aGVHD standard and experimental therapies

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Ematologia e Trapianto di midollo Osseo

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IRCCS San Martino Genova

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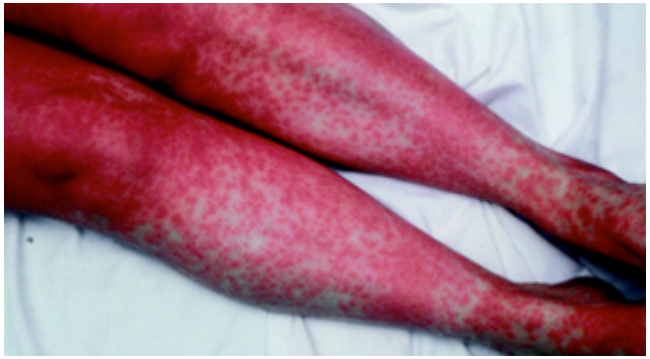
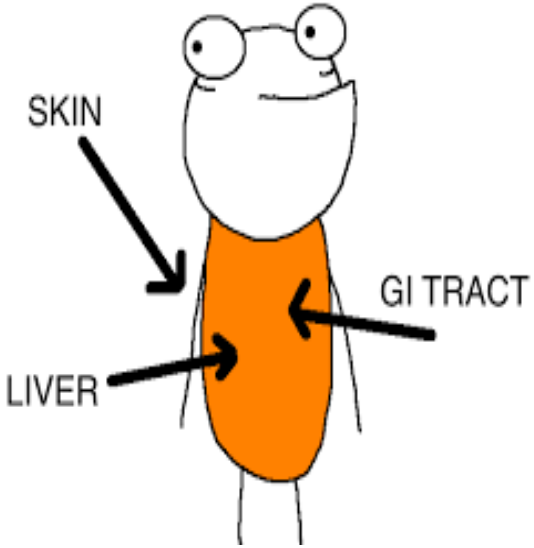
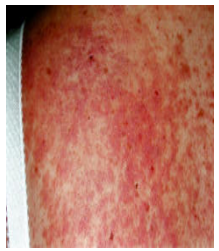
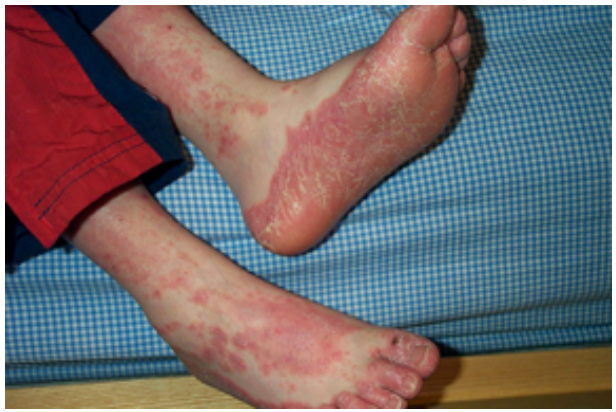


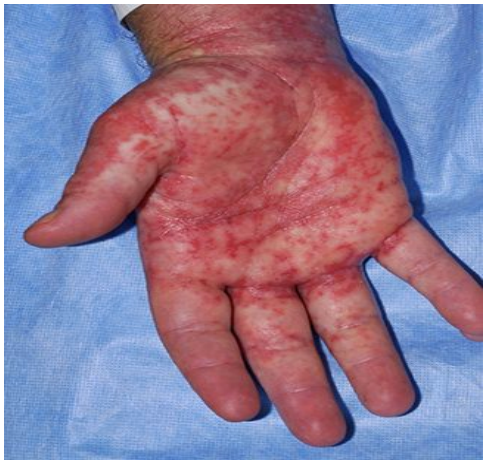


-Despite prophylactic treatment with immunosuppressive agents,**20% to 80%** of recipients develop acute graft-versus-host disease (GVHD) after allogeneic hematopoietic cell transplantation (HCT).

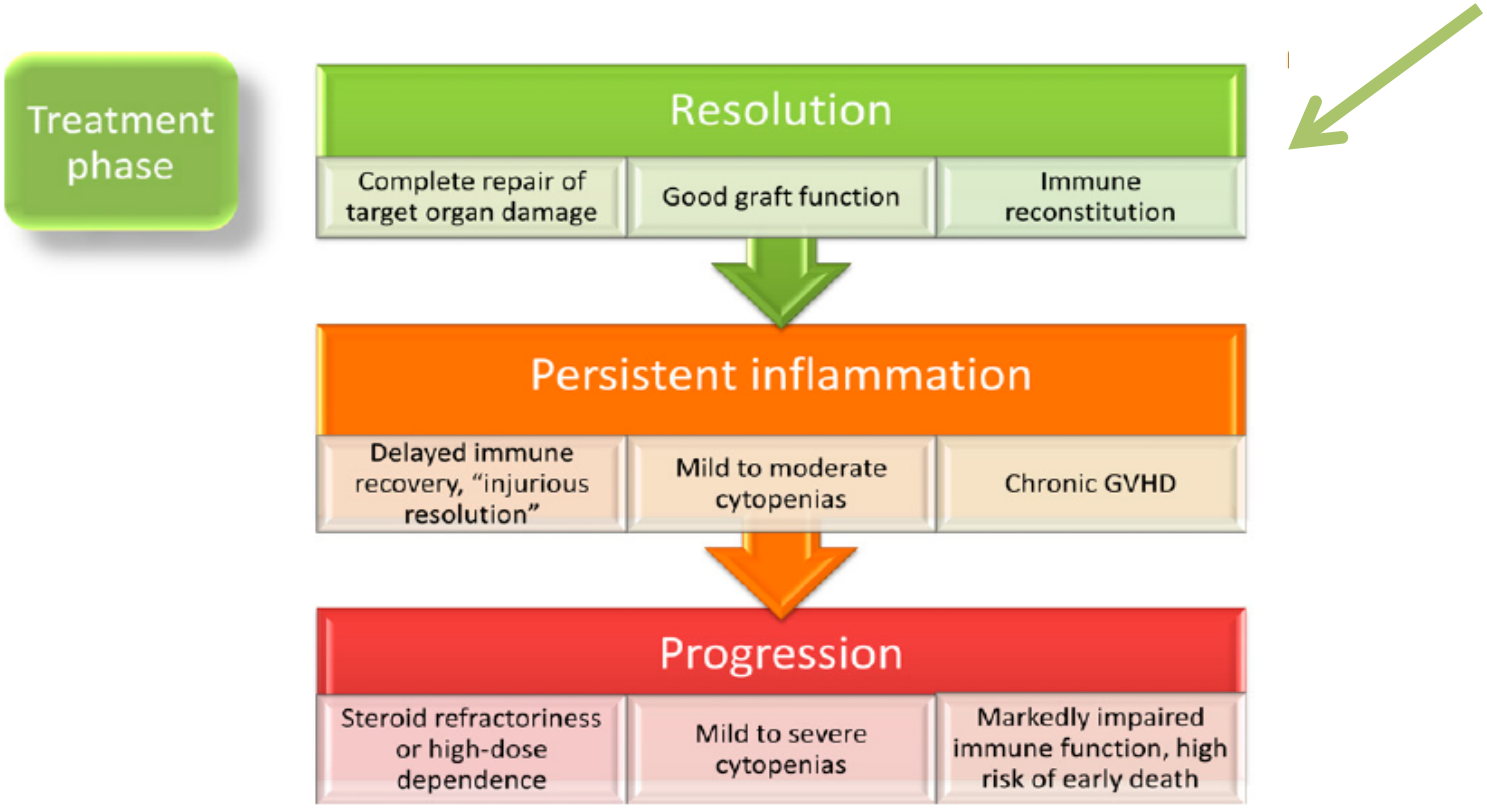
-Development of either acute or chronic GVHD is the **second cause of death** (after malignant relapse) in allogeneic HCT recipients.







aGVHD standard and experimental therapies



Holtan et al. Blood 2014

aGVHD standard and experimental therapies

aGVHD standard therapies (diagnosis)

1) When?

Therapy for grade I ?

2) How?

Initial steroid dose?

Association with steroid?

3) Why?

The same therapeutic approch is effective for all patients?

Therapy for grade I ?

RAMP

ACUTE GRAFT VERSUS HOST DISEASE GRADE I :
final analysis of a GITMO randomized trial of prednisolone vs no treatment

(EUDTRACT 2008-000413-29)

Patients with a GVHD grade I
(rash< 50% s.c. no liver, no gut)

Randomization

Observation arm (n=85)

or

Treatment arm (n=86)
1 mg/kg
if GvHD did not progress , 6MPred would be tapered and discontinue on day +30.

