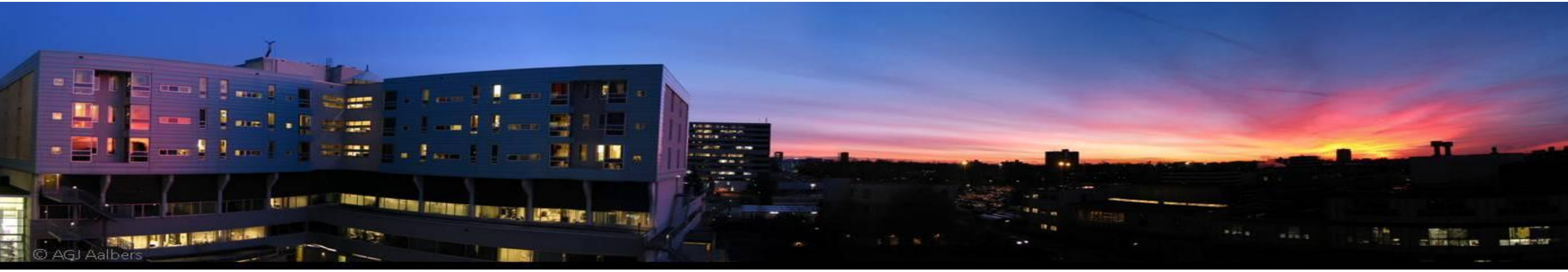
Mutatie positief longkanker



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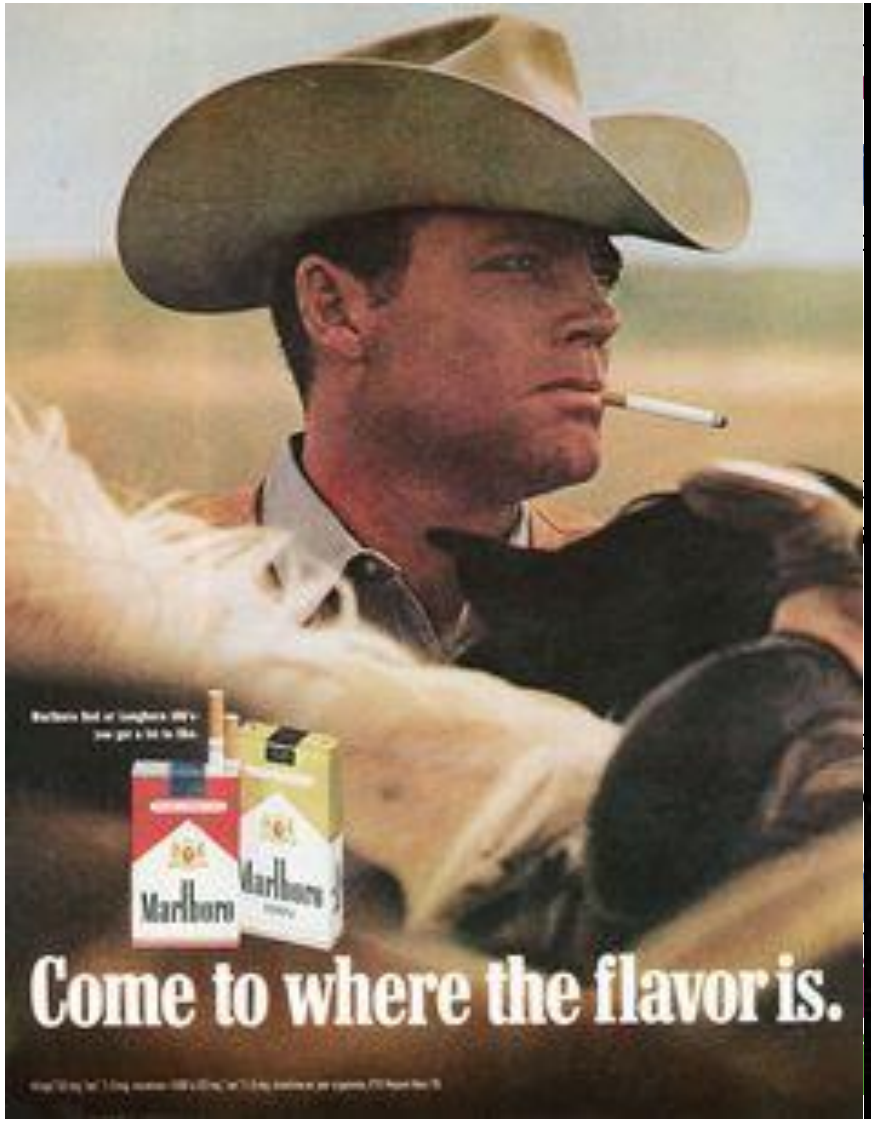
Disclosures

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

Longkanker is een heterogene ziekte



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DNA analyse matcht de juiste medicatie aan de juiste patient

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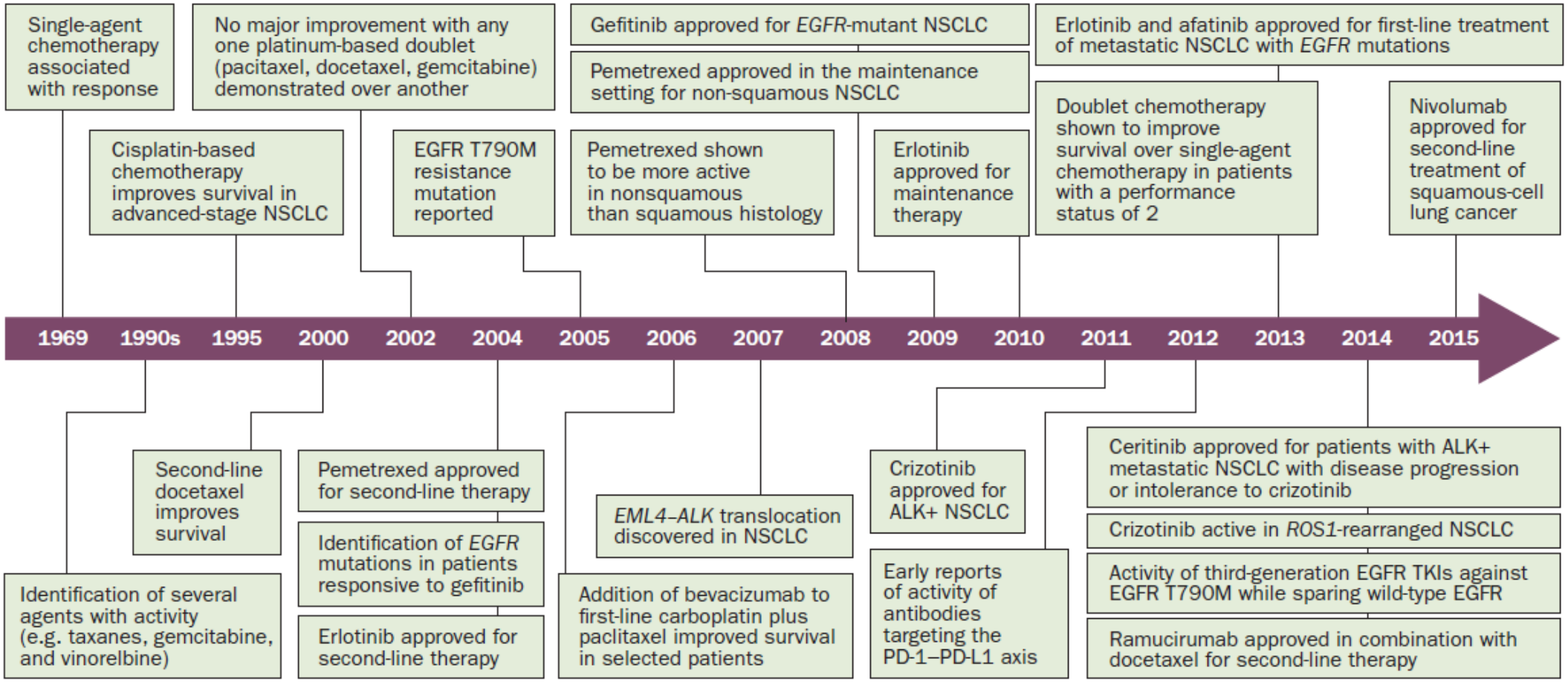
Stroomversnelling in medicijnontwikkeling



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Matches tussen genetische driver en medicatie

Gene	Perc.	Alteration	Treatment
• KRAS G12C	15%	Mutation	Sotorasib, Adagrasib, etc.
• KRAS other	24%	Mutation	RMC-6291
• EGFR	10%	Mutation	Osimertinib, amivantamab, furmonertinib, etc.
• ALK	4%	Translocation	Alectinib, lorlatinib, etc.
• BRAF	2%	Mutation	Dabrafenib en trametinib
• ROS1	1%	Translocation	Crizotinib, entrectinib, repotrectinib, etc.
• RET	1%	Translocation	Selpercatinib
• MET	4%	Mutation and amplification	Capmatinib, tepotinib, savolitinib, crizotinib
• HER2	2%	Mutation and amplification	T-DXd, Zongertinib, BAY 2927088
• NTRK	<1%	Fusion	Entrectinib, Larotrectinib, Reptrectinib
• MEK	<1%	Mutation	Trametinib
• NRG-1	<1%	Fusion	Zenocutuzumab, Afatinib
• **Total:**	**>60%**		

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Mutation positive NSCLC has a low TMB and depends on the gene alteration for tumor growth

Somatic Variants

Gene	Variant	Impact	Read Depth	Hotspot	Ploidy (VAF)	Clonality	Biallelic	Driver
EGFR *	c.2235_2249delGGAATTAA GAGAAGC	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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‘Common’ NSCLC has a high TMB and multiple pathways are involved in tumor growth

HR-Deficiency Score

0.07

Low — High

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)

MSS — MSI

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)

Low — High

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.

Low — High

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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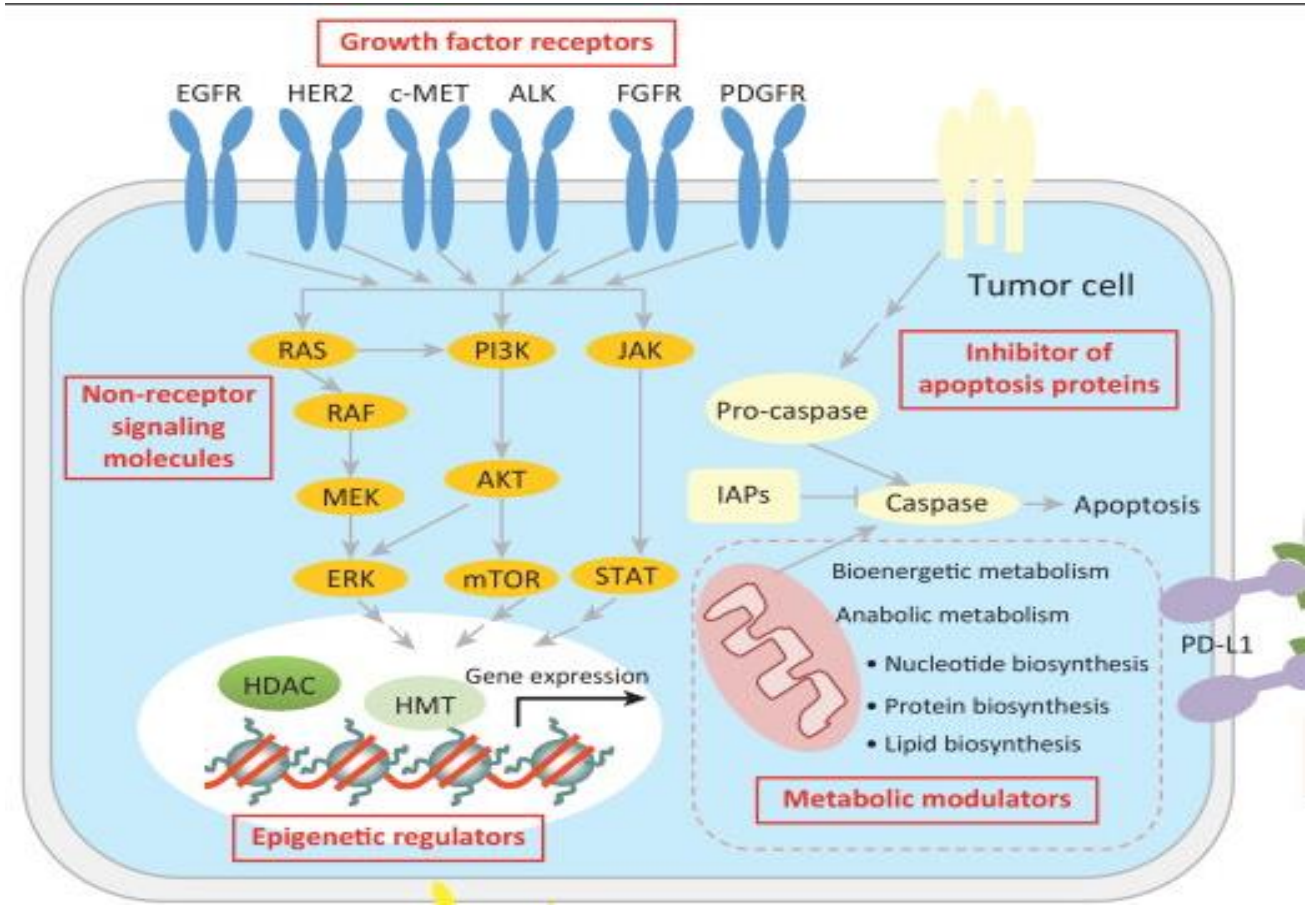
Oncogenes drive tumorigenesis



Minari R, et al. Transl Lung Cancer Res 2016

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Case 1 – Wat betekent deze vooruitgang voor patienten?

- 33 year old female patient.
- Maried, 2 young children.
- Never smoked.

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Case 1 - Introduction

- 2015-06 Stage IV NSCLC, adenocarcinoma LLL, cT2aN3M1b with bone metastases.
  - Treatment with cisplatin-pemetrexed x 4 and maintenance pemetrexed.
- 2016-03 Progressive disease.
  - Treatment with nivolumab.
- 2016-06 Progressive disease.
  - Treatment with docetaxel.
- 2017-01 Progressive disease.
  - No options, BSC
  - Referred for second opinion at AvL

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Case 1 – Second opinion at AvL

MOLECULAIRE ANALYSE (Overige Analyse)
Referentienummer: R24-0797; reden aanvraag: therapiekeuze; gevraagd onderzoek: fusiegen analyse - longcarcinoom; Analyse op RNA
Datasheet Ovm analyse panel: https://www.palga.nl/datasheet/DNA/Pathologie-DNA_NGS_RNA_ROCA_v1.pdf
Percentage neoplastische cellen: 60% (geen sampling); beoordeeld door LE; hoeveelheid RNA: voldoende

MOLECULAIR RESULTAAT (Overige Analyse)
Aangevraagde genen:
ROS1 [ENST00000368508]: CD74-ROS1 fusietranscript: CD74 [ENST00000353334] exon 6::ROS1 [ENST00000368508] exon 34 aangetoond
(99534 reads van 1661752 total mapped fusion panel reads)

