Doelgerichte behandeling

EGFR

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

umcg Oncologie
Comprehensive Cancer Center

Disclosure

- Advisory board/Lectures:
  - Lilly
  - Boehringer-Ingelheim
  - Pfizer
  - AstraZeneca
  - Roche (diagnostics)
  - Takeda
  - Janssen
- Grant:
  - Boehringer-Ingelheim
  - Pfizer
  - AstraZeneca
  - Roche
  - Takeda

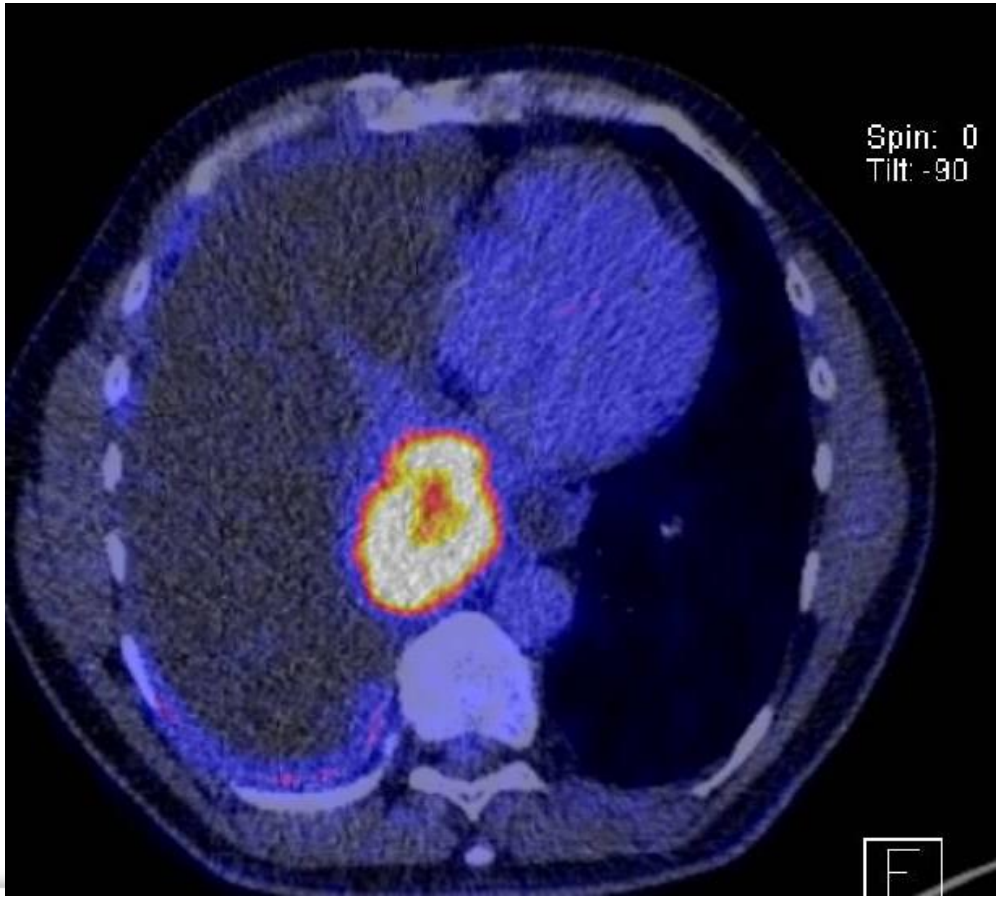
umcg Oncologie
Comprehensive Cancer Center

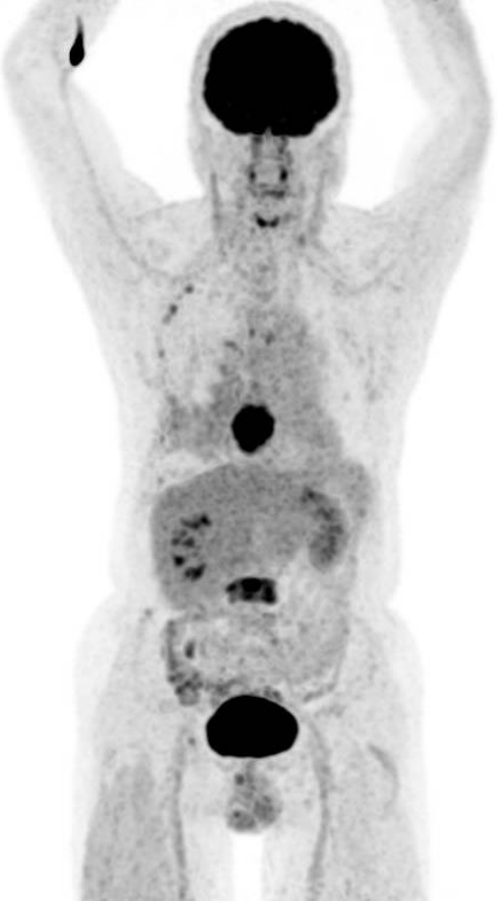
Inleiding

- Welke geneesmiddelen zijn er?
- Wat gebeurt er bij resistentie?
- Welke trials zijn er en waar vind ik deze?

