Belang van predictief testen bij vroeg stadium longkanker

Oncologie update 2022

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Disclosures

Interest	Company/organisation
Grants/research support	Roche, Boehringer Ingelheim, AstraZeneca, Takeda (institution), BeiGene under negotiation
Honoraria or consultation fees	Advisory boards: BMS, Roche, Boehringer Ingelheim, Lilly, Takeda, Amgen, Pfizer, MSD, Janssen, Novartis, Merck (all institution, Roche also once self)
Participation in a company sponsored bureau	Not applicable
Stock shareholder	Not applicable
Spouse/partner	Not applicable
Other support/potential conflict of interest	Interviews for Roche, Lilly, Bayer (institution), mentorship program with key opinion leaders funded by AstraZeneca; PI pharma studies AstraZeneca, GSK, Novartis, Merck Serono, Roche, Takeda, Blueprint Medicines, Mirati, Janssen, Abbvie, Gilead (all institution); travel support Roche, BMS (self); speaker educationals for MSD, Lilly, Bayer, AstraZeneca (institution); webinars Medtalks, Benecke, VJOncology (self), high5oncology (institution); member Dutch guideline brain metastases from solid tumors, NSCLC and

Inhoud

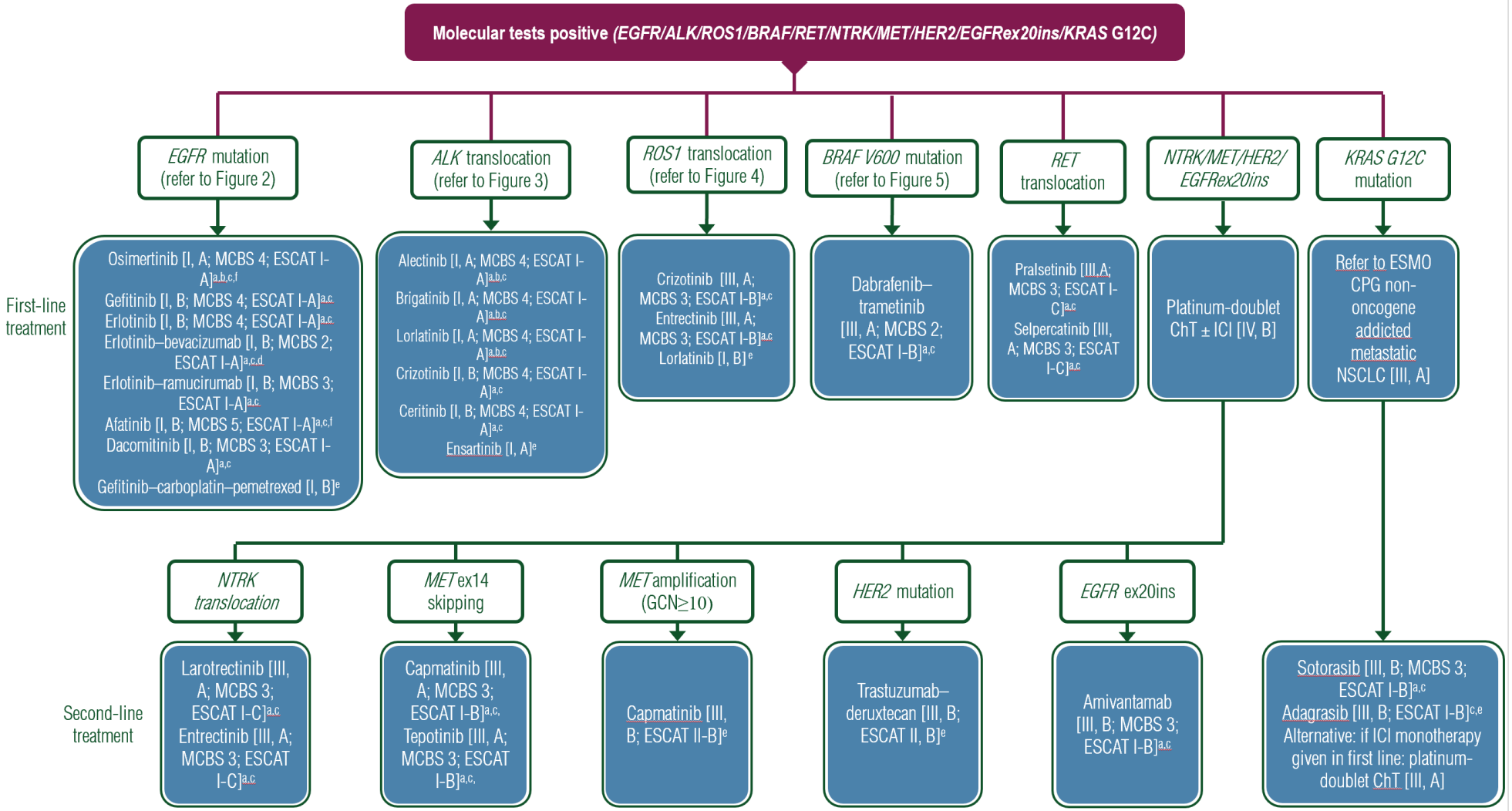
Een stapje terug: biomarker testing in stadium IV NSCLC

Neoadjuvant – adjuvant immuno en TKI:

- Wat was er?
- Wat is er?
- Toekomst

Take home messages

ESMO 2022 richtlijn stad IV NSCLC oncogene addicted (submitted)



10 drivers die getest moeten worden

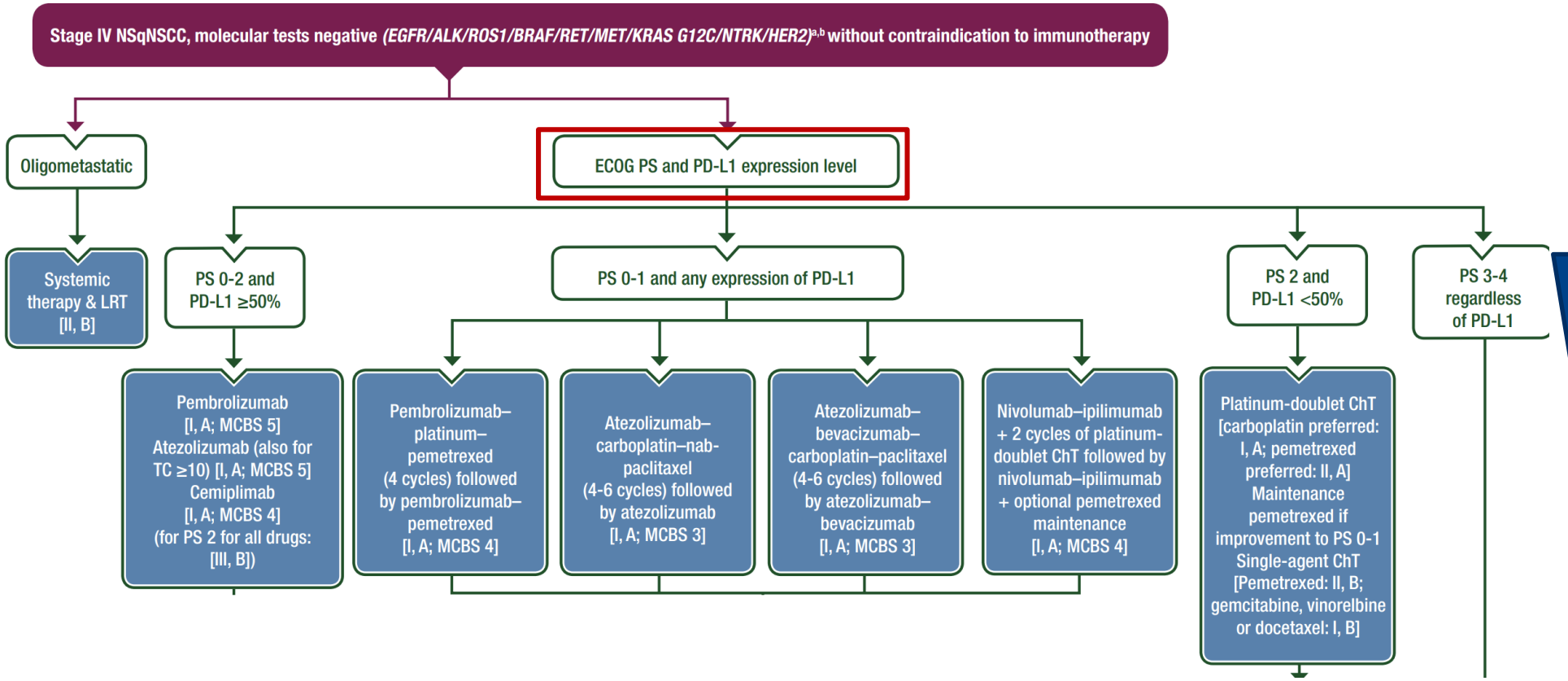
ORR vaak > 50%

Meestal lange DoR

4-jaars OS 30-70%

Hendriks Ann Oncol (submitted); Ramalingam NEJM 2019; Mok Ann Oncol 2020; Planchard ASCO 2020; Shaw Ann Oncol 2019

ESMO 2022 richtlijn stad IV NSCLC non-oncogene addicted (submitted)



PD-L1 belangrijk

5-jaar OS

PD-L1 ≥50%: ±23-30%

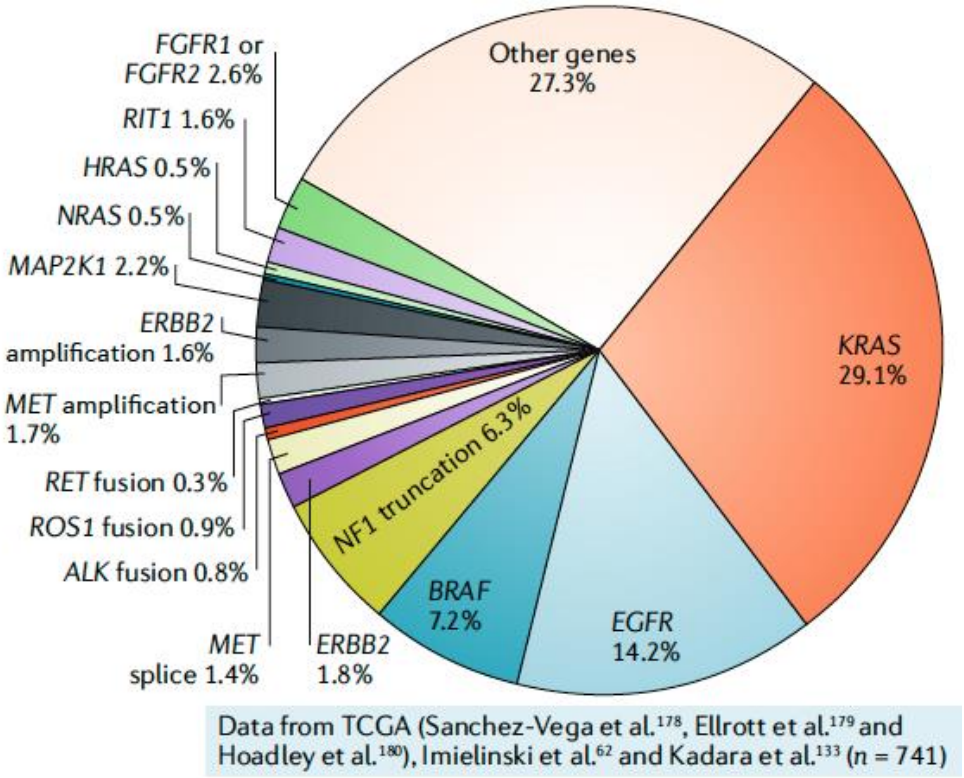
PD-L1 1-49%: ±20%

PD-L1<1%: ±10-19%

Hendriks Ann Oncol (submitted); Brahmer JCO 2022; Garassino ESMO 2022; Novello ESMO 2022

