

# **Emerging role of immunotherapy in lung cancer**

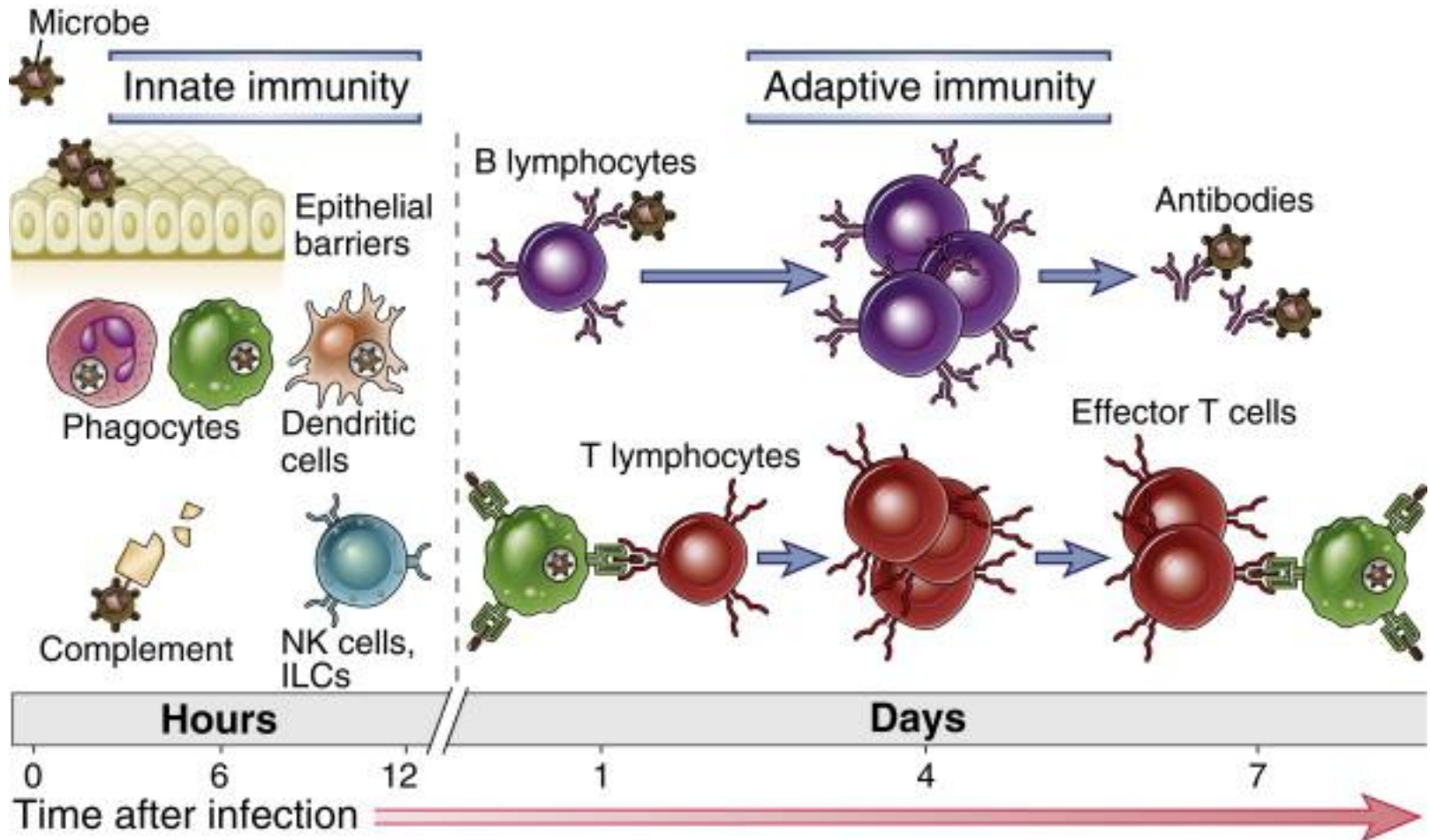
대구가톨릭의대 호흡기내과  
정치영

# Contents

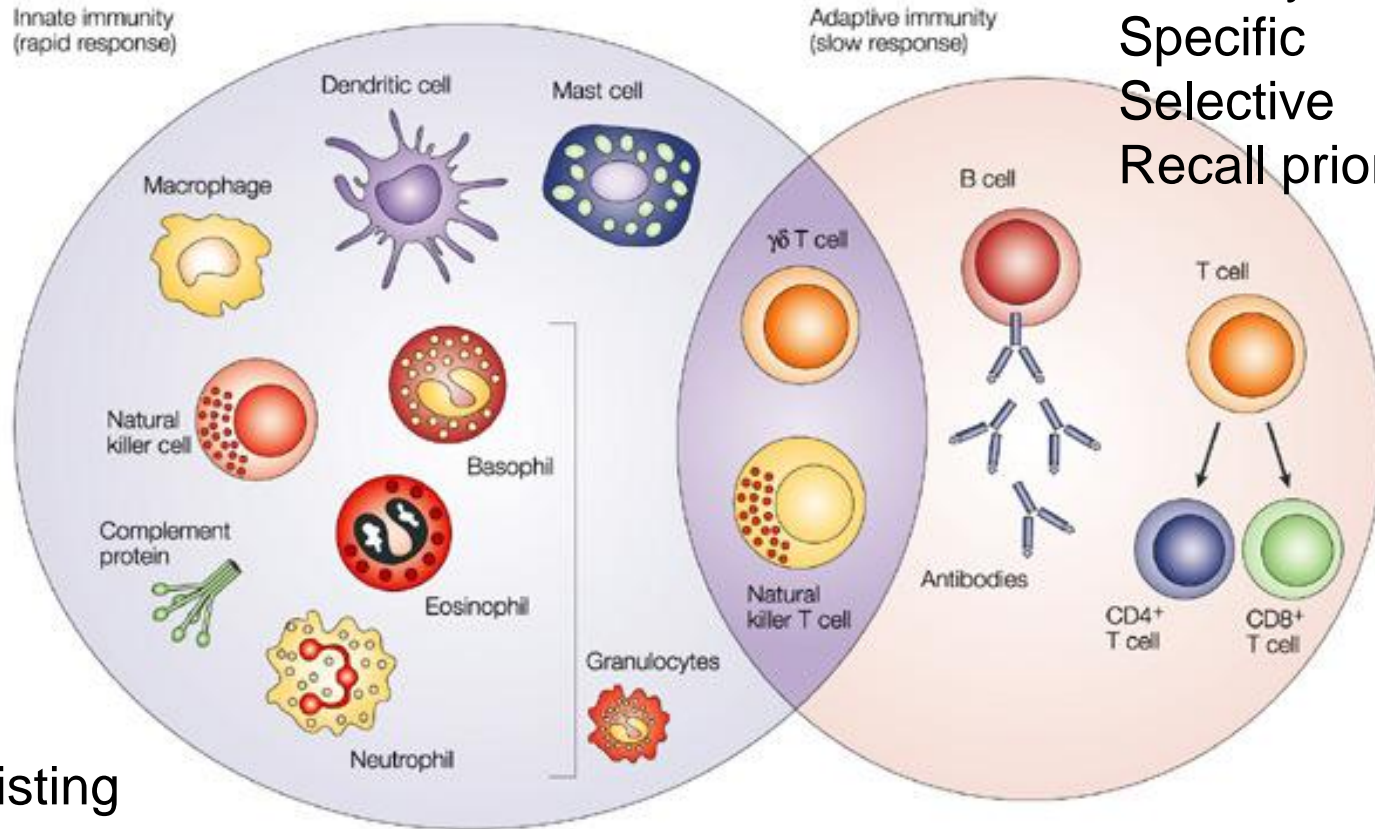
- **Immune system and cancer**
- **Role of the immune system in lung cancer**
- **Immunotherapy**
  - : vaccine**
  - immune checkpoint inhibitors**

# **Immune system & cancer**

# Innate and adaptive immunity



# Innate and adaptive immunity

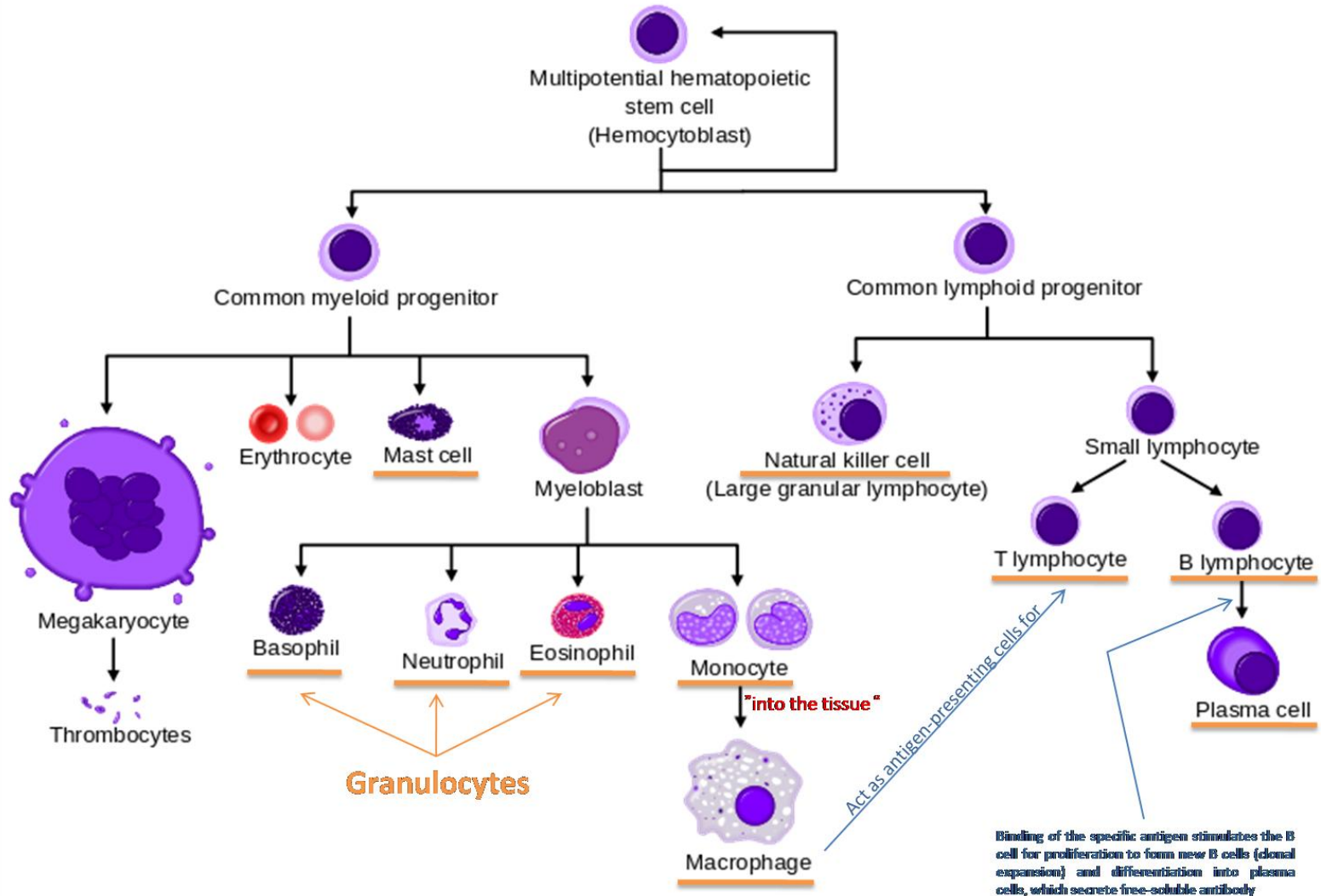


Educated  
Memory  
Specific  
Selective  
Recall prior exposure

Preexisting  
Ready to respond  
Not educated  
Not selective

Nature Reviews | [Cancer](#)

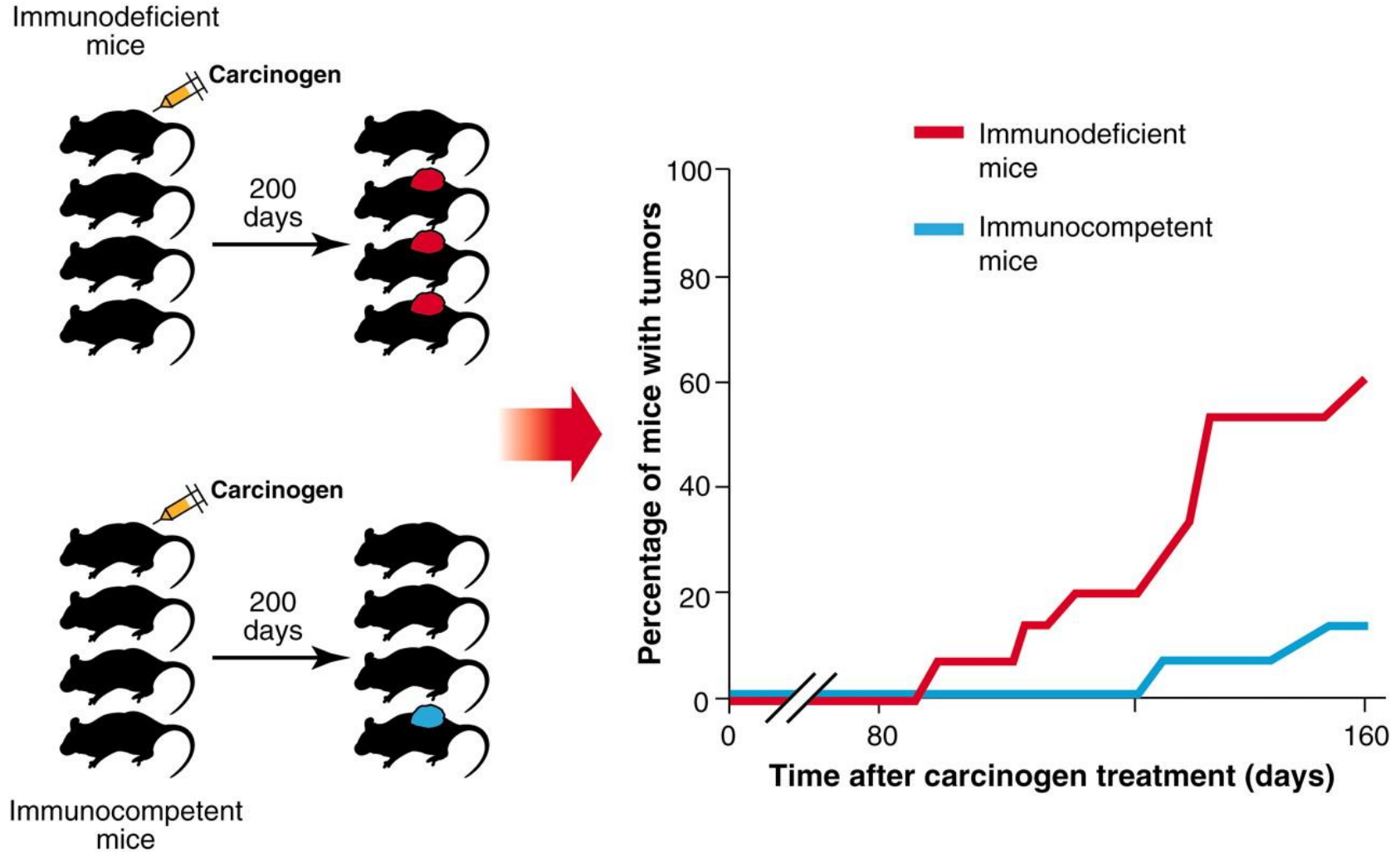
# Hematopoiesis



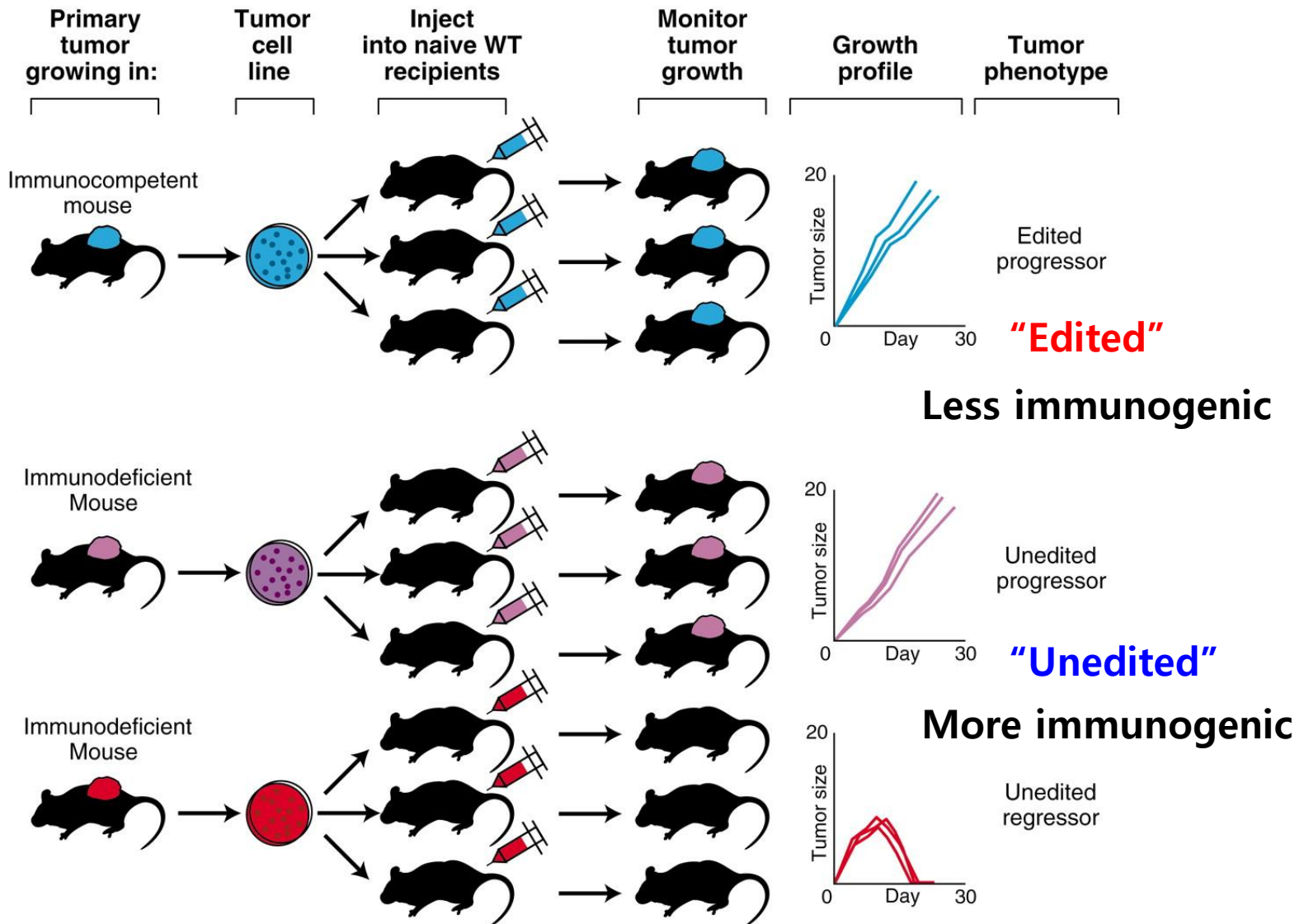
# **Advantage of immunotherapy**

- **Cancer cells are immunogenic**
- **Migrate to tissue**
- **Memory, specific**
- **Long-term cancer remission**
- **No side effect as chemotherapy and radiation**

