



Longcarcinoom: chemo-
immunotherapie,
adjuvante immunotherapie

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11-02-2020

Disclosures

(Potentiële) Belangenverstrengeling

Geen

- Inleiding
- Landschap
 - Chemo-immunotherapie
- Waar staan we
 - Longcarcinoom: chemo-immunotherapie
 - Adjuvante immunotherapie
- Wat is nieuw
 - Combinatie immunotherapie

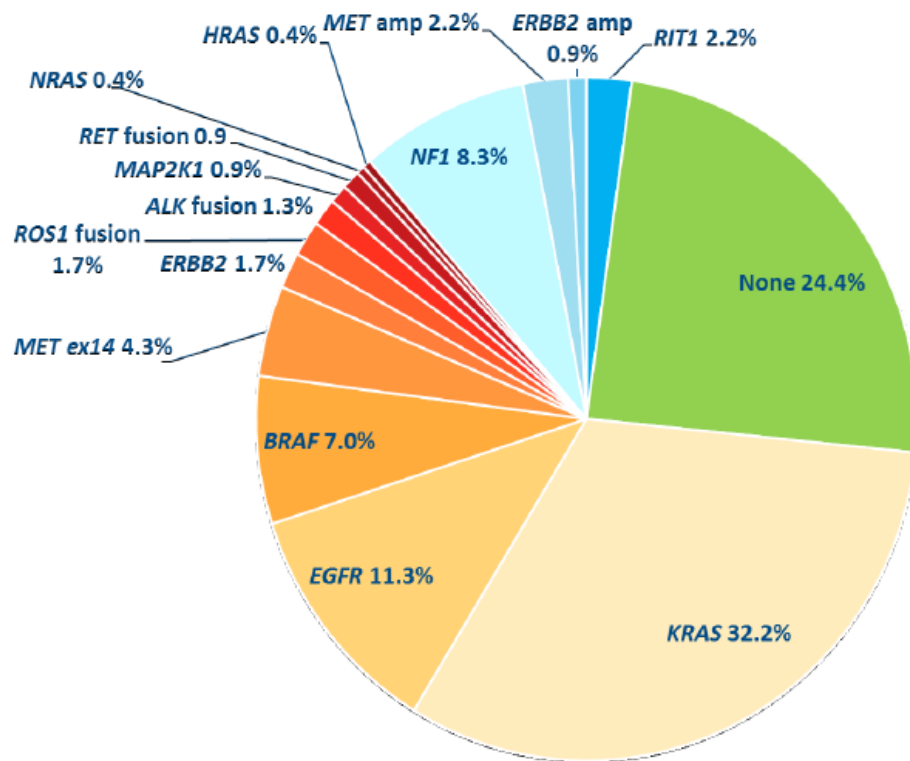
Achtergrond

- Longkanker > 12.000 nieuwe ziektegevallen per jaar in NL.
- Meer dodelijk dan borst-, prostaat-, darm- en alvleesklierkanker samen.
- Behandeling: Met beperkte ziekte opereren of bestralen.
- Met uitgezaaide ziekte chemotherapie en/of immunotherapie of TKI's $\pm 90\% \pm 10\%$.

Immunotherapie en Longkanker

- Longkanker wordt gekenmerkt door sterke immunosuppressieve omgeving
- Longtumoren vertonen meer dan 200 mutaties per tumor
- Rokers hebben 10 keer zoveel somatische mutatie als die van niet rokers

FREQUENCY OF ONCOGENIC DRIVERS IN LUNG ADENOCARCINOMA



Cancer Genome Atlas Research Network. *Nature* 2014;511(7511):543-50.

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Chemotherapie VS immunotherapie

- Chemotherapie
 - Toxisch
 - Beschadigd alle cellen
 - Onvoorspelbaar bij wie het zal aanslaan
- Immunotherapie
 - Niet-toxisch
 - Afweercellen vernietigen de tumorcellen
 - Deels voorspelbaar a.h.v. “PD-L1”

Ontwikkeling van immunotherapie



Tumor cellen

Hun identiteit verbergen:

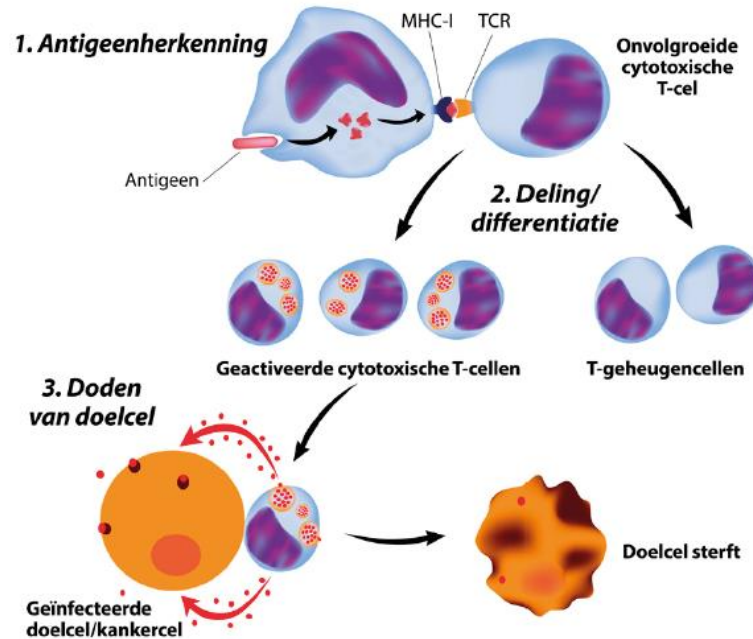
- een kankercel kan de expressie van **tumorantigenen** op zijn oppervlak verminderen
- het **immuunsysteem** kan moeilijker als abnormaal identificeren

Een barrière opwerpen:

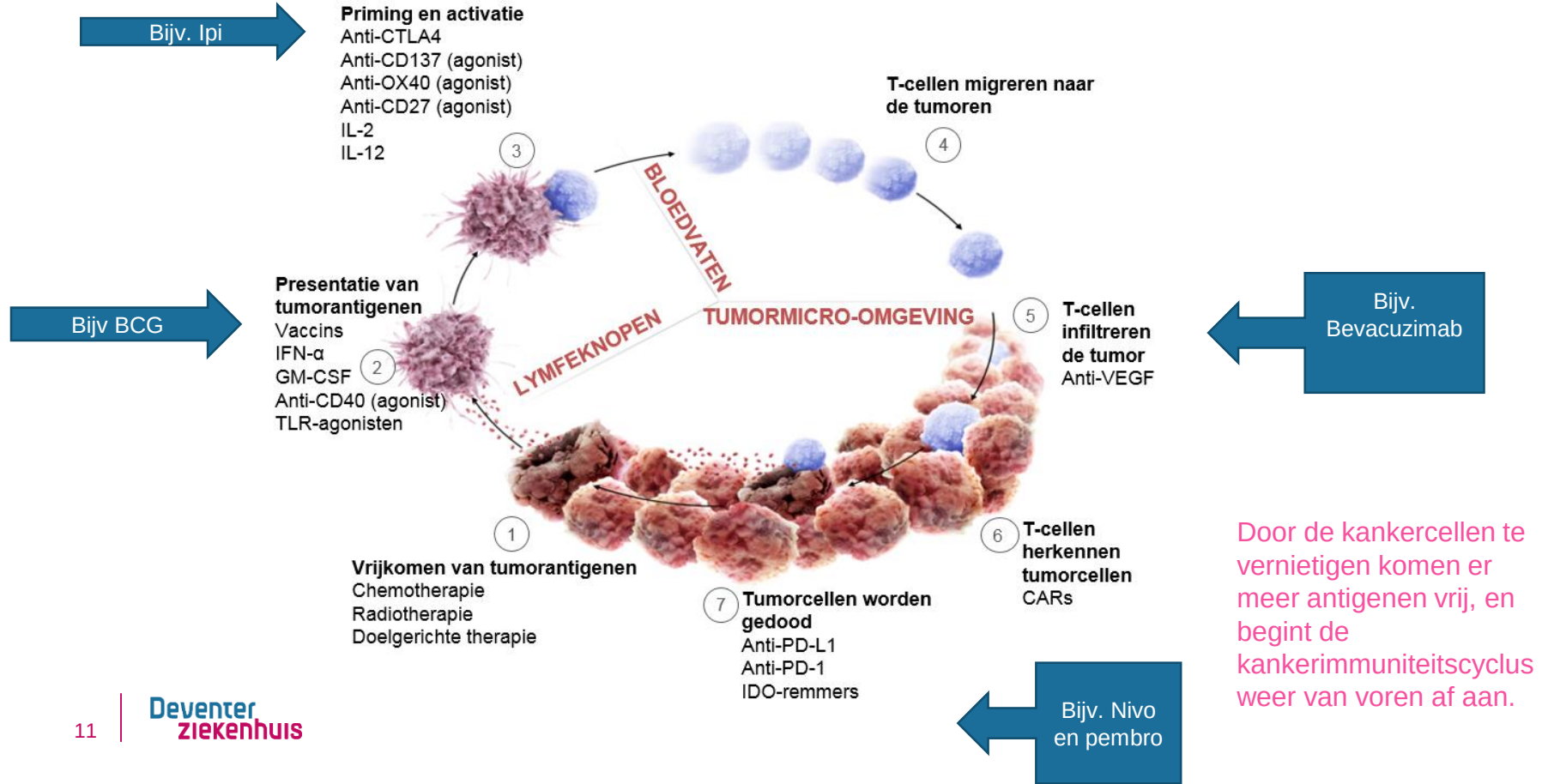
- een kankercel kan **eiwitten** op zijn oppervlak tot expressie brengen die een **immuuncel** inactiveren
- Andere cellen beïnvloeden: een kankercel kan cellen in de buurt beïnvloeden zodat ze stoffen afgeven die de immuunreactie onderdrukken

