A MICROBIOTA BASED MODEL OF ANTICANCER INTERVENTION

J. Jimeno MD, PhD.

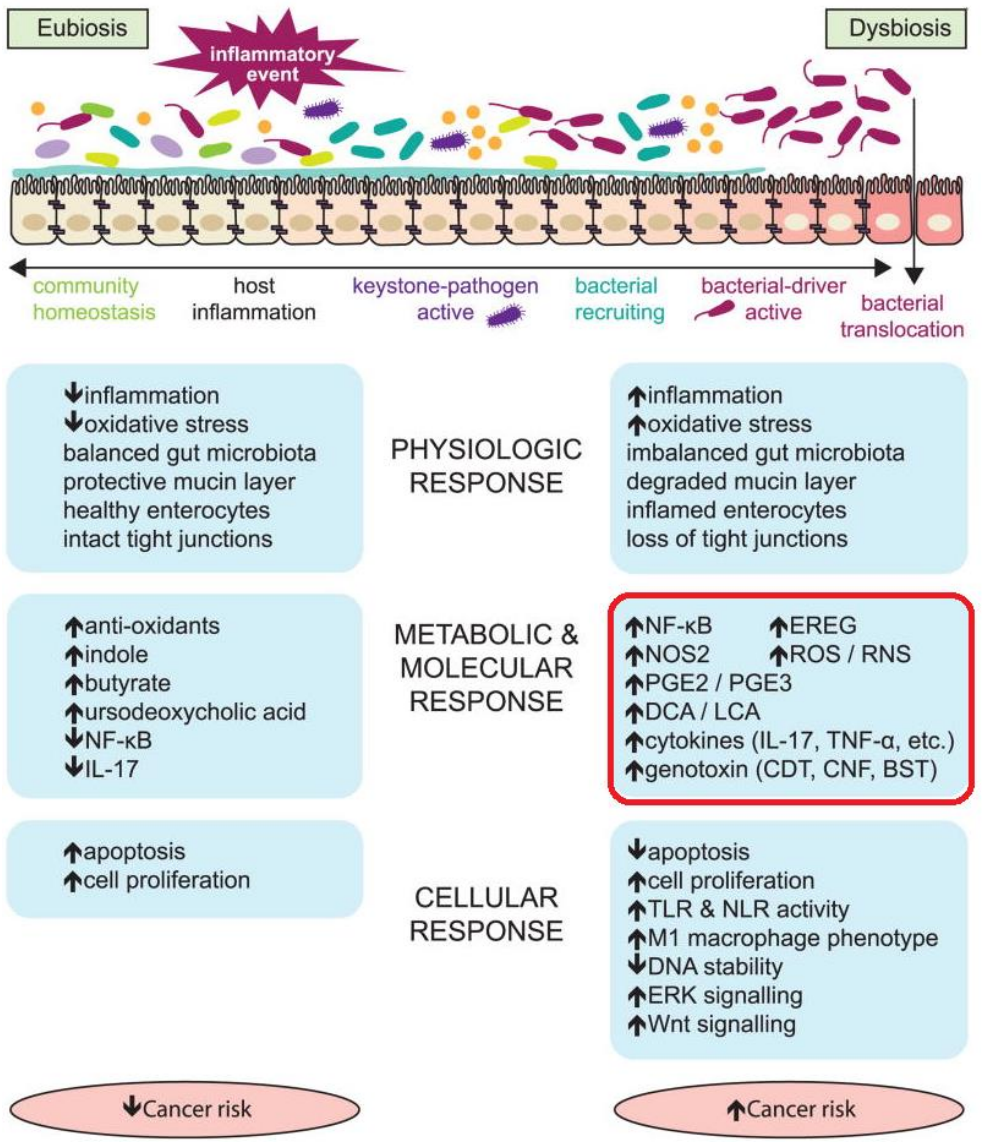
PAMM Winter Meeting Split, Croatia, 2017

