Cancer Institute

Zeldzame Mutaties
ALK, ROS1, BRAF, RET, MET, HER2

Webinar Longkanker Nederland

Prof Anne-Marie Dingemans, longarts

DECLARATION OF INTERESTS

Erasmus MC Cancer Institute

2021-2023, All paid to institute

Advisory role or speakers bureau: Amgen, Astra Zeneca, Bayer, Boehringer Ingelheim, Daiichi, Eli Lilly, Janssen, Pfizer, Roche, Sanofi

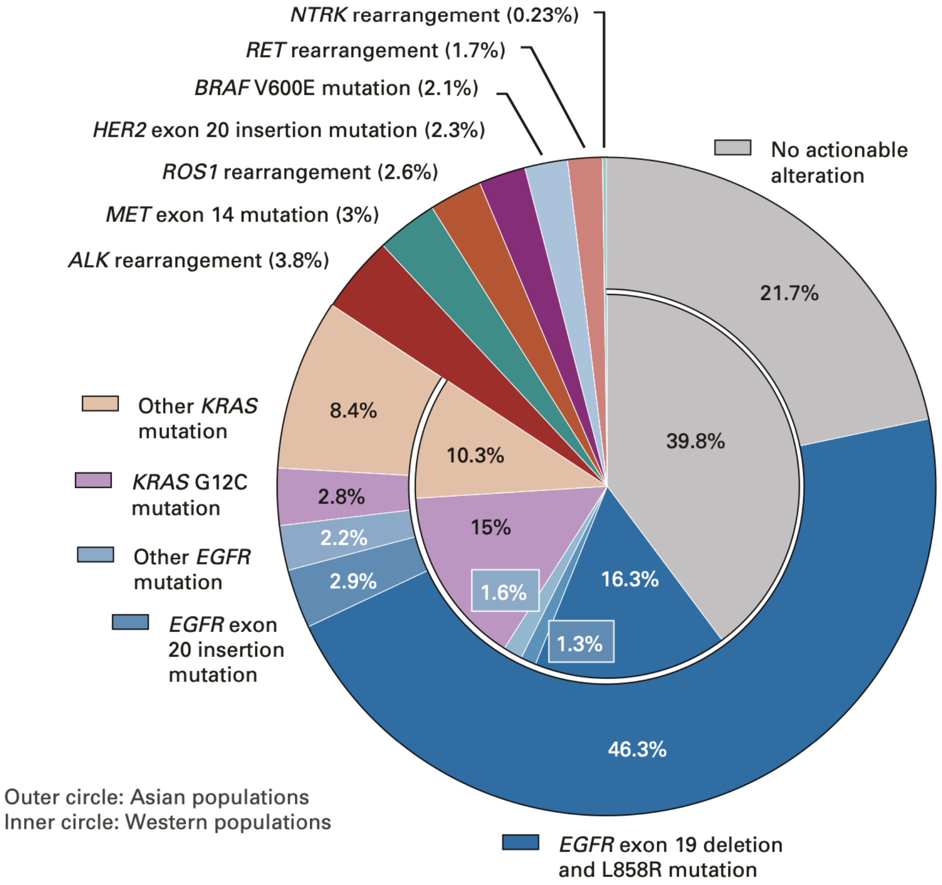
IDMC: Roche, Takeda

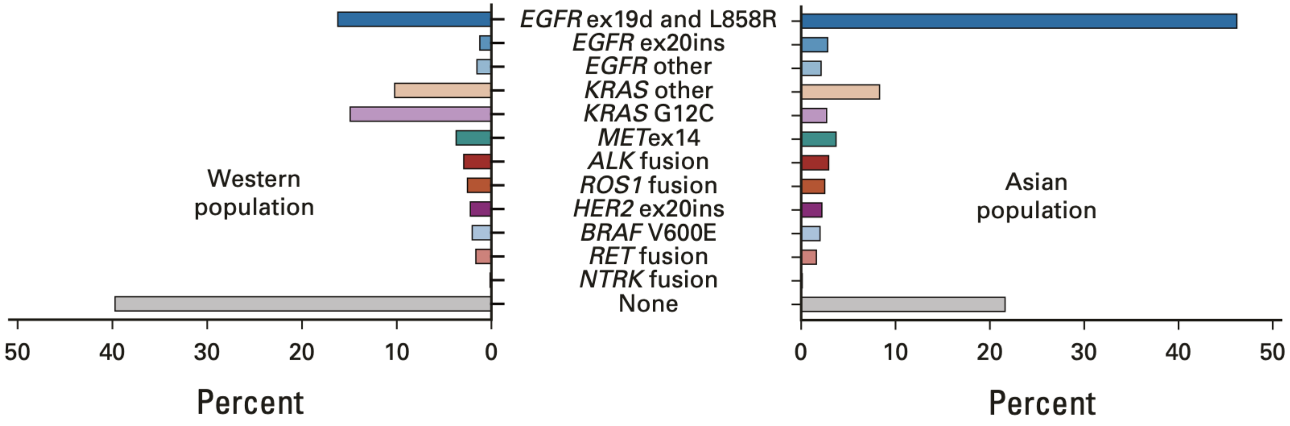
Steering Committee: Roche, Lilly, Amgen

Institutional research grants: Amgen

Leadership: Chair EORTC Lung Cancer Group

Zeldzame ziekte, maar in totaal ~15-20% van alle longkanker





DEFINITIE WEESZIEKTE:
< 6 / 100.000 PERSONEN PER JAAR

Tan et al, JCO 2022; 40611-625.

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Naar welk ziekenhuis kan ik voor zeldzame vormen van longkanker?

Doelgerichte therapie voor zeldzame longkankers (die minder dan 5% voorkomen) wordt alleen in expertisecentra gegeven.

Voorbeelden van zeldzame longkankers zijn ALK, BRAF, HER2, NRG1, NTRK, MET, RET en ROS-1.

Ook bij zeldzame vormen van EGFR zoals de EGRF exon 20 en bij progressie van ziekte (groei van de kanker na of tijdens de eerste behandelvorm) bij EGFR moet de behandeling plaatsvinden in een expertisecentrum.

De expertisecentra zijn UMCG, MUMC, AVL, Amsterdam UMC, Erasmus MC, LUMC en het Radboudumc.

Doel van de behandeling bij uitgezaaide kanker

ZO LANG MOGELIJK LEVEN

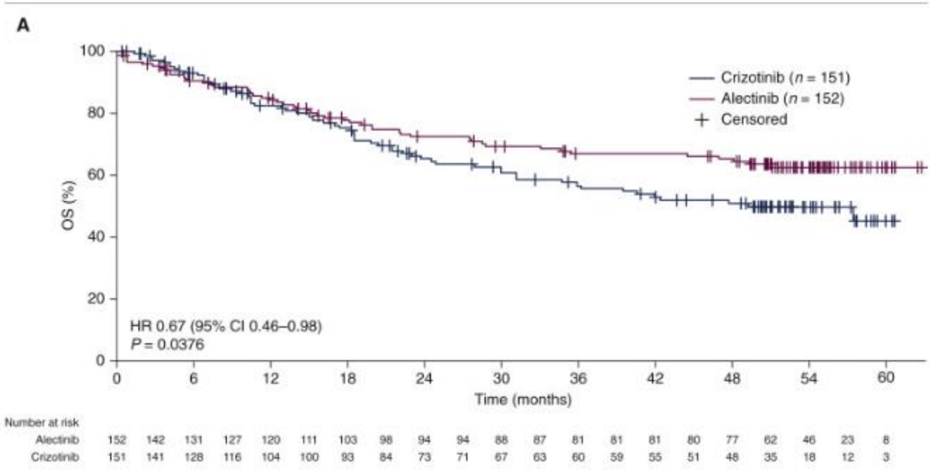
MET

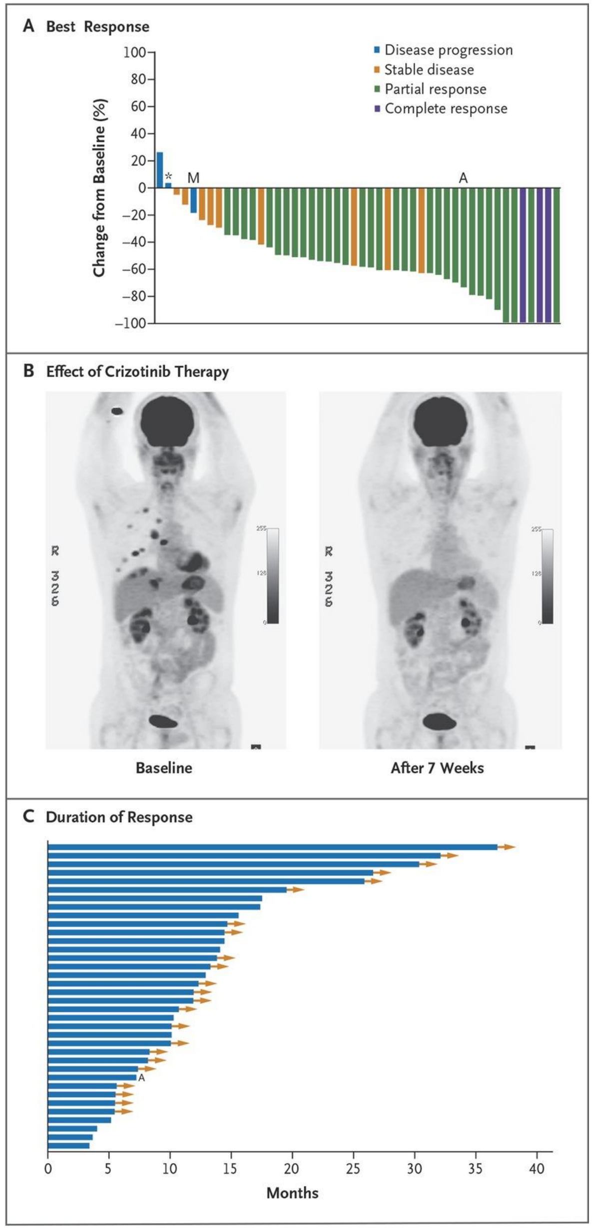
KWALITEIT VAN LEVEN

Als er na een aantal maanden gebruik van Alectinib bij de Alk-mutatie niks meer zichtbaar is op de scan, kan het dan ook zo zijn dat de mutatie niet meer terugkomt?

ZELDZAME ZIEKTE
EN NIEUWE BEHANDELING

KAPLAN MEIER CURVE





WATERFALL PLOT

VOORBEELDEN

SWIMMER PLOT

Shaw et al, NEJM, 2014;371:1963-1971
Mok et al, Ann Oncol 2020;31:1056

Zeldzame kanker en toelating EMA

Why is Vitrakvi authorised in the EU?

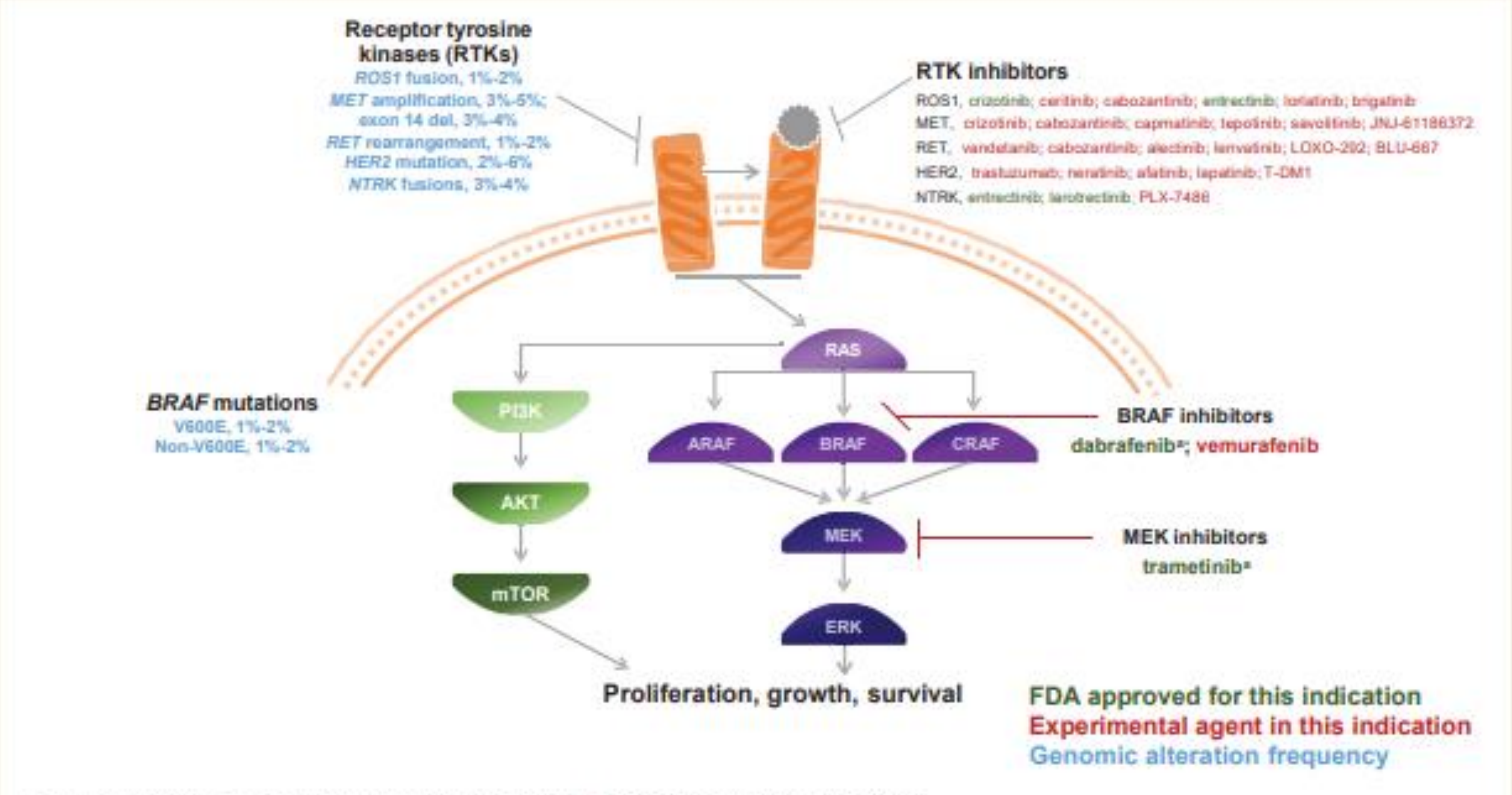
Vitrakvi differs from many other cancer medicines by targeting certain tumours with [illegible]ific gene arrangement wherever they occur in the body. Although studies are still underway, the results released so far show that it is effective at reducing the size of patients' tumours. In addition, the short time taken to shrink the tumours is important in relieving patients' symptoms.

As for its safety, the side effects of Vitrakvi appear manageable. The European Medicines Agency therefore concluded that its benefits are greater than its risks and that it can be authorised for use in the EU.

Vitrakvi has been given 'conditional authorisation'. This means that there is more evidence to come about the medicine, which the company is required to provide. Every year, the Agency will review any new information that becomes available and this overview will be updated as necessary.

Larotrectinib EMA Approval 10/2019

Figure 1 Targeting Rare Oncogenic Alterations in Non–Small-Cell Lung Cancer



[a] Approved by the FDA as combination therapy for treatment of patients with *BRAF* V600E–mutant metastatic NSCLC.

Marmarelis ME, Langer CJ. *Clin Lung Cancer.* 2020;21:395-406.

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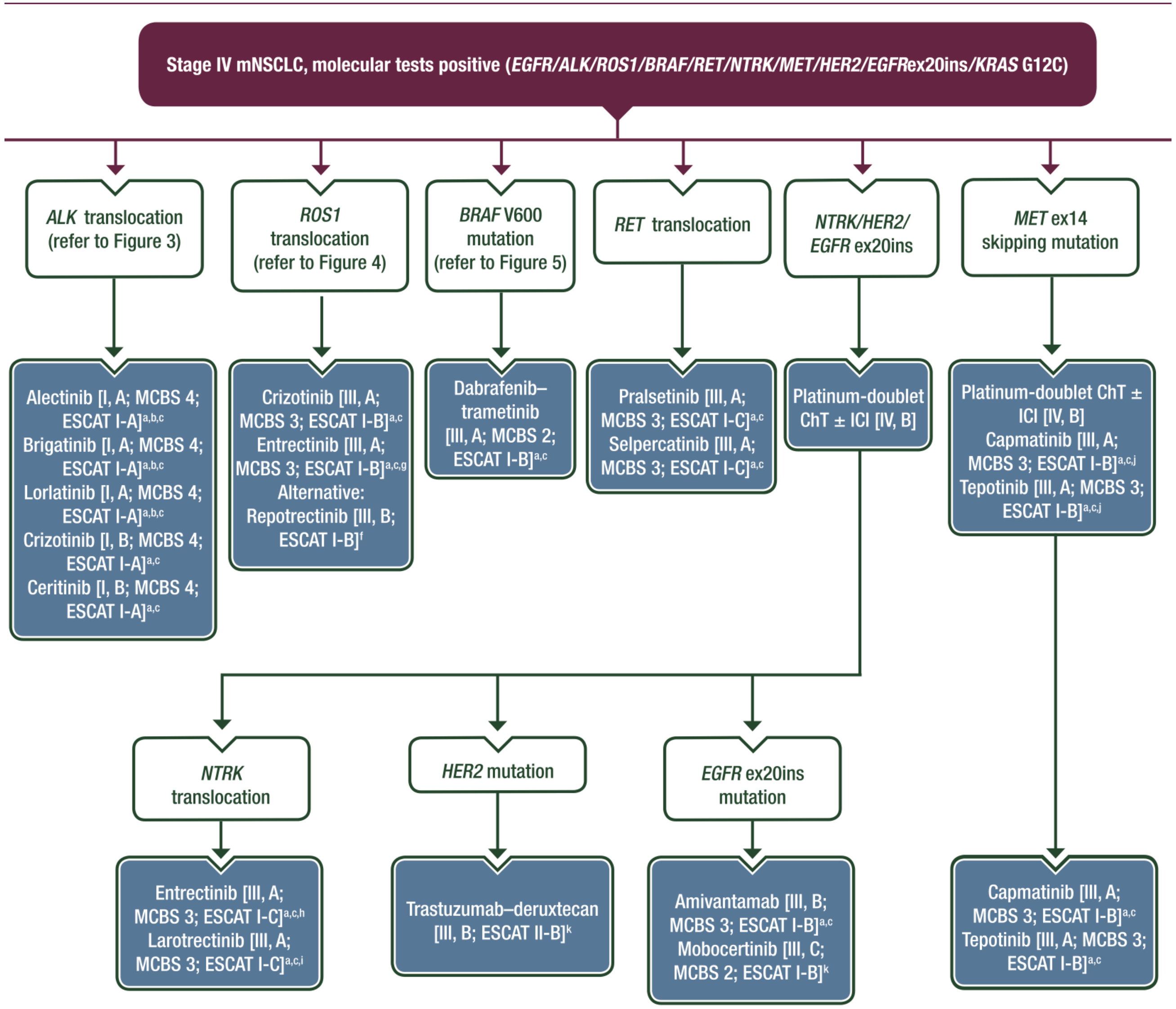

Hendriks et al, Ann Oncol 2023

Wat is op dit moment de gemiddelde levensverwachting bij gebruik van Alectinib voor ALK patienten stadium 4?

