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Partnering for Education & Optimizing Treatment in ImmunoScience

Biomarkers for immuno-oncology: how to maximize chances of therapeutic success

Karim Y. Vermaelen, MD, PhD
UZ Gent

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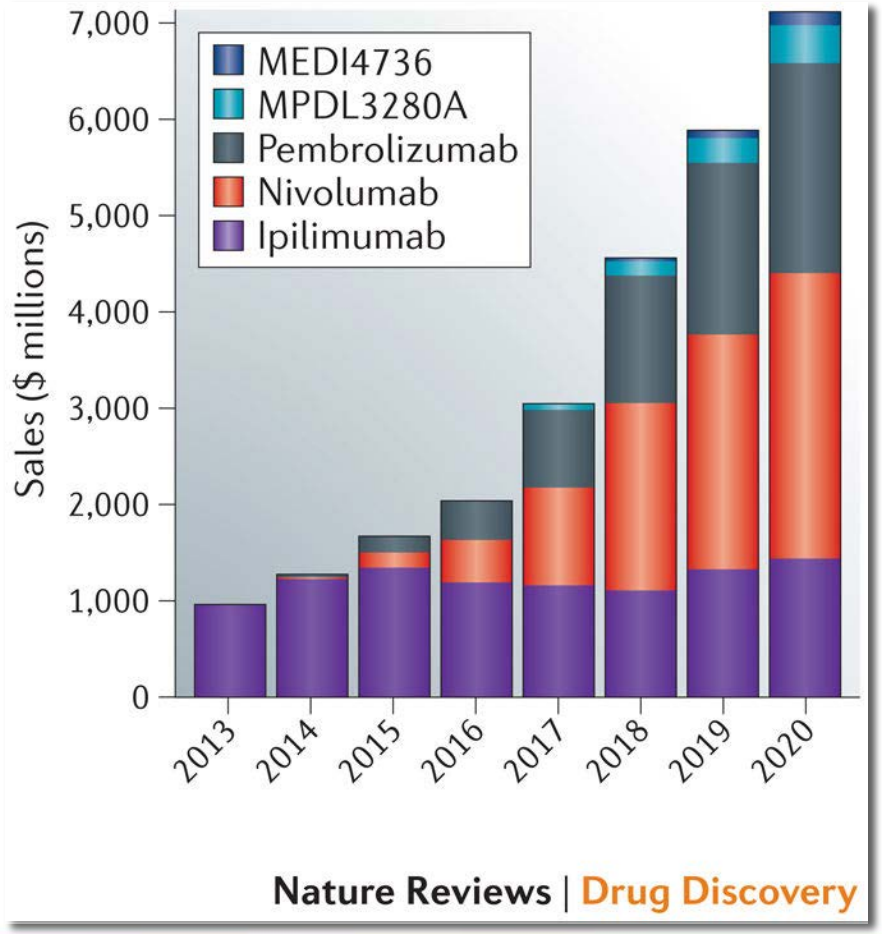
ICIs drive the I-O revolution

Expanding indications

- **Melanoma[1-3]**
- **Non-small cell lung cancer[1,2,4,5]**
- **Renal cell cancer[2]**
- **Urothelial (bladder) cancer[1,2,4]**
- **Head-neck cancer[1,2]**
- **Hodgkin lymphoma[1,2]**
- **Merkel cell carcinoma[6]**
- ***All* cancers with microsatellite instability (MSI+) *regardless of origin*[7]**

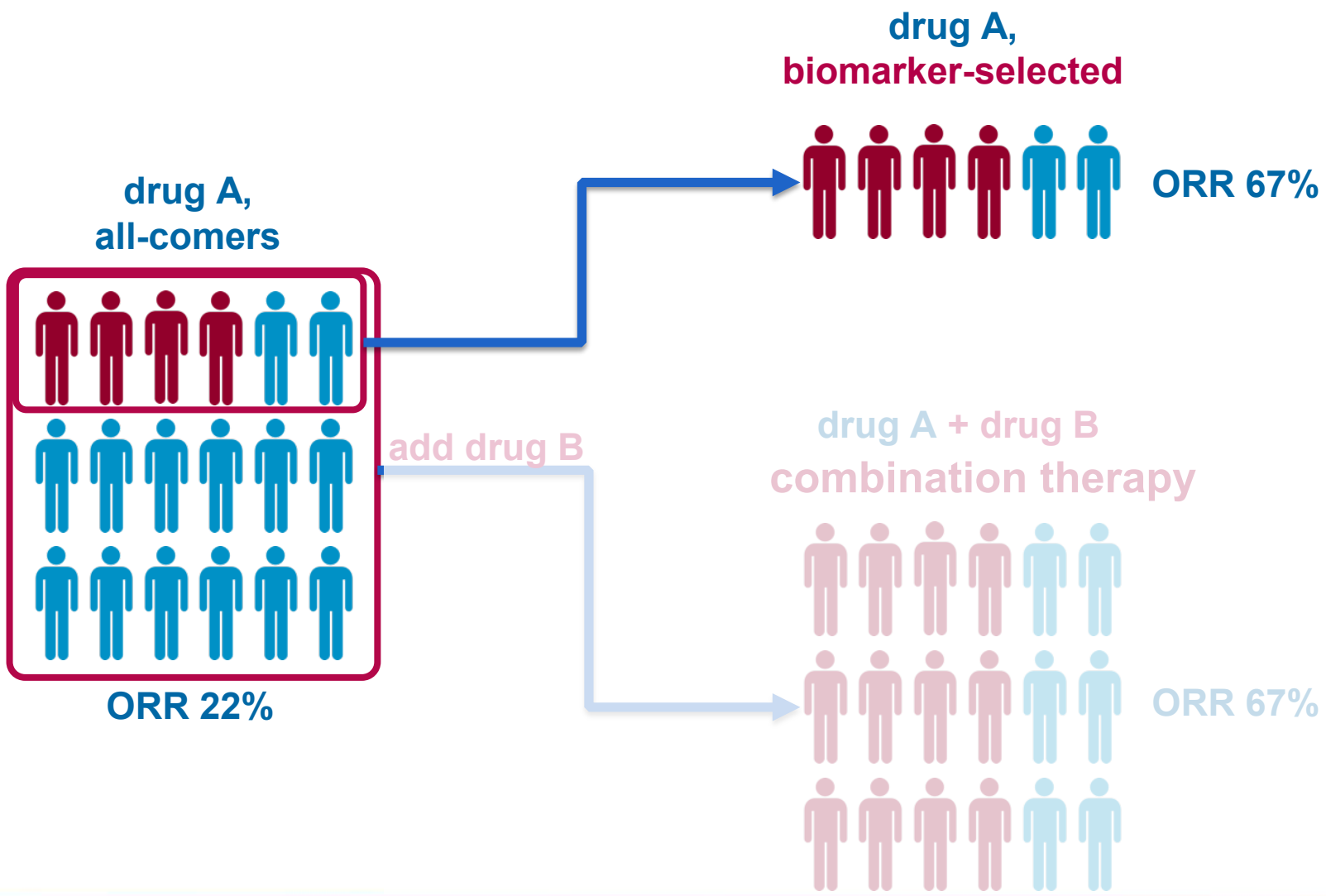
Expanding economical impact[8]



ICI, immune-checkpoint inhibitors; I-O, immuno-oncology.

1. Keytruda Summary of Product Characteristics. 2. Opdivo Summary of Product Characteristics. 3. Yervoy Summary of Product Characteristics. 4.Tecentriq Summary of Product Characteristics. 5. Imfinzi Summary of Product Characteristics. 6. Bavencio Summary of Product Characteristics. 7. Ciombor KK and Goldberg RM. *Drugs* 2018;78:155–162. 8. Webster RM. *Nature Reviews Drug Discovery* 2014;13:883–884.

Why do we need biomarkers in (immuno-)oncology?



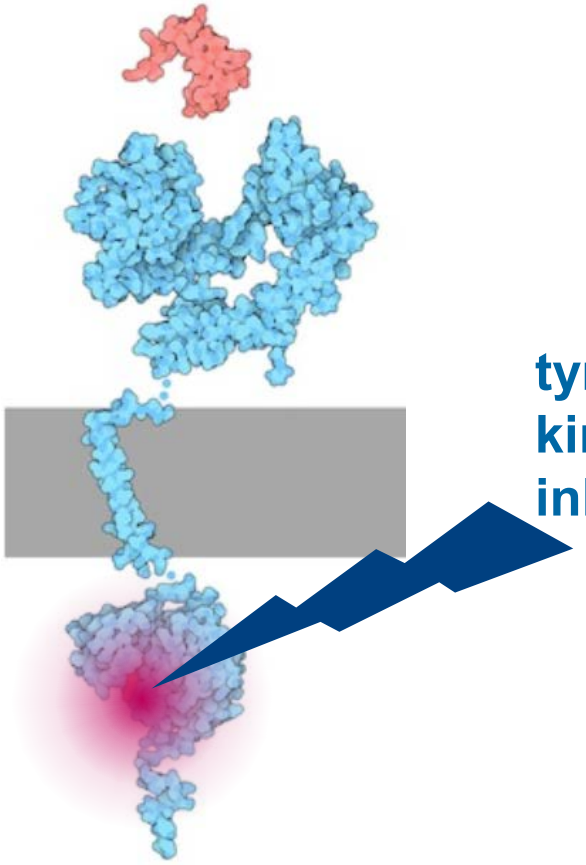
Why do we need biomarkers in (immuno-)oncology?

- To increase efficacy of a drug (identify optimal ‘responders’)
  - = avoid unnecessarily treating non-responders
- To avoid toxicity (identify individuals at risk for major side-effects)
- To keep healthcare sustainable in the face of constrained government budgets

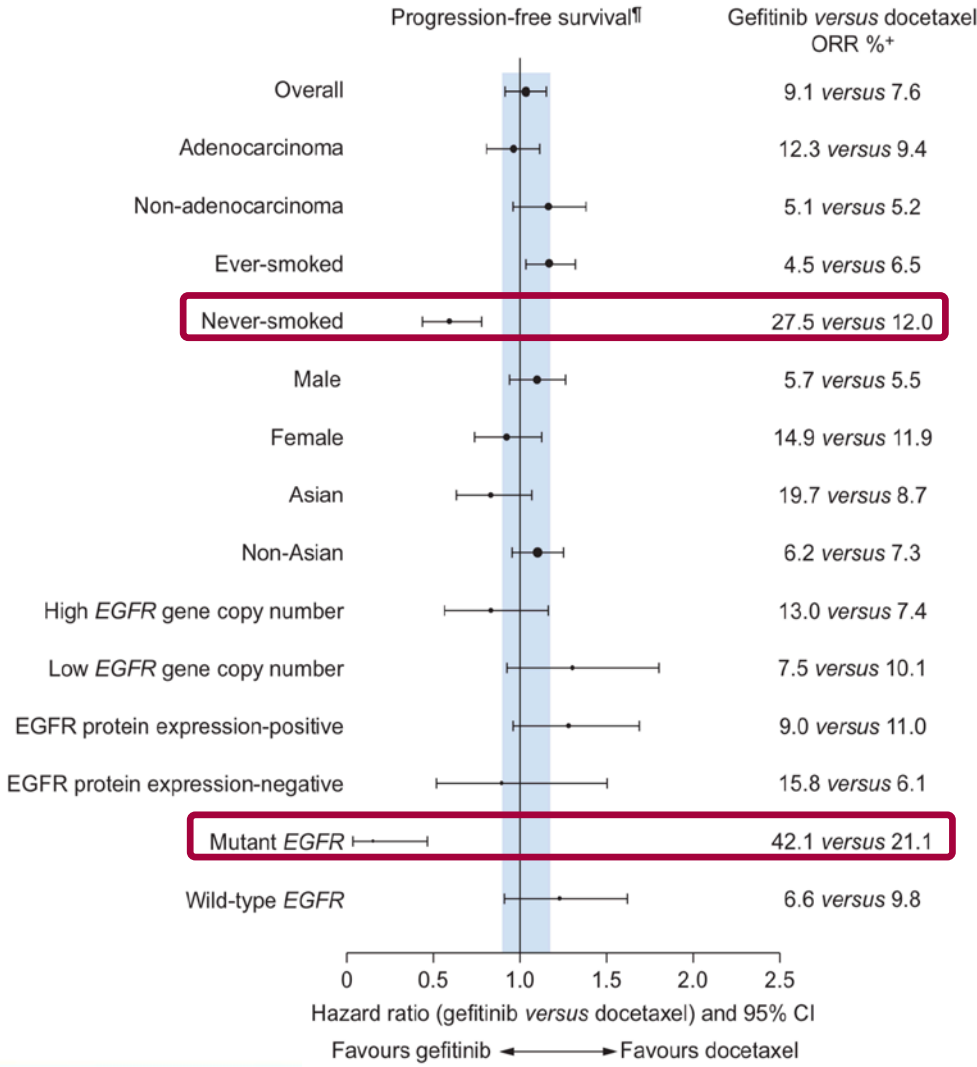
Karim Vermaelen, personal communication, 2018.

