Agnostic tumor approaches: a limited or an extended field in oncology ?

Prof. Hans Prenen

BSMO

Universiteit Antwerpen

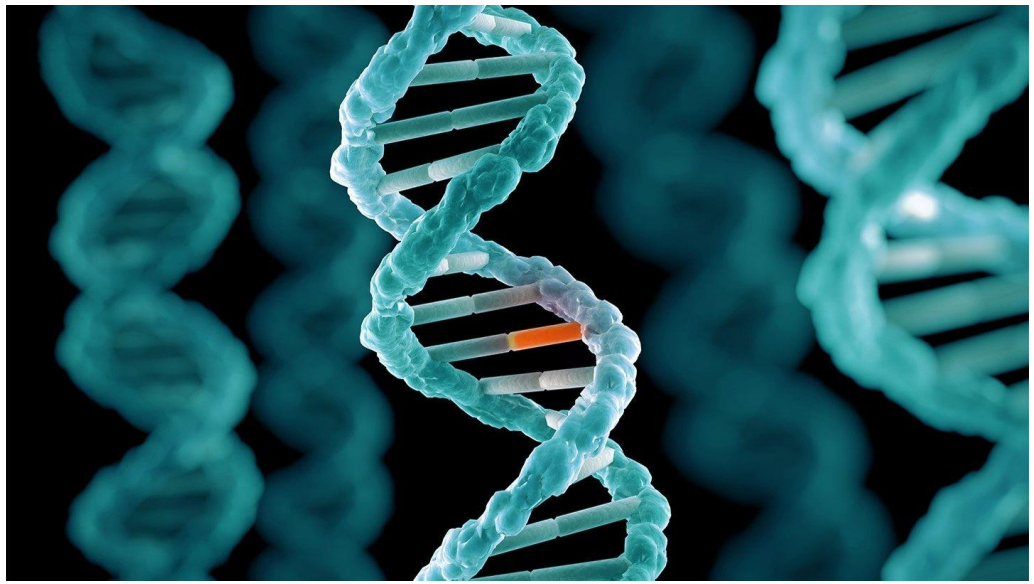
UZA

Definition tumor-agnostic therapies

To target specific genomic anomalies or molecular features

REGARDLESS of

tumor of origin



Treatment metastatic lung cancer 2019

Diagnostic workup

1. Multidisciplinary discussion to determine optimal procedure for tissue procedure
2. Biopsy
3. Morphology
4. Review of patient and tumour data

Molecular profiling

Integrated NGS-based assay to detect mutations, amplifications, and translocations

Patient selection

EGFR
ALK
ROS1
BRAF
MET
RET
NTRK1/2/3
NRG1
HER2
No actionable alterations
PD-L1, TMB

Treatment

Gefitinib, erlotinib, afatinib, dacomitiinb osimertinib

Crizotinib Alectinib Ceritinib Brigatinib Lorlatinib

Crizotinib
Ceritinib Lorlatinib Cabozantinib Entrectinib Ropotrectinib DS-6051b

Dabrafenib + trametinib
Vemurafenib

Crizotinib Cabozantinib **Capmatinib** **Savolitinib** **Tepotinib** Merestinib Glesatinib

Cabozantinib Vandetanib Sunitinib Lenvetanib Alectinib Ponatinib BLU-667 LOXO-292 RXDX-105

Entrectinib **Larotrectinib** Loxo-195 Cabozantinib DS-6051b Repotrectinib

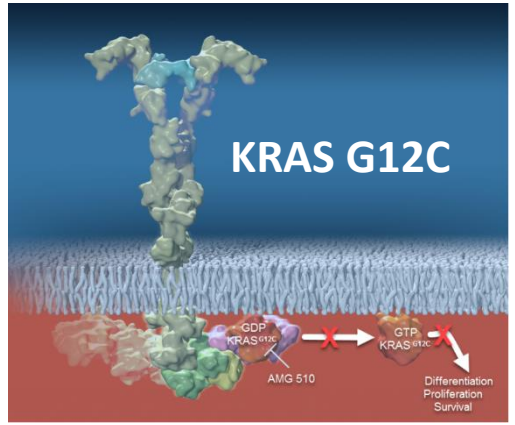
ERBB3 inh

Neratinib+/- Temsirolimus Afatinib Dacomatinib **Poziotinib** **Pyrotinib** **TAK-788** Trastuzumab **TDM-1** **DS-8201a**

