



university of
groningen



umcg

Immunotherapie bij endometriumcarcinoom,

“Baarmoeder-sparende behandeling - fictie of werkelijkheid”

13.25 – 14.25

**Verpleegkundig Oncologisch Symposium
vrijdag 21 januari 2022**

Disclosure

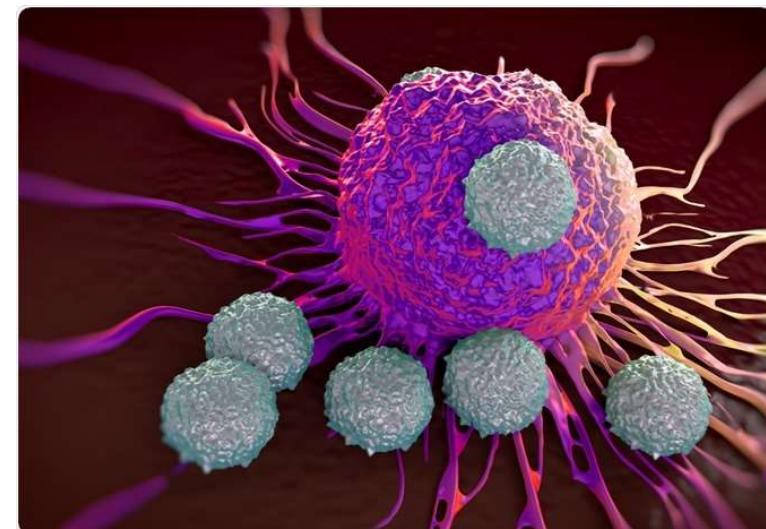
- Founder, director clinical research ViciniVax
- Collaborations / unrestricted grants:
 - Biontech, Immunicum, Merck, Synaffix, Third Rock, and Aduro
- Grants :
 - The Dutch Organisation for Health Research and Development
 - Dutch Cancer Society
 - Cancer Research UK

Wat gaan we doen

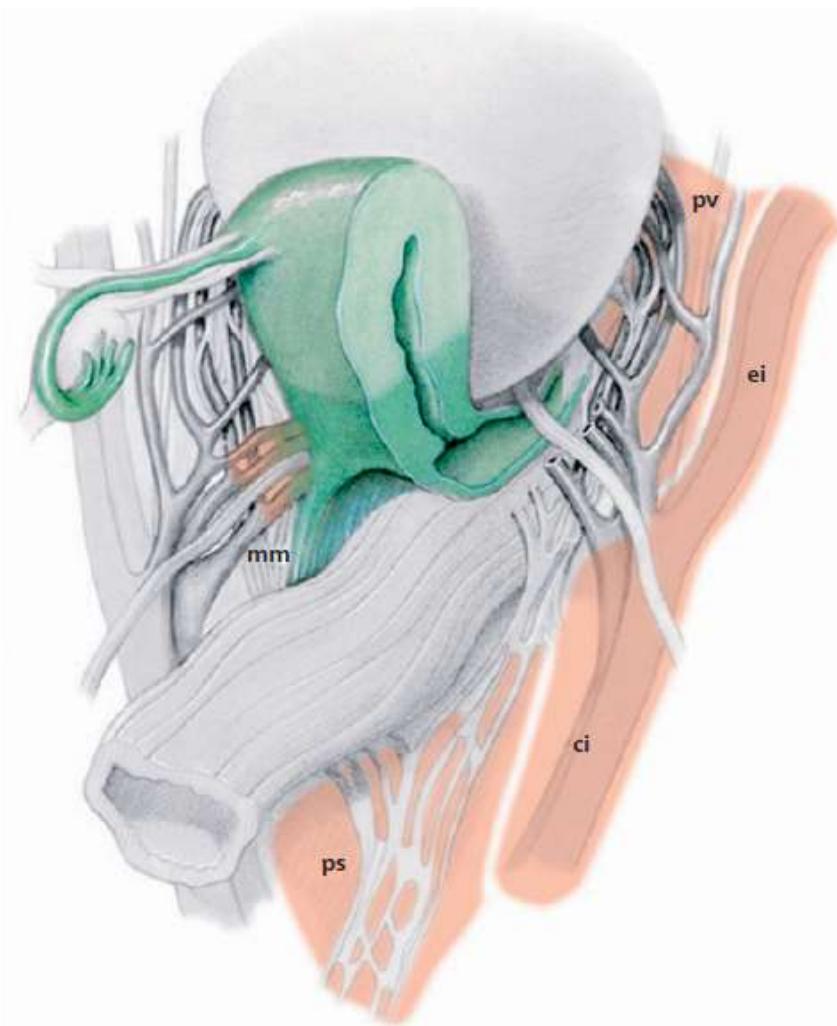
- Introductie op endometriumcarcinoom



- De mooie wereld van de tumorimmunologie, ihb
endometriumcarcinoom

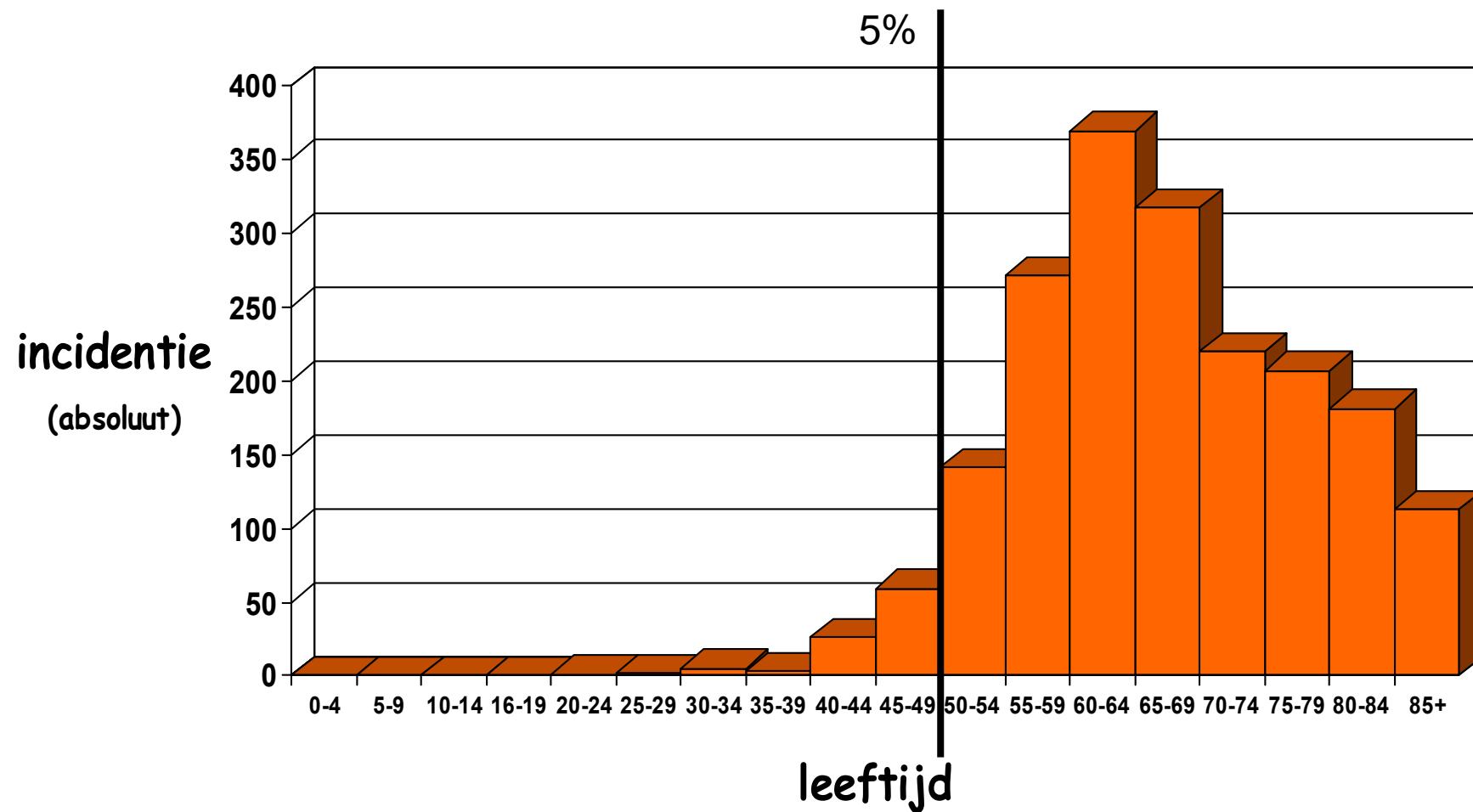


Anatomie van baarmoeder



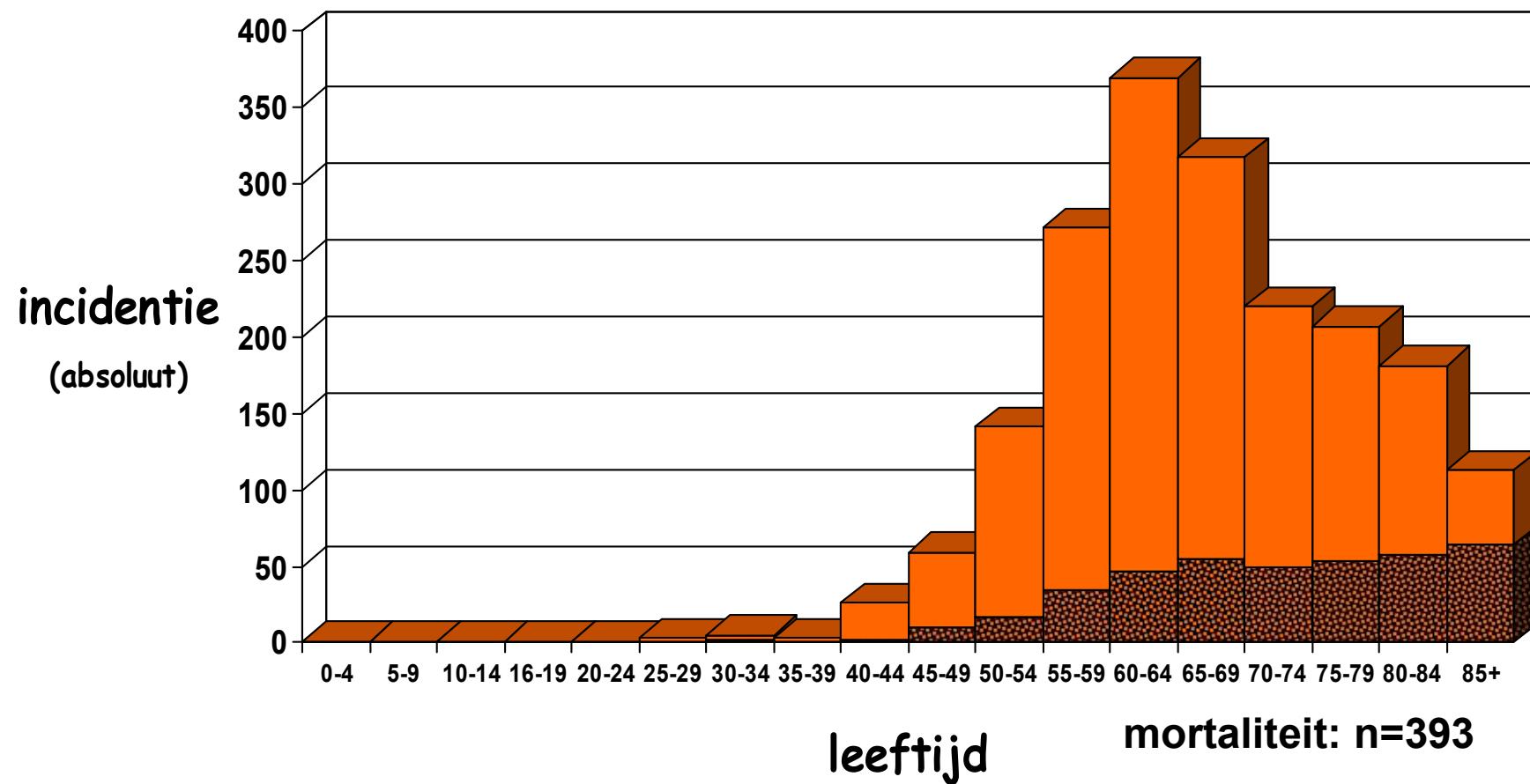
Endometriumcarcinoom

epidemiologie



Endometriumcarcinoom

epidemiologie



Aantal nieuwe kankerpatienten in 2020

		2020	2019	
plaveiselcelcarcinoom van de huid		14.900	14.700	+
longkanker		13.900	14.200	-
borstkanker ↓		13.200	14.900	---
prostaatkanker		12.800	13.500	--
darmkanker ↓		11.700	12.800	--
hematologische maligniteiten		9.900	10.300	-
melanoom van de huid		6.800	7.000	-
blaaskanker**		3.700	3.600	+
slok darmkanker (incl. cardia)		3.100	3.100	0
hoofd-halskanker		3.000	3.100	-
alvleesklierkanker		2.700	2.800	-
nierkanker		2.600	2.700	
baarmoederkanker		2.100	2.100	0
eierstokkanker (incl. eileider)		1.400	1.500	--
hersentumor		1.400	1.400	0
maagkanker		1.000	1.100	--
totaal***		115.000	119.000	-

