IKCS: NORTH AMERICA
INTERNATIONAL KIDNEY CANCER SYMPOSIUM

Clinical outcomes with nivolumab/ipilimumab with or without CBM588 in metastatic renal cell carcinoma: Long-term follow-up of a randomized phase Ib clinical trial

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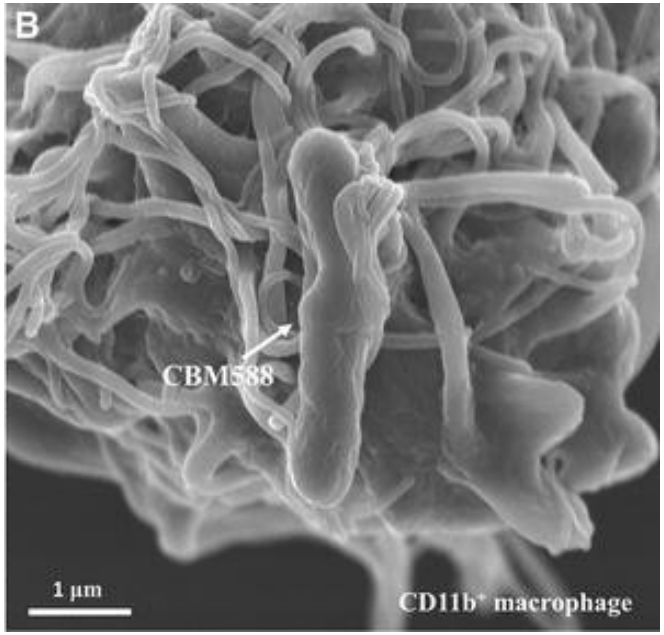
Background

- Live bacterial product that contains *Clostridium butyricum*, a butyrate-producing anaerobic spore-forming bacterium
- Isolated from a soil sample in Nagano, Japan, in 1963
- Commonly used and studied in GI conditions in Japan



Hagihara *et al* Clostridium butyricum Modulates the Microbiome to Protect Intestinal Barrier Function in Mice with Antibiotic-Induced Dysbiosis iScience 2020

Background

- Retrospective analysis of 118 patients with non-small cell lung cancer treated with immune checkpoint inhibitors

CANCER IMMUNOLOGY RESEARCH | CANCER IMMUNOLOGY MINIATURES

Association of Probiotic *Clostridium butyricum* Therapy with Survival and Response to Immune Checkpoint Blockade in Patients with Lung Cancer

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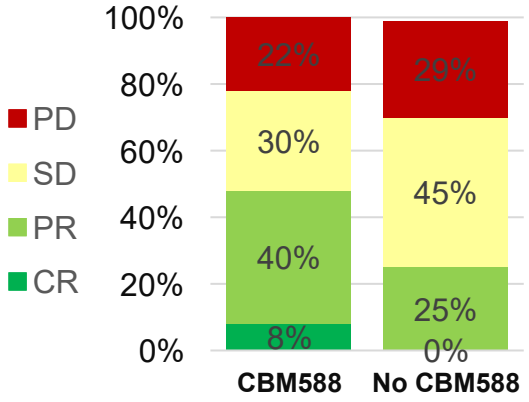
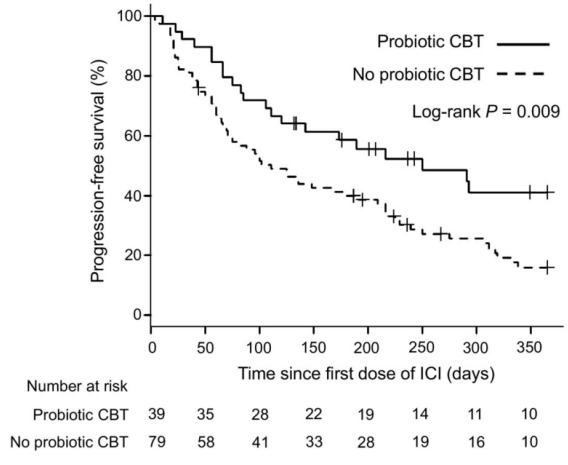
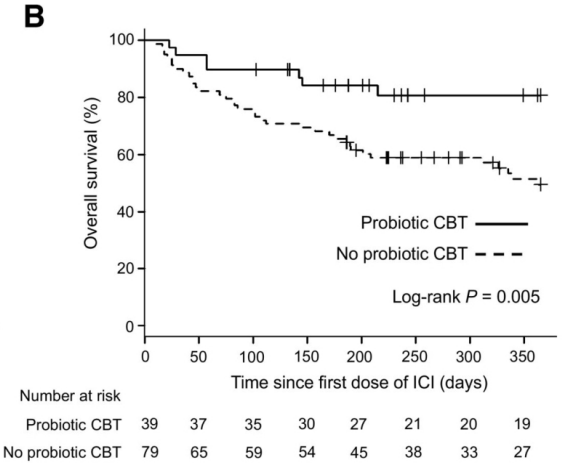




