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MICROBIOTERAPIA FECAL ALOGÉNICA COMO TRATAMIENTO DE LA EICR AGUDA GASTROINTESTINAL REFRACTARIA: RESULTADOS DEL PROGRAMA DE ACCESO TEMPRANO EN EUROPA

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LXVI Congreso nacional SEHH. Sesión TPH
Palma de Mallorca, 25 de octubre 2024

Disclosures

Speaker honoraria: Pfizer, MSD, Gilead, AMGEN, Novartis

Consultant or advisor: Kite, Novartis, Jazz, Sanofi, Maat Pharma

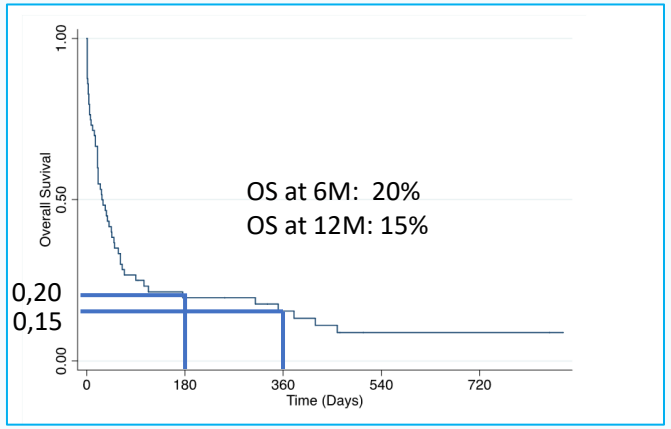
Introduction

Fecal microbiotherapy and gastro-intestinal acute GvHD

Treatment of GI-aGvHD is an unmeet medical need

aGvHD after ruxo resistance/intolerance: unmet medical need, poor survival

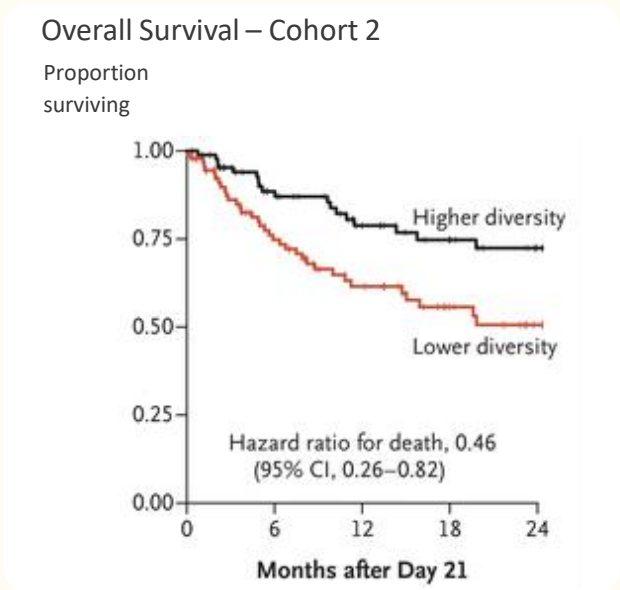
No validated treatments are available for acute GvHD that is refractory to steroids and ruxolitinib, and therefore it remains an unmet medical need



Median survival of 28 (range: 15-253) days

Abedin et al, 2021 - Malard et al, 2023

Link between gut microbiota dysbiosis and GvHD outcomes is well established



Peled, J.U. & al N Engl J Med 2020382:822-34

FMT was proven to be safe and effective in highly immunosuppressed patients

Promising results with FMT for SR-GI-aGvHD in case reports and small series

Abbreviations: SR-GI-aGVHD, steroid-refractory gastro-intestinal acute graft-versus host disease