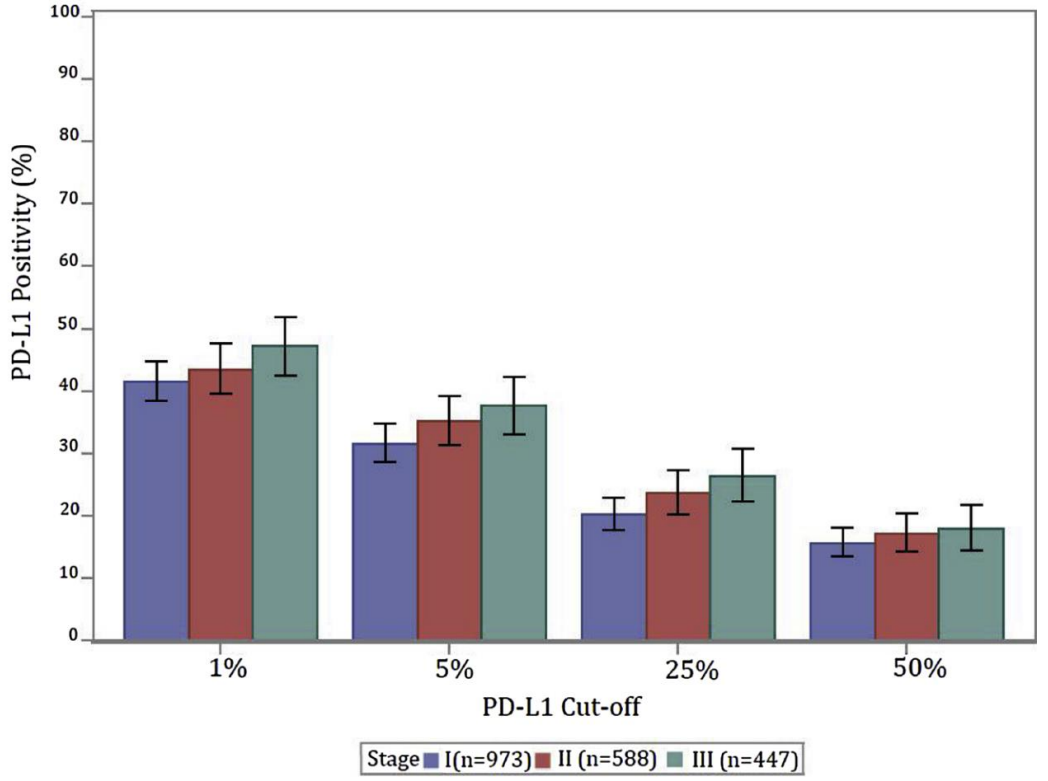
Wat weten we van biomarkers in vroeg stadium NSCLC?

Oncogene drivers



Data from TCGA (Sanchez-Vega et al.[178], Ellrott et al.[179] and Hoadley et al.[180]), Imielinski et al.[62] and Kadara et al.[133] (n = 741)

PD-L1



Discussie of oncogene drivers of PD-L1 positiviteit geassocieerd zijn met slechtere DFS/OS

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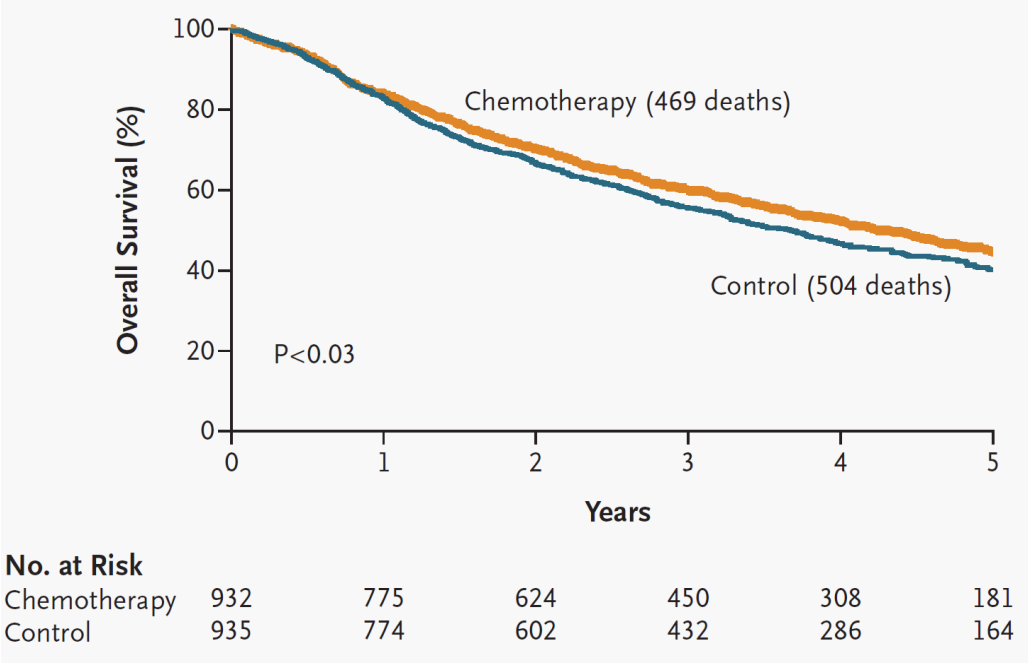
Skoulidis Nature Rev Cancer 2019; Mordant Clin Lung Cancer 2022; Zenke ASCO 2020; Kerr Lung Cancer 2019; Gallina Cancers 2022

Tot voor kort deden we hier niets mee……

SoC = chemo
+5% OS @5jaar met toevoegen chemo



TNM8: <70% 5jaar OS vanaf stad

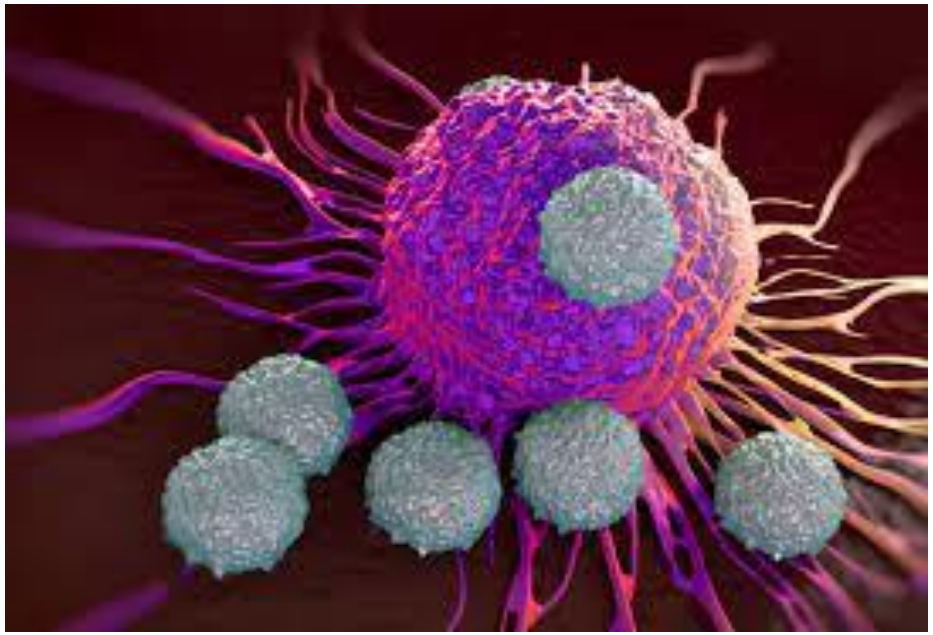
Proposed	Events / N	MST	24 Month	60 Month
IA1	68 / 781	NR	97%	92%
IA2	505 / 3105	NR	94%	83%
IA3	546 / 2417	NR	90%	77%
IB	560 / 1928	NR	87%	68%
IIA	215 / 585	NR	79%	60%
IIB	605 / 1453	66.0	72%	53%
IIIA	2052 / 3200	29.3	55%	36%

Mage-A3 / gefitinib / beva geen baat

Merendeel recidief op afstand, systemische controle nodig

Goldstraw JTO 2015 * NSCLC MA Collaborative group – Lancet 2010 & Lancet 2014 * Wu – JTO 2022 * La Monica – J Exp Clin Cancer Res 2019

Immunotherapie data



IMpower010: de eerste adjuvante fase III met

Geen exclusie drivers

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

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

Cisplatin + pemetrexed, gemcitabine, docetaxel or vinorelbine

1-4 cycles

N=1280

R 1:1

No crossover

Atezolizumab 1200 mg q21d 16 cycles

N=1005

BSC

Survival follow-up

Stratification factors

- Male/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:
  - PD-L1 TC ≥1% (per SP263) stage II-IIIA population
  - All-randomized stage II-IIIA population
  - ITT population (stage IB-IIIA)

Key secondary endpoints

- OS in ITT population
- DFS in PD-L1 TC ≥50% (per SP263) stage II-IIIA population
- 3-y and 5-y DFS in all 3 populations

Hierarchical statistical testing of endpoints

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 (stage IB-IIIA)[b]

If positive:

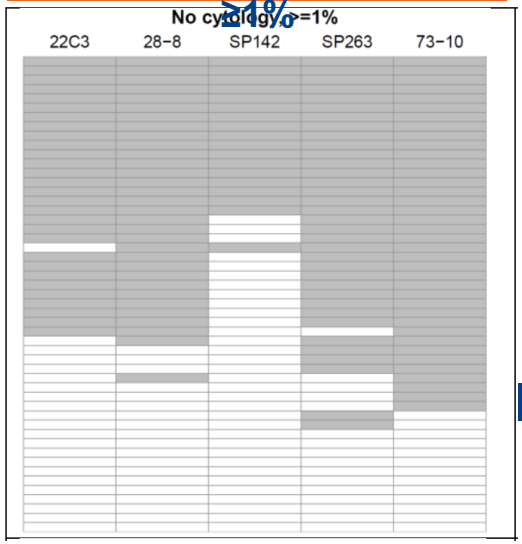
OS in ITT population[b]

Endpoint was met at DFS IA

Endpoint was not met at DFS IA and follow up is ongoing

Endpoint was not formally tested

SP142 and SP263 concordantie voor PD-L1 ≥1%



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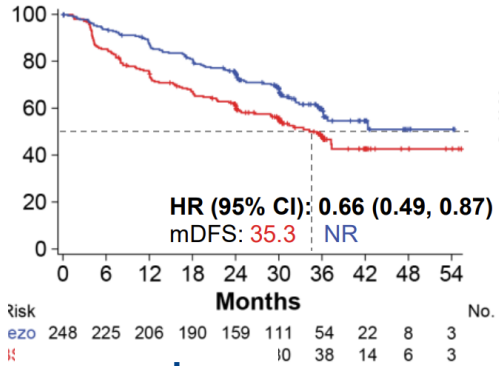
Wakelee Lancet 2021; Tsao JTO 2018

IMpower010 – uitkomsten in relatie tot PD-L1 en EGFR/ALK

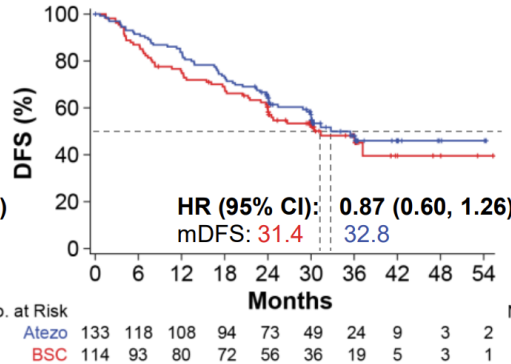
DFS

Incl EGFR/ALK

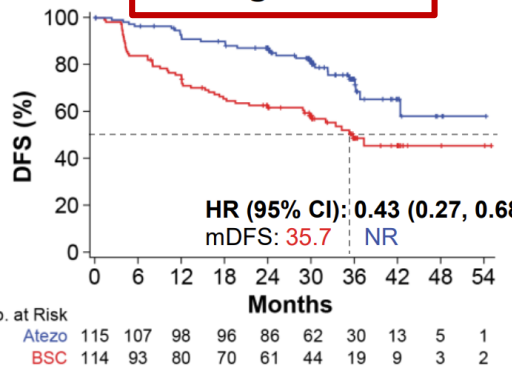
PD-L1 TC ≥1% stage II-IIIA



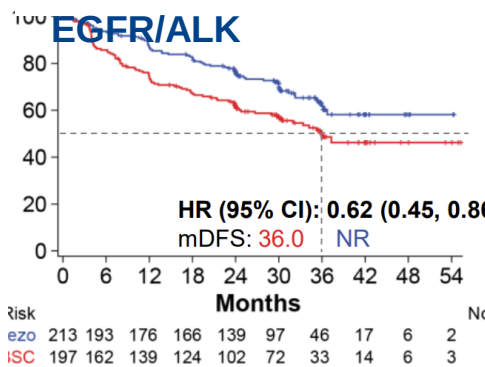
PD-L1 TC 1%-49% stage II-IIIA

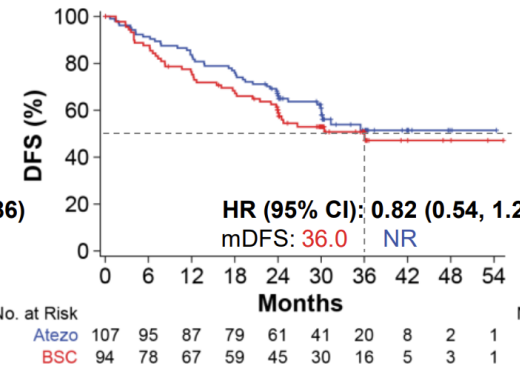


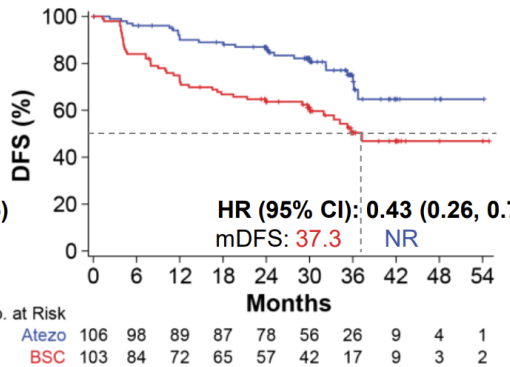
PD-L1 TC ≥50% stage II-IIIA



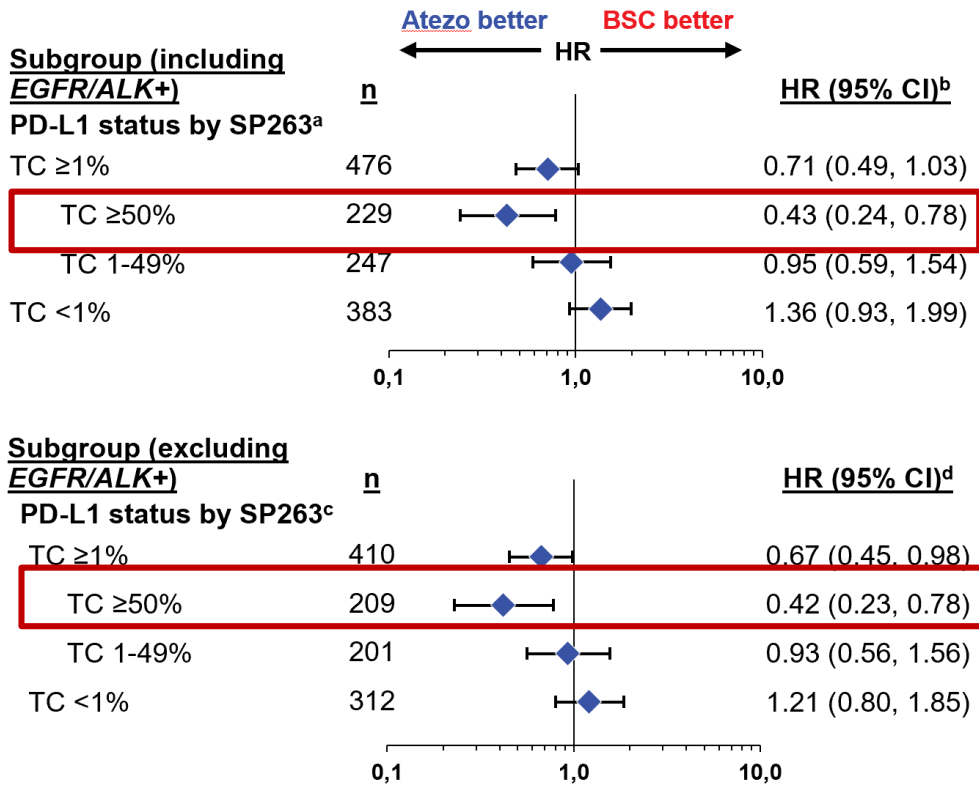
excl EGFR/ALK







OS

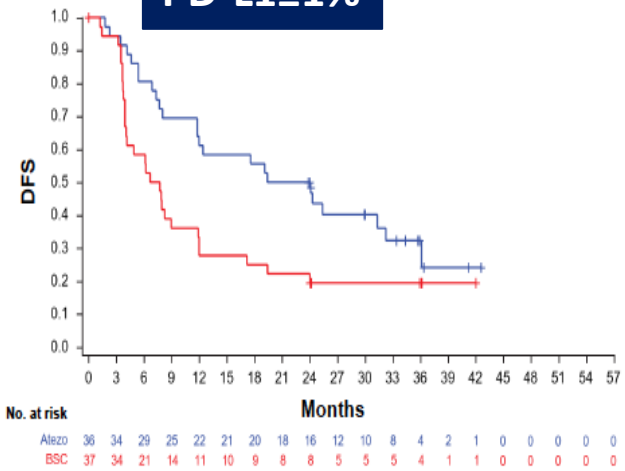


Kunnen we in toekomst ctDNA gebruiken of wint PD-L1? IMpower010 data

MERMAID-1 & 2: ICI in MRD+ (tumor-informed) early stage NSCLC

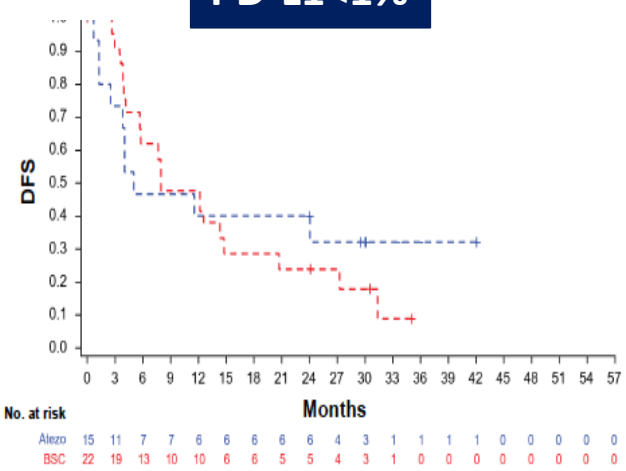
DFS ctDNA+ stad II/IIIA

PD-L1≥1%



ctDNA+	PD-L1 TC ≥1%	
	Atezo (n=36)	BSC (n=37)
mDFS, mo	21.8	7.2
HR (95% CI)	0.54 (0.31, 0.93)	

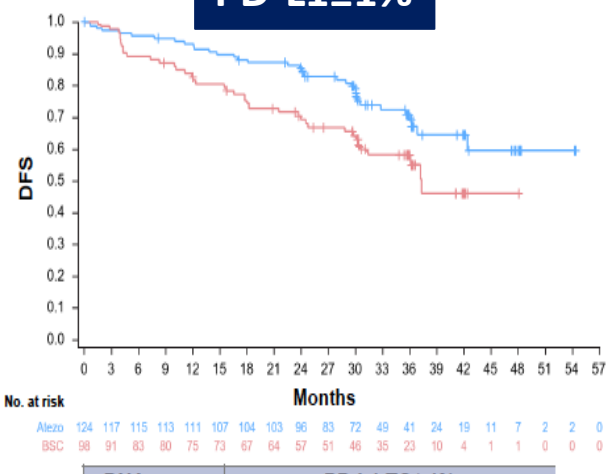
PD-L1<1%



ctDNA+	PD-L1 TC <1%	
	Atezo (n=15)	BSC (n=22)
mDFS, mo	5.1	8.0
HR (95% CI)	0.88 (0.40, 1.91)	

