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**Terapia combinata di farmaci e procedure nella
gestione della GVHD**

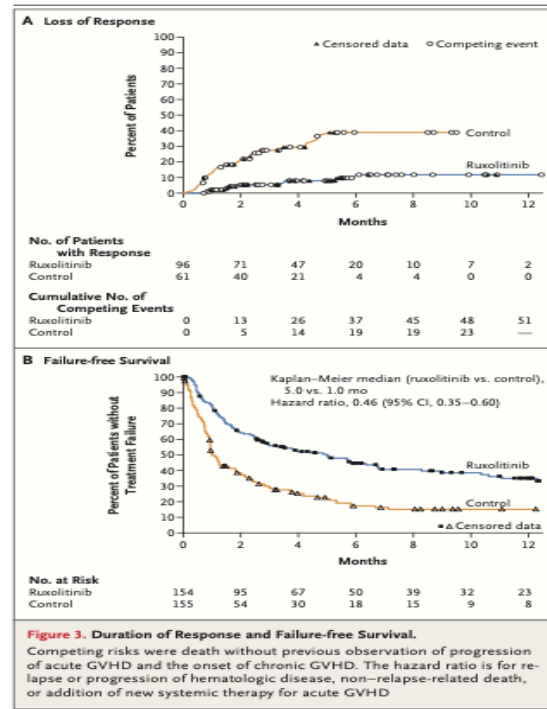
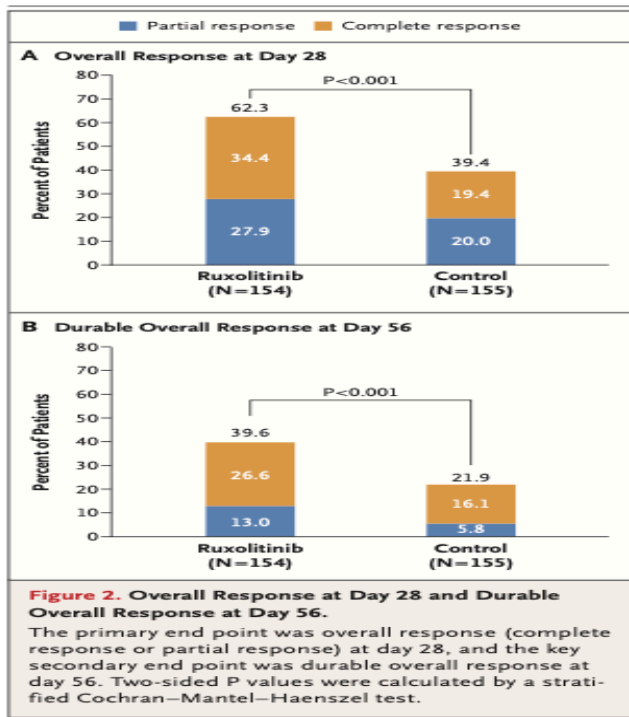
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Disclosures of Francesca Patriarca

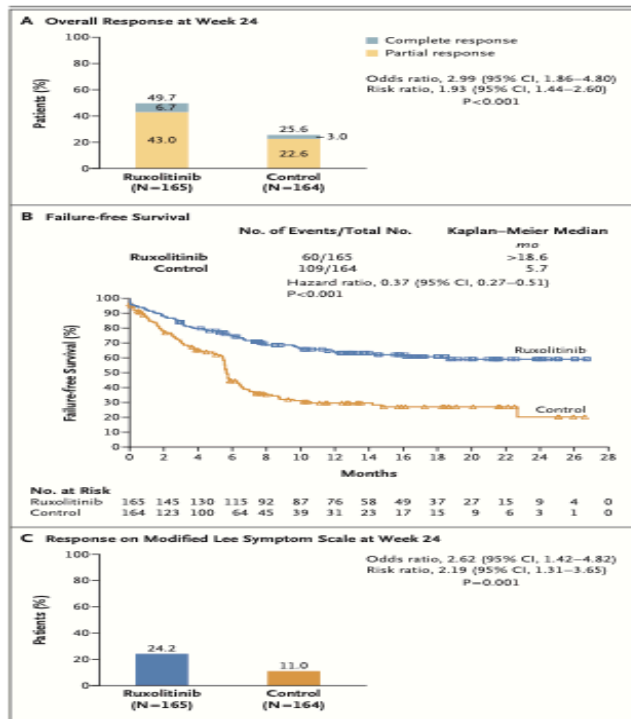
Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Johnson & Johnson						X	
BMS					X	X	
Novartis						X	
Sanofi					X	X	
Menarini					X		x
Takeda					X	X	
Medac					X		

Why do we need combination treatment of acute GVHD?



Steroid-refractory aGVHD is still an unmet clinical need with than less than 50% FFS at 6 month after second-line treatment start

Why do we need combination treatment of chronic GVHD?



Adverse events leading to dose adjustments or interruptions occurred in 62 patients (37.6%) who received ruxolitinib and in 26 patients (16.5%) who received control therapy.

