Restoration of gut microbiota diversity with oral pooled fecal microbiotherapy in acute myeloid leukemia patients after intensive chemotherapy: the phase 1b CIMON trial

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MaaT Pharma was the sponsor of the trial.

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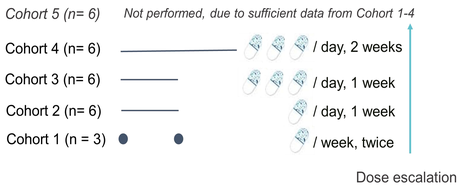
INTRODUCTION

- Acute myeloid leukemia (AML) treatment combines intensive chemotherapy (IC) with broad-spectrum antibiotics (ATB) that induces a strong gut microbiota dysbiosis, promoting pathological conditions and increasing incidence of complications.
- Restoration of the full gut microbiota ecosystem is a promising therapeutic tool to improve clinical outcomes in patients with acute myeloid leukemia (AML) receiving IC and ATB.
- Here we report the tolerability, safety and efficacy of MaaT033, an oral, delayed-release capsule containing lyophilized pooled full ecosystem fecal microbiota, in restoring the gut microbiota in 21 AML patients having undergone IC and ATB: results from the Phase Ib CIMON trial (NCT04150393).

METHODS AND OBJECTIVES

CIMON study design
Phase I, open-label, single-arm
6 investigational sites in France

DOSE ESCALATION DESIGN
5 cohorts : dose escalation of MaaT033



STUDY OBJECTIVES
- ✓ MaaT033 tolerability
- ✓ Dose regimen evaluation (based on safety and MaaT033 activity / engraftment)
- ✓ Patient compliance

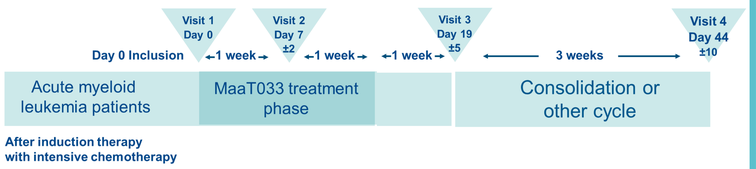
GUT MICROBIOTA CHARACTERIZATION
- ✓ 16S sequencing

MaaT033 CHARACTERISTICS
Oral pooled fecal microbiota
- ✓ *Strict screening process for healthy donors* (> 40 tested parameters)
- ✓ High-richness
- ✓ High-diversity
- ✓ Full ecosystem
- ✓ Ileo-caecal delivery
- ✓ *> 10^9 viable bacteria/capsule*

STUDY FLOW CHART

Main inclusion criteria
- Age ≥ 18 years
- Patients diagnosed with **AML or high-risk myelodysplastic syndrome**, receiving intensive chemotherapy
- Patients healthy enough to likely receive **their consolidation or second cycle of chemotherapy after induction chemotherapy**
- Patients healthy enough to likely receive HSCT
- Patient recovered from neutropenia

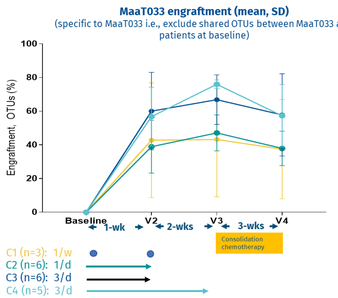
Main exclusion criteria
- **Active uncontrolled infection** according to the attending physician
- Any gastro-intestinal **bleeding in the past 3 months**
- [...]

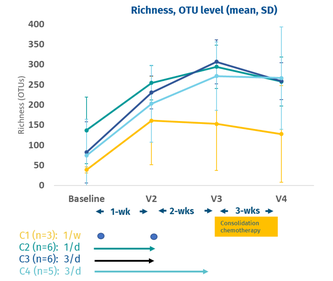


PATIENTS' CHARACTERISTICS

		Treated patients (N=21), n(%)
Gender, n (%)	Male	16 (76%)
	Female	5 (24%)
Age at inclusion (years)	Median [range]	62 [22-77]
Leukemia risk category (ELN 2022), n (%)	Favorable	7 (33%)
	Intermediate	6 (29%)
	Adverse	8 (38%)
Induction chemotherapy, n (%)	Cytarabine + anthracycline	20 (95%)
	Azacitidine	1 (5%)
Consolidation chemotherapy, n (%)	Cytarabine alone or in combination	17 (81%)
	Daunorubicin	1 (5%)
	Azacitidine + Venetoclax	1 (5%)
	None	1 (5%)
	Unknown	1 (5%)
Patients who received antibiotics during induction chemotherapy, n (%)	Prophylactic antibiotics	10 (48%)
	Therapeutic antibiotics	19 (90%)
	No systemic antibiotics	2 (5%)
Patients who received antibiotics during consolidation chemotherapy, n (%)	Prophylactic antibiotics	3 (14%)
	Therapeutic antibiotics	10 (48%)
	No systemic antibiotics	7 (33%)
	Unknown	1 (5%)

