Jeroen Bosch Ziekenhuis

State of the Art:

Longcarcinoom

chemo-immunotherapie, combi-immunotherapie, adjuvante immunotherapie

Bianca van Veggel, longarts Jeroen Bosch Ziekenhuis

V&VN Symposium Immuuntherapie, 27 september 2022

Longkanker

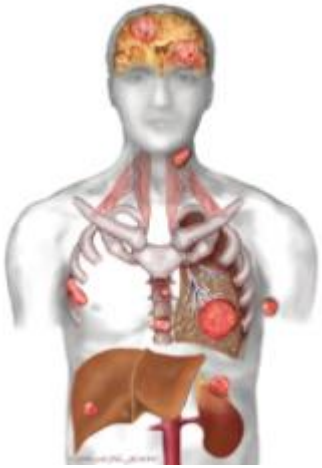
- Jaarlijks ruim 14.000 nieuwe diagnoses in Nederland
- In 2018 wereldwijd meest voorkomende vorm van kanker
- Meest voorkomende kankergerelateerde doodsoorzaak
  - 1,76 miljoen doden
- Sterk geassocieerd met roken
- Dagelijks roken 70 kinderen hun eerste sigaret…

Behandeling niet-kleincellig longcarcinoom

- Stadium I (II)
  - Chirurgie
  - Stereotactische radiotherapie
  - Evt adjuvant chemotherapie

- Stadium III
  - Radiotherapie + chemotherapie
  - Adjuvant immunotherapie

- Stadium IV
  - Systeemtherapie
    - Chemotherapie
    - Immunotherapie
    - Doelgerichte therapie



5 jaars overleving bij longkanker

- **Stadium IB**

  (tumoren van 3-4 cm zonder uitzaaiingen)

- **Stadium IIB**

  (tumoren van 0-5 cm met hilaire lymfklieren of tumoren van 5-7 cm)

- **Stadium IIIA**

  (mediastinale lymfklieren)

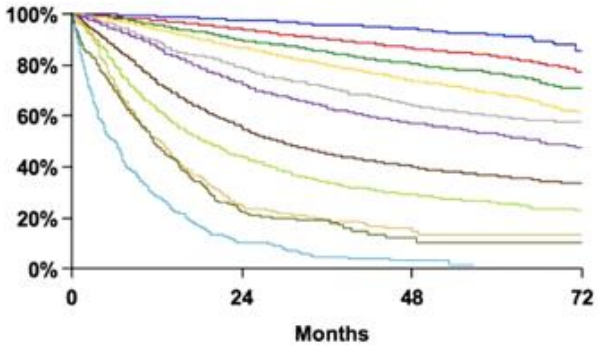
5 jaars overleving bij longkanker

- **Stadium IB 68%**
  (tumoren van 3-4 cm zonder uitzaaiingen)

- **Stadium IIB 53%**
  (tumoren van 0-5 cm met hilaire lymfklieren of tumoren van 5-7 cm)

- **Stadium IIIA 36%**
  (mediastinale lymfklieren)

Uitkomsten NSCLC
8e TNM classificatie



Proposed	Events / N	MST	24 Month	60 Month
IA1	68 / 781	NR	97%	92%
IA2	505 / 3105	NR	94%	83%
IA3	546 / 2417	NR	90%	77%
IB	560 / 1928	NR	87%	68%
IIA	215 / 585	NR	79%	60%
IIB	605 / 1453	66.0	72%	53%
IIIA	2052 / 3200	29.3	55%	36%
IIIB	1551 / 2140	19.0	44%	26%
IIIC	831 / 986	12.6	24%	13%
IVA	336 / 484	11.5	23%	10%
IVB	328 / 398	6.0	10%	0%

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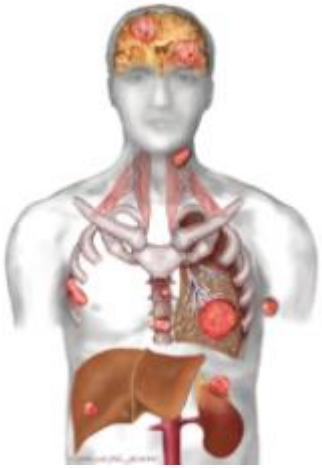
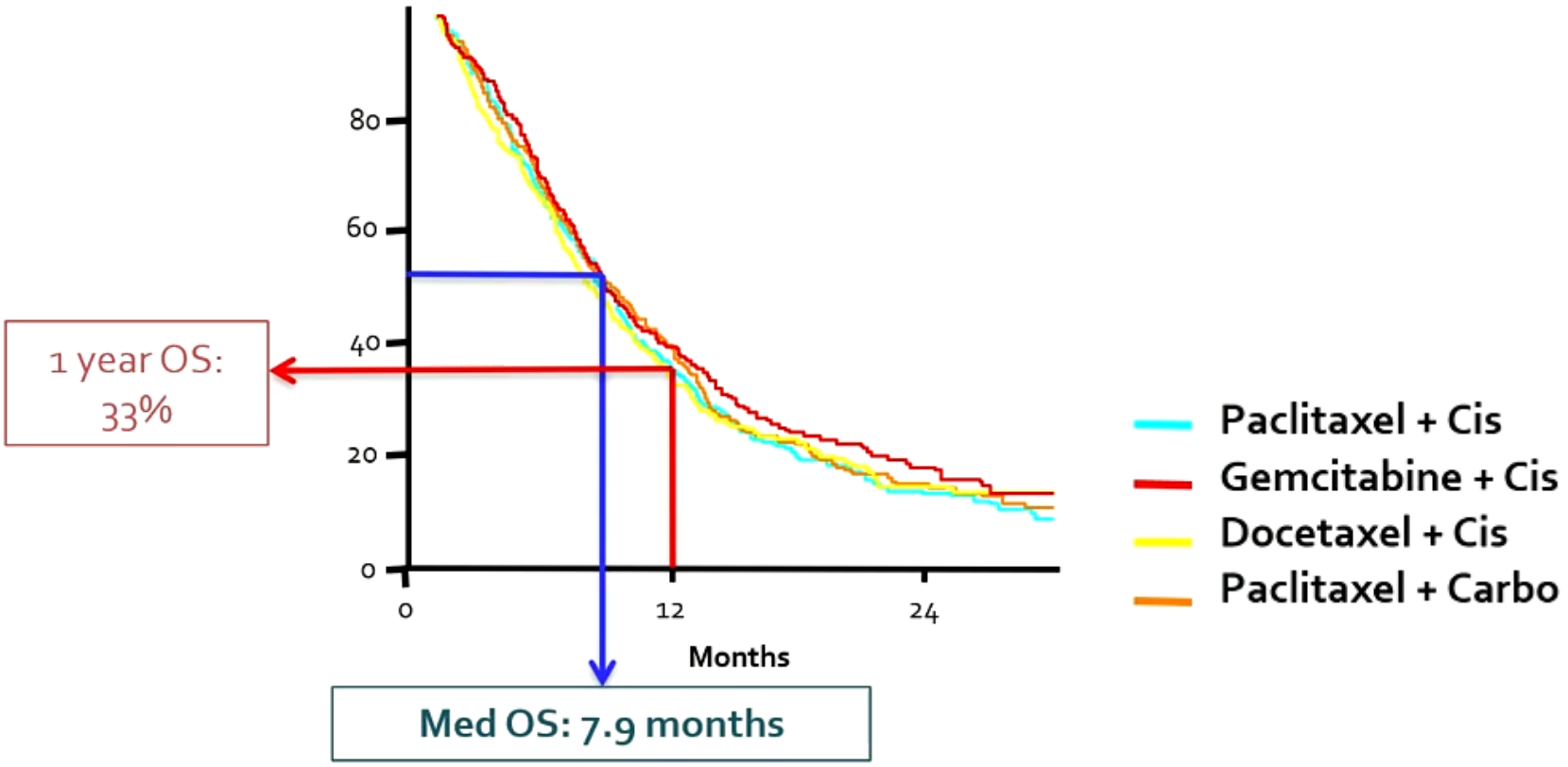
    - Doelgerichte therapie



