Targeting the Microbiome & Optimizing Immunotherapy in Cancer

Sumanta Kumar Pal, M.D.
Professor & Vice Chair of Academic Affairs
Department of Medical Oncology & Experimental Therapeutics
City of Hope Comprehensive Cancer Center
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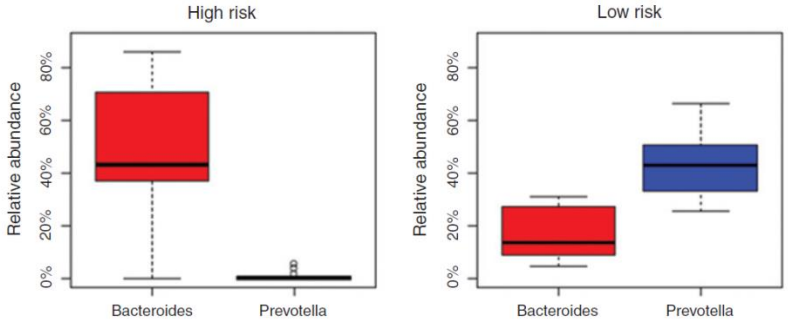
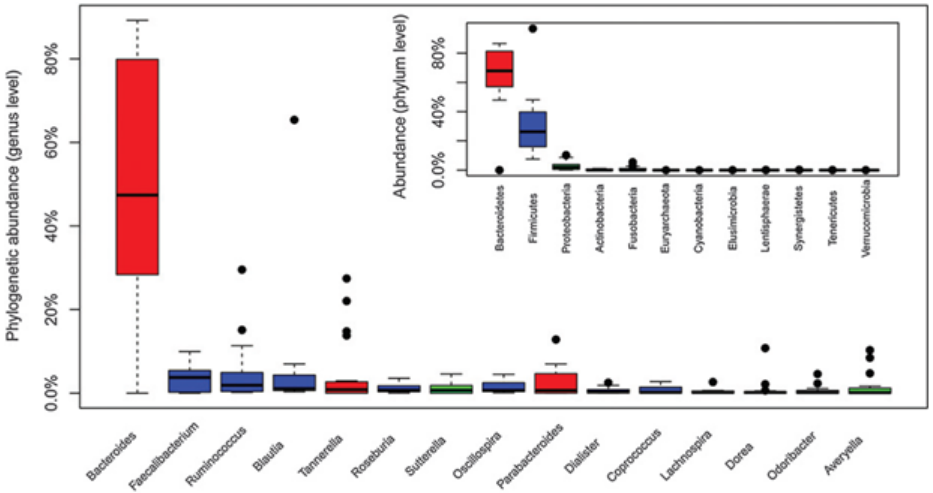
Optimizing Sequencing: Targeting the Microbiome

Summary:
- **20 patients with mRCC**
- **Receiving VEGF-TKIs**
- **Median of 2 prior lines of therapy**
- **Objective: To determine association between bacteriomic profile and presence or absence of diarrhea**





Pal SK … Frankel P *et al* CCR 2015

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Microbiome in Renal Cell Carcinoma

Patients with mRCC with planned treatment with VEGF-TKIs
(n=30)

2:1 Randomization

Probiotic Supplemented Group
Bifidobacterium-containing food supplement (ActiviaTM)
Dose: 4 Oz serving twice daily

Probiotic Restricted Group
Restriction of probiotic containing food or supplement consumption
i.e.: yogurt, kefir

Dizman *et al. Cancer Med 2020*

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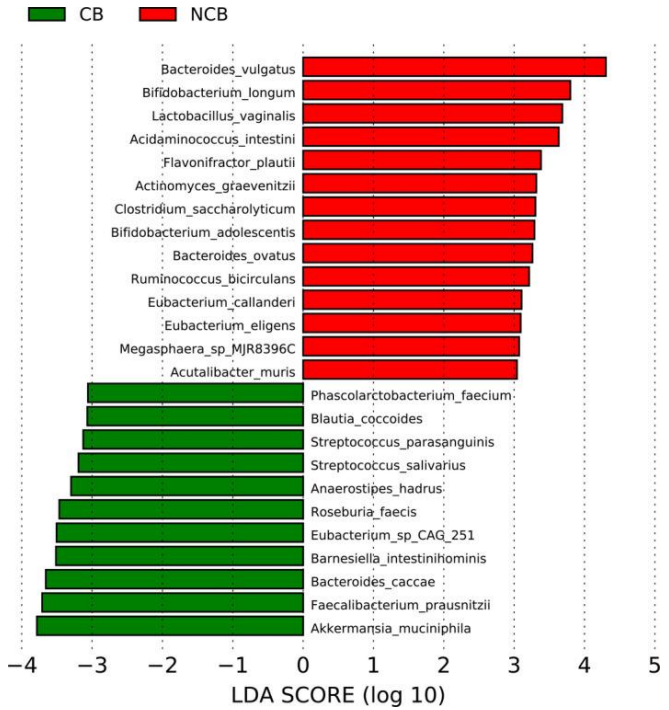
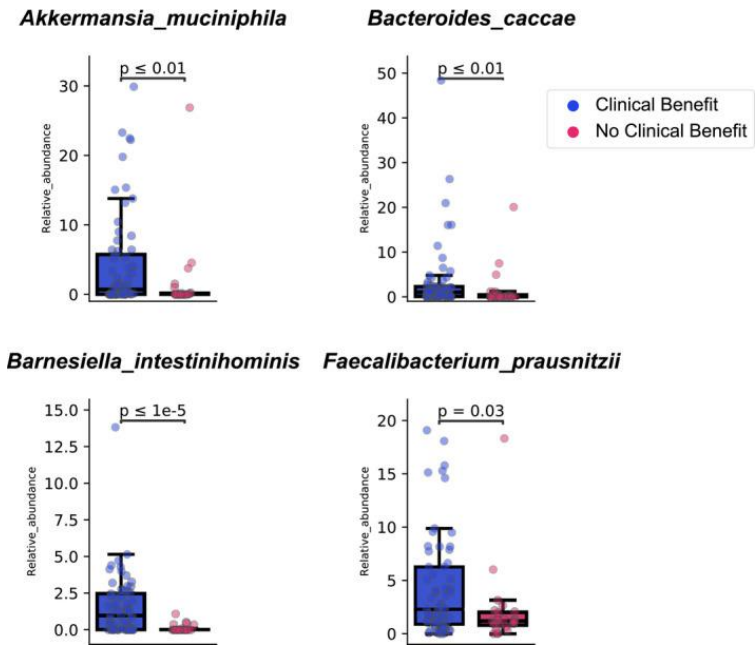
Microbiome in Renal Cell Carcinoma





Dizman *et al. Cancer Med 2020*

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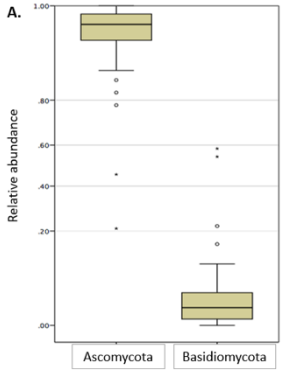
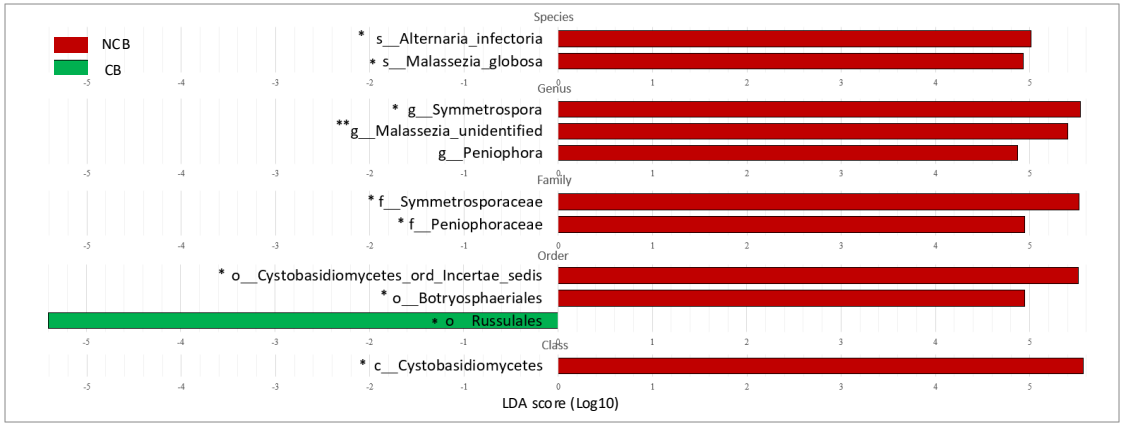
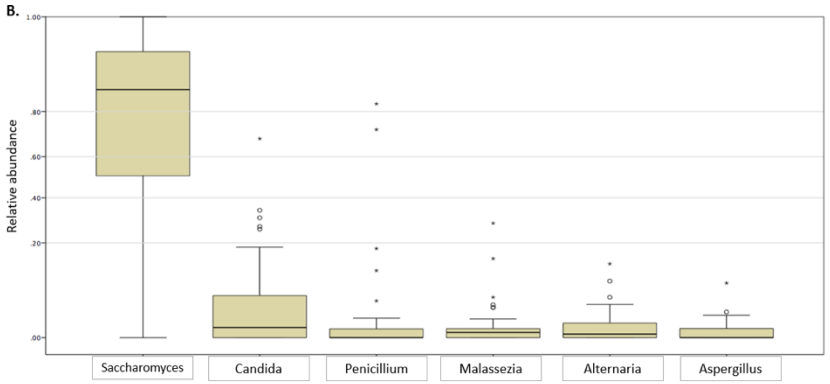
Microbiome in Renal Cell Carcinoma