Steroid-refractory (including steroid dependent and intolerant) cGVHD is still an unmet clinical need with less than 50% responsive patients to second-line treatment

Prophylaxis and management of graft-versus-host disease after stem-cell transplantation for haematological malignancies: updated consensus recommendations of the European Society for Blood and Marrow Transplantation

**Olaf Penack, *Monia Marchetti, Mahmoud Aljurf, Mutlu Arat, Francesca Bonifazi, Rafael F Duarte, Sebastian Giebel, Hildegard Greinix, Mette D Hazenberg, Nicolaus Kröger, Stephan Mielke, Mohamad Mohty, Arnon Nagler, Jakob Passweg, Francesca Patriarca, Tapani Ruutu, Hélène Schoemans, Carlos Solano, Radovan Vrhovac, Daniel Wolff, Robert Zeiser, Anna Sureda, Zinaida Peric*

Panel 2: Recommendations on aGVHD treatment

New recommendations

- In adults with steroid-refractory acute graft-versus-host disease (SR-aGVHD) we recommend **ruxolitinib** (National Comprehensive Cancer Network [NCCN] classification 1)
 - o Large beneficial effect on overall response rate and failure-free survival in a randomised trial and three meta-analyses, with no relevant increase of undesirable effects⁴⁹⁻⁵²

As future perspectives, we consider the following areas as research priorities:

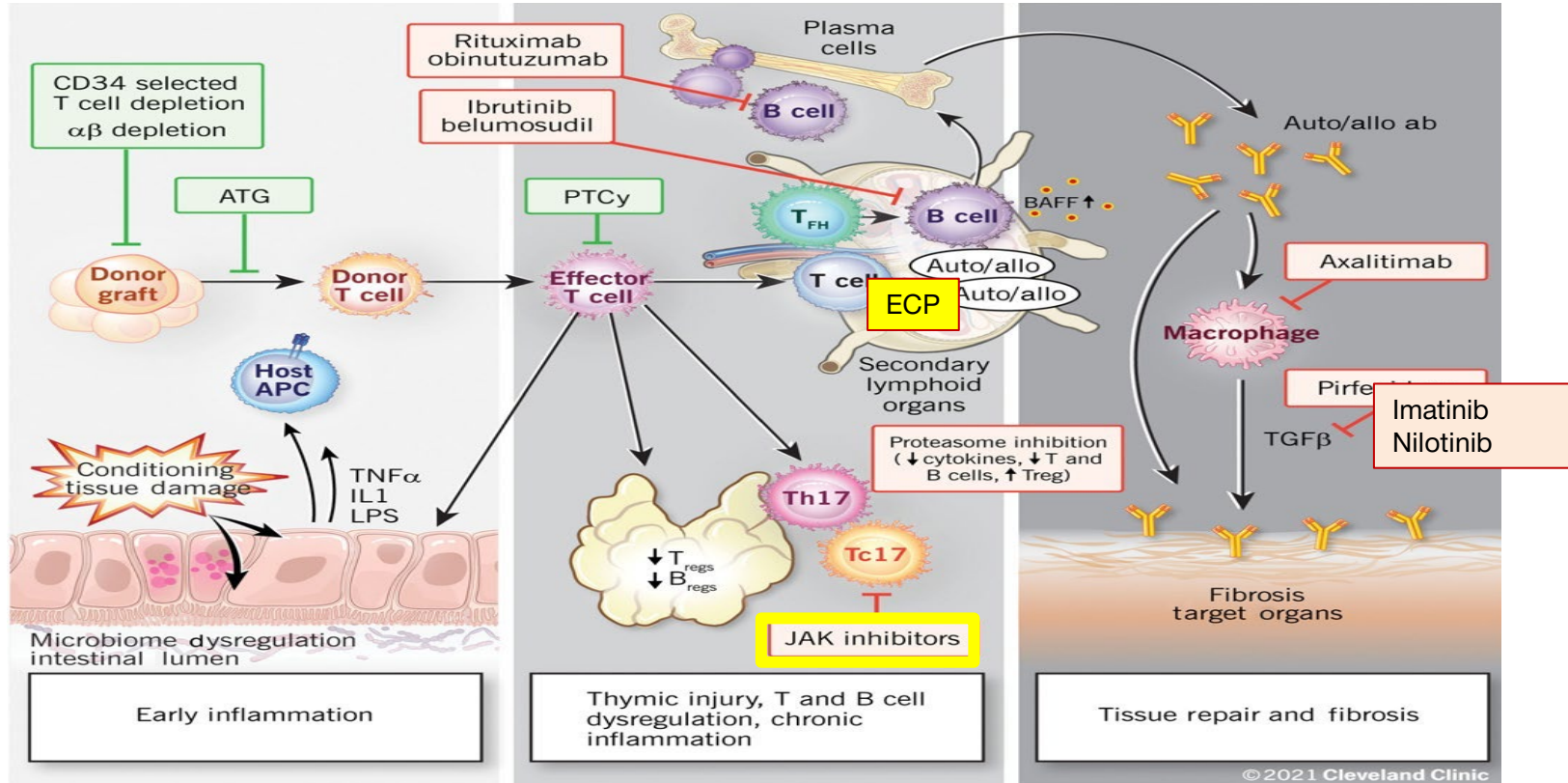
(1) combination therapies as first treatment or salvage treatments of aGVHD and cGVHD (eg, using ECP as combination partner)

Panel 3: Recommendations on cGVHD treatment

New recommendations

- In adults with steroid-refractory chronic graft-versus-host disease (SR-cGVHD), we recommend **ruxolitinib** (National Comprehensive Cancer Network [NCCN] classification 1)
 - o Large beneficial effect on overall response rate and failure-free survival in a randomised trial, a propensity-adjusted retrospective analysis, and three meta-analyses^{50-52,61,62}
- In adults with SR-cGVHD, **belumosudil** is a potential therapeutic option (NCCN classification 2C)
 - o Encouraging overall response rates in non-randomised trials showing a low drug induced toxicity profile⁶³⁻⁶⁶
- In adults with SR-cGVHD, **ibrutinib** is a potential therapeutic option (NCCN classification 2B)
 - o Encouraging overall response rates in non-randomised trials in patients with moderate GVHD burden and an acceptable toxicity profile⁶⁷⁻⁷¹

GVHD treatments have pleiotropic mechanism of actions, that could be synergistic and have different toxicities, that could not be overlapping