* invasieve tumoren ** incl. nierbekken/urineleider

*** excl. basaalcelcarcinoom van de huid

bron IKNL

Endometriumcarcinoom

histologie

- Endometrioid adenocarcinoom >80 %
- Serous carcinoma 5-7 %
- Clear cell carcinoma 1-5 %
- Mucinous carcinoma <2 %

% Lymfkliermetastasen

invasion	grade	I		II		III	
		p n=180	a	p n=288	a	p n=153	a
none n=86	0%	0%	3%	3%	0%	0%	
superficially n=281	3%	1%	5%	4%	9%	4%	
intermediate n=115	0%	5%	9%	0%	4%	0%	
deep n=139	11%	6%	19%	14%	34%	23%	

Creasman et al., Cancer 1987

Chirurgie is de hoeksteen van de behandeling

- https://www.youtube.com/watch?v=W3aLKbRch_o



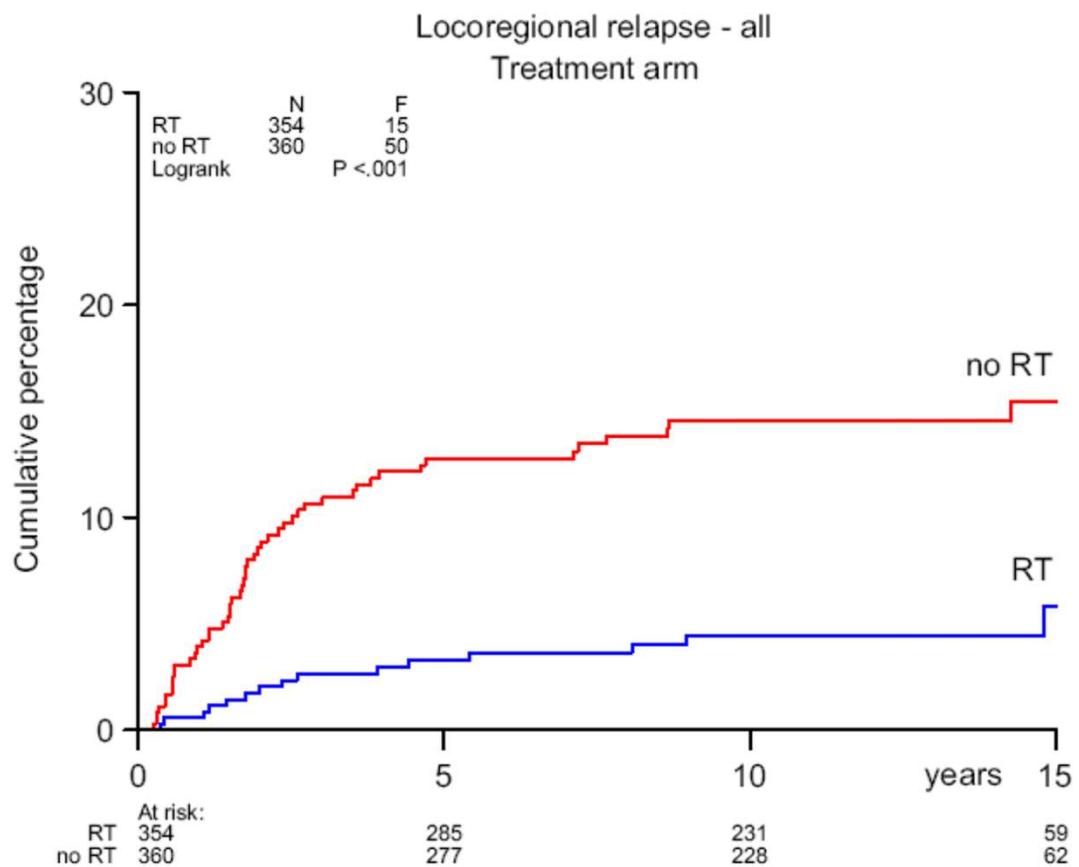
Adjuvante behandeling na chirurgie bij endometriumcarcinoom

- Radiotherapie



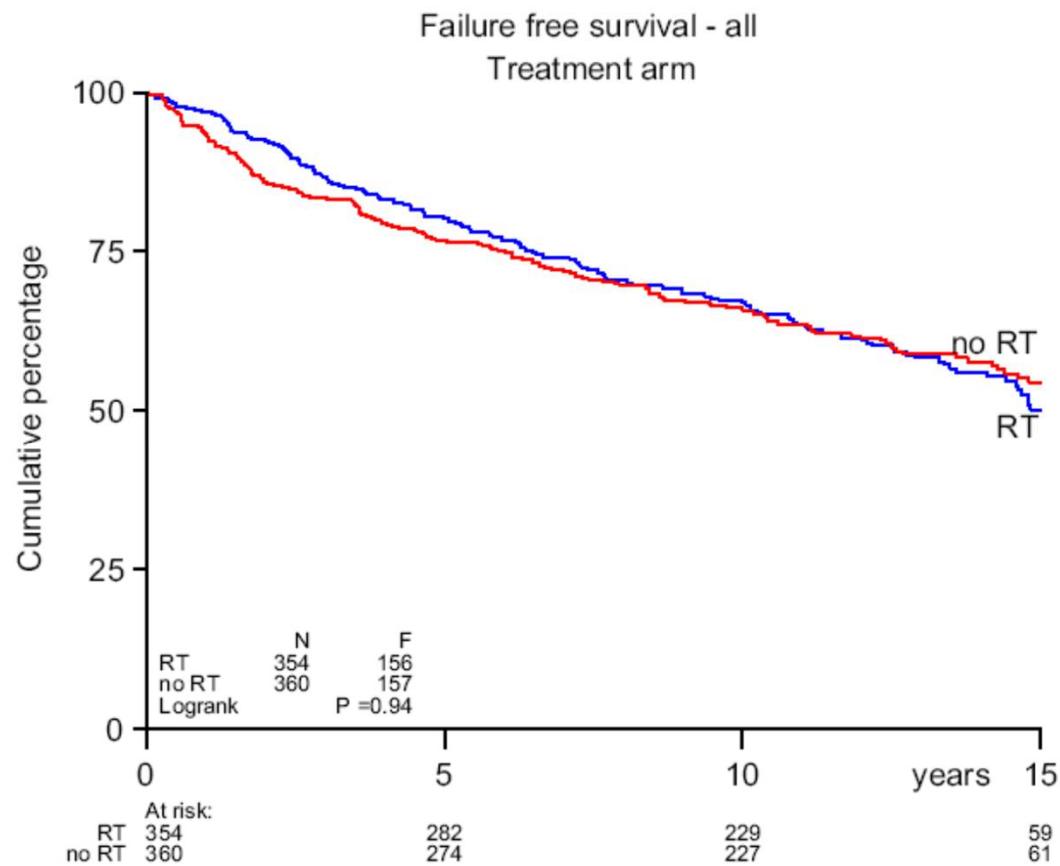
- Systemisch
 - Chemotherapie
 - Hormoontherapie

Endometriumcarcinoom resultaten PORTEC-1 – 15 jaar later



Creutzberg et al., IJROBP 2011

Endometriumcarcinoom resultaten PORTEC-1 – 15 jaar later



Creutzberg et al., IJROBP 2011

Developments in risk-based treatment

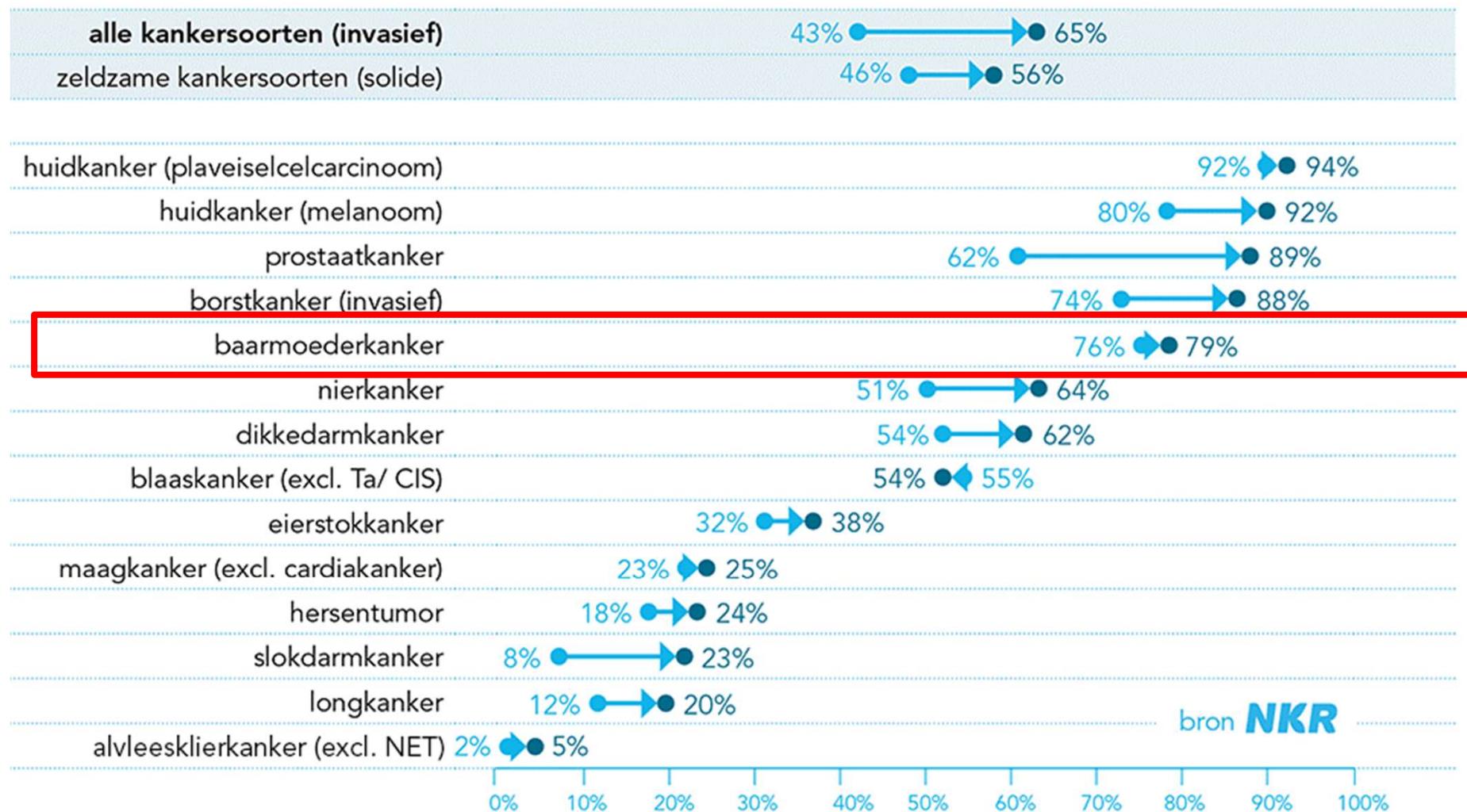
- **Low risk** – 50-55% of patients
stage 1A, grade 1 or 2
endometrioid type EC
- **Intermediate risk** – 30% of patients
stage 1B grade 1-2
endometrioid type EC
- **High risk** - 15% of patients
stage I grade 3; stage II
stage 3 disease
serous or clear-cell cancer