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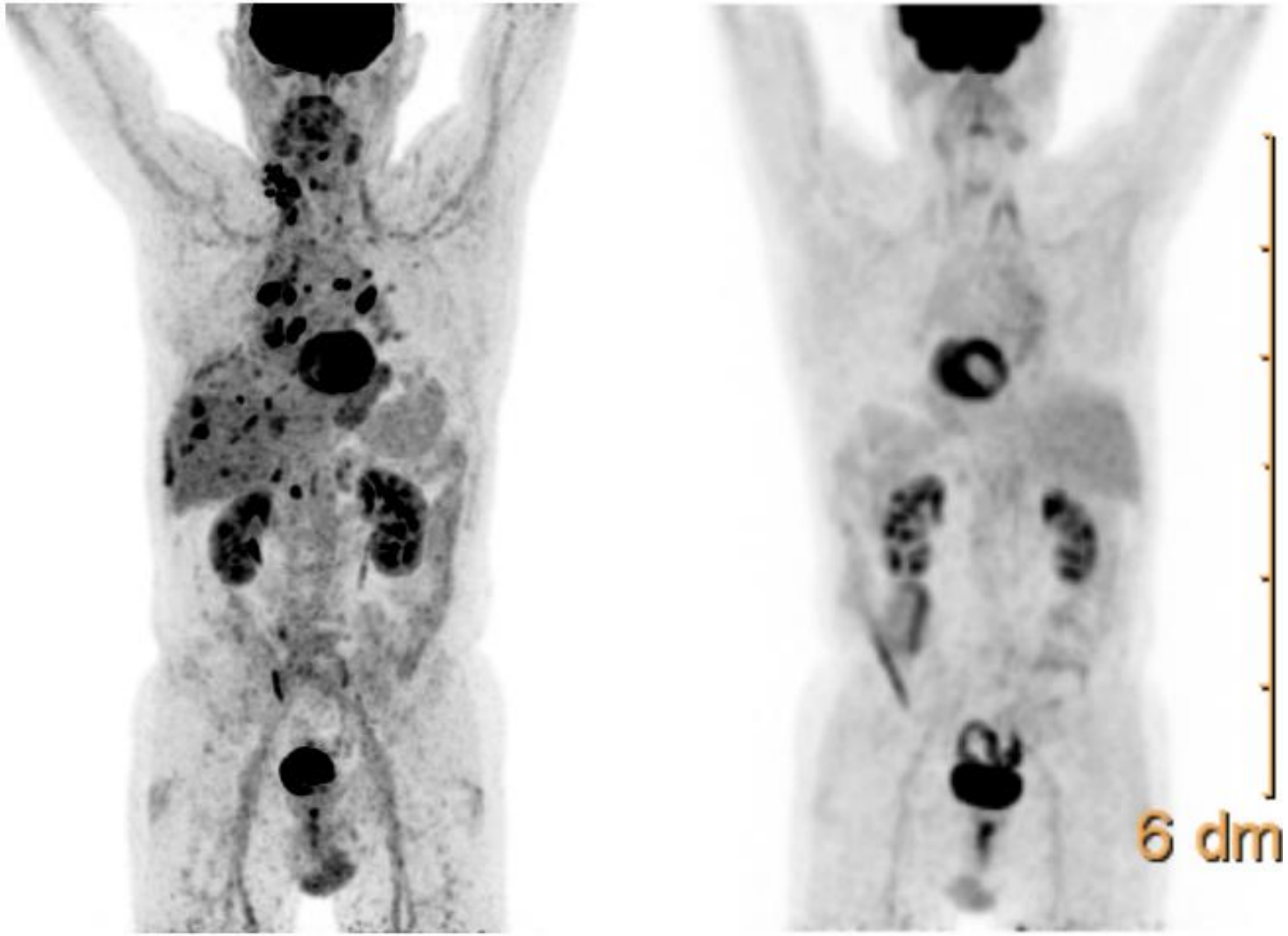
Case 1 – Treatment with crizotinib



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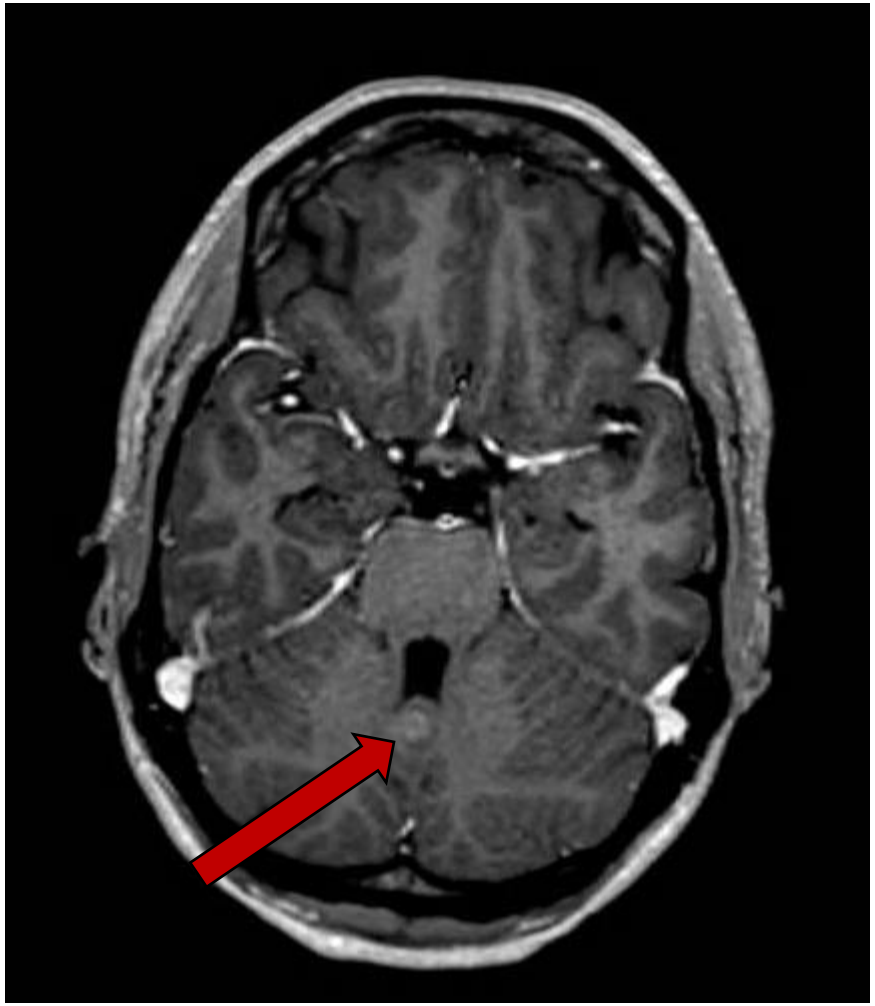
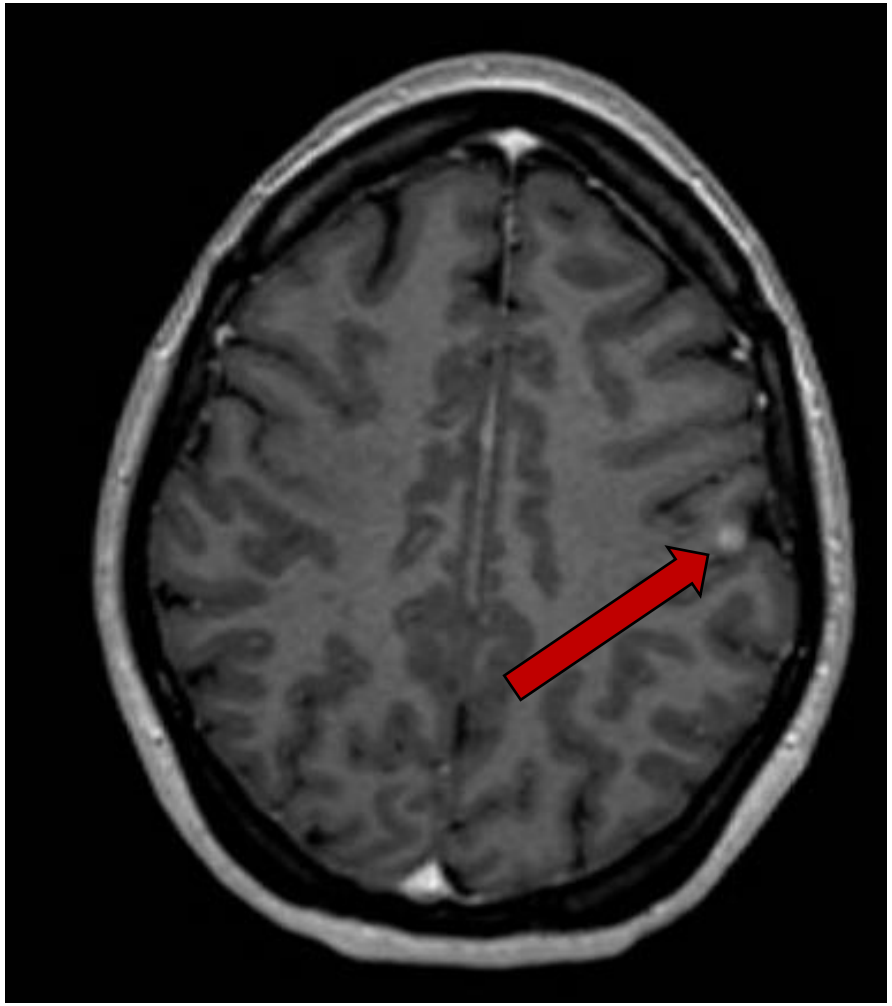
Case 1 – 6 months later





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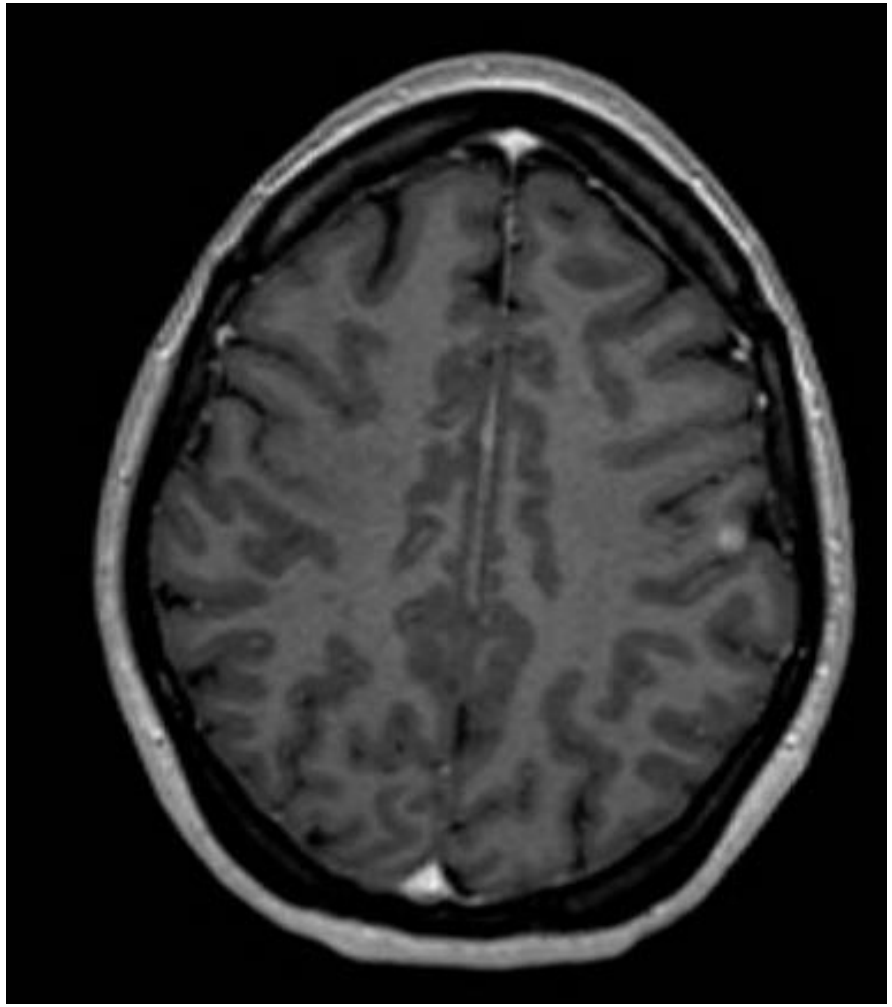
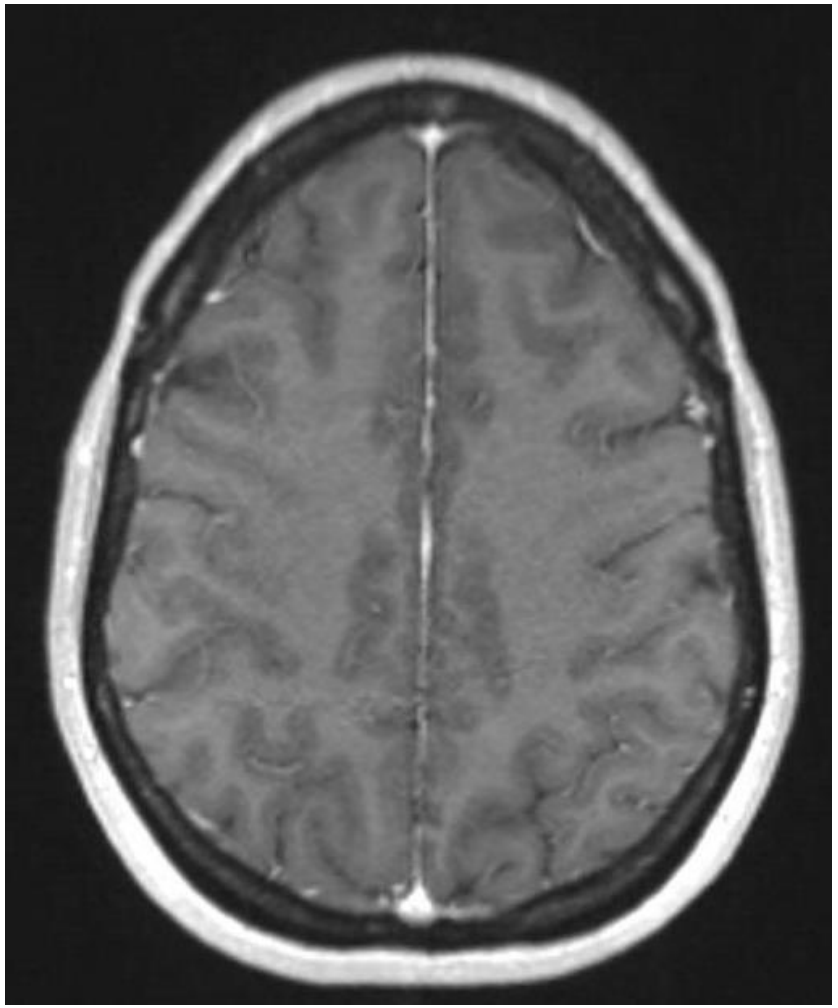
Case 1 – Switch to lorlatinib





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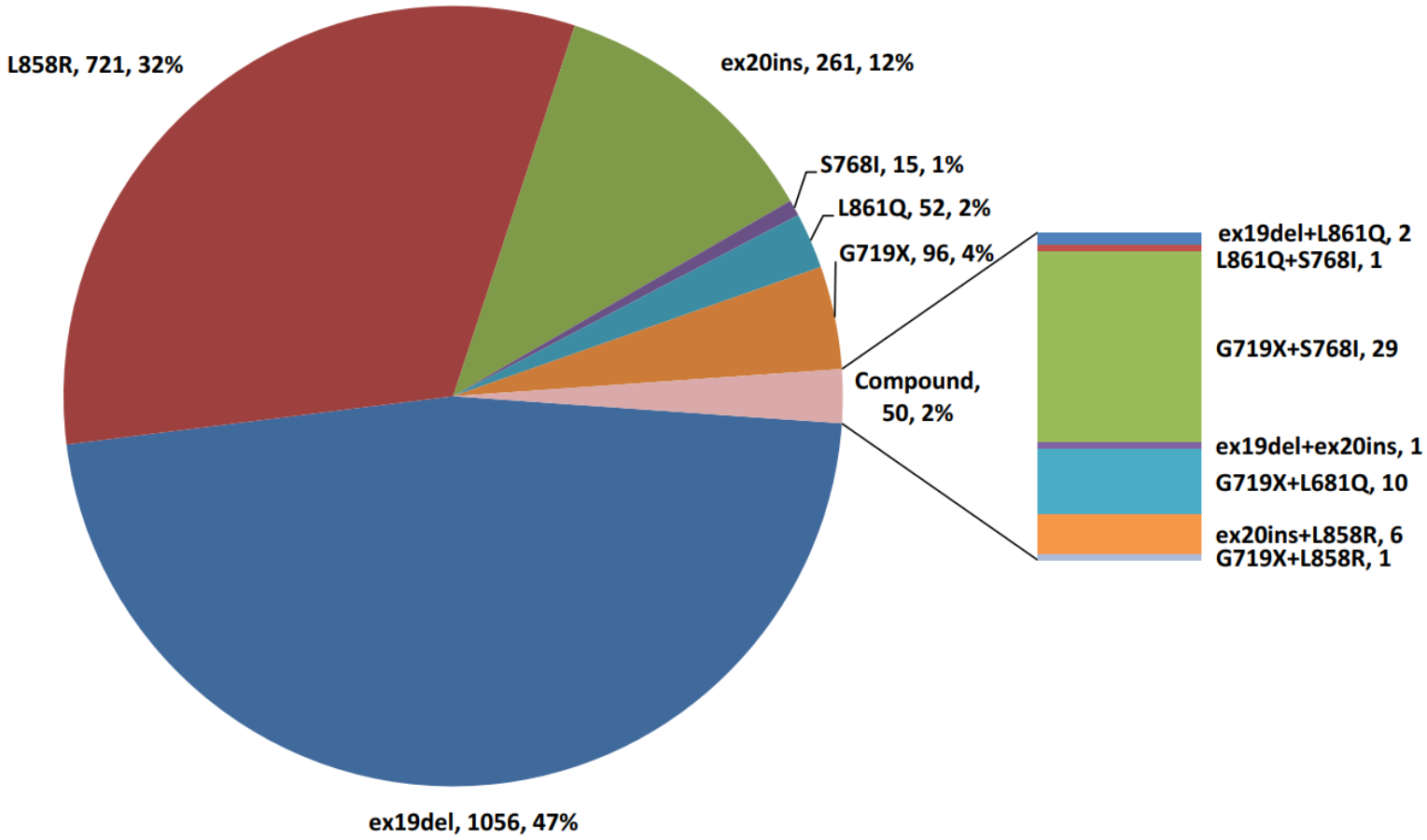
Case 1 – Current situation

