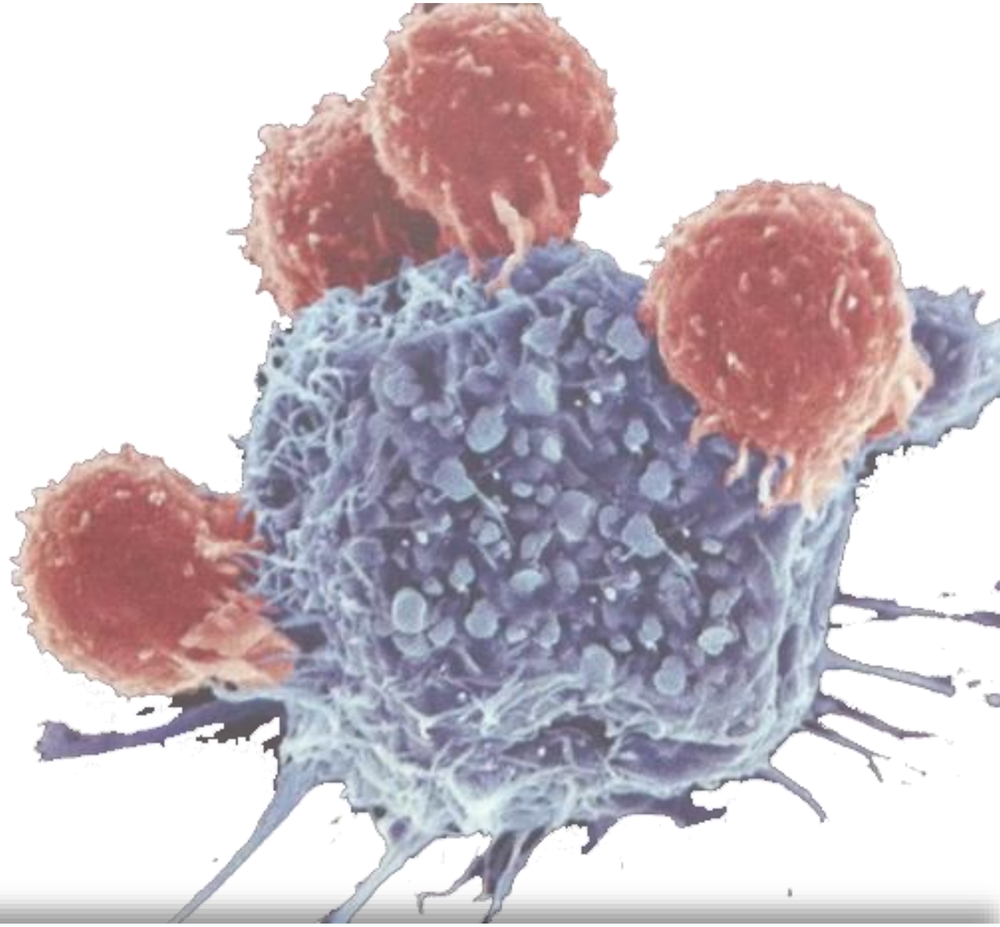
FACULTY OF MEDICINE AND HEALTH SCIENCES

DEPT. OF INTERNAL MEDICINE
PULMONARY MEDICINE

IMMUNOTHERAPY BEYOND CHECKPOINT INHIBITION:

WHY ARE WE STRUGGLING?

Karim Y. Vermaelen, MD, PhD – UZG Thoracic Oncology



BSMO

INSTITUT JULES BORDET

14th BSMO-Bordet symposium on the Integration of Molecular Biology Advances into Oncology Clinical practice | Nov 27-28 2020

UZ GENT

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CRIG

ION immuno-oncology network Ghent

CANCER IMMUNOTHERAPY: EVOLUTION AND REVOLUTION

clinical benefit

SURGERY

RADIATION

CHEMOTHERAPY

CHEMOTHERAPY COMBINATIONS

TARGETED THERAPY

TARGETED THERAPY PLUS CHEMOTHERAPY

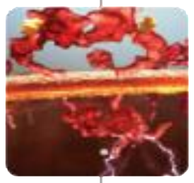
NEXT-GENERATION TARGETED THERAPY

IMMUNOTHERAPY

IMMUNOTHERAPY COMBINATIONS









1970s | 1980s | 1990s | 2000s | PRESENT

source: The Lung Cancer Project

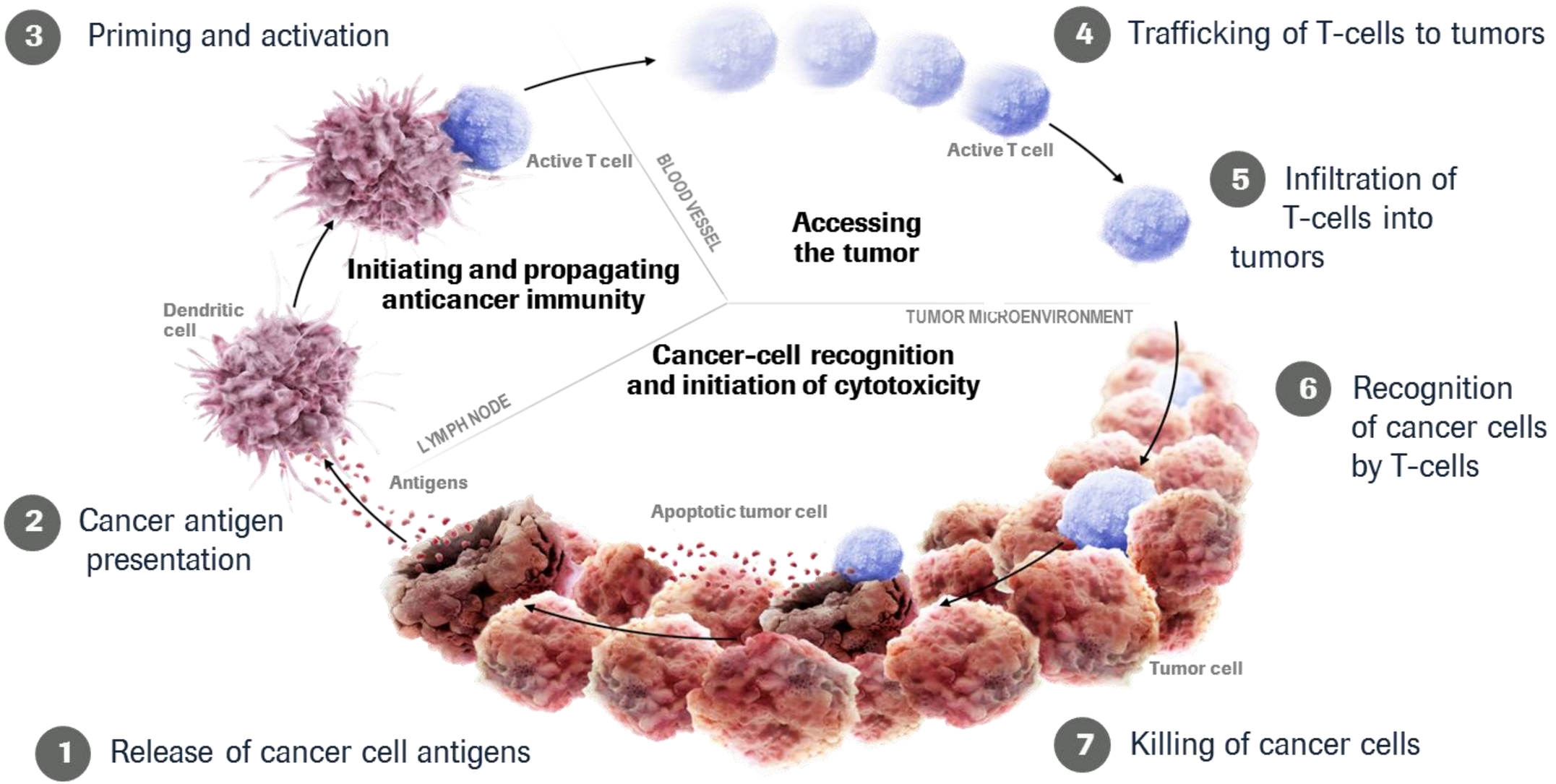
CANCER IMMUNOTHERAPY: EVOLUTION AND REVOLUTION

KNOWLEDGE GAPS IN TODAY's IMMUNO-ONCOLOGY PRACTICE

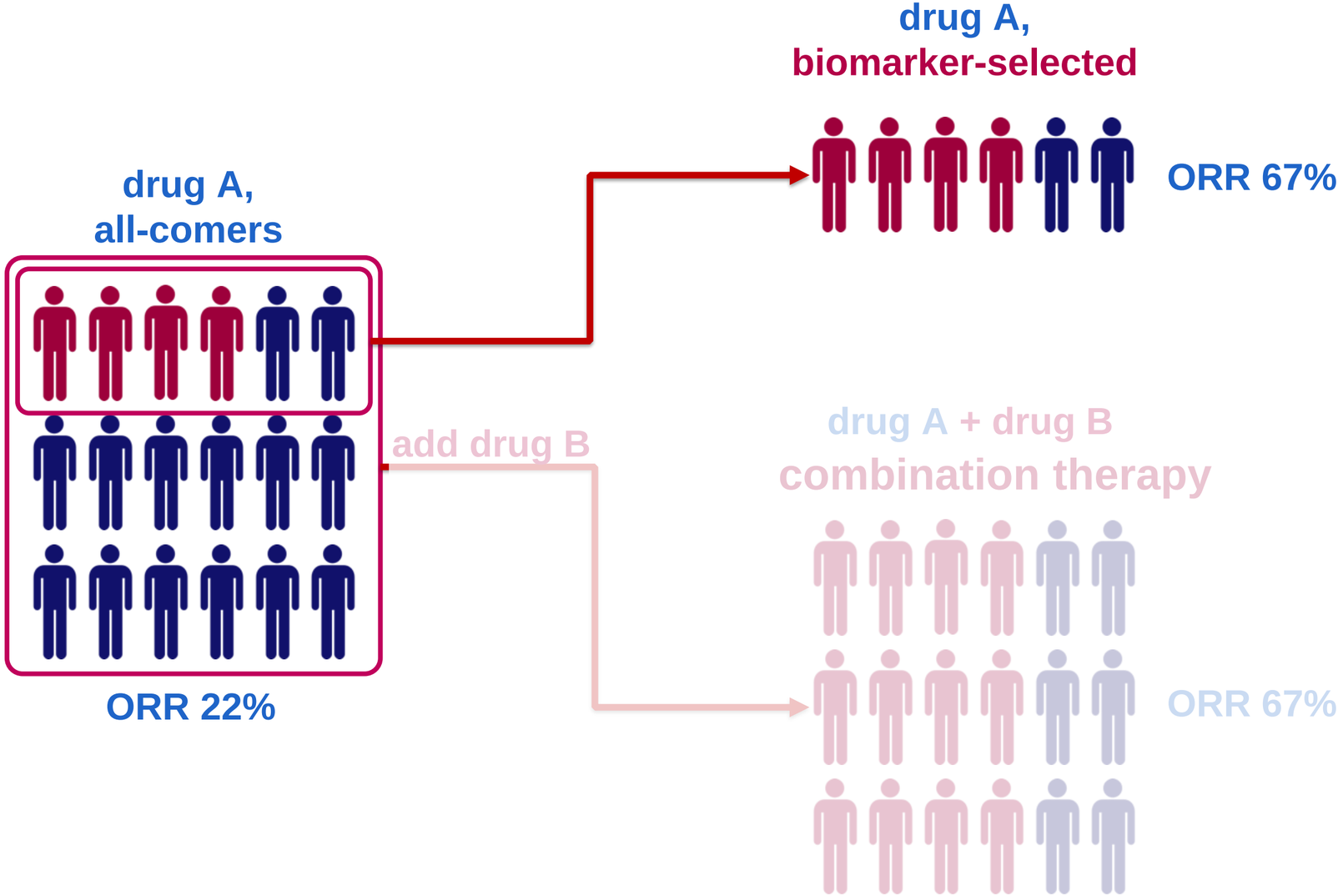
- **selection of optimal responders**
- **selection of optimal combination partner**(s)
- **understanding resistance mechanisms**
- **prediction of severe toxicity risk**
- ***mechanism of action of CPIs***

UNDERSTANDING UNDERLYING BIOLOGY

ANTI-CANCER IMMUNITY IS A MULTI-STEP PROCESS



INCREASING RESPONSE RATES: SELECTION *vs* COMBINATION

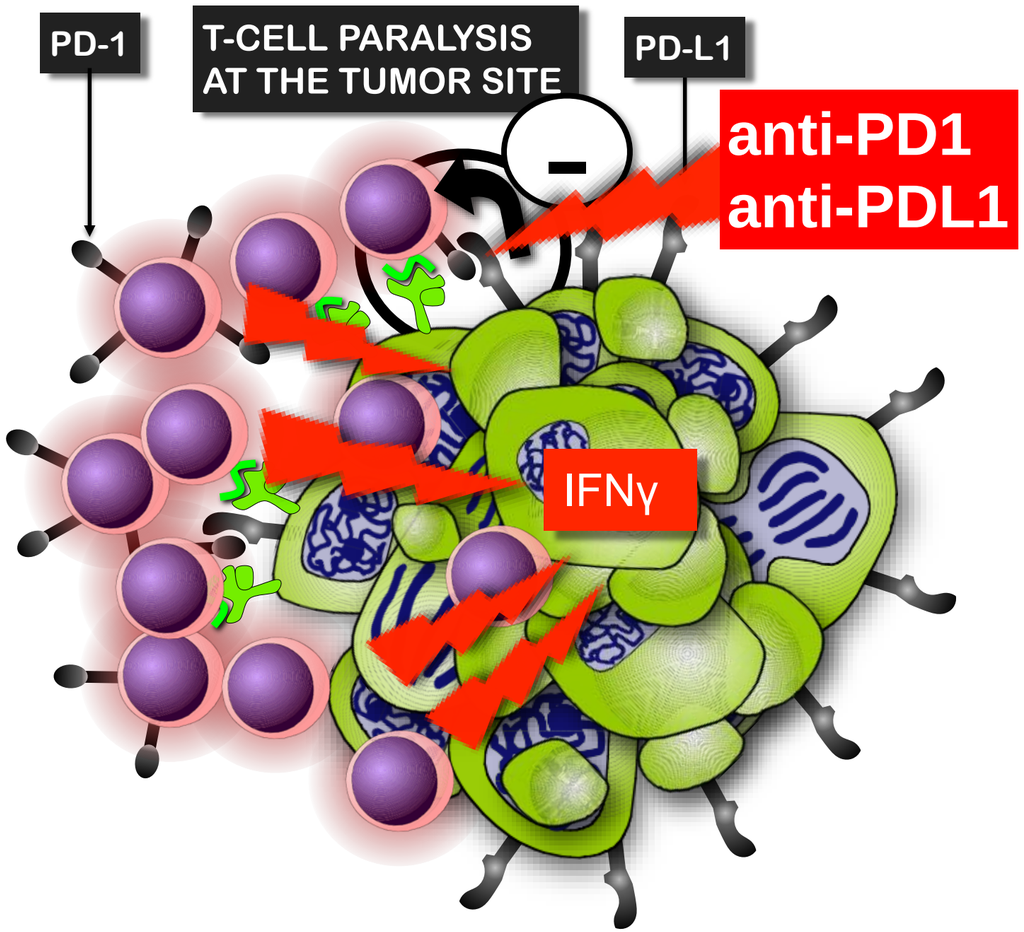


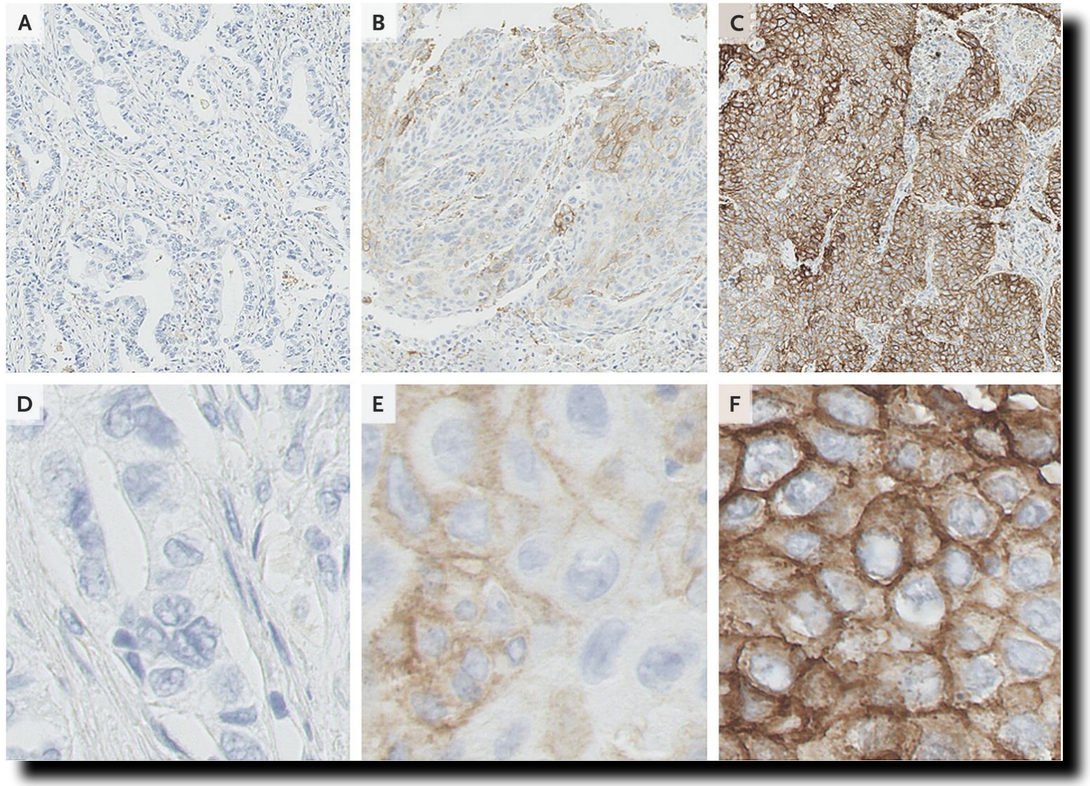
are we doing a good job at this today?

