PHASE 2 STUDY RESULTS OF MURLENTAMAB, A MONOCLONAL ANTIBODY TARGETING THE ANTI-MULLERIAN-HORMONE-RECEPTOR II (AMHRII), ACTING THROUGH TUMOR ASSOCIATED MACROPHAGE (TAM) ENGAGEMENT IN ADVANCED/METASTATIC COLORECTAL CANCERS

214

Eric Van Cutsem[1], Bohuslav Melichar[2], Marc Van Den Eynde[3], Jana Prausova[4], Karen Geboes[5], Jeroen Dekervel[1], Denisa Vitaskova[2], Astrid De Cuyper[3], Zdenek Linke[4], Nathalie Van Acker[6], François-Xavier Frenois[6], Grégory Noël[7], Jean-François Prost[8], Jean-Marc Barret[8], Bérengère Jean[8], Isabelle Tabah-Fisch[8]

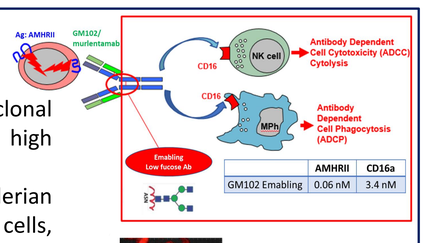
[1]University Hospitals Gasthuisberg/Leuven & KULeuven, Leuven, Belgium; [2]Olomouc University Hospital, Olomouc, Czech Republic; [3]Cliniques Universitaires Saint-Luc, Brussels, Belgium; [4]Motol University Hospital, Praha, Czech Republic; [5]Gent University Hospital, Gent, Belgium; [6]Institut Universitaire du Cancer Toulouse–Oncopole, Toulouse, France; [7]Institut Jules Bordet-Université Libre de Bruxelles, Brussels, Belgium; [8]GamaMabs Pharma, Toulouse, France.

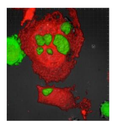
INTRODUCTION

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)



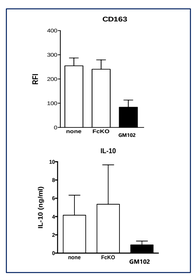


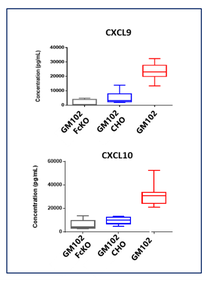
In vitro GM102 induced phagocytosis
Green tumor cells (COV434-AMHRII)
Red : M2 macrophages

Murlentamab restores tumor associated macrophages (TAM) antitumoral functions and NK engagement, resulting in enhanced tumor phagocytosis and cytotoxicity.

Macrophage shift from M2 to M1 phenotype

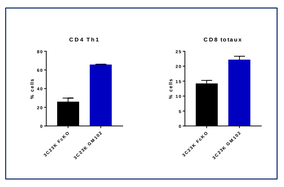
- Downregulation of CD163 and decrease of immunosuppressive cytokines (i.e. IL10)
- Release of proinflammatory cytokines and chemokines (CXCL9 and CXCL10)





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 expressing tumor cell line

Tumor immunology and immunotherapy AACR special conference Miami November 2018

AMHRII EXPRESSION IN SOLID TUMORS

Fixed tissues, IHC study:

- 907 samples analyzed
- AMHRII staining frequency and intensity similar to gynecological cancers in 4 other solid tumors

Cancer type	N samples	% samples > 1.5 global score and ≥1 membrane
Renal Cell	35	71
Hepatocarcinoma	40	68
Colon	30	64
Lung	19	48

Barret JM, AACR 2018

Fresh tissues, FACS study:

- 52 samples analyzed in CRC and ovarian cancer (OC)
- **In CRC,** AMHRII expression observed in 73% of samples:
  - mean 56.000 receptors per cell,
  - homogeneous intratumor distribution,
  - no expression in healthy margins

	Histological subtype	N	Nb of AMHRII+ samples (%)	Nb of receptors per cell (RPC)	AMHRII+ samples	
					Mean RPC	% of AMHRII+ cell (mean)
OC	Granulosa Sexual cords EOCs	16	11/16 (69%)	0 – 168,000	40,000	85%
CRC	Adenocarcinoma Mucinous	36	26/36 (73%)	0 – 363,000	56,000	80%

C201 STUDY DESIGN

C201 STUDY
MURLENTAMAB IN LOCALLY ADVANCED OR METASTATIC COLORECTAL CANCER
Mesurable disease
Having failed previous line of treatment
Performance status ≤ 1, adequate organ function
Biopsable lesion (2 biopsies planned – baseline and under treatment)

COHORT I – murlentamab (7 mg/kg q1w)
15 evaluable* patients

- Refractory patients (all therapeutic options exhausted)

COHORT II – murlentamab (7 mg/kg q1w) + trifluridine/tipiracil (FTD/TPI)
15 evaluable* patients

