Identifying new targets for immuno-oncology

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Sheba Medical Center

Disclosures

Gal Markel

• **Roles**	4c BioMed (CSO), Ella Tx (CMO), Biond Biologics (SAB)
• **IP**	Kitov Pharmaceuticals, 4c Biomed, Ella Tx
• **Shares/Options**	Kitov Pharmaceuticals, 4c Biomed, Biond Biologics, Ella Tx, NucleAI
• **Honoraria**	MSD, BMS, Novartis, Roche, Medison
• **Research grants**	Novartis, BMS
• **Local advisory**	BMS, MSD, Novartis, Medison
• **International advisory**	MSD, BMS, Novartis

שיבא - מרכז רפואי אקדמי מצטיין

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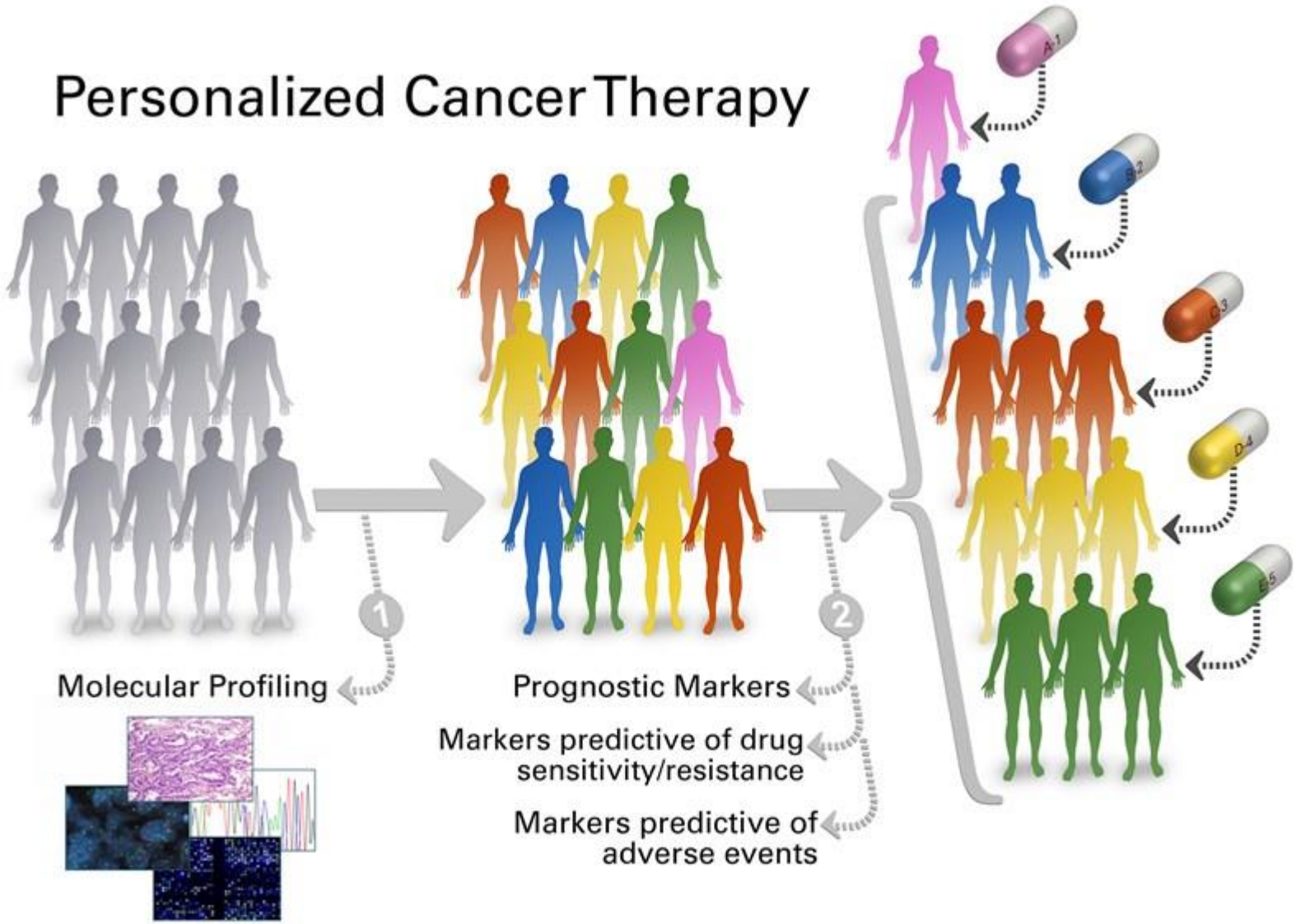
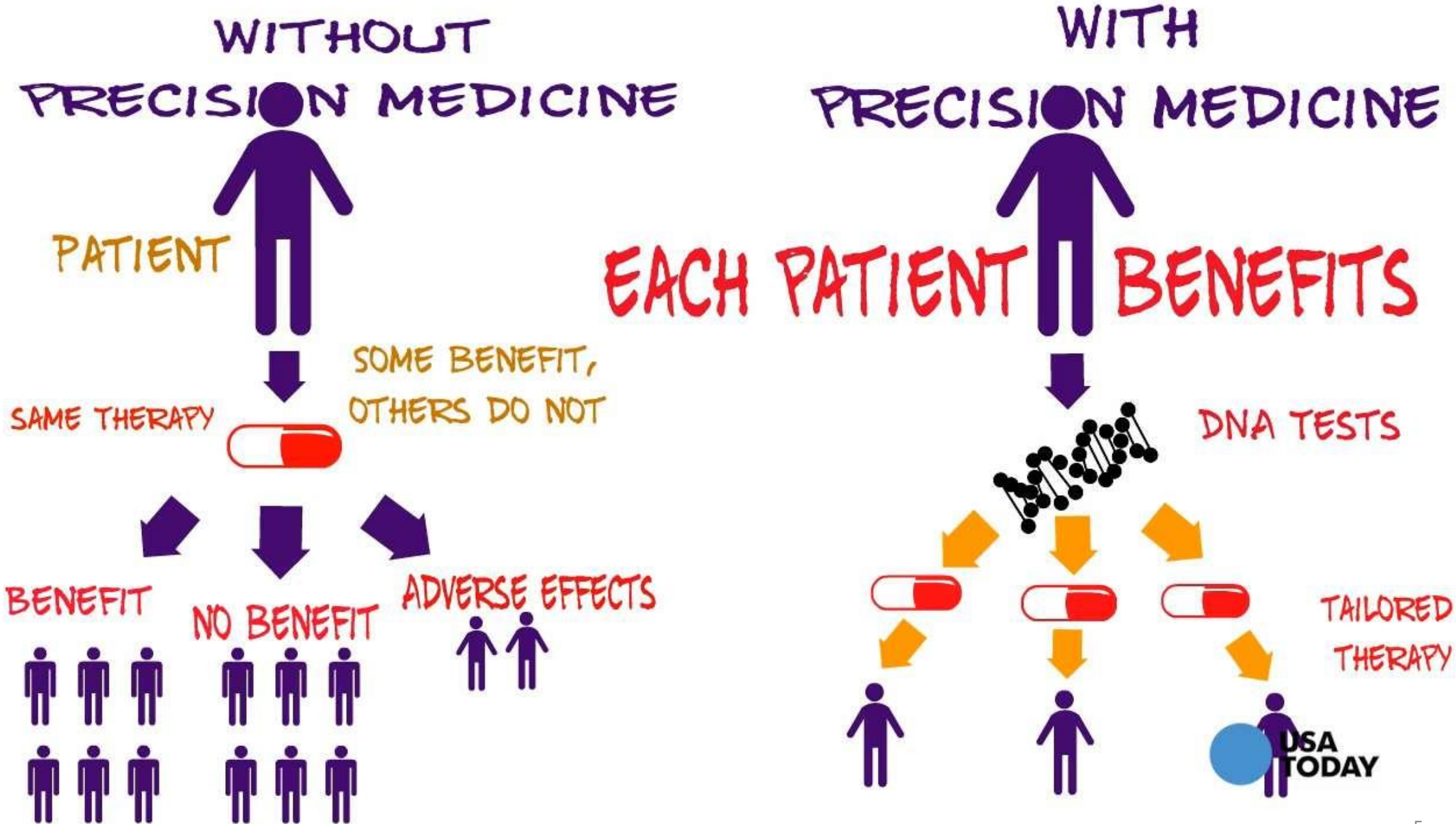
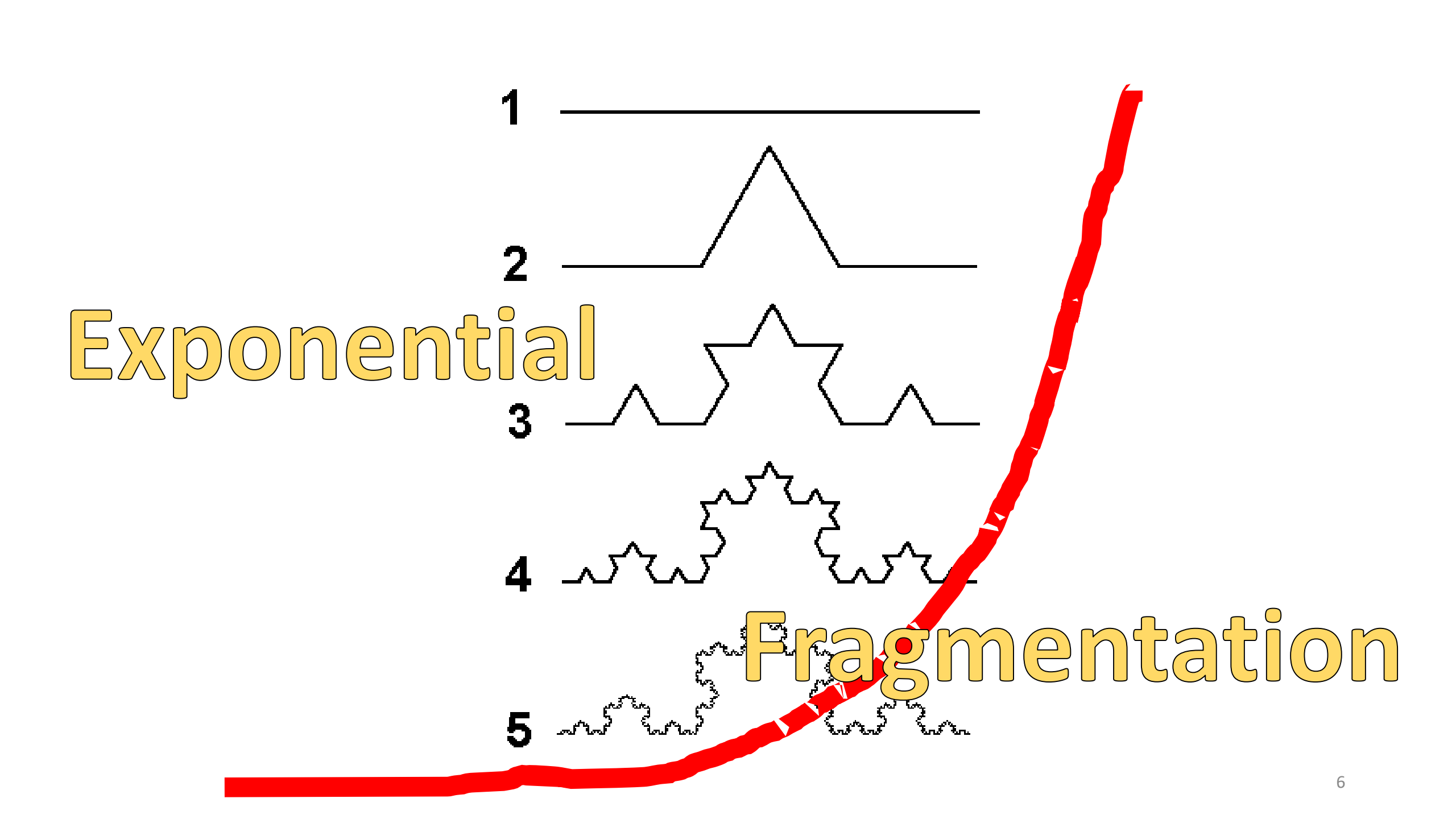
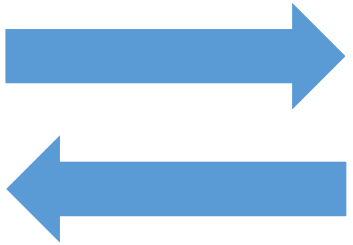
ONE-SIZE FITS ALL
STORE
SALE


Personalized Cancer Therapy
A-1
B-2
C-3
D-4
E-5
1
2
Molecular Profiling
Prognostic Markers
Markers predictive of drug sensitivity/resistance
Markers predictive of adverse events

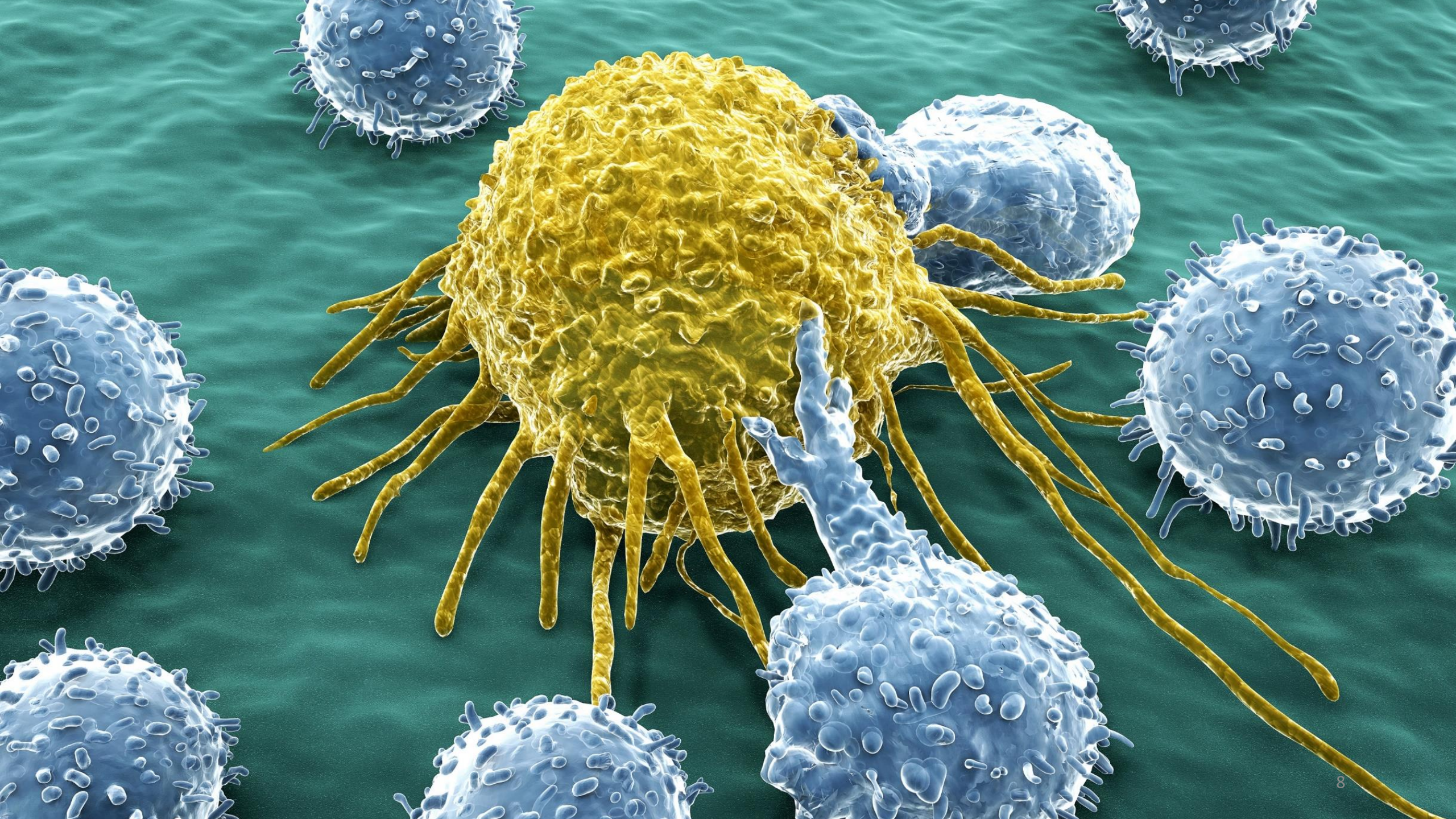

WITHOUT
PRECISION MEDICINE
PATIENT
SAME THERAPY
SOME BENEFIT,
OTHERS DO NOT
BENEFIT
NO BENEFIT
ADVERSE EFFECTS
WITH
PRECISION MEDICINE
EACH PATIENT BENEFITS
DNA TESTS
TAILORED
THERAPY
USA
TODAY


1
2
3
4
5
Exponential
Fragmentation

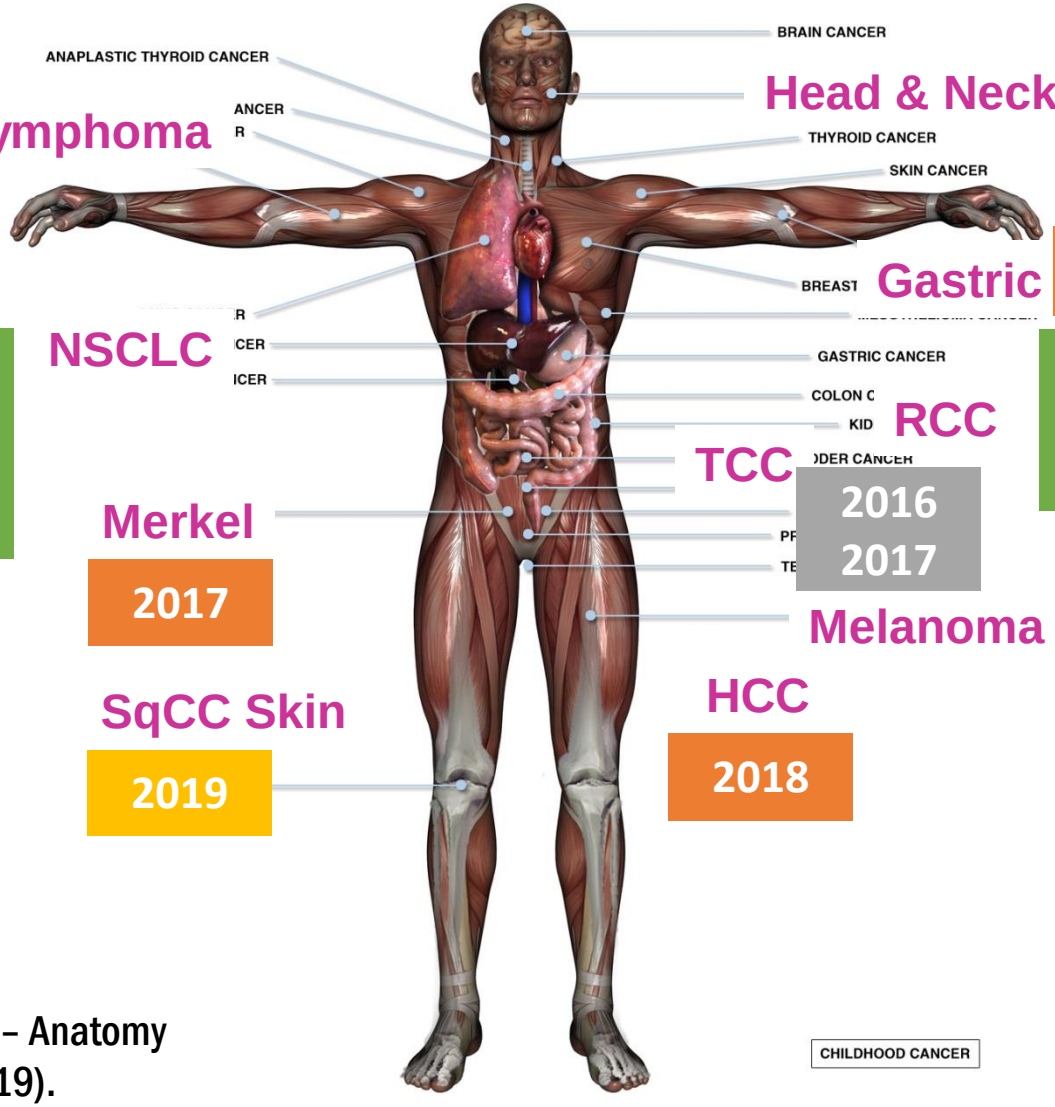
Reversed Personalized Medicine



“Tailor” the patient to the treatment



PD-1 axis blockade FDA approvals



2016
2017

Lymphoma

Head & Neck

2016
2017

2017

Gastric

2015
2016
2017
2018

NSCLC

2015
2017
2019

RCC

TCC

2016
2017

Merkel

2017

Melanoma

Met.
2014

Adjuvant
2017
2018

2017

MSI^{high}

SqCC Skin

2019

HCC

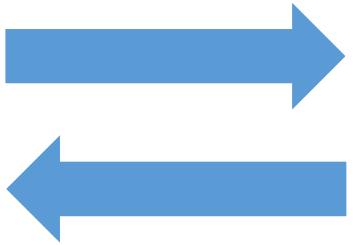
2018

Adapted from: Insides of the Human Body Images – Anatomy www.anatomymedicalook.com (Accessed 17 Oct. 19).

Primary & Secondary Resistance to PD-1 blockade is a major clinical challenge


Combinations

Reversed Personalized Medicine



“Tailor” the patient to the treatment

Advantages in principle

- **Short time** to clinical testing
- Relatively **low costs** (not development of new molecules)
- Potential **big impact**
- Maximizing existing drugs --- **Win-Win with industry**
- **New opportunities** for business

What should we be looking at?

Pre-treatment melanoma samples

TIL treated patients — N=83

- Responders N=30
- Non-Responders N=53

Proteomics, RNAseq, Pathology

PD-1 blockade treated patients — N=50

- Responders N=33
- Non-Responders N=17

Proteomics, RNAseq, Pathology

Common processes?