GALENIC DEVELOPMENT - IG1608

- Dysbiotic Signature in Serum from Cancer Patients.
- 30 symbiotic bacteria panel as a tool.
- Fermentation Process from selected strains from the panel.
- Pilot Manufacturing 30 l. fermentation tank, 20% yield aprox.
- Feasibility for up-scale under GMPs.
- Extract (drug substance /API) is subject of formulation, 200 mg API capsules.
- Extract chemically stable, hydrophobic.
- Structure Characterization ongoing, by Mass Spectrometry.
- Data available, work in progress confirms IG1608 as a posbiotic extract containing multiple secondary metabolites and proteins.
- Development of an analytical method for PK/PD purposes ongoing.
- Supply warranted for the full prospective clinical program in Cancer and other disease settings.

A MICROBIOTA BASED MODEL OF ANTICANCER INTERVENTION

THE NOTION OF DYSBIOSIS



From AM. Shhelffin et all (modified)

MICROBIOTA AS A CONTEMPORARY THERAPEUTIC TOOL

Sciencexpress

Commensal *Bifidobacterium* promotes antitumor immunity and facilitates anti– PD-L1 efficacy.

Ayelet Sivan,[1] Leticia Corrales,[1] Nathaniel Hubert,[2] Jason B. Williams,[1] Keston Aquino-Michaels,[3] Zachary M. Earley,[2] Franco W. Benyamin,[1] Yuk Man Lei,[2] Bana Jabri,[2] Maria-Luisa Alegre,[2] Eugene B. Chang,[2] Thomas F. Gajewski[1,2]

[1]Department of Pathology, University of Chicago, Chicago, IL, USA. [2]Department of Medicine, University of Chicago, Chicago, IL, USA. [3]Section of Genetic Medicine, University of Chicago, Chicago, IL, USA.

T cell infiltration of solid tumors is associated with favorable patient outcomes, yet the mechanisms underlying variable immune responses between individuals are not well understood. One possible modulator could be the intestinal microbiota. We compared melanoma growth in mice harboring distinct commensal microbiota and observed differences in spontaneous antitumor immunity, which were eliminated upon cohousing or following fecal transfer. 16S ribosomal RNA sequencing identified Bifidobacterium as associated with the antitumor effects. Oral administration of Bifidobacterium alone improved tumor control to the same degree as anti–PD-L1 therapy (checkpoint blockade), and combination treatment nearly abolished tumor outgrowth. Augmented dendritic cell function leading to enhanced CD8+ T cell priming and accumulation in the tumor microenvironment mediated the effect. **Our data suggest that manipulating the microbiota may modulate cancer immunotherapy**.

Sciencexpress, November 5, 2015

Science Translational Medicine

Cancer and the gut microbiota: An unexpected link

Laurence Zitvogel,[1,2] Lorenzo Galluzzi,[1,3,4,5] Sophie Viaud,[1,2] Marie Vétizou,[1,2] Romain Daillère,[1,2] Miriam Merad,[6] Guido Kroemer[3,4,5,7,8]

[1]Gustave Roussy Comprehensive Cancer Center, Villejuif, France. [2]INSERM, Villejuif, France. [3]Equipe 11 Labellisée par la Ligue Nationale Contre le Cancer, Centre de Recherche des Cordeliers, Paris, France. [4]Université Paris Descartes/ Paris V, Sorbonne Paris Cité, Paris, France. [5]INSERM, U1138, F-75006 Paris, France. [6]Department of Oncological Sciences, Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, New York, USA. [7]Pôle de Biologie, Hôpital Européen Georges Pompidou, Paris, France. [8]Metabolomics and Cell Biology Platforms, Gustave Roussy Comprehensive Cancer Center, France

Changes in the interactions among the gut microbiota, intestinal epithelium, and host immune system are associated with many diseases, including cancer. We discuss how environmental factors influence this cross-talk during oncogenesis and tumor progression and how manipulations of the gut microbiota might improve the clinical activity of anticancer agents.

Science Translational Medicine, January 21, 2015

MICROBIOME AS A CONTEMPORARY THERAPEUTIC TOOL

Science

Commensal Bacteria Control Cancer Response to Therapy by Modulating the Tumor Microenvironment.