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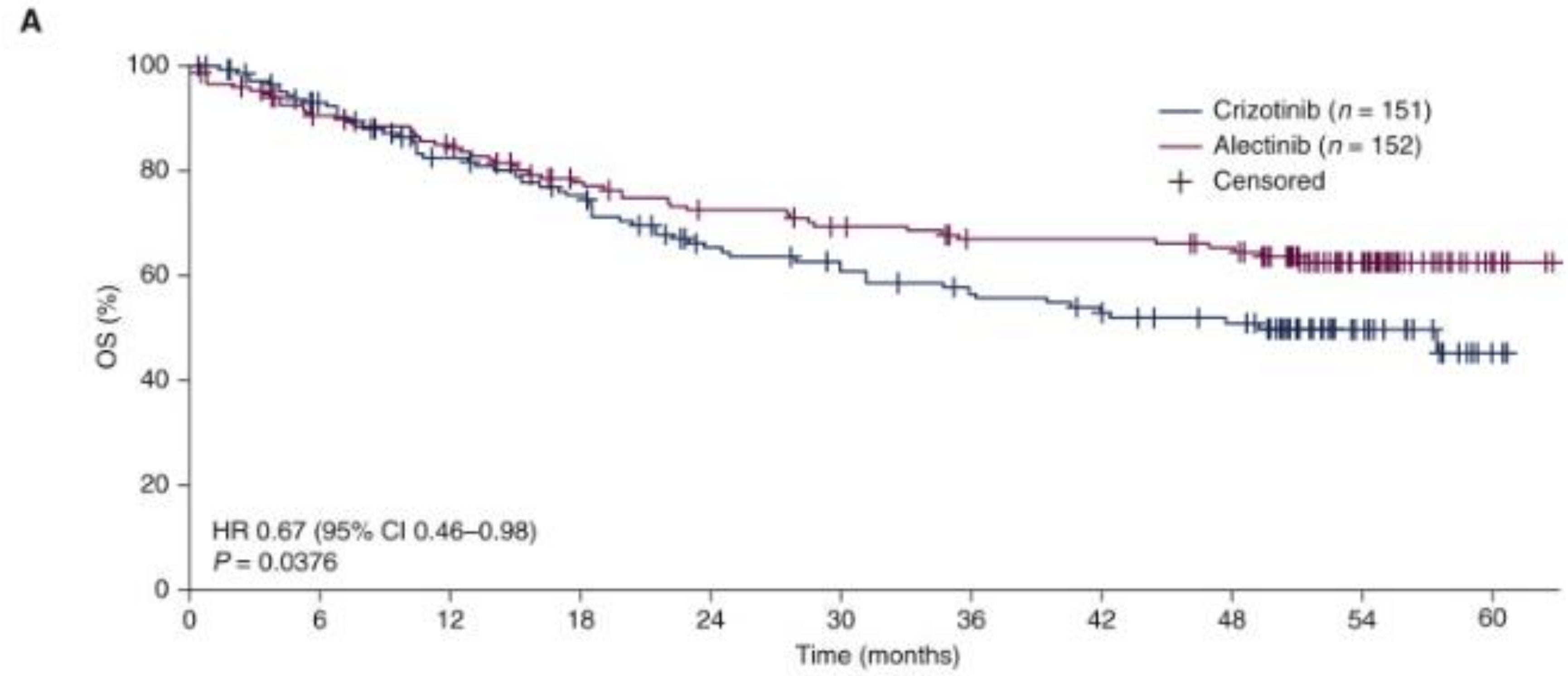
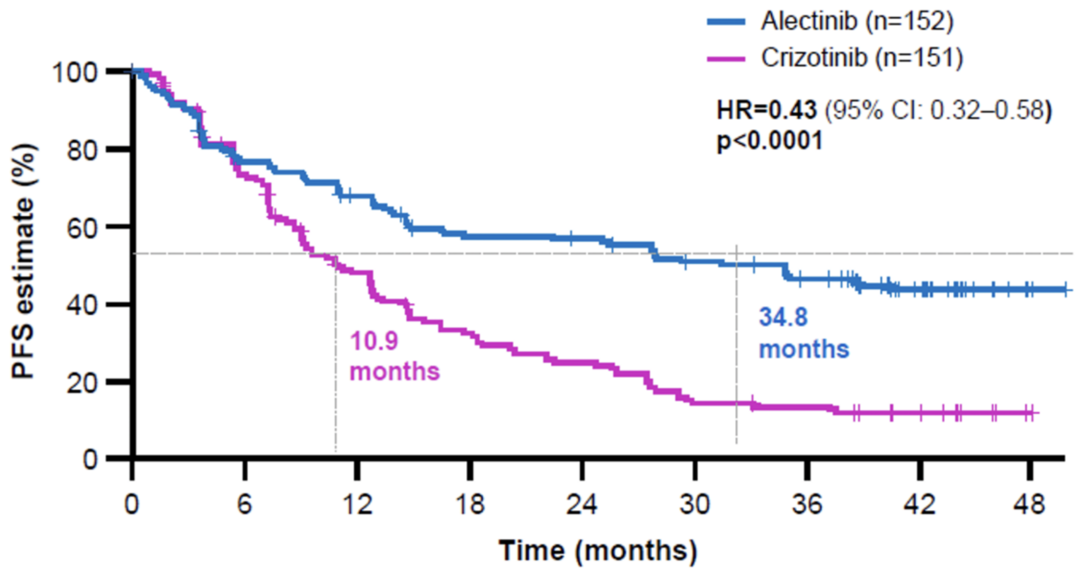
ALK+= 3-5% NSCLC
Overleving 5 jaar ~63%

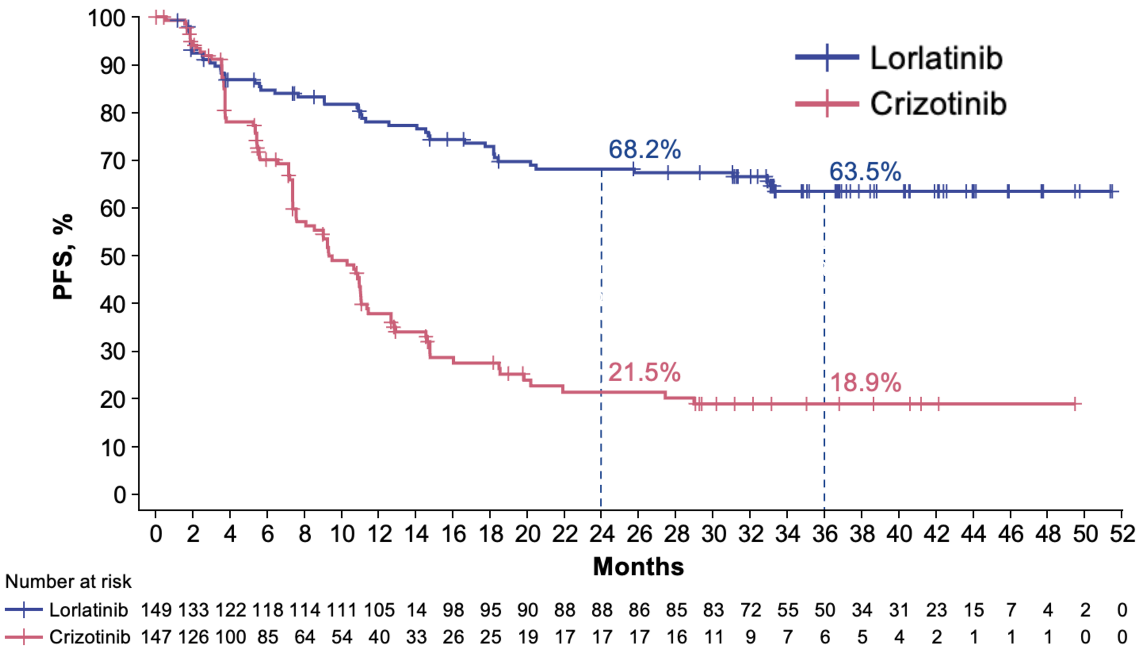


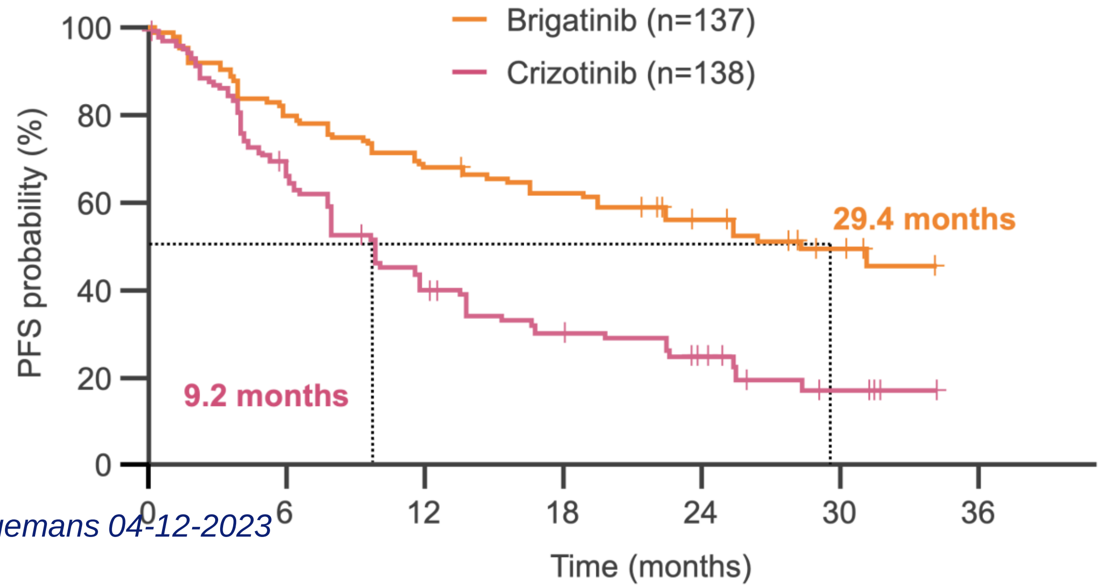
Number at risk																					
Alectinib	152	142	131	127	120	111	103	98	94	94	88	87	81	81	81	80	77	62	46	23	8
Crizotinib	151	141	128	116	104	100	93	84	73	71	67	63	60	59	55	51	48	35	18	12	3

Mok et al , Ann Oncol, 2020;31:1056

Meerdere medicamenten beschikbaar voor ALK







Ook effect op hersenmetastasen

Heeft de grote van de tumor bij de diagnose bij ALK ook invloed op de levensverwachting?
B.v. je hebt een heel klein tumortje is de levensverwachting dan ook langer?

Verschillend bijwerkingen profiel

	Alectinib	Brigatinib	Lorlatinib
AEs > 15%	Constipation 36.8%; peripheral oedema 19.1%; fatigue 22.4%; AST 17.1%, ALT 17.8%, **Bilirubine increase 21.7%**; Myalgia 17.1%; Anaemia 26.3%,	**Diarrhea 58%; CPK 50% lipase 24% and amilase 18% increase ; Cough 36%; Nausea 33%** Hypertension 32%; AST 26% ALT 23% increase; **Back pain 26% Dyspnea 24%; Headache 24%, Vomiting 22%**; Fatigue 21% **Pruritus 21%**; Constipation 20%; Arthralgia 20%; **Rash 19%; Dizziness 17%; Pyrexia 16%**	**Hypercholesterolaemia 72% Hypertriglyceridaemia 66%** Oedema 56% **Weight increased 44% Peripheral neuropathy 40%** Arthralgia 26% **Cognitive effects 26%** Anaemia 22% Diarrhoea 22% Hypertension 22% Constipation 19% **Vision disorder 19%** ALT increased 18% **Mood effects 17%**
G3 ≥ AEs	52.0%	78%	76%
AEs LEADING TO TREATMENT DISCONTINUATION	14.5%	13%	38%

Mok T, Ann Oncol 2020; Camidge DR, JTO 2021; Solomon BJ, Lancet Resp Med 2023

Analysis of Serious Weight Gain in Patients Using Alectinib for *ALK*-Positive Lung Cancer

Check for updates

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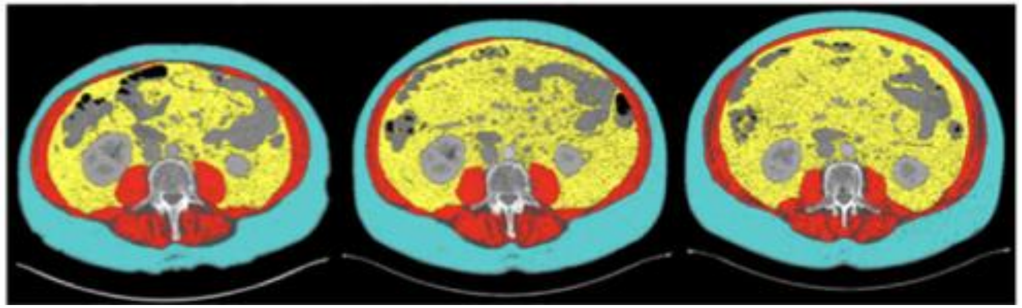
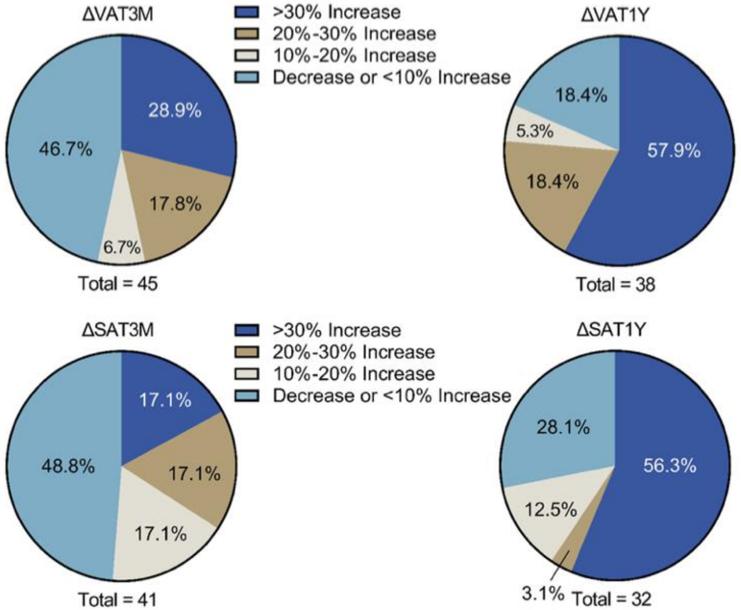
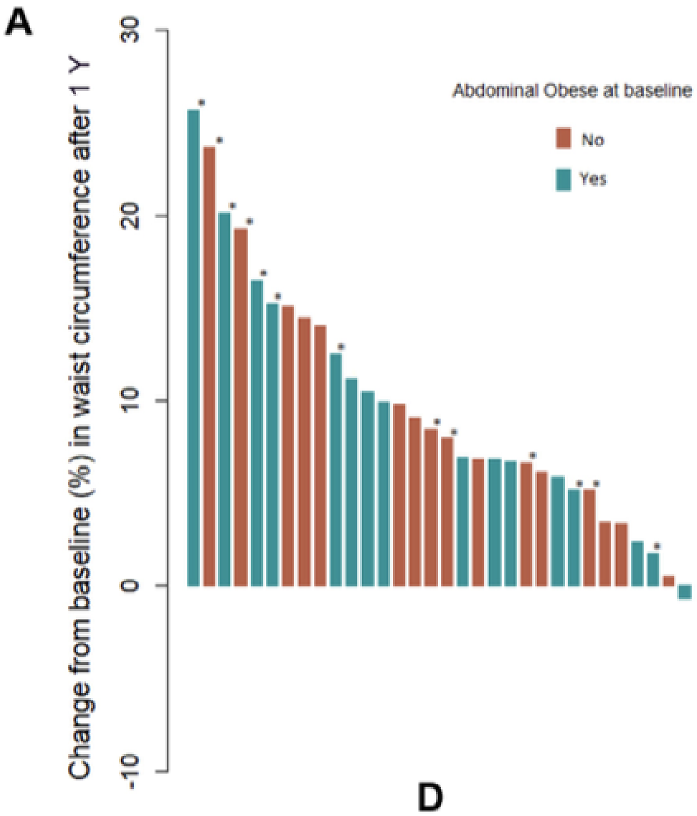