Going back in time: biomarkers for targeted therapies

EGFR with activating mutation



tyrosine kinase inhibitor

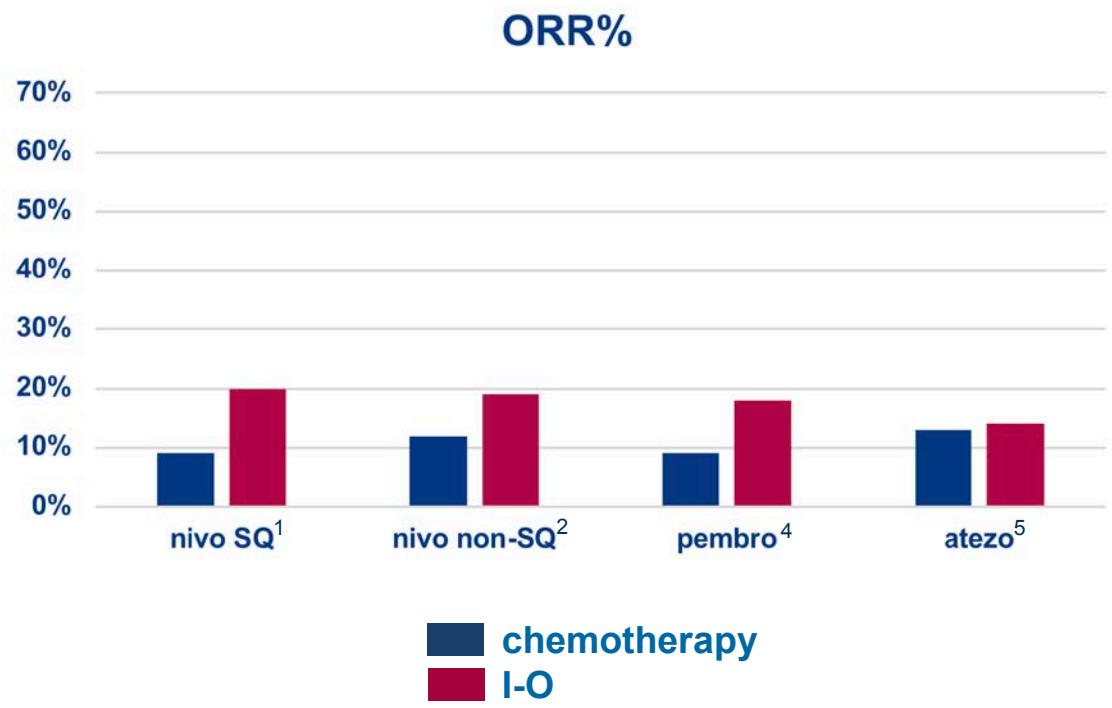


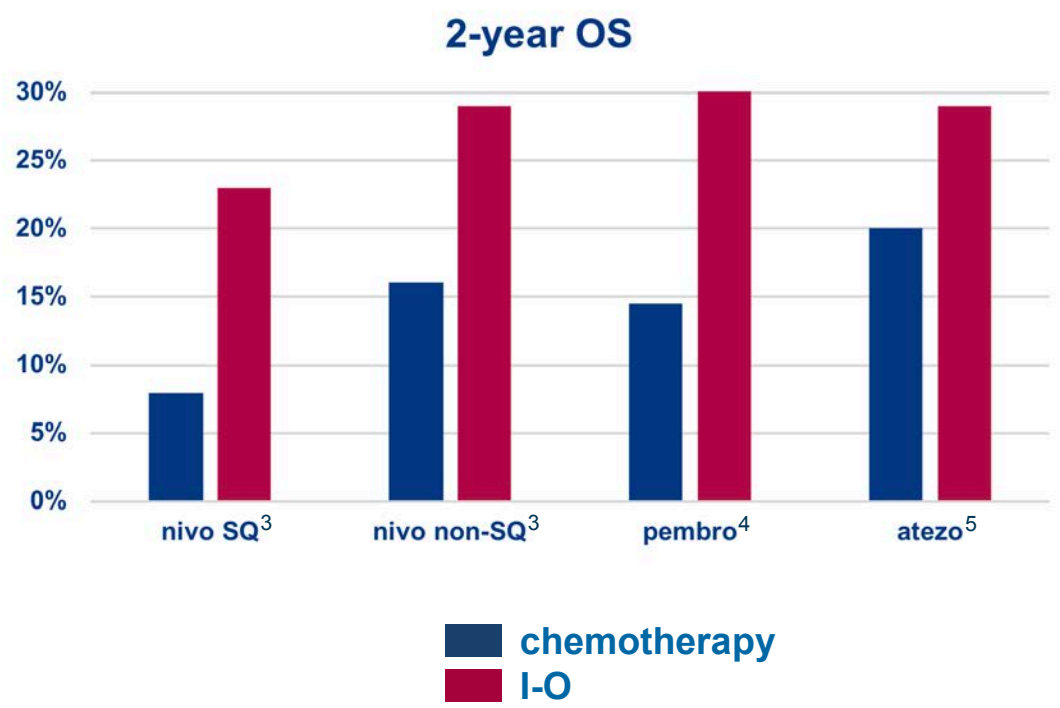
CI, confidence interval; EGFR, epidermal growth factor receptor; ORR, overall response rate.

Armour AA and Watkins CL. *Eur Resp Rev* 2010;19:186–196.

Performance plateau of checkpoints in monotherapy

Immune checkpoint inhibition in monotherapy: performance in second-line NSCLC



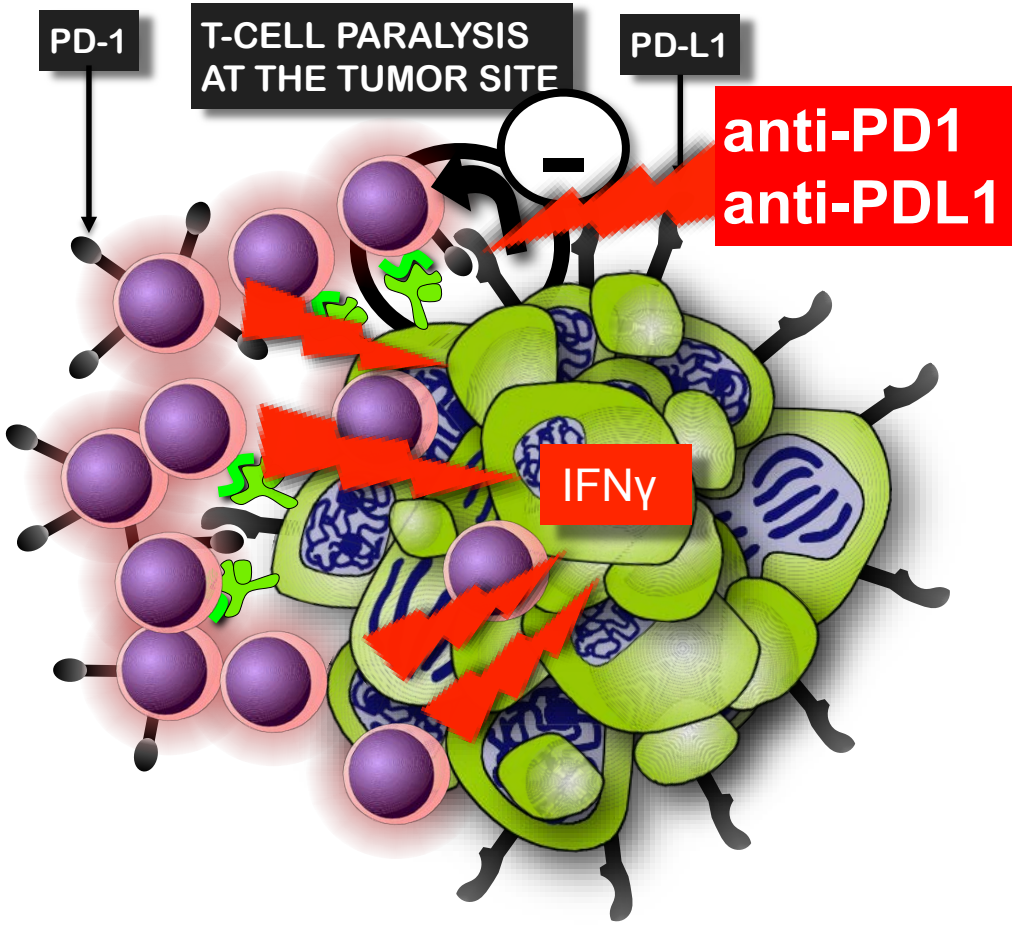


I-O, immuno-oncology; NSCLC, non-small-cell lung carcinoma; ORR, overall response rate; OS, overall survival; SQ, squamous.

1. Brahmer J et al. *N Engl J Med* 2015;373:123-35. 2. Borghaei H et al. *N Engl J Med* 2015;373:1627–1639 3. Horn L et al. *J Clin Oncol* 2017;35:3924–3933. 4. Herbst R et al. *Lancet*. 2016;387:1540–50. 5. Rittmeyer A et al. *Lancet* 2017;389:255–265.

Predictive biomarkers for immunotherapy: PD-L1

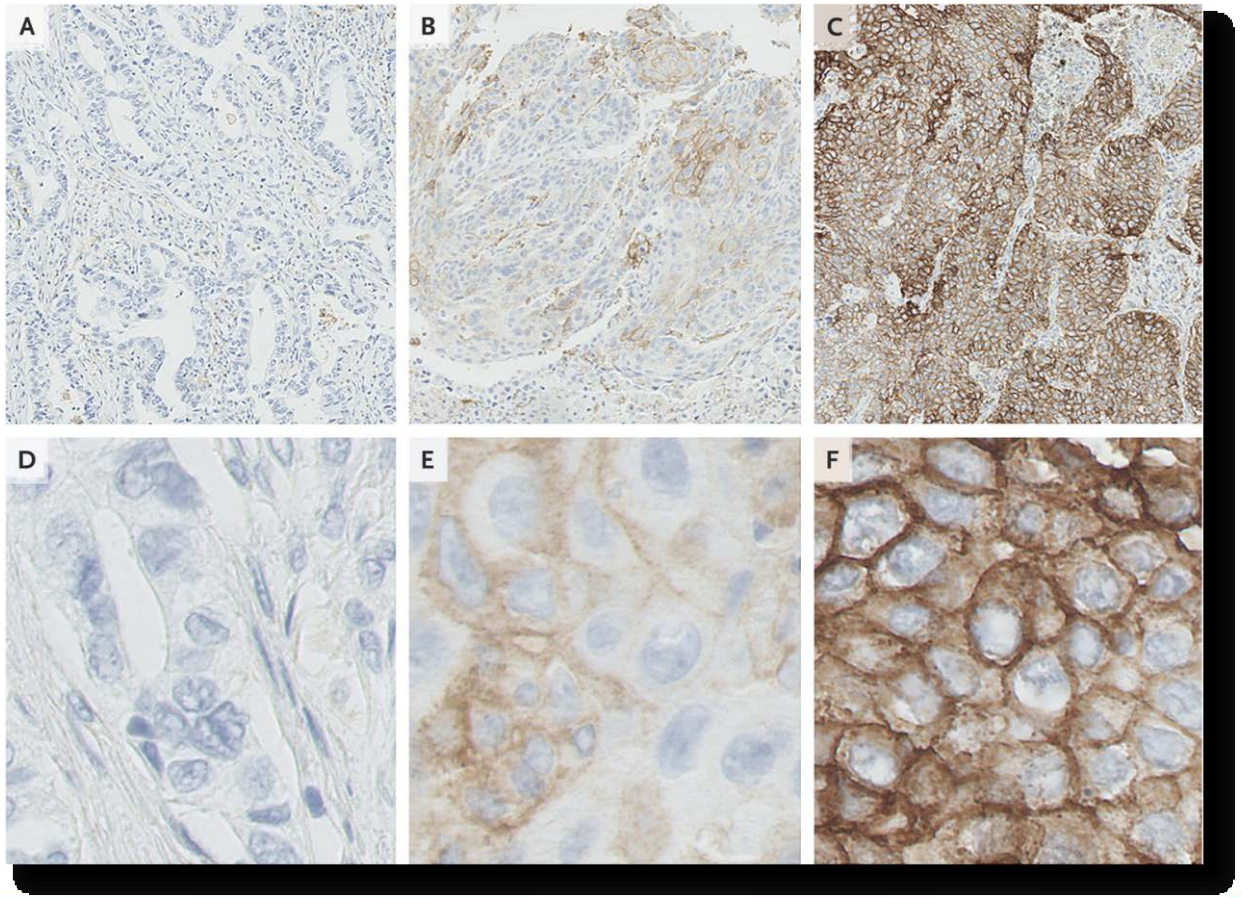
- PD-L1 appears on cancer cells following immune attack
- PD-L1 paralyzes immune cells carrying PD-1



IFN, interferon; PD-L1, programmed death-ligand 1.
Karim Vermaelen, personal communication, 2018.

Predictive biomarkers for immunotherapy: PD-L1

PD-L1 expression is scored on tumor samples (biopsies, some cytological samples)

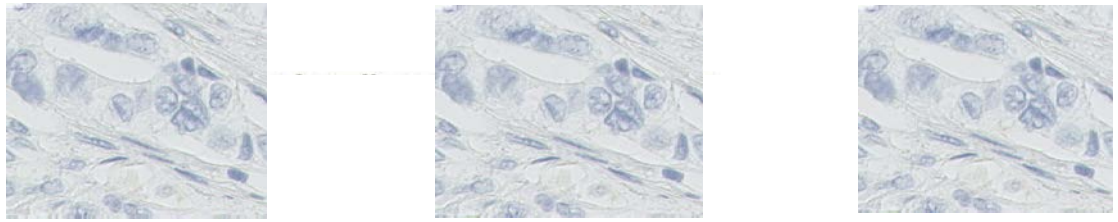


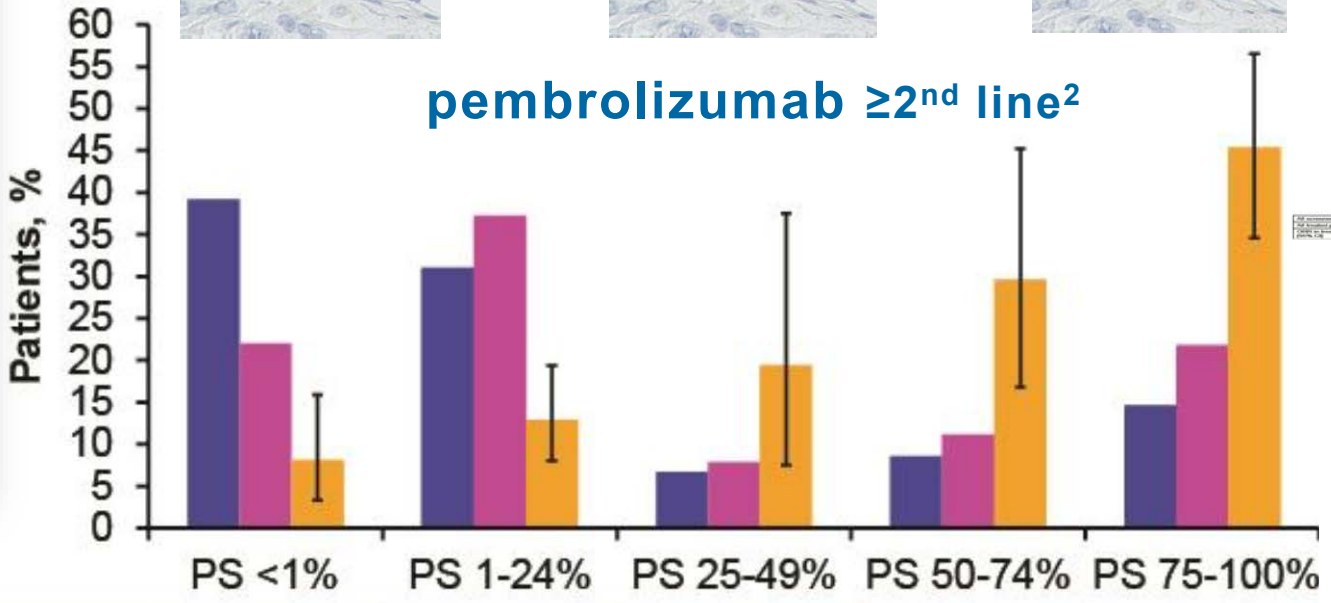
PD-L1, programmed death-ligand 1.

