Ontwikkelingen in vroeg-stadium NSCLC

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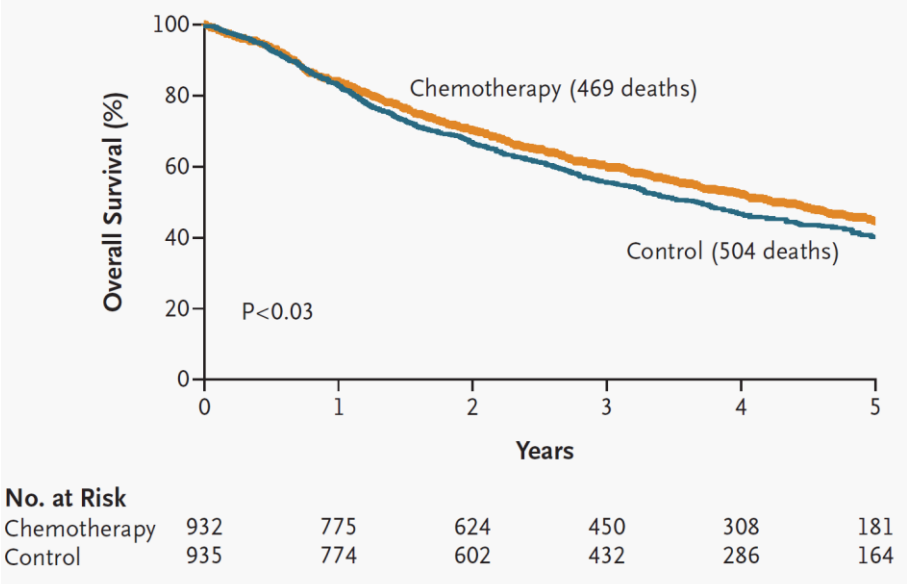
ONCOLOGIE UPDATE 2023

Predictieve diagnostiek voor immuun- en doelgerichte therapie

Disclosures

Research grants from AstraZeneca, Sanofi and Regeneron.

HET VERLEDEN



5y OS +5%

Neoadjuvante chemotherapie ongeveer gelijk voordeel

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%

TNM8: <70% 5y OS from stage ≥IB

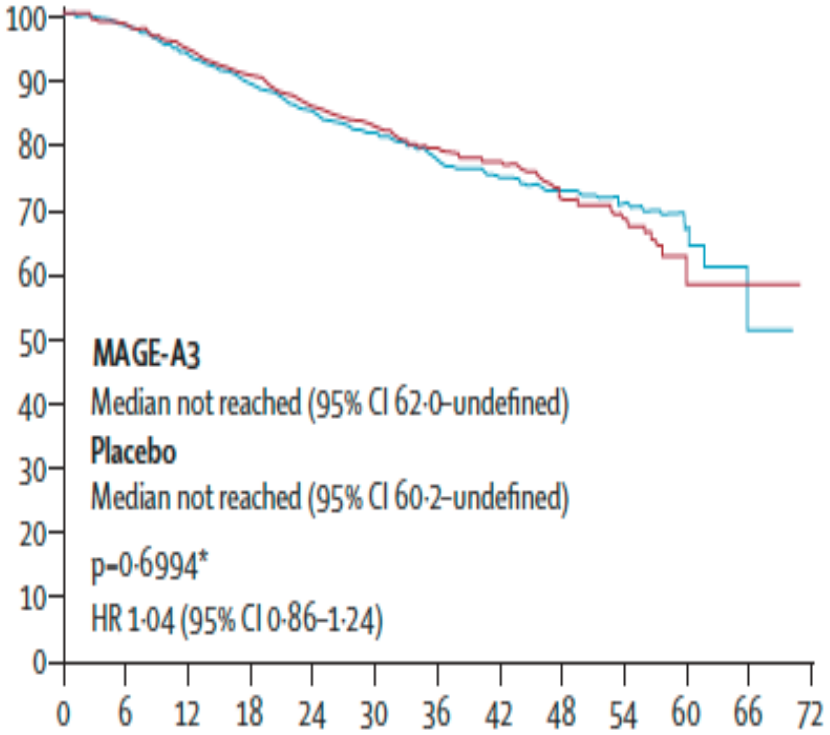
Merendeel faalt obv metastasering op afstand, dus oplossing meest waarschijnlijk op systemisch gebied. NB. Ong 1/3 van de gereseceerde patiënten ontvangt geen chemotherapie.

Goldstraw, JTO 2015; NSCLC MA Collaborative group. Lancet 2010 & Lancet 2014; Kehl, JAMA Oncol 2022

