Emerging biomarkers in immuno-oncology

Prof. Dr. Hans Prenen

UZA Edegem

iridium kankernetwerk

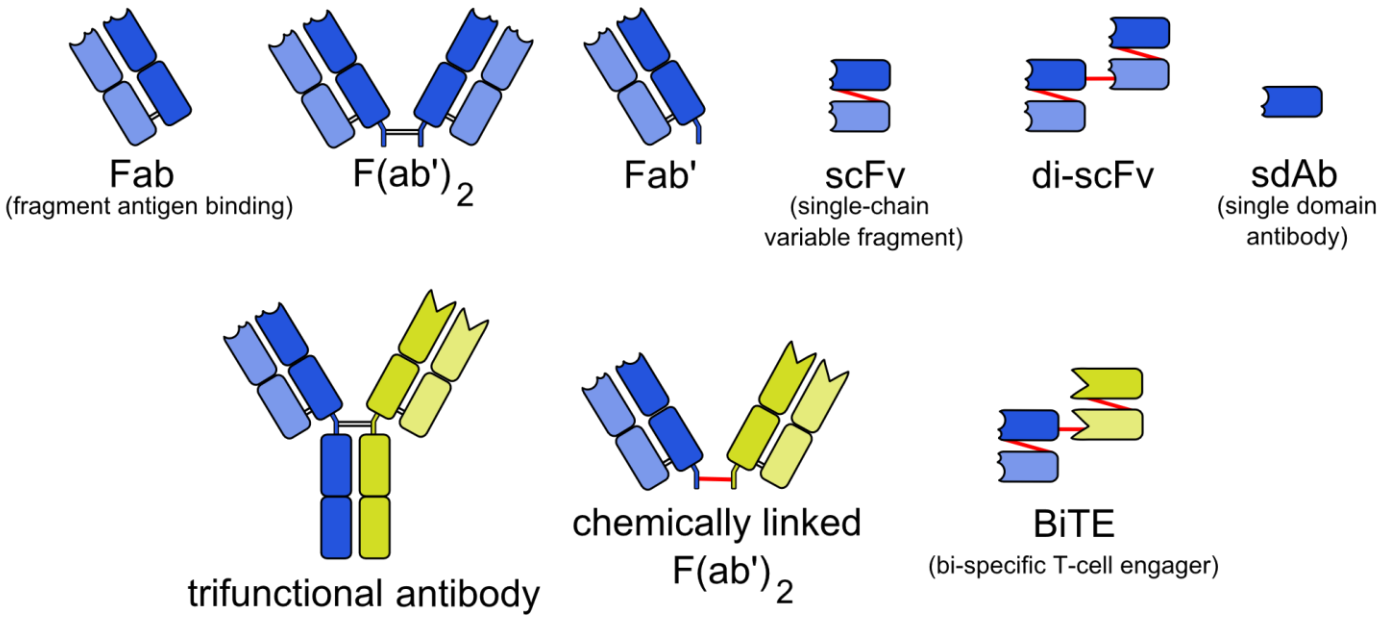
helix ziekenhuizen

Universiteit Antwerpen

UZA

Different types of immunotherapy

- Cellular immunotherapy
  - Dendritic cell therapy
  - CAR-T cell therapy
- Antibody therapy
  - Anti-PD(L)1
  - Anti-CTLA4
  - …