Chemotherapy Or / and immunotherapy

Therapy switch/combination based on re-biopsies or liquid therapy

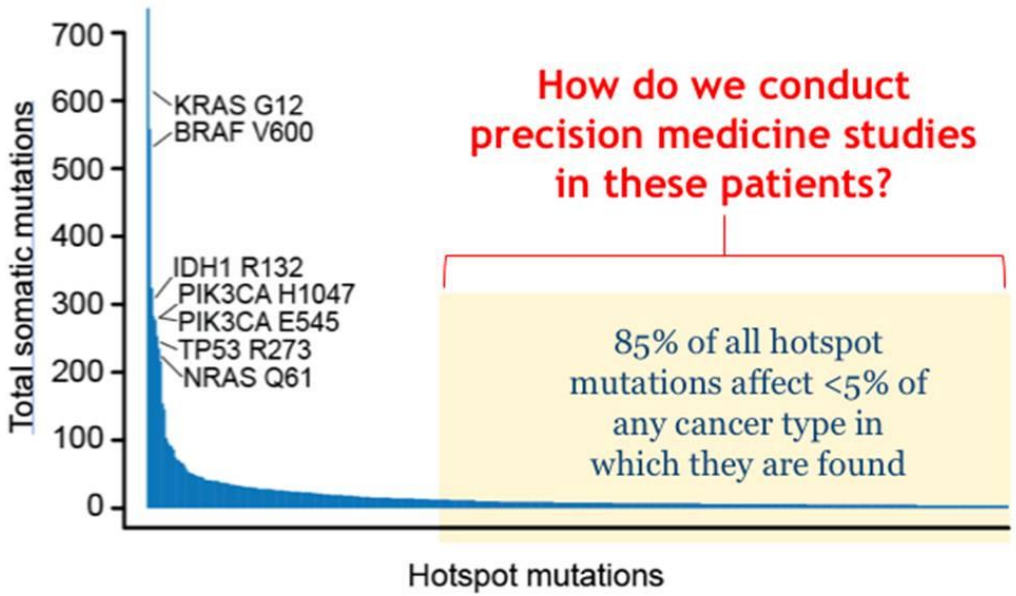
2020

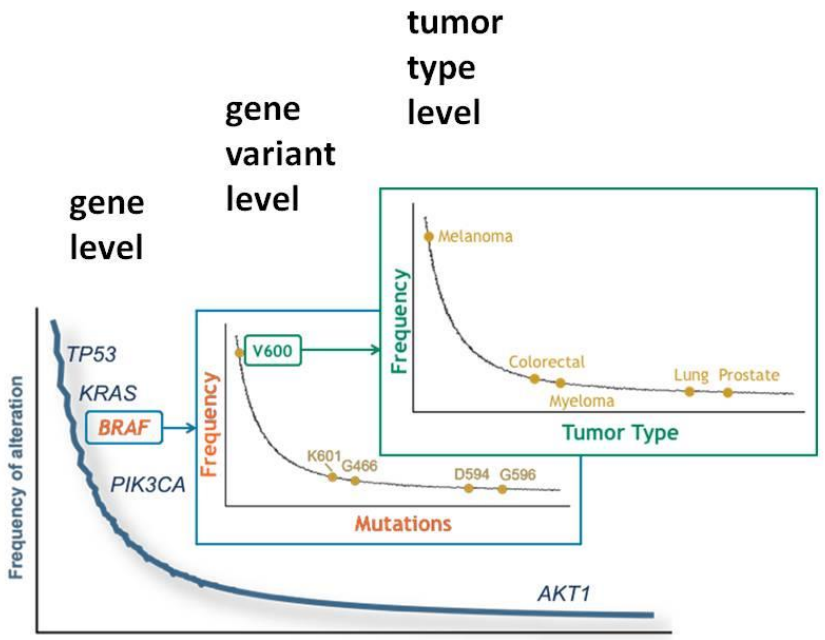


Universiteit Antwerpen

UZA

There is a ‘long tail’ of hotspot mutations across different cancers





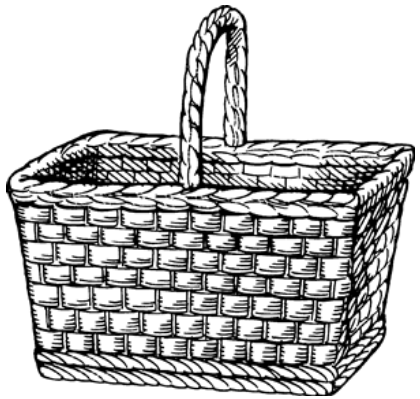
Chang, MT et al. Nat Biotechnol. 2016 Feb;34(2):155-63

Universiteit Antwerpen UZA

Tumor agnostic approach: challenges

- Context independent activity versus context specific activity

- Growing importance of « basket » trials, but challenging



Typically single arm, early phase, small sample size

Universiteit Antwerpen

UZA

AGNOSTIC ONCOLOGY: Context independent

- Microsatelity instability (MSI)