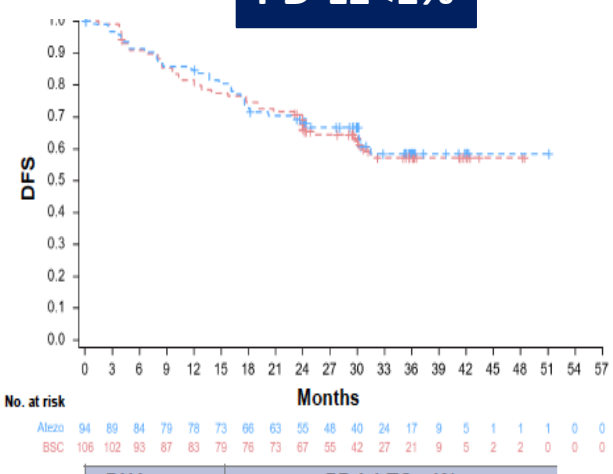
DFS ctDNA- stad II/IIIA

PD-L1≥1%



ctDNA–	PD-L1 TC ≥1%	
	Atezo (n=124)	BSC (n=98)
mDFS, mo	NR	37.3
HR (95% CI)	0.57 (0.36, 0.90)	

PD-L1<1%



ctDNA–	PD-L1 TC <1%	
	Atezo (n=94)	BSC (n=106)
mDFS, mo	NR	NR
HR (95% CI)	0.95 (0.60, 1.50)	

Zhou – ESMO IO 2021

SLIDE COURTESY J REMON, modified

KEYNOTE 091/PEARLS adjuvante fase III

Eligibility for Registration
- Confirmed stage IB (T ≥4 cm), II, or IIIA NSCLC per AJCC v7
- Complete surgical resection with negative margins (R0)
- Provision of tumor tissue for PD-L1 testing

PD-L1 testing
done centrally using PD-L1 IHC 22C3 pharmDx

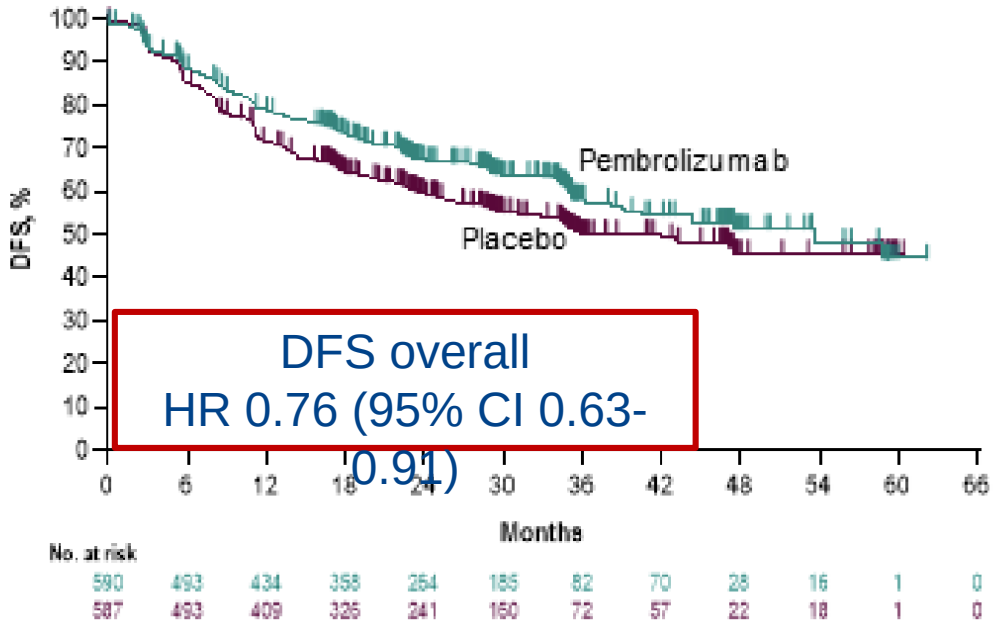
Eligibility for Randomization
- No evidence of disease
- ECOG PS 0 or 1
- Adjuvant chemotherapy
  - Considered for stage IB (T ≥4 cm) disease
  - Strongly recommended for stage II and IIIA disease
  - Limited to ≤4 cycles

R 1:1

Pembrolizumab 200 mg Q3W for ≤18 administrations (~1 yr)

Placebo Q3W for ≤18 administrations (~1 yr)

Geen exclusie



DFS overall
HR 0.76 (95% CI 0.63-0.91)

Primaire eindpunten
- DFS overall
- DFS in PD-L1 ≥50%

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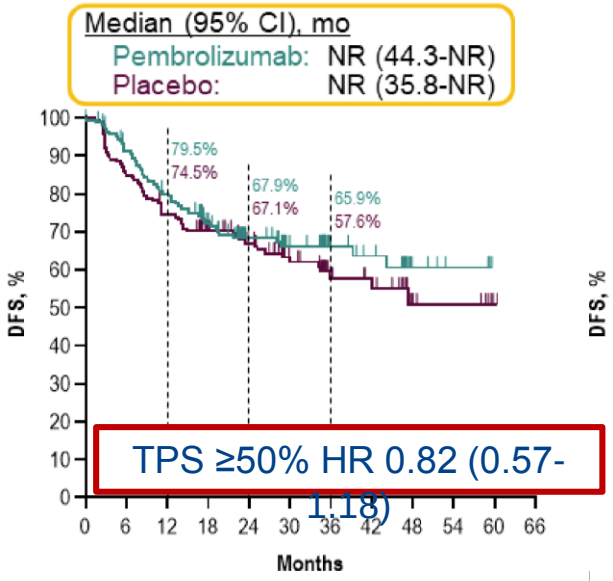
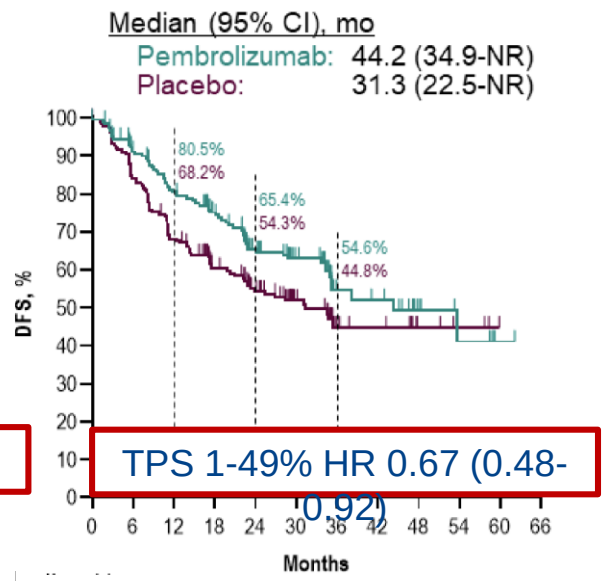
O'Brien Lancet Oncol 2022

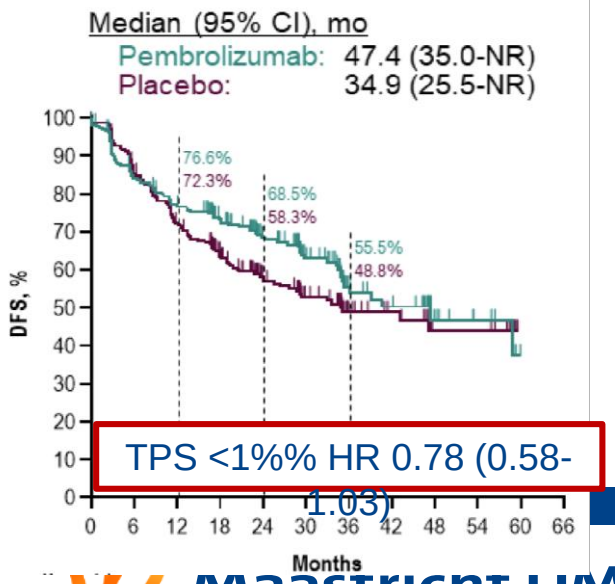
KEYNOTE 091/PEARLS DFS in relatie tot PD-L1 & andere subgroepen



TPS ≥50% HR 0.82 (0.57-1.18)



TPS 1-49% HR 0.67 (0.48-0.92)



TPS <1%% HR 0.78 (0.58-1.03)

	Events/participants		Hazard ratio (95% CI)
	Pembrolizumab	Placebo	
Age, years			
<65	94/285	119/273	0·73 (0·56–0·96)
≥65	118/305	141/314	0·84 (0·66–1·07)
Sex			
Female	71/189	87/184	0·73 (0·54–1·00)
Male	141/401	173/403	0·81 (0·65–1·01)
Geographical region			
Asia	44/106	52/105	0·74 (0·49–1·10)
Eastern Europe	42/116	48/113	0·84 (0·56–1·27)
Western Europe	109/303	136/301	0·77 (0·60–1·00)
Rest of the world	17/65	24/68	0·74 (0·40–1·39)
Race			
White	156/450	192/455	0·82 (0·66–1·01)
All others†	49/118	58/113	0·71 (0·48–1·04)
ECOG performance status score			
0	138/380	150/343	0·78 (0·62–0·99)
1	74/210	110/244	0·79 (0·59–1·06)
Smoking status			
Current	15/75	38/90	0·42 (0·23–0·77)
Former	155/428	185/431	0·84 (0·68–1·04)
Never	42/87	37/66	0·72 (0·47–1·13)
Disease stage			
IB	21/84	25/85	0·76 (0·43–1·37)
II	102/329	144/338	0·70 (0·55–0·91)
IIIA	89/177	89/162	0·92 (0·69–1·24)
Received adjuvant chemotherapy			
No	35/84	29/83	1·25 (0·76–2·05)
Yes	177/506	231/504	0·73 (0·60–0·89)
Histology			
Non-squamous	146/398	184/363	0·67 (0·54–0·83)
Squamous	66/192	76/224	1·04 (0·75–1·45)
PD-L1 TPS			
<1%	89/233	106/232	0·78 (0·58–1·03)*
1–49%	69/189	91/190	0·67 (0·48–0·92)*
≥50%	54/168	63/165	0·82 (0·57–1·18)*
***EGFR* mutation**			
No	84/218	102/216	0·78 (0·59–1·05)
Yes	18/39	22/34	0·44 (0·23–0·84)
Unknown	110/333	136/337	0·82 (0·63–1·05)
Overall population	212/590	266/587	0·76 (0·63–0·91)*

