Investor R&D DAY

June 7th, 2022

Introduction & Opening remarks

Hervé Affagard

CEO

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Today's agenda

The Microbiome Revolution	**Dr. Joël Doré-** Research Director, INRAE and Scientific Advisor at MaaT Pharma
Driving Value in the Microbiome Space	**Hervé Affagard** - CEO and co-founder
The Microbiome: a new frontier in hematological cancer treatment?	**Pr. Ernst Holler, M.D** –Senior Professor on Clinical and Experimental Allogeneic SCT, Dept of Internal Medicine 3, University Hospital Center Regensburg, Germany
MaaT013, first-in-class Microbiome Ecosystem Therapy in Phase 3 in graft-vs-host-disease	**Dr. Florent Malard, M.D** – Professor of Hematology, Saint Antoine Hospital (AP-HP) and Associate Professor, Sorbonne University **Dr Emilie Plantamura** – Head of Clinical Development
MaaT033, oral Microbiome Ecosystem Therapy aiming to improve outcomes for patients with liquid tumors	**Pr. Mohamad Mohty** – Professor, Sorbonne University and Head of the Clinical Hematology and Cellular Department, Saint-Antoine Hospital
The microbiome is gaining momentum in cancer immunotherapy	**Pr. Hassane Zarour -** Professor of Medicine. Immunology and Dermatology, University of Pittsburgh
Proof-of-concept Phase 2 clinical trial in melanoma, sponsored by AP-HP	**Dr Emilie Plantamura** – Head of Clinical Development
MaaT Pharma's strategy to leverage the microbiome potential to improve cancer therapies	**Marianne Robin** – Research & Development Manager **Dr. Carole Schwintner** – Chief Technology Officer
Ending remarks & expected newsflow	**Hervé Affagard** - CEO and co-founder
Q&A SESSION	**15-20'**

Key messages for today

Unique strategy positioning in a growing microbiome market

- Based on the tremendous progress of microbiome science in the past 15 years, the microbiome global industry is now becoming more mature
- MaaT Pharma is pioneering Microbiome Ecosystem Therapies, offering a differentiated approach focused on addressing severe medical needs in oncology

Leading position in microbiome therapeutic in oncology

- Two candidates:
  - MaaT013, the company's lead asset, is currently in a Phase 3 in Europe in acute graft vs host disease
  - MaaT033, our first oral drug candidate, has completed a dose-ranging Phase 1b in hematology
- Our MET drug development platform is generating new preclinical assets

Clear company strategy and secured cash runway

- MaaT Pharma is delivering on what we announced during the IPO
- We are anticipating the future and building of a new cGMP manufacturing facility
- The way forward is clear, with the aim to build to a global reference in microbiome

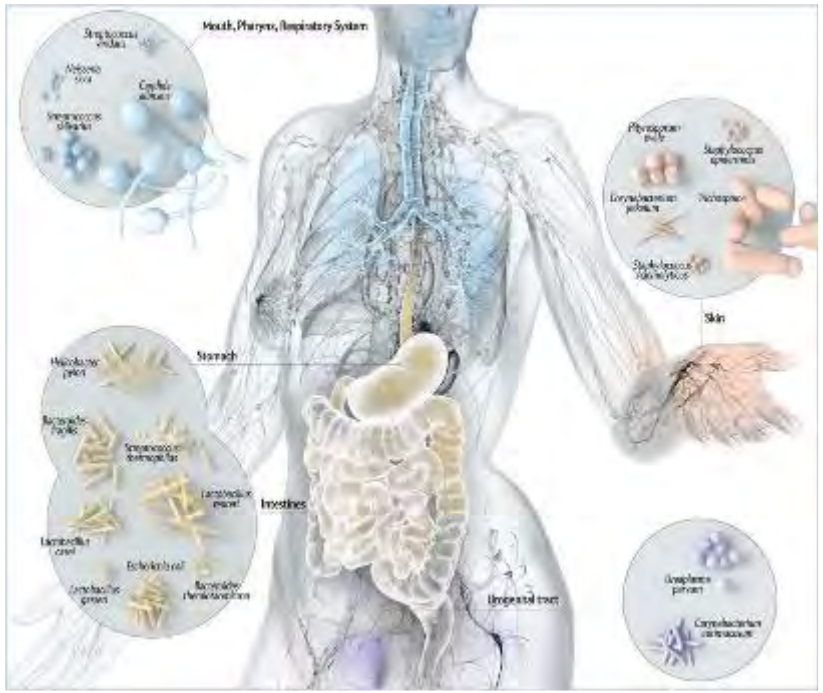
The microbiome revolution

Dr. Joël Doré

INRAE Research Director, Scientific Director of Métagénopolis, Scientific Advisor

The human is microbial: ecosystem and symbiosis

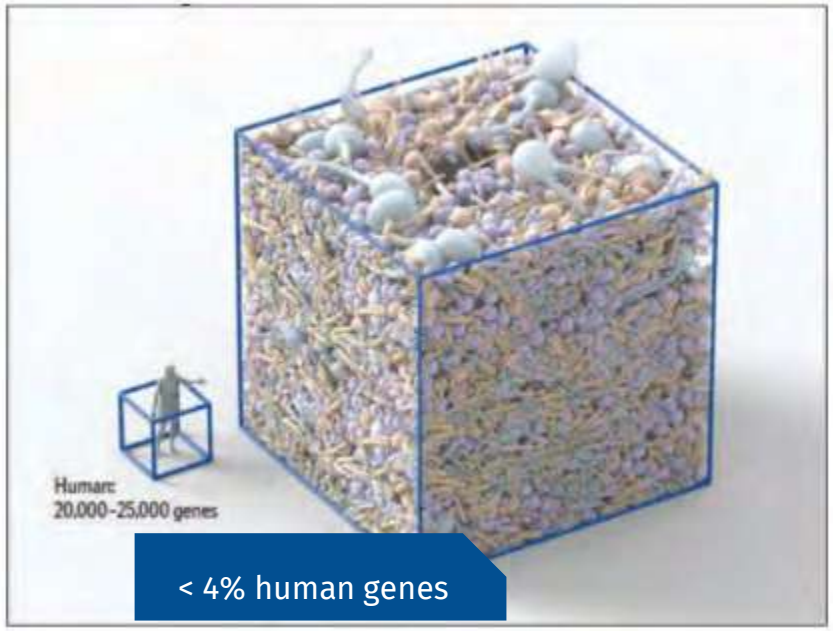
~50 000 000 000 000 bacteria: as many as human cells in our body



→ our microbiomes are “autochthonous” and specific to ecological niches they occupy

> 600 000 microbial genes*:

25 X the number of human genes



→ Microbiome science changes the landscape

** per individual*

Qin et al MetaHIT Consortium, Nature 2010; HMP Consortium et al., Nature 2012

The microbiota provides key protective functions microbiota

Human genes and their functions

Host-microbes SYMBIOSIS

Microbial genes and their functions

The microbiota acts as:

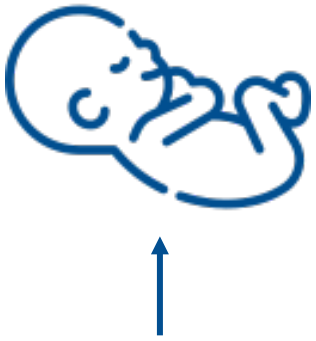
Endocrine-metabolic regulator

Immuno-inflammatory regulator

Antimicrobial “barrier”

Neuro-vegetative regulator

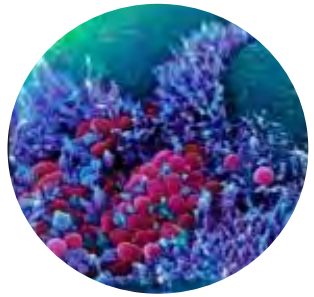
Host-microbes symbiosis:
A symbiotic relationship that starts at birth



Immune maturation

&

Microbiota development



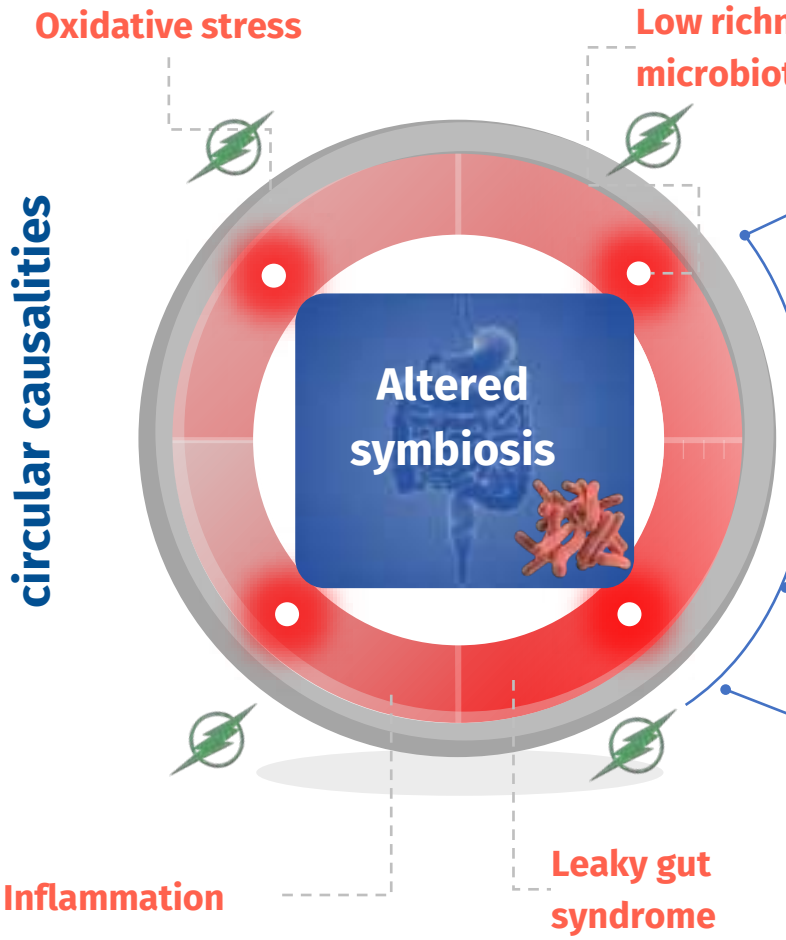
‘UNIQUE’ SYMBIOSIS: microbiota recognized as a component of ‘SELF’

Maintenance of symbiosis
- ✓ Health and well-being

Disruption of ecology :
- Loss of ‘barrier’ function
- Risk of infection (i.e. *C. diff*)

Disruption of immune tolerance:
- Loss of immune homeostasis
- Risk of immune-related conditions and/or non-response to treatments

25% of the worldwide population is affected by an atrophied microbiome and dysbiosis[1]



Conditions with uncontrolled rising incidence

CNS
- Autism Spectrum Disorders
- Major Depressive Disorders
- Multiple sclerosis

GI
- IBD (CD, UC)
- IBS
- NASH syndrome
- Cirrhosis

Metabolism
- Insulin resistance (T2D)
- Metabolic syndrome
- Obesity

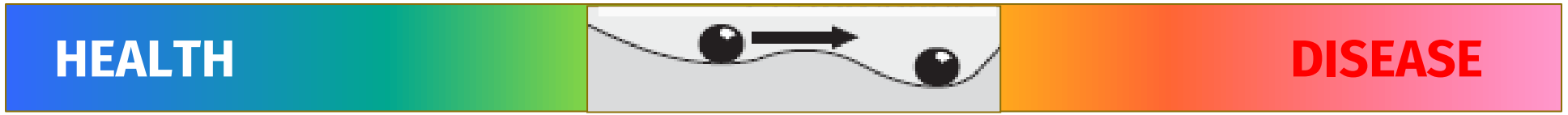
Infections
- *C. difficile*
- MDRB

Immunity
- Allergies
- Auto-immune diseases
- Cancer ; GvHD

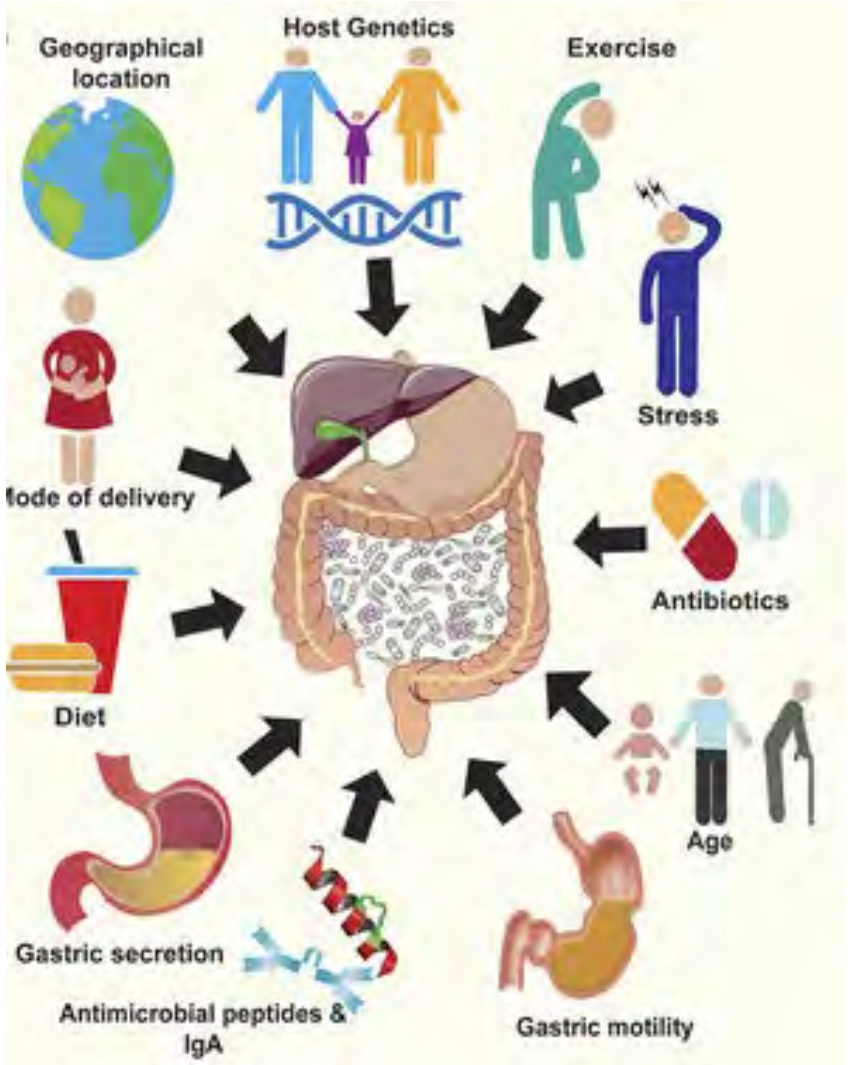
At least **4** actionable levers to support :
- ✓ Diagnosis
- ✓ Monitoring
- ✓ Prediction
- ✓ Prevention
- ✓ Therapy

Le Chatelier Nature 2013 & Cotillard Nature 2013; Doré Thérapie 2017; Van de Guchte Microbiome 2018; Van de Guchte Microbiome 2020; Van de Guchte Gastroenterology 2021; Van de Guchte, Blottiere & Doré., Microbiome. 2018.

Homo symbiosus — erc



Urgent paradigm shift: Adopting a **holistic** approach to health, taking into account the microbiome/host symbiosis



Key features of a health-associated microbiota

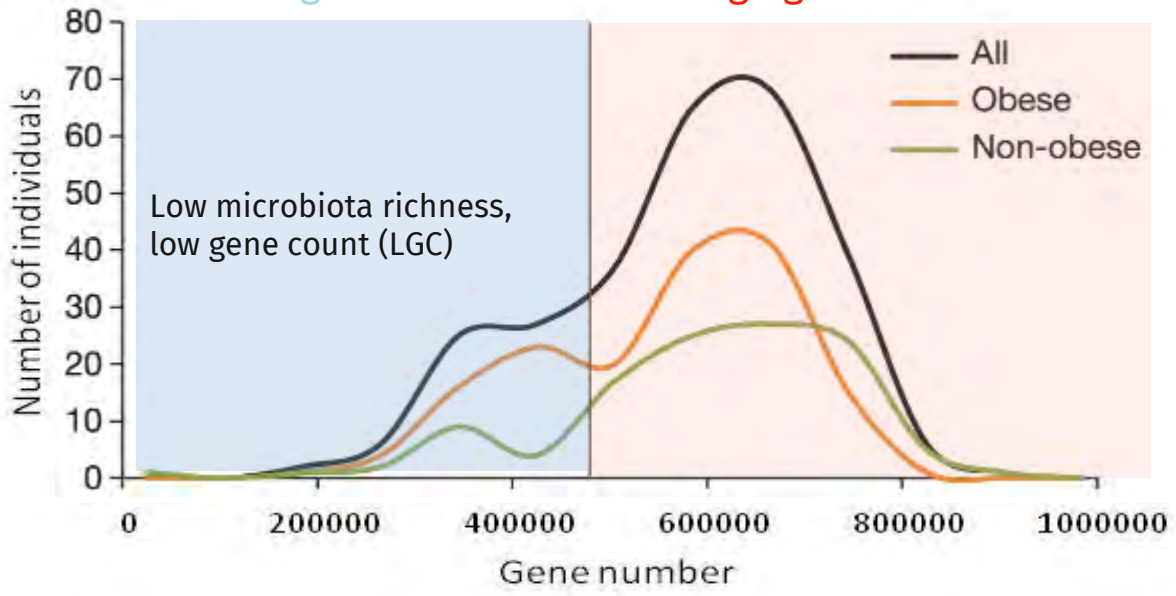
- High richness
- Robustness: resistance and resilience
- Shared core microbiome
- Symbionts driving immune-homeostasis
- Influenced by numerous factors
- Amenable to modulation by nutrition and microbiotherapy

→ Maintaining / restoring microbes-host symbiosis should be a major target in prevention / therapy

Microbiota richness is a major health stratifier…

Bimodal distribution of population (FR, DK) based on microbiota gene-count

low gene-count to high gene-count



LGC:
≈ 15 % in non obese

≈ 40% in overweight

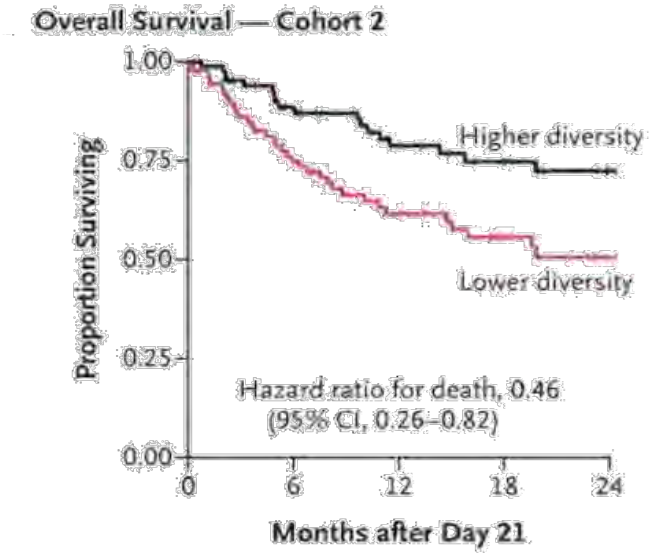
≈ 75% in morbid obesity

A low gene count is associated with :

- Altered metabolic & inflammatory phenotype in overweight and obesity (LeChatelier et al., Nature 2013)
- Non-response to calory-restriction in overweight and obesity (Cotillard et al., Nature 2013)
- Higher severity and faster progression in cirrhosis (Qin et al., Nature 2014; Solé et al., Gastroenterology 2020)
- Non-response to cancer therapy (Routy et al., Science 2018, Gopalakrishnan et al., Science 2018)

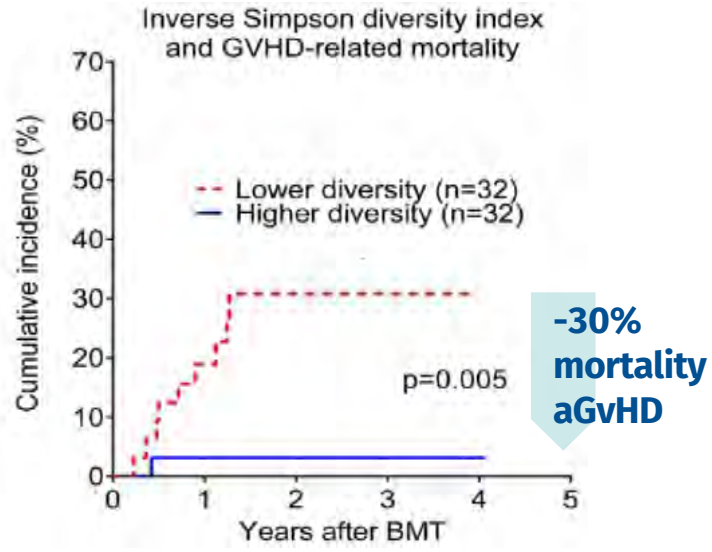
… specifically in cancer therapy, a low gene count is associated with…

… lesser overall survival in patients receiving allogenic stem cell transplants



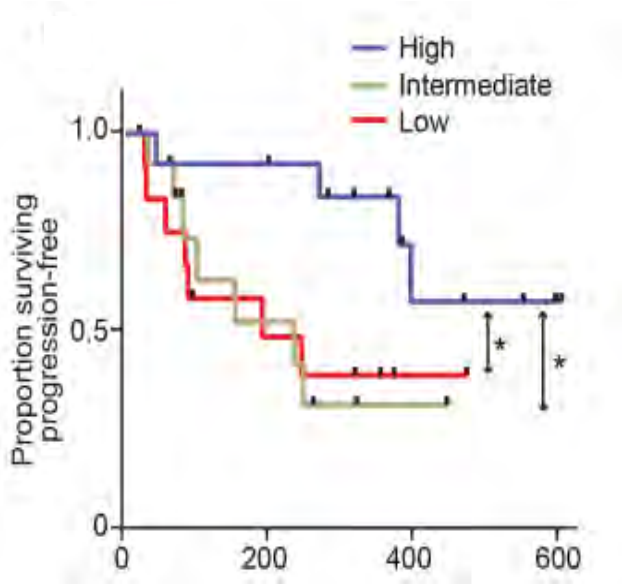
Peled et al., NEJM 2020

… higher mortality by acute Graft versus Host Disease



Jenq et al., BBMT 2015

… lesser progression-free survival with immunotherapy in melanoma and in lung cancer



Gopalakrishnan et al., *Science* 2018

Modulating the microbiome opens new horizons towards personalized holistic approaches

1. Symbiosis: Human tissues and organs interact with the microbiota, with mutual benefits
2. Alteration of symbiosis comes with loss of protective functions
3. The gut microbiota is a relevant target for the maintenance and restoration of host-microbes symbiosis
4. Reconditioning and modulating host-microbes symbiosis will be a major line of innovation of the microbiome-medicine of the future, from prevention of onset of mild chronic disease to treatment of severe iatrogenic conditions i.e. in oncology.
5. Key features of a healthy host-microbes symbiosis can be restored by MaaT Pharma's strategy using *Microbiota as a Therapy*.

Thank you for your attention

Nicolas Lapaque,
Joël Doré,
Hervé Blottière,
Catherine Juste,
Christel Béra-Maillet,
Jean-Marc Lelièvre,
Alexandre Jamet,
Maarten van de Guchte,
Stanislas Mondot,
et al....

MetagenoPolis

Alexandre Cavezza
S. Dusko Ehrlich
Joël Doré
Hervé Blottière
Mathieu Almeida
Christian Morabito
Hugo Roume
Florence Haimet
Nicolas Pons
Emmanuelle Le Chatelier
Véronique Lejard
Magali Berland
et al....