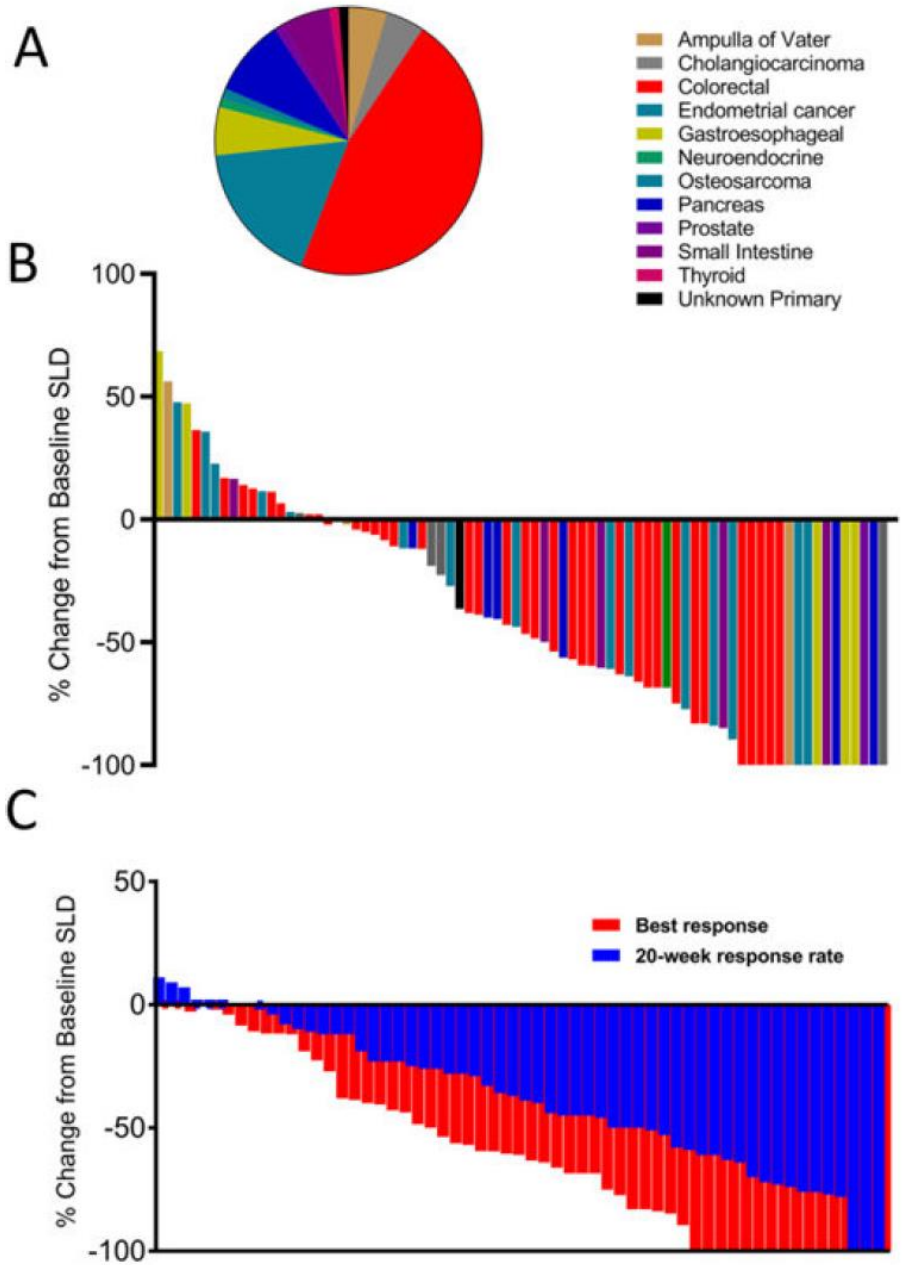
FDA Approved Tumor Agnostic Therapy

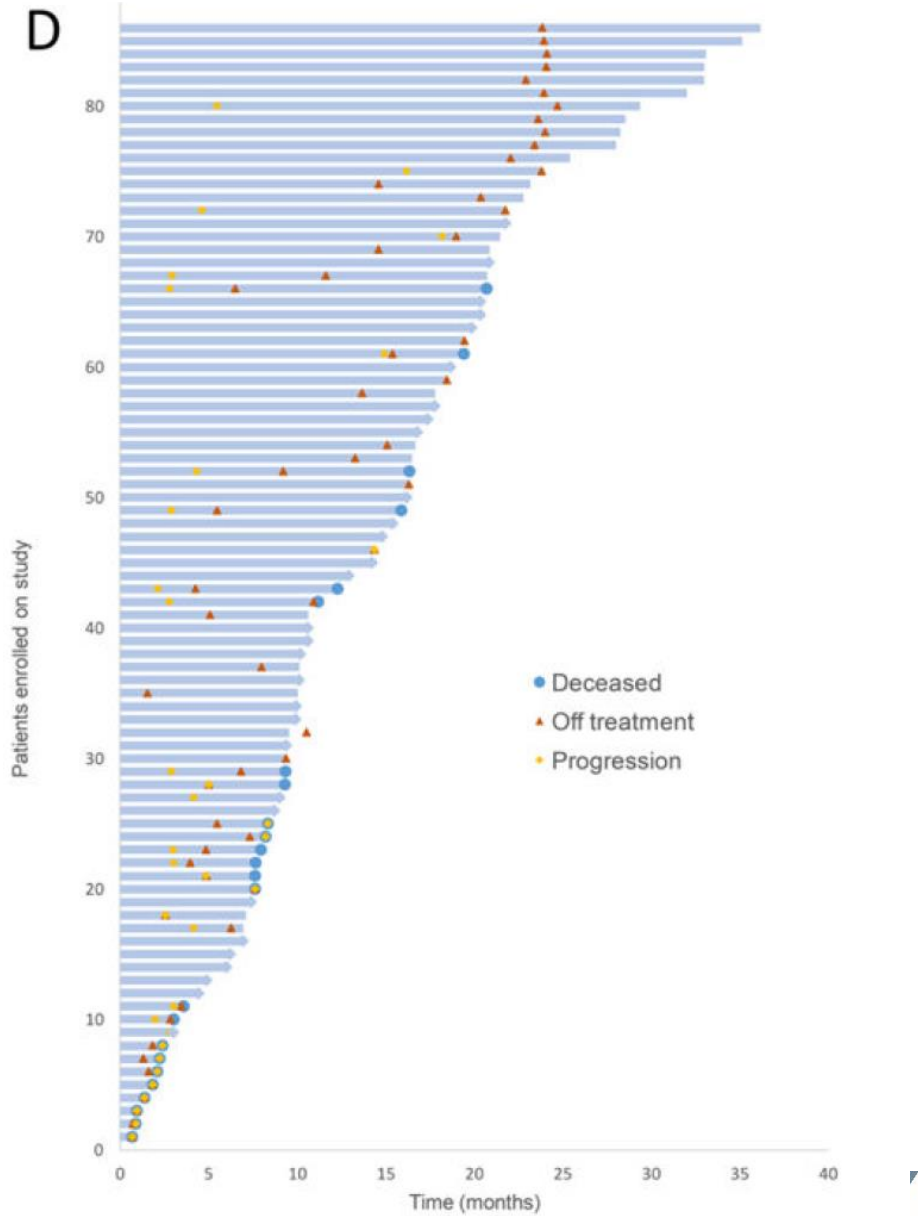
KEYTRUDA® (pembrolizumab) Injection 100 mg