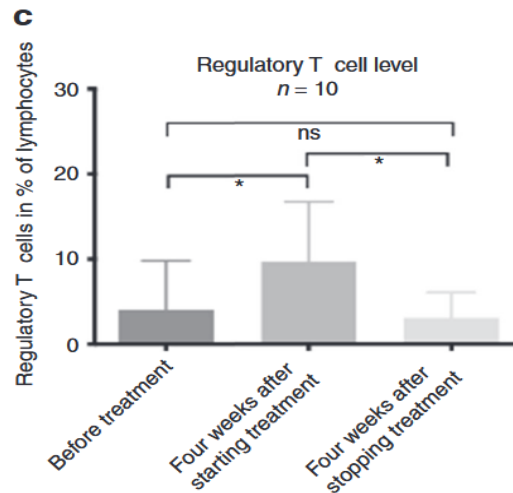
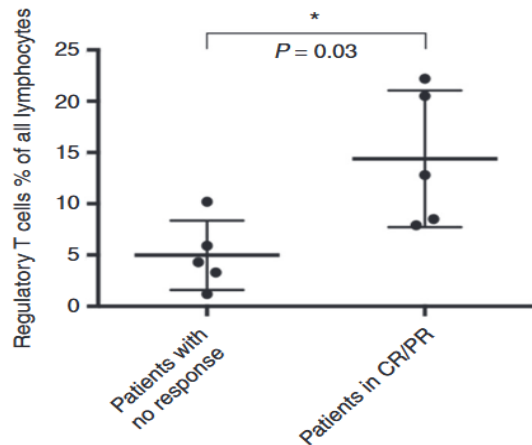
ECP in acute Graft-versus-Host Disease

Greinx et al. [34] (n = 59)	Prospective, single-arm, phase II	ECP + CS in second-line	70/60	CR in skin 82%, liver 61% and gut 61%; 4-yr OS 47% (59% and 11% in ECP responders and non-responders); 4-yr TRM 36% (14% and 73% in ECP responders and non-responders)
Amat et al. [35] (n = 37)	Prospective, multicenter	ECP + CS in second-line	73/40.5	ORR in skin 71%, liver 54.5% and gut 67%; significant longer OS in CR pts (median > 47 mo vs 12 mo)
Jagasia et al. [36] (n = 108)	Retrospective, multicentre	ECP + CS vs Inolimomab/ Etanercept + CS in second-line	66/54 vs 32/20 (p = 0.001)	ECP as independent predictor of ORR (HR, 3.42, p = 0.007), OS (HR, 2.12, p = 0.018); ECP associated with superior OS (HR, 4.6, p = 0.016) in SR aGvHD grade II and lower NRM (HR, 0.45, p = 0.018)
DasGupta et al. [37] (n = 128)	Retrospective, multicentre	ECP + CS in second-line	77/67	6-mo-FFTF 77%; 2-yr OS 56%; 2-yr TRM 34%
Worel et al. [38] (n = 99)	Retrospective, single center	ECP + CS in second-line	75/53	ORR in skin 80%, liver 61% and GI 75%; 1-yr and 5-yr TRM 22% and 31%; 1-yr and 5-yr OS 69% and 50%
Calore et al. [39] (n = 72, children)	Retrospective	ECP + CS ± other IS	83/64	CR in skin in 70%, liver in 84%, and gut in 71%; 5-yr OS 71%
Niittyvuopio et al. [40] (n = 52)	Retrospective, single center	ECP + CS in second-and third line	62/48	CR in skin 77%, liver 33%, and gut 34%; 1-yr OS 51%
Perotti et al. [41] (n = 50, children)	Retrospective, single center	ECP + CS	68/32	ORR in skin 83%, liver 67%, and gut 73%; 1-yr OS 64%
Malagola et al. [42] (n = 45)	Retrospective, multicentre	ECP + CS in second-line	Na/91	CR in grade II 97% and grades III/IV 67%
Messina et al. [43] (n = 33, children)	Retrospective, single center	ECP + CS ± other IS	75/54	CR in skin 76%, liver 60% and gut 75%; 5-yr OS 69%

ECP was the most frequently used BAT in the REACH 2 trial (Zeiser 2020)

Ruxolitinib in combination with ECP in acute Graft-versus-Host Disease

- 18 patients with steroid-refractory grade III-IV lower gut acute GVHD
- ECP (biweekly for a median of 20.5 treatments) in combination with ruxolitinib (median dose 20 mg for a median of 60 days)
- CR 44%, PR 11%, 2 y- OS 56% new grade III cytopenia 17% CMV reactivation 67%



COMPARISON RUXO+ ECP vs RUXO ALONE IN HAMBURG CENTRE

Table 2 Graft-versus-host disease characteristics

	Ruxo-ECP	Ruxo alone
SR-aGVHD	n = 49 (63 %)	n = 29 (37 %)
grade II	n = 0	n = 11 (38 %)
grade III	n = 27 (55 %)	n = 14 (48 %)
grade IV	n = 22 (45 %)	n = 4 (14 %)
Skin GVHD		
grade I	n = 14 (29 %)	n = 1 (3. %)
grade II	n = 7 (14 %)	n = 5 (17 %)
grade III	n = 11 (22 %)	n = 12 (41 %)
grade IV	n = 3 (6 %)	n = 1 (3. %)
Liver GVHD		
grade I	n = 5 (10. %)	n = 1 (3 %)
grade II	n = 3 (6 %)	n = 1 (3. %)
grade III	n = 5 (10. %)	n = 0
grade IV	n = 0	n = 0
GI GVHD		
grade I	n = 2 (4 %)	n = 5 (17 %)
grade II	n = 6 (12 %)	n = 9 (31 %)
grade III	n = 19 (39 %)	n = 5 (17 %)
grade IV	n = 22 (45 %)	n = 3 (10 %)
Interval between start of steroid first-line treatment and beginning of ruxolitinib, median days	12 (r: 4 – 65)	10 (r: 4 – 63)
Duration of Ruxo continued treatment, median days	77 (r: 13 – 335)	46 (r: 2 – 735)
Ruxolitinib and ECP cycles, median	15 (r: 2 – 76)	
Time from Ruxo and start of ECP treatment, median days	9 (r: 3 – 69)	
Type of SR-aGVHD		
progression after 3 days	n = 7 (14 %)	n = 3 (10 %)
no improvement after 7 days	n = 16 (33 %)	n = 9 (31 %)
inability to taper steroids < 0.5 g/kg	n = 26 (53 %)	n = 17 (59 %)

