Immune System and Pancreatic Cancer

T. Macarulla

Vall d´Hebrón University Hospital
Barcelona, Spain

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Declaration of conflict of interest

I have received honoraria for consultancy from Shire Pharmaceuticals, Roche, Tesaro, Batxer, Sanofi, Celgene, QED Therapeutics, Genzyme Europe, Baxalta, and received support for travel or accommodation from Merck, H3 Biomedicine, Bayer, Sanofi.

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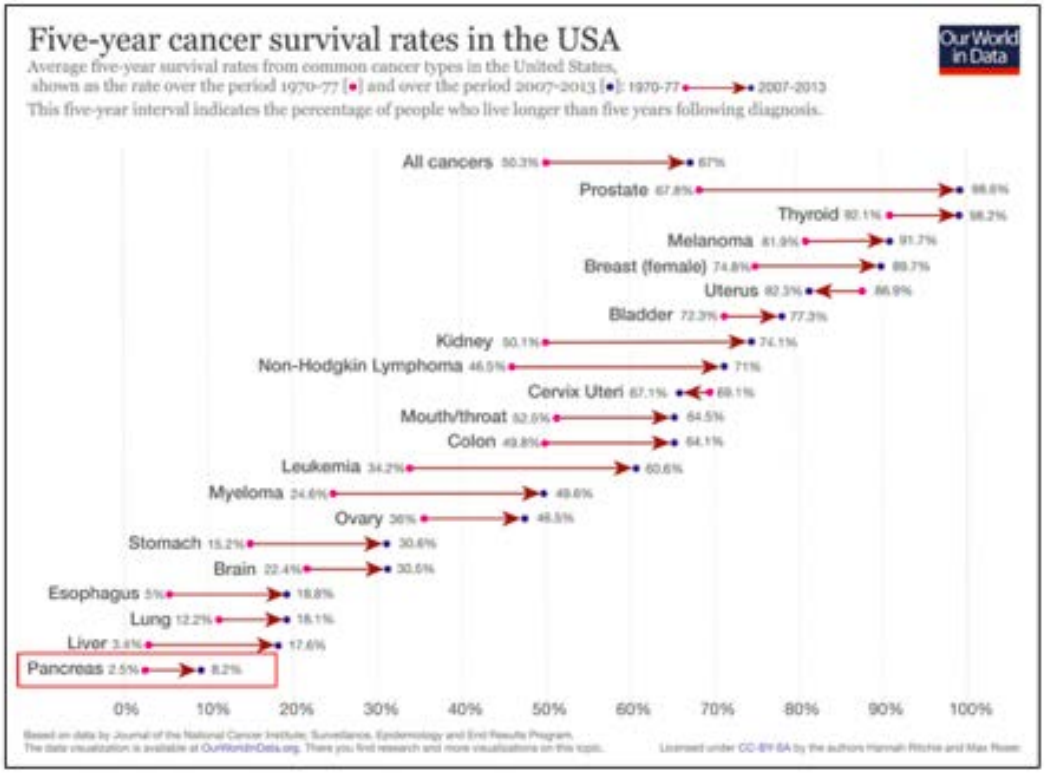
Good illustration of progress in cancer, albeit with some notable Master title style



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ACTA ONCOLOGICA, 2016
VOL. 55, NO. 9-10, 1158–1160
http://dx.doi.org/10.1080/0284186X.2016.1197419

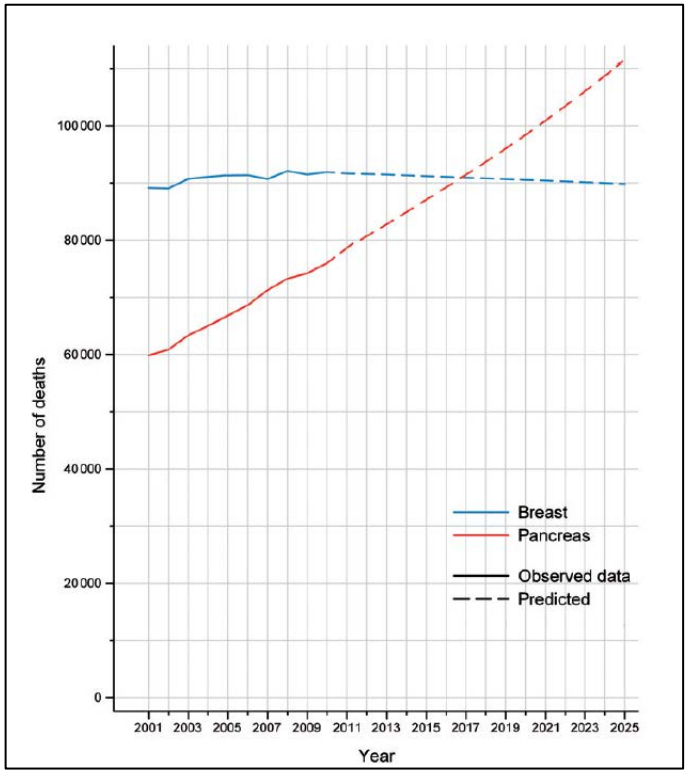
Taylor & Francis
Taylor & Francis Group

ORIGINAL ARTICLE

More deaths from pancreatic cancer than breast cancer in the EU by 2017

J. Ferlay[a], C. Partensky[b] and F. Bray[a]

[a]Section of Cancer Surveillance, International Agency for Research on Cancer, Lyon, France; [b]Section of Infections and Cancer Epidemiology, International Agency for Research on Cancer, Lyon, France



-In 2017: More deaths from PC will occur (91.500) than breast cancer (91.000).
-By 2025, deaths from PC are predicted to be 25% higher.
Coordinated efforts are necessary

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Immunotherapy: Facts and hopes

Who benefits from checkpoint immunotherapy?

The main type of immunotherapy uses drugs known as checkpoint inhibitors. Checkpoint immunotherapy has different rates of success with different types of cancer:

Advanced melanoma – about 5 in 10 people (50%) benefit from checkpoint immunotherapy

Advanced kidney cancer, bladder cancer, lung cancer, head and neck cancer or Hodgkin lymphoma – 2–3 in 10 people (20–30%) benefit from checkpoint immunotherapy

Most other types of advanced cancer – less than 1 in 10 people (1–10%) benefit from checkpoint immunotherapy

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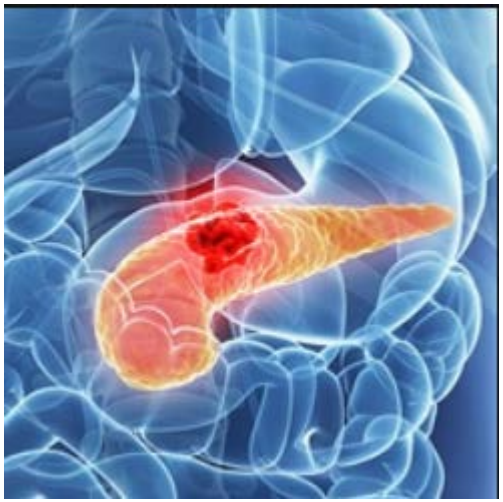
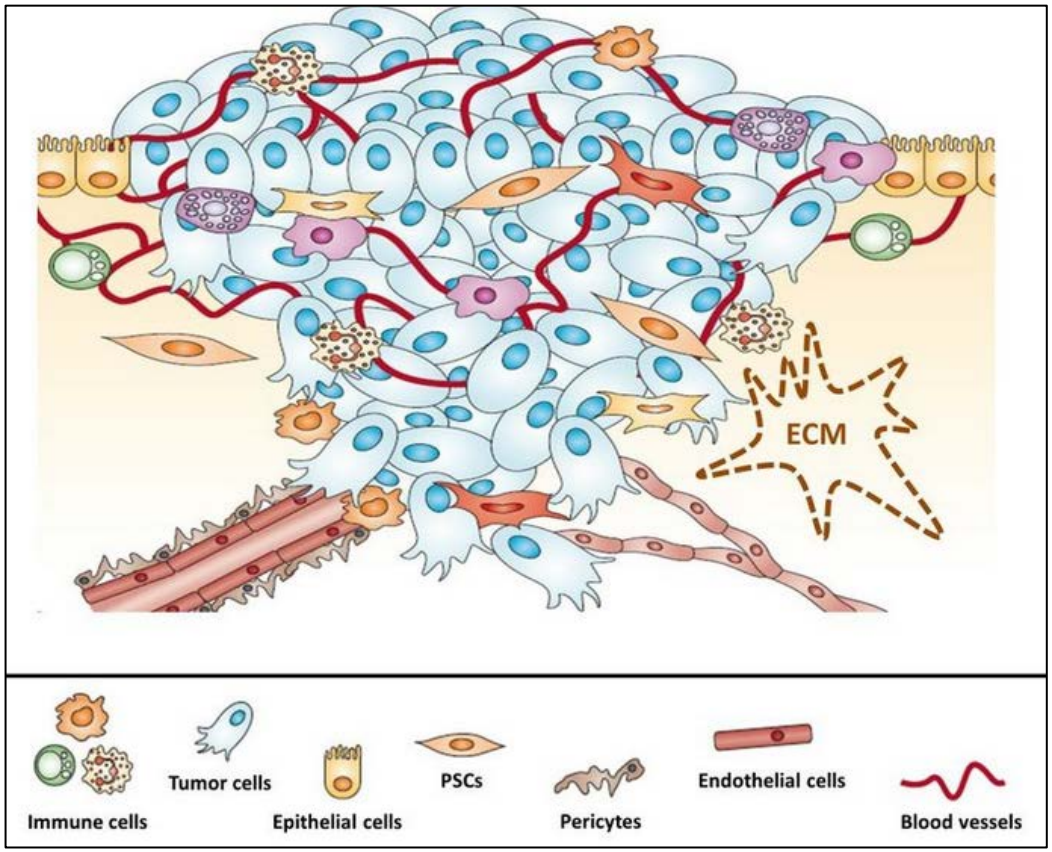
Pancreatic cancer: Non immunogenic disease