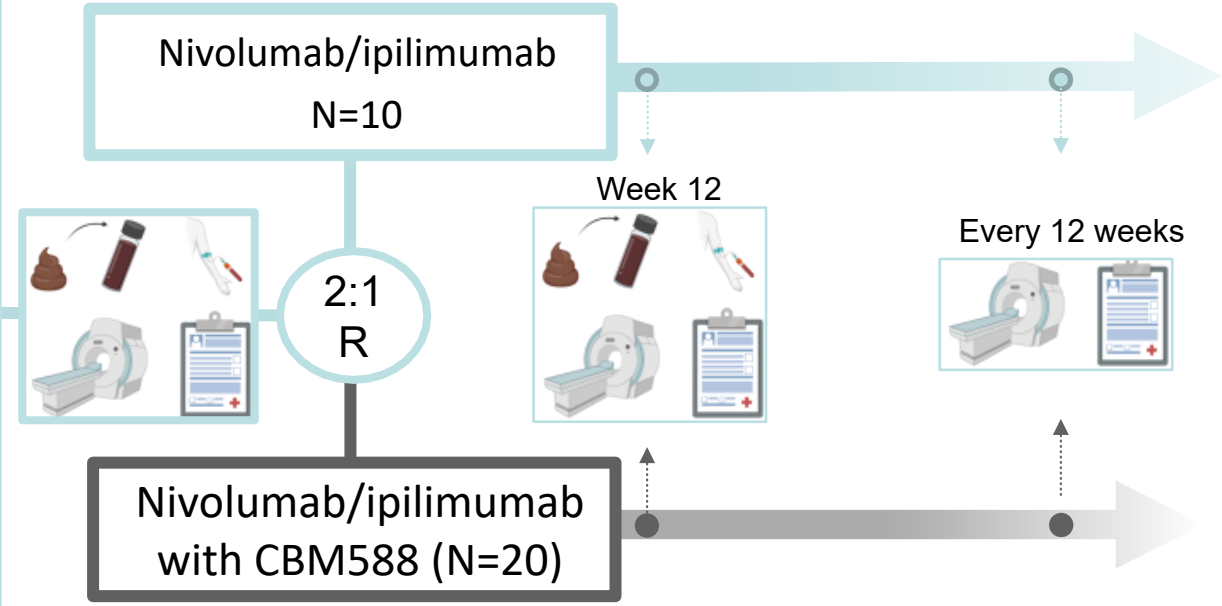


Tomita et al Association of Probiotic Clostridium butyricum Therapy with Survival and Response to Immune Checkpoint Blockade in Patients with Lung Cancer Cancer Immunol Res 2020

Methods

Metastatic renal cell carcinoma and:

- Measurable metastatic disease
- Clear cell and/or sarcomatoid histology
- ECOG performance status 0-1
- No prior systemic therapy for metastatic disease
- Intermediate- or poor-risk disease by IMDC classification



Methods

Primary Endpoint	Effect of CBM588 on the relative abundance of *Bifidobacterium* spp.
Secondary/ Exploratory Endpoints	Progression free survival, objective response rate per independent radiology review (RECIST 1.1)
	Toxicity profile assessed by providers
	Change in serum cytokine levels, immune cell populations and stool metabolic pathways

