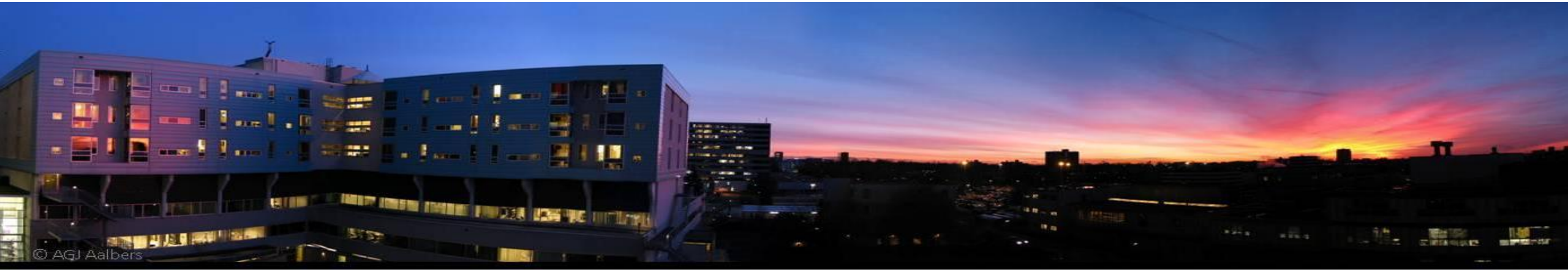
Targeted treatment for HER addicted NSCLC

Why does it work (or not)



Joop de Langen, MD, PhD

j.d.langen@nki.nl

Netherlands Cancer Institute, Amsterdam, The Netherlands

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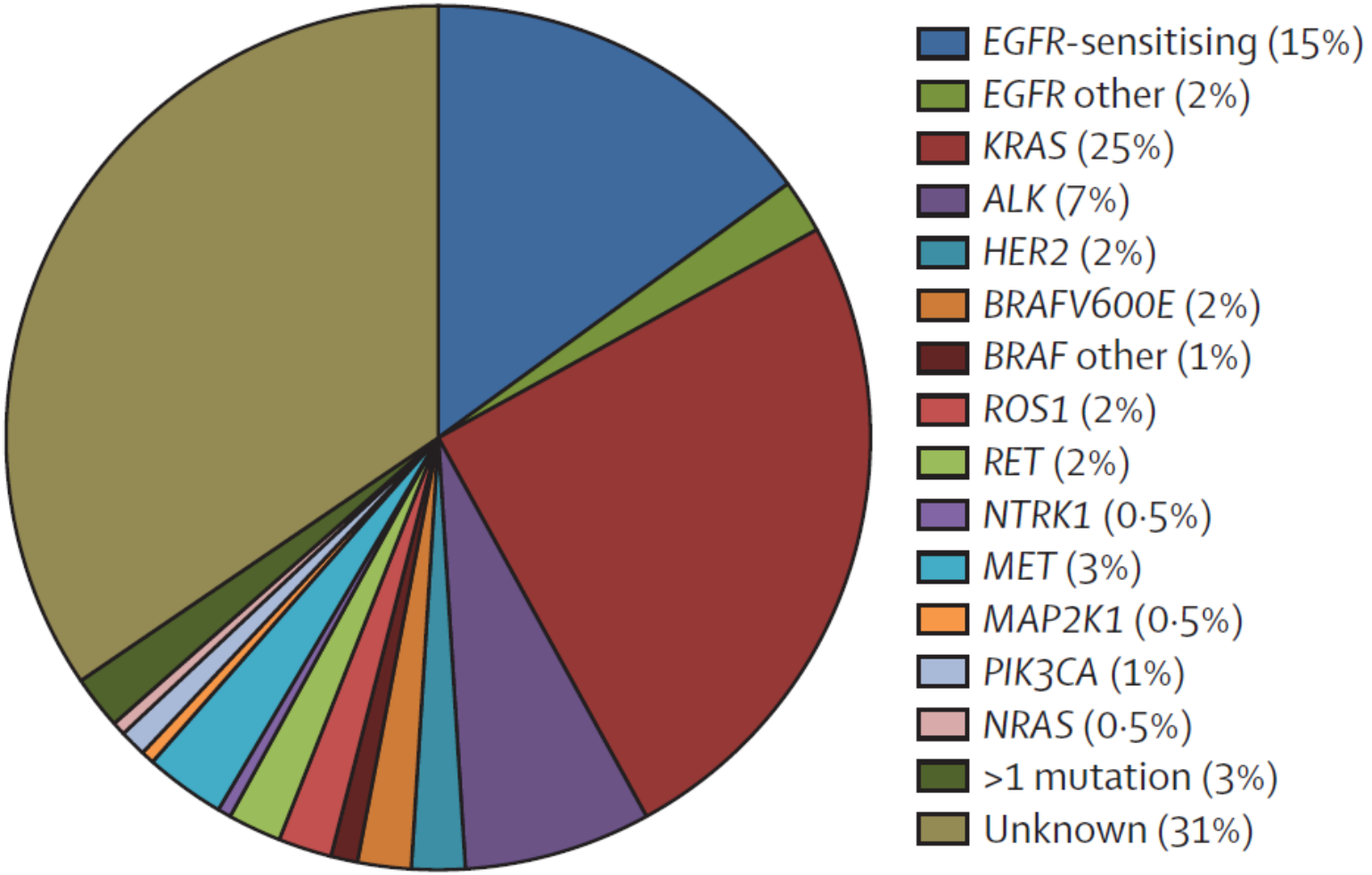
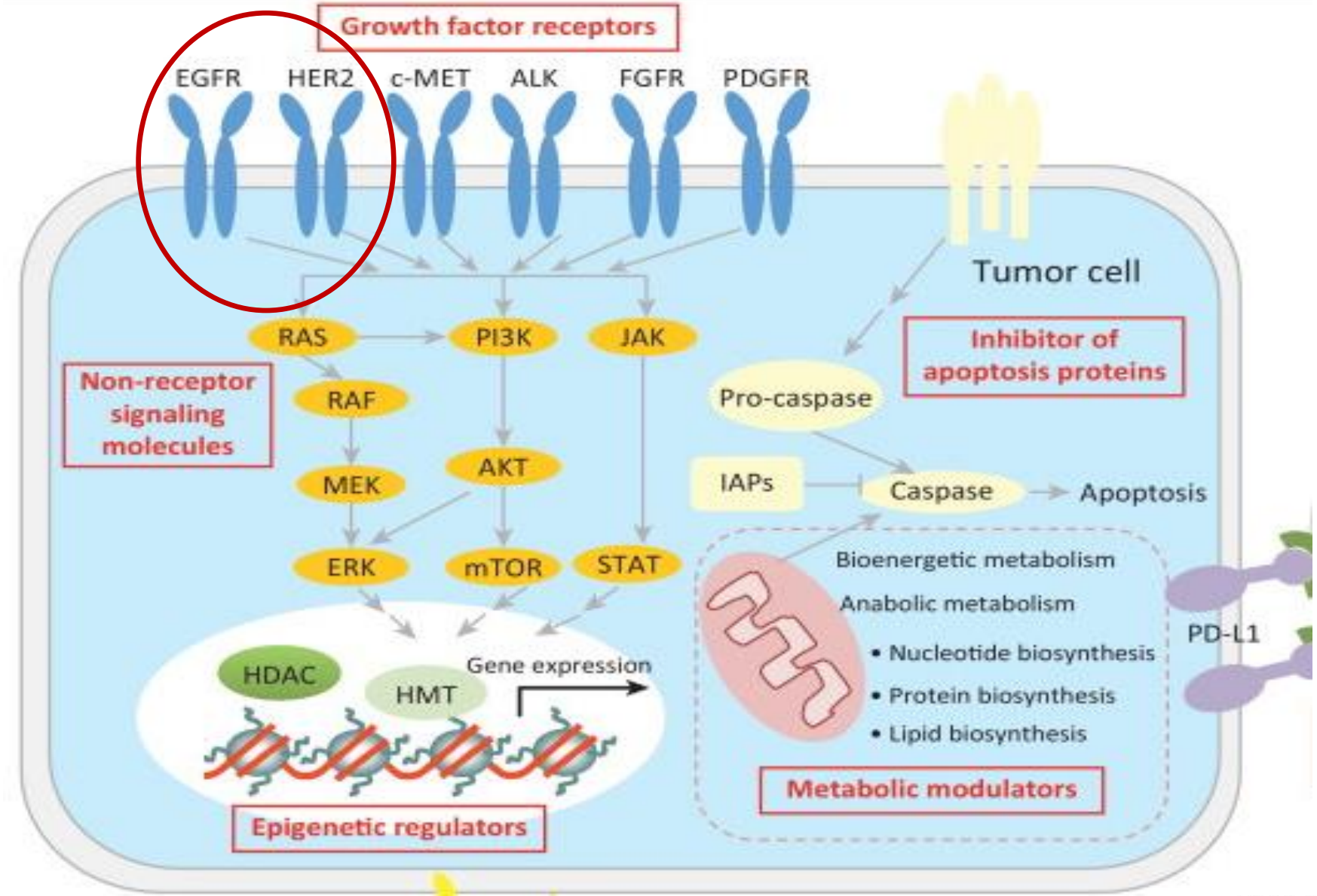
Disclosures

- Advisor for AstraZeneca, BMS, Boehringer, Pfizer and MSD.
- Research grants from AstraZeneca, Boehringer, BMS and MSD.

Molecular alterations in NSCLC



Hirsch FR, et al. Lancet 2016



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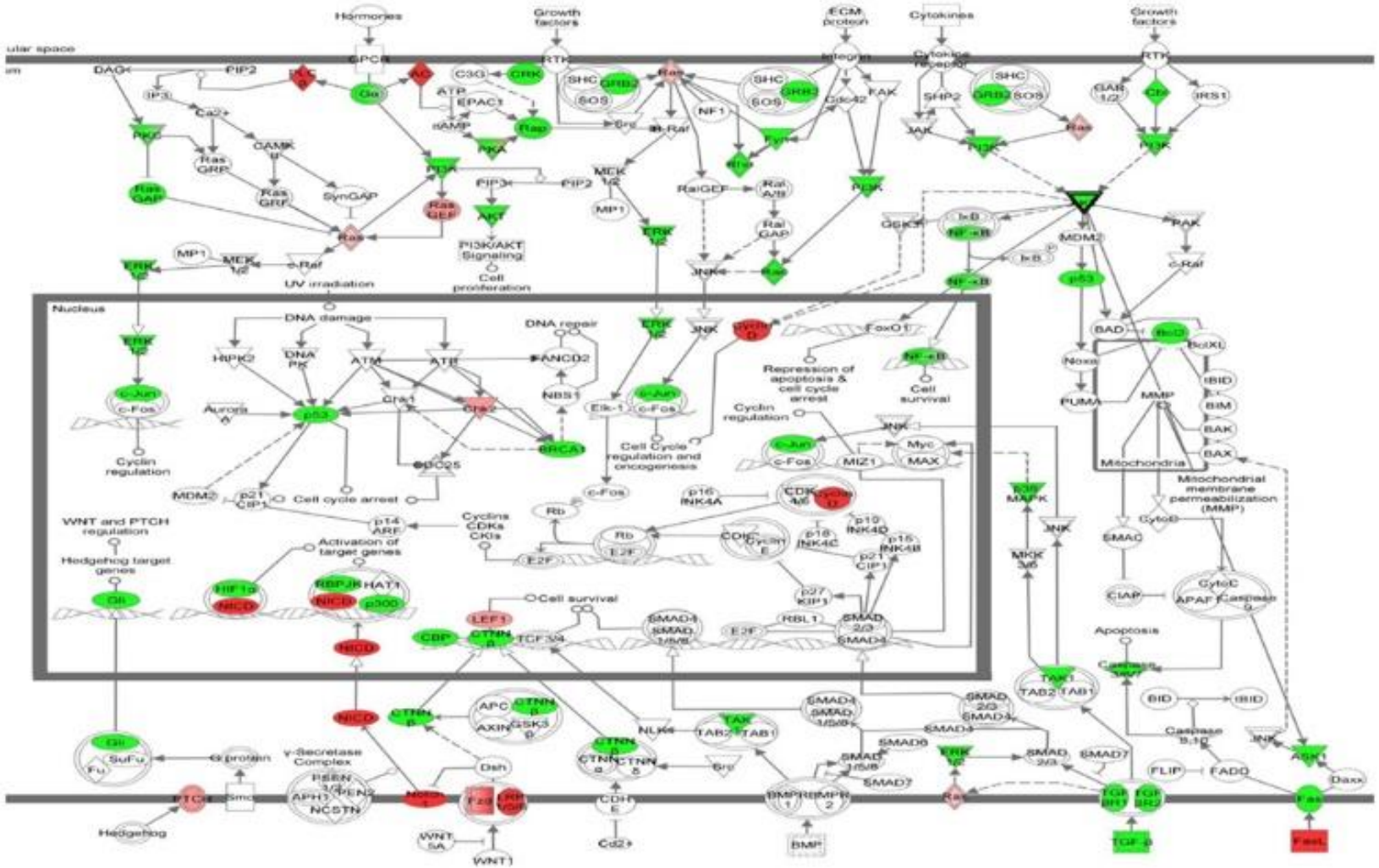