Patients progressing to GvHD II+ were treated with 6MPred 2 mg/kg/day as required.

The **primary end point** was the cumulative incidence of patients progressing to grade II-IV aGvHD

RAMP

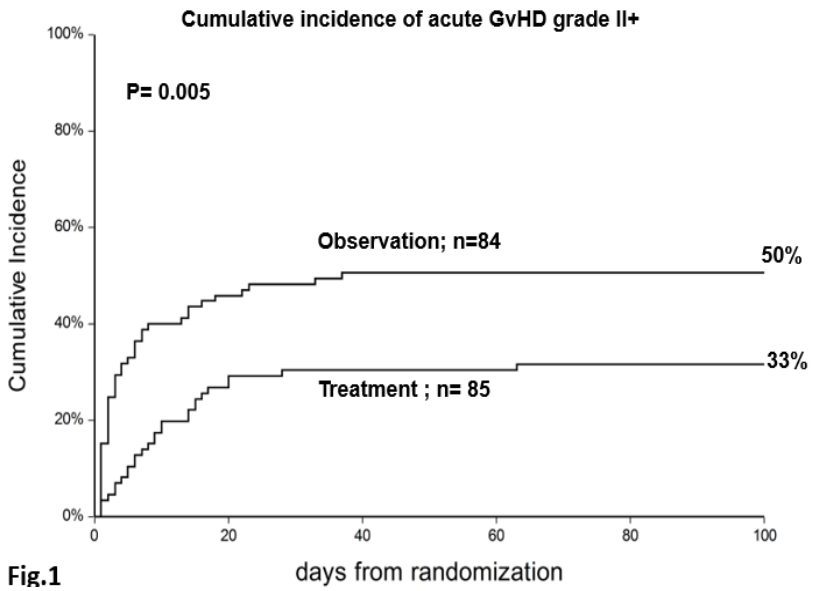


Fig.1

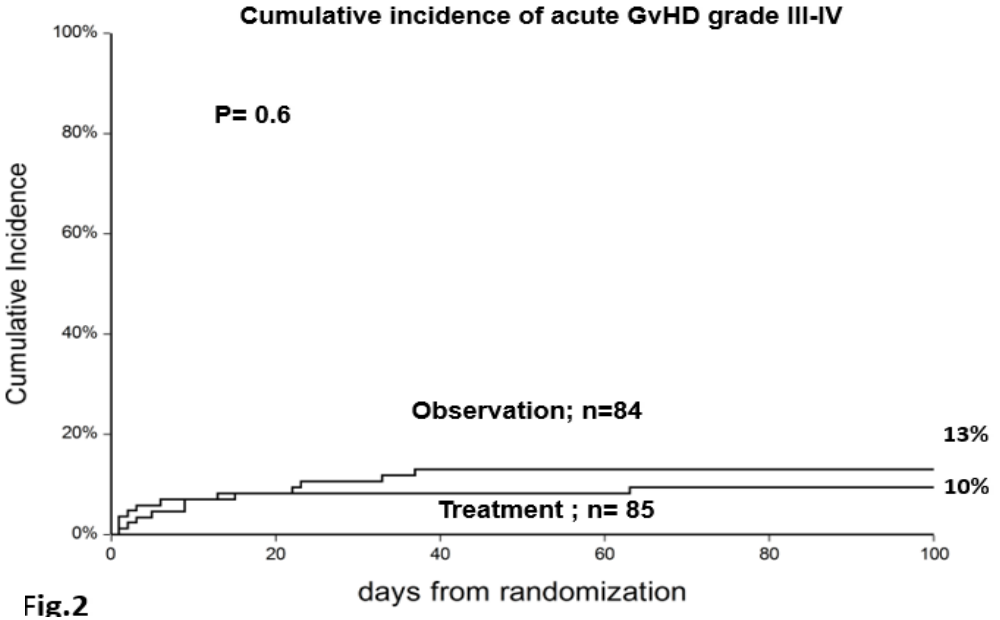


Fig.2

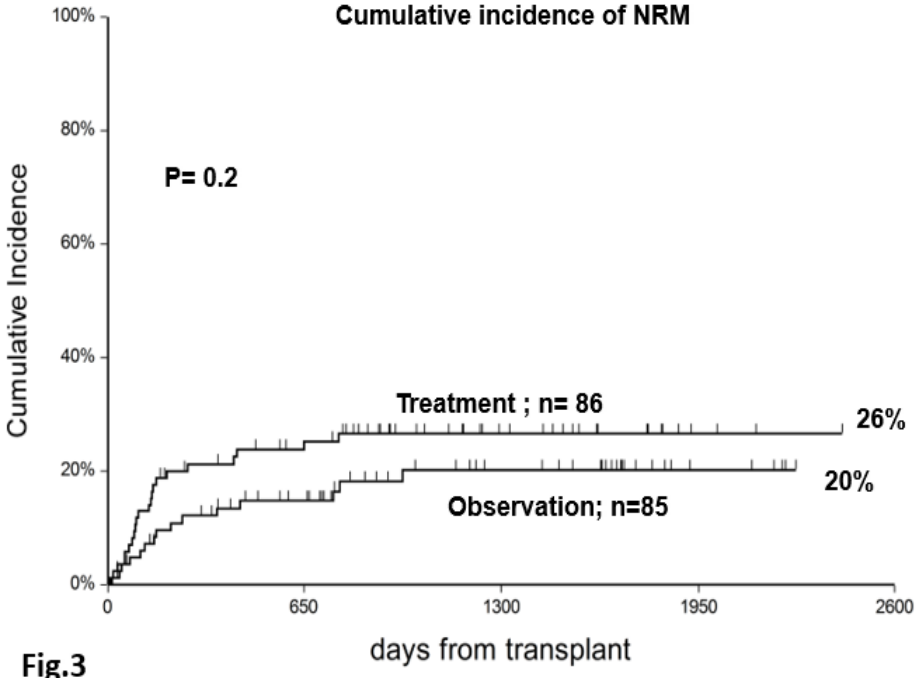
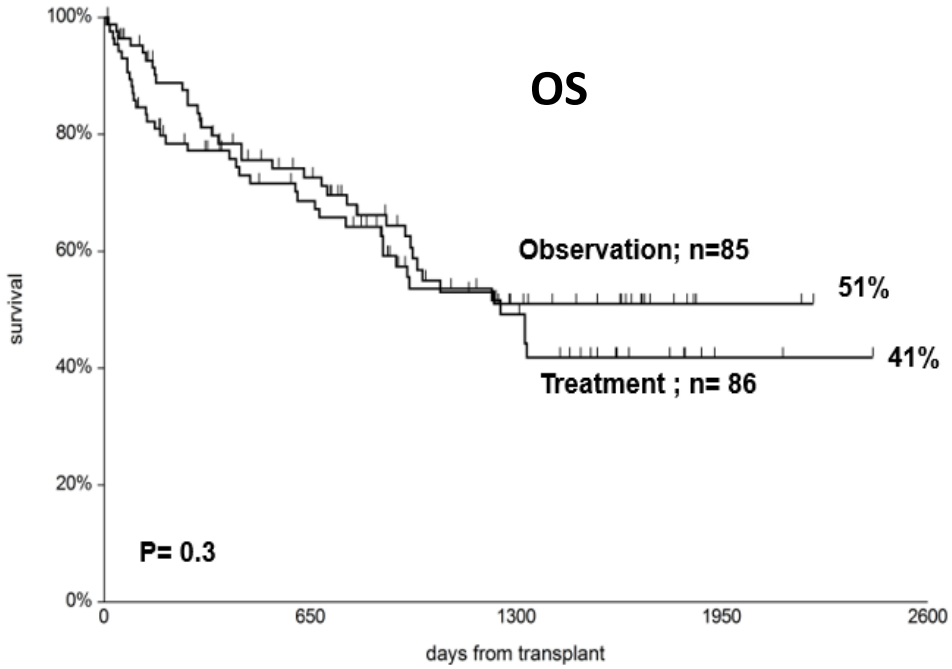


Fig.3



RAMP

- Patients randomized to receive treatment, at diagnosis of grade I GvHD, had a significantly **lower probability to progress to grade II or more GvHD** , when compared to untreated patients (33% vs 50%).

- Early steroid treatment of grade I GvHD does **not protect** patients against **GvHD grade III-IV**, nor against **chronic GvHD NRM , RRD and survival** are unchanged.

- Therefore patients with grade I GvHD could be left untreated.

Conventional treatment

Initial steroid dose at aGVHD diagnosis?

- Prospective randomized studies have not shown a demonstrable benefit for treatment of acute GvHD with prednisone at doses higher than 2 mg/kg/day.

