Post ONS 2016

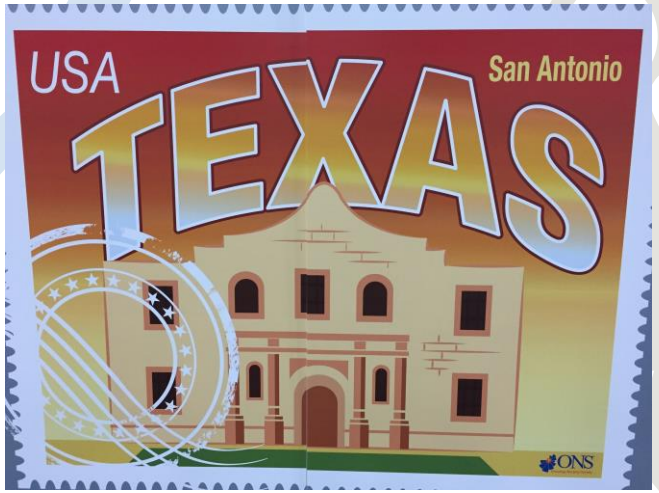
Stichting Oncowijs

Hot Topics

Jan Ouwerkerk

Research Coördinator Oncologie

Leids Universitair Medisch Centrum



Stichting Oncowijs

Disclosure belangen spreker

(potentiële) belangenverstrengeling	Geen
Voor bijeenkomst mogelijk relevante relaties met bedrijven	Roche, Bayer, Teva Advies
• Sponsoring of onderzoeksgeld • Honorarium of andere (financiële) vergoeding • Aandeelhouder • Andere relatie, namelijk …	Geen

San Antonio Crew

Stichting Oncowijs

Nieuwe ontwikkelingen in de USA in de afgelopen 3 jaar

2013

Regorafenib bij GIST	Stivarga ®	Bayer
Radium 223		Bayer
Catumaxomab	Removab®	
Pertuzumab	Perjeta ®	Roche
Axitinib	Inlyta ®	Pfizer

Nieuwe ontwikkelingen in de USA in 2014

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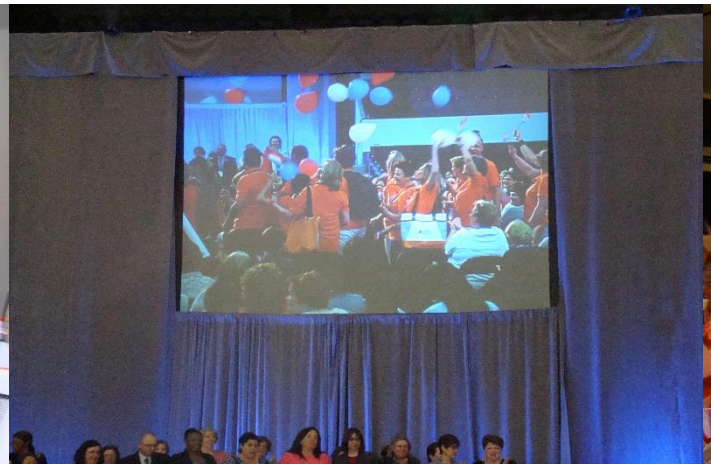
Afatinib	Gilotrif ®	Boehringer-Ingelheim
Trastuzumab-emtansine	Kadcyla®	Roche
Entazulamide	Xtandi ®	Astellas
Luer-access valves	Curos ®	Ivera Medcor



Nieuwe ontwikkelingen in de USA in 2015

Ramucirumab	Cyramza ®	Lilly
Pembrolizumab	Keytruda ®	Merck (MSD)
Lenvatinib	Lenvima ®	Eisai
Palbociclib	Ibrance ®	Pfizer
Obinutuzumab	Gazyvaro ®	Roche
Tegaderm IV Port dressing	Tegaderm CHG ™	3M

Nieuwe ontwikkelingen in de USA in 2016

Die nieuwe therapien: hoe zit het ook al weer???

Trifluridine+Tipiracil (TAS-102)	Lonsurf®	Servier
Ceritinib	Zykadia®	Novartis Oncology
Alectinib	Alecensa®	Roche
Vasculair Imaging	Veinsite™	Vuetek Scientific

Hot Topic 2016

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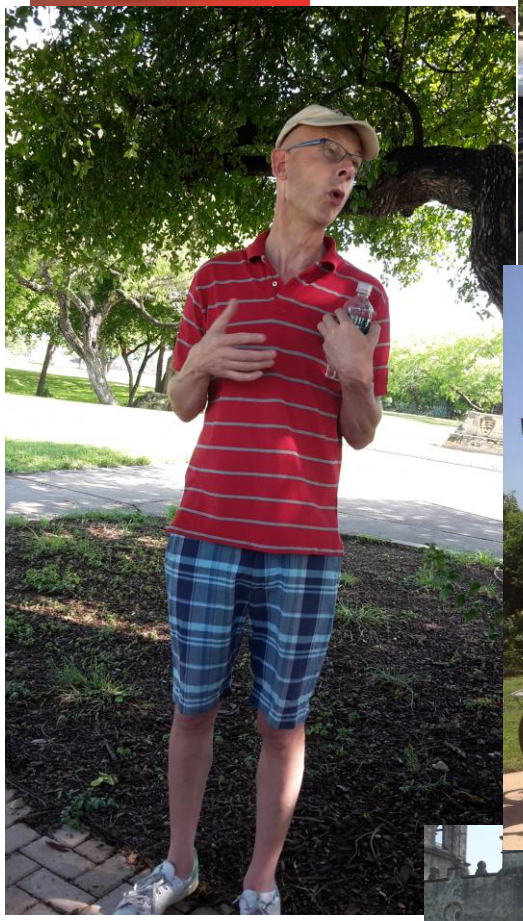

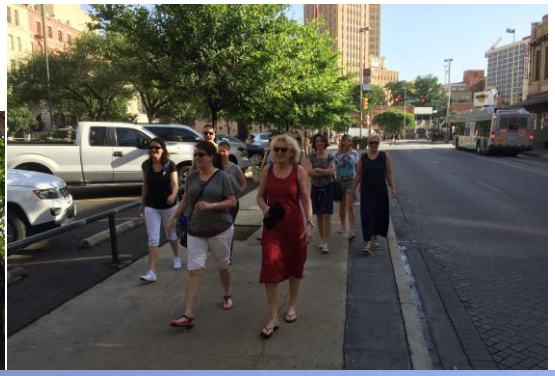

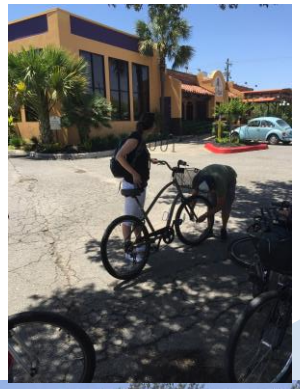

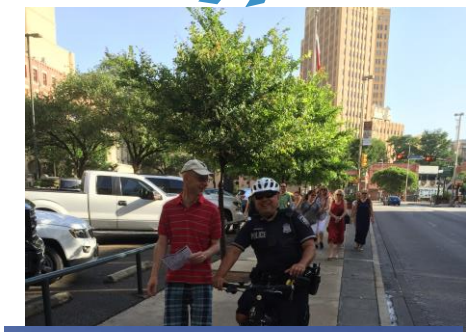

Stichting Oncowijs

ONS 41ST ANNUAL Congress

Stichting Oncowijs

ONS 41ST ANNUAL Congress

April 28–May 1, 2016
San Antonio, TX

BIG CHANGE STARTS HERE

NSCongress
gChangeStartsHere

ONS
Oncology Nursing Society

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Hoe zat het ook alweer met al die nieuwe anti-kanker therapieën

- Weet om welke medicatie het gaat
  - **Small molecule, monoclonaal antibody**
- Ken de generische naam : ceritinib /bevacizumab
- Weet wat de target is en hoe het normaal in het lichaam werkt (b.v. net als andere soortgelijke middelen).
- Weet of de medicatie “personalized” is voor het genetische profiel van de tumor bij jou patiënt

ibs (tinibs, anibs, rafenibs, brutinib, metanib, lisib, parib, ciclib, degib)

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- Small molecules
- Tabletten
  - Therapietrouw
  - Mogelijk medicatie/voedsel, medicatie/medicatie interacties
  - Patiënt voorlichting
- Voorbeelden
  - Erlotinib, imatinib, pazopanib, sunitinib, sorafenib,

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Mabs

- Monoclonale antibodies
- Intraveneus/subcutaan
- Mogelijkheid voor infusie reacties
- Voorbeelden:
  tositumomab, rituximab, trastuzumab, panitumumab, bevacizumab

Wat betekent de naam?

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Monoclonal antibody = mab

- tositumomab and iodine 131
- rituximab
- trastuzumab
- panitumumab
- bevacizumab

http://www.ama-assn.org/ama/pub/physician-resources/medical-science/united-states-adopted-names-council/naming-guidelines/naming-biologics/monoclonal-antibodies.page

Wat betekent de naam?

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- tositumomab and iodine 131
  - mo = mouse
- rituximab
  - xi = chimeric or cross between mouse and human
- trastuzumab, bevacizumab
  - zu = humanized
- panitumumab
  - u = fully human

Wat betekent de naam?

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TU = tumor

- tositumomab and iodine 131
- rituximab
- trastuzumab
- panitumumab

Big Change starts here

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New Kids on the block

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Lonsurf®
(trifluridine and tipiracil) tablets

ALECENSA™
alectinib 150 mg capsules

TAS 102 / Lonsurf®
trifluradine & tipiracil
bij gem. Colorectaal tumoren

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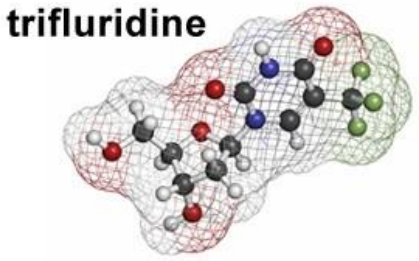
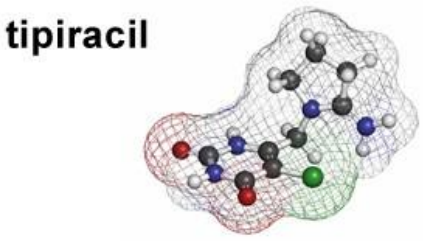
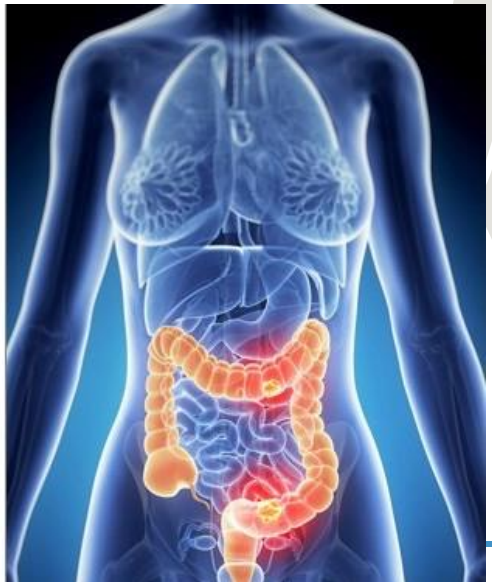
Voor de behandeling van patienten met gemetastaseerd colorectal kanker die eerder behandeld zijn met 5-Fu, Oxaliplatin, Irinotecan, een anti-VEGF therapie, en als KRAS WT een anti-EGFR therapie







Trifluradine & tipiracil (LONSURF) ®

- Monoclonal antibody of een small molecule?
  Geen van beide = cytostatische therapie

- Orale therapie: geen bewezen medicatie /medicatie
  geen medicatie/voeding interactie

- Trifluridine is een anti-neoplastic thymidine-based nucleoside en tipiracil helpt om bloed concentraties in stand te houden van trifluradine door remming van het enzyme dat zorgt voor de afname van de concentratie van trifluridine

- geen personalized medicine

Feiten over colorectal kanker in de USA

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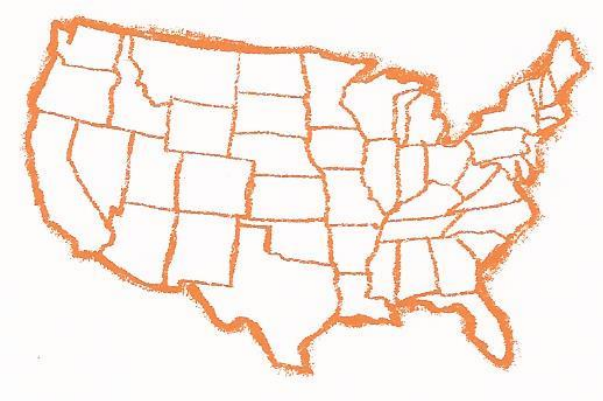
- Ongeveer 1 op de 20 Amerikanen zal de diagnose colon of rectum kanker krijgen gedurende hun leven
- In 2014 was het aantal mensen met de diagnose colorectal kanker in de USA:
  - 71.830 (mannen)
  - 65.000 (vrouwen)



- In 2015 in Nederland:
  - 8500 (mannen)
  - 6500 (vrouwen)

Historie van Trifluridine (FTD), de antitumor component

- Serum half-life van trifluridine is relatief kort na i.v. injectie daarom werden split dosis behandelingen en single bolus injecties ontwikkeld[1]

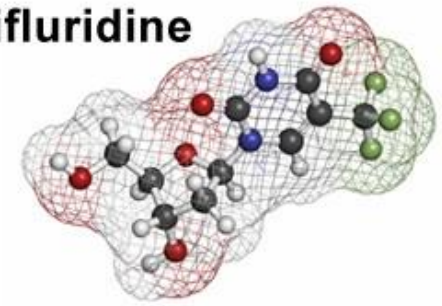
- I.V. injectie van trifluridine als een single agent werd niet als behandeling ingezet door slechte effectiviteit en toxiciteit[2]

- Trifluridine instabiliteit in serum is een resultaat van degradatie door thymidine phosphorylase[3]
  - Tipiracil zorgt voor directe hepatische degradatie van trifluridine door zich te gedragen als een thymidine phosphorylase inhibitor (remmer)
  - Co-administratie van tipiracil met trifluridine verhoogt het effect in vivo trifluridine concentraties

1. Dexter DL et al., Cancer Res. 1972;32:247–253.
2. Ansfield FJ, Ramirez G. Cancer Chemother Rep. 1971;55:205–208.
3. Fukushima M, et al. Biochem Pharmacol. 2000;59:1227–1236.

Trifluridine + Tipiracil (TAS-102) is a Novel Oral Anti-tumor Nucleoside

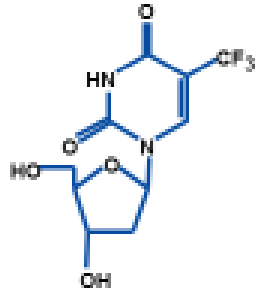
- Trifluridine (**FTD**) is a thymidine-based nucleoside, which is incorporated into DNA in tumor cells following phosphorylation
- Tipiracil hydrochloride, a thymidine phosphorylase inhibitor (**TPI**) prevents degradation of FTD
  - Employed to increase the effective *in vivo* FTD concentration



TAS-102

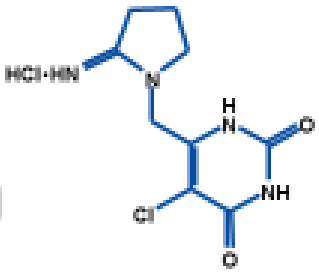
FTD is the active component

2'-deoxy-5-(trifluoromethyl)uridine (trifluridine, FTD) [1]



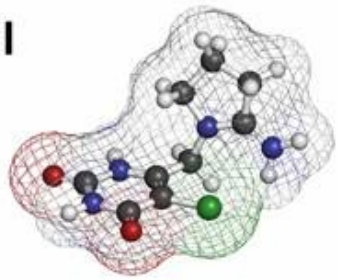
+

5-chloro-6-[(2-iminopyrrolidin-1-yl)methyl]pyrimidine-2, 4(1*H*,3*H*)-dione monohydrochloride (tipiracil hydrochloride, TPI) [0.5]



[Molar ratio]
[1:0.5]

TPI prevents degradation of FTD, allowing clinically active serum levels of FTD to be reache

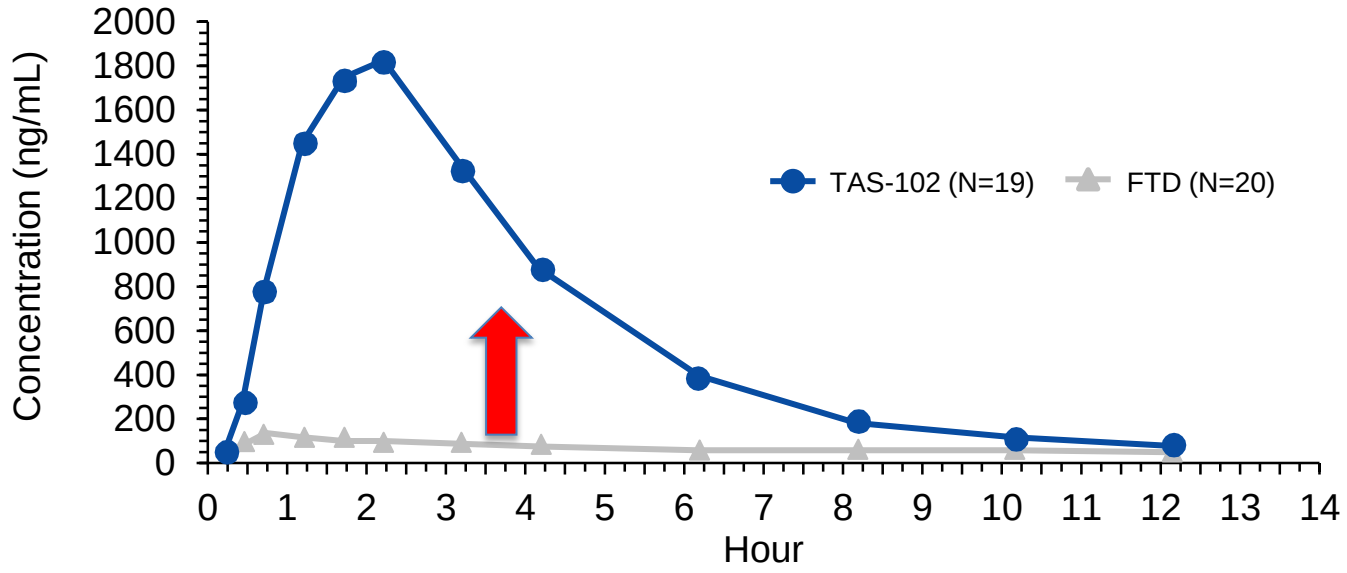


Thymidylate synthase inhibition is the primary mechanism of action when FTD is given intravenously.

