IL MANAGEMENT 2.0 DELLA GVHD: Terapie di Combinazione

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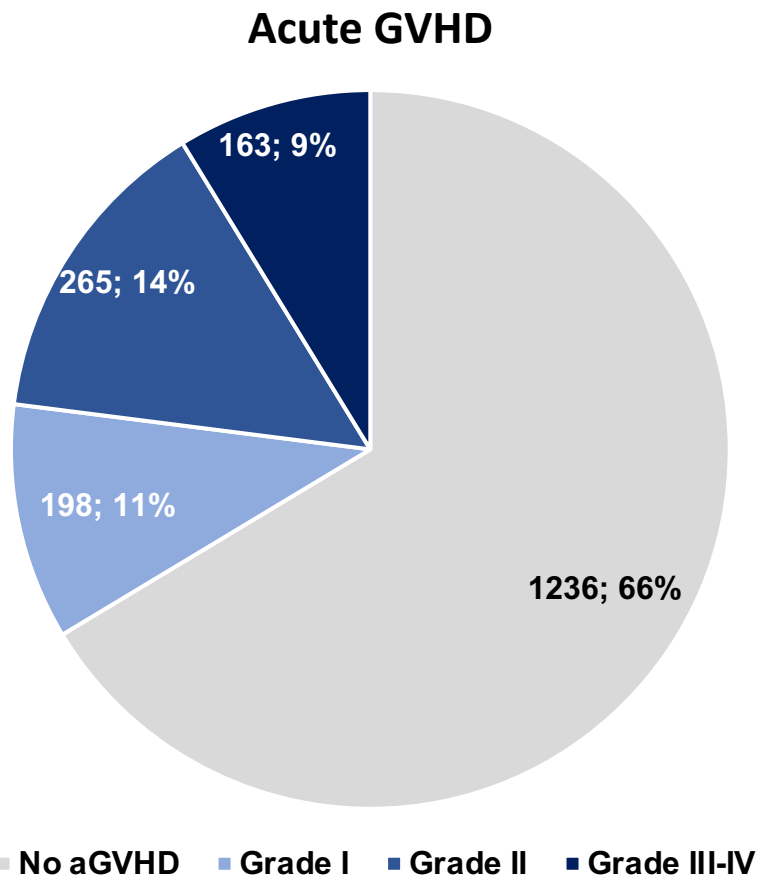
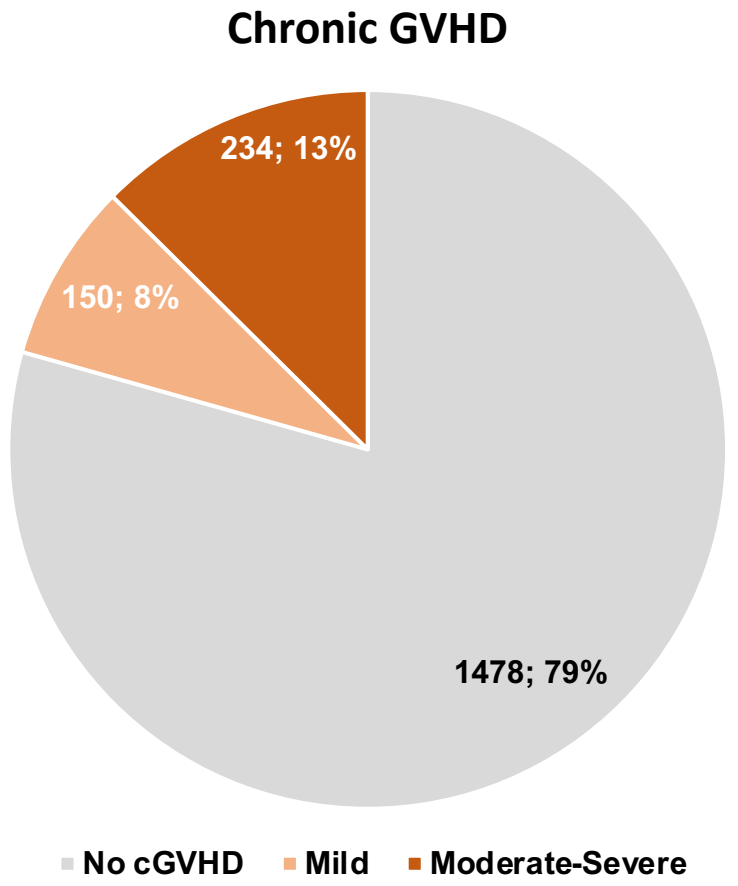
Disclosures of Nicola Polverelli

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Novartis			X		X	X	
Sanofi							X
Medac					X		
Therakos							X
Neovii							X

