



KNOW THE ABC'S OF VIRAL HEPATITIS

More than 4 million people in the US are living with viral hepatitis. Most don't know it!

A Hepatitis A can be prevented with a safe, effective vaccine.

B Many people got infected with hepatitis B before the vaccine was widely available.

C Treatments are available that can cure hepatitis C.

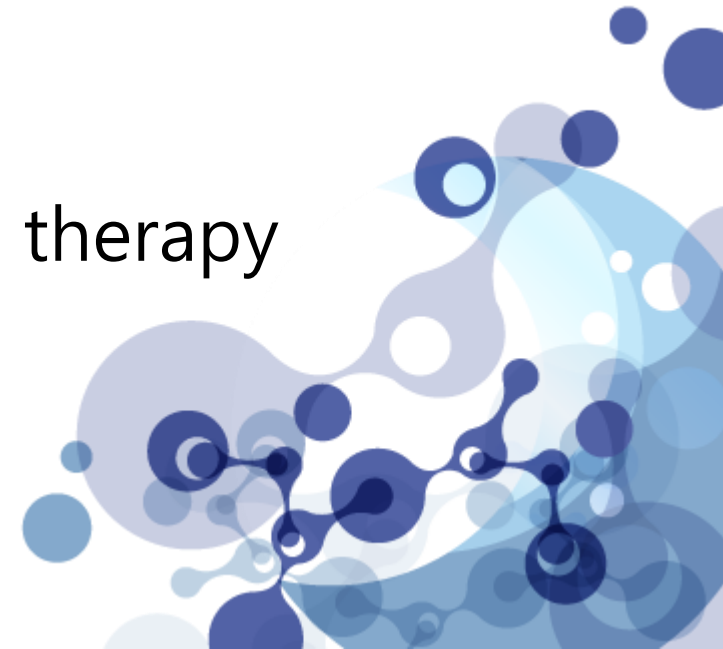
Take the CDC Online Risk Assessment to see if you should be vaccinated or tested for viral hepatitis:
www.cdc.gov/hepatitis/riskassessment

The ABCs of Immunotherapy

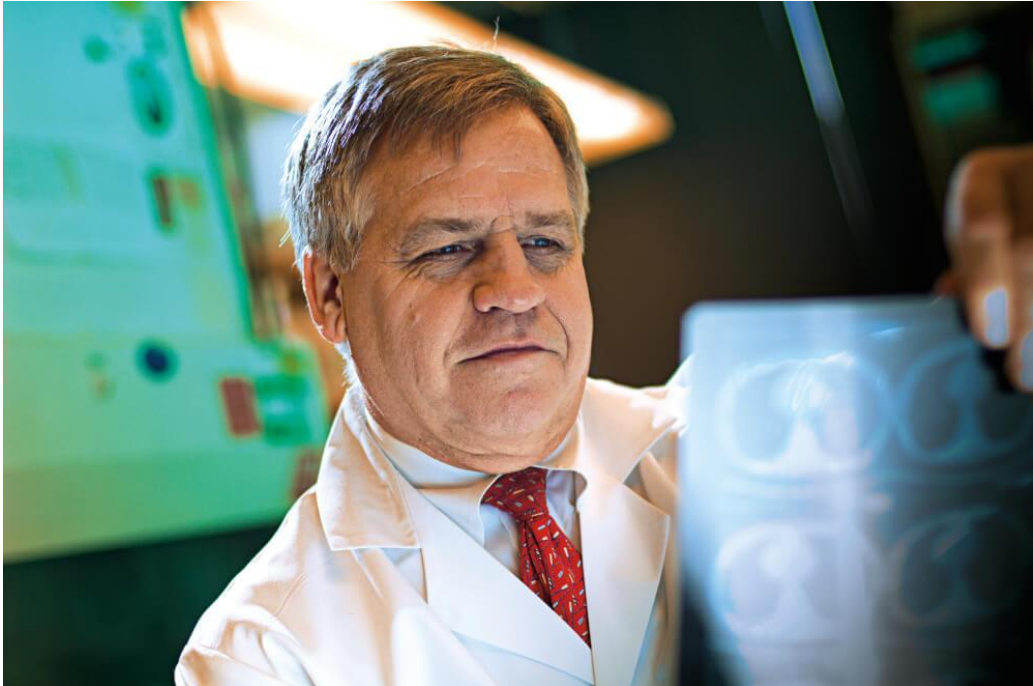
Anti-PD-1/PD-L1 inhibitor

Biomarker

Combination or **C**AR T cell therapy



When is Immunotherapy the Right Treatment for Lung Cancer?

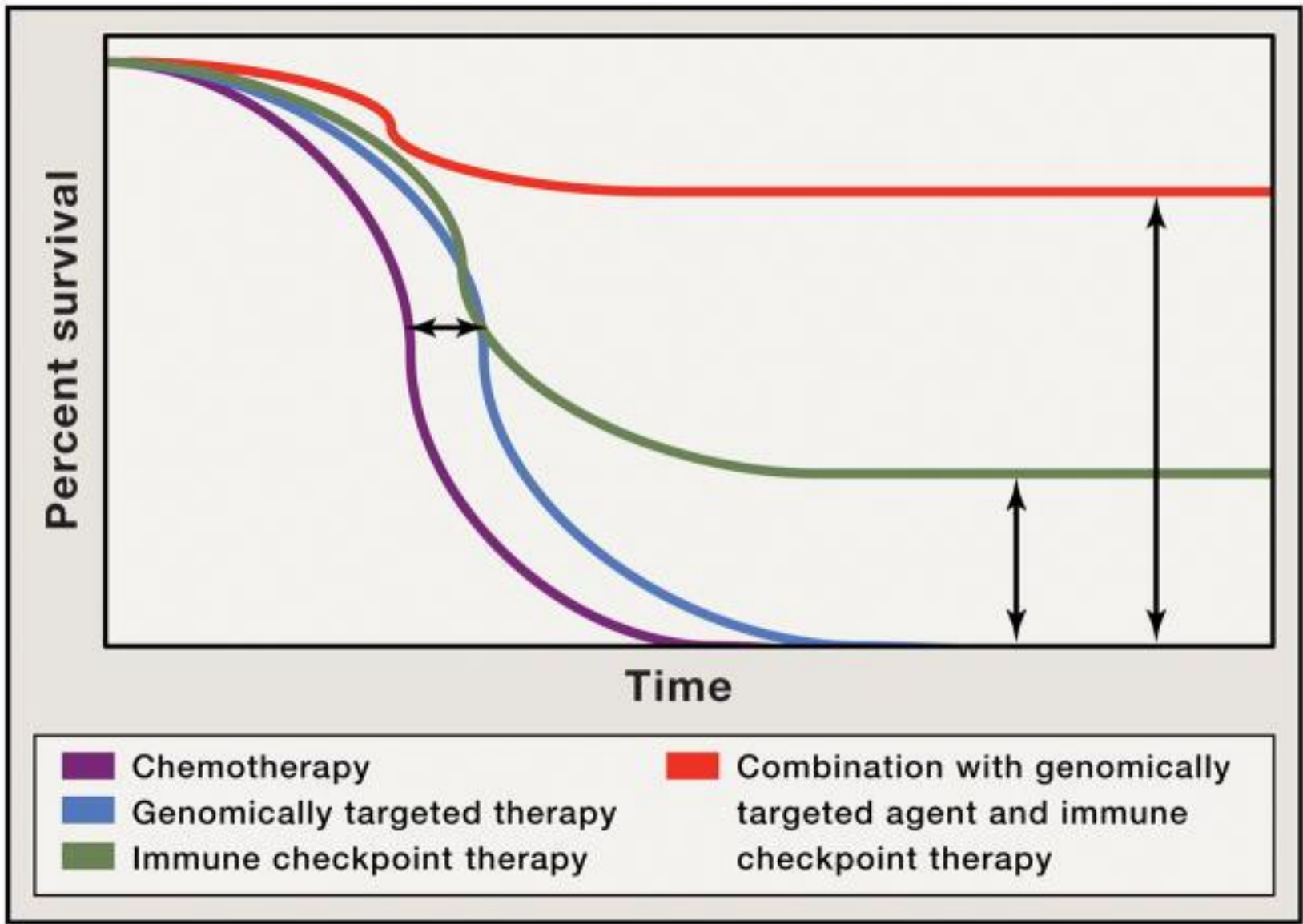


Bruce Johnson, MD

“dramatic transformation”

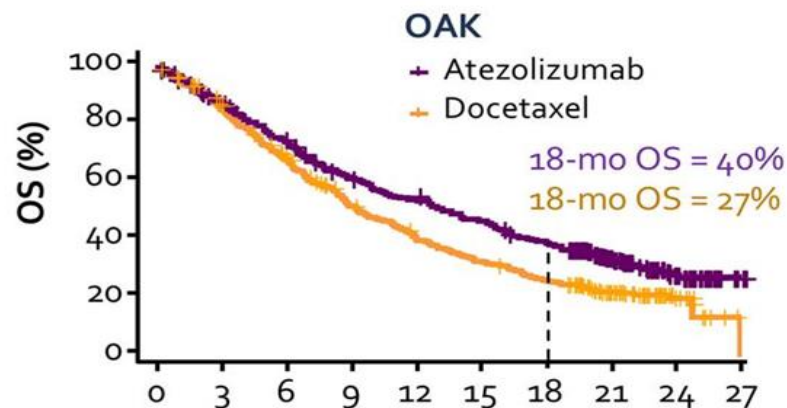
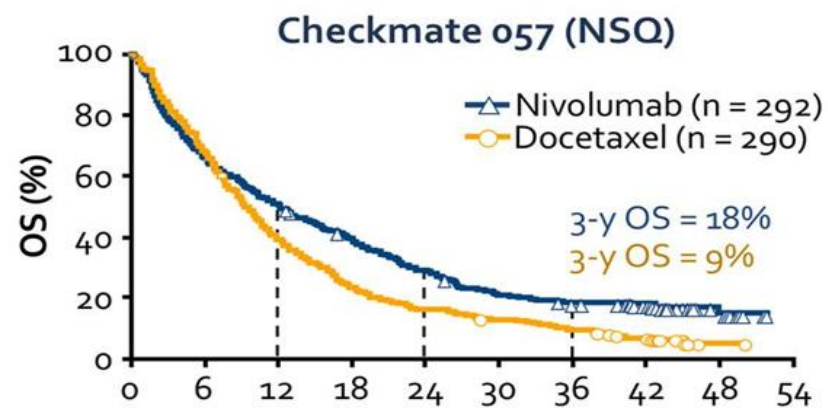
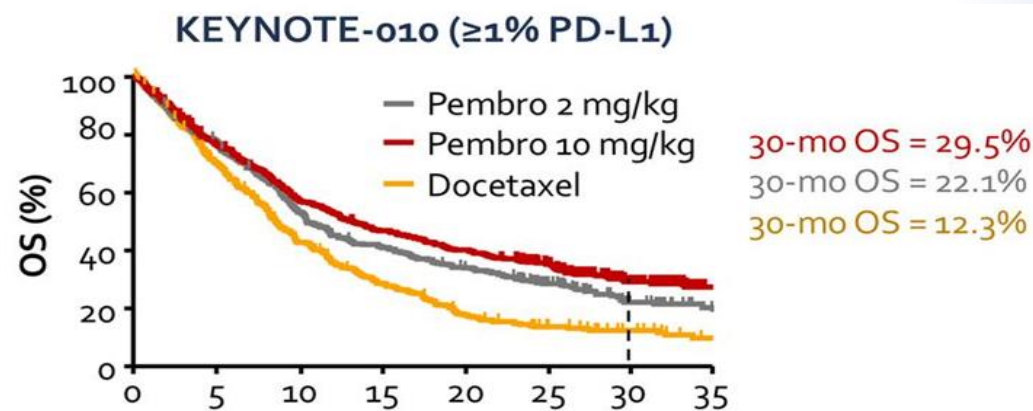
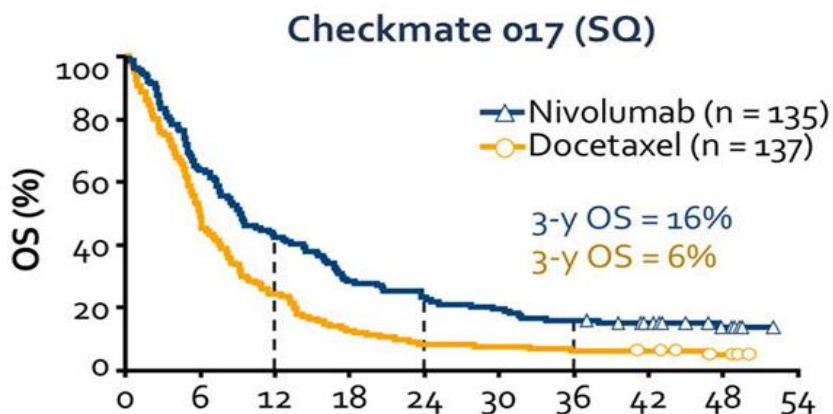
“Today, nearly **half** of all patients presenting with lung cancer can be **initially treated** with **targeted agents or immunotherapy** rather than chemotherapy.”

“The estimated three-year survival rates are 17 percent and the curve remains relatively flat out toward five years,”





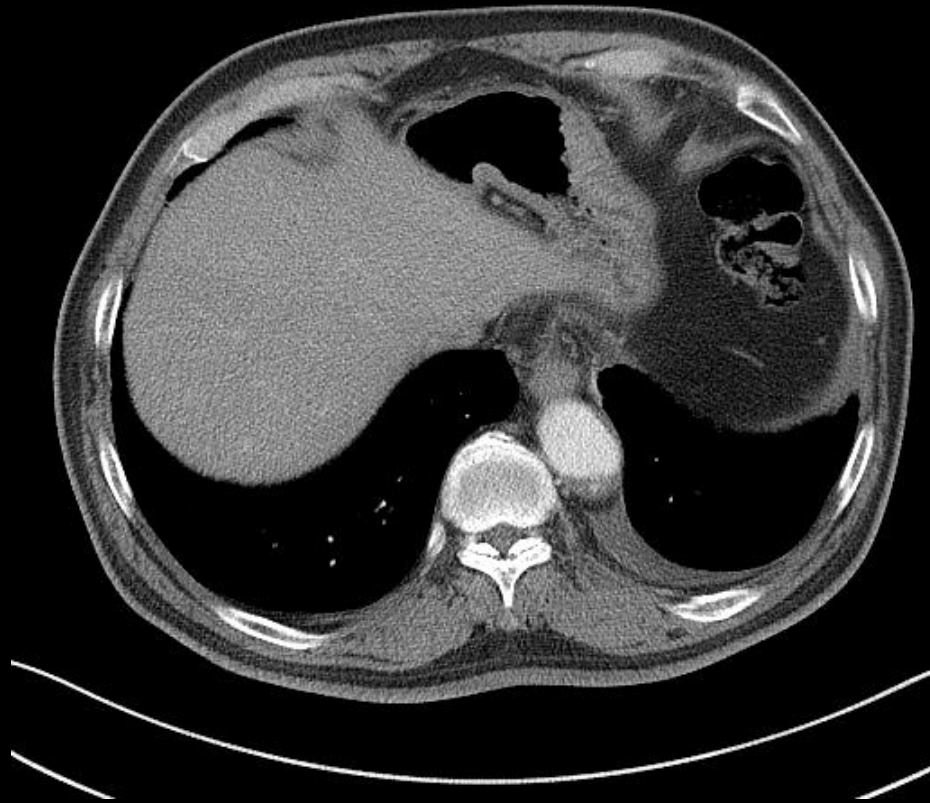
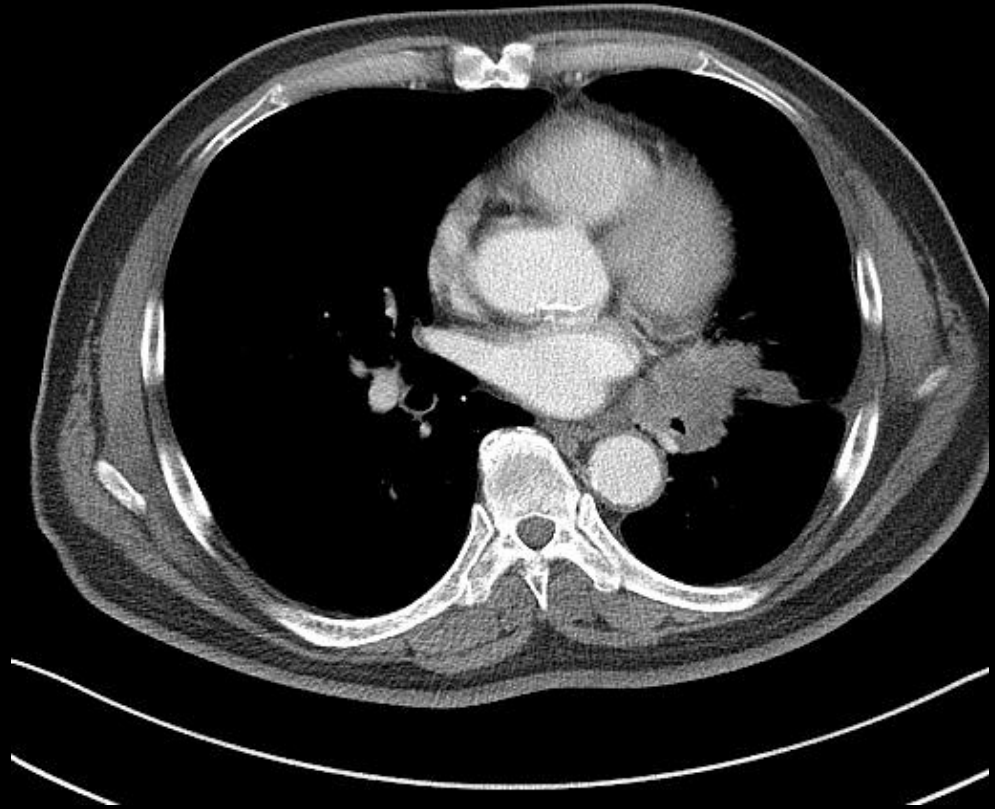
A consistent but limited OS benefit in 2nd line



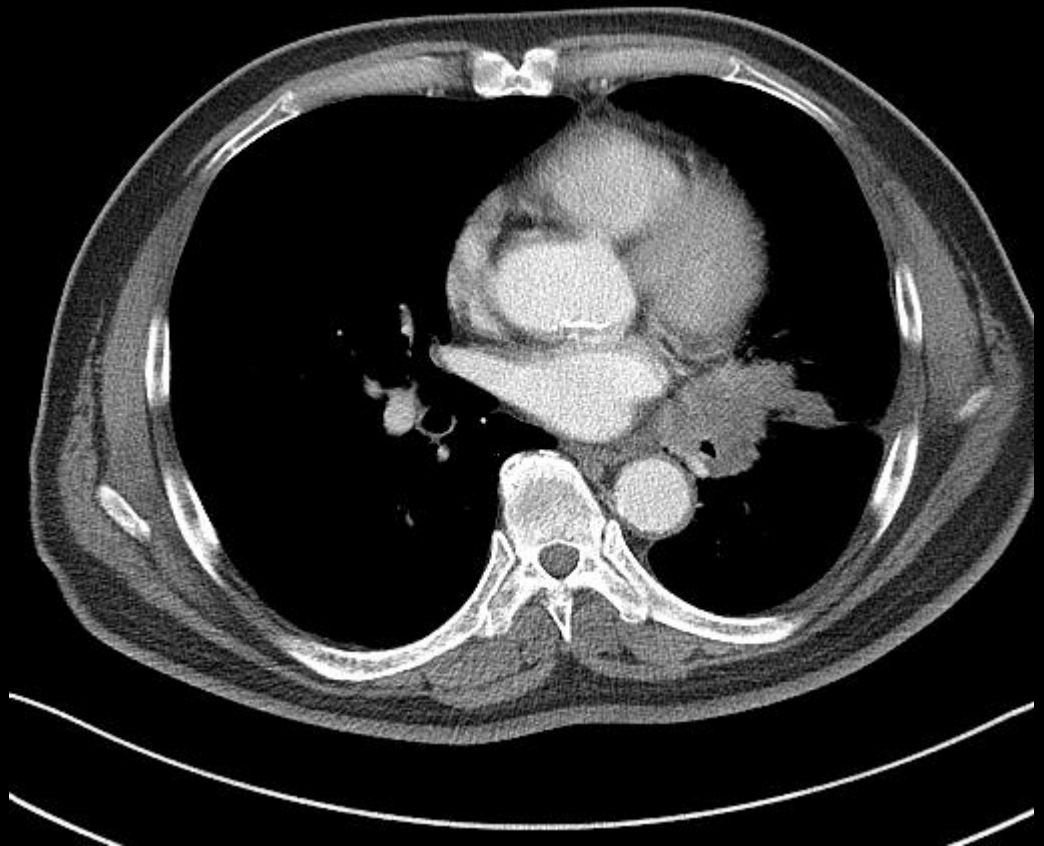
Felip, ESMO 2017; Herbst, ASCO 2017; Rittmeyer, Lancet 2017

Male - 72 years old

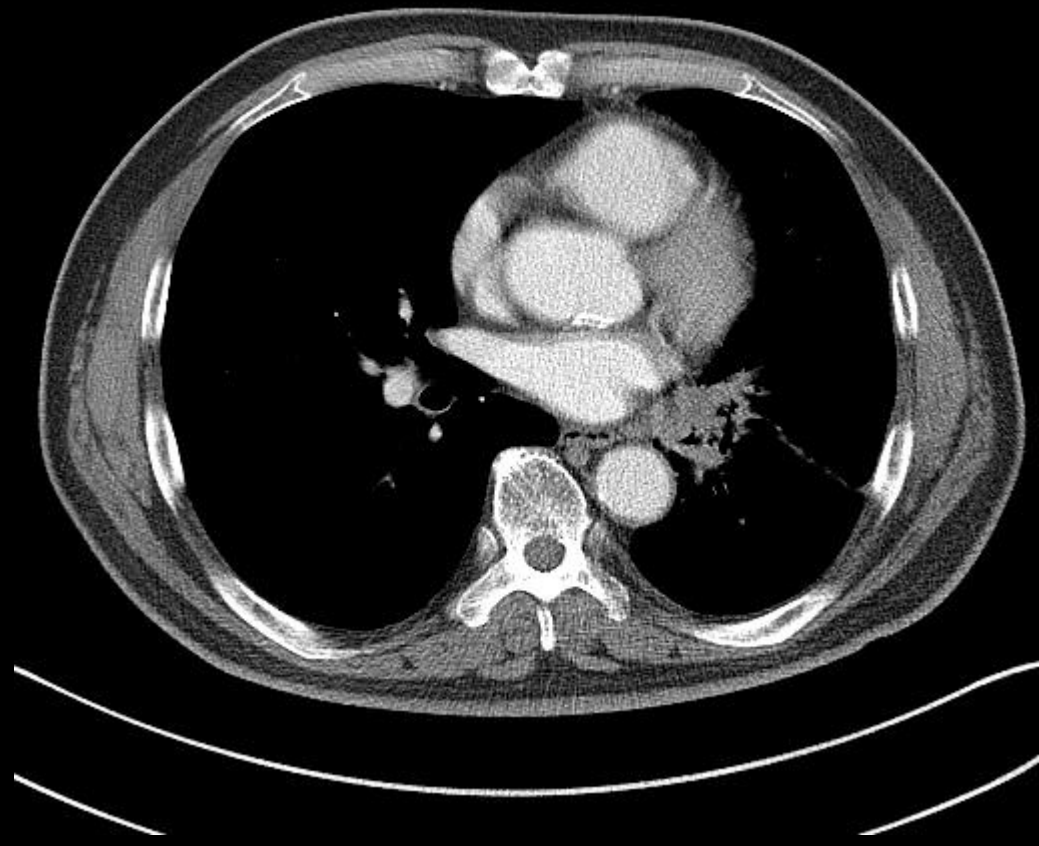
- 2017.5 Hemoptysis
- Squamous cell carcinoma GP#4



Male - 72 years old after GP #4

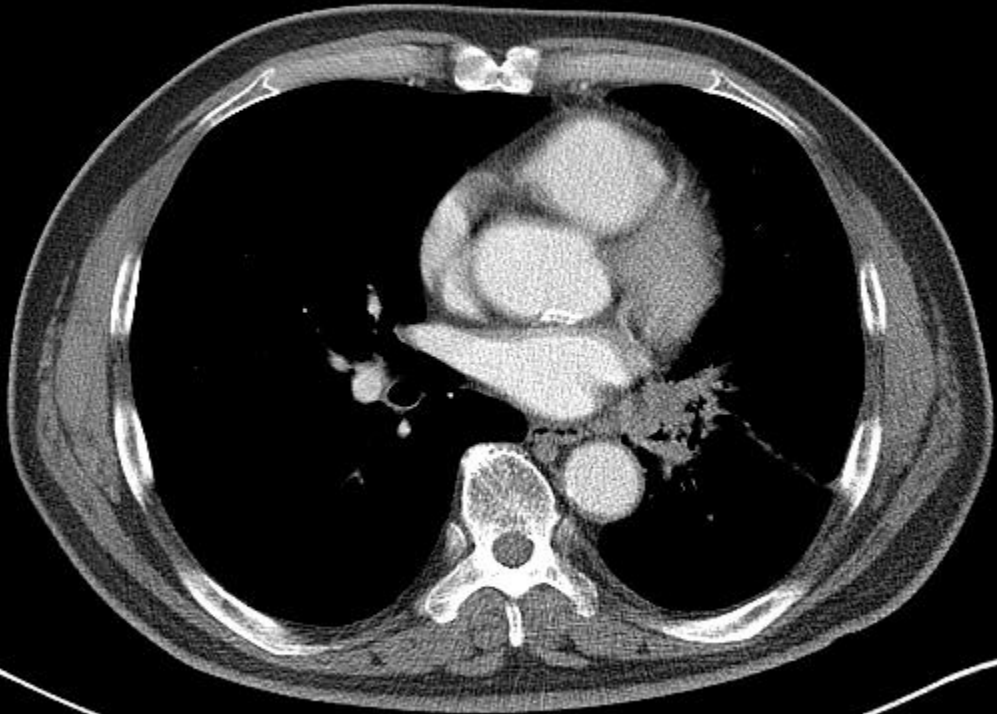


2017.5.15

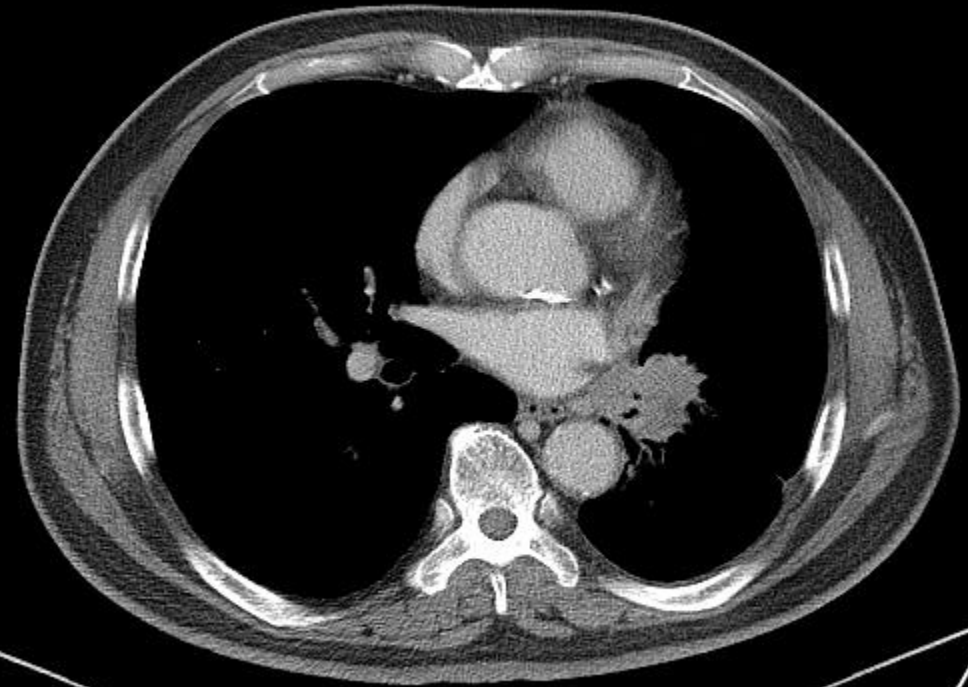


2015.7.22

Male - 72 years old – PD



2015.7.22



2017.10.20

Male - 72 years old

- PD-L1 : Positive (+) ($\geq 1\%$)

