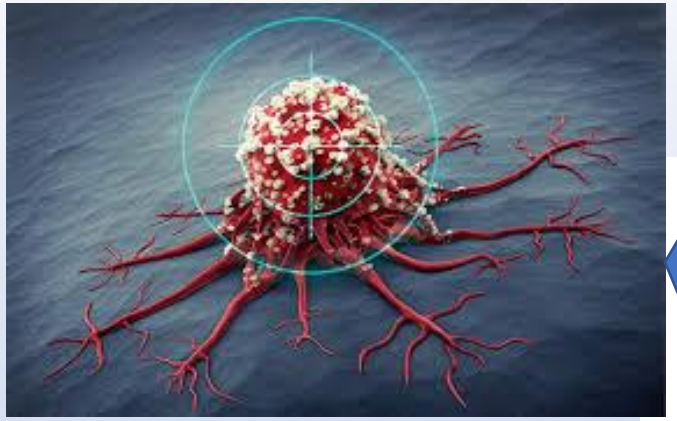
Longkanker en immuuntherapie

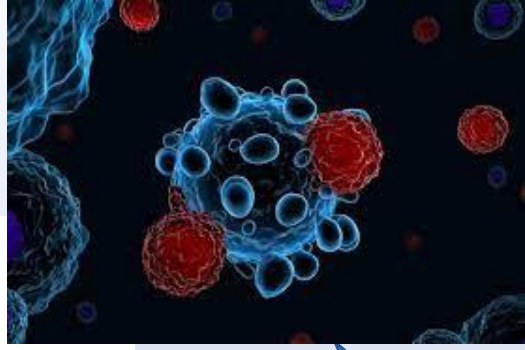
Cor van der Leest

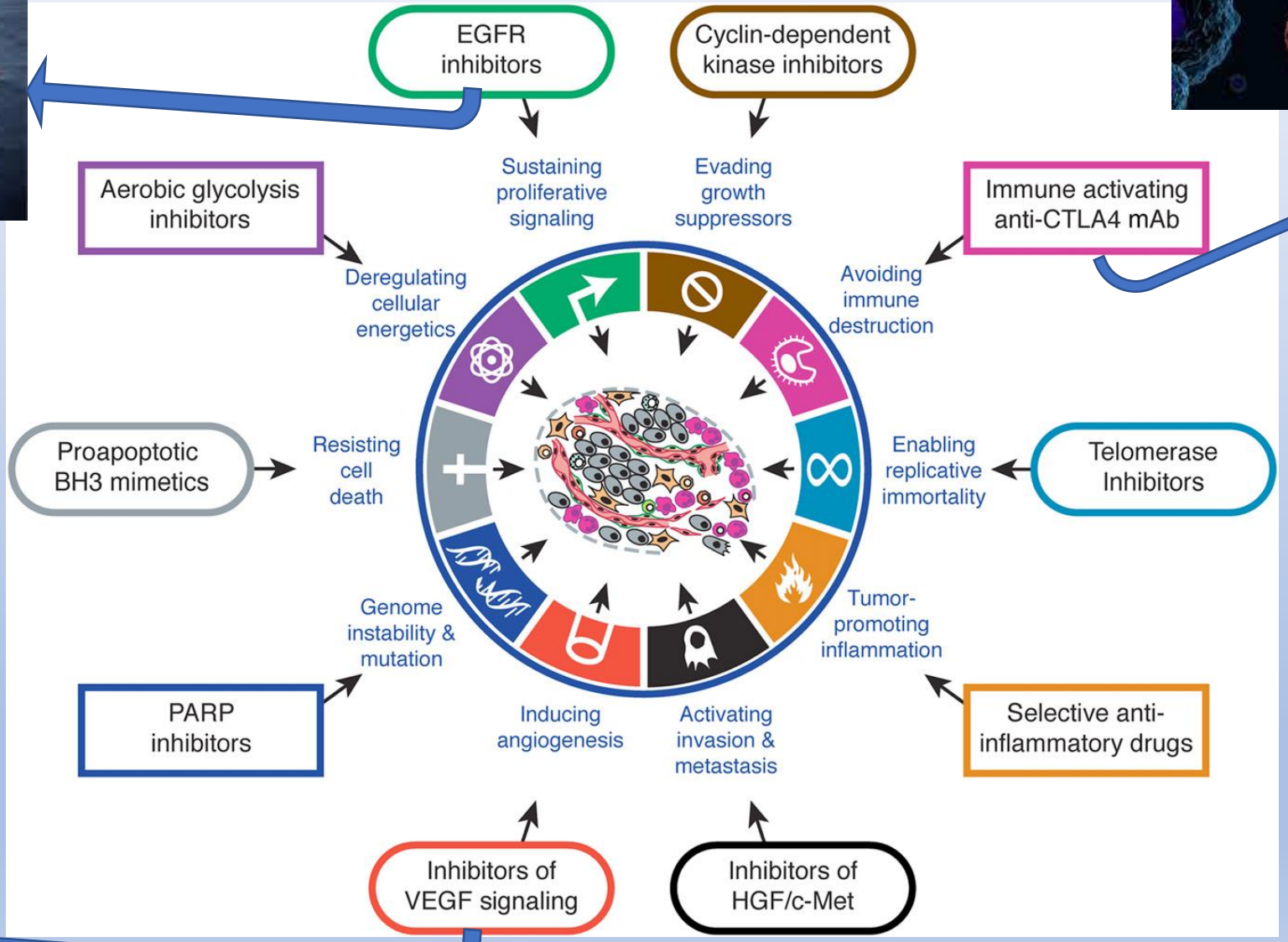
Longarts

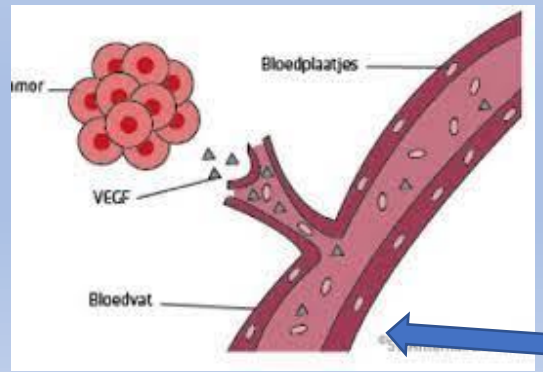
Amphia ziekenhuis

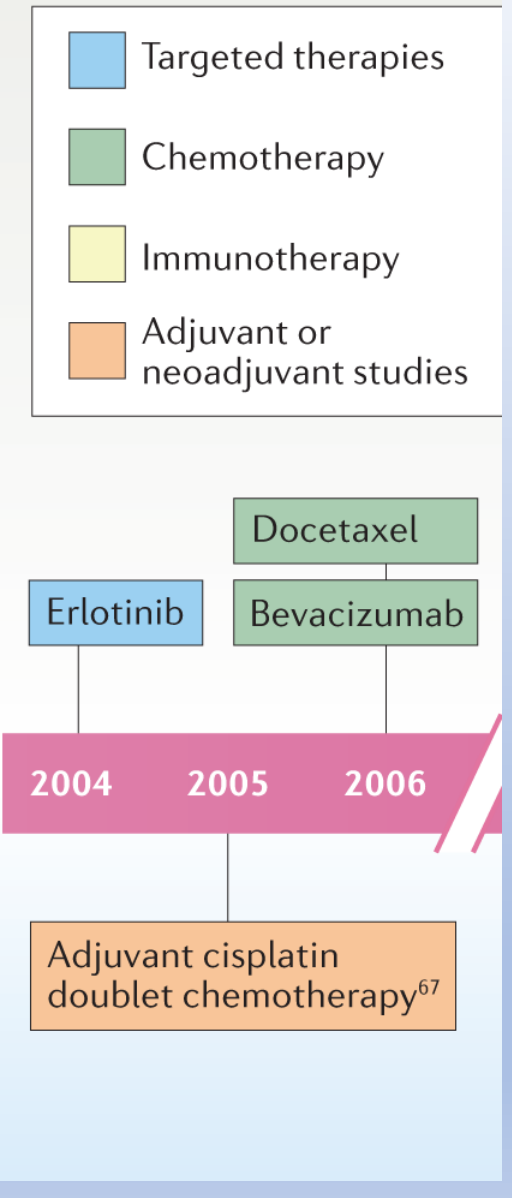
Hallmarks of cancer



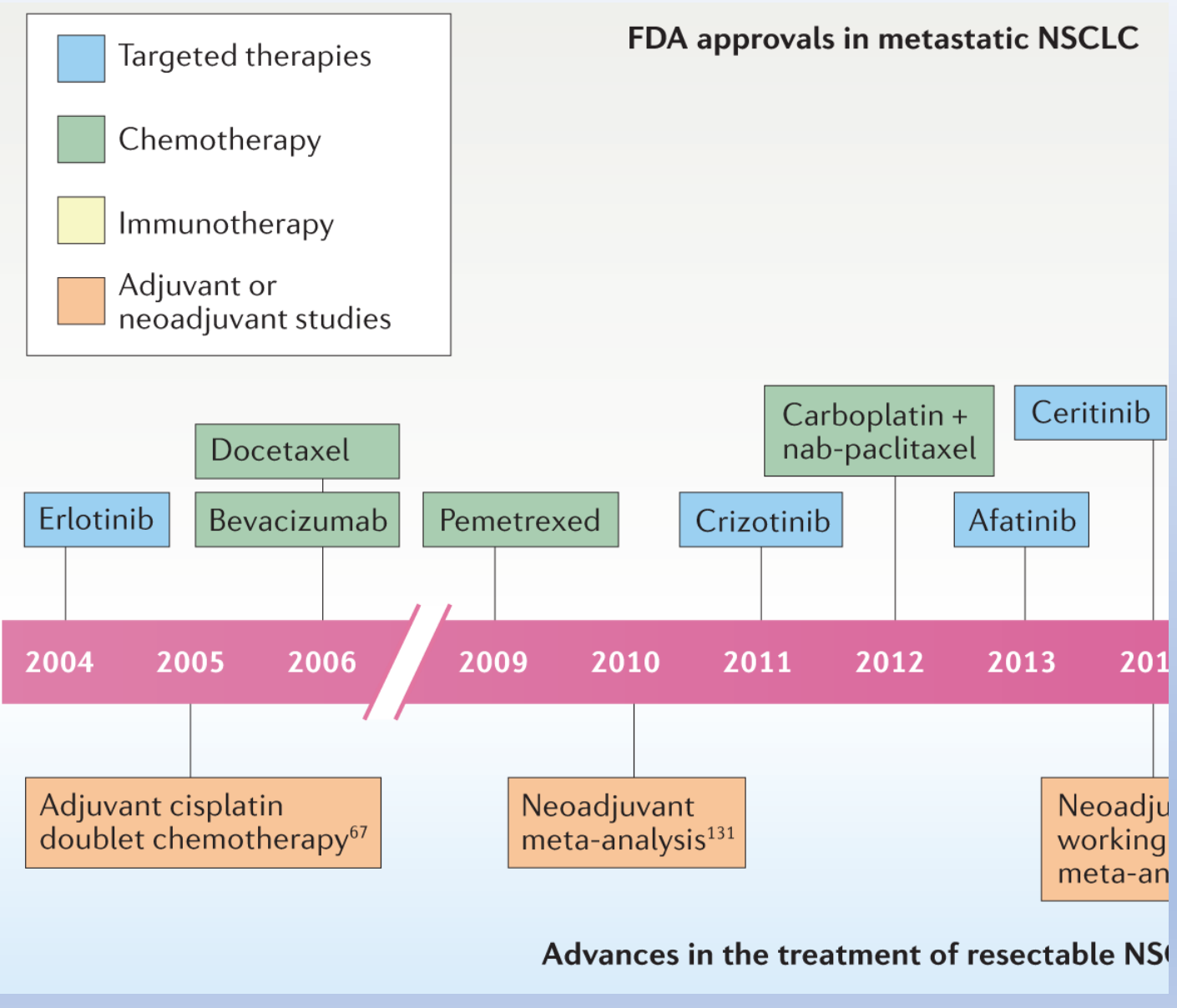






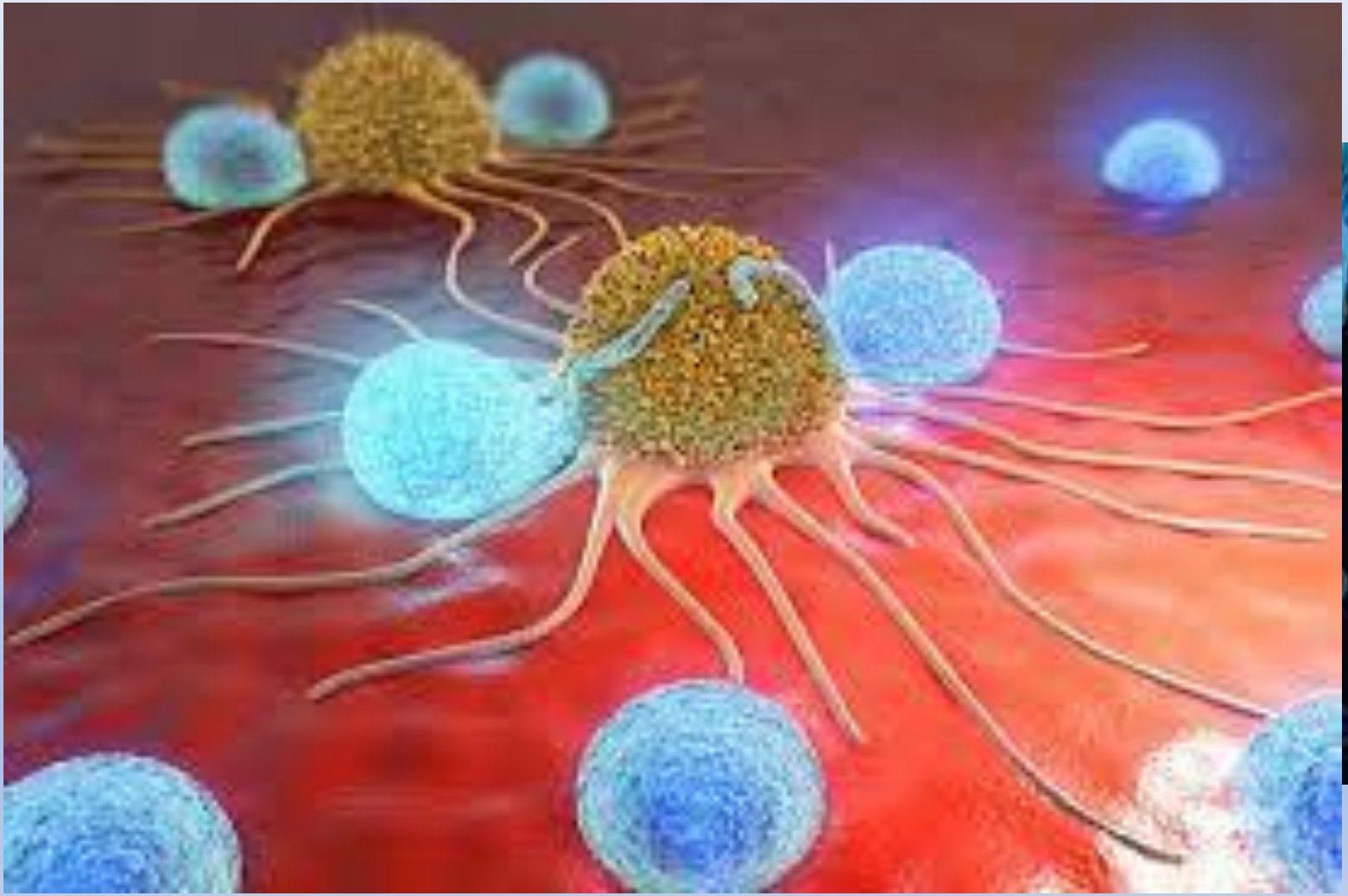


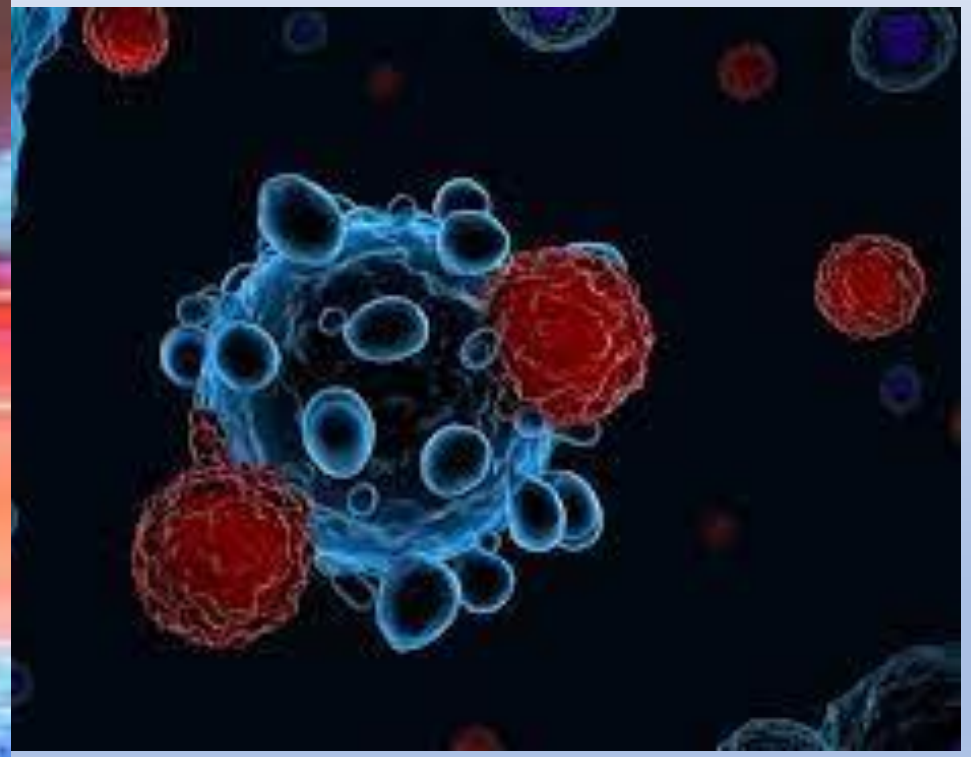
- Lancet Oncol 2016; 17: e347–62



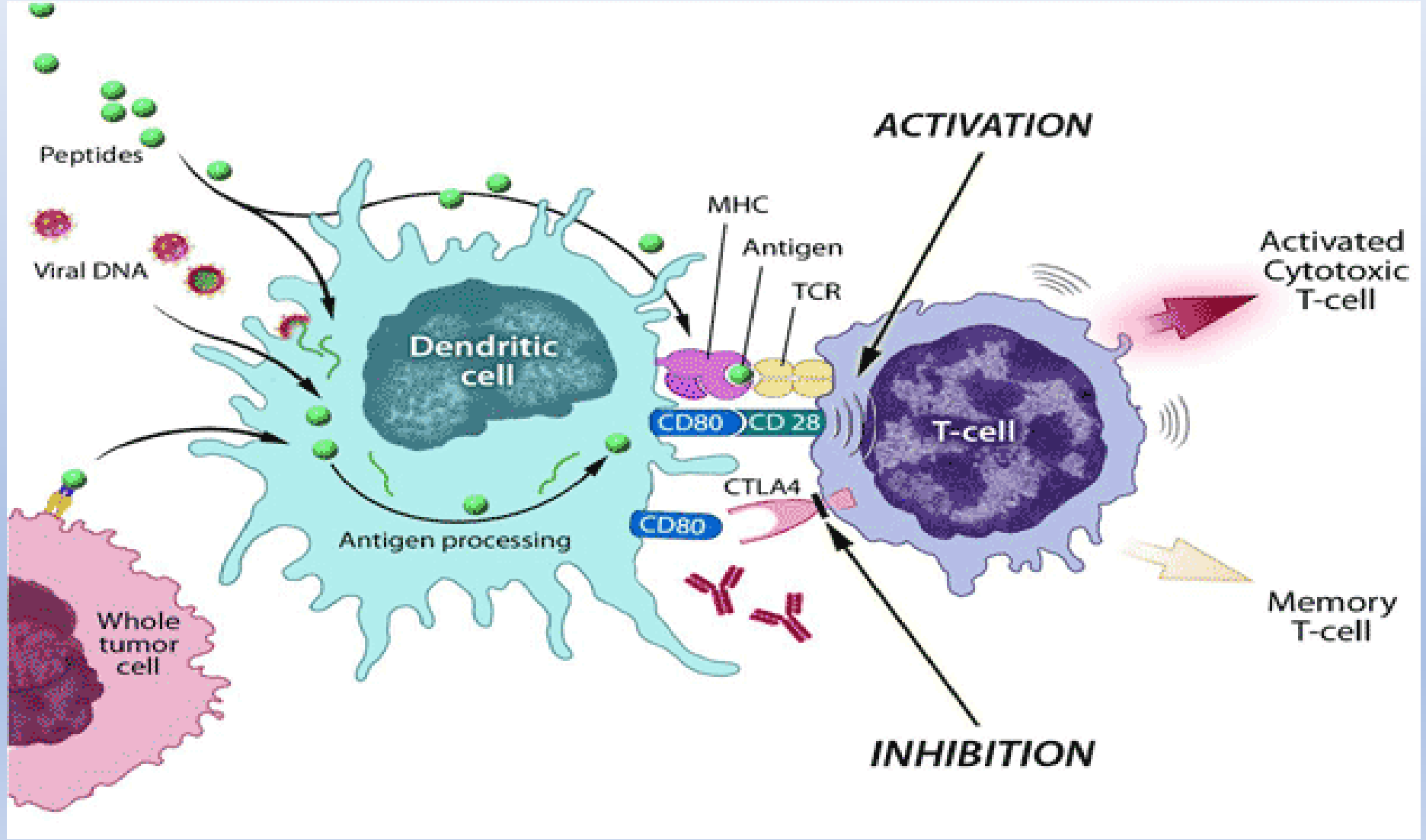
- Lancet Oncol 2016; 17: e347–62

Immuuntherapie (IO)
2015



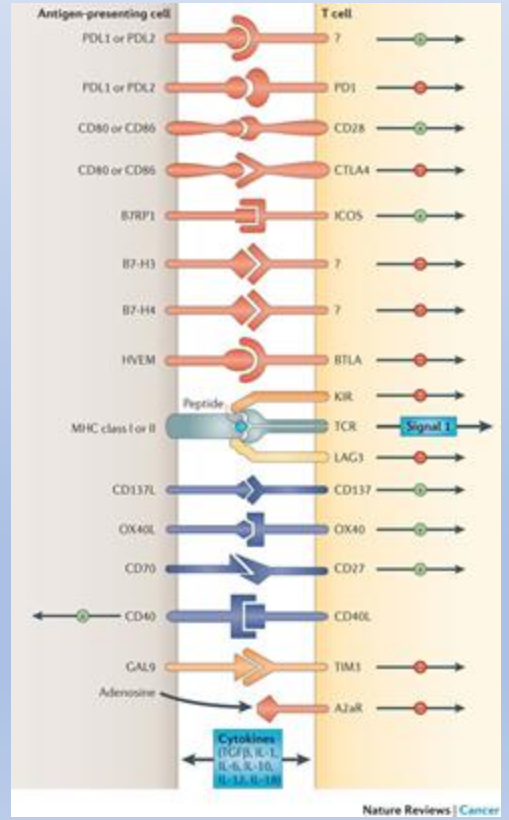


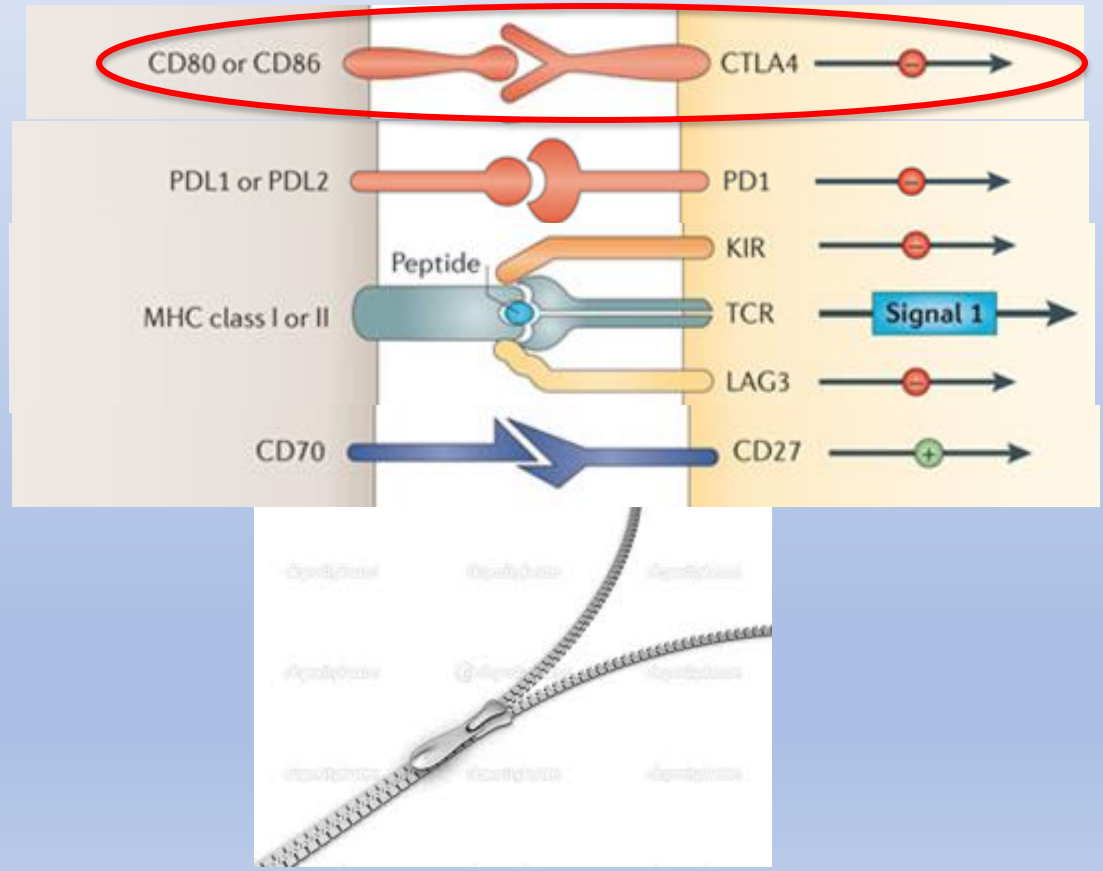
Antigeen presenting cells (APC)
Major histocompatibility complex (MHC)