- Disease in remission (both intra- and extracranially)
- Good clinical condition
- Proud mother of 2 children (now 10 and 13 years old).
- Thoracic / upper abdomen CT every 3 months and brain MRI every 6 months

Individual genes - EGFR



Riess et al, JTO 2018

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EGFR exon 19 del and exon 21 L858R

First line options

Drug	Class	ORR	mPFS (months)	Grade 3 tox
Osimertinib	EGFR TKI	80%	18.9	34%
Osimertinib + chemotherapy	EGFR TKI + chemo	83% vs 76%	25.5 vs 16.7	64% vs 27%
Lazertinib + amivantamab	*EGFR TKI + EGFR/MET mAb*	*86% vs 85%*	*23.7 vs 16.6*	*75% vs 43%*

Second line options

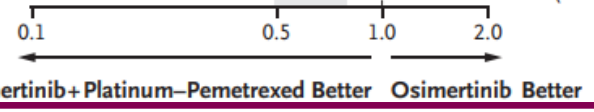
Drug	Class	ORR	mPFS (months)	Grade 3 tox
Chemotherapy + amivantamab	*EGFR TKI + chemo*	*64% vs 36%*	*6.3 vs 4.2*	*72% vs 48%*
Chemo-bev-immunotherapy	Chemo + anti-VEGF + anti-PD-L1	71% vs 42%	10.2 vs 6.9	64% vs 57%

Soria J-C, et al. N Engl J Med 2017; Planchard D, et al. N Engl J Med 2023; Cho BC, et al. N Engl J Med 2024

Passaro A, et al. Ann Oncol 2023; Reck M, et al. ELCC 2019; Ahn M-J, et al. ESMO 2023

Who needs what? - Considerations for first line

Subgroup	Osimertinib+ Platinum–Pemetrexed	Osimertinib	Hazard Ratio for Disease Progression or Death (95% CI)
	no. of events/no. of patients		
Overall			
Stratified log-rank analysis	120/279	166/278	0.62 (0.49–0.79)
Unadjusted Cox proportional-hazards analysis	120/279	166/278	0.62 (0.49–0.78)
Sex			
Male	51/106	73/109	0.54 (0.37–0.77)
Female	69/173	93/169	0.67 (0.49–0.92)
Race			
Asian Chinese	26/71	43/69	0.49 (0.30–0.81)
Asian non-Chinese	54/107	65/107	0.76 (0.53–1.09)
Non-Asian	40/101	58/102	0.55 (0.37–0.83)
Method used for tissue testing			
Central	52/121	67/119	0.73 (0.51–1.05)
Local	68/158	99/159	0.55 (0.40–0.74)
Age at screening			
<65 yr	73/174	97/166	0.59 (0.44–0.80)
≥65 yr	47/105	69/112	0.68 (0.47–0.98)
History of smoking			
Yes	43/91	57/97	0.63 (0.42–0.94)
No	77/188	109/181	0.61 (0.46–0.82)
EGFR mutation at randomization			
Exon 19 deletion	65/172	94/169	0.60 (0.44–0.83)
L858R mutation	55/106	70/107	0.63 (0.44–0.90)
WHO performance-status score			
0	48/101	57/102	0.79 (0.54–1.16)
1	72/178	109/176	0.53 (0.39–0.72)
CNS metastases at baseline			
Yes	52/116	79/110	0.47 (0.33–0.66)
No	68/163	87/168	0.75 (0.55–1.03)



Planchard D, et al. N Engl J Med 2023

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Who needs what? - Considerations for first line

Design Details

Primary Purpose : Treatment
Allocation : Randomized
Interventional Model : Crossover Assignment
Interventional Model Description: A phase 2 randomized study of osimertinib versus osimertinib plus chemotherapy for patients with metastatic EGFR-mutant lung cancers that have detectable EGFR mutant cfDNA in plasma after initiation of osimertinib treatment.
Masking : None (Open Label)

Arms and Interventions

Participant Group/Arm	Intervention/Treatment
Experimental: Osimertinib alone All patients will receive osimertinib 80mg orally daily. Subjects randomized to Arm A may be dispensed osimertinib for 2 cycles from Cycle 4 onward. Patients will be required to complete a pill diary beginning at Cycle 4.	Drug: Osimertinib • 80mg orally daily
Experimental: Osimertinib plus Carboplatin and Pemetrexed All patients will receive osimertinib 80mg orally daily. Patients receive Carboplatin (AUC 5 IV q 3 weeks) and Pemetrexed (500mg/m2 IV q 3 weeks) for a total of 4 cycles followed by pemetrexed maintenance from cycle 8 onwards. Patients will be required to complete a pill diary beginning at Cycle 4.	Drug: Osimertinib • 80mg orally daily Drug: Carboplatin • Carboplatin (AUC 5 IV q 3 weeks) Drug: Pemetrexed • Pemetrexed (500mg/m2 IV q 3 weeks) for a total of 4 cycles

Study Details | Osimertinib Alone or With Chemotherapy for EGFR-Mutant Lung Cancers | ClinicalTrials.gov

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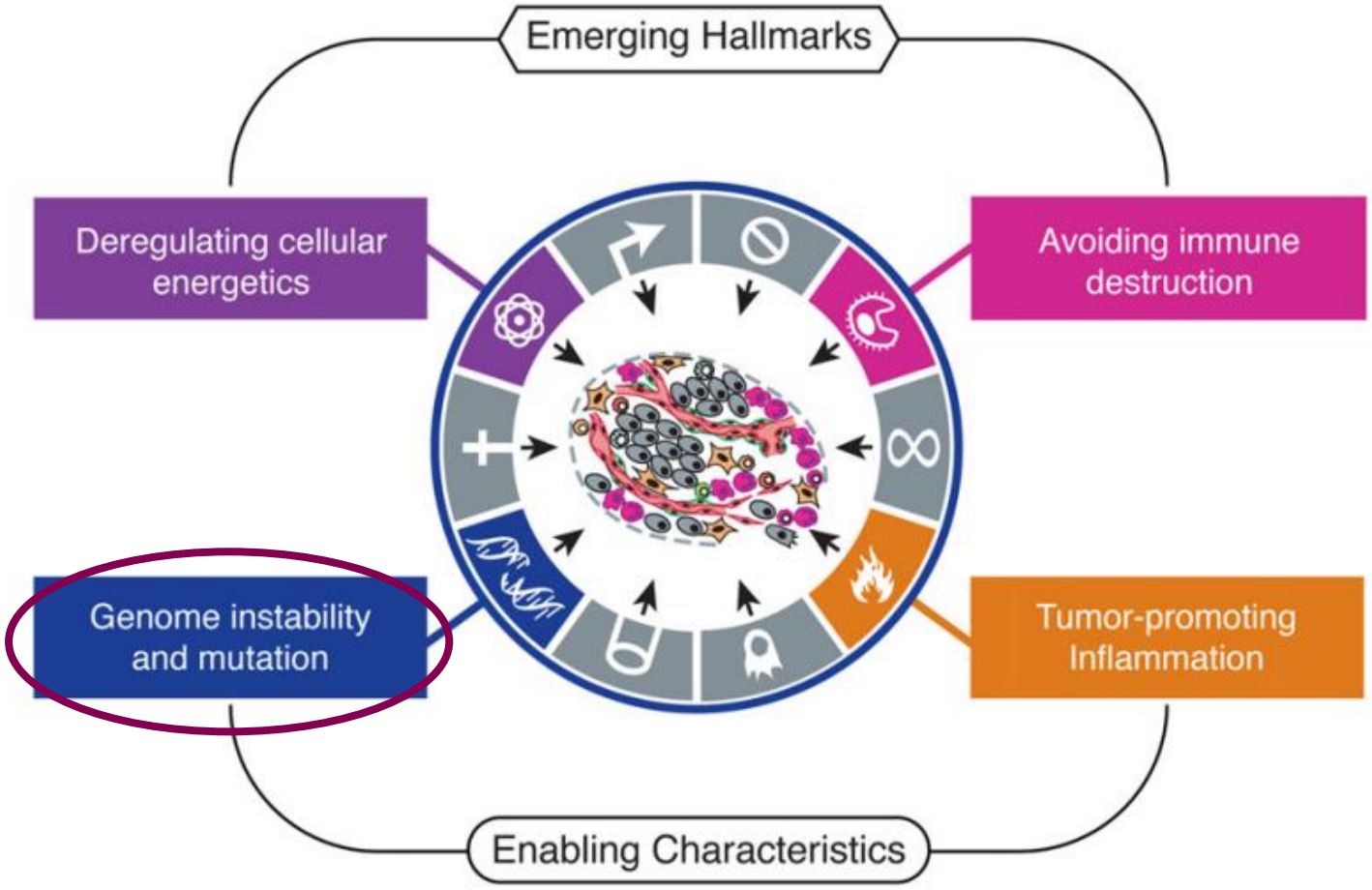
What to do when the tumor starts growing during osimertinib?

- Oligo?
- Very slow multi-site progression?
- More rapid mutisite progression?

Cancer is characterized by genomic instability



Hanahan D, et al. Cell 2011

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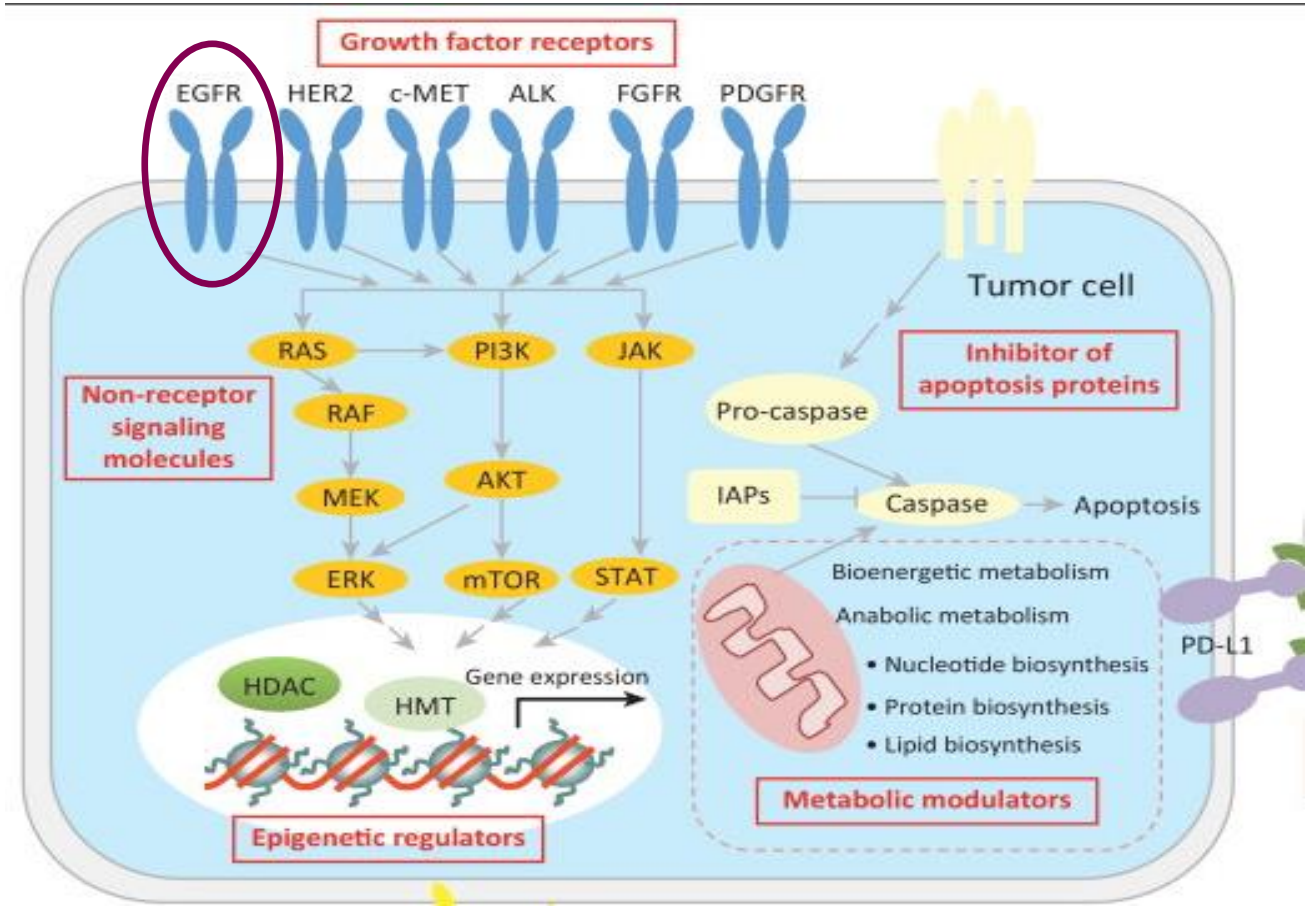
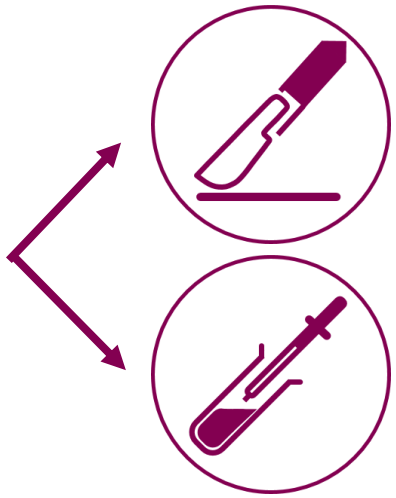
Oncogenes drive tumorigenesis, but also TKI resistance



Minari R, et al. Transl Lung Cancer Res 2016

OSIRIS: Osimertinib resistance analysis in EGFRm NSCLC that have progressed on osimertinib treatment