Van Lint Blood 1998

- Initial treatment with lower dose prednisone (1 mg/kg/day) of patients with aGvHD gr I-IIa(rash involving 50% bsa and stool volumes 1.0 L/day with or without anorexia, nausea, and vomiting) did not compromise disease control, OS, NRM, relapse and was associated with a reduced risk of invasive fungal infections (HR:0,59)
(FHCRC Seattle, large retrospective analysis: pts = 733, 2000 - 2005.).

Mielcarek Blood 2009

- Patients (n=130) with **acute GVHD gr.I-IIa** were treated with **systemic steroids** and then randomized with **oral beclomethasone** dipropionate (BDP)(n=65) versus **placebo (n=65)**.

  1)The cumulative rate of GVHD-treatment failure was 31% for BDP versus 48% for placebo (HR= 0,55 p=0,02).

  2)The risk of mortality was lower for patients randomized to BDP compared with placebo (HR 0.63; P 0.03).

Hockenbery Blood 2007

haematologica

Effectiveness and safety of lower dose prednisone for initial treatment of acute graft-versus-host disease: a randomized controlled trial.

Phase III trial (April 2009 - May 2013)

Cohort A: aGVHD IIa (n=104)

1 mg/kg or 0,5 mg/kg

Cohort B: =/>GVHD IIb (n=60)

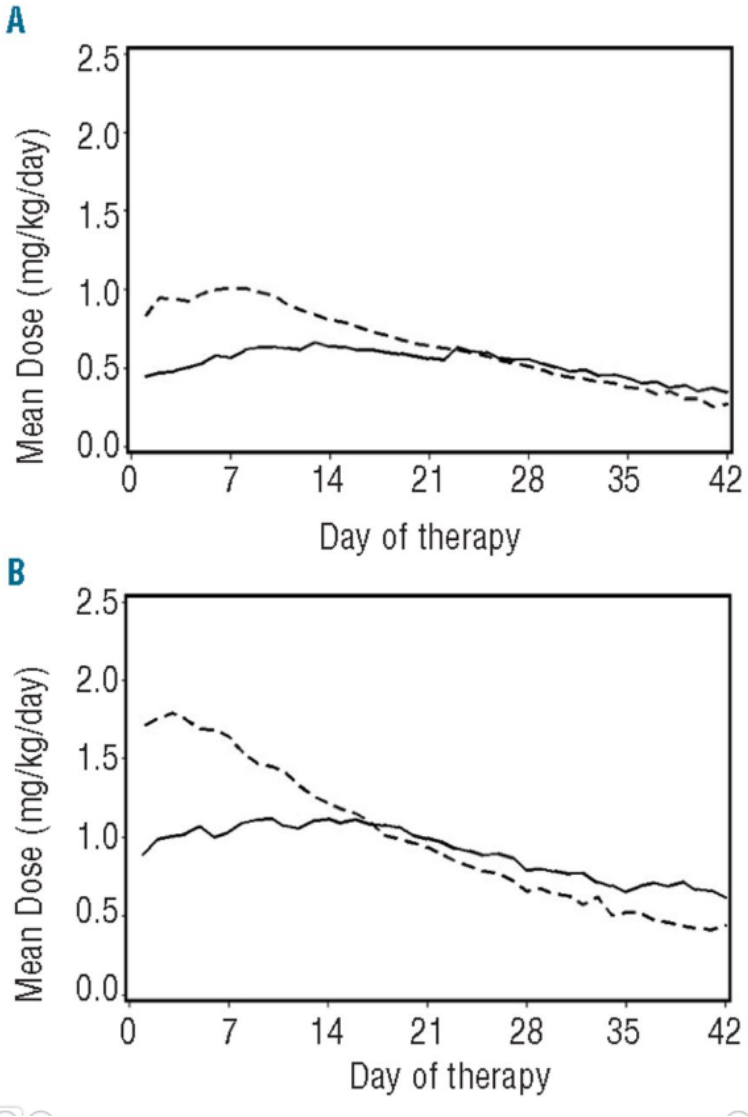
1 mg/kg or 2 mg/kg

Primary end point: the primary end point of the study was a 33% or more reduction of the mean cumulative prednisone dose by day 42.

Secondary end points: -Overall mortality at one year after the initiation of therapy .
-The cumulative incidences of progression to grades III–IV acute GvHD.
-Secondary systemic therapy for acute GvHD by one year after enrollment.

Mielcarek 2015

Primary end point: the primary end point of the study was a 33% or more reduction of the mean cumulative prednisone dose by day 42: **NOT REACHED**



1 mg/kg vs 0,5 mg/kg
18% reduction; *P*=0.08

2 mg/kg vs 1 mg /kg
7% reduction; *P*=0.4

Secondary end points *''no harm'': OS, progression to grade III–IV acute GvHD and secondary systemic immunosuppressive therapy*: **no significative difference**

At diagnosis:
association with steroid?

Etanercept, mycophenolate, denileukin, or pentostatin plus corticosteroids for acute graft-versus-host disease: a randomized phase 2 trial from the Blood and Marrow Transplant Clinical Trials Network

BMT CTN 0302

Alousi et al. Blood 2009

180 patients with a GVHD diagnosis (August 2005 - March 2008)

2 mg /kg MP

+

Etanercept
Patients received a dose of 25 mg subcutaneously twice weekly for 4 weeks
n=46

or

MMF
Patients received a dose of 20 mg/kg twice daily
N=45

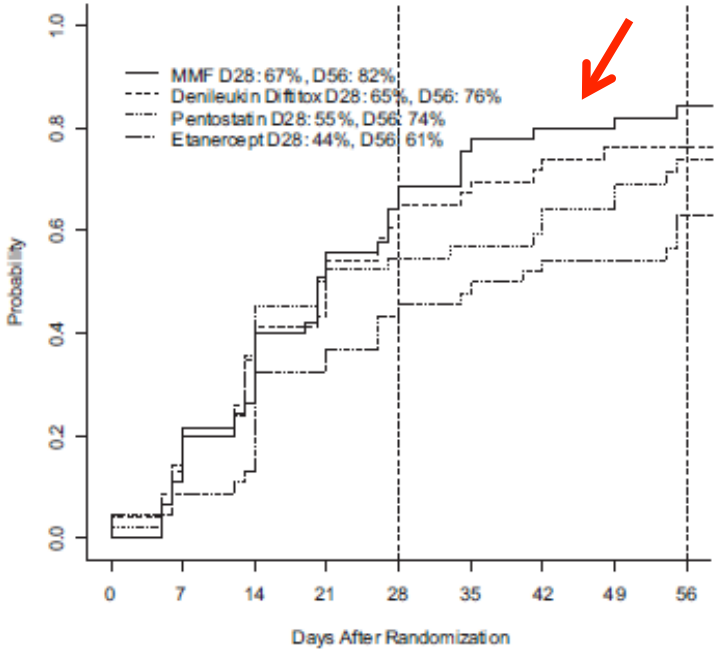
or

Denileukin
Patients received a dose of 9 g/kg intravenously over 1 hour on days 1, 3, 5, 15, 17, and 19 of study.
n=47

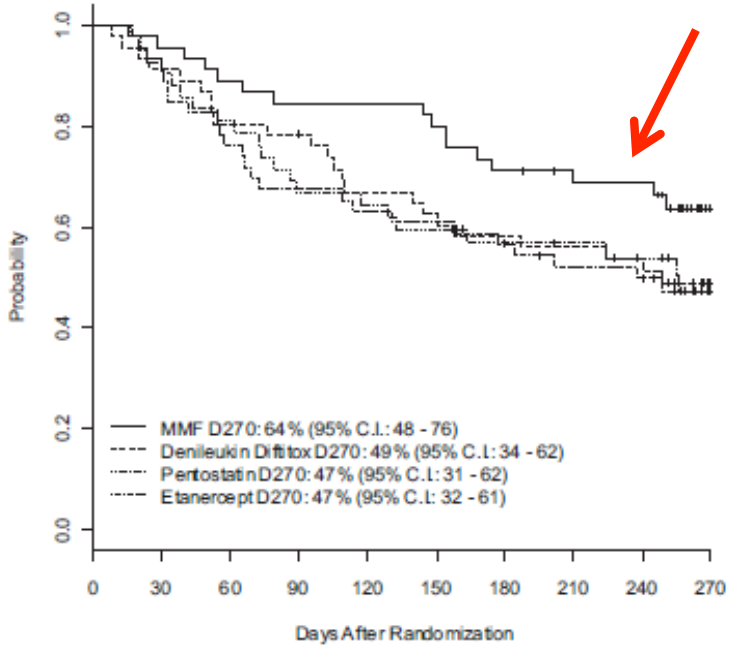
or

Pentostatin
Patients received a dose of 1.5 mg/m2 intravenously over the course of 15 to 30 minutes daily on days 1 to 3 and 15 to 17
n=42

