Doelgerichte behandeling

Hoe zit het met mutaties?

dr. A.J. van der Wekken/ drs. B.I. Hiddinga
Longarts-oncoloog

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Disclosure

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

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Inleiding

- Welke mutaties bij longkanker zijn er?
- Hoe worden deze getest?
- Welke geneesmiddelen zijn er?

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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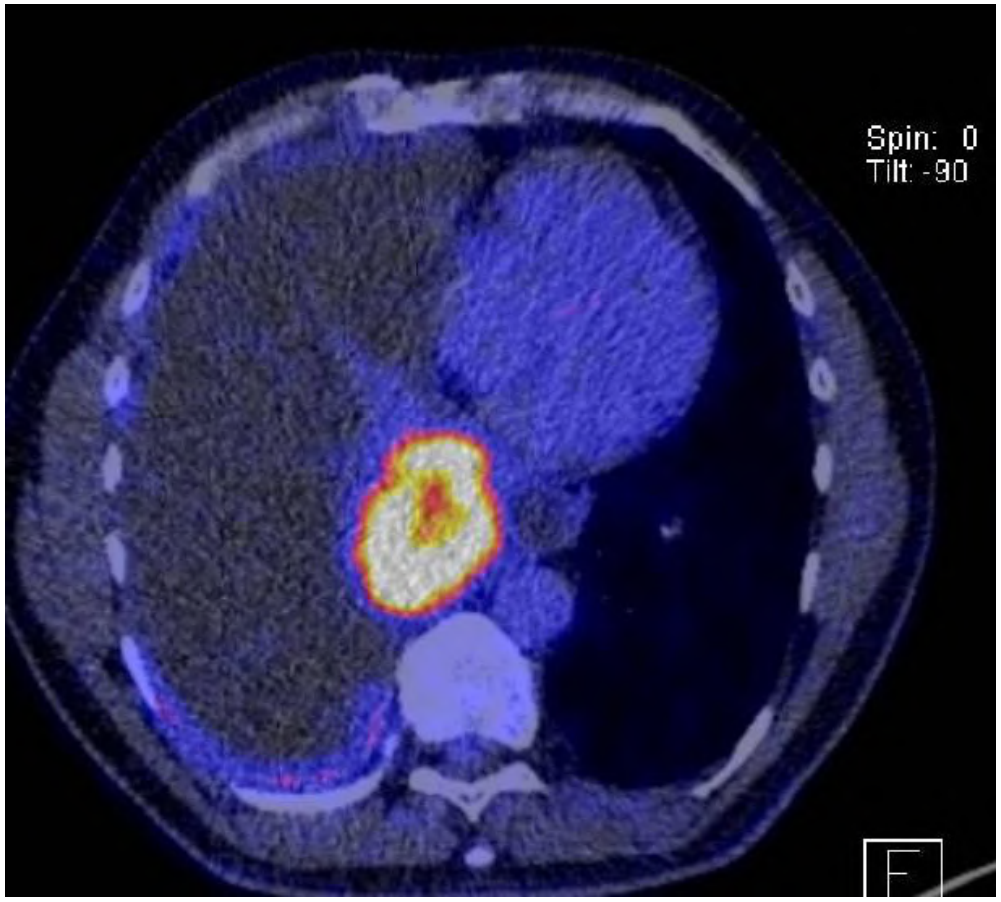

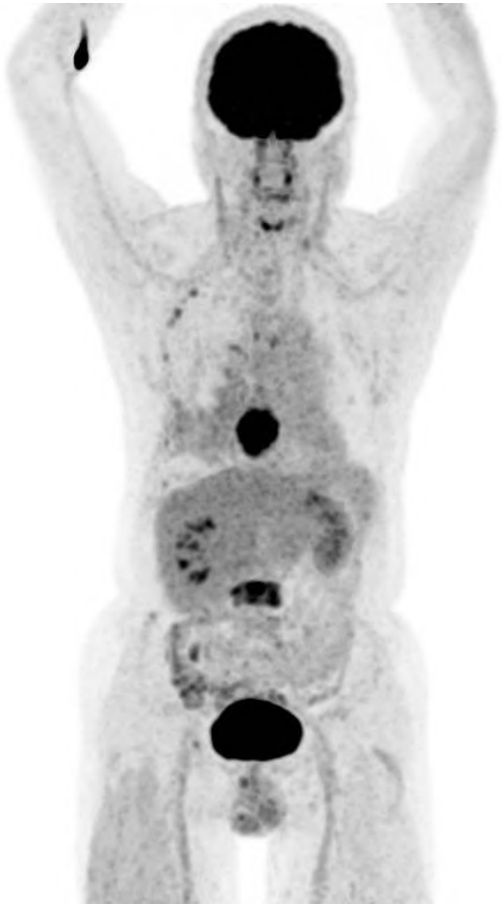

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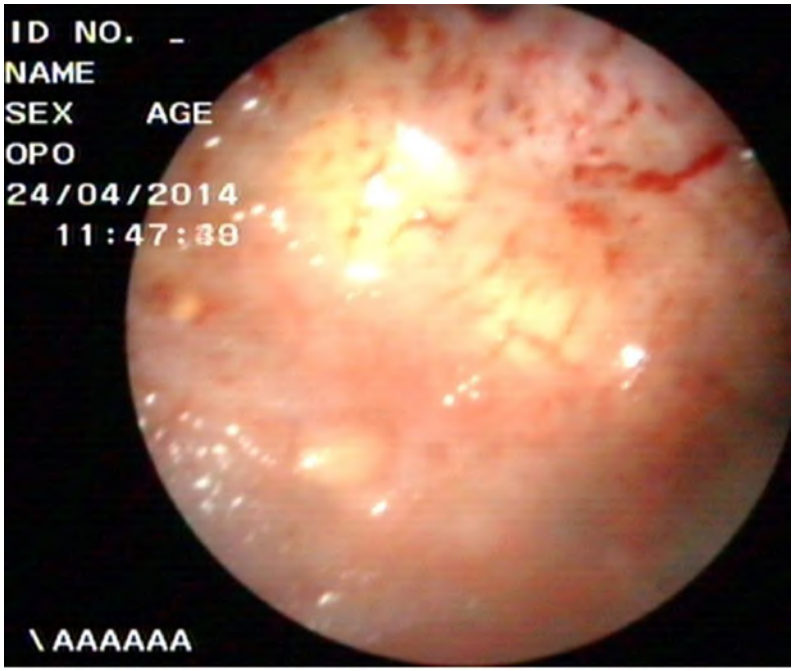
Thoracoscopie



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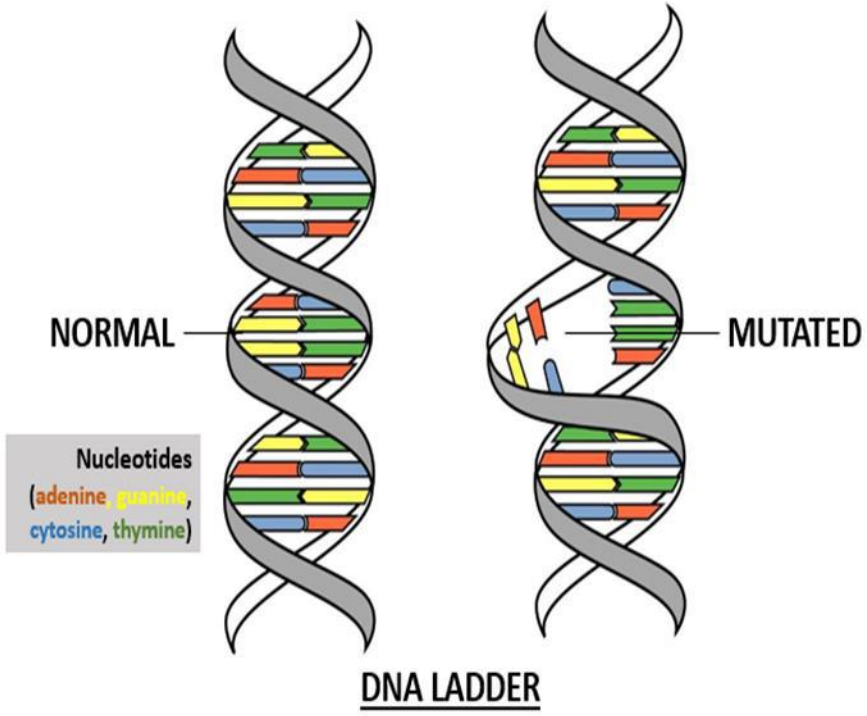
Pathologie verslag