SLIDE COURTESY L Hendriks

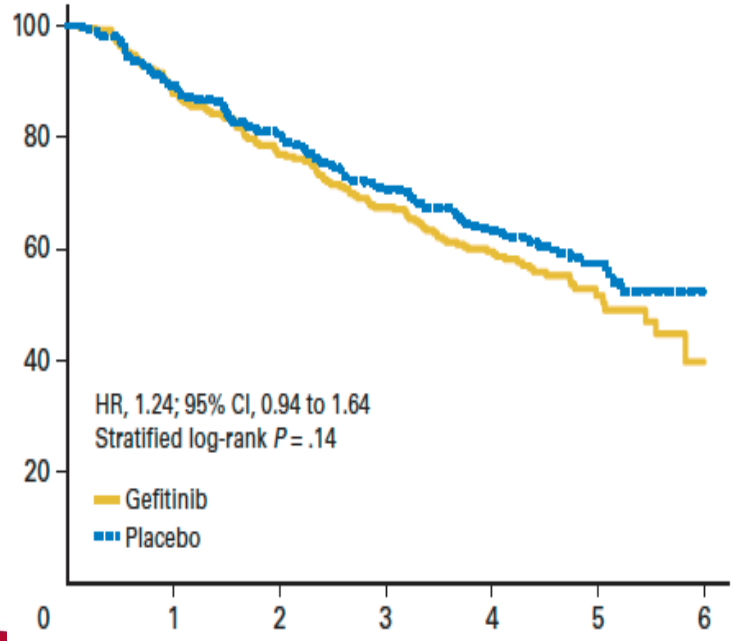
MAGRIT TRIAL

MAGE-A3 vaccine



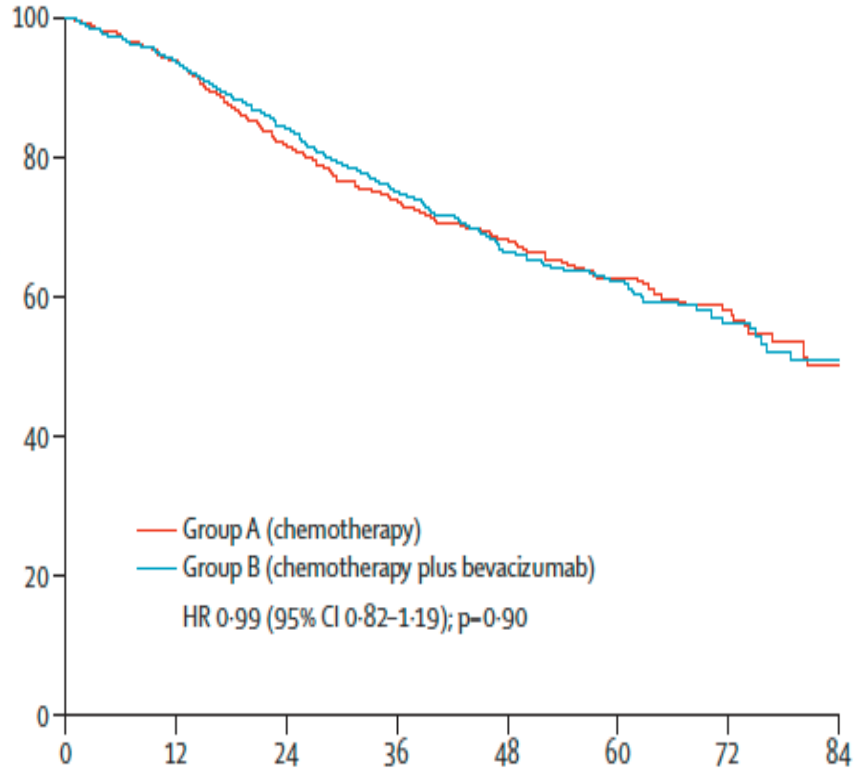
BR19 TRIAL

Gefitinib



ECOG1505 TRIAL

Bevacizumab

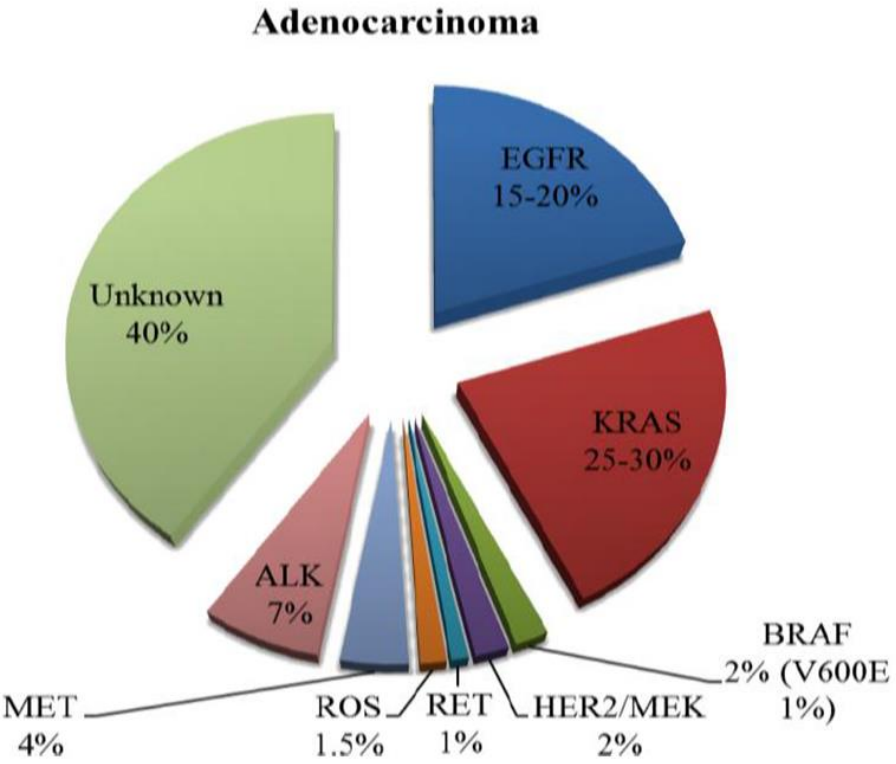


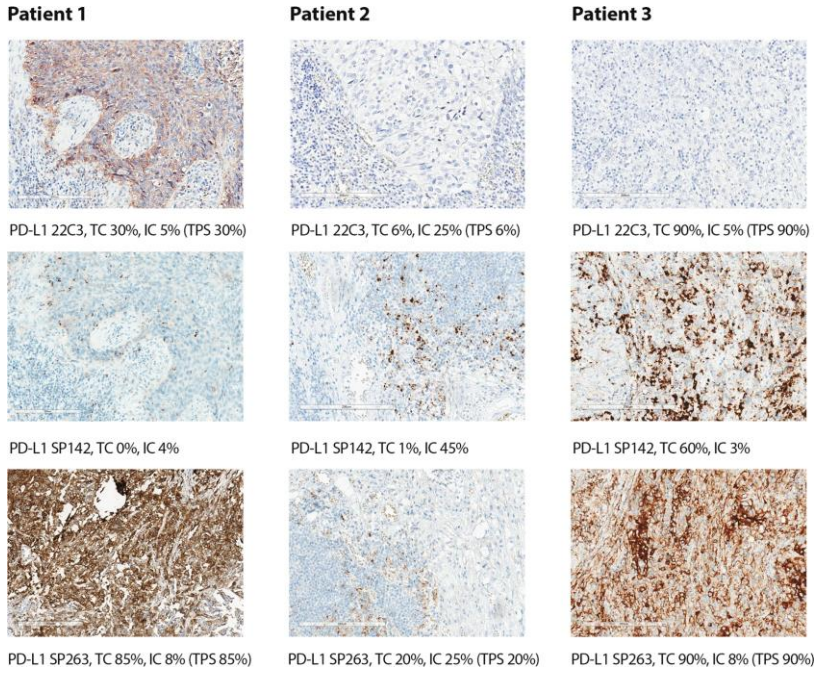
>5.000 patienten adjuvant behandeld, geen OS voordeel.

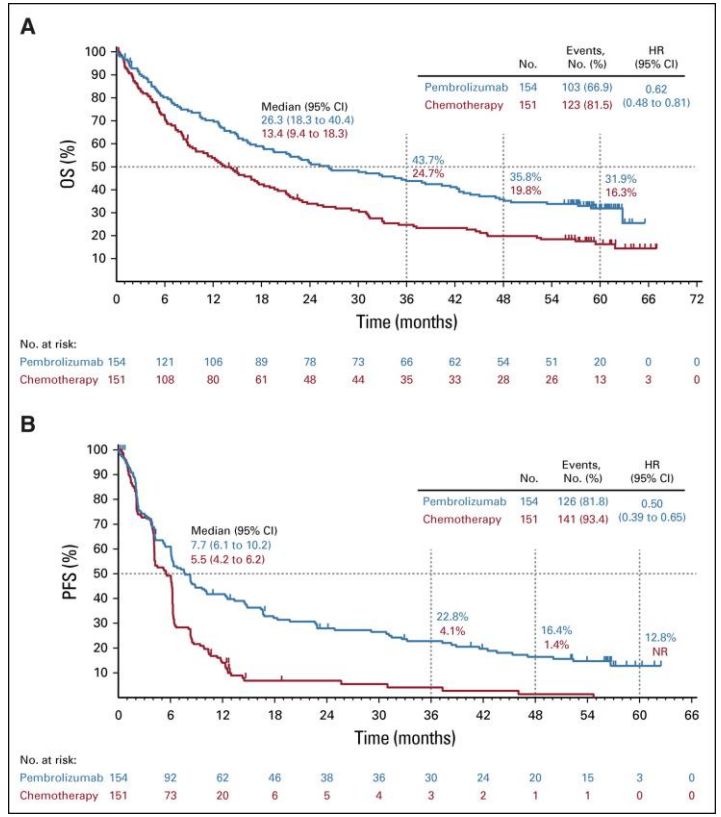
Vansteenkiste, Lancet Oncol 2016; Goss, JCO 2013; Wakelee, Lancet Oncol 2017 / WCLC 2019

SLIDE COURTESY L Hendriks

NIEUWE ONTWIKKELINGEN IN GEMETASTASEERDE ZIEKTE: DOELGERICHTE EN IMMUUNTHERAPIE.







Tsimafeyeu et al. CLOVER comparison study. 2020; Reck et al. Five-Year Outcomes With Pembrolizumab Versus Chemotherapy for Metastatic Non–Small-Cell Lung Cancer With PD-L1 Tumor Proportion Score ≥ 50%. JCO 2021

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VROEG-STADIUM IS EEN HETEROGEEN BEGRIP

TNM 8th - Primary tumor characteristics	
T_x	Tumor in sputum/bronchial washings but not be assessed in imaging or bronchoscopy
T_0	No evidence of tumor
T_{is}	Carcinoma in situ
T_1	≤ 3 cm surrounded by lung/visceral pleura, not involving main bronchus
$T_{1a(mi)}$	Minimally invasive carcinoma
T_{1a}	≤ 1 cm
T_{1b}	> 1 to ≤ 2 cm
T_{1c}	> 2 to ≤ 3 cm