* Approximate Number of Viable Tumor Cells: ≥ 100

* Negative Control Reagent Acceptance: Yes

* Tissue Specimen Scoring of Tumor Cells

- PD-L1 Expression: Strong Positive ($\geq 50\%$)

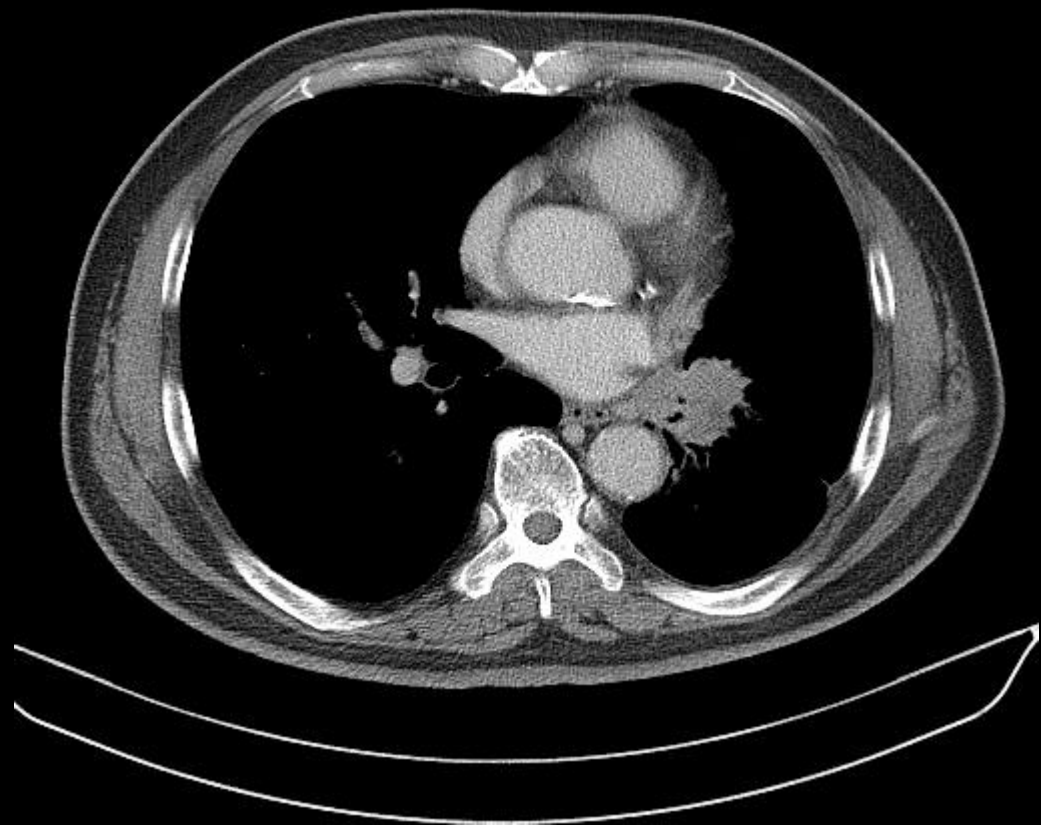
- TPS (Tumor proportion score): 100 %

- Predominant staining intensity: 3+ (Strong staining)

Pemblizumab #23 Stable disease

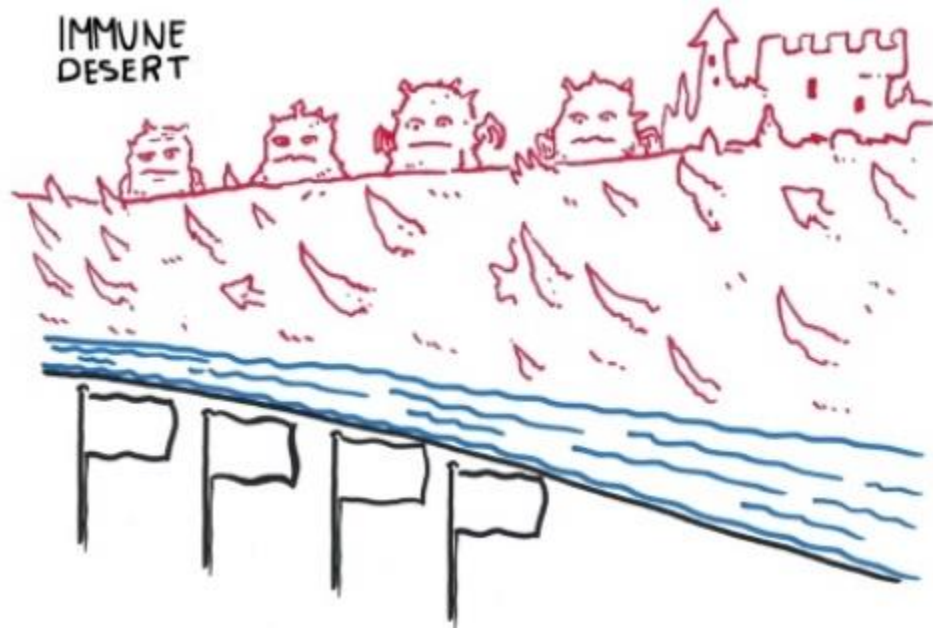


2017.09.15



2017.10.20

Immune phenotypes



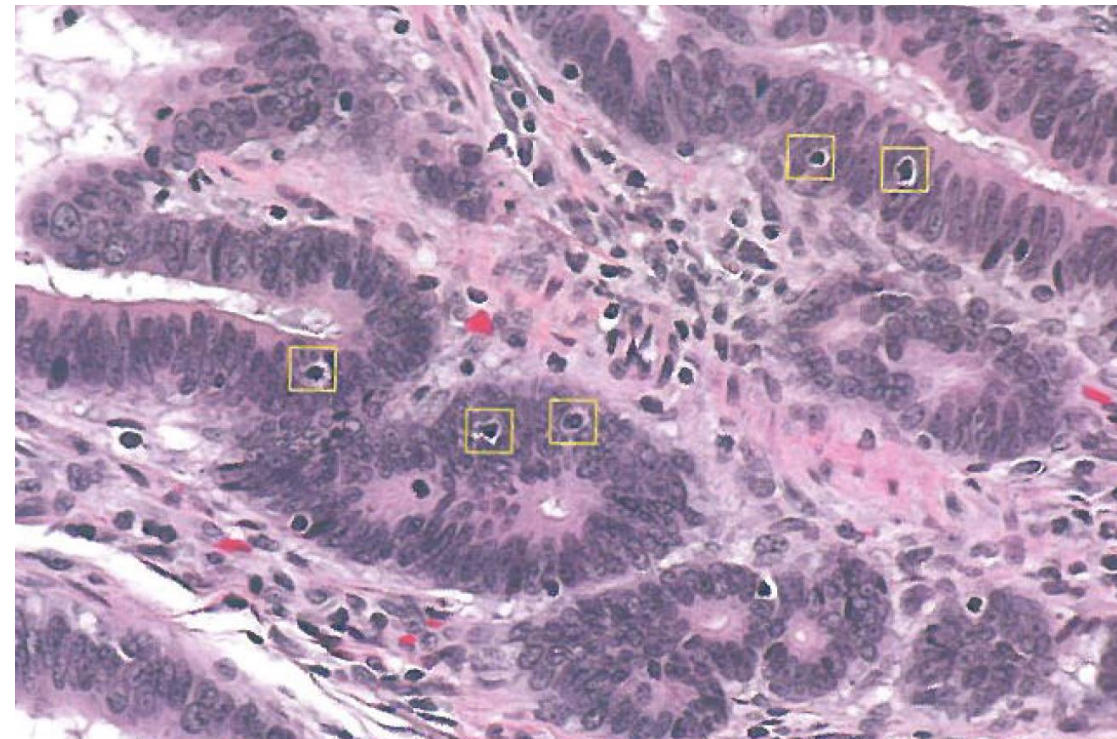
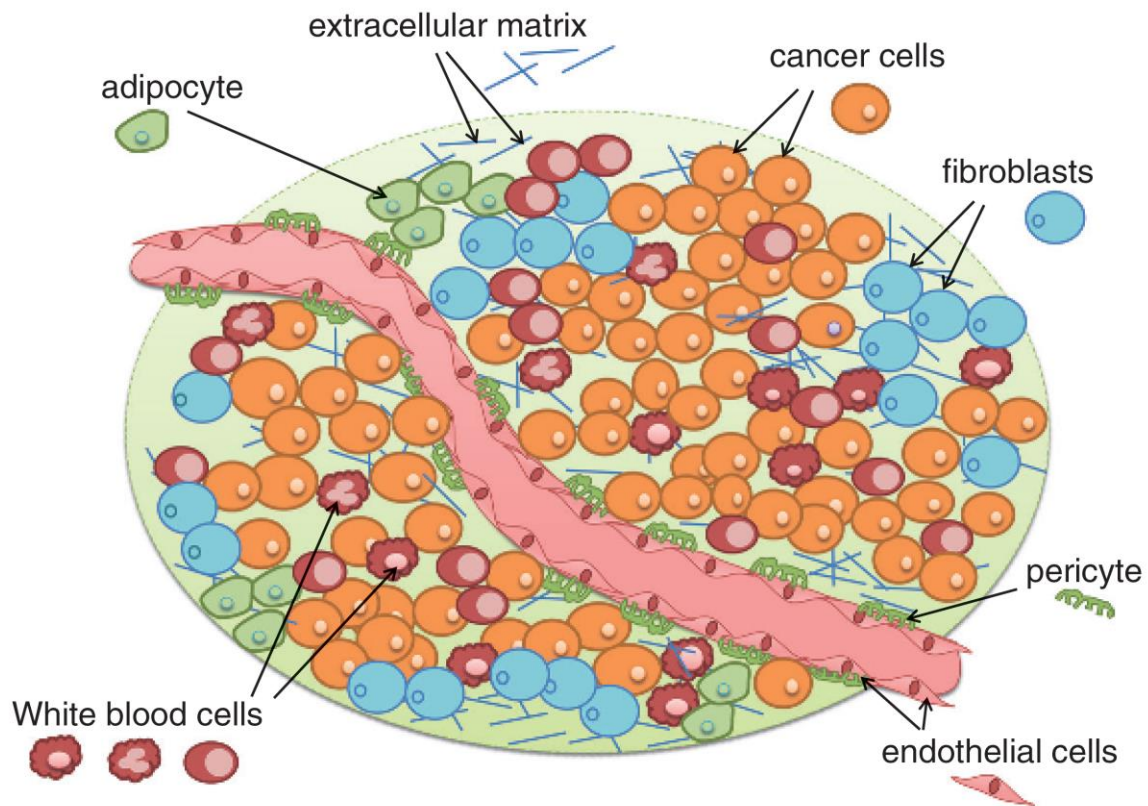
https://www.roche.com/research_and_development/what_we_are_working_on/oncology/cancer-immunotherapy/beyond-the-immunity-cycle.htm

Immune phenotypes

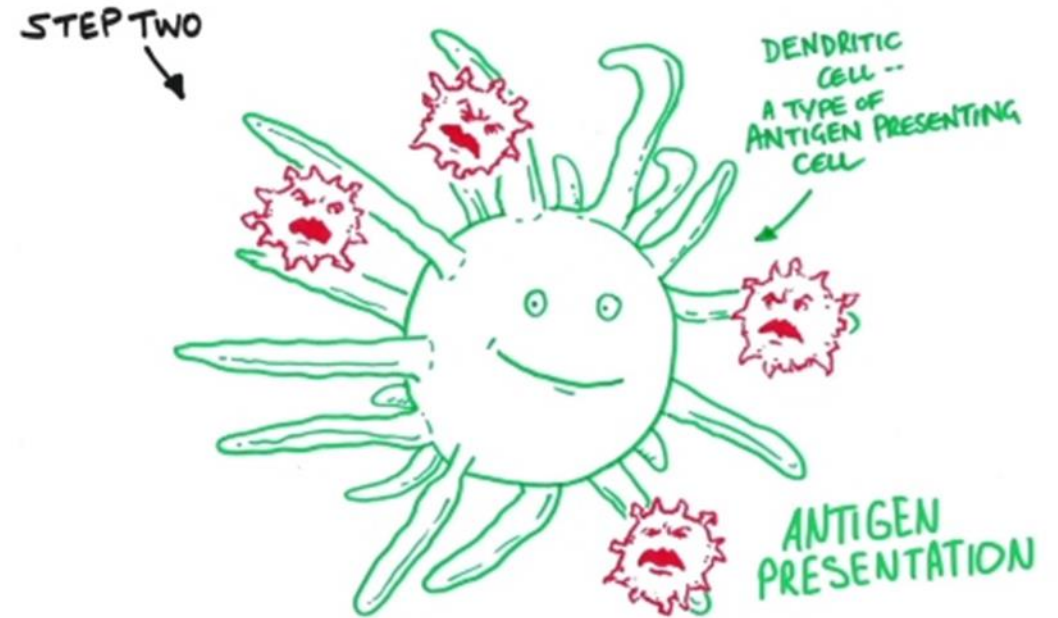
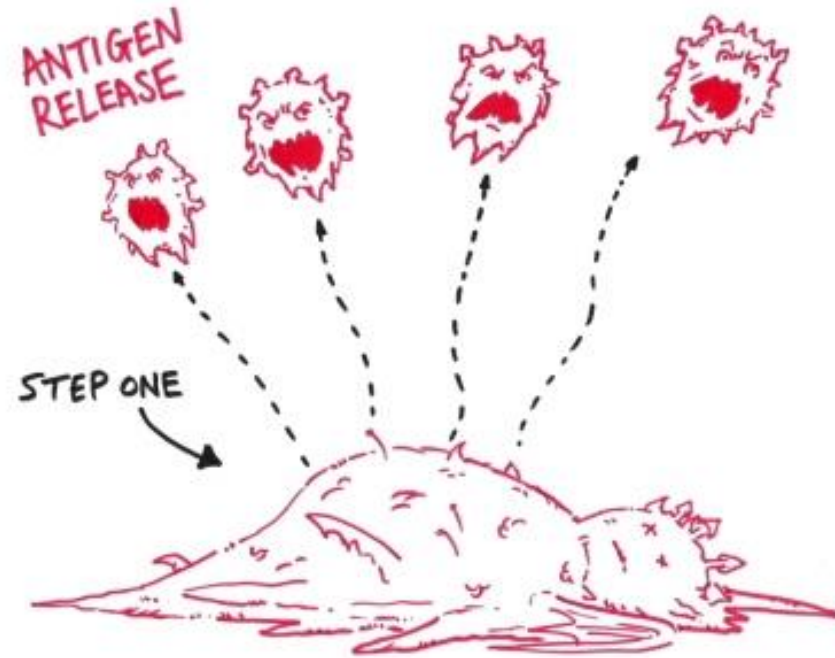


https://www.roche.com/research_and_development/what_we_are_working_on/oncology/cancer-immunotherapy/beyond-the-immunity-cycle.htm

Cancer microenvironment

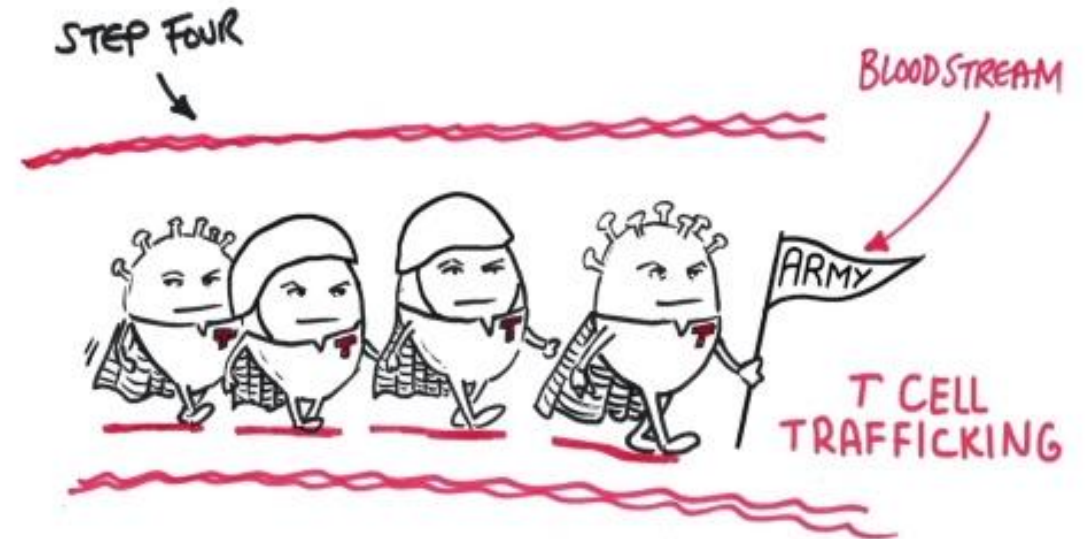
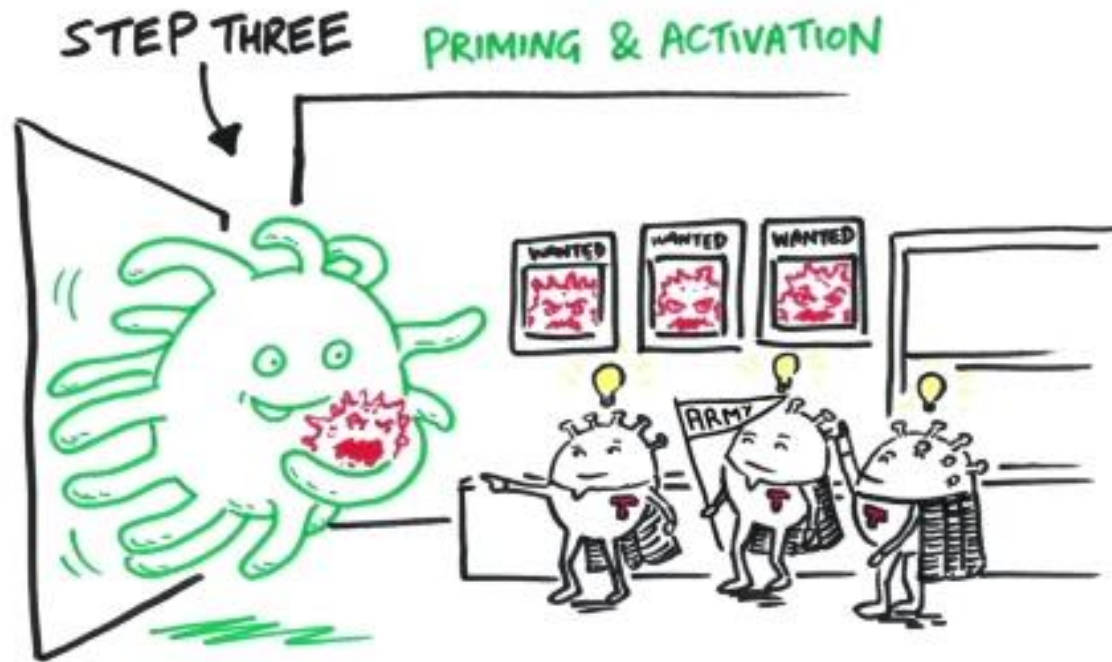


The cancer immunity cycle – Seven Step



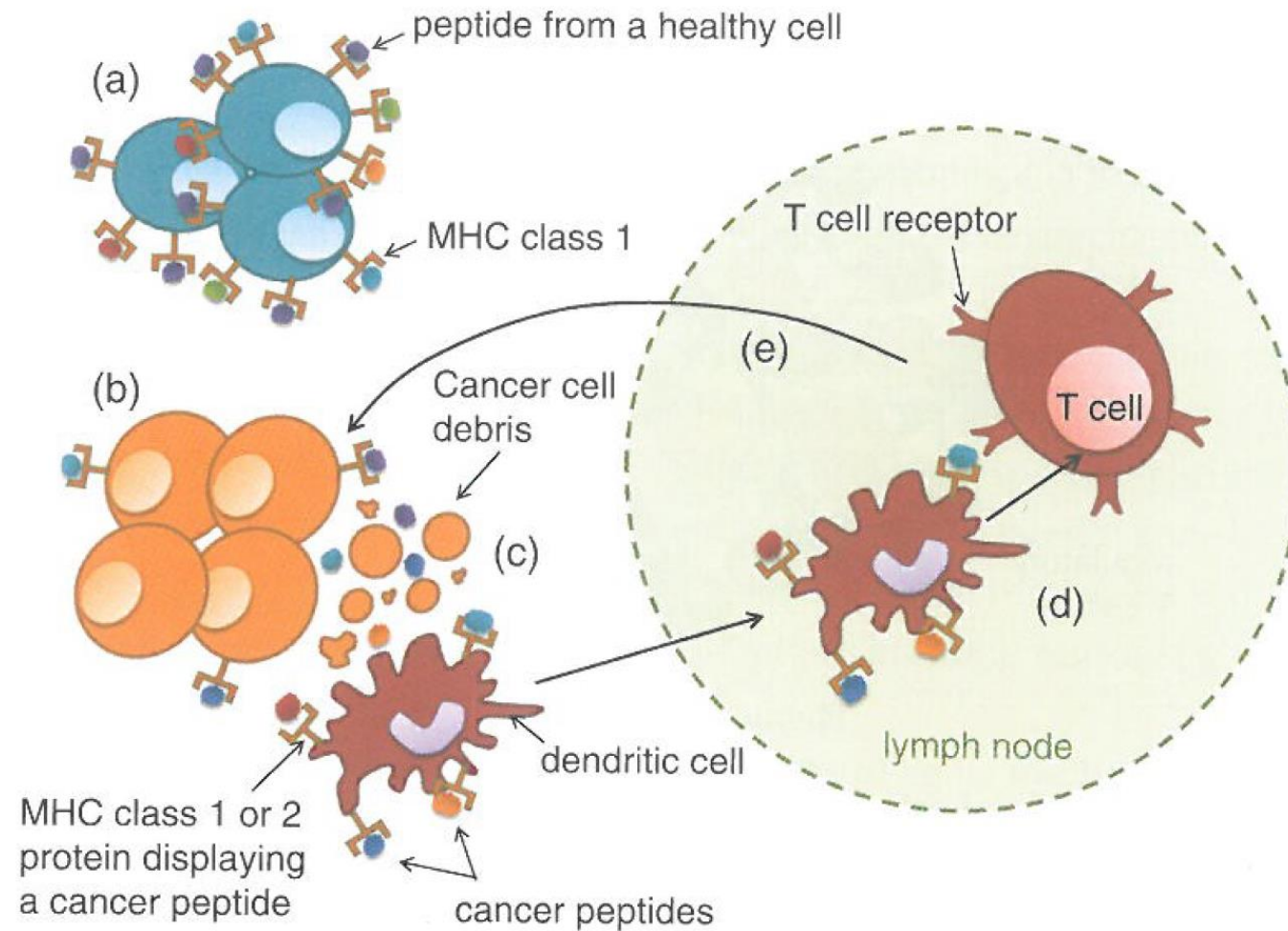
https://www.roche.com/research_and_development/what_we_are_working_on/oncology/cancer-immunotherapy/beyond-the-immunity-cycle.htm

The cancer immunity cycle

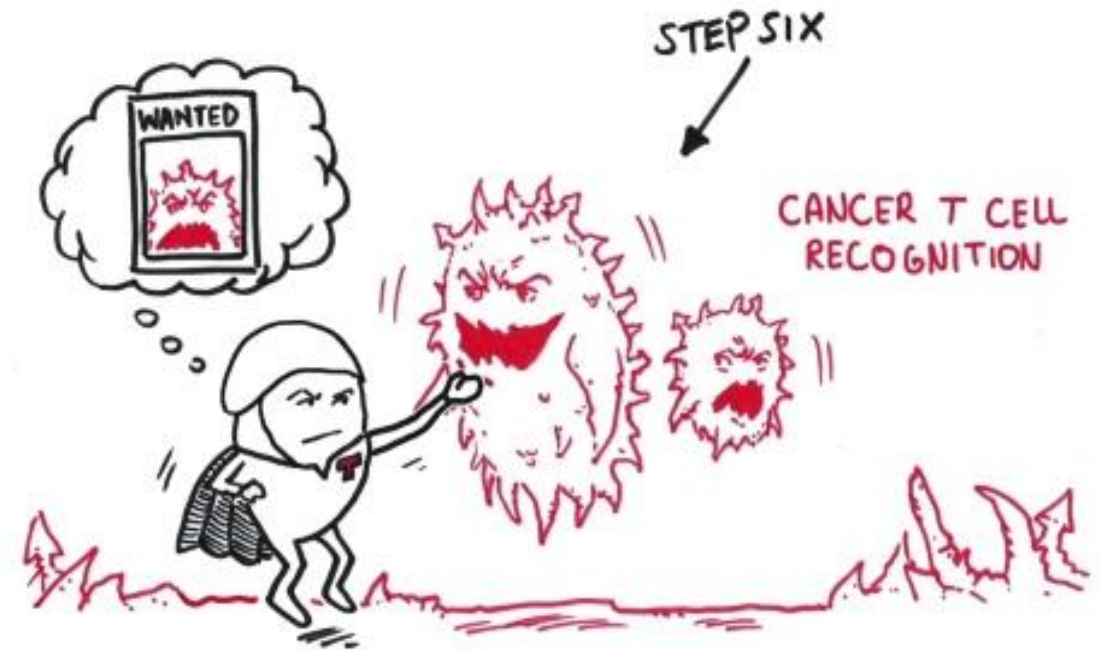
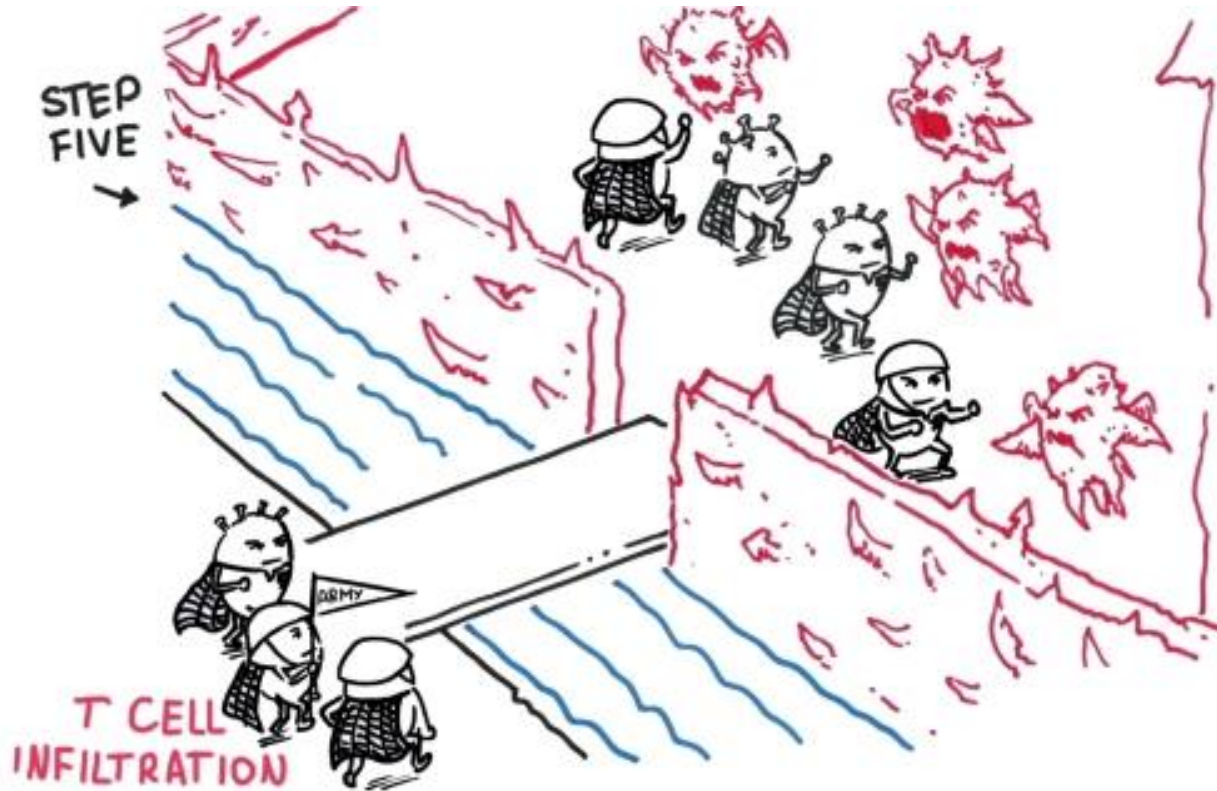