Acute and Chronic GVHD: epidemiological data

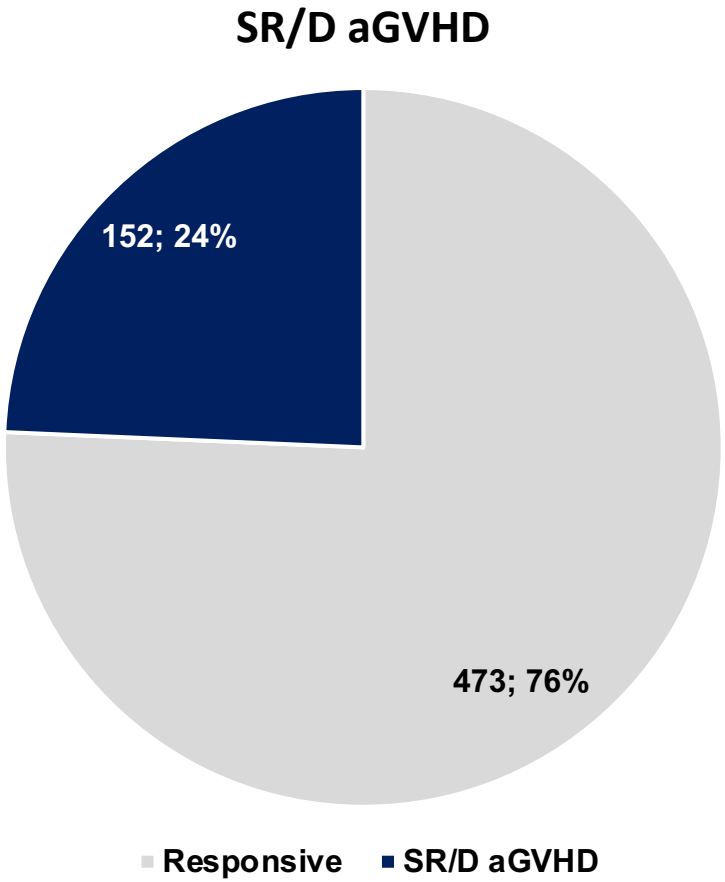


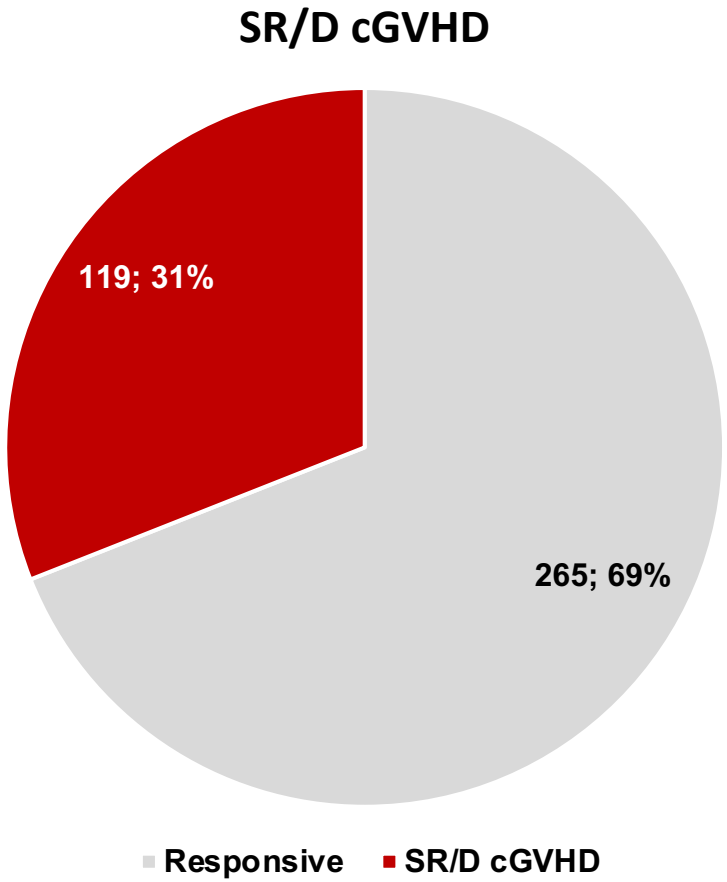


Data on 1862 transplants (**93.0% of 2023 Italian transplant activity**) performed in 56 GITMO Centers (90.3%)

Polverelli N et al. ***AJH 2025***; epub ahead of print

SR/D GVHD: the size of the problem

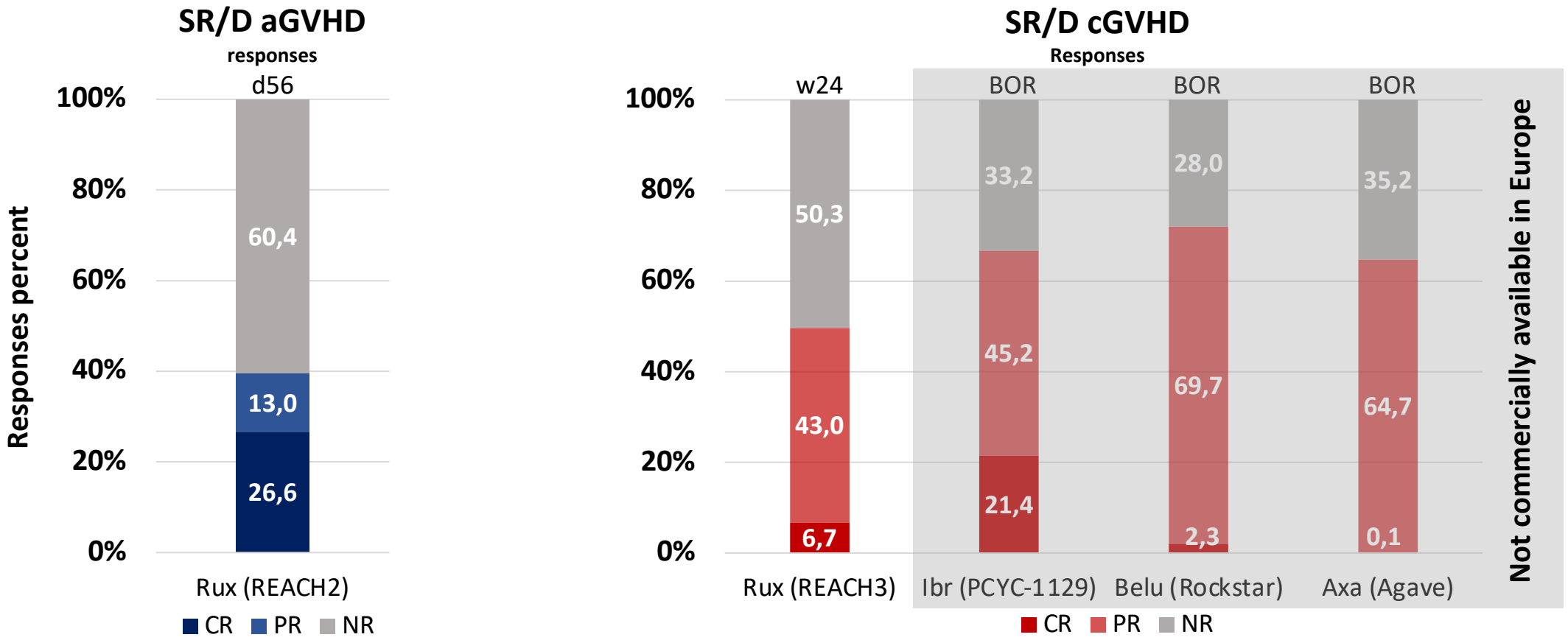




A **higher proportion** of **SR/D aGVHD** cases was observed in the **pediatric population** (38.7% vs. 22.3%, p=0.002), while no significant differences emerged for SR/D cGVHD (36.8% vs. 30.4%, p=0.411).

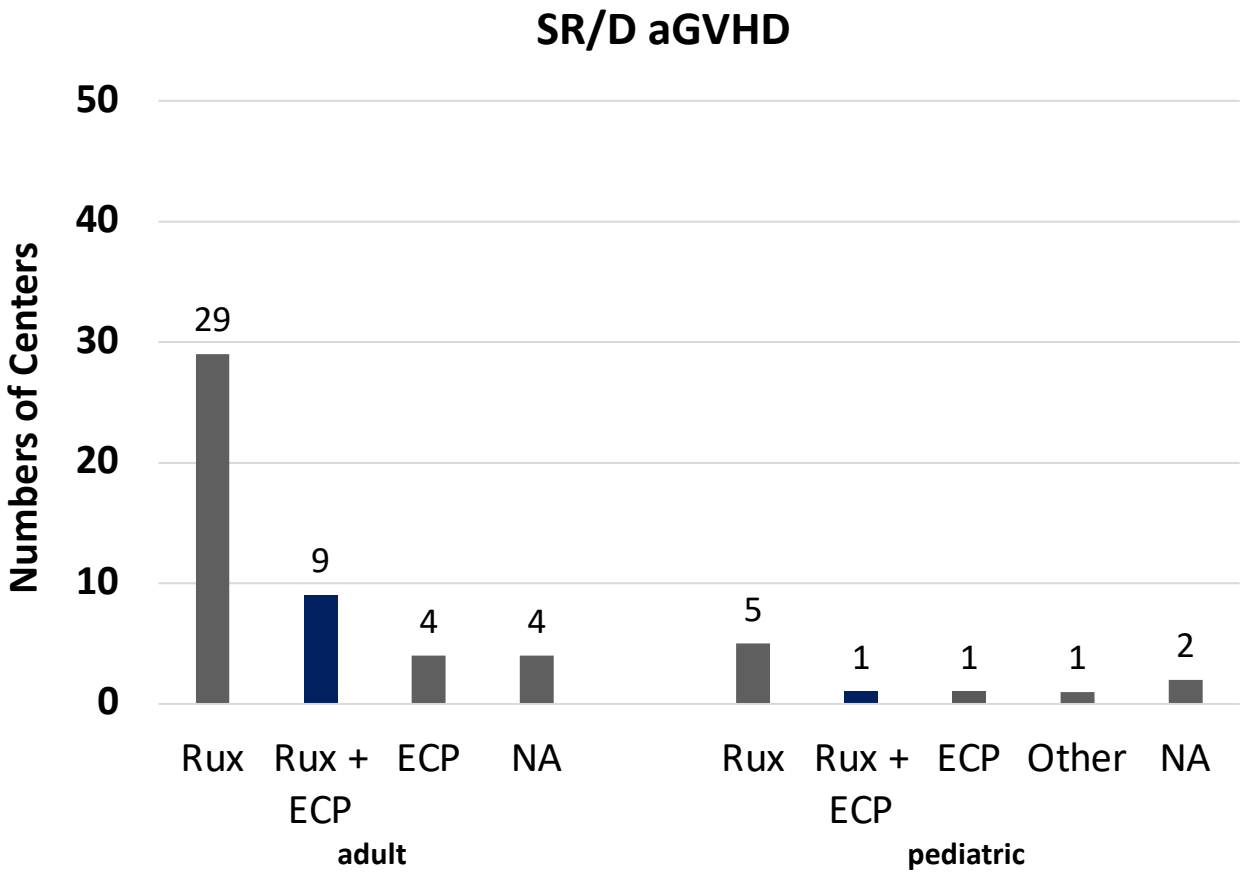
Polverelli N et al. ***AJH 2025***; epub ahead of print