Noriho Iida,[1] Amiran Dzutsev,[1,2] C. Andrew Stewart,[1] Loretta Smith,[1] Nicolas Bouladoux,[3] Rebecca A. Weingarten,[4] Daniel A. Molina,[5] Rosalba Salcedo,[1] Timothy Back,[1] Sarah Cramer,[1] Ren-Ming Dai,[1,2] Hiu Kiu,[1] Marco Cardone,[1] Shruti Naik,[3] Anil K. Patri,[6] Ena Wang,[7] Francesco M. Marincola,[7,8] Karen M. Frank,[4] Yasmine Belkaid,[3] Giorgio Trinchieri,1†‡ Romina S. Goldszmid1

[1]Cancer and Inflammation Program, National Cancer Institute, Frederick, USA. [2]Leidos Biomedical Research, Inc., Frederick National Laboratory, Frederick,, USA. [3]Mucosal Immunology Section, Laboratory of Parasitic Diseases, National Institute of Allergy and Infectious Diseases, Bethesda,, USA. [4]Microbiology Service, Department of Laboratory Medicine, Clinical Center, National Institutes of Health, Bethesda,, USA. [5]Technical Resources International, Inc., Bethesda,, USA. [6]Nanotechnology Characterization Laboratory, Advanced Technology Program, Leidos Biomedical Research, Inc., Frederick National Laboratory, USA. [7]Department of Transfusion Medicine, Clinical Center, National Institutes of Health,, USA. [8]SidraMedical and Research Centre, Doha,Qatar.

The gut microbiota influences both local and systemic inflammation. Inflammation contributes to development, progression, and treatment of cancer, but it remains unclear whether commensal bacteria affect inflammation in the sterile tumor microenvironment. Here, we show that disruption of the microbiota impairs the response of subcutaneous tumors to CpG-oligonucleotide immunotherapy and platinum chemotherapy. In antibiotics-treated or germ-free mice, tumor-infiltrating myeloid-derived cells responded poorly to therapy, resulting in lower cytokine production and tumor necrosis after CpG-oligonucleotide treatment and deficient production of reactive oxygen species and cytotoxicity after chemotherapy. Thus, optimal responses to cancer therapy require an intact commensal microbiota that mediates its effects by modulating myeloid-derived cell functions in the tumor microenvironment. These findings underscore the importance of the microbiota in the outcome of disease treatment.

Science, November 23, 2013

Cell

Microbiome and Anticancer Immunosurveillance

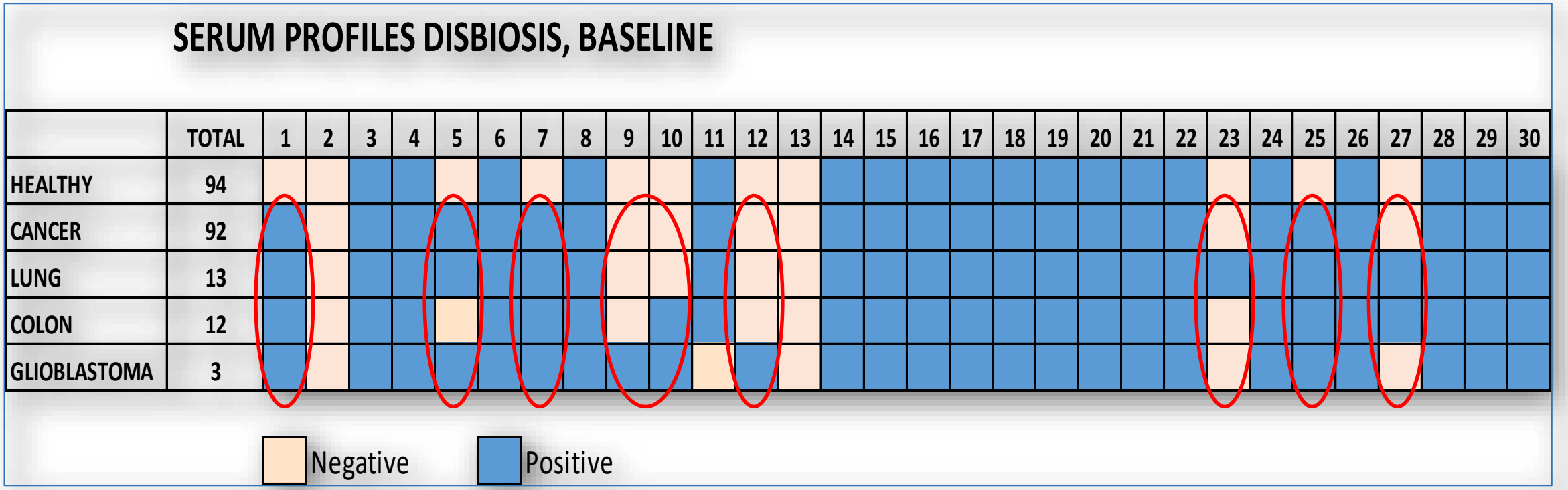
Laurence Zitvogel,1,2,3, Maha Ayyoub,1,2,3 Bertrand Routy,1,2,3 and Guido Kroemer4,5,6,7,8,9,10,