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Immunotherapy for Pancreatic Cancer

- PC is **non immunogenic** because:

  -Immunosuppressive cells and cytokines

  -Low tumour mutation burdern

  -Paucity of T-cells in tumours (number and function).

- Single-agent therapeutic approaches focusing on overcoming T-cell immunogenic endpoint with immune checkpoint inhibitors or vaccines are not encouraging.

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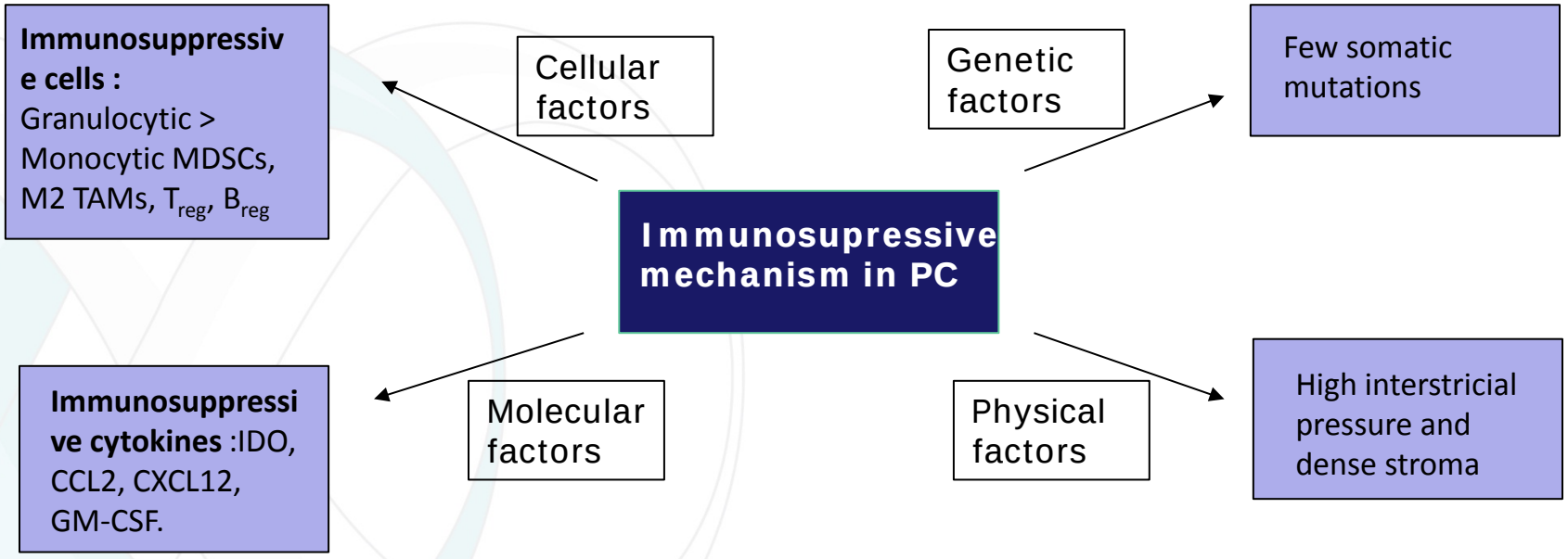
Immunosuppressive Mechanisms in PC



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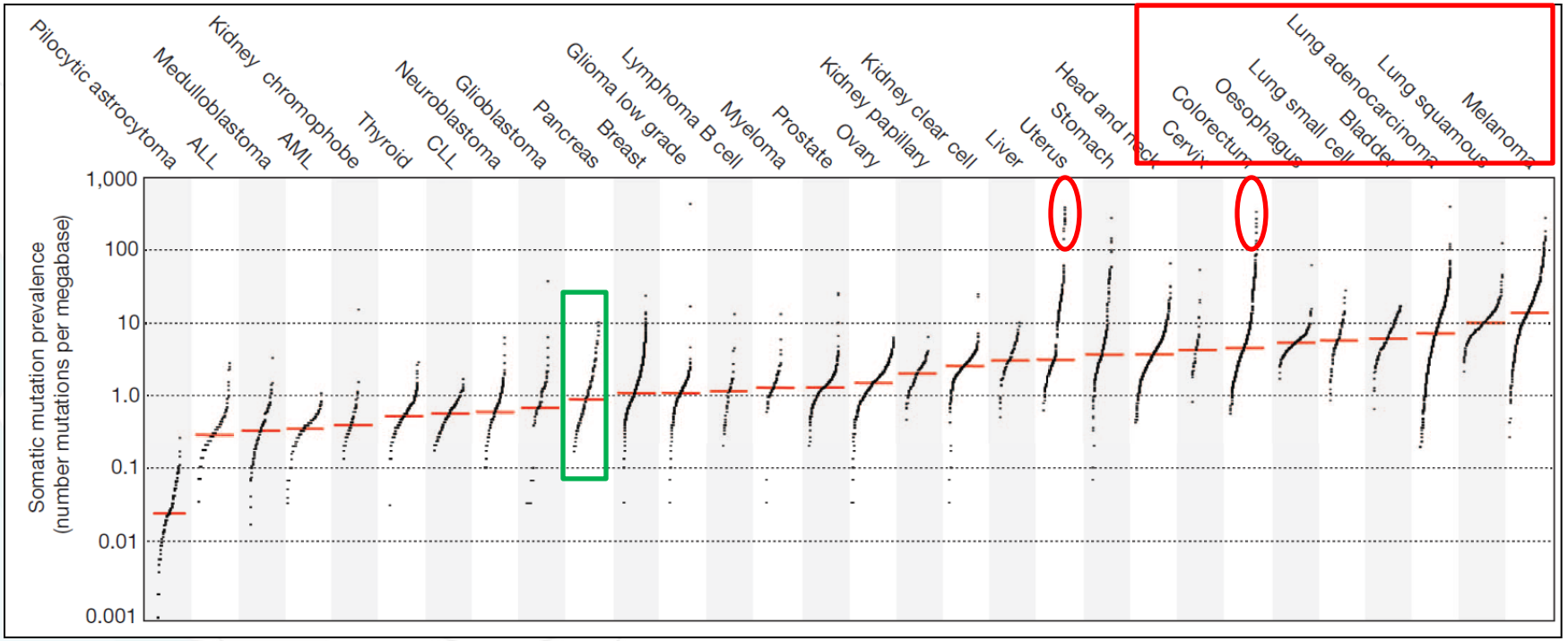
Why IO does not work in PDAC?