THE QUEST FOR THE IDEAL SELECTION BIOMARKER

THE QUEST FOR THE IDEAL SELECTION BIOMARKER

- PD-L1 appears on cancer cells following immune attack
- PD-L1 paralyzes immune cells carrying PD-1

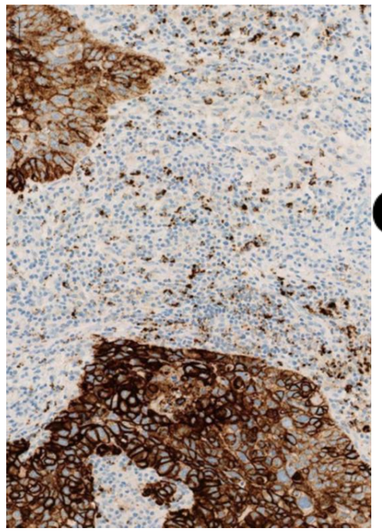


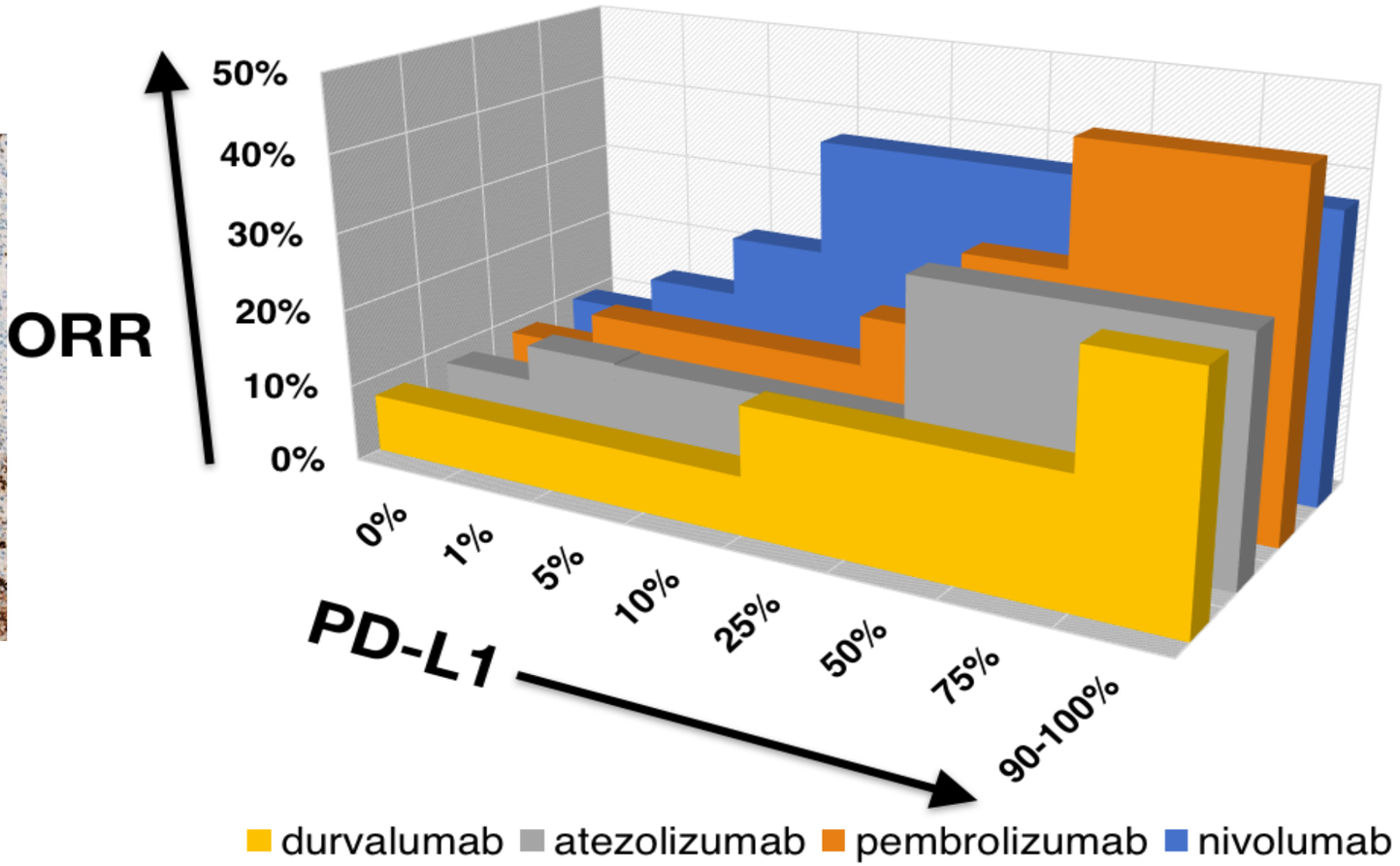


E. Garon *et al*, NEJM 2015

THE QUEST FOR THE IDEAL SELECTION BIOMARKER

Lung cancer: higher PD-L1 expression enriches for better outcomes



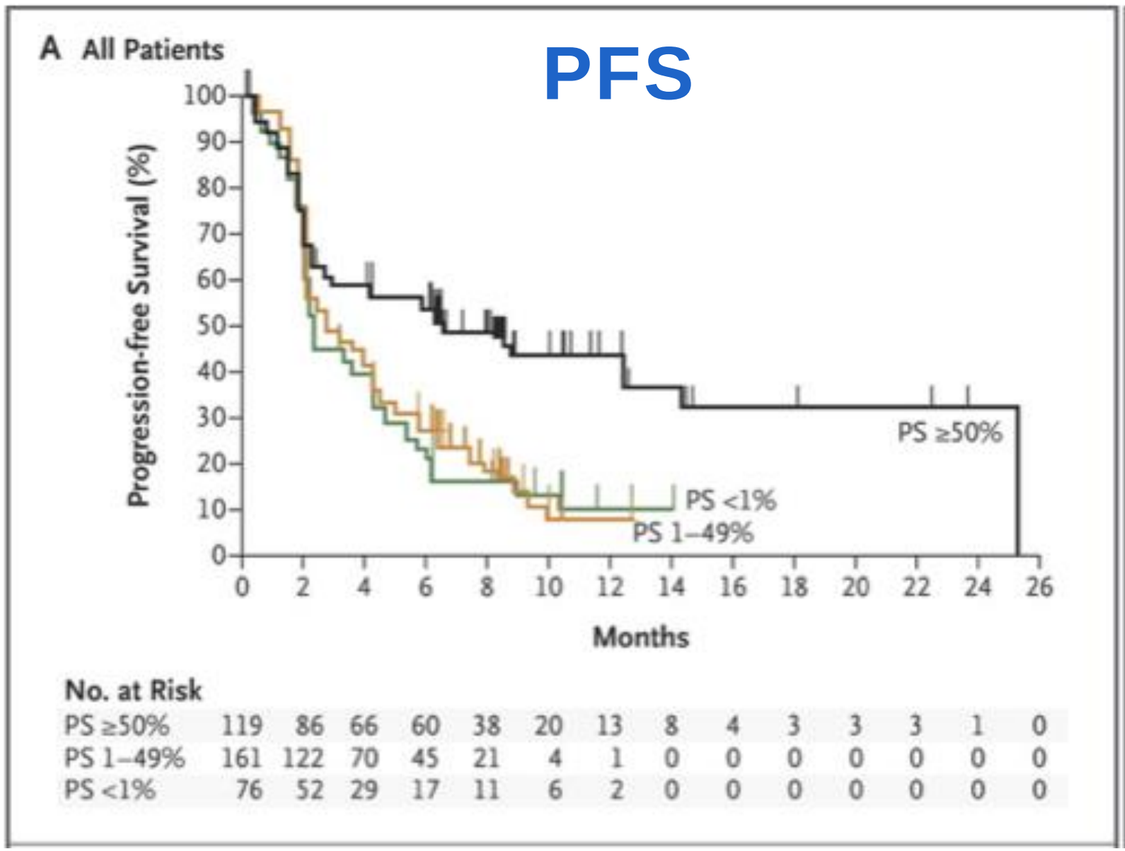


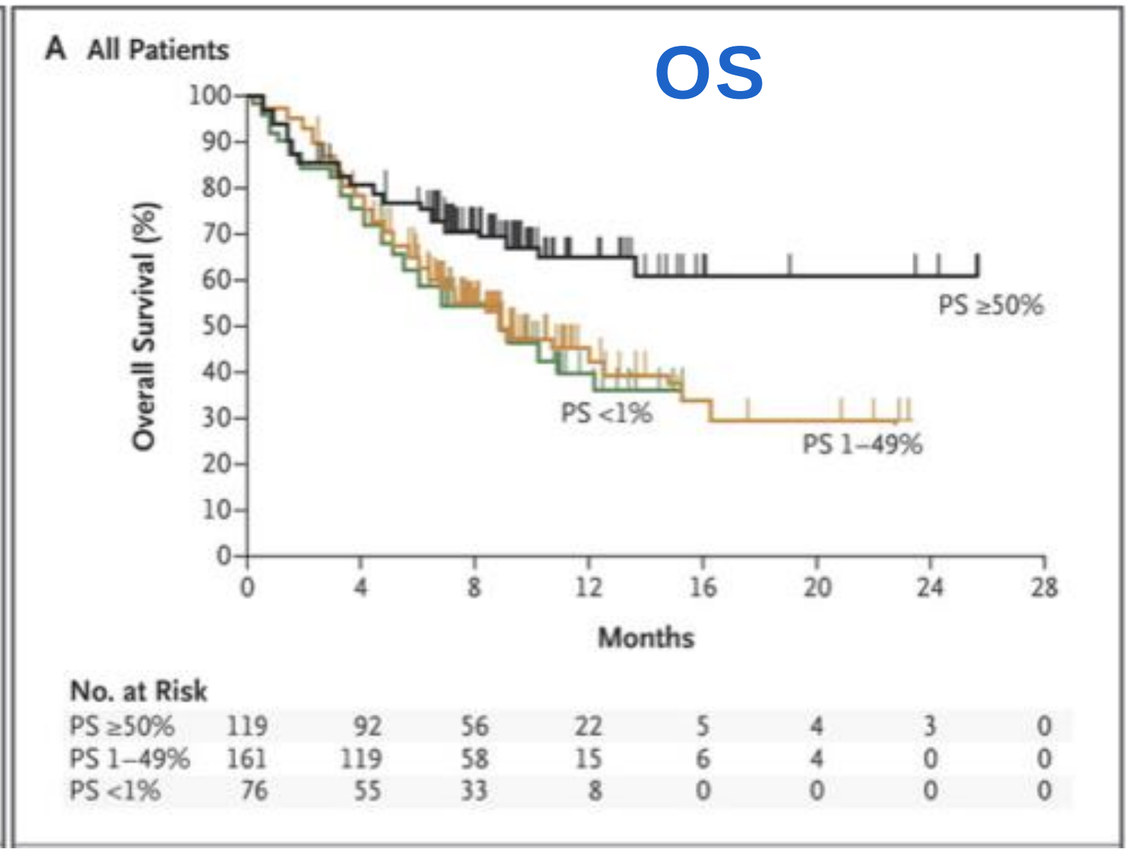
K. Vermaelen et al, Seminars in Cancer Biology 2018

THE QUEST FOR THE IDEAL SELECTION BIOMARKER

Lung cancer: higher PD-L1 expression enriches for better outcomes

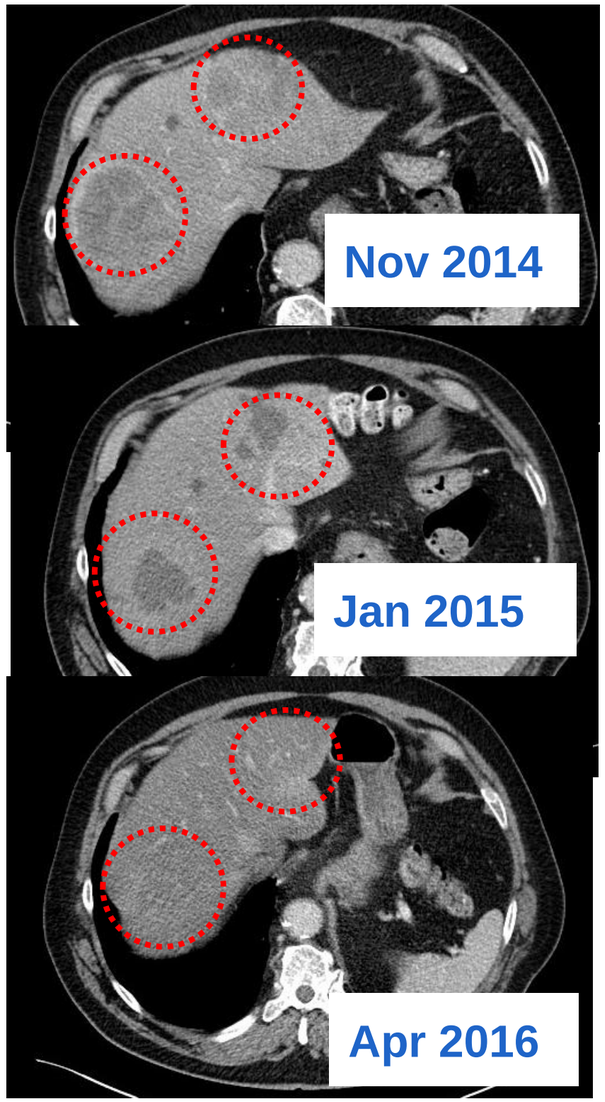
pembrolizumab ≥2nd line





E. Garon et al, NEJM 2015

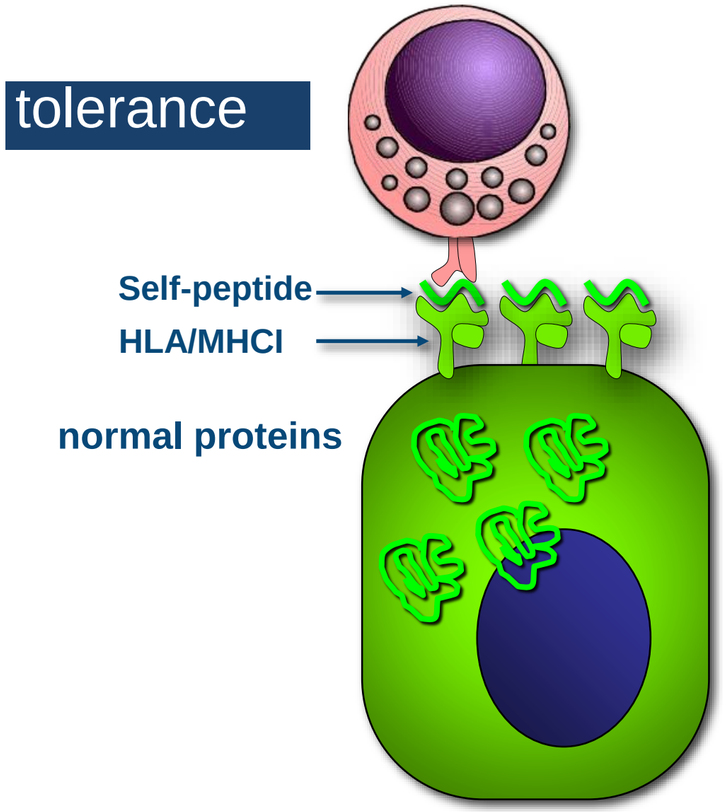
THE QUEST FOR THE IDEAL SELECTION BIOMARKER