# Immune status: susceptibility to tumor

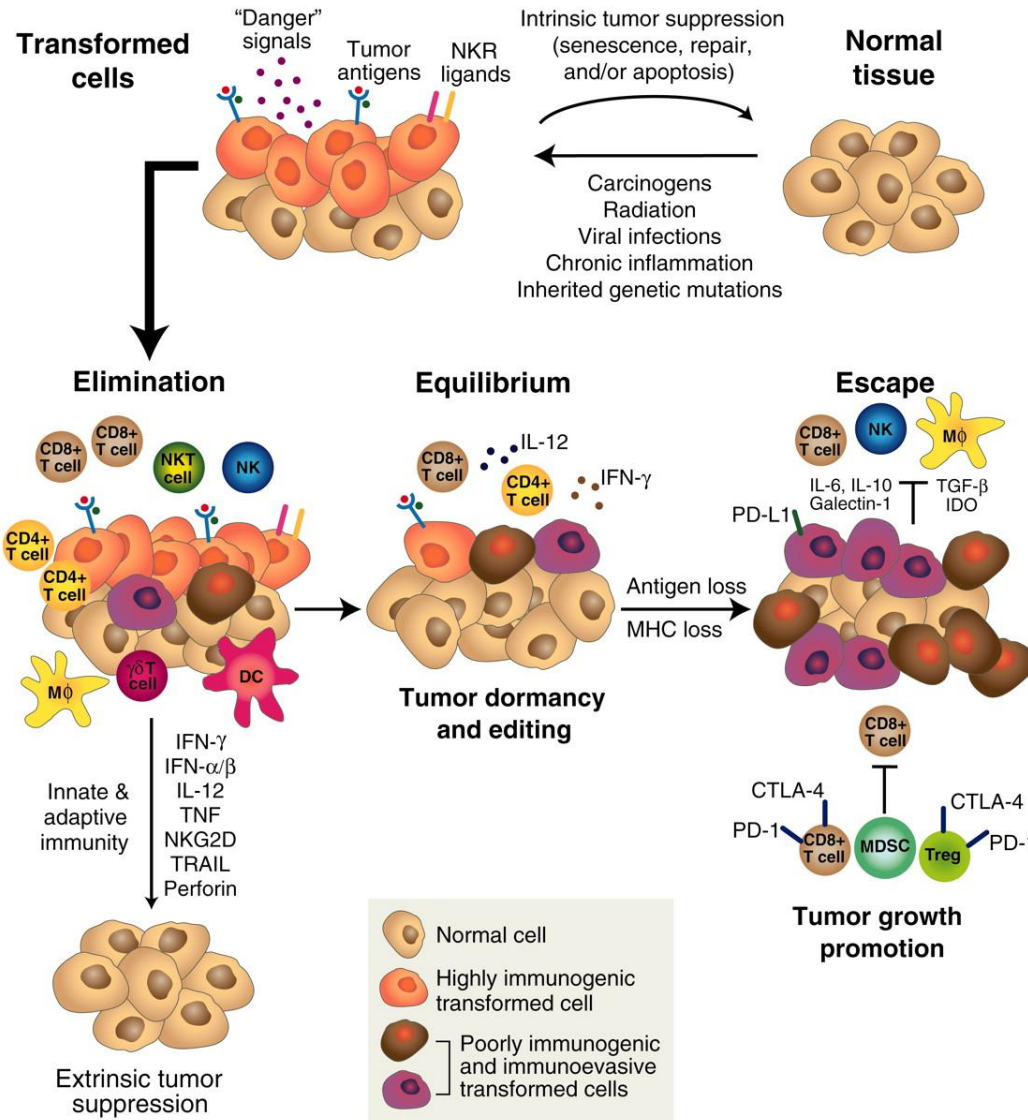


# Cancer immunoediting hypothesis

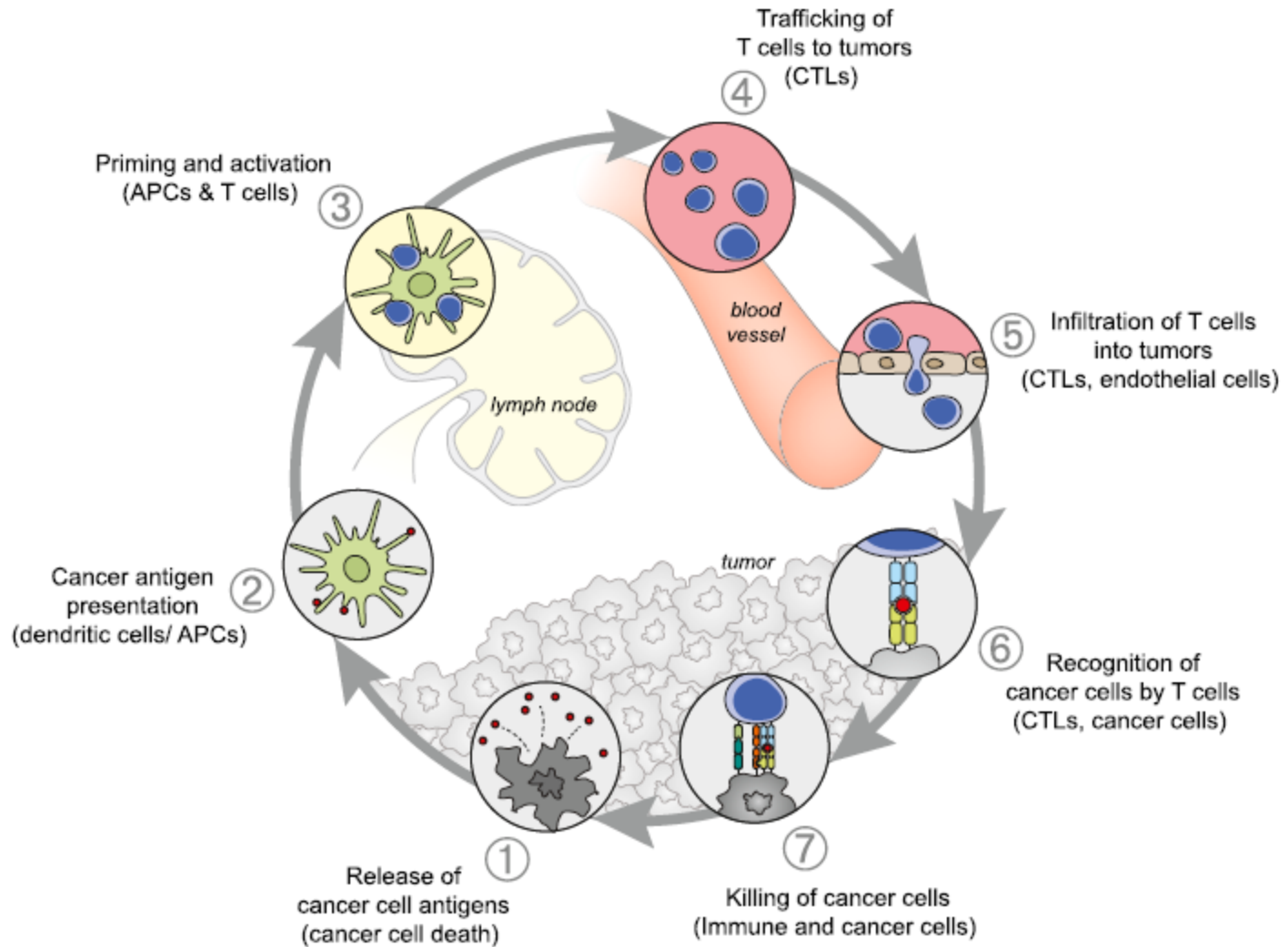


# Cancer immunoediting concept

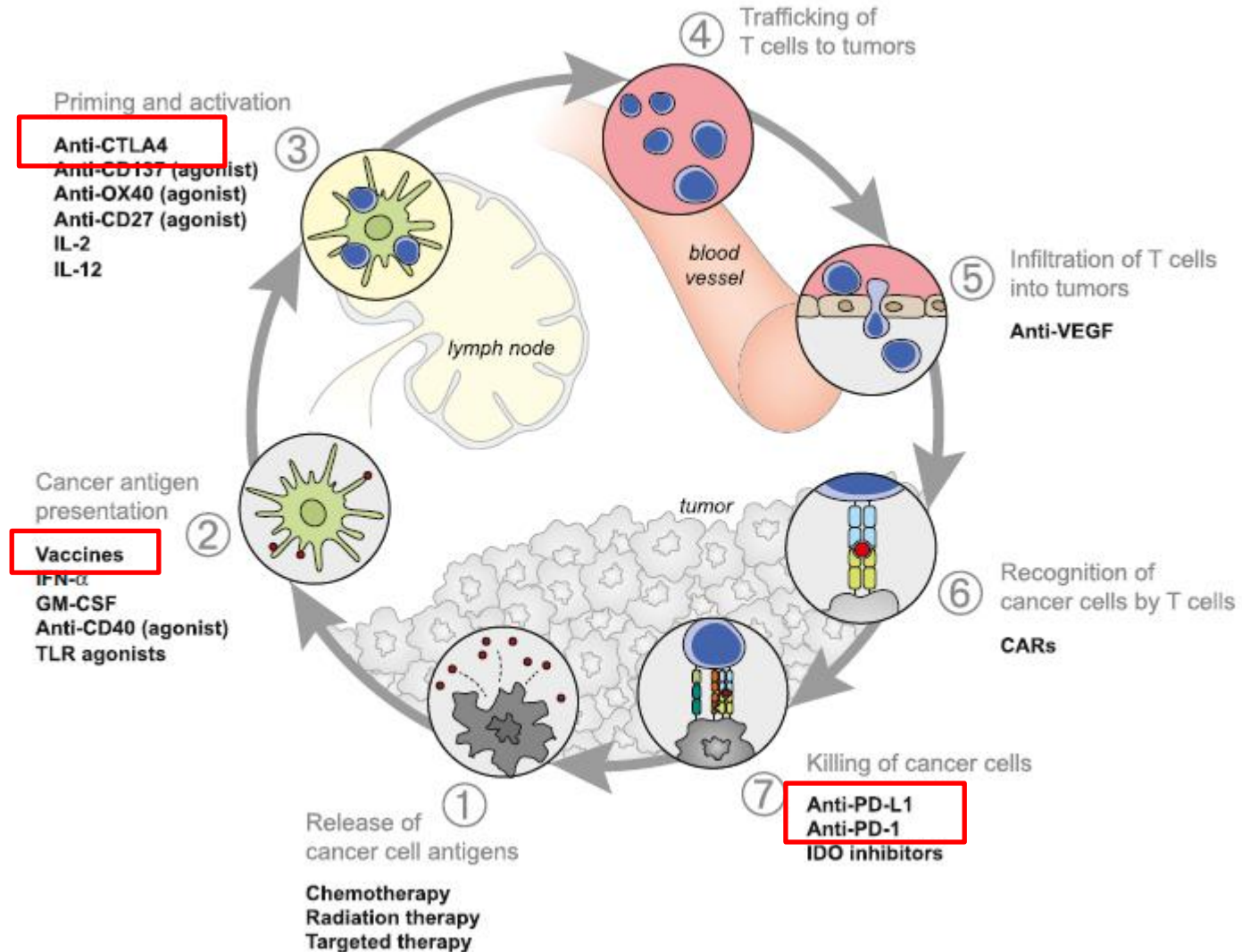
Extrinsic tumor suppressor mechanism



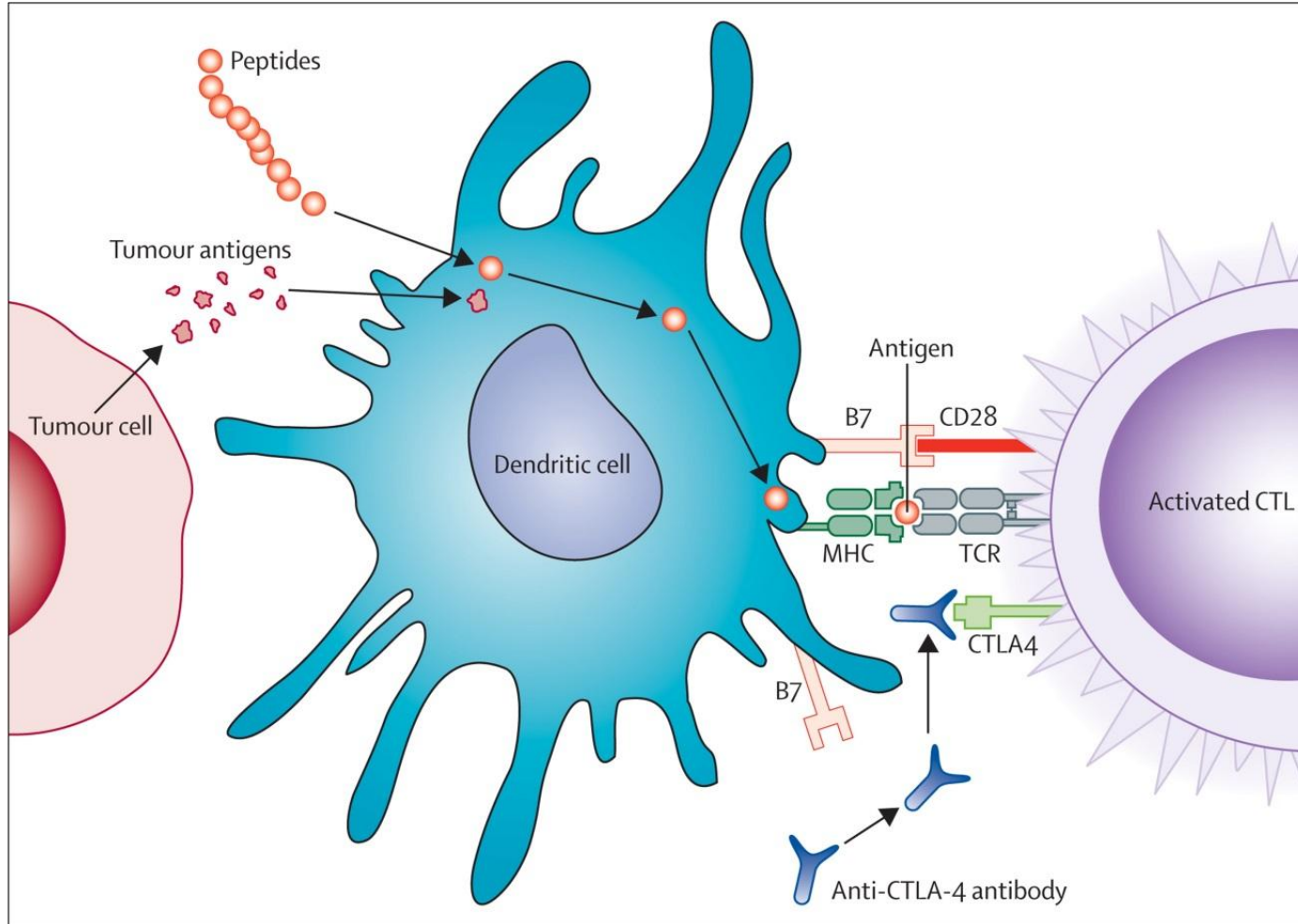
# Cancer immunity cycles

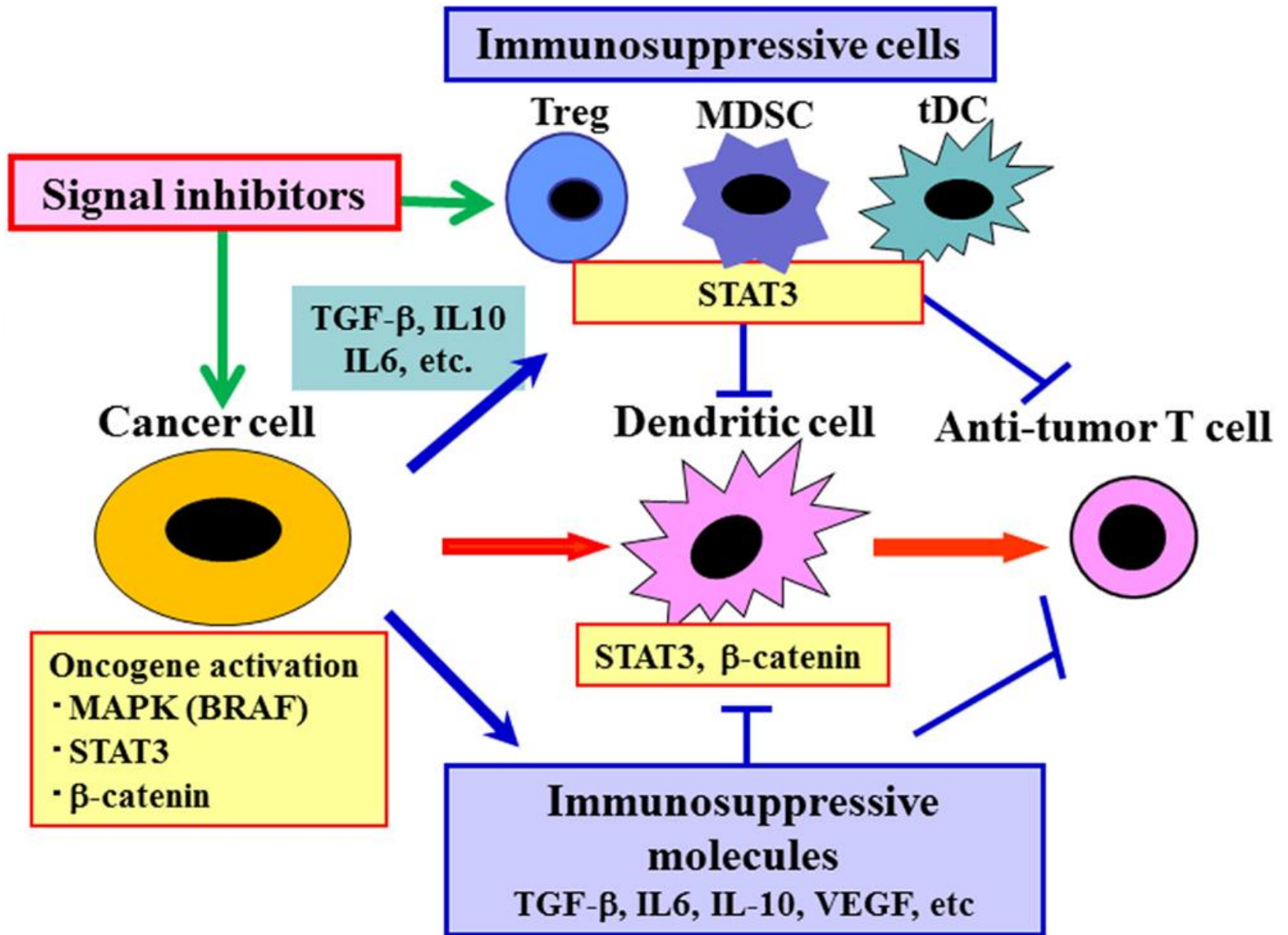


# Cancer immunity cycles: Therapies



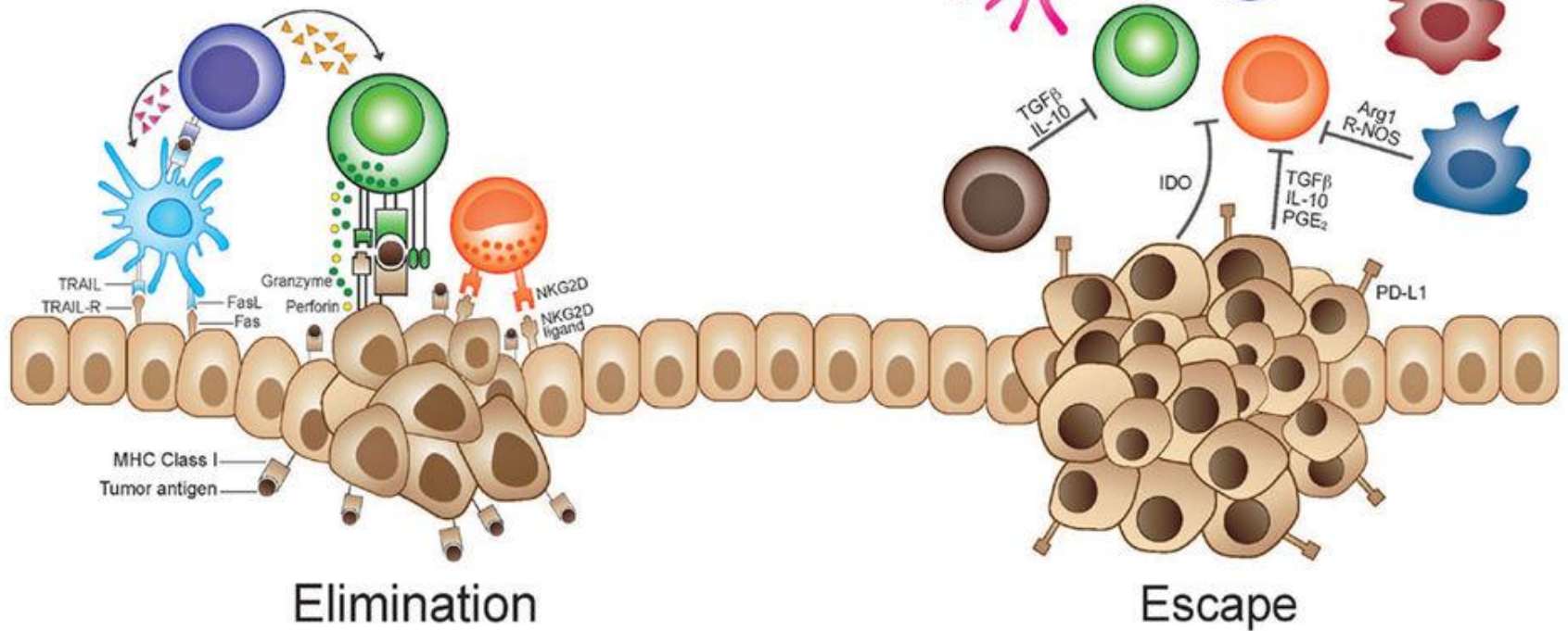
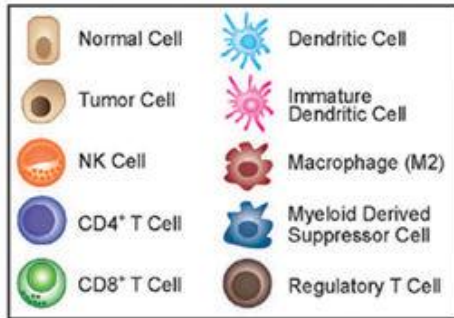
# APC and T-cell interaction



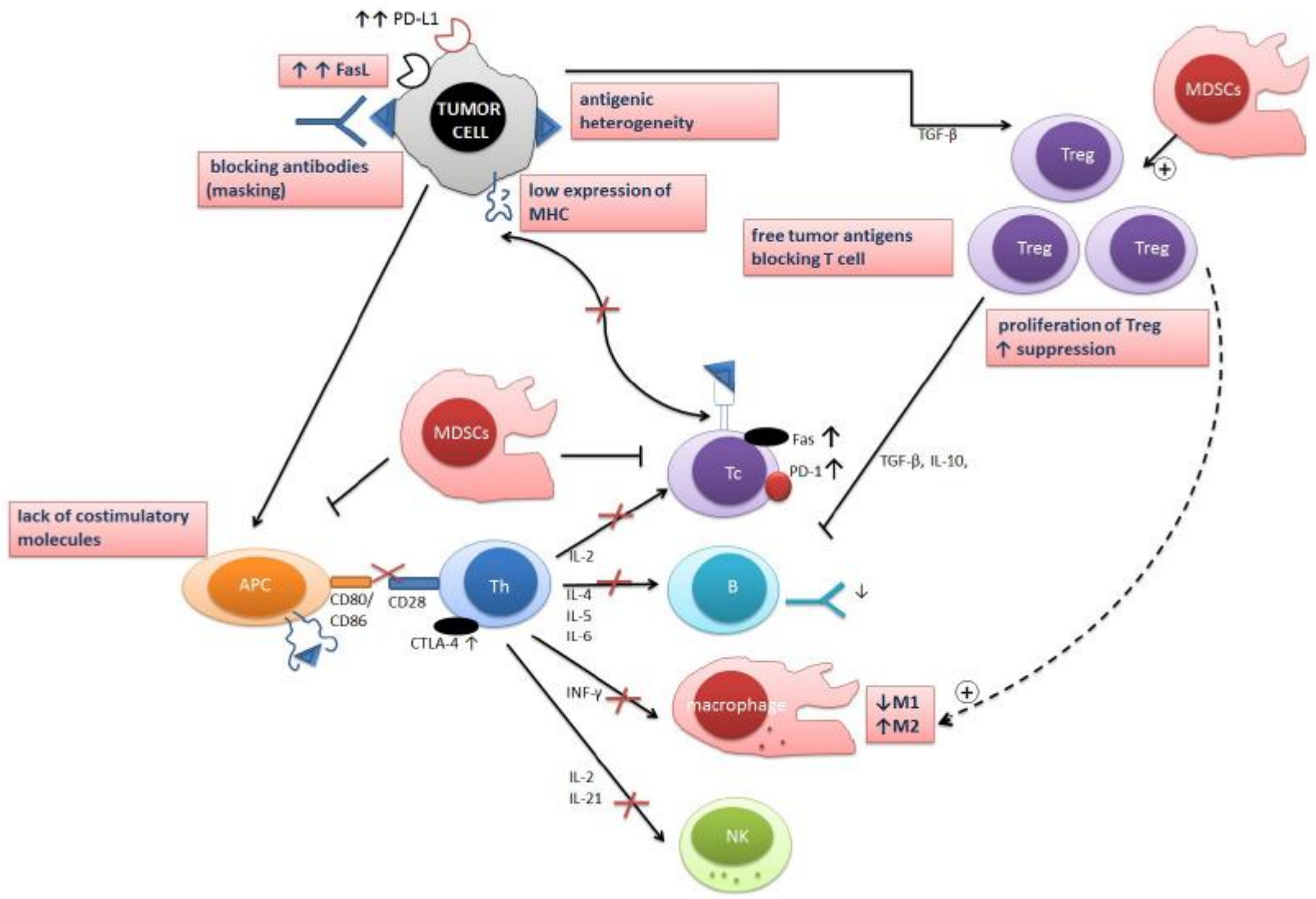


# **Role of immune system in lung cancer**

# Tumor microenvironment: immunosuppressive



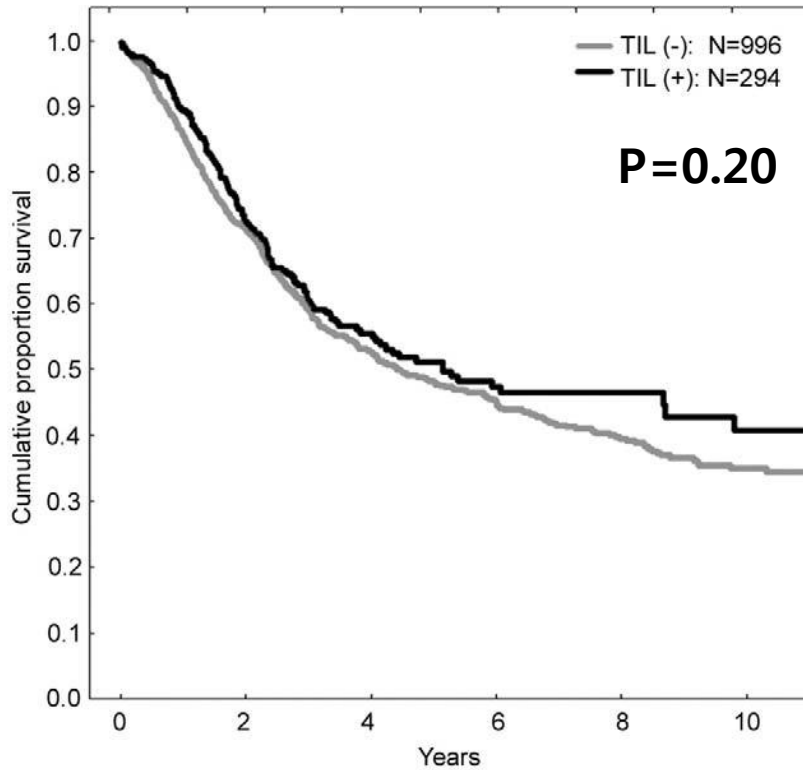
# Lung cancer escape from immunosurveillance



**Involvement of the immune  
system in lung cancer?**

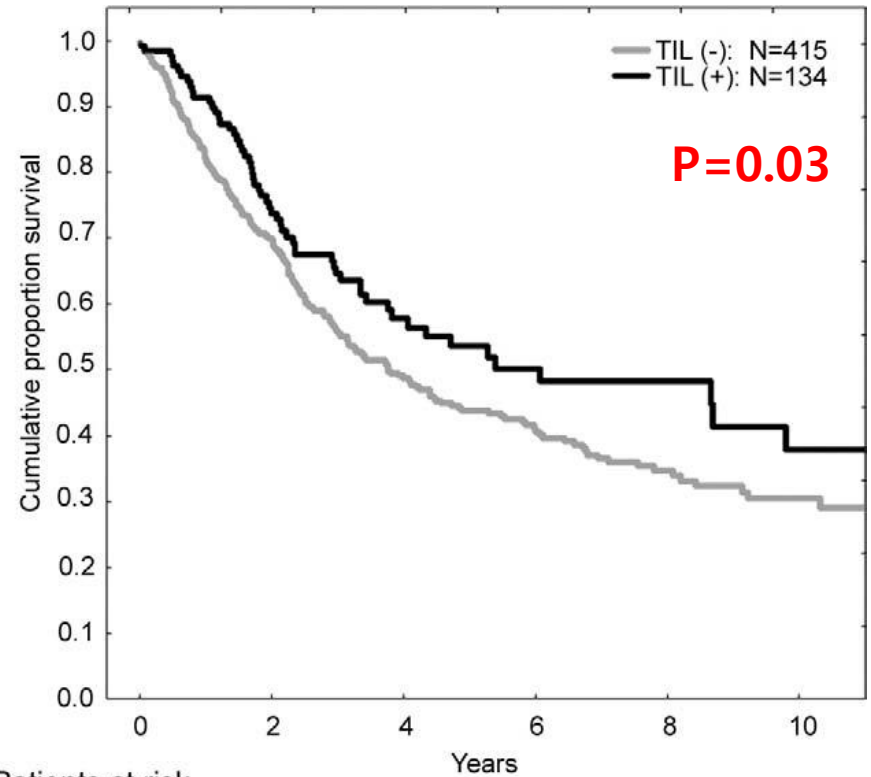
# Tumor infiltrating lymphocytes (CD8+): Survival

**All**



Patients at risk						
	0	2	4	6	8	10
TIL (-)	996	602	350	205	134	74
TIL (+)	294	179	102	49	33	20

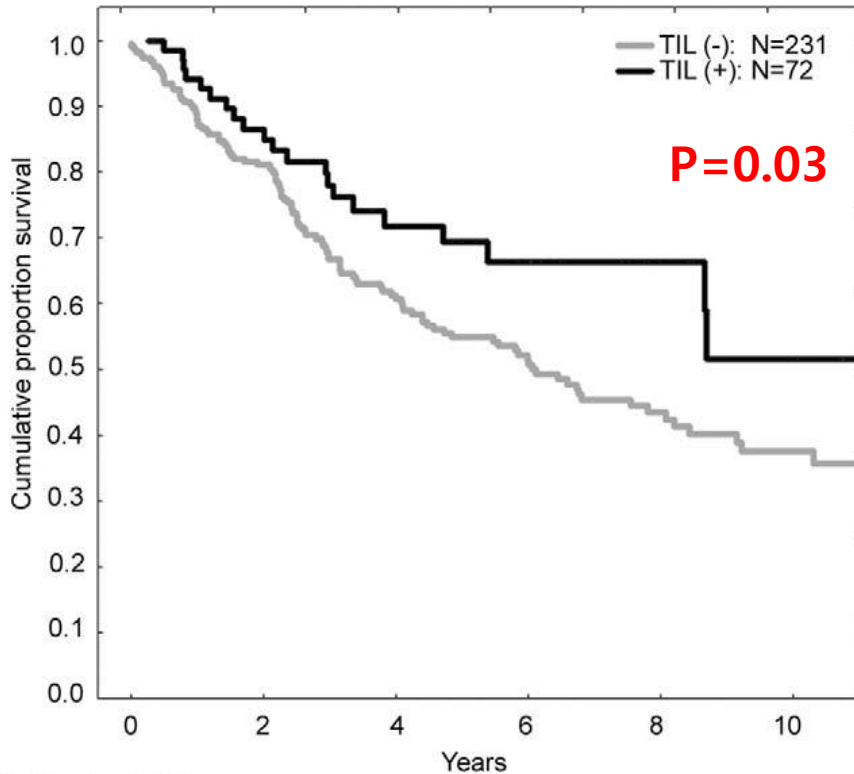
**SQ**



Patients at risk						
	0	2	4	6	8	10
TIL (-)	415	228	150	77	49	31
TIL (+)	134	81	51	23	17	12

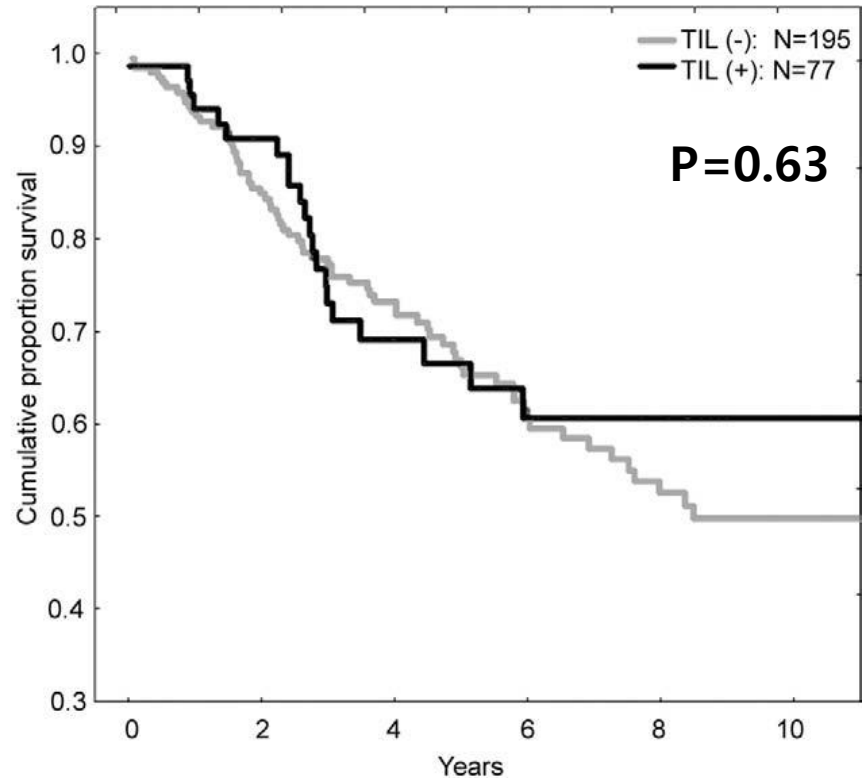
# TILs (CD8+): Survival

## SQ stage I



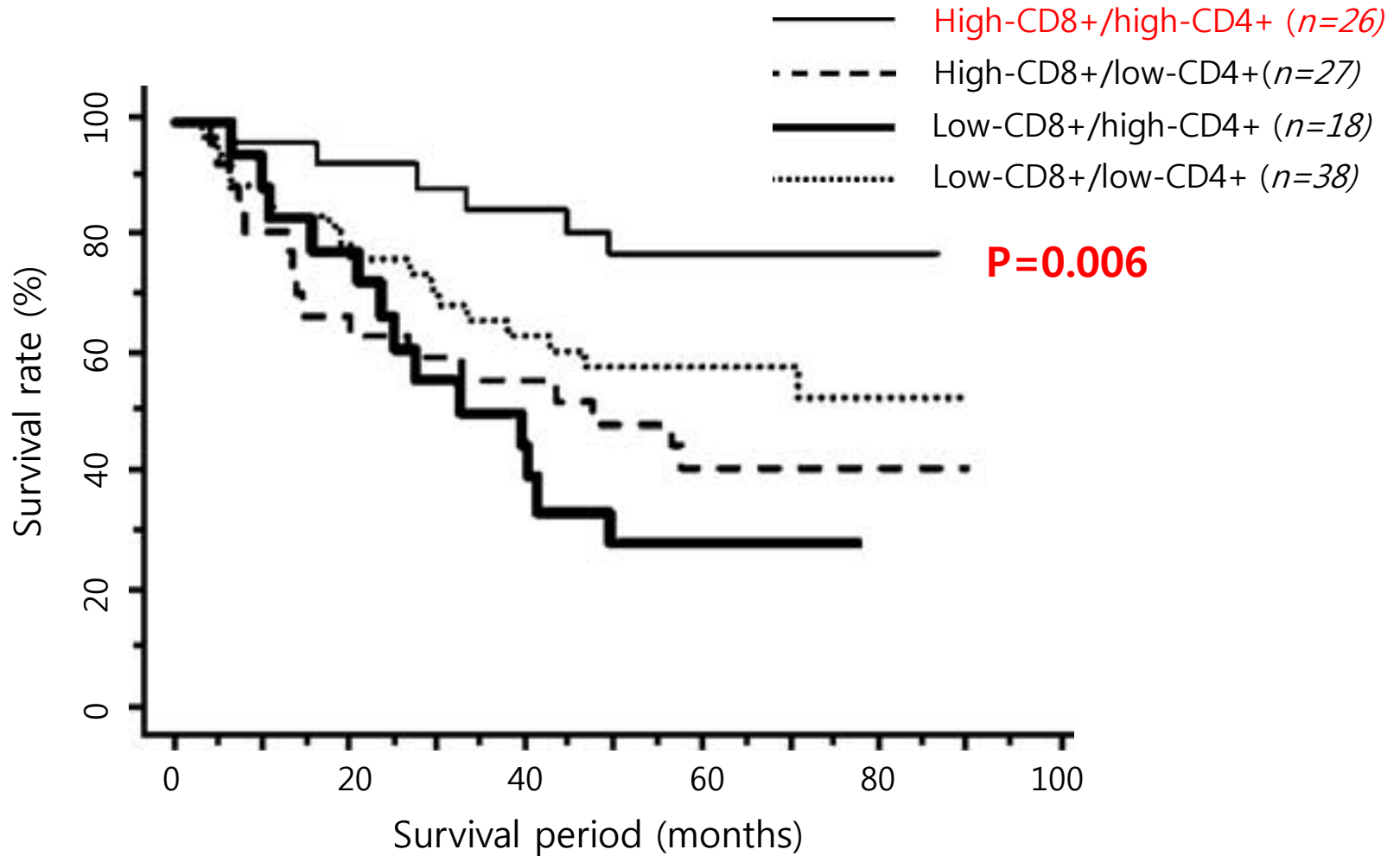
Patients at risk		0	2	4	6	8	10
TIL (-)	231	159	93	64	43	28	
TIL (+)	72	53	29	18	12	7	

