Dr René Laennec

Melanoma defined as a clinical entity

Immunotherapy Beyond CPI

UCLouvain
Université

INSTITUT ROI ALBERT II
CANCÉROLOGIE ET HÉMATOLOGIE
Cliniques universitaires SAINT-LUC I UCL Bruxelles

Prof J-Fr. BAURAIN
Medical Oncology Department

16th BSMO-Bordet
Dolce La Hulpe
3 December 2022

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Melanoma defined
as a clinical entity

PD-1/PD-L1

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Conflict of Interest

Payments to my institution for consulting, advisory roles or lectures for Bristol-Myers Squibb, MSD, Novartis, Sanofi, Regeneron, Merck, Pfizer, Pierre-Fabre, Sun Pharma, AstraZeneca, Immunocore, GSK

GT 40, Ford

456, Ferrari

Taycan, Porsche

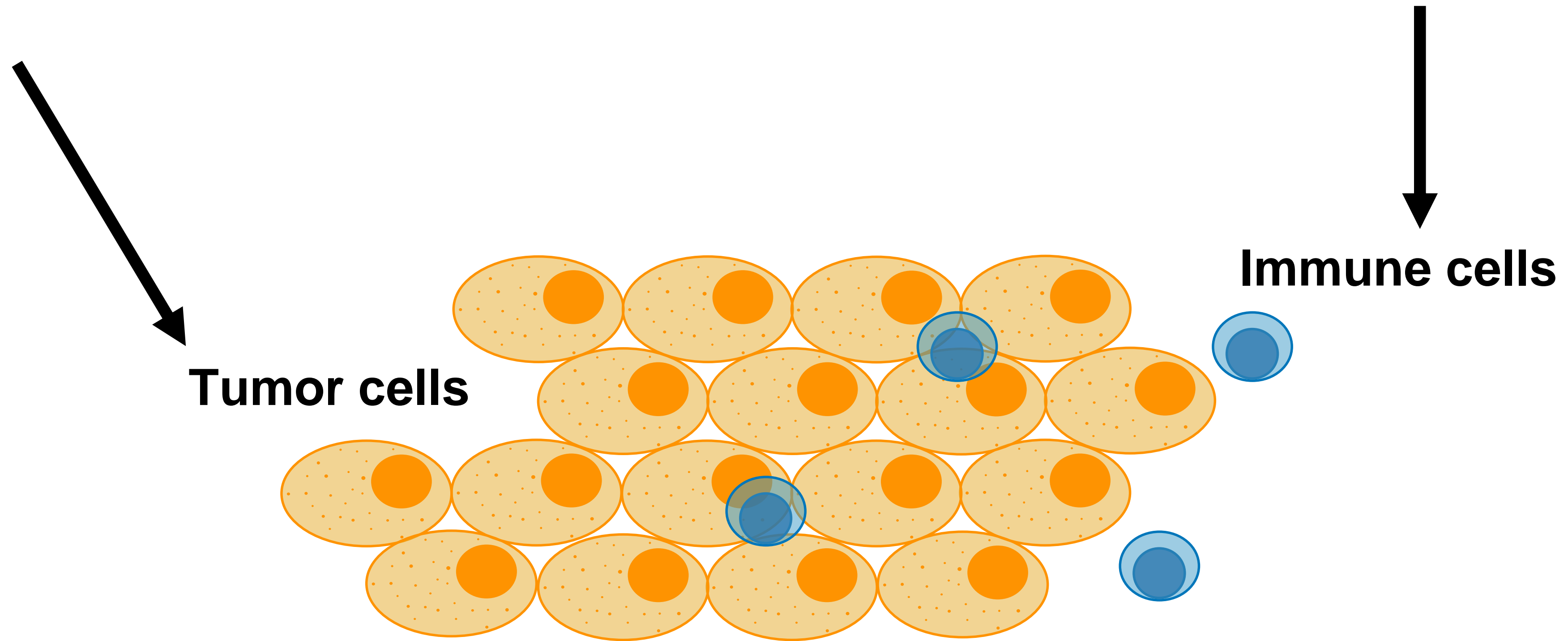**Mustang Cobra, Ford**

Mustang Mach-E, Ford

e-tron GT, Audi

Basis of Immunotherapy : Deliberate Stimulation of Immune cells

CHEMOTHERAPY

TARGETED THERAPY
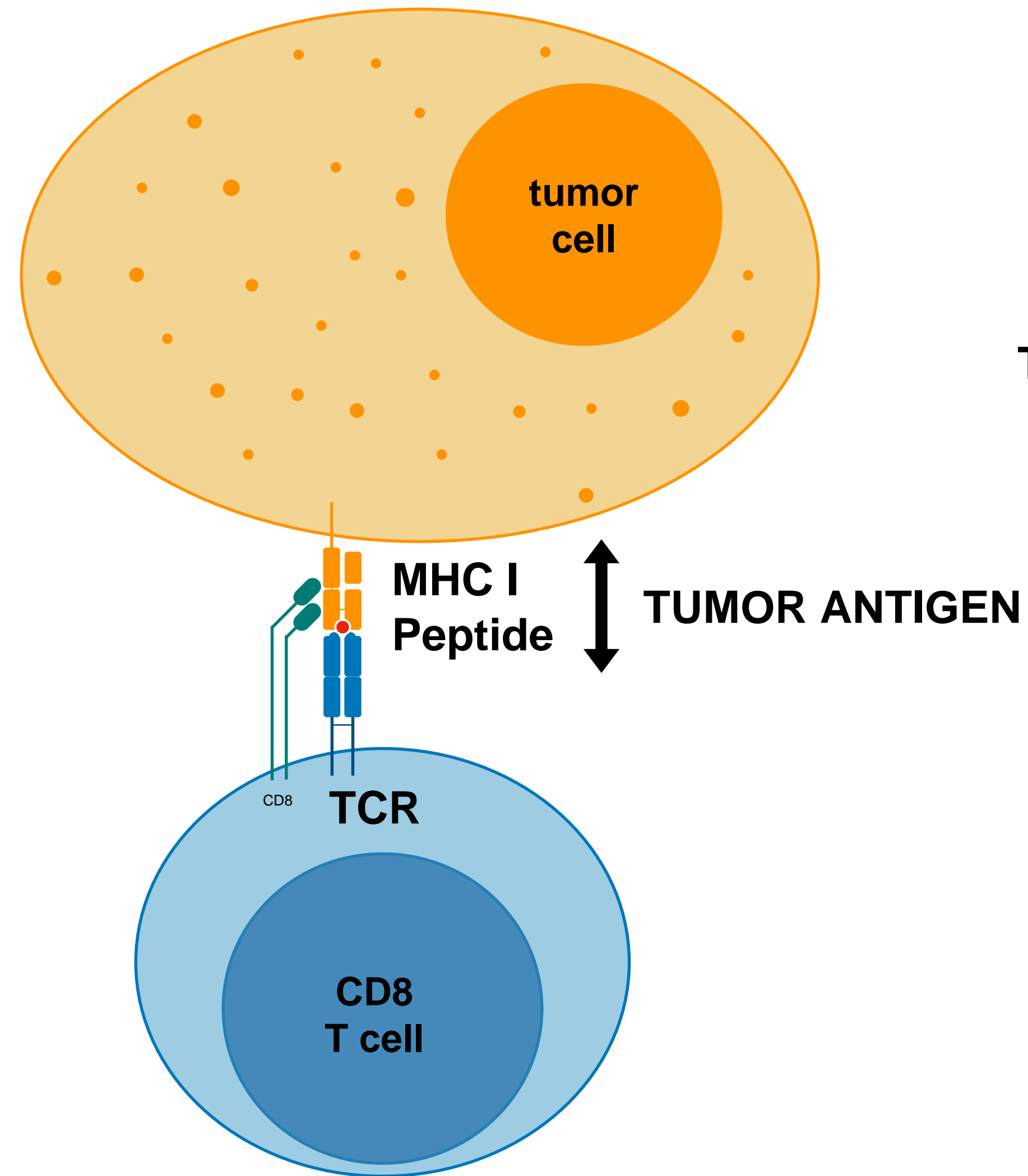
IMMUNOTHERAPY

Immune cells

Tumor cells

THE ANTITUMORAL ACTIVITY OF ALL CLASSICAL TREATMENTS STOPS WITH THE TREATMENTS
This is not the case for Immunotherapy !

Basis of Immunotherapy : a Belgian Discovery
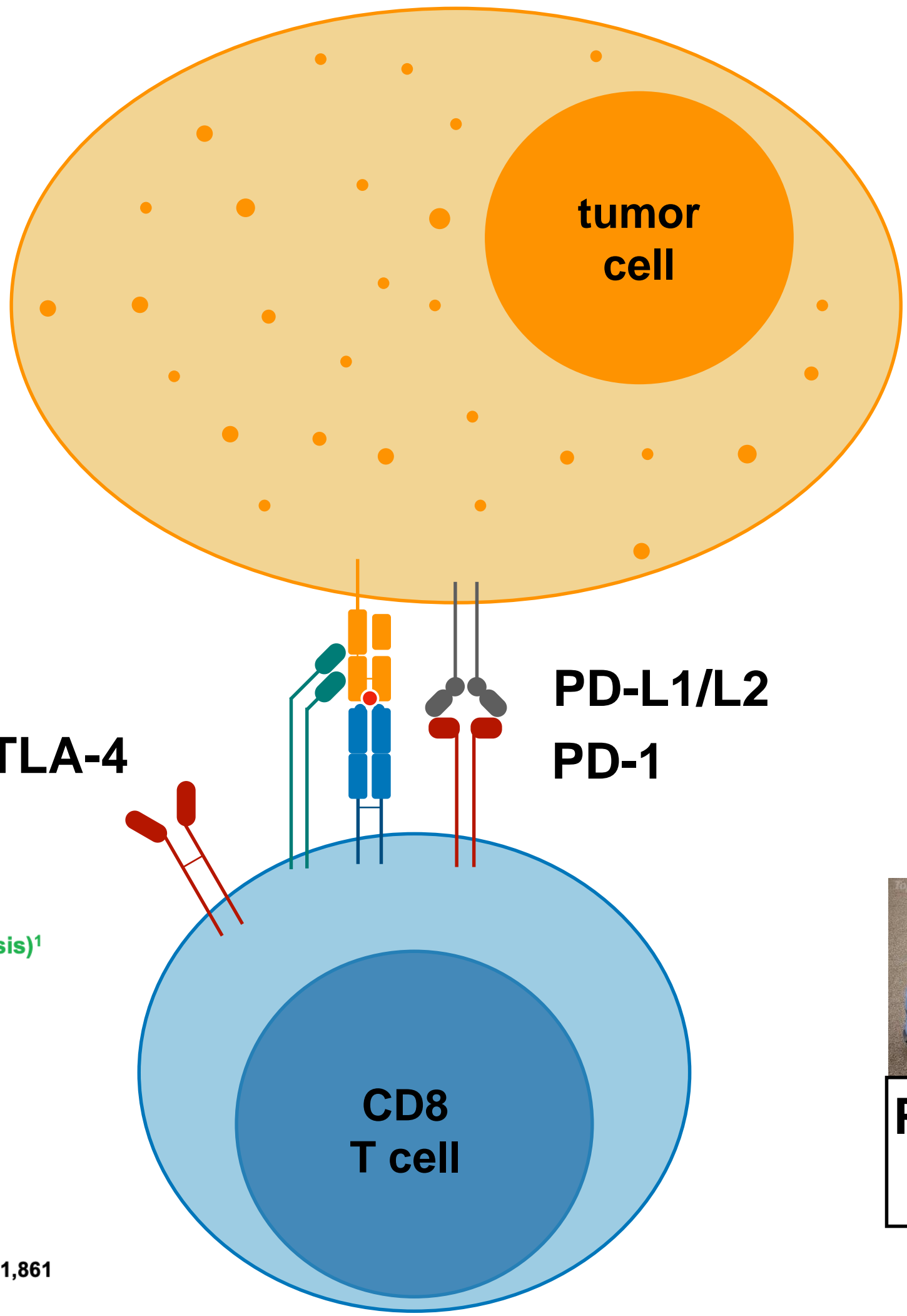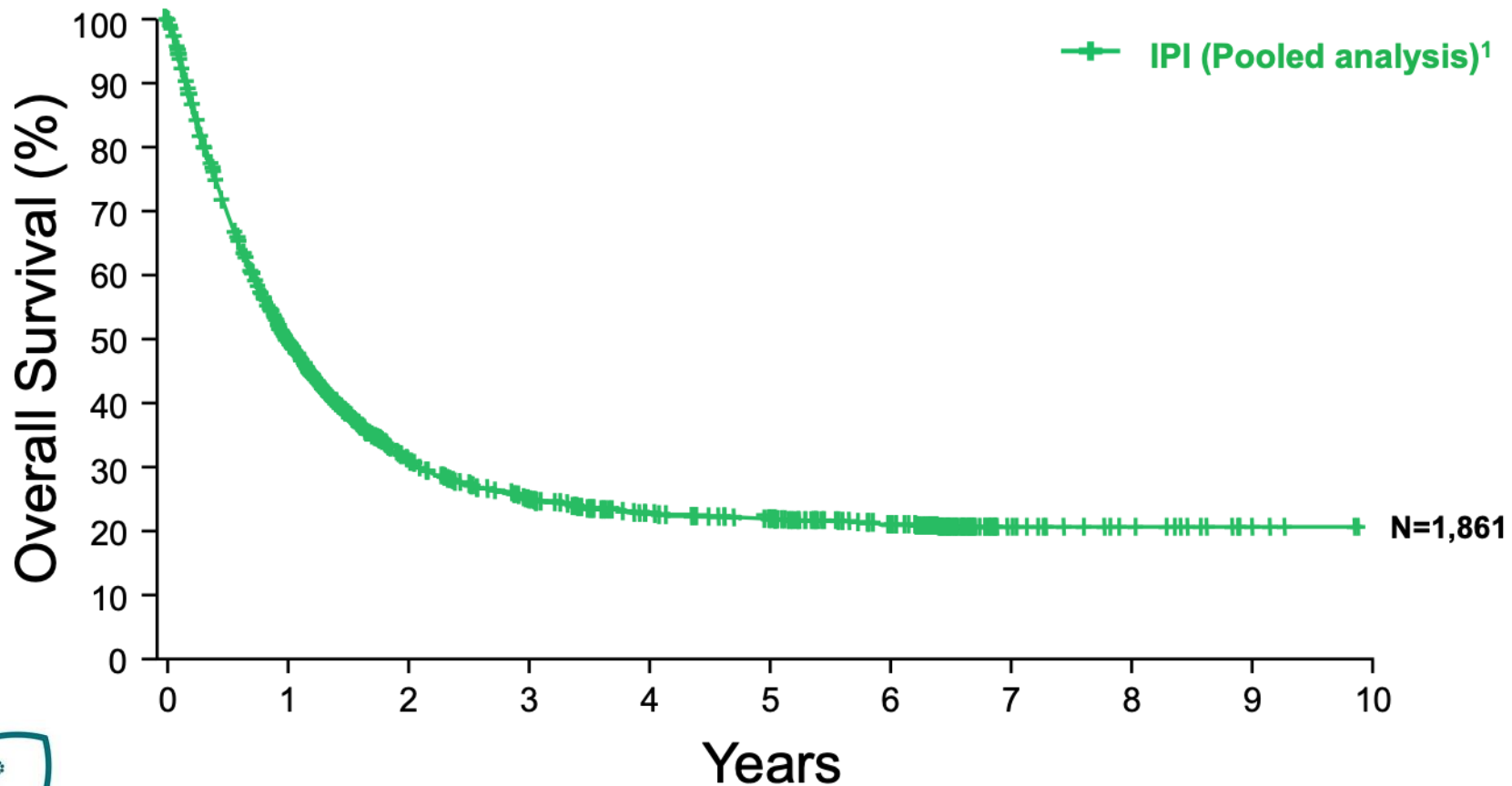

**Thierry Boon *et al.*
1989**

tumor
cell

MHC I
Peptide

TUMOR ANTIGEN

CD8

TCR

CD8
T cell

Basis of Immunotherapy : Checkpoint Inhibitors (CPI)