Patient Characteristics

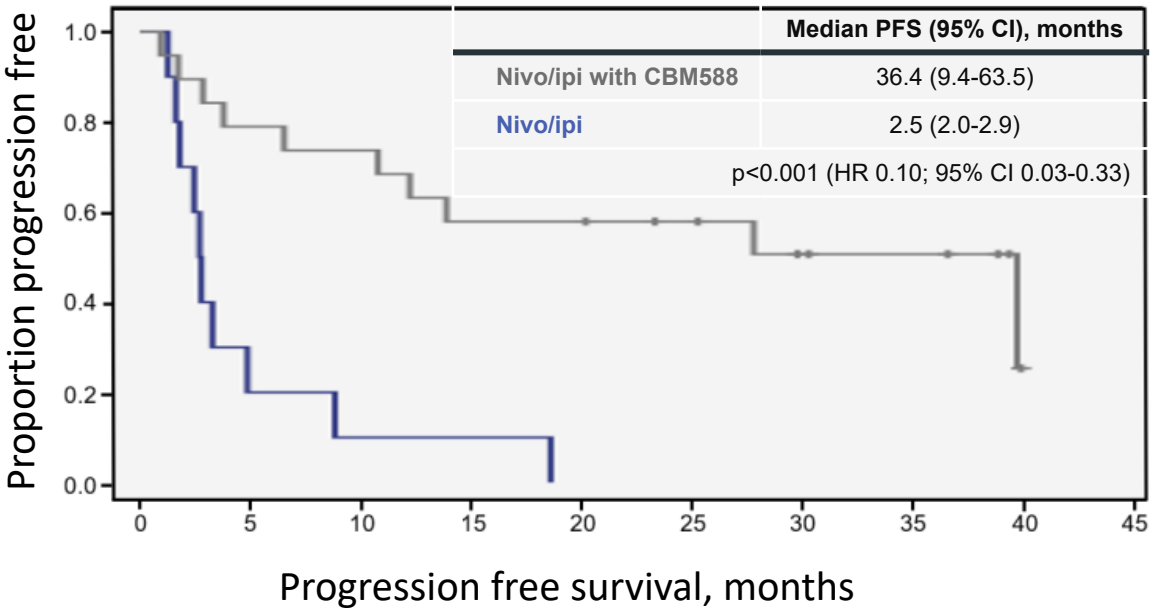
	Nivolumab/ipilimumab (N=10)	Nivolumab/ipilimumab with CBM588 (N=19)
Age (median, range) – years	64 (45-79)	66 (45-90)
Gender – no. (%)		
Male	8 (80%)	13 (68%)
Female	2 (20%)	6 (32%)
Histologic subtype – no. (%)		
Clear cell	7 (70%)	12 (63%)
Clear cell with sarcomatoid features	2 (20%)	5 (26%)
Papillary with sarcomatoid features	1 (10%)	1 (5%)
Sarcomatoid dedifferentiation	-	1 (5%)
IMDC prognostic risk – no. (%)		
Intermediate	7 (70%)	17 (89%)
Poor	3(30%)	2 (11%)
Previous nephrectomy – no. (%)	4 (40%)	9 (47%)
Number of metastatic sites – no. (%)		
≥2	10 (100%)	19 (100%)
Most common metastatic sites – no. (%)		
Lung	6 (60%)	13 (68%)
Lymph node	7 (70%)	8 (42%)
Bone	4 (40%)	7 (37%)
Soft tissue	3 (30%)	7 (37%)
Liver	2 (20%)	3 (16%)
Pancreas	1 (10%)	3 (16%)

Objective Response Rate

	Nivolumab/ ipilimumab with CBM588 (n=19)	Nivolumab/ ipilimumab (n=10)	*p* value
Objective response rate, n (%)	11 (58%)	2 (20%)	0.06
Partial response, n (%)	11 (58%)	20% (20%)	
Stable disease, n (%)	4 (21%)	20% (20%)	
Progressive disease, n (%)	4 (21%)	6 (60%)	
Disease control rate, n (%)*	15 (79%)	2 (20%)	0.004