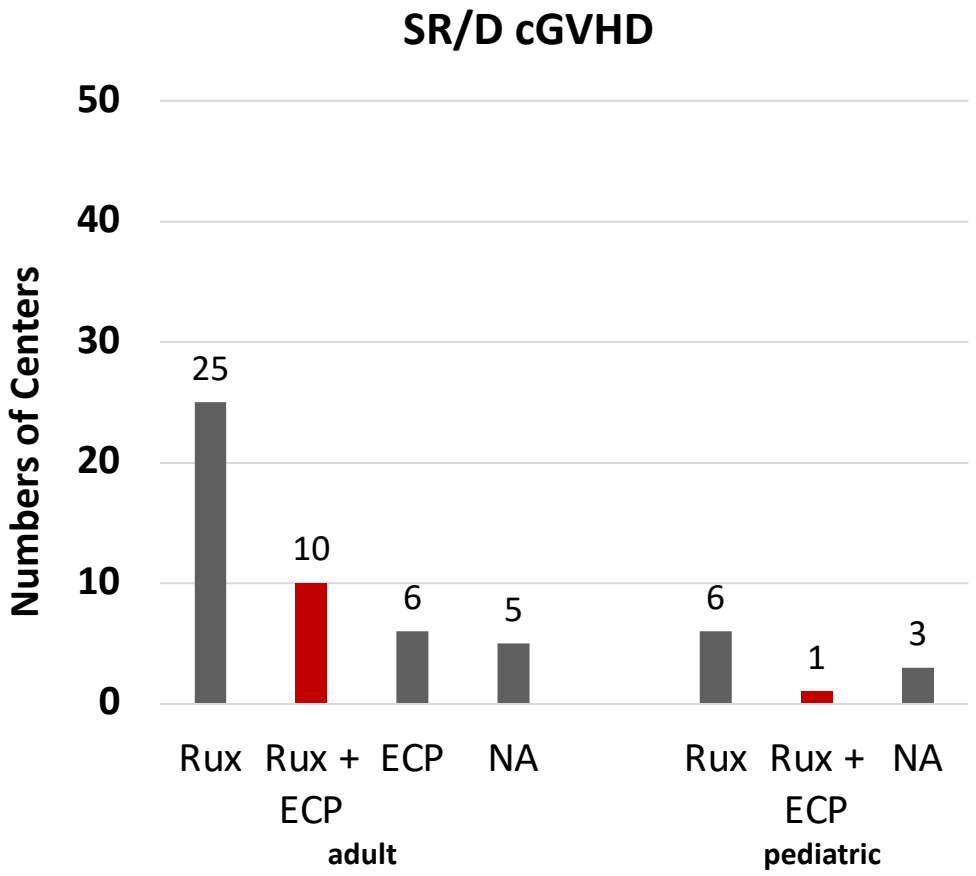
Limitation of second lines in the treatment of SR/D GVHD



Zeiser R et al. ***NEJM 2020***; 382: 1800-10; Zeiser R et al. ***NEJM 2021***; 385: 228-38; Cutler C et al. ***Blood 2021***; 138: 2278-89; wolff D et al. ***NEJM 2024***; 391:1002-1014

SR/D GVHD: current treatment policy in Italy



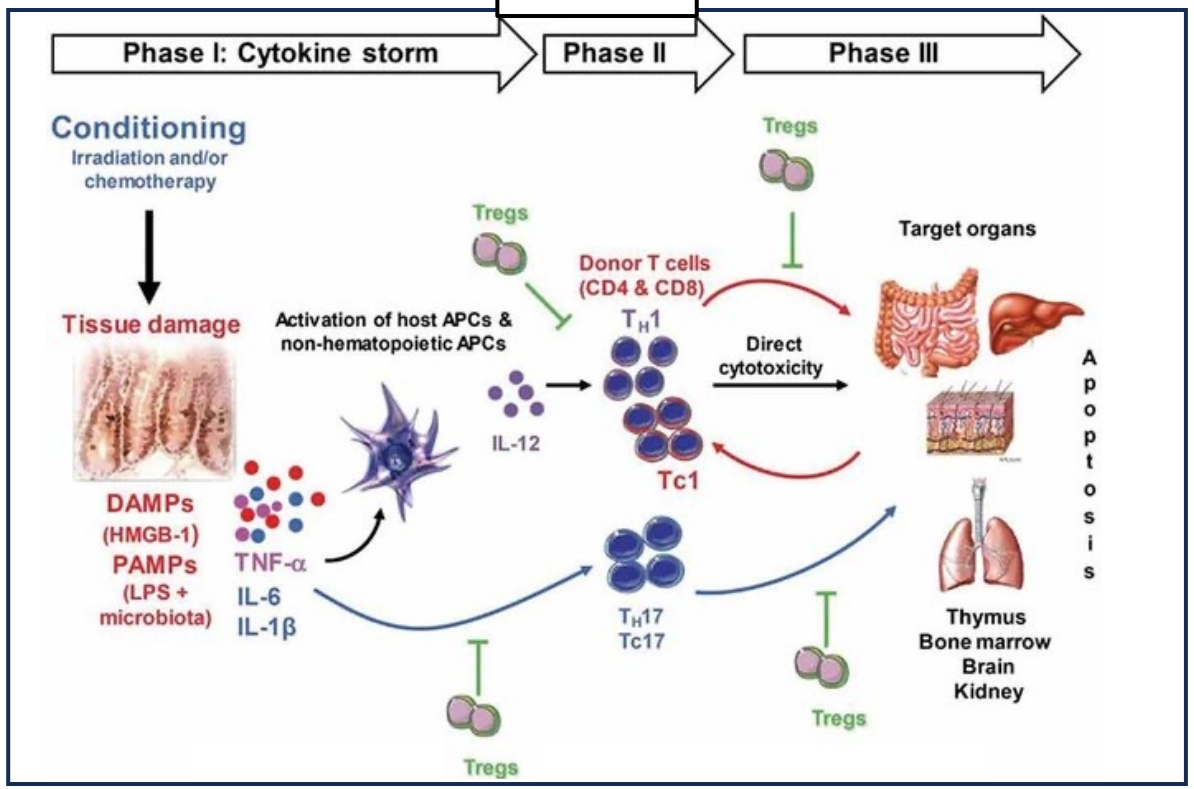


Overall, **17.9%** and **19.6%** of **Centers** utilized a **combinatory second line treatment** in aGVHD and cGVHD, respectively.