[1]INSERM, U1015, Equipe labellisée Ligue Nationale Contre le Cancer, Gustave Roussy Cancer Campus, France [2]University of Paris Sud XI, 94270 Le Kremlin-Bicêtre, France [3]Center of Clinical Investigations in Biotherapies of Cancer, Villejuif, France [4]Equipe 11 labellisée par la Ligue contre le Cancer, Centre de Recherche des Cordeliers, Paris, France [5]Cell Biology and Metabolomics platforms, Gustave Roussy Comprehensive Cancer Center, France [6]INSERM, U1138, 75006 Paris, France [7]Université Paris Descartes, Sorbonne Paris Cité , Paris, France [8]Université Pierre et Marie Curie, 75006 Paris, France [9]Pôle de Biologie, Hôpital Européen Georges Pompidou, AP-HP, 75015 Paris, France [10]Karolinska Institute, Department of Women's and Children's Health, Karolinska University Hospital, 17176 Stockholm, Sweden

Anticancer immune responses can be considered a desirable form of autoimmunity that may be profoundly shaped by the microbiome. Here, we discuss evidence for the microbiome's influence on anti-tumor immunosurveillance, including those that are indirect and can act at a distance, and we put forward hypotheses regarding mechanisms of how these effects are implemented. These may involve cross-reactivity between microbial and tumor antigens shaping T cell repertoires and/or microbial products stimulating pattern recognition receptors that influence the type and intensity of immune responses. Understanding how the microbiome impacts natural cancer immunosurveillance as well as treatment-induced immune responses will pave the way for more effective therapies and prophylactics.

Cell, April 7, 2016

CHARACTERIZATION OF DYSBIOTIC PROFILES IN SERUM



1.-	75%	9.-	23%
5.-	65%	10.-	40%
7.-	78%	12.-	35%

- ✓ Blood Sample (12 ml)
- ✓ Inmuno-precipitation with commensal bacteria derived products (30 symbiotic bacteria panel)
- ✓ Samples from Healthy individuals vs 92 advanced cancer patients
- ✓ Identification of a selective profile Cancer vs no Cancer

IG1608 - 1ST COMPREHENSIVE ANALYSIS,

COMPASSIONATE COHORT IN ADVANCED CANCER PATIENTS

- Implemented as per patient demand, under consent, and considered relevant to gain information on IG1608 therapeutic index in cancer patients.
- All patients consented for blood sampling at baseline and during IG1806 exposure. Process done in a CLIA like certified lab and under in situ supervision by a board certified oncologist.
- Access to the full set of lab and imaging data.
- Evaluation of QoL , EORTC C30, implemented prospectively as a planned analysis.
- IG1608 given p.o. at a dose of 600 mg per day in a continuous basis.