Chemotherapie bij stadium IV NSCLC



Het tijdperk van immunotherapie

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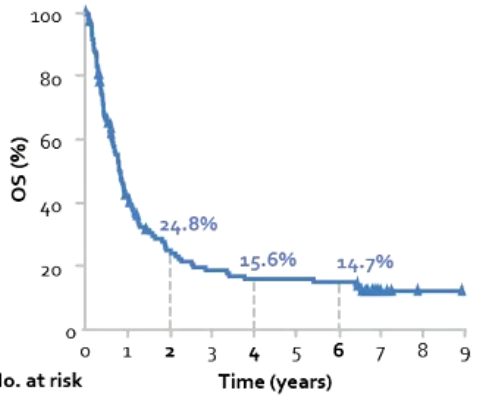
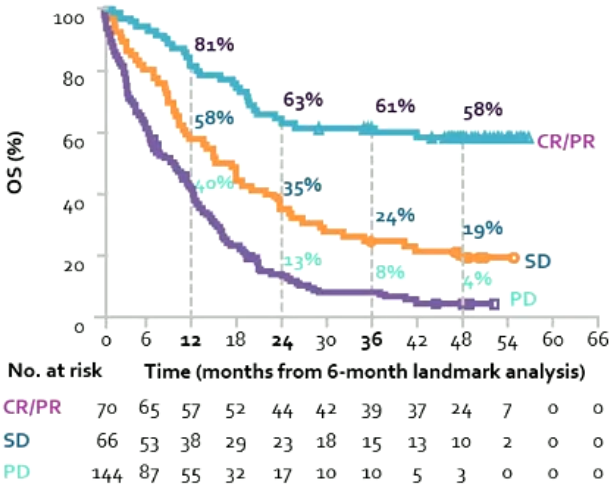
CheckMate 003 (6-year OS) Previously Treated Patients

	NIVO
Median OS (95% CI), mo	9.9 (7.8-12.4)



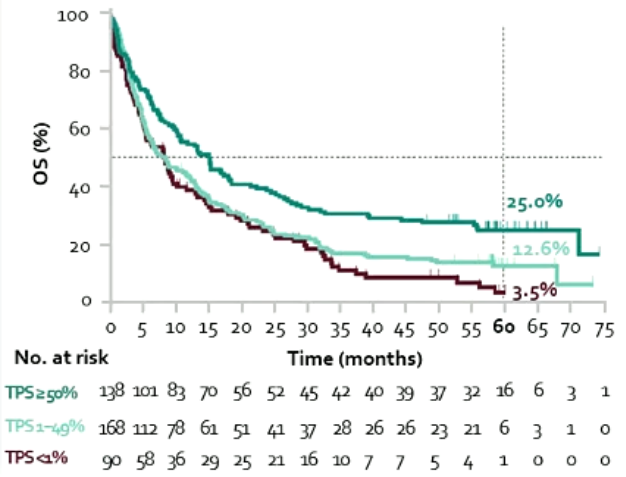
CheckMate 017/057 (4-year OS) Previously Treated Patients

	NIVO		
	CR/PR	SD	PD
Median OS (95% CI), mo	NR (25.6-NR)	16.1 (10.2-23.5)	9.1 (6.2-11.4)
HR vs PD	0.18	0.52	–



Keynote-001 (5-year OS) Previously Treated Patients by PD-L1

	Pembro		
	TPS ≥50%	TPS1–49%	TPS <1%
Median OS (95% CI), mo	15.4 (10.6–18.8)	8.5 (6.0–12.6)	8.6 (5.5–10.6)