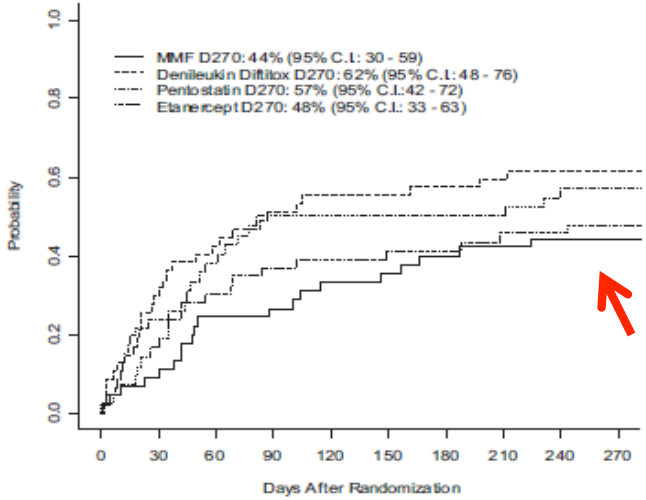
%RC of aGVHD+ 56



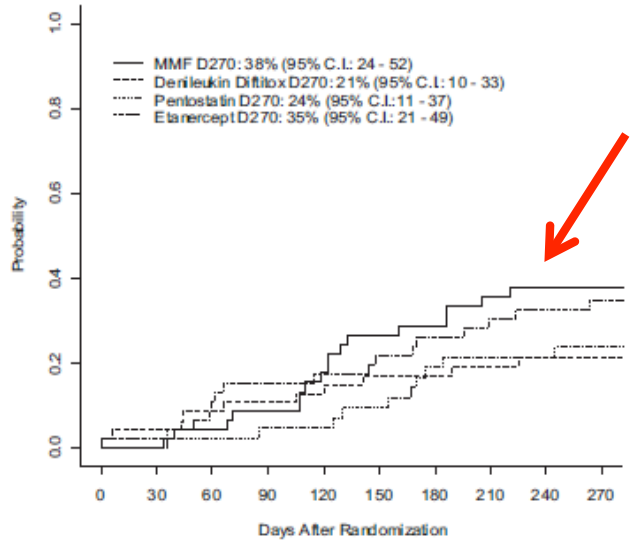
%OS + 9m



CI of severe life-thretening/fatal infection



CI of discontinuation of all immunosoppression.



Conclusion: this randomized phase 2 trial has identified MMF plus corticosteroids as the most promising combination for future investigation as initial aGVHD therapy.

Phase 3 clinical trial of steroids/mycophenolate mofetil vs steroids/placebo as therapy for acute GVHD: BMT CTN 0802

Javier Bolan˜os-Meade Blood 2014

BMT CTN 0802

236 patients with a GVHD diagnosis (February 2010 - November 2011)

2 mg /kg MP

+

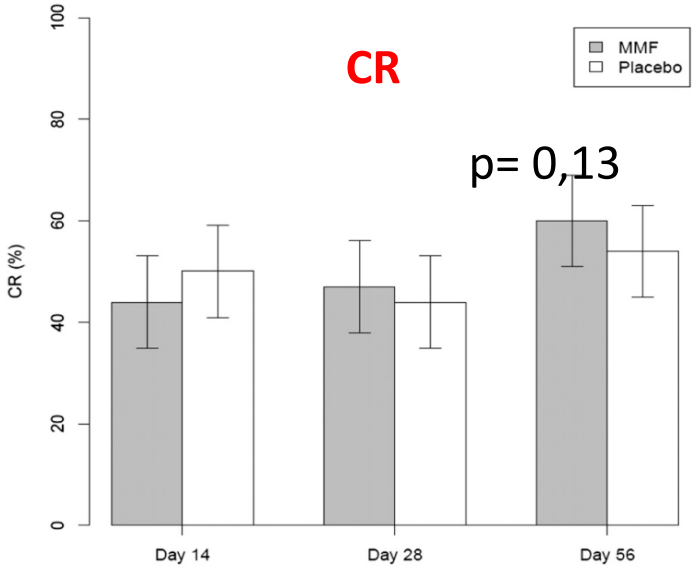
MMF 1000 mg or 20 mg/kg
(for patients<60 kg) orally or IV every 8 hours.
n=116

or

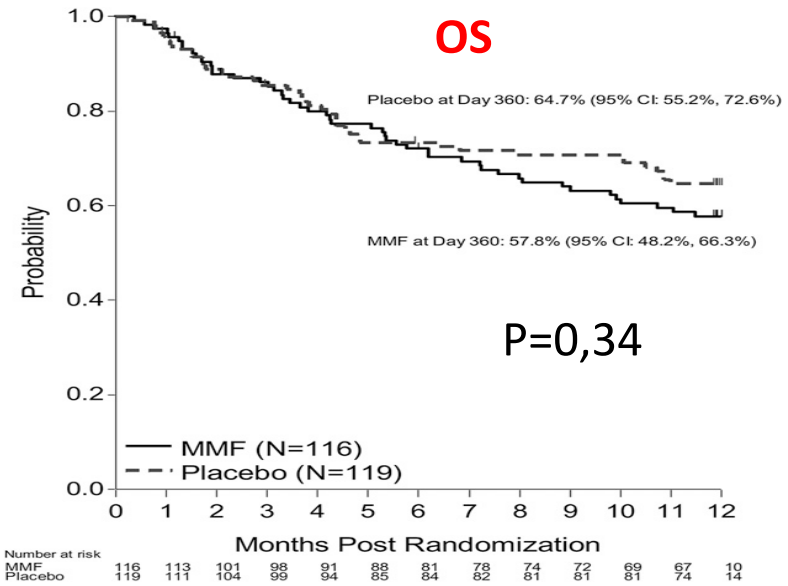
Placebo
n=119

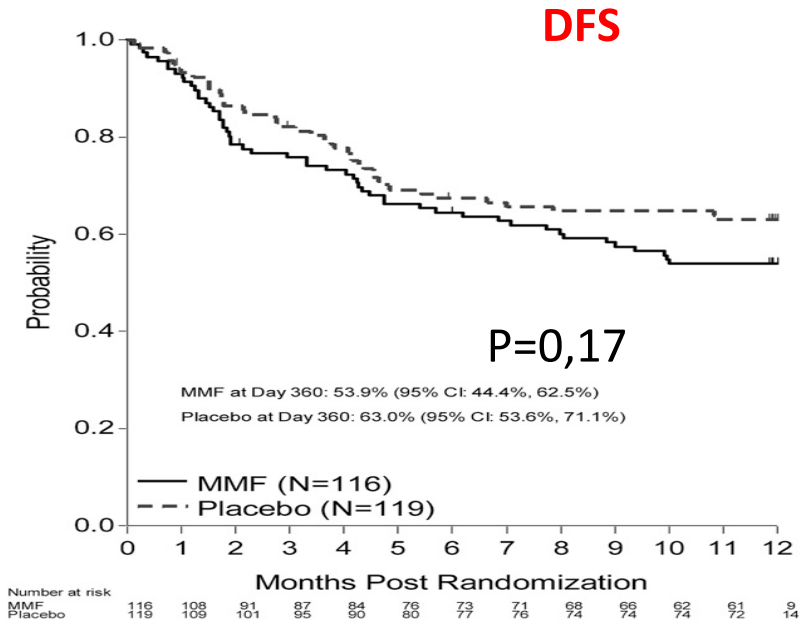
Primary end point: GVHD-free survival at day 56 after randomization.

Randomization was stratified by transplant center and grade of aGVHD(I-II vs III-IV) at study entry.



No differences in day 56 GVHD-free survival:
1)grades 3-4 (MMF, 54.1%; placebo, 51.2%; P= 0.8).
2)liver/gut involvement (MMF, 51.6%; placebo, 60.3%, P= 0.34).