Immuno-oncologie

Activering en werking van cytotoxische T-cellen



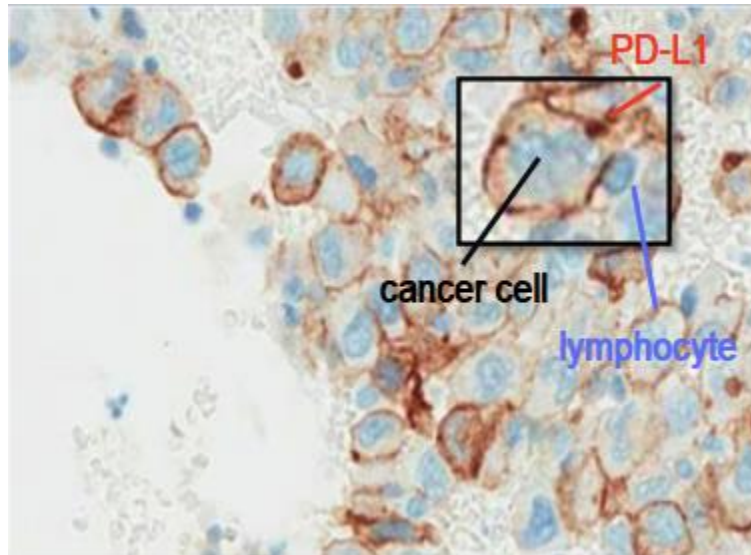
Immuunrespons op tumoren



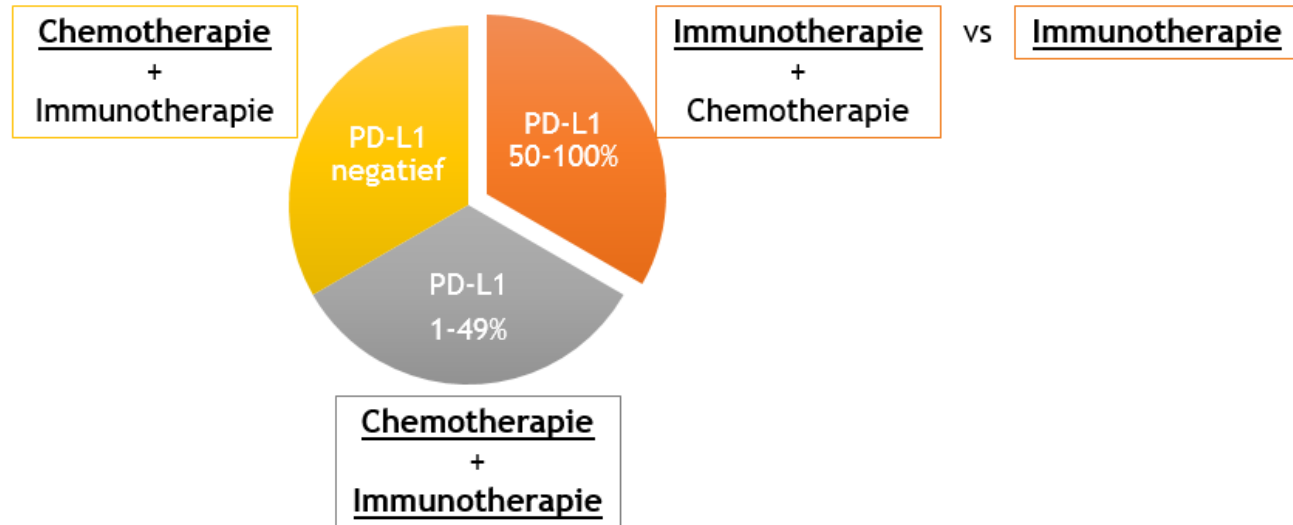
Meerdere middelen

PD-1	<i>Nivolumab</i> BMS-936558	<i>Fully human IgG4 mAb</i>	<i>Bristol-Myers Squibb</i>	<i>Phase III</i>
	<i>Pembrolizumab</i> MK-3475	<i>Humanized IgG4 mAb</i>	<i>Merck</i>	<i>Phase III</i>
	Pidilizumab CT-011	Humanized IgG1 mAb	CureTech	Phase II
	PDR001	Humanized IgG4 mAb	Novartis	Phase II
	AMP-224	Recombinant PD-L2-Fc fusion protein	GlaxoSmithKline	Phase I
	MEDI-0680	Humanized IgG4 mAb	Medimmune - AZ	Phase I
	REGN2810	Humanized IgG4 mAb	Regeneron/Sanofi	Phase I
PD-L1	<i>Durvalumab</i> Medl-4736	<i>Engineered human IgG1 mAb</i>	<i>MedImmune - AZ</i>	<i>Phase III</i>
	<i>Atezolizumab</i> MPDL-3280A	<i>Engineered human IgG1 mAb</i>	<i>Genentech</i>	<i>Phase III</i>
	Avelumab MSB0010718C	Engineered human IgG1 mAb	EMD Serono	Phase III
	BMS-936559	Fully human IgG4 mAb	Bristol-Myers Squibb	Phase II

PDL1 immunohistochemisch



NSCLC Stadium IV



Landschap van behandeling NSCLC

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 NOVEMBER 10, 2016 VOL. 375 NO. 19

Pembrolizumab versus Chemotherapy for PD-L1–Positive Non–Small-Cell Lung Cancer

Martin Reck, M.D., Ph.D., Delvys Rodríguez-Abreu, M.D., Andrew G. Robinson, M.D., Rina Hui, M.B., B.S., Ph.D., Tibor Csösz, M.D., Andrea Fülöp, M.D., Maya Gottfried, M.D., Nir Peled, M.D., Ph.D., Ali Tafreshi, M.D., Sinead Cuffe, M.D., Mary O'Brien, M.D., Suman Rao, M.D., Katsuyuki Hotta, M.D., Ph.D., Melanie A. Leiby, Ph.D., Gregory M. Lubiniecki, M.D., Yue Sheeru, Ph.D., Reshma Bangwala, M.D., Ph.D., and Julie R. Brahmer, M.D., for the KEYNOTE-024 Investigators*

FDA Approved: October 24, 2016
PD-L1 ≥ 50%; non-squamous and squamous

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Pembrolizumab plus Chemotherapy in Metastatic Non–Small-Cell Lung Cancer

L. Gandhi, D. Rodríguez-Abreu, S. Gadgeel, E. Esteban, E. Felip, F. De Angelis, M. Domine, P. Clingan, M.J. Hochmair, S.F. Powell, S.Y.-S. Cheng, H.G. Bischoff, N. Peled, F. Grossi, R.R. Jennens, M. Reck, R. Hui, E.B. Garon, M. Boyer, B. Rubio-Viqueira, S. Novello, T. Kurata, J.E. Gray, J. Vida, Z. Wei, J. Yang, H. Raftopoulos, M.C. Pietanza, and M.C. Garassino, for the KEYNOTE-189 Investigators*

FDA Approved: August 17, 2018
Non-squamous; PD-L1 irrespective

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Pembrolizumab plus Chemotherapy for Squamous Non–Small-Cell Lung Cancer

L. Paz-Ares, A. Luft, D. Vicente, A. Tafreshi, M. Güümüş, J. Mazières, B. Hermes, F. Çay Şenler, T. Csösz, A. Fülöp, J. Rodríguez-Cid, J. Wilson, S. Sugawara, T. Kato, K.H. Lee, Y. Cheng, S. Novello, B. Halmos, X. Li, G.M. Lubiniecki, B. Piperdi, and D.M. Kowalski, for the KEYNOTE-407 Investigators*

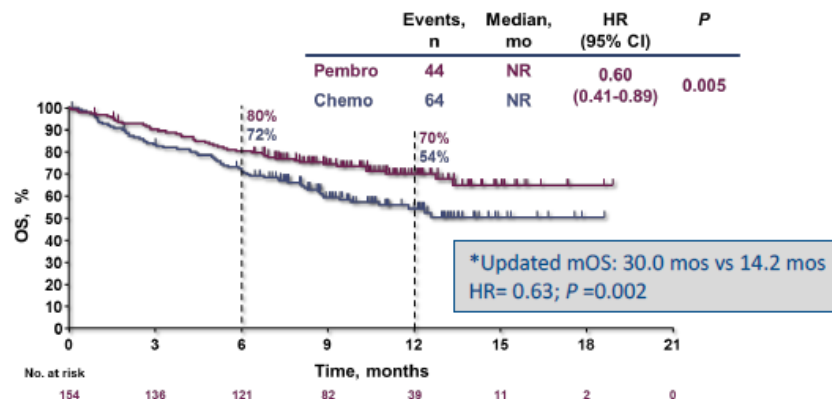
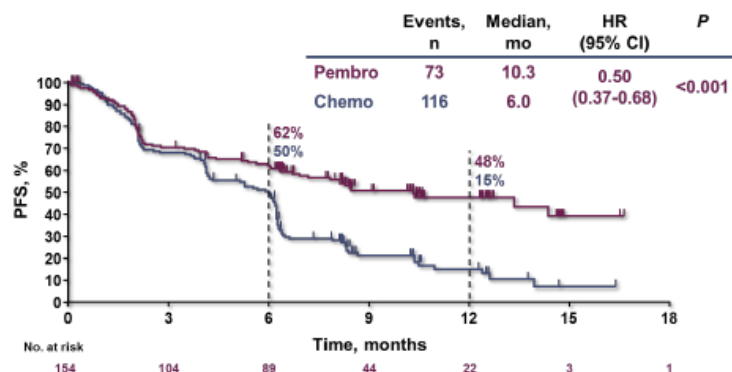
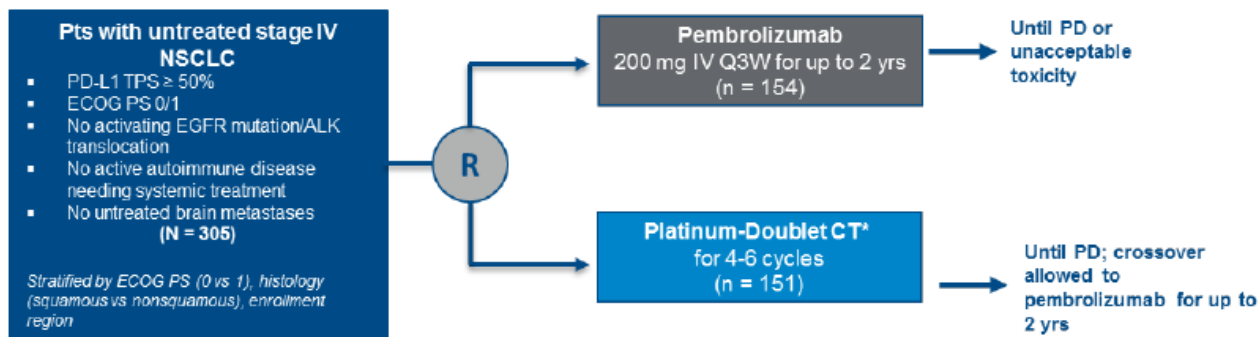
FDA Approved: October 30, 2018
Squamous; PD-L1 irrespective

Vragen die relevant zijn bij start therapie

- Wat is beter: de combinatie of immunotherapie alleen?
- Ik heb nú een respons nodig: wat moet ik kiezen?
- Weegt de evt. winst van de chemo op tegen de bijwerkingen?
- Wat biedt op de langere termijn de meeste ziektecontrole?



KEYNOTE 024: NEW 1L TREATMENT PARADIGM



Reck M, et al. N Engl J Med. 2016;375:1823-1833. *Brahmer, et al. WCLC 2017 Yokohama, Japan (Abstract OA 17.06).

