



Oncologisch Netwerk
Zuidoost-Nederland

Ontwikkelingen thoracale oncologie

POST ESMO-WCLC OncoZON update

19 november 2018





Nobelprijs Geneeskunde voor 'mijlpaal in strijd tegen kanker'

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AANGEPAST: 20 UUR GELEDEN

De Nobelprijs voor de Geneeskunde 2018 is toegekend aan de Amerikaan James P. Allison en de Japanner Tasuku Honjo voor de ontwikkeling van speciale therapieën voor de behandeling van kanker.

Dat is bekendgemaakt in Zweden. De twee onderzoekers krijgen gezamenlijk een bedrag van 9 miljoen Zweedse kronen, zo'n 870.000 euro.

Volgens de verklaring van het instituut hebben de twee wetenschappers ontdekkingen gedaan "die een mijlpaal vormen in onze strijd tegen kanker". Ze werkten parallel aan het stimuleren van het immuunsysteem van het menselijk

Immuuntherapie geeft longkankerpatiënt nieuwe hoop

27-07-2018 om 06:05 door Hennie Jeukens

Print



18.25-18.50
Immunotherapie

Dr G Bootsma, Zuyderland

Afbeelding: iStock



427
shares

Hoop voor longkankerpatiënten. Begin 2019 kan een groot aantal van hen in aanmerking voor immuuntherapie komen. 70 procent van hen is na een jaar nog in leven, veel meer dan vroeger.

Disclosure belangen spreker	
(potentiële) Belangenverstengeling	Geen
Voor bijeenkomst mogelijk relevante relaties met bedrijven¹	Bedrijfsnamen
<ul style="list-style-type: none"> • Sponsoring of onderzoeksgeld² • Honorarium of andere (financiële) vergoeding³ • Aandeelhouder⁴ • Andere relatie, namelijk ...⁵ 	

Met dank aan Lizza Hendriks voor een deel van de dia's

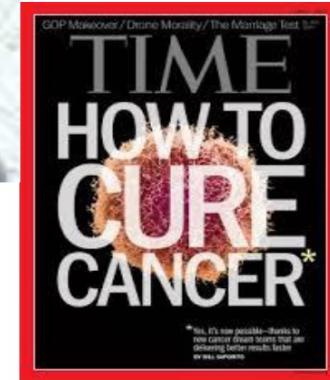
Wordt interessante rit....



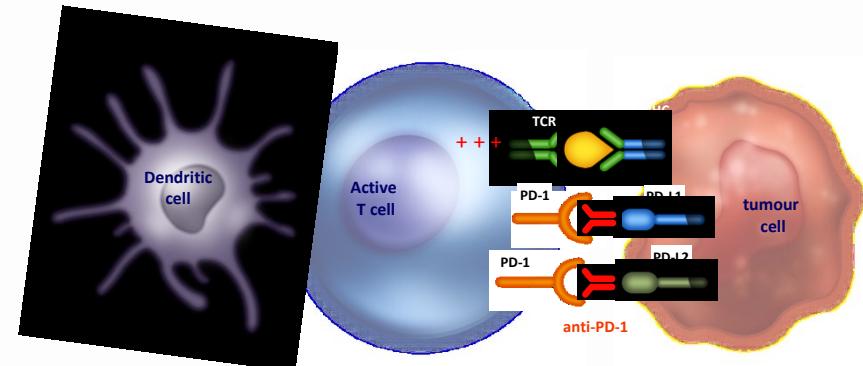
Programma

- Inleiding Immunotherapie
- ip slechts update St IV NSCLC
- Andere thoracale maligniteiten (kort)
- Niet (heb maar 20"....):
 - St III -> ook practice changing ! (Dirk)
 - st I en II -> ook grote ontwikkelingen ! – near future
 - Selectie (PDL1, TMB, etc...)
 - combinaties behalve chemo





Immuno-oncologie



Immuunsysteem en niet
tumor aangrijppingspunt

Herkennen en vernietigen van
kanker door immuunsysteem

Geheugen van immuunsysteem waardoor
responsen aanhouden

Werking immuno-oncologie



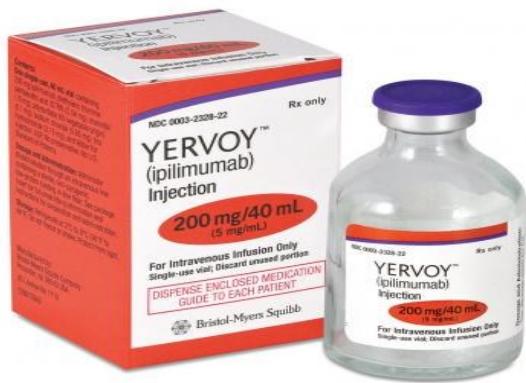
Afweersysteem



Werking immuno-oncologie



Immuno-oncologie



—



Werking immuno-oncologie



Bijwerkingen immuno-oncologie

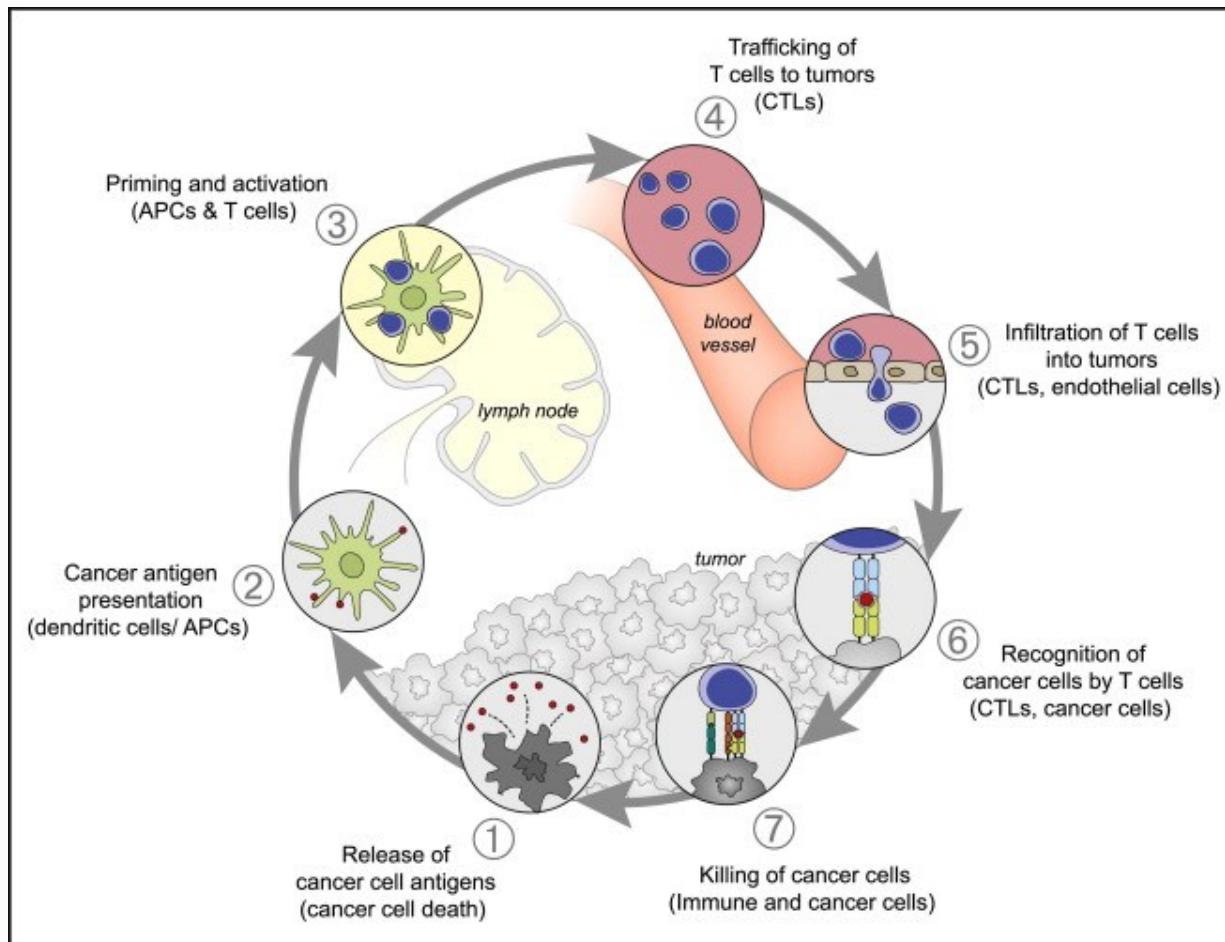


De gevolgen



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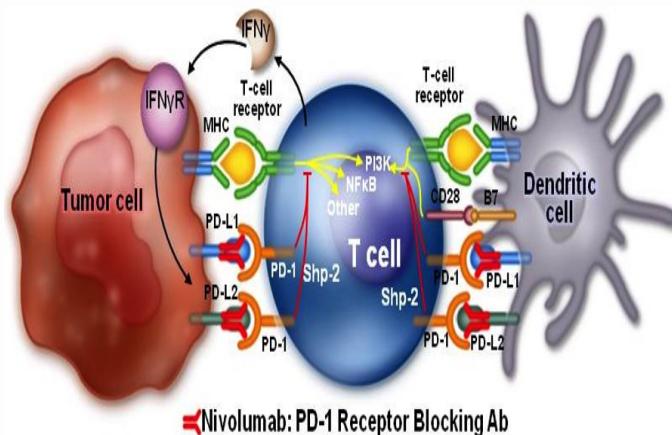
Cancer-Immunity Cycle



Daniel S. Chen, Ira Mellman, Oncology Meets Immunology: The Cancer-Immunity Cycle null, Volume 39, Issue 1, 2013, 1–10 <http://dx.doi.org/10.1016/j.immuni.2013.07.012>

A Phase III Study (CheckMate 017) of Nivolumab (Anti-Programmed Death-1) vs Docetaxel in Previously Treated Advanced or Metastatic Squamous (SQ) Cell Non-Small-Cell Lung Cancer (NSCLC)

David R. Spigel,¹ Karen Reckamp,² Naiyer Rizvi,³ Elena Poddubskaya,⁴ Howard West,⁵ Wilfried Ernst Erich Eberhardt,⁶ Paul Baas,⁷ Scott J. Antonia,⁸ Adam Pluzanski,⁹ Everett E. Vokes,¹⁰ Esther Holgado,¹¹ David Waterhouse,¹² Neal Ready,¹³ Justin Gainor,¹⁴ Osvaldo Arén Frontera,¹⁵ Leora Horn,¹⁶ Luis Paz-Ares,¹⁷ Christine Baudelet,¹⁸ Brian Lestini,¹⁸ Julie Brahmer¹⁹