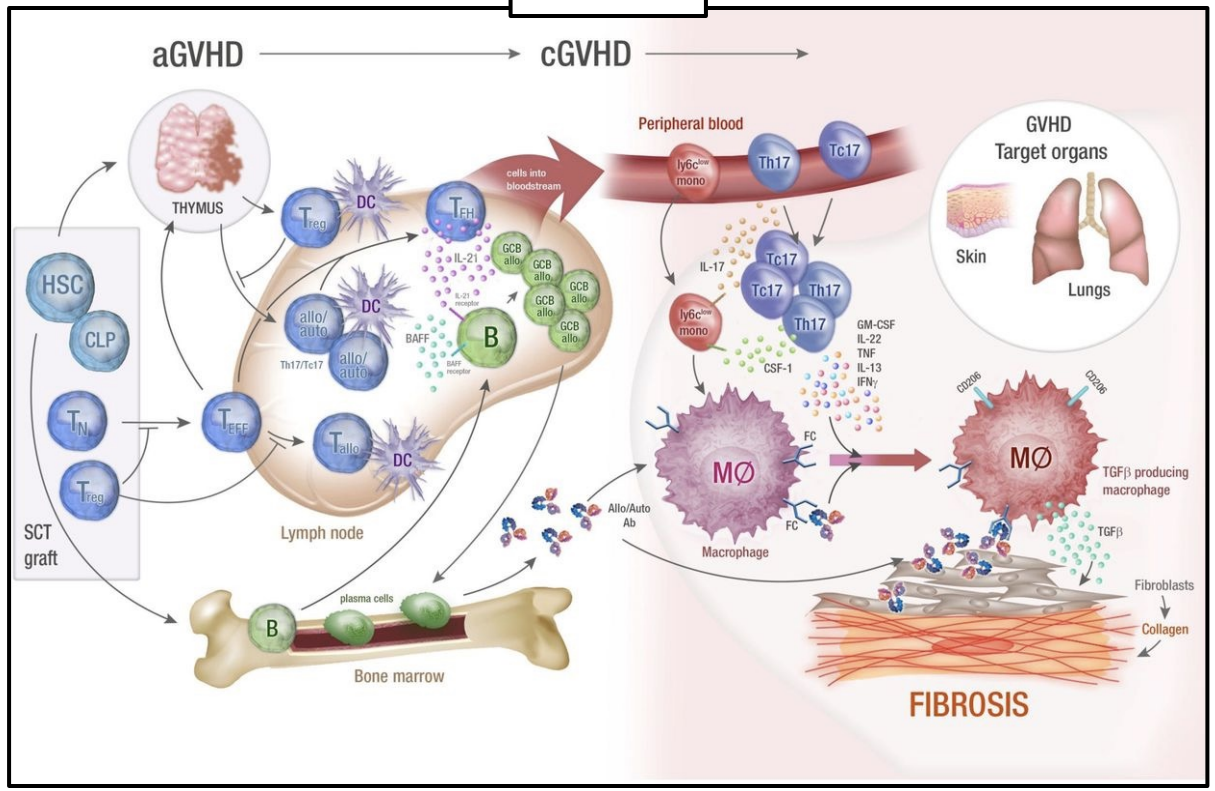
Polverelli N et al. ***AJH 2025***; epub ahead of print

Understanding the complexity of GVHD pathogenesis

aGVHD

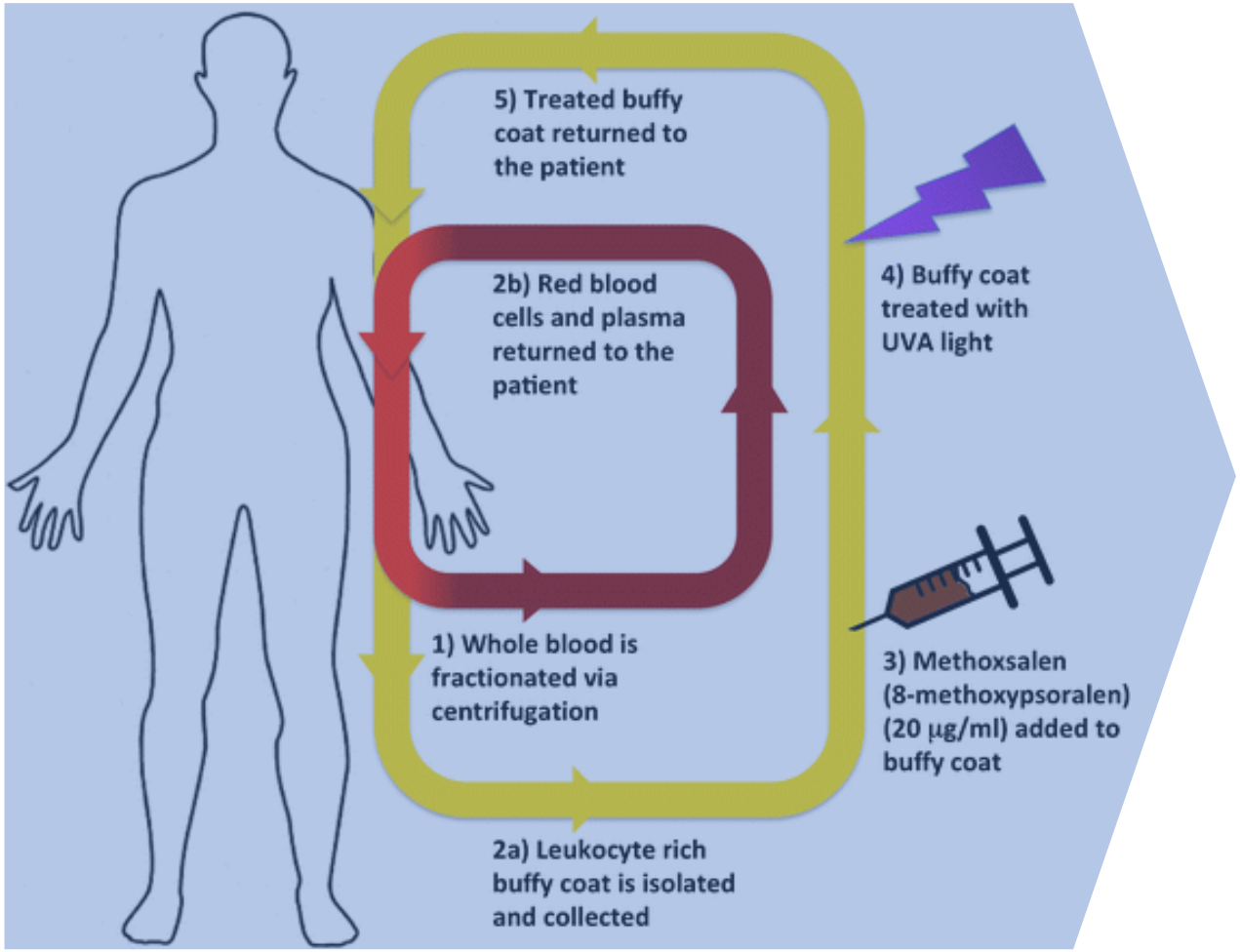


cGVHD

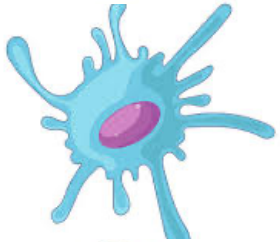


Chuckhlovin A et al. ***CTT 2017***; 6: 19; MacDonald KPA et al. ***Blood 2017*** 129:13-21