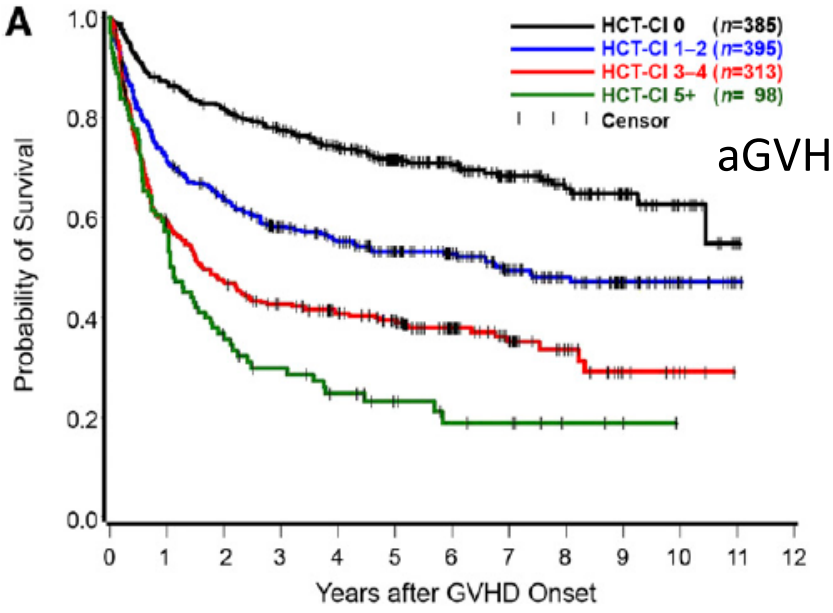
- No statistically significant differences were seen in the incidence of cGVHD.
- The corticosteroid doses at day 28 and day 56 were not different between treatment groups
- The only toxicity that was significantly different was a higher incidence of leukopenia on the MMF arm (MMF, 52.7%; placebo, 34.8%; P = 0.01).

Why?

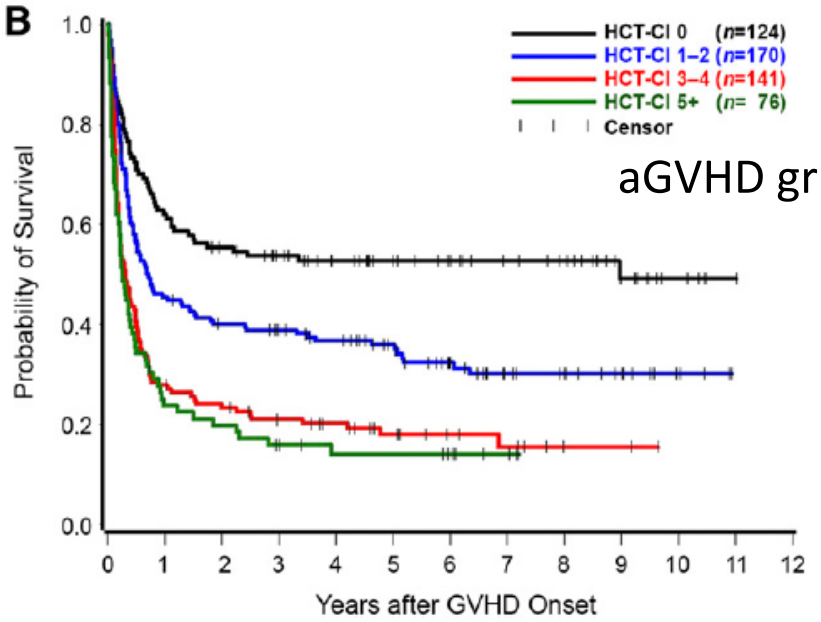
The same therapeutic approch is effective for all patients?

Pretransplant comorbidities predict severity of acute graft-versus-host disease and subsequent mortality

Sorror Blood 2014



aGVHD gr.II



aGVHD gr.III-IV

Multi-institutional retrospective study.

2985 recipients from HLA-matched related or unrelated donors.

1 January 2000 and 31 December 2006.

	Risk of mortality following grade 2 acute GVHD		Risk of mortality following grades 3 to 4 acute GVHD	
HCT-CI scores	HR (95% CI)	*P*	HR (95% CI)	*P*
0	1		1	
1-2	1.67 (1.32-2.11)	<.0001	1.59 (1.15-2.20)	.006
3-4	2.52 (1.99-3.20)	<.0001	2.35 (1.68-3.27)	<.0001
5+	3.37 (2.48 −4.56)	<.0001	2.77 (1.90-4.05)	<.0001

A Risk adapted approch

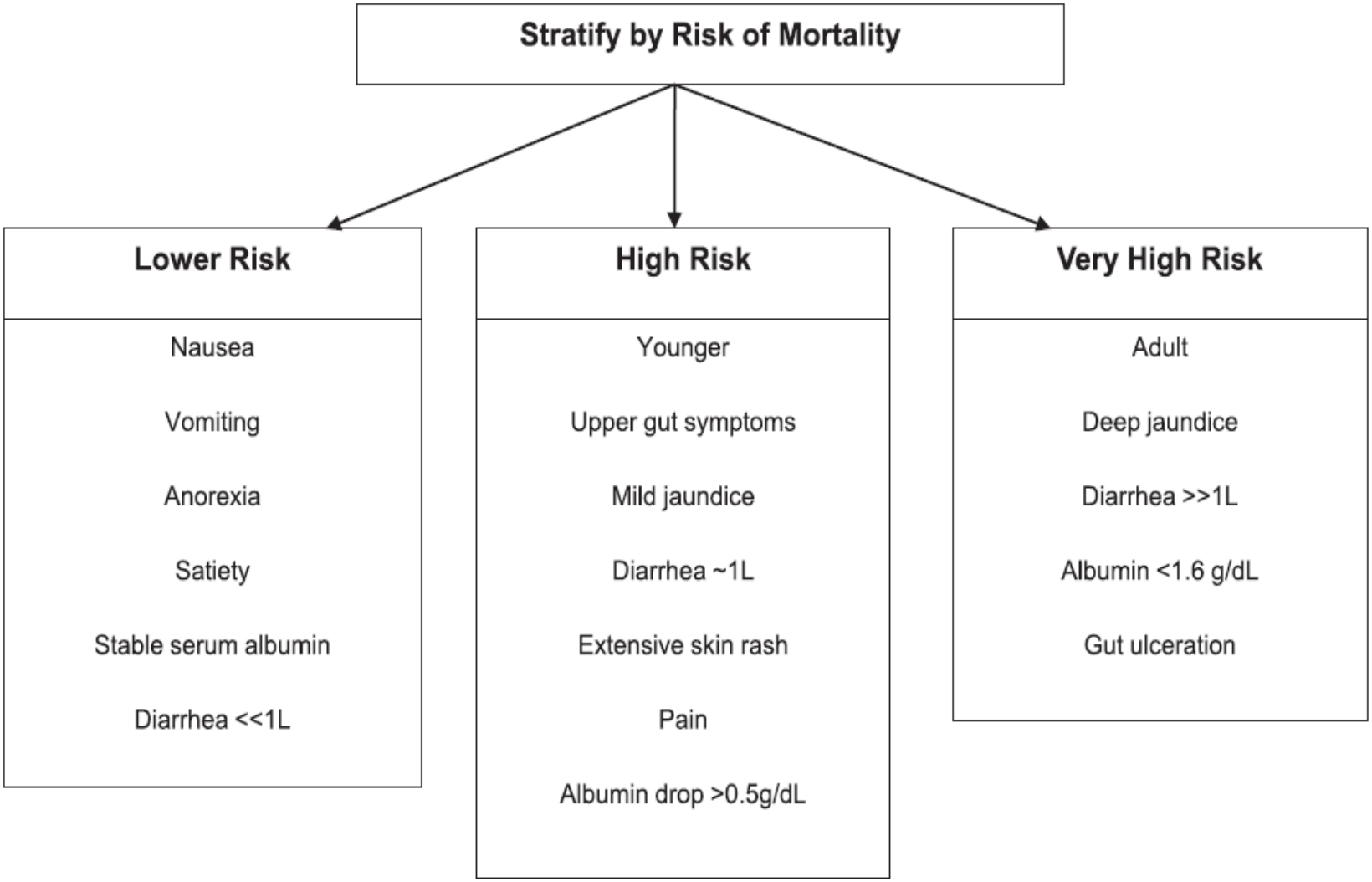


Figure 1. Triage of patients for initial treatment of acute GVHD, based on risk of GVHD-related mortality.

McDonald Blood 2016

aGVHD standard therapies

1) When?

Therapy for grade I ? **''Wait and see'' is reasonable**

2) How?

Initial steroid dose? **-aGVHD grade II a 1-2 mg/kg+/- Beclometasone**
-aGVHD > grade IIb 2 mg/kg

Association with steroid? **No evidence**

3)The treatment principle should be ''to each according to his need''.

McDonald Blood 2016

Steroid Refractory

Approximately half (>70% HR)of patients will not achieve a sustained complete response to first line therapy with steroids .

