Microbiote en hématologie

Prof. Florent Malard, MD, PhD
Hematology Department
Sorbonne University
Hôpital Saint-Antoine
Paris

Important diversity in patients with hematological malignancies

Standard chemotherapy

Intensive chemotherapy (acute leukemia, autoHCT)

Hematologic malignancies
- Elderly patients
- Impaired nutritional status
- Prolonged hospitalization
- High ATB exposure +++

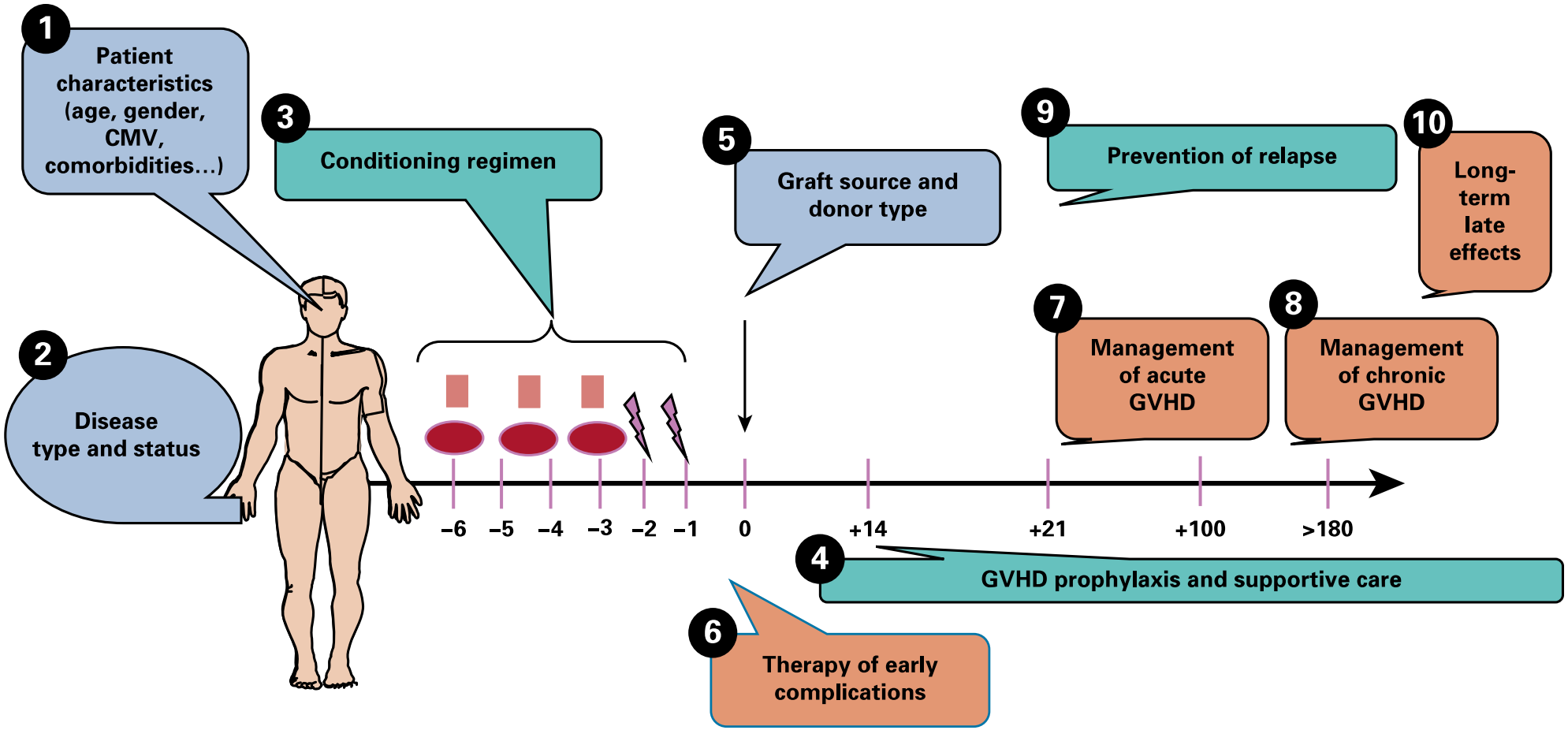
Targeted therapy

Allogeneic hematopoietic cell transplantation

CAR T-cells

Immunotherapy

Allogeneic hematopoietic cell transplantation

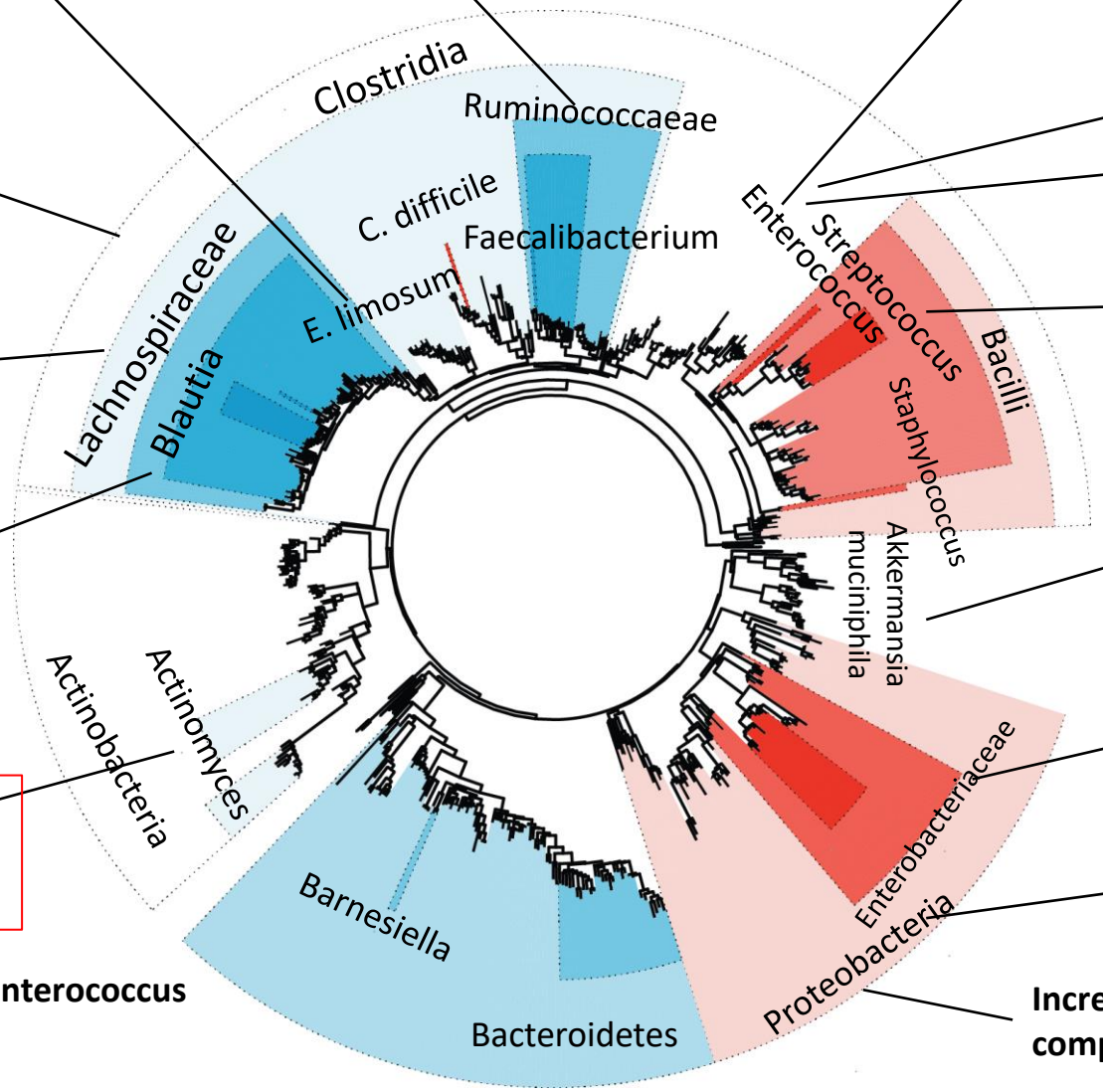


➔ AlloHCT antitumoral effect rely mainly on the *Graft-versus-Tumor* effect

➔ *Graft-versus-Host* disease is the main cause of non relapse morbidity and mortality

Mohty M and Malard F, JCO, 2021

Gut microbiota is associated with alloHCT outcome



Decreased relapse
Peled 2017

Decreased indoxyl sulfate; reduced mortality
Holler 2014

reduced indoxyl sulfate; increased mortality
Holler 2014

increased mortality and GVHD related mortality
Stein-Thoeringer 2019

Decreased indoxyl sulfate; and reduced mortality
Holler 2014

intestinal domination; VRE bacteremia
Taur 2012

intestinal domination
Taur 2012

Increased overall survival
Taur 2014

Mucus layer thinning worse GVHD
Shono 2016

Decreased GVHD
Jenq 2015

Decreased overall survival
Taur 2012

Increased overall survival
Taur 2012

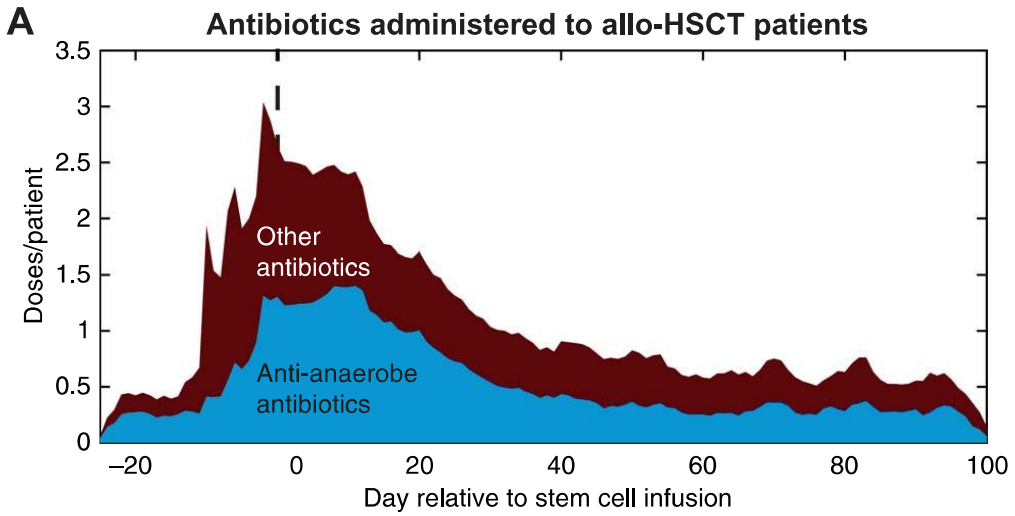
intestinal domination; Gram negative bacteremia
Taur 2012

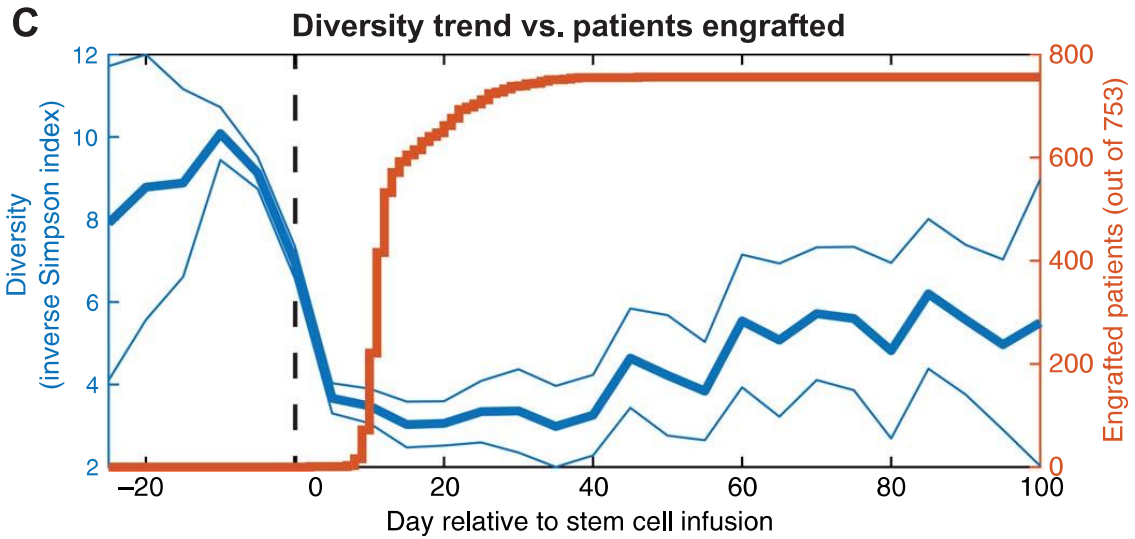
Protection against Enterococcus domination
Ubeda 2013