Fungal microbiome aka mycobiome in mRCC (n=24)







Dizman *et al.* ASCO GU Cancers Symposium 2020

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A Triumvirate of Key Papers in *Science* (January 2018)

RESEARCH

CANCER IMMUNOTHERAPY

Gut microbiome modulates response to anti–PD-1 immunotherapy in melanoma patients

V. Gopalakrishnan,[1,2]* C. N. Spencer,[2,3]* L. Nezi,[3]* A. Reuben,[1] M. C. Andrews,[1] I. V. Karpinets,[3] P. A. Prieto,[1] D. Vicente,[1] K. Hoffman,[3] S. C. Wei,[1] A. P. Cogdill,[1,2] L. Zhao,[3] C. W. Hudgens,[4] D. S. Hutchinson,[1] T. Manzo,[4] M. Petaccia de Macedo,[4] T. Cotechini,[4] T. Kumar,[2] W. S. Chen,[5] S. M. Reddy,[5] R. Szczepaniak Sloane,[2] J. Galloway-Pena,[1] H. Jiang,[1] P. L. Chen,[6] E. J. Shpall,[2] K. Rezvani,[2] A. M. Alousi,[2] R. F. Chemaly,[2] S. Shelburne,[2,3] L. M. Vence,[1] P. C. Okhuysen,[2] V. B. Jensen,[2] A. G. Swennes,[7] F. McAllister,[2,8] E. Marcelo Riquelme Sanchez,[2,8] Y. Zhang,[2,8] E. Le Chatelier,[9] L. Zitvogel,[9,10] N. Pons,[9] J. L. Austin Brennan,[3] L. E. Hayden,[3] E. M. Burton,[3] J. M. Gardner,[3] E. Sirmans,[3] J. Hu,[3] A. J. Lazar,[4,8] T. Tsujikawa,[4] S. Diab,[4] H. Tawbi,[4] I. C. Glitza,[4] W. J. Hwu,[4] S. P. Patel,[4] S. E. Woodman,[4] E. N. Amaria,[4] M. A. Davies,[4] J. E. Gershenwald,[4] P. Hwu,[4] J. E. Lee,[4] J. Zhang,[4] L. M. Coussens,[4] Z. A. Cooper,[1,2]† P. A. Futreal,[4]† C. R. Daniel,[4,8] N. J. Ajami,[7] J. F. Petrosino,[7] M. T. Tetzlaff,[4,8] P. Sharma,[1,2]† J. P. Allison,[2] R. R. Jenq,[2]† J. A. Wargo[1,2]*†‡

Preclinical mouse models suggest that the gut microbiome modulates tumor response to checkpoint blockade immunotherapy; however, this has not been well-characterized in human cancer patients. Here we examined the oral and gut microbiome of melanoma patients undergoing anti–programmed cell death 1 protein (PD-1) immunotherapy ($n = 112$). Significant differences were observed in the diversity and composition of the patient gut microbiome of responders versus nonresponders. Analysis of patient fecal microbiome samples ($n = 43$, 30 responders, 13 nonresponders) showed significantly higher alpha diversity ($P < 0.01$) and relative abundance of bacteria of the Ruminococcaceae family ($P < 0.01$) in responding patients. Metagenomic studies revealed functional differences in gut bacteria in responders, including enrichment of anabolic pathways. Immune profiling suggested enhanced systemic and antitumor immunity in responding patients with a favorable gut microbiome as well as in germ-free mice receiving fecal transplants from responding patients. Together, these data have important implications for the treatment of melanoma patients with immune checkpoint inhibitors.

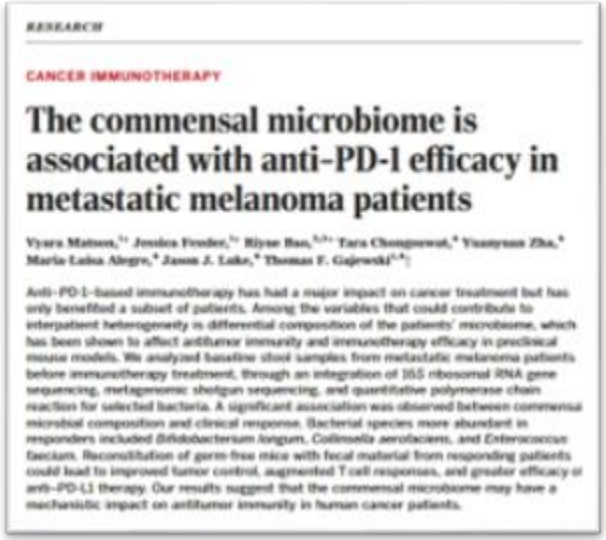
RESEARCH

CANCER IMMUNOTHERAPY

Gut microbiome influences efficacy of PD-1–based immunotherapy against epithelial tumors

Bertrand Routy,[1,2,3]† Emmanuelle Le Chatelier,[4]† Lisa Derosa,[1,2,3]† Connie P. M. Duong,[1,2,3] Maryam Tidjani Alou,[1,2,3] Romain Daillère,[1,2,3] Aurélie Fluckiger,[1,2,3] Meriem Messaoudene,[1,2] Conrad Rauber,[1,2,3] Maria P. Roberti,[1,2,3] Marine Fidelle,[1,2,3] Caroline Flament,[1,2,3] Vichnou Poirier-Colame,[1,2,3] Paule Opolon,[5] Christophe Klein,[5] Kristina Iribarren,[1,2,3,6,7,8,9,10,11] Laura Mondragón,[6,7,8,10,11,12] Nicolas Jacquelot,[1,2,3] Bo Qu,[1,2,3] Gladys Ferrere,[1,2,3] Céline Clémenson,[1,13] Laura Mezquita,[1,14] Jordi Remon Masip,[1,14] Charles Naltet,[15] Sofenia Brosseau,[15] Courtney Kaderbhai,[16] Corentin Richard,[16] Hiira Rizvi,[17] Florence Levenez,[4] Nathalie Galleron,[4] Benoit Quinquis,[4] Nicolas Pons,[4] Bernhard Ryffel,[18] Véronique Minard-Colin,[1,19] Patrick Gonin,[1,20] Jean-Charles Soria,[1,14] Eric Deutsch,[1,21] Yohann Loriot,[1,2,14] François Ghiringhelli,[16] Gérard Zalcman,[22] François Goldwasser,[6,23,24] Bernard Escudier,[1,14,25] Matthew D. Hellmann,[14,26] Alexander Eggermont,[1,2,14] Didier Raoult,[26] Laurence Albiges,[1,2,14] Guido Kroemer,[6,8,10,11,12,27,28]* Laurence Zitvogel[1,2,3,11]*

Immune checkpoint inhibitors (ICIs) targeting the PD-1/PD-L1 axis induce sustained clinical responses in a sizable minority of cancer patients. We found that primary resistance to ICIs can be attributed to abnormal gut microbiome composition. Antibiotics inhibited the clinical benefit of ICIs in patients with advanced cancer. Fecal microbiota transplantation (FMT) from cancer patients who responded to ICIs into germ-free or antibiotic-treated mice ameliorated the antitumor effects of PD-1 blockade, whereas FMT from nonresponding patients failed to do so. Metagenomics of patient stool samples at diagnosis revealed correlations between clinical responses to ICIs and the relative abundance of *Akkermansia muciniphila*. Oral supplementation with *A. muciniphila* after FMT with nonresponder feces restored the efficacy of PD-1 blockade in an interleukin-12–dependent manner by increasing the recruitment of $CCR9^+CXCR3^+CD4^+$ T lymphocytes into mouse tumor beds.