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

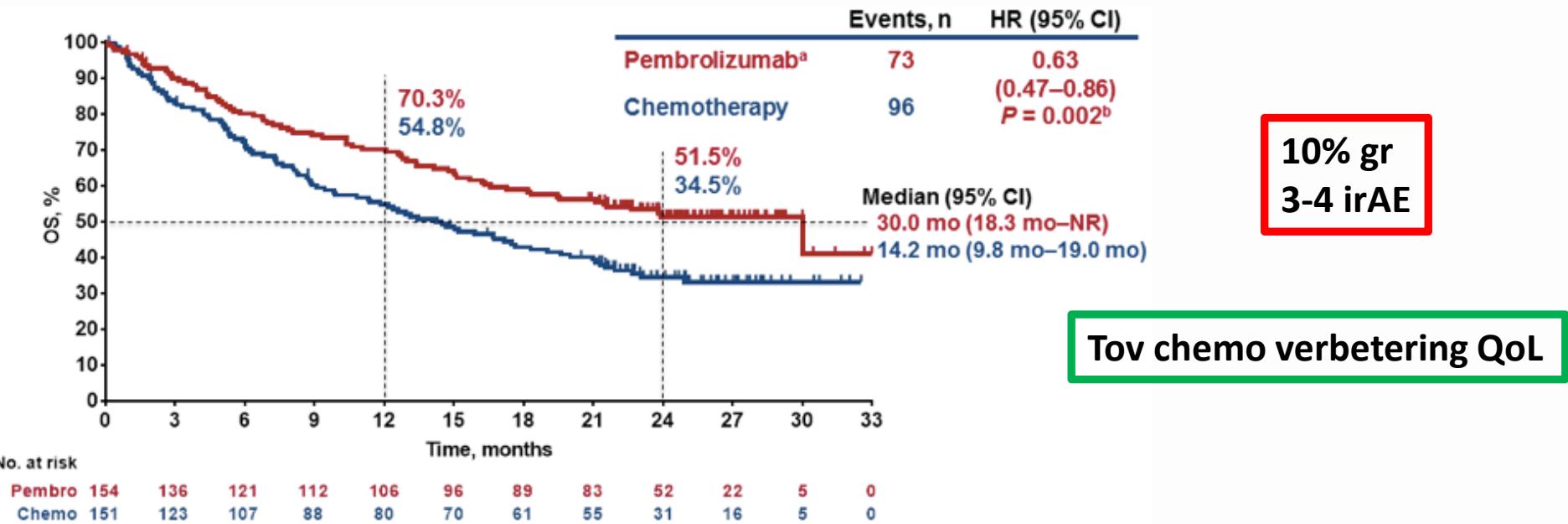
Nivolumab versus Docetaxel in Advanced Squamous-Cell Non-Small-Cell Lung Cancer

Julie Brahmer, M.D., Karen L. Reckamp, M.D., Paul Baas, M.D., Lucio Crinò, M.D., Wilfried E.E. Eberhardt, M.D., Elena Poddubskaya, M.D., Scott Antonia, M.D., Ph.D., Adam Pluzanski, M.D., Ph.D., Everett E. Vokes, M.D., Esther Holgado, M.D., Ph.D., David Waterhouse, M.D., Neal Ready, M.D., Justin Gainor, M.D., Osvaldo Arén Frontera, M.D., Libor Havel, M.D., Martin Steins, M.D., Marina C. Garassini, M.D., Joachim G. Aerts, M.D., Manuel Domine, M.D., Luis Paz-Ares, M.D., Martin Reck, M.D., Christine Baudelet, Ph.D., Christopher T. Harbison, Ph.D., Brian Lestini, M.D., Ph.D., and David R. Spigel, M.D.

This article was published on May 31, 2015,
and updated on June 17, 2015, at NEJM.org.

DOI: 10.1056/NEJMoa1504627

KEYNOTE 024 overall survival



10% gr
3-4 irAE

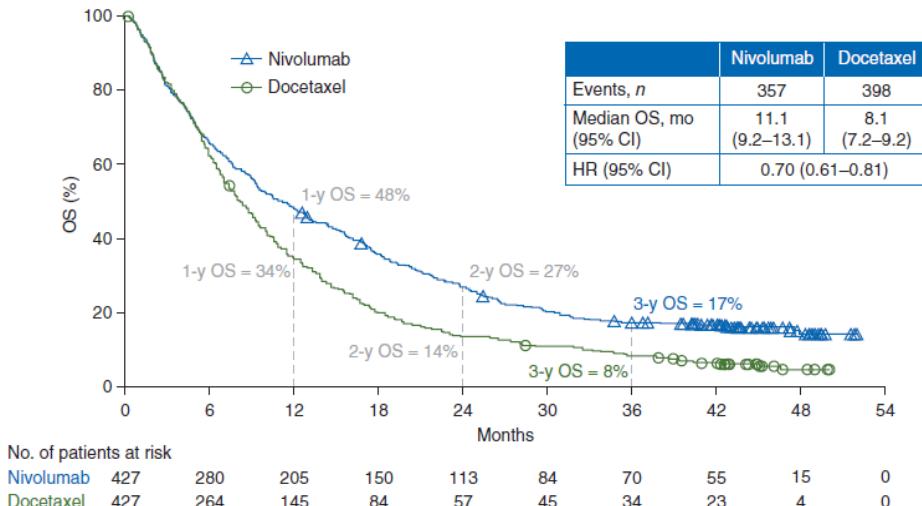
Tov chemo verbetering QoL

Reck et al, NEJM 2016
Reck, WCLC 2016 abstr 7153

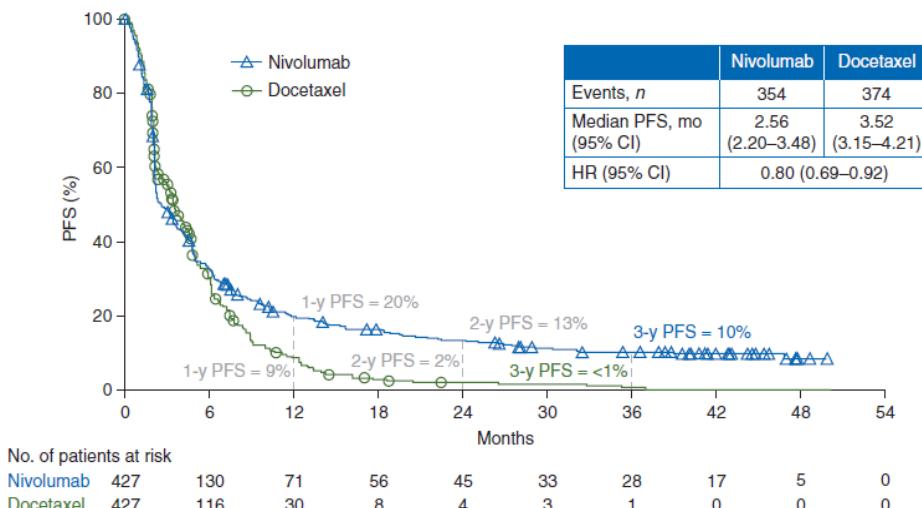
Maar nieuwe ontwikkelingen (gaat hard)

- Ook 1^e lijn st IV -> 2018 standaard
- Adjuvant aan st III -> 2018 standaard
- Neo – en adjuvant st I-II: zeer veel belovend
- DUS straks ALLE longkanker patienten...

A OS in Pooled CheckMate 017/057



B PFS in Pooled CheckMate 017/057



Update CM 017 en CM 057



ORIGINAL ARTICLE

Annals of Oncology 29: 959–965, 2018
doi:10.1093/annonc/mdy041
Published online 2 February 2018

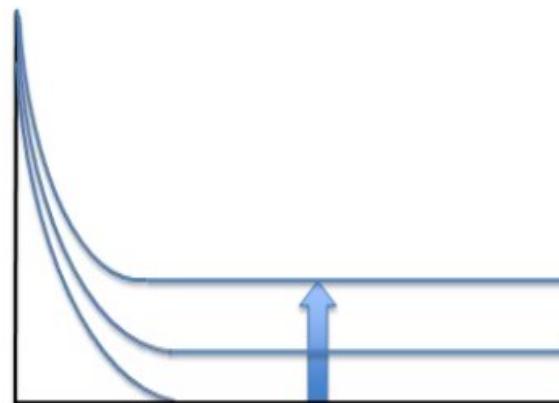
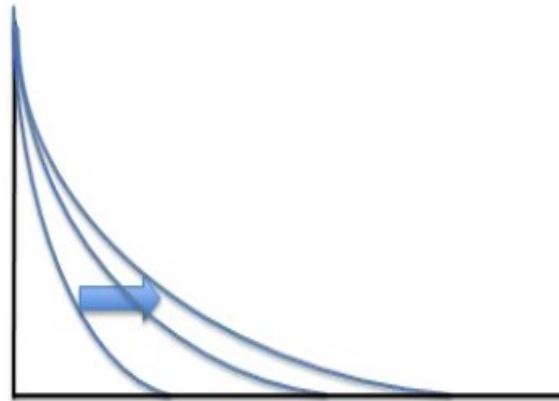
Nivolumab versus docetaxel in previously treated advanced non-small-cell lung cancer (CheckMate 017 and CheckMate 057): 3-year update and outcomes in patients with liver metastases

E. E. Vokes^{1*}, N. Ready², E. Felip³, L. Horn⁴, M. A. Burgio⁵, S. J. Antonia⁶, O. Arén Frontera⁷, S. Gettinger⁸, E. Holgado⁹, D. Spigel^{10,11}, D. Waterhouse^{12,13}, M. Domine¹⁴, M. Garassino¹⁵, L. Q. M. Chow¹⁶, G. Blumenschein Jr¹⁷, F. Barlesi¹⁸, B. Coudert¹⁹, J. Gainor²⁰, O. Arieta²¹, J. Brahmer²², C. Butts²³, M. Steins²⁴, W. J. Geese²⁵, A. Li²⁵, D. Healey²⁵ & L. Crino⁵

Annals of Oncology 29: 959–965, 2018
doi:10.1093/annonc/mdy041
Published online 2 February 2018

Figure 1. Kaplan-Meier curves of (A) overall survival (OS) and (B) progression-free survival (PFS)^a in all randomized pooled patients with squamous or nonsquamous non-small-cell lung cancer (NSCLC) with 3 years' minimum follow-up. ^aInvestigator-assessed. CI, confidence interval; HR, hazard ratio.

Bending the survival curve in metastatic cancer



1^e lijns Pembro vs chemo bij PDL1 > 50%

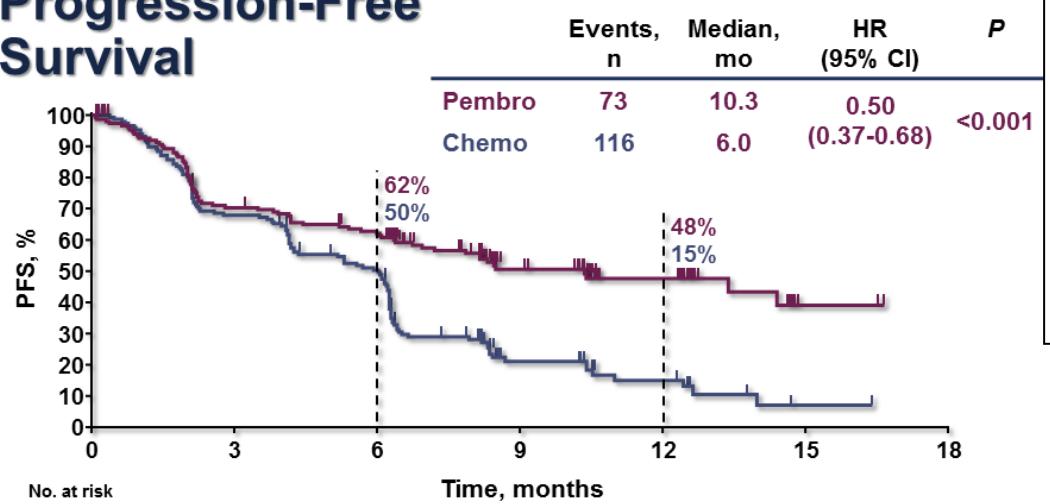
The NEW ENGLAND
JOURNAL *of* MEDICINE

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 Csőszi, 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 Shentu, Ph.D., Reshma Rangwala, M.D., Ph.D., and Julie R. Brahmer, M.D.,
for the KEYNOTE-024 Investigators*

Progression-Free Survival



Assessed per RECIST v1.1 by blinded, independent central review.
Data cut-off: May 9, 2016.