- Pembrolizumab was the first therapy to receive a tumor agnostic approval from the FDA
  - Treatment of adult and pediatric patients with unresectable or metastatic, microsatellite instability-high (MSI-H) or mis-match repair deficient (dMMR) solid tumors

Science. 2017 July 28; 357(6349): 409–413. doi:10.1126/science.aan6733.

Mismatch-repair deficiency predicts response of solid tumors to PD-1 blockade



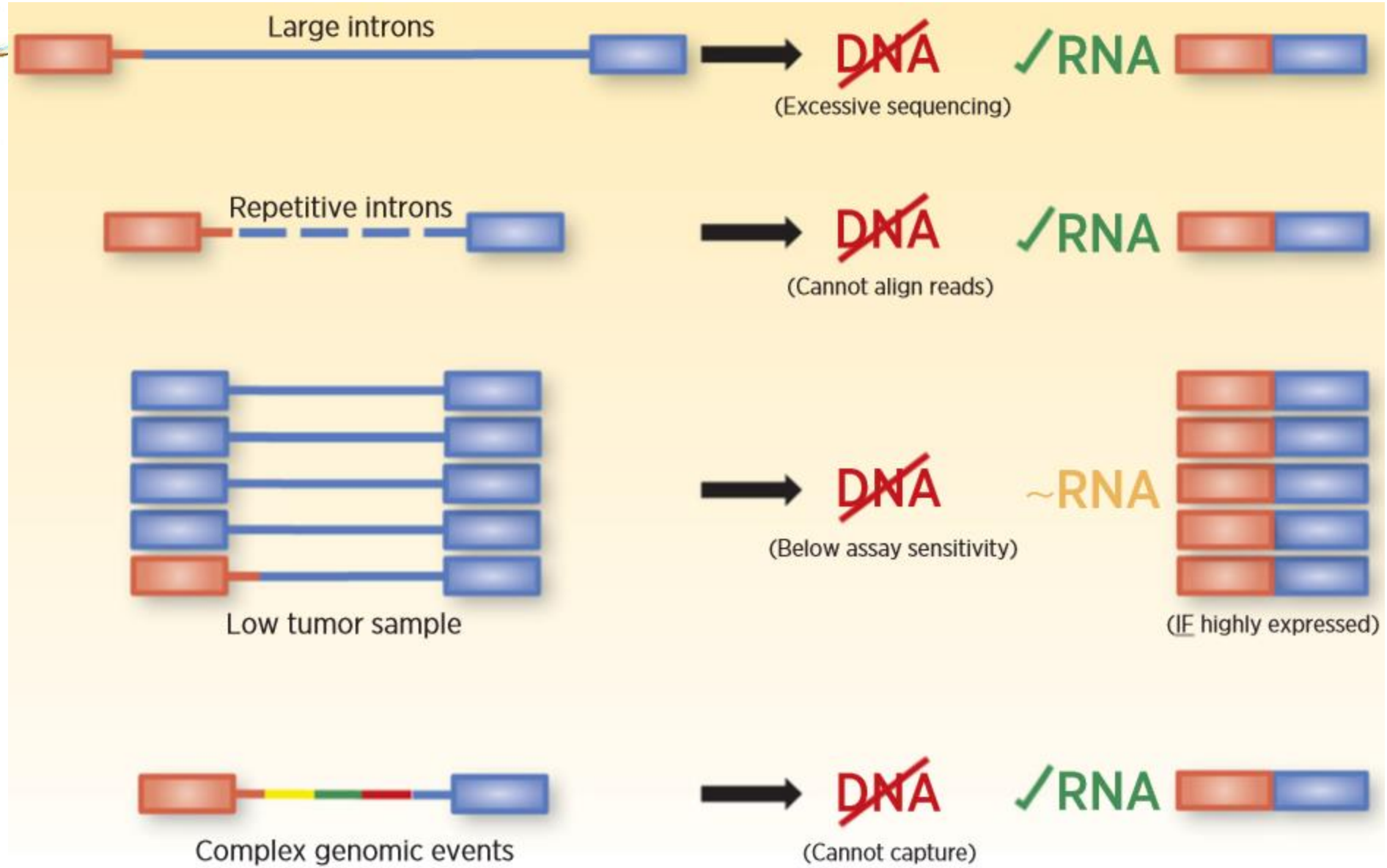