Increased pulmonary complications Harris 2016

Courtesy of Peled J, adapted from Taur Y, Virulence, 2016

Gut microbiota disruption during alloHCT



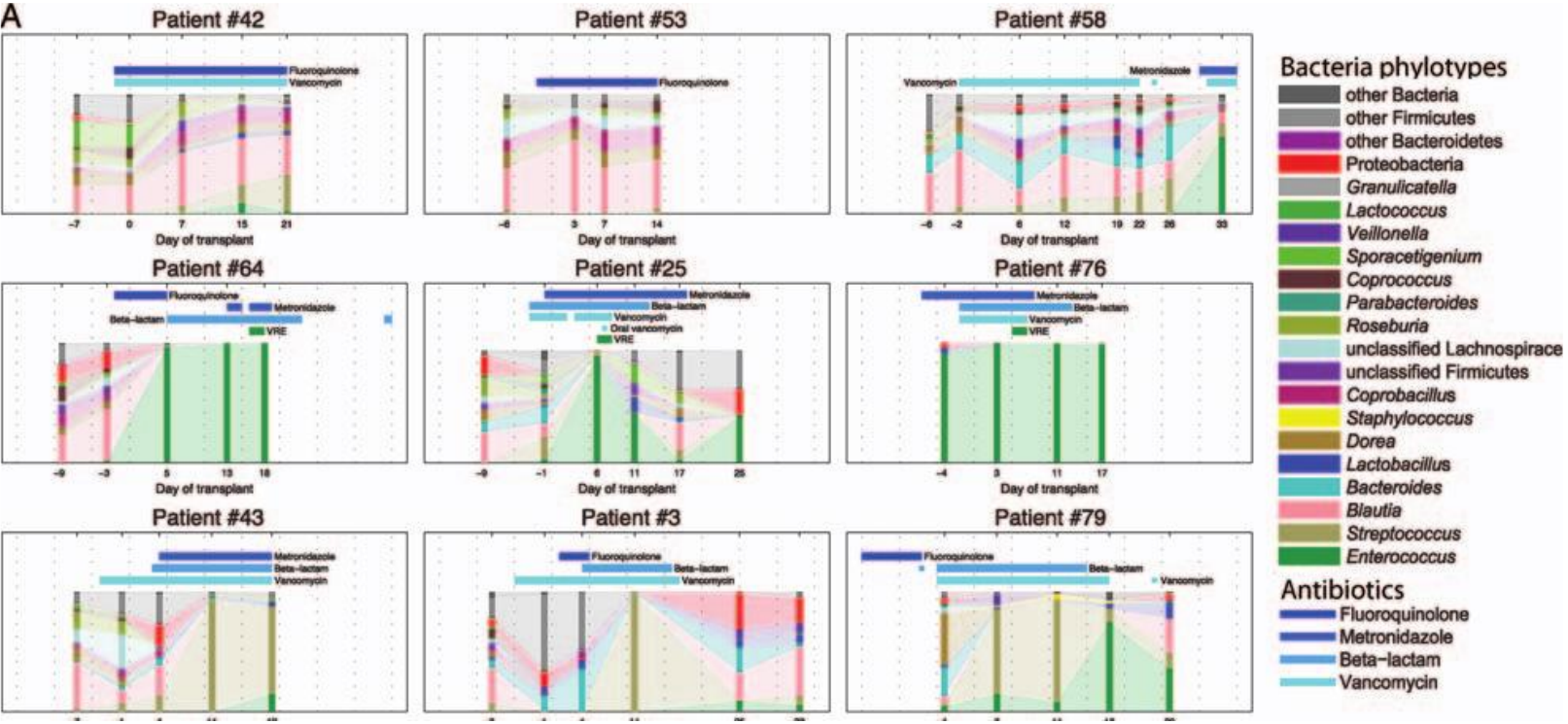


N=753 alloHCT patients

Taur et al. STM 2018

Intestinal domination is frequent after alloHCT and is associated with bacteremia

N=94

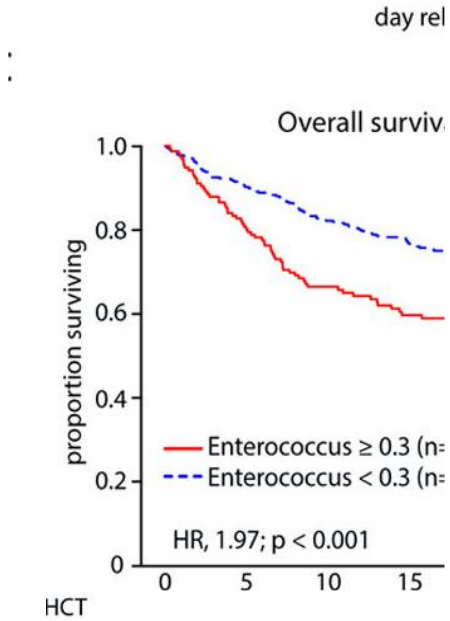


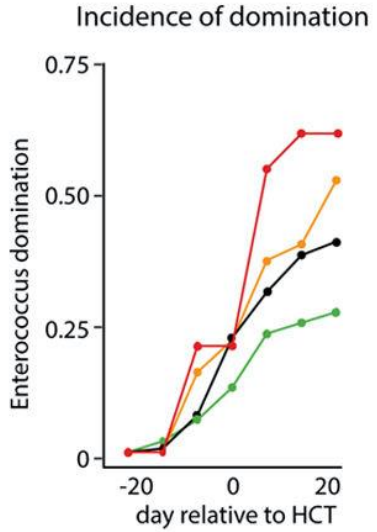
	VRE Bacteremia	
Dominating Taxon[b]	HR (95% CI)	*P*
Enterococcus	9.35 (2.43–45.44)	.001
Streptococcus	0.21 (.00–1.75)	.184
Proteobacteria	0.75 (.01–6.14)	.837

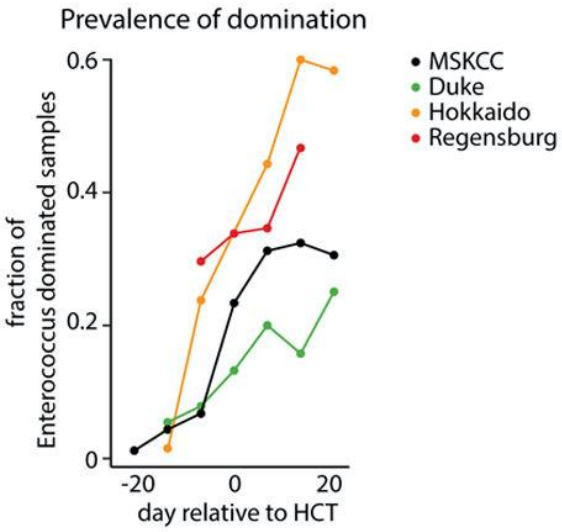
	Gram-negative Bacteremia	
Dominating Taxon[b]	HR (95% CI)	*P*
Enterococcus	1.35 (.25–5.08)	.690
Streptococcus	0.82 (.09–3.65)	.823
Proteobacteria	5.46 (1.03–19.91)	.047

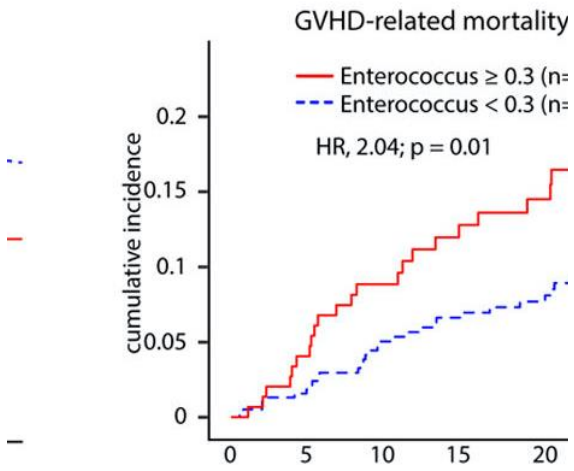
Taur et al. CID 2012

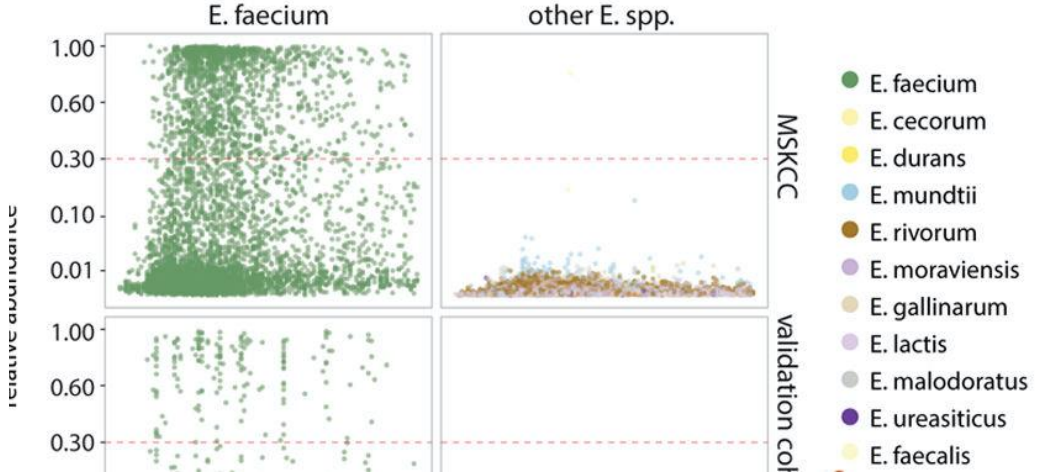
Enterococcus domination occurs globally and increases risk of GVHD and mortality after allo-HCT.







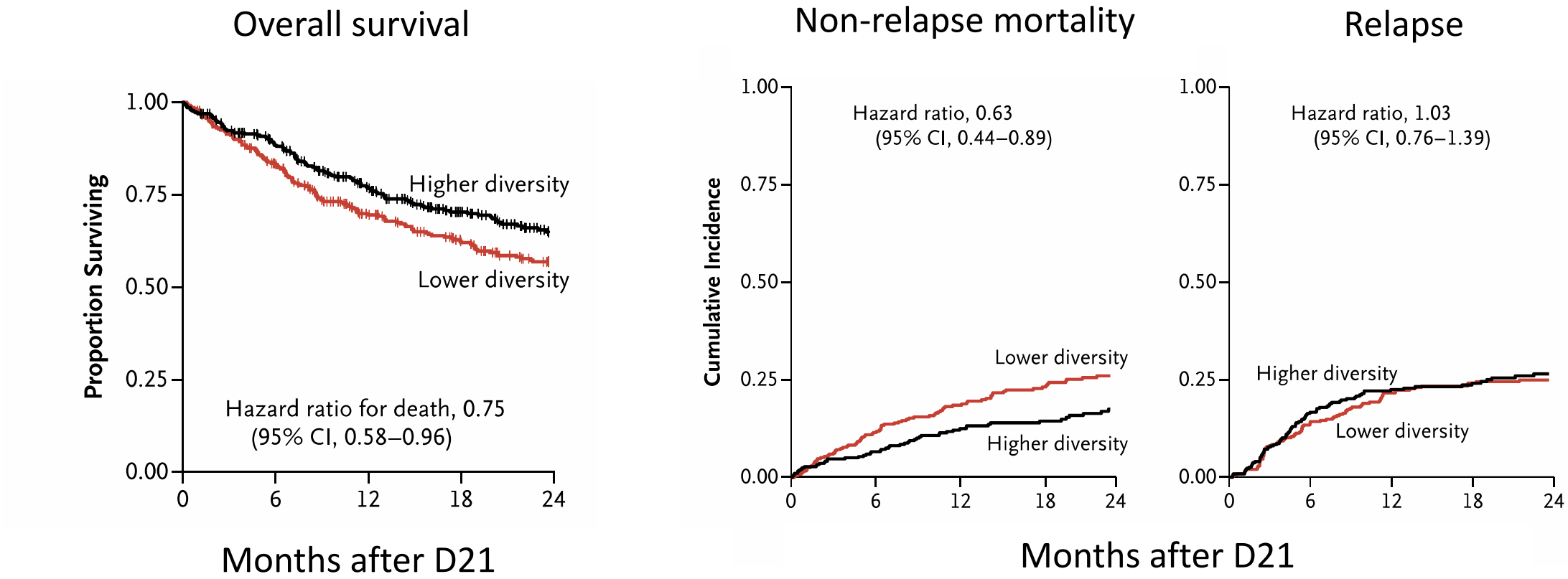




Stein-Thoeringer C et al. Science 2019

Low bacterial diversity at engraftment is associated with reduced overall survival and increased non-relapse mortality

n=1132

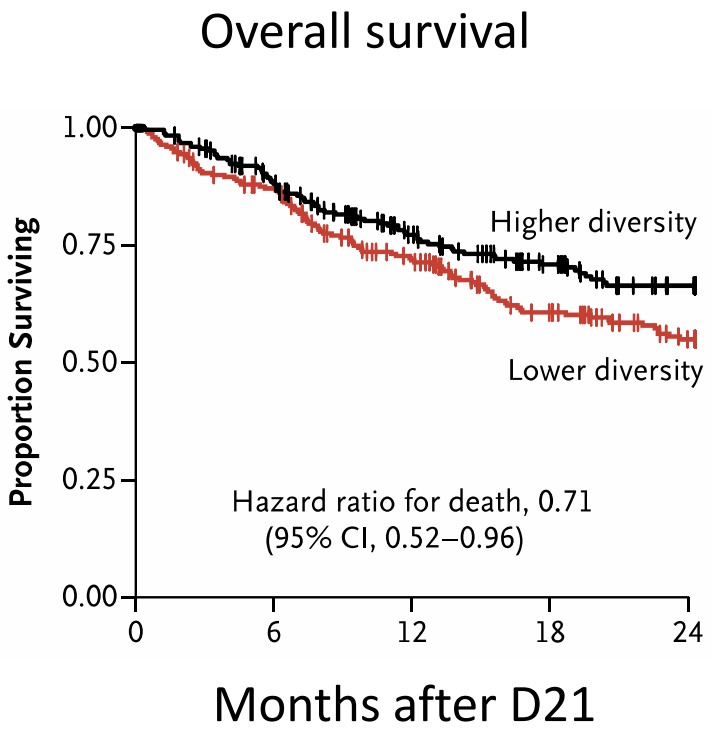


Patients treated in the USA, Europe (Germany) et Asia (Japan)