Conclusie KEYNOTE-024

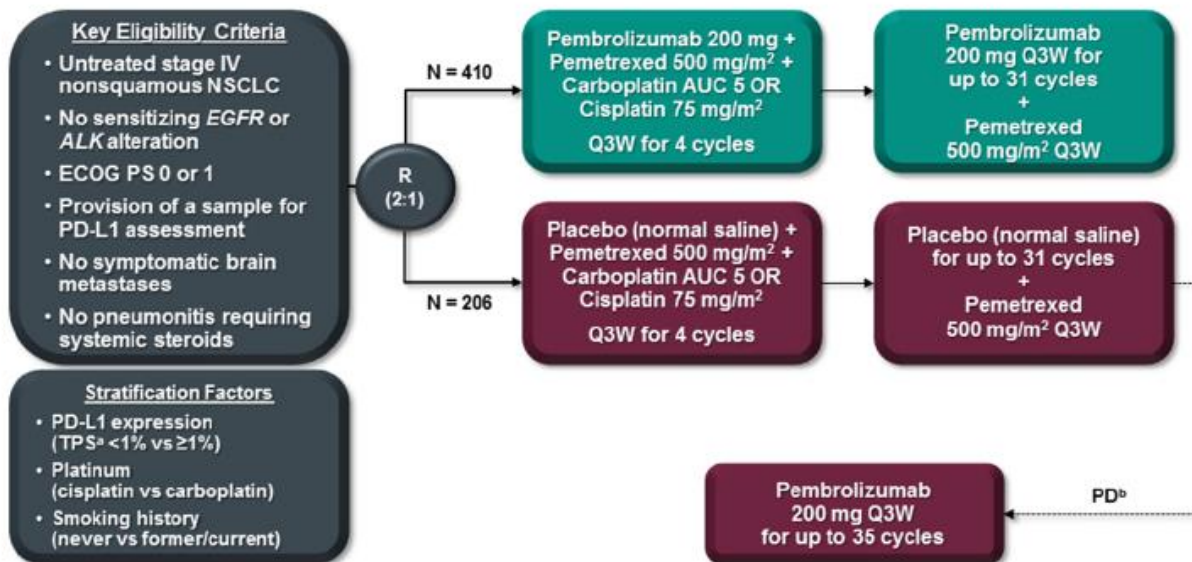
- Monotherapie In eerstelijnsbehandeling van gemetastaseerd niet-kleincellig longcarcinoom (NSCLC)
- Bij volwassenen met tumoren die PD-L1-expressie vertonen met een *tumour proportion score* (TPS) ≥ 50 %
- Zonder EGFR- of ALK-positieve tumormutaties

Combinatie chemo-immunotherapie



KEYNOTE 189

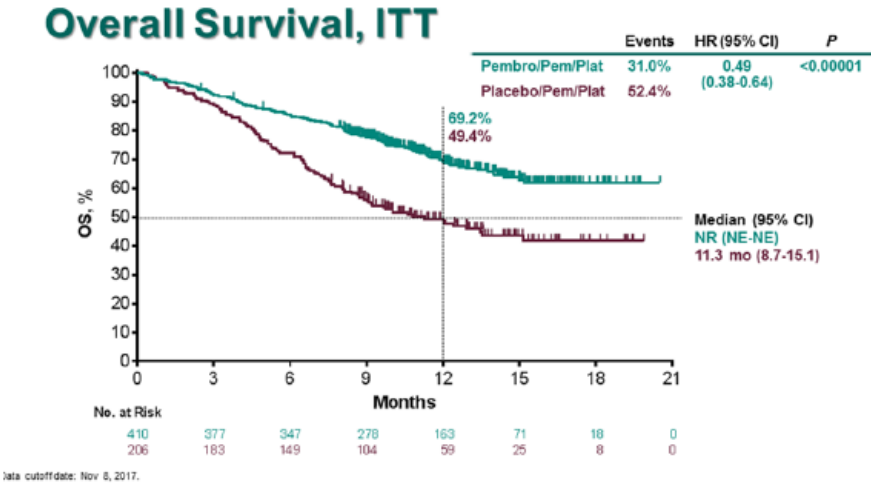
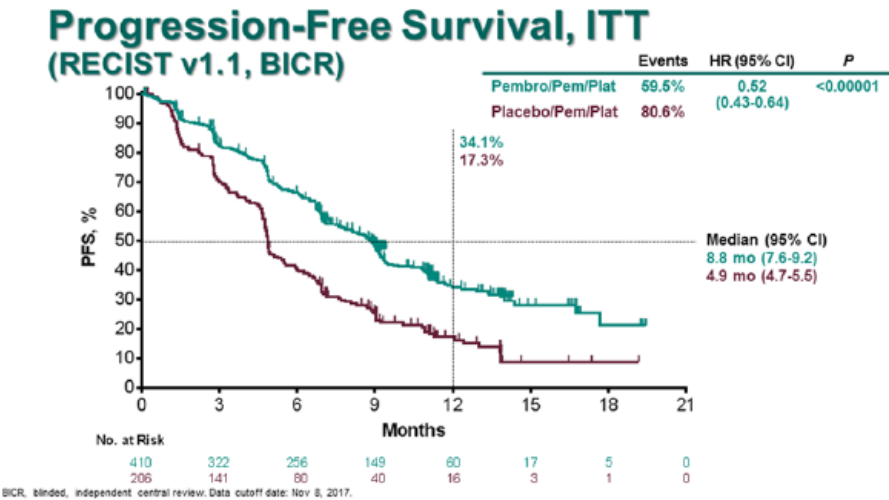
RANDOMIZED, DOUBLE-BLIND, PHASE III STUDY OF PLATINUM+PEMETREXED CHEMOTHERAPY WITH OR WITHOUT PEMBROLIZUMAB IN FIRST LINE METASTATIC NON-SQUAMOUS NON-SMALL CELL LUNG CANCER SUBJECTS



Frequency of PDL1 TPS	<1%	1-49%	≥50%	NE
Pembro/Chemo	31	31.2	32.2	5.6
Chemo	30.6	28.2	34	7.3

Gandhi, L. NEJM 2018.

KEYNOTE 189 CO-PRIMARY ENDPOINTS: MEDIAN PFS AND MEDIAN OS

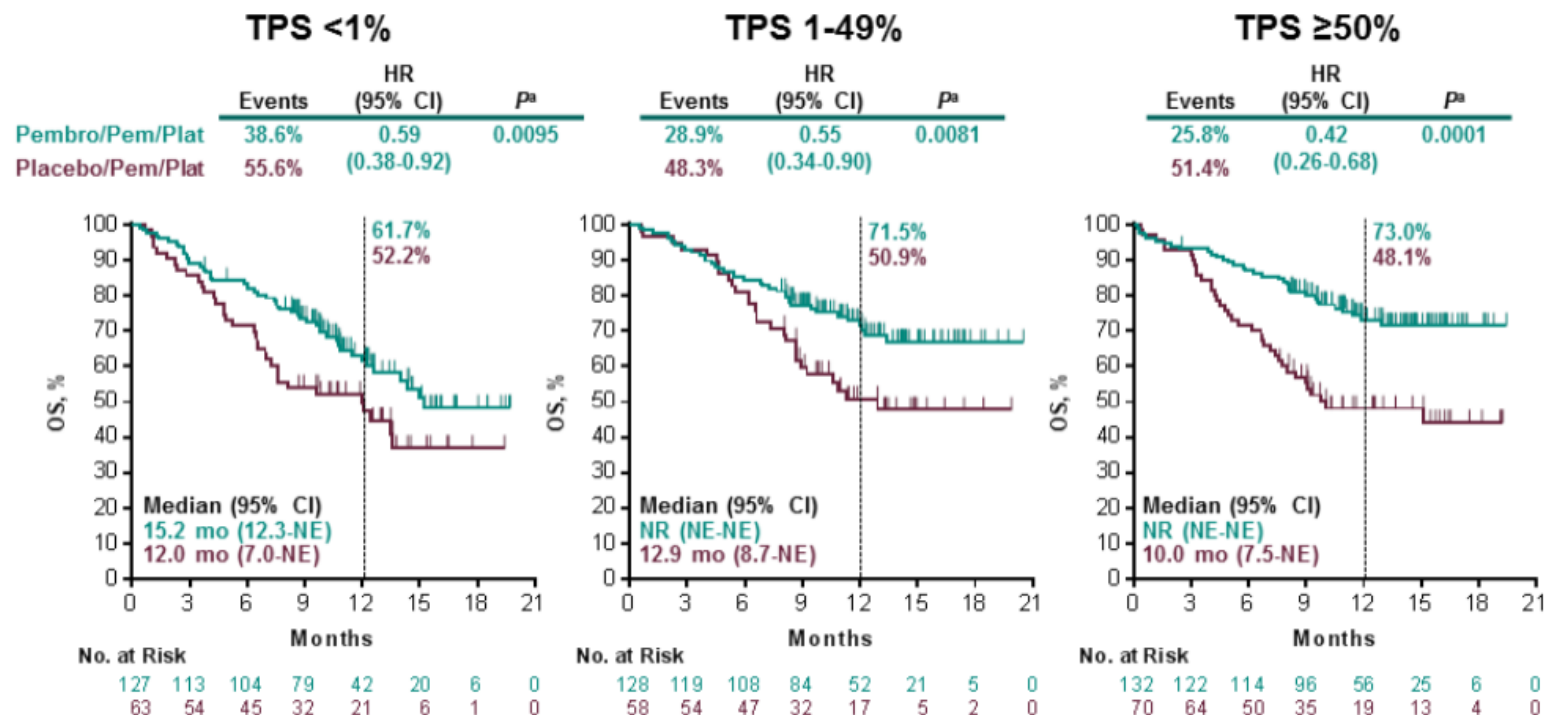


	CPP	Control
mPFS (mo)	8.8 (7.6-9.2)	4.9 (4.7-5.5)
HR, 95% CI, <i>p</i> value	0.52 (0.43-0.64) <i>P</i> = <0.00001	

	CPP	Control
mOS (mo)	NR	11.3 (8.7-15.1)
HR, 95% CI, <i>p</i> value	0.49 (0.38-0.64) <i>P</i> = <0.00001	

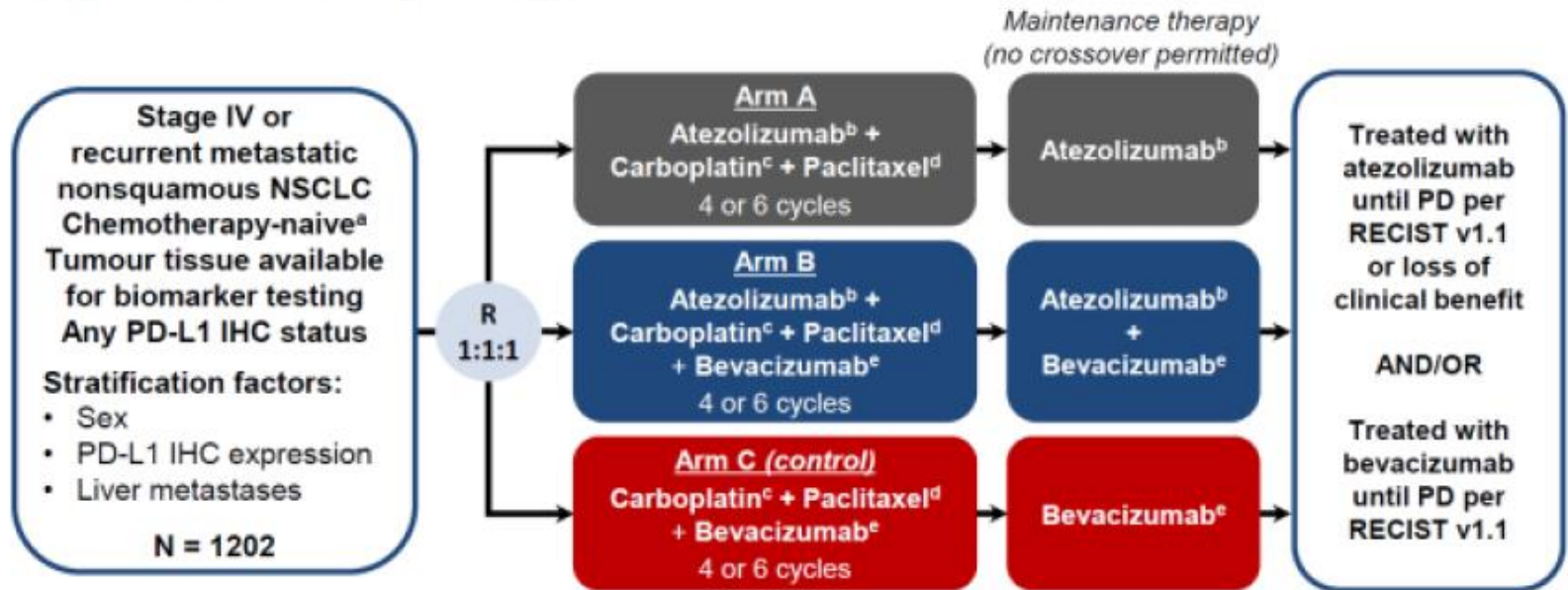
Gandhi, L. NEJM 2018.