RESULTS: GUT MICROBIOTA AND HOST PARAMETERS ANALYSIS



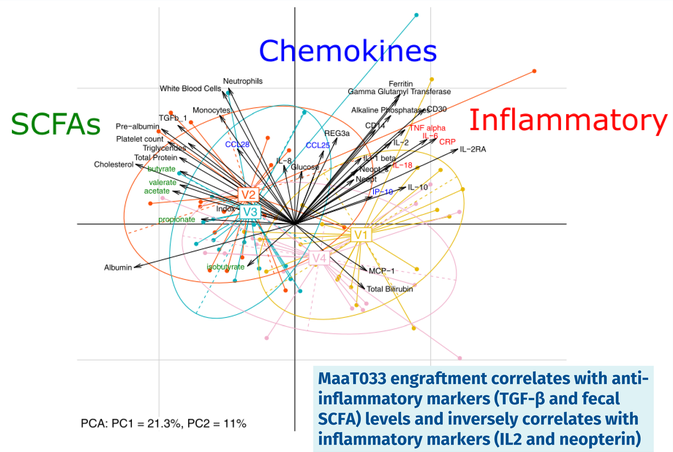


- **MaaT033 induces an increased microbiota richness at OTUs level**
- **MaaT033 displays a strong and persistent bacterial engraftment , higher in cohort 3 and cohort 4 (3 capsules per day) compared t o cohorts 1 and 2 (1 capsule per week / 1 capsule per day).**
- **MaaT033 bacterial engraftment is inversely correlated with patients' baseline microbiota richness**

(up) Microbiota richness, defined as number of OTUs found in patients' gut microbiota, described for each cohort

(down) Engraftment of MaaT033 in each cohort

Engraftment = ratio of OTUs that were not present in patient at baseline but were present in MaaT033 and were found in patient after treatment. Redundant OTUs found in patient and MaaT033 are not taken into account.



MaaT033 engraftment correlates with anti-inflammatory markers (TGF-β and fecal SCFA) levels and inversely correlates with inflammatory markers (IL2 and neopterin)

Principal Component Analysis performed with the host parameters dataset.
Individual samples are represented by points, colored and linked according to the corresponding visit. The arrows depict the variables, here the host parameters. The longer they are the more they drive the samples projections, the closer they are, the more they vary together. Specific parameter groups are highlight in color (SCFAs, Chemokine, and inflammatory parameters). For a better visualization, variables with neglectable impact on sample projections (with small arrows) were removed from the figure after computation.

OTU: operational taxonomic unit; V: visit; V1 (baseline): after induction chemotherapy and neutropenia recovery, before MaaT033 start; V2: 1 week after MaaT033 start, V3: before consolidation cycle; V4: at the end of consolidation cycle; C: Cohort; SCFAs: short chain fatty acids; wk: week

SAFETY

4 serious adverse events (SAEs) reported in 4 patients. Only one (in bold) was considered as possibly related by the investigator.

Event	Cohort 1 (N=3) n (%)	Cohort 2 (N=6) n (%)	Cohort 3 (N=6) n (%)	Cohort 4 (N=6) n (%)	Total (N=21) n (%)
Febrile neutropenia	0	1 (17%)	0	0	1 (5%)
Neutropenic colitis	0	0	1 (17%)	0	1 (5%)
Diarrhoea infectious	0	0	0	1 (17%)	1 (5%)
Hyperkalaemia	0	1 (17%)	0	0	1 (5%)

The SAE infectious diarrhea with enteropathogenic *E. coli* (EPEC) started 3 days after MaaT033 treatment initiation.
- ✓ **EPEC strain not found in MaaT033 batch** (genome sequencing) nor in patient's feces before MaaT033 administration
- ✓ Absence of pillbox contamination verified by PCR

=> **Relationship to MaaT033 was unlikely**, although it could not be formally excluded.

Six infectious events reported :
- 1 during MaaT033 treatment phase (SAE described above)
- 5 after MaaT033 treatment and during the consolidation cycle : cellulitis, Escherichia sepsis, paronychia, Pseudomonas infection, skin infection, ***none of them being reported as serious nor potentially related to MaaT033***

MaaT033 treatment is safe :
After IC in immunocompromised AML patients : good tolerance, minimal toxicity after treatments and post-neutropenia

CONCLUSIONS

- MaaT033 appears to be **safe and effective for gut microbiota restoration** in AML patients receiving IC and ATB.
- **3 MaaT033 capsules per day for 1 week** induce an **increase in microbiota richness** and an **effective and persistent MaaT033 bacterial engraftment** in AML patients
- A Phase IIb trial is planned to start in 2023 to evaluate MaaT033 as an adjunctive and maintenance treatment in patients with hematological malignancies receiving allogeneic hematopoietic stem cell transplantation.