- case: NSCLC, squamous, rapid & near complete response to durvalumab
- PD-L1 0% on primary tumor and liver metastasis

→ PD-L1 does not capture the full picture of cancer-immune system interactions

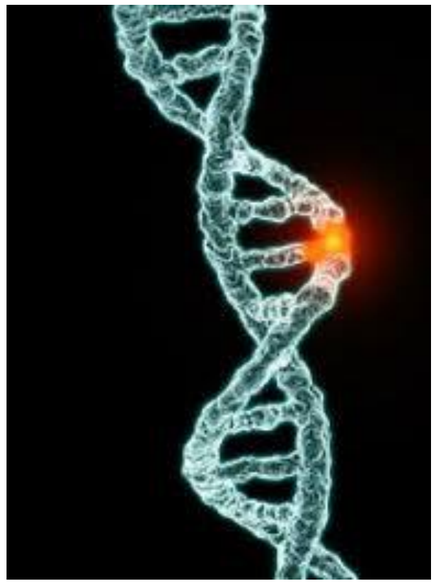
THE QUEST FOR THE IDEAL SELECTION BIOMARKER

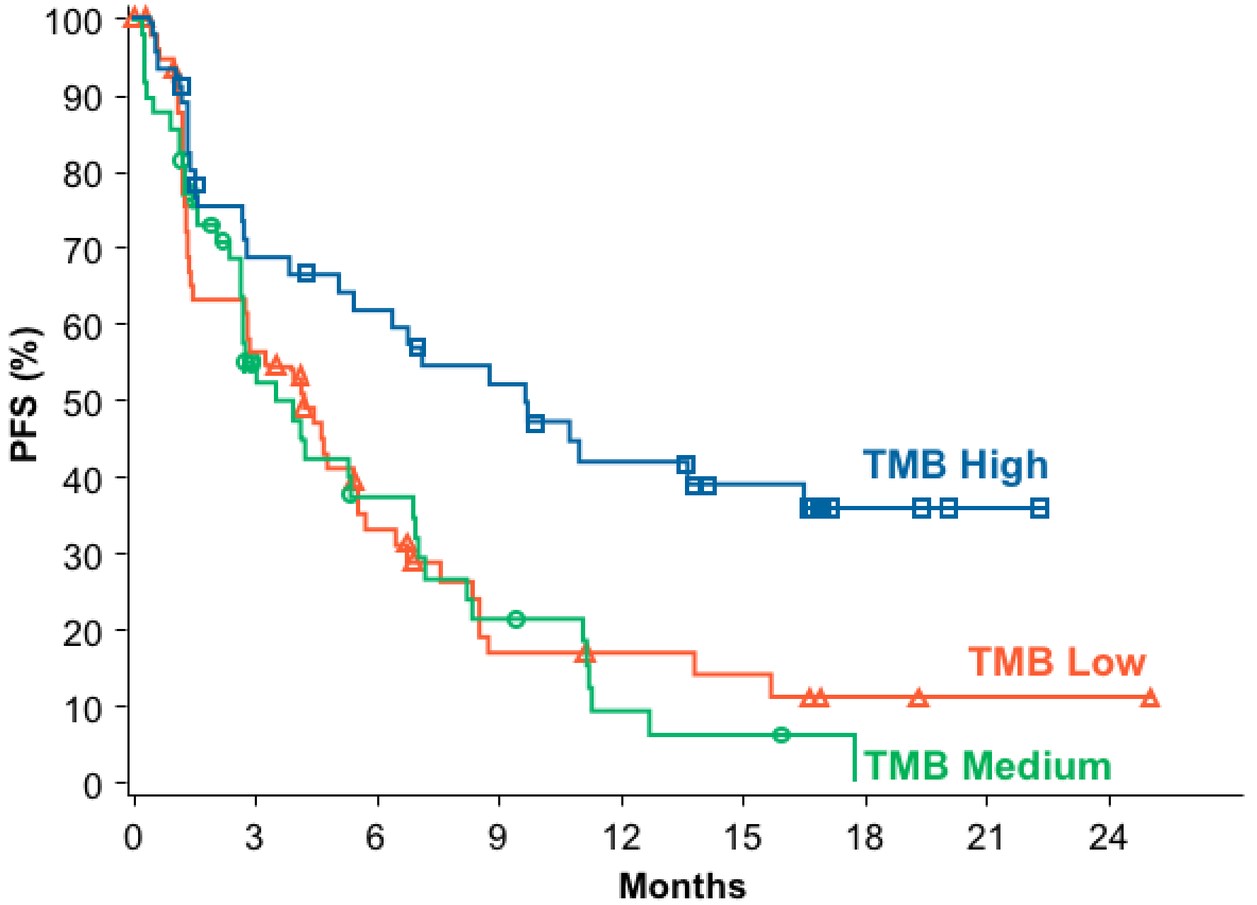


normal cell

THE QUEST FOR THE IDEAL SELECTION BIOMARKER

Tumor Mutational Burden can enrich for better response and PFS under PD1-blockade (not so clear for OS)

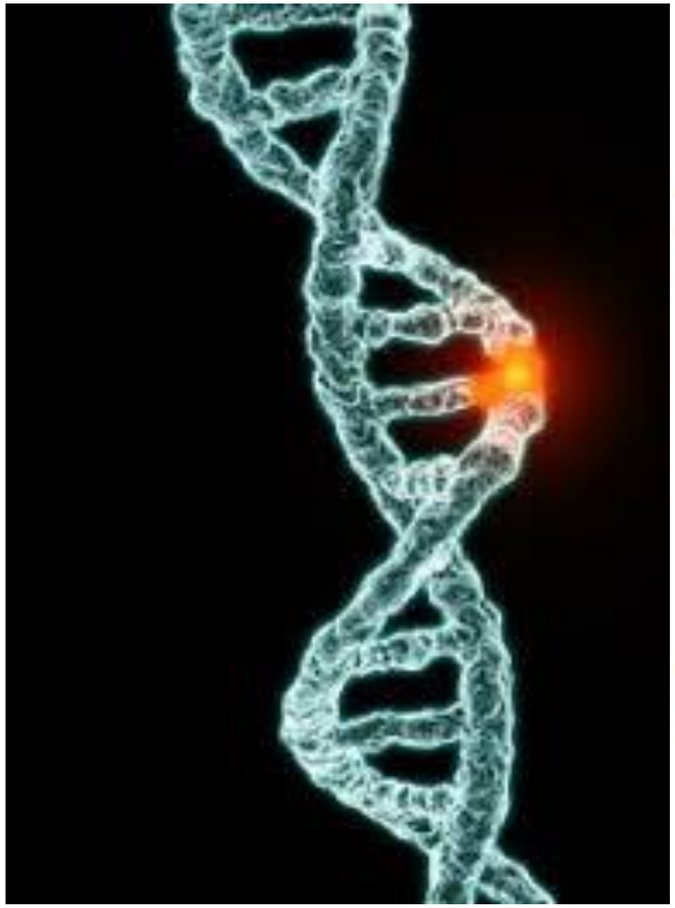


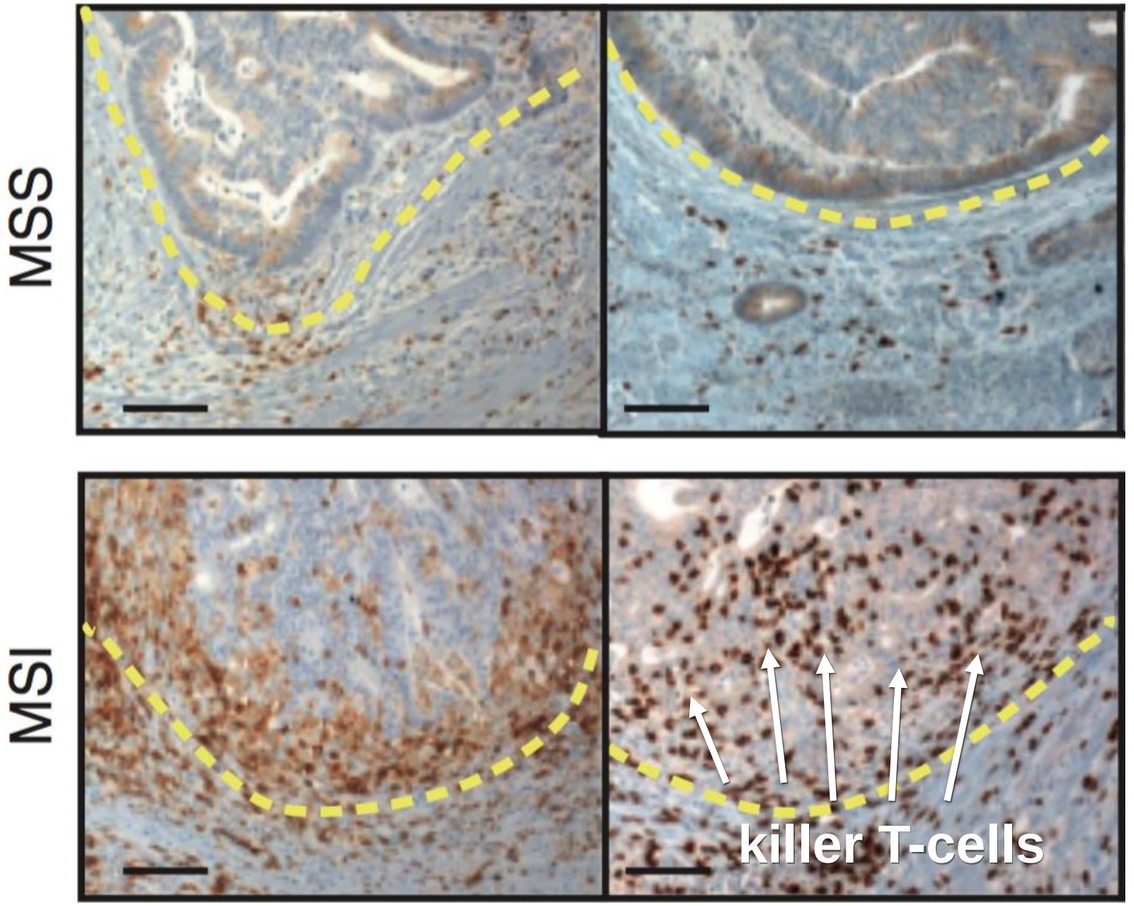


TUMOR MUTATIONAL BURDEN IS A DRIVER OF IMMUNOGENICITY

Cancers with defects in DNA repair (MSI+) are heavily infiltrated with immune cells

"MSI-test" is predictive of response to checkpoint blockade (regardless of cancer origin)

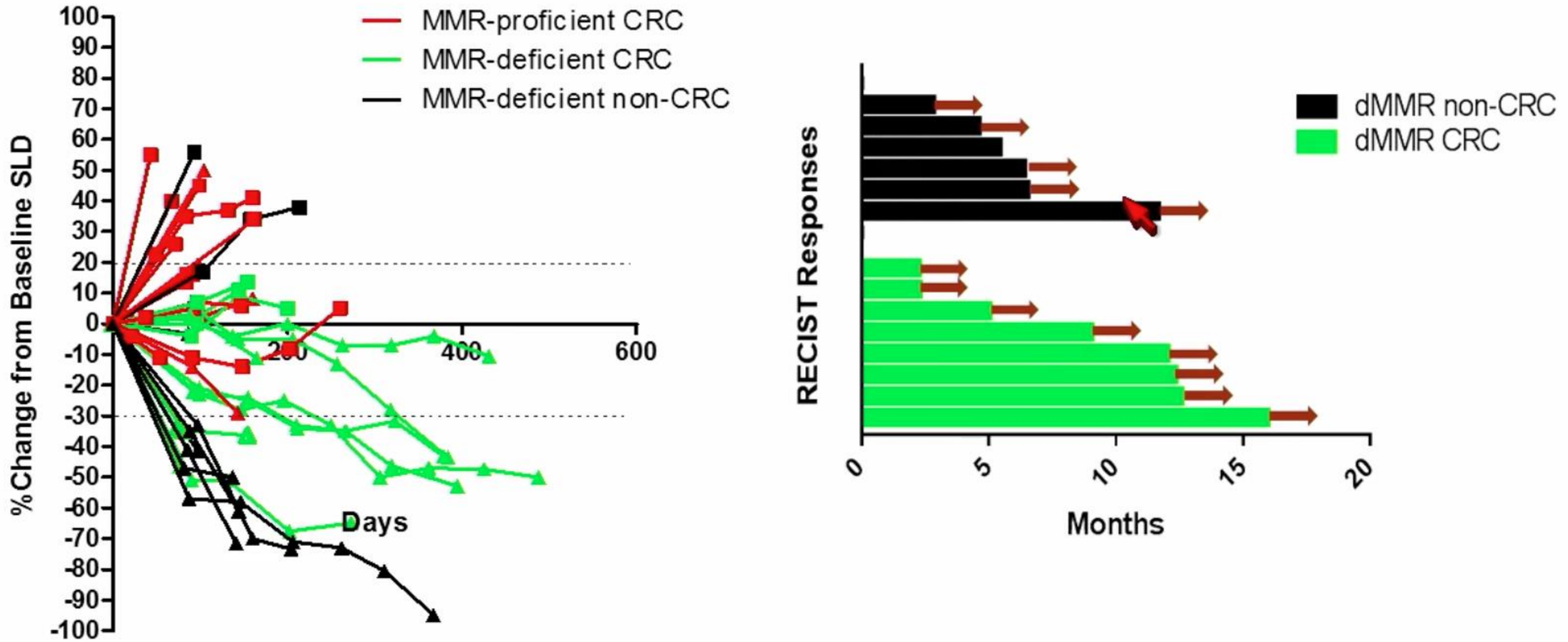




N.J. Llosa et al Cancer Discovery 2014

TUMOR MUTATIONAL BURDEN IS A DRIVER OF IMMUNOGENICITY

Cancers with defects in DNA repair (MSI+) are exceptional responders to anti-PD1
(regardless of organ origin)



Dung T. Le ASCO 2015

TUMOR MUTATIONAL BURDEN IS A DRIVER OF IMMUNOGENICITY

FDA News Release

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

SHARE | TWEET | LINKEDIN | PIN IT | EMAIL | PRINT

For Immediate Release May 23, 2017

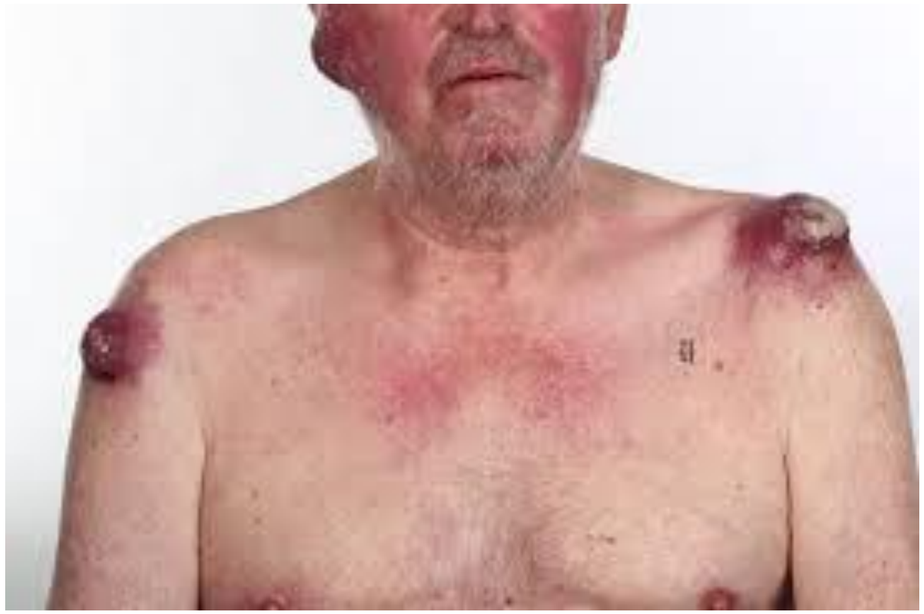
Release

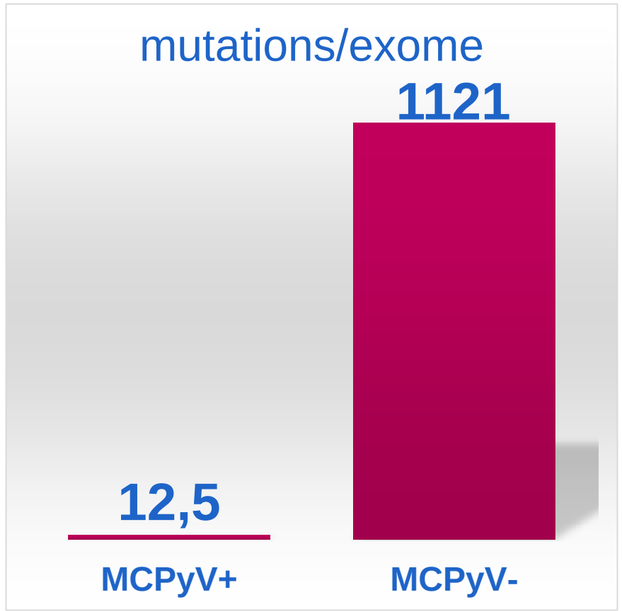
The U.S. Food and Drug Administration today granted accelerated approval to a treatment for patients whose cancers have a specific genetic feature (biomarker). This is the first time the agency has approved a cancer treatment based on a common biomarker rather than the location in the body where the tumor originated.