KEYNOTE 189: OVERALL SURVIVAL BY PD-L1 TPS

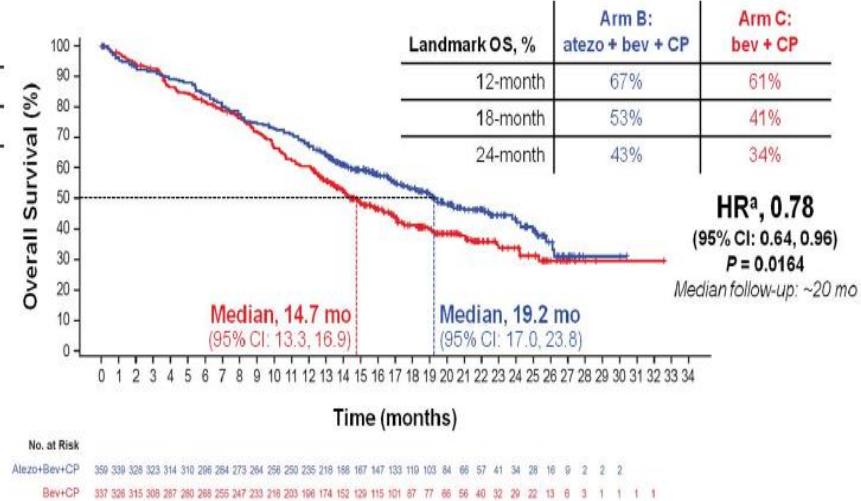
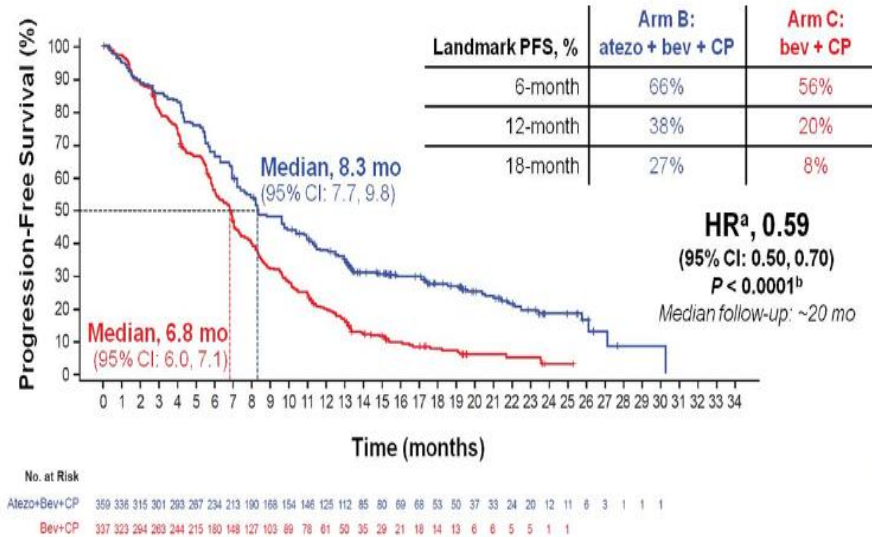


IMPOWER 150

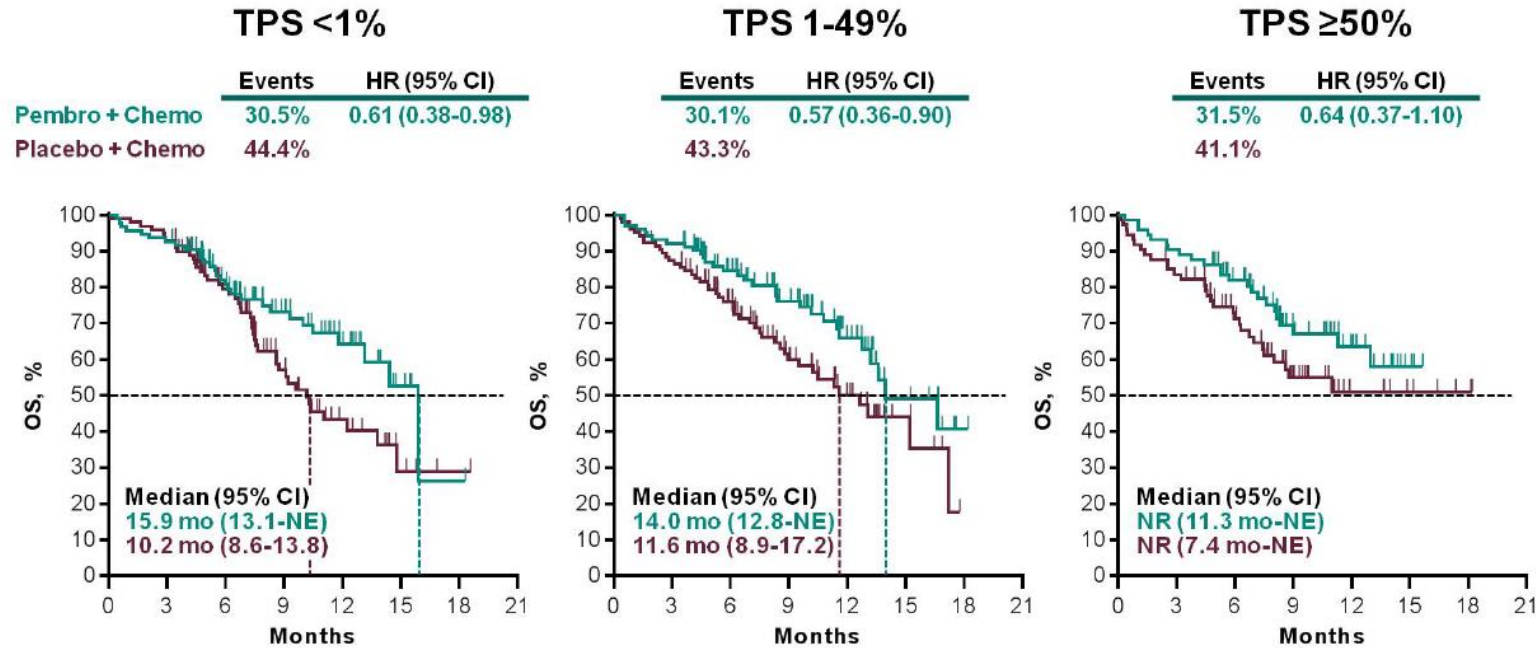
IMpower150 Study Design



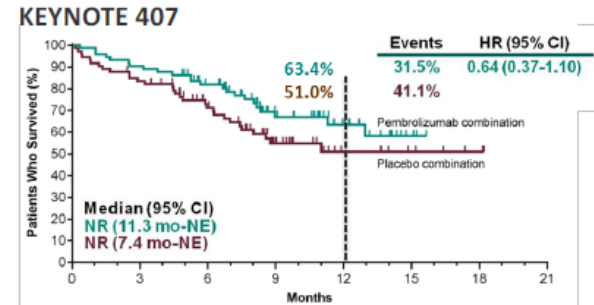
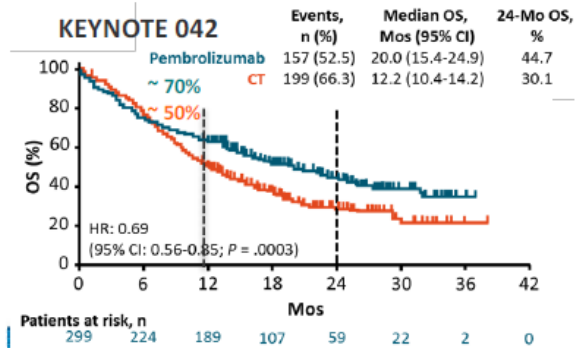
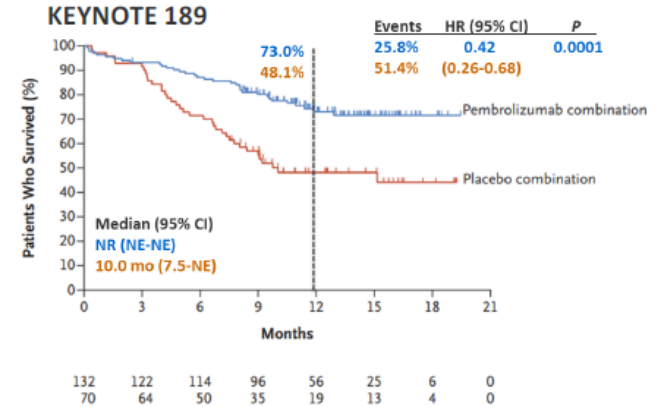
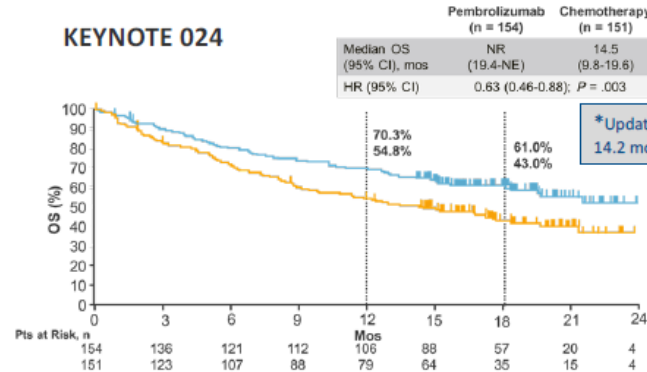
IMPOWER150: MEDIAN PFS (UPATED) AND OS IN THE ITT-WT