RESEARCH

CANCER IMMUNOTHERAPY

The commensal microbiome is associated with anti–PD-1 efficacy in metastatic melanoma patients

Vyara Matson,[1]† Jessica Fessler,[1]† Riyue Bao,[2,3]† Tara Chongsuwat,[4] Yuanyuan Zha,[4] Marie-Luisa Alegre,[4] Jason J. Luke,[4] Thomas F. Gajewski[1,4]‡

Anti–PD-1–based immunotherapy has had a major impact on cancer treatment but has only benefited a subset of patients. Among the variables that could contribute to interpatient heterogeneity is differential composition of the patients' microbiome, which has been shown to affect antitumor immunity and immunotherapy efficacy in preclinical mouse models. We analyzed baseline stool samples from metastatic melanoma patients before immunotherapy treatment, through an integration of 16S ribosomal RNA gene sequencing, metagenomic shotgun sequencing, and quantitative polymerase chain reaction for selected bacteria. A significant association was observed between commensal microbial composition and clinical response. Bacterial species more abundant in responders included *Bifidobacterium longum*, *Collinsella aerofaciens*, and *Enterococcus faecium*. Reconstitution of germ-free mice with fecal material from responding patients could lead to improved tumor control, augmented T cell responses, and greater efficacy of anti–PD-L1 therapy. Our results suggest that the commensal microbiome may have a mechanistic impact on antitumor immunity in human cancer patients.

Three papers linking gut microbiome to outcome with PD-1 inhibitors.

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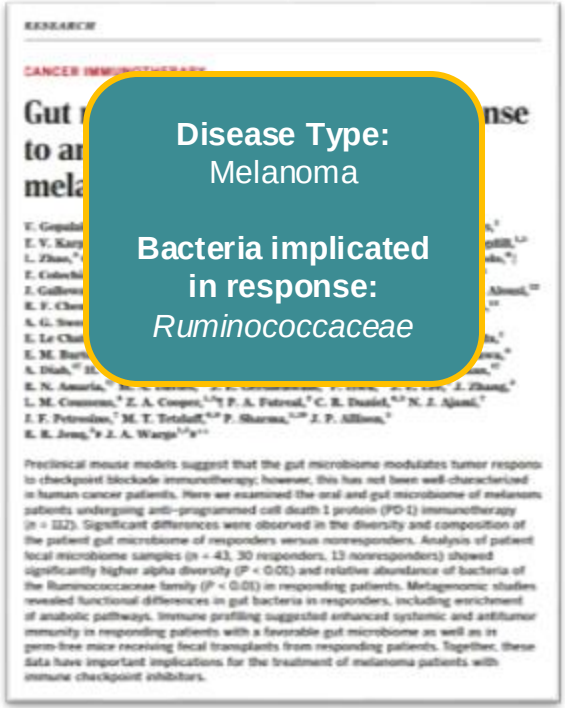
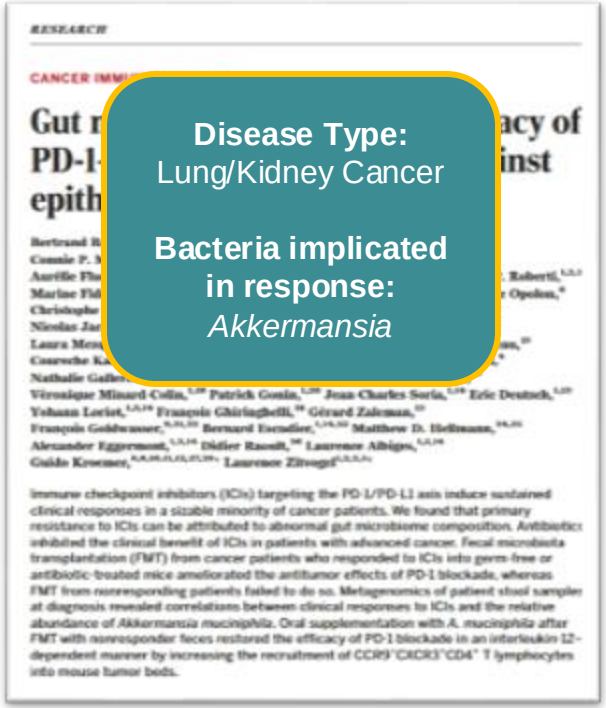
A Triumvirate of Key Papers in *Science* (January 2018)



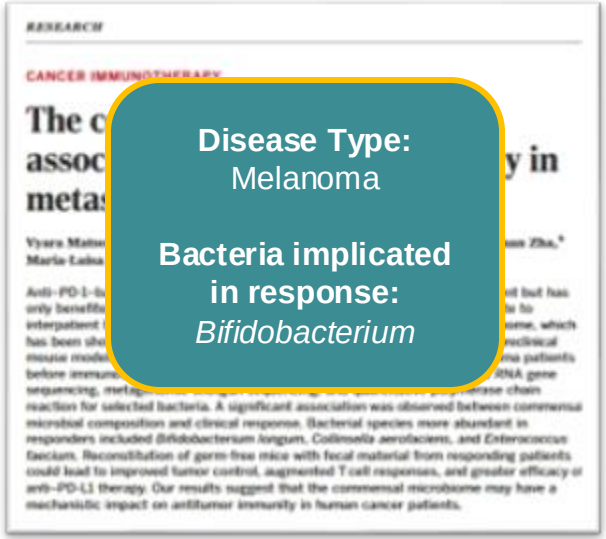
Disease Type:
Melanoma

Bacteria implicated in response:
Ruminococcaceae



Disease Type:
Lung/Kidney Cancer

Bacteria implicated in response:
Akkermansia



Disease Type:
Melanoma

Bacteria implicated in response:
Bifidobacterium

Three papers linking gut microbiome to outcome with PD-1 inhibitors.

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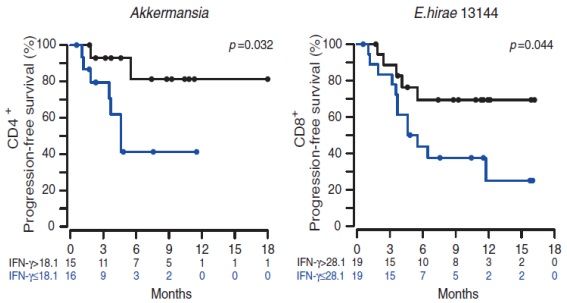
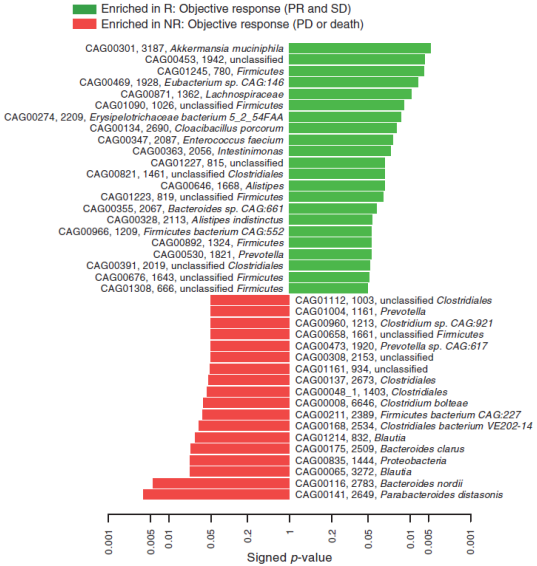
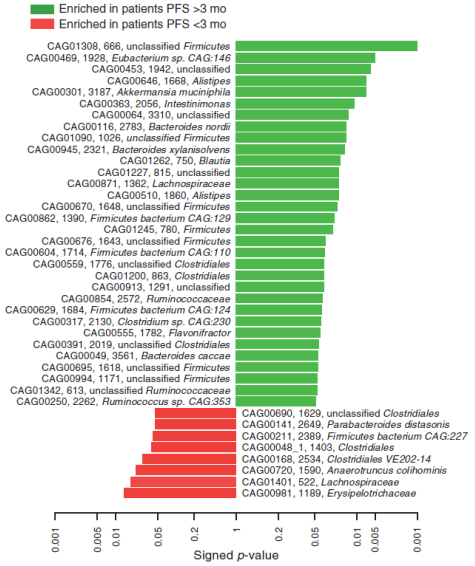
Microbiome in Renal Cell Carcinoma

Summary:

- 60 pts with NSCLC
- 40 pts with RCC
- Baseline and serial stool collections after checkpoint inhibitor initiated
- Specific bacterial species associated with response







Routy B et al Science 2017 (RCC Investigators: DeRosa, Albiges, Escudier)