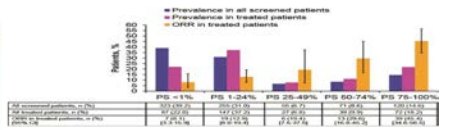
Garon EB et al. N Engl J Med. 2015;372:2018–2028.

Predictive biomarkers for immunotherapy: PD-L1

PD-L1 expression enriches for higher response rate and better survival[1]







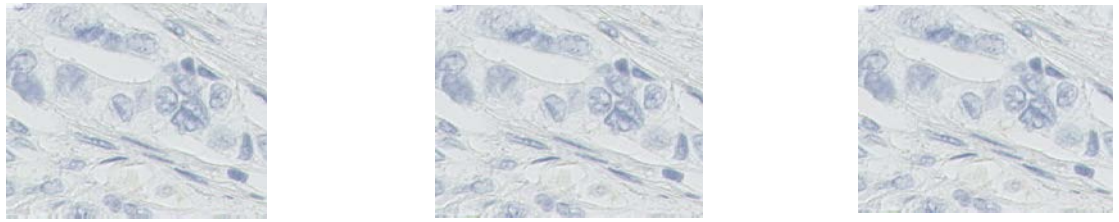
	PS <1%	PS 1-24%	PS 25-49%	PS 50-74%	PS 75-100%
All screened patients, n (%)	323 (39.2)	255 (31.0)	55 (6.7)	71 (8.6)	120 (14.6)
All treated patients, n (%)	87 (22.0)	147 (37.2)	27 (6.8)	39 (9.9)	72 (18.2)
ORR in treated patients, n (%) [95% CI]	7 (8.1) [3.3-15.9]	19 (12.9) [8.0-19.4]	6 (19.4) [7.5-37.5]	13 (29.6) [16.8-45.2]	39 (45.4) [34.6-56.5]

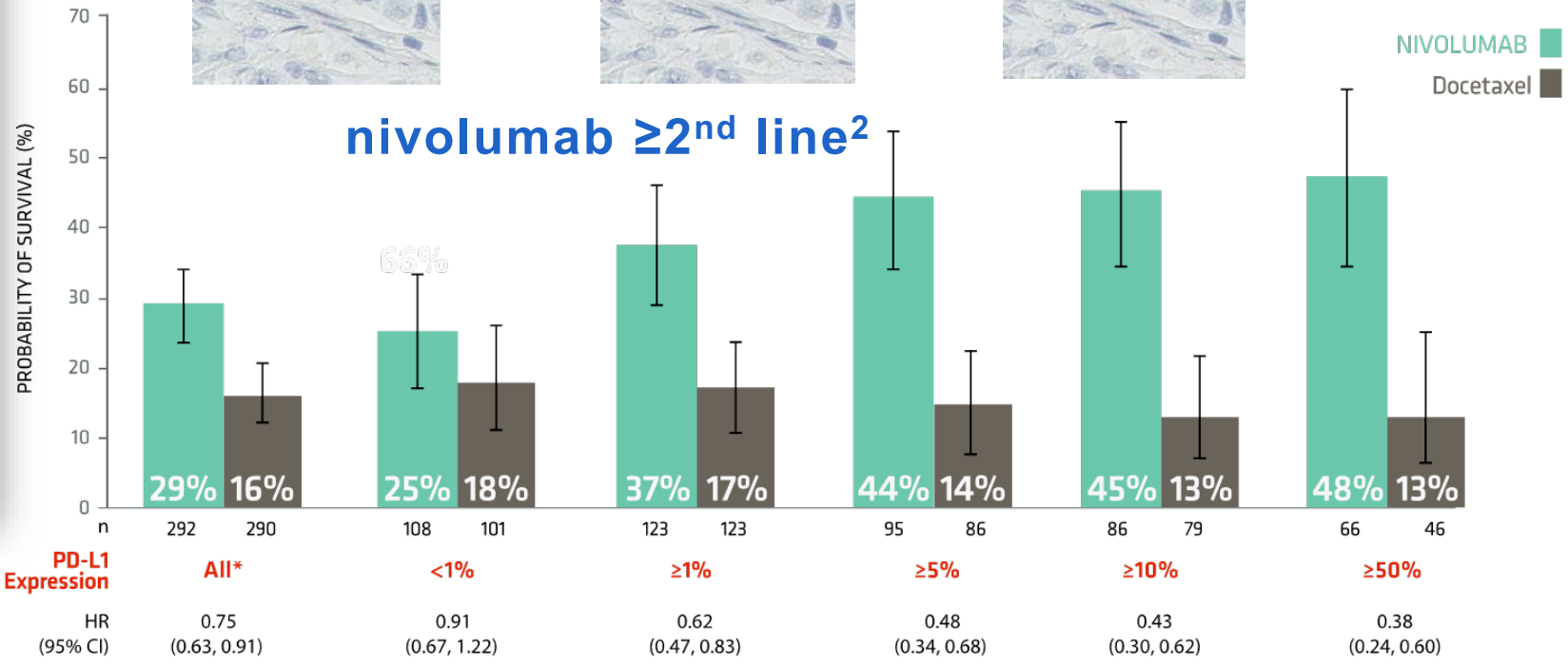
CI, confidence interval; ORR, overall response rate; PD-L1, programmed death-ligand 1; PS, proportion score.

1. Garon EB et al. *N Engl J Med*. 2015;372:2018–2028. 2. Garon EB et al. *N Engl J Med*. 2015;372:2018–2028 supplementary material.

Predictive biomarkers for immunotherapy: PD-L1

PD-L1 expression enriches for higher response rate and better survival[1,2]



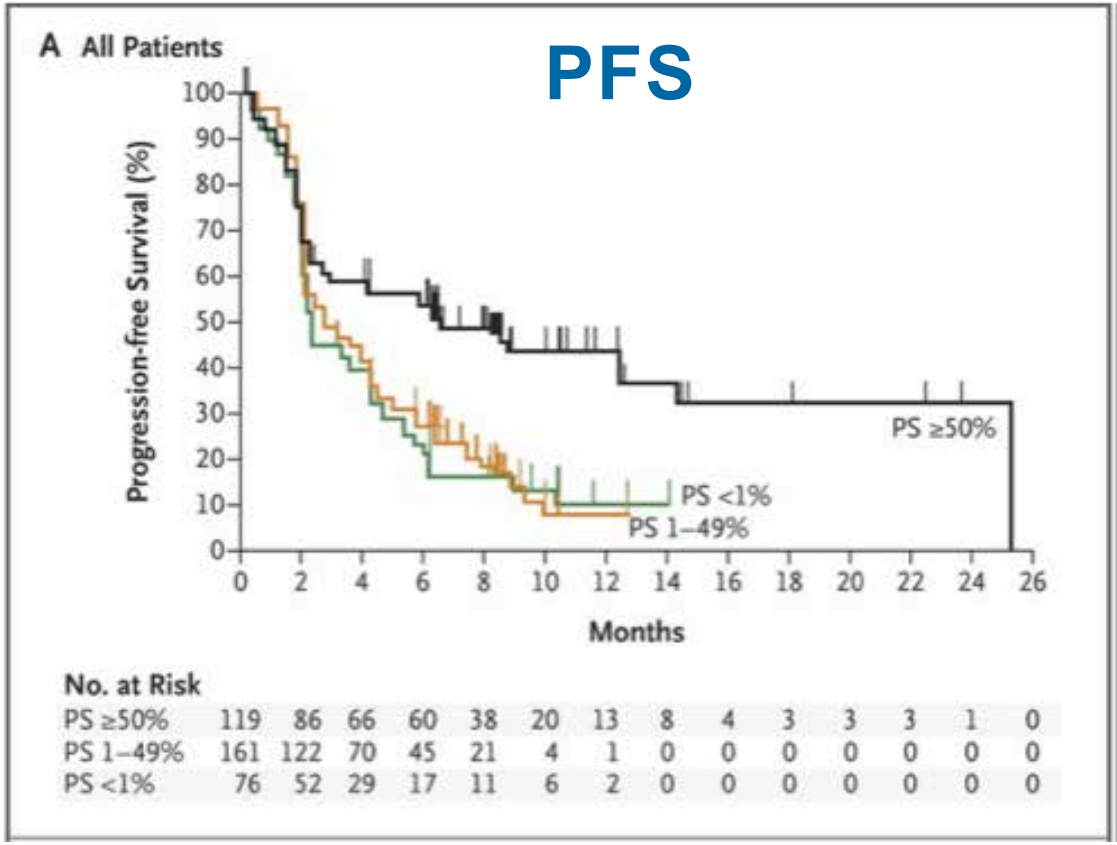


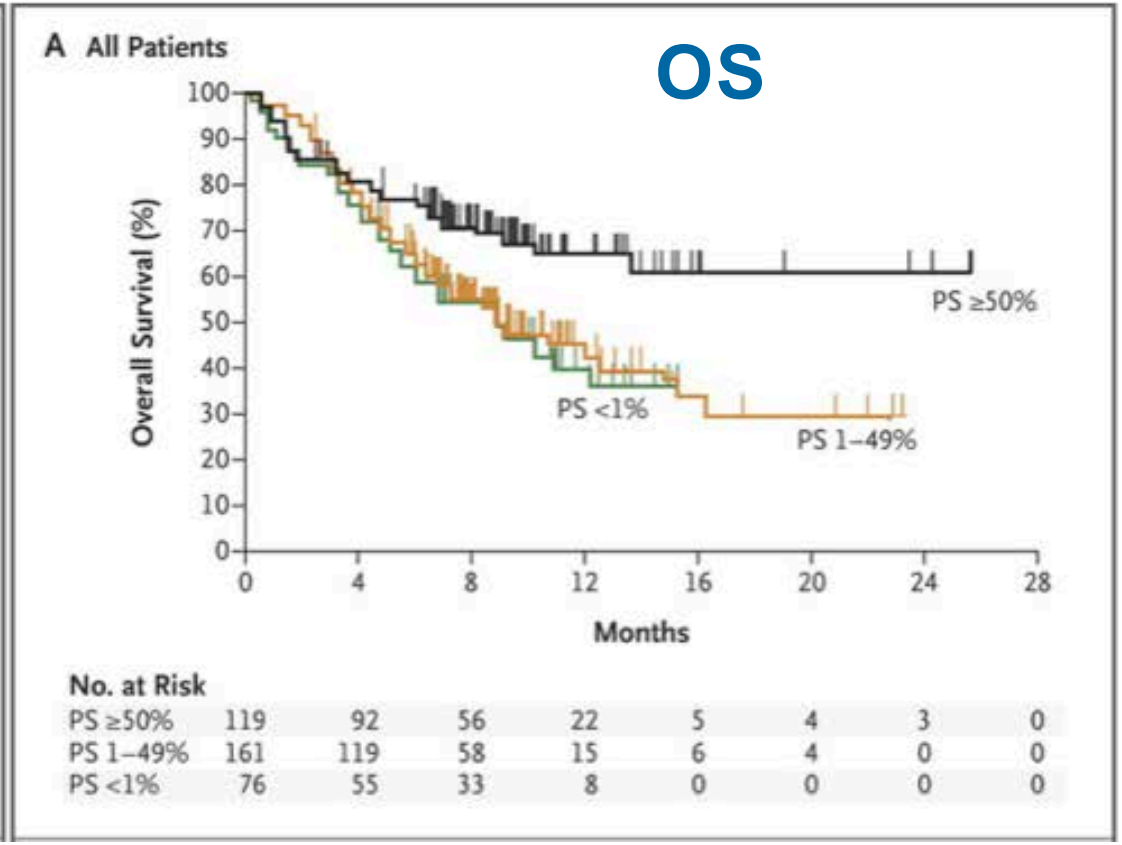
*All patients include those with no quantifiable PD-L1 expression
**Belgium
CI, confidence interval; HR, hazard ratio; PD-L1, programmed death-ligand 1.
1. Garon EB et al. *N Engl J Med*. 2015;372:2018–2028. 2. Horn L et al. *J Clin Oncol*. 2017;35:3924–3933.