MSI: frequency

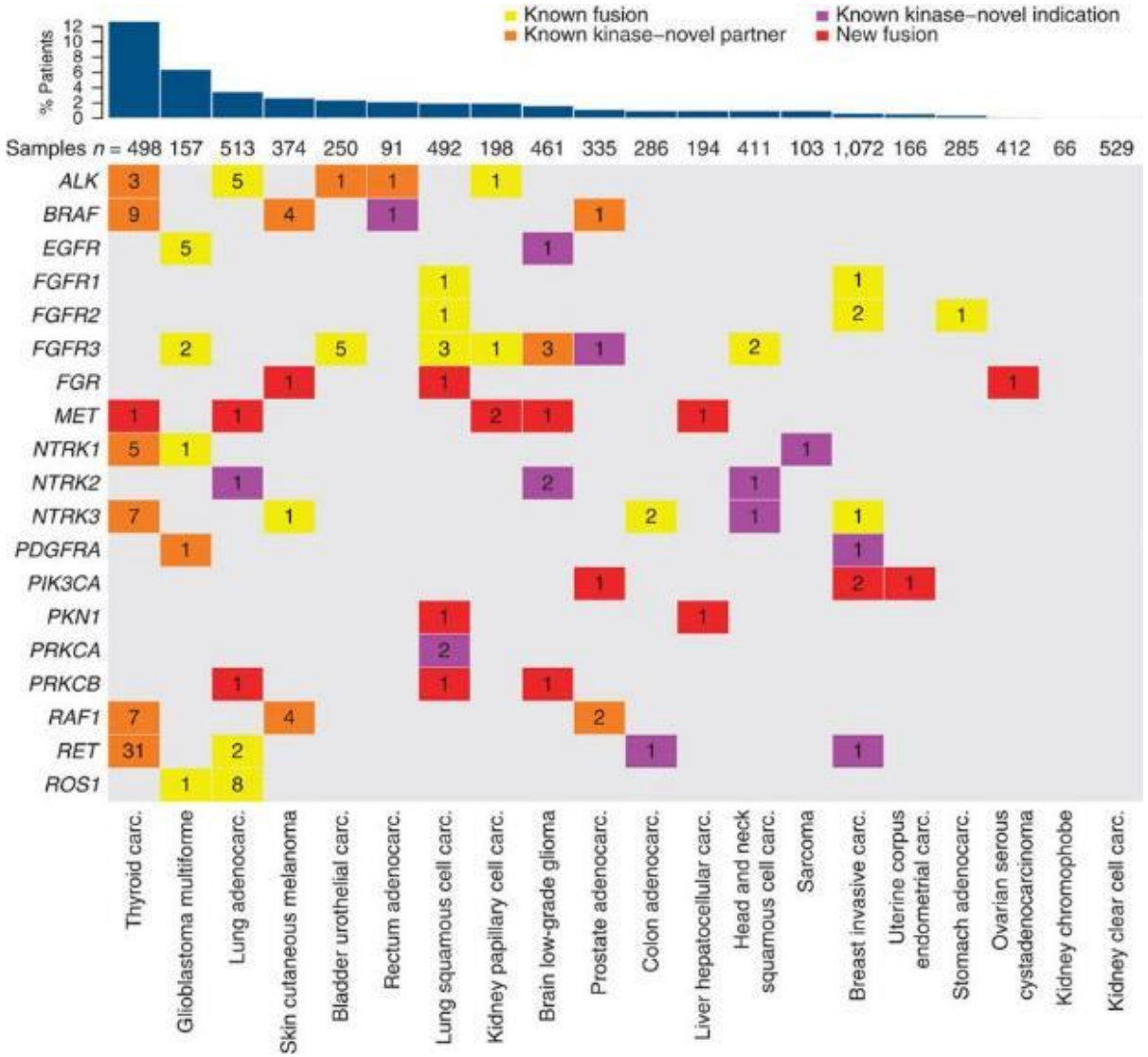
- Most frequent:
  - Colorectal cancer
  - Endometrial
  - Gastric
  - Ampullary carcinoma
- But also:
  - Skin, ovarian, cervical, esophageal, head and neck, pancreas, bile duct, sarcoma, ……

AGNOSTIC ONCOLOGY: Context independent

- Fusion genes:
  - Joining parts of 2 different genes
  - Ex. BCR/ABL1 fusion gene in CML
  - Fusion genes play an important role in tumorgenesis