Bioinformatics

Eldad Shulman

Dr Ran Elkon

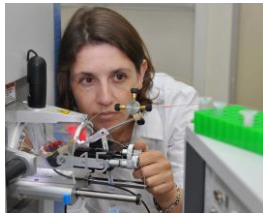
Dr Ettai Markovitc

Dr Erez Baruch

Proteomics

Dr Michal Harel

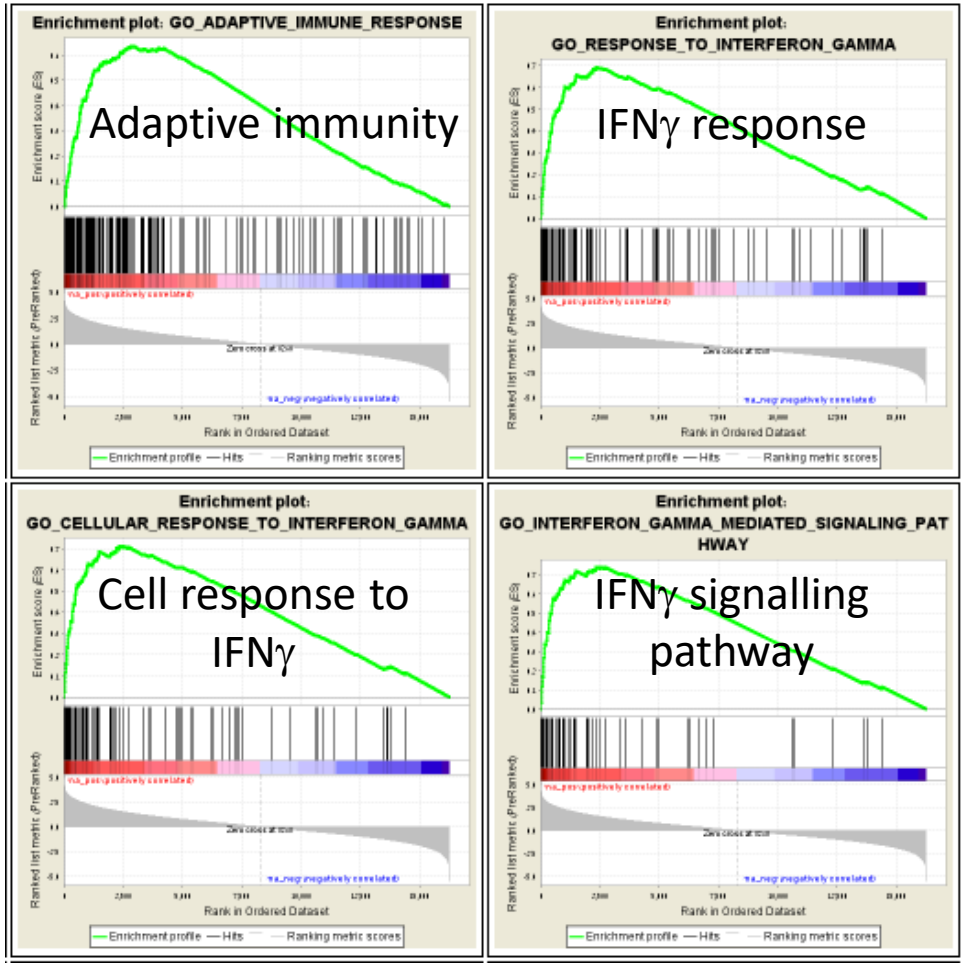
Prof Tami Geiger

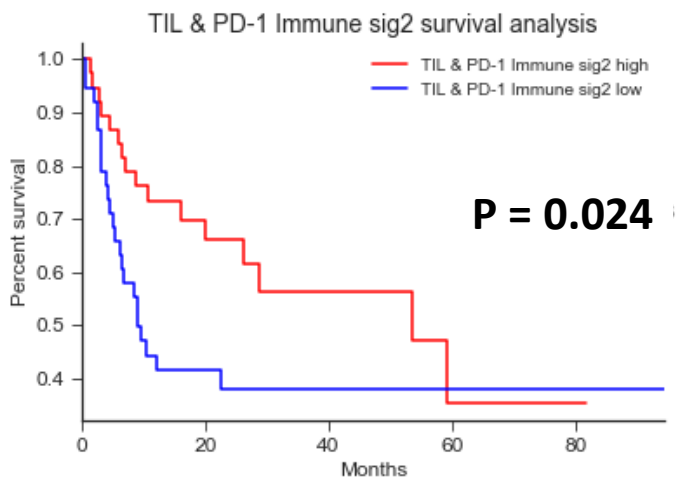


Retrospective cohorts

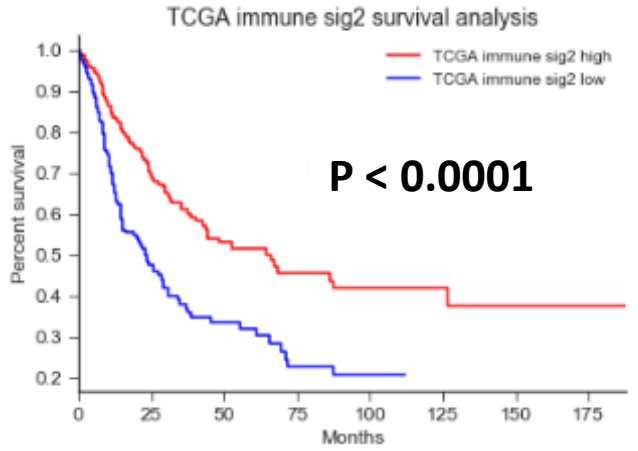
	TIL			PD-1		
	Responders	**Non-Responders**	P val.	**Responders**	**Non-Responders**	P val.
N	30	53	n/a	33	17	n/a
Gender (male)	76%	55%	0.32	51%	53%	1.0
Age	54y	52y	0.8	55y	56y	1.0
PS = 0-1	100%	100%	1.0	73%	70%	1.0
BRAF	46%	38%	0.48	42%	52%	0.55
Previous lines	2.2 (2-3)	2.3 (2-3)	0.61	0.54 (0-3)	0.64 (0-3)	0.69
PFS	**28.3m**	**2.5m**	**$8x10^{-8}$**	**20.9m**	**2.1m**	**$5x10^{-8}$**

RNAseq --- Immune signature





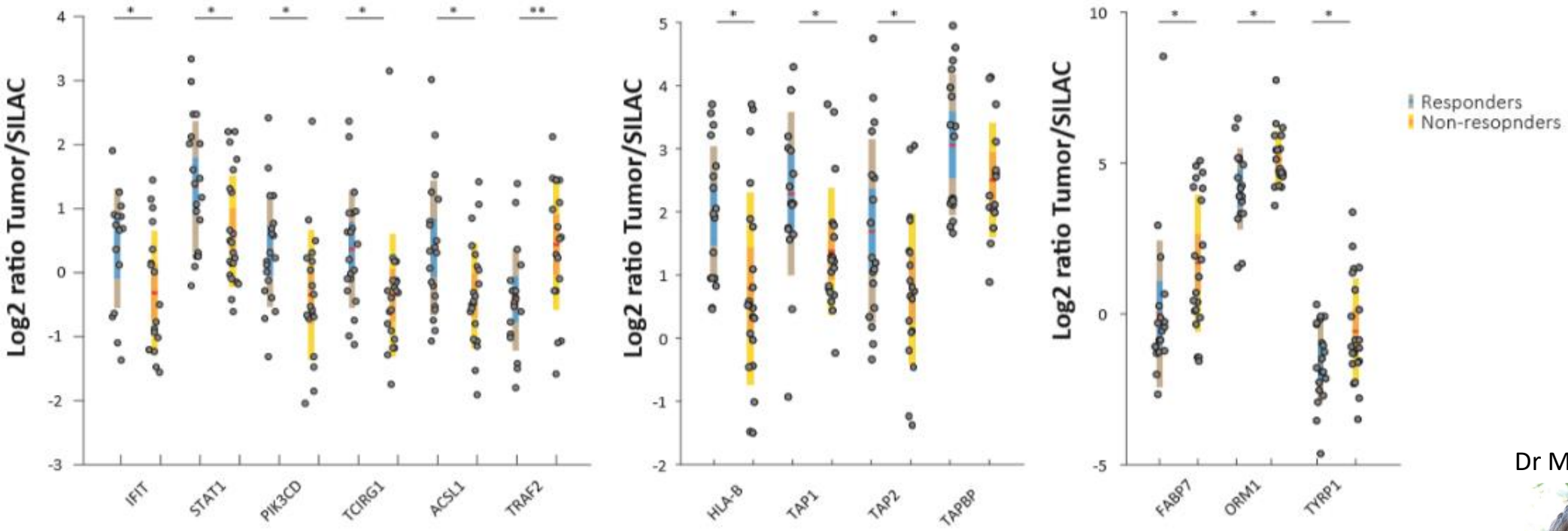
Our cohorts



TCGA

Dr Ettai Markovitc

Proteomics - Enhanced IFN signaling pathway



Dr Michal Harel

Proteomics reveals new patterns

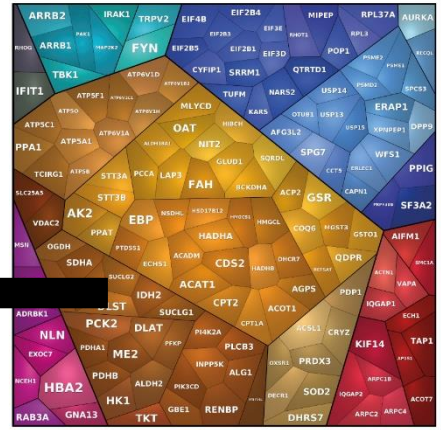
A

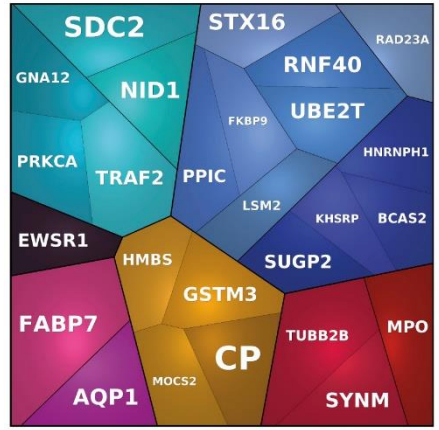
Responders

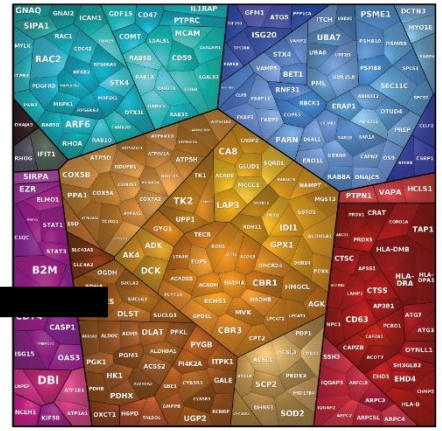
Non-Responders

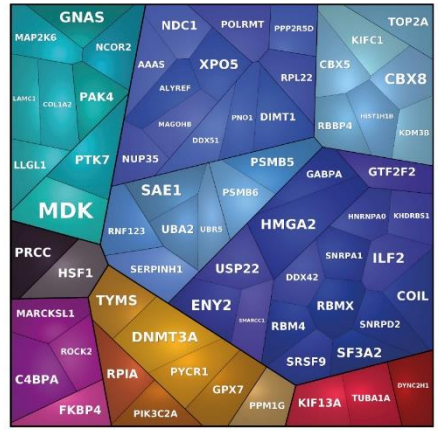
TIL cohort

αPD-1 cohort









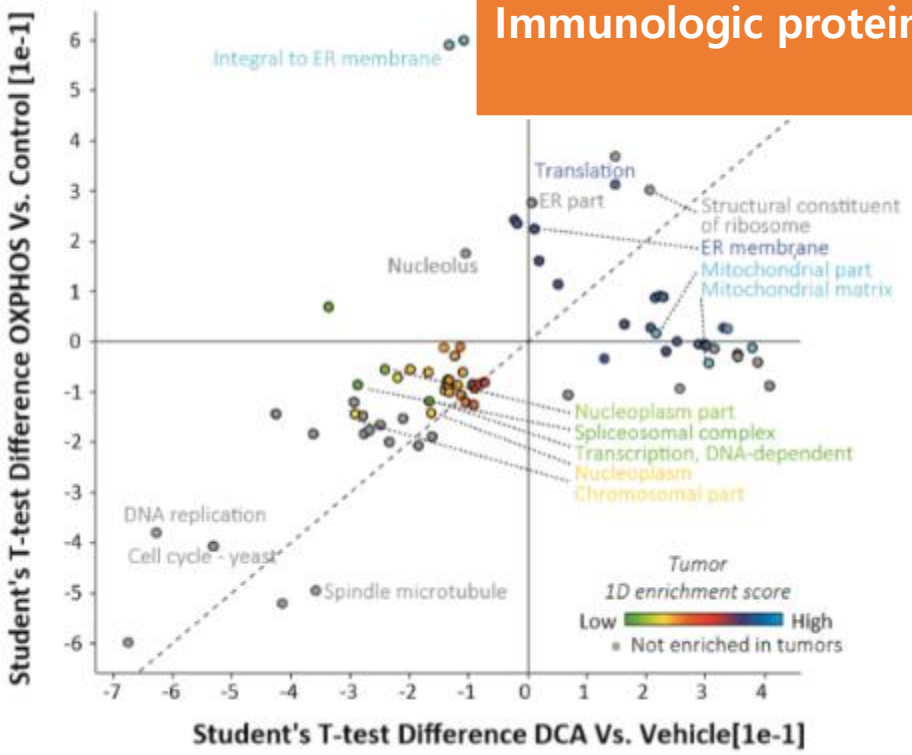
- Genetic Information Processing
- Metabolism
- Organismal systems
- Environmental information processing
- Human diseases
- Cellular processes

Harel et al, Cell 2019

Aerobic conditions enhance antigen presentation

Low glucose medium

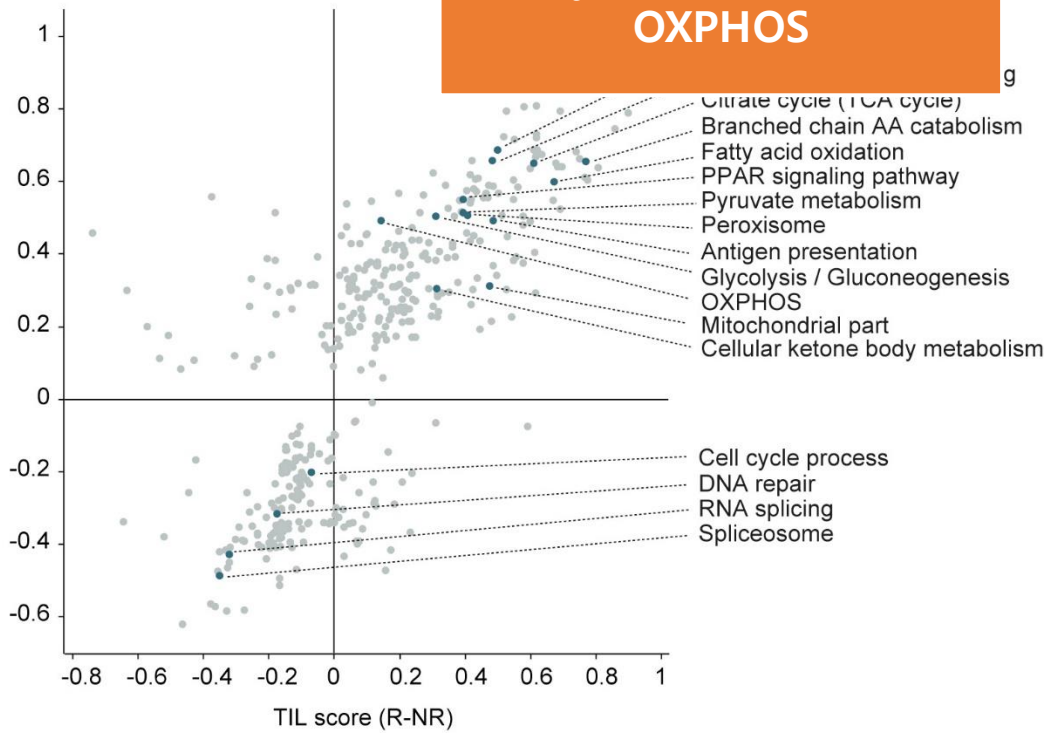
Mitochondria
Immunologic proteins



Stimulate mitochondria

Anti PD-1 Score (R-NR)

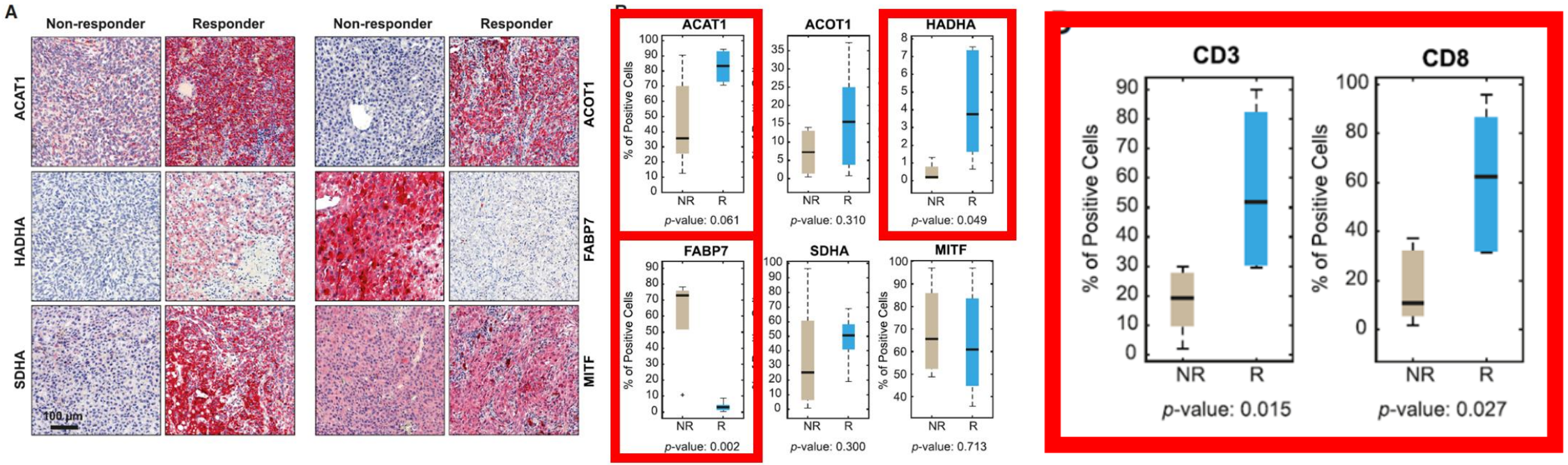
Immunologic proteins
Fatty acid metabolism
OXPHOS



TIL score (R-NR)

Harel et al, Cell 2019

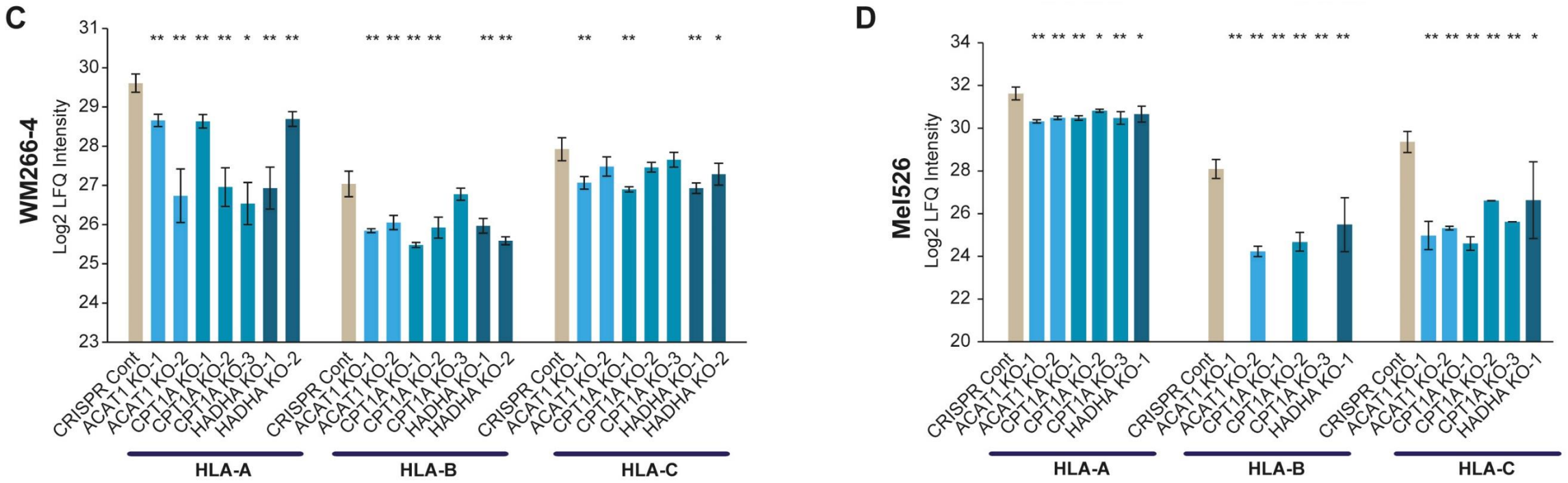
Confirmation in patients



Harel et al, Cell 2019

KO of mitochondrial proteins confers immune resistance

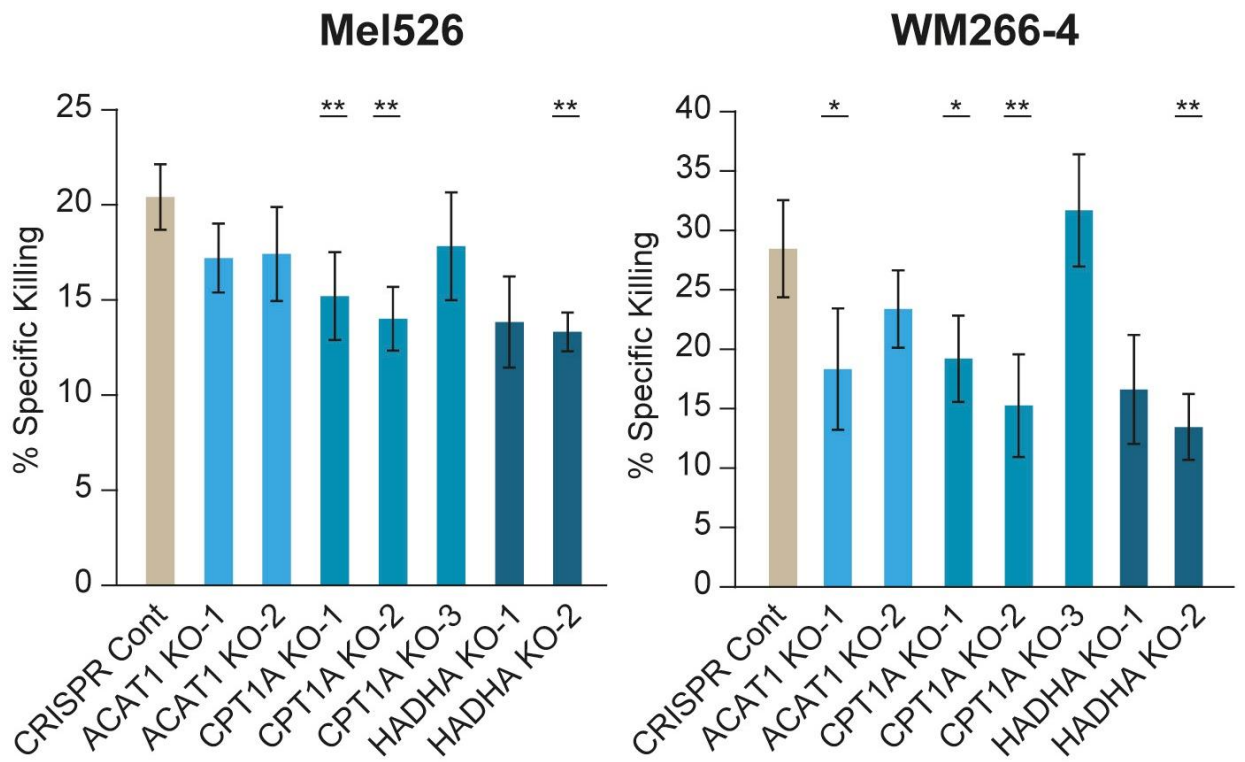
In vitro downregulation of MHC class I alleles