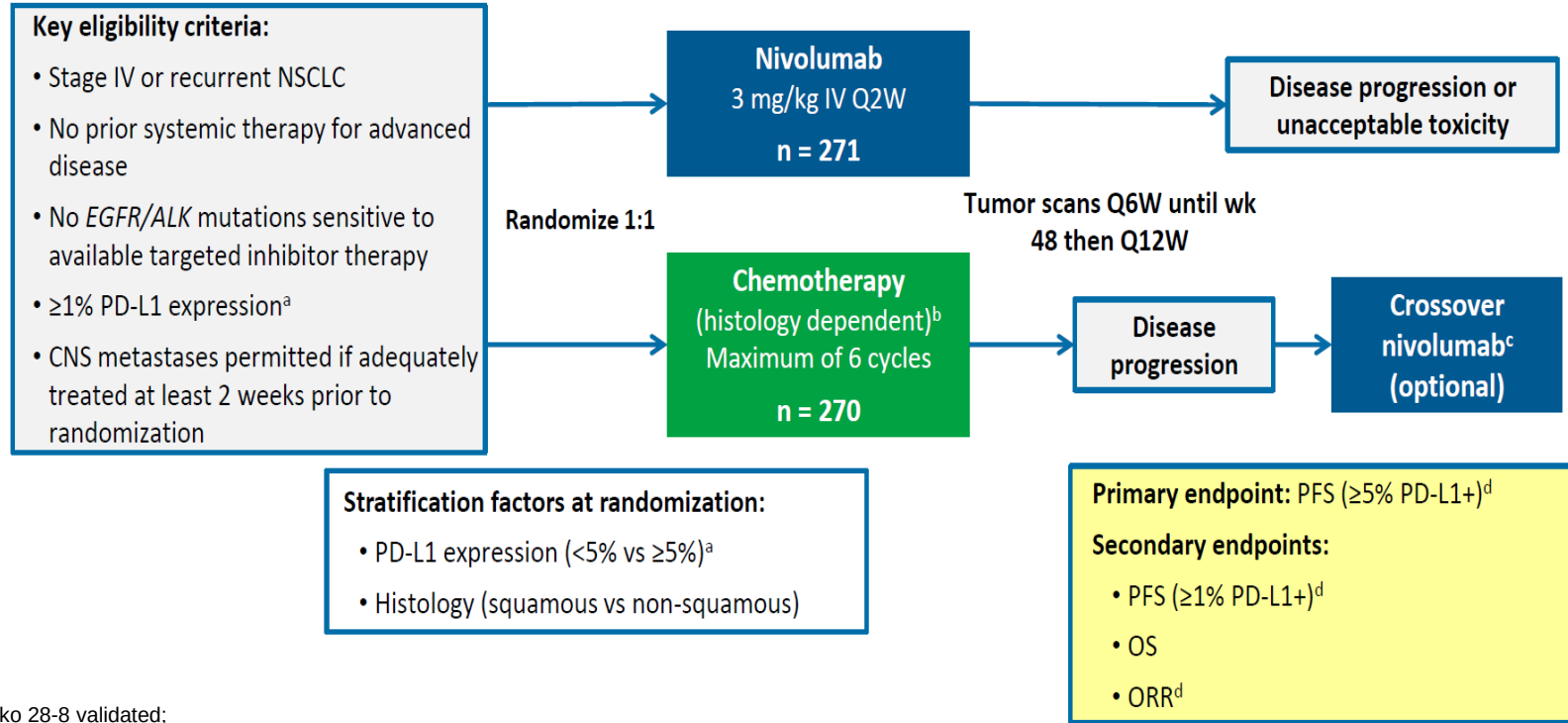
KEYNOTE 407: OS AT IA2 BY PD-L1 TPS



Bij PDL-1 >50% patiënten monotherapie is niet inferieur

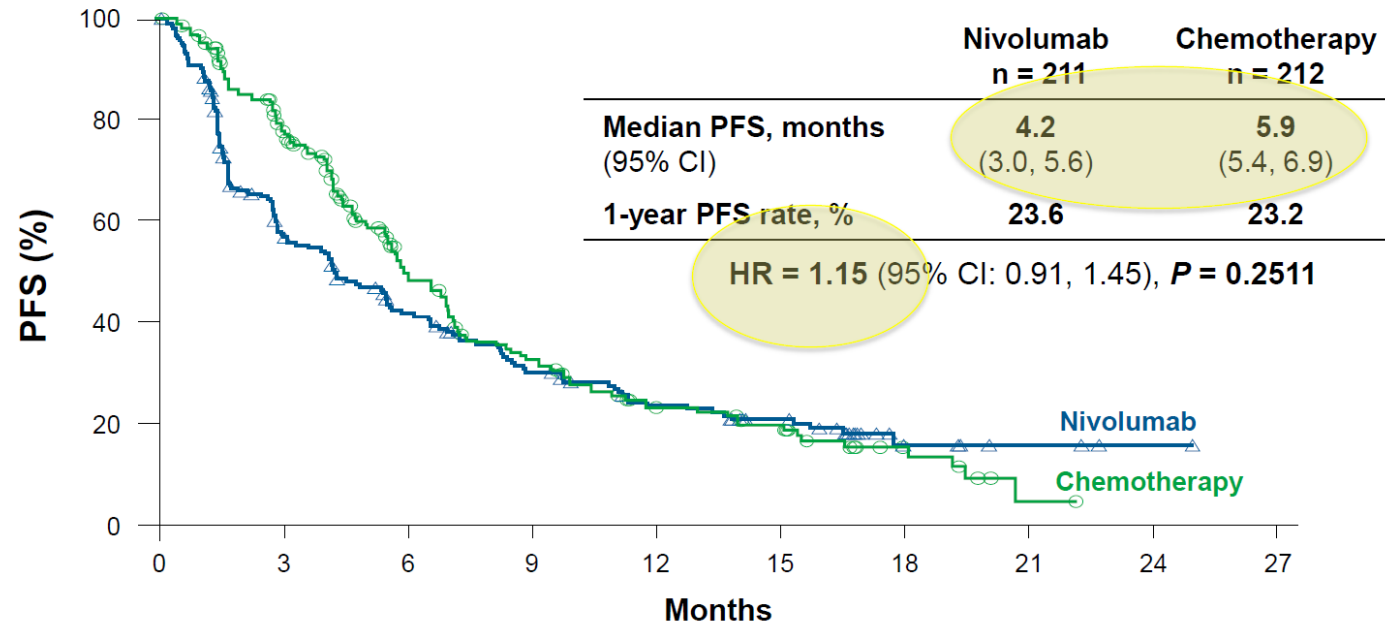


Phase 3 CheckMate 026 Study Design: Nivolumab vs Chemotherapy in First-line NSCLC



aDako 28-8 validated;

Nivolumab vs Chemotherapy in First-line NSCLC



No. of patients at risk:

Nivolumab	211	104	71	49	35	24	6	3	1	0
Chemotherapy	212	144	74	47	28	21	8	1	0	0

All randomized patients ($\geq 1\%$ PD-L1+): HR = 1.17 (95% CI: 0.95, 1.43)

Socinsky, ESMO 2016

Optimale 1^{ste} lijntherapie

Monotherapy Pro	Monotherapy Con	Combination Pro	Combination Con
• Prospective data show clear benefit for pembrolizumab and/or atezolizumab vs chemotherapy	• Long time to treatment response	• May reduce risk of progression • Can quickly reduce tumor burden, if needed	• Toxicity

Bij PDL-1 meer dan 50%

Wanneer IO alleen?

- Oudere patiënt
- Bij bijwerkingen

Wanneer combinatie therapie Chemo +IO

- Symptomatische patiënt
- Snel progressieve ziekte
- Patient die meer dan >10 mg corticosterioden krijgen

Wat hebben we geleerd

- KEYNOTE 189 Adenocarcinoom pembro + chemo (pemetrexed + carboplatin)
- KEYNOTE 407 Plaveiselcelcarcinoom pembro + chemo (paclitaxel + carboplatin)
- IMPOWER 150 Atezolizumab + chemo (carboplatine + paclitaxel met of zonder Bevacizumab)

Opties Stadium IV

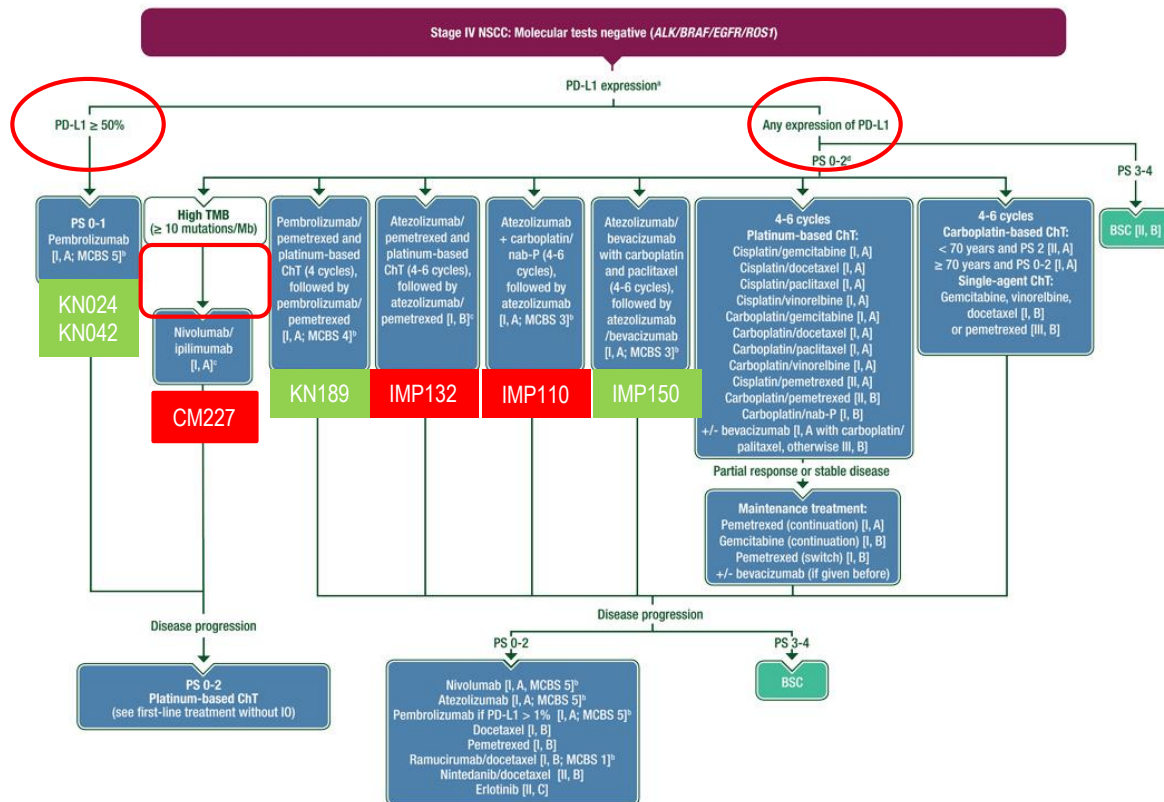
Trial	n	Population	IMP	PDL1 Stratum	OS HR (95%CI)
KN024 ¹	305	All histologies	<u>Pembro</u>	≥50%	0.63 (0.47-0.86)
KN042 ²	1,274	All histologies	<u>Pembro</u>	≥50%	0.69 (0.56-0.85)
				1-49%	0.92 (0.77-1.11)
KN189 ³	616	Non-squamous	<u>Pembro +</u> <u>Plat-Pem</u>	≥50%	0.42 (0.26-0.68)
				1-49%	0.55 (0.34-0.90)
				<1%	0.59 (0.38-0.92)
KN407 ⁴	559	Squamous	<u>Pembro +</u> <u>Carbo-Tax/</u> <u>(nab)Tax</u>	≥50%	0.64 (0.37-1.10)
				1-49%	0.57 (0.36-0.90)
				<1%	0.61 (0.38-0.98)

1, Reck et al. JCO (2019); 2, Mok et al. Lancet (2019); 3, Gandhi et al. NEJM (2018); 4, Paz-Ares et al. NEJM (2018)