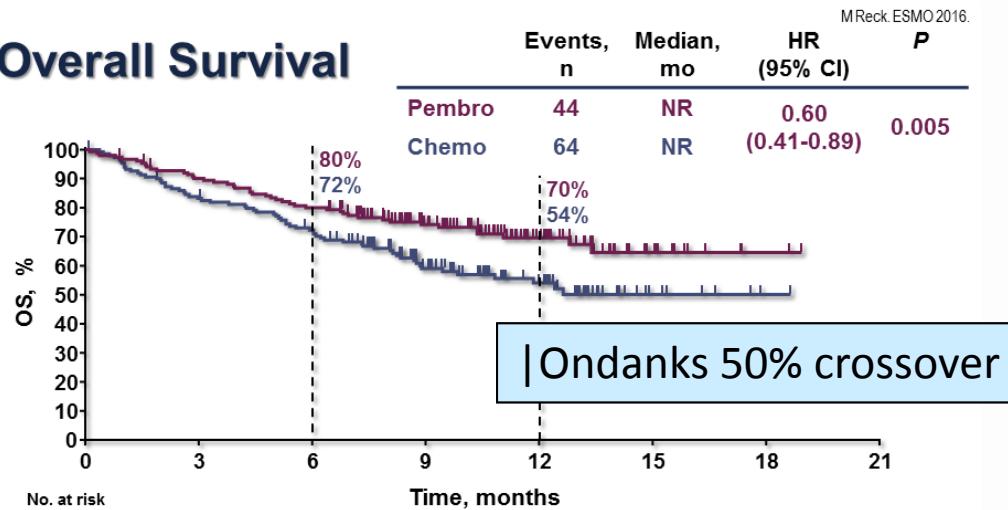
KEYNOTE-024: Pembrolizumab vs Platinum-Based Chemotherapy as First-Line Therapy for Advanced NSCLC With a PD-L1 TPS ≥50%

Martin Reck,¹ Delvys Rodríguez-Abreu,² Andrew S. Robinson,³ Rina Hui,⁴ Tibor Csöszsi,⁵ Andrea Fülop,⁶ Maya Gottfried,⁷ Nir Peled,⁸ Ali Tafreshi,⁹ Sinead Cuffe,¹⁰ Mary O'Brien,¹¹ Suman Rao,¹² Katsuyuki Hotta,¹³ Melanie A. Leiby,¹⁴ Gregory M. Lubiniecki,¹⁴ Yue Shentu,¹⁴ Reshma Rangwala,¹⁴ and Julie R. Brahmer¹⁵ on behalf of the KEYNOTE-024 investigators

¹Lung Clinic Grosshadern, Airway Research Center North (ARCN), member of the German Center for Lung Research (DZL), Grosshadern, Germany; ²Hospital Universitario Insular de Gran Canaria, Las Palmas, Spain; ³Cancer Centre of Southeastern Ontario at Kingston General Hospital, Kingston, ON, Canada; ⁴Westmead Hospital and the University of Sydney, Sydney, NSW, Australia; ⁵Jász-Nagykun-Szolnok County Hospital, Szolnok, Hungary; ⁶Országos Korányi TBC és Pulmonológiai Intézet, Budapest, Hungary; ⁷Meir Medical Center, Kfar-Saba, Israel; ⁸Davidoff Cancer Center, Tel Aviv University, Petah Tikva, Israel; ⁹Southern Medical Day Care Centre, Wollongong, NSW, Australia; ¹⁰St. James' Hospital and Cancer Trials Ireland, Dublin, Ireland; ¹¹ICRG – All Ireland Cooperative Oncology Research Group, Dublin, Ireland; ¹²The Royal Marsden Hospital, London, UK; ¹³MedStar Franklin Square Hospital, Baltimore, MD, USA; ¹⁴Okayama University Hospital, Okayama, Japan; ¹⁵Merck & Co., Inc., Kenilworth, NJ, USA; ¹⁶Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD, USA

esmo.org

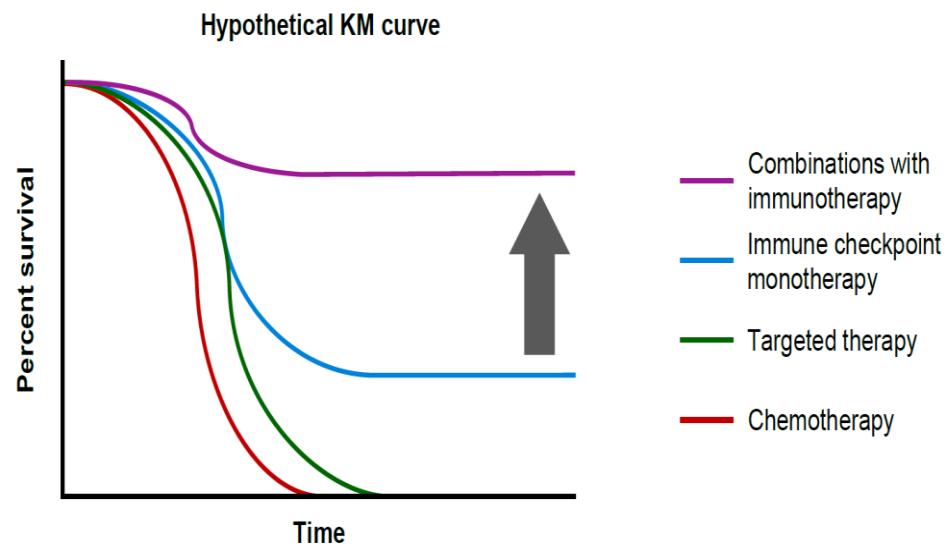
Overall Survival



DMC recommended stopping the trial because of superior efficacy observed with pembrolizumab

Hoe uitkomsten te verbeteren?

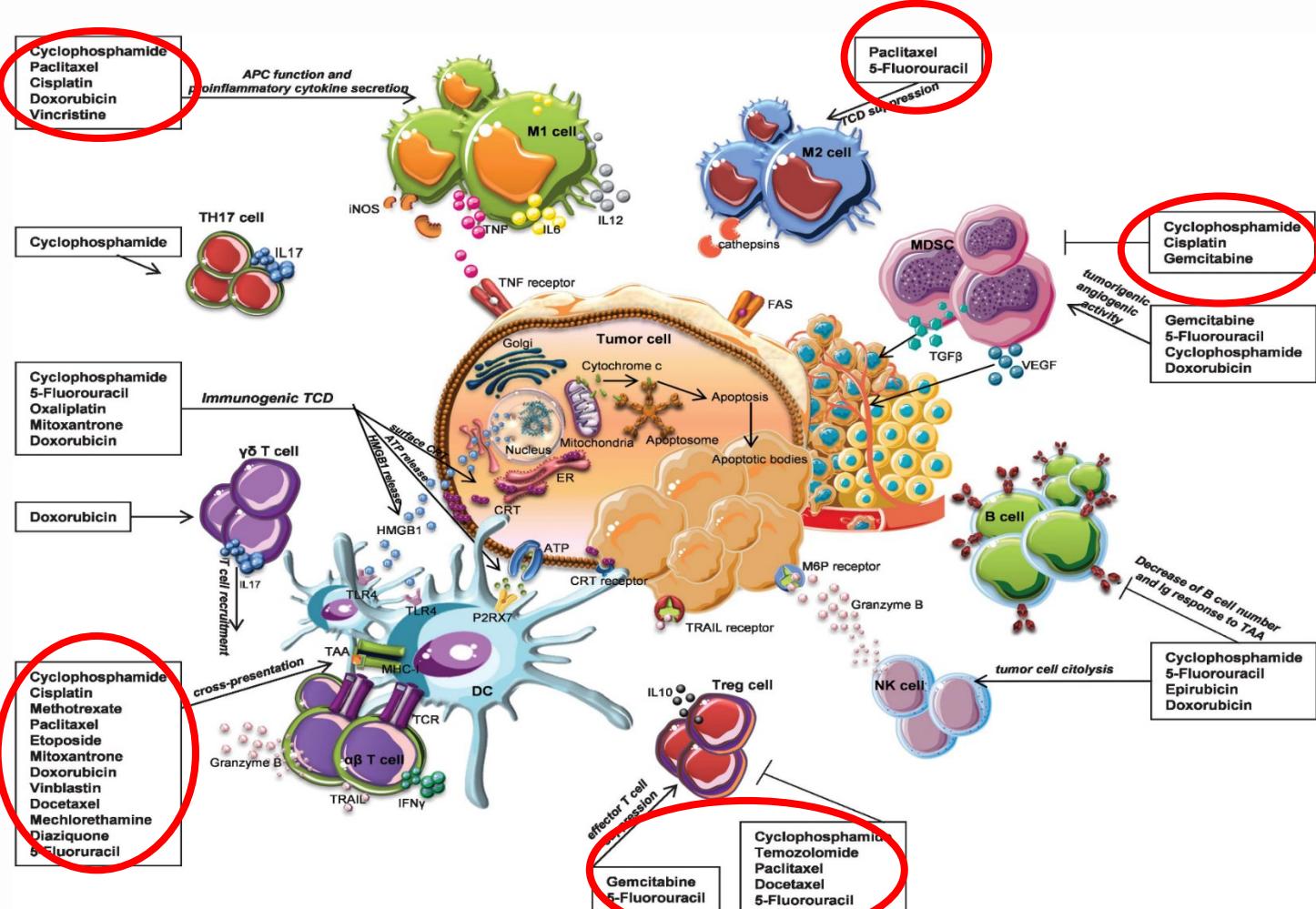
- Combinations with chemotherapy
- PD-(L1) blockade combined with CTLA-4 blockade
- Combinations with targeted therapy
- Combinations with radiotherapy
-



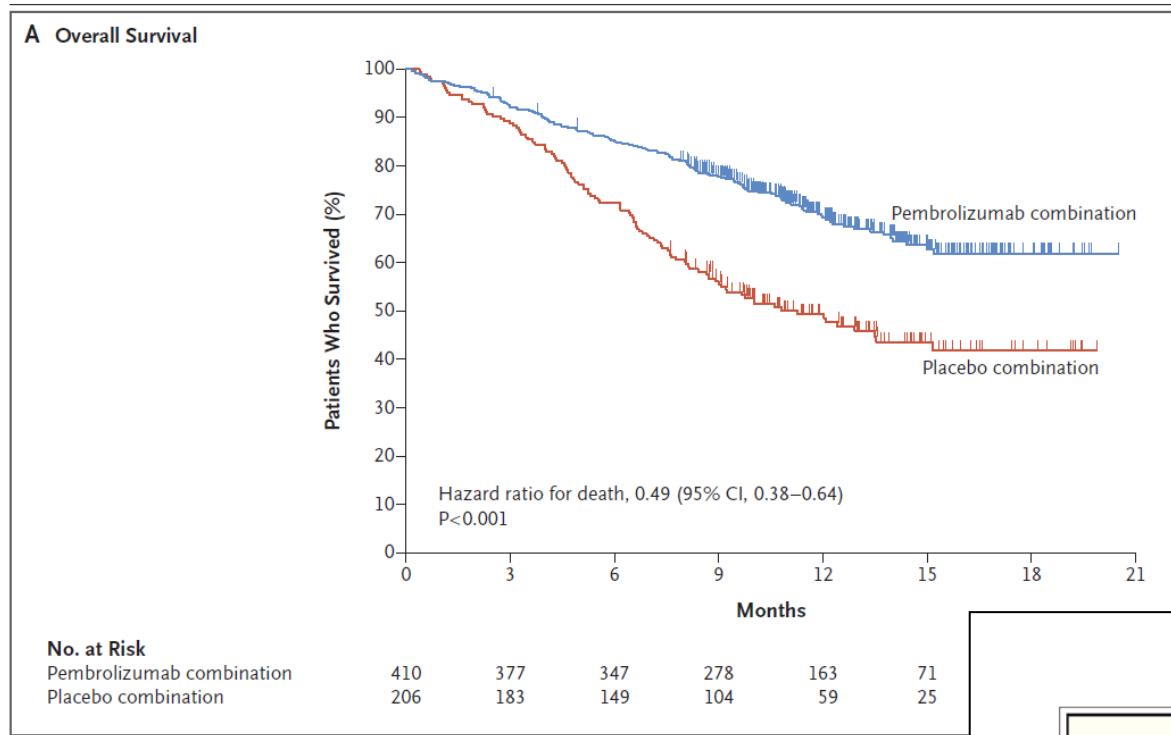
Adapted from Sharma and Allison. Cell 2015