Harel et al, Cell 2019

Knockout of aerobic metabolism proteins

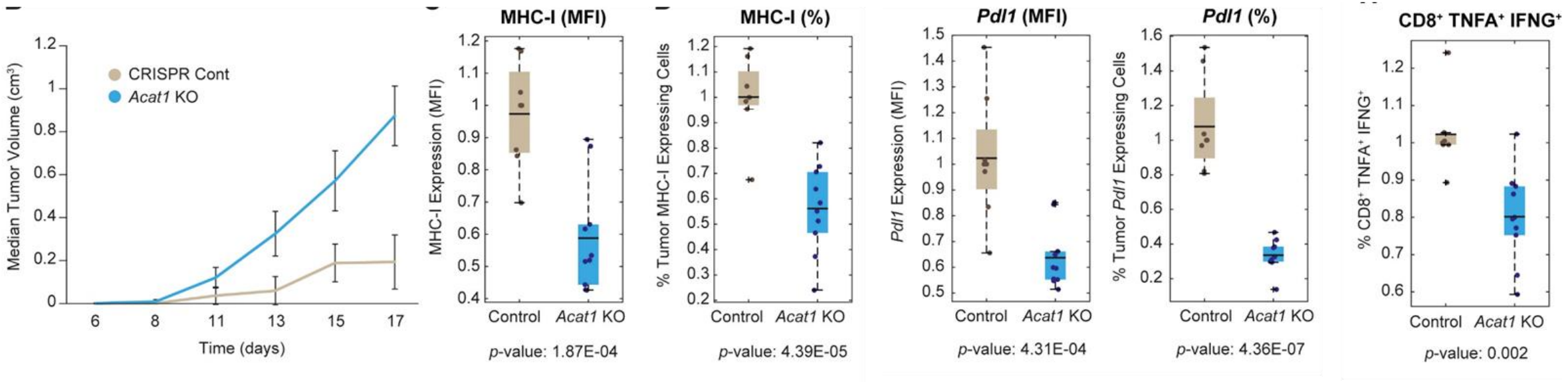
In vitro resistance to immune cells



Harel et al, Cell 2019

Knockout of aerobic metabolism proteins

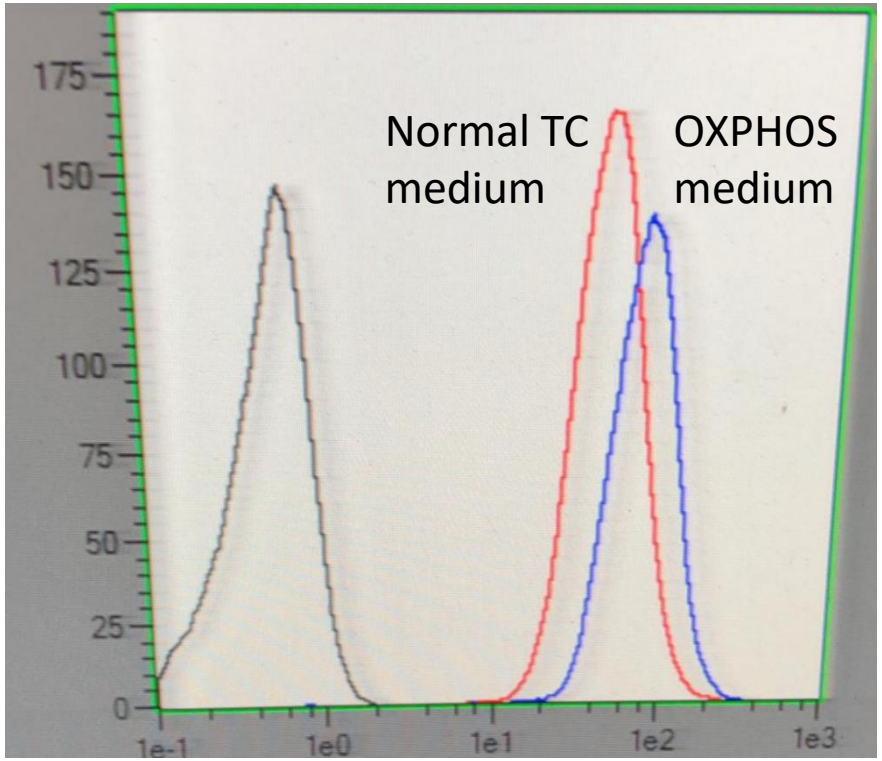
In vivo immune resistance



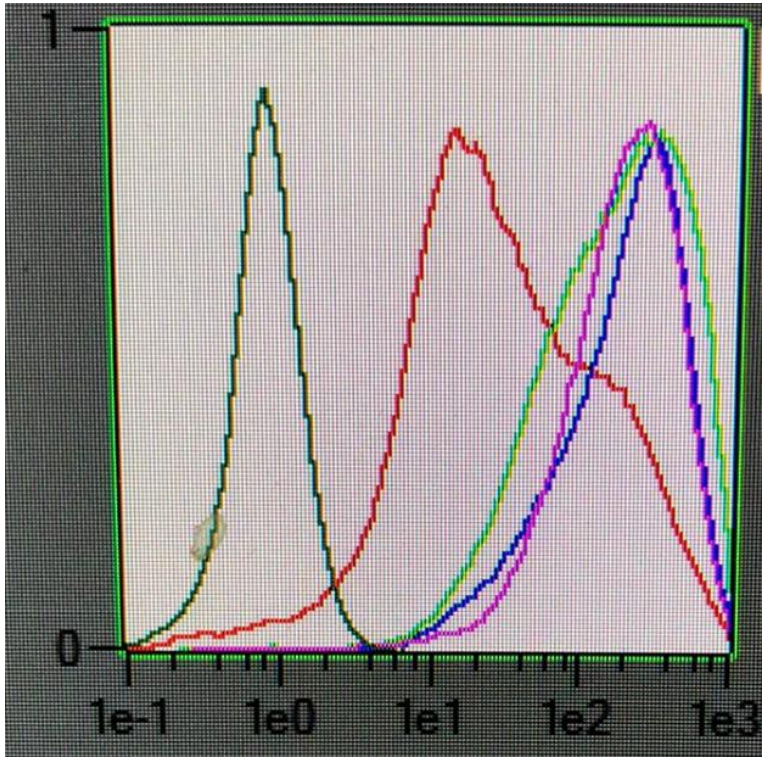
Harel et al, Cell 2019

Driving towards aerobic metabolism

OXPHOS conditions



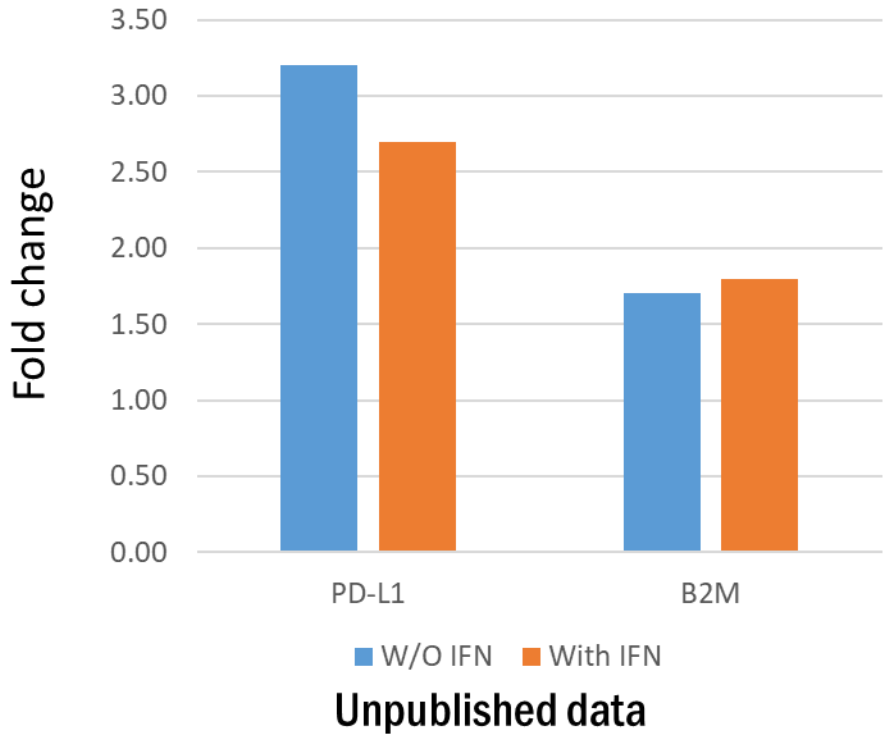
Mitochondrial stimulation



MHC class I ⟶

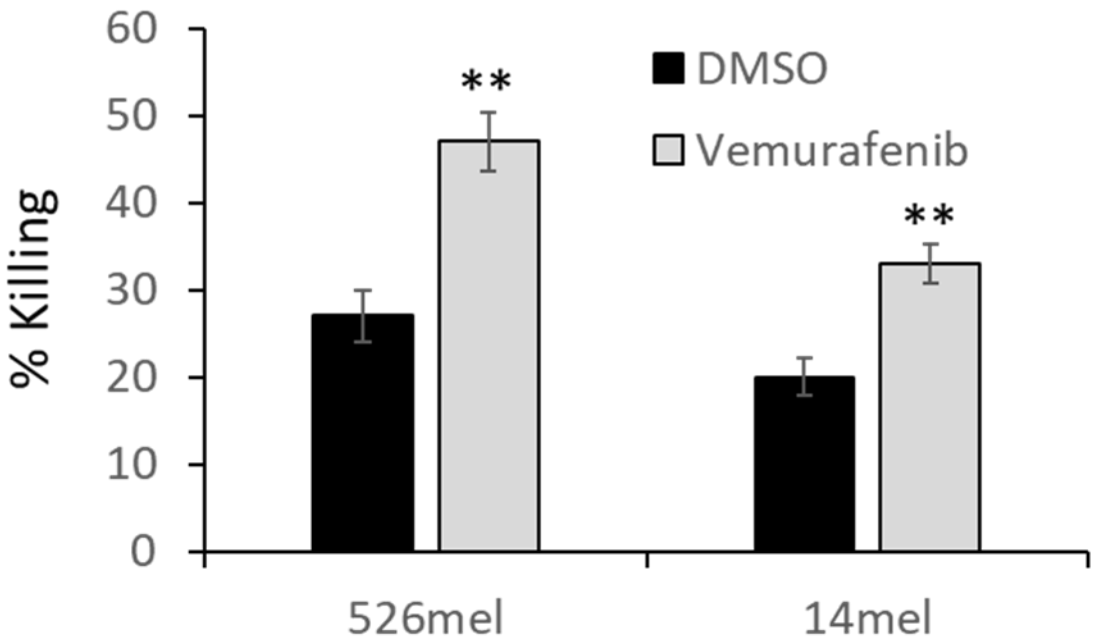
Driving towards aerobic metabolism

- BRAFV600 inhibits OXPHOS in melanoma (Hall et al, Oncotarget 2013)
- BRAF inhibitors restore OXPHOS in melanoma (Haq et al, Clin Cancer Res 2014)



Unpublished data

Hana Moualem



Kfir et al, Neoplasia 2018

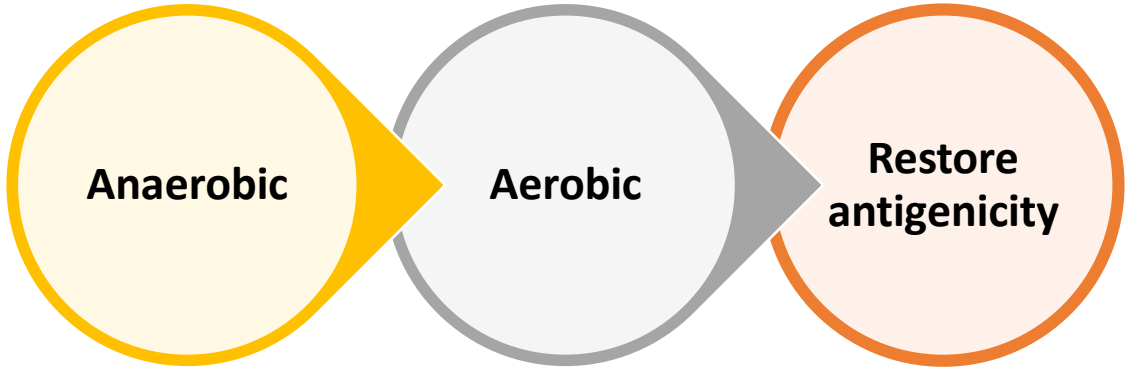
Karin Kfir

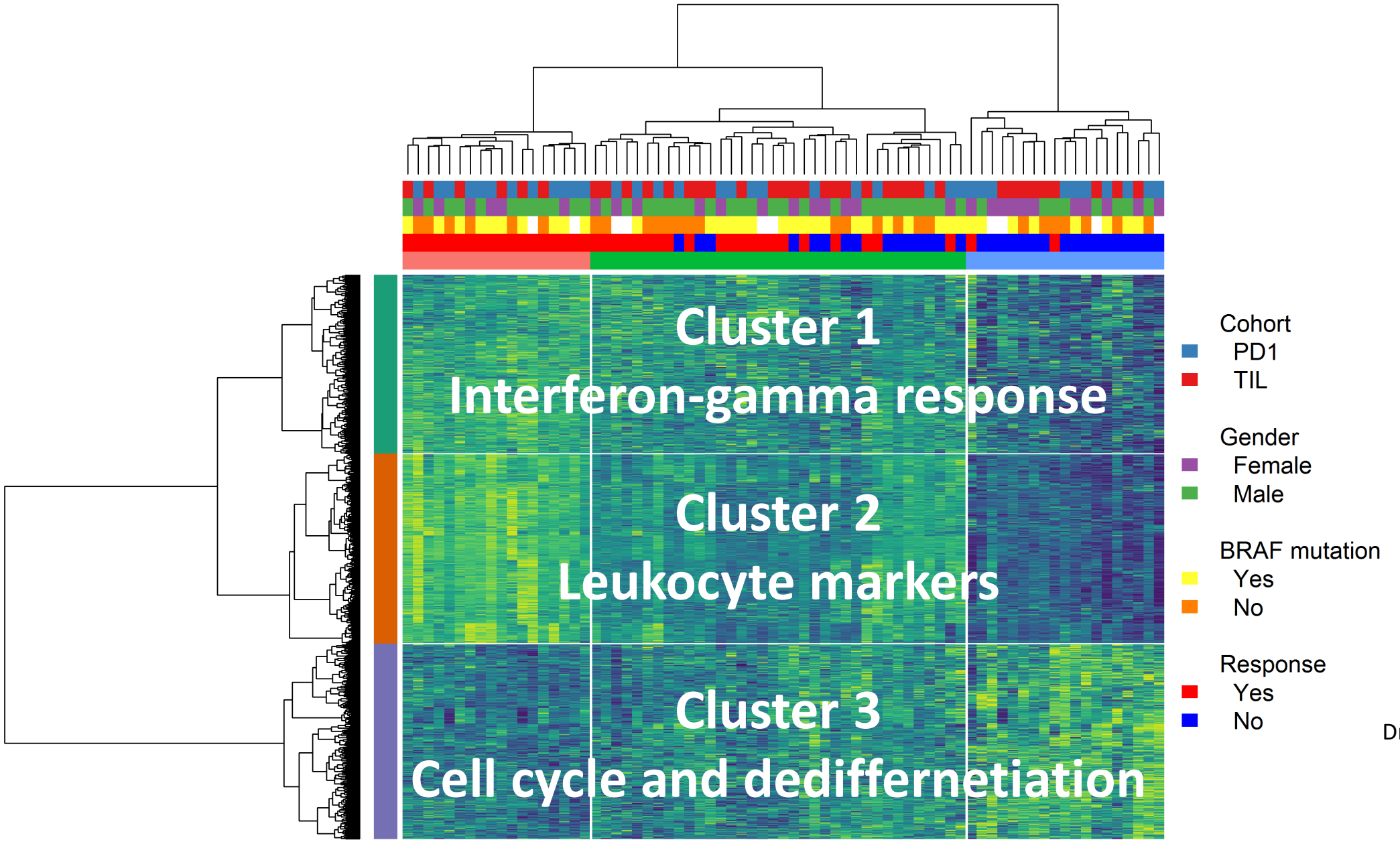
Conclusion 1 (anaerobic metabolism)