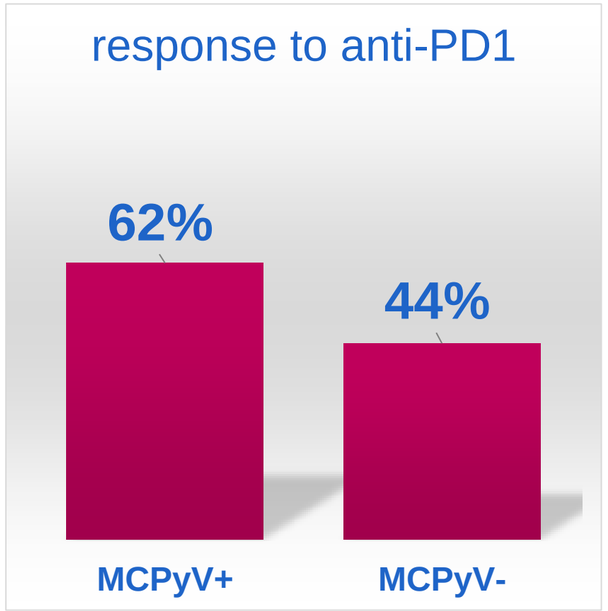
Keytruda (pembrolizumab) is indicated for the treatment of adult and pediatric patients with unresectable or metastatic solid tumors that have been identified as having a biomarker referred to as microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR). This indication covers patients with solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options and patients with colorectal cancer that has progressed following treatment with certain chemotherapy drugs.

MUTATIONAL BURDEN: QUANTITY *vs* QUALITY?

NOT ALL MUTATIONS ARE CREATED EQUAL
MERKEL CELL CARCINOMA: polyomavirus+ en polyomavirus-



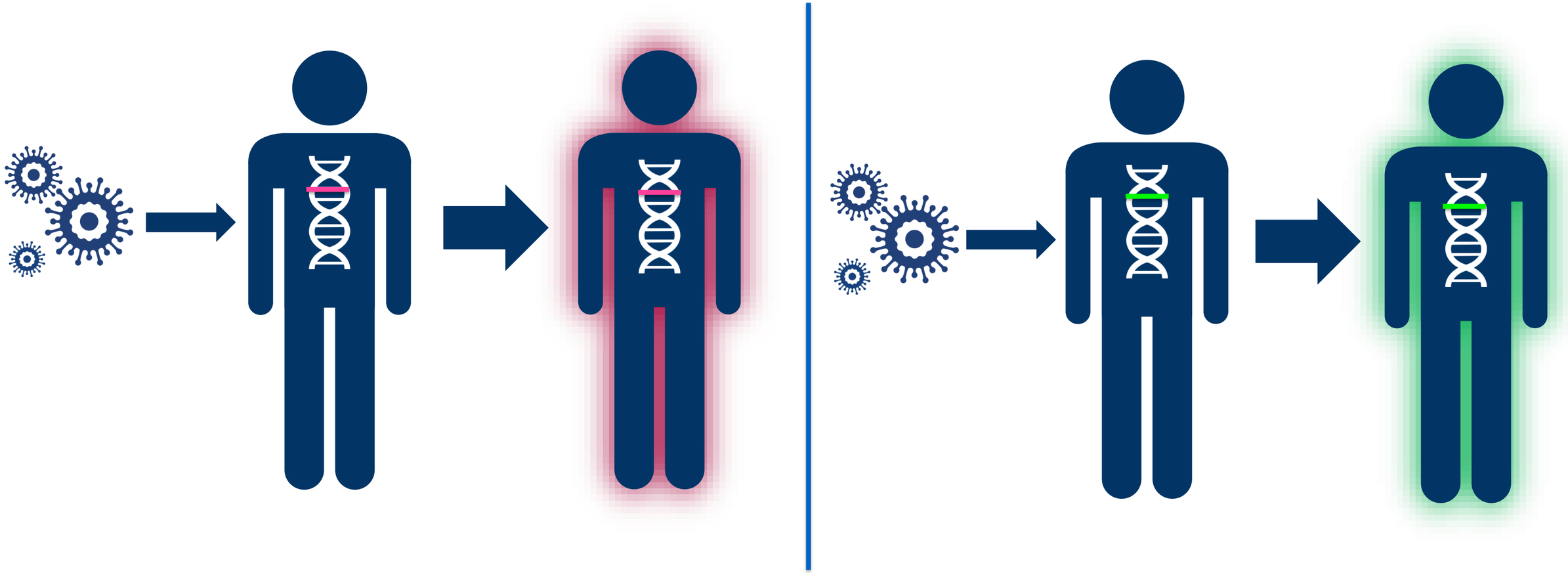




Adapted from: G. Goh et al, Oncotarget 2016, P. Nghiem et al, NEJM 2016

IS RESPONSE TO IMMUNOTHERAPY IN THE “HOST” GENES?

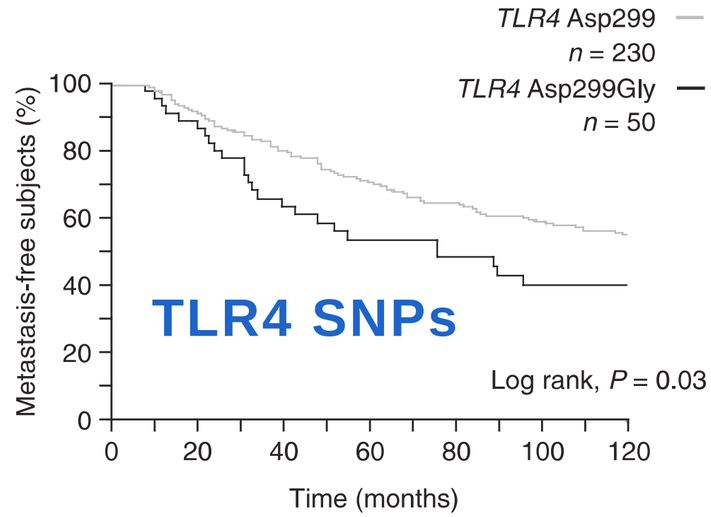
germline polymorphisms in immune-related genes determine the diversity in immune responses to pathogens



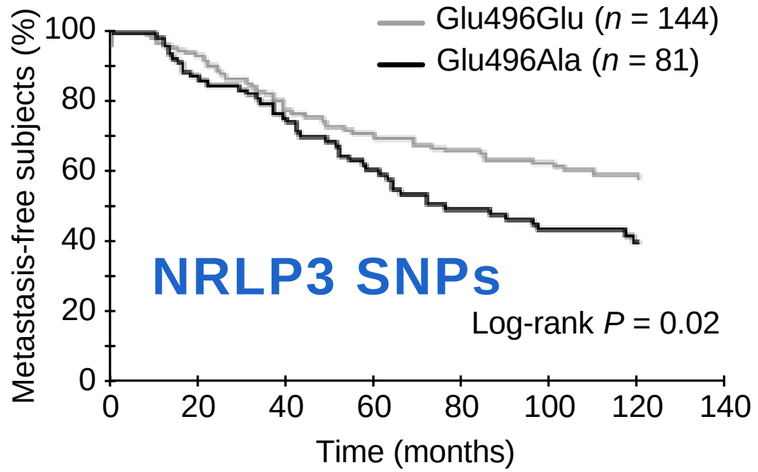
“HOST” FACTORS: SNPs in IMMUNE-RELATED GENES

germline polymorphisms in immune-related genes impact therapeutic efficacy of chemotherapy and immune checkpoint inhibition

RFS%



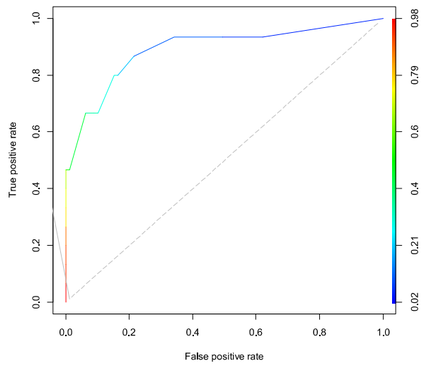
RFS%

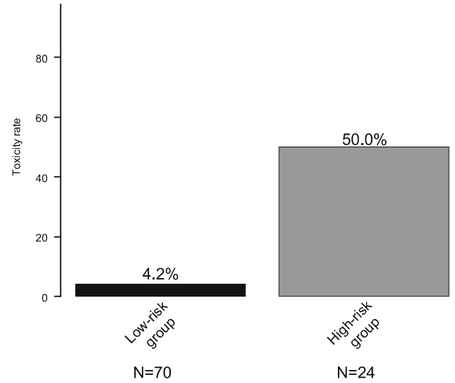


Apetoh et al, Nat Med 2007, Ghiringelli et al, Nat Med 2009

5-immune gene SNP signature

toxicity





6-immune gene SNP signature

ORR%

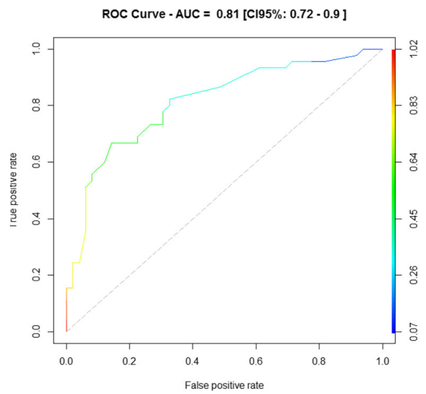


Fig. 1 ROC curves representation and AUC estimation for predictive model

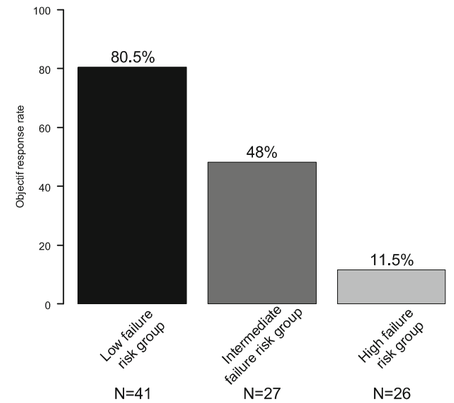
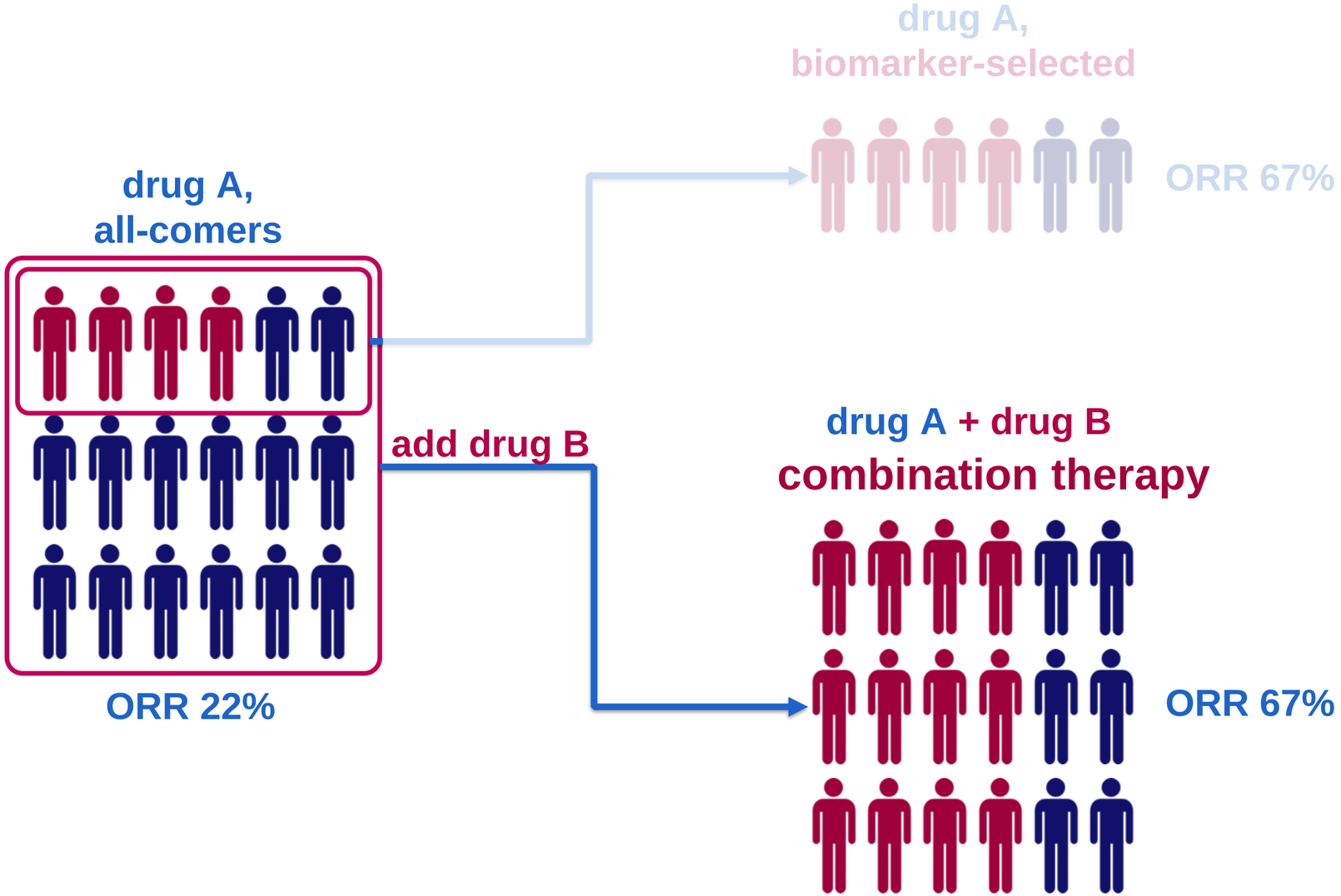


Fig. 2 Patients distribution in the different risk groups according on the predictive model

Refae et al, Invetigational New Drugs 2019

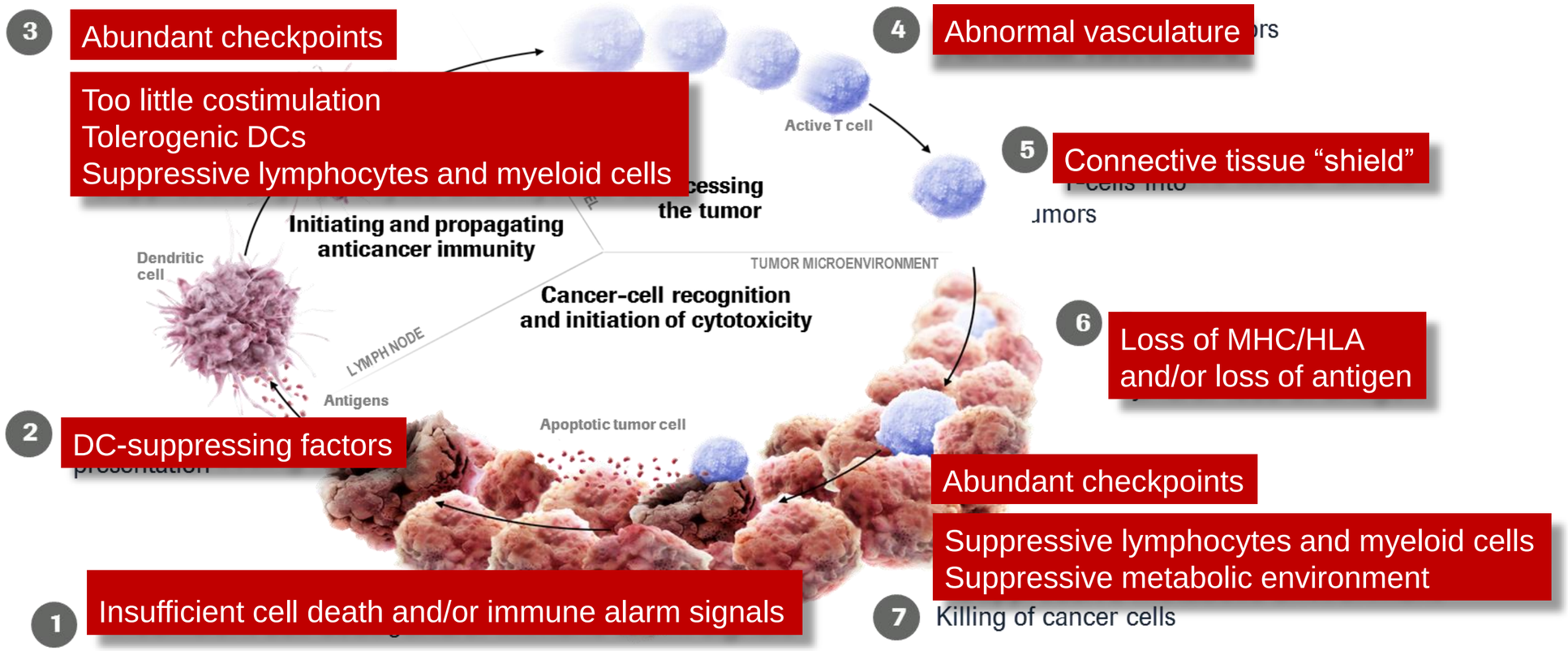
THE QUEST FOR THE OPTIMAL I-O COMBINATION THERAPY

