graft factors	
Stem cell source	PBSC > BM > UCB
Graft composition	Higher CD34+ count > Lower CD34+ cell count Higher T cell dose > Lower T cell dose
Transplantation factors	
Conditioning intensity	Myeloablative > reduced-intensity regimens

4

GVHD WITH STANDARD PROPHYLAXIS



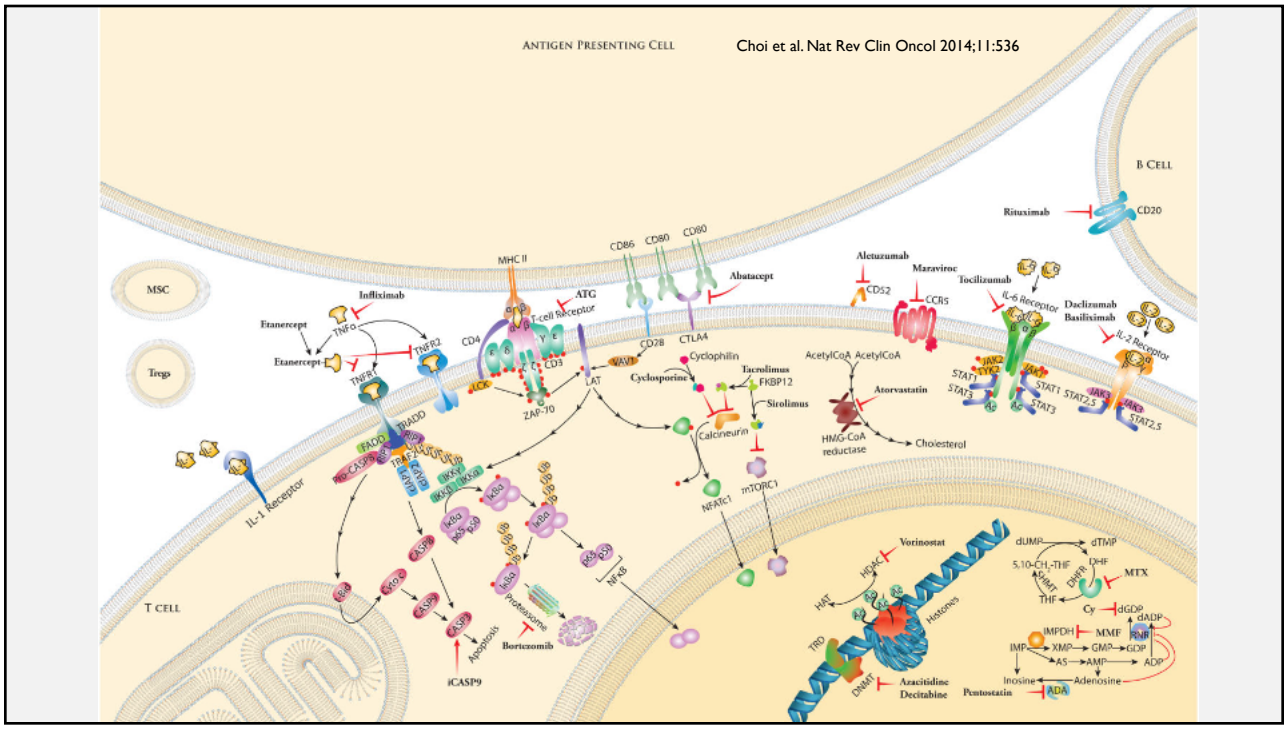
Beatty PG, et al. *N Engl J Med*. 1985;313(13):765-771. Powles RL, et al. *Lancet*. 1983;1(8325):612-615.