MetaHIT consortium

Karine Clément (ICAN, CHU Pitié Salpétrière)
& MetaCardis Consortium
Harry Sokol (Hôpital Saint Antoine)
Sven Pettersson et col. (Karolinska Institute)
Maria Rescigno (IEO, Milan)
Oluf Pederson (Novo Nordisk Fundation, Copenhague)
Francisco Guarner (Val Hebron Hosp., Barcelone)
Mark Morisson (U of Queensland, Brisbane)

Homo symbiosus

Driving value in the microbiome space

Hervé Affagard

CEO

Pioneering innovative microbiome therapy for the benefit of millions of patients fighting cancer

Leveraging the complexity of the microbiome

Pioneering a **full ecosystem approach** to restore host/microbiome **immune symbiosis**, based on proprietary **AI** and manufacturing capacities

Manufacturing versatility

cGMP manufacturing scalability for both native and co-fermented products and building of a new plant

Oncology focus

Addressing **high unmet needs** in the hemato-oncology and immuno-oncology therapeutic areas

Established proof of concept

First company to reach Phase 3 testing for a microbiome product in oncology globally

Balanced pipeline focused on oncology

Microbiome Ecosystem Therapies (MET)

gut Print

cGMP Platform

Native

MaaT013

- ✓ **High diversity**
- ✓ Full ecosystem
- ✓ **Butycore™** (anti-inflammatory)

MaaT033

Co-fermented

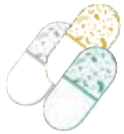
MaaT03X

- ✓ **Indication-specific designed ecosystem** (from clinical data)
- ✓ Innovative **ecosystem co-fermentation technology**

[1] **Butycore**: Group of 15 different genera known to produce short-chain fatty acids with anti-inflammatory properties

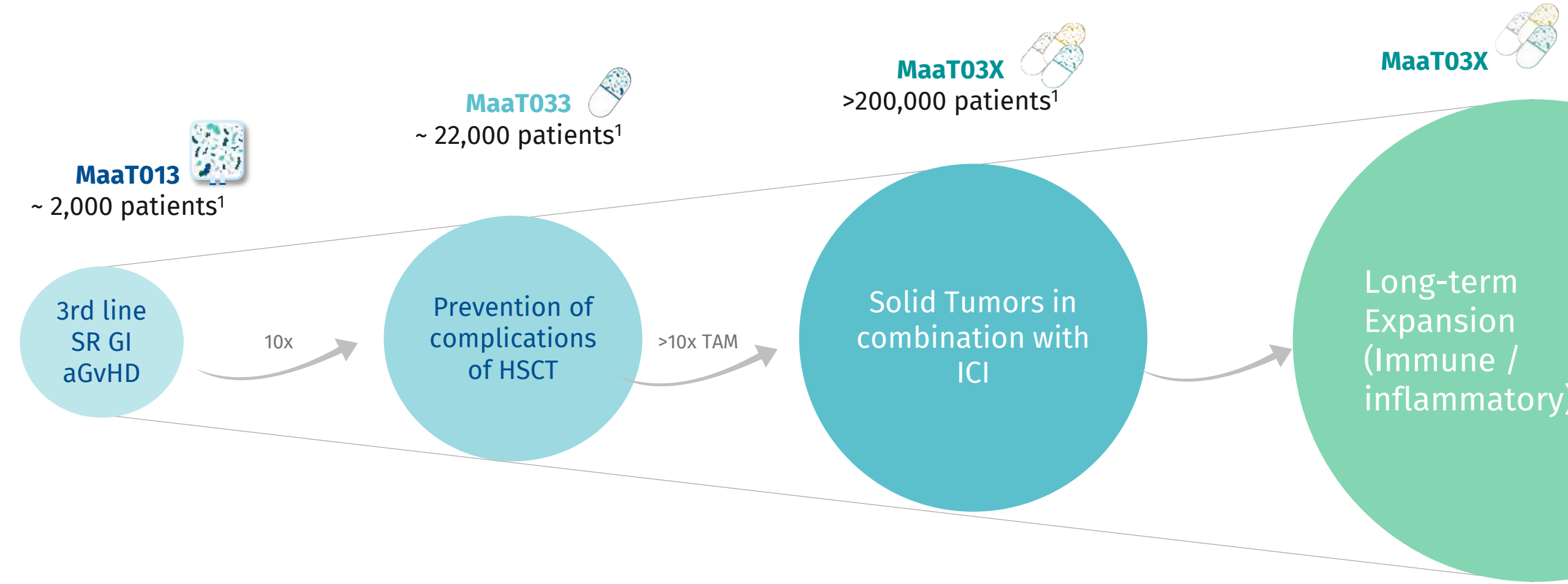
[2] *Sponsored by AP-HP*

Delivering on our objectives

		Milestones announced at IPO *(Nov 2021)*	Status
Onco-hematology	 **MaaT013 (pooled enema)** *FDA & EMA Orphan Drug Designation*	*Launch of the first Phase 3 trial in oncology in the world*	✓
	 **MaaT033 (pooled capsule)** *Post allo HSCT*	*Completion of Phase 1b trial and positive preliminary safety and engraftment data*	✓
Immuno-oncology	 **MaaT013 (pooled enema)** *Improving ICI responses in metastatic melanoma*	*Launch of Phase 2 trial* - POC*	✓
	 **MaaT03X (fermented capsule)** *Undisclosed indications*	*Preclinical activities to enter clinical development in H1 2023*	✓
cGMP production	 **Increasing cGMP production capacities** Skyepharma	*Partnership with Skyepharma to build the first and largest exclusive Microbiome Ecosystem Therapies facility in Europe*	✓

** Sponsored by AP-HP*

Looking ahead: addressing growing market opportunities with severe medical need



[1] *EU5, US, and Japan*

Hemato-Oncology

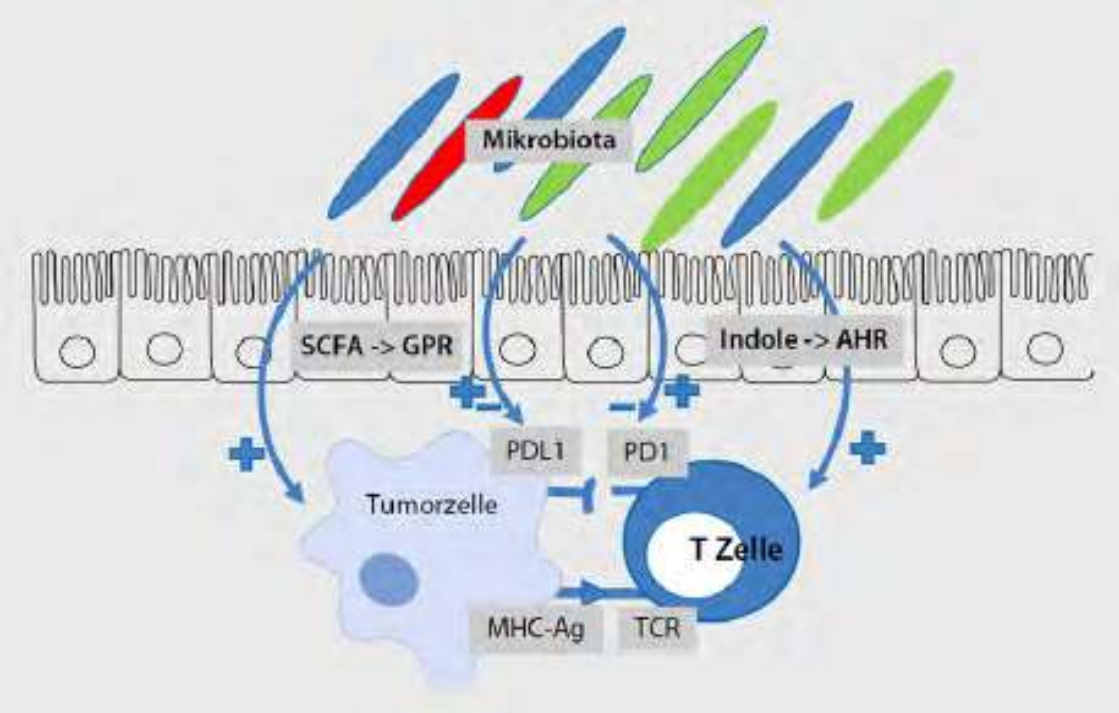
Microbiome: a new frontier in hematological cancer treatment?

Pr. Ernst Holler

Senior Professor on Clinical and Experimental Allogeneic SCT, Dept of Internal Medicine 3, University Hospital Center Regensburg, Germany

R&D Day June 7, 2022

The Concept



Holler et al, Gastroenterologe und Best Practice Onkologie 2019

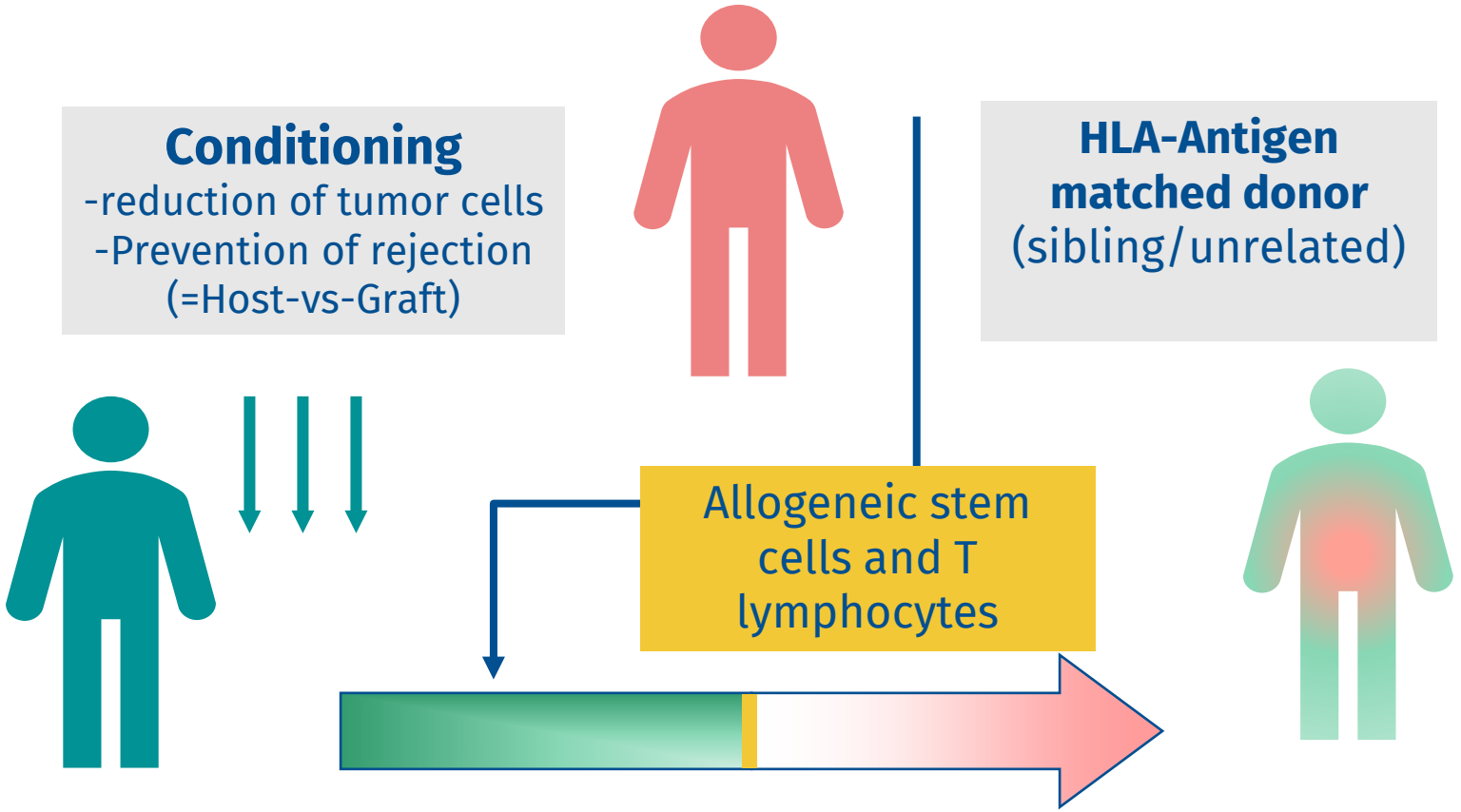
Ménage à trois:

Microbiome
(metabolites of commensals)

Immune cells

Tumor cells

The Principles of allogeneic Stem Cell Transplantation (SCT)



Aplasia -> Hematopoietic reconstitution
<- Immunosuppressive and anti-infectious prophylaxis->

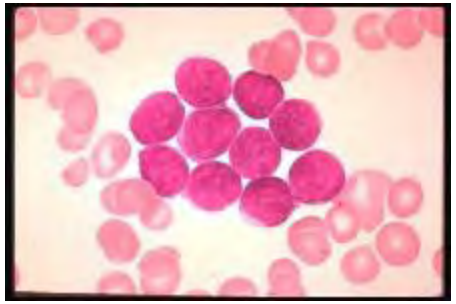
Graft-versus Host (GvH) and Graft-versus-Leukemia (GvL) reactions by donor cells

The clinical problem:

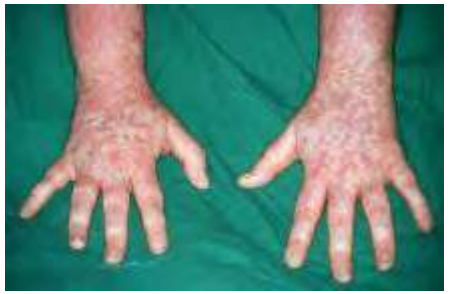
- Only 50 – 70% of patients can be cured
- Treatment related mortality by GvHD (20-30%) and morbidity
- Mortality increases to 80% if GvHD is **refractory** to treatment

+

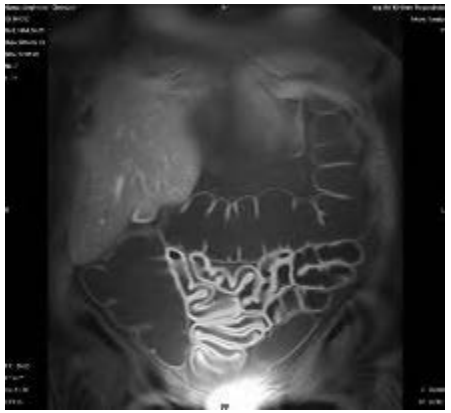
Relapse of underlying disease
(10 -40%) due to lack of GvL



GvL



GvH skin



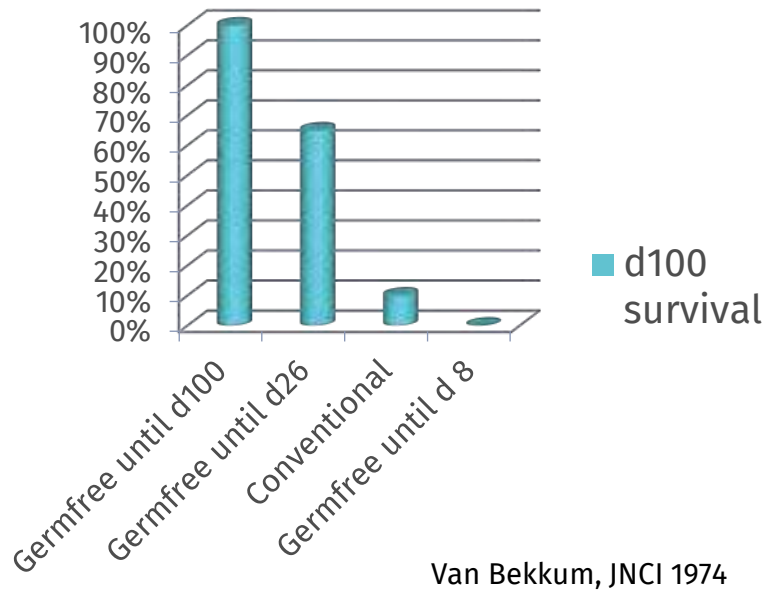
GvH gut

Gut microbiome: an old player in allogeneic hematopoietic stem cell transplantation (HSCT)

Microbiota and complications of stem cell transplantation 1980-2000

No GvHD observed in germ-free mice

D100 survival after BMT in mice



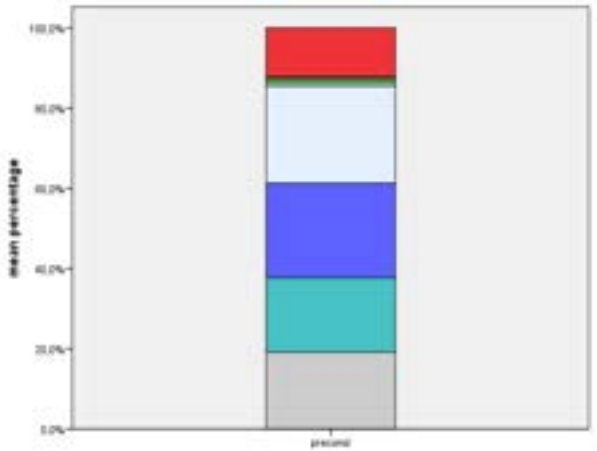
Van Bekkum, JNCI 1974

- **Comparable results:**
  - Rhesus monkeys (van Bekkum 1975)
  - Dogs (Vriesendorp 1981)
  - Complete decontamination in children (JM Vossen,1979; JM Vossen et al, PLOSone 9,9;2014)

Microbial “decontamination” and antibiotic prophylaxis was standard practice until 2015…

A new era in HSCT : Molecular microbiota analysis revealed severe dysbiosis in HSCT patients

Dysbiotic “scar” in leukemia patients

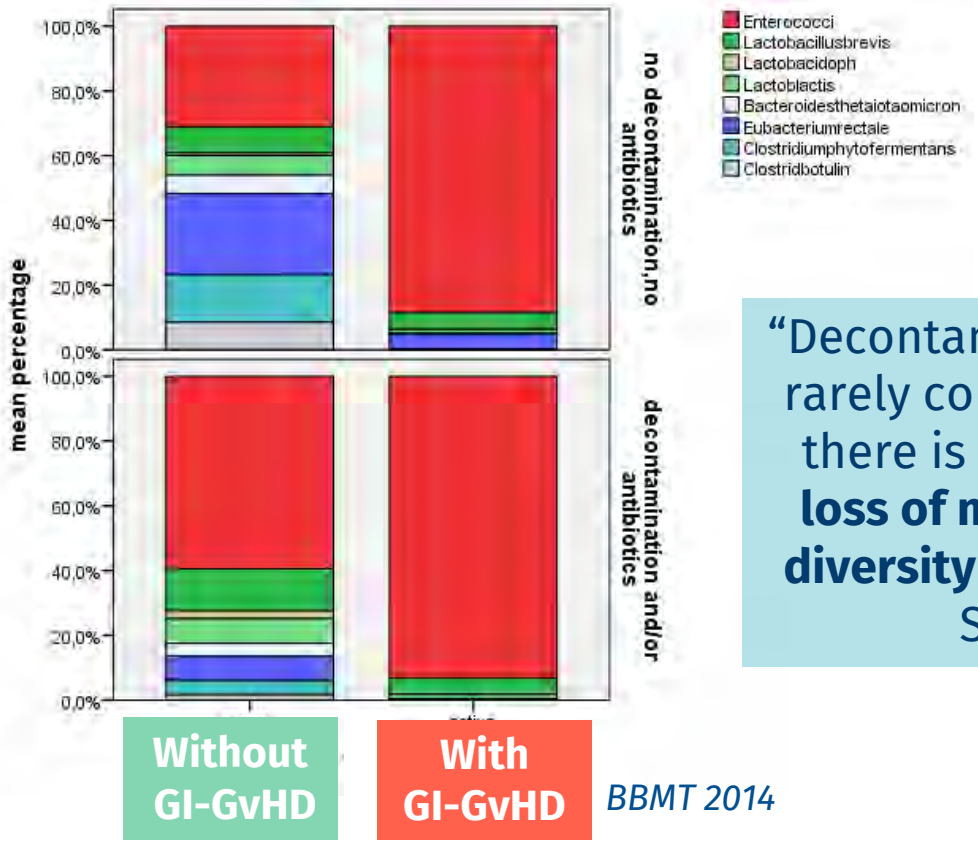


Patient before transplantation

Non cultural 16s rRNA analyses allowed detection of >60% new non cultivated species:

No Antibiotics

With Antibiotics



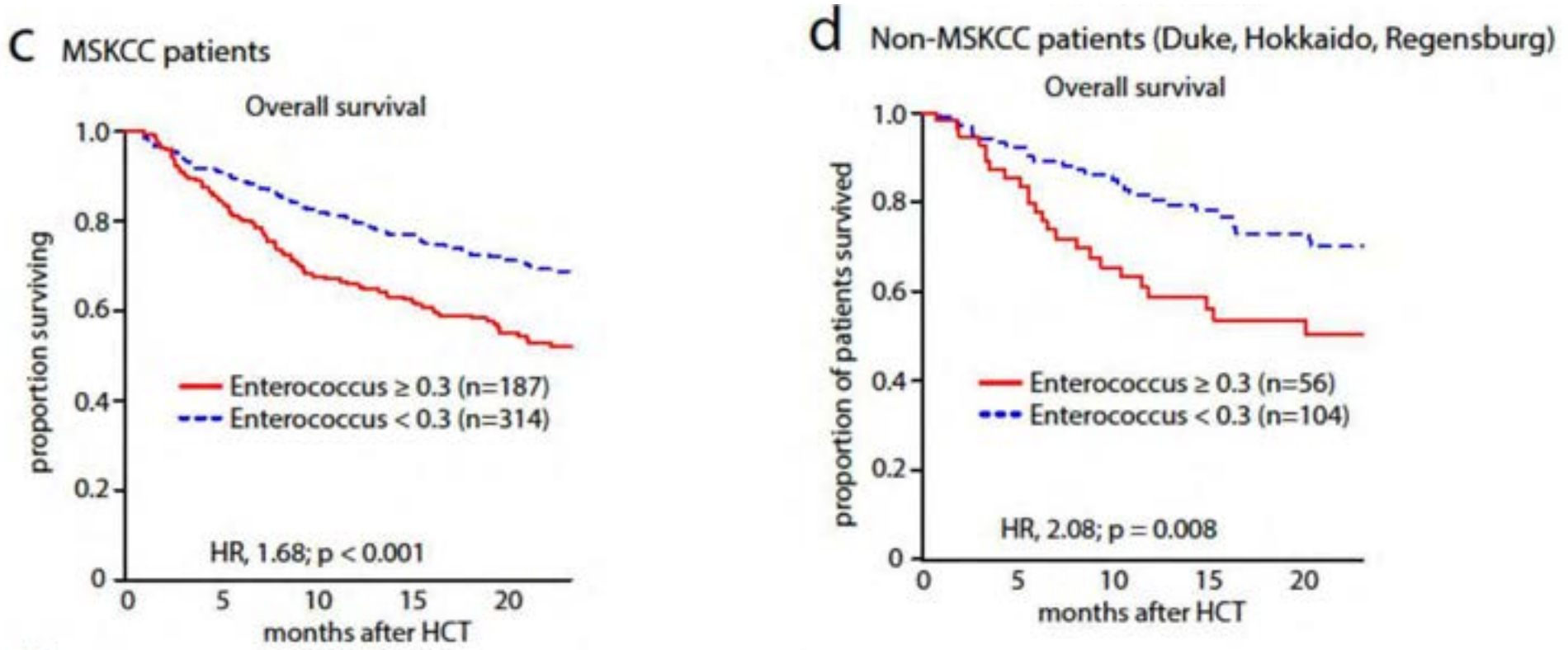
BBMT 2014

“Decontamination” is rarely complete but there is a **massive loss of microbiota diversity** early after SCT

A universal finding: loss of intestinal commensal microbiota affects outcome after HSCT across centers 1/2

(New York, Duke, Hokkaido, Regensburg)

Lactose drives enterococcal expansion to promote GvHD

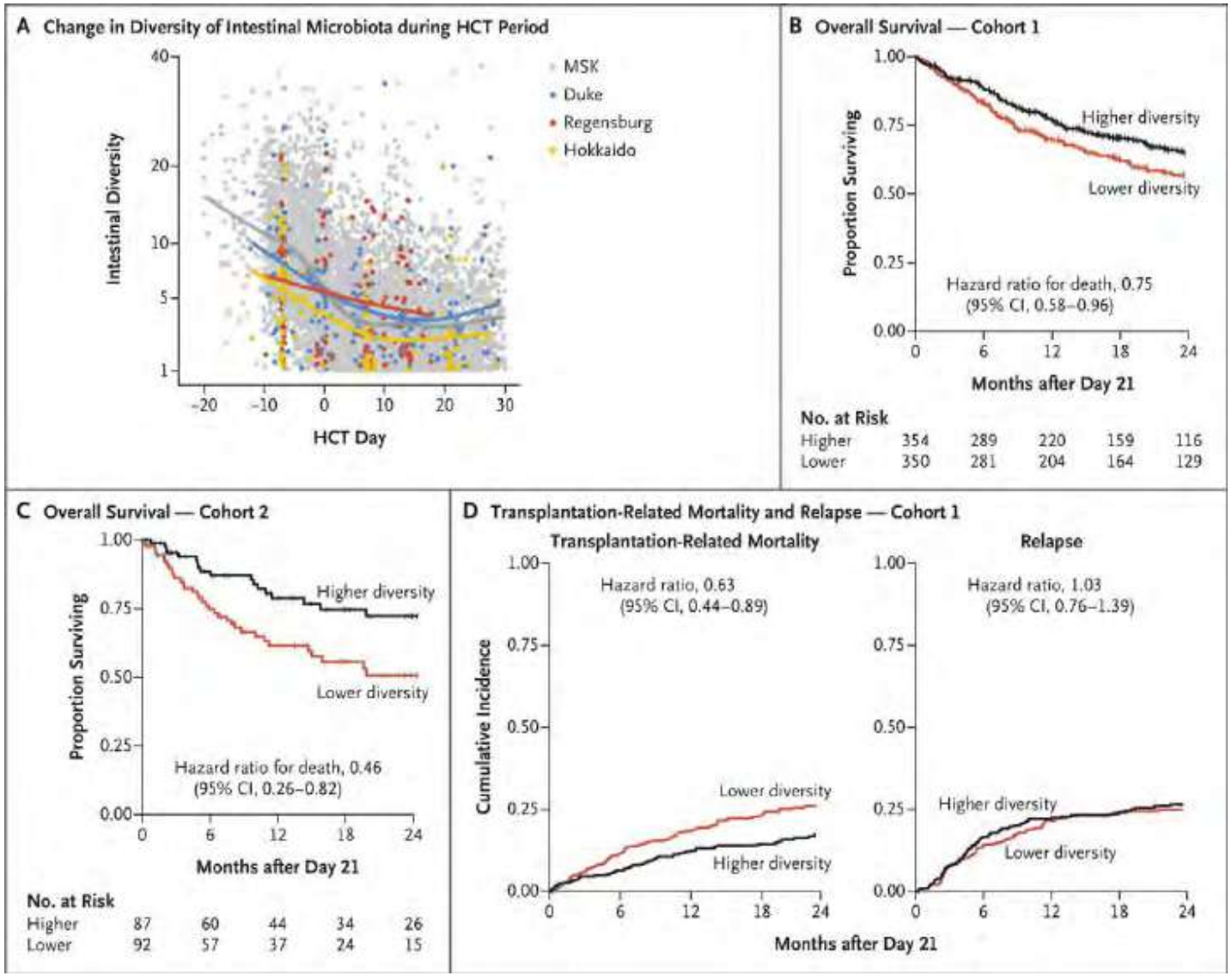


Ch Stein-Thoeringer et al, Science 2019

A universal finding: loss of intestinal commensal microbiota affects outcome after HSCT across centers 2/2