INCREASING RESPONSE RATES: SELECTION *vs* COMBINATION



THE QUEST FOR THE RIGHT I-O COMBINATION THERAPY

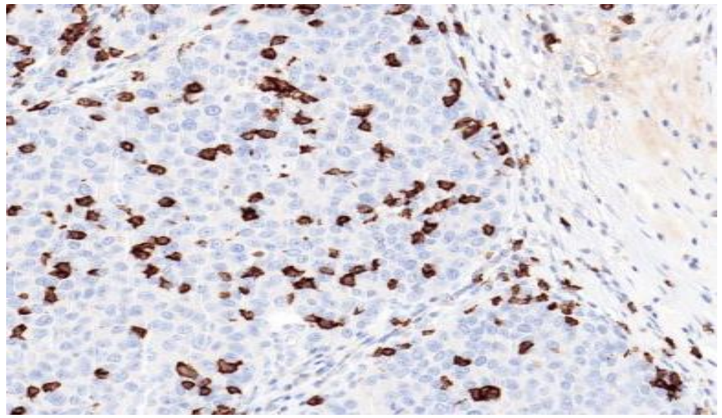
Designing optimal combination immunotherapies requires a comprehensive understanding of the tumor “immune climate”



THE QUEST FOR THE RIGHT I-O COMBINATION THERAPY

Designing optimal combination immunotherapies requires a comprehensive understanding of the tumor “immune climate”

INFLAMED



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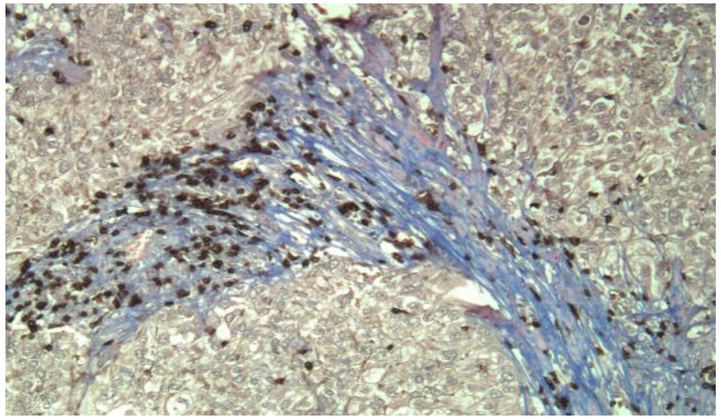
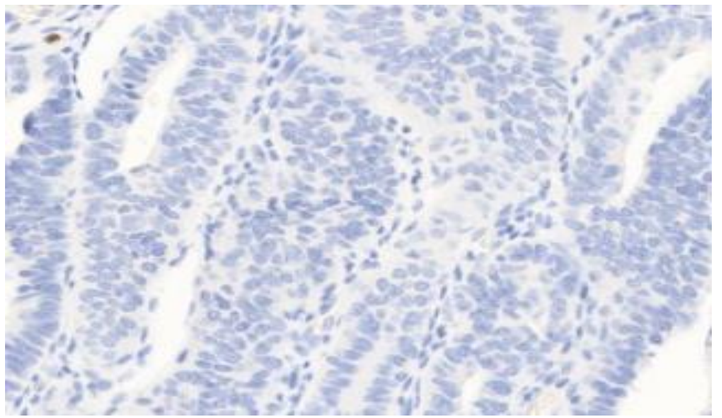


IMMUNE DESERT



Essential T-cell activity required

KILL **tumour**	**INFILTRATE** **tumour**	**GENERATE** **active, tumour-directed T cells**
→ **”Just” add checkpoint inhibitor**	→ **Normalize vasculature**, disrupt stromal shield	→ **Increase immune priming** add anti-CTLA4, chemo- or radiotherapy, *vaccines, …*

Chen and Mellman. Immunity 2013; Hegde, et al. Clin Cancer Res 2016; Kim and Chen. Ann Oncol 2016; Chen and Mellman. Nature 2017

THE QUEST FOR THE RIGHT I-O COMBINATION THERAPY

conventional cytotoxic therapies (chemo, radiation) + immunotherapy: the “one-two punch” strategy

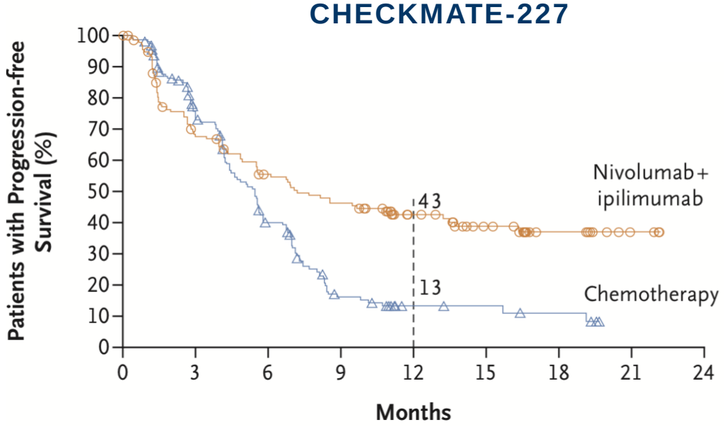
1.

2.

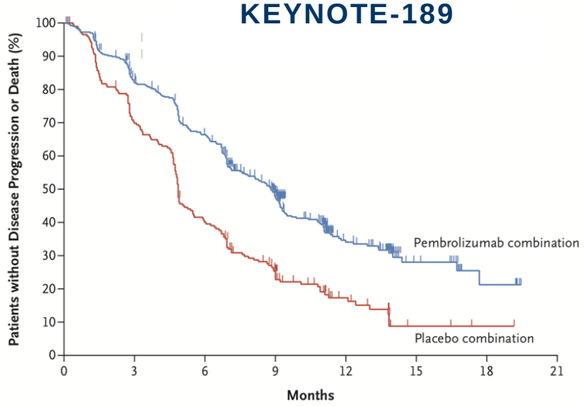
THE QUEST FOR THE RIGHT I-O COMBINATION THERAPY

Combination immunotherapy can push the performance of IO monotherapy upward
→ 2018: **7** phase III combination trials in 1st line advanced NSCLC

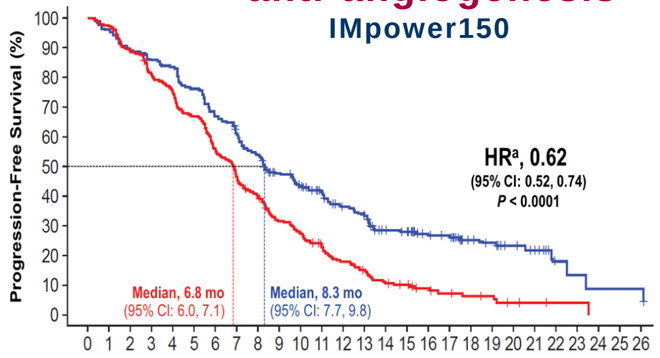
I-O + I-O
CHECKMATE-227



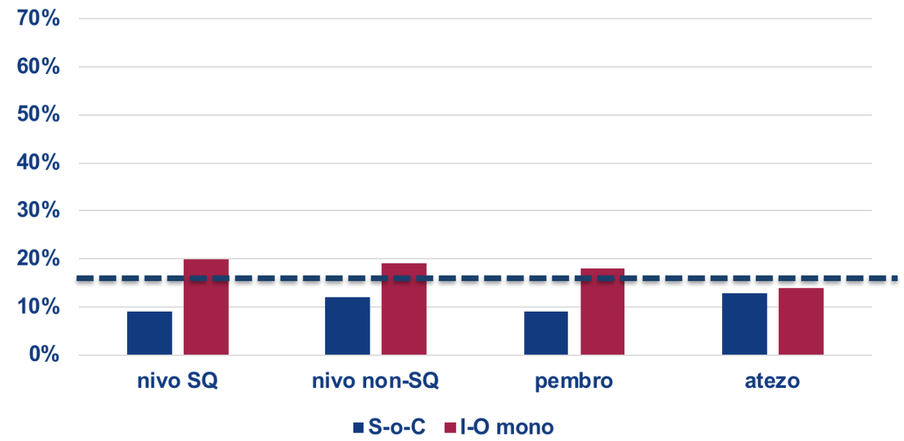
I-O + chemo
KEYNOTE-189



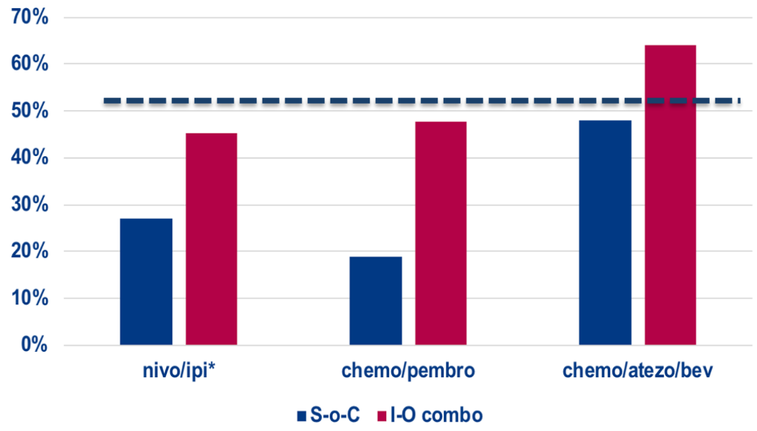
I-O + chemo +anti-angiogenesis
IMpower150



Response rates monotherapy



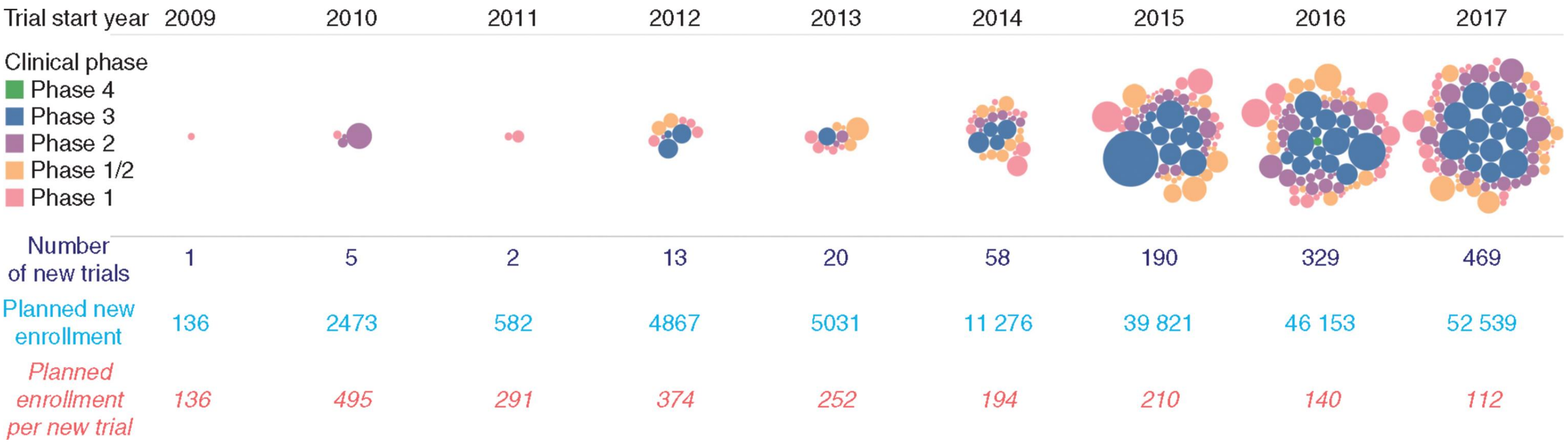
Response rates combo therapies



K. Vermaelen 2020

THE QUEST FOR THE RIGHT I-O COMBINATION THERAPY

The wild proliferation of immuno-oncology combination trials

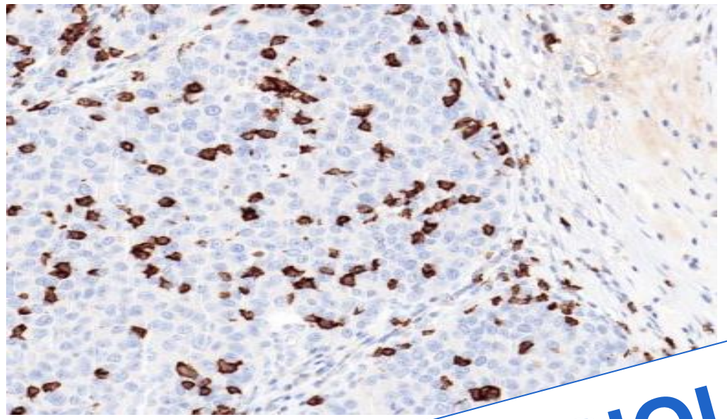


From: Comprehensive analysis of the clinical immuno-oncology landscape

Ann Oncol. 2017;29(1):84-91. doi:10.1093/annonc/mdx755

THE QUEST FOR THE RIGHT I-O COMBINATION THERAPY

INFLAMED



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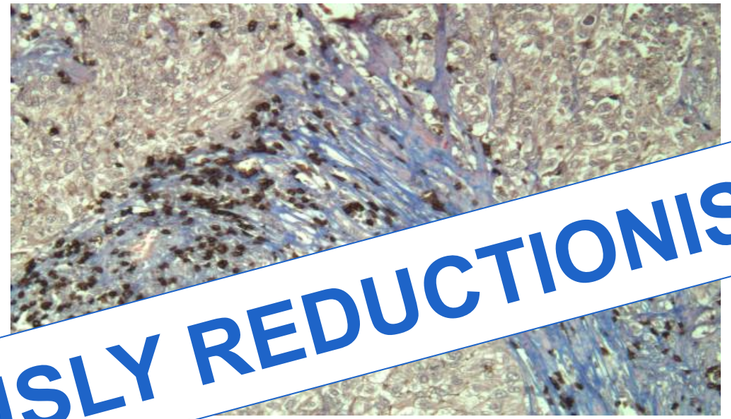