Reduces antigenicity

Immune resistance

Enriched in PD-1 resistant

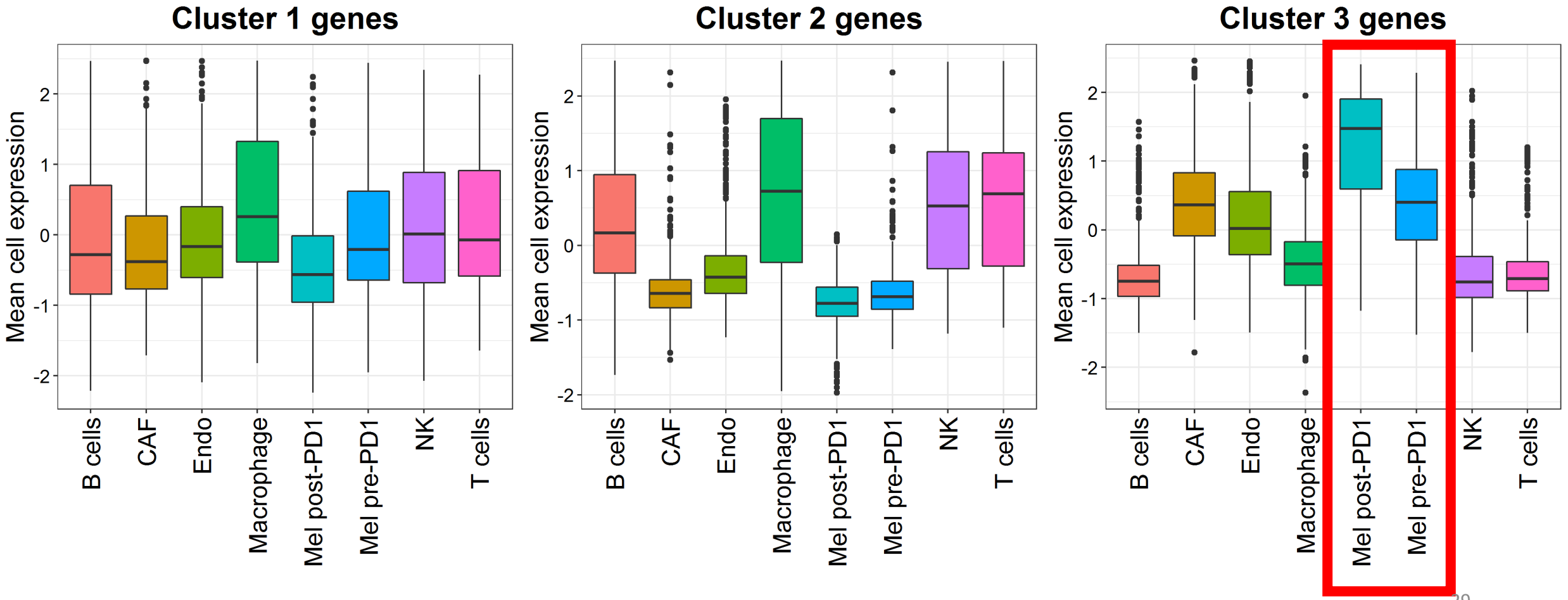




Dr Ettai Markovitc

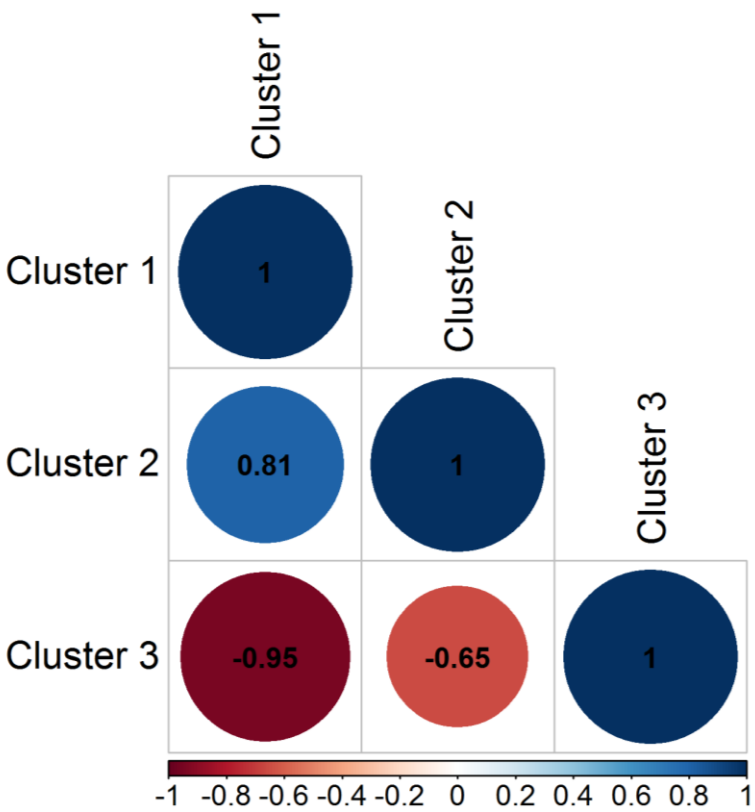
Markovitc et al, SMR 2019

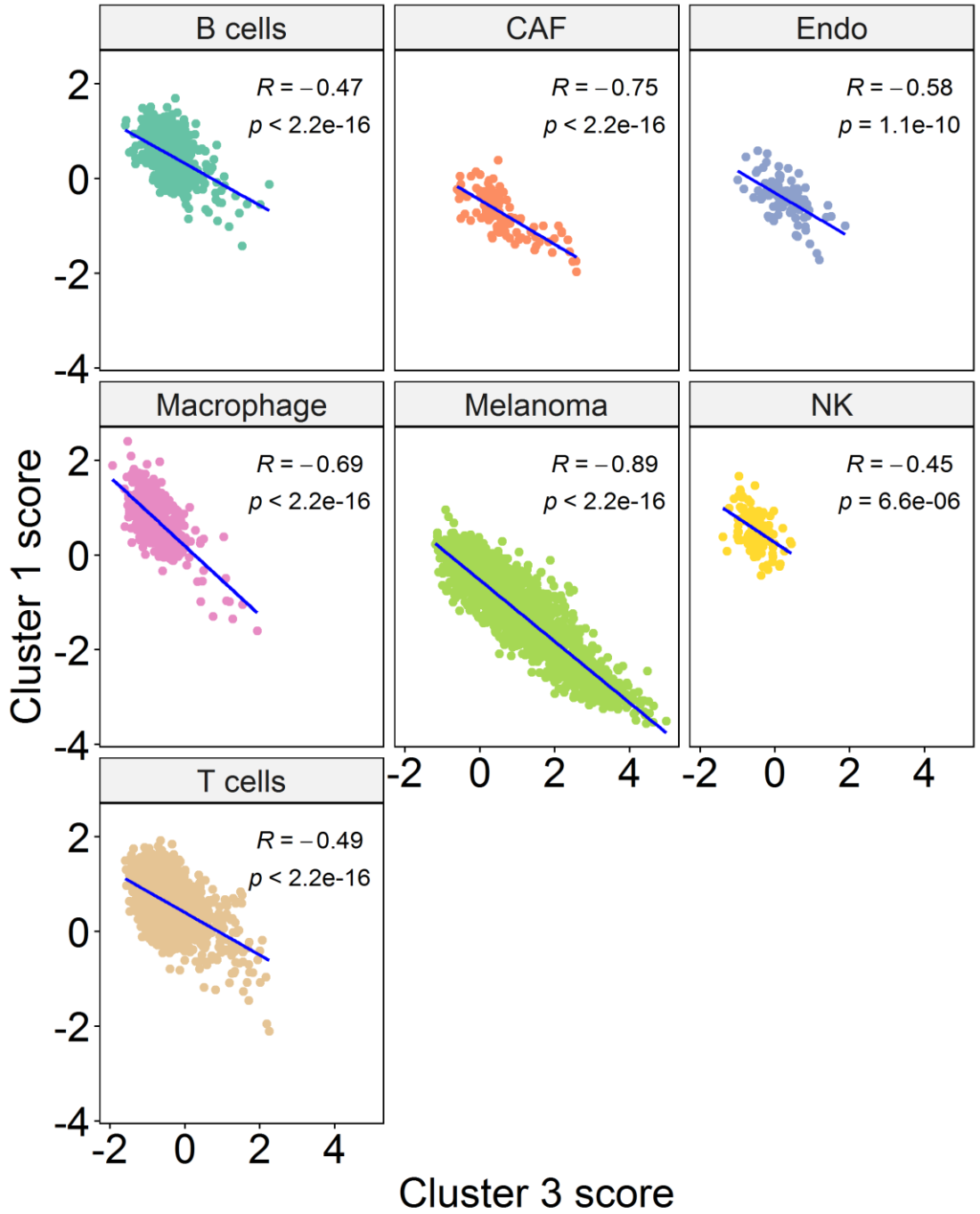
DEGs of each cluster in scRNA data



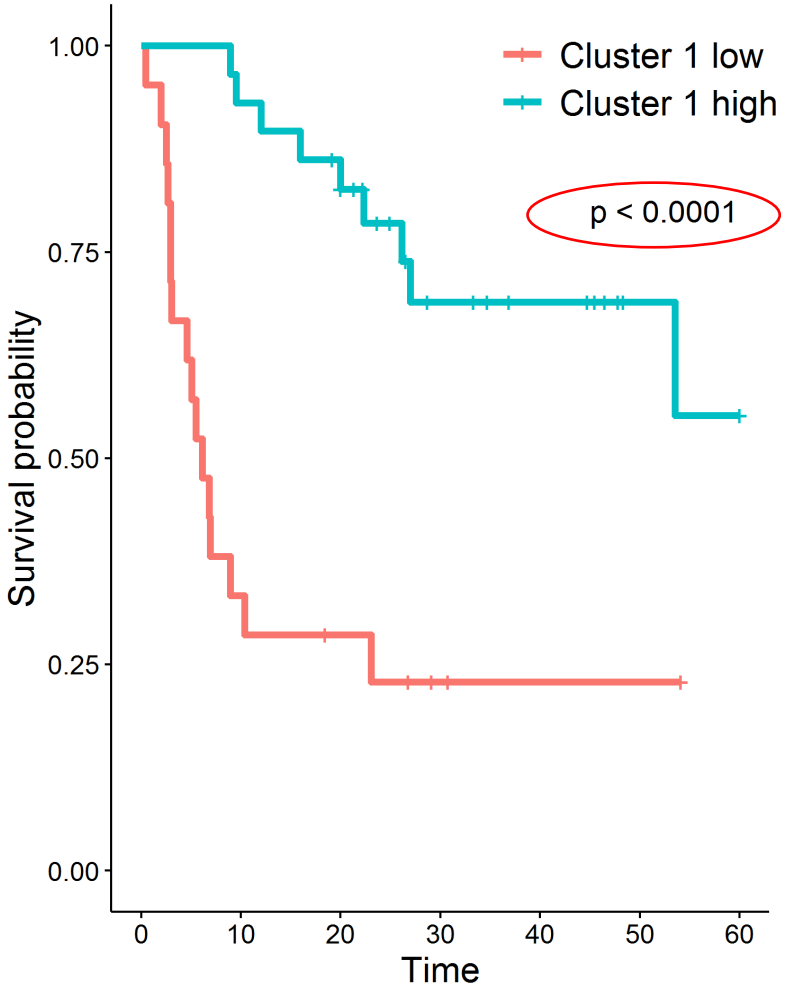
Markovitc et al, SMR 2019

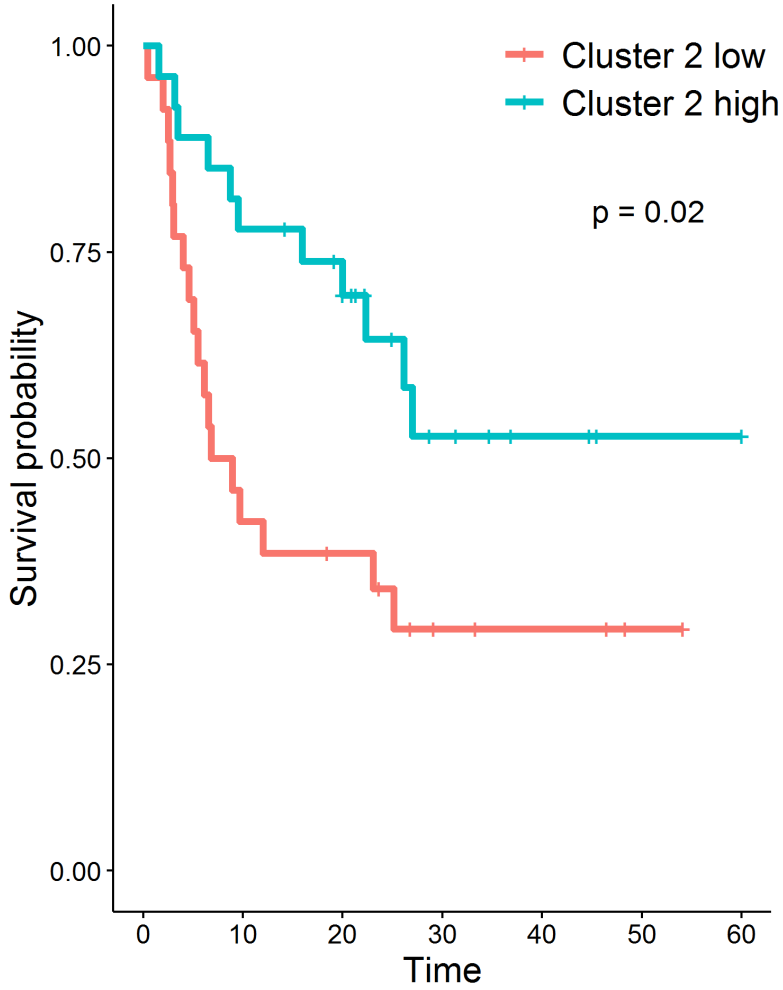
Cluster 1 and 3 are mutually exclusive

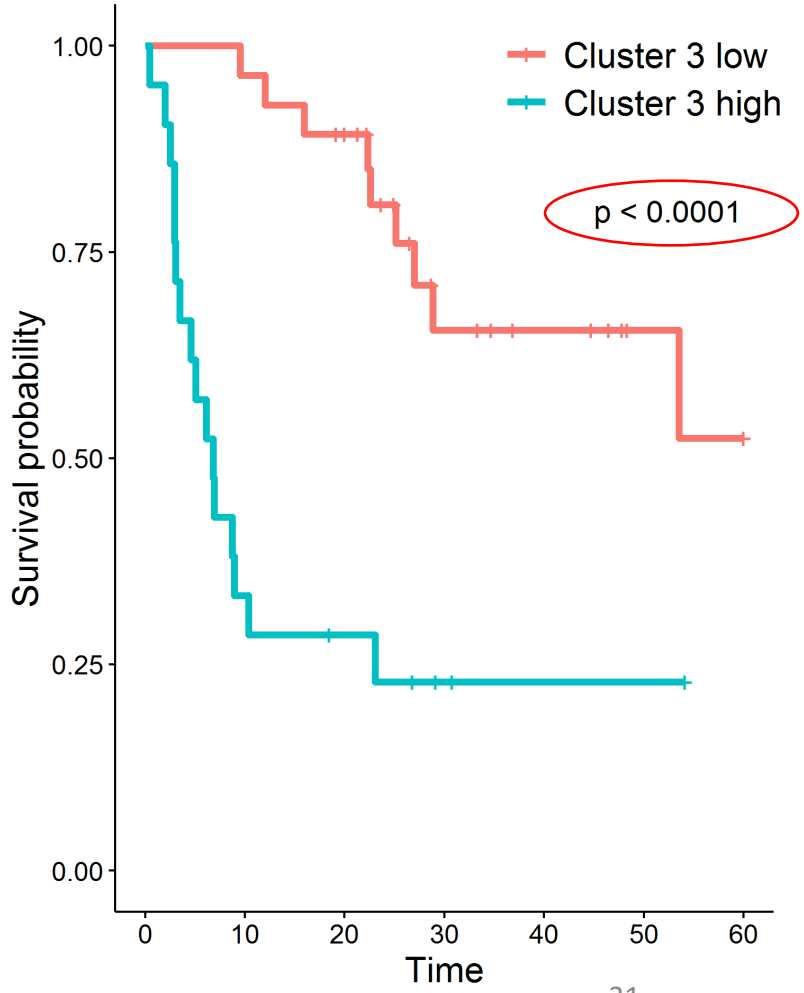




Survival by clusters (Sheba cohorts)

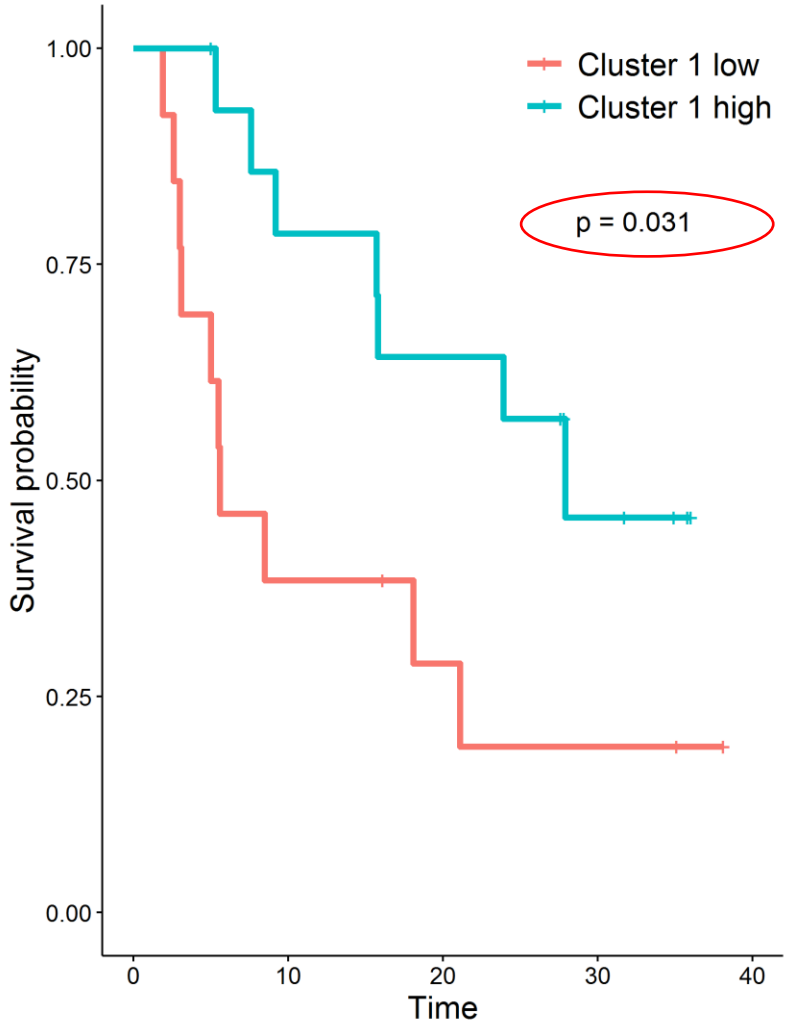


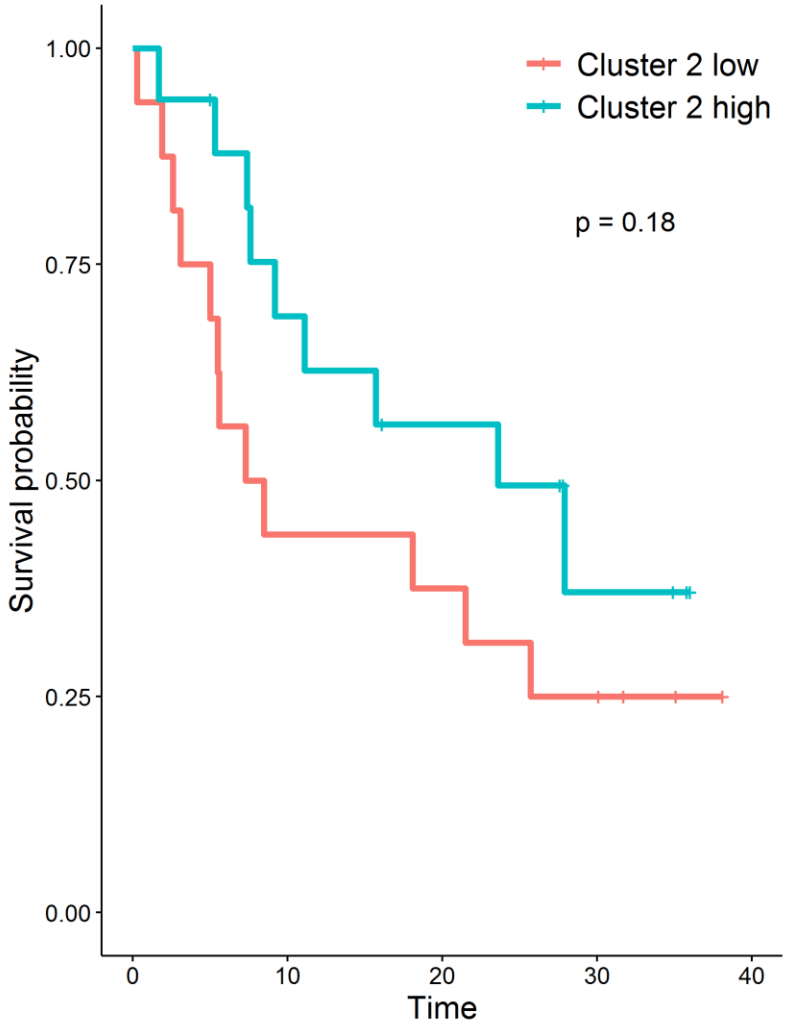


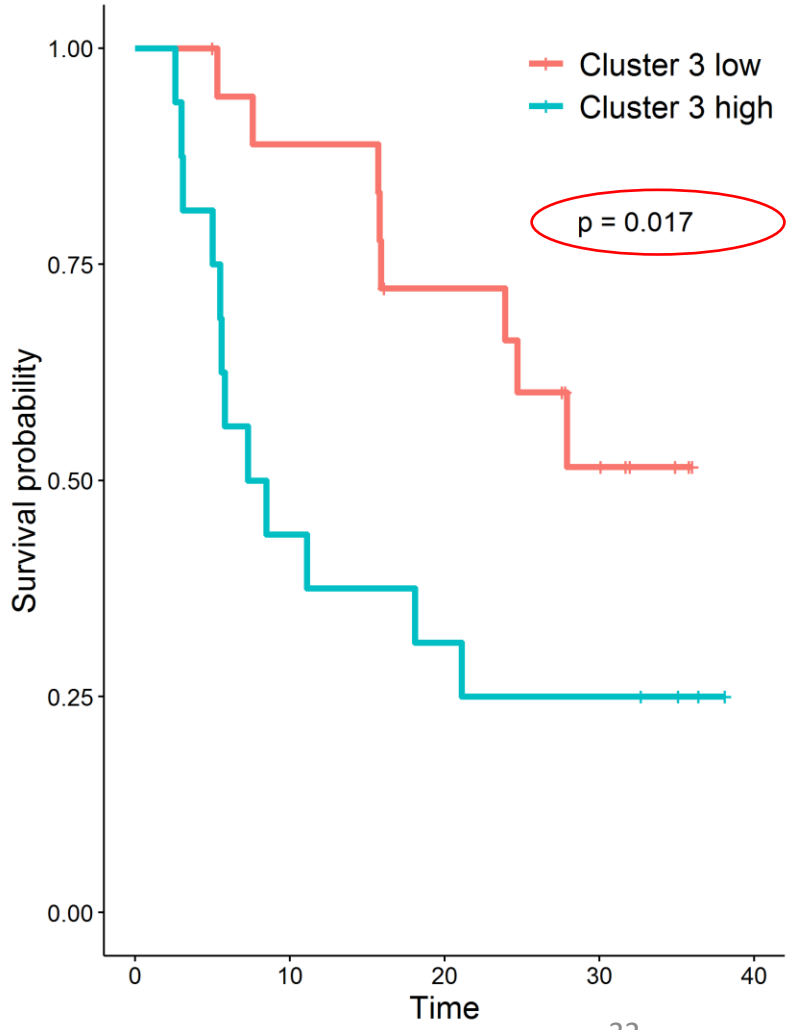


Markovitc et al, SMR 2019

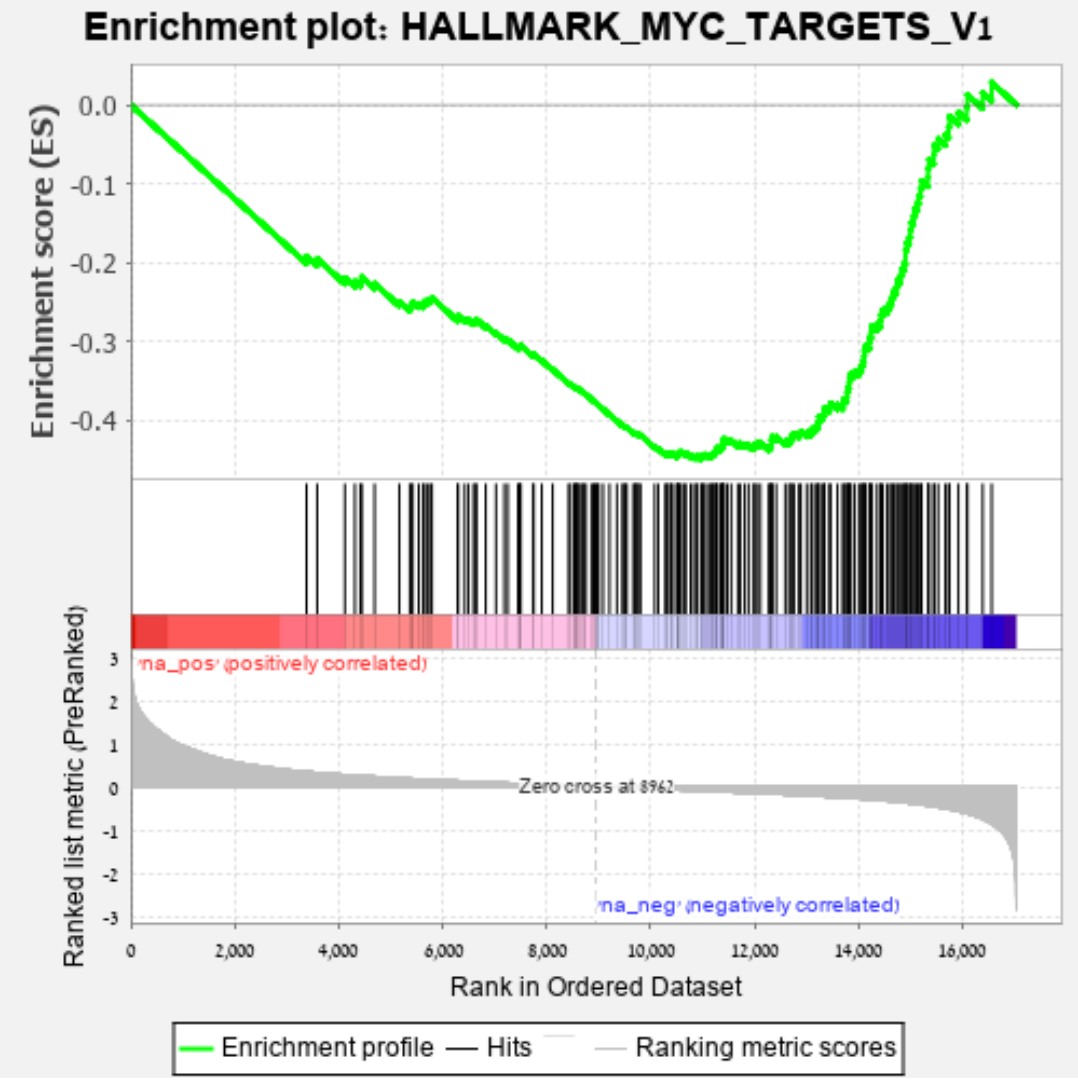
Survival by clusters (BMS cohort)