N = 200
PD on
osimertinib



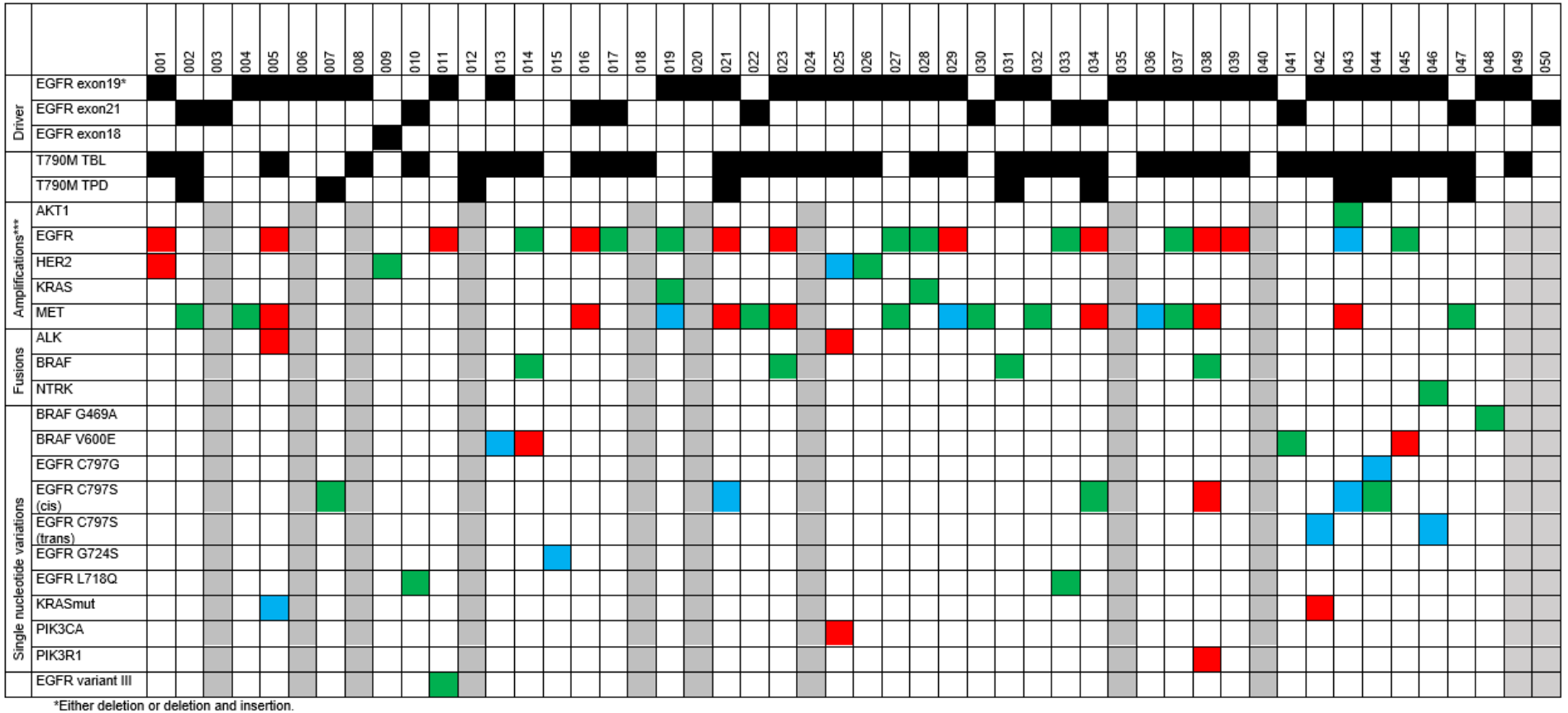
WGS on tumor biopsy
NGS on ctDNA

Sequencing report

- Identification of resistance mechanism
- Targetable yes/no
- Preferred treatment

MTB report to treating physician

OSIRIS - Results

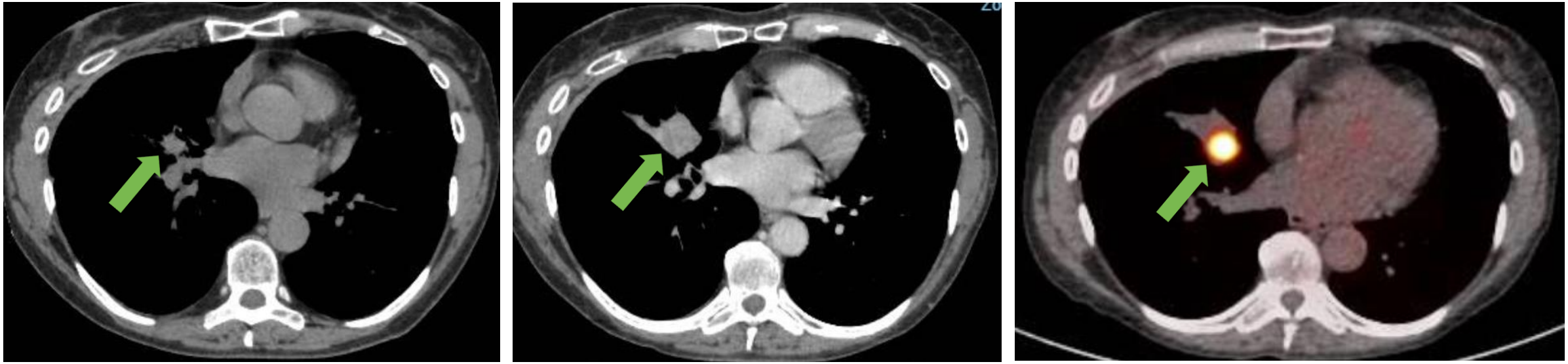


*Either deletion or deletion and insertion.
**Amplification in NGS and/or DISH for HER2 and MET.
TBL= tissue on baseline, TPD= tissue on progressive disease.

Potential resistance mechanism detected in tissue only
Potential resistance mechanism detected in plasma only
Potential resistance mechanism detected in tissue and plasma
No potential resistance mechanism detected

Case 2 – single mechanism of resistance

- 57 year old female patient, progressive after 2nd line osimertinib for EGFR exon 19 del mutation positive NSCLC

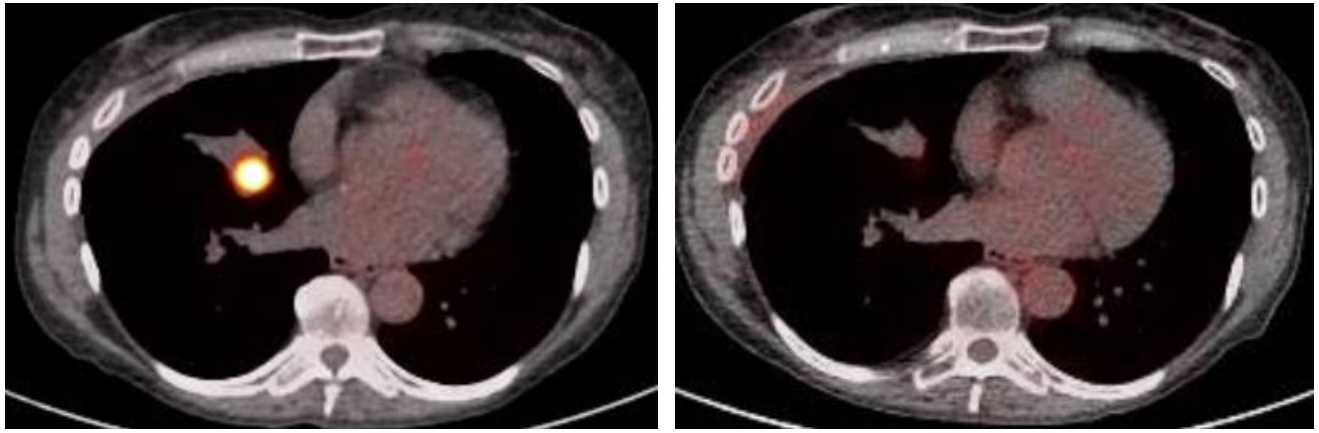


Van der Wel, et al. WCLC 2021

Case 2 – Single mechanism of resistance

Date	Biopsy	cfDNA
08-2020	EGFR exon 19 del VAF 75% High MET amplification	EGFR exon 19 del VAF 1.10%

	Baseline	1st RE	2nd RE	3rd RE	4th RE
EGFR exon 19 del (mol/ml)	27	0	0	0	0
CNV					
Treatment	Osimertinib	Osimertinib + MET TKI	Osimertinib + MET TKI	Osimertinib + MET TKI	Osimertinib + MET TKI
CT response	PD (on osimertinib)	CR	CR	CR	CR



Van der Wel, et al. WCLC 2021

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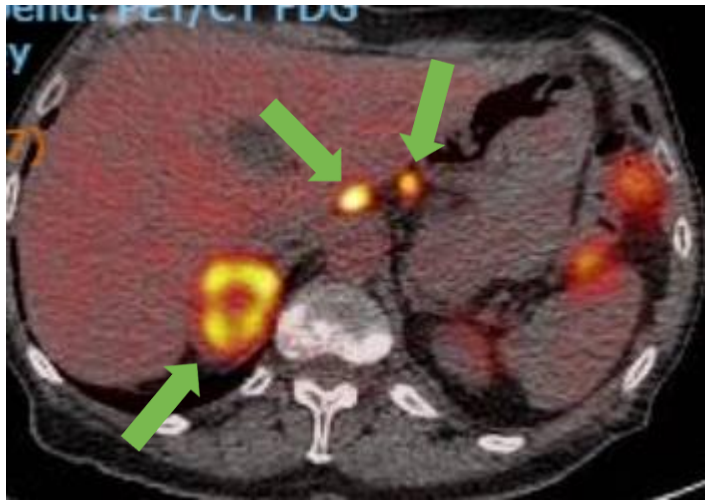
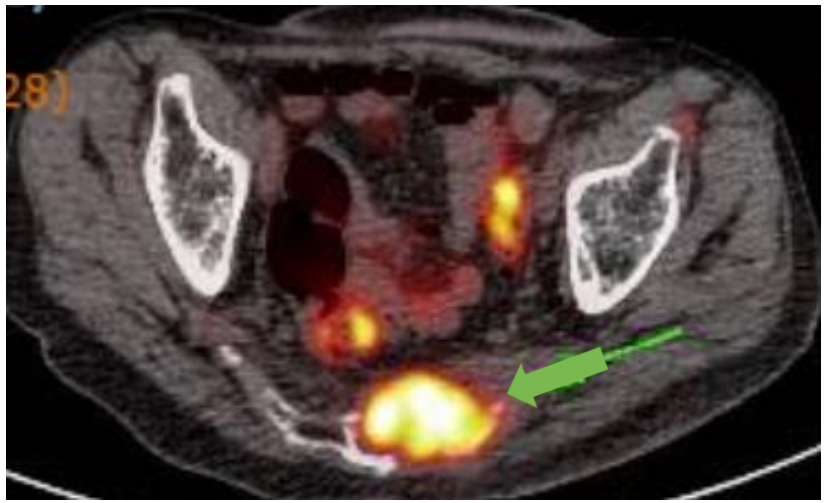
Case 3 – multiple mechanisms of resistance

- 71 year old female patient, progressive after 2nd line osimertinib for EGFR exon 19 del mutation positive NSCLC



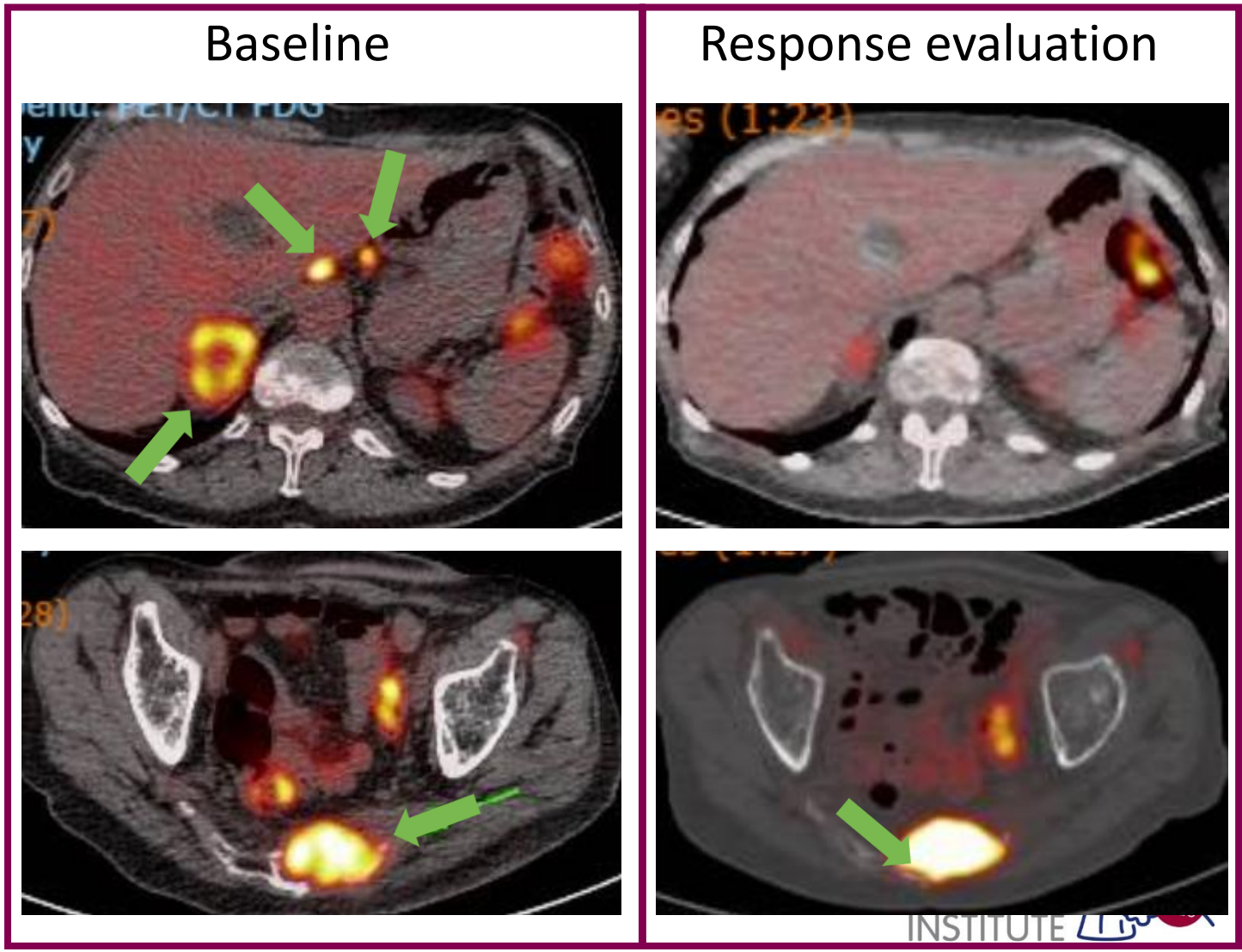


Van der Wel, et al. WCLC 2021

Case 3 – multiple mechanisms of resistance

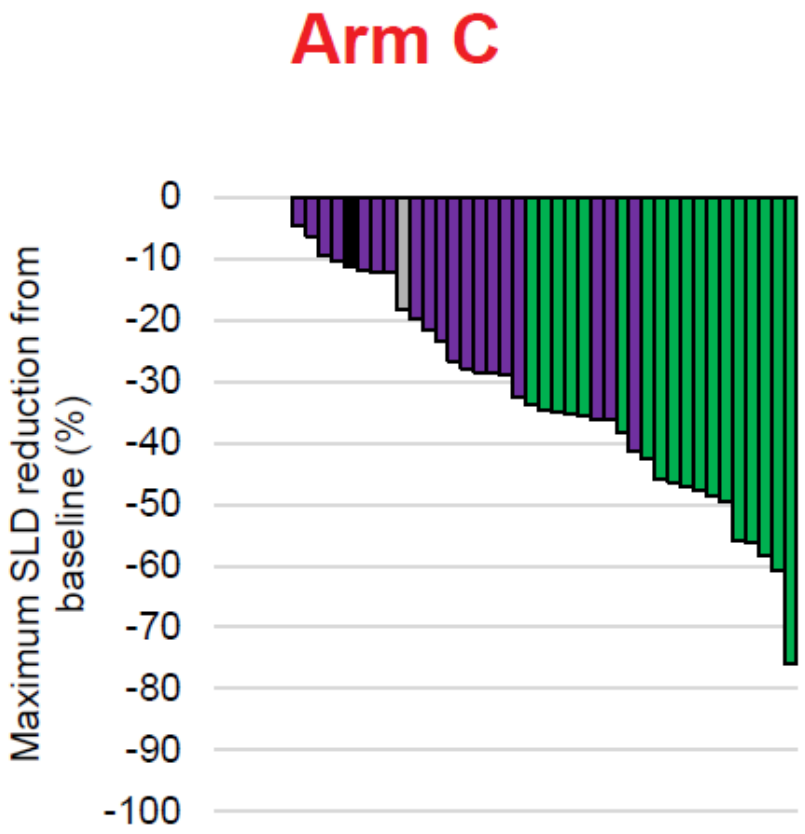
Date	Biopsy	cfDNA
10-2019	EGFR exon 19 del VAF 66% EML4-ALK fusion	EGFR exon 19 del VAF 20% EML4-ALK fusion KRAS Q61H VAF 2.94% EGFR amplification

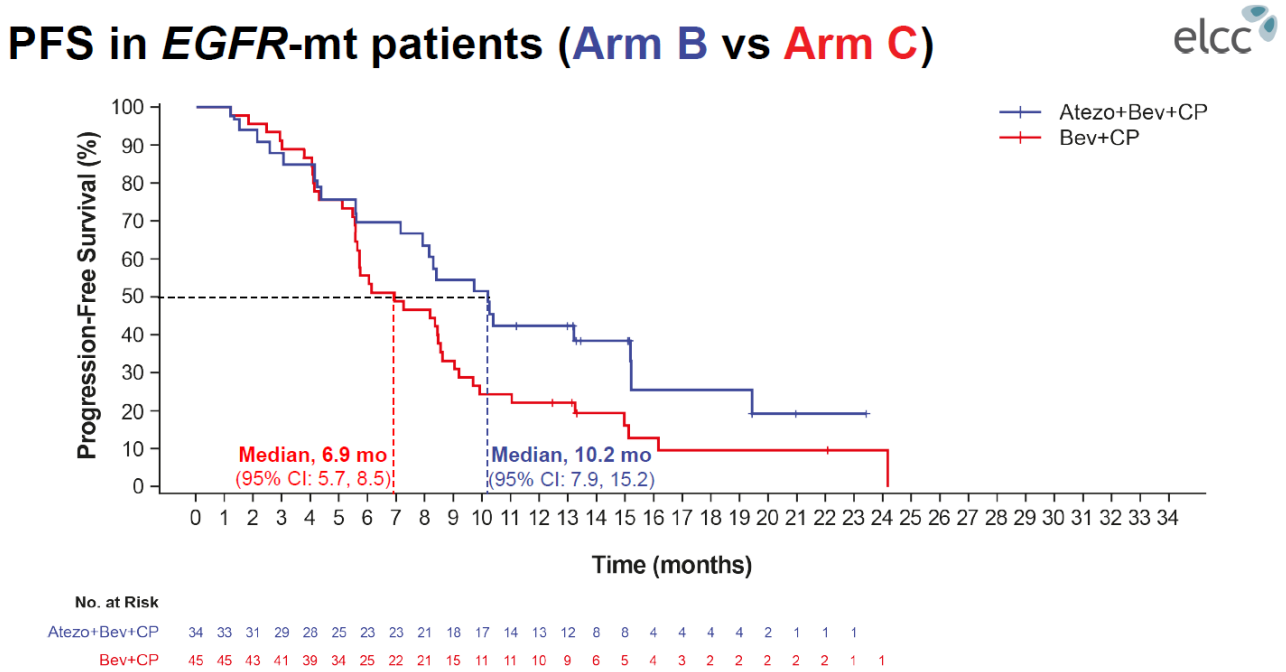
	Baseline	1st RE
EGFR exon 19 del (mol/ml)	553	200
KRAS Q61H	81	109
CNV	EGFR amp	
Fusions	EML4-ALK fusion	
Treatment	osimertinib	Osimertinib + ALK TKI
CT response	PD (on osimertinib)	Mixed response



Van der Wel, et al. WCLC 2021

Value of the addition of immunotherapy to chemotherapy





Reck M, et al. ELCC 2019

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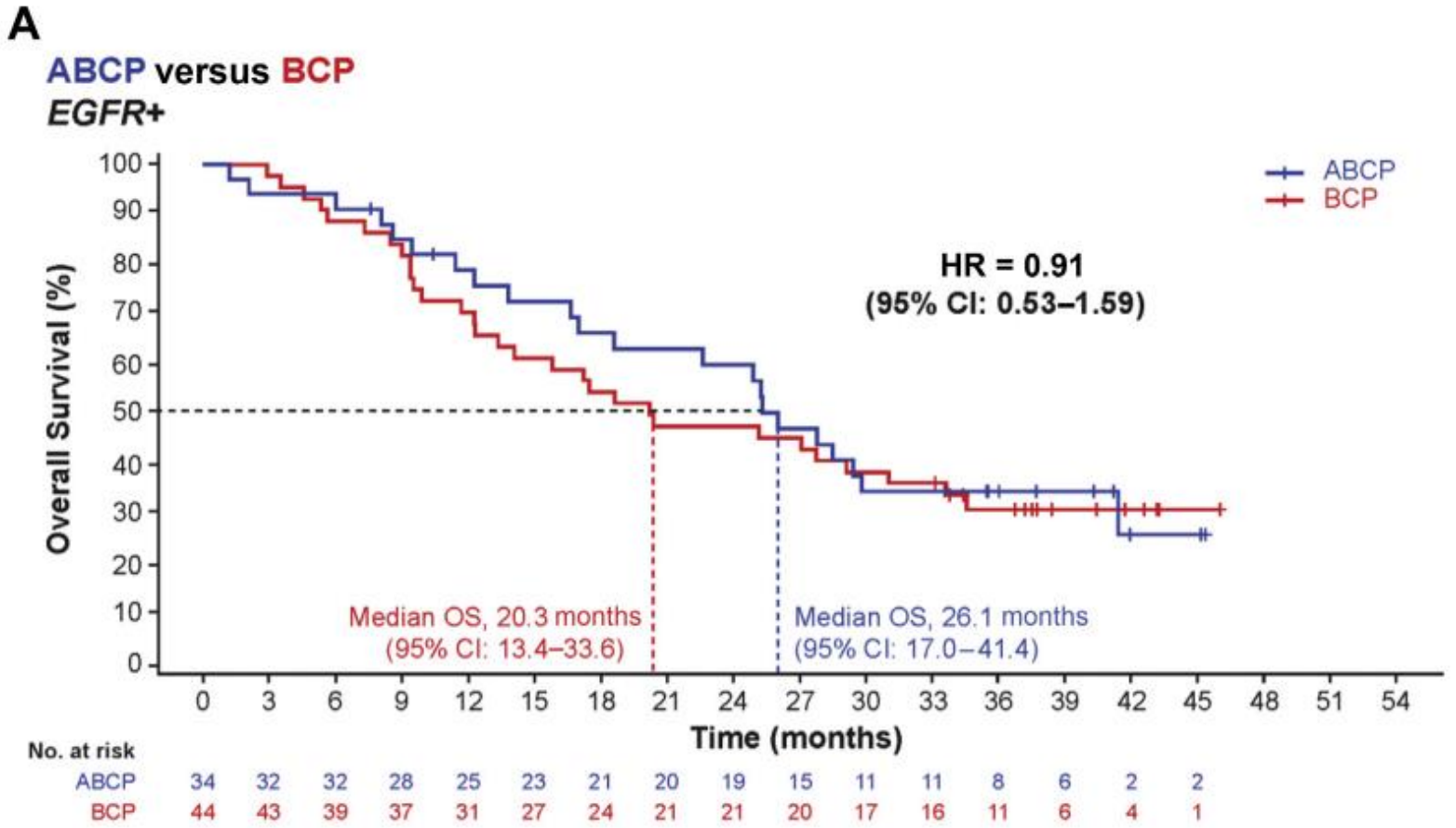
Value of the addition of immunotherapy to chemotherapy



Nogami M, et al. J Thor Oncol 2021

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EGFR exon 20 insertion mutations

EGFR exon 20 treatment in second line and beyond

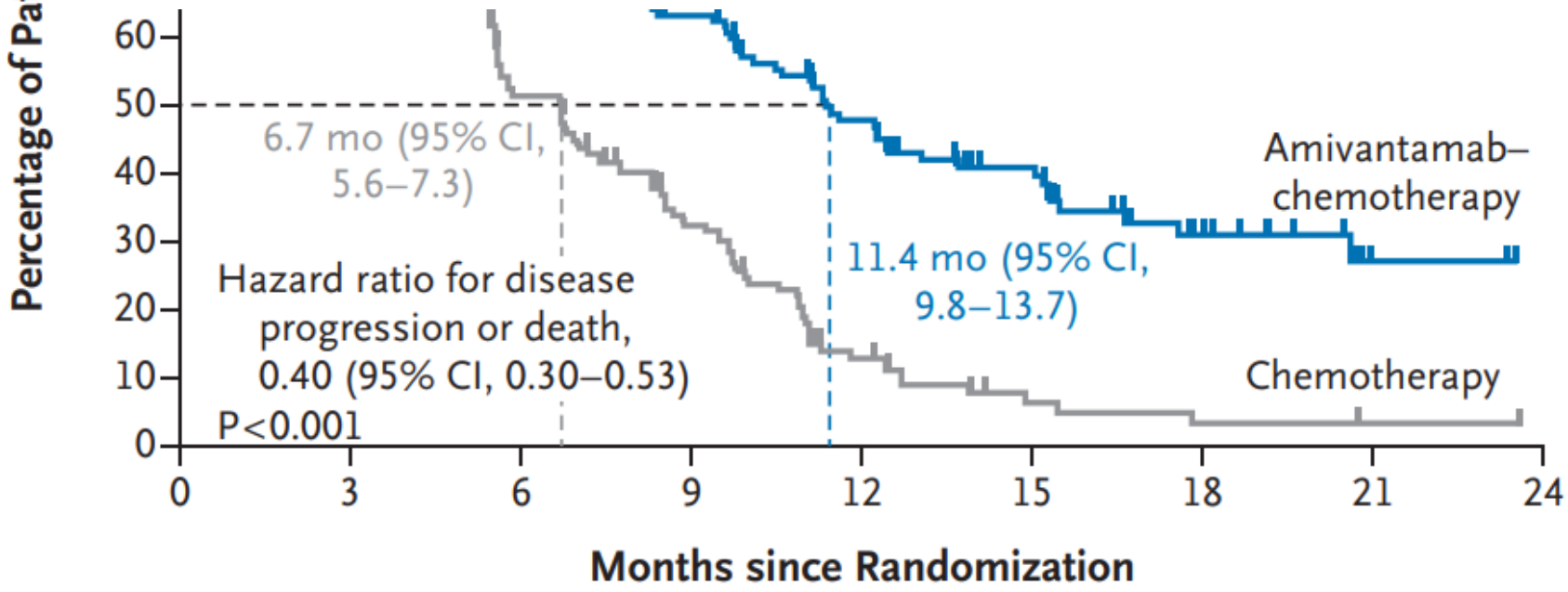
			Efficacy		Toxicity		
Drug	**Class**	**N**	**ORR (95% CI)**	**mPFS (95% CI)**	**Rash all / gr 3**	**Diarrhoea**	**Other**
Amivantamab	EGFR-MET bispecific mAb	81	40% (29-51%)	8.3 (6.5-10.0)	86% / 4%	12% / 4%	Infusion reactions, edema
Sunvozertinib	EGFR TKI	104	61% (50-71%)	n.a.	80% / 1%	20% / 3%	
Zipalertinib	EGFR TKI	73	38% (27-49%)	10 (6-12)	80% / 1%	30% / 3%	
Furmonertinib	EGFR TKI	26	46% (27-67%)	n.a.	21% / 0%	86% / 0%	

Park K, et al. JCO 2021; Zhou C, et al. JAMA Oncology 2022; Elamin YY, et al. Cancer Cell 2022; Wang M, et al. ASCO Annual Meeting 2023; Piatrowska Z, et al. JCO 2023; Han B, et al. WCLC Annual Meeting 2023

Amivantamab + chemotherapy in first line

Progression-free Survival, Blinded Independent Central Review

Adverse Events	Amivantamab–Chemotherapy (N=151)		Chemotherapy (N=155)	
	All Grades	Grade ≥3	All Grades	Grade ≥3
	number of patients (percent)			
Any event	151 (100)	114 (75)	152 (98)	83 (54)



Zhou C, et al. NEJM 2023

NETHERLANDS CANCER INSTITUTE
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EGFR exon 20 TKIs in first line

Drug	Class	N	ORR (95% CI)	mPFS (95% CI)
Sunvozertinib	EGFR TKI	104	71.4% (n.a.)	n.a.
Furmonertinib	EGFR TKI	26	78.6% (59-72%)	n.a.

Park K, et al. JCO 2021; Zhou C, et al. JAMA Oncology 2022; Elamin YY, et al. Cancer Cell 2022; Wang M, et al. ASCO Annual Meeting 2023; Piatrowska Z, et al. JCO 2023; Han B, et al. WCLC Annual Meeting 2023

Phase 3 trial in EGFR exon 20 ins pos NSCLC

- Amivantamab + platinum-pemetrexed vs platinum-pemetrexed
- Zipalertinib + platinum-pemetrexed vs platinum-pemetrexed
- Sunvozertinib vs platinum-pemetrexed
- Furmonertinib vs platinum-pemetrexed

Phase 3 trial in EGFR exon 20 ins pos NSCLC

- Amivantamab + platinum-pemetrexed vs platinum-pemetrexed
- Zipalertinib + platinum-pemetrexed vs platinum-pemetrexed
- Sunvozertinib vs platinum-pemetrexed
- Furmonertinib vs platinum-pemetrexed

- Who needs what in first line?
- Differences between TKI's with respect to CNS activity?
- Can we sequence these targeted drugs?
- Do we need to identify resistance mechanisms?
- Cross-trial comparison
- Amivantamab + TKI?

Zipalertinib in EGFR exon 20 ins positive NSCLC after prior amivantamab

Key eligibility criteria

- Locally advanced or metastatic NSCLC
- Documented *EGFR* exon 20 insertion
- *Progressed on or after amivantamab*
- ECOG PS 0 or 1
- Stable/asymptomatic brain metastases allowed

→

Zipalertinib
100 mg BID oral

Primary endpoint:

- ORR and DOR per RECIST v1.1

Secondary endpoints:

- Safety
- PFS
- DCR

Passaro A, et al. ESMO Annual Meeting 2024

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1913 2013

Zipalertinib in EGFR exon 20 ins positive NSCLC after prior amivantamab

Statistics, n (%) [95% CI]	Ami only (n=18)	Ami + other ex20ins (n=12)	Total (N=30)
Confirmed ORR	9 (50.0) [26.0–74.0]	3 (25.0) [5.5–57.2]	12 (40.0) [22.7–59.4]
CR	1 (5.6) [0.1–27.3]	0	1 (3.3) [0.1–17.2]
PR	8 (44.4) [21.5–69.2]	3 (25.0) [5.5–57.2]	11 (36.7) [19.9–56.1]
SD	7 (38.9) [17.3–64.3]	8 (66.7) [34.9–90.1]	15 (50.0) [31.3–68.7]
DCR (CR+PR+SD)	16 (88.9) [65.3–98.6]	11 (91.7) [61.5–99.8]	27 (90.0) [73.5–97.9]

- Median PFS: 9.7 months (90% CI: 4.1–NE)

Passaro A, et al. ESMO Annual Meeting 2024

Individual genes – ALK

ALK fusion

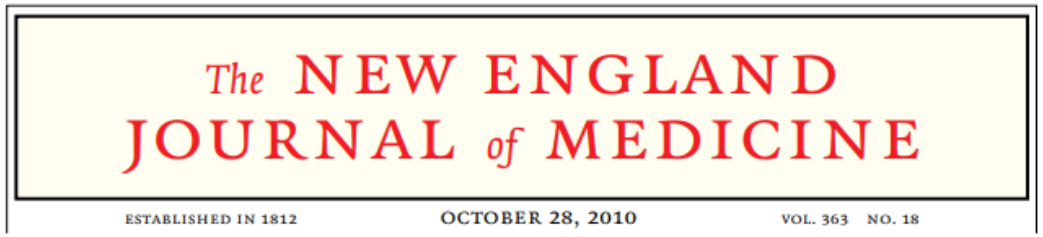
Drug	ORR	mPFS (months)	Grade 3 tox
Alectinib	83% vs 76%	34.8 vs 10.9 4-year PFS 44%	41% vs 50%
Brigatinib	71% vs 60%	24.0 vs 11.1	70% vs 56%
Lorlatinib	76% vs 58%	NR vs 9.1 5-year PFS 60%	72% vs 56%

Peters S, et al. N Engl J Med 2017; Mok T, et al. Ann Oncol 2020; Camidge DR, et al. N Engl J Med 2018; Camidge DR, et al. J Thorac Oncol 2021; Shaw AT, et al. N Engl J Med 2020;

Solomon BJ, et al. J Clin Oncol 2024

ALK – patient journey benefiting from drug development

- 61 year old male patient (now 73) with stage IV ALK fusion positive NSCLC
  - 08-2012: Diagnosis. Chemotherapy
  - 09-2013: PD. ALK fusion detected. Crizotinib



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 OCTOBER 28, 2010 VOL. 363 NO. 18

Anaplastic Lymphoma Kinase Inhibition in Non–Small-Cell Lung Cancer

Eunice L. Kwak, M.D., Ph.D., Yung-Jue Bang, M.D., Ph.D., D. Ross Camidge, M.D., Ph.D., Alice T. Shaw, M.D., Ph.D., Benjamin Solomon, M.B., B.S., Ph.D., Robert G. Maki, M.D., Ph.D., Sai-Hong I. Ou, M.D., Ph.D., Bruce J. Dezube, M.D., Pasi A. Jänne, M.D., Ph.D., Daniel B. Costa, M.D., Ph.D., Marileila Varella-Garcia, Ph.D., Woo-Ho Kim, M.D., Thomas J. Lynch, M.D., Panos Fidias, M.D., Hannah Stubbs, M.S., Jeffrey A. Engelman, M.D., Ph.D., Lecia V. Sequist, M.D., M.P.H., WeiWei Tan, Ph.D., Leena Gandhi, M.D., Ph.D., Mari Mino-Kenudson, M.D., Greg C. Wei, Ph.D., S. Martin Shreeve, M.D., Ph.D., Mark J. Ratain, M.D., Jeffrey Settleman, Ph.D., James G. Christensen, Ph.D., Daniel A. Haber, M.D., Ph.D., Keith Wilner, Ph.D., Ravi Salgia, M.D., Ph.D., Geoffrey I. Shapiro, M.D., Ph.D., Jeffrey W. Clark, M.D., and A. John Iafrate, M.D., Ph.D.