Emura T, et al Int. J. Oncology 2004 25(3): 571-578

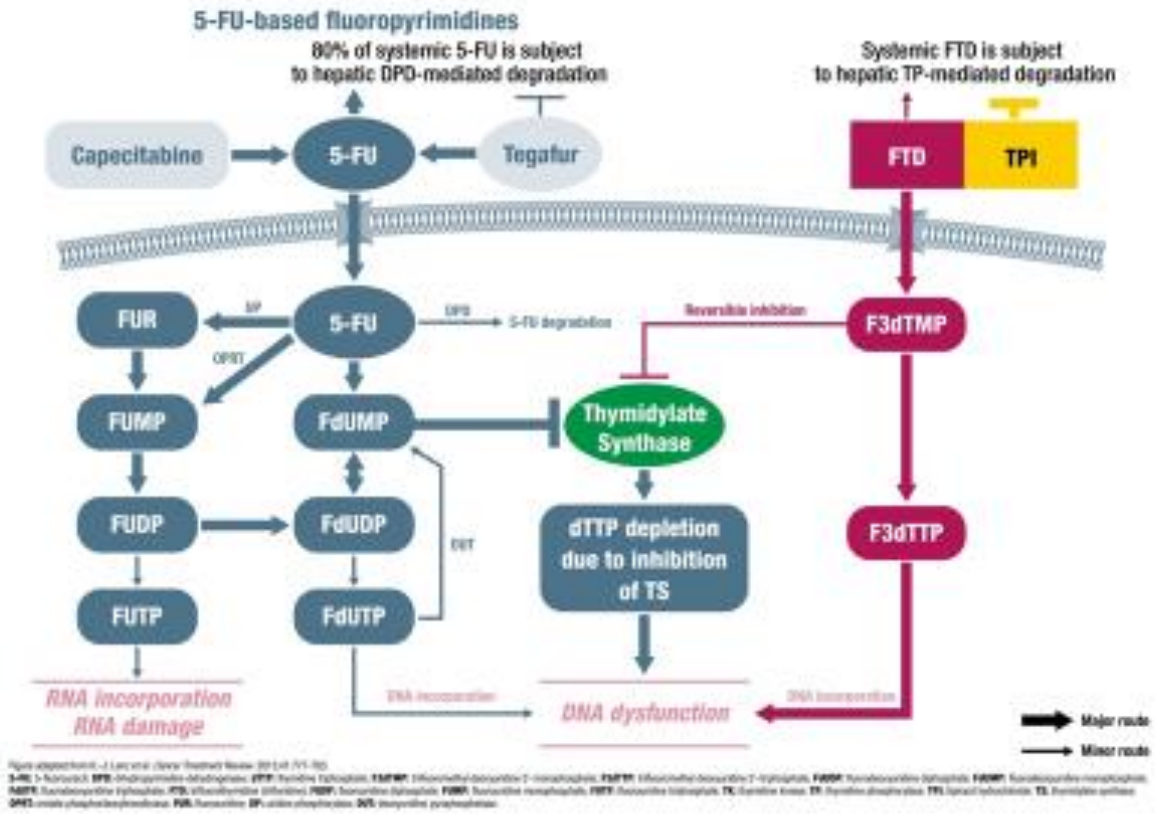
PK Contribution Study: TPI effect on FTD exposure

Mean plasma concentration time profile after single dose of TAS-102 or FTD: FTD (single-dose PK contribution population)



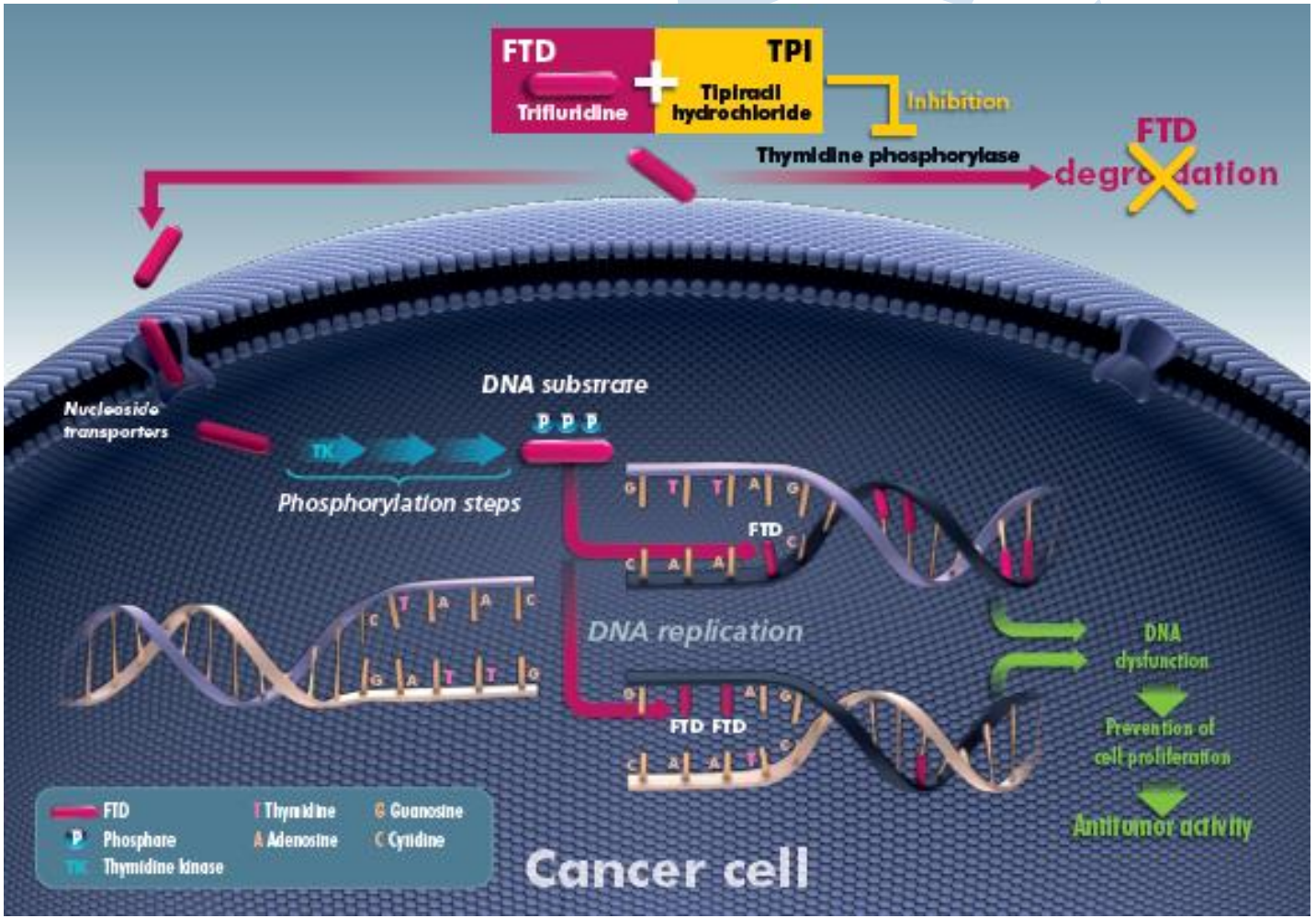
Exposure to FTD was significantly increased when FTD administered in combination with TPI (TAS-102) compared to administration of an equivalent dose of FTD alone

Trifluridine + Tipiracil (TAS-102) mechanism of action



Adapted from H.J. Lenz et al. Cancer Treatment Reviews 41 (2015) 777–783

Werkingsmechanisme



Werkingmechanisme

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The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

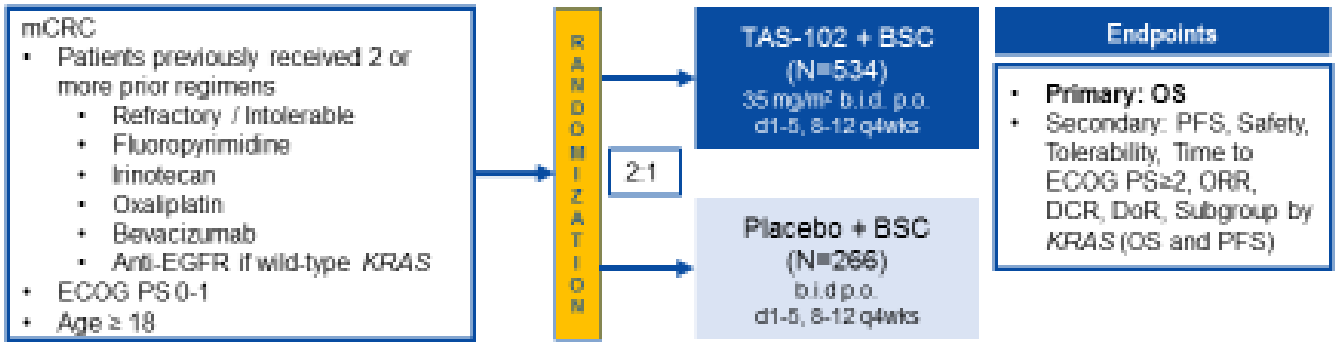
Randomized Trial of TAS-102 for Refractory Metastatic Colorectal Cancer

Robert J. Mayer, M.D., Eric Van Cutsem, M.D., Ph.D., Alfredo Falcone, M.D., Takayuki Yoshino, M.D., Rocio Garcia-Carbonero, M.D., Ph.D., Nobuyuki Mizunuma, M.D., Ph.D., Kentaro Yamazaki, M.D., Yasuhiro Shimada, M.D., Josep Tabernero, M.D., Ph.D., Yoshito Komatsu, M.D., Ph.D., Alberto Sobrero, M.D., Eveline Boucher, M.D., Marc Peeters, M.D., Ph.D., Ben Tran, M.B., B.S., Heinz-Josef Lenz, M.D., Alberto Zaniboni, M.D., Howard Hochster, M.D., James M. Cleary, M.D., Hans Prenen, M.D., Ph.D., Fabio Benedetti, M.D., Hirokazu Mizuguchi, M.S., Lukas Makris, Ph.D., Masanobu Ito, M.S., and Atsushi Ohtsu, M.D., Ph.D., for the RECOURSE Study Group*

Mayer RJ, et al. N Engl J Med 2015;372(20):1909–19. doi: 10.1056/NEJMoa1414325

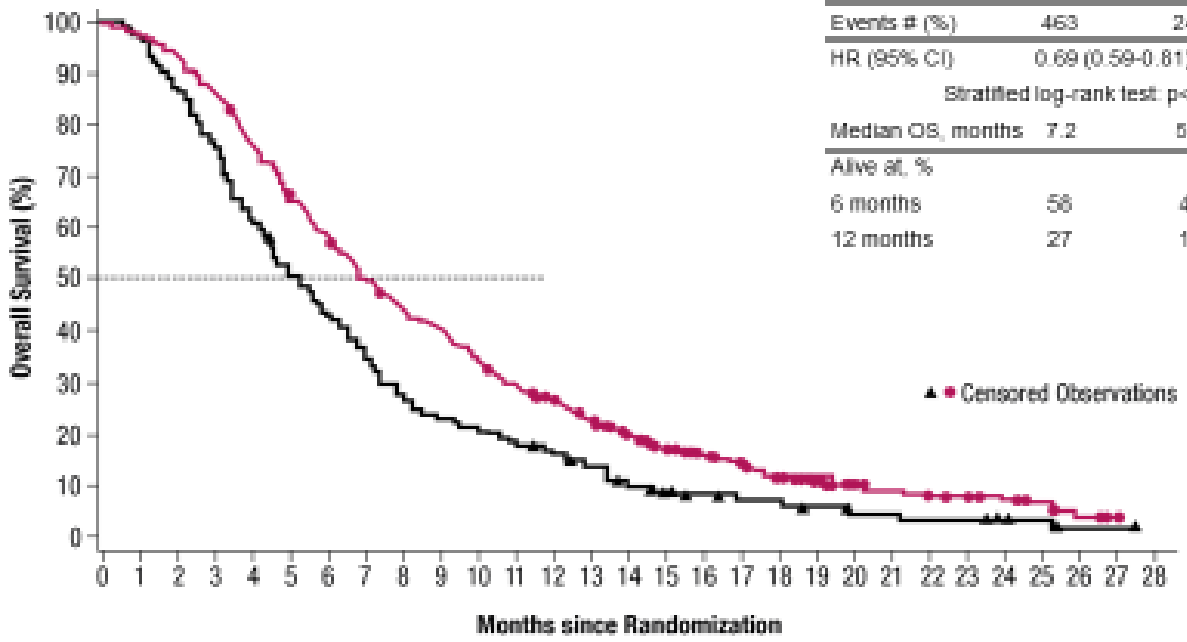
RECOURSE: Refractory Colorectal Cancer Study (NCT01607957)

- Global, multicentre, randomized, double-blind, placebo-controlled, phase III
  - Stratification: *KRAS* status, time from diagnosis of metastatic disease, geographical region
- Treatment continuation until progression, intolerant toxicity or patient refusal
- Sites: 13 countries, 114 sites



Mayer RJ, *et al. N Engl J Med.* 2015;372:1909-1919. DOI: 10.1056/NEJMoa1414325

RECOURSE: Updated Overall Survival



	TAS-102 (N=534)	Placebo (N=266)
Events # (%)	463	249
HR (95% CI)	0.69 (0.59-0.81)	
	Stratified log-rank test: p<0.0001	
Median OS, months	7.2	5.2
Alive at, %		
6 months	58	43
12 months	27	17

TAS-102	534	521	499	459	406	355	308	267	231	212	180	156	137	117	95	74	59	49	38	29	20	17	14	12	10	7	4	1	0
Placebo	266	259	232	198	163	137	114	94	71	62	56	51	43	36	27	21	16	15	14	10	8	7	6	6	4	3	1	1	0

Mayer RJ, et al. ASCO GI 2016 Abstract 634 updated

Cut off October 5th, 2014: 712 events (138 additional events vs primary analysis)

RECOURSE: Frequency of Adverse Events*

Event	TAS-102 (N=533)		Placebo (N=265)	
	Any Gr.	Gr. ≥3	Any Gr.	Gr. ≥3
Any event, %	98	69	93	52
Any serious event, %	30		34	
Most common events[a], %				
Nausea	48	2	24	1
Vomiting	28	2	14	<1
Decreased appetite	39	4	29	5
Fatigue	35	4	23	6
Diarrhea	32	3	12	<1
Abdominal pain	21	2	18	4
Fever	19	1	14	<1
Asthenia	18	3	11	3

- AEs primary reason for discontinuation in 3.6% TAS-102 and 1.5% placebo treated patients
- Dose reductions due to AEs occurred in 14% of patients in the TAS-102 arm

Per NCI CTCAE version 1.03

[a]Adverse events of any grade that occurred in ≥10% of patients in the TAS-102 group and in a greater percentage in that group than in the placebo group.

*as-treated population

RECOURSE: Adverse Events of Special Interest*

Event	TAS-102 (N=533)			Placebo (N=265)		
	All Gr.	Gr. 3	Gr. 4	All Gr.	Gr. 3	Gr. 4
Febrile neutropenia	3.8	2.8	0.9	0	0	0
Stomatitis	7.9	0.4	0	6.0	0	0
Hand-foot syndrome	2.3	0	0	2.3	0	0
Alopecia	6.8	0	0	1.1	0	0
Proteinurea	4.1	0	0	1.9	0	0
Cardiac ischaemia events, %	0.4	0.2	0	0.4	0	0.4
Thromboembolic events, %	3.9	1.7	0.2	2.3	1.1	0.4
Pulmonary embolism	1.7	1.3	0.2	0	0	0

*as-treated population

Mayer RJ, et al. N Engl J Med. 2015;372:1909-1919. DOI: 10.1056/NEJMoa1414325
Data on File. Taiho Oncology, Inc. Section 12 TPU-TAS-102-301 CSR Final Aug 2014

Lonsurf is een oraal Chemotherapie van 2 medicijnen in 1

Stichting Oncowijs

- Tabletten in 2 doseringen 15 mg of 20 mg
- 35 mg/m²
- Verdeeld over 2 giften per dag direct na de maaltijd tot 1 uur na de maaltijd (ontbijt /diner)
- Dag 1 t/m 5 (Ma – Vrij) 2 dagen rust
- Dag 8 t/m 12 (Ma – Vrij) 16 dagen rust
- Cyclus = 28 dagen

Dosering / Inname

LONSURF 28-Day Dosing Schedule for _____

LONSURF® (trifluridine and tipiracil) comes in 2 strengths. Your healthcare provider may prescribe both strengths for your prescribed dose.

Morning dose: _____ 15-mg tablets* _____ 20-mg tablets*

Evening dose: _____ 15-mg tablets _____ 20-mg tablets

Tablets shown are not actual size.

Day 1:	Day 2:	Day 3:	Day 4:	Day 5:	Day 6: REST	Day 7: REST
Day 8:	Day 9:	Day 10:	Day 11:	Day 12:	Day 13: REST	Day 14: REST
Day 15: REST	Day 16: REST	Day 17: REST	Day 18: REST	Day 19: REST	Day 20: REST	Day 21: REST
Day 22: REST	Day 23: REST	Day 24: REST	Day 25: REST	Day 26: REST	Day 27: REST	Day 28: REST

Conclusie

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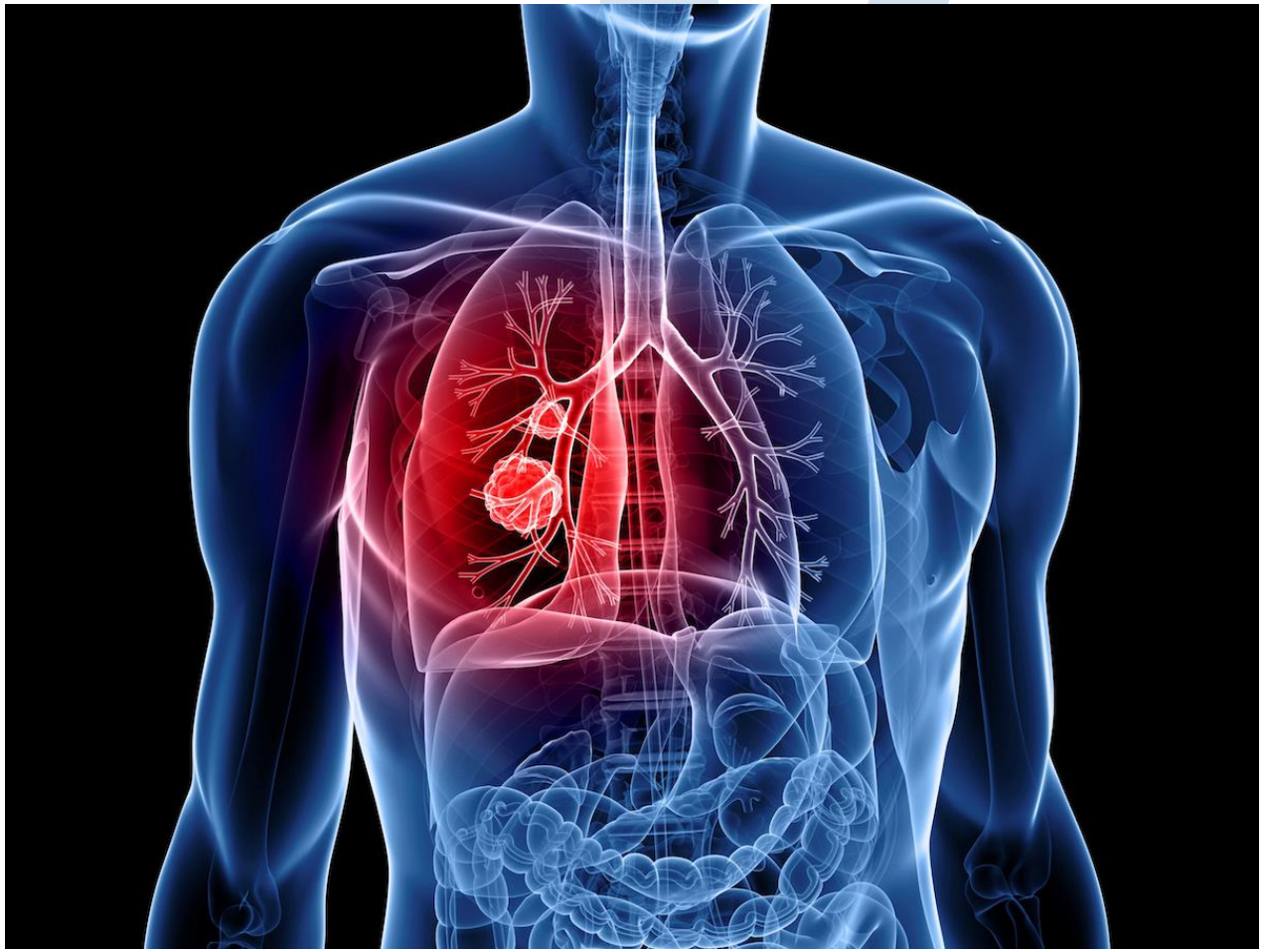
- Trifluridine + tipiracil (TAS-102) laat een vooruitgang zien in overleving en progressie vrije overleving als je het vergelijkt met placebo/best supportive care bij patiënten met gemetastaseerd colorectaal kanker die geen baat meer hebben met standaard therapiën

- Trifluridine + tipiracil (TAS-102) heeft een acceptabel toxiciteits profiel
  - Weinig ernstige bijwerkingen gezien
  - De meest voorkomende bijwerkingen in studies waren gastrointestinale en hematologische bijwerkingen (febriele neutropenie 3.8%)

Mayer RJ, et al. N Engl J Med. 2015;372:1909-1919. DOI: 10.1056/NEJMoa1414325

Stichting Oncowijs

Ontwikkelingen bij longkanker



Roken?