**Jim Allison *et al.*
1996**

Ipilimumab

YERVOY®

**Thierry Boon *et al.*
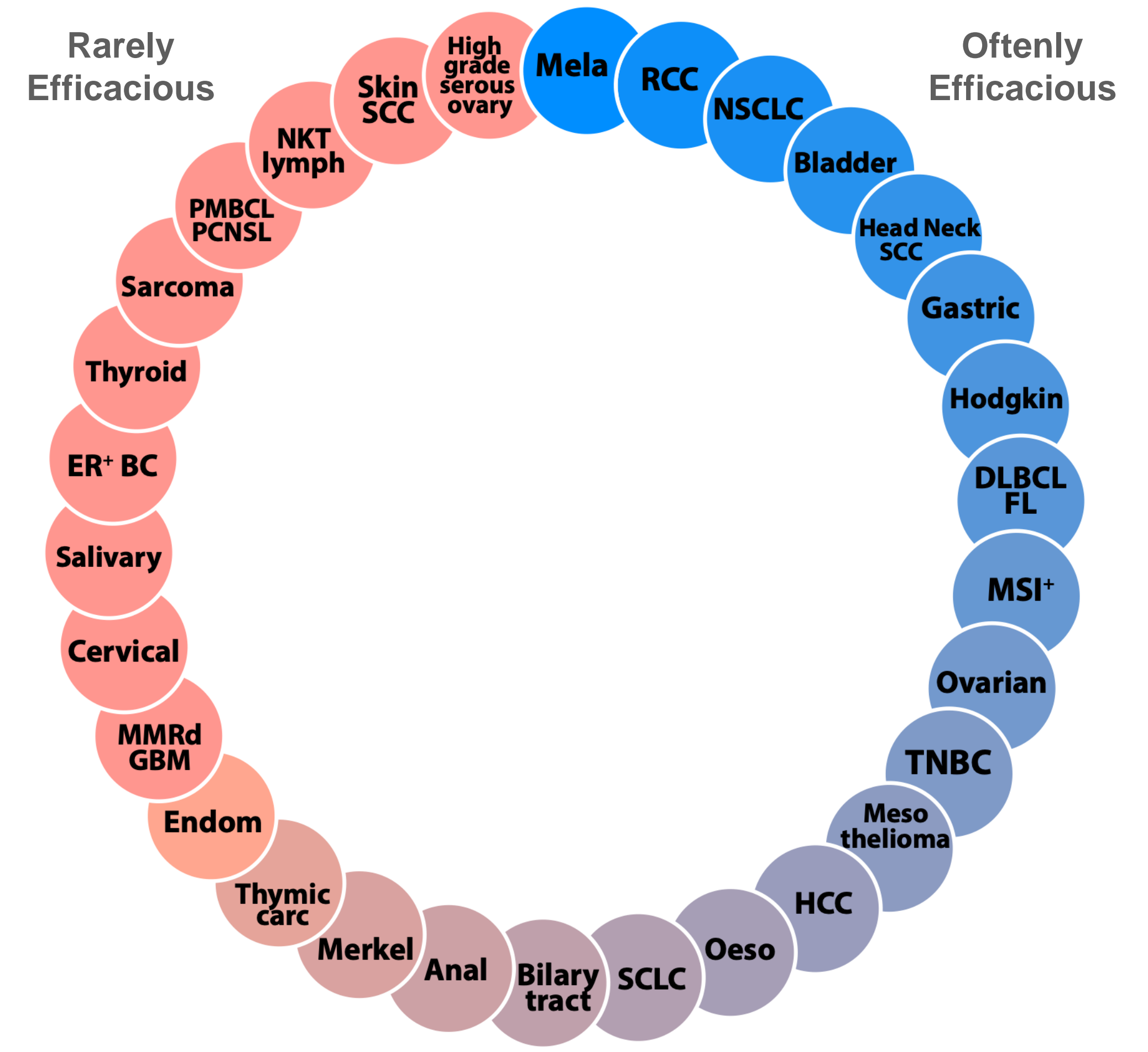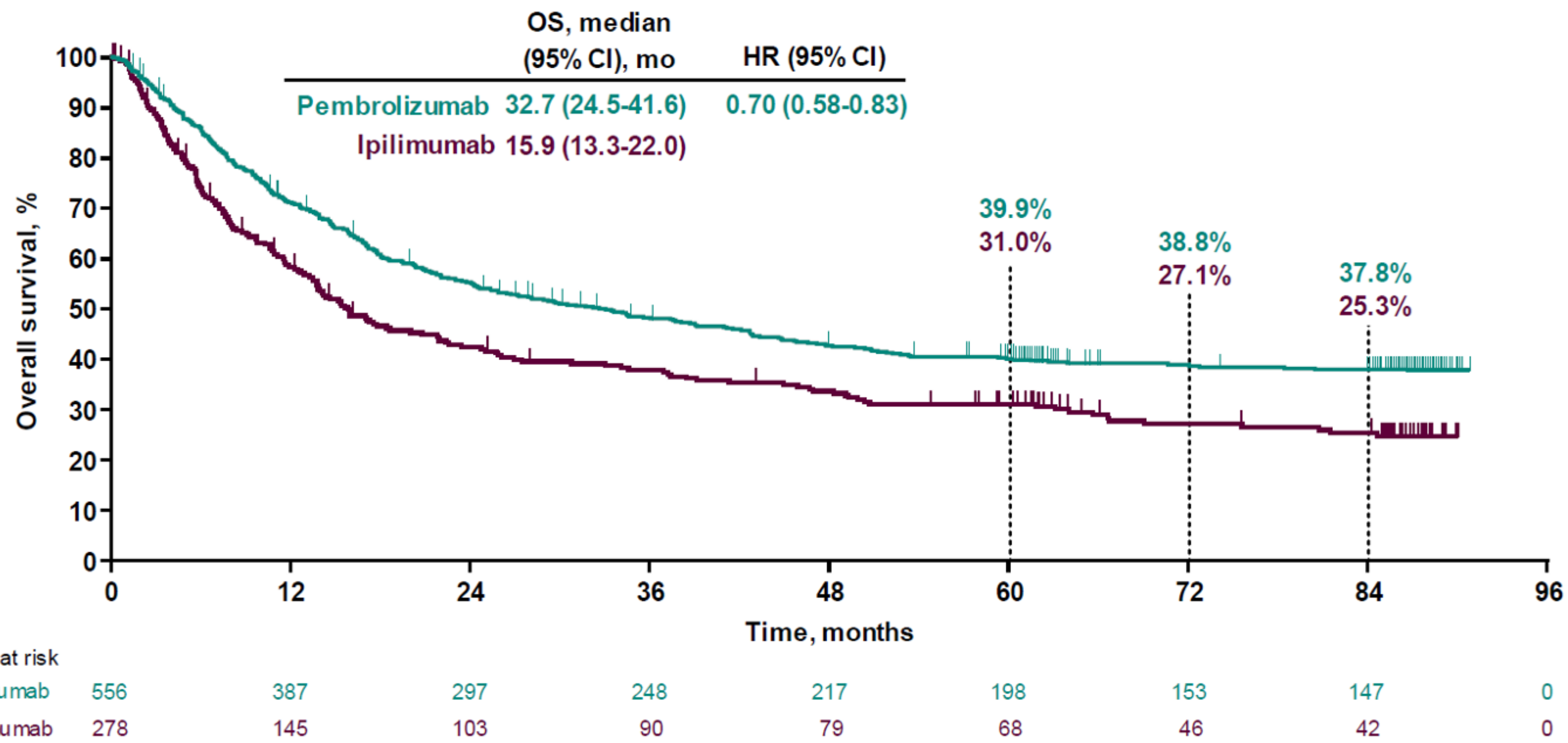1989**

Pembrolizumab

KEYTRUDA®

**Tasuku Honjo *et al.*
1996**

tumor
cell

CTLA-4

PD-L1/L2
PD-1

CD8
T cell

IPI (Pooled analysis)[1]

N=1,861

Overall Survival (%)

Years

Schadendorf et al , JCO 2015
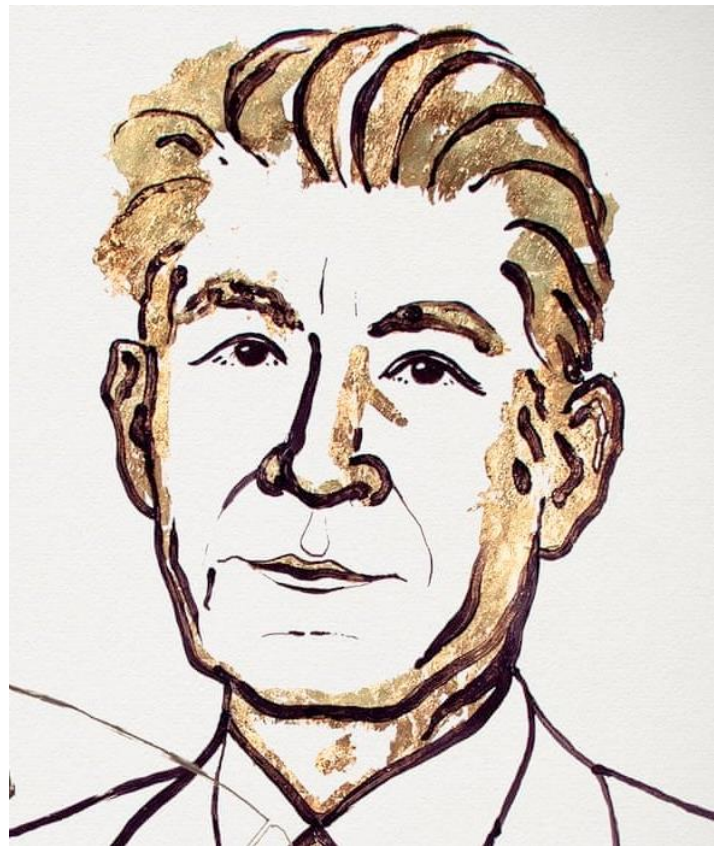
Anti-PD-1 antibodies (CPI) have a major effect on Melanoma Survival
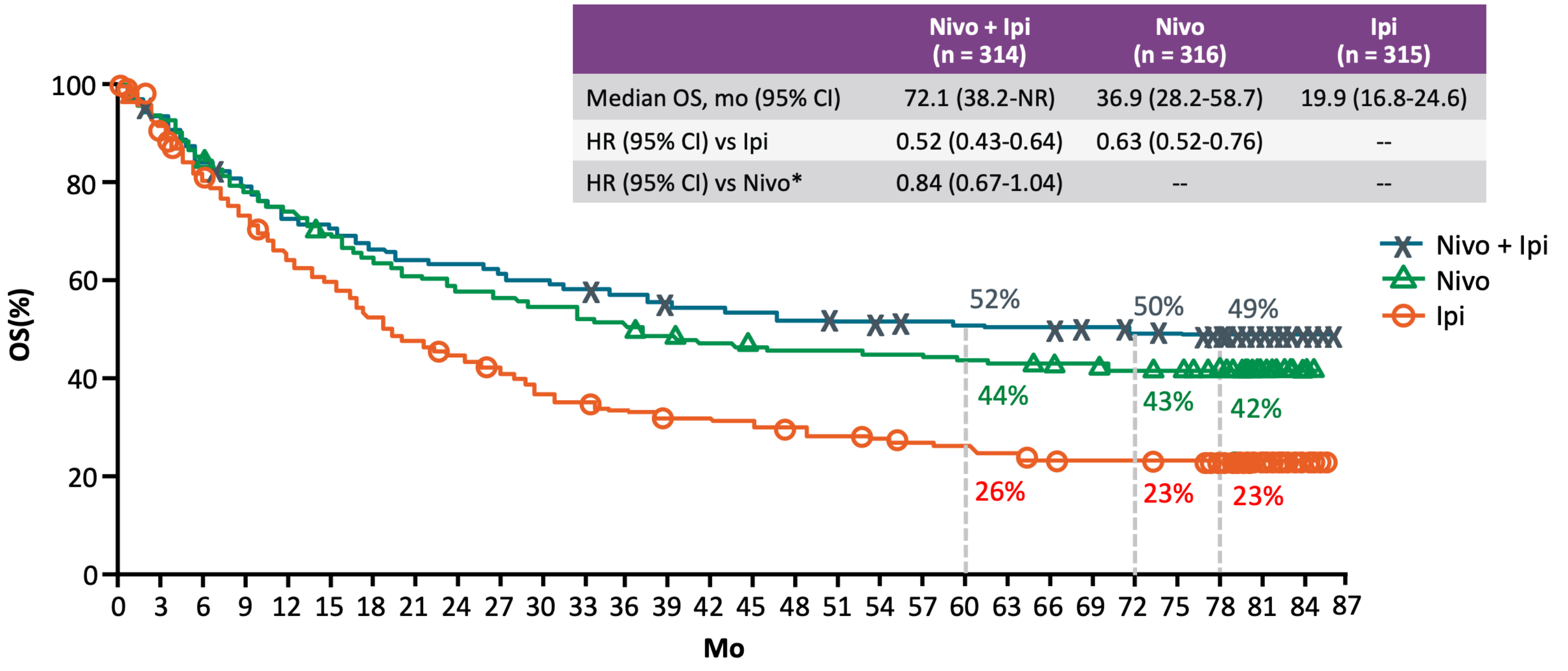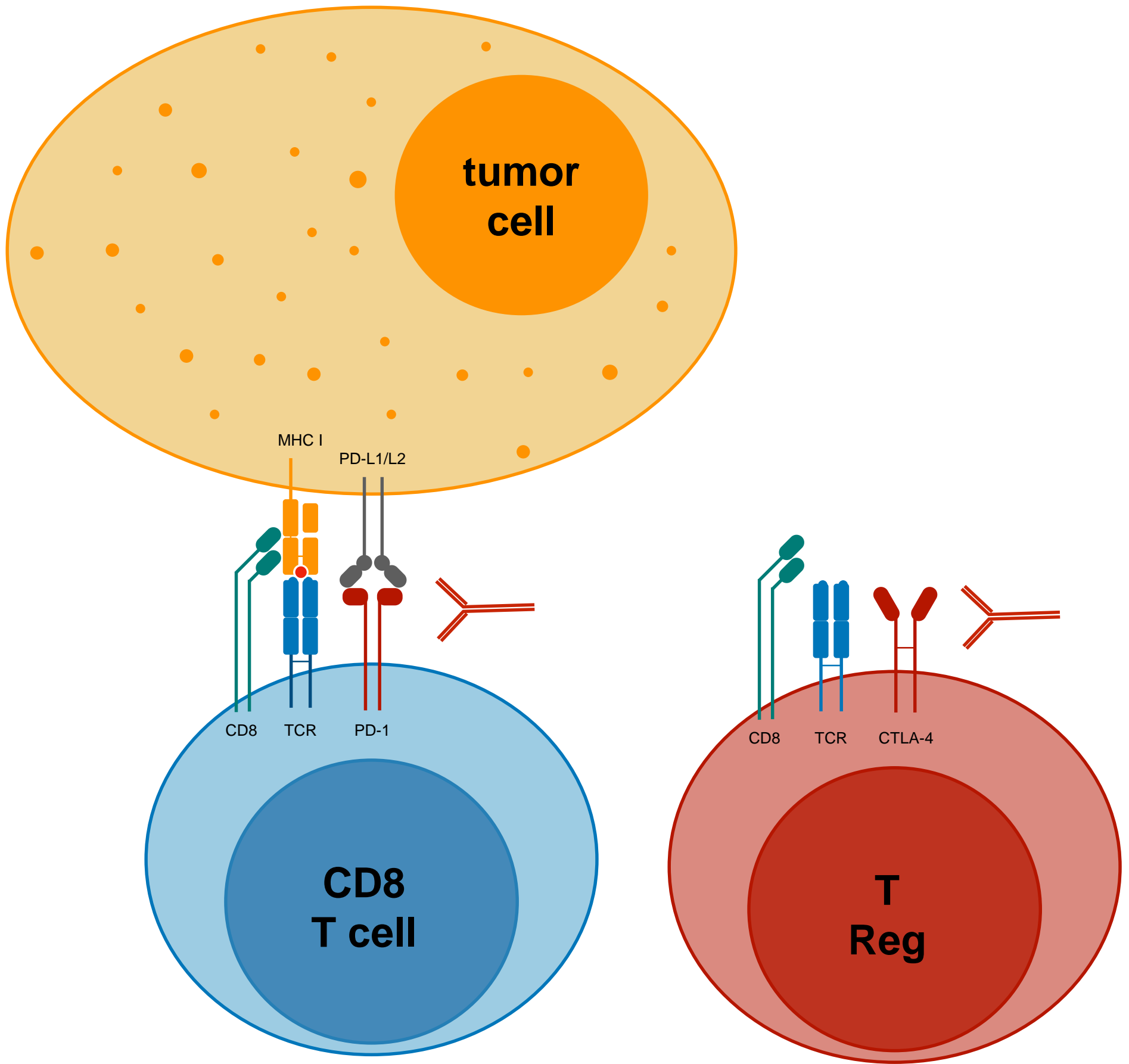
KN-006 : OS at 7-y median Follow-up

	OS, median (95% CI), mo	HR (95% CI)
Pembrolizumab	32.7 (24.5-41.6)	0.70 (0.58-0.83)
Ipilimumab	15.9 (13.3-22.0)	

No. at risk									
Pembrolizumab	556	387	297	248	217	198	153	147	0
Ipilimumab	278	145	103	90	79	68	46	42	0

Pembrolizumab
KEYTRUDA®

Courtesy of Pierre Coulie

Rarely Efficacious

Oftenly Efficacious

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Long G et al , ASCO 2021

Combining Different Immune Checkpoint Inhibitors : CM-067

	Nivo + Ipi (n = 314)	Nivo (n = 316)	Ipi (n = 315)
Median OS, mo (95% CI)	72.1 (38.2-NR)	36.9 (28.2-58.7)	19.9 (16.8-24.6)
HR (95% CI) vs Ipi	0.52 (0.43-0.64)	0.63 (0.52-0.76)	--
HR (95% CI) vs Nivo*	0.84 (0.67-1.04)	--	--

Nivo + Ipi
Nivo
Ipi

52% 50% 49%
44% 43% 42%
26% 23% 23%

OS(%)