5

GVHD PROPHYLAXIS

- No truly standard regimen
- Choice based on:
  - Underlying disease
  - Degree of HLA disparity
  - Conditioning regimen
  - Patient characteristics

6



7

COMMON PHARMACOLOGIC REGIMENS

- **CNI+MTX:**
  - CSA+MTX: Most common regimen in myeloablative regimens. Together better than each drug alone *(Storb et al. NEJM 1986;314:729)*

  - Tacro+MTX: Similar to CSA.
- Less aGVHD (*Ratanatharathorn et al. Blood 1998;92:2303, Hiraoka et al. BMT 2001;28:181)* and less severe cGVHD with tacrolimus *(Ratanatharathorn et al. Blood 1998;92:2303)**
- Large retrospective study shows no difference in outcomes between CSA and Tacrolimus *(Inamoto et al. BBMT 2011;17:1088)*
- In AA used more frequently in older patients in both MRD and URD transplant. Lower risk of mortality in URD *(Inamoto, Flowers et al. BBMT 2015;21:1776)*
- **Mini-Dose MTX**: As effective as regular dose MTX in mismatched and MUD transplant *(Przepiorka et al. BMT 1999;24:763; Blood 1996;88:4383))*

** In this study Tacrolimus was more effective in the prevention of aGVHD than CSA in patients with CML inn CP or AP*

8

THE CLASSICS

- **Tacrolimus/Sirolimus:**
  - Based on RCT, it offers an alternative to MTX with similar outcomes, less mucositis and faster PMN/PLT engraftment *(Cutler et al. Blood 2014;124:1372)*
  - CAUTION: SOS with myeloablative doses of busulfan, Cy/TBI, concomitant MTX *(Cutler et al. Blood 2008;112:4425)*
- **MMF:**
  - Several small prospective studies suggest similar efficacy to CNI+MTX in the prevention of aGVHD, particularly in the reduced intensity/nonmyeloablative setting
  - Possibly less mucositis and better engraftment than MTX *regimens (Bolwell et al. BMT 2004;34:621, Perkins et al. BBMT 2010;16:937)*

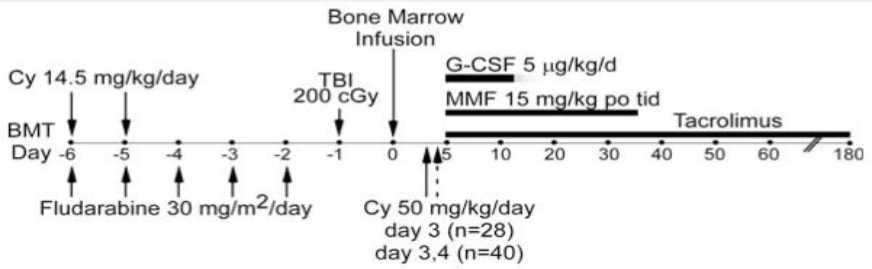
9

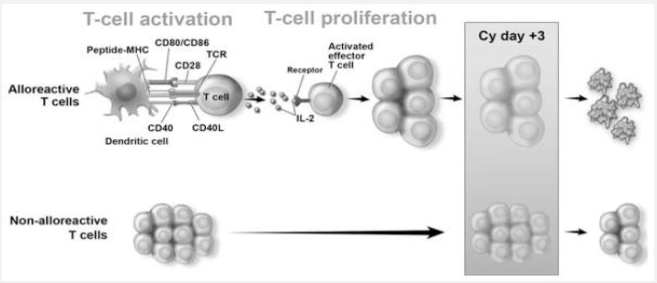
THE NEWER

- **Tocilizumab:** Phase I/II (n=48) shows low aGVHD of skin and GI tract (10% and 8% respectively) and low grade 3-4 aGVHD (4%) *(Kennedy et al. Lancet Oncol 2014;15:1451)*
- **Maraviroc:** The day-180 rates of grade 2-4 and grade 3-4 aGvHD were 27 ± 7% and 5 ± 4% respectively. At 1 year, the incidence of cGvHD was 8 ± 5%, disease relapse 30 ± 8%, and overall survival 70 ± 8% *(Reshef et al. BBMT 2017;23:S96)*
- **Vorinostat:** The CI of grade 2-4 aGVHD at day 100 was 22% and grade 3-4 was 8%. The CI of cGVHD was 29%; relapse, nonrelapse mortality, GVHD-free relapse-free survival, and overall survival at 1-year were 19%, 58 16%, 47%, and 76%, respectively. At day 30, vorinostat-treated patients had:
  - Enhanced histone (H3) acetylation in PBMCs
  - Reduced IL-6 (p=0.028) and GVHD biomarkers (Reg3, p=0.041; ST2, 60 p=0.002) *(Choi et al. Blood 2017;130:1760)*

10

HAPLOIDENTICAL TRANSPLANT: POST TRANSPLANT CY PROPHYLAXIS





Luznik, Fuchs. Immunol Res. 2010 Jul;47(1-3):65-77.

