Immunotherapie bij longkankerptn met oncogene driver mutaties

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23-10-2020

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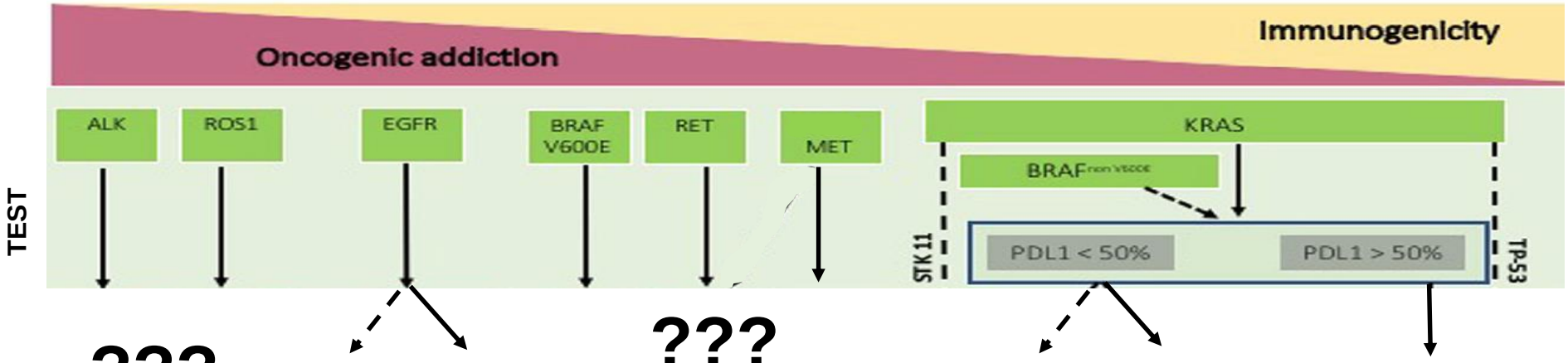
Plaats van ICI bij NSCLC met drivers



???

???

???

Immunotherapy + Chemotherapy

???

Target Therapy

???

???

chemotherapy

Immunotherapy

???

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Curr. Treat. Options in Oncol. (2019) 20: 60
DOI 10.1007/s11864-019-0652-3

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Rationale & Vraagstelling

- Alle longkanker-ptn met druggable drivers ontwikkelen resistentie tegen TKI
- De plaats van ICI bij deze ptn blijft onduidelijk

- Vragen zijn dus :
  - zijn ICI's (als mono- of combitherapie) bij longkanker gekenmerkt door driver-mutaties effectief ?
  - Zo ja, wat is dan hun plaats in de behandelschema's ?

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Hebben we goede data ? Ja, maar…

Editorial Commentary

Is the game over for PD-1 inhibitors in EGFR mutant non-small cell lung cancer?

María A. Vélez[1], Timothy F. Burns[2,3]

JAMA Oncology | Original Investigation

Clinical and Molecular Characteristics Associated Wit
Among Patients Treated With Checkpoint Inhibitc
Advanced Non–Small Cell Lung Carcinoma
ystematic Review and Meta-analysis

Annals of Oncology 30: 1321–1328, 2019
doi:10.1093/annonc/mdz167
Published online 24 May 2019

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ORIGINAL ARTICLE

Immune checkpoint inhibitors for patients with advanced lung cancer and oncogenic driver alterations: results from the IMMUNOTARGET registry

J. Mazieres[1*], A. Drilon[2], A. Lusque[3], L. Mhanna[1], A. B. Cortot[4], L. Mezquita[5], A. A. Thai[6], C

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

Annals of Oncology 30: 1311–1320, 2019
doi:10.1093/annonc/mdz141
Published online 14 May 2019

ORIGINAL ARTICLE

EGFR mutation subtypes and response to immune checkpoint blockade treatment in non-small-cell lung cancer

K. Hastings[1], H. A. Yu[2,3], W. Wei[4], F. Sanchez-Vega[5,6], M. DeVeaux[4†], J. Choi[7], H. Rizvi[8], A. Lisberg[9],

Durvalumab as third-line or later treatment for advanced non-small-cell lung cancer (ATLANTIC): an open-label, single-arm, phase 2 study

Marina Chiara Garassino, Byoung-Chul Cho, Joo-Hang Kim, Julien Mazières, Johan Vansteenkiste, Hervé Lena, Jesus Corral Jaime, Jhanelle E Gray,

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Data ICI en EGFR eerste lijn

ORIGINAL ARTICLE

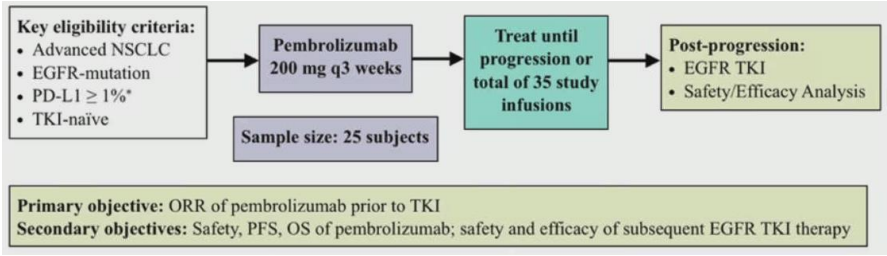
A Phase II Study of Pembrolizumab in EGFR-Mutant, PD-L1+, Tyrosine Kinase Inhibitor Naïve Patients With Advanced NSCLC

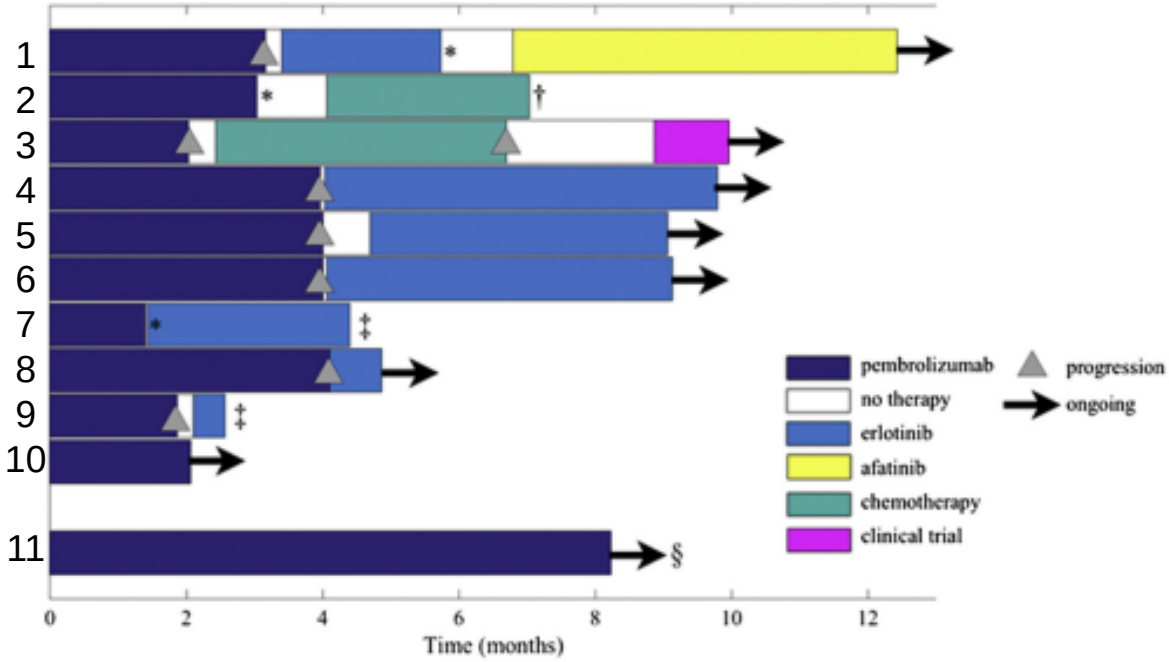
A. Lisberg, MD, A. Cummings, MD, J. W. Goldman, MD, K. Bornazyan, BS,

Check for updates

Idee : zie keynote-001 (n=4 TKI naïve pts vs n=26 die al TKI kregen: ORR 50% vs 4%)

Premisse : ORR van ICI is groot, en het effect van TKI bij progressie zou niet mogen zijn aangetast





ORR = 0%
9 kregen subseq therapie
7 daarvan met TKI
6/7 Tox met 1 fatale pneumonitis

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TKI na ICI blijken erg toxisch !

Brief Report

FREE

August 2018

EGFR-TKI-Associated Interstitial Pneumonitis in Nivolumab-Treated Patients With Non-Small Cell Lung Cancer

Yasuo Oshima, MD, PhD[1]; Tetsuya Tanimoto, MD[2]; Koichiro Yuji, MD, PhD[1]; et al

70 pts kregen nivolumab & TKI,
18 kregen ernstige pneumonitis = 26%

Bij 15 was de sequentie ICI/TKI gekend, het ging allemaal om ICI → TKI

Among the 18 patients with IP treated with both EGFR-TKI and nivolumab, we identified the order of administration in 15 cases; all were treated with EGFR-TKI after nivolumab (eResults in Supplement 1).

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TKI na ICI blijken erg toxisch !

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

Annals of Oncology 30: 839–844, 2019
doi:10.1093/annonc/mdz077
Published online 7 March 2019

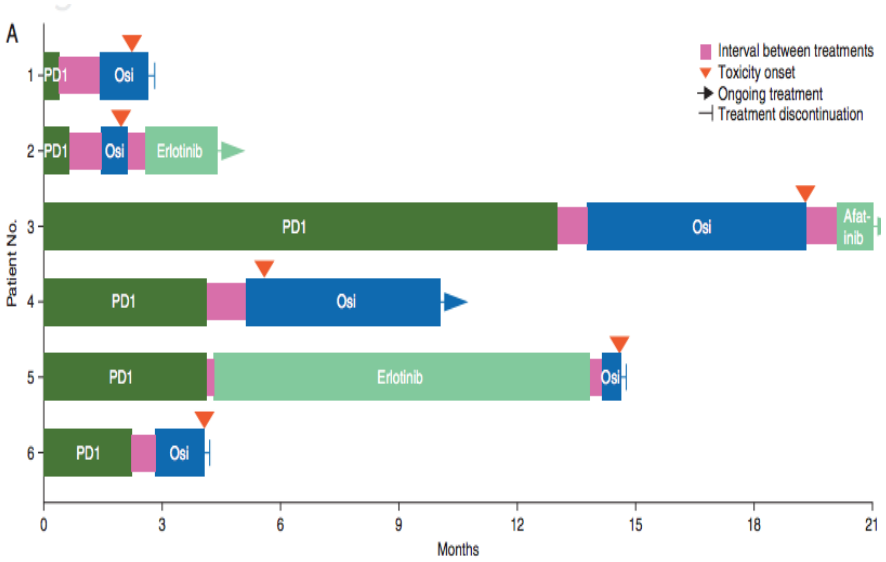
ORIGINAL ARTICLE

Severe immune-related adverse events are common with sequential PD-(L)1 blockade and osimertinib

A. J. Schoenfeld[1], K. C. Arbour[1], H. Rizvi[1], A. N. Iqbal[1], S. M. Gadgeel[2], J. Girshman[3], M. G. Kris[1], G. J. Riely[1], H. A. Yu[1*†] & M. D. Hellmann[1*†]

ICI → TKI
6/41 = 15% (vnl als TKI start <3mnd)

TKI → ICI
0/29 = 0%



B

Patient No.	IO regimen	Time on IO	Time interval between IO and Osimertinib	Time to onset of toxicity after 1st dose of Osimertinib	Toxicity	Toxicity grade	Need for hospitalization?	Response to steroids?
1	nivolumab	14 days	29 days	24 days	Pneumonitis	3	yes	yes
2	carboplatin, pemetrexed, pembrolizumab	21 days	23 days	15 days	Pneumonitis	3	no	yes
3	ipilimumab, nivolumab	392 days	22 days	167 days	Pneumonitis	3	yes	yes
4	pembrolizumab	126 days	28 days	14 days	Colitis	3	yes	no
5	pembrolizumab	126 days	314 days	15 days	Pneumonitis	3	yes	yes
6	nivolumab	68 days	39 days	39 days	Hepatitis	4	yes	no

Median 20d

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Dus :

- ICI bij EGFR in eerste lijn : werkt niet
- ICI gevolgd door TKI : toxisch

Subanalyses EGFR grote trials : ICI 2-3de lijn na TKI

JAMA Oncology | Original Investigation

Clinical and Molecular Characteristics Associated With Survival Among Patients Treated With Checkpoint Inhibitors for Advanced Non-Small Cell Lung Carcinoma

A Systematic Review and Meta-analysis

Figure 1. Flow Diagram of Study Inclusion and Exclusion

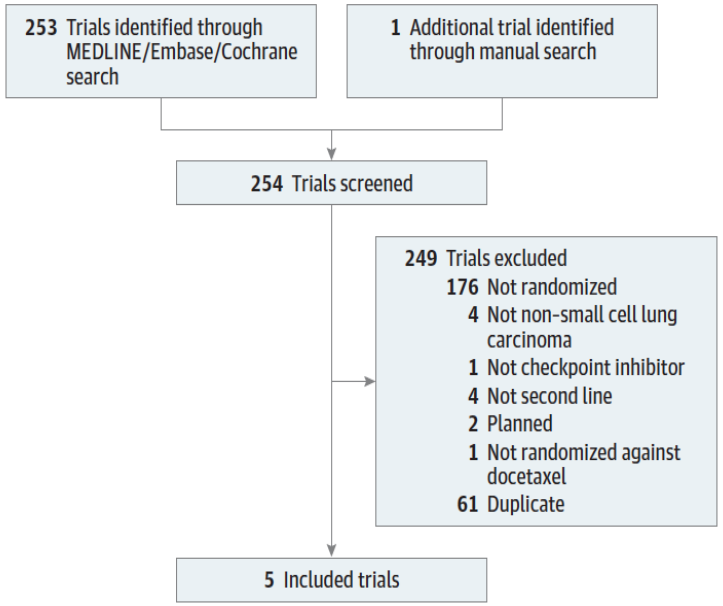

Table. Characteristics of Patients in Included Trials

Trials	Treatment Comparison	Median OS, mo[a]	Patients, *EGFR* Mutation
CheckMate 017,[5] 2015	Nivolumab vs docetaxel	9.2 vs 6.0	
CheckMate 057,[4] 2015	Nivolumab vs docetaxel	12.2 vs 9.4	82 (14)
Keynote 010,[6] 2016	Pembrolizumab vs docetaxel	10.4 vs 12.7[b] vs 8.5[c]	86 (8)
OAK,[7] 2017	Atezolizumab vs docetaxel	13.8 vs 9.6	85 (10)
POPLAR,[8] 2016	Atezolizumab vs docetaxel	12.6 vs 9.7	18 (6)

JAMA Oncol. 2018;4(2):210-216.

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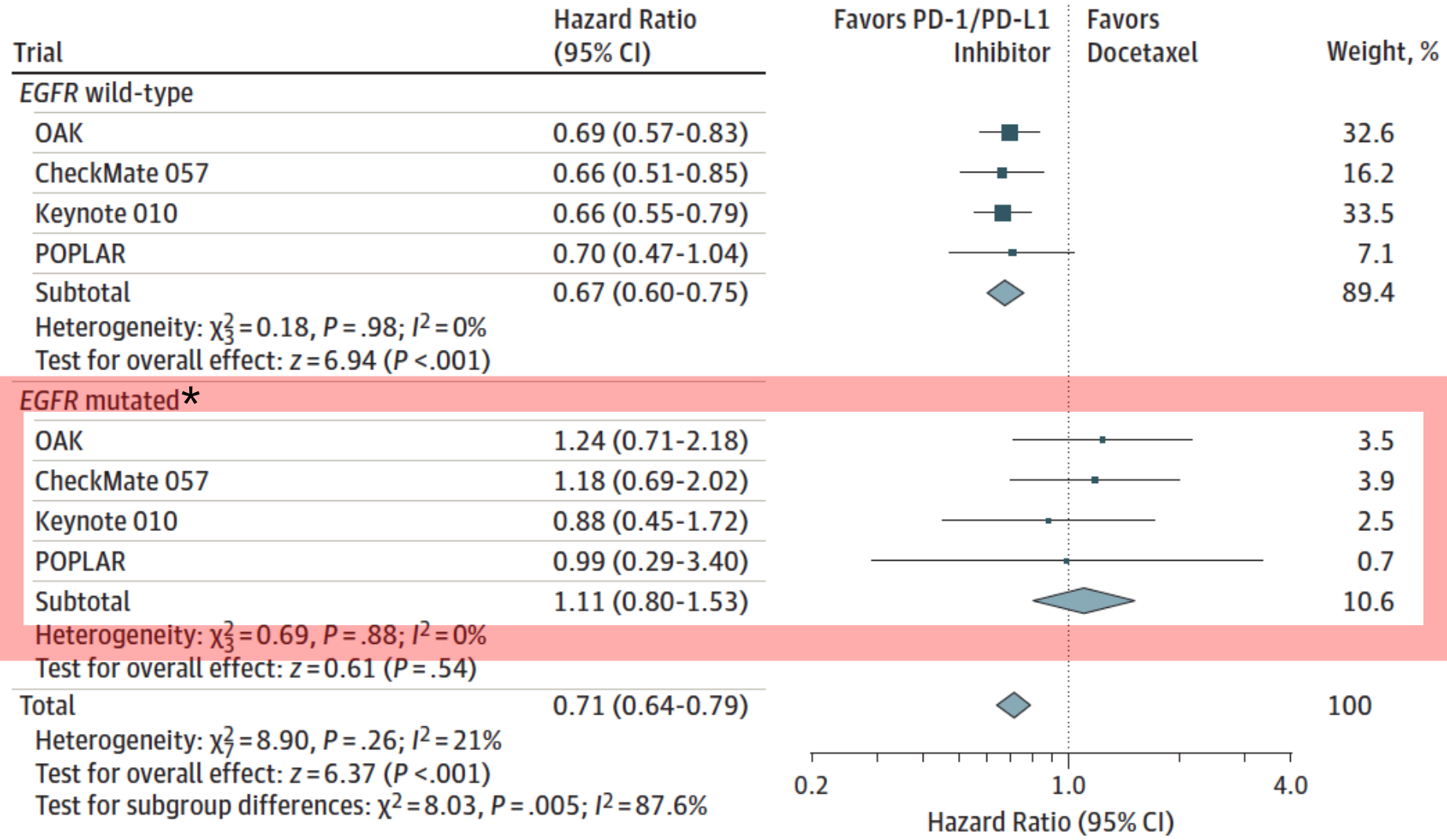

Geen overlevingsvoordeel bij
de EGFR-Mut behandeld met ICI, maar een trend
naar slechtere overleging ivm docetaxel

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* TKI → chemo → ICI

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Subanalyses EGFR grote trials : 2-3de lijn

Durvalumab as third-line or later treatment for advanced non-small-cell lung cancer (ATLANTIC): an open-label, single-arm, phase 2 study

* TKI → chemo → ICI ovv durvalumab

Marina Chiara Garassino, Byoung-Chul Cho, Joo-Hang Kim, Julien Mazières, Johan Vansteenkiste, Hervé Lena, Jesus Corral Jaime, Jhanelle E Gray,

	Cohort 1, EGFR+/ALK+		Cohort 2, EGFR−/ALK−*	
	<25%†	≥25%†‡	<25%†	≥25%†‡
Patients evaluable for response per independent central review§				
Total	28	74	93	146
Confirmed objective response	1 (3·6%, 0·1–18·3)	9 (12·2%, 5·7–21·8)	7 (7·5%, 3·1–14·9)	24 (16·4%, 10·8–23·5)
Full analysis set**				
Total	30	77	94	149
PFS, months	1·9 (1·8–1·9)	1·9 (1·8–3·6)	1·9 (1·8–1·9)	3·3 (1·9–3·7)
OS, months	9·9 (4·2–13·0)	13·3 (8·1–NC)	9·3 (5·9–10·8)	10·9 (8·6–13·6)
OS at 1 year	40·0% (22·1–57·4)	54·8% (41·5–66·3)	34·5% (25·0–44·1)	47·7% (39·3–55·5)

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‘Real world’ Retrospectieve cohortes

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

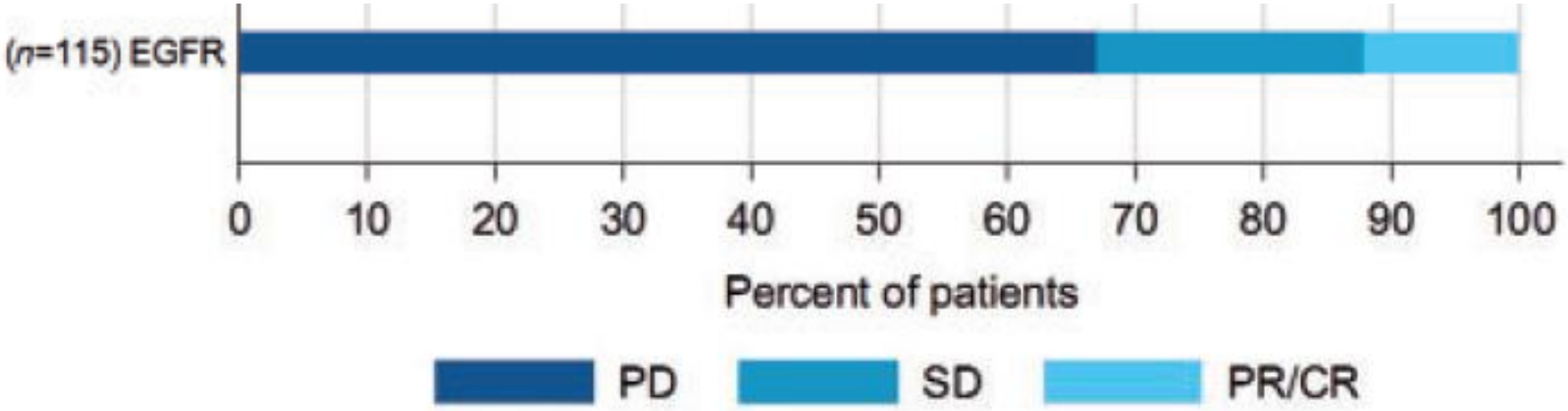
Annals of Oncology 30: 1321–1328, 2019
doi:10.1093/annonc/mdz167
Published online 24 May 2019

ORIGINAL ARTICLE

Immune checkpoint inhibitors for patients with advanced lung cancer and oncogenic driver alterations: results from the IMMUNOTARGET registry

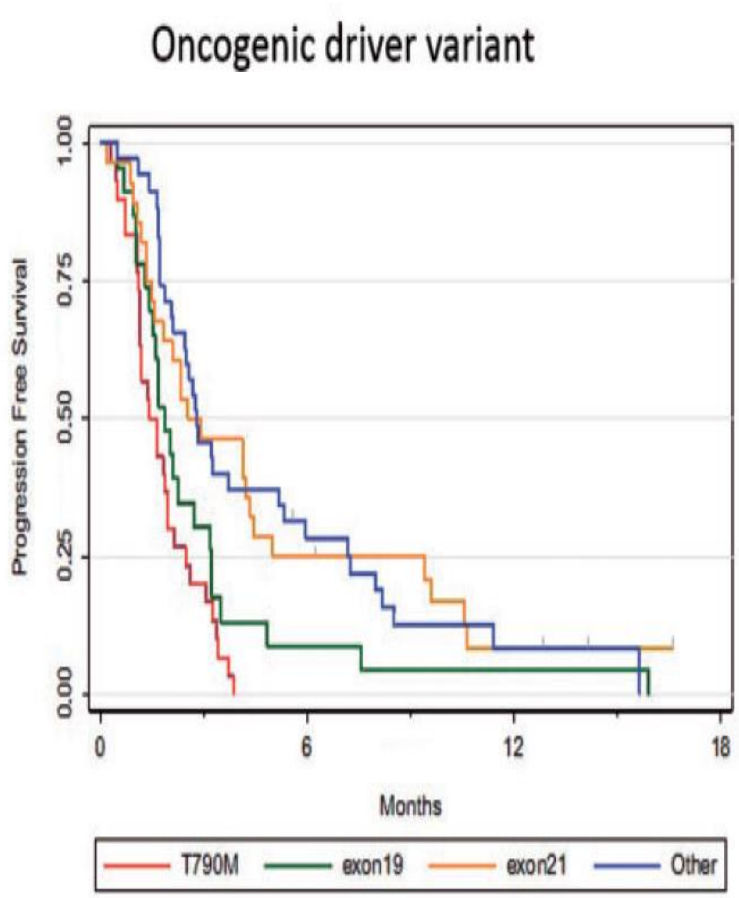
Table 1. Clinical and biological description according to mutation type

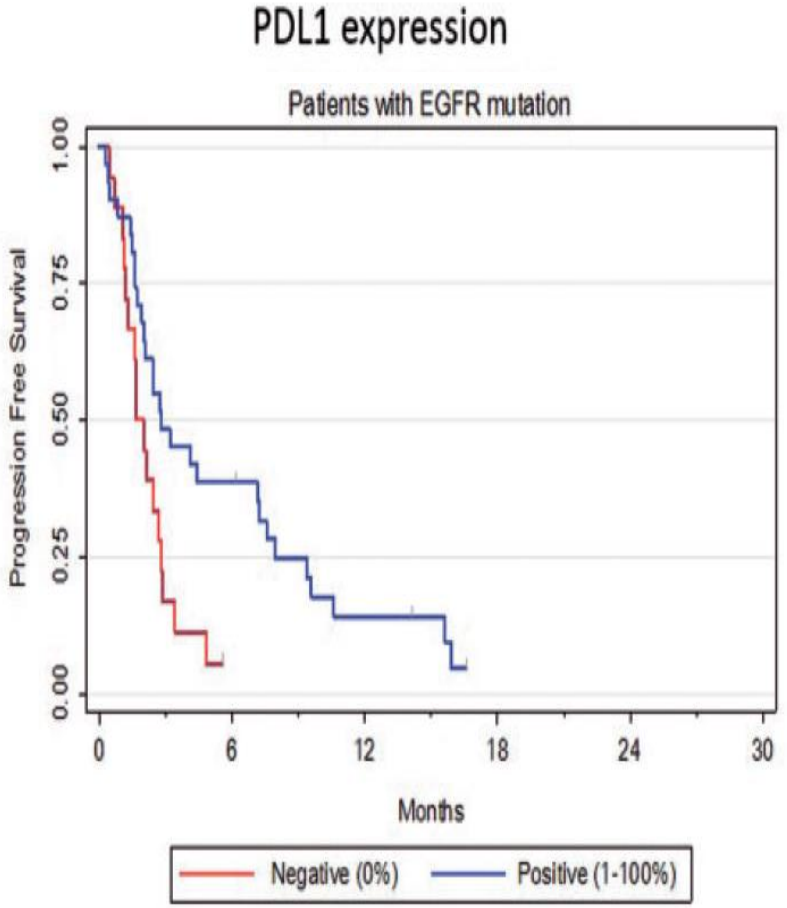
	EGFR *N* = 125		KRAS *N* = 271		ALK *N* = 23		BRAF *N* = 43		ROS1 *N* = 7		HER2 *N* = 29		RET *N* = 16		MET *N* = 36	
Gender (*n*=551)																
Male	48	38.4%	141	52%	12	52.2%	24	55.8%	5	71.4%	15	51.7%	7	43.8%	21	58.3%
Female	77	61.6%	130	48%	11	47.8%	19	44.2%	2	28.6%	14	48.3%	9	56.3%	15	41.7%



Immunotarget EGFR : belang vd varianten & PDL-1

EGFR





exon 21 doet het beter
dan **exon 19** op ICI

PDL1 1-100% doet het
Beter dan **PDL1 0%**

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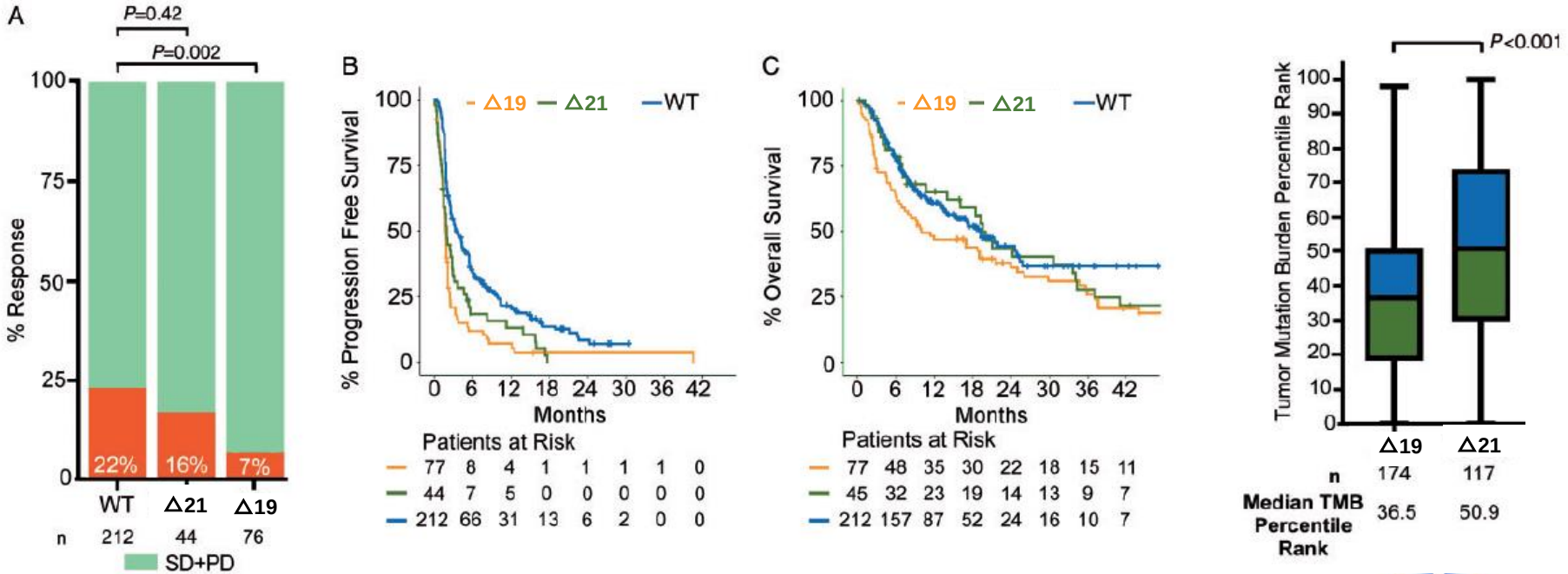
Exon 19 vs 21 : relevant voor ICI ?

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

Annals of Oncology 30: 1311–1320, 2019
doi:10.1093/annonc/mdz141
Published online 14 May 2019

ORIGINAL ARTICLE

EGFR mutation subtypes and response to immune checkpoint blockade treatment in non-small-cell lung cancer



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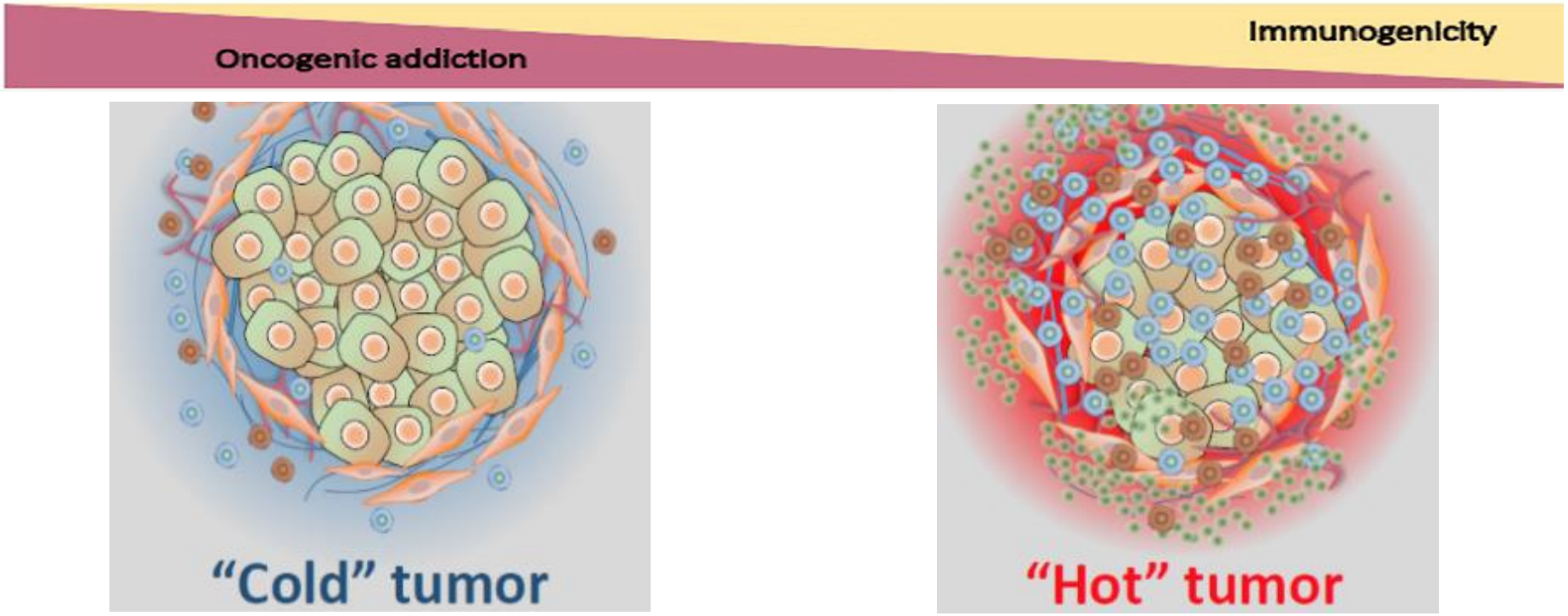
Waarom lukt het niet met ICI bij EGFR Mut ?



Oncogene verslaving
Lage TMB, weinig 'neo-Ag'
Nauwelijks inflammatie
(CD73 expressie)

Geen oncogene verslaving
Hoge TMB, veel 'neo-Ag'
Uitgesproken inflammatie

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Is die TBM dan zo relevant ?

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JUNE 22, 2017 VOL. 376 NO. 25

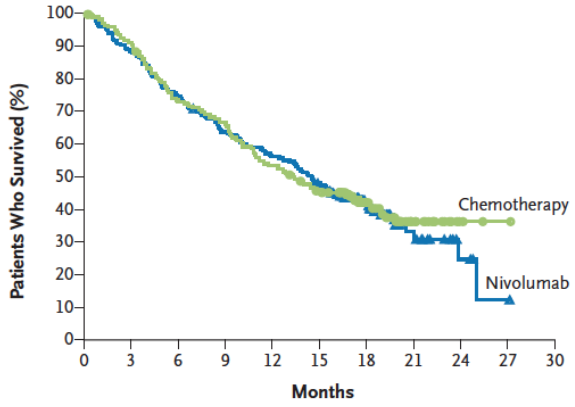
First-Line Nivolumab in Stage IV or Recurrent Non–Small-Cell Lung Cancer

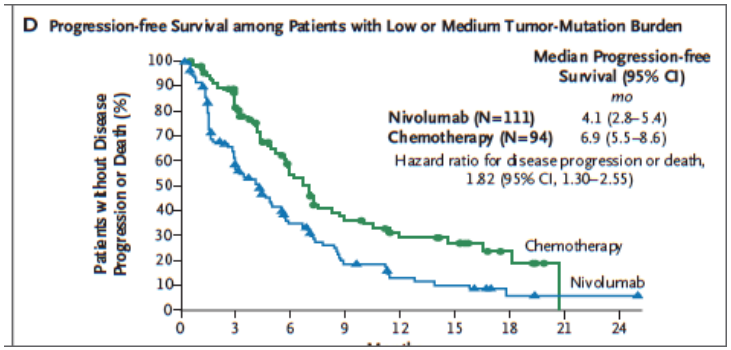
Checkmate 026

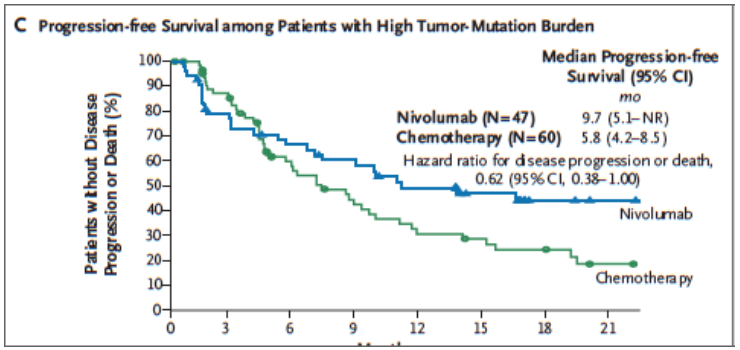
B Overall Survival

	Median Overall Survival (95% CI) *mo*	1-Yr Overall Survival Rate %
Nivolumab (N=211)	14.4 (11.7–17.4)	56
Chemotherapy (N=212)	13.2 (10.7–17.1)	54

Hazard ratio for death, 1.02 (95% CI, 0.80–1.30)







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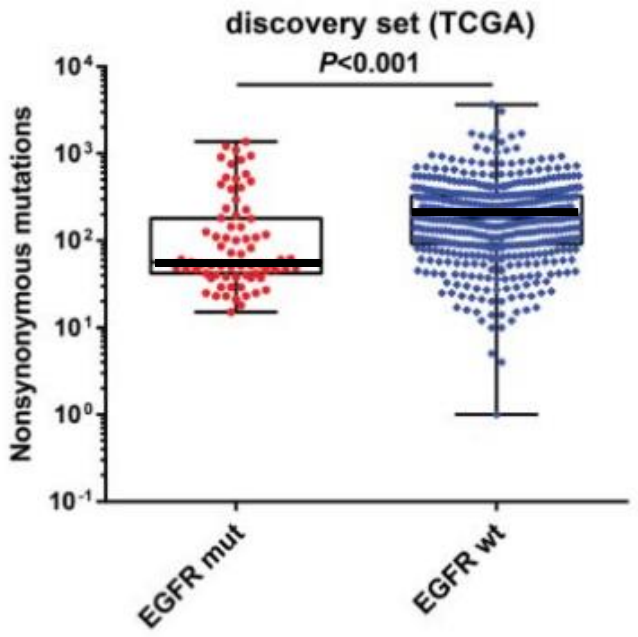
2017, VOL. 6, NO. 11, e1356145 (9 pages)
https://doi.org/10.1080/2162402X.2017.1356145

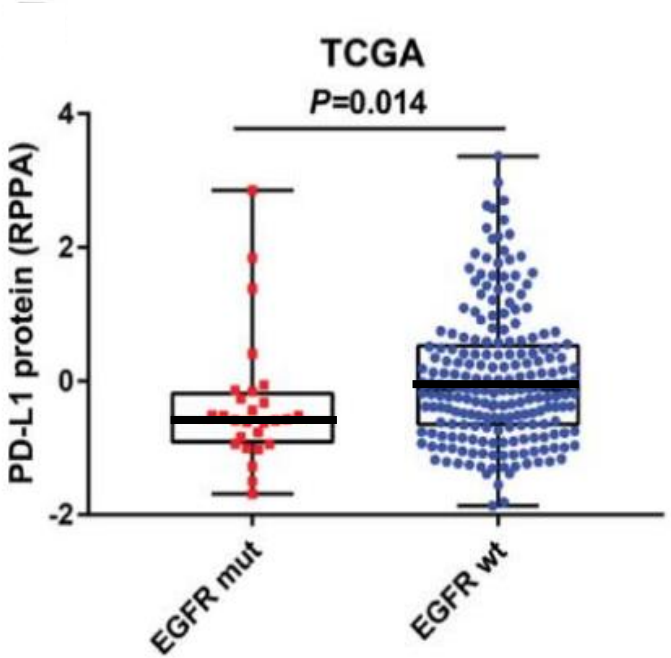
Taylor & Francis Group

ORIGINAL RESEARCH

EGFR mutation correlates with uninflamed phenotype and weak immunogenicity, causing impaired response to PD-1 blockade in non-small cell lung cancer

Zhong-Yi Dong[a,b,#], Jia-Tao Zhang[a,#], Si-Yang Liu[a,#], Jian Su[a], Chao Zhang [a], Zhi Xie[a], Qing Zhou[a], Hai-Yan Tu[a],





Kunnen we het beter doen ?

- Combinatie TKI + ICI
- Combinatie Chemo + ICI na TKI

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Data ICI+TKI bij EGFR-mutanten

TABLE 1. EGFR-TKI in Combination With ICI for Patients With Nonsquamous, EGFR-Mutant NSCLC

TKI	Erlotinib	Erlotinib	Gefitinib	Erlotinib/Gefitinib	Osimertinib
ICI	Atezolizumab	Nivolumab	Durvalumab	Pembrolizumab	Durvalumab
Trial phase	Ib	I	I	I/II	Ib Tatton-trial
Line of treatment	First or second	First or second	First	First	First or second
No. of patients	28	20	56	19	44
ORR	75%	Second line: 15%	63%	41.7%	First line: 70%
Halted	No	No	No	No	Yes
Grade 3–5 toxicity	43%	25%	70%	71.4% (gefitinib arm)	38%
Main toxicity	ALT increase, pyrexia, rash, diarrhea	Liver enzyme, diarrhea, weight loss	ALT/AST increase; > 50% treatment-emergent adverse events leading to discontinuation	Liver toxicity, rash	Interstitial lung disease

ICI + TKI tezamen leiden tot onaanvaardbare toxiciteit

ICI + TKI niet effectiever dan TKI alleen

(Tatton = Flaura)

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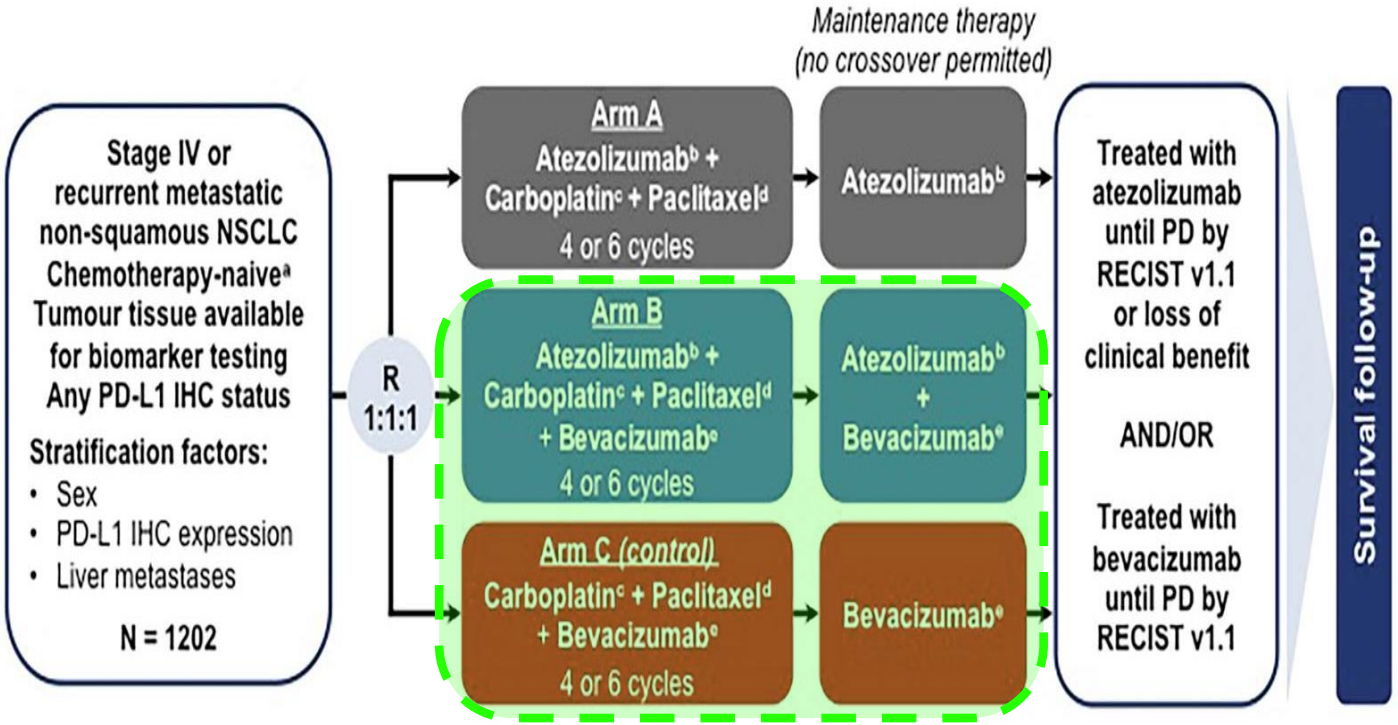
Data ICI + chemo : opportuniteit ?

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Atezolizumab for First-Line Treatment of Metastatic Nonsquamous NSCLC

M.A. Socinski, R.M. Jotte, F. Cappuzzo, F. Orlandi, D. Stroyakovskiy, N. Nogami,



Impower 150 (non-squamous)

Table 1. Baseline Characteristics of All Enrolled Patients (Intention-to-Treat Population).*

Characteristic	ABCP Group (N=400)	BCP Group (N=400)
Median age (range) — yr	63 (31–89)	63 (31–90)
Age group — no. (%)		
<65 yr	215 (53.8)	226 (56.5)
65–74 yr	149 (37.2)	132 (33.0)
75–84 yr	33 (8.2)	39 (9.8)
≥85 yr	3 (0.8)	3 (0.8)
Male sex — no. (%)	240 (60.0)	239 (59.8)
Liver metastases absent at enrollment — no. (%)	347 (86.8)	343 (85.8)
Race or ethnic group — no. (%)†		
White	322 (80.5)	335 (83.8)
Asian	56 (14.0)	46 (11.5)
Black	3 (0.8)	12 (3.0)
American Indian or Alaska Native	3 (0.8)	1 (0.2)
Multiple	3 (0.8)	0
Unknown	13 (3.2)	6 (1.5)
ECOG performance-status score — no./total no. (%)‡		
0	159/397 (40.1)	179/397 (45.1)
1	238/397 (59.9)	218/397 (54.9)
History of tobacco use — no. (%)		
Never	82 (20.5)	77 (19.2)
Current	90 (22.5)	92 (23.0)
Previous	228 (57.0)	231 (57.8)
Nonsquamous histologic subtype — no. (%)		
Adenocarcinoma	378 (94.5)	377 (94.2)
Other§	19 (4.8)	17 (4.2)
Unknown or not assessed	3 (0.8)	6 (1.5)
EGFR mutation status — no. (%)¶		
Positive	35 (8.8)	45 (11.3)
Negative	352 (88.0)	345 (86.3)
EML4-ALK rearrangement status — no. (%)‖		
Positive	13 (3.2)	21 (5.2)
Negative	383 (95.8)	375 (93.8)
KRAS mutation status — no. (%)**		
Positive	47 (11.8)	38 (9.5)
Negative	59 (14.8)	77 (19.2)

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Impower 150 (non-squamous)

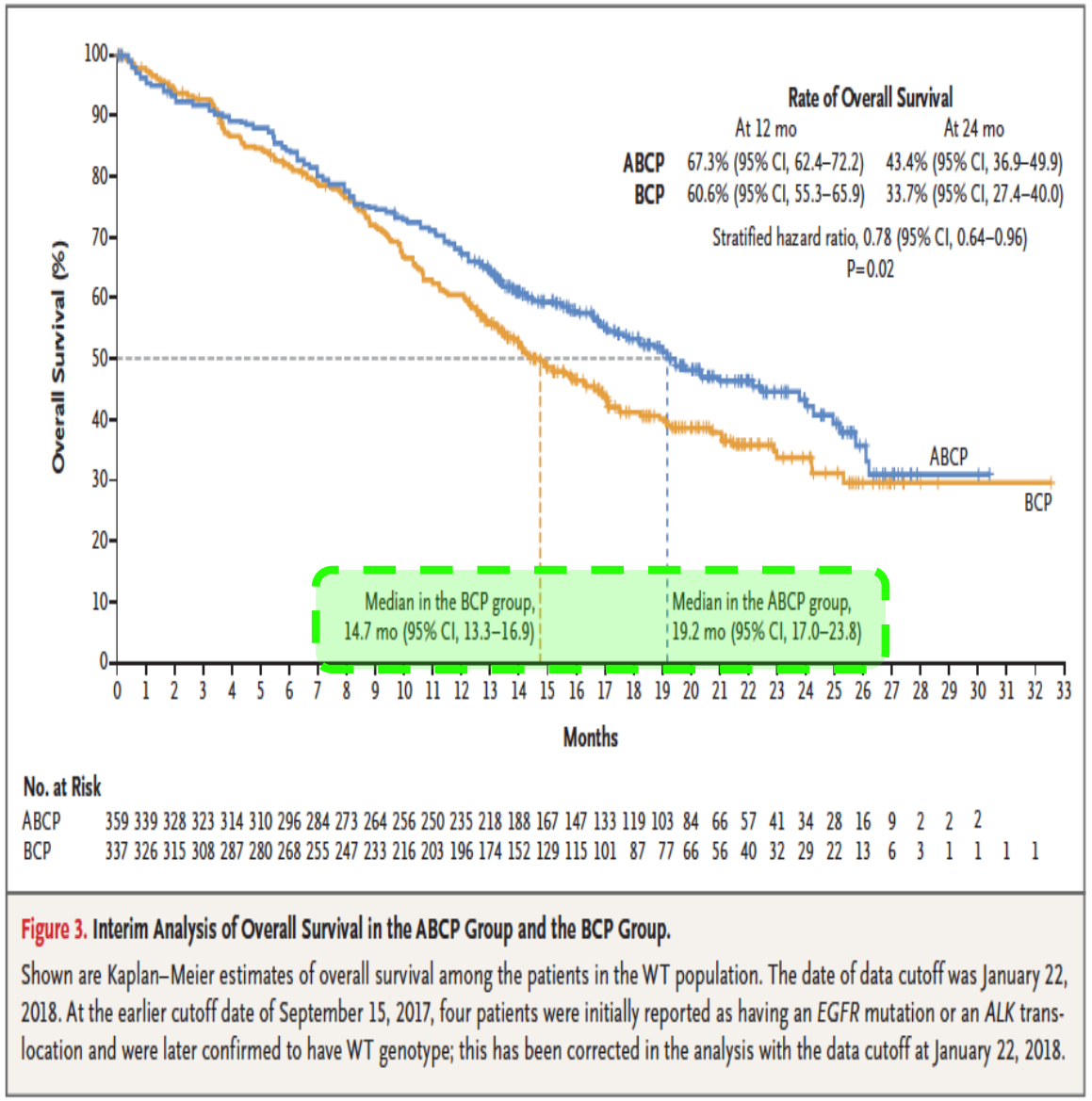

Figure 3. Interim Analysis of Overall Survival in the ABCP Group and the BCP Group.

Shown are Kaplan–Meier estimates of overall survival among the patients in the WT population. The date of data cutoff was January 22, 2018. At the earlier cutoff date of September 15, 2017, four patients were initially reported as having an *EGFR* mutation or an *ALK* translocation and were later confirmed to have WT genotype; this has been corrected in the analysis with the data cutoff at January 22, 2018.

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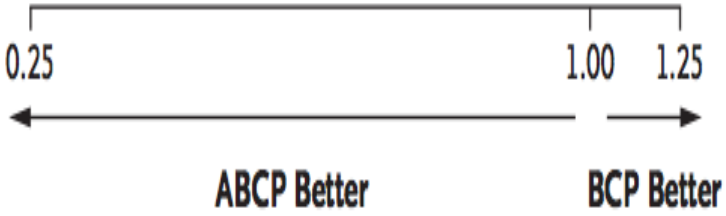
Population	No. of Patients (%)	Median Progression-free Survival (mo)		Hazard Ratio (95% CI)
		ABCP	BCP	
ITT population	800 (100)	8.3	6.8	0.61 (0.52–0.72)
Patients with *EGFR* or *ALK* genetic alternations	108 (14)	9.7	6.1	0.59 (0.37–0.94)
WT population	692 (87)	8.3	6.8	0.62 (0.52–0.74)



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IMpower150: Updated Efficacy Analysis in Patients With EGFR Mutations

Abstract #1882
Poster #1293P

Martin Reck,[1] Tony Mok,[2] Mark A. Socinski,[3] Robert M. Jotte,[4,5] Darren Wan-Teck Lim,[6] Federico Cappuzzo,[7] Francisco Orlandi,[8] Daniil Stroyakovskiy,[9] Naoyuki Nogami,[10] Delvys Rodriguez-Abreu,[11] Denis Moro-Sibilot,[12] Christian A. Thomas,[13] Fabrice Barlesi,[14] Gene Finley,[15] Geetha Shankar,[16] Wei Yu,[16] David Merritt,[17] Makoto Nishio[18]

ITT
(All randomised patients)

ITT-WT[a]
(87% patients)

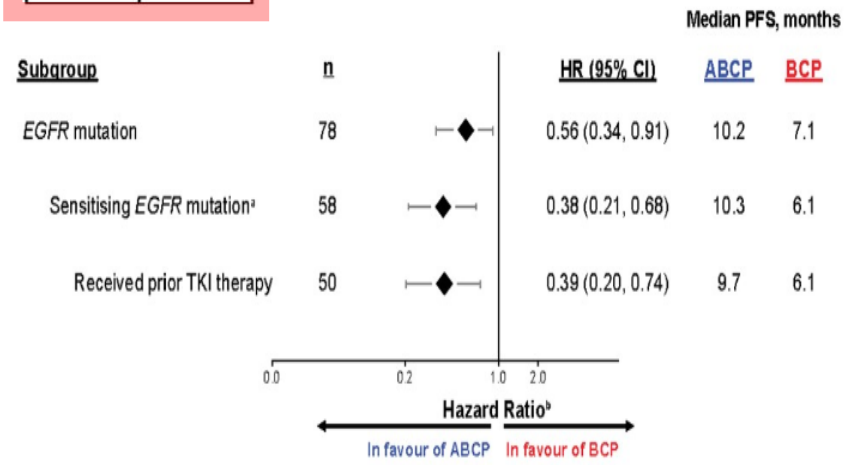
EGFR/ALK +
(13% patients)

ALK +
(3% patients)

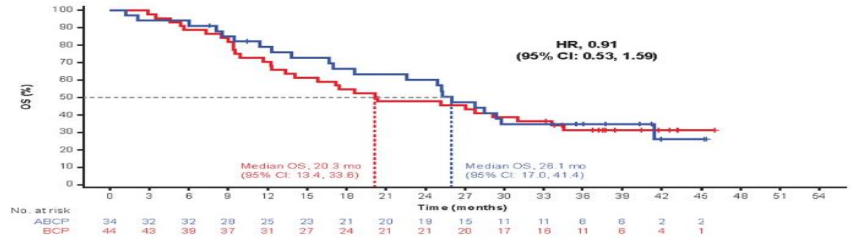
EGFR-mt
(10% patients)

ORR (95% CI)[a]	
ABCP (n = 34)	BCP (n = 44)
73.5%	40.9%

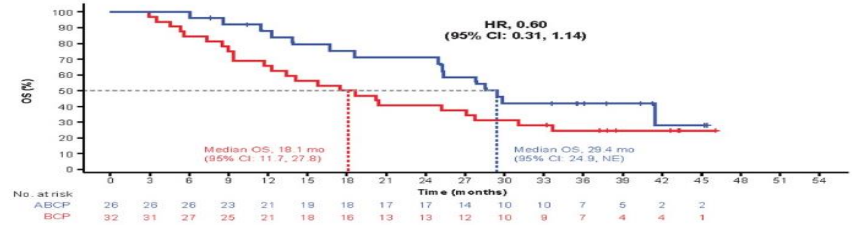
ABCP vs BCP



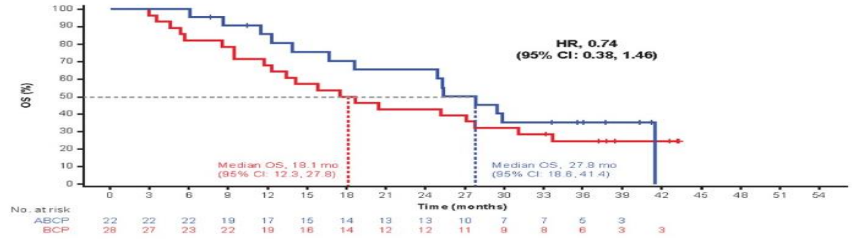
ABCP vs BCP *EGFR+*



ABCP vs BCP Sensitising *EGFR+*



ABCP vs BCP Sensitising *EGFR+* With Prior TKI Therapy



Safety

- The safety profile of ABCP was consistent with the safety profile of the individual medicines and was well-tolerated in patients with *EGFR*+ NSCLC despite a longer duration of therapy (Table 3)
- Grade 3 or 4 treatment-related AEs were reported in 57%, 67% and 56% of patients who received ACP, ABCP and BCP treatment, respectively
- Only 1 treatment-related Grade 5 AE was reported in the BCP treatment arm

Ander onderzoek : Keynote 789

P1.01-81 Phase 3 Study of Pemetrexed-Platinum with or without Pembrolizumab for TKI-Resistant/EGFR-Mutated Advanced NSCLC: KEYNOTE-789

G. Riely • R. Hui • D. Carbone • ... X. Xu • T. Dang • J. Chih-Hsin Yang • Show all authors

Actual Study Start Date :	June 29, 2018
Estimated Primary Completion Date :	June 15, 2023
Estimated Study Completion Date :	June 15, 2023

ClinicalTrials.gov Identifier: NCT03515837

Recruitment Status : Active, not recruiting
First Posted : May 4, 2018
Last Update Posted : July 7, 2020

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EGFR en ICI samengevat

- Als eerste lijnstherapie
  - monotherapie : neen (ineffectief)
  - combinatie met TKI : neen (niet beter en tox)
- Als tweede lijnstherapie
  - monotherapie : neen (quid exon 21)
  - combinatie met TKI : neen (niet beter en tox)
  - Als combinatie in ABCP schema : optie
- Herinner : ICI → TKI is toxisch, dus wacht op resultaat Molec OZ

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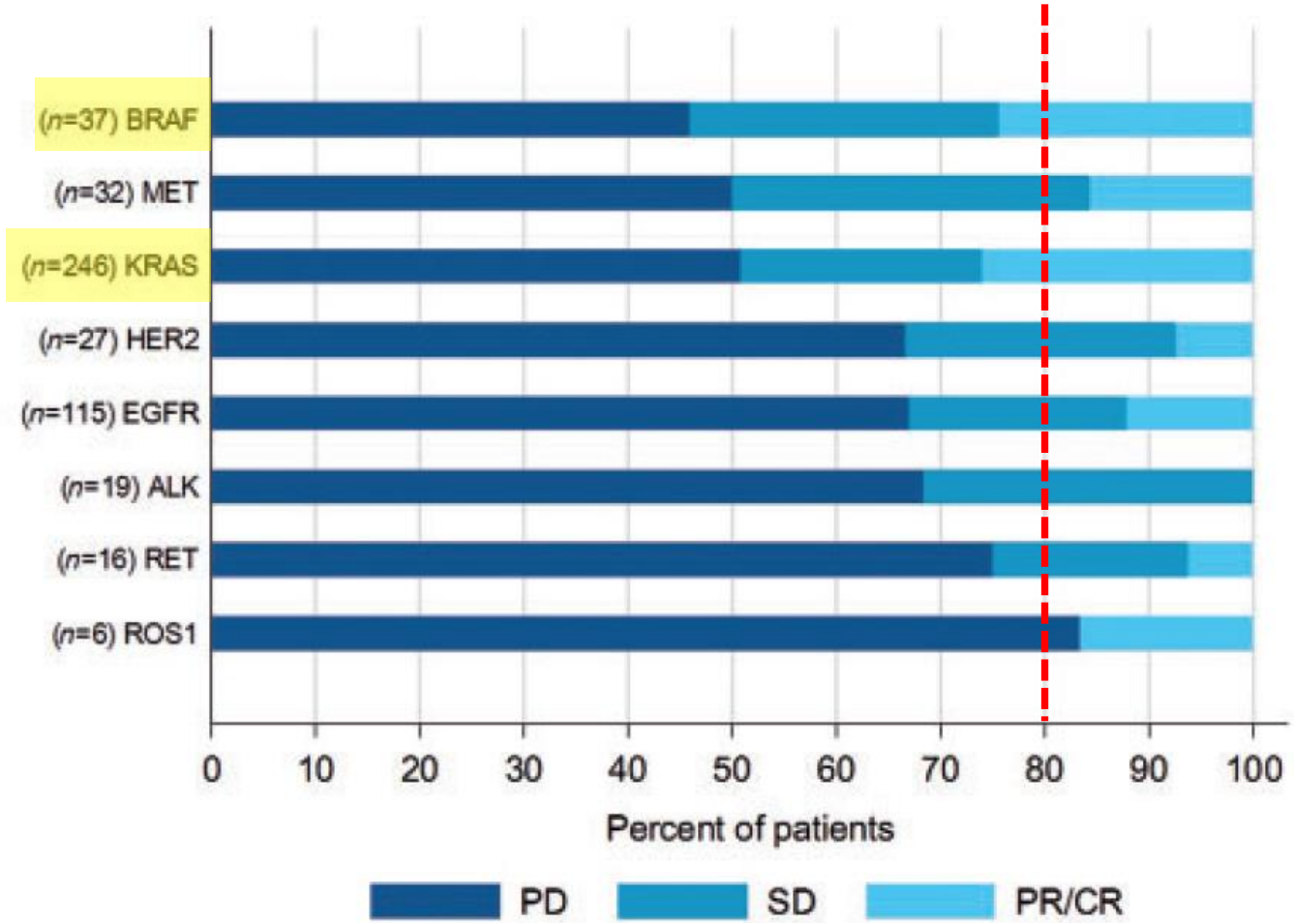
Andere mutaties en ICI



ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

Annals of Oncology 30: 1321–1328, 2019
doi:10.1093/annonc/mdz167
Published online 24 May 2019

ORIGINAL ARTICLE

Immune checkpoint inhibitors for patients with advanced lung cancer and oncogenic driver alterations: results from the IMMUNOTARGET registry

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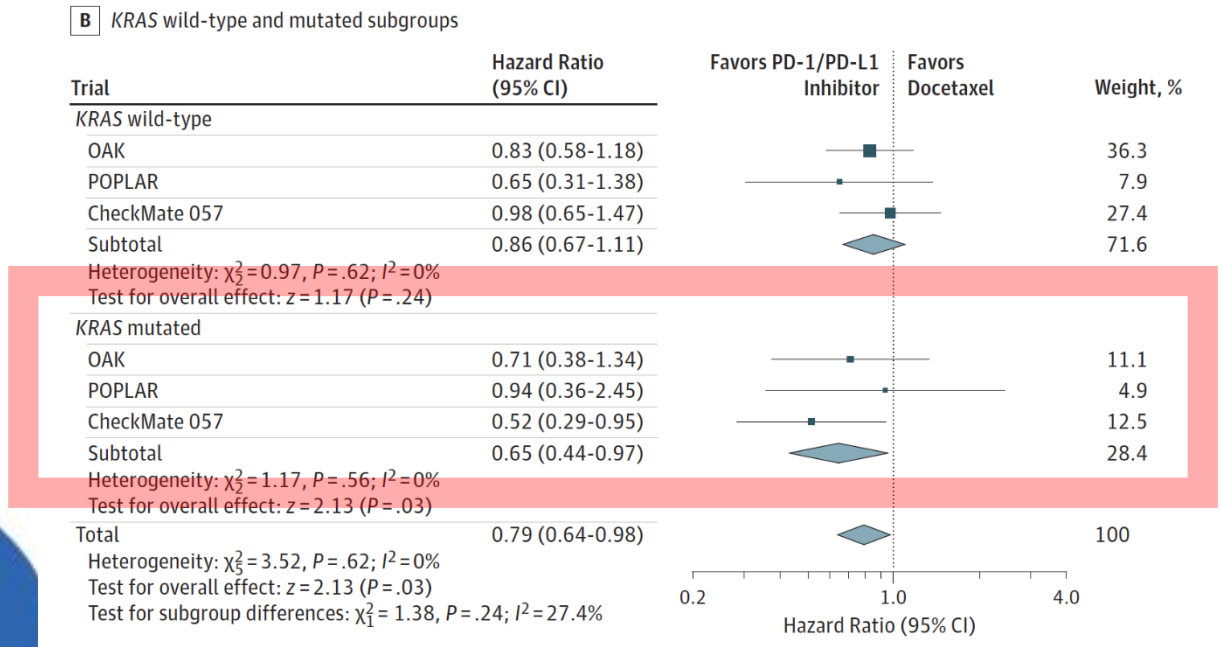
Andere mutaties : KRAS en ICI

- KRAS is de meest frequente mutatie
- Prognostisch ongunstig factor
- Gekenmerkt door hoge TMB (tobacco)

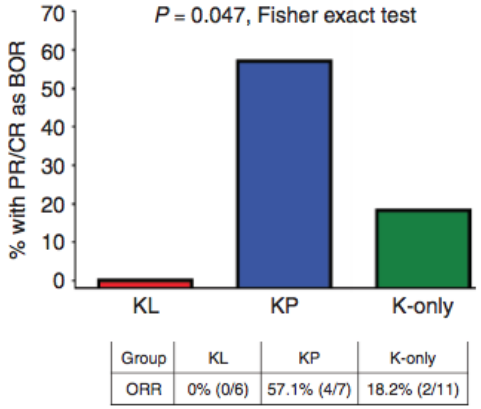


JAMA Oncol. 2018;4(2):210-216.

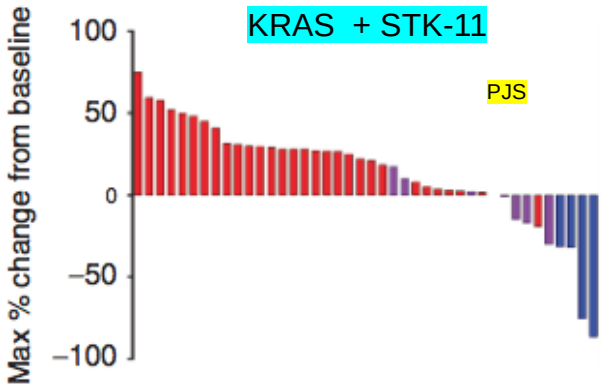
Andere mutaties : KRAS en ICI

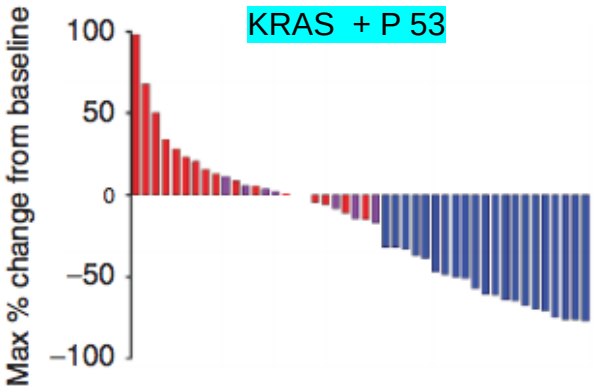
- PDL-1 expressie predictief voor ORR
- ORR 57% (1L) – 25% (2L)

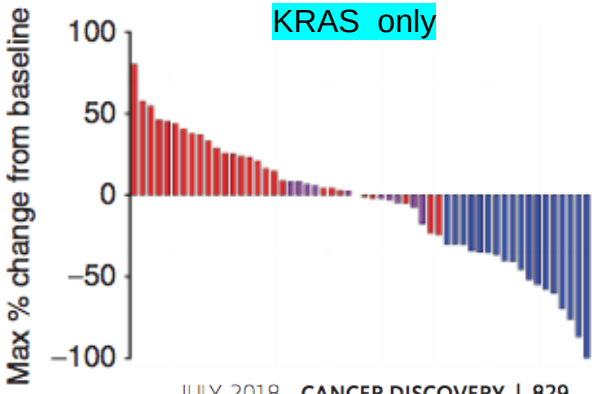
- Exploratief (co-mutaties):
  - KRAS + STK-11 : ORR 0%
  - KRAS + P53 : ORR 57%



Group	KL	KP	K-only
ORR	0% (0/6)	57.1% (4/7)	18.2% (2/11)



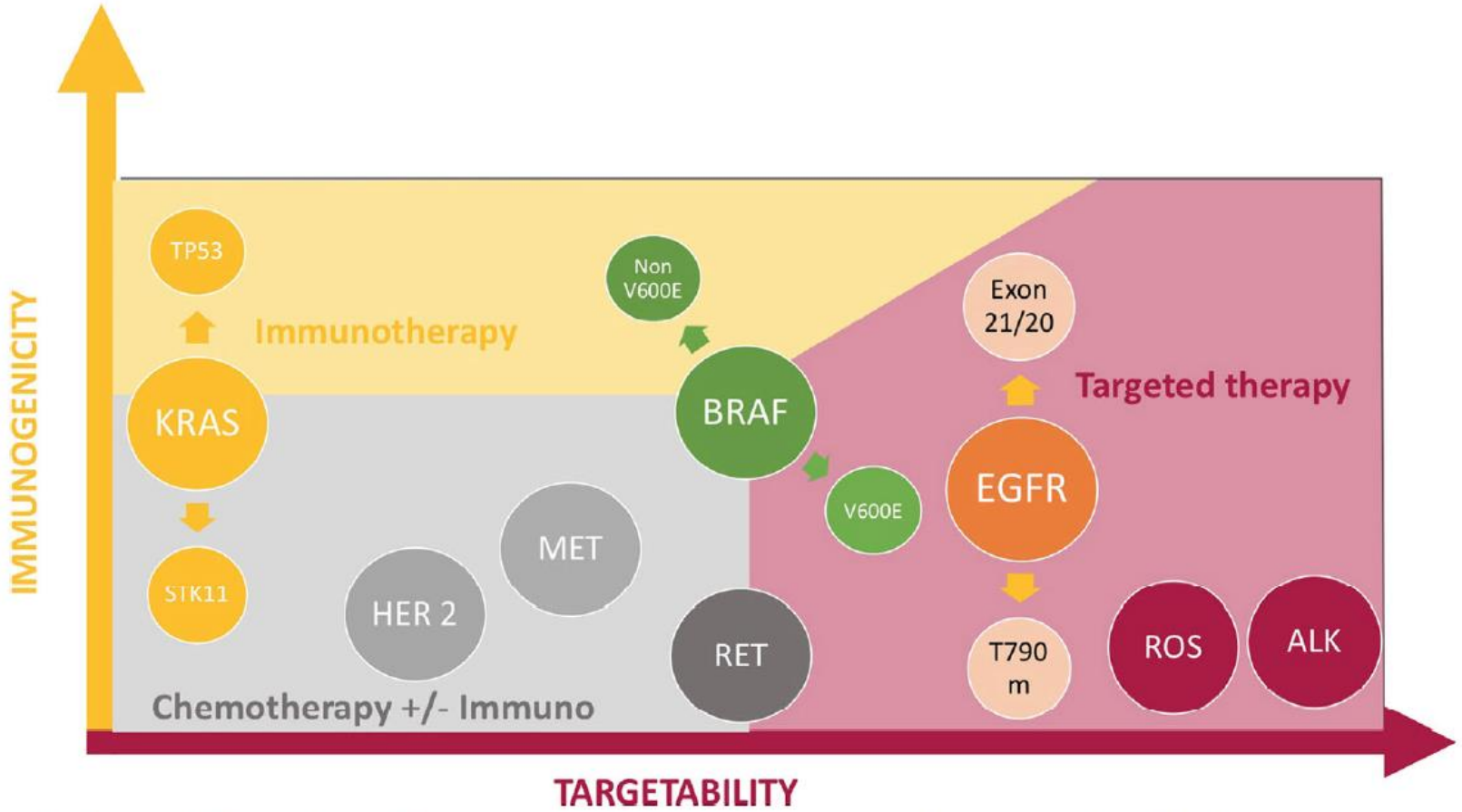




Andere mutaties : BRAF en ICI

- BRAF (V600E vs non-V600E)
- Gekenmerkt door hoge PDL-1
- Eerste lijn voor de V600E : BRAF-inh + MEK-inh
- ORR voor ICI : 10-30%
- PFS voor ICI : 3 mnd

Andere mutaties:ALK/ROS/RET/MET



Likelihood of sensitivity to ICI and/or genotype-directed agents in each oncogenic addiction setting.

Curr. Treat. Options in Oncol. (2019) 20: 60
DOI 10.1007/s11864-019-0652-3

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Andere drivers en ICI : Samengevat

- ICI bij ‘andere drivers’ : weinig data
- KRAS en BRAF hebben een ORR >20%
- De rest doet het slecht tot zeer slecht

  (incl data ICI, ICI+TKI of ICI + chemo)

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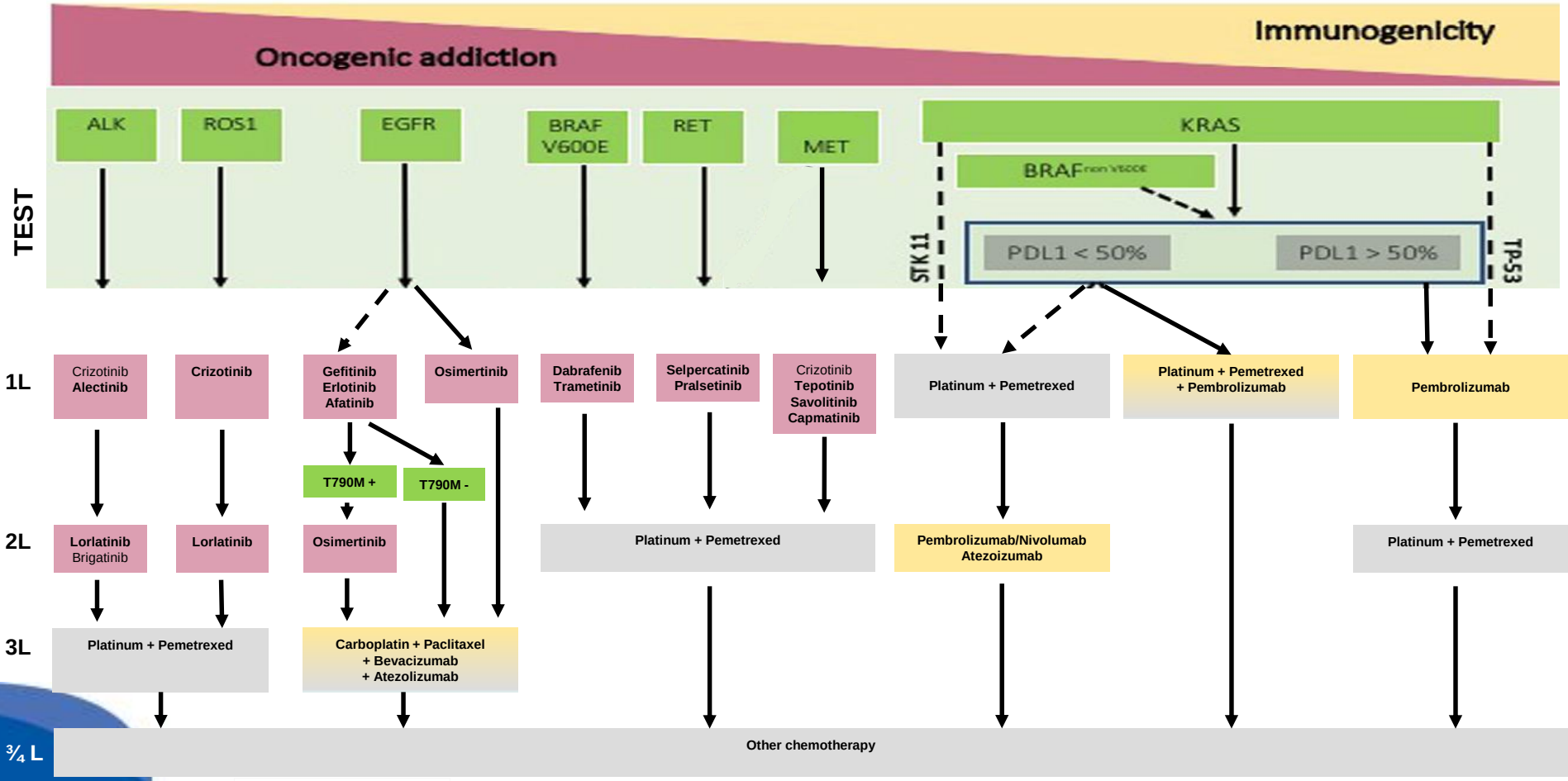
Plaats van ICI bij NSCLC met drivers



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Adapted from Curr. Treat. Options in Oncol. (2019) 20: 60
DOI 10.1007/s11864-019-0652-3

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Take Home Boodschap

Voor de pt met IV – NSCLC

- De plaats van ICI's bij ptn met IV-NSCLC met driver's blijft voor discussie zorgen
- Wacht op Molec OZ voor start ICI (zeker bij de pt die nooit gerookt heeft en dus sterk vermoeden van driver)
- Target therapie als start heeft steeds de voorkeur in geval een driver aanwezig is (uitz : KRAS / BRAF-non V600E)
- ICI als monoR/ doen het over het algemeen gesproken in deze groep niet goed (uitz : KRAS / BRAF-non V600E)

Dank voor uw aandacht

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