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Longkanker

Cancer Center

Clinical relevance and scope of the problem: Lung Cancer

Leading Sites of New Cancer Cases and Deaths – 2015 Estimates

Estimated New Cases*		Estimated Deaths	
Male	**Female**	**Male**	**Female**
Prostate 220,800 (26%)	Breast 231,840 (29%)	Lung & bronchus 86,380 (28%)	Lung & bronchus 71,660 (26%)
Lung & bronchus 115,610 (14%)	Lung & bronchus 105,590 (13%)	Prostate 27,540 (9%)	Breast 40,290 (15%)
Colon & rectum 69,090 (8%)	Colon & rectum 63,610 (8%)	Colon & rectum 26,100 (8%)	Colon & rectum 23,600 (9%)
Urinary bladder 56,320 (7%)	Uterine corpus 54,870 (7%)	Pancreas 20,710 (7%)	Pancreas 19,850 (7%)
Melanoma of the skin 42,670 (5%)	Thyroid 47,230 (6%)	Liver & intrahepatic bile duct 17,030 (5%)	Ovary 14,180 (5%)
Non-Hodgkin lymphoma 39,850 (5%)	Non-Hodgkin lymphoma 32,000 (4%)	Leukemia 14,210 (5%)	Leukemia 10,240 (4%)
Kidney & renal pelvis 38,270 (5%)	Melanoma of the skin 31,200 (4%)	Esophagus 12,600 (4%)	Uterine corpus 10,170 (4%)
Oral cavity & pharynx 32,670 (4%)	Pancreas 24,120 (3%)	Urinary bladder 11,510 (4%)	Non-Hodgkin lymphoma 8,310 (3%)
Leukemia 30,900 (4%)	Leukemia 23,370 (3%)	Non-Hodgkin lymphoma 11,480 (4%)	Liver & intrahepatic bile duct 7,520 (3%)
Liver & intrahepatic bile duct 25,510 (3%)	Kidney & renal pelvis 23,290 (3%)	Kidney & renal pelvis 9,070 (3%)	Brain & other nervous system 6,380 (2%)
All sites 848,200 (100%)	All sites 810,170 (100%)	All sites 312,150 (100%)	All sites 277,280 (100%)

*Excludes basal cell and squamous cell skin cancers and in situ carcinoma except urinary bladder.

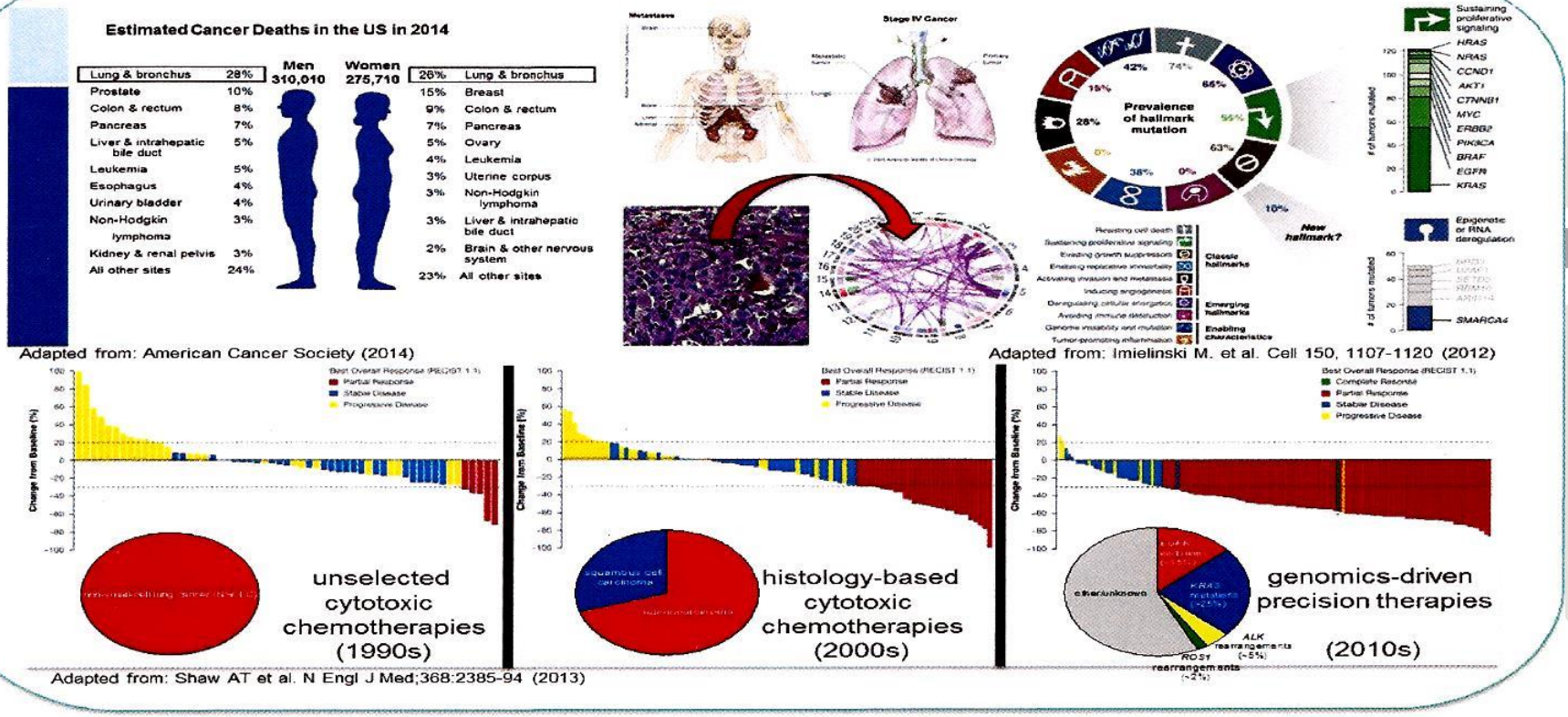
Beth Israel Deaconess Medical Center
HARVARD MEDICAL SCHOOL TEACHING HOSPITAL

Longkanker in 2016

Cancer Center

Contemporary View of Lung Cancer in 2016:

Non-small-cell lung cancers (NSCLCs) are heterogeneous at the genomic leve



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ALK+ longkanker is een specifieke groep bij het NSCLC

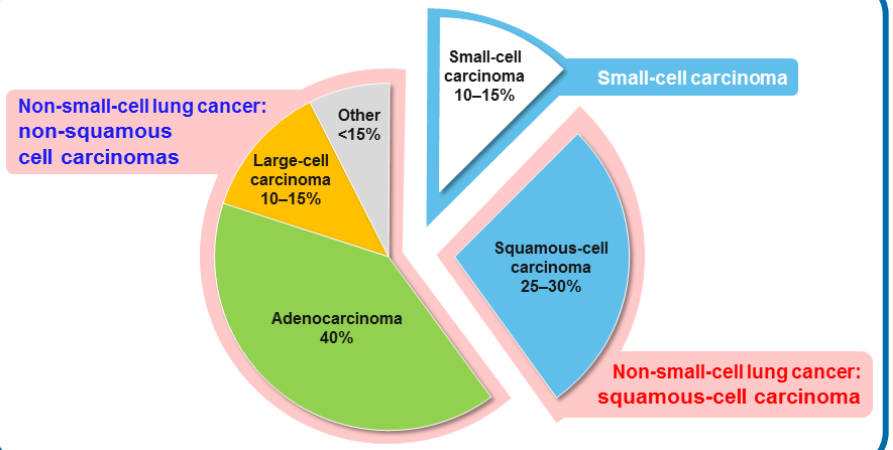
ALK+ disease occurs in ~5% of patients with advanced NSCLC[1–5]

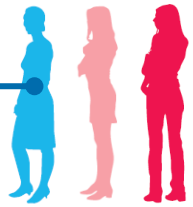
More than 75,000 patients per year diagnosed[7]

The incidence of *ALK+* NSCLC is higher in

- Patients with non-squamous histology[2,8]
- Never or former smokers[2,8]
- Younger patients[2,8]
- Females[2]
- Patients who do not have *EGFR* or *KRAS* mutations[2,8]

Histological classification of lung cancer[6]



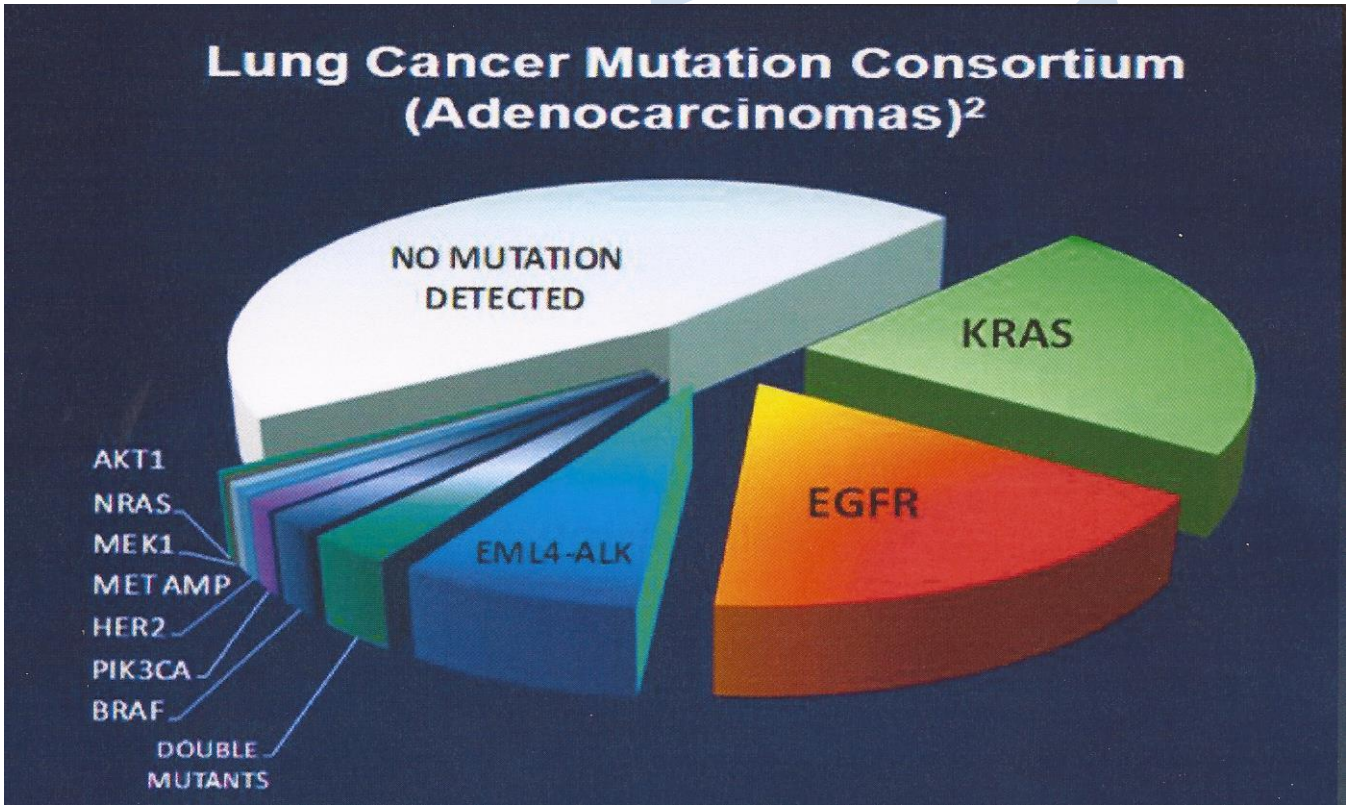


Clinical characteristics do not always predict the presence of *ALK+* NSCLC[9,10]

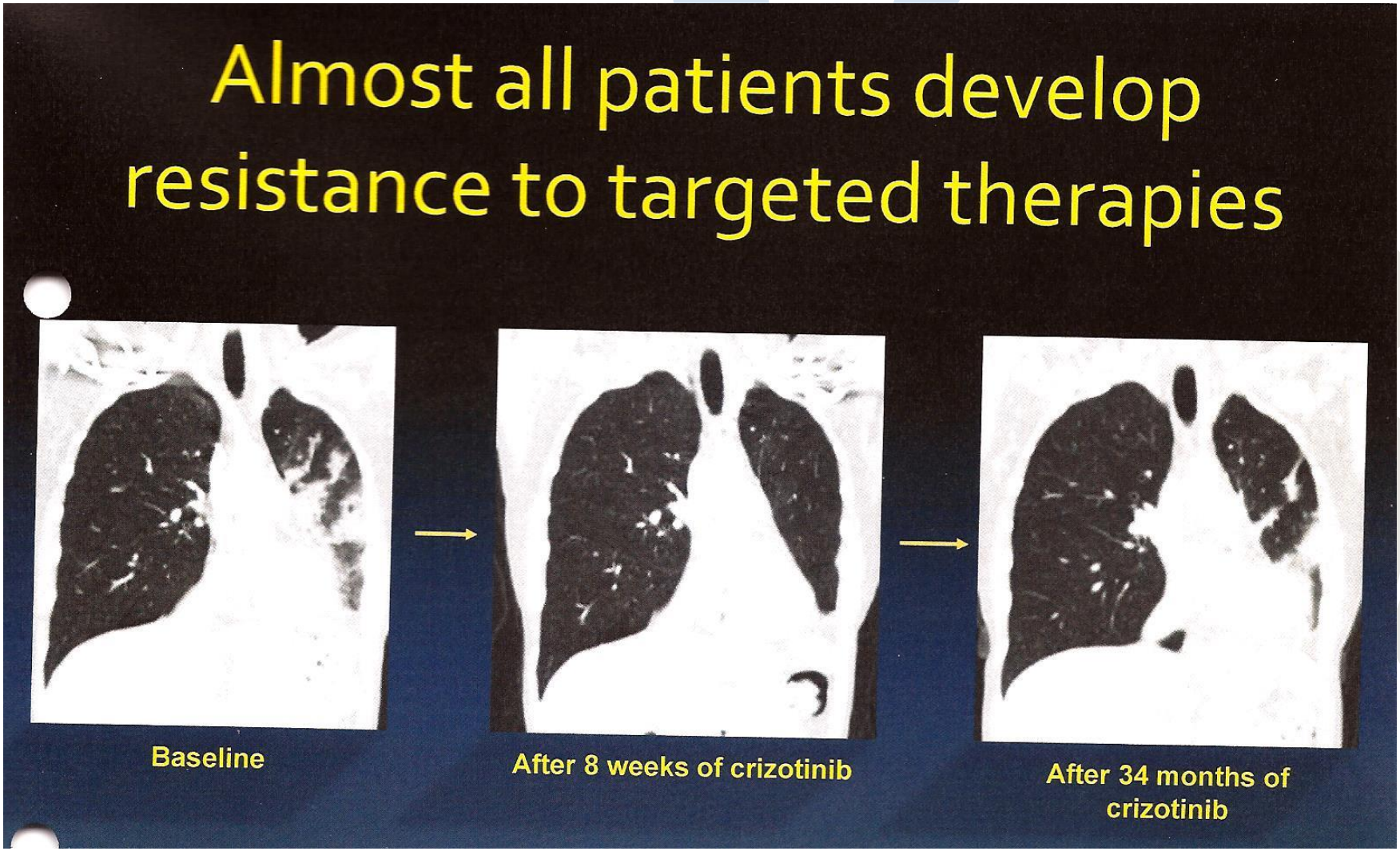
ALK = anaplastic lymphoma kinase
EGFR = epidermal growth factor receptor
NSCLC = non-small cell lung cancer

1. Dearden, et al. Ann Oncol 2013; 2. Gridelli, et al. Cancer Treat Rev 2014
3. Hallberg, et al. Nat Rev Cancer 2013; 4. Rikova, et al. Cell 2007
5. Soda, et al. Nature 2007; 6. American Cancer Society 2013
7. Torre, et al. CA Cancer J Clin 2015; 8. Perez, et al. Lung Cancer 2014
9. Lindeman, et al. J Thorac Oncol 2013; 10. Leighl, et al. J Clin Oncol 2014