Regulatie van T cell respons

- via co-stimulatie en inhiberende interactie

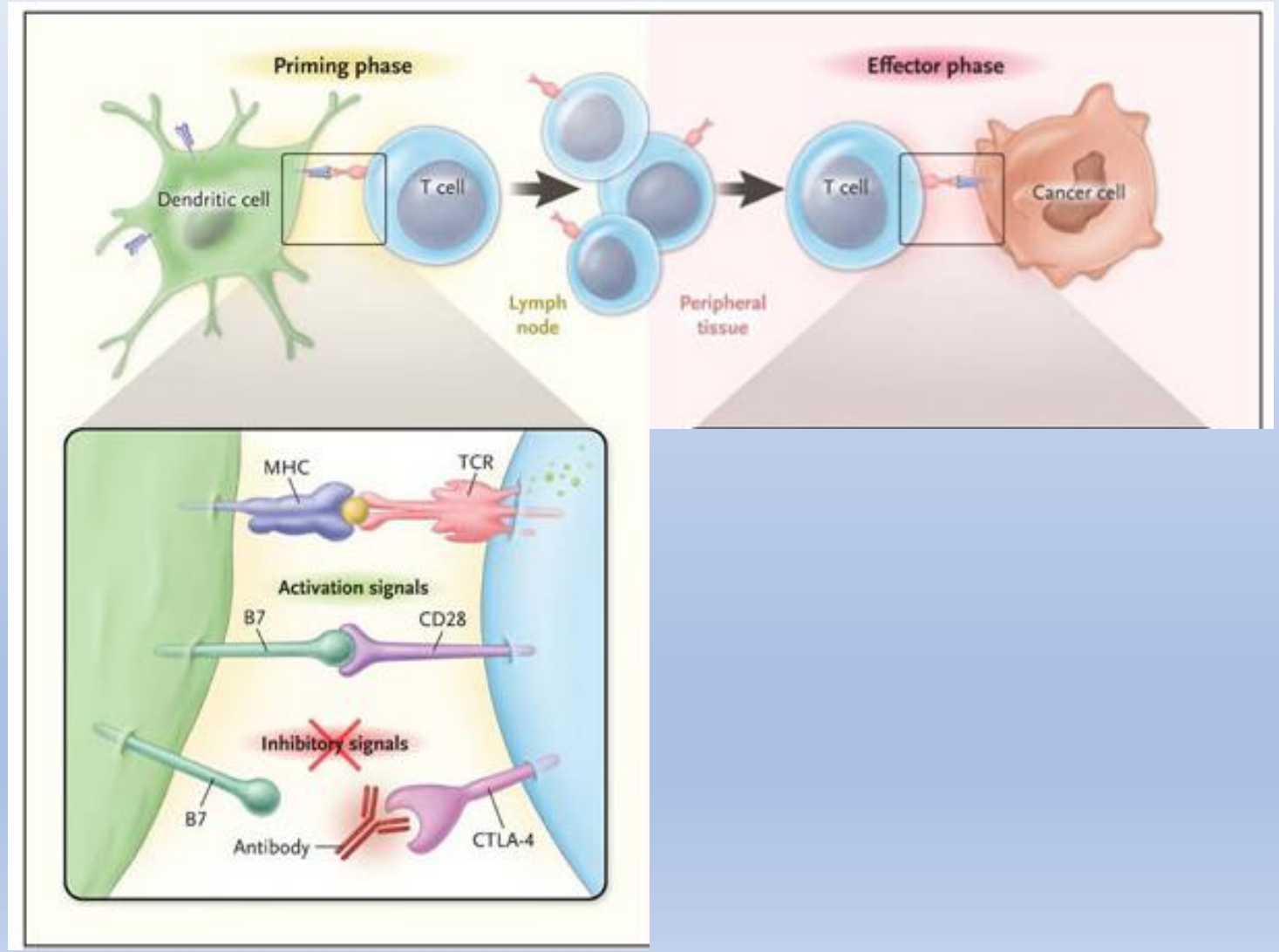




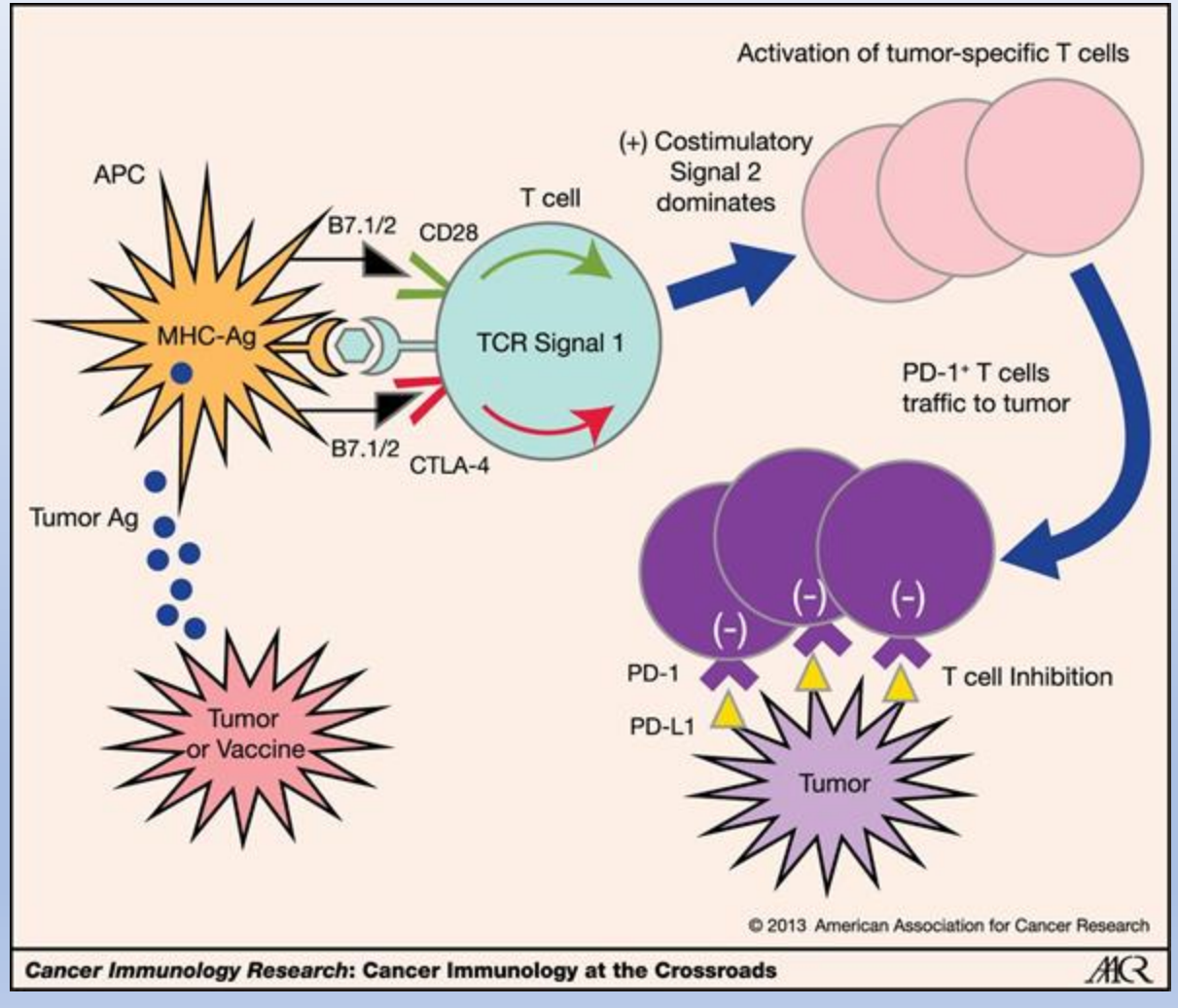
Nature Reviews Cancer 12, 252-264 (April 2012)

Drew M. Pardoll

Ipilimumab (anti CTLA-4)

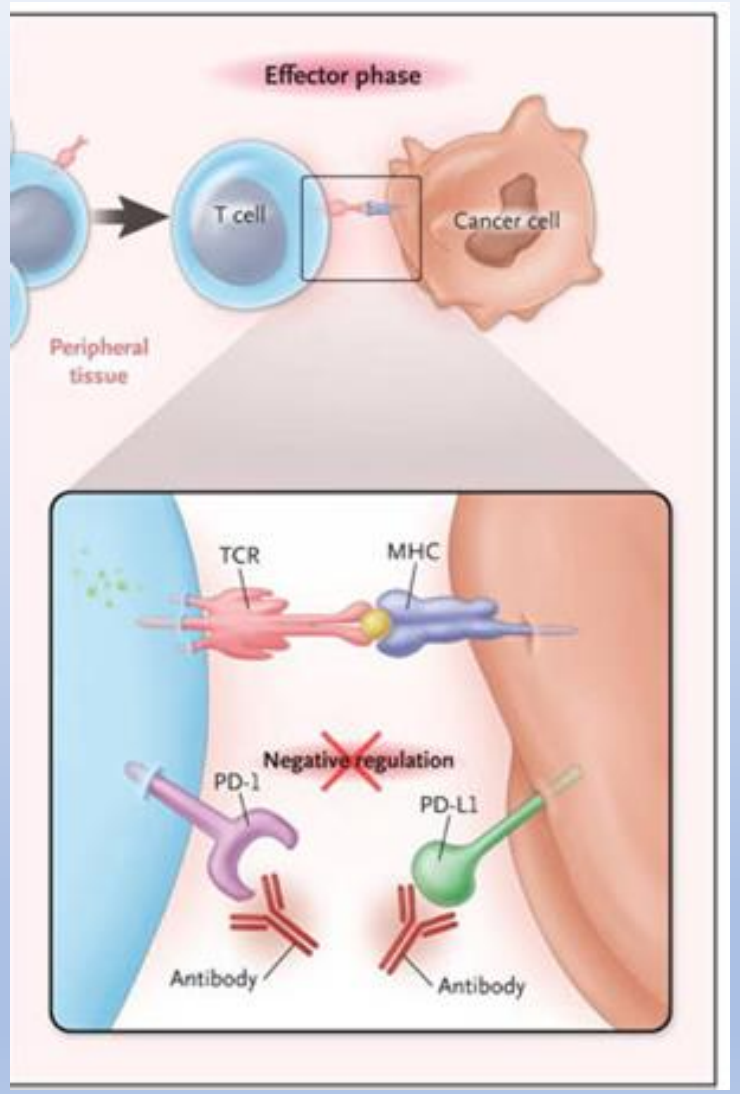


Programmed-death 1
PD-(L)1

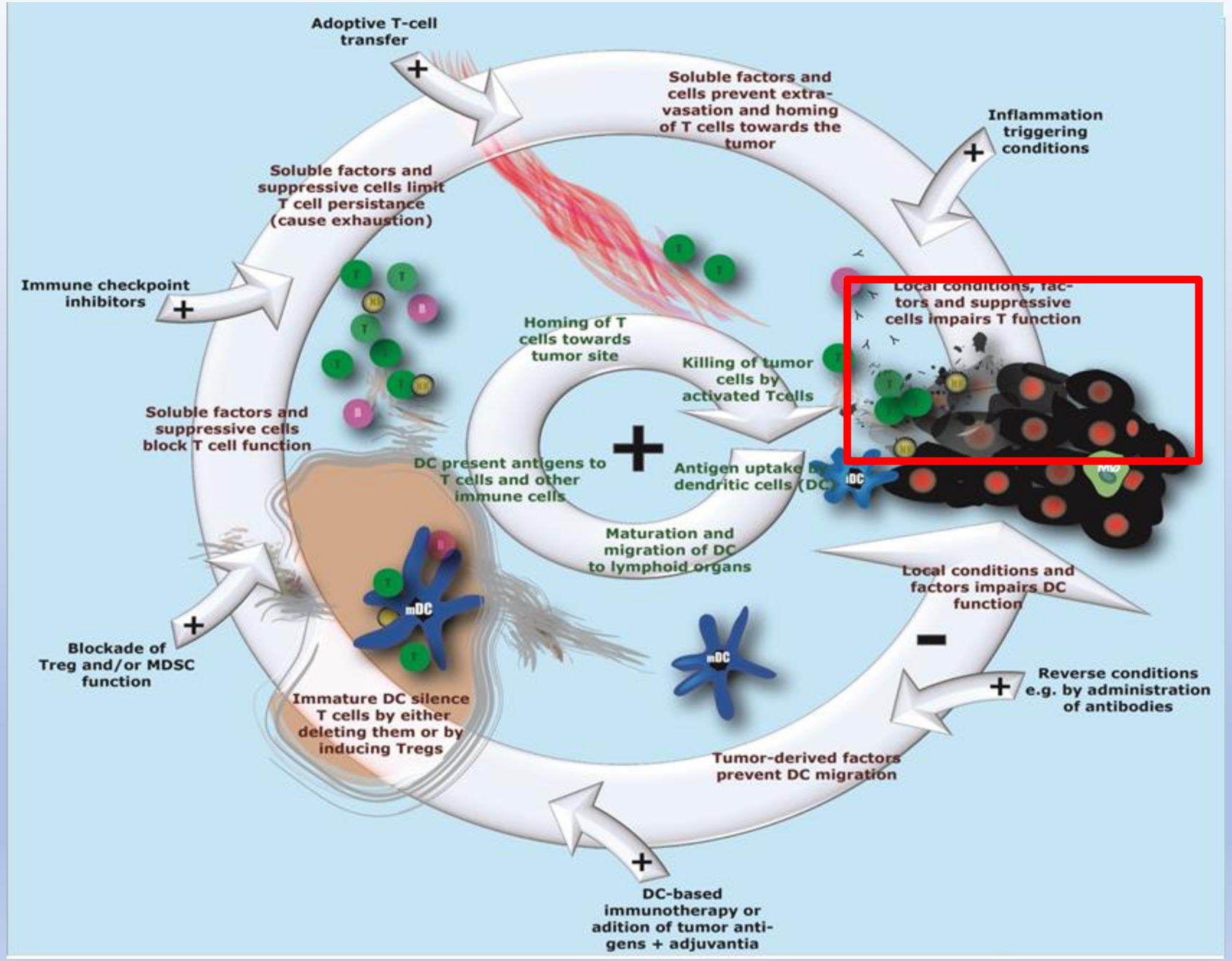


Julie R. Brahmer and Drew M. Pardoll, Immune Checkpoint Inhibitors: Making Immunotherapy a Reality for the Treatment of Lung Cancer Cancer Immunol Res; 1(2) August 2013

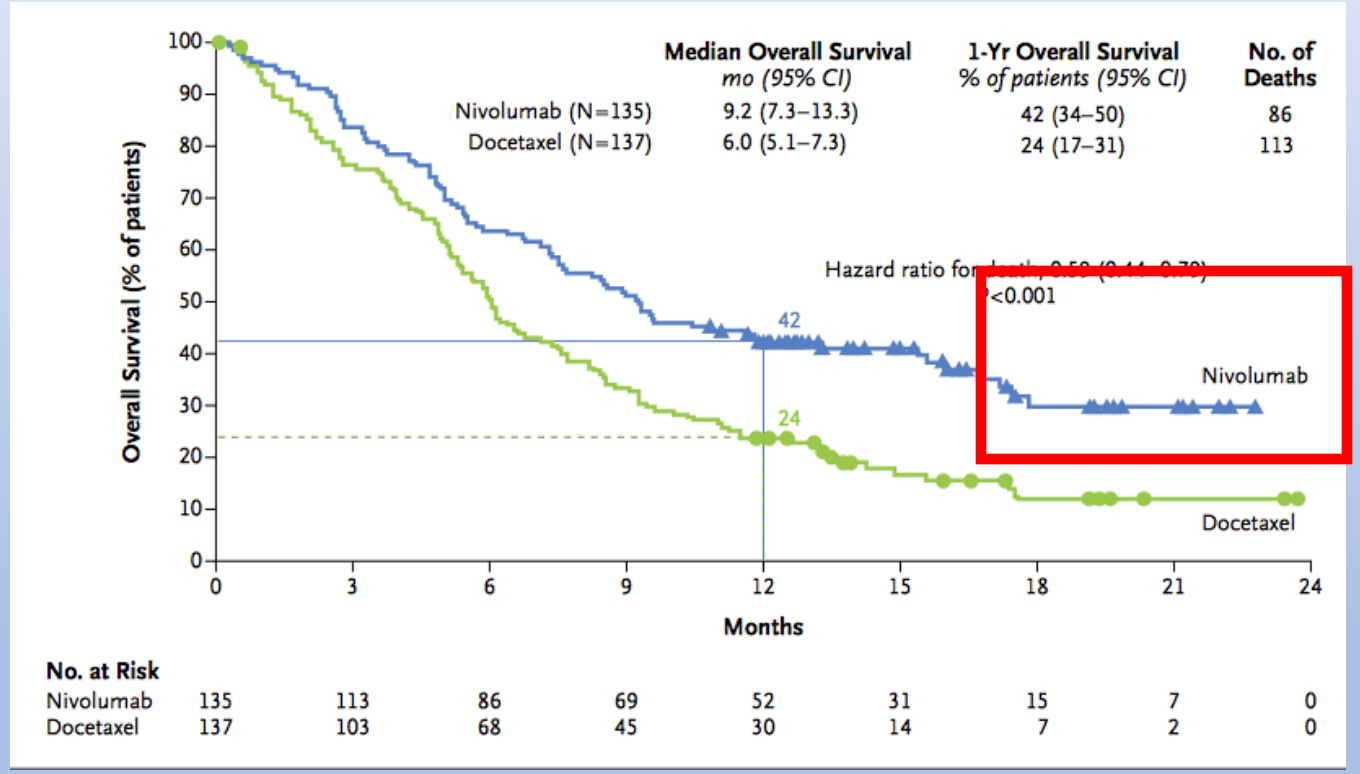
PD-1 en PD-L1 binding



Tumor Immunotherapy Directed at PD-1
Antoni Ribas NEJM june 2012

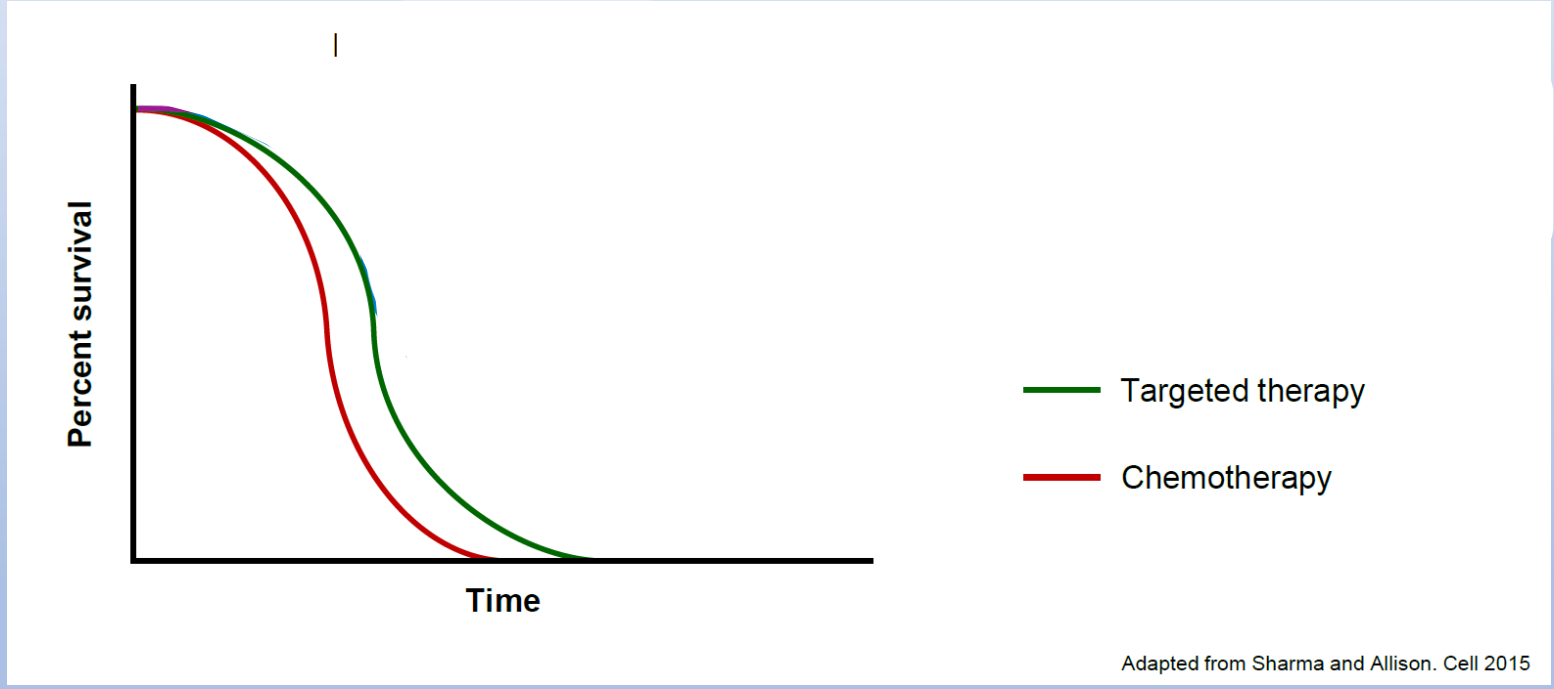

Adoptive T-cell transfer
Soluble factors and cells prevent extra-vasation and homing of T cells towards the tumor
Inflammation triggering conditions
Soluble factors and suppressive cells limit T cell persistance (cause exhaustion)
Immune checkpoint inhibitors
Local conditions, fac-tors and suppressive cells impairs T function
Homing of T cells towards tumor site
Killing of tumor cells by activated Tcells
Soluble factors and suppressive cells block T cell function
DC present antigens to T cells and other immune cells
Antigen uptake by dendritic cells (DC)
Maturation and migration of DC to lymphoid organs
Local conditions and factors impairs DC function
Blockade of Treg and/or MDSC function
Reverse conditions e.g. by administration of antibodies
Immature DC silence T cells by either deleting them or by inducing Tregs
Tumor-derived factors prevent DC migration
DC-based immunotherapy or adition of tumor anti-gens + adjuvantia