(New York, Duke, Hokkaido, Regensburg)

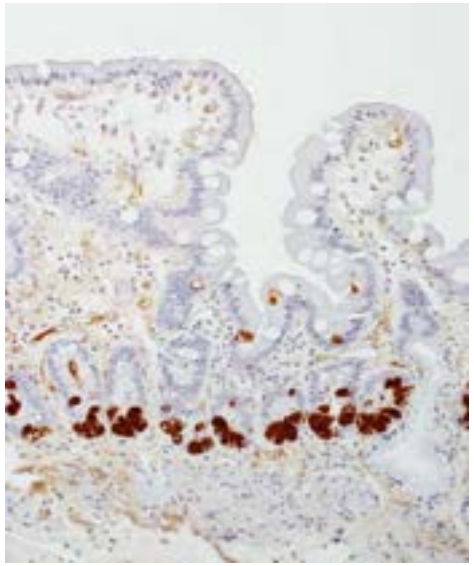
Microbiota as Predictor of Mortality in ASCT a multicenter observational study



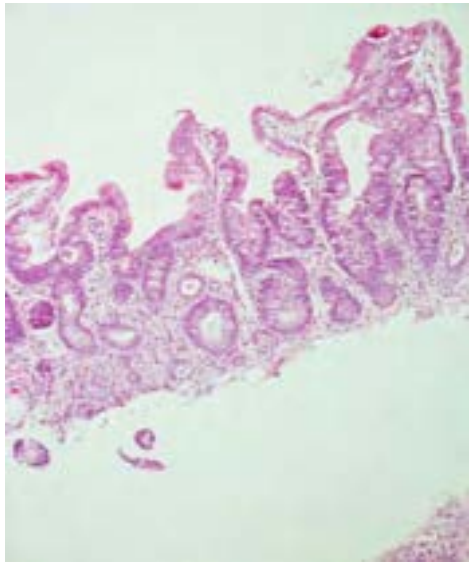
Peled J et *al*, NEJM 2020

Causes of dysbiosis (1): Paneth cell damage by GvHD itself

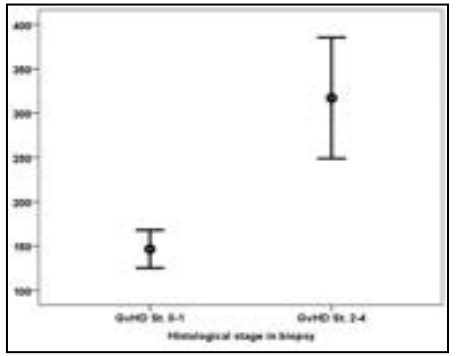
No GvHD:
no crypt destruction



GvHD: crypt destruction

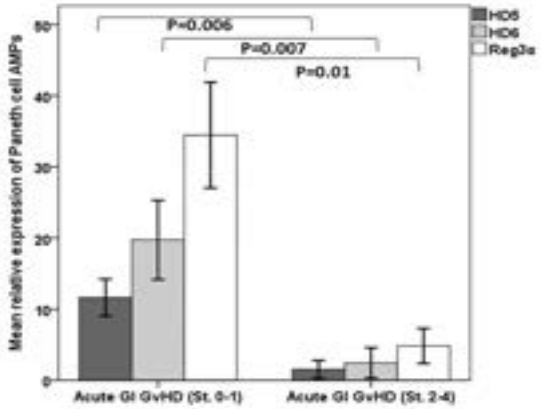


Corresponding systemic Reg3a serum levels



Blood

GvHD



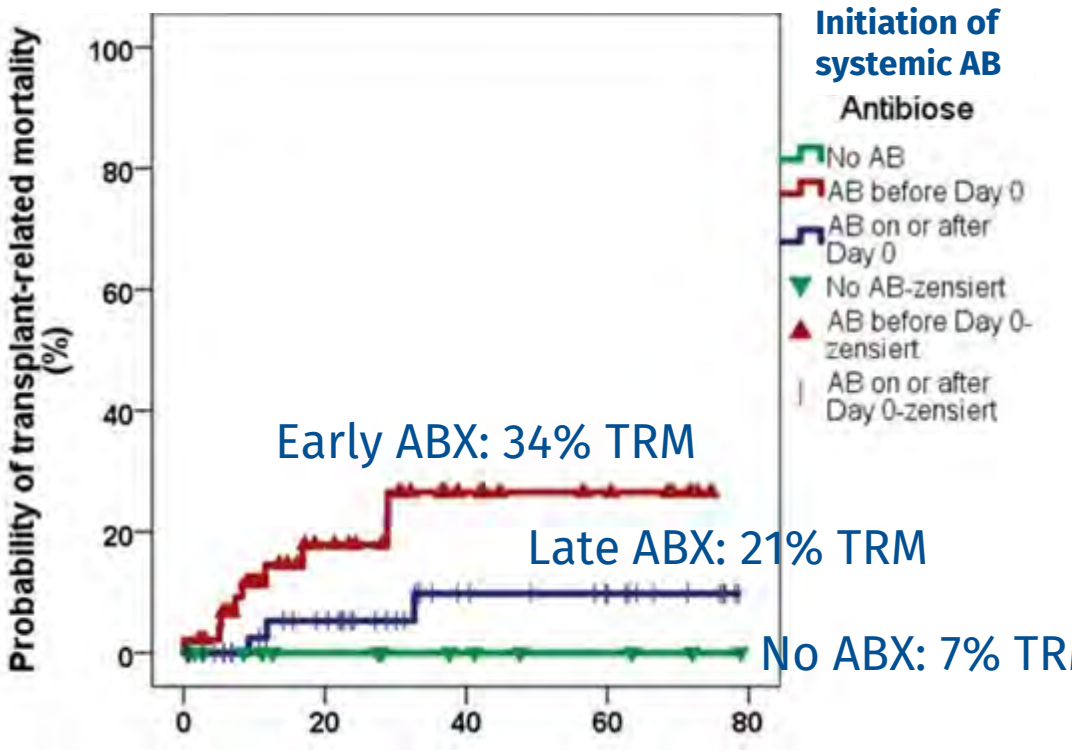
GI tract

GvHD

Levine et al, Blood 2013, Weber et al, PLoSone 2017

Expression of antimicrobial peptides (alpha-Defensins 5 and 6, Reg3a) in small bowel biopsies

Causes of dysbiosis (2):
Early and prolonged use of broad-spectrum antibiotics



Weber D, Holler E, van den Brink M, BBMT 2017

Retrospective analysis of 621 patients from 2 centers (MSKCC, Regensburg):

Early vs late AB: p=0.001

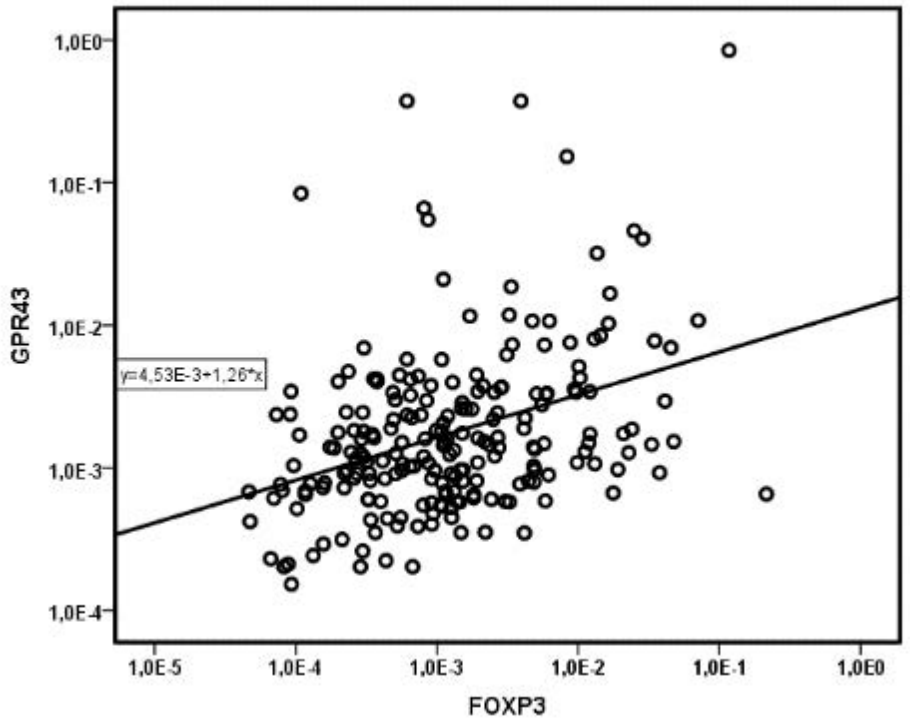
Early vs no AB: p<0.001

- Early antibiosis was associated with more severe **loss of commensal Clostridia**

- Early antibiosis was an **independent risk factor** and not associated with clinical know risk factors of poor outcome

Consequences of antibiotic treatment: Loss of protective metabolites (SCFA like Butyrate and Indoles) and subsequent loss of protective immunoregulation in GvHD tissues

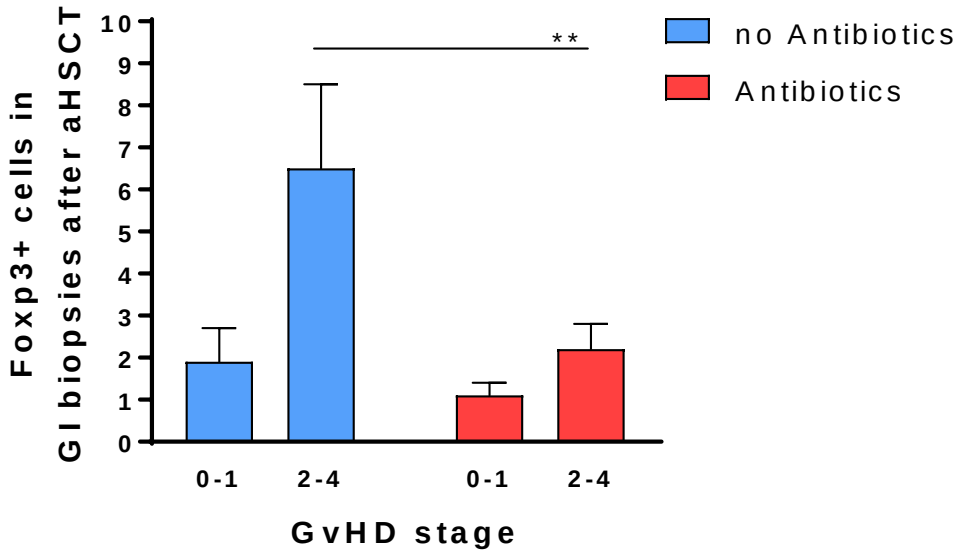
Correlation of Butyrate receptors with regulatory T cells (p 0.005)



Dysbiosis prevents induction of regulatory T cells!

Broad spectrum iv ABX at biopsy

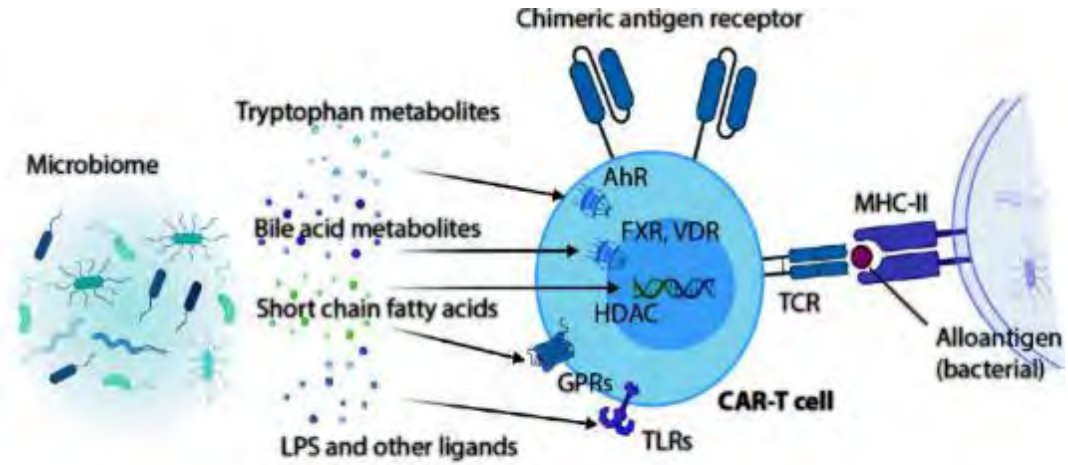
No (30) Yes (54)



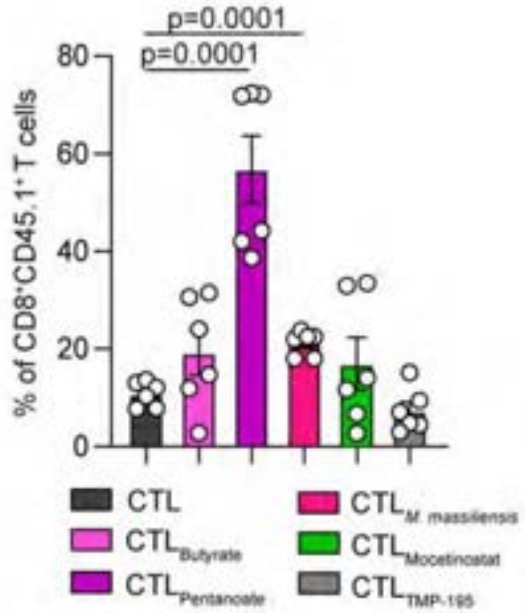
Antibiotics prevent increase in regulatory T cells (p 0.01)

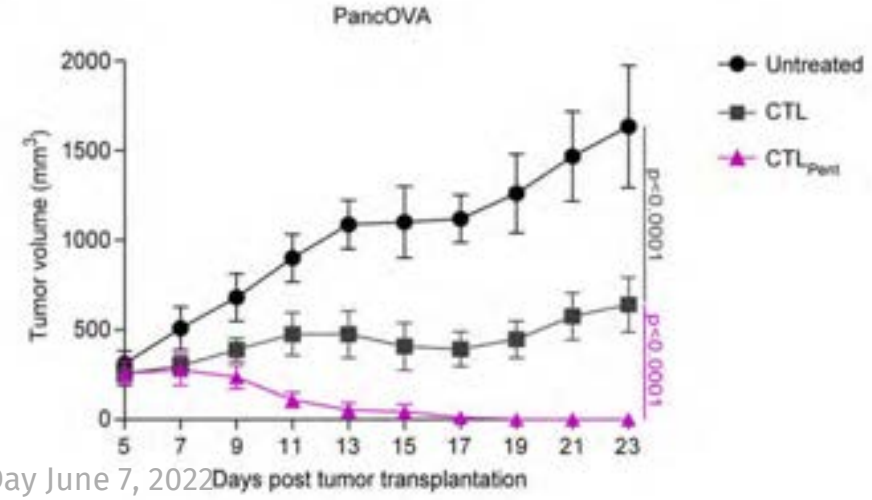
Ghimire S et al, Frontiers of Immunology 12, 2021

And the next association: Microbiota derived SCFA improve antigen-specific T cell and CAR-T cell9 treatment



The concept of microbiota –CAR-T cell interaction (Schubert ML et al, Front.Immun.2021; 12)





Some proof:

Luu M, Riester Z, Baldrich A, et al. Microbial short-chain fatty acids modulate CD8⁺ T cell responses and improve adoptive immunotherapy for cancer. *Nat Commun.* 2021;12(1):4077.

Conclusion

Microbiota restoration?

SCFA

Microbiota

Indoles

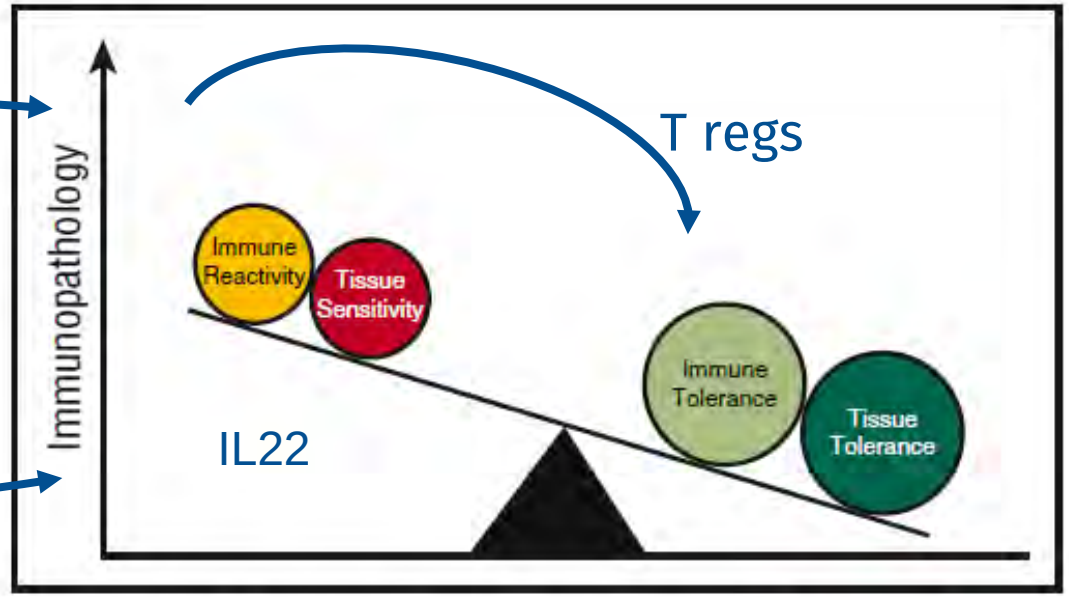


Figure 2. Tissue tolerance interacts with immune tolerance to mediate immunopathology.

The concept of tissue tolerance P Reddy, Blood Perspective Blood 2017; 129 (13)

Right balance needed

MaaT013, first-in-class Microbiome Ecosystem Therapy in Phase 3 in Graft-vs-Host-Disease

Dr. Florent Malard
Professor of Haematology

Emilie Plantamura
Head of clinical development

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R&D Day June 7, 2022

aGvHD

Results from Phase 2 Clinical Trial and Early Access Program

Pr. Florent Malard

Professor of Haematology

R&D Day June 7, 2022

An urgent medical need in acute Graft-vs-host-Disease (aGvHD)

Intestinal dysbiosis is associated with higher mortality in hemato-oncology

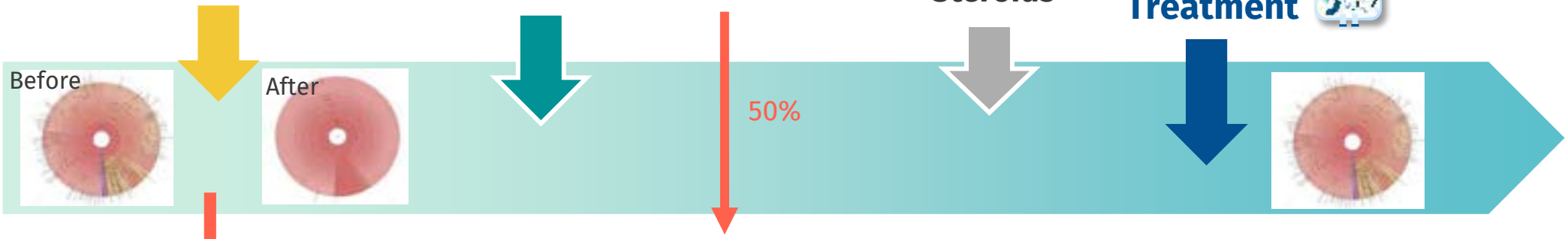
Chemotherapy
Antibiotics
Irradiation,
Immunosuppressors

Allogenic Hematopoietic Stem Cell Transplantation (allo-HSCT)
~ 22 000 patients/yr[1]

Steroids

MaaT013 Treatment

Patients with liquid tumors
(Leukemia, lymphoma, myeloma…)



Loss of diversity (dysbiosis)

- Infections
- Complications

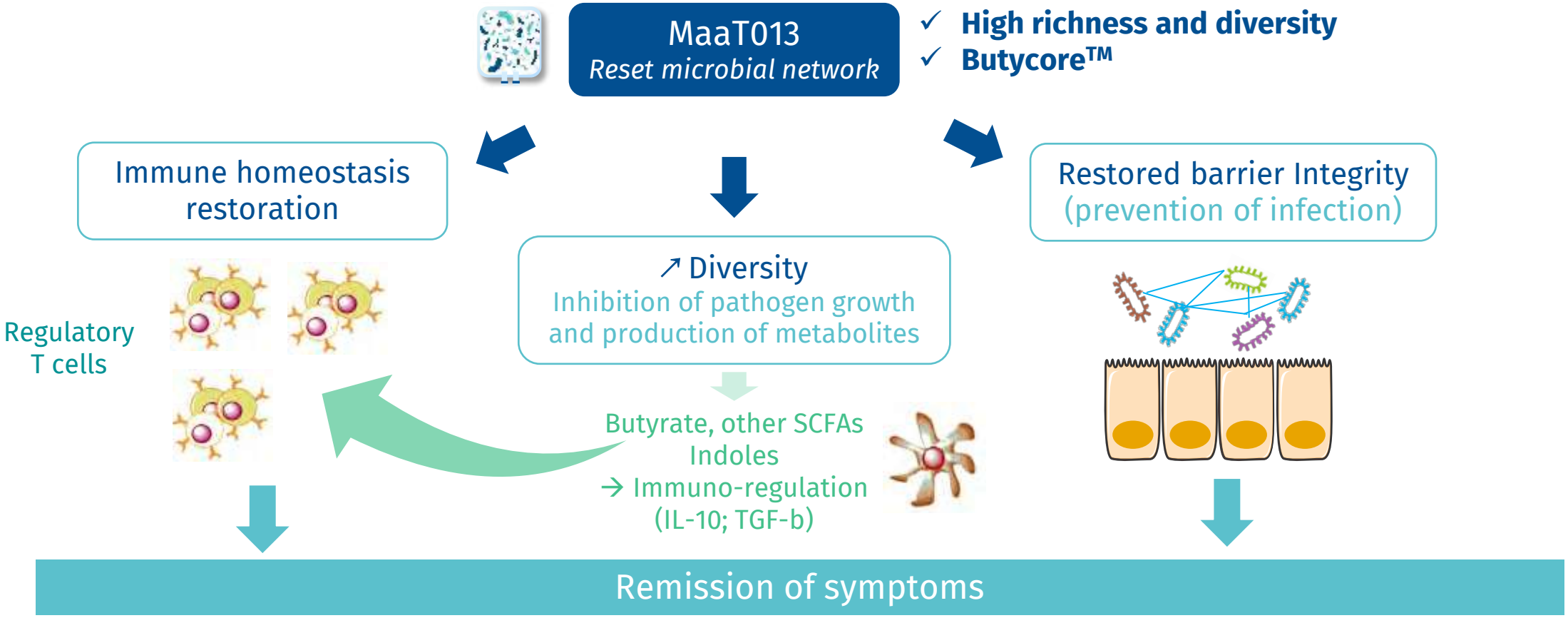
Acute Graft-versus-Host Disease (aGvHD)

~ 10 000 patients/yr[1]

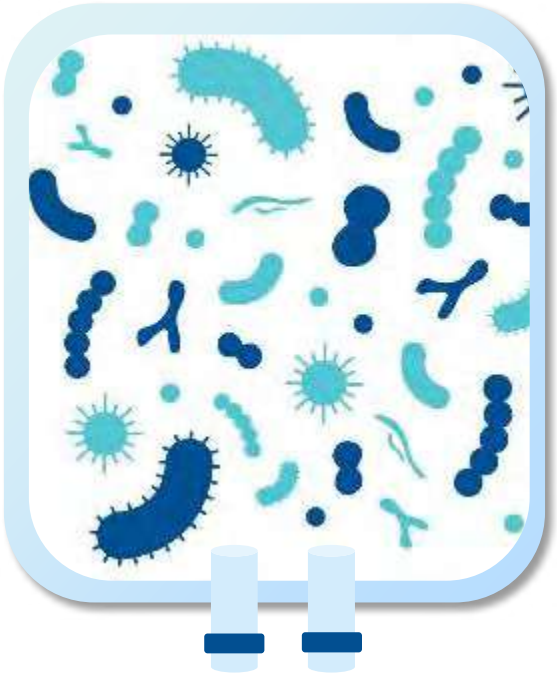
~ 50% steroid-resistant
~ 60% with GI symptoms
~ 70-90% 1-yr mortality

1. EU5 + US : (~ 20 500 primary procedures with an additional 7%-10% recurring)

MaaT013 aims to restore interaction between the microbiome and the immune system to treat aGvHD



MaaT013: restore the microbiome to *cure* acute Gastro-Intestinal graft vs. Host disease.