Introduction
MaaT013

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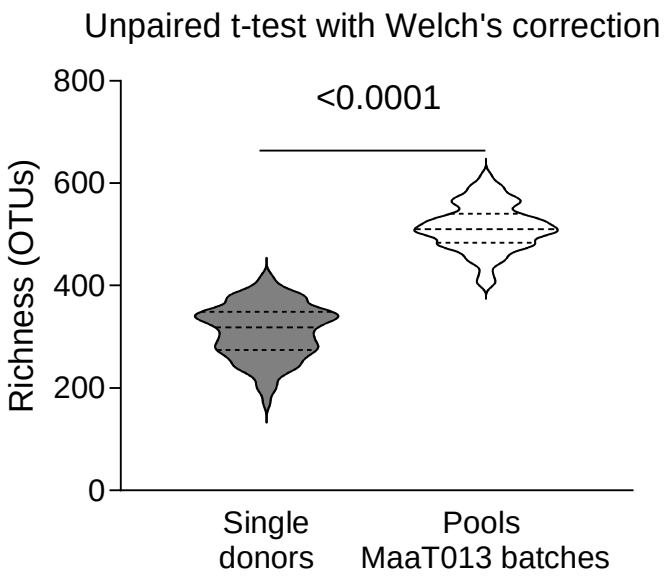
An immunosuppressant sparing agent to restore the microbiome and treat aGvHD

Organ drug designation status from EMA and FDA



Significant increase of pooled product richness
when compared to mono-donor products

Characteristics
Pooled microbiota: a high-richness, high-diversity, full ecosystem, containing Butycore™, 24 months stability at -80°C

Administration
3 doses (150 mL enema bag) within 2 weeks

Available Clinical Data
- ✓ HERACLES Phase 2 Clinical Trial, n=24,
- ✓ Early Access Program, data on n=140, ongoing (> 150 patients treated as of March 2024)

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

Malard et al, eclinical medicine 2023

Introduction

MaaT013: Mechanism of action

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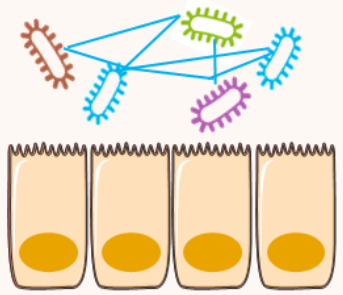
Novel Agent to Treat aGvHD Acting by Restoring Immune Homeostasis and Gut Barrier Integrity

MaaT013

Resets microbial network

1 Restoration of barrier integrity

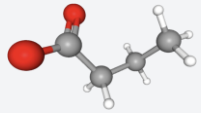


Restoration of microbial homeostasis and network

- Increasing diversity,
- Eradication of MDRB,
- Pathobiont growth inhibition

~~SEPSIS~~

2 Production of immunoregulatory metabolites



- SCFA (Butyrate, Proprionate)
- Immunoregulation (IL-10…)

3 Modulation of immune homeostasis

Regulatory T cells

- Immune homeostasis restoration
- Remission of symptoms

Based on preclinical and ongoing clinical studies: MaaT013 could restore microbiome diversity, regenerates gut barrier's protective effect, and significantly curbs inflammation.

Methods

Early access program indications

- In France: Authorized by the French regulator (ANSM) with Governing protocol for use
- In other countries in Europe: compassionate use

» **140 patients treated from July 2018 to October 2023, in 26 European sites (France, Italy, Spain, Austria, Germany)**

Indications:

- Adult patients with GI-aGvHD
- Known resistance to, or dependence on, corticosteroids (CS) alone or with failure of other lines of treatments
- GvHD with overlap syndrome

Contra-indications:

- **Active uncontrolled infection**
- Relapsed/ persistent malignancy requiring rapid immune suppression withdrawal
- Current or past veno-occlusive disease or other uncontrolled complication
- Absolute neutrophil count < 500/uL
- Absolute platelet count <10 000/uL
- Patients with negative EBV serology
- Current or past evidence of toxic megacolon, bowel obstruction or GI perforation
- Pregnancy, breastfeeding
- Known allergy to trehalose and maltodextrin

Results

Patient and disease characteristics

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Characteristics	All patients (N=140)
• **Age, median (range)**	58 (12-74)
• **Gender**	
○ Male	77 (55%)
○ Female	63 (45%)
• **Disease**	
○ Acute myeloid leukemia	55 (39%)
○ Myelodysplastic syndrome	26 (19%)
○ Myeloproliferativesyndrome	17 (12%)
○ Lymphoma	15 (11%)
○ Acute lymphoblastic leukemia	15 (11%)
○ Other	12 (9%)