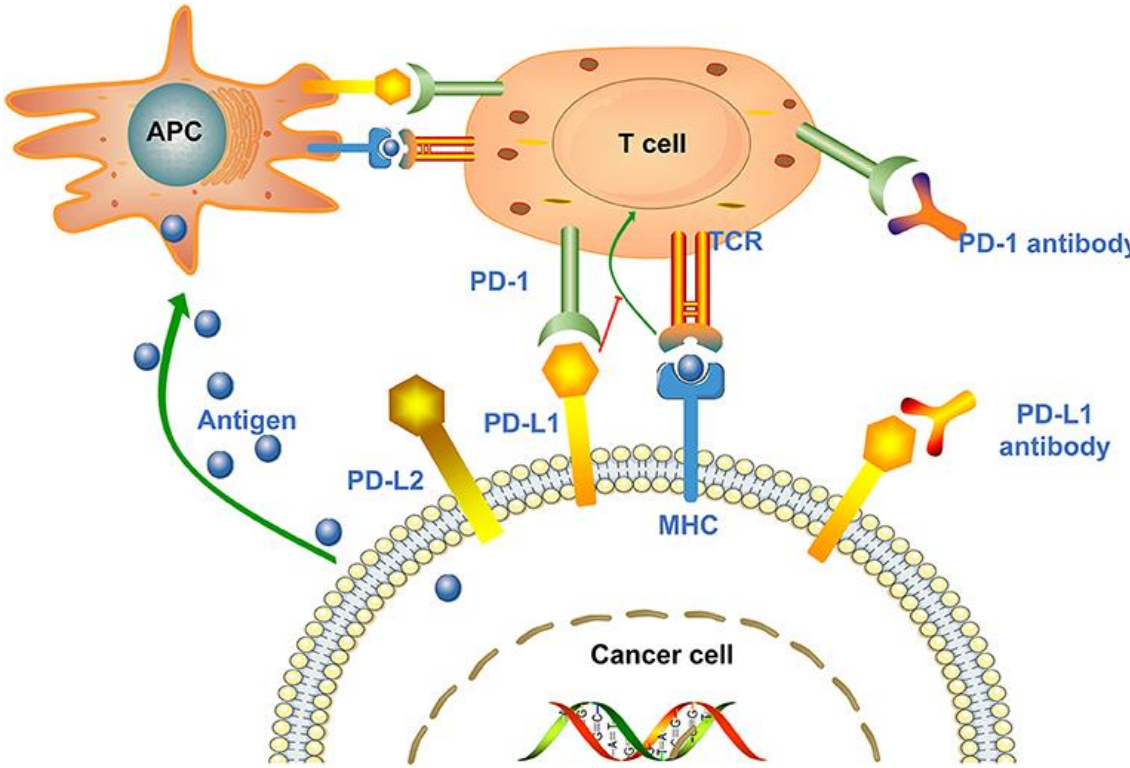


Universiteit Antwerpen

UZA

2 major immune checkpoint blockers

- CTLA4:
  - Works more on the T-cell priming stage
- PD1/PDL1:
  - Acts more on tumor microenvironment



Biomarkers for immunotherapy

- Tumor Antigens
- Immune suppresion markers
- Inflamed tumor markers

Biomarkers for immunotherapy

- **Tumor Antigens**
- Immune suppresion markers
- Inflamed tumor markers

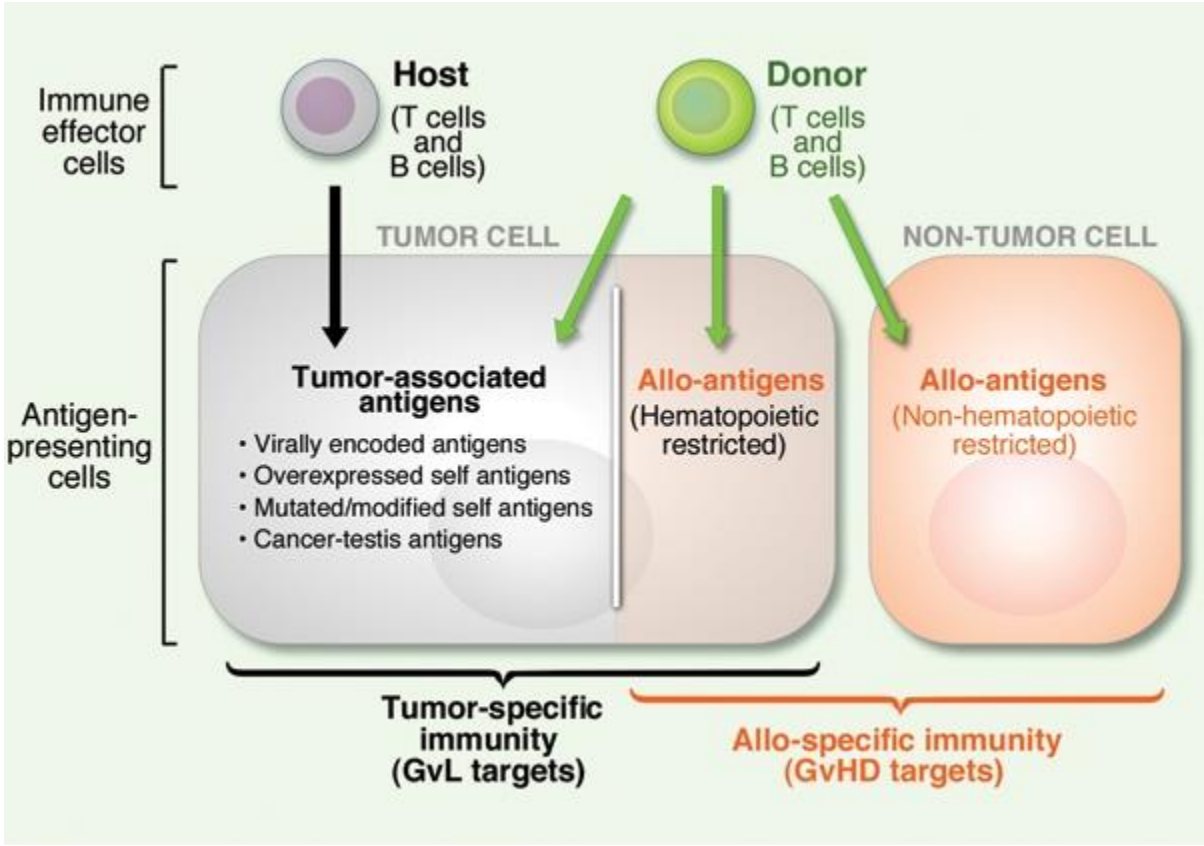
Universiteit Antwerpen

UZA

Tumor Antigens

- Tumor antigen is an antigenic substance produced in tumor cells, i.e., it triggers an immune response in the host.