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History

- SCLC
- NSCLC
  - Adeno
  - Sqaumous
  - NOS

Past

- HRM / PCR / FISH
  - EGFR
  - ALK
  - +/- selected other genes

Present

- NGS
  - Mutations
  - Fusions
  - CNV

(Near) Future

- WGS
  - Mutations
  - Fusions
  - CNV

Mevr. T, 43 jaar

- St IV NSCLC, never smoker
- EGFR mutation
- *C.2235_2249del*

Mevr. A, 43 jaar

- St IV NSCLC, never smoker
- EGFR mutation
- *C.2300_2308dup*

Mevr. W, 59 jaar

- St IV NSCLC, never smoker
- EGFR mutation
- *C.2240_2257delins*

- Erlotinib
- Gefitinib
- Afatinib
- Osimertinib

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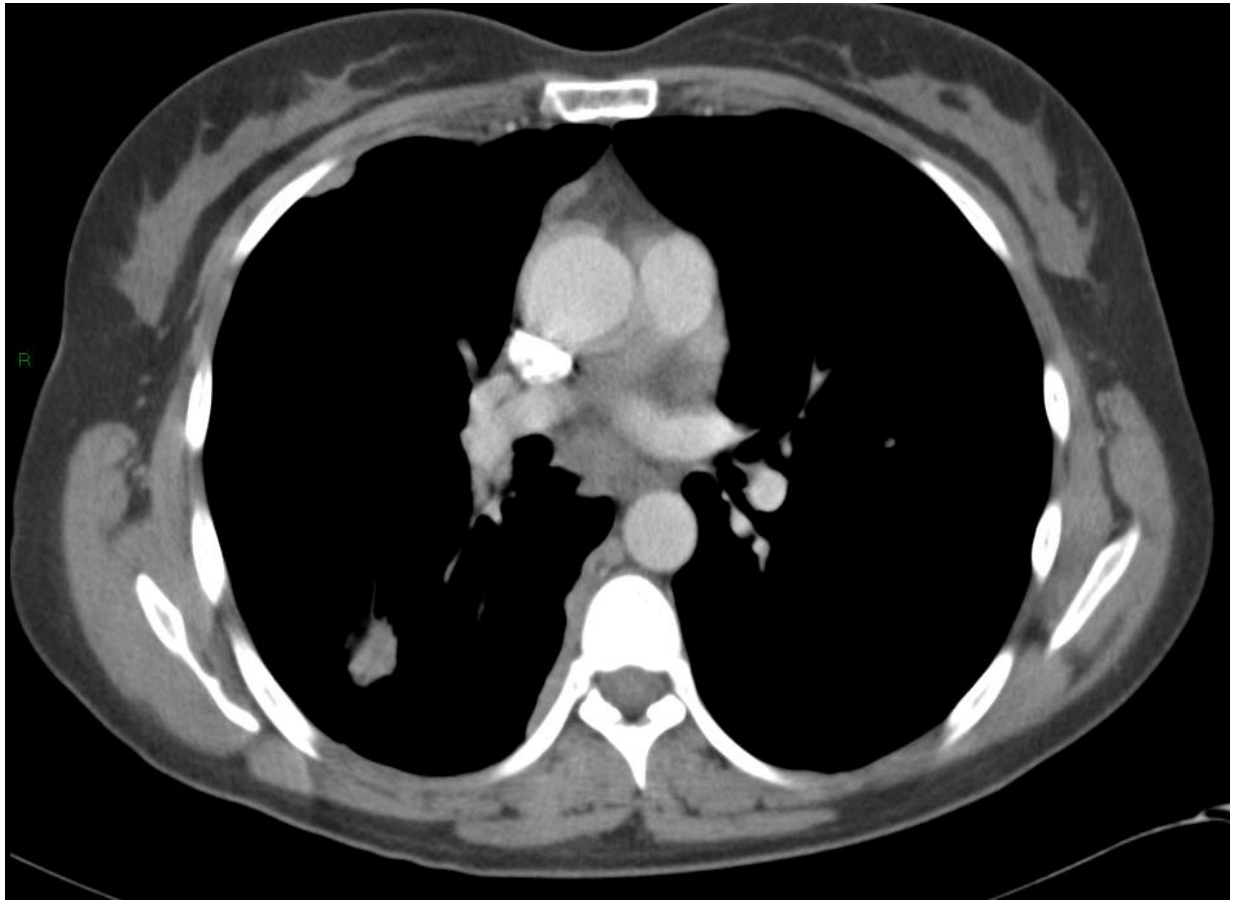
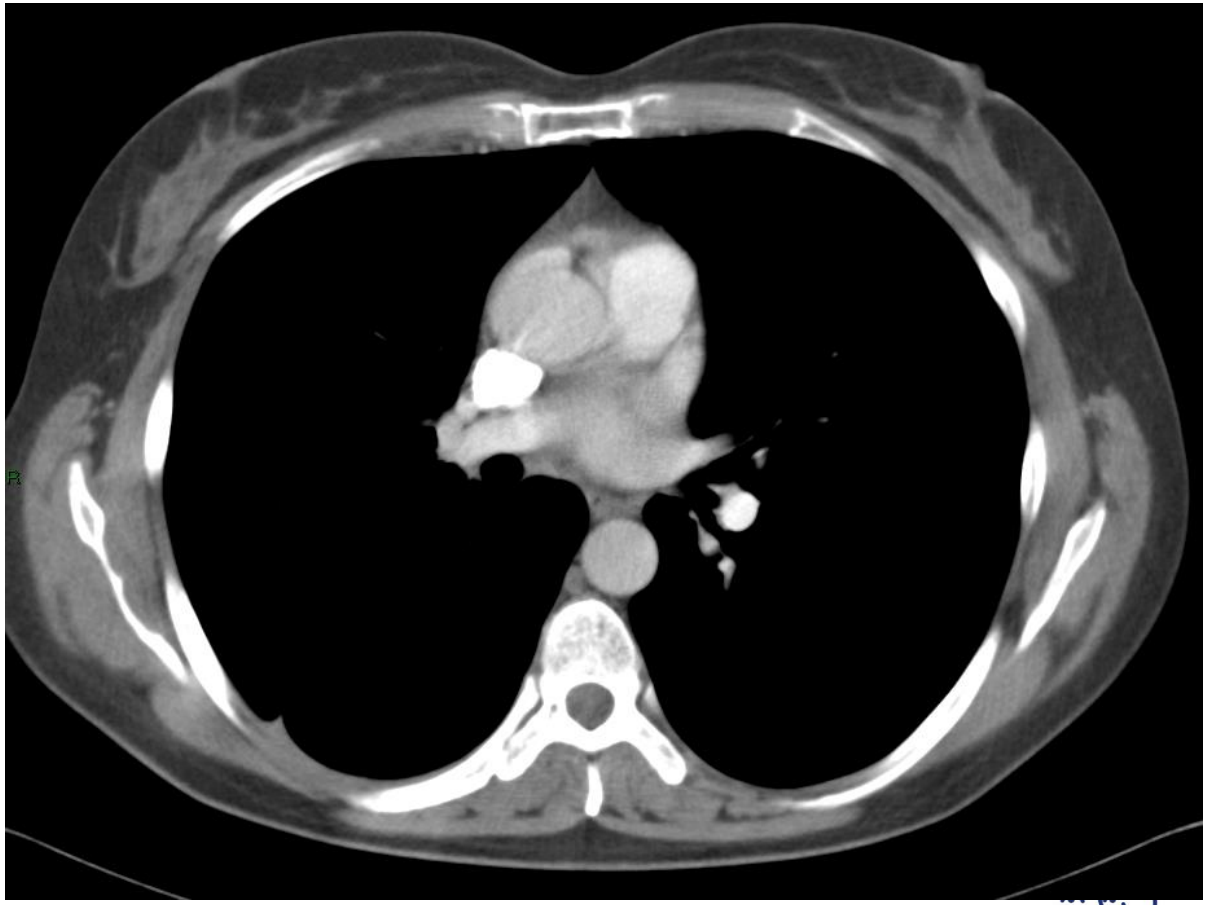
Mevr. T, 43 jaar. Gefitinib.

c.2235_2249del





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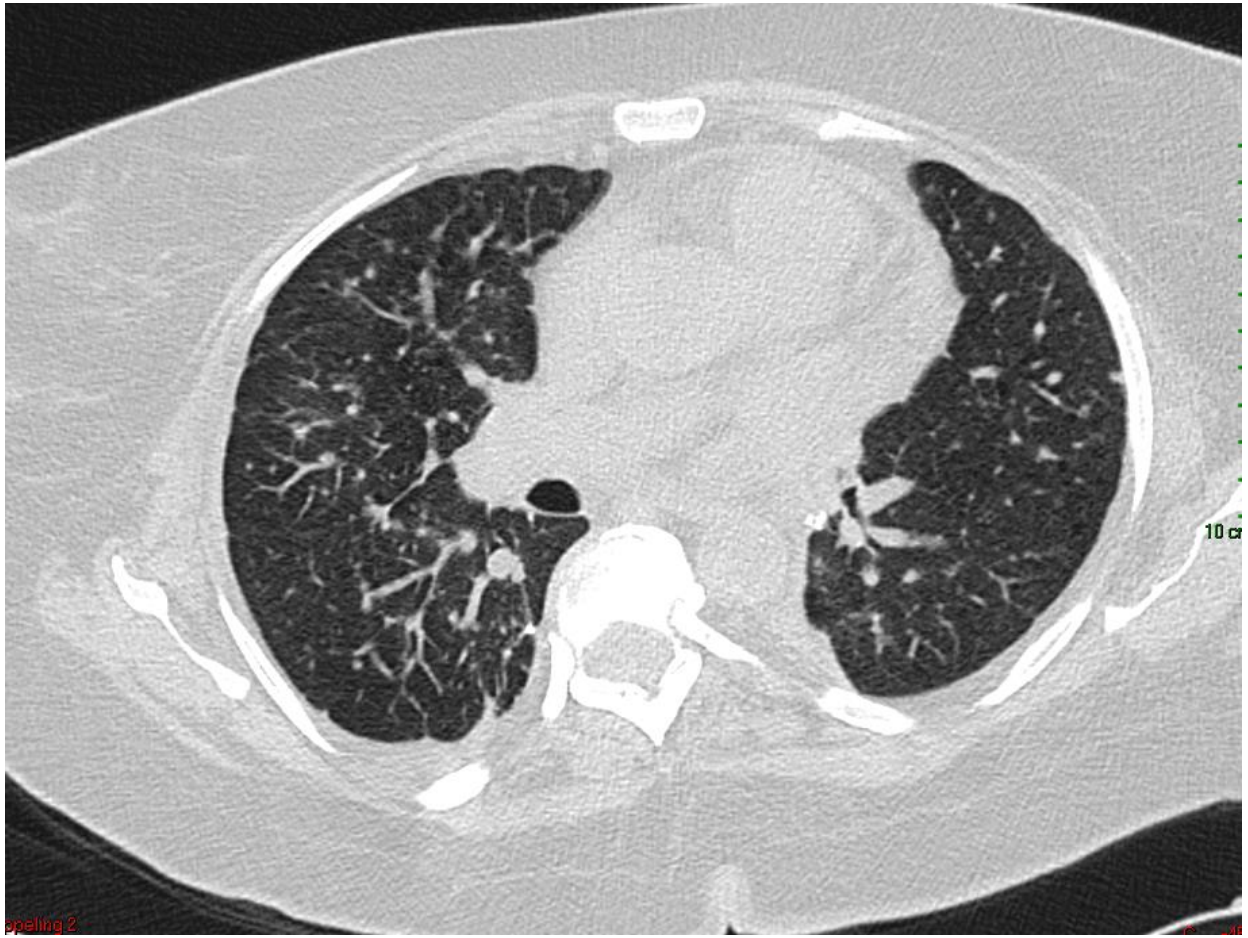
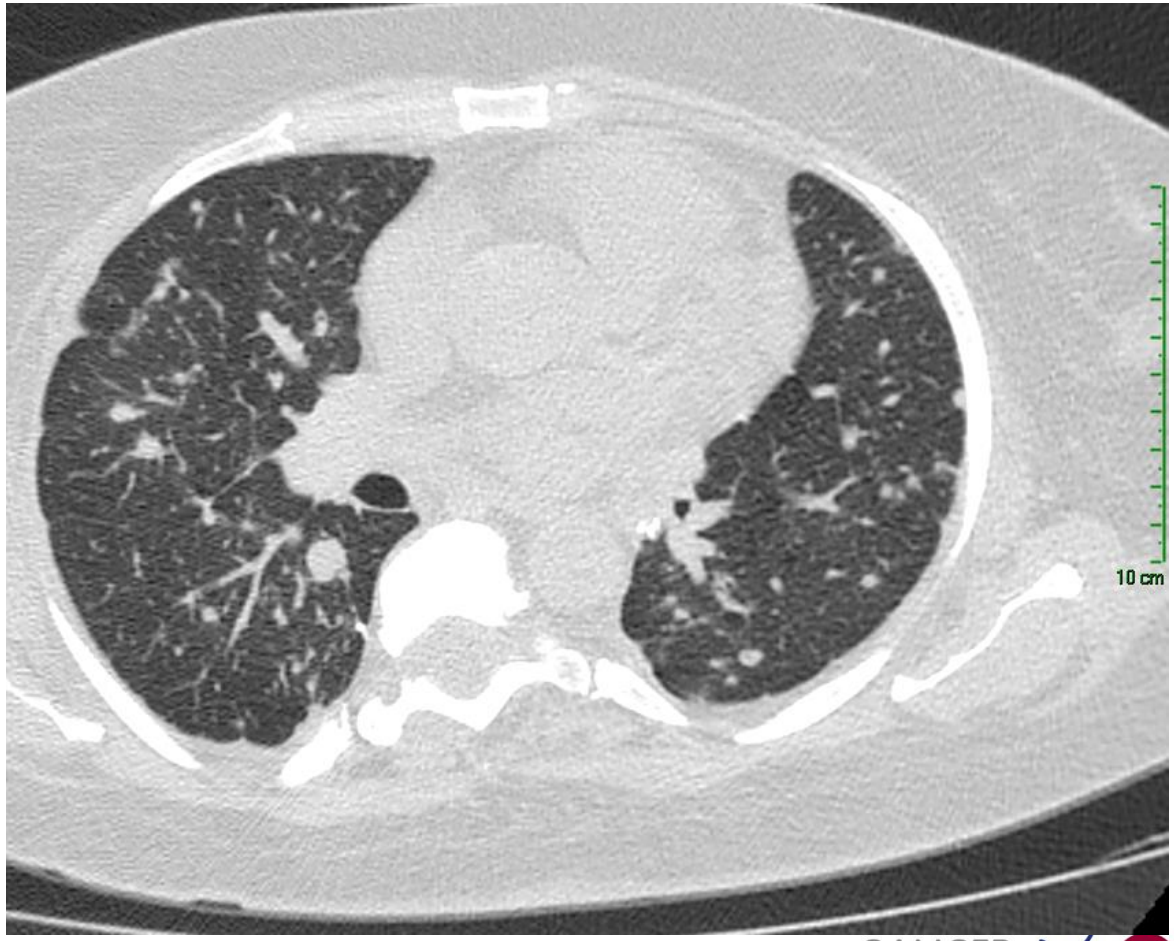
Mevr. A, 43 jaar. Erlotinib and later osimertinib

c.2300_2308dup





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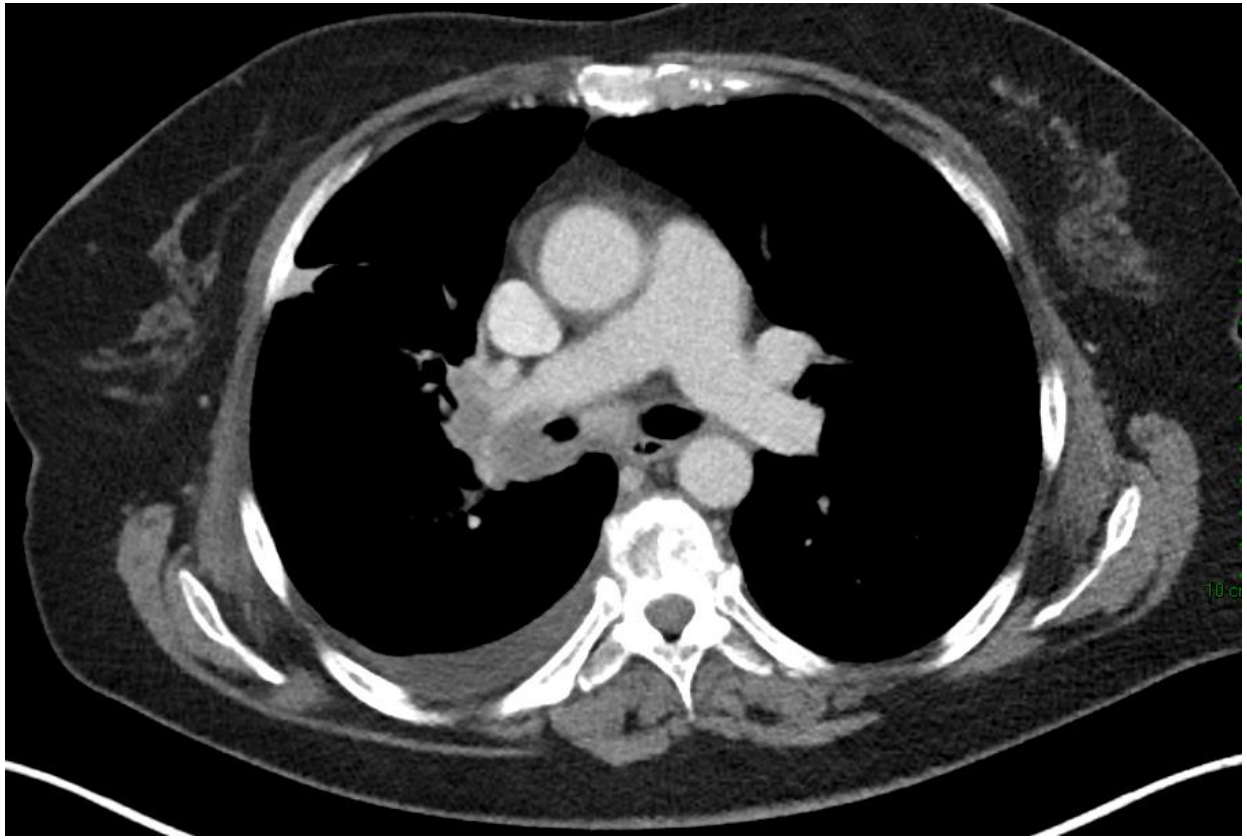
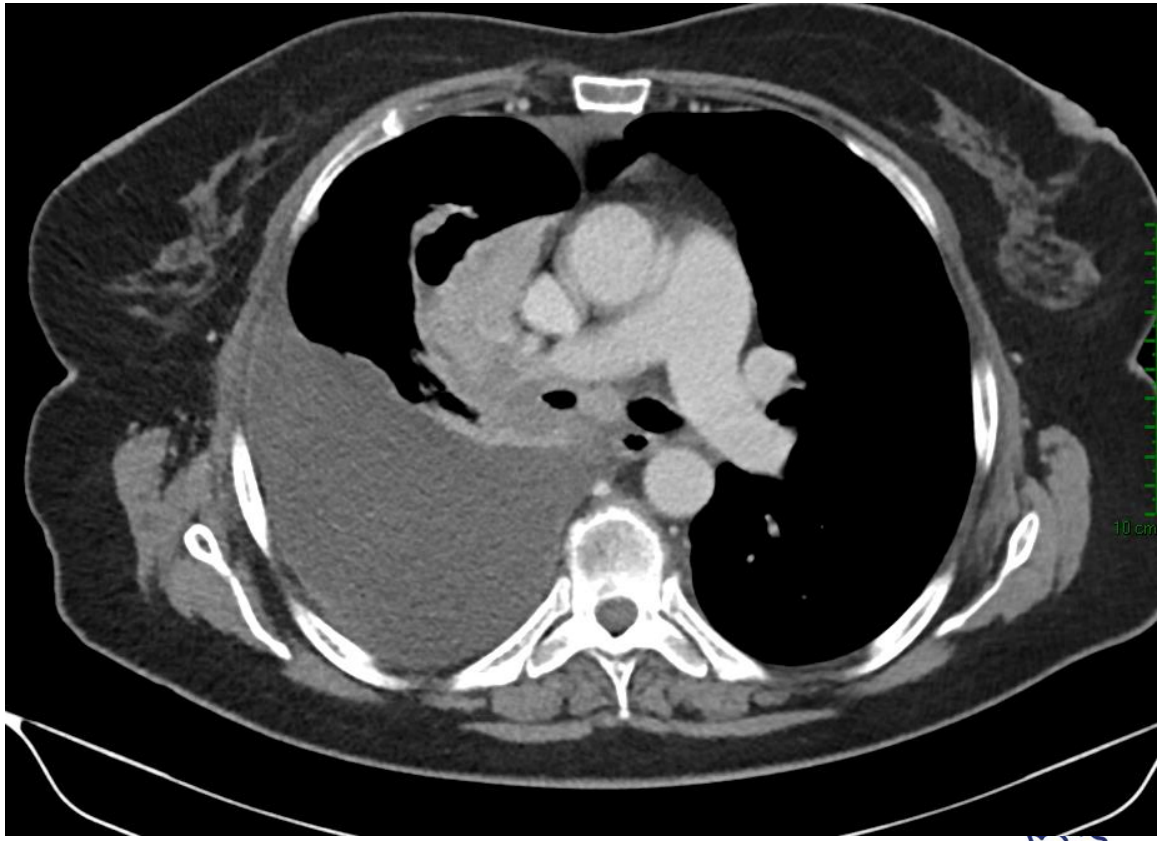
Mevr. W, 59 jaar. Erlotinib, later osimertinib, later afatinib