## AD stage I

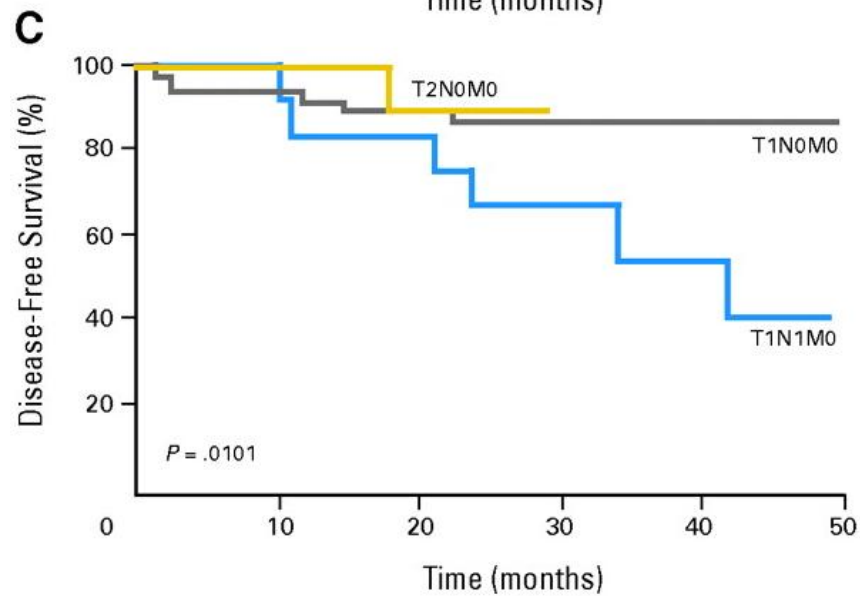
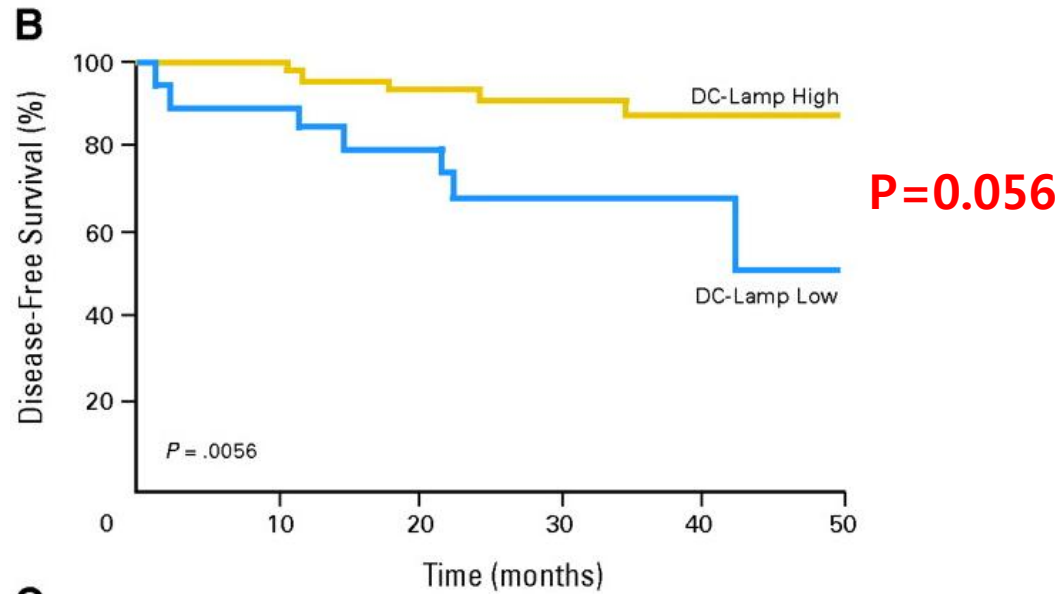


Patients at risk		0	2	4	6	8	10
TIL (-)	195	144	83	57	40	23	
TIL (+)	77	81	25	17	12	4	

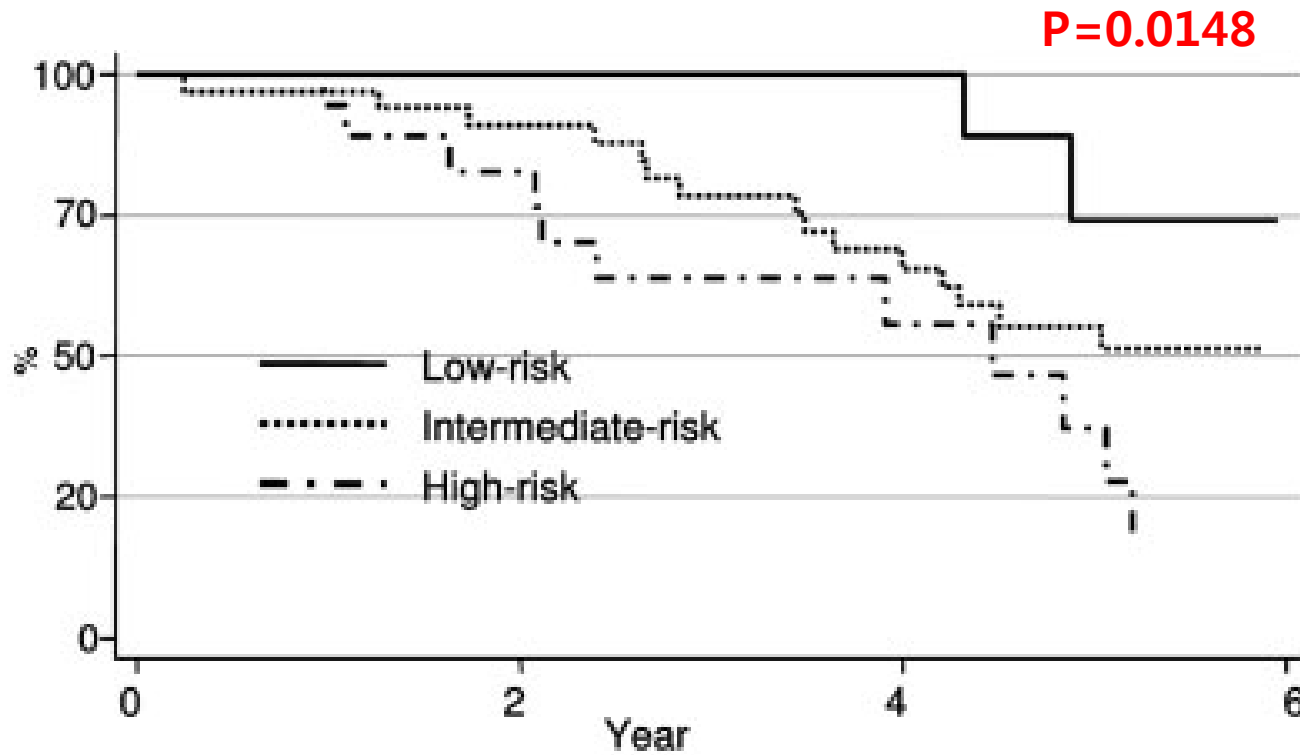
# TILs (CD8+ CD4+): Survival



# Mature dendritic cell (DC): DFS



# Regulatory T- cell (CD3+, Foxp3+): Survival

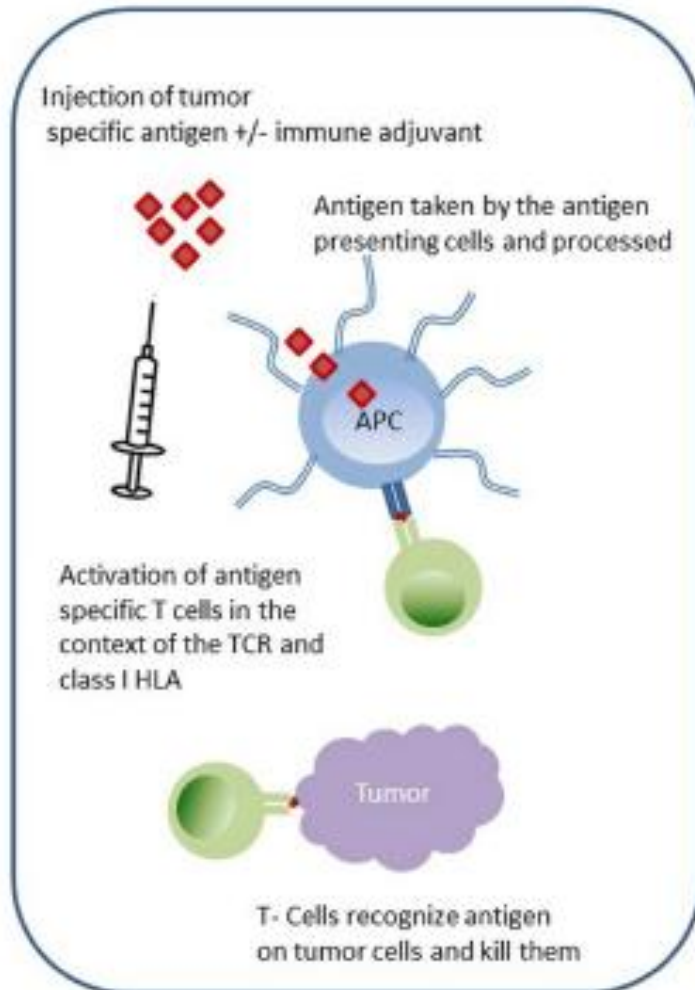


여름방과 비취

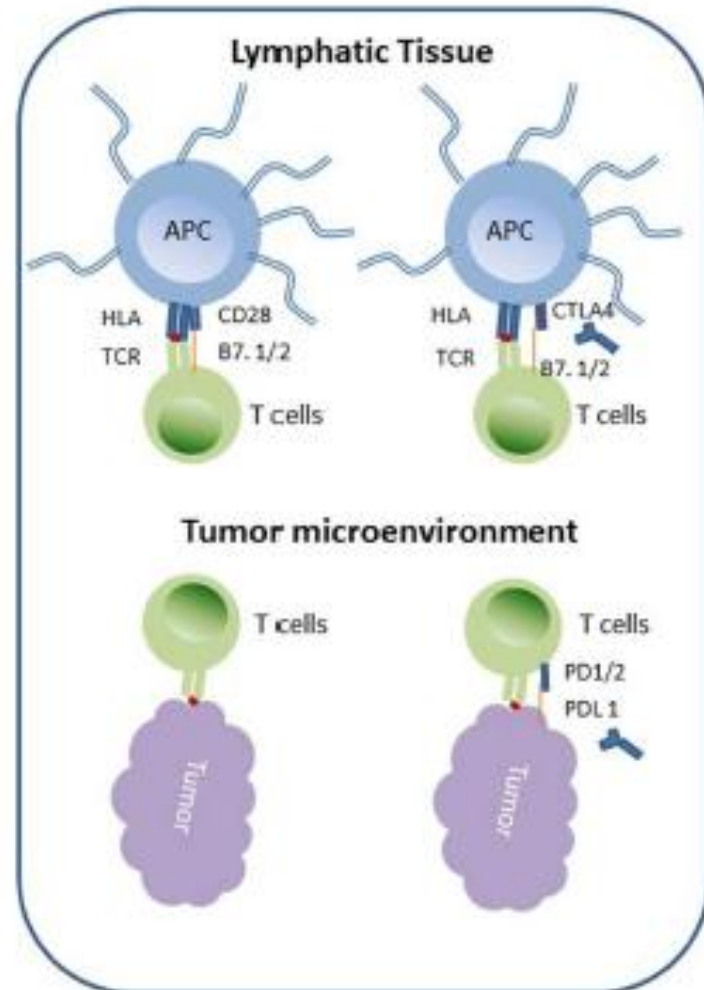
# Immunotherapy

# Immunotherapeutic strategies in NSCLC

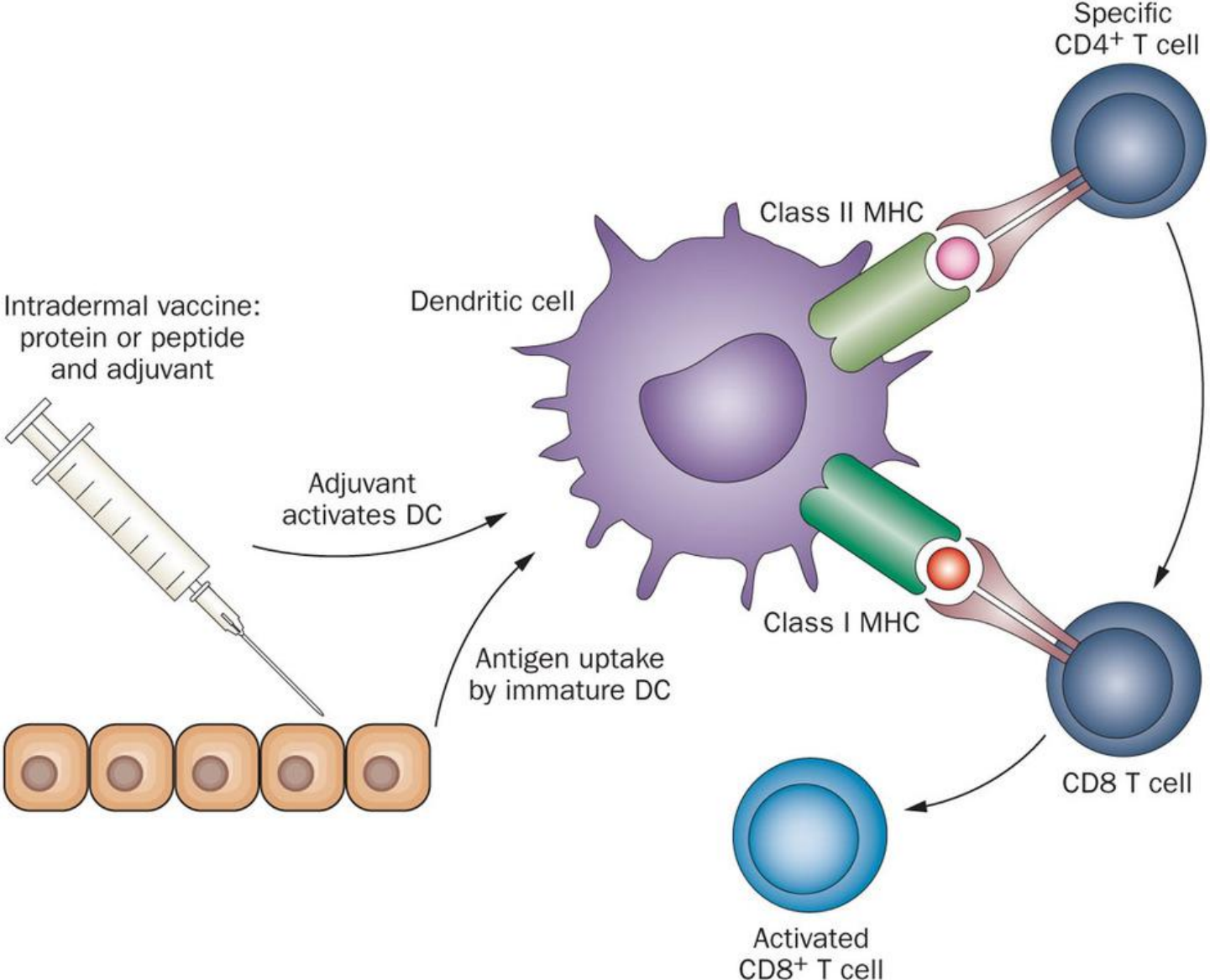
## Mechanism of action of Vaccines



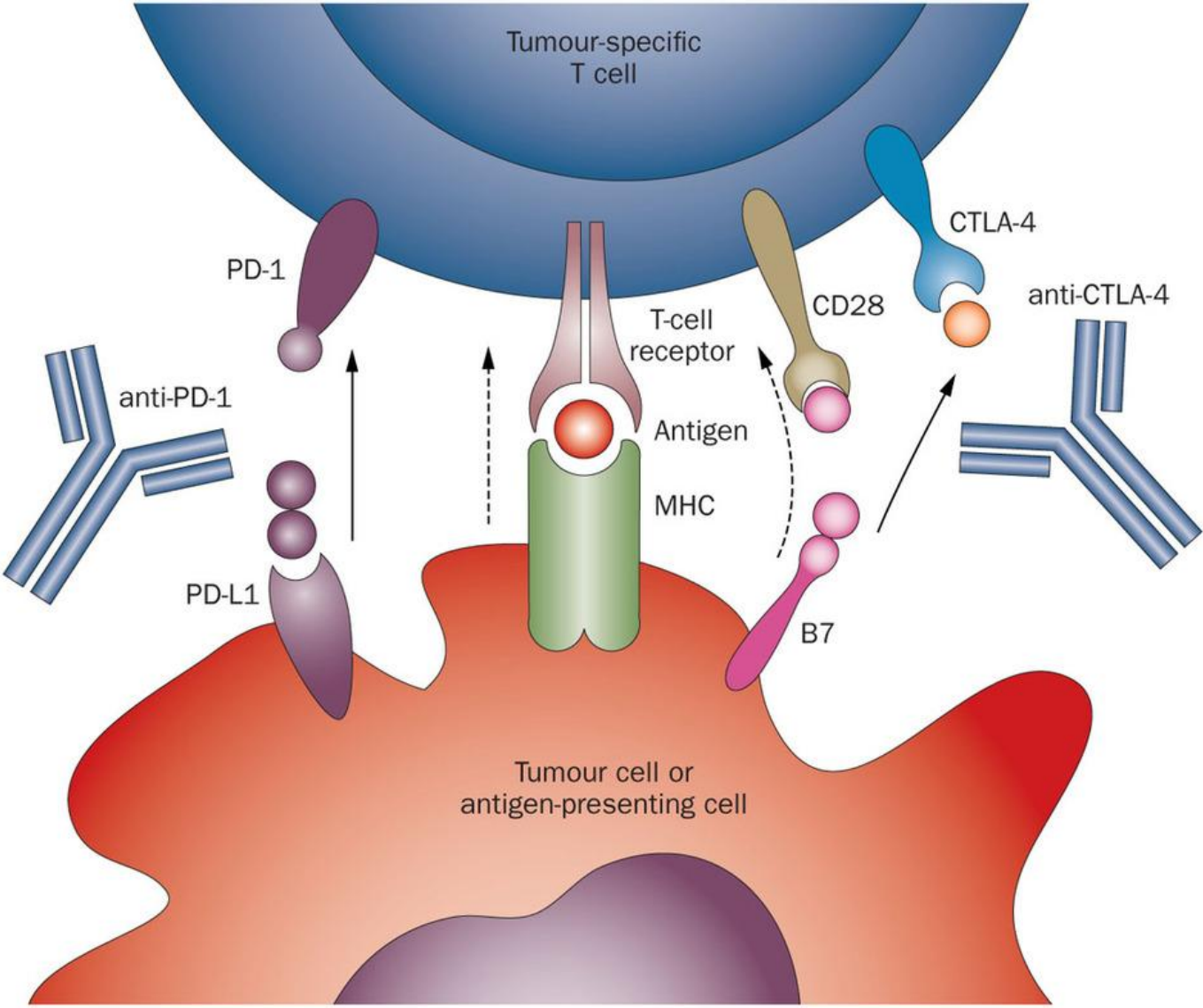
## Immune Checkpoint Inhibitors



# Cancer vaccine



# Immune checkpoint inhibitor blockade



# MAGE-A3

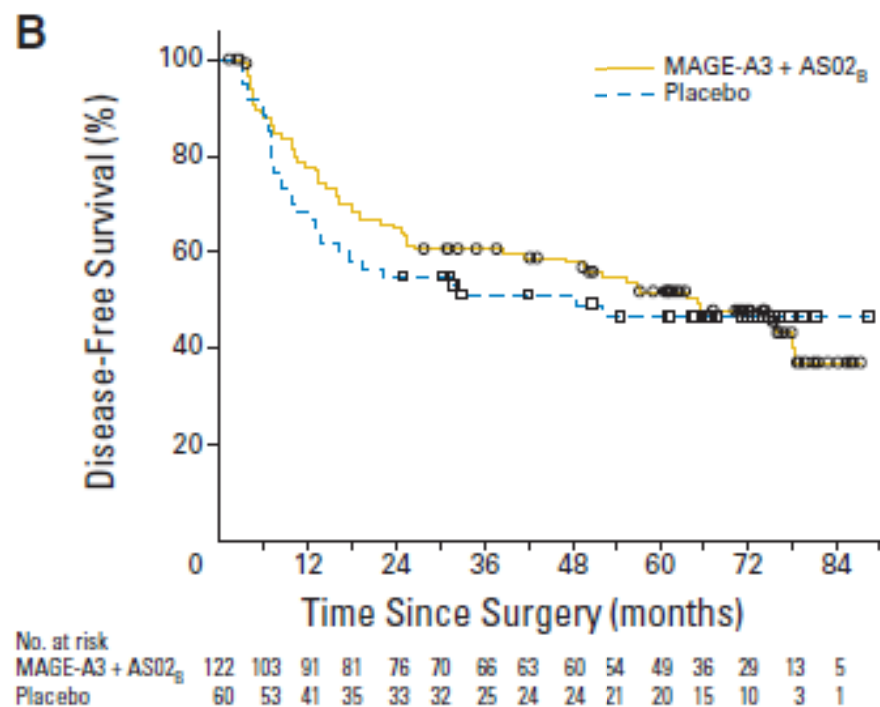
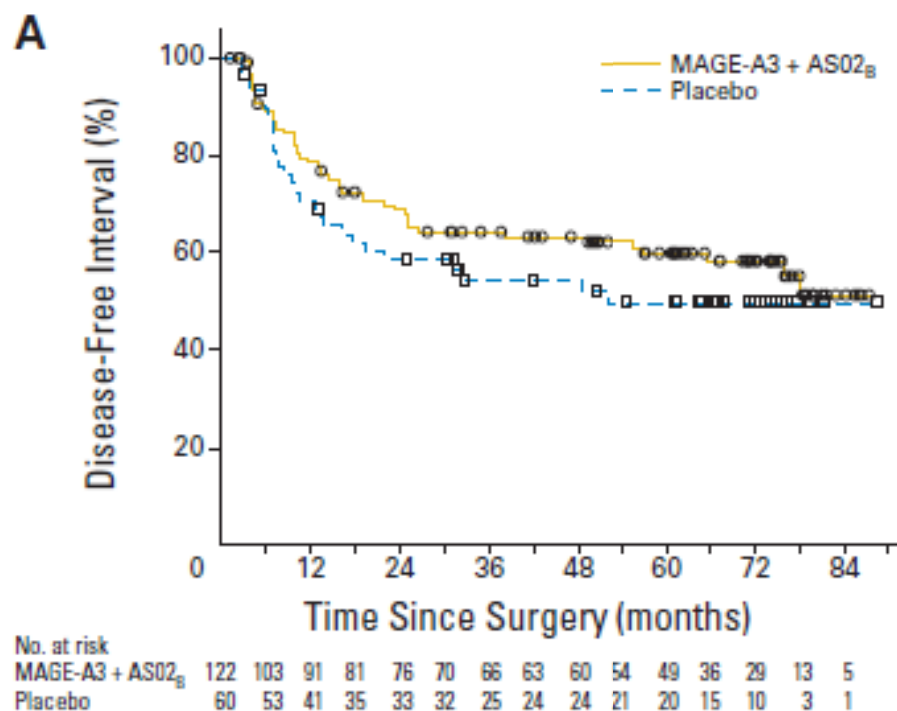
- **MAGE: melanoma-associated antigen**
- **Expressed in 35-55% of NSCLC**
- **Independent predictor of poor outcomes in adenocarcinoma of lung**
- **MAGE A3 antigen-specific cancer immunotherapeutics**
  - : **postoperative adjuvant** setting
  - : **vaccine may have the greatest clinical activity due to minimal tumor burden**

Gridelli C, et al. Oncologist 2009;14:909-20.

Gure AO, et al. Clin Cancer Res 2005;11:8055-62.