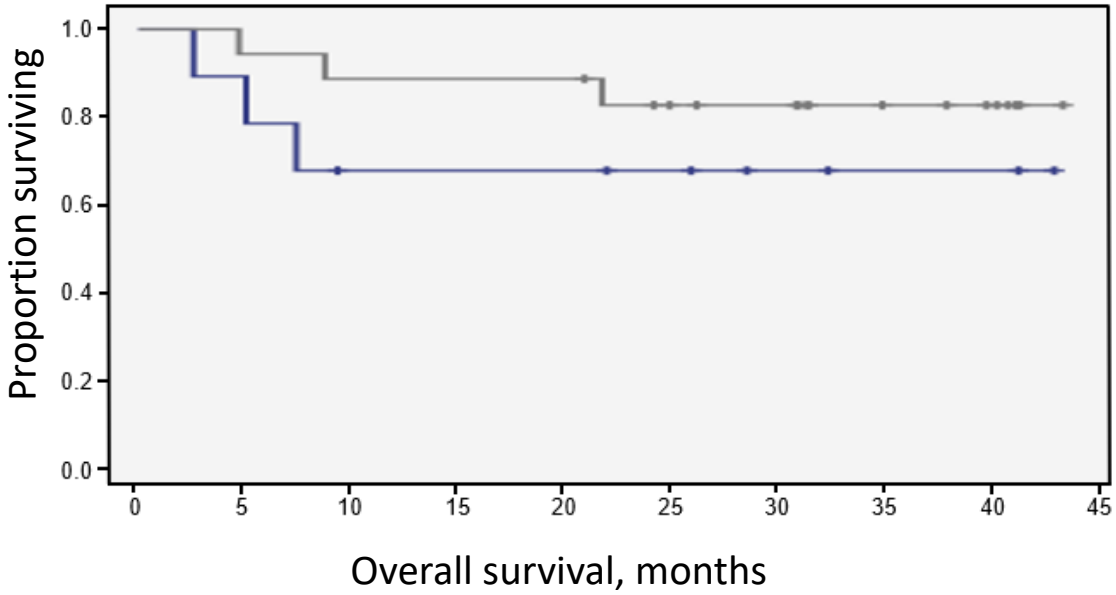
Disease control rate defined as complete response, partial response, stable disease exceeding 6 months