ESMO CLINICAL PRACTICE GUIDELINES

ADVANCED NSCLC

Update September 2019, non-squamous

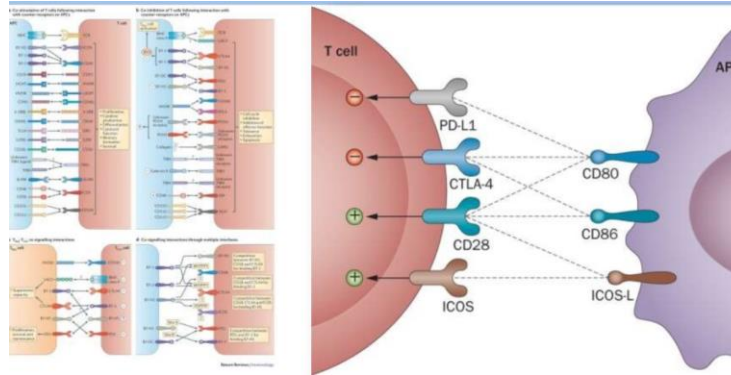


EMA approved

Not EMA approved

Combinatie therapie Ipilimumab/Nivolumab

- Er lijkt sprake te zijn van synergetisch effect van de combinatietherapie
- Chemotherapie sparend
- Met combinatie of kunnen we grotere groep patiënten behandelen zonder chemotherapie
- Duur van respons bij combinatie chemo-immunotherapie is nog altijd kort

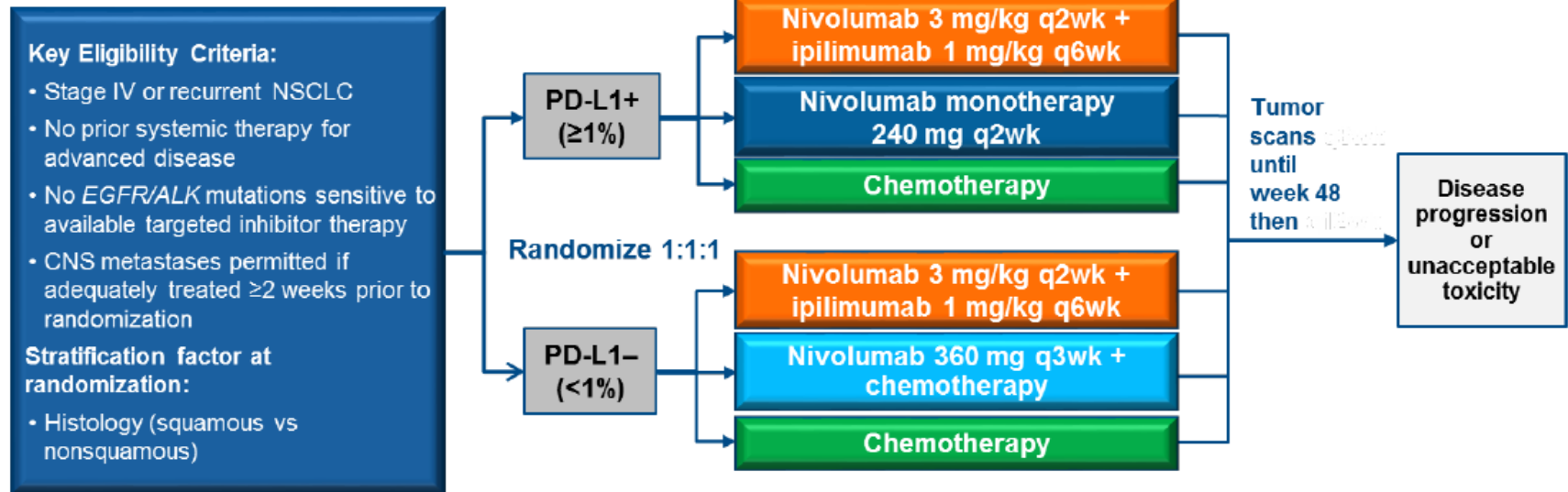


Synergetisch effect van de combinatietherapie

- **CTLA-4-remmers**
 - CTLA-4 wordt aangemaakt door T-cellen
 - Inactiveert de T-cel respons
 - Door deze inactivering te blokkeren, versterken CTLA-4-remmers de anti-tumor immuunreactie
 - Daarnaast effect op T-geheugencellen
- **PD-1-routeremmers (PD-1/PD-L1-remmers)**
 - **PD-1** activiteit van T-cellen matigt hun reactie op kanker, zodra ze op de plek van de **tumor** zijn aangekomen.
 - Door te voorkomen dat **PD-1** (het 'slot') zich bindt aan **PD-L1** (de 'sleutel'), komt anti tumor reactie opgang

Check Mate 227

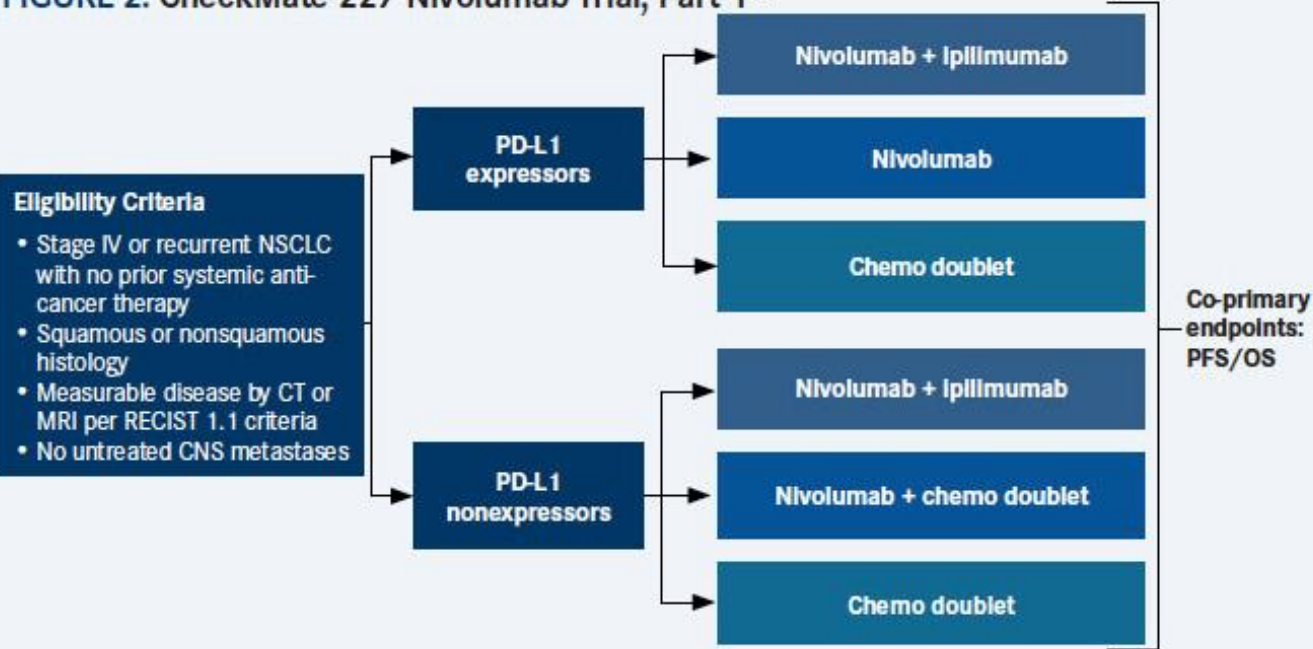
Randomized, open-label, multipart phase III trial



Combinatie van immuno- en chemotherapie

Checkmate-227

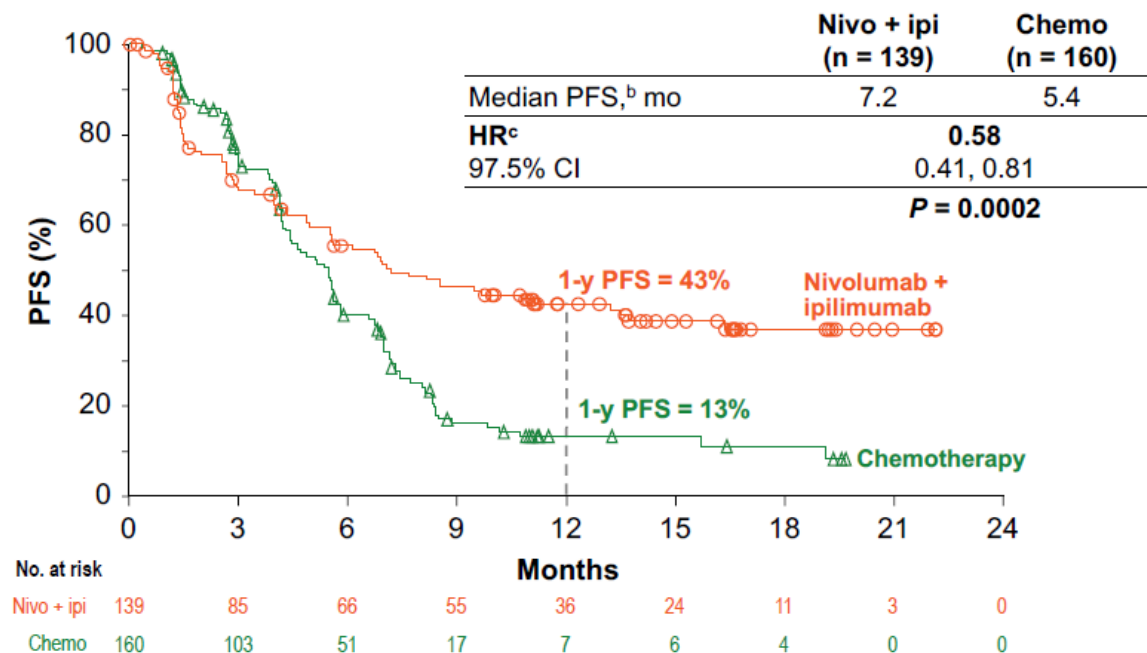
FIGURE 2. CheckMate-227 Nivolumab Trial, Part 1¹⁰



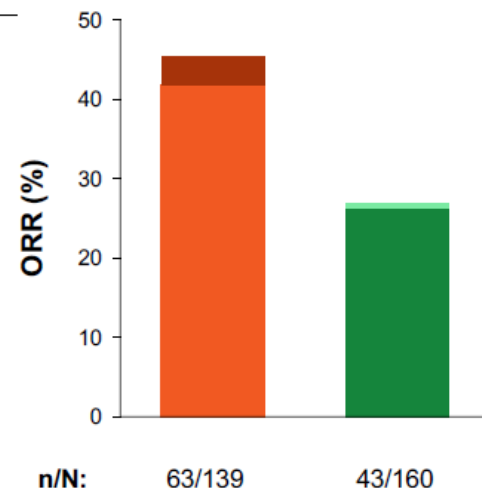
The chemotherapy doublet depends upon tumor histology. For squamous tumors, the combination is gemcitabine plus cisplatin or carboplatin; for nonsquamous, it is pemetrexed plus cisplatin or carboplatin.

CNS indicates central nervous system; CT, computed tomography; MRI, magnetic resonance imaging; NSCLC, non-small cell lung cancer; PD-L1, programmed death ligand-1; RECIST, Response Evaluation Criteria in Solid Tumors.