Results

Acute GVHD characteristics

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Characteristics	All patients (N=140)
• **Steroid status**	
○ Steroid resistance	**115 (82%)**
○ Steroid dependence	25 (18%)
• **Type of aGvHD**	
○ Classical	86 (61%)
○ Late onset	13 (9%)
○ Overlap syndrome	20 (14%)
○ Hyper-acute	20 (14%)
○ Chronic	1 (1%)
• **aGvHD grade at the time of ATU request (Harris, 2016)**	
○ I	0
○ II	16 (11%)
○ III	**68 (49%)**
○ IV	**56 (40%)**
• **GvHD organ involvement at inclusion**	
○ GI only	**84 (60%)**
○ GI + skin	**34 (24%)**
○ GI + liver	8 (6%)
○ GI + skin + liver	6 (4%)
○ Missing data for skin and liver	8 (6%)

Results

Acute GVHD characteristics

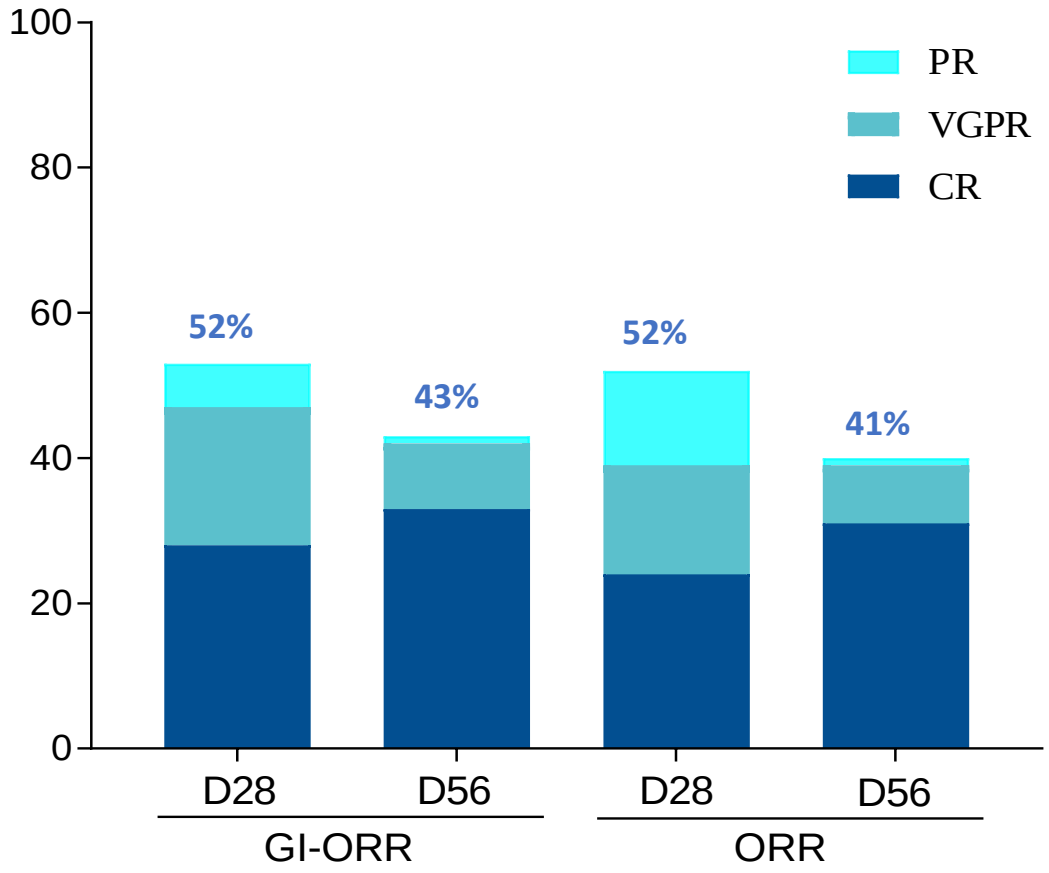
Characteristics	All patients (N=140)
• Median number of previous treatments for aGvHD (including CS) (range)	**2 (1-6)**
○ CS	140 (100%)
○ Ruxolitinib	121 (84%)
• Median number of MaaT013 doses administered (range)	3 (1-6)
• Route of MaaT013 administration	
○ Enema	139 (99%)
○ Nasogastric tube	1 (1%)

Results

Treatment response: all patients

D28 response, N (%)	Total N=140
• GI-ORR	73 (52%)
○ CR	39 (28%)
○ VGPR	26 (19%)
○ PR	8 (6%)
• Global ORR	74 (52%)
○ CR	34 (24%)
○ VGPR	21 (15%)
○ PR	18 (13%)