Low tumor mutation burden in PDAC

Alexandrov et al Nature 2013

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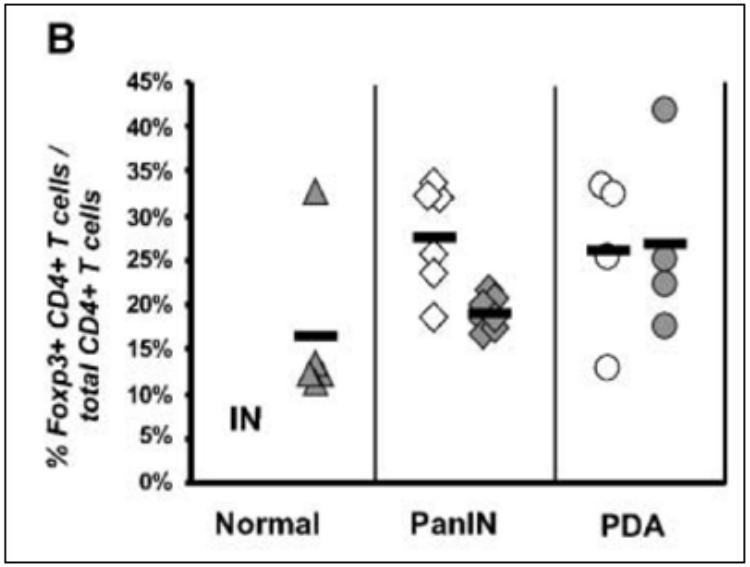
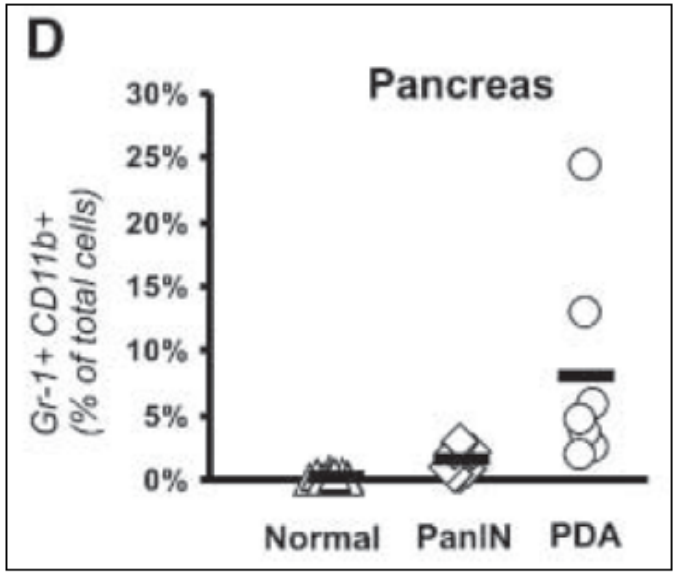
Immune survillance is impared early in PDAC





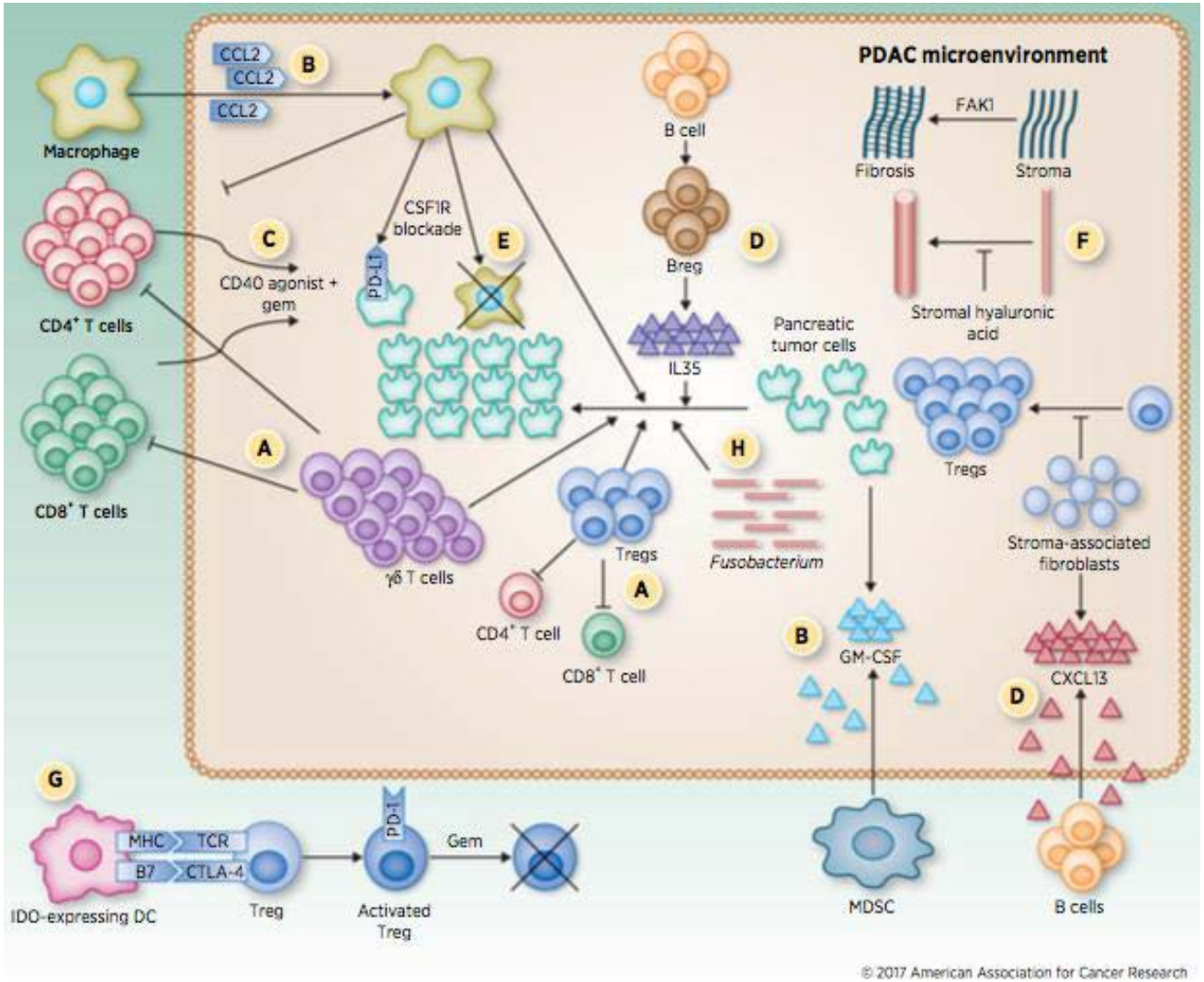
Foxp3+ CD4+ Tregs

MDSC Gr-1+ CD11b+

MDSC myeloid derived suppressor cells

Clark et al. Can Res 2007

Complex Cellular Immune and Inflammatory Cell Interactions!!



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Johnson BA 3rd, et al. *Clin Cancer Res*. 2017;23(7):1656-1669.

CHECKPOINTS INHBITORS

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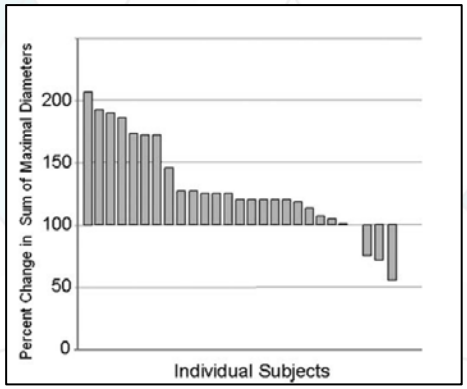
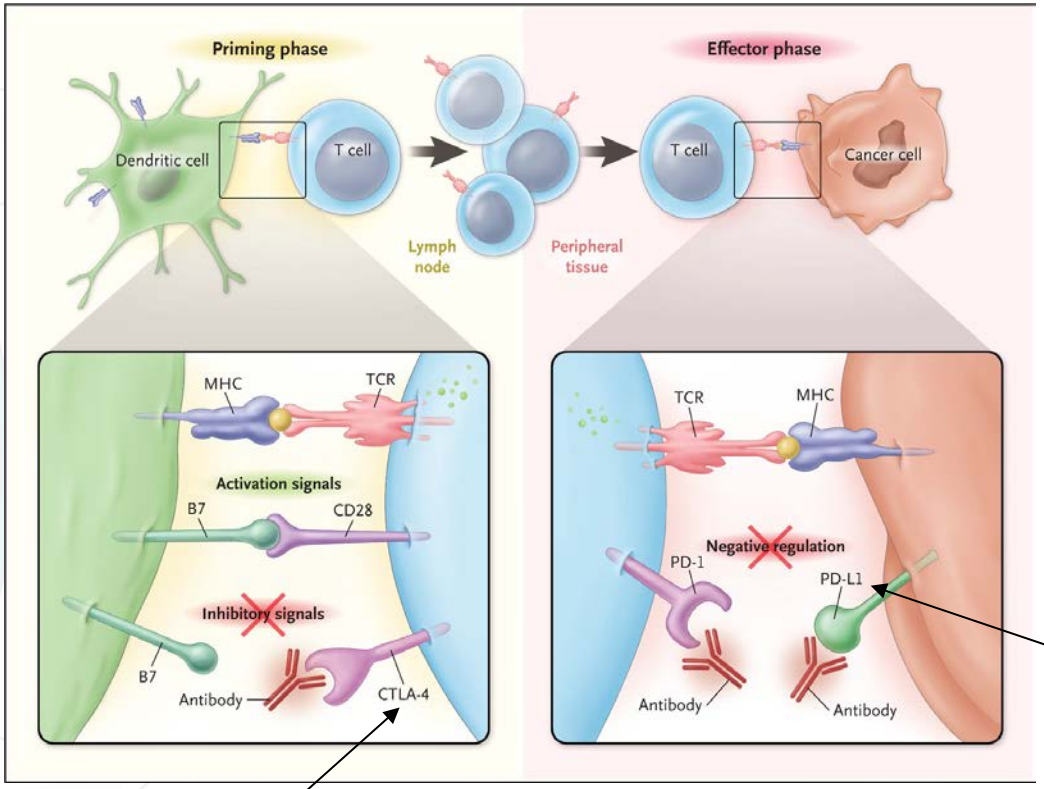
Single agent check-point inhibitor treatment in PC is not a valid option