Characteristics
Pooled microbiota: a high-richness, high-diversity, full ecosystem, containing Butycore™

Administration
3 doses *(150 mL enema bag)*

Available Clinical Data
- ✓ HERACLES Phase 2 Clinical Trial, n=24, 2L
- ✓ Early Access Program, data on n=52, 3L-6L, program still ongoing
- 100 patients total treated to date

Efficacy evaluation (GI ORR at Day28)
Complete response, Very Good Partial Response, Partial Response

Current indication
Gastrointestinal Acute Graft-versus-Host Disease

MaaT013 has received Orphan Drug Designation from FDA and EMA

Two complementary approaches generating data on MaaT013

Phase 2 clinical trial - HERACLES

- Phase 2 clinical trial HERACLES (NCT03359980)
  - 24 patients, 4 countries
- Gastro-intestinal aGvHD grade III-IV
- Steroid-refractory
- 3 doses of MaaT013 as a monotherapy over 2 weeks
- 2nd line of treatment

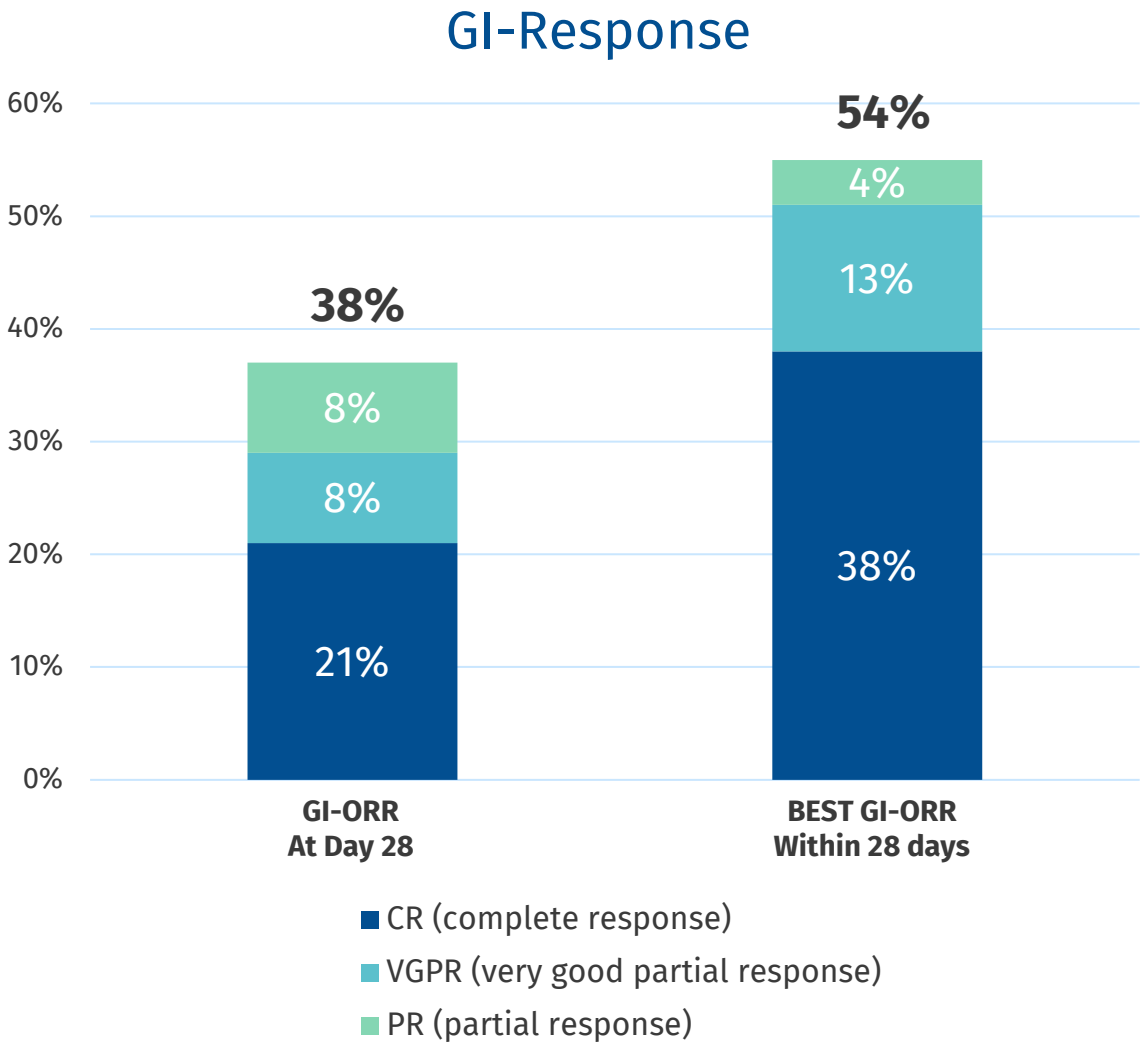
Early Access Program (ex « ATU »)

- Authorized par the French regulator (ANSM)
  - 52 patients, France
- Gastro-intestinal aGvHD grade II-IV
- Steroid-refractory or steroid-dependent
- 3 doses of MaaT013 as monotherapy or in combination over 2 weeks
- After 1 to 6 lines of treatment

Clinical evaluation

✓ GI Response Rate at Day 28
✓ Overall Survival at 12 months

HERACLES Phase 2 Clinical Trial (N=24)
Promising results in a very severe population (grade III-IV)

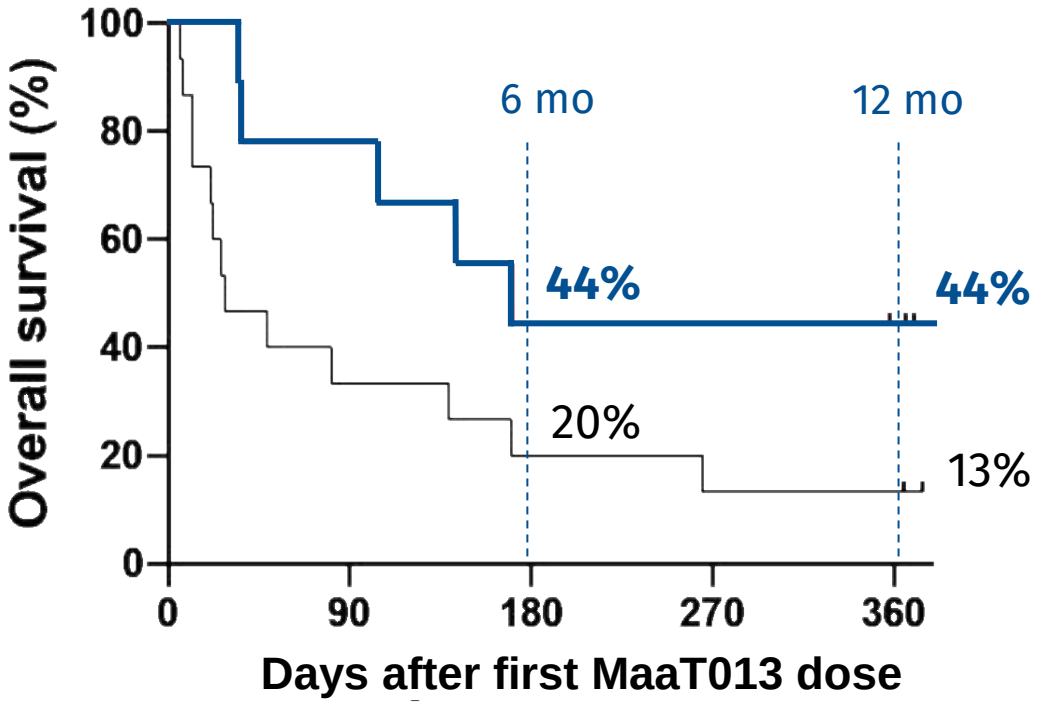


- 2nd line
  - 96% grade III, 4% grade IV
  - 100% steroid-resistant (SR)
  - Gastrointestinal (GI) predominant
- Very good safety and tolerability profile
  - 39 adverse events reported within 24 hours of administration
  - Safety signals consistent with adverse events profile expected in this fragile patient population
- GI-CR and VGPR strongly correlate with survival

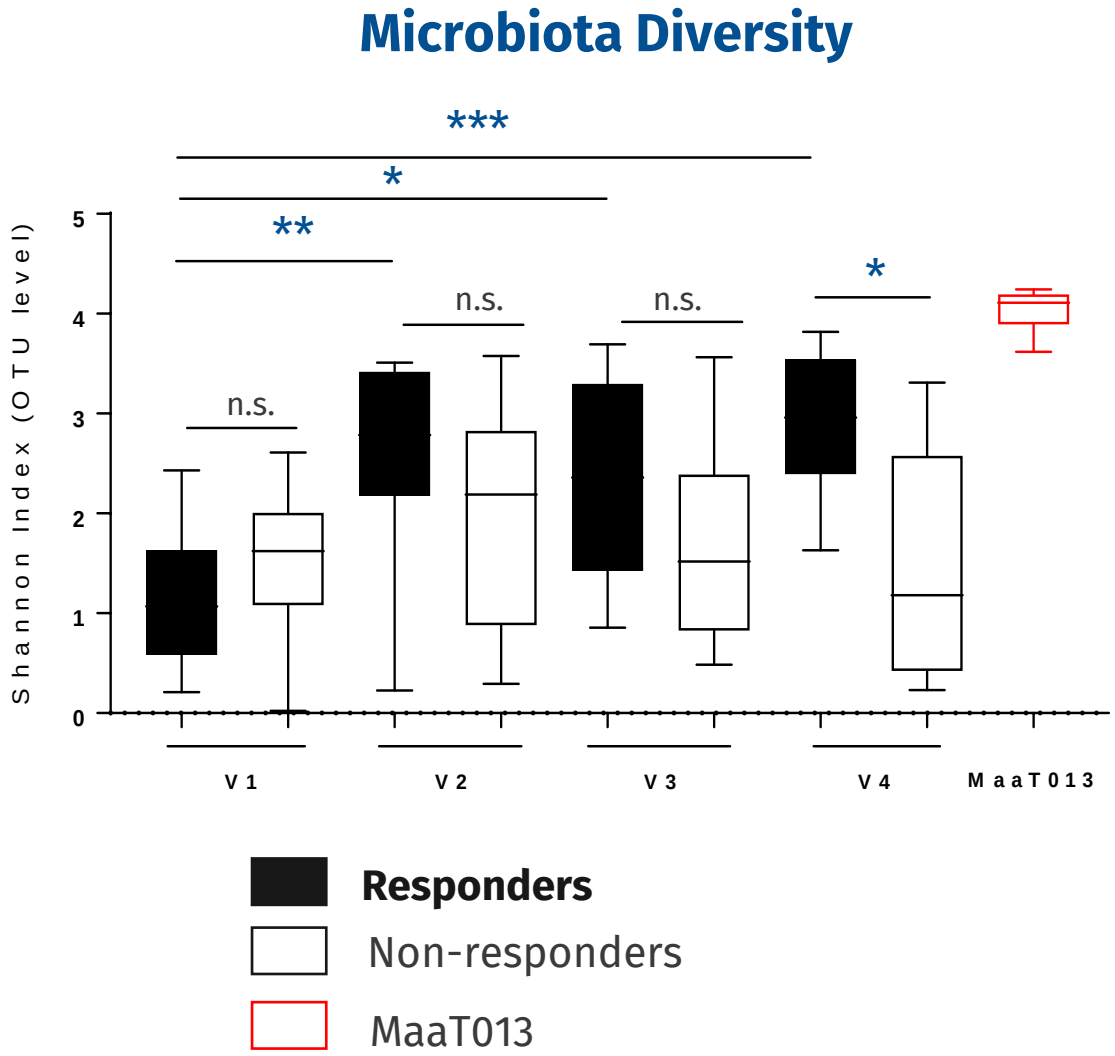
HERACLES Phase 2 Clinical Trial
MaaT013 increases Responders' survival

Overall Survival Rate

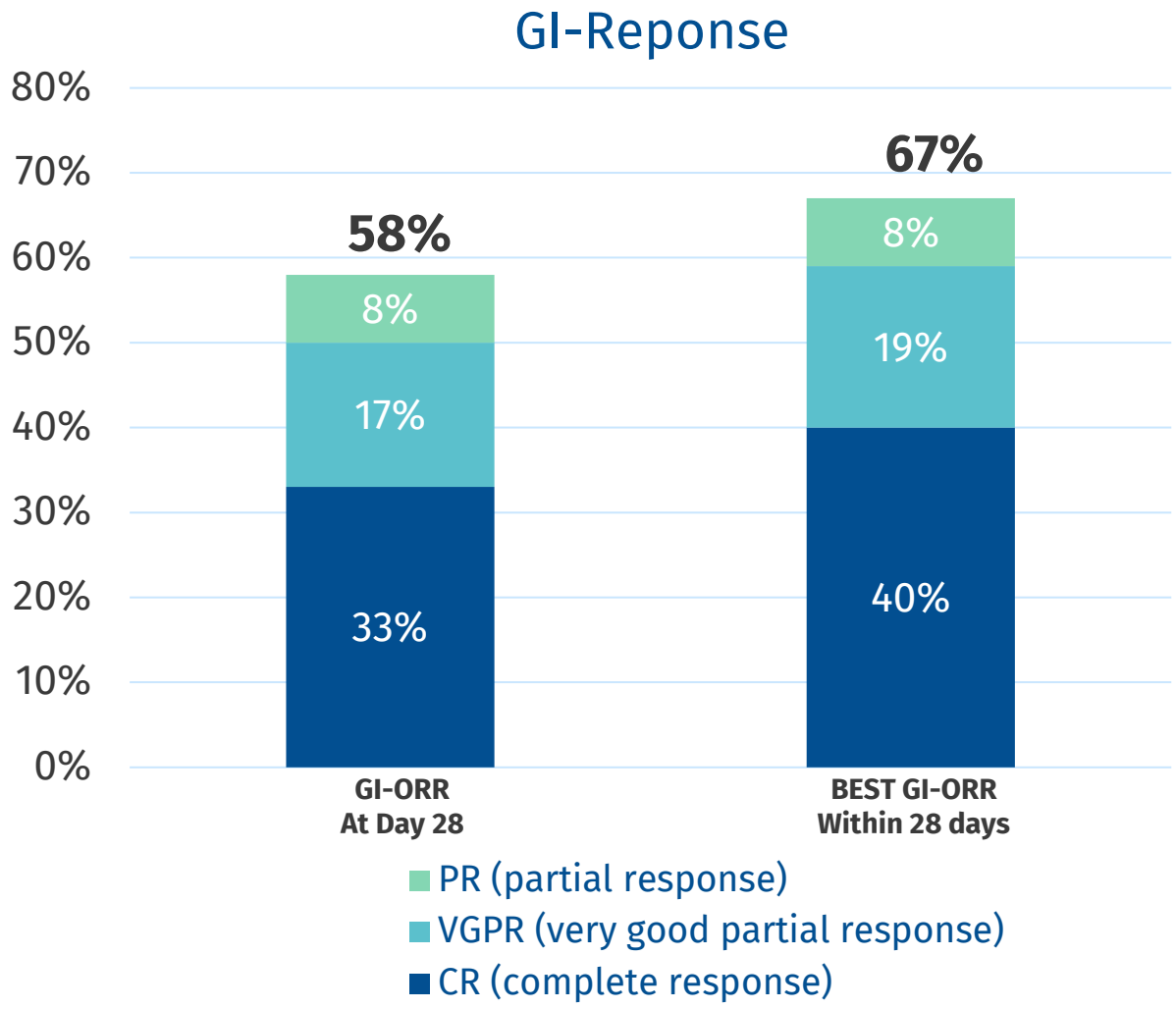
Responders vs. Non responders



HERACLES: MaaT013 increases Responders' gut microbiome diversity



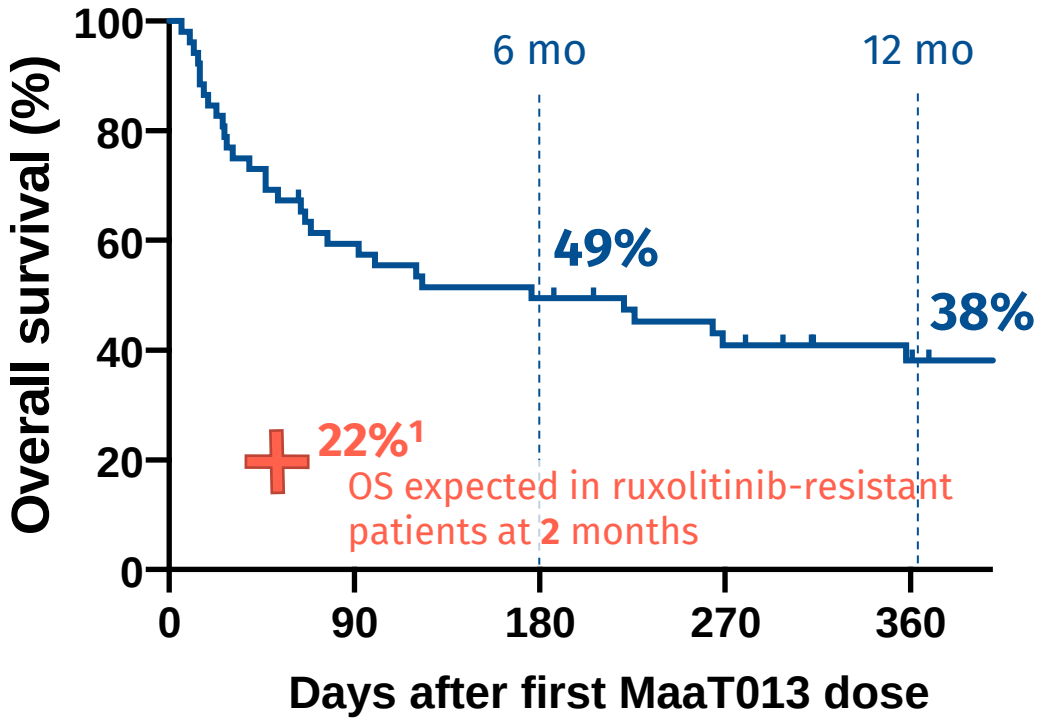
Early Access Program (EAP):
A promising confirmation in a more diverse population



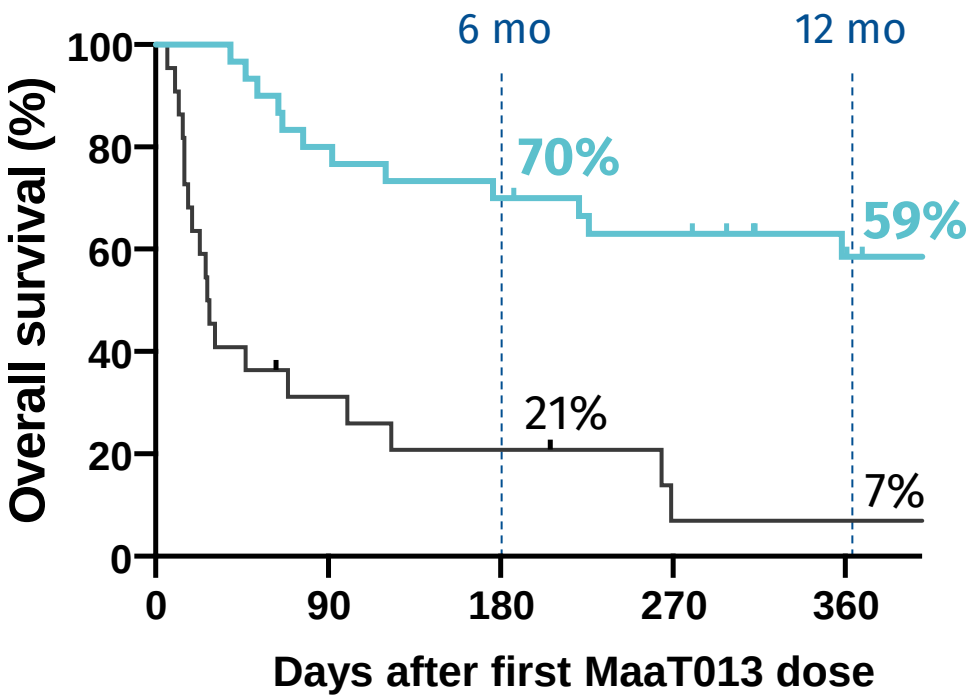
- 3 doses , 2nd to 7th line (median 4)
- 52 patients
  - 83% steroid-resistant / 17% steroid-dependent
  - 94% grade III
  - 100% GI involvement
  - 77% have received ruxolitinib
- Good tolerability and safety profile in a fragile population
- GI-CR and VGPR strongly correlate with survival

Early Access Program (EAP):
Very promising overall survival results at 6 mo and 1 year

Overall Survival Rate
All patients



Overall Survival Rate
Responders vs. Non responders



Median of follow-up in alive patients: 361 days (63-731)

1. Data from REACH 1 study

Promising clinical results supporting the launch of pivotal Phase 3

- MaaT013 increases Responders' microbiome diversity.
- The clinical response to MaaT013 translates in increased overall survival in both patient populations tested.
- Overall safety is good
  - SAEs were consistent with the adverse events profile expected in this fragile, immuno-compromised patient population.
- Data strongly supports the hypothesis that restoring gut microbiome diversity can significantly impact survival outcomes in aGvHD patients.

Acknowledgments

Patients, Caretakers and Healthy Donors involved

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- Karin Bilger (CHU Strasbourg)
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- Delphine Martineau (CHU Bordeaux)
- Helene Labussière-Wallet (CHU Lyon)
- Marie-Anne Couturier (CHU Brest)
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- Sylvain Chantepie (CHU Caen)
- Patrice Ceballos (CHU Montpellier)
- Mohamad Mohty (Hôpital Saint-Antoine, AP-HP)

ARES

ARES Study, a pivotal Phase 3 clinical trial investigating MaaT013 in aGvHD

Emilie Plantamura

Head of clinical development

ARES, a pivotal study to treat GI-aGvHD

ARES

- International study incl. **6 to 8 countries** with first-time countries working with MaaT013 – up to 50 reference centers
- **Pivotal single arm trial** of MaaT013 as 3rd line (steroid- & ruxolitinib-refractory patients)
- 29 months total duration
- Up to one year follow-up
- Est. **75 patients**
- **First patient treated in March 2022** in Spain

ClinicalTrials.gov Identifier: NCT04769895

Countries with active sites

Potential additional countries

Targeted timelines ARES trial

ARES

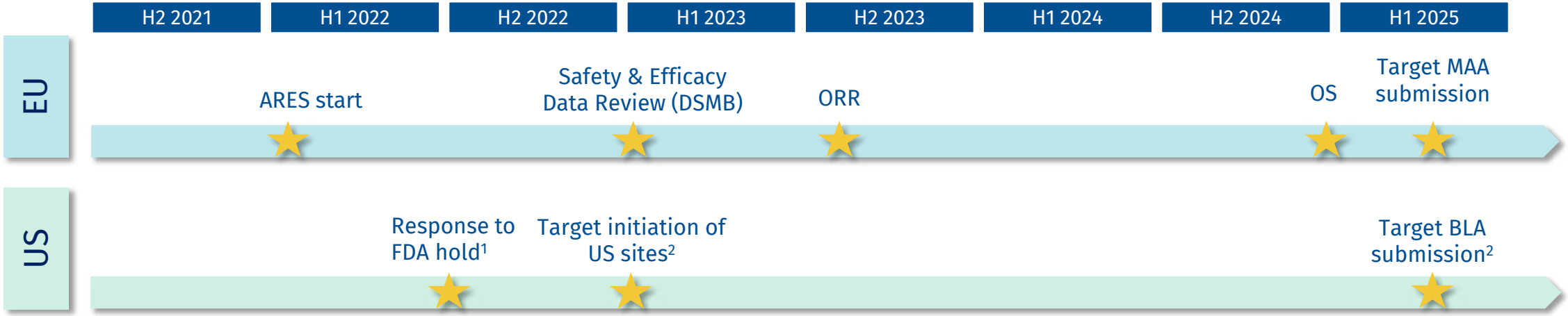
EUROPE :

- ✓ CTA approved in 3 European countries.
  Expected to expand to additional EU countries

USA:

- FDA requested further information – on clinical hold.