Predictive biomarkers for immunotherapy: PD-L1

PD-L1 expression enriches for higher response rate, better survival

pembrolizumab ≥2nd line



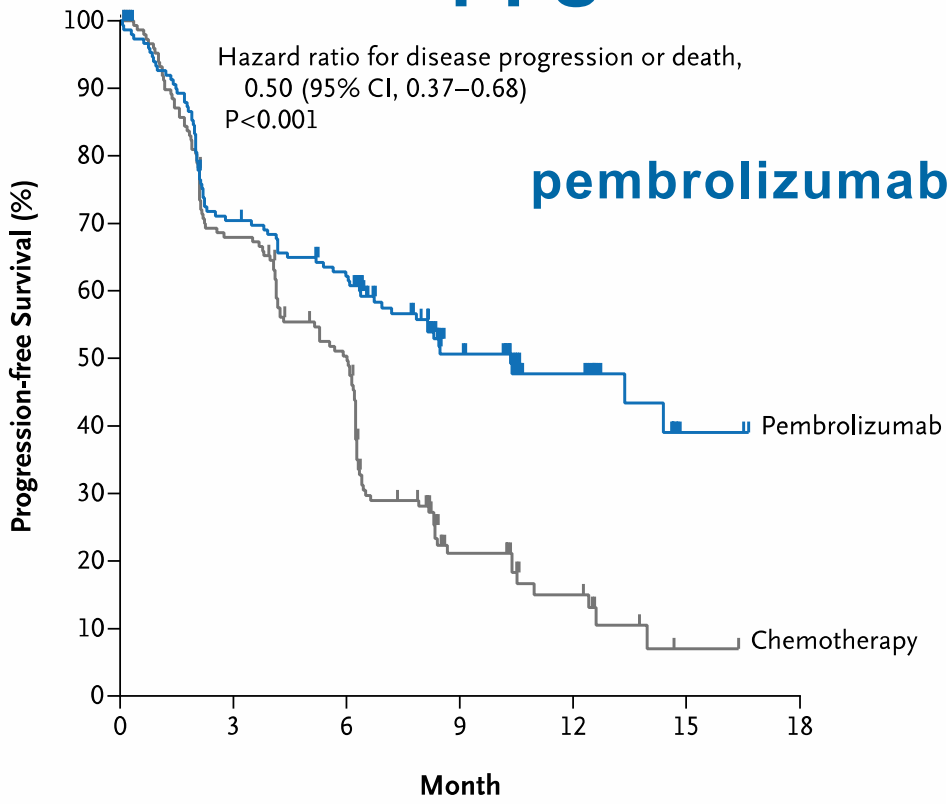


OS, overall survival; PD-L1, programmed death-ligand 1; PFS, progression free survival; PS, proportion score.
Garon EB et al. *N Engl J Med*. 2015;372:2018–2028.

Predictive biomarkers for immunotherapy: PD-L1

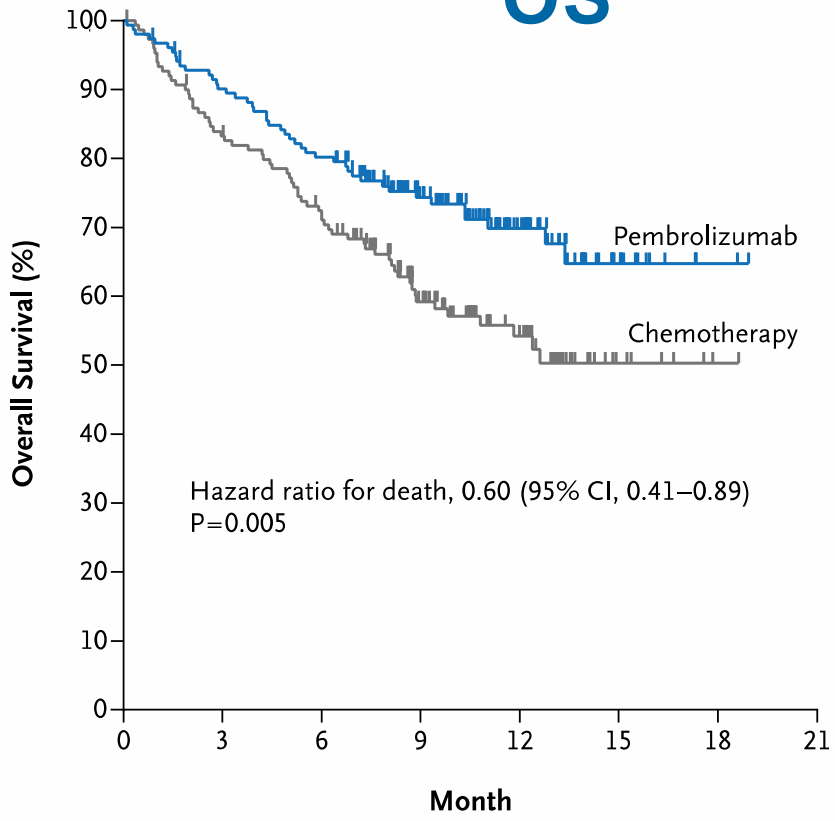
PD-L1 > 50% → immunotherapy beats chemotherapy in 1st line

PFS



No. at Risk							
Pembrolizumab	154	104	89	44	22	3	1
Chemotherapy	151	99	70	18	9	1	0

OS



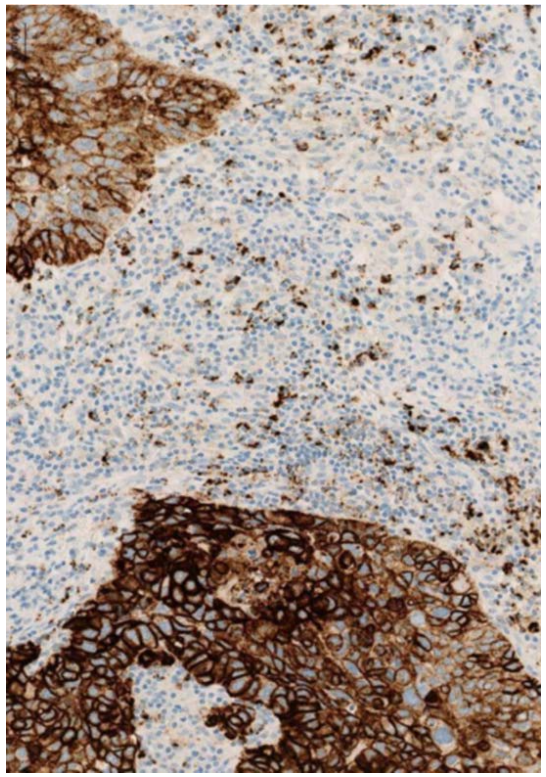
No. at Risk								
Pembrolizumab	154	136	121	82	39	11	2	0
Chemotherapy	151	123	106	64	34	7	1	0

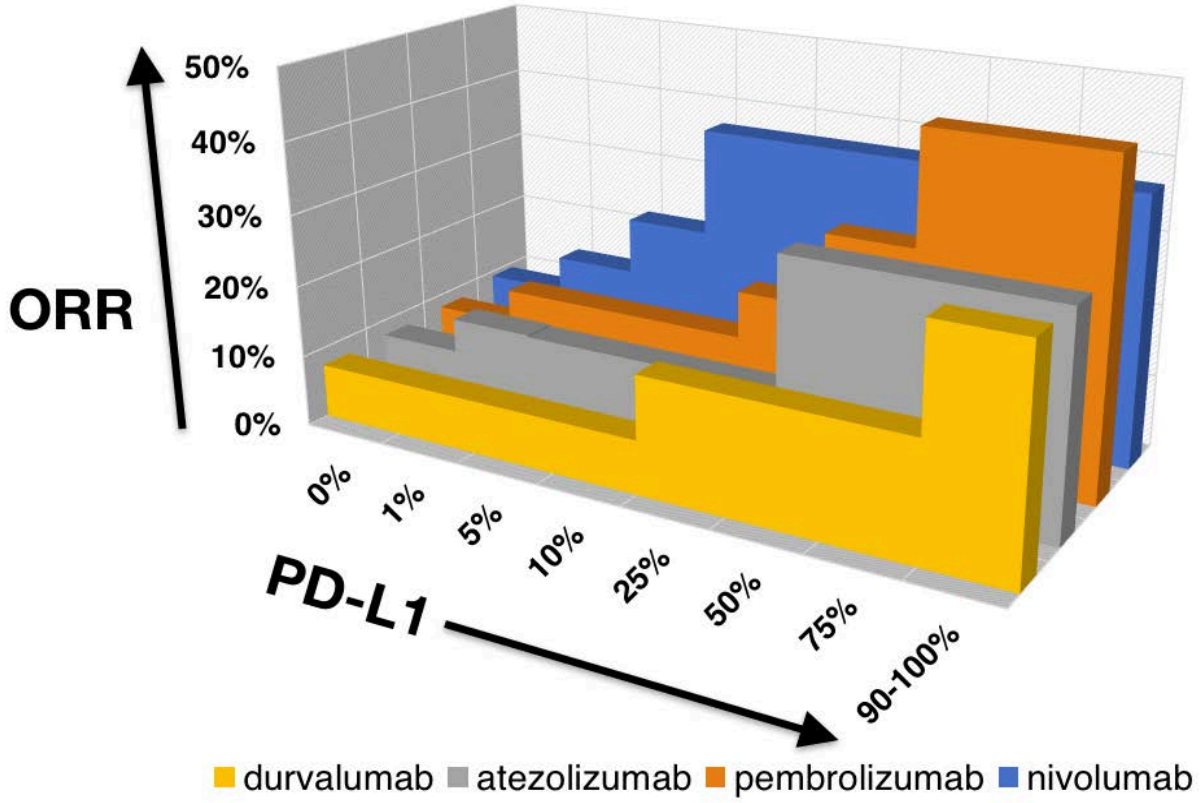
CI, confidence interval; OS, overall survival; PD-L1, programmed death-ligand 1; PFS, progression free survival.

Reck M et al. *N Engl J Med.* 2016;375:1823–1833.

Predictive biomarkers for immunotherapy: PD-L1

PD-L1 expression enriches for higher response rate, better survival

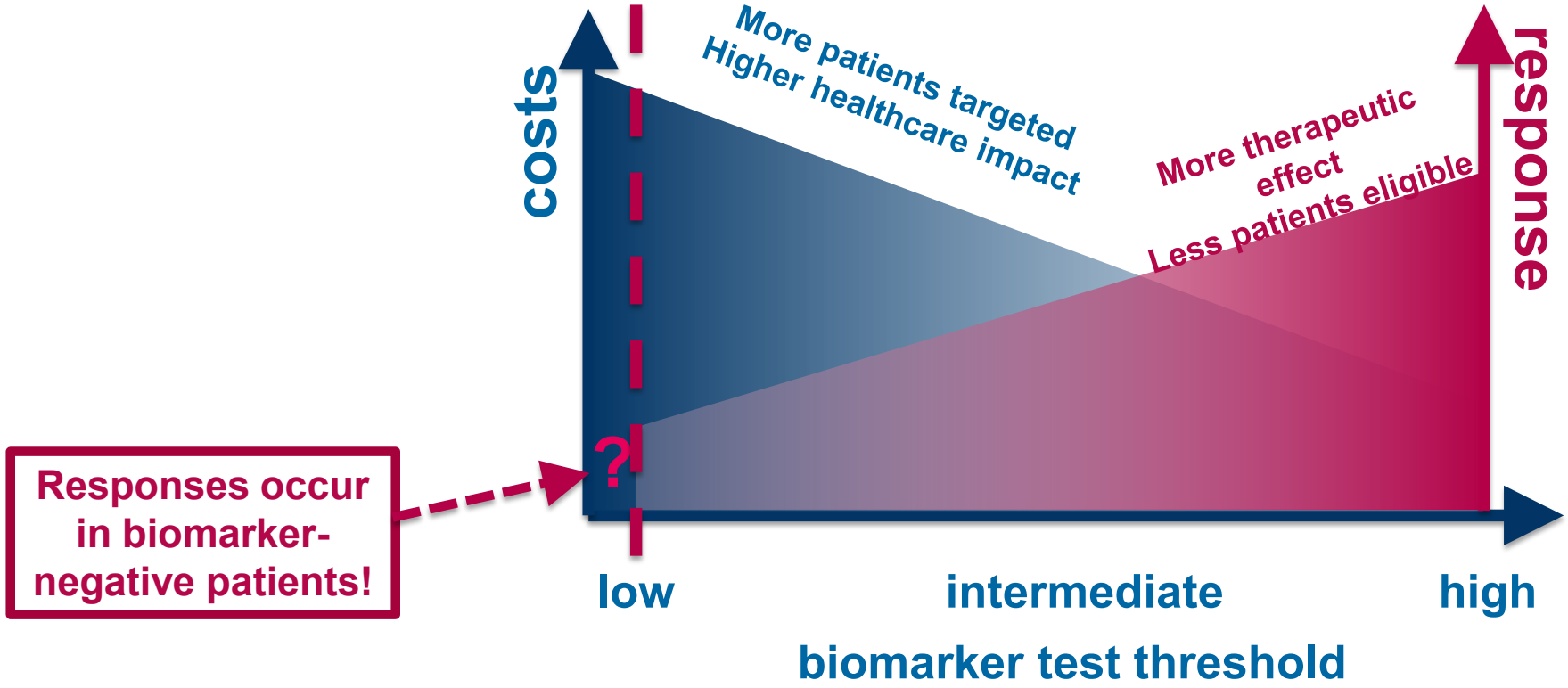




ORR, overall response rate; PD-L1, programmed death-ligand 1.
Vermaelen K et al. *Semin Cancer Biol* 2018;52:166–177.

Predictive biomarkers for immunotherapy: PD-L1

PD-L1 testing does not provide a sharp cut-off to separate responders from non-responders

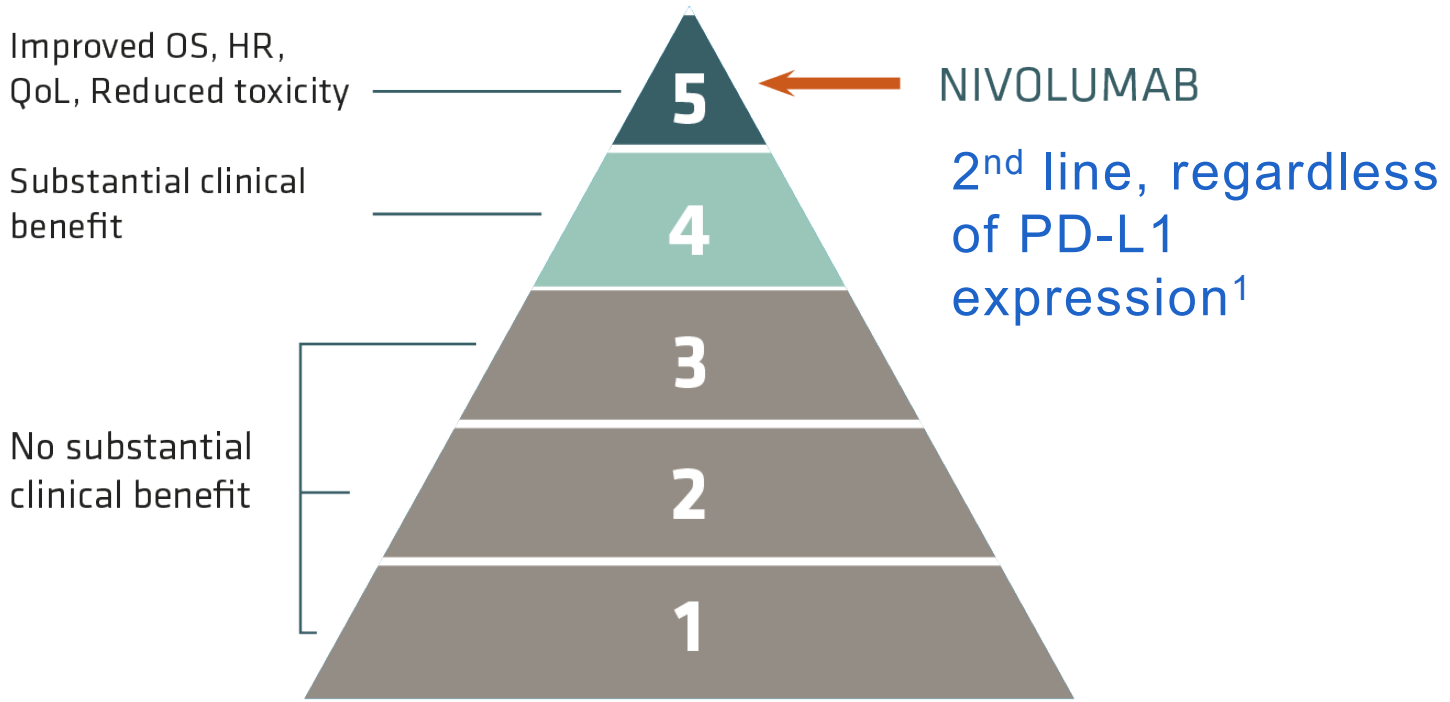


PD-L1, programmed death-ligand 1.
Karim Vermaelen, personal communication, 2018.