11

POST TRANSPLANT CYCLOPHOSPHAMIDE

- Data suggests that a short course of PTCy can result in selective removal of alloreactive donor T cells
- In haploidentical BMT with NMA conditioning aGVHD grades II–IV and III–IV GVHD occurred in 34% and 6% of patients, respectively, and cGVHD developed in 15% (*Luznik et al. Immunol Res. 2010;47:65)*
- PBSC vs BM in haploidentical setting: Variable results, in general slight increase in Grade II/IV aGVHD but no difference in survival outcomes *(Mussetti et al. Expert Rev Hematol. 2017;10:479)*
- In MRD and MUD with MA BMT (PTCy sole agent): Incidence of aGvHD was low (40% grades II-IV acute, 10% grades III/IV acute, 10% chronic). The actuarial overall survival and event-free survivals at 2 years after transplantation were 55% and 39%There was no difference between related or unrelated donors *(Luznik et al. Blood 2010;115:3224)*

12

HAPLOIDENTICAL TRANSPLANTS AND PT-CY: THE PROFILE OF ACUTE GVHD

Acute Graft-Versus-Host Disease Is Less Severe and Associated with Lower Non-Relapse Mortality after Haploidentical Transplantation (Saliba, Ciurea et al ASTCT 2020)

- Comparison of aGVHD characteristics and non-relapse mortality (NRM) in adult patients with grade 2-4 aGVHD after HAPLO (N=758) or MUD (N=2586) reported to CIBMTR.
- The 6-m cumulative incidence (CumInc) of grade 2-4 aGVHD (35 vs 45%, <0.001) was significantly lower in HAPLOs, with a lower prevalence (28% vs 39%, p=0.001) of grade 3-4.
- The 2-yrs and overall CumInc of NRM since aGVHD was 18% and 19% in HAPLOs; and 30% and 51% in MUDs.
- In multivariate analysis, grade 2-4 aGVHD in HAPLOs was associated with significantly lower NRM, but this effect was limited to donor-recipient pairs (CumInc: 15 vs 30%, HR=0.5, p=0.002) that were not sex-mismatched

Conclusions
Compared with 8/8 HLA-matched unrelated SCT with standard GVHD prophylaxis, aGVHD tends to be less severe and associated with lower NRM after HAPLO SCT with PTCy GVHD prophylaxis. This effect is more pronounced in recipients ≥60 years of age.

13

DEFINING RISK IN AGVHD: CLINICAL

Table 2 Comparison of the different guidelines available for acute GvHD assessment: overall severity grading

From: EBMT–NIH–CIBMTR Task Force position statement on standardized terminology & guidance for graft-versus-host disease assessment

overall Glucksberg/MAGIC grade	Original Glucksberg criteria [13]	"Modified Glucksberg" or "Keystone" criteria [14]	MAGIC criteria[16]	IBMTR criteria [15]	overall IBMTR grade
0	no organ involvement (skin=0; and liver=0; and GI=0) corresponds to the absence of aGvHD				0
I	skin=1 or 2, without liver/GI involvement or decrease in performance status/fever	skin=1 or 2, without liver/GI involvement		skin=1, without liver/GI involvement	A
II	skin=1 or 2 and (liver and/or GI involvement=1 or 2) with mild decrease in performance status	skin=3; and/or liver=1; and/or GI=1		skin=2; and/or liver=1 or 2; and/or GI=1 or 2	B
III[a]	(skin and/or liver and/or GI=2, 3 or 4) with marked decrease in performance status	liver=2 or 3; and/or GI=2, 3 or 4[a]	liver=2 or 3;and/or GI=2 or 3	skin=3; and/or liver=3; and/or GI=3	C
IV[b]	(skin and/or liver and/or GI=2, 3 or 4) with Karnofsky <30%	skin=4;and/or liver=4[b]	skin=4; and/or liver=4; and/or GI=4		D