-**Combined strategies** (tremelimumab + durvalumab, NCT02558894)
-Combination **with QTA** (NCT02268825, NCT02309177)





Ipilimumab: negative

BMS-936559: negative

A. Ribas, N Engl J Med 2012

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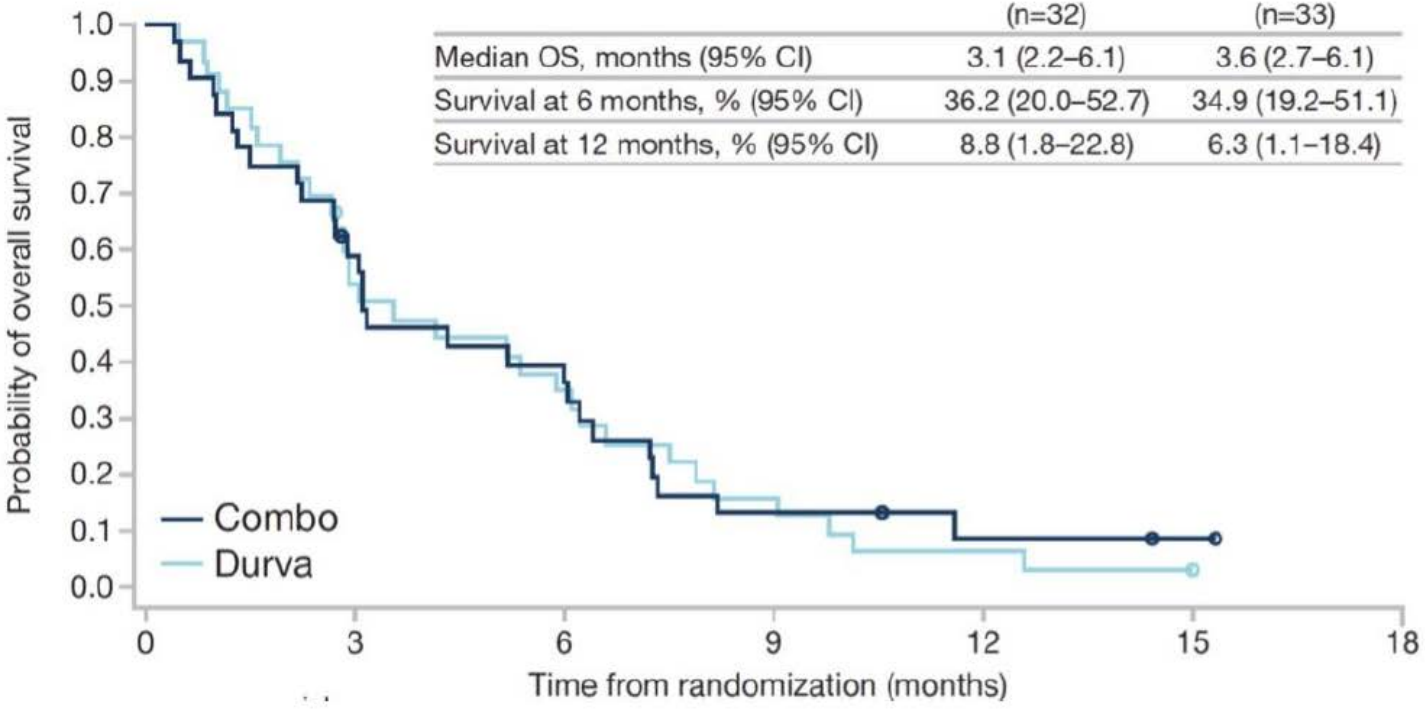
PD-1 Inhibitor (Durvalumab) With or Without CTLA4 Inhibitor (Tremelimumab): Did Not work!

	D + T (n=32)	D (n=33)
Median OS, months (95% CI)	3.1 (2.2–6.1)	3.6 (2.7–6.1)
Survival at 6 months, % (95% CI)	36.2 (20.0–52.7)	34.9 (19.2–51.1)
Survival at 12 months, % (95% CI)	8.8 (1.8–22.8)	6.3 (1.1–18.4)



O'Reilly EM, et al. *J Clin Oncol.* 2018;36(suppl 4S): Asbtract 217.

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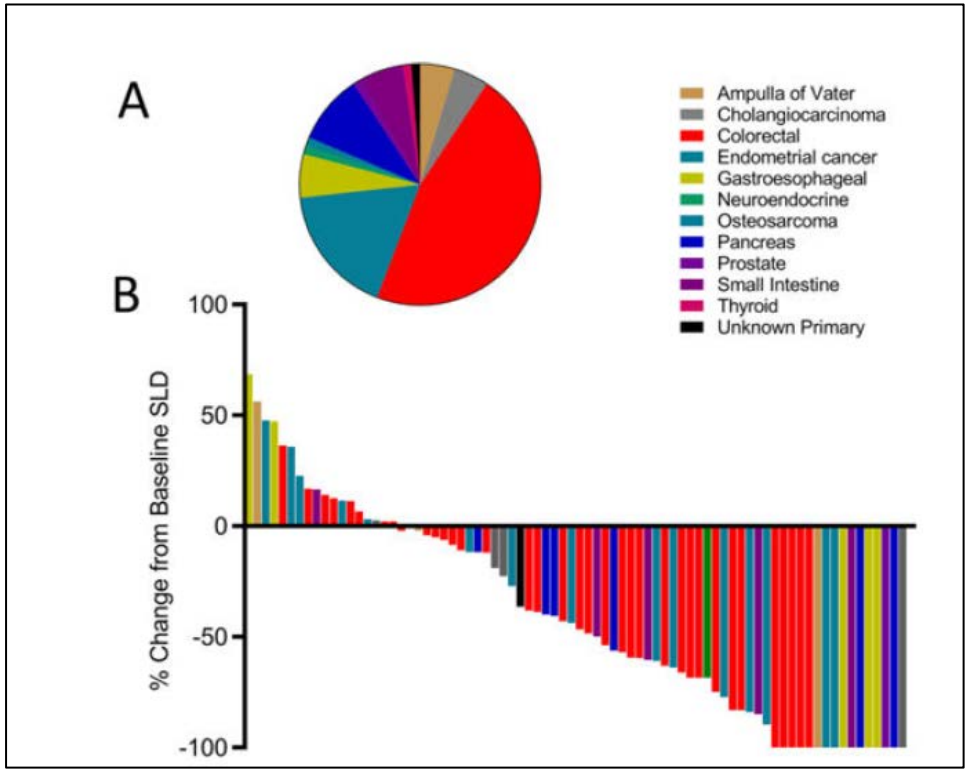
Mismatch-repair deficiency predicts response of solid tumours to PD-1 blockade



FDA News Release

FDA approves first cancer treatment for any solid tumor with a specific genetic feature

How we can identify this patients?
KRAS WT?
Different hystological subtype?

N 86 patients with 12 tumor types
MSI-H treated with pembrolizumab.
4PC (1PR, 3 SD).