Stadium IV niet-kleincellig longcarcinoom

Pembrolizumab versus chemotherapie

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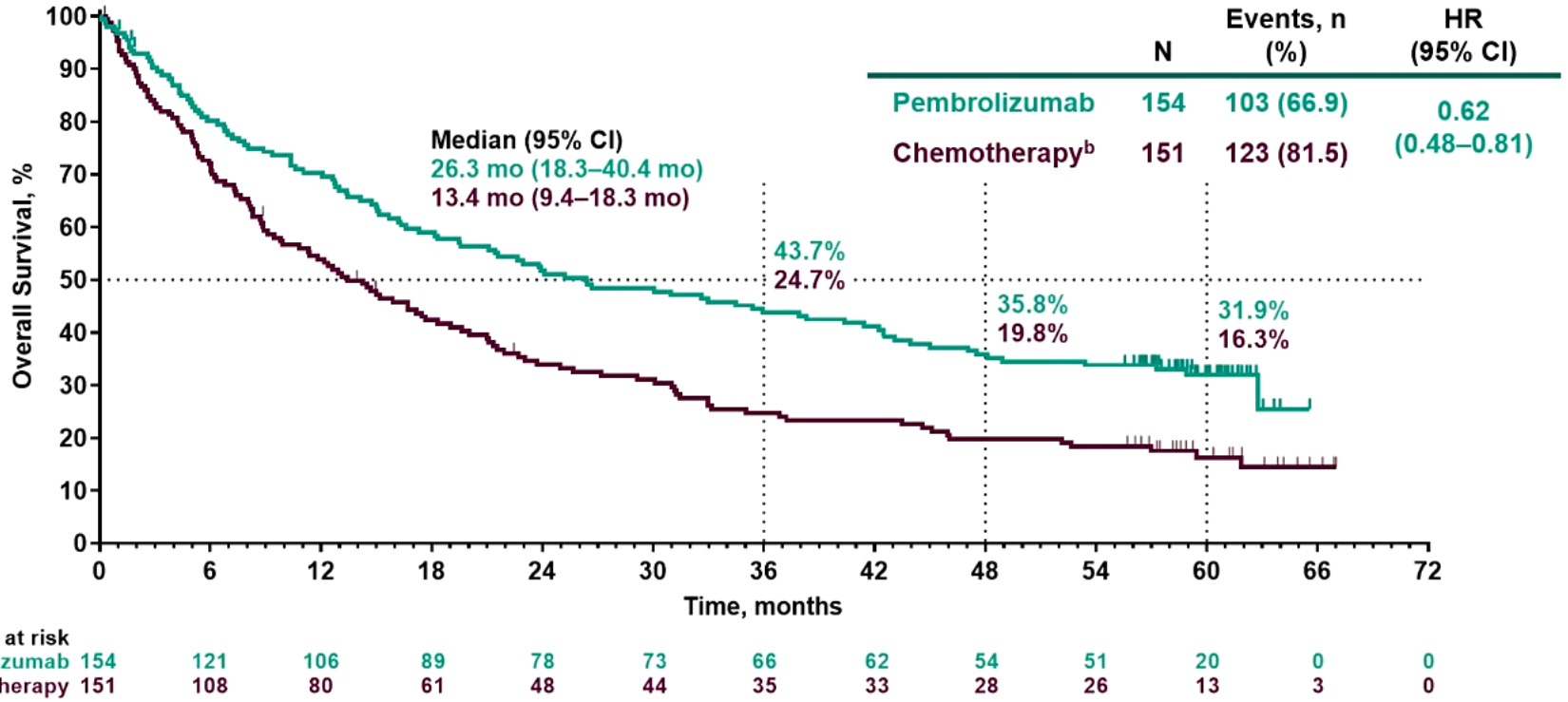
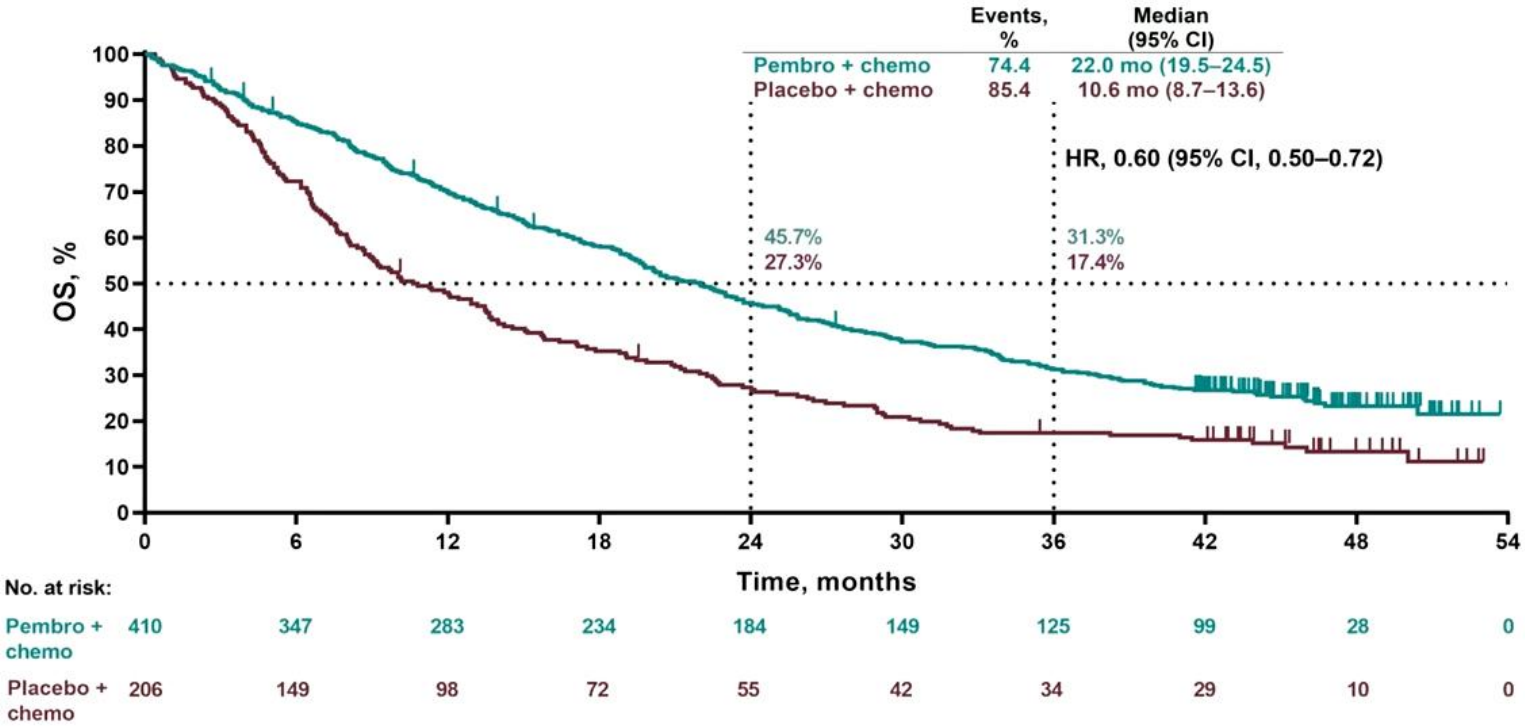
KEYNOTE-024 in PD-L1 ≥50%