- 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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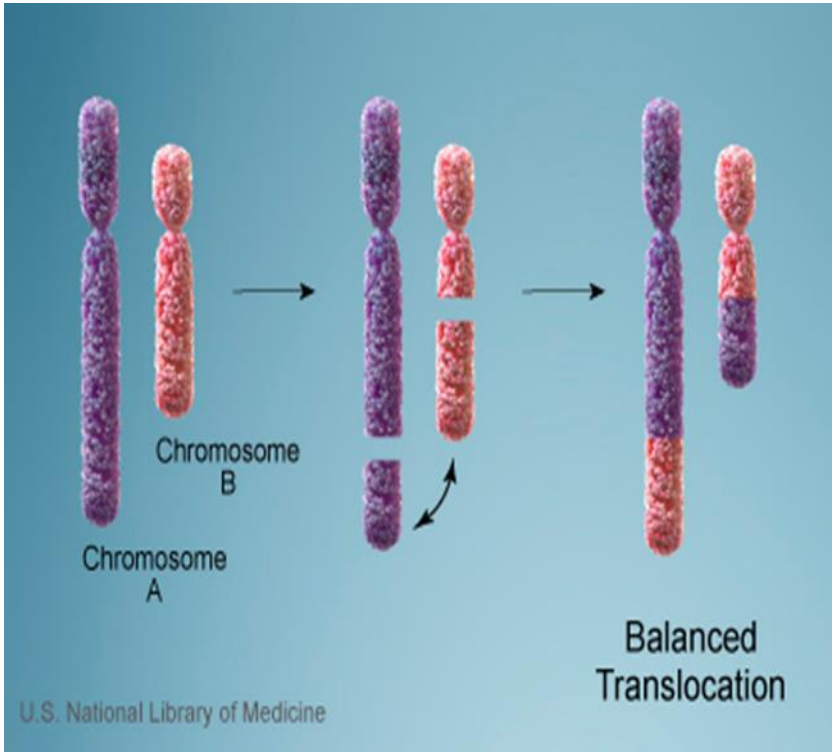

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Mutaties

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

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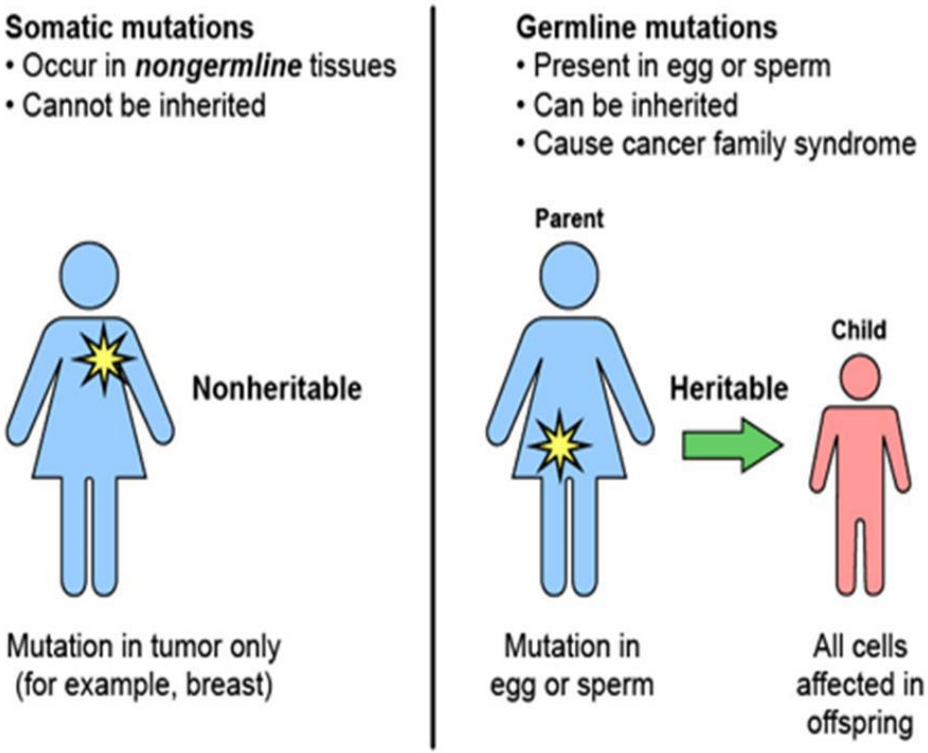
Moleculaire pathologie: alleen somatische mutaties



Adapted from the National Cancer Institute and the American Society of Clinical Oncology

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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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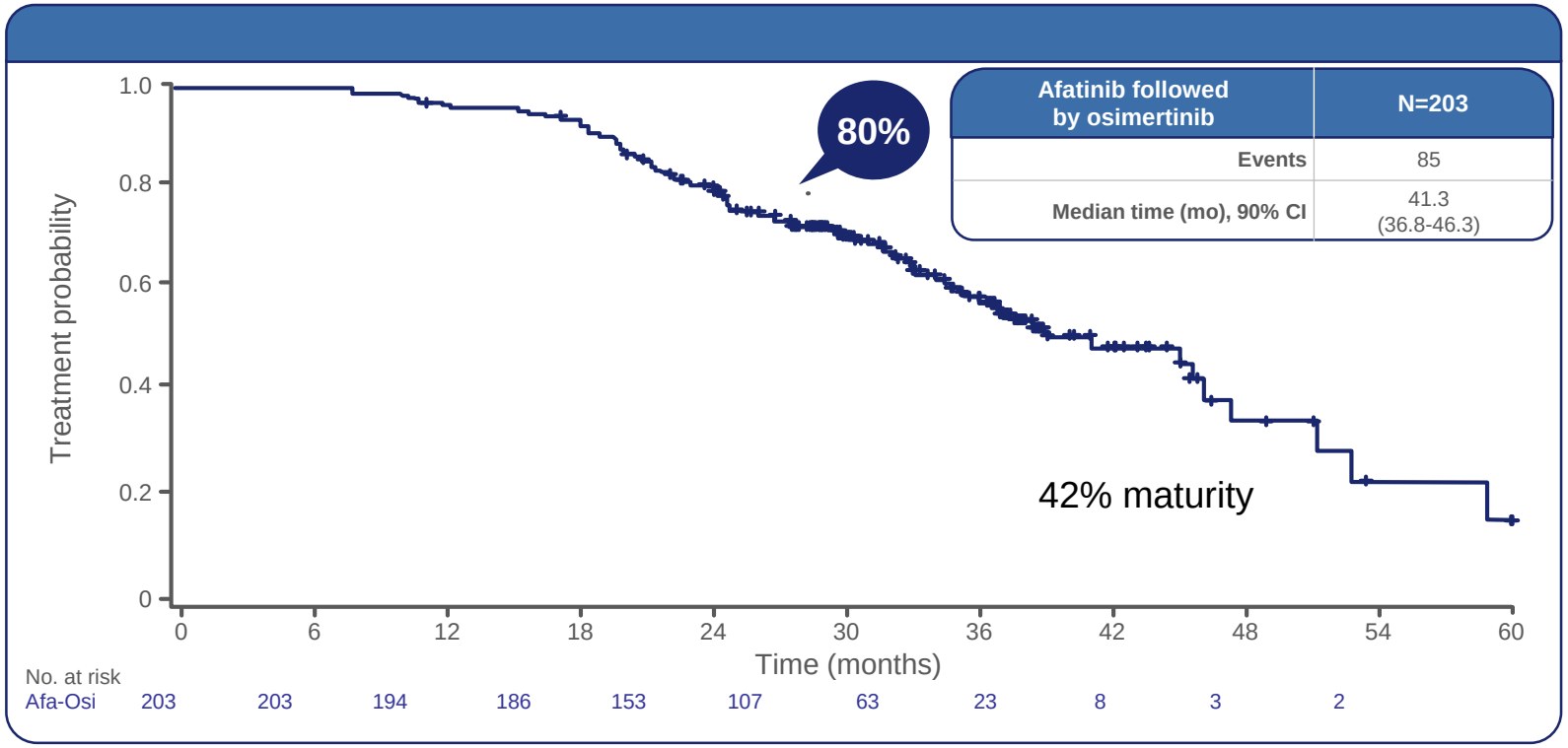
Trial	ORR EGFR TKI	ORR control arm	PFS EGFR TKI	PFS control arm	OS EGFR TKI	OS control arm
Ipass Gefitinib	71%	47% (chemo)	9.5	6.3	21.6	21.9
NEJ002 Gefitinib	74%	31% (chemo)	10.8	5.4	30.5	23.6
WJTOG Gefitinib	62%	32% (chemo)	9.2	6.3	30.9	NR
Optimal Erlotinib	83%	36% (chemo)	13.1	4.6	22.6	28.8
Eurtac 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

Overall Survival



CI = confidence interval.