IMMUNE DESERT

SERIOUSLY REDUCTIONIST VIEW

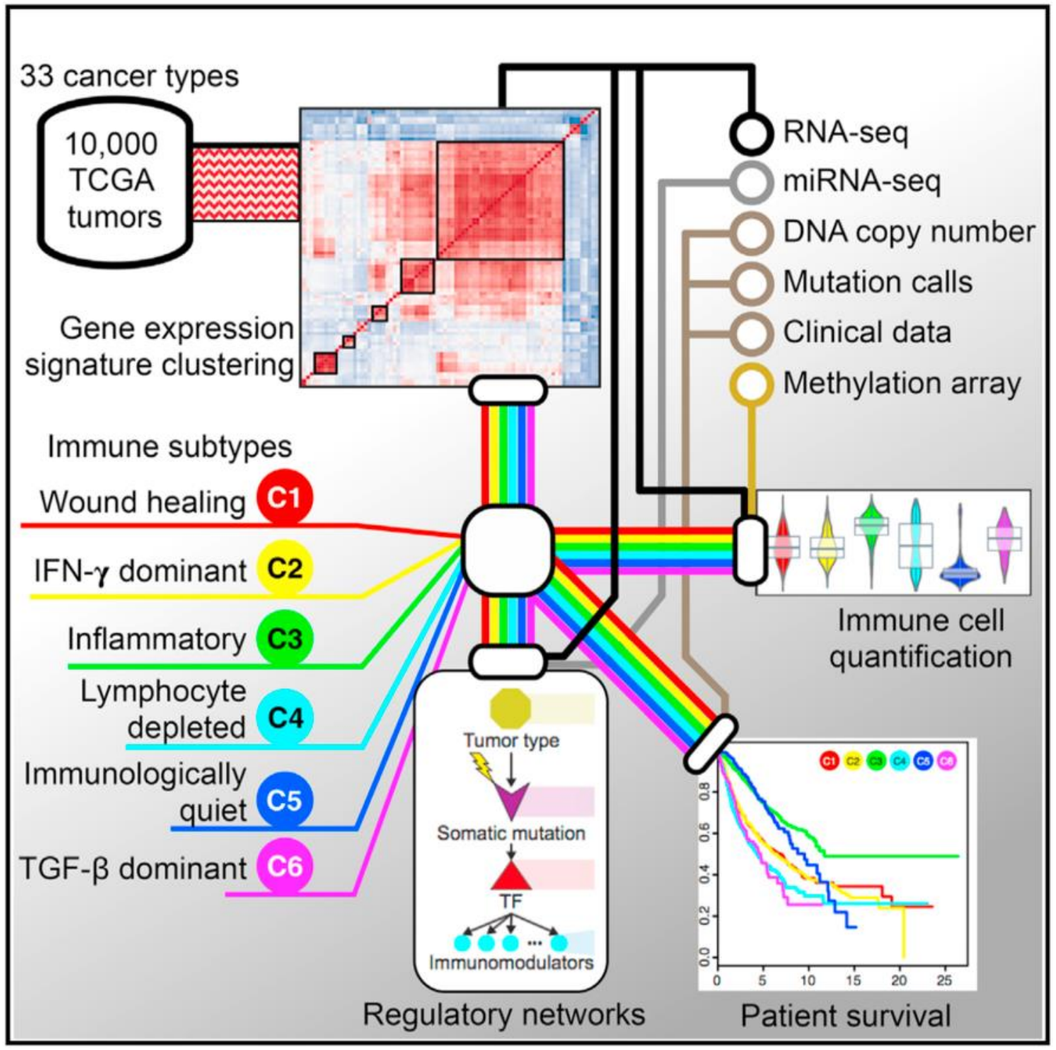
Essential T

KILL tumour	**INFILTRATE** tumour	**GENERATE** active, tumour-directed T cells
→ **"Just" add checkpoint inhibitor**	→ **Normalize vasculature**, disrupt stromal shield	→ **Increase immune priming** add anti-CTLA4, chemo- or radiotherapy, *vaccines, …*

Chen and Mellman. Immunity 2013; Hegde, et al. Clin Cancer Res 2016; Kim and Chen. Ann Oncol 2016; Chen and Mellman. Nature 2017

THE QUEST FOR THE RIGHT I-O COMBINATION THERAPY

The “tumor immunome”: the more we look, the more complex it gets



The Immune Landscape of Cancer

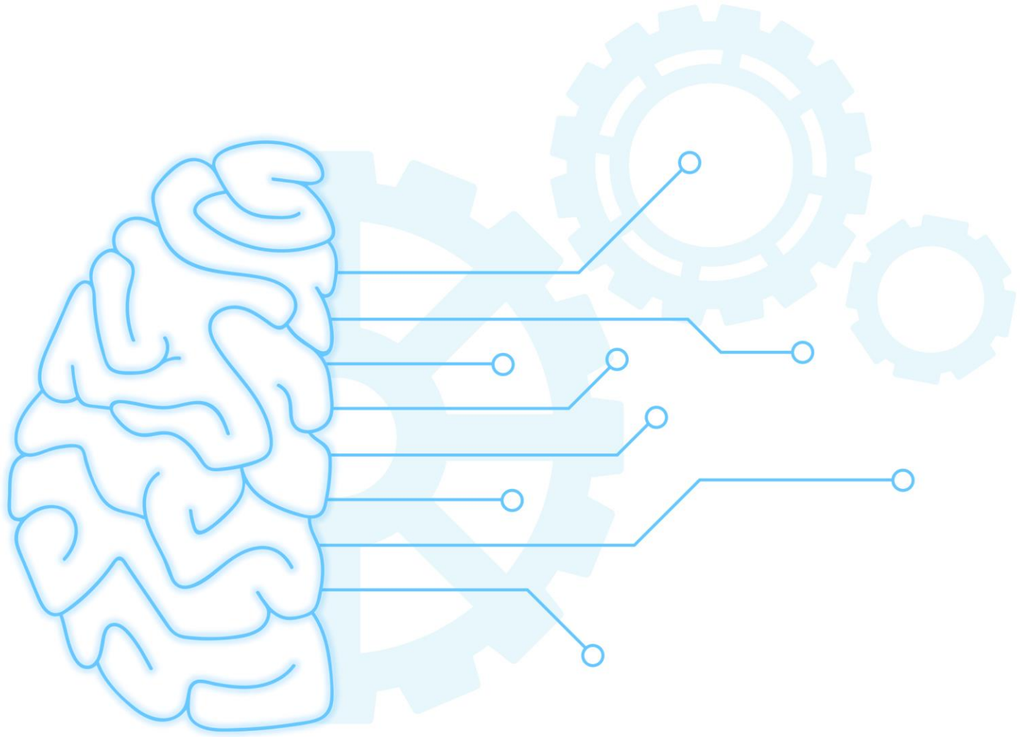
Vésteinn Thorsson,[1,36,*] David L. Gibbs,[1,35] Scott D. Brown,[2] Denise Wolf,[3] Dante S. Bortone,[4] Tai-Hsien Ou Yang,[5] Eduard Porta-Pardo,[6,7] Galen F. Gao,[8] Christopher L. Plaisier,[1,9] James A. Eddy,[10] Elad Ziv,[11] Aedin C. Culhane,[12] Evan O. Paull,[13] I.K. Ashok Sivakumar,[14] Andrew J. Gentles,[15] Raunaq Malhotra,[16] Farshad Farshidfar,[17] Antonio Colaprico,[18] Joel S. Parker,[4] Lisle E. Mose,[4] Nam Sy Vo,[19] Jianfang Liu,[20] Yuexin Liu,[19] Janet Rader,[21] Varsha Dhankani,[1] Sheila M. Reynolds,[1] Reanne Bowlby,[2] Andrea Califano,[13] Andrew D. Cherniack,[8] Dimitris Anastassiou,[5] Davide Bedognetti,[22] Arvind Rao,[19] Ken Chen,[19] Alexander Krasnitz,[23] Hai Hu,[20] Tathiane M. Malta,[24,25] Houtan Noushmehr,[24,25] Chandra Sekhar Pedamallu,[26] Susan Bullman,[26] Akinyemi I. Ojesina,[27]

Immunity *48*, 812–830, April 17, 2018

What will come next?

THE QUEST FOR THE RIGHT I-O COMBINATION THERAPY

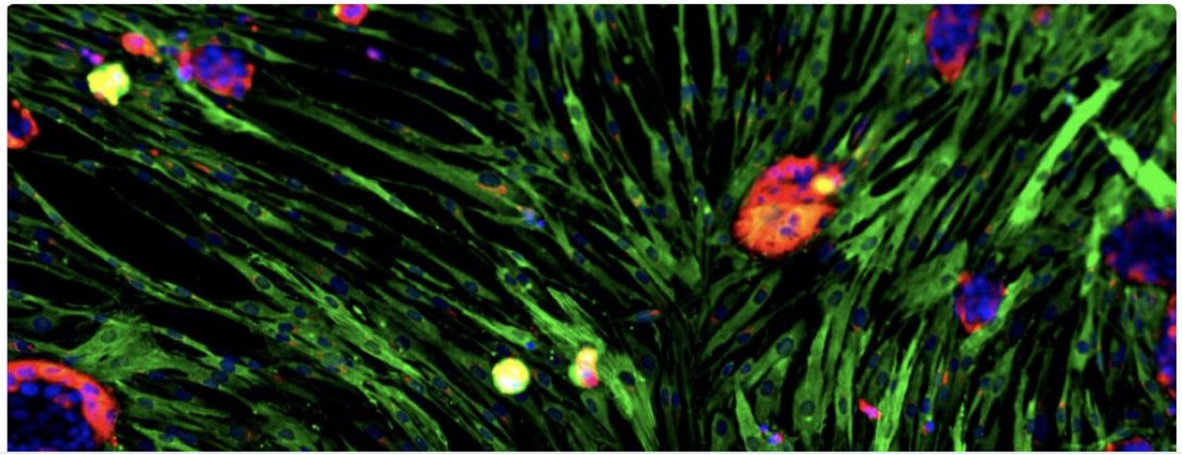
Leveraging emerging technologies to enable “precision immuno-oncology”



Phenomic AI Retweeted

Pharma Tech Focus
@PharmaTechFocus

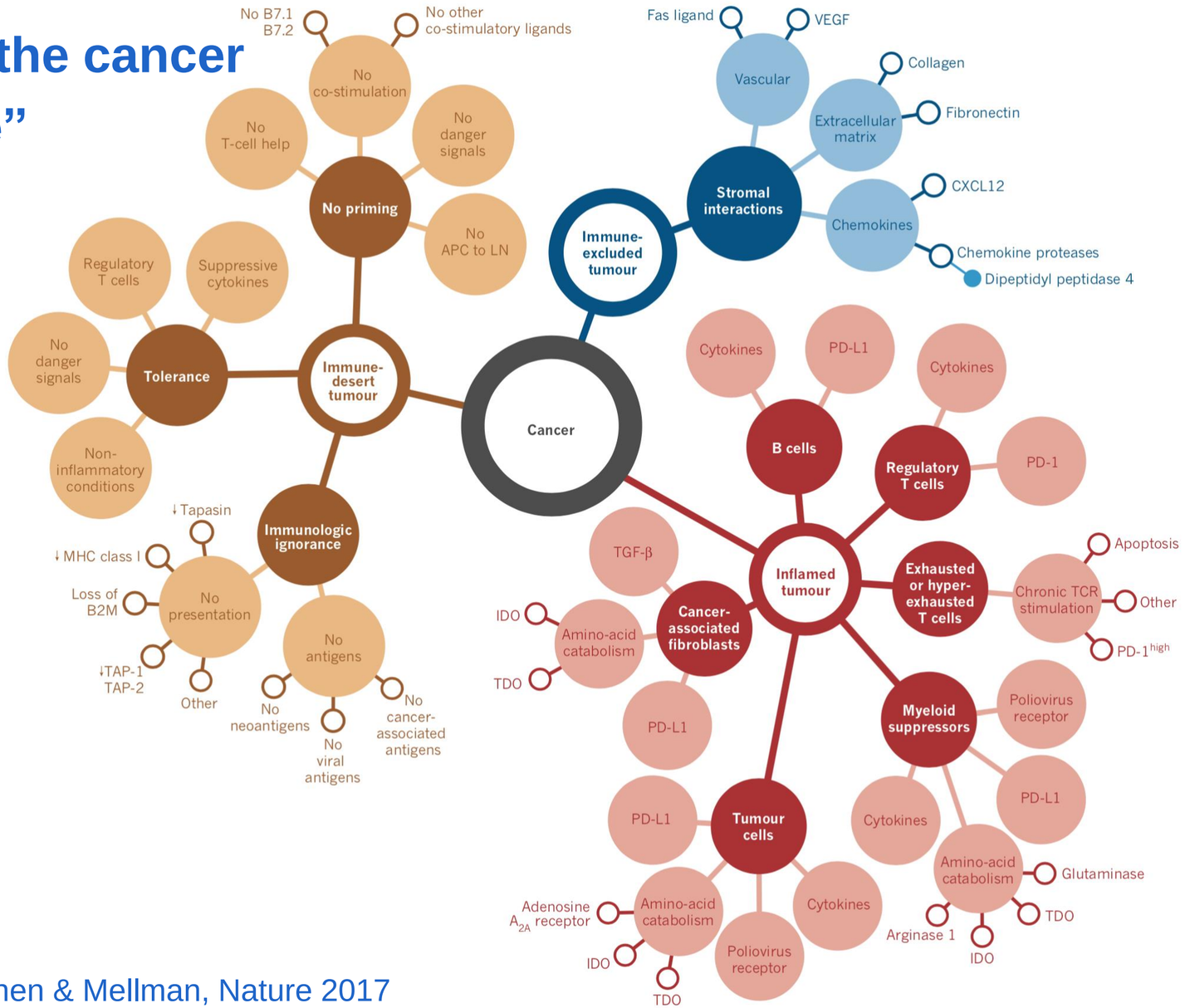
Targeting the tumour stroma: @PhenomicAI launches with $6m seed financing#targetingthetumourstroma #treatingsolidtumours #seedfinancing bit.ly/340yDy9



AI algorithm → interrogate cell-cell interactions in tumor stroma → drug screen
→ antibody candidates to disrupt tumor stroma and relieve obstacles to CPI action

TOWARDS “PRECISION IMMUNO-ONCOLOGY”

Structuring the cancer “immunome”



Chen & Mellman, Nature 2017

individualized targets

response biomarkers

toxicity

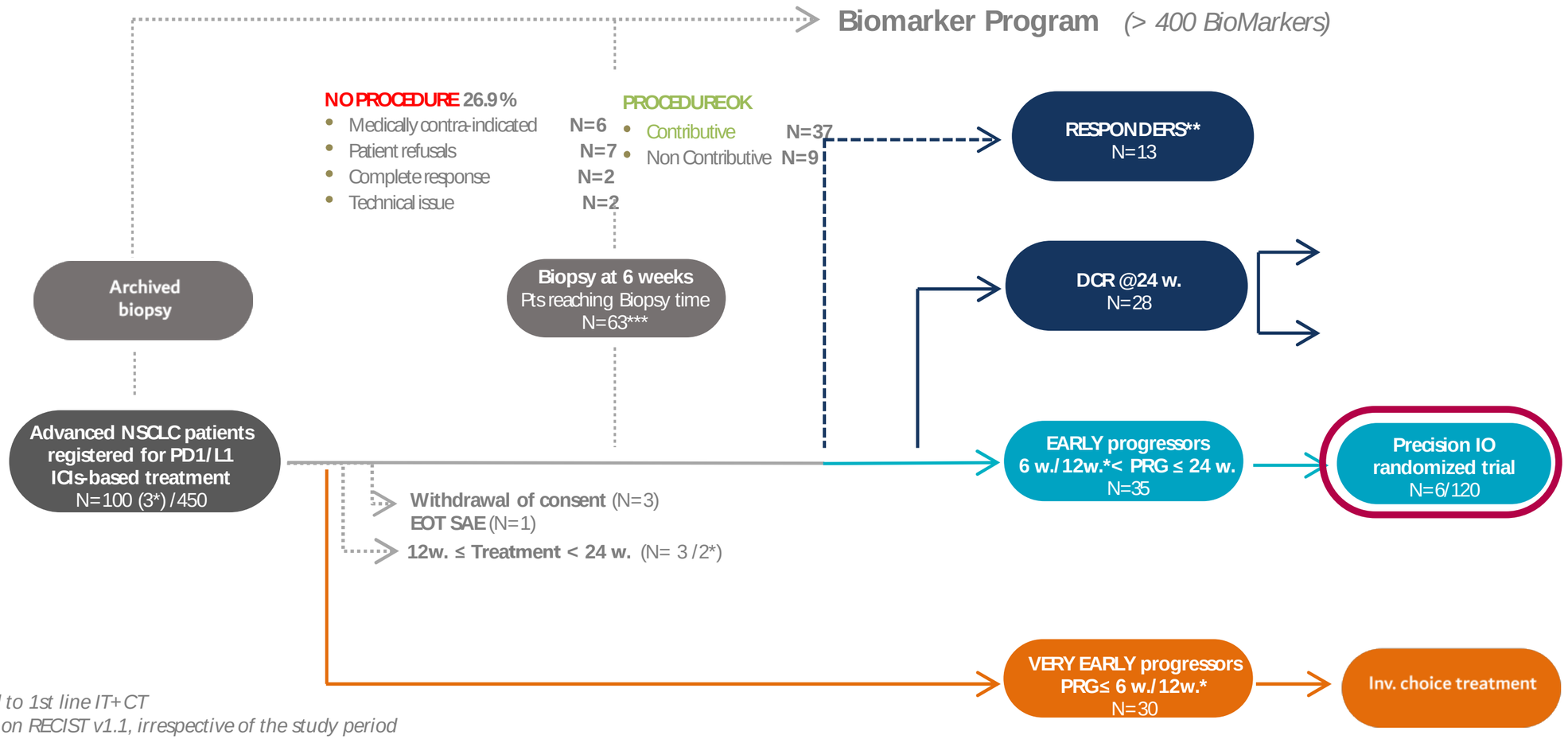
TOWARDS “PRECISION IMMUNO-ONCOLOGY”