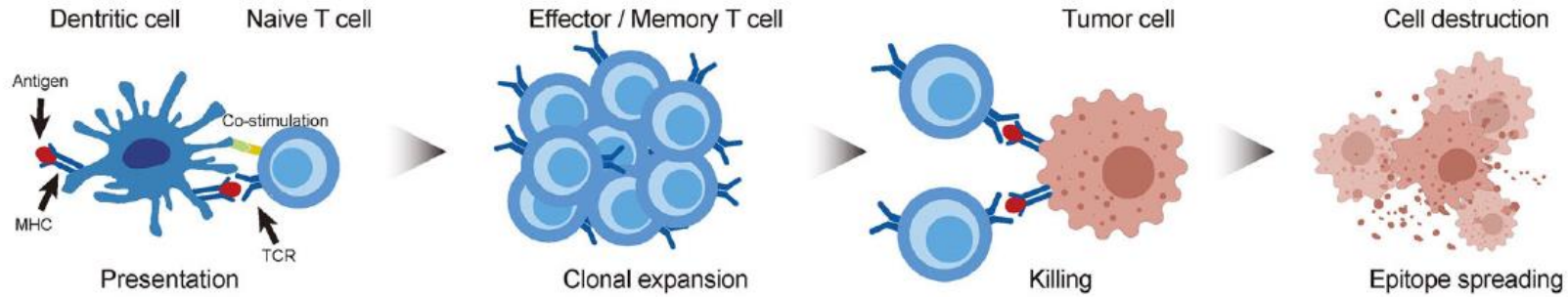
- **<u>Neo-Antigen</u>**:
  - newly formed antigens that arise from mutated tumor proteins
  - May help predict sensitivity to I-O



Neo-antigens

- Higher number of DNA mutations are assocated with higher number of candidate peptides, and results in an increased probability of successfully presented neo-antigens

- TMB = Tumor mutational burden
  - total number of mutations per tumor (when assessed by WES)
  - Normalized to mutations per megabase by gene panel assays



Universiteit Antwerpen

UZA

TMB (tumor mutational burden)

- Role of TMB in immunotherapy remains controversial, since not all mutations produce neoantigens
  - Sometimes minimal mutational burden causes strong anti-tumor response (if high quality neoantigens)
- Often cutoff of 10mut/Mb is used for response to IO when Foundation assay is used
- Positive correlation between TMB and Tumor Neoantigen Burdon (TNB)

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ANNALS OF ONCOLOGY driving innovation in oncology

ORIGINAL ARTICLE

High tumor mutation burden fails to predict immune checkpoint blockade response across all cancer types

D. J. McGrail[1*], P. G. Pilié[2], N. U. Rashid[3,4], L. Voorwerk[5], M. Slagter[6,7,8], M. Kok[5,9], E. Jonasch[2], M. Khasraw[10], A. B. Heimberger[11], B. Lim[12], N. T. Ueno[12], J. K. Litton[12], R. Ferrarotto[13], J. T. Chang[14,15], S. L. Moulder[12] & S.-Y. Lin[1*]

- Association in melanoma, lung and bladder cancer
- No association in breast, prostate and brain cancer

Universiteit Antwerpen UZA

Association of tumour mutational burden with outcomes in patients with advanced solid tumours treated with pembrolizumab: prospective biomarker analysis of the multicohort, open-label, phase 2 KEYNOTE-158 study