Extracorporeal photoapheresis for the treatment of GVHD



Apoptosis of lymphocytes



Differentiation of dendritic cells

Increase in Tregs

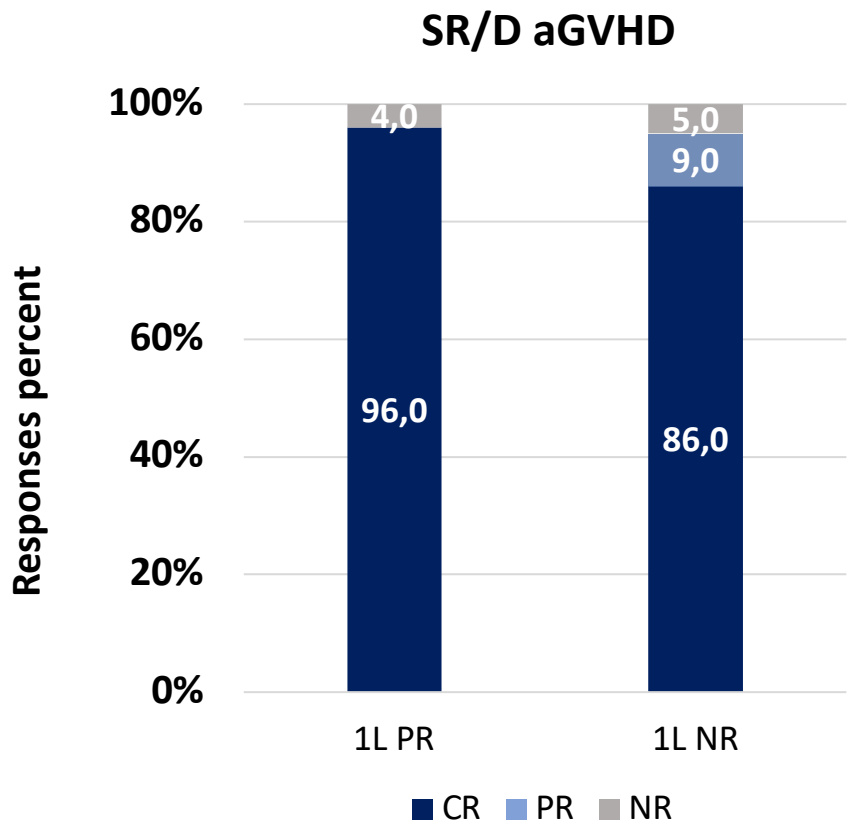
Anti-inflammatory cytokines

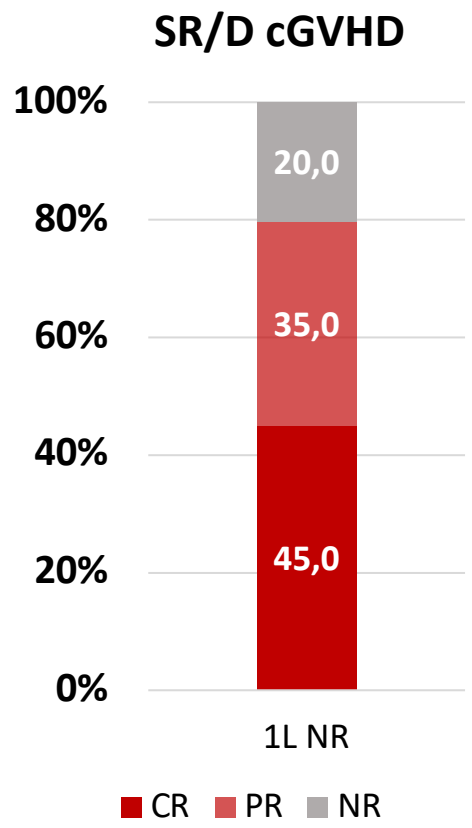
Pro-inflammatory cytokines

Drexler B et al. ***Transfus Med Hemother 2020***;47:214–224

The efficacy of ECP treatment: the GITMO report

A total of 94 patients (48% with aGVHD) were recruited in 19 GITMO Centers



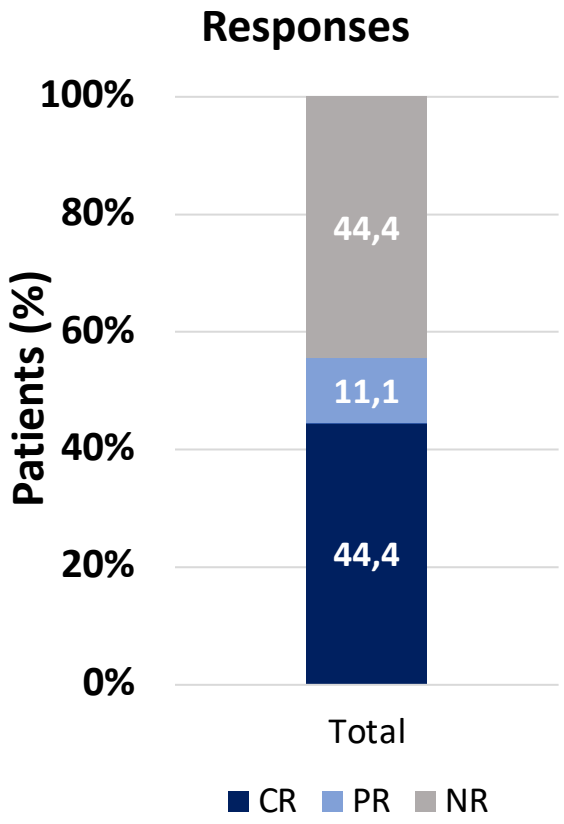


Malagola M et al. ***Transplantation 2016***;100:e147–155

ECP: the ideal partner for combination strategies?

Overall, **18 patients** with severe low GI SR aGVHD, were treated with **ruxolitinib** + **ECP**

Features	Total (18)
Underliying disease	
MDS	6 (33%)
PMF	5 (28%)
ALL	4 (22%)
AML	2 (11%)
MM	1 (5%)
aCML	1 (5%)
Median age, y (range)	55 (21-73)
Donor	
MRD	8 (44%)
MUD	7 (39%)
MMUD	3 (17%)
Grade III-IV aGVHD, n (%)	18 (100%)



Safety profile:
Grade III-IV leukopenia (5,6%)
Grade III-IV anemia (0%)
Grade III-IV thrombocytopenia (5,5%)