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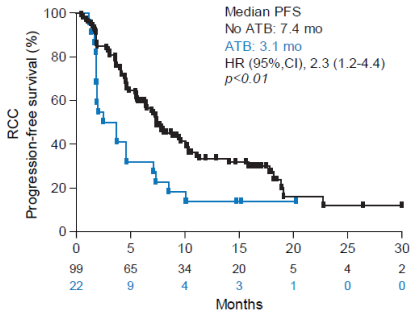
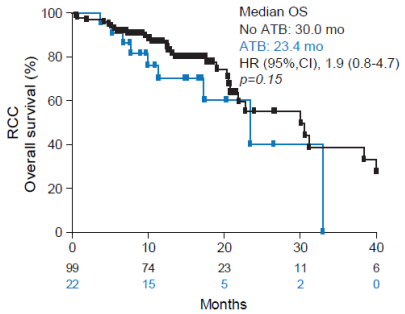
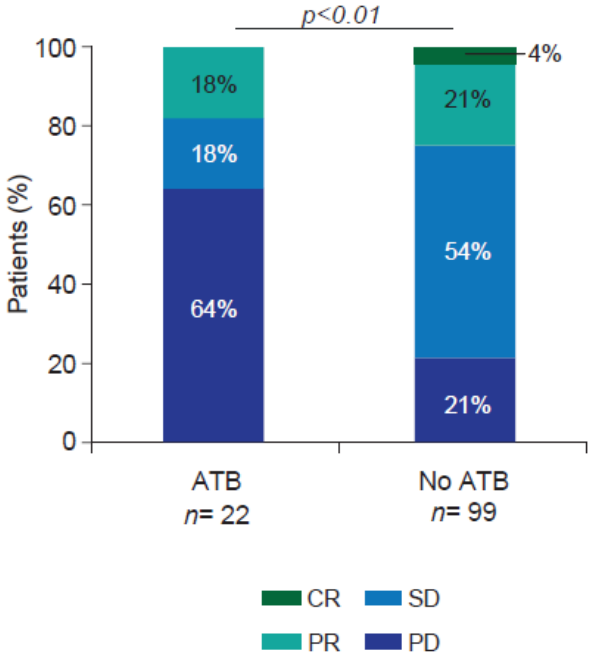
Microbiome in Renal Cell Carcinoma

Summary:
- **121 pts with RCC**
- **239 pts with NSCLC**
- **Antibiotic use associated with inferior outcome in pts receiving checkpoint inhibitors**
- **Similar trends in NSCLC and RCC pts**







Derosa L *et al* Ann Oncol 2018 (RCC Investigators: DeRosa, Albiges, Escudier)

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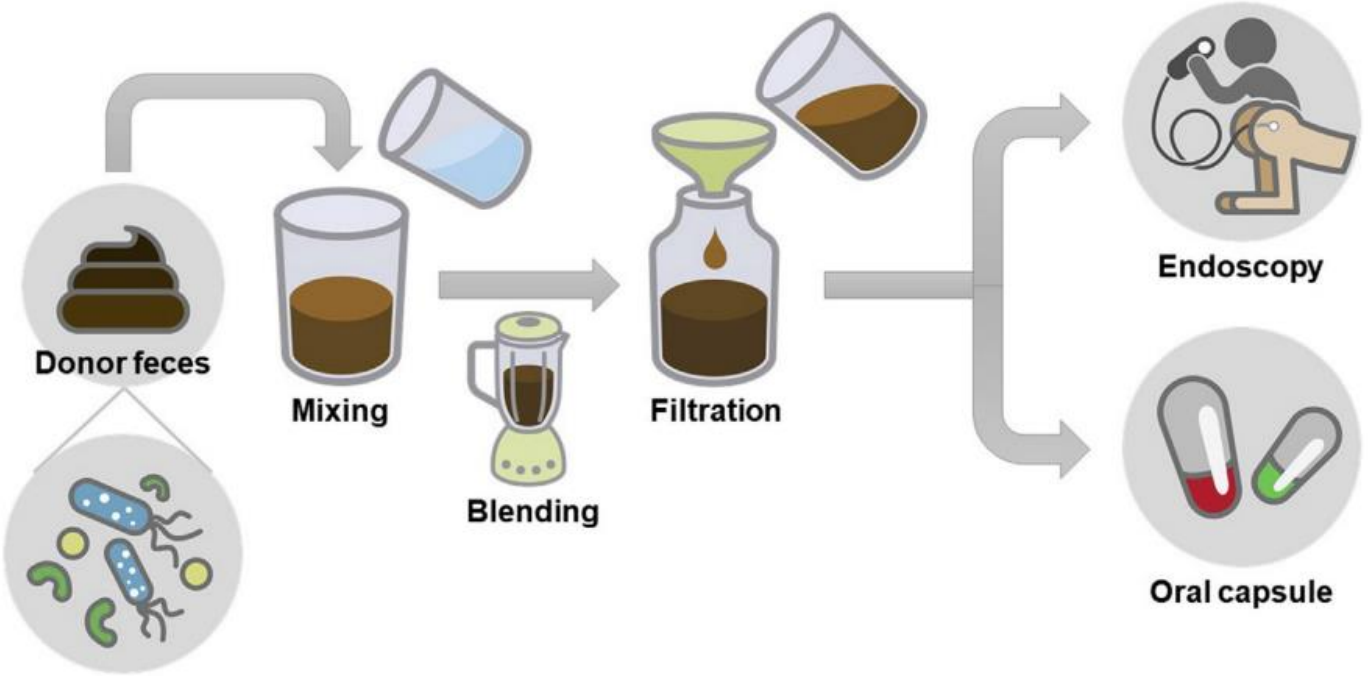
Modulating the Microbiome: Fecal Microbiome Transplant (FMT)



Wang *et al* JFMA 2019

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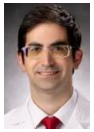
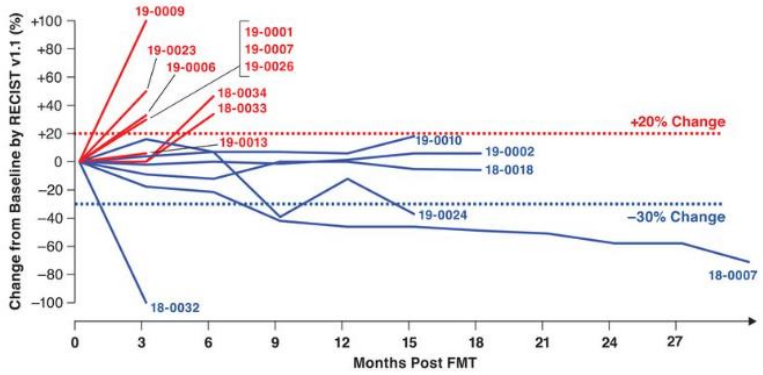
Modulating the Microbiome: Fecal Microbiome Transplant (FMT)



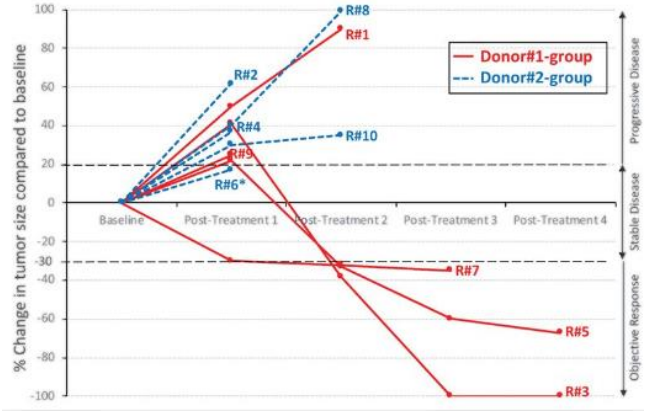
Primary progression on PD-1 inhibitor for melanoma

Rechallenge with PD-1 inhibitor + FMT from responder



Progression on PD-1 inhibitor for melanoma

Rechallenge with PD-1 inhibitor + FMT from responder



Davar *et al* Science 2021; Baruch *et al* Science 2020

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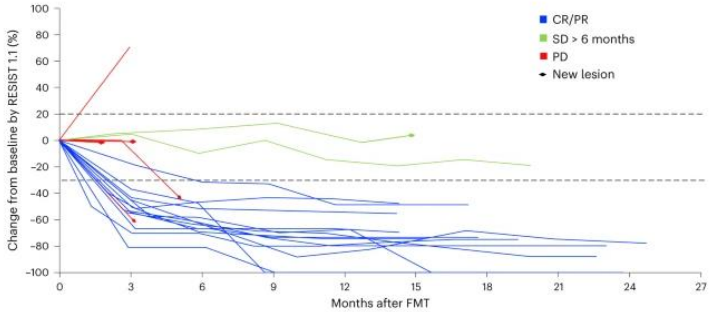
Modulating the Microbiome: Fecal Microbiome Transplant (FMT)

Treatment naïve advanced melanoma

PD-1 inhibitor + Healthy Donor FMT



Routy *et al* Nat Med 2023

Challenges to FMT

- Requires substantial resources/ infrastructure
- Challenging to ensure sourcing and consistency of product
- Potential safety risks (e.g., pathogenic transmission)
- Unknown what optimal FMT product constitutes (e.g., healthy donor or responder?)