Casus 1 Dhr T 51jr

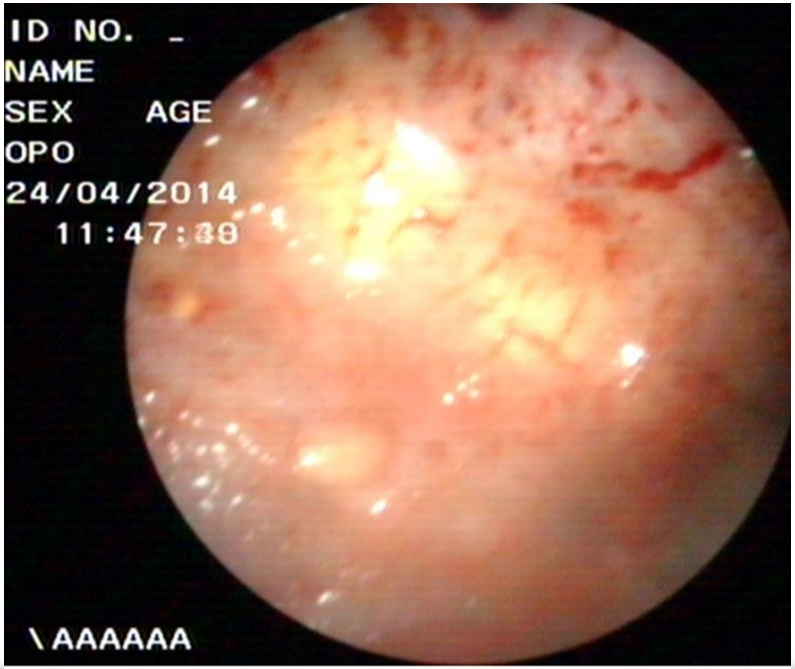
- Voorgeschiedenis:
- Hypertensie COPD
- 2014 april: bezoek SEH ivm kortademigheid: drainage pleuravocht rechts
- PA: adenocarcinoom van de long





umcg Oncologie
Comprehensive Cancer Center

Thoracoscopie



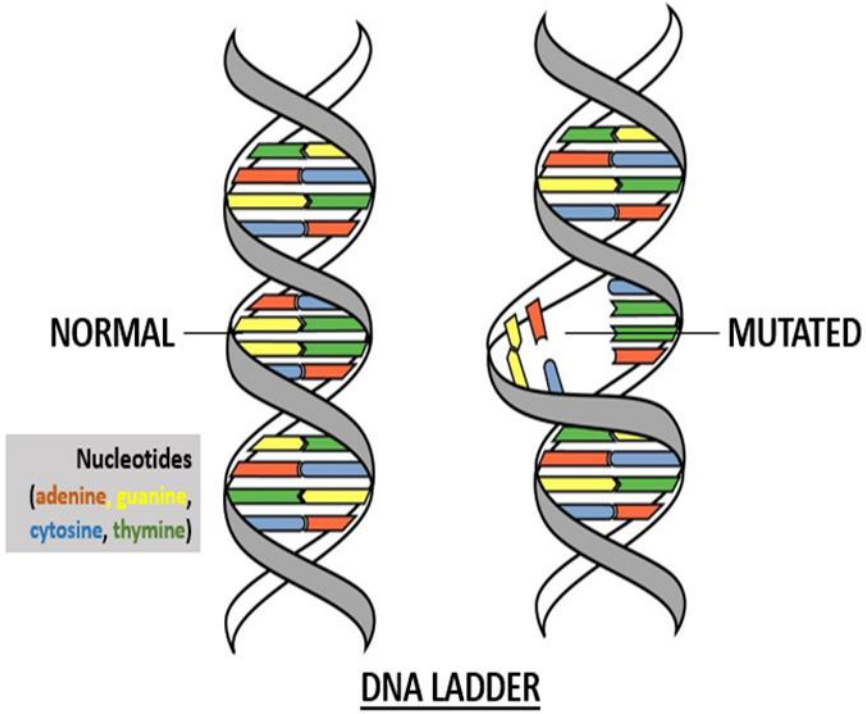
umcg Oncologie
Comprehensive Cancer Center

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.