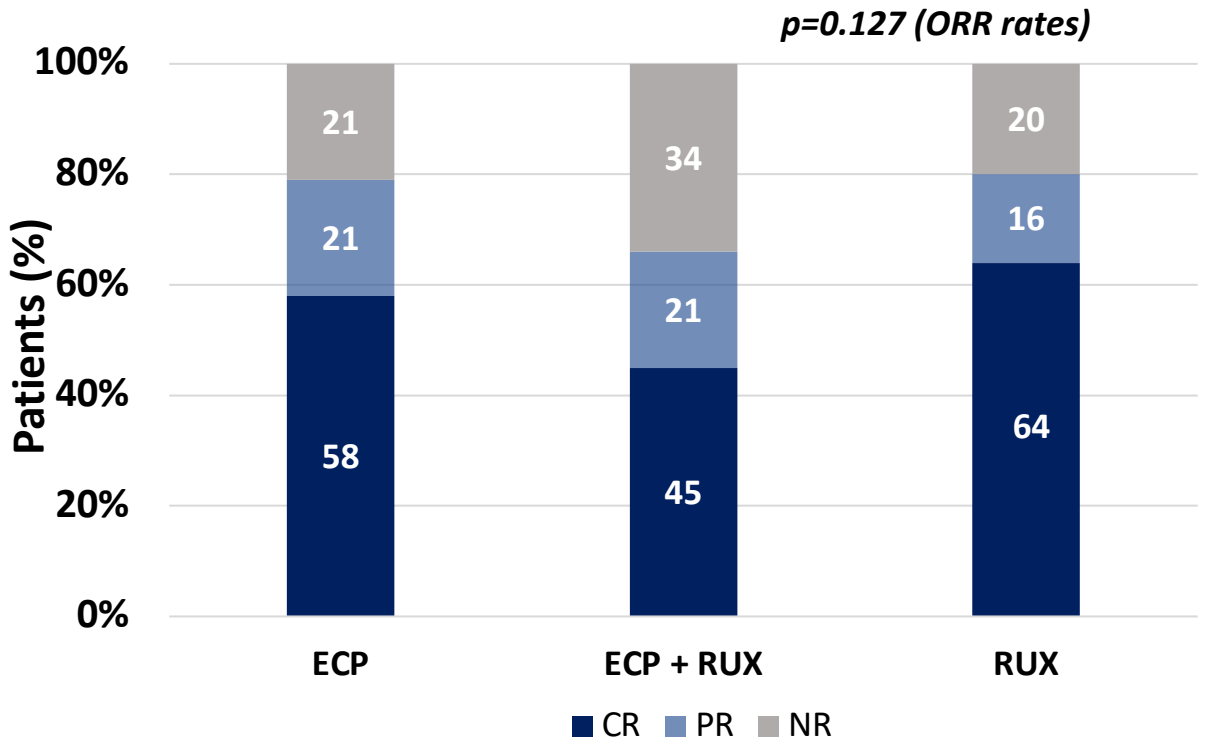
CMV reactivations (67%)

Modemann F et al. ***BMT 2020***;55:2286-93

ECP vs ECP + RUX vs RUX: a comparative GITMO analysis

A total of 233 adult patients with SR/D aGVHD requiring 2L treatment from January 2015 to December 2021 were included

Parameter	ECP (n=124)	ECP + RUX (n=53)	RUX (n=56)	p
Age (median)	53 (18–73)	55 (20–75)	54 (19–71)	0.52
Male (%)	65%	68%	59%	0.59
AML diagnosis	38%	45%	43%	0.79
Period 2019–2021	47%	74%	68%	**0.001**
SR-aGVHD gIII–IV	29%	74%	61%	**<0.001**
SR-aGVHD multiorgan	36%	64%	41%	**0.002**
SR-aGVHD lower GI	39%	79%	64%	**<0.001**
SR-aGVHD skin-only	52%	21%	23%	**<0.001**

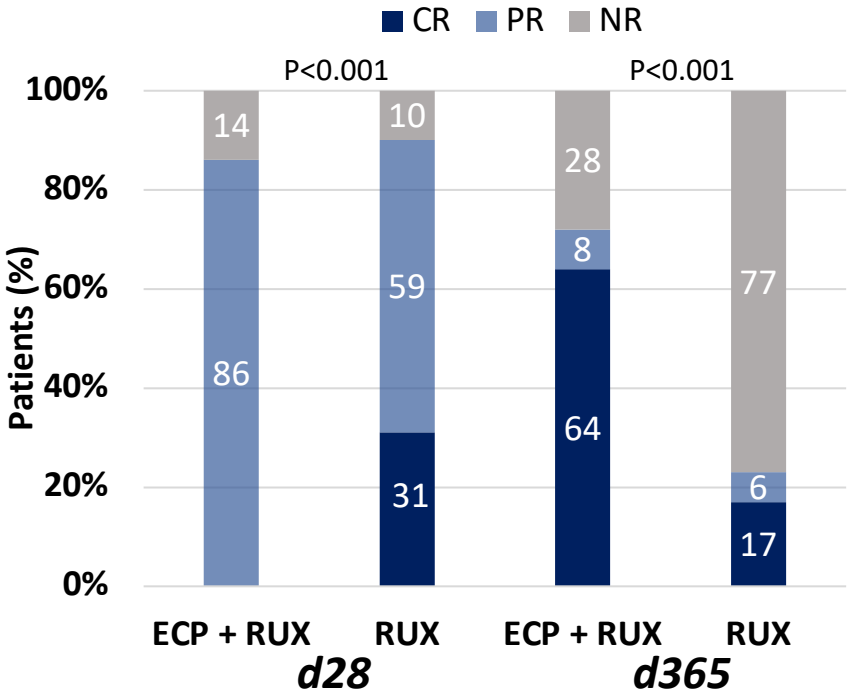


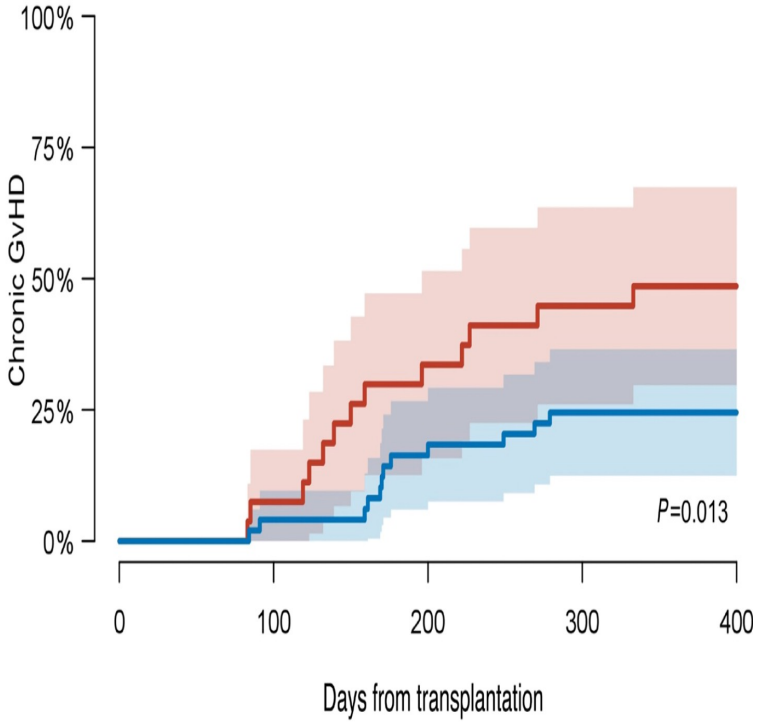
Battista ML et al. ***BMT 2025***;60:1406-09

ECP + Ruxo in aGVHD: Influence on cGVHD

A single center experience on **78 patients with SR/D aGVHD treated** from January 2015 to December 2022

Parameter	ECP + RUX (n=49)	RUX (n=29)
Age (median)	62	59
Male (%)	59%	45%
AML diagnosis	18%	21%
Grade III-IV SR aGVHD	100%	64%
Stage III-IV low GI	84%	27%
Median duration of RUX	77d	46d