IG1608 - PATIENTS' CHARACTERISTICS

		Nº	%
N patients		**35**	**100%**
Median age		58,4	
Females		15	43%
ECOG			
	0	0	0%
	1	6	30%
	2	9	45%
	3	5	25%
Stage			
	IIIB	2	6%
	IV	33	94%

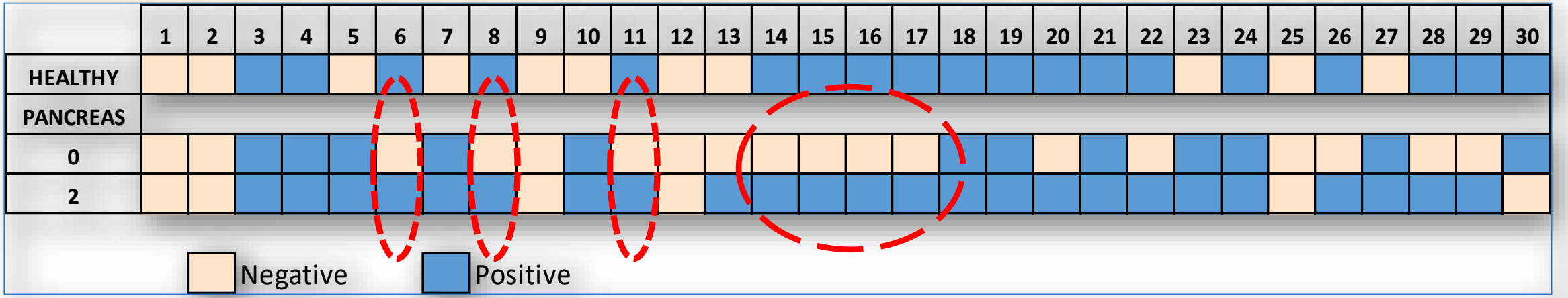
	Nº	%
Liver mets	10	29%
Bone mets	10	29%
Liver and bone mets	2	6%
Tx		
Only Igen	9	26%
CT + Igen	22	63%
Rt/H + Igen	4	11%
Liver mets	10	29%
Bone mets	10	29%
Tx Length IG1806		
6-12 months	1	3%
12-24 months	4	11%
>24 months	30	86%

IG1608 TUMOR TYPES

Tumor type	Count	Median age	Only IG18036 single agent
LUNG CA	8	57	2
COLORECTAL CA	7	65	2
PROSTATE CA	7	74	1
BREAST CA	2	50	0
SBM	2	30	1
PANCREAS CA	1	55	0
ESOPHAGEAL CA	2	61,5	1
UTERINE ADENOCA	2	59	0
HD	2	36	0
PHEOCHROMOCYTOMA	1	48	1
MFH	1	50	1