0·2 0·5 1·0 2·0 5·0

Favours pembrolizumab Favours placebo

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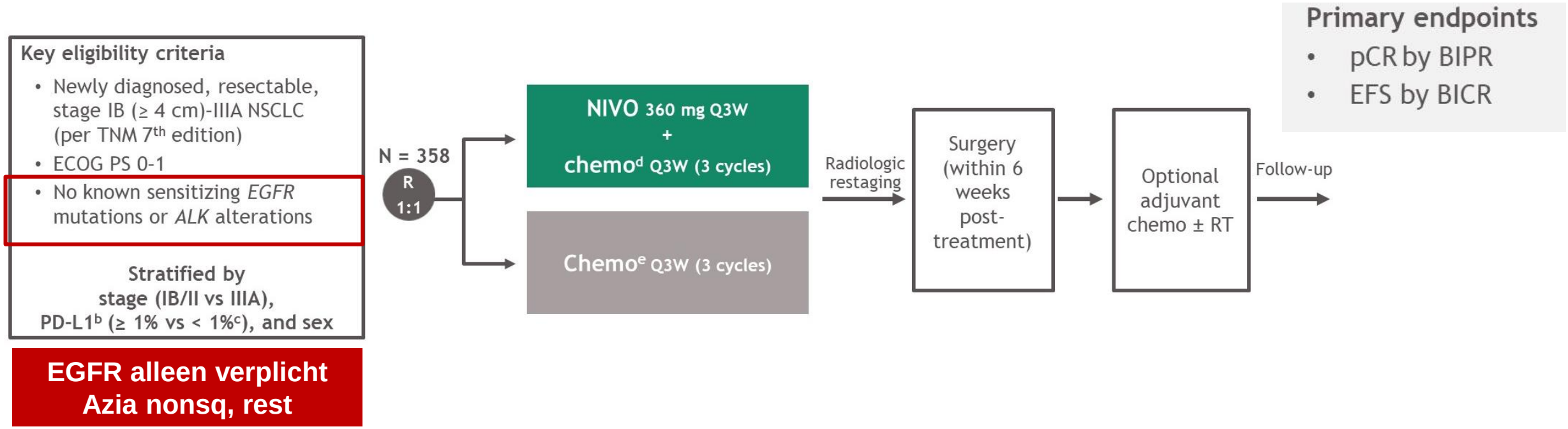
Peters ESMO 2020; O'Brien Lancet Oncol 2022

CheckMate816 – eerste fase III RCT neoadjuvant



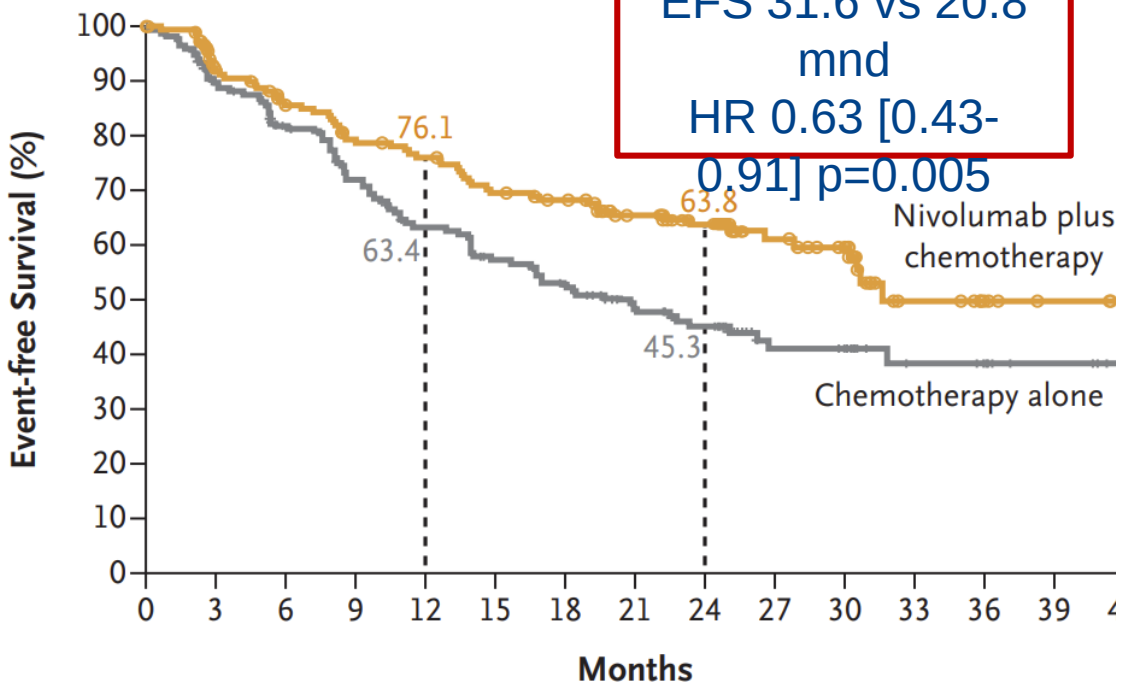
EGFR alleen verplicht
Azia nonsq, rest

ICI arm numeriek vaker geopereerd, minder conversies naar thoracotomie, meer R0

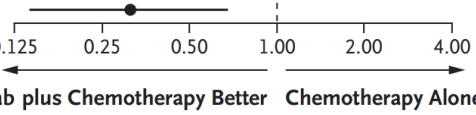
12-17% geen resectie bij ICI arm, 13-25% bij chemo arm

Forde NEJM 2022

CM816 EFS en subgroepen



Subgroup	No. of Patients	Median Event-free Survival (95% CI)		Unstratified Hazard Ratio for Disease Progression, Disease Recurrence, or Death (95% CI)
		Nivolumab plus chemotherapy (N=179)	Chemotherapy alone (N=179)	
		mo		
Overall	358	31.6 (30.2–NR)	20.8 (14.0–26.7)	0.63 (0.45–0.87)
Age				
<65 yr	176	NR (31.6–NR)	20.8 (14.0–NR)	0.57 (0.35–0.93)
≥65 yr	182	30.2 (23.4–NR)	18.4 (10.6–31.8)	0.70 (0.45–1.08)
Sex				
Male	255	30.6 (20.0–NR)	16.9 (13.8–24.9)	0.68 (0.47–0.98)
Female	103	NR (30.5–NR)	31.8 (13.9–NR)	0.46 (0.22–0.96)
Geographic region				
North America	91	NR (25.1–NR)	NR (12.8–NR)	0.78 (0.38–1.62)
Europe	66	31.6 (13.4–NR)	21.1 (10.2–NR)	0.80 (0.36–1.77)
Asia	177	NR (30.2–NR)	16.5 (10.8–22.7)	0.45 (0.29–0.71)
ECOG performance-status score				
0	241	NR (30.2–NR)	22.7 (16.6–NR)	0.61 (0.41–0.91)
1	117	30.5 (14.6–NR)	14.0 (9.8–26.2)	0.71 (0.41–1.21)
Disease stage at baseline				
IB or II	127	NR (27.8–NR)	NR (16.8–NR)	0.87 (0.48–1.56)
IIIA	228	31.6 (26.6–NR)	15.7 (10.8–22.7)	0.54 (0.37–0.80)
Histologic type of tumor				
Squamous	182	30.6 (20.0–NR)	22.7 (11.5–NR)	0.77 (0.49–1.22)
Nonsquamous	176	NR (27.8–NR)	19.6 (13.8–26.2)	0.50 (0.32–0.79)
Smoking status				
Current or former smoker	318	31.6 (30.2–NR)	22.4 (15.7–NR)	0.68 (0.48–0.96)
Never smoked	39	NR (5.6–NR)	10.4 (7.7–20.8)	0.33 (0.13–0.87)
PD-L1 expression level				
<1%	155	25.1 (14.6–NR)	18.4 (13.9–26.2)	0.85 (0.54–1.32)
≥1%	178	NR (NR–NR)	21.1 (11.5–NR)	0.41 (0.24–0.70)
1–49%	98	NR (27.8–NR)	26.7 (11.5–NR)	0.58 (0.30–1.12)
≥50%	80	NR (NR–NR)	19.6 (8.2–NR)	0.24 (0.10–0.61)
TMB				
<12.3 mutations/megabase	102	30.5 (19.4–NR)	26.7 (16.6–NR)	0.86 (0.47–1.57)
≥12.3 mutations/megabase	76	NR (14.8–NR)	22.4 (13.4–NR)	0.69 (0.33–1.46)
Type of platinum therapy				
Cisplatin	258	NR (25.1–NR)	20.9 (15.7–NR)	0.71 (0.49–1.03)
Carboplatin	72	NR (30.5–NR)	10.6 (7.6–26.7)	0.31 (0.14–0.67)



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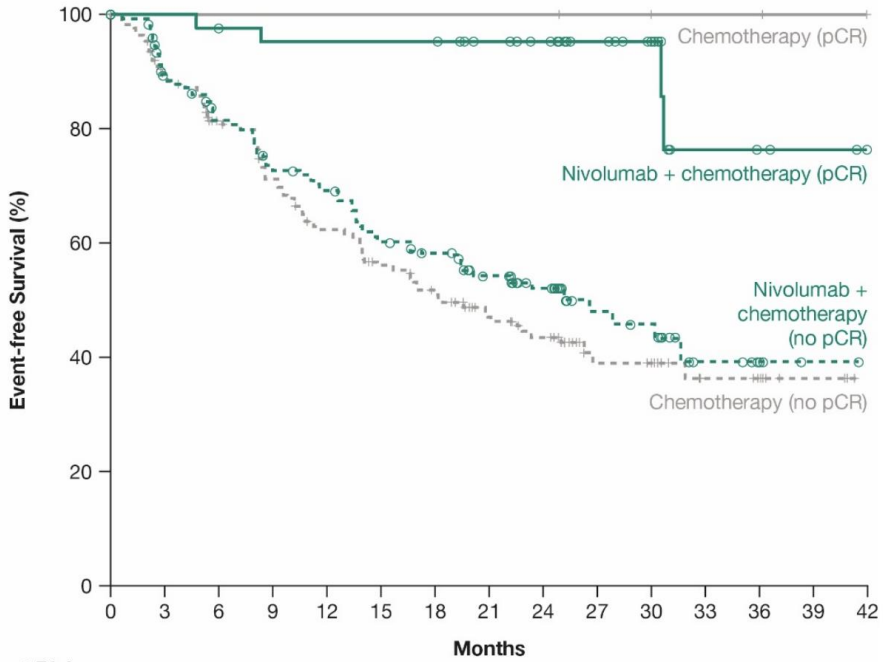
CM816: surrogaat EFS eindpunten