Mutaties

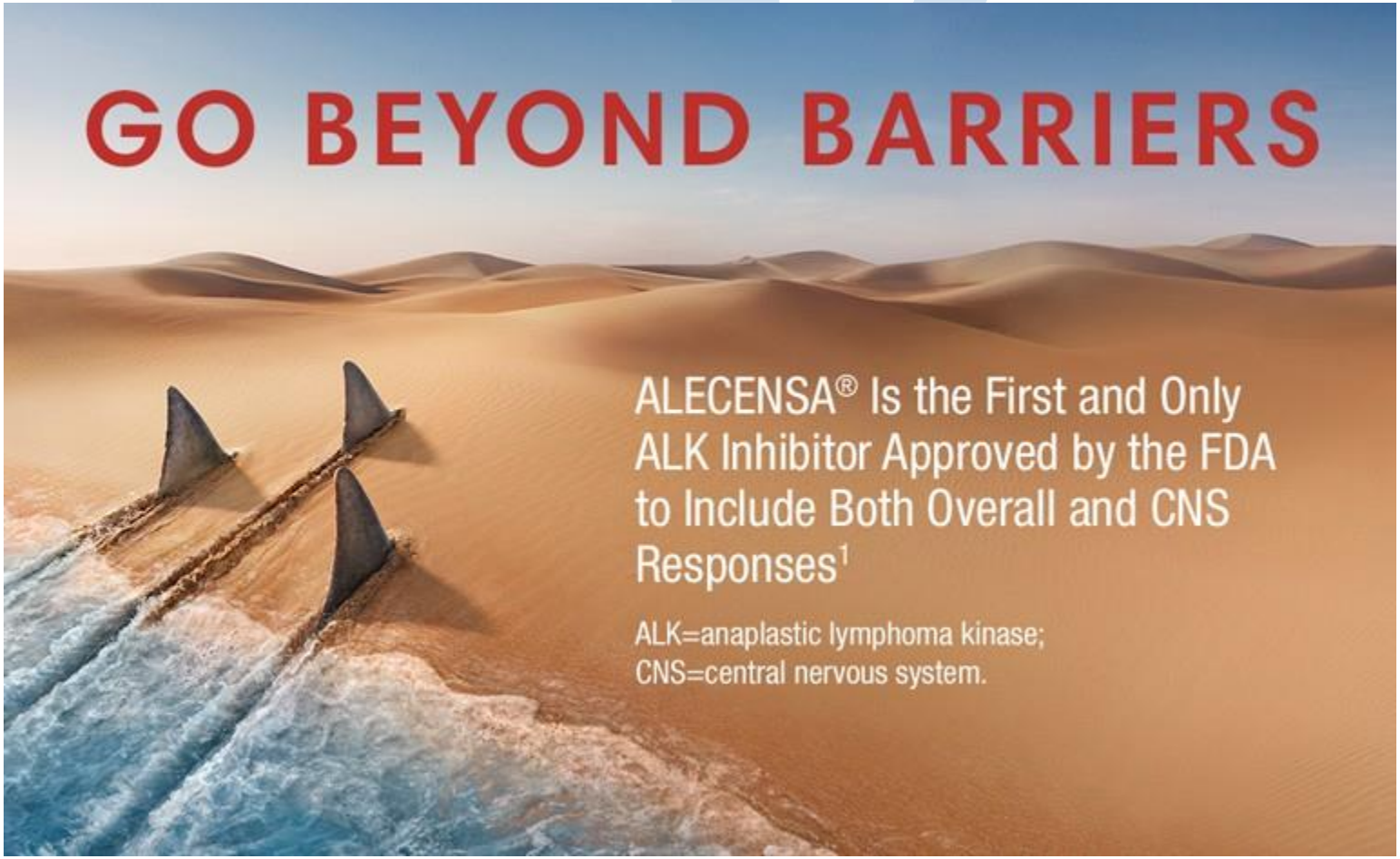

Lung Cancer Mutation Consortium
(Adenocarcinomas)²
NO MUTATION DETECTED
KRAS
EGFR
EML4-ALK
AKT1
NRAS
MEK1
MET AMP
HER2
PIK3CA
BRAF
DOUBLE MUTANTS

Wat te doen bij resistentie



Alectinib /Alecensa®

Stichting Oncowijs



Alectinib /Alecensa®

Stichting Oncowijs

- Alectinib voor de behandeling van patiënten met anaplastic lymphoma kinase (ALK)-positief gemetastaseerd non-small cell lung cancer (NSCLC) die progressief zijn of intolerant zijn voor crizotinib
- Alectinib is de eerste en enige ALK remmer tot nu toe die ook bij hersenmetastasen responses laat zien (passeert de bloed hersenbarierre)

  - Small molecule kinase inhibitor (orale medicatie)
  - Geen bewezen interacties bij medicatie / medicatie
    Geen medicatie / voeding interacties
  - Targets: ALK translocaties
  - Personalized medicine voor ALK positieve tumoren

ALECENSA™
alectinib 150 mg capsules

Goedkeuring 11-12-2015

Stichting Oncowijs

Alectinib – Food and Drug Administration (FDA) approval history

Cancer Center

http://www.cancer.gov/cancertopics/druginfo/

- **Approved for locally advanced or metastatic non-small cell lung cancer (NSCLC) that is anaplastic lymphoma kinase (ALK)-positive as detected by an FDA-approved test and crizotinib resistance/intolerance since 2015.**

On **December 11, 2015**, the U. S. Food and Drug Administration granted accelerated approval to alectinib (ALECENSA, Roche) for the treatment of patients with anaplastic lymphoma kinase (ALK)-positive, metastatic non-small cell lung cancer (NSCLC) with disease progression on or who are intolerant to crizotinib.

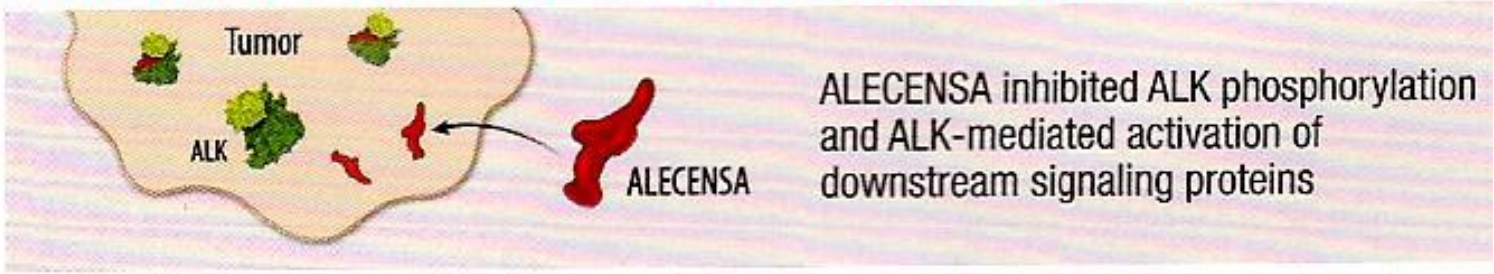
Efficacy Parameter	Study 1 (North American) n=87		Study 2 (Global) n=138	
	IRC* Assessment	Investigator Assessment	IRC* Assessment	Investigator Assessment
Objective Response Rate (ORR, primary endpoint)				
ORR (%) (95% CI)	38 (28, 49)	46 (35, 57)	44 (36, 53)	48 (39, 57)
Number of Responders				
Number of responders	33	40	61	66
Duration of Response (DOR, secondary endpoint)				
DOR (median in months) CI)	7.5 (4.9, Not Estimable)	NE (4.9, Not Estimable)	11.2 (9.6, Not Estimable)	7.8 (7.4, 9.2)

CNS Efficacy (secondary endpoints, based on a pooled analysis of 51 people in Studies 1 and 2 with measurable CNS lesions at baseline according to RECIST v1.1**)	
CNS ORR (%) (95% CI)	61 (46, 74)
CNS complete response rate (%)	18
CNS partial response rate (%)	43
CNS DOR (median in months) (95% CI)	9.1 (5.8, Not Evaluable)

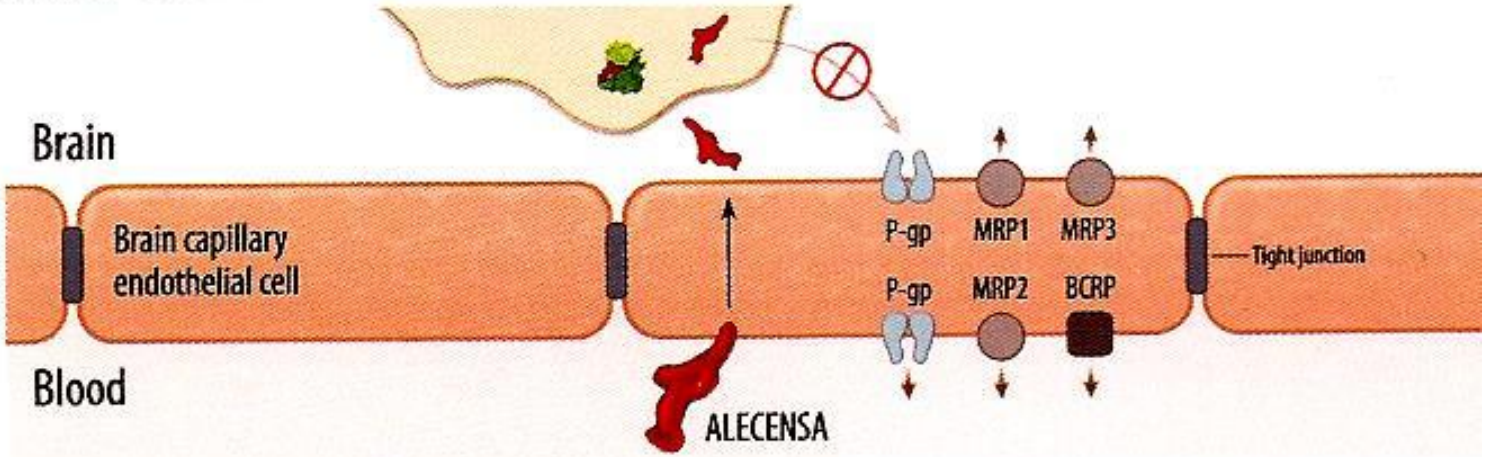
Werkingsmechanisme

Stichting Oncowijs

PROPOSED MECHANISM OF ACTION FOR ALECENSA[1,7]



PROPOSED DISTRIBUTION IN THE CNS FOR ALECENSA[1,7,9-11]



Studies / Effectiviteit

Stichting Oncowijs

STUDY 1—NORTH AMERICAN TRIAL DESIGN[1]

87 patients with locally advanced or metastatic ALK+ NSCLC who progressed on crizotinib

ALECENSA 600 mg twice daily with food

Major efficacy outcome:
- ORR (IRC)

Additional key outcomes:
- ORR (Investigator)
- DOR
- CNS ORR
- CNS DOR

STUDY 2—INTERNATIONAL TRIAL DESIGN[1]

138 patients with locally advanced or metastatic ALK+ NSCLC who progressed on crizotinib

ALECENSA 600 mg twice daily with food

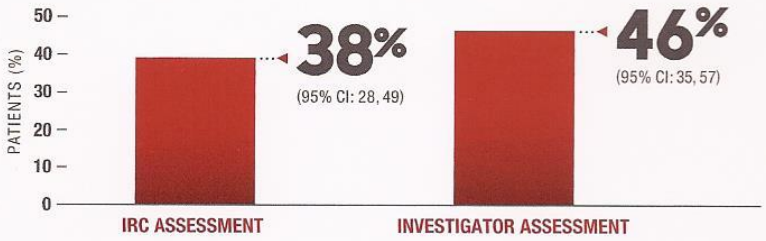
Major efficacy outcome:
- ORR (IRC)

Additional key outcomes:
- ORR (Investigator)
- DOR
- CNS ORR
- CNS DOR

Stichting Oncowijs

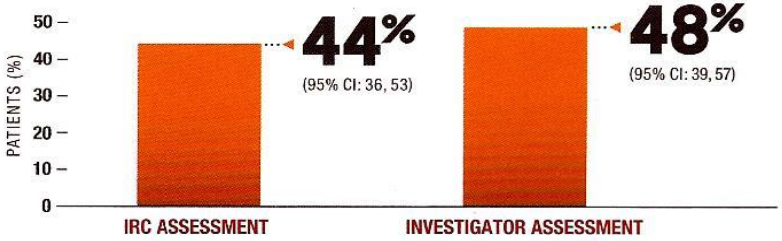
Effectiviteit

ORR IN STUDY 1 (N=87)[1]



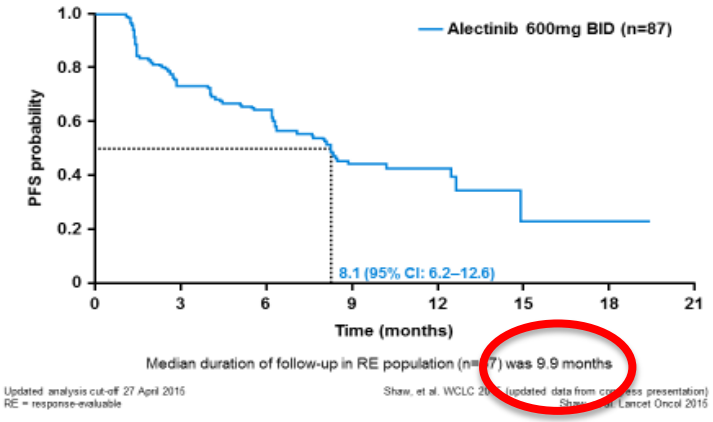
- The major efficacy outcome in Study 1 was ORR according to RECIST v1.1 as evaluated per IRC[1]
- 18 patients in Study 1 did not have measurable disease at baseline per IRC assessment and were classified as non-responders in the IRC analysis[1]
- All responses were partial responses[1]

ORR IN STUDY 2 (N=138)[1]

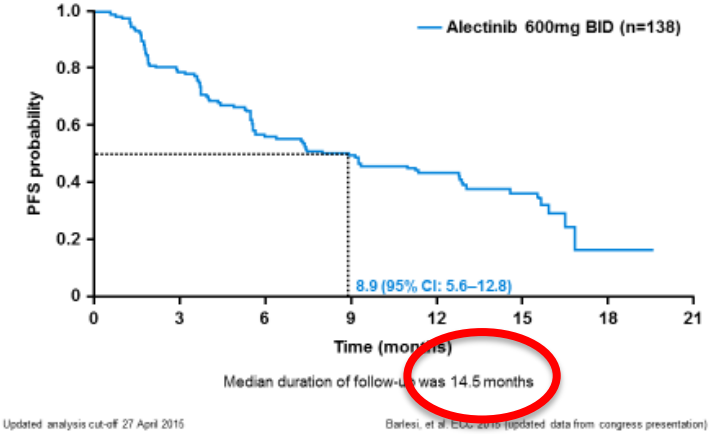


- The major efficacy outcome in Study 2 was ORR according to RECIST v1.1 as evaluated per IRC[1]
- 16 patients in Study 2 did not have measurable disease at baseline per IRC assessment and were classified as non-responders in the IRC analysis[1]
- All responses were partial responses[1]

NP28761: PFS

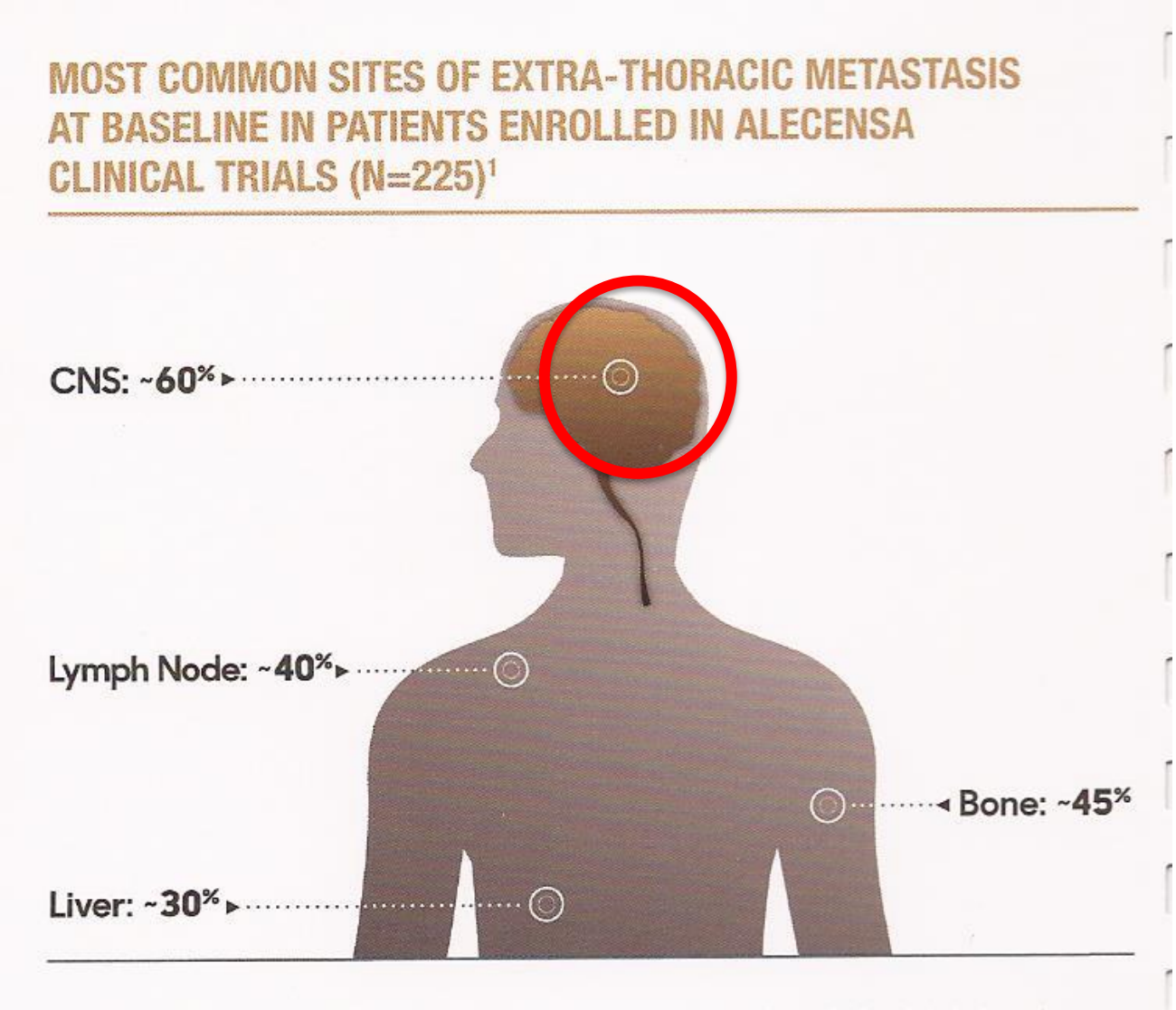


NP28673: PFS



Metastasen buiten de long

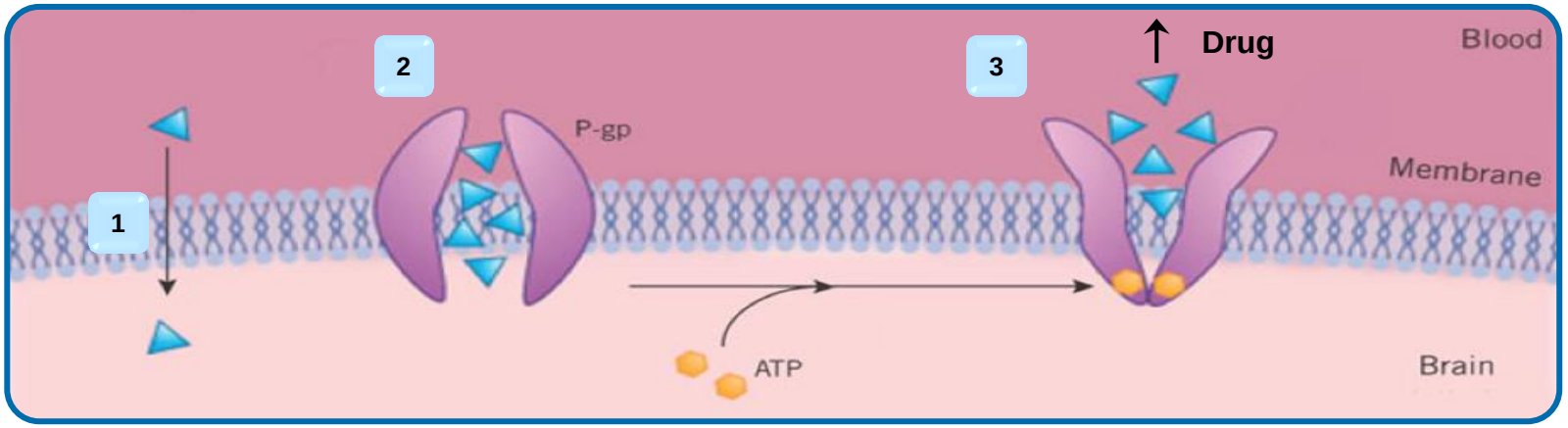
Stichting Oncowijs



Alectinib is not transported out of the brain

The brain is protected by the BBB, a network of tightly connected cells

1. Drugs enter the brain by crossing the BBB
2. The drug-efflux-transporter protein P-gp is expressed at high levels in the brain[1,2]
3. P-gp actively exports drugs back across the BBB into the bloodstream in an ATP-dependent manner[2,3]