COMPARISON RUXO+ ECP vs RUXO ALONE IN HAMBURG CENTRE

	d28 OR (CR)	d56 OR(CR)	D 180 OR (CR)	D 360 OR (CR)	N° deaths (%)
Ruxo n=29	90 (31)	90 (72)	50 (40)	23 (17)	11 (38%)
Ruxo+ECP n=49	86 (0)	86 (19)	61 (50)	72 (64)	24 (49%)

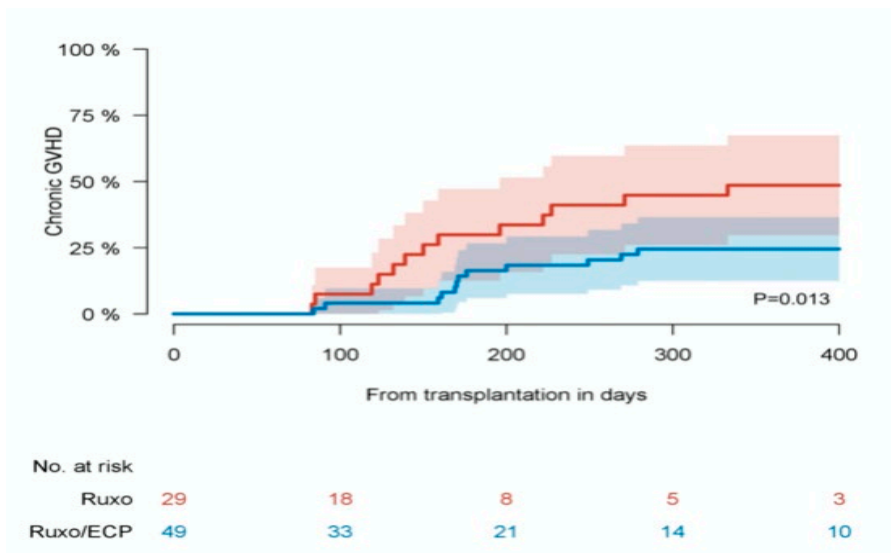
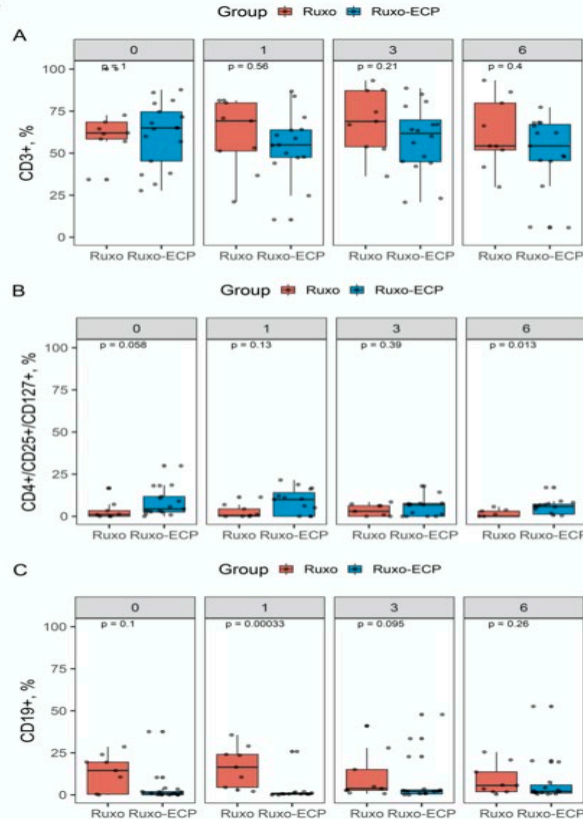


Figure 4



Faster CD3+ ly reconstitution in ruxo monotherapy

Higher T regulatory ly count in ruxo+ECP only at 1 month

Faster B CD19+ ly reconstitution in ruxo monotherapy

possibly linked to higher cGVHD incidence

Real-world study in steroid-refractory acute graft versus host disease: comparison of efficacy and tolerability of ruxolitinib alone or ruxolitinib in association with extracorporeal photopheresis or extracorporeal photopheresis monotherapy.

Running title: salvage therapies for steroid-refractory aGvHD

Marta Lisa Battista¹, Gabriele Facchin¹, Maria De Martino², Patrizia Chiusolo^{3,4}, Domenico Russo⁵, Michele Malagola⁵, Francesco Saraceni⁶, Giorgia Mancini⁶, Alessandro Rambaldi⁷, Irene Maria Cavattoni⁸, Albana Lico⁹, Chiara Nozzoli¹⁰, Angela Cuoghi¹¹, Marco Ladetto¹², Vincenzo Federico¹³, Maria Caterina Micò¹⁴, Maria Teresa Lupo-Stanghellini¹⁵, Elena Oldani⁷, Eliana Degrandi¹⁶, Anna Maria Gallina¹⁷, Matteo Parma¹⁸, Alessandra Biffi¹⁹, Franca Fagioli²⁰, Cristina Skert²¹, Antonella Geromin¹, Chiara Savignano²², Miriam Isola², Renato Fanin^{1,2}, Fabio Ciceri^{15,23}, Massimo Martino¹⁴, Francesca Patriarca^{1,2}