T_2	> 3 to ≤ 5 cm *or* involvement of main bronchus without carina, regardless of distance from carina or invasion visceral pleural *or* atelectasis or post obstructive pneumonitis extending to hilum
T_{2a}	>3 to ≤4cm
T_{2b}	>4 to ≤5cm
T_3	>5 to ≤7cm in greatest dimension *or* tumor of any size that involves chest wall, pericardium, phrenic nerve *or* satellite nodules in the same lobe
T_4	> 7cm in greatest dimension *or* any tumor with invasion of mediastinum, diaphragm, heart, great vessels, recurrent laryngeal nerve, carina, trachea, oesophagus, spine *or* separate tumor in different lobe of ipsilateral lung
N_1	Ipsilateral peribronchial and/or hilar nodes and intrapulmonary nodes
2	Ipsilateral mediastinal and/or subcarinal nodes
3	Contralateral mediastinal or hilar; ipsilateral/contralateral scalene/ supraclavicular
M_1	Distant metastasis
M_{1a}	Tumor in contralateral lung or pleural/pericardial nodule/malignant effusion
M_{1b}	Single extrathoracic metastasis, including single non-regional lymphnode
M_{1c}	Multiple extrathoracic metastases in one or more organs

	N0	N1	N2	N3
T1	IA	IIB	IIIA	IIIB
T2a	IB	IIB	IIIA	IIIB
T2b	IIA	IIB	IIIA	IIIB
T3	IIB	IIIA	IIIB	IIIC
T4	IIIA	IIIA	IIIB	IIIC
M1a	IVA	IVA	IVA	IVA
M1b	IVA	IVA	IVA	IVA
M1c	IVB	IVB	IVB	IVB

Wat is resectabel NSCLC?