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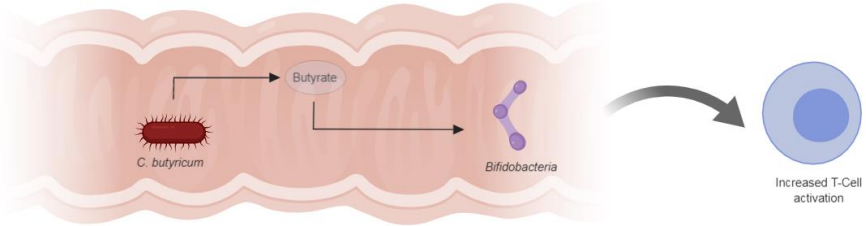
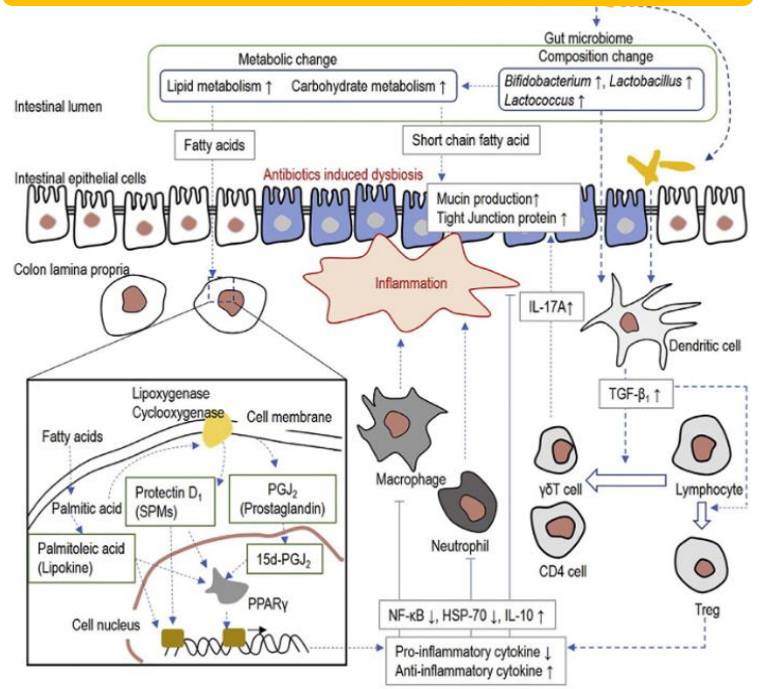
Modulating the Microbiome: Live Bacterial Products

Simple



Complicated



Hagihara *et al* iScience 2020

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Modulating the Microbiome: Live Bacterial Products


Nivolumab/Ipilimumab +/- CBM588

Metastatic renal cell carcinoma and:
- Measurable metastatic disease
- ECOG performance status 0-1
- No prior systemic therapy for metastatic disease
- Intermediate- or poor-risk disease by IMDC classification
- No history of autoimmune disease

2:1 Randomization

Nivolumab 3 mg/kg IV every 3 weeks x 4
+ Ipilimumab 1 mg/kg IV every 3 weeks x 4
→ Nivolumab 480 mg IV monthly
+
CBM-588 80 mg oral twice daily

Nivolumab 3 mg/kg IV every 3 weeks x 4
+ Ipilimumab 1 mg/kg IV every 3 weeks x 4
→ Nivolumab 480 mg IV monthly

Primary Endpoint: Change in *Bifidobacterium* spp from baseline to week 12
Secondary Endpoints: Change in Shannon index, progression-free survival (PFS), response rate (RR) and toxicity

Statistical Analysis: With 30 patients (randomized 2:1), 80% power to detect a 1-standard deviation change in specific *Bifidiobacterium* spp between study arms using a two-group t-test with a 1-sided type I error of 0.05.

Dizman *et al* Nature Medicine 2022

Cabozantinib/Nivolumab +/- CBM588

Metastatic renal cell carcinoma and:
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2:1 Randomization

Cabozantinib 40 mg oral daily +
Nivolumab 480 mg IV monthly
+
CBM-588 80 mg oral twice daily

Cabozantinib 40 mg oral daily +
Nivolumab 480 mg IV monthly

Primary Endpoint: Change in *Bifidobacterium* spp from baseline to week 12
Secondary Endpoints: Change in Shannon index, progression-free survival (PFS), response rate (RR) and toxicity

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Ebrahimi *et al* Nature Medicine 2024

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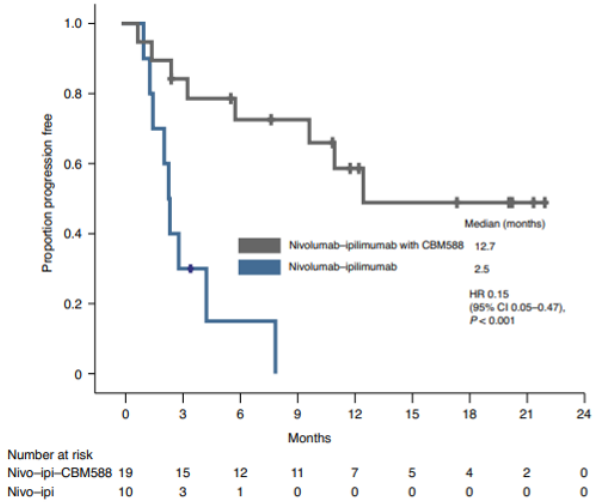
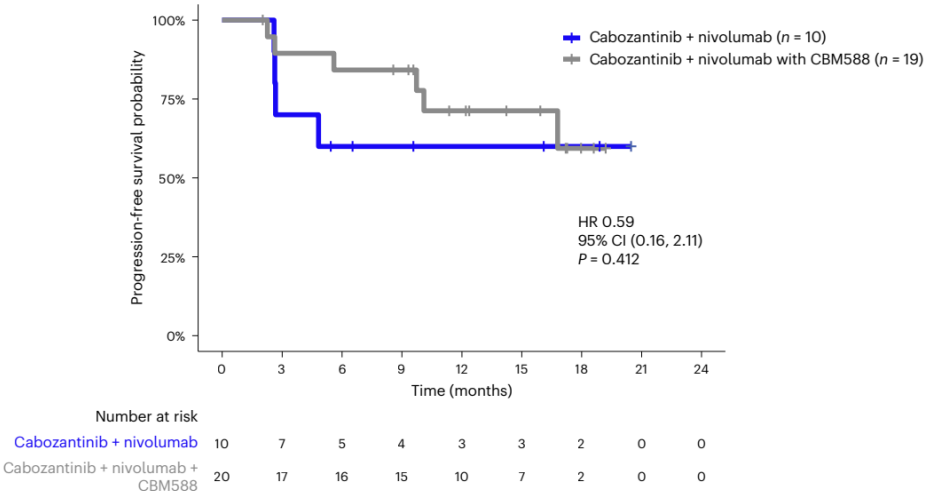
Modulating the Microbiome: Live Bacterial Products


Nivolumab/Ipilimumab +/- CBM588



Dizman *et al* Nature Medicine 2022

Cabozantinib/Nivolumab +/- CBM588



Ebrahimi *et al* Nature Medicine 2024

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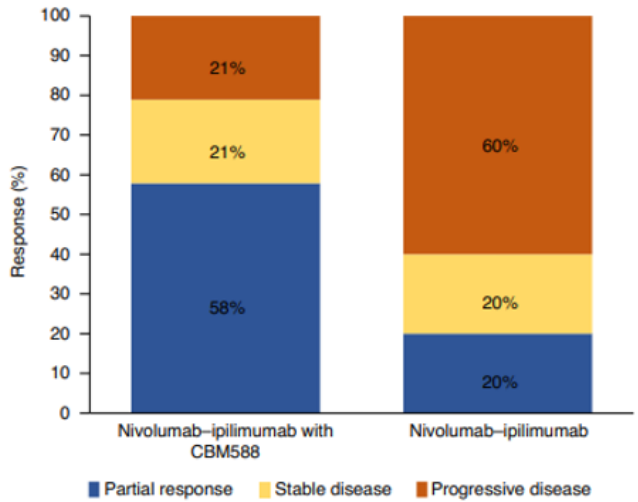
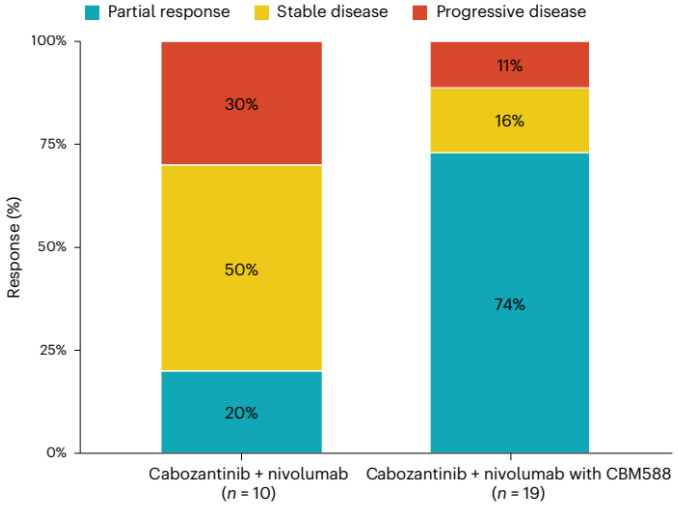
Modulating the Microbiome: Live Bacterial Products


