A First-In-Human phase I trial of Murlentamab, a first-in-class Anti-Müllerian-Hormone-Receptor II (AMHRII) monoclonal antibody acting through Tumor-Associated Macrophage engagement, as single agent and in combination with carboplatin and paclitaxel in AMHRII-expressing advanced/metastatic gynecological cancer patients

2521

Alexandra Leary[1], Ahmad Awada[2], Jean-Pierre Delord[3], Anne Floquet[4], Isabelle Ray-Coquard[5], Cyril Abdeddaim[6], Michel Fabbro[7], Elsa Kalbacher[8], Ignace Vergote[9], Susana Banerjee[10], François-Xavier Frenois[11], Grégory Noel[2], Olivier Lantz[12], Lydie Cassard[13], Agnès Coste[14], Marine Villard[15], Fanny Lemée[16], Isabelle Tabah-Fisch[16], Christophe Le Tourneau[12]

[1]GINECO Group and Gustave Roussy Cancer Campus, Villejuif, France; [2]Institut Jules Bordet- Université Libre de Bruxelles, Brussels, Belgium; [3]Institut Universitaire du Cancer Toulouse – Oncopole, Toulouse, France; [4]GINECO Group and Institut Bergonié, Bordeaux, France; [5]GINECO Group and Centre Léon Bérard, Lyon, France; [6]Centre Oscar Lambret, Lille, France; [7]Institut du Cancer de Montpellier, Montpellier, France; [8]CHRU Jean Minjoz, Besançon, France; [9]University Hospitals Leuven, Leuven Cancer Institute, Leuven, Belgium; [10]Royal Marsden Hospital, London, United-Kingdom; [11]Institut Universitaire du Cancer Toulouse – CHU Toulouse, Toulouse, France; [12]Institut Curie, Paris, France; [13]Laboratory of Immunomonitoring in Oncology, Gustave Roussy, Villejuif, France; [14]UMR152 UPS-IRD Toulouse, France; [15]Hospices Civils de Lyon, Pierre Benite, France; [16]GamaMabs Pharma, Toulouse, France.

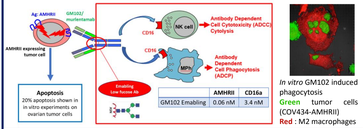
INTRODUCTION

Murlentamab (GM102)

Murlentamab is a glyco-engineered monoclonal humanized IgG1 antibody displaying high affinity towards both:

- AMHRII, the receptor of Anti-Müllerian hormone of type II, present on tumor cells, via its Fab fragment
- CD16, present on effector cells, via its low fucose Fc fragment (Emabling technology platform)

Murlentamab acts through tumor associated macrophages (TAM) and NK engagement, resulting in enhanced tumor phagocytosis and cytotoxicity



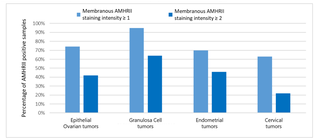
In vitro GM102 induced phagocytosis
Green tumor cells (COV434-AMHRII)
Red : M2 macrophages

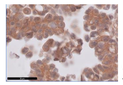
AMHRII is widely detected in gynecological tumors

(IHC, fixed tissues)

AMHRII membrane is detected in > 60% gynecological cancers

251 samples from C101 study prescreening





High Grade Serous Ovarian Cancer AMHRII membranous score 2

STUDY OBJECTIVES AND STATUS

Objectives

Primary	- Determine murlentamab recommended dose(s) for phase 2 (RP2D) (DLT during first cycle)
Secondary	- Safety - Pharmacokinetics (PK) - Immunogenicity (ADA detection) - Antitumor activity (RECIST1.1 and biomarkers)
Exploratory	- Circulating immune cell changes in peripheral blood - Immunological changes (lymphocytes T, macrophages, NK cells) in the Tumor MicroEnvironnment (biopsies)