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The cancer immunity cycle

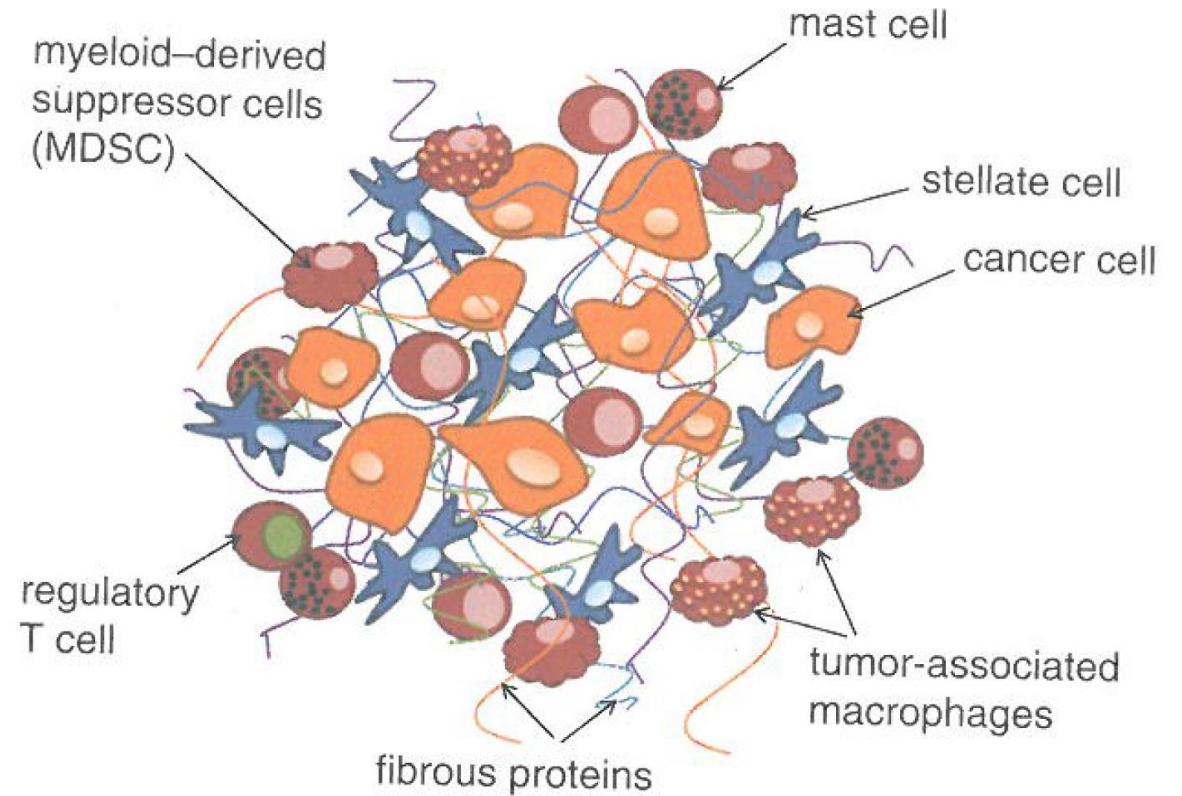
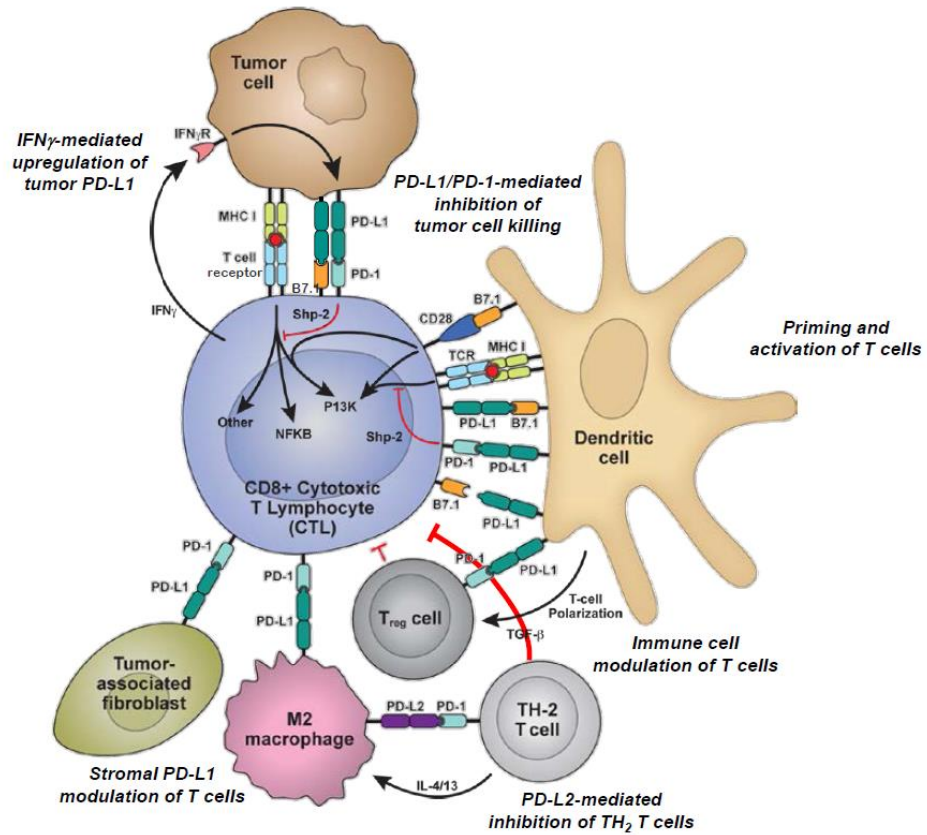


The cancer immunity cycle

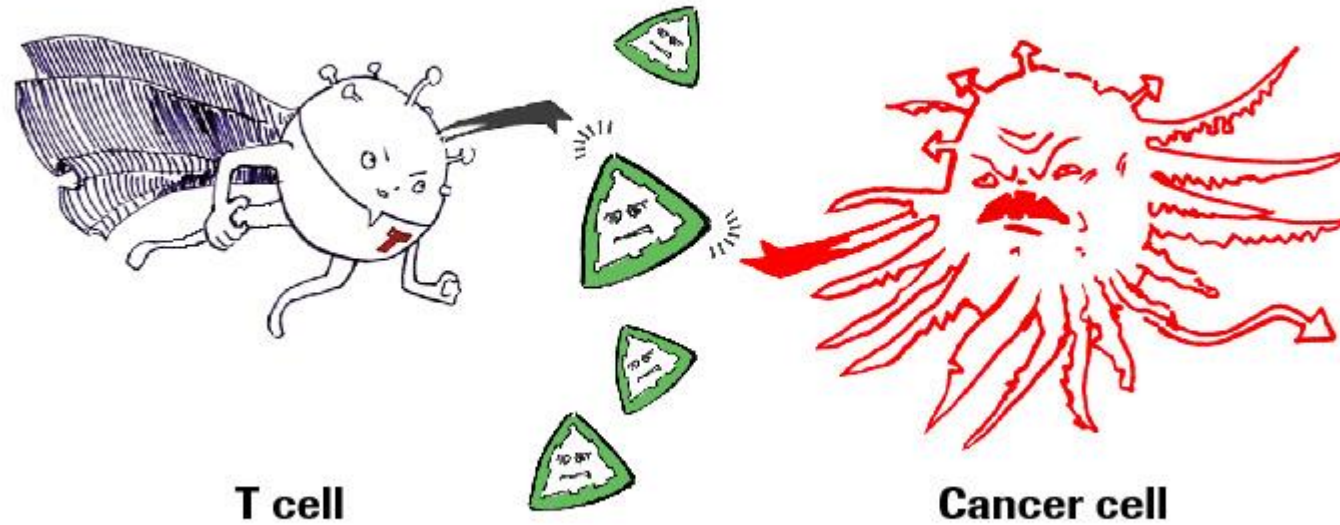


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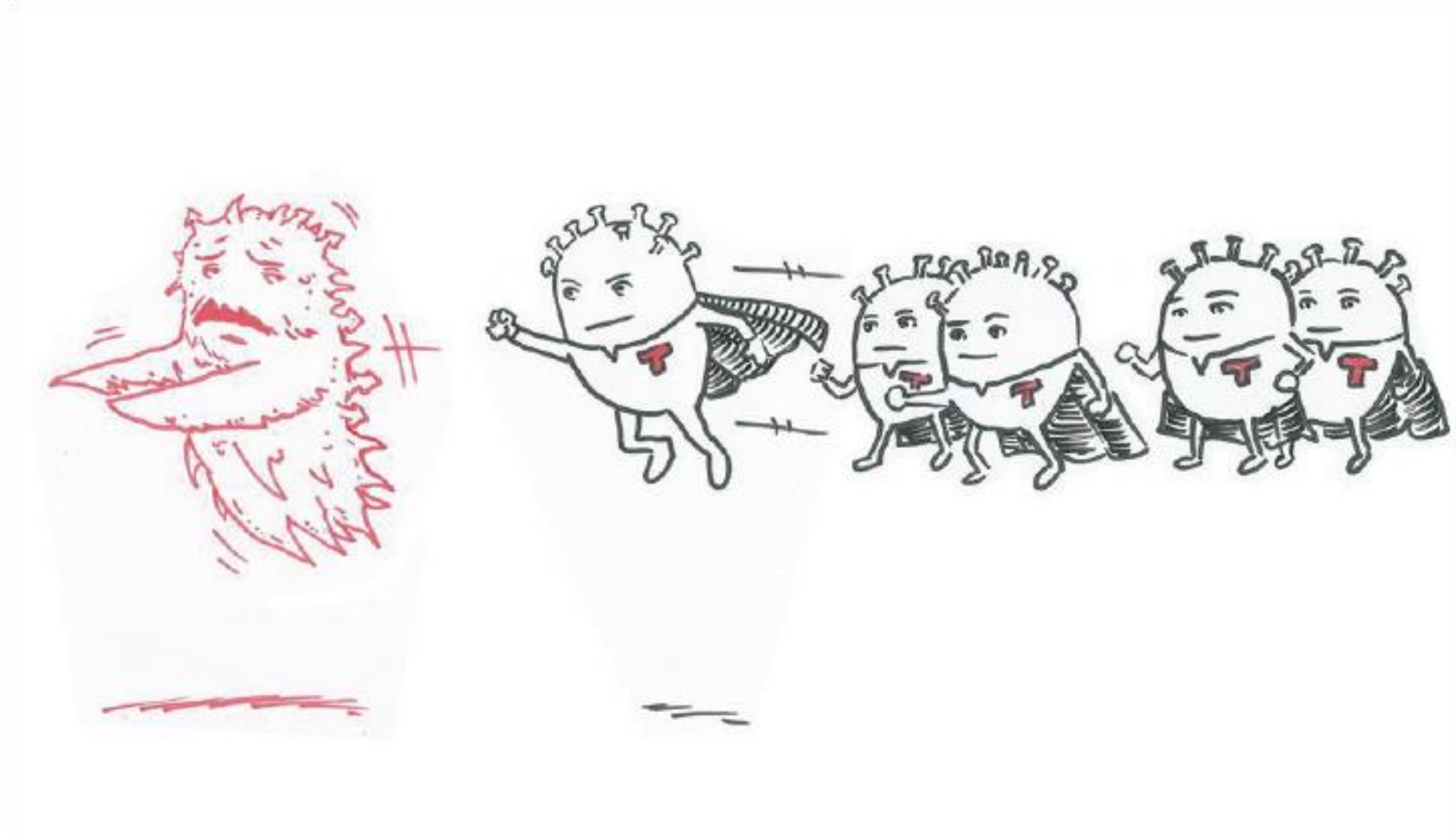
Role of White bloods



The cancer immunity cycle – T cell killing



The cancer immunity cycle – T cell killing

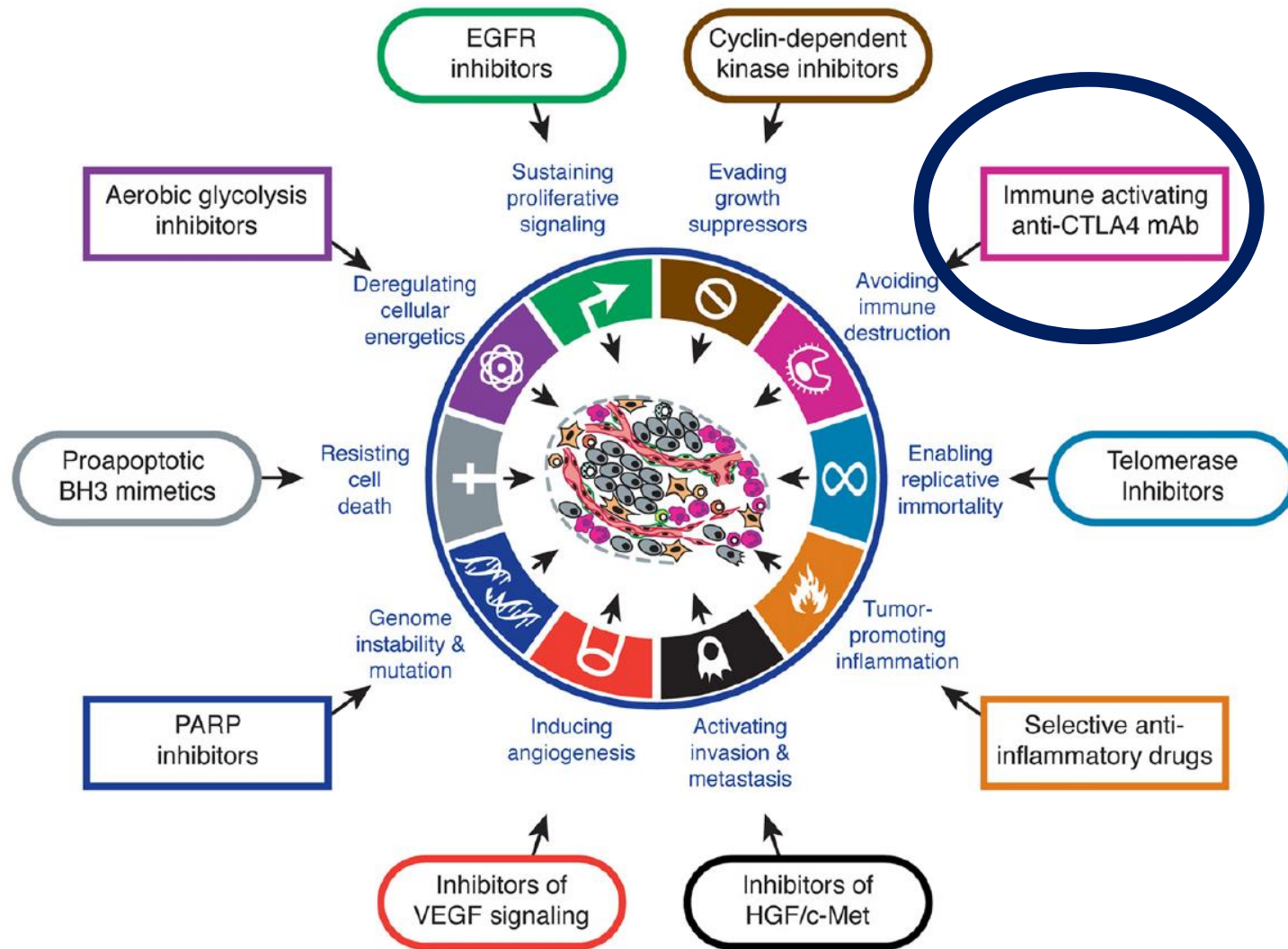


The cancer immunity cycle – T cell killing



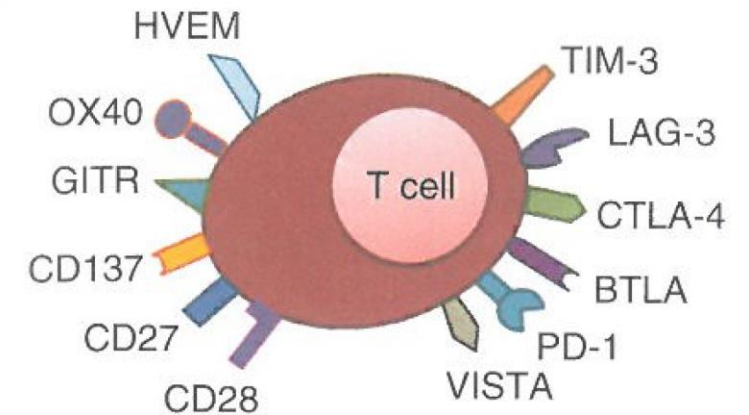
https://www.roche.com/research_and_development/what_we_are_working_on/oncology/cancer-immunotherapy/beyond-the-immunity-cycle.htm

Avoiding immune destruction



(a) Activating/stimulatory checkpoint proteins

(b) Inhibitory checkpoint proteins

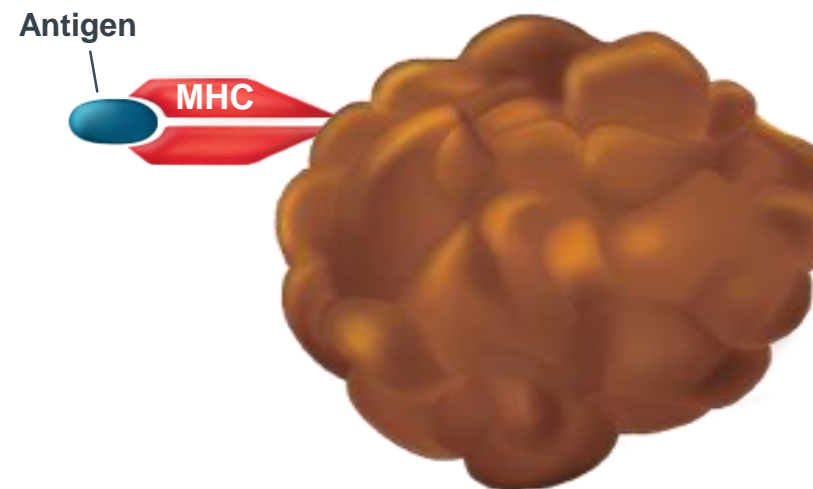




- Designed to suppress the immune system
- Healthy organs are not damaged
- Cancer cells can take over these checkpoints

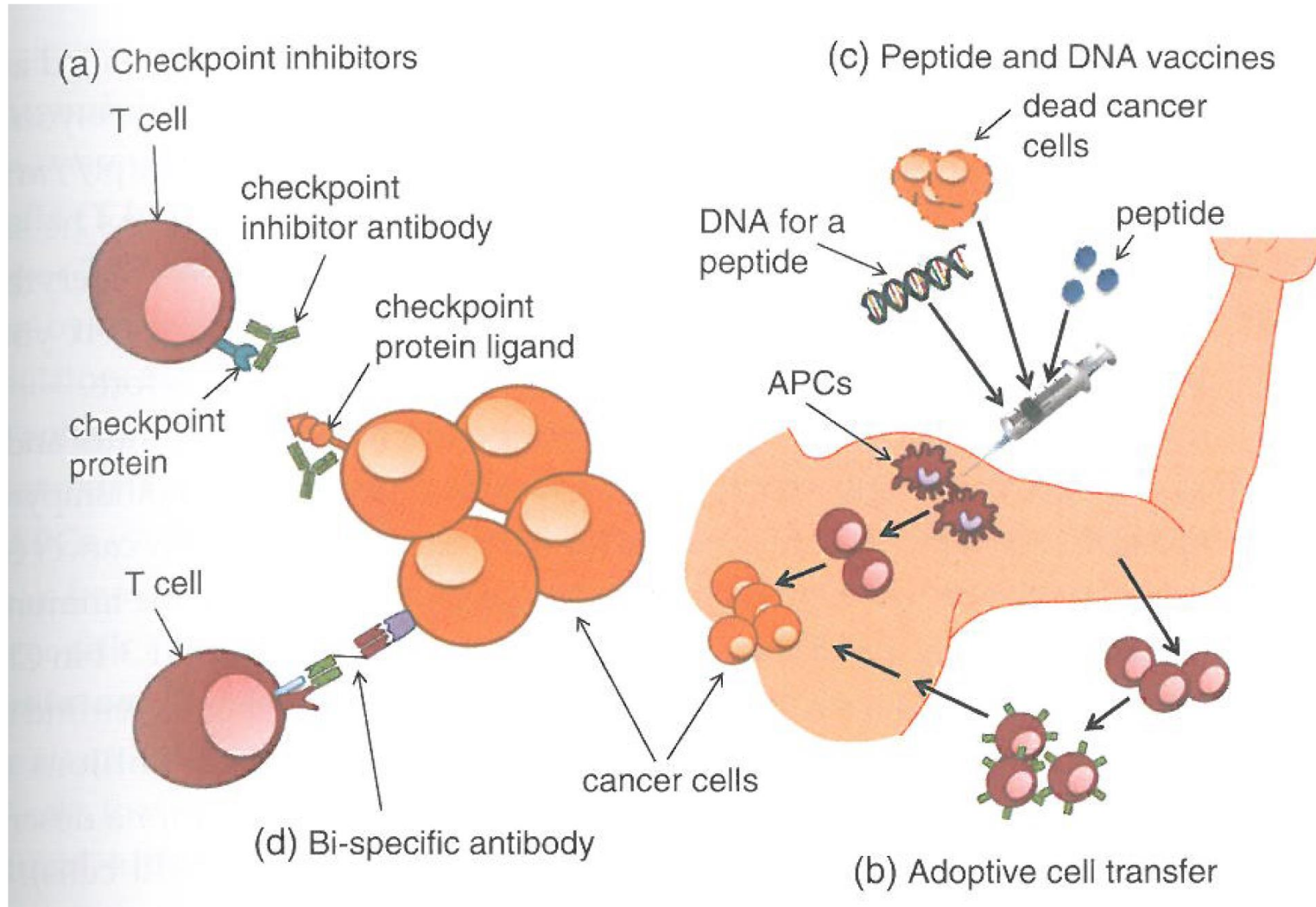


Inactivated
cytotoxic T cell



Tumor cell

Mechanism of action of immunotherapy



Check point inhibitors

Cell therapy

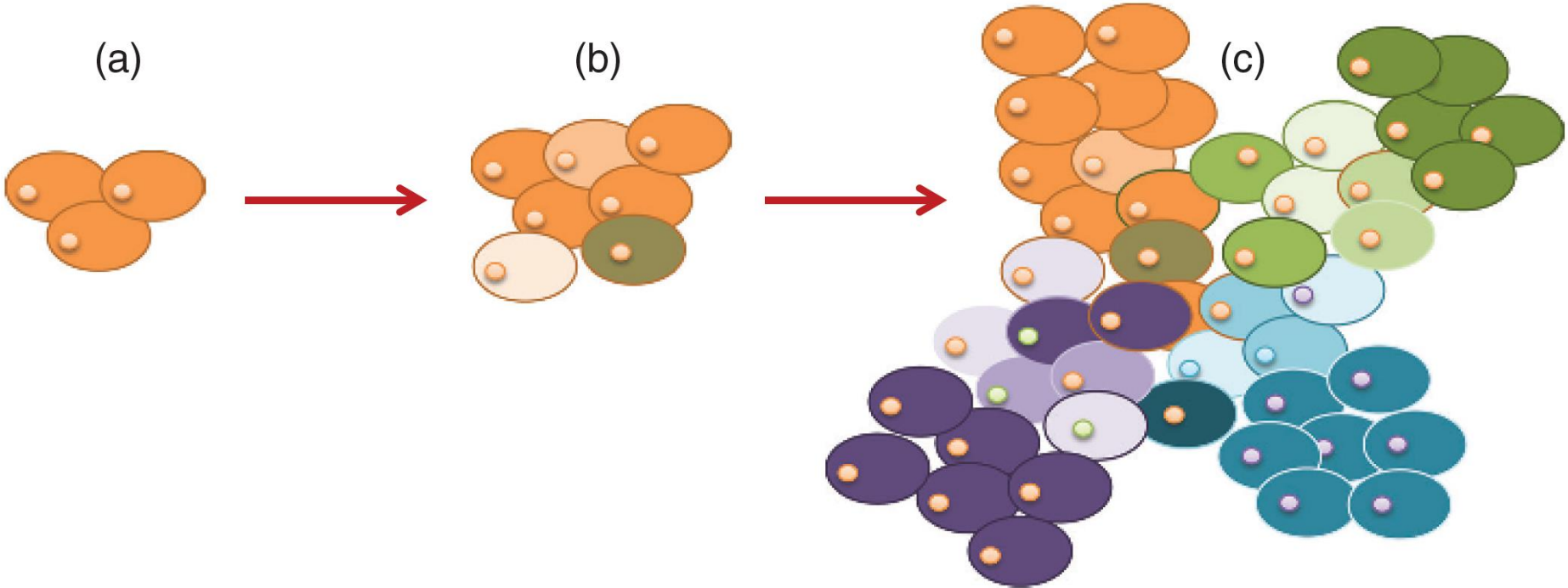
Vaccines

Bi-specific Ab

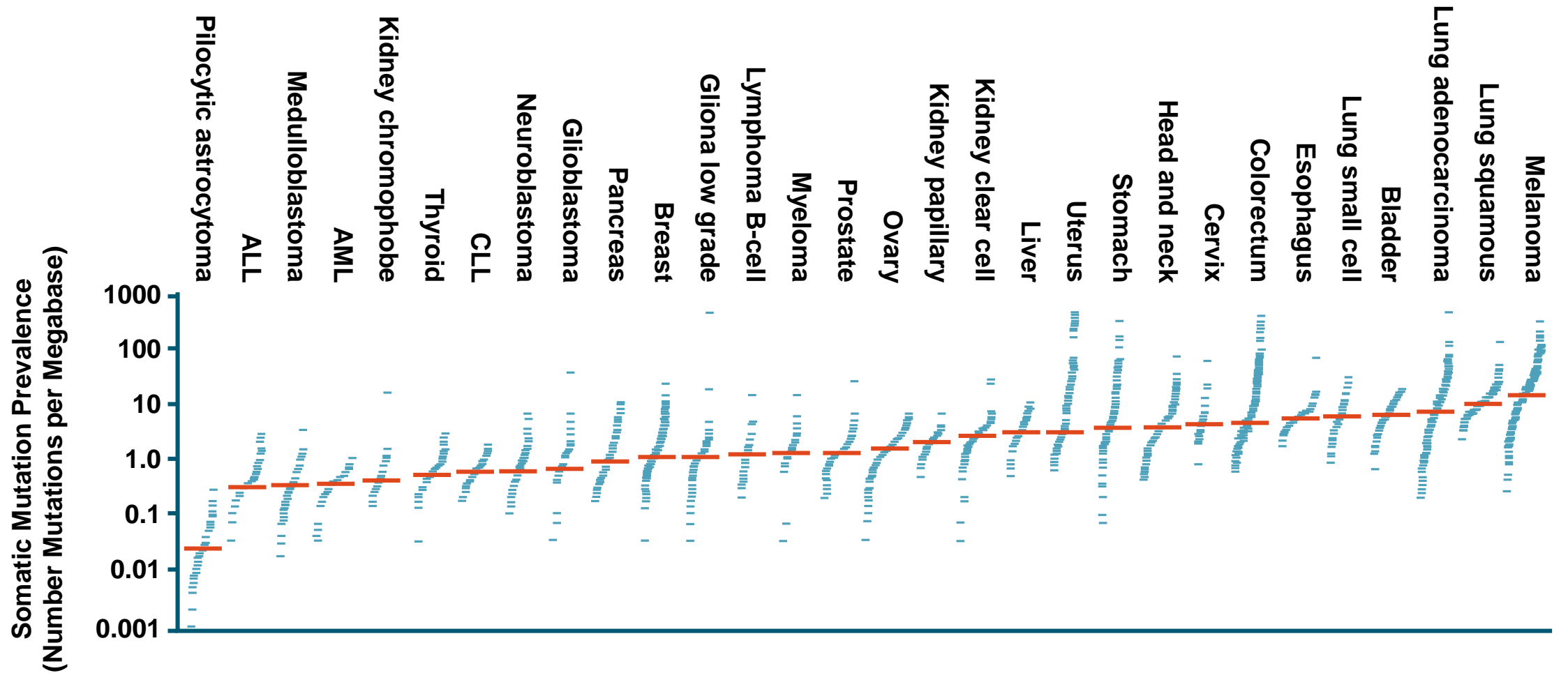
Not everyone benefits from immunotherapy