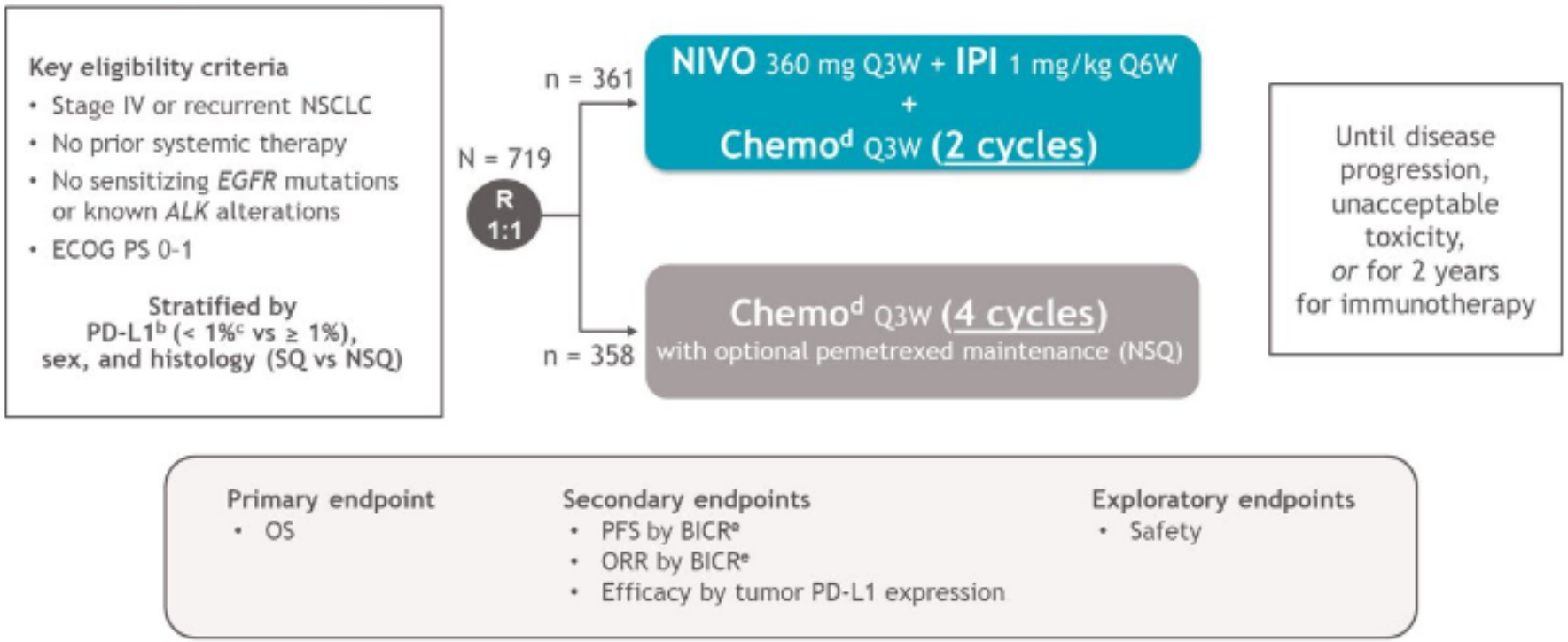


Chemo-immunotherapie

KEYNOTE-189: 4 years update

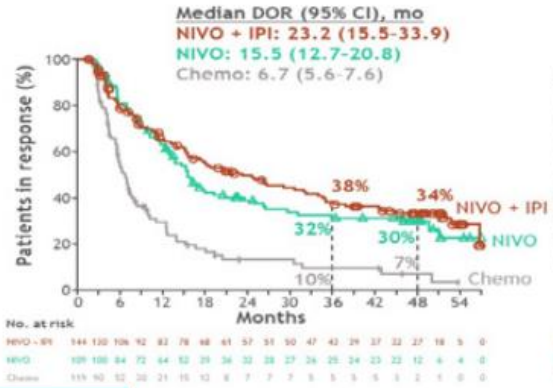


Doublet immunotherapie: Checkmate 9 LA-studie

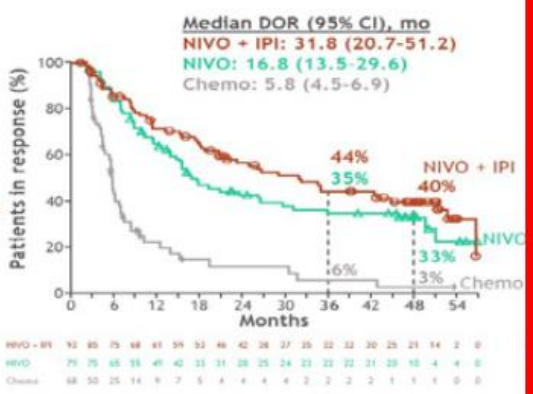


CheckMate 227

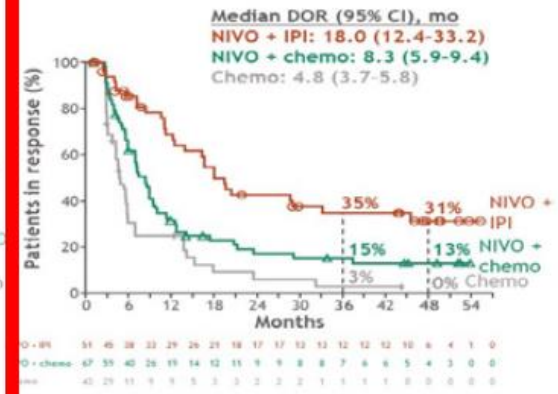
PD-L1 ≥ 1%



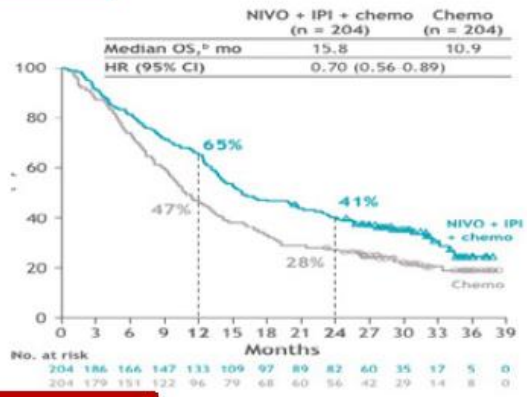
PD-L1 ≥ 50%

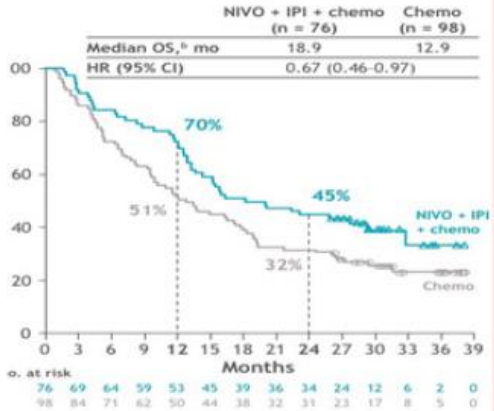


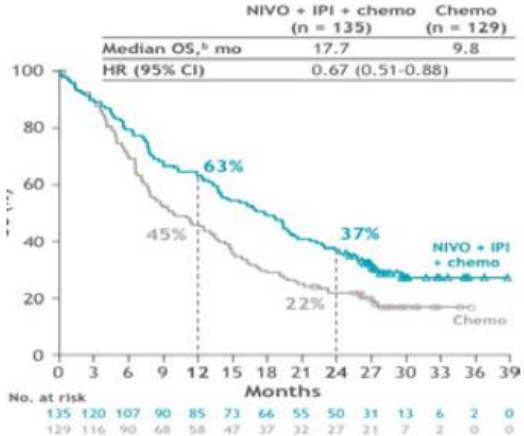
PD-L1 < 1%



CheckMate 9LA



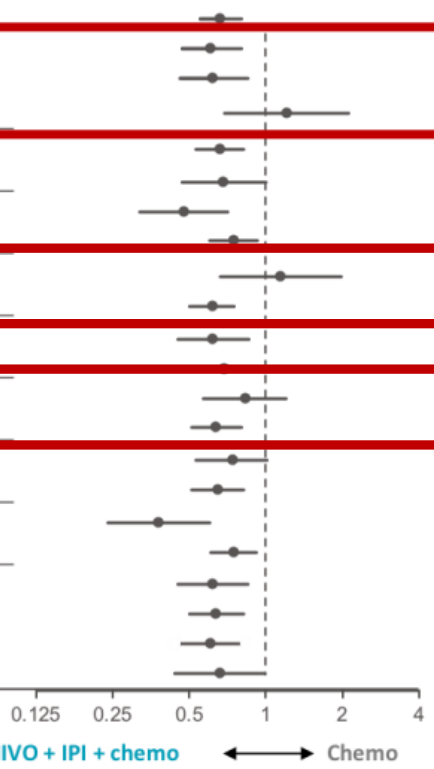




SLIDE COURTESY J REMON

Post-hoc analyse

Subgroup	Median OS, mo		Unstratified HR
	NIVO + IPI + chemo n = 361	Chemo n = 358	
All randomized (N = 719)	15.6	10.9	0.66[a]
< 65 years (n = 354)	15.6	10.7	0.61
65 to < 75 years (n = 295)	19.4	11.9	0.62
≥ 75 years (n = 70)	8.5	11.5	1.21
Male (n = 504)	14.1	9.8	0.66
Female (n = 215)	19.4	15.8	0.68
ECOG PS 0 (n = 225)	NR	15.4	0.48
ECOG PS 1 (n = 492)	13.6	9.7	0.75
Never smoker (n = 98)	14.1	17.8	1.14
Smoker (n = 621)	15.6	10.4	0.62
Squamous (n = 227)	14.5	9.1	0.62
Non-squamous (n = 492)	17.0	11.9	0.69
Liver metastases (n = 154)	10.2	8.1	0.83