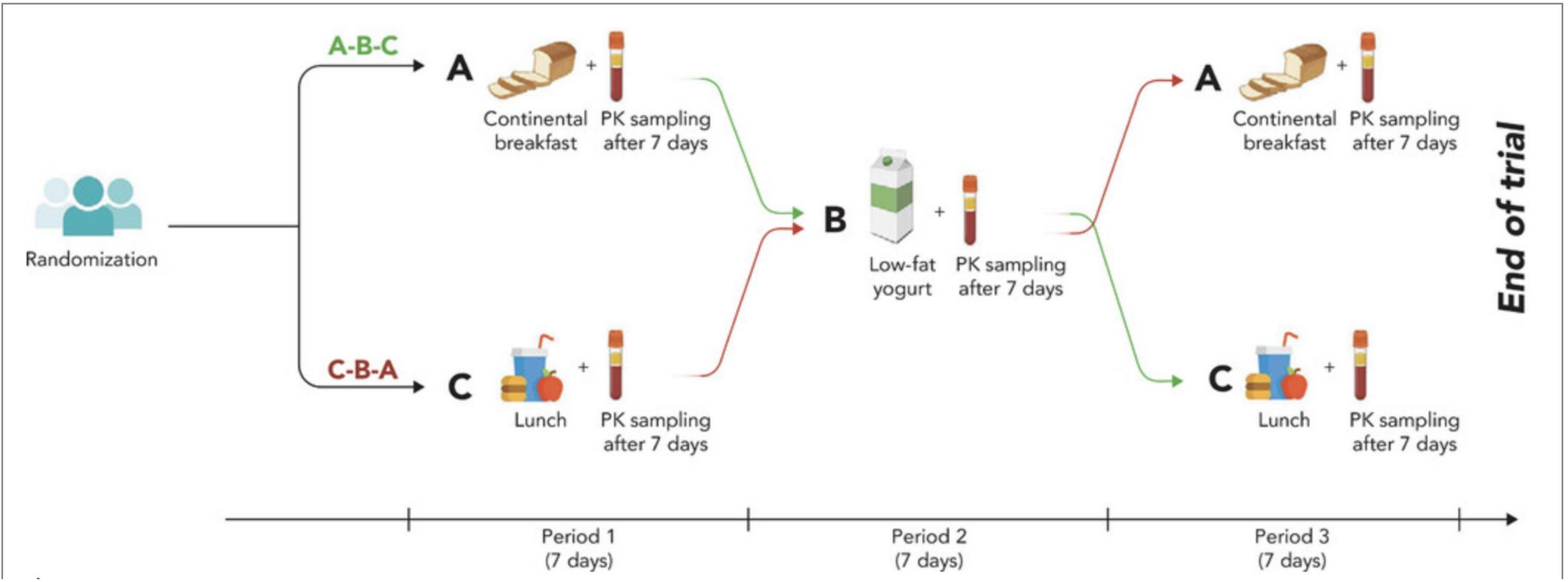


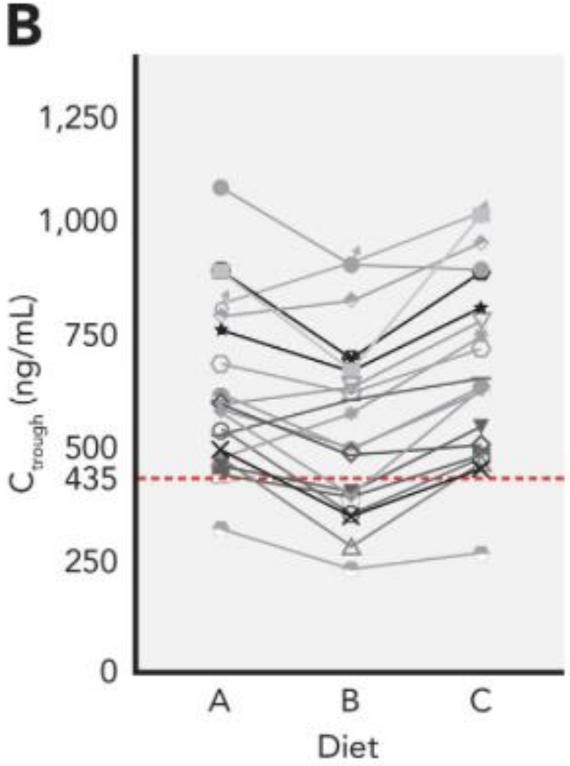


De Leeuw et al, JTO 2023; 18:1017

Influence of Food With Different Fat Concentrations on Alectinib Exposure: A Randomized Crossover Pharmacokinetic Trial

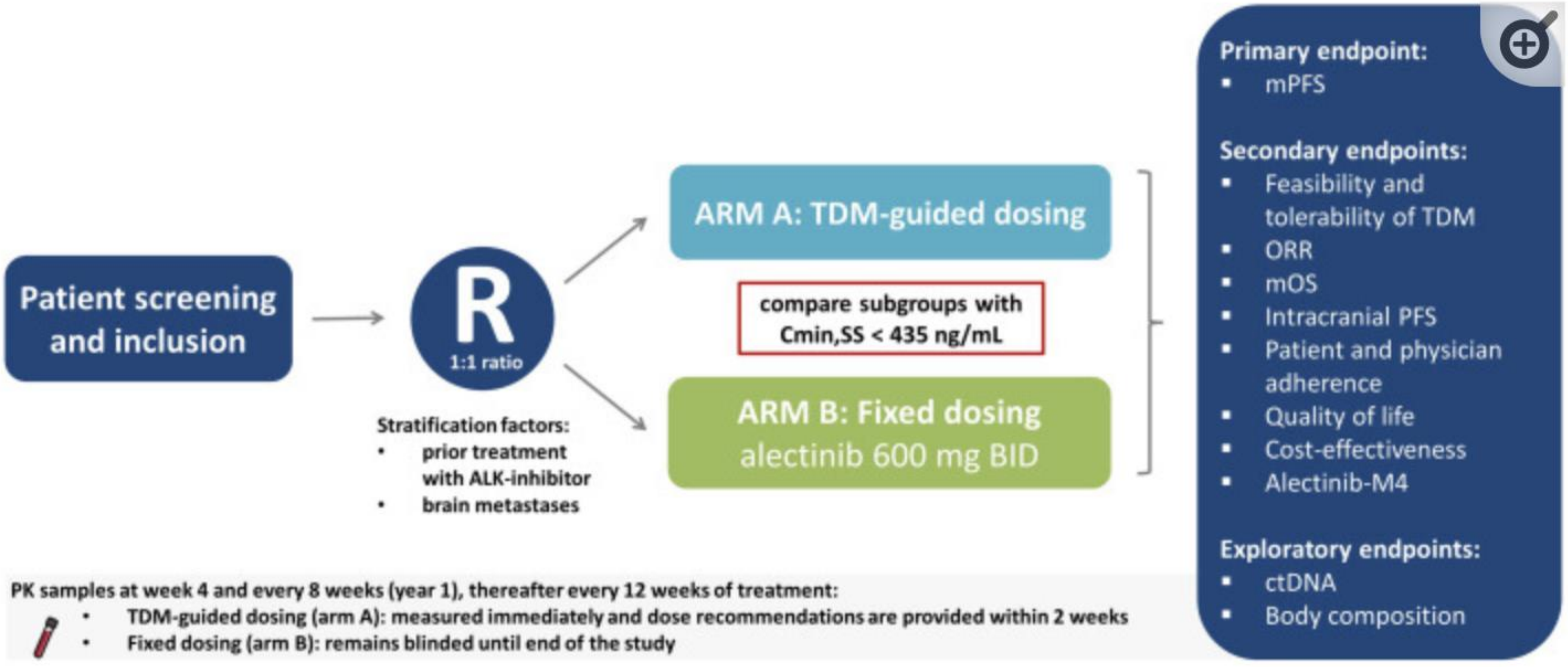
Daan A.C. Lanser, MSc[1]; Simon P. de Leeuw, MD[1,2]; Esther Oomen-de Hoop, PhD[1]; Peter de Bruijn[1]; Marthe S. Paats, MD, PhD[2]; Daphne W. Dumoulin, MD[2]; Stijn L.W. Koolen, PharmD, PhD[1,3]; Anne-Marie C. Dingemans, MD, PhD[2]; Ron H.J. Mathijssen, MD, PhD[1]; and G.D. Marijn Veerman, MD[1]





Lanser et al, JNCCN,2023

ADEPT ALEC


Patient screening and inclusion
R
1:1 ratio
Stratification factors:
• prior treatment with ALK-inhibitor
• brain metastases
ARM A: TDM-guided dosing
compare subgroups with Cmin,SS < 435 ng/mL
ARM B: Fixed dosing alectinib 600 mg BID
Primary endpoint:
mPFS
Secondary endpoints:
Feasibility and tolerability of TDM
ORR
mOS
Intracranial PFS
Patient and physician adherence
Quality of life
Cost-effectiveness
Alectinib-M4
Exploratory endpoints:
ctDNA
Body composition
PK samples at week 4 and every 8 weeks (year 1), thereafter every 12 weeks of treatment:
• TDM-guided dosing (arm A): measured immediately and dose recommendations are provided within 2 weeks
• Fixed dosing (arm B): remains blinded until end of the study

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Kun je het supplement SHILAJIT samen gebruiken met Alectinib?
Of heeft dit consequenties voor de werking van Alectinib?

Het is wel belangrijk om te weten dat er nog bijkomend onderzoek nodig is om deze gezondheidsclaims verder te kunnen onderbouwen. Bovendien moeten deze stellingen nog worden goedgekeurd door de Europese Commissie.

*Gezondheidsclaims in afwachting van goedkeuring door de Europese Commissie.

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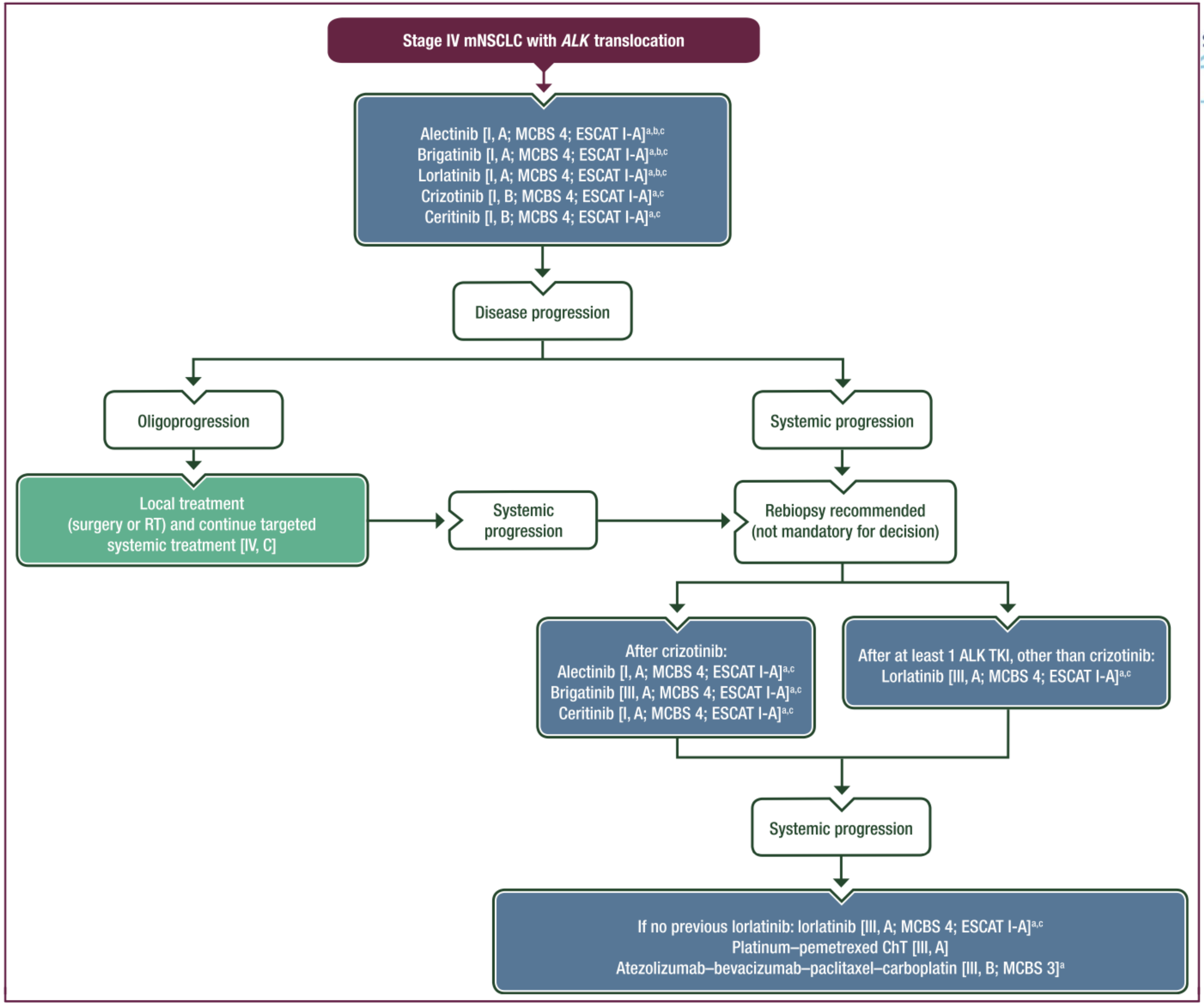
Wat is na Alectinib de 2e lijns medicatie voor ALK?



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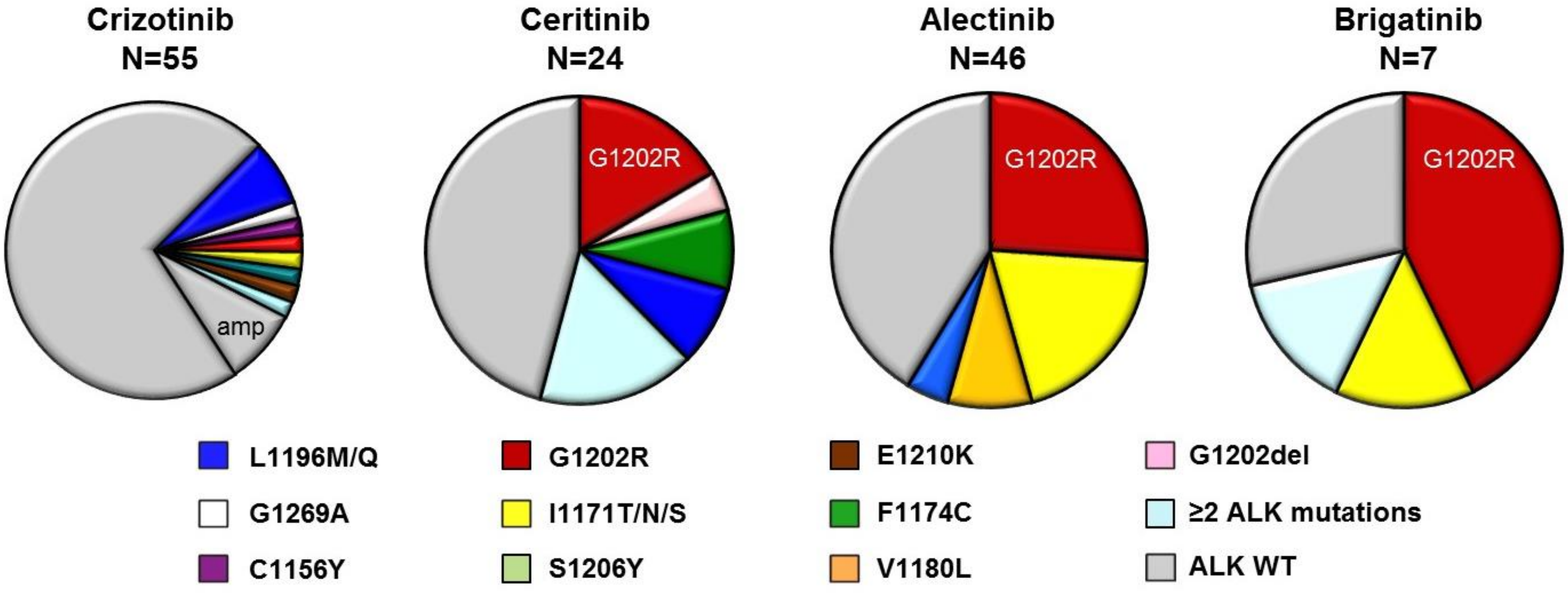
Hendriks et al, Ann Oncol 2023

Verschillende reden van ongevoeligheid



Gainor, ASCO 2019.