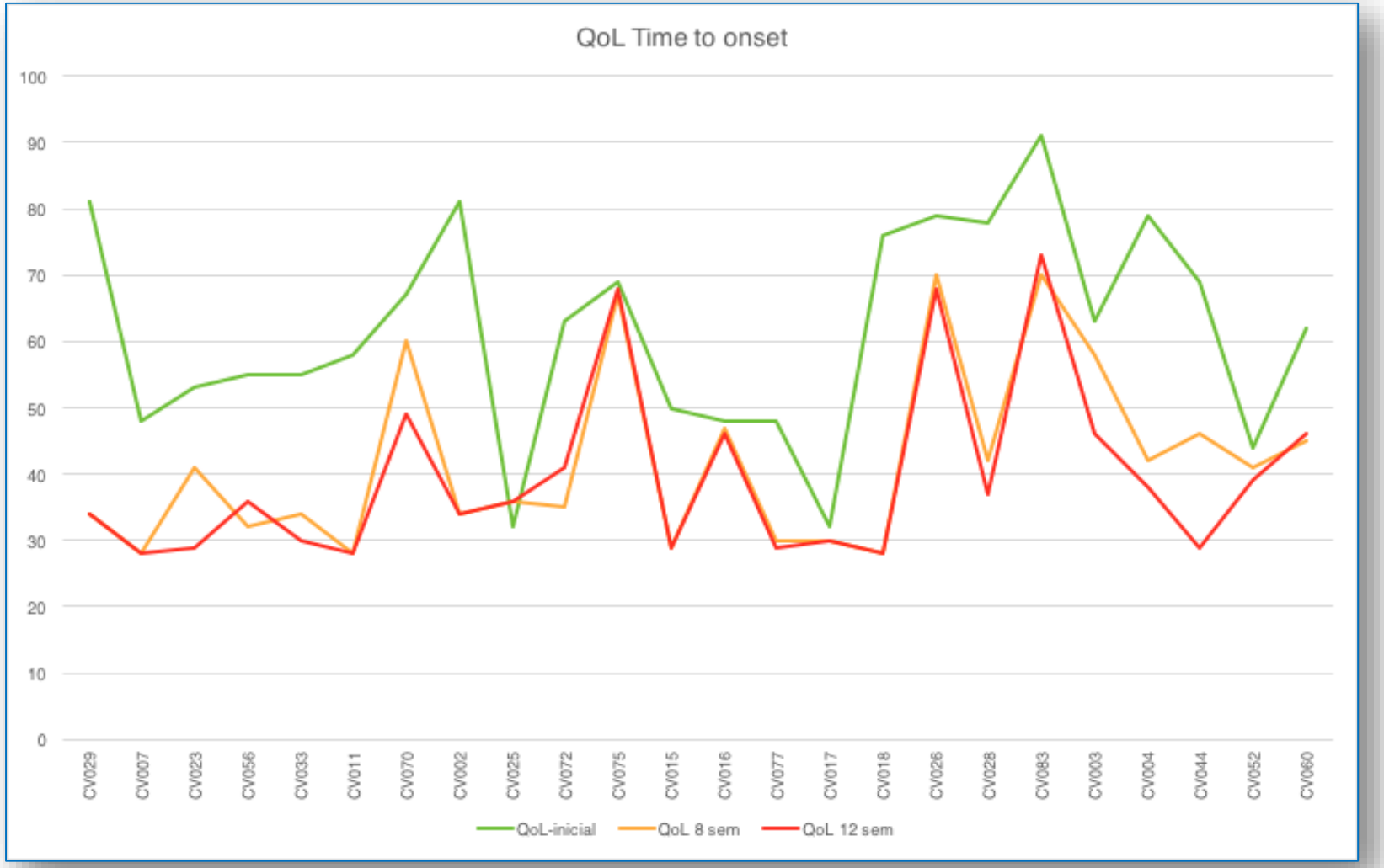
PANCREATIC CA, BEGAN IG1608 WHILE ON FOLFORINOX