c.2240_2257delins





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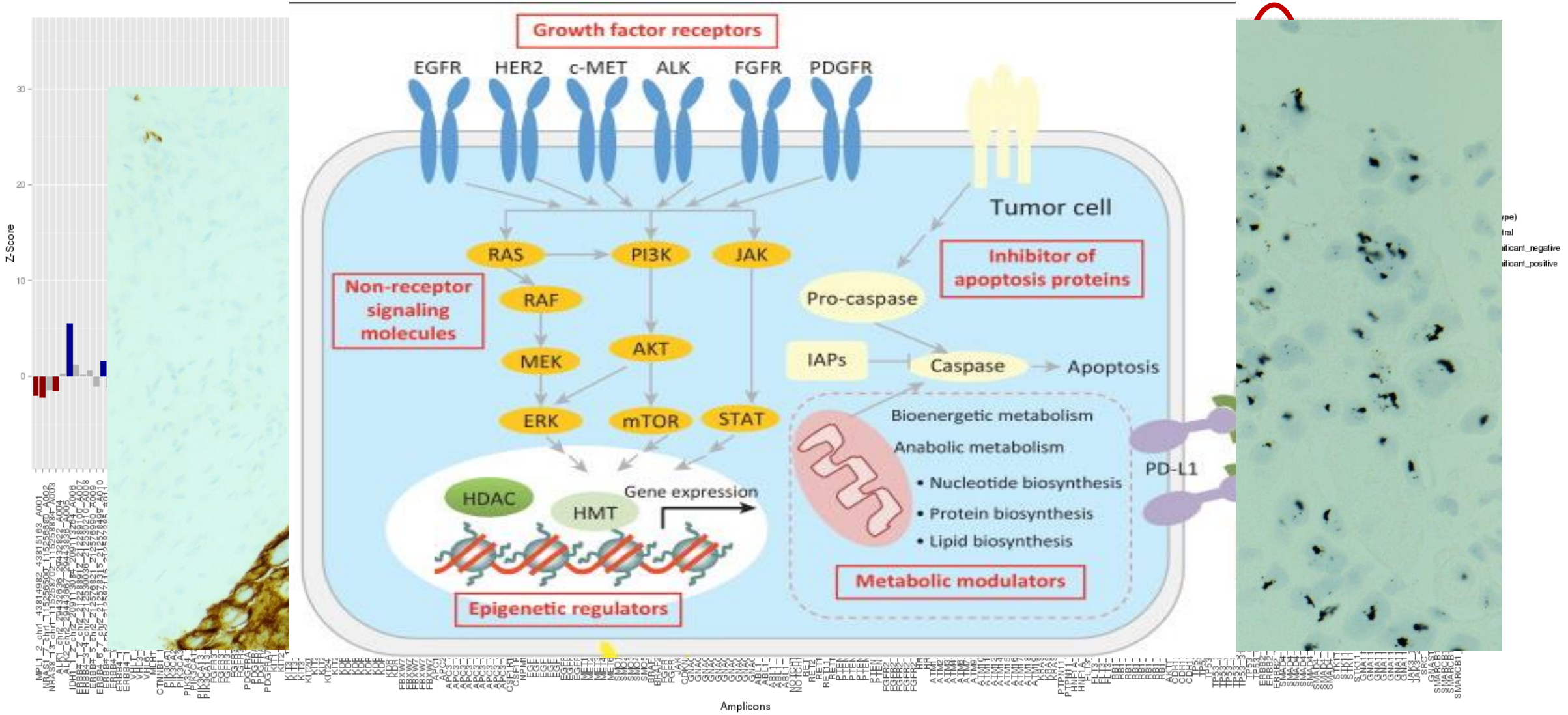
Mevr. W, 59 jaar *c.2240_2257delins*



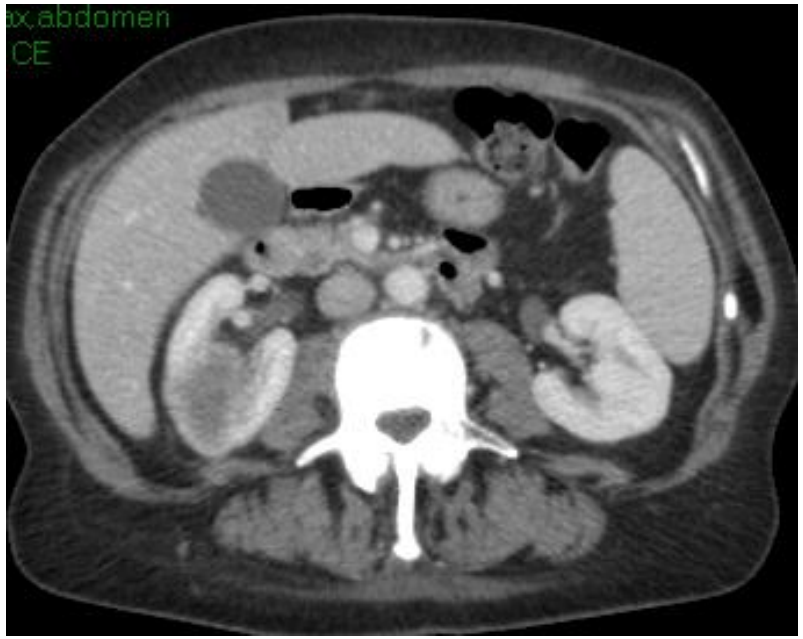
The Drug Rediscovery Protocol (DRUP trial)

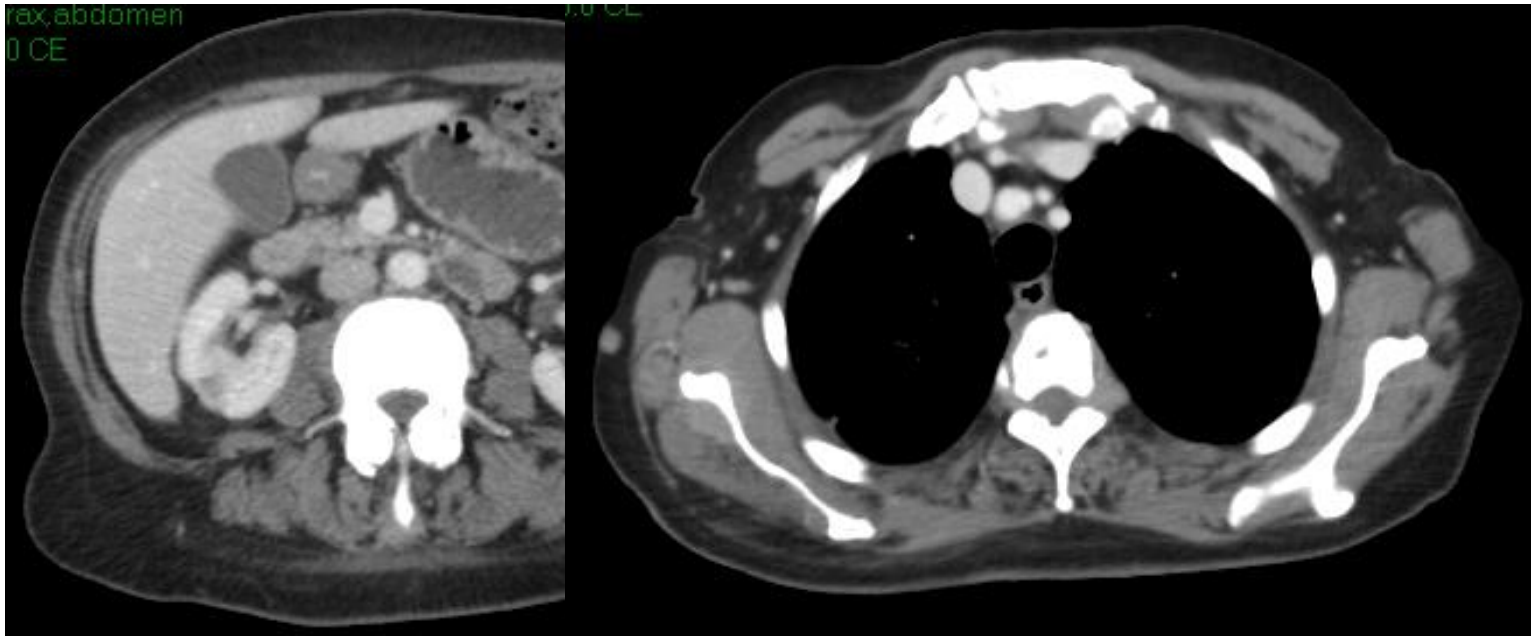
Title

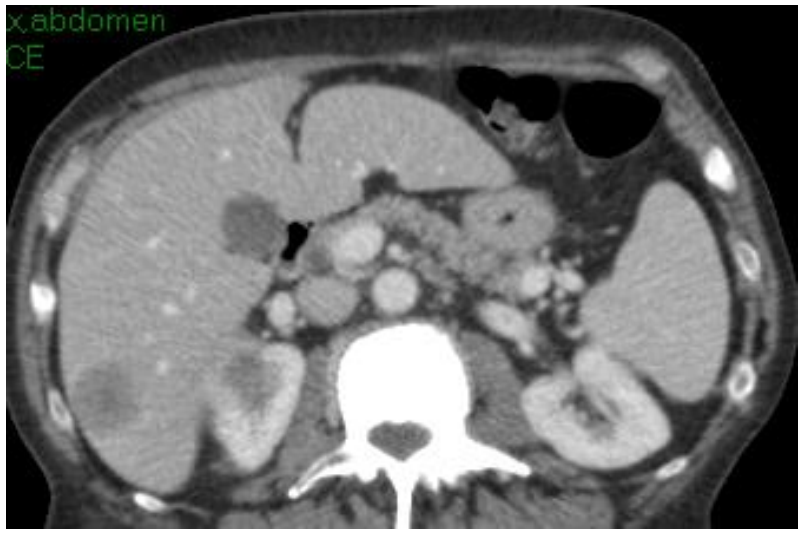
A Dutch National Study on behalf of the Center for Personalized Cancer Treatment (CPCT) to Facilitate Patient Access to Commercially Available, Targeted Anti-cancer Drugs to determine the Potential Efficacy in Treatment of Advanced Cancers with a Known Molecular Profile.

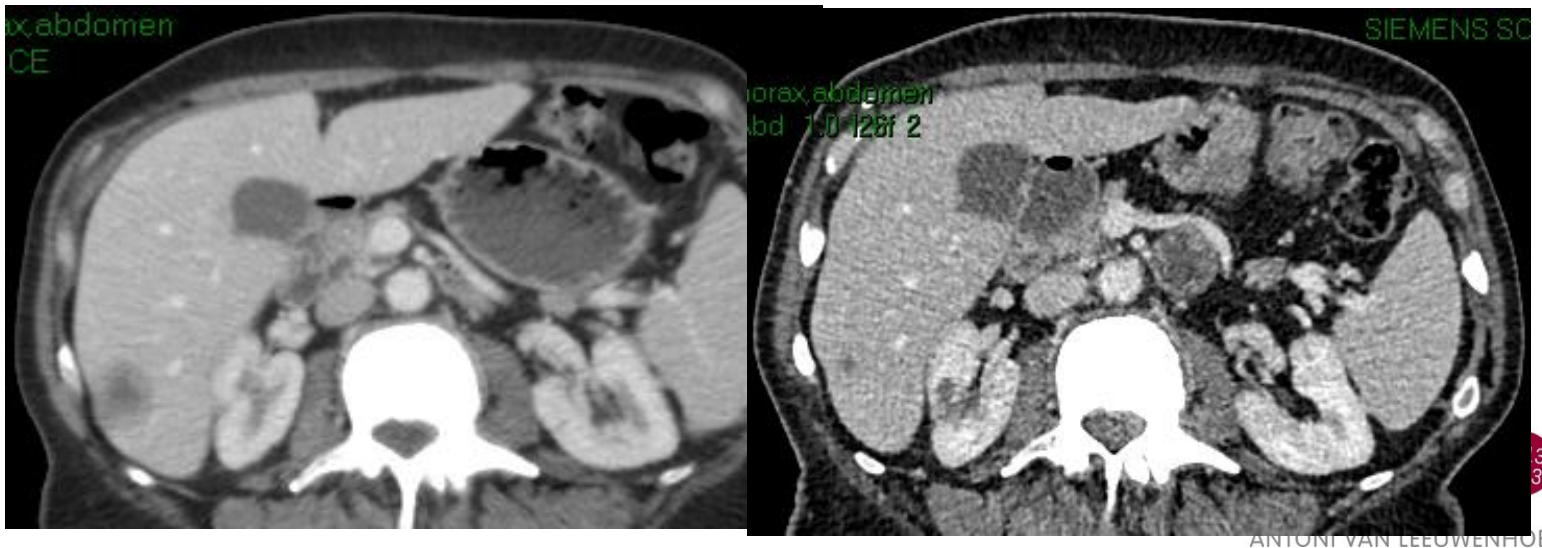
Home
About CPCT
CPCT for
- Patients
- CPCT and you

DRUP Study: Trastuzumab-Pertuzumab









Mevr. A, 43 jaar *c.2300_2308dup*

- Female, 42 years old
- 2011: NSCLC LLL. Lobectomy, adj cis-pem.
- 2013: Bone and lung mets. Erlotinib. Best response: PD.
- 2013: Cisplatin-pemetrexed. Best response: PR.
- 2015: Brain mets. WBRT.
- 03-2016: PD. Gemcitabin. Best response: SD.
- 06-2016: PD. Osimertinib. Best response: SD.
- 10-2016: PD. WHO PS 3, wheelchair, on oxygen treatment.

Molecular tumorboard meeting

- Molecular tumour board
  - (Thoracic) Oncologist
  - Pathologist
  - Clinical molecular biologist

  - Sensitivity molecular alteration
  - Clinical study available
  - Type of treatment
  - Location of treatment

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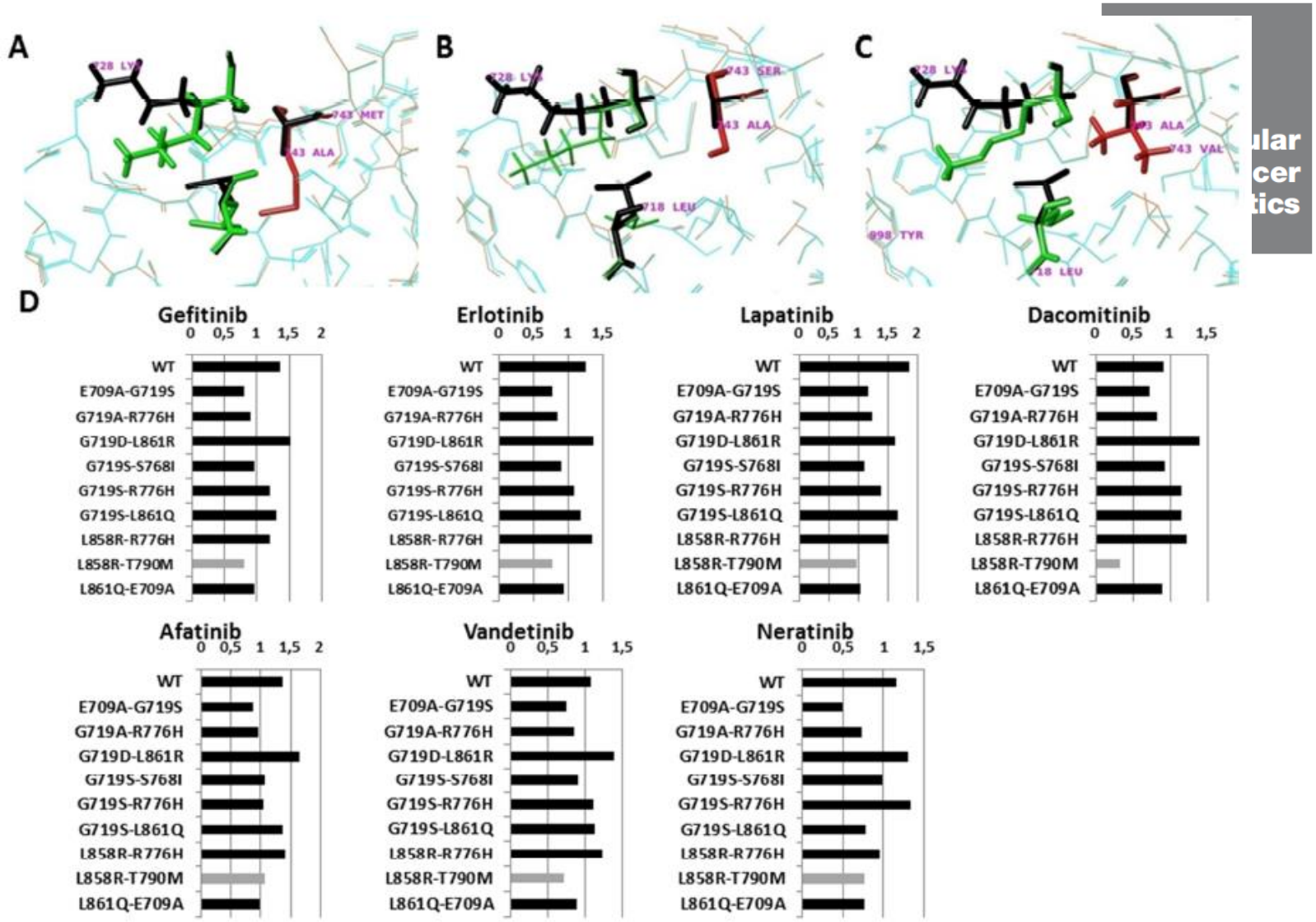
Sensitivity molecular alteration