pCR en EFS

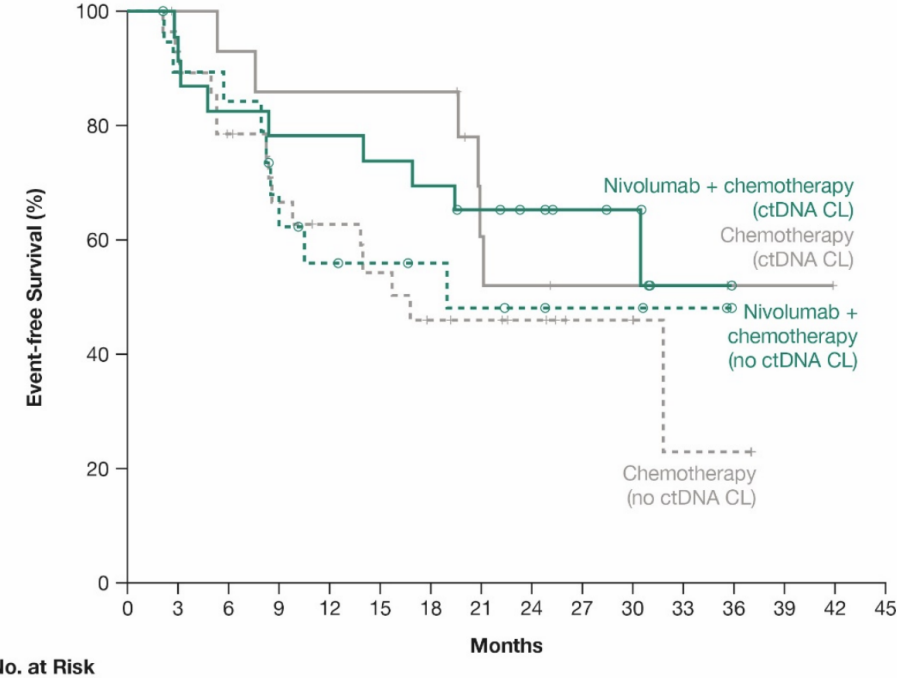
	Nivolumab + chemotherapy		Chemotherapy	
	pCR (n=43)	No pCR (n=136)	pCR (n=4)	No pCR (n=175)
Median EFS, mo (95% CI)	NR (30.6–NR)	26.6 (16.6–NR)	NR (NR–NR)	18.4 (13.9–26.2)
HR (95% CI)*	0.13 (0.05–0.37)		Not computed†	



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

ctDNA en EFS

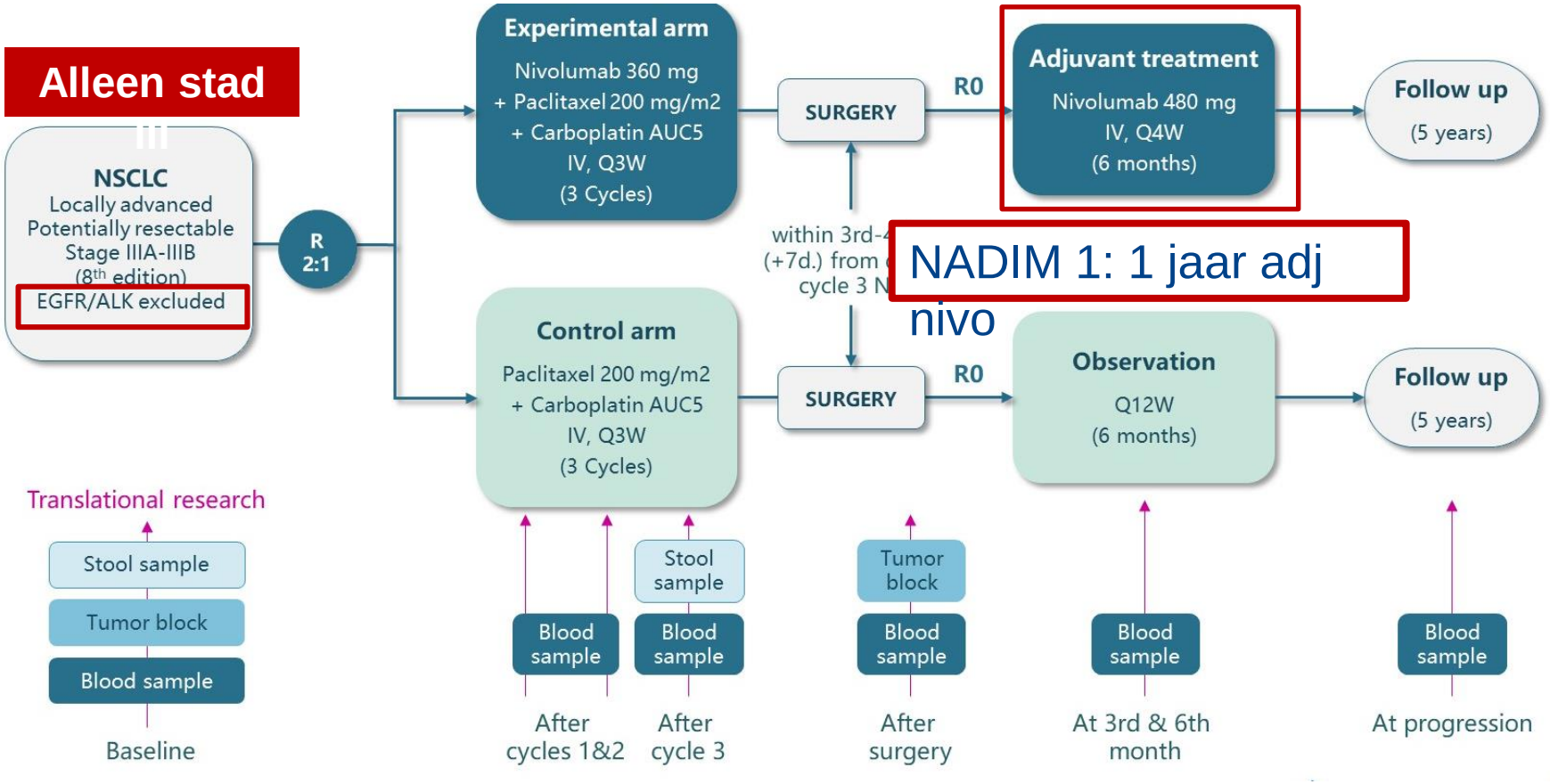
	Nivolumab + chemotherapy		Chemotherapy	
	ctDNA CL (n=24)	No ctDNA CL (n=19)	ctDNA CL (n=15)	No ctDNA CL (n=28)
Median EFS, mo (95% CI)	NR (16.8–NR)	18.9 (8.3–NR)	NR (19.6–NR)	16.8 (8.3–NR)
HR (95% CI)	0.60 (0.20–1.82)		0.63 (0.20–2.01)	



No. at Risk															
Nivolumab + chemotherapy (ctDNA CL)	24	21	19	18	18	17	16	13	11	8	7	1	0	0	0	0
Chemotherapy (ctDNA CL)	15	14	13	12	12	12	12	7	6	5	5	5	3	1	0	0
Nivolumab + chemotherapy (no ctDNA CL)	19	17	16	12	9	8	7	6	5	3	3	2	0	0	0	0
Chemotherapy (no ctDNA CL)	28	26	21	17	15	13	10	9	7	4	3	1	1	0	0	0

Neoadjuvant – NADIM II fase II RCT

Alleen stad



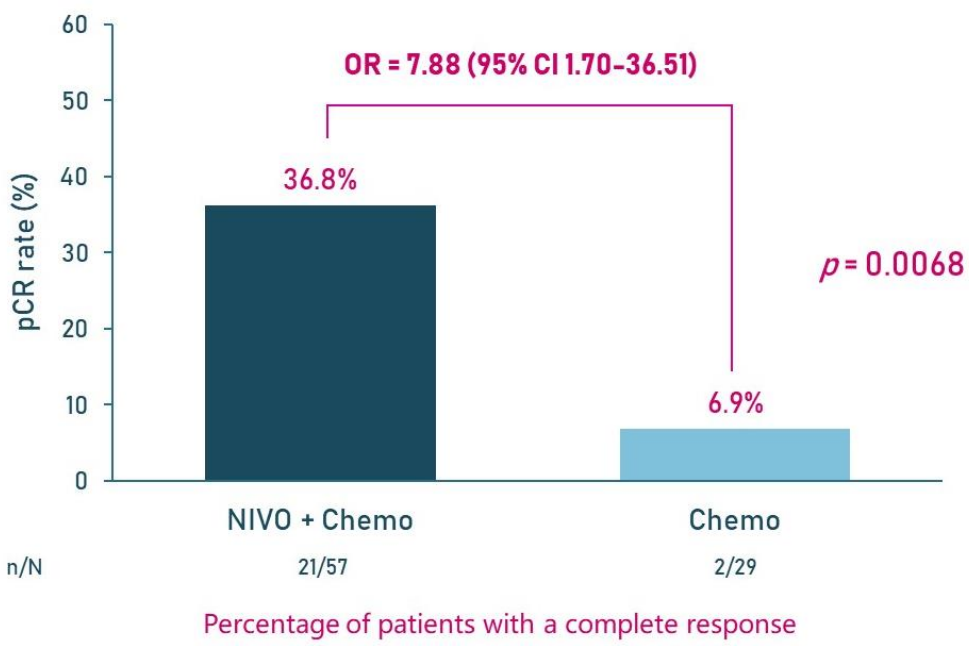
NADIM 1: 1 jaar adj nivo

N = 86
Resectie: 97% (ICI) vs 69%
Pt karakteristieken vergelijkbaar
1/3 multistation N2