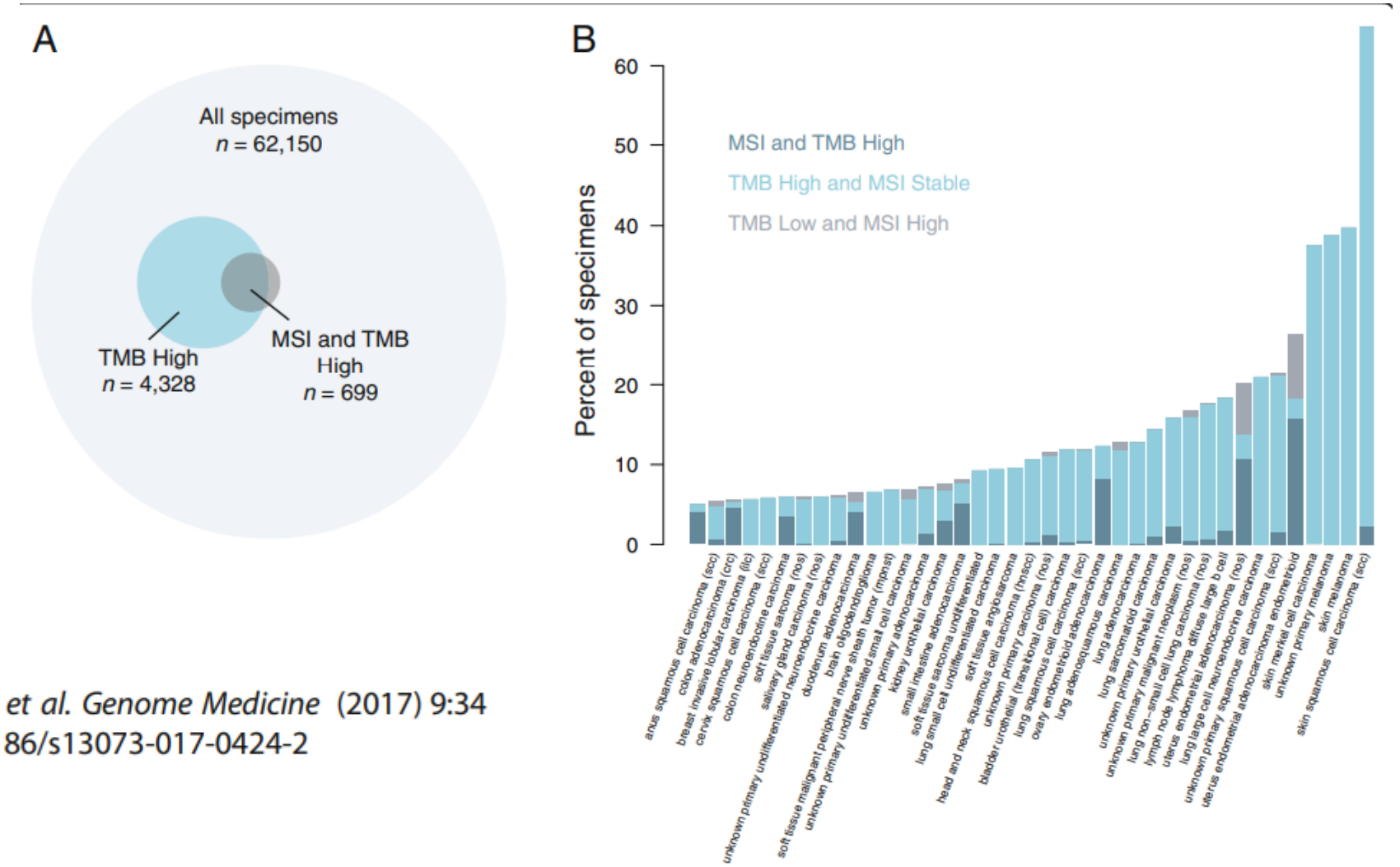
Aurélien Marabelle, Marwan Fakih, Juanita Lopez, Manisha Shah, Ronnie Shapira-Frommer, Kazuhiko Nakagawa, Hyun Cheol Chung, Hedy L Kindler, Jose A Lopez-Martin, Wilson H Miller Jr, Antoine Italiano, Steven Kao, Sarina A Piha-Paul, Jean-Pierre Delord, Robert R McWilliams, David A Fabrizio, Deepti Aurora-Garg, Lei Xu, Fan Jin, Kevin Norwood, Yung-Jue Bang

www.thelancet.com/oncology Vol 21 October 2020

- Anal, biliary, cervical, endometrial, salivary, thyroid, vulvar carcinoma, mesothelioma, NET, SCLC
- 105 TMB high (≥10)
- ORR 29%

Universiteit Antwerpen UZA

Relation between TMB and MSI



Chalmers *et al. Genome Medicine* (2017) 9:34
DOI 10.1186/s13073-017-0424-2

Universiteit Antwerpen

UZA

MSI and immunotherapy

Published in final edited form as:
Science. 2017 July 28; 357(6349): 409–413. doi:10.1126/science.aan6733.

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

- ORR 53%, durable
- 12 different tumor types

MSI and immunotherapy

Phase II Open-Label Study of Pembrolizumab in Treatment-Refractory, Microsatellite Instability–High/Mismatch Repair–Deficient Metastatic Colorectal Cancer: KEYNOTE-164

Dung T. Le, MD[1]; Tae Won Kim, MD[2]; Eric Van Cutsem, MD, PhD[3]; Ravit Geva, MD[4]; Dirk Jäger, MD[5]; Hiroki Hara, MD[6]; Matthew Burge, MBChB, FRACP[7]; Bert O'Neil, MD[8]; Petr Kavan, MD, PhD[9]; Takayuki Yoshino, MD[10]; Rosine Guimbaud, MD, PhD[11]; Hiroya Taniguchi, MD, PhD[12]; Elena Elez, MD, PhD[13]; Salah-Eddin Al-Batran, MD[14]; Patrick M. Boland, MD[15]; Todd Crocenzi, MD[16]; Chloe E. Atreya, MD, PhD[17]; Yi Cui, PhD[18]; Tong Dai, MD, PhD[19]; Patricia Marinello, PharmD[19]; Luis A. Diaz Jr, MD[20]; and Thierry André, MD[21]

- ORR 33%
- Previously treated mCRC

Universiteit Antwerpen UZA

MSI and immunotherapy

VOLUME 36 · NUMBER 8 · MARCH 10, 2018

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Durable Clinical Benefit With Nivolumab Plus Ipilimumab in DNA Mismatch Repair–Deficient/Microsatellite Instability–High Metastatic Colorectal Cancer