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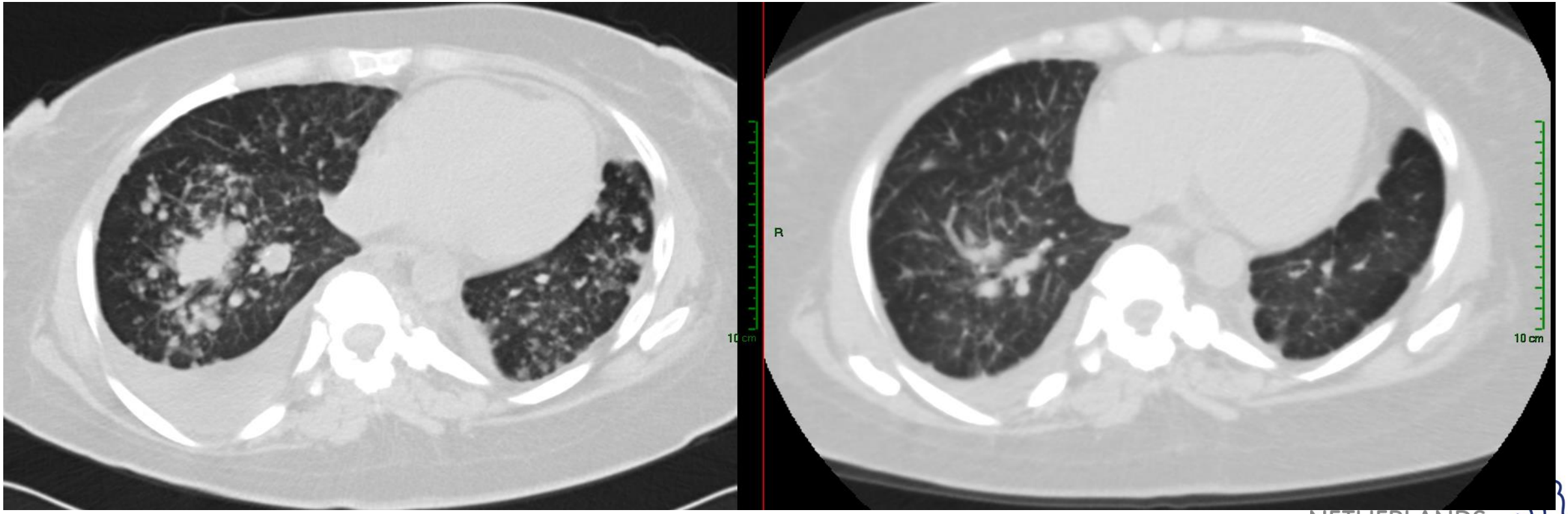
Mevr. A, 43 jaar

- Treatment with combination EGFR TKI and EGFR mAb



Van Veggel B, De Langen, AJ, et al. JTO 2018

Abstract 14152

Osimertinib treatment for patients with EGFR exon 20 mutation positive non-small cell lung cancer

van Veggel B[1], van der Wekken AJ[2], Hashemi SMS[3], Cornelissen R[4], Monkhorst K[5], Heideman DAM[6], Radonic T[6], Schuuring E[7], Smit EF[1,3], de Langen AJ[1]

[1] Department of Thoracic Oncology, The Netherlands Cancer Institute, Amsterdam, The Netherlands; [2] Dept of Pulmonary Diseases, University of Groningen and University Medical Center Groningen, Groningen, The Netherlands; [3] Dept of Pulmonary Diseases, VU University Medical Center, Amsterdam, The Netherlands; [4] Dept of Pulmonary Diseases, Erasmus Medical Center, Rotterdam, The Netherlands; [5] Dept of Pathology, The Netherlands Cancer Institute, Amsterdam, The Netherlands ; [6] Cancer Center Amsterdam, Dept of Pathology, VU University Medical Center, Amsterdam, The Netherlands; [7] Dep of Pathology and Medical biology, University of Groningen and University Medical Center Groningen, Groningen, The Netherlands

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Introduction

- Epidermal growth factor receptor (*EGFR*) exon 20 insertion mutations are identified in 9-12% of all *EGFR* mutations in non-small cell lung cancer (NSCLC). [1,2]
- EGFR exon 20 mutations are associated with primary resistance to first and second generation EGFR tyrosine kinase inhibitors (TKIs). [3,4]
- *In vitro* and preclinical animal studies have shown that osimertinib, a third generation EGFR TKI, exerts antitumor activity in *EGFR* exon 20 insertion positive NSCLC. [5]
- We report on a cohort of 20 patients with advanced stage *EGFR* exon 20 mutation positive NSCLC that were treated with osimertinib.

Methods

- 20 patients with advanced NSCLC harboring an *EGFR* exon 20 mutation were treated with osimertinib 80 mg once daily, in four institutions in the Netherlands.
- Data were obtained retrospectively.
- *EGFR* mutation status was assessed by next-generation sequencing.
- Objective response rate (ORR), progression free survival (PFS) and disease control rate (DCR) at five months were assessed according to RECIST v1.1.

Results

Table 1. Patient and tumor characteristics

	n=20 (%)
Age (years)	62 (Range 38-82)
Men	6 (30%)
Mutation type	
EGFR exon 20 insertion/duplication	16 (80%)
EGFR exon 20 (bi/tri) nucleotide substitutions	4 (20%)
Number of lines for advanced disease	
0	6 (30%)
1	7 (35%)
2	5 (25%)
3	2 (10%)
Median	1
Prior platinum based chemotherapy	12 (60%)
Prior TKI	
First generation	1 (5%)
Second generation	2 (10%)

Figure 1. Waterfall plot of best percentage change in tumor size during osimertinib treatment

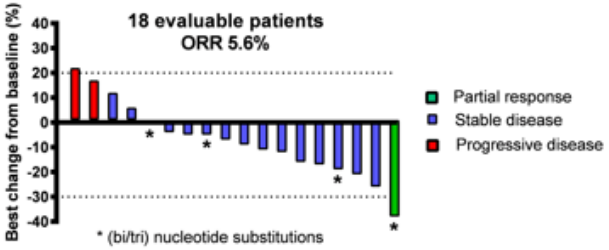
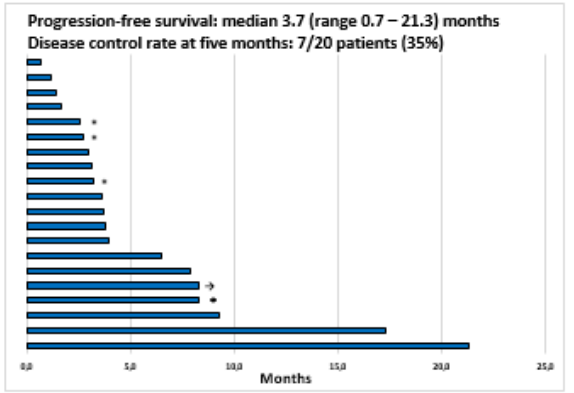


Table 2. Response to treatment

Patient	Mutation type	Best response	PFS (months)
1	p.(Ala767_Val769dup)	SD	4
2	p.(His773delinsTyrAsnProTyr)	SD	3.6
3	p.(Asn771delinsThrHis)	PD	1.2
4	p.(Ala767_Val769dup)	PD [1]	0.7
5	p.(Ser768_Asp770dup)	SD	3.8
6	p.(Asn771delinsGlyHis)	SD	3
7	p.(Asn771_Pro772insArgHis)	SD	9.3
8	p.(His773_Val774delinsLeuMet) [2]	PR	8.3
9	p.(Asn771delinsGlyTyr)	SD	21.3
10	p.(Val769_Asp770insGlyGly)	SD	3.7
11	p.(Asn771_His773dup)	SD	17.3
12	p.(Ala767_Val769dup)	PD [1]	3.1
13	p.(Ser768_Val769delinsIleLeu) [2]	SD	2.6
14	p.(Pro772_His773insThrHisPro)	SD	6.5
15	p.(Asn771_His773dup)	SD	7.9
16	p.(Val769_Asp770insSerPheLeu)	PD	1.7
17	p.(His773_Val774delinsLeuMet) [2]	SD	3.2
18	p.(Gly779Phe) [2]	SD	2.7
19	p.(Ala767_Val769dup)	SD	8.3
20	p.(Asn771_Pro772insHis)	SD	1.4

[1] Not evaluable according to RECIST v1.1.
[2] (bi/tri) nucleotide substitution
PFS; progression-free survival, SD; stable disease, PD; progressive disease, PR; partial response

Figure 2. Progression-free survival



Arrow indicates patient with ongoing response at data cutoff.
* Indicates (bi/tri) nucleotide substitution

Conclusions

- Osimertinib has limited antitumor activity in patients with *EGFR* exon 20 mutated NSCLC, with an ORR of 5.6%.
- Durable responses (≥5 months) were seen in 35% of patients.
- One patient experienced a partial response during osimertinib treatment. This patient harbored an *EGFR* exon 20 binucleotide substitution.

References

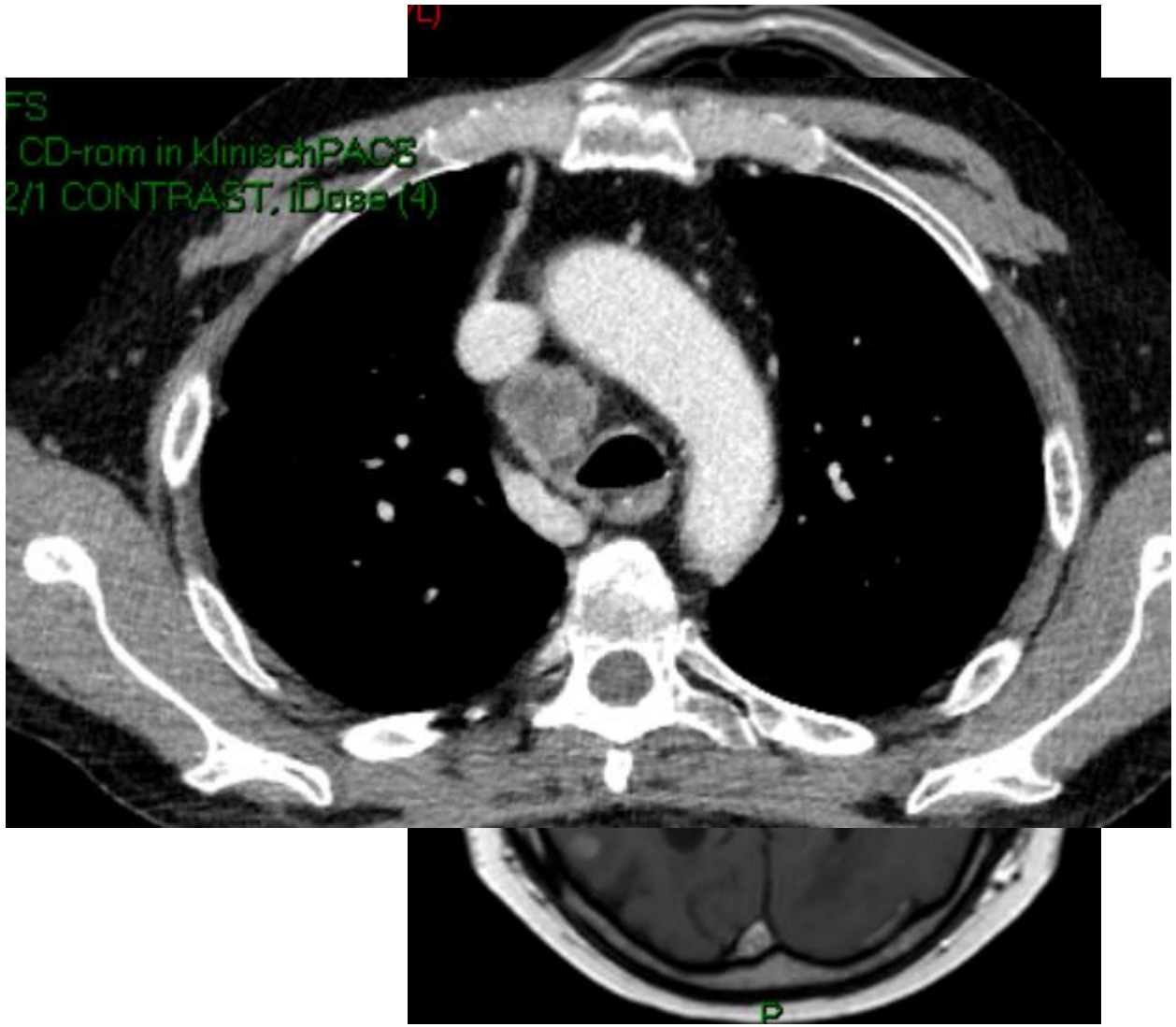
1. Arcila, M.E. et al., Mol Cancer Ther, 2013. 12:220-2292; 2. Riess , J.W. et al., J Thorac Oncol, 2018. Epub ahead of print; 3. Yasuda, H. et al., Sci Transl Med, 2013. 5:216ra177; 4. Robichaux, J.P. et al., Nat Med, 2018. 24(5): 638–646; 5. Hirano, T. et al., Oncotarget, 2015. 6:38789-38803

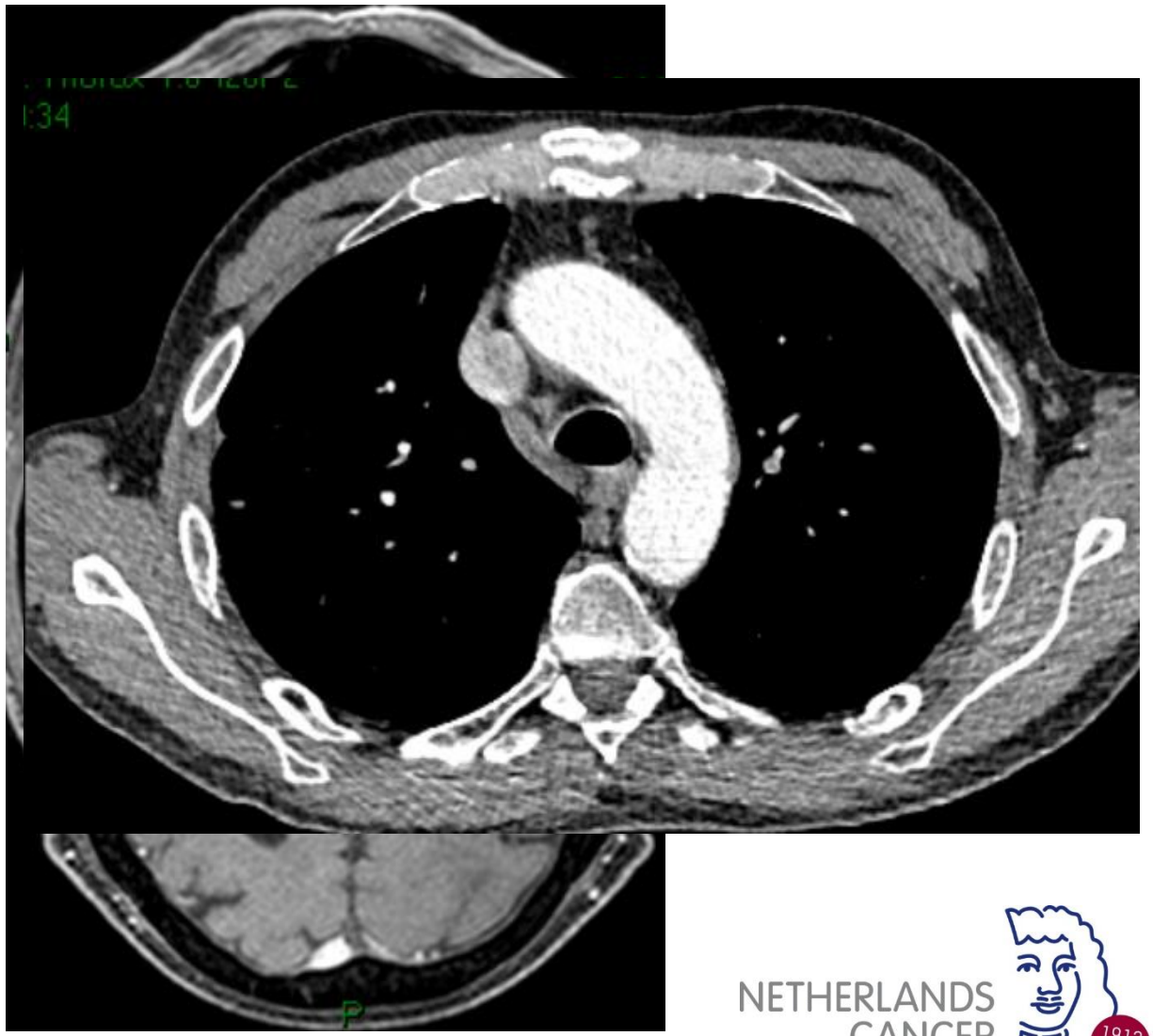
Corresponding author: b.v.veggel@nki.nl

58 jarige man, EGFR p.His773_Val774DelinsLeuMet

- 03-2017 St IV adenoca, EGFR p.His773_Val774DelinsLeuMet. Multiple brain mets for which WBRT. Thereafter carboplatin-pemetrexed x 4.
- 06-2017 SRS on oligoprogression of brain met.
- 09-2017 Extra-CNS tumor progression. Erlotinib.
- 11-2017 PD in and outside the brain. Re-WBRT and referral

Van Veggel B, De Langen, AJ, et al. JTO 2018





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IASLC
INTERNATIONAL ASSOCIATION FOR THE STUDY OF LUNG CANCER
IASLC 19th World Conference on Lung Cancer
September 23–26, 2018 Toronto, Canada
WCLC2018.IASLC.ORG
#WCLC2018