Rationale IO + chemotherapie

niet iedere chemo heeft hetzelfde effect



AACR 2018: 1^e lijns st IV NSCLC Niet Plaveiselcel onafhankelijk PDL1 expressie



nejm.org on April 16, 2018.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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

L. Gandhi, D. Rodriguez-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*

PFS en OS in niet-plaveiselcel IO – chemo studies

Trial	Patients	PFS	OS
KEYNOTE 189 (Pembro/Cis or Carb/Pem vs Cis or Carb/Pem)	616	5.6 vs 4.9 m HR 0.52; p<0.00001	Nr vs 11.3 m HR 0.49; p<0.00001
IMpower 132 (Atezo/Cis or Carb/Pem vs Cis or Carb/Pem)	578	7.6 vs 5.2 m HR 0.6; p<0.0001	18.1 vs 13.6 m HR 0.81; p=0.0797
IMpower 150 Atezo/Bev/Carb/Pac vs Bev/Carb/Pac	800	8.3 vs 6.8 m HR 0.59; p<0.0001	19.2 vs 14.7 m HR 0.78; p=0.016
IMpower 130 Atezo/Carbo/NabPacl vs Carbo/NabPac	679	5.5 vs 7.0 m HR 0.64; p < 0.0001	13.9 vs 18.6 m HR 0.79; p=0.033

Slide adapted from prof Reck

Capuzzo ESMO 2018; Ghandi NEJM 2018; Socinski NEJM 2018; Papadimitrakopoulos WCLC 2018



News > Medscape Medical News > International Approvals

EC Approves Frontline Lung Cancer Combo

Considered a New Standard of Care

Nick Mulcahy

DISCLOSURES | September 13, 2018



Read Comments



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The European Commission has approved the combination of pembrolizumab (*Keytruda*, Merck), pemetrexed (*Aliimta*, Lilly), and platinum chemotherapy for the first-line treatment of metastatic non–small cell lung cancer (NSCLC), according to Merck.

The approval is for nonsquamous NSCLC, which is the most common form of lung cancer. The drug is restricted to patients whose tumors have no *EGFR* or *ALK* mutations.

This approval is also the first in Europe for an anti–programmed cell death protein–1 therapy in combination with chemotherapy, the company said.

The new decision was based on efficacy and safety data from the phase 3 KEYNOTE-189 trial in patients with advanced disease.

Information from Industry

Panel of experts discuss a new treatment option in 1L aRCC[Learn more](#)

PIGLB/ITV/2017.51.01 Dec 2017

The trial demonstrated an improvement in overall response rate (ORR), progression-free survival (PFS), and overall survival (OS) across all groups of patients, irrespective of programmed cell death–ligand-1 tumor expression status.

The KEYNOTE-189 results were presented earlier this year at the annual meeting of the American Association for Cancer Research and were

En plaveiselcelcarcinoom dan?

KEYNOTE 407

ASCO 2018; update ESMO 2018

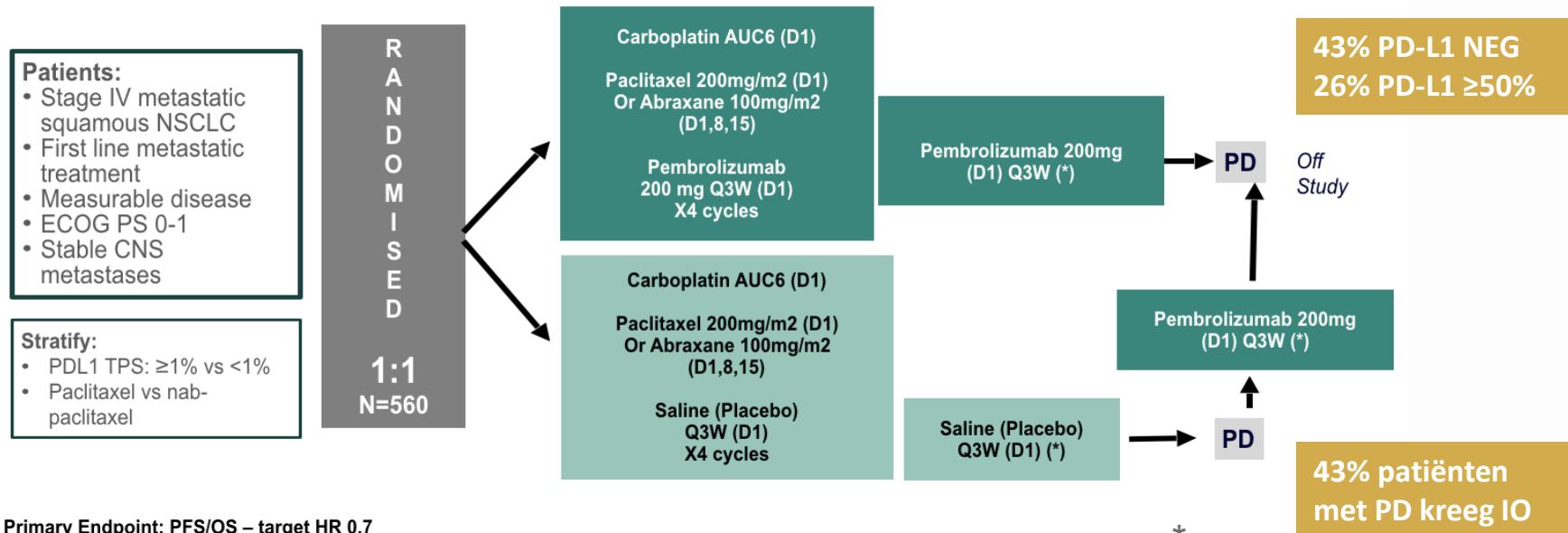
IMPOWER 131

ASCO 2018; update ESMO 2018



KEYNOTE 407

KEYNOTE-407: A Study of Carboplatin-Paclitaxel/Nab-Paclitaxel Chemotherapy With or Without Pembrolizumab (MK-3475) in Adults With First Line Metastatic Squamous Non-small Cell Lung Cancer



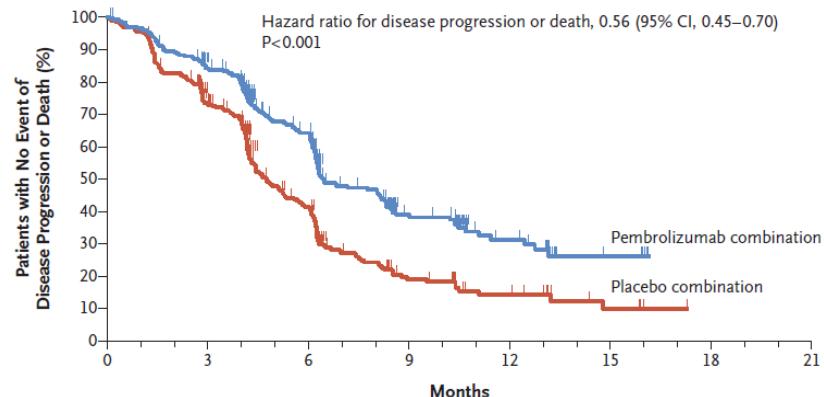
Primary Endpoint: PFS/OS – target HR 0.7

Secondary Endpoints: ORR, AE

Exploratory Endpoints: QoL

KEYNOTE 407

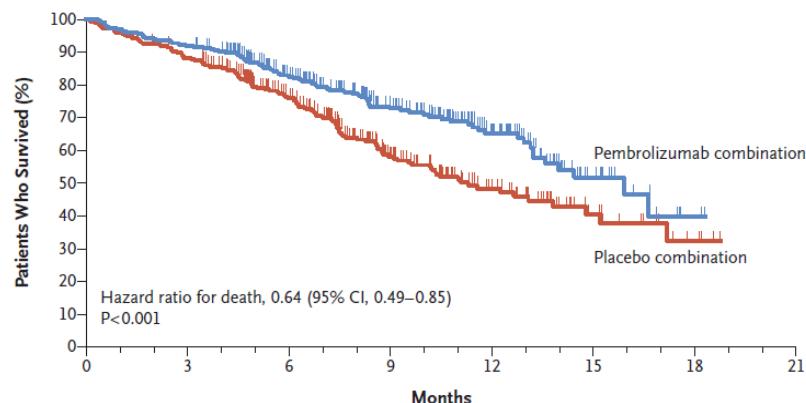
A Progression-free Survival



No. at Risk

	0	3	6	9	12	15	18	21
Pembrolizumab combination	278	223	142	57	23	5	0	0
Placebo combination	281	190	90	26	12	4	0	0

A Overall Survival



No. at Risk

	0	3	6	9	12	15	18	21
Pembrolizumab combination	278	256	188	124	62	17	2	0
Placebo combination	281	246	175	93	45	16	4	0

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. Gümüş, J. Mazières, B. Hermes, F. Çay Şenler, T. Csörszi, A. Fülop, 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*

This article was published on September 25, 2018, at NEJM.org.

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Approved Drugs

Hematology/Oncology (Cancer)
Approvals & Safety Notifications

Drug Information Soundcast in
Clinical Oncology (D.I.S.C.O.)

Approved Drug Products
with Therapeutic
Equivalence Evaluations
(Orange Book)

FDA approves pembrolizumab in combination with chemotherapy for first-line treatment of metastatic squamous NSCLC

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On October 30, 2018, the Food and Drug Administration approved pembrolizumab (KEYTRUDA, Merck & Co. Inc.) in combination with carboplatin and either paclitaxel or nab-paclitaxel as first-line treatment of metastatic squamous non-small cell lung cancer (NSCLC).

Approval was based on KEYNOTE-407 (NCT02775435), a randomized, multi-center, double-blind, placebo-controlled trial in 559 patients with metastatic squamous NSCLC, regardless of PD-L1 tumor expression status, who had not previously received systemic therapy for metastatic disease. Patients were randomized (1:1) to pembrolizumab 200 mg or placebo in combination with carboplatin, and investigator's choice of either paclitaxel every 3 weeks or nab-paclitaxel weekly on a 3-week cycle for 4 cycles followed by pembrolizumab or placebo. Patients continued pembrolizumab or placebo until disease progression, unacceptable toxicity, or a maximum of 24 months.