Nivolumab/Ipilimumab +/- CBM588



Dizman *et al* Nature Medicine 2022

Cabozantinib/Nivolumab +/- CBM588



Ebrahimi *et al* Nature Medicine 2024

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Modulating the Microbiome: Live Bacterial Products


SWOG Proposal: A Definitive Study Assessing CBM588

Metastatic renal cell carcinoma and:
- Measurable metastatic disease
- ECOG performance status 0-1
- No prior systemic therapy for metastatic disease
- No history of autoimmune disease

1:1 Randomization

IO-based therapy + CBM588

IO-based therapy + placebo

PIs: Barata/Pal/Vaishampayan

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Ongoing Microbiome/RCC Studies at City of Hope

Nivolumab/Ipilimumab + CBM588

Metastatic renal cell carcinoma and:
- Measurable metastatic disease
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- No prior systemic therapy for metastatic disease
- Intermediate- or poor-risk disease by IMDC classification
- No history of autoimmune disease

Nivolumab/Ipilimumab + CBM588 DL1

Nivolumab/Ipilimumab + CBM588 DL2

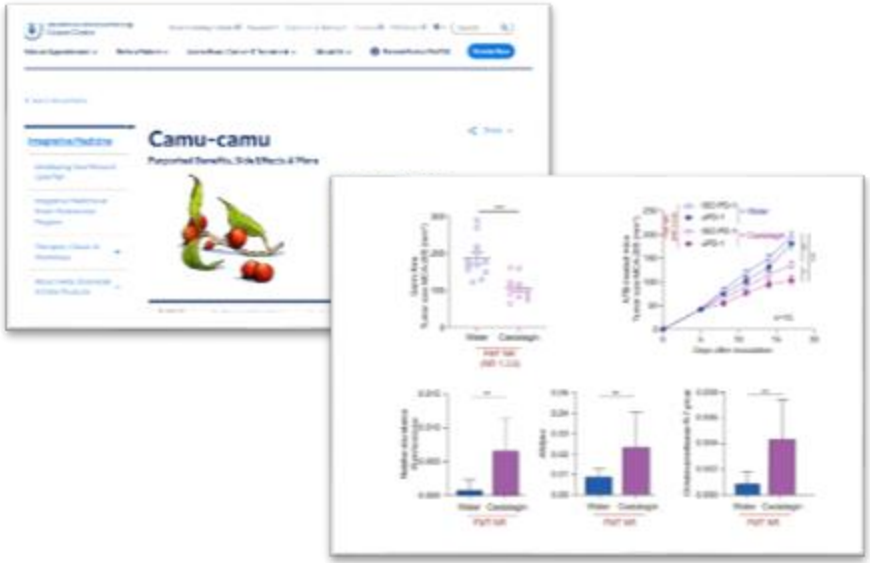
Nivolumab/Ipilimumab + CBM588 DL3

Primary Endpoint: Safety of novel CBM588 formulation
Secondary Endpoints: Change in Shannon index, progression-free survival (PFS), response rate (RR) and toxicity

Statistical Analysis: Classical 3+3 design

PI: Alexander Chehrazi-Raffle, MD

Nivolumab/Ipilimumab +/- Camu Camu



PI: Regina Barragan-Carrillo, MD

MSKCC Integrative Medicine Website; Messaoudene *et al* Cancer Discovery 2022

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Ongoing Microbiome/RCC Studies at City of Hope

Nivolumab/Ipilimumab + CBM588

Metastatic renal cell carcinoma and:
- Measurable metastatic disease
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→ Nivolumab/Ipilimumab + CBM588 DL1 → Nivolumab/Ipilimumab + CBM588 DL2 → Nivolumab/Ipilimumab + CBM588 DL3

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Statistical Analysis: Classical 3+3 design

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Nivolumab/Ipilimumab +/- Camu Camu

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- ECOG performance status 0-1
- No prior systemic therapy for metastatic disease
- Intermediate- or poor-risk disease by IMDC classification
- No history of autoimmune disease

→ 2:1 Randomization → Nivolumab/Ipilimumab + Camu camu

→ 2:1 Randomization → Nivolumab/Ipilimumab

Primary Endpoint: Change in *Ruminococcus* spp from baseline to week 12
Secondary Endpoints: Change in Shannon index, progression-free survival (PFS), response rate (RR) and toxicity

Statistical Analysis: With 30 patients (randomized 2:1), 80% power to detect a 1-standard deviation change in specific *Ruminococcus* spp between study arms using a two-group t-test with a 1-sided type I error of 0.05.

PI: Regina Barragan-Carrillo, MD

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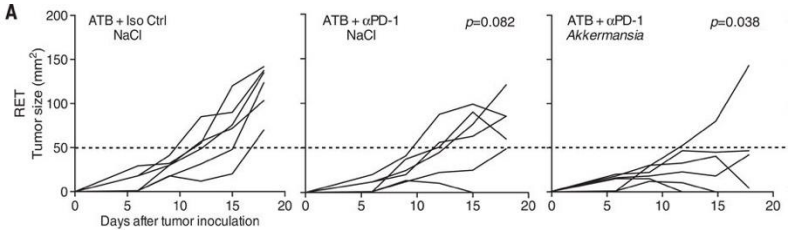
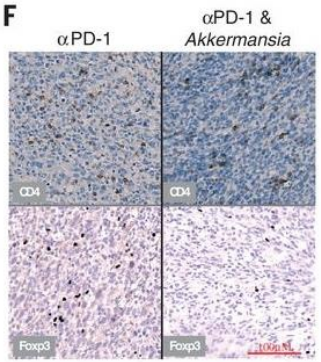
On the Horizon: Oncobax AK





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A Study of Oncobax®-AK in Patients With Advanced Solid Tumors

The safety and scientific validity of this study is the responsibility of the study sponsor and investigators. Listing a study does not mean it has been evaluated by the U.S. Federal Government. Know the risks and potential benefits of clinical studies and talk to your health care provider before participating. Read our disclaimer for details.

ClinicalTrials.gov Identifier: NCT05865730

Recruitment Status : Recruiting
First Posted : May 19, 2023
Last Update Posted : May 19, 2023

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Routy *et al* Science 2017

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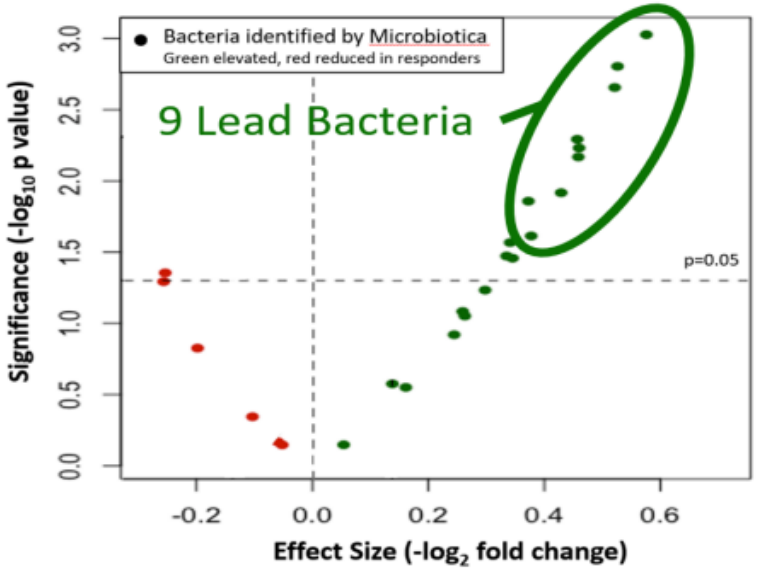
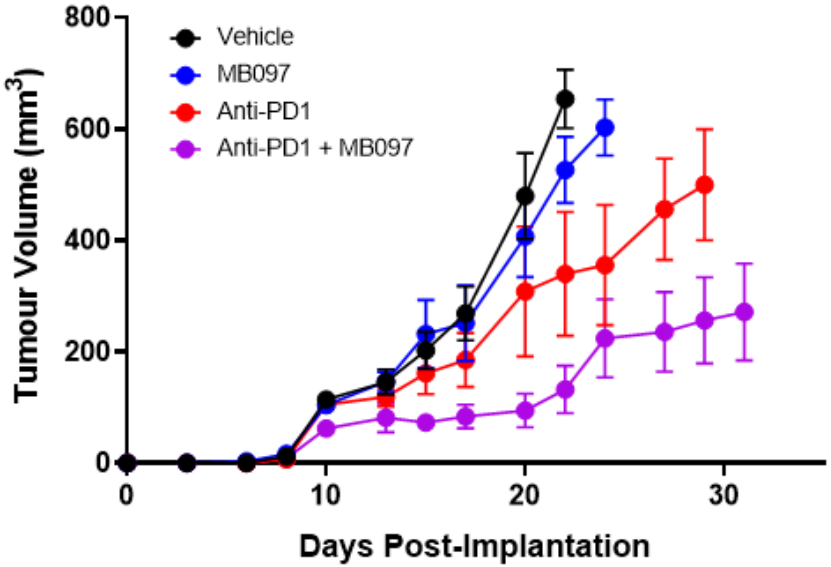
On the Horizon: MB097