Surgery -> laparoscopic
Follow-up

Pelvic RT -> Vaginal
brachytherapy

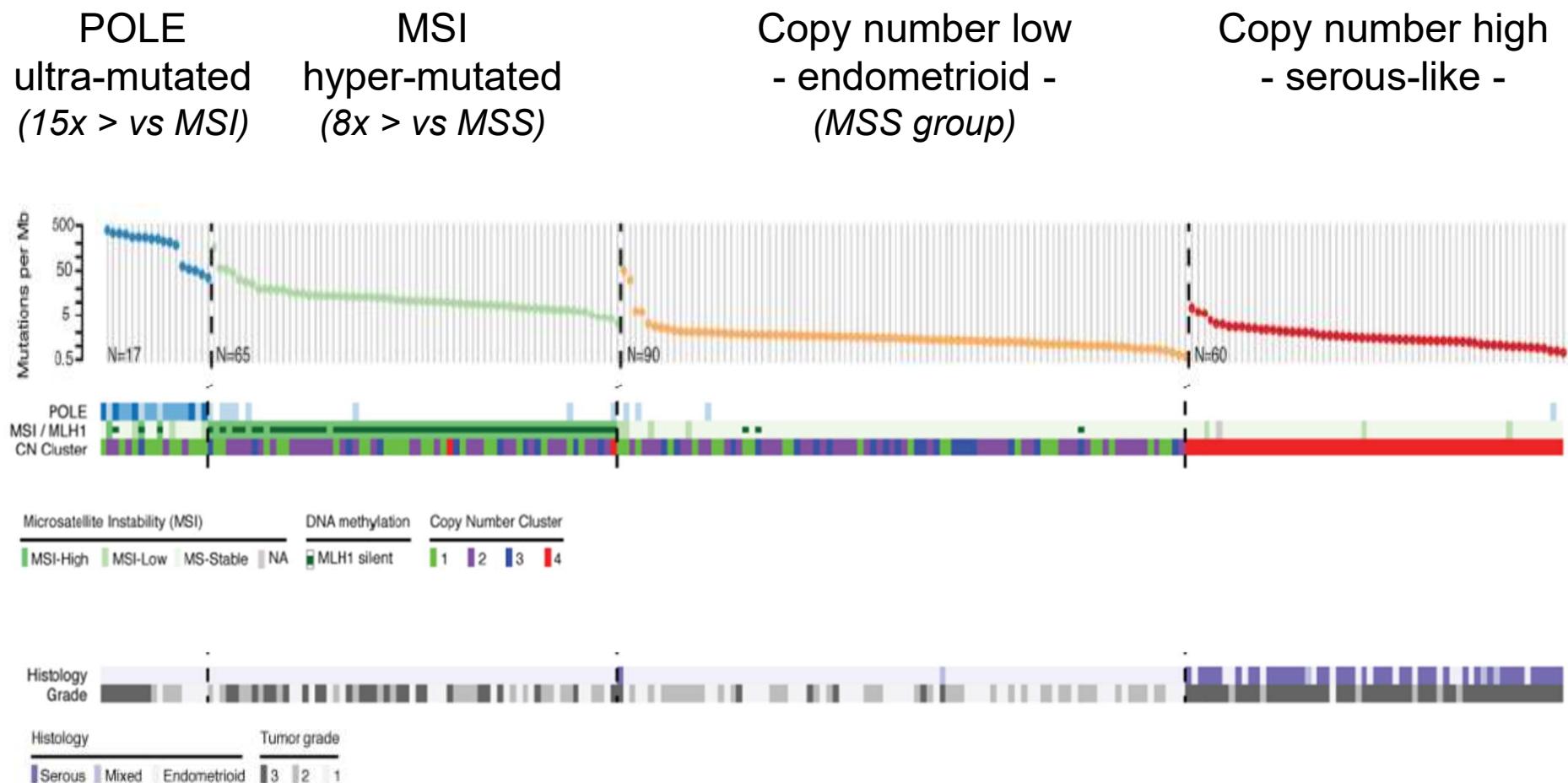
Pelvic radiotherapy +/-
Chemotherapy

5 jaaroverleving van diagnosejaar 1990 versus 2013



Endometrial Cancer (EC) – Four molecular subtypes

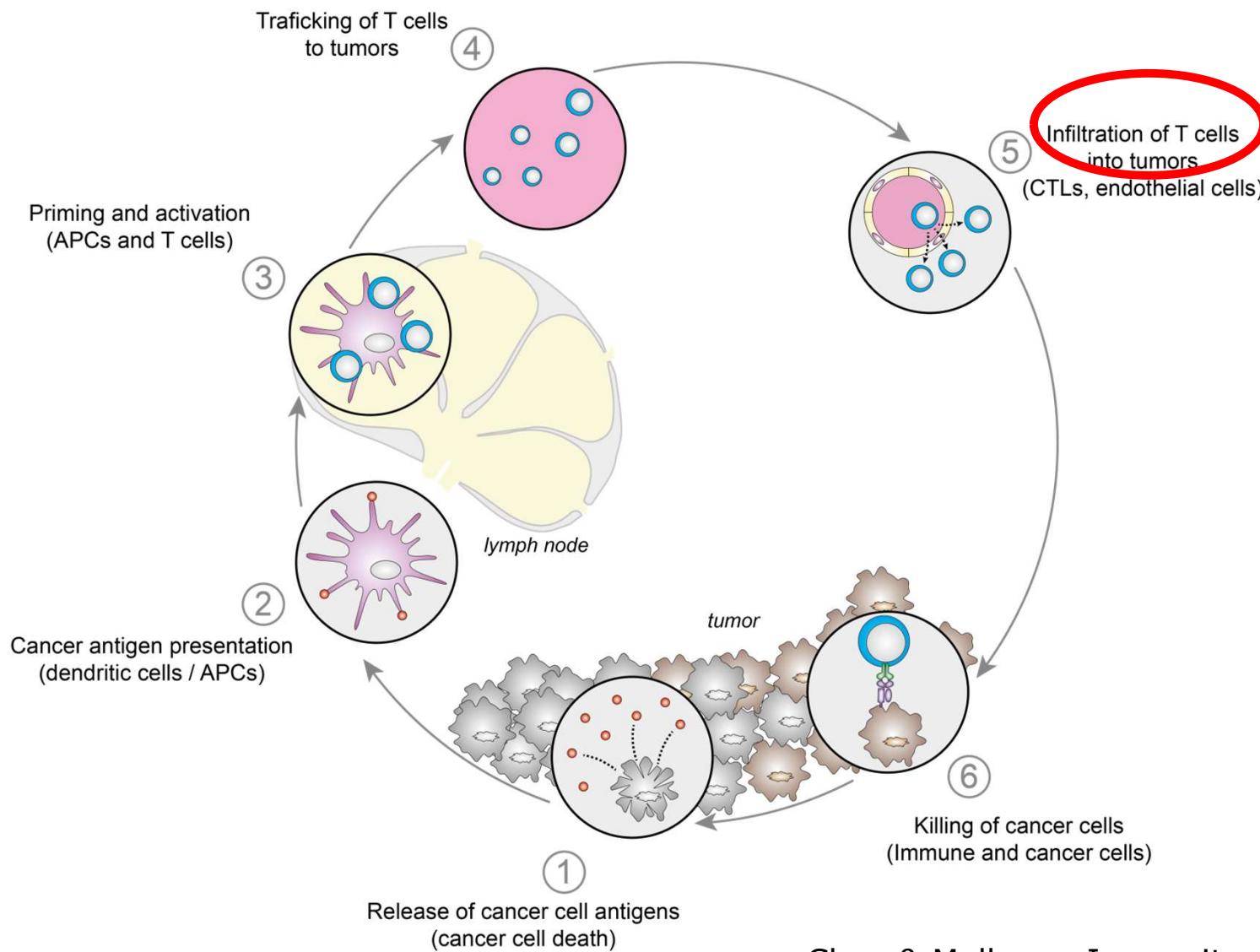
(Integrated genomic, transcriptomic and proteomic characterization)



Even rust

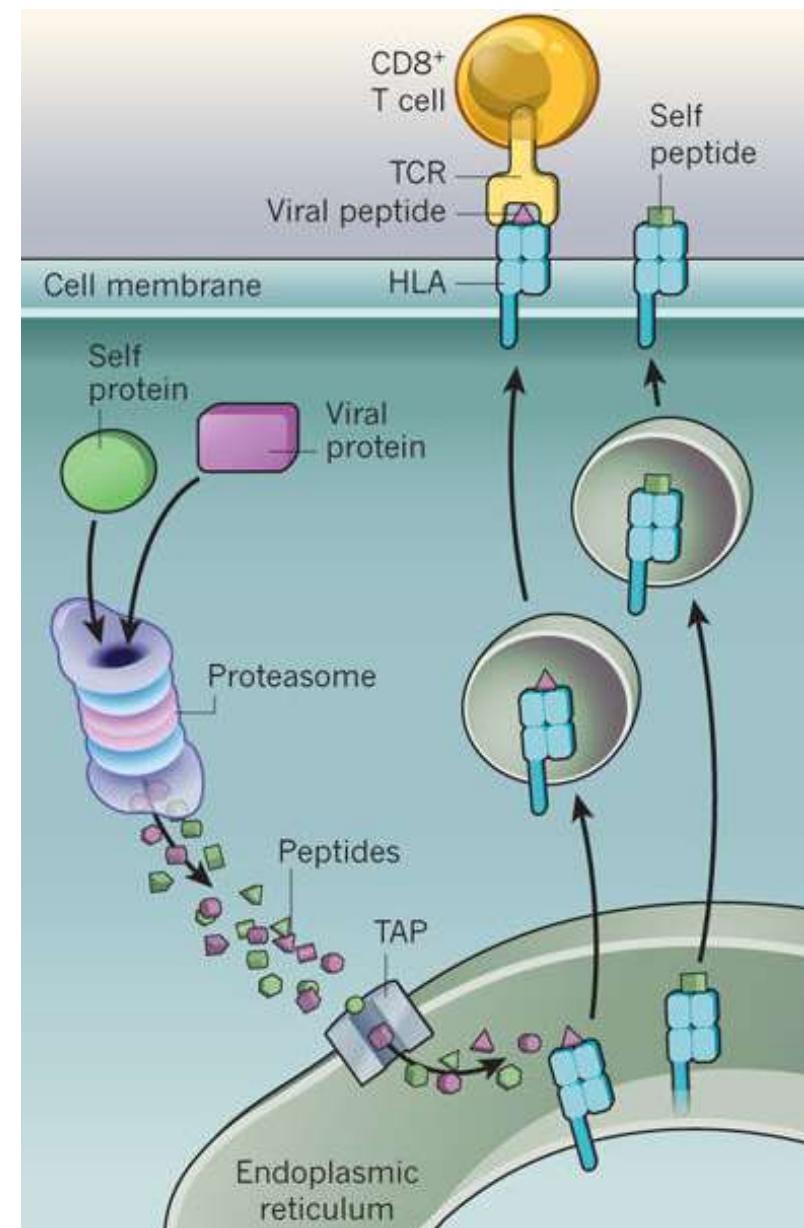
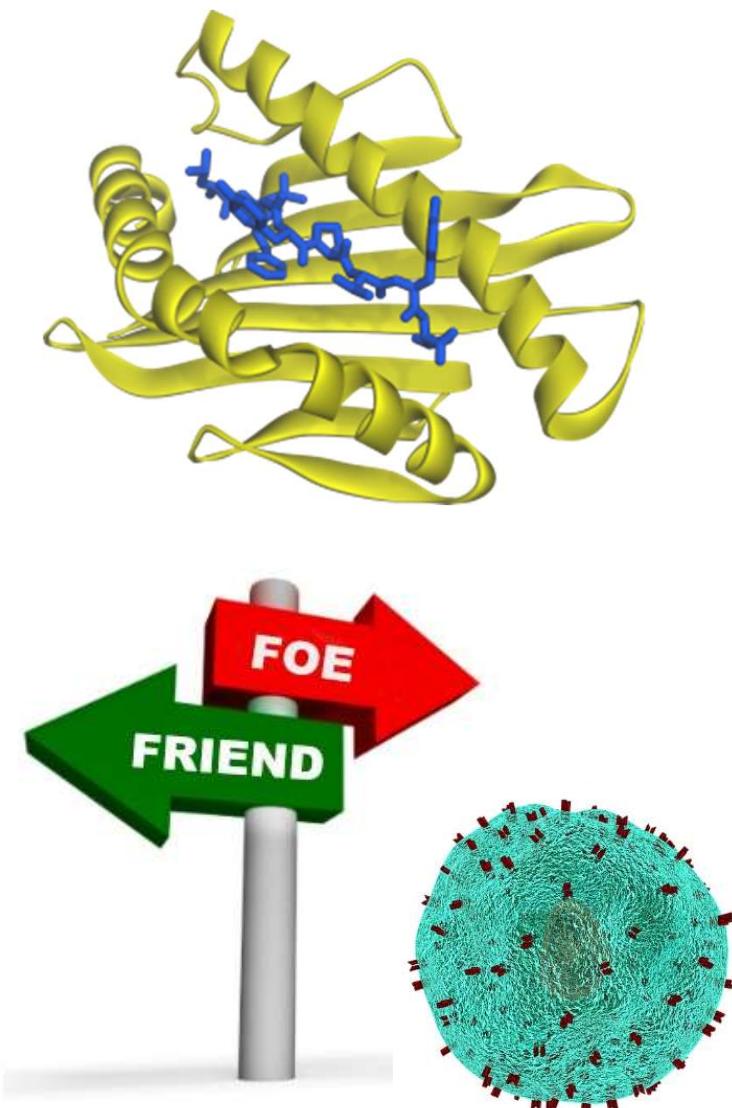


Cancer immunity cycle adapted from Mellman et al.