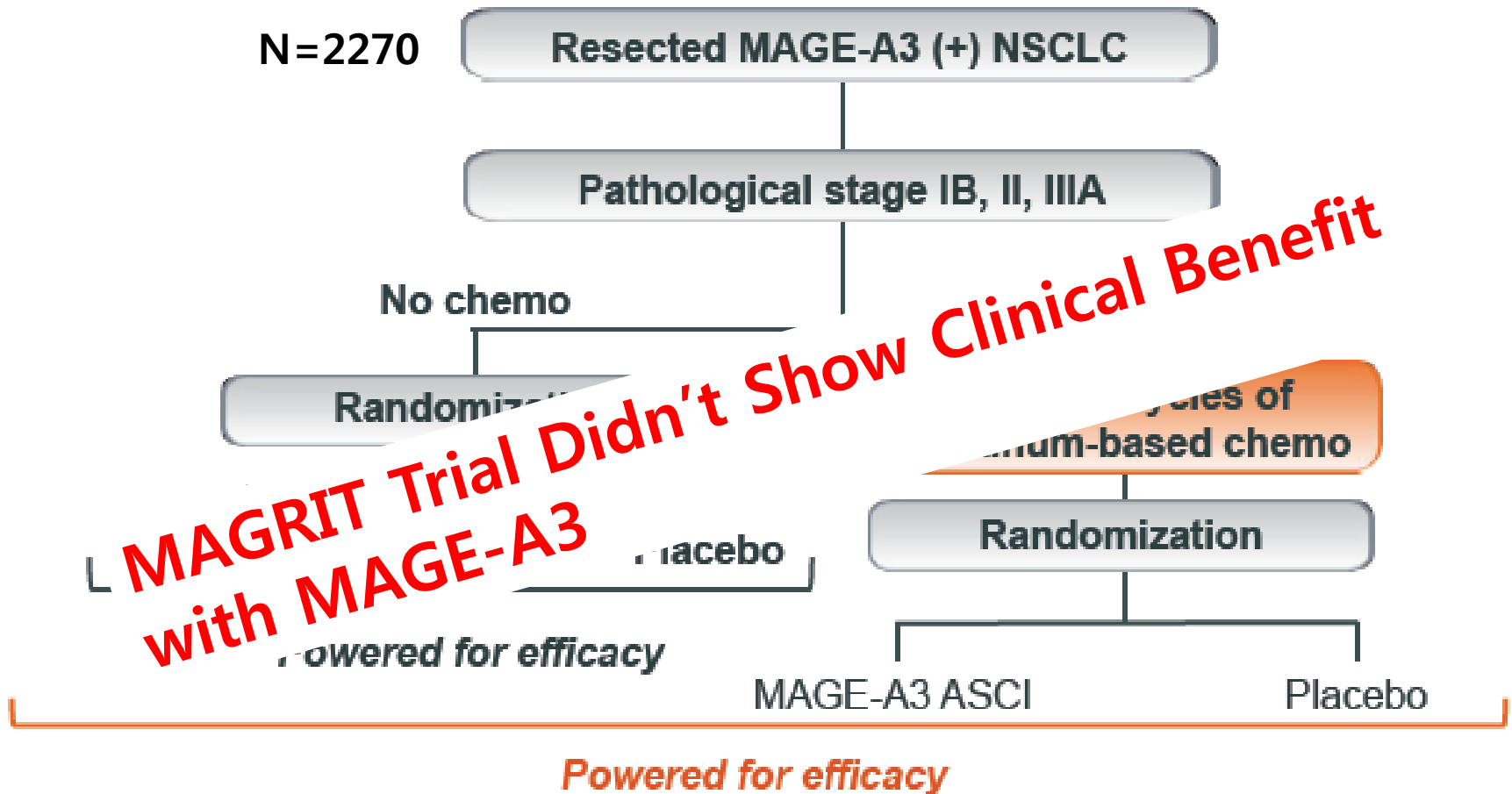
## Adjuvant MAGE-A3 Immunotherapy in Resected Non-Small-Cell Lung Cancer: Phase II Randomized Study Results

Johan Vansteenkiste, Marcin Zielinski, Albert Linder, Jubrail Dahabreh, Emilio E. Gonzalez, Wojciech Malinowski, Marta Lopez-Brea, Tonu Vanakesa, Jacek Jassem, Haralabos Kalofonos, Jakub Perdeus, Reiner Bonnet, Jazeps Basko, Richard Janilionis, Bernward Passlick, Tom Treasure, Marc Gillet, Frédéric F. Lehmann, and Vincent G. Brichard



# MAGRIT: Phase III trial

MAGE-A3 as Adjuvant non-small cell lung cancer Immunotherapy



# L-BLP25

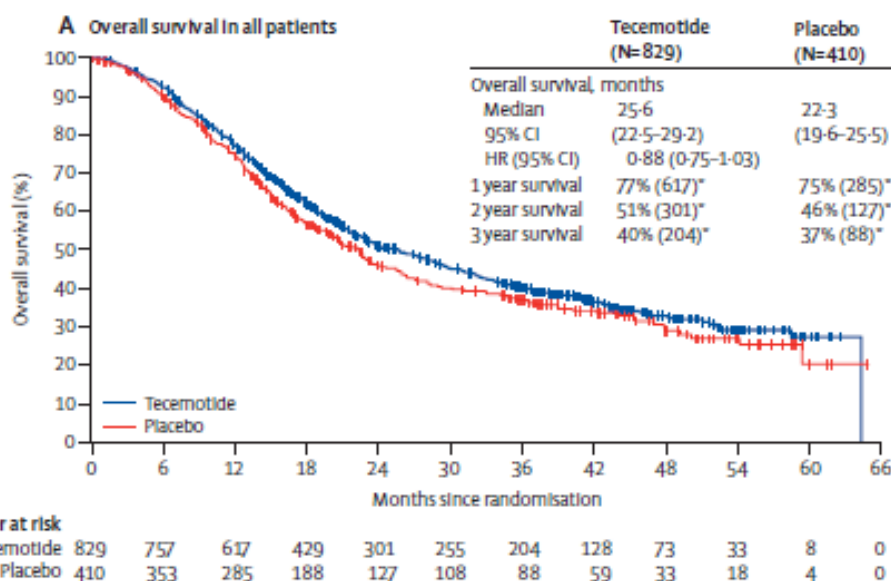
- **MUC1: mucin 1**, cell-surface glycoprotein aberrantly expressed in various cancers, including breast, **lung**, pancreatic, ovarian, gastric, colon cell transformation, migration, immunosuppress...
- **L-BLP25 (Tecemotide) Stimuvax<sup>®</sup>**: peptide vaccine targets the exposed core peptide of MUC1 comprises BLP25 lipopeptide, immunoadjuvant monophosphoryl lipid A & three lipids form a liposomal product

Ho SB, et al. Cancer Res 1993;53:641-51.

Butts C, et al. J Clin Oncol 2005;23:6674-81.

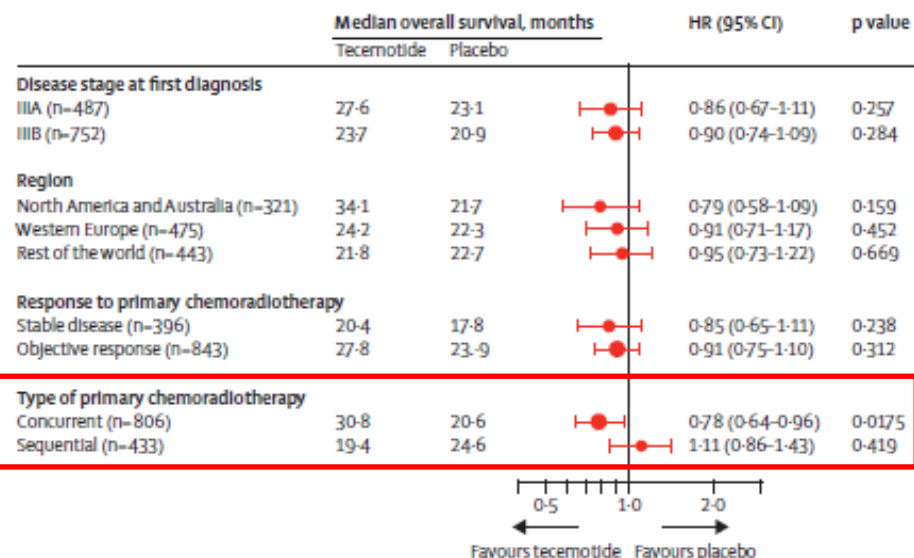
# Tecemotide (L-BLP25) versus placebo after chemoradiotherapy for stage III non-small-cell lung cancer (START): a randomised, double-blind, phase 3 trial

Charles Butts, Mark A Socinski, Paul L Mitchell, Nick Thatcher, Libor Havel, Maciej Krzakowski, Sergiusz Nawrocki, Tudor-Eliade Ciuleanu, Lionel Bosqu e, Jos  Manuel Trigo, Alexander Spira, Lise Tremblay, Jan Nyman, Rodryg Ramlau, Gun Wickart-Johansson, Peter Ellis, Oleg Gladkov, Jos  Rodrigues Pereira, Wilfried Ernst Erich Eberhardt, Christoph Helwig, Andreas Schr der, Frances A Shepherd, on behalf of the START trial team\*



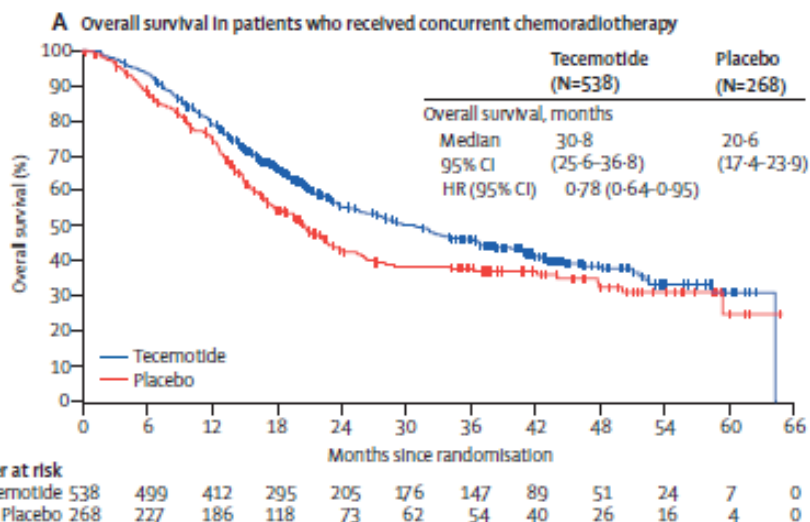
**P=0.123**

**B Overall survival in subgroups of all patients**



# START: Phase III trial

OS: **Concurrent** chemoradiotherapy

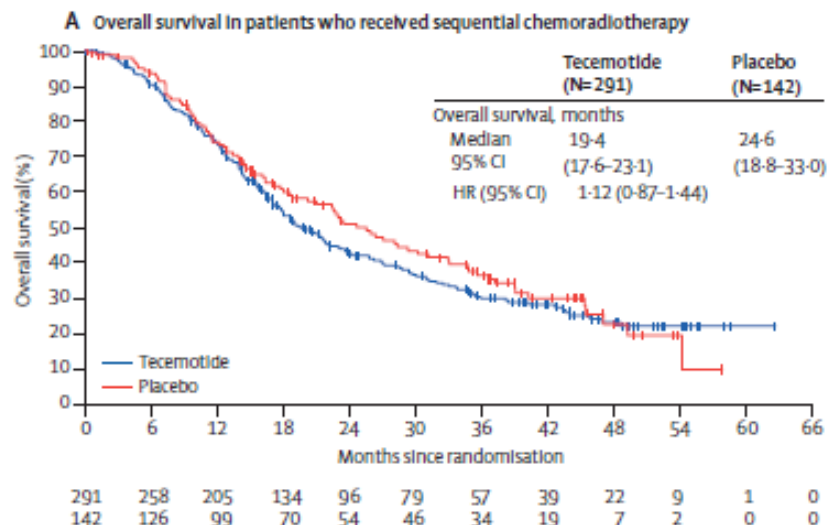


**P=0.016**

**HR 0.78 (0.64-0.95)**

**Tecemotide 30.8 vs Placebo 20.6**

OS: **Sequential** chemoradiotherapy

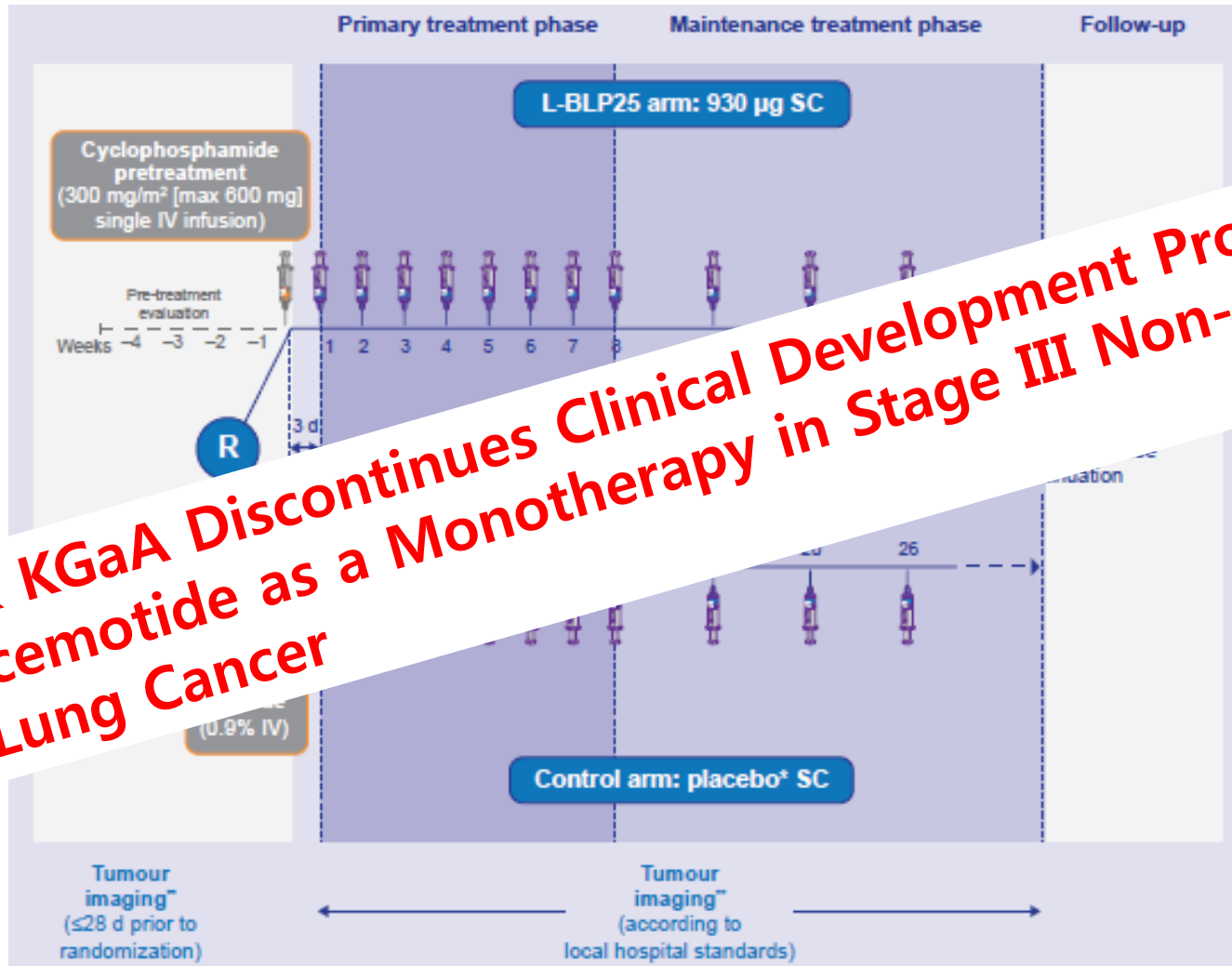


**P=0.38**

# INSPIRE: Phase III trial

Stimuvax trial **I**n Asian **NSCLC** Patients: Stimulating **I**mmune **R**esponse

N=420

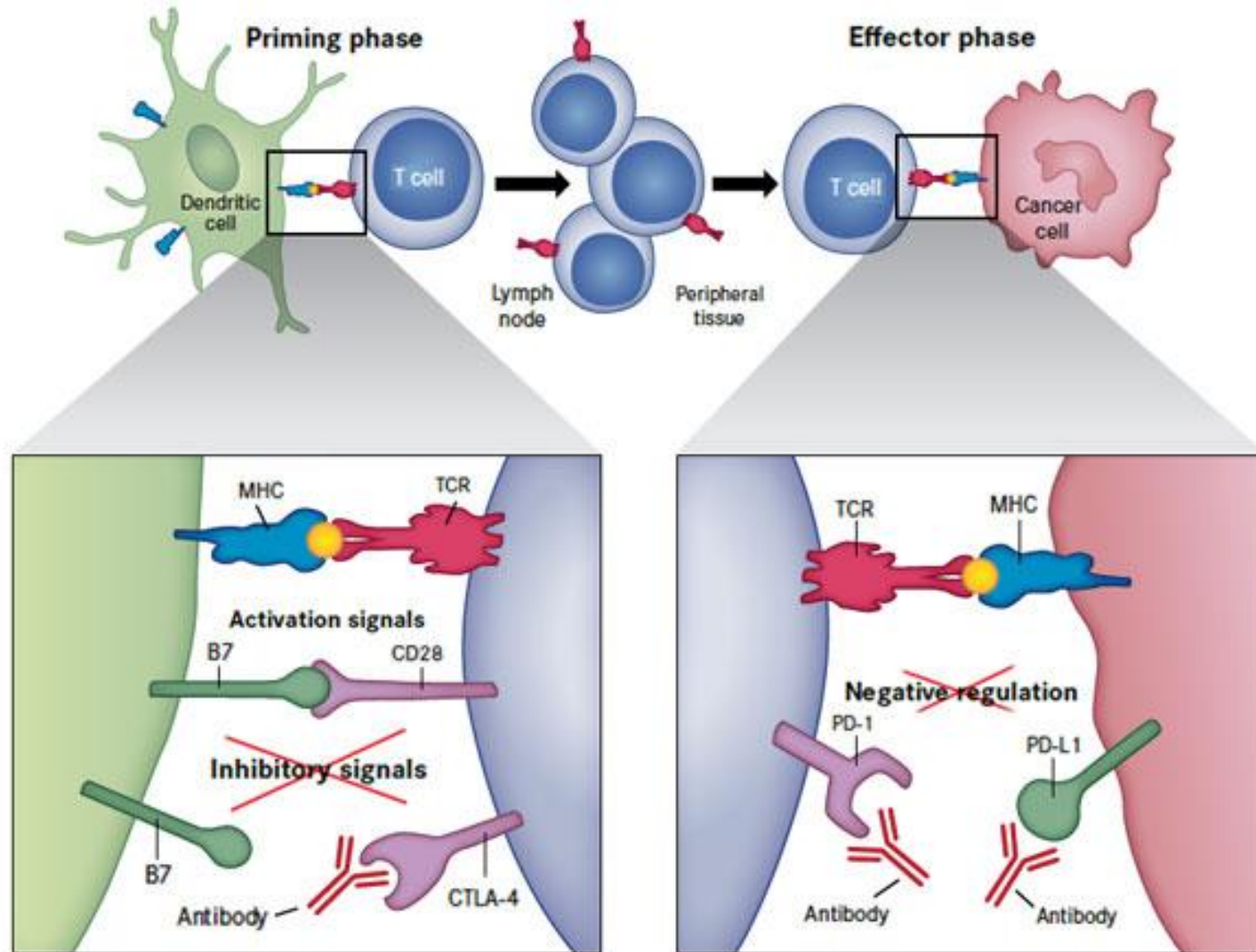


**Merck KGaA Discontinues Clinical Development Program of Tecemotide as a Monotherapy in Stage III Non-Small Cell Lung Cancer**

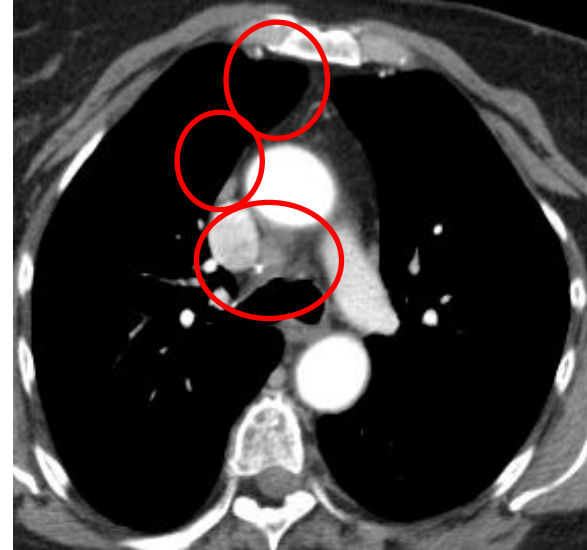
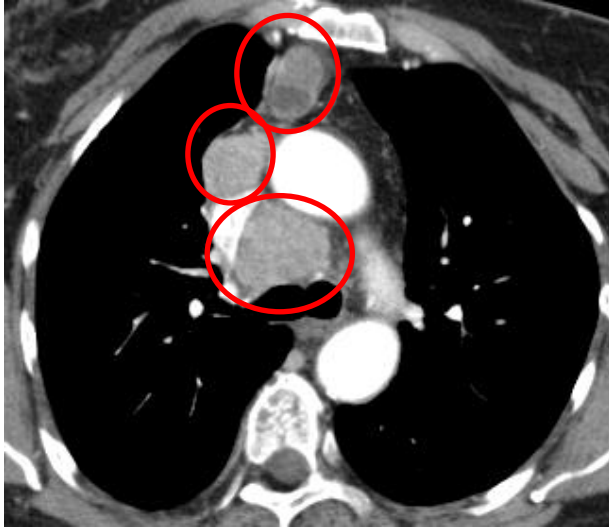
# “Hurdles” in cancer vaccine development

- **Vaccines might still be suboptimal**
  - induction of the desired immune responses is weak
  - responses are short lived
  - memory formation defective
- **Tumor microenvironment**
  - potently **immunosuppressive**
- **One consistent finding**
  - effective in **minimal disease** burden

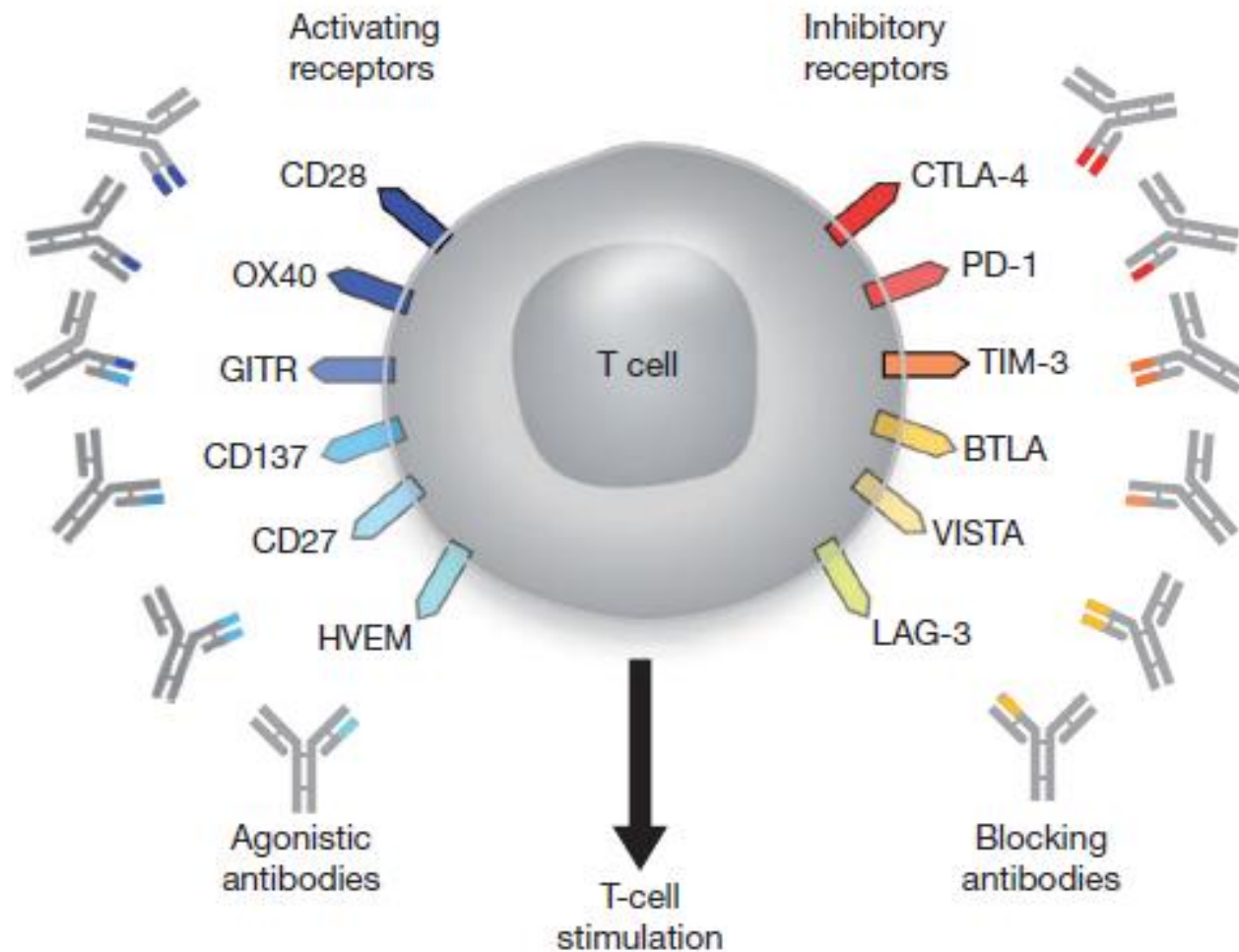
# Immune checkpoint inhibitor



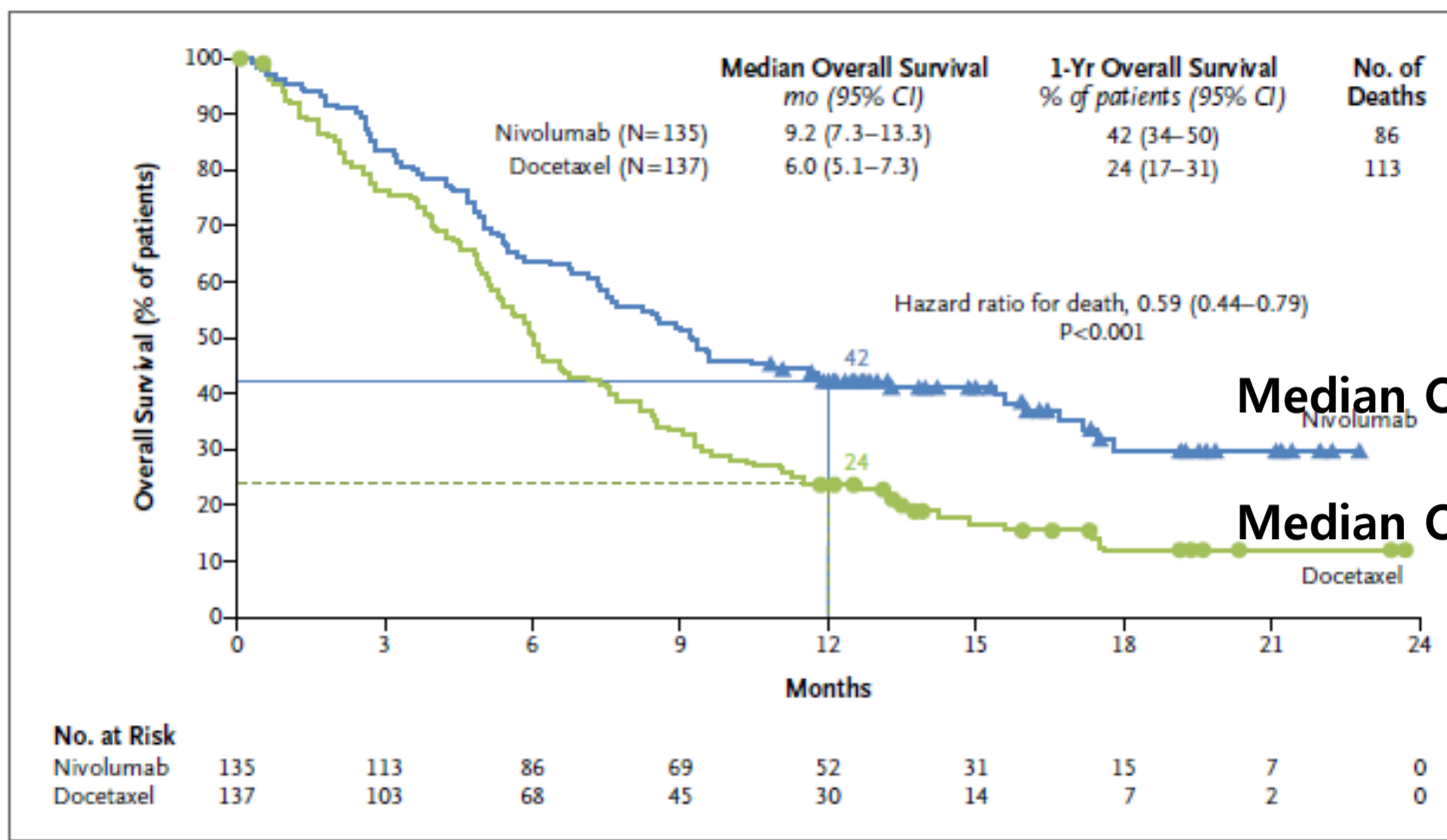
# Single agent Anti-PD1 can produce durable responses