2de lijns studie NSCLC,

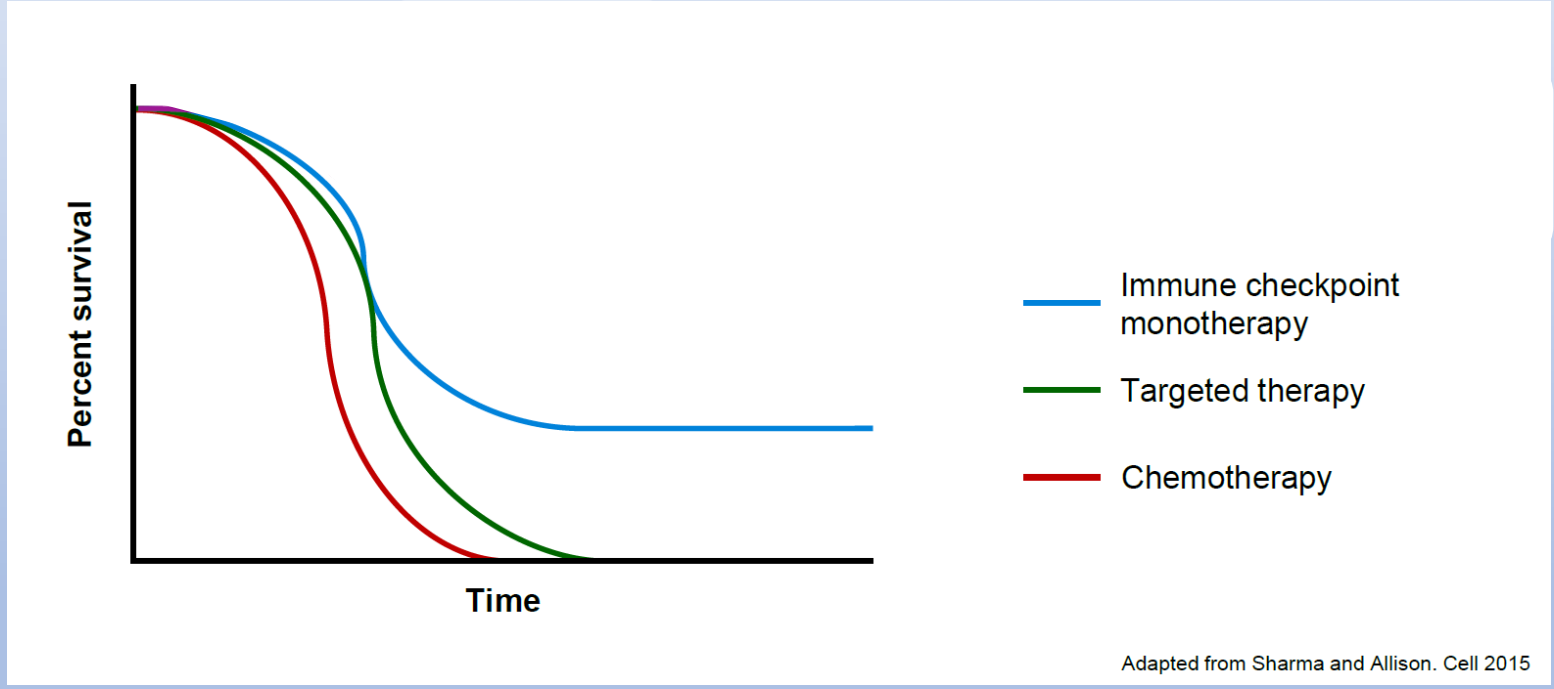


NEJM june 2015 Checkmate 057

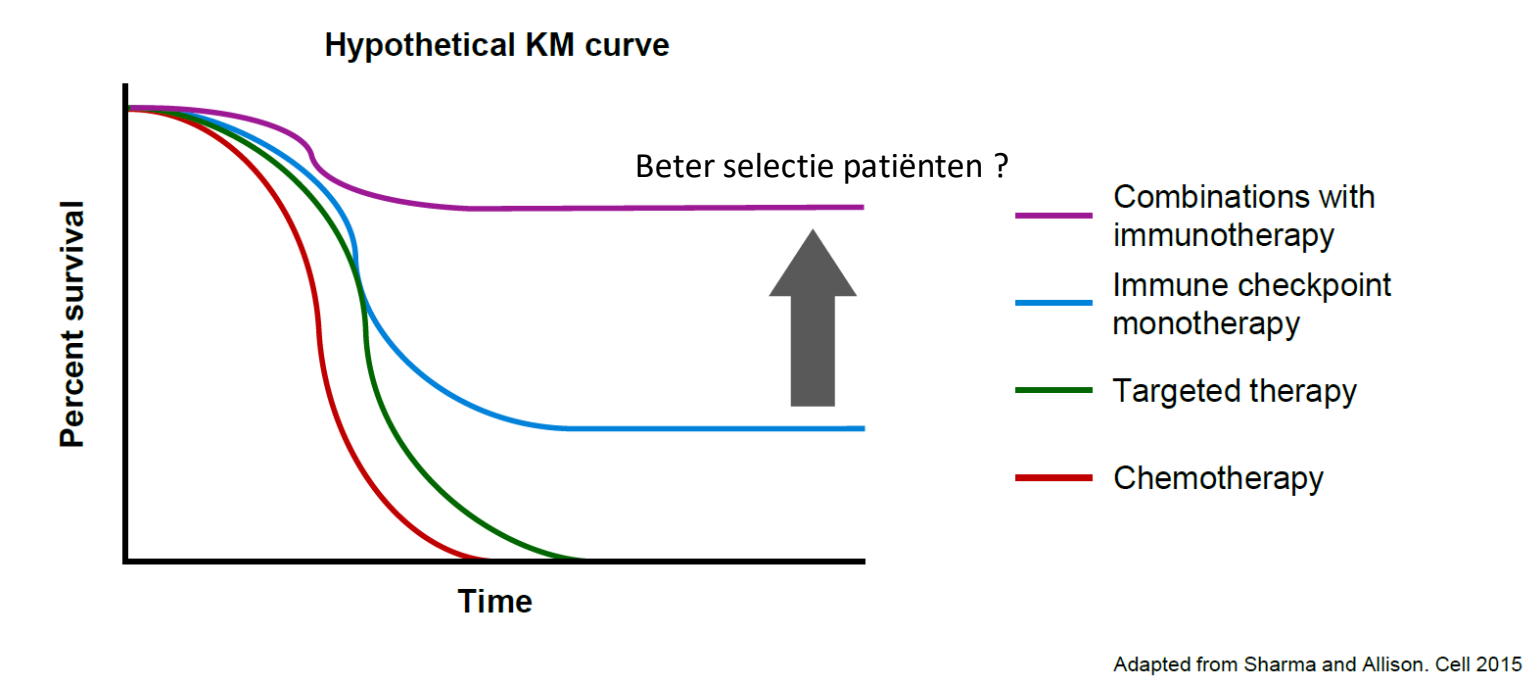
Immuuntherapie in stadium IV NSCLC



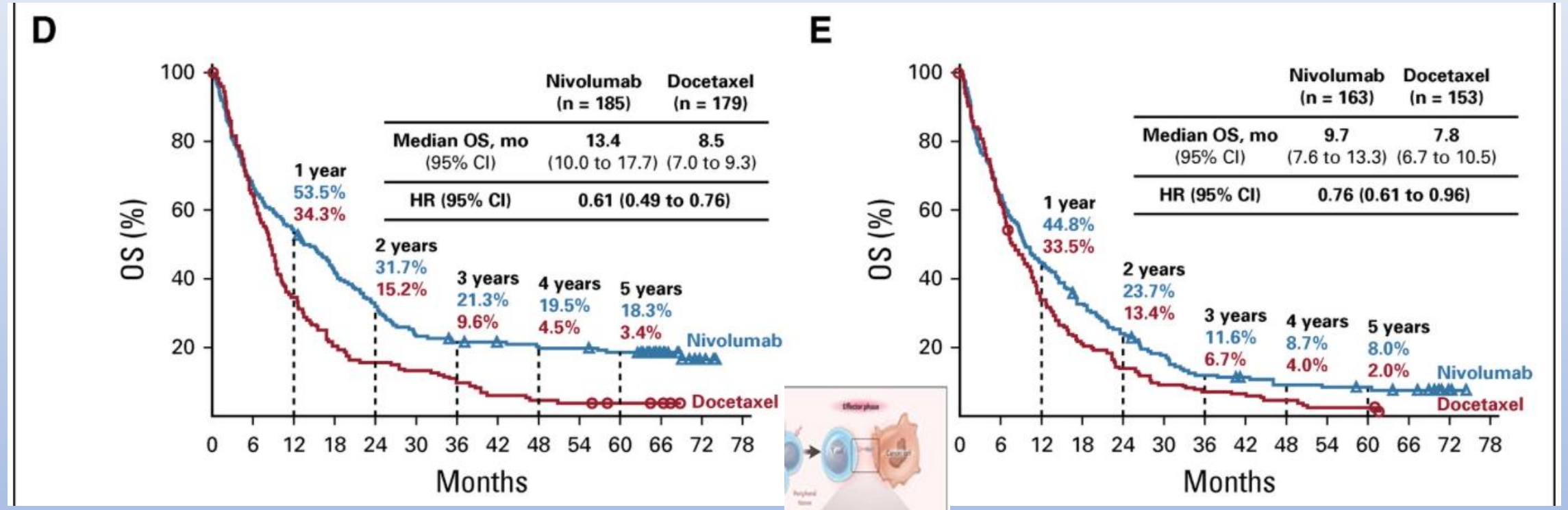
Immuuntherapie in stadium IV NSCLC

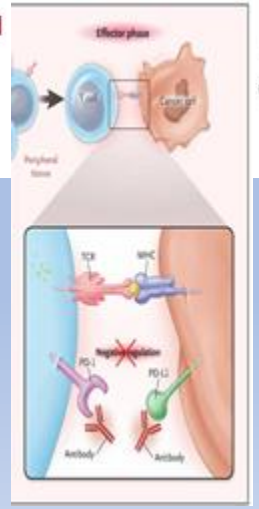


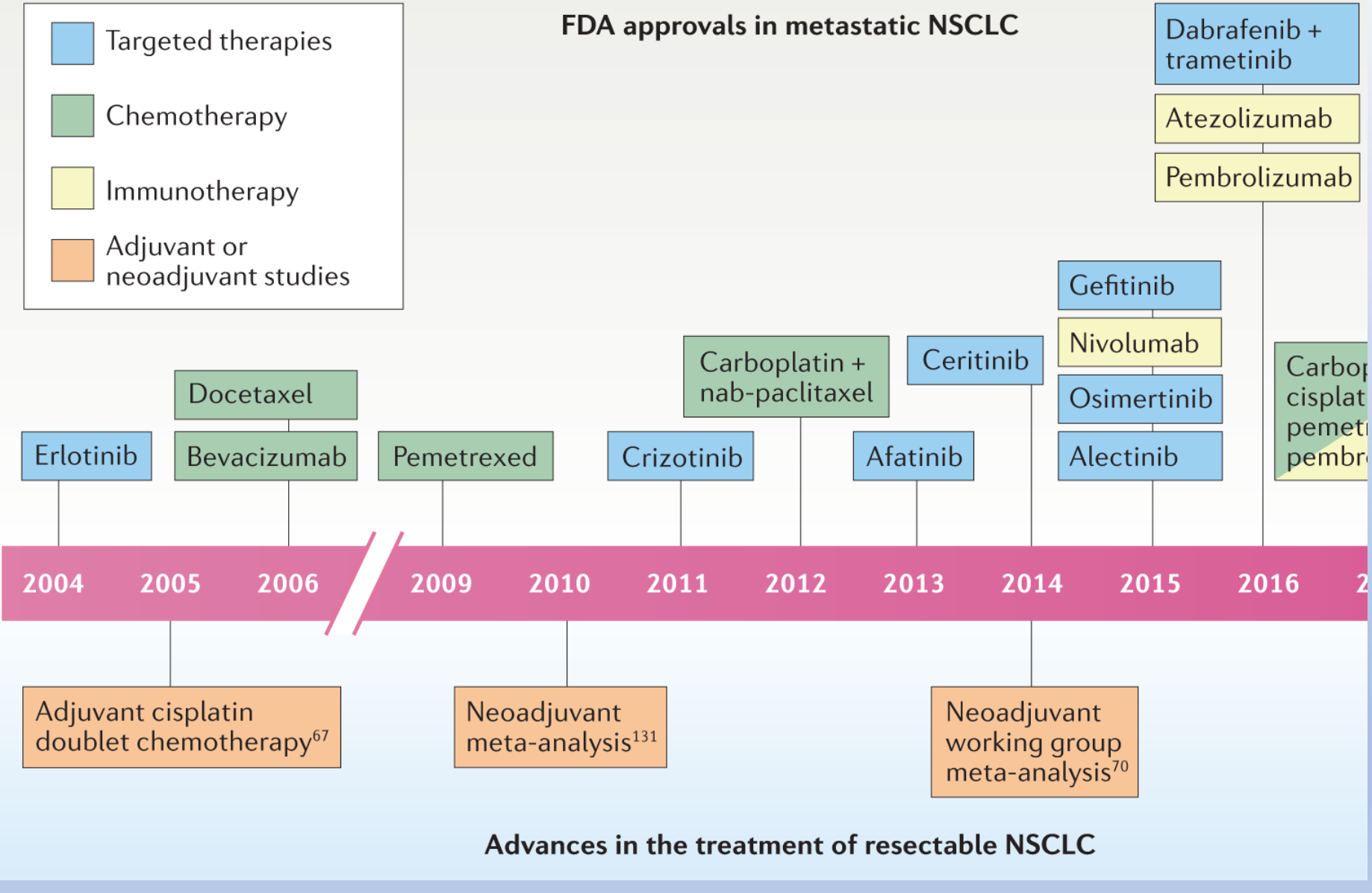
Immuuntherapie in stadium IV NSCLC



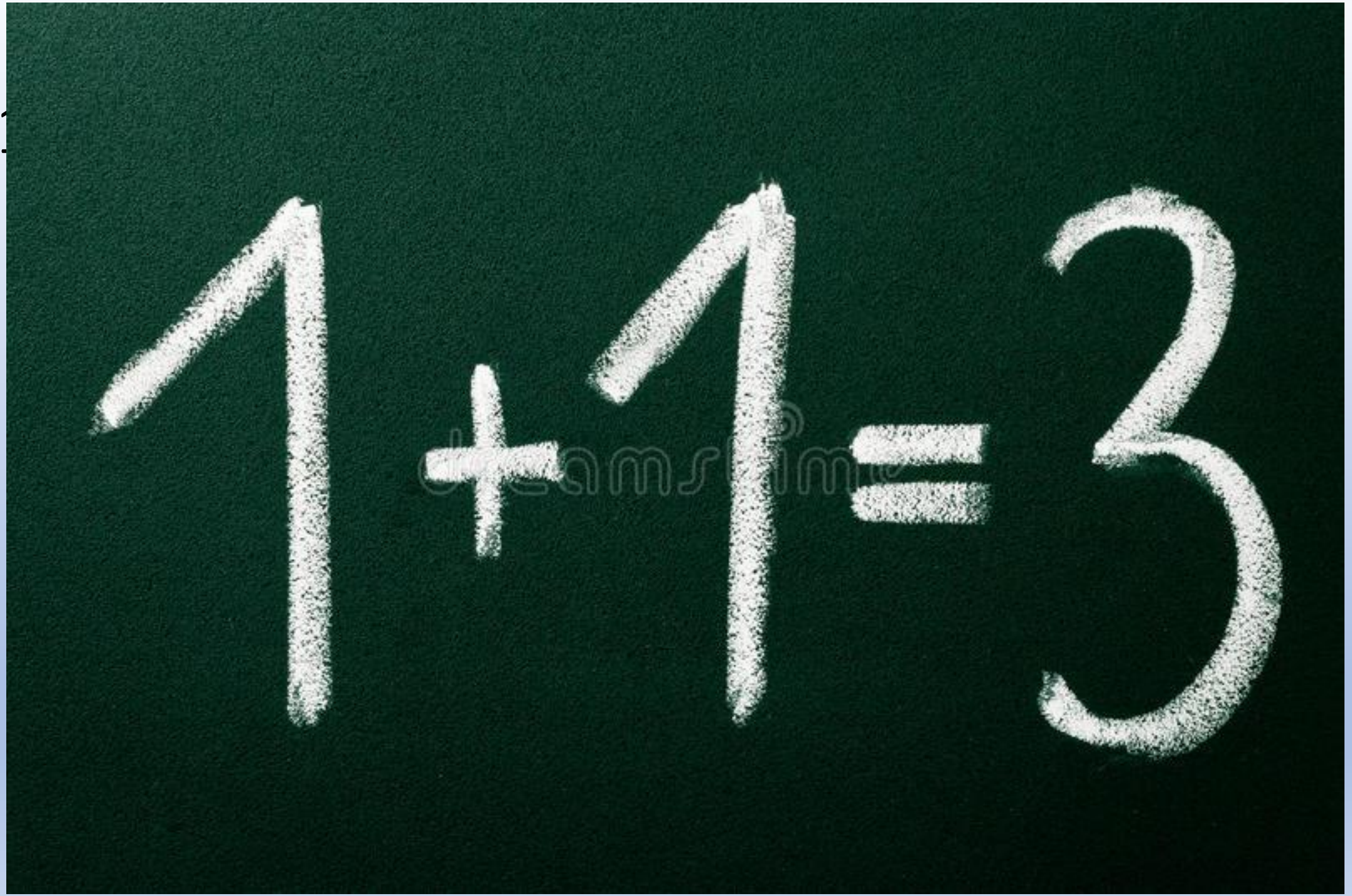
Tumoren met hoge PD-L1 beter dan tumoren met lage PD-L1