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Doelgerichte therapie in vroeg-stadium NSCLC

ONCOLOGIE UPDATE 2023

Predictieve diagnostiek voor immuun- en doelgerichte therapie

DOELGERICHTE THERAPIE IN VROEG-STADIUM NSCLC: EGFR

ADAURA Phase III double-blind study design

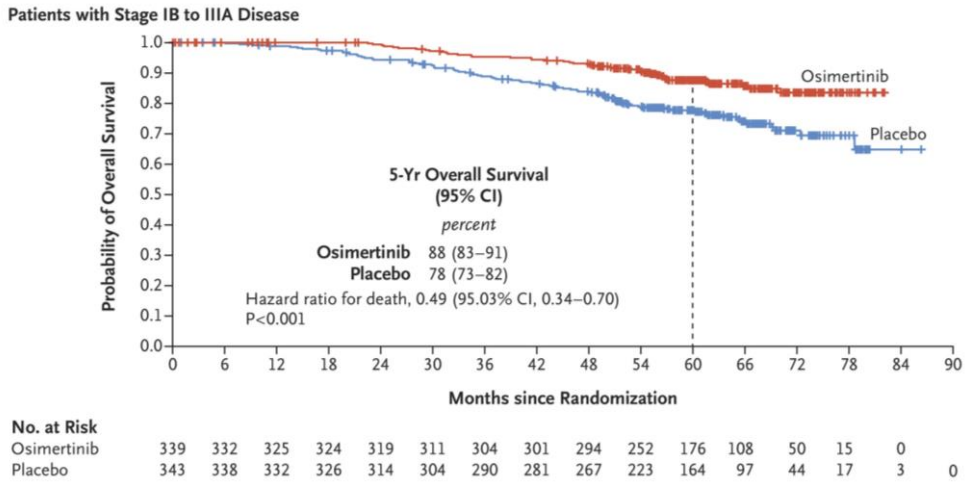
Patients with completely resected stage* IB, II, IIIA NSCLC, with or without adjuvant chemotherapy†

Key inclusion criteria:
- ≥18 years (Japan / Taiwan: ≥20)
- WHO performance status 0 / 1
- Confirmed primary non-squamous NSCLC Ex19del / L858R‡
- Brain imaging, if not completed pre-operatively
- Complete resection with negative margins§
- Max. interval between surgery and randomization:
  - 10 weeks without adjuvant chemotherapy
  - 26 weeks with adjuvant chemotherapy

Stratification by:
stage (IB vs II vs IIIA)
EGFRm (Ex19del vs L858R)
race (Asian vs non-Asian)

Randomization 1:1 (N=682)

- Osimertinib 80 mg, once daily
- Placebo, once daily



Behandelduur osimertinib 3 jaar
Primaire eindpunt: DFS st II en IIIA

NB. Geen verplichting tot SoC adjuvante chemotherapie of SoC pre-op PET/MRI-hersenen
NB. 43% in de placebo arm hebben osimertinib gekregen.

Tsuboi et al. Overall Survival with Osimertinib in Resected EGFR-Mutated NSCLC. N Engl J Med 2023

DOELGERICHTE THERAPIE IN VROEG-STADIUM NSCLC: ALK

ALINA study design*

Resected Stage IB (≥4cm)–IIIA *ALK*+ NSCLC
per UICC/AJCC 7th edition

Other key eligibility criteria:
- ECOG PS 0–1
- Eligible to receive platinum-based chemotherapy
- Adequate end-organ function
- No prior systemic cancer therapy

Stratification factors:
- Stage: IB (≥ 4cm) vs II vs IIIA
- Race: Asian vs non-Asian

R 1:1

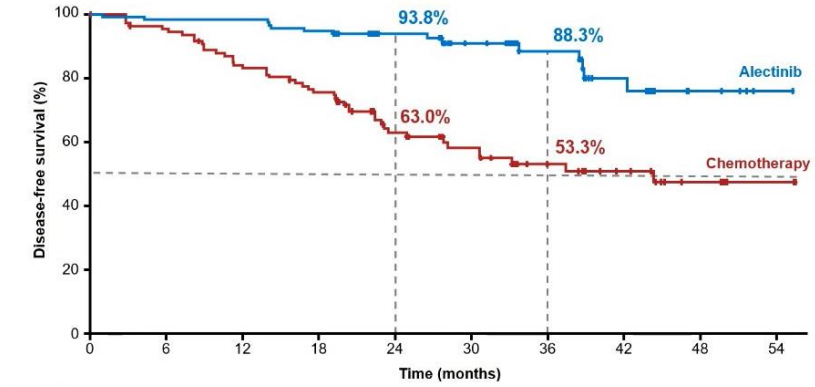
N=257

- **Alectinib 600 mg BID** 2 years → **Recurrence**
- **Platinum-based chemotherapy†** Q3W; 4 cycles → **Recurrence**

→ **Further treatments at investigator's choice and survival follow-up**

Behandelduur alectinib 2 jaar
Primaire eindpunt: DFS st II en IIIA

Disease-free survival: stage II–IIIA*



	Alectinib (N=116)	Chemotherapy (N=115)
Patients with event Death Recurrence	14 (12%) 0 14	45 (39%) 1 44
Median DFS, months (95% CI)	Not reached	44.4 (27.8, NE)
DFS HR (95% CI)	**0.24** (0.13, 0.45) p†<0.0001	

NB. 76% in de chemo arm hebben later alectinib gekregen.
NB. mPFS alectinib in st IV is 34,8m