# T cell targets for immunoregulatory antibody tx.



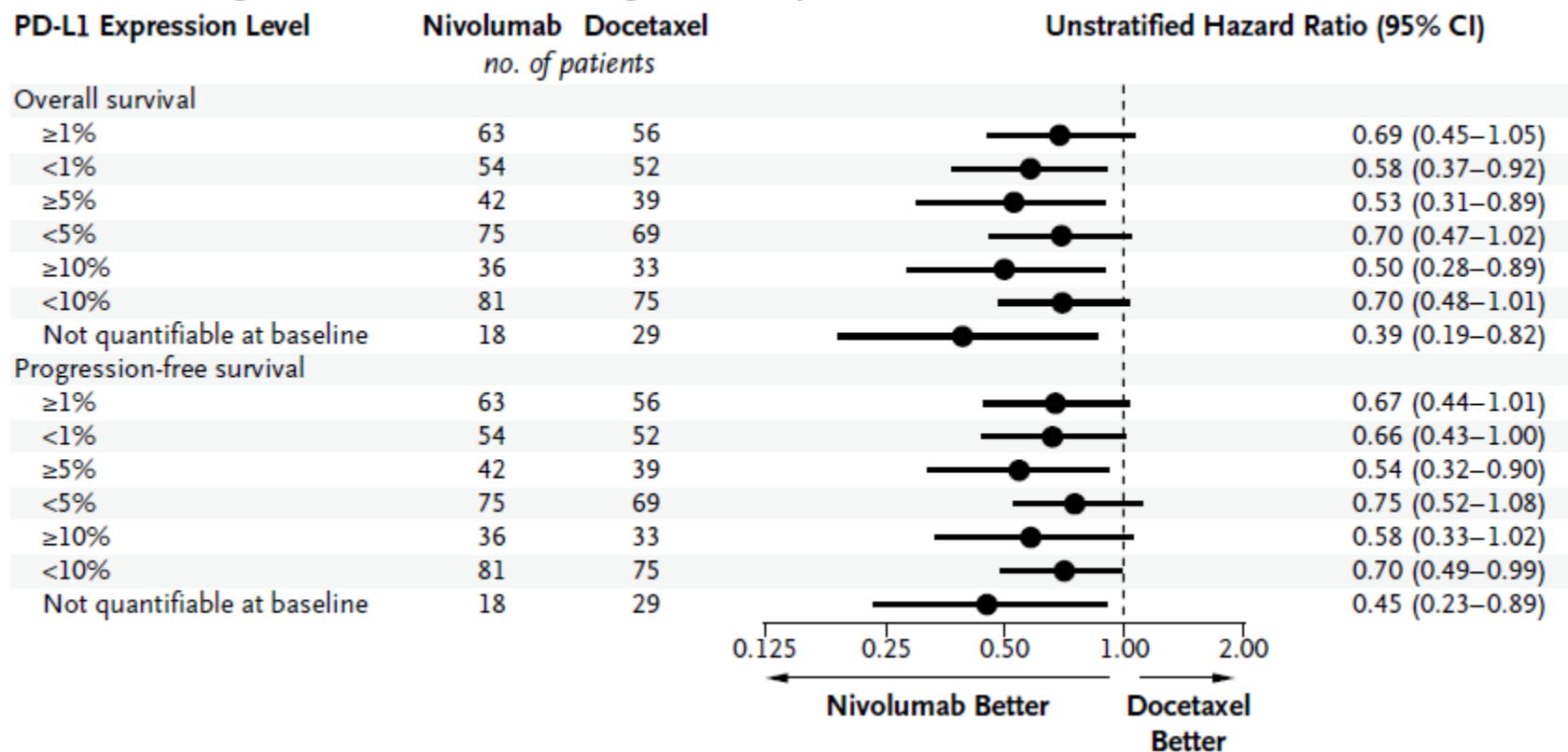
# Nivolumab: phase III, 2<sup>nd</sup> line Squamous NSCLC CheckMate 017



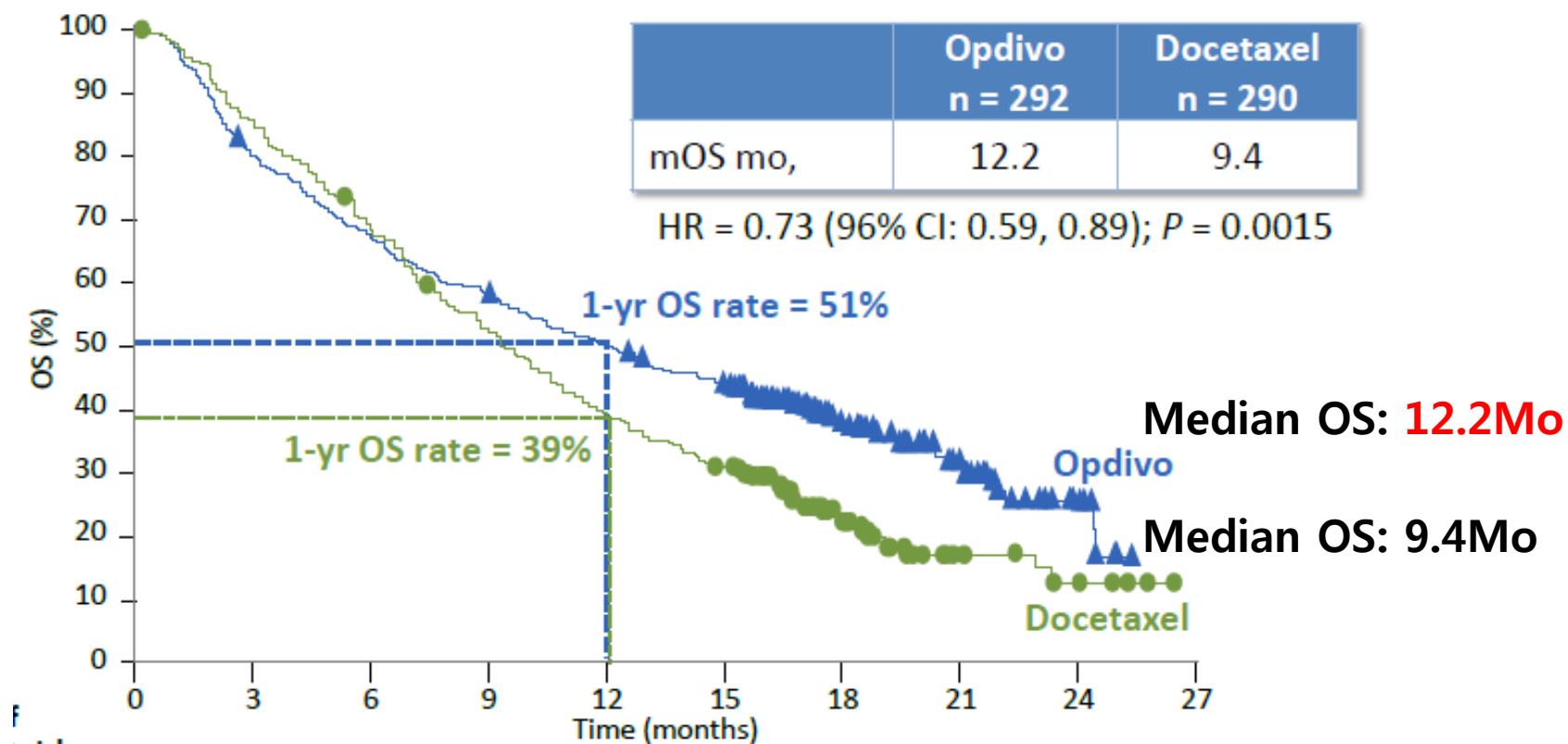
Response rate: 20%

# Nivolumab: phase III, 2<sup>nd</sup> line Squamous NSCLC CheckMate 017

## C Overall and Progression-free Survival According to PD-L1 Expression Level

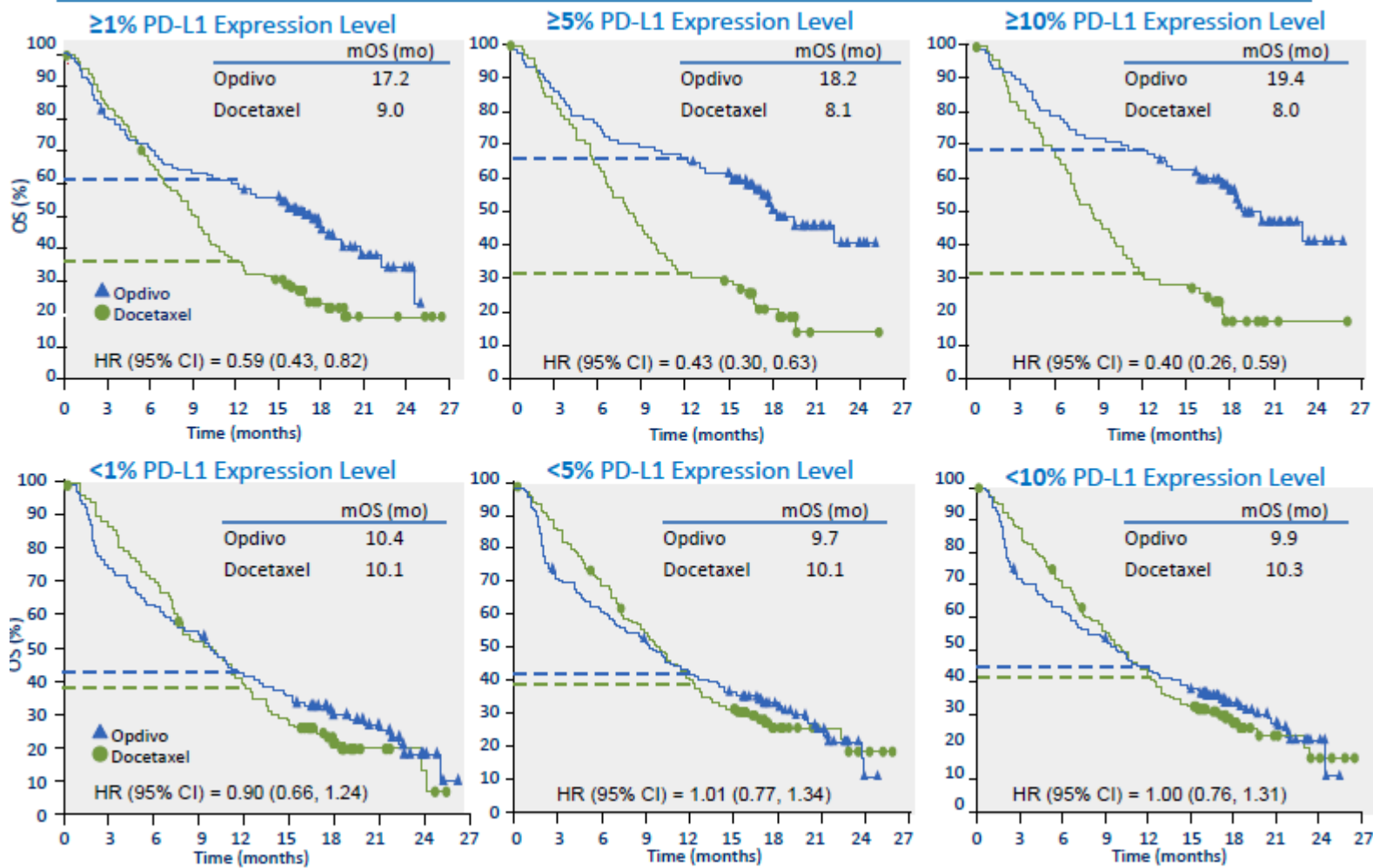


# Nivolumab: phase III, 2<sup>nd</sup> line Non-Squamous NSCLC CheckMate 057

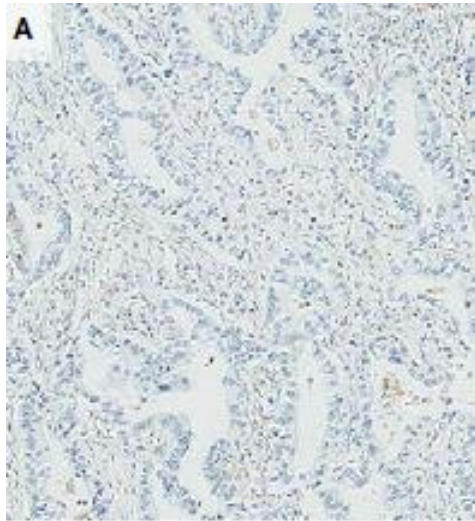


Response rate: 19%

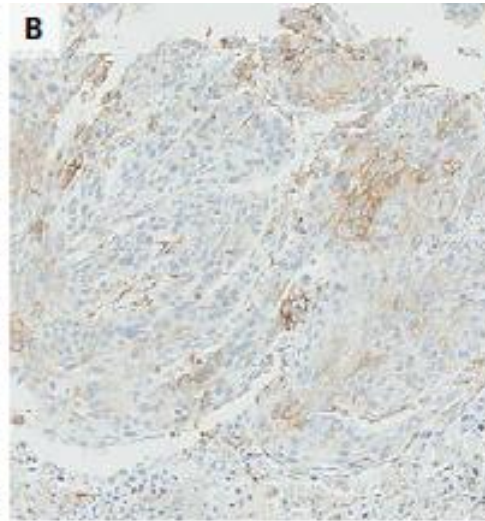
# Nivolumab: OS by PD-L1 expression Non-Squamous NSCLC



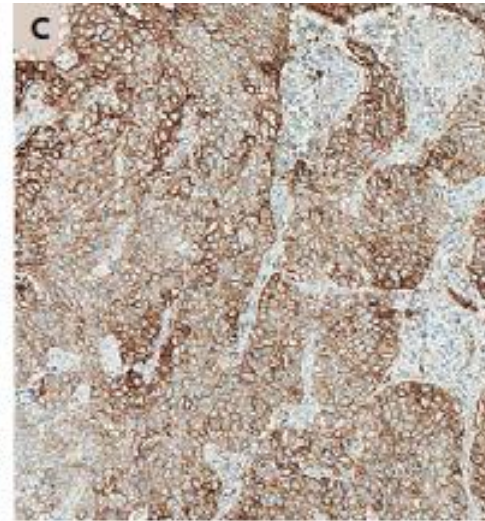
# Pembrolizumab: PD-L1 expression KEYNOTE 001



**PS <1%**



**PS 1-49%**

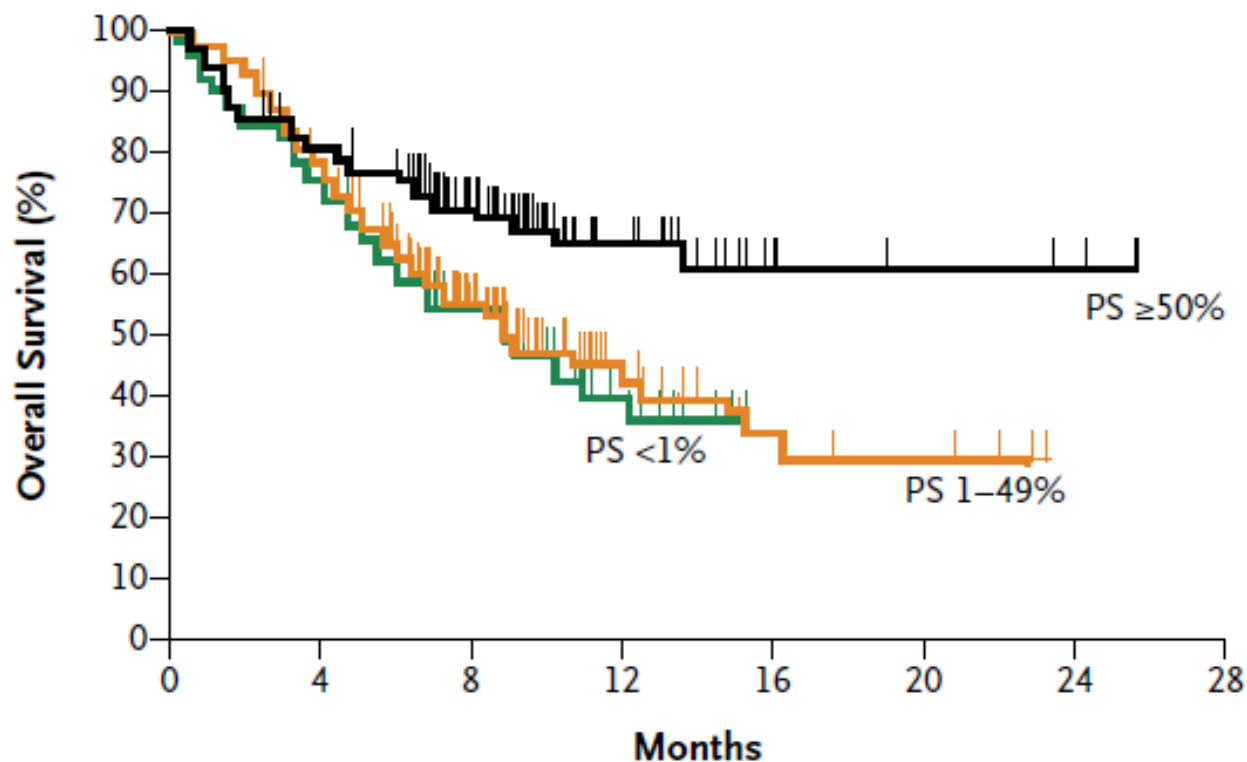


**PS ≥50%**

# Pembrolizumab: OS by PD-L1 expression

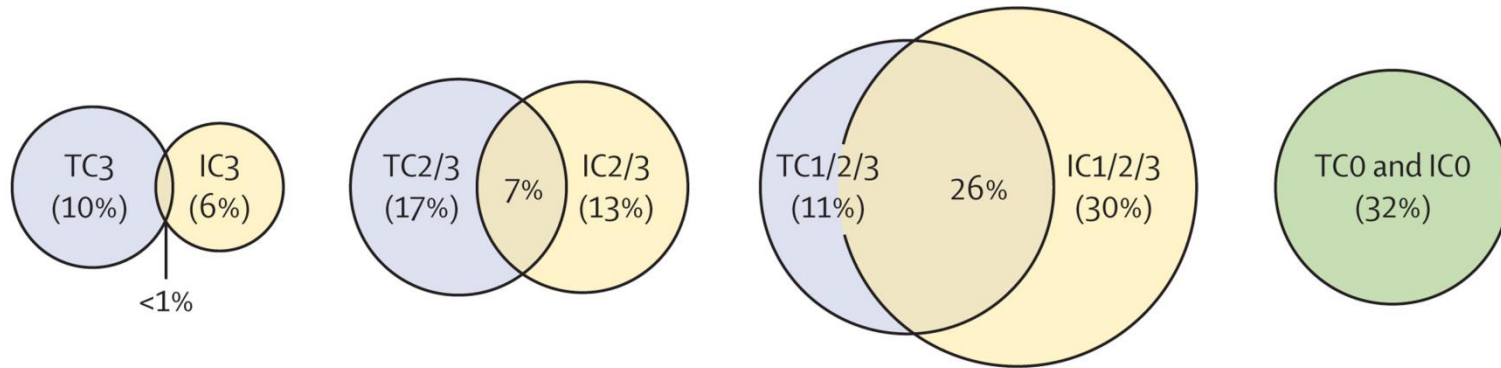
## KEYNOTE 001

All Patients



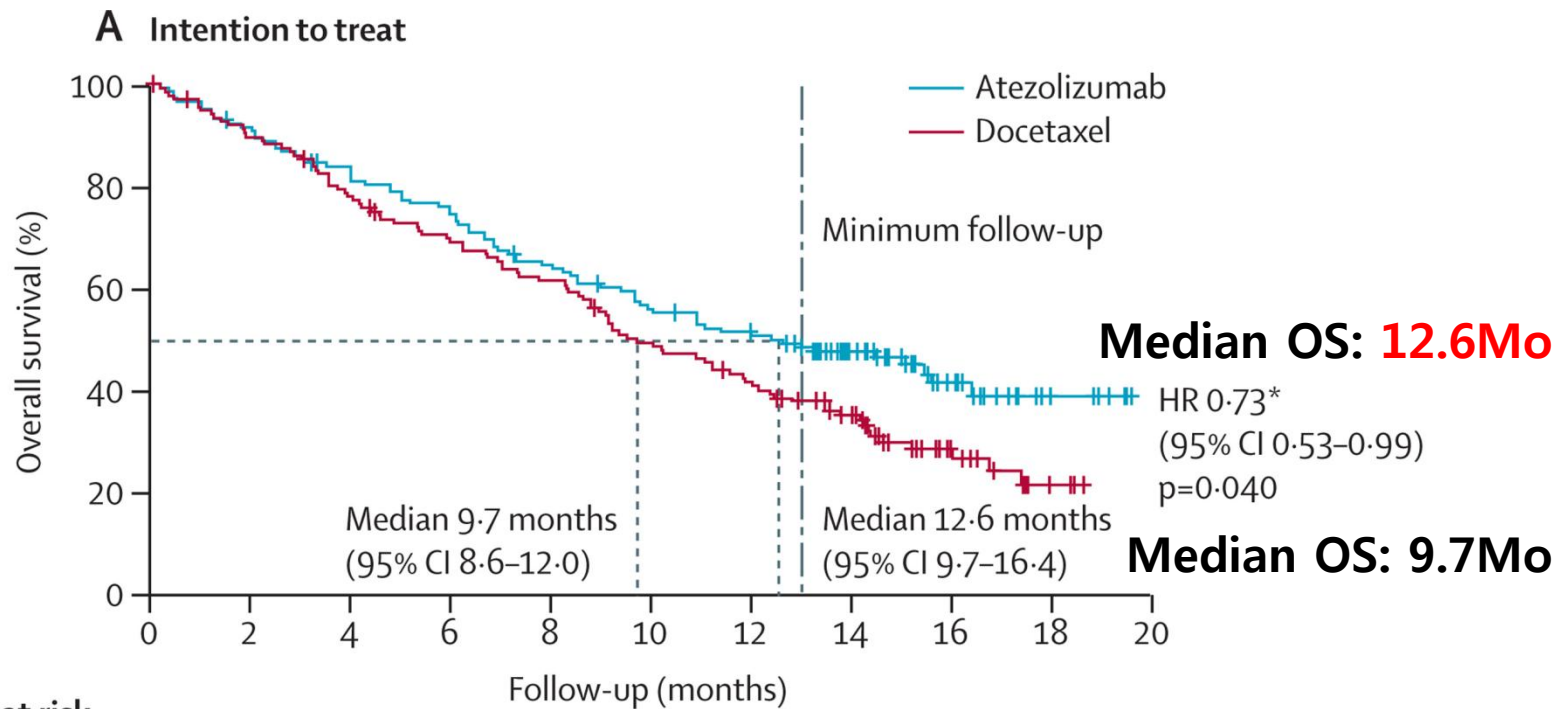
ORR: 19.4%, PS ≥50%: 45.2%

# Atezolizumab (MPDL3280A): phase II, 2<sup>nd</sup>/3<sup>rd</sup> line NSCLC POPLAR



PD-L1 tumour cell scoring		PD-L1 tumour-infiltrating immune cell scoring		Overall prevalence	
Score	Percentage of PD-L1-expressing cells	Score	Percentage of PD-L1-expressing cells	Subgroup	Proportion
TC3	≥50%	IC3	≥10%	TC3 or IC3	16%
TC2	≥5% and <50%	IC2	≥5% and <10%	TC2/3 or IC2/3	37%
TC1	≥1% and <5%	IC1	≥1% and <5%	TC1/2/3 or IC1/2/3	68%
TC0	<1%	IC0	<1%	TC0 and IC0	32%

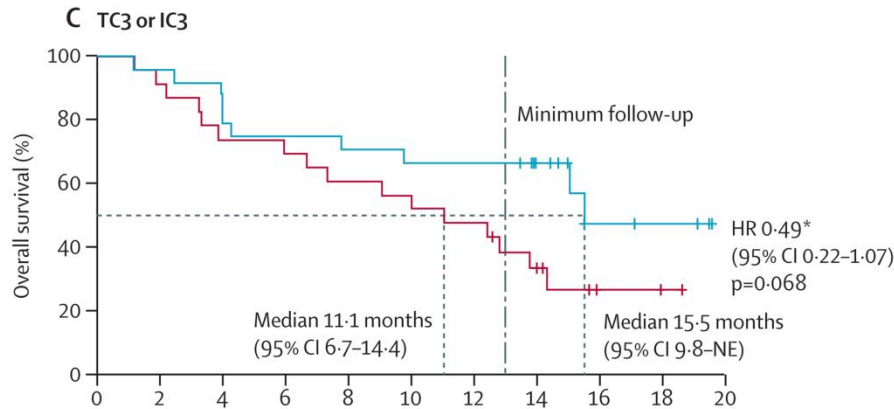
# Atezolizumab: phase II, 2<sup>nd</sup>/3<sup>rd</sup> line NSCLC POPLAR



**Number at risk**

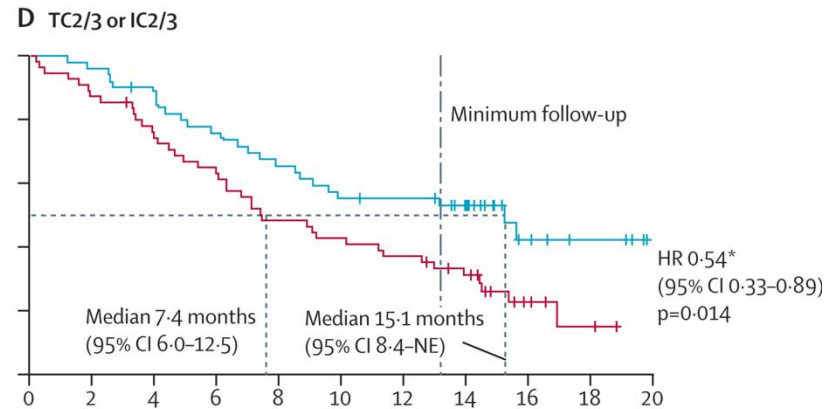
Atezolizumab	144	131	117	106	90	78	69	42	20	7	0
Docetaxel	143	123	106	92	82	65	54	39	17	3	0

# Atezolizumab: OS in PD-L1 subgroups POPLAR

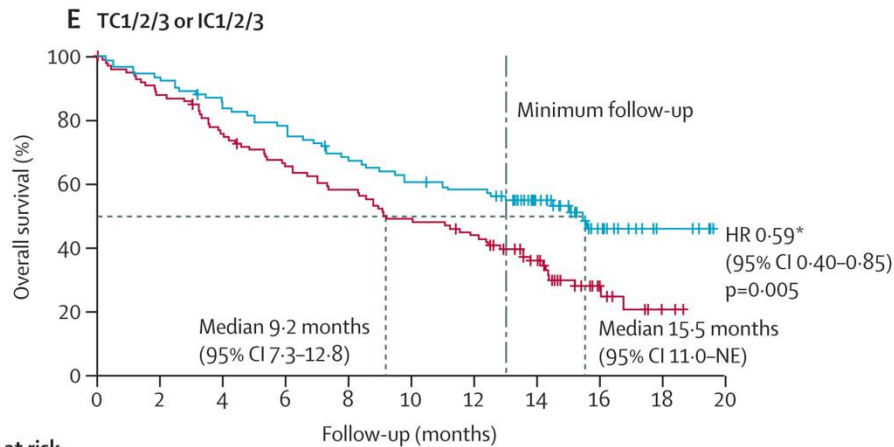


**Number at risk**

Atezolizumab	24	23	21	18	17	16	16	11	4	3	0
Docetaxel	23	21	17	16	14	13	11	7	2	1	0