The overall aGvHD grade typically corresponds to the highest grade conferred by the individual staging of each organ. GI (Gastro-intestinal tract); GvHD (Graft versus Host Disease); IBMTR (International Bone Marrow Transplantation Registry); MAGIC (Mount Sinai Acute GvHD International Consortium)

[a]In the Minnesota criteria [19], overall grade III refers to liver = 2, 3 or 4; and/or GI = 2 or 3

[b]In the Minnesota criteria [19], overall grade IV refers to skin = 4; and/or GI = 4

14

DEFINING RISK IN AGVHD: CLINICAL

GVHD risk score	One organ (n)	Two organs (n)	Three organs (n)
Standard risk (N = 1454, 84%)	Stage 1-3 skin (901)	Stage 1-3 skin plus stage 1 GI (223)†	--
	Stage 1-2 GI (279)**	Stage 1-3 skin plus stage 1–4 liver (51)	--
High risk* (N = 269, 16%)	Stage 4 skin (13)	Stage 1-3 skin plus stage 2 GI (54)	Stage 1-3 skin plus stage 1-2 GI plus Stage 1-3 liver (23)
	Stage 3-4 GI (74)††	Stage 1-2 lower GI plus stage 1-3 liver (12)	
	Stage 1-4 liver (25)***	Stage 3-4 GI plus stage 1-3 skin (45)	Stage 1-3 skin plus stage 3-4 GI plus stage 1-4 liver (13)
		Stage 3-4 GI plus stage 1-4 liver (10)	

UGI plus Lower GI considered as single organ disease

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

**Stage 1-2 GI includes:
UGI alone (n = 115)
Stage 1-2 lower GI alone (100)
UGI and stage 1 lower GI (64)

††Stage 3-4 GI includes:
Stage 3 lower GI alone (65)
Stage 4 lower GI alone (9)

***Stage 1-4 liver includes:
Stage 1 liver alone (7)
Stage 2 liver alone (10)
Stage 3 liver alone (5)
Stage 4 liver alone (3)

†Stage 1-3 skin plus stage 1 GI includes:
Stage 1-3 skin plus UGI (90)
Stage 1-3 skin plus stage 1 lower GI (71)
Stage 1-3 skin plus UGI and stage 1 lower GI (62)

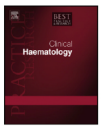
MacMillan ML, et al. *Biol Blood Marrow Transplant*. 2015;21(4):761-767.

15

BIOLOGICAL STRATIFICATION

Contents lists available at ScienceDirect

Best Practice & Research Clinical Haematology
DECEMBER 2019
journal homepage: www.elsevier.com/locate/issn/15216926



MAGIC biomarkers of acute graft-versus-host disease: Biology and clinical application

Hrishikesh K. Srinagesh, James L.M. Ferrara*

- ST2 AND REG3α:
  - Combined in a competing regression model they generate a single estimated probability of 6- month NRM: Magic Algorythm Probability=**MAP**

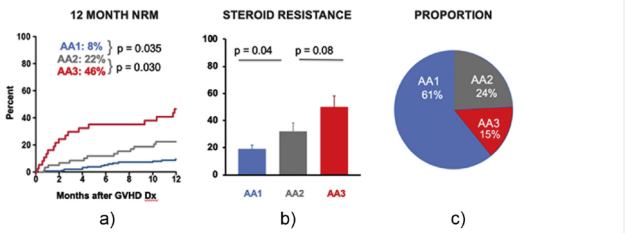


Fig. 1. MAGIC biomarker probability predicts long-term outcomes in patients with Glucksberg Grade II GVHD at diagnosis. Patients with Glucksberg Grade II GVHD at diagnosis were stratified by their Ann Arbor score. are Ann Arbor 1 (MAP < 0.141), are Ann Arbor 2 (0.141 ≤ MAP ≤ 0.290), and are Ann Arbor 3 (MAP > 0.290). (A) Cumulative incidence curves of NRM for 12 months after diagnosis. (B) Proportion of patients with steroid resistance after four weeks of treatment. (C) Proportion of patients in each Ann Arbor group.