Not everyone benefits from immunotherapy

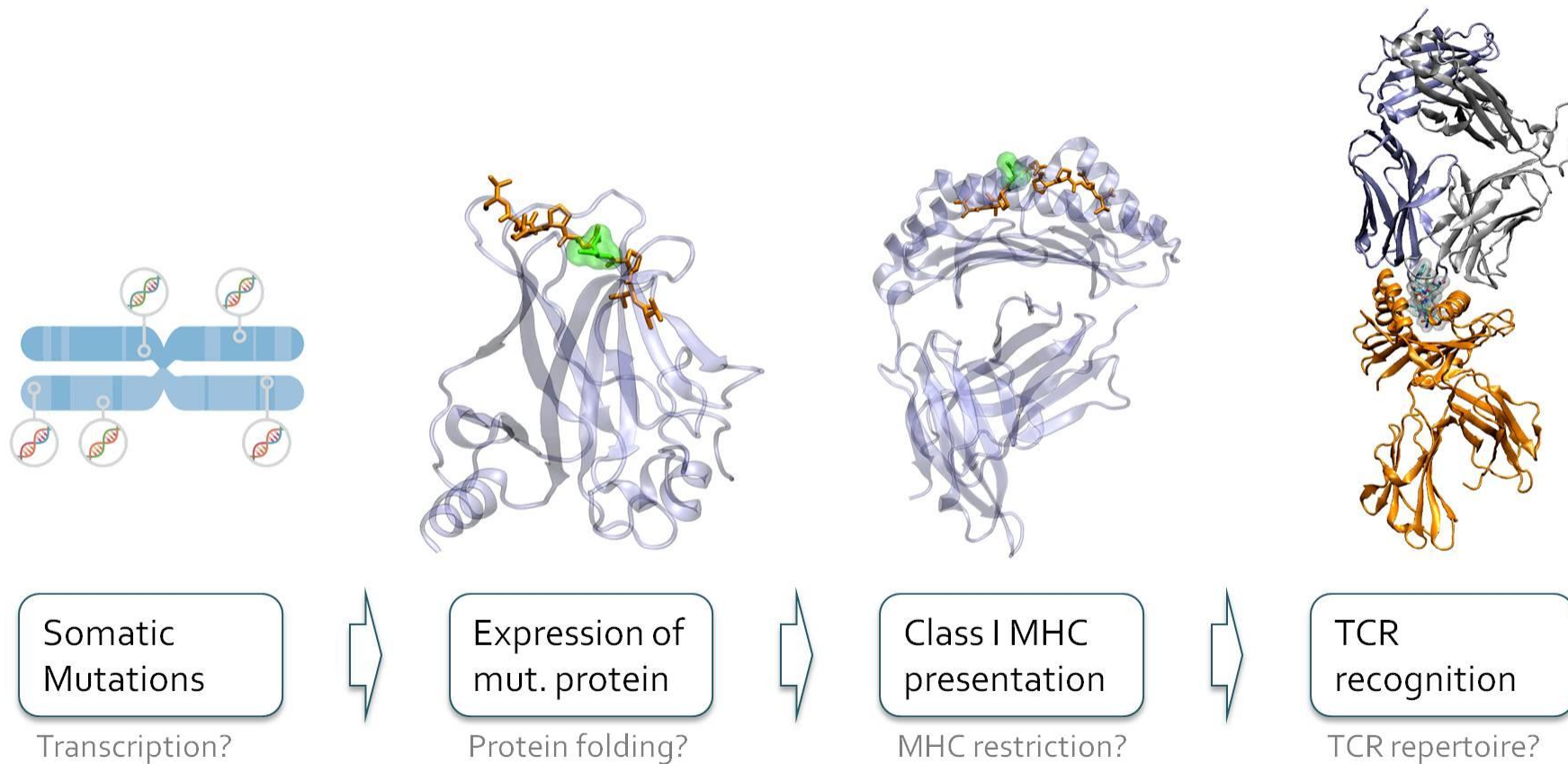


Tumor Mutational Burden in Various Tumor Types

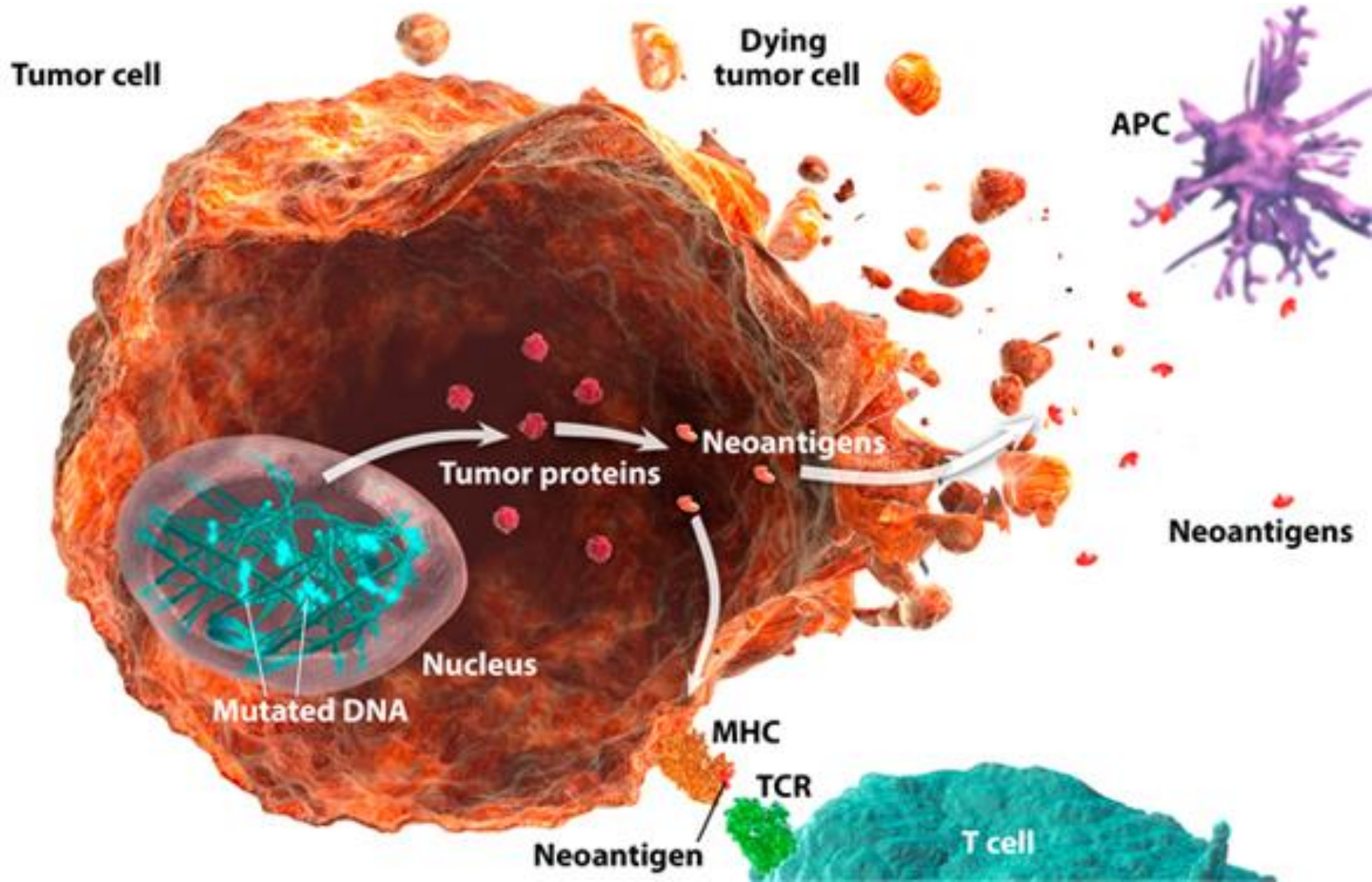




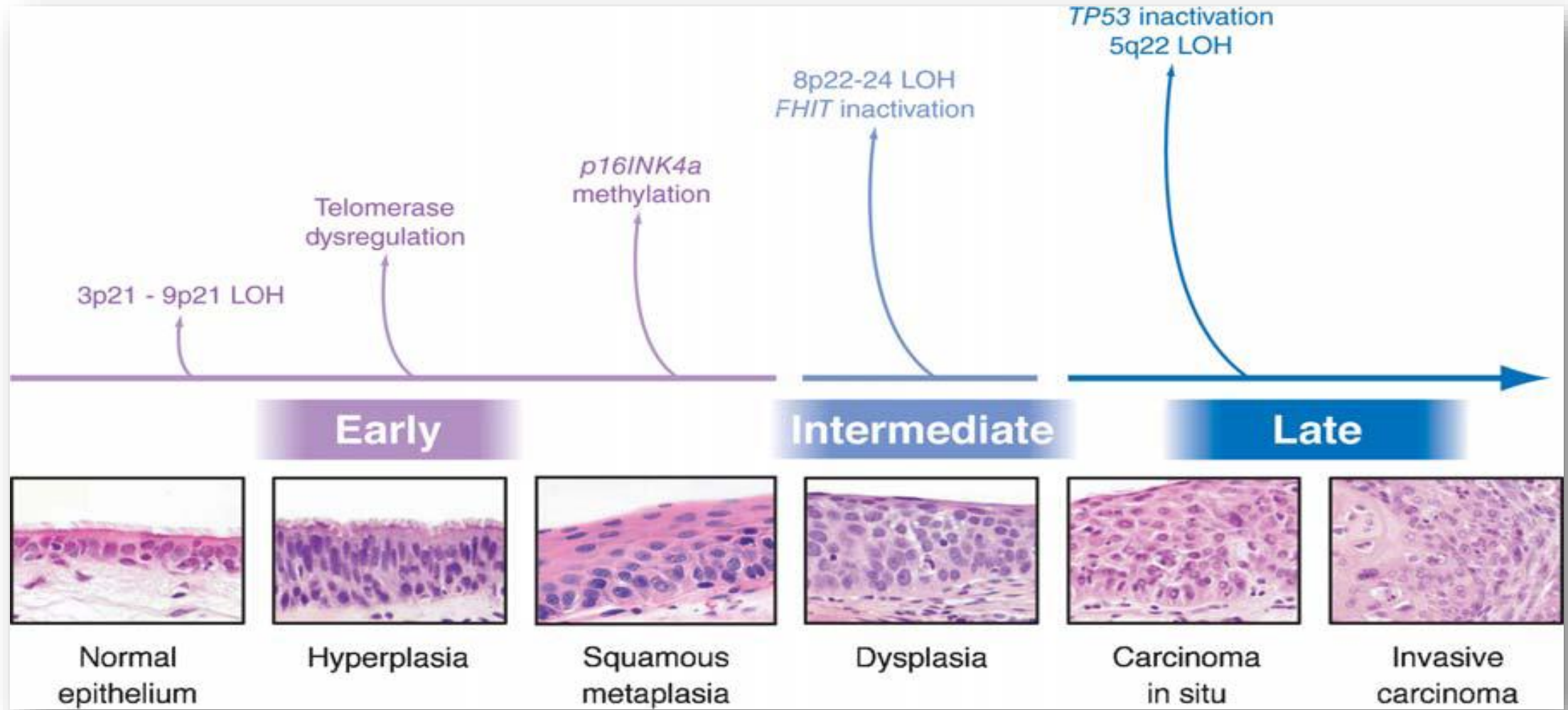
Only a minority of mutations produce neoantigens



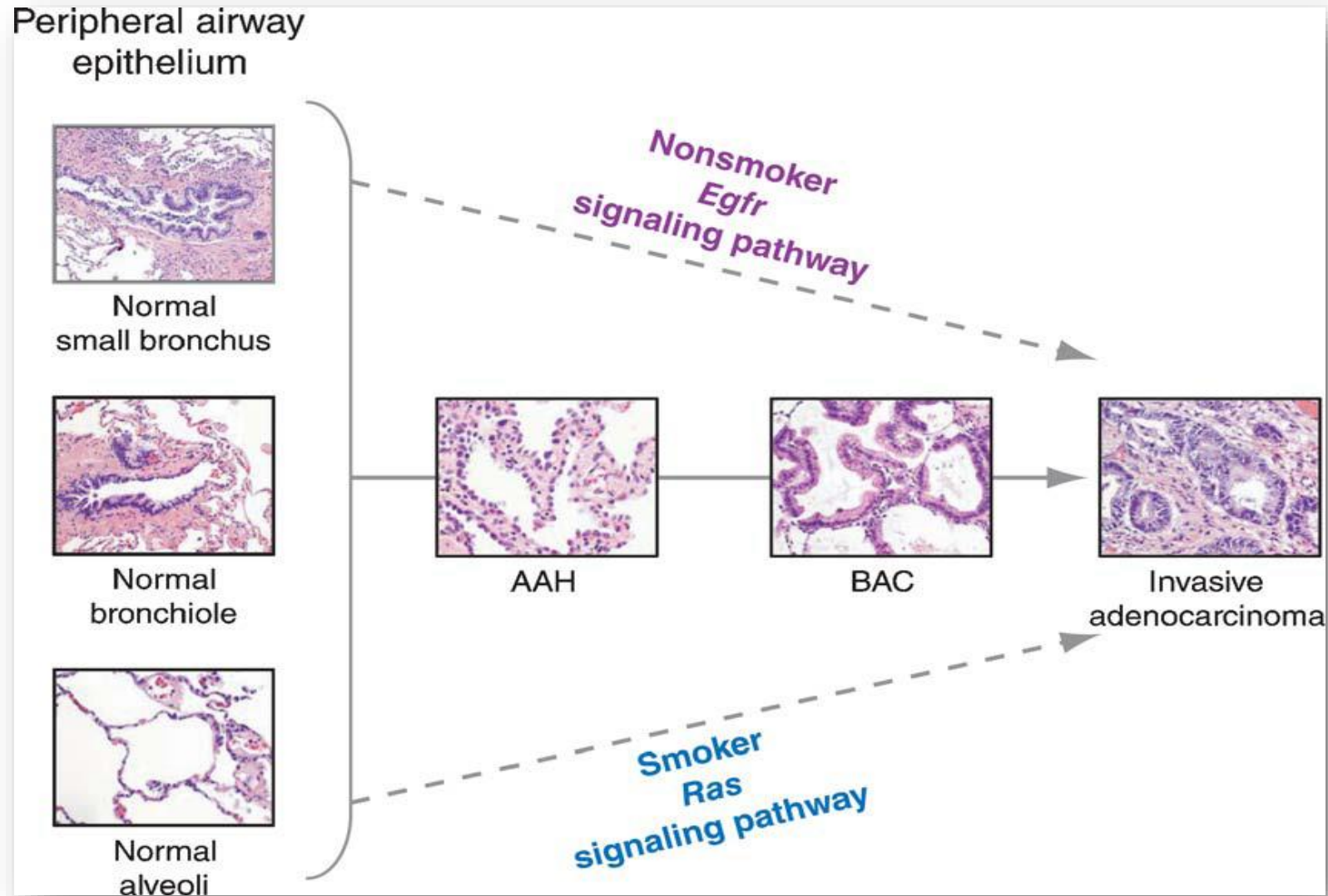
Adapted from Michielin, ELCC 2018



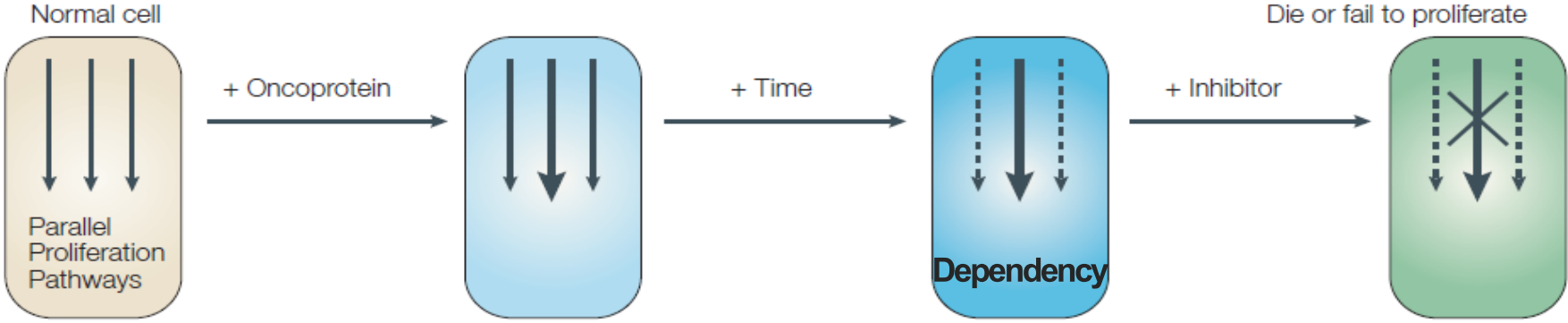
Histology of squamous dysplasia in SqCC



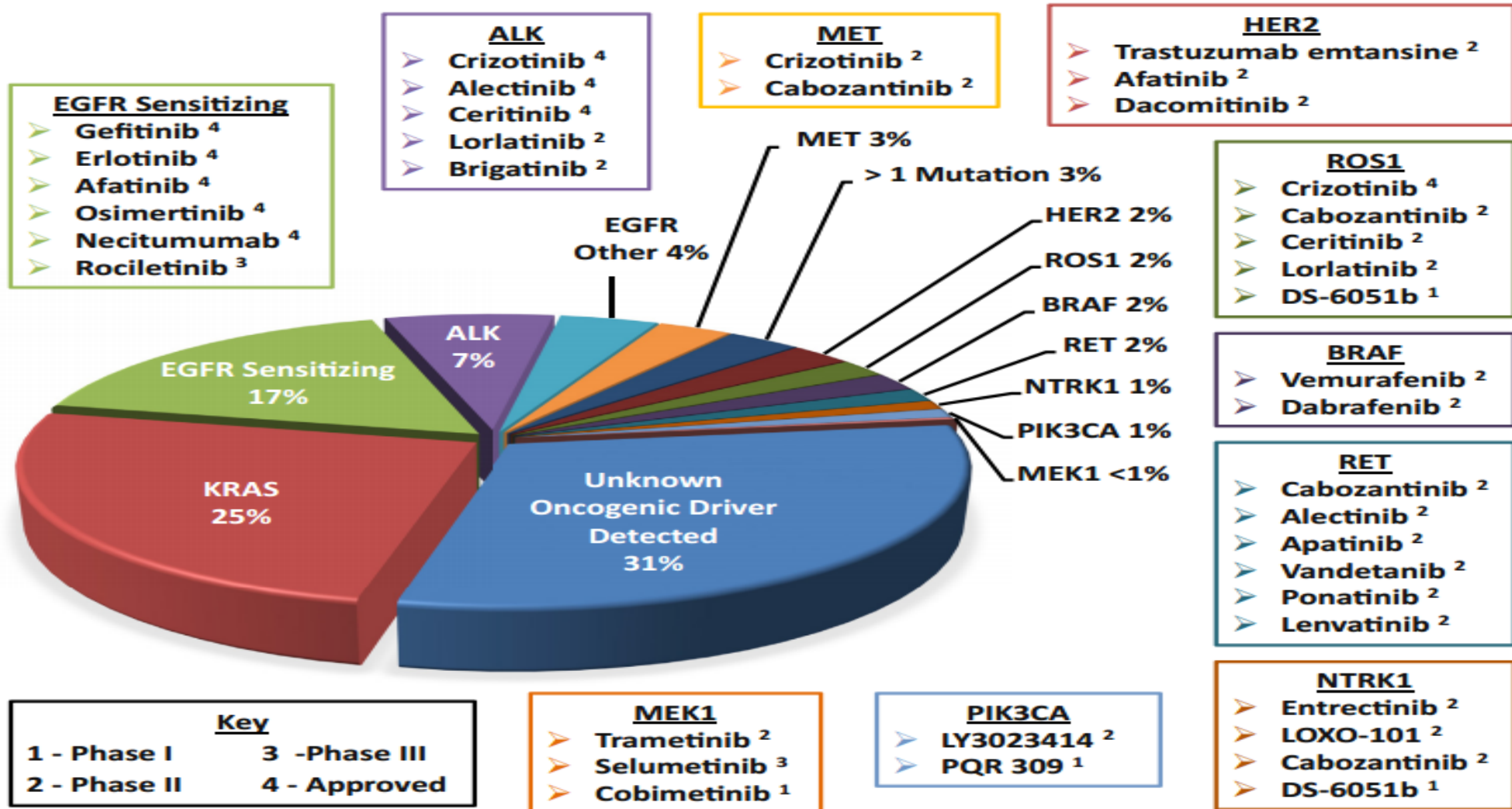
Adenocarcinoma precursor lesions

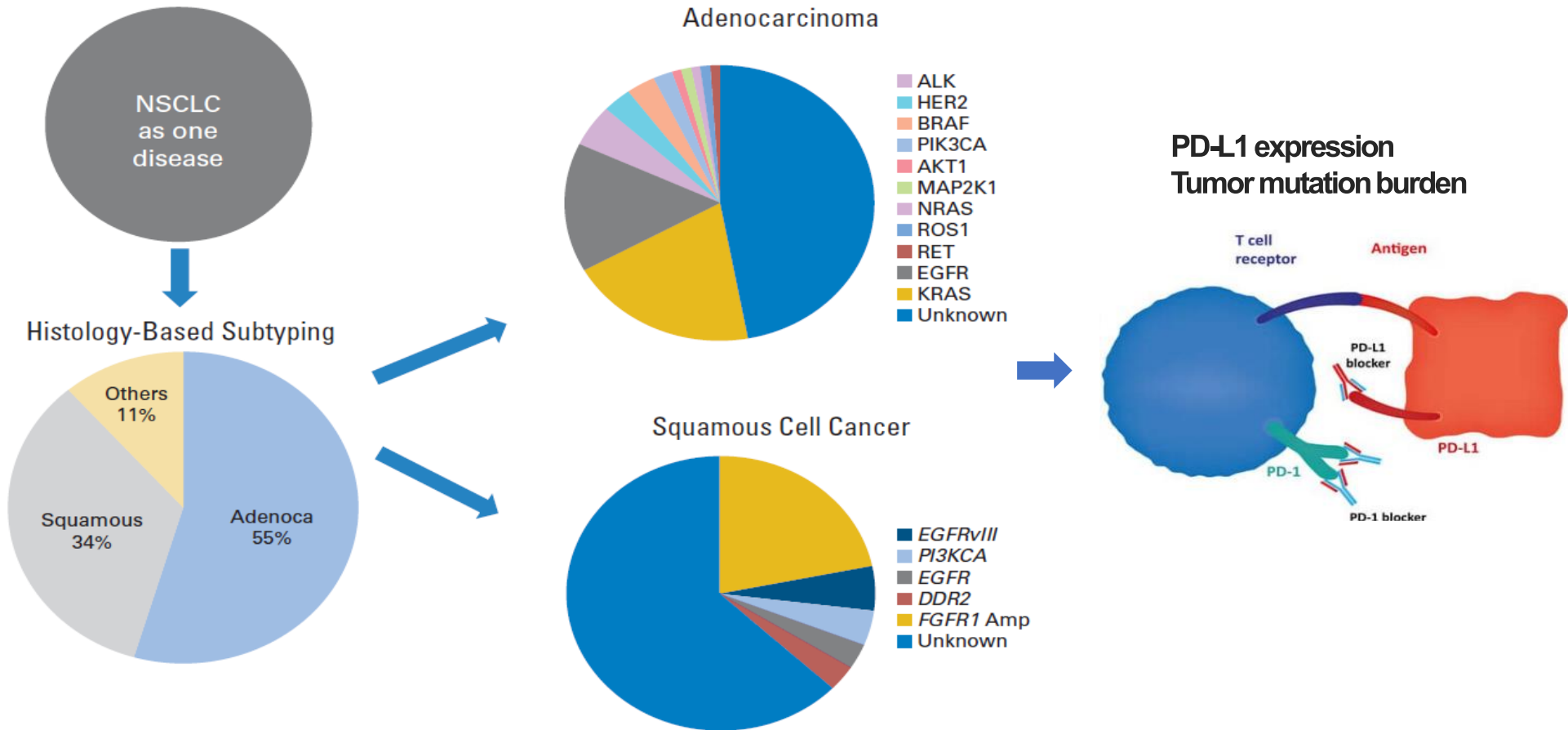


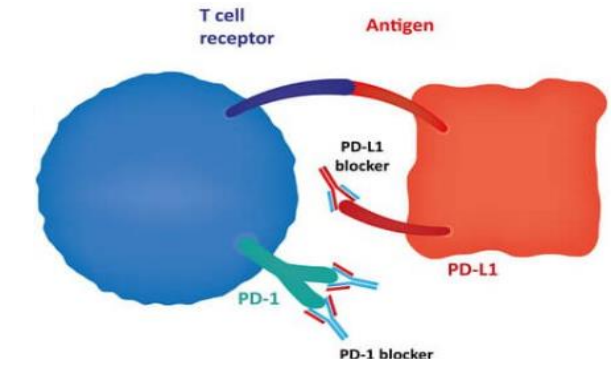
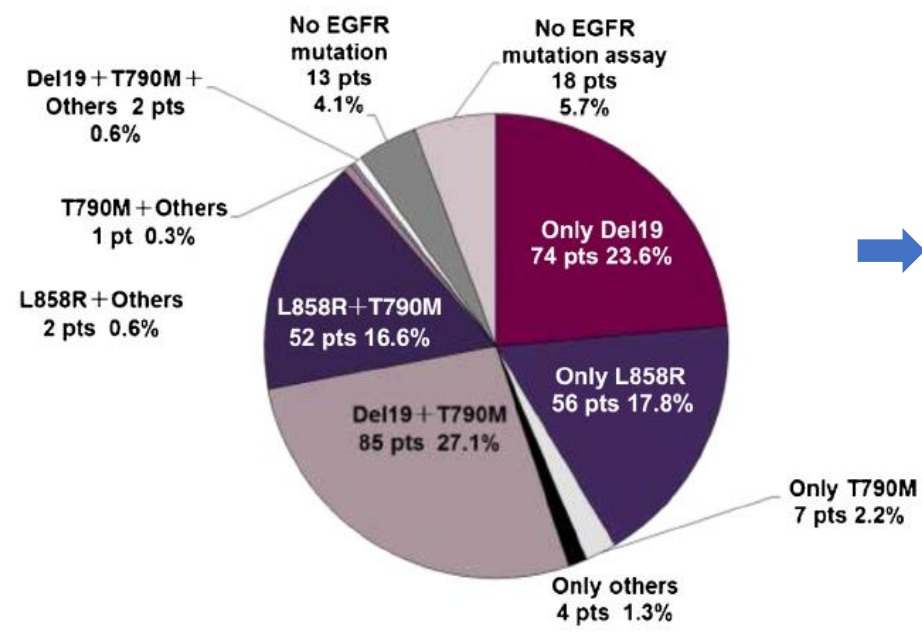
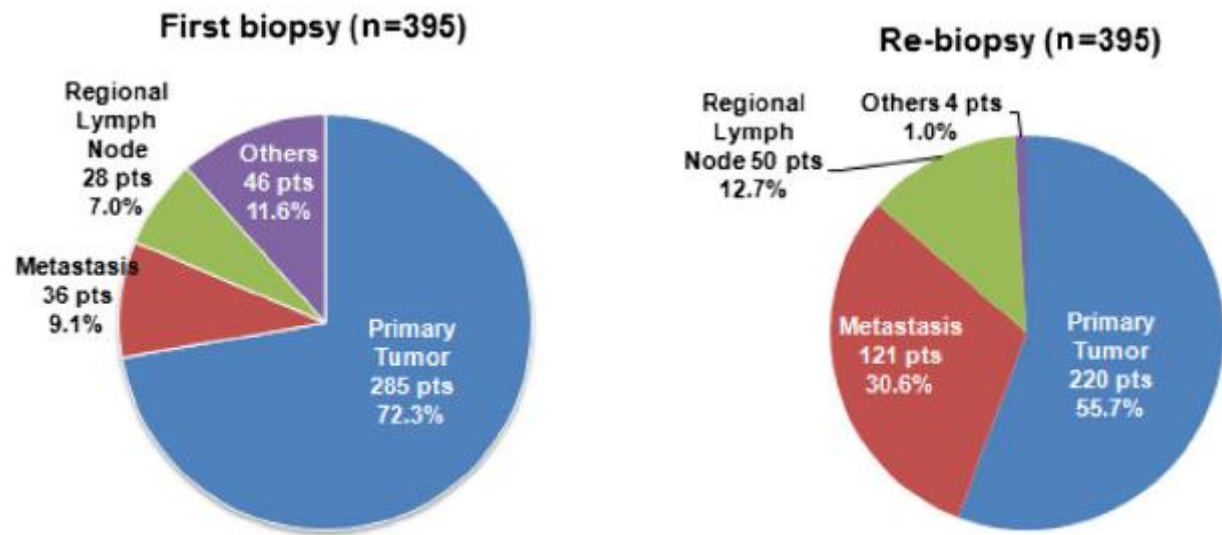
Oncogene addiction



What about targeted therapy?