Characteristics	Overall n=233	Group 1 n=124 ECP	Group 2 n=53 ECP + Ruxolitinib	Group 3 n=56 Ruxolitinib	p-value
aGvHD grading at onset, n (%)	n=228	n=121		n=54	
• I	39 (17)	23 (19)	8 (15)	8 (15)	0.322
• II	97 (43)	58 (48)	19 (36)	20 (37)	
• III	64 (28)	29 (24)	19 (36)	16 (30)	
• IV	28 (12)	11 (9)	7 (13)	10 (18)	
aGvHD post DLI, n (%)	13 (6)	4 (3)	4 (8)	5 (9)	0.200
Median time from transplant to SRaGVHD, days (range)	56 (11-1707)	51 (17-1707)	60 (21-810)	63 (11-1208)	0.265
SRaGVHD grade, n (%)	n=230	n=121			<0.001
• III-IV	108 (47)	35 (29)	39 (74)	34 (61)	
SRaGVHD multiorgan involvement, n (%)	102 (44)	45 (36)	34 (64)	23 (41)	0.002
SRaGVHD single-organ skin, n (%)	89 (38)	65 (52)	11 (21)	13 (23)	<0.001

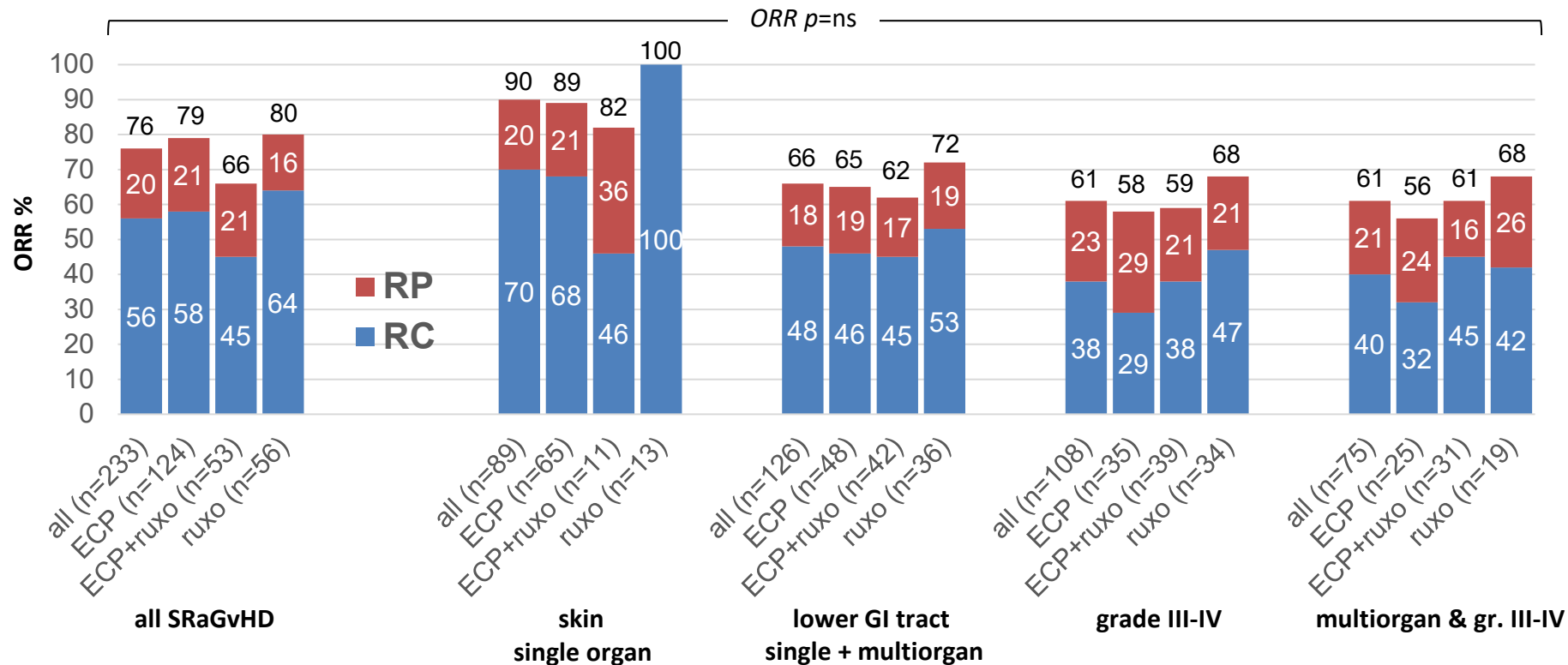
Second-line treatments management.

Characteristics	Group 1 n=124 ECP	Group 2 n=53 ECP + Ruxolitinib	Group 3 n=56 Ruxolitinib	p-value
Median duration of ruxolitinib treatment, days (range)		144 (7-1142)	97 (10-980)	0.094
Median duration of ECP treatment, days (range)	82 (2-1295)	61 (2-883)		0.804
Median number of ECP procedures, n (range)	13 (2-99)	12 (2-51)		
Median interval of ruxolitinib-ECP start in group 2, days (range)		8 (0-14)		
Ruxolitinib-ECP first start in group 2, n (%) <ul style="list-style-type: none"> • ruxolitinib first • ECP first • simultaneous 		n=47 19 (40) 22 (47) 6 (13)		
Ruxolitinib starting dose, n (%) <ul style="list-style-type: none"> • 20 mg/die • 10-15 mg/die 		n=49 22 (45) 27 (55)	n=53 33 (62) 20 (38)	0.078
Discontinuation for severe infections and cytopenia, n (%)	5 (4)	9 (17)	16 (29)	<0.001
Discontinuation for inadequate or unavailable venous access, n (%)	6 (5)	4 (7)		
Reduction of ruxolitinib dose (without suspension), n (%)		14 (26)	16 (29)	0.801

Infectious complications during second-line treatment; p-value, level of significance. Significant values are marked in bold.