→ Submitted a request for a "Type A" meeting to the FDA by the end of 2021, with the support of well-respected regulatory consultants, aiming to resolve the clinical hold and expand ARES to US sites. Exchanges ongoing.



[1] Subject to regulatory agency's review timelines [2]Subject to the lifting of the FDA clinical hold ;
ORR: overall response rate ; OS: overall survival ; MAA: Market approval application; BLA: Biological License Application; DSMB: Data and Safety Monitoring Board

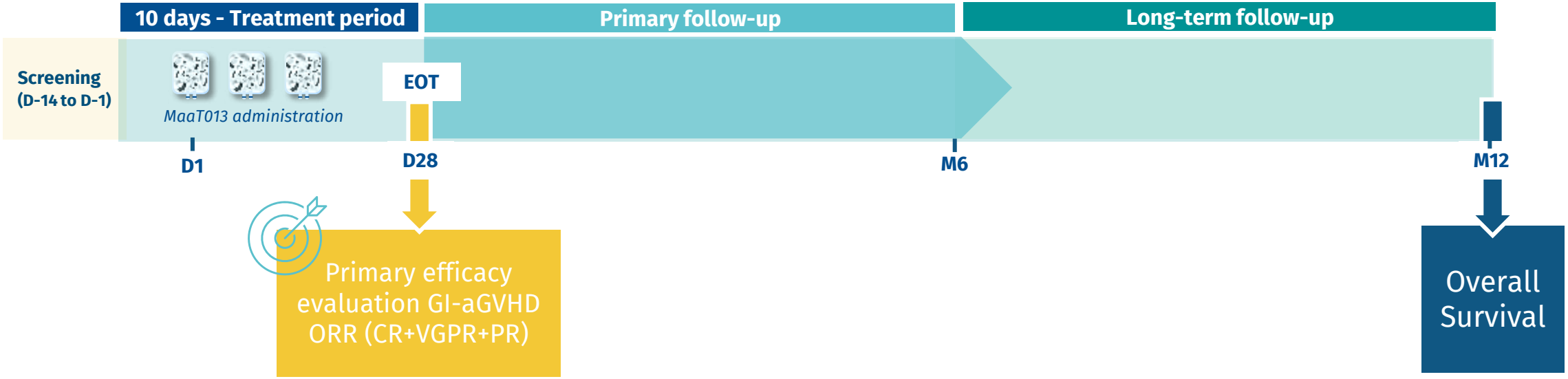
ARES, a pivotal Phase 3 trial to treat aGvHD in 3rd line

ARES

Patients with SR-GI-aGvHD

Inclusion criteria

- ✓ **Refractory or intolerant to ruxolitinib**
- ✓ Refractory to corticosteroids
- ✓ aGvHD with GI symptoms
- ✓ Allo-HSCT
- ✓ Age > 18



Abbreviations:

- D: Day, M: Month, EOT: End of treatment
- SR-GI-aGvHD: Steroid-refractory gastro-intestinal acute Graft-versus-Host Disease
- ORR: Overall Response Rate; CR: Complete Response; VGPR: Very Good Partial Response; PR: Partial Response

ARES Objectives

ARES

Primary: Evaluation of treatment response

MaaT13 efficacy evaluation assessed by the **ORR**
(CR, VGPR and PR) of GI-aGVHD response at Day 28

Secondary - SAFETY

Overall Safety Assessment
- AEs
- SAEs
- Laboratory abnormalities

Secondary - EFFICACY

- ORR for GI and all organs up to M3
- Duration of response
- Overall survival, Progression-free survival
- Incidence of chronic GvHD
- Quality of life

Secondary - EXPLORATORY

- MaaT013 activity on immune markers
- Resource utilization evaluation

MaaT013 to cure aGvHD

- MaaT013 is a first-in-class, high-richness, high-diversity full ecosystem microbiome therapy, containing Butycore™
- MaaT013 aims to restore the microbiome to cure Gastro-Intestinal acute Graft vs. Host disease, a severe complication of allogeneic stem cell transplant affecting circa 10,000 new patients each year in the US and Europe.
- In more than 100 patients treated to date in Phase 2 trial and in Early access program (EAP), MaaT013 showed:
  - ✓ A very good safety profile in this highly immunocompromised population
  - ✓ Promising efficacy results (GI-ORR and overall survival at 6 and 12 months)

✓ MaaT013 is a first Microbiome Therapy in the world to enter Phase 3 in hemato-oncology

- Next Step: First data review of ARES is expected in H1 2023

Hemato-Oncology

15 min

MaaT033, oral Microbiome Ecosystem Therapy aiming to improve outcomes for patients with liquid tumors

Pr. Mohamad Mohty

Professor & Head of the Clinical Hematology and Cellular Department - Saint-Antoine Hospital

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R&D Day June 7, 2022

MaaT033: An optimized oral capsule to restore and maintain a healthy gut microbiome in patients with severe dysbiosis

Characteristics

A high-richness and high-diversity full-ecosystem intestinal Microbiome Ecosystem Therapy

Administration

Oral (a lyophilized capsule)

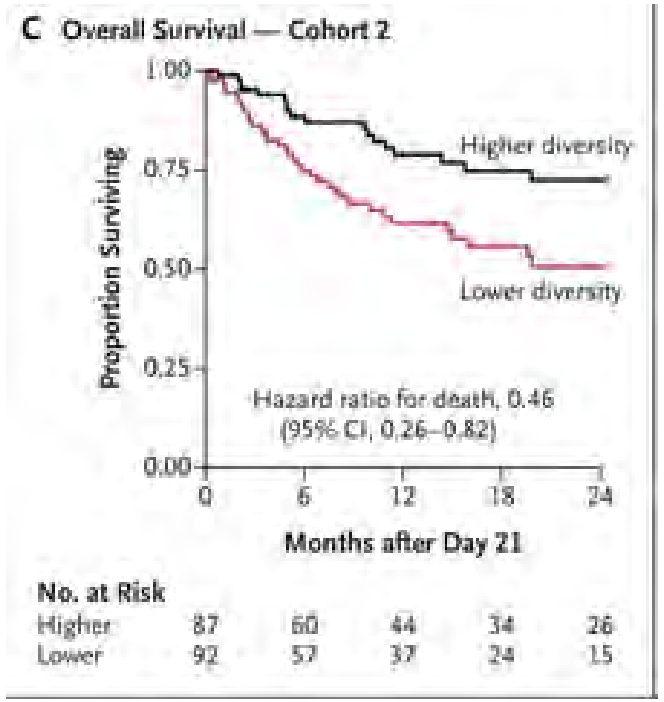
Clinical program

✓ CIMON Ph1b: Dose-finding study (completed)
→ OR-ALLO trial: Prevention of allo-HSCT complications

Indication

Prevention of allo-HSCT complications

MaaT033 aims to restore and preserve the gut microbiota, to avoid allo-HSCT complications (infections & aGvHD)



Patients with liquid tumors (Leukemia, lymphoma, myeloma…)

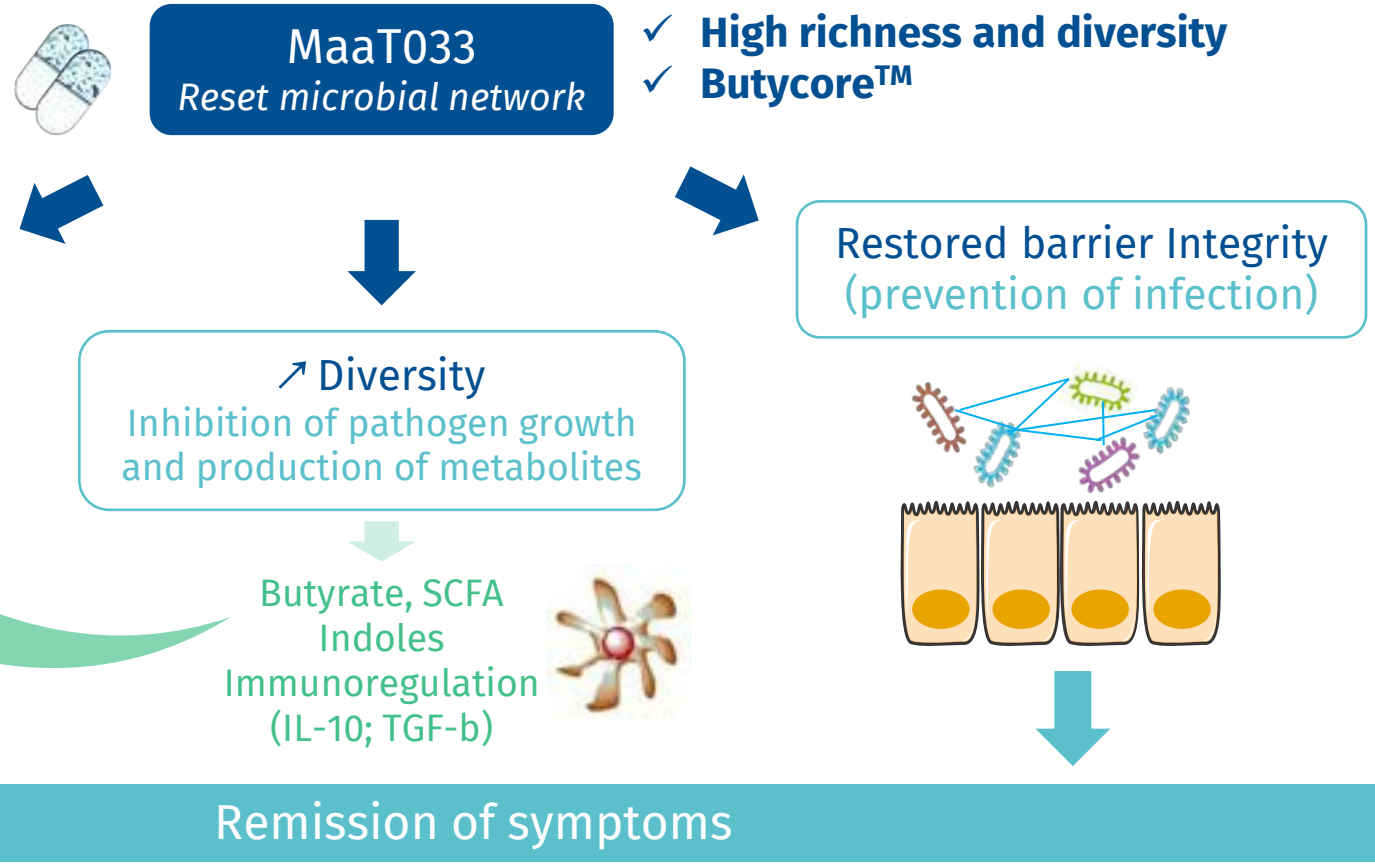
Chemotherapy
Antibiotics
Irradiation,
Immunosuppressors

Allogenic Hematopoietic Stem Cell Transplantation (allo-HSCT)

Loss of diversity (dysbiosis)

- Acute Graft-versus-Host Disease (aGvHD)
- Infections

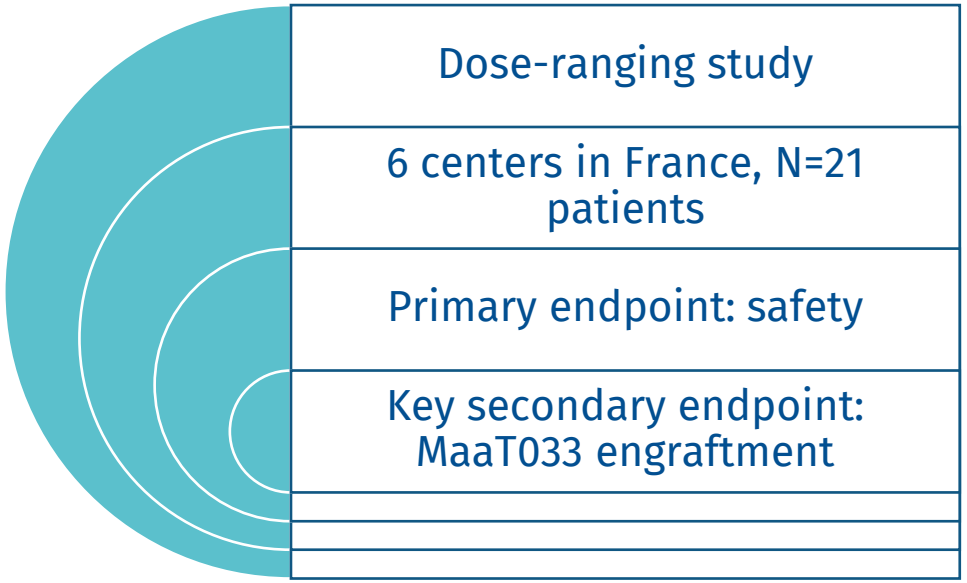
MaaT033's MOA aims to to restore and protect the gut microbiota, to improve allo-HSCT outcome and avoid complications (infections, aGvHD, etc.)



Introducing CIMON, the first clinical trial evaluating MaaT033 …

CIMON
Restoring the gut barrier for Life
By MaaT Pharma

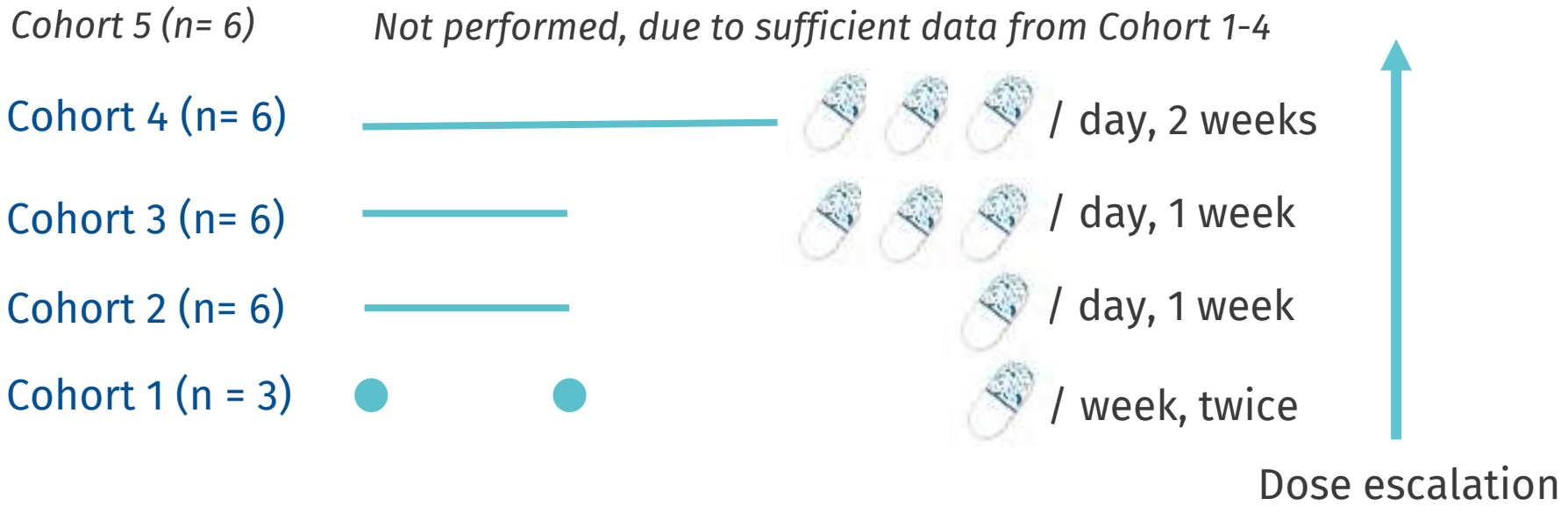
Phase 1 evaluation of MaaT033 in patients with acute Myeloid Leukemia or High-Risk Myelodysplastic Syndrome, after intensive chemotherapy



Learn more about the trial: NCT04150393

… a Phase 1b open-label, dose finding study

After induction therapy
with intensive chemotherapy

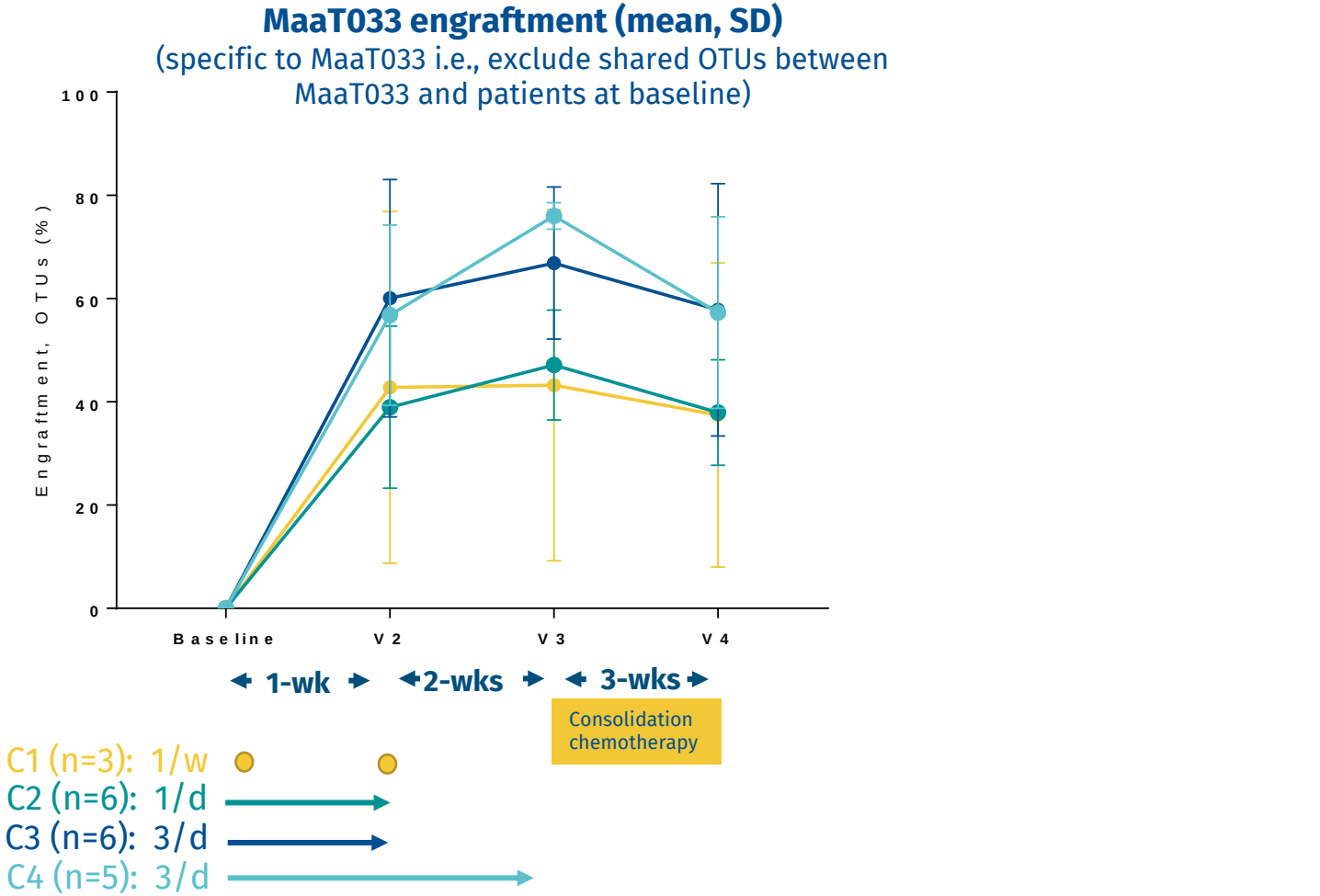


MaaT033 displayed a good safety profile in CIMON study

- ✓ 21 patients exposed, 20 completed.
- ✓ 100% drug compliance.
- ✓ 4/4 positive DSMB meetings recommending cohort escalations:
  - 4 SAEs considered “not related” to study drug by the investigator.
  - 1 SAE “possibly related” : infectious diarrhea event: DLT as per protocol definition, no detection of pathogen in MaaT033 product. Patient recovered within 4 days.
  - Most frequent AEs: GI disorders (86% of patients, 97% mild/moderate): consistent with the AE profile expected in this patient population.
  - No SARSCoV-2 infection during the study.

SAE: Serious Adverse Event; AE: Adverse Event; GI: Gastro-intestinal; Pts: patients; DLT: Dose Limiting Toxicity

MaT033 displayed strong, rapid and persistent engraftment in CIMON study



→ Dose selected for planned Phase II-III pivotal OR-ALLO study

CIMON results open an attractive market opportunity: Prevention of complications in patients receiving allo-HSCT and in hematological malignancies overall

United States

c. 7,800 primary procedures

EU 5

c. 9,600 primary procedures

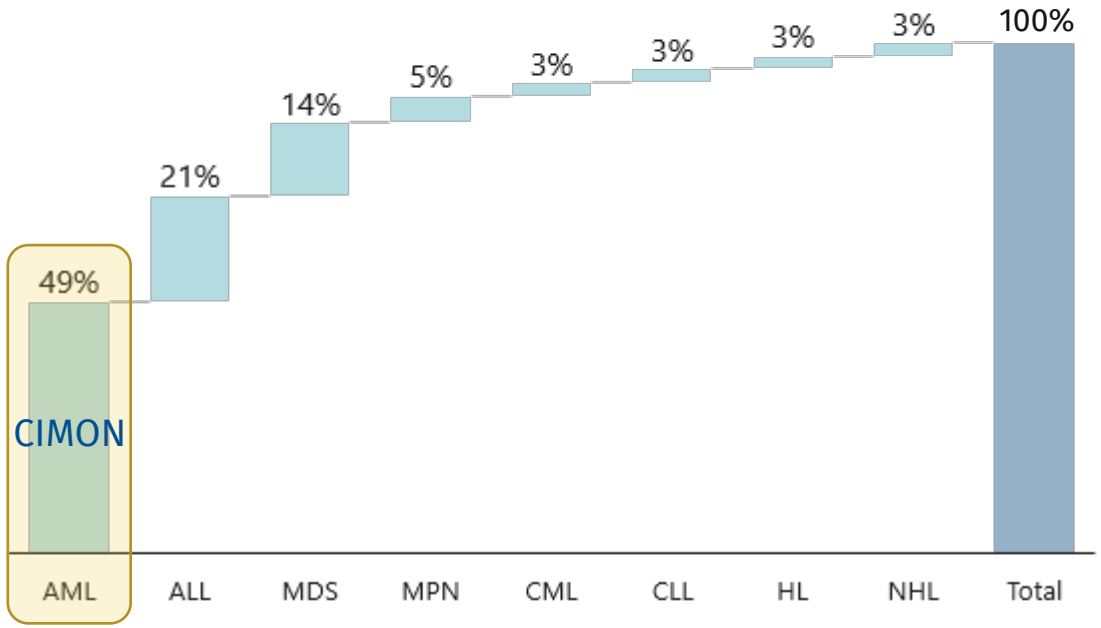
Japan

c. 3,000 primary procedures

Additional 7%-10% recurrent procedures

Approximately 22,500 procedures/year

Hematological Malignancy Patients Receiving Allo-HSCT[1]

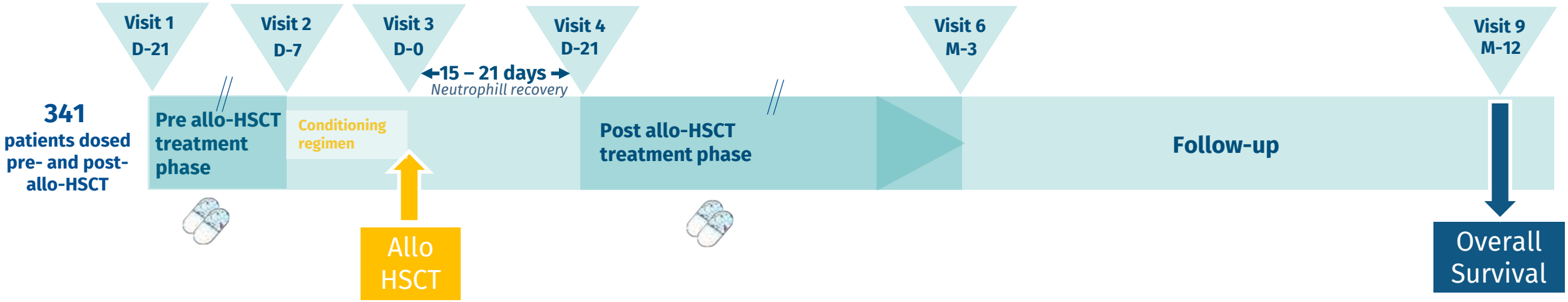


AML : acute myeloid leukemia; ALL : acute lymphoblastic leukemia ; MDS : myelodysplastic syndrome; MPN : myeloproliferative neoplasms ; CML: chronic myeloid leukemia ; CLL : chronic lymphocytic leukemia ; HL: Hodgkin's Lymphoma ; NHL: Non Hodgkin Lymphoma

[1]EBMT aHCT Survey, 2017 (published in Bone Marrow Transplantation (2019) 54:1575–1585), Global Data 2020

Next step: Randomized clinical trial evaluating MaaT033 to prevent complications of allo-HSCT

- 341 patients in a randomized, double-blind, placebo-controlled study
- Evaluate safety and tolerability before and after allo-HSCT
- Evaluate engraftment and efficacy of MaaT033 in improving overall survival and preventing allo-HSCT complications
- Targeted initiation: Q4 2022



MaaT033: Promising new treatment for allo-HSCT

- MaaT033 is an oral, high-richness, high-diversity microbiome therapy
- MaaT033 aims to restore and maintain a healthy microbiome in patients with severe dysbiosis
- MaaT033 promotes SCFA including butyrate and other metabolites production to regulate the immune system and restore homeostasis
- Ultimately, MaaT033 aims to improve survival in >20,000 patients receiving allo-HSCT each year

- In a Phase 1b trial, MaaT033
  - ✓ Showed a good safety profile
  - ✓ Displayed high, rapid and persistent engraftment

- Next Step: Pivotal randomized, placebo-controlled study in patients with allo-HSCT. Planned to start Q4 2022.