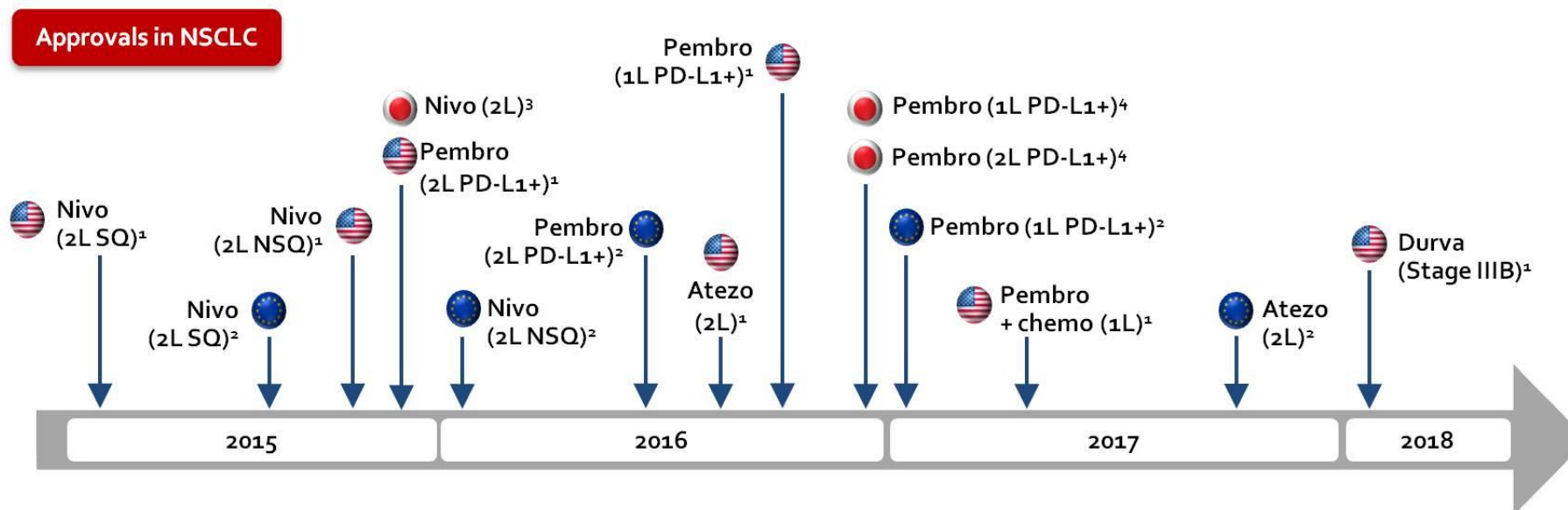






Checkpoint inhibitors in NSCLC

Key milestones

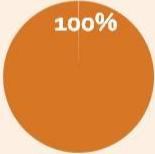







Many ongoing trials in early stage NSCLC

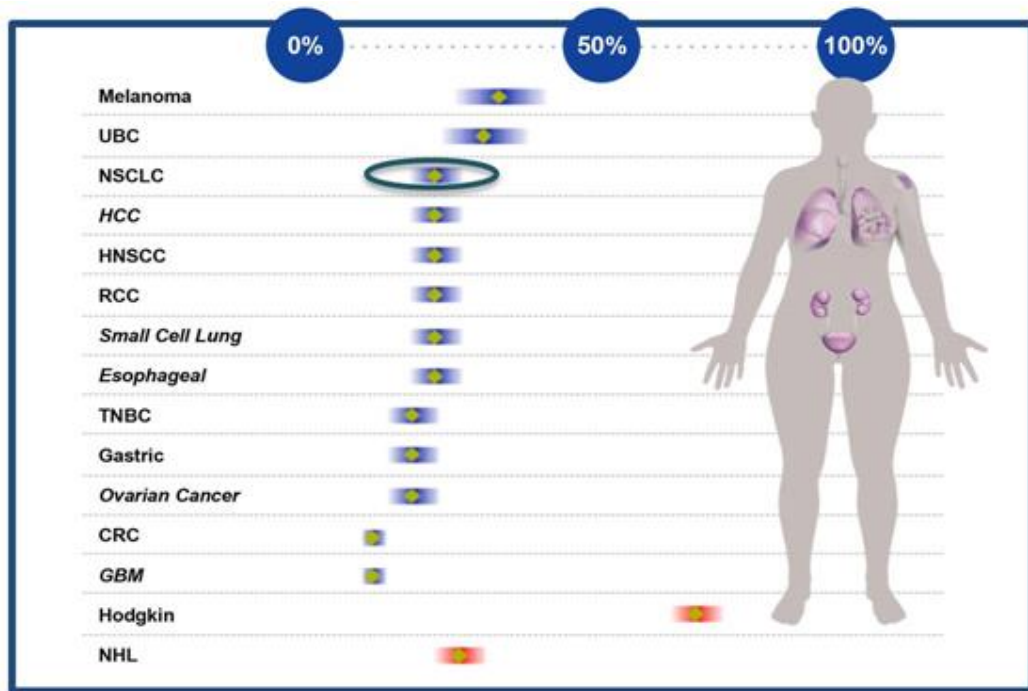
1. U.S. Food and Drug Administration. 2. European Medicines Agency. 3. ONO Pharmaceutical Co., Ltd. 4. Merck [press release]. December 19, 2016.



PD-L1 and evidence-based thresholds to use

Immunotherapy (IO)	Nivolumab	Pembrolizumab	Durvalumab	Avelumab	Atezolizumab
Detection antibody	28-8	22C3	SP263	73-10	SP142
IHC platform	Dako	Dako	Ventana	Dako	Ventana
Cell types scored for NSCLC	TC	TC	TC	TC	TC & IC
Cut-off definitions for positivity (complementary vs companion)	>5%	First line: PD-L1+ ≥50% Late lines: PD-L1+ ≥1%	>25%	None	None
Estimated PD-L1 biomarker positivity in 2 nd line at registration level					
Estimated PD-L1 biomarker positivity in 1 st line at registration level					

Who can receive Immune Check Point Inhibitor?



건강보험심사평가원
HEALTH INSURANCE REVIEW & ASSESSMENT SERVICE

로그인 | 회원가입 | 글자 + - | ENG

병원·약국 | 진료비 | **의료정보** | 제도·정책 | 국민참여 | 정보공개 | 알림 | 기관소개 | 전체메뉴

암질환사용약제및요법

홈 > 의료정보 > 의약품정보 > 암질환사용약제및요법 > 항암화학요법

공고 | 공고예고 | **항암화학요법** | FAQ

- 건강보험심사평가원에서는 암질환심의위원회를 거쳐 보험급여가 되는 항암화학요법에 대한 유익한 정보를 제공하고 있습니다.
- 건강보험심사평가원장이 공고한 항암화학요법 등이 참고한 외국 가이드라인을 보시려면 해당 가이드라인을 선택 하세요.
- 항암화학요법 관련정보 [항암화학요법 등 공고내용 전문](#) | [허가초과 항암요법](#) | [급여인정되지 아니한 요법](#) | [안내문](#)
- 외국 암관련정보 사이트 [NCCN](#) | [ESMO](#) | [ASCO](#)

암별분류: [호흡기,두경부,연조직육종](#) | [소분류 - 전체](#) | [전체보기](#)

추가분류: [전체](#)

Q 검색

OPDIVO[®]
(nivolumab)
INJECTION FOR INTRAVENOUS USE 10 mg/mL

2nd line PD-L1 10%

KEYTRUDA[®]
(pembrolizumab) for Injection 50 mg

2nd line PD-L1 50%

TECENTRIQ[®]
atezolizumab INJECTION FOR
INTRAVENOUS USE 1200 mg

2nd line TC2/3 or IC2/3

IMFINZI[™]
durvalumab
Injection for Intravenous Use 50 mg/mL



건강보험심사평가원
HEALTH INSURANCE REVIEW & ASSESSMENT SERVICE

OPDIVO[®]
(nivolumab)

INJECTION FOR INTRAVENOUS USE 10 mg/mL

KEYTRUDA[®]
(pembrolizumab) for Injection 50 mg

TECENTRIQ[®]
atezolizumab INJECTION FOR
INTRAVENOUS USE 1200 mg

IMFINZI[™]
durvalumab
Injection for Intravenous Use 50 mg/mL



2nd line

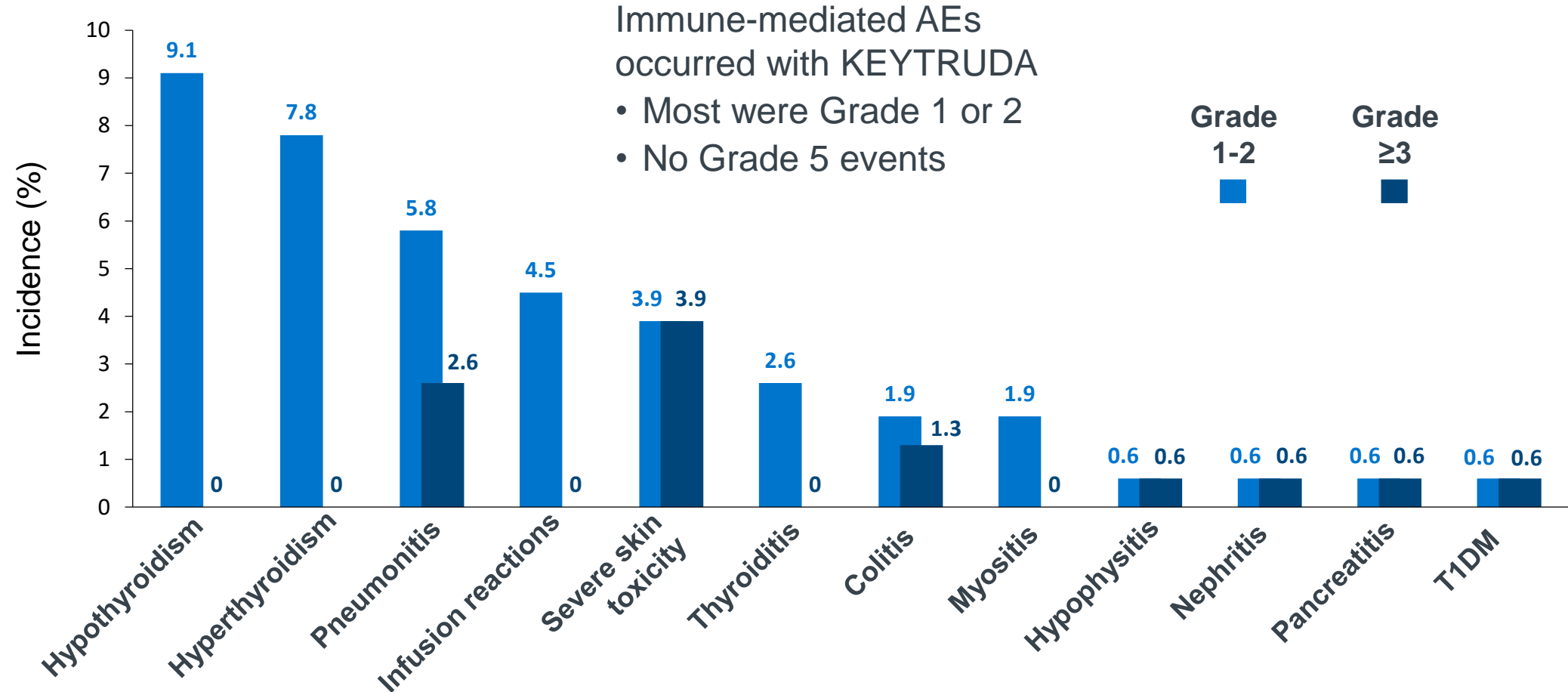
**1st line PD-L1 1% or with
Pemetrexed + Platinum**

식약처

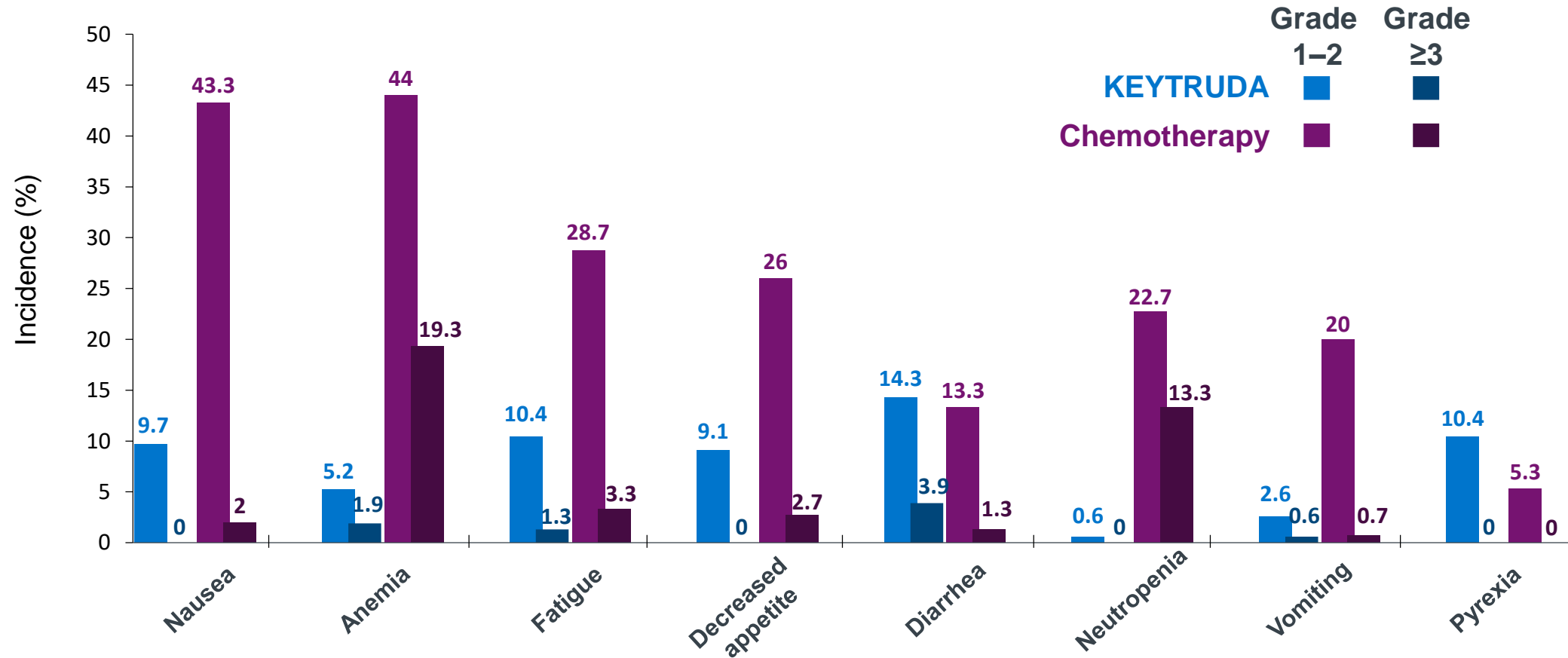
**2nd line or
1st line with
Avastin + Paclitaxel + Platinum**

***Unresectable Stage III**

What are the side effects of immunotherapy?



What are the side effects of immunotherapy?



Male - 72 years old

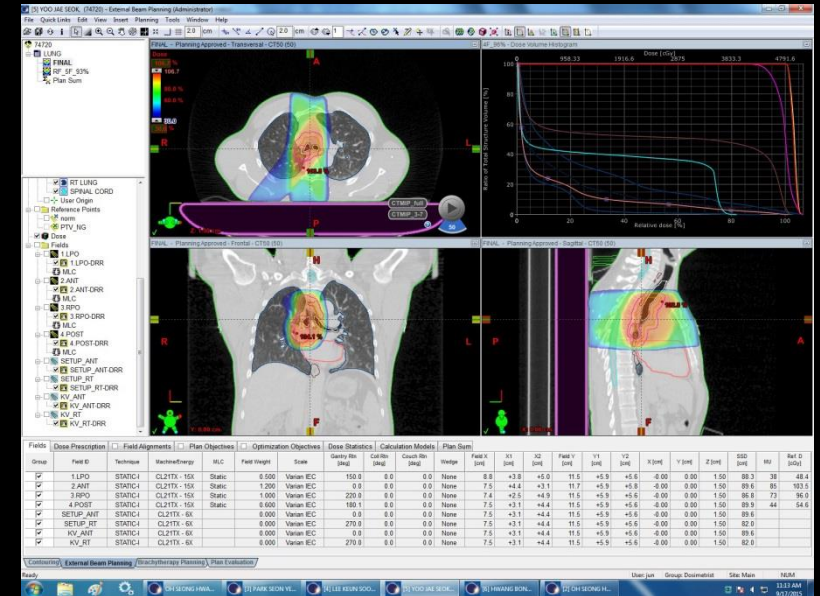
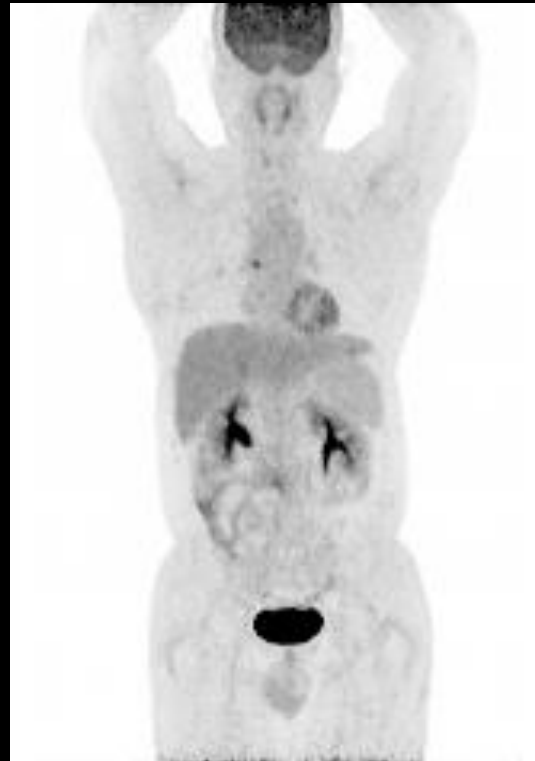
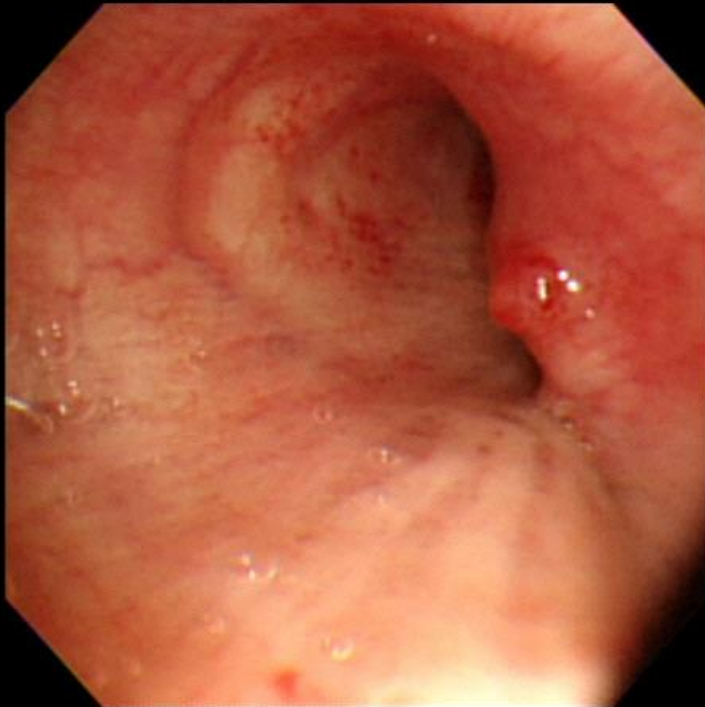
- 2013.10.02 RULobectomy Squamous cell carcinoma T2N1M0 PD-L1 30%
- 2015.8.19 Stump site recurrence

Y
J S
Sex: Age:
D.O.Birth:

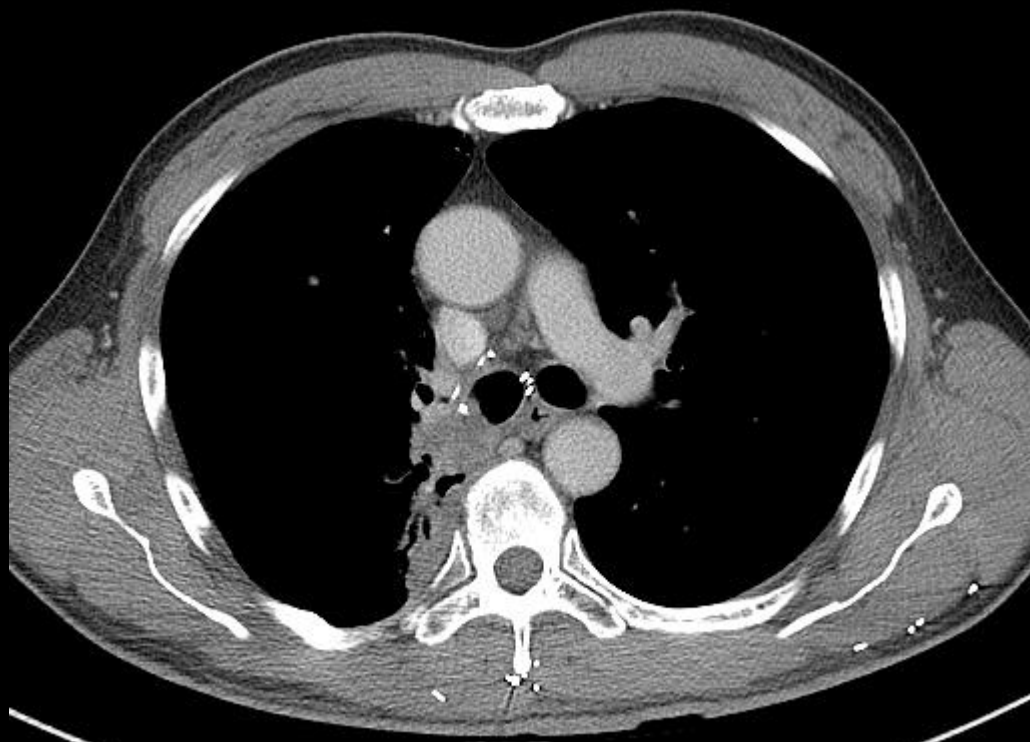
08/10/2015
10:08:11

Cr: N Et: A1
Ce: O

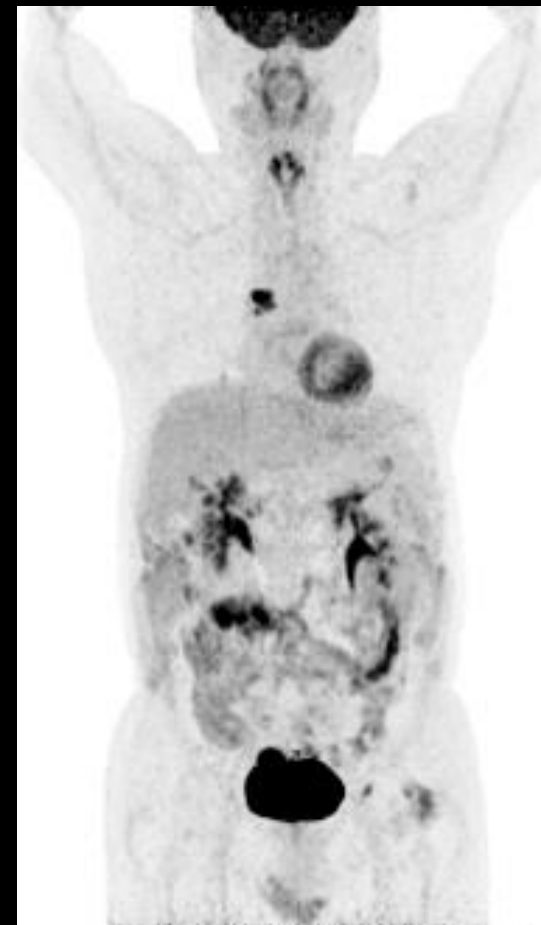
Physician:
Comment:



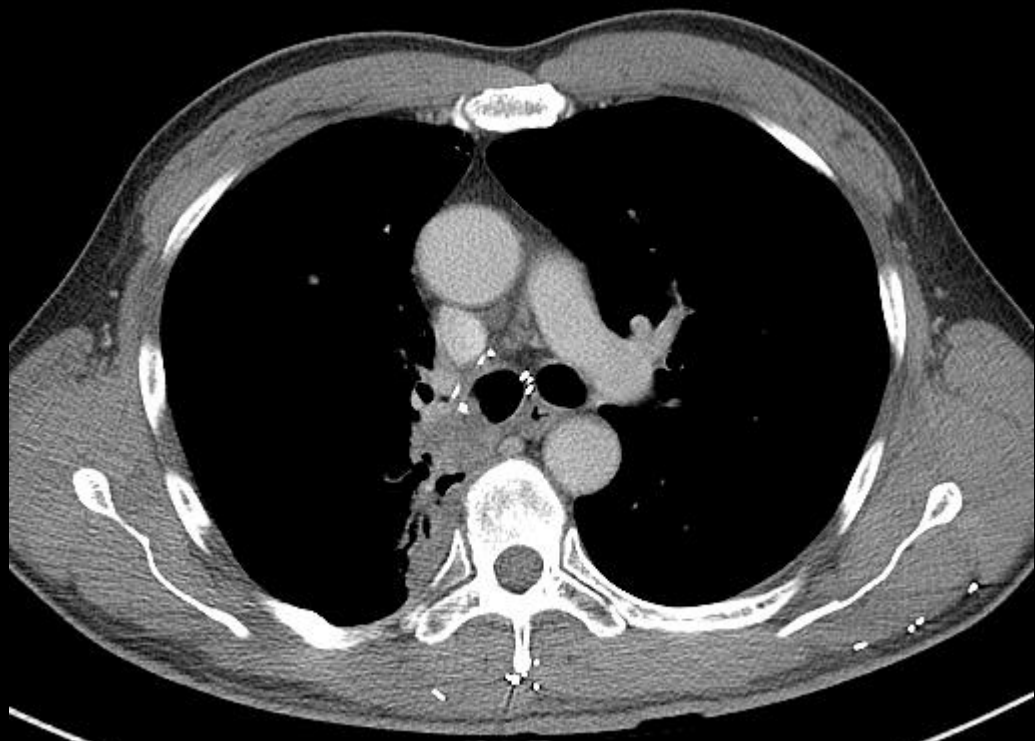
Male - 72 years old 2 years later



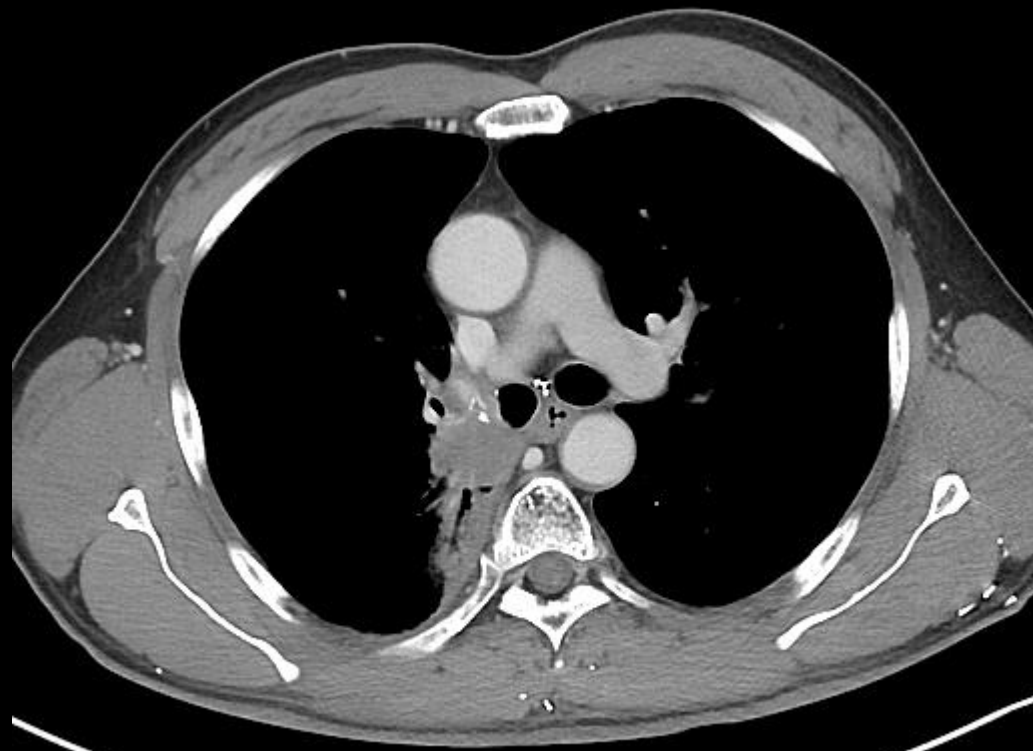
2017.11.23



다음 치료는?