Predictive biomarkers for immunotherapy: PD-L1

Clinical benefit can be observed across the whole range of PD-L1 score

ESMO Clinical Guidelines



ESMO Magnitude of Clinical Benefit Scale (ESMO-MCBS) V1.0*2

*The ESMO Magnitude of Benefit Scale (ESMO-MCBS) is a validated and reproducible tool to assess the magnitude of clinical benefit for cancer medicines. The potential benefits of a new treatment can be summarized as either living longer and/or living better, compared with a control (usually the best current standard care). For second-line treatment of EGFR- and ALK-negative disease, Nivolumab at 3 mg/kg every 2 weeks is recommended in pretreated patients with advanced squamous cell carcinoma (SCC) [I, A; ESMO-MCBS v1.0 score: 5] and it represents a treatment option in pretreated patients with advanced non-squamous cell carcinoma (NSCC) [I, B; ESMO-MCBS v1.0 score: 5]. For NSCC, PD-L1-positive tumour patients benefitted from the use of Nivolumab, compared with docetaxel [II,A] and in PD-L1-negative tumours, Nivolumab and docetaxel showed similar results, with a more favourable toxicity profile for Nivolumab [II,B].

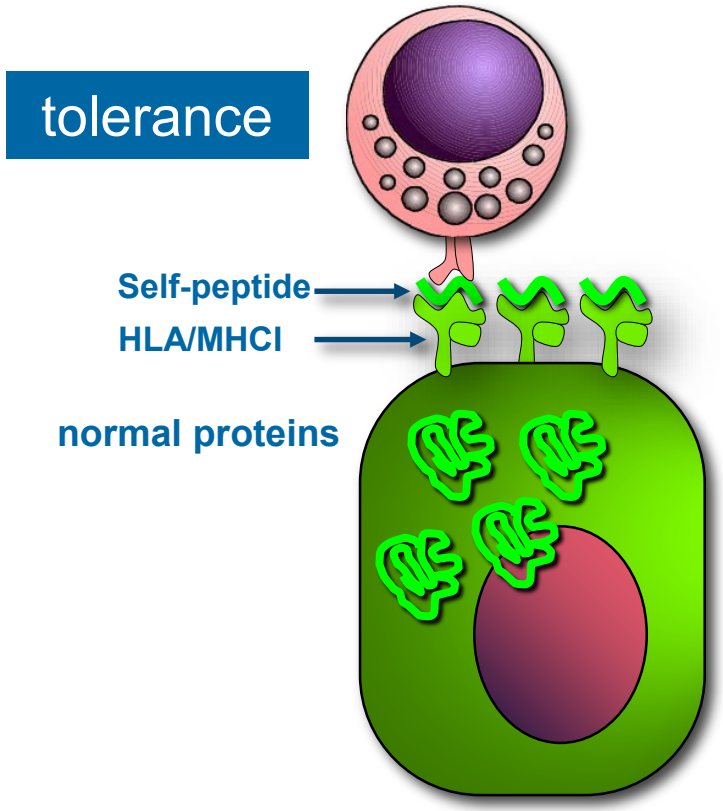
HR, hazard ratio; OS, overall survival; PD-L1, programmed death-ligand; QoL, quality of life. 1. Novello S et al. *Ann Oncol*. 2016;27(suppl 5):v1-v27. 2. Chery NI et al. *Annals of Oncol* 2015;26:1547–1573.

New predictive biomarkers for immuno-oncology

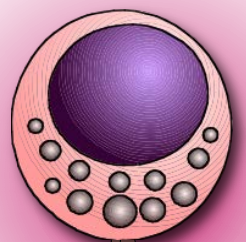
PD-L1: is there anything better on the horizon?

PD-L1, programmed death-ligand 1.

Is response to immunotherapy in the tumor genes?



killer T-cell

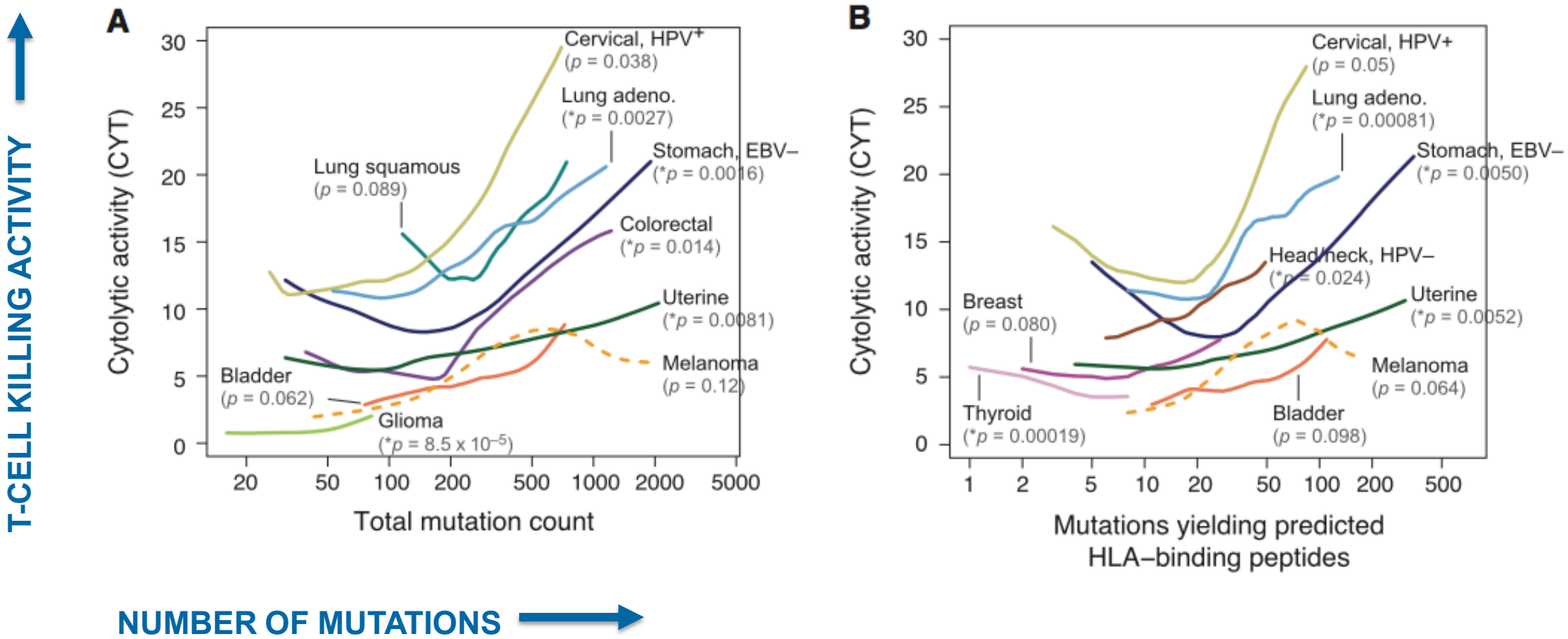


immune detection & attack

normal cell

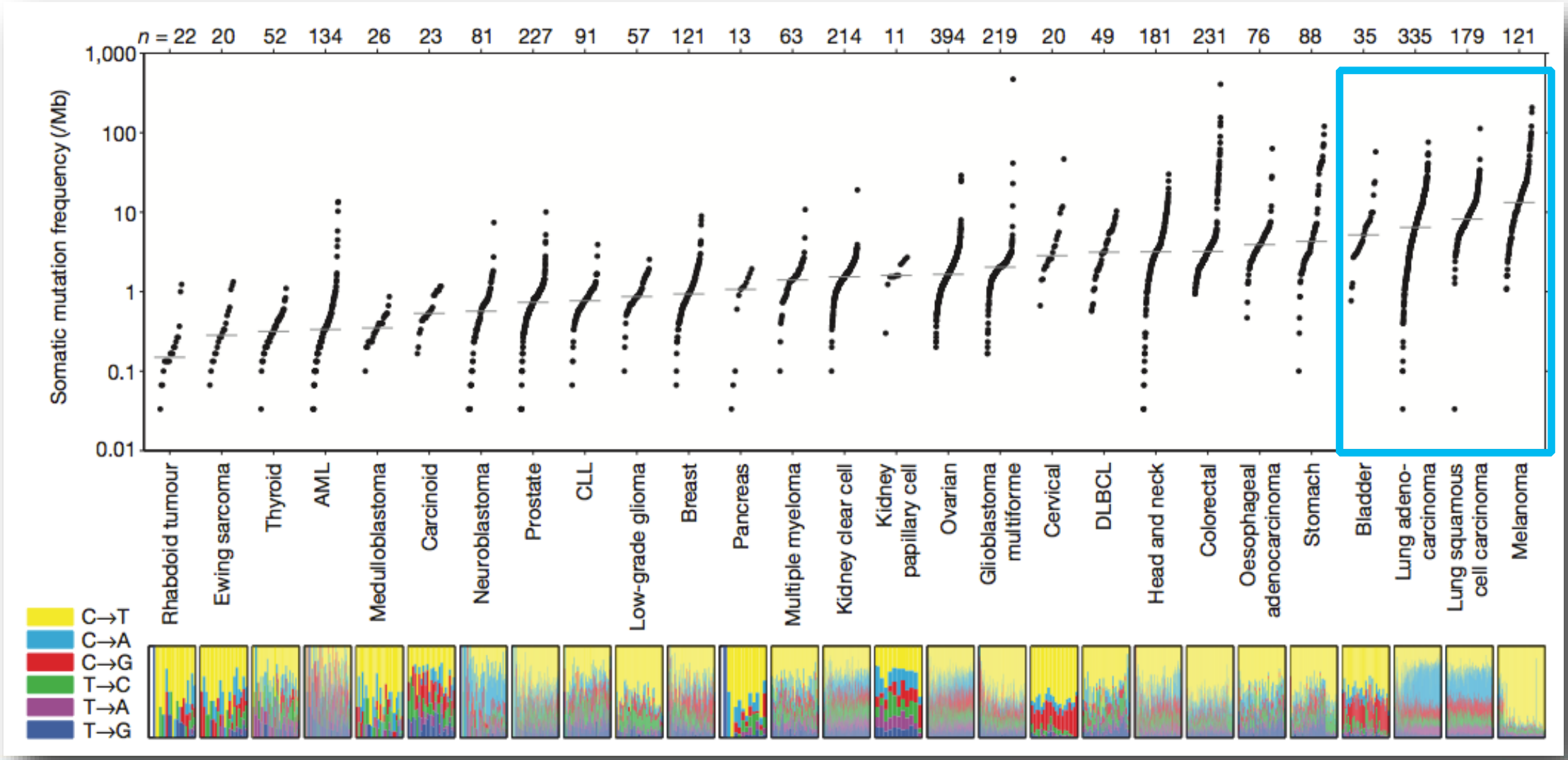
HLA, human leukocyte antigen; MHCI, major histocompatibility complex class I.
Karim Vermaelen, personal communication, 2018.

Tumor mutational burden is a driver of immunogenicity



EBV, Epstein-Barr virus; HLA, human leukocyte antigen; HPV, human papilloma virus.
Rooney MS et al. *Cell* 2015;160:48–61.