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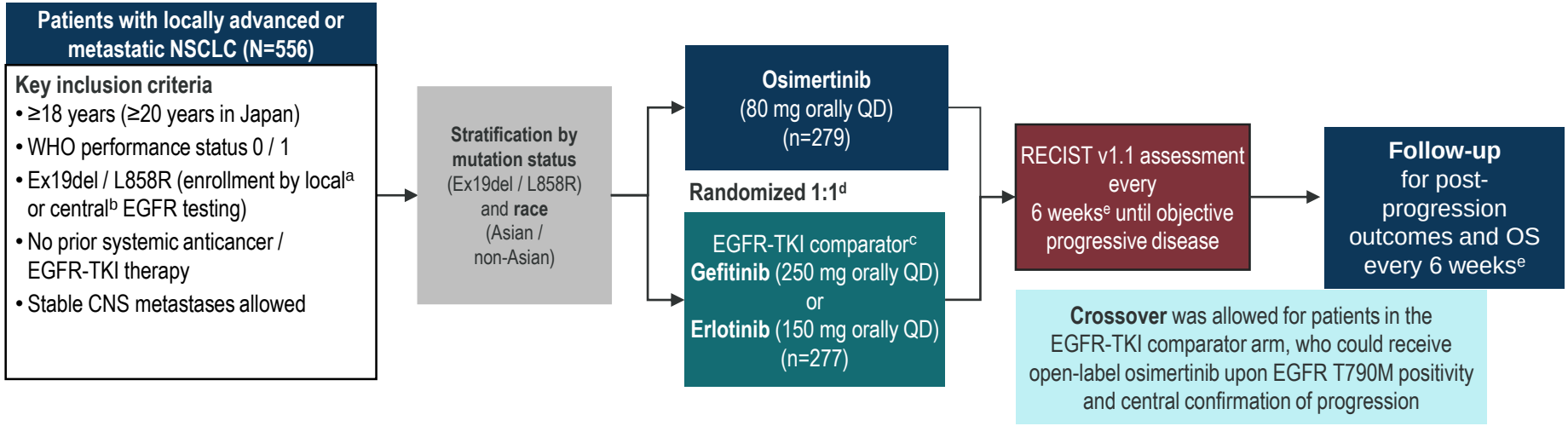
FLAURA study design

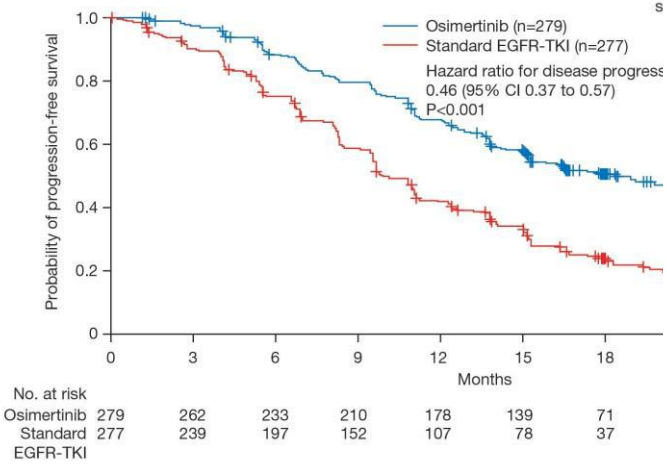


Endpoints

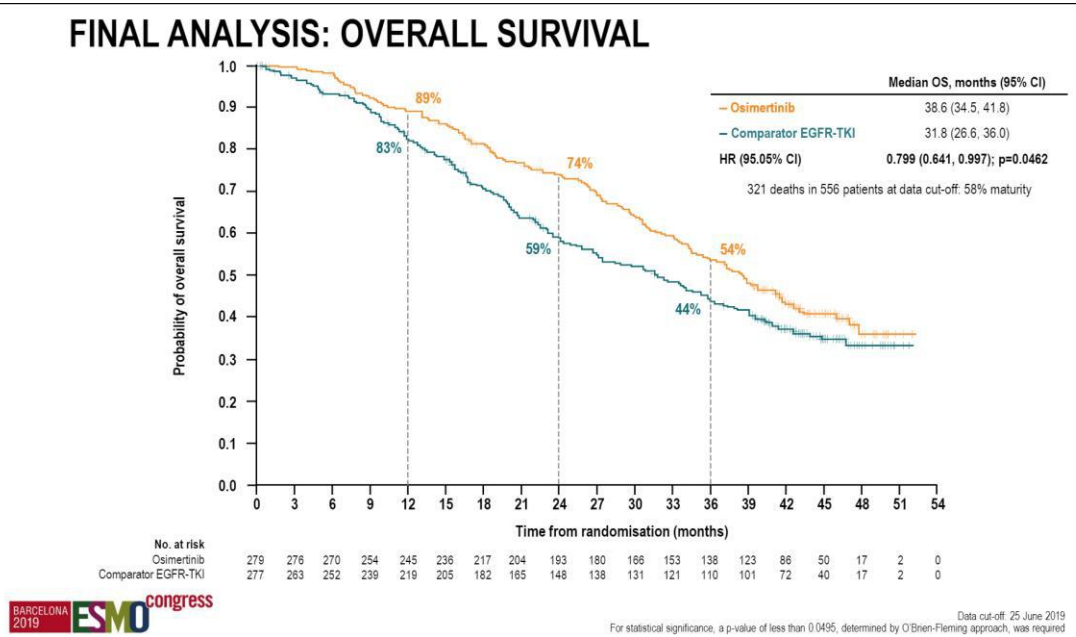
- **Primary endpoint:** PFS based on investigator assessment (according to RECIST v1.1)
  - The study had a 90% power to detect a hazard ratio of 0.71 (representing an improvement in median PFS from 10 months to 14.1 months) at a two-sided alpha-level of 5%
- **Secondary endpoints:** Objective response 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.

Phase III Osimertinib vs Pt-Pemetrexed in first line EGFR TKI resistant EGFRmut NSCLC



The New England Journal of Medicine ©2017



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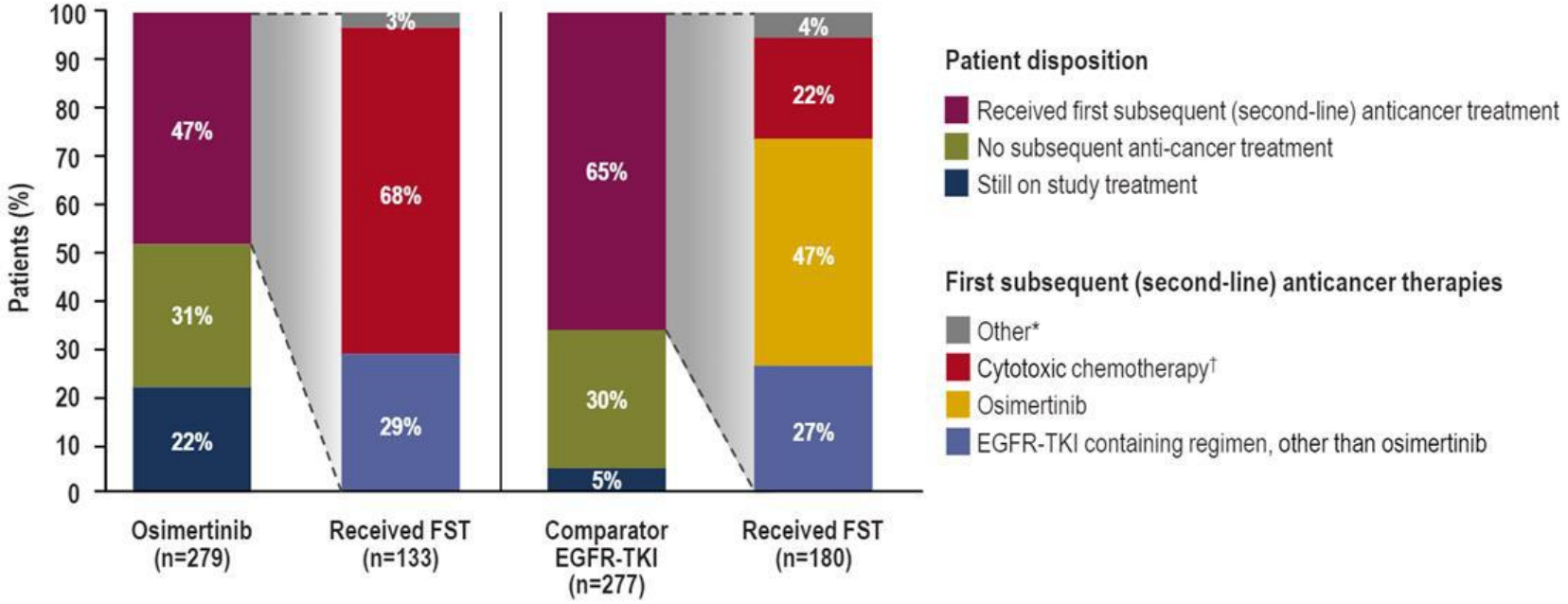
SECOND-LINE TREATMENT FOLLOWING PROGRESSION

- Of the 180 patients in the comparator EGFR-TKI arm who received a first subsequent treatment, **85 patients (47%) crossed over to osimertinib** (31% of all patients randomised from the comparator EGFR-TKI arm)



BARCELONA 2019 ESMO congress

Data cut-off: 25 June 2019

*Refers to those patients who did not receive either chemotherapy or an EGFR-TKI; †The majority of patients who received cytotoxic chemotherapy received a platinum-based chemotherapy regimen
FST, first subsequent treatment

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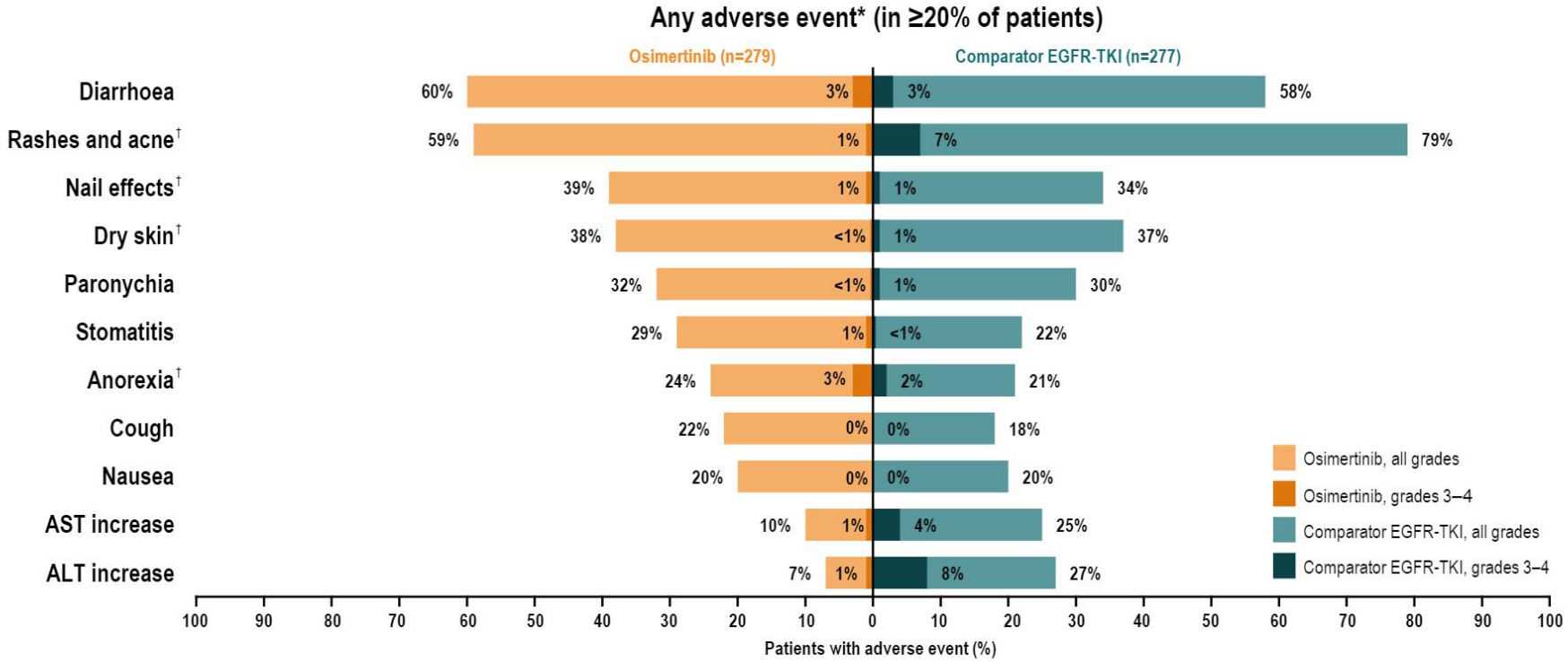
SAFETY SUMMARY

- Median duration of exposure: osimertinib, 20.7 months; comparator EGFR-TKI, 11.5 months
- Grade ≥3 possibly causally related AEs: osimertinib, 51 patients (**18%**); comparator EGFR-TKI, 79 patients (**29%**)



BARCELONA 2019 ESMO congress

Data cut-off: 25 June 2019

*As assessed by the investigator; 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; †Grouped term

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Putting OS into context

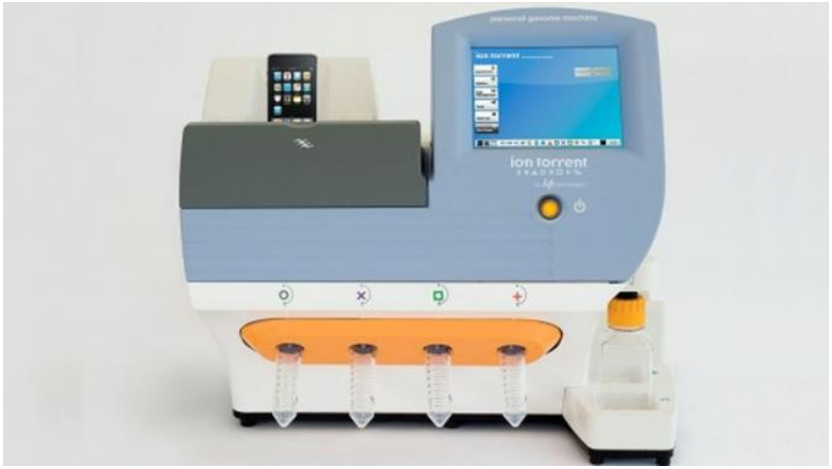
- 1st Gen TKIs: 22-28 months (limited osimertinib usage)[1-4]
- Afatinib: 32-38 months (limited osimertinib usage)[5]
- Dacomitinib: 34-37 months (limited osimertinib usage, excl. brain mets)[6]
- Osimertinib: 34-41 months[7]
- Afatinib – osimertinib: 36-46 months (T790M+ only)[8]

Combinations:

- Gefitinib + chemotherapy: 52 months (Japanese data)[9]
- Erlotinib + bevacizumab: 47 months (Japanese data, excl. brain mets)[10]
- Erlotinib + ramucirumab: immature[11]

1. Fukuoka et al. *J Clin Oncol*. 2011;29:2866; 2. Inoue et al. *Ann Oncol*. 2013;24:54; 3. Leon et al. *Ann Oncol* 2014 25(suppl_4):iv426 (poster presentation); 4. Wu et al. *Ann Oncol*. 2015;26:1883; 5. Yang et al. *Lancet Oncol*. 2015;16:141; 6. Mok et al. *J Clin Oncol*. 2018;36(22):2244 (oral presentation); 7. Ramalingham et al. Presented at ESMO 2019. Abstract LBA5_PR (oral presentation); 8. Hochmair et al. *Future Oncol*. 2019;15:2905; 9. Nakamura et al. *J Clin Oncol*. 2018;36(suppl):9005 (oral presentation); 10. Yamamoto et al. *J Clin Oncol*. 2018; 36(suppl): 9007 (oral presentation); 11. Nakagawa et al. *J Clin Oncol*. 2019;37(suppl):9000 (oral presentation).

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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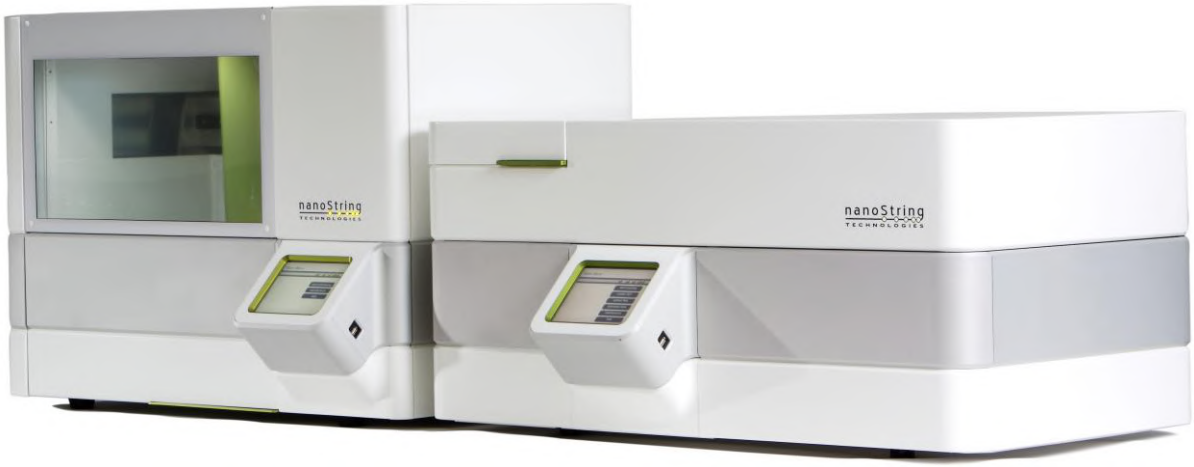
Translocaties

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



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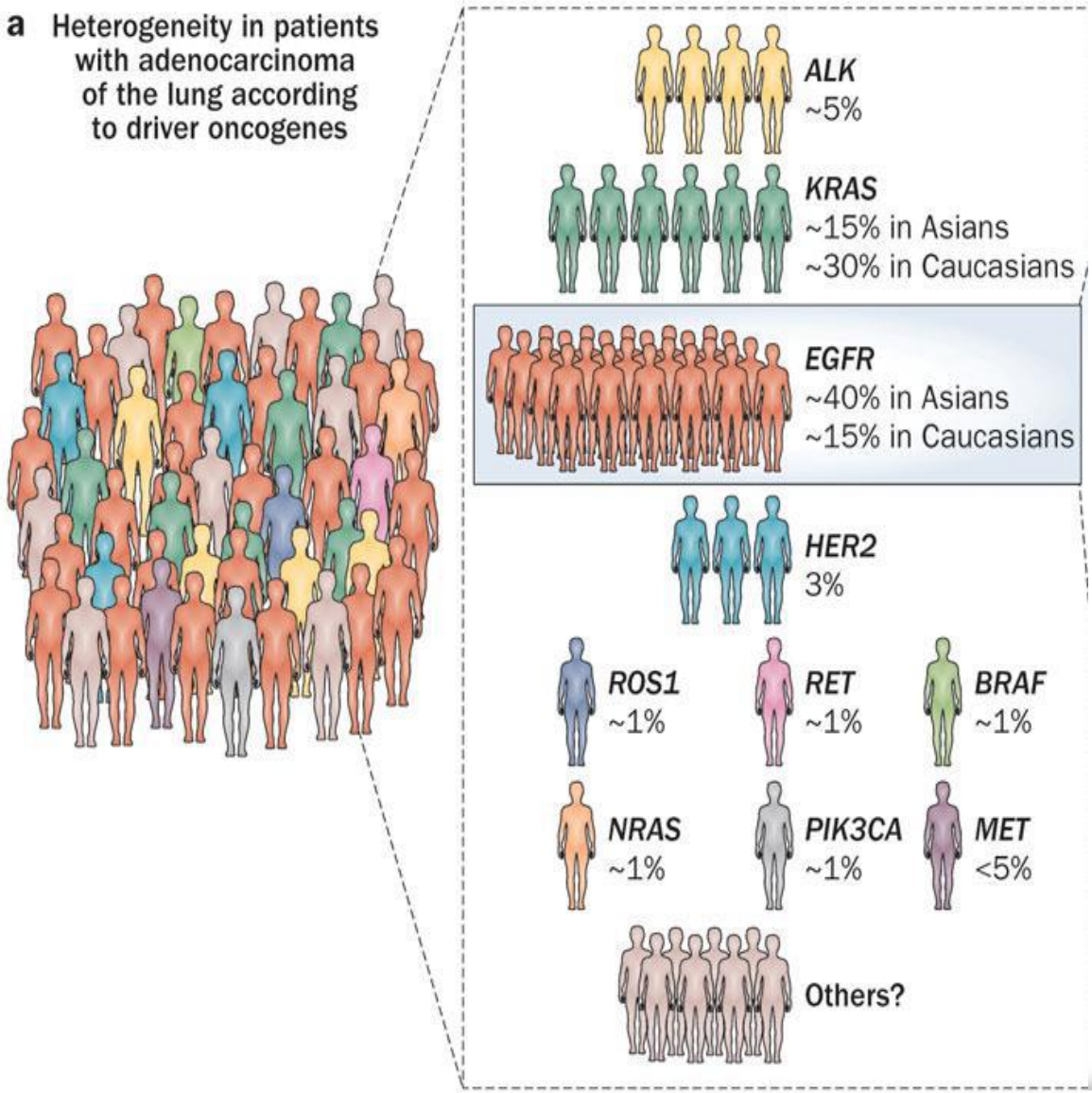

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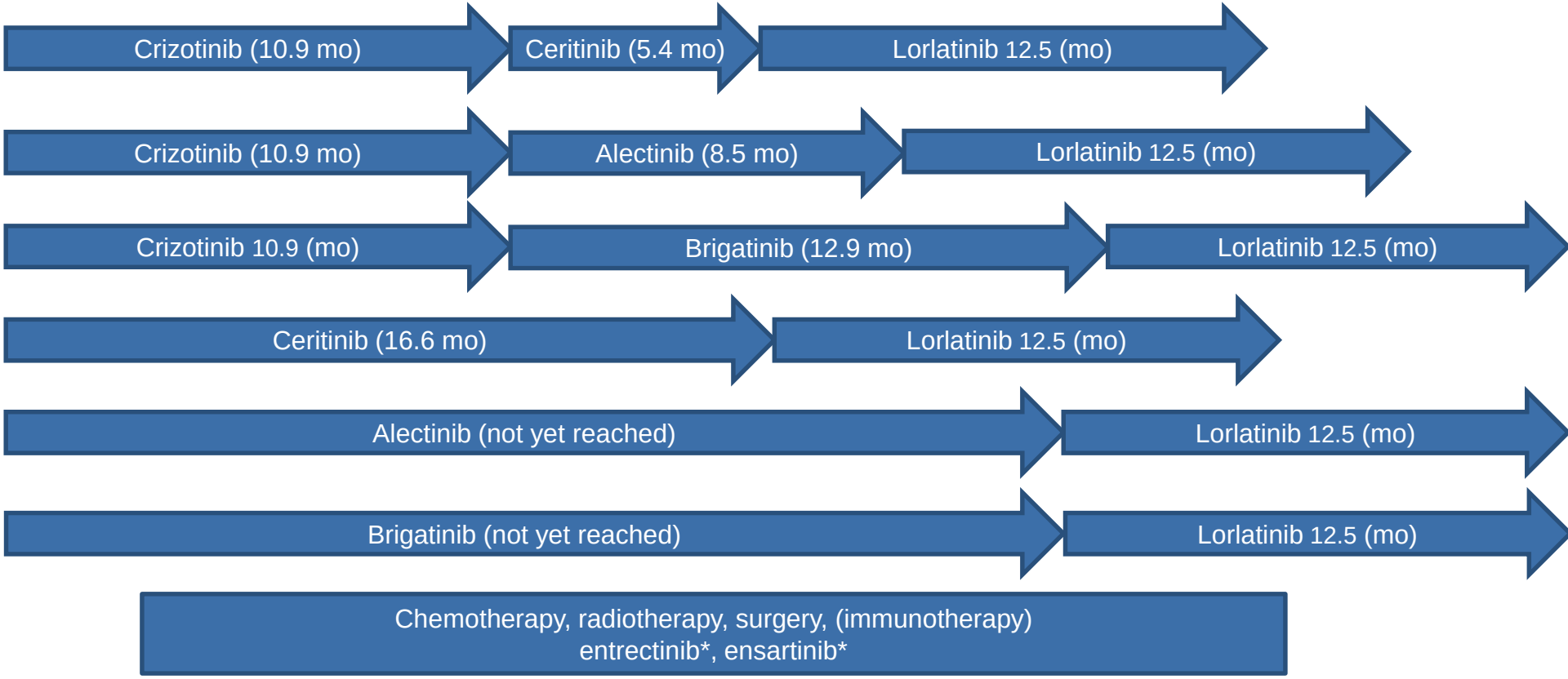
ALK

Beste volgorde van TKI's bij ALK



Adapted from De Langen AJ. Translational Cancer Research 2017.

* Nog niet geregistreerd door de EMA

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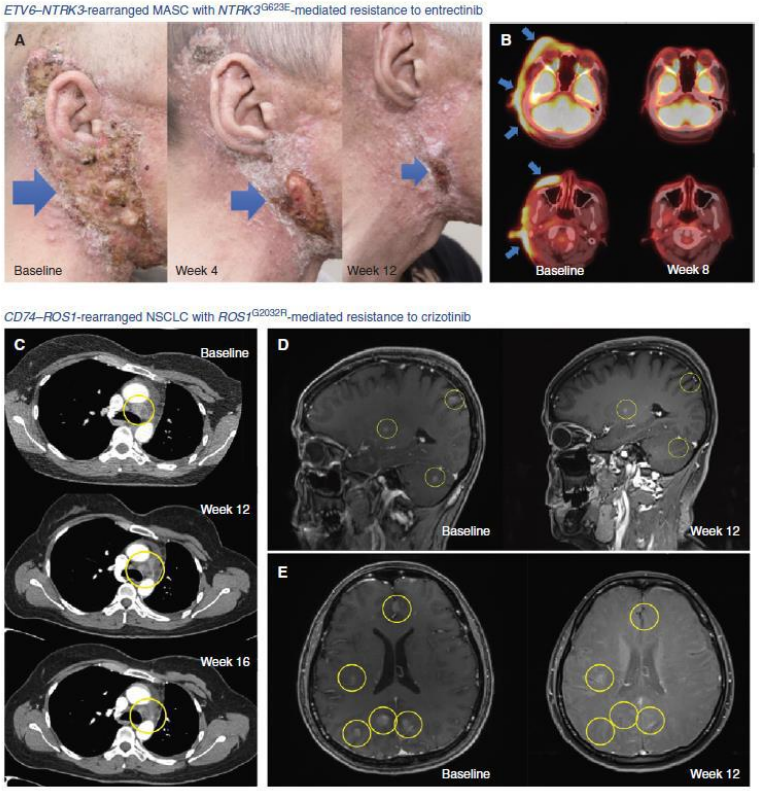
ROS1

First data of repotrectinib (TPX0005)



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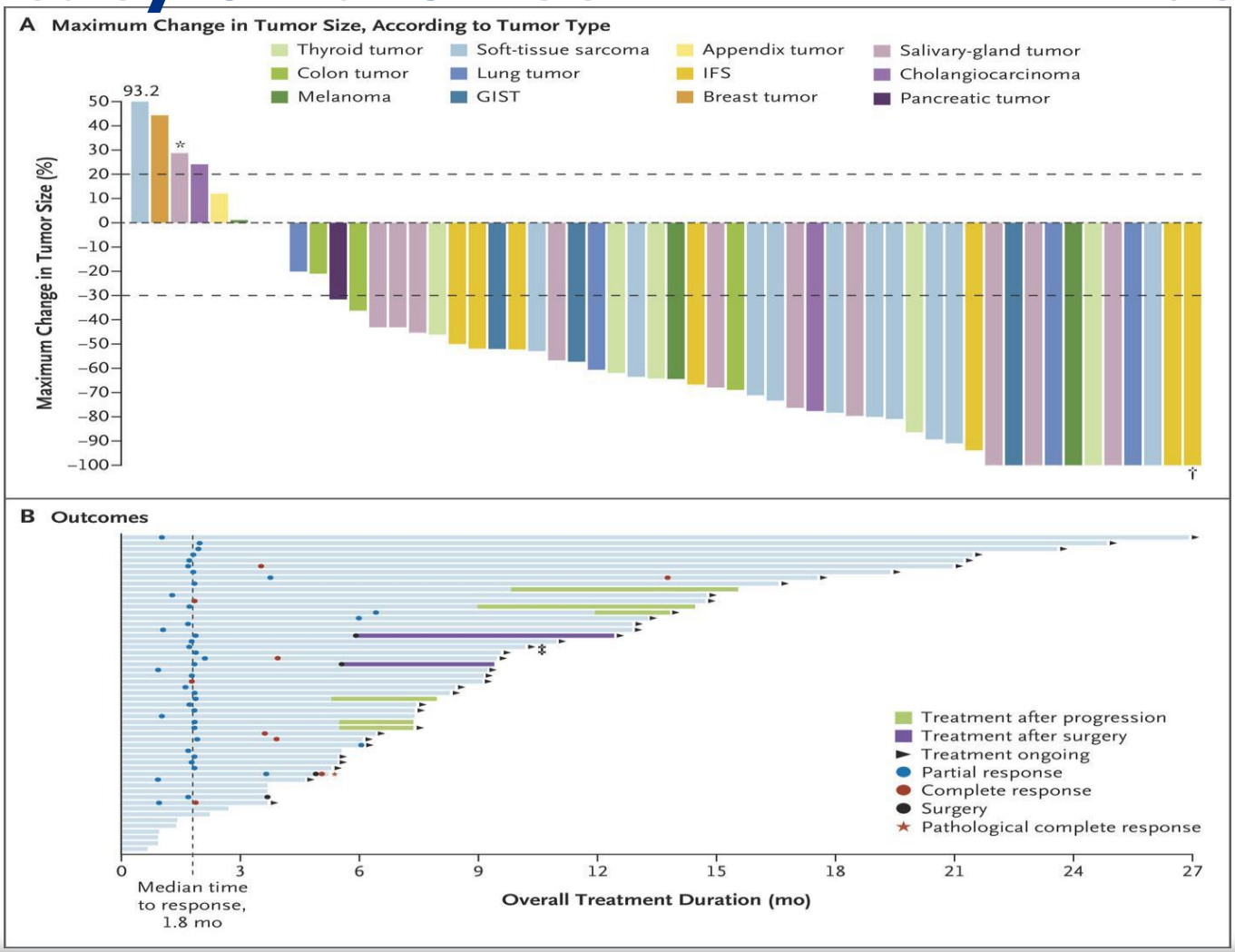
NTRK

Efficacy of larotrectinib in NTRK fusions



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

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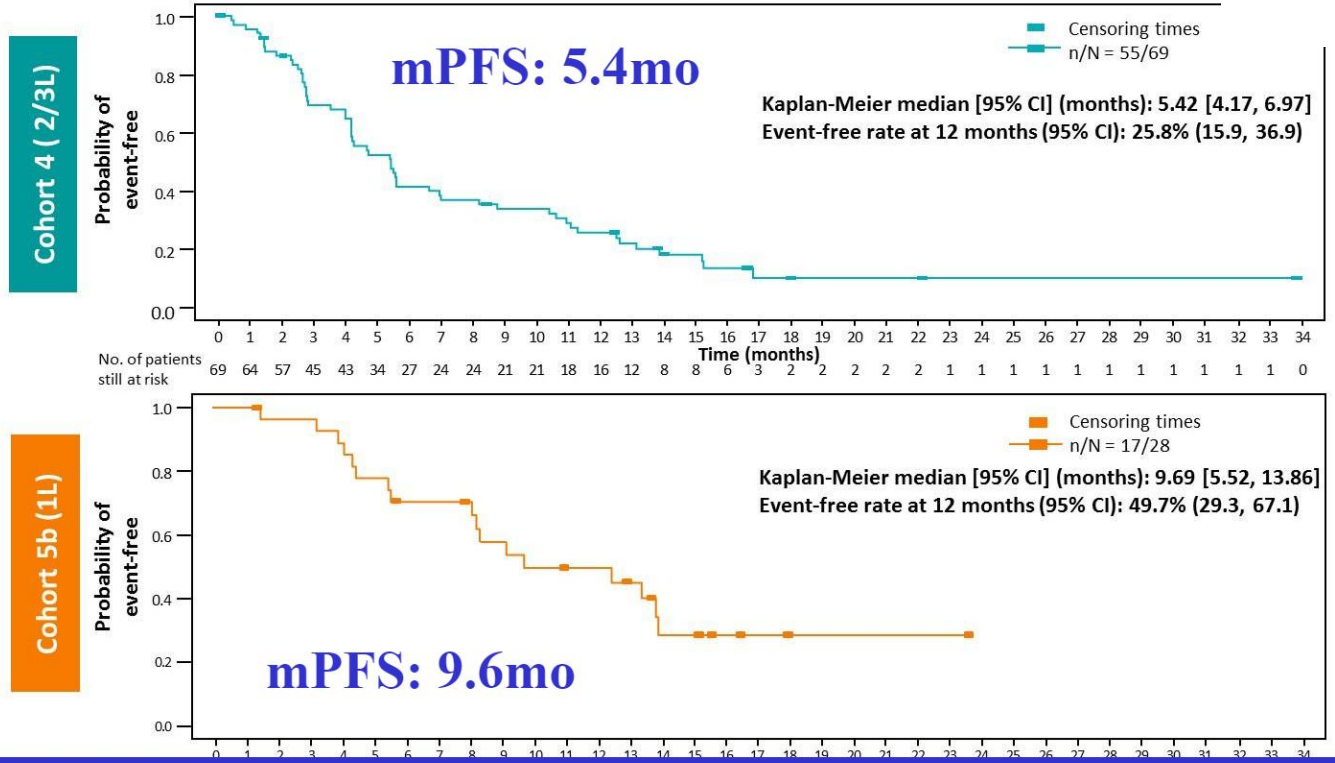
MET

Capmatinib: PFS per BIRC

Median PFS was 5.42 months in Cohort 4 (2/3L) and 9.69 months in Cohort 5



Sept 2019, cancer therapy capmatinib (INC280) granted FDA Breakthrough Therapy Designation for pts with MET-mutated advanced NSCLC

J.Wolf et al. ASCO 2019

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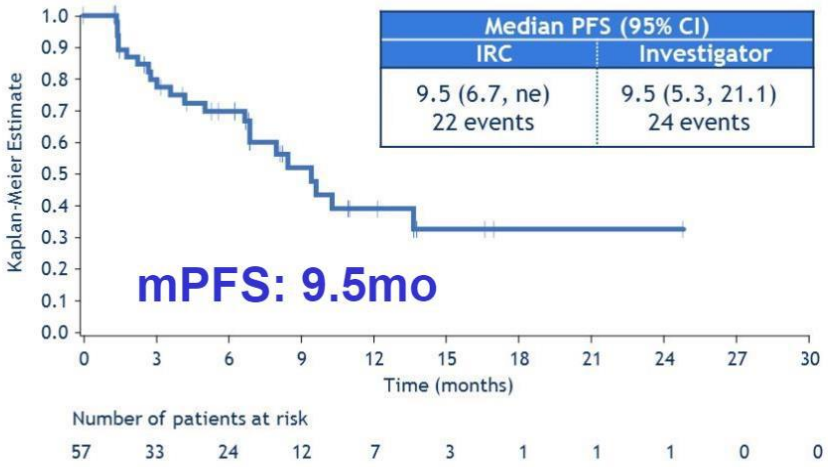
Tepotinib: PFS

PFS across all treatment lines

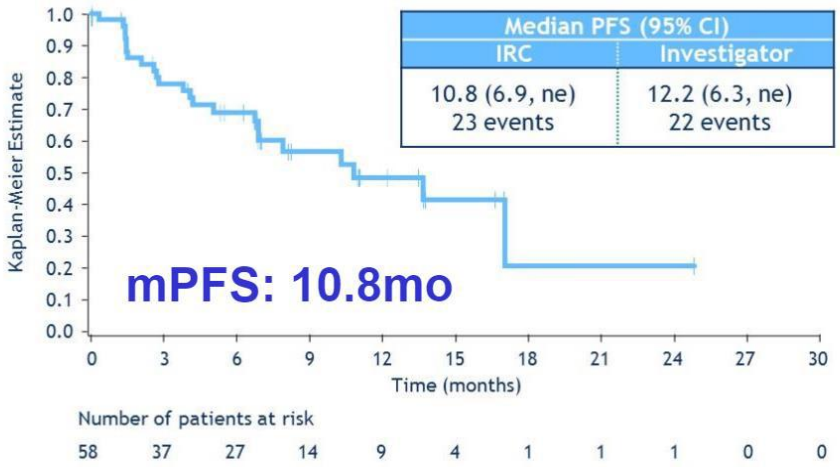
Liquid biopsy (L+) (n=57)

PFS by IRC



Tissue biopsy (T+) (n=58)

PFS by IRC



33/57 L+ patients and 31/58 T+ patients remain on treatment.

Median follow-up for PFS (IRC): 6.9 months (95% CI 5.5, 11.0).

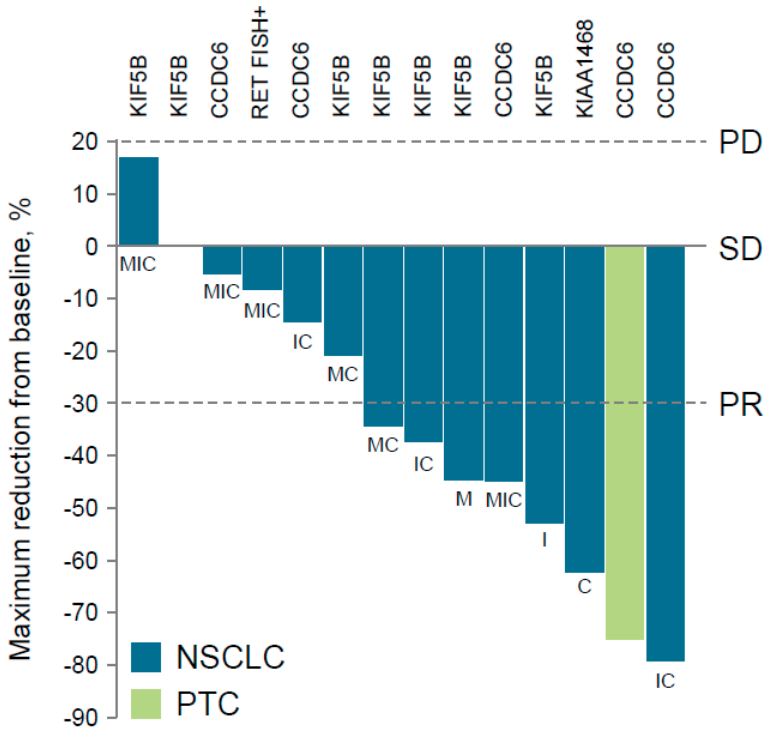
L+, *MET*ex14-skipping mutation-positive in ctDNA; T+, *MET*ex14-skipping mutation-positive in tissue.
IRC, independent review committee; ne, not estimable; PFS, progression-free survival.

P.K. Paik et al, ASCO 2019

RET

AACR 2018

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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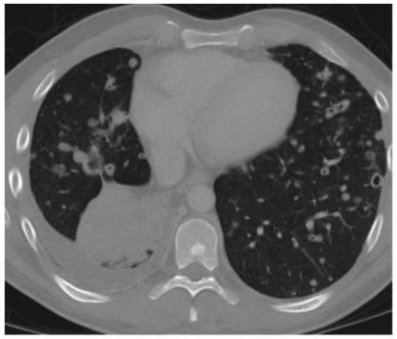
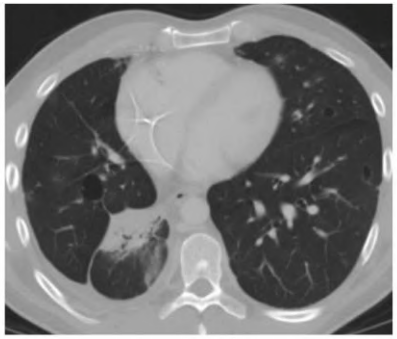
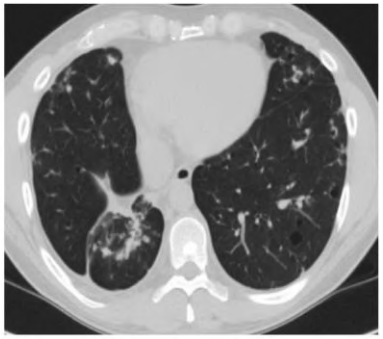
NRG1