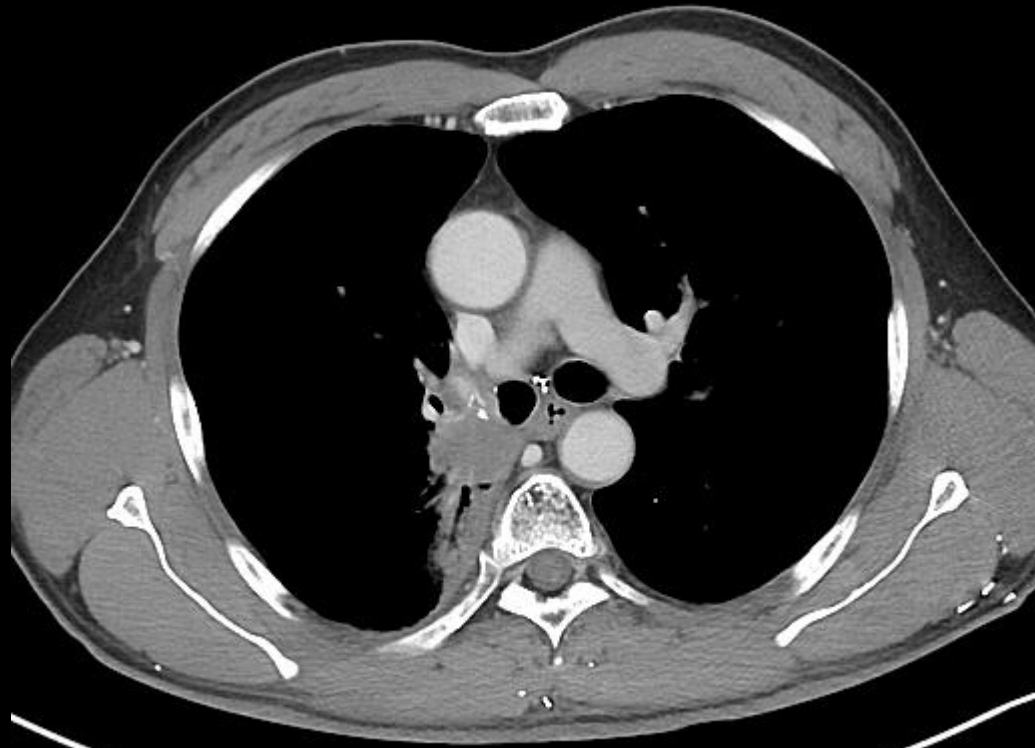


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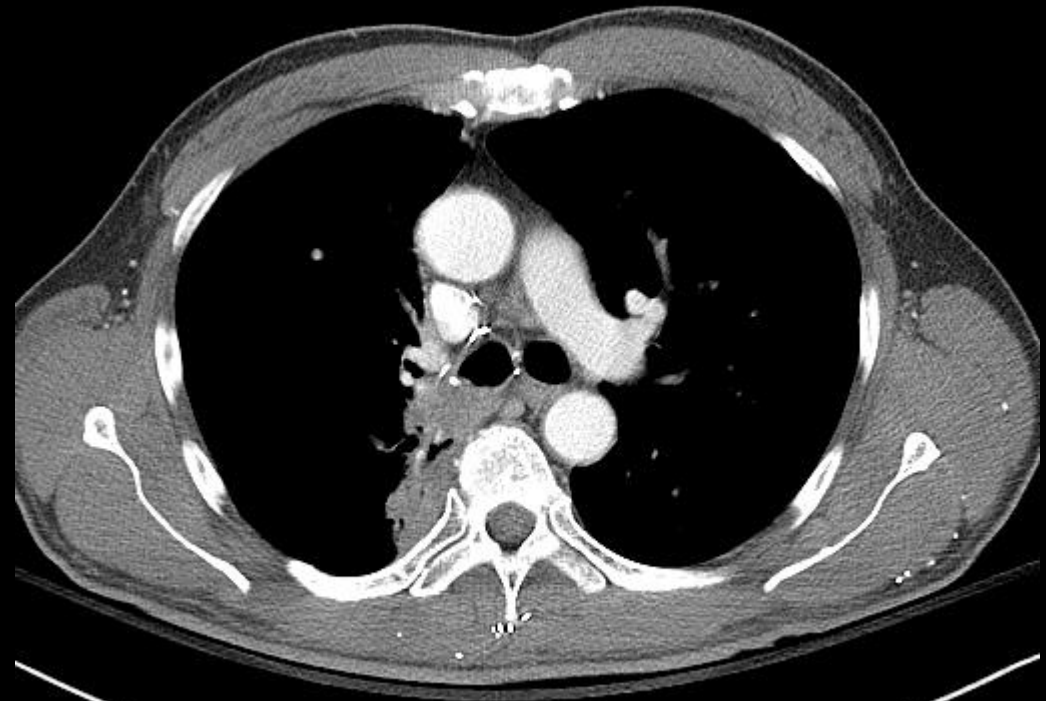


2018.02.14

Pembrolizumab Treatment

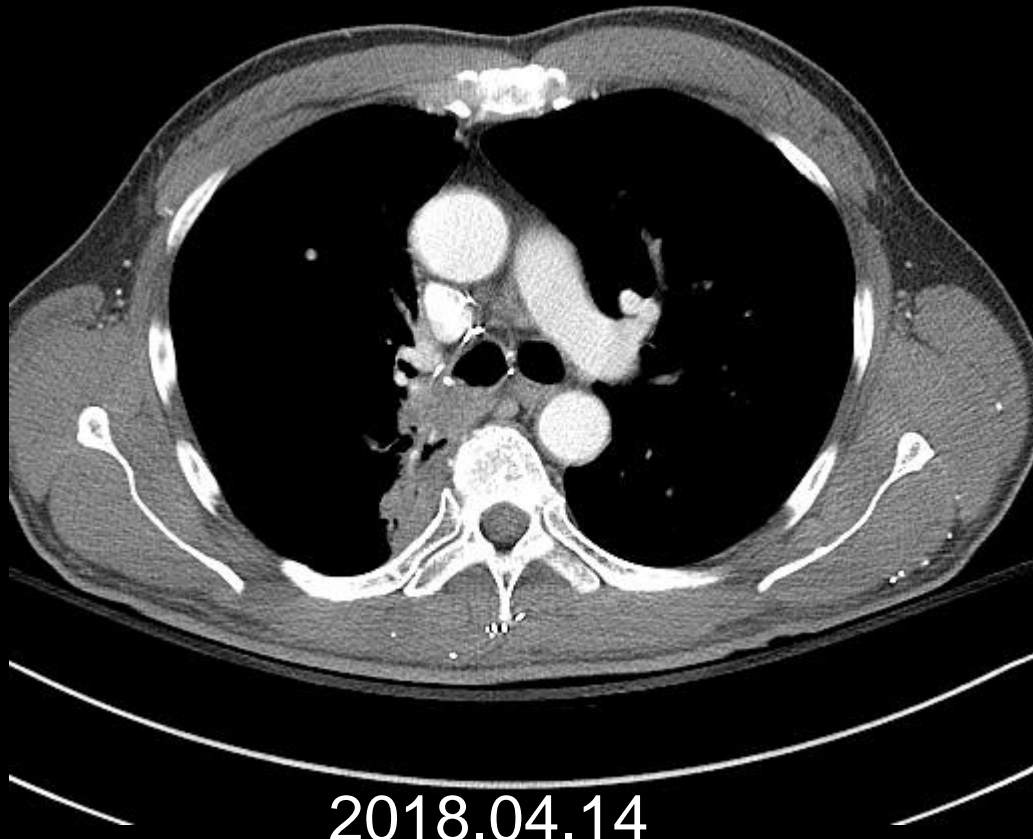


2018.2.14



2018.04.14

Pemblizumab Treatment



46235989
YJS

M 60

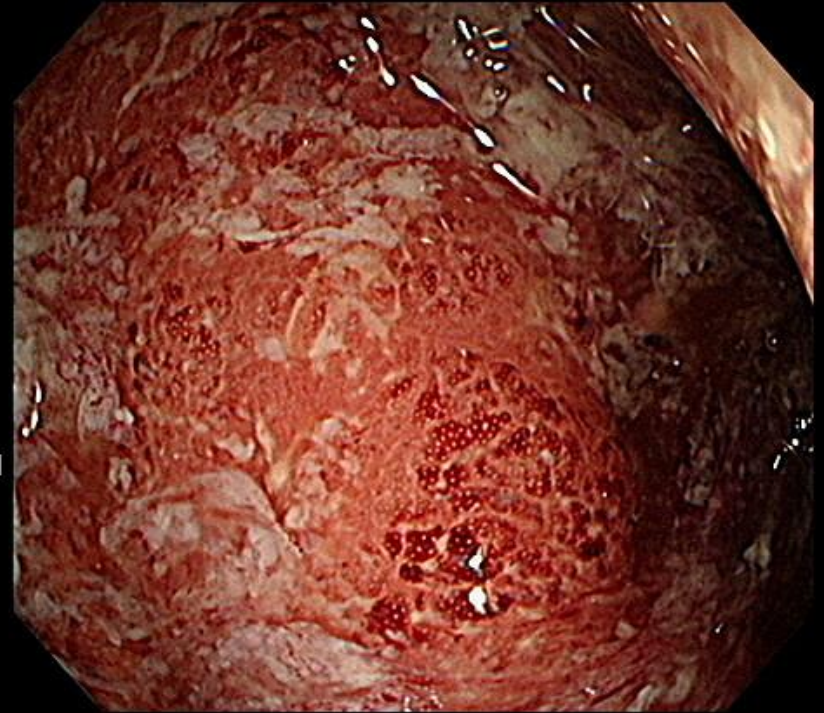
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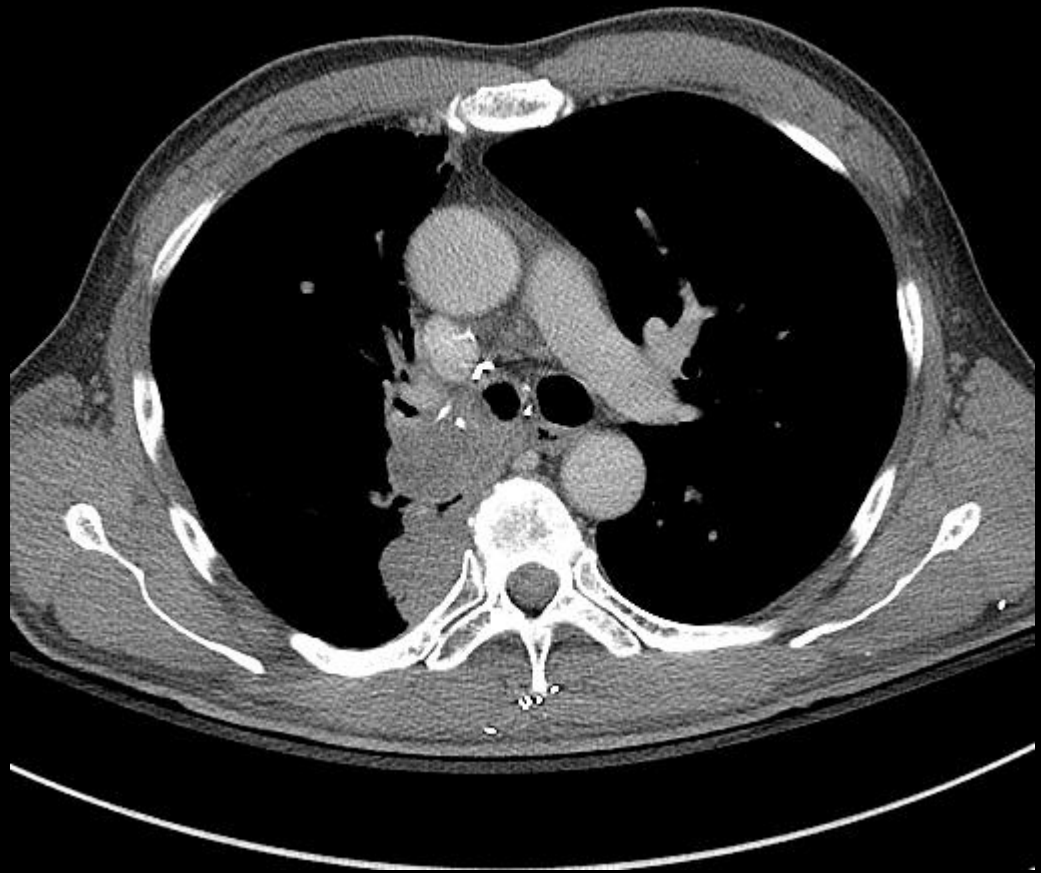
00:01:44



0/1
Eh:A7 Ce:0

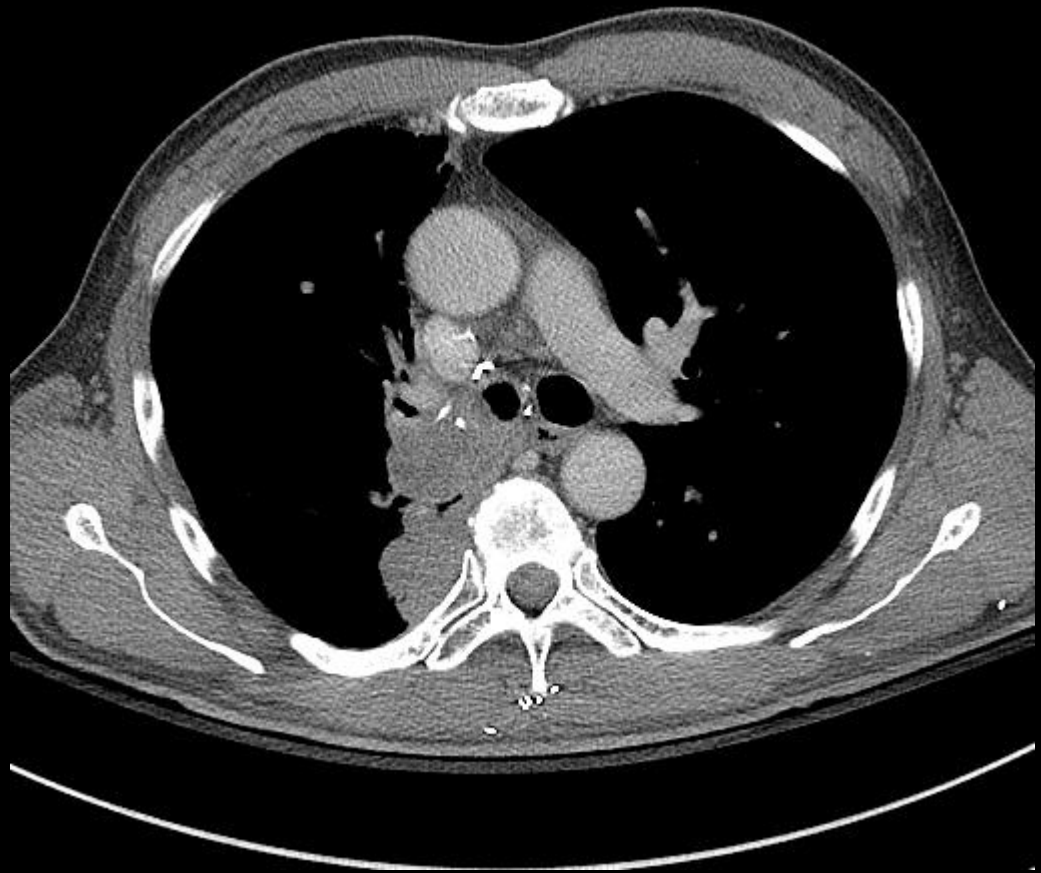
HMS|



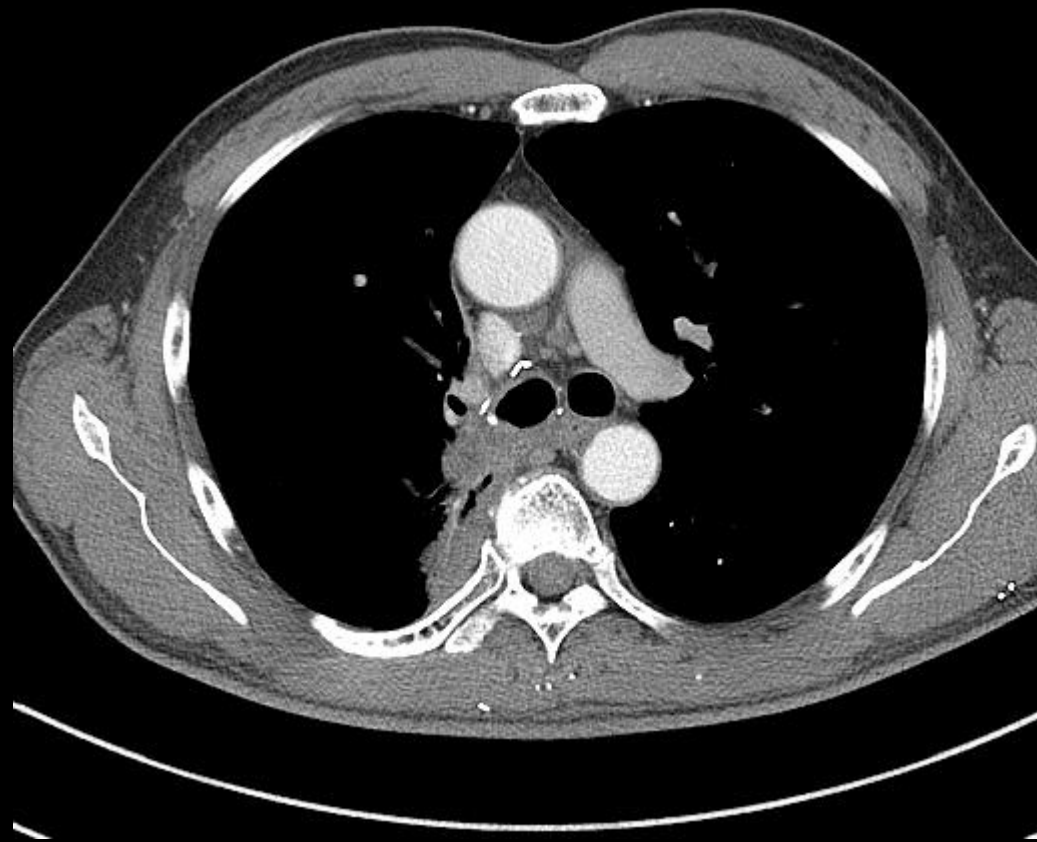


2017.7.12

■ 검사결과										<input type="checkbox"/> M	<input type="checkbox"/> S	<input checked="" type="checkbox"/> T	Action ▾
<input type="checkbox"/>	응답	특수	처방코드	처방명	검사결과값	비	하한	상한	단위				
H20 일반혈액검사 2018-07-12 14:01:29													
<input type="checkbox"/>	Y		AC0089	WBC (Qn)[C...	1.6	▼	4	10	x10 ⁹ /uL				
<input type="checkbox"/>	Y		AC0090	RBC (Qn)[Ch...	3.48	▼	4.2	6.3	x10 ¹² ...				
<input type="checkbox"/>	Y		AC0091	Hb (Qn)[Che...	10.8	▼	13	17	g/dl				
<input type="checkbox"/>	Y		AC0092	Hct (Qn)[Ch...	32.1	▼	39	52	%				
<input type="checkbox"/>	Y		AC0157	MCV (Qn)[C...	92.2		80	100	fl				
<input type="checkbox"/>	Y		AC0158	MCH (Qn)[C...	31.0		27	33	pg				
<input type="checkbox"/>	Y		AC0159	MCHC (Qn)[...	33.6		32	36	%				
<input type="checkbox"/>	Y		AC0123	RDW (Qn)[C...	14.2		11.5	14.5	%				
<input type="checkbox"/>	Y		AC0093	Platelet (Qn)...	230		150	350	x10 ⁹ /uL				
<input type="checkbox"/>	Y		AC0160	MPV (Qn)[C...	9.1		9.1	12.1	fl				
<input type="checkbox"/>	Y		AC0124	PDW (Qn)[C...	9.1	▼	9.4	15.0	fl				
<input type="checkbox"/>	Y		AC0132	E-ALC (Qn)[...	810				/uL				
<input type="checkbox"/>	Y		AC0115	E-neutrophil ...	4.9	▼	50	75	%				
<input type="checkbox"/>	Y		AC0116	E-lymphocyt...	50.0	▲	20	44	%				
<input type="checkbox"/>	Y		AC0117	E-monocyte ...	42.6	▲	2	9	%				
<input type="checkbox"/>	Y		AC0118	E-eosinophil ...	1.9		1	7	%				
<input type="checkbox"/>	Y		AC0119	E-basophil (...	0.6		0	2	%				
<input type="checkbox"/>	Y		AC0156	IG % (Qn)[C...	0.6				%				
<input type="checkbox"/>	Y		AC0131	E-ANC (Qn)[...	70				/uL				



2017.7.12



2018.10.7



Questions that can be answered by cancer biomarkers

Prognostic

Is it likely to develop this cancer?

Diagnostic

What type of cancer is it?

Predictive

Is this the optimal drug for my cancer?

Pharmacodynamics

What's the optimal dose for my body?

Recurrence

Will the cancer return?

Cyfra 21-1
Non smoker

TTF-1

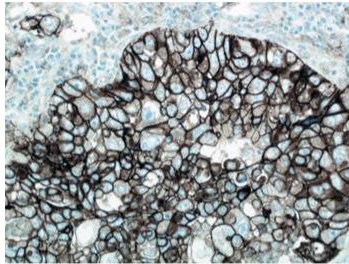
EGFR mutation

ALK FISH

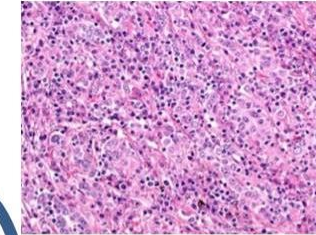
Biomarker



Biomarkers currently applied for NSCLC immunotherapy



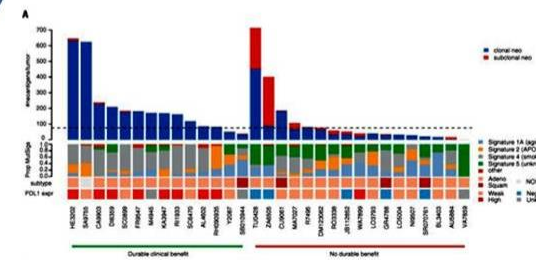
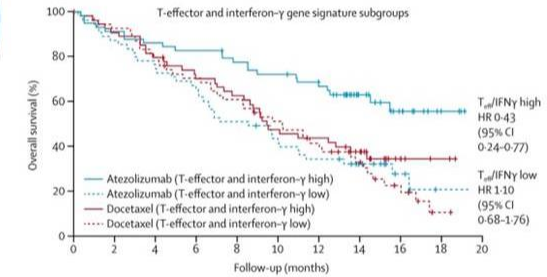
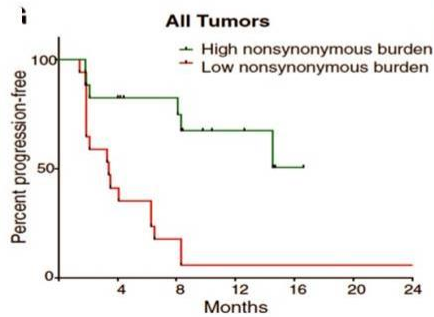
PD-L1 IHC



Surrogates of immune response
Immune cells
Gene signature

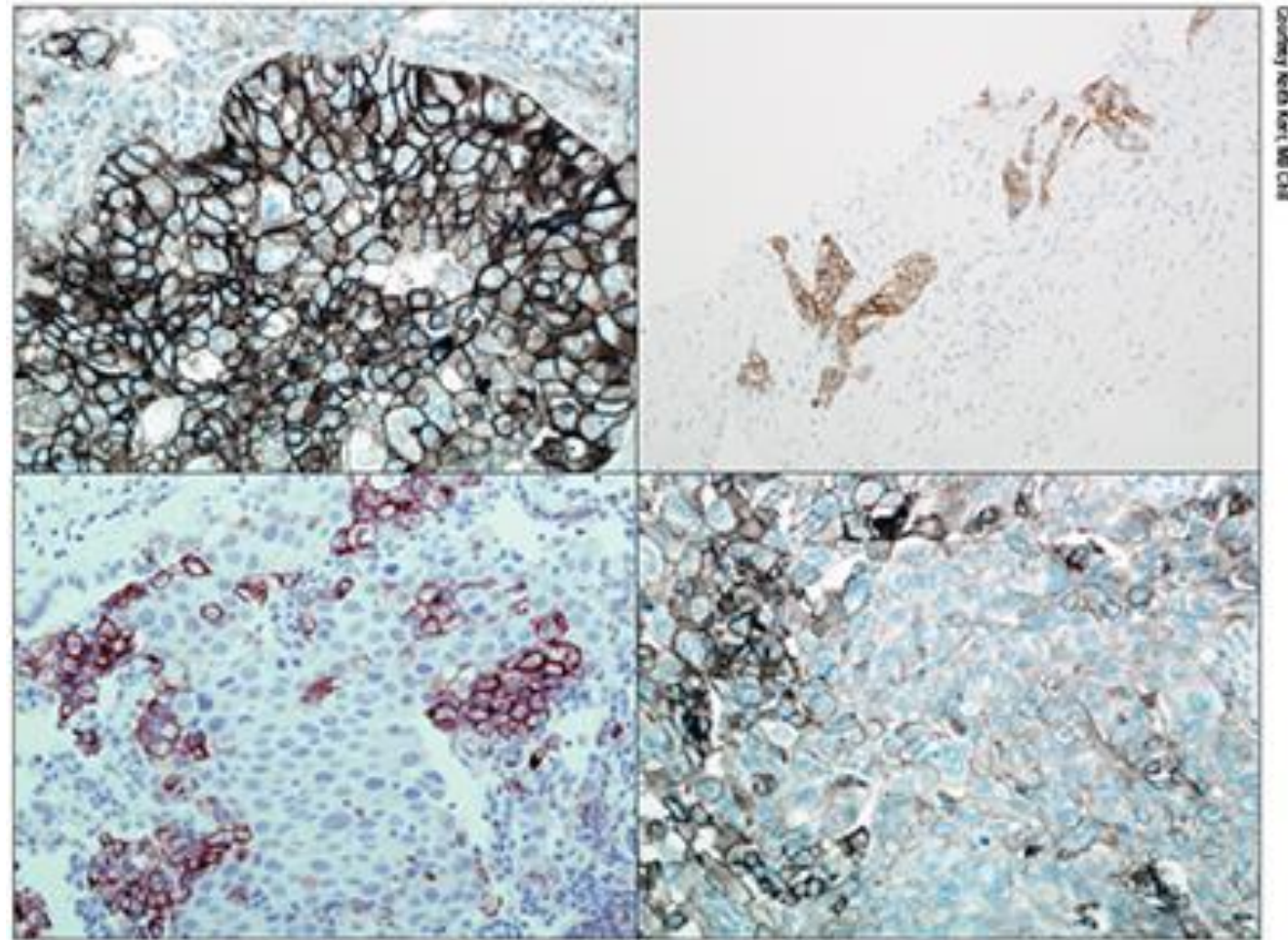
Mutational burden
or surrogate

Microsatellite
instability



Rizvi, Science 2015; Fehrenbacher, Lancet 2016; McGranahan, Science 2016; Kerr, ASCO 2016

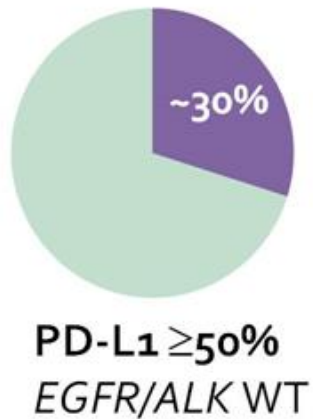
PD-L1: Interobserver Variability



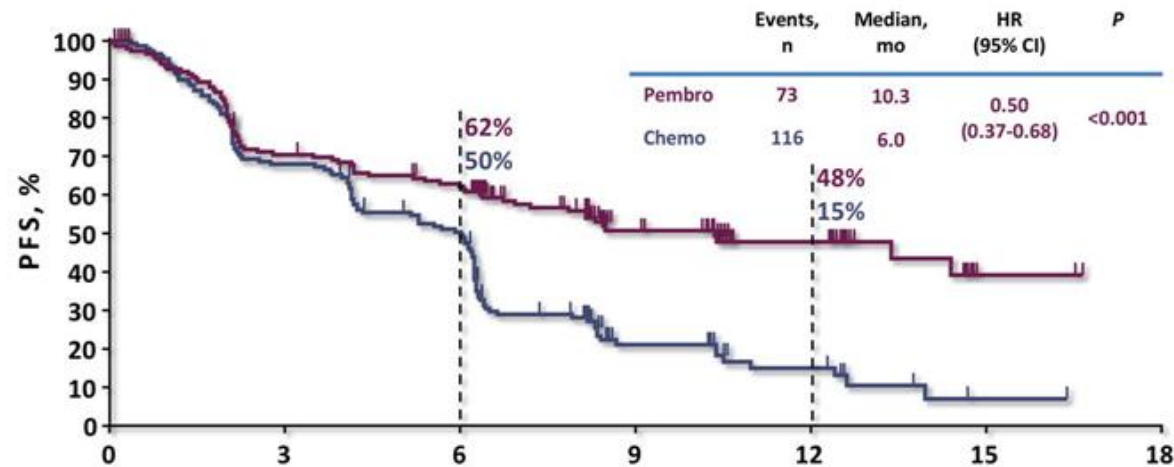
Who benefits most from Immunotherapy?