16

THE MAGIC ALGORITHM PROBABILITY (MAP) IS A VALIDATED RESPONSE BIOMARKER OF TREATMENT FOR ACUTE GRAFT-VERSUS-HOST DISEASE

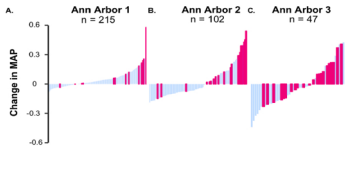


Figure 1. Changes in MAPs after four weeks according to initial Ann Arbor score. Reverse waterfall plots of changes in MAPs in consecutive patients who provided samples before and after four weeks of treatment according to initial Ann Arbor score in patients with (—) and without (—) six month NRM. A. Ann Arbor 1 patients (MAP < 0.141 at treatment initiation). B. Ann Arbor 2 patients (0.141 ≤ MAP ≤ 0.290 at treatment initiation). C. Ann Arbor 3 patients (MAP > 0.290).

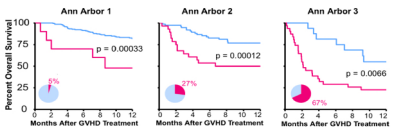


Figure 2. Long-term mortality by MAP threshold (0.290) after four weeks of treatment. Kaplan-Meier estimates of overall survival according to Ann Arbor score for patients whose MAPs after four weeks of treatment rose/remained above (—) or dropped/remained below (—) the threshold of 0.290. Ann Arbor scores were determined as in Figure 1.

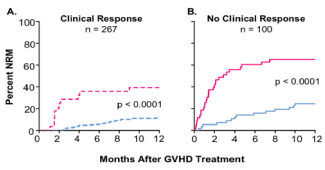


Figure 3. Cumulative incidence of NRM by clinical response according to high or low MAP. (A) Patients with complete or partial and (B) no response to systemic therapy after four weeks of treatment analyzed by high (—) or low (—) MAPs at the same time point.

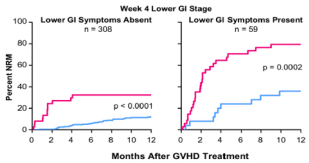


Figure 4. Non-relapse mortality in patients according to lower gastrointestinal symptoms during the first month of therapy analyzed by MAP. Left: Patients without lower GI symptoms at four weeks after treatment and either high (—, n=37) or low MAPs (—, n=271). Right: Patients lower GI symptoms at four weeks after treatment and either high (—, n=34) or low MAPs (—, n=25).

ASTCT 2020- Srinagesh et al

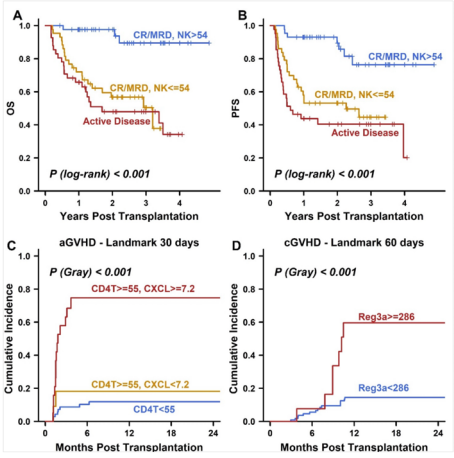
Conclusions: MAP is the first laboratory test validated as a response biomarker for acute GVHD treatment and more accurately predicts survival than clinical response after 28 days of treatment. The MAP may serve as a novel endpoint in future trials of GVHD treatment.

17

AI: COMING SOON TO HSCT

A Machine Learning Approach Deciphers the Effects of Immune Parameters on Clinical Outcomes after HLA-Haploidentical and HLA-Matched Allogeneic Bone Marrow Transplantation with Posttransplant Cyclophosphamide'. ASCT 2020. Shannon McCurdy et al.