Phase II trial of poziotinib for EGFR and HER2 exon 20 mutant NSCLC

John V. Heymach, MV Negrao, JP Robichaux, BW Carter, A Patel, M Altan, DL Gibbons, F Fossella, G Simon, V Lam, G Blumenschein, AS Tsao, JM Kurie, F Mott, DM Jenkins, D Mack, L Feng, B Roeck, Z Yang, V Papadimitrakopoulou, YY Elamin

University of Texas MD Anderson Cancer Center

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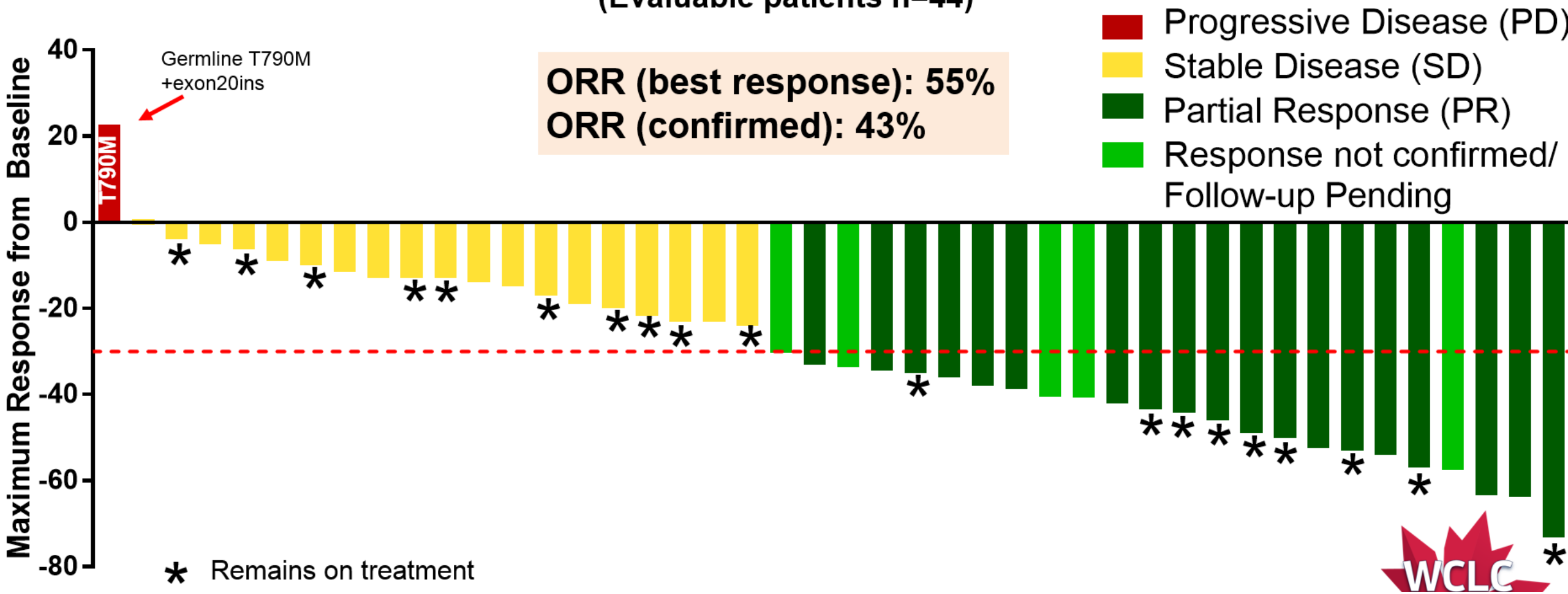
Poziotinib efficacy in EGFR Exon 20 mutant NSCLC

(Evaluable patients n=44)



WCLC

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EGFR exon 20 insertion positive NSCLC

- No registered medication.
- Heterogeneous population

- Poziotinib
- TAK-788
- TAS-6417
- Afatinib-Cetuximab
- Osimertinib

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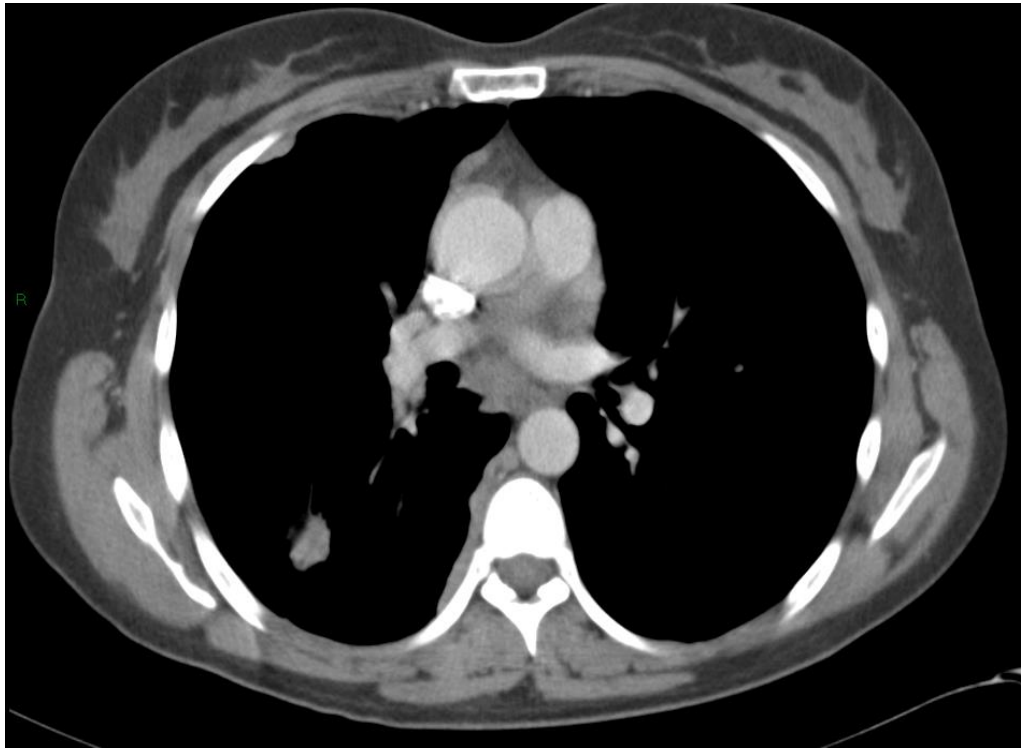
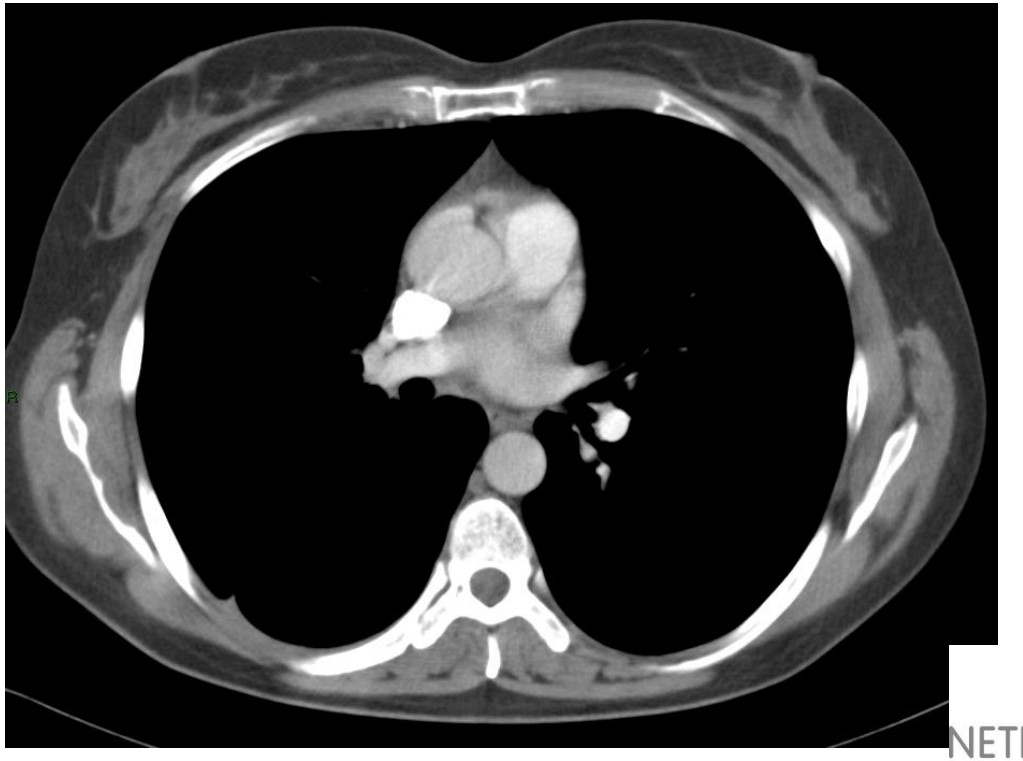
Mevr. T, 43 jaar *c.2235_2249del*

- 10-2014: Gefitinib. Best response: PR





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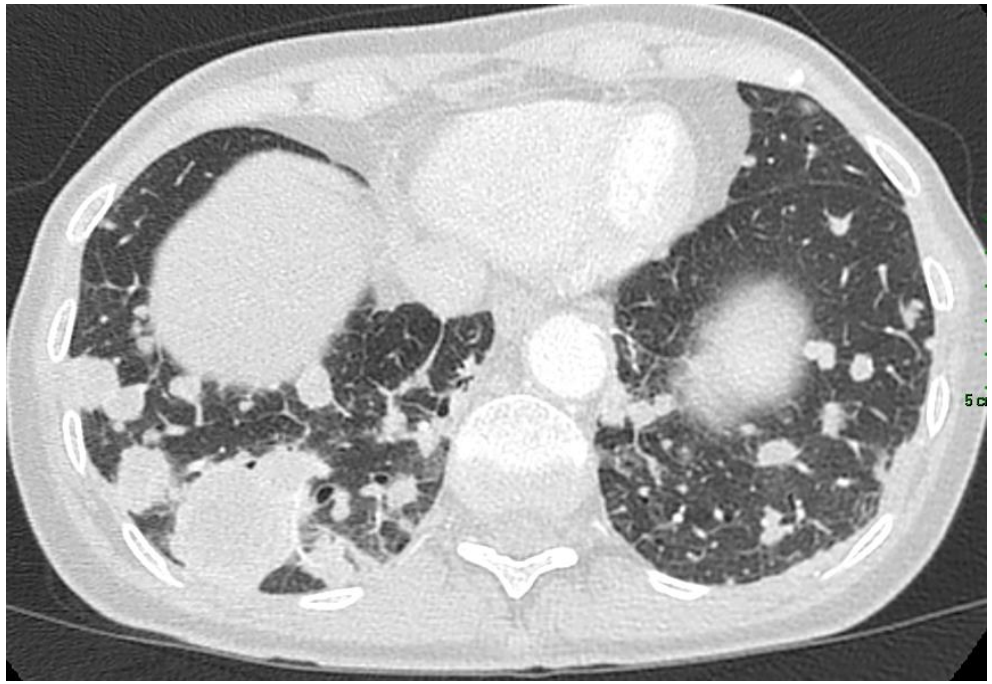
Mevr. T, 43 jaar

- 10-2014: Gefitinib. Best response: PR
- 03-2016: PD. T790M+. Osimertinib. Best response: PR
- 12-2016: PD.



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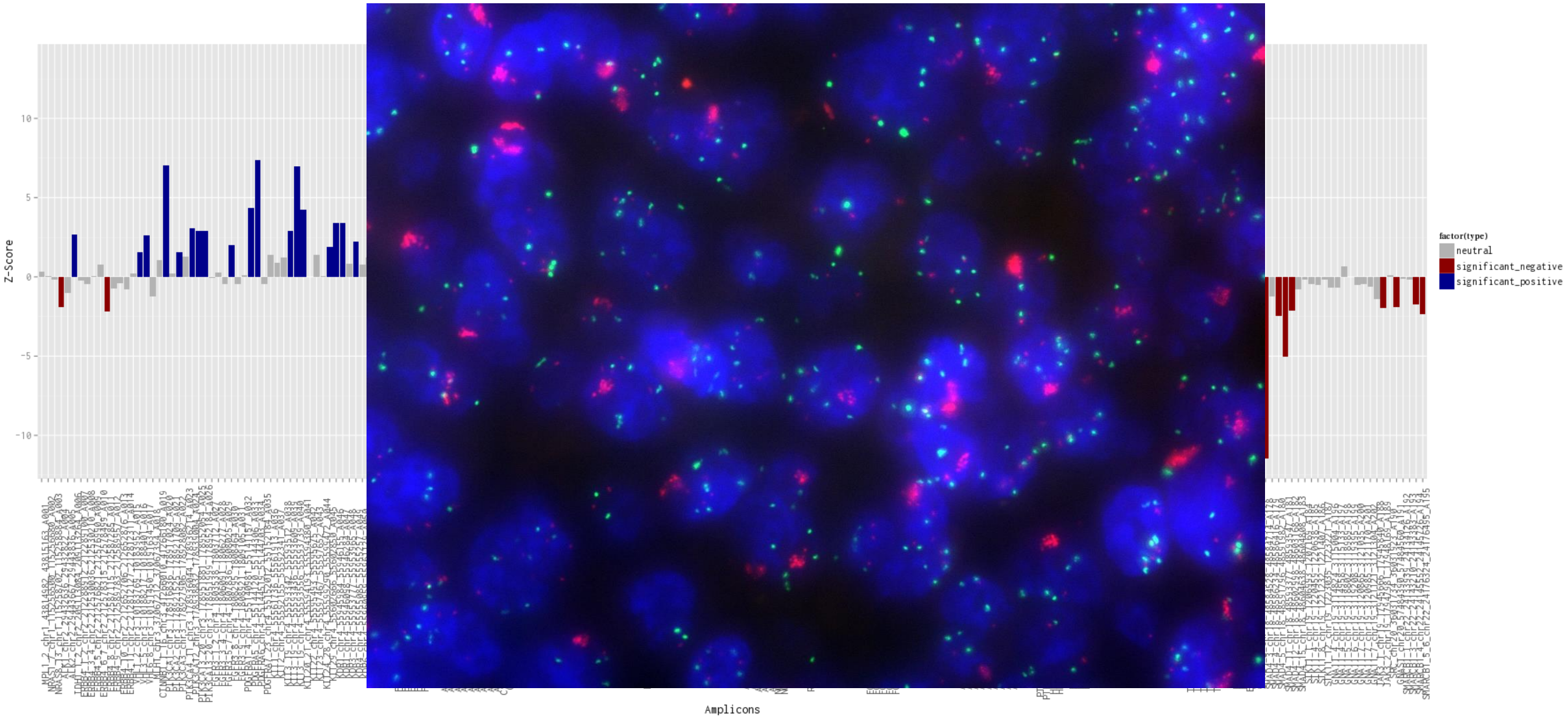
Mevr. T, 59 jaar

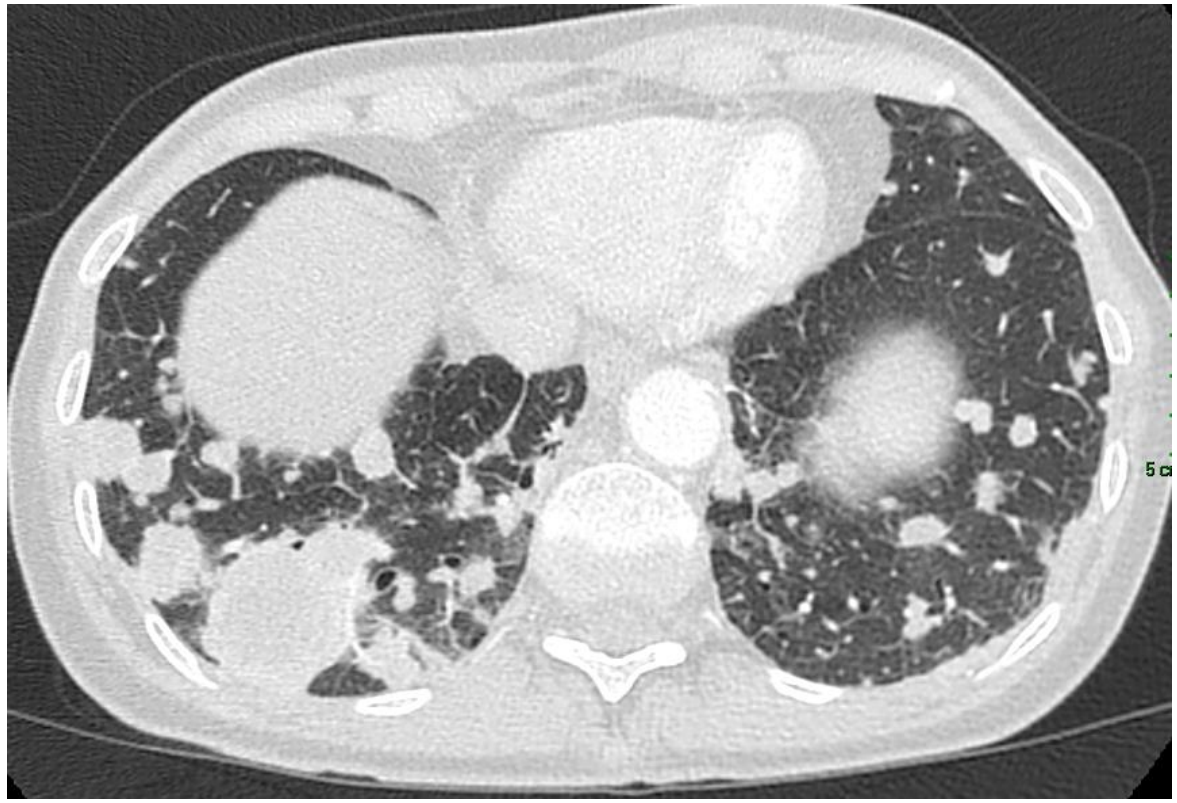
- Plasma
  - EGFR exon 19 del 127 copies/ml plasma. EGFR exon 20 T790M not detectable.