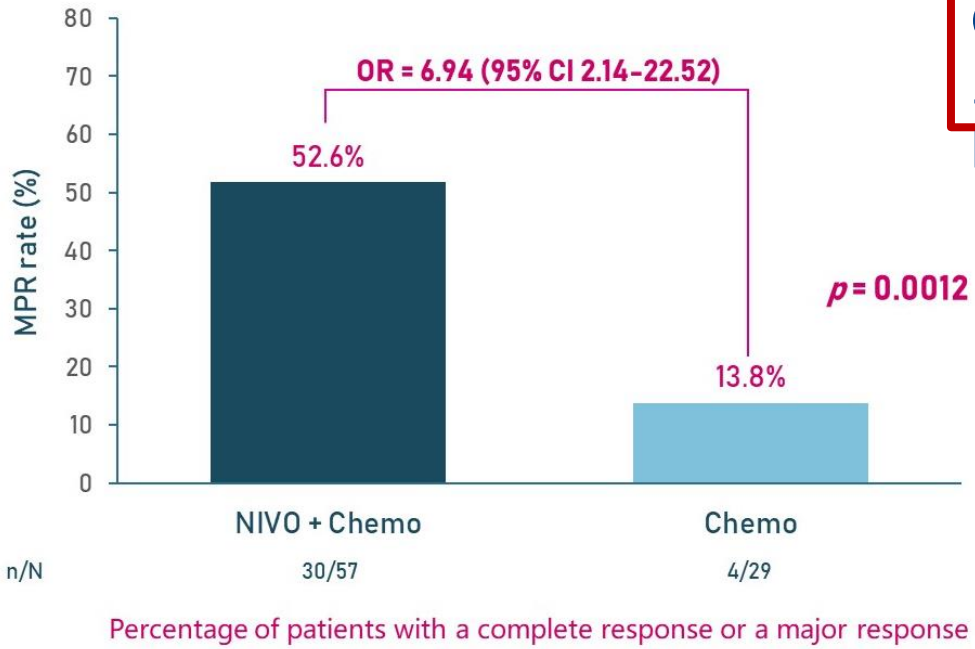
Primaire eindpunt: pCR rate
Secundair: oa MPR rate, chirurgie complicaties, veiligheid, biomarkers

NADIM II uitkomsten

pCR rate



MPR rate



ORR 75% vs 48%
Gr 3-4 tox 25 vs 10%
Nog geen EFS data

pCR vaker bij ↑ PD-L1

Bevestiging CM816 data
OS voor beiden nog niet bekend

Surrogaat PFS/OS eindpunten: NADIM I data

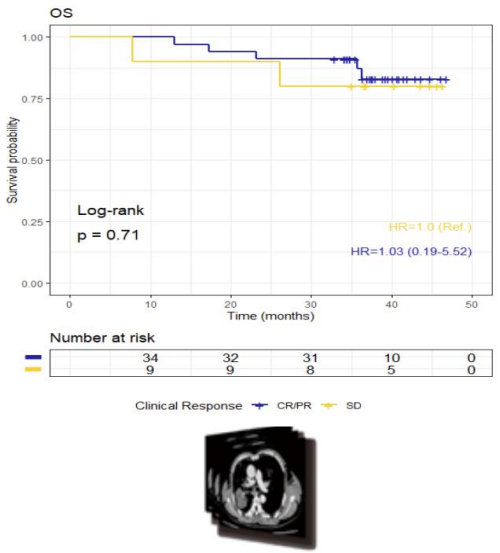
Survival surrogate	*HR (PFS)*	*95% CI*	*P*	*Adjusted PFS C-statistic*	*95% CI*	*HR (OS)*	*95% CI*	*P*	*Adjusted OS C-statistic*	*95% CI*
Clinical respone (CR+PR vs SD)	0.93	0.24-3.56	0.921	0.61	0.45-0.78	1.03	0.19-5.52	0.974	0.68	0.44-0.93
Pathological response (Complete vs Major+Incomplete)	0.25	0.06-1.00	**0.05**	0.68	0.52-0.84	--	--	--	0.83	0.75-0.91
ctDNA Clearance	0.3	0.08-1.11	**0.072**	0.62	0.43-0.81	0.05	0.00-0.68	**0.024**	0.79	0.55-1.03

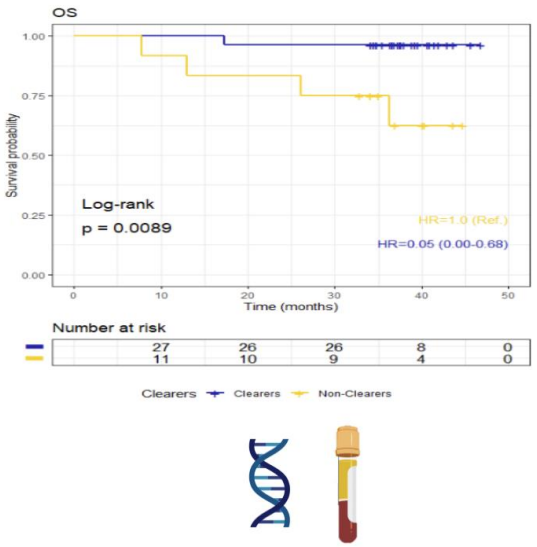
MOLECULAR RESPONSE

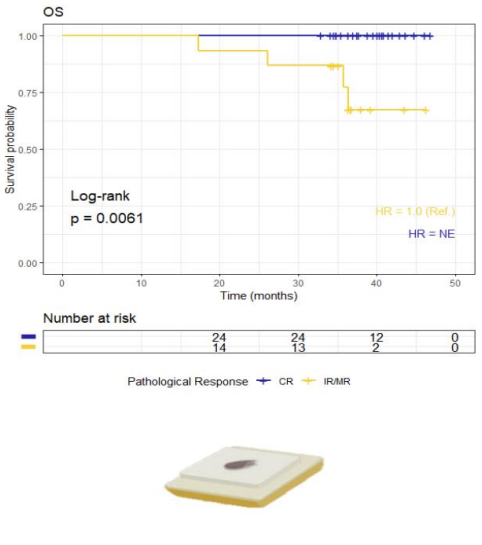
Clearers

Non-clearers

ctDNA clearance (i.e lack of detectable ctDNA at the end of neoadjuvant tx), **significantly predicted long-term survival.**







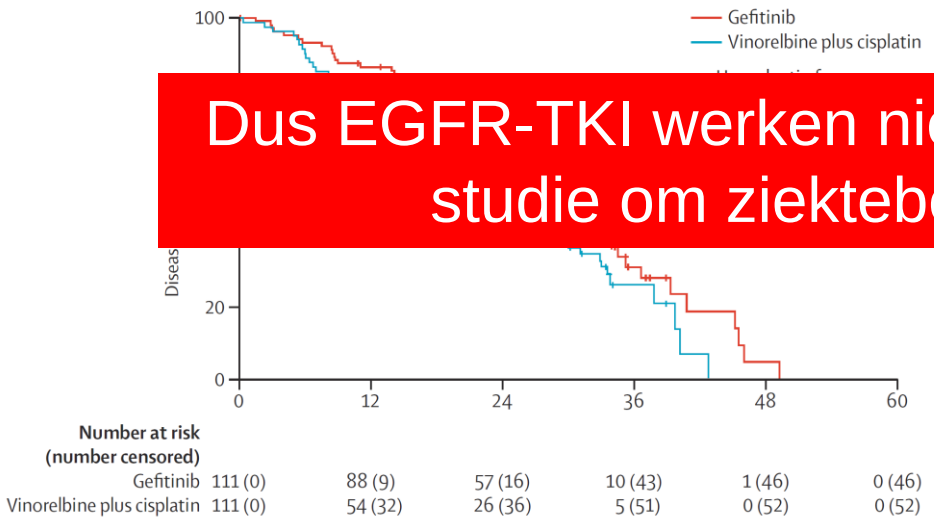
Maastricht UMC+

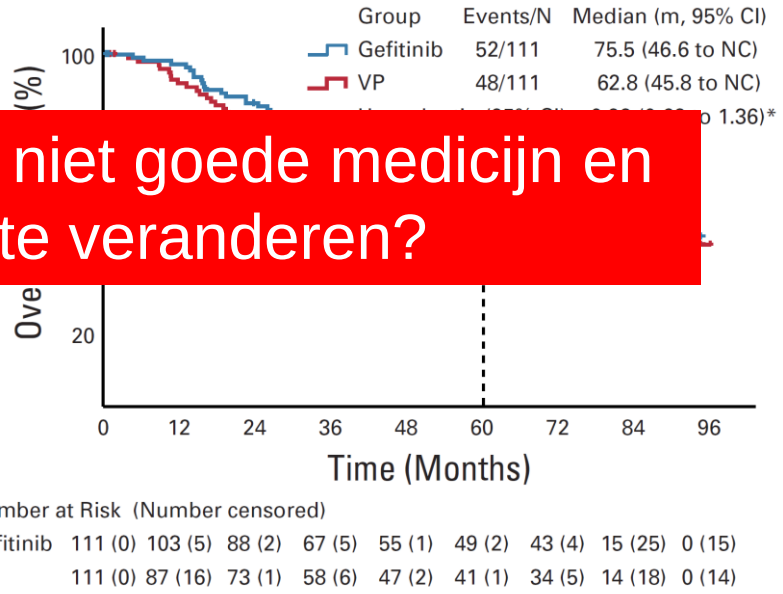
EGFR TKI data

4 kuren chemo vs 2 jaar gefitinib adjuvant bij EGFR+ NSCLC

N=222, 24% PET, 16% MRI brein

Mediane duur behandeling 21.9m





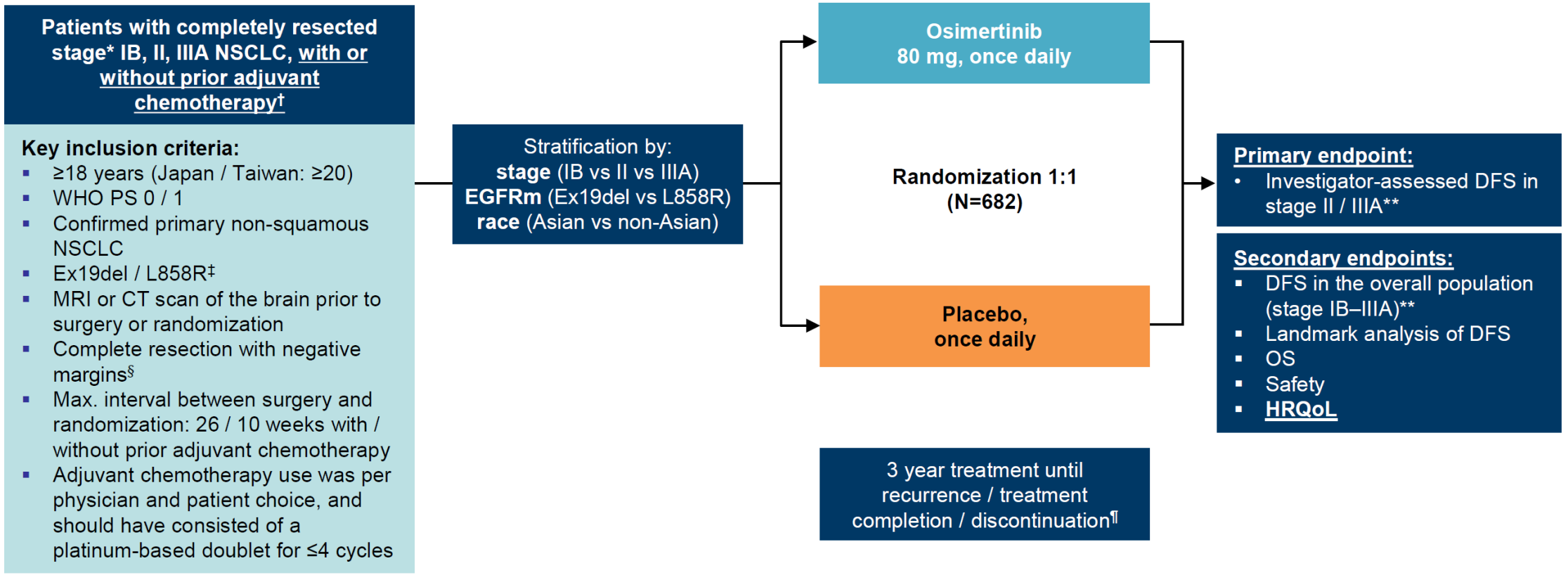
Dus EGFR-TKI werken niet? Of niet goede medicijn en studie om ziektebeloop te veranderen?