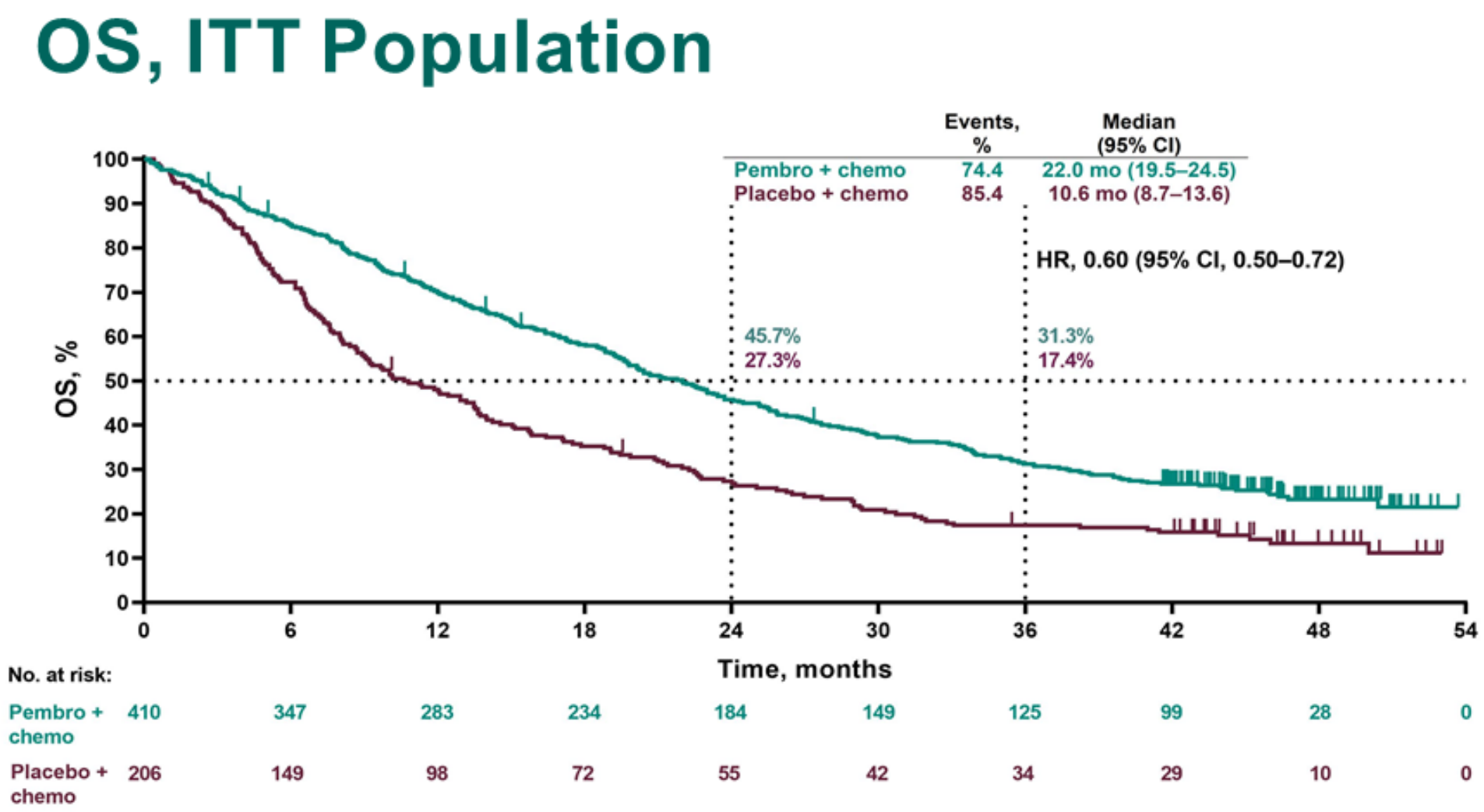


Advances in the treatment of resectable NSCLC


1+1=3

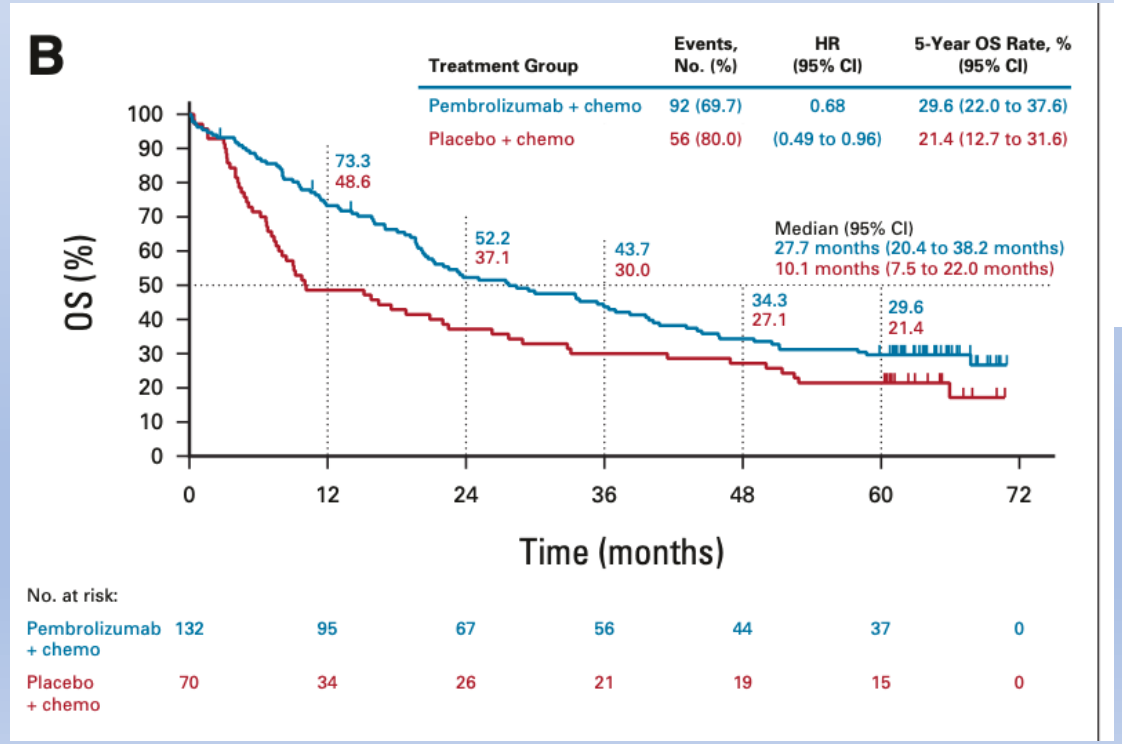
Combinatie chemo en immuuntherapie

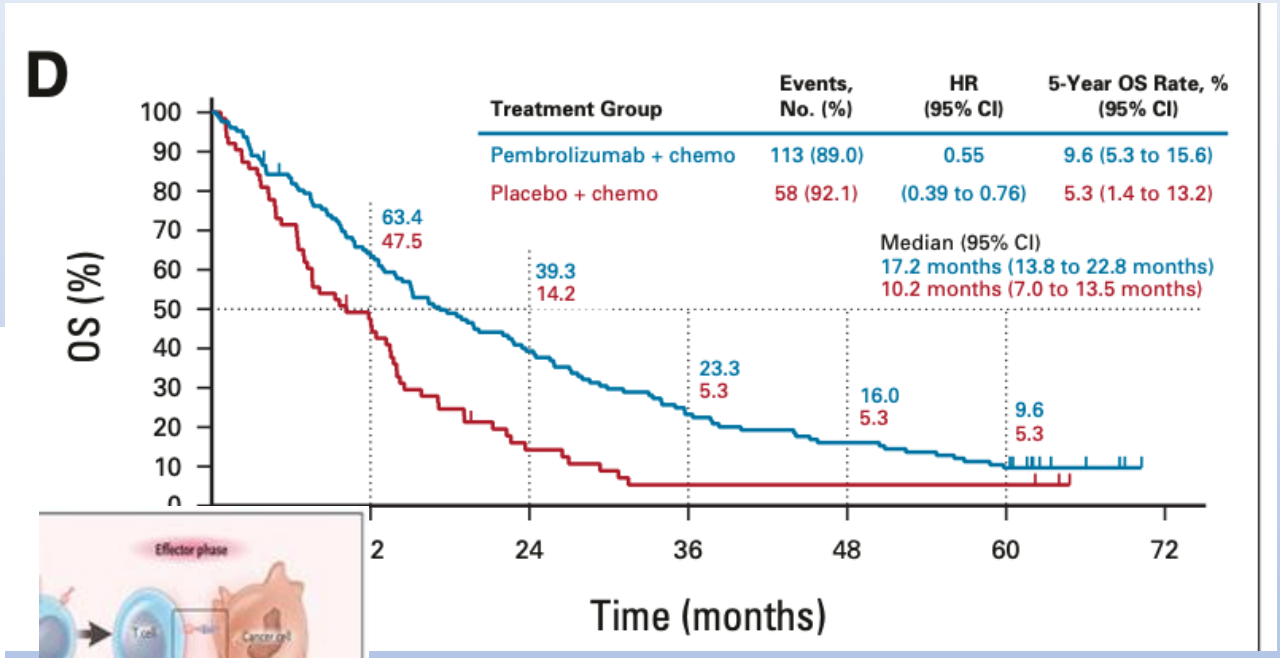
Gray MK-3475 KN189 WCLC 2020

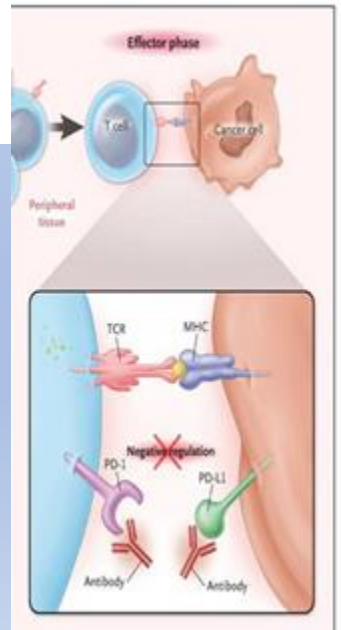


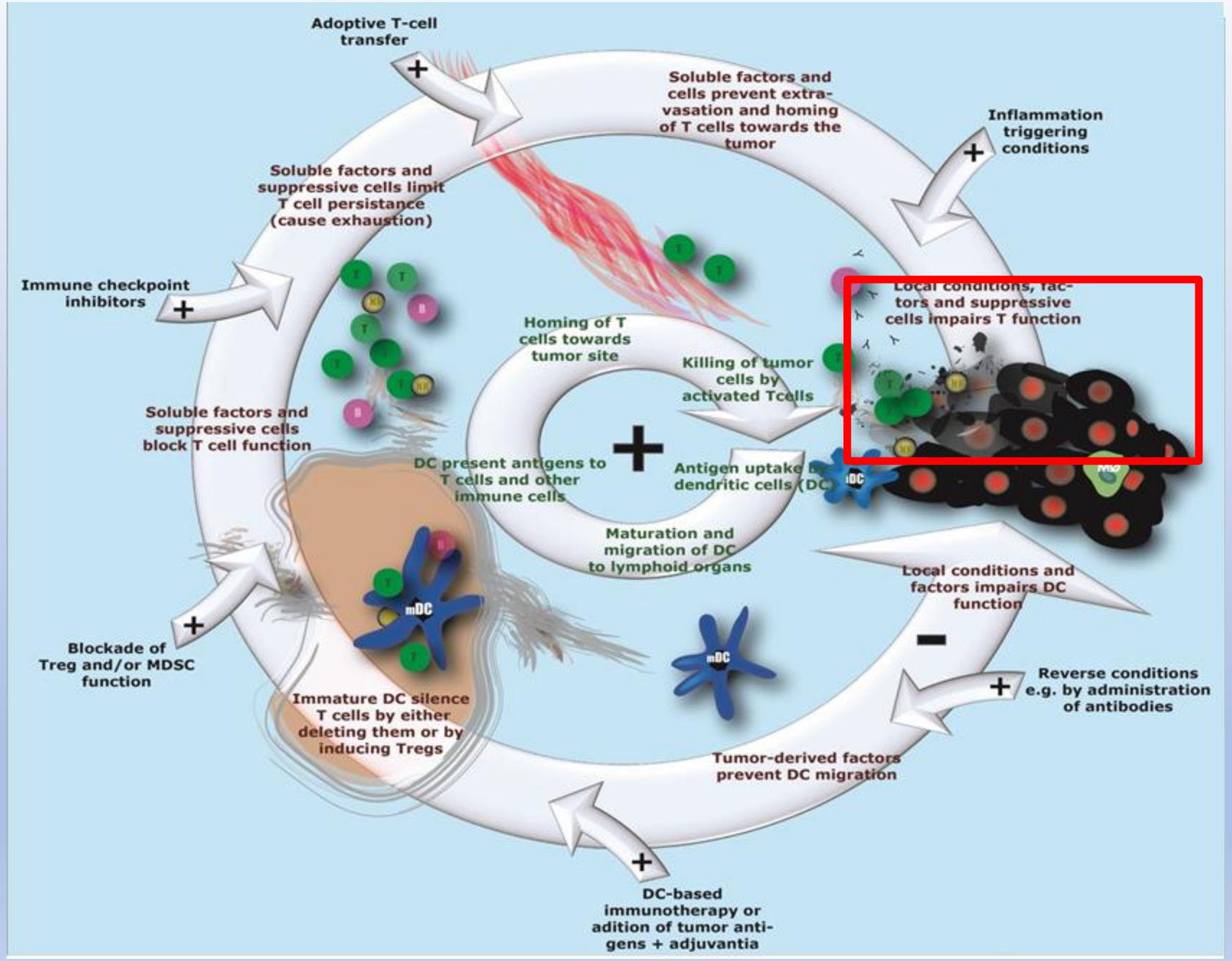
Data cutoff: August 28, 2020.

Tumoren met hoge PD-L1 beter dan tumoren met lage PD-L1

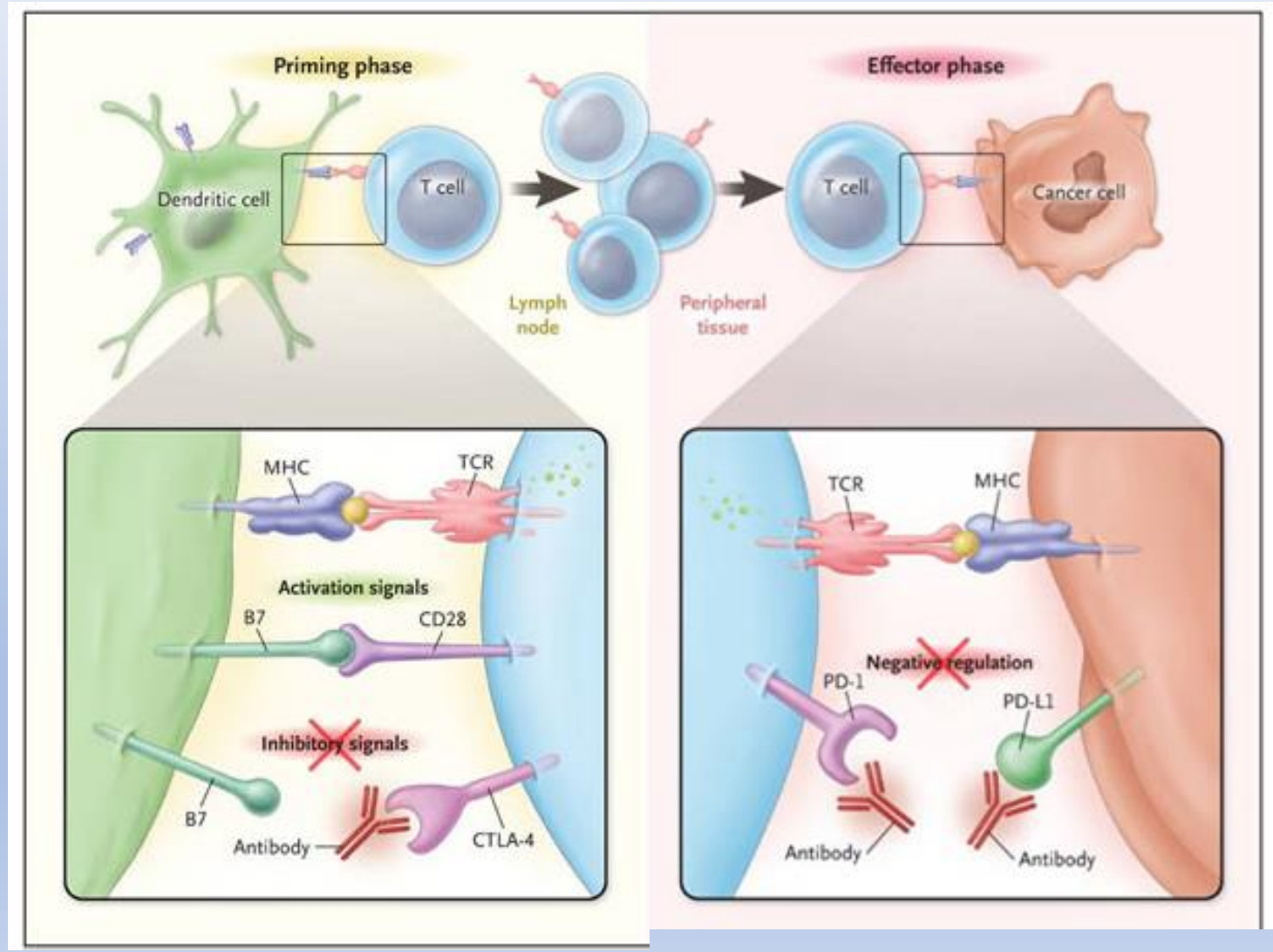






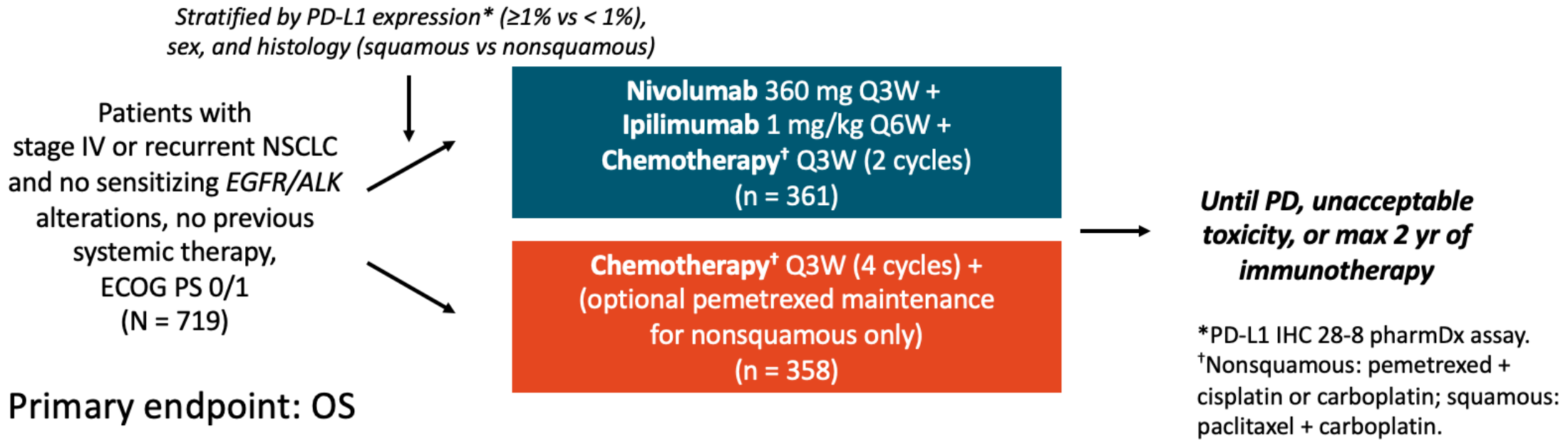

Adoptive T-cell transfer
Soluble factors and cells prevent extra-vasation and homing of T cells towards the tumor
Inflammation triggering conditions
Soluble factors and suppressive cells limit T cell persistance (cause exhaustion)
Immune checkpoint inhibitors
Local conditions, fac-tors and suppressive cells impairs T function
Homing of T cells towards tumor site
Killing of tumor cells by activated Tcells
Soluble factors and suppressive cells block T cell function
DC present antigens to T cells and other immune cells
Antigen uptake by dendritic cells (DC)
Maturation and migration of DC to lymphoid organs
Local conditions and factors impairs DC function
Blockade of Treg and/or MDSC function
Reverse conditions e.g. by administration of antibodies
Immature DC silence T cells by either deleting them or by inducing Tregs
Tumor-derived factors prevent DC migration
DC-based immunotherapy or adition of tumor anti-gens + adjuvantia

Ipilimumab (anti CTLA-4)



CheckMate 9LA 2-Yr Update: Study Design

- Randomized, open-label, phase III study (data cutoff: February 18, 2021; minimum/maximum follow up for OS: 24.4 mo/30.7 mo)



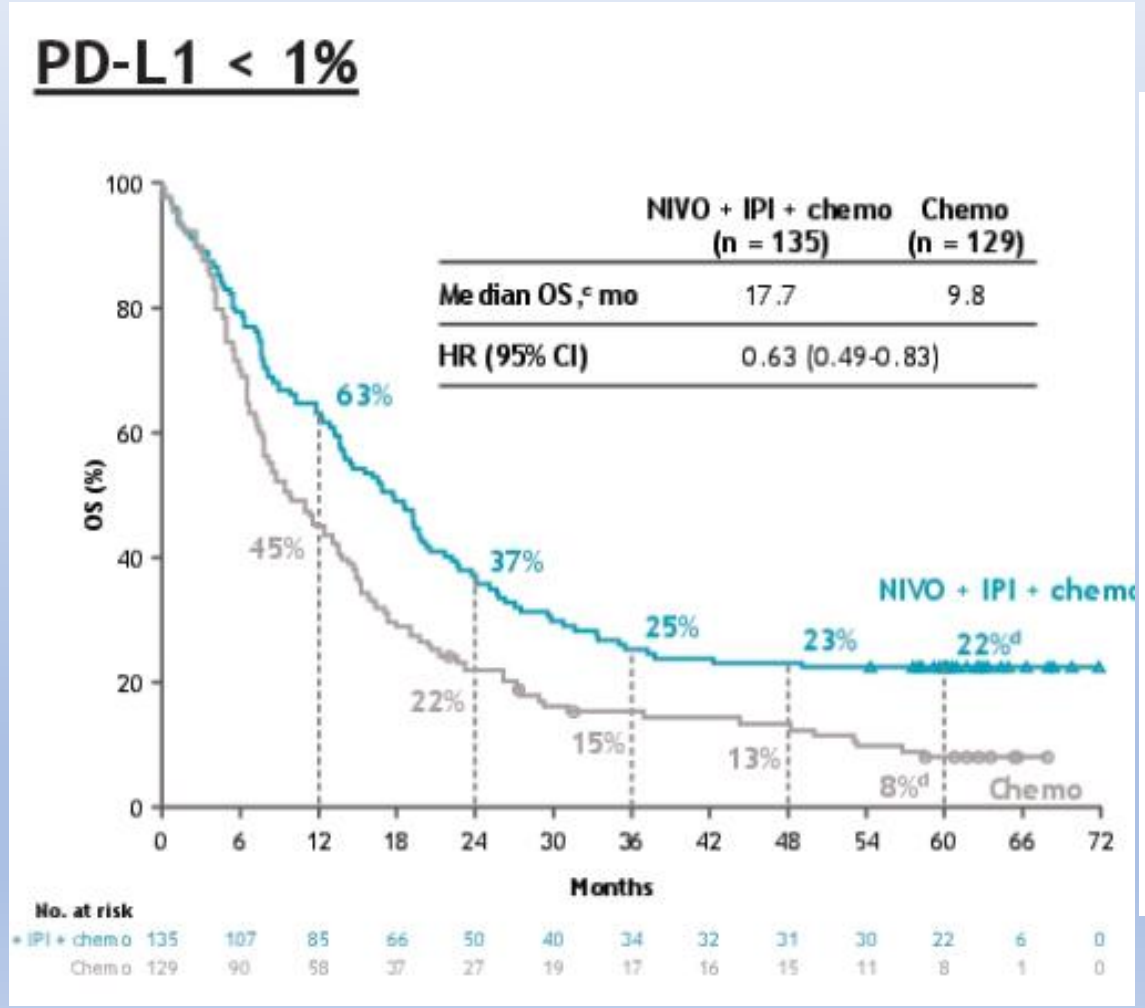
*PD-L1 IHC 28-8 pharmDx assay.
†Nonsquamous: pemetrexed + cisplatin or carboplatin; squamous: paclitaxel + carboplatin.

- Primary endpoint: OS
- Secondary endpoints: PFS (BICR), ORR (BICR), efficacy by tumor PD-L1 expression
- Exploratory endpoint: safety

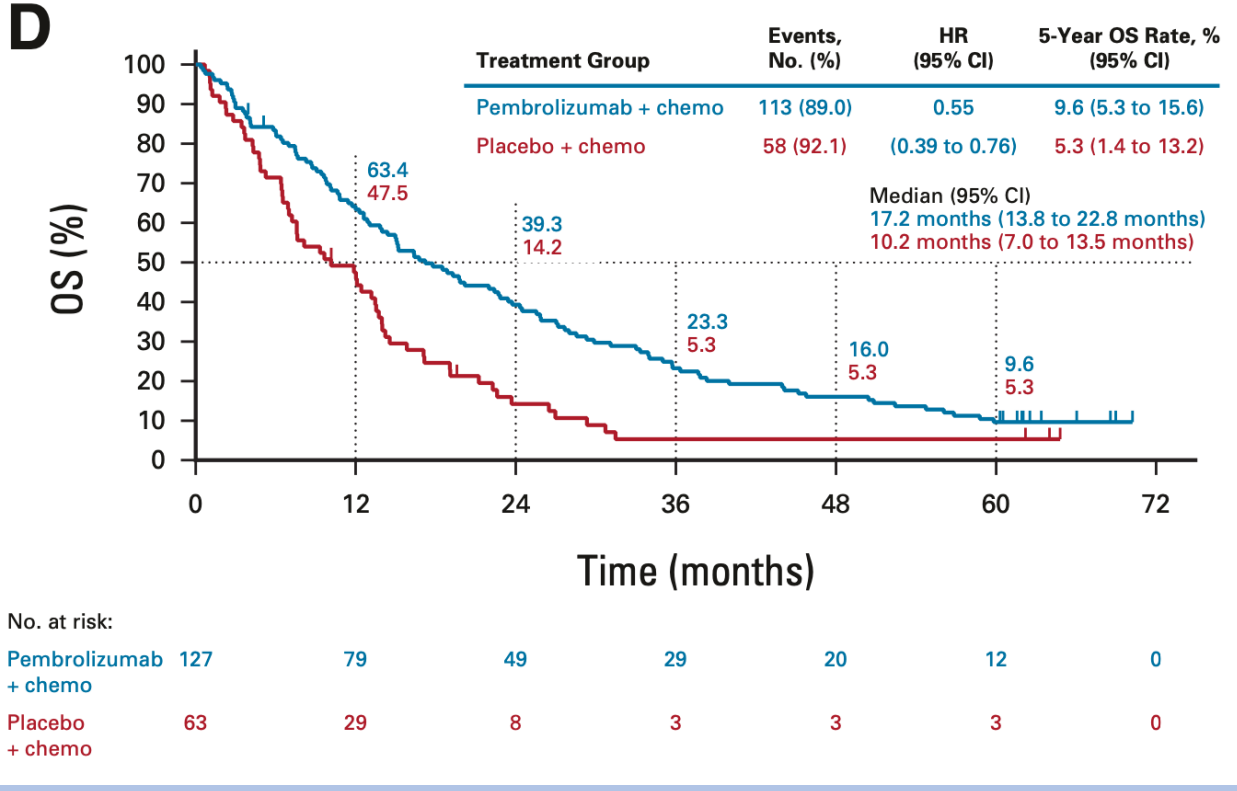
Reck. ASCO 2021. Abstr 9000.