Mo

Nivolumab OPDIVO® + **Ipilimumab** YERVOY®

BMS

tumor cell
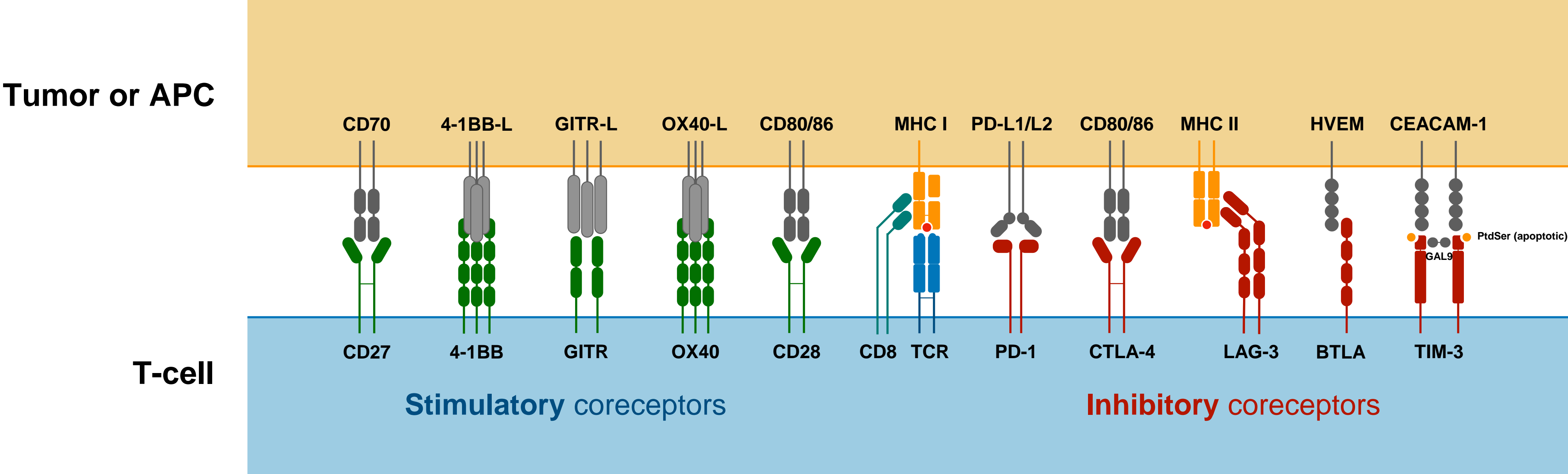
MHC I
PD-L1/L2

CD8 TCR PD-1

CD8 T cell

CD8 TCR CTLA-4

T Reg

Many candidates could be the next Generation of CPI in Immuno-Oncology

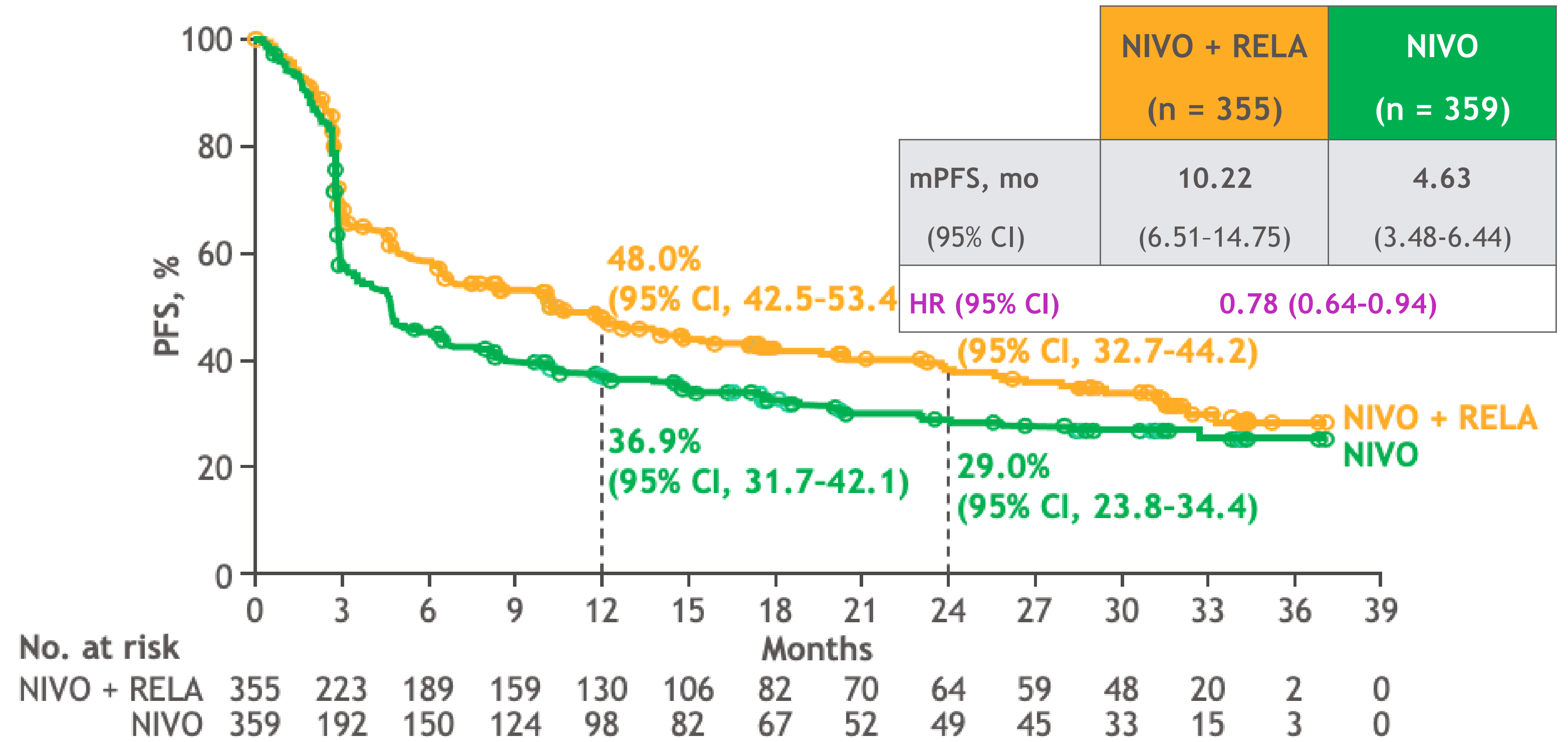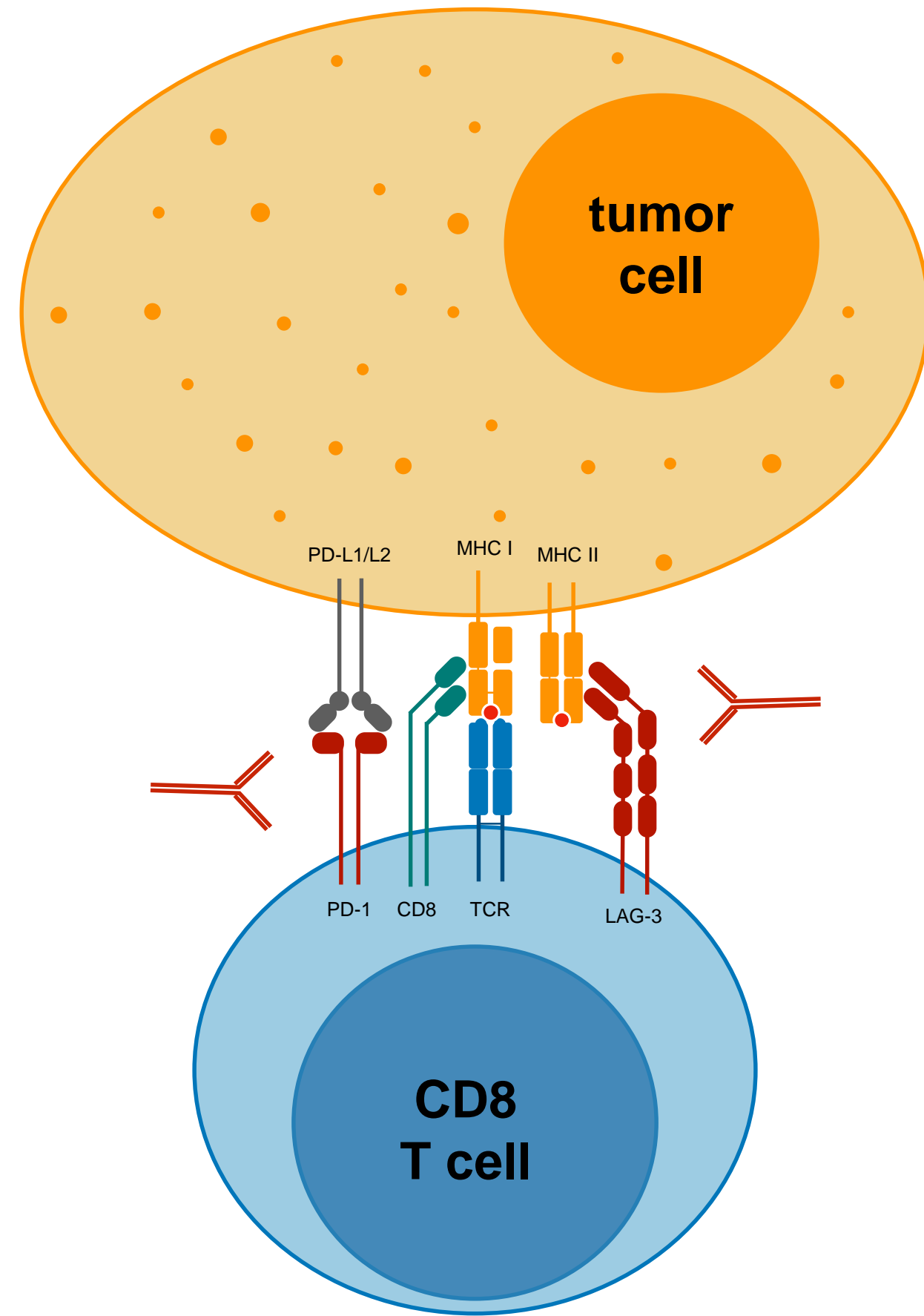## Fine tuning of T-cell Activation in time and space

Tumor or APC

CD70 4-1BB-L GITR-L OX40-L CD80/86 MHC I PD-L1/L2 CD80/86 MHC II HVEM CEACAM-1

PtdSer (apoptotic)
GAL9

T-cell

CD27 4-1BB GITR OX40 CD28 CD8 TCR PD-1 CTLA-4 LAG-3 BTLA TIM-3

Stimulatory coreceptors   **Inhibitory** coreceptors

Agonist antibodies

4-1BB : utomilumab
GITR : REGN6569
OX40 : ABVV-368

ICOS : *fefadilimab*

Antagonist antibodies

LAG-3 : relatlimab
TIGIT : tiragolumab

TIM-3 : *MGB453*

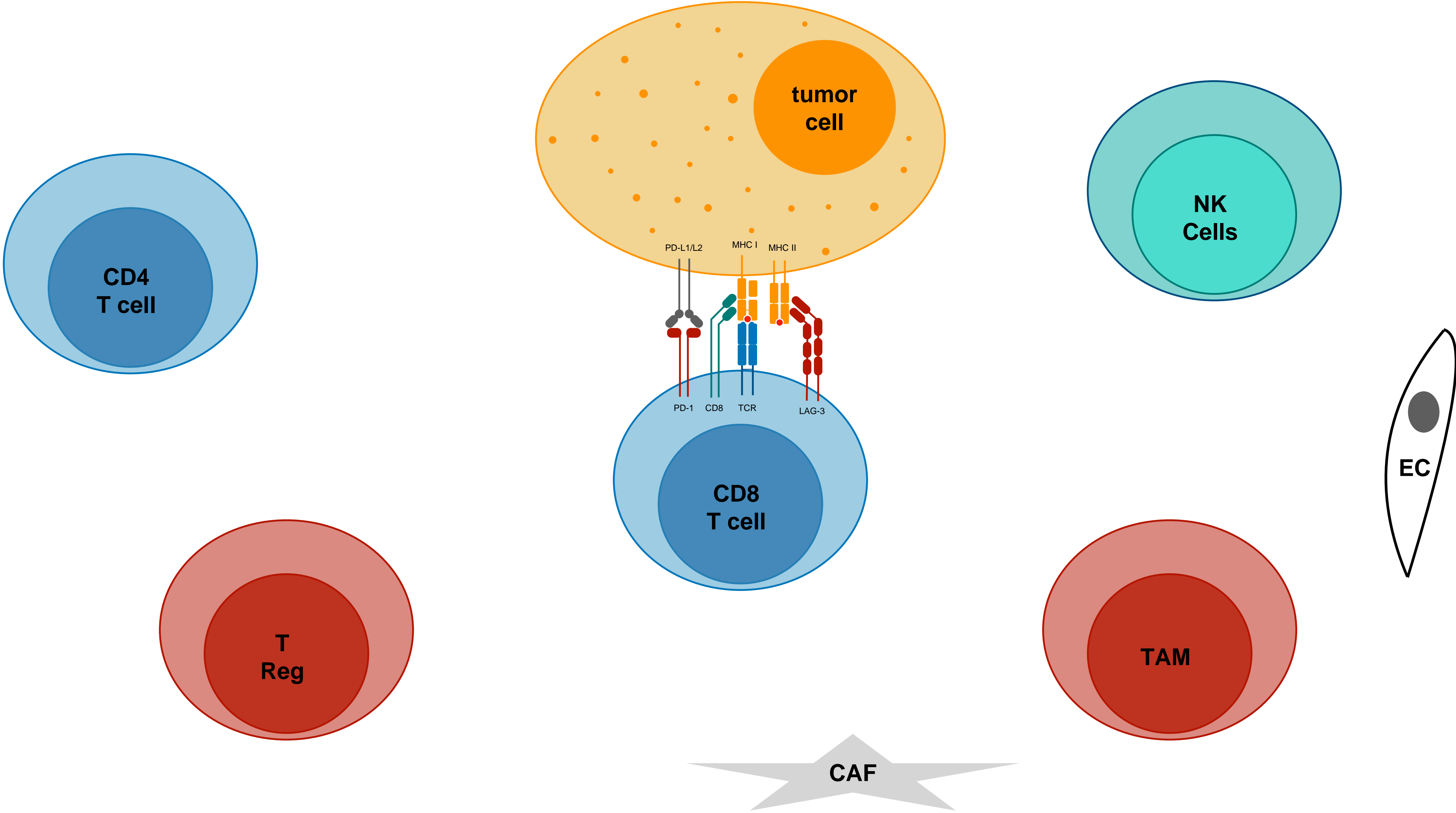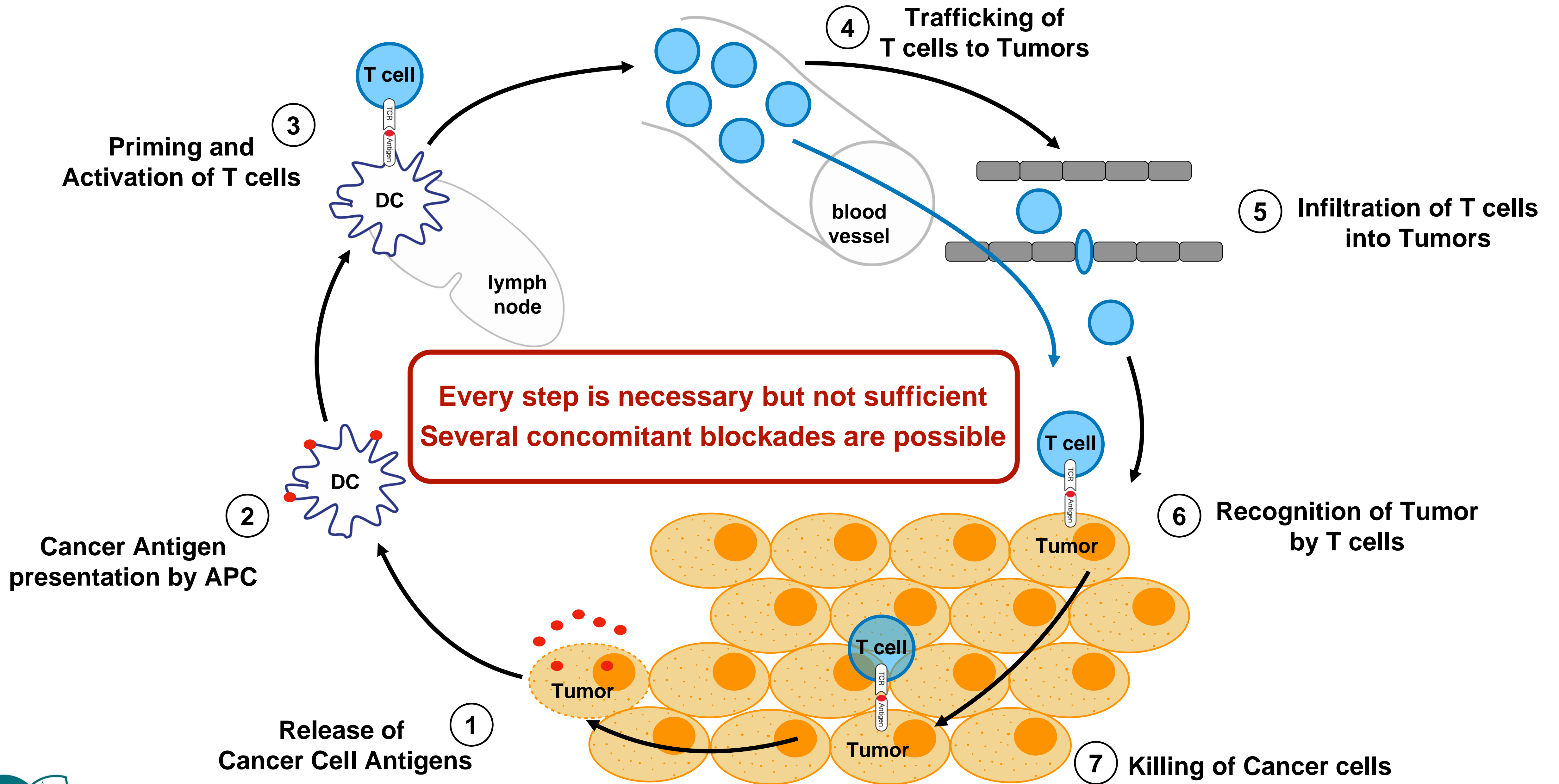# Combining Different Immune Checkpoint Inhibitors : RELA-047

	NIVO + RELA (n = 355)	NIVO (n = 359)
mPFS, mo (95% CI)	10.22 (6.51-14.75)	4.63 (3.48-6.44)
HR (95% CI)	0.78 (0.64-0.94)	

48.0% (95% CI, 42.5-53.4)

(95% CI, 32.7-44.2)

36.9% (95% CI, 31.7-42.1)

29.0% (95% CI, 23.8-34.4)

NIVO + RELA
NIVO

PFS, %

Months

No. at risk													
NIVO + RELA	355	223	189	159	130	106	82	70	64	59	48	20	2	0
NIVO	359	192	150	124	98	82	67	52	49	45	33	15	3	0