Tumor mutational burden is a driver of immunogenicity

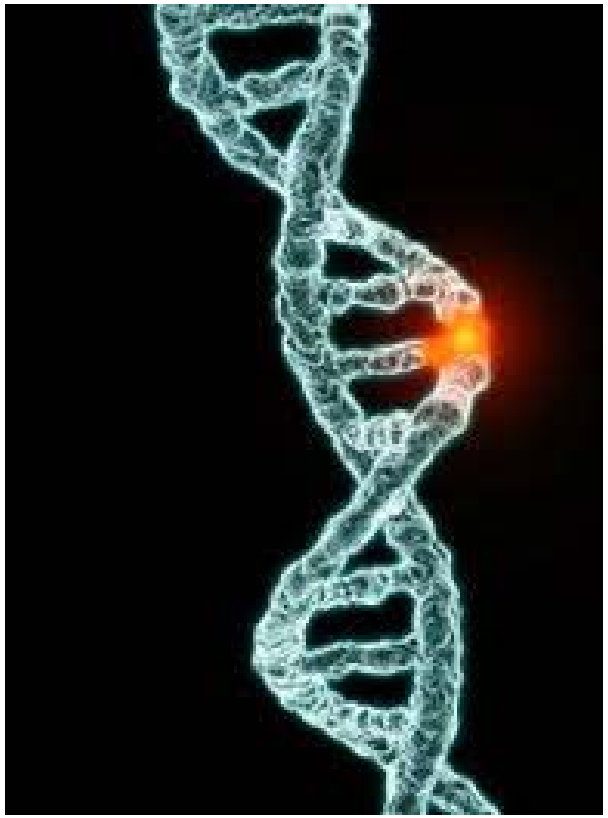


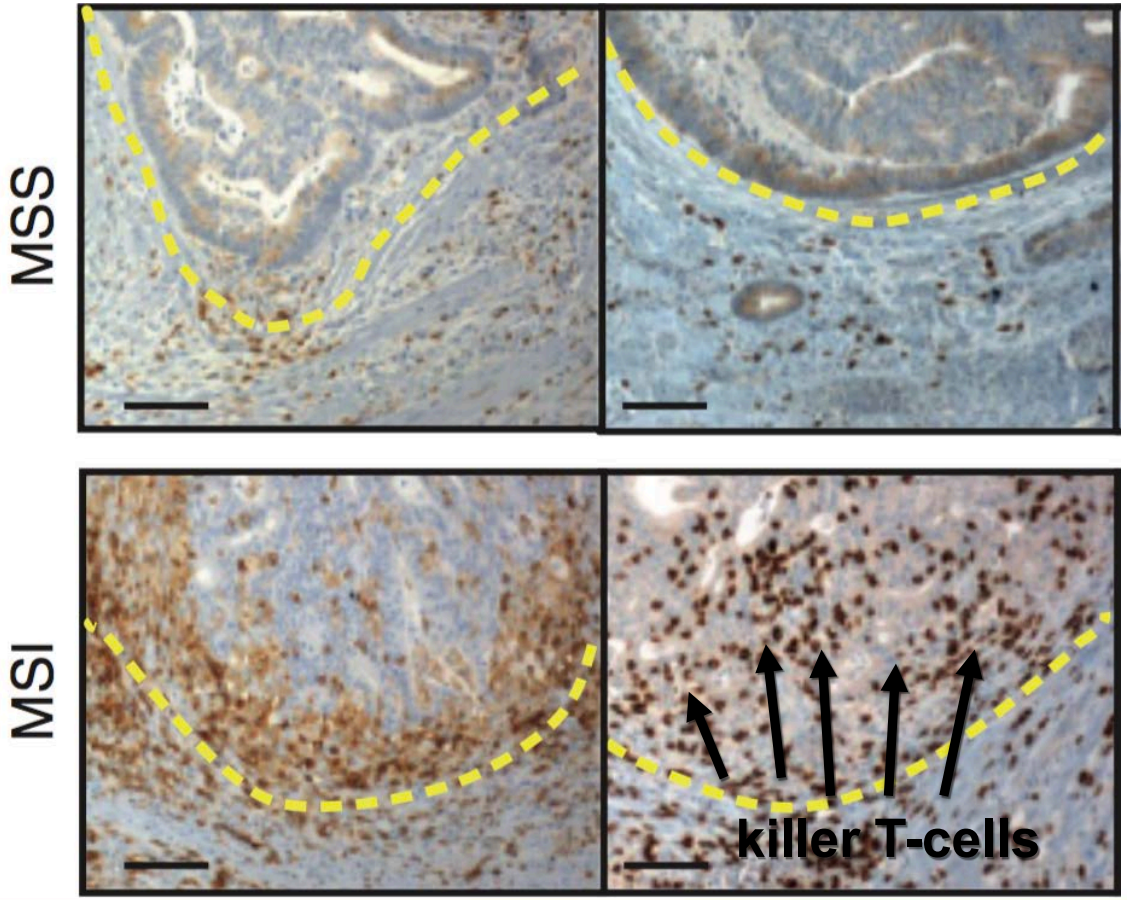
AML, acute myeloid leukemia; CLL, chronic lymphocytic leukaemia; DLBCL, diffuse large B-cell lymphoma.
Lawrence MS et al. *Nature* 2013;499:214–218.

Tumor mutational burden is a driver of immunogenicity

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

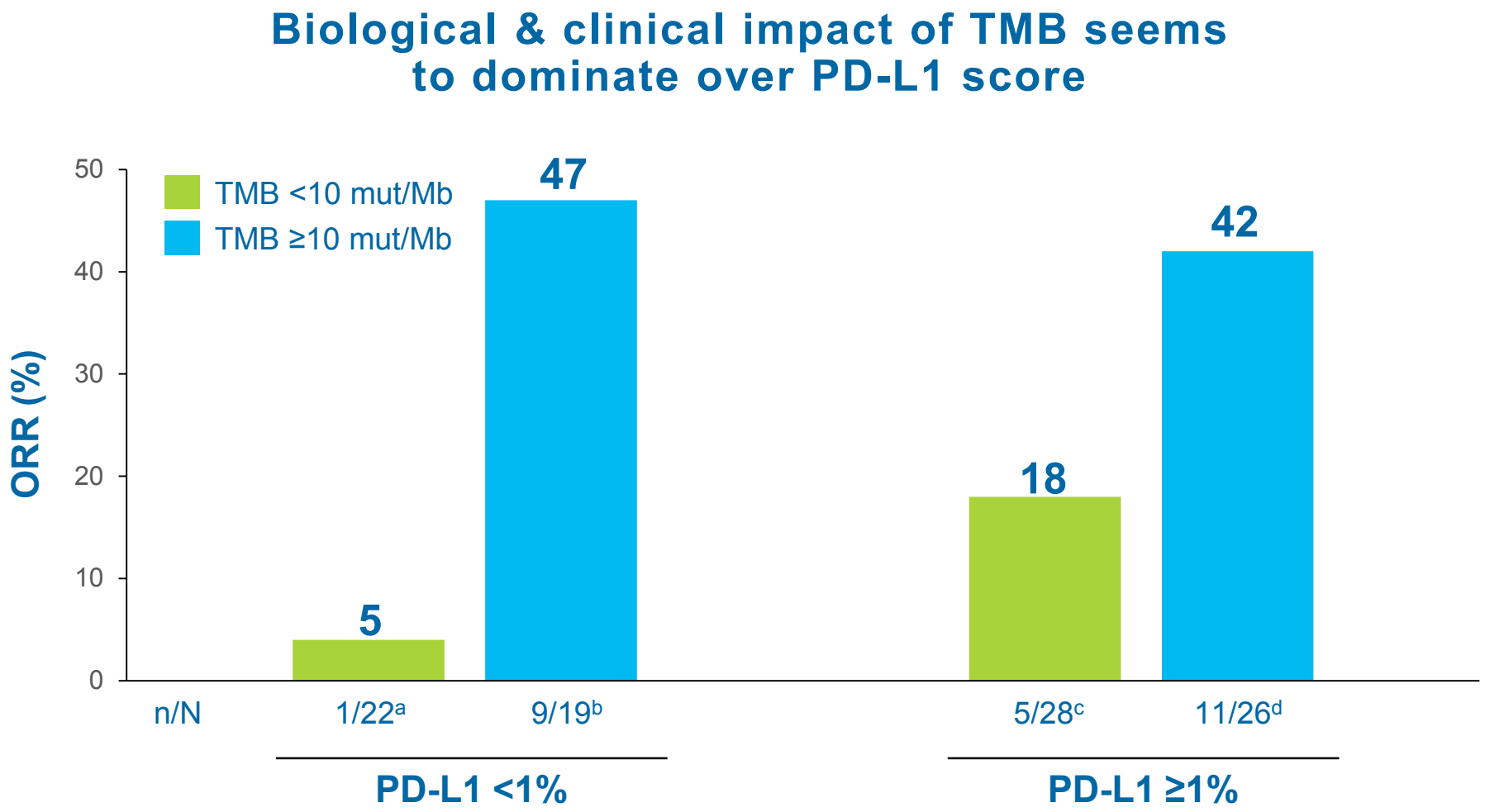
"MSI-test" as a potential biomarker of response to checkpoint blockade? → investigated





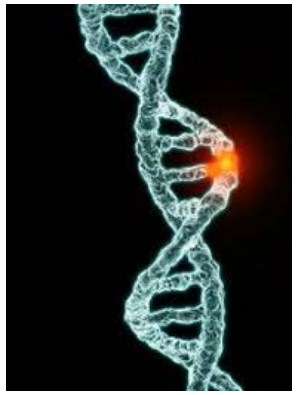
MSI, microsatellite instability MSS, microsatellite stability.
Llosa NJ et al. *Cancer Discov* 2015;5:43–51.

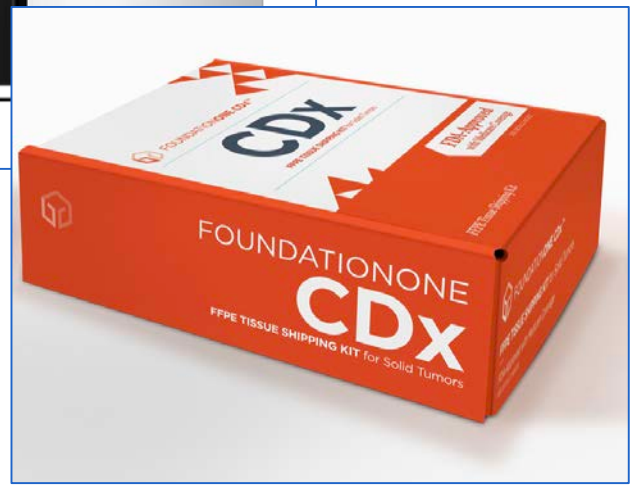
Tumor mutation burden as a predictor of response



[a]CR = 0; [b]CR = 16%; [c]CR = 4%; [d]CR = 4%.
CR, complete response; Mb, megabase; Mut, mutation; ORR, overall response rate; PD-L1, programmed death-ligand 1; TMB, tumor mutation burden.
Ramalingam S et al. AACR 2018; oral CT078.

Tumor mutation burden as a predictor of response





<u>Current</u> limitations of TMB testing for daily clinical practice:

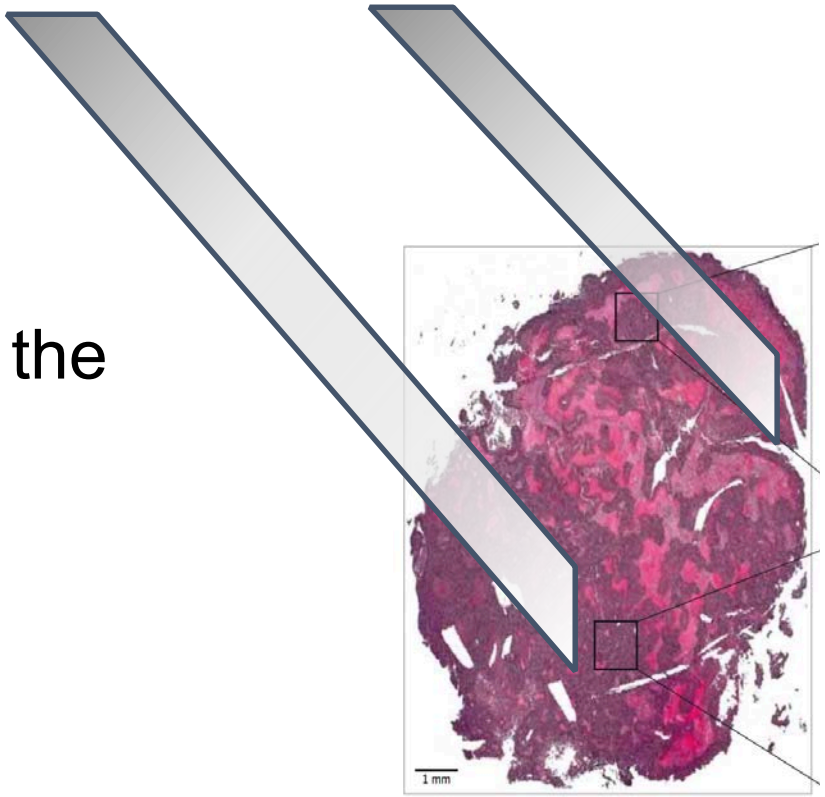
- **Time** to test result +/- 2 weeks
- **Price** per test (e.g. FMI-CDx 3000-4000€)
- Predictive power on **overall survival** warrants further investigation

TMB, tumor mutation burden.
Karim Vermaelen, personal communication, 2018.

Biomarkers in I-O: what does the future hold?

Limitations of current biomarkers:

- Limited access to tumor tissue in the metastatic setting
- Intratumor heterogeneity



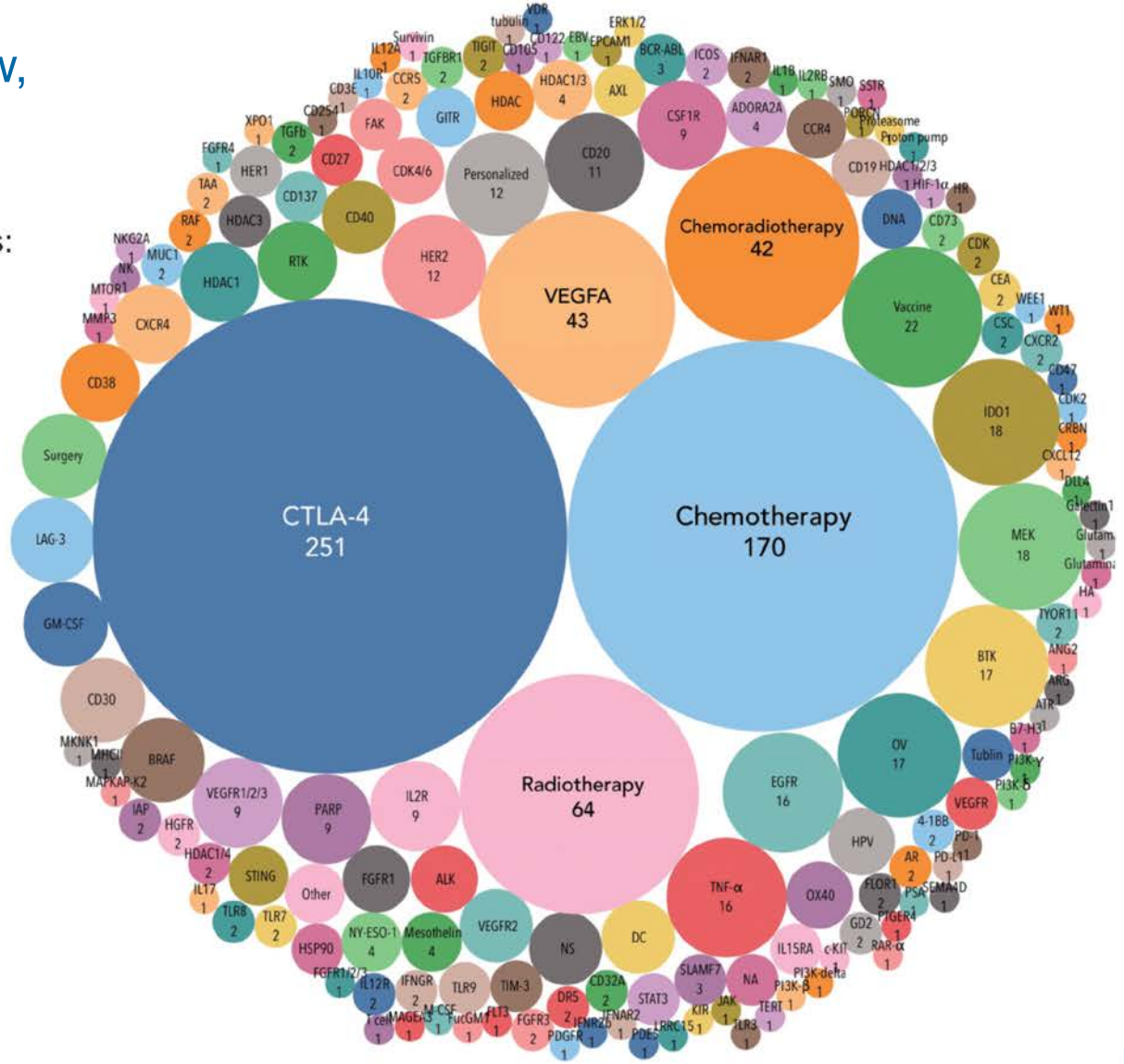
I-O, immuno oncology.
McLaughlin J et al, *JAMA Oncol* 2016;2:46–54.