McDonald Blood 2016,Holtan Blood 2014

Non response: 7-10 days.
Progression :3-4 days.

aGVHD response : 28 days.
aGVHD –free survival: 56 days.
6 month: treatment free.

mortality among early treatment failures was 49% compared with 27%among early responders

VL Blood 2006

Treatment of steroid refractory acute GVHD

- Policlonal antibodies
- Extracorporeal Photopheresis (ECP)
- Mycophenolate mofetil (MMF)
- Sirolimus
- Pentostatin
- Combinations
- Mesenchimal stromal cells
- **Monoclonal antibodies**

ASH 2016

-Infliximab+LD alemtuzumab

-ECP (2)

-Basiliximab + Etanercept

-INCB039110 (anti Jak1)

- Begelomab (against CD26)

-Ruxolitinib

Table 2. Summary of Studies Evaluating Agents for Second-Line Therapy of aGVHD[a]

Reference	Agent	Phase	No. of Patients	Response Assessment	CR Proportion	CR or PR Proportion	6-Month Survival
[34]	Methotrexate	Retro	12	Day 28[b]	0.42	0.58	0.58
[35]	MMF	Retro	13	Best	0.15	0.46	0.66
[36]	MMF	Retro	10	Best	0	0.60	0.77
[32]	MMF	Retro	48	Best	0.31	**0.79**	0.47
[37]	MMF	Retro	27	Best	0.26		0.52
[22]	ECP	Retro	33	Best[b]	**0.55**	0.76	**0.76**
[23]	ECP	Retro	23	Best[b]	0.48	0.48	0.57
[38]	Basiliximab	2	23	Day 7[b]	0.17	0.83	0.55
[39]	Daclizumab	2	43	Day 43	0.37	0.51	
[40]	Daclizumab	2	12	Day 28[b]	0.08	0.50	0.33
[25]	Daclizumab	Retro	57	Day 43	0.33	0.54	**0.28**
[41]	Inolimomab	2	14	Best[b]	0.14	0.43	0.36
[42]	Denileukin diftitox	1	32	Best	0.38	0.53	
[43]	Denileukin diftitox	2	22	Best	0.18	**0.27**	
[27]	Alemtuzumab	2	18	Day 28[b]	0.33	0.83	0.71
[26]	Alemtuzumab	2	10	Best[b]	0.20	0.50	**0**
[28]	Alemtuzumab	Retro	18	Day 56[b]	0.28	0.62	0.61
[33]	Horse ATG	Retro	22	Day 28		**0.18**	
[24]	Horse ATG	Retro	58	Day 21[b]	**0.07**	**0.28**	**0.17**
[20]	Horse ATG	Retro	79	Day 28	0.20	0.54	0.44
[44]	Horse ATG	2/3	47	Best[b]	0.32	0.57	0.45
[45]	Horse ATG	3	27	Best[b]	0.33	0.56	0.55
[46]	Etanercept	Retro	13	Day 56	0.38	0.46	0.77
[29]	Infliximab	Retro	21	Day 7[b]	**0.62**	0.67	0.52
[30]	Horse ATG + etanercept	Retro	16	Best[b]	**0.69**	0.81	0.56
[47]	Dacliz + etanercept	2	21	Best[b]	0.38	0.67	0.57
[21]	Dacliz + infliximab	Retro	22	Day 42[b]	0.45	0.82	**0.86**
[31]	Dacliz/inflix/horse ATG	Retro	12	Best[b]	**1.00**	**1.00**	0.73
[48]	Sirolimus	Retro	34	Best	0.44	0.76	0.48

Martin PJ BBMT 2012 ; 18:982

The anti-CD26, begelomab, in the treatment of steroid resistant aGvHD

CD26

CD26 is a co-stimulatory molecule and marker of T cell activation *(Fox et al, 1984; Morimoto et al, 1989; Dang et al, 1990; Tanaka et al, 1992; Morimoto & Schlossman, 1998; Ohnuma et al, 2008).*

CD26 is mainly expressed on activated T lymphocytes implicated in autoimmune conditions as well as in aGvHD and transplant rejection *(NEJM 1985; 312:1405, Clin Immunol Immunopathol 1996; 80: 31; J Rheumatol 1996; 23:2022; Clin Exp Immunol, 1994; 98: 252; J Immunol 2001; 166(3): 2041-8)*

CD26 is highly expressed on T cells migrating through endothelial cell monolayers in vitro *(J Immunol, 1992; 148: 1367).*

These findings imply that CD26+ T cells

play an important role in the inflammation process and subsequent tissue damage in such diseases, and suggest that CD26 + T cells appear to be effectorT cells.

The anti-CD26, begelomab, in the treatment of steroid resistant aGvHD

Anti CD26

- It is a murine IgG2b monoclonal antibody and its molecular weight is about 150KDa.

- It binds to CD26 glycoprotein expressed on T activated lymphocytes.

- Mechanism of action:

  -Inhibition of CD26 impairs T cells migration across the endothelial barrier

  Trends in Immunology 2008; 29:295

  -blocking proliferation of $CD3^{+}CD26^{+}$ T lymphocytes, reducing the immune response occurring in steroid-resistant aGvHD.

  -induces surface modulation/internalisation of CD26

  - Blocks co-stimulatory activity for the T Cell Receptor

  Hatano BJH 2013, Blazar Nat.Rew. Imm 2013

Study1 (EUDRACT code 2007-005809-21): safety and efficacy of anti-CD26 in SR-aGvHD

Type of Study	Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Dosage Regimen; Route of Administration	Duration of treatment	Number of Subjects	Healthy Subjects or Diagnosis of Patients
Efficacy, safety and PK	Study EUDRACT 2007-005809-21	The primary efficacy variable of the study was the percentage of responder patients at Day +10.	Pilot, open-label, uncontrolled study	2 mg iv	5 consecutive days	14	Steroid-resistant aGvHD

Results

- Enrolled: 14 patients
  - Patients with acute GvHD not responsive to first cycle of steroids lasting 5 days
  - 50% had received prior second line treatment
  - 91% grade III and 9% grade IV aGvHD

- Responder:
  - Day +10 = **59%**
  - Day +30 = **83%**
  - Day +60 = **92%** (CR = 35%; PR = 57%)

- Overall survival 58% at day +180 and 33% at day +365

Conclusion

- Positive results for Primary Objective with 59% responders at day +10 and 83% at day +30

- Reduction by organ stage, including gut GvHD (stage II-IV from 75% to 25% at day +30)

- Karnofsky Index (scale to classify functional improvement) improved over long term

Study2 (EUDRACT 2012-001353-19): dose finding study binding of anti-CD26 to circulating CD3+CD26+ T cells.

Type of Study	Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Dosage Regimen; Route of Administration	Duration of treatment	Number of Subjects	Healthy Subjects or Diagnosis of Patients
Efficacy, safety and PK/PD	Study EUDRACT 2012-001353-19	The primary objective of this study was to evaluate the Minimum Effective Dose (MED) and pharmacodynamic/ pharmacokinetic assessment	Dose-finding, open-label, uncontrolled study	2mg/m^2 iv	5 consecutive days	16	Steroid-resistant aGvHD
				3mg/m^2 iv	5 consecutive days		
				3mg/m^2 iv	5 consecutive days and day +10,+14, +17,+21,+24,+28		
				4.5 mg/m^2 iv	5 consecutive days		

Results

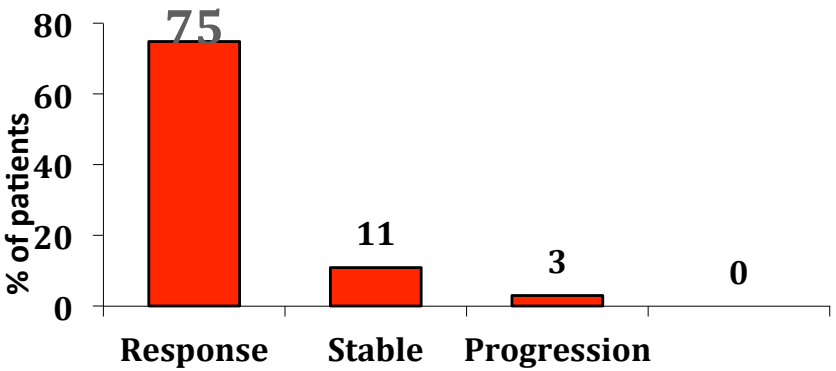
- Enrolled: 16 patients
  - 16/16 completed
  - 56% grade III/IV and 44% grade II aGvHD
- Responder:
  - 2mg, 3mg, 4,5mg= 67%,
  - 3mg+ day 10,14, 17, 21, 24,28 (n=7): **71**%

Conclusions

- 3 mg/m2 IV, 5 consecutive days and days +10, +14, +17, +21, +24, +28 identified as optimum dose for begelomab
  - TRM of c.30% at day +180
- 80% of patients chronic GvHD-free at day +180
- OS at day +180 in DL2bis group: 71%