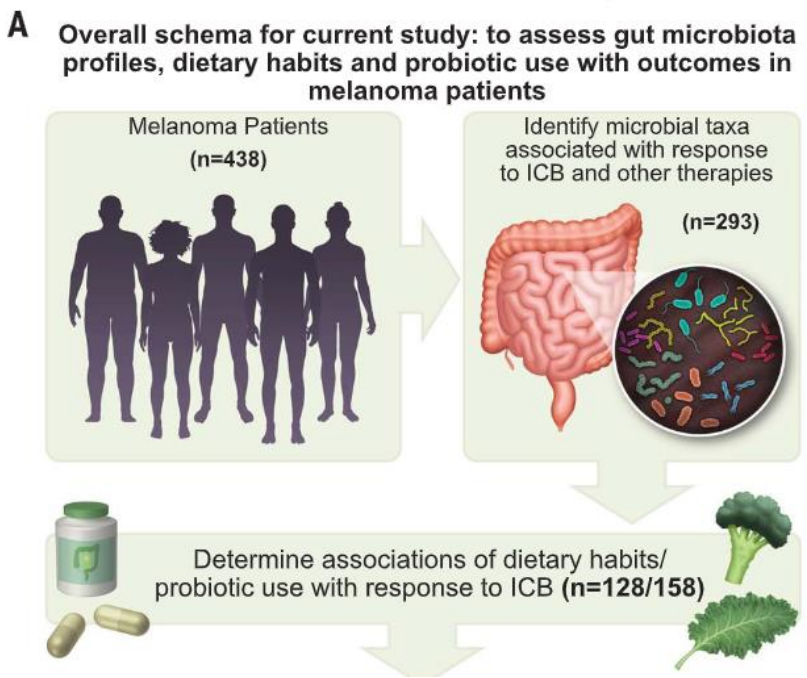
Corrie *et al* ESMO 2022

Other Interesting Data: Interplay of Diet?

IMMUNOTHERAPY

Dietary fiber and probiotics influence the gut microbiome and melanoma immunotherapy response

Christine N. Spencer[1]†‡, Jennifer L. McQuade[2]†, Vancheswaran Gopalakrishnan[1]†§, John A. McCulloch[3]†, Marie Vetizou[3]†, Alexandria P. Cogdill[1,4]†¶, Md A. Wadud Khan[1], Xiaotao Zhang[5], Michael G. White[1], Christine B. Peterson[6], Matthew C. Wong[1], Golnaz Morad[1], Theresa Rodgers[2], Jonathan H. Badger[3], Beth A. Helmink[1]#, Miles C. Andrews[1,7], Richard R. Rodrigues[8], Andrey Morgun[9], Young S. Kim[10], Jason Roszik[2], Kristi L. Hoffman[11], Jiali Zheng[5]**, Yifan Zhou[4], Yusra B. Medik[4], Laura M. Kahn[4,12], Sarah Johnson[1], Courtney W. Hudgens[13], Khalida Wani[13], Pierre-Olivier Gaudreau[14], Angela L. Harris[15], Mohamed A. Jamal[16], Erez N. Baruch[17], Eva Perez-Guijarro[18], Chi-Ping Day[18], Glenn Merlino[18], Barbara Pazdrak[2], Brooke S. Lochmann[2], Robert A. Szczepaniak-Sloane[1], Reetakshi Arora[1], Jaime Anderson[2], Chrystia M. Zobniw[2], Eliza Posada[2], Elizabeth Sirmans[2], Julie Simon[1], Lauren E. Haydu[1], Elizabeth M. Burton[1], Linghua Wang[16], Minghao Dang[16], Karen Clise-Dwyer[19,20], Sarah Schneider[19], Thomas Chapman[1], Nana-Ama A. S. Anang[4], Sheila Duncan[1], Joseph Toker[21,22], Jared C. Malke[1], Isabella C. Glitza[2], Rodabe N. Amaria[2], Hussein A. Tawbi[2], Adi Diab[2], Michael K. Wong[2], Sapna P. Patel[2], Scott E. Woodman[2], Michael A. Davies[2], Merrick I. Ross[1], Jeffrey E. Gershenwald[1], Jeffrey E. Lee[1], Patrick Hwu[2]††, Vanessa Jensen[23], Yardena Samuels[24], Ravid Straussman[24], Nadim J. Ajami[16], Kelly C. Nelson[25], Luigi Nezi[26], Joseph F. Petrosino[11], P. Andrew Futreal[16], Alexander J. Lazar[12,16,27], Jianhua Hu[28], Robert R. Jenq[16,29], Michael T. Tetzlaff[30], Yan Yan[31], Wendy S. Garrett[32], Curtis Huttenhower[31,33,34,35], Padmanee Sharma[4,36,37], Stephanie S. Watowich[4], James P. Allison[4,37], Lorenzo Cohen[38]‡‡, Giorgio Trinchieri[3]*‡‡, Carrie R. Daniel[5]*‡‡, Jennifer A. Wargo[1,16]*‡‡



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Other Interesting Data: Interplay of Diet?

Table 1. Associations of baseline probiotic supplement use and dietary fiber intake in late-stage melanoma patients treated with ICB and followed for tumor response and progression-free survival. Dashes indicate not applicable. HR, hazard ratio; CI, confidence interval; OR, odds ratio; N/R, not reached; ref, referent group.

Comparison	*n*	Progression-free survival					Odds of response to ICB			
		Events	Median months	HR*	95% CI	*P* value†	Responder *n* (%)	OR*	95% CI	*P* value†
Probiotic supplement use										
Total	158	85	–	–	–	–	65%	–	–	–
No	109	56	23	1.00	ref	–	74 (68%)	1.00	ref	–
Yes	49	29	17	1.30	0.82, 2.07	0.27	29 (59%)	0.79	0.37, 1.66	0.52
Dietary fiber intake										
Total	128	73	–	–	–	–	65%	–	–	–
Per 5 g/day increase	–	–	–	0.71	0.52, 0.98	0.04	–	1.70	0.97, 3.00	0.06
Insufficient	91	57	13	1.00	ref	–	55 (60%)	1.00	ref	–
Sufficient	37	16	N/R	0.59	0.33, 1.04	0.07	28 (76%)	2.20	0.86, 5.61	0.10
Dietary fiber intake + probiotic supplement use										
Total	123	72	–	–	–	–	63%	–	–	–
Sufficient fiber + no probiotics	22	8	N/R	0.44	0.21, 0.92	0.03	18 (82%)	2.94	0.87, 9.94	0.08
Other‡	101	64	13	1.00	ref	–	60 (59%)	1.00	ref	–

*HR and 95% CI estimated using Cox proportional hazards regression. OR and 95% CI estimated using logistic regression. All models include multivariable adjustment for subtype, stage, lactate dehydrogenase level, and BMI. †*P* value by Wald test. ‡Other category includes patients who either reported insufficient fiber intake or probiotic use.