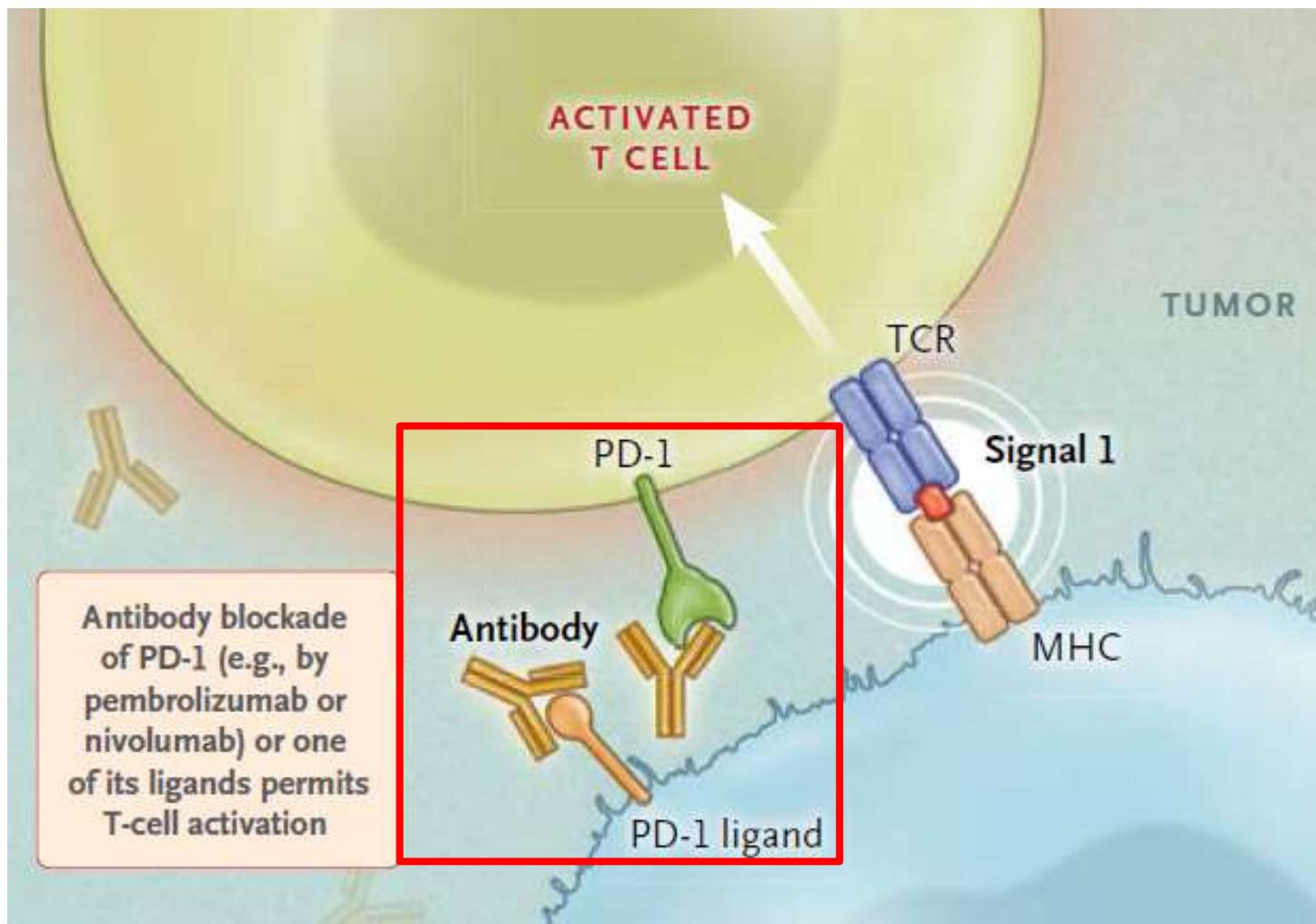


Chen & Mellman, Immunity, 2013

MHC class I antigen processing & presentation

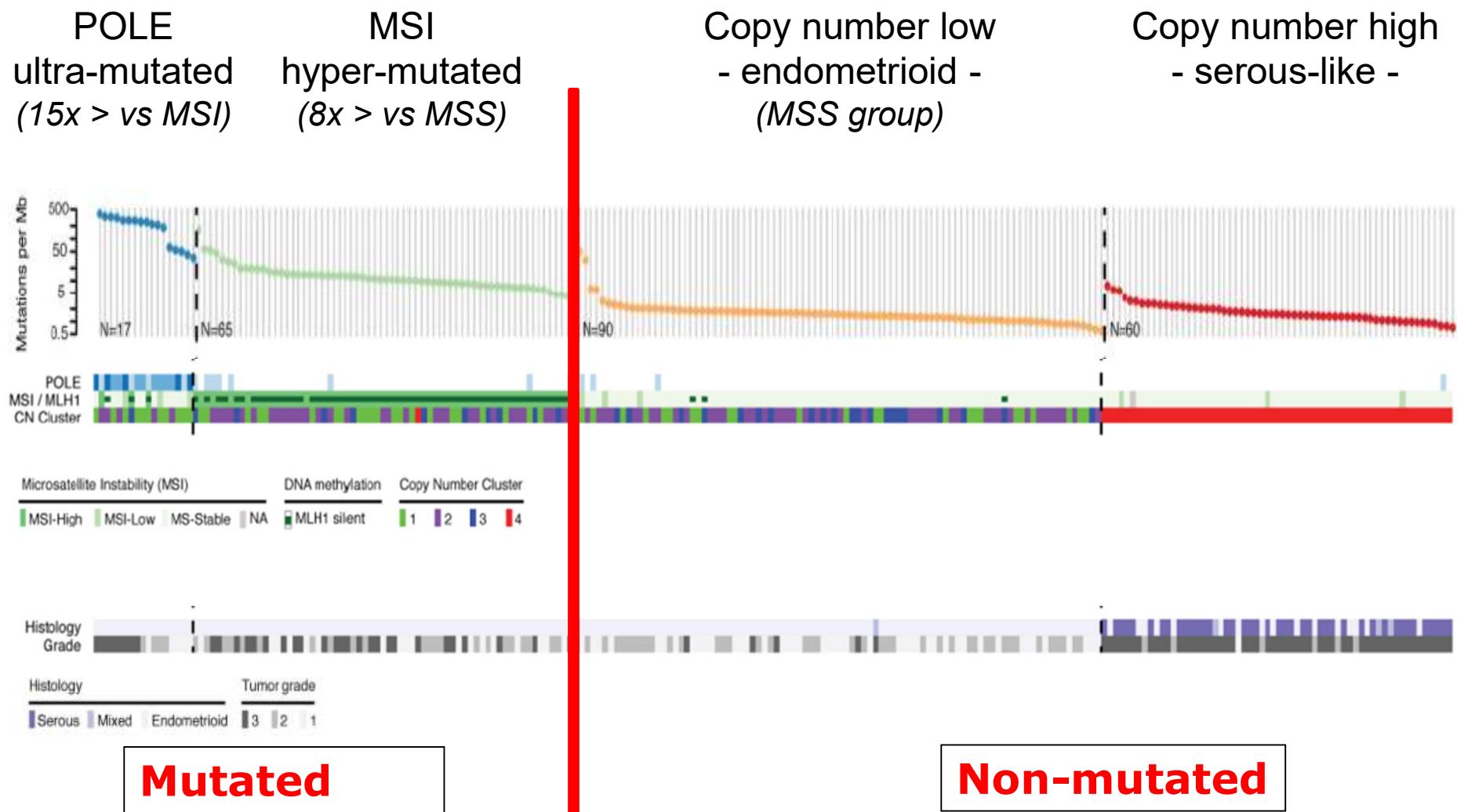


Releasing the brakes using immune checkpoint blockade (ICB) therapy

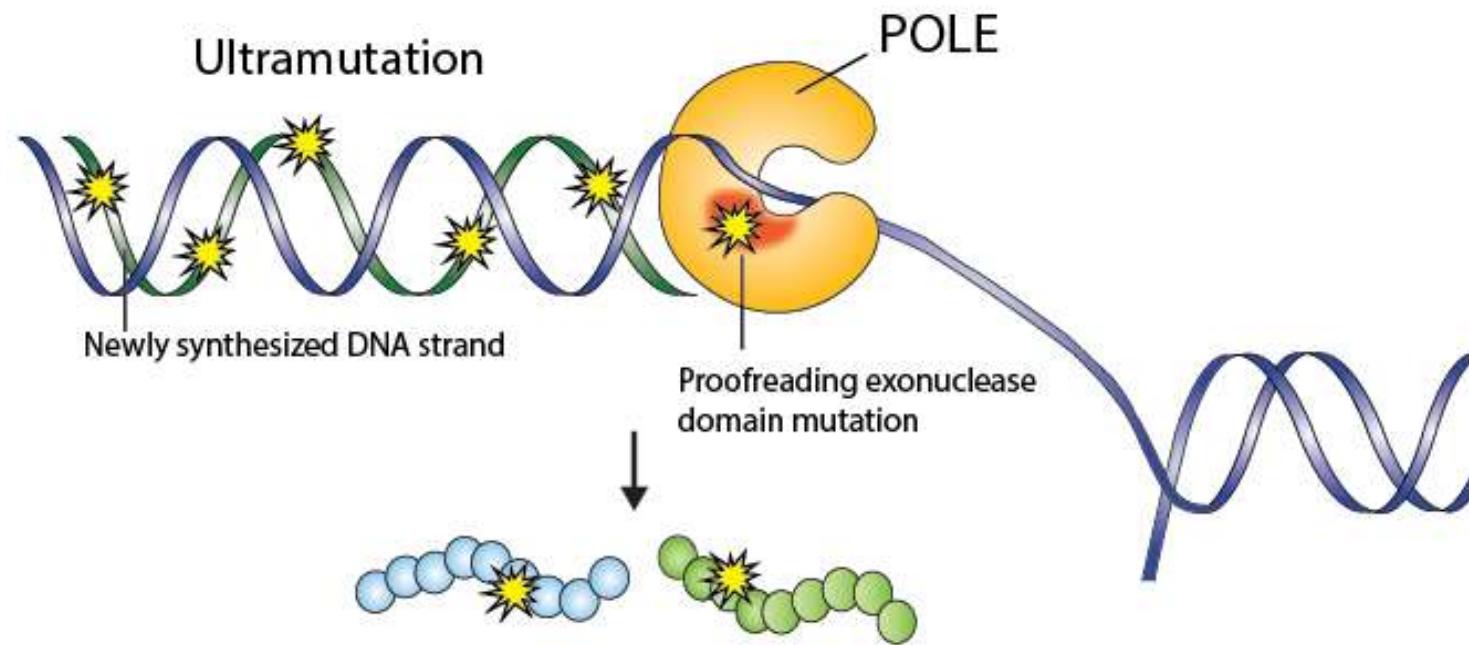


Endometrial Cancer (EC) – Four molecular subtypes

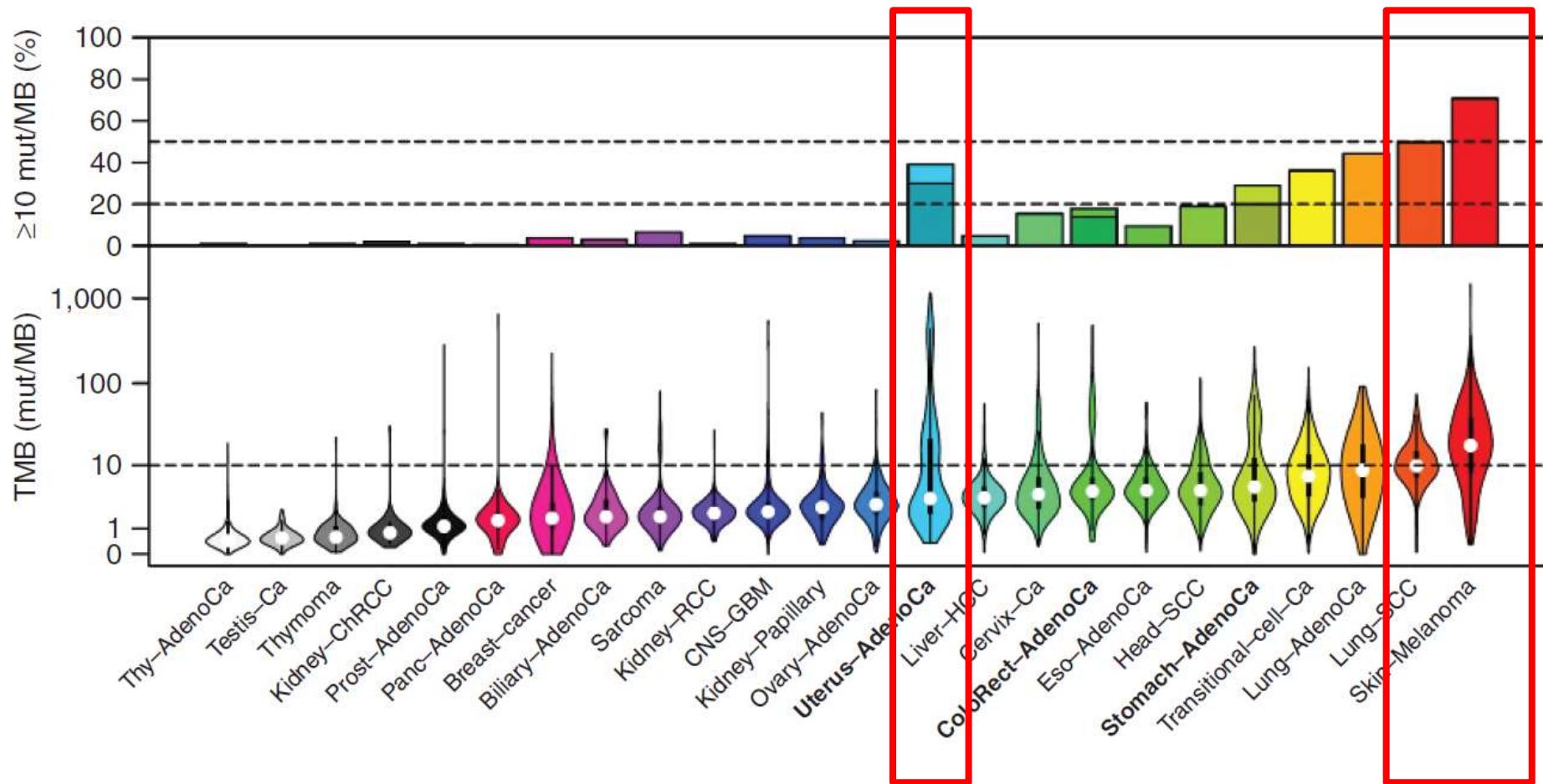
(Integrated genomic, transcriptomic and proteomic characterization)