Le et al, Science 2017

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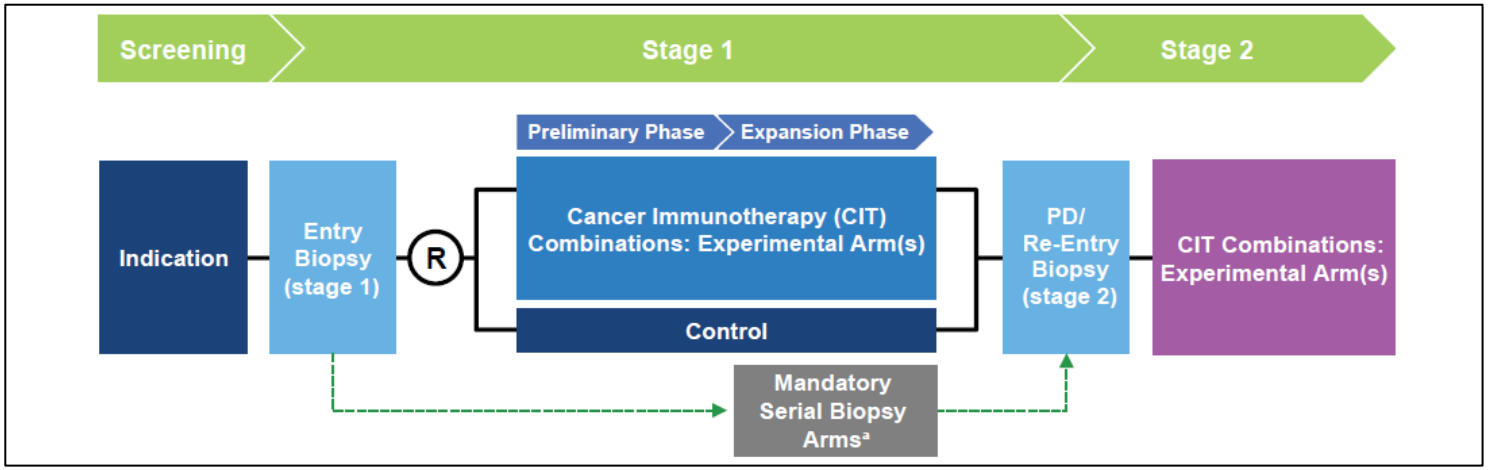
THE MORPHEUS PLATFORM



	MORPHEUS-GC		MORPHEUS-PDAC
Arms	**1L Cohort**	**2L Cohort**	**2L Cohort**
Control	mFOLFOX-6	Ramucirumab + paclitaxel	mFOLFOX-6 or gemcitabine + nab-paclitaxel
Arm A	mFOLFOX-6 + atezolizumab + cobimetinib	Atezolizumab + cobimetinib[a]	Atezolizumab + cobimetinib[a]
Arm B	mFOLFOX-6 + atezolizumab	Atezolizumab + PEGPH20	Atezolizumab + PEGPH20
Arm C	–	Atezolizumab + BL-8040	Atezolizumab + BL-8040
Arm D	–	Atezolizumab + linagliptin	–

mFOLFOX-6, modified folinic acid, fluorouracil, and oxaliplatin.
[a] Combination available in stages 1 and 2 of the study.

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Presented as TP in GI ASCO meeting 2018

Clinical case

- 67 years old patient
- No toxic habits
- No relevant family history
- Past medical history:
  - Hypertension
  - Diabetes mellitus treated with insulin

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Clinical case

- In January 2016 he presented a pain in the back, and abdominal pain.
- He was referred to the GP, who indicates a blood test showing only grade 1 anemia.
- He started with some medication for the pain but with no improvement
- April 2016 a CT was performed

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Clinical case

- He was diagnosed with pancreatic cancer (head of the pancreas) and bone metastasis.
- A pancreatic biopsy confirmed that it was an adenocarcinoma.
- CA 19.9 1500 UI/L
- The patient was not eligible for the HALO 302 trial, because we don´t have enough tissue to determine HA.

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Clinical case

- He started with gemcitabine and nab-paclitaxel. He achieved a SD. CA 19.9 250
- Pain improvement.
- Toxicity: grade 2 D/P, grade 1 anemia.
- After 11 cycles of treatment the patient presented a progressive disease in the liver.

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Clinical case

- He started nal-IRI + 5FU with a SD and CA 19.9 50.
- After 6 months of treatment the liver mets progressed.
- We started with FOLFOX in the Morpheus trial (control arm).
- Patient progressed after 2 months of treatment.

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Clinical case

- He started in the same trial with atezolizumab and cobimetinib (PDL-1 inh + MEK inhibitor). After 2 months of treatment a CT scan showed a PR with reduction of 40% of target lesions.
- After 6 months of treatment patient presented 60% of tumor reduction in liver and primary tumour. CA 19.9 within the normal range.
- ECOG 0
- After 11 months the patient presented a progressive disease in the liver. Ca 19.9 2500 UI/L
- We are performing molecular analysis of the tissue from liver metastases.

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TARGETING MACROPHAGES

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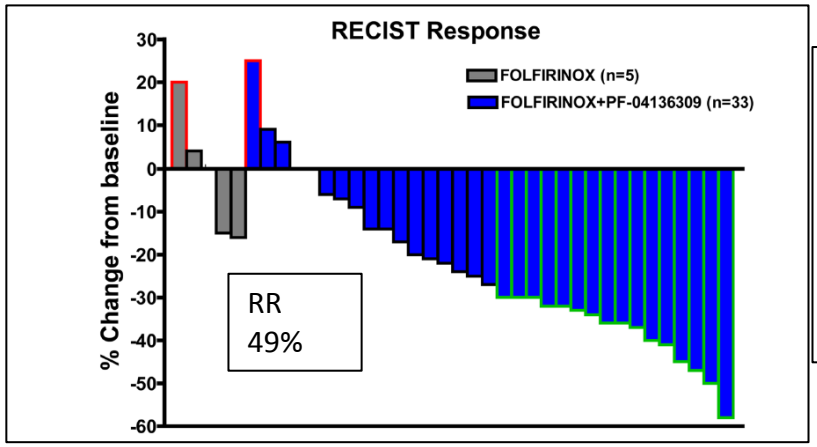
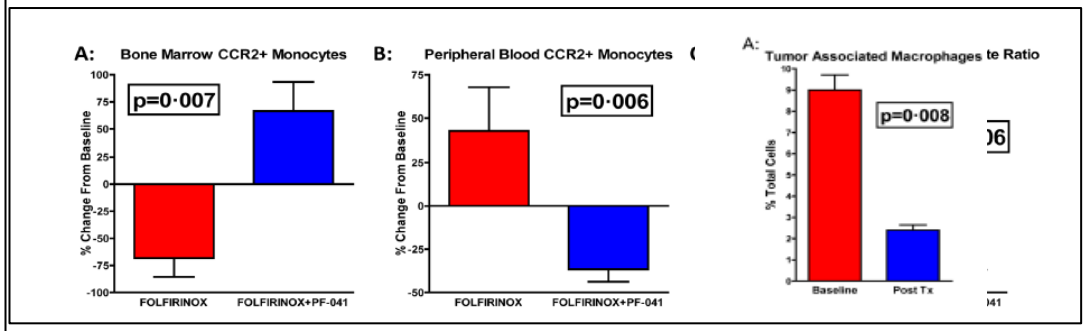
FOLFIRINOX and anti CCR2 PF-04136309 IN BR or LA PANCREATIC CANCER

-CCR2 recruits supressive macrophage in PDAC

-N 47 PDAC treated with PF-04136309 (CCR2 inhib) + FOLFIRINOX





Nywening et al, Lancet Oncol 2016

CCR2 Targeted therapy with PF-04136309 in combination with FOLFIRINOX is safe, promising activity and CCR2 blockade reduces TAM and alteres TME

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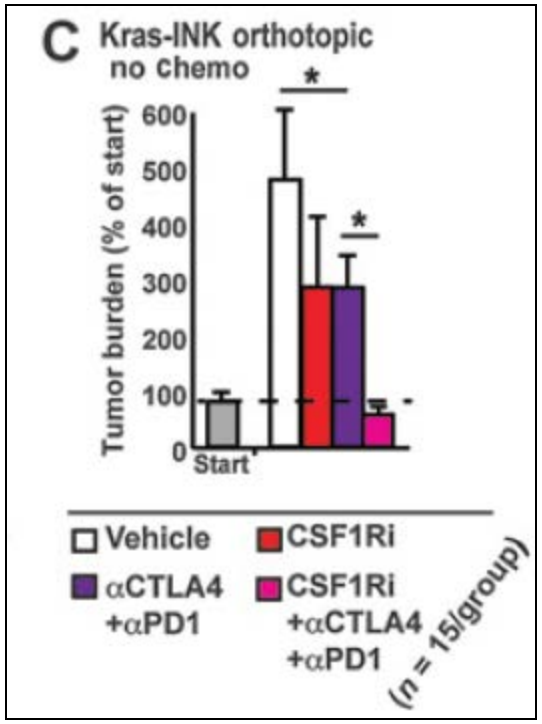
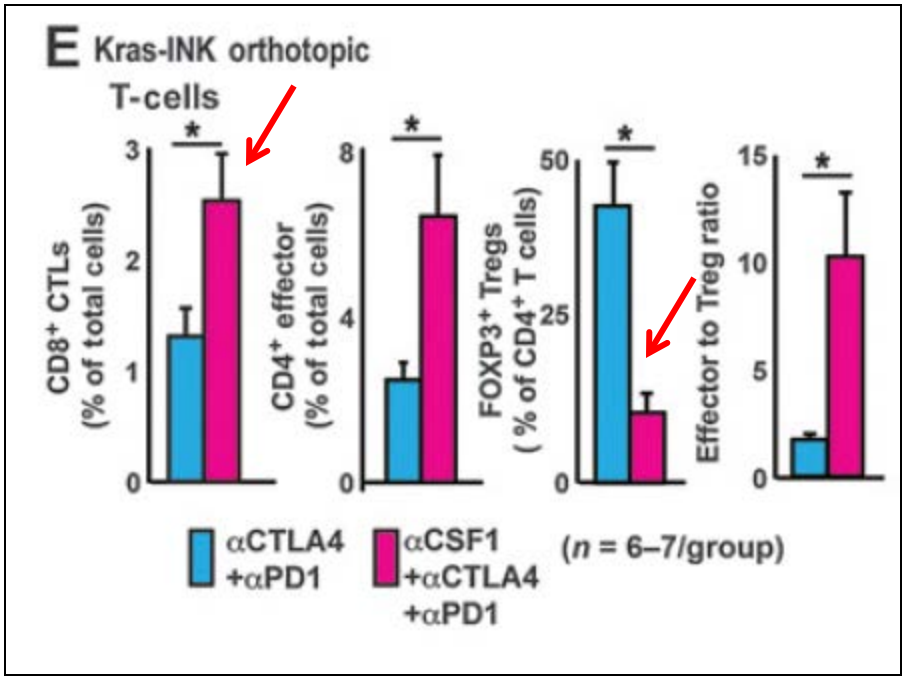
Reprograming TME with CSF1Ri