F. Barlesi et al, ESMO 2020

VIRTUAL 2020 ESMO congress

PIONeeR Biomarkers

Design and Flow Chart



** Related to 1st line IT+CT*
*** Based on RECIST v1.1, irrespective of the study period*
**** Including 3 Very Early Progressors , with a radiologic progression (inclusion in clinical trial)*

TOWARDS “PRECISION IMMUNO-ONCOLOGY”

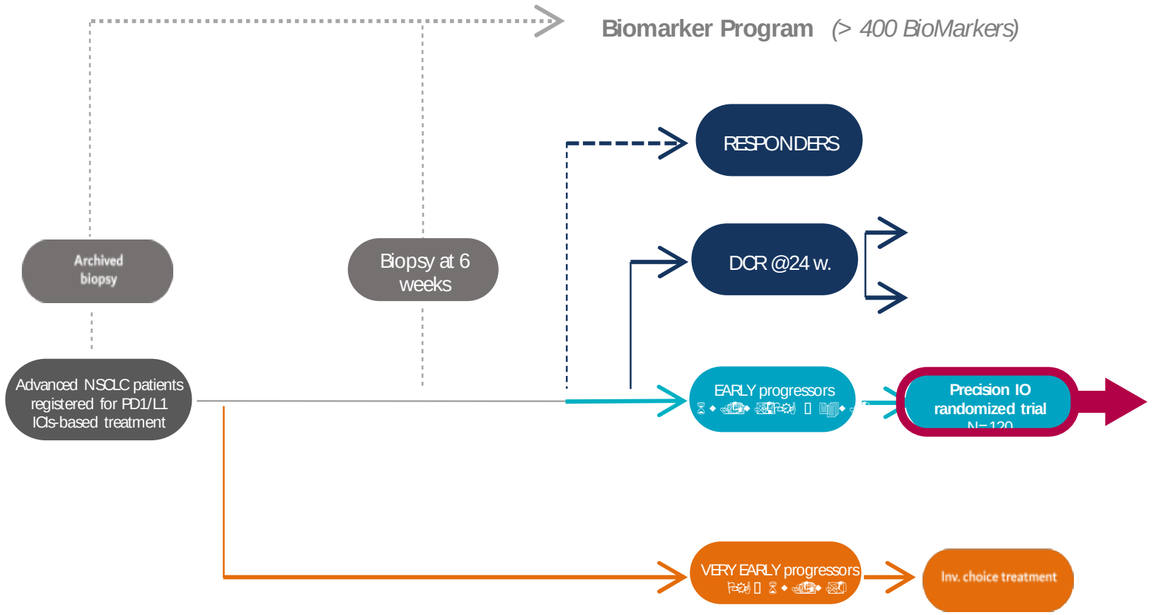
F. Barlesi et al, ESMO 2020

VIRTUAL 2020 ESMO congress

The PIONeeR project

Understand, Predict and Overcome resistances to PD-(L)1i in adv. NCSLC pts

Understand and Predict: PIONeeR biomarkers trial



** Related to 1st line IT+CT*

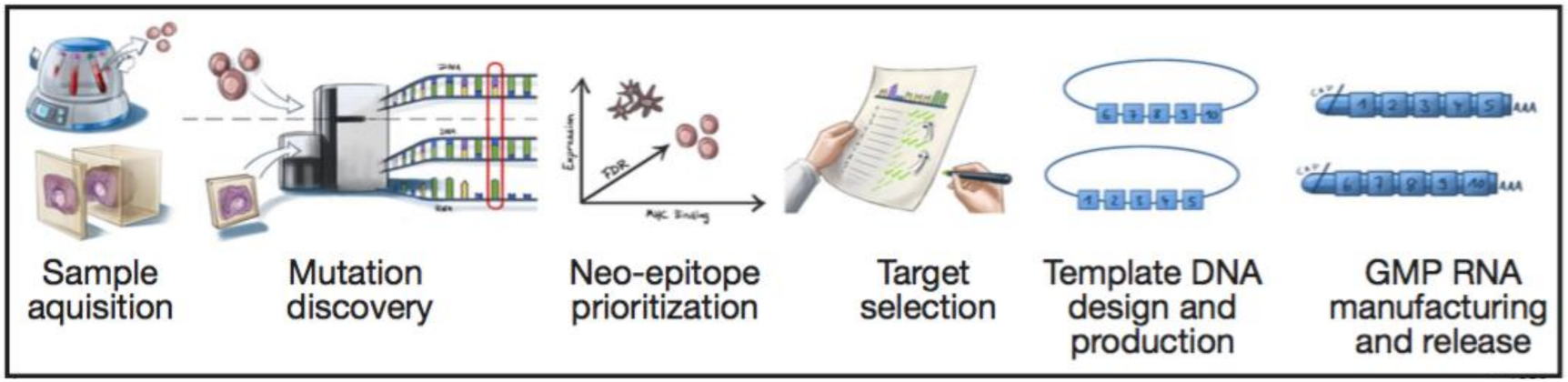
TOWARDS “PRECISION IMMUNO-ONCOLOGY”

Tumor mutanome-derived neo-antigens as individualized vaccine targets

Personalized RNA mutanome vaccines mobilize poly-specific therapeutic immunity against cancer

BIONTECH

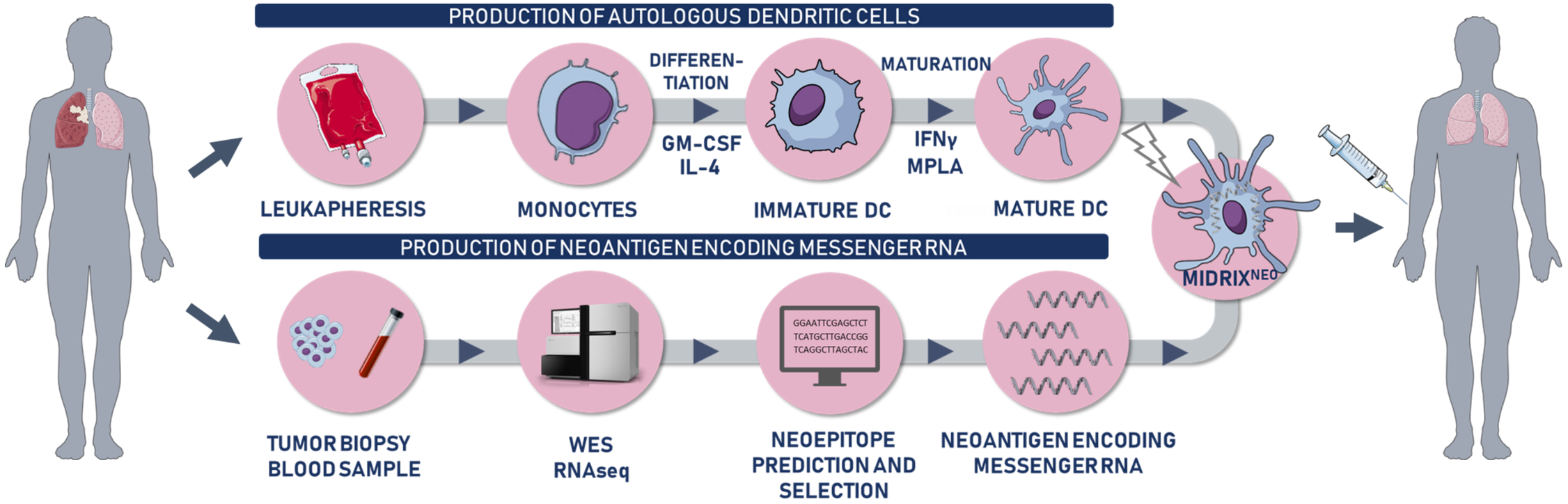
U. Sahin et al, Nature 2017



TOWARDS “PRECISION IMMUNO-ONCOLOGY”

Tumor mutanome-derived neo-antigens as individualized vaccine targets

MIDRIX^{NEO}-LUNG NCT04078269



J. Ingels et al, unpublished

TOWARDS “PRECISION IMMUNO-ONCOLOGY”

Tumor mutanome-derived neo-antigens as individualized vaccine targets

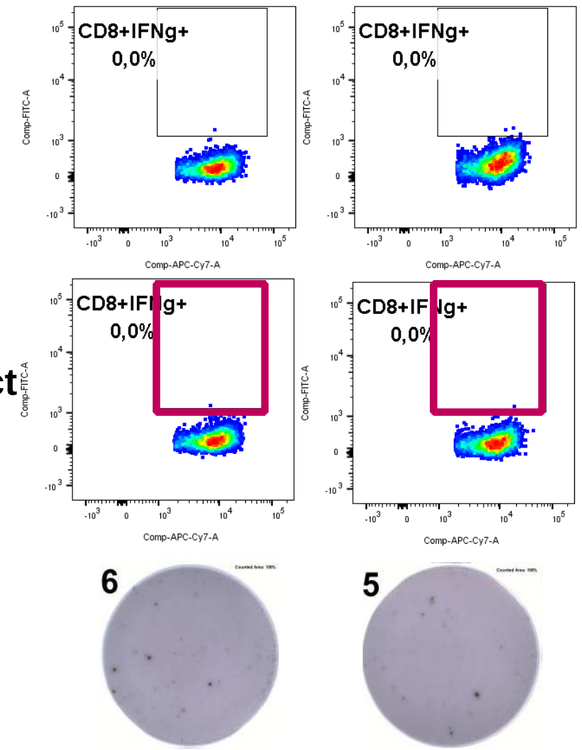
MIDRIX^{NEO}-LUNG NCT04078269

UZ GENT UNIVERSITEIT GENT

PRE-DC VAX

irrelevant antigen
BFP mRNA EP

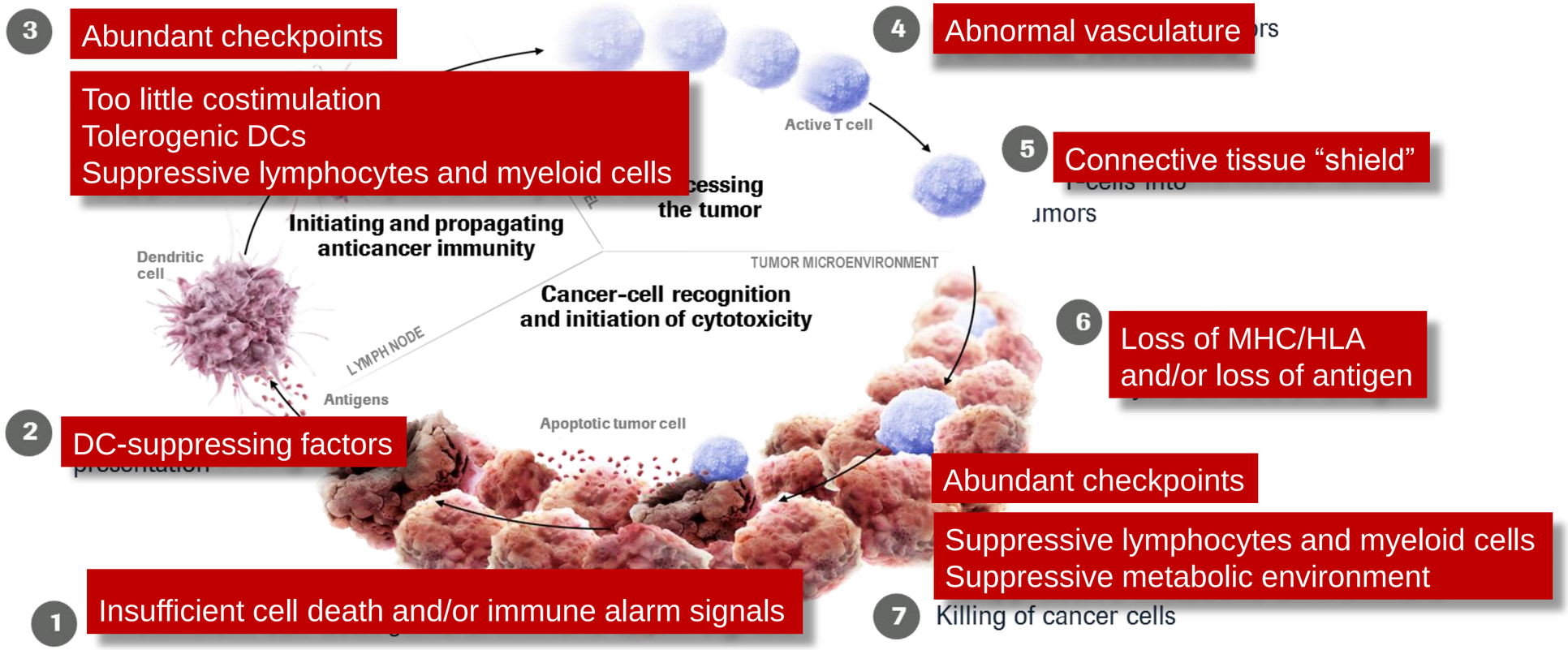
5 neo-antigens tandem construct
TTE mRNA EP



J. Ingels et al, unpublished

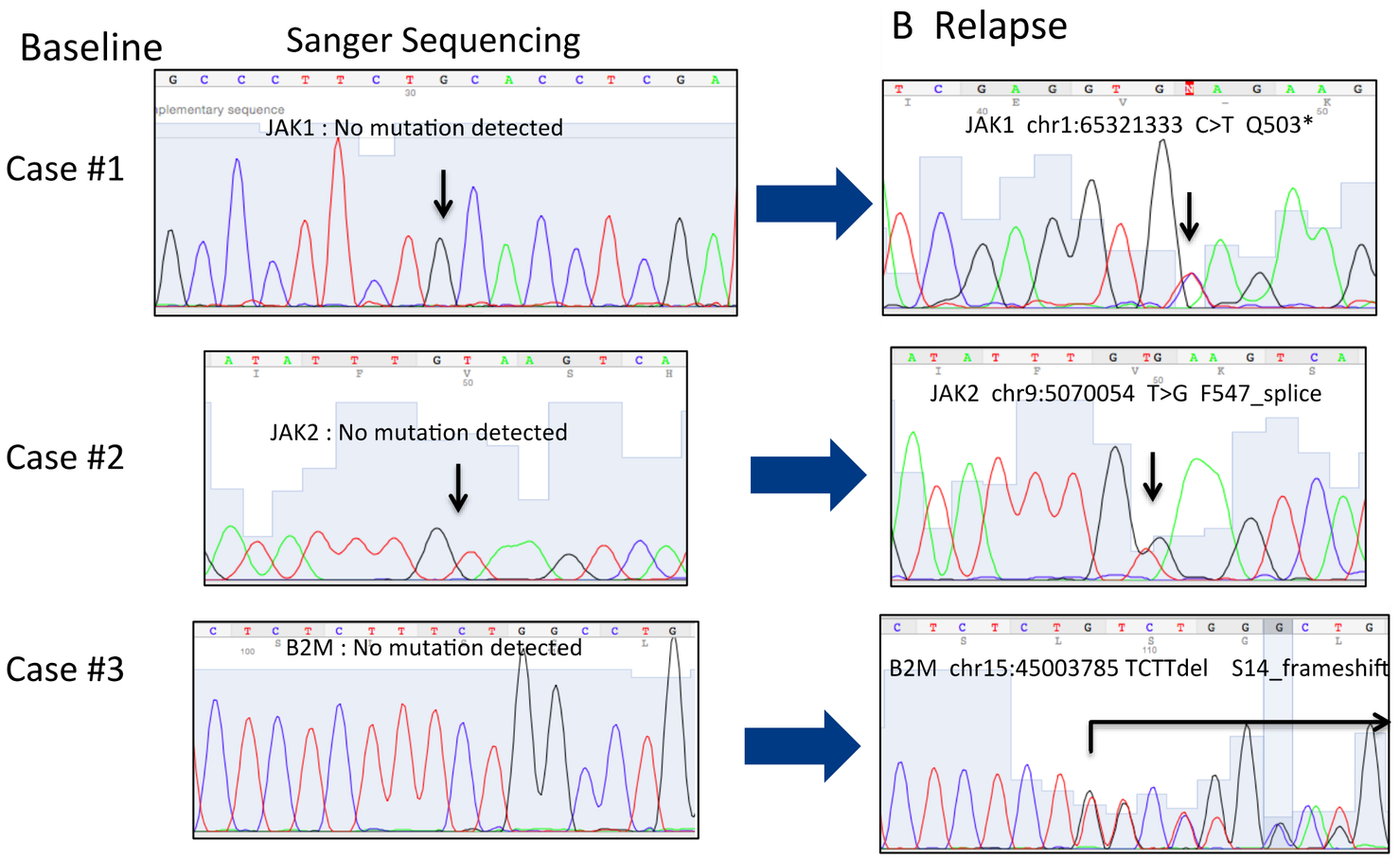
UNDERSTANDING RESISTANCE MECHANISMS TO CPI