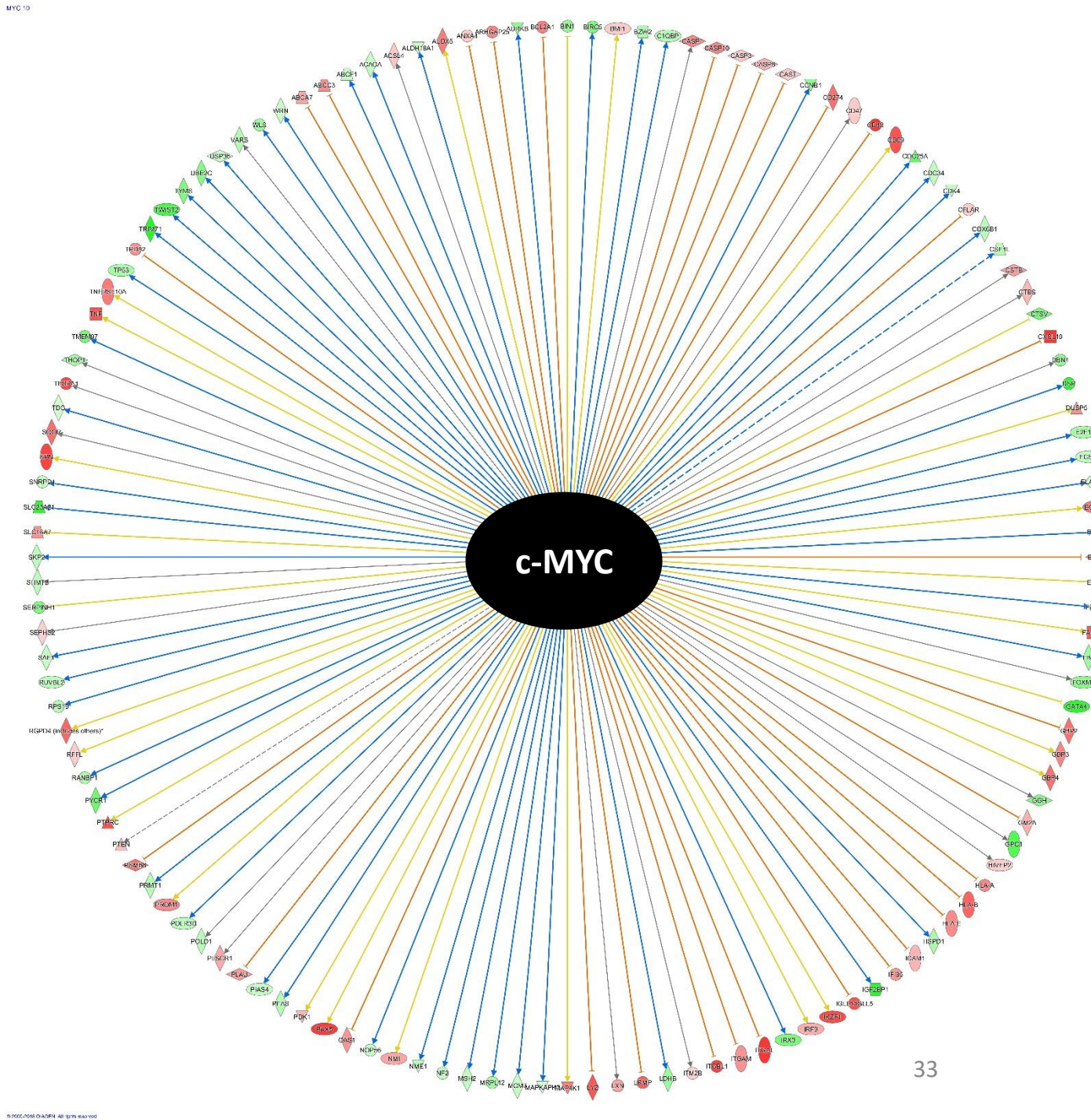






Markovitc et al, SMR 2019



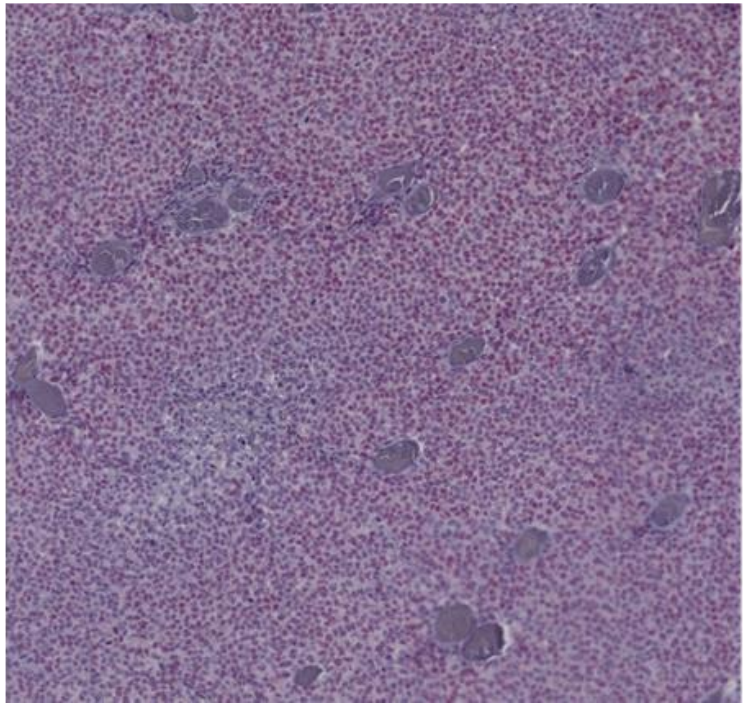


Markovitc et al, SMR 2019

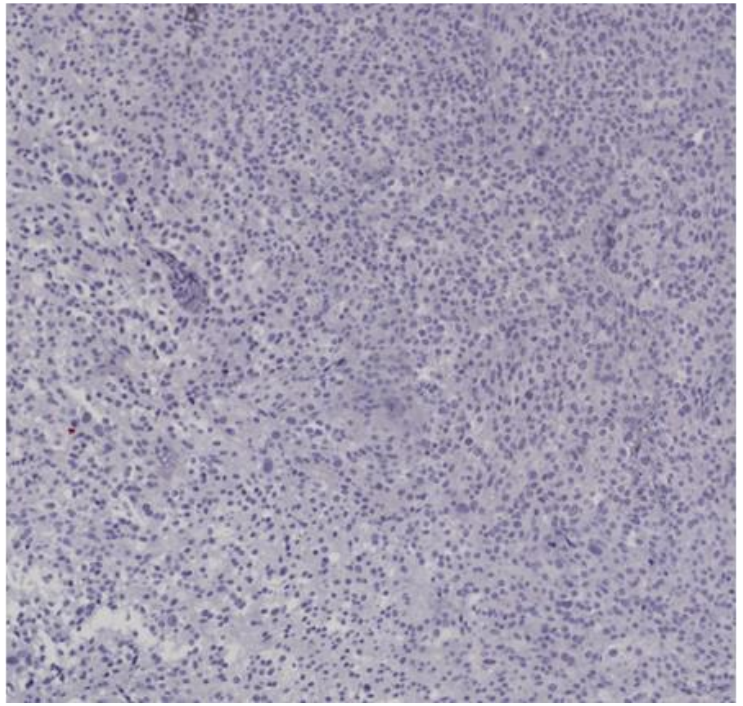
High c-Myc in PD-1 primary resistance

- IHC on 33 melanoma pre-anti PD-1 biopsies
- 2.5 fold increase in nuclear c-Myc in primary resistance (56% vs 24%, p=0.05)

PD1 Failure



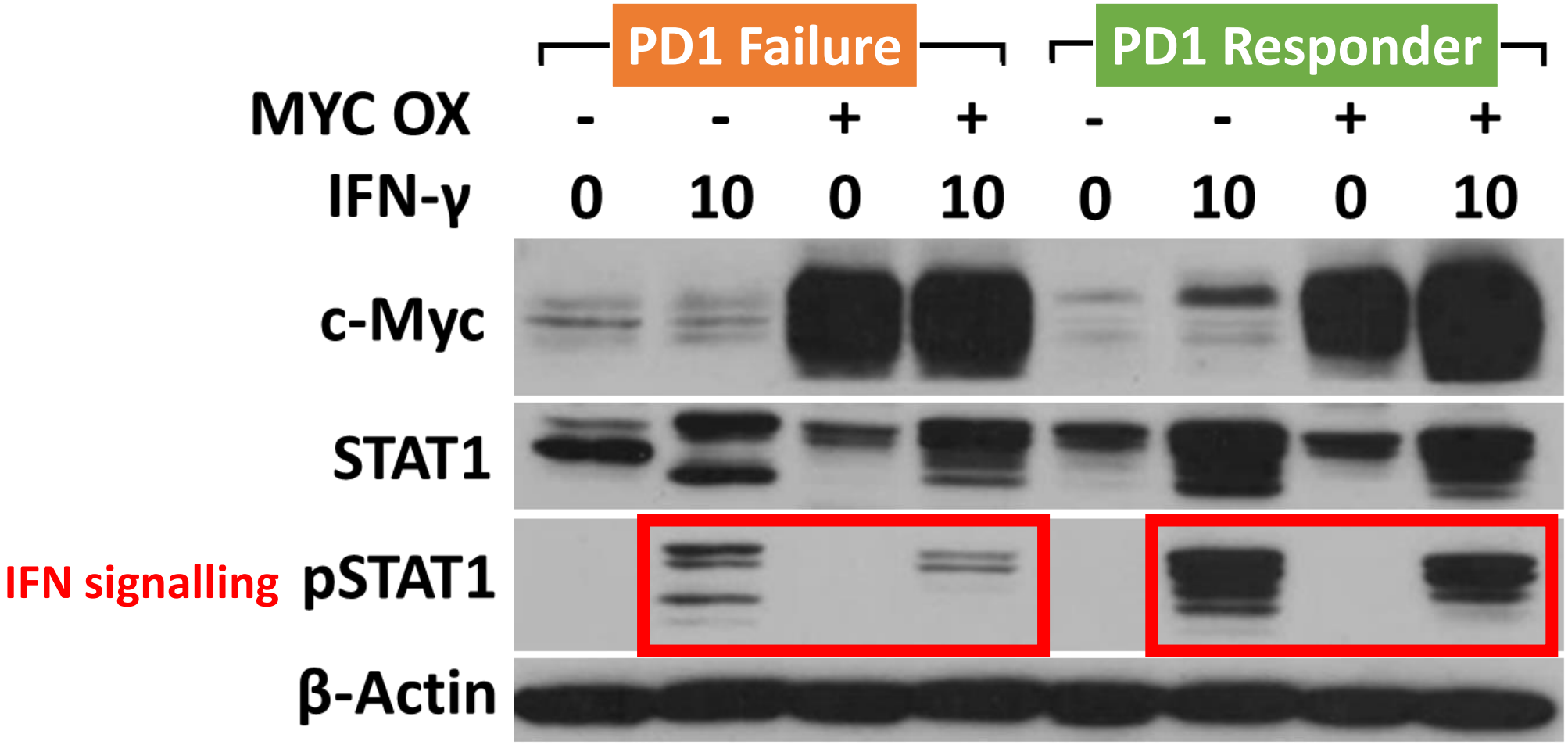
PD1 Responder



c-Myc

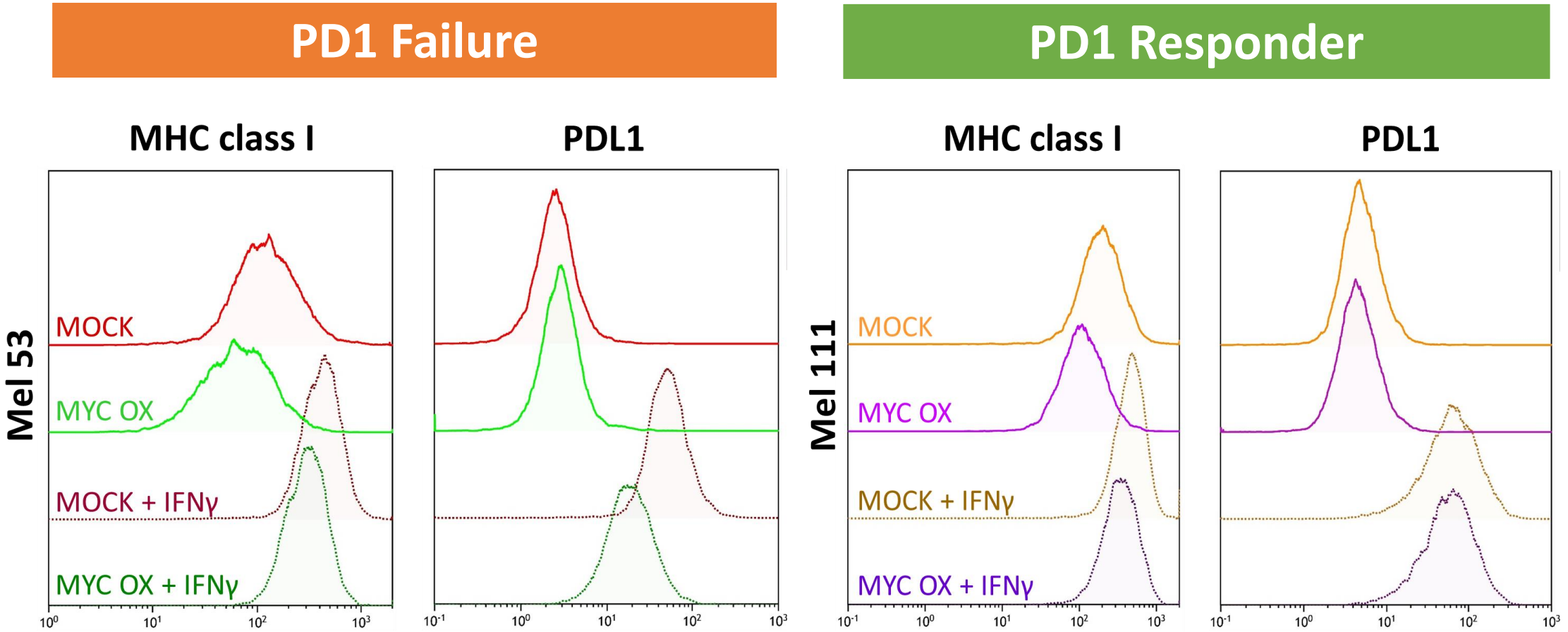
Markovitc et al, SMR 2019

c-Myc confers IFN resistance in PD-1 failures



Markovitc et al, SMR 2019

c-Myc confers IFN resistance in PD-1 failures



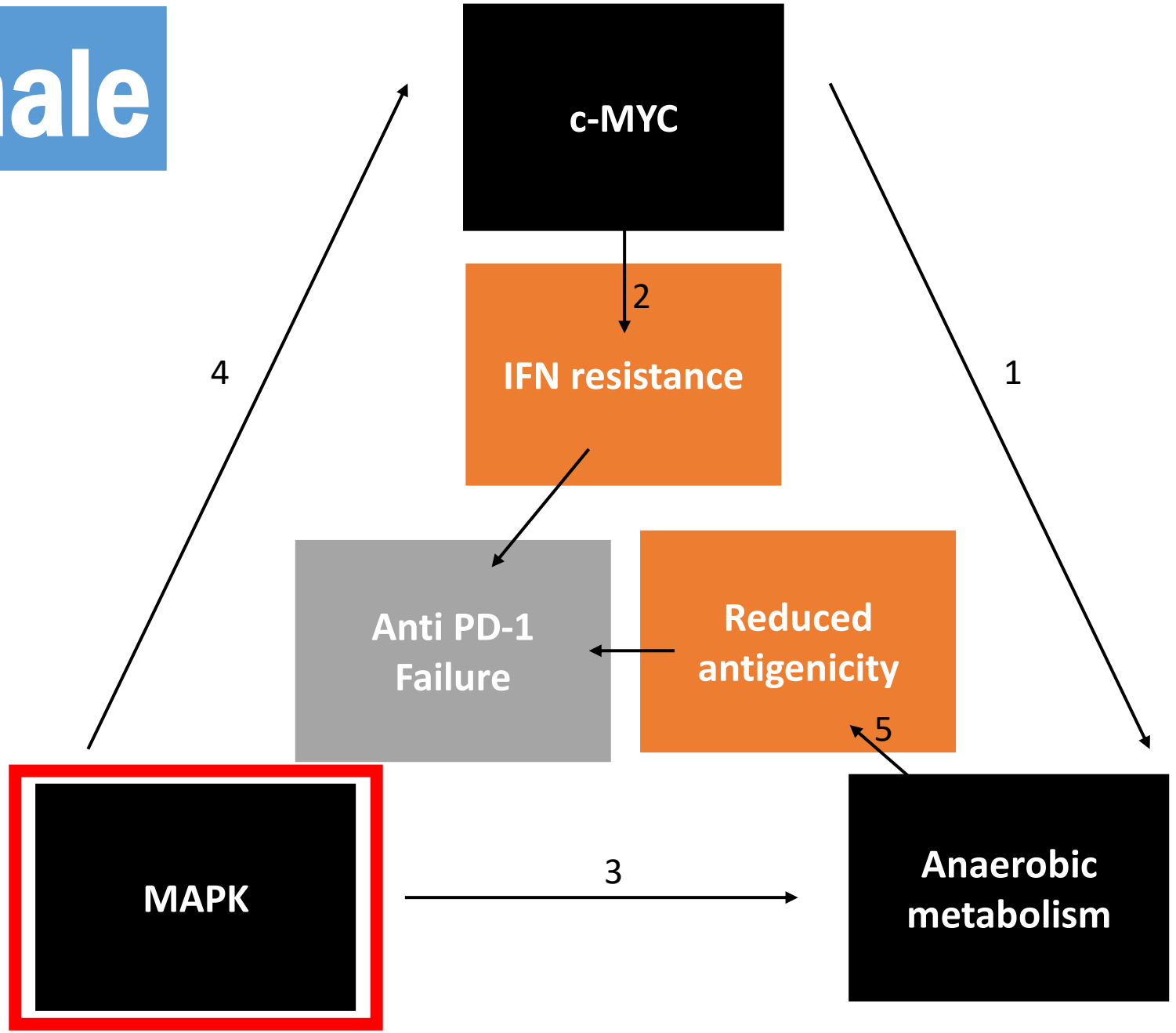
Markovitc et al, SMR 2019

Conclusions 2 (c-MYC)

- c-MYC is a central upstream player in primary PD-1 resistance
- c-MYC is highly expressed in primary PD-1 resistance
- The mechanism is through IFN resistance

Can we render a non-responder responsive?