Michael J. Overman, Sara Lonardi, Ka Yeung Mark Wong, Heinz-Josef Lenz, Fabio Gelsomino, Massimo Aglietta, Michael A. Morse, Eric Van Cutsem, Ray McDermott, Andrew Hill, Michael B. Sawyer, Alain Hendlisz, Bart Neyns, Magali Svrcek, Rebecca A. Moss, Jean-Marie Ledeine, Z. Alexander Cao, Shital Kamble, Scott Kopetz, and Thierry André

- JCO, march 2018
- ORR 55%

First-Line Nivolumab Plus Low-Dose Ipilimumab for Microsatellite Instability-High/ Mismatch Repair-Deficient Metastatic Colorectal Cancer: The Phase II CheckMate 142 Study

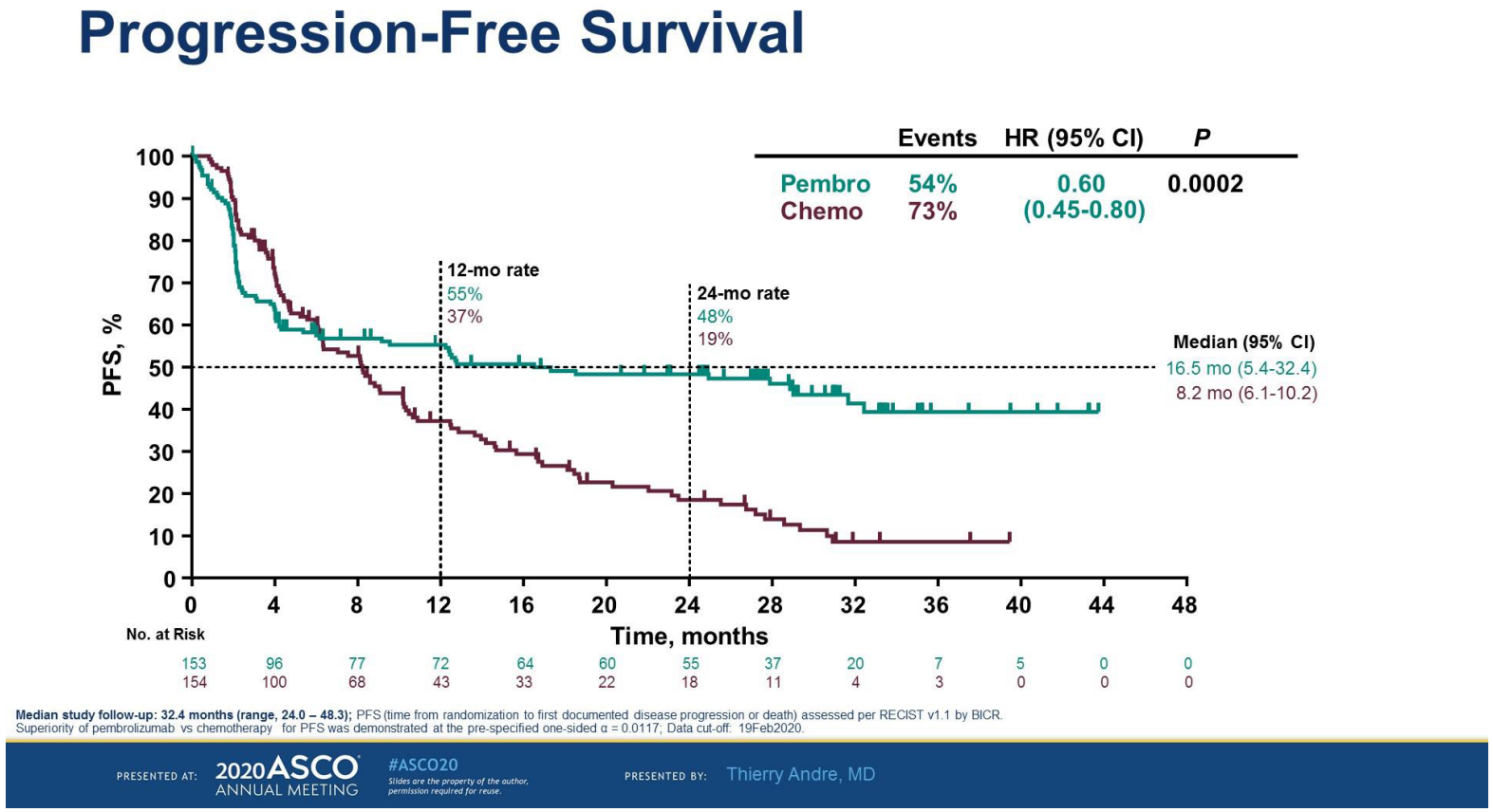
Heinz-Josef Lenz, MD[1]; Eric Van Cutsem, MD, PhD[2]; Maria Luisa Limon, MD[3]; Ka Yeung Mark Wong, PhD[4]; Alain Hendlisz, MD, PhD[5]; Massimo Aglietta, MD, PhD[6]; Pilar García-Alfonso, MD[7]; Bart Neyns, MD, PhD[8]; Gabriele Luppi, MD[9]; Dana B. Cardin, MD[10]; Tomislav Dragovich, MD, PhD[11]; Usman Shah, MD[12]; Sandzhar Abdullaev, MD, PhD[13]; Joseph Gricar, MS[13]; Jean-Marie Ledeine, MS[13]; Michael James Overman, MD[14]; and Sara Lonardi, MD[15]