Co-primary Endpoint: PFS With Nivolumab + Ipilimumab vs Chemotherapy in Patients With High TMB (≥ 10 mut/Mb)^a



ORR (TMB ≥ 10 mut/Mb)^b



- In patients with TMB < 10 mut/Mb treated with nivo/ipi vs chemo, HR was 1.07 (95% CI: 0.84, 1.35)^d

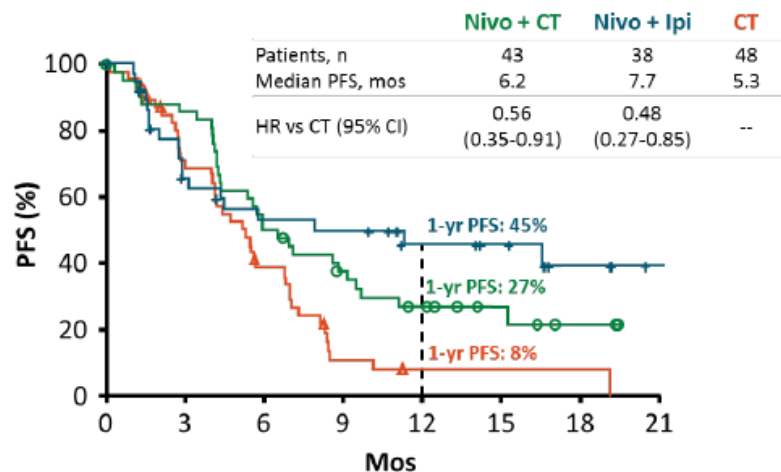
- Median time to response was 2.7 mo Nivo/Ipi and 1.5 months with chemotherapy

^dThe P-value for the treatment interaction was 0.0018

^a Per BICR; ^bORR in patients with TMB < 10 mut/Mb was 24.6% in nivo + ipi arm and 25.9% in chemo arm

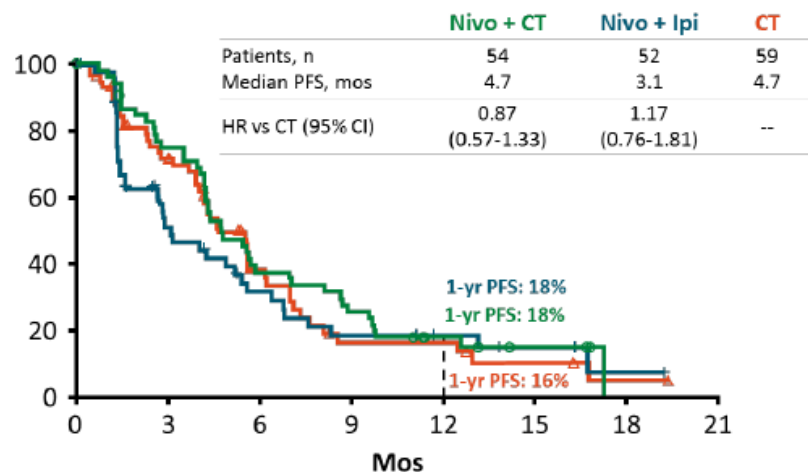
Exploratory Analysis of PFS by TMB in Patients With < 1% PD-L1 Expression

TMB ≥ 10 mut/Mb



Patients at Risk, n								
Nivo + CT	43	36	21	14	9	5	2	0
Nivo + Ipi	38	20	16	15	10	8	4	1
CT	48	30	16	4	1	1	1	0

TMB < 10 mut/Mb



Patients at Risk, n								
Nivo + CT	54	38	19	13	6	3	0	0
Nivo + Ipi	52	22	12	7	5	3	1	0
CT	59	39	16	6	6	3	1	0

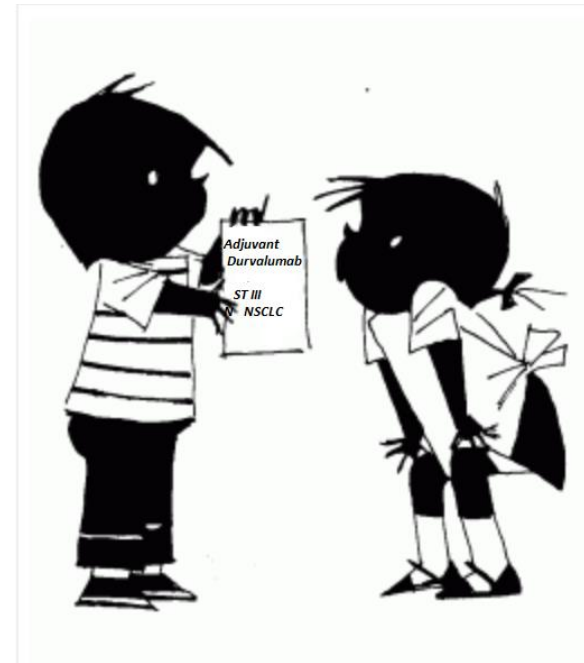
Borghaei H, et al. ASCO 2018. Abstract 9001.

Nieuws: checkmate 227 2,5 Y follow-up

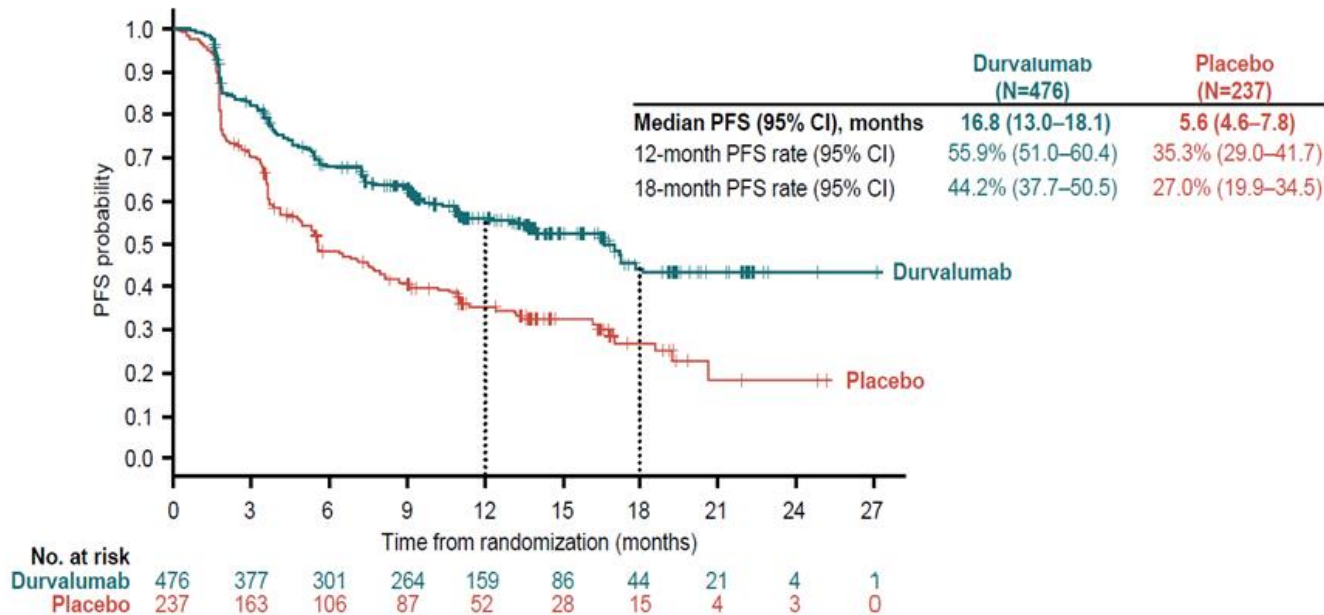
- Betere Progression-Free Survival (PFS) met Nivolumab plus Ipilimumab (median OS 17,1) versus chemotherapy (median OS 14,9) Nivolumab (median OS 15,7)
- Langdurige respons Nivolumab plus Ipilimumab 23 mnd 15,5 mnd bij Nivolumab
- Dit geldt met name bij PDL-1 > 50%

Adjuvant Durvalumab na chemoradiotherapie St. III

- Stadium III NSCLC (33%)
- Chemoradiotherapie
- Doel curatie echter 15-20% lukt
- Mediane overleving 8-10 mnd



Progressievrije overleving **PACIFIC studie**

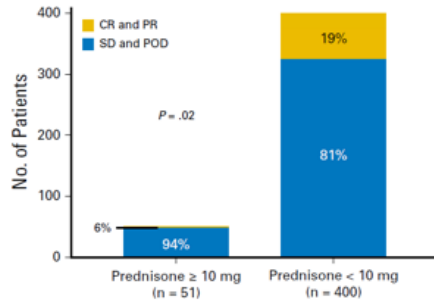


BICR, blinded independent central review; CI, confidence interval; ITT, intention-to-treat; PFS, progression-free survival

Conclusies PACIFIC studie

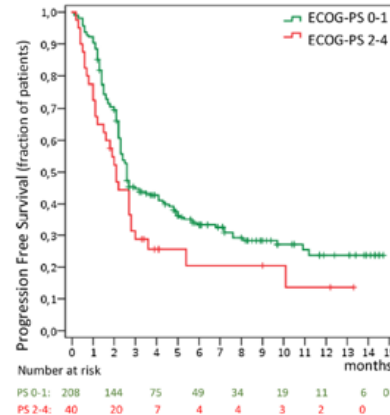
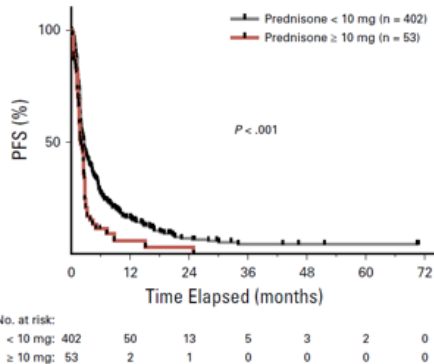
- Patiënten met lokaal gevorderde, niet-resecteerbare NSCLC was PFS 11 maanden langer bij patiënten die Durvalumab kregen dan bij degenen die placebo kregen
- De langere progressievrije overleving werd bereikt in een biomarker-onafhankelijke populatie
- De incidentie van pneumonitis / radiatie pneumonitis was toegenomen

Baseline corticosteroiden gebruik is geassocieerd met slechte uitkomst



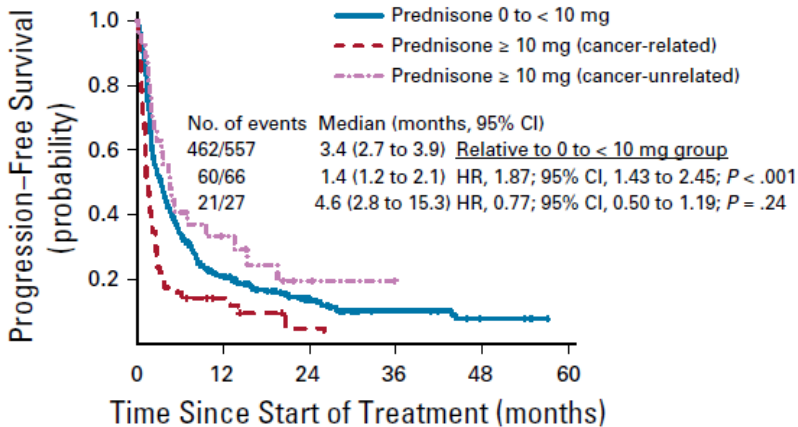
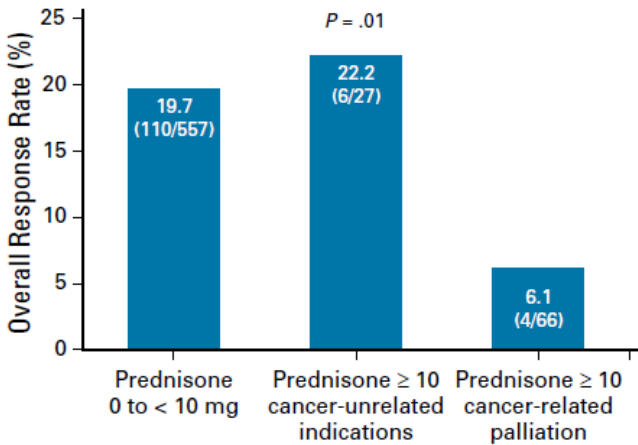
Corticosteroids and Immunotherapy: Guilty or Guilt By Association?