Current status

- 78 patients enrolled
- Single agent dose escalation part completed, escalation combination cohorts and phase 1b expansion cohorts ongoing
- **Interim Analysis (IA)** (N=68): cut-off date 31 Dec 2018

EFFICACY - OBJECTIVE RESPONSES AND CLINICAL BENEFIT

Investigator's assessment

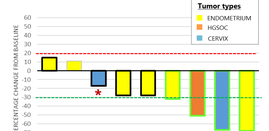
	Murlentamab single agent			murlentamab + CP
	Dose escalation N=28	**Expansion SCST** N=15[1]	**Expansion EOC** N=15	**Dose escalation** N=9
Objective Responses	**1 PR** central review (GCT)	**0****	**0**	**4** (44%)**, including 1 CR (2 endometrium, 1 cervix, 1 HGSOC)
Clinical Benefit* *at 4 months*	**7 (25%)** (4 GCT, 2 HGSOC, 1 cervix)	**7 (47%)** (all GCT)	**2 (13%)**	**6 (67%)** (4 endometrium, 2 cervix)

***SCST**: Sex-Cord Stromal Tumors; **EOC**: Epithelial Ovarian Cancer; **CP**: carboplatin-Paclitaxel [1]: 14 patients with Granulosa Cell Tumors and 1 patient with sex-cord tumor with annular tubules; *Clinical benefit = complete response + partial response + stable disease; **Additional PR in patients 07-10 and 03-07 not included in IA*

Murlentamab single agent, subset of GCT patients (N=20)

Since IA, 1 further GCT has shown objective PR (patient 07-10)

Murlentamab + carboplatin-paclitaxel (N=9)



Best Overall Response (*RECIST 1.1*)

PD SD PR ★ PR per central radiological review ★ PR post-IA cut-off

EFFICACY IN TWO DEMONSTRATIVE CASES

Investigator's and central radiological review assessments

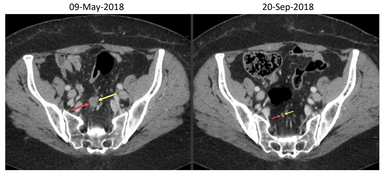
Patient 03-05 (combination with chemotherapy)

48-year-old female, diagnosed in 2009 with endometrioïd carcinoma

Two previous chemotherapy lines; progression after 4,6 months under carboplatin-caelyx; last treatment was megestrol (6 months) with progression 6 months after discontinuation; best response was stable disease

Achieved rapid (end C2) and durable (>10 cycles) **Complete Response** under **murlentamab 7 mg/kg q1w in combination with carboplatin-paclitaxel**

Baseline 09-May-2018 | End Cycle 6 20-Sep-2018



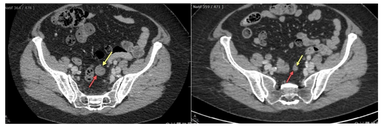
Patient 07-10 (single agent, post-IA)

68-year-old female, diagnosed in 1996 with granulosa cell tumor

Four relapses treated by surgeries (1996, 2007, 2014, 2017) and 2 chemotherapy lines (2007 and 2017), progression after 15 months under carboplatin-paclitaxel (last line)

Achieved **Partial Response** (from end C4 confirmed at end C6) under **murlentamab 15 mg/kg q2w single agent**

Baseline 29-Nov-2018 | End Cycle 4 25-Mar-2019



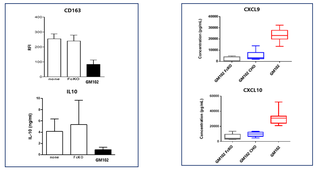
MURLENTAMAB RESTORES TAM ANTI-TUMORAL FUNCTIONS

In-vitro data

Murlentamab results in macrophage M1 polarization and subsequent activation of cytotoxic T cells

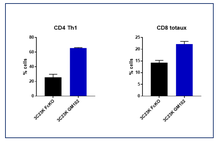
Macrophage shift from M2 to M1 phenotype