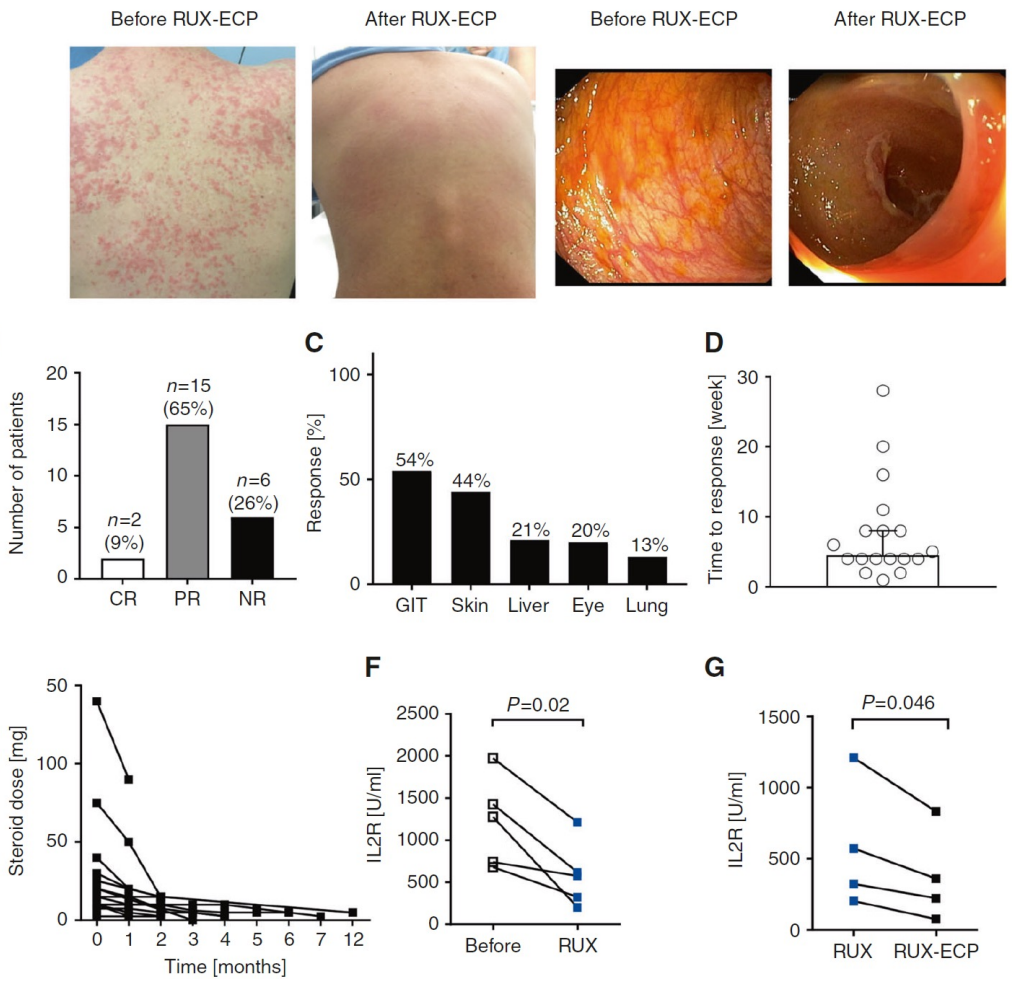




Lastovytska I et al. ***Haematologica 2025***; 110(7):1536-1544.

ECP + RUX combination in refractory severe cGVHD

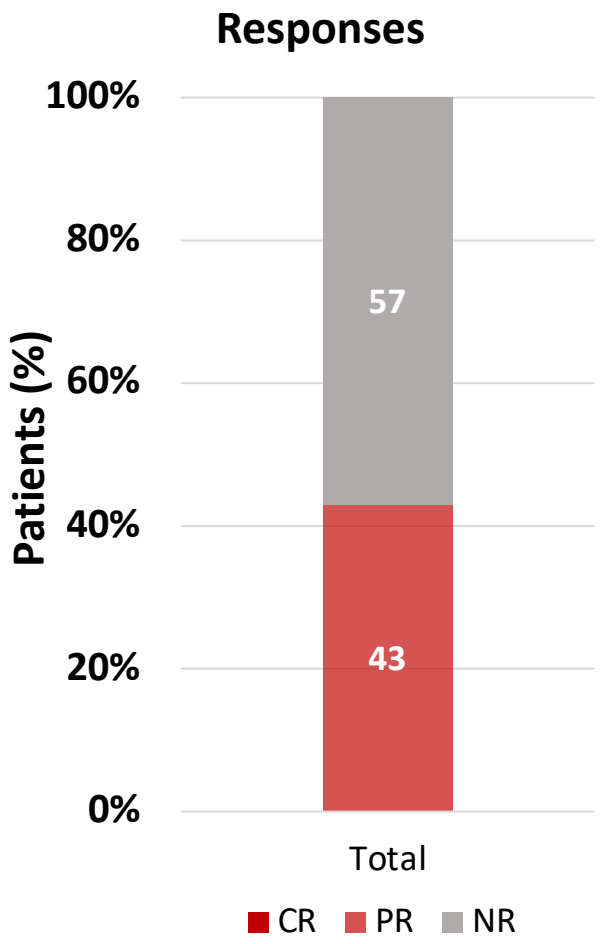
Clinical Parameter	Total n=23
Median duration of cGVHD	2m (range, 0.5–35)
Median duration of ECP-RUX	6m (1–27)
Start of treatments	
Simultaneously	35% (8/23)
ECP first	30% (7/23)
RUX first	35% (8/23)
Organ involvement ≥2 organs	87% (20/23)
Most frequent organs	
Skin	78% (18/23)
Liver	61% (14/23)
GIT	57% (13/23)
Eye	43% (10/23)
Lung	35% (8/23)
Musculoskeletal	4% (1/23)
grade III NIH cGVHD	57% (13/23)
Treatment line >2	91% (21/23)



Mass-Bauer K et al. ***BMT 2021***;56:909-16

Other Combination: RUX plus BELU in cGHVD

Variable	N = 14
Median age, years	48 (34–78)
Median number of LOT	3 (2–5)
Median time on RUX before BELU, months	37 (6–69)
cGVHD severity	
Severe	12
Moderate	2
Median number of organs	4 (1–6)
Organ involvement	
Skin	10
Eye	10
Mouth	9
Joint/Fascia	7
Lung	5
GIT	3
Vulvo-vaginal	2/5
Median follow-up on B + R, months	10.7 (1–13)