Peled J et al. NEJM, 2020

Low bacterial diversity at before transplantation is associated with reduced overall survival

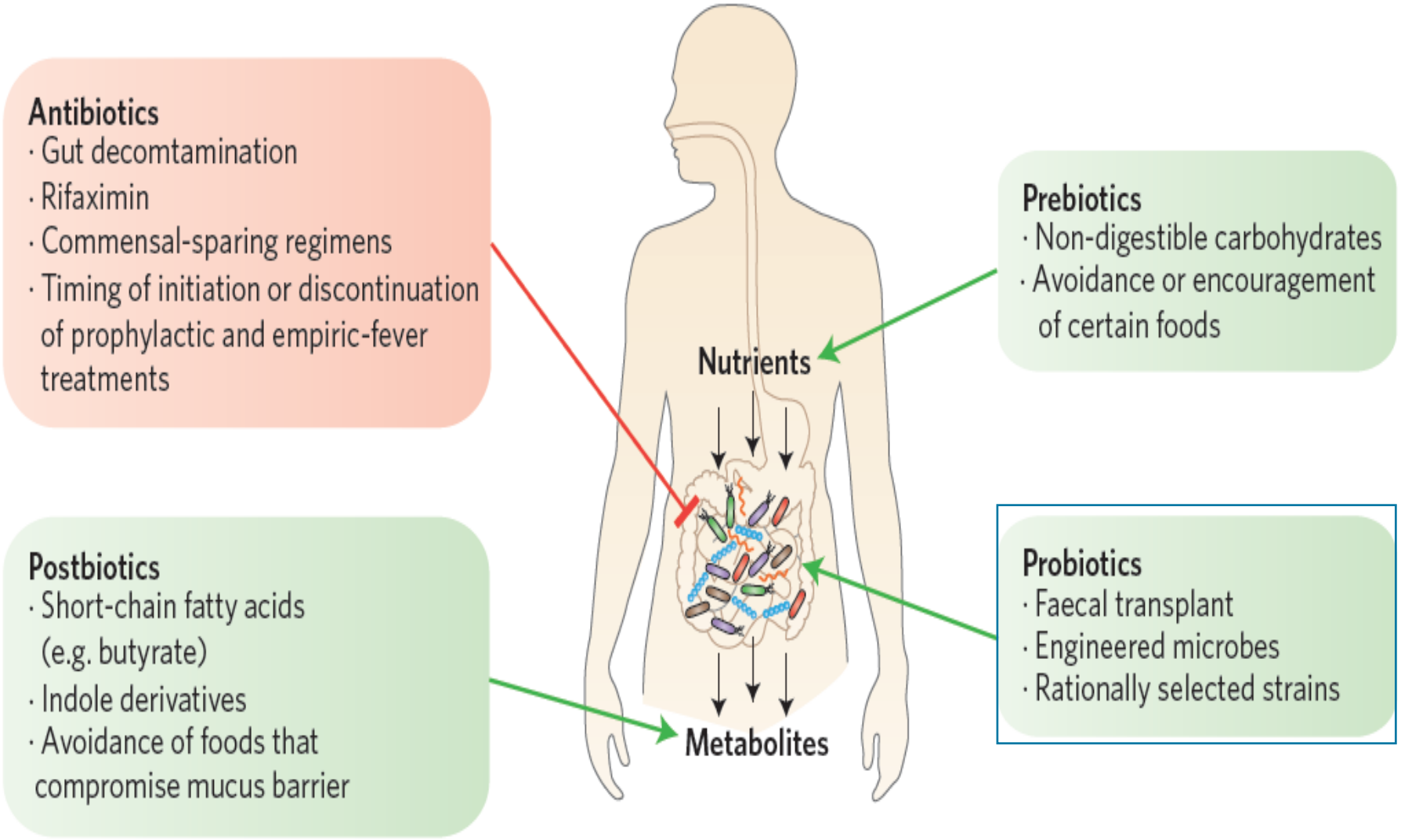
n=1132



Patients treated in the USA, Europe (Germany) et Asia (Japan)

Peled J et al. NEJM, 2020

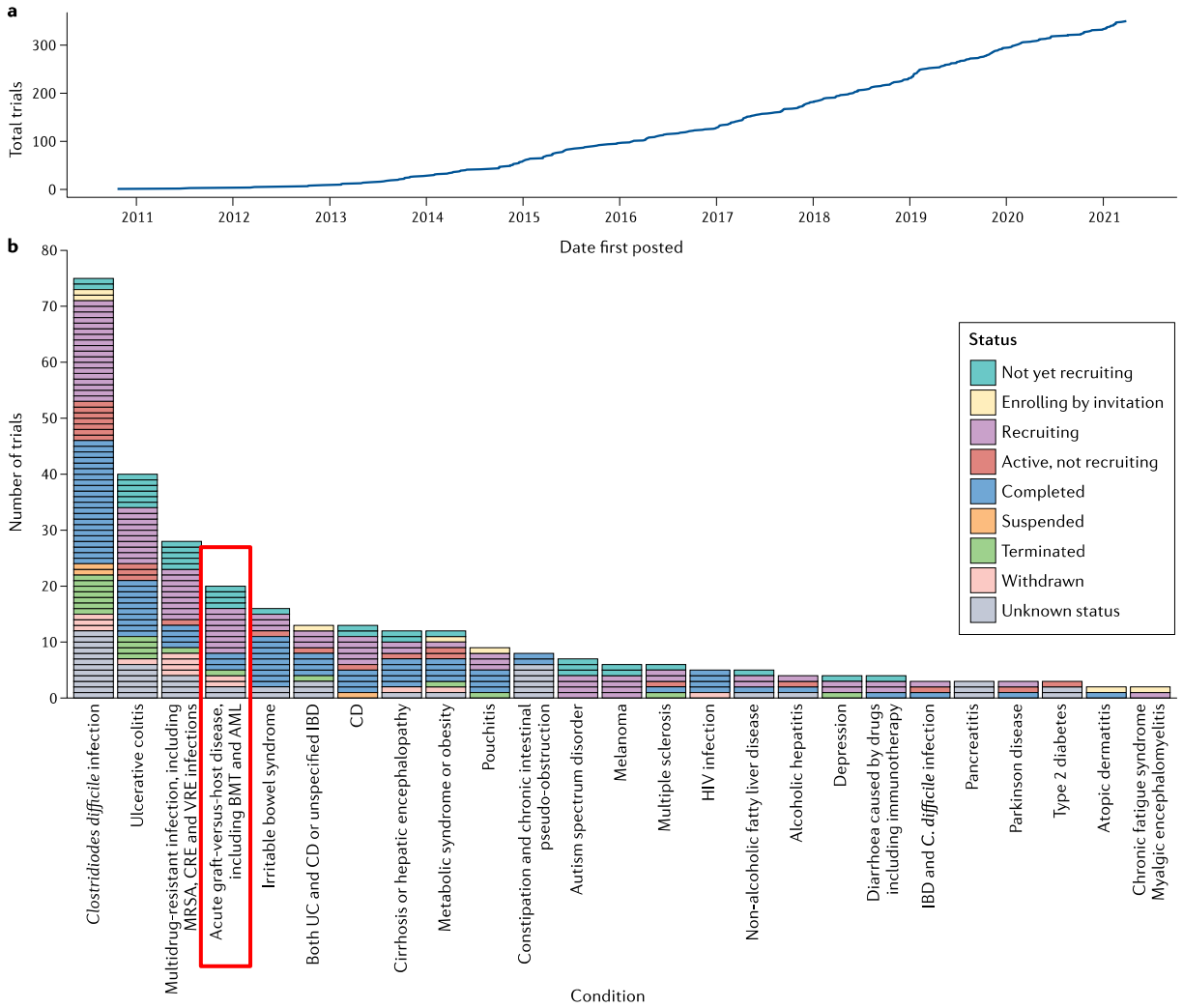
Developing strategies to address microbiota injury in alloHCST



Peled et al. Nature Microbiology 2016

Fecal microbiota transplantation

Increase number of clinical trial evaluating FMT in numerous indication



Sorbara et Pamer. Nature microbiology, 2022

FMT is safe in immunocompromised patients

- Retrospective analysis in N=80 immunocompromised patients
- FMT for *C. difficile*

- Death:
- 1 pneumonia at day 13 (patient with SOT)
- 1 aspiration at day 1 (patients with SOT and oesophagal cancer)

- Infectious adverse events
- 2 fever at day 4 and 1
- 1 influenza B at day 3
- 1 catheter infection at day 14
- 1 *Pertussis* before day 30

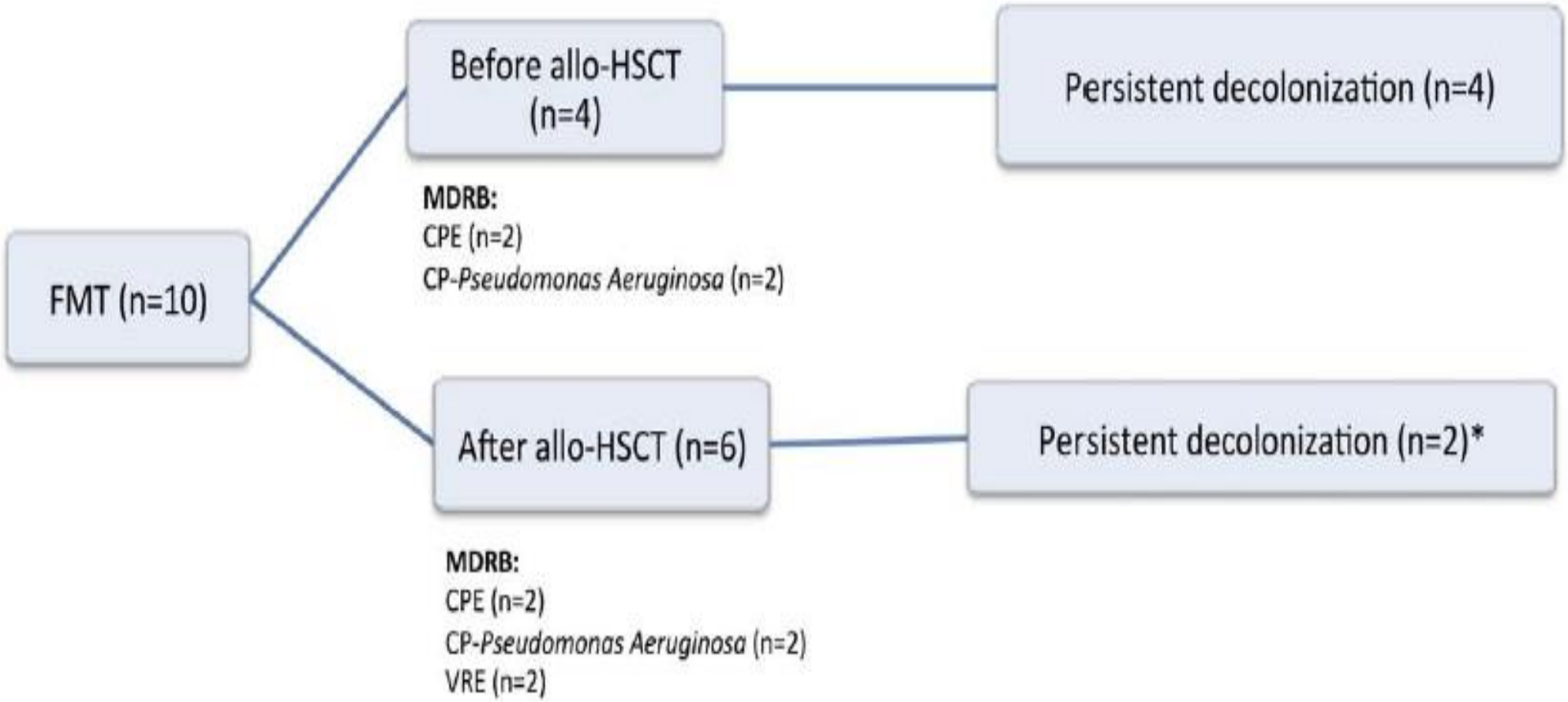
Kelly et al. Am J Gastroenterol 2014

FMT studies in alloHCT recipient for *C. difficile*

Study	Indication	N° of patients/ population	Administration	Study	Donor	N° of FMT	AE	Response
Neemann et al. 2012	Severe fulminant CDI	1 alloHCT	Naso-jejunal tube	Case report	Husband	1	No SAE	1/1 resolution of CDI
Moss et al. 2017	Recurrent CDI	8 auto/alloHCT	Naso-duodenal tube	Retrospective, case series	Unrelated	8	No SAE	7/8 no recurrence of CDI
Bluestone et al. 2018	Recurrent CDI	3 alloHCT pediatric	Gastric tube/colonoscopy	Retrospective, case series	Relative/ unrelated	8	No SAE	1/3 no recurrence of CDI

→ Effective in 9 out of 12 patients, no SAE

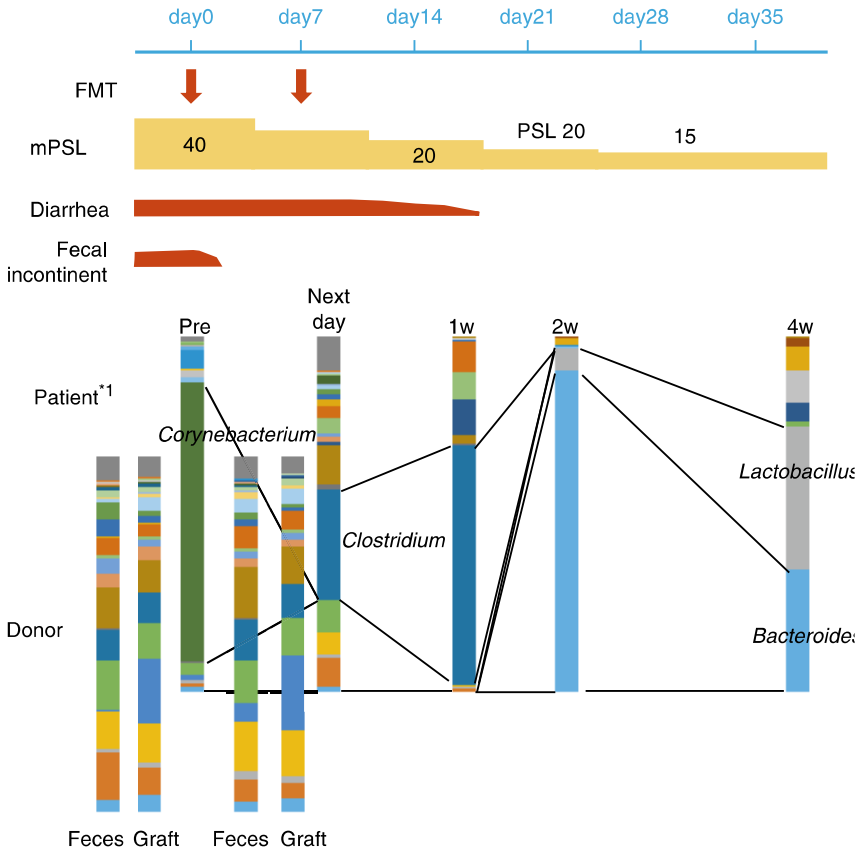
FMT is safe and effective for MDR bacteria eradication in patients with hematological malignancies



Battipaglia, Malard et al, Haematologica, 2019

Can we modulate the microbiota to treat acute GVHD after allo-HCT?