- Downregulation of CD163
- Decrease of immunosuppressive cytokines (i.e. IL10)
- Release of proinflammatory cytokines and chemokines (CXCL9, CXCL10)



Activation and recruitment of T lymphocytes

- Increase of CD4-Th1 and total cytotoxic CD8



Studies conducted in an *in vitro* model of co-culture with M2 macrophages (PBMC differentiated with IL10+GMCSF) and AMHRII stably expressing tumor cell line

Tumor immunology and immunotherapy AACR special conference Miami November 2018

PATIENT BASELINE CHARACTERISTICS

	Phase Ia Single agent GM102 (N=29)	Phase Ia GM102 + CP (N=9)	Phase Ib sex-cord tumors (N=15)	Phase Ib epithelial ovarian cancers (N=15)
Age (years) *Median (min-max)*	64 (23.0-79.3)	64 (48.8-79.4)	65 (40.5-80.2)	59 (48.1-81.6)
Number of previous systemic therapies *Median (min-max)*	4 (1-13)	3 (1-5)	4 (2-12)	5 (1-7)
TTP under previous line of therapy (months) *Median (min-max)*	4.16 (0.4-46.9)	5.98 (1.7-9.3)	5.75 (1.8-72)	6.44 (1.2-15.2)

CP: carboplatin-paclitaxel; TTP: Time To Progression; TFI: Treatment Free Interval

SAFETY – MURLENTAMAB-RELATED TOXICITIES

No DLT observed at all doses and schedules tested

Murlentamab was very well tolerated with few and transient immune toxicities

Preferred Term	Grade≥3 events (patients)	SUSARs (patients)	Immune AEs, all grades (patients)
Phase Ia – GM102 monotherapy N=29			
Rash/erythema/rash erythematous	-	-	7 (4)
Influenza-like illness	-	1 (1)	4 (1)
Asthenia	1 (1)	-	-
Decreased appetite	1 (1)	1 (1)	-
Weight decrease	1 (1)	-	-
Atrial fibrillation	-	1 (1)	-
Arthralgia	-	-	1 (1)
Phase Ia – GM102 + CP N=9			
Neutropenia	1 (1)	-	-
ALAT increased	1 (1)	-	-
ASAT increased	1 (1)	-	-
Phase Ib – GM102 monotherapy N=30			
Arthralgia	1 (1)	-	3 (2)
Facial Oedema	-	1 (1)	2 (1)
Vomiting	1 (1)	-	-
Nausea	1 (1)	-	-
Asthenia	1 (1)	-	-
Fatigue	1 (1)	-	-
Neutropenia	1 (1)	-	-
Rash	-	-	2 (2)

PHARMACOKINETICS & ADA DETECTION

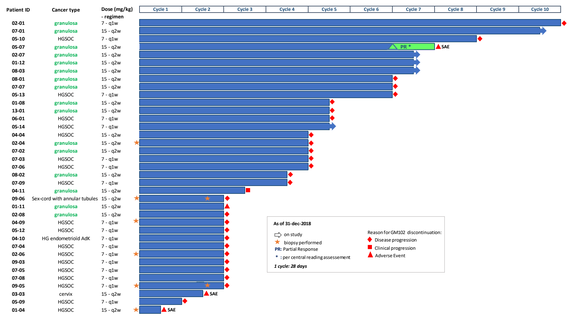
- The average terminal half-life was 4-6 days
- Chemotherapy did not alter murlentamab PK
- From first infusion, 28 days were needed to reach murlentamab Steady State
- A first cycle loading dose of murlentamab 10mg/kg q1w is recommended
- No ADA detected under murlentamab

PATIENT OVERVIEW AS OF DEC 31, 2018

Murlentamab single agent at RP2D (N=37)