Primaire eindpunt DFS HR 0.60 (0.42-

Geen OS benefit na mediane FU 80 mnd

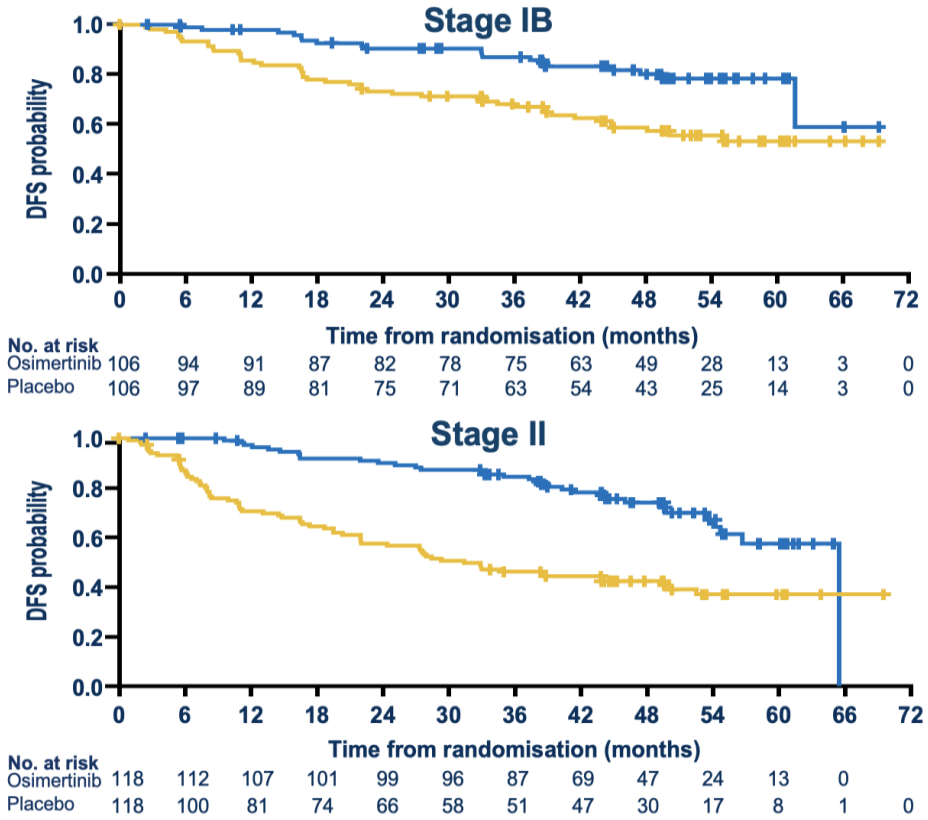
Zhong Lancet Oncol 2018 * Zhong JCO 2021

ADAURA refresher: studie design

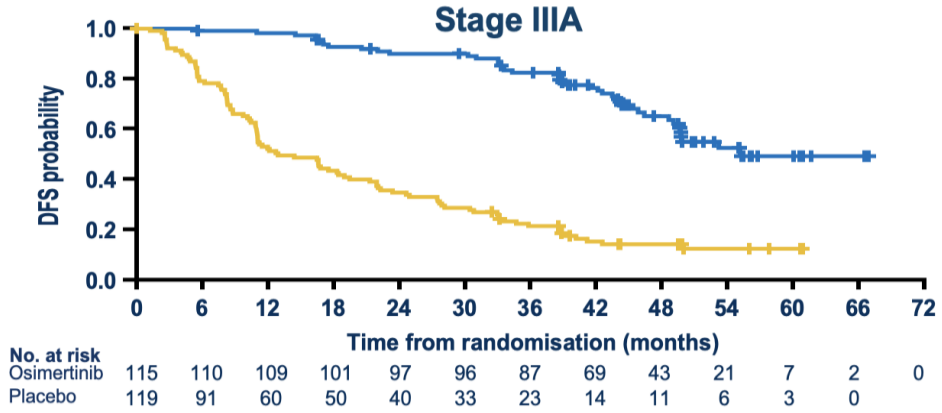


Wu NEJM 2020

ADAURA geupdate DFS data per stadium (TNM7)



	Stage IB	Stage II	Stage IIIA
4 year DFS rate, % (95% CI)			
– Osimertinib	80 (70, 87)	74 (64, 82)	65 (54, 74)
– Placebo	59 (48, 68)	42 (33, 51)	14 (8, 22)
Overall HR (95% CI)	**0.41 (0.23, 0.69)**	**0.34 (0.23, 0.52)**	**0.20 (0.14, 0.29)**



Multipele studies met neoadjuvant / adjuvant TKI (+/- chemo of ICI) lopende voor oa EGFR, ALK, RET, ROS1, NTRK, BRAFV600E, MET, KRAS G12C, HER2

Dus moeten we in vroeg stadium alleen PD-L1, EGFR (& ALK) testen?

NCCN 2022 neo-adjuvante ICI & adjuvante ICI – TKI adviezen

Neoadjuvant Systemic Therapy

- Nivolumab 360 mg and platinum-doublet chemotherapy every 3 weeks for 3 cycles[10,*]
  - Platinum-doublet chemotherapy options include:
    - ◊ Carboplatin AUC 5 or AUC 6 day 1, paclitaxel 175 mg/m² or 200 mg/m² day 1 (any histology)
    - ◊ Cisplatin 75 mg/m² day 1, pemetrexed 500 mg/m² day 1 (non-squamous histology)
    - ◊ Cisplatin 75 mg/m² day 1, gemcitabine 1000 mg/m² or 1250 mg/m² days 1 and 8 (squamous histology)
    - ◊ Cisplatin 75 mg/m² day 1, paclitaxel 175 mg/m² or 200 mg/m² day 1 (any histology)
  - Chemotherapy Regimens for Patients with Comorbidities or Patients Not Able to Tolerate Cisplatin
    - ◊ Carboplatin AUC 5 or AUC 6 day 1, pemetrexed 500 mg/m² day 1 (non-squamous histology)
    - ◊ Carboplatin AUC 5 or AUC 6 day 1, gemcitabine 1000 mg/m² or 1250 mg/m² days 1 and 8 (squamous histology)

Niets over

Adjuvant Systemic Therapy

- Osimertinib 80 mg daily[11]
  - Osimertinib for patients with completely resected stage IB–IIIA *EGFR* (*exon 19* deletion, *L858R*) NSCLC who received previous adjuvant chemotherapy or are ineligible to receive platinum-based chemotherapy.
- Atezolizumab 840 mg every 2 weeks, 1200 mg every 3 weeks, or 1680 mg every 4 weeks for up to 1 year[12]
  - Atezolizumab for patients with completely resected stage IIB–IIIA or high risk stage IIA PD-L1 ≥1% NSCLC who received previous adjuvant chemotherapy.

EGFR & PD-L1

PD-L1 ≥50%

Meerdere (neo)-adjuvante ICI studies gaande: EGFR/ALK wisselend geexcludeerd

ALK – ROS1 – RET – METex14 – HER2 vaker PD-L1 ↑
In stad IV meestal slechte uitkomst ICI bij oncogene driver (muv KRAS &

NCCN guidelines NSCLC v5.2002

TEVENS VAKER TOX VAN TKI NA ICI BESCHREVEN

ICI lange T1/2

Lisberg fase II pembro 1st line in EGFR+
- Geen responsen
- Frequent hepatitis & pneumonitis van TKI hierna

Table 2 Safety of sequential CPI/TKI and TKI/CPI therapy

References	Phase	Oncogenic driver	No. patients	Arms/Treatment	Safety
Lin et al. [38]	Retrospective	ALK (3), ROS-1 (3), MET (5)	11	Pembrolizumab followed by crizotinib (6) Nivolumab followed by crizotinib (3) Atezolizumab followed by crizotinib (1) Nivolumab + ipilimumab followed by crizotinib (1)	G3/4 increase ALT 45.5% (5/11) G3/4 increase AST 36.4% (4/11)
Schoenfeld et al. [39]	Retrospective	EGFR	41	Nivolumab followed by osimertinib (24) Pembrolizumab followed by osimertinib (9) Atezolizumab followed by osimertinib (8)	AE 15% (6/41) G3 pneumonitis (n = 4), G3 colitis ($n = 1$), G4 hepatitis ($n = 1$)
Oshima et al. [40]	Retrospective	EGFR	70	Nivolumab followed TKI	ILD 25.7% (18/70)
Garassino et al. [44]	II	EGFR	111	TKIs followed by Durvalumab	G3/4 AE 5% (6/111), G3 pneumonitis ($n = 1$)

Adderley Cancer Immunology Immunotherapy 2020; Lisberg JTO 2018

TAKE HOME MESSAGES

Neoadjuvante & adjuvante (chemo)-ICI op weg naar nieuwe standaard bij vroeg stadium NSCLC

Bekende EGFR/ALK geexcludeerd (neoadjuvant) of kans slechtere uitkomsten (adjuvant)

Adjuvant osimertinib standaard bij stad IB-IIIA NSCLC met EGFRex19del of ex21 L858R

Bij stad III / IV merendeel oncogene drivers geassocieerd met slechte uitkomsten ICI

Reële kans toxiciteit van TKI na eerdere ICI

Mijns inziens breed testen in vroeg stadium: toegang studies – verminderen kans (financiele) toxiciteit

Rol ctDNA/MRD moet nog verder worden gedefinieerd