UNDERSTANDING RESISTANCE MECHANISMS TO CPI



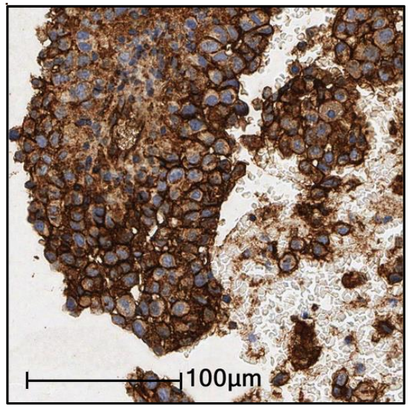
UNDERSTANDING RESISTANCE MECHANISMS TO CPI

Mutations Associated with Acquired Resistance to PD-1 Blockade in Melanoma

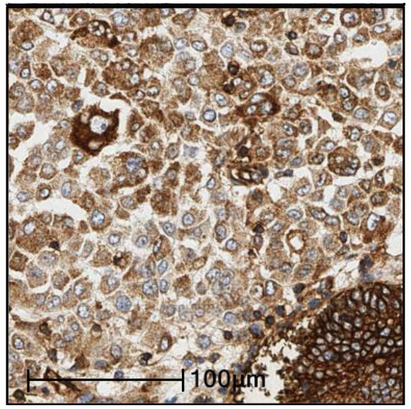


Zaretsky et al, NEJM 2016

MHC/HLA class I baseline



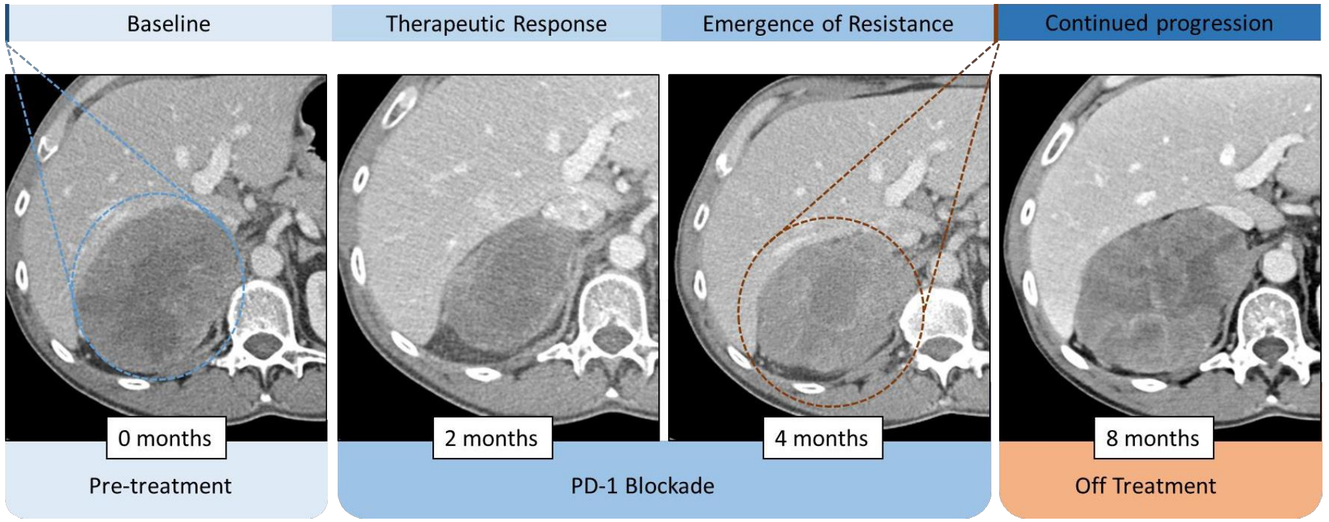
relapse



UNDERSTANDING RESISTANCE MECHANISMS TO CPI

Effective CPI-induced anti-tumor immune responses lead to loss of immunogenic clones and tumor escape

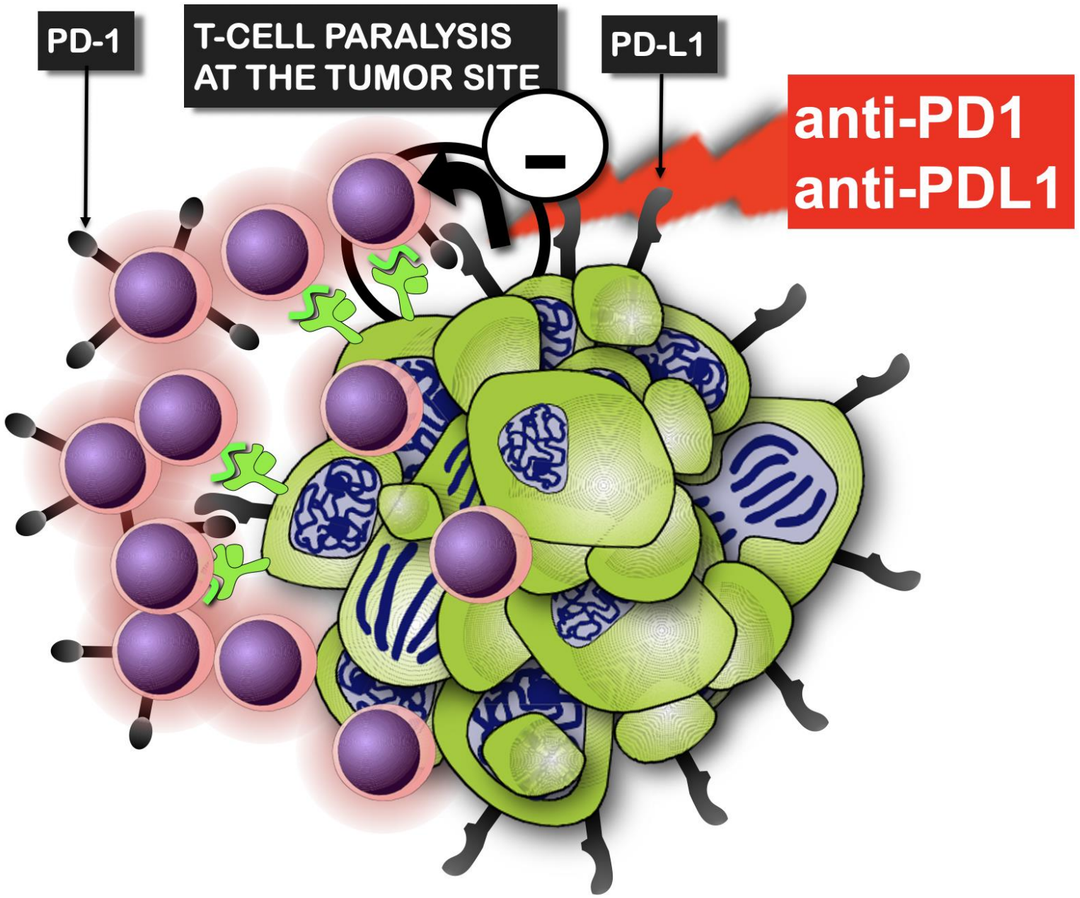
V. Anagnostou et al Cancer Discovery 2016

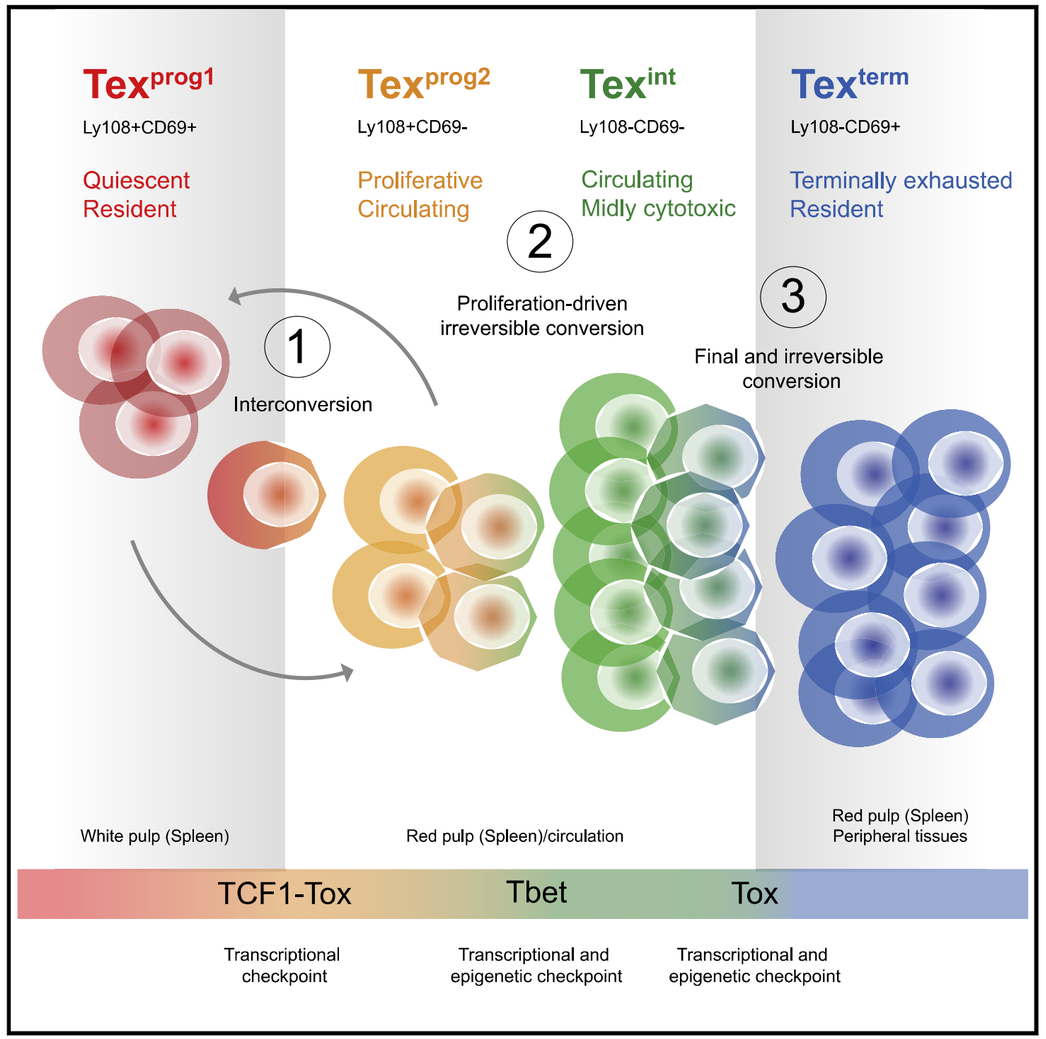


I-O: IT ALL STARTS (AND ENDS) WITH IMMUNOLOGY…

DO WE REALLY UNDERSTAND HOW CPIs ACTUALLY WORK?

- “exhausted” cytotoxic T-lymphocytes are a dynamic, heterogenous family
- CPIs can only rescue one specific subset

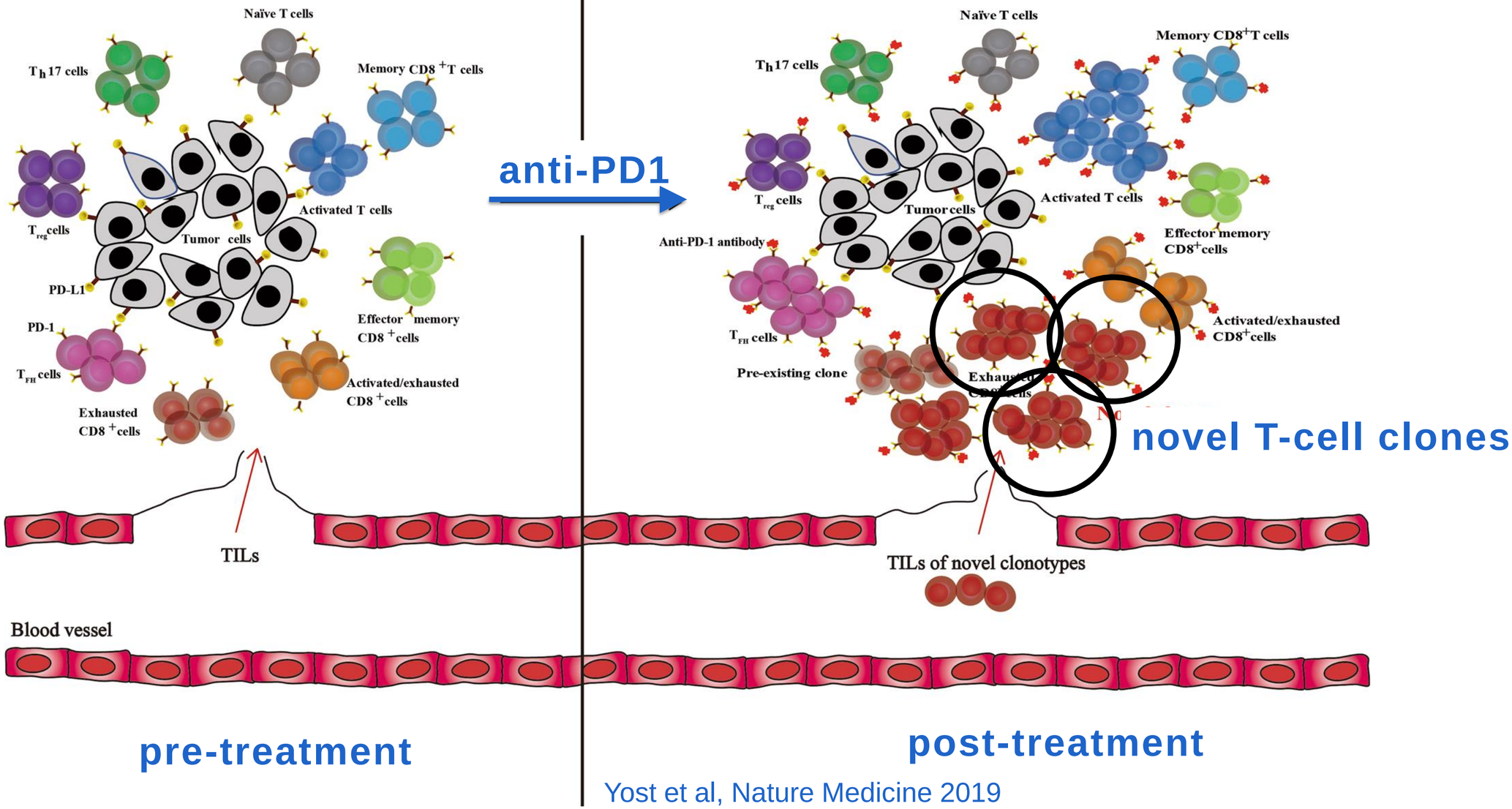




Beltra et al, Immunity 2020

DO WE REALLY UNDERSTAND HOW CPIs ACTUALLY WORK?

CPI not only ”re-awaken” exhausted T-cells but also recruit T-cell clones with novel specificity (“**clonal replacement**”)



Yost et al, Nature Medicine 2019

DO WE REALLY UNDERSTAND HOW CPIs ACTUALLY WORK?

the intestinal microbiome impacts therapeutic efficacy of CPIs

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

Vétizou et al, *Science* 2015

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

Gopalakrishnan et al, *Science* 2017

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

Matson et al, *Science* 2018

Gut microbiome influences efficacy of PD-1-based immunotherapy against epithelial tumors Routy et al, *Science* 2018

CANCER IMMUNOTHERAPY BEYOND CPI : TAKE-HOME MESSAGES

STATE-OF-THE-UNION IN I-O TODAY:

- WE HAVE BIOMARKERS (they are so-so)
- WE HAVE COMBINATION REGIMEN (they still don't benefit the majority)
- WE ARE MOSTLY HELPLESS IN FRONT OF ACQUIRED RESISTANCE

WE NEED WAYS TO CAPTURE THE FULL COMPLEXITY OF THE CANCER "IMMUNOME" in a clinician-friendly way

- "ONE SIZE FITS ALL" THERAPY COMBINATIONS?
- OR FULLY PATIENT-INDIVIDUALIZED?
- WILL EVERY NEW COMBINATION REGIMEN REQUIRE ITS OWN COMPANION BIOMARKER TEST??

UZ GENT

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THANK YOU FOR YOUR ATTENTION!