FMT is a promising treatment of for steroid-resistant acute GVHD of the gut



FMT in GI steroid resistant aGVHD

→GI aGVHD symptoms resolution

→N=4: 3 CR, 1 PR

→Steroids decrease

→Gut microbiote diversity restoration

Kakihana et al. Blood 2016

FMT studies in allo-HSCT recipients for the treatment of acute GVHD

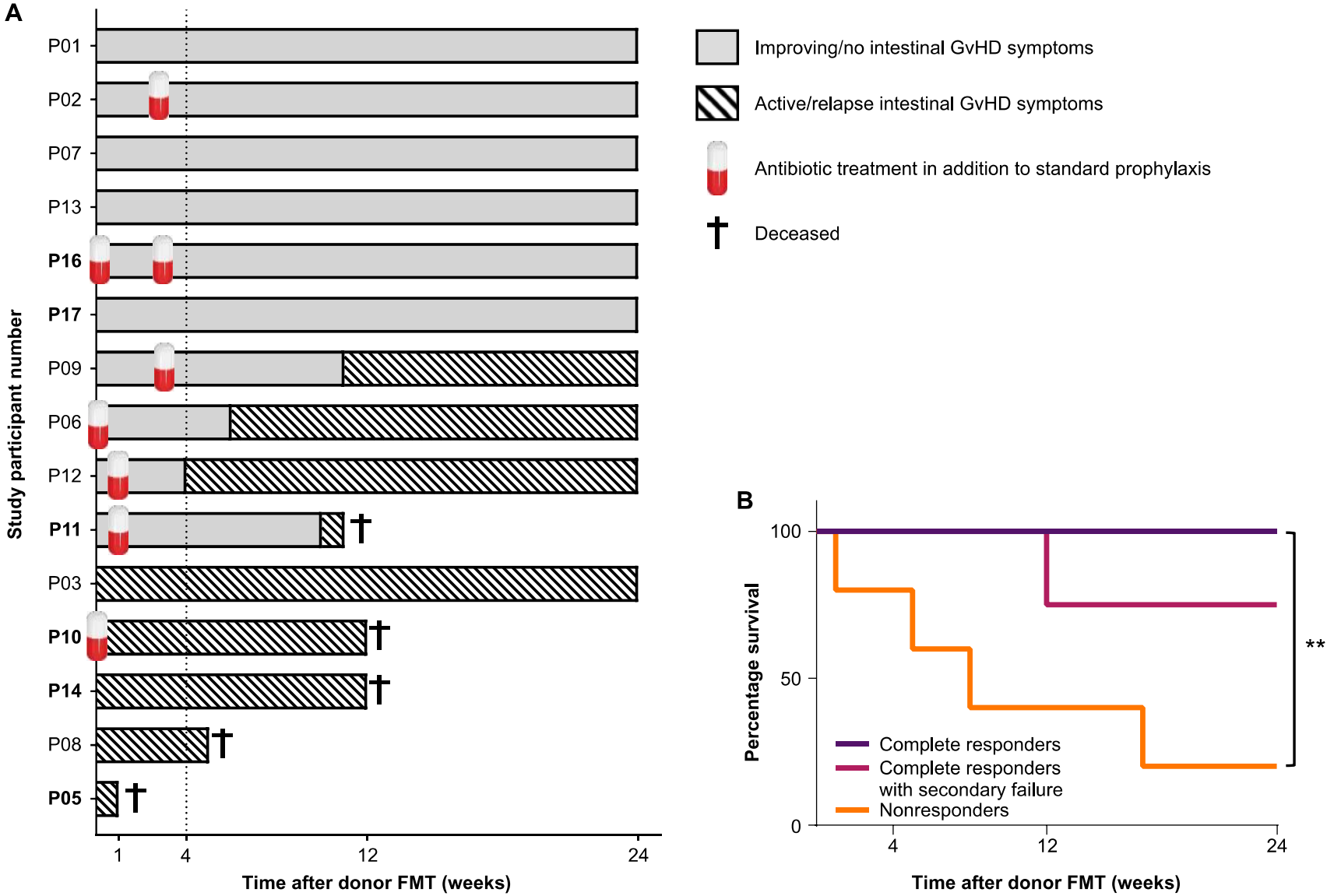
Study	Indication /population	N° of pts	Administration route	Study type	Donor relation	N° of FMT's	Adverse Events	Response
Kakihana et al. 2016	Steroid resistant/ dependent gut GVHD	4	Naso-gastric tube	Prospective	Spouse /relative	7	1- lower GI bleeding, hypoxemia (probably not related)	n=3, CR; n=1, PR
Spindelboeck et al. 2017	Steroid resistant grade IV gut GvHD	3	Colonoscopy	Retrospective, Case series	Unrelated/sibling	9	No SAE	n=2, CR; n=1, PR
Qi et al., 2018 (NCT03148743)	steroid resistant GvHD	8	Naso-duodenal tube	Prospective	Unrelated	12	No SAE	n=5, CR n=1, PR
Shouval et al. 2018 (NCT 03214289)	Steroid resistant/ dependent GvHD	7	Oral capsules	Prospective	Unrelated	15	2-Bacteremia (deemed unrelated)	n=2, CR
van Lier et al. 2019	Steroid resistant/ dependent GvHD	15	Naso-duodenal tube	Prospective	Unrelated	15	No SAE	n=11, CR
Goeser et al. 2021	steroid resistant GvHD	11	Naso-duodenal tube Or capsule	Retrospective	Mostly unrelated	11	No SAE	↘ stool frequencies and volume and aGVHD grading

FMT is a promising treatment of for steroid-resistant acute GVHD of the gut

N=6 SR aGVHD
N=9 steroid dependant aGVHD
At day 28: 10 patients in CR
- SR aGVHD: 3/6
- SD aGVHD 7/9

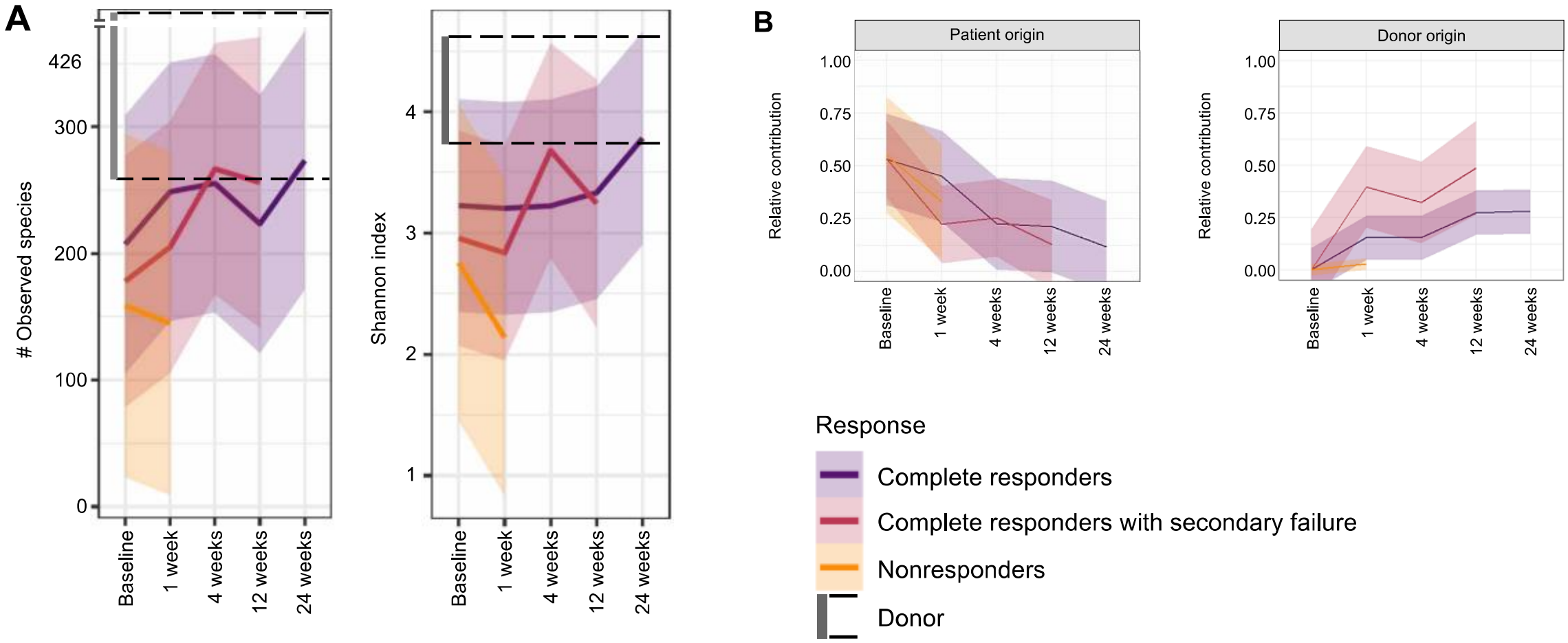
Single donor:
- Donor 1 for P01
- Donor 2 for others patients

<u>Fresh</u> donor feces delivered via a nasoduodenal tuble



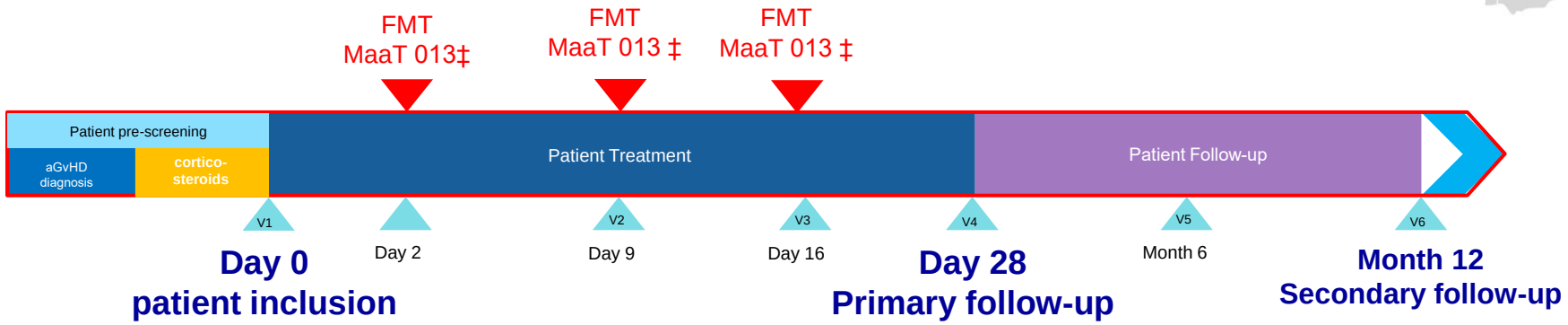
Van Lier et al. STM 2020

Patients responding to FMT have higher α diversity and donor engraftement



Van Lier et al. STM 2020

Heracles trial: FMT using pool of donor (MaaT013) for SR aGVHD



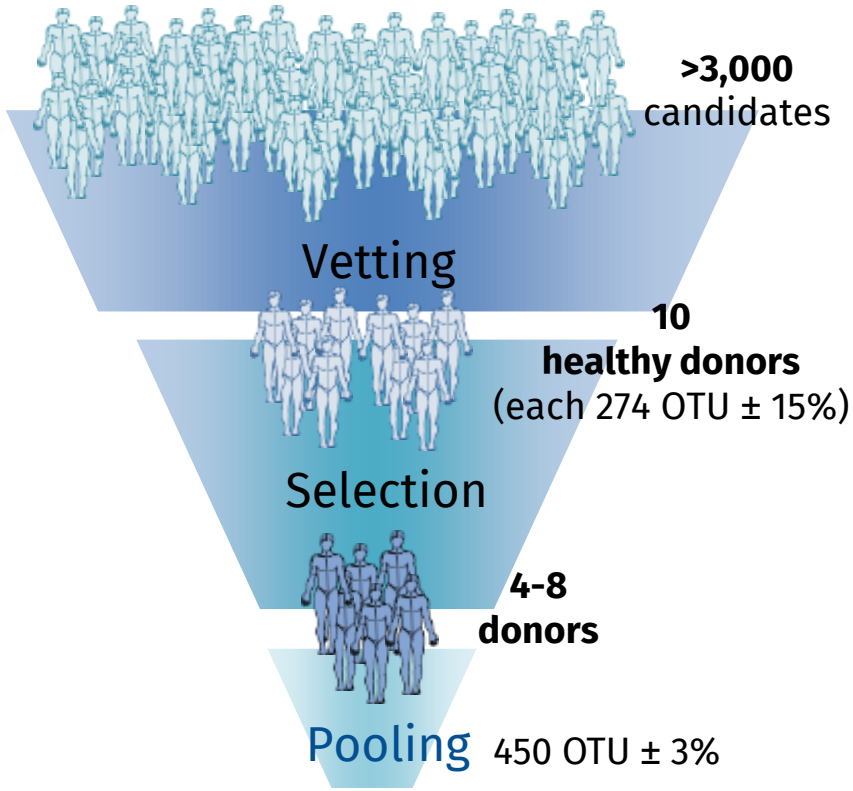
- N=24 patients with steroid refractory gastrointestinal acute GVH