- JCO, oct 2021
- ORR 69%

Universiteit Antwerpen

UZA

KEYNOTE-177: Pembrolizumab vs Chemotherapy for MSI-H/dMMR Metastatic CRC



NEJM 2020

Universiteit Antwerpen

UZA

TNB (tumor neo-antigen burden)

- Emerging biomarker
- Many algorithms (computational pipelines) try to predict neo-antigens
  - Based on peptide affinity with MHC
  - Tumor epitope selections alliance
    - Bioinformatics consortium with scientists from neo-antigen research groups
    - Independently mine the open database of tumor sequencing, predict potential neoantigens and rank candidate peptides.
- TNB correlates with tumor-infiltrating lymphocytes

TNB (tumor neo-antigen burden)

- Limitations:
  - Cut-off value unknown
  - Intra-tumoral heterogeneity (local / between primary and M+)
  - Difficulty of exploring the entire tumor through a partial biopsy
  - Several obstacles hinder the patient immune response, such as the loss of HLA
  - Maybe quality more important than number,…

Biomarkers for immunotherapy

- Tumor Antigens
- **Immune suppresion markers**
- Inflamed tumor markers

Universiteit Antwerpen

UZA

Immune suppression markers

- Lymphocyte-activation gene 3 (LAG-3)
  - Expressed on activated cytotoxic T cells and regulatory T cells
  - Increased expression can promote T-cell exhaustion
  - Preclinical: when PD1 pathway is blocked, LAG-3 may be upregulated

Nivolumab and Relatlimab Combination Shows Promise in Advanced Melanoma

ASCO 2021
Relatlimab = human IgG4 LAG3 Ab

Immune suppression markers

- Tregs (regulatory T-lymphocytes) or suppressor cells
  - Suppress immunity
  - Negative biomarker for IO

- Myeloid-derived suppressor cells
  - Suppress immunity
  - Negative biomarker for IO

Biomarkers for immunotherapy

- Tumor Antigens
- Immune suppresion markers
- **Inflamed tumor markers**

Universiteit Antwerpen

UZA

Inflamed tumor markers: PDL1

- PDL1 may be expressed on tumor and/or immune cells (0-100%)
- Varies by tumor type, histology, location and line of therapy
- Cut-off for high PDL1 differs among tumor types and line of therapy

Clone	Manufacturer	Platform	Scoring method	Companion drug
22C3 pharmDx	Agilent, Dako	Dako Autostainer Link 48	TPS or CPS	Pembrolizumab
28–8	Agilent, Dako	Dako Autostainer Link 48	TPS	Nivolumab
73–10	Agilent, Dako	Dako Autostainer Link 48	Not yet established	Avelumab
SP142	Ventana	BenchMark Ultra	IC for TNBC IC and TC for NSCLC	Atezolizumab
SP263	Ventana	BenchMark Ultra	TPS TC and IC for urothelial carcinoma	Durvalumab

Universiteit Antwerpen

UZA

Inflamed tumor markers: PDL1

- TPS score = Tumor proportion score

$$\text{TPS}\ (\%) = \frac{\textit{Positive tumour cells}}{\textit{Total number of tumour cells}} \times 100$$

- CPS score = Combined positivity score

$$\text{CPS} = \frac{\textit{Positive tumour cells} + \textit{Positive intratumoural immune cells}}{\textit{Total number of tumour cells}} \times 100$$

- Tumor cell and immun cell area

$$\text{TC}\ (\%) = \frac{\textit{Positive tumour cells}}{\textit{Total number of tumour cells}} \times 100$$

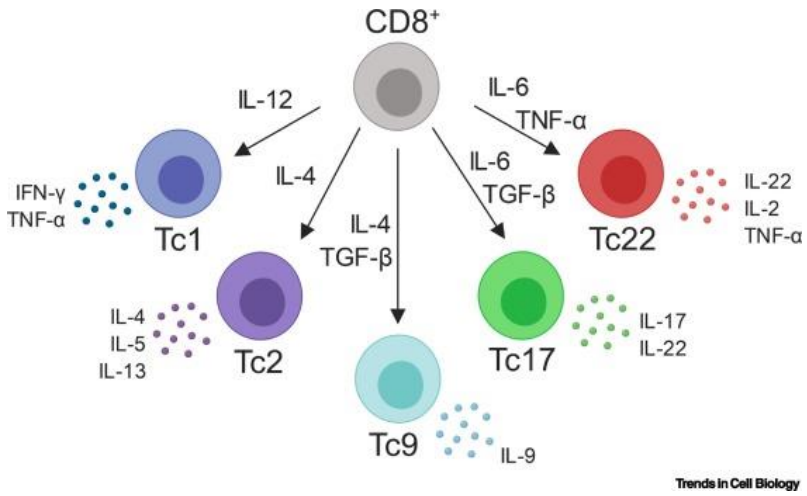
$$\text{IC-Area}\ (\%) = \frac{\textit{Area occupied by positive immune cells}}{\textit{Total area occupied by tumour associated immune cells}} \times 100$$