POLE mutation leads to more mutations



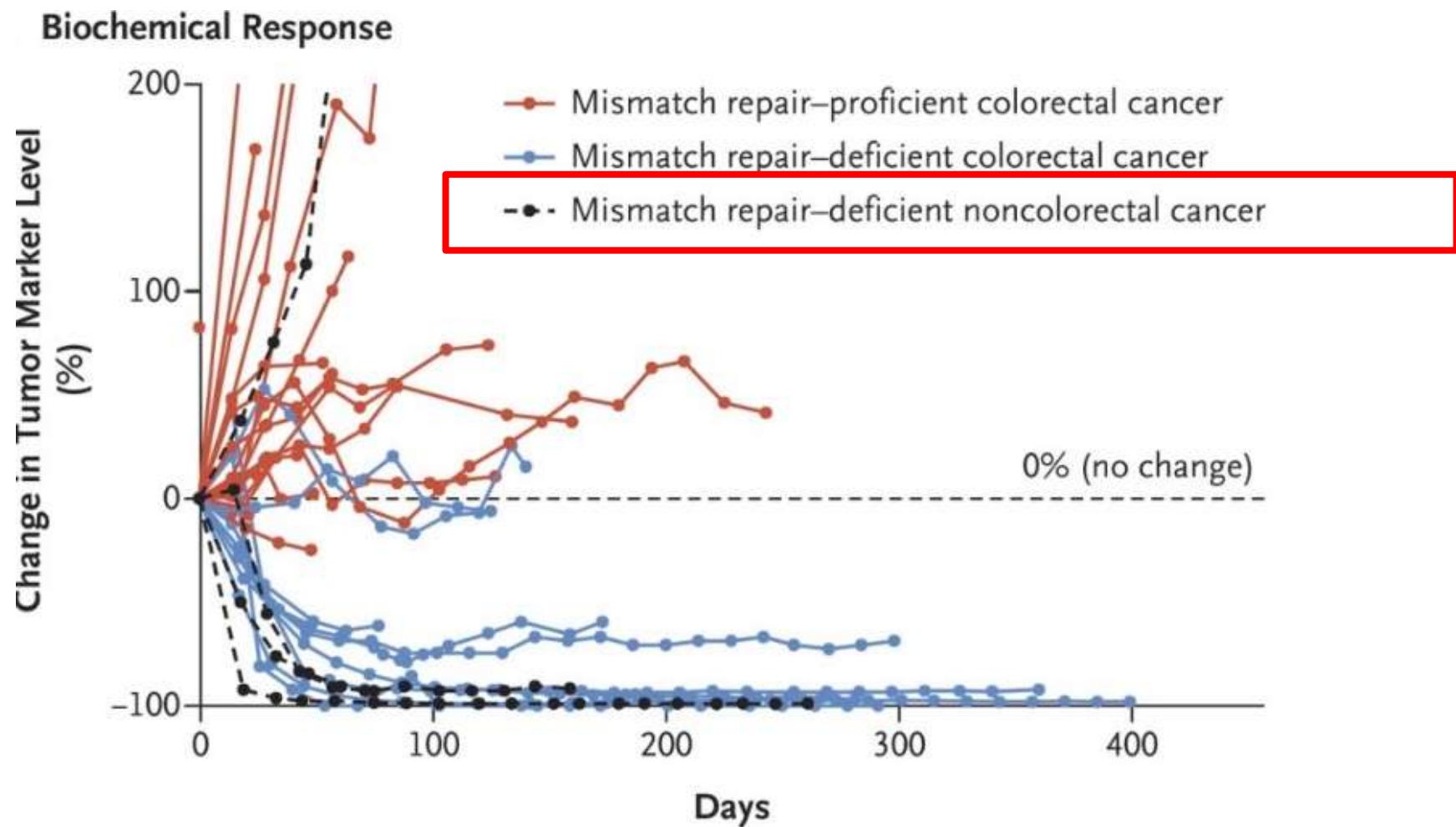
POLE mutant and MSI high resemble melanoma in mutation prevalence



Sha et al. Cancer Discovery 2020

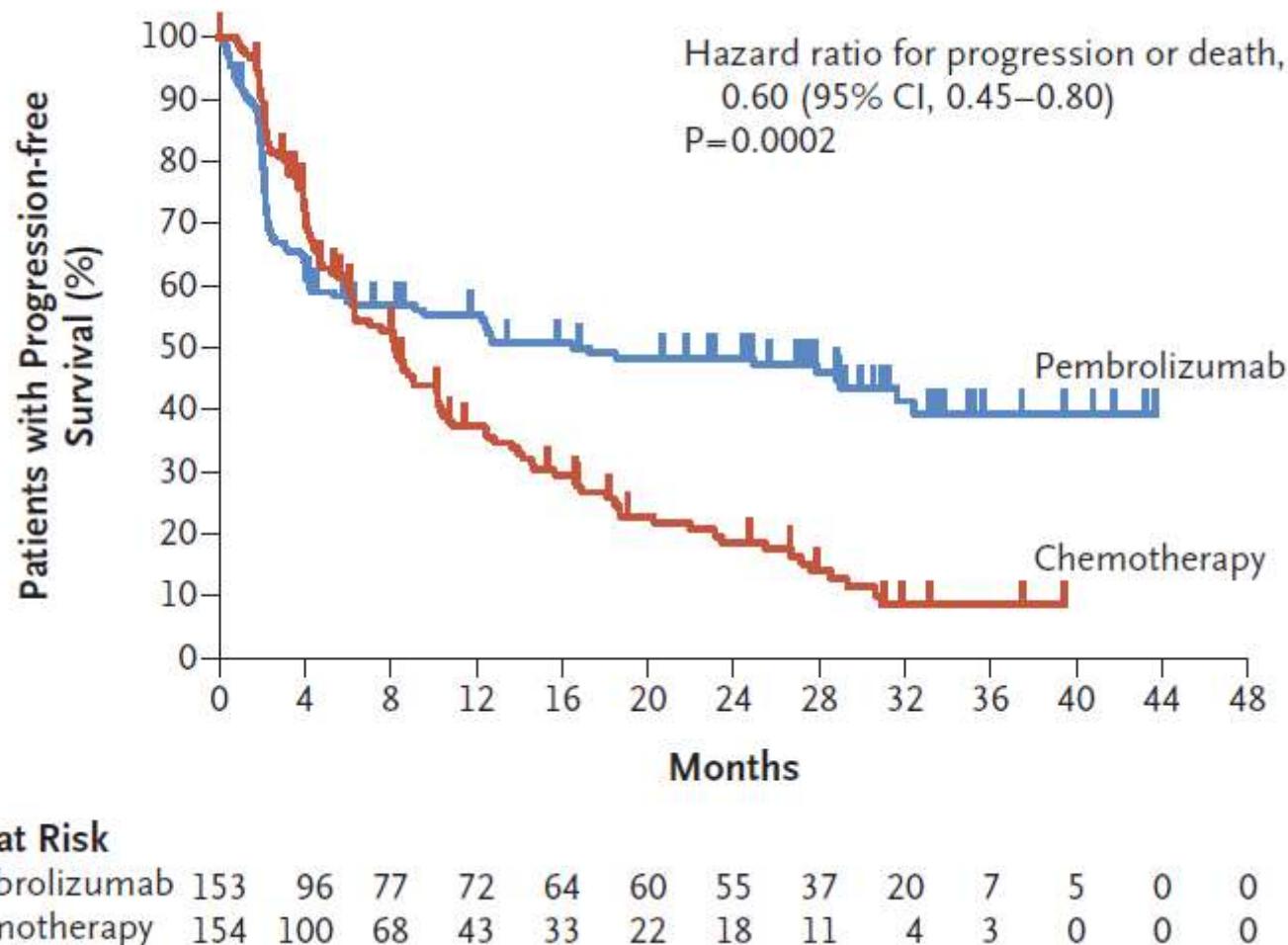
Van Gool et al, Oncoimmunology 2015

Pembrolizumab in tumors with mismatch-repair deficiency

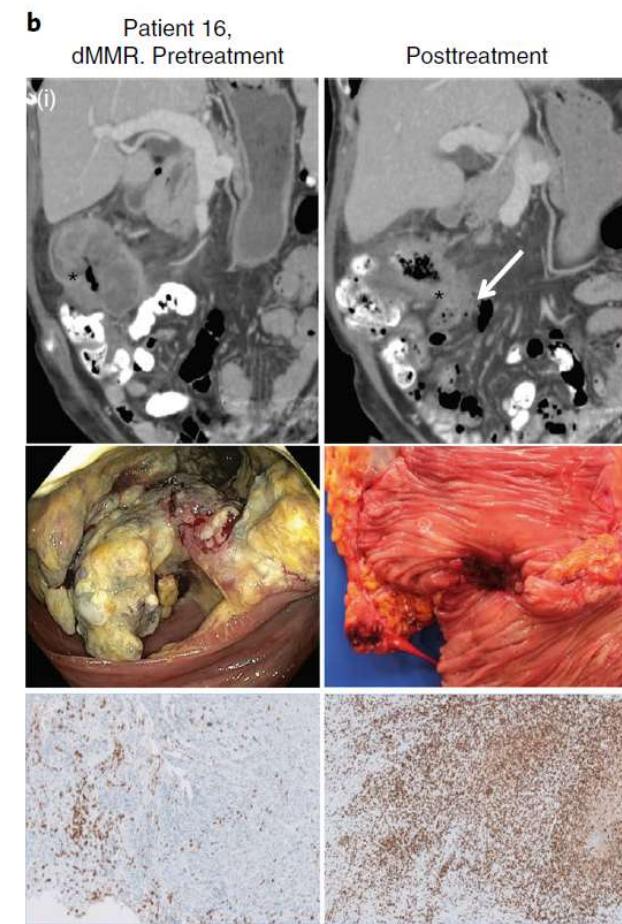
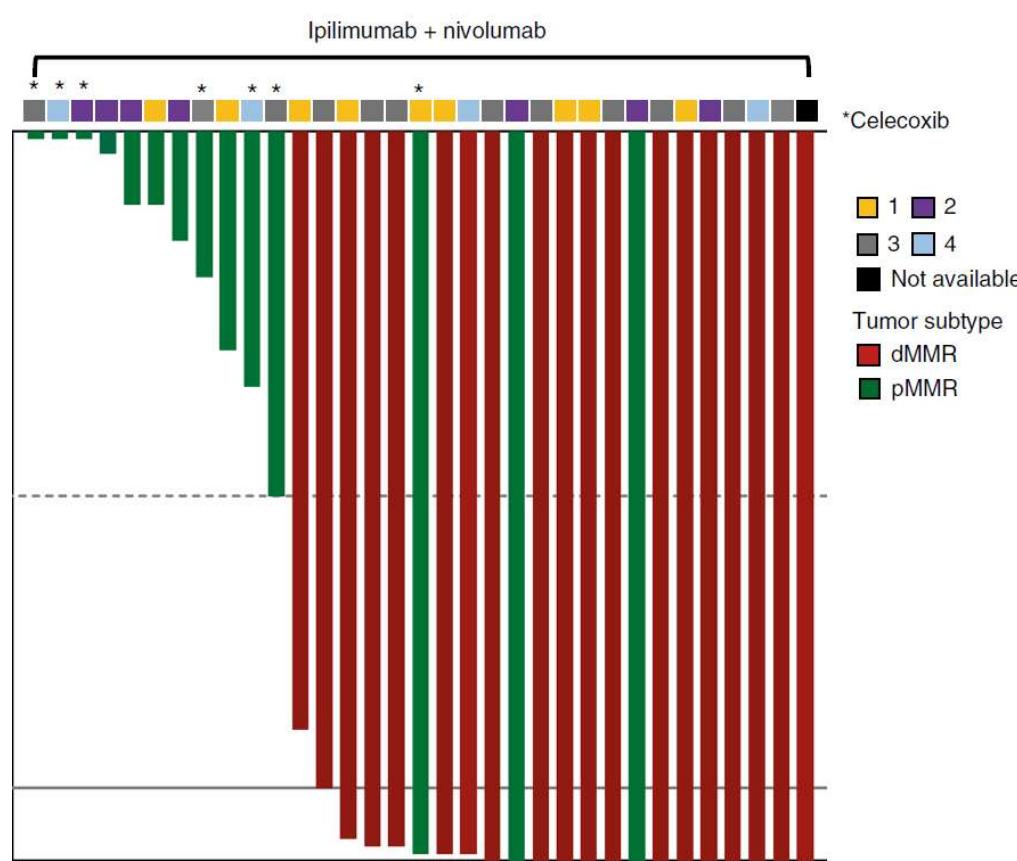


Le et al, NEJM 2015
Le et al, Science 2017 24

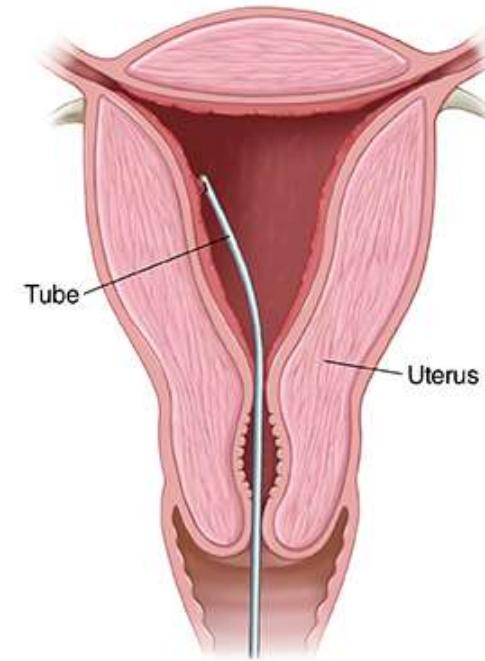
dMMR CRC tumors respond to immune checkpoint blockade therapy



