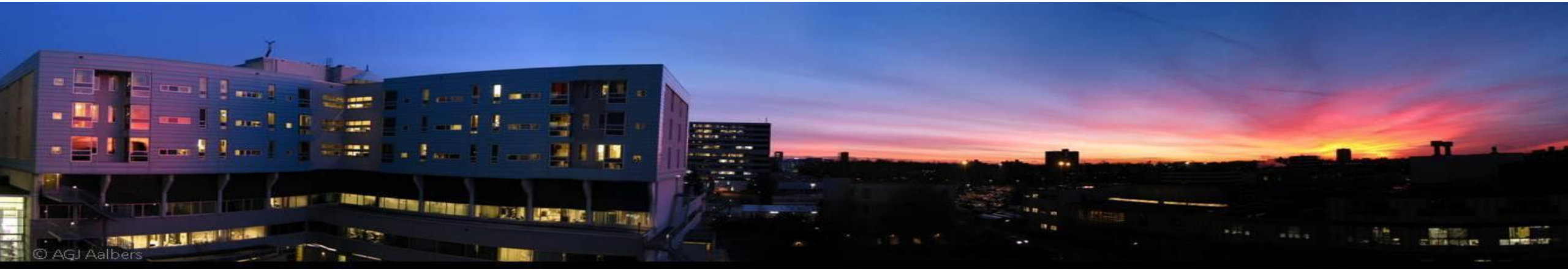
Behandeling van longkanker ontstaan door een genmutatie



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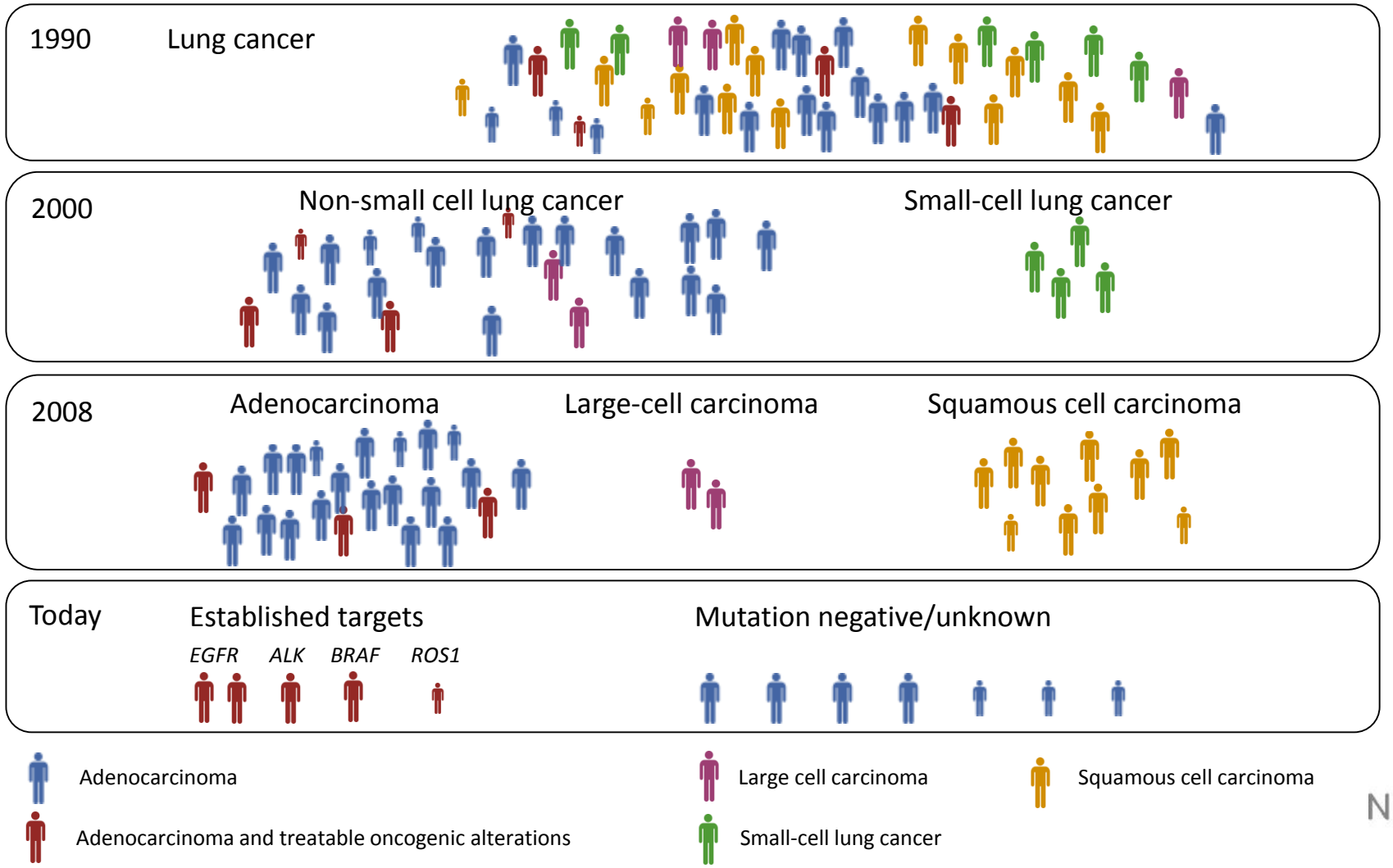
Geen longkanker is hetzelfde = DNA gematchte medicijnen



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Doelgerichte therapie voor longkanker ontstaan door een genmutatie

- Naar welke mutaties moet worden gezocht?
- Hoe kunnen deze het beste worden behandeld?
- Waarom resistentie en hoe dit te behandelen?
- Welke ontwikkelingen komen er aan?

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Naar welke mutaties moet worden gezocht?

Gene	Perc.	Alteration	Treatment
• EGFR	8%	Mutation	gefitinib, erlotinib, afatinib, osimertinib
• ALK	4%	Translocation *and mutation*	crizotinib, ceritinib, alectinib, brigatinib, lorlatinib
• ARAF	1%	Mutation	regorafenib
• BRAF	2%	Mutation	dabrafenib en trametinib
• ROS1	1%	Translocation *and mutation*	crizotinib, lorlatinib, entrectinib
• RET	1%	Translocation	BLU-667, LOXO-292
• MET	4%	Mutation and amplification	crizotinib, cabozantinib, capmatinib, savolitinib
• NTRK	<1%	Fusion	entrectinib, larotrectinib
• HER2	2%	Mutation and amplification	T-DM1, neratinib, DS-8201a
• MEK	<1%	Mutation	trametinib
• PIK3CA	1%	Mutation	AZD5363
• NRG-1	<1%	Fusion	afatinib, MCLA-128
• KRAS	25%	Mutation	?
• NRAS	<1%	Mutation	regorafenib

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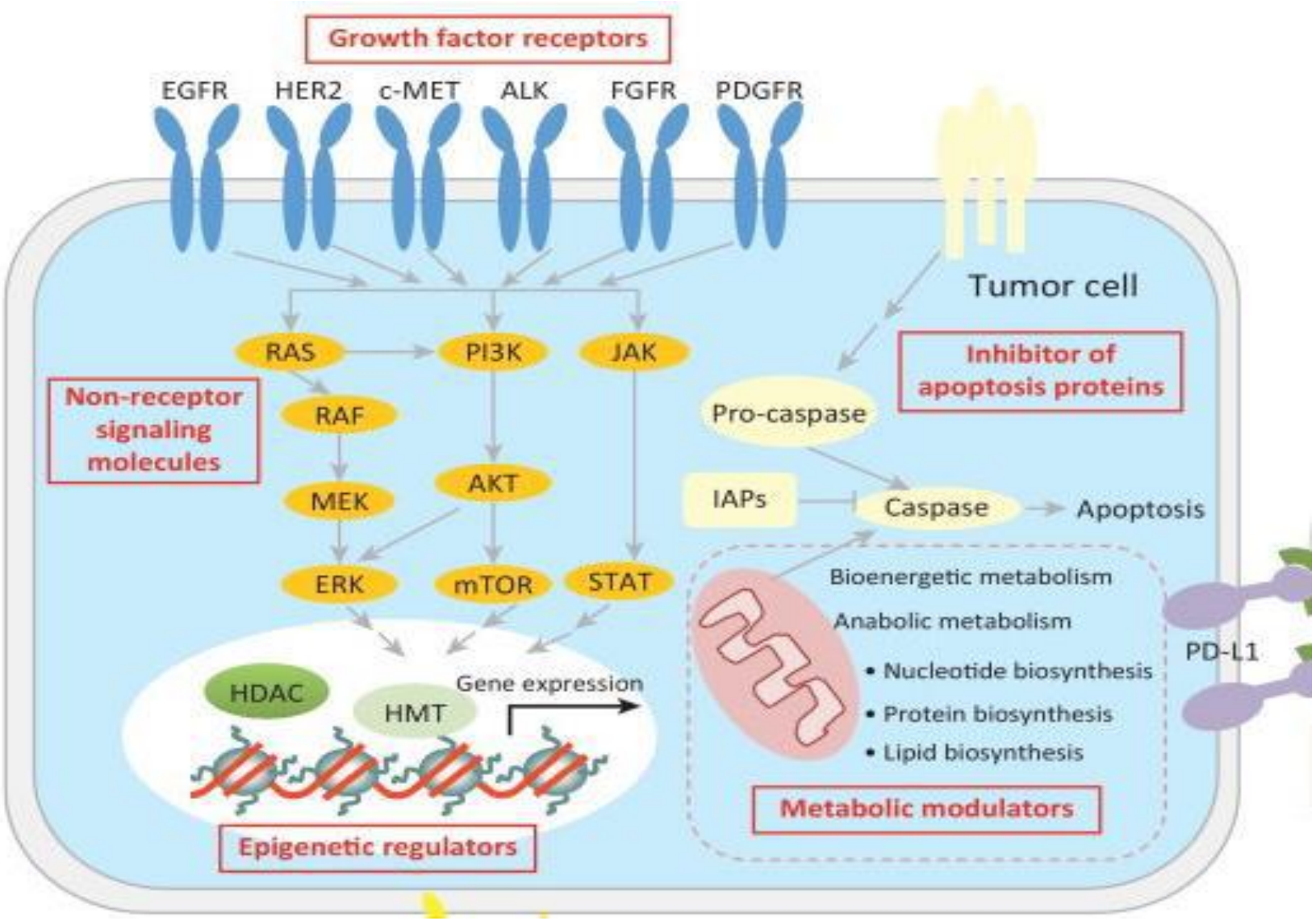
Waarom kan het zo goed werken?



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Mutatie positief longkanker heeft een lage mutatie-load en is afhankelijk van de genmutatie voor tumorgroei

Somatic Variants

Gene	Variant	Impact	Read Depth	Hotspot	Ploidy (VAF)	Clonality	Biallelic	Driver
EGFR *	c.2235_2249delGGAATTAAGAGAAGC	p.Glu746_Ala750del	138 / 176	Near	A[11x]B (83%)	Clonal		High

Tumor Mutational Load

Low (83)

The tumor mutational load represents the total number of somatic missense variants across the whole genome of the tumor. Patients with a mutational load over 140 could be eligible for immunotherapy within the DRUP study.

Tumor Mutational Burden

3.8 variants per Mb.

The tumor mutational burden score represents the number of all somatic variants across the whole genome of the tumor per Mb.

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‘Gangbaar’ longkanker heeft een hoge mutatie-load en heeft een groot aantal groeifactoren

HR-Deficiency Score

0.07

The HR-deficiency score is determined by CHORD, a WGS signature-based classifier comparing the signature of this sample with signatures found across samples with known BRCA1/BRCA2 inactivation.

Microsatellite Status

Stable (0.3837)

The microsatellite stability score represents the number of somatic inserts and deletes in (short) repeat sections across the whole genome of the tumor per Mb. This metric can be considered as a good marker for instability in microsatellite repeat regions. Tumors with a score greater than 4.0 are considered microsatellite unstable (MSI).

Tumor Mutational Load

High (688)

The tumor mutational load represents the total number of somatic missense variants across the whole genome of the tumor. Patients with a mutational load over 140 could be eligible for immunotherapy within the DRUP study.

Tumor Mutational Burden

42.8041 variants per Mb.

The tumor mutational burden score represents the number of all somatic variants across the whole genome of the tumor per Mb.

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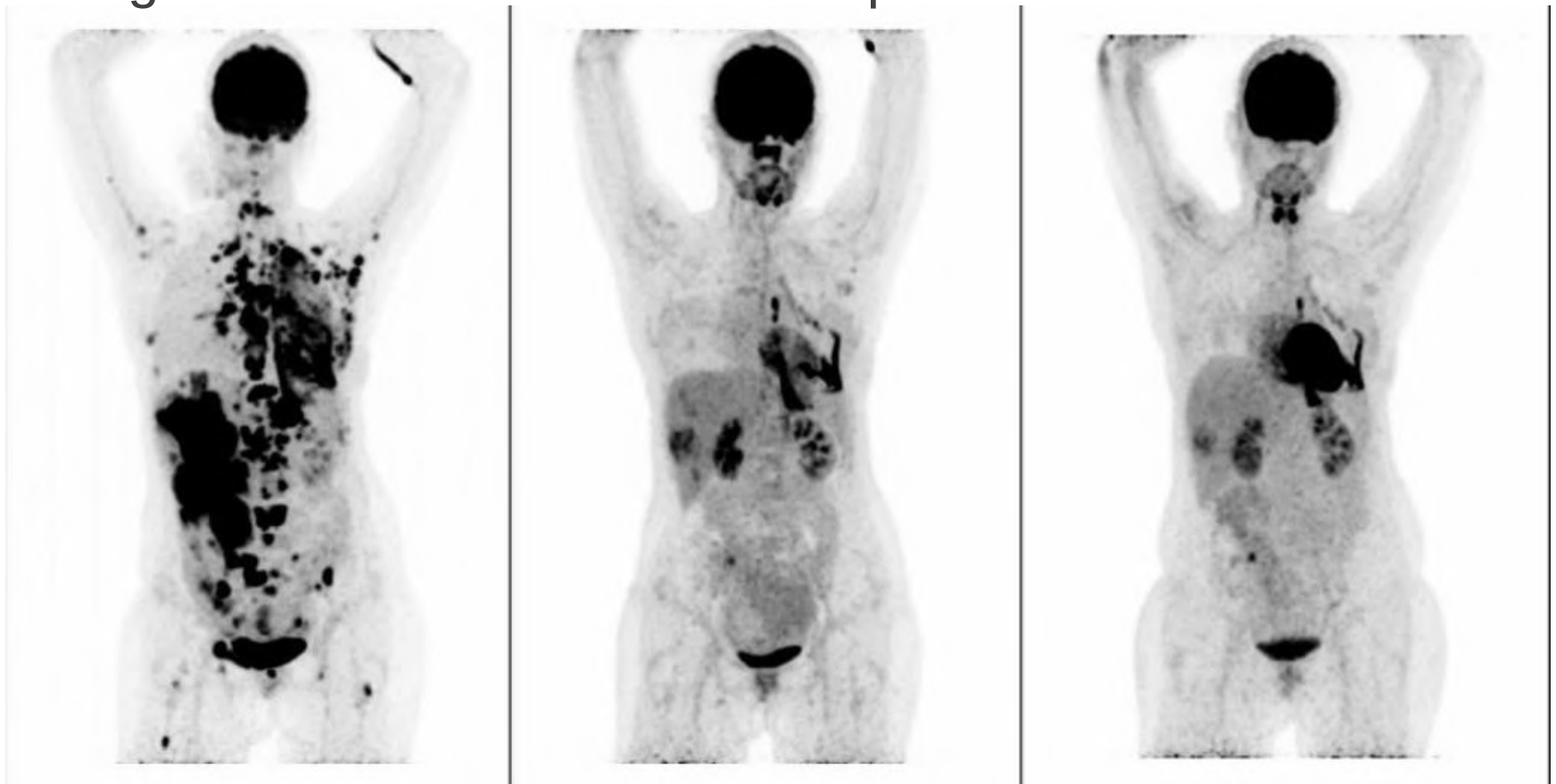
Doelgerichte behandeling voor longkanker met een genmutatie werkt

- 68 year old women.
- 30 PY
- Stage IV BRAF V600E mutation positive NSCLC.



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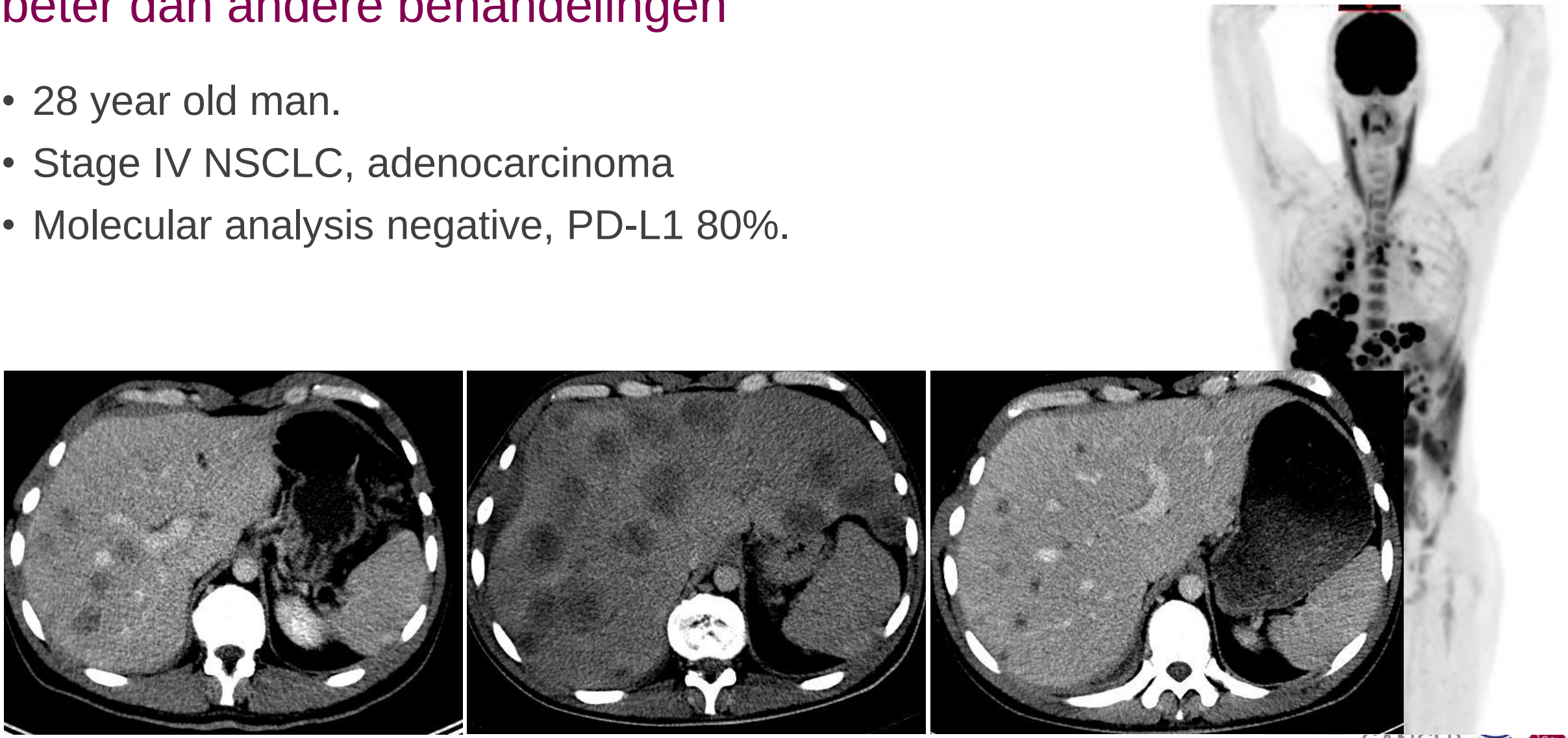
Doelgerichte behandeling voor longkanker met een genmutatie werkt beter dan andere behandelingen

- 28 year old man.
- Stage IV NSCLC, adenocarcinoma
- Molecular analysis negative, PD-L1 80%.



De genmutatie vinden maakt een (groot) verschil

- 66 year old man.
- Never smoker.
- Molecular analysis negative, PD-L1 60%.
- 2015-02 lobectomie RBK en adjuvante chemotherapie.
- 2017-04 recidief rechts wv cCRT.
- 2017-11 nieuwe laesie ROK wv SRS
- 2018-07 groei van lymfeklieren wv pembrolizumab
- 2018-09 hersenmetastase. Naar huis met BSC.

De genmutatie vinden maakt een (groot) verschil

- Ter revisie ontvangen, lobectomie rechter bovenkwab: conform, adenocarcinoom.
- Therapiekeuzetest longadenocarcinoom:
- -KRAS: niet aangetoond
- -EGFR: niet aangetoond
- -BRAF: niet aangetoond
- -HER2: niet aangetoond
- -Overige genen: niet aangetoond
- -ALK fusie: immunohistochemisch (clone 5A4): negatief
- **-ROS1 fusie: immunohistochemisch (clone D4D6): deels positief, score 1+. FISH: WEL een ROS1 translocatie aangetoond**
- -TRKpan fusie: immunohistochemisch (clone A7H6R): negatief
- -RET fusie:vervalt
- -MET exon 14 skipping: RT-PCR: niet aangetoond
- -PD-L1 immunohistochemie (clone 22C3 LDT): In dit materiaal (membraneus) positief in 55% van de tumorcellen
-
- **Aanvulling d.d. 18.12.2018:**
- **Archer Fusieanalyse: ROS1 fusie aangetoond: LRIG3 - ROS1.**

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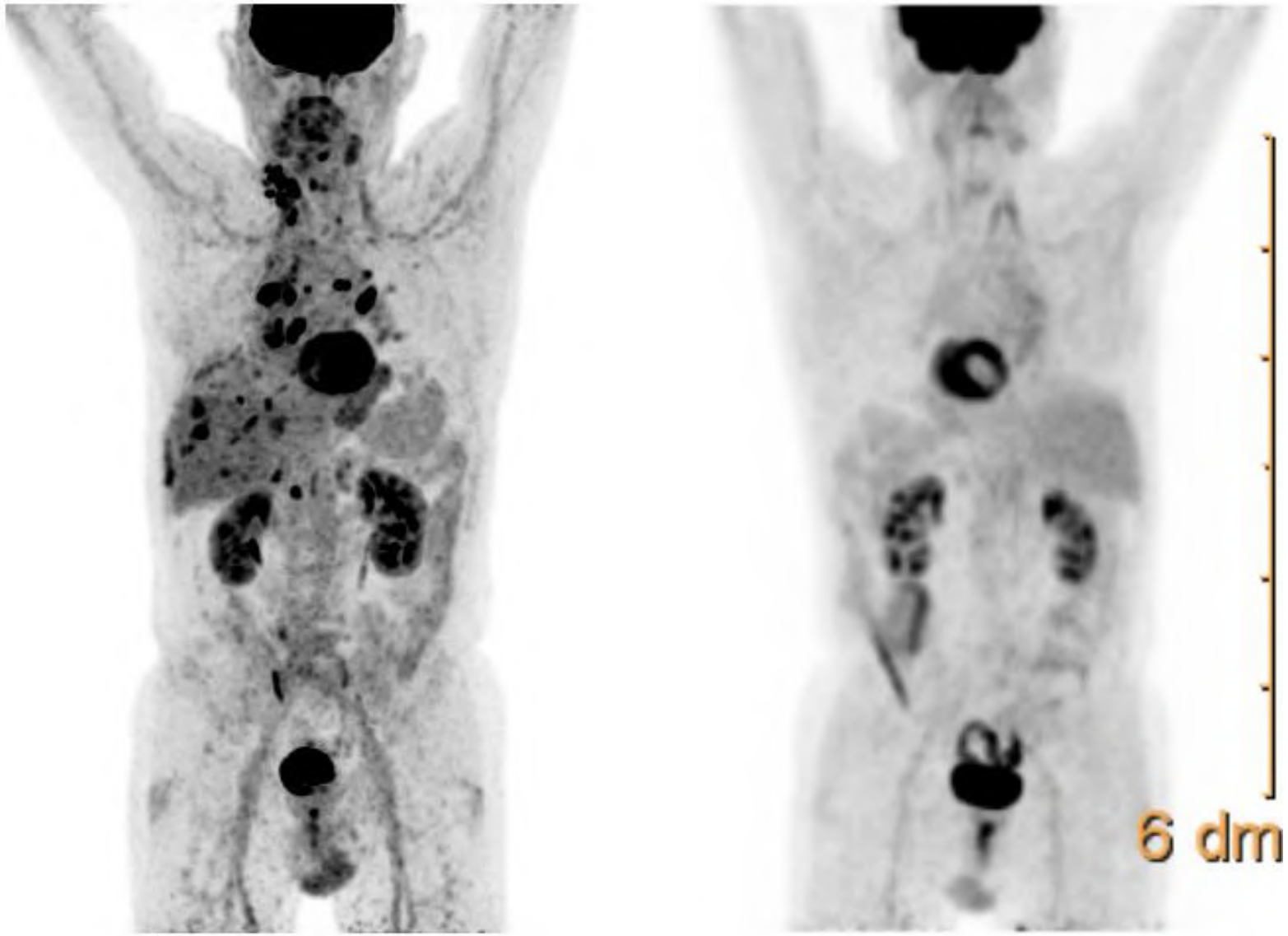
De genmutatie vinden maakt een (groot) verschil



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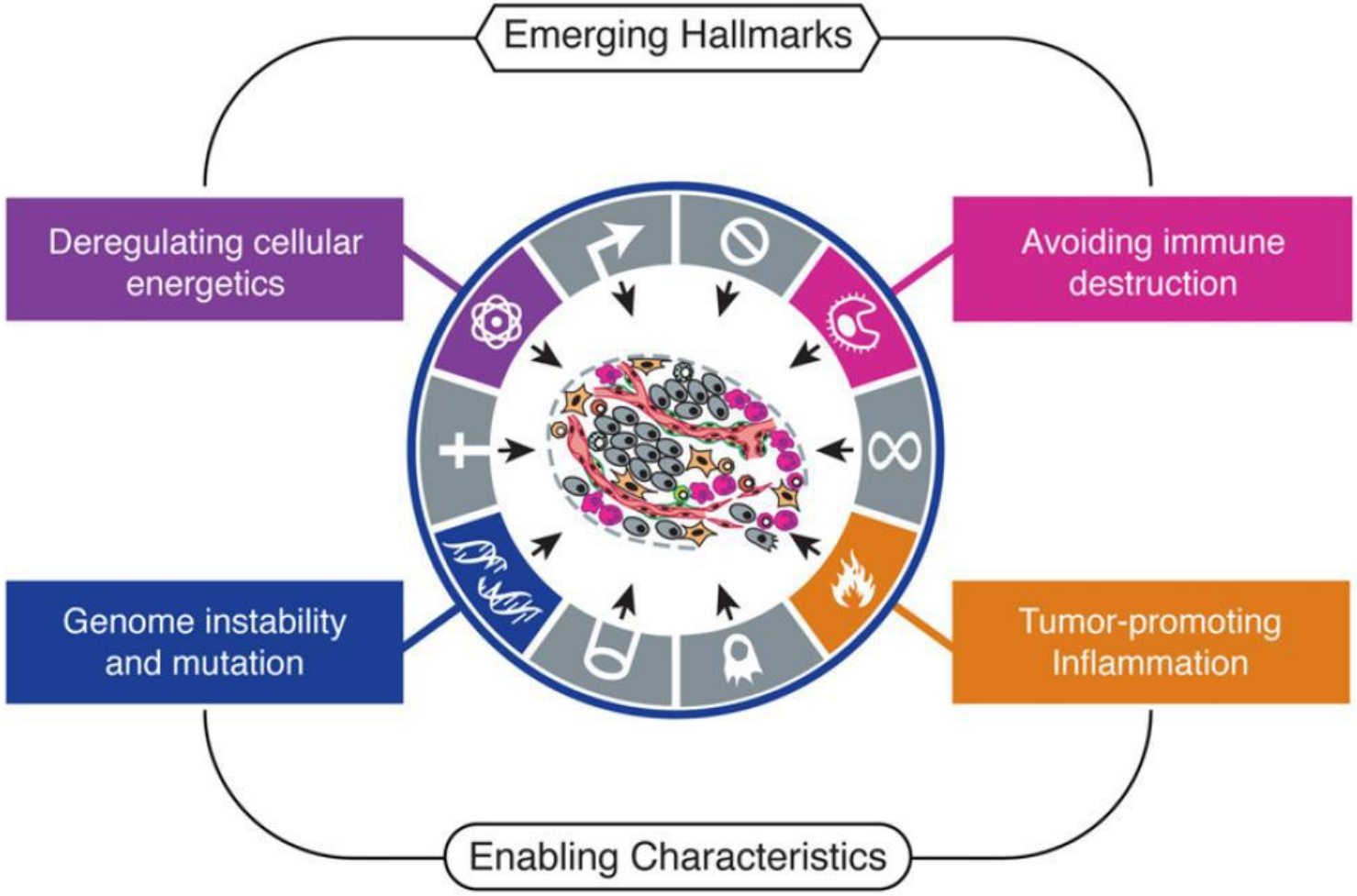
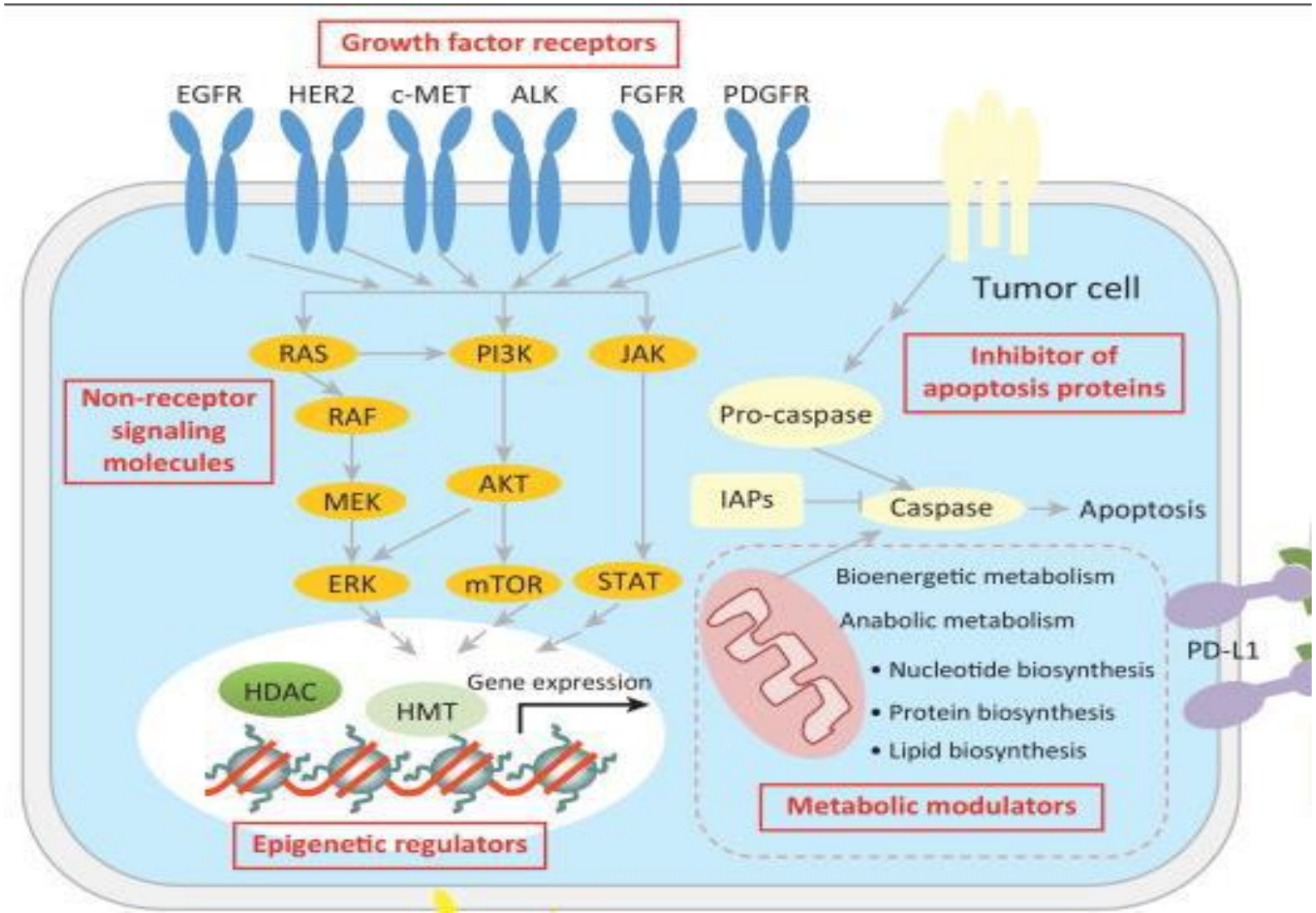
Waarom leidt doelgerichte behandeling niet tot genezing?



Hanahan D and Weinberg RA. Cell 2011

Resistentie treedt altijd op en is divers



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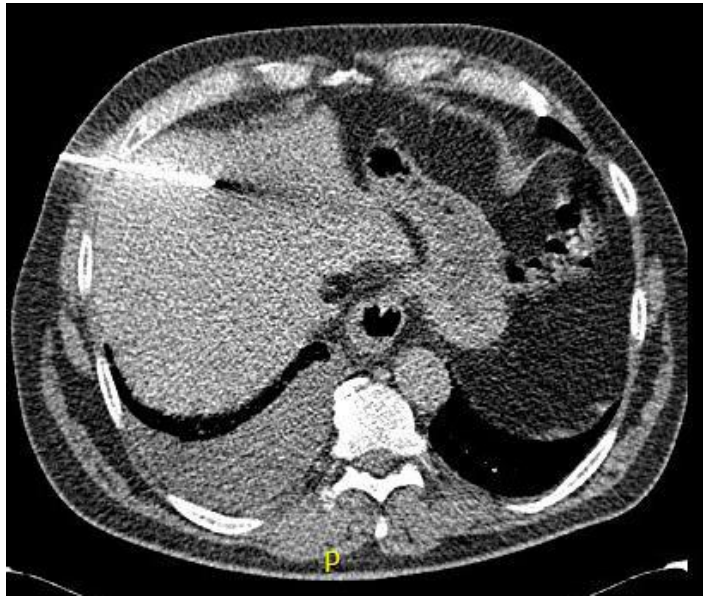
Volledige resistentie-analyse = biopt en bloed analyse



PROS
- High sensitivity *(when successful)*
- High specificity

CONS
- Not always possible
- ‘Long’ turn-around time
- Only info on biopsied lesions

PROS
- High specificity
- Short turn-around time
- Info on all lesions

CONS
- Lower sensitivity

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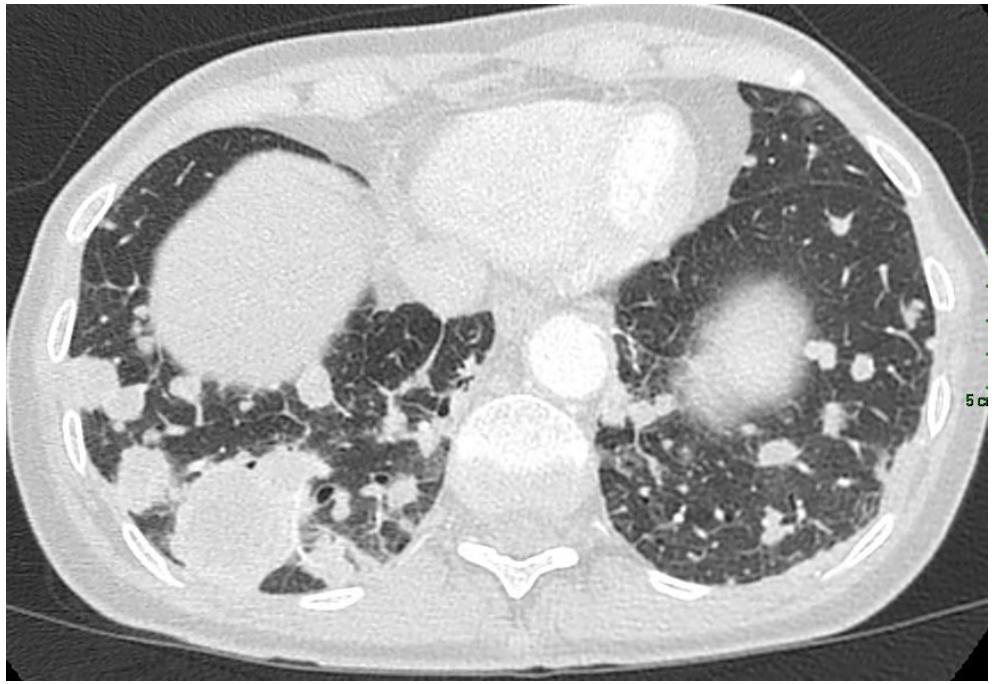
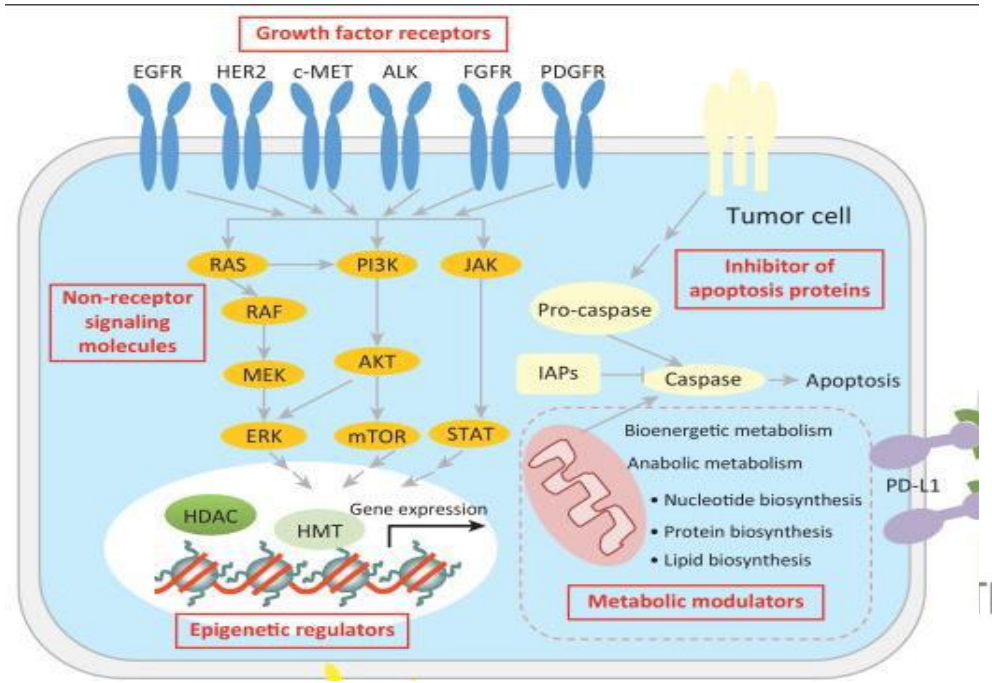
Behandeling van TKI resistentie werkt - EGFR

- 54 year old women with stage IV EGFRm positive NSCLC.
- 10-2014: Erlotinib. Best response: PR
- 03-2016: PD. T790M+. Osimertinib. Best response: PR
- 12-2016: PD.





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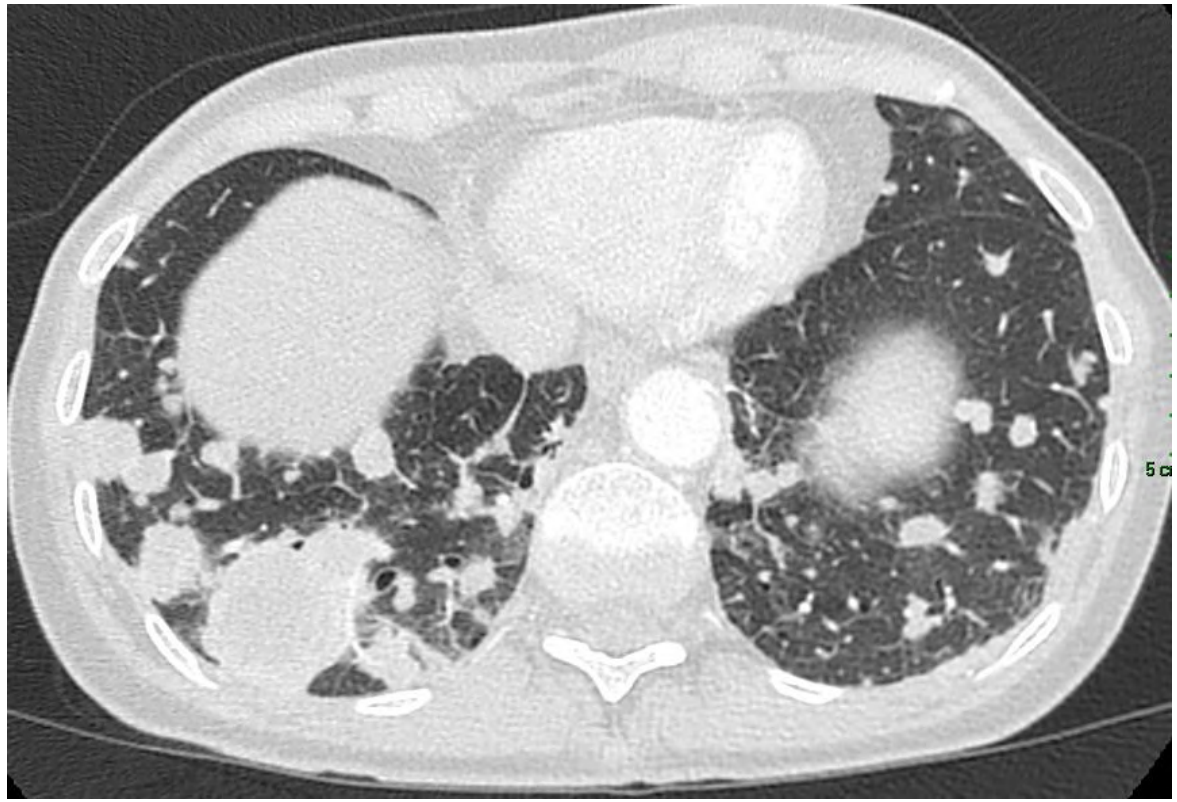
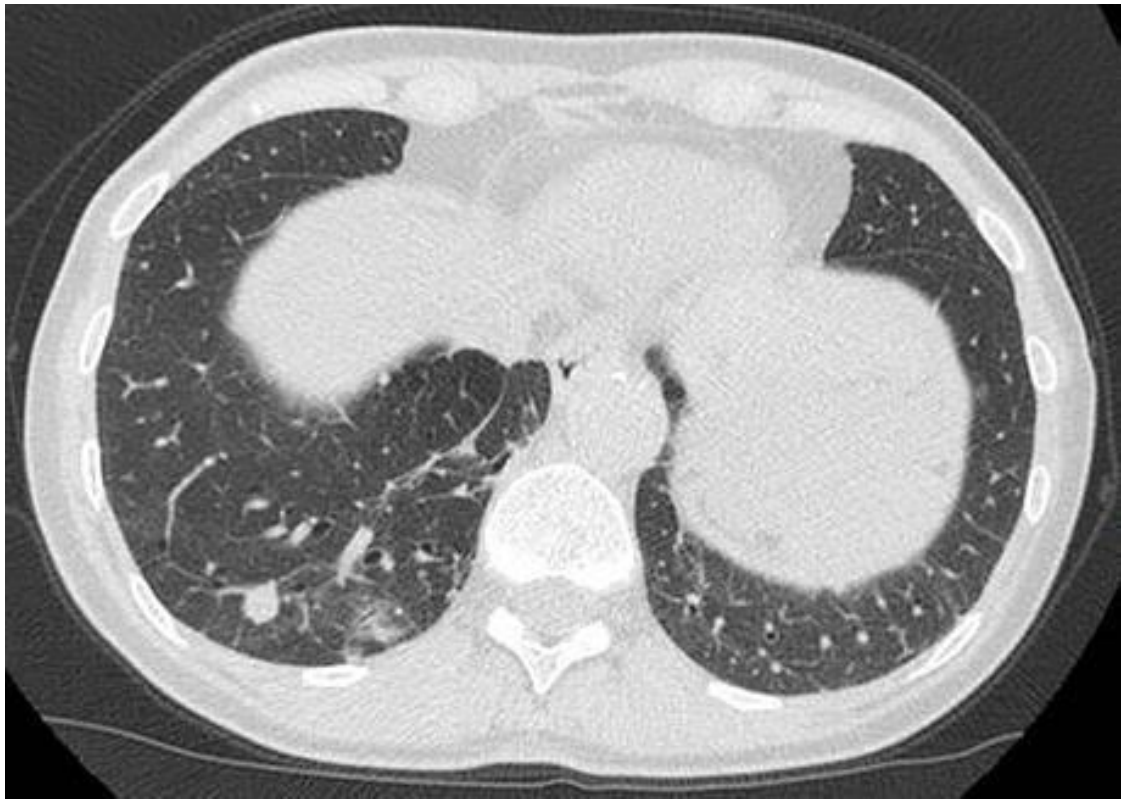
Osimertinib en Trastuzumab behandeling





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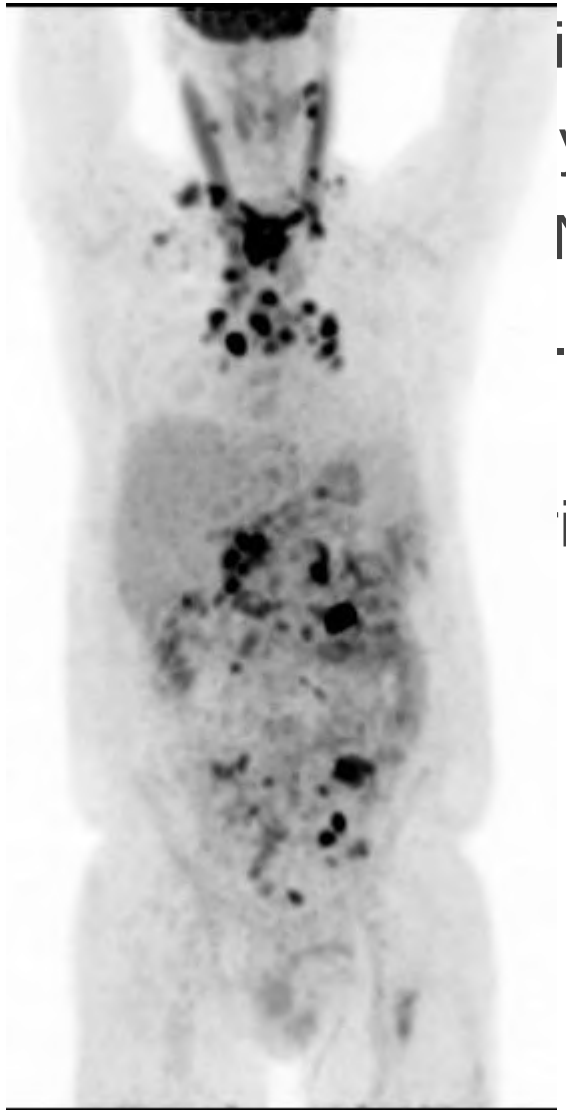
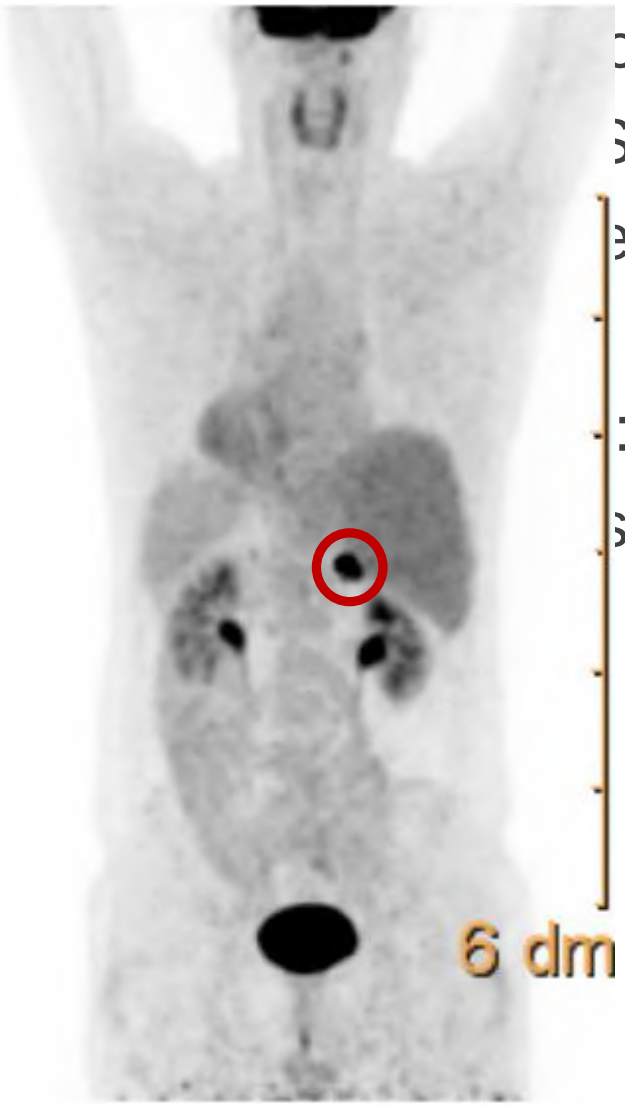
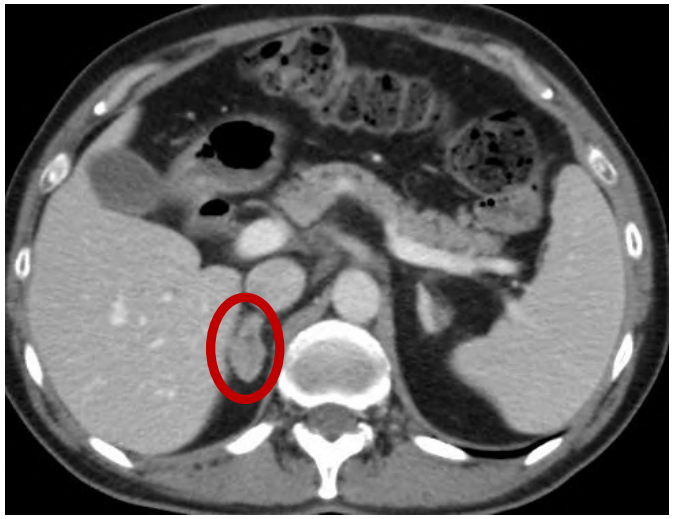
Behandeling van TKI resistentie werkt - ALK



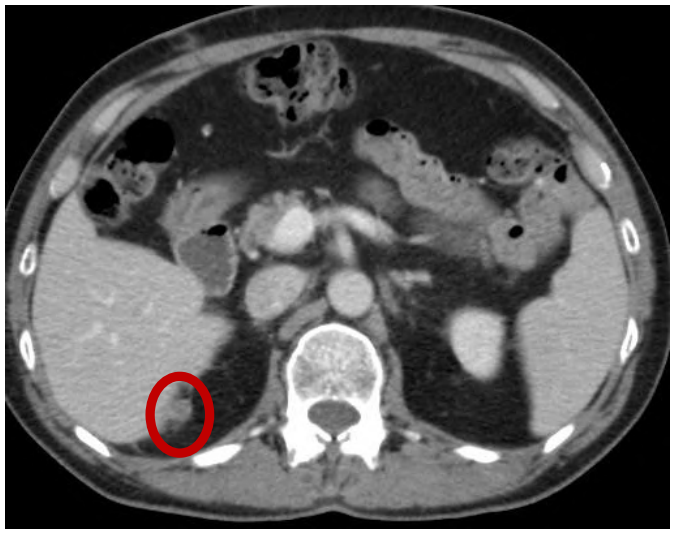


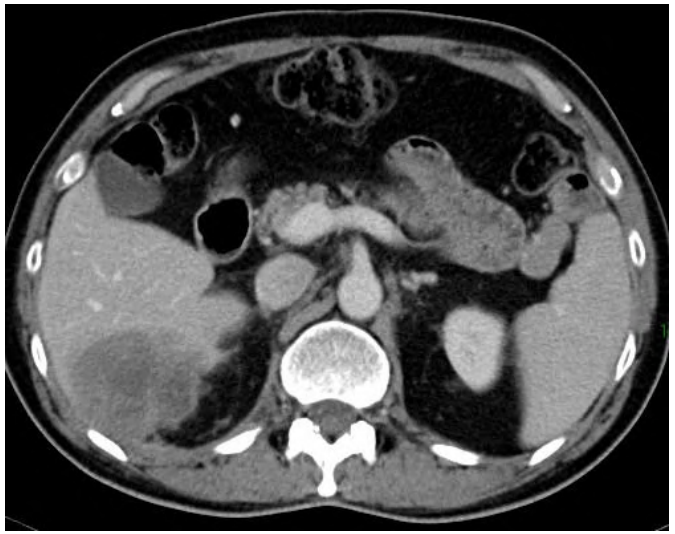
- ith cation positive NSCLC.
- y F SCLC.
- NS edure. ALK+.
- . D
- ale : PR.
- igh stasis.

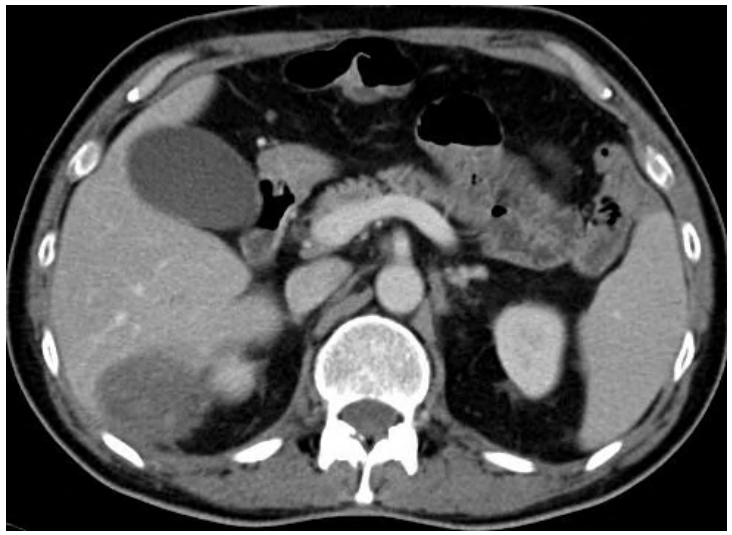
Behandeling van TKI resistentie werkt - ALK



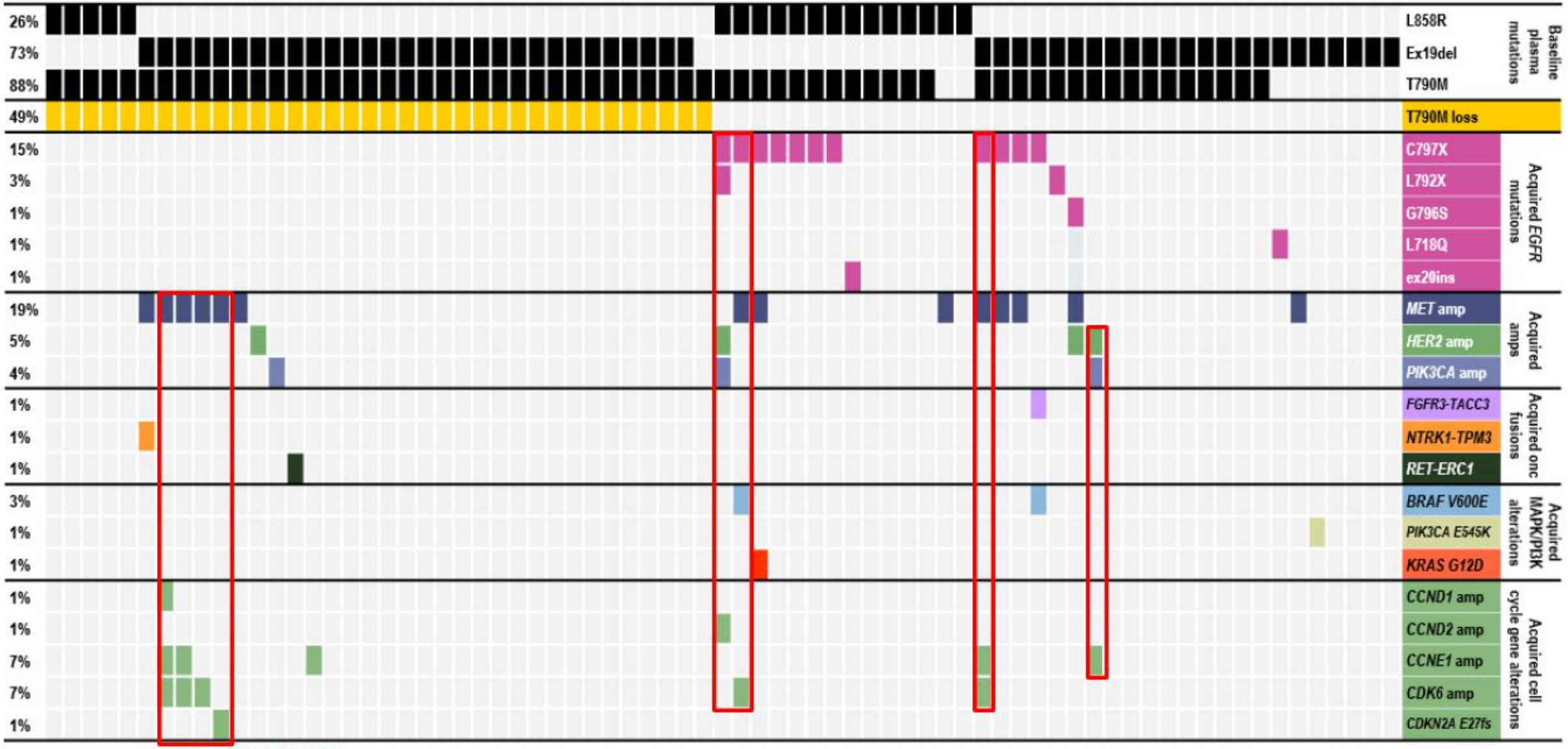
- Analyse resistentie mechanismen ALK (therapiekeuzetest):
- ALK IHC en FISH positief.
- TP53 exon 6: c.610G>T (p.Glu204*) - frequentie 16.63%
- ALK exon 22: c.3512T>A (p.Ile1171Asn) - frequentie 10.20%
- PD-L1 (22C3): 100% van de tumorcellen membraneus positief.







Osimertinib-treated patients: acquired alterations



MUNICH 2018 ESMO congress

- Cell cycle gene alterations were acquired in 12% of samples, with *MET* amplification (5%), *HER2+PIK3CA* amplification (3%), *MET* amplification+EGFR C797X (1%), and *MET* amplification+C797X+BRAF V600E (1%)

Immunotherapie weinig effectief bij longkanker veroorzaakt door een genmutatie – ook niet als PD-L1 sterk positief is.

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, N. Reese, MD, T. Wang, MD, P. Coluzzi, MD, B. Ledezma, MSN NP, M. Mendenhall, MSN NP, J. Hunt, BS, B. Wolf, BS, B. Jones, BS, J. Madrigal, BS, J. Horton, BS, M. Spiegel, BS, J. Carroll, BS, J. Gukasyan, BS, T. Williams, BS, L. Sauer, BS, C. Wells, BS, A. Hardy, BS, P. Linares, BS, C. Lim, BS, L. Ma, BS, C. Adame, BS, Edward B. Garon, MD, MS*

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Immunotherapie weinig effectief bij longkanker veroorzaakt door een genmutatie – ook niet als PD-L1 sterk positief is.

Table 1. Subject Characteristics by Patient

Age (y)	Sex	Race	Smoker	Histology	EGFR Mutation	PD-L1 (%)	trAE (Grade)	Best Response	Time on Trial (m)	Reason Off Trial	TKI After Trial	TKI-Related AE (Grade)
54	F	Asian	Never	ADC	L858R	5	Decreased TSH (1)	SD	3.2	PD	Y	Transaminitis (1, 3) Diarrhea (3)
61	F	White	Prior	ADC	E330K	95	Rash (1) Flu-like symptoms (1) Chills (1) Diarrhea (1, 2) Transaminitis (1-3)	SD	3.0	trAE	N	N/A
35	M	Asian	Never	SCC	Exon 20 ins	50	None	PD	2.0	PD	N	N/A
56	M	Asian	Prior	ADC	Exon 19 del	55	None	SD	4.0	PD	Y	Rash (2)
71	F	Asian	Never	ADC	L858R	10	Rash (1, 1) Fatigue (2) Adrenal insufficiency (2)	SD	4.0	PD	Y	Rash (2)
61	M	White	Prior	ADC	Exon 19 del	30	None	SD	4.0	PD	Y	Rash (1)
67	M	Asian	Active	ADC	None[a]	80	Rash (1) Flu-like symptoms (1)	PR	8.2	OT	N/A	N/A
52	F	White	Never	ADC	Exon 19 del	90	Diarrhea (1)	N/A[b]	1.4	trAE	Y	Pneumonitis (5), Diarrhea (2)
61	F	White	Never	ADC	L858R	55	None	SD	4.1	PD	Y	Rash (1)
65	F	White	Never	ADC	Exon 20 ins	70	None	PD	1.9	PD	Y	None
63	F	White	Prior	ADC	L858R	80	Rash (1)	SD	2.1	OT	N/A	N/A

[a]Subject found not to have EGFR mutation.
[b]Subject only received 1 dose of study treatment.
ADC, adenocarcinoma; AE, adverse event; del, deletion; F, female; inc, increased; ins, insertion; M, male; N, no; N/A, not applicable; OT, continues on trial; PD, progressive disease; SCC, squamous cell carcinoma; SD, stable disease; TKI, tyrosine kinase inhibitor; trAE, treatment-related AE; TSH, thyroid stimulating hormone; Y, yes; PR, partial response; PD-L1, programmed death ligand 1.

Lisberg A, et al. JTO 2018

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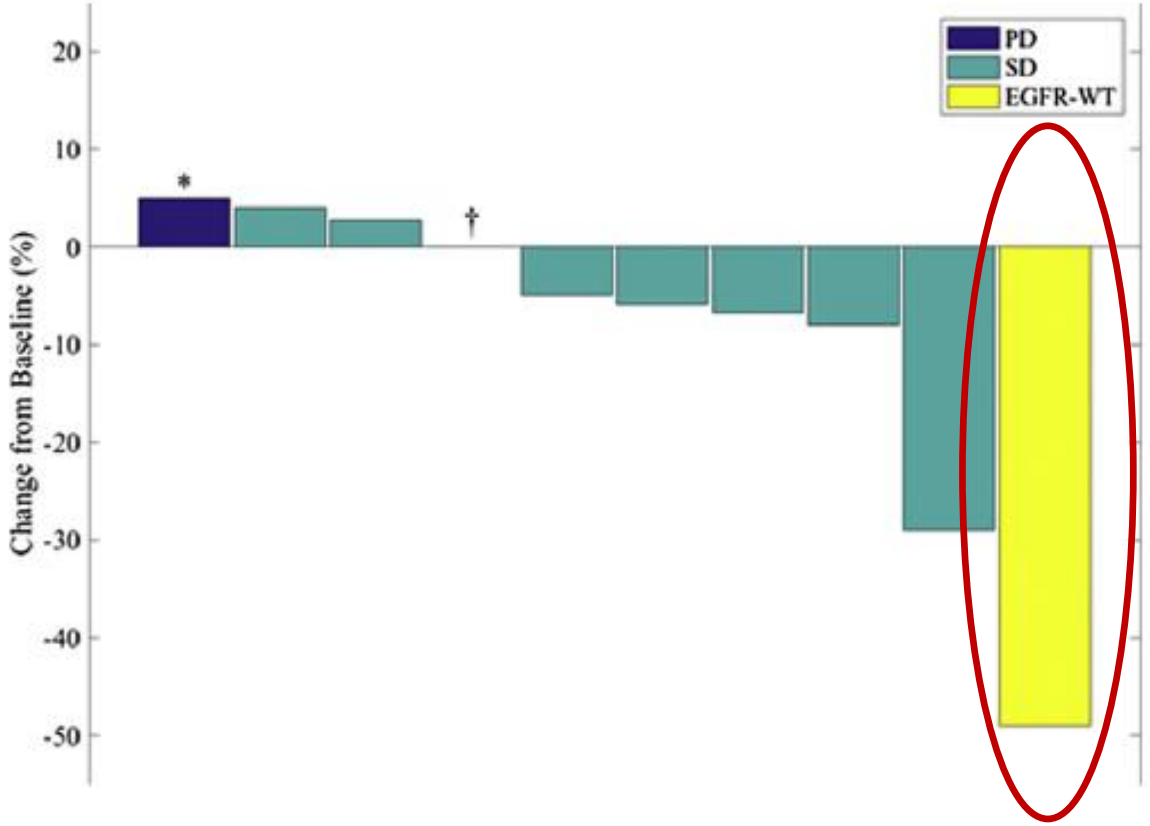
Immunotherapie weinig effectief bij longkanker veroorzaakt door een genmutatie – ook niet als PD-L1 sterk positief is.



Lisberg A, et al. JTO 2018

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Gerookt of niet maakt wel een verschil

	Overall		Never-Smokers			Former or Current Smokers		
Response Category	*EGFR* Mutant (n = 102)	*EGFR* Wild-Type (n = 1293)	All Never-Smokers (n = 305)	*EGFR* Mutant (n = 51)	*EGFR* Wild-Type (n = 236)	All Smokers (n = 1125)	*EGFR* Mutant (n = 34)	*EGFR* Wild-Type (n = 960)
CR, n (%)	0 (0)	7 (0.5)	0 (0)	0 (0)	0 (0)	8 (0.7)	0 (0)	6 (0.6)
PR, n (%)	9 (8.8)	246 (19.0)	28 (9.2)	1 (2.0)	26 (11.0)	234 (20.8)	7 (20.6)	205 (21.4)
Stable disease, n (%)	22 (21.6)	339 (26.2)	100 (32.8)	10 (19.6)	80 (33.9)	288 (25.6)	9 (26.5)	243 (25.3)
PD, n (%)	65 (63.7)	661 (51.1)	168 (55.1)	39 (76.5)	123 (52.1)	563 (50.0)	17 (50.0)	482 (50.2)
Unknown, n (%)	6 (5.9)	40 (3.1)	9 (3.0)	1 (2.0)	7 (3.0)	32 (2.8)	1 (2.9)	24 (2.5)
ORR, n (%) (95% CI)	9 (8.8) (3.3-14.3)	253 (19.6) (17.4-21.7)	28 (9.2) (5.9-12.4)	1 (1.9) (0-5.8)	26 (11.0) (7.0-15.0)	242 (21.5) (19.1-23.9)	7 (20.6) (7.0-34.2)	211 (22.0) (19.4-24.6)
p Value	0.007		0.0001	0.04		0.85		
DCR, n (%) (95% CI)	31 (30.4) (21.5-39.3)	592 (45.8) (43.1-48.5)	128 (42.0) (36.4-47.5)	11 (21.6) (10.3-32.9)	106 (44.9) (38.6-51.3)	530 (47.1) (44.2-50.0)	16 (47.1) (30.3-63.8)	454 (47.3) (44.1-50.4)
p Value	0.003		0.11	0.002		0.98		
mPFS, mo (range)	3.0 (2.7-3.3)	3.0 (2.8-3.1)	3.0 (2.8-3.2)	2.0 (1.6-2.4)	3.0 (2.6-3.4)	4.0 (3.8-4.2)	4.0 (2.4-5.6)	4.0 (3.8-4.2)
HR (95% CI); *p* value	1.38 (1.11-1.72); 0.004		—	1.74 (1.26-2.40); 0.001		—	0.98 (0.67-1.44); 0.92	
			1.27 (1.11-1.46); 0.001					
6-mo PFS (%)	20.6	34.1	27.2	9.8	29.7	35.9	36.4	35.5
12-mo PFS, %	14.0	21.9	12.5	4.9	13.2	24.5	30.3	24.1
mOS mo (range)	8.3 (2.2-14.4)	11.0 (10.0-12.0)	10.0 (8.1-11.9)	5.6 (3.4-7.8)	11.0 (9.4-12.6)	11.6 (10.1-13.1)	14.1 (4.1-24.1)	11.3 (9.8-12.8)
HR (95% CI); *p* value	1.11 (0.84-1.47); 0.46		—	1.34 (0.91-1.98); 0.14		—	0.91 (0.56-1.51); 0.73	
			1.15 (0.97-1.37); 0.11					
12-mo OS, %	48.2	47.5	44.2	37.8	45.3	49.3	55.6	48.3

Garassino MC, et al. JTO 2018.

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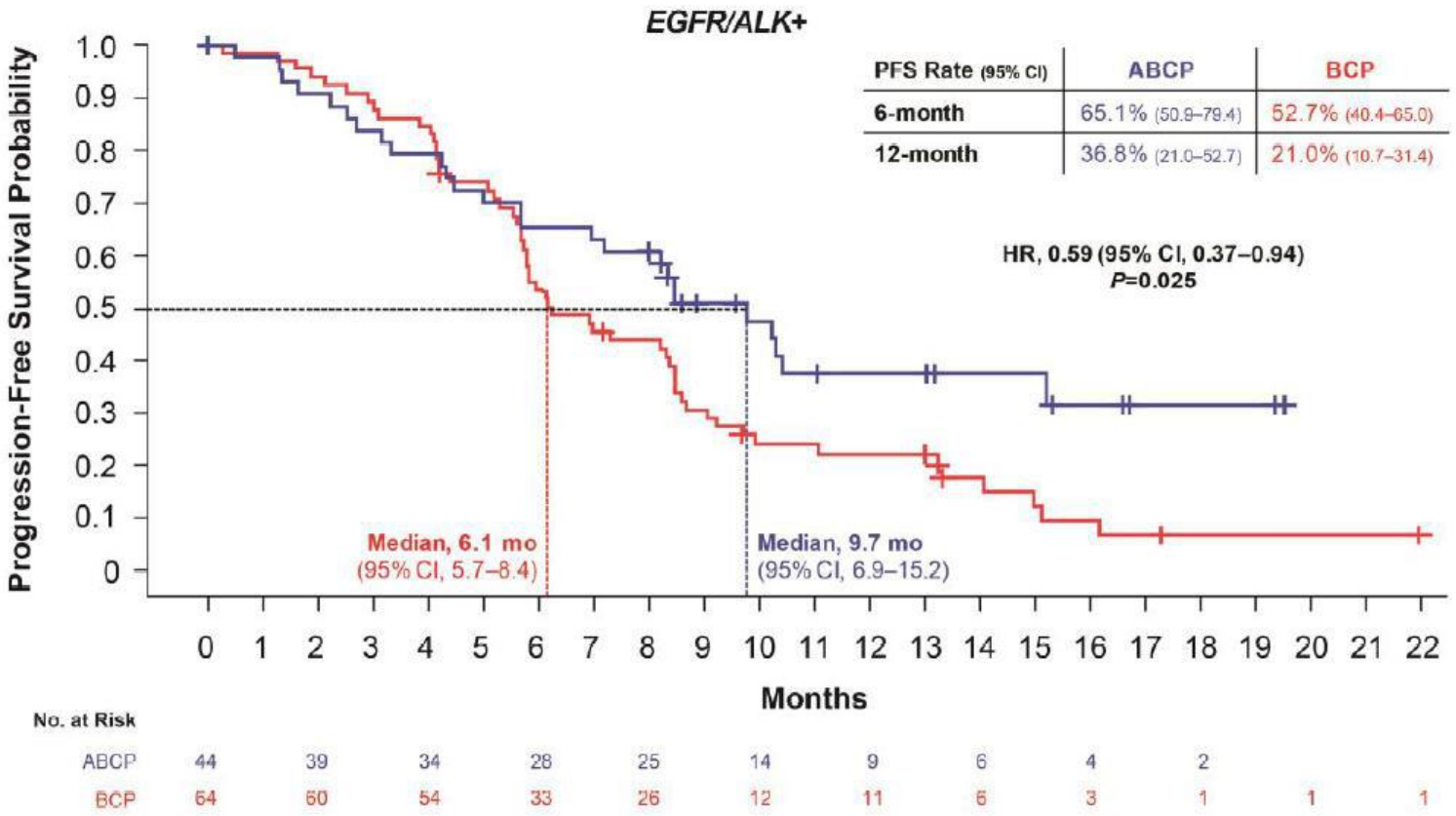
Combinatie immuno-chemotherapie kan wel werken



Socinski MA, et al. NEJM 2018.

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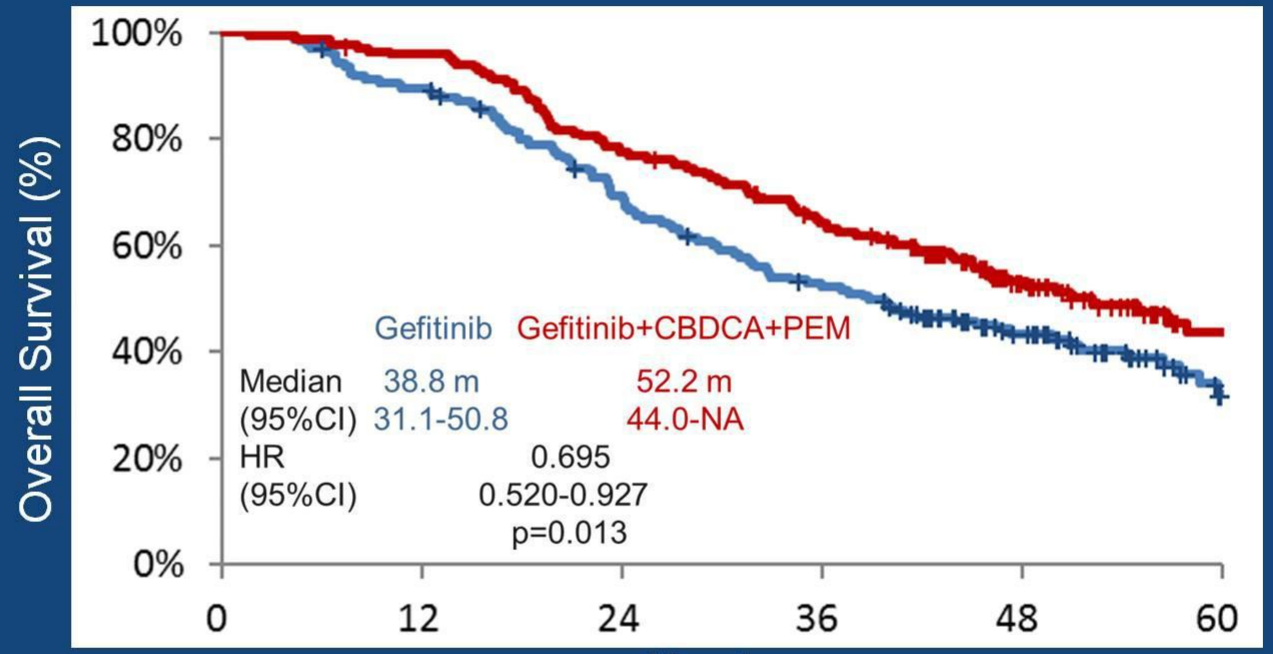
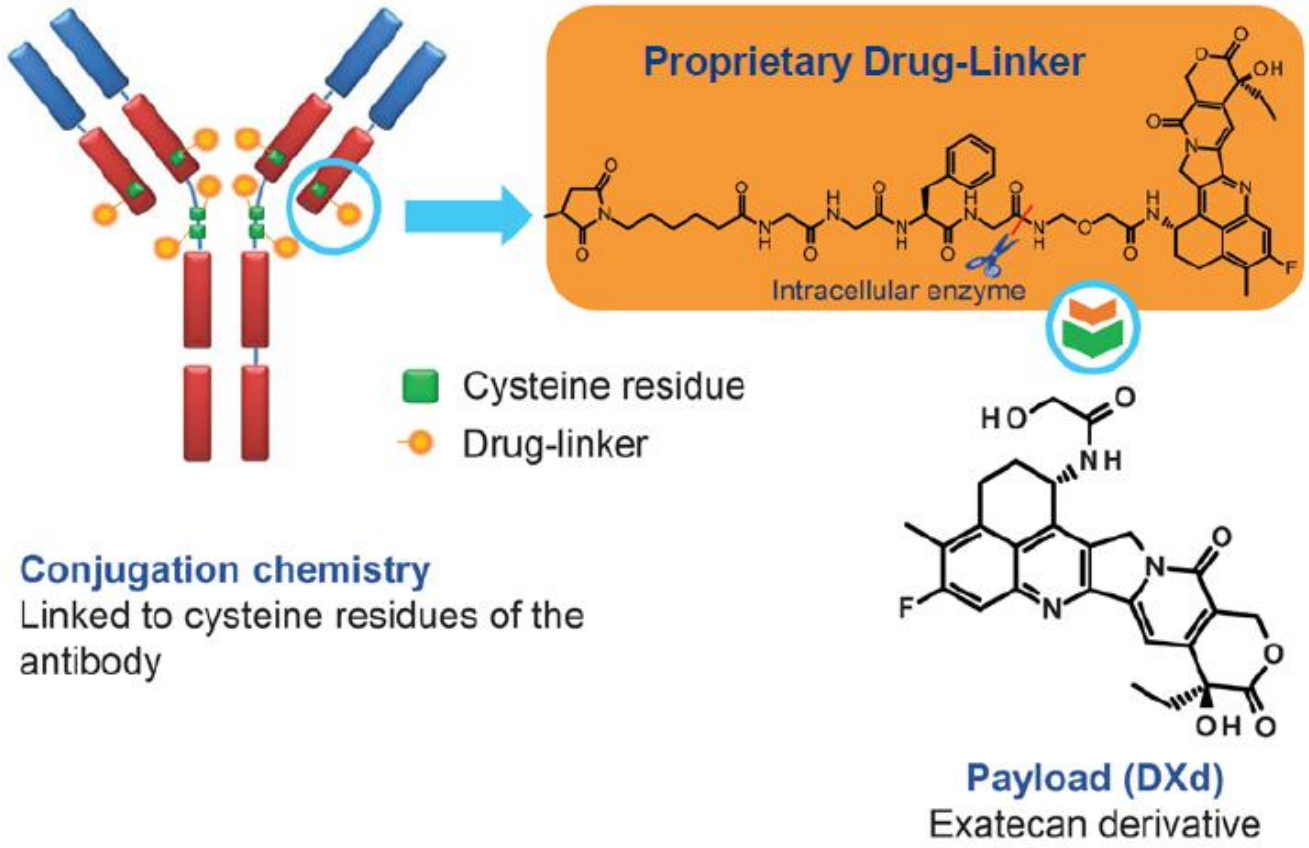
Nieuwe ontwikkelingen

Overall Survival



No. at Risk						
Gefitinib	172	153	115	86	50	14
Gefitinib+CBDCA+PEM	170	162	131	105	57	20

Nieuwe ontwikkelingen



Critical DXd-ADC design features

- High drug-to-antibody ratio (DAR)
- Highly stable linker
- Tumor-selective linker cleavable
- Unique and high potency payload
- Bystander effect
- Payload with short systemic half-life

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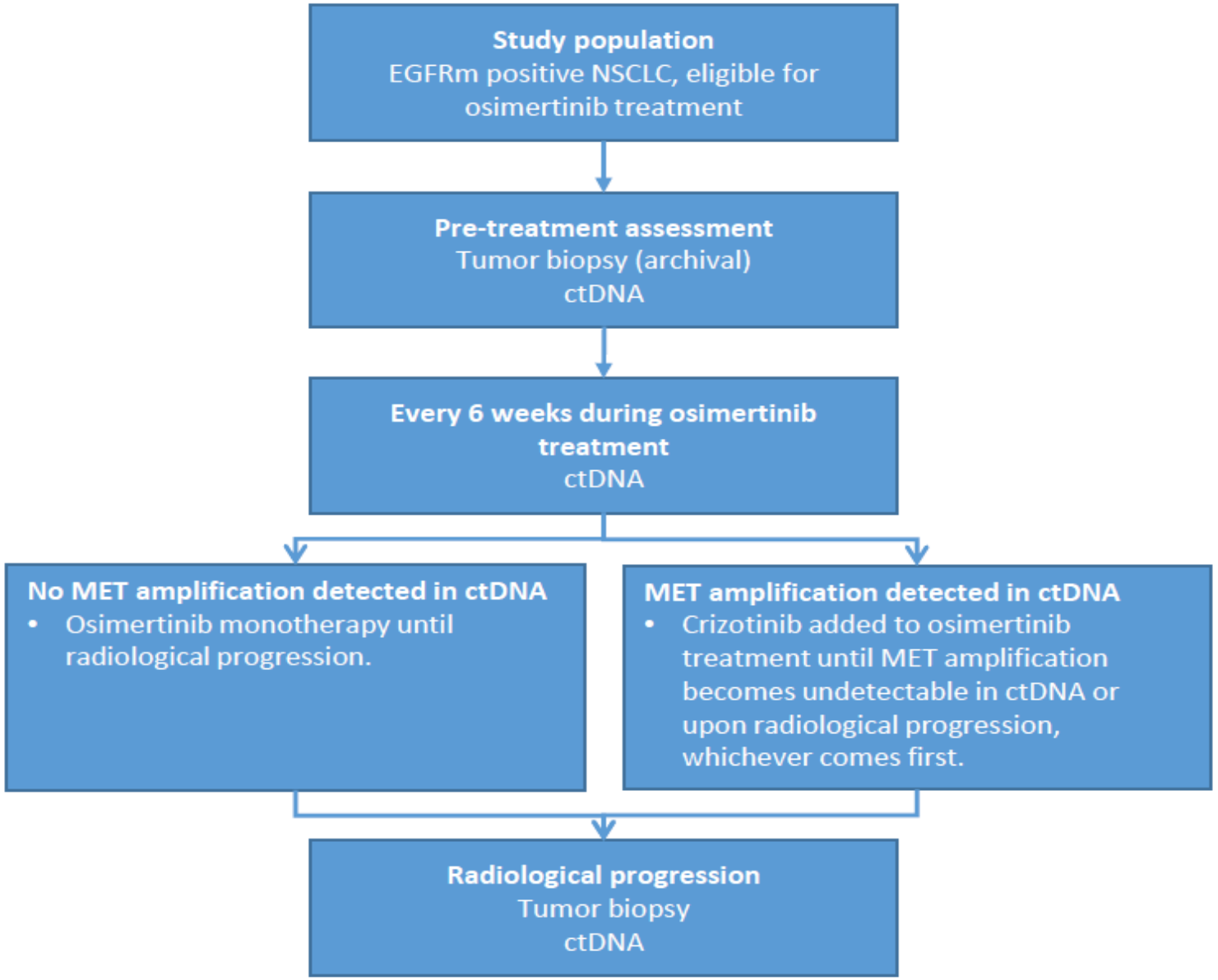
Nieuwe ontwikkelingen: TATIN - Track and treat in EGFRm positive NSCLC

- ctDNA guided recistance monitoring during osimertinib treatment
- Early treatment of MET amplification

Centra:

- NKI-AVL
- EMC



Conclusies

- Volledige genetische analyse van longtumor is essentieel.
- Start met TKI behandeling als genmutatie is gevonden.
- Bij progressie op TKI volledige resistentie-analyse.
- Chemotherapie is een goede behandeling.
- Geen immuno-monotherapie.
- Mee doen aan behandeling in studieverband helpt

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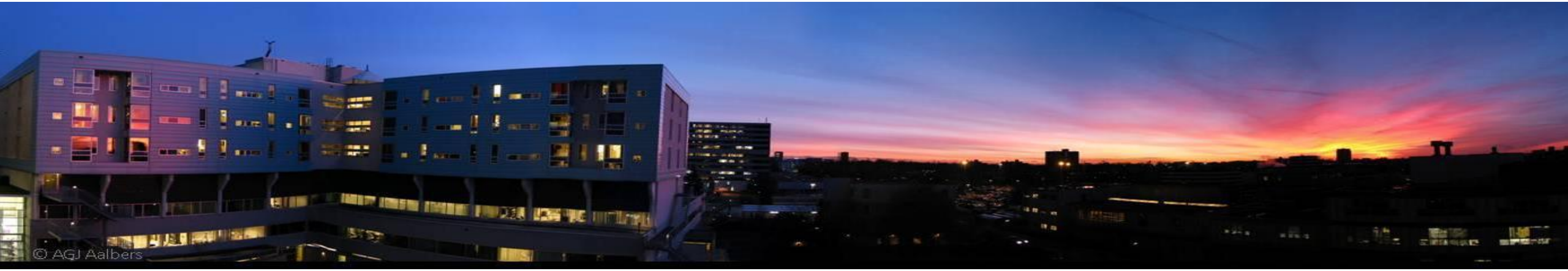

Dank voor uw aandacht

Vragen?

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