No liver metastases (n = 565)	19.4	12.4	0.64
Bone metastases (n = 207)	11.9	8.3	0.74
No bone metastases (n = 512)	20.5	12.4	0.65
CNS metastases (n = 122)	NR	7.9	0.38
No CNS metastases (n = 597)	15.4	11.8	0.75
PD-L1 < 1% (n = 264)	16.8	9.8	0.62
PD-L1 ≥ 1% (n = 407)	15.8	10.9	0.64
PD-L1 1–49% (n = 233)	15.4	10.4	0.61
PD-L1 ≥ 50% (n = 174)	18.0	12.6	0.66



Minimum follow-up: 12.7 months.

[a]Stratified HR; unstratified HR was 0.67 (95% CI, 0.55–0.81).

Reck M *et al.* ASCO 2020.

Doublet immunotherapie

- Effectiviteit onafhankelijk van PD-L1 status.

- Bij PD-L1 positieve tumoren is het effect vergelijkbaar met de huidige standaard behandeling.

- Pittige behandeling: meer bijwerkingen dan mono therapie.
- Percentage dat stopt < 20%
- Mortaliteitspercentage ongeveer 2%.

- Behandeling lijkt niet geschikt voor:
  - > 75 jaar
  - Niet rokers
  - Levermetastasen

- Kosten: 15.089,94 euro per 6 weken (zonder chemotherapie)
  261.558,96 euro voor 2 jaar

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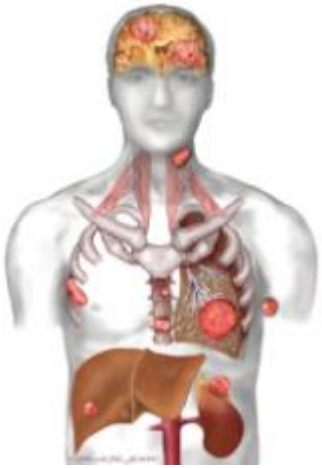
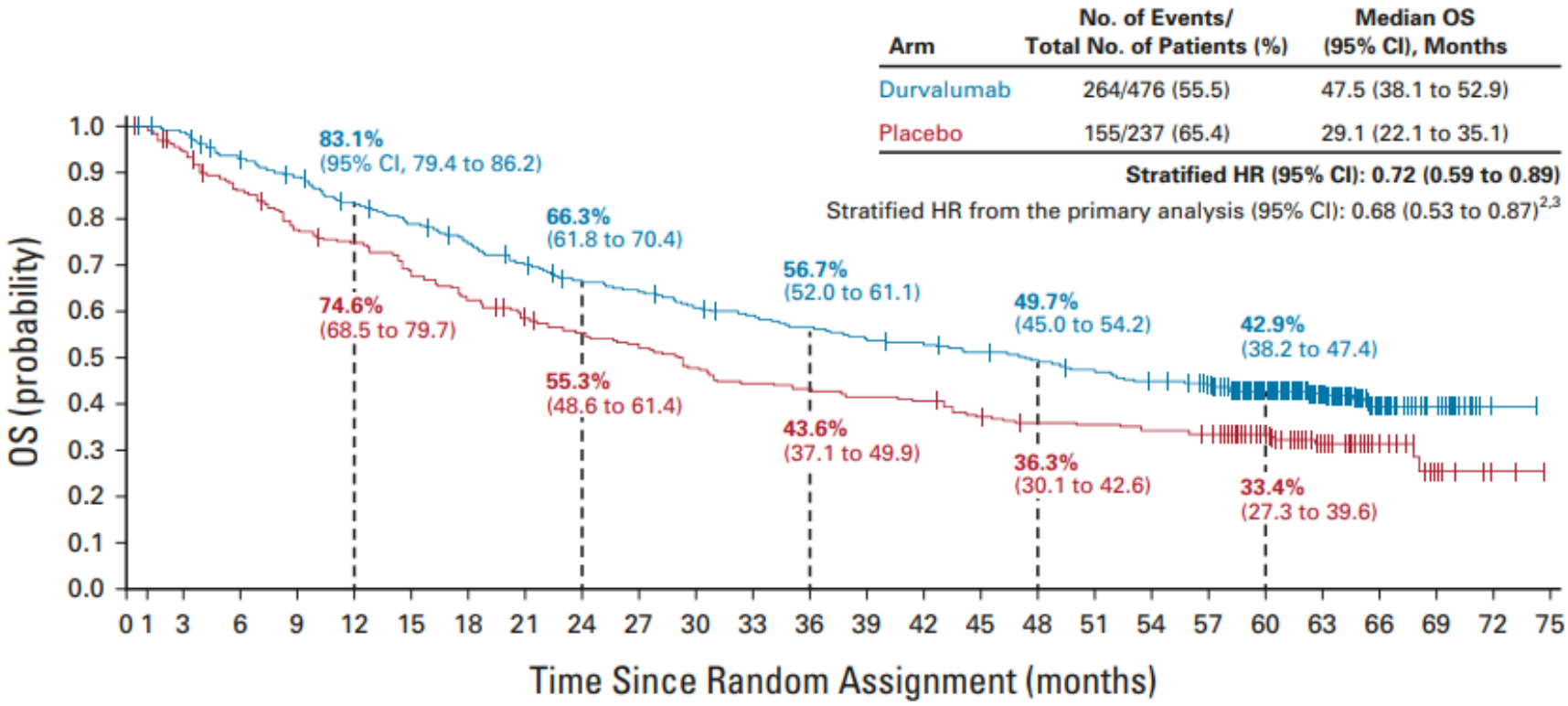