Universiteit Antwerpen

UZA

Inflamed tumor markers: Tumor infiltrating lymphocytes (TILS)

- Cytotoxic T cells and Natural killer cells

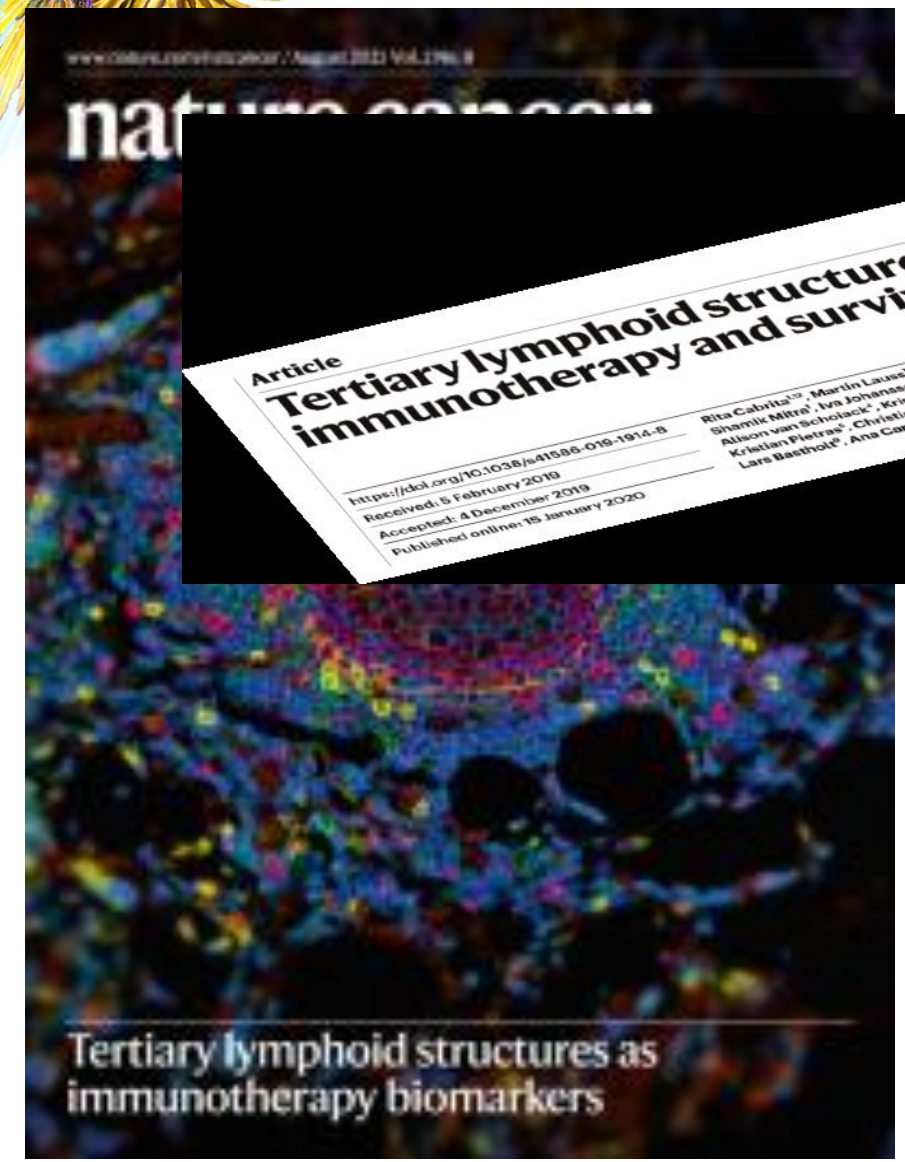


The association between CD8+ tumor-infiltrating lymphocytes and the clinical outcome of cancer immunotherapy: A systematic review and meta-analysis

Feng Li[a,#], Caichen Li[a,#], Xiuyu Cai[b,#], Zhanhong Xie[c,#], Liquan Zhou[a,d], Bo Cheng[a], Ran Zhong[a], Shan Xiong[a], Jianfu Li[a], Zhuxing Chen[a], Ziwen Yu[a], Jianxing He[a,*], Wenhua Liang[a,*]

Conclusion: High intratumoral, stromal, or invasive marginal but not circulating CD8+ T cells, can predict outcomes in patients with ICIs therapy accross different cancers

Universiteit Antwerpen UZA



Tertiary lymphoid structures

f mature tertiary lymphoid

nposed of a T cell zone and

)

o

BRIEF COMMUNICATION
https://doi.org/10.1038/s43018-021-00232-6
nature cancer

Check for updates

Mature tertiary lymphoid structures predict immune checkpoint inhibitor efficacy in solid tumors independently of PD-L1 expression