‡ This product is used off-label in this setting

ClinicalTrials.gov Identifier: NCT03359980, Malard et al. ASH 2021 oral abstract 262

MaaT013 Full Ecosystem Therapeutics

cGMP Process



MaaT013

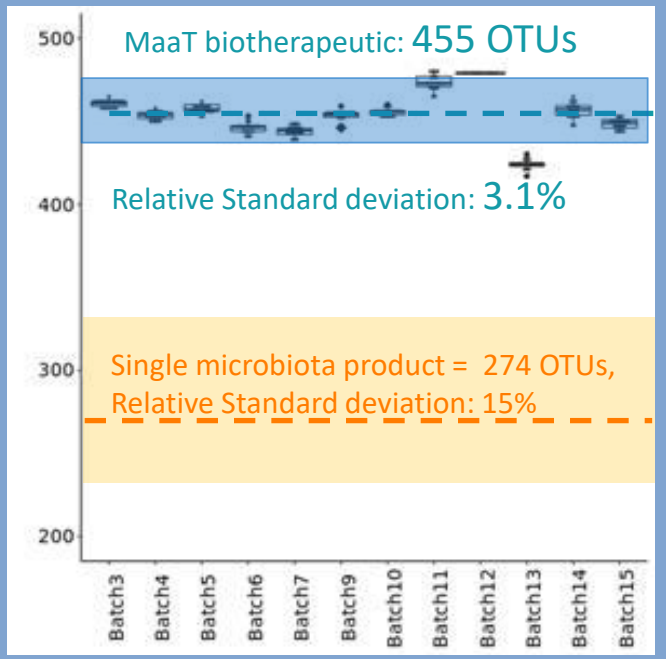
- ✓ Strict screening tests based on European consensus recommendations, ANSM guidelines and discussions with national regulatory agencies
- ✓ Sars-cov2 detection

- ✓ Full Ecosystem biotherapeutics
- ✓ Standardized, off-the shelf
- ✓ High, consistent richness and diversity
- ✓ Preserved Butycore (patented cryoprotectant)
- ✓ Manufactured under cGMP conditions

MaaT013

- ✓ Enema for direct colonic delivery
- ✓ 80% restoration
- ✓ 1 bag > 10^{11} CFU
- ✓ 24 months stability at -80°C

Microbial richness



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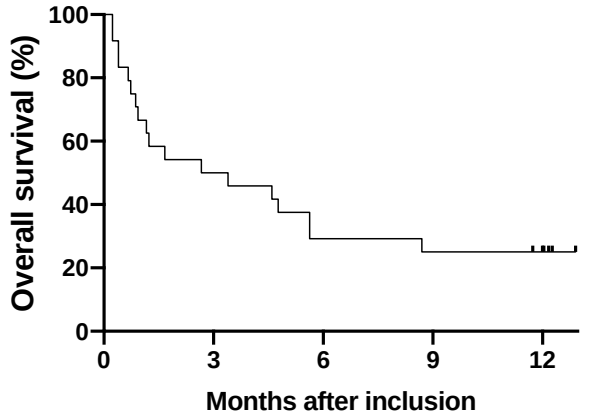
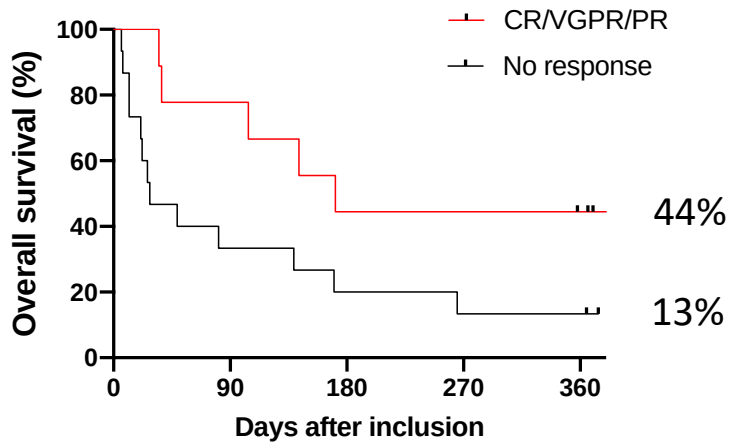
Cammarota et al., 2016; Dubuisson et al., 2018; Sebastian D. Burz et al. 2019
Drug Product characteristics presented during EMBO|EMBL

Heracles phase 2: GI SR aGVHD response

Response	Patients (N=24) N (%)
• **GI aGVHD response at D28**	**9 (38%)**
○ Complete response	5 (21%)
○ Very good partial response	2 (8%)
○ Partial response	2 (8%)
• **Best GI aGVHD response before D28**	**13 (54%)**
○ Complete response	9 (38%)
○ Very good partial response	3 (13%)
○ Partial response	1 (4%)





P=0.047

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HERACLES Phase 2 : Safety

- Excellent tolerance reported, reviewed by independent DSMB

- 39 adverse events reported within 24 hours of MaaT013 administration including 4 serious adverse events:
  - 1 cerebral infarction (Grade 4)
  - 1 thrombotic microangiopathy (Grade 3),
  - 1 general physical health deterioration (Grade 5)
  - 1 Escherichia sepsis (Grade 3)

The *E. coli* strain isolated from the blood sample of the patient was not identified in the MaaT013 received by the patient.

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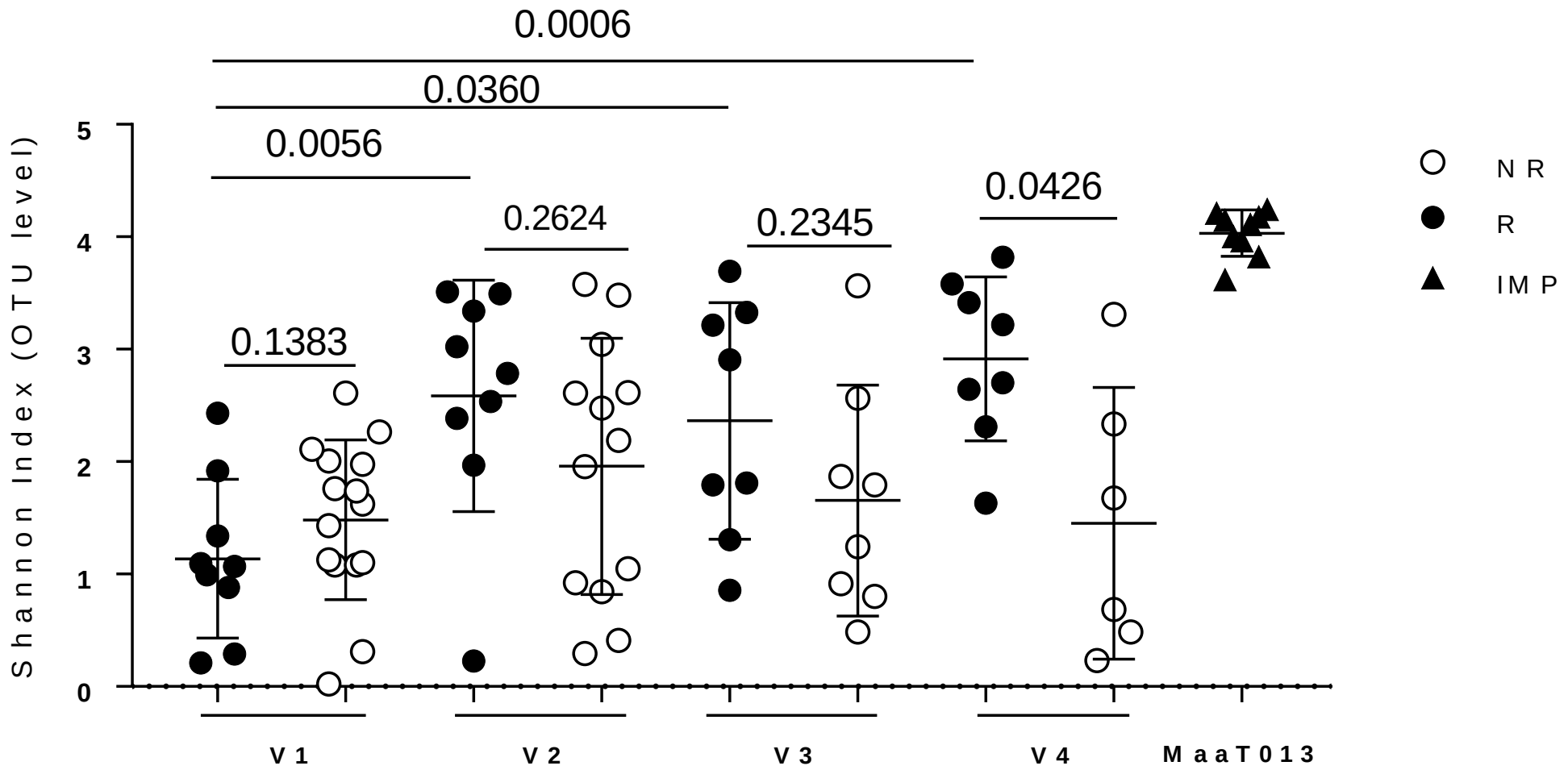
Alpha diversity is significantly increased after MaaT013 in responding patients



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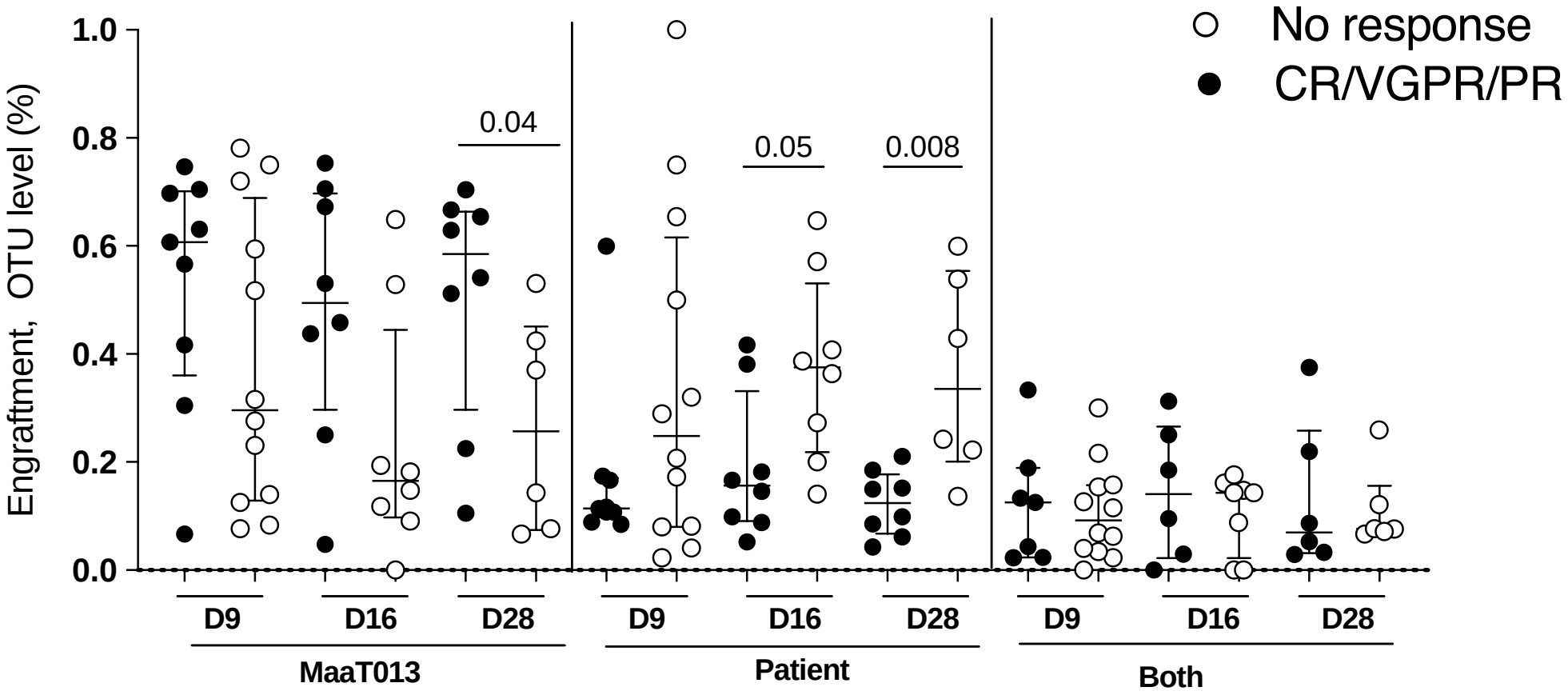
MaaT013 engraftment is significantly higher is responding patients