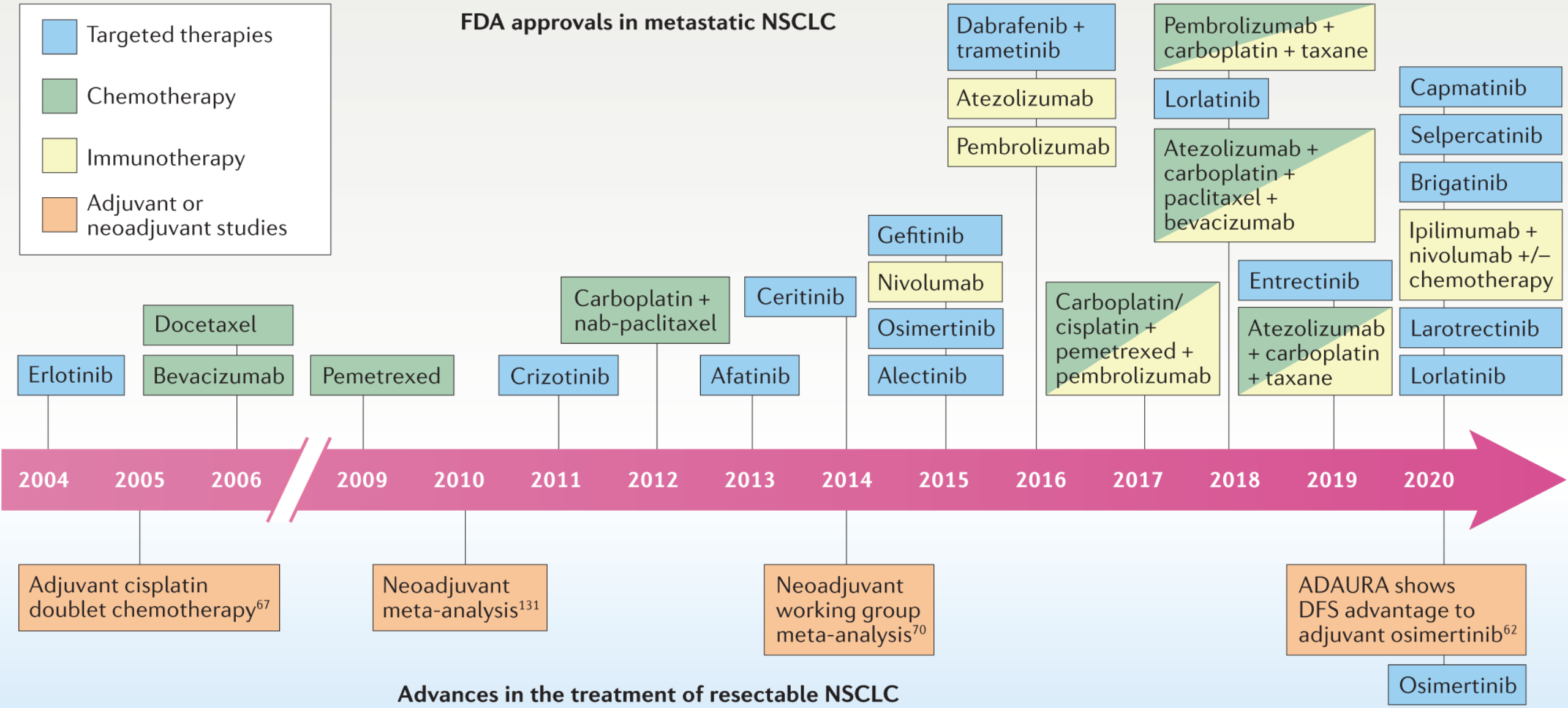
Slide credit: clinicaloptions.com

PD-L1 < 1%

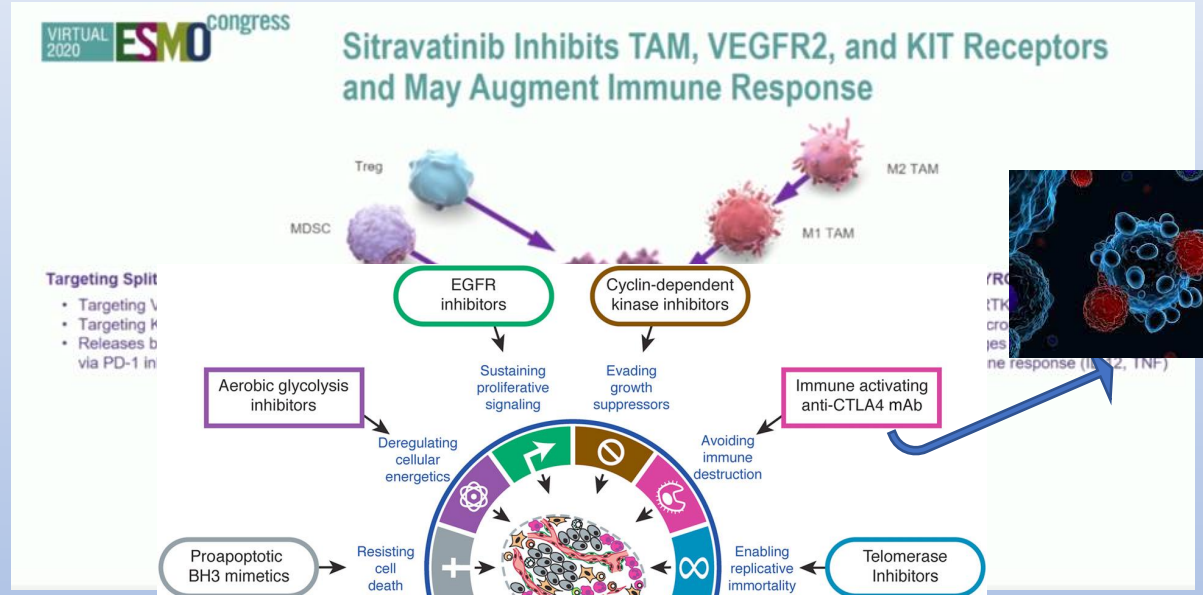

NIVO + IPI + chemo (n = 135)
Chemo (n = 129)
Median OS, mo 17.7 9.8
HR (95% CI) 0.63 (0.49-0.83)
OS (%)
100
80
60
40
20
0
63%
45%
37%
25%
23%
22%[d]
22%
15%
13%
8%[d]
NIVO + IPI + chemo
Chemo
0 6 12 18 24 30 36 42 48 54 60 66 72
Months
No. at risk
+ IPI + chemo 135 107 85 66 50 40 34 32 31 30 22 6 0
Chemo 129 90 58 37 27 19 17 16 15 11 8 1 0

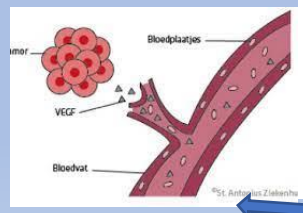
D

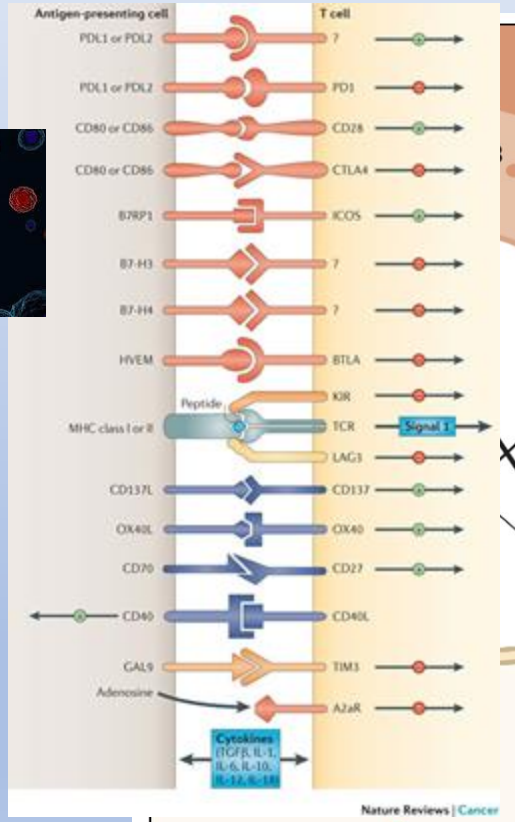

Treatment Group
Events, No. (%)
HR (95% CI)
5-Year OS Rate, % (95% CI)
Pembrolizumab + chemo 113 (89.0) 0.55 9.6 (5.3 to 15.6)
Placebo + chemo 58 (92.1) (0.39 to 0.76) 5.3 (1.4 to 13.2)
Median (95% CI)
17.2 months (13.8 to 22.8 months)
10.2 months (7.0 to 13.5 months)
OS (%)
100
90
80
70
60
50
40
30
20
10
0
63.4
47.5
39.3
14.2
23.3
5.3
16.0
5.3
9.6
5.3
0 12 24 36 48 60 72
Time (months)
No. at risk:
Pembrolizumab + chemo 127 79 49 29 20 12 0
Placebo + chemo 63 29 8 3 3 3 0

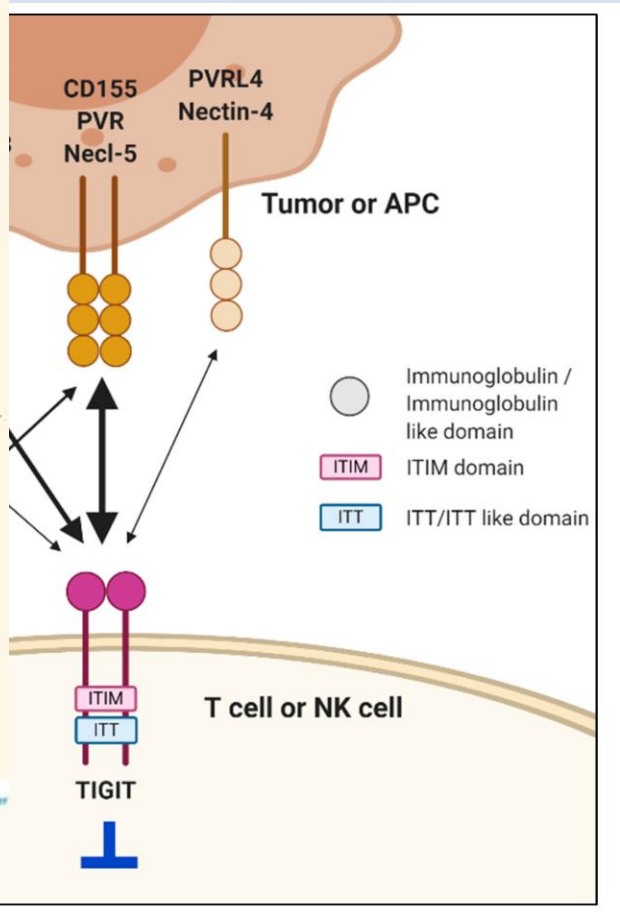

Targeted therapies
Chemotherapy
Immunotherapy
Adjuvant or neoadjuvant studies
FDA approvals in metastatic NSCLC
Erlotinib
Docetaxel
Bevacizumab
Pemetrexed
Crizotinib
Carboplatin + nab-paclitaxel
Afatinib
Ceritinib
Gefitinib
Nivolumab
Osimertinib
Alectinib
Dabrafenib + trametinib
Atezolizumab
Pembrolizumab
Carboplatin/ cisplatin + pemetrexed + pembrolizumab
Pembrolizumab + carboplatin + taxane
Lorlatinib
Atezolizumab + carboplatin + paclitaxel + bevacizumab
Entrectinib
Atezolizumab + carboplatin + taxane
Capmatinib
Selpercatinib
Brigatinib
Ipilimumab + nivolumab +/– chemotherapy
Larotrectinib
Lorlatinib
2004
2005
2006
2009
2010
2011
2012
2013
2014
2015
2016
2017
2018
2019
2020
Adjuvant cisplatin doublet chemotherapy[67]
Neoadjuvant meta-analysis[131]
Neoadjuvant working group meta-analysis[70]
ADAURA shows DFS advantage to adjuvant osimertinib[62]
Osimertinib
Advances in the treatment of resectable NSCLC

Nieuwe ontwikkelingen in stadium IV NSCLC? Studies in het Amphia ziekenhuis

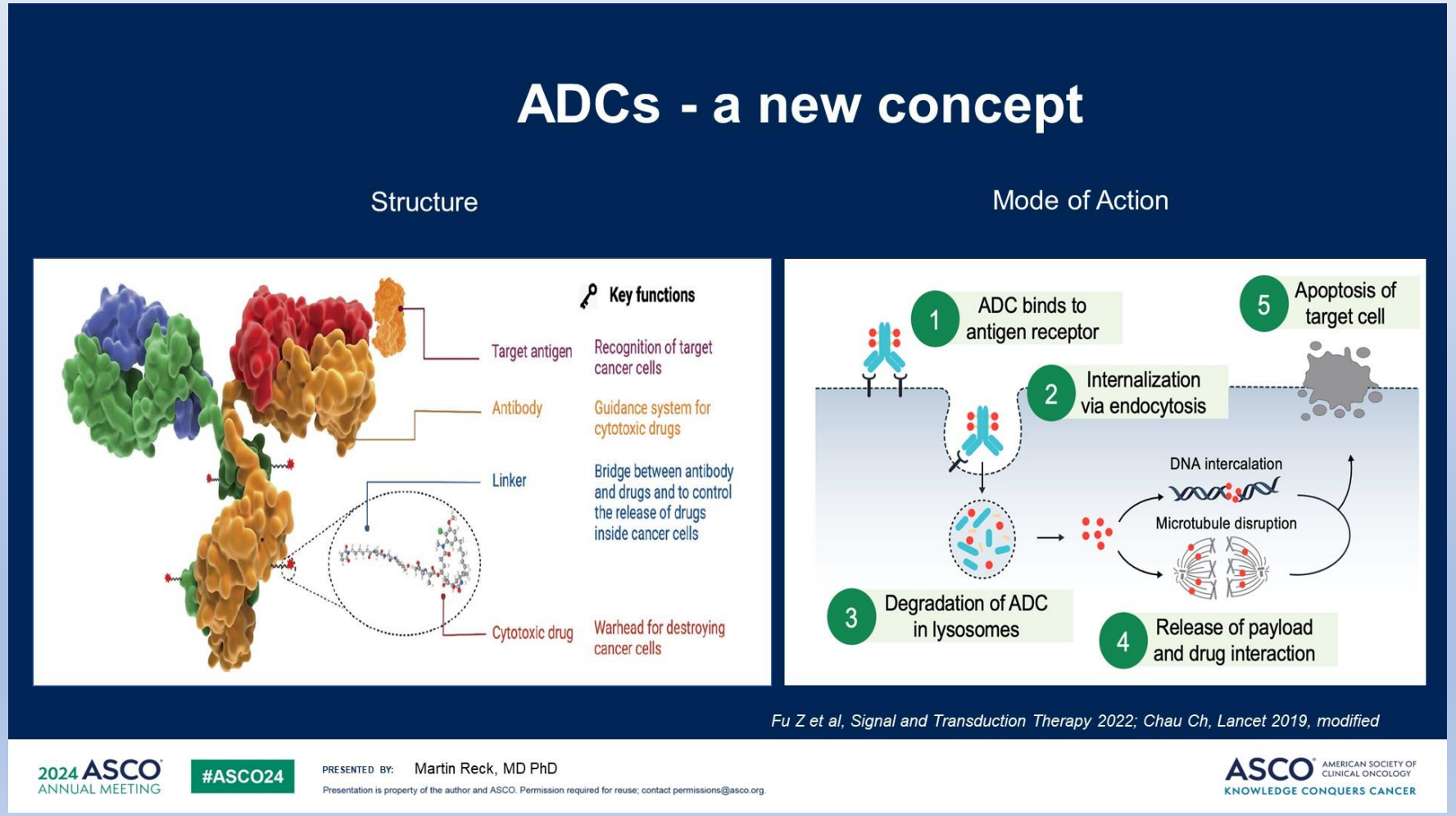




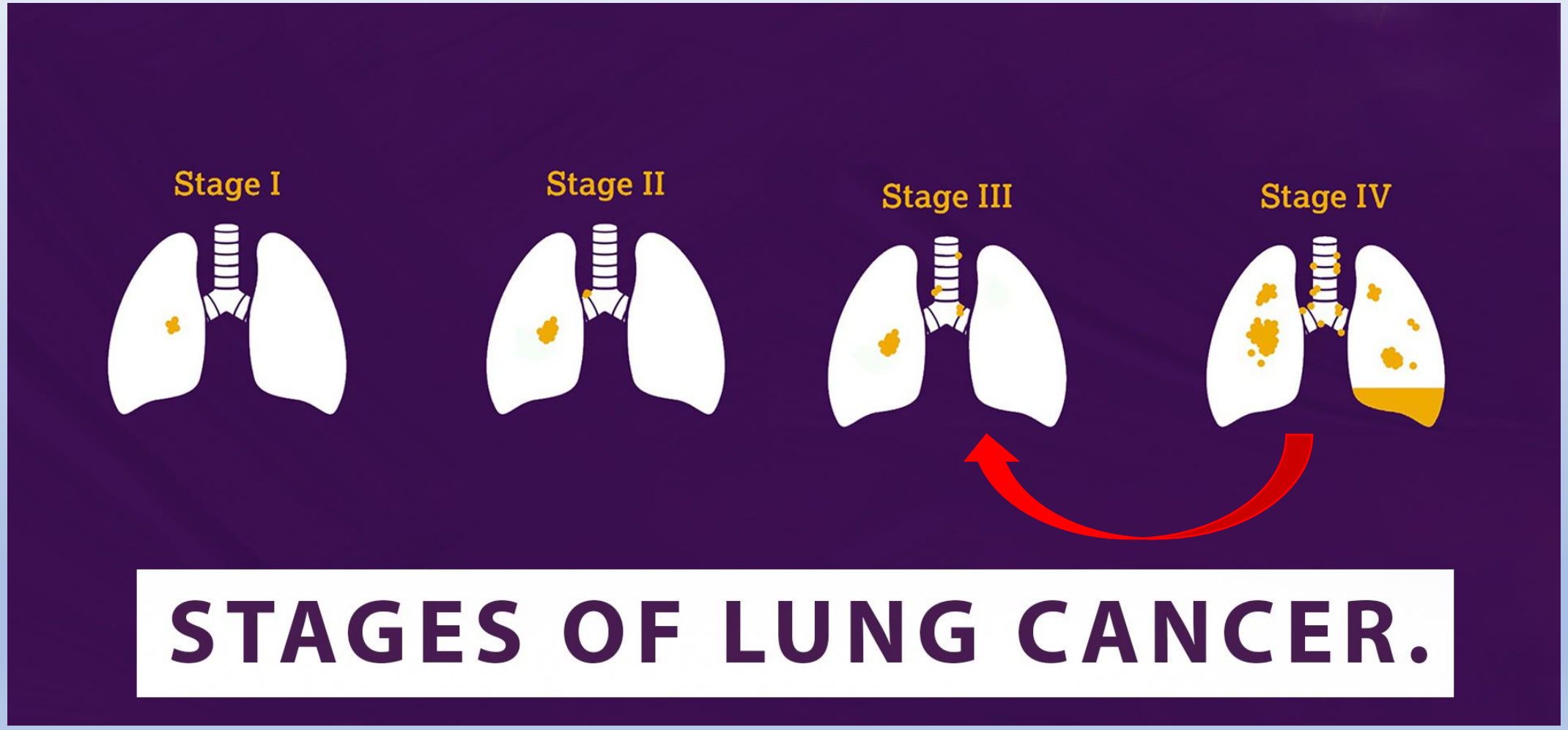




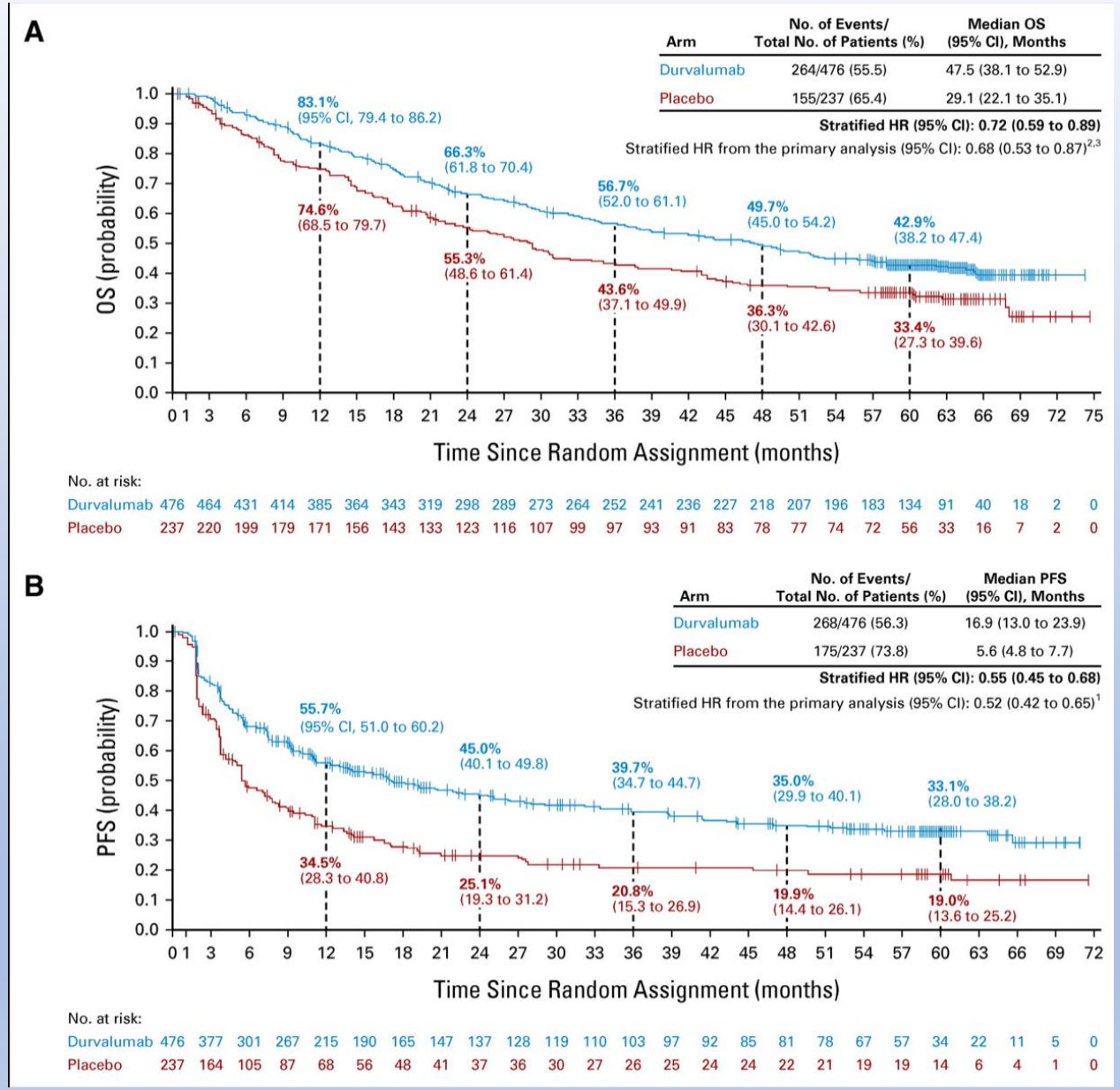
Studies met ADC's met immuuntherapie najaar 2024 van start in Amphia