- CSF1R (colony-stimulating factor 1 receptor) expressed in TAM and MDSC



Combined block induced tumor regression



Increased effector CD8+ T cells
Decreased T regs

TME = tumor microenvironment

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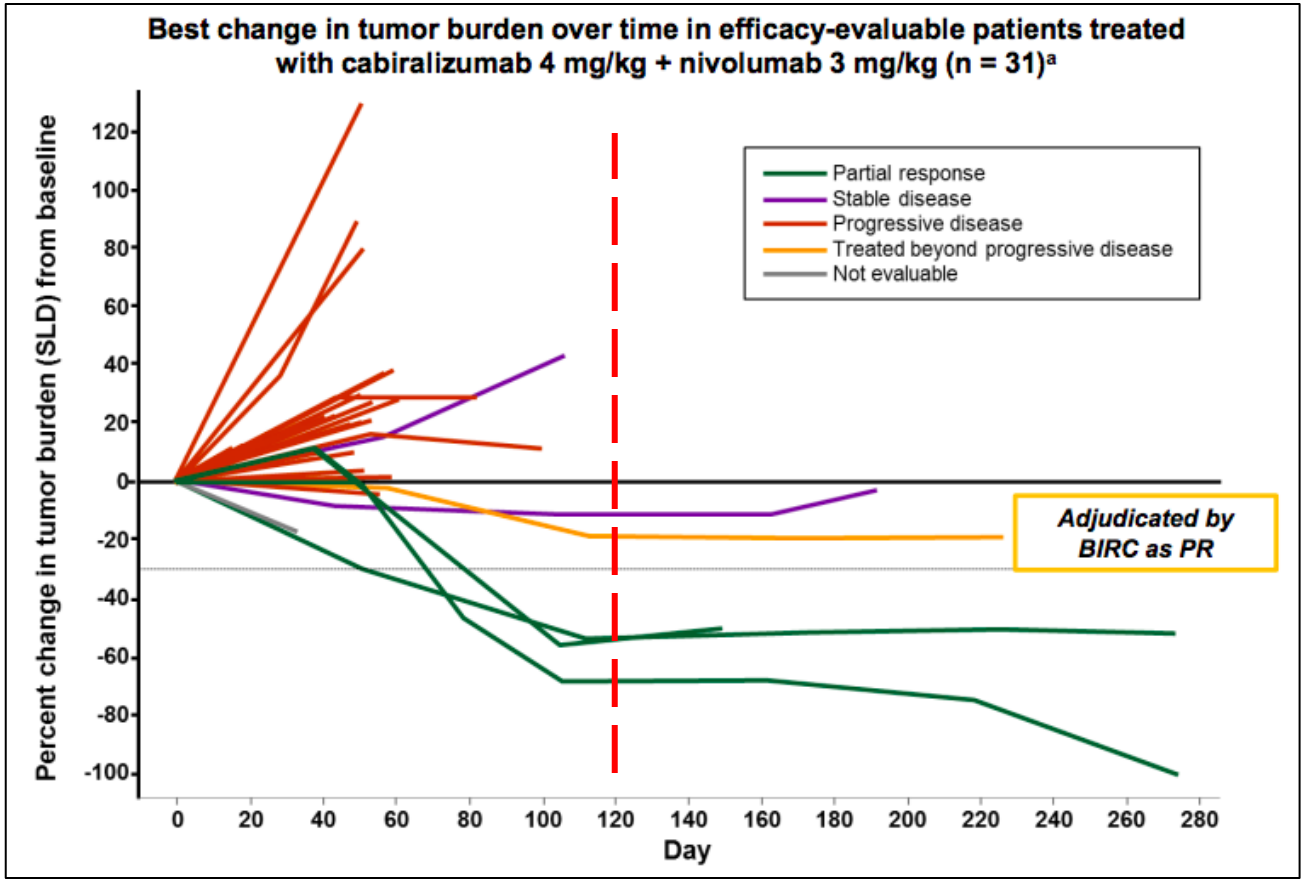
Zhu et al. Can Res 2014

Anti-PD1 plus anti-CSF-1R a novel strategy in PDAC



PDAC N=33

66% ≥ 2 lines for metastatic disease

Overall response rate 4/33 = 13%

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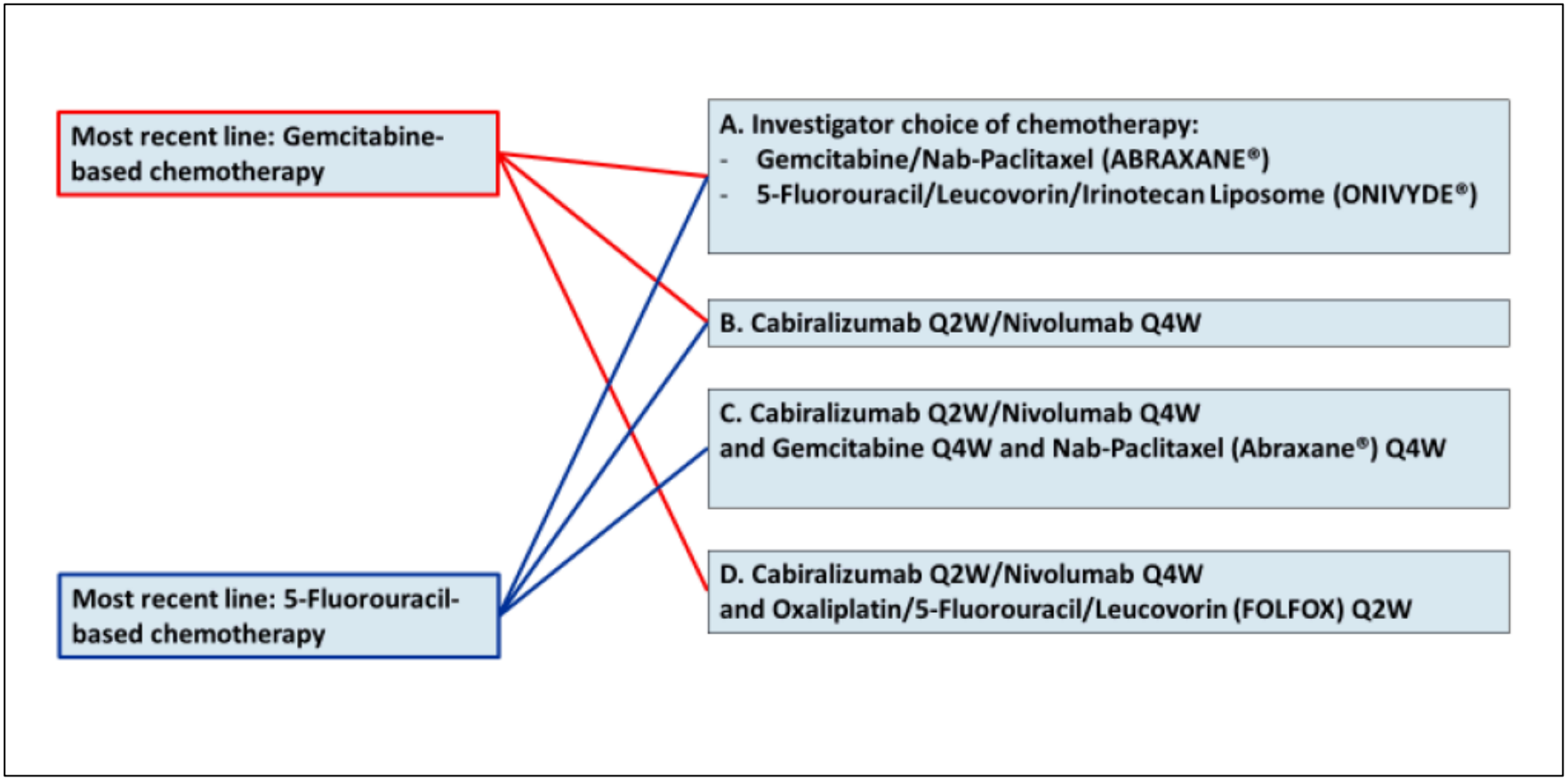
Wainberg et al SITC 2017