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ALK – patient journey benefiting from drug development

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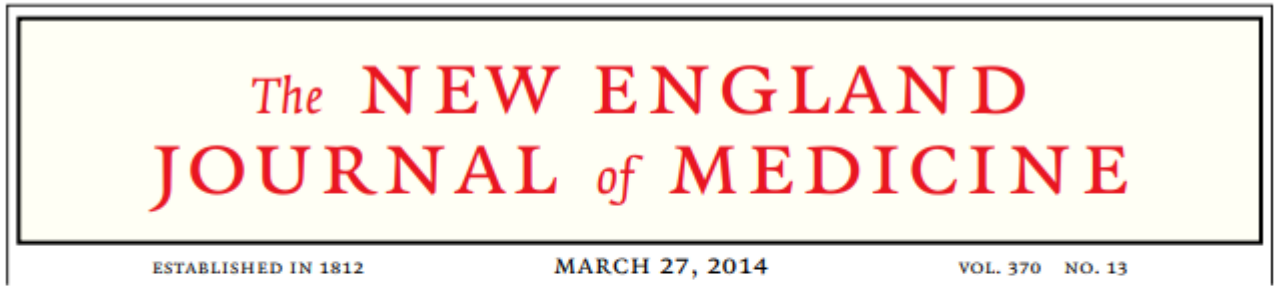

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MARCH 27, 2014 VOL. 370 NO. 13

Ceritinib in *ALK*-Rearranged Non–Small-Cell Lung Cancer

Alice T. Shaw, M.D., Ph.D., Dong-Wan Kim, M.D., Ph.D., Ranee Mehra, M.D., Daniel S.W. Tan, M.B., B.S., Enriqueta Felip, M.D., Ph.D., Laura Q.M. Chow, M.D., D. Ross Camidge, M.D., Ph.D., Johan Vansteenkiste, M.D., Ph.D., Sunil Sharma, M.D., Tommaso De Pas, M.D., Gregory J. Riely, M.D., Ph.D., Benjamin J. Solomon, M.B., B.S., Ph.D., Juergen Wolf, M.D., Ph.D., Michael Thomas, M.D., Martin Schuler, M.D., Geoffrey Liu, M.D., Armando Santoro, M.D., Yvonne Y. Lau, Ph.D., Meredith Goldwasser, Sc.D., Anthony L. Boral, M.D., Ph.D., and Jeffrey A. Engelman, M.D., Ph.D.

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  - 06-2020: PD. ALK F1174C mutation. Brigatinib

Activity and safety of brigatinib in *ALK*-rearranged non-small-cell lung cancer and other malignancies: a single-arm, open-label, phase 1/2 trial

Scott N Gettinger, Lyudmila A Bazhenova, Corey J Langer, Ravi Salgia, Kathryn A Gold, Rafael Rosell, Alice T Shaw, Glen J Weiss, Meera Tugnait, Narayana I Narasimhan, David J Dorer, David Kerstein, Victor M Rivera, Timothy Clackson, Frank G Haluska, David Ross Camidge

Summary

Background Anaplastic lymphoma kinase (*ALK*) gene rearrangements are oncogenic drivers of non-small-cell lung cancer (NSCLC). Brigatinib (AP26113) is an investigational ALK inhibitor with potent preclinical activity against ALK mutants resistant to crizotinib and other ALK inhibitors. We aimed to assess brigatinib in patients with advanced malignancies, particularly *ALK*-rearranged NSCLC.

Lancet Oncol 2016; 17: 1683–96
Published Online
November 7, 2016
http://dx.doi.org/10.1016/
S1470-2045(16)30392-8

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1913 2013

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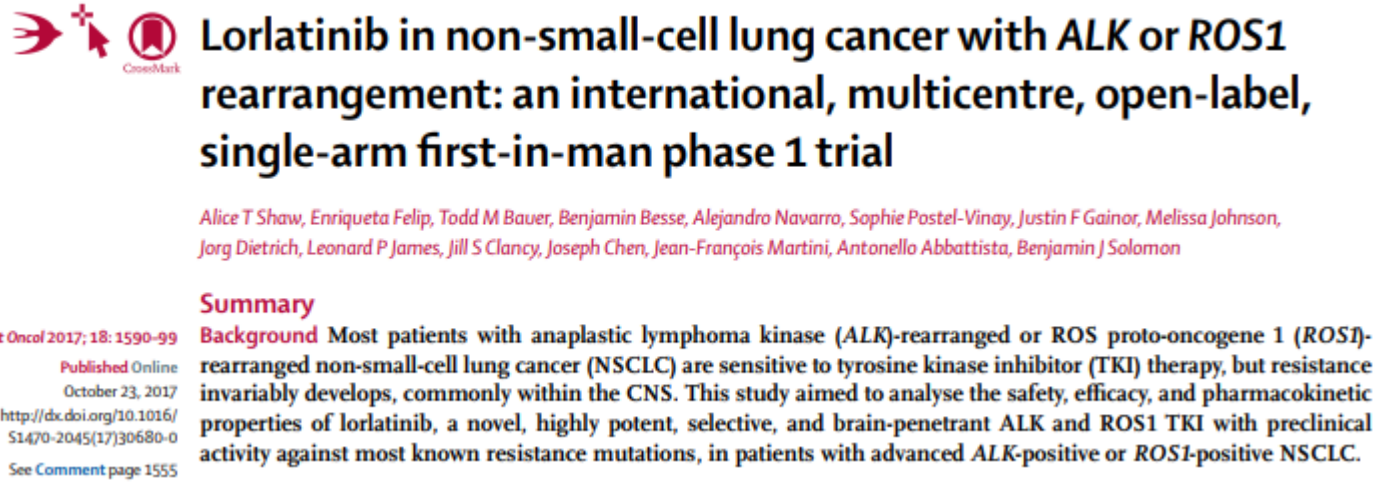
  - 06-2020: PD. ALK F1174C mutation. Brigatinib
  - 02-2021: PD. No biopsy possible. Lorlatinib



Lorlatinib in non-small-cell lung cancer with *ALK* or *ROS1* rearrangement: an international, multicentre, open-label, single-arm first-in-man phase 1 trial

Alice T Shaw, Enriqueta Felip, Todd M Bauer, Benjamin Besse, Alejandro Navarro, Sophie Postel-Vinay, Justin F Gainor, Melissa Johnson, Jorg Dietrich, Leonard P James, Jill S Clancy, Joseph Chen, Jean-François Martini, Antonello Abbattista, Benjamin J Solomon

Lancet Oncol 2017; 18: 1590–99
Published Online
October 23, 2017
http://dx.doi.org/10.1016/S1470-2045(17)30680-0
See Comment page 1555

Summary

Background Most patients with anaplastic lymphoma kinase (*ALK*)-rearranged or ROS proto-oncogene 1 (*ROS1*)-rearranged non-small-cell lung cancer (NSCLC) are sensitive to tyrosine kinase inhibitor (TKI) therapy, but resistance invariably develops, commonly within the CNS. This study aimed to analyse the safety, efficacy, and pharmacokinetic properties of lorlatinib, a novel, highly potent, selective, and brain-penetrant ALK and ROS1 TKI with preclinical activity against most known resistance mutations, in patients with advanced *ALK*-positive or *ROS1*-positive NSCLC.

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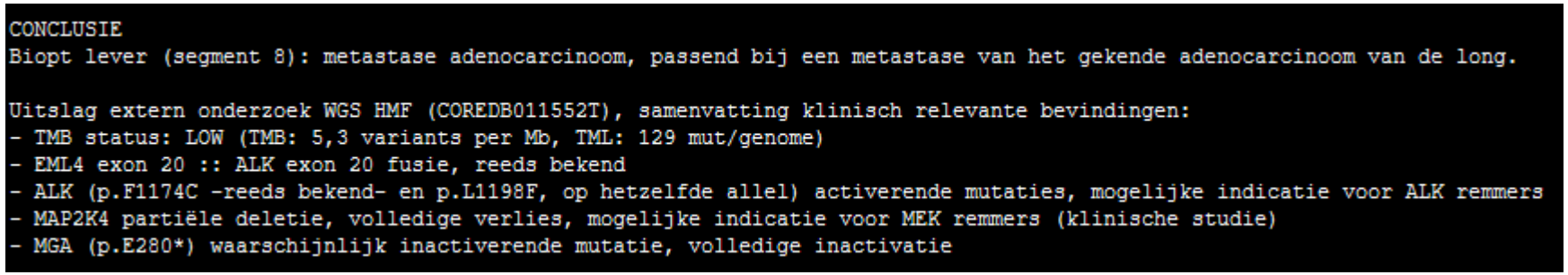
  - 02-2021: PD. No biopsy possible. Lorlatinib
  - 07-2024: PD. Biopsy: ALK F1174C + L1198F mutation.



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CONCLUSIE
Biopt lever (segment 8): metastase adenocarcinoom, passend bij een metastase van het gekende adenocarcinoom van de long.