Immuno-Oncology

The microbiome is gaining momentum in cancer immunotherapy

Pr. Hassane Zarour

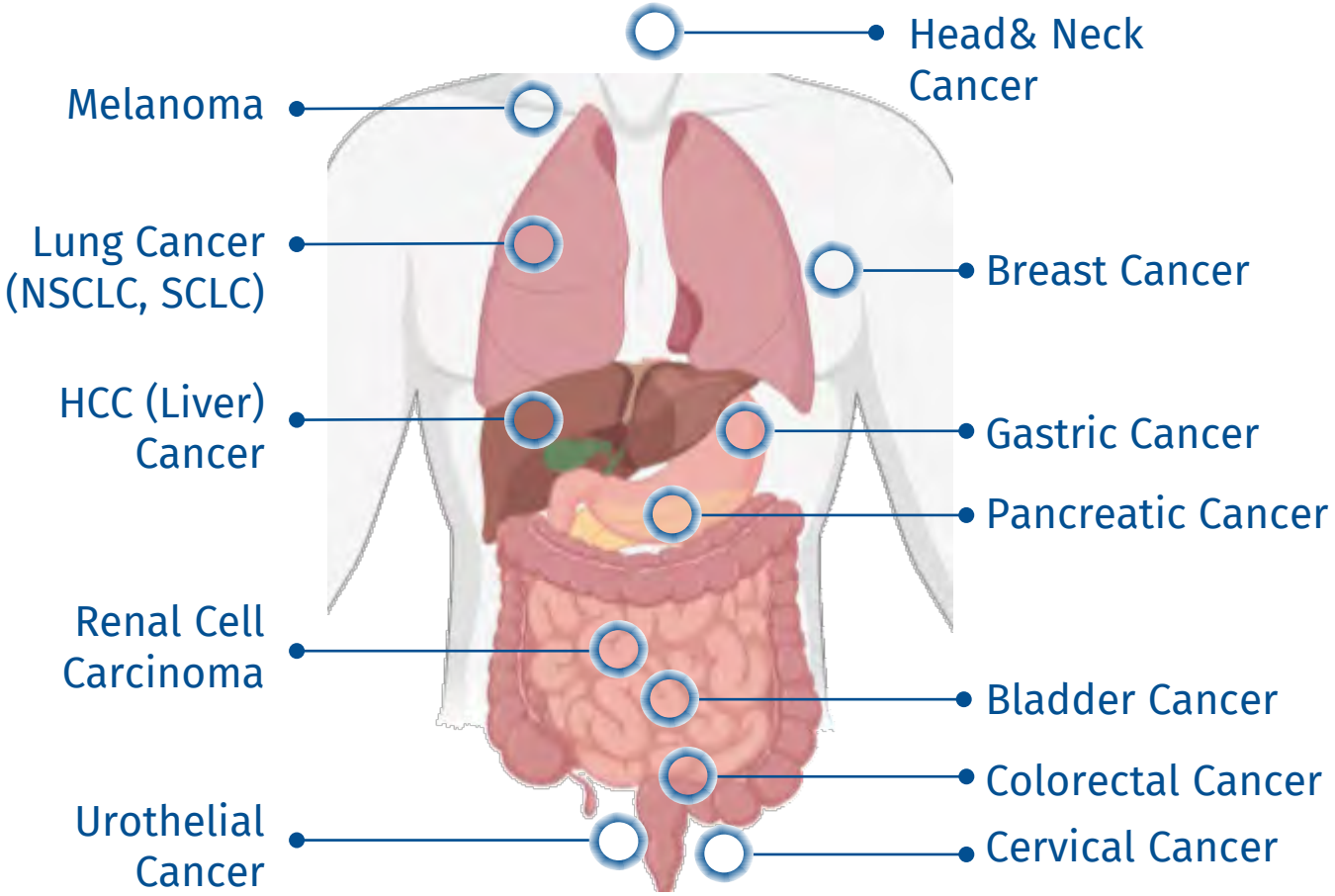
Professor of Medicine, Immunology and Dermatology

University of Pittsburgh

University of Pittsburgh

R&D Day June 7, 2022

Immune Checkpoint Inhibitors (ICI) have become one of the most potent therapy of solid tumors



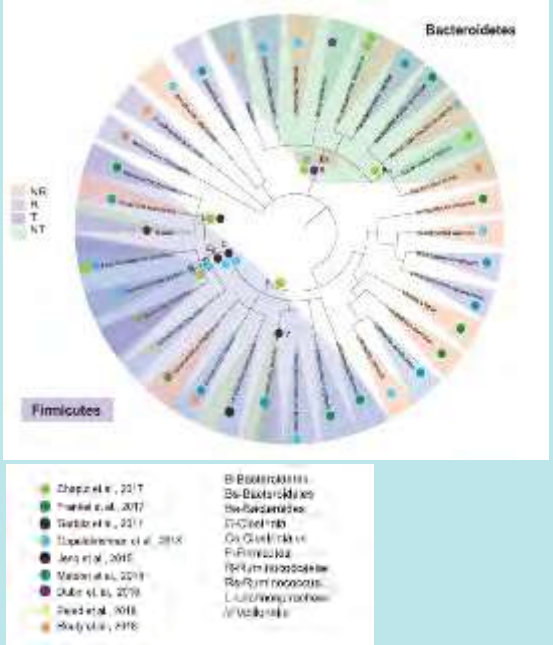
… and many more
(>15 different indications)

- In the US, 70% of melanoma patients will receive an ICI.
- ICI are first-line treatments in metastatic melanoma, NSCLC, RCC, MSI high tumors,……
- However, a medical need remains, as not all patients respond to treatment (overall response rate varying from 20-70% depending on indications)

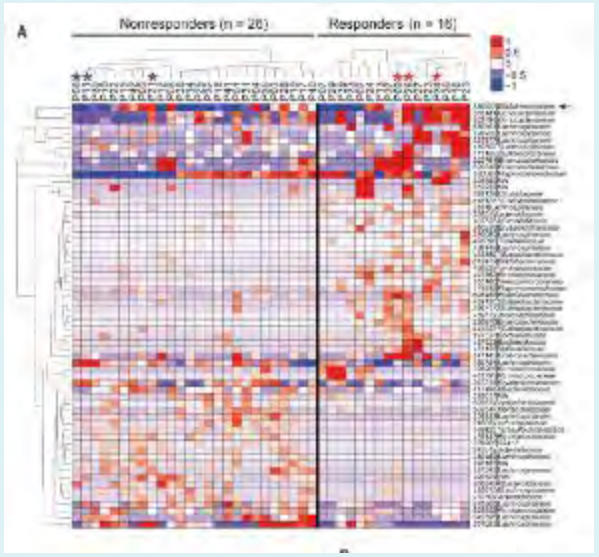
The *baseline* gut microbiome influences response rate to ICI

- Multiple studies show an impact of the gut microbiome composition on ICI response rate in metastatic melanoma (and other solid tumors indications: lung cancer, colorectal, bladder…)
- Responders and non-responders show different microbiome profiles, but there is a lack of a signature consensus between published studies so far.

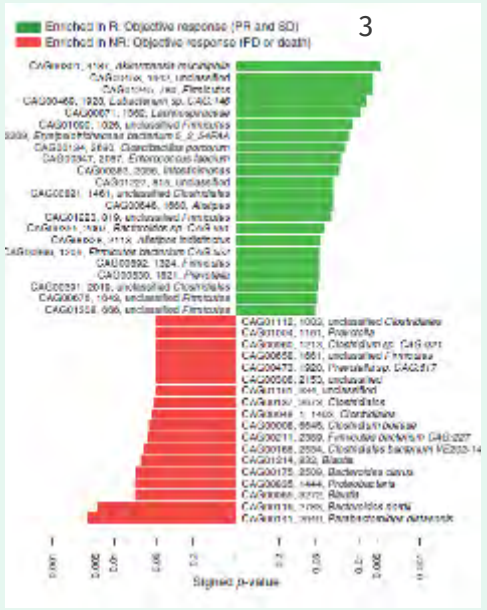
… "Melanoma responders had increased Firmicutes"[1]



… "Melanoma responders had increased Bifidobacterium"[2]



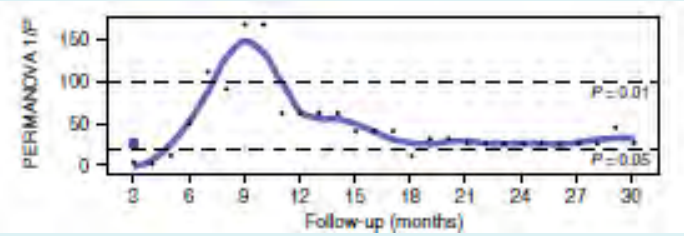
… "Melanoma responders had increased Akkermansia & Firmicutes"[3]

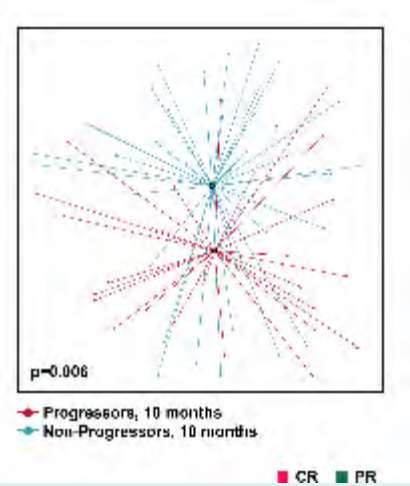


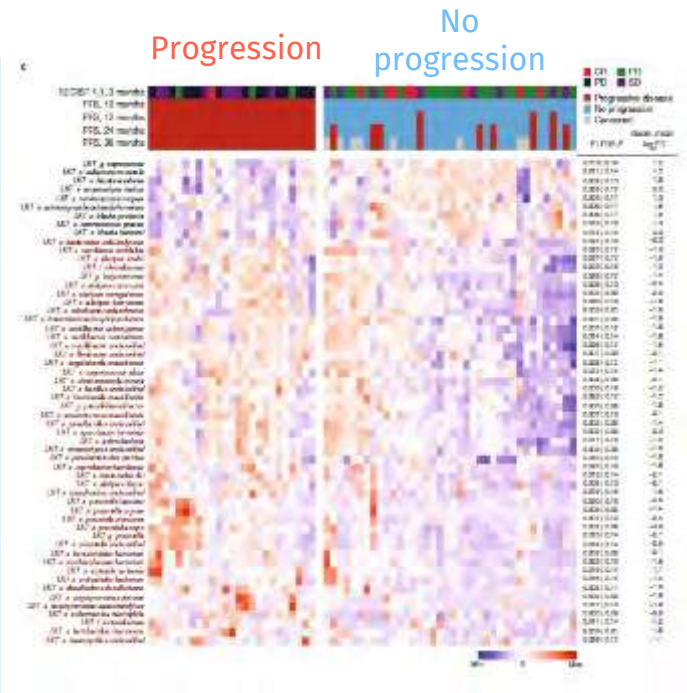
(1) Gopalakrishnan et al, Science 2018, (2) Matson, et al Science 2018; (3) Routy et al, Science 2017, see also Sheikh et al, Clin Can Res 2021.

Baseline fecal microbiome of anti- PD-1-treated melanoma patients predicts PFS at 9-10 months

Maximal impact of (baseline) gut microbiota is observed at **10 months**, which is when patients typically escape therapy

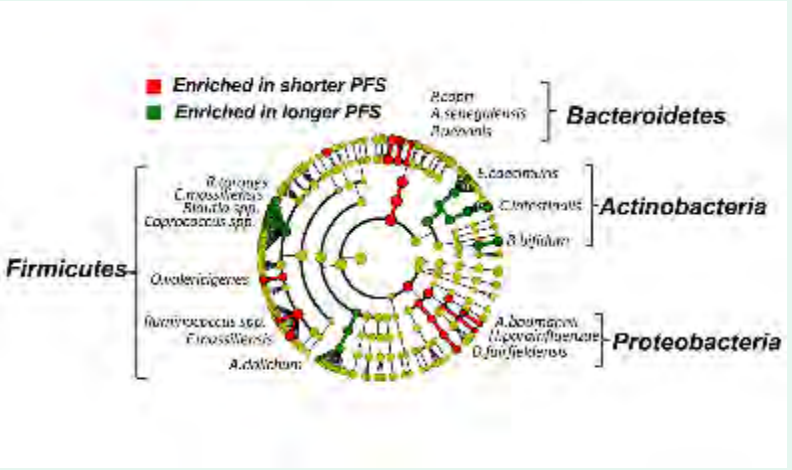






Responders and Non-Responders have **distinct gut microbiota profiles**

Beneficial and detrimental taxa linked with response to anti-PD-1 immunotherapy

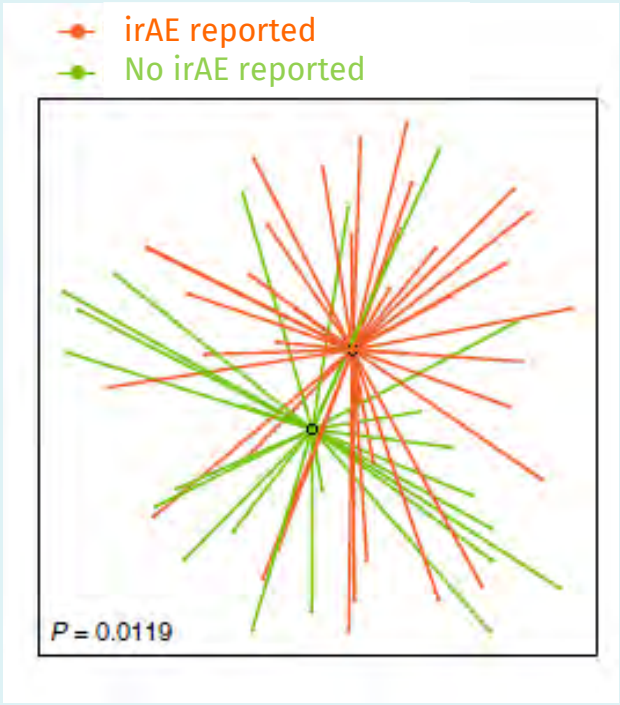


→ Microbiome intervention may improve clinical outcome of ICIs.

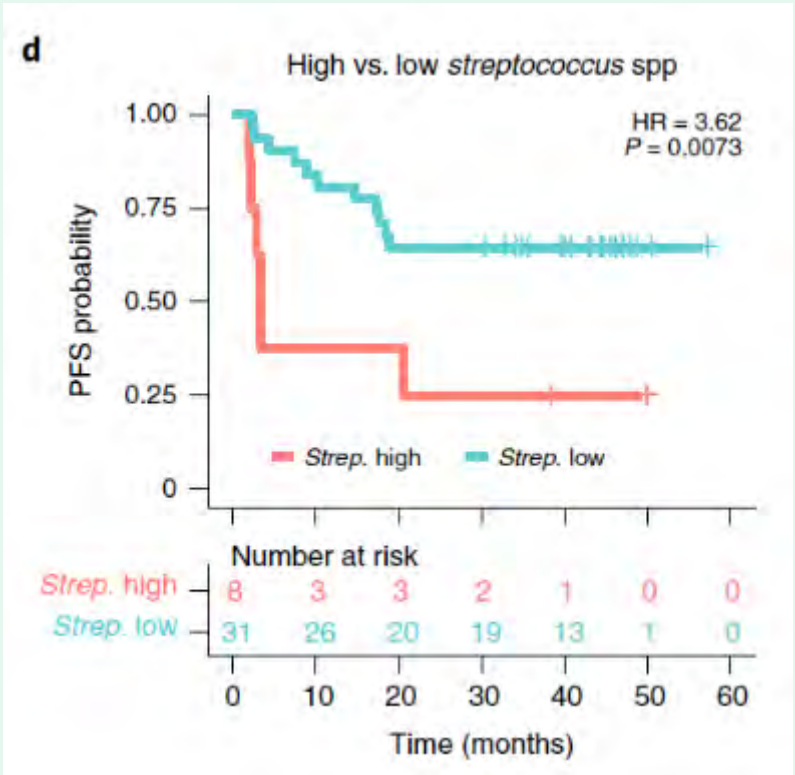
Mc Culloch et al, Nat Med 2022, see also Lee at al , Nat Med 2022

The *baseline* gut microbiome *also* influences treatment-related adverse events

Patients with treatment-related adverse-events (irAE) have a distinct microbiome profile



Sensitivity to irAE and related survival are impacted by specific gut microbiota species

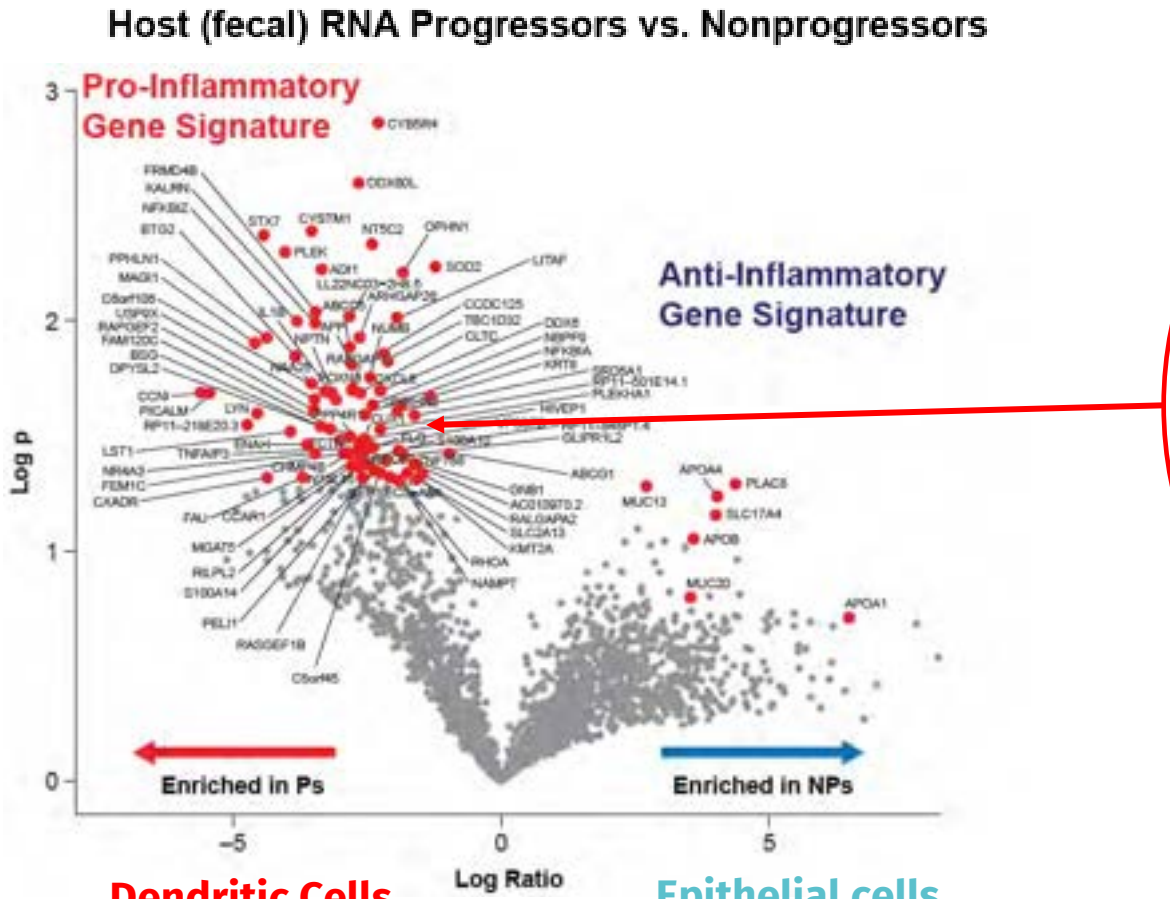


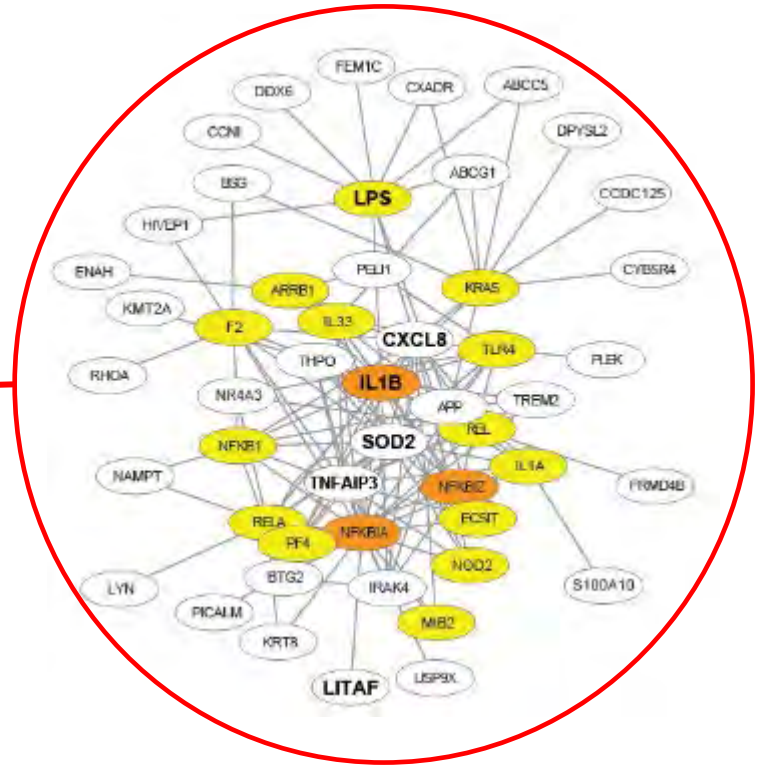
- Baseline microbiome composition is a predictor of occurrence of irAE
- Baseline microbiome may be impacted by other treatments (such as proton pump inhibitors)
- Microbiome influence seems most important for irAEs occurring in T-cell-rich tissues (gut, lung, skin, …)

→ Microbiome intervention may decrease occurrence of serious adverse events upon ICIs.

Mc Culloch et al, Nat Med 2022

Host (human) fecal transcriptome shows in progressor patients a pro-inflammatory gene signature





Dendritic Cells
Macrophages
Neutrophils

Epithelial cells
T cells
Basophils

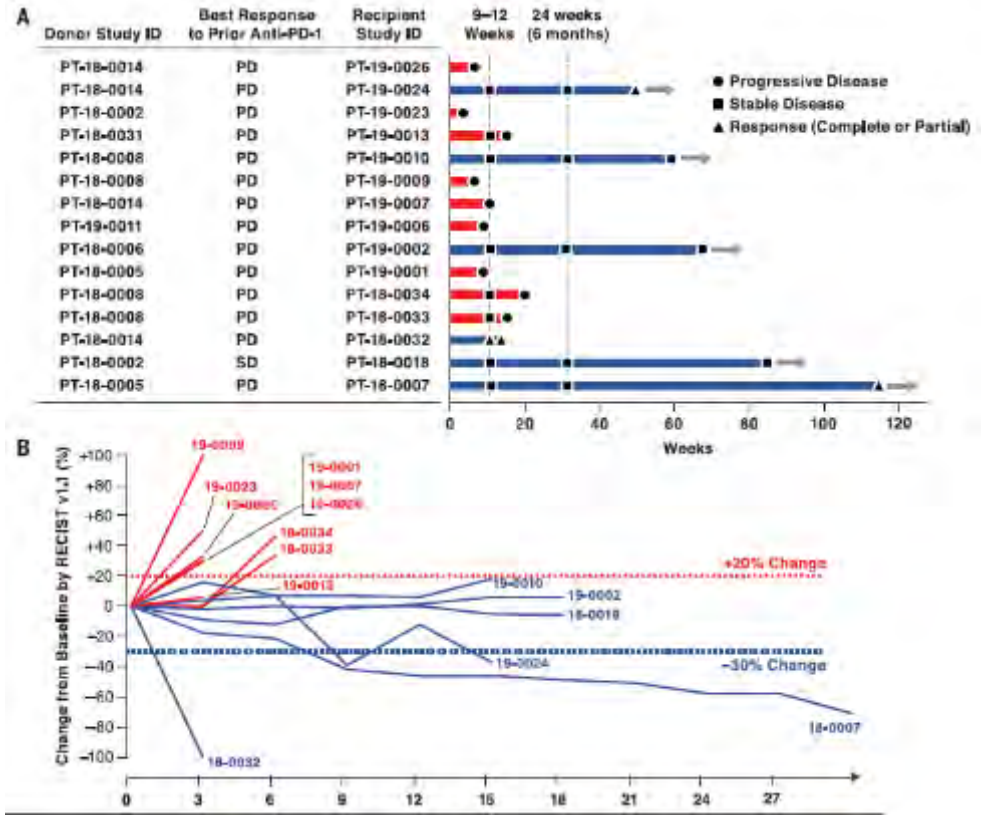
Gene Set Enrichment Analysis (GSEA)

→ Microbiome intervention may overcome the mechanisms driving a pro-inflammatory gene signature in the gut.