5 jaars overleving na adjuvant durvalumab

5 year OS 43% vs 33%

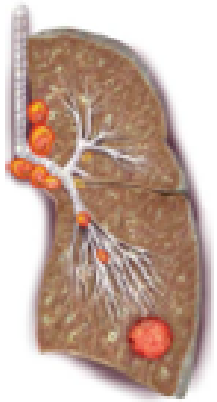
5 year PFS 33% vs 19%



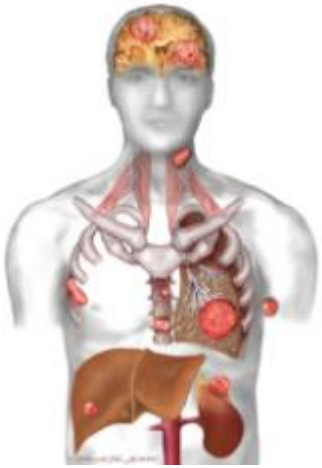
Behandeling niet-kleincellig longcarcinoom

- Stadium I (II)
  - Chirurgie
  - Stereotactische radiotherapie
  - Evt adjuvant chemotherapie
  - **Evt adjuvant immunotherapie: PD-L1 > 50%**

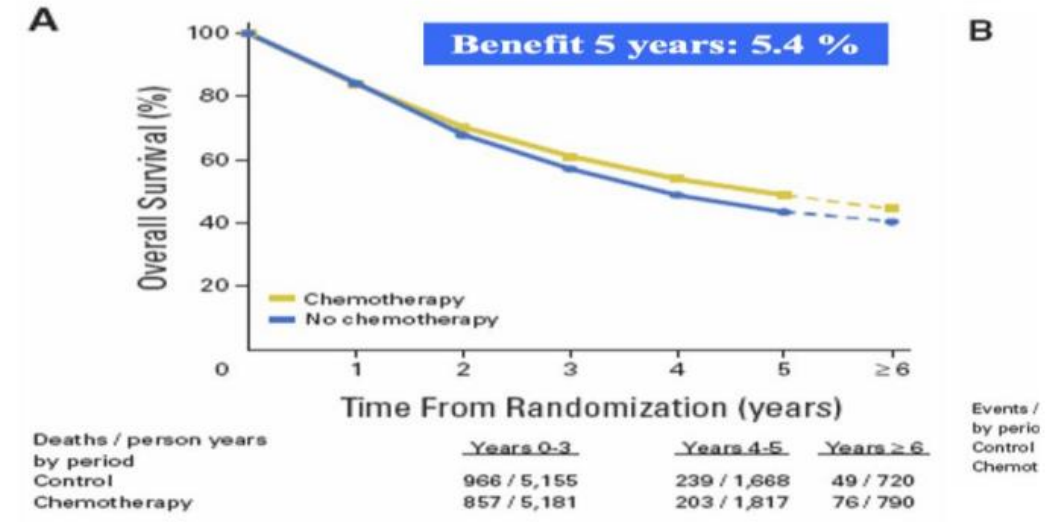
- Stadium III
  - Radiotherapie + chemotherapie
  - Adjuvant immunotherapie



- Stadium IV
  - Systeemtherapie
    - Chemotherapie
    - Immunotherapie
    - Doelgerichte therapie



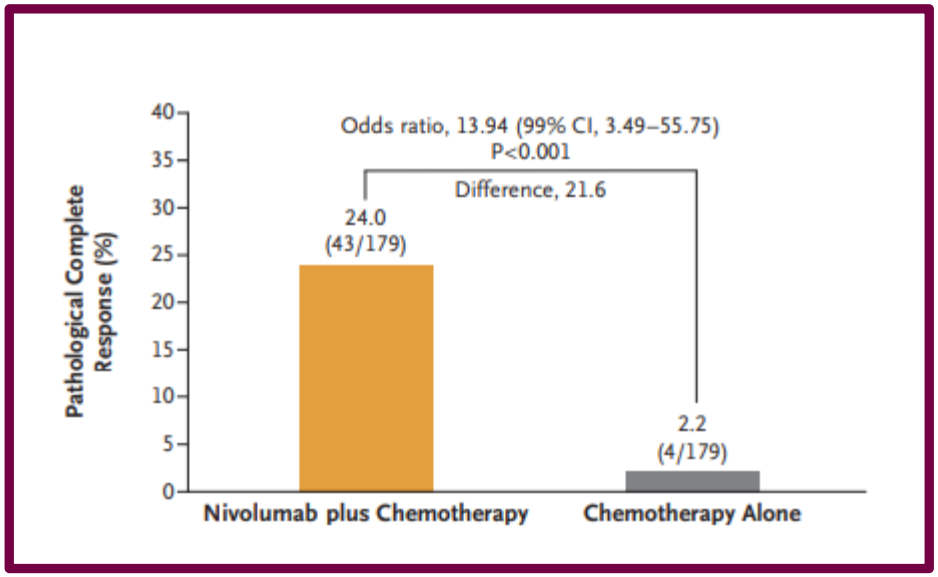
Longkanker na resectie: where do we come from?