Uitslag extern onderzoek WGS HMF (COREDB011552T), samenvatting klinisch relevante bevindingen:
- TMB status: LOW (TMB: 5,3 variants per Mb, TML: 129 mut/genome)
- EML4 exon 20 :: ALK exon 20 fusie, reeds bekend
- ALK (p.F1174C -reeds bekend- en p.L1198F, op hetzelfde allel) activerende mutaties, mogelijke indicatie voor ALK remmers
- MAP2K4 partiële deletie, volledige verlies, mogelijke indicatie voor MEK remmers (klinische studie)
- MGA (p.E280*) waarschijnlijk inactiverende mutatie, volledige inactivatie
```

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ALK – patient journey benefiting from drug development

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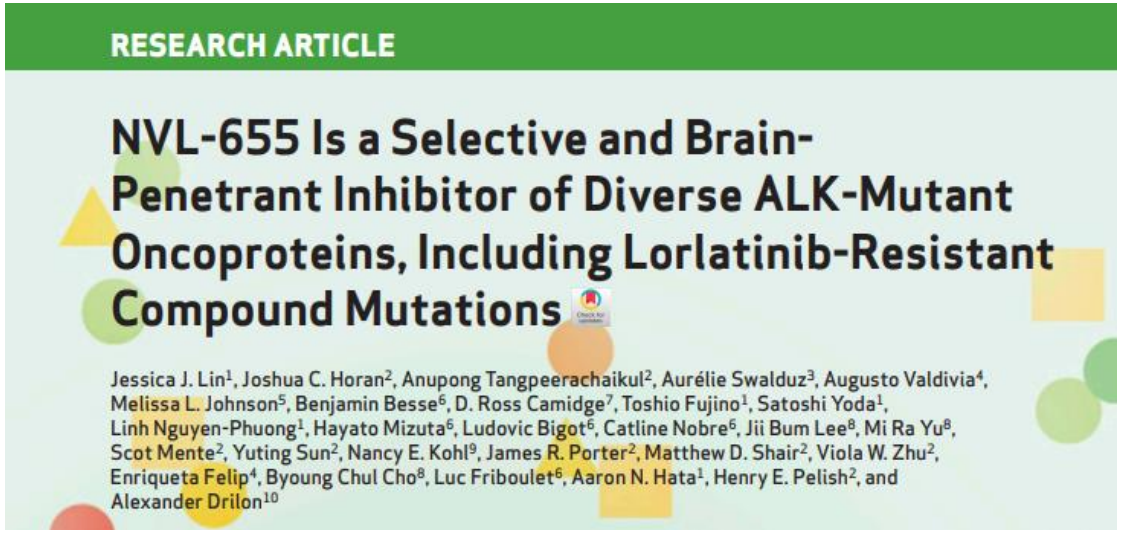
RESEARCH ARTICLE

NVL-655 Is a Selective and Brain-Penetrant Inhibitor of Diverse ALK-Mutant Oncoproteins, Including Lorlatinib-Resistant Compound Mutations

Jessica J. Lin[1], Joshua C. Horan[2], Anupong Tangpeerachaikul[2], Aurélie Swalduz[3], Augusto Valdivia[4], Melissa L. Johnson[5], Benjamin Besse[6], D. Ross Camidge[7], Toshio Fujino[1], Satoshi Yoda[1], Linh Nguyen-Phuong[1], Hayato Mizuta[6], Ludovic Bigot[6], Catline Nobre[6], Jii Bum Lee[8], Mi Ra Yu[8], Scot Mente[2], Yuting Sun[2], Nancy E. Kohl[9], James R. Porter[2], Matthew D. Shair[2], Viola W. Zhu[2], Enriqueta Felip[4], Byoung Chul Cho[8], Luc Friboulet[6], Aaron N. Hata[1], Henry E. Pelish[2], and Alexander Drilon[10]

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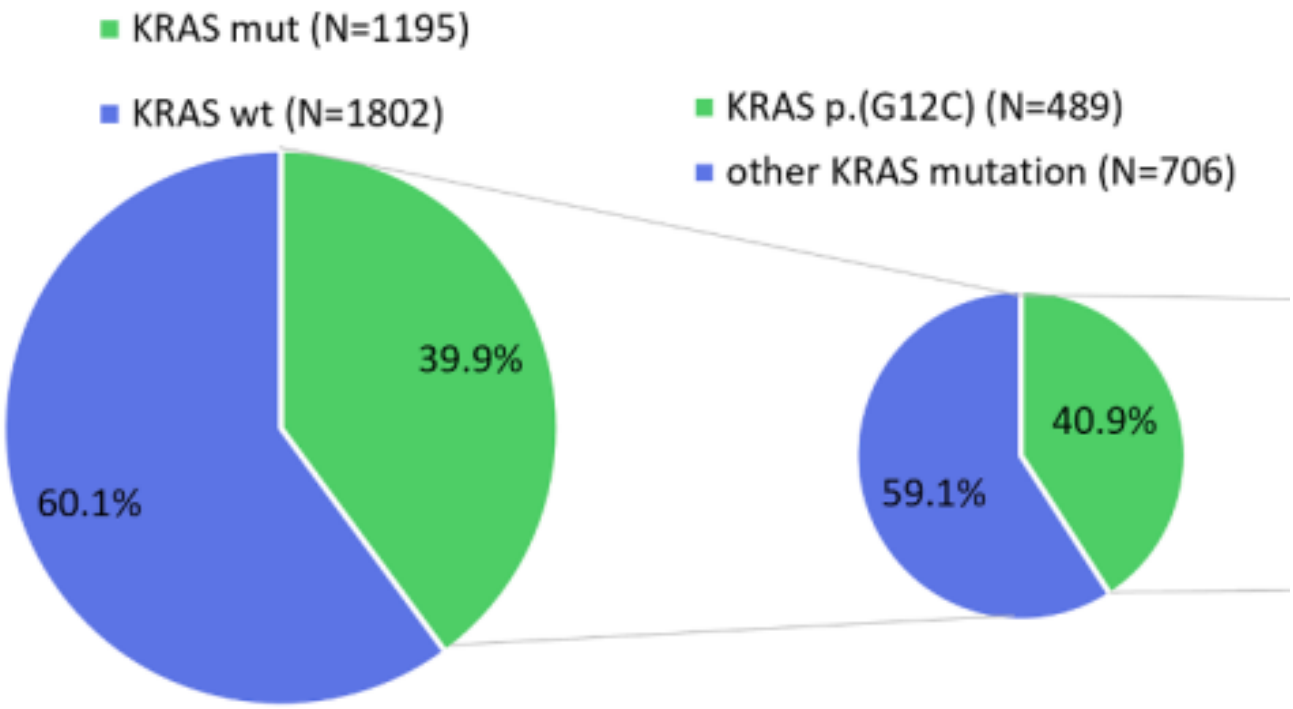
Individual genes – KRAS

KRAS



1. Garcia BNC, et al. Lung Cancer 2022

KRAS – How does it compare to other molecular drivers?

- KRAS positive NSCLC is not the typical driver
  - Heavily associated with smoking
  - High TMB
  - Many co-mutations
  - Sensitive to PD-(L)1 checkpoint inhibition

KRAS G12C-GDP off inhibitors

- LY3537982 (olomorasib)
- GDC-6036 (divarasib)
- D-1553 (garsorasib)
- HBI-2438
- JDQ443 (opnurasib)
- JAB-21822
- HS-10370
- IBI-351 (GFH925)
- BI-1823911
- MK-1084
- Etc, etc

- Differences in?
  - Potency to inhibit KRAS G12C
  - CNS activity
  - Tolerability as monotherapy
  - Tolerability in combinations

KRAS G12C-GTP on and pan-RAS inhibitors

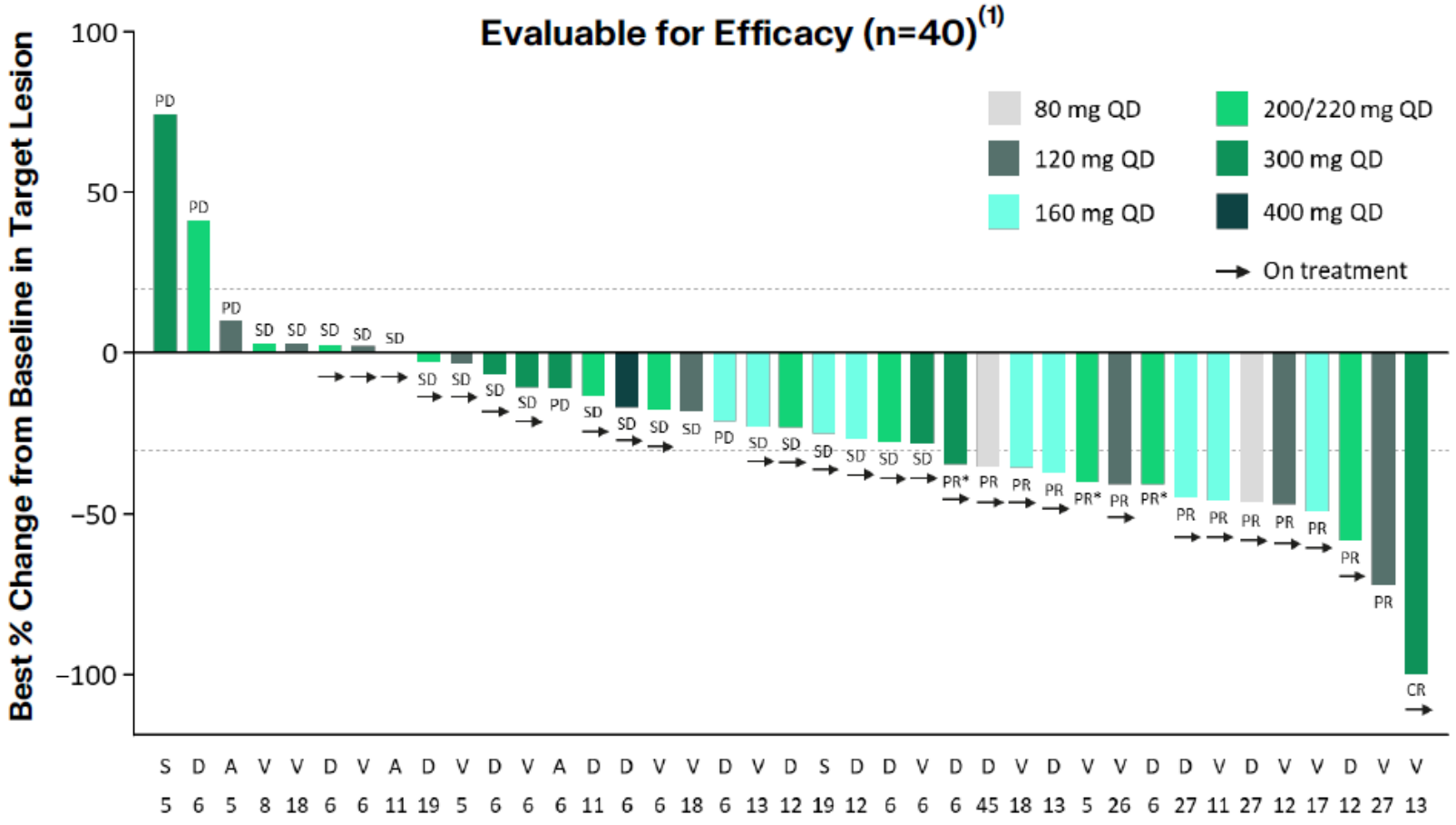
Compound	Characteristics	Subjects	Efficacy
• RMC-6291 G12C-GDP inh	KRAS G12C-GTP inh	KRAS G12C	ORR 50% (5/10) in KRAS pretreated pts ORR 43% (3/7) in KRAS G12C-GDP inh naïve pts
• BBO-8520	KRAS G12C-GTP inh KRAS G12C-GDP inh		No clinical data available yet
• BI-2865	KRAS pan-GDP inh	KRAS pan	No clinical data available yet
• MRTX-1133	KRAS G12D-GDP inh	KRAS G12D	No clinical data available yet
•	KRAS G12D-GTP inh		
• RMC-6236	KRAS pan-GTP inh	KRAS G12X (non G12C)	ORR 38% (15/40)
• Etc, etc			

Janne PA, et al. AACR-NCI-EORTC International Conference on Molecular Targets and Cancer Therapeutics 2023;

Arbour KC, et al. ESMO Annual meeting 2023

Pan-RAS inhibitors

KRAS G12X NSCLC: Best Overall Response to RMC-6236



RMC-6236-001: Clinical Activity in KRAS G12X NSCLC[2]	
Best overall response, n (%)	
Complete response	1 (3)
Partial response	14 (35)
Stable disease	19 (48)
Progressive disease	5 (13)
Not evaluable[3]	1 (3)
ORR, n (%)	15 (38)
Confirmed, n	12
DCR (CR+PR+SD), n (%)	34 (85)
SOC Benchmark[4]	
Docetaxel, ORR (%)	(13)
DCR (%)	(60)

Janne PA, et al. AACR-NCI-EORTC International Conference on Molecular Targets and Cancer Therapeutics 2023;

Arbour KC, et al. ESMO Annual meeting 2023

Pan-RAS inhibitors

Case Report: Patient with KRAS^{G12V} NSCLC

Demographics and Baseline Characteristics

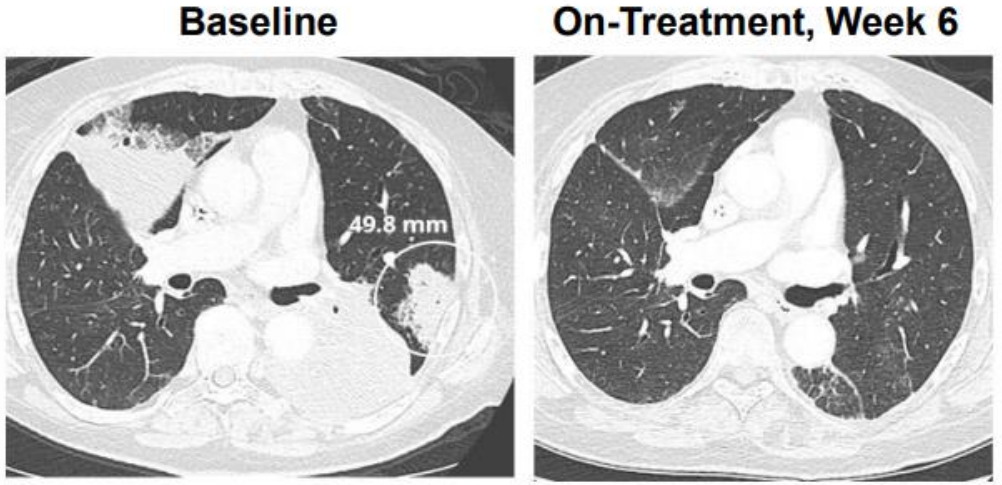
- 83-year-old woman
- Former smoker (~60 pack years)
- Diagnosed with NSCLC in 2021

Treatment History

- Prior therapies:
  - Ipilimumab/nivolumab
  - Paclitaxel
  - Carboplatin/pemetrexed

RMC-6236 Treatment Course

- Started at 300 mg QD
- Clinical improvement in cough and dyspnea within one week of start of treatment
- Dose reduced to 200 mg due to Grade 2 fatigue
- Complete response achieved at Week 6 (confirmed); ongoing



Target Lesion: Lung, Left Lower Lobe

Target Lesion	Baseline	On Treatment
1. Lung (left upper lobe)	11.6 mm	0 mm
2. Lung (left lower lobe)	49.8 mm	0 mm
Sum of Diameters	61.4 mm	0 mm (−100% ↓)
Overall Response (RECIST 1.1)	--	CR

Arbour KC, et al. ESMO Annual meeting 2023

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First line KRAS G12C inh + pembrolizumab

KRYSTAL-7 (849-007) Phase 2 Cohorts

Key Eligibility Criteria

- Advanced, unresectable or metastatic NSCLC with $KRAS^{G12C}$ mutation[a]
- No prior systemic therapy for locally advanced/ metastatic disease[b]
- Stable brain metastases allowed
- Known PD-L1 TPS score[c]

Cohorts 1a and 2[c]
Adagrasib 400 mg BID +
Pembrolizumab 200 mg Q3W
N=148

Key Study Objectives

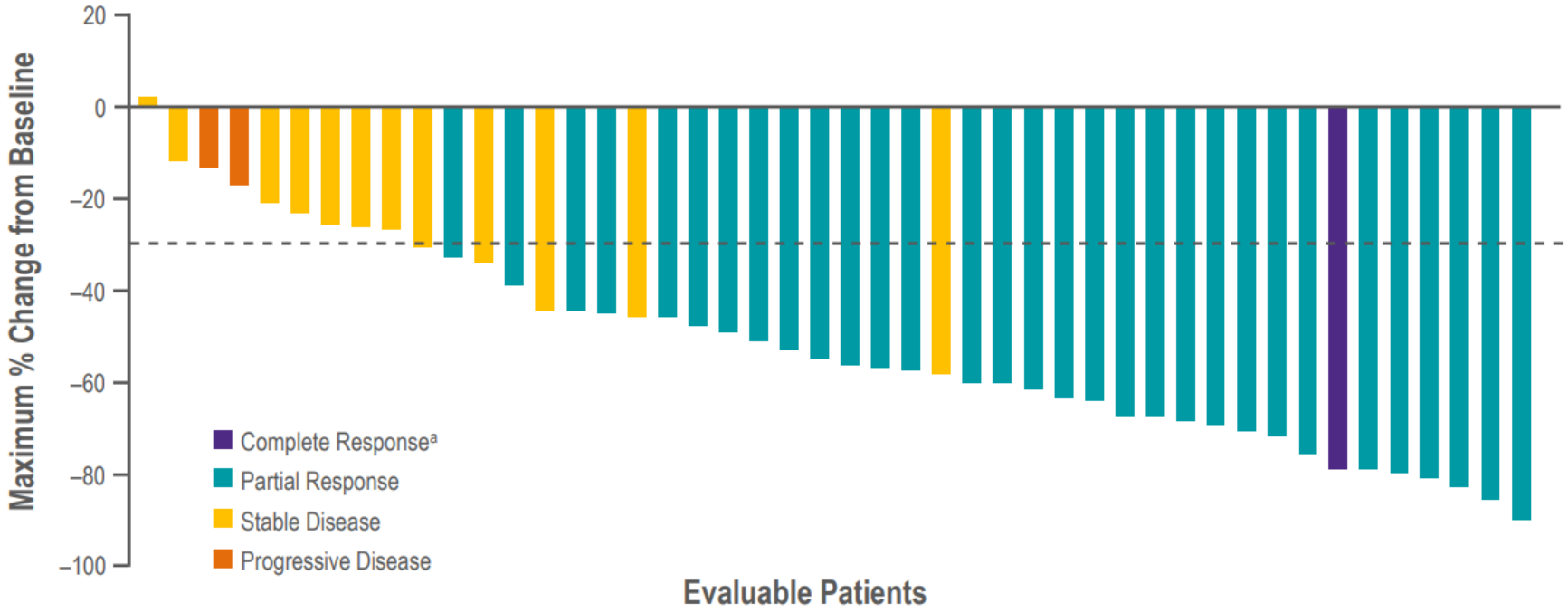
- Primary endpoint: ORR (RECIST v1.1 per investigator assessment)
- Secondary endpoints: DOR and PFS (per investigator assessment), OS, safety, PK

- We report safety in all treated patients (N=148) and efficacy in patients with PD-L1 TPS ≥50% (n=51[d]) from the KRYSTAL-7 study evaluating adagrasib[e] + pembrolizumab (200 mg IV Q3W) in treatment-naïve patients with NSCLC harboring a $KRAS^{G12C}$ mutation
- Median follow-up for all treated patients, 8.7 months; PD-L1 TPS ≥50%, 10.1 months

Garassino MC, Theelen WSME, et al. ESMO Annual Meeting 2023

First line KRAS G12C inh + pembrolizumab

ORR and Best Tumor Change from Baseline in Patients With PD-L1 TPS ≥50%



- Confirmed ORR was 63% (32/51; 95% CI, 48–76) and DCR was 84% (43/51; 95% CI, 71–93)
- Of those patients who experienced any grade hepatotoxicity[b], ORR was 70% (14/20; 95% CI, 46–88)