Progression Free Survival



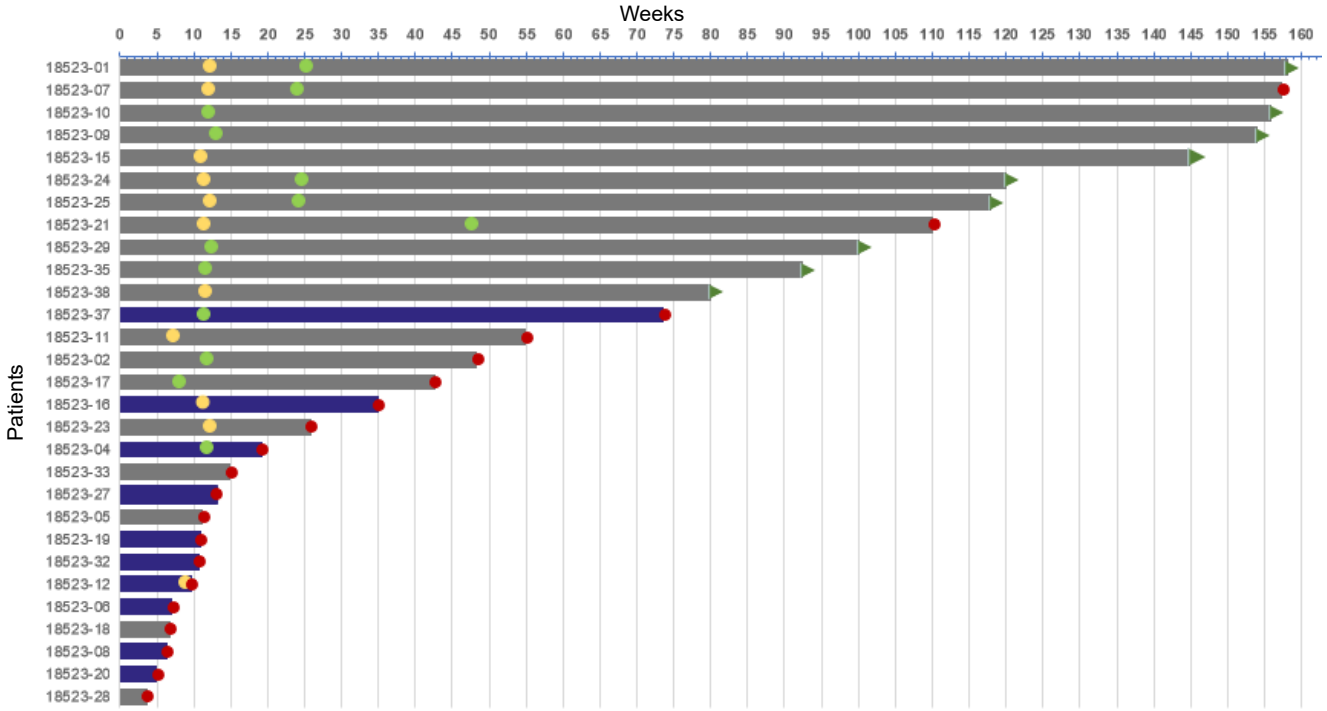
Overall Survival

- Median overall survival was not reached in either arm
- 82.8% of the cohort was alive at the time of data cut-off



Duration of Response

Median duration of response with nivolumab/ipilimumab with CBM588 30.7 months*



Duration of response defined as time from first documentation of response to progression of disease or last follow up

Safety

	Nivolumab/ ipilimumab (n=10)	Nivolumab/ ipilimumab with CBM588 (n=19)
All grade, n (%)	9 (90%)	19 (100%)
Grade ≥2, n (%)	5 (50%)	11 (63%)

	Nivolumab/ipilimumab (N=10)			Nivolumab/ipilimumab with CBM588 (N=19)		
	Grade 2	Grade 3	Grade 4	Grade 2	Grade 3	Grade 4
All adverse events	4 (40%)	5 (50%)		16 (84%)	12(63%)	1 (5%)
Neutrophil count decreased	1 (10%)					1 (5%)
Adrenal insufficiency				4 (21%)	1 (5%)	
Fatigue		1 (10%)		3 (16%)	1 (5%)	
Rash maculo-papular				2 (11%)	1 (5%)	
Arthritis/arthralgia				2 (11%)	1 (5%)	
Diarrhea		1 (10%)		1 (5%)	1 (5%)	
Acute Kidney Injury		1 (10%)		1 (5%)	1 (5%)	
Abdominal pain				1 (5%)	1 (5%)	
Transaminitis	1 (10%)	2 (20%)		5 (26%)	1 (5%)	
Glucose intolerance		1 (10%)		1 (5%)	1 (5%)	
Alkaline phosphatase increased					1 (5%)	
Dehydration		1 (10%)				
Pruritus		1 (10%)				
Pancreatitis					1 (5%)	
Nephritis					2 (11%)	
Acidosis					1 (5%)	
Chest wall pain					1 (5%)	
Hyperthyroidism				3 (16%)		
Hypothyroidism	1 (10%)			3 (16%)		
Pain				3 (16%)		
Weight gain				2 (11%)		
Pericarditis				1 (5%)		
Hyponatremia				1 (5%)		
Hypoglycemia				1 (5%)		
Myalgia/myositis				1 (5%)		

Conclusion

- Although limited by sample size, nivolumab/ipilimumab with CBM588 demonstrated superior clinical activity over nivolumab/ipilimumab.
- PFS and ORR with nivolumab/ipilimumab with CBM588 also exceeded those observed with nivolumab/ipilimumab in historical datasets.
- No new safety signals were observed with long term use of CBM588 with nivolumab/ipilimumab.
- Larger efforts investigating the impact of CBM588 on clinical outcomes are underway.