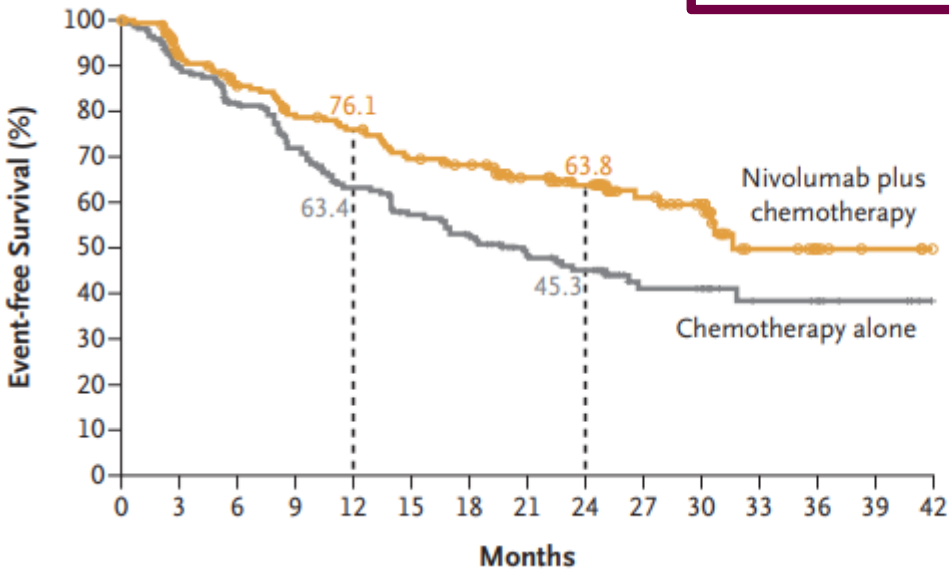


Pignon JP. J Clin Oncol 2008

Proposed	Events / N	MST	24 Month	60 Month
IB	560 / 1928	NR	87%	68%
IIA	215 / 585	NR	79%	60%
IIB	605 / 1453	66.0	72%	53%
IIIA	2052 / 3200	29.3	55%	36%

Neo-adjuvante behandeling CheckMate 816



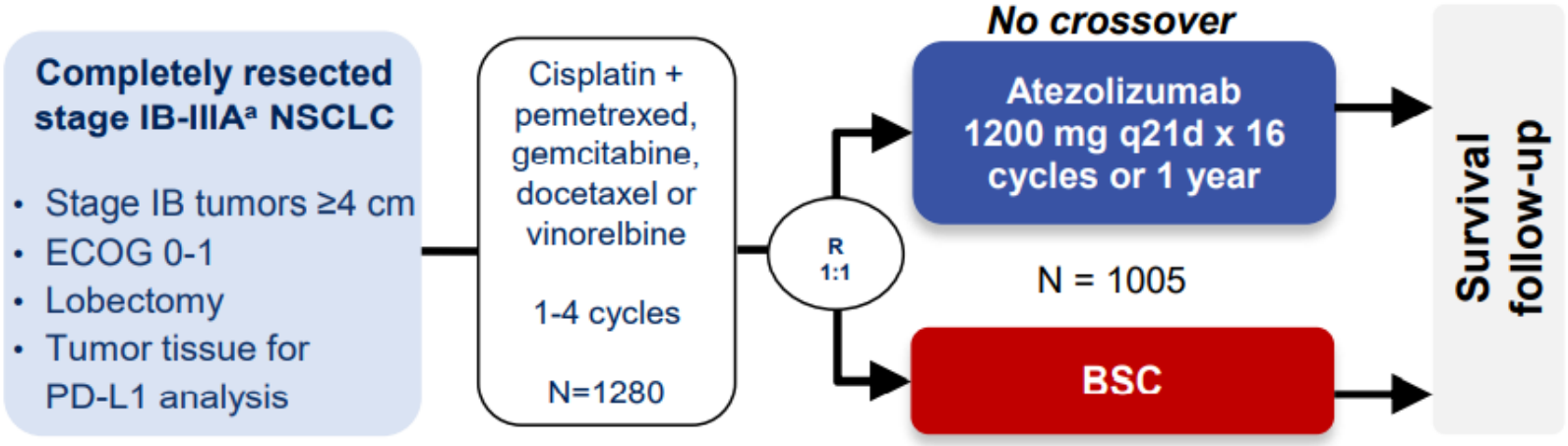


	No. of Patients	Median Event-free Survival (95% CI) *mo*
Nivolumab plus Chemotherapy	179	31.6 (30.2–NR)
Chemotherapy Alone	179	20.8 (14.0–26.7)

Hazard ratio for disease progression, disease recurrence, or death, 0.63 (97.38% CI, 0.43–0.91)
P=0.005

Adjuvant atezolizumab after adjuvant chemotherapy in resected stage IB–IIIA non-small-cell lung cancer (IMpower010): a randomised, multicentre, open-label, phase 3 trial

*Enriqueta Felip, Nasser Altorki, Caicun Zhou, Tibor Csőszi, Ihor Vynnychenko, Oleksandr Goloborodko, Alexander Luft, Andrey Akopov, Alex Martinez-Marti, Hirotsugu Kenmotsu, Yuh-Min Chen, Antonio Chella, Shunichi Sugawara, David Voong, Fan Wu, Jing Yi, Yu Deng, Mark McCleland, Elizabeth Bennett, Barbara Gitlitz, Heather Wakelee, for the IMpower010 Investigators**