The main efficacy outcome measures were overall survival (OS), progression-free survival (PFS) and overall response rate (ORR) as assessed by blinded independent review. The trial demonstrated statistically significant improvements in OS, PFS and ORR for patients receiving pembrolizumab plus chemotherapy compared with those randomized to placebo plus chemotherapy. The median OS was 15.9 and 11.3 months for the pembrolizumab plus chemotherapy and placebo plus chemotherapy arms, respectively (HR 0.64; 95% CI: 0.49, 0.85; p=0.0017). The median PFS was 6.4 and 4.8 months for the pembrolizumab plus chemotherapy and placebo plus chemotherapy arms, respectively (HR 0.56; 95% CI: 0.45, 0.70; p<0.0001). The analysis of ORR was limited to the initial 204 patients randomized. The ORRs were 58% and 35%, favoring the pembrolizumab-containing arm (difference of 23.6%; 95% CI: 9.9, 36.4; p=0.0008). The estimated median response durations were 7.2 and 4.9 months, respectively.

The most common adverse reactions in at least 20% of patients who received pembrolizumab on KEYNOTE-407 were fatigue/asthenia, nausea, constipation, diarrhea, vomiting, pyrexia, decreased appetite, rash, cough, dyspnea, alopecia, and peripheral neuropathy.

The recommended pembrolizumab dose for metastatic squamous NSCLC is 200 mg intravenously every 3 weeks, prior to chemotherapy when given on the same day, until disease progression, unacceptable toxicity, or 24 months after initiation.

[View full prescribing information for KEYTRUDA.](#)

FDA granted this application priority review.

Healthcare professionals should report all serious adverse events suspected to be associated with the use of any medicine and device to FDA's [MedWatch Reporting System](#) or by calling 1-800-FDA-1088.

Approved immunotherapies NSCLC 2018

- stage IV

- **Metastatic NSCLC (no EGFR or ALK mutation):**
- 1st line
 - PD-L1 ≥ 50% Pembrolizumab monotherapy
 - Independent of PD-L1 expression for non-squamous histology: Pembrolizumab + pemetrexed and platinum chemotherapy
- 2nd line
 - PD-L1 ≥ 1% Pembrolizumab
 - Independent of PD-L1 expression: Atezolizumab & Nivolumab

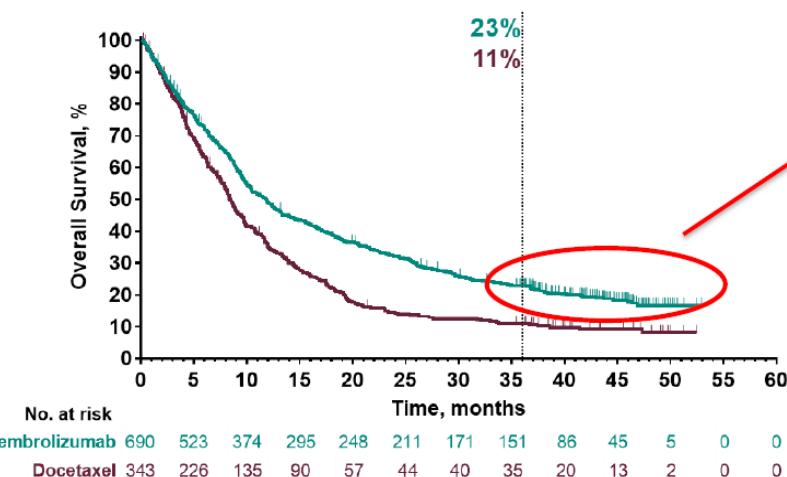
Belangrijke vragen: Poster discussion ESMO Ekman (discussant):

Discussion

Important patient groups in relation to immune checkpoint inhibitors studied in the three abstracts:

- long-term survivors
- re-challenge
- PS2 patients
- combination therapy

Long term survivors: LBA63 R.Herbst KN-010



The tale of the tail

- 79 patients completed 35 cycles or 2 years of pembrolizumab
- 48 patients (64%) had ongoing response

Who are these patients?

- PD-L1:

Characteristic, n (%)	Pembrolizumab (n = 690)	Docetaxel (n = 343)	35 Cycles or 2 Years of Pembrolizumab (n = 79) ^a
PD-L1			
TPS ≥50%	290 (42)	152 (44)	58 (73)
TPS 1–49%	400 (58)	191 (56)	21 (27)
Current/former smoker	565 (82)	269 (78)	72 (91)
EGFR mutation	61 (9)	26 (8)	1 (1)

- Other predictive biomarkers: genetic and immunological e.g. TMB, TILs, TCR, SNPs, miRNAs, microbiome

- Higher rate of irAEs?

Sato et al.: ORR irAEs vs non-irAEs 63.6% vs 7.4%, p <0.01, mPFS NR vs 49 days (n=38)

Toi et al.: ORR irAE vs non-irAEs 57% vs 12%, mPFS 12.0 vs 3.6 m (n=70)

PS2 patients

- frequently excluded from clinical trials
- poor prognosis vs PS 0-1 patients
- discordance in PS scoring between doctors and patients, risk for underestimation (43% agreement in study by Lilenbaum et al.¹)
- chemotherapy and targeted agents prolong survival and improve quality-of-life in PS2 advanced NSCLC patients²
- prevalence of PS2 uncertain; not routinely required in cancer registries:
 - 30.8% PS2 in Polish community-based registry
(Radzikowska et al. 2002³)
 - 10.6% of advanced stage Swedish patients
(Sandelin et al. 2017⁴)

Pembrolizumab voor NSCLC PS2: PePS2 trial

- Inclusion & exclusion criteria explicitly included the **ECOG** definitions of **PS=2** status incorporated into the eligibility checklist for registration. PS was assessed by the treating physician and **PS=2** status had to be stable for at least weeks prior to trial entry.
WHO PS:
2 weken stabiel
- Patients were eligible **regardless of TPS** on the archival specimen. If the TPS could not be assessed on the sample, a repeat biopsy was mandatory. However, if TPS could not be ascertained on this repeat biopsy the patient could be included in the trial.
- Patients were not allowed immunosuppressive therapy within seven days prior to first dose.
- Pembrolizumab was given at a flat **200mg dose 3 weekly**. Response was assessed by RECIST v1.1 and CT assessments were performed 9 weekly.
- Co-primary outcomes were:
 - durable clinical benefit**, defined as CR / PR / SD without prior PD at or after the second scheduled CT scan, scheduled to occur at 18 weeks;
 - toxicity**, defined as treatment-related dose delay or treatment discontinuation due to AE

Total cohort

	DCB (%)	Toxicity (%)	PR (%)	No RECIST	Median OS (95% CI)	Median PFS (95% CI)
All (n = 60)	20 (33.3)	13 (21.7)	17 (28.3)	16 (26.7)	11.7 (6.8 - NR)	5.4 (3.5 - 8.5)

KEYNOTE-010 study:

- PR 18.0% (2 mg/kg) and 18.5% (10mg/kg)
- Median OS 10.4 m (2 mg/kg) and 12.7 m (10 mg/kg)
- Median PFS 3.9 m (2 mg/kg) and 4.0 m (10 mg/kg)

Line of therapy

	DCB (%)	Toxicity (%)	PR (%)	No RECIST	Median OS (95% CI)	Median PFS (95% CI)
All (n = 60)	20 (33.3)	13 (21.7)	17 (28.3)	16 (26.7)	11.7 (6.8 - NR)	5.4 (3.5 - 8.5)
Line of therapy						
First line (n = 9)	1 (11.1)	3 (33.3)	0 (0.0)	3 (33.3)	6.8 (2.4 - NR)	2.9 (1.9 - NR)
Subsequent line (n = 51)	19 (37.3)	10 (19.6)	17 (33.3)	13 (25.5)	12.1 (8.1 - NR)	6.0 (3.5 - 11.4)

- Limited clinical benefit in 1st line treatment, however only 9 patients – question remains about clinical efficacy in PS2 patients

Belangrijke vragen: Poster discussion ESMO Ekman (discussant):

Conclusions

Important patient groups in relation to immune checkpoint inhibitors studied:

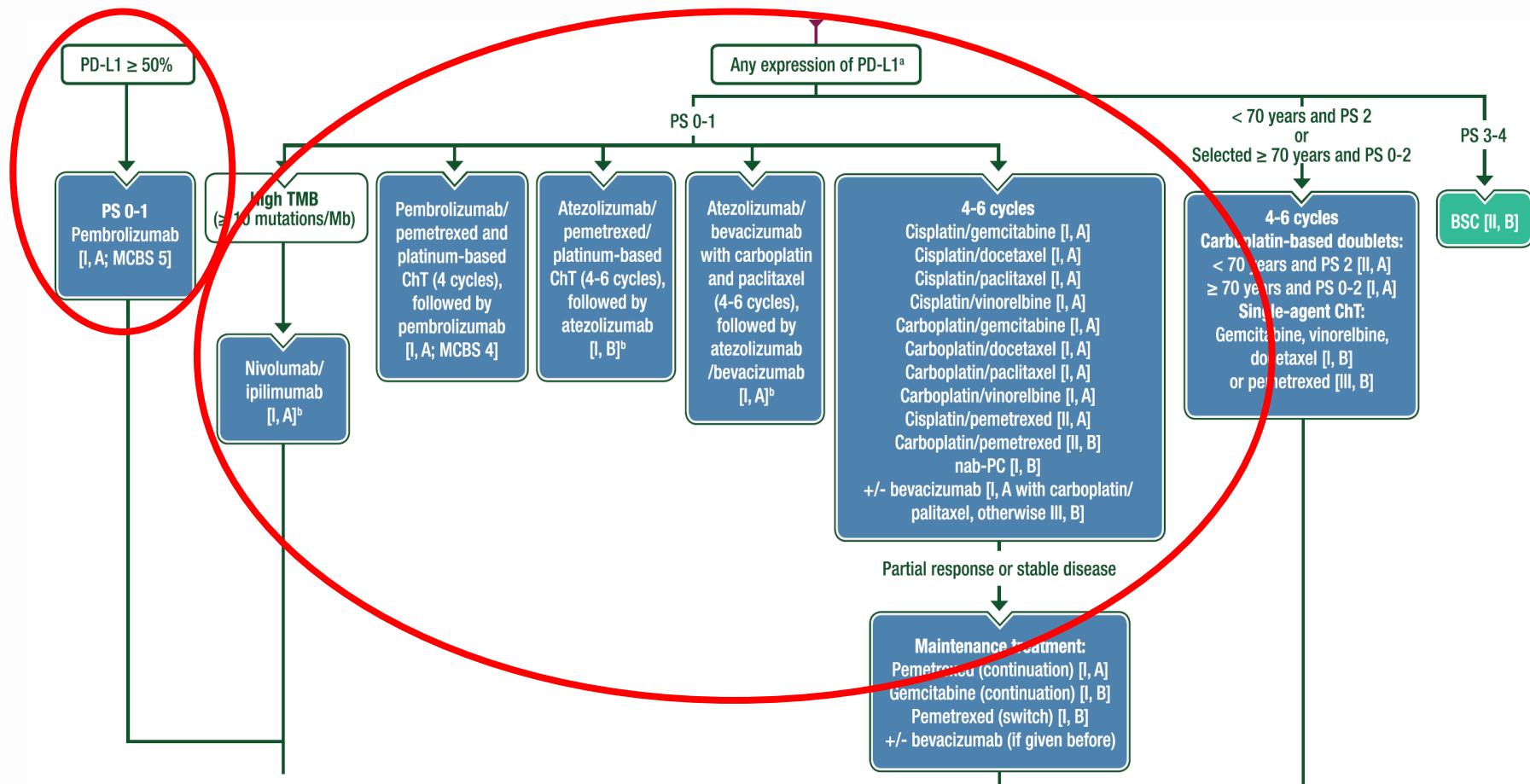
- long-term survivors – significant long-term survival at 3 yrs with pembrolizumab
- re-challenge
 - possible with signs of clinical efficacy
- PS2 patients
 - clinical efficacy with pembrolizumab comparable to PS 0-1 patients beyond 1st line and with tolerable toxicity