By Thomas E. Stinchcombe, MD
November 10, 2018



Arbour KC, et al. JCO 2018; Schouten R, et al. Lung Cancer 2018

Baseline corticosteroiden



No. at risk:

	0	12	24	36	48	60
Prednisone 0 to < 10 mg	557	91	35	10	4	0
Prednisone ≥ 10 mg (cancer-related)	66	6	1	0	0	0
Prednisone ≥ 10 mg (cancer-unrelated)	27	8	2	0	0	0

Respons relatie Steroïden en IO

- Corticosteroïden lijken een confounder te zijn
- Omdat de meeste patiënten met steroïden krijgen voor kanker gerelateerde klachten zoals oedeem bij hersenmetastasen
- Slechte prognose
- Patiënten die steroïden krijgen voor niet-kanker gerelateerde klachten, hebben net zo hoge responskans hebben als patiënten die geen steroïden krijgen.
- Derhalve lijkt het dus niet zo te zijn dat baseline steroïden er voor zorgen dat je geen respons kan maken op IO

Standaard care benadering: combi immunotherapie en chemotherapie

- NSCLC adenocarcinoom
 - Keynote-189 laat zien trippel therapie beter is (**ongeacht PDL1 status**)
 - Keynote-42 bevestigt dat patiënten met hoog PDL1 expressie redelijk doen met alleen Pembrolizumab
 - Geen duidelijk rol voor Pembrolizumab bij PDL1 expressie (1-49%)
- NSCLC plaveiselcelcarcinoom
 - Keynote-407 laat zien dat Triple therapie (Paclitaxel Carbo en Pembro) beter is dan standaard therapie
 - Toch lijkt dit bij plaveiselcelcarcinoom beter te zijn bij hoge PDL1 expressie

Follow-up tot 5 jaar

CA209-003

Nivo

5-YEAR FOLLOW-UP RESULTS

- Nivolumab continued to show long-term overall survival and progression-free survival benefit compared to docetaxel, with 5-year survival rates of 13.4% vs 2.6% and progression-free survival rates of 8% vs 0%.
- No new safety signals were observed with longer follow-up.

KEYNOTE-001

Pembro

Key Points

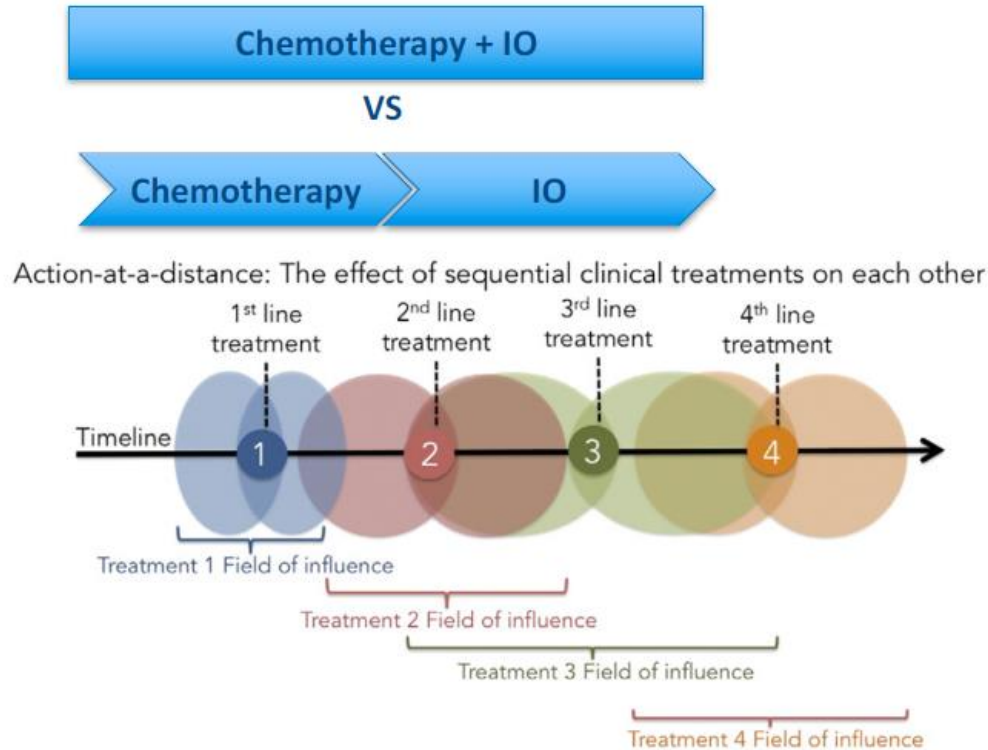
- In treatment-naïve patients, 29.6% with PD-L1 expression of 50% or more were alive after 5 years, compared with 15.7% with PD-L1 expression levels below 50%.
- In patients who had received previous treatment, 25% who had PD-L1 expression levels of 50% or more were alive after 5 years, compared with 12.6% with PD-L1 expression levels between 1% and 49%. Only 3.5% of people with PD-L1 expression levels below 1% were alive after 5 years.

Take Home Message

- Immunotherapie heeft een grote effect op overleving
- Triple therapie chemo-immunotherapie bij PD-L1 <50
- Bij PDL-1 >50% patiënten monotherapie is niet inferieur
- Combinatie immunotherapie (Ipi/Nivo) kan langdurig een betere respons bewerkstelligen (bijwerkingen en de plaats hiervan?)



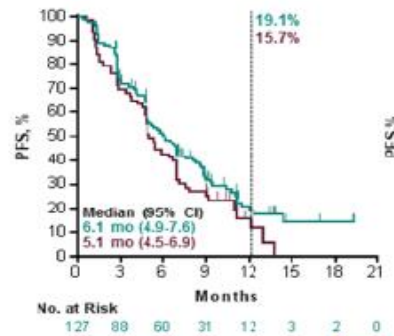
Als PDL1 <1%, kan zijn dat Sequentiele therapie beter is?



KEYNOTE 189

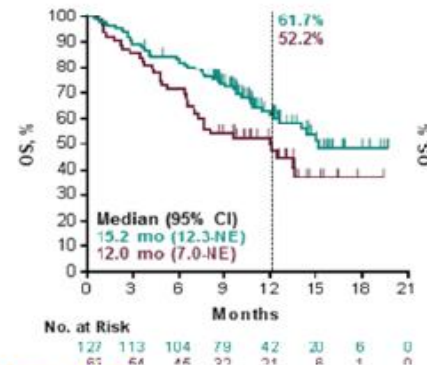
TPS <1%

	Events	HR (95% CI)	p ^a
Pembro/Pem/Plat	72.4%	0.75	0.0476
Placebo/Pem/Plat	85.7%	(0.53-1.05)	



TPS <1%

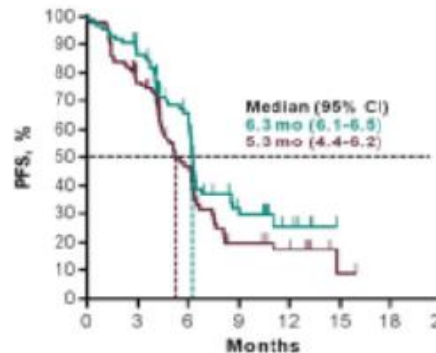
	Events	HR (95% CI)	p ^a
Pembro/Pem/Plat	38.6%	0.59	0.0095
Placebo/Pem/Plat	55.6%	(0.38-0.92)	



KEYNOTE 407

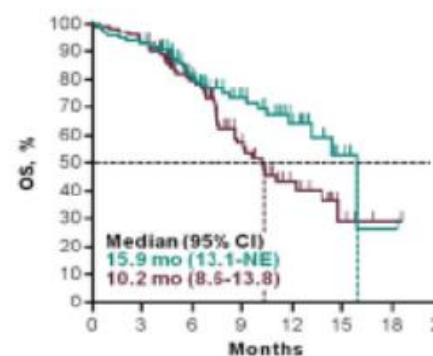
TPS <1%

	Events	HR (95% CI)
Pembro + Chemo	57.9%	0.68 (0.47-0.98)
Placebo + Chemo	67.7%	



TPS <1%

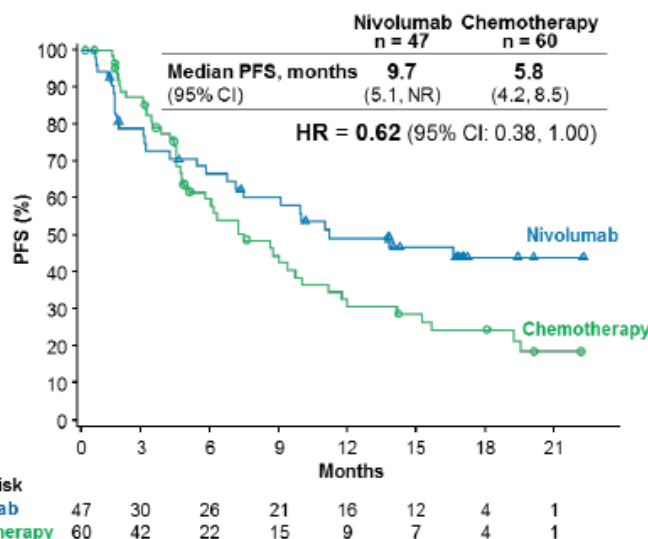
	Events	HR (95% CI)
Pembro + Chemo	30.5%	0.61 (0.38-0.98)
Placebo + Chemo	44.4%	



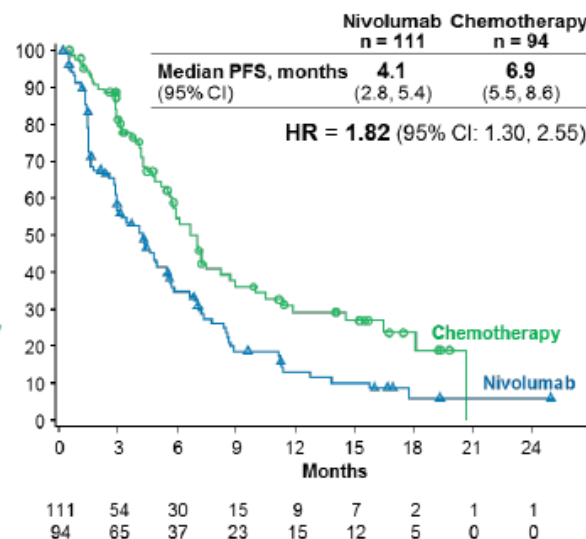
CheckMate 026 TMB Analysis: Nivolumab in First-line NSCLC

PFS by Tumor Mutation Burden Subgroup

High TMB



Low/medium TMB



Peters et al. AACR Annual Meeting 2017