Sustainable response at D56



N=138 for Day 56, 2 missing data

Abbreviations: CR, complete response; VGPR, very good partial response; PR, partial response; ORR, overall response rate; GI, gastro-intestinal

Results

Treatment response: steroid dependent vs refractory

GI response N (%)	SR-aGvHD, N= 115	SD-aGvHD, N= 25
GI-ORR	**54 (47%)**	**20 (80%)**
CR	**25 (22%)**	**14 (56%)**
VGPR	20 (17%)	6 (24%)
PR	9 (8%)	0

Abbreviations: CR, complete response; VGPR, very good partial response; PR, partial response; ORR, overall response rate; GI, gastro-intestinal

Results

Treatment response: 3rd line ruxolitinib refractory

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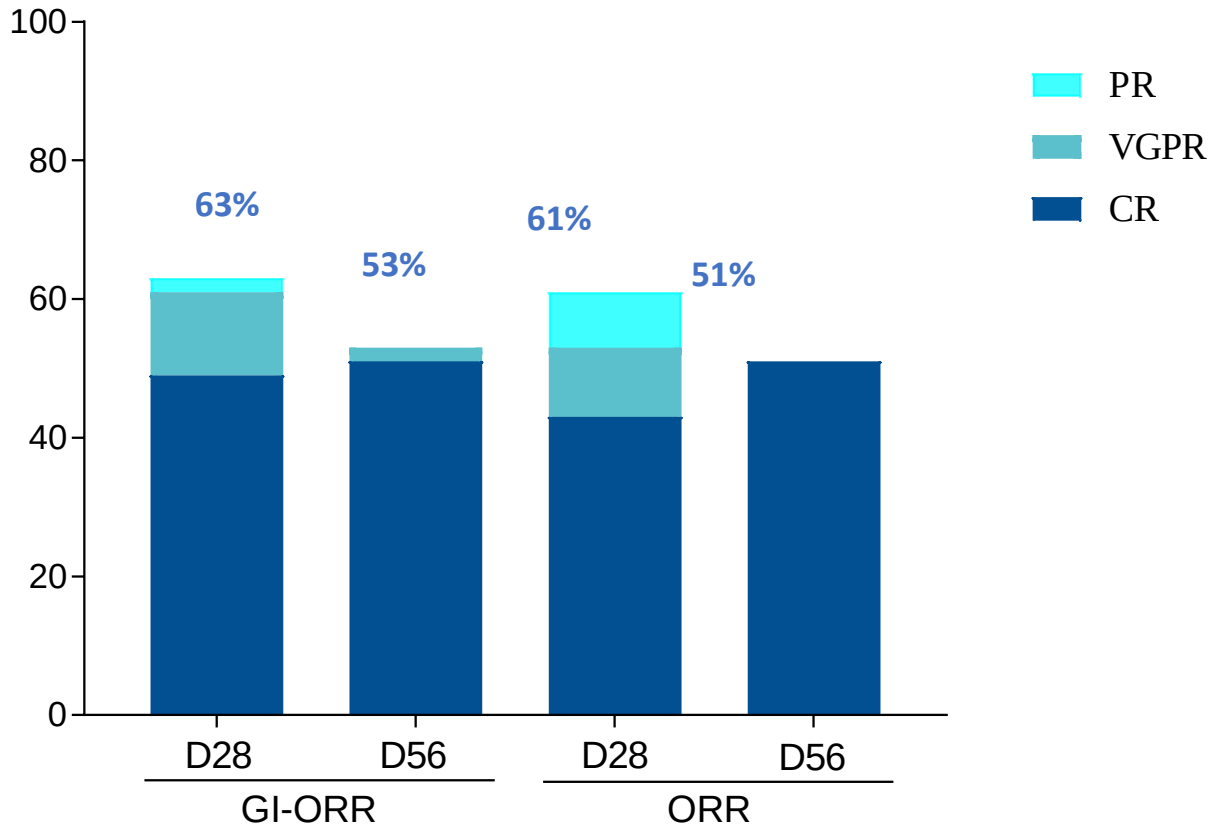
High rates of CR and VGPR
Sustainable response at D56