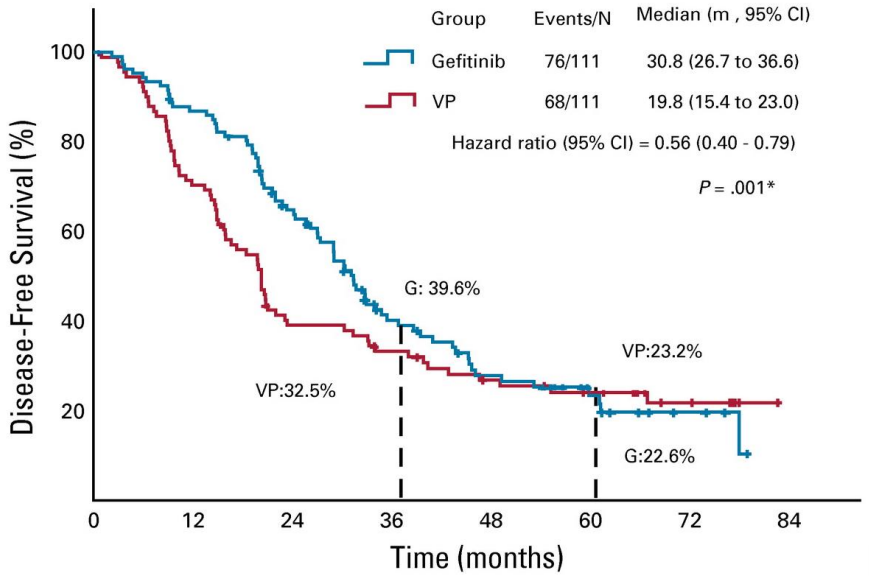
Soloman et al. Efficacy and safety of adjuvant alectinib vs. chemotherapy in patiets with earlystage ALK+ NSCLC. ESMO 2023

RUIMTE VOOR DISCUSSIE

Wat is het doel van systeemtherapie bij in opzet curatieve locale behandeling?

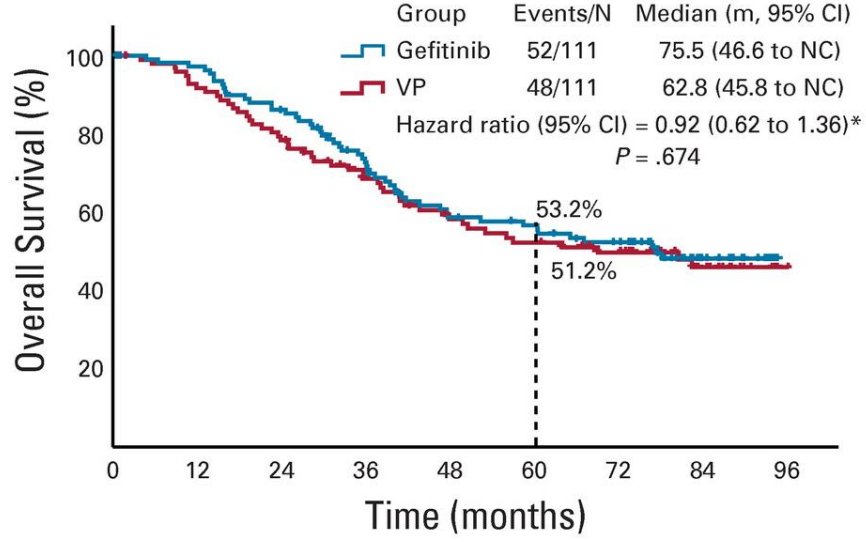
- Is weglaten van chemo uberhaupt verstandig?
- Is EFS/PFS een adequaat surrogate marker?
- Hoe controleren/beschermen we tegen onderbehandeling in de controle arm?

ADJUVANT-CTONG1104 (DFS in II-IIIA)



Number at Risk (Number Censored)

Gefitinib	111 (0)	91 (6)	61 (5)	33 (7)	21 (2)	12 (6)	4 (6)	0 (3)
VP	111 (0)	63 (21)	33 (2)	26 (2)	19 (2)	15 (2)	6 (8)	0 (6)



Number at Risk (Number censored)

Gefitinib	111 (0)	103 (5)	88 (2)	67 (5)	55 (1)	49 (2)	43 (4)	15 (25)	0 (15)
VP	111 (0)	87 (16)	73 (1)	58 (6)	47 (2)	41 (1)	34 (5)	14 (18)	0 (14)

Zhong et al. Gefitinib Versus Vinorelbine Plus Cisplatin as Adjuvant Treatment for Stage II-IIIA (N1-N2) EGFR-Mutant NSCLC. JCO 2021

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Immuuntherapie in vroeg-stadium NSCLC

IMMUUNTHERAPIE:
IMMUNE CHECKPOINT INHIBITORS (ICI)

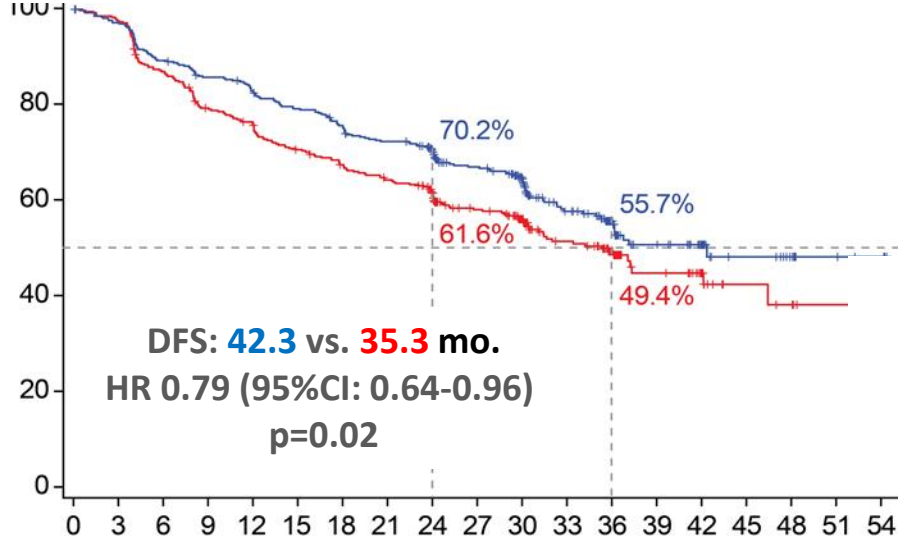
Ratio voor success van ICI in NSCLC, gemetastaseerd vs vroeg-stadium:

- Immuunsysteem fitter in vroeg stadium ziekte
- Hogere tumor burden geassocieerd met systemische immuunsuppressie
- T-cell functie ↓ bij meer vergevorderde ziekte
- ↑ Systemische inflammatie bij hoger stadium

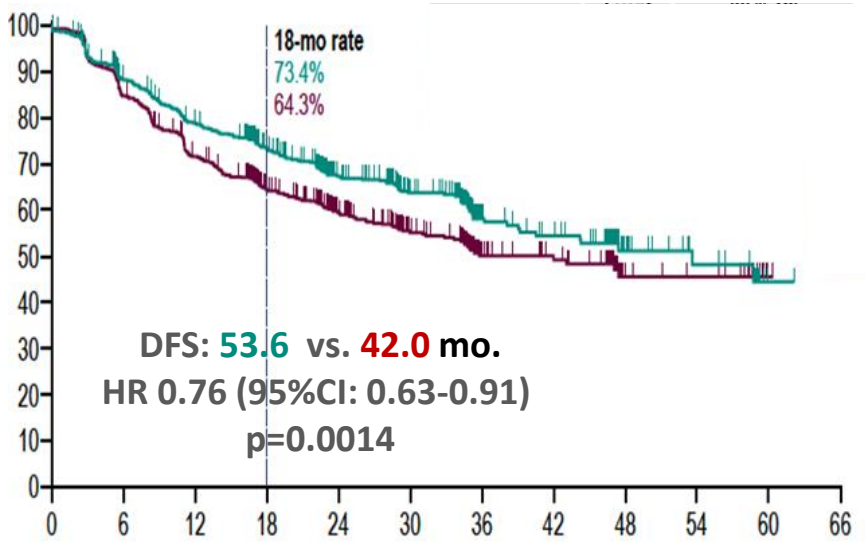
Reviewed in Versluis Nat Med 2020; Cascone AACR 2018; Martin-Ruiz Sci rep 2020

ICI - ADJUVANT

IMpower 010 (EFS in II-IIIA)



PEARLS (EFS in overall population)



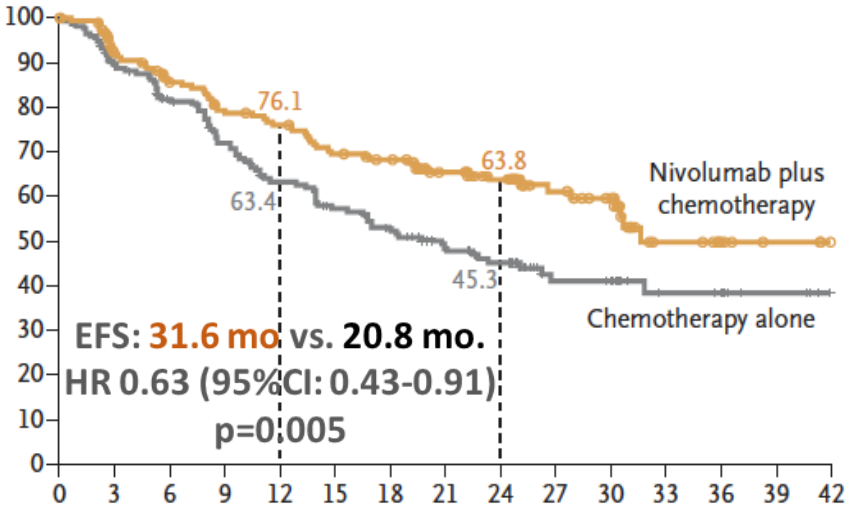
Atezolizumab (aPD-L1)	Pembrolizumab (aPD-1)
Stadium IB (T ≥4cm), II of IIIA (geen exclusie EGFR/ALK)	
Adjuvante chemo verplicht	Adjuvante chemo optioneel
Inclusie st IIIA 41%	Inclusie st IIIA 30%
OS: HR 0.43 st II-IIIA met PD-L1 ≥50%	OS not mature

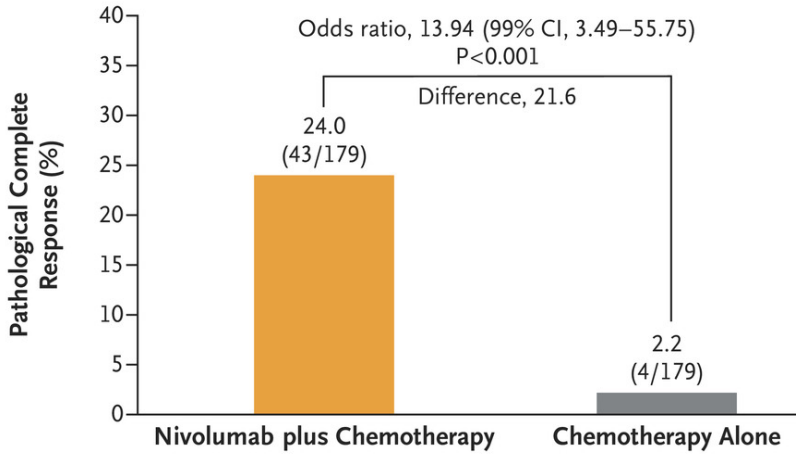
Felip, The lancet, 2021; Felip, Annal Oncol 2023; Paz-Ares, ESMO plenary 2022