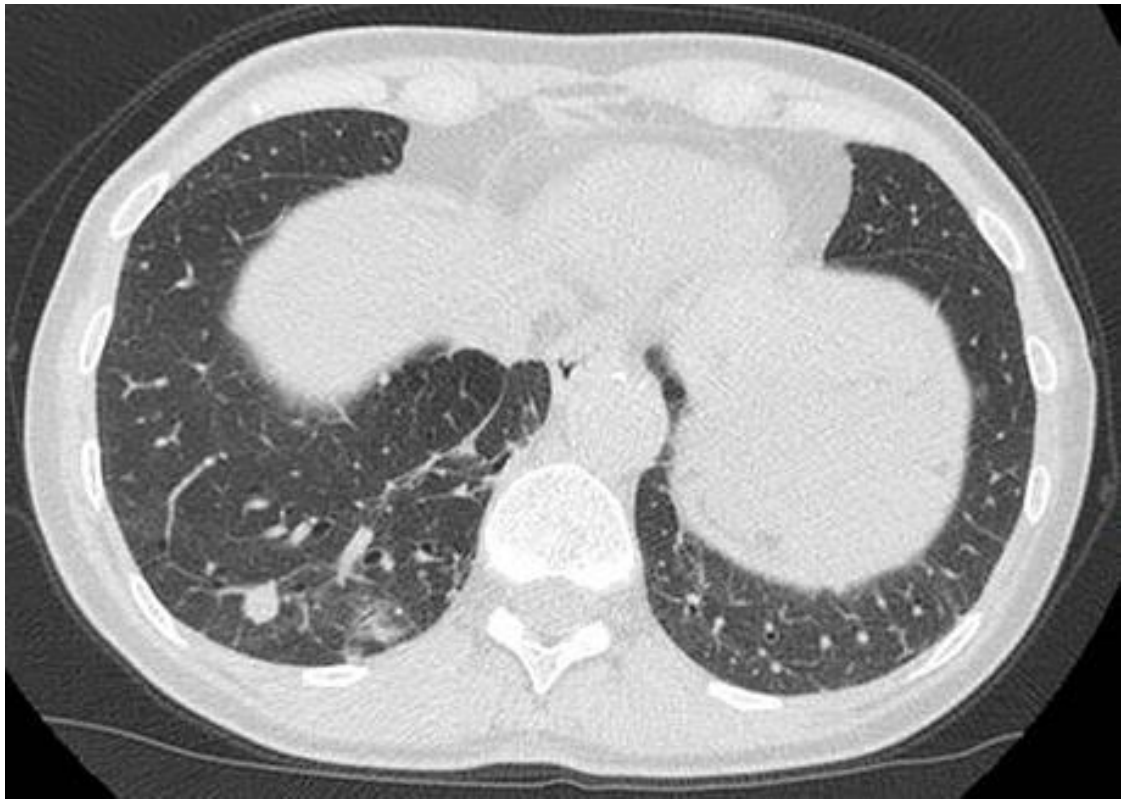
- Biopsy
  - NGS: EGFR exon 19 del+, T790M-, P53 mutation.
  - PD-L1 IHC: 100% positive.

Mevr. T, 59 jaar



Osimertinib and Crizotinib treatment (EGFR and MET TKI)





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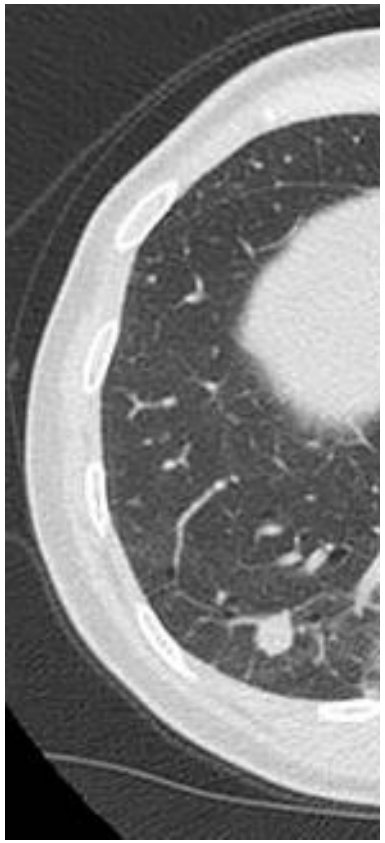
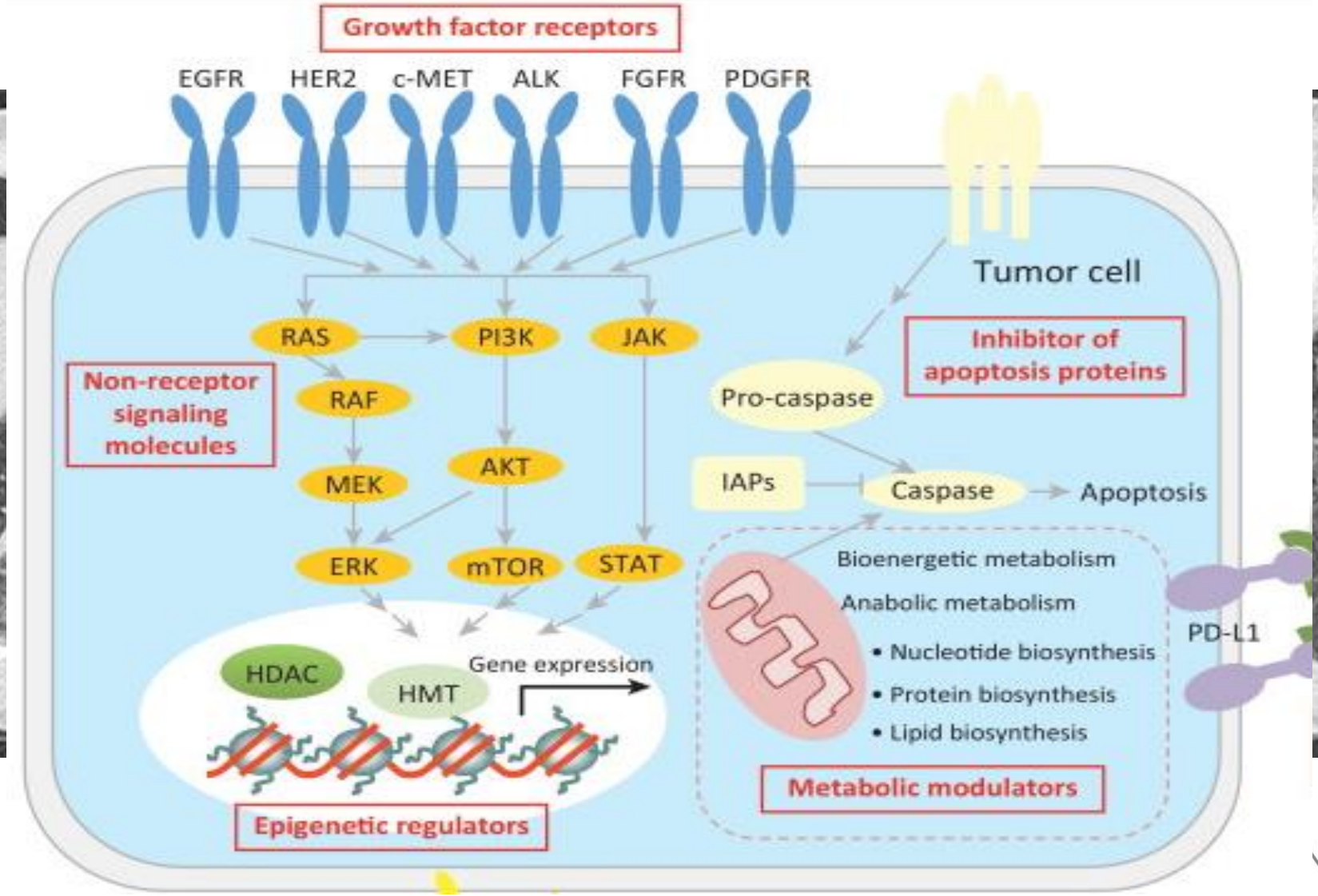
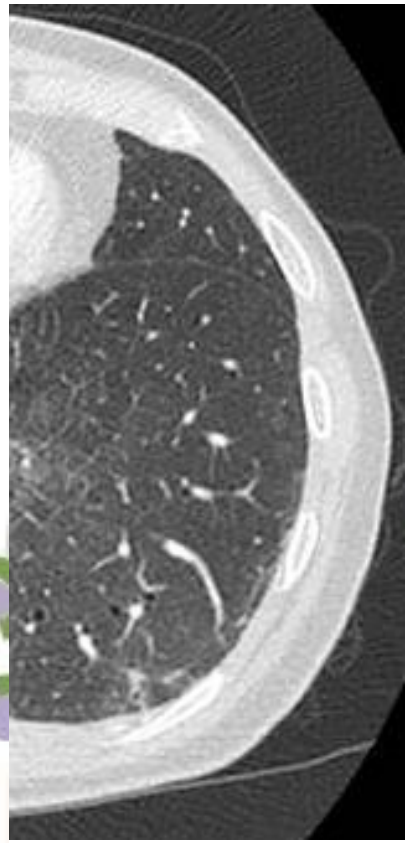
Resistance in the resistance







Van Veggel B, De Langen, AJ, et al. Lung Cancer 2018

Resistance – analysis beyond mutations

- Allelic frequency of resistance
- Allelic contexture of mutations

Mevr. E, 79 jaar

- St IV NSCLC, never smoker
- EGFR mutation
- C.2235_2249del
- Erlotinib treatment
- c.2369C>T p.Thr790Met (p.T790M)
- Osimertinib treatment
- c.2390G>C p.Cys797Ser (p.C797S)

Mevr. G, 68 jaar

- St IV NSCLC, never smoker
- EGFR mutation
- C.2235_2249del
- Erlotinib treatment
- c.2369C>T p.Thr790Met (p.T790M)
- Osimertinib treatment
- c.2390G>C p.Cys797Ser (p.C797S)

Mevr. E, 79 jaar

- EGFR c.2235_2249del p.Glu746_Ala750del (p.E746_A750del). AF 64%
- EGFR c.2369C>T p.Thr790Met (p.T790M). AF 20%
- EGFR c.2389T>A p.Cys797Ser (p.C797S) . AF 15%
- De EGFR codon 797 mutatie ligt in trans met p.T790M.
- TP53 c.216delC p.Val73fs (p.V73fs) AF 30%.
- RB1 c.2077G>T p.Glu693* (p.E693*) AF 89%

Mevr. G, 68 jaar

- EGFR c.2235_2249del p.Glu746_Ala750del (p.E746_A750del). AF 74%
- EGFR c.2369C>T p.Thr790Met (p.T790M). AF 30%
- EGFR c.2389T>A p.Cys797Ser (p.C797S) . AF 31%
- De EGFR codon 797 mutatie ligt in cis met p.T790M.
- Amplificatie van het EGFR gen. Z-score = 6.8
- CTNNB1 c.134C>T p.Ser45Phe (p.S45F). AF 100%.

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Molecular tumorboard meeting

- Molecular tumour board
  - (Thoracic) Oncologist
  - Pathologist
  - Clinical molecular biologist

  - Sensitivity molecular alteration
  - Clinical study available
  - Type of treatment
  - Location of treatment

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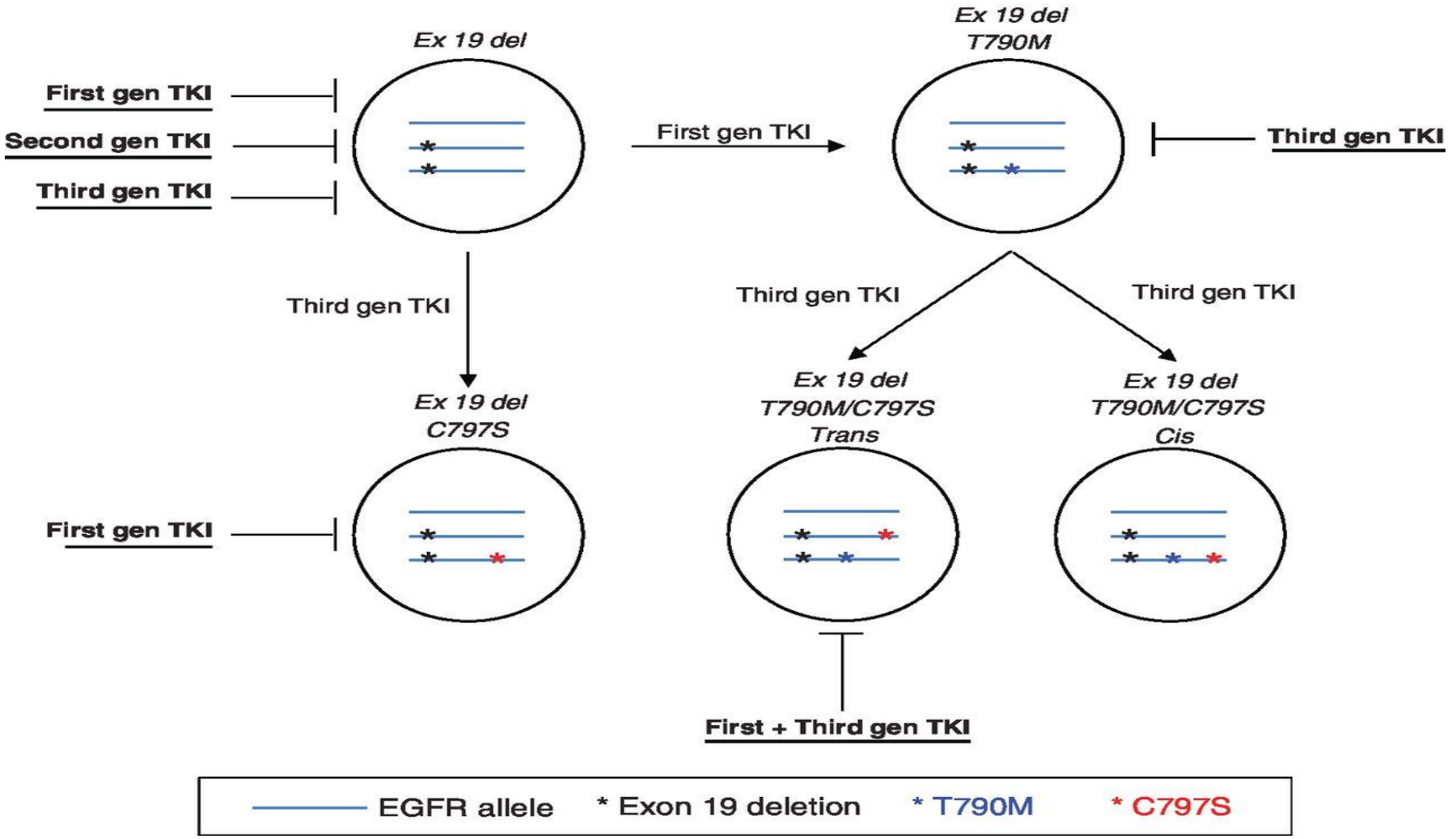
Schematic representation of EGFR resistance mutations in response to TKI treatment and sensitivity to subsequent therapies.



Matthew J. Niederst et al. Clin Cancer Res 2015;21:3924-3933

Clinical Cancer Research
NETHERLANDS CANCER
AACR American Association for Cancer Research
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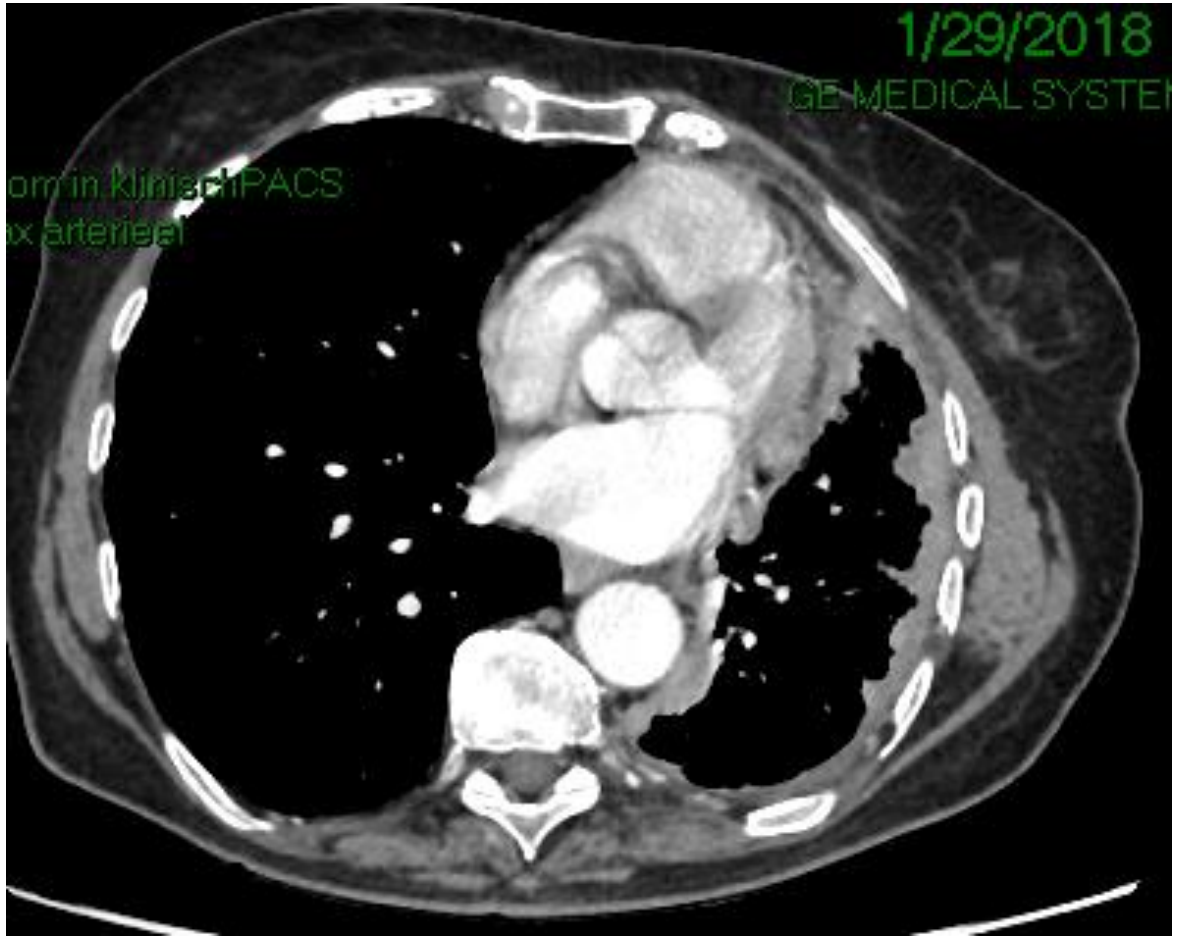
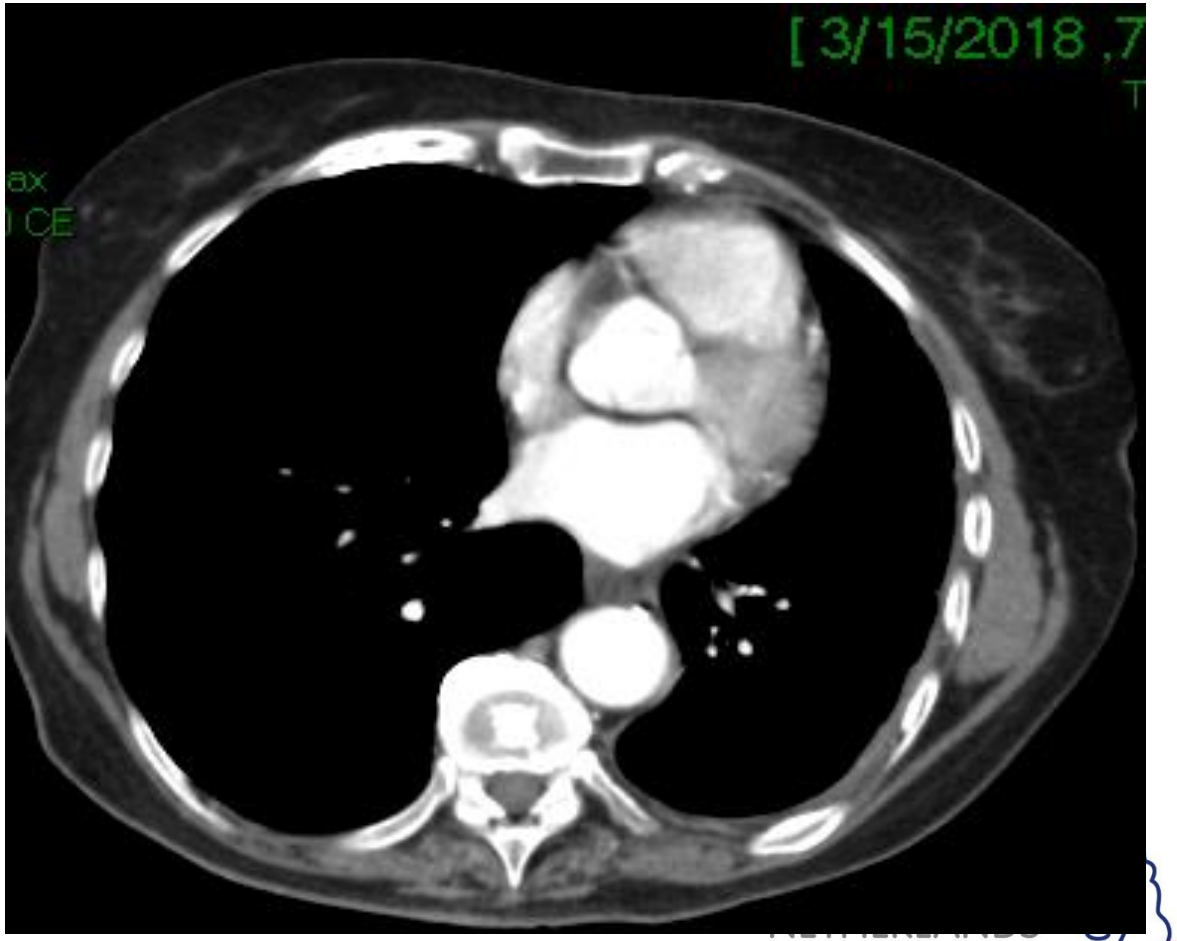
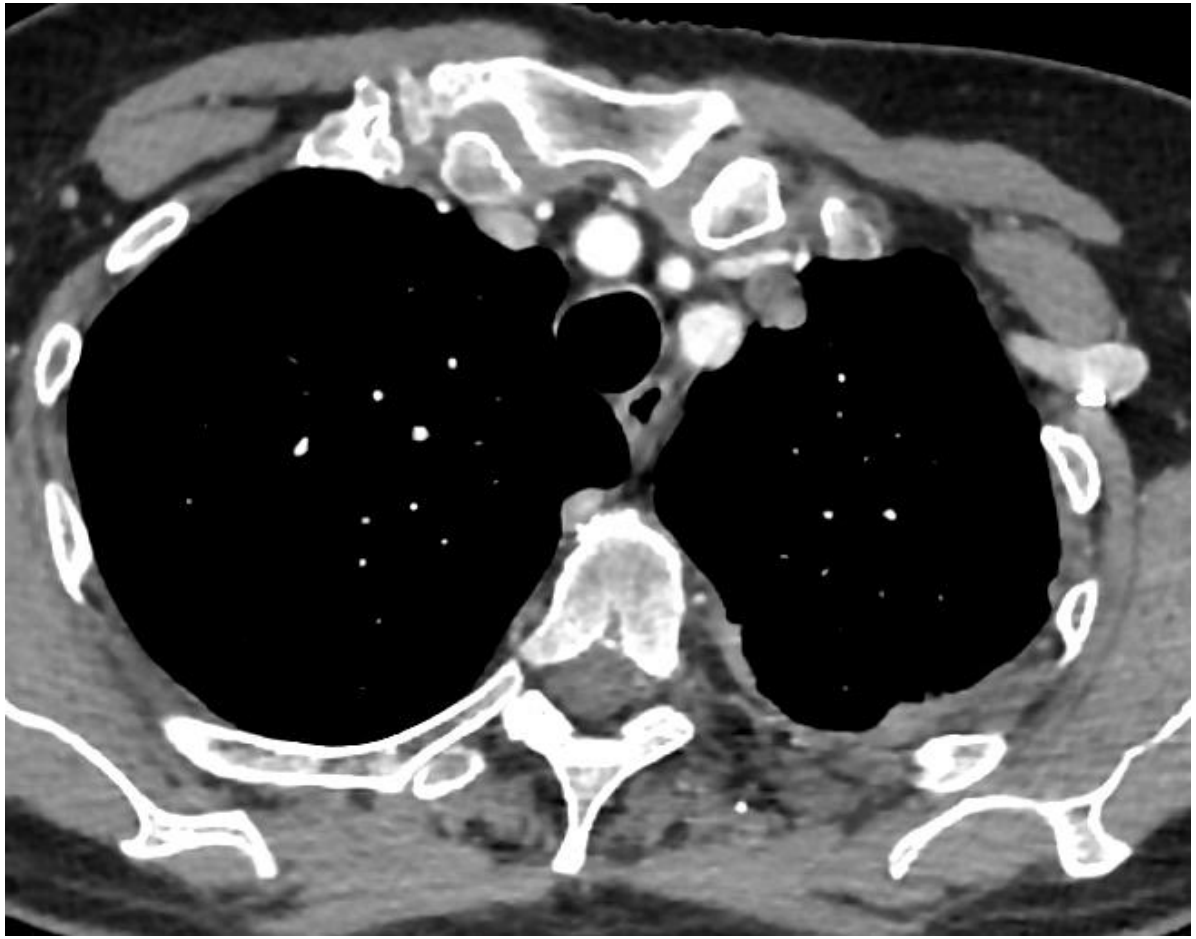
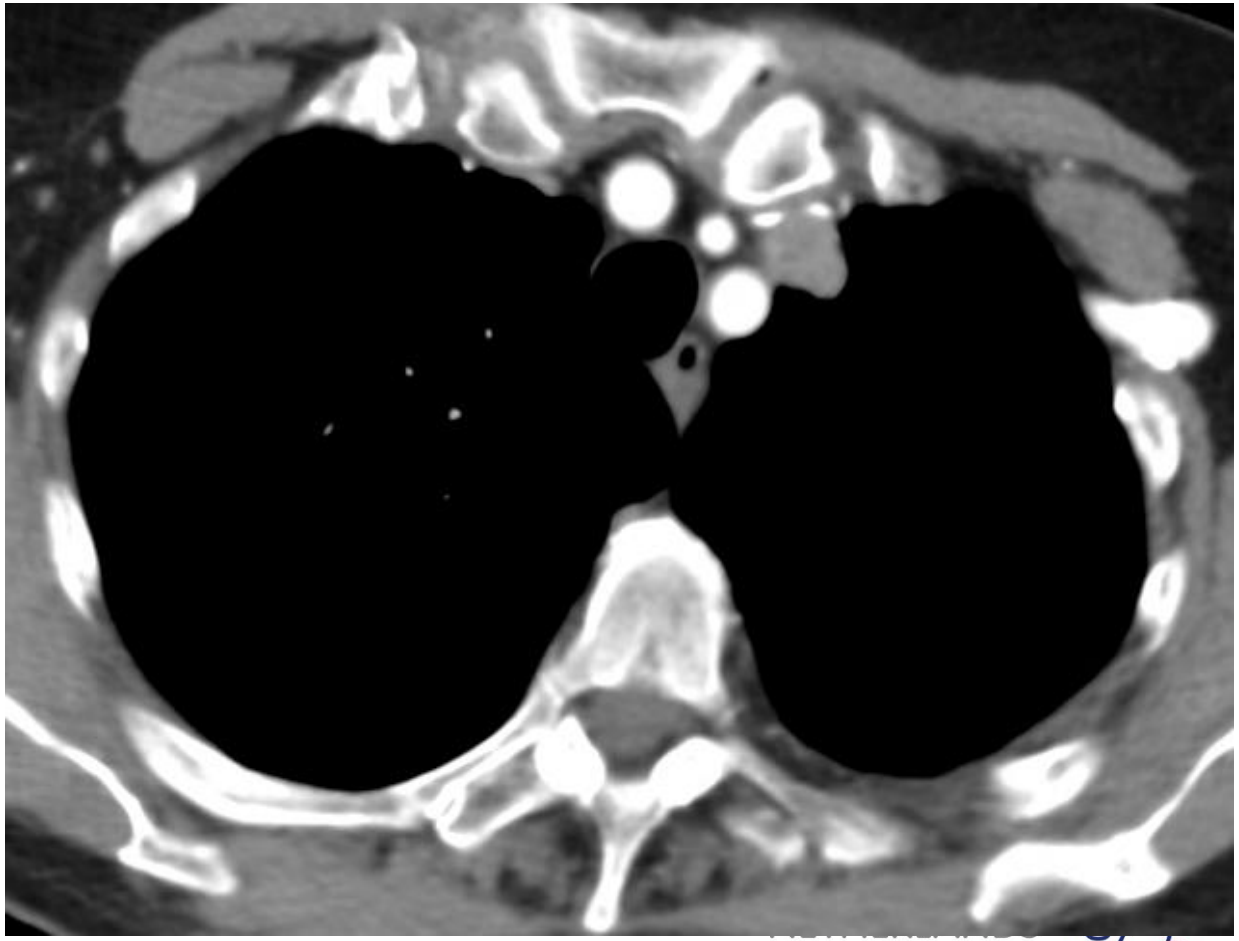
Mevr. E, 79 jaar – Erlotinib + Osimertinib





Mevr. E, 79 jaar – Erlotinib + Osimertinib



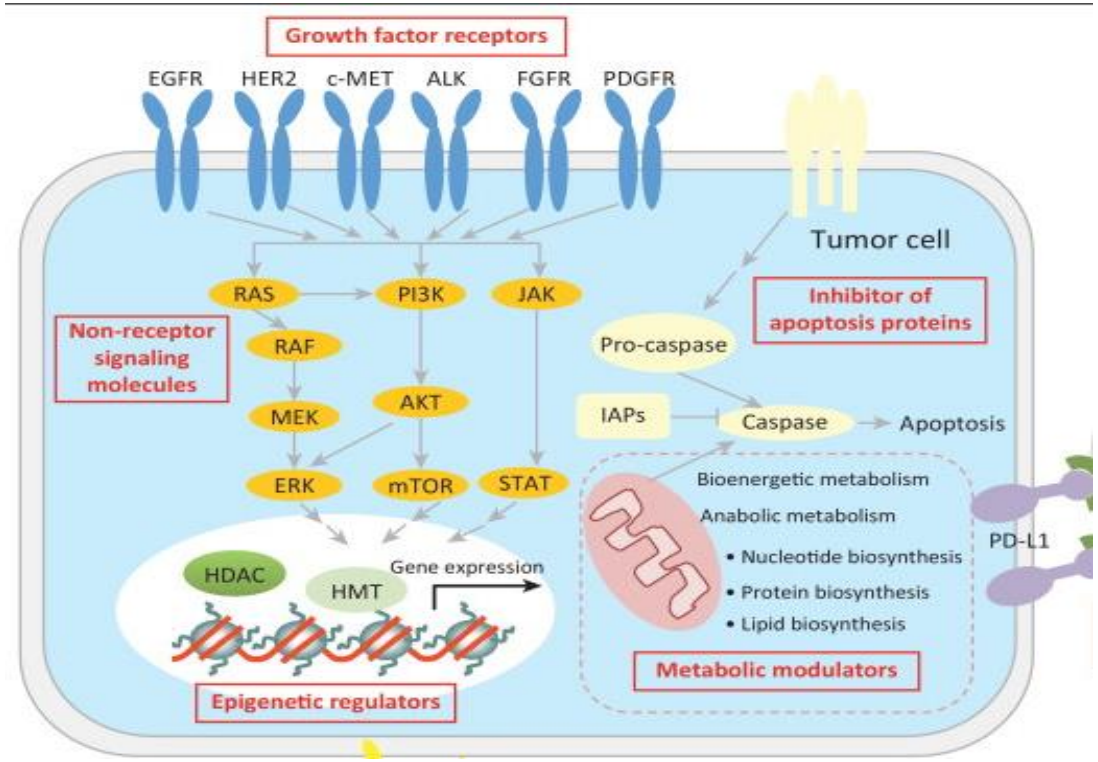


Resistance mechanisms to osimertinib

- On target
  - Tertiary EGFR mutations
  - EGFR amplification
- Vertical resistance
  - BRAF V600E mutation
  - KRAS mutations
  - KRAS amplification
- Horizontal resistance
  - MET amplification
  - HER2 amplification
  - HER2 mutation
  - ALK translocation
  - ROS1 translocation
  - RET translocation
  - FGFR-1 amplification

HER2 driven NSCLC

- HER2 mutation (mainly exon 20 insertions)
- HER2 amplification
- HER2 overexpression



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46 year old male patient

- 01-2017: St IV NSCLC, TTF-1+ adenocarcioma, primary LUL with mediastinal, hilar and axillary lnn mets and lung mets.
- COPD Gold 3
- Drug abuse
- Bronchiectasis
- Smoking history: 30 PY
- Currently being screened for tuberculosis

46 year old male patient

- Pathology:
  - NGS: RB1, TP53, SMO mutations, HER2 copy number gain
  - IHC: HER2 100% 3+ intensity staining
  - IHC: PD-L1 0%
  - FISH: HER2 >10 gene copies / nucleus.