Nivolumab + Relatlimab
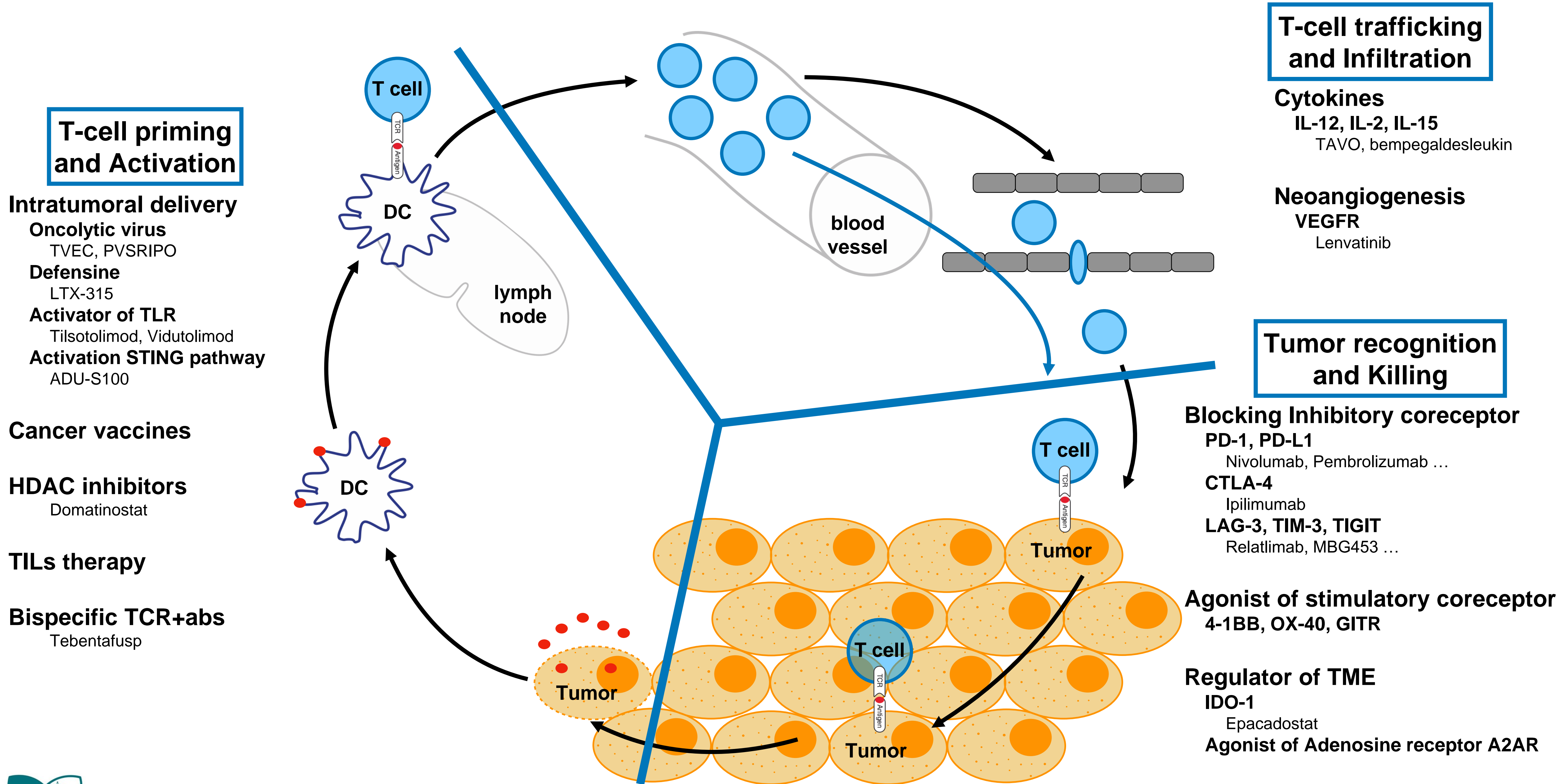
Opdualac®

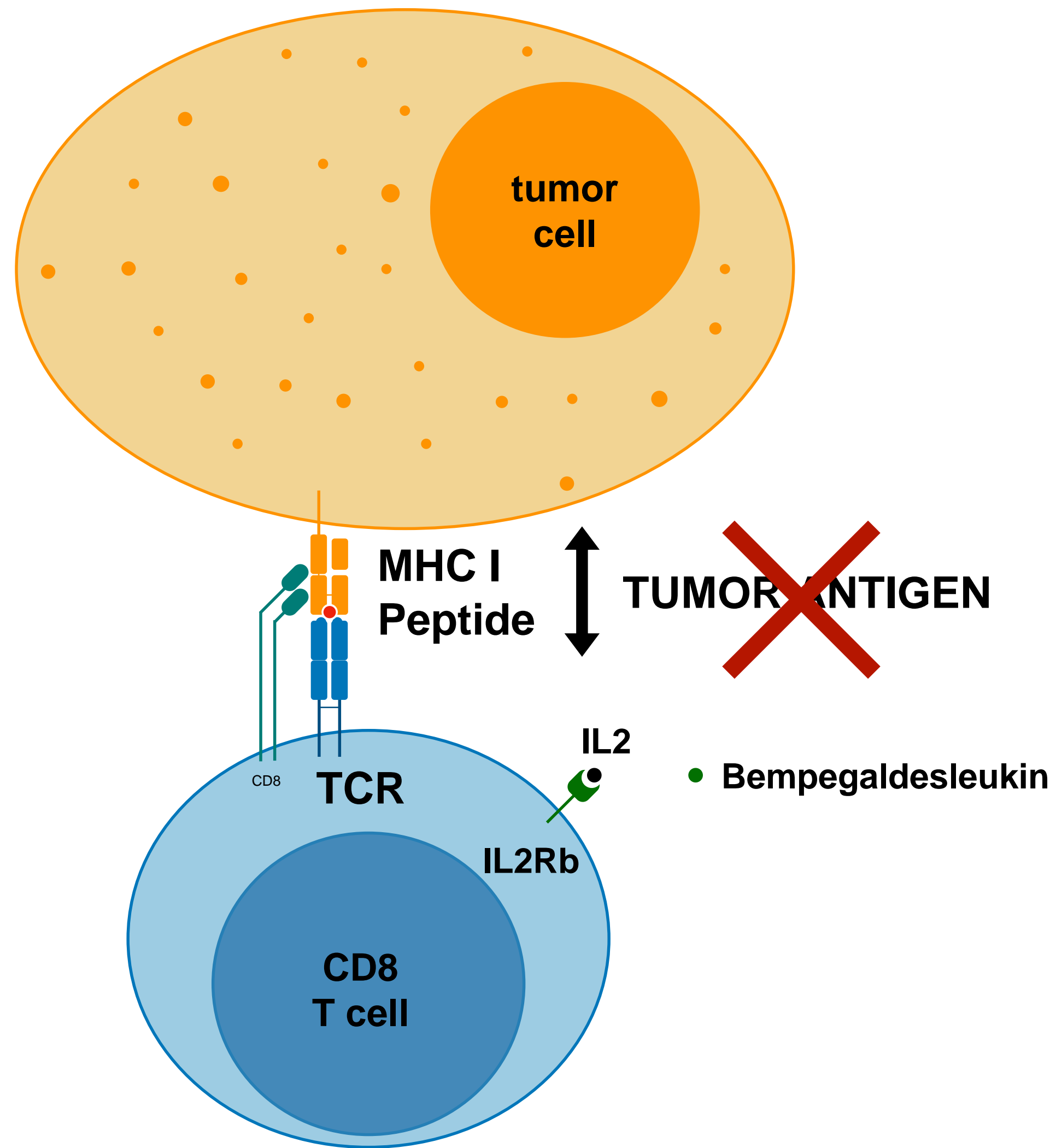BMS

Tawbi.H. et al , ASCO 2022

More Complex than just a T cell and a Tumor

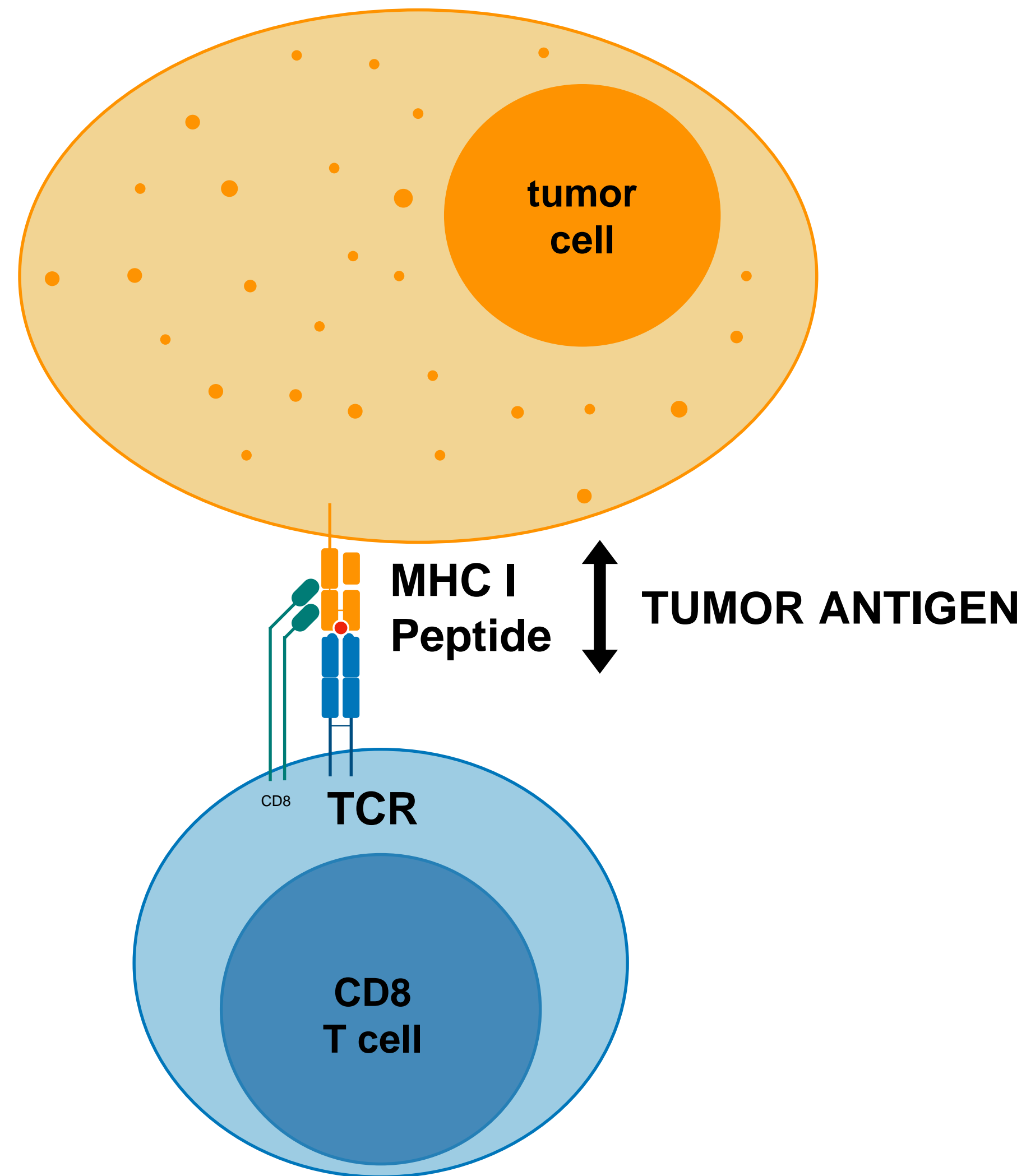# Immunologists have organized it with the help of the Cancer-Immunity Cycle

Trafficking of T cells to Tumors (4)

Priming and Activation of T cells (3)

T cell

DC

lymph node

blood vessel

Infiltration of T cells into Tumors (5)

Every step is necessary but not sufficient
Several concomitant blockades are possible

DC

Cancer Antigen presentation by APC (2)

T cell

Tumor

Recognition of Tumor by T cells (6)

T cell

Tumor

Tumor

Release of Cancer Cell Antigens (1)

Killing of Cancer cells (7)

Beyond CPI : Therapeutics in development based on T-cell infiltration in tumors

T cell

T-cell trafficking and Infiltration

Cytokines
IL-12, IL-2, IL-15
TAVO, bempegaldesleukin

Neoangiogenesis
VEGFR
Lenvatinib

T-cell priming and Activation

Intratumoral delivery
Oncolytic virus
TVEC, PVSRIPO
Defensine
LTX-315
Activator of TLR
Tilsotolimod, Vidutolimod
Activation STING pathway
ADU-S100

Cancer vaccines

HDAC inhibitors
Domatinostat

TILs therapy

Bispecific TCR+abs
Tebentafusp

DC

T cell
TCR
Antigen

lymph node

blood vessel

DC

Tumor recognition and Killing

Blocking Inhibitory coreceptor
PD-1, PD-L1
Nivolumab, Pembrolizumab …
CTLA-4
Ipilimumab
LAG-3, TIM-3, TIGIT
Relatlimab, MBG453 …

T cell
TCR
Antigen
Tumor

Agonist of stimulatory coreceptor
4-1BB, OX-40, GITR

T cell
TCR
Antigen

Regulator of TME
IDO-1
Epacadostat
Agonist of Adenosine receptor A2AR

Tumor

Tumor

Beyond CPI : T-cell Priming and Activation

Beyond CPI : T-cell Priming and Activation

tumor cell

MHC I
Peptide

TUMOR ANTIGEN

CD8

TCR

CD8 T cell

NO T CELLS

1- Making *in vivo* T cells
- Vaccine
- Intra-tumoral
- ? Radiotherapy

2- Injecting T cells
- TILs
- Tebentafusp

Phase III study - TILs in second-line metastatic melanoma patients
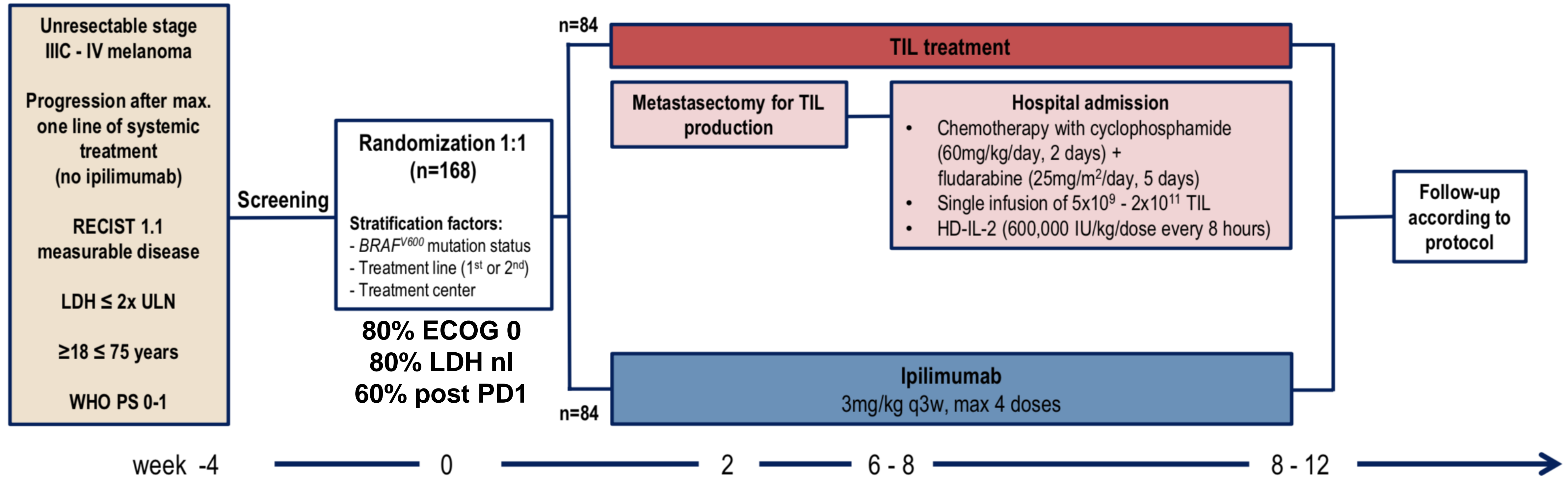
Primary endpoint: Progression-free survival (PFS) according to RECIST 1.1 per investigator review in the intention-to-treat population (ITT)*

*Using the stratified (unweighted) log-rank test and the stratified cox regression model. The study was considered to be positive when PFS after TIL is significantly longer than ipilimumab, based on the log-rank test with a two-sided p-value below 0.05.