Lucile Vanhersecke[1,2,11], Maxime Brunet[2,3,11], Jean-Philippe Guégan[4], Christophe Rey[4], Antoine Bougouin[5], Sophie Cousin[3], Sylvestre Le Moulec[6], Benjamin Besse[7], Yohann Loriot[7], Mathieu Larroquette[2,3], Isabelle Soubeyran[1], Maud Toulmonde[3], Guilhem Roubaud[3], Simon Pernot[3], Mathilde Cabart[3], François Chomy[3], Corentin Lefevre[3], Kevin Bourcier[3], Michèle Kind[8], Ilenia Giglioli[5], Catherine Sautès-Fridman[5], Valérie Velasco[1], Félicie Courgeon[4], Ezoglin Oflazoglu[9], Ariel Savina[9], Aurélien Marabelle[7], Jean-Charles Soria[7], Carine Bellera[10], Casimir Sofeu[10], Alban Bessede[4,11], Wolf H. Fridman[5,11], François Le Loarer[1,2,11] and Antoine Italiano[2,3,7,11] ✉

Universiteit Antwerpen

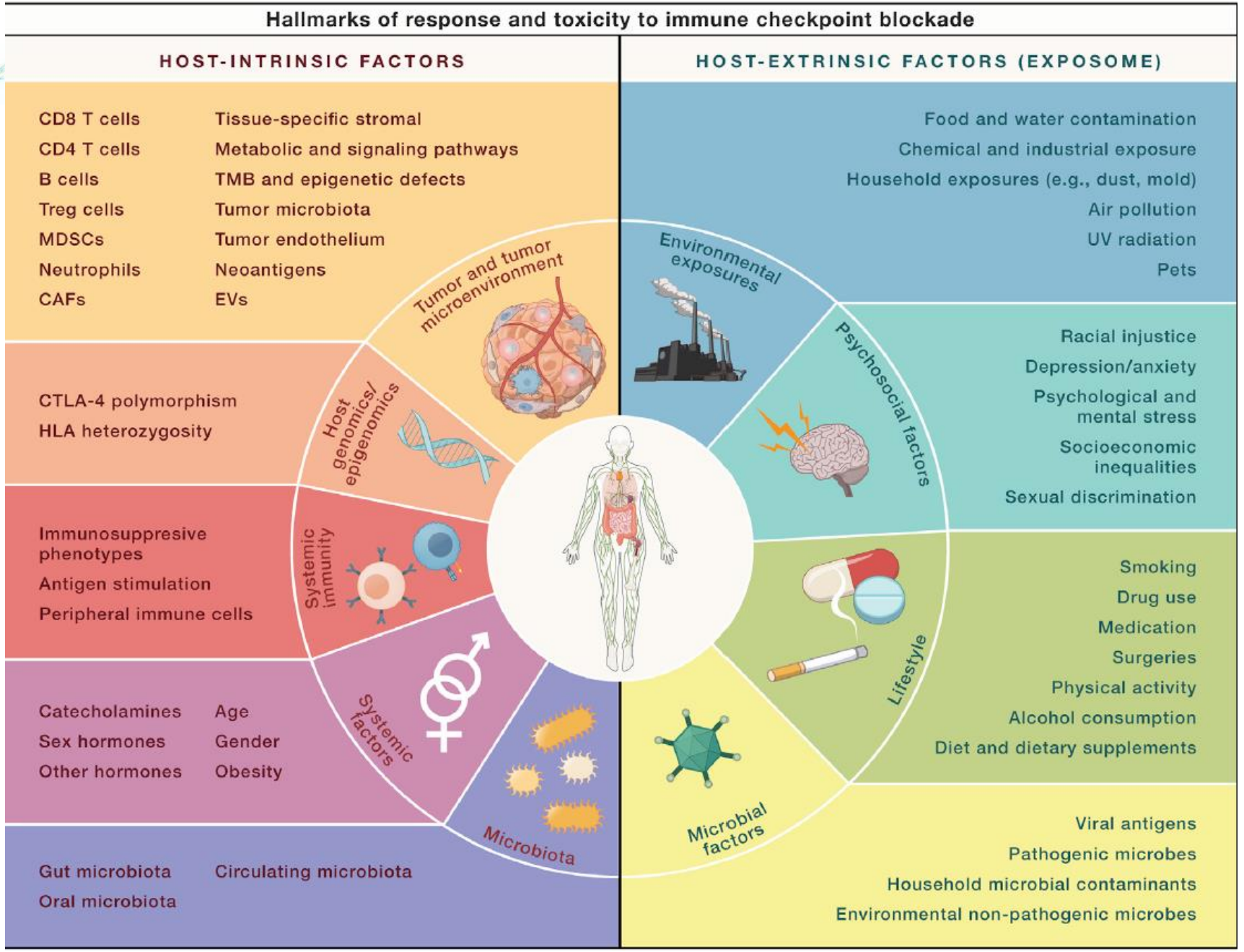
UZA

Future

- Machine learning models (integrating genomic, molecular, demographic and clinical data): cfr recent publication in nature biotechnology (nov 2021)
- mRNA inflammation signatures
- Microbiome
- …..

Universiteit Antwerpen

UZA



Universiteit Antwerpen

UZA

Thanks for your attention

Universiteit Antwerpen

UZA