OUTCOME DYSBIOTIC PROFILE IN AN ADVANCED PANCREATIC CANCER

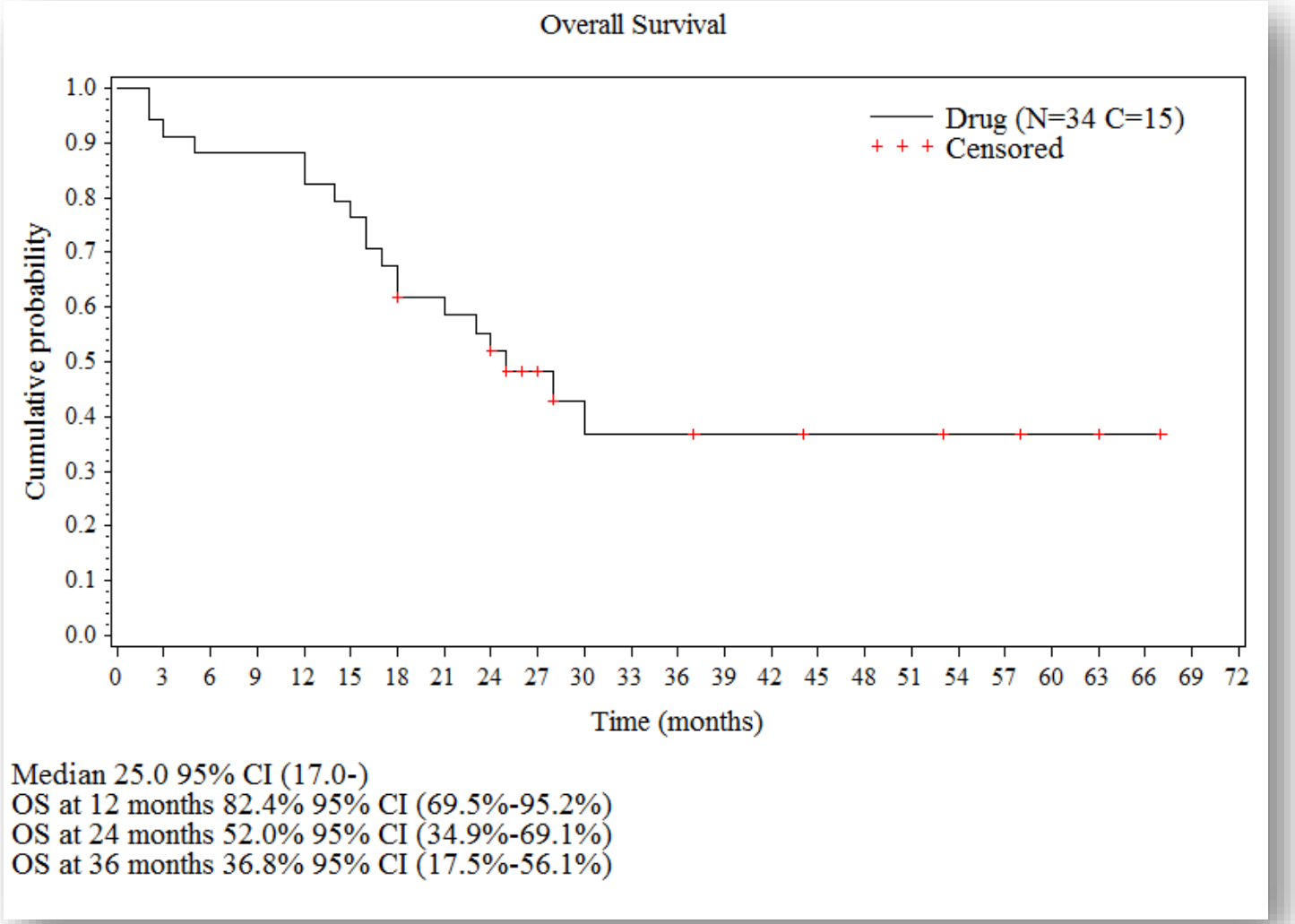


IG1608 Induces a correction of the dysbiotic profile
0= Baseline
2= 2 months on IG1608

IMPACT OF IG1608 ON QOL. QoL TIME TO ONSET



OVERALL OUTCOMES SURVIVAL



Early Conclusions

- Data recorded internally.
- Patients threated to best standard care plus IG1608 compound.
- Compassionate cohort / observational IG1806 exposed to cancer.

Summary
N=34
Events 19 (55.9%)
Censored 15 (44.1%)
Median 25.0 95% CI (17.0-)
OS at 12 months 82.4% 95% CI (69.5%-95.2%)
OS at 24 months 52.0% 95% CI (34.9%-69.1%)
OS at 36 months 36.8% 95% CI (17.5%-56.1%)

PATIENT CHARACTERISTICS COHORT IMPROVED C30 QoL > 20

Tumor type		Only IG1806
LUNG	4	0
COLON	2	0
PROSTATE	2	1
BREAST	1	1
SNC	1	0
UTERUS	2	1
LYMPHOMA	1	1
PHEOCHROMOCYTOMA	1	1
TOTAL	14	36%

Variable	Nº	%
N patients	14	
Age	54	
Women	6	43%
ECOG		
0	0	0%
1	2	22%
2	5	56%
3-4	2	22%
Stage		
IIIB	2	14%
IV	12	86%
Treatment		
Only IG1806	5	36%
QT + IG1806	9	64%
Rt/H + IG1806	5	36%
Side of disease		
Liver	2	14%
Bone	5	36%
Liver + Bone	2	14%