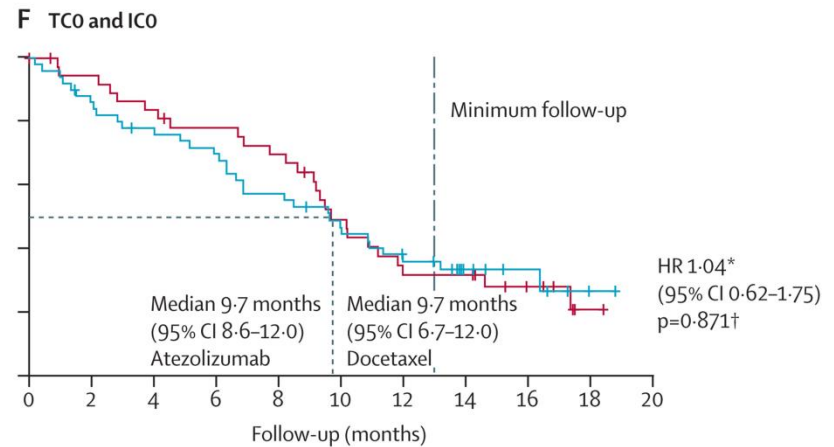


Atezolizumab	50	48	43	37	32	27	26	17	6	4	0
Docetaxel	55	48	40	33	26	23	20	15	4	1	0



**Number at risk**

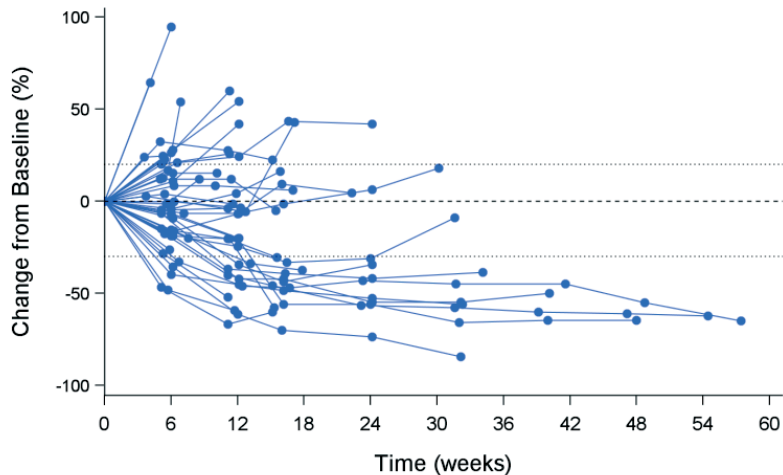
Atezolizumab	93	87	79	72	62	55	52	34	15	5	0
Docetaxel	102	88	75	64	57	48	42	28	10	2	0



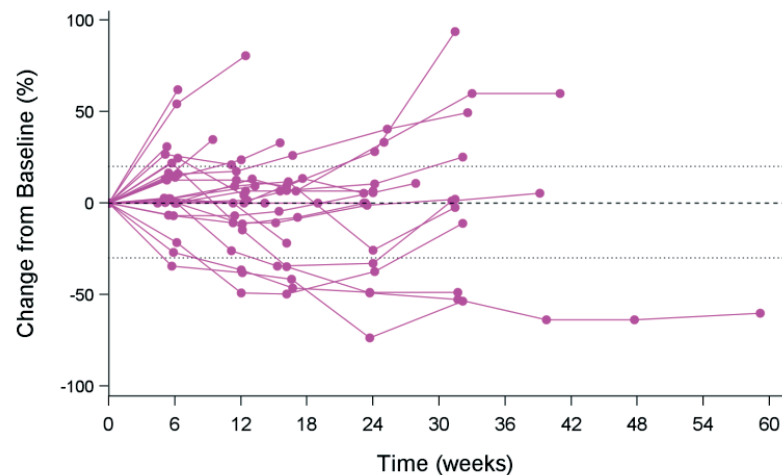
Atezolizumab	51	44	38	34	28	23	17	8	5	2	0
Docetaxel	41	35	31	28	25	17	12	11	7	1	0

# Durvalumab (MEDI4736): Study 1108

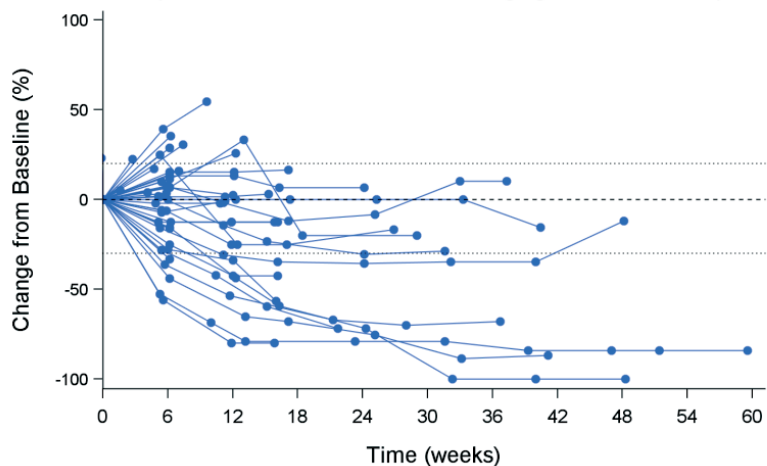
## Squamous PD-L1+ (n=40)



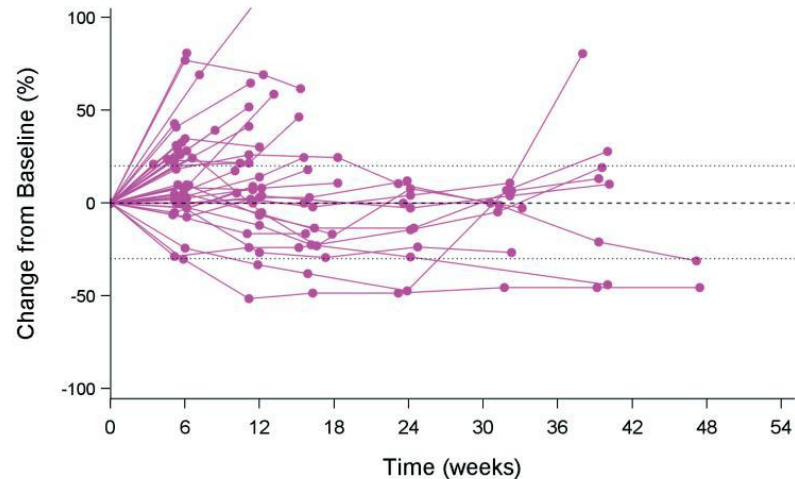
## Squamous PD-L1- (n=29)



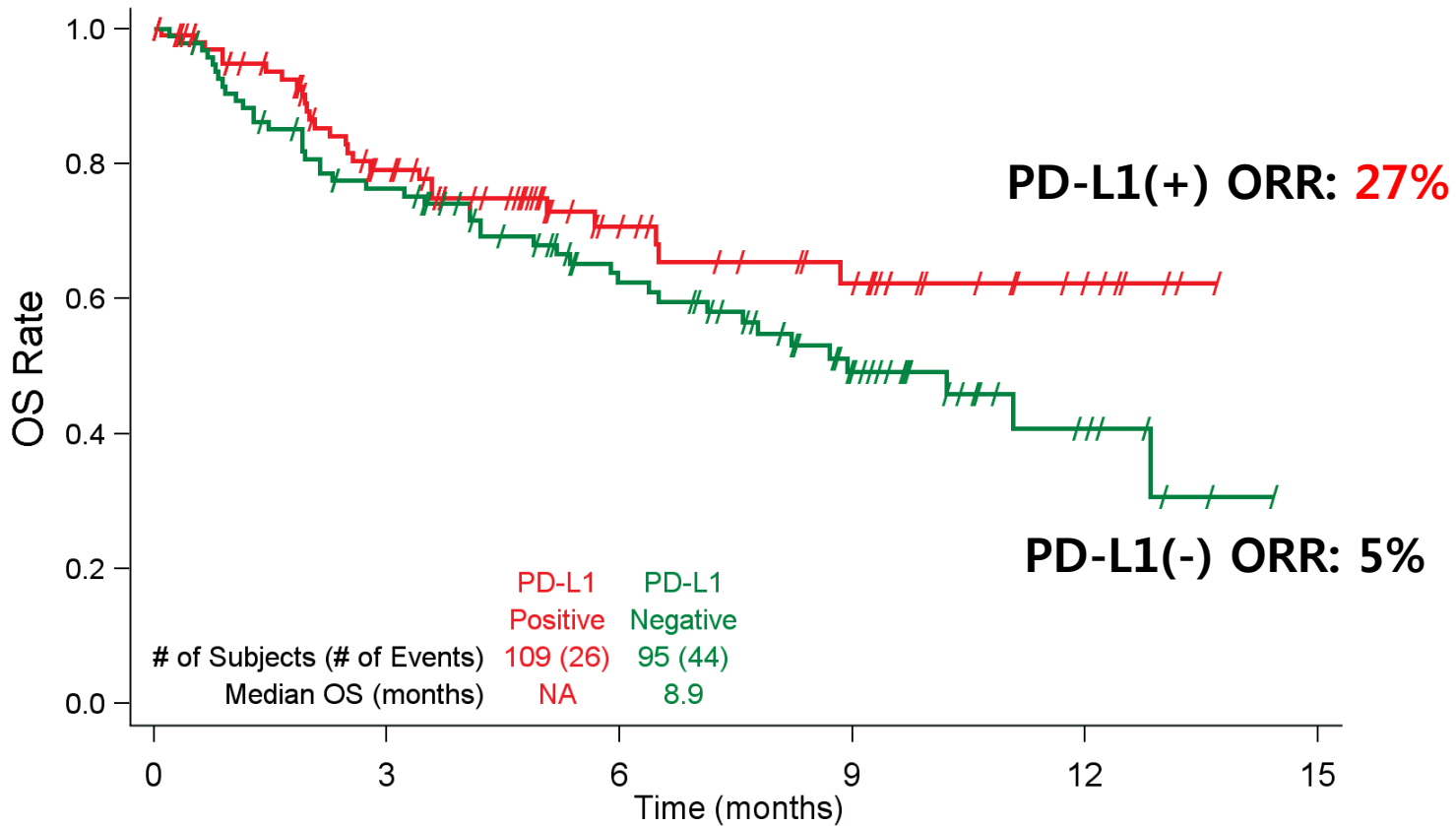
## Non-Squamous PD-L1+ (n=40)



## Non-Squamous PD-L1- (n=43)

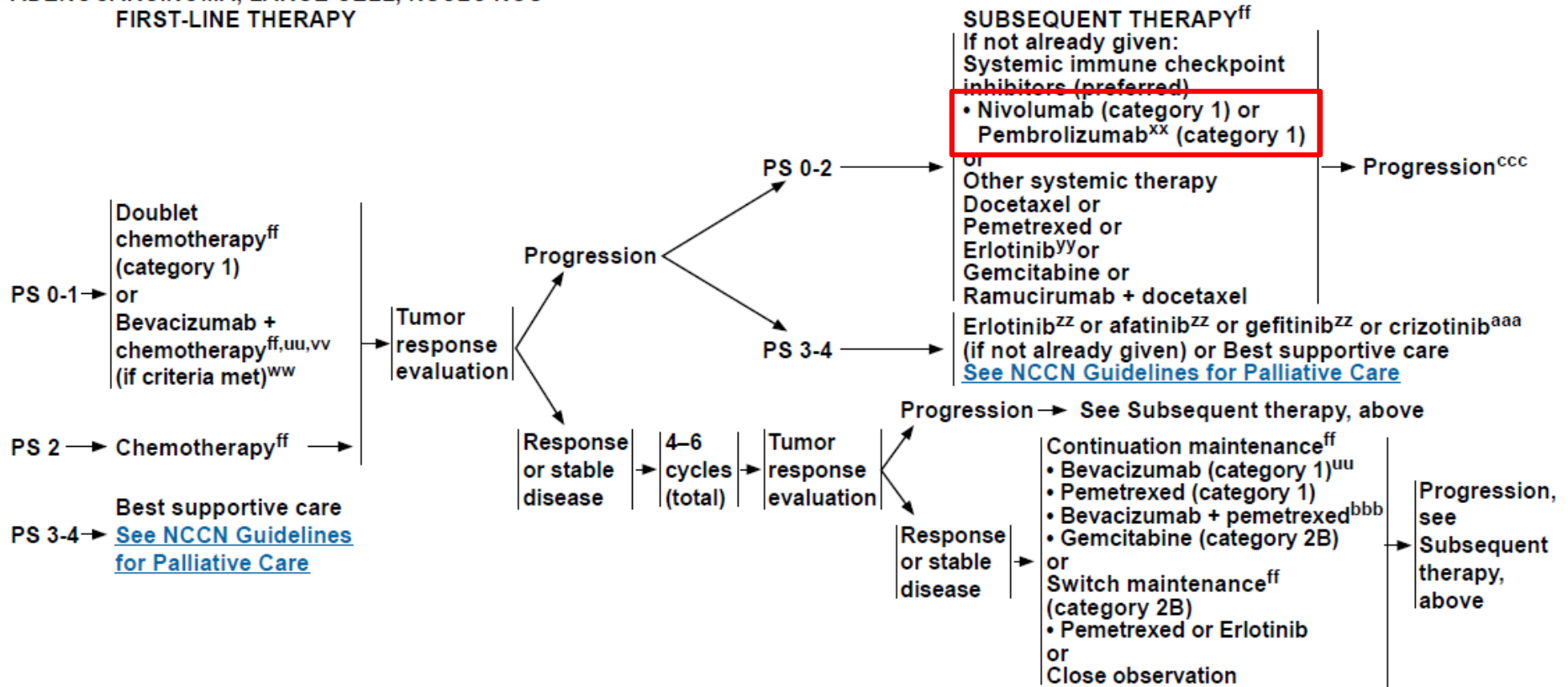


# Durvalumab: OS by PD-L1 expression



	0	3	6	9	12	15
# of Subjects at Risk	109	60	30	20	6	1
	95	68	44	23	7	1

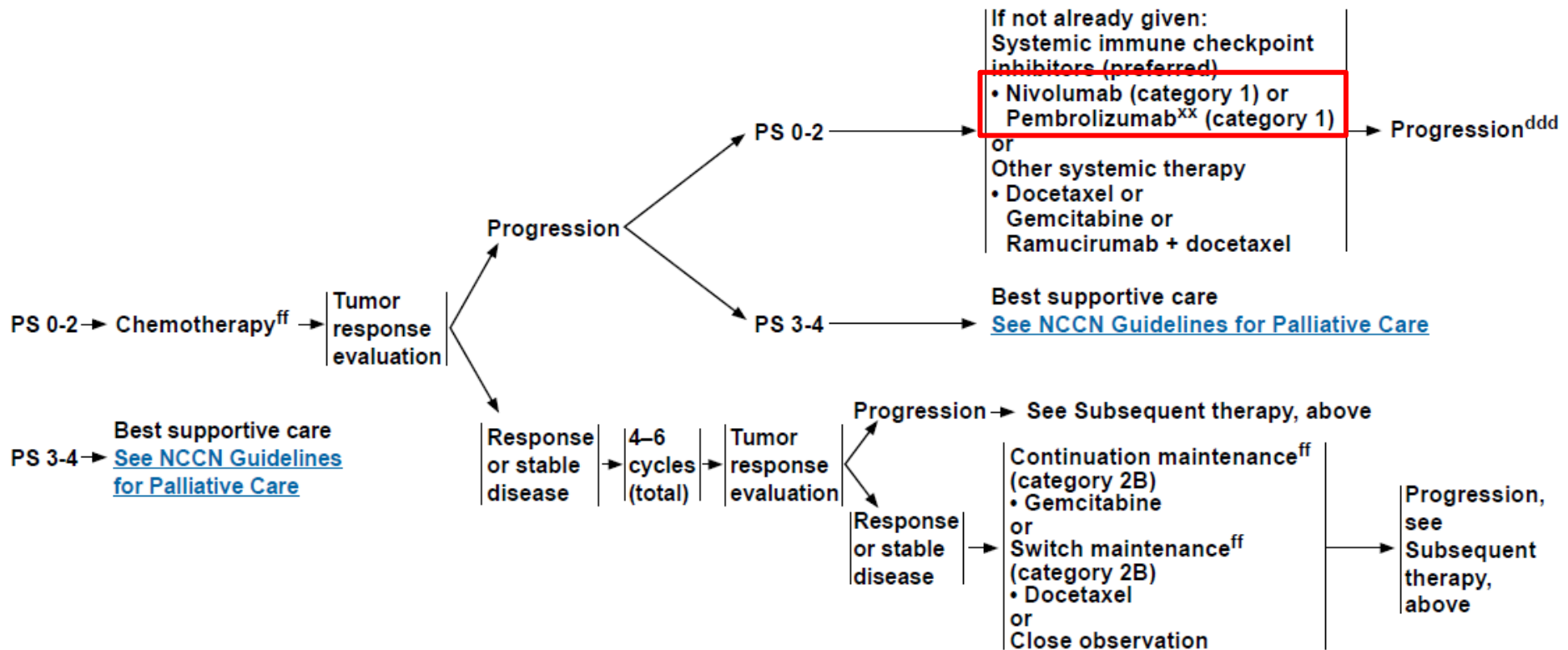
**ADENOCARCINOMA, LARGE CELL, NSCLC NOS<sup>tt</sup>**  
**FIRST-LINE THERAPY**



SQUAMOUS CELL CARCINOMA<sup>tt</sup>

FIRST-LINE THERAPY

SUBSEQUENT THERAPY<sup>ff</sup>



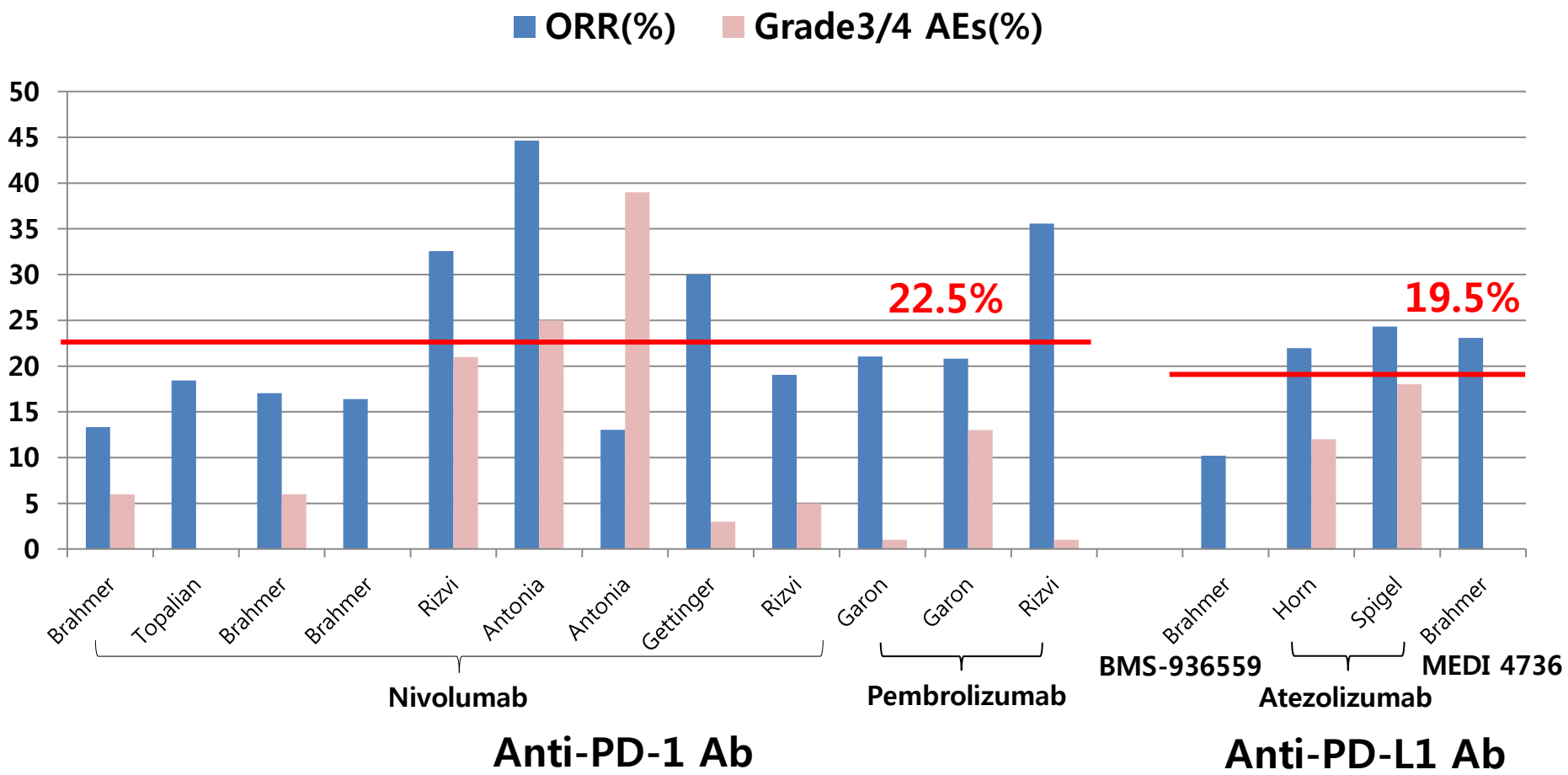
# Objective response rates with anti PD-1/PD-L1 therapy

Weighted averages of reported objective response rates and number of patients (*n*) with multiple different types of advanced cancers treated with PD-1/PD-L1 blockade

	Anti-PD-1			Anti-PD-L1		
	Nivolumab	Pembrolizumab	Pidilizumab	BMS-936559	MEDI4736	MPDL3280A
Melanoma	35% (424) [10,35,36]	27% (653) [12,13**,14]	6% (85) [15]	17% (52) [11]	–	30% (43) [16**]
NSCLC	19% (149) [10,17,18]	21% (226) [19,20]	–	10% (49) [11]	16% (58) [21]	23% (53) [16**]
RCC	20% (292) [10,22,33]	–	–	12% (17) [11]	–	14% (56) [16**]
Bladder	–	24% (29) [24]	–	–	–	26% (65) [25]
Prostate	0% (17) [10]	–	–	–	–	–
Hodgkin lymphoma	87% (23) [26**]	53% (15) [27]	–	–	–	–
Ovarian	23% (15) [29]	–	–	6% (17) [11]	–	–
Breast	–	19% (27) [30]	–	–	–	33% (9) [31]
CRC	1 <sup>a</sup> (33) [8,10]	–	–	–	–	–
Gastric	–	31% (29) [33]	–	–	–	–
SCCHN	–	20% (56) [32]	–	–	14% (22) [33]	–

<sup>a</sup> The one patient who demonstrated a response had a microsatellite instability (MSI)-high tumor.

# Anti PD-1/PD-L1 therapy: ORR & AE



# Intratumoral PD-L1 expression is associated with increased clinical benefit across PD-1/PD-L1-directed therapy with low specificity

## Nivolumab

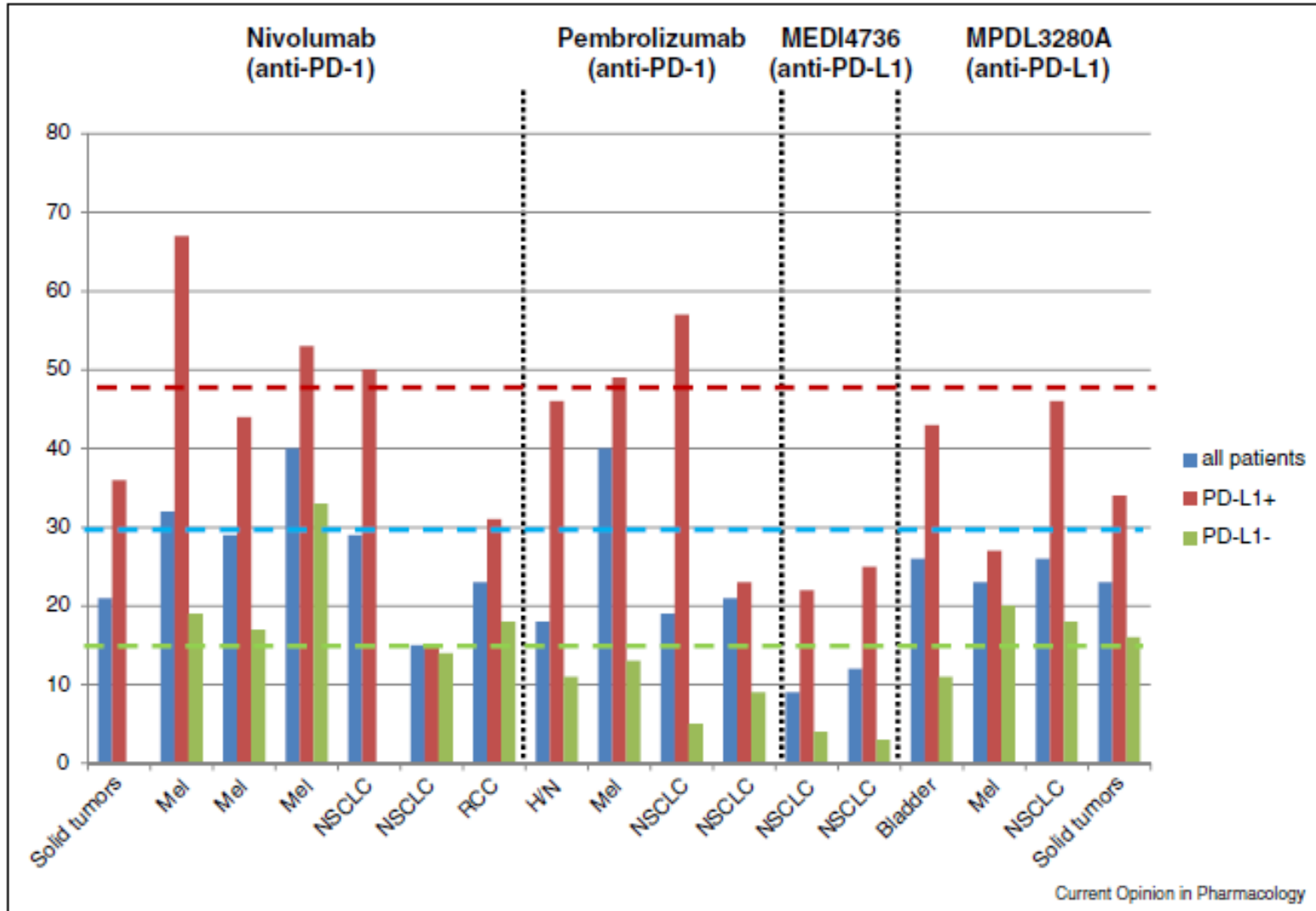
## Pembrolizumab

## MPDL3280A

## MEDI4736

	Solid Tumors	Melanoma	Melanoma	Melanoma	Non-Small-Cell Lung Cancer	Head and Neck	Melanoma	Solid Tumors	Melanoma	Non-Small-Cell Lung Cancer	Bladder	Solid Tumors
	Topalian NEJM 2012[45]	Weber JCO 2013[53]	Grosso ASCO 2013[52]	Daud AACR 2014[58]	Gandh AACR 2014[60]	Seiwert ASCO 2014[61]	Ribas ASCO 2014[59]	Herbst ASCO 2013[55]	Hamid ASCO 2013[44]	Soria ECC 2013[57]	Powles ASCO 2014[56]	Segal ASCO 2014[26]
N=	42	44	34	113	129	55	411	94	30	53	65	179
	Objective Response Rate											
Unselected	21%	32%	29%	40%	19%	18%	40%	21%	29%	23%	26%	11%
PD-L1+	36%	67%	44%	49%	37%	46%	49%	36%	27%	46%	43%	22%
PD-L1-	0%	19%	17%	13%	11%	11%	13%	13%	20%	15%	11%	4%
Treatment	Anti-PD-1 antibody						Anti-PD-L1 antibody					
Assay	Membranous pattern on tumor cells						Immune infiltrate					NR