Garassino MC, Theelen WSME, et al. ESMO Annual Meeting 2023

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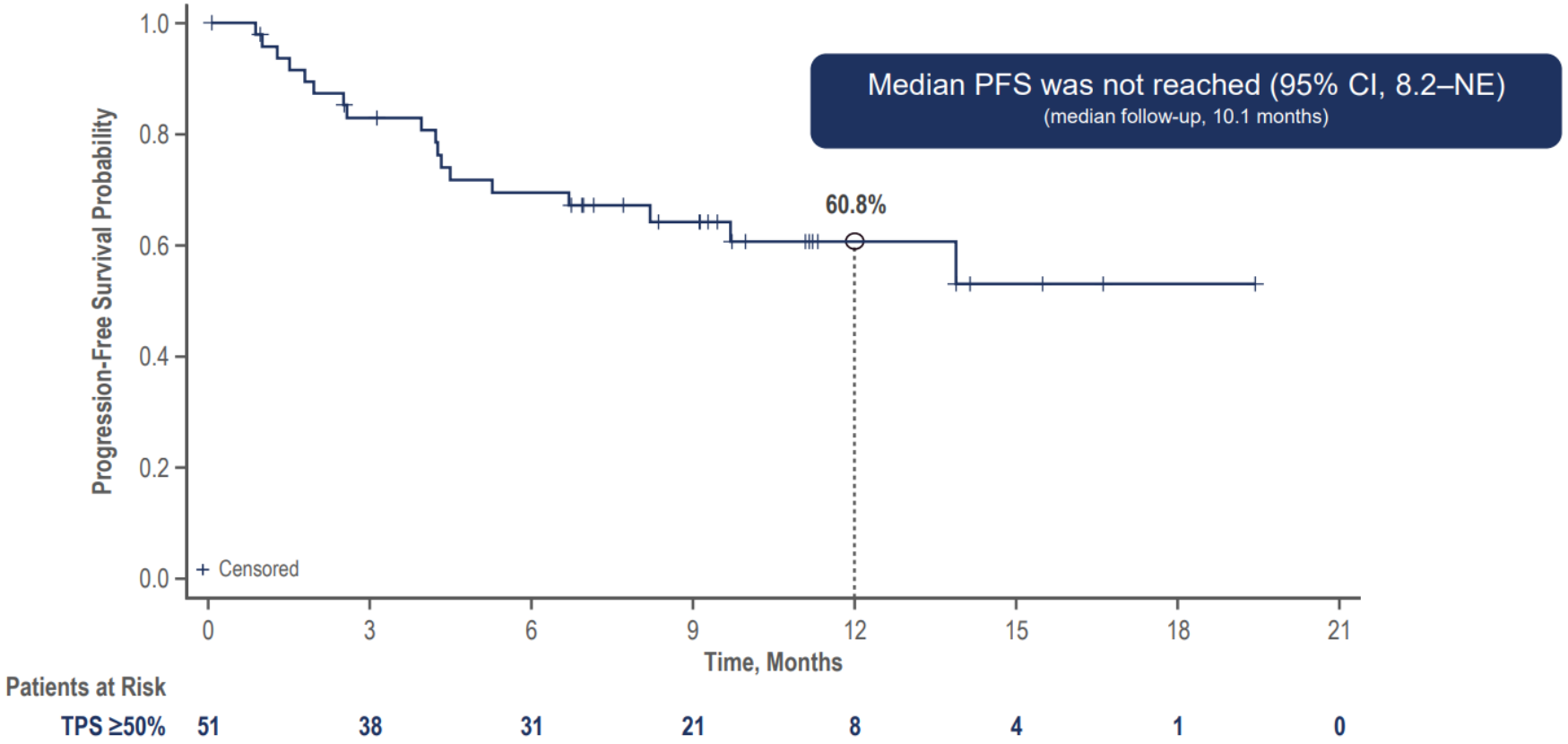
First line KRAS G12C inh + pembrolizumab

Progression-Free Survival in Patients With PD-L1 TPS ≥50%



Garassino MC, Theelen WSME, et al. ESMO Annual Meeting 2023

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How to move forward in KRAS?

Target	*Drug*	*Lijn*	*Studie*
KRAS G12C	*Adagrasib* *KRAS G12C-GDP inh*	*2nd and later lines*	*Trial of Two Adagrasib Dosing Regimens in NSCLC With KRAS G12C Mutation (KRYSTAL 21)*
KRAS G12C	Divarasib KRAS G12C-GDP inh	First line, all PD-L1	PD-L1 negative: carbo-pem-pembro-divarasib PD-L1 ≥1%: pembro-divarasib
KRAS G12C	RMC-6291 KRAS G12C-GTP inh RMC-6236 Pan-RAS-GTP inh	2nd and later lines	Phase 1b, Multicenter, Open-label, Dose Escalation and Dose Expansion Study of RMC-6291 in Combination with RMC-6236 in Participants with Advanced KRAS G12C-Mutated Solid Tumors.
All KRAS	RMC-6236 Pan-RAS-GTP inh	First line, all PD-L1	PD-L1 0-50%: carbo-pem-pembro-RMC-6236 PD-L1 ≥50%: pembro-RMC-6236

Individual genes – HER2

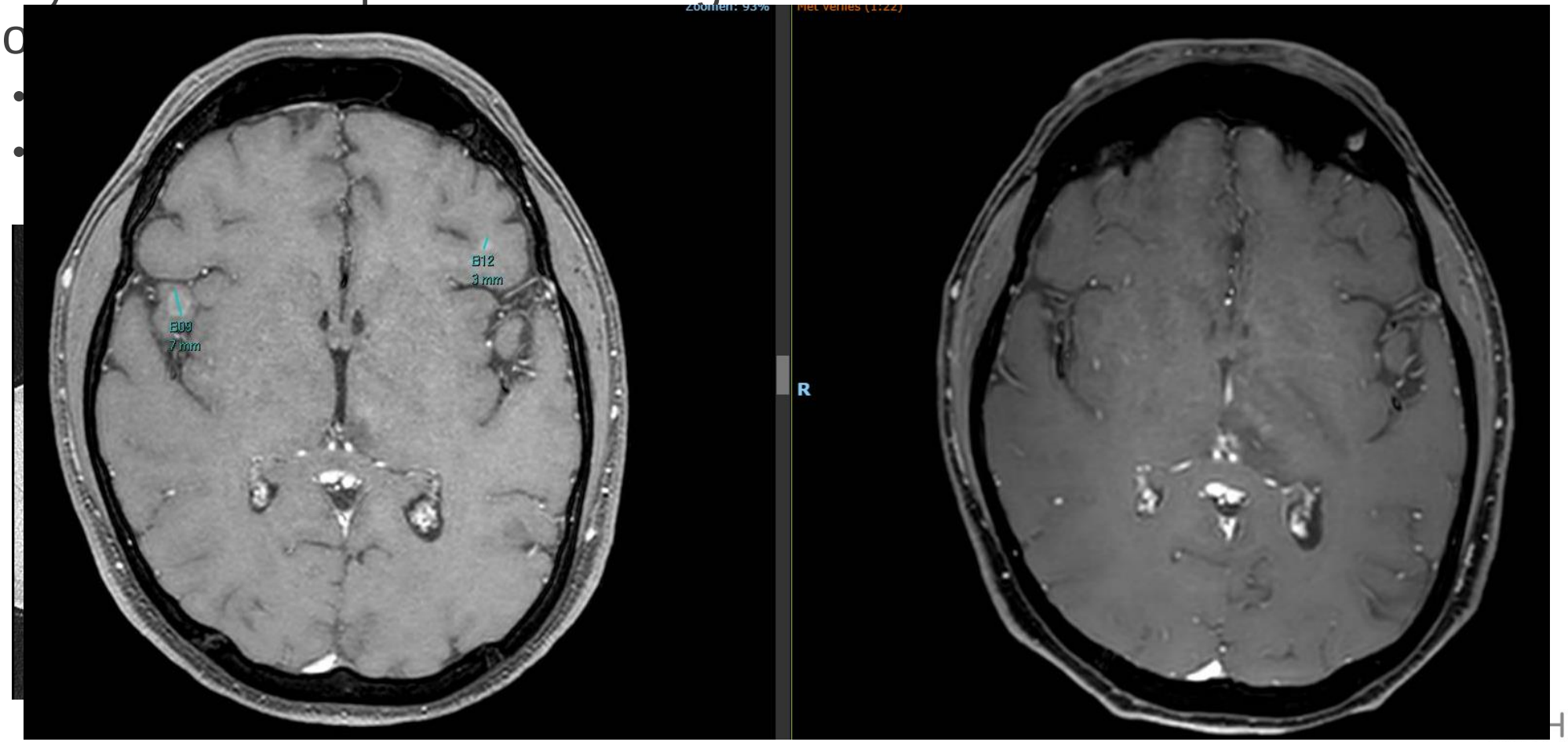
HER2

Drug	ORR	mPFS (months)	Grade 3 tox
Trastuzumab-deruxtecan	55%	8.2	46%
Zongertinib	72%	N.R.	18.2%
Bay 2927088	73%	7.5	41%

Li BT, et al. N Engl J Med 2021; Ruiter G, et al. WCLC Annual Meeting 2024; Le X, et al. WCLC Annual Meeting 2024.

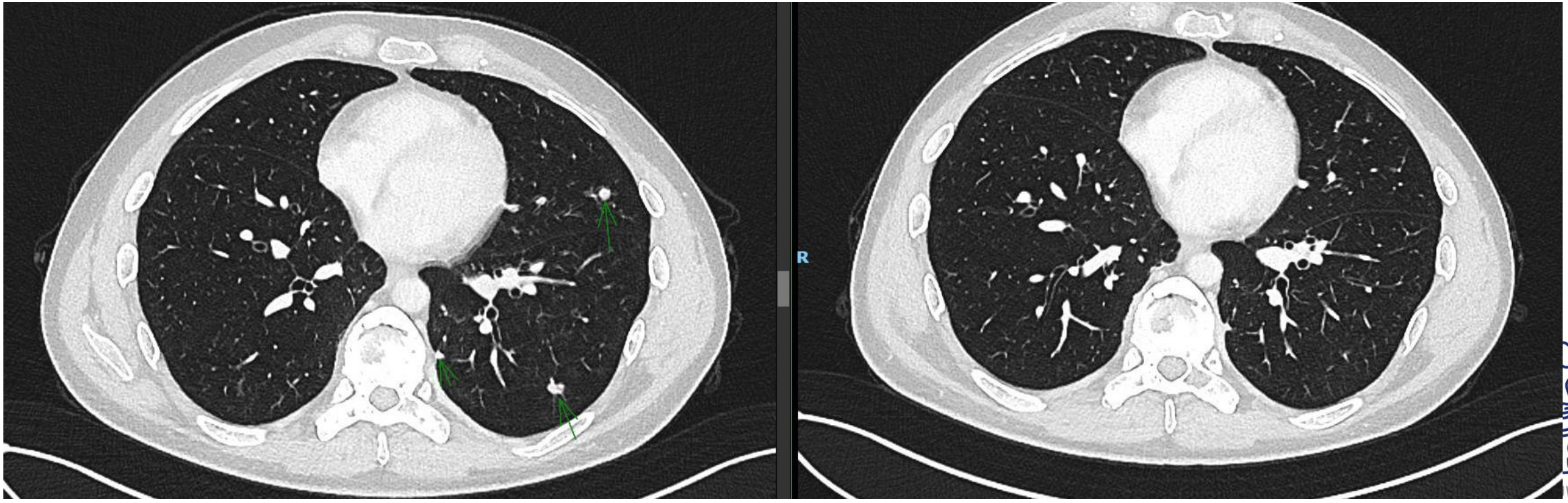
HER2

- 31 year old male patient with stage IV HER2 exon 20 insertion mutation po
  -
  -



HER2

- 31 year old male patient with stage IV HER2 exon 20 insertion mutation positive NSCLC
  - 08-2022: Diagnosis. Carboplatin-pemetrexed-pembrolizumab
  - 03-2023: PD. Trastuzumab-deruxtecan
  - 11-2023: PD. Zongertinib



Behandeling van RET fusie, BRAF V600E en MET exon 14 mutatie positief NSCLC

Driver	Eerste lijns behandeling	Tweede lijns behandeling
RET fusie	Selpercatinib	Chemotherapie +/- immunotherapie
BRAF V600E	Dabrafenib + trametinib Encorafenib + binimetinib	Chemotherapie + immunotherapie
MET exon 14 mutatie	Chemotherapie + immunotherapie	Tepotinib

Why should we biopsy all pts that progress on targeted therapy?

52 year old female patient (now 56) with stage KIF5B-RET fusion positive NSCLC

- 02-2020: Diagnosis. Carboplatin-paclitaxel-bevacizumab-atezolizumab
- 07-2021: PD. Selpercatinib
- 02-2023: PD. Biopsy: KIF5B-RET fusion and high MET amplification. Selpercatinib + tepotinib
- 02-2024: Oligoprogression in the liver. Microwave ablation
- 08-2024: Onveranderde restlaesie linkeronderkwab. Geringe afname ablatieholte lever. Geen nieuwe lymfadenopathie of metastasen.

ROS1 fusion

Drug	N	ORR (95% CI)	mPFS (95% CI)	Grade 3 toxicity
Crizotinib	50	72% (58-84%)	19.2 (14.4-n.r.)	28%
Entrectinib	53/134	77% (64-88%)	19.0 (12.2-36.6)	34%
Repotrectinib	71/426	79% (68-88%)	35.7 (27.4-n.r.)	51%
Zidesamtinib	71/104	73%	n.a.	1%?

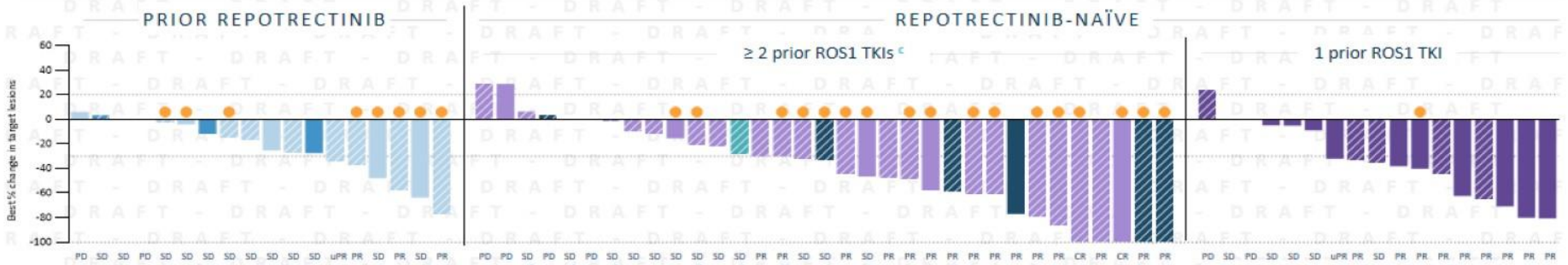
Shaw AT, et al. N Eng J Med 2014, Drilon A, et al. Lancet Oncol 2020, Drilon A, et al. N Engl J Med 2024

Zidesamtinib

Preliminary Activity: Radiographic Tumor Response Across Previously Treated Patients with ROS1+ NSCLC

All NSCLC Response Evaluable Patients *± chemotherapy*	Any Prior ROS1 TKI (range 1-4)		≥ 2 prior ROS1 TKIs			ROS1 G2032R Resistance Mutation [b]		1 prior ROS1 TKI (crizotinib)
	All	Repotrectinib-naive	All	Prior Lorlatinib	Repotrectinib-naive	Prior Repotrectinib	Repotrectinib-naive	
RECIST 1.1 ORR % (n/n) [a]	**44%** (31/71)	**51%** (27/53)	**41%** (21/51)	**44%** (17/39)	**47%** (17/36)	**38%** (3/8)	**72%** (13/18)	**73%** (8/11)
CR [*]	2	2	2	2	2	-	2	-

[*] 2 confirmed CRs ongoing with DOR 19.3+ and 26.3+ months. 5 additional CRs observed among patients without measurable disease (2 prior ROS1 TKIs [n=2], 1 prior ROS1 TKI (crizotinib [n=1], entrectinib [n=2])), all ongoing with DOR 3.6+, 3.7+, 13.8+, 13.9+, and 18.5+ months.



Data cut-off: 1 July 2024 . Response-evaluable patients with ROS1+ NSCLC, median follow-up 12.1 months (range 1.0, 29.4 months)
CR, complete response; **DOR**, duration of response; **ORR**, objective response rate; **RECIST 1.1**, Response Evaluation Criteria in Solid Tumours version 1.1; **TKI**, tyrosine kinase inhibitor.
[a] Includes two ongoing Partial Responses pending confirmation.
[b] ROS1 mutations as per local or central testing of blood (ctDNA) or tissue. Responses also observed in patients with ROS1 resistance mutations other than G2032R (S1986F, D2033N).
[c] Three response-evaluable patients not shown due to incomplete or missing post-baseline tumor assessments in the setting of symptomatic deterioration.

KEY: PATIENT DETAILS

Prior Repotrectinib:	Repotrectinib-naive:		
≥ 2 prior ROS1 TKIs	4 prior ROS1 TKIs	2 prior ROS1 TKIs	+ chemotherapy
1 prior ROS1 TKI	3 prior ROS1 TKIs	1 prior ROS1 TKI	ROS1 G2032R mutation

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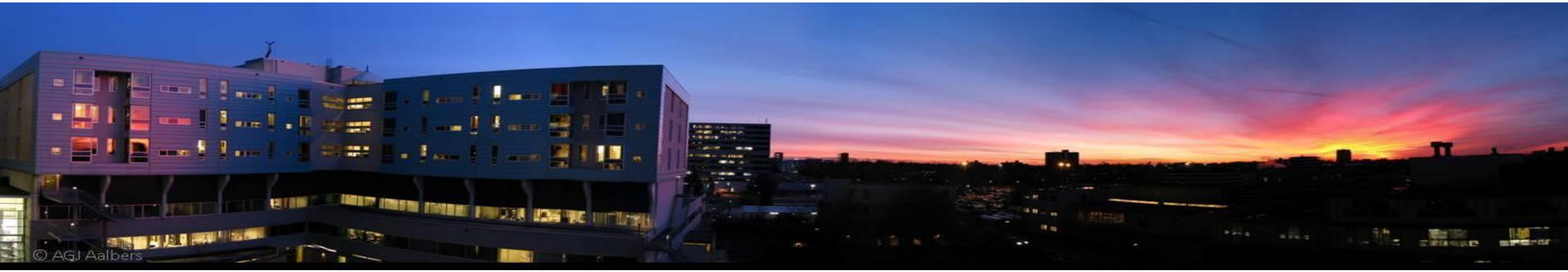
Where should we head to?

- Targeted therapy for everybody
  - ~50% of pts with advanced stage NSCLC receive BSC
  - Targeted therapy has excellent efficacy-toxicity ratio and works fast

- Immunotherapy for everybody
  - Targeted therapy almost never cures pts
  - Needs time to work
  - We need to move beyond checkpoint inhibition

Conclusions

- DNA and RNA NGS or WGS with matching to SOC + clinical trials should be available for every patient.
- Targeted treatment as well as immunotherapy needs to be developed for all patients
- Biopsy after progression on targeted therapy directs subsequent therapy, even in low prevalent mutations



Thank you for listening

Questions?

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