Phase III study - TILs increases PFS and ORR comparing to Ipilimumab
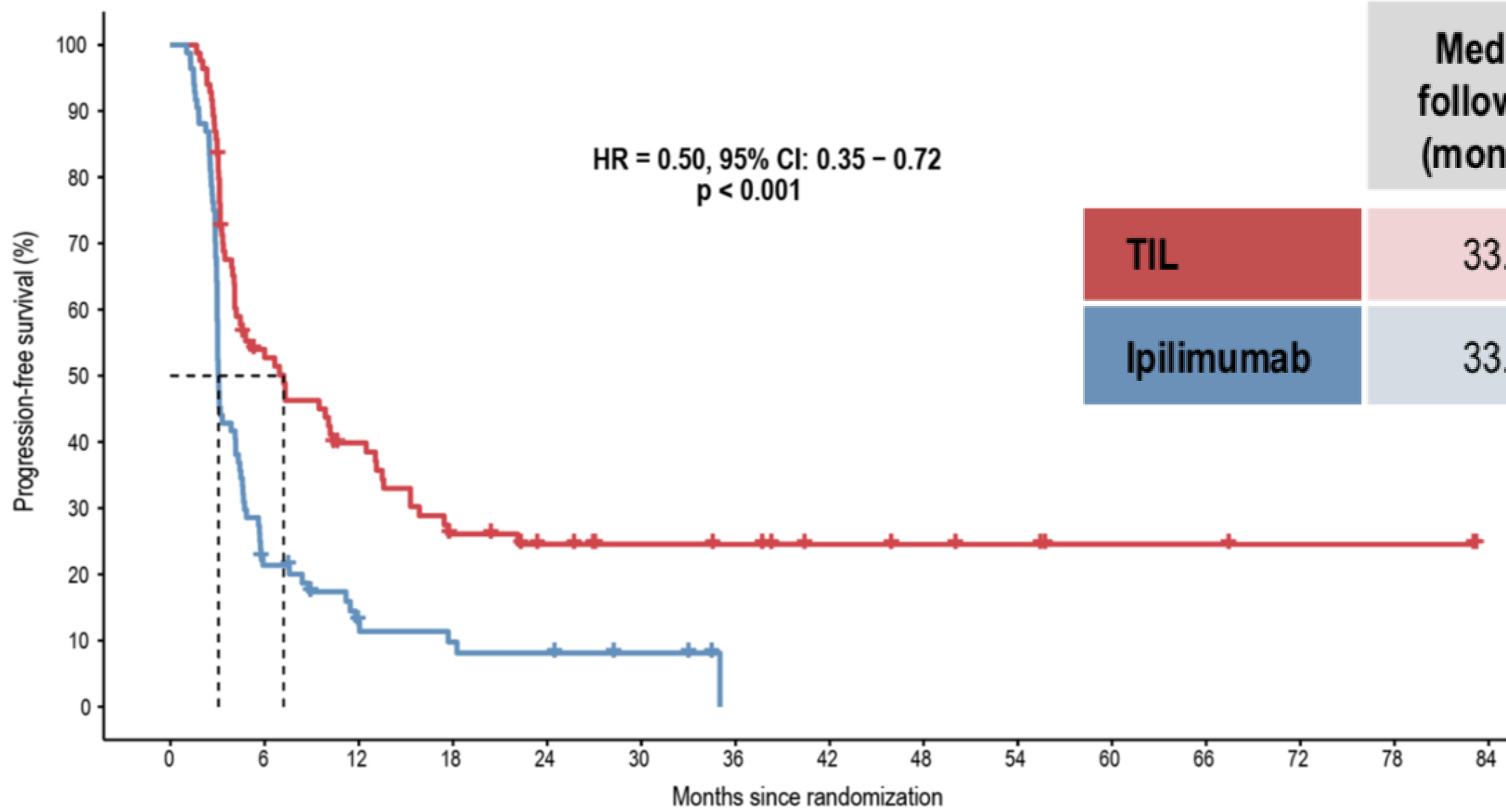
	Median follow-up (months)	Median PFS (months)	95% CI
TIL	33.5	7.2	4.2 - 13.1
Ipilimumab	33.0	3.1	3.0 - 4.3

HR = 0.50, 95% CI: 0.35 − 0.72
p < 0.001

Best overall response	TIL (n=84) n (%)	Ipilimumab (n=84) n (%)
Complete response	17 (20.2)	6 (7.1)
Partial response	24 (28.6)	12 (14.3)
Stable disease	16 (19.1)	15 (17.9)
Progressive disease	24 (28.6)	40 (47.6)
Not evaluable/done[#]	3 (3.6)	11 (13.1)
Overall response[†]	41 (48.8)	18 (21.4)
Clinical benefit[‡]	57 (67.9)	33 (39.3)

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Haanen J. et al , ESMO 2022

Phase III study - TILs in second-line metastatic melanoma patients

NCI Trial with TILs
Median PFS < 1year

PFS
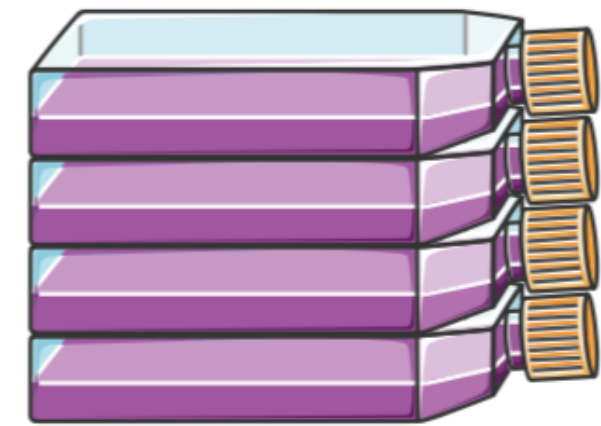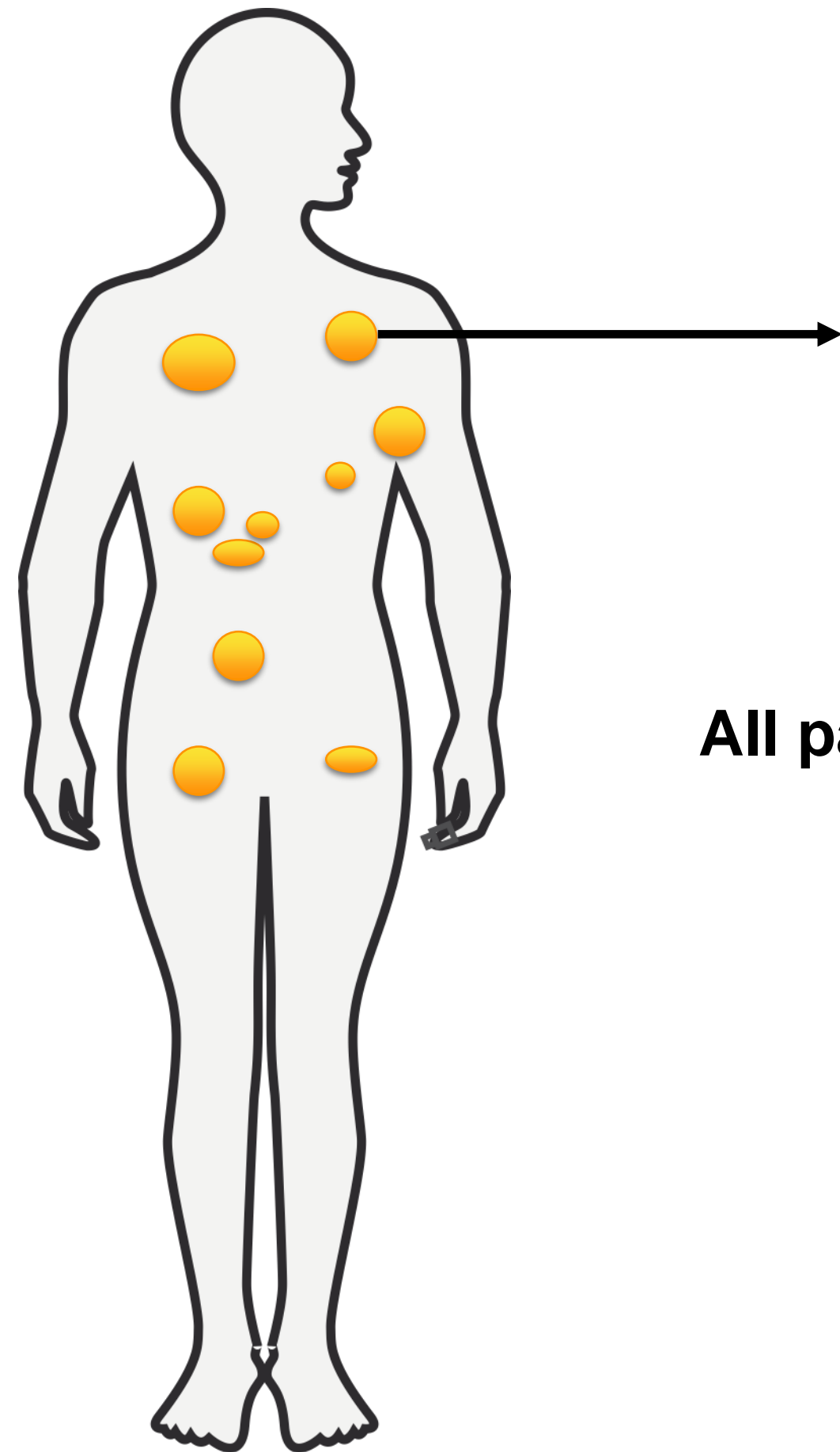
Take Time

All patients had grade 3/4 AE

High dose IL2
270 patients (US-UK)
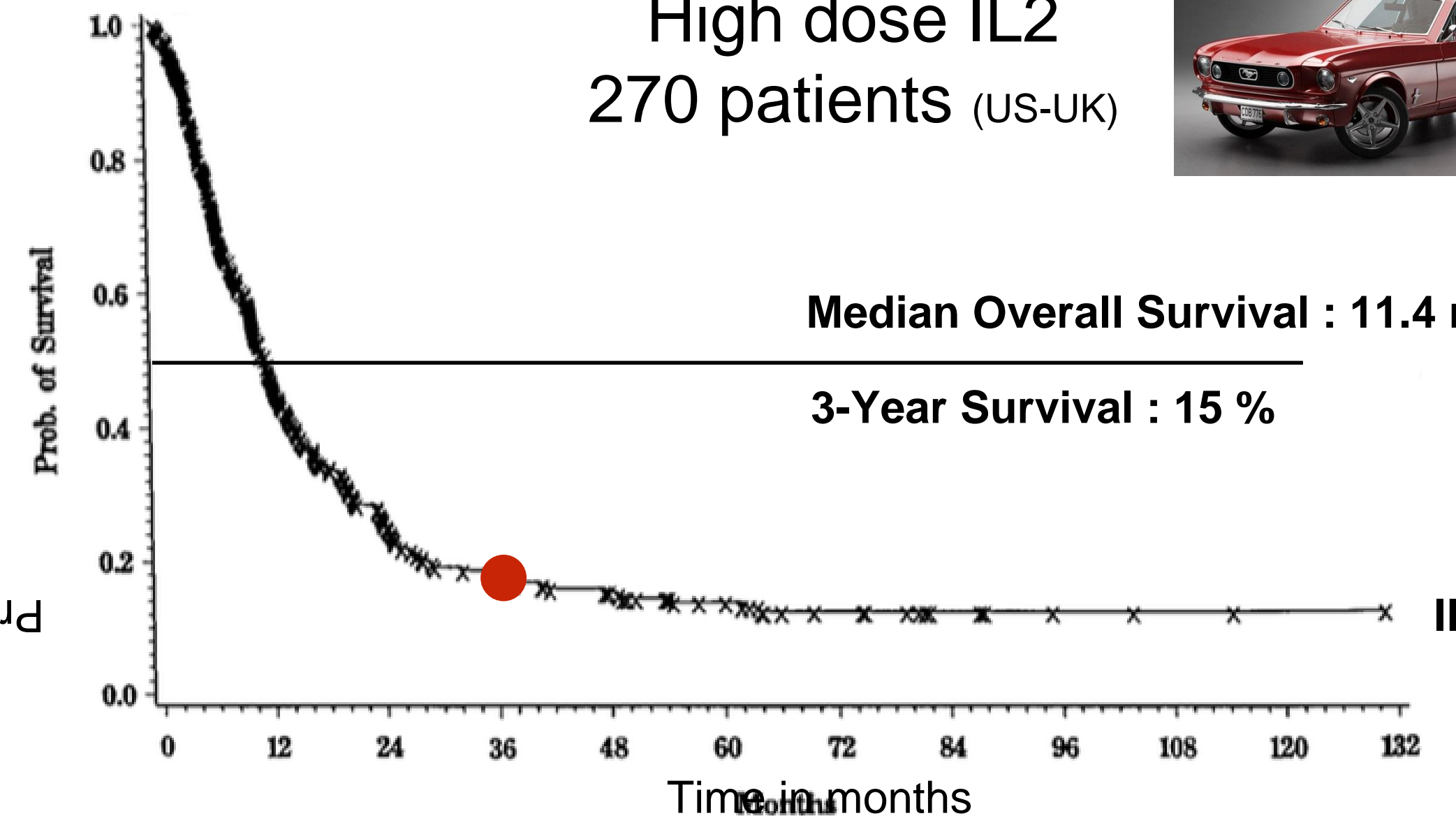
Median Overall Survival : 11.4 months

3-Year Survival : 15 %

NKI Trial with TILs
Median OS : 25.8 mos
Immature data

Proportion of patients alive

IL-2

Time in months

Rosenberg S. Et al, 1996; Atkins et al JCO 1999

Tebentafusp : a bispecific soluble TCR + anti-CD3
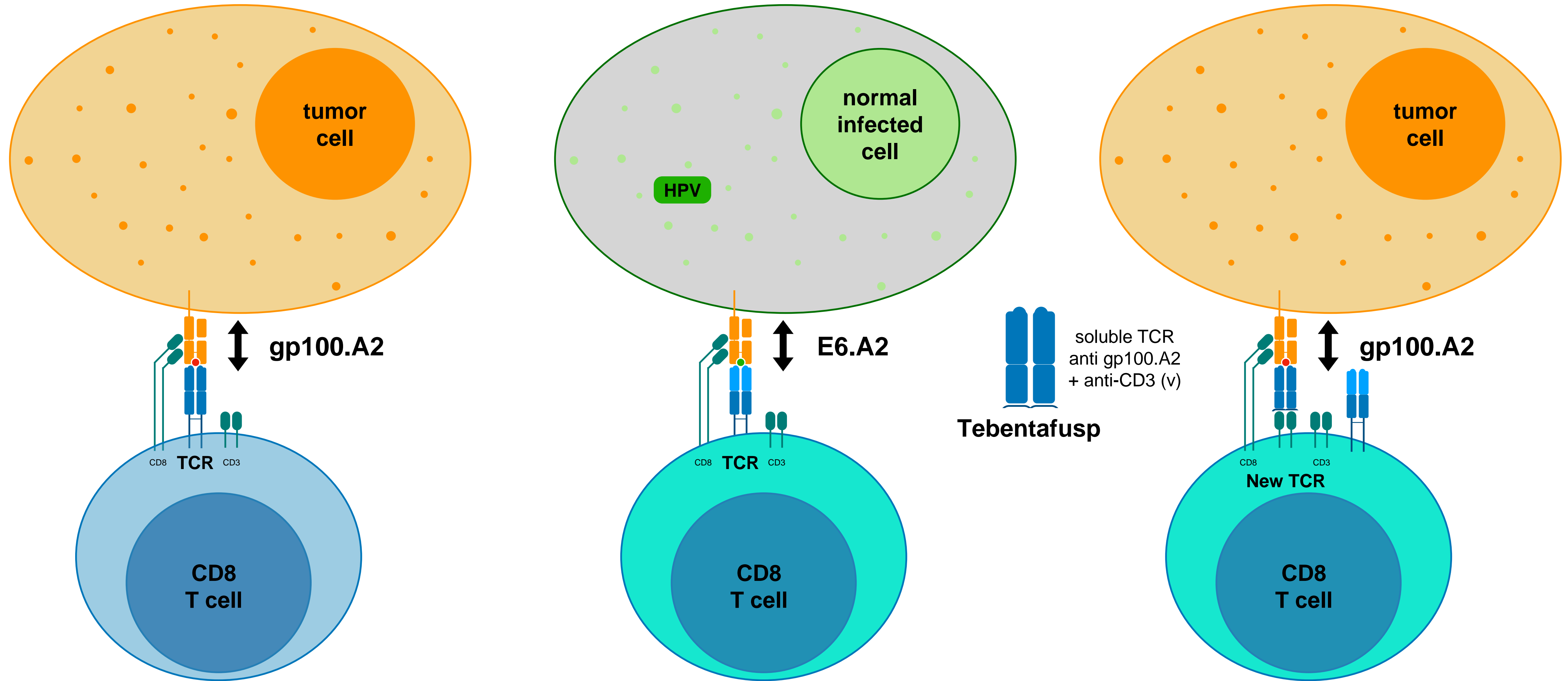
IMC202 : Phase III with Tebentafusp in metastatic uveal melanoma

Median Overall Survival (95% CI)

mo
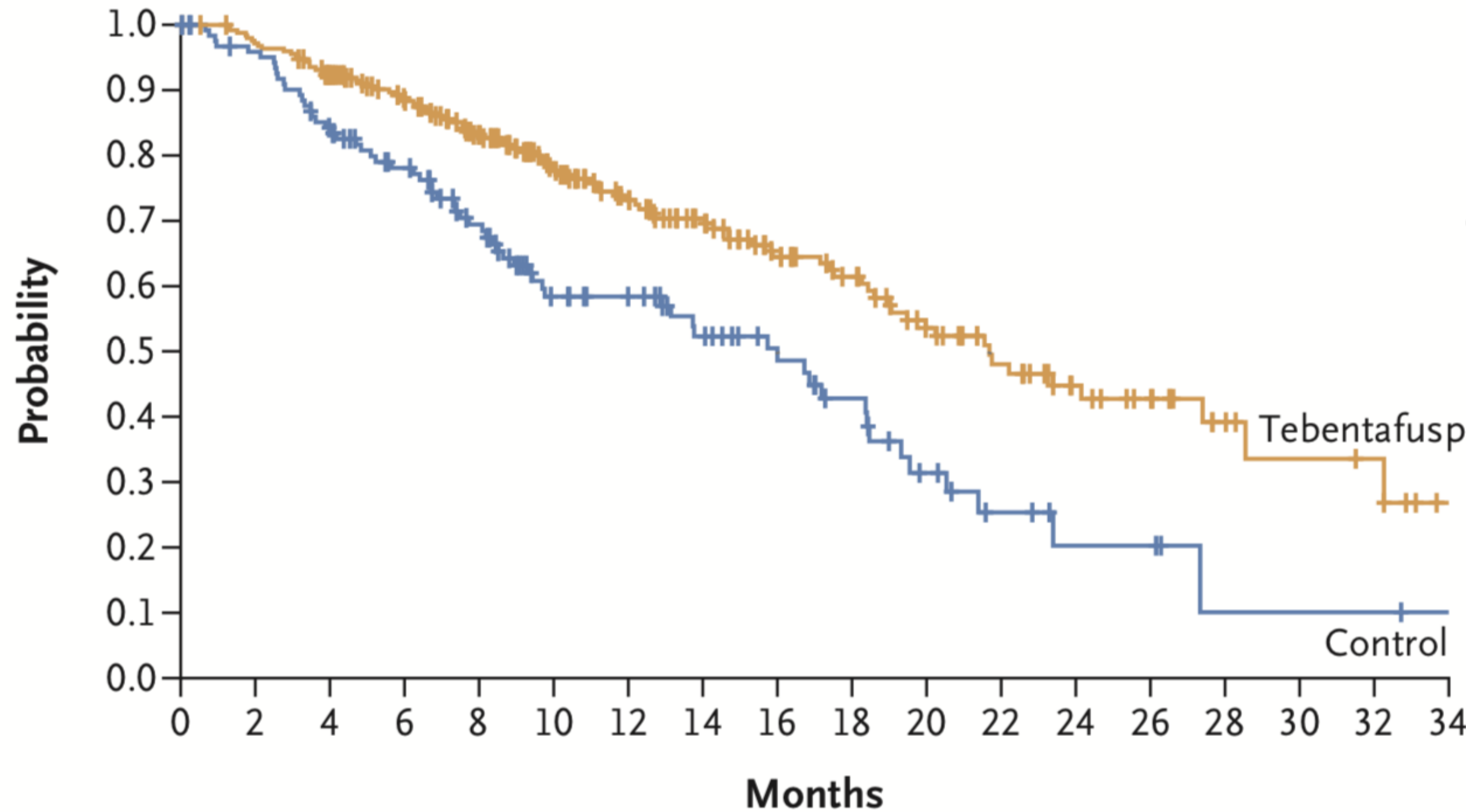
	Median OS
Tebentafusp	21.7 (18.6–28.6)
Control	16.0 (9.7–18.4)