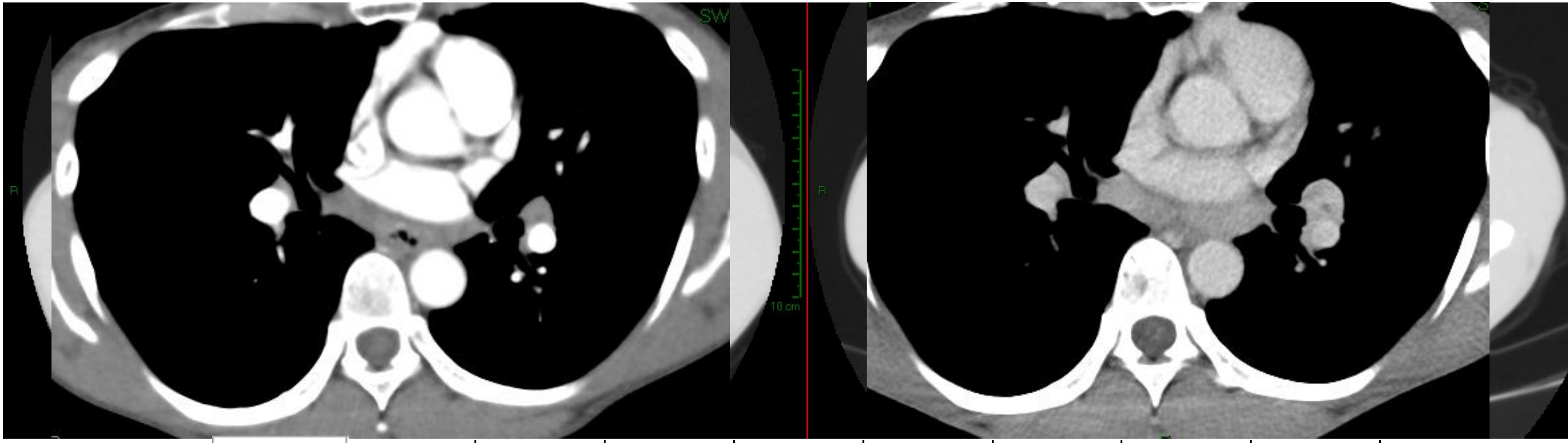
The Drug Rediscovery Protocol (DRUP trial)

Title

A Dutch National Study on behalf of the Center for Personalized Cancer Treatment (CPCT) to Facilitate Patient Access to Commercially Available, Targeted Anti-cancer Drugs to determine the Potential Efficacy in Treatment of Advanced Cancers with a Known Molecular Profile.

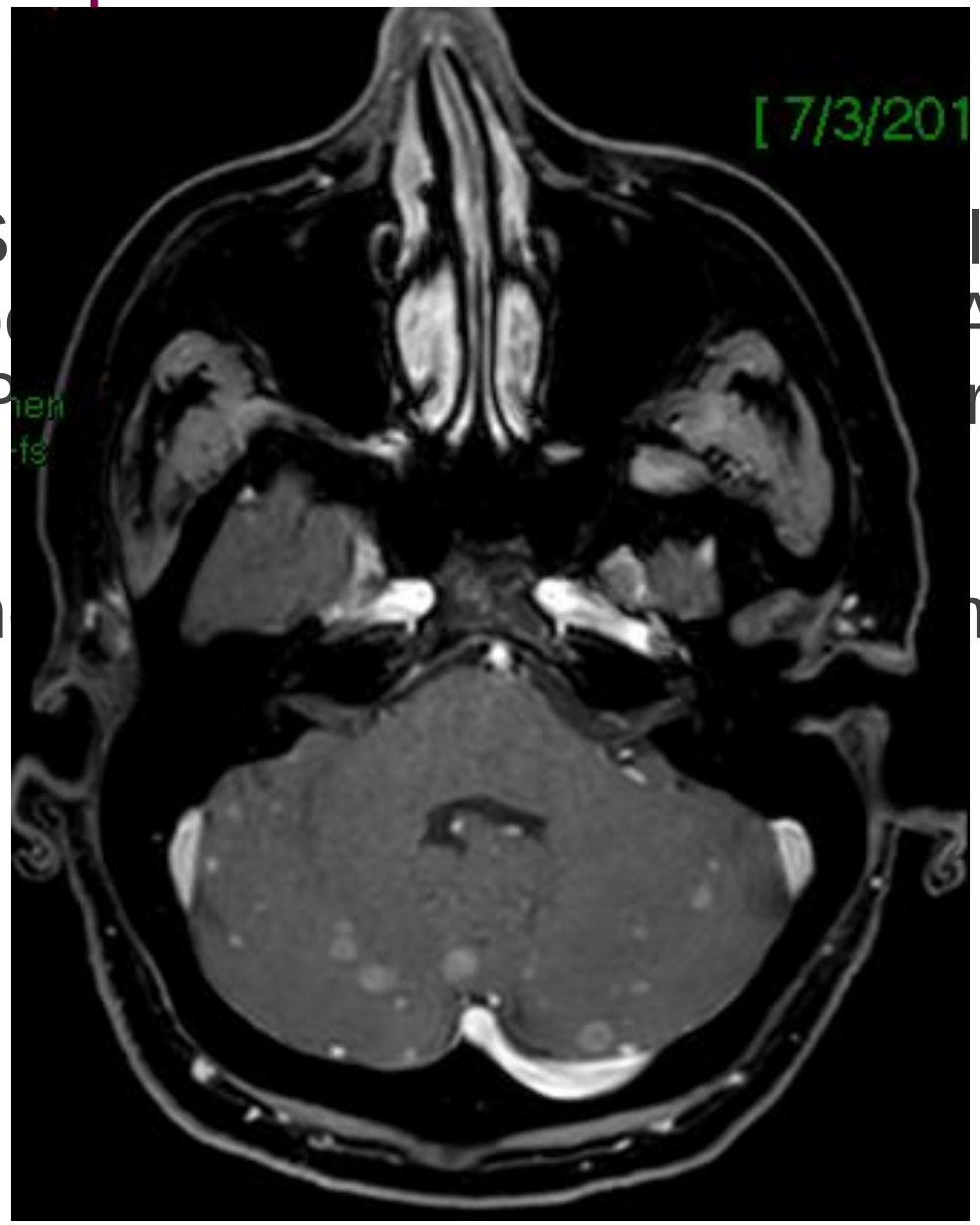
Home
About CPCT
CPCT for
- Patients
- CPCT and you

DRUP Study: Trastuzumab-Pertuzumab



Test	09-08-2018 09:00	29-12-2017 09:10	07-12-2017 11:24	16-11-2017 10:11	26-10-2017 09:20	05-10-2017 11:25	14-09-2017 09:35	25-08-2017 07:50	28-07-2017 09:10	14-07-2017 10:19
−Tumormerkers										
☑ CEA	6 H	5	-	7 H	11 H	22 H	62 H	-	-	297 H
☐ CA125	13	10	-	7	8	6	7	-	-	8
☐ SCC	-	2.1 H	-	1.6	1.7	1.2	<Memo>	-	-	1.1
☐ Cyfra 21.1	1.8	2.2 H	-	1.9	1.7	2.2 H	2.2 H	-	-	4.0 H
☐ NSE	11.2	13.5 H	-	10.8	15.0 H	12.9 H	Hemolyt.	-	-	16.1 H

56 year old female patient



- 09-2017: St IV NS le brain mets. WBRT, thereafter carbo-p A: HER2 exon 20 V777L mutation, P r.
- 06-2018: PD.
- 07-2018: screenin mab / pertuzumab study

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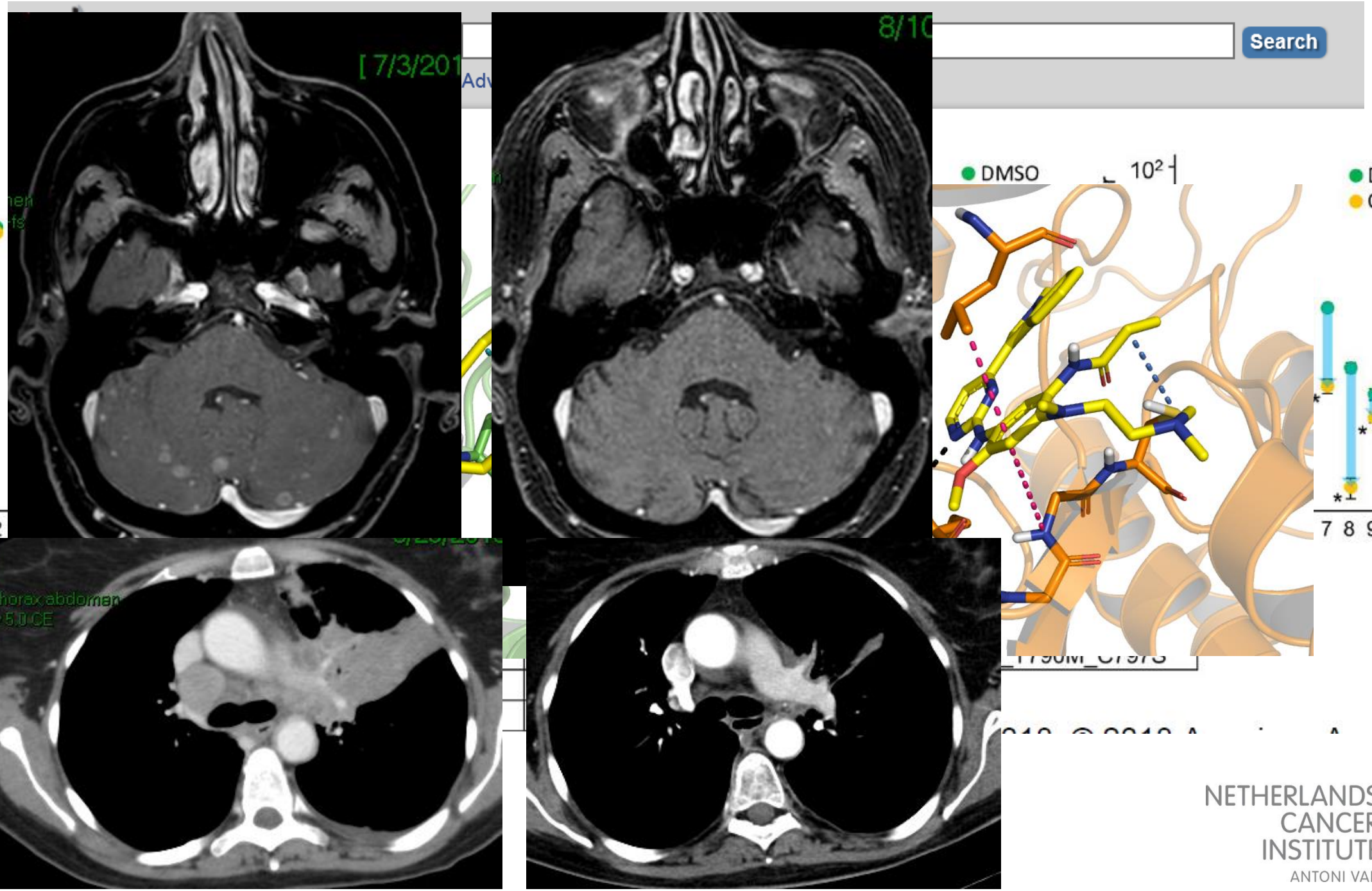
Search
Relative cell proportion in tumor
10^2
10
1
10^{-1}
10^{-2}
1 2
DMSO
10^2
DMSO
Osimertinib
7 8 9 10 11 12 13
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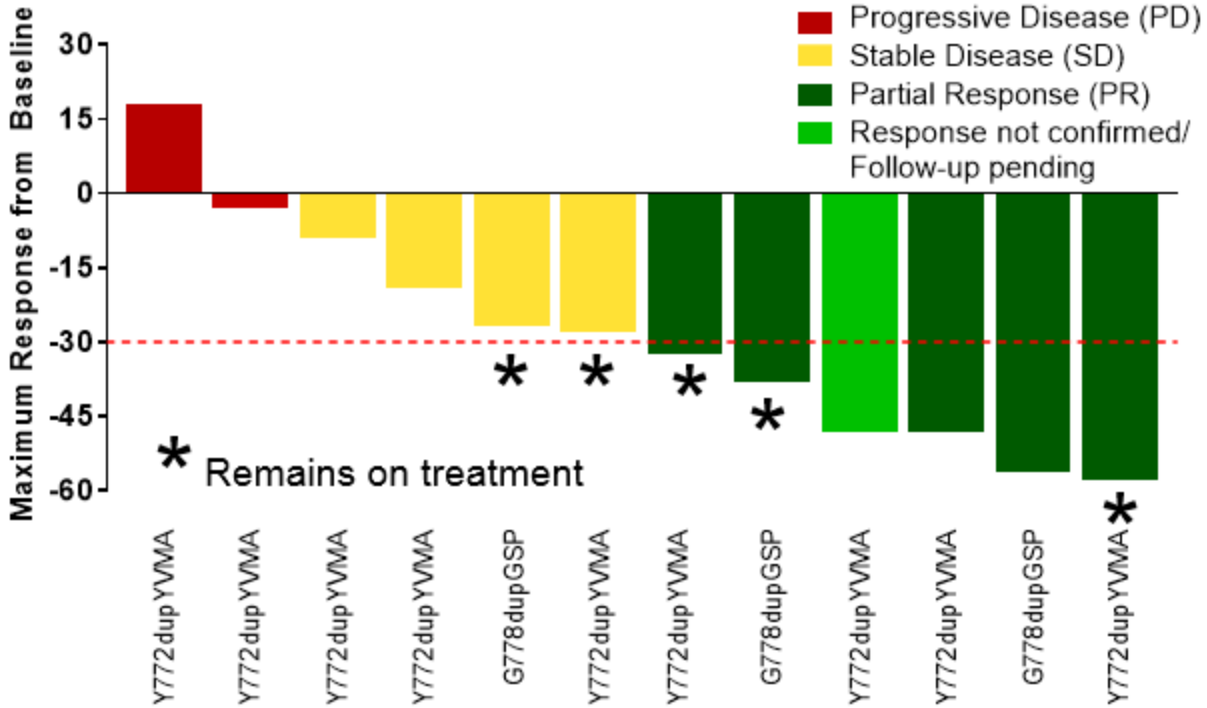
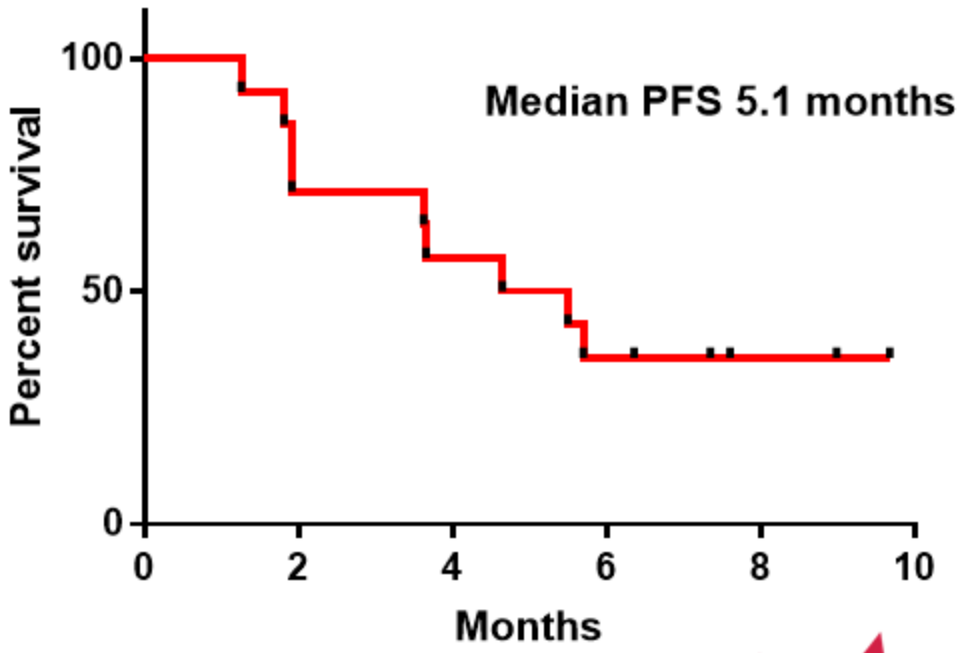
Poziotinib efficacy in HER2 Exon 20 insertion mutant NSCLC

Best response HER2 (Evaluable patients n=12)



Progression-free Survival HER2 (All patients n=13)



HER2 exon 20 insertion positive NSCLC

- No registered medication.
- Heterogeneous population

- Poziotinib
- T-DM1
- TAK-788

Van Veggel B, De Langen, AJ, et al. JTO 2018

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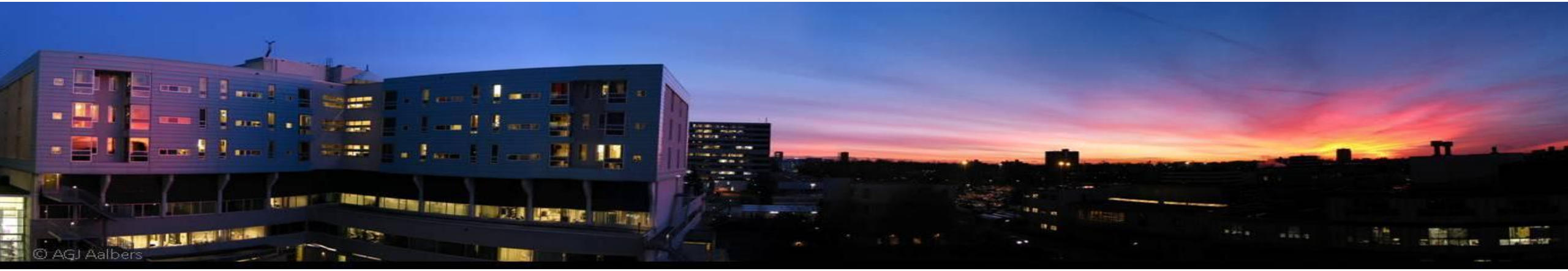
Conclusions

- It all starts with finding the oncogenic driver or driver of resistance
- Test everything anytime (mutations, CNV and fusions)
- Allelic frequency
- Allelic contexture
- Concurrent molecular alterations
- Molecular tumorboard
- Chemo-immunotherapy is just as important as targeted treatment.
- Treat in clinical studies wherever possible



Thank you for listening

Questions?

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