Opschuiven van indicatie voor IO

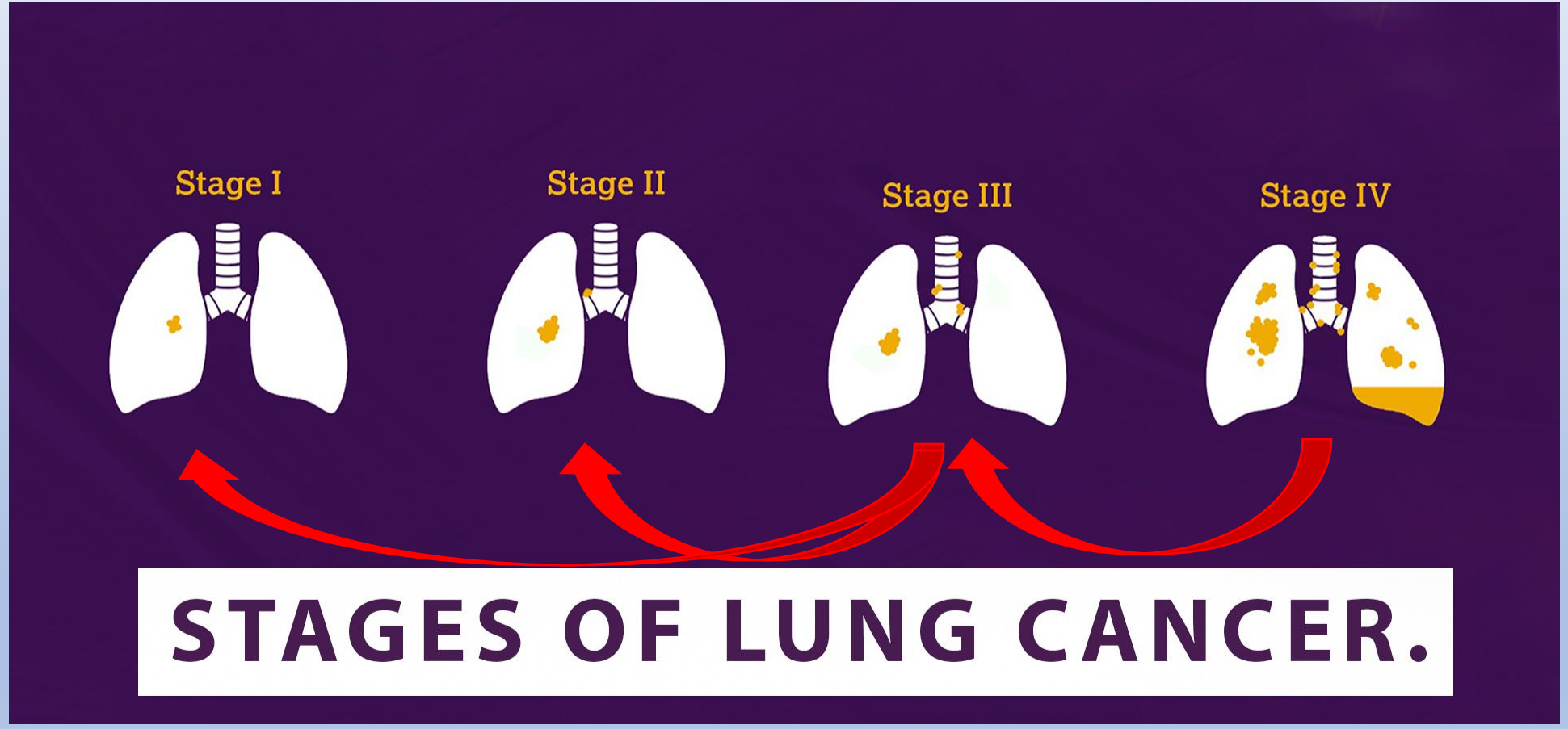


Pacific trial

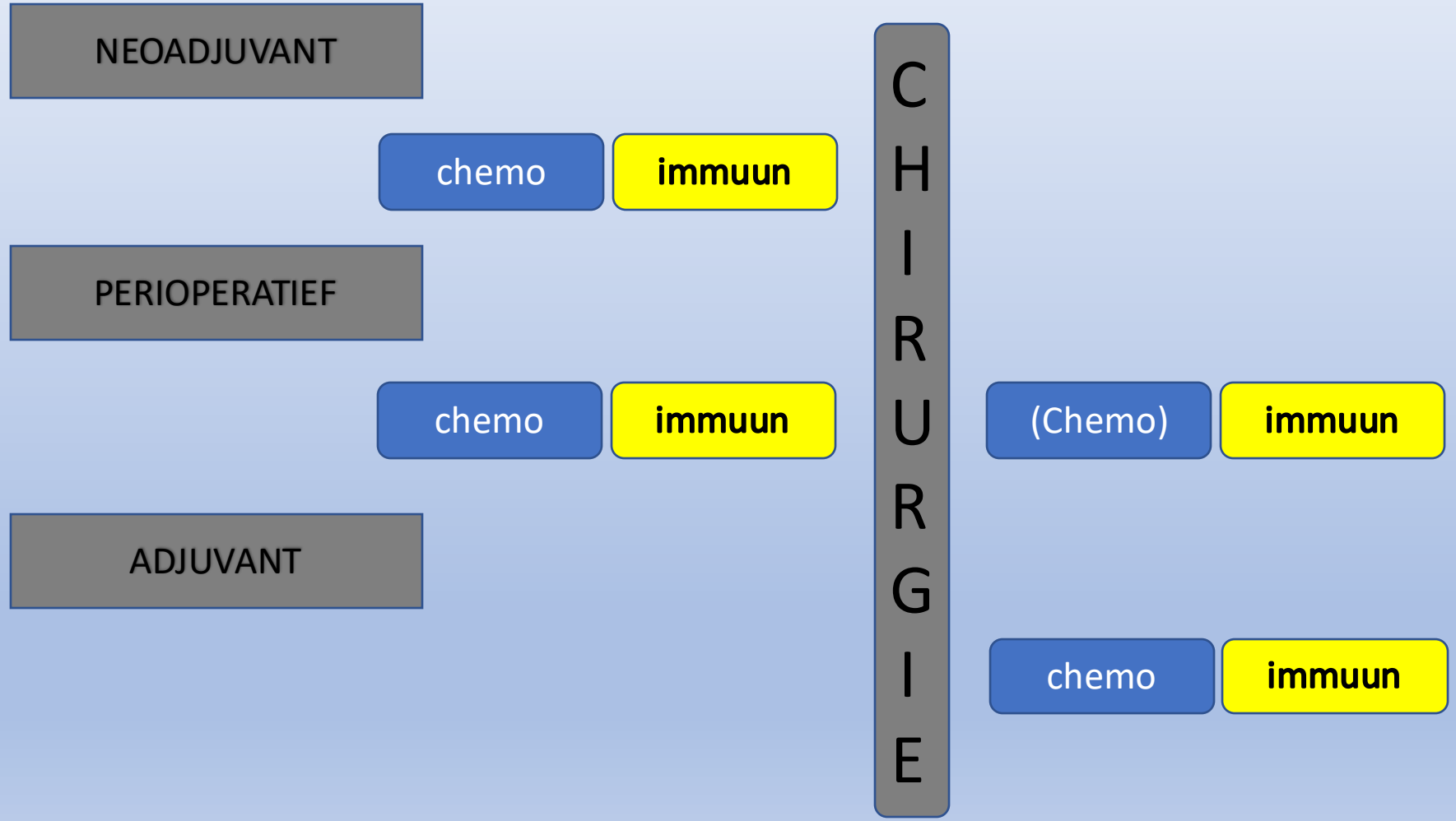


Five-Year Survival Outcomes From the PACIFIC Trial: Durvalumab After Chemoradiotherapy in Stage III Non–Small-Cell Lung Cancer. *Journal of Clinical Oncology* 40, no. 12 (April 20, 2022) 1301-1311.

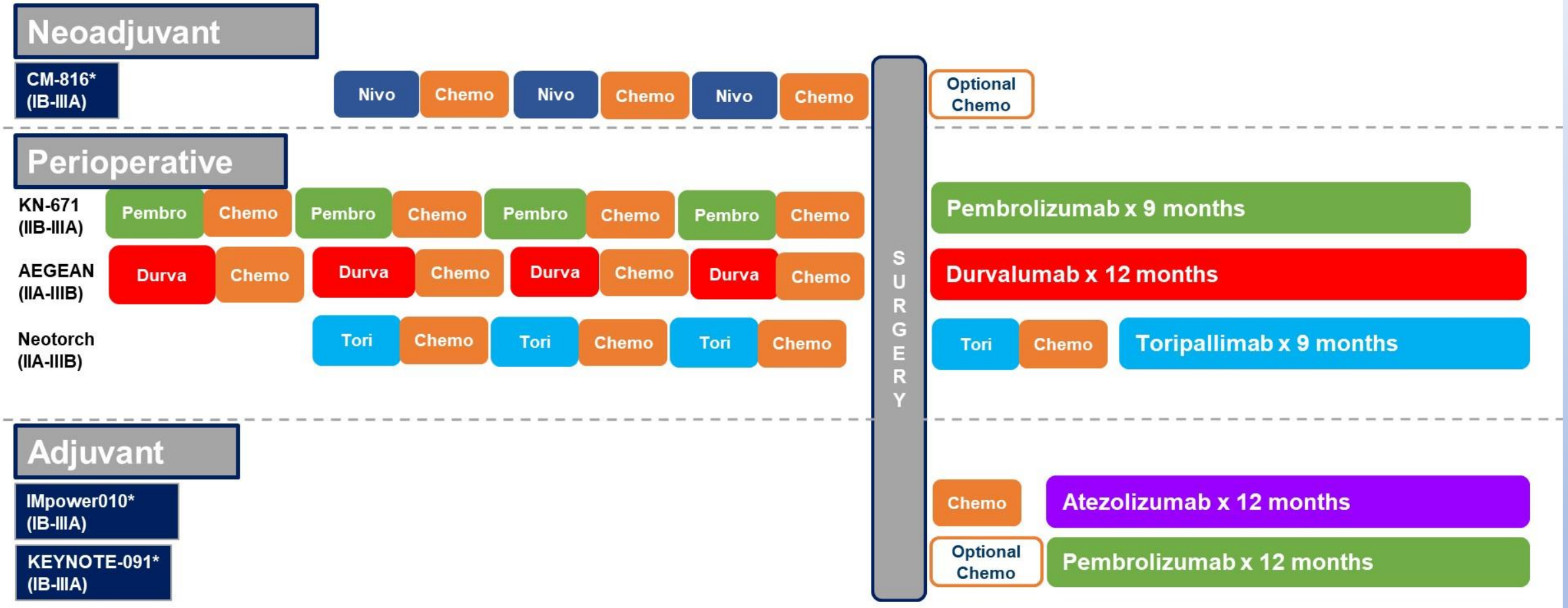
Opschuiven van indicatie voor IO



Behandel opties



Many evolving approaches:
Neoadjuvant vs. adjuvant vs. perioperative ICIs



Adjuvant Immuuntherapie

IMpower010 study design

Completely resected stage IB-IIIA NSCLC per UICC/AJCC v7

- Stage IB tumors ≥4 cm
- ECOG PS 0-1
- Lobectomy/pneumonectomy
- Tumor tissue for PD-L1 analysis

1-4 cycles cisplatin + pemetrexed, gemcitabine, docetaxel or vinorelbine

N=1280

R 1:1

No crossover

Atezolizumab *1200 mg q21d 16 cycles*

N=1005

BSC

Survival follow-up

Stratification factors

- Male vs female
- Stage (IB vs II vs IIIA)
- Histology
- PD-L1 tumor expression status[a]: TC2/3 and any IC vs TC0/1 and IC2/3 vs TC0/1 and IC0/1

Primary endpoints

- Investigator-assessed DFS tested hierarchically:
  1. PD-L1 TC ≥1% (SP263) stage II-IIIA population
  2. All-randomized stage II-IIIA population
  3. ITT (all-randomized stage IB-IIIA) population

Hierarchical statistical testing

DFS in PD-L1 TC ≥1% stage II-IIIA population[b]

If positive:

DFS in all-randomized stage II-IIIA population[b]

If positive:

DFS in ITT population[b] (all-randomized stage IB-IIIA)

If positive:

OS in ITT population[b] (all-randomized stage IB-IIIA)

- Endpoint was met at DFS IA
- Endpoint was not met at DFS IA, and follow-up is ongoing
- OS data were immature, and endpoint was not formally tested

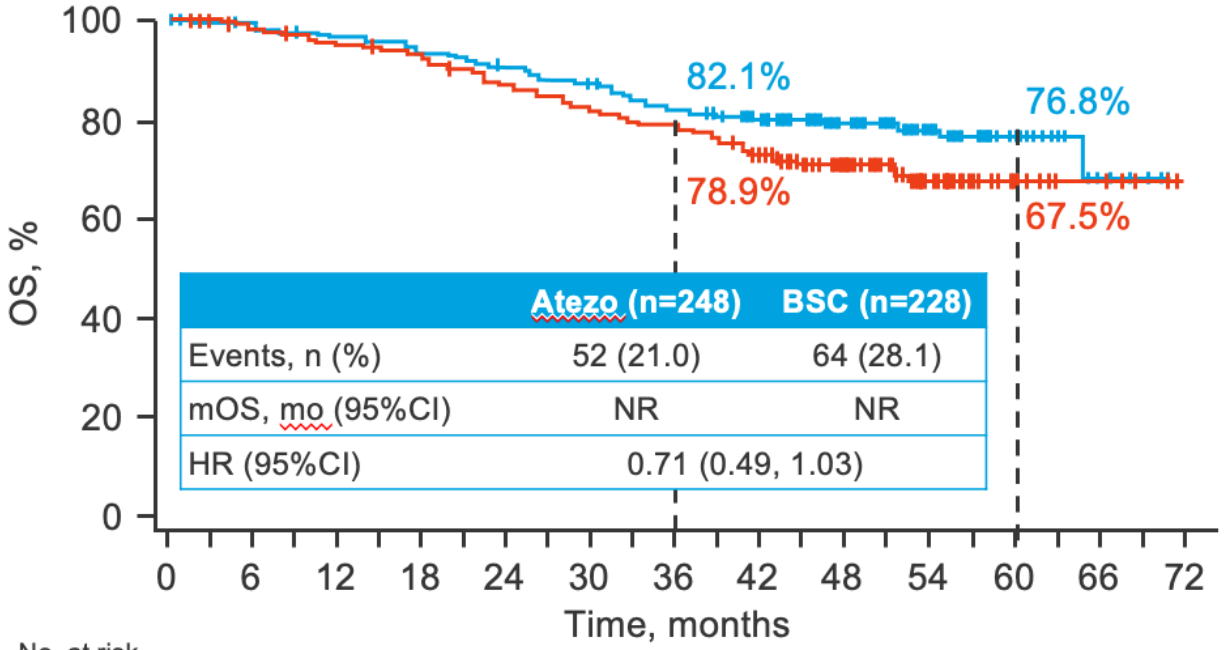
Both arms included observation and regular scans for disease recurrence on the same schedule.
IC, tumor-infiltrating immune cells. [a] Per SP142 assay. [b] Two-sided α=0.05.

PL03.09: IMpower010:Overall Survival Interim Analysis of a Phase III Study of Atezolizumab vs Best Supportive Care in Resected NSCLC – Felip E, et al

- **Key results**

Overall survival

PD-L1 TC ≥1% (stage II–IIIA)

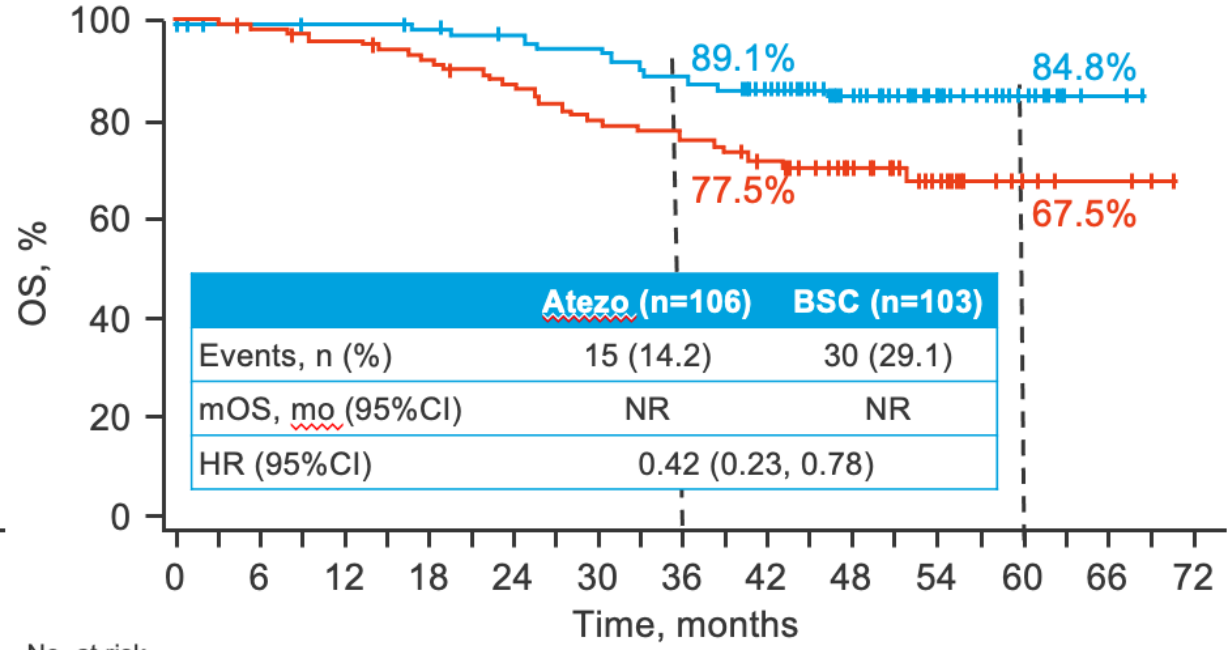


	Atezo (n=248)	BSC (n=228)
Events, n (%)	52 (21.0)	64 (28.1)
mOS, mo (95%CI)	NR	NR
HR (95%CI)	0.71 (0.49, 1.03)	

No. at risk

Atezolizumab	248	241	241	237	234	231	225	222	218	210	208	200	195	190	172	140	116	83	56	37	23	12	5	3	NE
BSC	228	220	214	210	205	201	198	192	185	180	172	167	166	158	140	110	95	72	49	27	15	8	7	4	NE

PD-L1 TC ≥50% (stage II–IIIA) excluding EGFR/ALK+



	Atezo (n=106)	BSC (n=103)
Events, n (%)	15 (14.2)	30 (29.1)
mOS, mo (95%CI)	NR	NR
HR (95%CI)	0.42 (0.23, 0.78)	

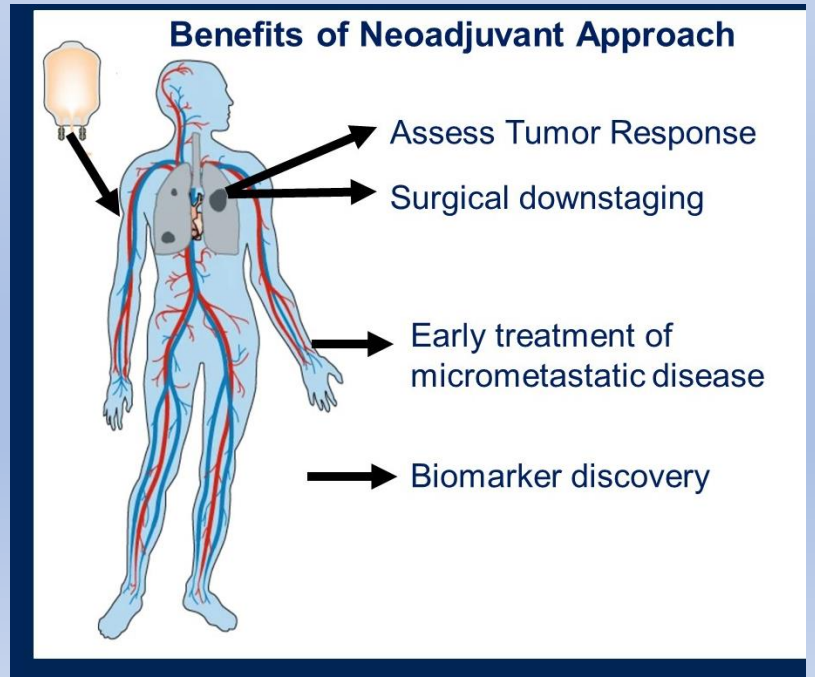
No. at risk

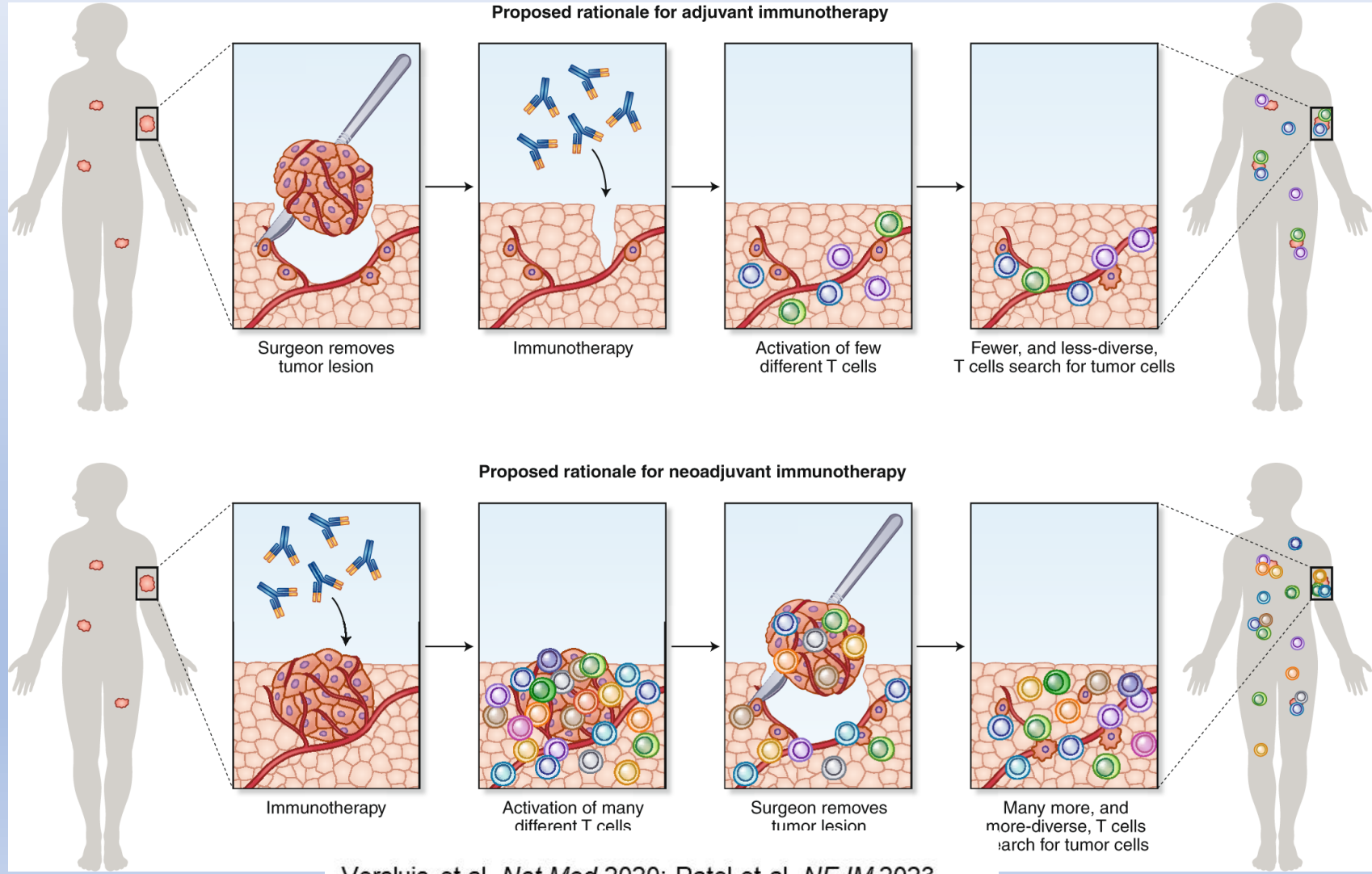
Atezolizumab	106	104	104	104	103	103	101	100	99	96	96	93	90	87	83	69	58	41	32	20	13	6	2	1	NE
BSC	103	101	98	96	95	92	90	87	84	80	77	76	75	71	64	52	45	35	24	14	8	4	3	2	NE