Biomarkers in I-O: what does the future hold?

New immunotherapy combinations will require new, specific biomarkers!

Numbers of trials using common combo strategies:

1. Anti-CTLA-4 agents: 251
2. Chemotherapies: 170
3. Radiotherapies: 64
4. Anti-VEGFA agents: 43
5. Chemoradiotherapy combos: 42

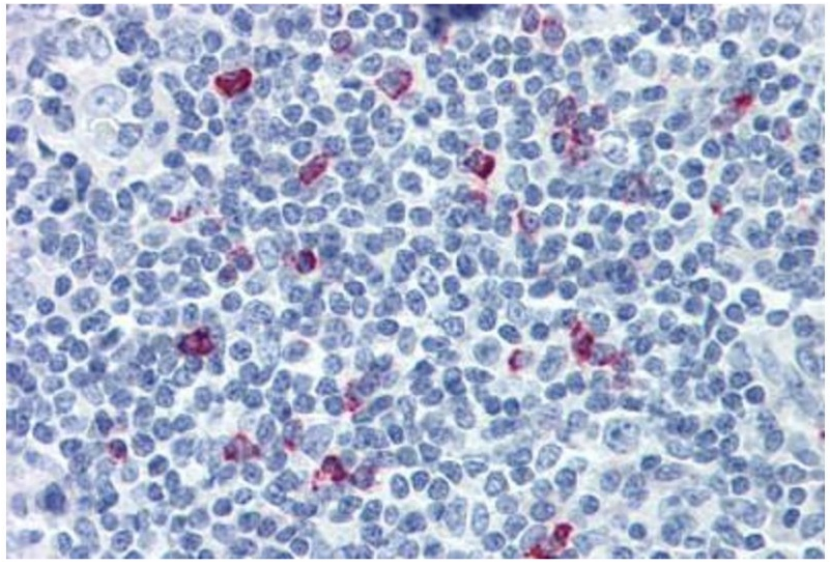


CTLA, cytotoxic T-lymphocyte-associated; I-O, immuno oncology; VEGFA, vascular endothelial growth factor A.
Tang J et al. *Annals of Oncol* 2018;29:84–91.

Biomarkers in I-O: what does the future hold?

New immunotherapy combinations may require new, specific biomarkers!

Example: LAG3 -new kid on the immune checkpoint block

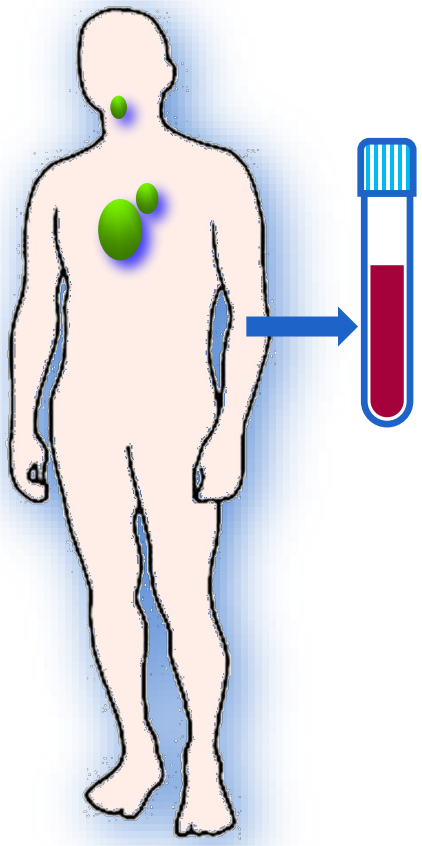


→ Early indications that LAG3-positivity on tumor tissue samples enriches for response to LAG3-targeted combination immunotherapy

→ Under investigation

LAG, lymphocyte-activation gene 3; I-O, immuno oncology.
Karim Vermaelen, personal communication, 2018.

Non-invasive biomarkers to predict response to I-O



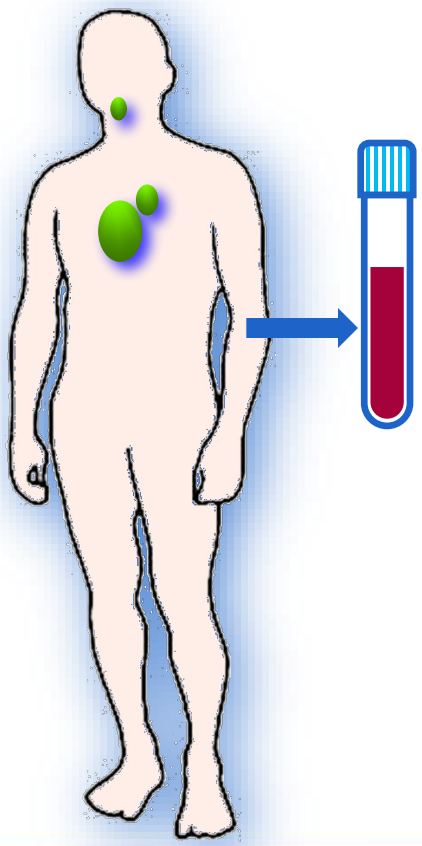
In contrast to oncogene-targeted therapies, there is no “liquid biopsy” test yet to guide treatment decision in I-O

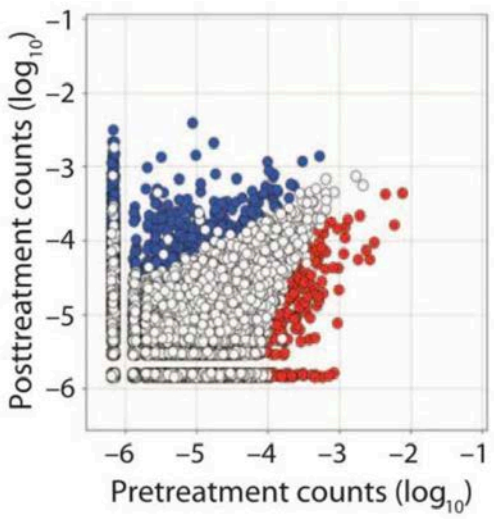
→ **TMB testing on blood is now in development**

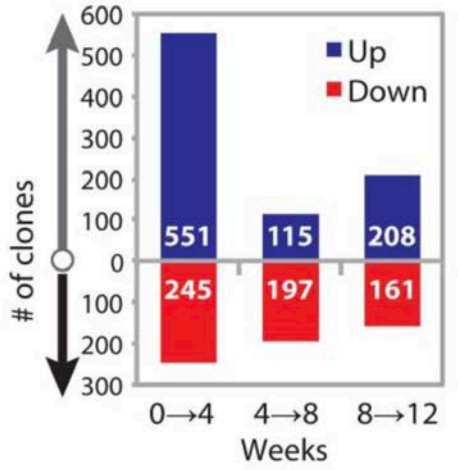
I-O, immuno oncology; TMB, tumor mutational burden.
Karim Vermaelen, personal communication, 2018.

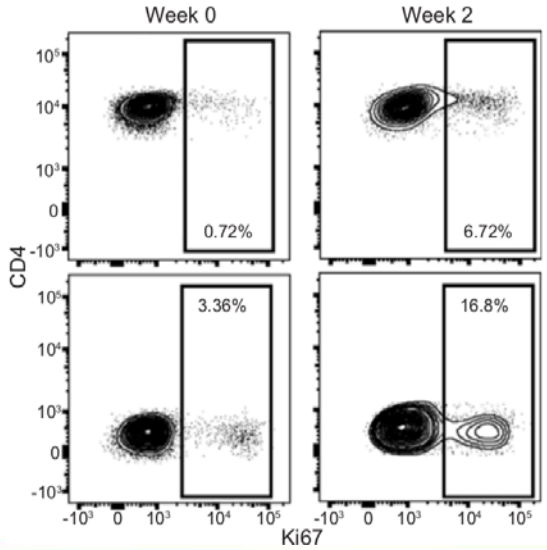
Non-invasive biomarkers to predict response to I-O

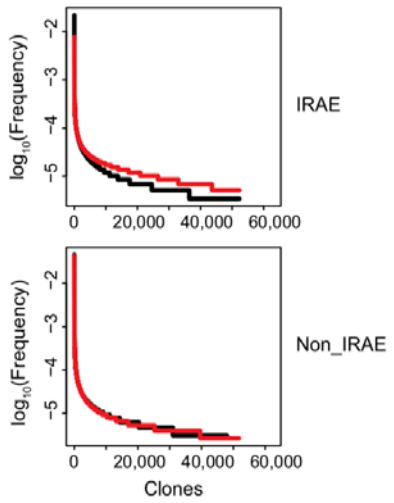
Shifts in peripheral blood T-cell clonality can potentially predict response and toxicity to immune checkpoint inhibition







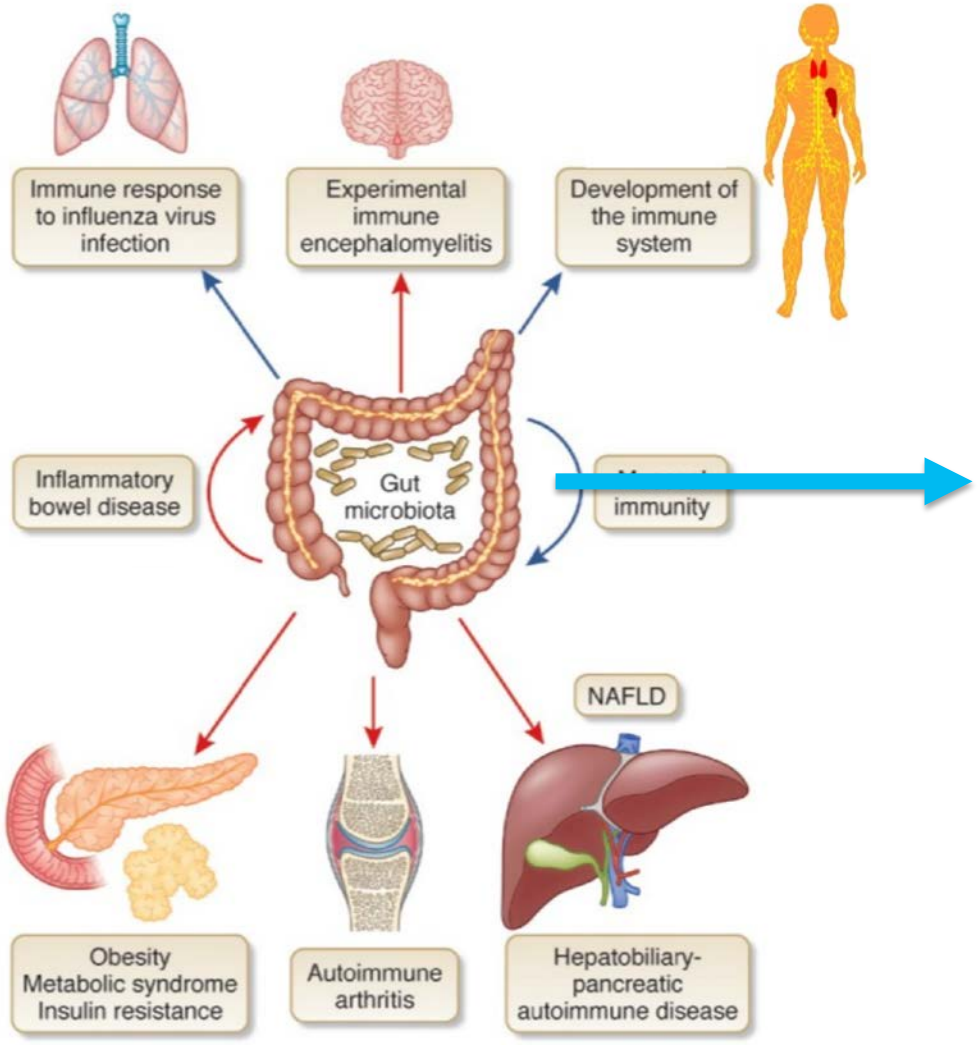




I-O, immuno oncology.

1. Cha E et al. *Sci Transl Med* 2014;6:238ra70. 2. Oh DY et al, *Cancer Res* 2017;77:1322–1330.

Biomarkers in I-O: what does the future hold?