umcg Oncologie
Comprehensive Cancer Center

Terug naar de casus

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

- Combinaties
  - Erlotinib - bevacizumab
  - Erlotinib - ramucirumab

Trial	ORR EGFR TKI	ORR control arm	mPFS EGFR TKI (months)	mPFS control arm (months)	mOS EGFR TKI (months)	mOS control arm (months)
Ipass Gefitinib	71%	47% (chemo)	9.5	6.3	18.8	17.4
NEJ002 Gefitinib	74%	31% (chemo)	10.8	5.4	27.7	26.6
WJTOG Gefitinib	62%	32% (chemo)	9.2	6.3	34.9	37.3
Optimal Erlotinib	83%	36(chemo)	13.1	4.6	22.8	27.2
Eurtac Erlotinib	58%	15% (chemo)	9.7	5.2	19.3	19.5
Lux-Lung 3 Afatinib	56%	23% (chemo)	11.1	6.9	28.2	28.2
Lux-Lung 6 Afatinib	67%	23% (chemo)	11.0	5.6	23.1	23.5
Lux-Lung 7 Afatinib	70%	56% (gefitinib)	11.0	10.9	27.9	24.5
Archer 1050 Dacomitinib	75%	72% (gefitinib)	14.7	11.0	34.1	27.0
Flaura Osimertinib	80%	76% (gefitinib / erlotinib)	18.9	10.2	38.6	31.8
NEJ026 Erlotinib-bevacizumab	72%	66% (erlotinib)	16.9	13.3	50.7	46.2
Relay Erlotinib-ramucirumab	76%	75% (erlotinib)	19.4	12.4	NR	NR

Trial	ORR EGFR TKI	ORR control arm	mPFS EGFR TKI (months)	mPFS control arm (months)	mOS EGFR TKI (months)	mOS control arm (months)
Ipass Gefitinib	71%	47% (chemo)	9.5	6.3	18.8	17.4
NEJ002 Gefitinib	74%	31% (chemo)	10.8	5.4	27.7	26.6
WJTOG Gefitinib	62%	32% (chemo)	9.2	6.3	34.9	37.3
Optimal Erlotinib	83%	36(chemo)	13.1	4.6	22.8	27.2
Eurtac Erlotinib	58%	15% (chemo)	9.7	5.2	19.3	19.5
Lux-Lung 3 Afatinib	56%	23% (chemo)	11.1	6.9	28.2	28.2
Lux-Lung 6 Afatinib	67%	23% (chemo)	11.0	5.6	23.1	23.5
Lux-Lung 7 Afatinib	70%	56% (gefitinib)	11.0	10.9	27.9	24.5
Archer 1050 Dacomitinib	75%	72% (gefitinib)	14.7	11.0	34.1	27.0
Flaura Osimertinib	80%	76% (gefitinib / erlotinib)	18.9	10.2	38.6	31.8
NEJ026 Erlotinib-bevacizumab	72%	66% (erlotinib)	16.9	13.3	50.7	46.2
Relay Erlotinib-ramucirumab	76%	75% (erlotinib)	19.4	12.4	NR	NR

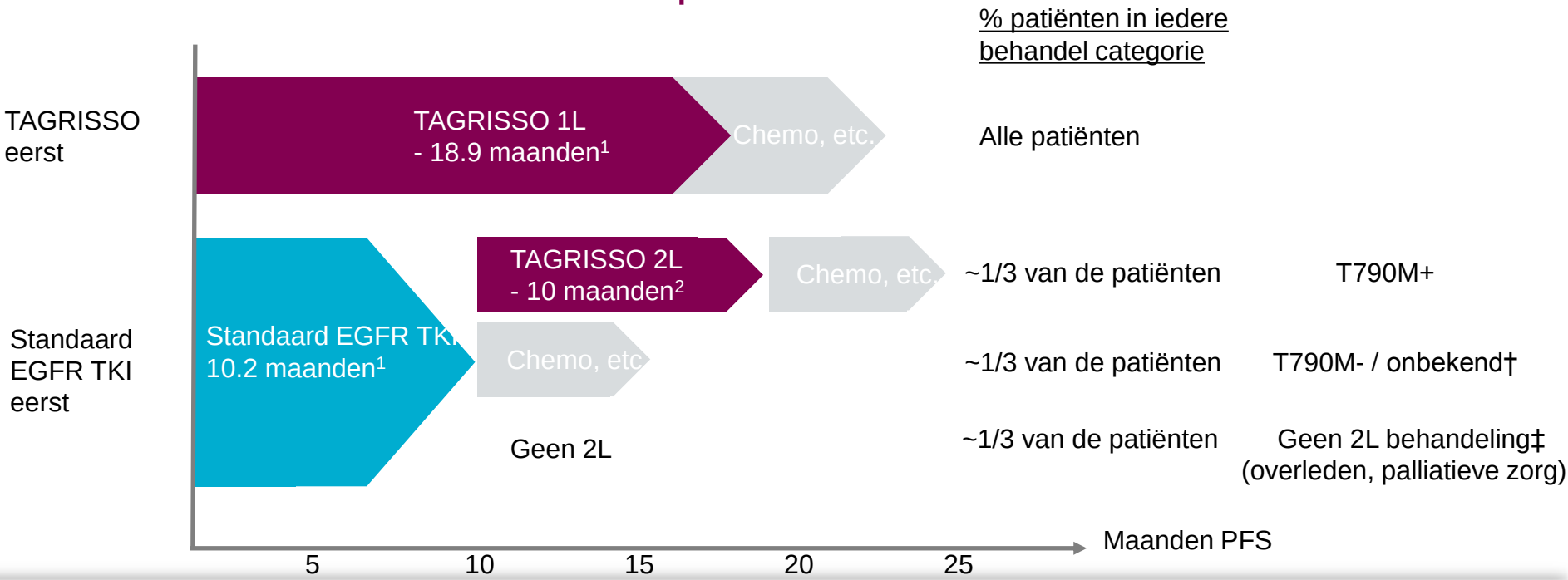
Trial	ORR EGFR TKI	ORR control arm	mPFS EGFR TKI (months)	mPFS control arm (months)	mOS EGFR TKI (months)	mOS control arm (months)
Ipass Gefitinib	71%	47% (chemo)	9.5	6.3	18.8	17.4
NEJ002 Gefitinib	74%	31% (chemo)	10.8	5.4	27.7	26.6
WJTOG Gefitinib	62%	32% (chemo)	9.2	6.3	34.9	37.3
Optimal Erlotinib	83%	36(chemo)	13.1	4.6	22.8	27.2
Eurtac Erlotinib	58%	15% (chemo)	9.7	5.2	19.3	19.5
Lux-Lung 3 Afatinib	56%	23% (chemo)	11.1	6.9	28.2	28.2
Lux-Lung 6 Afatinib	67%	23% (chemo)	11.0	5.6	23.1	23.5
Lux-Lung 7 Afatinib	70%	56% (gefitinib)	11.0	10.9	27.9	24.5
Archer 1050 Dacomitinib	75%	72% (gefitinib)	14.7	11.0	34.1	27.0
Flaura Osimertinib	80%	76% (gefitinib / erlotinib)	18.9	10.2	38.6	31.8
NEJ026 Erlotinib-bevacizumab	72%	66% (erlotinib)	16.9	13.3	50.7	46.2
Relay Erlotinib-ramucirumab	76%	75% (erlotinib)	19.4	12.4	NR	NR

Trial	ORR EGFR TKI	ORR control arm	mPFS EGFR TKI (months)	mPFS control arm (months)	mOS EGFR TKI (months)	mOS control arm (months)
Ipass Gefitinib	71%	47% (chemo)	9.5	6.3	18.8	17.4
NEJ002 Gefitinib	74%	31% (chemo)	10.8	5.4	27.7	26.6
WJTOG Gefitinib	62%	32% (chemo)	9.2	6.3	34.9	37.3
Optimal Erlotinib	83%	36(chemo)	13.1	4.6	22.8	27.2
Eurtac Erlotinib	58%	15% (chemo)	9.7	5.2	19.3	19.5
Lux-Lung 3 Afatinib	56%	23% (chemo)	11.1	6.9	28.2	28.2
Lux-Lung 6 Afatinib	67%	23% (chemo)	11.0	5.6	23.1	23.5
Lux-Lung 7 Afatinib	70%	56% (gefitinib)	11.0	10.9	27.9	24.5
Archer 1050 Dacomitinib	75%	72% (gefitinib)	14.7	11.0	34.1	27.0
Flaura Osimertinib	80%	76% (gefitinib / erlotinib)	18.9	10.2	38.6	31.8
NEJ026 Erlotinib-bevacizumab	72%	66% (erlotinib)	16.9	13.3	50.7	46.2
Relay Erlotinib-ramucirumab	76%	75% (erlotinib)	19.4	12.4	NR	NR

Trial	ORR EGFR TKI	ORR control arm	mPFS EGFR TKI (months)	mPFS control arm (months)	mOS EGFR TKI (months)	mOS control arm (months)
Ipass Gefitinib	71%	47% (chemo)	9.5	6.3	18.8	17.4
NEJ002 Gefitinib	74%	31% (chemo)	10.8	5.4	27.7	26.6
WJTOG Gefitinib	62%	32% (chemo)	9.2	6.3	34.9	37.3
Optimal Erlotinib	83%	36(chemo)	13.1	4.6	22.8	27.2
Eurtac Erlotinib	58%	15% (chemo)	9.7	5.2	19.3	19.5
Lux-Lung 3 Afatinib	56%	23% (chemo)	11.1	6.9	28.2	28.2
Lux-Lung 6 Afatinib	67%	23% (chemo)	11.0	5.6	23.1	23.5
Lux-Lung 7 Afatinib	70%	56% (gefitinib)	11.0	10.9	27.9	24.5
Archer 1050 Dacomitinib	75%	72% (gefitinib)	14.7	11.0	34.1	27.0
Flaura Osimertinib	80%	76% (gefitinib / erlotinib)	18.9	10.2	38.6	31.8
NEJ026 Erlotinib-bevacizumab	72%	66% (erlotinib)	16.9	13.3	50.7	46.2
Relay Erlotinib-ramucirumab	76%	75% (erlotinib)	19.4	12.4	NR	NR

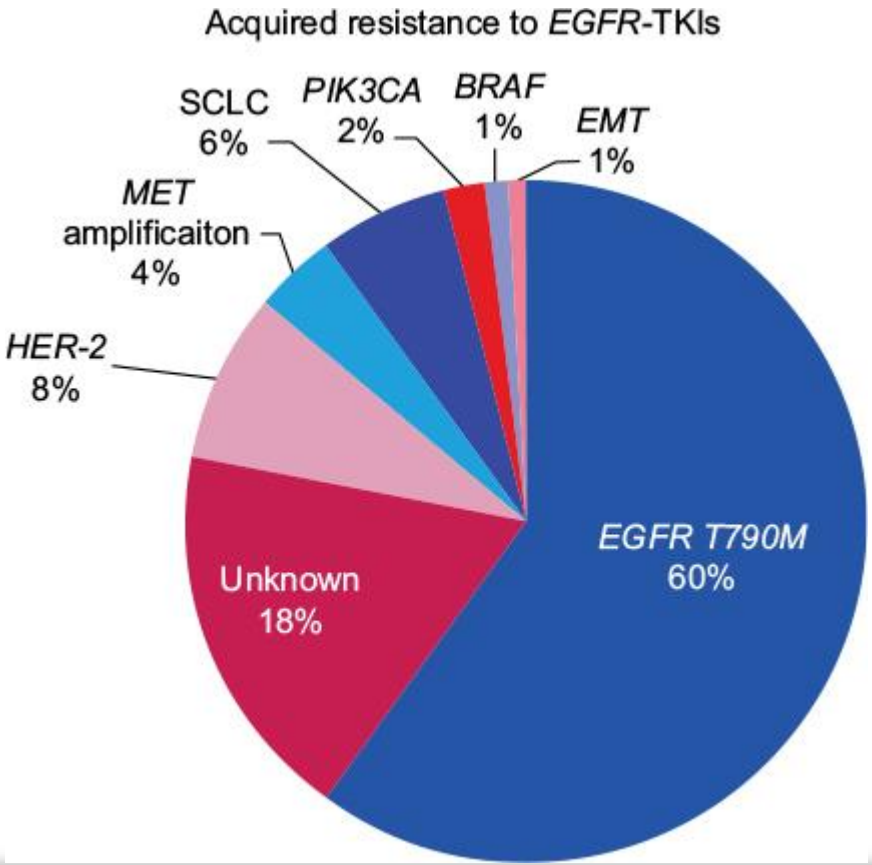
Trial	ORR EGFR TKI	ORR control arm	mPFS EGFR TKI (months)	mPFS control arm (months)	mOS EGFR TKI (months)	mOS control arm (months)
Ipass Gefitinib	71%	47% (chemo)	9.5	6.3	18.8	17.4
NEJ002 Gefitinib	74%	31% (chemo)	10.8	5.4	27.7	26.6
WJTOG Gefitinib	62%	32% (chemo)	9.2	6.3	34.9	37.3
Optimal Erlotinib	83%	36(chemo)	13.1	4.6	22.8	27.2
Eurtac Erlotinib	58%	15% (chemo)	9.7	5.2	19.3	19.5
Lux-Lung 3 Afatinib	56%	23% (chemo)	11.1	6.9	28.2	28.2
Lux-Lung 6 Afatinib	67%	23% (chemo)	11.0	5.6	23.1	23.5
Lux-Lung 7 Afatinib	70%	56% (gefitinib)	11.0	10.9	27.9	24.5
Archer 1050 Dacomitinib	75%	72% (gefitinib)	14.7	11.0	34.1	27.0
Flaura Osimertinib	80%	76% (gefitinib / erlotinib)	18.9	10.2	38.6	31.8
NEJ026 Erlotinib-bevacizumab	72%	66% (erlotinib)	16.9	13.3	50.7	46.2
Relay Erlotinib-ramucirumab	76%	75% (erlotinib)	19.4	12.4	NR	NR

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.

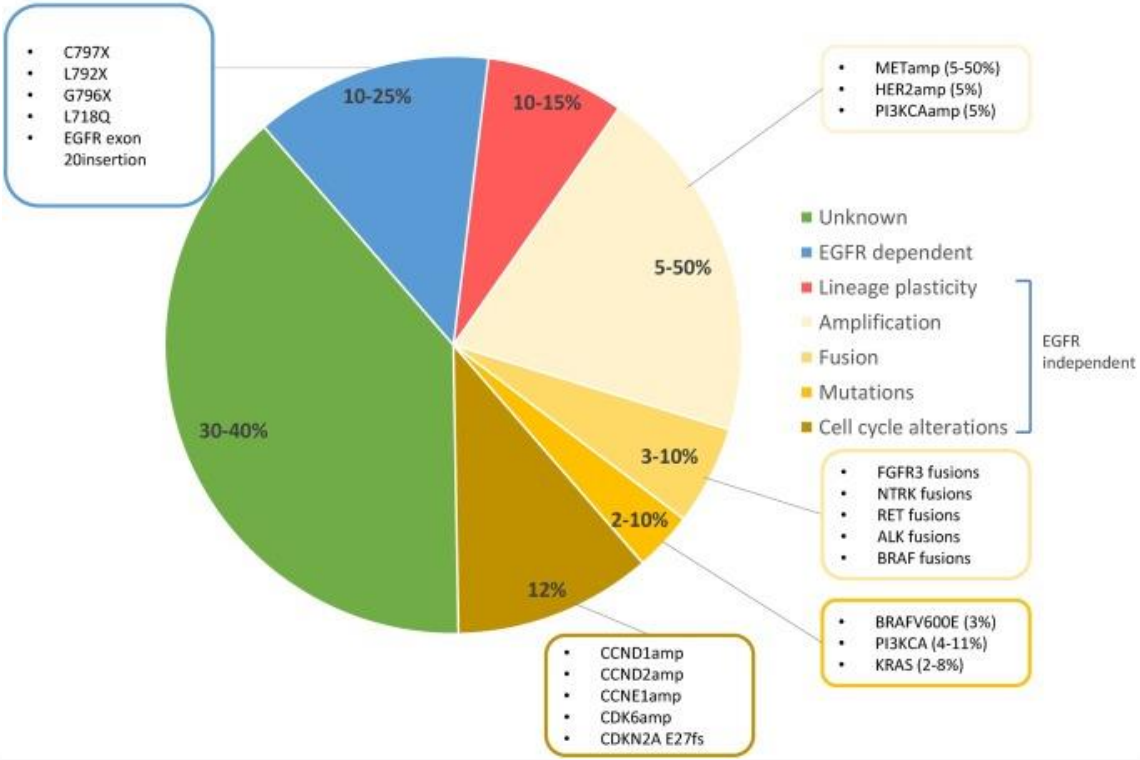
umcg Oncologie
Comprehensive Cancer Center



umcg Oncologie
Comprehensive Cancer Center

Oxnard et al. JAMA oncol 2018

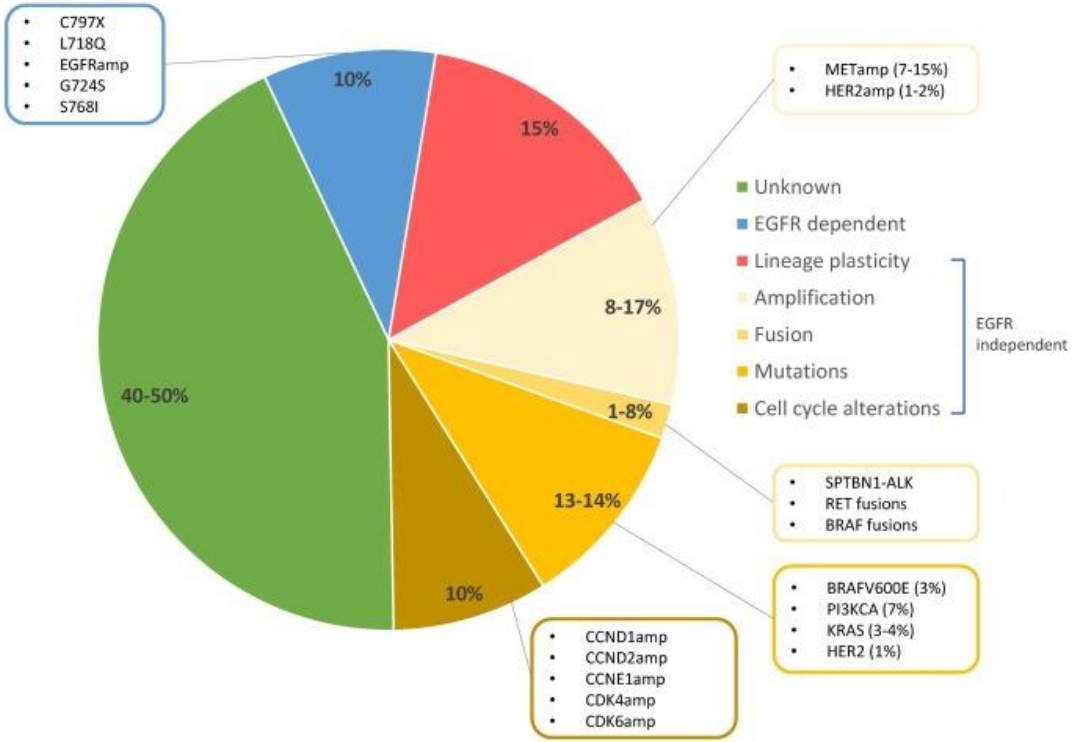
Resistance Mechanisms To Second-Line Osimertinib



umcg Oncologie
Comprehensive Cancer Center

Schmid et al. Lung cancer 2020

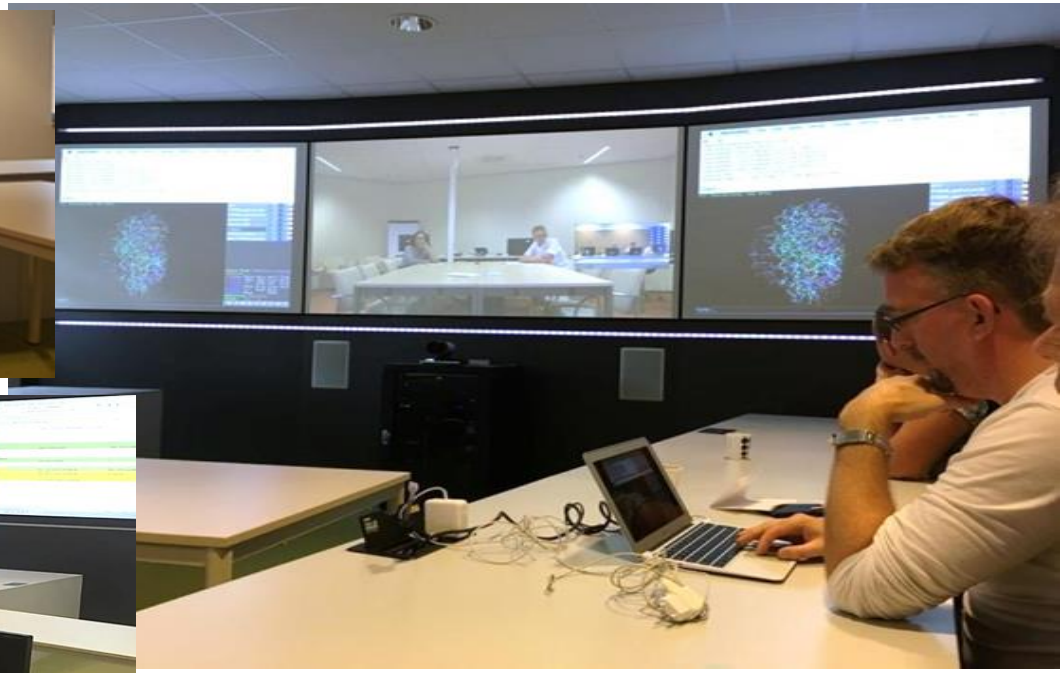
Resistance Mechanisms To First-Line Osimertinib

