GM102, a first-in-class monoclonal glyco-engineered antibody (Ab) targeting Anti-Mullerian-Hormone-Receptor II (AMHRII): safety and hints of activity in Granulosa Cell Tumors (GCT)

LBA15

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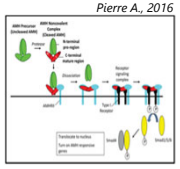
AMHRII plays a driving role in sexual differentiation of the embryo

- **Exclusive Type II receptor of Anti-Müllerian Hormone (AMH)**
  - Responsible for AMH induced **regression of Mullerian Duct** in male foetus
  - Member of **TGF-beta receptors super-family**
- **Part of serine/threonine receptor kinase activated in a multi-step pathway**
  1. **Tetra-merizing** upon AMHRII ligand binding
  2. Triggering **serine-threonine kinase activity of AMHRI** (activine like kinase receptor)
  3. Activating **Smad intracellular pathway**
  4. Resulting in **cell apoptosis** (embryo)

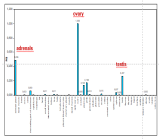
Pierre A., 2016

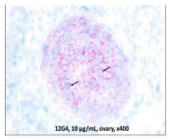


AMHRII is repressed in adult normal tissue

- **AMHRII is fully repressed in normal tissues, only expressed in :**
  - Testis : Leydig and Sertoli cells
  - Ovary : Granulosa cells, with a major role in primary follicles maturation
- **Confirmed organ selectivity by qRT-PCR on 48 normal tissues panel**

Origen –GM unpublished data





AMHRII is re-expressed in cancers

- **As an embryonic receptor AMHRII is re-expressed in Müllerian-derived cancers** i.e gynecological tumors including ovarian cancers (Bakkum, 2008)
  - **Membranous expression in 60-70% of samples,**
  - **Induced by WT1** as a potent transcription factor (Klattig, 2007; Poole, 2011)
  - **Associated with EMT or stem cell characteristics** (Meirelles, 2012)
- **Also shown to be expressed in several solid tumors**
  - **Including CRC**, NSCLC, RCC and HCC (Barret , 2018)
- **Constitutive AMHRII expression in Granulosa Cell Tumors (GCT)**
  - **Biomarker associated with the pathognomonic FOX L2**

Significant AMHRII expression has been confirmed in GCT

- **At the transcriptomic level**
  - qRT-PCR on 13 FFPE

A. Leary, IGR,Villejuif

AMHRII RNA over expressed in all samples

AMHRII protein IHC detected correlated to its RNA transcript

- **At the protein level**
  - IHC on TMA of 198 samples

A. Farkkila, Helsinki

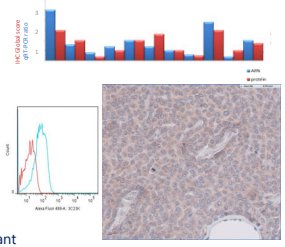
Expression in > 90% of cases

Over-expression in 60%

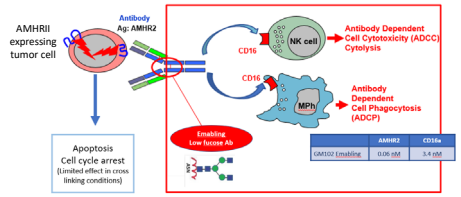
  - FACS on 5 fresh GCT

Ch. Dumontet, Léon Bérard Lyon

Preliminary data show a significant expression ~ **69.000 receptors/cell**



Glyco-engineered GM102 displays high bi-specific affinities towards both AMHRII and CD16



Estupina P. et al., Oncotarget 2017

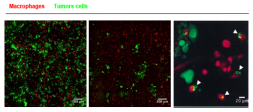
➡ **High affinity towards AMHRII and CD16 allows**

- Close recognition via Fab of AMHRII positive tumor cells by GM102
- Strong subsequent engagement via FC of TAM into targeted phagocytosis

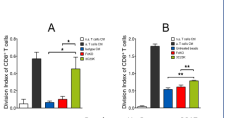
GM102 induces M2-dependent ADCP followed by T cell proliferation

- **Coculture experimental conditions mimics in vivo TME**
  - **Effector cells**: M2 macrophages (CD206$^+$/CD163$^+$; PBMC cultivated and polarized 4d with M-CSF) **(Red cells)**
  - **Target cells**: COV434-AMHRII (40 000 receptor/cell) **(Green cells)**
  - **Effector/target ratio** (1:2) similar to that observed in tumors
  - 4-day incubation with GM102/3C23K or 3C23K FcKO (10µg/ml)

- **GM102 induces full phagocytosis by M2-like macrophages**



- **Phagocytosis by GM102 then results in CD8+ T cell proliferation**



Bougherara H., Oncotarget 2017

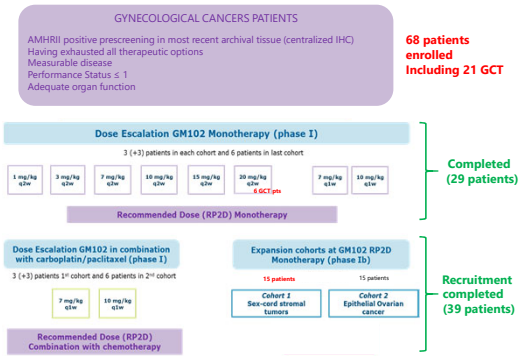
- **Indirect T cell activation by GM102 is due** to strong concomitant release of
  - pro-inflammatory CK (IL1b, IL6, IL12 responsible for T Cell activation)
  - and chemokines responsible for T cell trafficking (CXCL9, CXCL10)
- **This effect is not shown with non glyco-engineered version of GM102**