Infectious events	All	N. of infectious events for treatment group			p-value
		Group 1 ECP	Group 2 ECP + Ruxolitinib	Group 3 Ruxolitinib	
N. of patients for groups	233	124	53	56	
csCMV infections, N(%)	53 (23)	24 (19)	15 (28)	14 (25)	0.385
Bacteremia, N (%)	36 (14)	13 (10)	8 (15)	15 (27)	0.019
Pneumonia, N (%)	23 (10)	14 (11)	4 (7)	5 (9)	0.747

Overall Response Rate at d28: comparison among groups for organ type and grading



Outcome

Median FU after the start of 2L treatment 14 months (range 0.4-90.6)

» **1y-OS after 2L therapy 60% (95% CI 53-66)**

(ECP) 63% (95%CI 54-71)
(ECP+ruxo) 56% (95%CI 41-68)
(Ruxo) 55% (95%CI 40-67)

**1y CI moderate-severe cGVHD
24% (95% CI 19-31)**

group 1 - ECP 26% (95%CI 18-34)
group 2 - ECP+ruxo 24% (95%CI 13-37)
group 3 - ruxo 22% ((95%CI 11-35)
(p=.783)

**1y CI NRM
31% (95% CI 25-37)**

group 1 - ECP 29% (95%CI 21-37)
group 2 – ECP+ruxo 39% (95%CI 25-52)
group 3 - ruxo 27% (95%CI 16-40)
(p=.092)

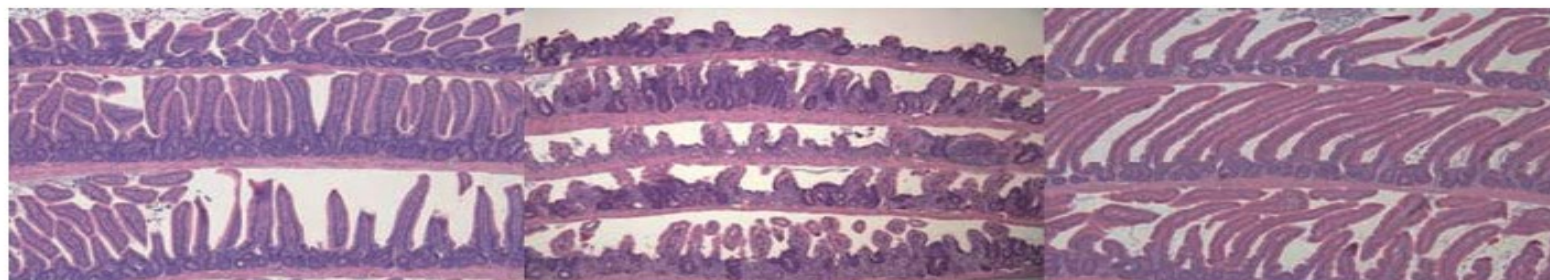
Maat-013 as salvage therapy in acute GVHD patients with gastrointestinal involvement refractory to ruxolitinib

	Sex/birth year	dx	Transplant date	Donor	GVHD	timing	Salvage treatments After steroid failure	outcome
1	Male/1955	Mantle cell lymphoma	5/5/22	10/10 MUD	Late grade 3 lower gut	26/9/22	Ruxolitinib since 29/10/22 ECP since 9/11 Maat13 : 22/12; 29/12; 5/1/23→PR	Dead 11/5/23 due to infection in poor graft function
2	Male/19477	LAM	29/8/23	aplo	Grade 3 lower gut	26/9/23	Ruxolitinib since 7/10/25 Maat13 : 20/10; 24/10; 31/10/23→CR	Dead 15/1/24 due to leukemia relapse
3	Male/1956	LAM	3/7/24	10/10 MUD	Grade 4 lower gut	15/9/24	Ruxolitinib since 11/10/22 ECP since 17/10 Maat13 : 8/11; 31/11→PRO etanercept	Dead 21/12/24 due to liver GVHD
4	Male/1956	MDS	25/7/24	aplo	Recurrent grade 2 lower gut	14/1/25	Ruxolitinib 14/1-20/2/25 Etanercept Maat13 : 3/3; 10/3;17/3/11→CR	Alive, CR

ROLE OF THE GLUCAGON-LIKE PEPTIDE 2 ANALOG, APRAGLUTIDE, IN THE TREATMENT OF GASTROINTESTINAL ACUTE GRAFT-VERSUS-HOST DISEASE

Apraglutide , a glucagon-like peptide 2 (GLP-2) analog, has been recently FDA approved to treat malabsorption in patients with short bowel syndrome and intestinal failure on the basis of a randomized phase 2 trial.

Apraglutide was studied in mice where it showed improved survival rates and reduced weight loss when administered after chemotherapy , with preservation of the morphological integrity of the GI mucosa and protection of Paneth cells and intestinal stem cells,



Control/vehicle

Melphalan

Melphalan/apraglutide

SAFETY AND EFFICACY OF THE GLUCAGON-LIKE PEPTIDE 2 ANALOG APRAGLUTIDE IN COMBINATION WITH RUXOLITINIB IN STEROID-REFRACTORY GASTROINTESTINAL ACUTE GRAFT-VERSUS-HOST DISEASE: THE PHASE 2 STARGAZE TRIAL

Apraglutide , a glucagon-like peptide 2 (GLP-2) was initiated within 5 days of starting 2L ruxolitinib therapy at different doses (high, low , fixed) weekly for 7 weeks in 31 patients with inadequate response to GCs

Twenty-seven (87.1%) patients had grade III–IV aGvHD and 20 (64.5%) had lower-GI stage 3–4 aGvHD.