Stratified hazard ratio for death, 0.51 (95% CI, 0.37–0.71)

Median FUP = 14.1 mos

No. at Risk

	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34
Tebentafusp	252	242	221	197	167	132	109	90	71	59	44	33	22	17	9	6	5	0
Control	126	116	100	86	69	48	43	34	27	20	12	7	4	4	1	1	1	0

Beyond CPI : T-cell Trafficking and Infiltration
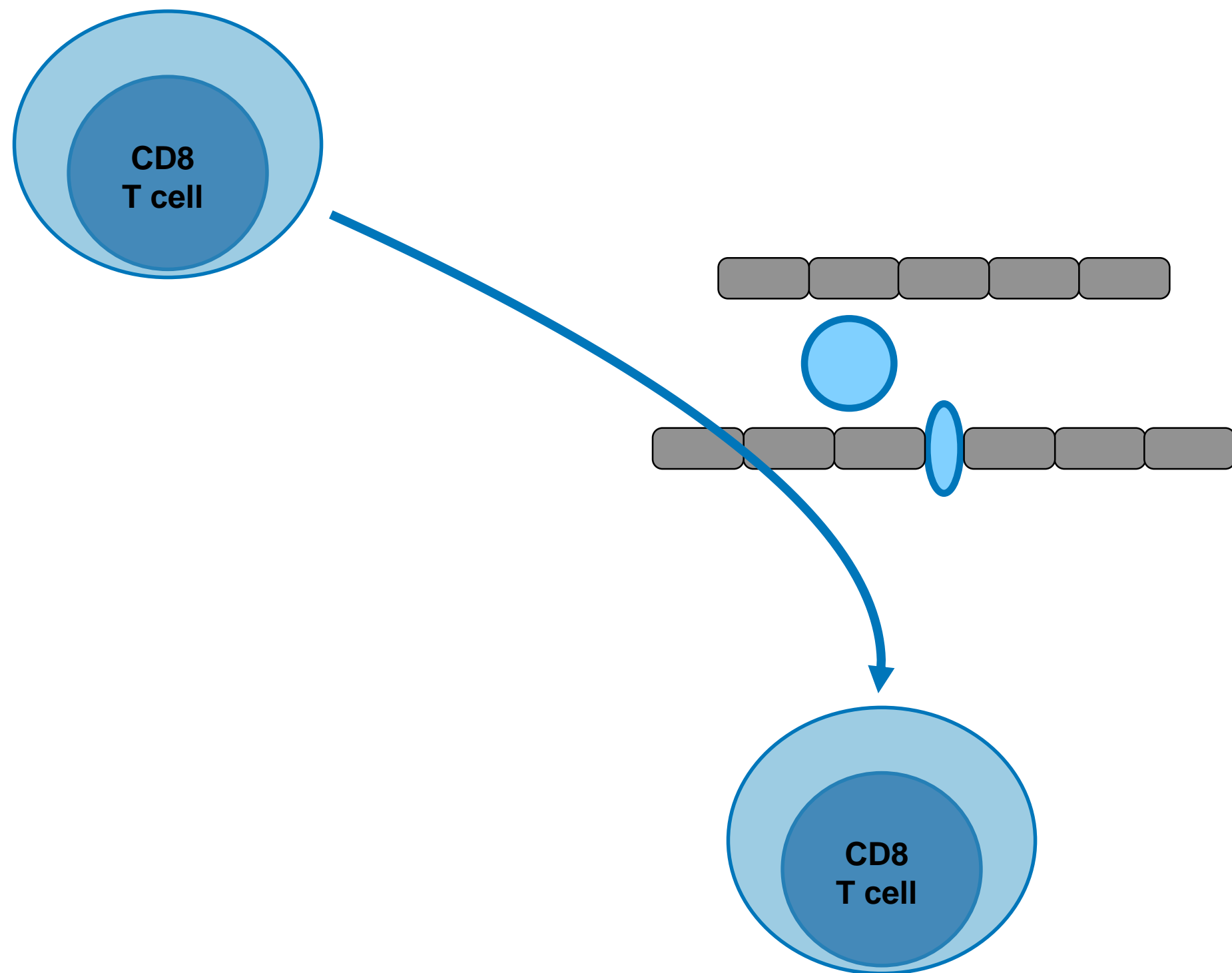
Lenvatinib is a multikinase inhibitor blocking i.e. VEGFR

KN-775 : OS at 1-y md FUP (Endometrial Cancer)
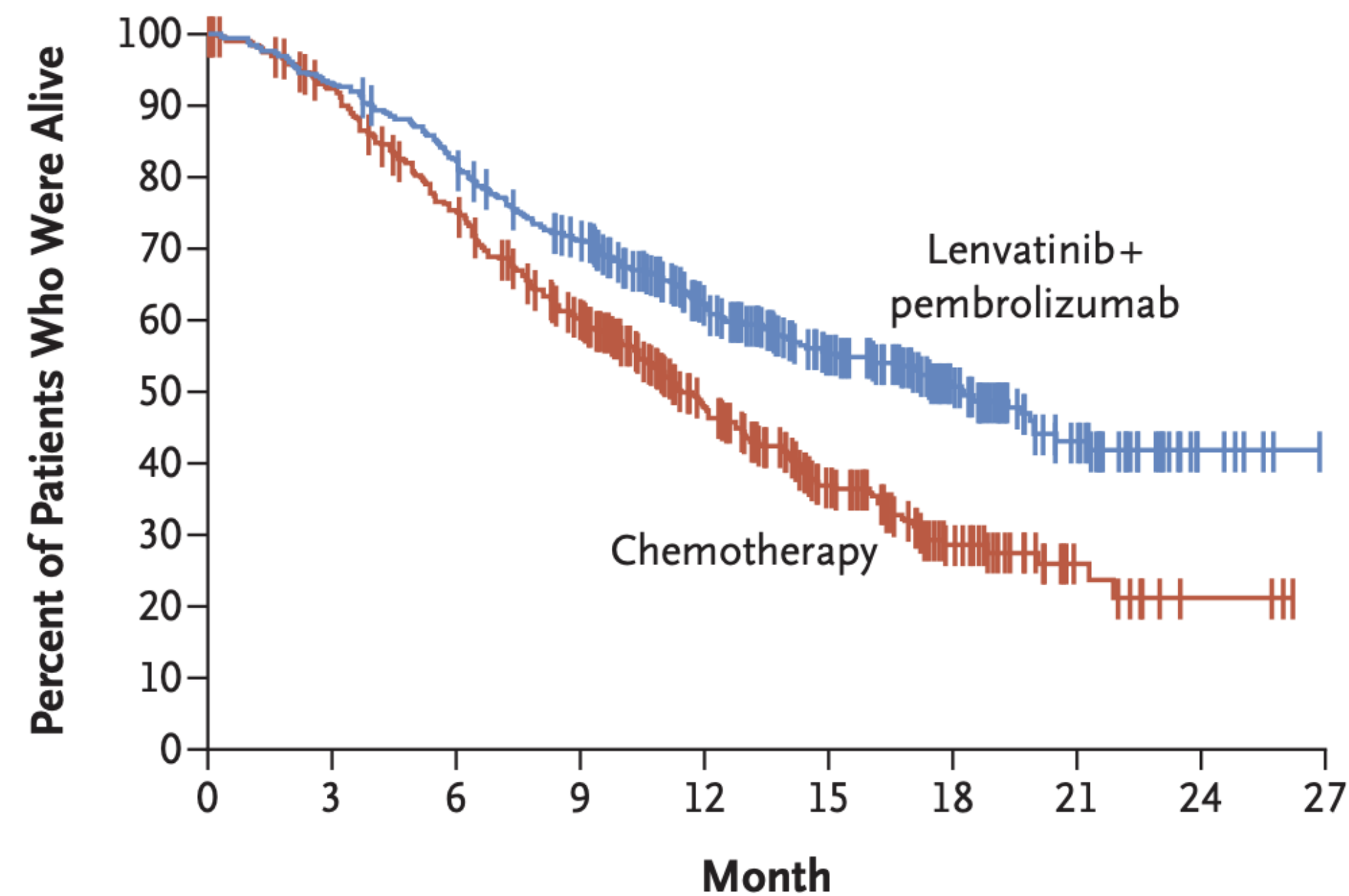
	Median Overall Survival (95% CI) *mo*
Lenvatinib+ Pembrolizumab	18.3 (15.2–20.5)
Chemotherapy	11.4 (10.5–12.9)

Hazard ratio for death,
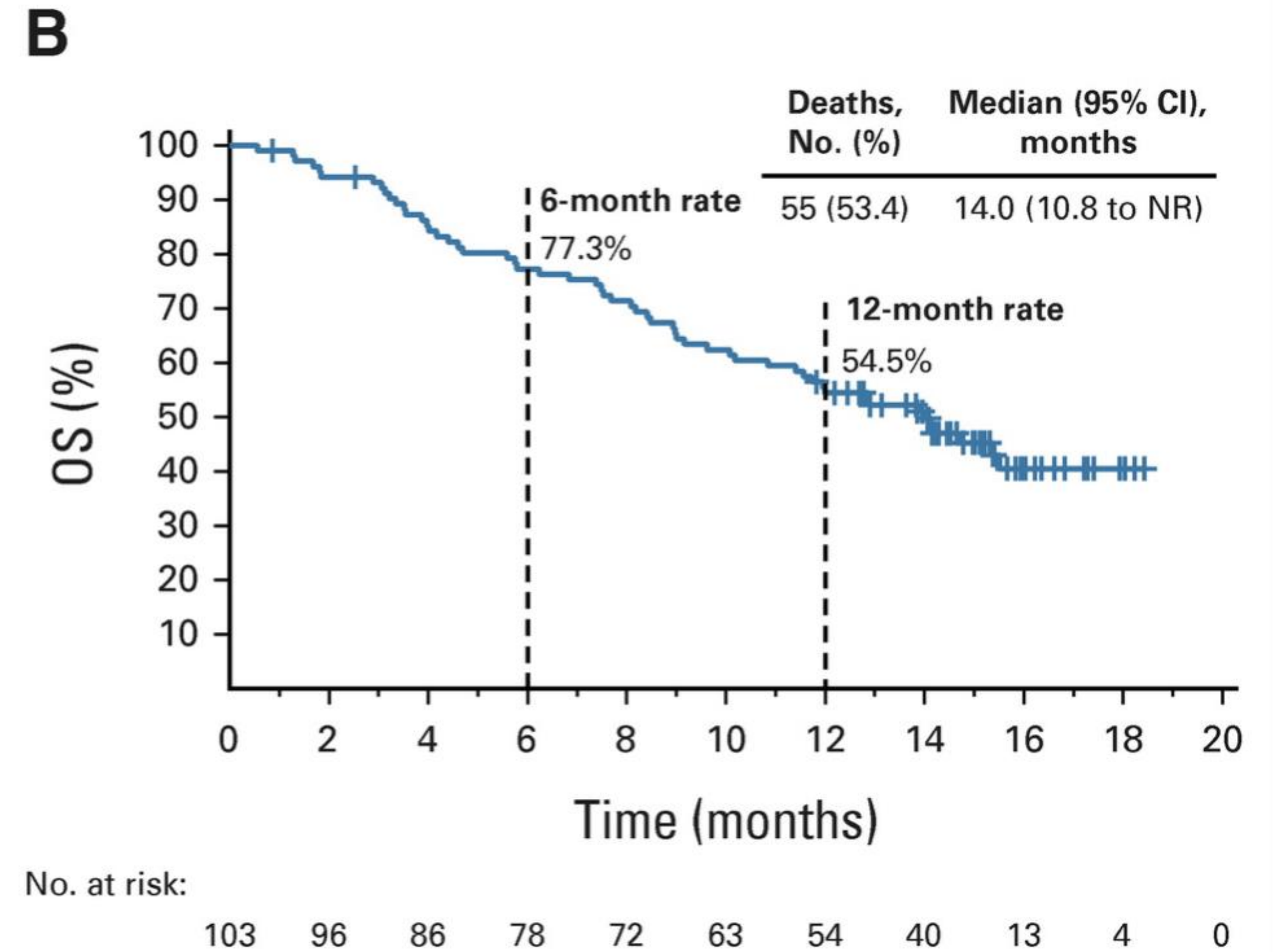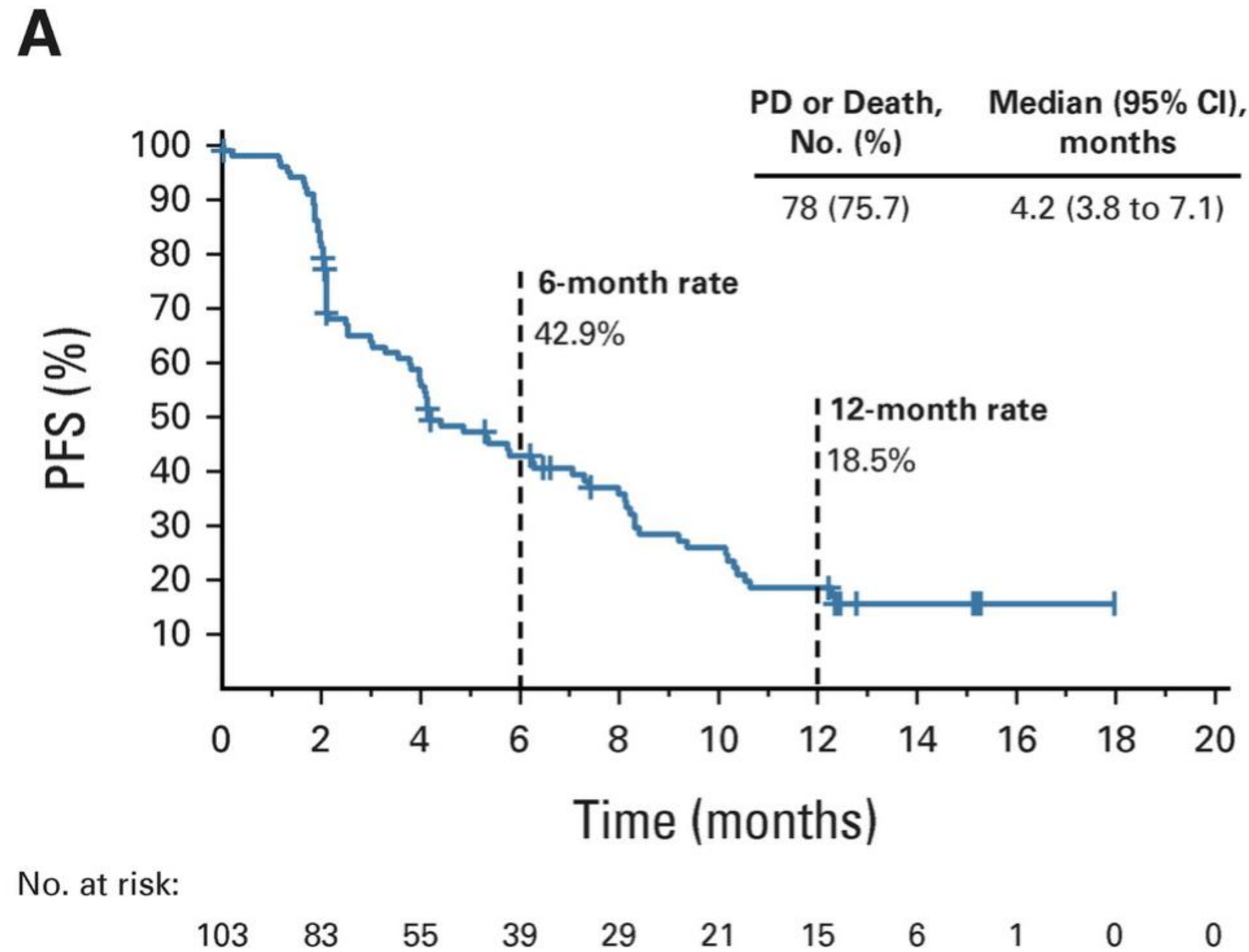0.62 (95% CI, 0.51–0.75)
P<0.001

ORR : 30% vs 15%

No. at Risk

	0	3	6	9	12	15	18	21	24	27
Lenvatinib+pembrolizumab	411	383	337	282	198	136	81	40	7	0
Chemotherapy	416	373	300	228	138	80	40	11	3	0