(Allain T., accepted for Tumor Immunology and Immunotherapy, 2018)

Granulosa cell tumor (GCT) is a rare orphan ovarian cancer (OC)

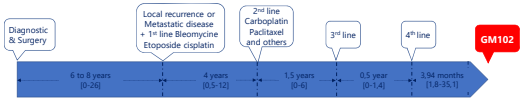
- **GCT represents about 6.5% of all OCs** (22,400 OCs in USA every year, 27,100 in EU5)
- **It is a hormonally active tumor**, typically secreting estrogen and associated with symptoms of hyperestrogenism
- **GCT evolution is characterized by indolent course**, **late and multiple recurrences**
- **Diagnosis is made at Stage 1** in 74 to 95% of patients
- **Initial treatment of GCT is based on surgery;** adjuvant chemotherapy or hormonotherapy can be proposed, depending on tumor stage
- **20% of initially resectable GCT patients are estimated to relapse** 4 to 5 years later
- **Relapses management is based on** BEP and/or combo Carboplatin Paclitaxel
- **Median survival after a recurrence is 5 years**
- **Unmet medical need:** no targeted therapy is approved in GCT.

C101 Phase I Study in advanced gynecological cancer EudraCT 2015-004252-22, NCT02978755



C101- GCT cohort (n=21)

- Median age: 65 years [41-80]
- Median interval since initial diagnosis: **18 years** [8-33]
- All patients had surgery at initial presentation
- Heavily pre-treated patients with multiple lesions in multiple organs, **88% patients were metastatic** (12% had a loco-regional recurrence)
- In median, **patients received 4 previous lines** of systemic treatment [3-12] (GM102 given as 5th line)



C101 study- initial results as of November 5th, 2018

Excellent safety

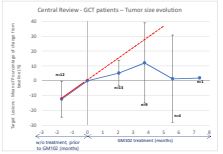
- **No dose limiting toxicity** up to 10mg/kg Q1W and 15mg/kg Q2W
- Toxicities mostly grade 1-2 fatigue in one third of patients (N=7), and grade 3 anorexia and weight loss (N=1).

Linear pharmacokinetics

- Half life ~ 7 days

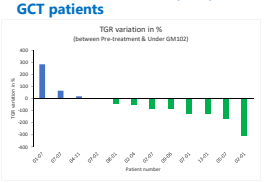
Hints of activity

- **1 PR** according to central review
- **4/20 (20%) patients had a tumor size decrease** under GM102
- **11/20 (50%) pts had Disease Control (PR or SD) at 4 months**
- 5/15 (33%) patients had Disease Control at 6 months – (5 ongoing)



Tumor Growth Rate (TGR) change under GM102

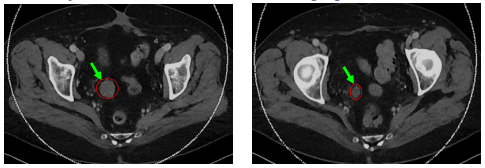
- Central review (Banook) on the 12 evaluated patients (Sept 3rd 2018)
- **TGR decreased in 8/12 (66%) GCT patients**
- **Mean decrease in TGR was 52%**



	Pretreatment TGR % mean [min ; max]	Under GM102 TGR % mean [min ; max]	TGR variation % mean [min ; max]
TGR variation	19,2 [2,5 ; 78,3]	6,1 [-16,6 ; 26,5]	-52,7 [-311,7 ; +283]

Partial response in a GCT patient

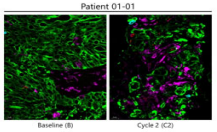
- **Partial response (central review) with transient inhibin B decrease after 6 cycles of GM102 at the dose of 15 mg/kg Q2W (RECIST v1.1)**



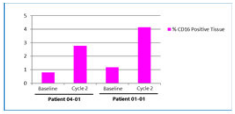
Baseline (15-Mar-2017) **End Cycle 6 (28-Aug-2017)**

GM102 PD effects in the Tumor Micro Environment (TME)

- Evolution of TME markers under GM102 in 2 paired biopsies (2 OC pts)
- CD16+ cells are abundantly present in the TME
- Under GM102 CD16 expression showed a dramatic increase



CD16 (pink), CD8 (red) and Grandzyme B (blue) expression at baseline and cycle 2 on tumor biopsies (patient 01-01). Pan-cytokeratin (green) is used as a tumor cell marker.



Percentage of CD16 + stained area evaluated using the HALO HighPlex Immunofluorescence module of Indica Labs, at baseline and cycle 2 on tumor biopsies (patients 04-01 and 01-01).

Conclusion

- AMRH2 is an embryonic receptor re-expressed in solid tumors, especially in GCT where it is constitutive
- Glyco-engineered GM102 displays high bi-specific affinities towards both AMHRII and CD16 resulting in targeted phagocytosis through M2 macrophages engagement followed by T Cell activation of the TME
- In GCT patients GM102 administrated as a single agent (15mg/kg Q2W) is well tolerated and shows objective signs of activity with tumor volume reduction in 20% of the cases and 50% TGR inhibition
- Those encouraging results in an orphan disease with high unmet need and no approved therapies beyond platinum, pave the way for further development in GCTs.