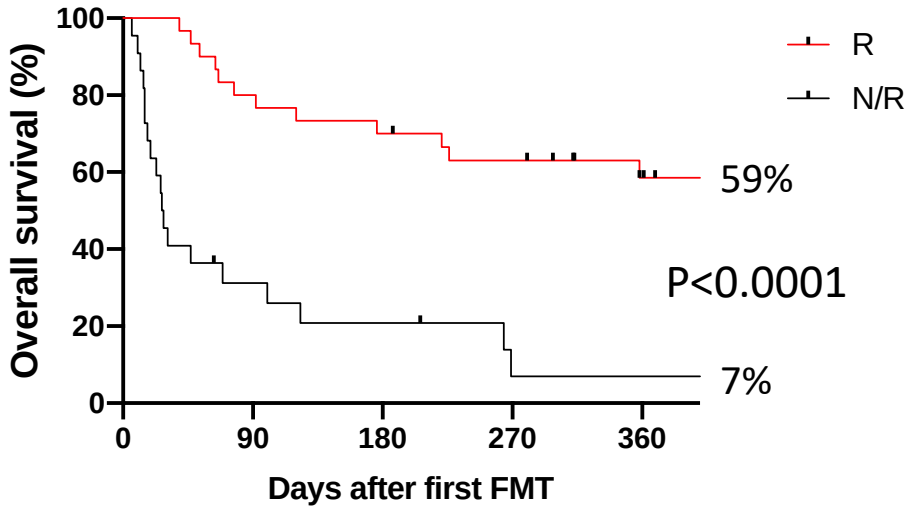


Malard et al. unpublished data

Compassionate Use and Expanded Access Program: GI SR aGVHD response

- CUP: N=52 steroid-resistant GI-aGVHD (resistance n=22, dependance n=7)
  - Median 3 previous line of treatment (range, 1-6)
  - 40 (77%) received ruxolitinib

Response	Patients (N=52) N (%)
• **GI aGVHD response at D28**	**30 (58%)**
○ Complete response	17 (33%)
○ Very good partial response	9 (17%)
○ Partial response	4 (8%)
• **Best GI aGVHD response before D28**	**35 (67%)**
○ Complete response	21 (40%)
○ Very good partial response	10 (19%)
○ Partial response	4 (8%)



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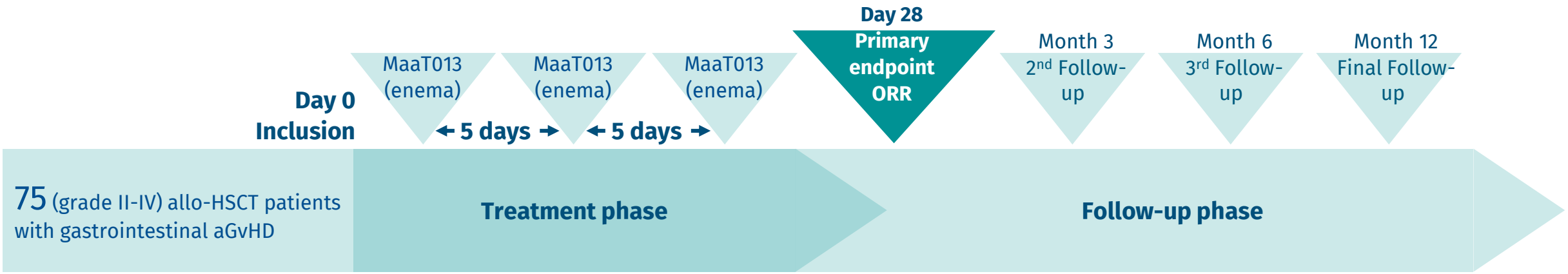
The ARES Phase III study: FMT (MaaT013) as the 3rd line agent in GI aGvHD treatment



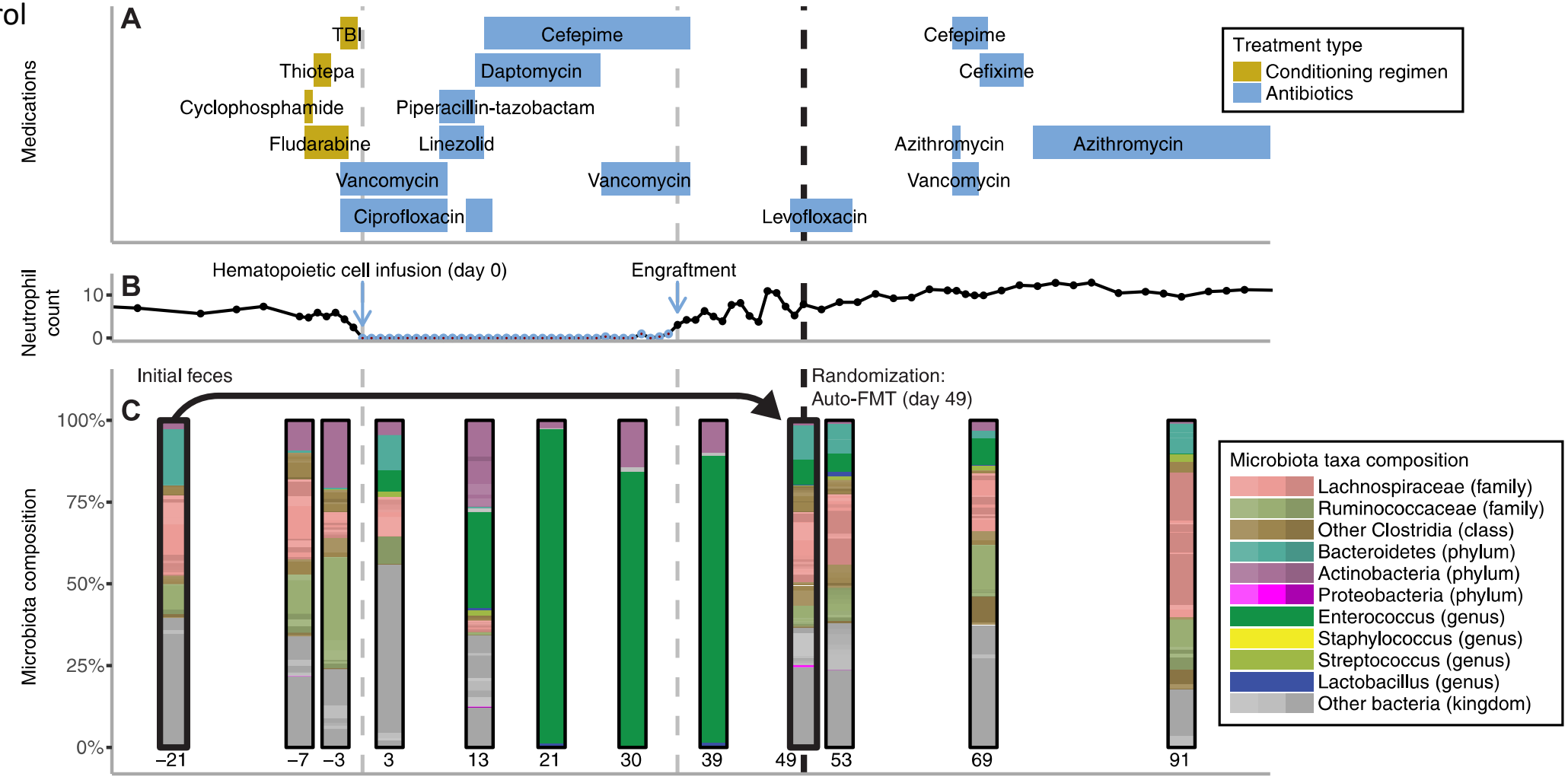
- Pivotal single-arm study of MaaT013
- Targeting 3rd line in patients with GI aGvHD who are refractory to both steroids and ruxolitinib
- Primary endpoint: GI response at Day 28
- Study start end of 2021 in Europe
- Expansion to US sites expected in 2022

FMT studies for restoring gut microbiota diversity

Study	Indication	Patients	Administration	Study	Donor	N° of FMT	AE	Response
Taur et al., 2018	Gut microbiota diversity restoration after alloHCT	25 (n=14 auto-FMT; n=11 control)	Enema	Essai prospectif randomisé	Autologous FMT	25	No SAE	Gut microbiota diversity restoration
DeFilipp et al., 2018	Gut microbiota diversity restoration after alloHCT	13	Oral capsule	Prospective	Third party donor	13	1 abdominal pain	Gut microbiota diversity improvment
Malard et al., 2021	Gut microbiota diversity restoration after induction chemotherapy in AML	25	Enema	Prospective	Autologous FMT	25	No SAE	

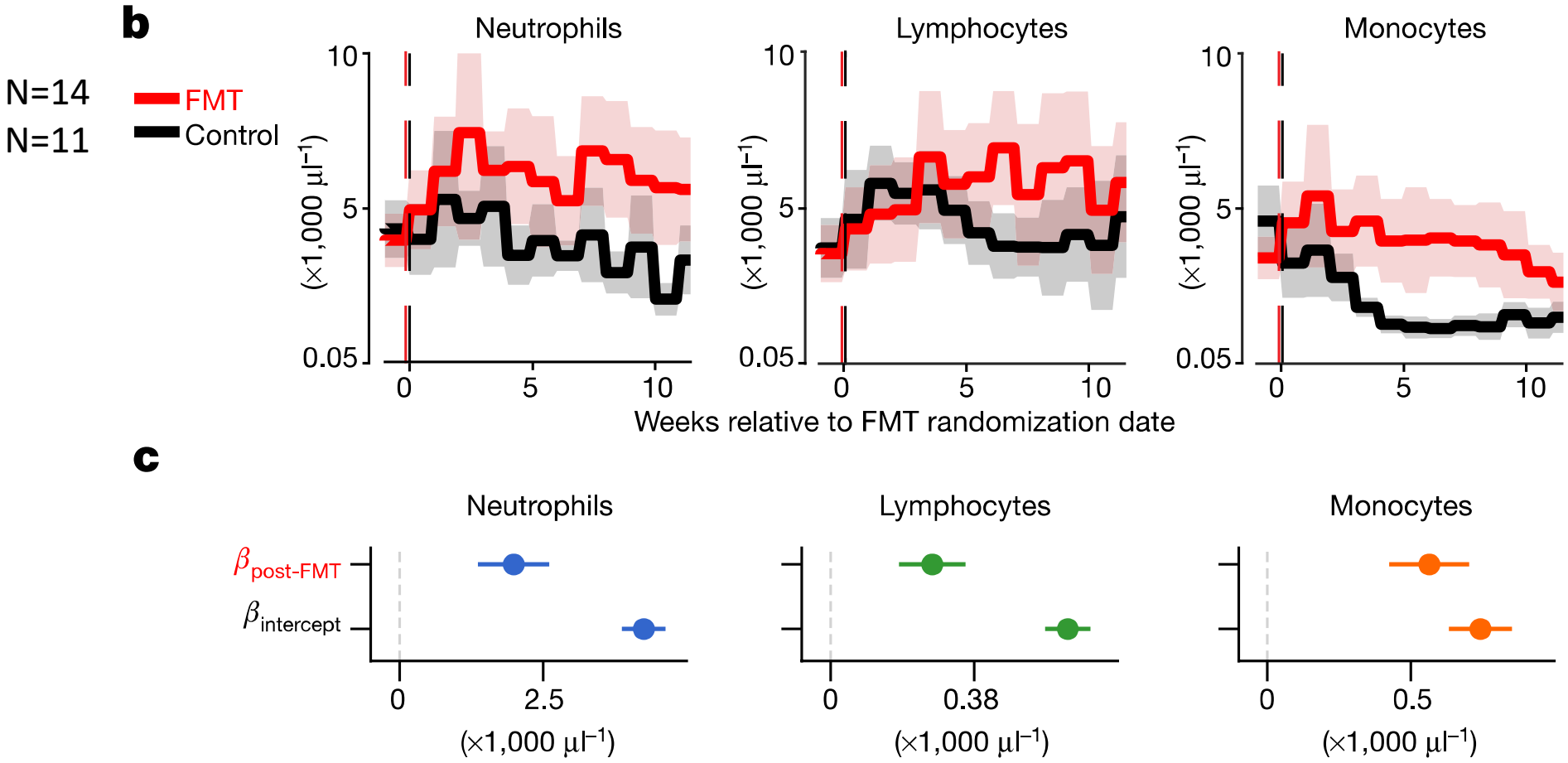
Auto-FMT after alloHCT accelerate microbiota diversity recovery after alloHCT

n=14 auto-FMT
n=11 control



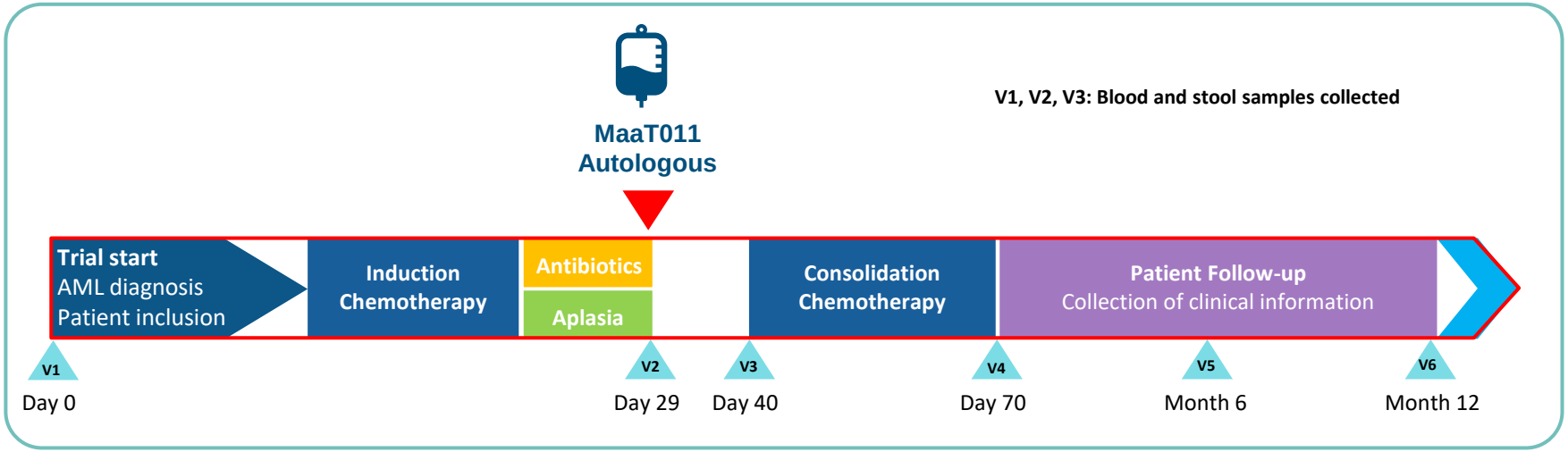
Taur et al. Sci Transl Med 2018

Autologuous fecal microbiota transplantation drive hematopoietic recovery after alloHCT