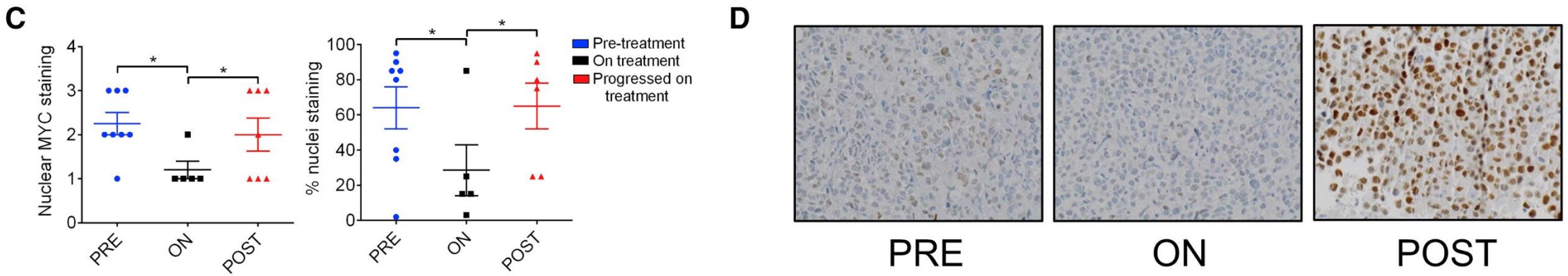
Rationale



[1]Dejure & Eiler, EMBO 2017; [2]**Markovitc et al, SMR 2019**; [3]Haq et al, Clin Cancer Res 2014; [4]Singleton et al, Cell Rep 2017; [5]**Harel et al, Cell 2019**

Rationale for adding MAPK inhibitors

- BRAF inhibition reverses anaerobic metabolism to aerobic metabolism[1], increases MHC class I[2] and in vitro sensitivity to T cells[3]
- Encouraging data from UPFRONT PD-1/BRAFi/MEKi in KN-022[4]
- BRAF inhibition deactivates MYC in patients[5]



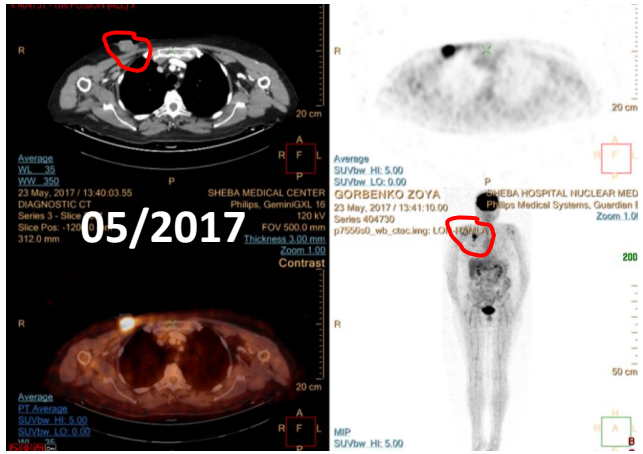
[1]Haq et al, Clin Cancer Res 2014; [2]Hu-Lieskovan et al, Sci Trans Med. 2015; **[3]Kfir et al, Neoplasia 2018**; [4]Ferrucio et al, SMR 2019; [5]Singleton et al, Cell Rep 2017;

Hypothesis

- Transient addition of BRAFi/MEKi will deactivate c-MYC and drive aerobic metabolism in the tumor
- c-MYC reduction and aerobic metabolism will increase immune sensitivity and IFN responsiveness
- This will revert primary resistance and support perpetual effect with further PD-1 blockade

Patient ZG**

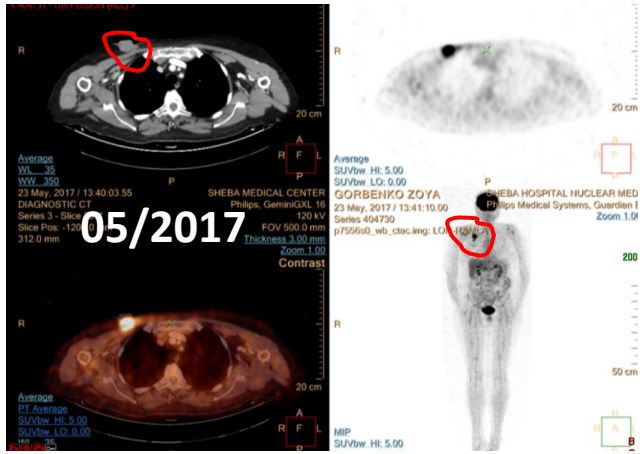
11/2016	12/2016	02/2017	04/2017	05/2017
• Inop. Chest wall • Rapid growth • BRAFmut	• Ipi/Nivo x1 • G3 cardiac, G3 weakness • Discontinued	• PD • Initiate Nivo	• PD (chest wall) • **Concomitant BRAFi+MEKi for 6w**	• Minor response • Stop BRAFi • Continue Nivo

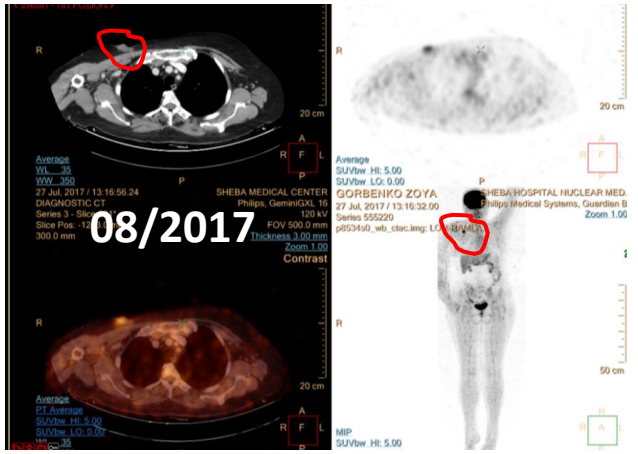


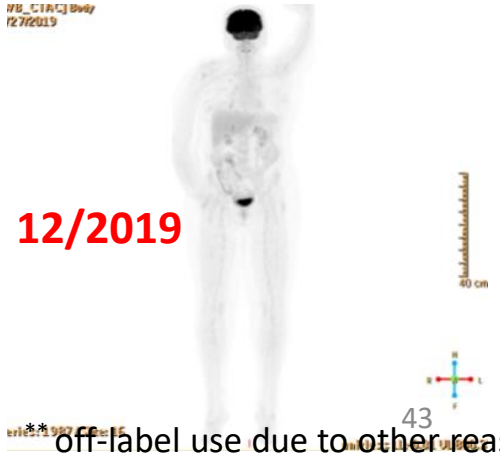
** off-label use due to other reasons

Patient ZG**

11/2016	12/2016	02/2017	04/2017	05/2017	08/2017	**03/2018**	12/2019
• Inop. Chest wall • Rapid growth • BRAFmut	• Ipi/Nivo x1 • G3 cardiac, G3 weakness • Discontinued	• PD • Initiate Nivo	• PD (chest wall) • Concomitant BRAFi+MEKi 6w	• Minor response • Stop BRAFi • Continue Nivo	• PR on **Nivo only**	• **Reached CR** • **Treated until 03/2019**	• Ongoing CR with no Tx







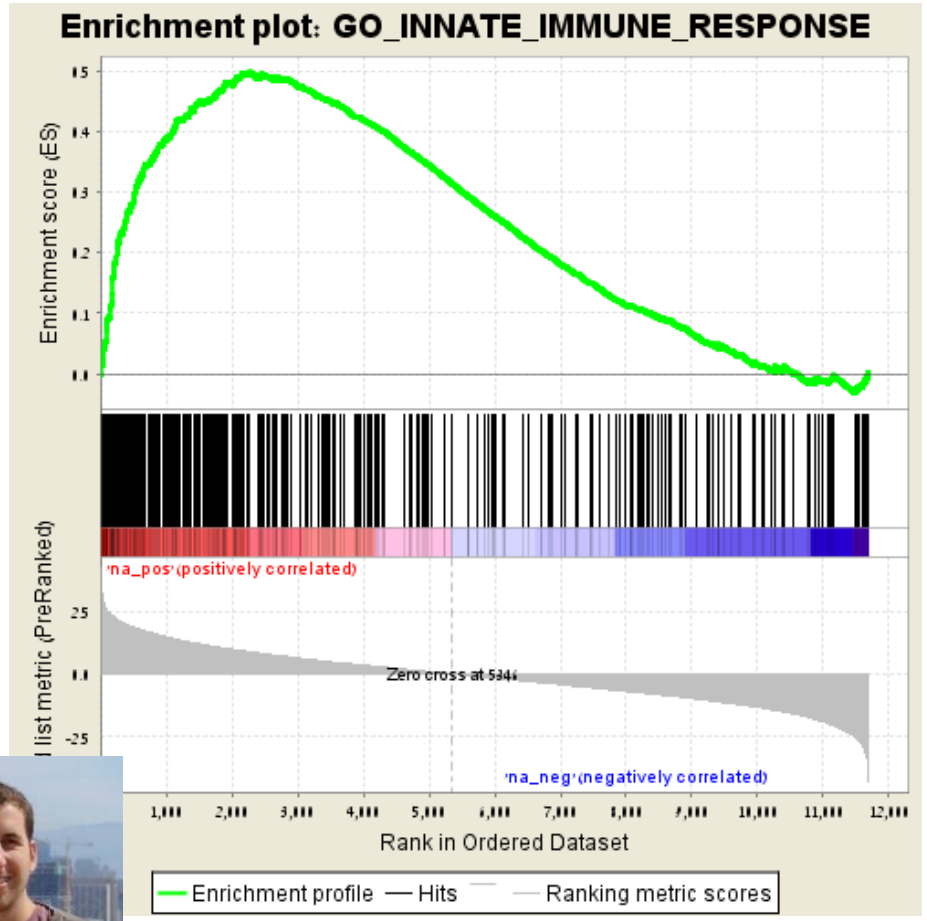
** off-label use due to other reasons

Could this be done with other agents affecting metabolism?

Could this be done with a dietary approach (intermittent ketogenic diet)?

Can we induce generalized immune modulation in the patient?

Microbiome related pathways?



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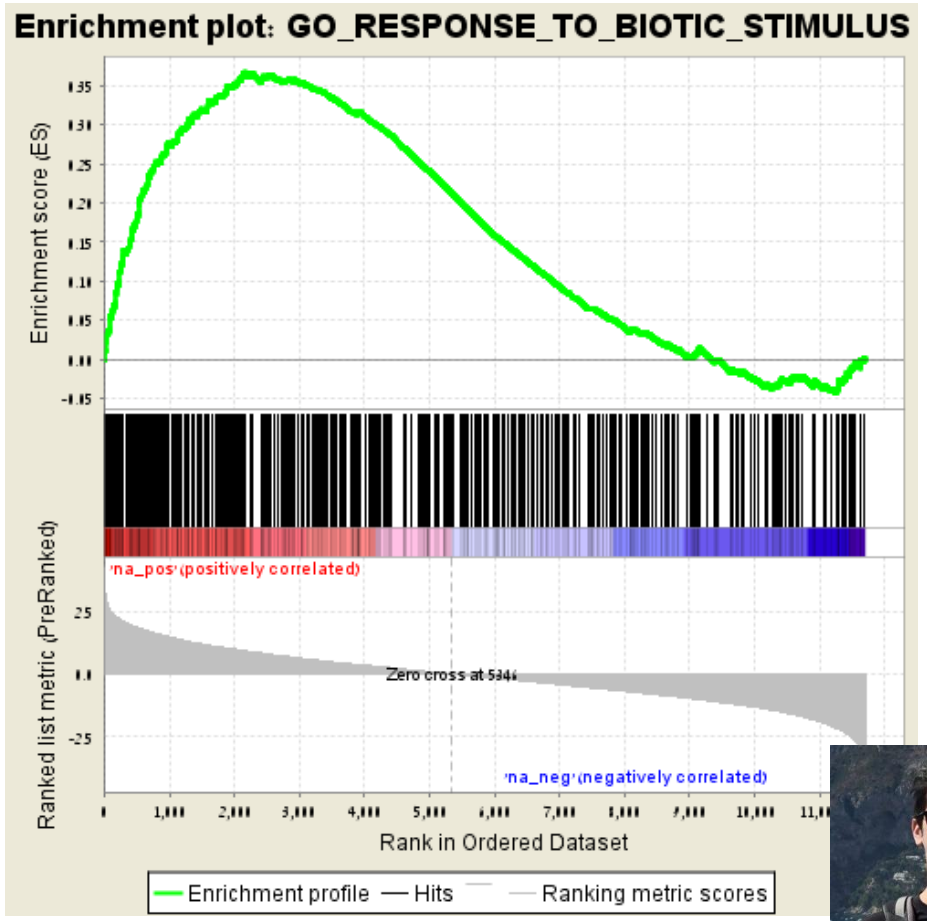
Dr Ettai Markovits



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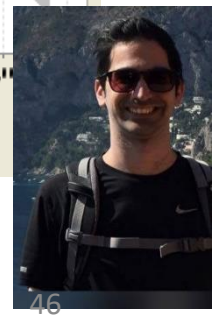
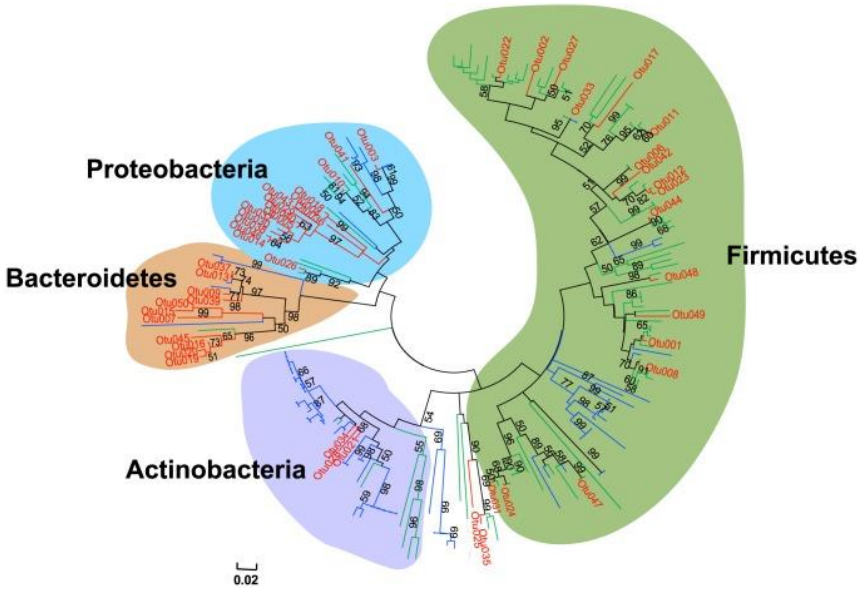
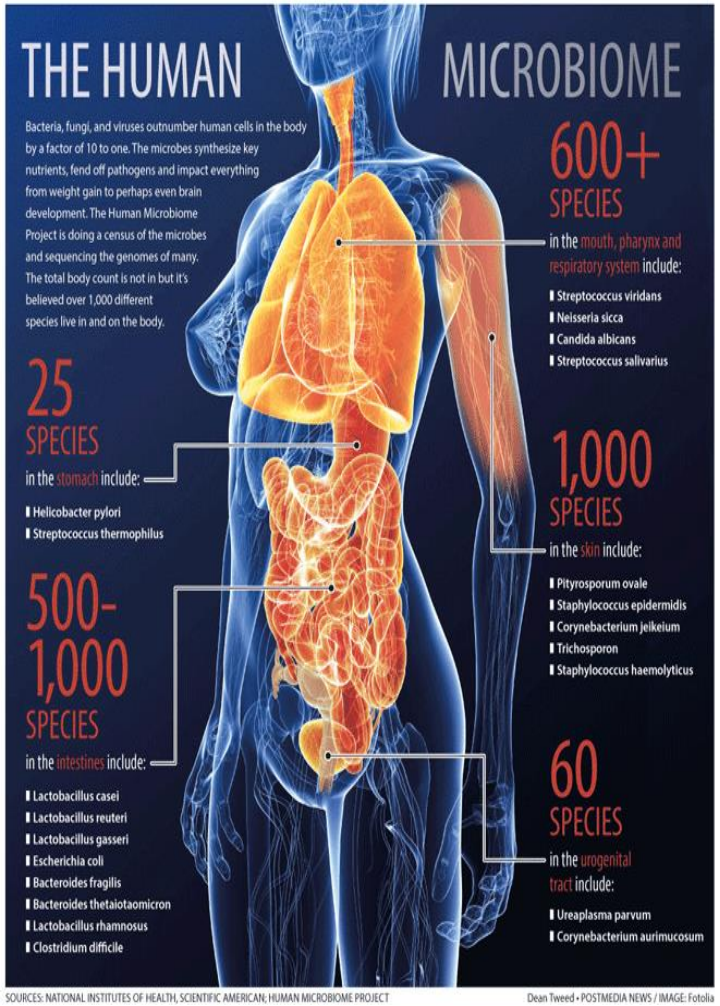


Dr Erez Baruch

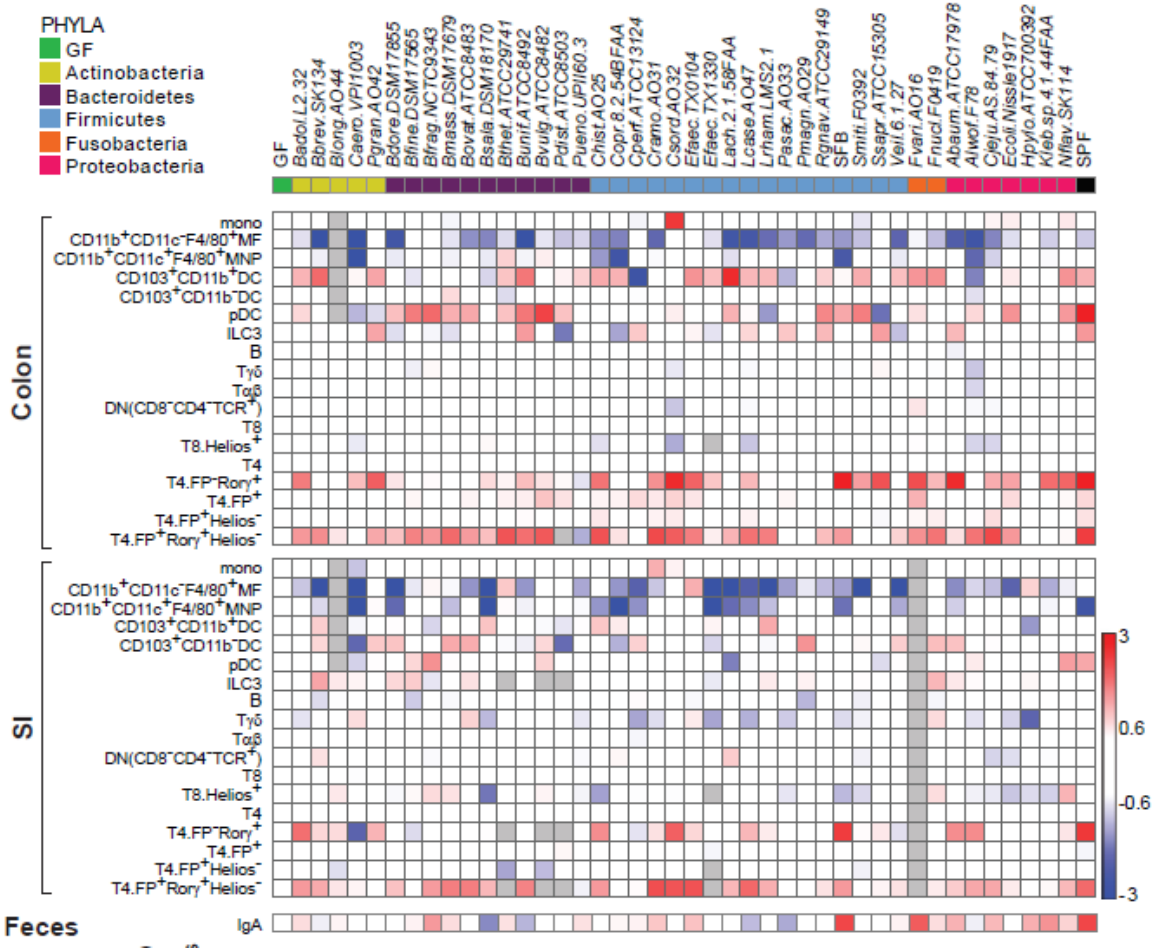
Microbiota ≈ Microbiome

- Collective **genome** of the bacteria in a niche
- Skin, nasopharynx, distal GU, **Gut**





Interplay of microbiota & Immune system



To avoid infections

To preserve micro-organisms essentials to the body need

Geva-Zatorsky et al., Cell 2017

Published in final edited form as:
Science. 2015 November 27; 350(6264): 1079–1084. doi:10.1126/science.aad1329.

Anticancer immunotherapy by CTLA-4 blockade relies on the gut microbiota

Marie Vétizou[1,2,3], Jonathan M. Pitt[1,2,3], Romain Daillère[1,2,3], Patricia Lepage[4], Nadine Waldschmitt[5], Caroline Flament[1,2,6], Sylvie Rusakiewicz[1,2,6], Bertrand Routy[1,2,3,6], Maria P. Roberti[1,2,6], Connie P. M. Duong[1,2,6], Vichnou Poirier-Colame[1,2,6], Antoine Roux[1,2,7], Sonia Becharef[1,2,6], Silvia Formenti[8], Encouse Golden[8], Sascha Cording[9], Gerard Eberl[9], Andreas Schlitzer[10], Florent Ginhoux[10], Sridhar Mani[11], Takahiro Yamazaki[1,2,6], Nicolas Jacquelot[1,2,3], David P. Enot[1,7,12], Marion Bérard[13], Jérôme Nigou[14,15], Paule Opolon[1], Alexander Eggermont[1,2,16], Paul-Louis Woerther[17], Elisabeth Chachaty[17], Nathalie Chaput[1,18], Caroline Robert[1,16,19], Christina Mateus[1,16], Guido Kroemer[7,12,20,21,22], Didier Raoult[23], Ivo Gomperts Boneca[24,25,*], Franck Carbonnel[3,26,*], Mathias Chamaillard[5,*], and Laurence Zitvogel[1,2,3,6,†]

Science

Cite as: V. Go
Science 10.1126/scien

).1126/science.aac4255.