Neo-adjuvant immune checkpoint blockade (CRC)

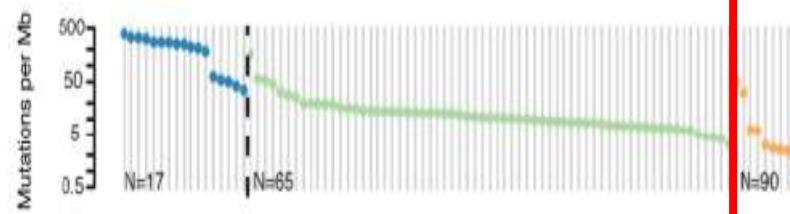


Molecular analysis – Guide for decision making



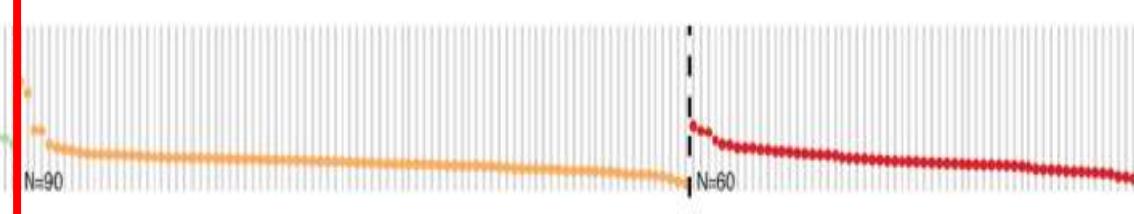
POLE
ultra-mutated
($15x > vs\ MSI$)

MSI
hyper-mutated
($8x > vs\ MSS$)

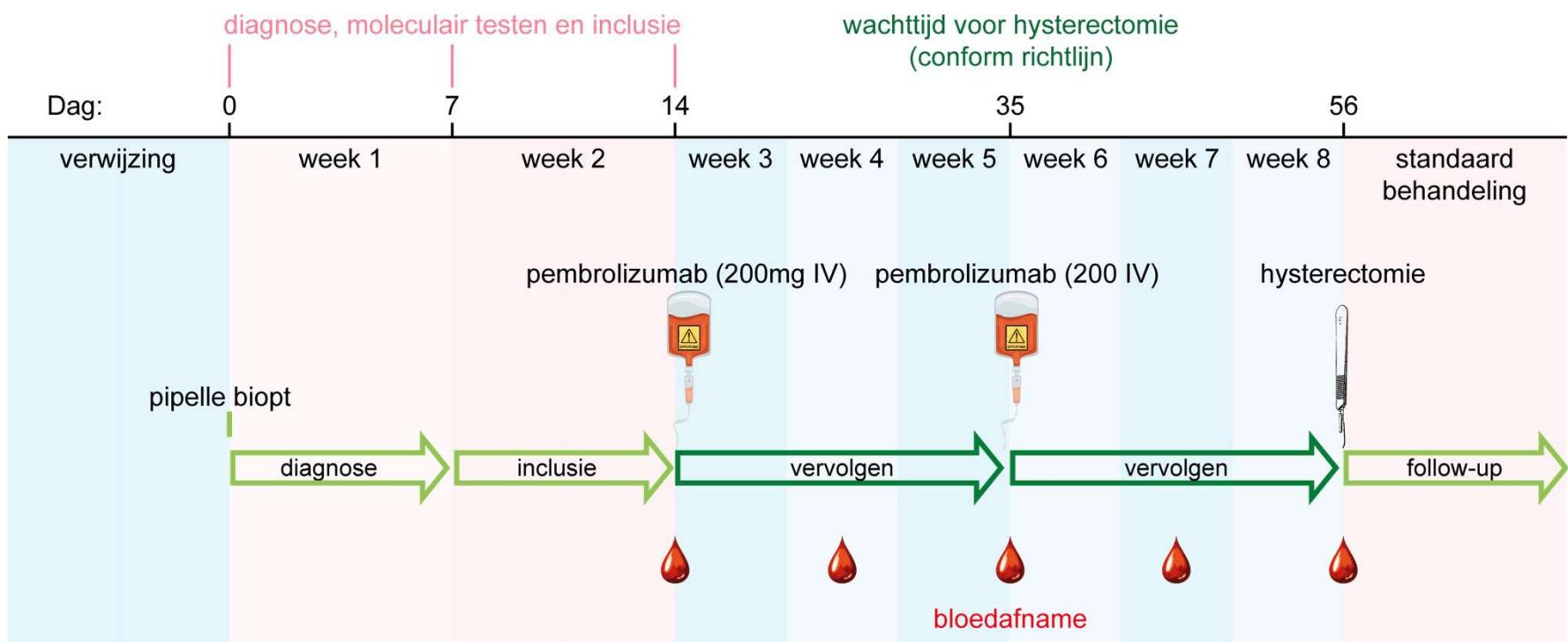


Copy number low
- endometrioid -
(MSS group)

Copy number high
- serous-like -



Neo-adjuvant immune checkpoint blockade (dMMR and POLE-mutant EC)



Even rust

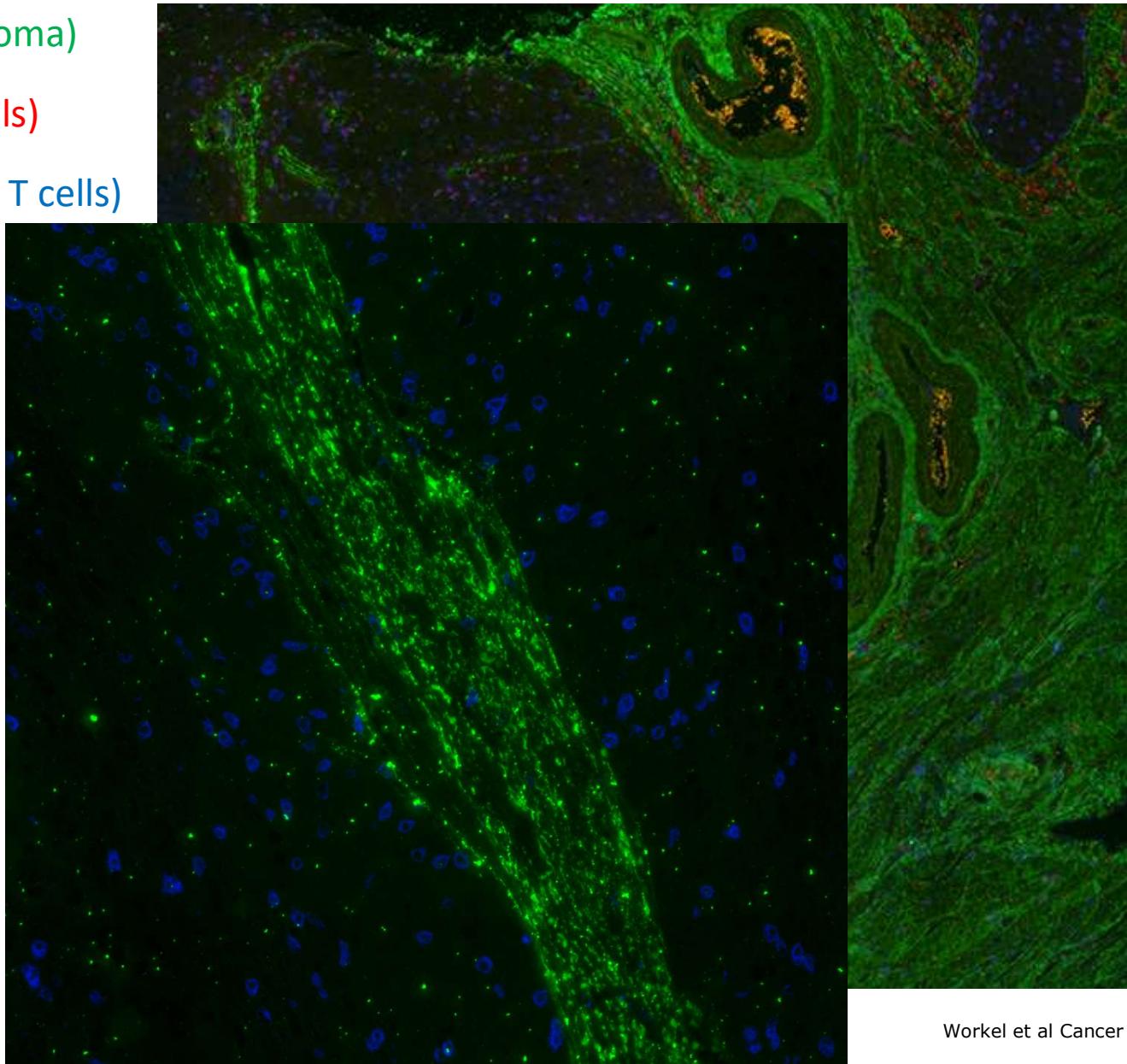


Location, location, location: CD103 defines intraepithelial CTL

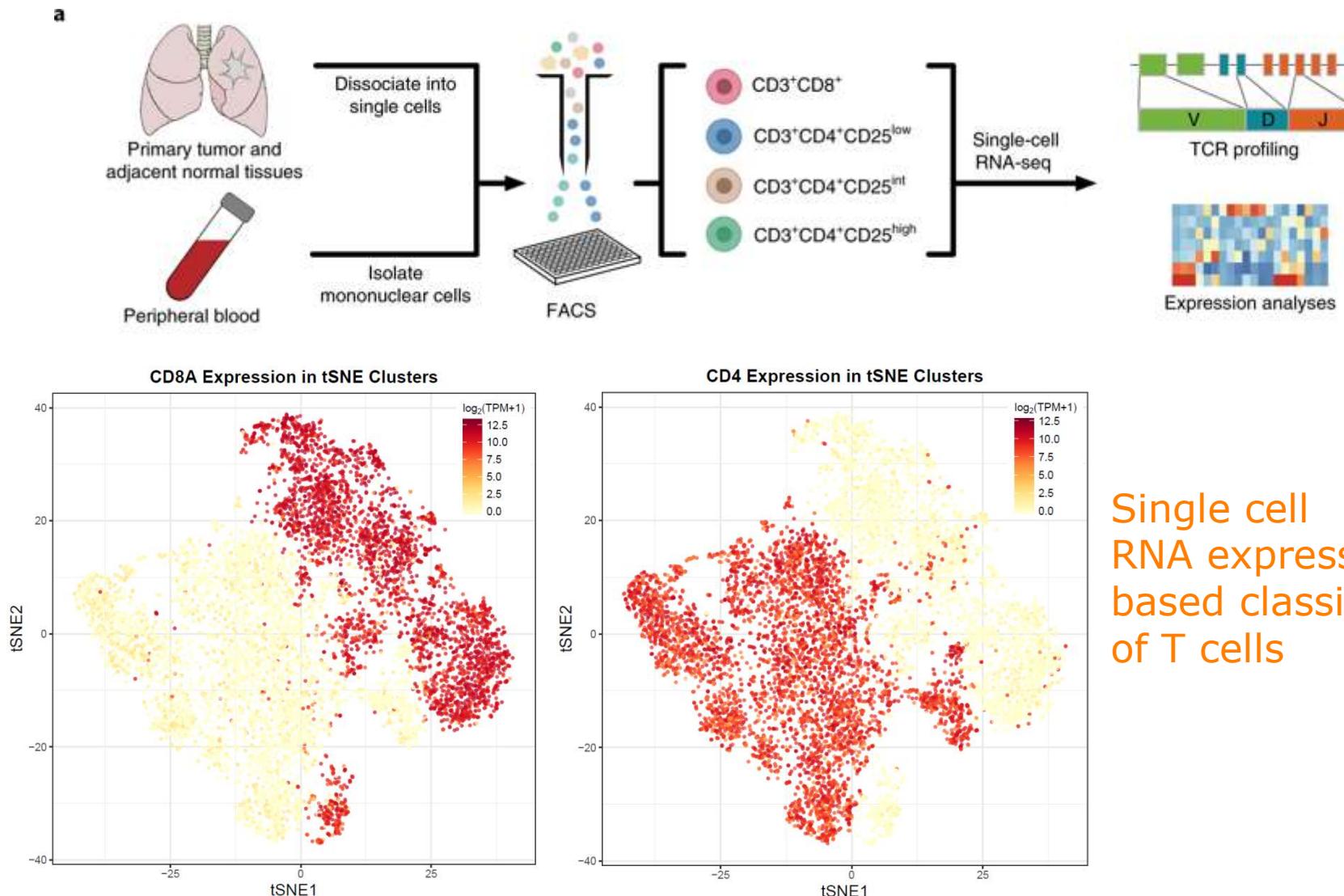
Fibronectin (stroma)

CD8 (CD8+ T cells)