Table 1. All -organ and lower-GI response rates and durable response rates (N=31)*

	D28 ORR	D28 CR	D56 ORR	D56 Durable response†	D56 CR	D56 Durable CR	D91 ORR	D91 CR	D91 Durable response*
All-organ response rate (95% CI)§	58.1% (39.1, 75.5)	25.8% (11.9, 44.6)	51.6% (33.1, 69.8)	45.2% (27.3, 64.0)	29.0% (14.2, 48.0)	29.0% (14.2, 48.0)	45.2% (27.3, 64.0)	29.0% (14.2, 48.0)	41.9% (24.5, 60.9)
Lower-GI response rate (95% CI)§	54.8% (36.0, 72.7)	29.0% (14.2, 48.0)	51.6% (33.1, 69.8)	45.2% (27.3, 64.0)	29.0% (14.2, 48.0)	29.0% (14.2, 48.0)	48.4% (30.2, 66.9)	32.3% (16.7, 51.4)	45.2% (27.3, 64.0)

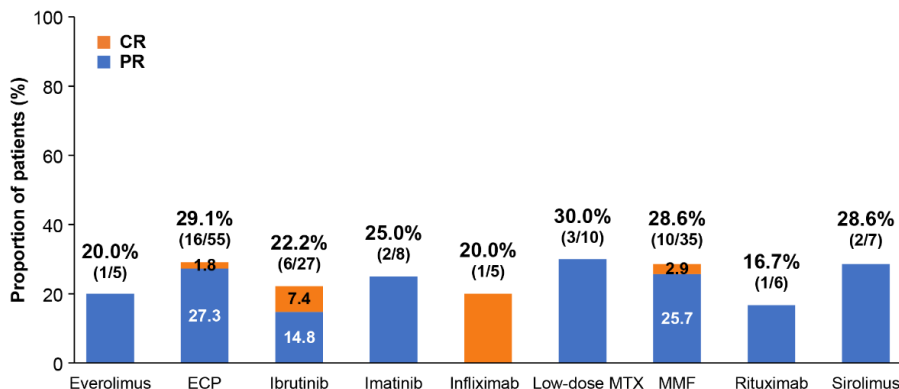
*Interim analysis. Data cut-off date: Dec 1, 2023. †Durable overall response from Day 28 to 56. *Durable overall response from Day 56 to 91.

§Clopper-Pearson Exact method.

CI, confidence interval; CR, complete response; GI, gastrointestinal; ORR, overall response; ORR, overall response rate.

ECP in chronic Graft-versus-Host Disease

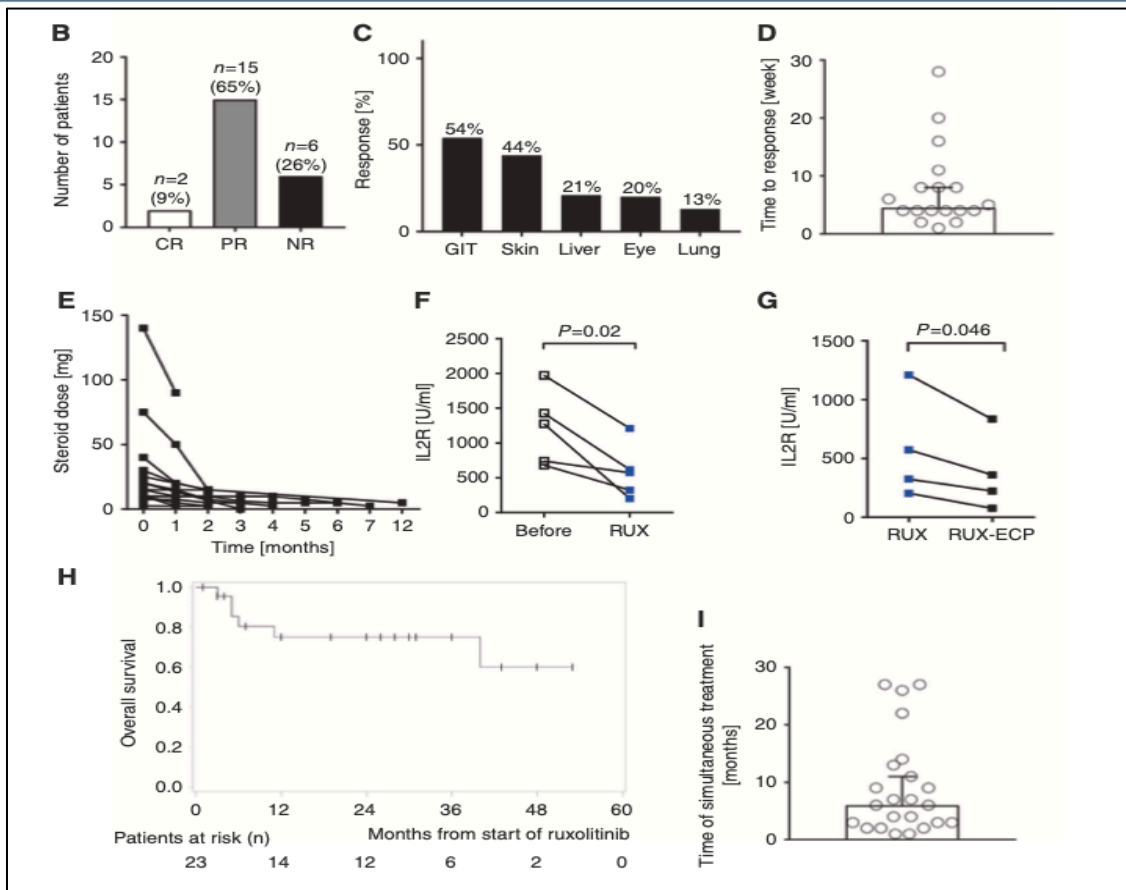
Flowers et al. [44] (n = 95; 48 vs 47)	Prospective, randomized, multicenter	ECP + CS ± other IS vs CS ± other IS	40 vs 10 at w12 in skin (p = 0.002)	ORR in eye 30% vs 7% (p = 0.04) and mouth 53% vs 27% (p = 0.06); median % improvement of TSS at week 12 14.5% vs 8.5%, at week 24 31.4% in the ECP arm.
Greinix et al. [45] (n = 29)	Prospective, crossover, multicentre	ECP + CS ± other IS	31% at w24 in skin	ORR in liver 50%, mouth 70%, and joints 36%; median % improvement of TSS at week 24 25.8%
Sakellari et al. [46] (n = 88)	Prospective, single center	ECP + CS	73/40	ORR in skin sclerosis 83%, visceral involvement 53% and lung 27%; 5-yr TRM 24%; 5-yr OS 64.5%
Gandelman et al. [47] (n = 77)	Prospective, multicentre	ECP + CS ± other IS	62/14	ORR in skin 55%; ECP responses independent of risk factors of poor outcome
Dignan et al. [48] (n = 82)	Retrospective, single center	ECP + CS ± other IS	79/na	ORR in skin 92% and mouth 91% at 6 mo; 3-yr OS 69%
Couriel et al. [49] (n = 71)	Retrospective, single center	ECP + CS ± other IS	61/20	ORR in skin 57%, liver 71% and mouth 78%; 1-yr OS 53%; response to ECP and platelet count at ECP start significantly predict NRM
Greinix et al. [50] (n = 47)	Retrospective, single center	ECP + CS ± other IS	83/na	CR in skin 68%, mouth 81%, and liver 68%