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Makker V. et al , NEJM 2022

Phase II: LEAP-004 Study with Pembrolizumab + Lenvatinib in second-line melanoma

EFFICACY

	NKI-TILs	LEAP-004
ORR	49%	21%
PFS md	7.2 mos	4.2 mos
OS md	25.8 mos	14.0 mos

PATIENTS CHARACTERISTICS

	NKI-TILs	LEAP-004
ECOG 0	80%	60%
LDH nl	80%	45%
Post PD1	60%	82%

Beyond CPI : T-cell Recognition and Killing
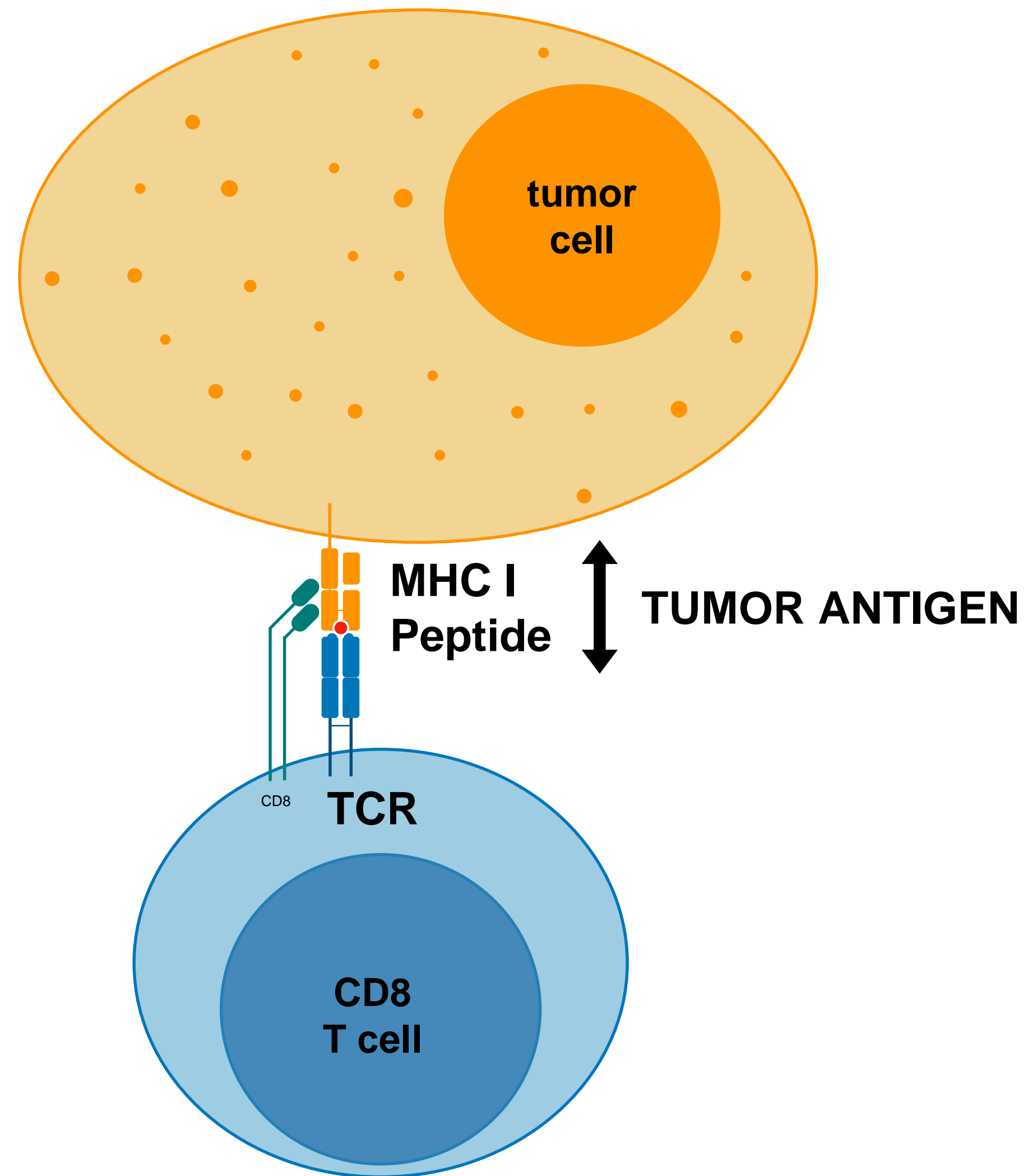
Regulator of the TME

- IDO1
- TGFb/GARP
- A2AR

tumor
cell

MHC I
Peptide

TUMOR ANTIGEN

CD8

TCR

CD8
T cell

Blocking the Adenosine Pathway
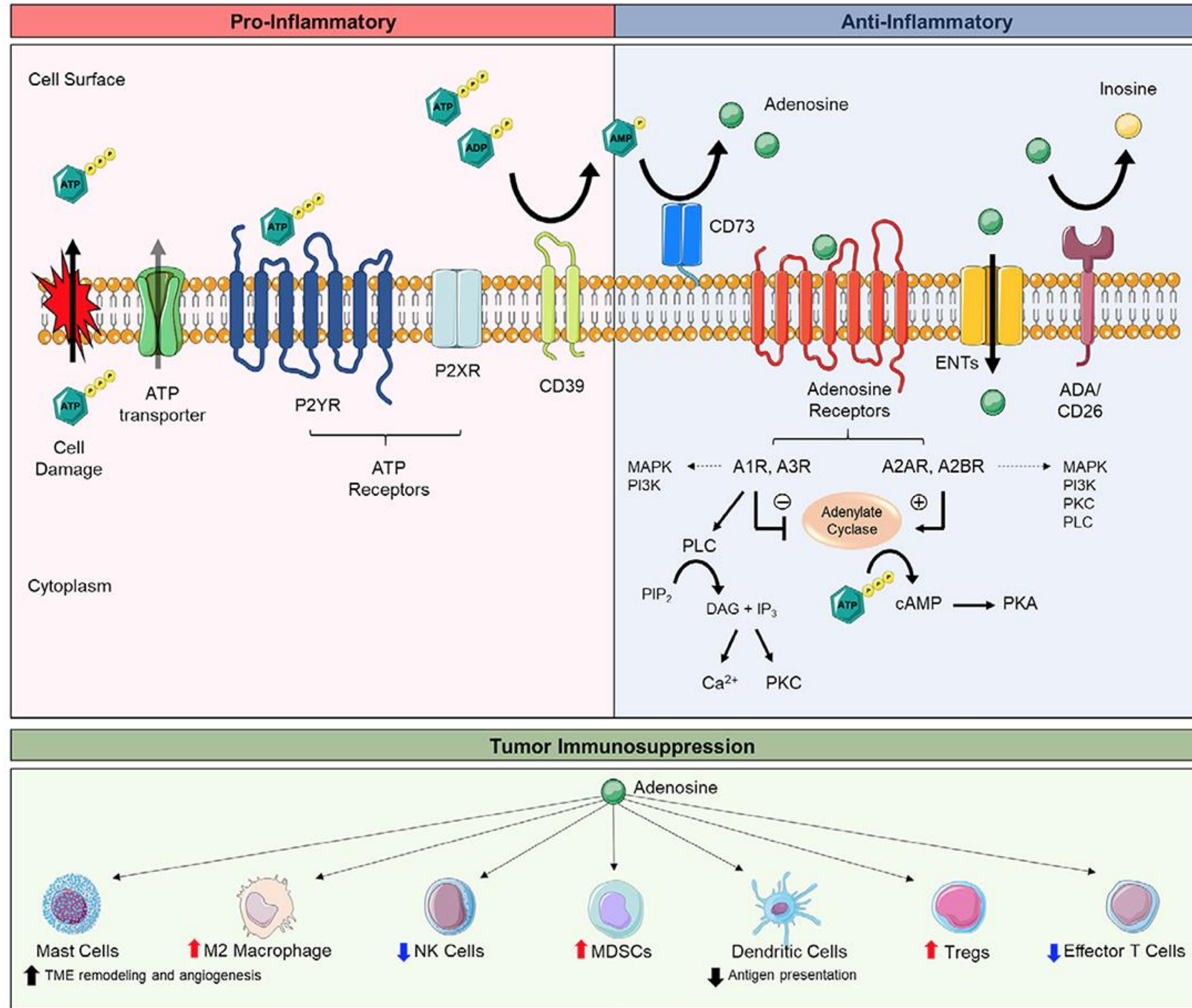
Antagonist A2AR

Ciforadenant (CPI-444)
Taminadenant (NIR-178)
Imaradenant (AZD4635)
Inupadenant (EOS-850)

Antagonist A2AR-A2BR

Etrumadenant (AB928)
INCB106385

Anti-CD73
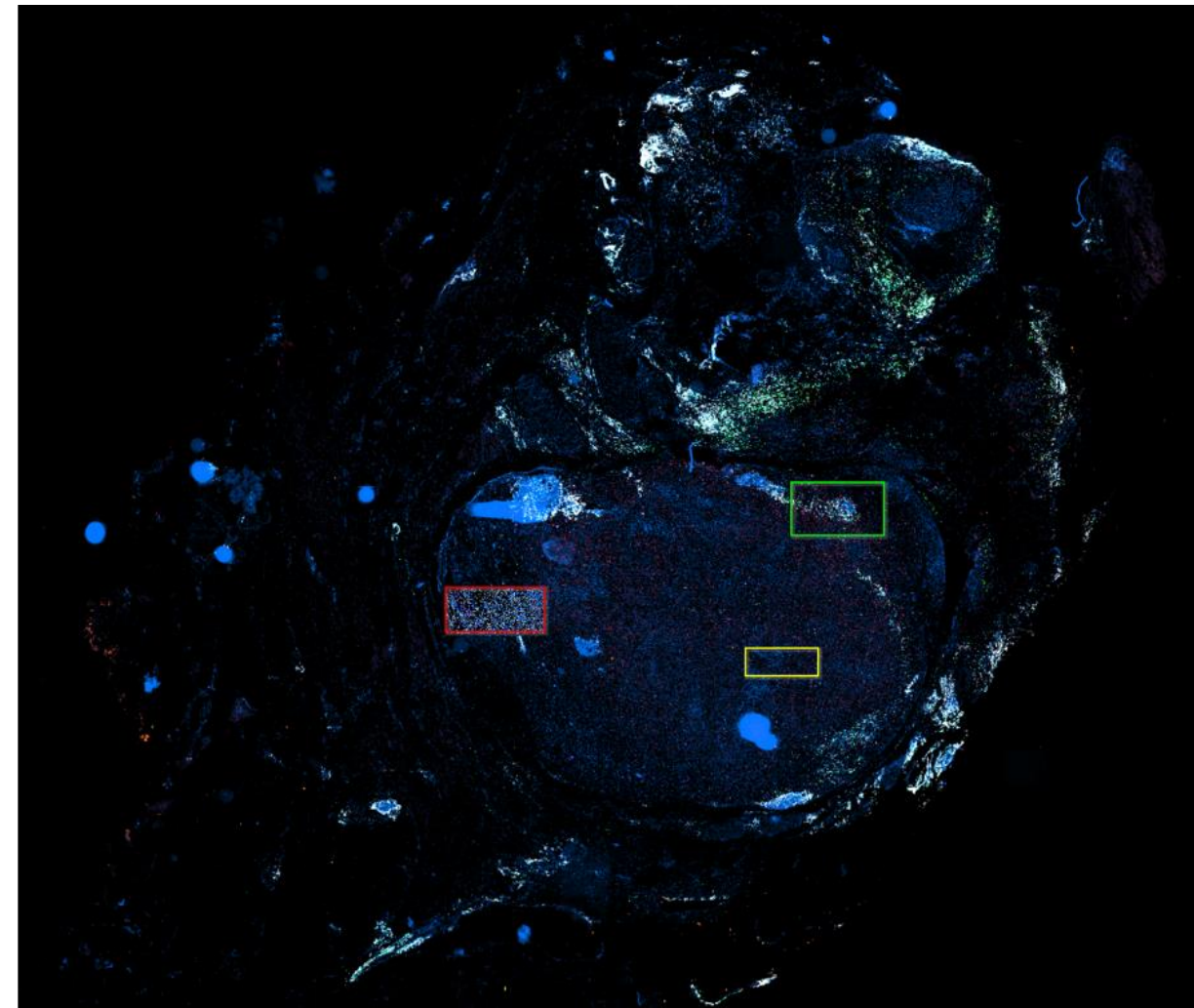
AB680
INCA00186

We were lucky with anti-PD1 and Melanoma
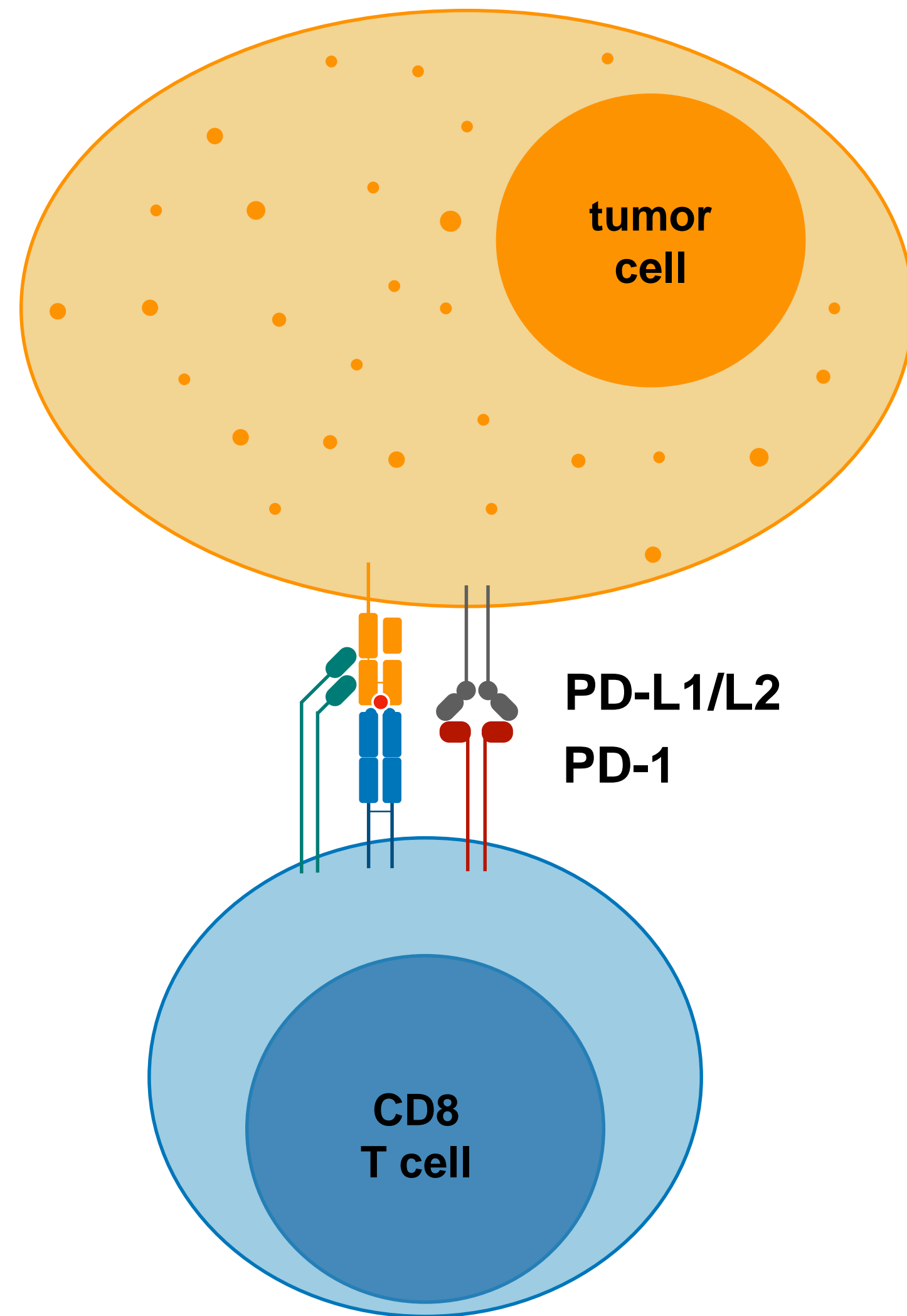
Biomarkers for Responses

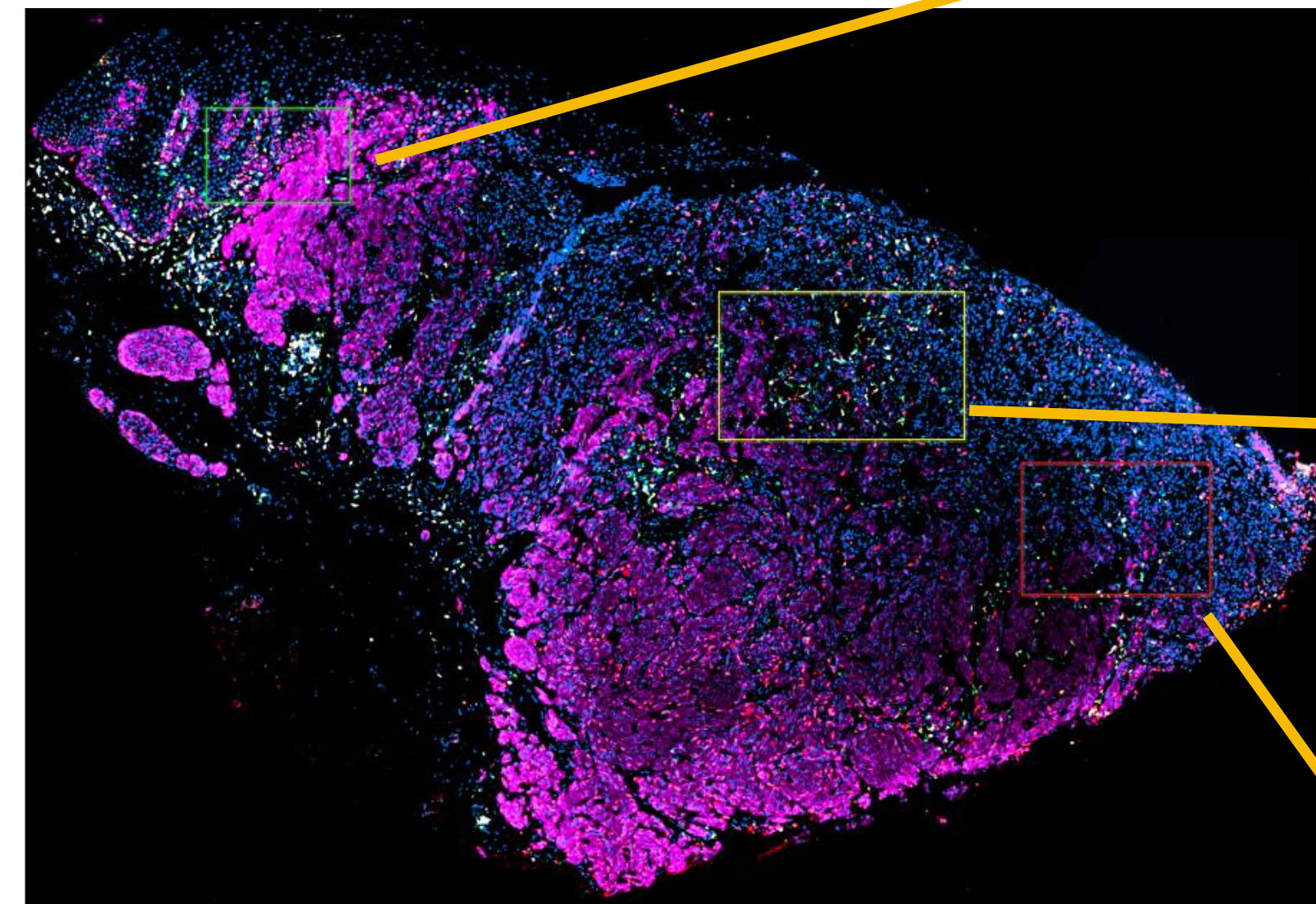- PD-L1
- TMB
- IFNg signature
- ctDNA
- …