Schluter J et al. Nature, 2020

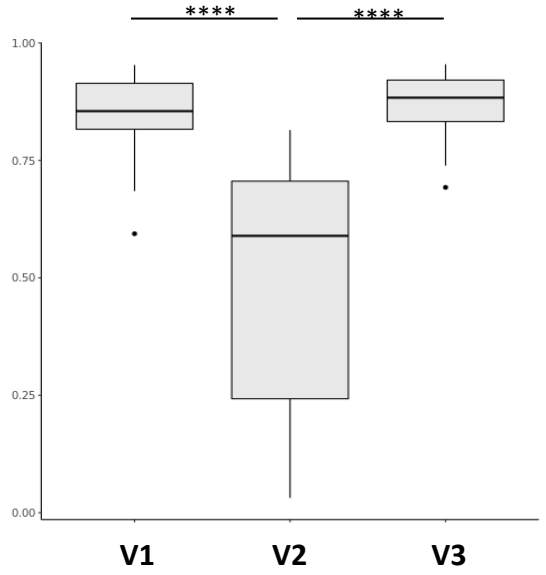
Autologous fecal transplantation in newly diagnosed AML patients



- N=25 AML patients, follow-up: 12 months
- Primary objective: Impact of auto-FMT on recovery of microbiota diversity and correction of dysbiosis in AML patients treated with intensive chemotherapy

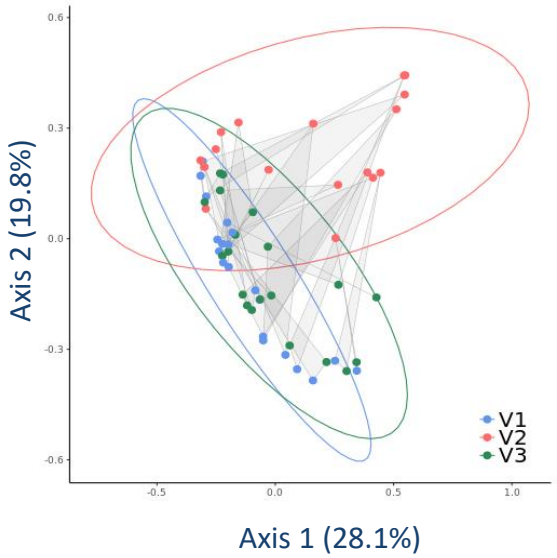
Malard et al., Nature Communication, 2021; ClinicalTrials.gov Identifier: NCT02928523.

Microbiome Recovery in AML Patients after autologous FMT



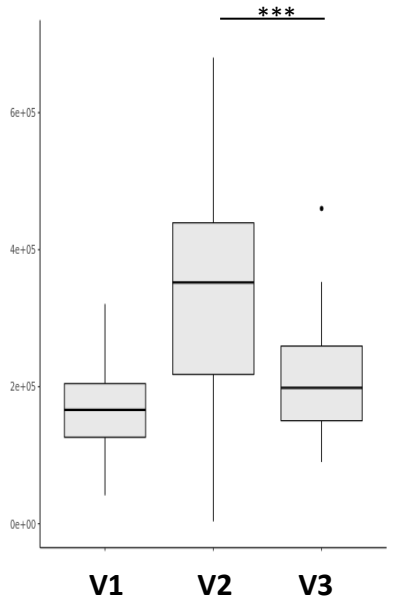
Simpson Index

Auto-FMT restores >90% of baseline diversity



PCoA of Bray-Curtis Indexes

Auto-FMT restores baseline taxonomic composition

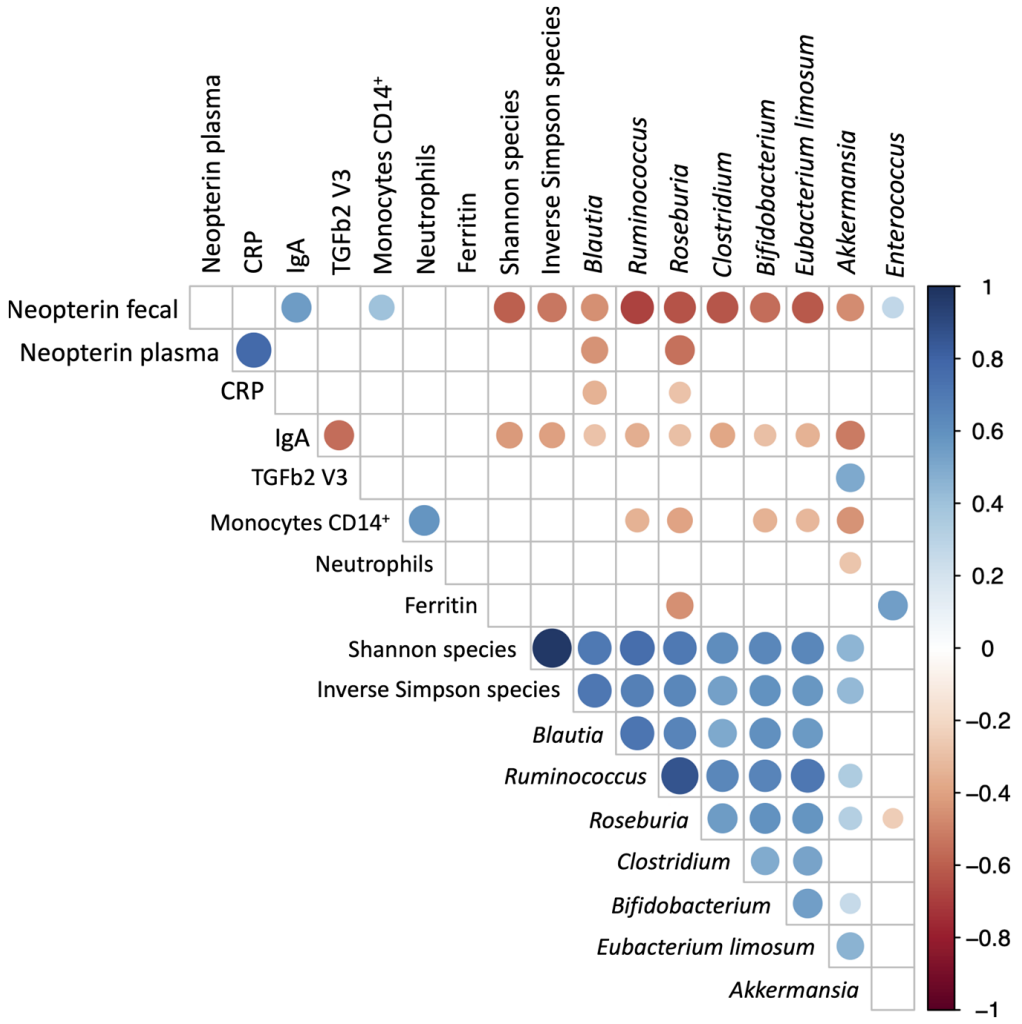


ABR copycount

Auto-FMT reduce antibiotic resistance gene by 43%

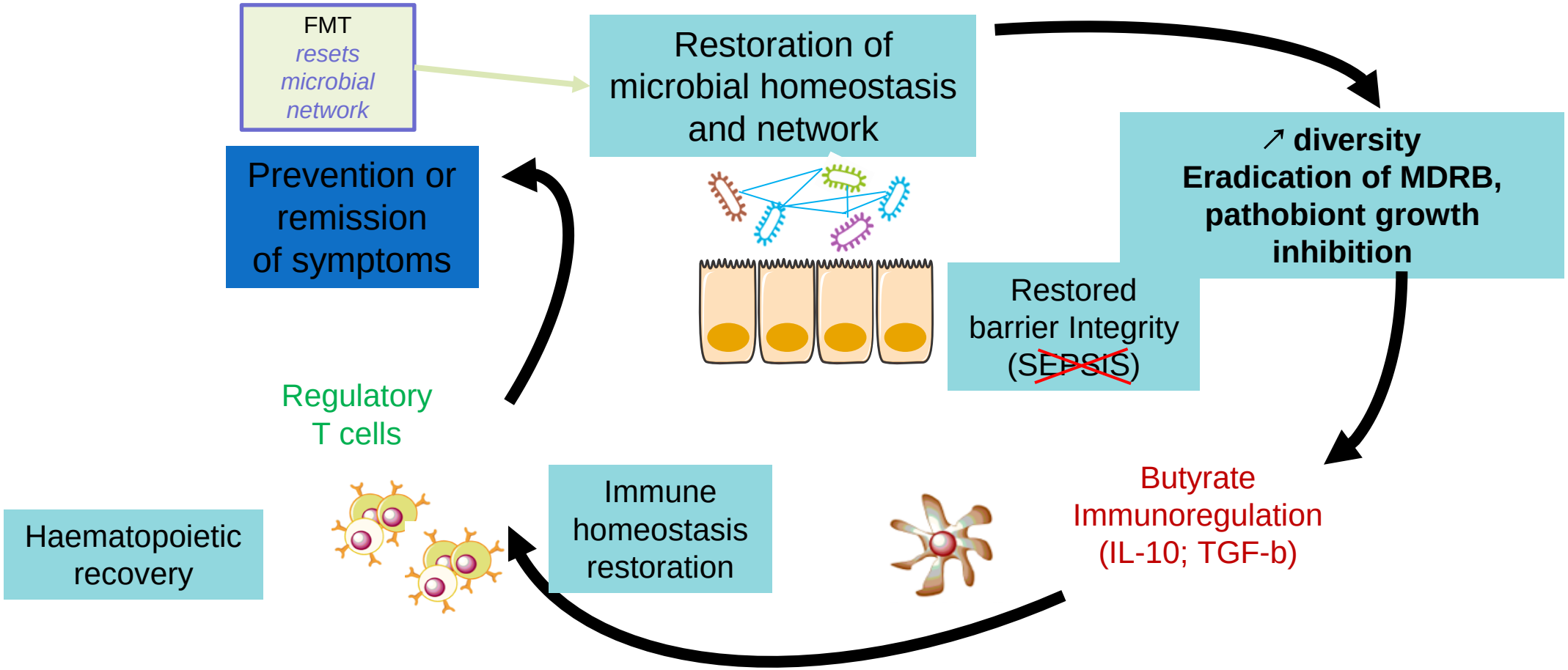
Malard et al., Nature Communication, 2021; ClinicalTrials.gov Identifier: NCT02928523.

Butyrate producing bacteria correlate negatively with inflammation



Malard et al., Nature Communication, 2021; ClinicalTrials.gov Identifier: NCT02928523.