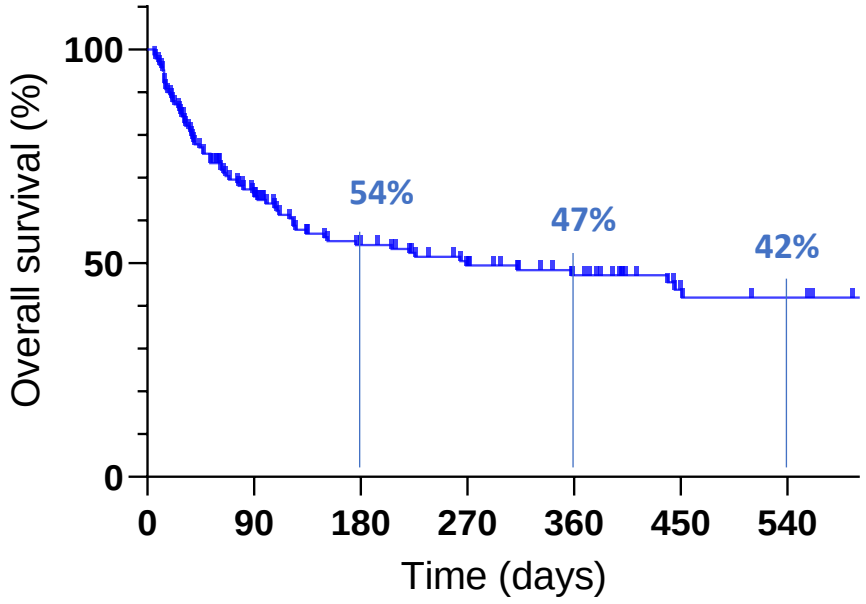
Response N (%)	Ruxolitinib refractory in 2nd line, MaaT013 in 3rd line N=49	
	GI-ORR	**ORR**
ORR	**31 (63%)**	**30 (61%)**
CR	**24 (49%)**	**21 (43%)**
VGPR	6 (12%)	5 (10%)
PR	1 (2%)	4 (8%)

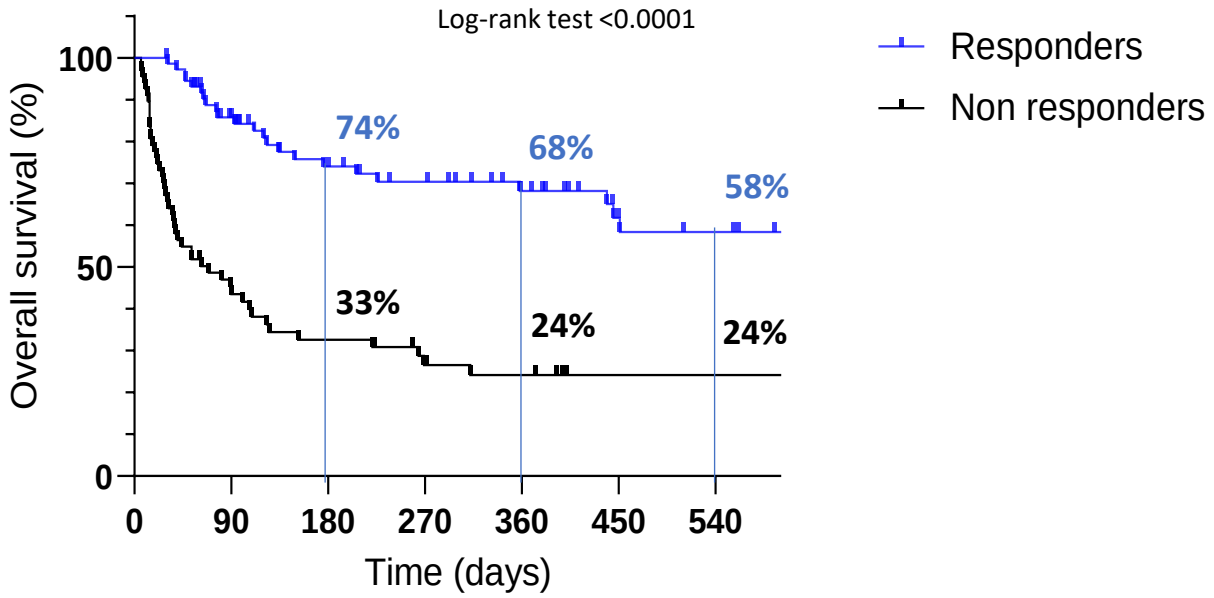


Abbreviations: CR, complete response; VGPR, very good partial response; PR, partial response; ORR, overall response rate; GI, gastro-intestinal

