THE ODYSSEE STUDY: PREVENTION OF DYSBIOSIS COMPLICATIONS WITH AUTOLOGOUS FECAL MICROBIOTA TRANSFER (FMT) IN ACUTE MYELOID LEUKEMIA (AML) PATIENTS UNDERGOING INTENSIVE TREATMENT : RESULTS OF A PROSPECTIVE MULTICENTER TRIAL

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Abstract #14444

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INTRODUCTION AND OBJECTIVE

- AML standard intensive chemotherapy (IC) combined with wide-spectrum antibiotics dramatically altered composition of the gut microbiota, leading to dysbiosis, promoting a pathological condition with uncontrolled local immune responses, systemic inflammation and increased incidence of comorbidities and complications.
- Proof-of-concept study to evaluate the use of microbiota-based drug during AML induction treatment to restore the gut microbiota diversity, and thereby ultimately controlling complications to improve outcomes in AML.

STUDY DESIGN AND PATIENTS

- Single arm phase I/II multicenter trial (NCT02928523)
- Treatment: 2 doses of 150mL auto-FMT biotherapeutic drug by rectal enema

STUDY MAIN OBJECTIVES

- Primary: Impact of auto-FMT on recovery of microbiota diversity and correction of dysbiosis
- Secondary:
  - ✓ Safety and feasibility of auto-FMT
  - ✓ Impact of auto-FMT on several patient-related outcomes (clinical status, immune status and recovery)
  - ✓ Exploratory assessment of a dysbiosis biosignature

Key Inclusion Criteria

- ≥ 18 and ≤ 75 years old
- *de novo* diagnosis of **AML**
- Intensive chemotherapy ("7+3" or equivalent)

Key Exclusion Criteria

- Antibiotics ≥ 4 days at V1
- Detection of resistant or pathogenic bacteria, parasites, viruses in faeces at V1
- Severe colitis or digestive disorders within 3 months before V1

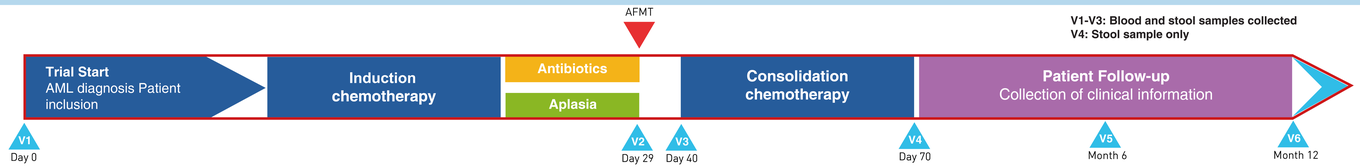
Demographics and Baseline Characteristics

- **62 AML** patients aged between 24 and 69 years old (median: 58) **were screened**.
- 25 patients fulfilling all inclusion criteria were treated (FAS population); **20 were included in the per-protocol (PP) population**. Results from the PP population are presented.

Age, years; median (range)	50 (24-68)
Gender, n(%)	F: 5 (25%); M:15 (75%)
Induction chemotherapy (IC):	Ara-C + Daunorubicin : 7 (35%) Ara-C + Idarubicin: 12 (60%) Other: 1 (5%)
Leukemia risk category (ELN2010):	Favorable: 2 (10%) Intermediate 1: 1 (5%) Intermediate 2: 15 (75%) Unfavorable: 2 (10%)
FLT3-ITD Mutation:	Yes: 14 (87.5%); No: 2 (12.50%); ND: 4 (25%)
NPM1 Mutation:	Yes: 11 (55%); No: 9 (45%)

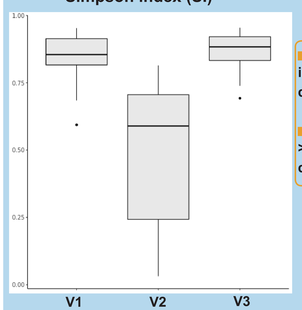
METHODS and RESULTS

- Faeces were collected at the time of patient's admission and AML diagnosis. After rigorous screening according to standard recommendations, faeces were conditioned, processed with a patented diluent under GMP conditions and stored frozen until administration in MaaT pharma's integrated MaaT Microbiome Restoration Biotherapeutic (MMRB) platform. After recovery from aplasia and before the second course of chemotherapy, two inocula were administered as enema 24h apart (D30 and 31).
- Microbiome analysis: QiAmp fast DNA stool for DNA extraction; sequencing on HiSeq 2500 2x125bp, 40 million reads/sample; RefSeq2015 for phylogenetic analysis.
- Antibiotic resistance gene carriage (ABR copycount) was evaluated through mapping of readouts on the MEGARES database.