Microbiome intervention (FMT) may help restore or induce response to Immune Checkpoint Inhibitors

Fecal microbiota transplant overcomes resistance to anti–PD-1 therapy in melanoma patients

Diwakar Davar[1]*, Amiran K. Dzutsev[2]*, John A. McCulloch[2], Richard R. Rodrigues[2,3], John M. Kirkwood[1], Giorgio Trinchieri[2]‡§, Hassane M. Zarour[1,9]‡§



Davar et al, Science 2021

2 recent proof-of-concept studies with FMT:

- Davar et al (Science 2021)
  - ✓ Responders' microbiota transferred to Non-Responders
  - ✓ Single FMT *before* ICI treatment
  - ✓ 6/15 NR→ R, with lasting response

- Similar data from Baruch et al (Science 2021)
  - ✓ 3/10 NR → R

→ Future Microbiome Therapies may aim to mimic a Responder's profile to achieve efficacy

Microbiome therapies open a new horizon to improve outcomes for patients receiving ICIs

- In cancer patients with solid tumors, the gut microbiome composition modulates both clinical responses and immune-related adverse events to ICIs

-> Microbiome interventions can be used in the clinic to :

  - Improve survival in patients receiving ICIs in melanoma and other indications
  - Limit ICIs toxicity as more and more patients have access to them in a large range of indications

- Multiple microbial signatures/enterotypes pre-treatment are associated with favorable or unfavorable clinical outcome: :
  - Function (Genes) > Form (Taxonomy): Genes are redundant across species.
  - Distinct enterotypes/microbiotypes are associated with beneficial or detrimental clinical outcome

  → Microbial therapies of cancer may be designed based on complex ICI responders' gut microbiome composition enriched in certain enterotypes

  - Classical FMT obtained from long-term responders are difficult to implement in clinical practice

  → There is a need for novel FMT-like products, easily feasible in clinical practice.

Immuno-Oncology

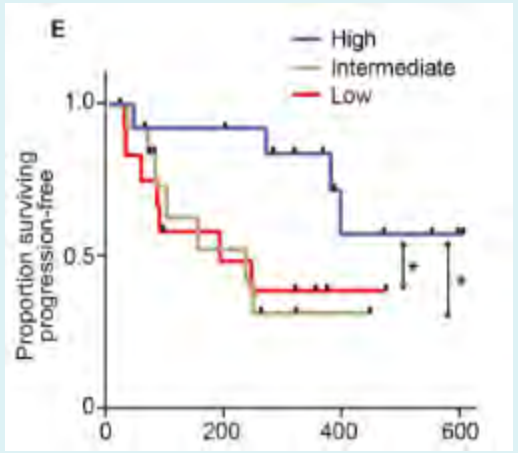
PICASSO: Proof-of-concept Phase 2 clinical trial in melanoma, sponsored by AP-HP

Emilie Plantamura

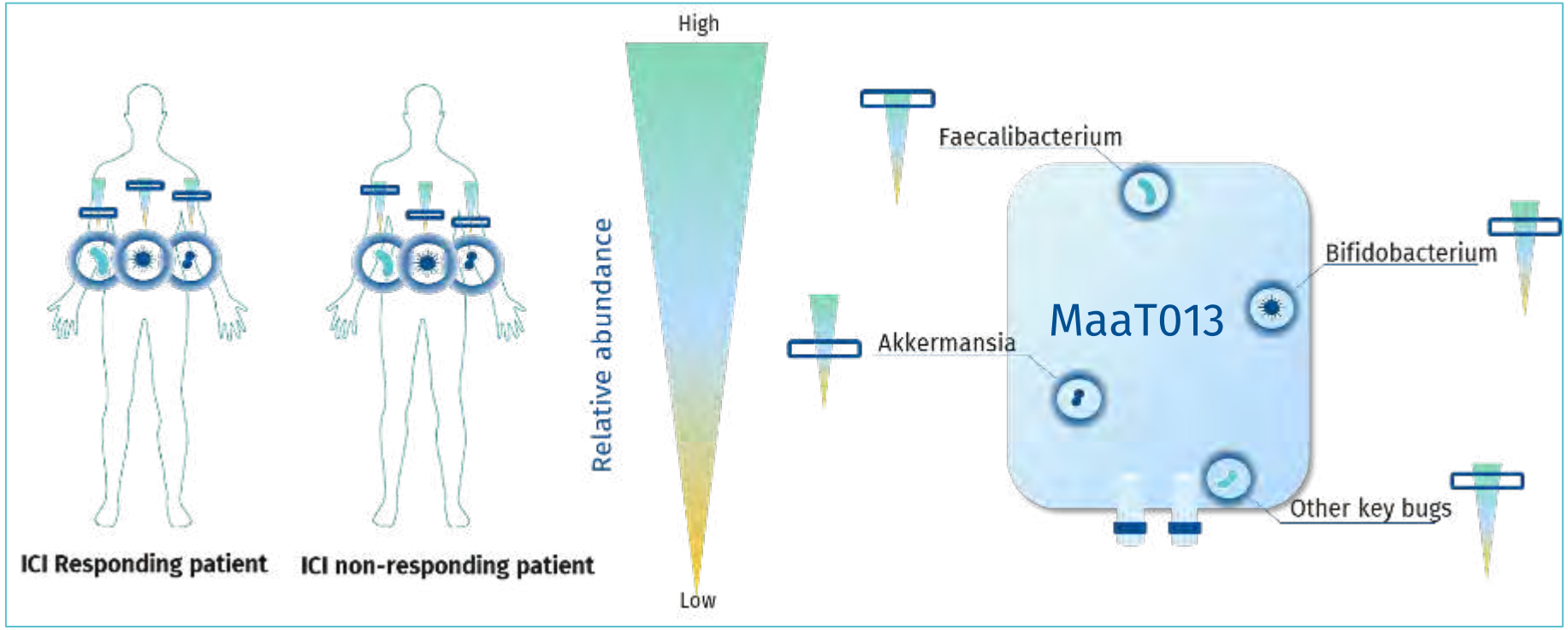
Head of clinical development

MaaT013 is designed to maximize richness and contains specific bacterial strains that have been identified to improve ICI response

Higher microbiome richness → better response rate to ICI in patients with metastatic melanoma



Gopalakrishnan et al, Science 2018



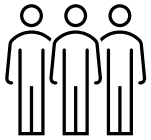
Introducing the PICASSO trial: evaluating MaaT013 in patients with metastatic melanoma receiving ICIs

Sponsored by

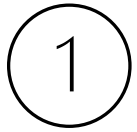
ASSISTANCE PUBLIQUE HÔPITAUX DE PARIS

Multi-center, French study, sponsored by AP-HP

Randomized, placebo-controlled study



60 patients



First patient treated in April 2022

Key study endpoints after 23 weeks of treatment:

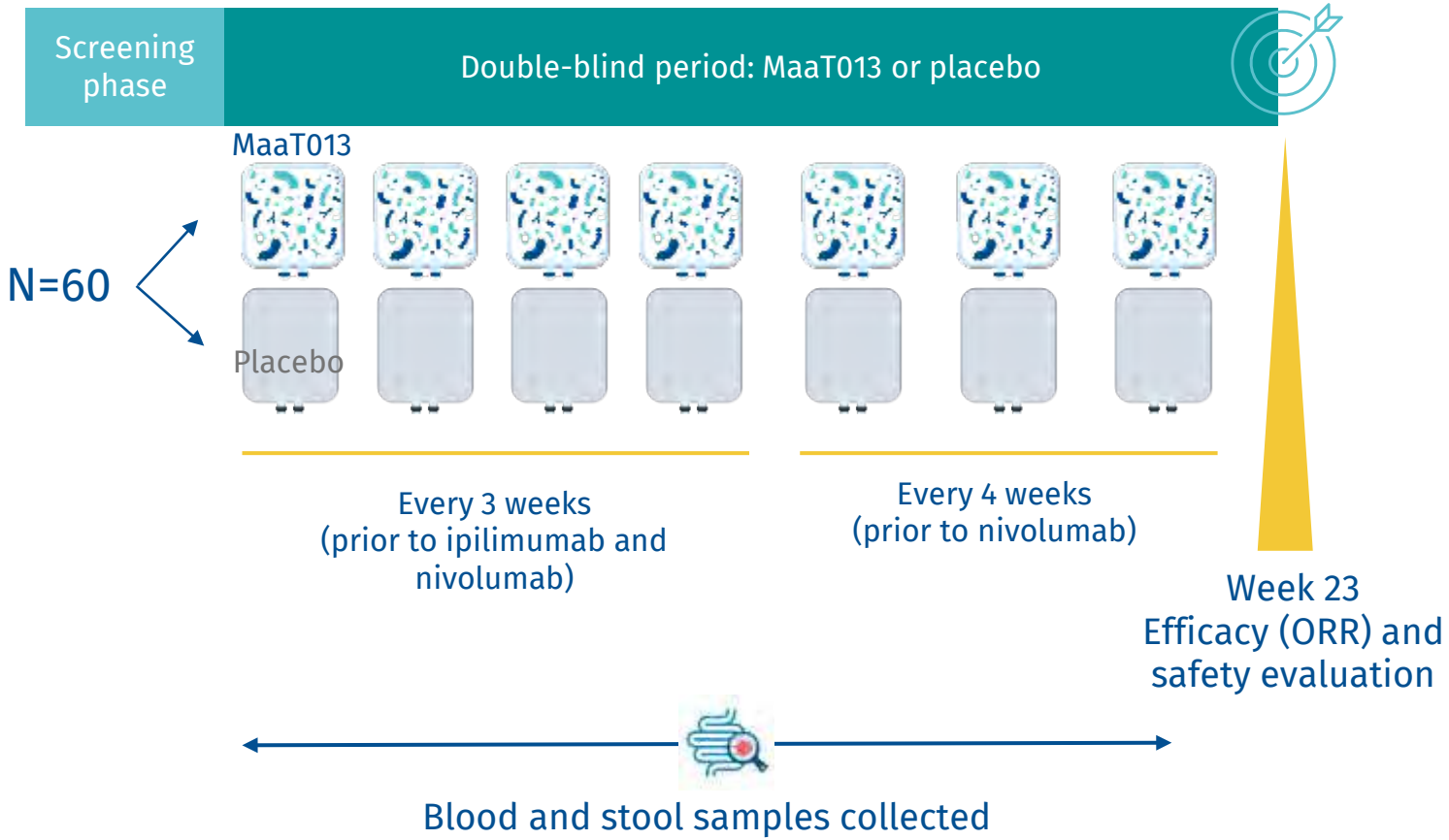
- MaaT013 safety profile vs placebo as add-on treatment to Ipilimumab + Nivolumab*
- MaaT013 best-overall response rate vs placebo as add-on treatment to Ipilimumab + Nivolumab*

ClinicalTrials.gov Identifier: NCT04988841, PHRC.

ASSISTANCE PUBLIQUE HÔPITAUX DE PARIS · GUSTAVE ROUSSY CANCER CAMPUS GRAND PARIS · INRAE · MaaT

PICASSO: Assessing tolerance and clinical benefit of MaaT013 in patients with metastatic melanoma naïve for ICI

Sponsored by
ASSISTANCE PUBLIQUE HÔPITAUX DE PARIS



MaaT Pharma's dual approach in immuno-oncology

- PICASSO is a proof-of-concept, exploratory trial allowing to better understand the impact of MaaT013's bacterial richness and diversity on response to Immune Checkpoint Inhibitors, developed in partnership with AP-HP, Institut Gustave Roussy and INRAE.

- In parallel, MaaT Pharma develops targeted, designed, new generation Microbiome Ecosystem Therapies aiming to install a responder-like profile in patients to:
  - Improve response rate to Immune Checkpoint Inhibitors
  - Mitigate their toxicity

MaaT Pharma's strategy to leverage the microbiome potential to improve cancer therapies

Carole Schwintner

Chief Technology Officer

Marianne Robin

Head of R&D

R&D Day June 7, 2022

MaaT Pharma's Microbiome Ecosystem Therapy (MET) platform has generated a diverse line of product candidates

gut Print

Microbiome Ecosystem Therapies (MET)

cGMP Platform

Native

MaaT013

MaaT033

- ✓ **High diversity**
- ✓ Full ecosystem
- ✓ **Butycore™** (anti-inflammatory)

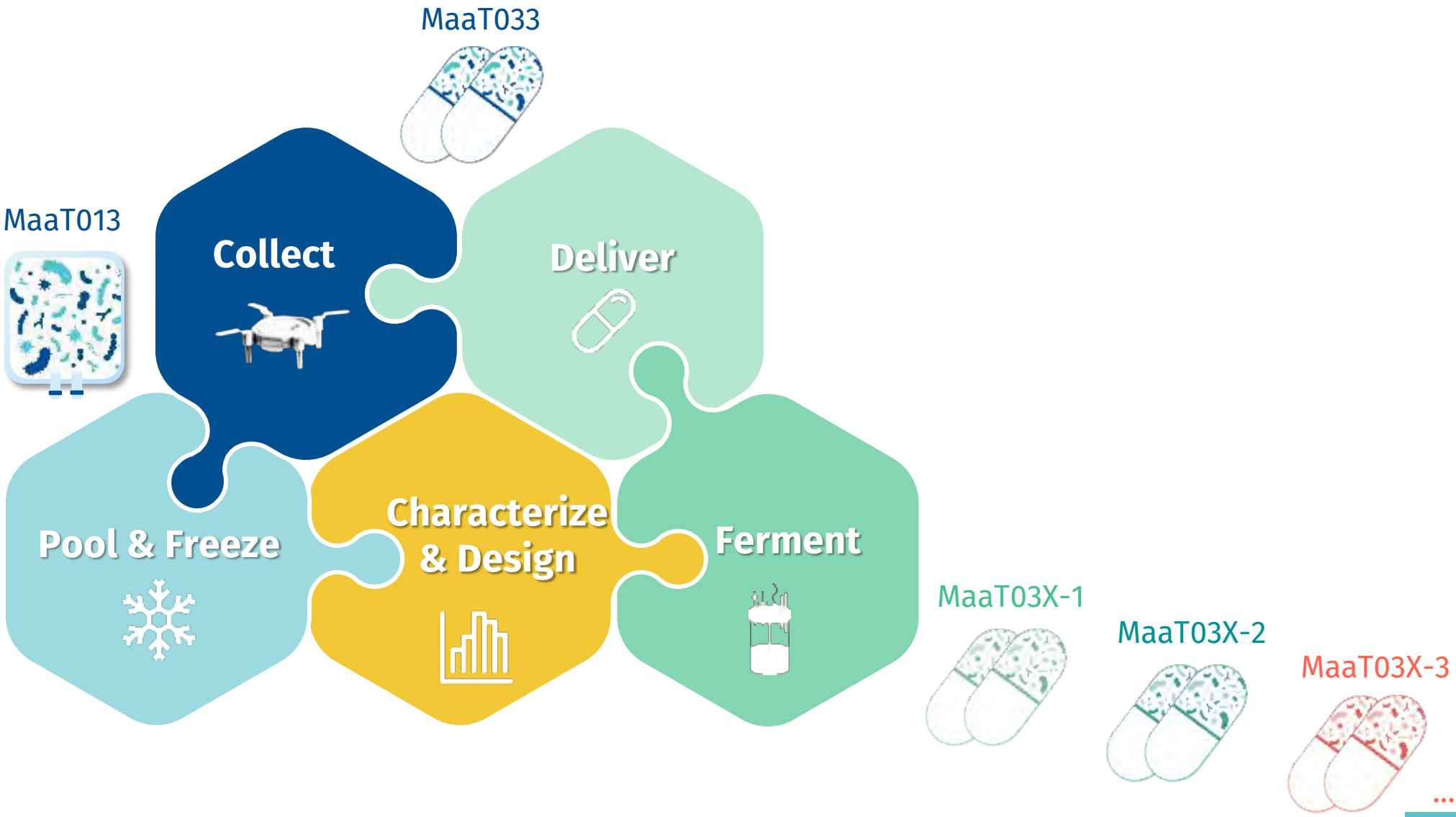
Co-fermented

MaaT03X

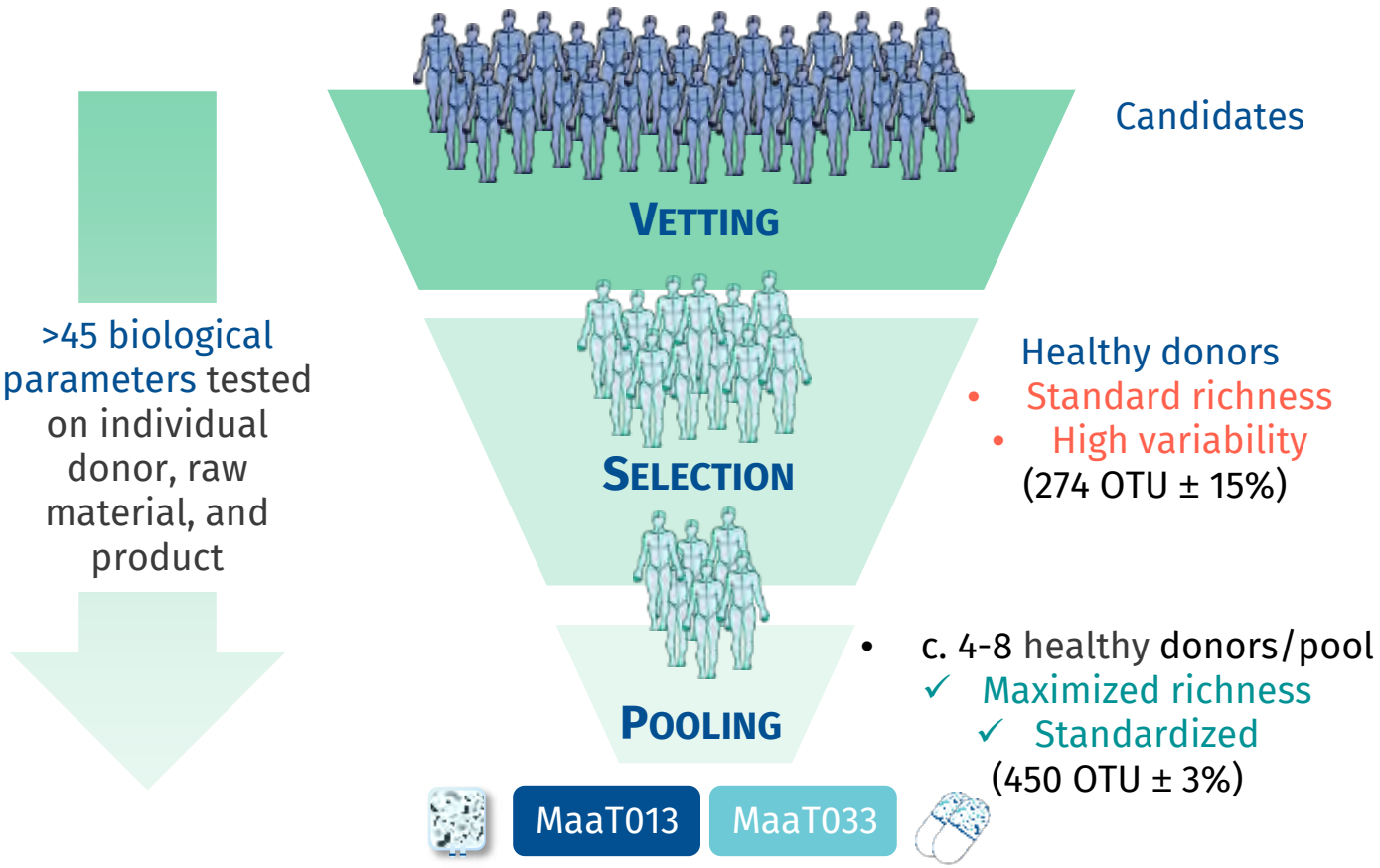
- ✓ **Indication-specific designed ecosystem** (from clinical data)
- ✓ Innovative **ecosystem co-fermentation technology**

[1] **Butycore**: Group of 15 different genera known to produce short-chain fatty acids with anti-inflammatory properties

Technological Bricks: foundations for a versatile products platform



Safety first:
Stringent vetting and testing of healthy donors

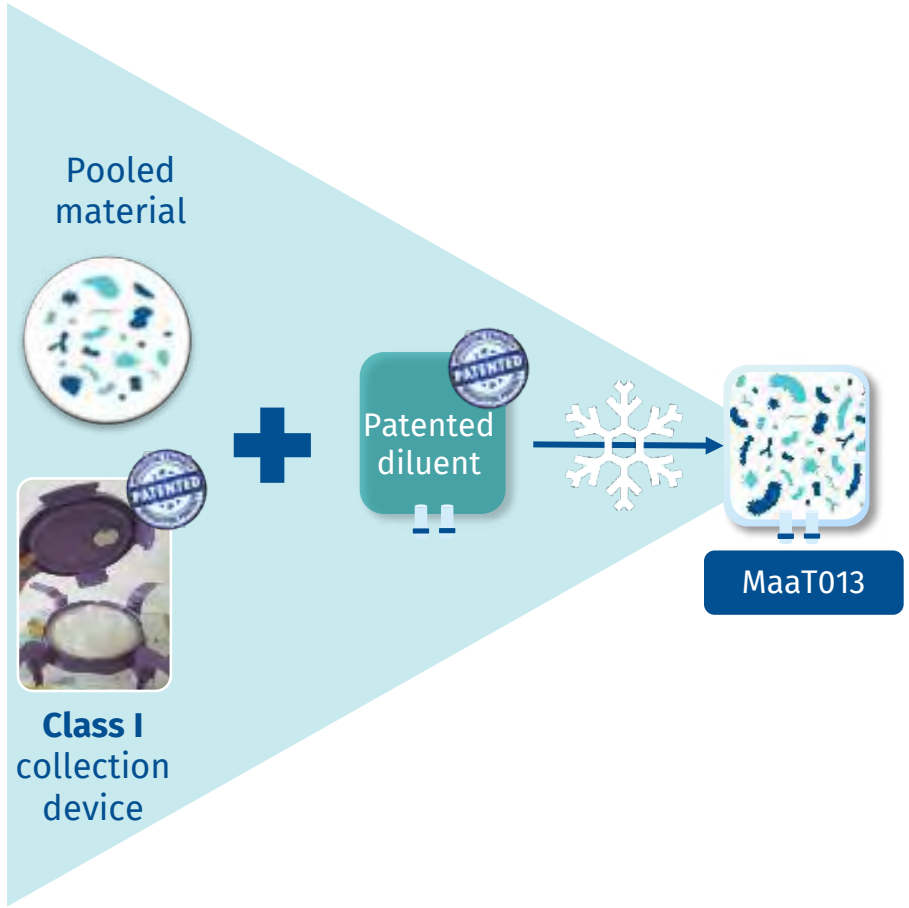


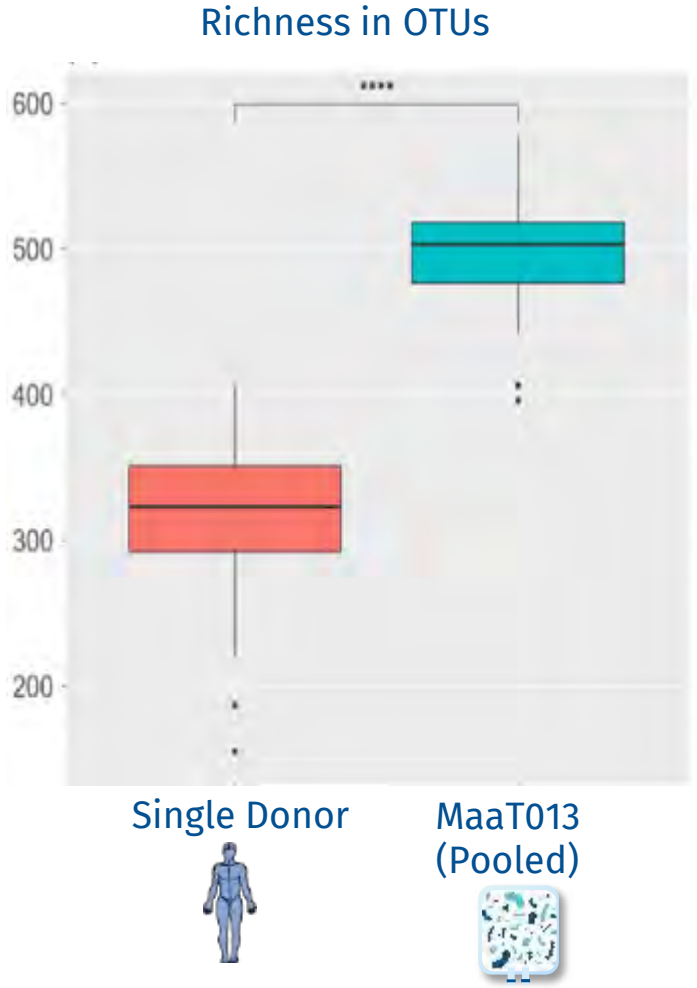
- ✓ Highly stringent vetting and testing procedures validated by multiple regulatory agencies
- ✓ Excellent safety profile observed in >100 fragile, immuno-compromised patients