Results

Overall survival: all patients



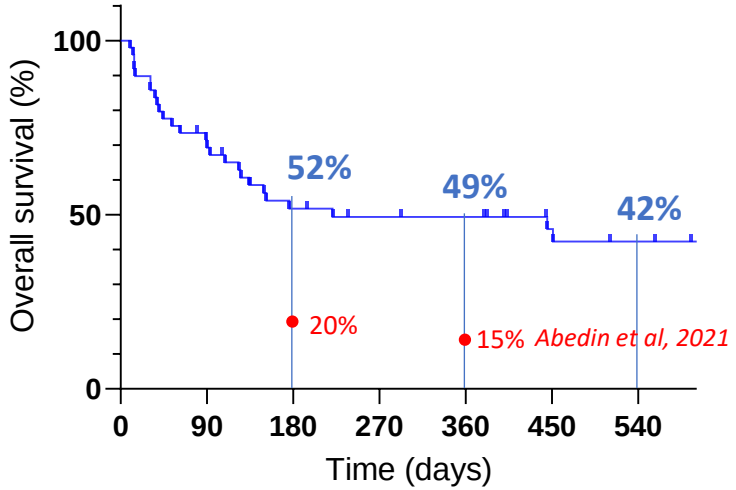


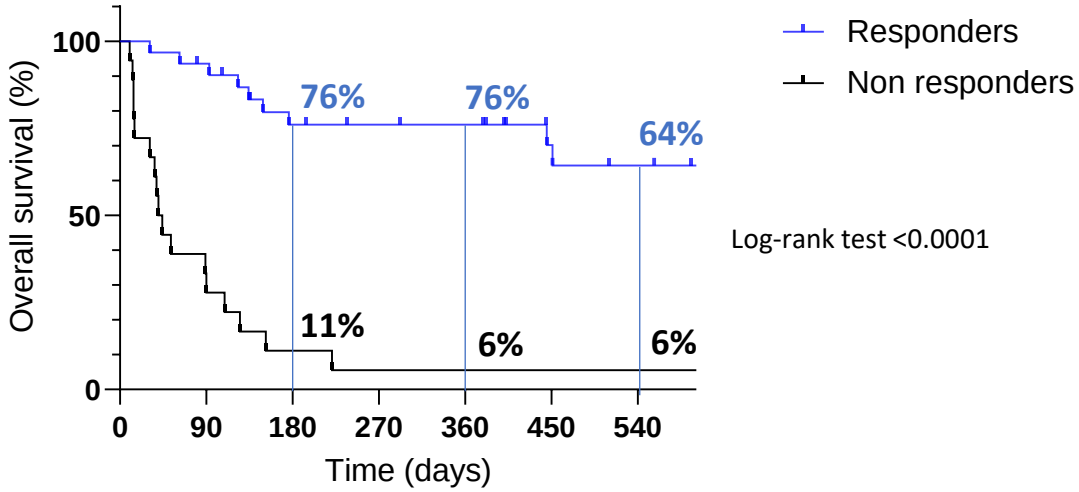
Clinical response to MaaT013 translates to increased overall survival

Abbreviations: CR, complete response; VGPR, very good partial response; PR, partial response

Results

Overall survival: 3rd line ruxolitinib refractory





Clinical response to MaaT013 translates to increased overall survival

Abbreviations: CR, complete response; VGPR, very good partial response; PR, partial response

Results

Safety

- 35 pharmacovigilance cases reported in 33 patients
  - 22 cases possibly related to MaaT013, including 10 bacteremia and 6 sepsis
  - 70 deaths reported: **GvHD in 28, severe infection in 24**, relapse in 11, hemorrhage in 2, neurological complications post allo-HCT in 1, respiratory distress in 1, cardiac arrest in 2 and unknown cause for 1 patient. No causality link with MaaT013 administration has been identified.
- 2 paediatric patients (aged 12 and 15) treated with MaaT013: well tolerated (no AE) and good efficacy
- Overall safety is good compared to historical data in such heavily pre-treated and fragile population