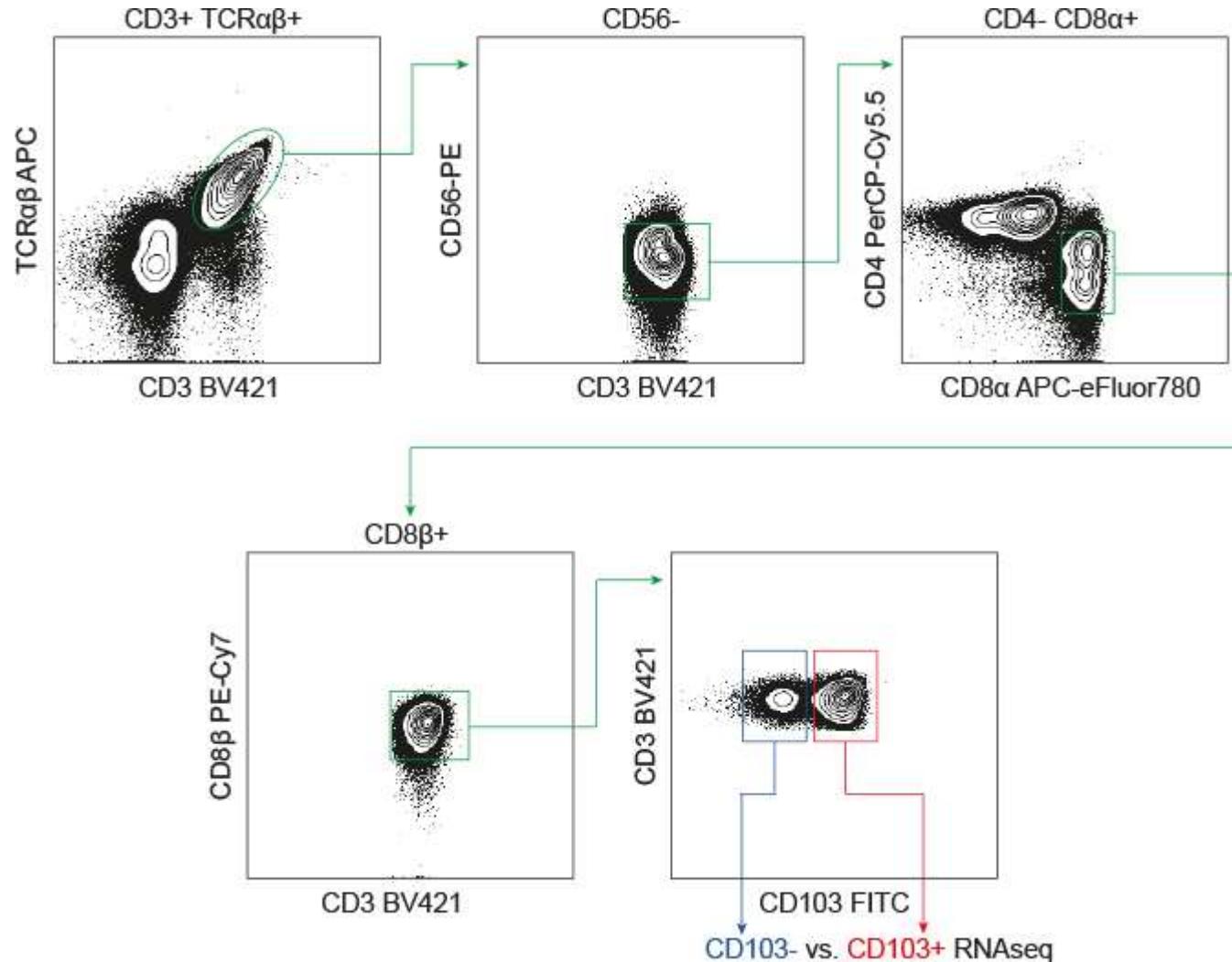
CD103 (CD103+ T cells)



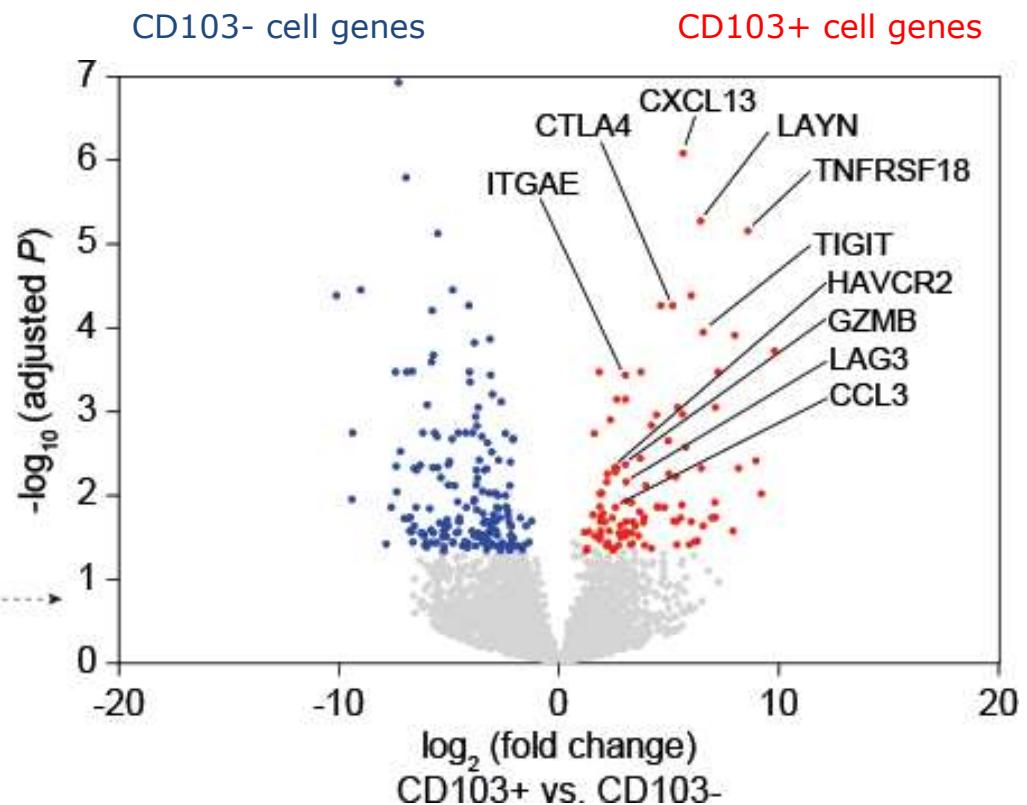
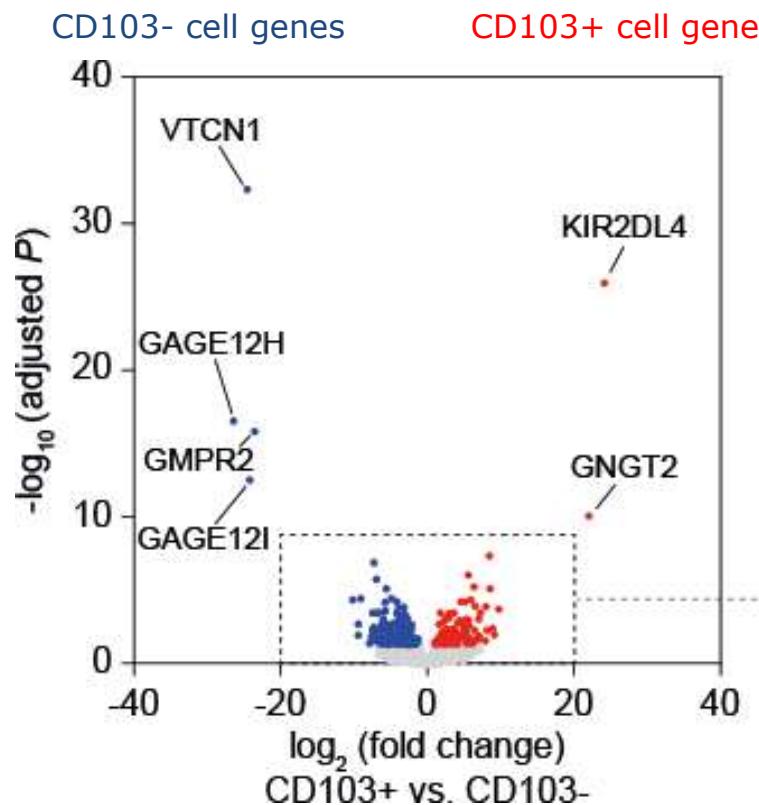
T cell subsets today



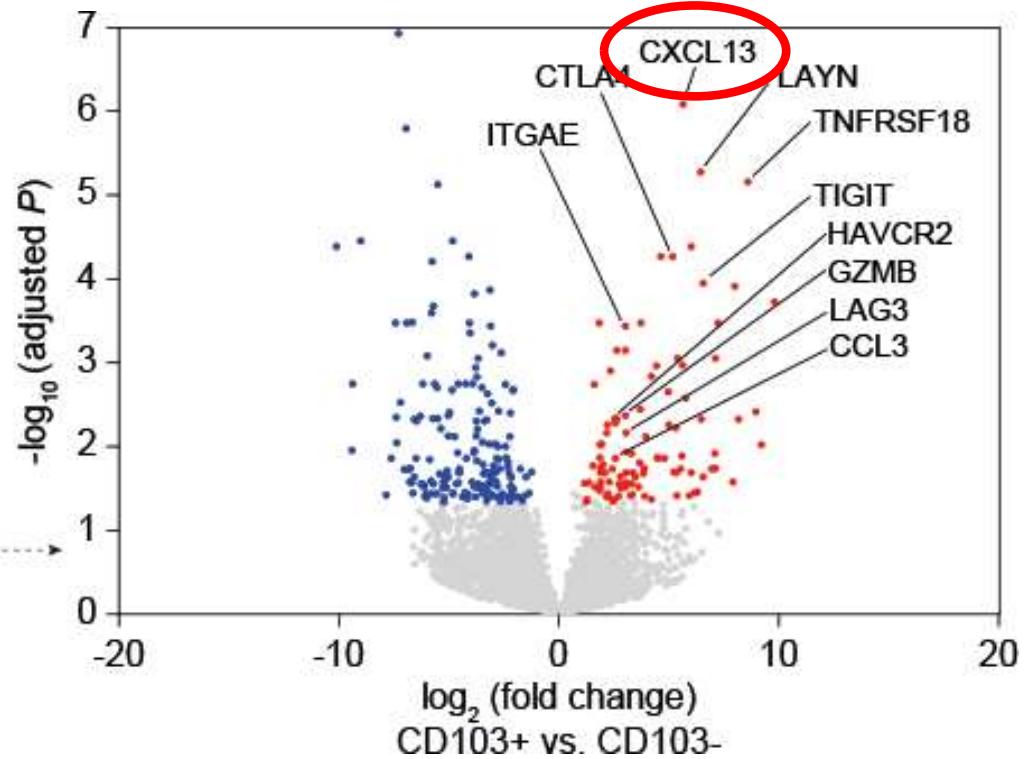
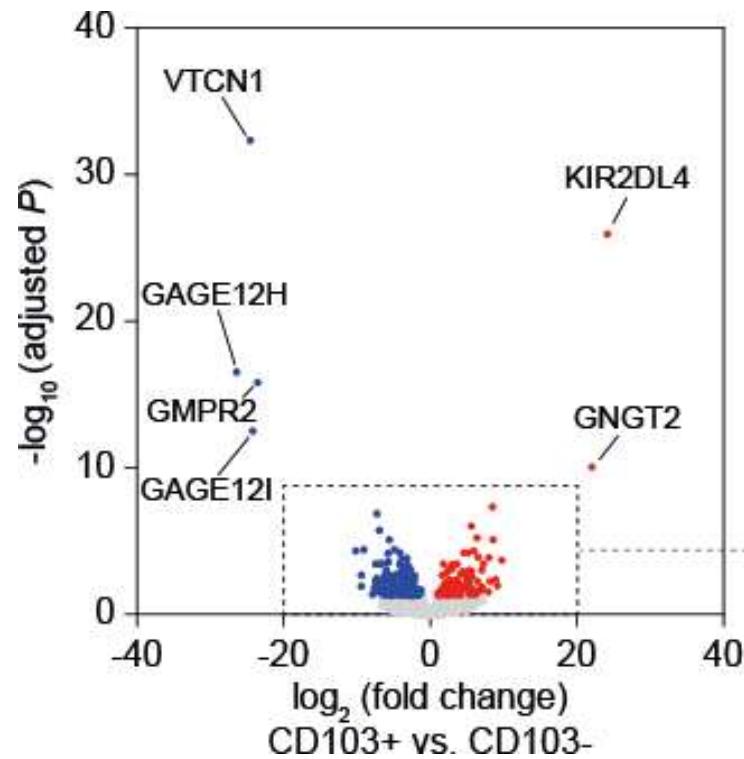
RNA sequencing of CD103+ T cells