Long G., ESMO 2022
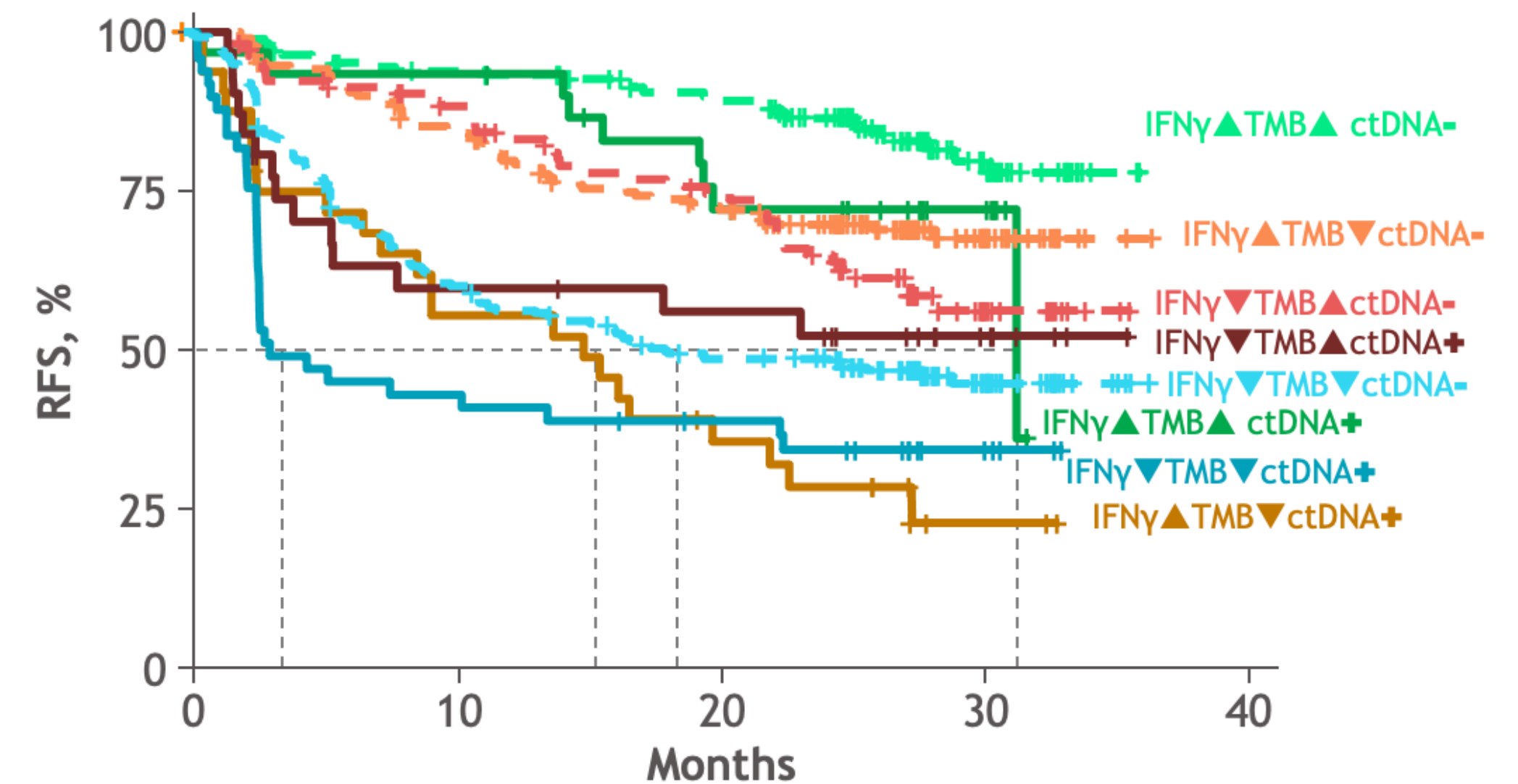
Tumour Heterogenity i.e. Immune Infiltration

Patient 1
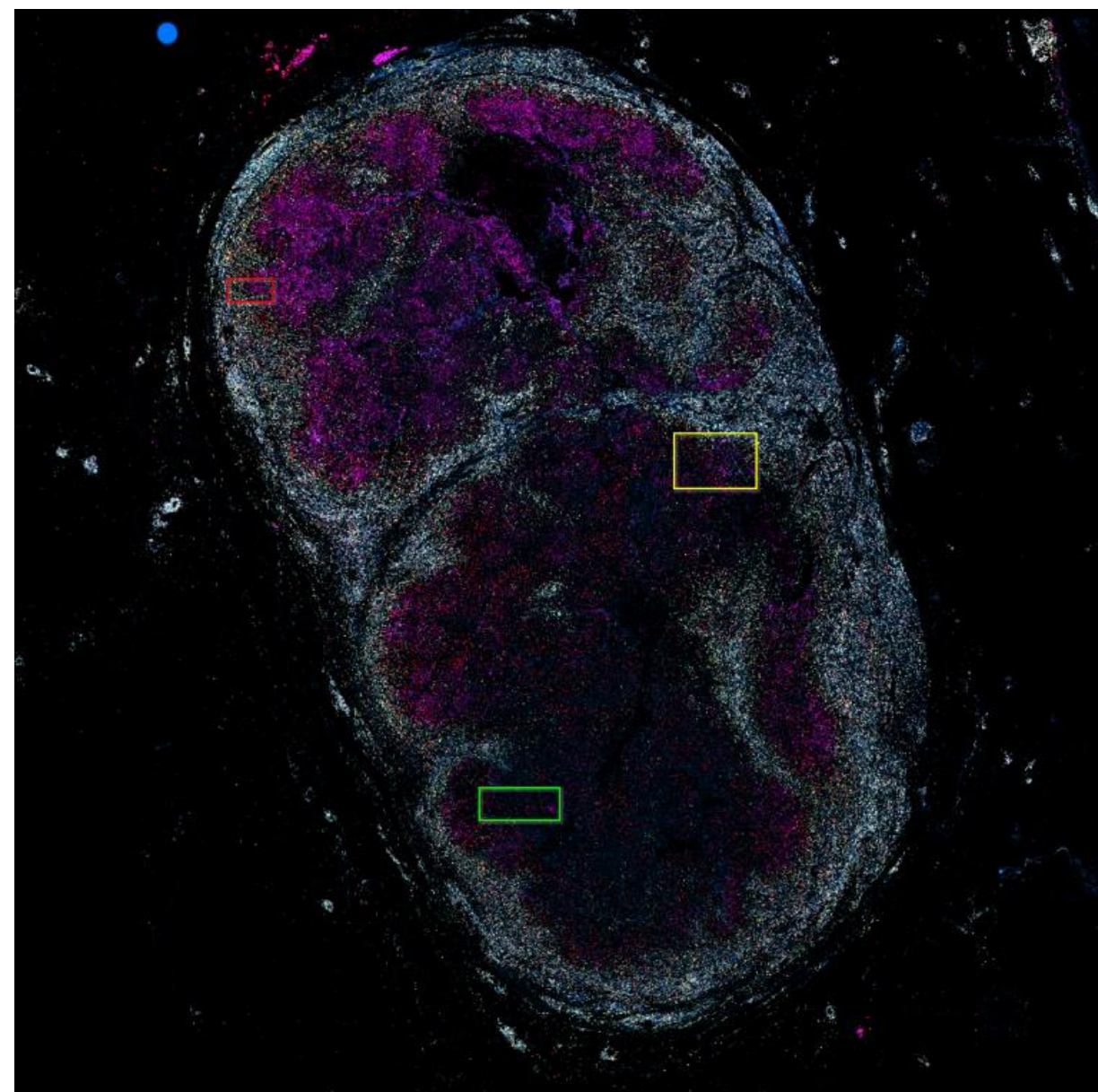
Patient 2

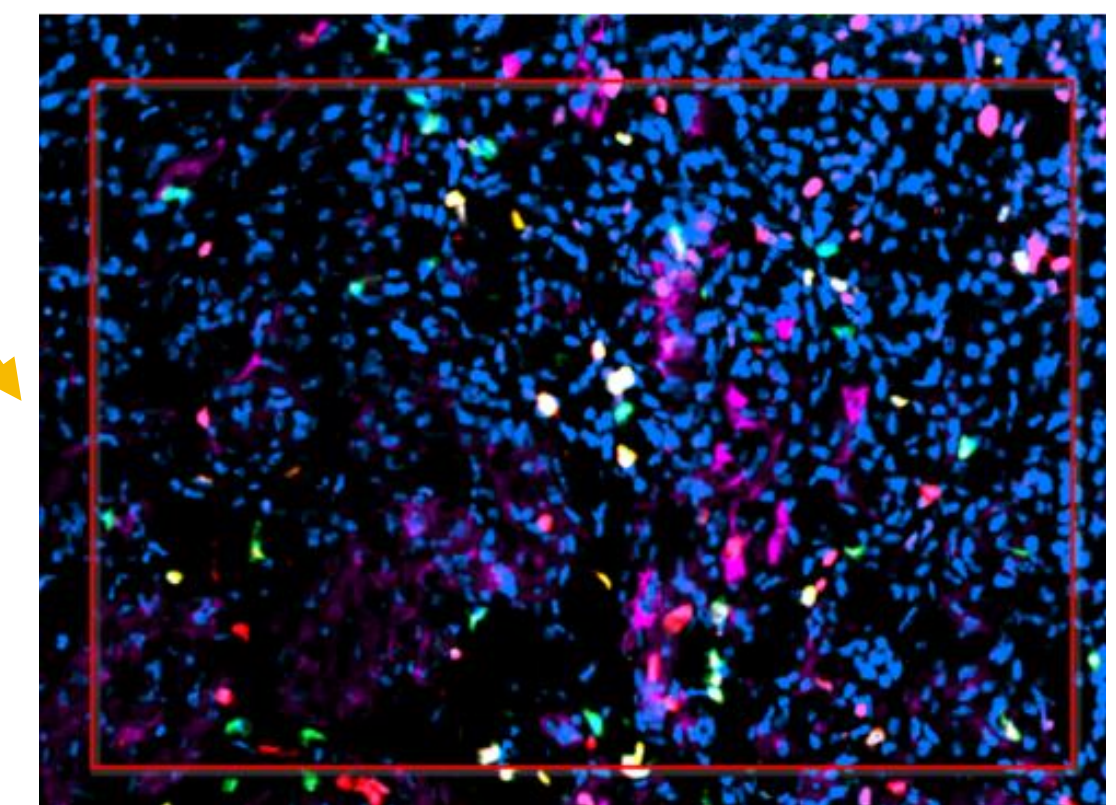Patient 3
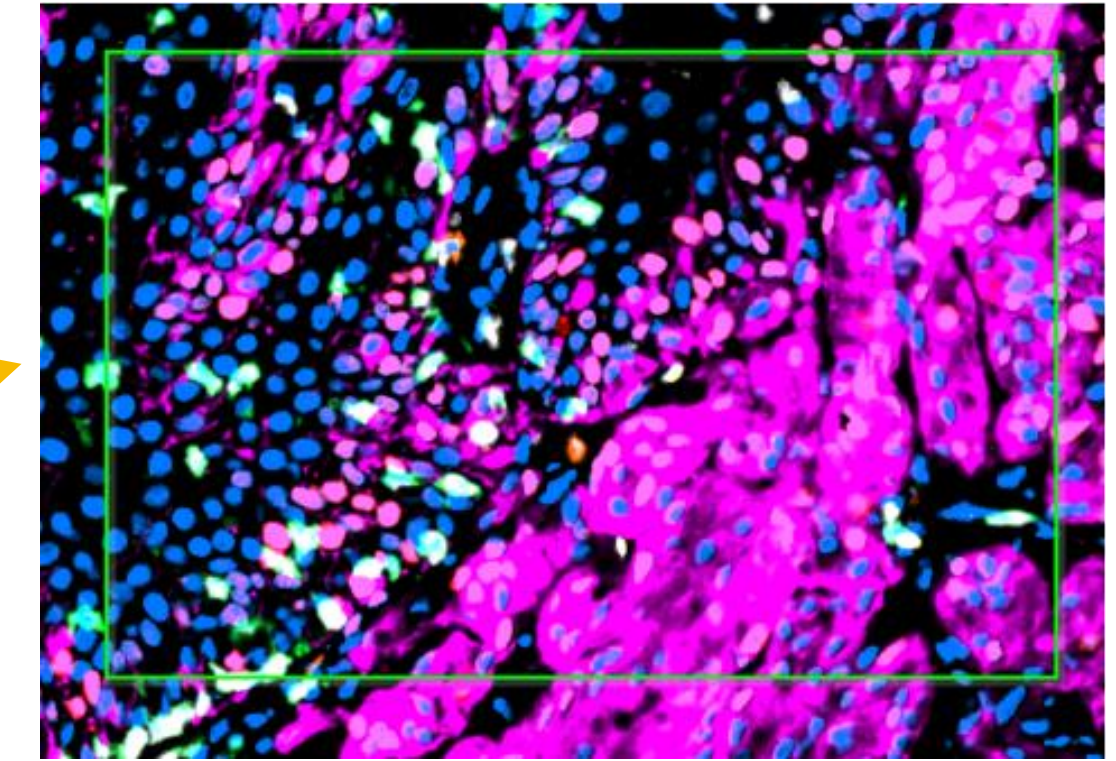
Zone 1
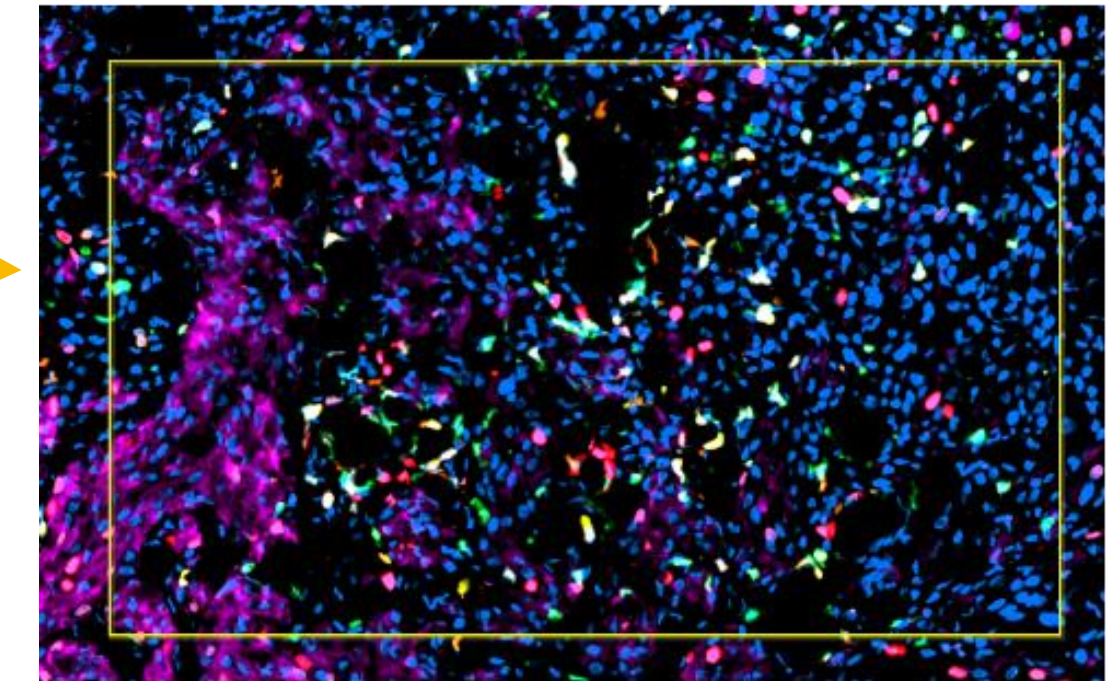
Zone 2

Zone 3

Legend

Nkp46 FoxP3 CD8 CD3 Ki67 PanMel Nuclei

Maestre F. & Baurain JF, unpublished data 2022

Take Home Messages

More questions than answers

Prime Time

- **Nivolumab + Ipilimumab**
- **Nivolumab + Relatlimab**
- **Tebentafusp**
- **Pembrolizumab + Lenvatinib**

To Follow

- **TILs**

To Do

Tailored analysis of tumors for personalized Immunotherapy