Cumulative results of Study 1 and Study2 two prospective studies

Response at day +28



OS at day +365: 46%

TRM at day +180: 28%

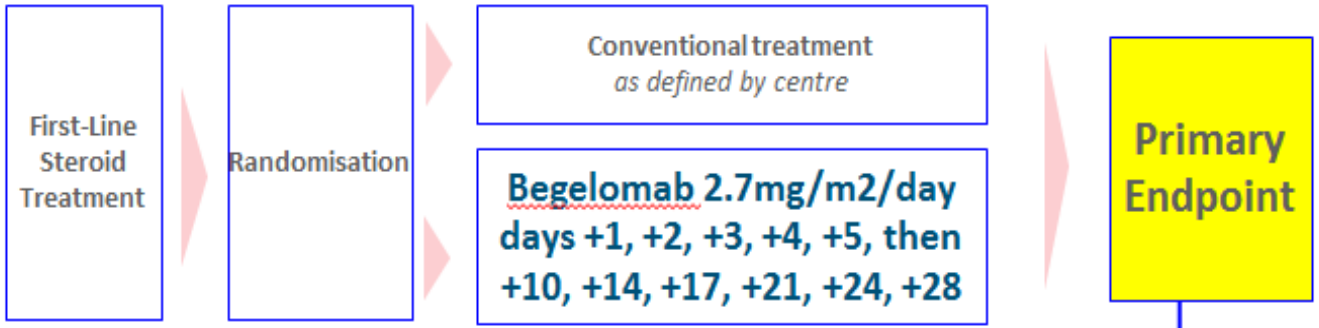
High levels of tolerability seen in phase I and phase II trials

There was no discontinuation of treatment

No treatment related death

There has been no evidence of anaphylaxis or anaphylactoid reactions after 200 administered doses of Begelomab

Pivotal study design



Primary Endpoint

ORR at day +28
TRM at day +180

Secondary Endpoint

- Change from baseline in stages of GvHD by target organ *(day +28)*
- Cumulative incidence of chronic GvHD *(up to day +180)*
- Overall response rate *(up to day +180)* and duration of response *(up to day +90)*
- Overall survival *(up to day +180)*
- Cumulative steroid dose *(day +28, +56, +90)*
- Cumulative incidence of relapse and relapse-related mortality *(up to day +180)*
- Karnofsky Performance Status Score *(up to day +180)*
- Adverse events *(up to day +56)*
- Pharmacokinetic and immunogenic assessments, vital signs, health assessment

Type	• Pivotal • Prospective • Randomised • Open-label • Controlled
Duration	• For an individual subject: 12 months, including screening, the 180 day experimental phase, and long-term follow up
Participating Centres	• Approximately 29 centres • 10 in US, 18 in Europe (Italy, UK, Spain, France, Germany and Switzerland)

JAK inhibitor for GVHD

Studies in experimental GVHD indicate that cytokines are important mediators of GVHD.

Blockade of single cytokine may not be sufficient (GVHD effect of multiple cytokines).

Teshima, Nature Med 2002 . Antin Blood 2002

Jak 1 relays the signaling function of **many inflammatory cytokines** with relevance for GVHD, including IL2, IL6, and IFN gamma.

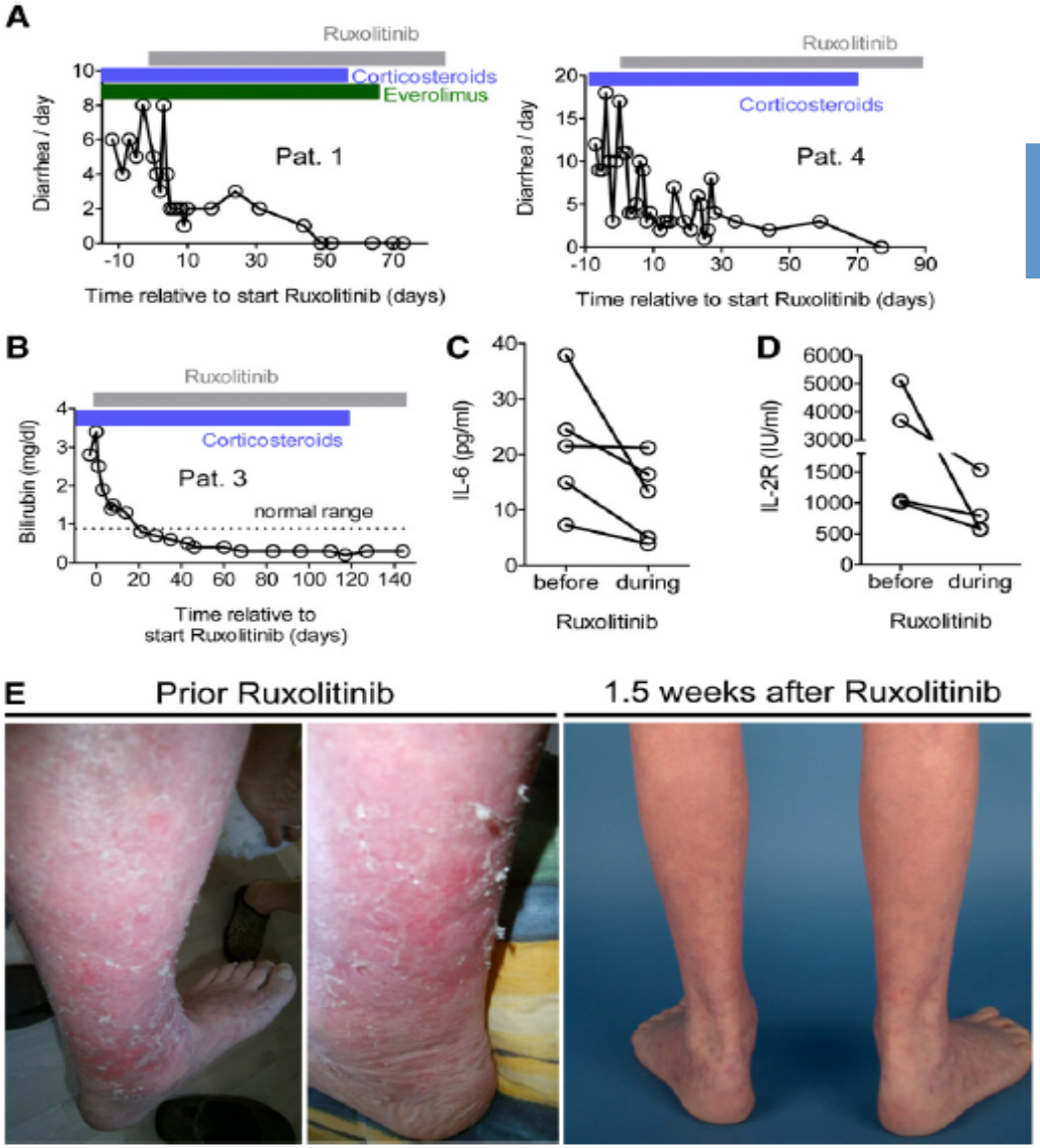
JAK1/2 signaling was also reported to play a central role in innate immunity, including activation of **neutrophils** .

Dendritic cells (DC) were shown to depend on JAK1/2 activation during differentiation and maturation.

Preclinical studies: JAK1/2 inhibitor Ruxolitinib suppresse GVHD in mice.