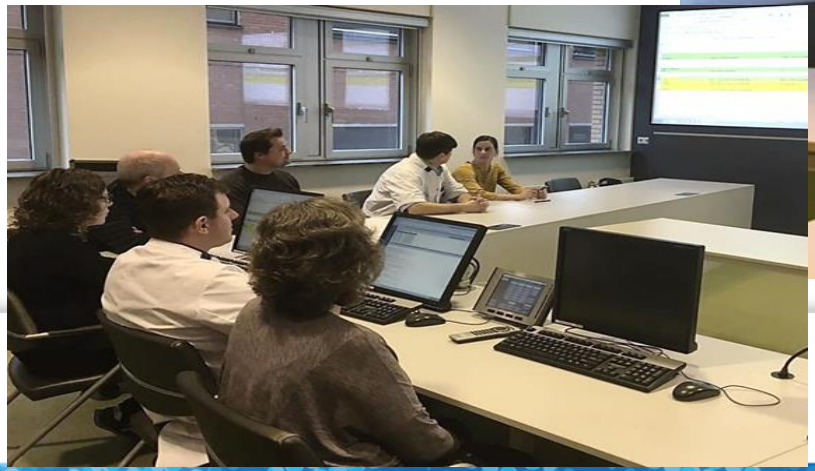


umcg Oncologie
Comprehensive Cancer Center

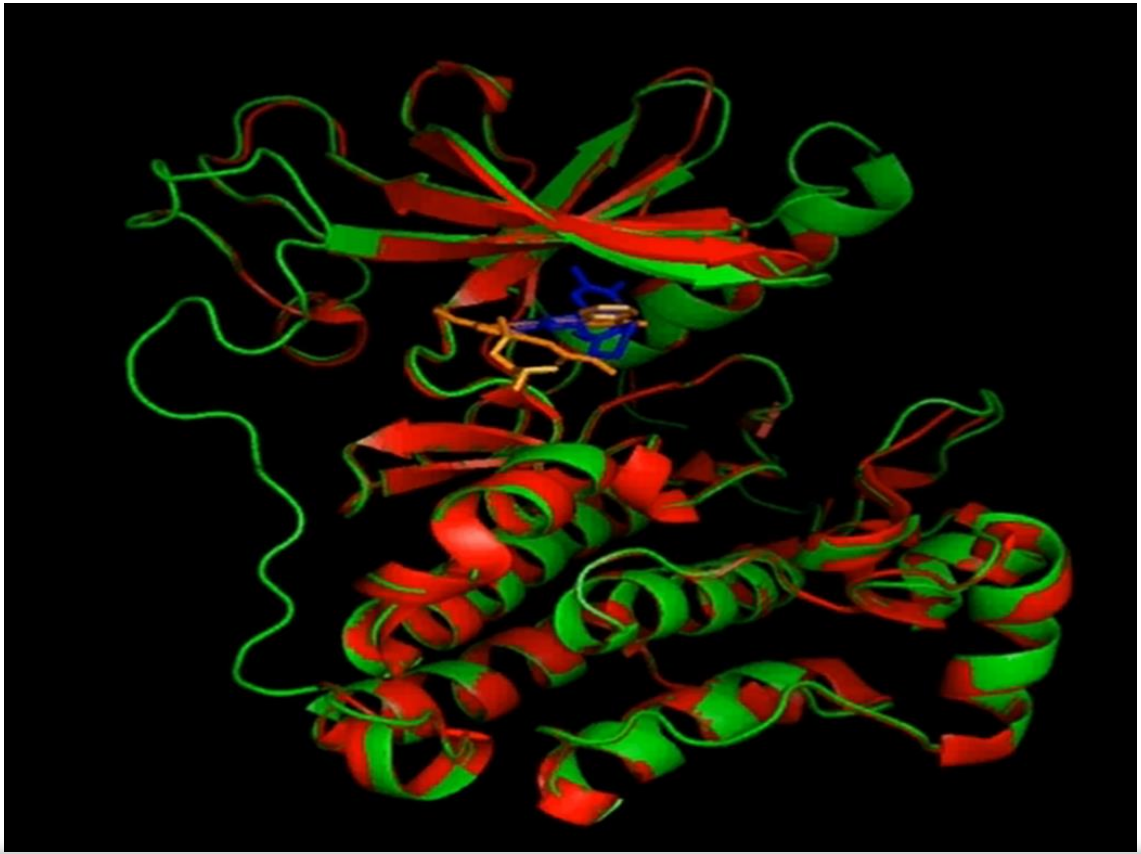
Schmid et al. Lung cancer 2020

Moleculaire Tumor Board



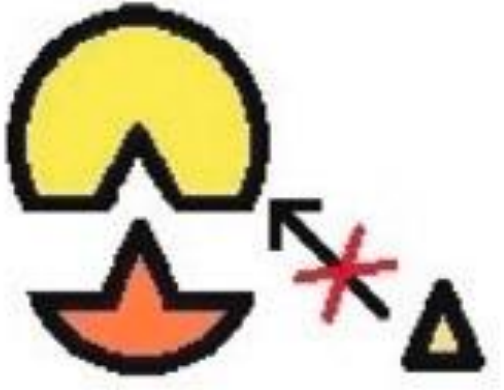


umcg Oncologie
Comprehensive Cancer Center

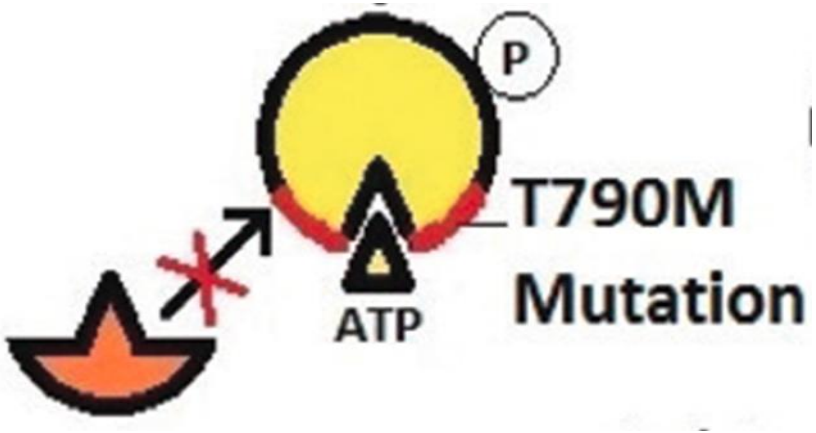


umcg Oncologie
Comprehensive Cancer Center

Welke behandeling is mogelijk?



gefitinib of erlotinib



Welke behandeling is mogelijk?

osimertinib

Centra zeldzame mutaties

umcg Oncologie
Comprehensive Cancer Center

Welke studies zijn er?

- 1e lijn therapie
  - Amivantamab vs osimertinib
  - Erlotinib ramucirumab bij TP53 mutaties

- Resistentie na EGFR-TKI
  - OSIRIS studie
  - ORCHARD
  - HER2: trastuzumab-emtansine + osimertinib
  - MET: INSIGHT 2 Tepotinib + osimertinib

Welke studies zijn er?

- Exon 20 inserties
  - POSITION 20 – dubbele dosis osimertinib
  - AfaCet – afatinib + cetuximab
  - Poziotinib

Take home message

- Beste therapieën: osimertinib en erlotinib-ramucirumab

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

Vragen

- Welke mutaties kunnen er ontstaan als je een EGFR mutatie hebt?

- Bij mij is 5 maanden geleden de EGFR mutatie vastgesteld. Ik heb longkanker met uitzaaiingen. Gelukkig heb ik het medicijn osimertinib en dit slik ik nu 3 maanden. De eerste scan gaf aan dat mijn tumoren flink verkleind waren en nu na mijn laatste scan waren ze nog steeds hetzelfde. Zouden ze nog kunnen verkleinen? En geeft dit al een verkeerd beeld nu de tumoren niet wederom zijn verkleind.
- Ik ben net 46 jaar geworden en mijn moeder hamert maar op een second opinion, terwijl ik denk ik heb de egfr mutatie en ik denk dat iedereen osimertinib zal adviseren. Ze halen niets weg omdat het al te veel in mijn lichaam zit. Zou een second opinion een optie zijn?

- Kan de overactieve egfr gen vanzelf (zonder tki) ook weer inactief worden? Hij heeft zich (bij mij) tenslotte ook 50 jaar koest gehouden.

- Angst interactie COVID vaccin en Tagrisso

cancercenter.umcg.nl

umcg Oncologie
Comprehensive Cancer Center