- At least 2 prior lines of standard chemotherapy for mCRC
- Eligible for single agent trifluridine/tipiracil: having failed or not considered candidates for fluopyrimidines-, oxaliplatin-, and irinotecan-based chemotherapies, anti-VEGF agents, regorafenib, and anti-EGFR agents

*having completed at least two 28-day cycles of treatment and with at least one tumor assessment under treatment

STUDY ENDPOINTS AND STATUS

ENDPOINTS

Primary
- Overall Response Rate (ORR) in each cohort

Secondary
- Tumor Growth Rate (TGR)
- Clinical Benefit Rate (CBR), defined as CR+PR+SD
- Progression Free Survival (PFS)
- Pharmacodynamic evaluation (tumors and peripheral blood)
- Overall Survival (OS)
- Safety

SAFETY

Murlentamab was very well tolerated with few toxicities

In total 36 murlentamab toxicities were reported in 10 patients in the combination cohort only

- All G1-2
- Most common: decreased appetite (9 events), vomiting, nausea, constipation and asthenia (3 events each)

No overlapping toxicities with trifluridine/tipiracil were observed in the combination cohort

Acknowledgements:

PATIENT CHARACTERISTICS AND DISPOSITION

Cut-off date 24 Apr 2018

		Cohort I murlentamab (N=21)	Cohort II murlentamab + FTD/TPI (N=18)	ALL (N=39)
Gender	Male	13 (61.9%)	11 (61.1%)	24 (61.5%)
	Female	8 (38.1%)	7 (38.9%)	15 (38.5%)
Age (years)	Median	63.0	59.0	60.0
	Min - Max	34 - 75	28 - 74	28 - 75
Time since diagnosis (years)	Median	3.8	2.2	3.2
	Min - Max	1.3 - 9.0	0.9 - 7.7	0.9 - 9.0
Primary tumor localisation	Rectum	5 (23.8%)	8 (44.4%)	13 (33.3%)
	Colon	16 (76.2%)	10 (55.6%)	26 (66.7%)
	Right colon	*8 (50.0%)*	*5 (50.0%)*	*13 (50.0%)*
	Left colon	*8 (50.0%)*	*5 (50.0%)*	*13 (50.0%)*
K-RAS status	Mutated	13 (61.9%)	12 (66.7%)	25 (64.1%)
	Wildtype	8 (38.1%)	6 (33.3%)	14 (35.9%
Nb of previous systemic lines	Median	4.0	2.0	3.0
	Min - Max	2 - 7	1 - 4	1 - 7
AMHRII expression (IHC)*	Yes	13/16 (81.2%)	16/18 (88.9%)	29/34 (85.3%)
Nb of patients evaluable for efficacy		14	15	29

** Retrospective centralized analysis on baseline biopsies*

CLINICAL ACTIVITY

Data as of 06-Jun-2019

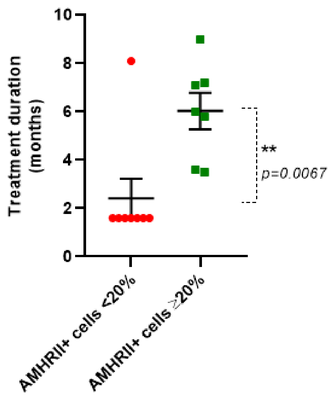
No objective response was observed in the evaluable for efficacy population

More than 30% of patients were stabilized at 6 months with murlentamab + trifluridine/tipiracil

Stable disease	Cohort I murlentamab	Cohort II murlentamab + FTD/TPI
At 2 months	21.4% (3/14)	53.3% (8/15)
At 4 months	7.1% (1/14)	40.0% (6/15)
At 6 months	-	30.8% (4/13)
At 8 months	-	8.3% (1/12)

Cohort II (murlentamab + trifluridine/tipiracil):
Treatment duration and AMHRII expression

Patient	Treatment duration (months)	% of AMHRII membranous-positive cells
05-05	1.6	0
05-06	1.6	1
02-01	1.6	5
05-09	1.6	5
01-07	1.6	10
02-07	1.6	15
04-01	1.6	15
04-05	3.5	15
02-12	3.5	20
05-13	5.3	60
01-13	5.8+	20
02-06	7.1	60
05-08	7.2	30
01-06	8.1+	5
02-09	9.0+	20



Mean ± SEM:
2,4 ± 0,8 *vs* 6,0 ± 0,8 months

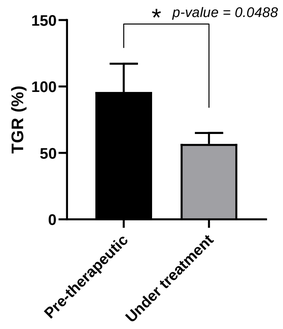
Wilcoxon-Mann-Whitney test, two-sided, α=5%