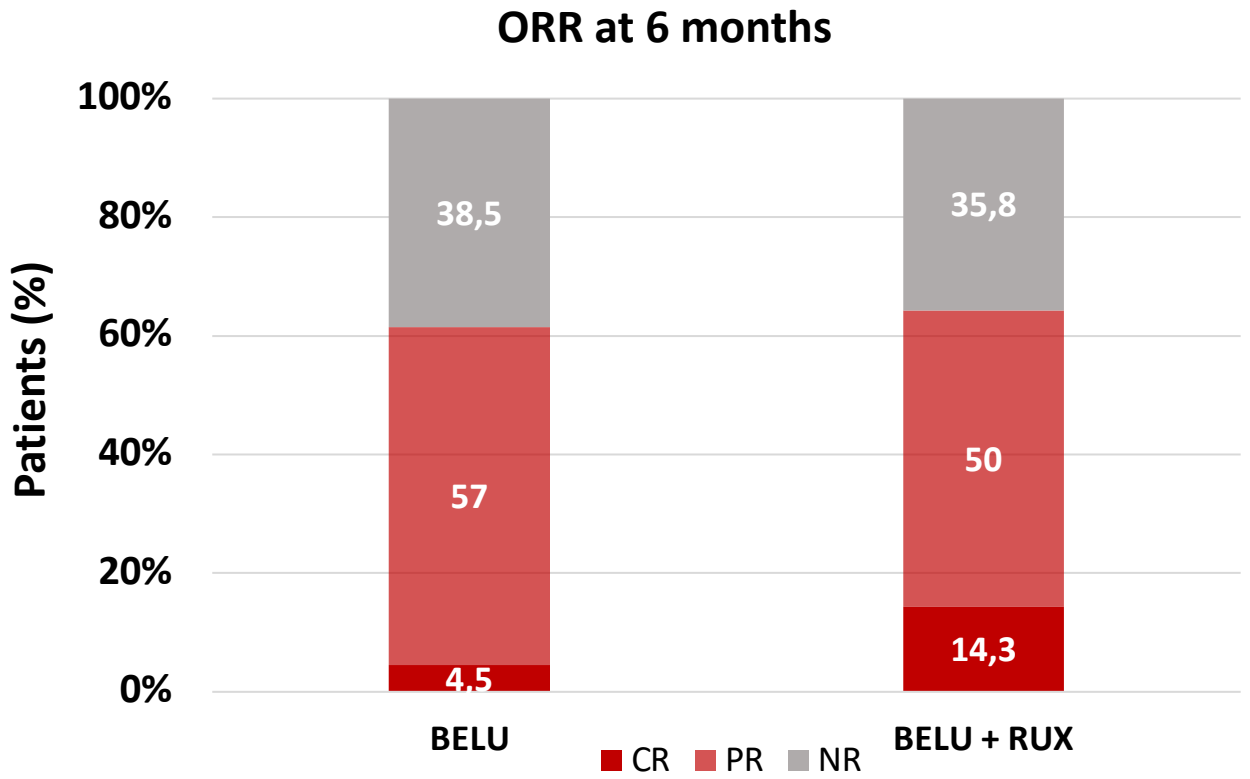
Safety profile (grade III-IV):
anemia (14%)
creatinine elevation (7%)
Bacterial infections (21%)
Respiratory viral infectiosn (36%)
VZV reactivation (7%)

No CMV nor fungal infections
No cases of disease relapse

Pusik I et al. ***BMT 2024***;59:282-4

RUX plus BELU: evidence of synergy?

Characteristic	BELU (n=53)	BELU + RUX (n=14)
Age, median	57 years	56 years
Sex (male)	~70%	~70%
Prior lines of cGVHD therapy	2 (1–7)	3 (1–6)
Prior ruxolitinib exposure	66–70%	100%
Multi-organ involvement	84%	86%
Time from HSCT to therapy	~30 months	~28 months
Disease severity	Similar	similar

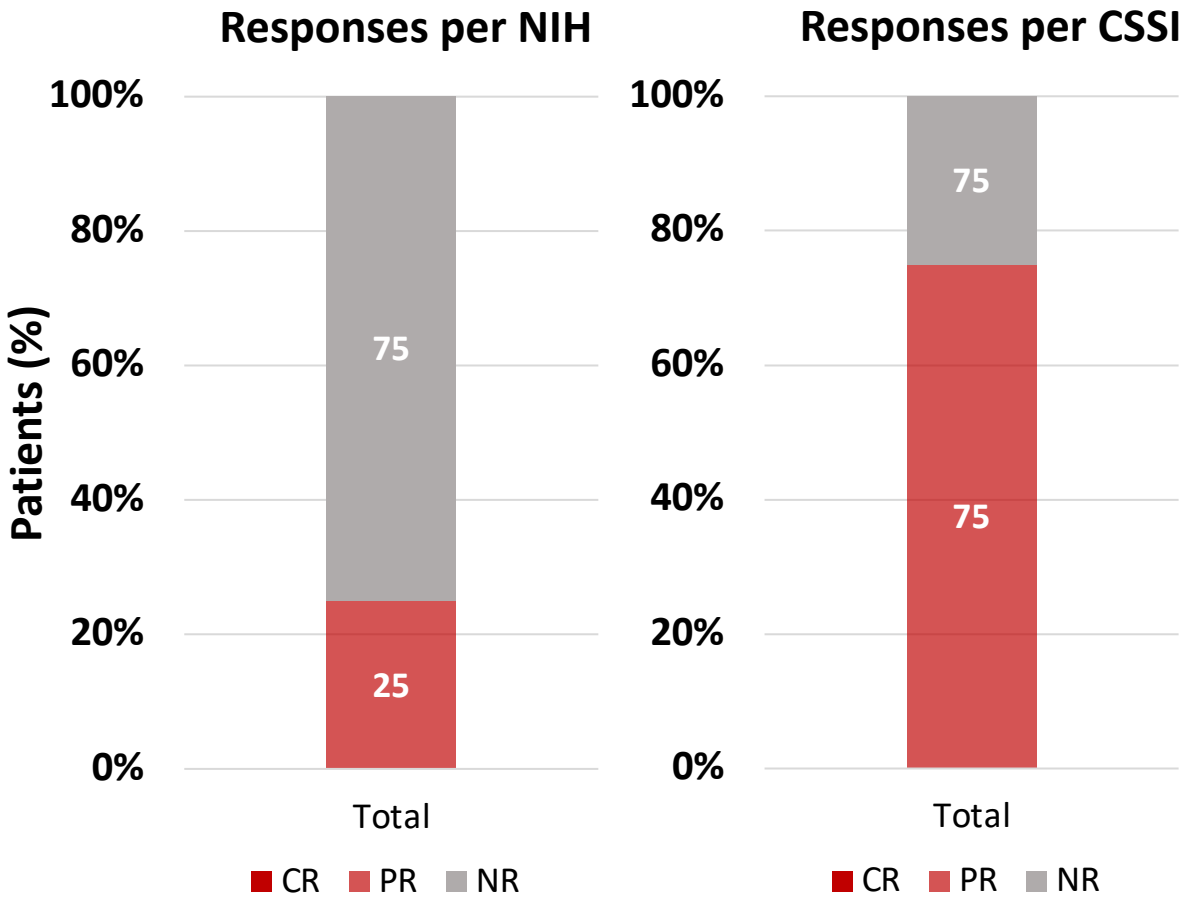


Patients treated with **BELU + RUX** had **similar incidence** of grade III-IV **TEAEs** (29% vs 27%)

Raju G et al. ***BMT 2025***; epub ahead of print

Does the RUX–BELU–AXA Triplet Outperform the Doublet?

Characteristic	Value
No. of patients	8
Male sex, n (%)	4 (50%)
Months post-transplant to cGVHD	5.1 (4–9.1)
Months from cGVHD to AXA, median (range)	21.1 (9.9–110.2)
cGVHD grade at axatilimab start, n (%)	
Severe	8 (100%)
Organ involvement severe at axatilimab start, n (%)	
Skin	5 (62.5%)
Oral	2 (25%)
Lung	2 (25%)
MSK	1 (12.5%)
Ocular	3 (37.5%)
Median number of therapies	5
Previous RUX and BELU monotherapy failure	8 (100%)



Caputo J et al. ***BMT 2025***; epub ahead of print

Summary

•**GVHD incidence is decreasing but remains clinically significant**, with **20–30% of cases becoming steroid-refractory/dependent (SR/D)**.

•**Current therapeutic options are limited**; in Italy, **ruxolitinib is the only approved agent**, and responses—particularly in **cGVHD**—are often modest.

•**ECP** remains a **viable option**, especially for patients without indication to ruxolitinib, and represents a **low-toxicity partner** for combination strategies.

•**Emerging combinations** such as **Ruxolitinib + ECP**, **Belumosudil + ECP**, and novel drugs (**Axatilimab)** show **promising activity with no major safety concerns**. In **heavily pretreated patients**, responses are not exceptional, but overall these regimens appear **feasible, tolerable, and clinically meaningful**.

•**Future directions:** robust prospective trials to define **optimal sequencing, timing, and the true role** of combination therapies in GVHD management.

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