Figure 1: Immune Cell Subsets and Biomarkers Successfully Predict Clinical Outcomes after Bone Marrow Transplantation with Posttransplant Cyclophosphamide



- Machine learning using immune cellular and soluble markers can be successfully applied to identify risk factors for BMT outcomes.
- High $CD4^+$ counts and CXCL-9 levels at day 28 predicted aGVHD and high reg3α at day 56 predicted cGVHD.
- Disease status and NK cell counts at day 28 predicted OS and PFS

18

ACUTE GVHD- INITIAL THERAPY CLINICAL TRIAL IS BEST

- **Standard initial therapy for grade II-IV GVHD (ASTCT and EBMT)**
  - Corticosteroids: Methylprednisolone (or prednisone equivalent) 2mg/kg/d
  - Complete response rate ~ 50%
  - Persistent complete response less common:
    - Matched Sibling Donor = 41%
    - Matched Unrelated Donor = 24%
- **Issues Addressed in Literature:**
  - Is more than 2mg/kg/d MP better?: **NO**
    One randomized phase III trial: 2mg/kg vs. 10 mg/kg
  - Can we get away with < 2mg/kg/d? **IT DEPENDS**
    One single-center retrospective study: 1mg/kg vs 2mg/kg
  - Does addition of other systemic agents to steroids as initial therapy improve response and extend survival?
    - 5 prospective phase III randomized trials, 1 retrospective **NO**

19

WHEN STEROIDS FAIL…

GVHD STEROID RESPONSE DEFINITIONS/CRITERIA

SUGGESTED DEFINITIONS FOR COMMONLY USED GVHD TERMINOLOGY[a]

	Acute GVHD Steroid Response	Chronic GVHD Steroid Response
Steroid Refractoriness or Resistance	Progression of acute GvHD within 3–5 days of therapy onset with ≥2 mg/kg/day of prednisone OR Failure to improve within 5–7 days of treatment initiation OR Incomplete response after more than 28 days of immunosuppressive treatment including steroids	Chronic GvHD progression while on prednisone at ≥1 mg/kg/day for 1–2 weeks OR Stable GvHD disease while on ≥0.5 mg/kg/day (or 1 mg/kg every other day) of prednisone for 1–2 months
Steroid Dependence	Inability to taper prednisone below 2 mg/kg/day OR A recurrence of acute GvHD activity during steroid taper	Inability to taper prednisone below 0.25 mg/kg/day (or >0.5mg/kg every other day) in at least two unsuccessful attempts separated by at least 8 weeks
Steroid Intolerance	Emergence of unacceptable toxicity due to the use of corticosteroids	

Schoemans HM, Lee SJ, Ferrara JL, et al. EBMT–NIH–CIBMTR Task Force position statement on standardized terminology & guidance for graft-versus-host disease assessment. Bone Marrow Transplantation 2018;53:1401-1415.

20

CHOICE OF SECOND LINE THERAPY

FACTORS TO CONSIDER

- Effect of any prior treatment
- Potential toxicity
- Drug interactions
- Convenience/accessibility
- Cost
- Familiarity and prior experience of the physician with the agent

21

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2020
Hematopoietic Cell Transplantation

NCCN Guidelines Index
Table of Contents
Discussion

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 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 (listed in alphabetical order)

Acute GVHD[1]	Chronic GVHD
The following agents are often used in conjuction with the original immunosuppressive agent	*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).*
• Alemtuzumab[2,3] • Anti-thymocyte globulin (ATG)[4] • Basilizimab[5] • Extracorporeal photopheresis (ECP)[a,6] • Infliximab[7] • Mycophenolate mofetil[8,9] • mTOR inhibitors (eg. Sirolimus)[10,11] • Pentostatin[12,13] • Ruxolitinib[b,14,15] • Tocilizumab[16-19]	• Abatacept[20] • Alemtuzumab[21] • Calcineurin inhibitors (eg. tacrolimus or cyclosporine) • Etanercept[22] • ECP[a,6] • Hydroxychloroquine[23] • Ibrutinib[c,24] • Imatinib[25,26] • Interleukin-2 (IL-2)[27] • Low-dose methotrexate • Mycophenolate mofetil[28] • mTOR inhibitors (eg. Sirolimus)[29-31] • Pentostatin[d,32-35] • Rituximab[36] • Ruxolitinib[37,38]