Spoerl et al Blood 2012

A pilot study of Ruxolitinib therapy for SR GVHD



	n	response	Time to response
acute	4	CR1, PR3	1-1,5 week

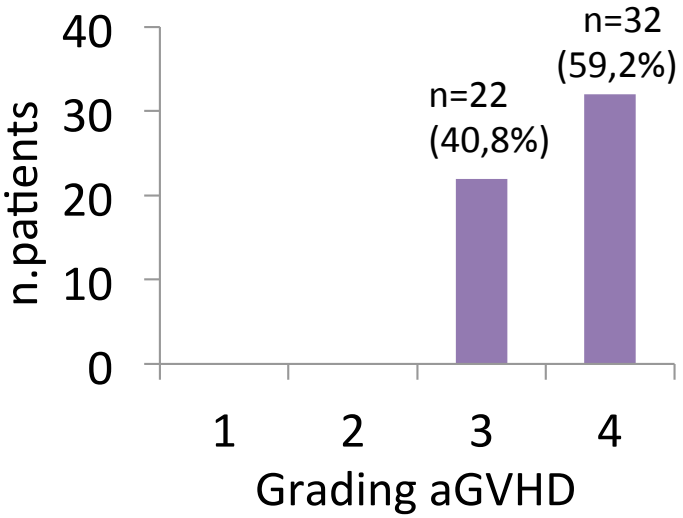
Spoerl et al. Blood 2014

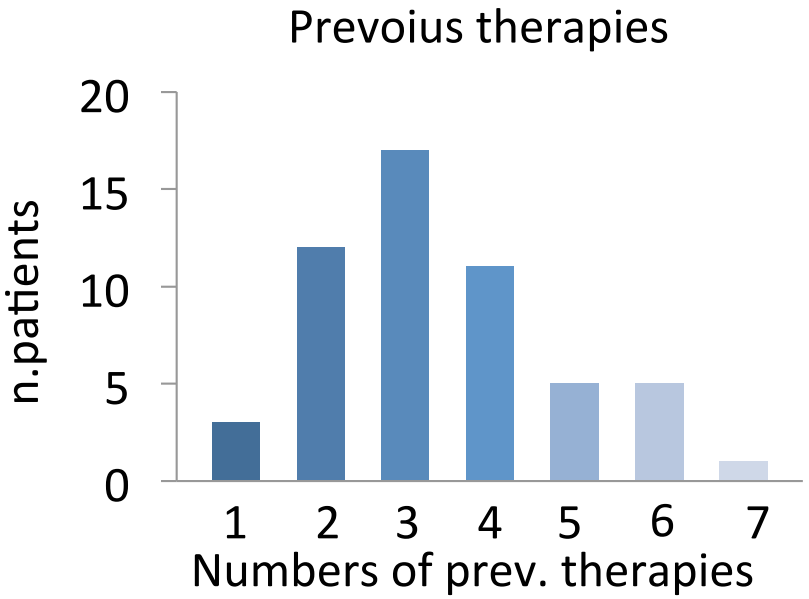
Ruxolitinib in SR GVHD: a multicenter survey

- 19 Stem Cell Transplant Centers in Germany, France, Switzerland, Greece, Sweden , Netherlands and the United States.
- Between 2012 to 2015: a total of 54 patients with aGVHD were enrolled.
- Definition of steroid refractory:
  No response to corticosteroids of a least 1 mg/kg given at least 1 week for a GVHD.
- The majority of patients was treated with ruxolitinib as an add-on immunosuppression therapy at a dose of 5–10 mg orally twice daily .

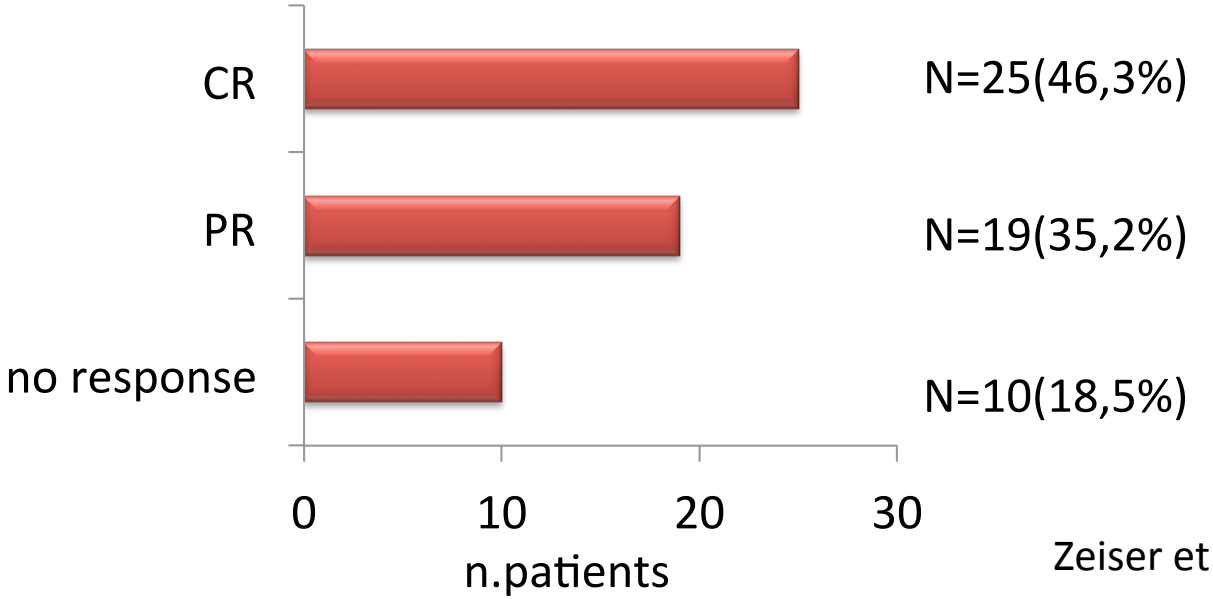
Zeiser et al Leukemia 2015

Ruxolitinib in SR GVHD: a multicenter survey





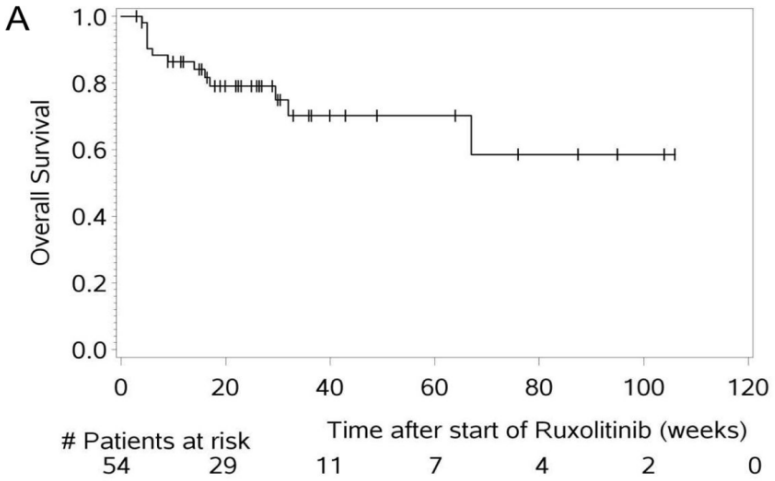
(n=54)



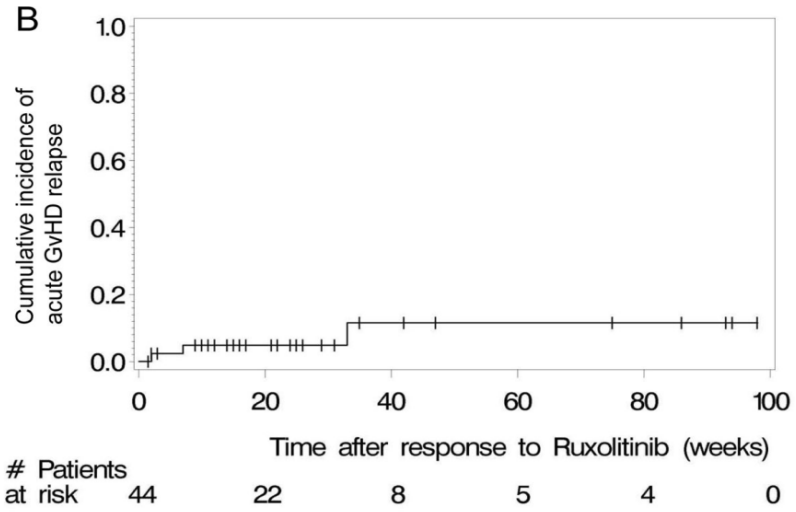
Zeiser et al Leukemia 2015

Ruxolitinib in SR GVHD: a multicenter survey

OS



GVHD relapse



Adverse events

Variable	aGvHD (n=54) % (absolute number)
CMV reactivation	33.3 (18)
Severe cytopenia (Grade 3 and 4)	33.3 (18)
Mild cytopenia (Grade 1 and 2)	22.2 (12)
Cytopenia before ruxolitinib	51.8 (28)
Malignancy relapse	9.2 (5)

Zeiser et al Leukemia 2015

Ruxolitinib in SR GVHD: a multicenter survey

Update ASH 2016

At follow-up, 22/54 (41%) of SR-aGVHD patients have an ongoing response and are free of any immunosuppression.

GVHD relapse or progression after achieved PR/CR was observed in 14/45 (31%) with SR-aGVHD.

Response to re-treatment with Ruxolitinib or any immunosupressive therapy was seen in 11/14 (78%) patients with SR-aGVHD.

Cytopenia (any grade) and CMV-reactivation were observed during ruxolitinib-treatment in SR-aGVHD (30/54, 55.6% and 18/54, 33.3%) patients.

ClinicalTrials.gov
A service of the U.S. National Institutes of Health

NCT02396628 study

- Multicenter phase 2 trial of ruxolitinib for steroid – refractory a GVHD
  1:1 to Ruxo vs. best available treatment
- Germany (Bubnoff)

NCT02913261

- Safety and Efficacy of Ruxolitinib Versus Best Available Therapy in Patients With Corticosteroid-refractory Acute Graft vs. Host Disease After Allogeneic Stem Cell Transplantation.
- Novartis

Grazie!

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