ICI- NEOADJUVANT

CheckMate 816 (EFS in IB-IIIA)

3 kuren chemo + nivolumab (aPD-1)
Stadium IB (T ≥4cm), II of IIIA (exclusie EGFR/ALK)
Adjuvante chemo +/- RT optioneel
Inclusie st IIIA 64%
Neoadjuvant: 3 cycles 93.8% vs 84.7% Chirurgie: 83.2% vs 75.4% Adjuvant chemo: 11.9% vs 22.2%





Forde, AACR 2021; Forde, NEJM 2022

IMMUUNTHERAPIE: NEOADJUVANT + ADJUVANT

4 trails leveren bewijs voor betere EFS bij perioperatief ICI in resectabel NSCLC

- AEGEAN: 4 kuren durvalumab (aPD-L1) + chemo => resectie => 1 jaar durva vs. placebo + chemo
- CheckMate 77t: 4 kuren nivolumab + chemo => resectie => 1 jaar nivo vs. placebo + chemo
- Neotorch: 3 kuren toripalimab (aPD-1) + chemo => resectie => 1 kuur tori + chemo => 1 jaar tori vs. placebo + chemo
- Keynote-671: 4 kuren pembrolizumab + chemo => resectie => 1 jaar pembro vs. placebo + chemo; **OS benefit HR 0.72 (95% CI, 0.56-0.93) p=0.005**

Resectie verricht in ~80% van de patienten voor beide armen.

Complete pathologische respons (pCR) ~20-25% in de experimentele arm.

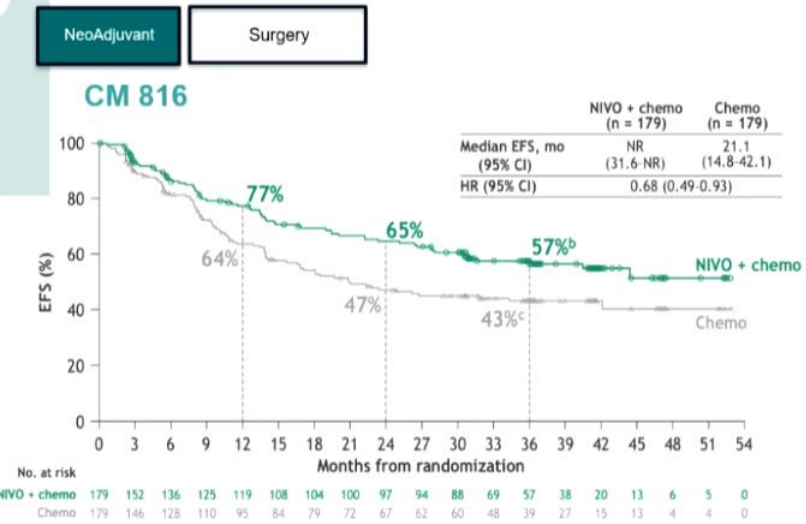
PD-L1 expressie is ook voorspellend voor voordeel in vroeg-stadium NSCLC.

⇒ 2 korte conclusies:

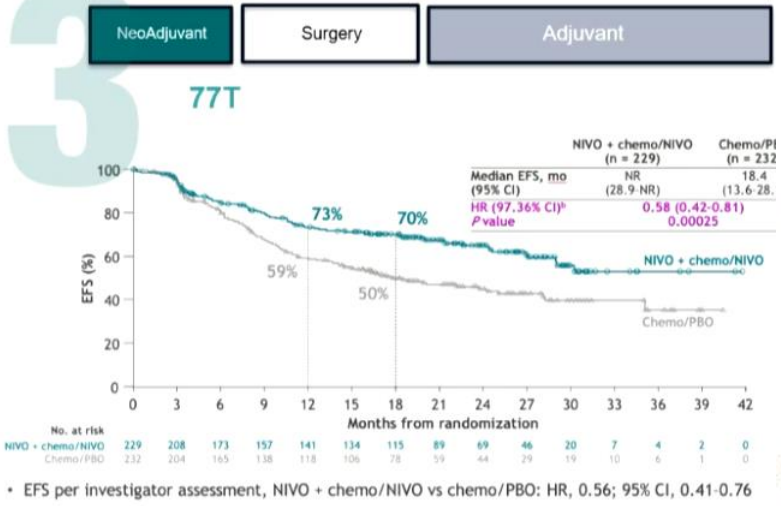
- ICI voor vroeg-stadium NSCLC geeft EFS voordeel
- Er zijn (te?) veel “me too drug” trials met mogelijk niet-optimale/klinisch-relevante eindpunten?

RUIMTE VOOR DISCUSSIE

Is perioperatief beter dan neoadjuvant?



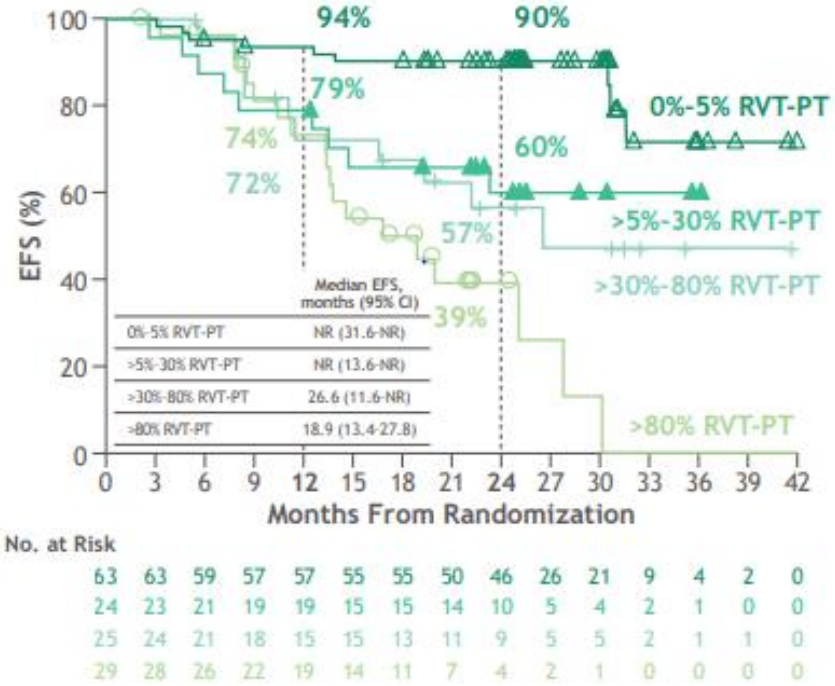
HR 0.68 (0.49-0.93)