But only about 30% of patients with advanced NSCLC have very high levels of PD-L1 expression



KEYNOTE-024



Primary endpoint PFS

PD-L1 IHC

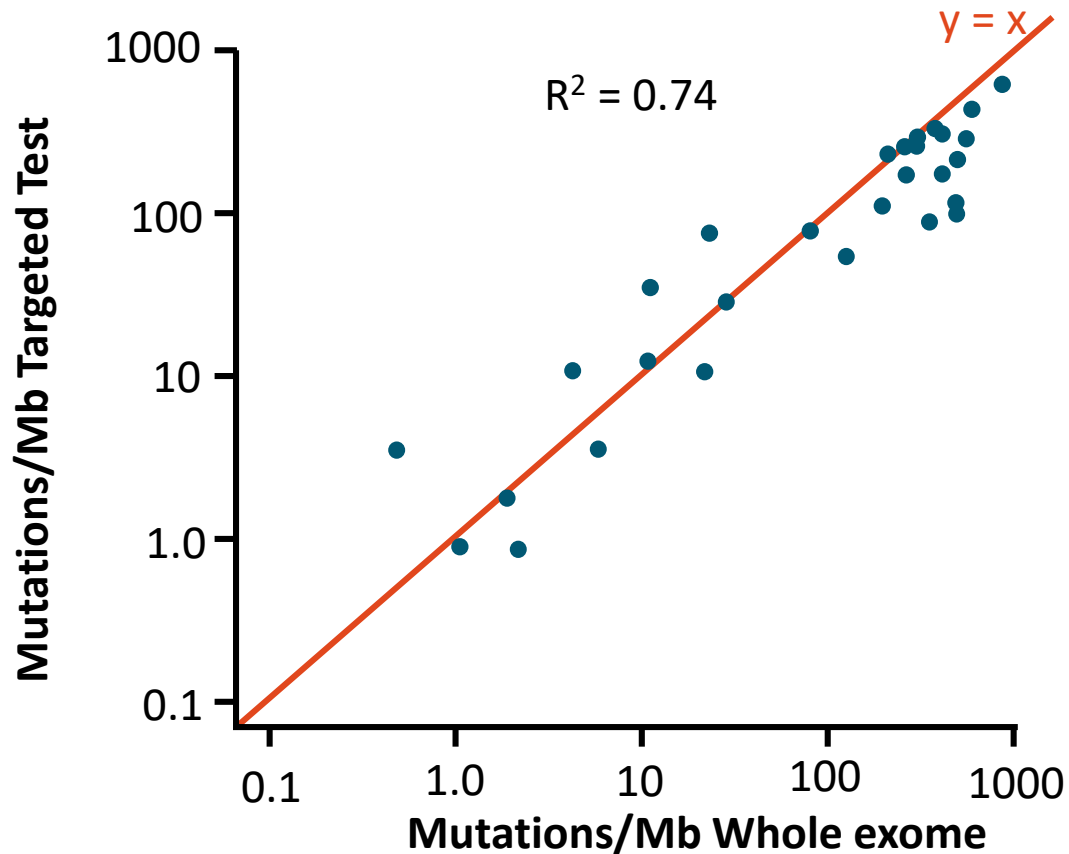


TMB



Tumor Mutational Burden

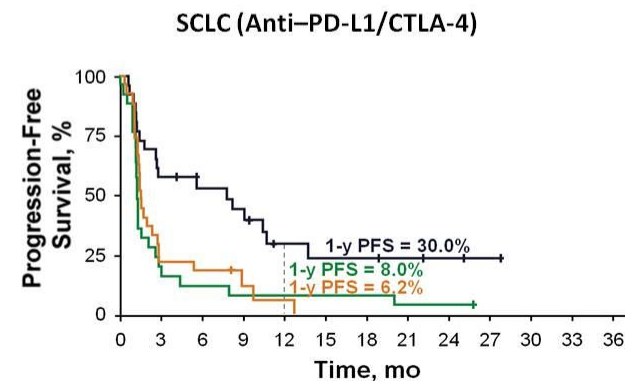
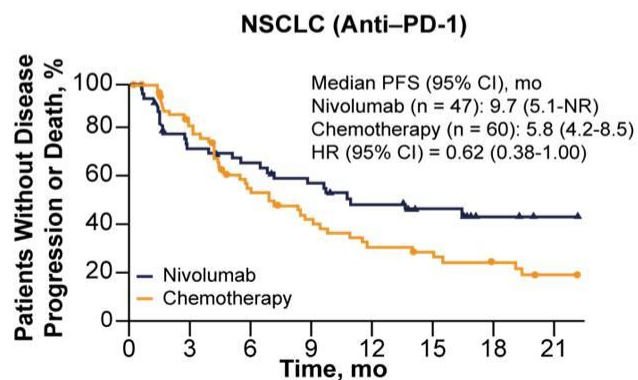
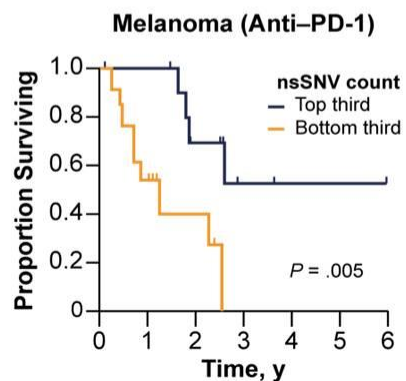
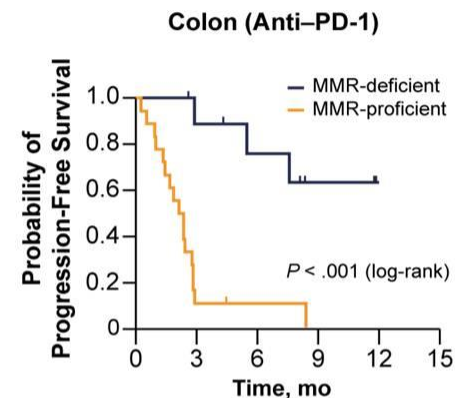
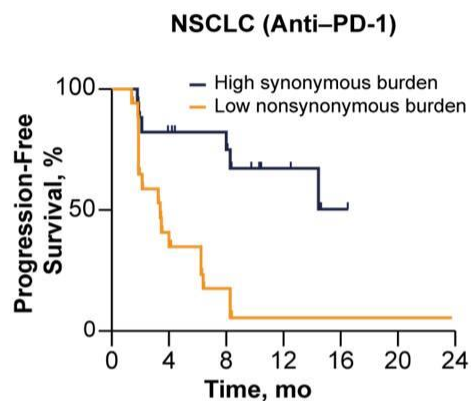
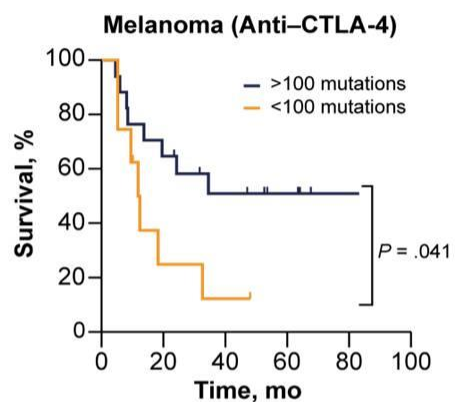
Large Targeted Panels (Without “Paired Normal”)



- **Coverage:** up to 405 genes (315 genes \approx 1.1 Mb coding genome)
 - Sample minimum: 20% tumor cells
 - Sample minimum: 50 ng DNA



TMB by Whole Exome Sequencing (WES) is predictive of immunotherapy activity across diseases

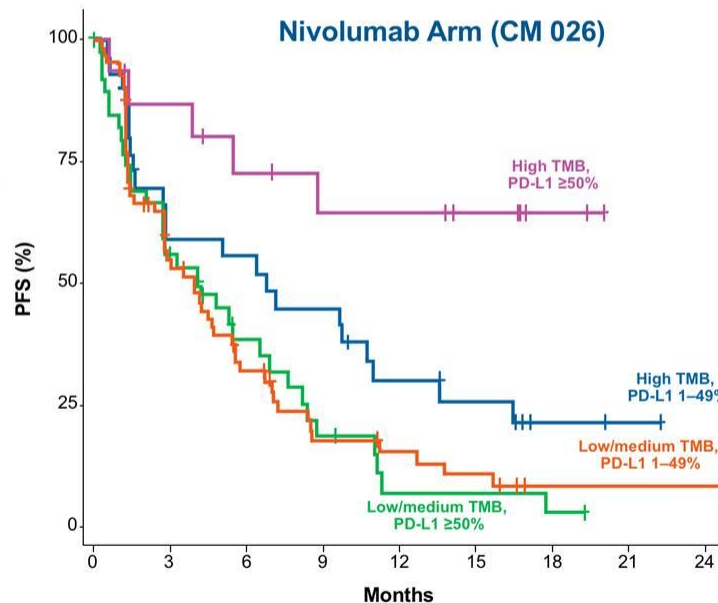
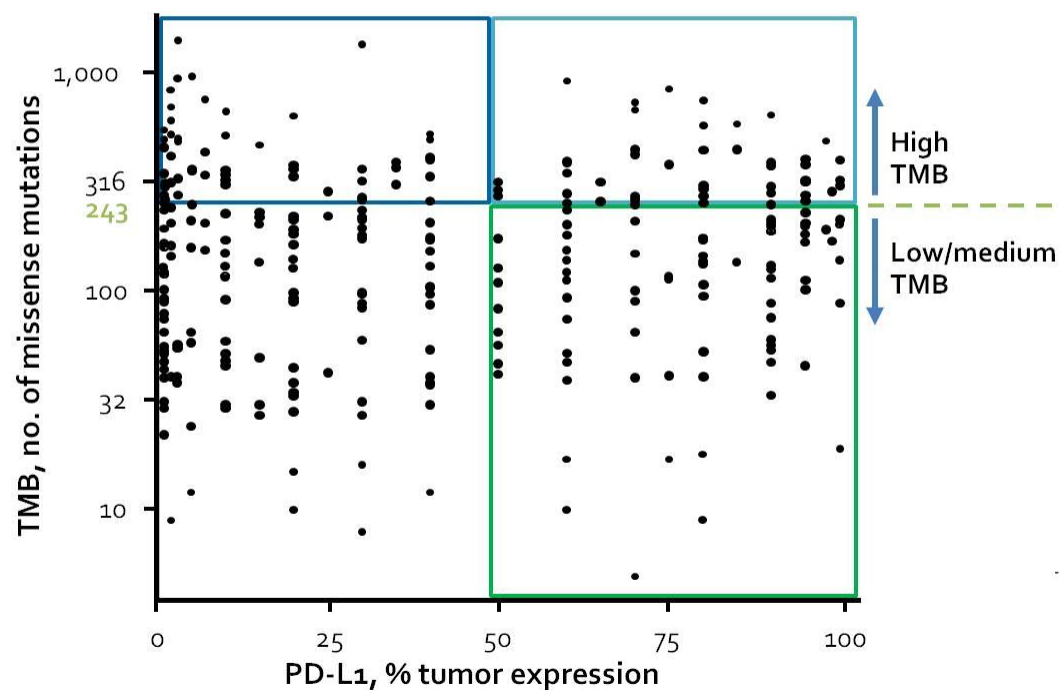


1. Snyder, *N Engl J Med.* 2014; 2. Rizvi, *Science.* 2015; 3. Le DT, *N Engl J Med.* 2015; 4. Van Allen EM, *Science.* 2015; 5. Hugo, *Cell.* 2016; 6. Carbone, *N Engl J Med.* 2017; 7. Rizvi, WCLC 2017



TMB is not correlated to PD-L1 expression

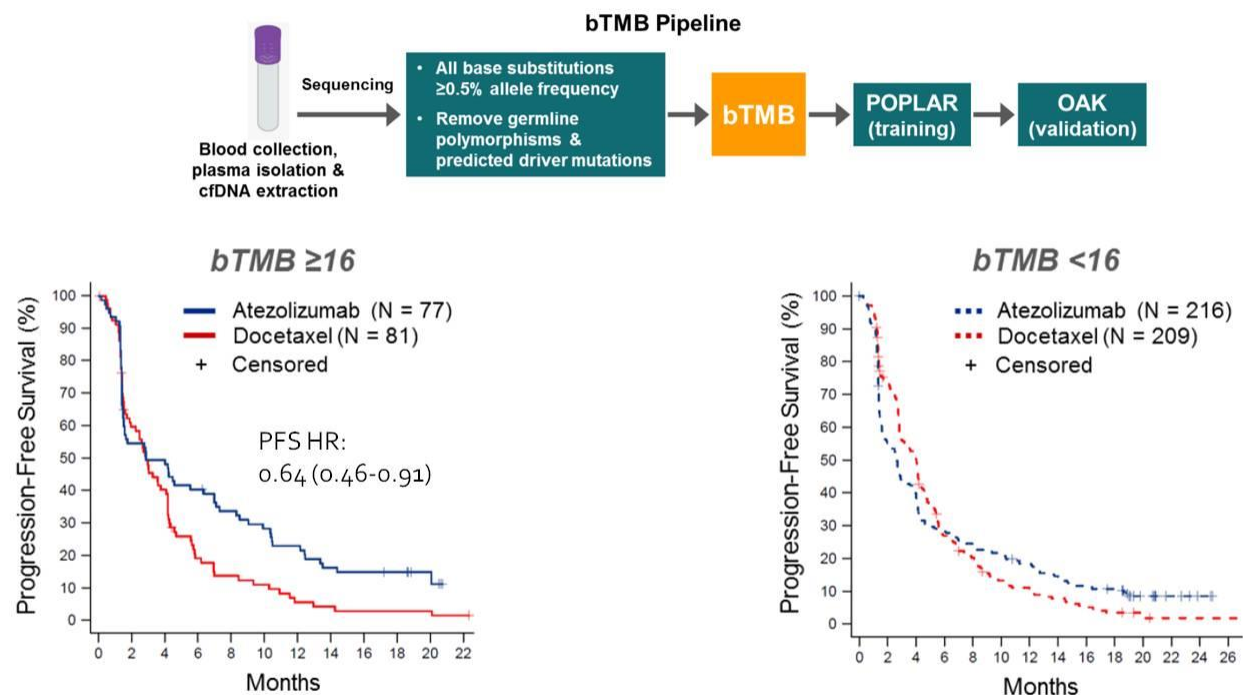
Both biomarkers might be additive



Peters, AACR 2017

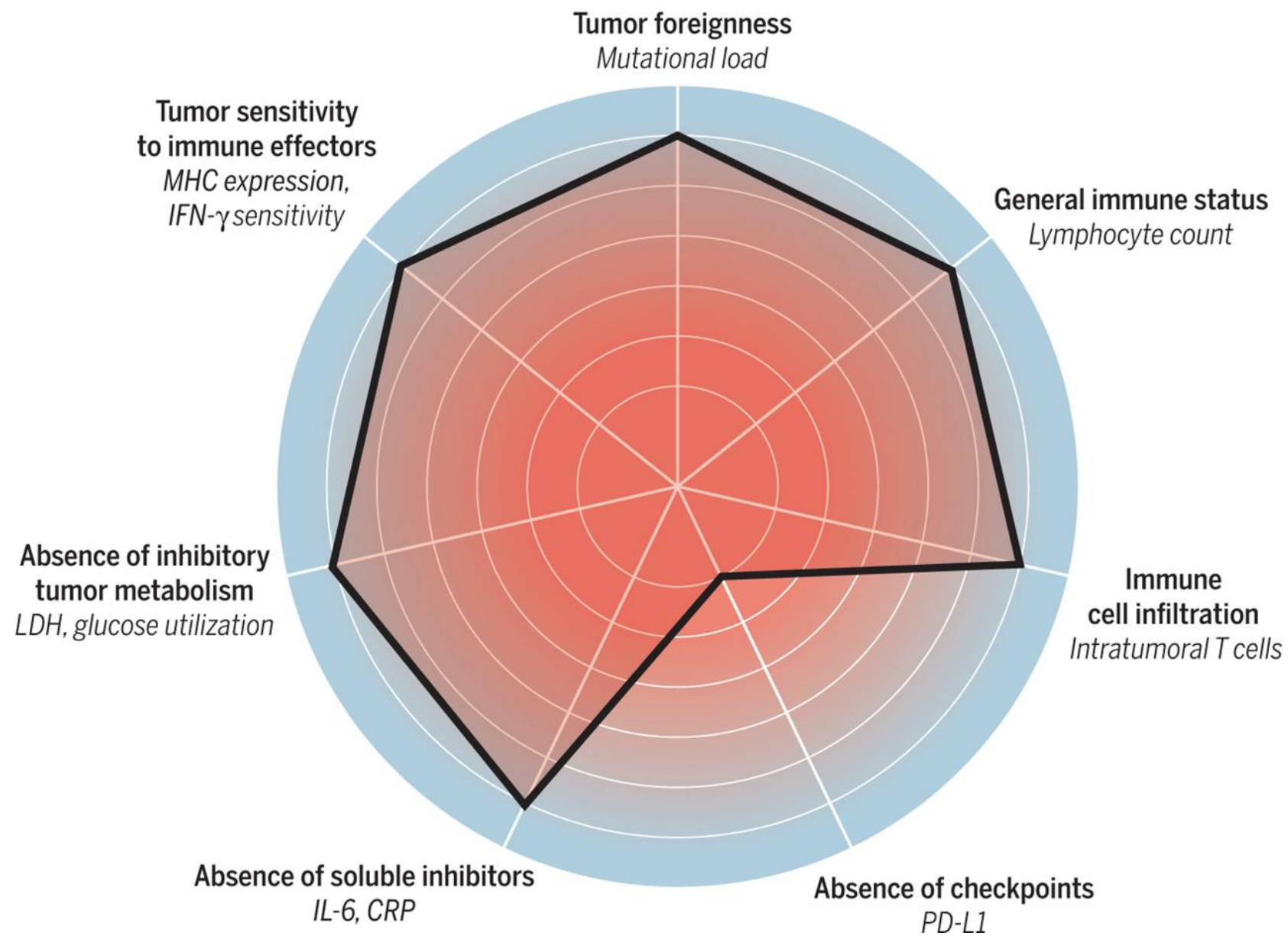


TMB is being developed as a blood-based biomarker



- >1,000 plasma samples from patients with advanced NSCLC
- Prevalence of the bTMB ≥ 16 in OAK: 27%.
- HR high TMB + high PD-L1 (not correlated): 0.38

Gandara, accepted in principle at Nature Medicine

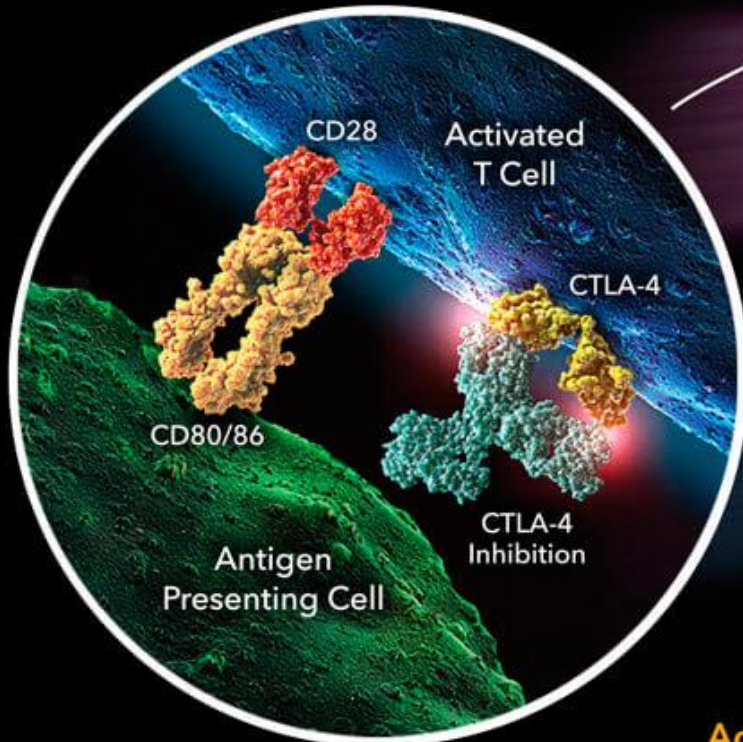


Combination therapy

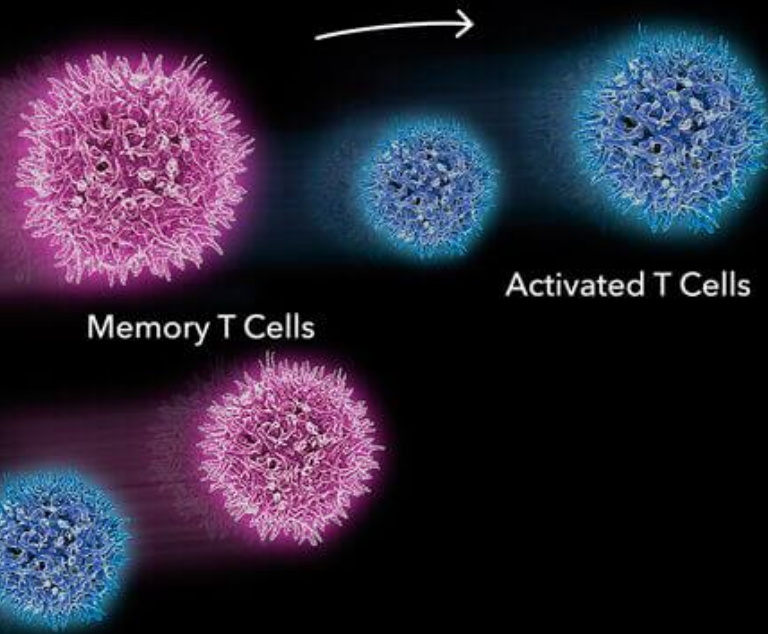


CTLA-4 Inhibition

T cell activation and proliferation^{7,8}
Memory T cell production⁹



Lymph Node

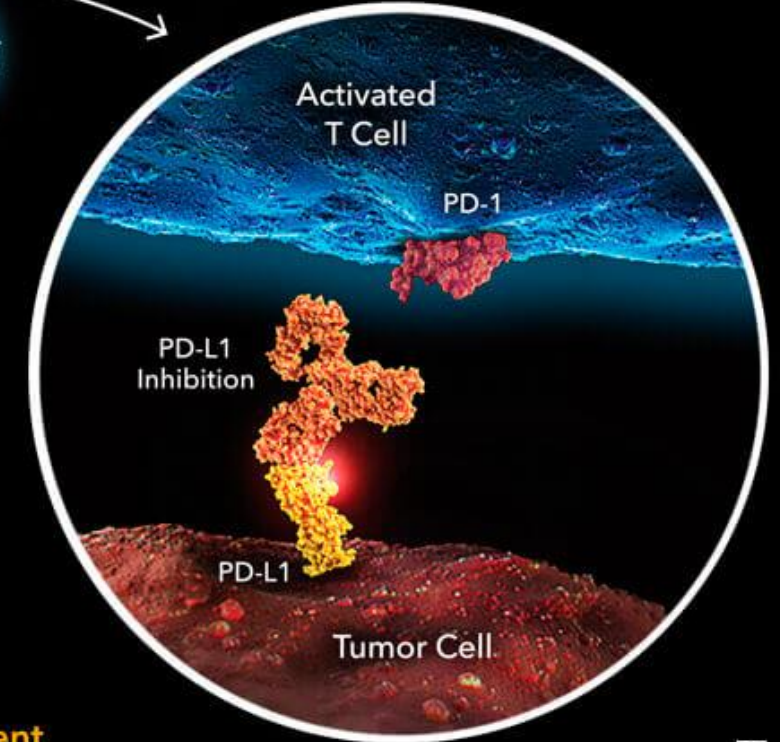


PD-L1 Upregulation

Activated T cells migrate to the tumor microenvironment, which may lead to PD-L1 upregulation.^{6,7}

PD-L1 Inhibition

Prevention of T cell suppression^{6,7}



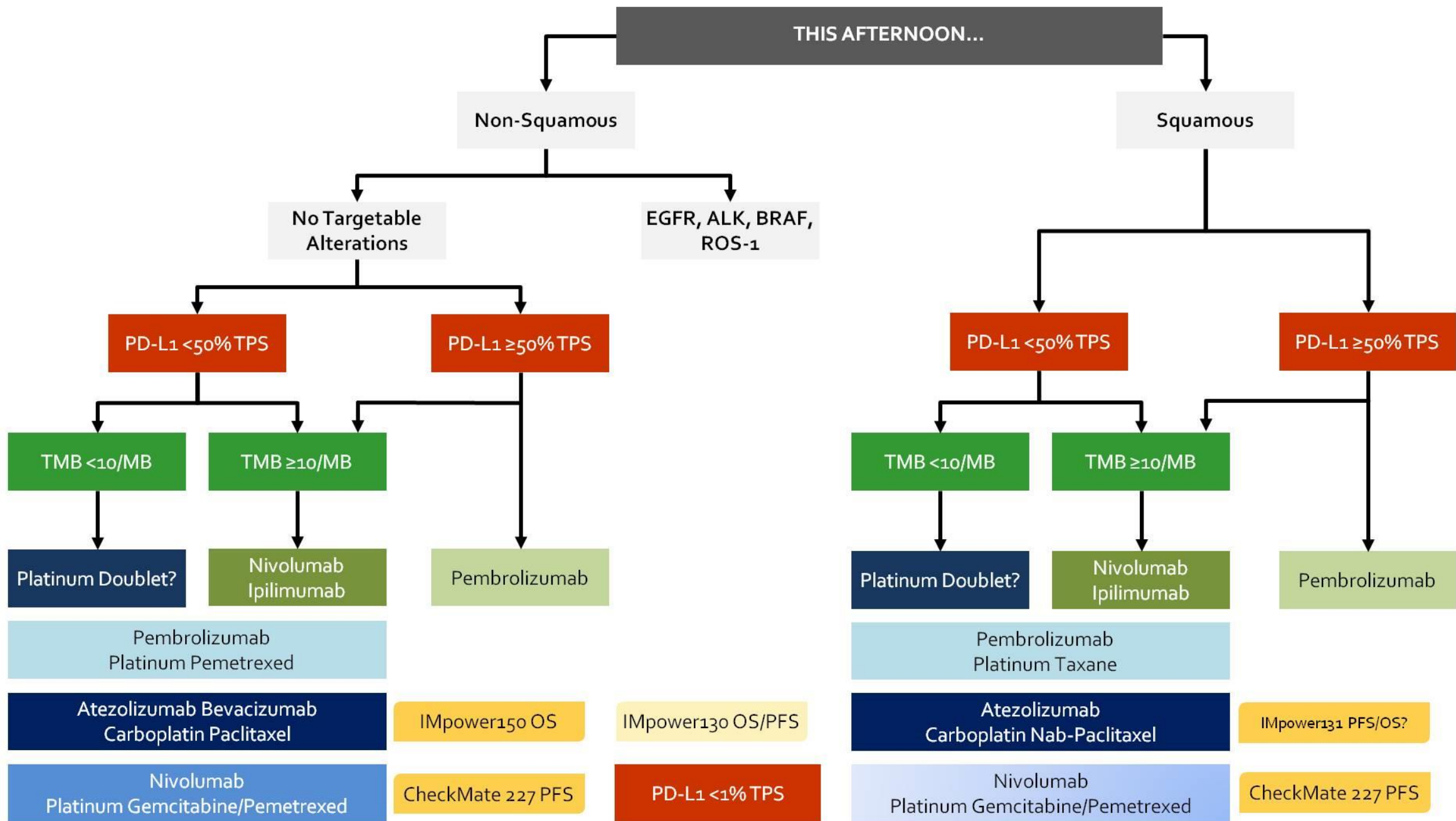
Tumor Microenvironment



Combination



Trial		PFS / OS (months)	PFS HR in PD-L1 neg.	Toxicities Grade 3-5
KEYNOTE-024 PD-L1 \geq 50%	Pembro	10.3 / 30	NA	27 vs 53%
	Plat/Pem or Gem or Pacli	6 / 14.2		
KEYNOTE-042 PD-L1 \geq 1%	Pembro	5.4 / 16.7	NA (in 1-49%: 0.92, NS)	18 vs 41%
	Plat/Pem or Pacli	6.5 / 12.1		
IMPower150 Non-squamous	Atezo + Beva + Plat/Pacli	8.3 / 19.2	0.72	59 vs 50%
	Plat/Pacli	6.8 / 14.4		
KEYNOTE-189 Non-squamous	Pembro + Plat/Pem	8.8 / 21.5	0.59	67 vs 65%
	Plat/Pem	4.9 / 11.3		
KEYNOTE-407 Squamous	Pembro + Plat/Pacli or NabPacli	6.4 / 15.9	0.68	70 vs 68%
	Plat/Pacli or NabPacli	4.8 / 11.3		
CheckMate 227 TMB \geq 10mut/Mb	Nivo + Ipi	7.2 / 23	0.48	31 vs 36%
	Plat/Pem or Gem	5.4 / 16.4		



2020

Across histologies

TMB <10/MB

No Targetable Alterations

TMB ≥10/MB

PD-L1 <50% TPS

PD-L1 ≥50% TPS

PD-L1 <50% TPS

PD-L1 ≥50% TPS

Platinum Doublet?