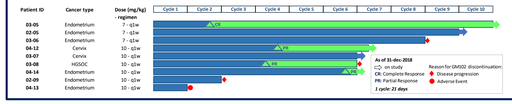
Patients with prolonged clinical benefit were mostly GCT patients

6/9 GCT patients had a longer PFS under murlentamab than under last systemic therapy



Murlentamab in combination with carboplatin-paclitaxel (N=9)

5/9 patients had a longer PFS under murlentamab + carboplatin-paclitaxel than under last systemic therapy



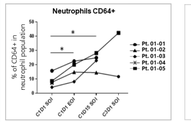
MURLENTAMAB INDUCED IMMUNE CELL ACTIVATION IN BLOOD AND TUMOR MICROENVIRONMENT

Exploratory analysis

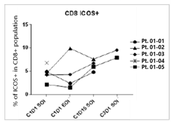
Peripheral Blood (flow cytometry)

Circulating immune cell activation under murlentamab was observed despite interpatient variability

Neutrophil activation (CD64)



T cell activation (ICOS)



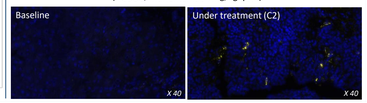
SOI: Start Of Infusion; EOI: End Of Infusion; EOT: End Of Treatment

TME (paired biopsies, fluorescent immunohistochemistry)

Macrophage activation under murlentamab was observed in 1/2 patients analyzed with a 3.4-fold increase of **CD86*** (**yellow dots**) (Halo software)

**CD86 is expressed on an antigen-presenting cells and provides costimulatory signals necessary for T cell activation*

Patient 09-05
(HGSOC; murlentamab 7mg/kg q1W)



C101 FIH STUDY DESIGN

C101 STUDY
MURLENTAMAB IN GYNECOLOGICAL CANCER PATIENTS

AMHRII positive in most recent archival tumor tissue *(IHC)*
Having exhausted available therapeutic options
Measurable disease (radiological target lesion)
Performance status ≤1, adequate organ functions

EudraCT: 2015-004252-22 - NCT02978755

Phase 1a Dose Escalation
3 (+3) patients in each cohort and 6 patients in last cohort

Murlentamab single agent							Murlentamab + carboplatin-paclitaxel	
1 mg/kg q2w	3 mg/kg q2w	7 mg/kg q2w	10 mg/kg q2w	15 mg/kg q2w	20 mg/kg q2w	7 mg/kg q1w	7 mg/kg q1w	10 mg/kg q1w

Recommended Doses
15 mg/kg q2w and 7 mg/kg q1w

Recommended Dose
7 mg/kg q1w

Phase 1b single agent RP2D Expansion cohorts

Sex-cord stromal tumors	Epithelial Ovarian cancers
15 mg/kg q2w n=25	7 mg/kg q1w n=15

q2w: every two weeks ; q1w: every week

CONCLUSIONS

- Murlentamab is a first-in-class mAb targeting AMHRII at the tumor level, acting through tumor-associated macrophage and NK engagement
- Murlentamab was very well tolerated at all doses and schedules tested, either as single agent or in combination with chemotherapy
- The recommended doses are 7 mg/kg weekly and 15 mg/kg every 2 weeks for murlentamab monotherapy and 7 mg/kg weekly in combination with chemotherapy. A loading dose of 10 mg/kg every week is recommended for the first cycle
- Murlentamab demonstrated immune activation in the tumor microenvironment and in peripheral blood
- Proof of concept for activity has been achieved in heavily pretreated patients:
  - 2 partial responses with murlentamab single agent in GCT patients
  - 4 responses with murlentamab + chemotherapy in patients who had achieved stable disease as best response under their last chemotherapy
  - Longer PFS than under previous chemotherapy in two third of patients (murlentamab single agent in GCT patients and murlentamab in combination with carboplatin-paclitaxel)
- These results support further development of murlentamab in combination with chemotherapy and/or immunological agents in TAM-infiltrated cancers expressing AMHRII.

Acknowledgements: