Doelgerichte behandeling

Hoe zit het met mutaties?

dr. A.J. van der Wekken
Longarts-oncoloog

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Disclosure

- Advisory board:
  - Lilly
  - Boehringer-Ingelheim
  - Pfizer
  - AstraZeneca
  - MSD
  - Roche (diagnostics)
- Grant:
  - AstraZeneca

- Lectures:
  - Lilly
  - Boehringer-Ingelheim
  - Pfizer
  - AstraZeneca
  - BMS
  - Roche (diagnostics)
  - Novartis


ALK airlines
LZ-ADV

Inleiding

- Welke mutaties bij longkanker zijn er?
- Welke geneesmiddelen zijn er?
- Wat zijn mogelijkheden qua opvolgende lijnen?
- Wat zijn voor- en nadelen van de verschillende geneesmiddelen?
- Welke trials zijn er en waar vind ik deze?

Casus 1 Dhr T 51jr

- Voorgeschiedenis:
- Hypertensie COPD
- 2014 april: bezoek SEH ivm kortademigheid: drainage pleuravocht rechts
- PA: adenocarcinoom van de long

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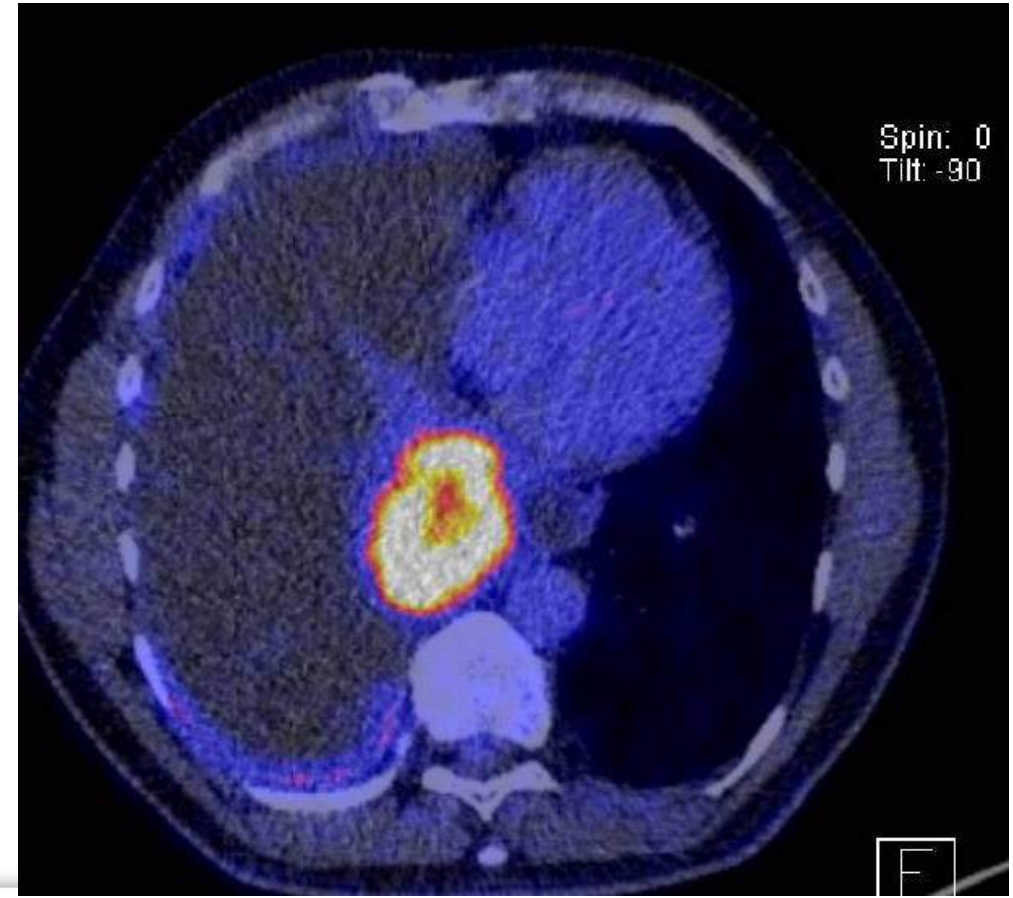

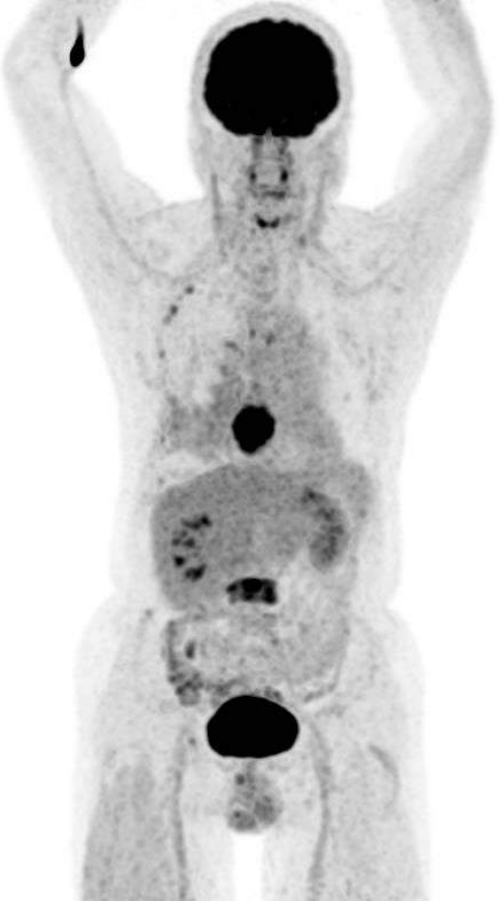

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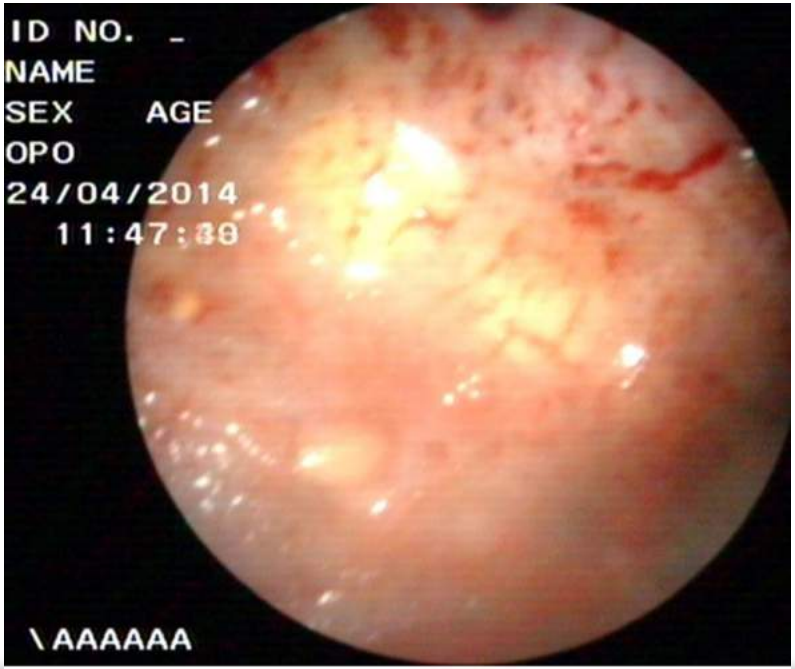
Thoracoscopie



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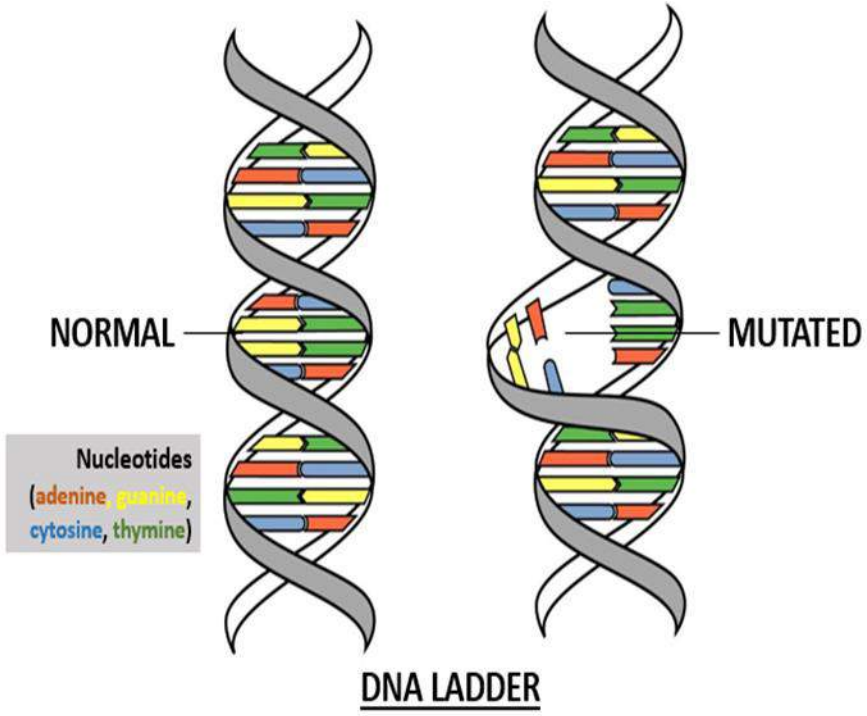
Pathologie verslag

- Biopt dorsale pariëtale pleura rechts: lokalisatie adenocarcinoom
- Mutatie analyse (UMCG): Er is een mutatie aanwezig in exon 19 van het EGFR-gen p.(E746_A750del).

Mutaties

- Verandering in het DNA
- Punt mutatie
- Insertie
- Deletie
- Translocatie
- Duplicatie
- Etc.



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Mutaties

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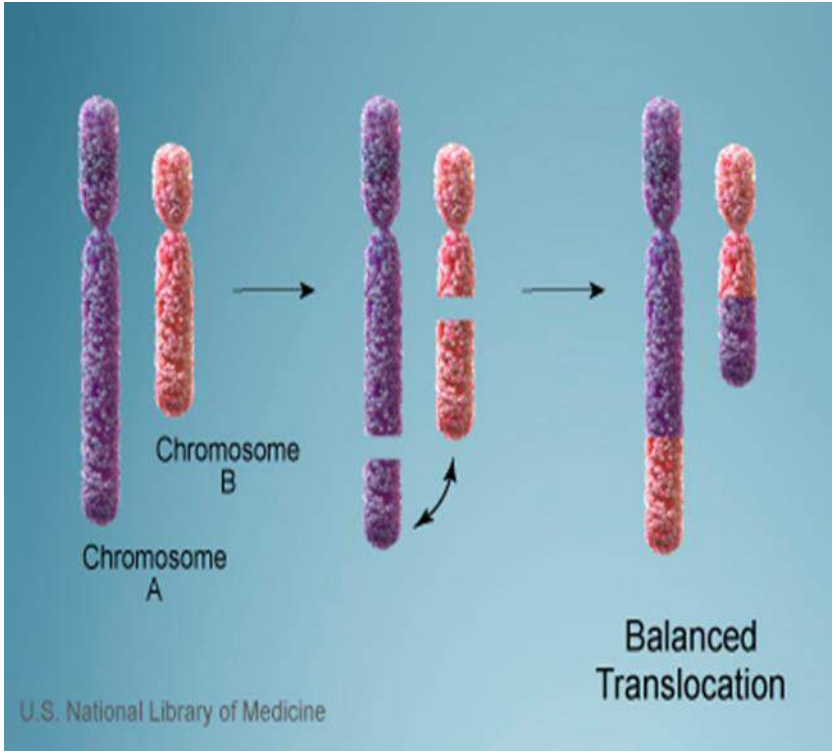

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Mutaties

- Verandering in het DNA
- Punt mutatie
- Insertie
- Deletie
- Translocatie
- Duplicatie
- Etc.

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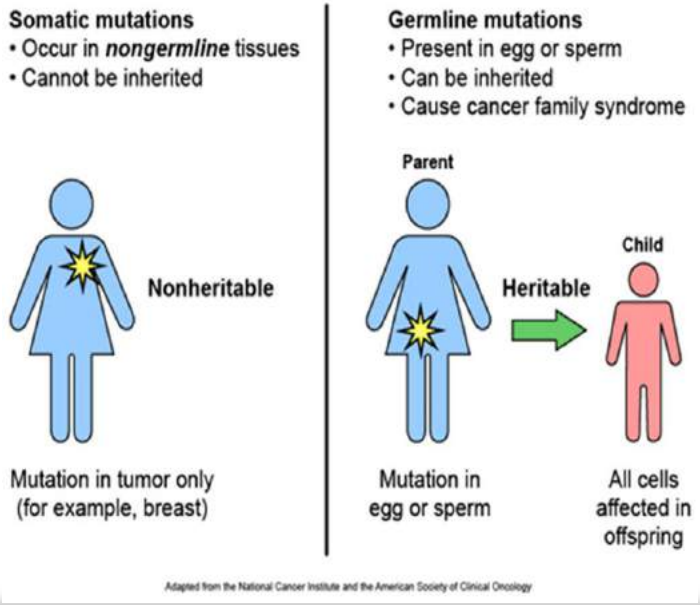
Moleculaire pathologie: alleen somatische mutaties



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Terug naar de casus

EGFR-TKI’s

- 1e generatie
  - Erlotinib
  - Gefitinib
- 2e generatie
  - Afatinib
  - Dacomitinib
- 3e generatie
  - Osimertinib

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Trial	ORR EGFR TKI	ORR control arm	PFS EGFR TKI	PFS control arm	OS EGFR TKI	OS control arm
Ipass Gefitinib	71%	47% (chemo)	9.5	6.3	21.6	21.9
NEJ002 Gefitinib	74%	31% (chemo)	10.8	5.4	30.5	23.6
WJTOG Gefitinib	62%	32% (chemo)	9.2	6.3	30.9	NR
Optimal Erlotinib	83%	36% (chemo)	13.1	4.6	22.6	28.8
Eurtac Erlotinib	58%	15% (chemo)	9.7	5.2	19.3	19.5
Lux-Lung 3 Afatinib	56%	23% (chemo)	11.1	6.9	NR	NR
Lux-Lung 6 Afatinib	67%	23% (chemo)	11.0	5.6	22.1	22.2
Lux-Lung 7 Afatinib	70%	56% (gefitinib)	11.0	10.9	27.9	25.0
Archer 1050 Dacomitinib	75%	72% (gefitinib)	14.7	11.0	NR	NR
Flaura Osimertinib	80%	76% (gefitinib or erlotinib)	18.9	10.2	NR	NR

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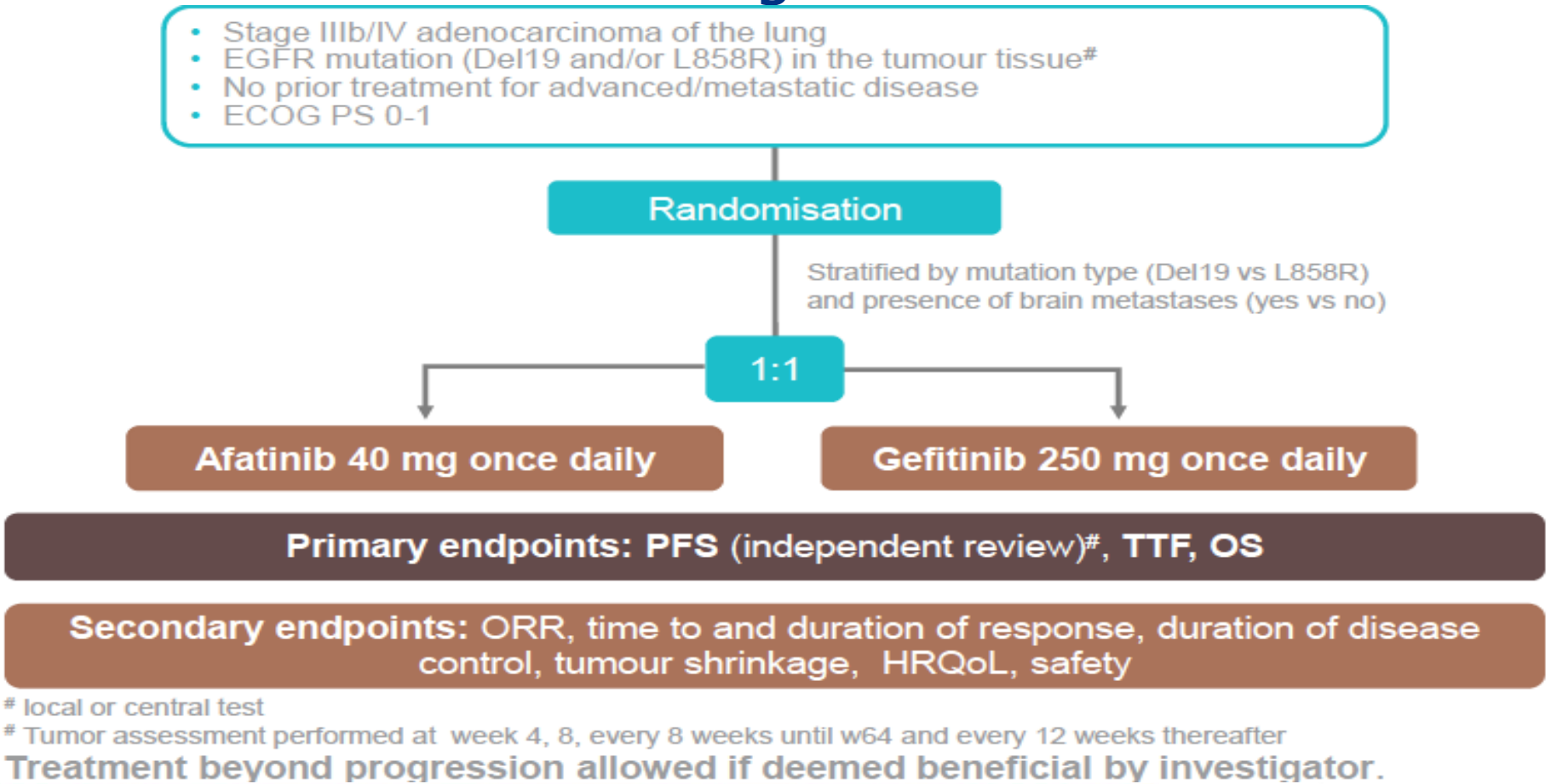
LUX-Lung 7 studie



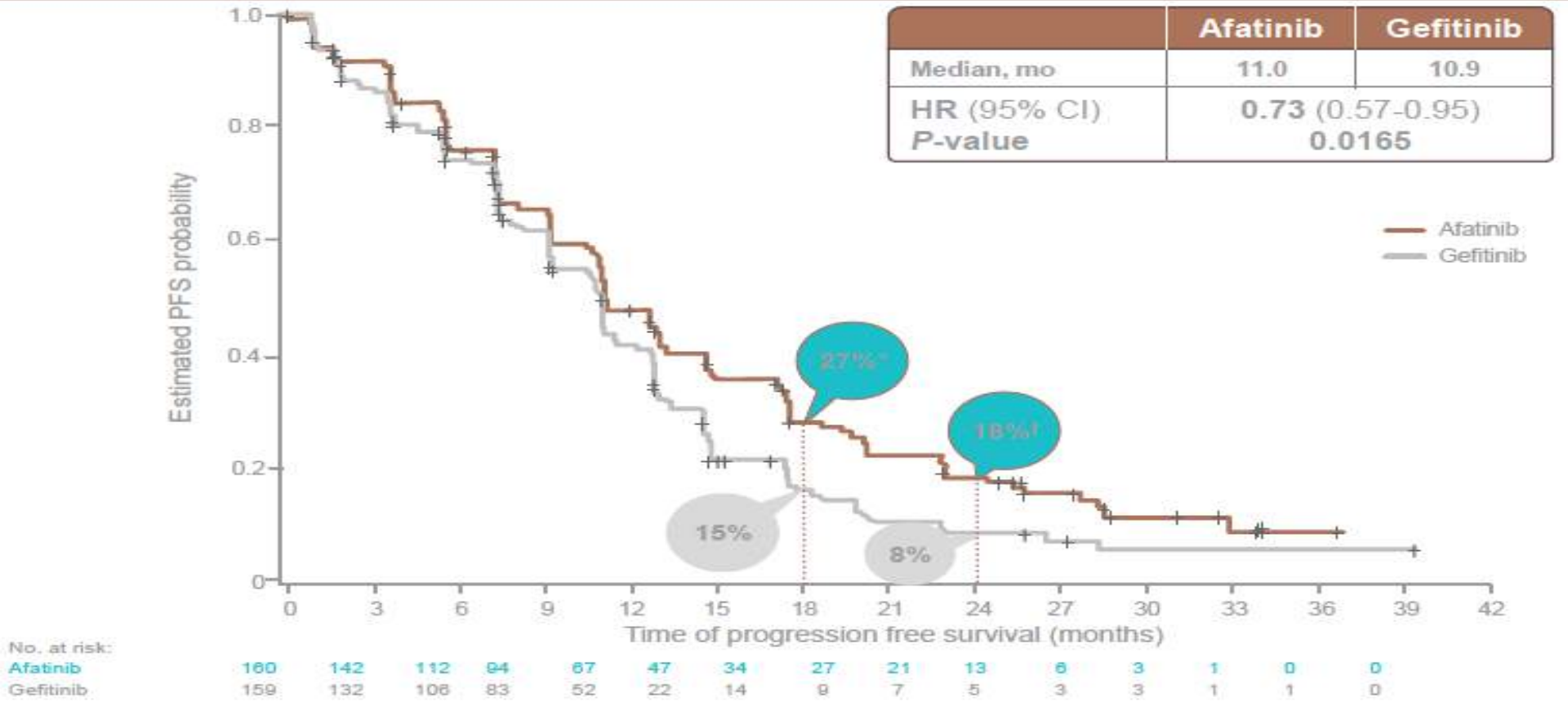
local or central test

Tumor assessment performed at week 4, 8, every 8 weeks until w64 and every 12 weeks thereafter

Treatment beyond progression allowed if deemed beneficial by investigator.

Park et al. Ann Oncol 2015

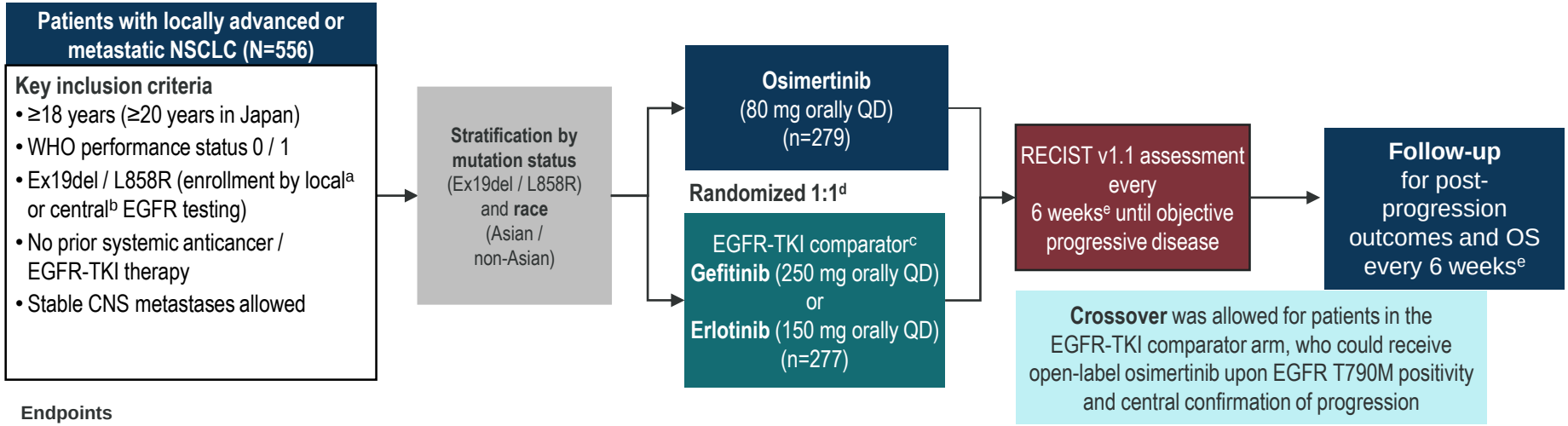
PFS independent review LUX-Lung 7



LUX-Lung 7 toxiciteit

	Afatinib			Gefitinib		
	All Gr	Gr3	Gr4	All Gr	Gr3	Gr4
Diarrhoea	144 (90.0)	19 (11.9)	1 (0.6)	97 (61.0)	2 (1.3)	
Rash/Acne*	142 (88.8)	15 (9.4)		129 (81.1)	5 (3.1)	
Stomatitis*	103 (64.4)	7 (4.4)		38 (23.9)		
Paronychia*	89 (55.6)	3 (1.9)		27 (17.0)	1 (0.6)	
Dry skin	52 (32.5)			59 (37.1)		
Pruritus	37 (23.1)			36 (22.6)		
Fatigue*	33 (20.6)	9 (5.6)		23 (14.5)		
Decr. appetite	26 (16.3)	1 (0.6)		19 (11.9)		
Nausea	26 (16.3)	2 (1.3)		22 (13.8)		
Alopecia	17 (10.6)			24 (15.1)		
Vomiting	17 (10.6)			6 (3.8)	1 (0.6)	
ALT increase	15 (9.4)			38 (23.9)	12 (7.5)	1 (0.6)
AST increase	10 (6.3)			33 (20.8)	4 (2.5)	

FLAURA study design



Endpoints

- **Primary endpoint:** PFS based on investigator assessment (according to RECIST v1.1)
  - The study had a 90% power to detect a hazard ratio of 0.71 (representing an improvement in median PFS from 10 months to 14.1 months) at a two-sided alpha-level of 5%
- **Secondary endpoints:** Objective response rate, duration of response, disease control rate, depth of response, overall survival, patient-reported outcomes, safety
- **Exploratory endpoint:** Post-progression efficacy

FLAURA data cut-off: 12 June 2017; NCT02296125.

[a]With central laboratory assessment performed for sensitivity; [b]cobas® EGFR Mutation Test (Roche Molecular Systems); [c]Sites to select either gefitinib or erlotinib as the sole comparator prior to site initiation; [d]Patients received randomized treatment until objective disease progression or as long as they were continuing to show clinical benefit, as judged by the investigator; [e]Every 12 weeks after 18 months.

CNS = central nervous system; EGFR = epidermal growth factor receptor; Ex19del = exon 19 deletion; NSCLC = non-small cell lung cancer; **OS = overall survival;** PFS = progression-free survival; RECIST v1.1 = Response Evaluation Criteria In Solid Tumors version 1.1; TKI = tyrosine kinase inhibitor; WHO = World Health Organization.

1. Soria J-C et al. Article and supplementary appendix. *N Engl J Med*. 2018;378:113-125. 2. Planchard D et al. Presented at: European Lung Cancer Congress; 11-14 April 2018; Geneva, Switzerland. 3. Ohe Y et al. Presented at: European Society for Medical Oncology Asia Congress; 17-19 November 2017; Singapore.

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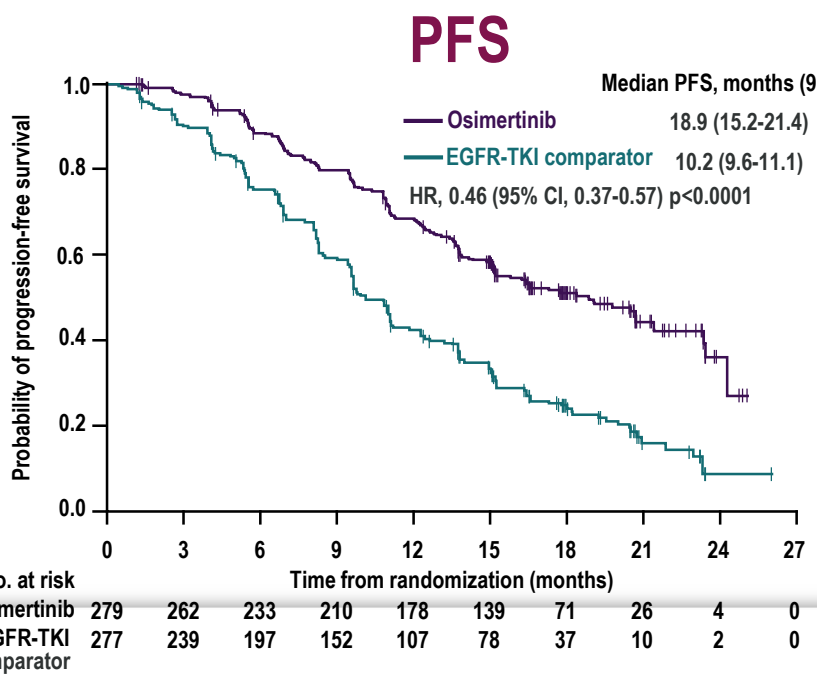
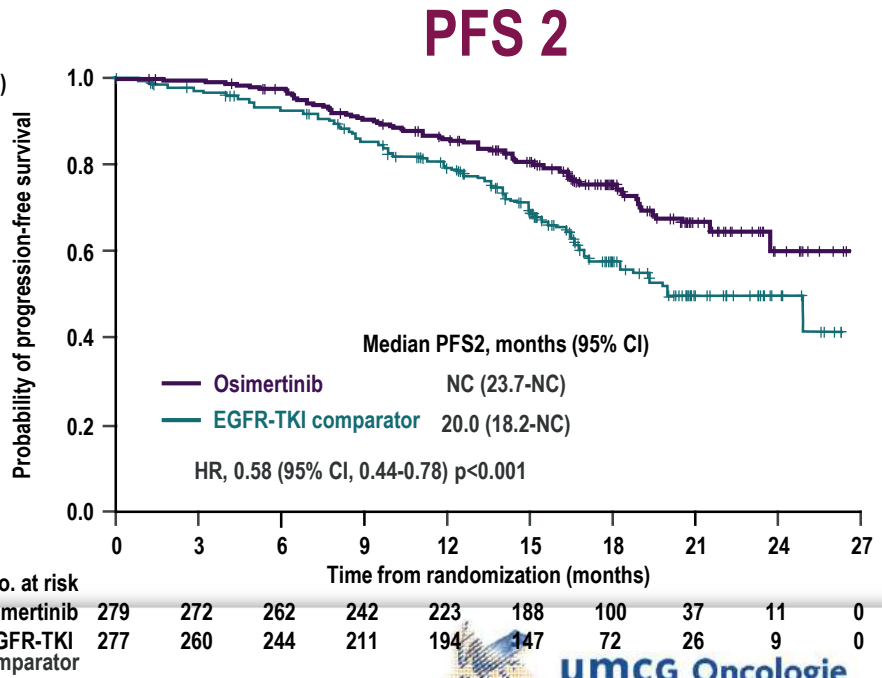
FLAURA studie

- PFS en PFS 2 voordeel voor osimertinib versus standaard EGFR-TKI
- het voordeel van osimertinib blijft behouden in de volgende behandellijn na initiële progressie





FLAURA data cut-off: 12 June 2017.
Tick marks in figures indicate censored data.
EGFR = epidermal growth factor receptor; HR = hazard ratio; NC = not calculable; PFS = progression-free survival; PFS2 = time from randomization to second progression on subsequent treatment or death; PPO = post-progression outcomes; TKI = tyrosine kinase inhibitor.

1. Soria J-C et al. Supplementary appendix. *N Engl J Med*. 2018;378:113-125. 2. Planchard D et al. Presented at: European Lung Cancer Congress; 11-14 April 2018; Geneva, Switzerland.

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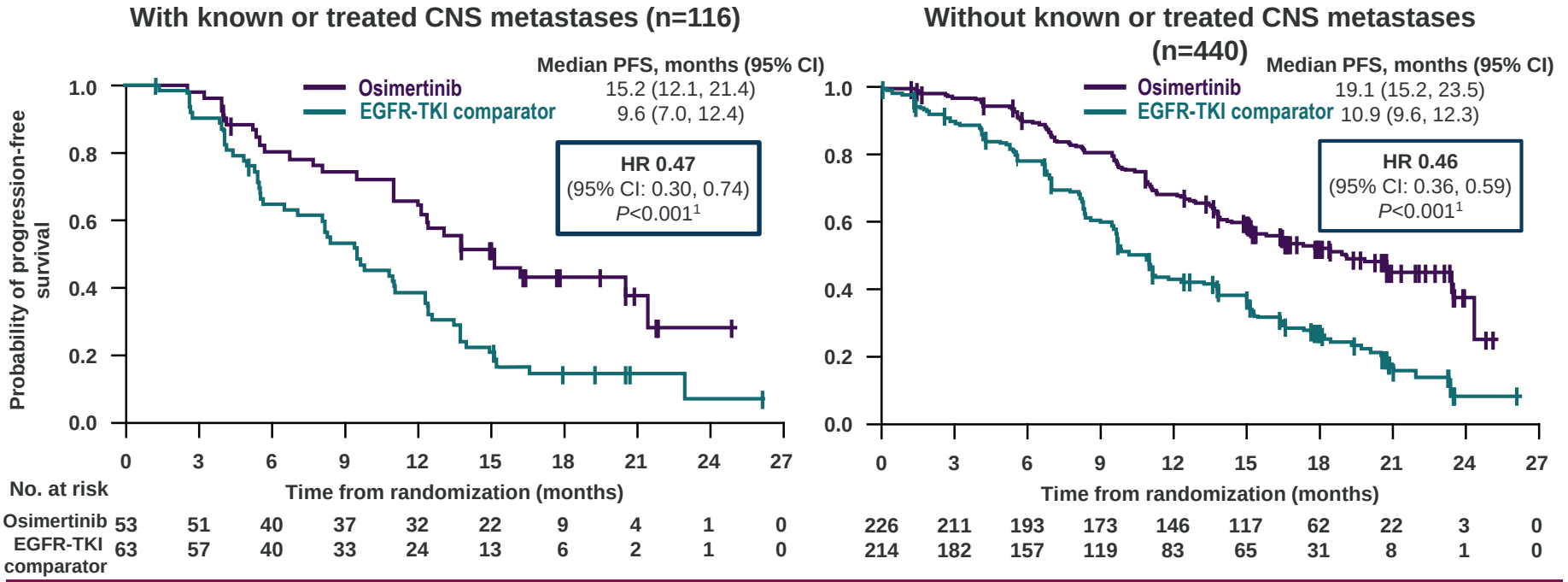
FLAURA PFS* voordeel osimertinib bij patiënten met en zonder CNS metastasen bij start van de studie



Fewer patients experienced CNS progression, and fewer patients progressed due to new CNS lesions, with osimertinib treatment compared with EGFR-TKI comparator

FLAURA data cut-off: 12 June 2017. Tick marks indicate censored data.
*By investigator assessment.
CI, confidence interval; CNS, central nervous system; EGFR, epidermal growth factor receptor; HR, hazard ratio; PFS, progression-free survival; TKI, tyrosine kinase inhibitor.
1. Soria JC, et al. *N Engl J Med*. 2018;378(2):113-125. 2. Ohe Y, et al. Presented at: European Society of Medical Oncology Asia Congress; 17-19 November 2017; Singapore. Abstract 413O.

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FLAURA Safety summary

AE, any cause,[a] n (%)	Osimertinib (n=279)	EGFR-TKI comparator (n=277)
Any AE	273 (98)	271 (98)
Any AE grade ≥3	94 (34)	124 (45)
Any AE leading to death	6 (2)	10 (4)
Any serious AE	60 (22)	70 (25)
Any AE leading to discontinuation	37 (13)	49 (18)
AE, possibly causally related,[b] n (%)		
Any AE	253 (91)	255 (92)
Any AE grade ≥3	49 (18)	78 (28)
Any AE leading to death	0	1 (<1)
Any serious AE	22 (8)	23 (8)

FLAURA data cut-off: 12 June 2017.

[a] Patients with multiple events in the same category counted only once in that category. Patients with events in more than one category counted once in each of those categories; [b] As assessed by the investigator. Includes AEs with an onset date on or after the date of first dose and up to and including 28 days following the date of last dose of study medication.

AE = adverse event; EGFR = epidermal growth factor receptor; TKI, tyrosine kinase inhibitor.

Ohe Y et al. Presented at: European Society for Medical Oncology Asia Congress; 17-19 November 2017; Singapore.

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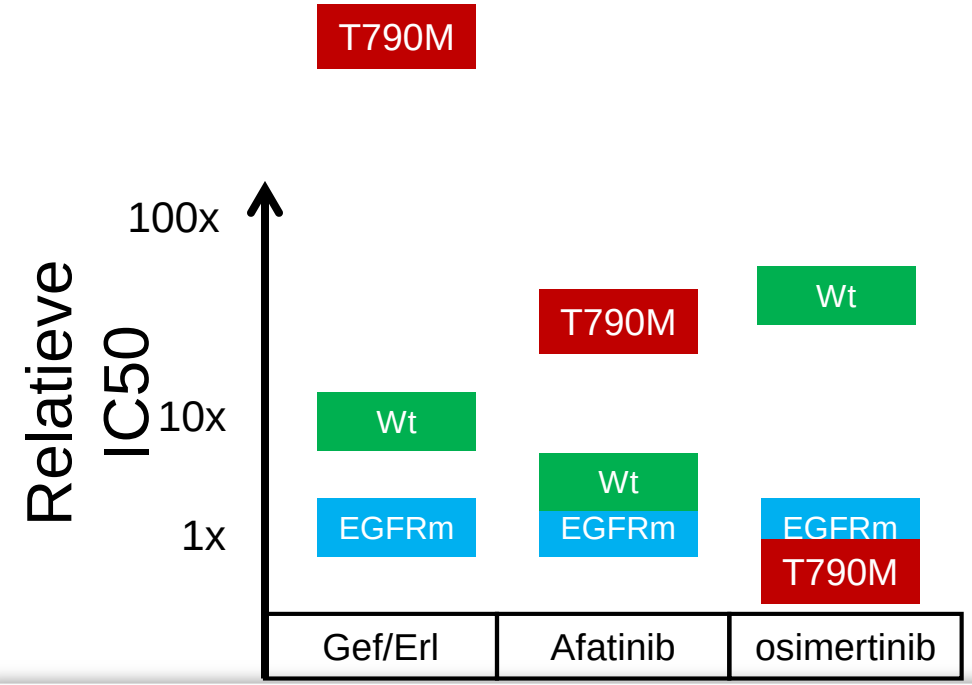
Verschillen in bindingsaffiniteit tussen EGFR TKIs



Wild-type EGFR

T790M

EGFR mutant: L858R, exon 19 del

- Lagere IC_{50} betekent hoge bindingsaffiniteit
- Hogere IC_{50} betekent lagere bindingsaffiniteit

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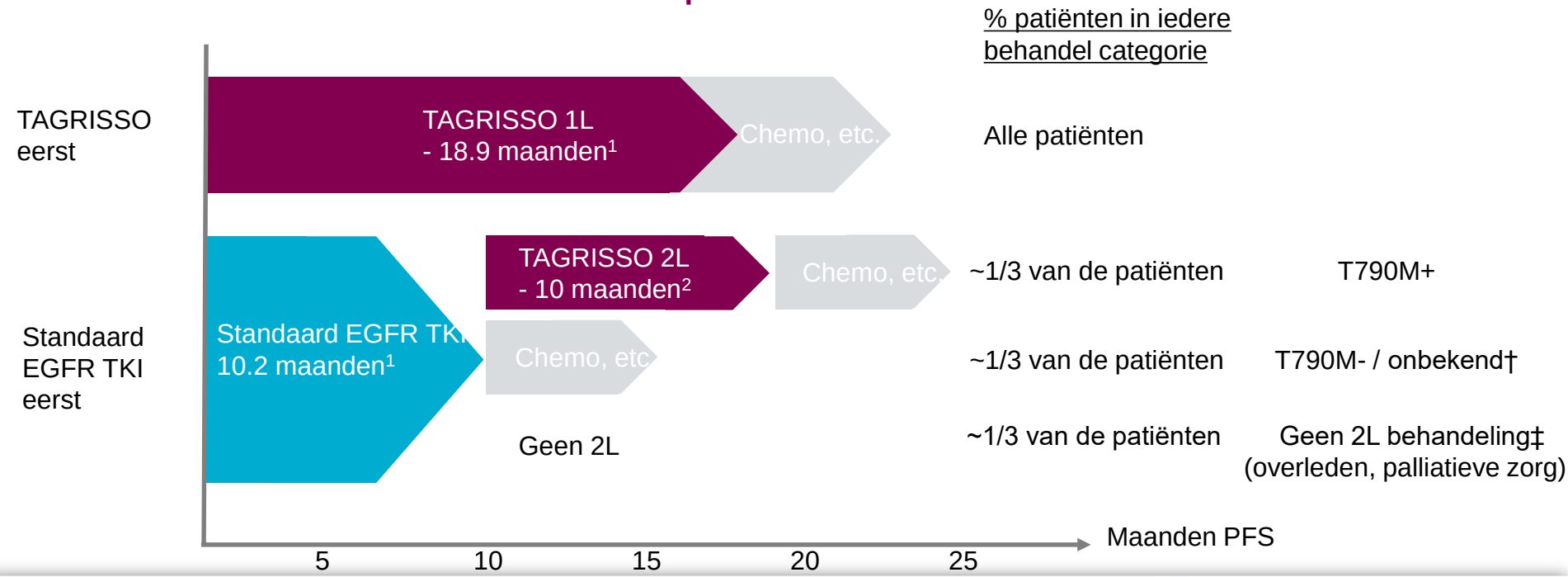
Li D, et al. Oncogene 2008; Cross DA, et al. Cancer Discov 2014; Hirano T, et al. Oncotarget 2015

Eerstelijns behandeling met osimertinib geeft PFS voordeel voor alle EGFRm patiënten in FLAURA



1. Ramalingam et al. Presented at ESMO conference: Sept 8-12, 2017; Madrid, Spain. 2. Mok et al. Article and supplementary appendix. N Engl J Med 2017; 376:629-40.
† About 50% EGFRm patients who are tested after progression on 1L EGFR TKI are T790M positive. Also 25% of patients are not eligible for a tissue biopsy upon progression, ~ 20% of re-biopsies yielding sufficient tissue and plasma testing for EGFR T790M mutations only ~ 53% sensitive vs tissue (AURA3).
‡ Across major EGFR TKI studies as in FLAURA ~ 30% of patients on standard EGFR TKIs receive no subsequent cancer therapy – they may die before a recorded progression event or for other reasons (e.g. rapid progression in the brain) receive palliative care only.

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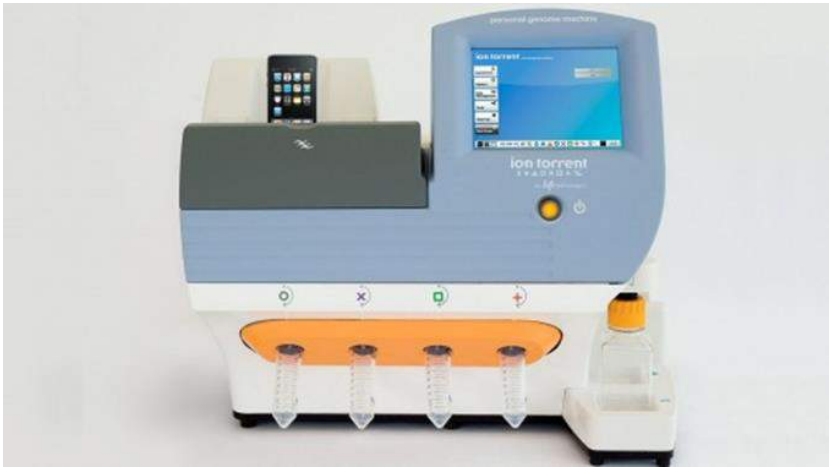
Mutatieanalyse

- AKT
- ALK
- AMELY
- BRAF
- EGFR
- ERBB2
- ESR1
- GNA11
- GNAQ
- GNAS
- H3F3A
- H3F3B
- HRAS
- IDH1
- IDH2



- JAK2
- KIT
- KRAS
- MAP2K1
- MET
- NRAS
- PDGFRA
- PIK3CA
- POLE
- ROS1

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Translocaties

- ALK
- ROS1
- RET
- NTRK
- MET
- NRG1

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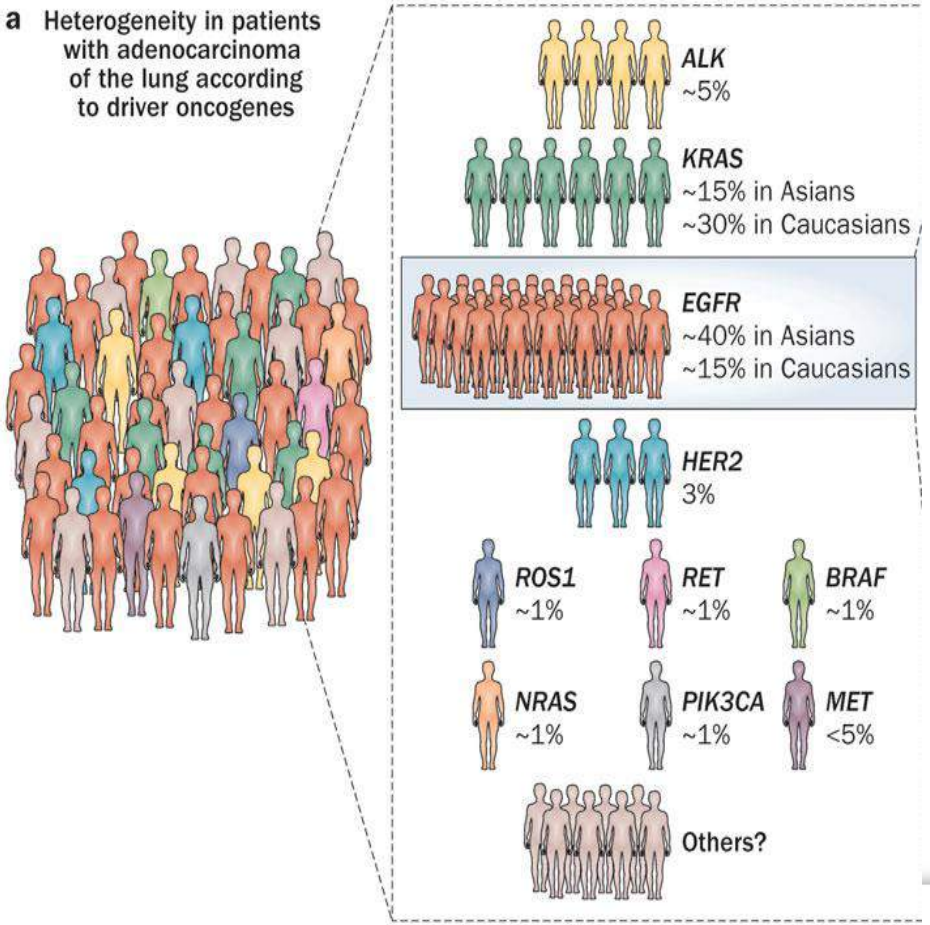

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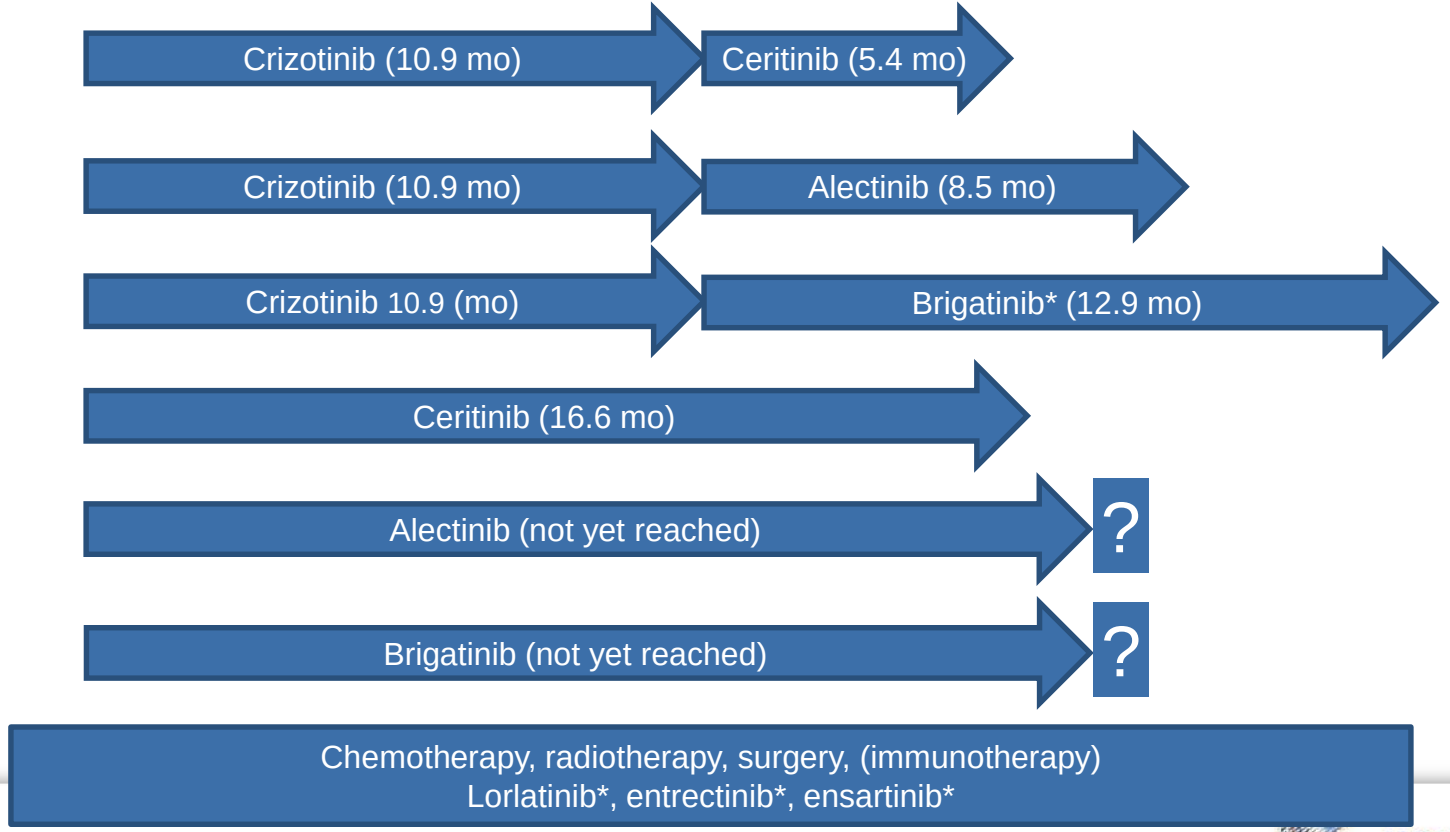
Beste volgorde van TKI's bij ALK



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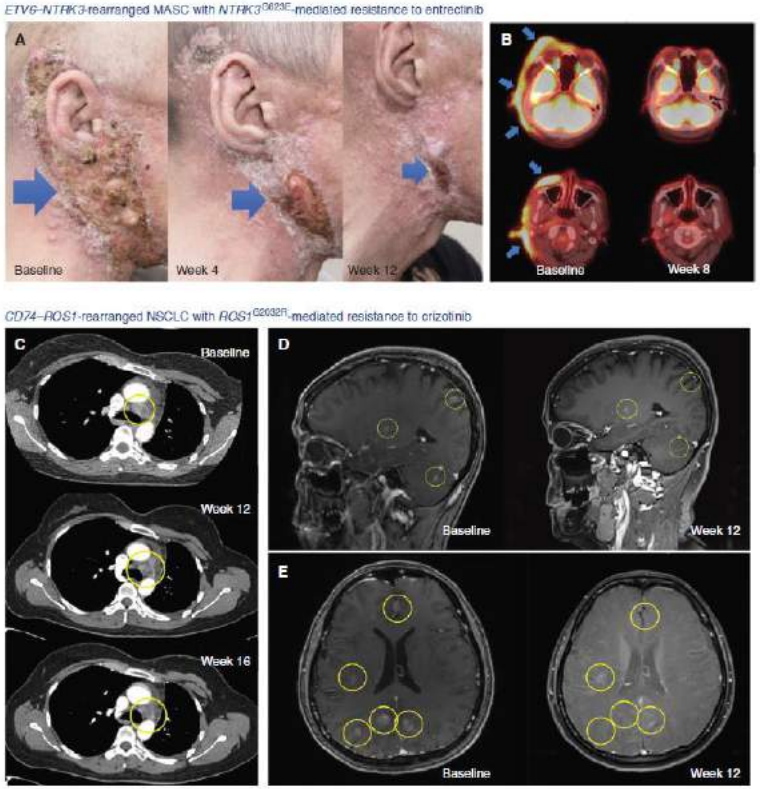
Adapted from De Langen AJ. Translational Cancer Research 2017.

* Nog niet geregistreerd door de EMA

First data of repotrectinib (TPX0005)



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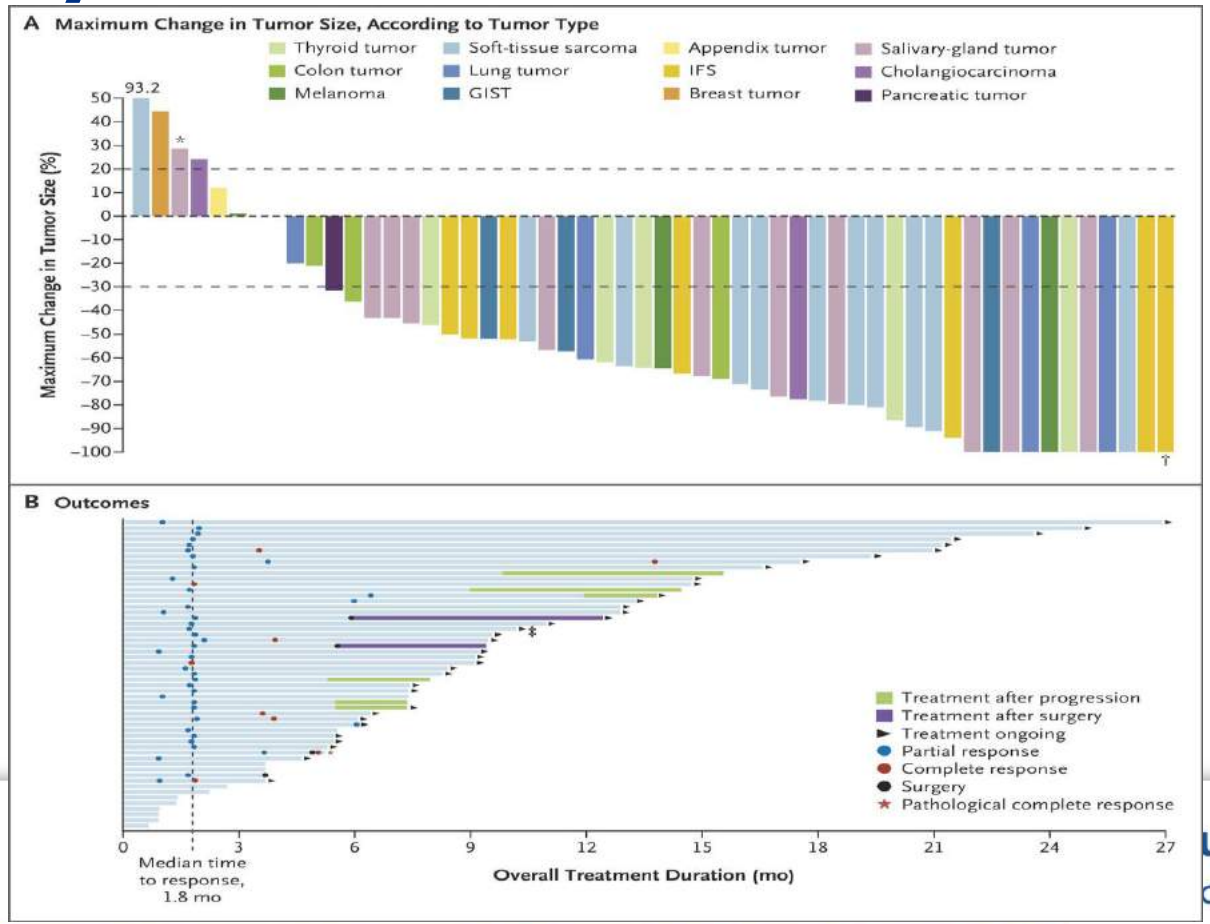
Efficacy of larotrectinib in NTRK fusions



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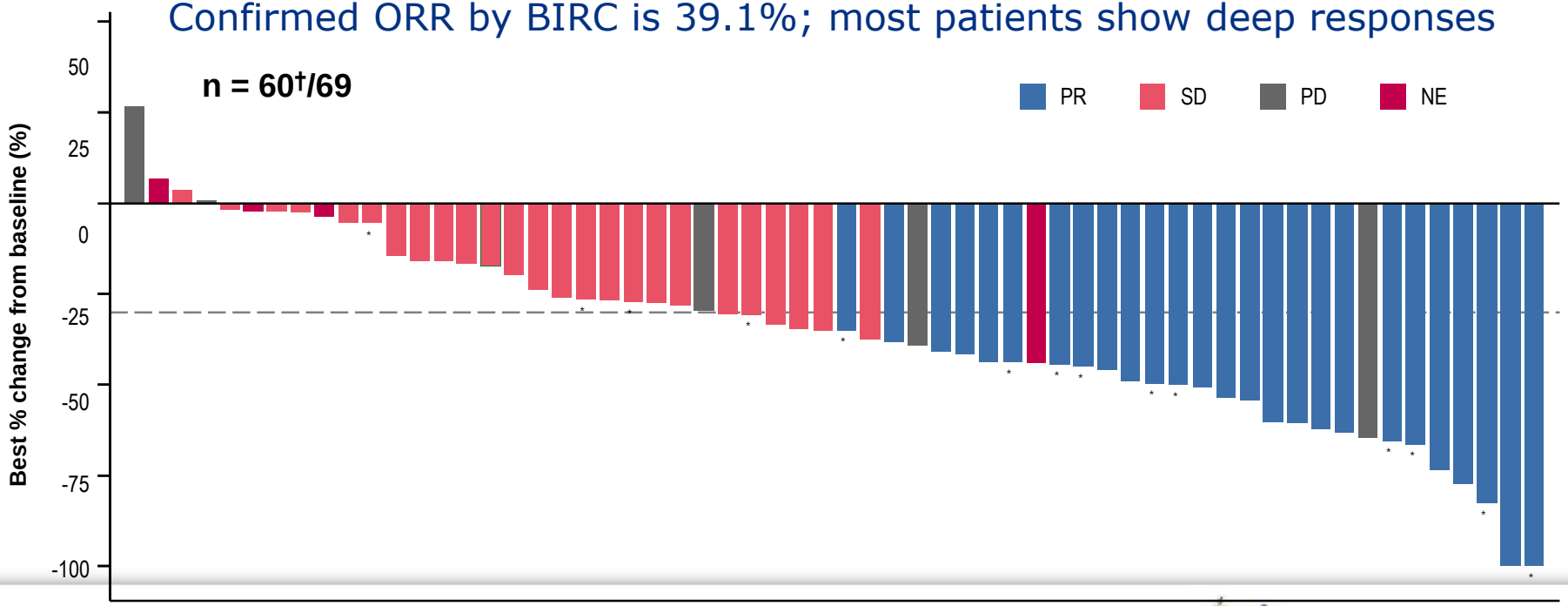
A Drilon et al. N Engl J Med 2018;378:731-739.

MET capmatinib
Tumor Response By BIRC (Pretreated COHORT 4)

Confirmed ORR by BIRC is 39.1%; most patients show deep responses



*Ongoing patients
†number of patients with measurable disease at baseline and ≥1 post-baseline assessment

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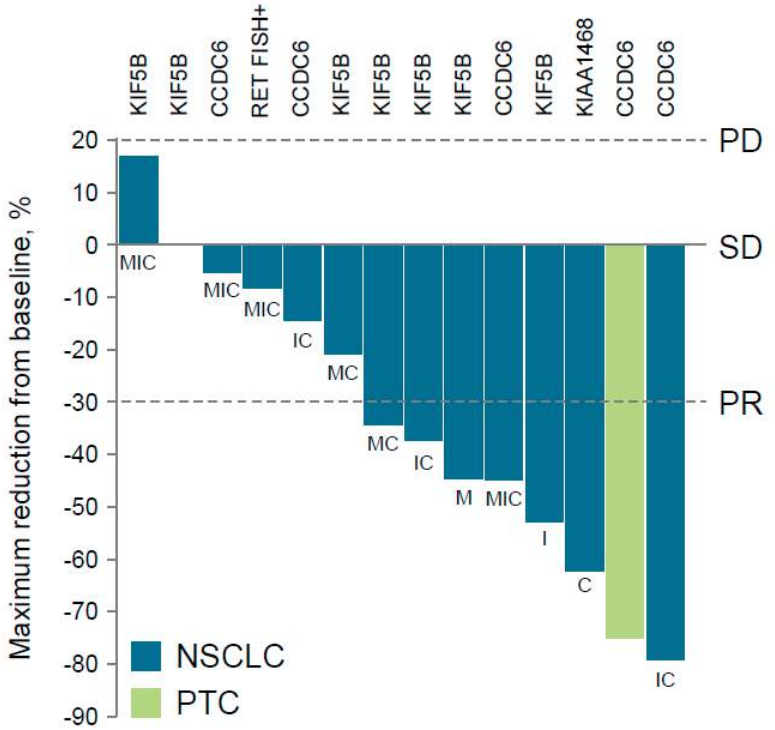
63% ORR in MKI-naive RET fusion tumors, including NSCLC



Best response	RET fusion (N=15*) n, (%)	MKI-naive (N=8) n , (%)
PR	8 (53)†	5 (63)
SD	5 (33)	6 (37)
PD	2 (13)	0

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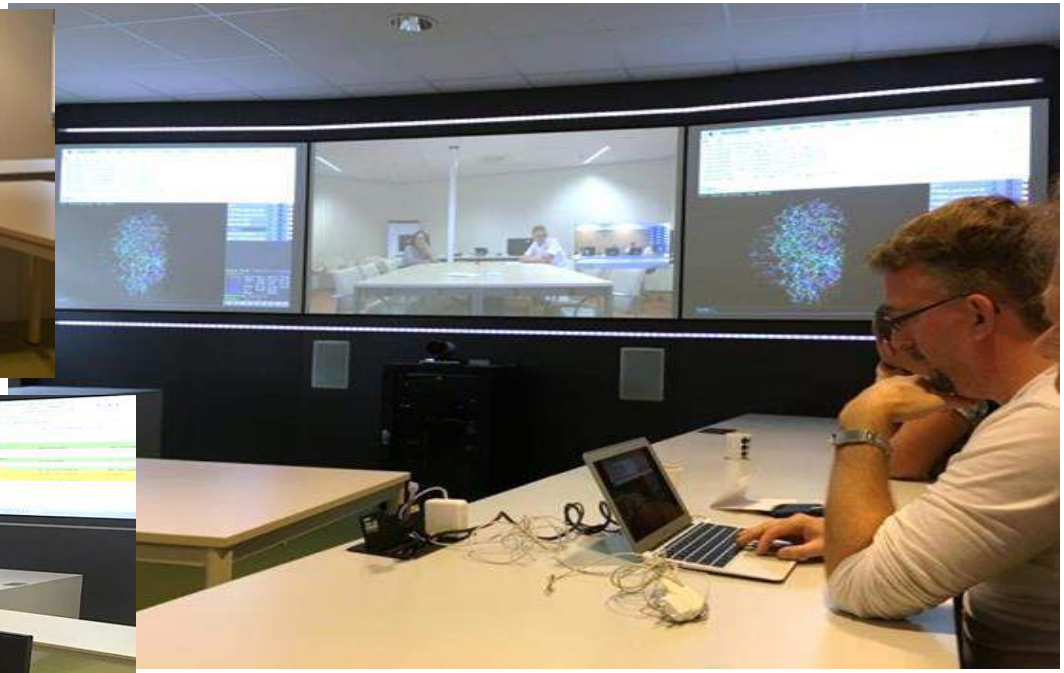
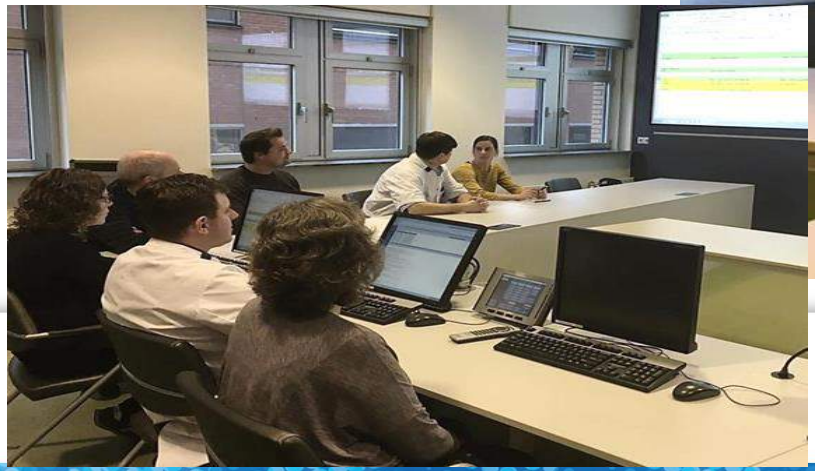
Moleculaire Tumor Board





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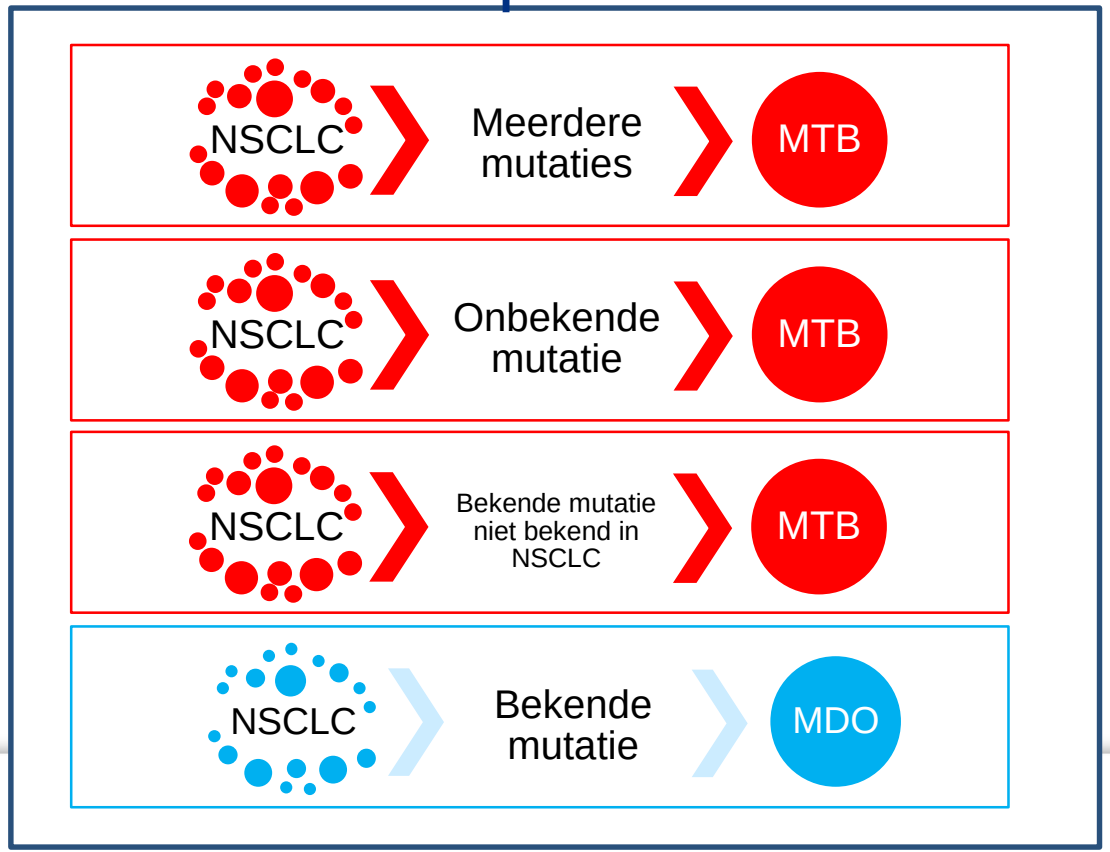
Moleculaire tumor board (MTB)

Opgericht oktober 2014

Moleculaire uitslag samen met:
- Klinische gegevens
- PA verslag

Aanbeveling:
- Klinische trial
- Off-label behandeling
- Standaard therapie

Wat wordt er besproken in de MTB



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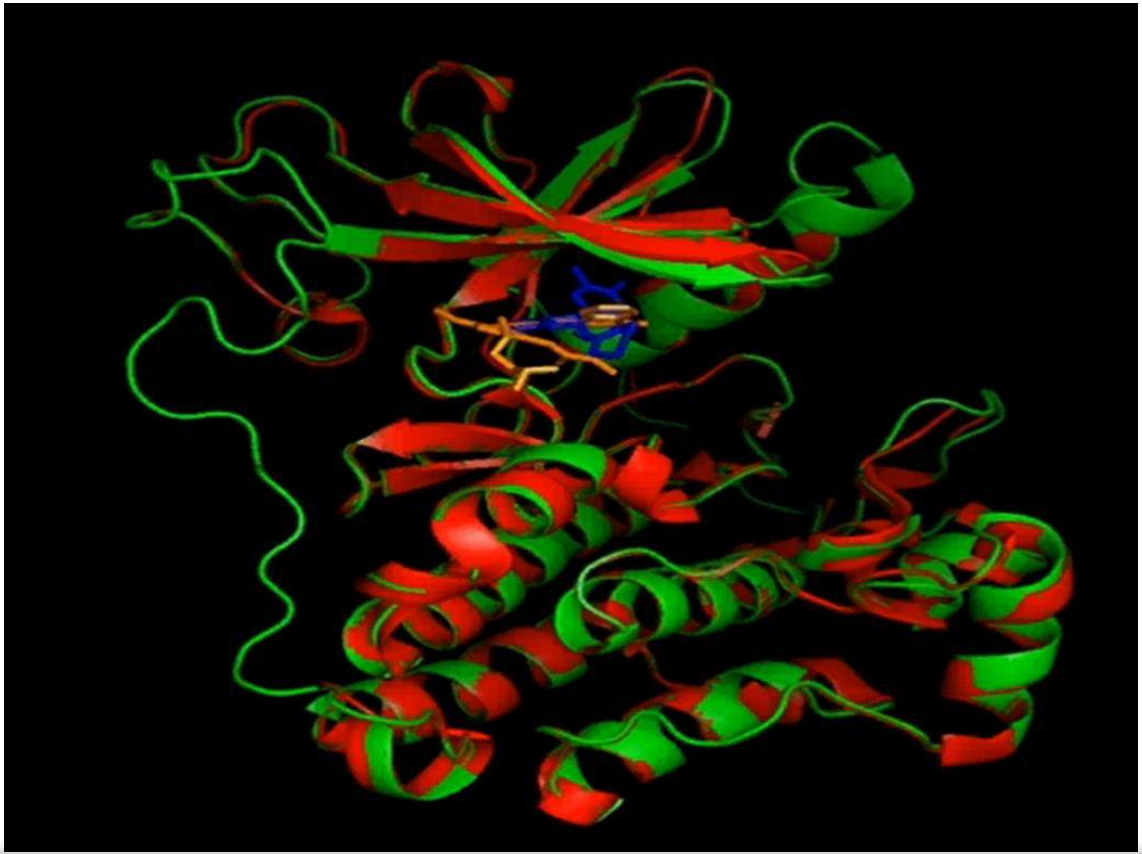

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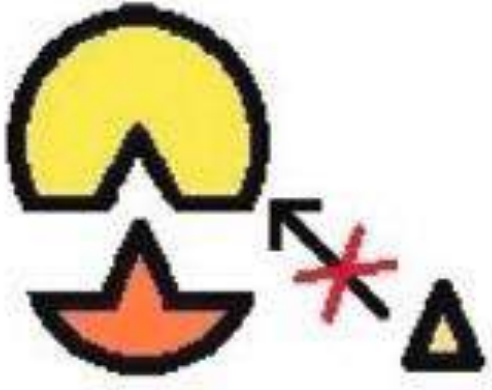
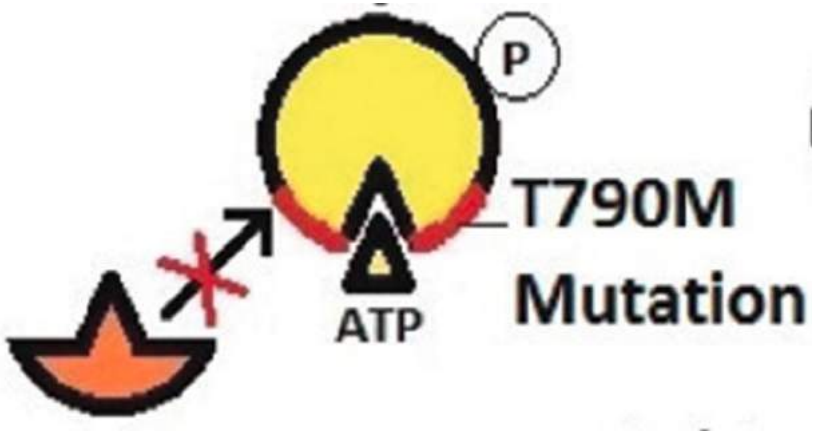
Welke behandeling is mogelijk?



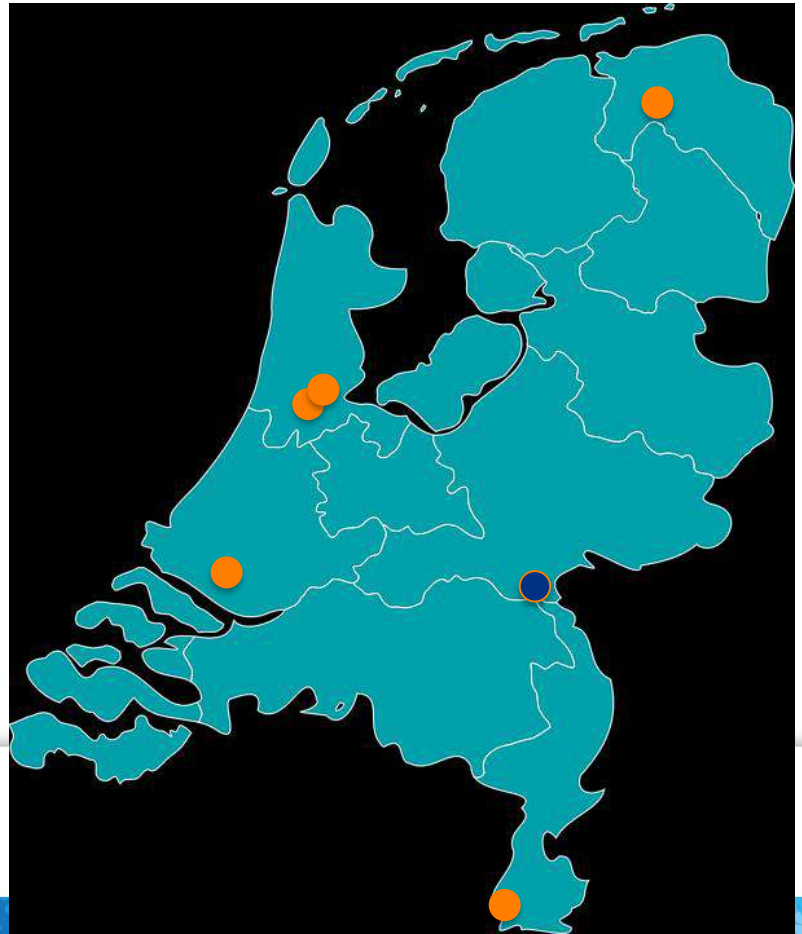
gefitinib of erlotinib



Welke behandeling is mogelijk?

osimertinib

Centra zeldzame mutaties



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Take home message

- Bij longcarcinoom anders dan plaveiselceltype
  - >> mutatieanalyse: EGFR, BRAF, KRAS, HER2
  - >> translocatieanalyse: ALK, ROS1, RET, MET, NTRK, NRG1

- Bij zeldzame mutaties behandeling in centra; daar zijn ook de studies te vinden.

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