	LEGTH OF TREATMENT	OVERALL SURVIVAL	ALIVE
CV002	67	70	+
CV004	15	48	
CV011	18	19	
CV015	30	162	
CV018	17	17	
CV028	23	334	
CV029	16	32	
CV033	18	66	
CV044	37	90	+
CV056	18	14	+
CV072	26	30	+
CV078	2	67	
CV079	16	76	
CV083	24	38	

PATIENT CHARACTERISTICS ALIVE > 24 MONTHS

Tumor Type		Only IG1806
LUNG	1	0
COLON	2	0
PROSTATE	5	2
BREAST	1	1
SNC	1	0
ESOPHAGUS	1	0
UTERUS	1	1
SARCOMA	1	1
RENAL	1	0
TOTAL	14	5

Variable	Nº	%
N patients	14	100%
Median age	57,3	
Women	6	43%
ECOG		
0	0	0%
1	4	29%
2	1	7%
3-4	3	21%
Stage		
IIIB	2	14%
IV	12	86%
Treatment		
Only IG1806	5	36%
QT + IG1806	6	43%
Rt/H + IG1806	3	21%
Side disease	17	100%
Liver	2	14%
Bone	3	21%
Liver + Bone	1	7%

	LEGTH OF TREATMENT	OVERALL SURVIVAL	ALIVE
CV002	67	70	+
CV007	63	65	+
CV015	30	162	
CV016	25	38	
CV017	53	168	+
CV023	28	24	
CV025	44	213	+
CV028	37	90	
CV044	25	50	+
CV056	28	115	+
CV060	24	64	+
CV083	25	39	+
CV084	24	14	+
CV008	26	30	+

PATIENT CHARACTERISTICS COHORT - IG1806 SINGLE AGENT

Tumor		Median age	IG1806
LUNG	1	72	1
SARCOMA	1	50	1
PROSTATE	3	76	3
BREAST	1	69	1
UTERUS	1	66	1
LYMPHOMA	1	36	1
PHEOCHROMOCYTOMA	1	48	1
TOTAL	9	60	100%

Variable	Nº	%
N patients	9	
Median age	60	
Women	3	33%
ECOG		
0	0	0%
1	1	14%
2	3	43%
3-4	3	43%
Stadium		
IIIB	1	11%
IV	8	89%
Treatment		
Only IG1806	9	100%
QT + IG1806	0	0%
Rt/H + IG1806	0	0%
Side disease		
Liver	0	0%
Bone	2	22%
Liver + Bone	0	0%

	LEGTH OF TREATMENT	OVERALL SURVIVAL	ALIVE
CV002	74	77	+
CV004	15	48	
CV011	18	19	
CV016	25	38	
CV017	60	176	+
CV018	17	17	
CV026	14	20	
CV028	23	334	
CV060	25	42	+

DYSBIOSIS PROFILE AT BASELINE AND IT´S CORRECTION UPON IG1806 EXPOSURE (2 MONTHS TIME POINT)

Patient	Tumor type	Disbiosis baseline	Disbiosis correction
1	BREAST Ca		
2	COLON Ca		
3	PROSTATE Ca		
4	COLON Ca		
5	BREAST Ca		
6	ANAL Ca		
7	RENAL Ca		
8	PANCREAS Ca		
9	BREAST Ca		
	DYSBIOSIS CORRECTION		
	DYSBIOSIS AND DYSBIOSIS NO CORRECTION		
IG1806 induced disbiosis correction rate 6/9 66 % (95 % CL 28-100%)			

SUMMARY

- A specific Dysbiotic Profile signature is prevalent in advanced cancer patients
- Such disbiotic signature get’s corrected (= to profile in healthy individuals) upon IG1806 exposure .
- The data gathered sustains the notion of IG1806 feability for chronic therapy.
- A clinically relevant proportion of patients has been exposed to IG1806 > 2 years .
- A clinically relevant % of patients have had a significant improvement QoL as per > 20 points improvement C-30 EORTC QoL scale.
- IG1806 appears to lack an negative interaction with systemic anticancer drugs.
- A prospective comparative double blind studies & an extensive translational program is under implementation