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] T. V. Karpinets,[3] P. A. Prieto,[1†] D. Vicente,[1] K. Hoffman,[4] S. C. Wei,[5] A. P. Cogdill,[1,5] L. Zhao,[3] C. W. Hudgens,[6] D. S. Hutchinson,[7] T. Manzo,[3] M. Petaccia de Macedo,[6‡] T. Cotechini,[8] T. Kumar,[3] W. S. Chen,[9] S. M. Reddy,[10] R. Szczepaniak Sloane,[1] J. Galloway-Pena,[11] H. Jiang,[1] P. L. Chen,[9§] E. J. Shpall,[12] K. Rezvani,[12] A. M. Alousi,[12] R. F. Chemaly,[11] S. Shelburne,[3,11] L. M. Vence,[5] P. C. Okhuysen,[11] V. B. Jensen,[13] A. G. Swennes,[7] F. McAllister,[14] E. Marcelo Riquelme Sanchez,[14] Y. Zhang,[14] E. Le Chatelier,[15] L. Zitvogel,[16] N. Pons,[15] J. L. Austin-Breneman,[1||] L. E. Haydu,[1] E. M. Burton,[1] J. M. Gardner,[1] E. Sirmans,[17] J. Hu,[18] A. J. Lazar,[6,9] T. Tsujikawa,[8] A. Diab,[17] H. Tawbi,[17] I. C. Glitza,[17] W. J. Hwu,[17] S. P. Patel,[17] S. E. Woodman,[17] R. N. Amaria,[17] M. A. Davies,[17] J. E. Gershenwald,[1] P. Hwu,[17] J. E. Lee,[1] J. Zhang,[3] L. M. Coussens,[8] Z. A. Cooper,[1,3¶] P. A. Futreal,[3] C. R. Daniel,[4,2] N. J. Ajami,[7] J. F. Petrosino,[7] M. T. Tetzlaff[6,9] P. Sharma,[5,19] J. P. Allison,[5] R. R. Jenq,[3#] J. A. Wargo,[1,3#**]

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] Maria-Luisa Alegre,[4] Jason J. Luke,[4] Thomas F. Gajewski[1,4†]

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], and Thomas F. Gajewski[1,2,†]

Science

REPORTS

Cite as: B. Routy *et al.*, *Science* 10.1126/science.aan3706 (2017).

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,[1,2,5] Maryam Tidjani Alou,[1,2,3] Romain Daillère,[1,2,3] Aurélie Fluckiger,[1,2,5] Meriem Messaoudene,[1,2] Conrad Rauber,[1,2,3] Maria P. Roberti,[1,2,5] Marine Fidelle,[1,3,5] Caroline Flament,[1,2,5] Vichnou Poirier-Colame,[1,2,5] Paule Opolon,[6] Christophe Klein,[7] Kristina Iribarren,[8,9,10,11,12] Laura Mondragón,[8,9,10,11,12] 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] Solenn Brosseau,[15] Coureche Kaderbhai,[16] Corentin Richard,[16] Hira 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,[1,13] Yohann Loriot,[1,3,14] François Ghiringhelli,[16] Gérard Zalcman,[15] François Goldwasser,[9,21,22] Bernard Escudier,[1,14,23] Matthew D. Hellmann,[24,25] Alexander Eggermont,[1,2,14] Didier Raoult,[26] Laurence Albiges,[1,3,14] Guido Kroemer,[8,9,10,11,12,27,28*] Laurence Zitvogel[1,2,3,5*]

Can we reprogram the immune system in patients?

Challenges & Hypothesis

FMT in immunotherapy-refractory melanoma patients:

Trial record **1 of 2** for: melanoma fecal

Previous Study | Return to List | Next Study

Fecal Microbiota Transplantation (FMT) in Metastatic Melanoma Patients Who Failed Immunotherapy

ClinicalTrials.gov Identifier: NCT03353402

Recruitment Status : Recruiting
First Posted : November 27, 2017
Last Update Posted : November 27, 2017

See **Contacts and Locations**

Sponsor:
Sheba Medical Center

Information provided by (Responsible Party):
Prof. Gal Markel, Sheba Medical Center

Study aims (NCT03353402)

- ***Primary***
  - **Safety**
    - FMT-related and immune-related AEs and SAEs per CTCAE 5.0
  - **Engraftment**
    - Similarity of recipients' post FMT to their donors ("cluster")
    - Dissimilarity between different clusters of donor + corresponding post-FMT recipients
- ***Secondary***
  - **Alteration of immune system activity**
    - Changes in Post FMT gut CD68+ cells
    - Changes in Post FMT intratumoral CD8+ cells
- ***Exploratory***
  - **Objective response to treatment**
    - iRECIST

Approach

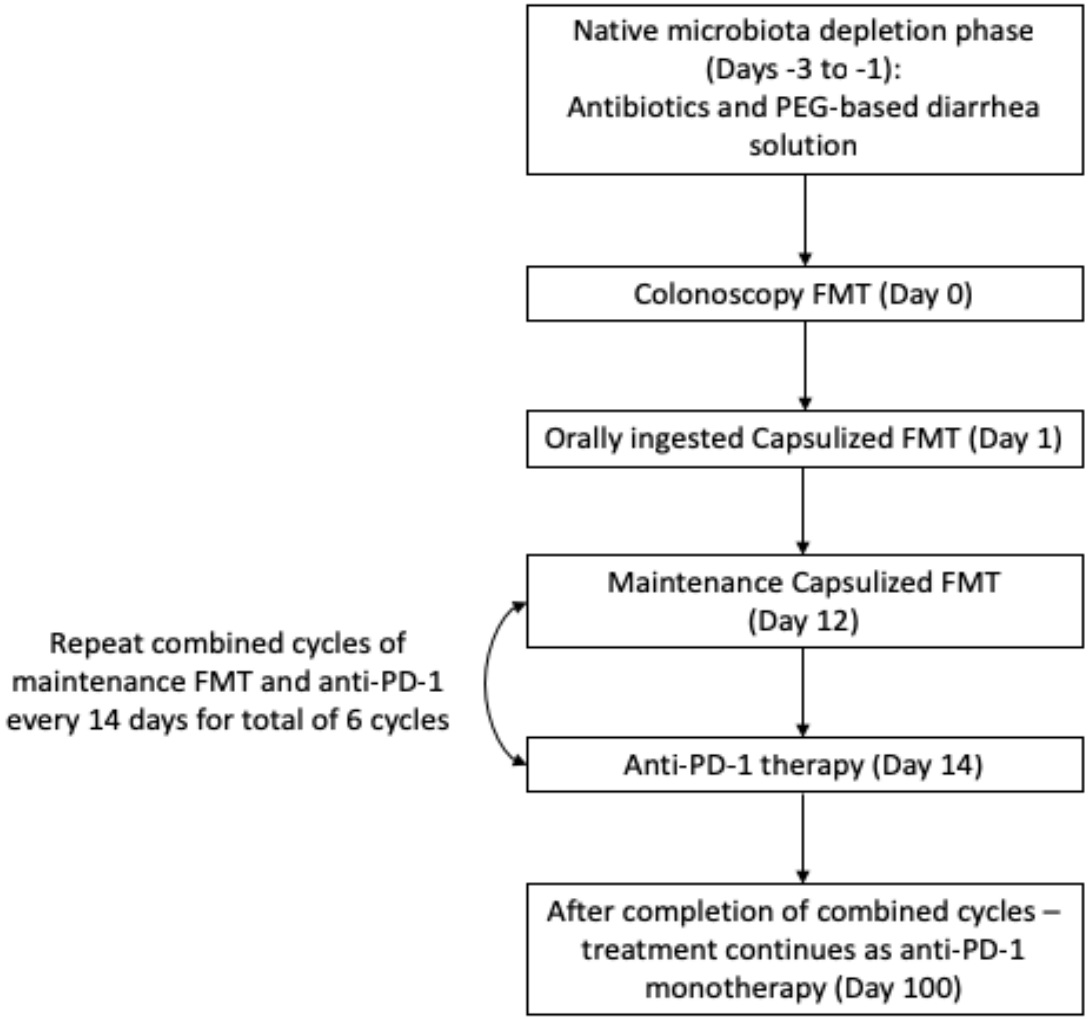
Donors

- Metastatic melanoma patients
- Durable ongoing CR to anti-PD-1
- Still on active treatment
- Approved feces donors according to current standard guidlines (AGA & MoH)

Recipients

FMT + Re-induction of Anti PD-1

Study design



Evaluations

- **Imaging (PET CT)**
  - Baseline, day 65 and then every 9-10 w
- **Gut biopsy by sigmoidoscopy**
  - Baseline and day 31
- **Tumor biopsy from the same metastasis**
  - Baseline and day 62-70

Sample collection

Pre and post – stool, blood, gut, tumor

Age	Gender	V600E BRAF mutation	Previous treatment lines	Anti-PD-1 therapy	Stage	# of Disease Sites	Time in complete response (months)
59	M	+	Vemurafenib	Nivolumab	M1d	3	12
41	F	+	Vemurafenib + Cobimetinib	Nivolumab	M1c	2	14

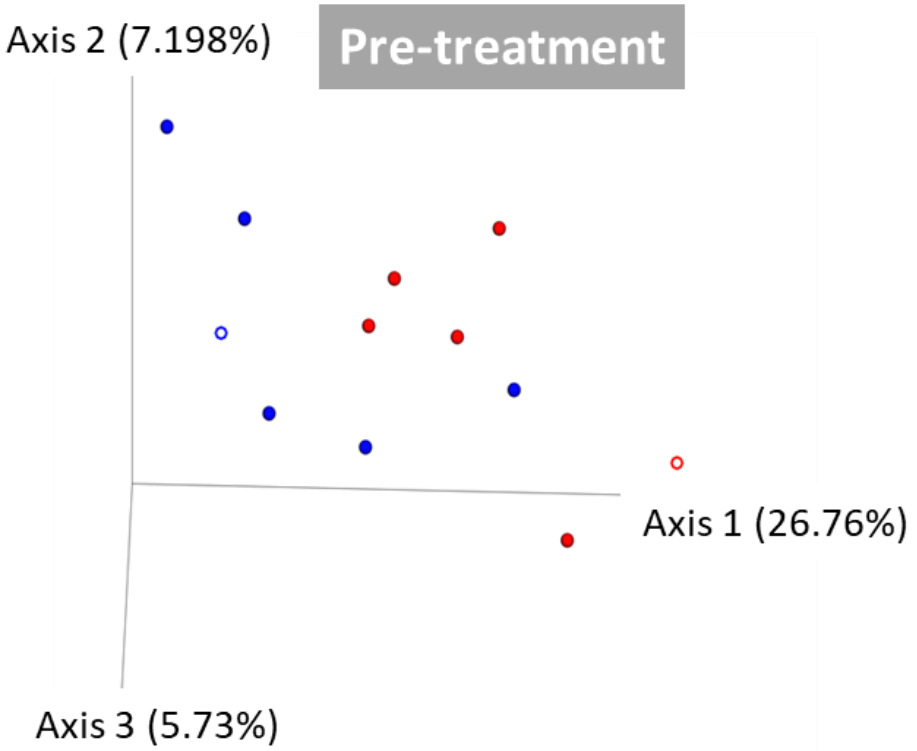
Patient characteristics

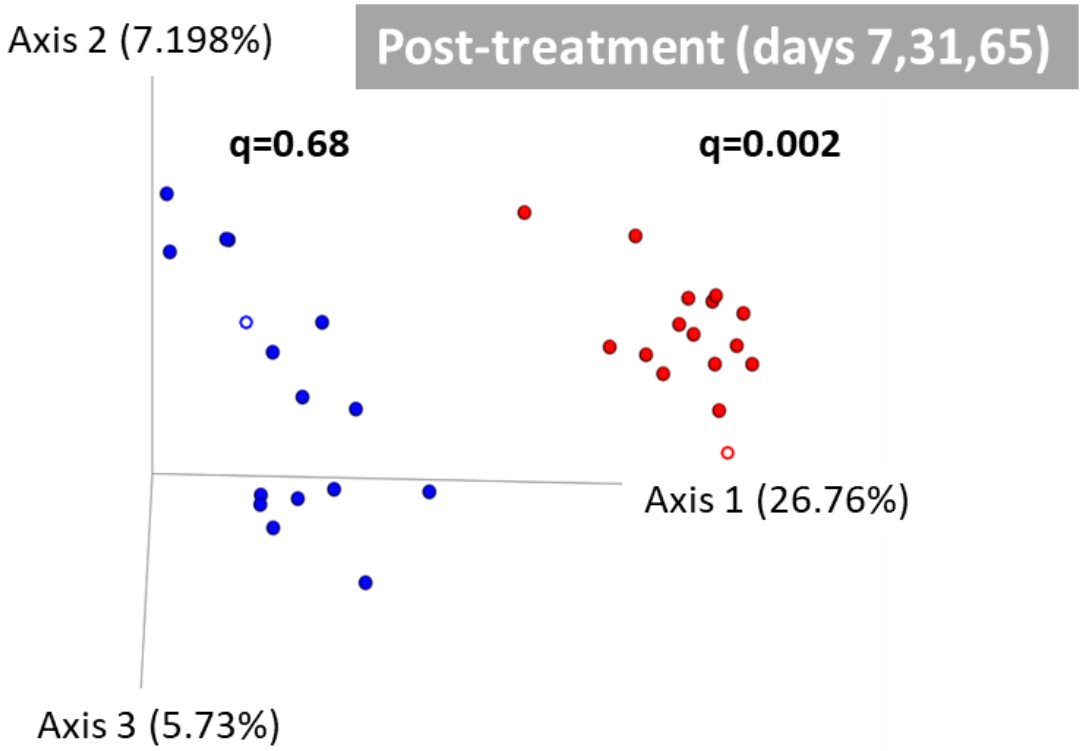
#	Age	Gender	BRAF	Previous treatment lines (in chronological order)	Stage	Baseline LDH	Primary anti-PD-1 failure*	Sum of target lesion diameter (mm)	Washout time (days)	Cycle number of previous anti-PD-1§
1	66	F	V600E	D+T; Nivo; D+T, Ipi+Nivo	M1d	High	Yes	136	43	9
2	70	M	WT	Pembro; Ipi; Pembro	M1b	High	No	145	100	5
3	78	M	WT	Pembro	M1a	Normal	Yes	44	52	10
4	69	F	WT	Nivo (adjuvant)	M1a	Normal	Yes	120	98†	6
5	66	M	WT	Ipi+Nivo	M1a	Normal	No	38	105†	30
6	33	M	V600E	Ipi; Pembro; D+T; Nivo, T-VEC + Nivo; TIL; D+T; Palbociclib; Carbo + Pacli	M1d	Normal	No	220	28	7
7	66	M	V600E	Pembro; D+T	M1c	High	No	132	28	35
8	65	M	WT	Ipi+Nivo	M1c	Normal	No	33	28	10
9	35	F	WT	Nivo (adjuvant); Ipi; Carboplatin + Paclitaxel	M1c	High	Yes	125	35	8
10	44	M	WT	Ipi+Nivo	M1c	Normal	No	85	43	11

Primary endpoint 1: Safety

- **FMT-related**
  - Patients fully recovered 3-4 hours post colonoscopy
  - No G2-4 AEs other SAEs (perforation, septic shock etc.)
- **Immune related adverse events**
  - No Grade 2-4 irAEs

Primary endpoint 2: Engraftment





Study aims (NCT03353402)

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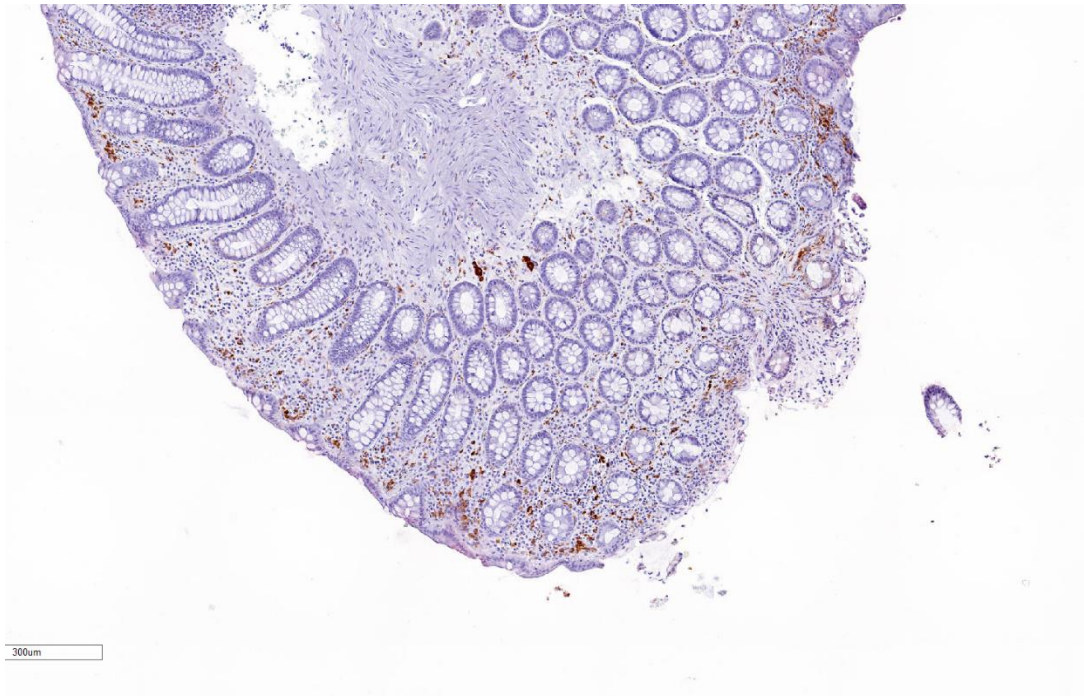
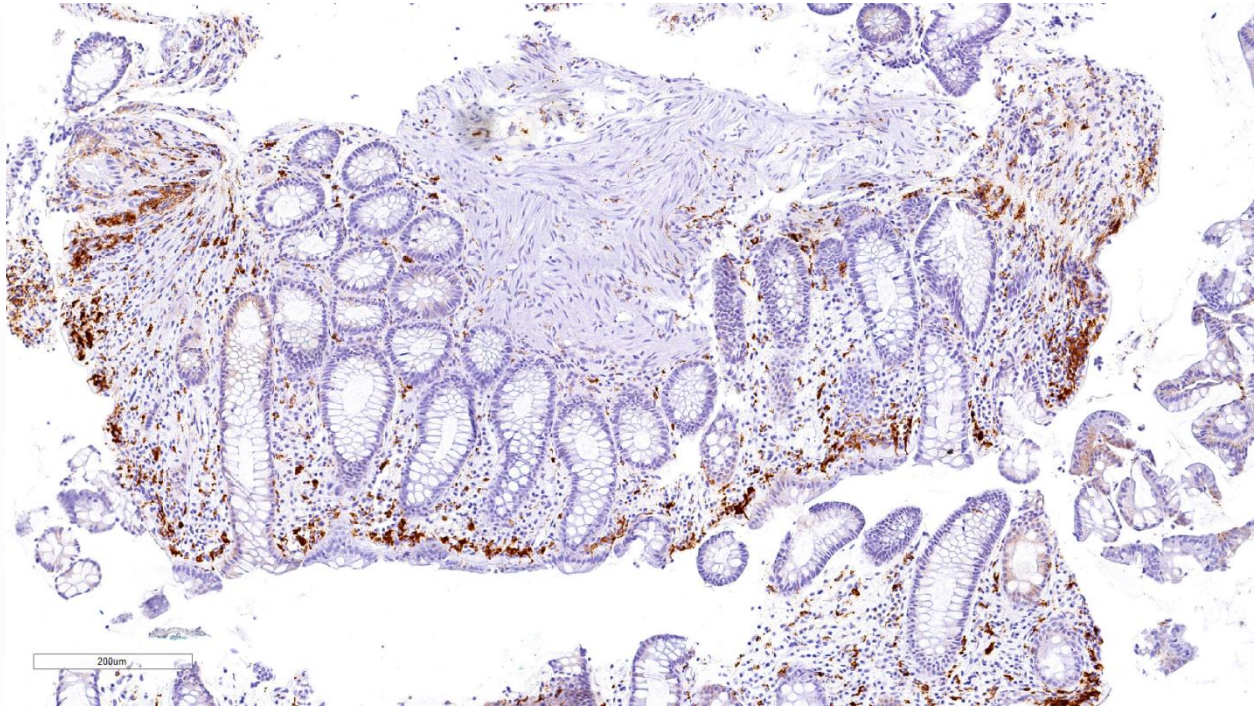
    - Changes in Post FMT gut CD68+ cells
    - Changes in Post FMT intratumoral CD8+ cells
- *Exploratory*
  - Objective response to treatment
    - iRECIST

Secondary endpoint: CD68+ in gut biopsies

- CD68 – General Marker for Antigen Presenting Cells (APC)