Felip E, et al. J Thorac Oncol 2022;17(suppl):Abstr PL03.09

Adjuvant of Neoadjuvant

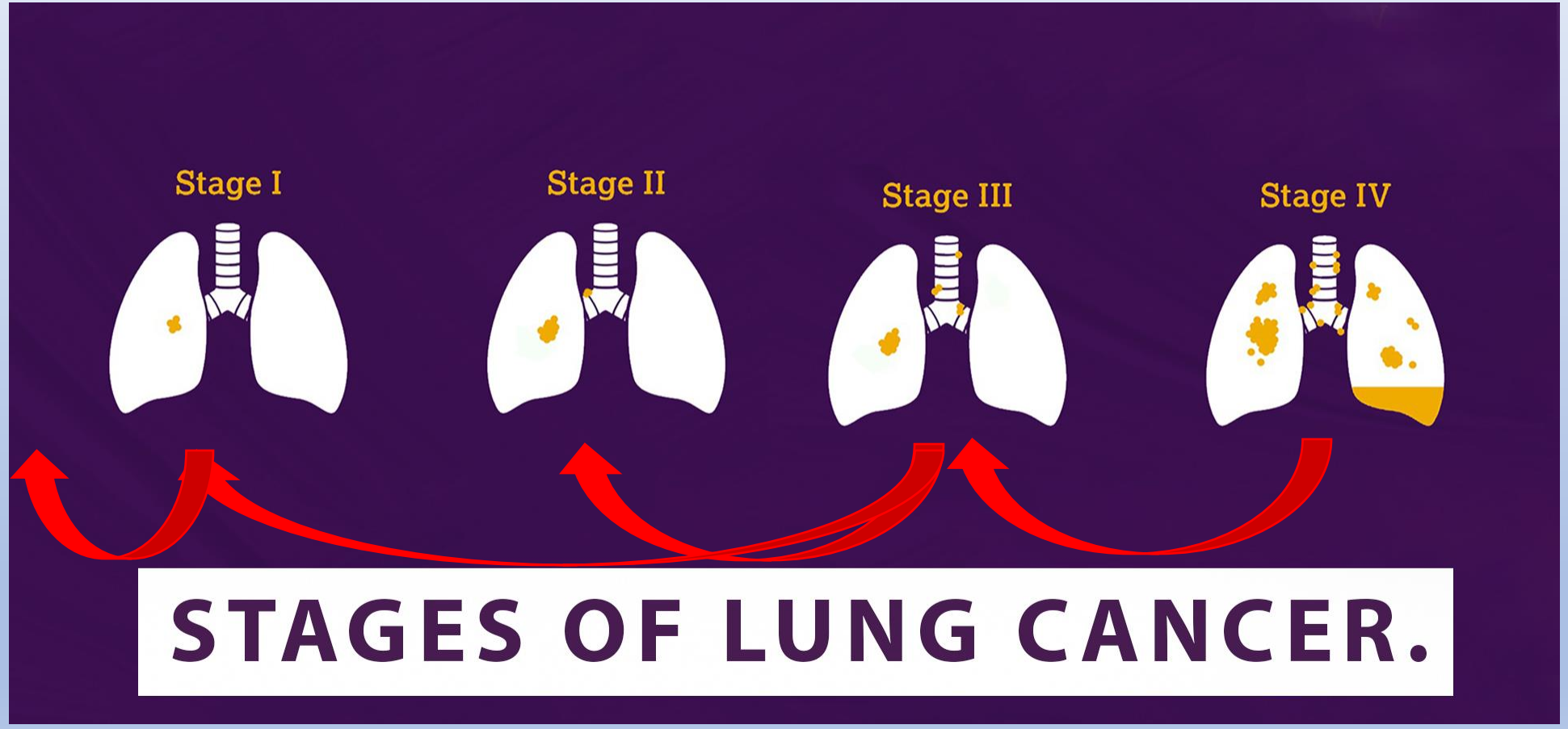
- ICI exposure aan in situ tumor
  - Meer verschillende T cells actief
  - Minder klonale resistentie
  - Maximale aanmaak T cell memory respons





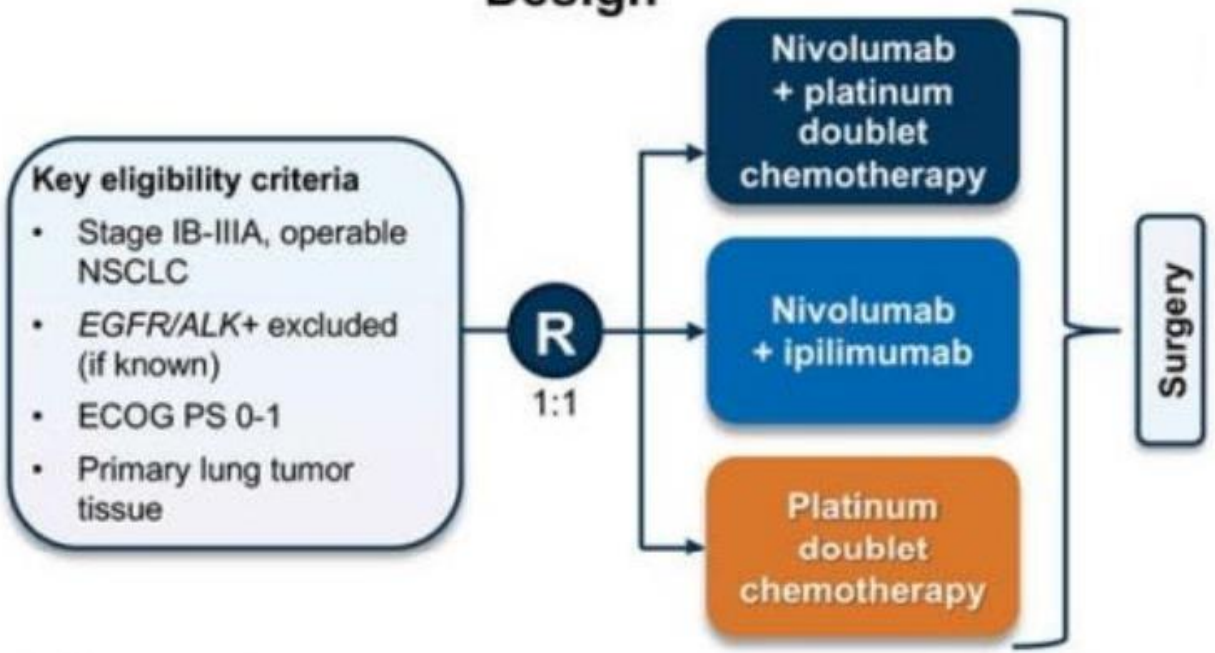
Versluis et al, *Nat Med* 2020; Patel et al, *NEJM* 2023

Opschuiven van indicatie voor IO



CheckMate -816: Design and Baseline Characteristics[1]

Design



Primary outcome measures
- EFS (time frame: up to 69 mo)
- pCR (time frame: at the time of surgery)

Secondary outcome measures
- OS, MPR, TTDM

Baseline Characteristics

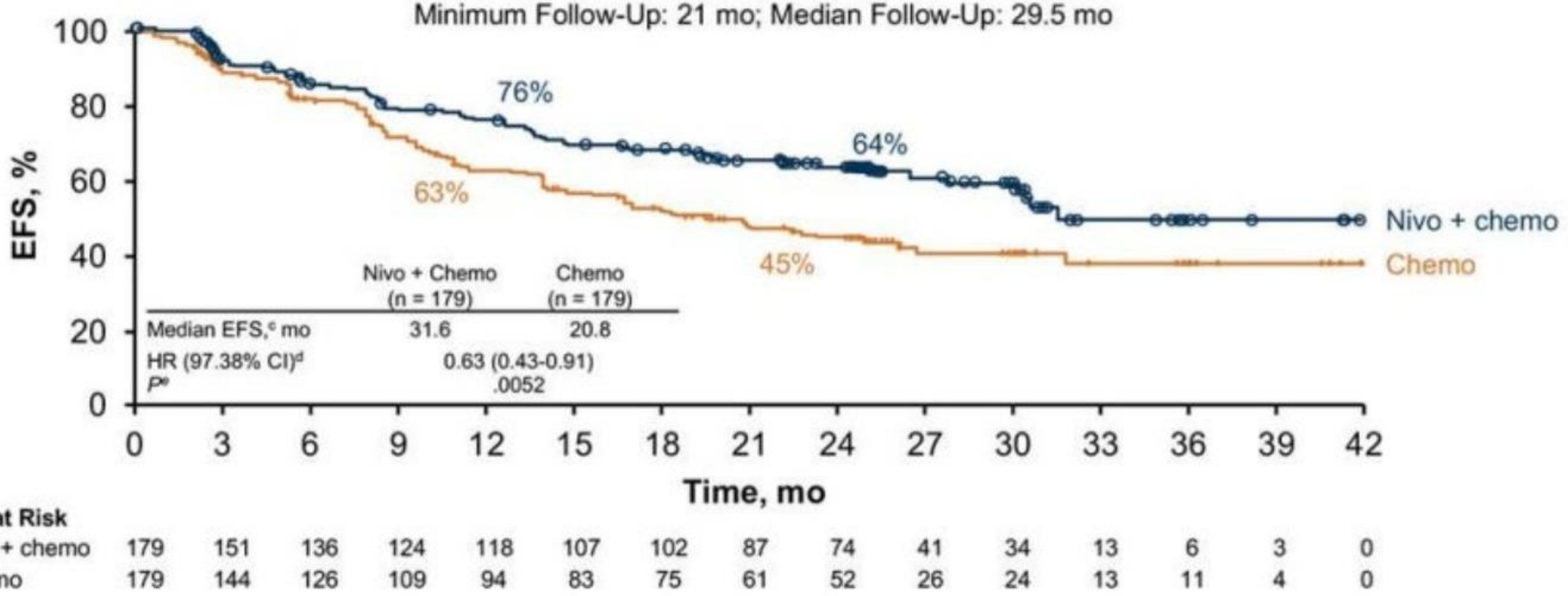
	Nivolumab + Chemotherapy (n = 179)	Chemotherapy (n = 179)
Age, median (range), y	64 (41-82)	65 (34-84)
Female, %	28	29
Region, %		
North America	23	28
Europe	23	14
Asia	48	51
Stage, %		
IB-II	36	35
IIIA	63	64
Histology, %		
Squamous	49	53
Nonsquamous	51	47
Smoking status, %		
Current/former	89	88
Never	11	11
Tumor PD-L1 expression, %		
NE	7	7
<1%	44	43
≥1%	50	50
1-49%	28	26
≥50%	21	24
TMB, %		
NE/NR	51	50
<12.3 mut/Mb	27	30
≥12.3 mut/Mb	22	21

1. Forde PM et al. AACR 2021. Abstract CT003.

CheckMate -816: EFS[1,2]

Primary Endpoint: EFS[a,b] With Neoadjuvant Nivo + Chemo vs Chemo

Minimum Follow-Up: 21 mo; Median Follow-Up: 29.5 mo



No. at Risk

Nivo + chemo	179	151	136	124	118	107	102	87	74	41	34	13	6	3	0
Chemo	179	144	126	109	94	83	75	61	52	26	24	13	11	4	0

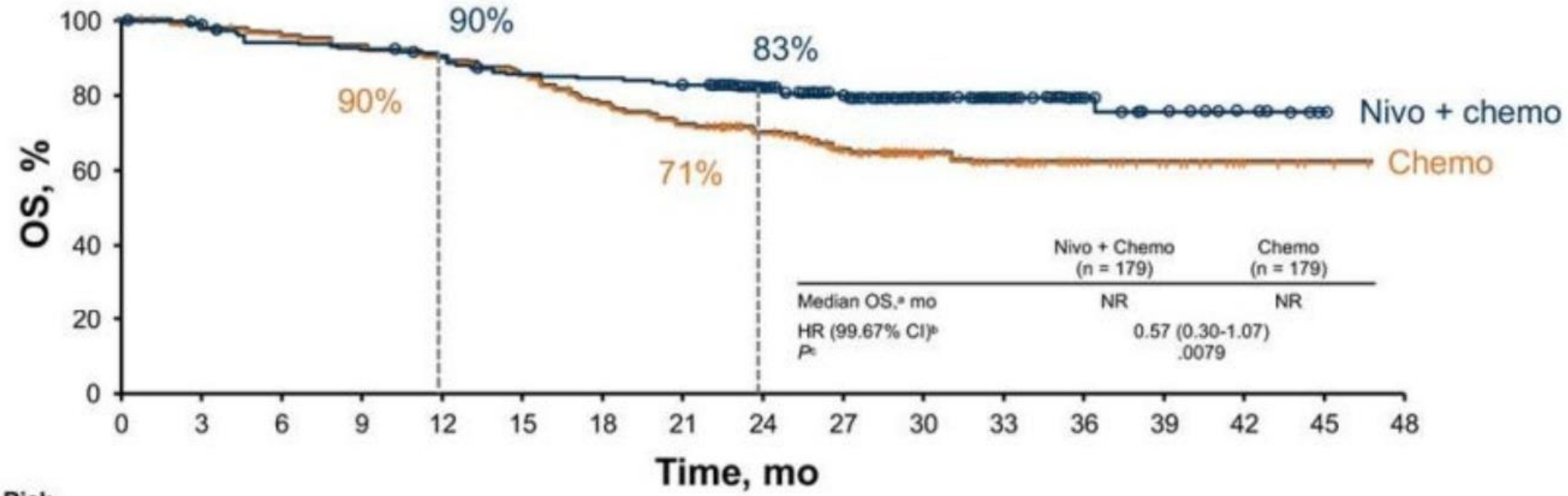
[a] Per BICR. [b] EFS defined as the time from randomization to any progression of disease precluding surgery, progression or recurrence of disease after surgery, progression for patients without surgery, or death due to any case; patients with subsequent therapy were censored at the last evaluable tumor assessment on or prior to the date of subsequent therapy. [c] 95% CI, 30.2-NR (nivo + chemo) and 14.0-26.7 (chemo). [d] 95% CI, 0.45-0.87. [e] The significance boundary at this interim analysis was .0262.

1. Girard N et al. AACR 2022. Abstract CT012. 2. Forde PM et al. *N Engl J Med*. 2022;26;386:1973-1985.

CheckMate -816: OS Interim Analysis[1]

Overall Survival: Interim Analysis

Minimum Follow-Up: 21 mo; Median Follow-Up: 29.5 mo



	Nivo + Chemo (n = 179)	Chemo (n = 179)
Median OS,[a] mo	NR	NR
HR (99.67% CI)[b]	0.57 (0.30-1.07)	
P[c]	.0079	

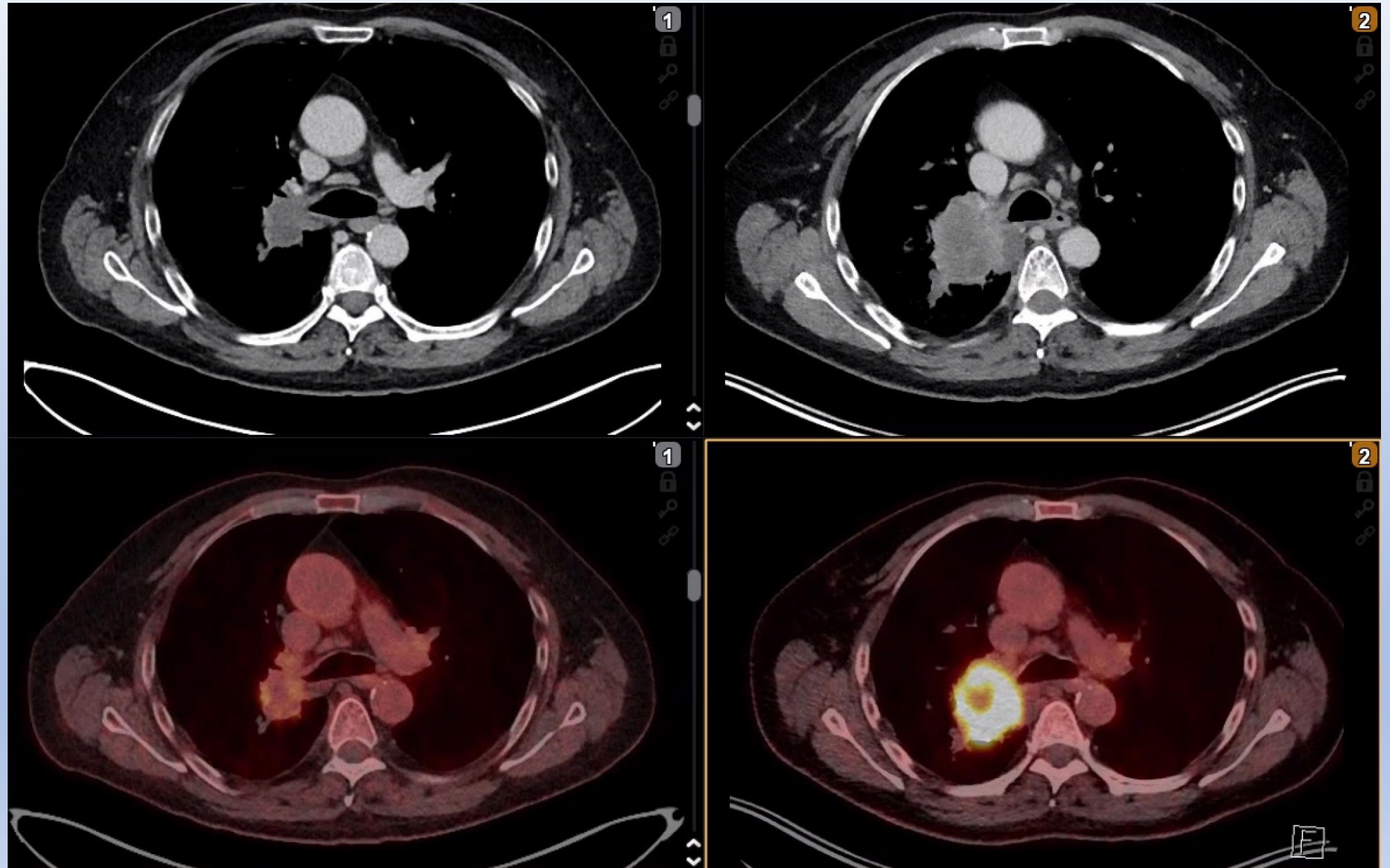
No. at Risk

Nivo + chemo	179	176	166	163	156	148	146	143	122	101	72	48	26	16	7	3	0
Chemo	179	172	165	161	154	148	133	123	108	80	59	41	24	16	7	2	0

[a] 95% CI, NR-NR (nivo + chemo) and NR-NR (chemo). [b] 95% CI, 0.38-0.87. [c] Significance boundary for OS (.0033) was not met at this interim analysis.

1. Girard N et al. AACR 2022. Abstract CT012.

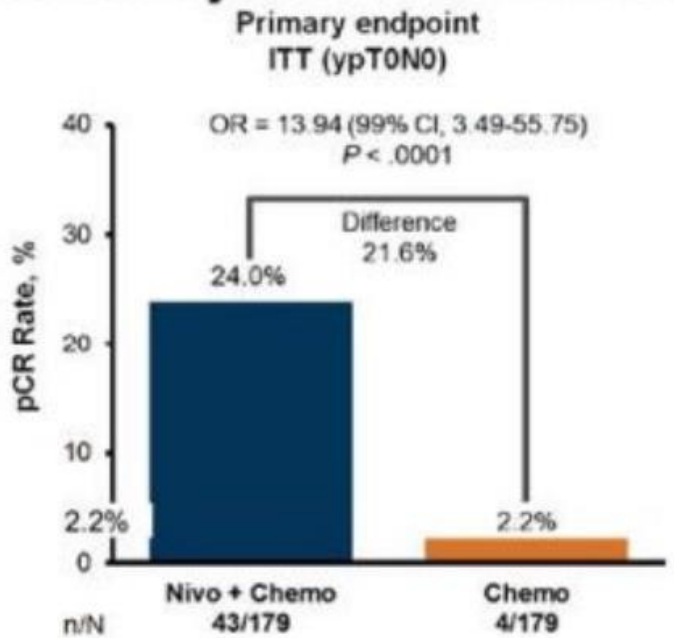
Na 4 kuren chemo en immuuntherapie



CheckMate -816: pCR Rate (Primary Endpoint)[1]

- The addition of nivo to chemo increased pCR from 2.2% with chemo alone to 24% with nivo + chemo ($P < .0001$)
- pCR was assessed by central pathologists who were blinded to trial arms

pCR Rate With Neoadjuvant Nivo + Chemo vs Chemo



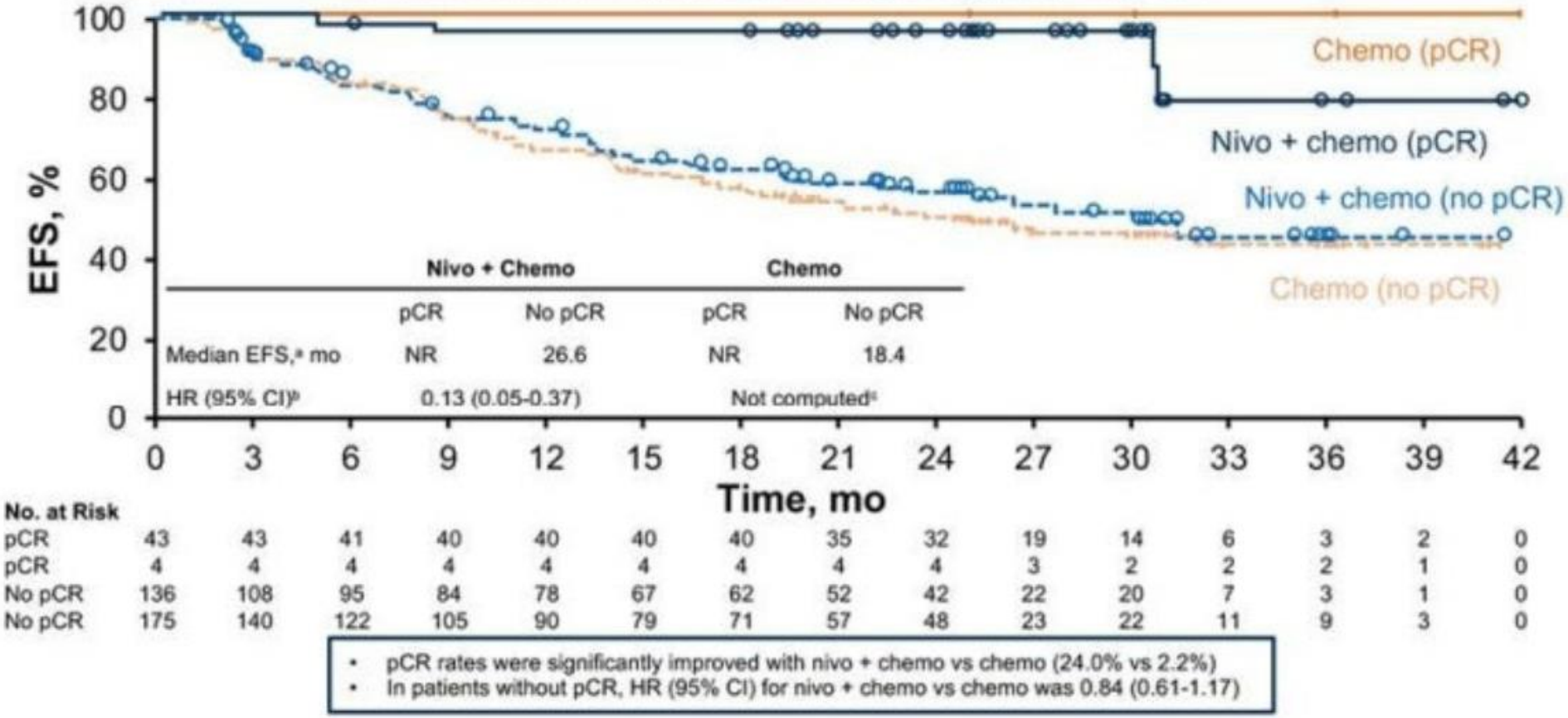
- **pCR rate in the exploratory nivo + ipi arm (ITT) was 20.4% (95% CI, 13.4-29.0)**

1. Forde PM et al. AACR 2021. Abstract CT003.

CheckMate -816: EFS by pCR Status[1]

Exploratory Analysis: EFS by pCR Status

Minimum Follow-Up: 21 mo; Median Follow-Up: 29.5 mo



	Nivo + Chemo		Chemo	
	pCR	No pCR	pCR	No pCR
Median EFS,[a] mo	NR	26.6	NR	18.4
HR (95% CI)[b]	0.13 (0.05-0.37)		Not computed[c]	

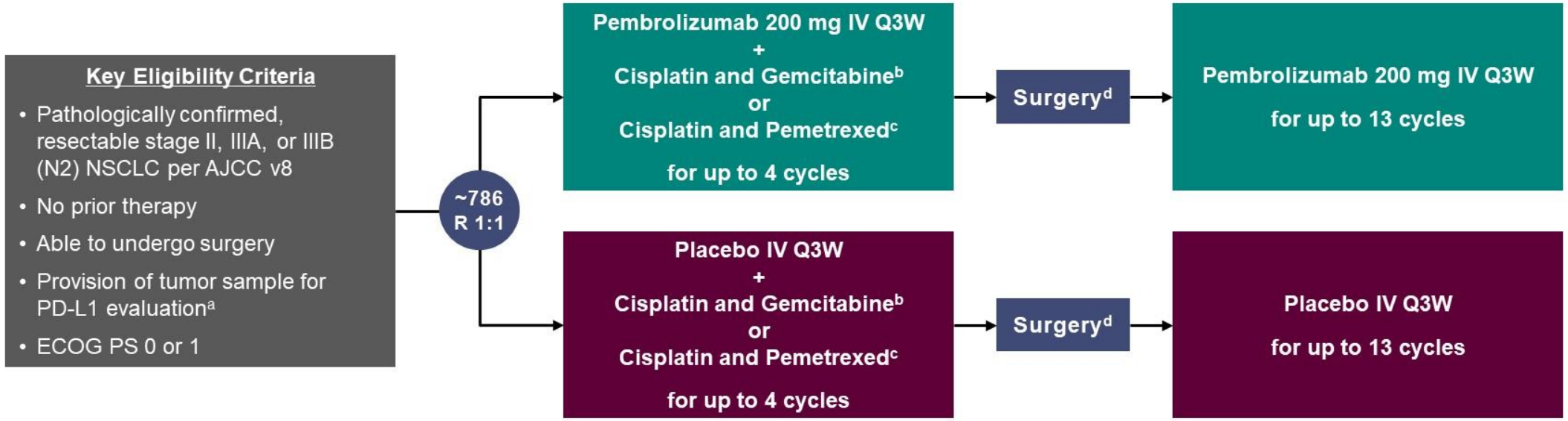
No. at Risk															
pCR	43	43	41	40	40	40	40	35	32	19	14	6	3	2	0
pCR	4	4	4	4	4	4	4	4	4	3	2	2	2	1	0
No pCR	136	108	95	84	78	67	62	52	42	22	20	7	3	1	0
No pCR	175	140	122	105	90	79	71	57	48	23	22	11	9	3	0

- pCR rates were significantly improved with nivo + chemo vs chemo (24.0% vs 2.2%)
- In patients without pCR, HR (95% CI) for nivo + chemo vs chemo was 0.84 (0.61-1.17)

[a] 95% CI, 30.6-NR (nivo + chemo, pCR), 16.6-NR (nivo + chemo, no pCR) and NR-NR (chemo, pCR), 13.9-26.2 (chemo, noPCR). [b] In the pooled patient population (nivo + chemo and chemo arms combined), EFS HR (95% CI) was 0.11 (0.04-0.29) for patients with pCR vs those without pCR. [c] HR was not computed for the chemo arm due to only 4 patients having a pCR.