Cellular ALK phosphorylation mean IC_{50} (nmol/L)

Mutation status	Crizotinib	Ceritinib	Alectinib	Brigatinib	Lorlatinib
Parental Ba/F3	763.9	885.7	890.1	2774.0	11293.8
EML4–ALK V1	38.6	4.9	11.4	10.7	2.3
EML4–ALK C1156Y	61.9	5.3	11.6	4.5	4.6
EML4–ALK I1171N	130.1	8.2	397.7	26.1	49.0
EML4–ALK I1171S	94.1	3.8	177.0	17.8	30.4
EML4–ALK I1171T	51.4	1.7	33.6[a]	6.1	11.5
EML4–ALK F1174C	115.0	38.0[a]	27.0	18.0	8.0
EML4–ALK L1196M	339.0	9.3	117.6	26.5	34.0
EML4–ALK L1198F	0.4	196.2	42.3	13.9	14.8
EML4–ALK G1202R	381.6	124.4	706.6	129.5	49.9
EML4–ALK G1202del	58.4	50.1	58.8	95.8	5.2
EML4–ALK D1203N	116.3	35.3	27.9	34.6	11.1
EML4–ALK E1210K	42.8	5.8	31.6	24.0	1.7
EML4–ALK G1269A	117.0	0.4	25.0	ND	10.0
EML4–ALK D1203N+F1174C	338.8	237.8	75.1	123.4	69.8
EML4–ALK D1203N+E1210K	153.0	97.8	82.8	136.0	26.6

$IC_{50} \leq 50$ nmol/L

$IC_{50} > 50 < 200$ nmol/L

$IC_{50} \geq 200$ nmol/L

Gainor, cancer disc 2016

UPCOMING 4TH GENERATION ALK TKIs

1. **Activity against ALK**
~5% of all non-small cell lung cancers (NSCLC) are ALK-positive[1]

2. **Activity against ALK resistance mutations**
such as G1202R, G1202R/L1196M, and G1202R/T1151M mutations that confer resistance to previous-generation therapies[2-3]

3. **Activity in the central nervous system (CNS)**
~40% of patients with ALK-positive NSCLC have brain metastases at diagnosis[4]

4. **Sparing TRKB**
TRKs, especially TRKB, are key off-target kinases whose inhibition in the CNS is associated with neurological adverse events and dose-limiting toxicities[5-9]

Feature	Crizotinib	2nd gen*	Lorlatinib	TPX-0131	NVL-655 TPP
ALK activity	Yes	Yes	Yes	Yes	Yes
G1202R activity	No	No	Yes	Yes	Yes
G1202R/L1196M activity	No	No	No	Yes	Yes
CNS activity	Not in label	Yes	Yes	Likely[10]	Yes
Sparing TRKB	Limited CNS penetrance	Yes	Limited at dose developed for ALK G1202R**	No	Yes

Murray BW, Mol Cancer Ther 2021; Lee JB, AACR 2023; Johnson M, ELCC 2023

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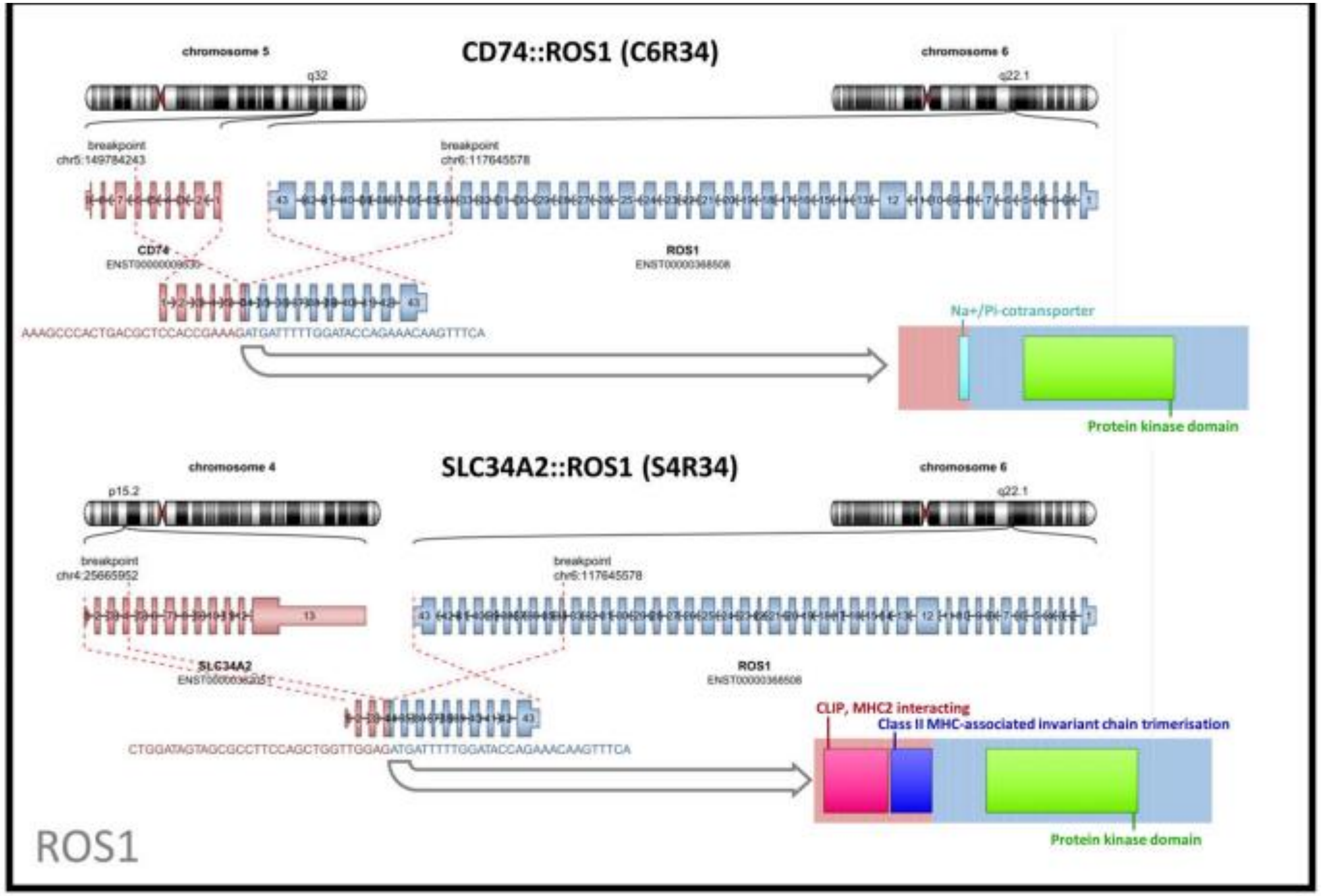
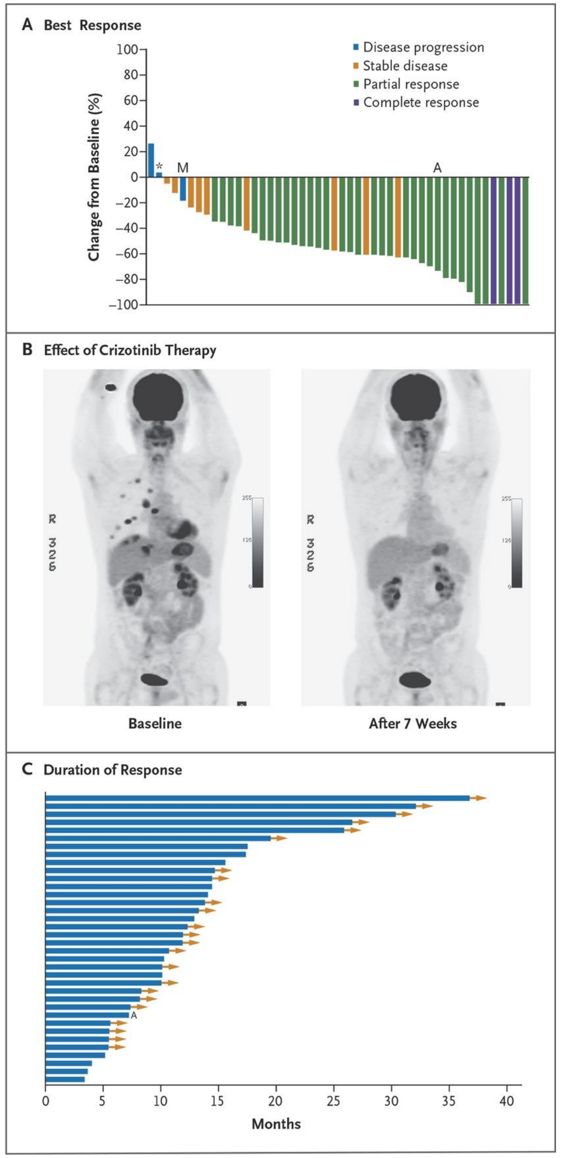
ROS1 fusion



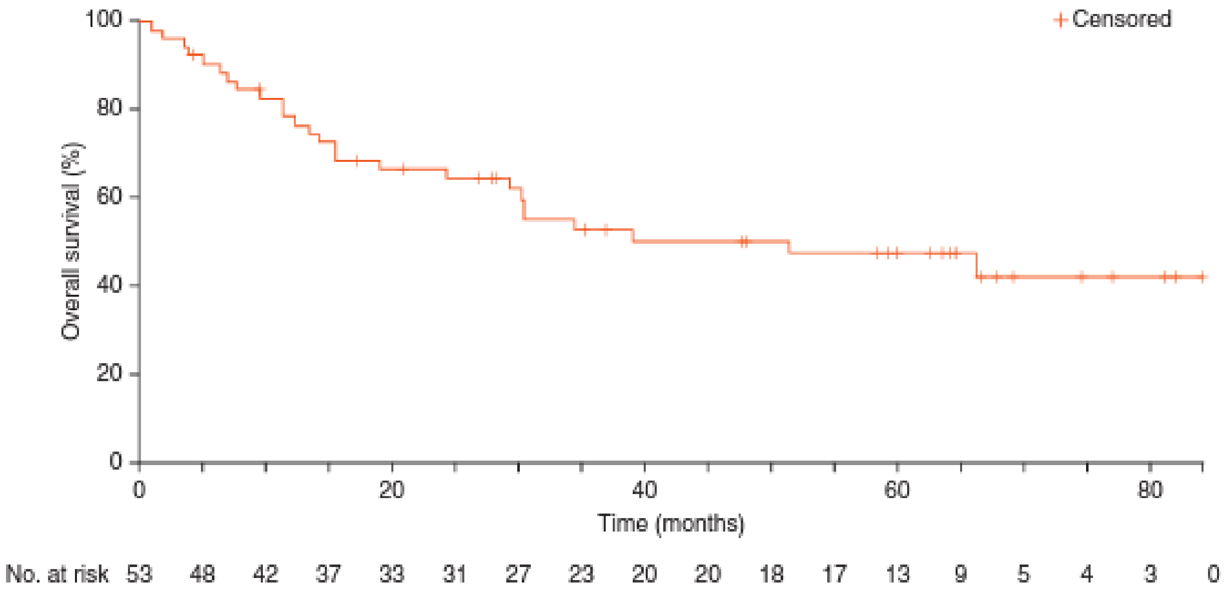
Method	
IHC	Screening
FISH	
(RNA-based) NGS	Fusion partner

Kazdal, *Genes Chromosomes Cancer 2022;61:244-260*

Crizotinib



Na 5 jaar meer dan 50% van de patienten in leven



Shaw, *NEJM, 2014;371:1963-1971*
Shaw, *Annals of Oncology 2019;30:1121-1126*

Entrectinib

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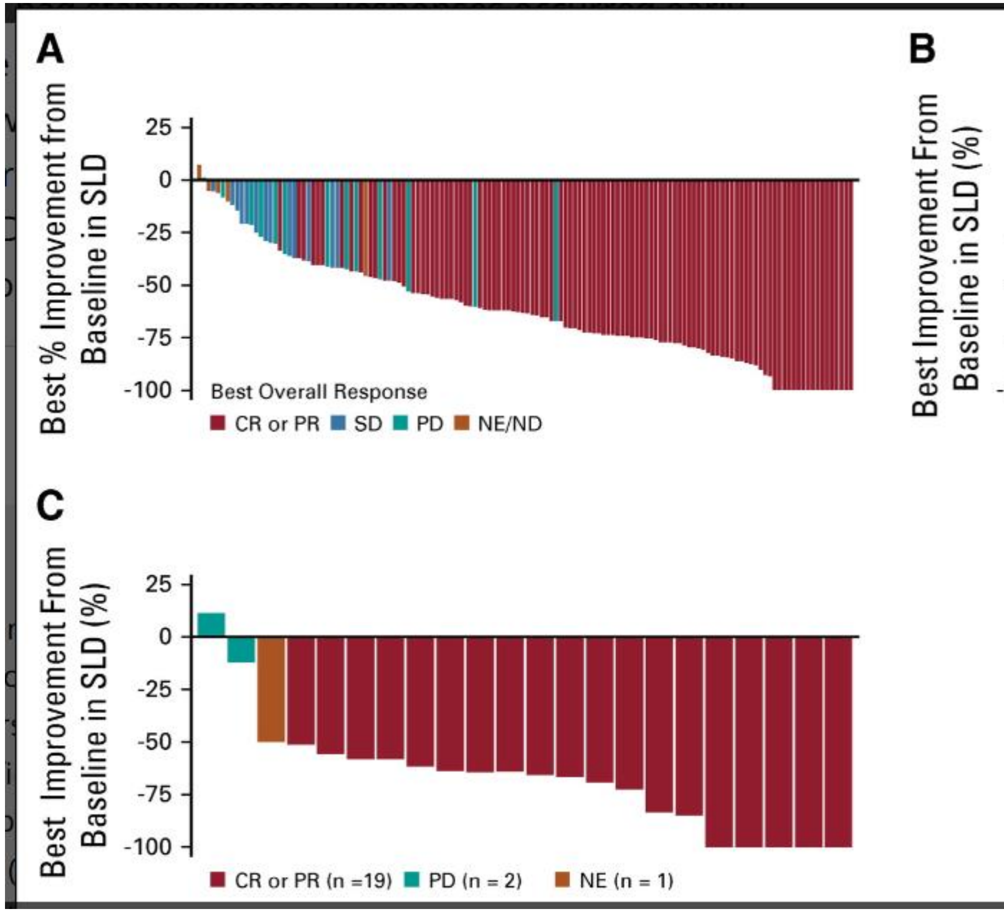

Effectief bij hersenmetastasen

Dziadziuszko, *JCO 2021;39:1253-1263*
Paz-Ares, *ESMO open;2021*

CLINICAL TRIALS

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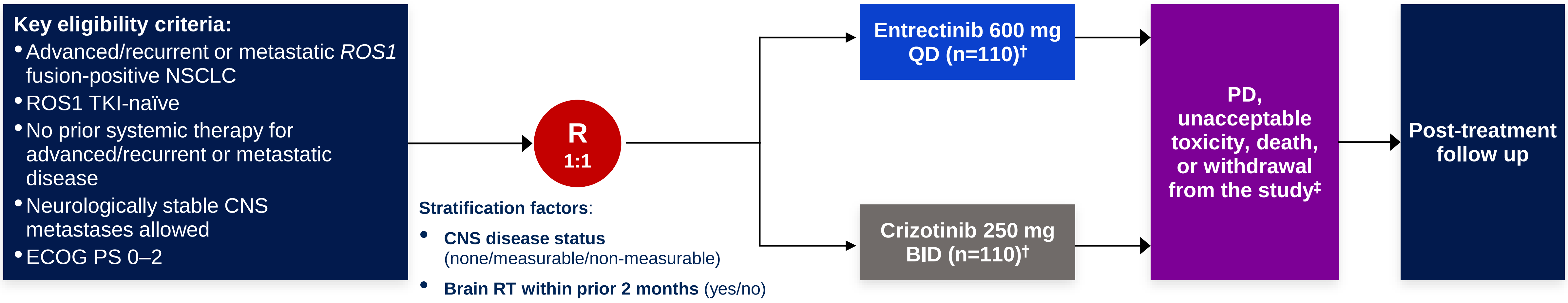
- This is a **randomized, open-label, multicenter, phase 3 head-to-head trial**, designed to compare the efficacy and safety of entrectinib vs crizotinib in adult patients with:
  - ROS1 TKI-naïve advanced/recurrent or metastatic *ROS1* fusion-positive NSCLC
  - With or without CNS metastases that are neurologically stable



NCT04603807

Randomization will be performed centrally via an interactive voice or web-based response system (IxRS); †Estimates based on planned enrollment; ‡Patients with radiographic disease progression or isolated asymptomatic CNS progression may continue treatment at the investigator's discretion

BID, twice daily; ECOG PS, Eastern Cooperative Oncology Group Performance Status; PD, progressive disease; QD, once daily; R, randomized; RT, radiotherapy

Dingemans, *ASCO 2022 TiP*

CLINICAL TRIALS

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DRUP the Drug Rediscovery Protocol

Table 2. Clinical activity of ROS1 TKIs.

ROS1 TKI	Clinical trial	Setting	Outcomes
Crizotinib	PROFILE 1001	Advanced ROS1^{+} NSCLC	mPFS 19 months; mOS 51.4 months 72% ORR
Crizotinib	NCT01945021	Advanced ROS1^{+} NSCLC	mPFS 15.9 months; 71% ORR
Crizotinib	EUCROSS	Advanced ROS1^{+} NSCLC	mPFS 16.8 months; 83.3% ORR
Crizotinib	Acsé	Advanced ROS1^{+} NSCLC	mPFS 5.5 months; mOS 17.2 months 69.4% ORR
Crizotinib	METROS	Advanced ROS1^{+} NSCLC	mPFS 22.8 months; mOS not reached; 65% ORR
Entrectinib	ALKA-372-001, STARTRK-1, STARTRK-2	Advanced ROS1^{+} NSCLC	mPFS 19 months; mOS not reached 77% ORR; 55% intracranial ORR
Ceritinib	NCT01964157	Advanced ROS1^{+} NSCLC	mPFS 9.3 months; mOS 24 months; ORR 62%
Lorlatinib	NCT01970865	TKI-pre-treated ROS1^{+} NSCLC	mPFS 21 months (TKI naive); mPFS 8.5 months (TKI pre-treated); 62% ORR (TKI naive); 35% ORR (TKI pre-treated)
Repotrectinib	TRIDENT-1	TKI-pre-treated ROS1^{+} NSCLC	86% ORR (TKI naive); 40–67% ORR (TKI pre-treated)
Taletrectinib	NCT02279433, NCT02675491	TKI-pre-treated ROS1^{+} NSCLC	66% ORR (TKI naive); 33% ORR (TKI pre-treated)

mOS, median overall survival; mPFS, median progression-free survival; NSCLC, non-small-cell lung cancer; ORR, overall response rate; TKI, tyrosine kinase inhibitor.