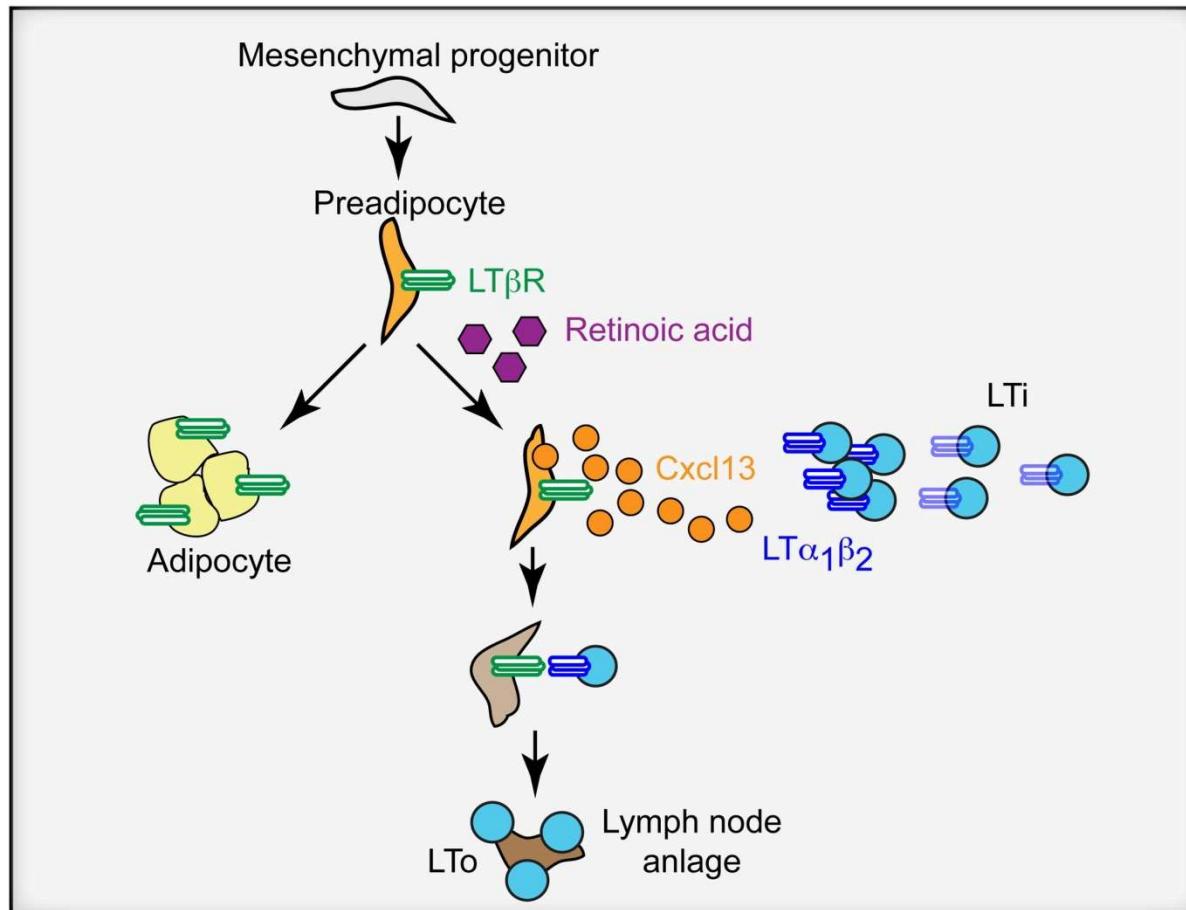
RNA sequencing of CD103+ T cells



RNA sequencing of CD103+ T cells

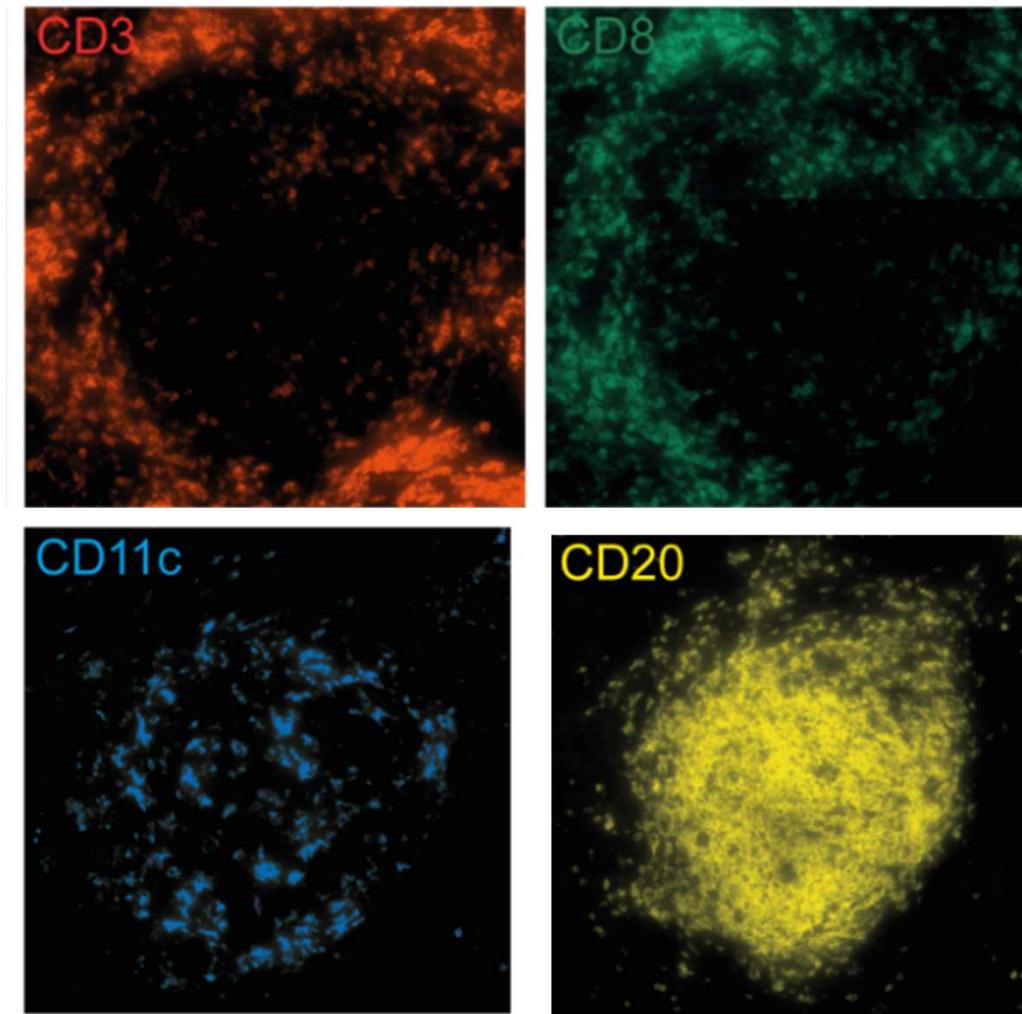


What is the function of CXCL13?



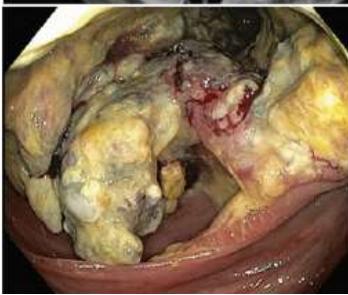
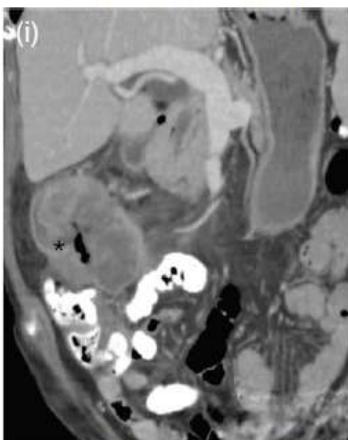
Essential for lymphoid tissue formation!

TLS in POLE mutant and MSI high EC

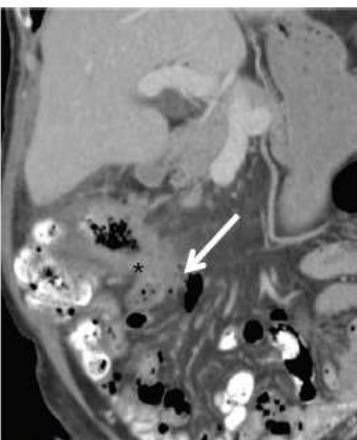


Formation of ectopic lymphoid tissue

b Patient 16,
dMMR. Pretreatment

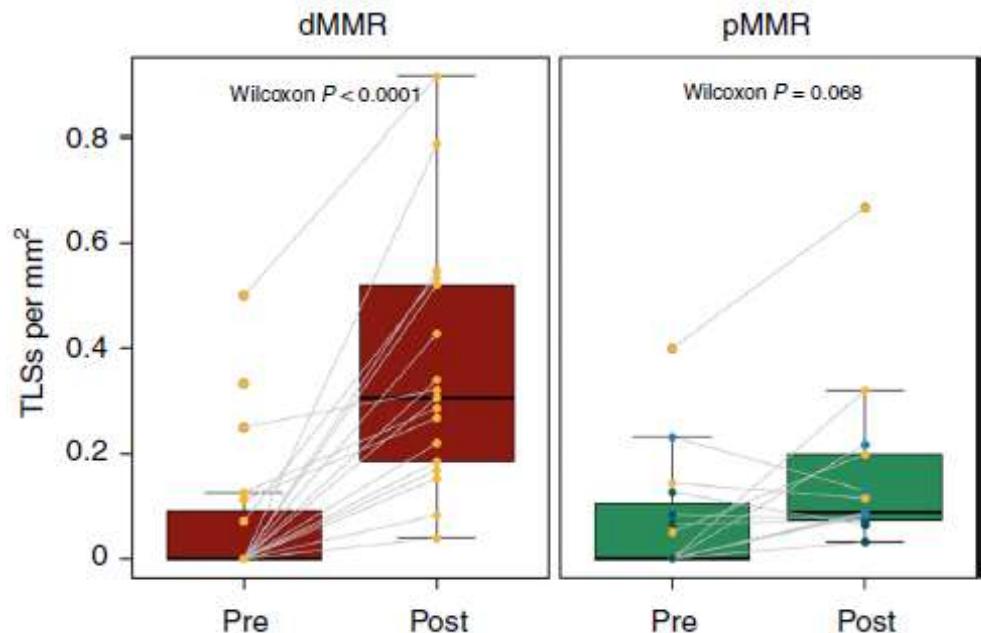


Posttreatment

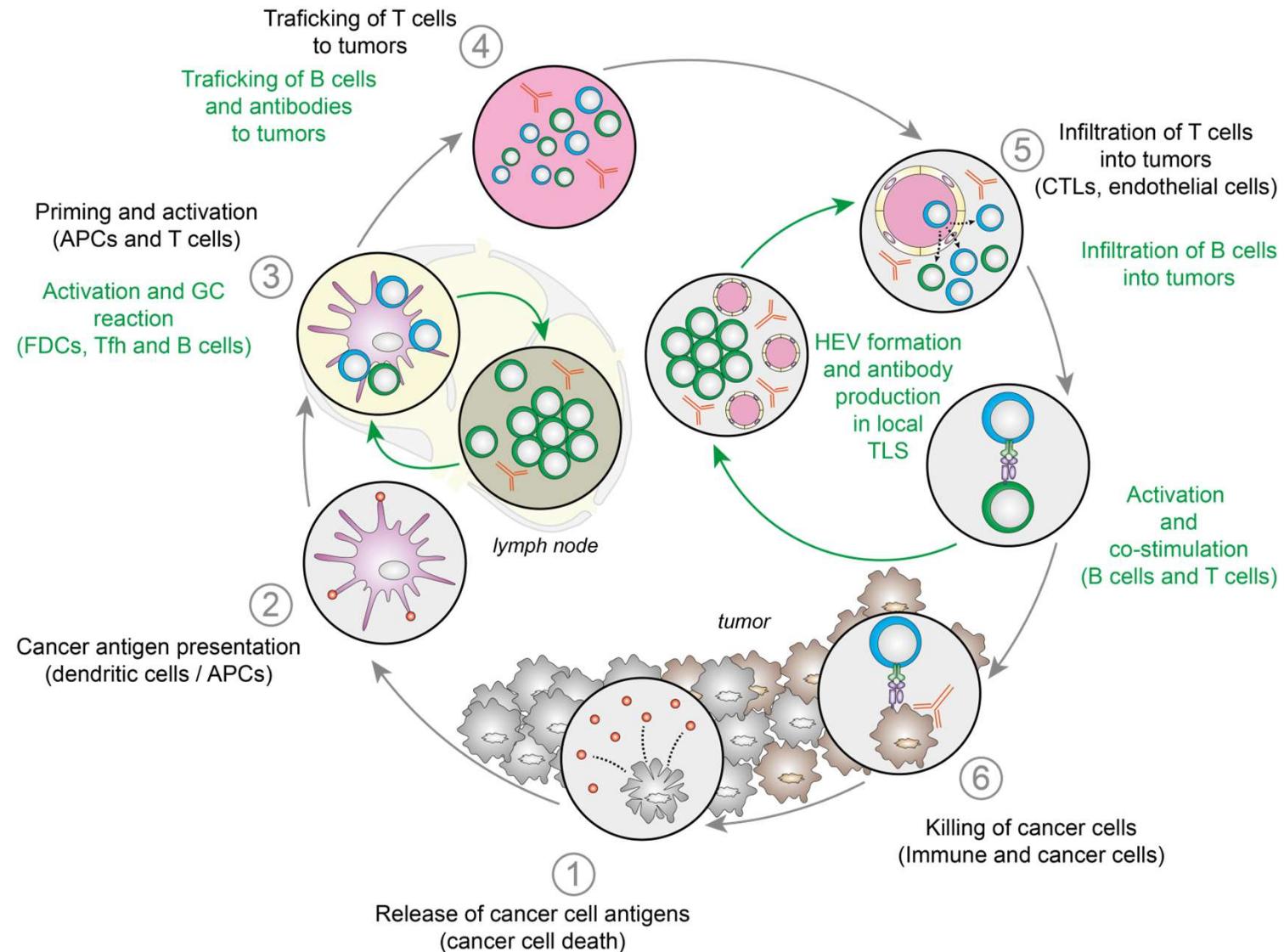


c

$P = 0.57$



Upgrade: cancer immunity cycle including B cell responses



Nespresso. What else ?





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