1. Girard N et al. AACR 2022. Abstract CT012.

KEYNOTE-671 Study Design
Randomized, Double-Blind, Phase 3 Trial



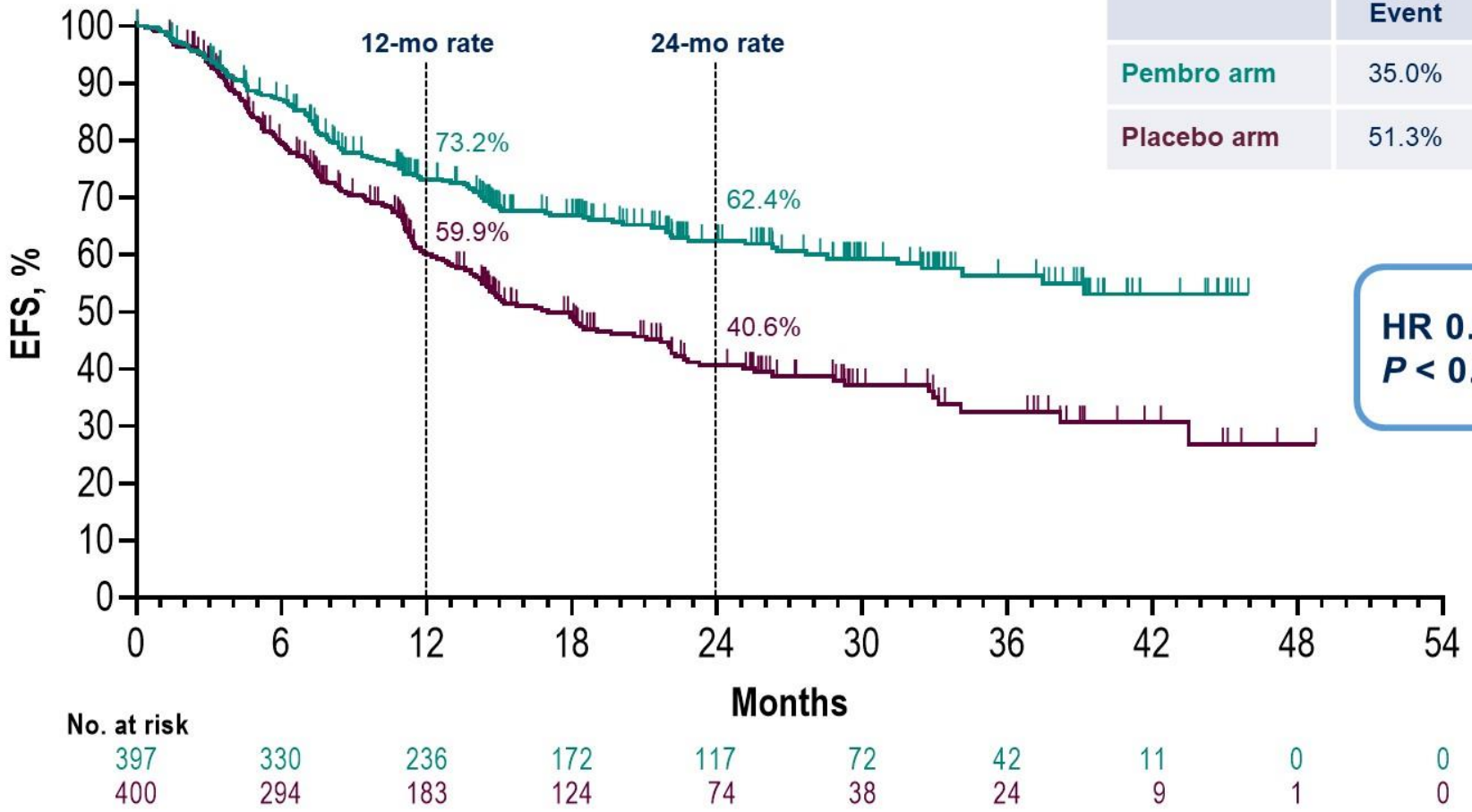
Stratification Factors
- Disease stage (II vs III)
- PD-L1 TPS[a] (<50% vs ≥50%)
- Histology (squamous vs nonsquamous)
- Geographic region (east Asia vs not east Asia)

Dual primary end points: EFS per investigator review and OS

Key secondary end points: mPR and pCR per blinded, independent pathology review, and safety

[a] Assessed at a central laboratory using PD-L1 IHC 22C3 pharmDx. [b] Cisplatin 75 mg/m^2 IV Q3W + gemcitabine 1000 mg/m^2 IV on days 1 and 8 Q3W was permitted for squamous histology only. [c] Cisplatin 75 mg/m^2 IV Q3W + pemetrexed 500 mg/m^2 IV Q3W was permitted for nonsquamous histology only. [d] Radiotherapy was to be administered to participants with microscopic positive margins, gross residual disease, or extracapsular nodal extension following surgery and to participants who did not undergo planned surgery for any reason other than local progression or metastatic disease. ClinicalTrials.gov identifier: NCT03425643.

Event-Free Survival



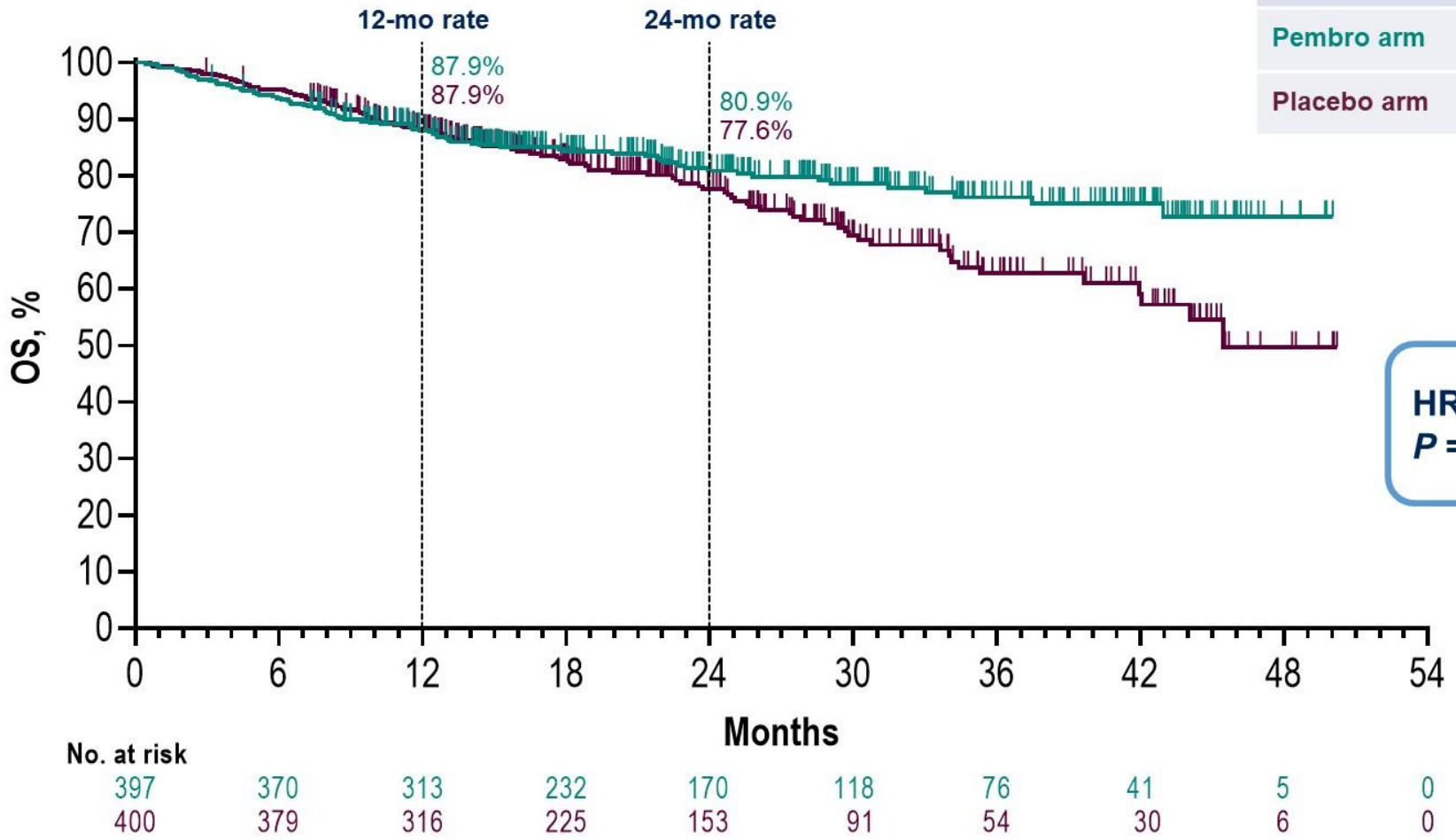
	Pts w/ Event	Median (95% CI), mo
Pembro arm	35.0%	NR (34.1-NR)
Placebo arm	51.3%	17.0 (14.3-22.0)

HR 0.58 (95% CI, 0.46-0.72)
***P* < 0.00001**

EFS defined as time from randomization to first occurrence of local progression precluding planned surgery, unresectable tumor, progression or recurrence per RECIST v1.1 by investigator assessment, or death from any cause.
Data cutoff date for IA1: July 29, 2022 (median follow-up, 25.2 mo [range, 7.5-50.6]).

Overall Survival

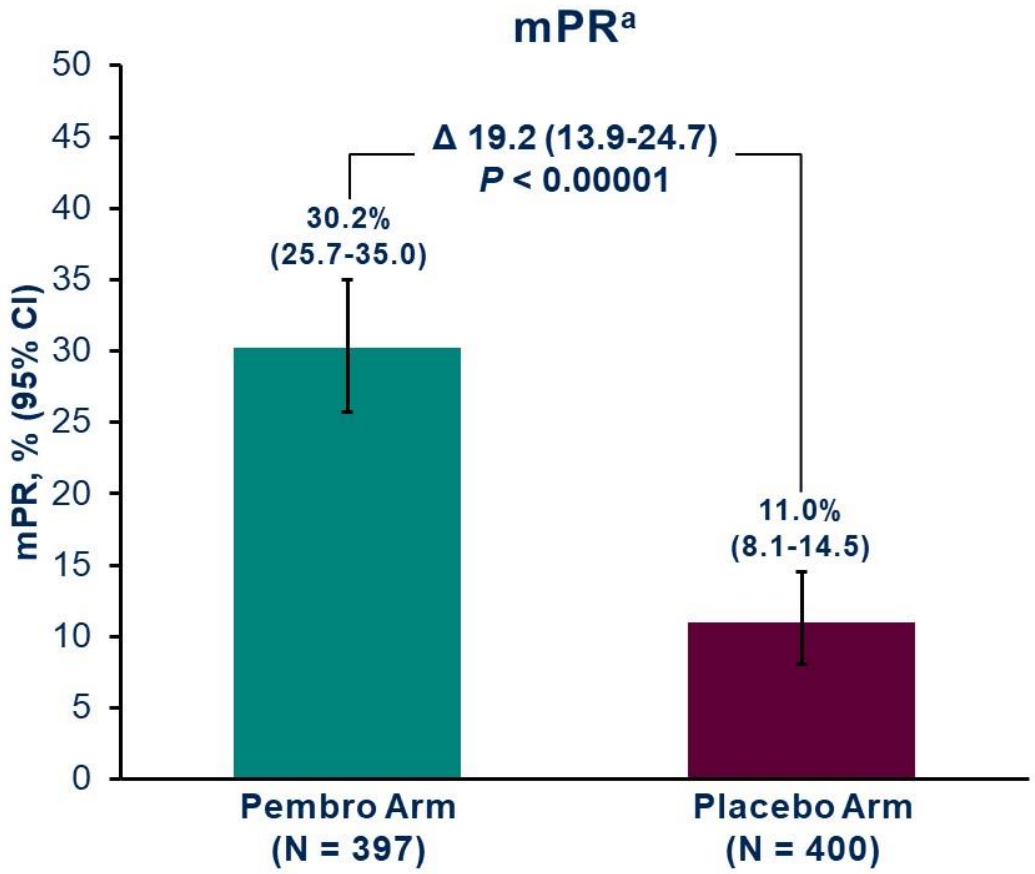
	Pts w/ Event	Median (95% CI), mo
Pembro arm	19.1%	NR (NR-NR)
Placebo arm	25.3%	45.5 (42.0-NR)

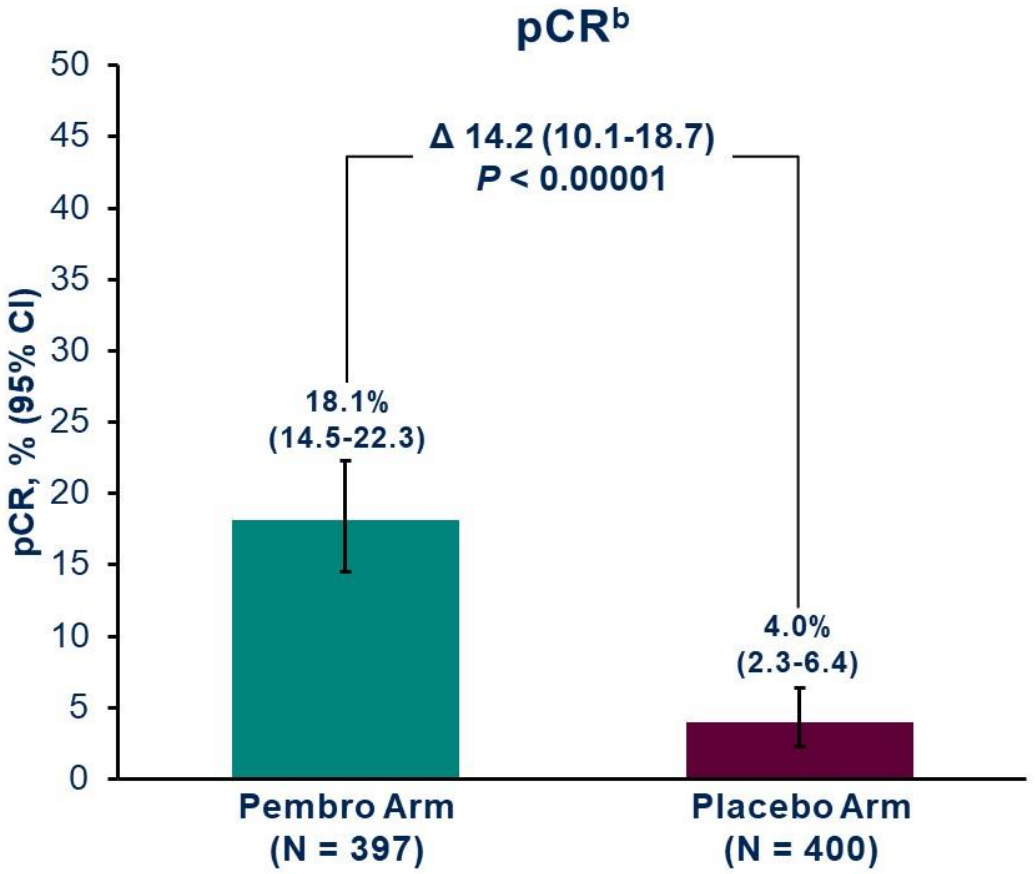


HR 0.73 (95% CI, 0.54-0.99)
***P* = 0.02124[a]**

OS defined as time from randomization to death from any cause. [a] Significance boundary not met at IA1; OS will continue to be tested according to the analysis plan. Data cutoff date for IA1: July 29, 2022 (median follow-up, 25.2 mo [range, 7.5-50.6]).

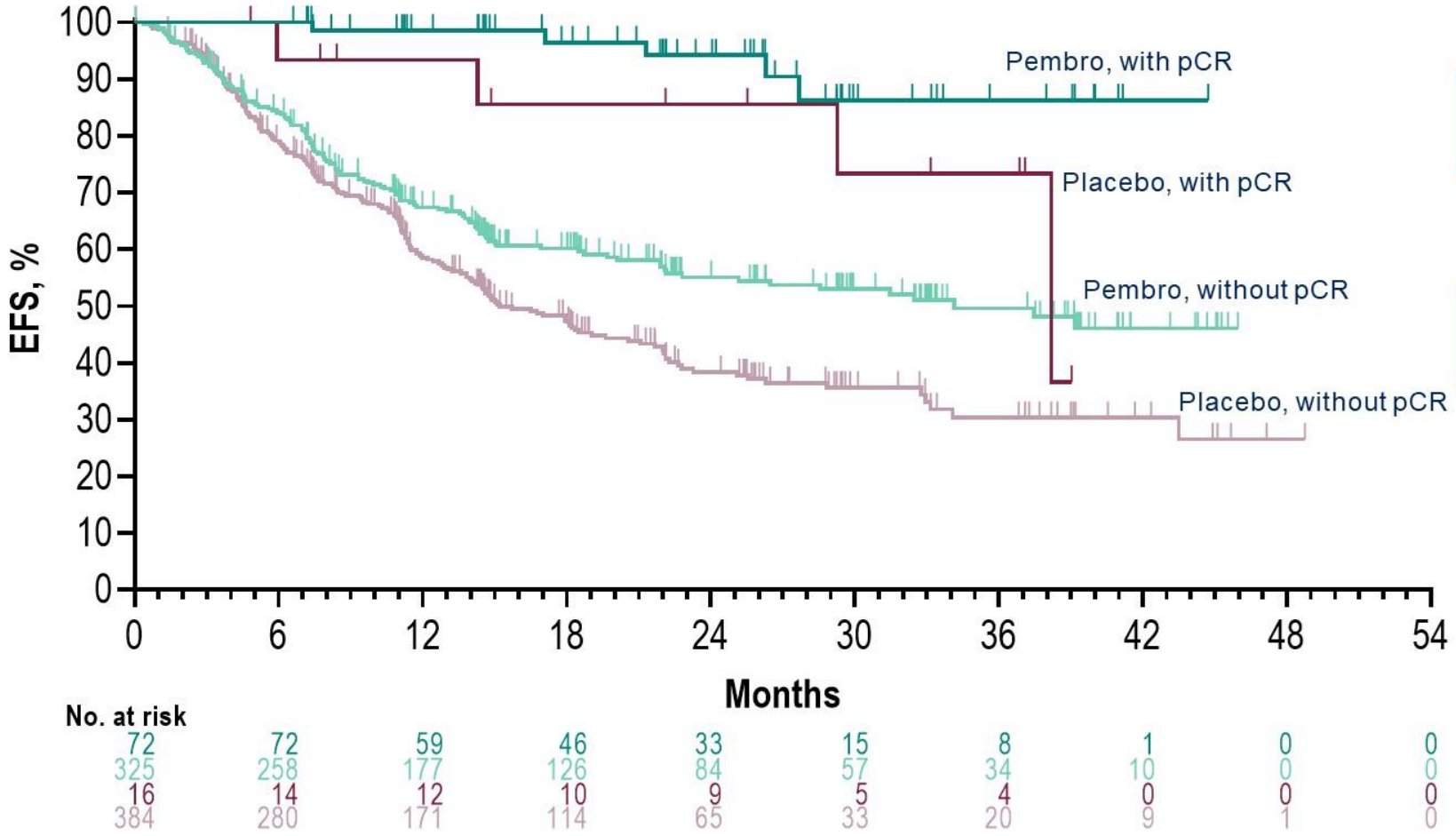
Pathologic Response
Assessed per Blinded, Independent Pathologist Review





[a] Defined as ≤10% viable tumor cells in resected primary tumor and lymph nodes. [b] Defined as absence of residual invasive cancer in resected primary tumor and lymph nodes (ypT0/Tis ypN0). Data cutoff date for IA1: July 29, 2022.

Exploratory Analysis of EFS by pCR Status



With pCR
HR 0.33 (95% CI, 0.09-1.22)

Without pCR
HR 0.69 (95% CI, 0.55-0.85)

pCR defined as absence of residual invasive cancer in resected primary tumor and lymph nodes (ypT0/Tis ypN0). EFS defined as time from randomization to first occurrence of local progression precluding planned surgery, unresectable tumor, progression or recurrence per RECIST v1.1 by investigator assessment, or death from any cause. Data cutoff date for IA1: July 29, 2022 (median follow-up, 25.2 mo [range, 7.5-50.6]).

Conclusies

- Immuuntherapie is niet meer weg te denken in de behandeling van longkanker zonder andere activerende mutaties.

- Steeds verdere implementatie van de immuuntherapie

- Verder onderzoek naar combinaties van therapieën
- Combinatie van chemo en immuuntherapie
- Combinatie van 2 verschillende immuuntherapieën.

- Verder uitzoeken waarom niet iedereen baat heeft van immuuntherapie

Vragen?