[1] **Butycore**: Group of 15 different genera known to produce short-chain fatty acids with anti-inflammatory properties

Pool & Freeze

Profile and activity matter: Proprietary process preserves microbiota key attributes

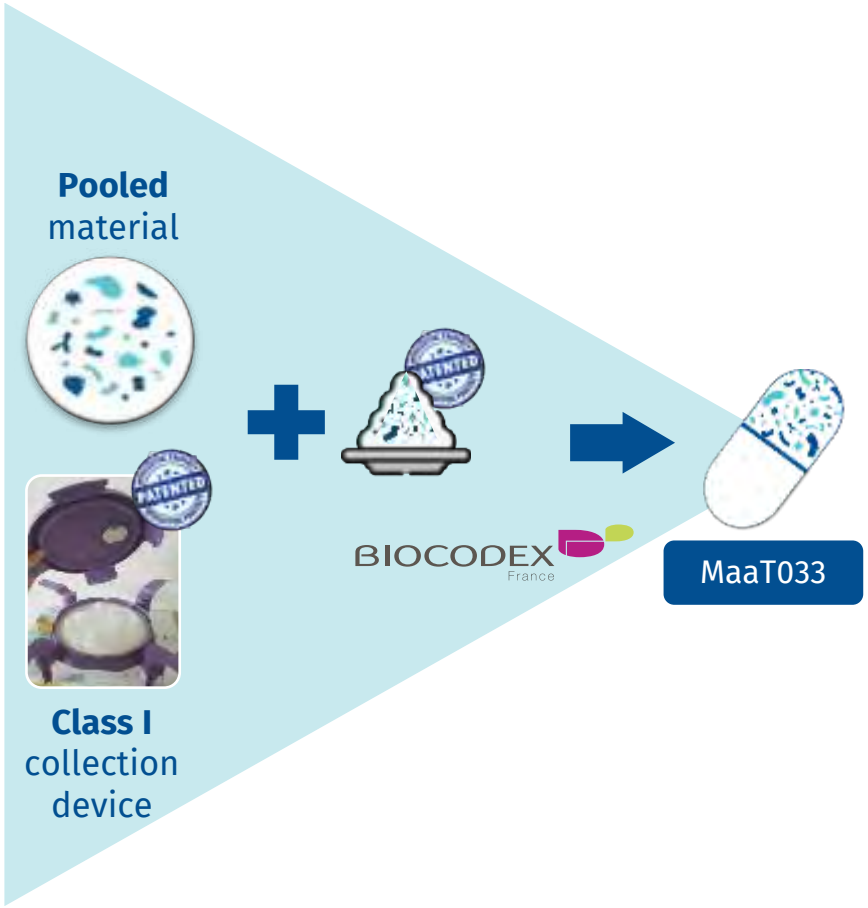


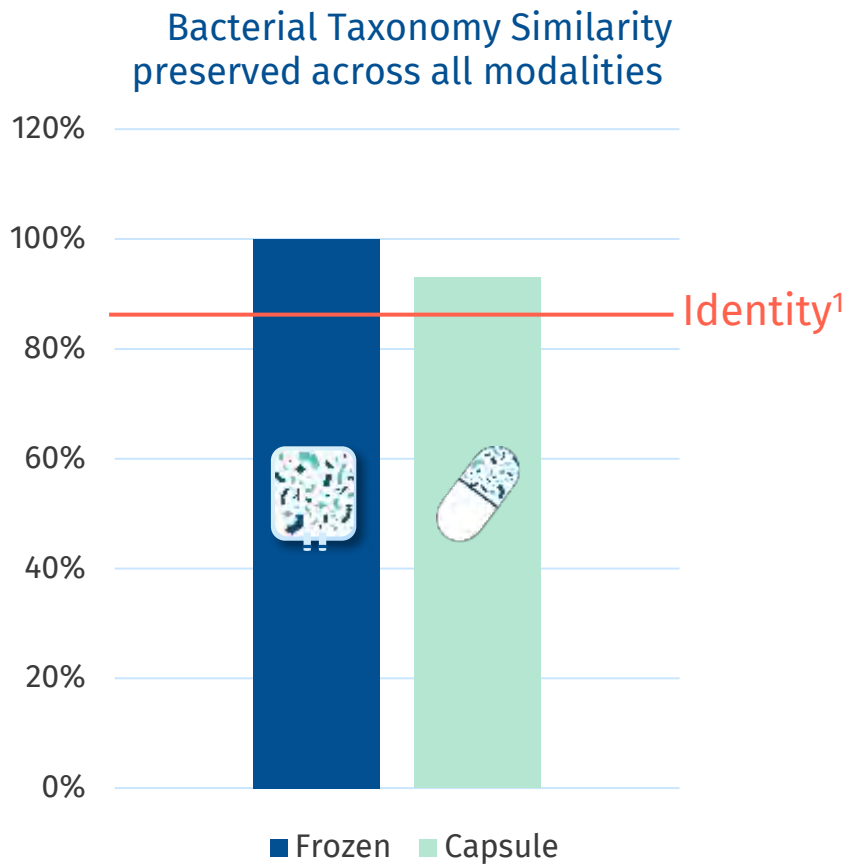


- ✓ Superior richness
- ✓ Maximizes Butycore™
- ✓ Standardized

- ✓ Characteristics and high biological activity preserved in frozen product

Optimize host/microbiome interaction: Oral formulation for targeted ileo-colonic delivery



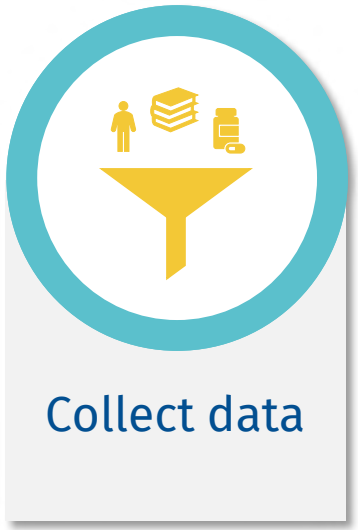


[1] **Identity** is defined as **intra-donor similarity** observed on a day-to-day basis and assessed with the Bray-Curtis similarity

- ✓ Oral formulation opens new indications
- ✓ Targeted ileo-colic delivery aims to maximize engraftment and interaction with immune system
- ✓ Safety and activity validated in clinical phase Ib study CIMON

gutprint®, the engine at the heart of our MET drug discovery platform

gutPrint® synergizes clinical, product and research data to develop innovative and personalized microbiome therapy, to improve patient survival in life-threatening diseases.



gutPrint® integrates all available data to generate knowledge

Collect

Clinical studies / Proprietary databases / Literature /Collaborations…

Host parameters (Omics, Clinical, immune…)

Gut microbiome parameters (Omics, indexes, …)

Product parameters (Omics, product characteristics…)

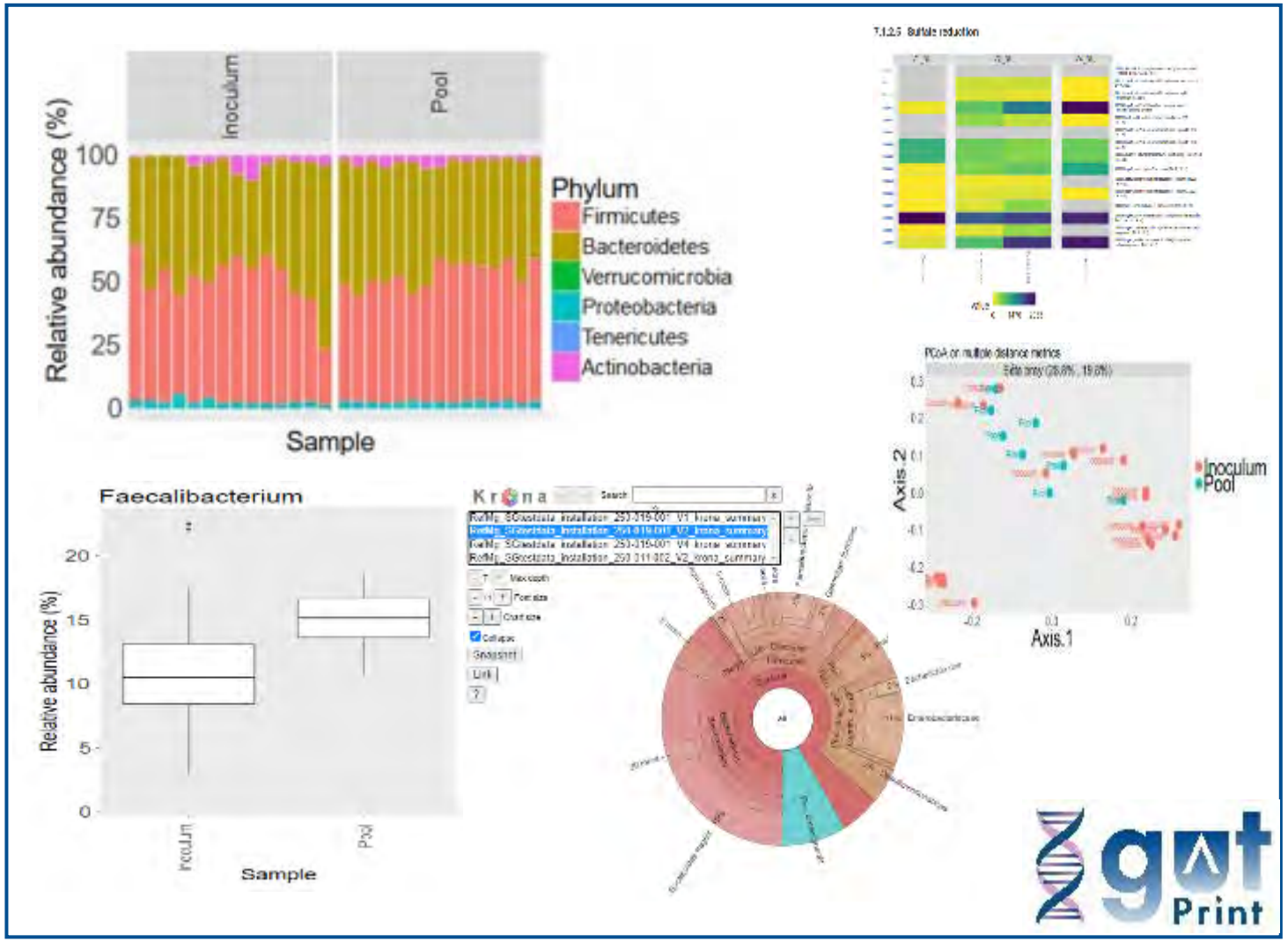
gutPrint

GAMP 5

AI
Learning

Characterization

gutPrint® provides critical data for drug development and manufacturing



- Proprietary tools for microbiota analysis:
  - All living microorganisms (bacteria, archaea, fungi…)

→ Taxonomy, diversity, metabolism, strain detection, biomarker identification, …

- Validated tools for cGMP processes:
  - ✓ Product analysis
  - ✓ Product monitoring
  - ✓ Product release

AI-based algorithms enable *in silico* indication-specific product design

Clinical & Donors Data

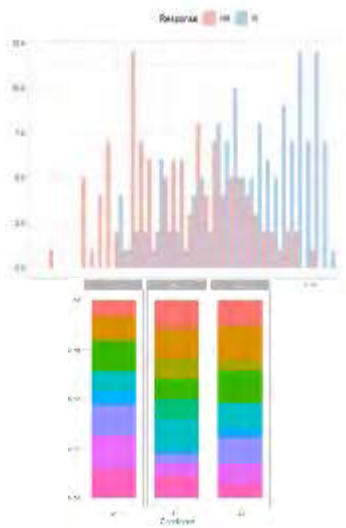
Literature

Host and microbiome parameters

gut Print

AI learning

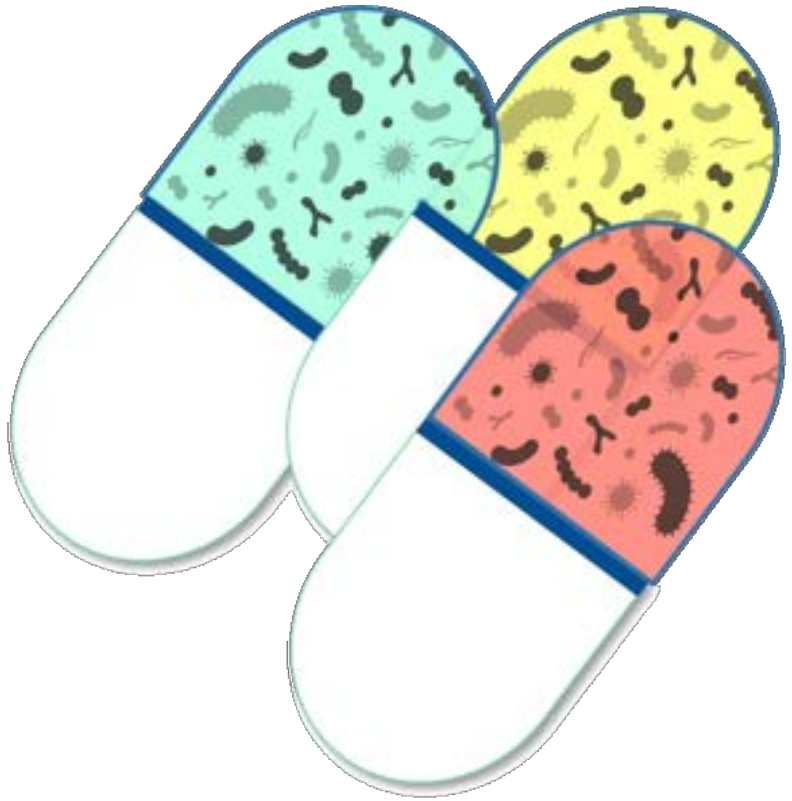
Characterization of target profile



Drug Design

Validation (*in vitro*/ *in vivo*/clinical)

MaaT03X: Modulate the gut microbiome to *improve* response rate to Immune Checkpoint Inhibitors treatment in solid tumors



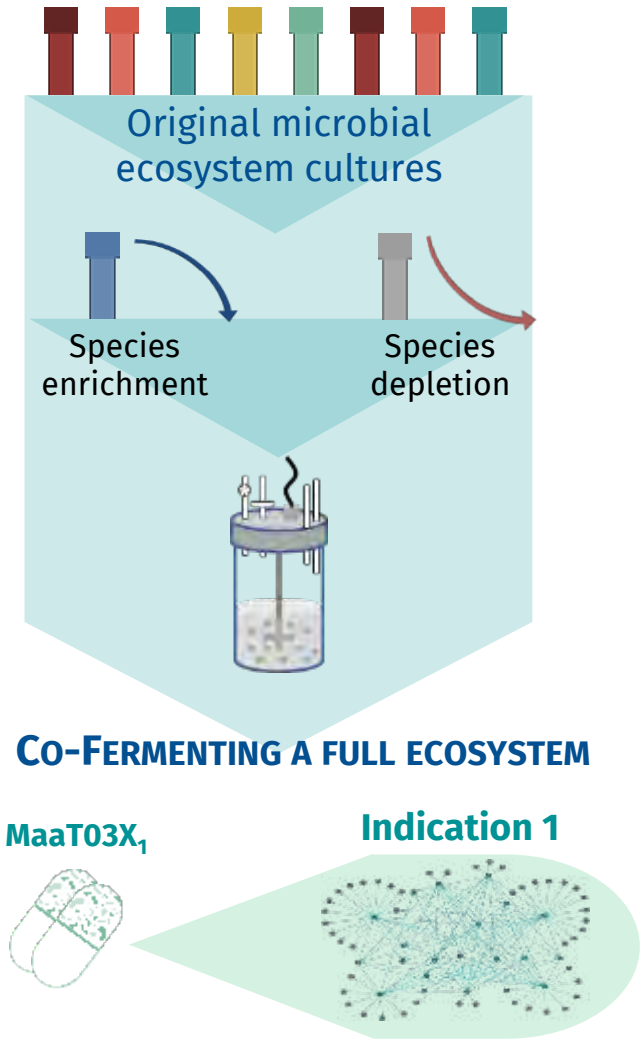
Microbial richness
High

Manufacturing technique
Co-fermented

Administration method
Proprietary oral capsule

Current indications
Improvement of response to ICIs in solid tumors
Potential development in a wide range of indications

A groundbreaking co-fermentation technology



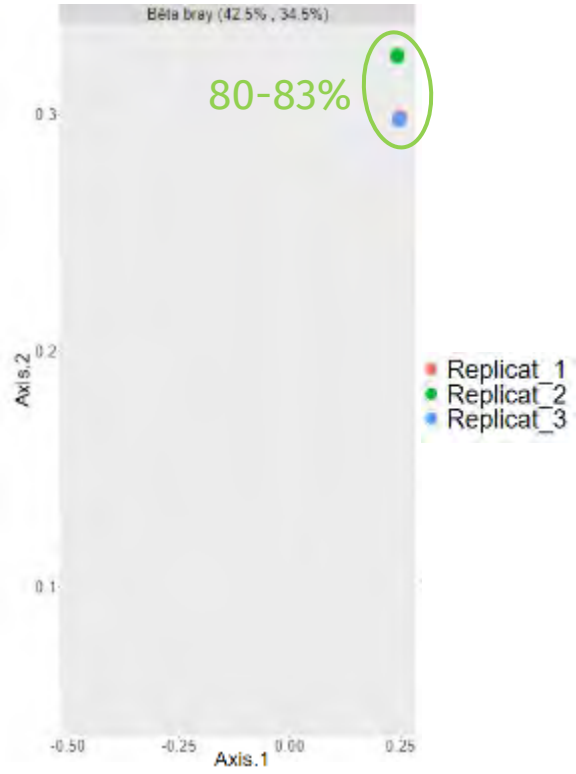
- ✓ Targeted profile maintained through fermentation
  - Supportive ecosystem

  AND
  - Indication-specific key functions
- ✓ Donor-independent and highly scalable
- ✓ Lower costs
- ✓ Pluggable on all technological bricks

Co-fermentation process maintains full supportive ecosystem and AI-selected key functionalities

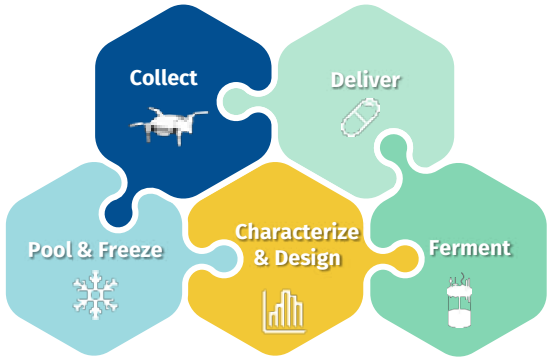
- ✓ Full supportive ecosystem maintained in over 15 microbiota profiles tested so far, with excellent reproducibility
- ✓ Taxonomic profile, viability and key indication-specific functionalities are maintained batch-to-batch through fermentation
  - ✓ Butycore
  - ✓ ICI-promoting functionalities

Parameter	Target	Obtained
Core microbiota	100% genera maintained	✓
Butycore™	High abundance	✓
Health index	High abundance	✓
Richness and diversity	Full suportive ecosystem	✓



Similarity between replicates (PCoA, Bray-Curtis, OTU level, distance)

What's next: building Europe's largest specialized cGMP manufacturing facility for MET



We are building a dedicated 1,500 square meter site (which could be doubled).

This plant is designed to support commercial manufacturing of MaaT013 and MaaT033 and clinical manufacturing of MaaT03X products

Our partner Skyepharma manufactures approved drugs for the USA and Europe and is regularly inspected by regulatory authorities

The new building will host manufacturing and R&D activities

Partnership with Skyepharma

Expected newsflow & ending remarks

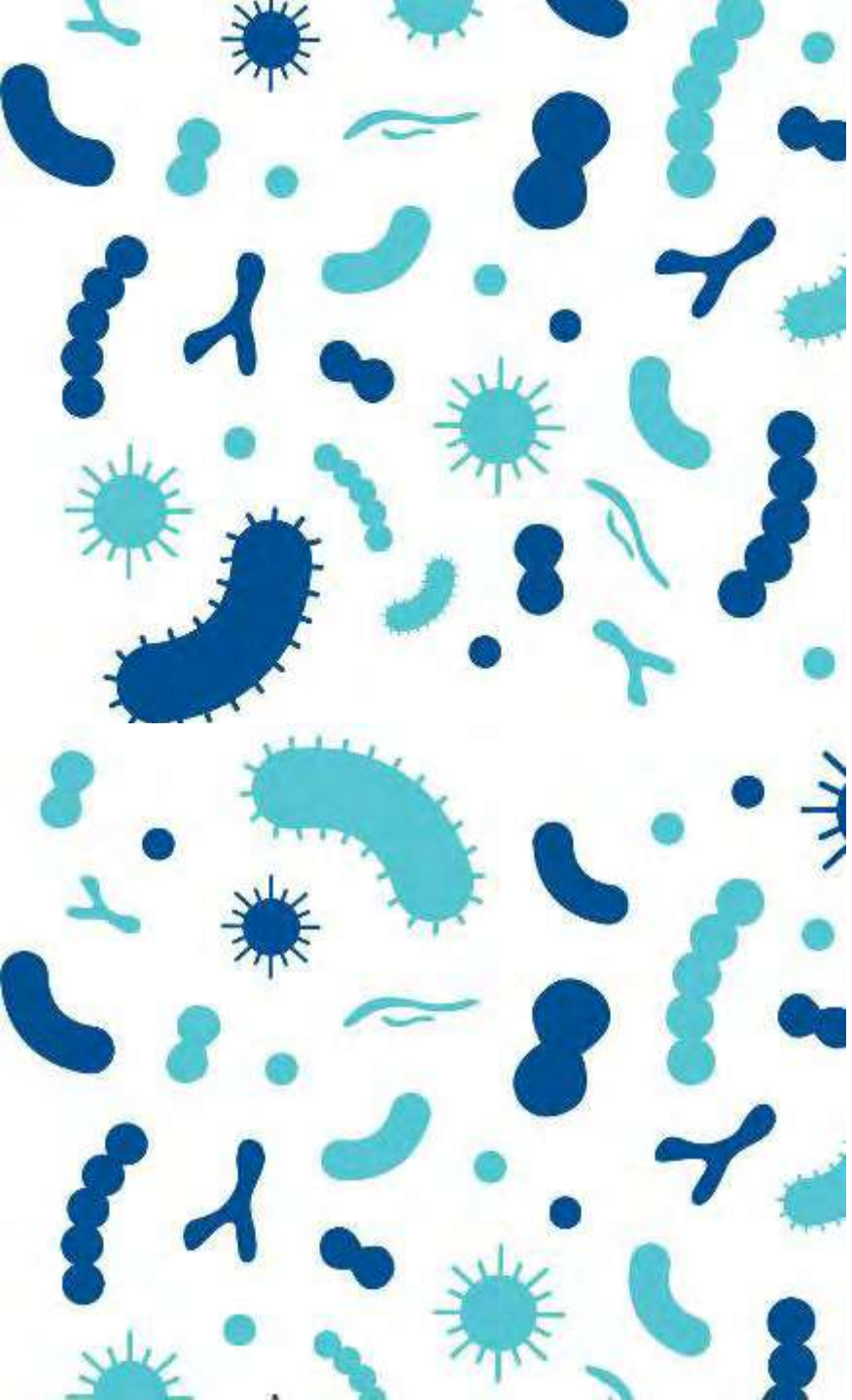
Hervé Affagard

CEO

Looking ahead

	Clinical program	Next step & timeline	
Onco-hematology	**MaaT013 (pooled enema)** *FDA & EMA Orphan Drug Designation*	Intermediate review ORR	*H1 2023* *H2 2023*
	MaaT033 (pooled capsule) *Post allo HSCT*	Launch of Phase 2/3 OR-ALLO (pivotal)	*Q4 2022*
Immuno-oncology	**MaaT013 (pooled enema)** *Improving ICI responses in metastatic melanoma*	Interim partial data review	*H1 2023*
	MaaT03X (fermented capsule) *Undisclosed indications*	Start of Phase 1/2	*H1 2023*
cGMP production	**Increasing cGMP production capacities**	Opening of the first and largest exclusive Microbiome Ecosystem Therapies facility in Europe	*2023*

** Sponsored by AP-HP*



THANK YOU

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