A Phase 2 Study of Cabiralizumab (BMS-986227, FPA008) Administered in Combination with Nivolumab (BMS-936558) with and without Chemotherapy in Patients with Advanced Pancreatic Cancer



Primary endpoint: PFS

N 160 patients

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NCT03336216

OTHER STRATEGIES DESIGNED TO INCREASE PANCREATIC TUMOR IMMUNOGENICITY

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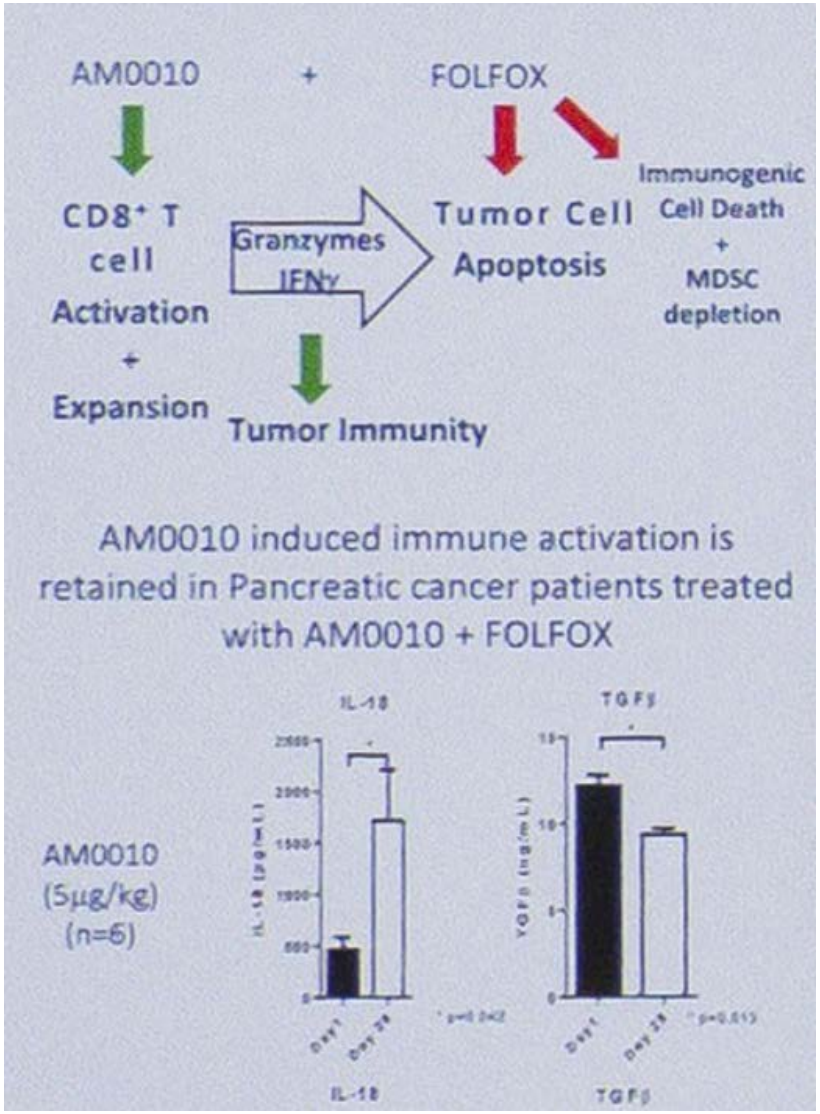
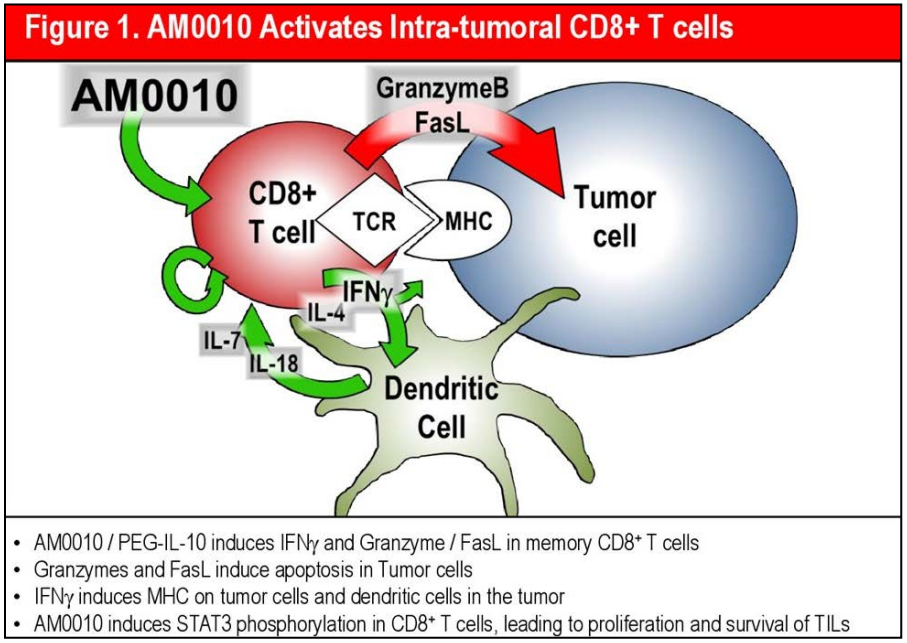
Pegylated recombinant human IL-10 (AM0010) increase CD8 T cells





Hecht et al, presented in GI ASCO meeting 2018 (abstr 374)

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Pegylated recombinant human IL-10 (AM0010) increase CD8 T cells

Treatment (n=Evaluable Patients/ Enrolled Patients)	Prior Therapies Median (Range)	DCR (%)	ORR (%)	CR (%)	mPFS[3,5] (Months)	mOS[3,5] (Months)	1-year OS (%)
AM0010 (n=15/22)[1]	3 (2-6)	53%[2]	0	0	1.7	3.8	22.7%
AM0010 + FOLFOX[4] (n=19/21)	2 (1-5)	74%	16%	11%	2.6	10.2	42.9%

Hecht et al, presented in GI ASCO meeting 2018 (abstr 374)

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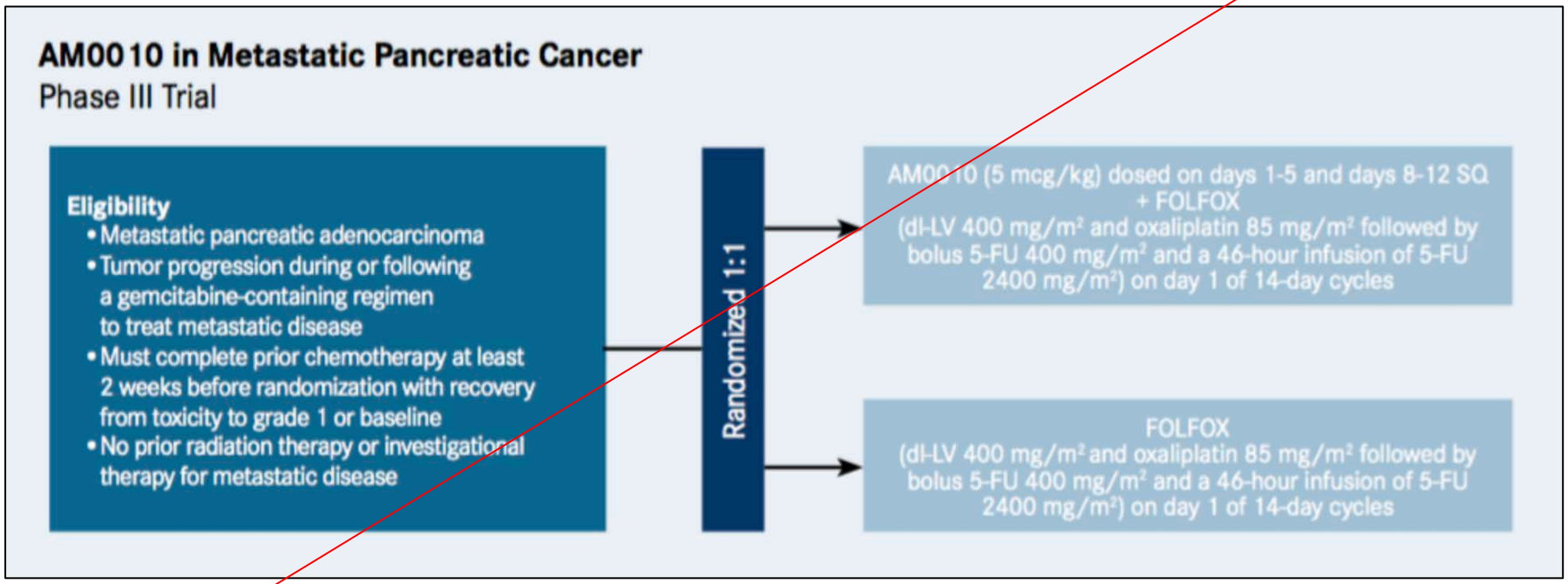
Ongoing randomized phase 3 trial