• EFS per investigator assessment, NIVO + chemo/NIVO vs chemo/PBO: HR, 0.56; 95% CI, 0.41-0.76

HR 0.58 (0.42-0.81)

Pathologische respons als biomarker?



Pathologische respons (pCR HR 0.18; MPR HR 0.26) sterkste associatie EFS tov radiologische respons (HR 0.32) of ctDNA clearance (HR 0.66)

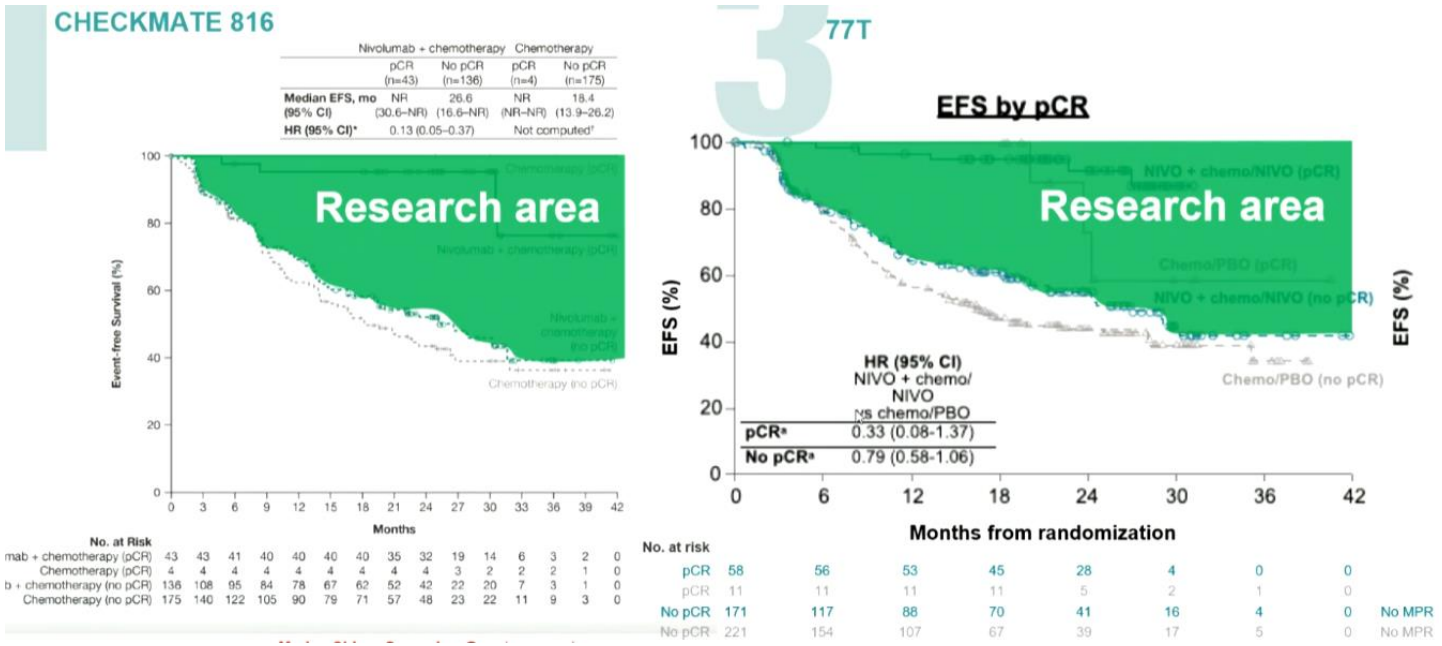
Geen relatie diepte path. respons met histologie, PD-L1, TMB, irAEs of LNN betrokkenheid

SLIDE thanks to M Garassino

Girard, ELCC 2023; Cascone, ESMO 2023; Deutsch, Nature 2023

RUIMTE VOOR VERBETERING

Geen pCR behoeft meer onderzoek:
biomarkers voor (non)response, bv drivermutaties
rol adjuvante therapie,
nieuwe middelen/combo's.



SLIDE thanks to M Garassino

TAKE HOME MESSAGE

Succes van doelgerichte en immuuntherapie binnen NSCLC st IV vertaalt zich ook in voordeel voor vroeg-stadium ziekte:

- 3 jaar adjuvante osimertinib na resectie van EGFR+ (Ex19del or L858R) st IB-IIIA NSCLC.
- 1 jaar adjuvante atezolizumab na resectie en chemotherapie bij st II/IIIA zonder EGFR/ALK en PD-L1 ≥50%.
- Verwachting van goedkeuring CM-816 neoadjuvant regiem.

Nog veel discussiepunten:

- Wat is het doel en wat zijn de juiste surrogaat eindpunten?
  - Risico op uitstel of annuleren chirurgie (neoadjuvant)
  - Risico op onnodig behandeling, bijwerkingen en kosten (adjuvant +/- neoadjuvant)
- Wat is resectabel en wanneer definieren we dat?
- Biomarkers: drivermutaties, PD-L1, ctDNA, pCR, ICI-resistentie enz…

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