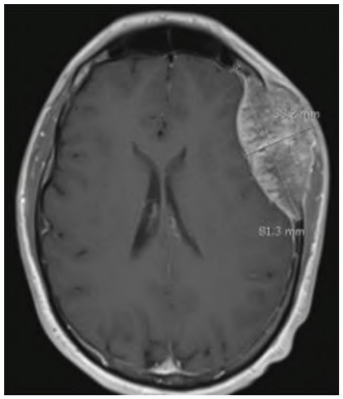
Pre-Afatinib



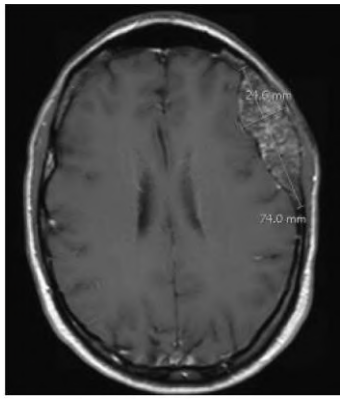
Two-months on Afatinib



Eight-Months on Afatinib



Prior to Afatinib



Eight Months on Afatinib

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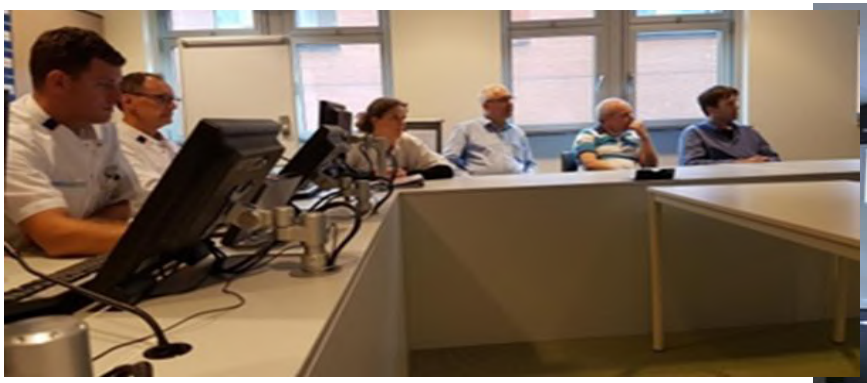
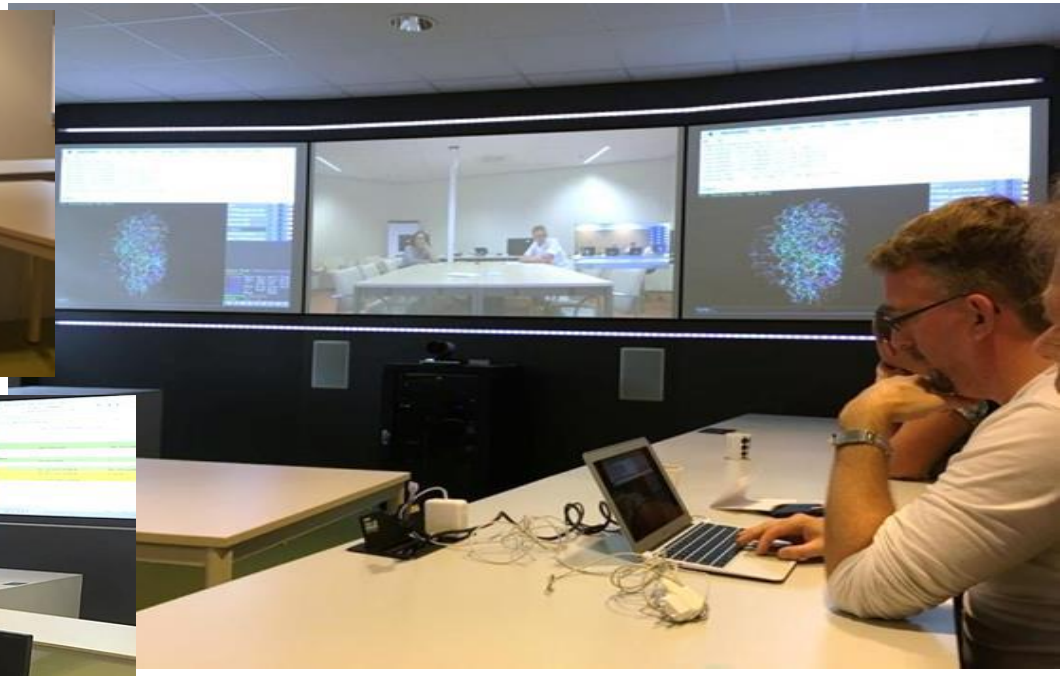
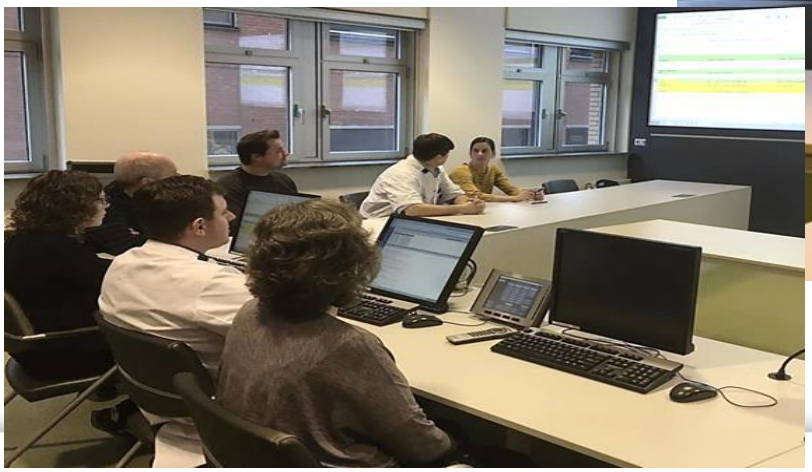
Moleculaire tumor board







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Moleculaire tumor board (MTB)

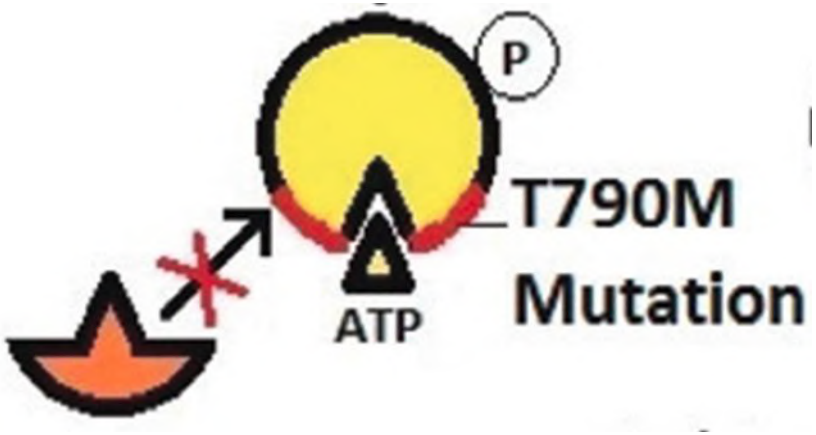
Opgericht oktober 2014

Moleculaire uitslag samen met:
- Klinische gegevens
- PA verslag

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

Welke behandeling is mogelijk?

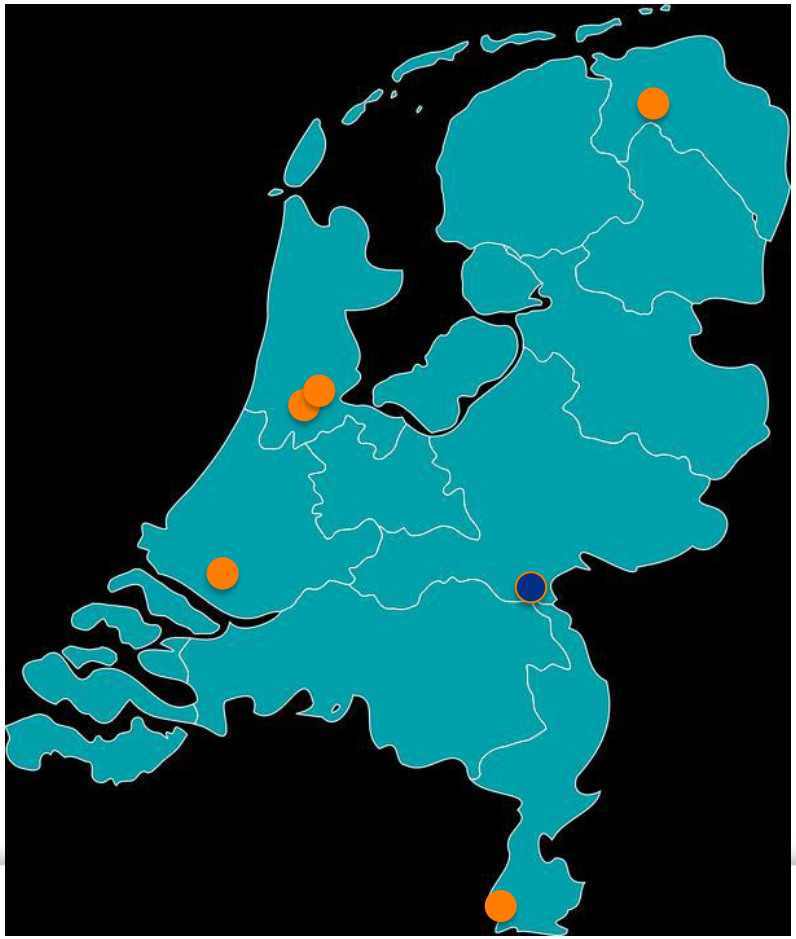
gefitinib of erlotinib



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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