Preclinical data show that alectinib is not a substrate for the drug efflux transporter P-gp[3], and is therefore not actively transported out of the brain

ATP = adenosine triphosphate
BBB = blood-brain barrier; P-gp = P-glycoprotein

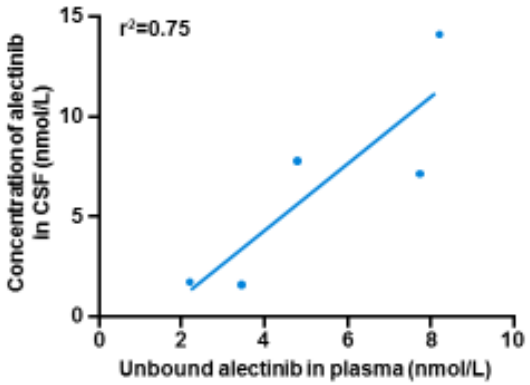
1. Thiebaut, et al. Proc Natl Acad Sci 1987; 2. Misra, et al. J Pharm Pharmaceut Sci 2003
3. Kodama, et al. Cancer Chemother Pharmacol 2014

Effect of CNS meta's

Stichting Oncowijs

AF-002JG/NP28761 (phase I portion): anti-tumour activity against CNS metastases

Alectinib penetrates into the CNS where it is able to exceed the in-vitro concentration required for ALK inhibition



Best intracranial response, %

Overall intracranial response rate	52
CR	29
PR	24
SD	38
PD	10

Patients with brain metastases at baseline (n=21)

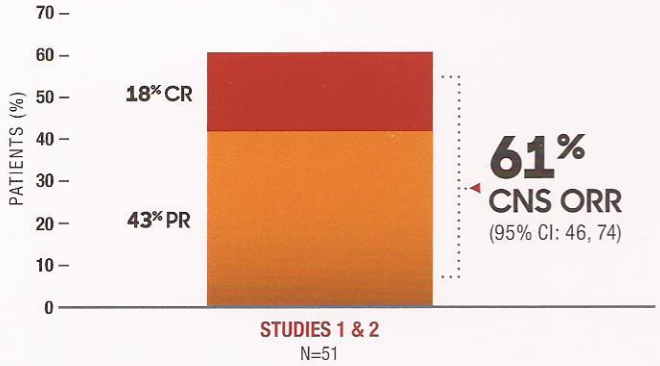
Extrapolated C_{trough} in CSF = 2.69nmol/L
Unbound systemic C_{trough} = 3.12nmol/L
In-vitro IC_{50} for ALK inhibition in cell-free assays = 1.9nmol/L

CSF = cerebrospinal fluid

Gadgeel, et al. Lancet Oncol 2014

ALECENSA Delivered Robust Objective Responses in CNS Metastases

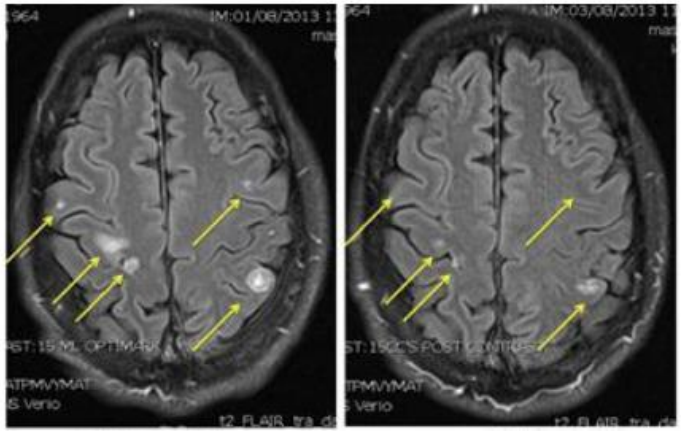
ORR IN PATIENTS WITH MEASURABLE CNS LESIONS[1]



- An assessment of ORR for CNS metastases in the subgroup of 51 patients in Studies 1 and 2 with measurable lesions in the CNS at baseline was assessed by IRC and determined by RECIST v1.1[1]
- 35 (69%) patients with measurable CNS lesions received prior brain radiation, including 25 (49%) who completed radiation treatment at least 6 months before starting treatment with ALECENSA[1]

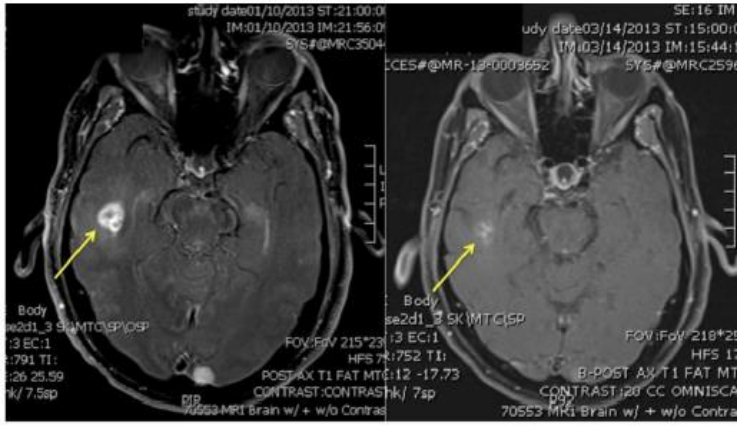
Snelle respons bij hersenmeta's die behandeld worden met alectinib

Patient 1



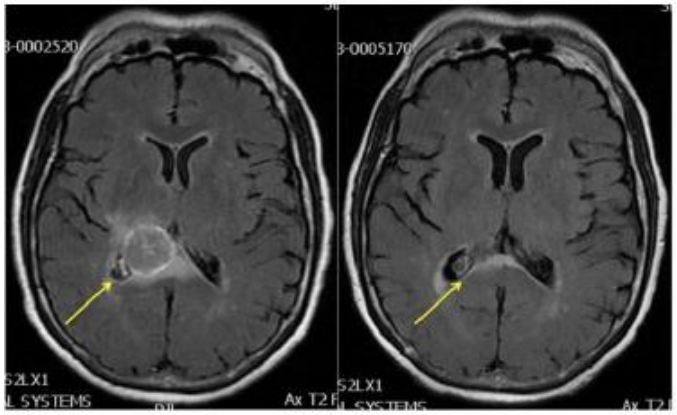
8 January 2013 — 8 March 2013

Patient 2



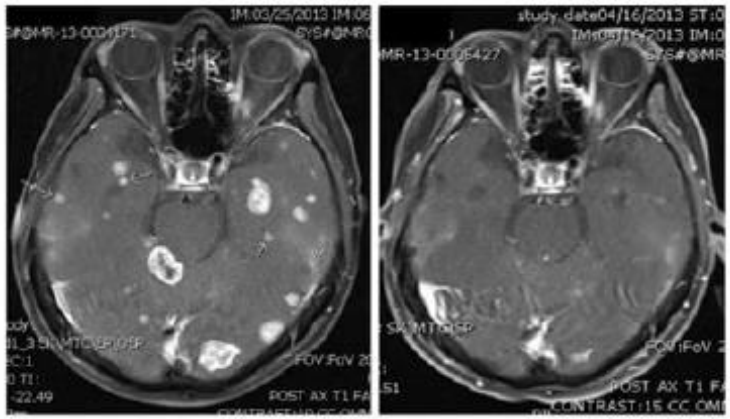
10 January 2013 — 14 March 2013

Patient 2



Day -12 — Day +23

Patient 3

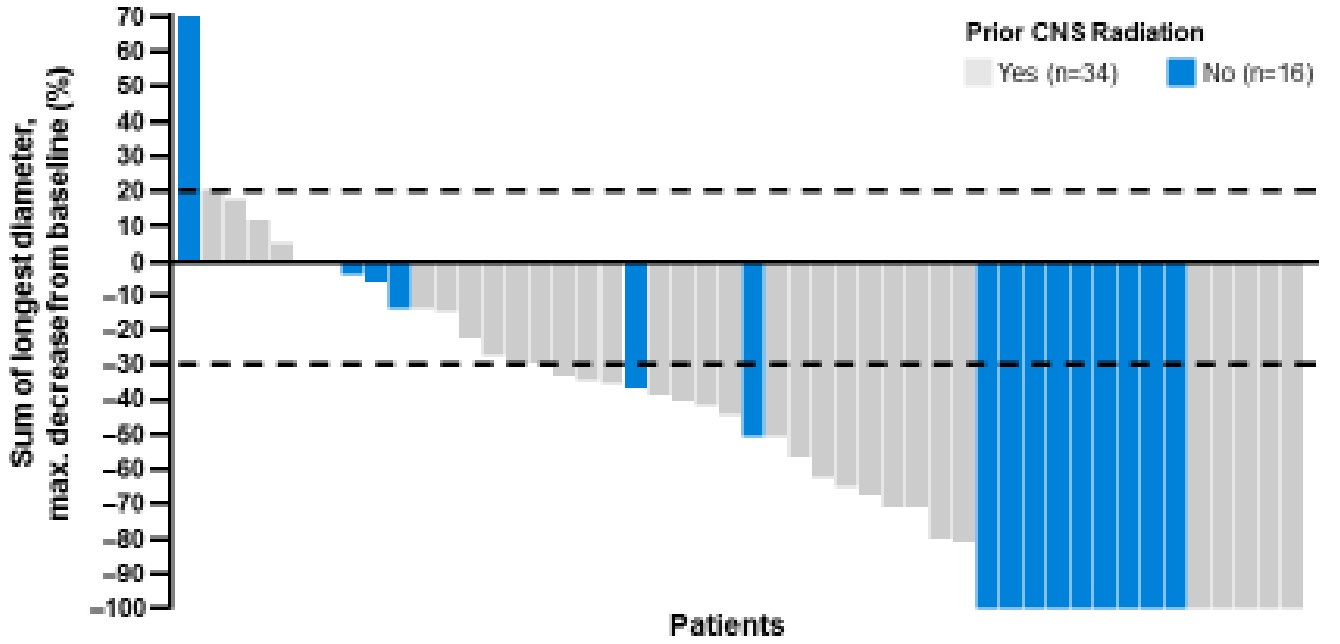


Day -4 — Day +18

Ou, et al. ESMO 2013 (updated data from congress presentation)

Effectiviteit bij CNS meta's

Pooled CNS analysis: response by prior radiation status



Alectinib is active in the CNS irrespective of prior radiation

Updated analysis cut-off 27 April 2015 for both studies

Gadgeel, et al. WCLC 2015 (updated data from congress presentation)

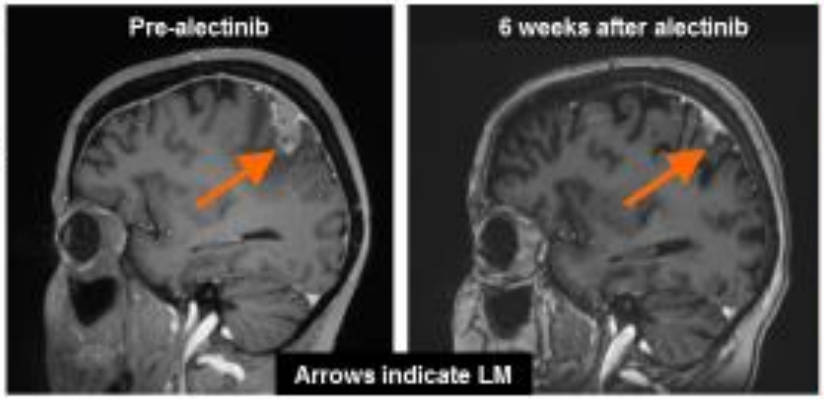
Effectiviteit bij CNS meta's

Patient cases: management of leptomeningeal metastases in *ALK*+ NSCLC

- LM occurs in 4% of patients with *ALK*+ NSCLC and prognosis is dismal
  - patients are rarely included in clinical trials, so management is poorly understood
- Case series reported on four patients with *ALK*+ NSCLC and LM, previously treated with crizotinib and ceritinib who received treatment with alectinib (600mg BID)

Case

- A 39 year old woman with metastatic *ALK*+ NSCLC
- Systemic disease control with initial crizotinib
- New LM was treated with WBRT and crizotinib was resumed
- Switched to ceritinib upon progression
- Patient had neurological symptoms and a brain MRI showed the LM enlarging
- Alectinib improved the neurological symptoms, reduced the LM and was well tolerated



In the four patient case series alectinib treatment led to significant clinical and radiographic improvements in LM in three patients and stable CNS disease in a fourth patient

LM = Leptomeningeal metastases; MRI = magnetic resonance imaging
WBRT = whole brain radiotherapy

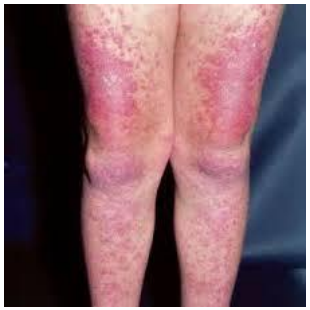
Gainor, et al. J Thorac Oncol 2015

Bijwerkingen

Stichting Oncowijs

ADVERSE REACTIONS IN ≥10% (ALL GRADES) OR ≥2% (GRADE 3-4) OF PATIENTS IN STUDIES 1 AND 2[1]

Adverse Reactions	ALECENSA N=253	
	All Grades (%)	Grades 3-4 (%)[a]
Fatigue[b]	41	1.2
Constipation	34	0
Edema[c]	30	0.8
Myalgia[d]	29	1.2
Cough	19	0
Rash[e]	18	0.4
Nausea	18	0
Headache	17	0.8
Diarrhea	16	1.2
Dyspnea	16	3.6[f]
Back pain	12	0
Vomiting	12	0.4
Increased weight	11	0.4
Vision disorder[g]	10	0



Description of selected adverse drug reactions[1]

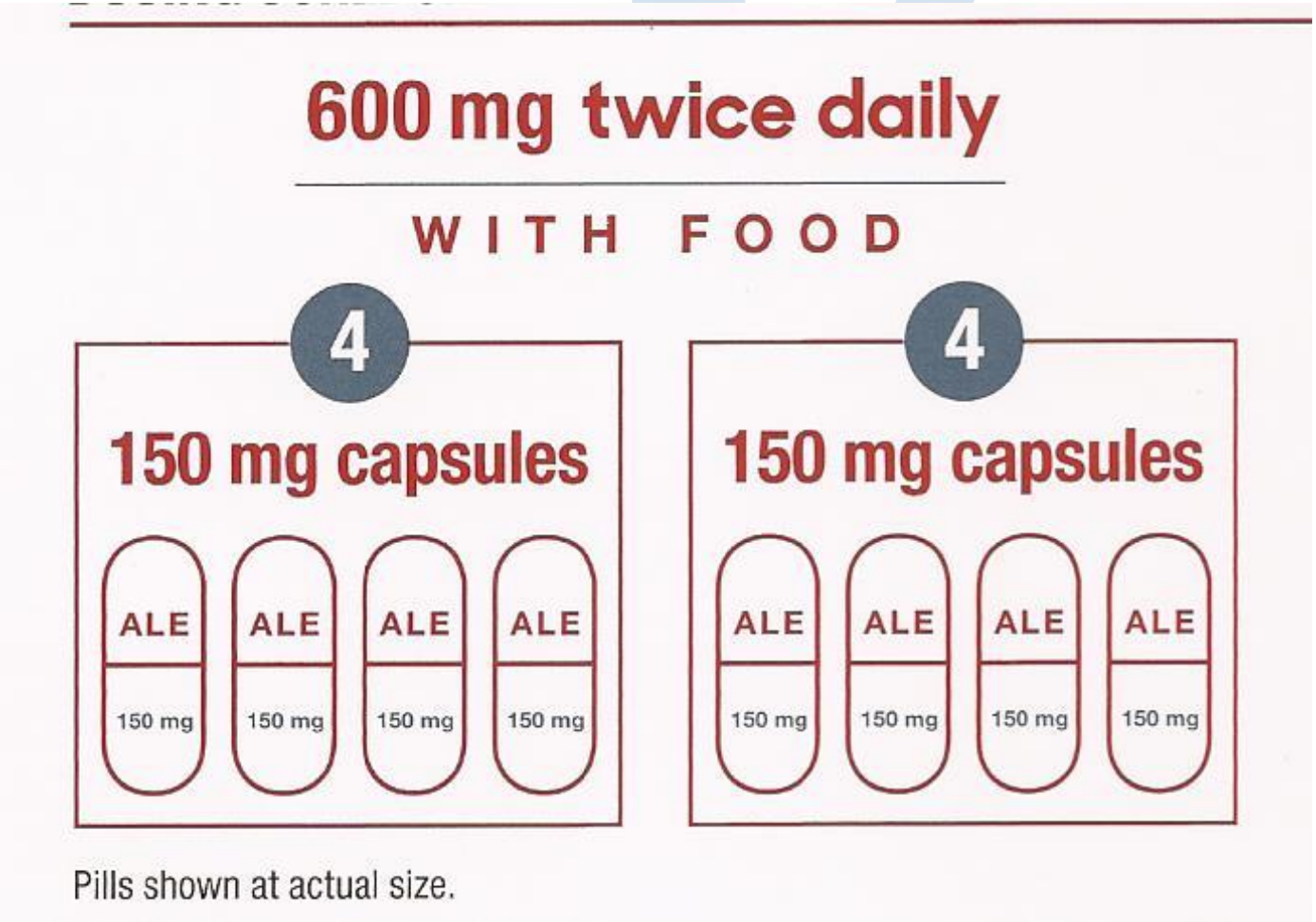
- Photosensitivity occurred in 9.9% of patients exposed to ALECENSA in Studies 1 and 2[1]
- Patients were advised to avoid sun exposure and to use broad-spectrum sunscreen[1]