FMT in acute GVHD: potential mechanism of action, restoration of homeostasis and gut barrier



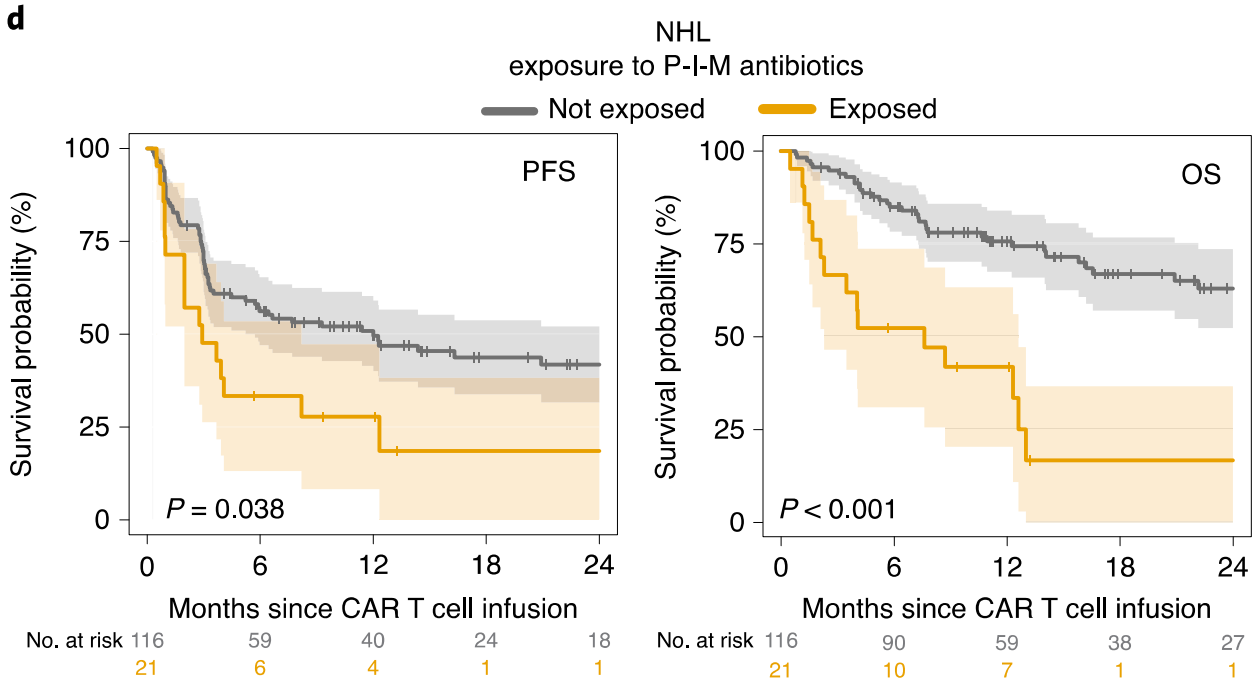
➢ Proposed mechanism of action: FMT restores microbiome diversity, regenerates gut barrier's protective effect, and significantly curbs inflammation.

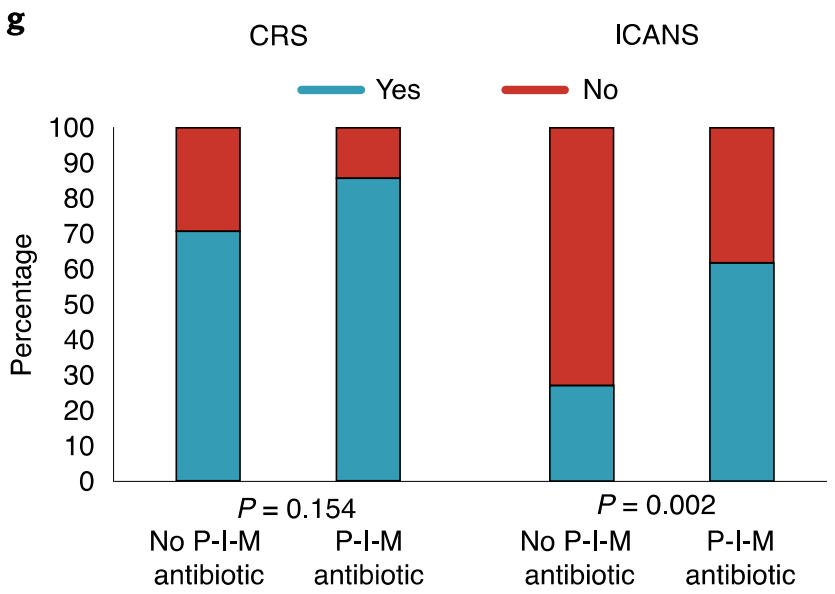
Adapted from Malard et Mohty, Blood, 2021

And beyond alloHCT?

Use of antibiotic with large anti-anaerobic spectrum within 4 weeks before CAR T-cells lead to decrease PFS, OS and increases neurological toxicity

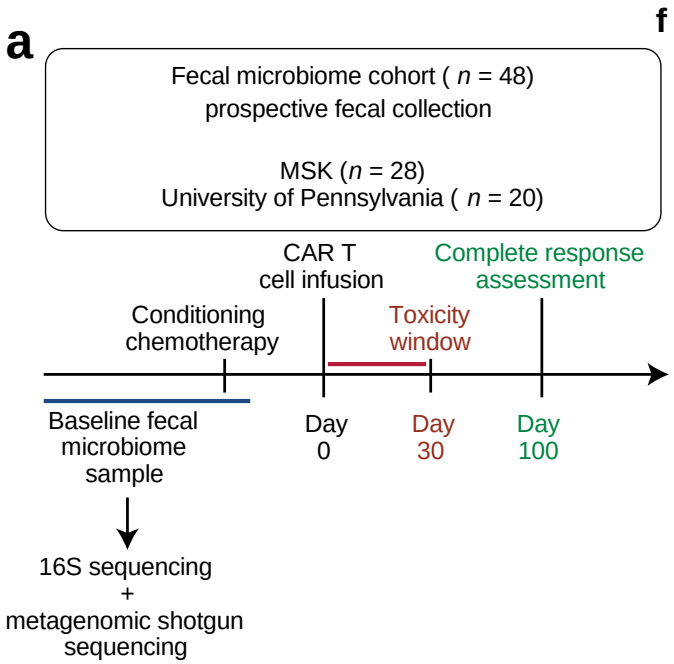
N=228

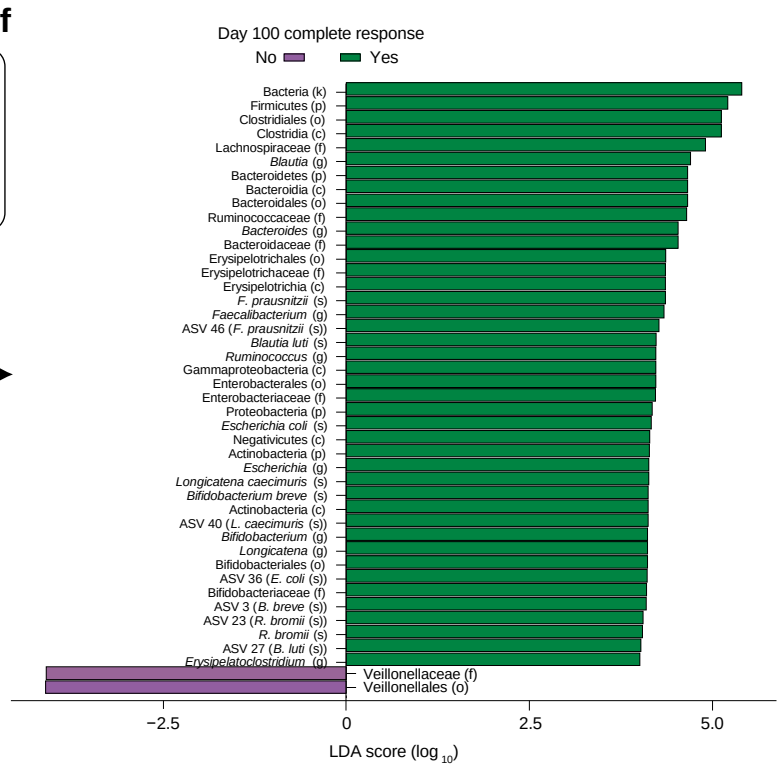


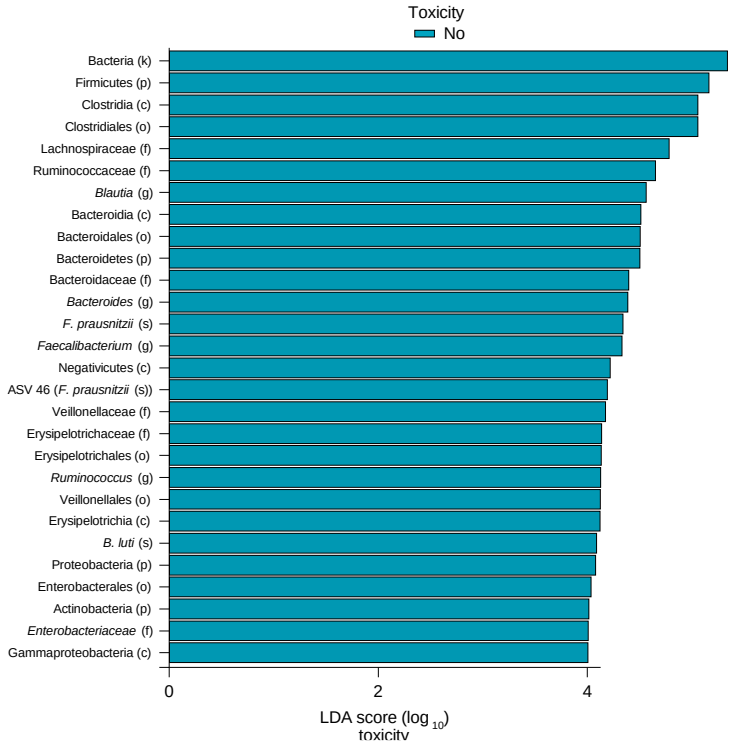


Smith M et al., Nat Med, 2022

Association of baseline fecal microbiota with clinical response in recipients of CD19 CAR T cells



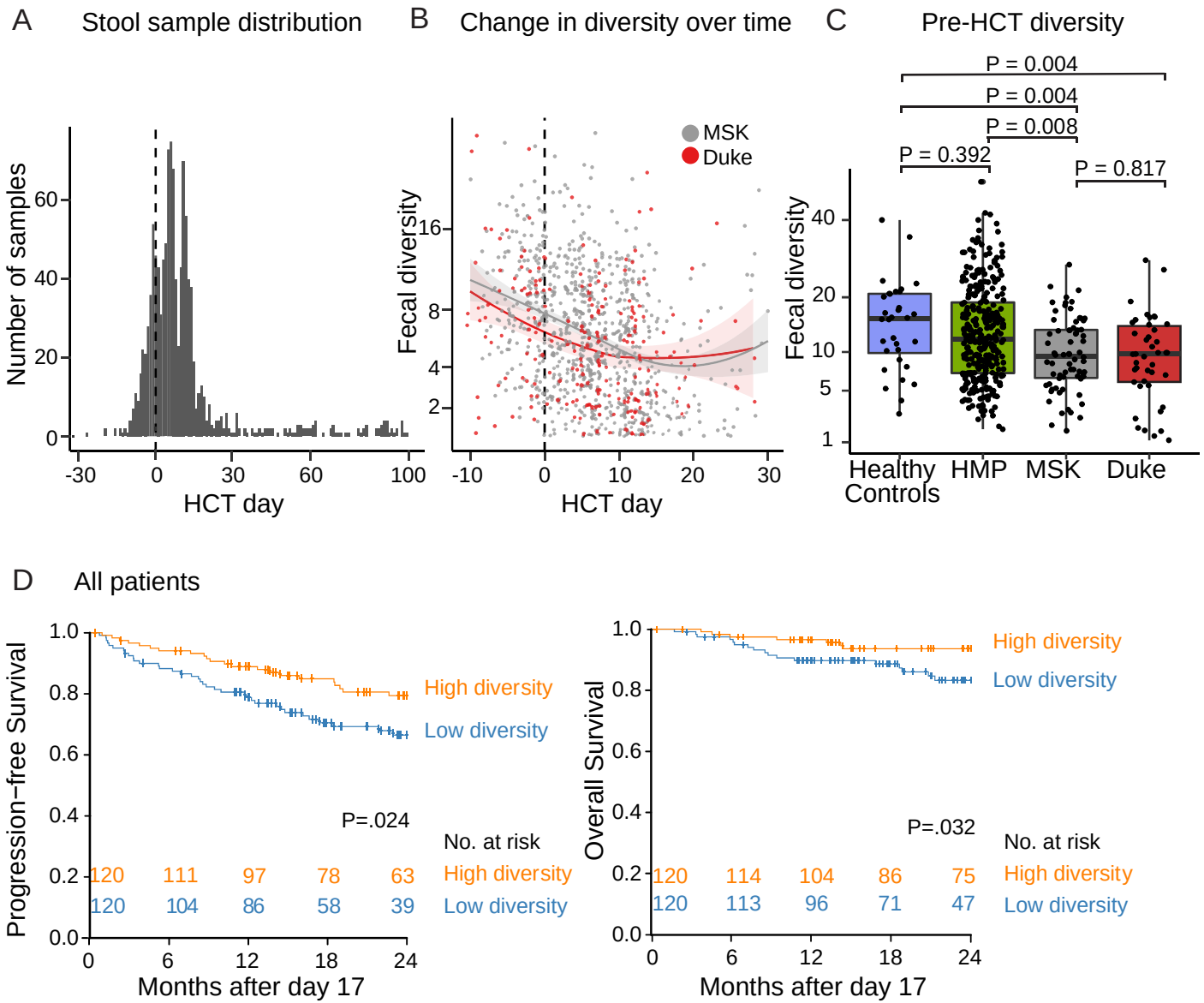




Smith M et al., Nat Med, 2022

Gut microbiota is impaired during autoHCT and associated with patients outcomes

n=535



Khan N et al. Blood, 2021

Conclusion

- Link between gut microbiota composition and patients outcome well established for allo-HCT (OS, lethal GVHD, bacteremia/sepsis, relapse…)

- Fecal microbiota transplantation is under investigation:
  - Treatment of gastro-intestinal acute GVHD after allo-HCT
  - Prevention of gut microbiota dysbiosis and transplant complications after allo-HCT

- Important perspectives in others setting in hematological malignancies
  - CAR T-cells
  - Autologous hematopoietic cell transplantation

➔ New horizon in hematological disease: manipulation of the microbiome

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