Marinelli, *Drugs in Contaxt 2022;11*

RET translocations

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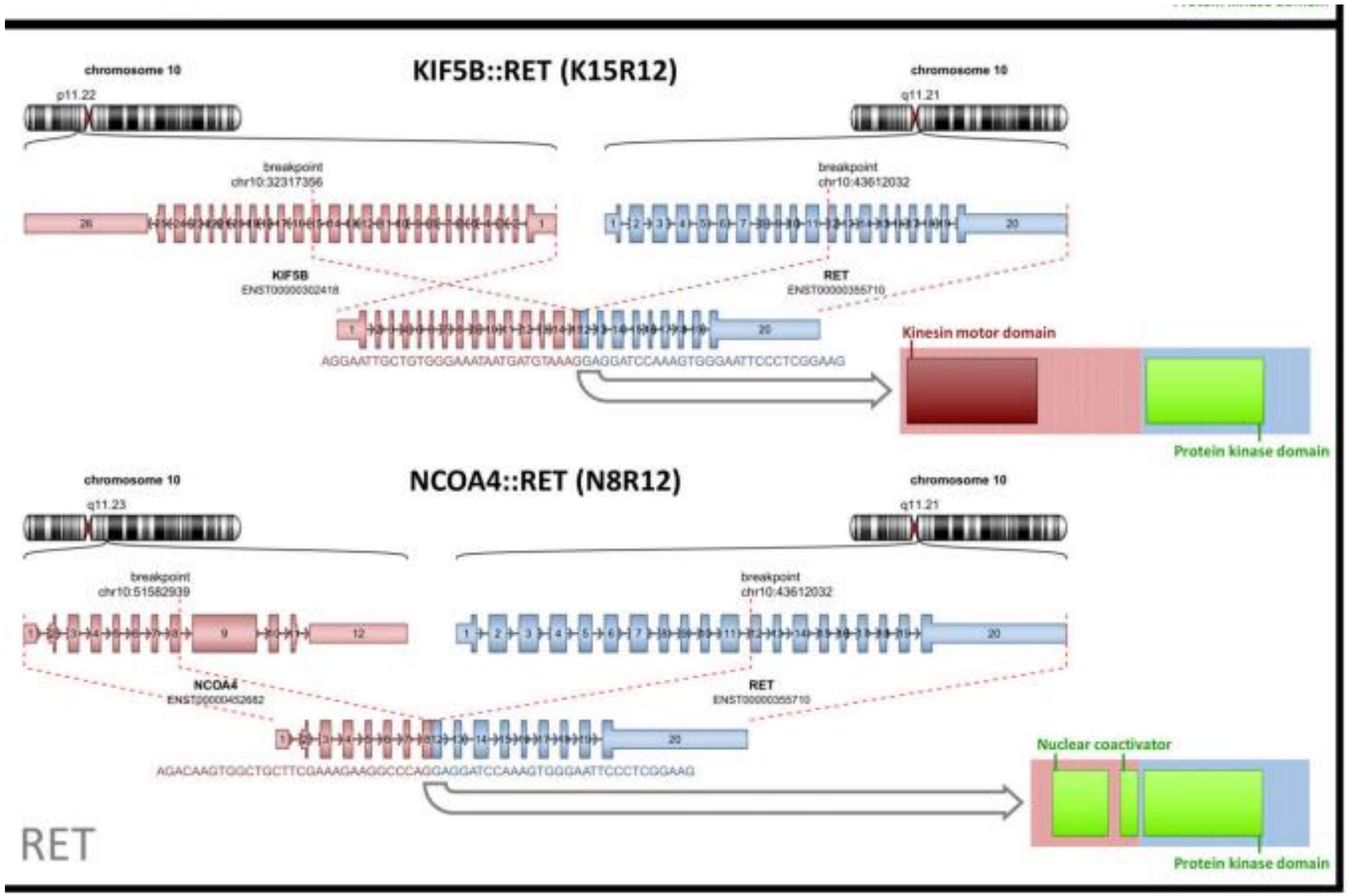
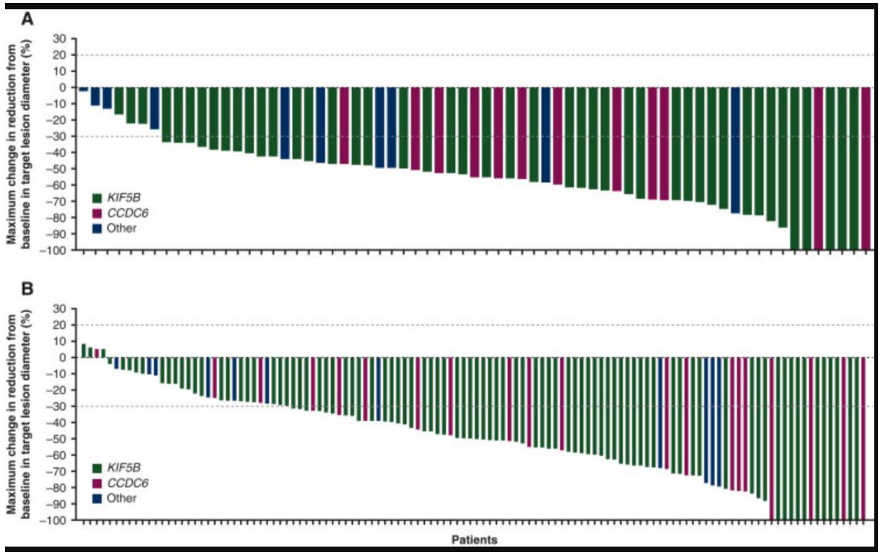


Method	
IHC	Screening
FISH	
(RNA-based) NGS	Fusion partner

Not restricted to Adenocarcinoma!

Kazdal, *Genes Chromosomes Cancer 2022;61:244-260*

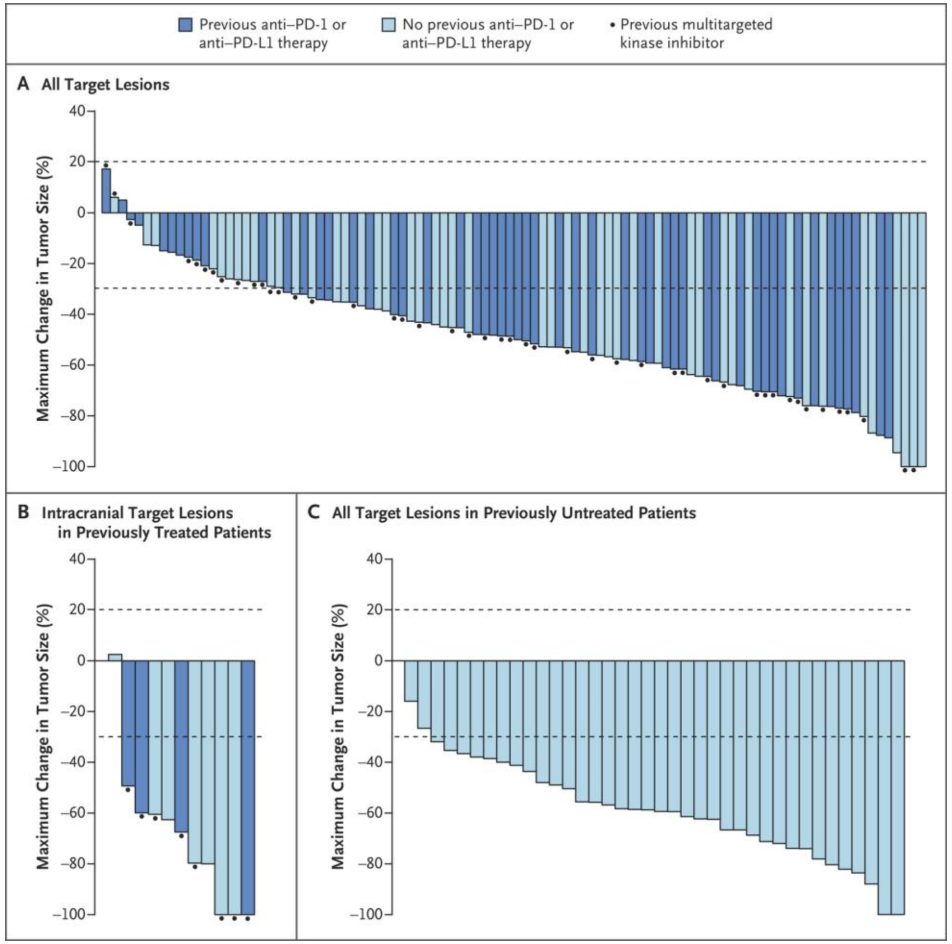
Pralsetinib



Treatment naive (N=75):
ORR 72% (95% CI 60-82)

Prior treatment (N=136)
ORR 59% (95% CI 50-67)

Selpercatinib



Griesinger, *Annals of Oncology 2022;33:1168-11778*
Drilon, *NEJM 2020;383:813*

Selpercatinib versus chemotherapie: langere ziekte vrije overleving

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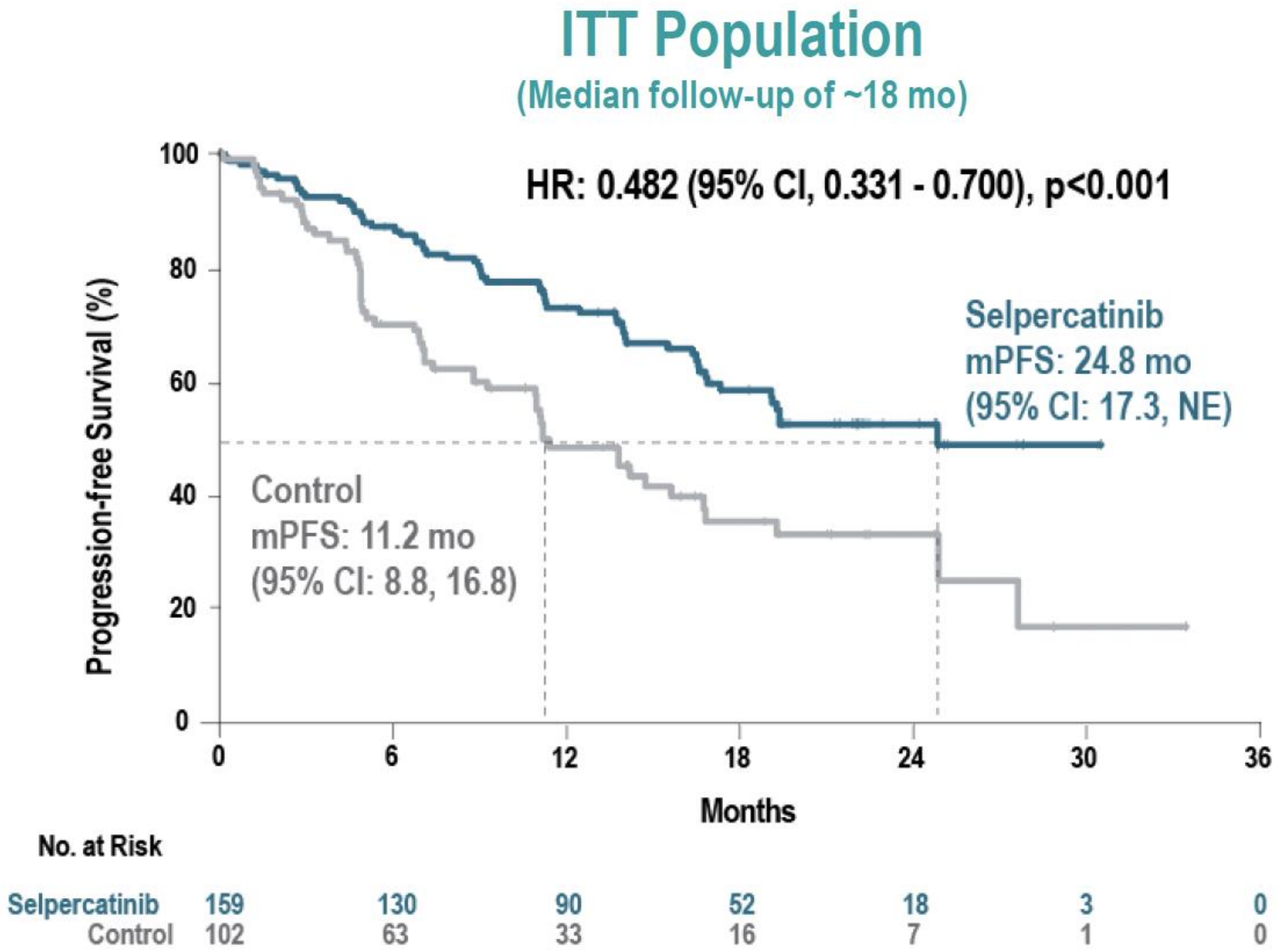

Loong et al, ESMO 2023

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Zelfs voor zeer zeldzame ziekte nieuwe medicatie in ontwikkeling!

Addressing On-Target Resistance to RET TKIs

Next-generation RET TKIs

Compound	*RET* Substitution Coverage			VEGFR2	Other Non-RET Kinases	CNS?	Status
	V804X Gatekeeper	G810X Solvent Front	Other *RET* Mutation				
TPX-0046[1]	Less potent	✓	Y806N (hinge)	-	TRKA-C, SRC, FGFR1-2, FLT3, JAK2	?	Phase I/II (NCT04161391)
LOXO-260[2]	✓	✓	G810S+V804M	-	TRKC (40x selectivity)	?	Phase I/II (NCT05241834)
Vepafestinib[3,4] **(TAS0953/HM06)**	✓	✓	Y806C/N	-		✓	Phase I/II (NCT04683250)
EP0031[5] **(A400/KL590586)**	✓	✓		-	JAK1/2 (10-22x selectivity)	✓	Phase I/II (NCT05443126)
APS03118[6]	✓	✓	Y806H	-		✓	Phase I/II (NCT05653869)

Data based on publicly-available preclinical data; grey = unknown

[1]Drilon A et al., ESMO 2019; [2]Kolakowski GR et al., AACR 2021; [3]Miyazaki I et al., AACR-NCI-EORTC 2021
[4]Odintsov I et al., AACR-NCI-EORTC 2021; [5]Zhou Q et al., ASCO 2023; [6]Drilon A et al., AACR 2022

cMET: mutaties en overexpressie

- **Different mechanisms of MET activation**
  - cMET overexpression, amplification, exon 14 skipping mutations, fusions, heterodimerisation
- **Convergent resistance mechanisms for several RTKs**
  - EGFR, KRAS, RET-rearranged NSCLC[1,2,3]
  - Significant cross-talk in pathways
- **Capmatinib and tepotinib (Class Ib) approved for MET exon 14 skipping mutations**
  - GEOMETRY[4]
    - **2/3L** ORR 41%, PFS 5.4 m
    - **1L** ORR 68% PFS 12.4 m
  - VISION[5]
    - **2/3L** ORR 47.7%, PFS 11.1 m
    - **1L** ORR 54.7%, PFS 15.3 m

Sarcomatoid Lung Cancer

Category	Drug	Status
TKI		
Type Ia	Crizotinib	Approved in ALK/ROS
Type Ib	Capmatinib Tepotinib	Approved Approved
Type II	Cabzantinib	Approved in RCC
Type III	Tivantinib	Failed phase III
Antibodies		
Anti HGF	Ficlatuzumab	Failed phase II
Anti cMET	Ornatuzumab	Failed phase III
cMET-EGFR Bispecific Ab	Amivantamab	Approved EGFR ex20ins

1. Chua et al. CCR 2021; 2. Awad et al. NEJM 2021; 3. Lin et al. Ann Oncol 2020; 4. Wolf et al. NEJM 2020; 5. Paik et al. NEJM 2020

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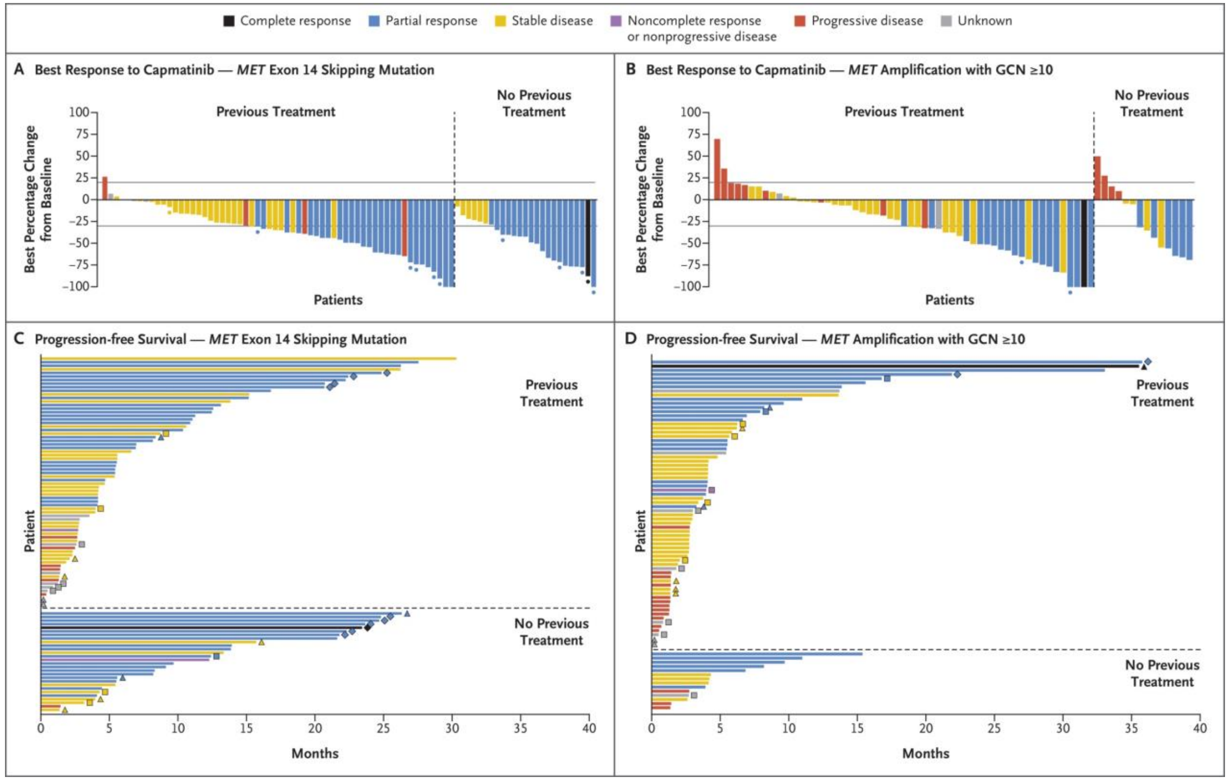
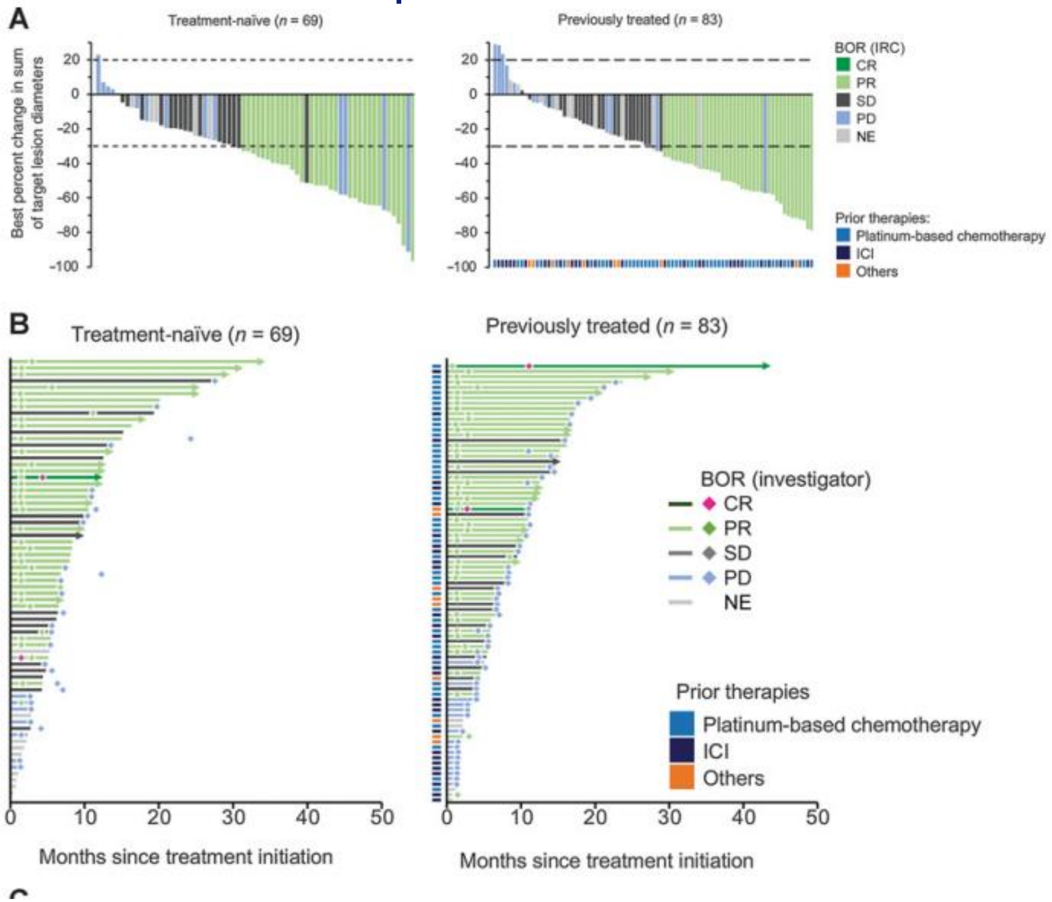
Capmatinib