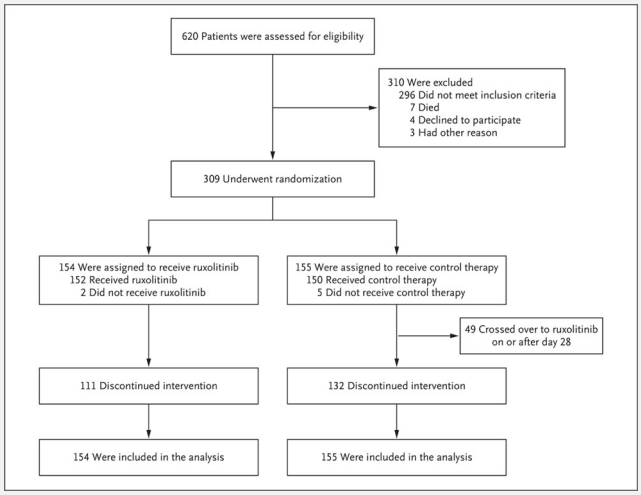
22

Original Article

Ruxolitinib for Glucocorticoid-Refractory Acute Graft-versus-Host Disease- REACH2

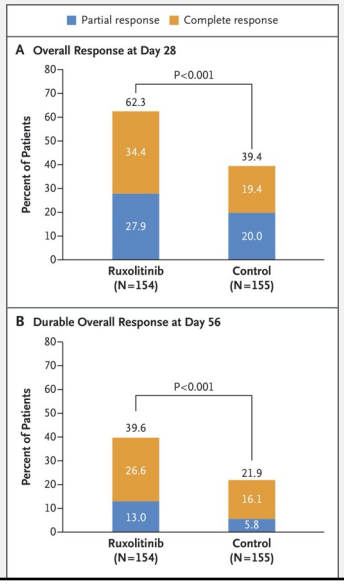
N Engl J Med
Volume 382(19):1800-1810
May 7, 2020

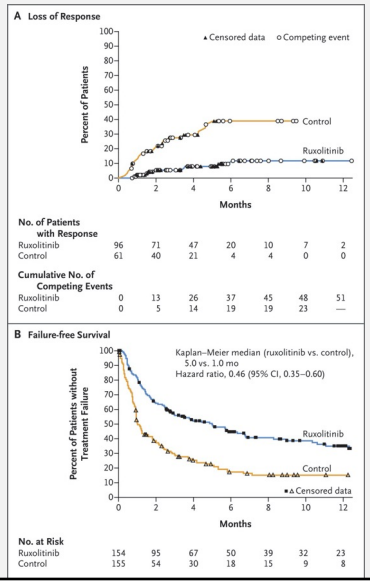
Robert Zeiser, M.D., Nikolas von Bubnoff, M.D., Jason Butler, F.R.A.C.P., Mohamad Mohty, M.D., Ph.D., Dietger Niederwieser, M.D., Reuven Or, M.D., Jeff Szer, F.R.A.C.P., Eva M. Wagner, M.D., Tsila Zuckerman, M.D., Bruyère Mahuzier, Pharm.D., Judith Xu, M.Sc., Celine Wilke, M.D., Kunal K. Gandhi, M.D., M.P.H., Gérard Socié, M.D., Ph.D., for the REACH2 Trial Group



23

OVERALL RESPONSE AT DAY 28 AND DURABLE OVERALL RESPONSE AT DAY 56, RESPONSE DURATION, FFS





CONCLUSIONS:

- RUXOLUTINIB was associated with imptovements in efficacy outcomes
- **FDA** approves **ruxolitinib** for acute **graft-versus-host disease**. On May 24, 2019, the FDA approved **ruxolitinib** for steroid-refractory acute **graft-versus-host disease** (**GVHD**) in adult and pediatric patients 12 years and older.

24

CONCLUSIONS

- The last several years have seen significant advances in the understanding of the pathophysiology, risk-stratification, prevention, supportive care and therapy of acute GVHD- much more optimistic prospect
- Multiple factors contributed to the growth in this field: HLA-typing, better understanding of the disease, new forms of prophylaxis, biomarkers, better risk stratification and novel, more active therapies
- There is a lot more work to be done- acute GVHD continues to be one of the main limitations to successful transplantation

25

26