# Association of PD-L1 expression with objective response to anti PD-1/PD-L1 therapy



Current Opinion in Pharmacology

# PD-L1 expression as prognostic factor : meta-analysis

## Overall Survival

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio	
				IV, Fixed, 95% CI	Year
<b>8.1.1 IHC</b>					
Mu 2011	0.65	0.28	15.3%	1.92 [1.11, 3.32]	2011
Ma 2011	0.19	0.89	1.5%	1.21 [0.21, 6.92]	2011
Chen YB 2012	1.02	0.26	17.7%	2.77 [1.67, 4.62]	2012
Azuma 2014	0.2	0.22	24.7%	1.22 [0.79, 1.88]	2014
Zhang 2014	0.5	0.53	4.3%	1.65 [0.58, 4.66]	2014
Yang 2014	0.09	0.73	2.2%	1.09 [0.26, 4.58]	2014
<b>Subtotal (95% CI)</b>			<b>65.7%</b>	<b>1.72 [1.32, 2.24]</b>	

Heterogeneity:  $\text{Chi}^2 = 6.49$ ,  $\text{df} = 5$  ( $P = 0.26$ );  $I^2 = 23\%$   
 Test for overall effect:  $Z = 4.01$  ( $P < 0.0001$ )

### 8.1.2 QIF

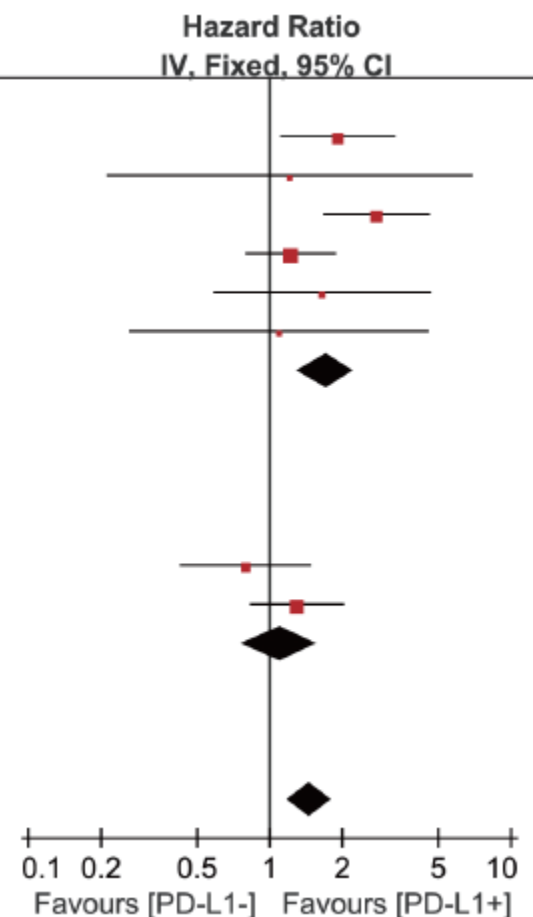
Velcheti(US) 2014	-0.23	0.32	11.7%	0.79 [0.42, 1.49]	2014
Velcheti(Greece) 2014	0.26	0.23	22.6%	1.30 [0.83, 2.04]	2014
<b>Subtotal (95% CI)</b>			<b>34.3%</b>	<b>1.10 [0.76, 1.58]</b>	

Heterogeneity:  $\text{Chi}^2 = 1.55$ ,  $\text{df} = 1$  ( $P = 0.21$ );  $I^2 = 35\%$   
 Test for overall effect:  $Z = 0.50$  ( $P = 0.62$ )

<b>Total (95% CI)</b>			<b>100.0%</b>	<b>1.47 [1.19, 1.83]</b>
-----------------------	--	--	---------------	--------------------------

Heterogeneity:  $\text{Chi}^2 = 11.81$ ,  $\text{df} = 7$  ( $P = 0.11$ );  $I^2 = 41\%$   
 Test for overall effect:  $Z = 3.54$  ( $P = 0.0004$ )

Test for subgroup differences:  $\text{Chi}^2 = 3.78$ ,  $\text{df} = 1$  ( $P = 0.05$ ),  $I^2 = 73.5\%$



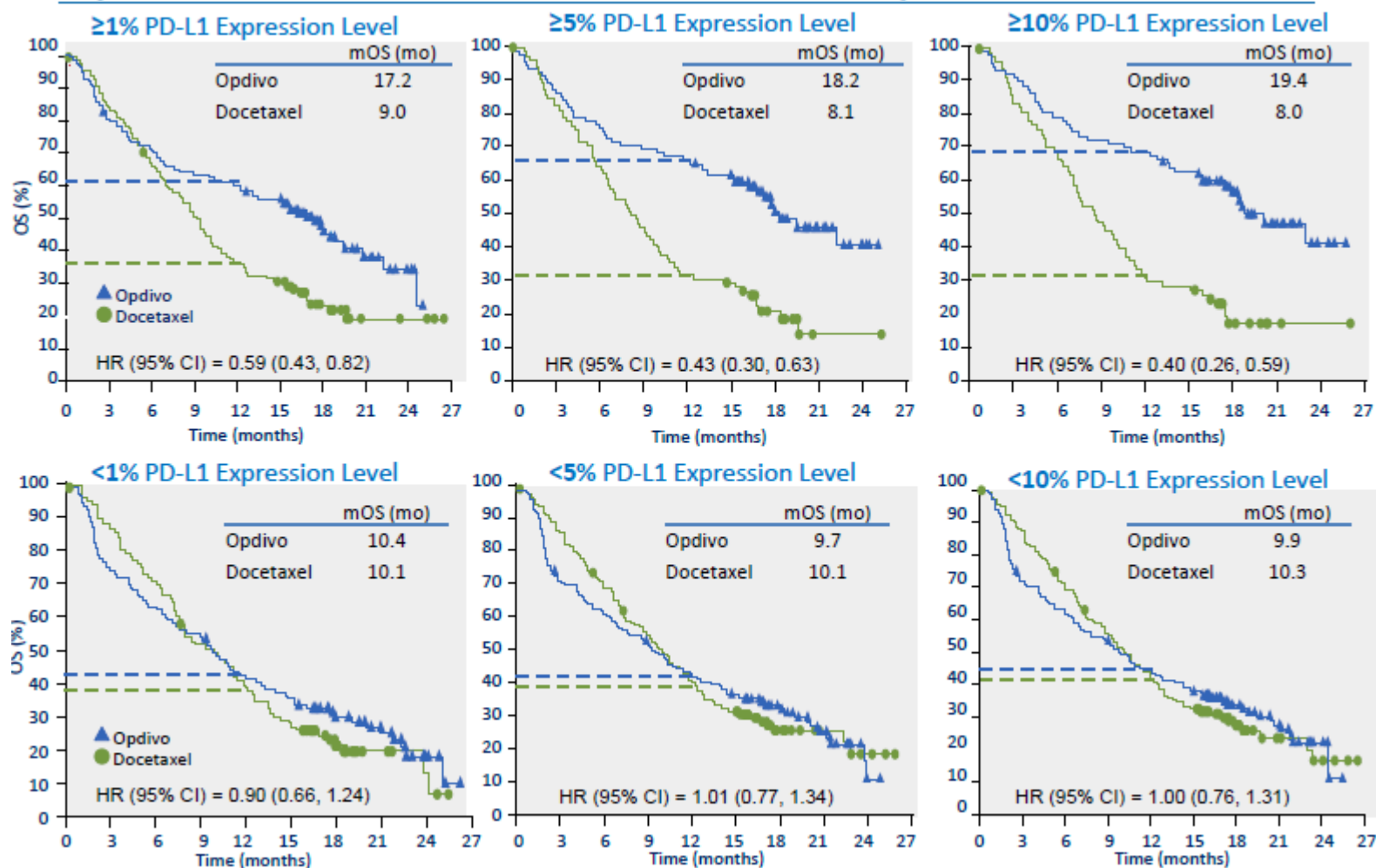
QIF, quantitative immunofluorescence;

# Nivolumab: phase III, 2<sup>nd</sup> line Squamous NSCLC

## CheckMate 017

Median OS by PD-L1 Expression Level,* Mos	Nivolumab	Docetaxel	Unstratified HR (95% CI)	Interaction <i>P</i> Value
≥ 1%	9.3	7.2	0.69 (0.45-1.05)	.56
< 1%	8.7	5.9	0.58 (0.37-0.92)	
≥ 5%	10.0	6.4	0.53 (0.31-0.89)	.47
< 5%	8.5	6.1	0.70 (0.47-1.02)	
≥ 10%	11.0	7.1	0.50 (0.28-0.89)	.41
< 10%	8.2	6.1	0.70 (0.48-1.01)	
Not quantifiable			0.39 (0.19-0.82)	

# Nivolumab: OS vs PD-L1 expression Non-Squamous NSCLC

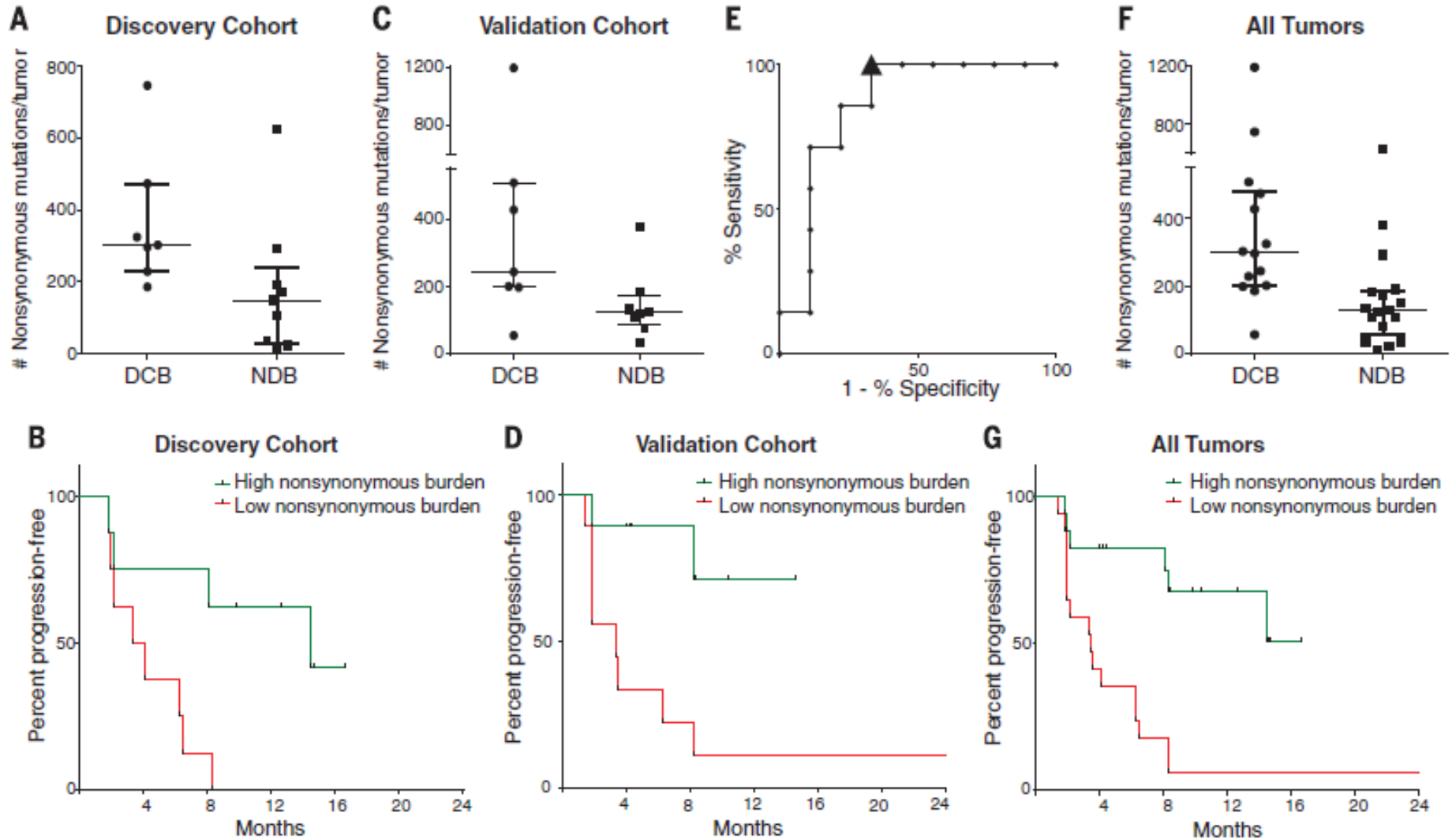


# Atezolizumab: OS in PD-L1 subgroups

## POPLAR

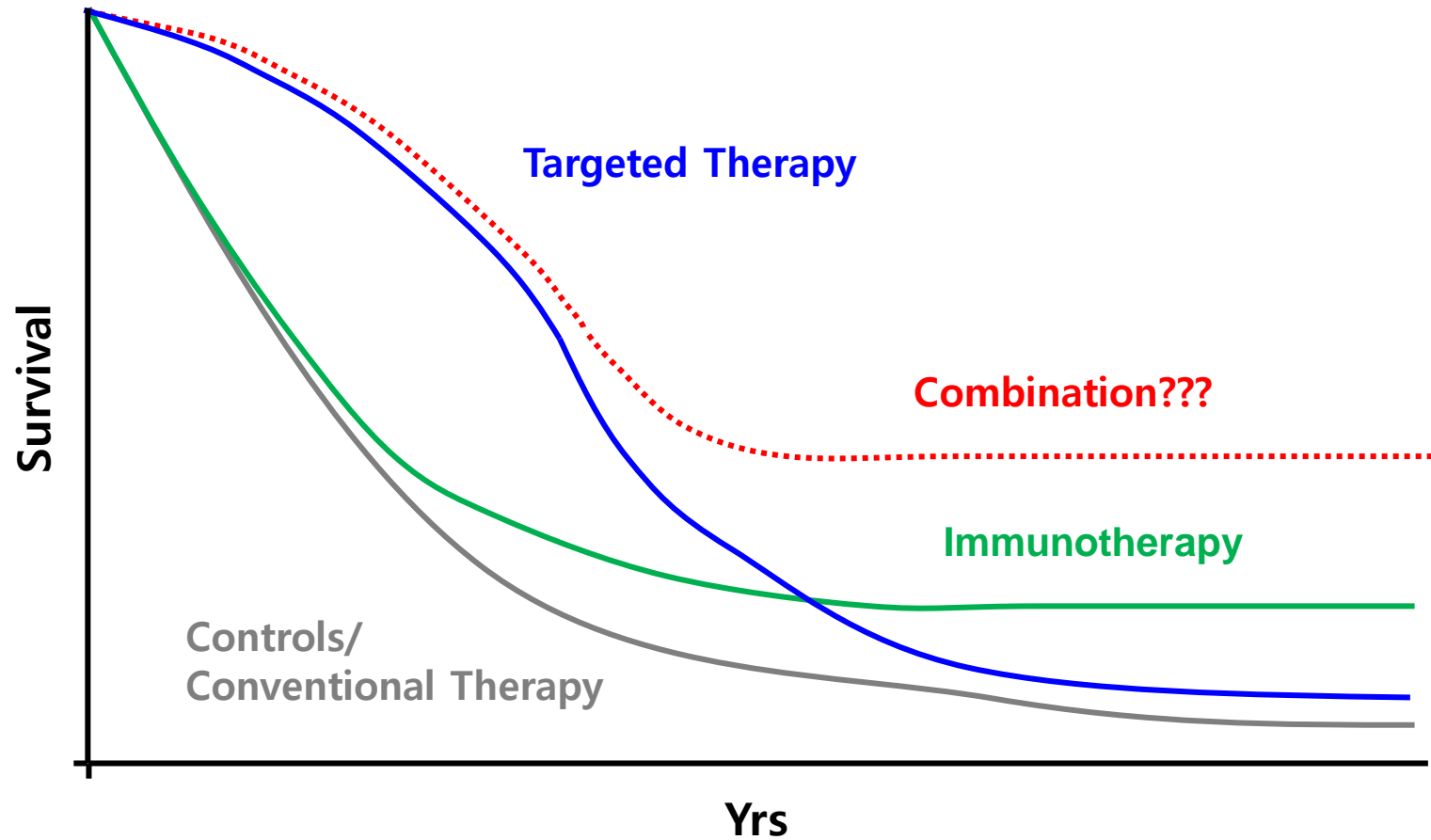
Interim Median OS Outcomes	Atezolizumab (n = 144)	Docetaxel (n = 143)	HR (95% CI)	P Value
ITT population (N = 287)	12.6	9.7	0.73 (0.53-0.99)	0.040
<b>Subgroups based on PD-L1 expression</b>				
TC0 and IC0 (n=92)	9.7	9.7	<b>1.04</b> (0.62-1.75)	0.871
TC1/2/3 or IC1/2/3 (n = 195)	<b>15.5</b>	9.2	<b>0.59</b> (0.40-0.85)	0.005
TC2/3 or IC2/3 (n = 105)	<b>15.1</b>	7.4	<b>0.54</b> (0.33-0.89)	0.014
TC3 or IC3 (n = 47)	<b>15.5</b>	11.1	<b>0.49</b> (0.22-1.07)	0.068

# Mutational landscape determines sensitivity to PD-1 blockade in NSCLC



\*DCB: durable clinical benefit (PR or SD >6mo), NDB: no durable benefit

# Combining immunotherapy & conventional tx



# **Future oncologic clinical investigations**

## **Personalized combinatorial therapies**

**+ chemotherapy, radiation, surgery**

**+ immunotherapy**

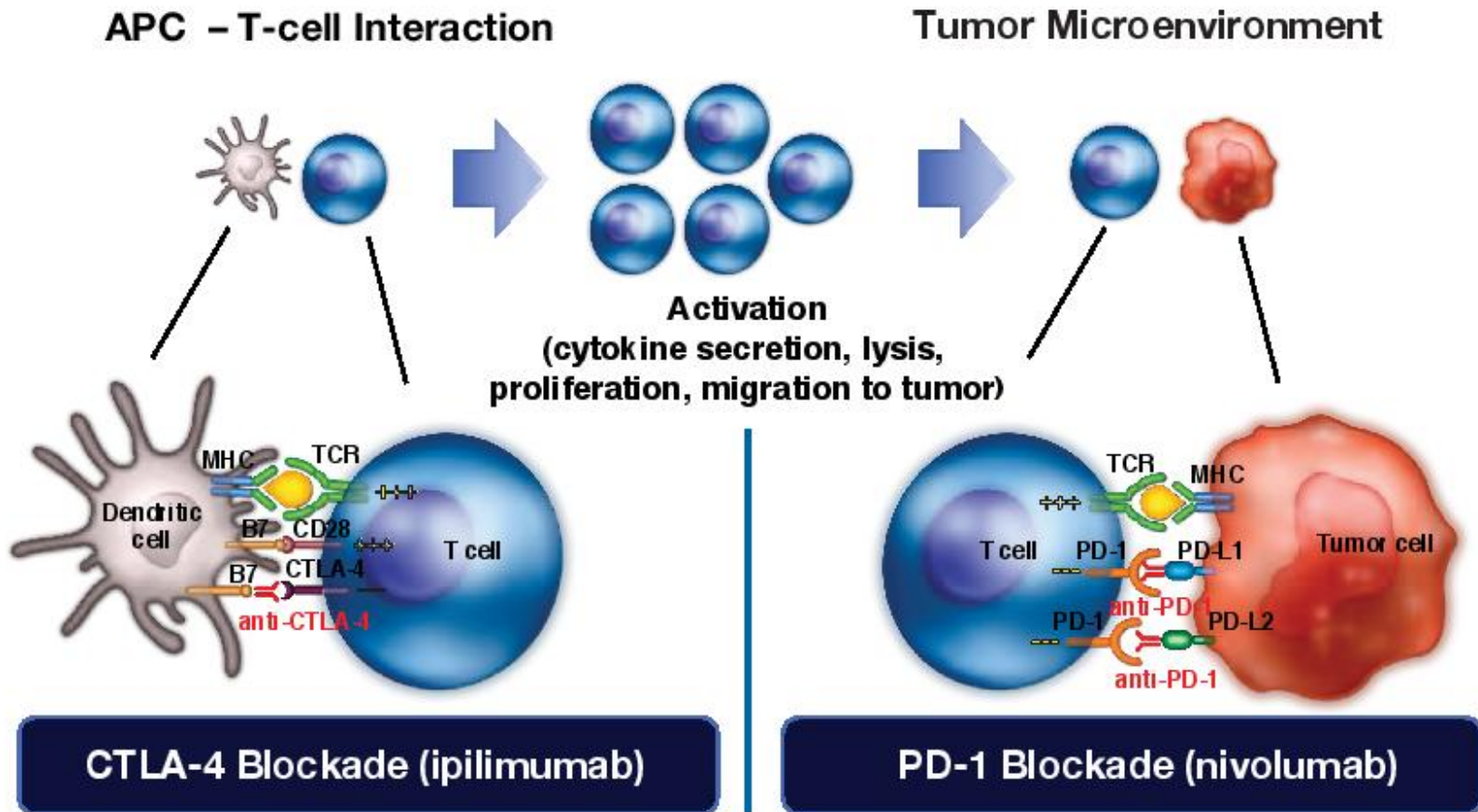
**+ epigenetic modulation**

**+ genetic characterization**

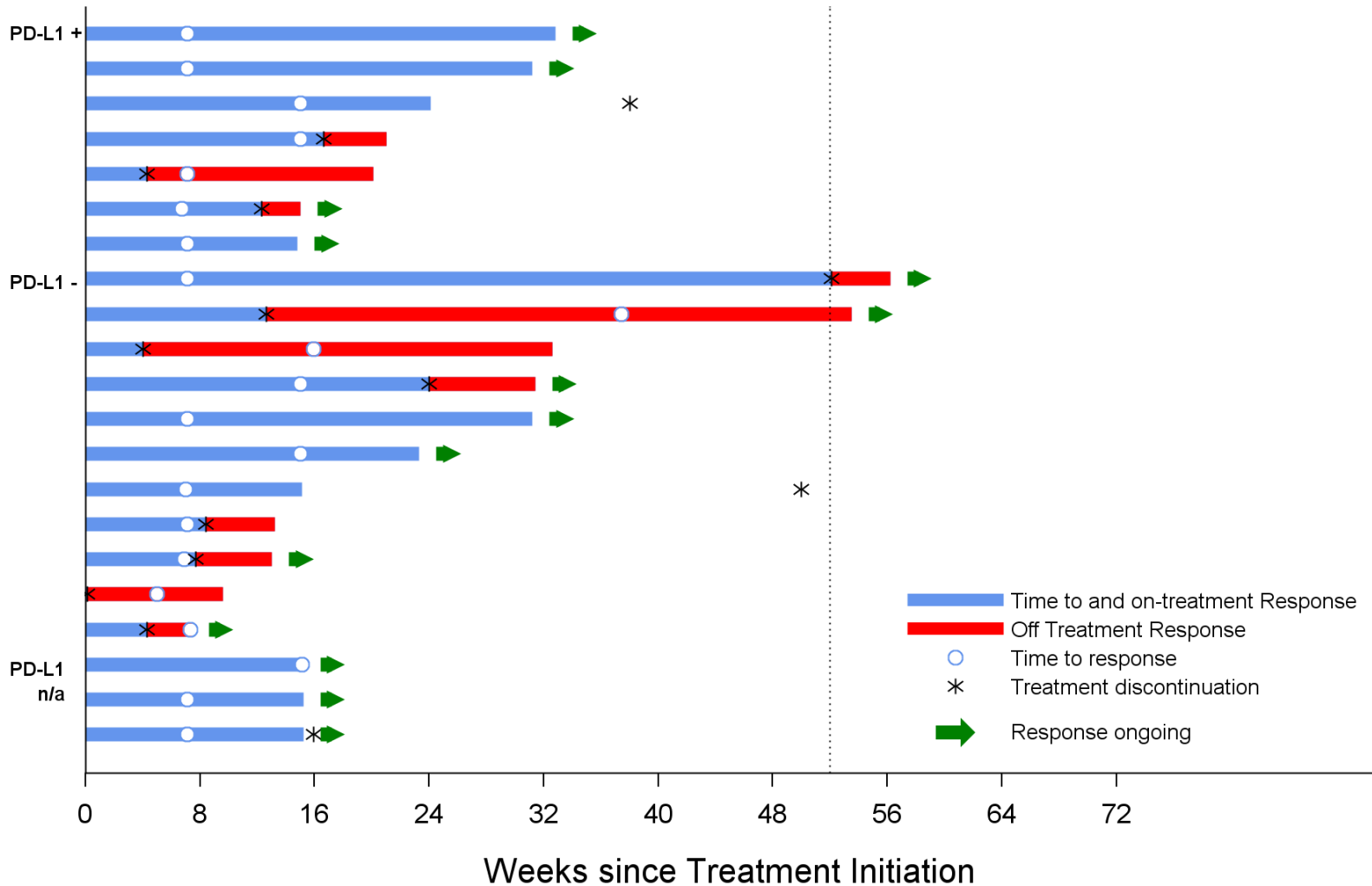
# **Combining immunotherapies that target distinct immune pathways**

- 1. Dual T-cell checkpoint blockade**
- 2. T-cell checkpoint blockade  
+ costimulatory receptor agonists**
- 3. T-cell checkpoint blockade  
+ improving the function of innate immune cells**
- 4. T-cell checkpoint blockade  
+ other immune system activators (Vaccine)**