AGNOSTIC ONCOLOGY: Context independent

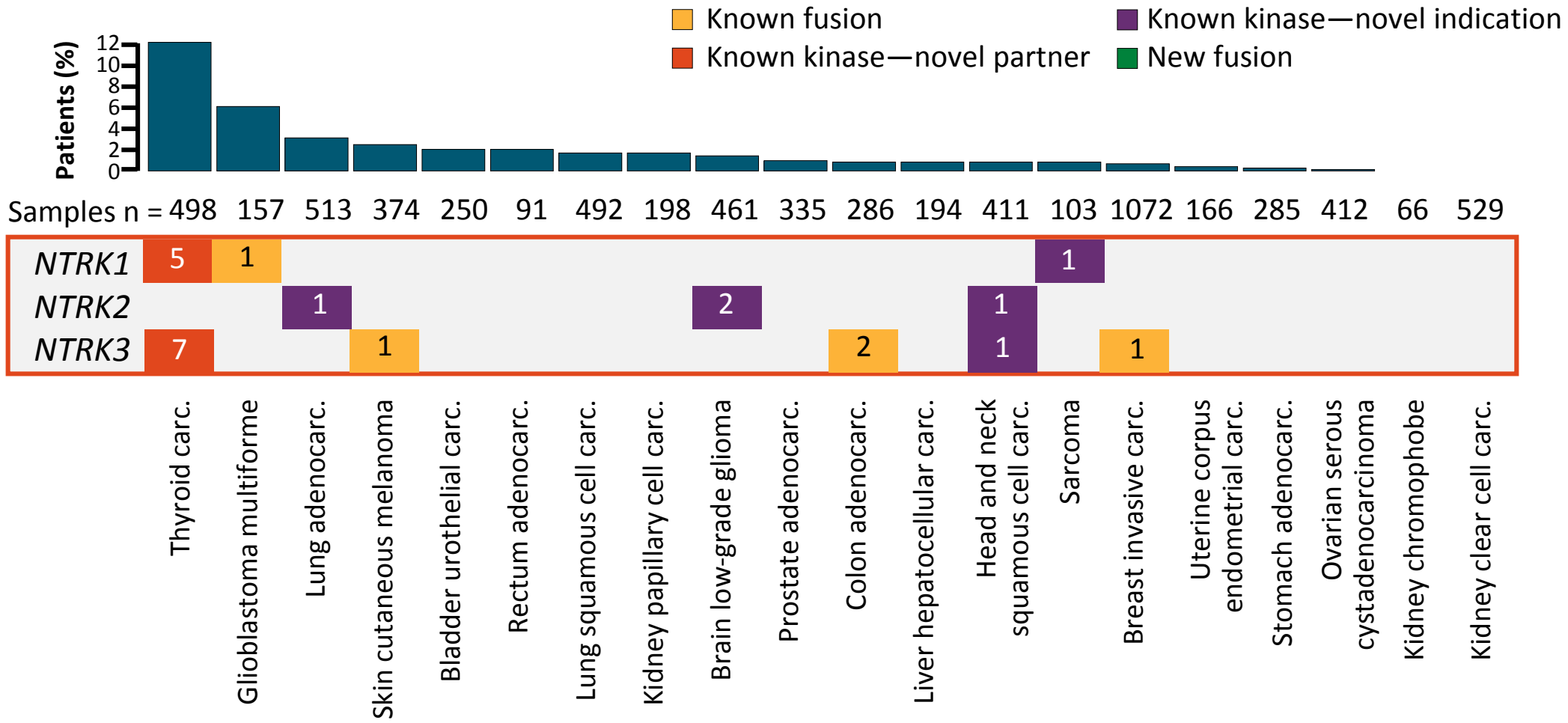


- « Long tail » of kinase fusions accross cancers

Universiteit Antwerpen

UZA

The “Long Tail” of Kinase Fusions Across Cancers

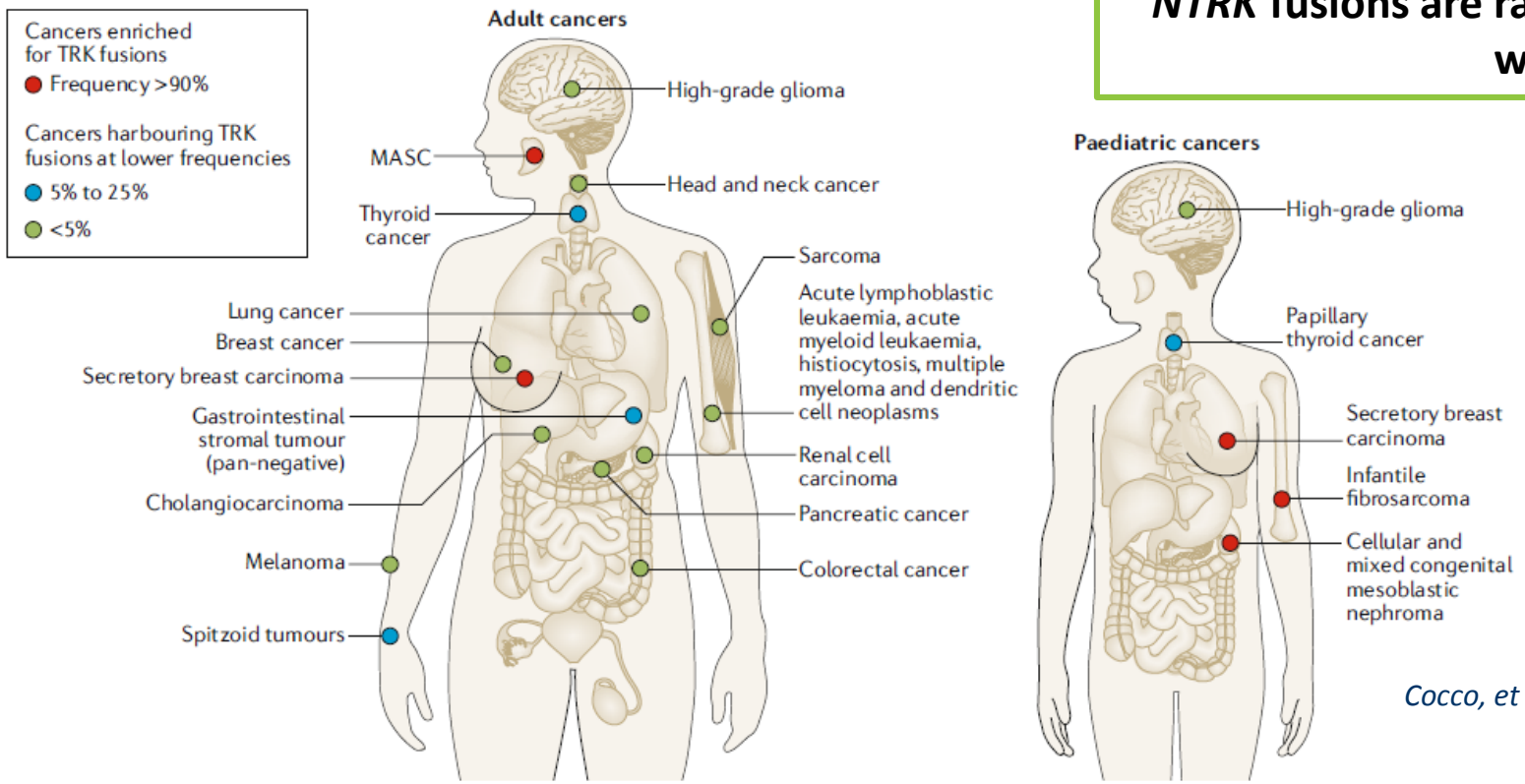


Stransky. Nat Commun. 2014;5:4846.

TRK Fusions Are Found Across Diverse CancerTypes In Both Adults and Children

REVIEWS

***NTRK* fusions are rare events: 0.21% across 11,116 patients with tumors of all types**



Cocco, et al. Nature Reviews Clinical Oncology 2018;15:731–47

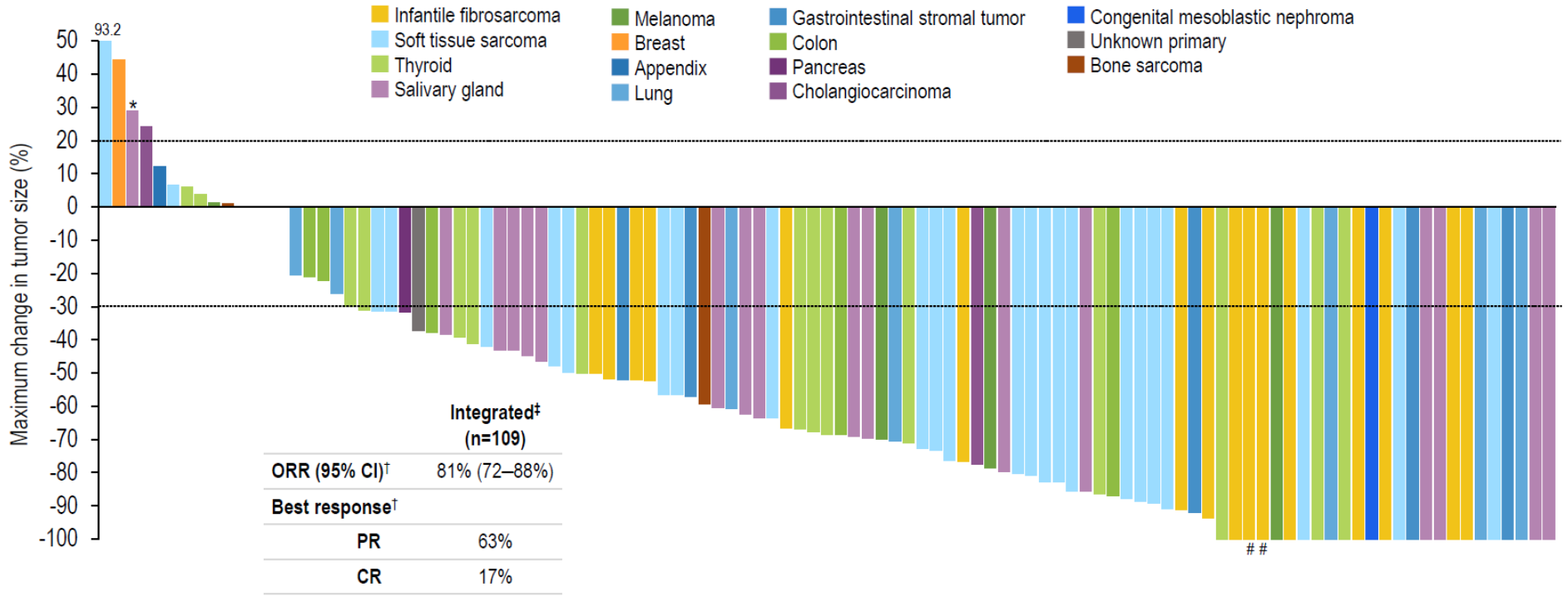
Fig. 4 | **Distribution and frequency of *NTRK* fusions in adult and paediatric tumours.** *NTRK* fusions are identified across multiple paediatric and adult cancer histologies. The frequency of these fusions varies from <1% in cancer types including lung, colorectal, pancreatic and breast cancers, melanoma and other solid or haematological cancers (green circles), up to 25% in tumours including thyroid, spitzoid and gastrointestinal stromal tumours (blue circles), to >90% in rare tumours types, specifically secretory breast carcinoma, mammary analogue secretory carcinoma (MASC), congenital infantile fibrosarcoma and cellular or mixed congenital mesoblastic nephroma (red circles) for which the *NTRK* fusions are considered practically pathognomonic.