Commensal Bacteria Control Cancer Response to Therapy by Modulating the Tumor Microenvironment

Noriho Iida,[1*] Amiran Dzutsev,[1,2*] C. Andrew Stewart,[1*] Loretta Smith,[1] Nicolas Bouladoux,[3] Rebecca A. Weingarten,[4] Daniel A. Molina,[5] Rosalba Salcedo,[1] Timothy Back,[1] Sarah Cramer,[1] Ren-Ming Dai,[1,2] Hiu Kiu,[1] Marco Cardone,[1] Shruti Naik,[3] Anil K. Patri,[6] Ena Wang,[7] Francesco M. Marincola,[7,8] Karen M. Frank,[4] Yasmine Belkaid,[3] Giorgio Trinchieri,[1]†‡ Romina S. Goldszmid[1]†‡

SCIENCE VOL 342 22 NOVEMBER 2013

I-O, immuno oncology.
Iida N et al. *Science* 2013;342:967–970.

Future biomarkers in immuno-oncology

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]* Laurence Zitvogel[1,2,3,6]†

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Future biomarkers in immuno-oncology

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†]

Matson *et al.*, *Science* **359**, 104–108 (2018) 5 January 2018

Science REPORTS

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

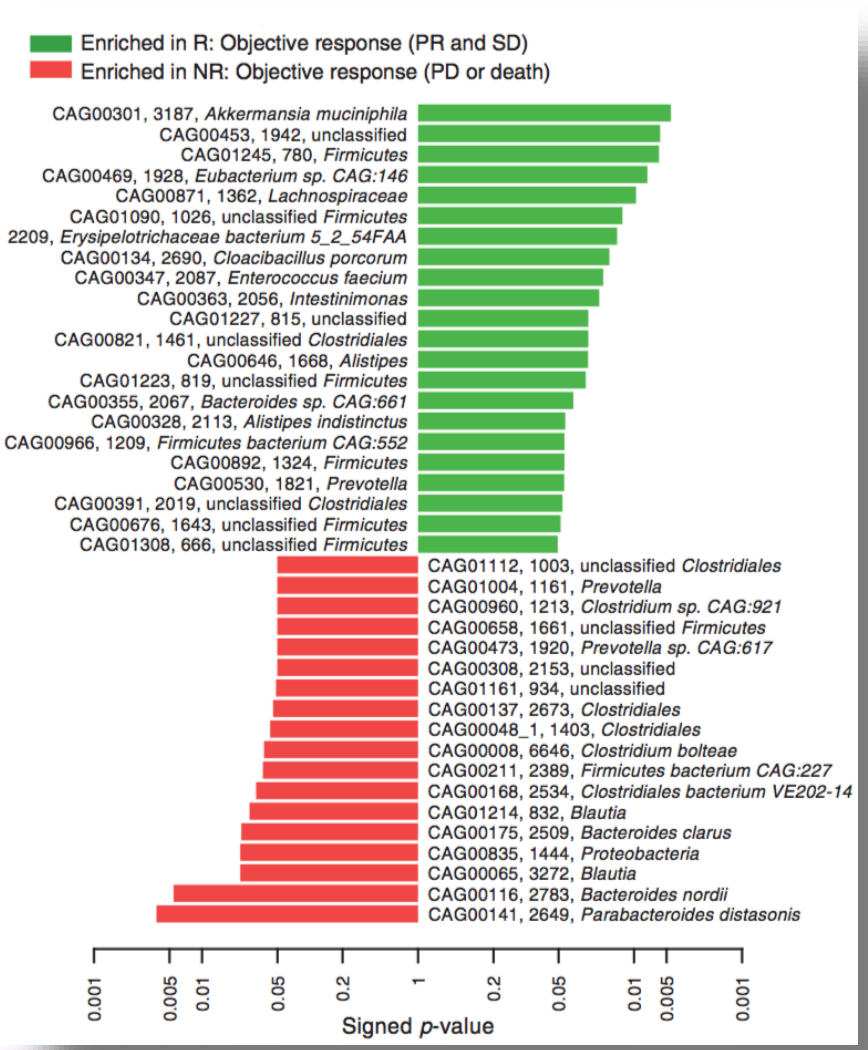
V. Gopalakrishnan,[1,2*] C. N. Spencer,[2,3*] L. Nezi,[3*] A. Reuben,[1] M. C. Andrews,[1] T. V. Karpinets,[3] P. A. Prieto,[1†] D. Vicente,[1] K. Hoffman,[4] S. C. Wei,[5] A. P. Cogdill,[1,5] L. Zhao,[3] C. W. Hudgens,[6] D. S. Hutchinson,[7] T. Manzo,[3] M. Petaccia de Macedo,[6‡] T. Cotechini,[8] 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#**]

1. Matson V et al. *Science* 2018;359:104–108. 2. Gopalakrishnan V et al. *Science* 2017;359:97–103.

Future biomarkers in immuno-oncology

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

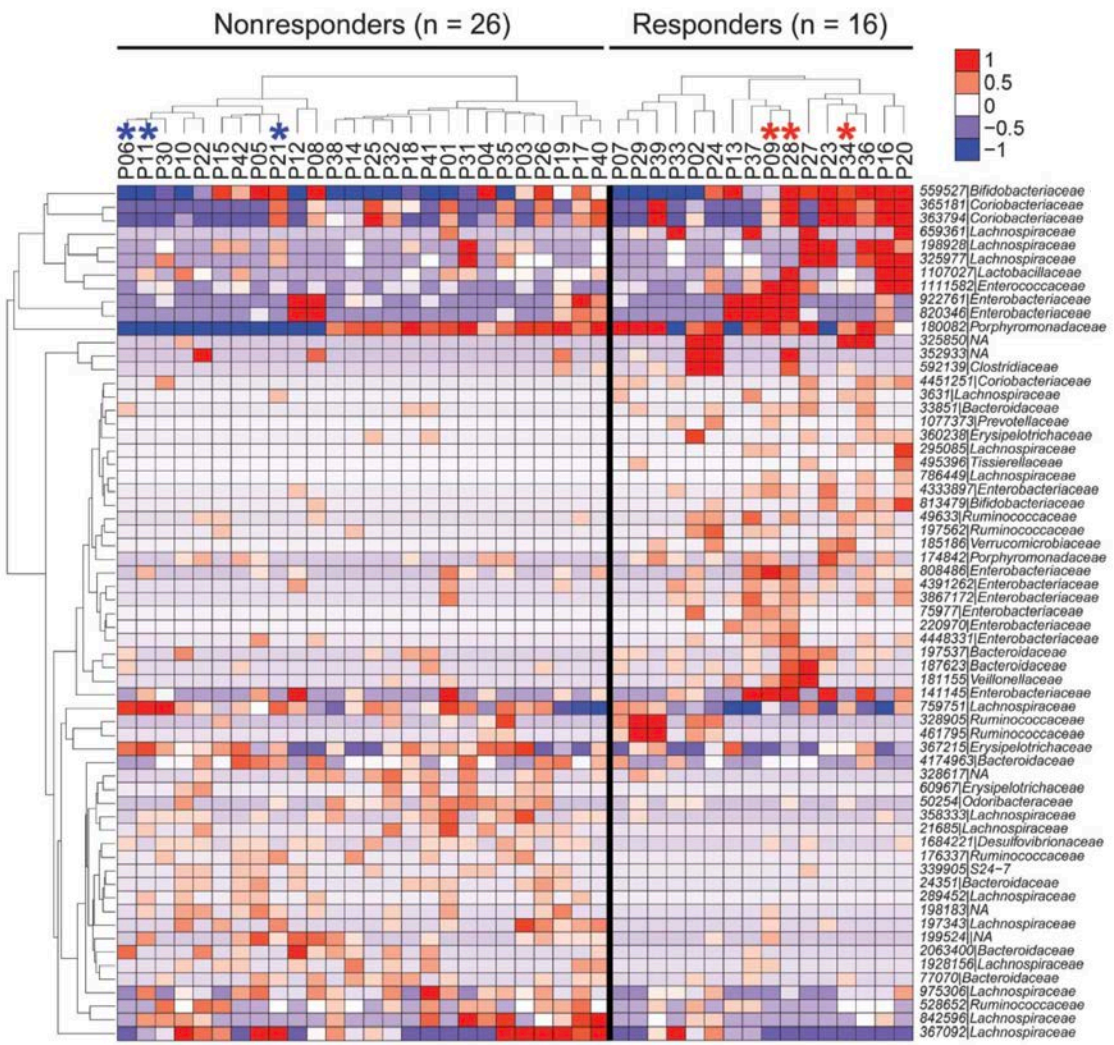
Bertrand Routy,[1,2,3] Emmanuelle Le Chatelier,[4] Lisa Derosa,[1,2,3] Connie P. M. Duong,[1,2,5] Maryam Tidjani Alou,[1,2,3] Romain Daillère,[1,2,3] Aurélie Fluckiger,[1,2,5] Meriem Messaoudene,[1,2] Conrad Rauber,[1,2,3] Maria P. Roberti,[1,2,5] Marine Fidelle,[1,3,5] Caroline Flament,[1,2,5] Vichnou 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*]

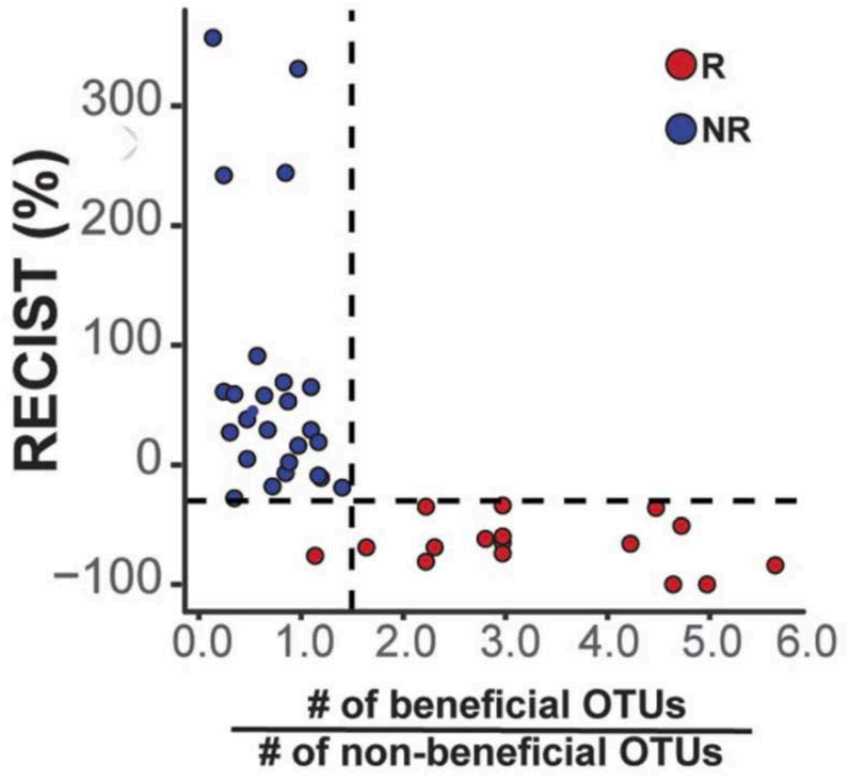


Routy B et al. *Science* 2018;359:91–97.

Future biomarkers in immuno-oncology

Could microbiome profiling provide a useful predictive biomarker?

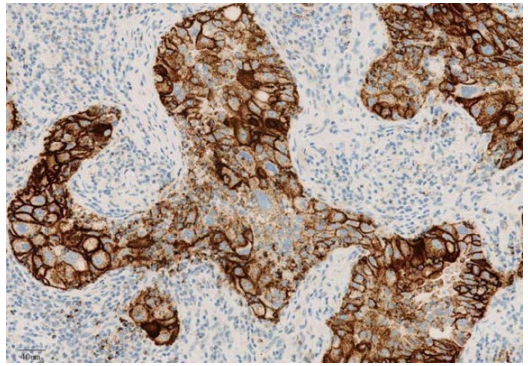




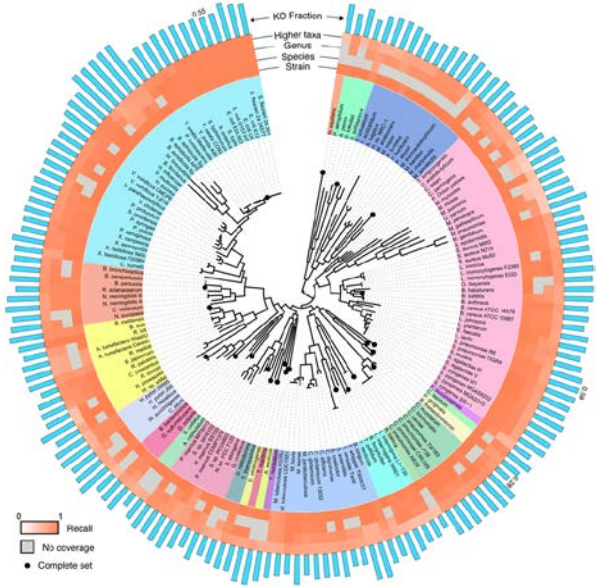
Matson V et al. *Science* 2018;359:104–108.

Future biomarkers in immuno-oncology

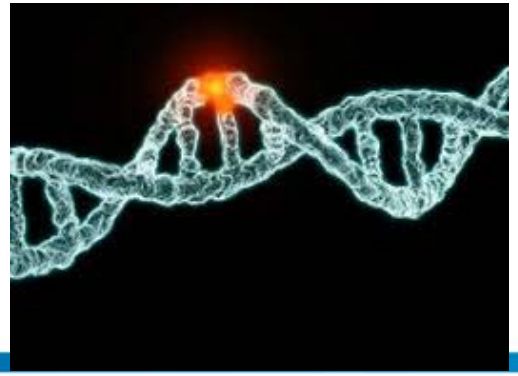
PD-L1, other immune markers



Microbiome profiling?



Total mutational burden



Karim Vermaelen, personal communication, 2018.

Biomarkers in I-O: conclusions / take home messages

Biomarkers should allow us to deliver "**precision immuno-oncology**"

- Identify responders / exclude non-responders (economical burden!)

Challenges for the future:

- Can we design the **ideal predictive test**: cost-effective, non-invasive, accurate, simple to interpret?
- Can we also find biomarkers to **predict severe toxicity**?
- Will every **combination therapy** require its own predictive test??
- Our understanding of cancer immunology keeps growing → leads to ever more complex candidate biomarkers (e.g. gut microbiota)

Karim Vermaelen, personal communication, 2018.

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