Tepotinib



DRUG Access Protocol

Wolf, *NEJM 2020;383:944-957*
Le, *CCR, 2022:28:1117-1126*

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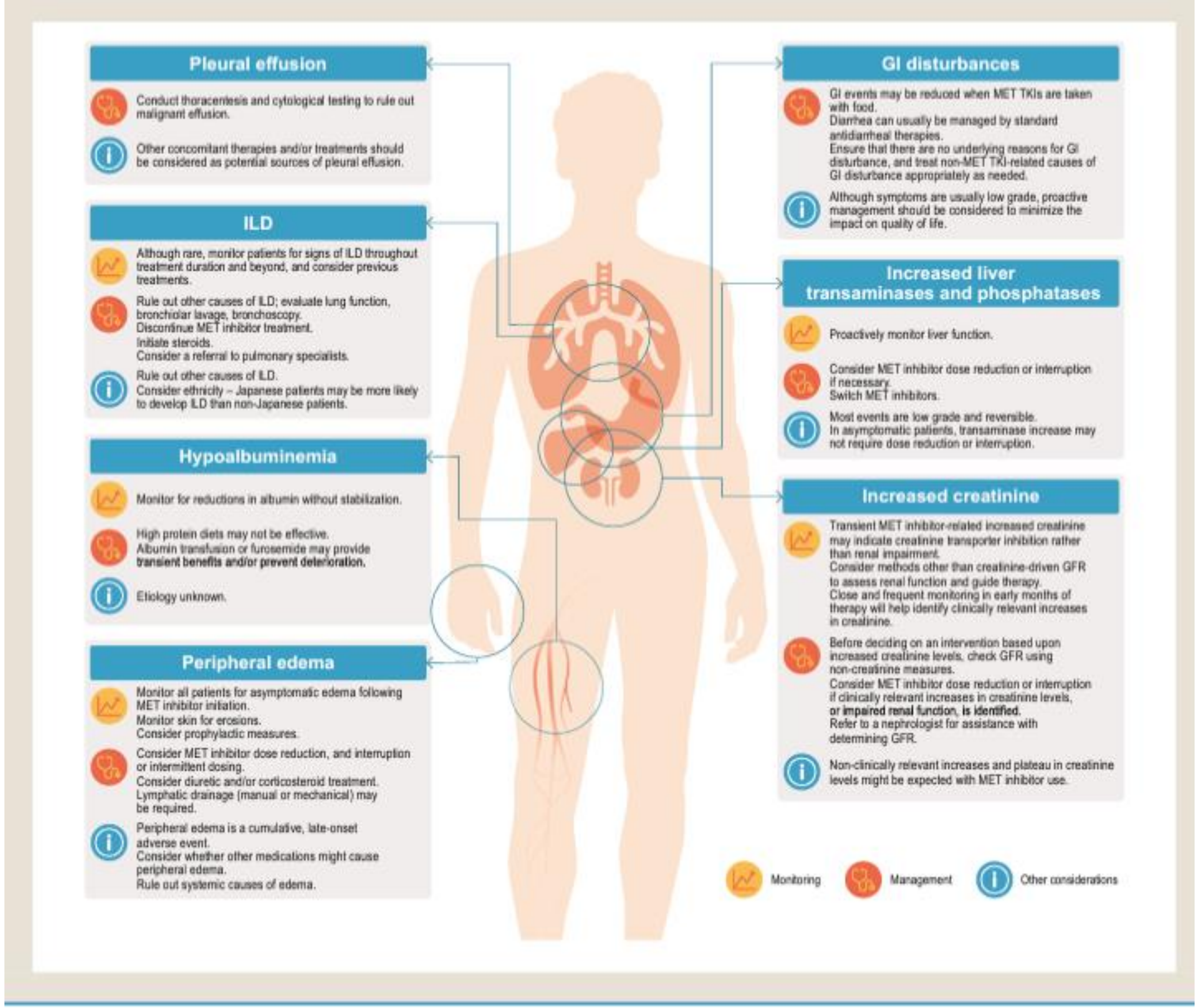
Bijwerkingen MET remmers



Cortot, *Clinical Lung Cancer, 2022;23:195-207*

Antibody Drug Conjugates

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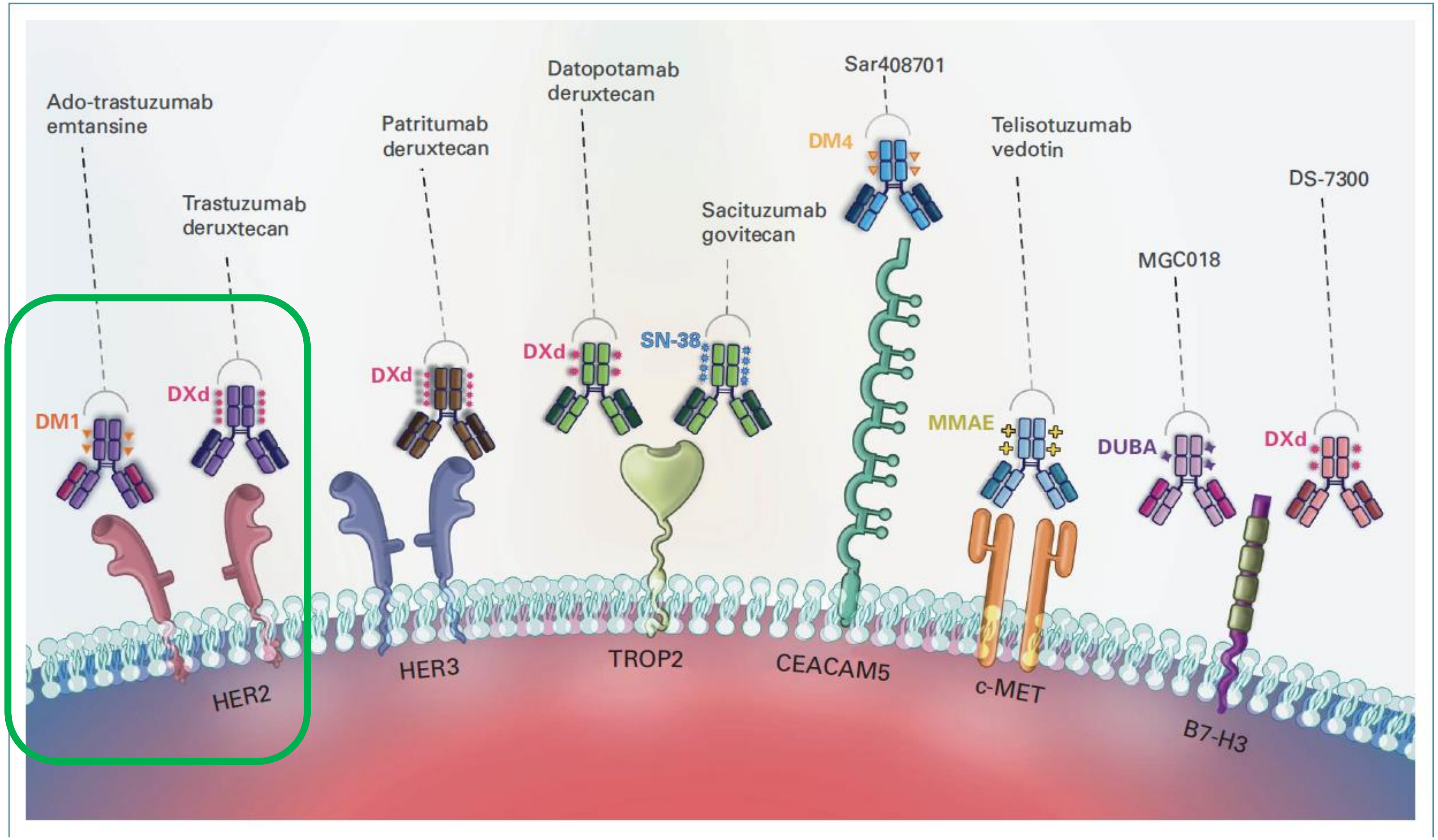

HER2 mutations

Passaro et al, JCO 41:3747, 2023

Trastuzumab-deruxtecan HER2 mutaties

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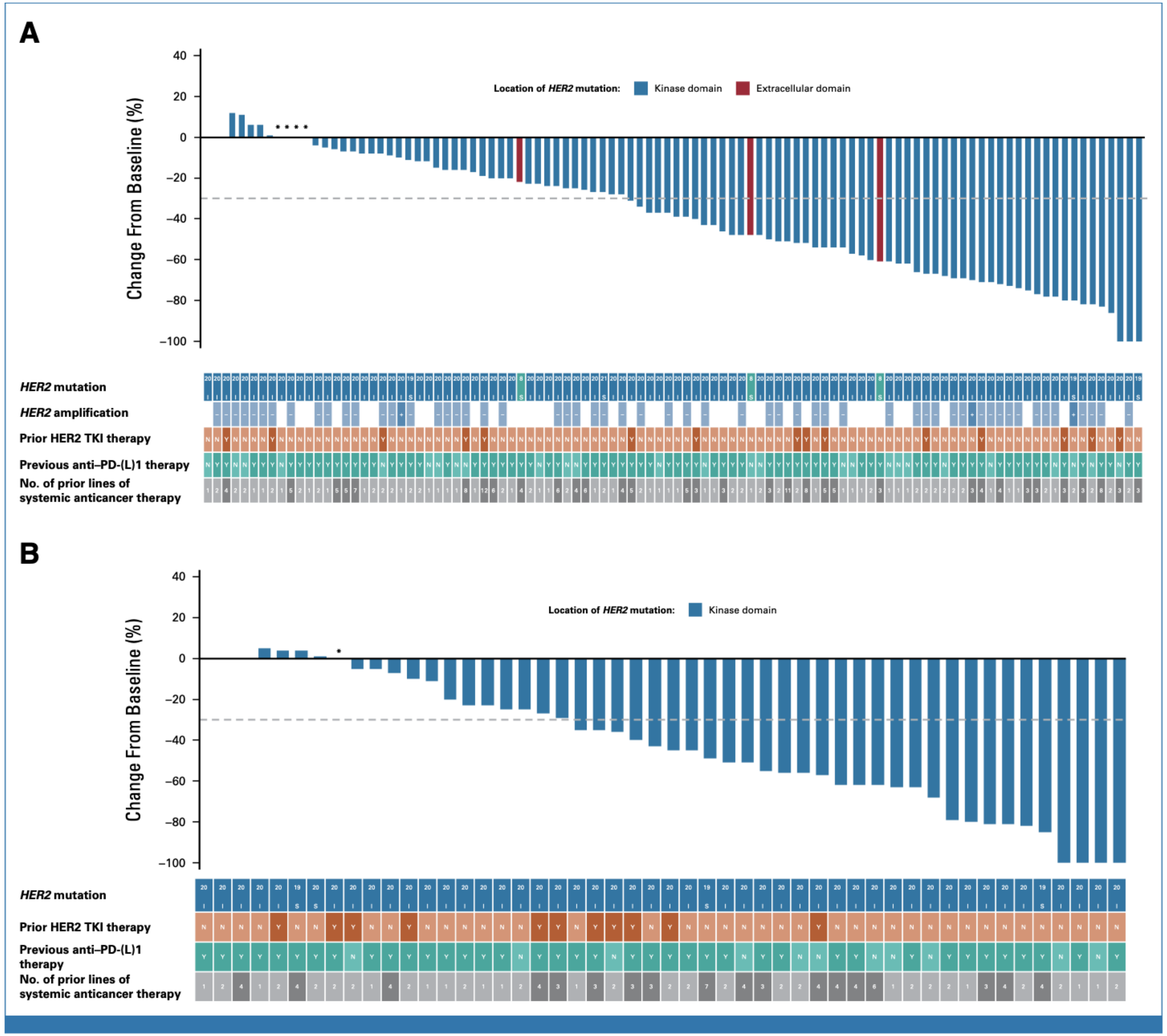

TABLE 2. Response to T-DXd in Patients With *HER2*-Mutant mNSCLC

Response Assessment by BICR	T-DXd 5.4 mg/kg Once Every 3 Weeks (n = 102)	T-DXd 6.4 mg/kg Once Every 3 Weeks (n = 50)
Confirmed ORR, No. (%)	50 (49.0)	28 (56.0)
95% CI	39.0 to 59.1	41.3 to 70.0
Best confirmed overall response, No. (%)		
CR	1 (1.0)	2 (4.0)
PR	49 (48.0)	26 (52.0)
SD	45 (44.1)	18 (36.0)
PD	4 (3.9)	2 (4.0)
Nonevaluable[a]	3 (2.9)	2 (4.0)
DCR, No. (%)	95 (93.1)	46 (92.0)
95% CI	86.4 to 97.2	80.8 to 97.8
DoR, months, median (95% CI)	16.8 (6.4 to NE)	NE (8.3 to NE)
TTIR, months, median (range)	1.8 (1.2-7.0)	1.6 (1.2-11.2)
Follow-up, months, median (range)	11.5 (1.1-20.6)	11.8 (0.6-21.0)

Goto et al, JCO, 2023

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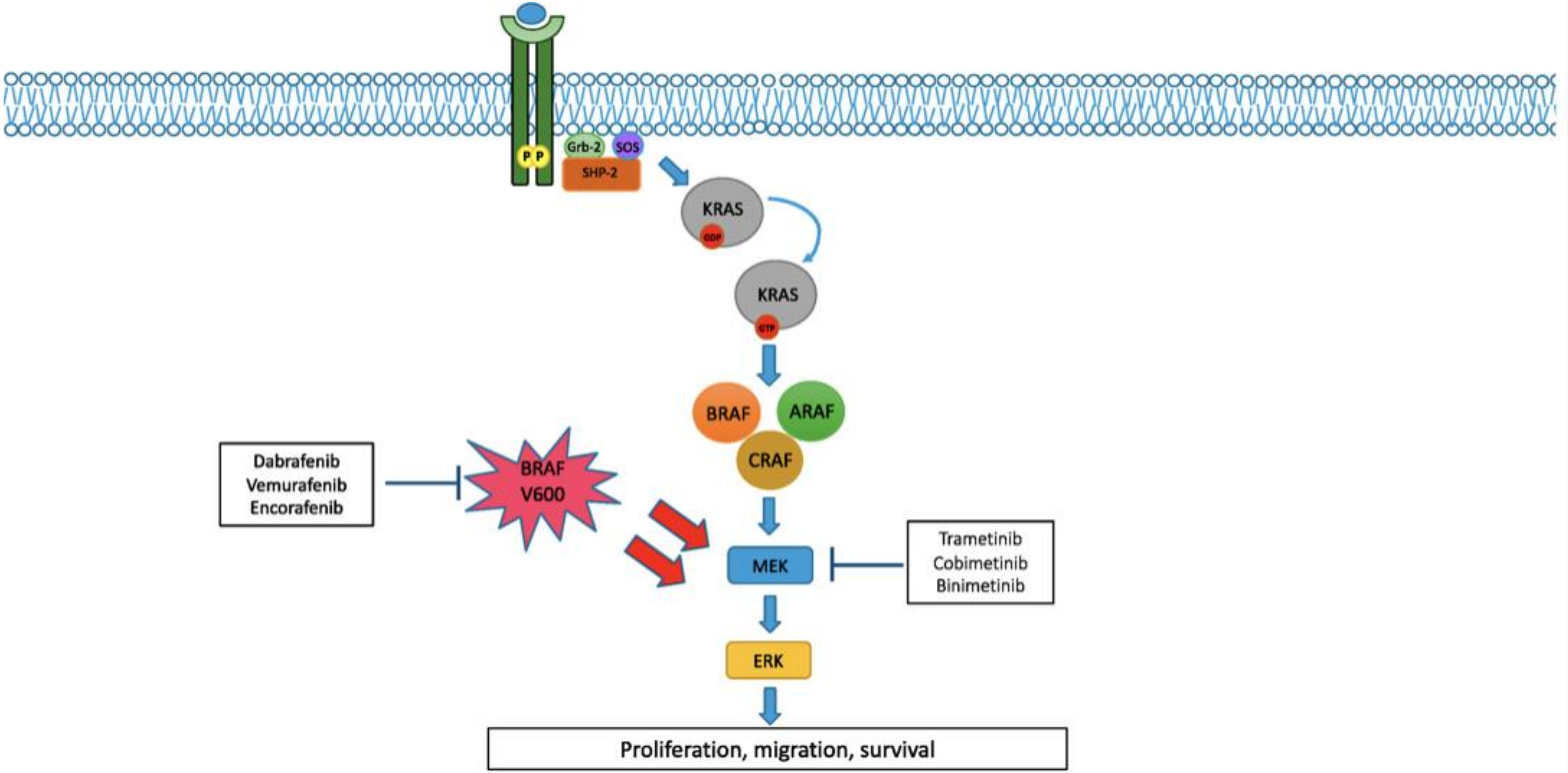
Ontwikkelingen HER2

	Drug	Target	Phase	ORR	mPFS	IC-ORR	Reference
TKI	**Afatinib**	HER	II	7.7%	15.9 weeks		Dziadziuszko R et al. *J Thorac Oncol* 2019
TKI	**Neratinib**	HER	II	4%	5.5 mo		Hyman DM et al. *Nature* 2018
TKI	**Dacomitinib**	HER	II	12%	3 mo		Kris MG et al. *Ann Oncol* 2015
TKI	**Pyrotinib**	HER	II	19.2%	5.6 mo		Song Z et al. *BMC Med* 2022
TKI	**Poziotinib**	EGFR/HER2	II	27.8%	5.5 mo		Le X et al. *J Clin Oncol* 2022
TKI	**ENLV-002**	HER2	I	-	-		-
TKI	**BI 1810631**	HER2	I	50%	-		Yamamoto N et al. WCLC 2023
TKI	**BAY 2927088**	EGFR/HER2	I	-	-		Tan D et al. AACR 2023
TKI	**ORIC-114**	EGFR/HER2	I	-	-		Murray BW et al. AACR 2022
ADC	**Trastuzumab emtansine (T-DM1)**	HER2	II	44%	5 mo		Li B et al., *J Clin Oncol* 2018
ADC	**Trastuzumab deruxtecan (T-DXd)**	HER2	II (5.4 mg/kg)	49.0%	9.9 mo	50.0%	Janne P et al., WCLC 2023 Planchard D et al., ESMO 2023

Lin et al, ESMO 2023

BRAF MUTATIES
Ook bij melanoom



Sforza et al, Cancers 2022

DABRAFENIB EN TRAMETINIB, NSCLC BRAF V600E

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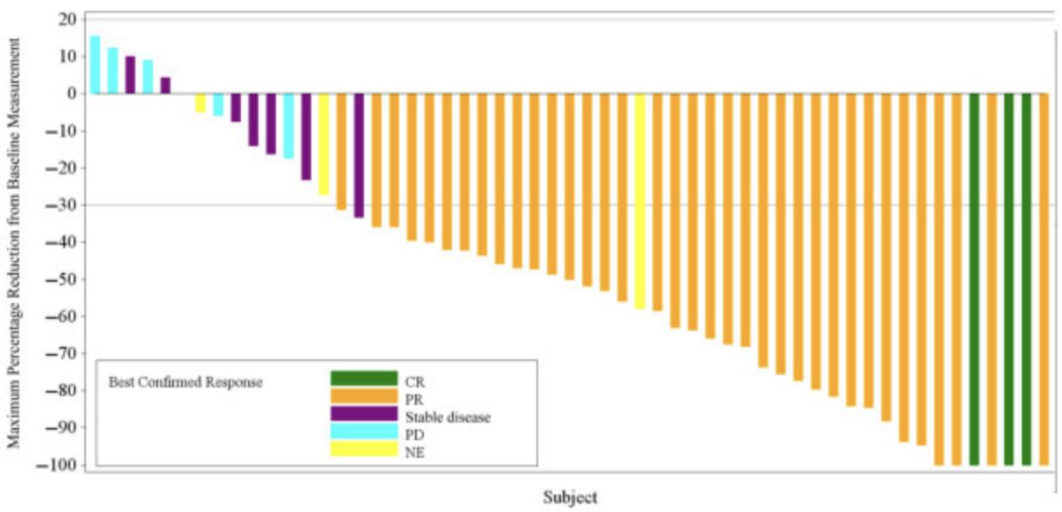
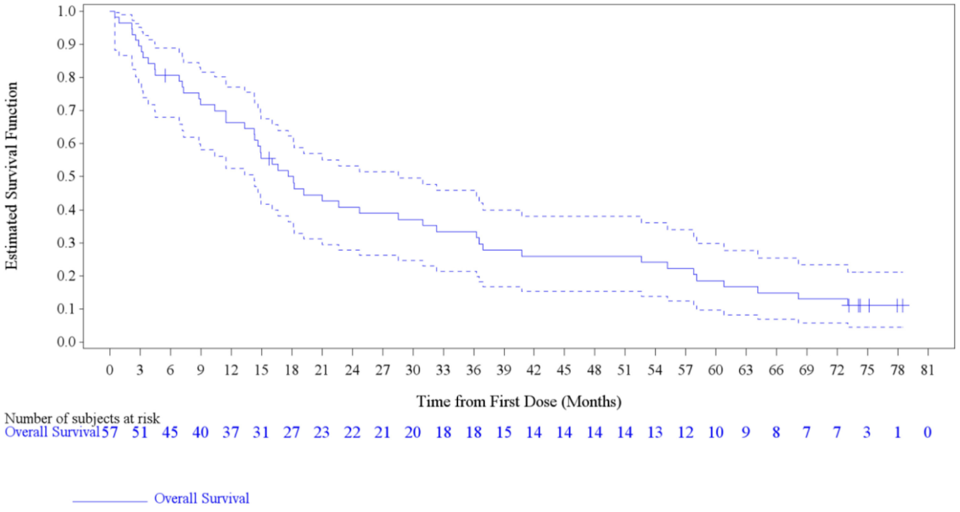
A





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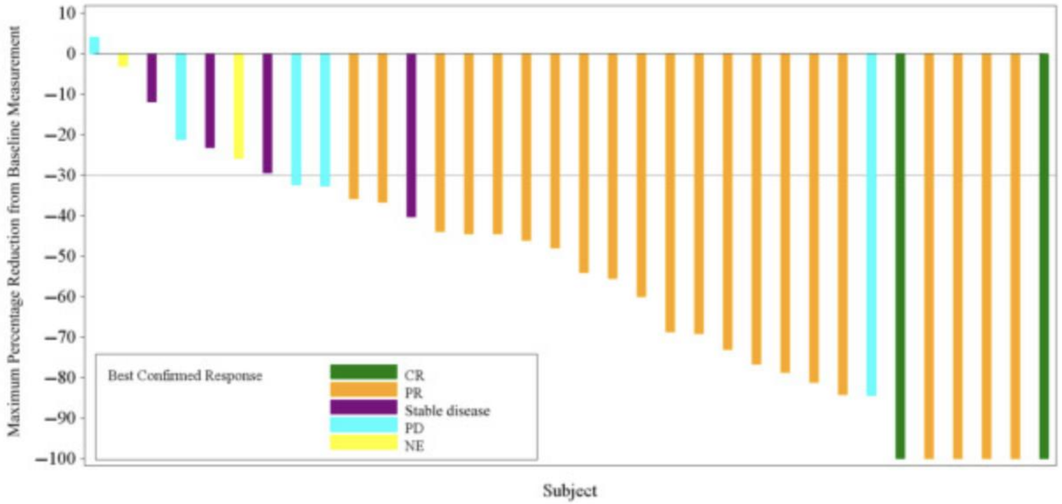
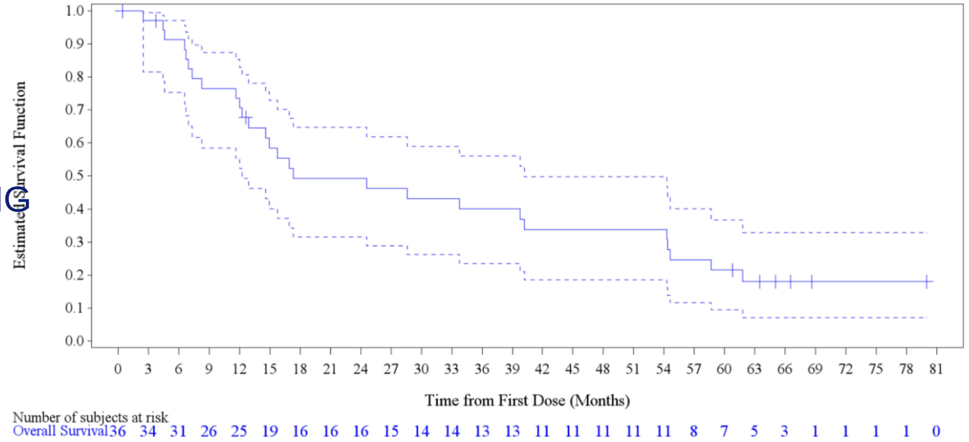
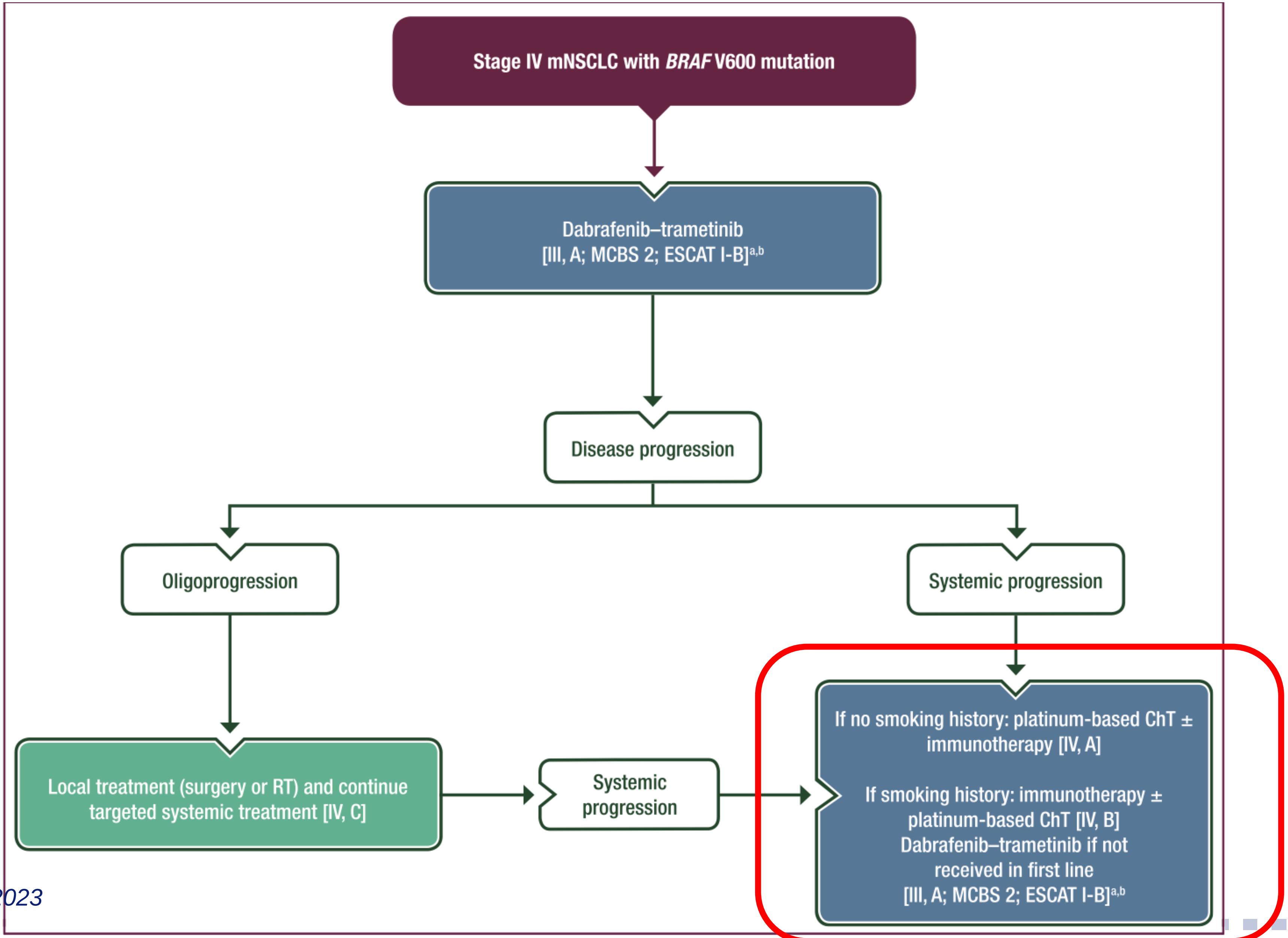


GEEN VOORBEHANDELING

D



Planchard et al, JTO 2022



Hendriks et al, Ann Oncol 2023

Wanneer, in welk stadium en bij welke mutaties wordt besloten een nieuw biopt van de tumor te nemen om te kijken of er sprake is van nieuwe/veranderde mutaties?

Wat als de kanker gaat groeien onder eerste behandeling

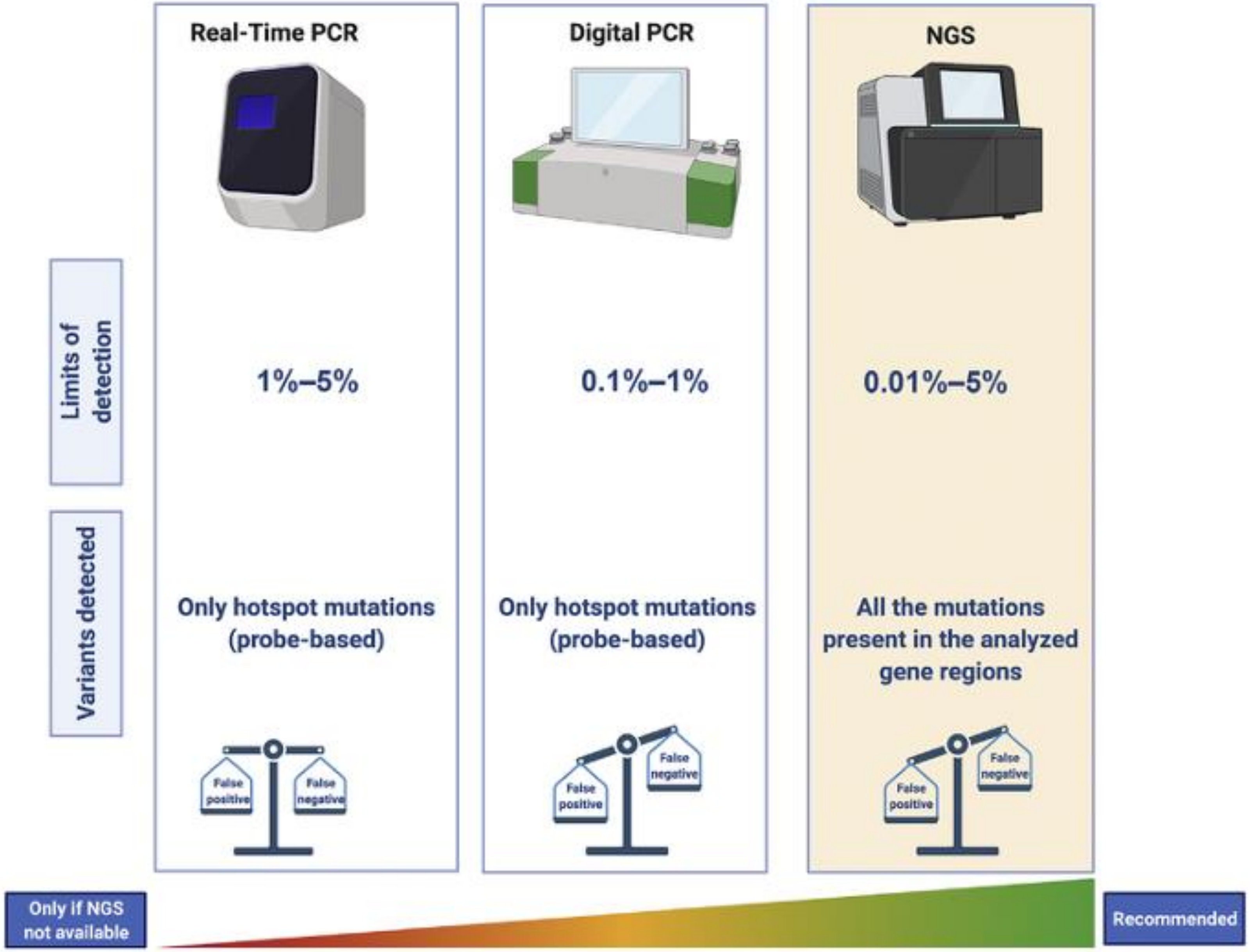
Resultaat eerste behandeling

Mate van groei:

- langzaam -> reden van groei en doorgaan
- op 1 plaats -> lokale behandeling?
- op veel plaatsen / klachten -> nieuw biopt / bloed analyse