Pembrolizumab?

Nivolumab
Ipilimumab

Anti-PD(L)-1
Platinum doublet

New immunotherapy combinations

Anti-PD(L)-1 / CTLA-4
Platinum doublet

T-cell therapies / vaccines

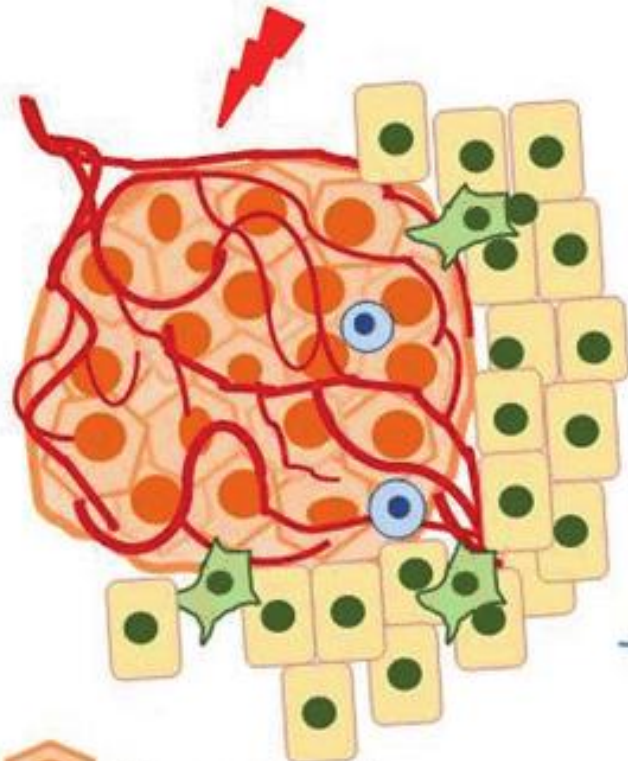
Atezolizumab + Bevacizumab
Carboplatin + Paclitaxel




Only non-squamous

Slide 33

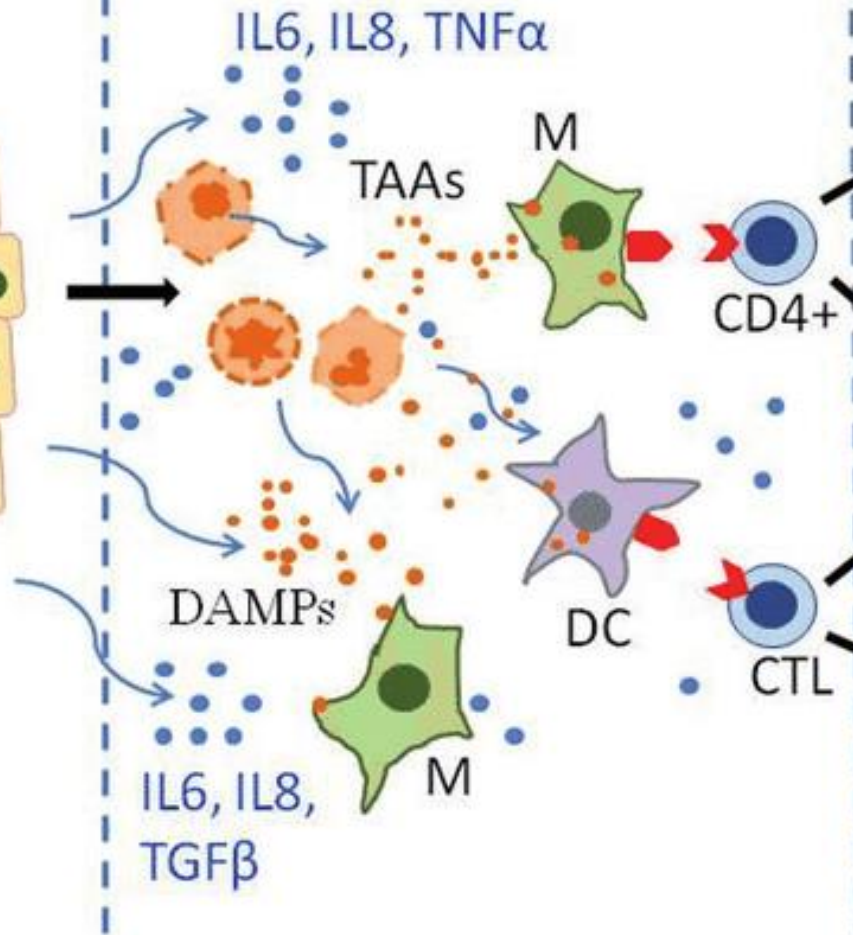


Radiotherapy

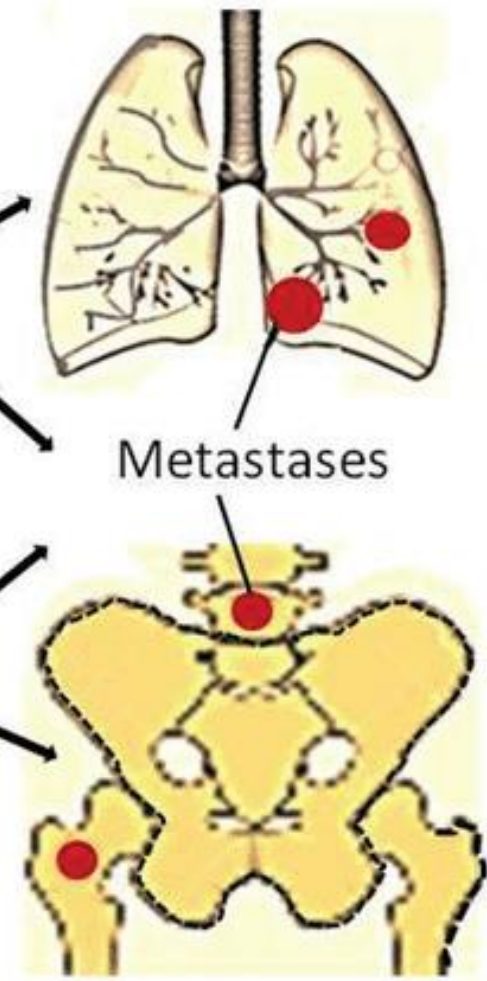


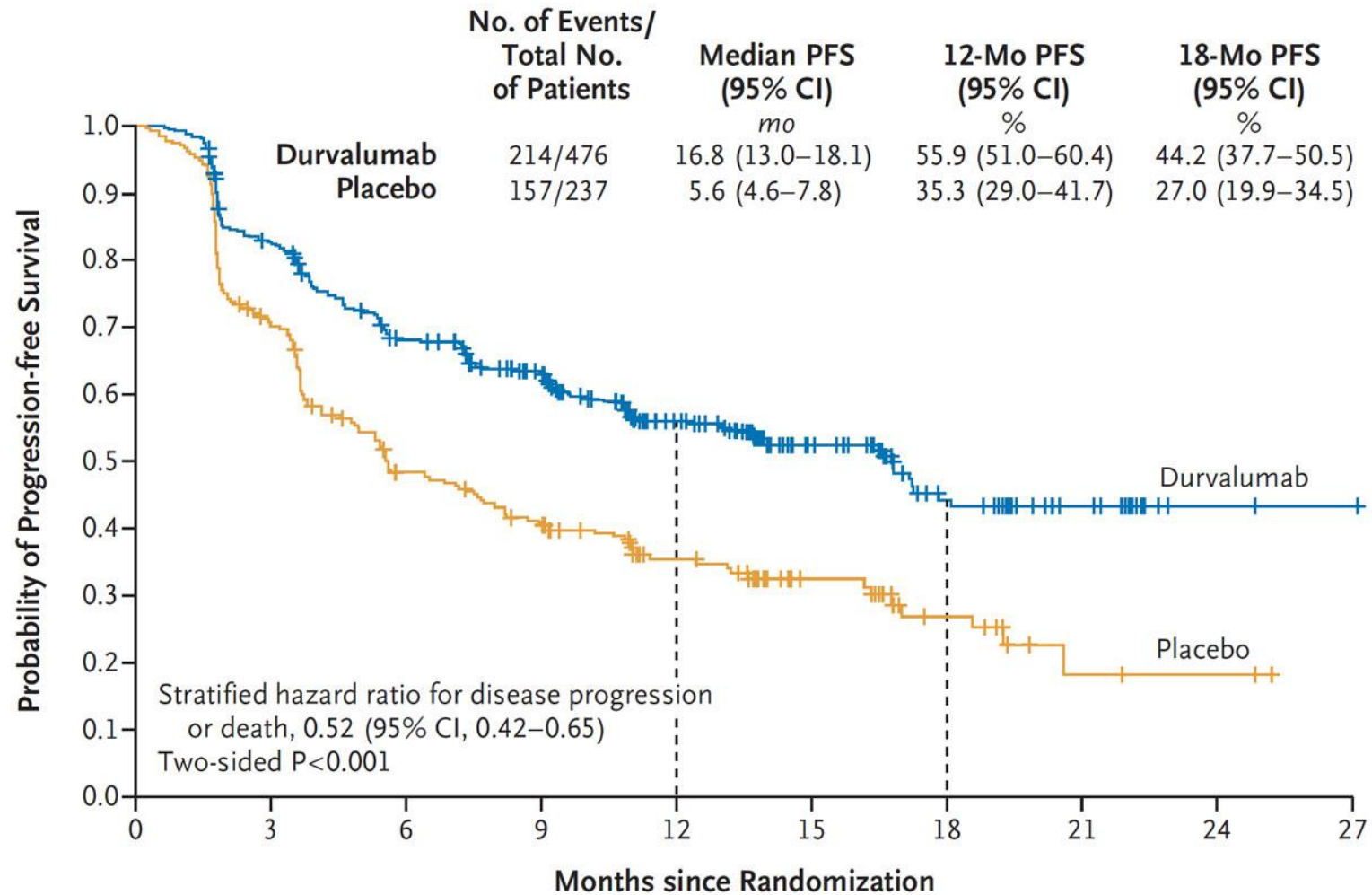
-  Cancer cells
-  Normal cells
-  Lymphocytes

Immune system activation



Distant organs





No. at Risk

Durvalumab

476

377

301

264

159

86

44

21

4

1

Placebo

237

163

106

87

52

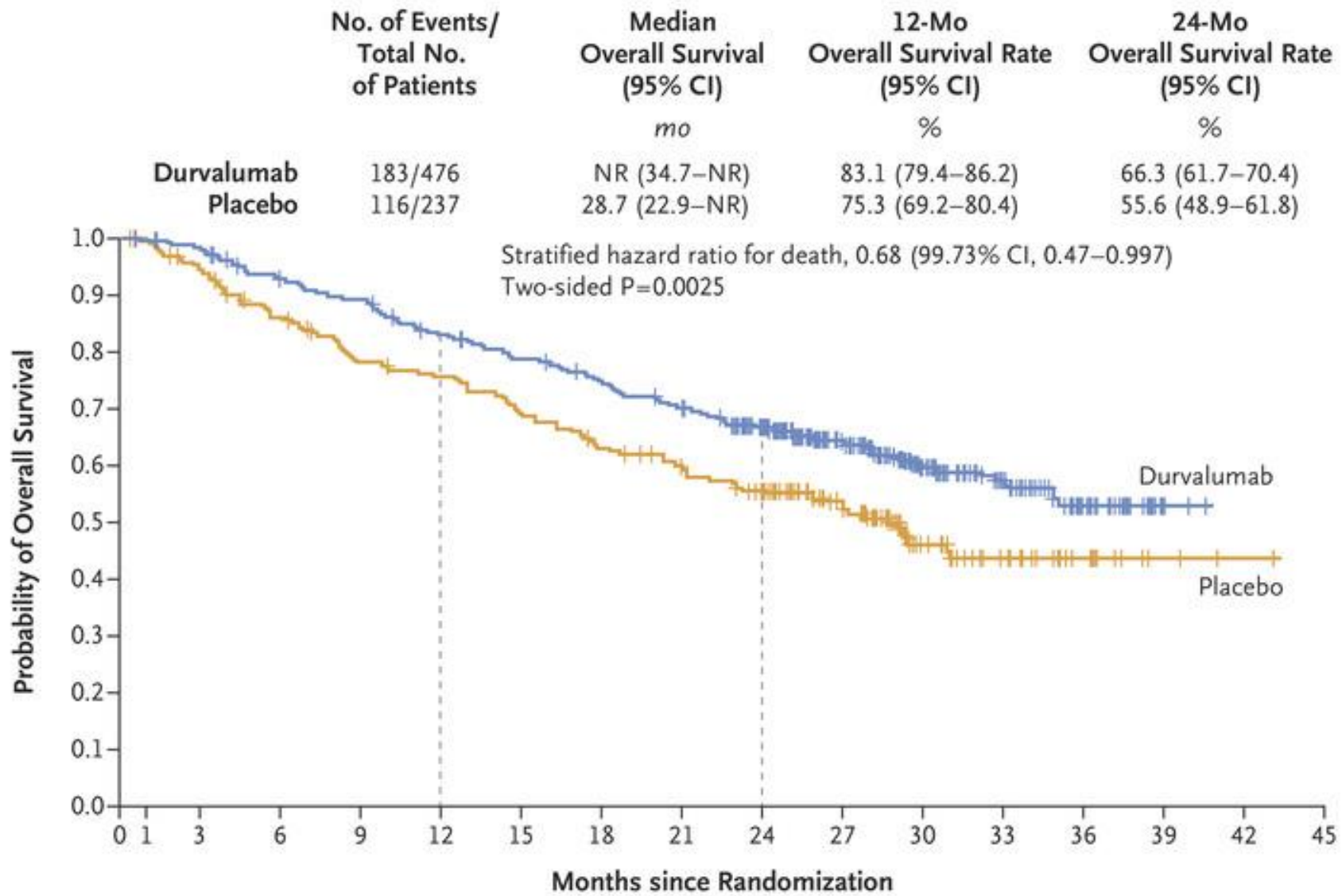
28

15

4

3

0



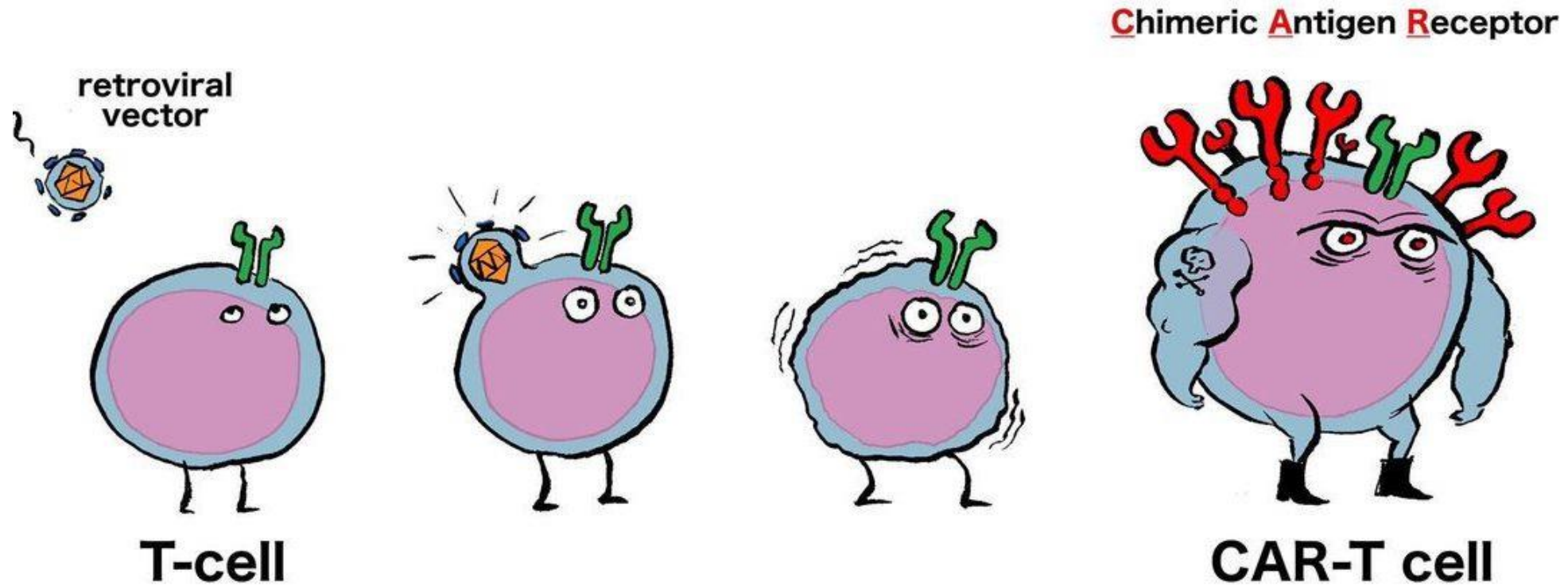
No. at Risk

Durvalumab	476	464	431	415	385	364	343	319	274	210	115	57	23	2	0	0
Placebo	237	220	198	178	170	155	141	130	117	78	42	21	9	3	1	0

What next in immunotherapy?

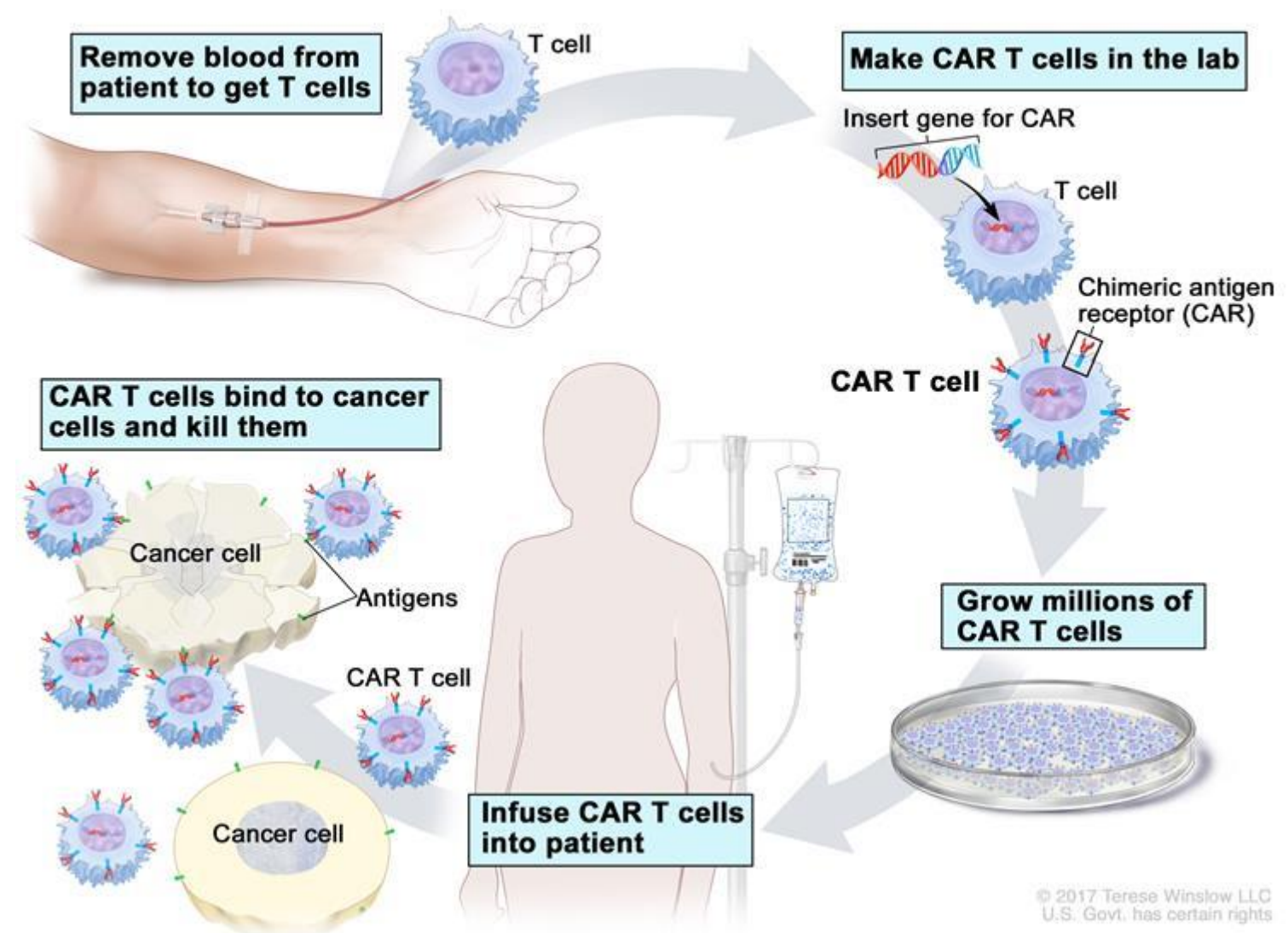


Generating super-soldiers the production of CAR-T cells





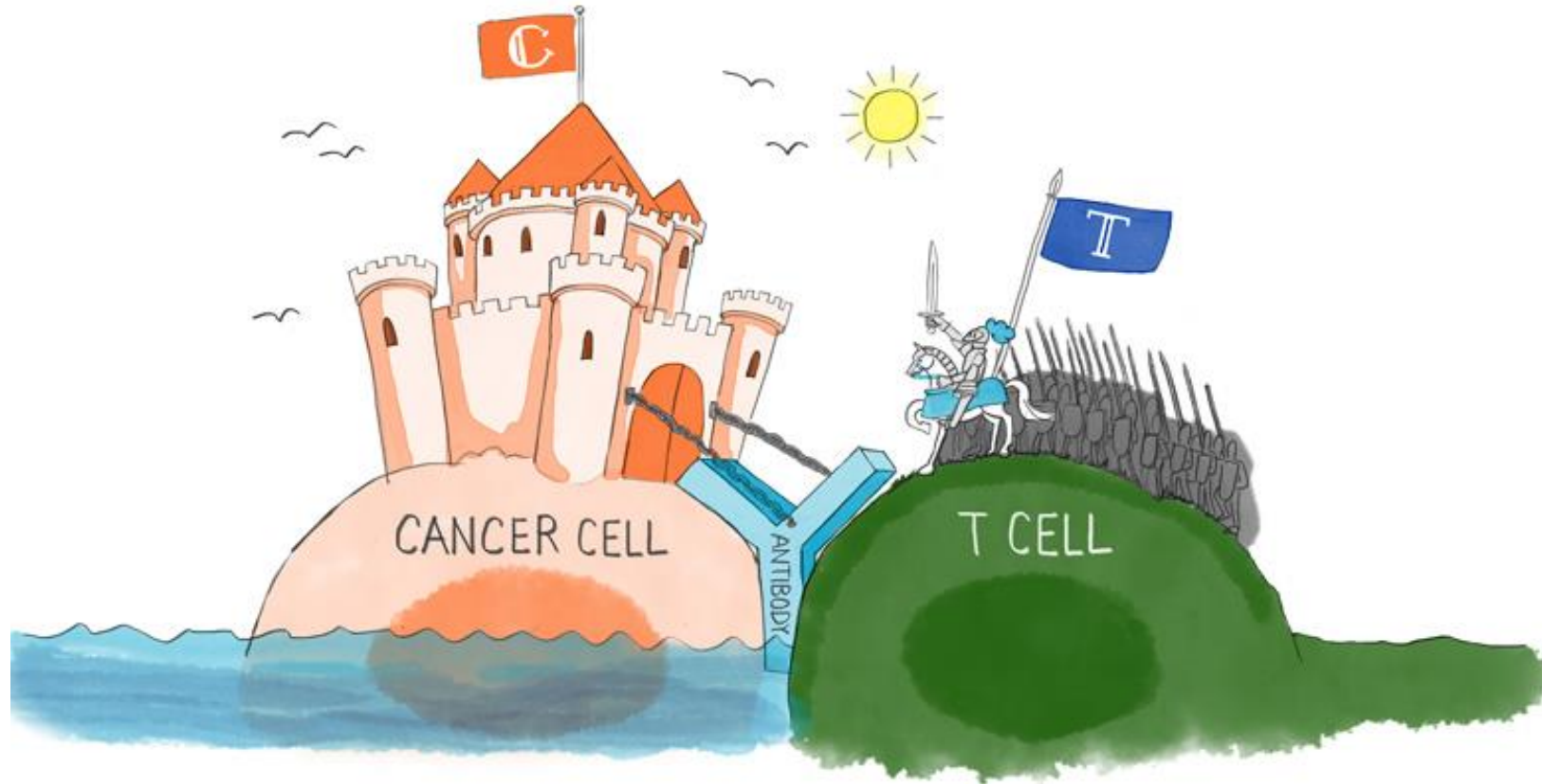
CAR T-cell Therapy



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CAR T cell can direct attach target cell

The ABCs of Immunotherapy



Anti-PD-1/PD-L1 inhibitor

Biomarker

Combination or **C**AR T cell therapy



Lung Cancer School 2019

2019년 7월 27일 서울아산병원 연구원지하대강당

폐암검진 질관리 및 전문인력 교육지원

폐암의 항암치료 - 증례중심의 교육



지금까지
이런 강의는 없었다!



주중에는 환자진료 주말에는 연수강좌

Lung Cancer School

2019.07.27