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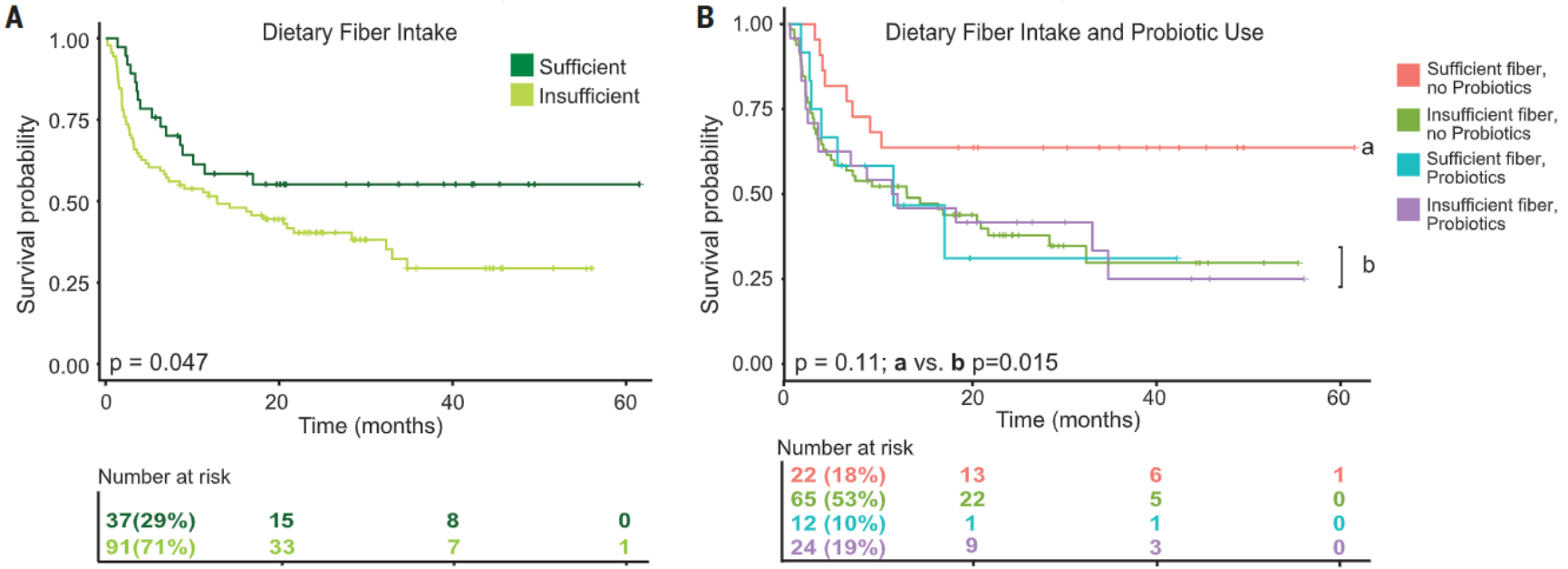
Other Interesting Data: Interplay of Diet?



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Other Interesting Data: How Do We Assess Diet?

Notably, all 26 items corresponding to foods or food groups assessed in the NCI-DSQ contribute to the derivation of dietary fiber and calcium intake; thus, patients with 2 or more missing responses to any query on the DSQ were excluded (n=38), while imputation by mode was applied for 4 patients with only 1 missing response. The threshold of 20 grams per day used to define "sufficient" versus "insufficient" dietary fiber intake (and other categorical dietary variables) was selected based on the statistical distribution within our cohort (Fig. S10).

While the NCI-DSQ was validated against 24-hour recalls (*17*), it is not a measure of an individual's absolute or true intake. For example, portion size is estimated using national survey data, not individual level data. Thus, to define sufficient vs. insufficient fiber intake categories our approach was informed by the NCI-DSQ evaluation and validation work by Thompson *et al.* in comparison to 24-hour recalls within a nationally representative sample (NHANES). Given that so few meet the U.S. dietary guidelines (i.e., ~14 g per 1,000 kcal daily based on sex, age and energy needs), these recommended levels are often in the lower or upper tails of the distribution of actual intake in a population. Similarly, we considered threshold values in the top quartile (25th percentile) or tertile (33rd percentile) of estimated usual intake to provide more accurate classifications when using the DSQ (*17*). As this threshold met by ~30% of our patients is not a specific recommendation, the value of 20 g/day should not be over-interpreted. Results are also presented in the context of an incremental 5 g/day increase with patient outcomes; a unit change that was informed by the standard deviation or sigma (Fig. S10).

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Other Interesting Data: The definition of a healthy gut?

Cell

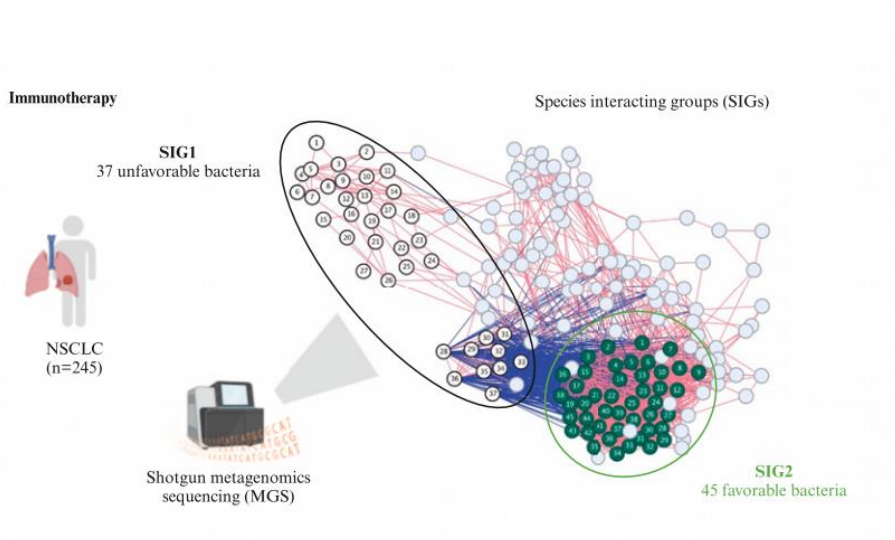
CellPress

Volume 187, Issue 13, 20 June 2024, Pages 3373-3389.e16

Article

Custom scoring based on ecological topology of gut microbiota associated with cancer immunotherapy outcome

Lisa Derosa [1 2 3 4 45 46], Valerio Iebba [1 5 45], Carolina Alves Costa Silva [1 2 3 45], Gianmarco Piccinno [6], Guojun Wu [7 8 9], Leonardo Lordello [1 3], Bertrand Routy [10 11], Naisi Zhao [12], Cassandra Thelemaque [1 3], Roxanne Birebent [1 2 3], Federica Marmorino [13 14], Marine Fidelle [1 2 3], Meriem Messaoudene [11], Andrew Maltez Thomas [6], Gerard Zalcman [15], Sylvie Friard [16], Julien Mazieres [17], Clarisse Audigier-Valette [18], Denis Moro- Sibilot [19], François Goldwasser [20 21 22]... Laurence Zitvogel [1 2 3 44]



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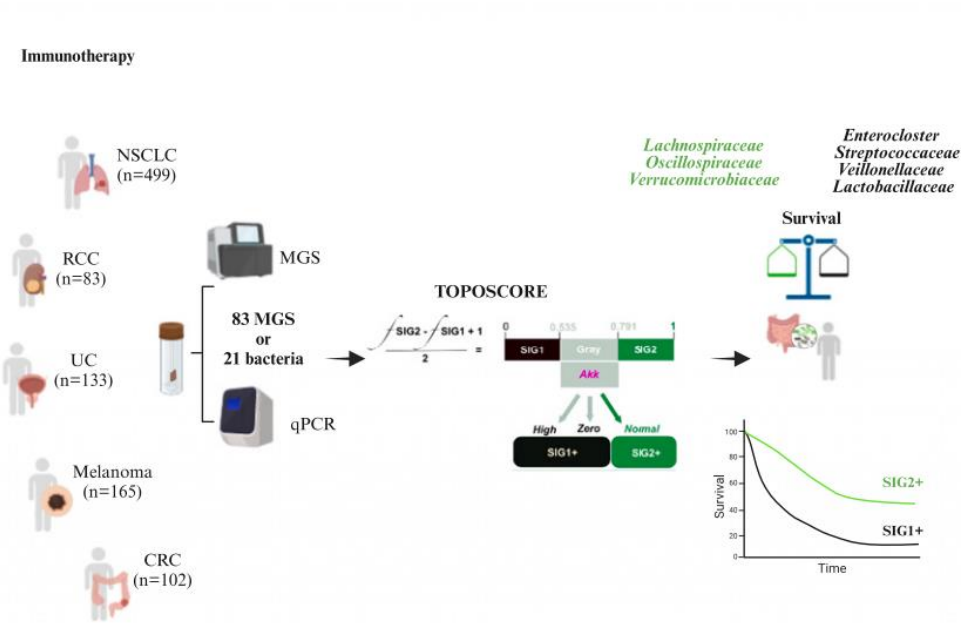
Other Interesting Data: The definition of a healthy gut?



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