Combinatie behandelingen stad IV

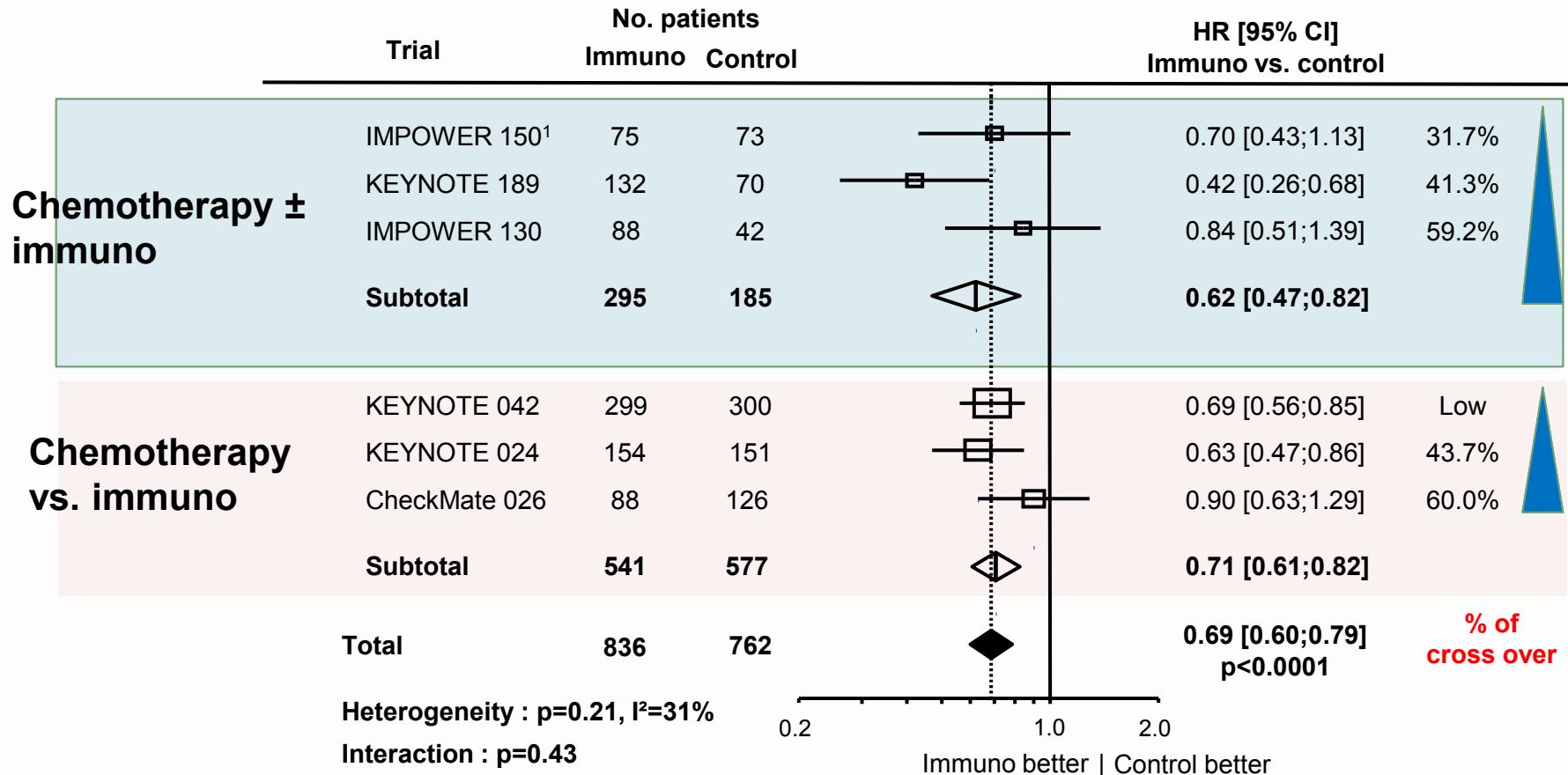
huidige vragen

- Combinatie voor iedereen?
- Wat als PDL1 > 50% ?
 - Hoe predictieve markers te vinden
 - Selectie marker nodig++

ESMO richtlijn 2018: non-squamous



PD-L1 ≥ 50% - OS



¹ paclitaxel + carboplatin + bevacizumab + atezolizumab versus paclitaxel + carboplatin + bevacizumab



SCLC – Progress at Last?

Presented by: Dr. J. van der Steene

SCLC and Immunotherapy

- ++ Tobacco exposure; TMB - median 7.37 mutations per Mb
- Presence of autoantibodies, CNS paraneoplastic syndromes prognostic
- Defects in MHC antigen presentation
- Effector T cells associated with better outcomes
- PDL-1 tumour expression ~10% in SCLC, not predictive of response
- PDL-1 immune cell expression higher (up to 40%)

Zimmermann & Peters J Thorac Oncol 2018; Pietanza et al Clin Cancer Res 2015; Pakkala & Owonikoko J Thorac Dis 2018; Gadgeel J Thorac Oncol 2018

Overview single agent IO in SCLC

Single agent activity in Pretreated SCLC						
Agent	N	ORR (%)	Duration of response	Median PFS (months)	Median OS (months)	Toxicity
Nivolumab ^{1,2}	98/109	10/12%	62% >12m 39% > 18 m	1.4	4.4	Limbic encephalitis seen
Pembrolizumab ³	24	33% (PDL1>=1%)	19.4 m (>3.6 - >20)	1.9	9.7	
Pembrolizumab ⁴	107	18.7%		2.0	9.1	Composite PDL-1 ↑ORR, PFS, OS
Durvalumab ⁵	21	9.5% (reduction 23.8%)	14.6 – 29.5+	1.5	4.8	
Atezolizumab ⁶	17	6% RECIST 18.3% irRECIST	7 m			
Single agent activity in Maintenance Therapy						
Pembrolizumab ⁷	45	11.1%	10.8 m	1.4 (1 yr 13%)	9.6 (1 yr 37%)	Composite PDL-1 ↑ORR
Combination in Pretreated SCLC						
Nivolumab (1mg) + Ipilimumab (3 mg) ¹	61	23%	7.7 m	2.6	7.7	Myasthenia

Antonia et al Lancet Oncol 2016; www.fda.gov (accessed 25 Sep 2018); Ott et al J Clin Oncol 2017; Chung et al Proc ASCO 2018, abstr 8506;
 Goldman et al Proc ASCO 2018 abstr 8518; Horn et al Proc ASCO 2018; Gadgeel et al J Thorac Oncol 2018

Liu, Presidential WCLC 2018

IMpower133 trial: 'NEW STANDARD OF CARE' 1 line

- IMpower133 is the first study in over 20 years to show a clinically meaningful improvement in OS over the current standard-of-care in 1L ES-SCLC
- The addition of atezolizumab to carboplatin and etoposide provided a significant improvement in OS and PFS, compared with carboplatin and etoposide alone in 1L ES-SCLC
 - mOS: 12.3 vs. 10.3 months; HR: 0.70 ($p = 0.0069$); 12-month OS: 51.7% vs. 39.2%
 - mPFS: 5.2 vs. 4.3 months; HR: 0.77 ($p = 0.017$); 12-month PFS: 30.8% vs. 25.7%
- The safety profile of atezolizumab plus carboplatin was acceptable
 - Rates of hematologic side effects were similar between treatment groups
 - Administration of atezolizumab did not compromise the administration of chemotherapy
 - The incidence and types of immune-related AEs were similar to those seen with atezolizumab monotherapy
- These data suggest that atezolizumab plus carboplatin should be considered the new standard of care for first-line treatment of ES-SCLC