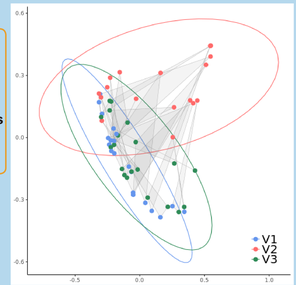
METAGENOMIC RESULTS

Simpson index (SI)



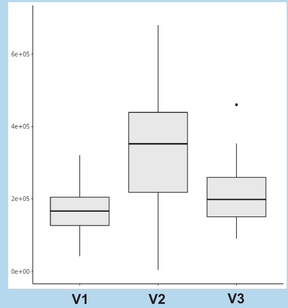
- **IC and antibiotics induce significant diversity decrease**
- **Auto-FMT restores >90% of baseline diversity**

PCoA based on Bray-Curtis dissimilarity



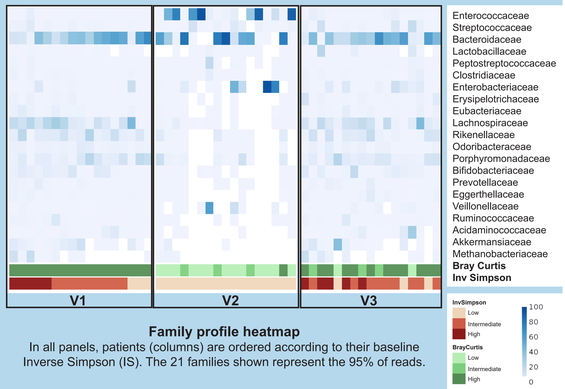
- **Dramatic microbiome structure shift after IC (V2)**
- **Auto-FMT restores base-line taxonomic composition (V3 co-localized with V1)**

ABR copycount



- **43% reduction of antibiotic resistance gene copycount between V2 and V3**

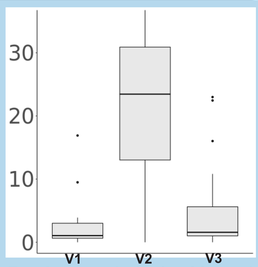
Parameter	Visits	Estimate (95% CI)	Test	P-value
Simpson (species level)	V2/V1	LS mean: 0.577 [0.413;0.742]	Value = 1, T-test	<0.0001 ****
	V3/V1	LS mean: 1.028 [0.967;+inf]	Value >0.9, T-test	0.0001 ****
Bray-Curtis (species level)	V2/V1	Mean score: 33.000	693.000 Wilcoxon test	<0.0001 ****
	V3/V1	Mean score: 15.520		
ABR copycount	V2	LS mean: 371423 [281532;490017]	RR V3 vs V2, Wald test 0.568	0.0008 ***
	V3	LS mean: 211128 [177269;251453]		



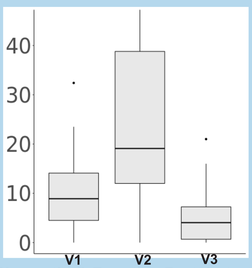
Family profile heatmap
In all panels, patients (columns) are ordered according to their baseline Inverse Simpson (IS). The 21 families shown represent the 95% of reads.

V2: Domination by pro-inflammatory families (Enterobacteriaceae, Enterococcaceae and Veillonellaceae) and some of them by Bacteroidaceae members.
V3: Good composition restoration and in particular Lachnospiraceae and Ruminococcaceae that include *Faecalibacterium*.

Inflammation Results



Fecal neopterin (ng/g of faeces)



Plasmatic C-Reactive Protein (mg/L)

Auto-FMT does not induce any deleterious inflammatory reaction and was moreover associated with significantly reduced inflammation at V3 with 89.6% and 85.2% reduction of neopterin and CRP levels respectively between V2 and V3.

Parameter	Visits	LS means estimate (95% CI)	Test	P-value
Fecal neopterin	V2/V1	12.958 [5.808; 28.913]	Value = 1, T-test	<0.0001 ****
	V3/V1	0.104 [0.042; 0.254]	Value = 1, T-test	0.0001 ****
C-Reactive Protein	V2/V1	2.681 [0.819;8.782]	Value = 1, T-test	0.0945 NS
	V3/V2	0.148 [0.044;0.494]	Value = 1, T-test	0.0051 **

Safety Summary

- Product well tolerated
- No SAE reported within 30 days after dosing
- 1 Suspected Unexpected Serious Adverse Reaction was doubtfully reported 93 days after second dosing: sepsis with digestive starting with E. coli contamination resolved after appropriate antibiotherapy.
- 1-year survival: 84% with 4 deaths among 25 patients (FAS population), none of which were related to the product: 2 multiple organ failures, 1 heart attack and 1 grade IV resistant GVHD. Median time to death from the 2nd dosing was 182.5 days (113-225 days)

CONCLUSIONS

- First prospective trial testing the safety and efficacy of microbiota-based drug in AML patients receiving intensive induction chemotherapy.
- Primary endpoint reached, establishing the capacity of these biotherapeutic drugs to restore a diverse microbiome with high levels of similarity to baseline, as well as reducing antibiotic resistance gene carriage and intestinal inflammation.
- Ecological data from AML patients that did not receive microbiota-based drugs could be of interest to reinforce the observed efficacy of the product in restoring gut microbiota diversity.
- A controlled randomized trial with repeated oral administrations during the different phases of AML treatment is currently planned to further evaluate the impact of donor-derived microbiota-based drugs on clinical outcomes such as infection-related complications, sequelae to the gastrointestinal tract, GVHD occurrence after hematopoietic stem cell transplantation and long-term survival. Indeed, the development of strategies to modulate the gut microbiota may improve overall disease management.

Disclosure
The trial was funded by MaaT Pharma whose product was tested in this protocol.
LB, CG and EP are MaaT Pharma employees.
MM and JD are scientific co-founders of MaaT Pharma and received honoraria and consulting fees.