- **No report of pathogen transmission**
- **Only 2 cases of non-pathogenic commensal bacteria associated with infectious events**

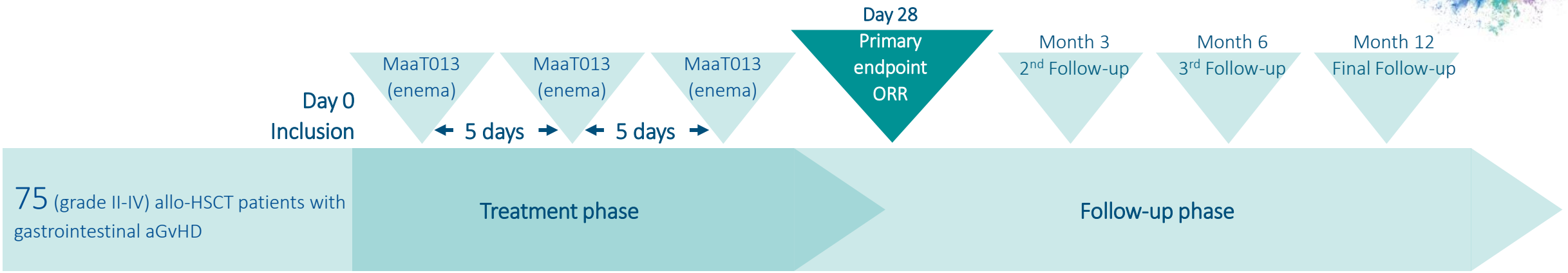
Conclusions

- MaaT013 seems effective therapy in R/R aGVHD
- Good safety profile
- High overall survival in this severe population
- Innovative mechanism of action based on immune modulation
- Further investigation currently ongoing in a phase 3 trial “ARES” (NCT04769895)

Abbreviations: ORR, overall response rate; GI, gastro-intestinal; SR-aGVHD, steroid-refractory acute graft-versus-host disease; SD-aGVHD, steroid-dependent acute graft-versus-host disease

Conclusions

Ares Phase 3 study: 3rd line agent in GI aGVHD



- 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
- Sites initiated in Europe in Q1 2022 (France, Germany, Spain, Italy, Austria, Belgium)
- First patient included in March 2022
- Positive review by DSMB in October (N=30): favorable benefit/risk ratio, with “high efficacy and low toxicity.”

ClinicalTrials.gov Identifier: NCT04769895

Acknowledgments

Patients, Caregivers and Healthy Donors involved

- Michael Loschi, Thomas Cluzeau (CHU Nice)
- Faezeh Legrand, Reynier Devillier, Angela Granata, Valerio Maisano (Institut Paoli Calmettes)
- Anne Huynh, Sarah Guenounou, Cécile Borel (Institut Universitaire du Cancer Toulouse)
- Corentin Orvain (CHU Angers)
- Amandine Charbonnier, Delphine Lebon (CHU Amiens)
- Deborah Desmier, Niels Moya (CHU Poitiers)
- Jean-Baptiste Mear, Faustine Lhomme, Stanislas Nimubona (CHU Rennes)
- Caroline Lejeune, Jérôme Cornillon (ICL St Priest en Jarez)
- Amandine Le Bourgeois, Patrice Chevallier (CHU Nantes)
- Clémence Médiavilla (CHU Bordeaux)
- Helene Labussière-Wallet (CHU Lyon)
- Marie-Anne Couturier (CHU Brest)
- Claude-Eric Bulabois, Martin Carré (CHU Grenoble)
- Hélène Lanic, Vincent Camus (Centre Henri Becquerel, Rouen)
- Sylvain Chantepie (CHU Caen)
- Patrice Ceballos, Jean-Jacques Tudesq (CHU Montpellier)
- David Beauvais (CHRU Lille)
- Etienne Daguindau (CHU Besançon)
- Karin Bilger (CHU Strasbourg)
- Stefan Klein (Mannheim, Germany)
- Sarah Altmeyer (Homburg, Germany)
- Francesca Patriarca (Udine, Italy)
- Francesco Saraceni (Ancona, Italy)
- Jakob Rudzki (Innsbruck, Austria)
- Florent Malard, Mohamad Mohty (Hôpital Saint-Antoine, AP-HP)
- MaaT Pharma’s team

Thank you!