Bijwerkingen

LABORATORY ABNORMALITIES OCCURRING IN >20% OF PATIENTS IN STUDIES 1 AND 2[1]

Parameter	ALECENSA N=250	
	All Grades (%)	Grades 3-4 (%)[h]
Chemistry		
Increased AST	51	3.6
Increased alkaline phosphatase	47	1.2
Increased CPK[i]	43	4.6
Hyperbilirubinemia	39	2.4
Hyperglycemia[j]	36	2.0
Increased ALT	34	4.8
Hypocalcemia	32	0.4
Hypokalemia	29	4.0
Increased creatinine[k]	28	0
Hypophosphatemia	21	2.8
Hyponatremia	20	2.0
Hematology		
Anemia	56	2.0
Lymphopenia[l]	22	4.6

Dosering / inname



Stichting Oncowijs

Conclusie

- Alectinib is een hoog selectieve , CNS-actieve remmer van ALK and RET tyrosine kinase[1,2]
- Alectinib heeft activiteit in preklinische muis modellen met *ALK+* NSCLC, inclusief intracraniale modellen[2,3]
- Alectinib heeft bewezen anti-tumour activiteit met langdurende responses bij *ALK+* NSCLC crizotinib naïve patiënten, als ook bij patiënten die progressief waren op crizotinib[4–7]
- De CNS blootstelling van alectinib is vergelijkbaar met normale systemische blootstelling en alectinib heeft een bewezen klinische activiteit bij patiënten met CNS metastasen[4–8]
- Alle klinische studies hebben laten zien dat alectinib goed wordt verdragen en een acceptabel bijwerkingen profiel heeft [4–8]

1. Sakamoto, et al. Cancer Cell 2011; 2. Kodama, et al. Cancer Chemother Pharmacol 2014;
3. Kodama, et al. Cancer Lett 2014
4. Ohe, et al. ASCO 2015; et al. Lancet Oncol 2014; 6. Shaw, et al. WCLC 2015; 7. Barlesi, et al. ECC 2015
8. G 5. Gadgeel, adgeel, et al. WCLC 2015;

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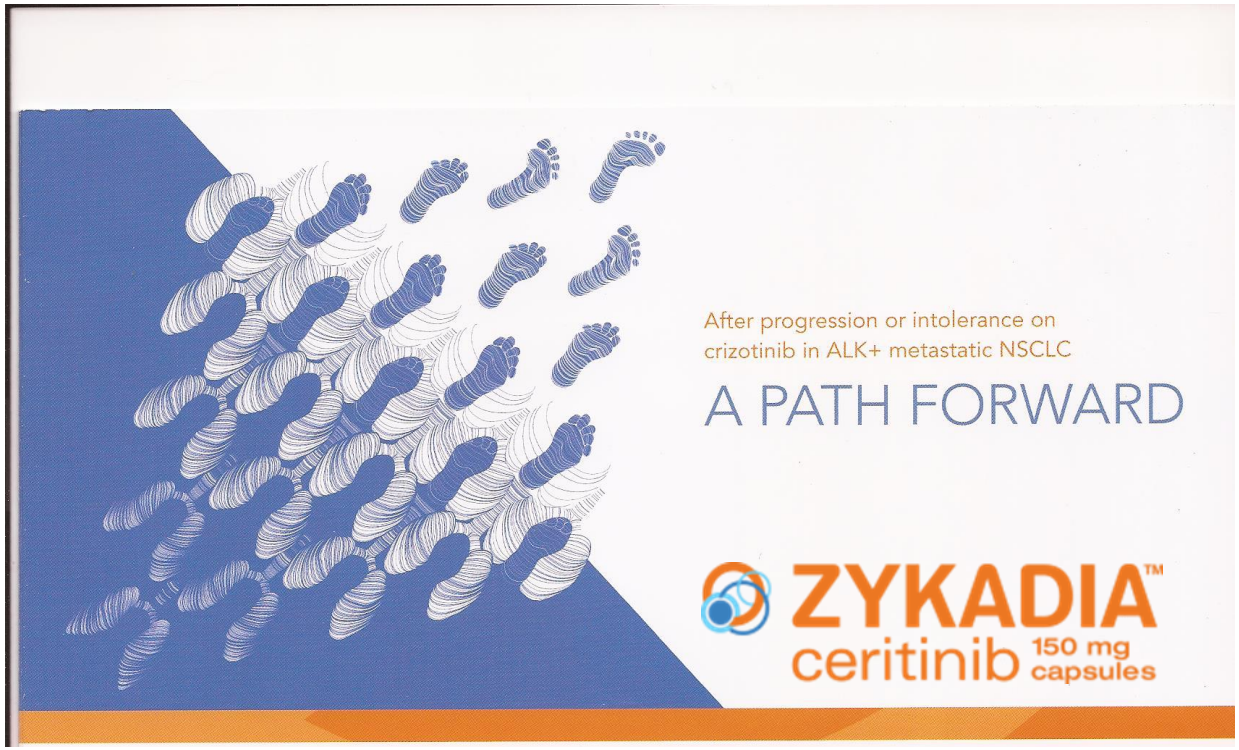
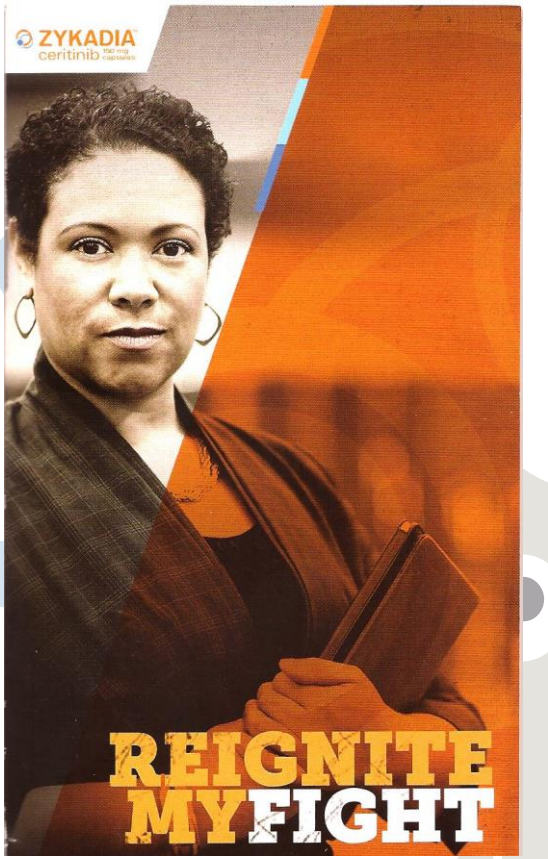
alectinib 150 mg capsules

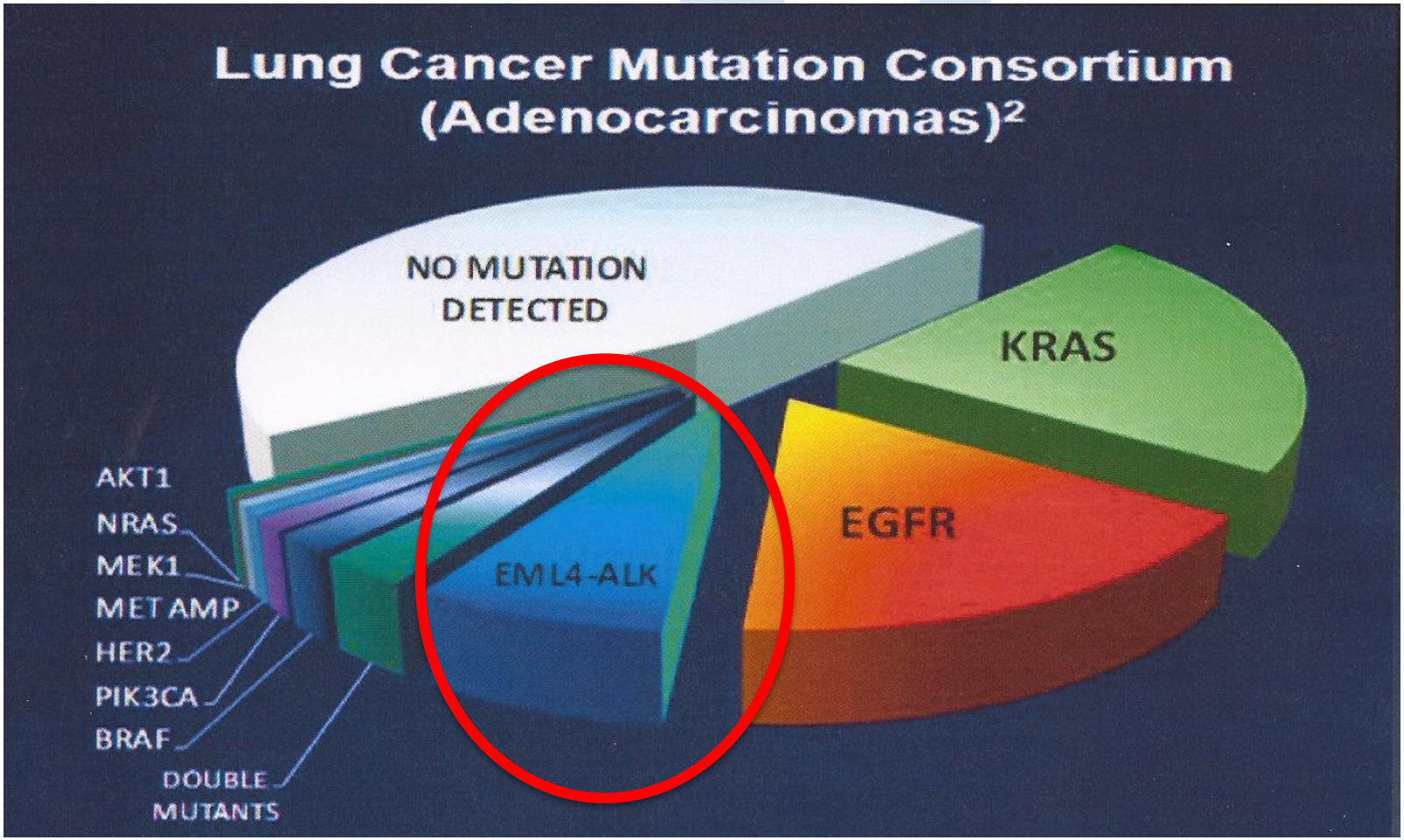
Ceritinib

Stichting Oncowijs





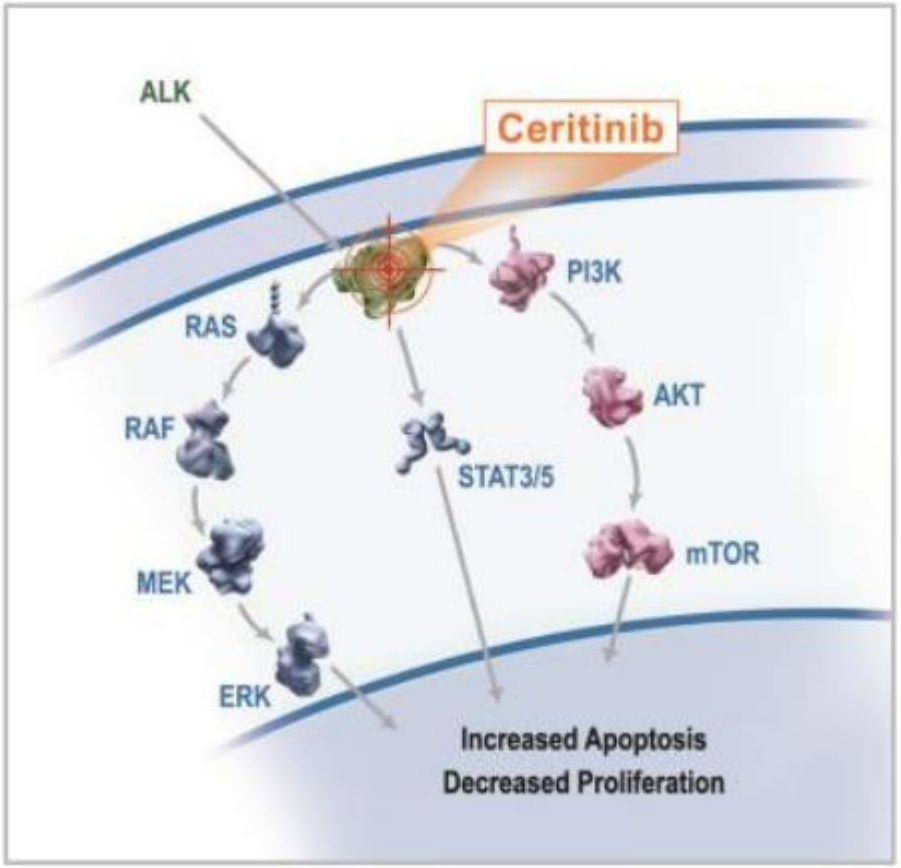
Mutaties


Lung Cancer Mutation Consortium
(Adenocarcinomas)²
NO MUTATION DETECTED
KRAS
EGFR
EML4-ALK
AKT1
NRAS
MEK1
MET AMP
HER2
PIK3CA
BRAF
DOUBLE MUTANTS

Ceritinib/Zykadia®
een tweede generatie ALK inhibitor

Nieuwe behandelmogelijkheid voor ALK+ NSCLC patiënten

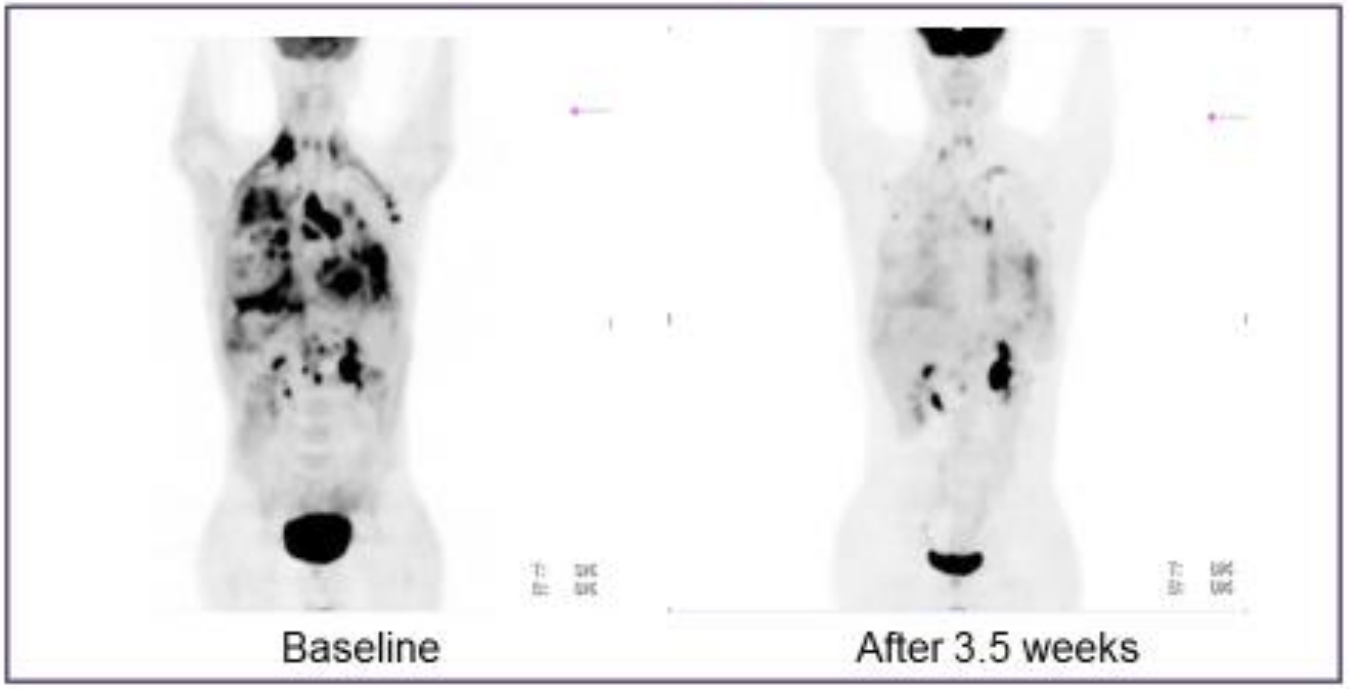
- Ceritinib is selectieve orale ALK inhibitor
- Geregistreerd voor volwassenen met ALK–positief, gevorderd niet–kleincellig longcarcinoom (NSCLC) die eerder zijn behandeld met crizotinib[1]



1. SmPC Zykadia 25-Aug-2015

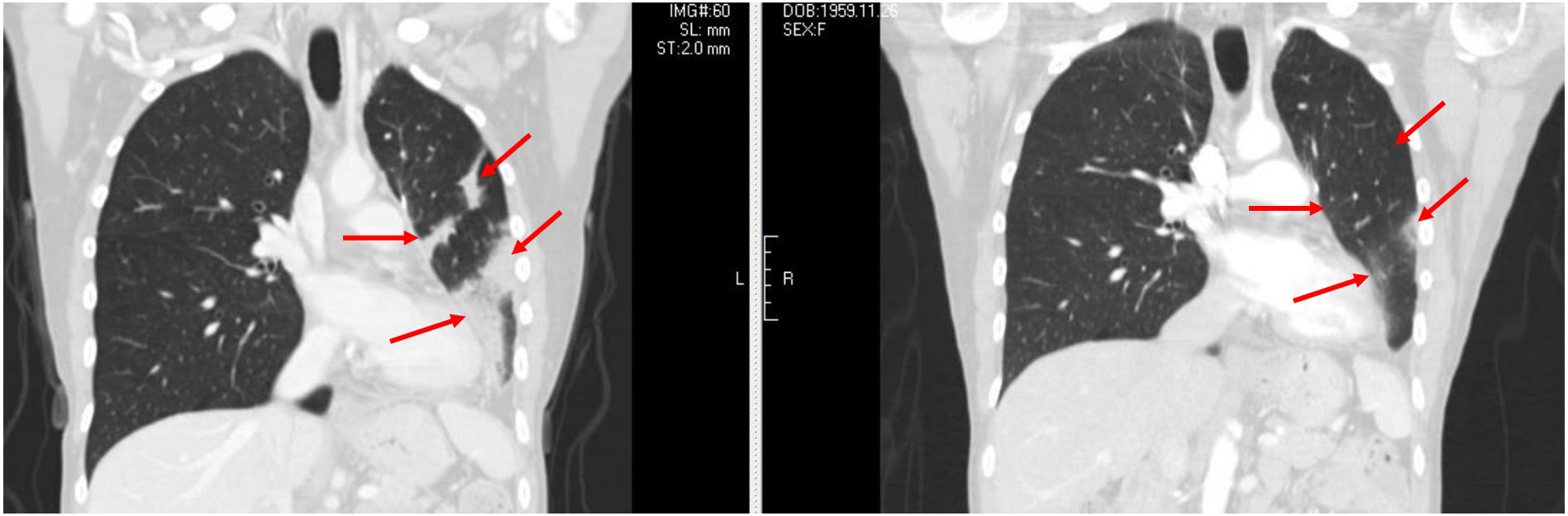
Opmerkelijke resultaten

Phase I First-in-human Study of ceritinib in Advanced Malignancies: Typical Response