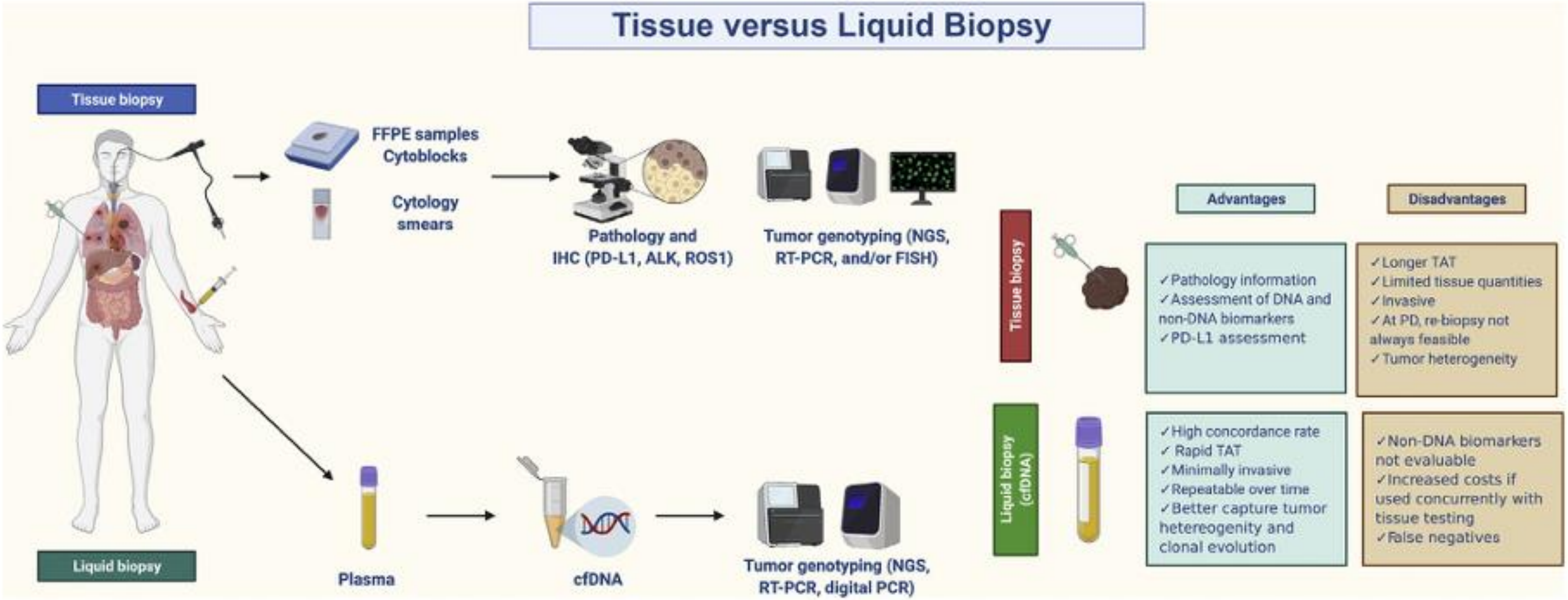
Reden van groei = resistentie mechanisme

Immunotherapie?



Rolfo, JTO 2021; 16:1646

Weefsel -Bloed



Rolfo et al, JTO 2021; 16:1646

Figure 1. The Patient Journey Through Oncology Treatment

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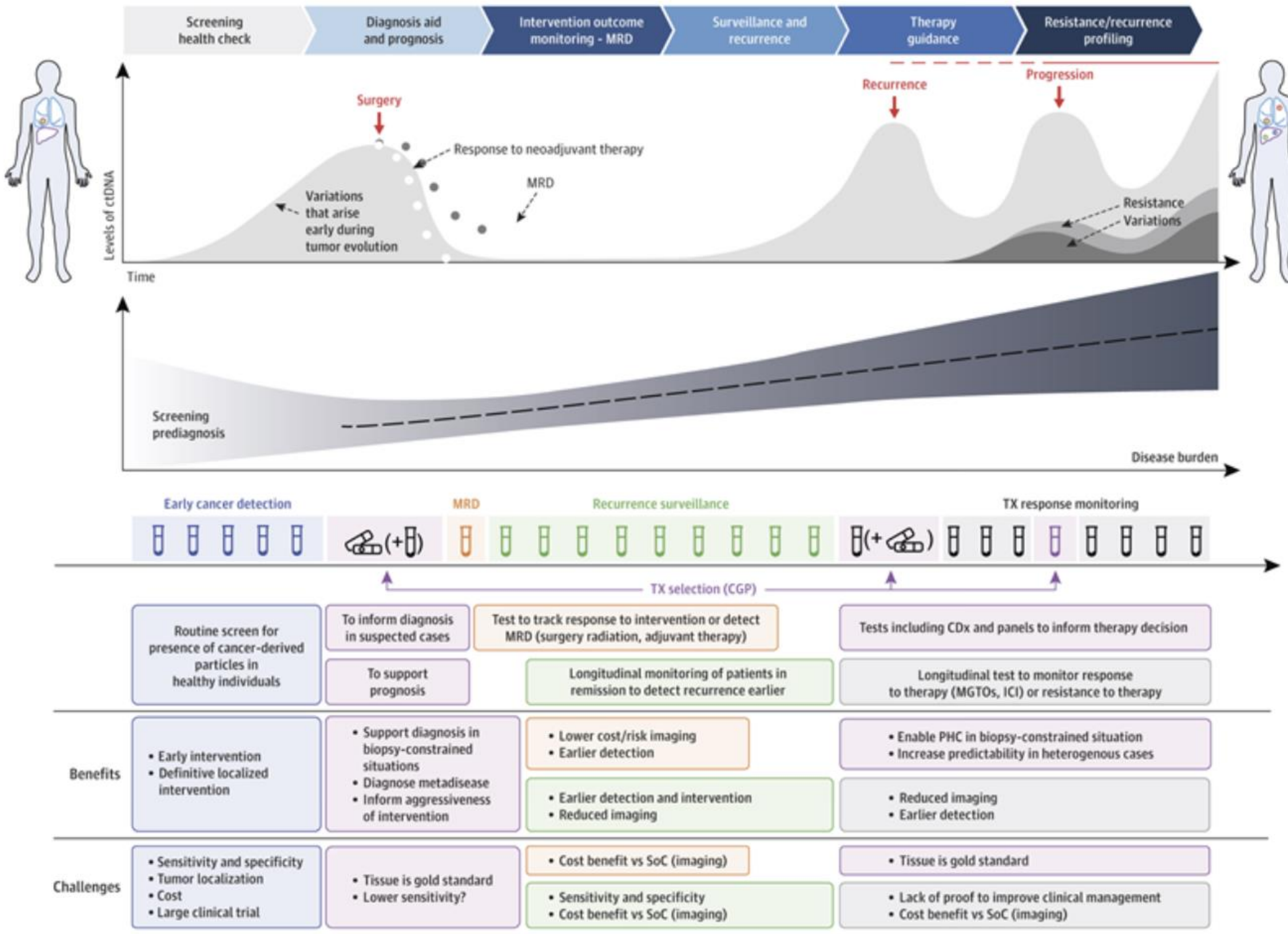

Overcoming Acquired Resistance Mutation MET D1228N to Crizotinib With Cabozantinib in NSCLC With MET Exon 14 Skipping Mutation

Melinda A. Pruis, MD[1,2]; M. S. Paats, MD, PhD[1]; W. R. R. Geurts, PhD[3]; H. J. Dubbink, PhD[3]; and A.-M. C. Dingemans, MD, PhD[1]

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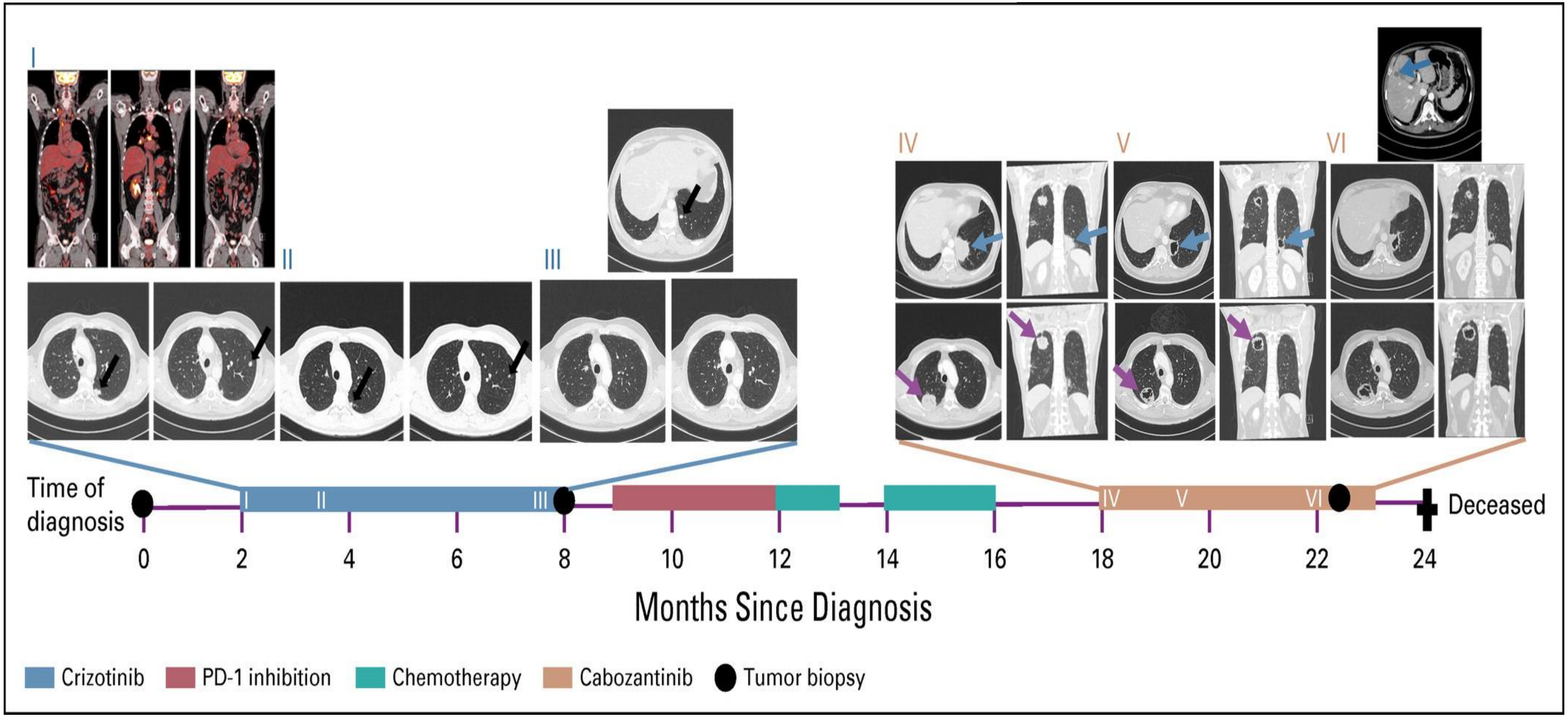
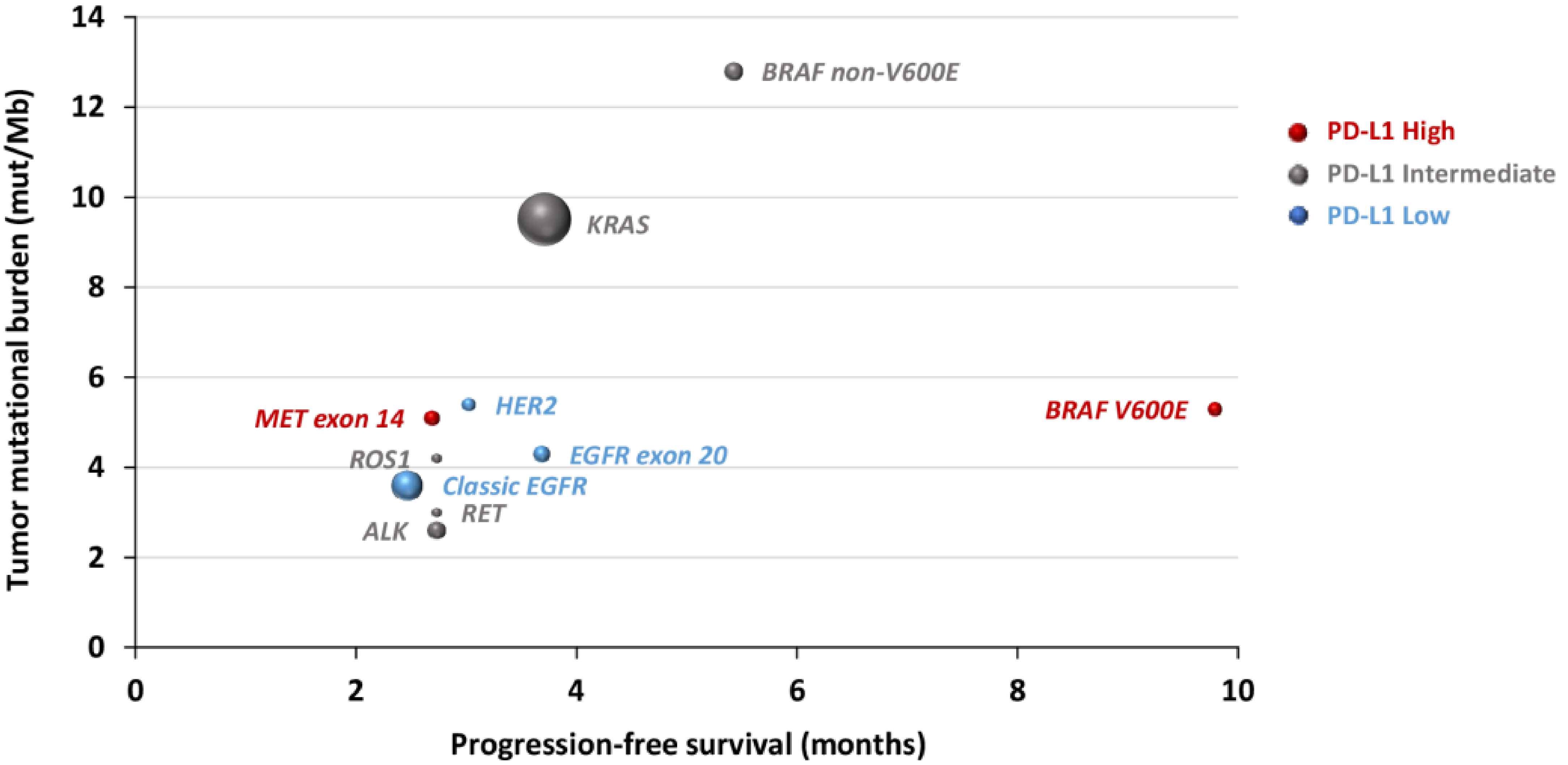


Pruis et al; JCO Precision Oncology 2021 5849-853.



Negrao et al, J Immunother Cancer 2021;9:e002891

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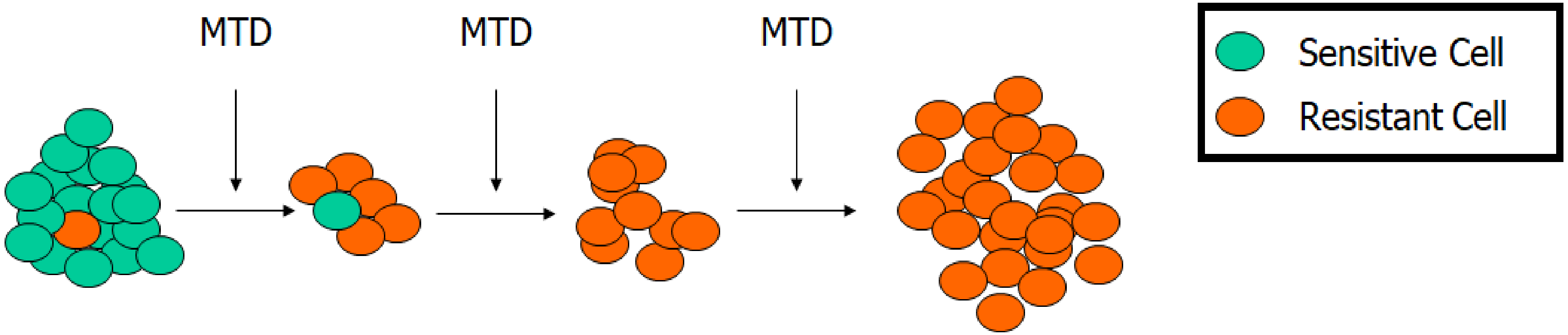
Wordt er bij de longkanker(mutaties) al gebruik gemaakt van de AI (kunstmatige intelligentie)?

Evolutionary therapy

Standard of care in metastatic cancers:

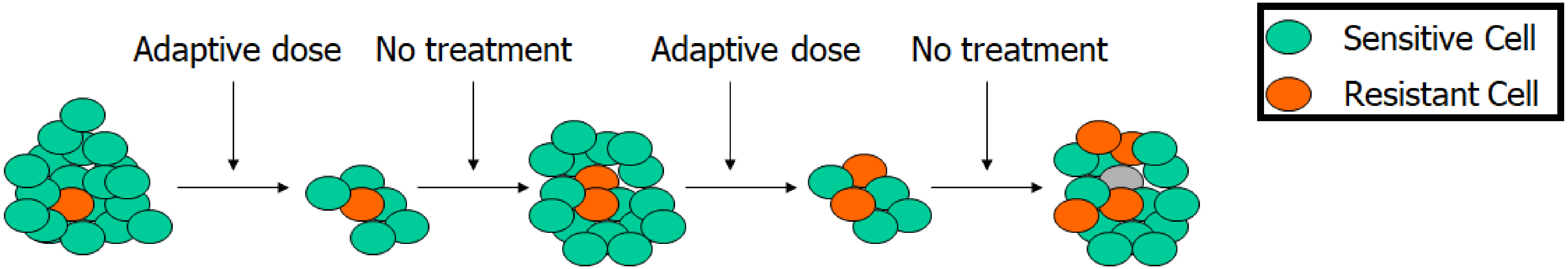


Evolutionary therapy:

game-theoretic models

resistance

Standard of Care



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Zeldzame mutaties