Motzer *et al* Nivolumab plus Ipilimumab versus Sunitinib in Advanced Renal-Cell Carcinoma NEJM 2018

Future Directions

Pirrotte Lab at Tgen
Kortylewski Lab at COH

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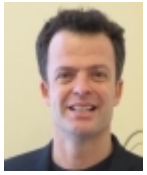

KCA Trailblazer Award 2022-2023

- Characterize changes in metabolomic profile in patients with mRCC receiving nivo/ipi and nivo/ipi/cbm588
- Assess changes in blood and stool metabolomic profile, immune response, tumor growth and survival kinetics in mice receiving anti-PD1/anti-CTLA-4 monoclonal antibodies with or without CBM588

- A randomized phase III double blind study comparing first-line CBM588 capsules and nivolumab/ipilimumab versus placebo and nivolumab/ipilimumab for intermediate and high risk advanced clear cell renal cell carcinoma

Acknowledgements

Patients and their families

City of Hope Comprehensive Cancer Center GU Medical Oncology, Duarte, CA

Translational Genomics Institute, AZ

All collaborators

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Thank you for your attention

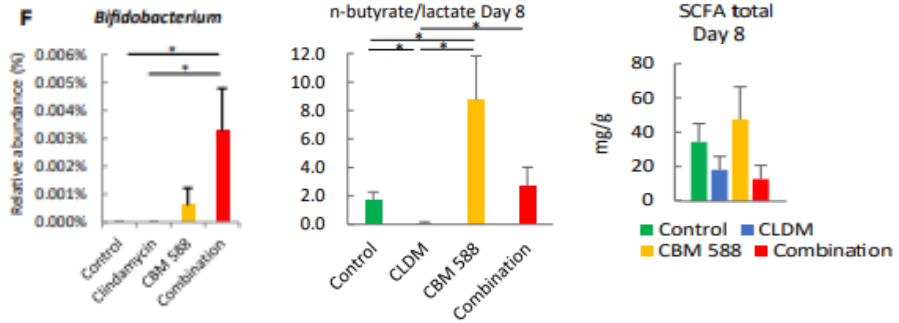
Background

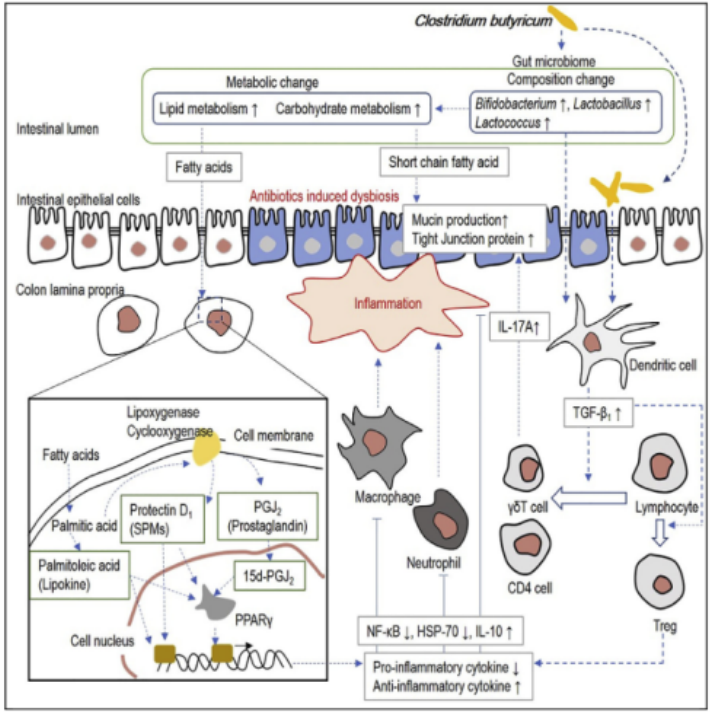
iScience

CellPress

Clostridium butyricum Modulates the Microbiome to Protect Intestinal Barrier Function in Mice with Antibiotic-Induced Dysbiosis

Mao Hagihara,[1] Yasutoshi Kuroki,[2,3] Tadashi Ariyoshi,[2,3] Seiya Higashi,[3] Kazuo Fukuda,[3] Rieko Yamashita,[1] Asami Matsumoto,[3] Takeshi Mori,[2] Kaoru Mimura,[4] Naoko Yamaguchi,[4] Shoshiro Okada,[4] Tsunemasa Nonogaki,[5] Tadashi Ogawa,[6] Kenta Iwasaki,[7] Susumu Tomono,[8] Nobuhiro Asai,[2] Yusuke Koizumi,[2] Kentaro Oka,[2,3] Yuka Yamagishi,[2] Motomichi Takahashi,[2,3] and Hiroshige Mikamo[2,9,*]





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