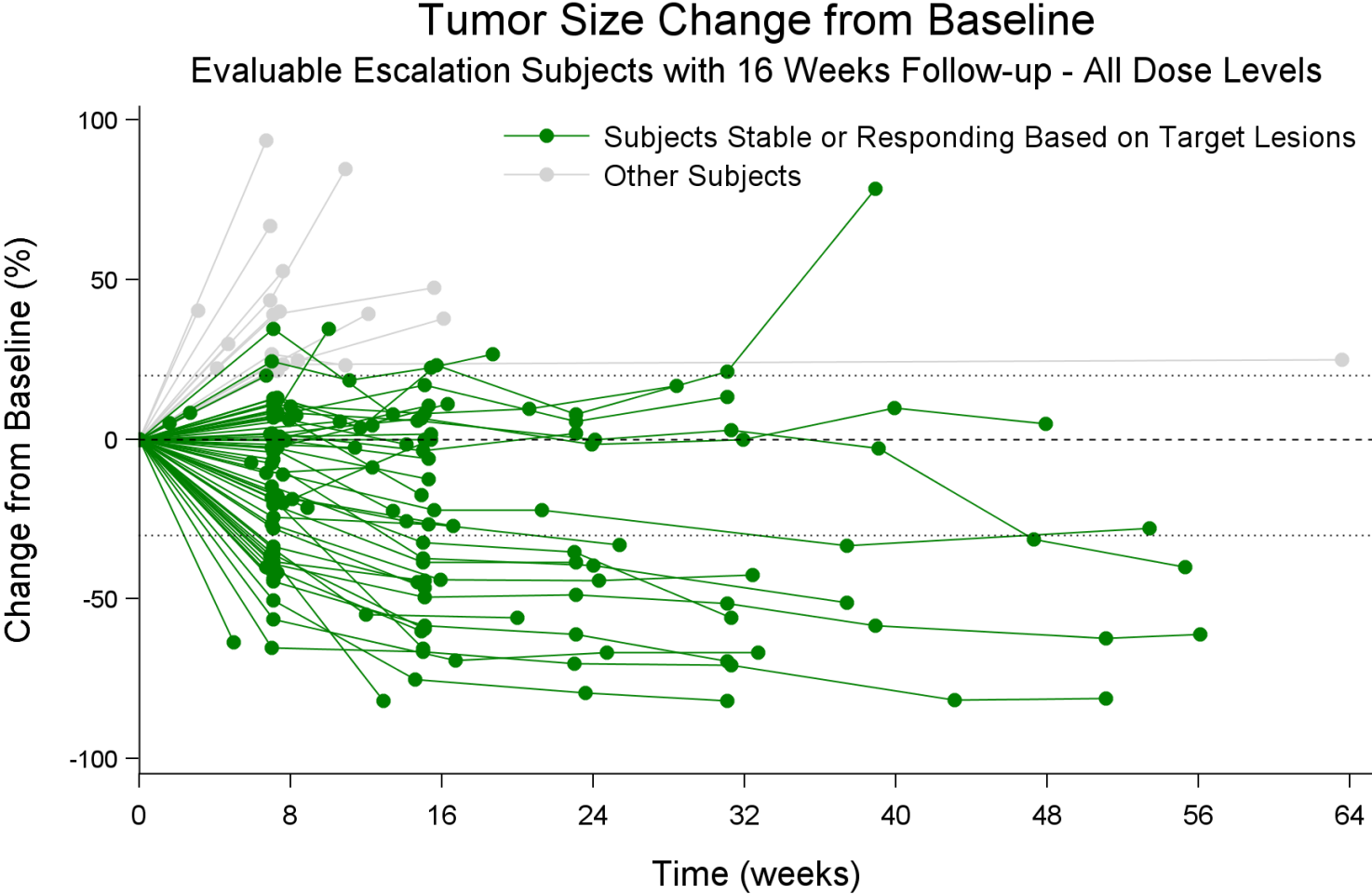
# Dual T-cell checkpoint blockade



# Durvalumab (anti-PD-L1)+Tremelimumab (anti-CTLA-4) durable response

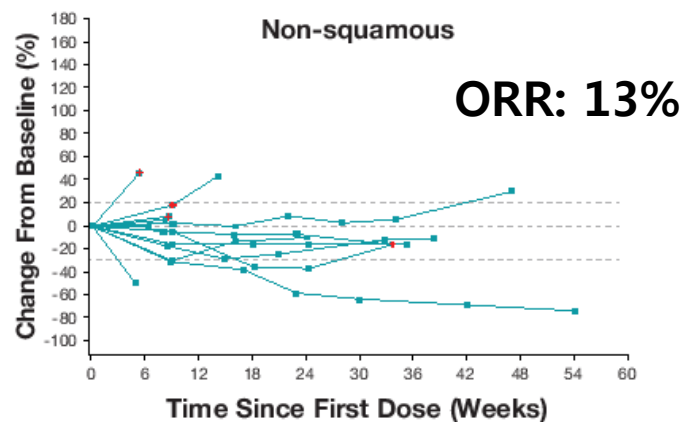
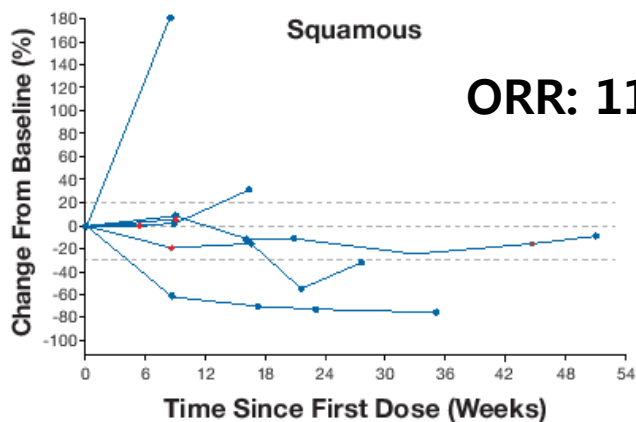


# Durvalumab+Tremelimumab: durable response

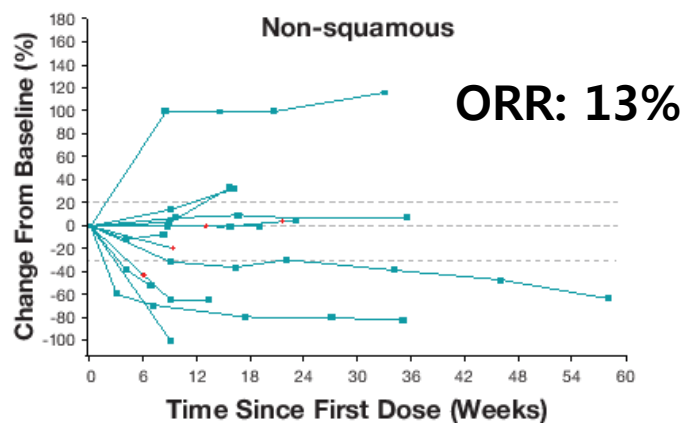
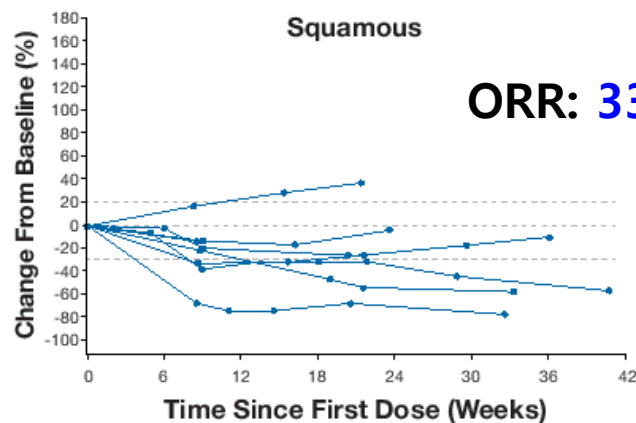


# Nivolumab (anti-PD-1) + Ipilimumab (anti-CTLA-4)

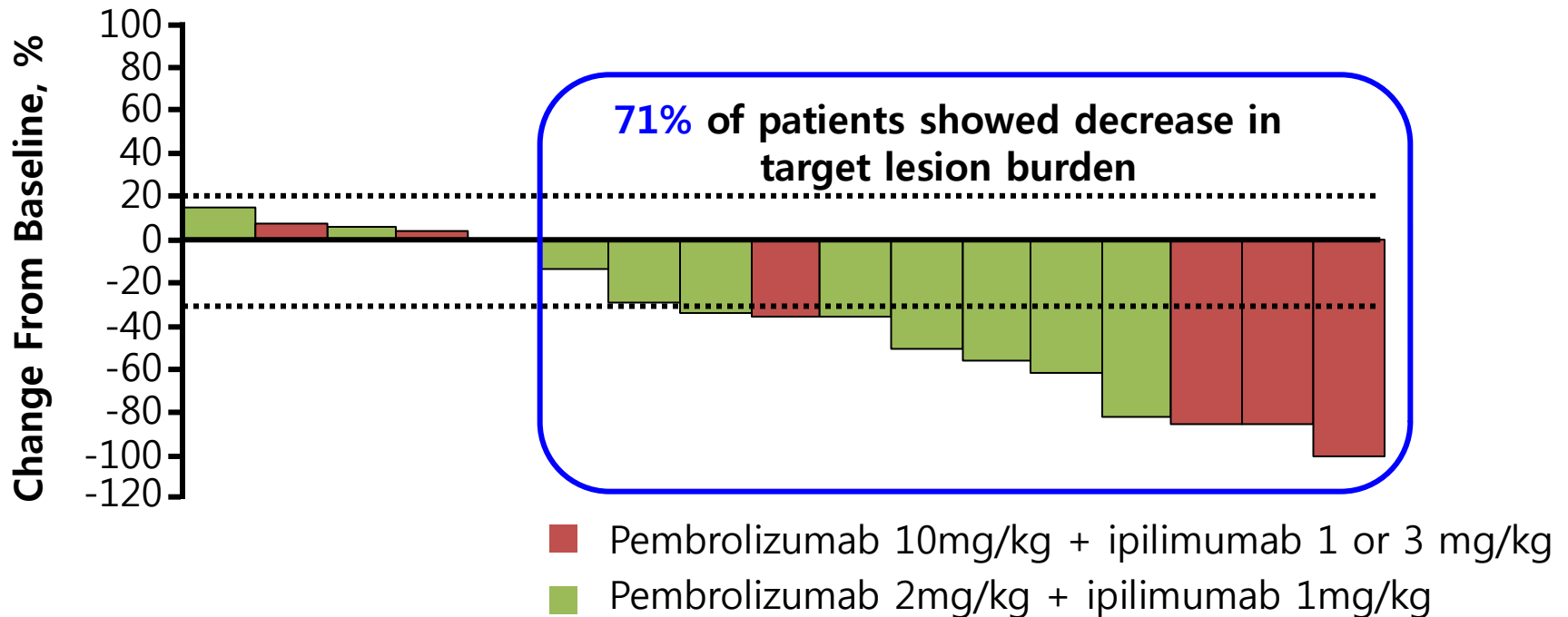
A Nivolumab 1 mg/kg + ipilimumab 3 mg/kg



B Nivolumab 3 mg/kg + ipilimumab 1 mg/kg



# Pembrolizumab (anti-PD-1) + Ipilimumab (anti-CTLA-4) KEYNOTE 021



- **ORR (N = 18): 39% including 1 CR**

# Combination approaches in immunotherapies

Drugs	Target	Development phase/tumor type
<b>Dual T-cell checkpoint blockade</b>		
Ipilimumab + nivolumab	CTLA-4 + PD-1	Phase III: melanoma; phase I/II: RCC, colon, NSCLC, triple-negative breast cancer, gastric cancer pancreatic cancer, and SCLC
Ipilimumab + pembrolizumab	CTLA-4 + PD-1	Phase I: melanoma, RCC, and NSCLC
Tremelimumab + MEDI4736	CTLA-4 + PD-L1	Phase I: NSCLC, solid tumors
Nivolumab + BMS-986016	PD-1 + LAG-3	Phase I: solid tumors
<b>T-cell blockade + costimulatory receptor agonists</b>		
CP-870,893 + tremelimumab	CTLA -4 + CD40	Phase I: metastatic melanoma
<b>T-cell blockade + improving the function of innate immune cells</b>		
Lirilumab + ipilimumab	CTLA-4 + KIR	Phase I: solid tumors
Lirilumab + nivolumab	PD-1 + KIR	Phase I: solid tumors
<b>T-cell blockade + other immune system activators</b>		
Denenicokin + ipilimumab	CTLA-4 + IL21	Phase I: melanoma
Denenicokin + nivolumab	PD-1 + IL21	Phase I: solid tumors
INCB024360 + ipilimumab	CTLA-4 + IDO	Phase I: melanoma
Indoximod + sipuleucel-T	IDO + vaccine	Phase II: prostate
Nivolumab + gp100, NY-ESO-1	PD-1 + vaccine	Phase I: melanoma
Ipilimumab + sipuleucel-T	CTLA-4 + vaccine	Phase II: prostate cancer
Ipilimumab + TriMix-DC	CTLA-4 + vaccine	Phase II: melanoma
Ipilimumab + NY-ESO-1 vaccine	CTLA-4 + vaccine	Phase I: melanoma
Ipilimumab + adoptive cell transfer	CTLA-4 + passive immunotherapy	Phase I/II: melanoma

# **Integrating immunotherapies with existing therapeutic modalities**

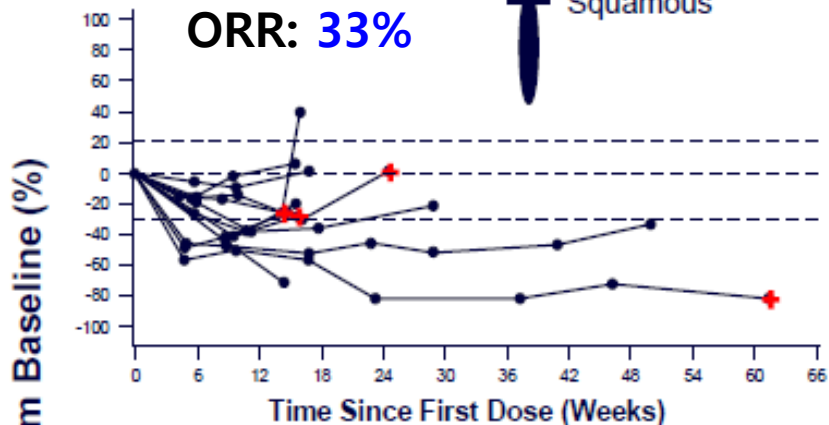
- 1. Immune checkpoint blockade  
+ Chemotherapy, Radiotherapy**
- 2. Immune checkpoint blockade  
+ Target therapy: EGFR-TKI, Anti-VEGF**
- 3. Immune checkpoint blockade  
+ Epigenetic agents: HDAC inhibitor**

# Nivolumab (anti-PD-1) + Chemotherapy :Checkmate012

### Nivolumab 10 mg/kg + Gem/Cis

ORR: 33%

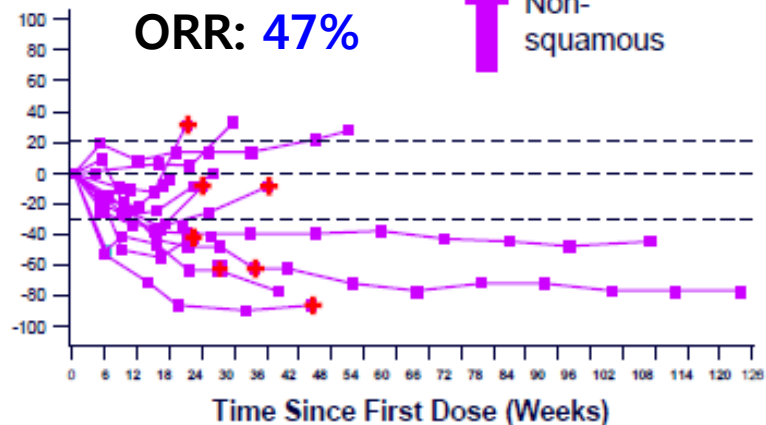
Squamous



### Nivolumab 10 mg/kg + Pem/Cis

ORR: 47%

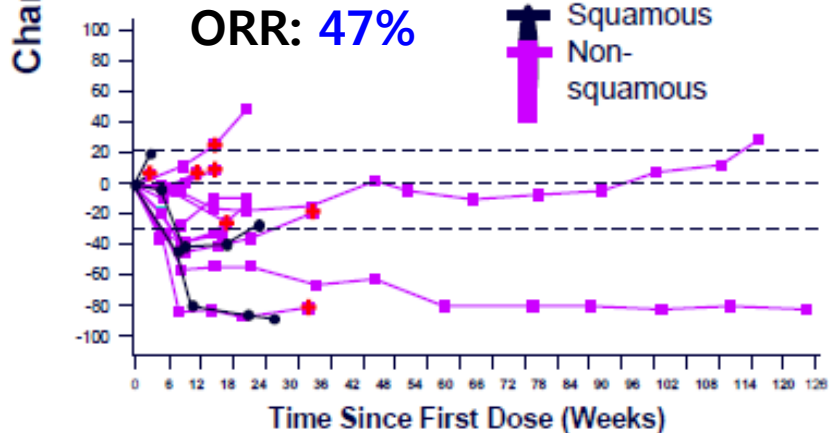
Non-squamous



### Nivolumab 10 mg/kg + Pac/Carb

ORR: 47%

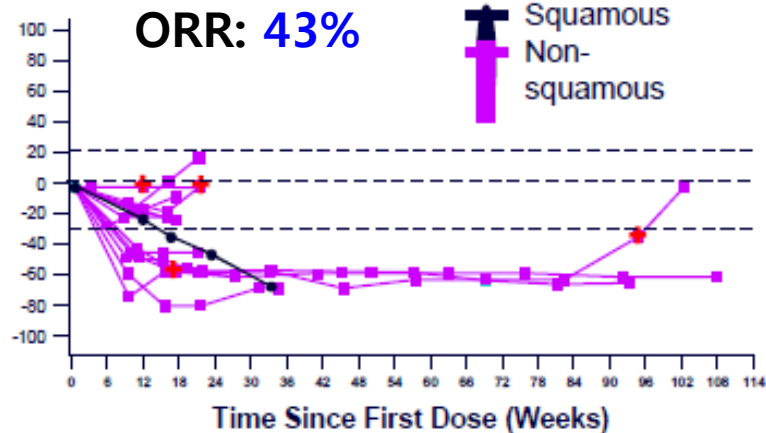
Squamous  
Non-squamous



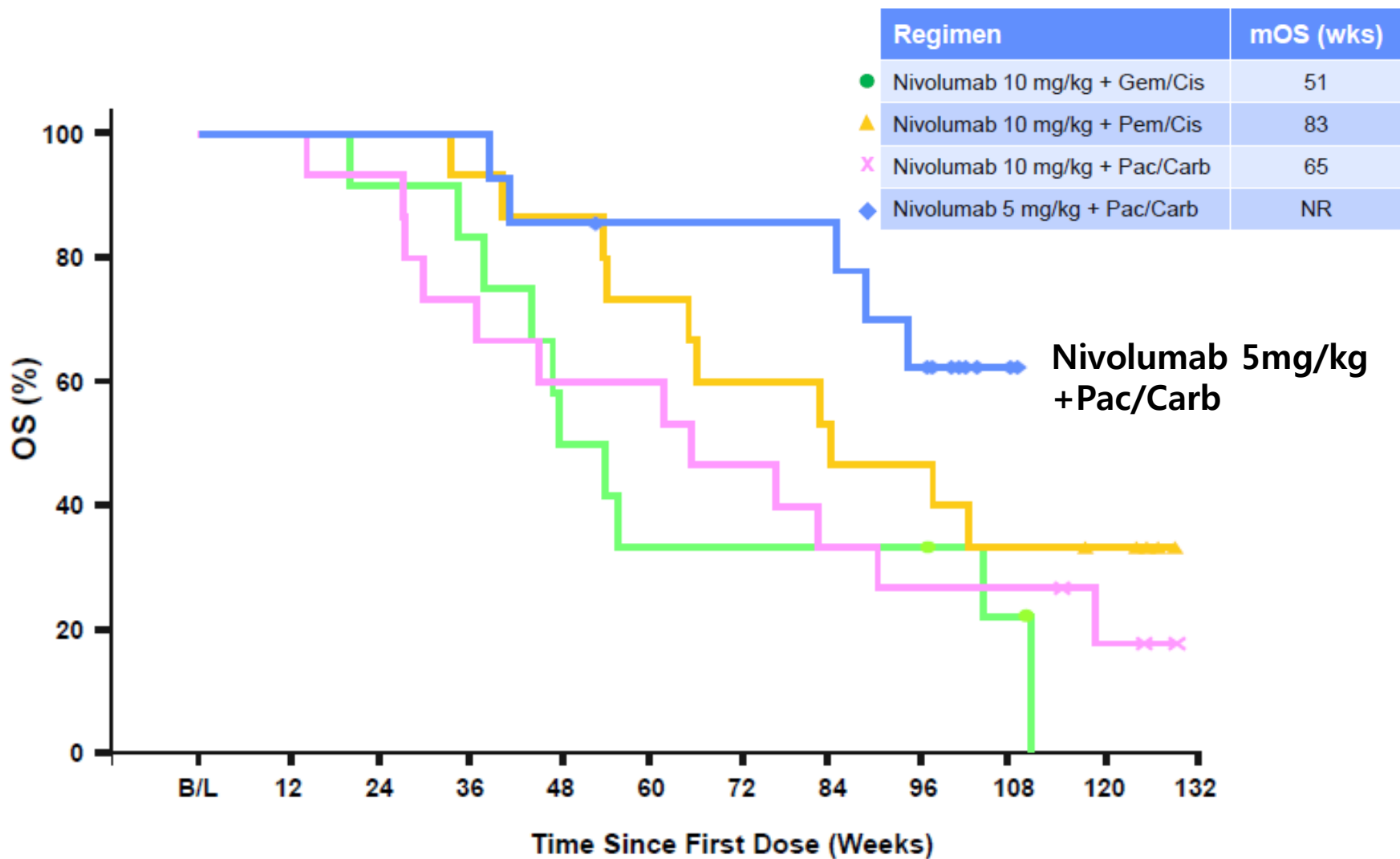
### Nivolumab 5 mg/kg + Pac/Carb

ORR: 43%

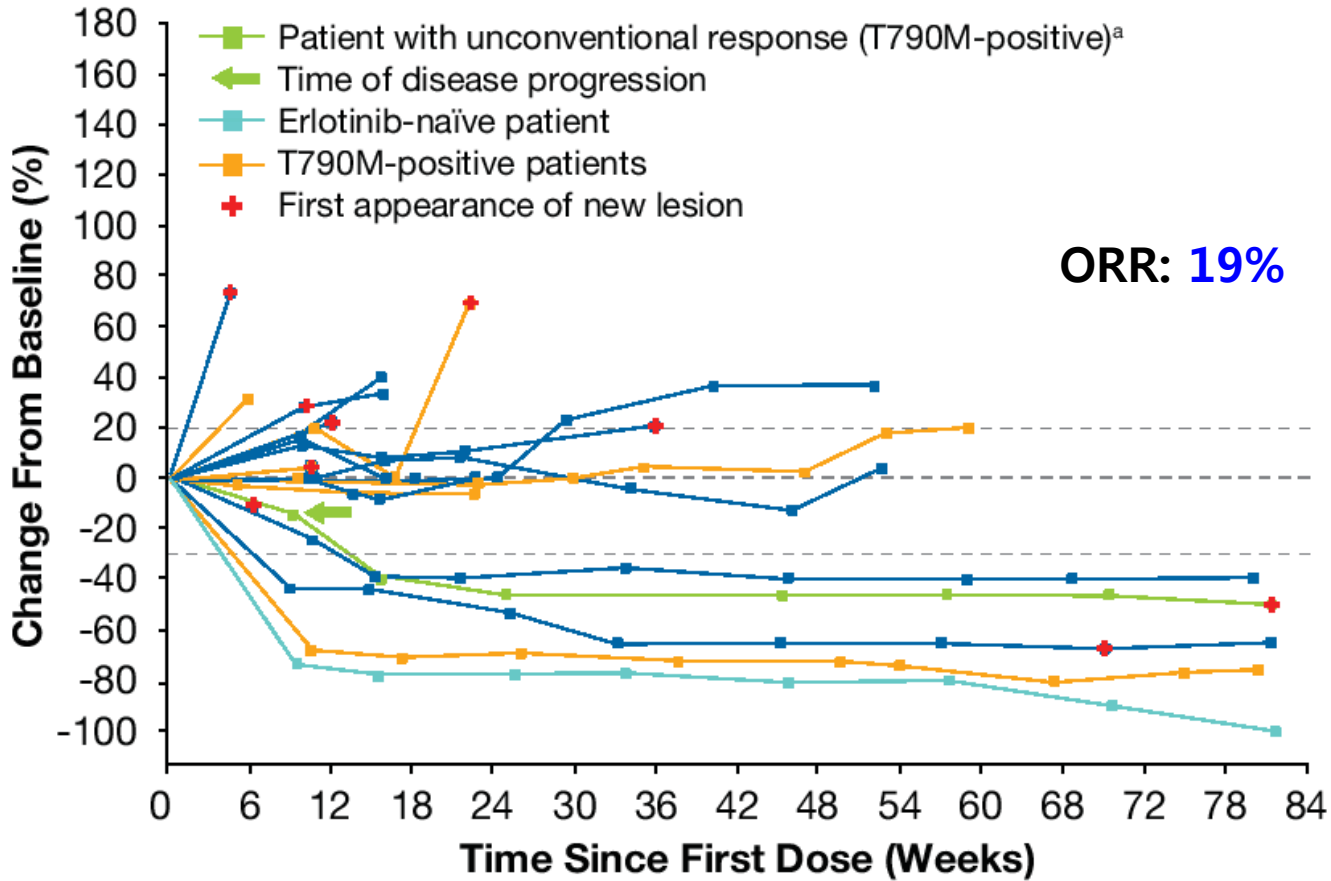
Squamous  
Non-squamous



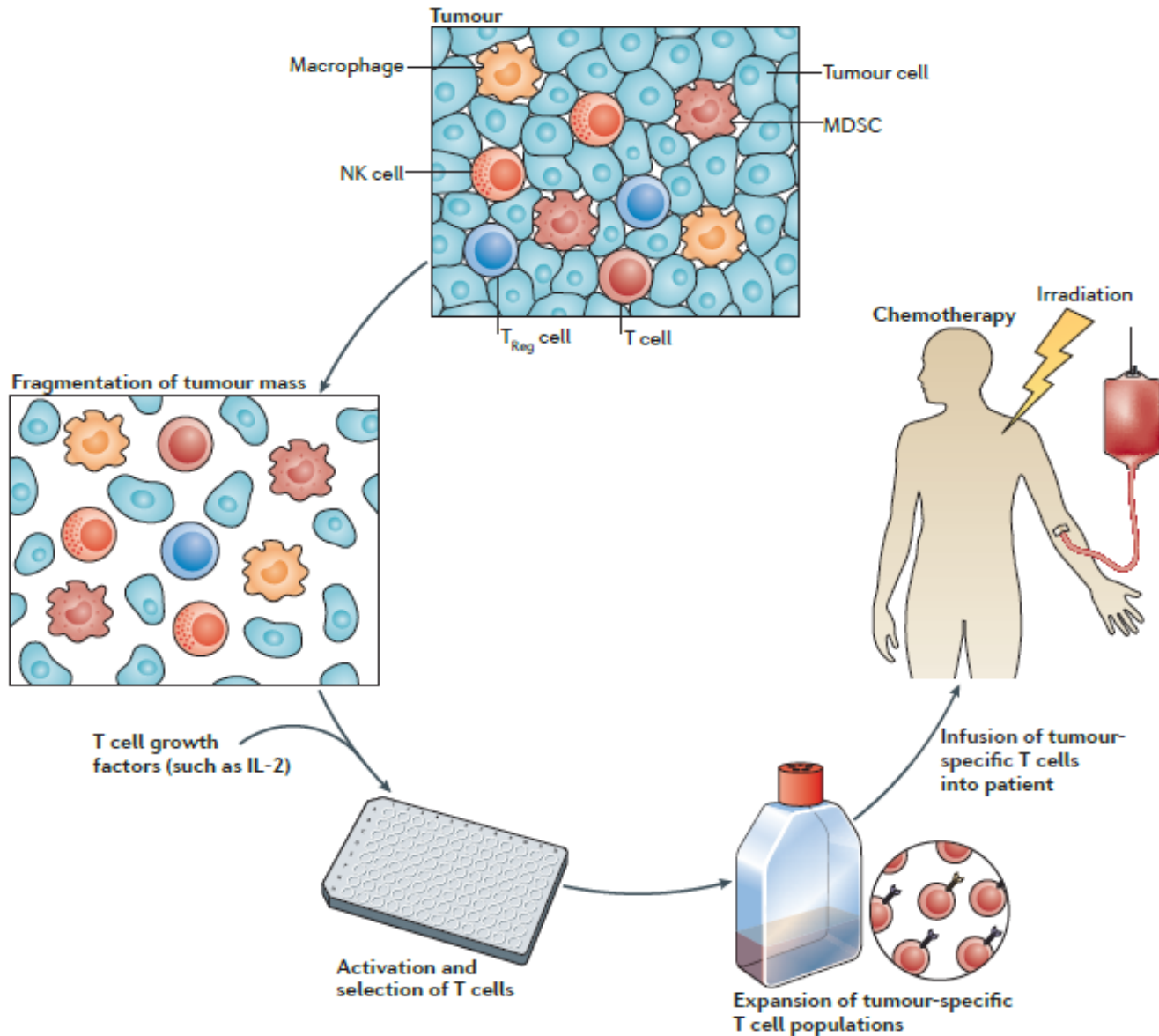
# Nivolumab (anti-PD-1) + Chemotherapy :Checkmate012



# Nivolumab (anti-PD-1) + Erlotinib (EGFR-TKI)



# Adoptive T cell therapy



# Summary

## 1. Vaccine

: might be still suboptimal

## 2. Immune checkpoint inhibitors

: ORR  $\approx$  20%, but durable response

# Summary

## 1. Predictive marker

PD-L1 expression

Mutational landscape

Immunosuppressive mechanisms

## 2. Combination therapy

Immune checkpoint inhibitor+other immunotherapy

Immune checkpoint inhibitor: CTx, RTx, Tareget Tx

Adoptive T cell therapy

→ **Personalized, biomarker-driven combinatorial therapies**



Where Dreams Come True

Walt Disney World Next Left	Epcot Magic Kingdom Disney's Animal Kingdom Straight Ahead	Disney's Hollywood Studios Downtown Disney Next Right
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