Stratification factors

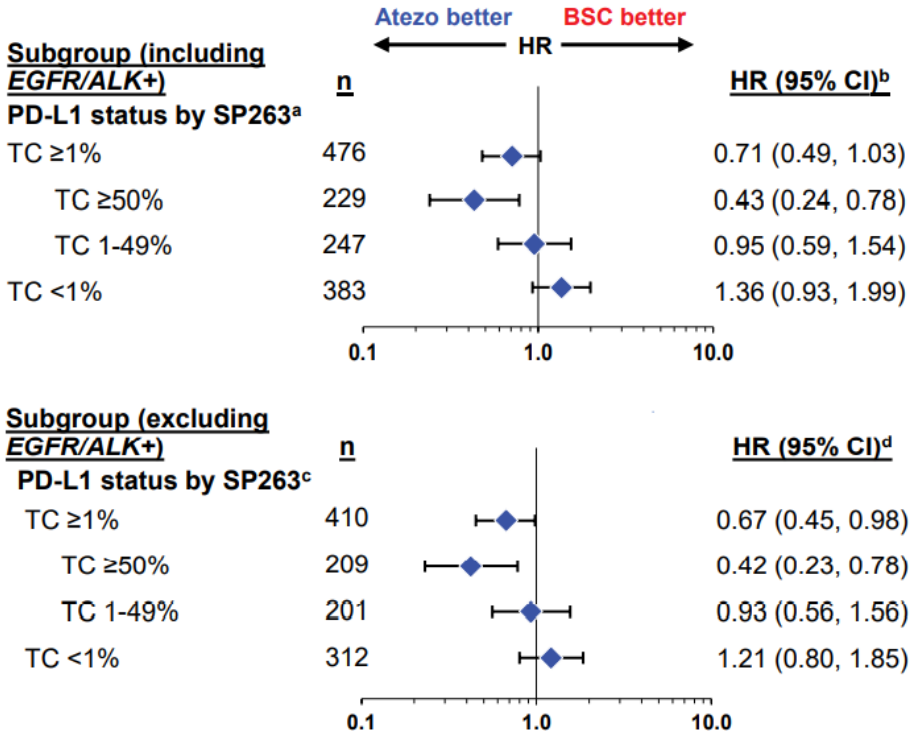
- Sex | Stage | Histology | PD-L1 status

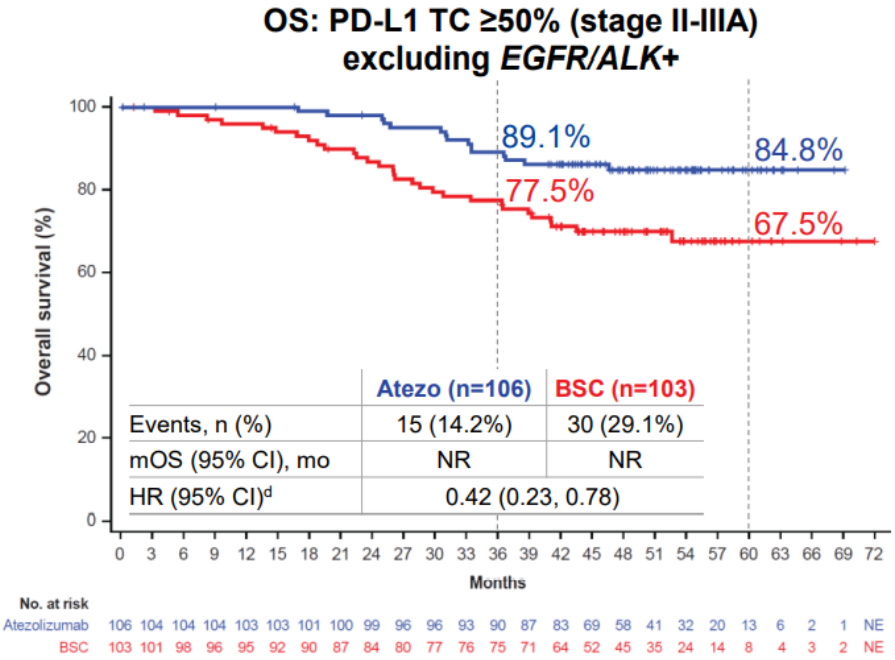
Primary endpoint

- Investigator-assessed DFS tested hierarchically

Key secondary endpoints

- OS in ITT | DFS in PD-L1 TC ≥50% | 3-yr and 5-year DFS


Atezo better
BSC better
HR
Subgroup (including EGFR/ALK+)
n
HR (95% CI)b
PD-L1 status by SP263a
TC ≥1% 476 0.71 (0.49, 1.03)
TC ≥50% 229 0.43 (0.24, 0.78)
TC 1-49% 247 0.95 (0.59, 1.54)
TC <1% 383 1.36 (0.93, 1.99)
0.1
1.0
10.0
Subgroup (excluding EGFR/ALK+)
n
HR (95% CI)d
PD-L1 status by SP263c
TC ≥1% 410 0.67 (0.45, 0.98)
TC ≥50% 209 0.42 (0.23, 0.78)
TC 1-49% 201 0.93 (0.56, 1.56)
TC <1% 312 1.21 (0.80, 1.85)
0.1
1.0
10.0


OS: PD-L1 TC ≥50% (stage II-IIIA) excluding EGFR/ALK+
Overall survival (%)
100
80
60
40
20
0
89.1%
84.8%
77.5%
67.5%
Atezo (n=106)
BSC (n=103)
Events, n (%) 15 (14.2%) 30 (29.1%)
mOS (95% CI), mo NR NR
HR (95% CI)d 0.42 (0.23, 0.78)
0 3 6 9 12 15 18 21 24 27 30 33 36 39 42 45 48 51 54 57 60 63 66 69 72
Months
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

Veiligheid

- 11% behandelingsgerelateerde graad 3-4 bijwerkingen.
- 8% immuungemedieerde bijwerkingen graad 3-4
  - Hepatitis
  - Huiduitslag
- 1% graad 5 bijwerkingen (myocarditis, pneumonitis, orgaanfalen en AML)
- 18% gestopt met behandeling.
- 12% met steroïden behandeld voor immuungerelateerde bijwerkingen.

Aandachtspunten

Kosten:

- Atezolizumab kost per 3 weken 4.032,99 euro.

- De totale medicatiekosten bij 1 jaar behandeling: 64.528 euro

Nederlandse praktijk:

- 40% stadium IIIA ziekte → chemoradiatie

Take home messages

- Immunotherapie heeft de 5 jaars overleving verbeterd bij stadium IV NSCLC

- Combinatie immunotherapie (nivolumab + ipilimumab):
  - Jonger dan 75 jaar
  - Rookvoorgeschiedenis
  - Zonder levermetastasen
  - PD-L1 < 1%

- Overlevingswinst van 10% na 5 jaar voor stadium III tumoren met adjuvant durvalumab.

- Atezolizumab geregistreerd voor stadium II of IIIA na resectie met PD-L1 status 50% of hoger (zonder EGFR of ALK mutatie)