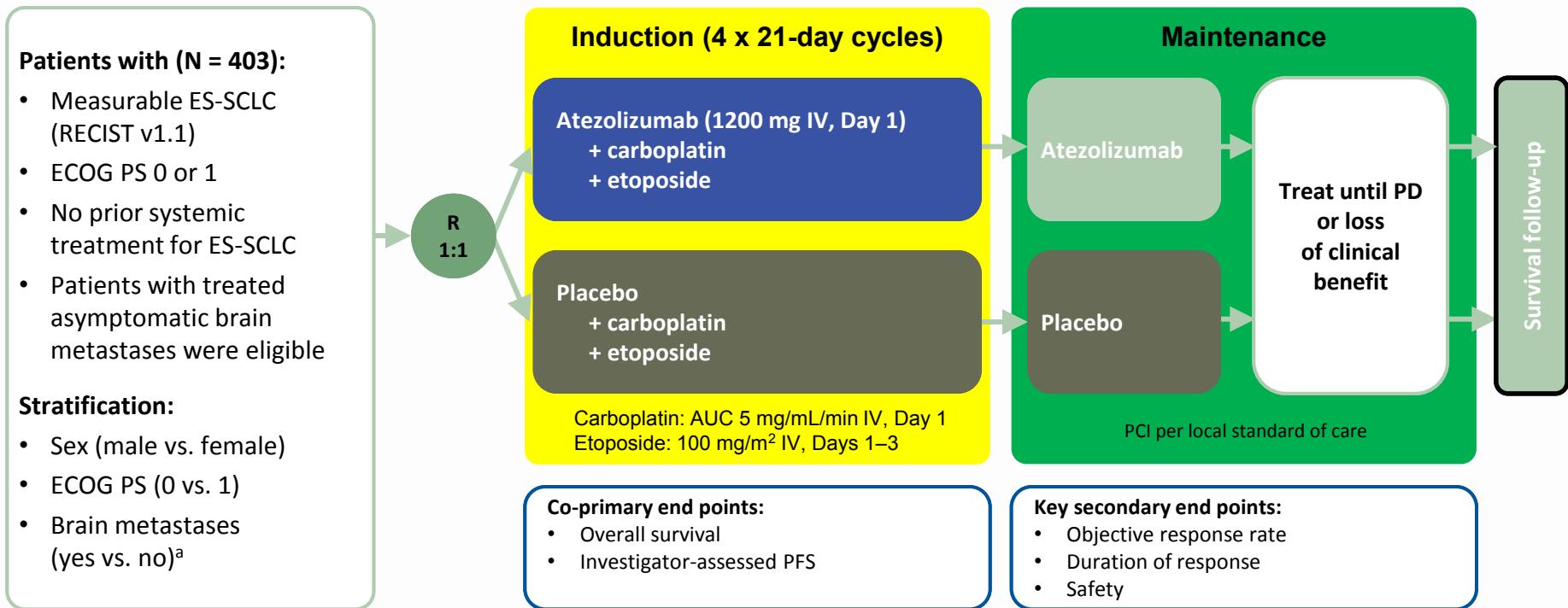
The NEW ENGLAND
JOURNAL of MEDICINE

ORIGINAL ARTICLE

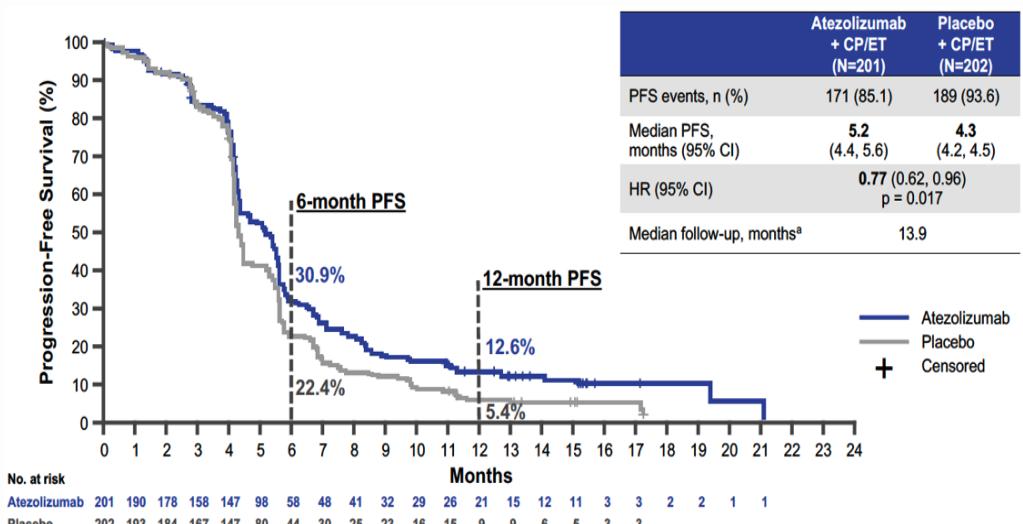
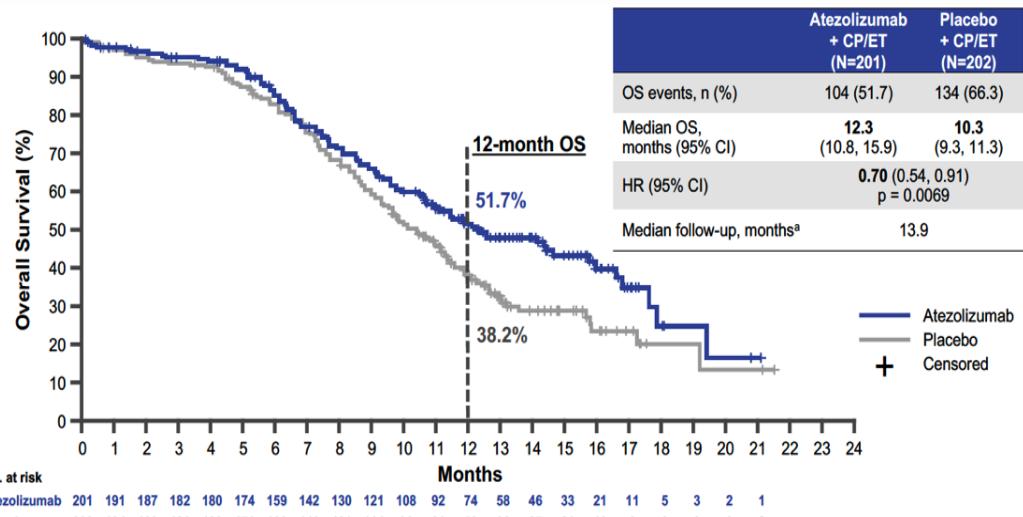
Atezolizumab plus Chemotherapy for First-Line Treatment of Extensive-Stage Small-Cell Lung Cancer

Leora Horn, M.D., Aaron S. Mansfield, M.D., Aleksandra Szczęsna, M.D.,
Libor Havel, M.D., Maciej Krzakowski, M.D., Ph.D.,
Maximilian J. Hochmair, M.D., Florian Huemer, M.D.,
György Losonczy, M.D., Ph.D., Melissa L. Johnson, M.D.,
Makoto Nishio, M.D., Ph.D., Martin Reck, M.D., Tony Mok, M.D.,
Sivuonathan Lam, Pharm.D., David S. Shames, Ph.D., Juan Liu, Ph.D.,
Beijing Ding, Ph.D., Ariel Lopez-Chavez, M.D., Fairooz Kabbinavar, M.D.,
Wei Lin, M.D., Alan Sandler, M.D., and Stephen V. Liu, M.D., for the IMpower133
Study Group*

IMpower133: Global Phase 1/3, double-blind, randomized, placebo-controlled trial evaluated atezolizumab + carboplatin + etoposide in 1L ES-SCLC

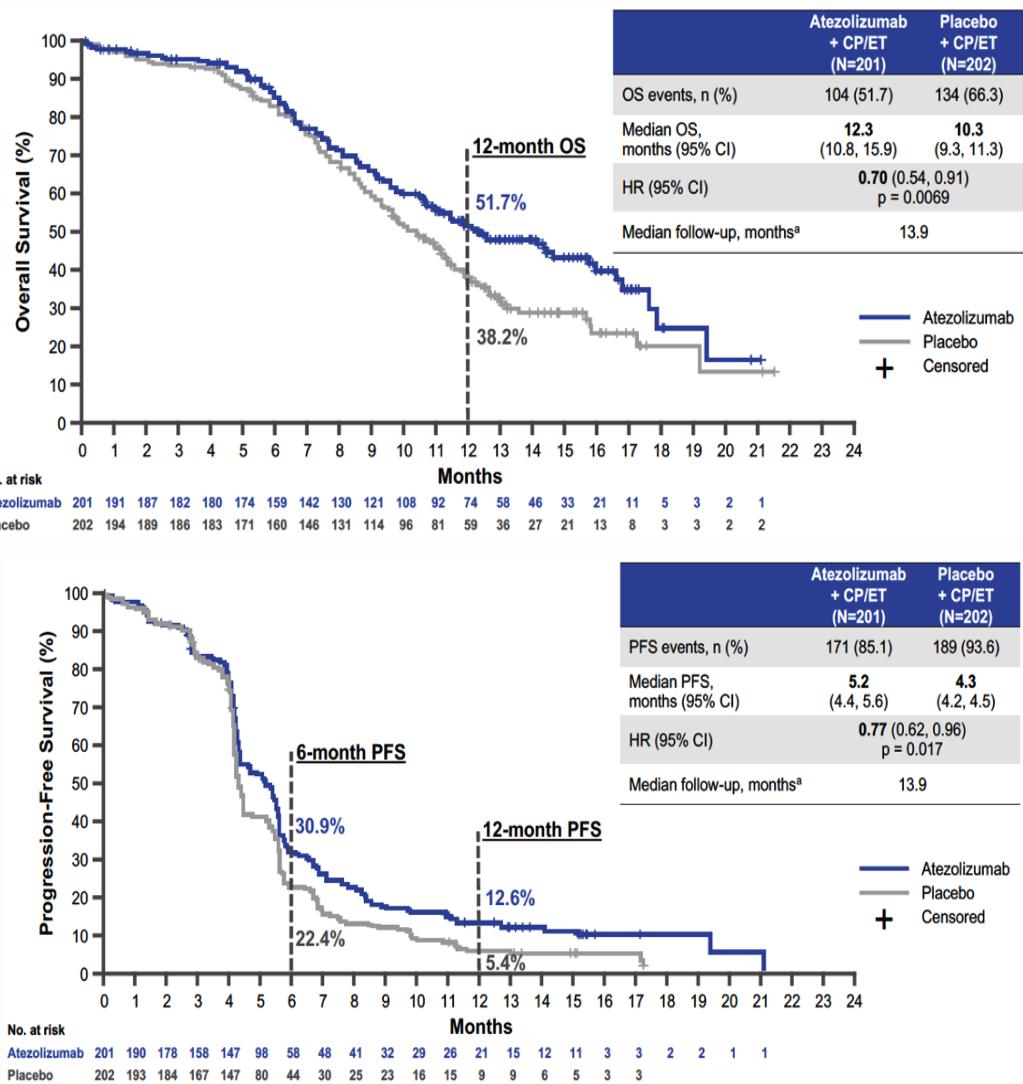


^a Only patients with treated brain metastases were eligible. ECOG PS, Eastern Cooperative Oncology Group Performance Status; IV, intravenous; PCI, prophylactic cranial irradiation; PD, progressive disease; PFS, progression-free survival; R, randomized; RECIST, Response Evaluation Criteria In Solid Tumors.



>1% Grade 3-4 AEs in either treatment group	Atezolizumab + CP/ET (N=198)			Placebo + CP/ET (N=196)		
	Grade 1-2	Grade 3-4	Grade 5	Grade 1-2	Grade 3-4	Grade 5
Rash	33 (16.7)	4 (2.0)	0	20 (10.2)	0	0
Hepatitis	11 (5.6)	3 (1.5)	0	9 (4.6)	0	0
Infusion-related reaction	7 (3.5)	4 (2.0)	0	9 (4.6)	1 (0.5)	0
Pneumonitis	3 (1.5)	1 (0.5)	0	3 (1.5)	2 (1.0)	0
Colitis	1 (0.5)	2 (1.0)	0	0	0	0
Pancreatitis	0	1 (0.5)	0	0	2 (1.0)	0

ORR: Response; DOR: duration of response; EF: event free
Liu et al WCLC2018 PL03



DISCUSSANT Leigh WCLC

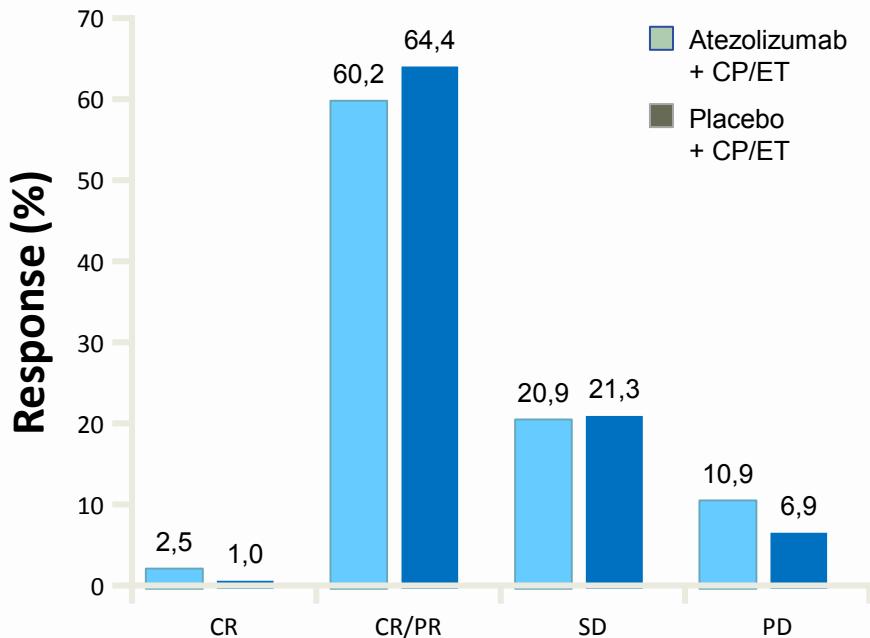
Are the results generalizable?