N 566 patients
Primary endpoint: OS

NCT02923921

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MICROBIOME AND PANCREATIC CANCER

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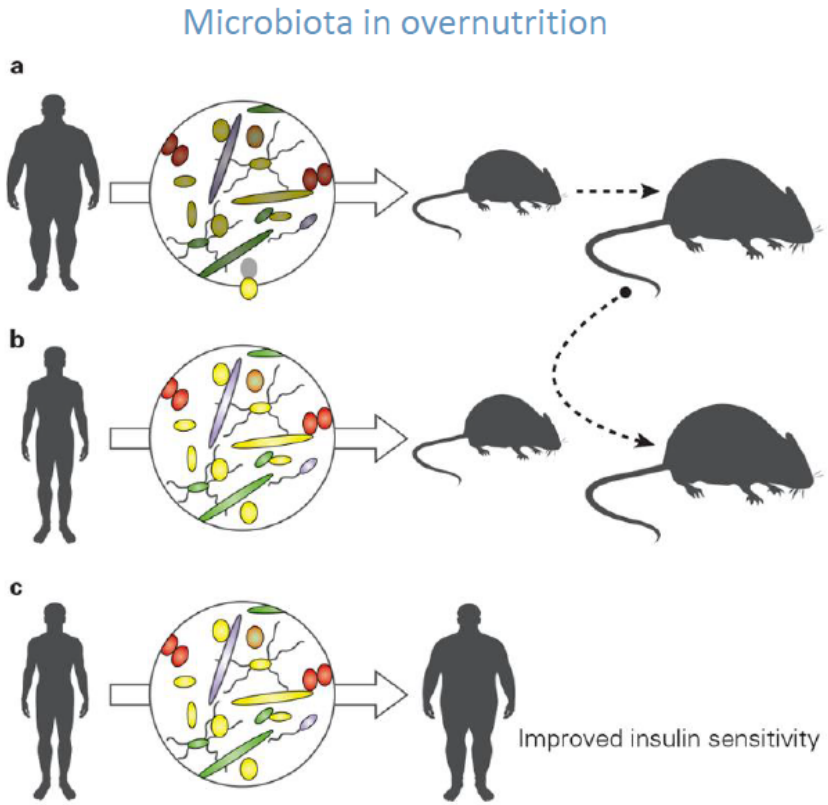
DIET REGULATES COMPOSITION OF MICROBIOTA



- Microbiota has been related with the risk of developing obesity and metabolic disorders
- Diet-induced obesity in experimental animals links with changes in the microbiota and suggests that the ***dietary impact exceeds that of genetics and immunity***.
- HH faecal microbial transplantation has also demonstrated the beneficial influence of a microbiota from a lean donor with improved insulin sensitivity in obese recipients

Shanahan et al. Gut 2017

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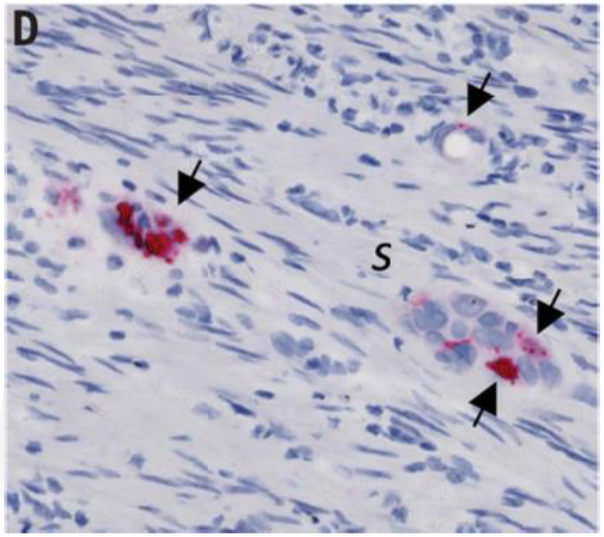
How did we get there

Science

Analysis of *Fusobacterium* persistence and antibiotic response in colorectal cancer

Susan Bullman,[1,2] Chandra S. Pedamallu,[1,2] Ewa Sicinska,[1] Thomas E. Clancy,[3] Xiaoyang Zhang,[1,2] Diana Cai,[1,2] Donna Neuberg,[1] Katherine Huang,[2] Fatima Guevara,[1] Timothy Nelson,[1] Otari Chipashvili,[1] Timothy Hagan,[1] Mark Walker,[2] Aruna Ramachandran,[1,2] Begoña Diosdado,[1,2] Garazi Serna,[4] Nuria Mulet,[4] Stefania Landolfi,[4] Santiago Ramon y Cajal,[4] Roberta Fasani,[4] Andrew J. Aguirre,[1,2,3] Kimmie Ng,[1] Elena Élez,[4] Shuji Ogino,[1,3,5] Josep Tabernero,[4] Charles S. Fuchs,[6] William C. Hahn,[1,2,3] Paolo Nuciforo,[4] Matthew Meyerson[1,2,3]*



Bullman et al. Science 2017

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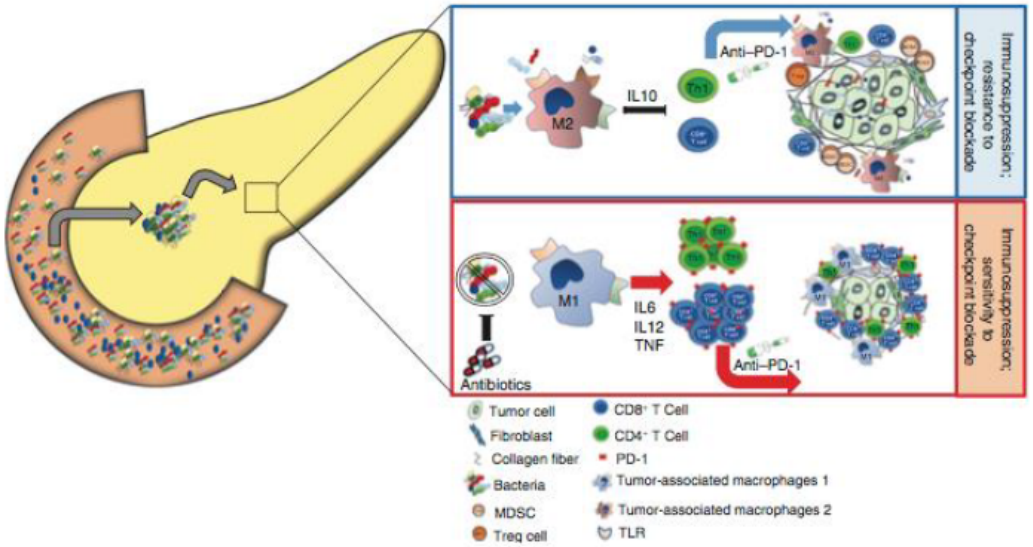
Microbiome and Pancreatic Cancer: Rapidly Evolving Research

- Bacteria in the duodenum, colon, and pancreas
- Drug resistance
- Local and systemic immune modulation



Pushalkar S, et al. *Cancer Discov.* 2018;8(4):403-416. Riquelme E, et al. *Cancer Discov.* 2018;8(4):386-388.

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Conclusions

- **PC presented a dismal prognosis**
- **Pancreatic Cancer is a non immunogenic disease.**
- **Immunotherapy failed in its traditional single-agent approach, but combinations may hold promise.**
- **Checkpoint inhibitors may induce a clinical response in MSI-H patients with mPC.**

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