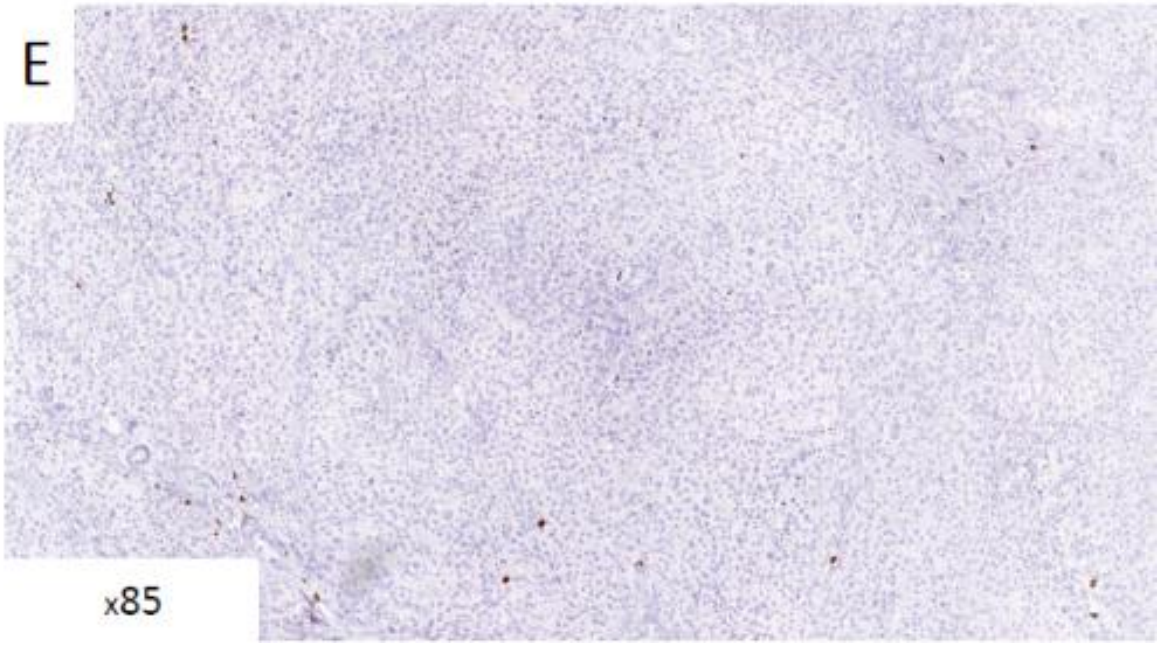


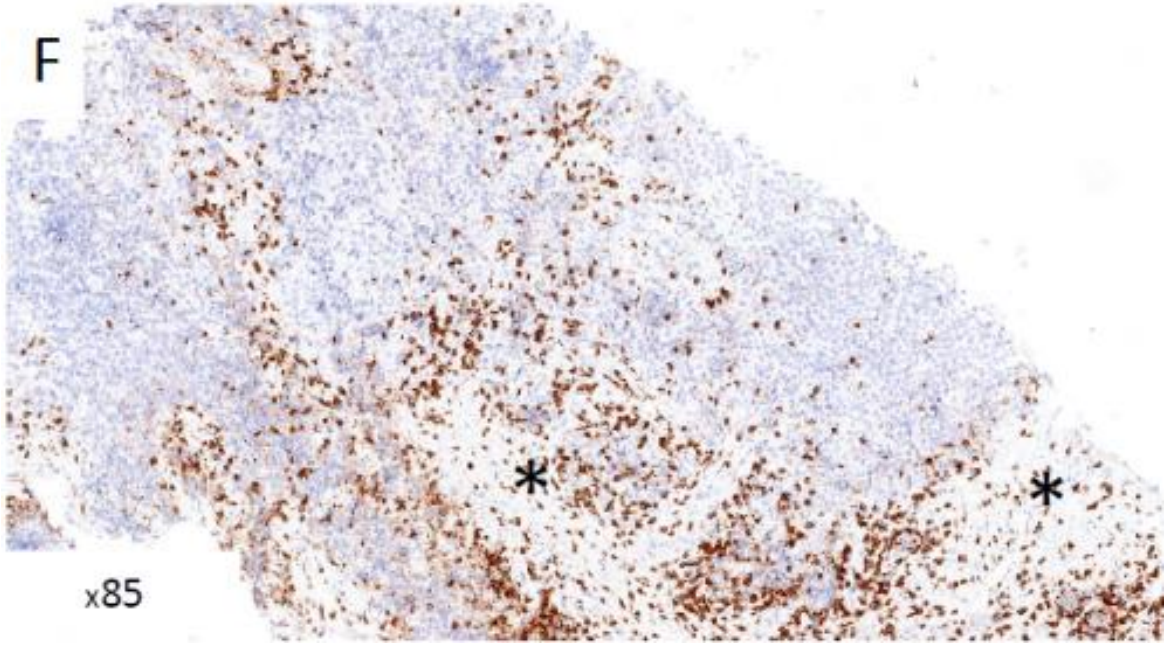


Pre

Post (31d)

Secondary endpoint: CD8+ in tumor biopsies





Pre

Post (70d) – same metastasis

Secondary endpoint: Immune alterations

The alteration occurs across donors

Recipient #	FMT Donor #	Gut CD68+ APC infiltration (cells/mm²)		Intra-tumoral CD8+ T-Cell infiltration (cells/mm²)	
		Baseline	Day 31	Baseline	Day 70
1	Donor#1	407	588	139	489
3	Donor#1	897	1057	41	736
4	Donor#2	436	569	12	233
5	Donor#1	506	567	572	N/A
6	Donor#2	140	837	59	30
7	Donor#1	294	145	92	330
8	Donor#2	180	274	152	49
9	Donor#1	160	276	85	36
10	Donor#2	353	631	153	728

Secondary endpoint: Immune alterations

The alteration occurs across donors

Recipient #	FMT Donor #	Gut CD68+ APC infiltration (cells/mm²)		Intra-tumoral CD8+ T-Cell infiltration (cells/mm²)	
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9	Donor#1	160	276	85	36
10	Donor#2	353	631	153	728

Secondary endpoint: Immune alterations

Gut		
Marker	**Direction**	**p**
CD68	↑	0.05
CD8	↓	0.09
CD4	↔	0.92

Tumor		
Marker	**Direction**	**p**
CD68	↔	0.89
CD8	↑	0.057
CD4	↔	0.56

Study aims (NCT03353402)

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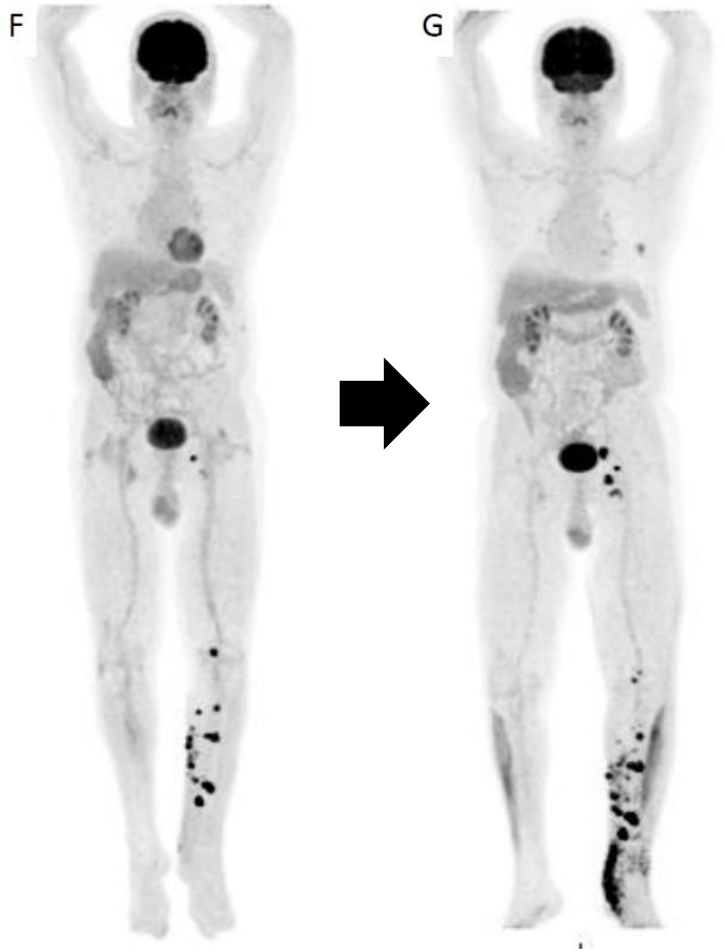
- ***Exploratory***
  - **Objective response to treatment**
    - iRECIST

Pseudoprogression (Patient #3)

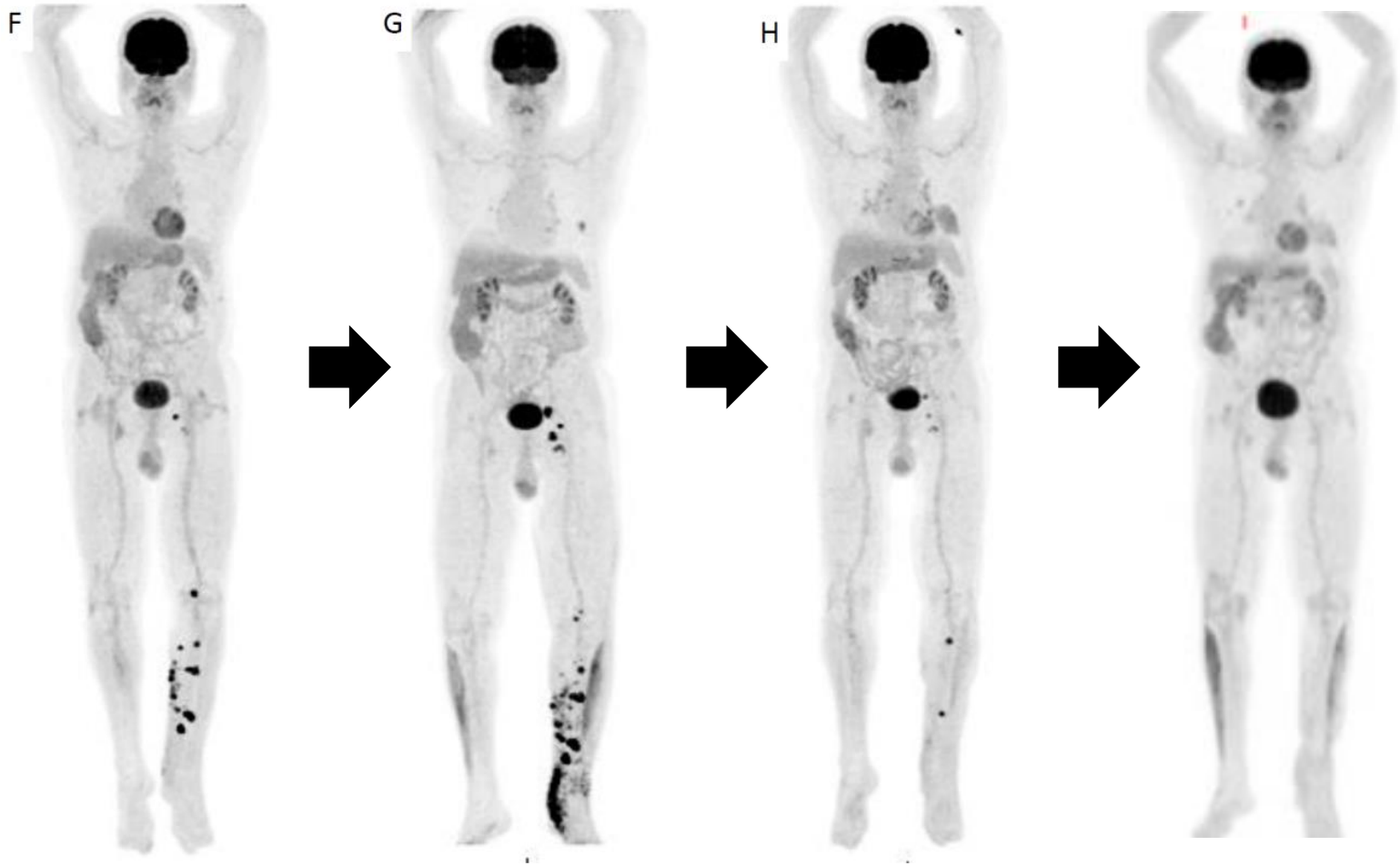


Baseline

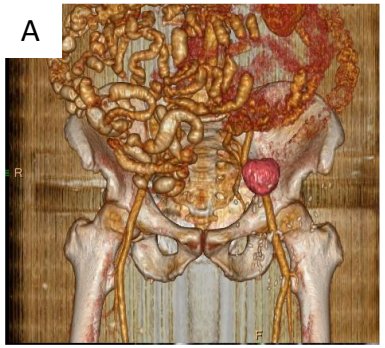
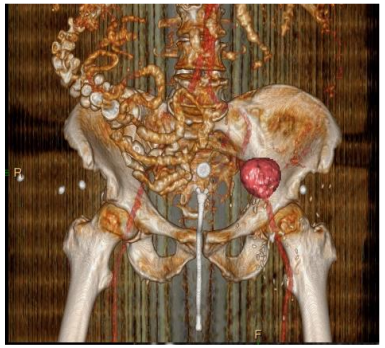
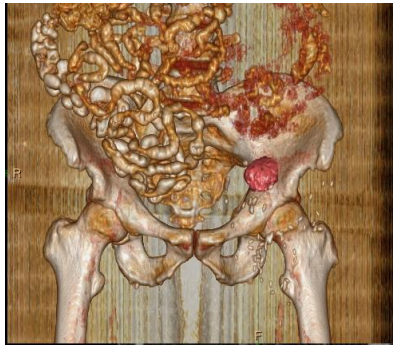
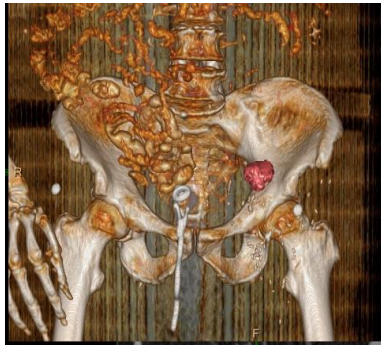
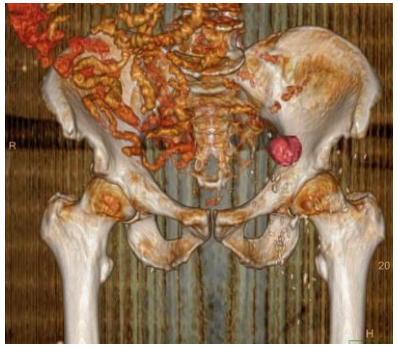
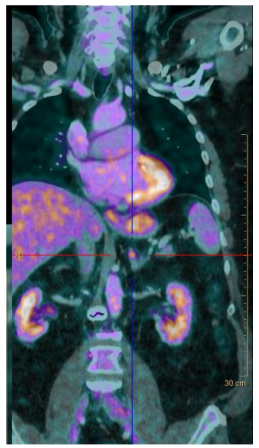
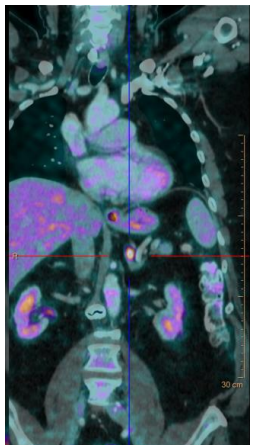
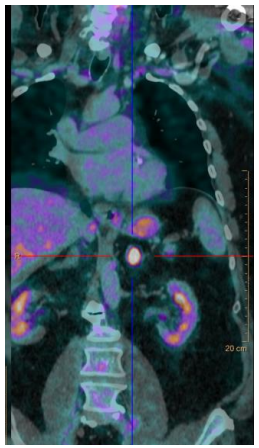
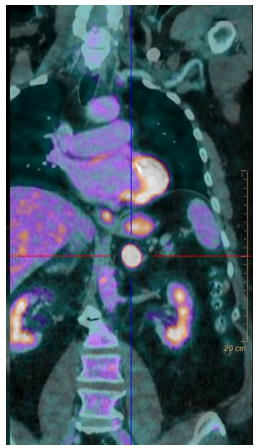
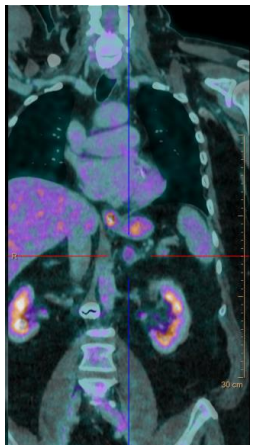
Evaluation 1

- 78y.o M, BRAF WT

Pseudoprogression and regression (Patient #3)

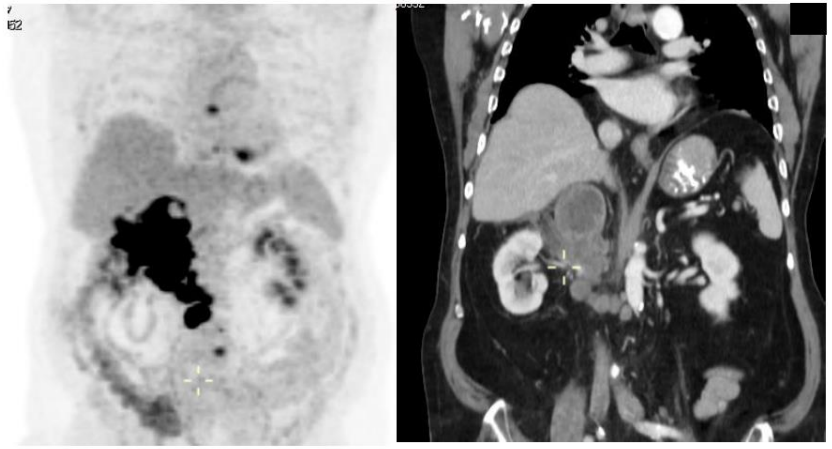


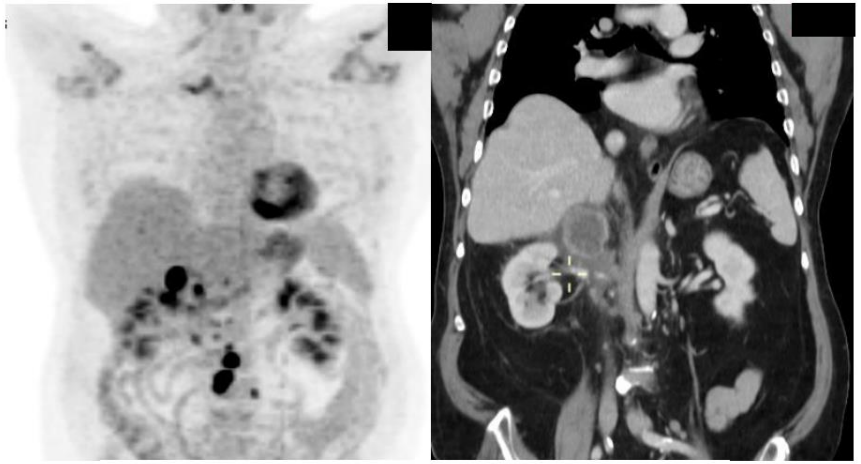
Pseudoprogression and regression (Patient #5)

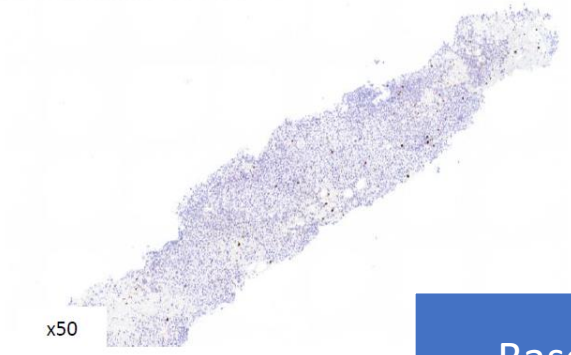
	Pre-treatment	Day 74	Day 102	Day 179	Day 235
A					
	Lesion volume in relation to baseline: 100%	Lesion volume in relation to baseline: 123%	Lesion volume in relation to baseline: 67%	Lesion volume in relation to baseline: 40%	Lesion volume in relation to baseline: 33%
B					
	SUV_{max} 4.46	SUV_{max} 7.09	SUV_{max} 9.27	SUV_{max} 13.48	SUV_{max} 3.13

Clinical effect (Patient #7)

- 66 y.o., M, BRAF V600E mutated
- Failed – Pembrolizumab, BRAF+MEK inhibitors

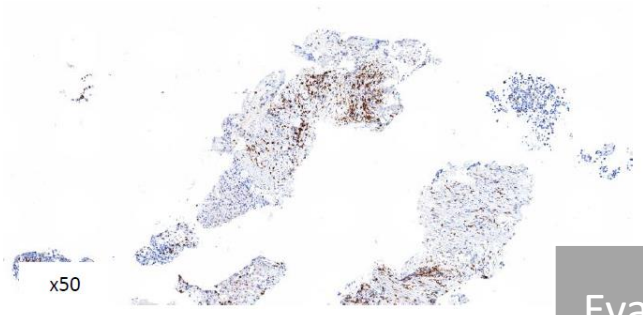






Pre-treatment

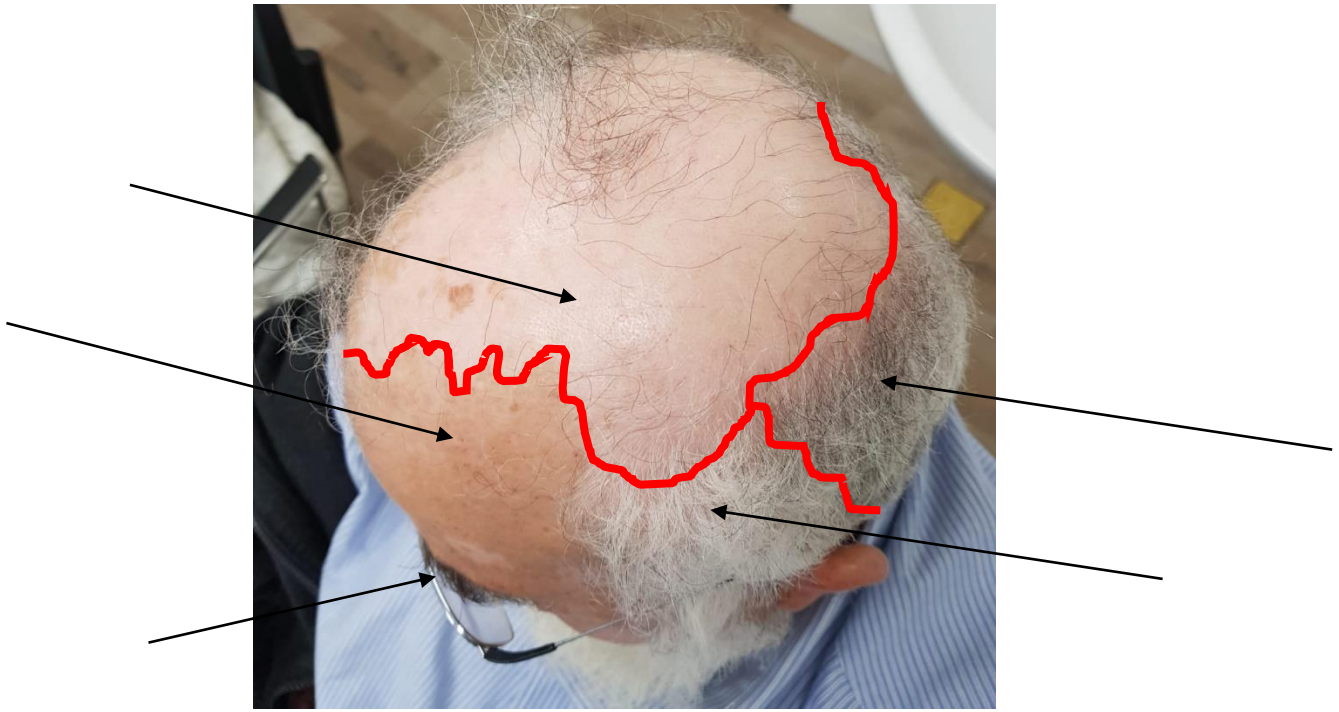
Baseline



Day 60 - 65

Evaluation 1

Clinical effect (Patient #7)



Resume immune order

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