➤ ECP was the most frequently used BAT in the REACH 3 trial (Zeiser 2021)

Ruxolitinib-ECP combinations in chronic GVHD

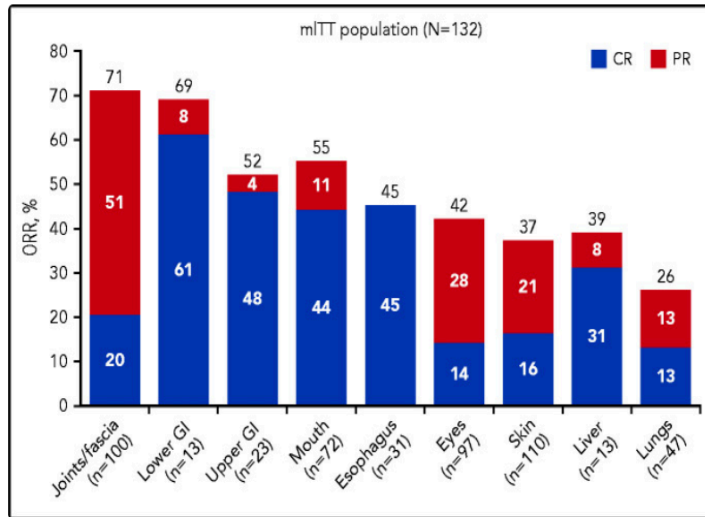
Author	Journal	N° pts	Median previous treatment	% OR (%CR)	outcome	Toxicities WHO 3-4
Maas-Bauer et al	BMT 2021	23	3 (1-4)	74 (9)	2y-os 76%	35% cytopenia
Wais et al	Leukemia Research 2024	27	3 (2-5)	88(12)	1y FFS 48%	18% trombocytopenia 33% infections



Belumosudil

This phase 2 randomized multicenter registration study evaluated belumosudil 200 mg daily (n = 66) and 200 mg twice daily (n = 66) in subjects with cGVHD (70% severe, 52% ≥ 4 organs involved) who had received 2 to 5 prior lines of therapy (21% prior ruxo)

The best ORR for belumosudil 200 mg daily and 200 mg twice daily was 74% (95% confidence interval [CI], 62-84) and 77% (95% CI, 65-87), respectively.



AE	Belumosudil, 200 mg daily (n = 66)	Belumosudil, 200 mg twice daily (n = 66)	Total (N = 132)
All grades in $\geq 20\%$ of subjects (overall)			
Fatigue	30 (46)	20 (30)	50 (38)
Diarrhea	23 (35)	21 (32)	44 (33)
Nausea	23 (35)	18 (27)	41 (31)
Cough	20 (30)	17 (26)	37 (28)
Upper respiratory tract infection	17 (26)	18 (27)	35 (27)
Dyspnea	21 (32)	12 (18)	33 (25)
Headache	13 (20)	18 (27)	31 (24)
Peripheral edema	17 (26)	13 (20)	30 (23)
Vomiting	18 (27)	10 (15)	28 (21)
Muscle spasms	13 (20)	13 (20)	26 (20)

The overall FFS rate was 75% (95% CI, 66-81) and 56% (95% CI, 47-64) at 6 and 12 months, respectively

Belumosudil combinations

Author	report	combination	N° pts	% OR (%CR)	observations
Pusic et al	BMT 2024	belu & ruxo	14	49	8/14 reduced ruxo
Caputo et al	TCT 2024, S285	belu & ruxo	20	55 (5)	No new cytopenias 2 pneumonia
Raju et al	TCT 2024, S281	belu & ruxo	14	70 (14)	1 PAP*
Swallow et al	Dermatology 2024, S163	ECP&belu	13	62	All scleroderma
Chiu et al	Blood 2022, S 140	Belu&ruxo and/or ECP and/or sirolimus and/or CNI	26	77	42% infections

*pulmonary alveolar proteinosis

CONCLUSIONS

- Combination treatment in refractory GVHD is common in clinical practice and finds its rational due to possible synergy of different mechanism of actions and no overlapping toxicities.
- A few retrospective studies showed efficacy of ECP plus ruxolitinib in acute and chronic GVHD.
- A phase 2 study tested ruxolitinib plus apraglutide in lower gut acute GVHD.
- Belumosudil was combined to ruxolitinib or ECP in chronic GVHD.

GRAZIE!