- selection for better PS (0,1)
- Tissue collection not mandated (~80% submitted tissue samples)
- Control arm performed as predicted
- Toxicity as expected, manageable
- No cases of limbic encephalitis

>1% Grade 3-4 AEs in either treatment group	Atezolizumab + CP/ET (N=198)			Placebo + CP/ET (N=196)		
	Grade 1-2	Grade 3-4	Grade 5	Grade 1-2	Grade 3-4	Grade 5
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Pancreatitis	0	1 (0.5)	0	0	2 (1.0)	0

ORR: Response; DOR: duration of response; EF: event free
Liu et al WCLC2018 PL03

Confirmed objective response and duration of response

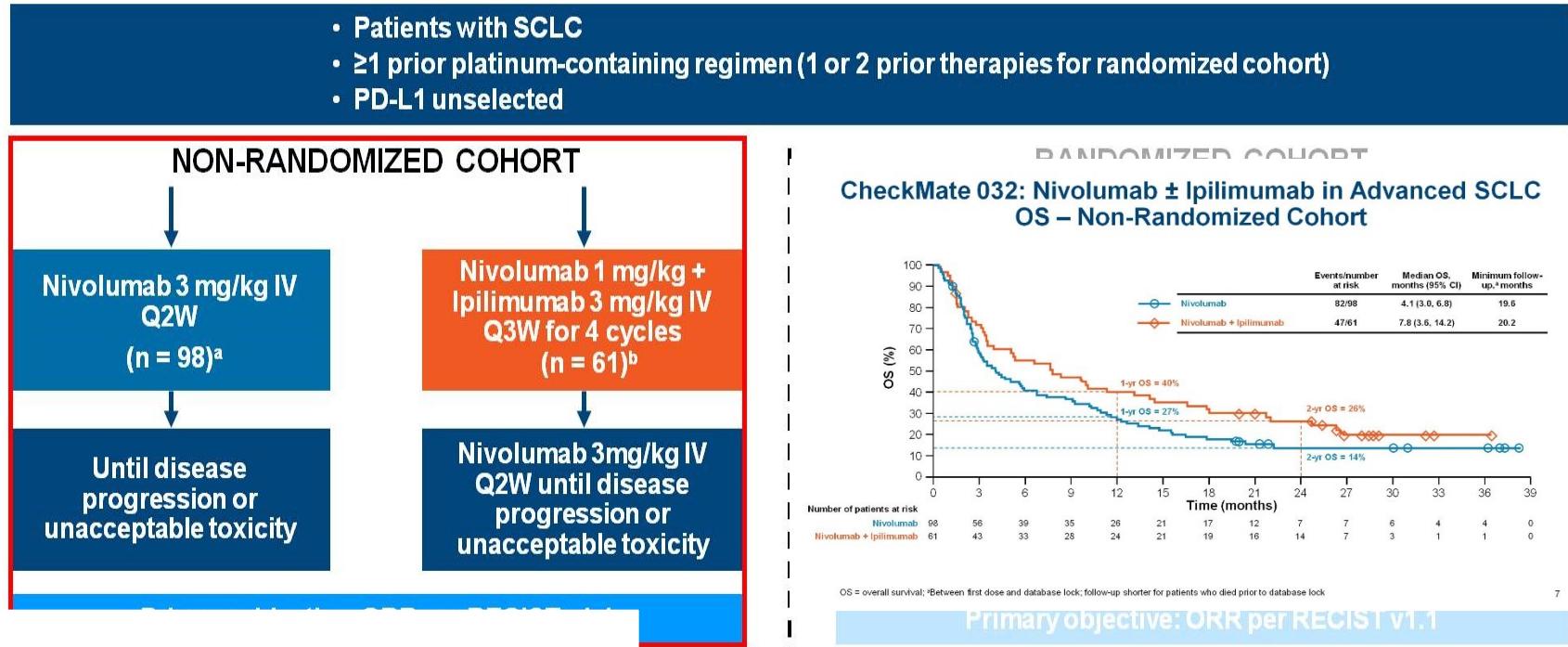


Duration of response	Atezolizumab + CP/ET (N = 121)	Placebo + CP/ET (N = 130)
Median duration, months (range)	4.2 (1.4 ^a to 19.5)	3.9 (2.0 to 16.1 ^a)
HR (95% CI)	0.70 (0.53, 0.92)	
6-month event-free rate — %	32.2	17.1
12-month event-free rate — %	14.9	6.2
Patients with ongoing response — no. (%) ^b	18 (14.9)	7 (5.4)

^a Censored. ^b At clinical cutoff date: April 24, 2018. CR, complete response; EFS, event-free survival; PD, progressive disease; PR, partial response; SD, stable disease.

CheckMate 032: Nivolumab ± Ipilimumab in Advanced SCLC

Phase I/II CheckMate 032 Study Design – Non-Randomized Cohort



PDL1 status did not impact the benefit

Database lock: March 30, 2017

	Nivolumab (n = 98)	Nivolumab + Ipilimumab (n = 61)
ORR, % (95% CI)	11 (6, 19)	23 (13, 36)
Median time to response, mo (range)	1.4 (1.1–4.1)	2.0 (1.0–4.1)
Median DOR, mo (range)	17.9 (2.8–34.6+)	14.2 (1.5–26.5+)
Patients with ongoing responses at 2 yr, ^a %	45	36

^aMedian follow-up 23.3 mo; ^bMedian follow-up 28.6 mo
Follow-up was calculated as time from first dose to database lock

Presented By Matthew Hellmann at 2017 ASCO Annual Meeting

Immunotherapy is a new standard of care for SCLC

...but room for further improvement

Nivolumab alone and nivolumab plus ipilimumab in recurrent small-cell lung cancer (CheckMate 032): a multicentre, open-label, phase 1/2 trial

Scott J Antonia, José A López-Martin, Johanna Bendell, Patrick A Ott, Matthew Taylor, Joseph Paul Eder, Dirk Jäger, M Catherine Pietanza, Dung T Le, Filippo de Braud, Michael A Morse, Paolo A Ascierto, Leora Horn, Asim Amin, Rathin N Pillai, Jeffrey Evans, Ian Chau, Petri Bono, Akin Atmaca, Padmanee Sharma, Christopher T Harison, Chen-Sheng Lin, Olaf Christensen, Emilio Calvo

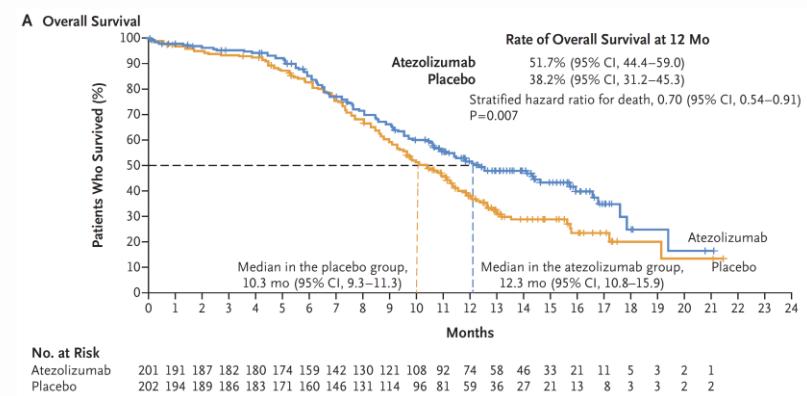
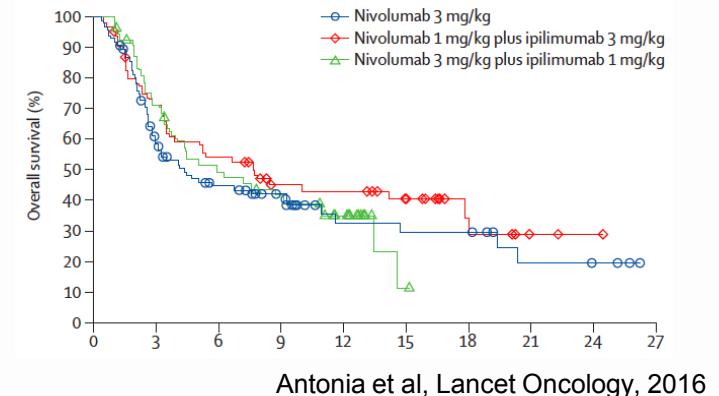
(*August 2018 - FDA approval of Nivo, 3rd line)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

First-Line Atezolizumab plus Chemotherapy in Extensive-Stage Small-Cell Lung Cancer

L. Horn, A.S. Mansfield, A. Szczesna, L. Havel, M. Krzakowski, M.J. Hochmair, F. Huemer, G. Losonczy, M.L. Johnson, M. Nishio, M. Reck, T. Mok, S. Lam, D.S. Shames, J. Liu, B. Ding, A. Lopez-Chavez, F. Kabbinavar, W. Lin, A. Sandler, and S.V. Liu, for the IMpower133 Study Group*



Conclusion

- Slow progress in SCLC
- Monotherapy PD-(L)1: no role
- More promising: combo chemo, combo IO
 - Role RT?
 - Role targeted agents + IO?
- Better biomarker selection needed

En de andere thoracale maligniteiten

IMMUNOTHERAPY FOR THYMIC TUMORS NOT A STANDARD, ADDITIONAL TRIALS NEEDED

EORTC-ETOP NIVOTHYM



EORTC

Primary objective:

To detect activity of nivolumab as single agent as second line treatment for type B3 thymoma and thymic carcinoma

Eligible patients

Nivolumab 240 mg IV q2 weeks

Primary endpoint: PFS rate at 6 months

PIs: N. Girard, S. Peters

Secondary endpoints:

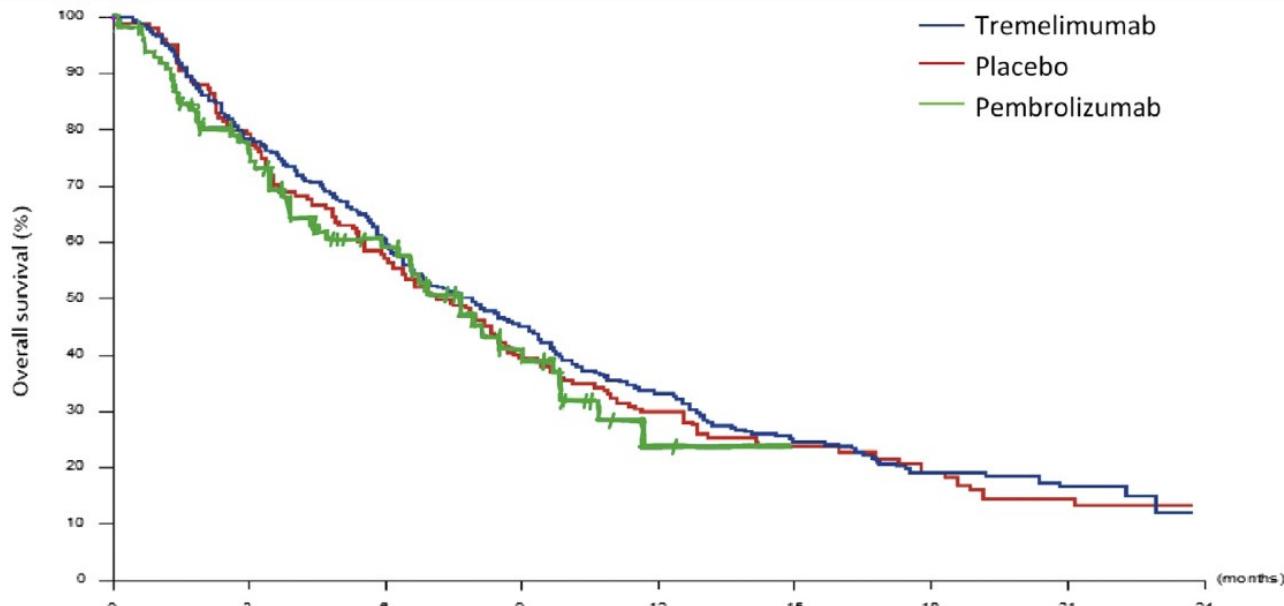
- ORR and DCR, Duration of response
- OS
- QOL
- Safety

Biomarkers: SPECTA

PD-L1
Cytokines
Molecular profiling

Treat it or Leave it: Immuno-Oncology in Mesothelioma Observed by the Eyes of Argus

Cornedine J. de Gooijer, MD, Paul Baas, MD, PhD*



Number at risk (number censored)

Tremelimumab	382 (0)	300 (6)	232 (11)	163 (13)	116 (13)	69 (29)	36 (48)	16 (63)	3 (72)
Pembrolizumab	93	63	36	17	5	3	-	-	
Placebo	189 (0)	147 (3)	103 (9)	70 (9)	48 (10)	32 (14)	17 (26)	8 (29)	0 (35)

Vragen?