TUMOR GROWTH RATE

TGR = calculated % increase of tumor volume over one month
TGR decrease under treatment demonstrated independently correlated with prolonged Progression Free Survival[(1)]

Cohort I (murlentamab): 1.7-fold TGR decrease

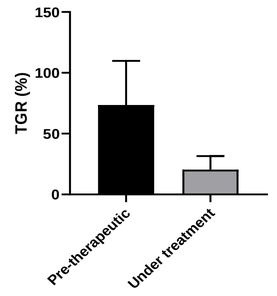
N=9	TGR pre-therapeutic	TGR under treatment (end C2)
Mean [+/- SD]	96.0% [+/-19.4]	56.9% [+/-24.5]



Wilcoxon matched-pairs non-parametric test, one-sided, α=5%

Cohort II (murlentamab + FTD/TPI): 3.6-fold TGR decrease

N=8	TGR pre-therapeutic	TGR under treatment (end C2)
Mean [+/- SD]	73.5% [+/-102.6]	20.5% [+/-29.3]

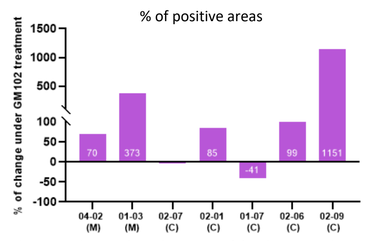


(1) Ferté et al, Clin Cancer Res 2014

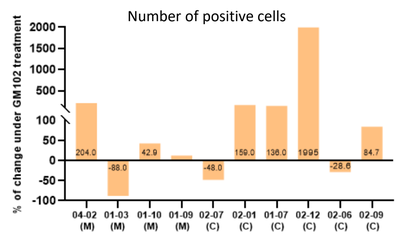
MURLENTAMAB-INDUCED IMMUNE CELL ACTIVATION IN TUMOR MICROENVIRONMENT AND IN BLOOD

TUMOR MICROENVIRONMENT

GranzymeB/CD16 colocalization increased under treatment in 5/7 paired biopsies analyzed



CD86 increased under treatment in 7/10 paired biopsies analyzed



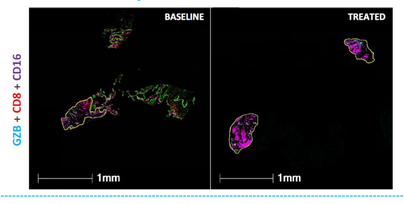
(M): cohort I: murlentamab single agent (C): cohort II: murlentamab + FTD/TPI

In 2 patients treated for at least 4 months under murlentamab + trifluridine/tipiracil:

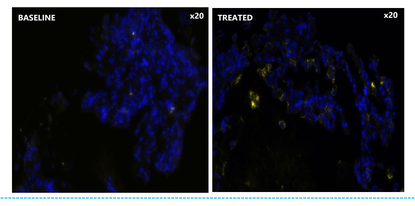
- CD86 staining increased, reflecting early macrophage activation
- CD8 staining increased, reflecting T cell activation

Patient 02-09 (murlentamab + trifluridine/tipiracil), SD at 9+ months

12.5-fold GranzymeB/CD16 colocalisation increase



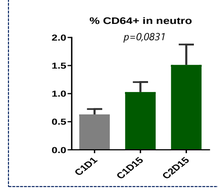
1.8-fold CD86 increase



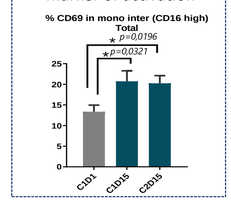
PERIPHERAL BLOOD

Circulating immune cells analysed at baseline and under treatment (flow cytometry, subset of 20 patients in Belgian centres)

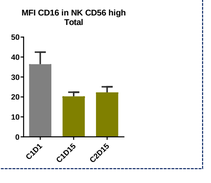
Neutrophil activation
CD64+ increase in cell % and in number of receptors per cell



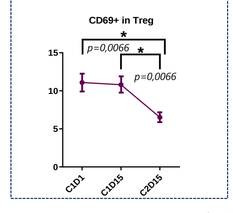
Monocyte activation
CD69+ increase, early marker of activation



NK cells engagement
CD16+ number of receptors decrease indicative of receptor engagement



T cells
Long-term CD69 decrease in Treg population



Krustal-Wallis test (ANOVA), α=5%

CONCLUSIONS

- This pilot study suggests longer than expected PFS for murlentamab + trifluridine/tipiracil in advanced mCRC, especially for patients with high AMHRII expression
- Immune activation of the macrophage / cytotoxic T cell cascade was observed in tumor microenvironment as well as in peripheral blood
- Murlentamab was very well tolerated with no overlapping toxicities with trifluridine/tipiracil
- These clinical results are encouraging for further development of murlentamab in combination with standard chemotherapies
- Translational research results open the field for exploring combination of murlentamab with other immunotherapy agents, especially targeting T cells