1. Shaw AT, et al. ESMO 2012;Abstr 4400.

Typische respons bij Ceritinib



Baseline – crizotinib-resistant

After 3 months of LDK378

1. Shaw et al. ASCO 2013.

Effectiviteit

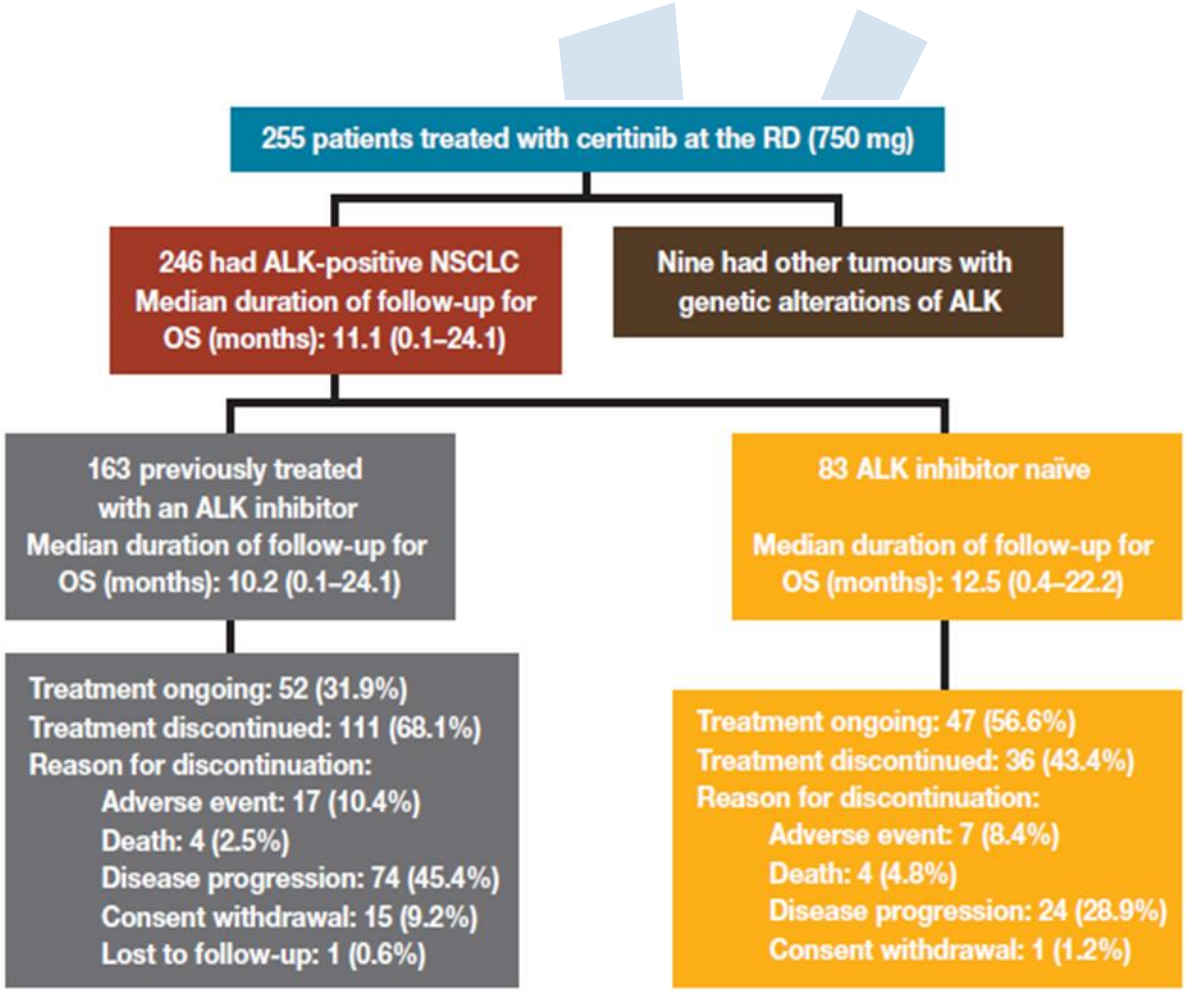
Stichting Oncowijs

PATIENTS PREVIOUSLY TREATED WITH CRIZOTINIB (n=163)[1,3]

Efficacy parameter	Investigator assessment	Blinded independent review committee assessment
Overall response rate (complete response + partial response)[a]	54.6% (95% confidence interval [CI]: 47, 62)	43.6% (95% CI: 36, 52)
Complete response	1.2%	2.5%
Partial response	53.4%	41.1%
Median DOR[a,b]	7.4 months (95% CI: 5.4, 10.1)	7.1 months (95% CI: 5.6, NE)

Stichting Oncowijs

Ascend 1 - Studie



Overall response in ALK+ NSCLC patients treated with ceritinib (750 mg daily)

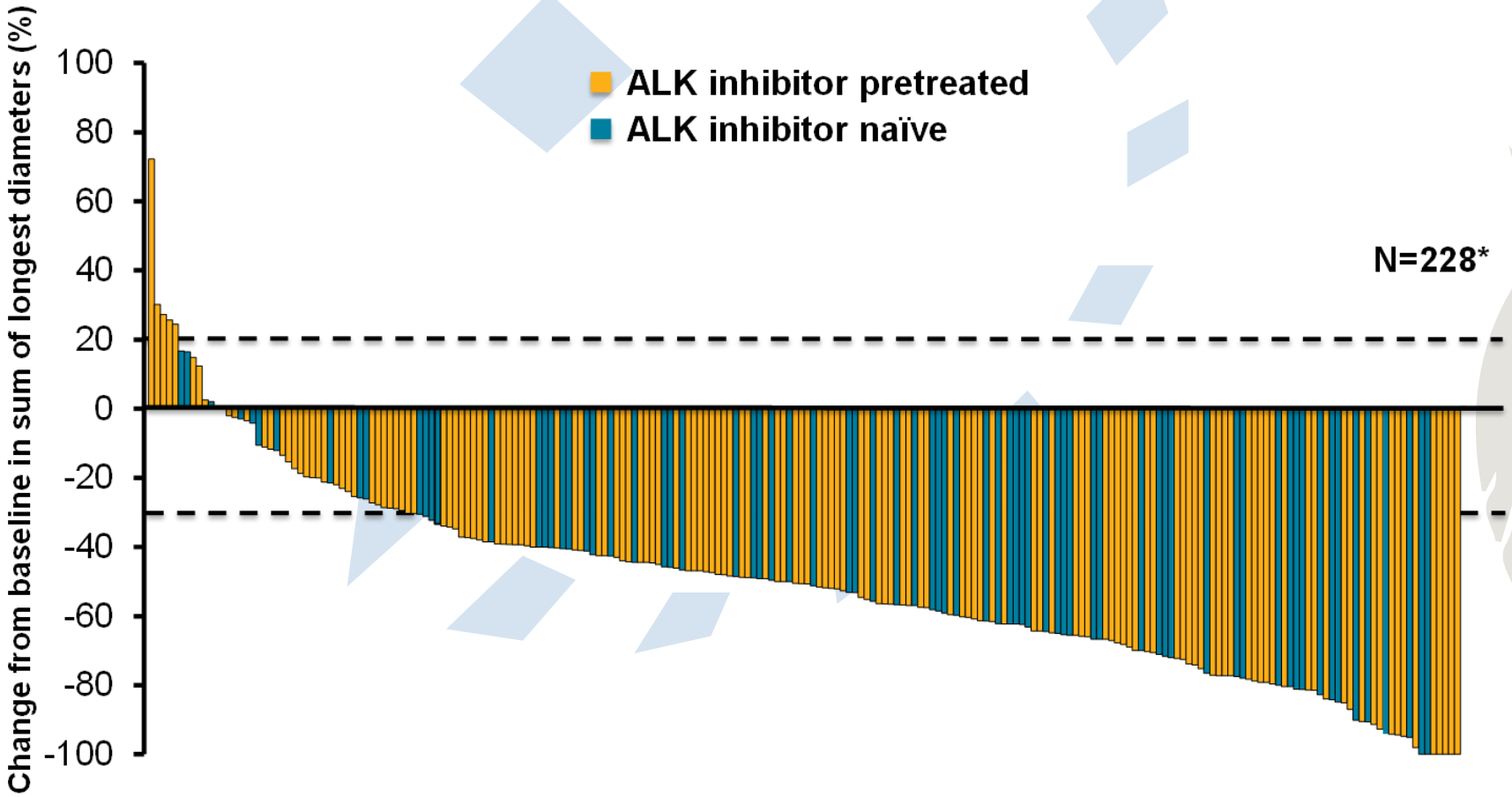
An ORR for ALK treated patients of 56.4% and 72.3% in treatment naïve patients; with an overall ORR of 61.8%.

Efficacy parameter	NSCLC with prior ALK inhibitor n=163	NSCLC ALK inhibitor naïve patients n=83	All NSCLC patients N=246
Complete response, n (%)	3 (1.8)	1 (1.2)	4 (1.6)
Partial response, n (%)	89 (54.6)	59 (71.1)	148 (60.2)
Stable disease, n (%)	29 (17.8)	14 (16.9)	43 (17.5)
Progressive disease, n (%)	16 (9.8)	0	16 (6.5)
Unknown, n (%)	26 (16.0)	9 (10.8)	35 (14.2)
Overall response rate, n (%) [95% CI]	92 (56.4) [48.5, 64.2]	60 (72.3) [61.4, 81.6]	152 (61.8) [55.4, 67.9]

1. Felip E et al. Presented at ESMO 2014 (abstr. 1295P)

Stichting Oncowijs

Tumor respons bij vooraf behandeld en bij naïve ALK+ patients



Bijwerkingen

Stichting Oncowijs

With infrequent grade 3/4 adverse events

All patients treated with 750 mg (N=255; includes nine non-NSCLC patients)		
Adverse events	All grades, n (%)	Grade 3/4, n (%)
Diarrhea	221 (86.7)	15 (5.9)
Nausea	211 (82.7)	15 (5.9)
Vomiting	157 (61.6)	12 (4.7)
Fatigue	109 (42.7)	13 (5.1)
Abdominal pain	98 (38.4)	3 (1.2)
Decreased appetite	95 (37.3)	4 (1.6)
Constipation	79 (31.0)	0 (0.0)
Cough	73 (28.6)	0 (0.0)
Dyspnea	63 (24.7)	11 (4.3)
Abdominal pain, upper	60 (23.5)	2 (0.8)
Weight decreased	46 (18.0)	5 (2.0)
Anemia	31 (12.2)	13 (5.1)
Pneumonia	25 (9.8)	12 (4.7)
Convulsion	15 (5.9)	8 (3.1)
Pneumonitis	9 (3.5)	7 (2.7)
Respiratory failure	6 (2.4)	6 (2.4)

Safety population of ASCEND-1 study n=255; X2101 ASCEND-1 study 14APR2014 cut-off
1. Felip E et al. Presented at ESMO 2014 (abstr. 1295P); 2. Novartis data on file.

Bijwerkingen

Stichting Oncowijs

Transient elevations in liver enzymes occurred in a proportion of patients

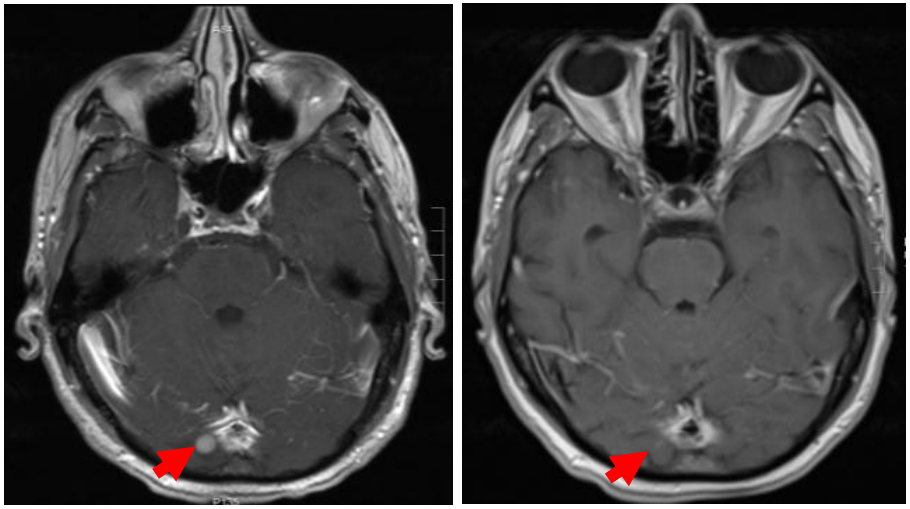
All patients treated with 750 mg (N=255; includes nine non-NSCLC patients)		
Adverse events	All grades, n (%)	Grade 3/4, n (%)
ALT increased	112 (43.9)	76 (29.8)
AST increased	83 (32.5)	25 (9.8)
Blood alkaline phosphatase increased	45 (17.6)	13 (5.1)
Hypokalemia	29 (11.4)	11 (4.3)
Lipase increased	24 (9.4)	16 (6.3)
Hyperglycemia	21 (8.2)	15 (5.9)
Hyponatremia	19 (7.5)	11 (4.3)
Amylase increased	18 (7.1)	8 (3.1)
Hypophosphatemia	16 (6.3)	8 (3.1)
Gamma-glutamyltransferase increased	14 (5.5)	7 (2.7)

Safety population of ASCEND-1 study n=255; X2101 ASCEND-1 study 14APR2014 cut-off
1. Felip E et al. Presented at ESMO 2014 (abstr. 1295P); 2. Novartis data on file.

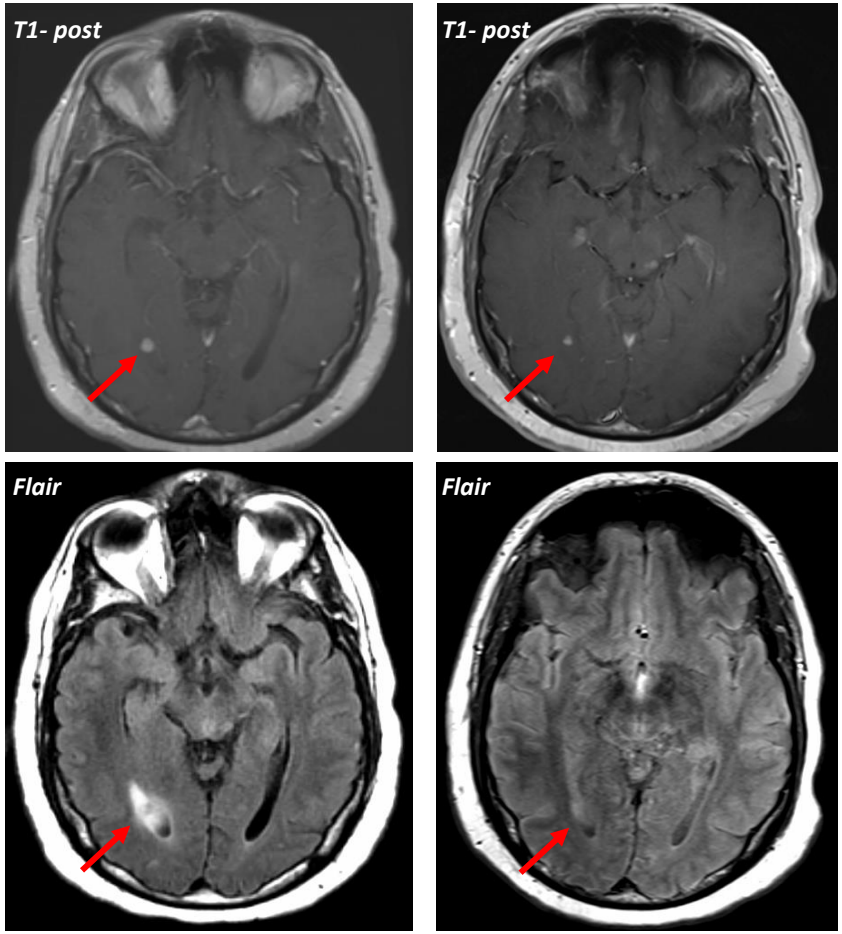
Initial promise of ceritinib's efficacy came from reports in the original ASCEND-1 analysis

SUSTAINED RESPONSES

CNS responses have been observed in patients receiving LDK378 (750 mg/day).[1,2]



Baseline MRI **After 7 weeks**



Baseline **After 6 weeks of LDK378**

CNS, Central Nervous System; MRI, Magnetic Resonance Imaging.

1. Shaw AT, et al. ESMO 2012;Abstr 440O; 2. Shaw AT, et al. J Clin Oncol 2013;31(suppl):Abstr 8010.

Ceritinib/Zykadia®

Stichting Oncowijs

aanbevolen dosering 750mg 1dd

1DD 5 CAPSULES OP EEN NUCHTERE MAAG

Geen voedsel **2** uur voor inname

Geen voedsel **2** uur na inname

- Zykadia is beschikbaar in capsules van 150 mg
- Zykadia innemen op een nuchtere maag d.w.z. 2 uur na een maaltijd. De patiënt mag na inname van Zykadia 2 uur geen maaltijd nuttigen
- Als de patiënt een dosis niet heeft ingenomen de dosering NIET verdubbelen, maar gewoon de voorgeschreven dosering innemen
- Indien nodig kan de dosering van Zykadia verlaagd worden met stappen van 150 mg per keer

Conclusie Ceritinib

Stichting Oncowijs

- Ceritinib een slectieve orale Alk remmer die is goedgekeurd door de FDA voor de behandeling van patienten met een anaplastisch lymphoma kinase (ALK)-positief gemetastaseerd non-small cell longcarcinoom (NSCLC) die progressief zijn of intolerant zijn voor crizotinib
- Meest frequente bijwerkingen zijn diarree, misselijkheid en braken (meestal graad 1–2), goed te behandelen volgens de richtlijn of door dosis modificatie
- Meest frequente laboratorium afwijkingen zijn ALT en AST stijgingen die te behandelnen zijn door dosis modificatie

ZYKADIA™
ceritinib 150 mg capsules

Ceritinib vs Alectinib

Stichting Oncowijs

Ceritinib and Alectinib

Efficacy in Crizotinib-Treated Patients

- No head-to-head comparison

Ceritinib	Alectinib
• ASCEND-1 – ALK inhibitor pretreated, n = 164 – ORR: 56% – mDOR: 8.3 months – mPFS: 6.9 months • ASCEND-2 – N = 140; chemo and crizotinib pretreated – ORR: 39%	• AF-002JG – N = 47, crizotinib treated – ORR: 55% • NP28761 – N = 87; chemo and crizotinib pretreated – ORR: 48% – mDOR: 13.5 months – mPFS: 8.1 months • NP28673 – N = 138; Chemo and crizotinib pretreated – ORR: 49% • Very high CNS penetration

Kim DW, et al. *Lancet Oncol*. 2016. [Epub ahead of print]; Gadgeel SM, et al. *Lancet Oncol.* 2014;15:1119-1128; Shaw AT, et al. *Lancet Oncol*. 2016;234-242; Ignatius Ou S-H, et al. *J Clin Oncol.* 2015;33:Abstract 8008.

Ceritinib vs Alectinib

Stichting Oncowijs

Ceritinib and Alectinib

Toxicity

Ceritinib	Alectinib
• GI toxicity (any grade, 96%) • Hepatotoxicity – ALT > 5x ULN (27%) • ILD/pneumonitis (4%) • QT interval prolongation (3%) • Hyperglycemia (13%) • Bradycardia (1%) • Pancreatitis (<1%) • Embryo-fetal toxicity	• Hepatotoxicity – AST > 5x ULN (4%) – ALT > 5x ULN (5%) – Bilirubin > 3x ULN (3%) • ILD/pneumonitis (0.4%) • Bradycardia (8%) • Myalgia (29%) • Embryo-fetal toxicity

ZYKADIA™ PI 2015; ALECENSA® PI 2015.

Stichting Oncowijs

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Veinsite

FDA CE

Intra-veneuze toegang

Het lijkt altijd relatief eenvoudig voor iedereen om een intra-veneus infuus aan te leggen omdat iedereen zich een expert voelt. In praktijk blijkt echter dat dit niet zo is en de patient is daarvan de dupe! Je hebt hiervoor excellente kennis en vaardigheden nodig!

Waar loop je tegen aan:

- ☑ Multiple IV stick attempts
- ☑ Unnecessary Central Lines/PICCs
- ☑ Increased risk of CLABSIs & other complications
- ☑ Treatment delays
- ☑ Increased hospital operational costs
- ☑ Decreased nurse efficiency
- ☑ Increased patient discomfort
- ☑ Lower patient satisfaction scores

veinsite by VueTek

VEINSITE

Veinsite stelt arts en verpleegkundige in staat om moeilijke oppervlakkige, subcutane vasculatuur te vinden op verschillende diepten die geschikt zijn voor perifere IV toegang, phlebotomy en de behandeling van veneuze insufficiencie / ziekte

Complete Portable, Hands-Free,
Vascular Imaging for Locating Veins

veinsite by VueTek

CONFIDENTIAL

Werkingsmechanisme

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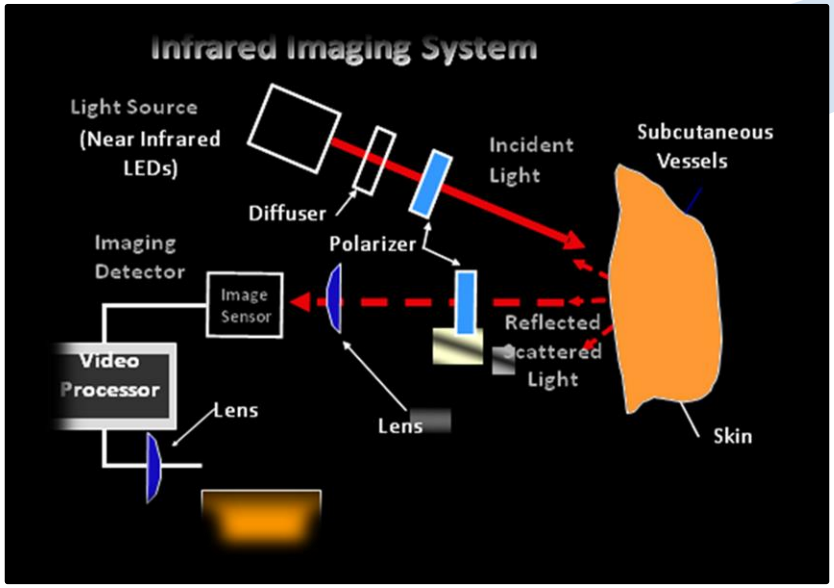
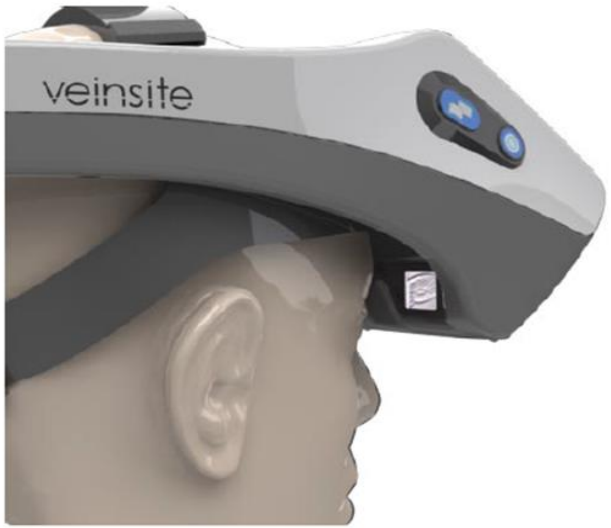
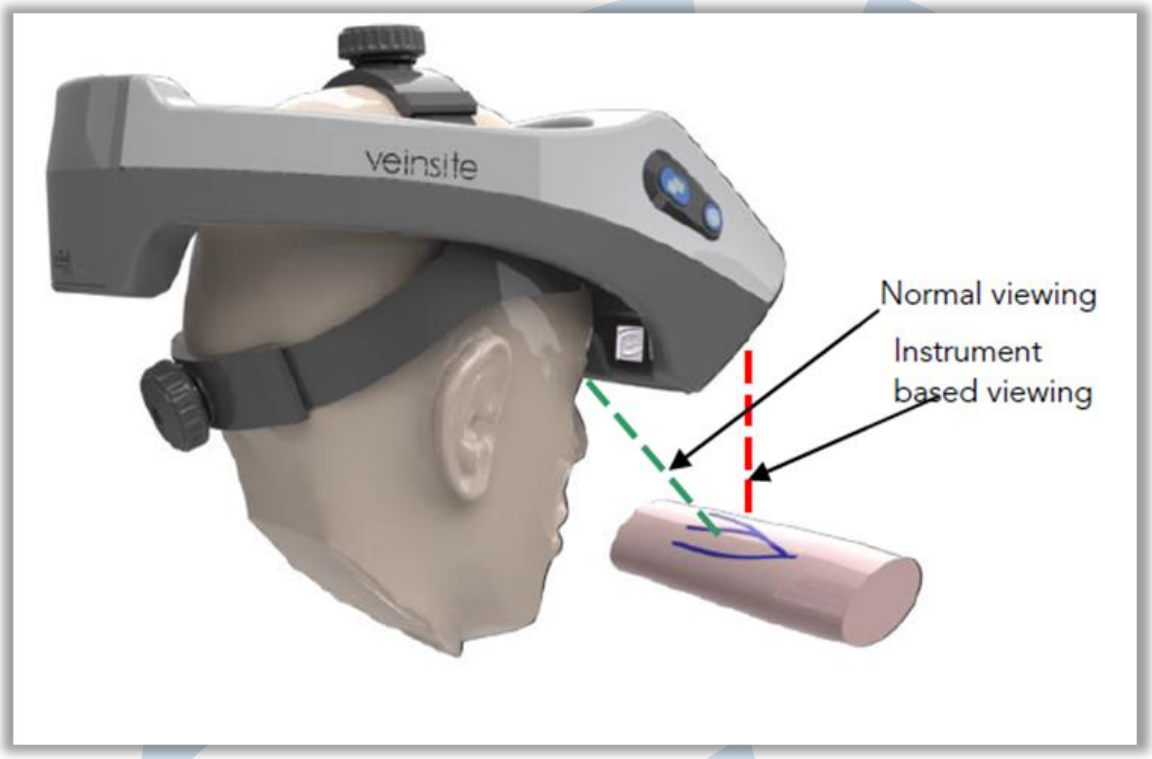




- ☑ Veinsite belicht de huid met behulp van infrarood licht (NIR)

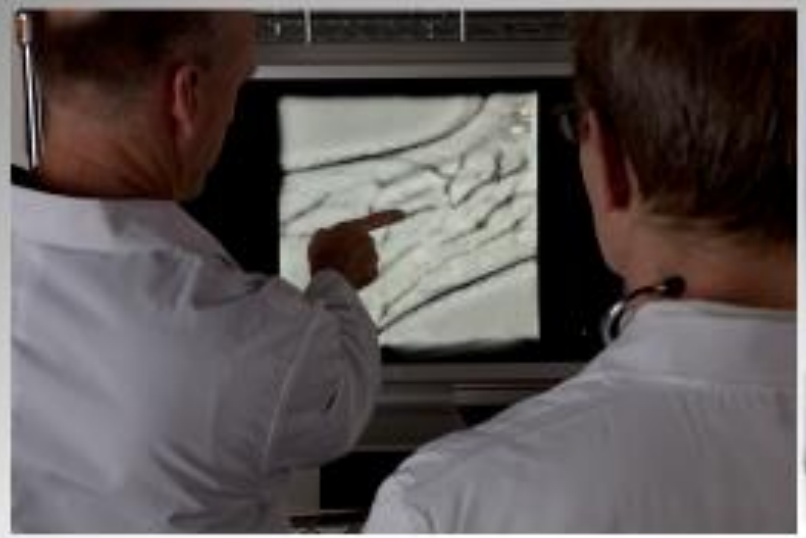
- ☑ NIR is geabsorbeerd door hemoglobine en verspreid door het omliggende weefsel
- ☑ Veinsite verwerkt het verschil in licht strooi en absorptie in een videobeeld van de aderen
- ☑ Dit wordt weergegeven voor de gebruiker in een LCD-scherm in de headset in de omgeving van real time

Klinische Praktijk



- Creëert geen overlap op de anatomie
- Verandert niets aan hoe de procedure wordt uitgevoerd

Remote Monitor Option



☑ Train ☑ Collaborate ☑ Educate

Monitor based demonstrations make a highly effective demonstration/sales tool

Eigenschappen & voordelen

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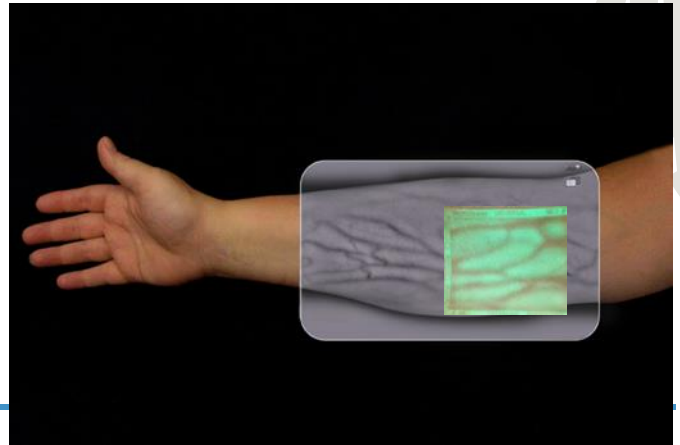
- Volledig handsfree-gebruik door de behandelaar voor de gehele procedure IV – (vitaal belang)
- Volgt moeiteloos de anatomie en volgt alle bewegingen van de patiënt
- Minimaliseert schending van steriel veld & kruisbesmetting



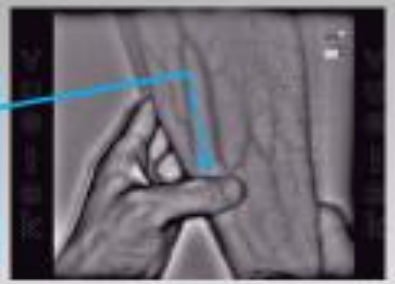
Veinsite potentiële voordelen

See veins otherwise not visible to the unaided eye (depths suitable for PIVCs)

- ☑ Identify valves & bifurcations
- ☑ Assess venous return (compare vessels)
- ☑ Improve site selection
- ☑ Improve catheter dwell times
- ☑ May spot hematoma
- ☑ Observe saline flush to help confirm placement

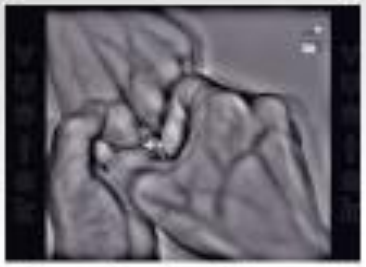
Veinsite Images (actual screen captures)

Sweeping the vein downward to distal end while applying gentle pressure

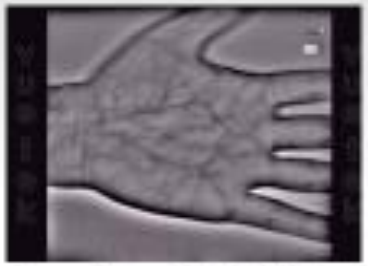


Produces visual indication of a valve here

Actual images seen through Veinsite depicting valve location by sweeping



Alignment of needle and vein as seen in Veinsite display



Images showing Veinsite's ability to see fine detail on small vessels helpful for pediatric and neonatal applications

Challenging Anatomy - examples

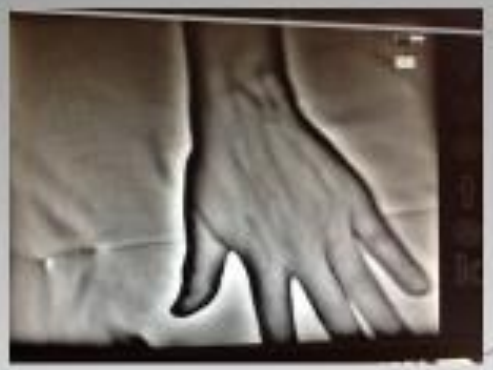


Image of dark pigmentation subject as seen with Veinsite, courtesy of Andrew Barton, Clinical Nurse Specialist in Vascular Access & IV Therapy, Frimley Park Hospital

Bariatric/obese patient, top hand and forearm as seen with Veinsite, courtesy of Andrew Barton, Clinical Nurse Specialist in Vascular Access & IV Therapy, Frimley Park Hospital

Uitkomsten studie

Stichting Oncowijs

IRB approved, non-significant risk validation clinical study: 118 subjects of diverse ethnic background, skin tone, weight and age new-born to elderly

veinsite

- ☑ Increase firsttime success rate of peripheral IVs
- ☑ Decrease multiple IV stick attempts
- ☑ Decrease unnecessary central lines/PICCs
- ☑ Decrease costly CLABSIs and possible complications
- ☑ Decrease hospital operational costs
- ☑ Increase nurse efficiency and compliance
- ☑ Empower clinicians to choose the optimal sites for vascular access
- ☑ Increase patient satisfaction scores (Press Ganey)
- ☑ Fewer treatment delays

*In a recent peer reviewed, clinical study published in the British Journal of Anaesthesia, Veinsite increased the detection of possible I.V. cannulation sites in 97% of especially difficult cases - including 1.7 additional vein sites for the infant group (**89% increase**) and 3.7 additional vein sites for African-Americans (**80% increase**). Obese subjects' vein visibility was also markedly improved by 4.0 (**82% increase**) and morbidly obese patients improved by 3.0 (**83% increase**).*

Voorbeelden

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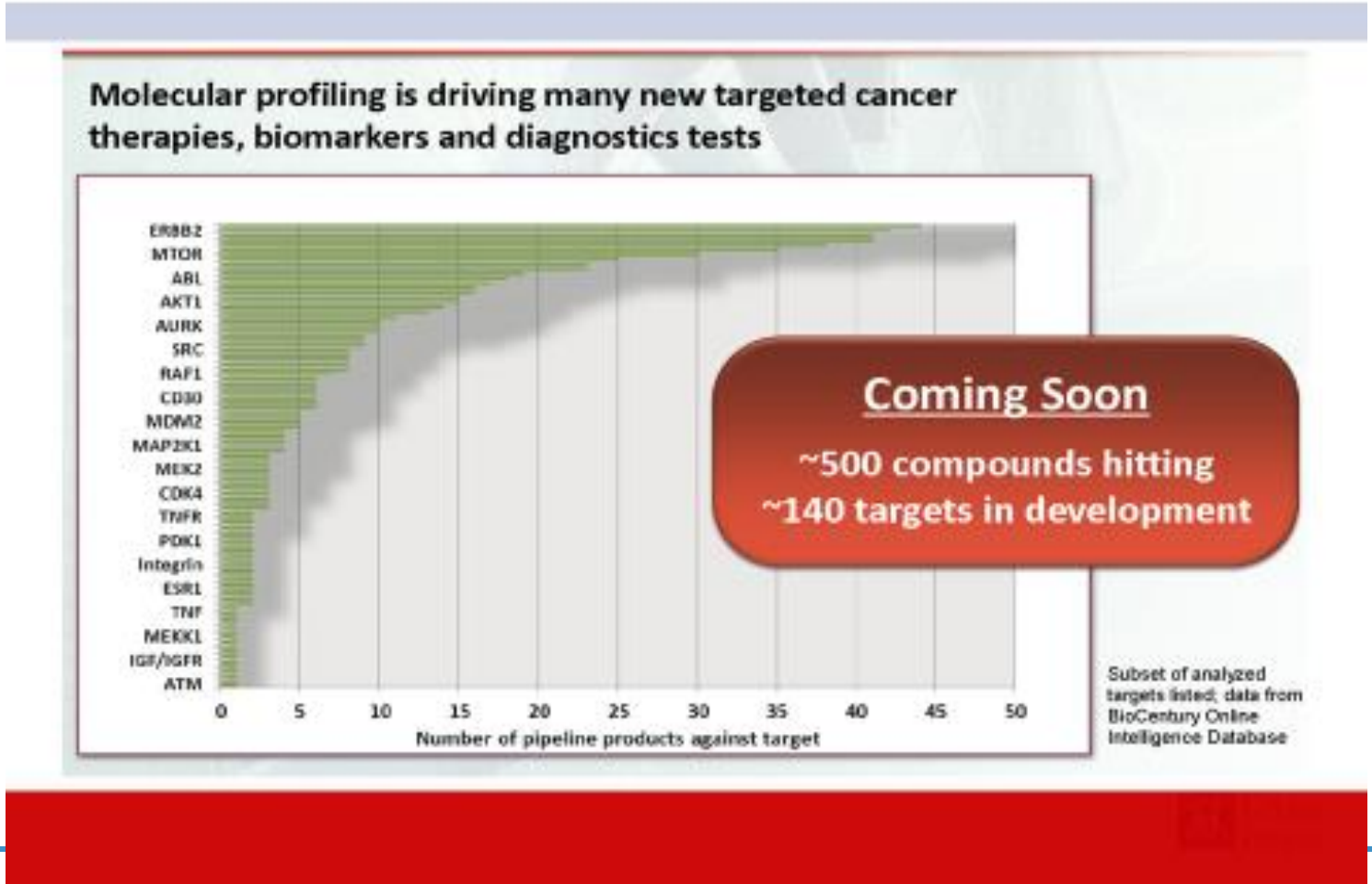
veinsite

by VueTek SCIENTIFIC

Redefining Vascular Imaging

Toekomst


Molecular profiling is driving many new targeted cancer therapies, biomarkers and diagnostics tests
ERBB2
MTOR
ABL
AKT1
AURK
SRC
RAF1
CD30
MDM2
MAP2K1
MEK2
CDK4
TNFR
PDK1
Integrin
ESR1
TNF
MEKK1
IGF/IGFR
ATM
0
5
10
15
20
25
30
35
40
45
50
Number of pipeline products against target
Coming Soon
~500 compounds hitting
~140 targets in development
Subset of analyzed targets listed; data from BioCentury Online Intelligence Database

Dank voor Uw aandacht
en tot volgend jaar

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