Universiteit Antwerpen

UZA

AGNOSTIC ONCOLOGY: Context independent

Integrated dataset: Larotrectinib is efficacious regardless of tumor type



	Integrated‡ (n=109)
ORR (95% CI)†	81% (72–88%)
Best response†	
PR	63%
CR	17%

‡Includes 9 unconfirmed PRs pending confirmation; does not include 13 patients continuing on study and awaiting initial response assessment
*Patient had TRKC solvent front resistance mutation (G623R) at baseline due to prior therapy; #Surgical CR; †RECIST 1.1
Note: Two patients not shown here. These patients discontinued treatment prior to any post-baseline tumor measurements.
CR, complete response; ORR, objective response rate; PR, partial response

MUNICH 2018 ESMO congress

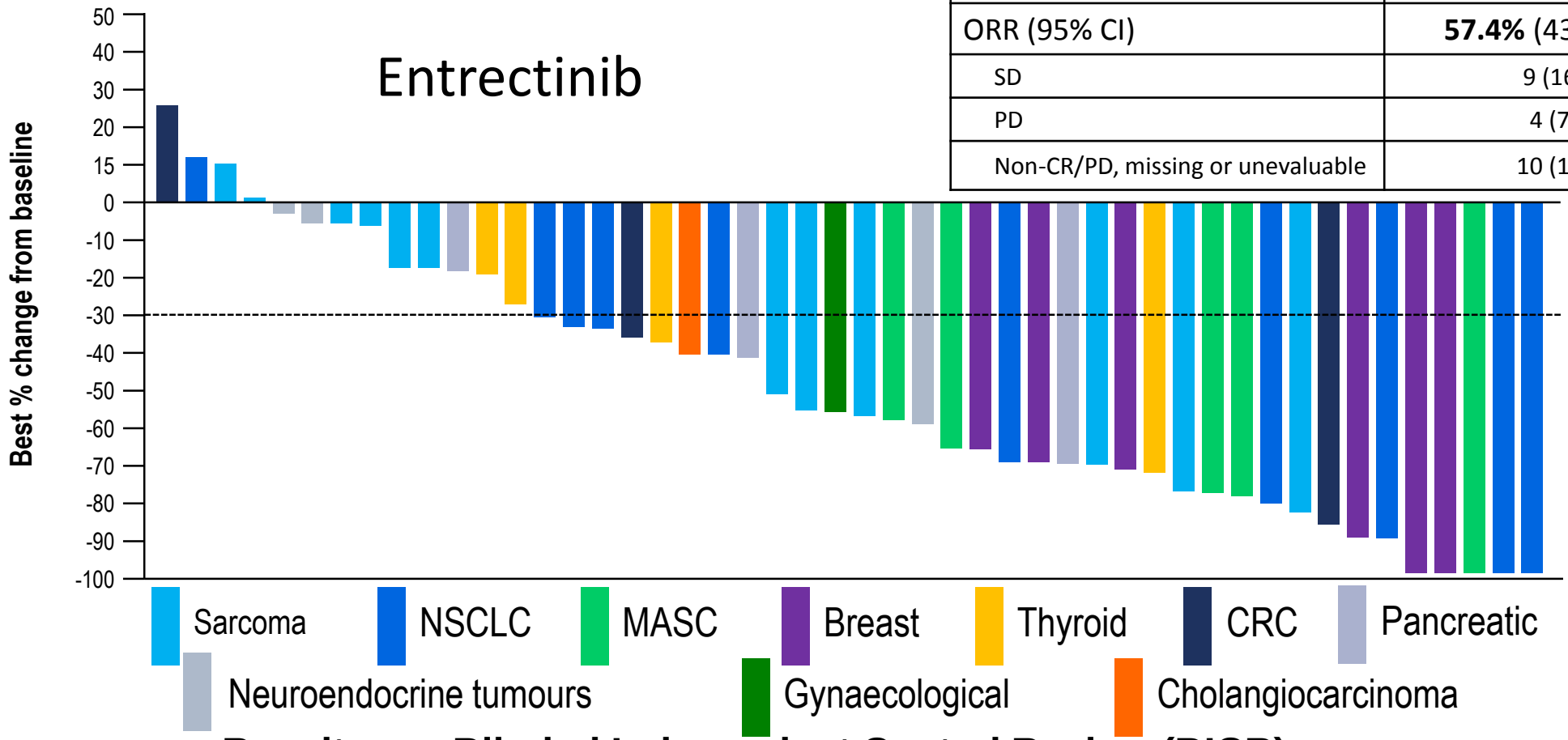
Investigator response assessments, as of 30 July 2018

Universiteit Antwerpen

UZA

AGNOSTIC ONCOLOGY: CONTEXT INDEPENDENT

	***NTRK*+ patients (n=54)**
ORR (95% CI)	**57.4%** (43.2–70.8)
SD	9 (16.7)
PD	4 (7.4)
Non-CR/PD, missing or unevaluable	10 (18.5)



Cut-off date: 31 May 2018

Note: Patients (n=6) without matched pre/post therapy scans were excluded from the plot

CI: confidence interval; CRC: colorectal cancer; MASC: mammary analogue secretory carcinoma; NSCLC: non-small cell lung cancer

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

Annals of Oncology 30: 1417–1427, 2019
doi:10.1093/annonc/mdz204
Published online 3 July 2019

SPECIAL ARTICLE

ESMO recommendations on the standard methods to detect *NTRK* fusions in daily practice and clinical research

AGNOSTIC ONCOLOGY: Context independent

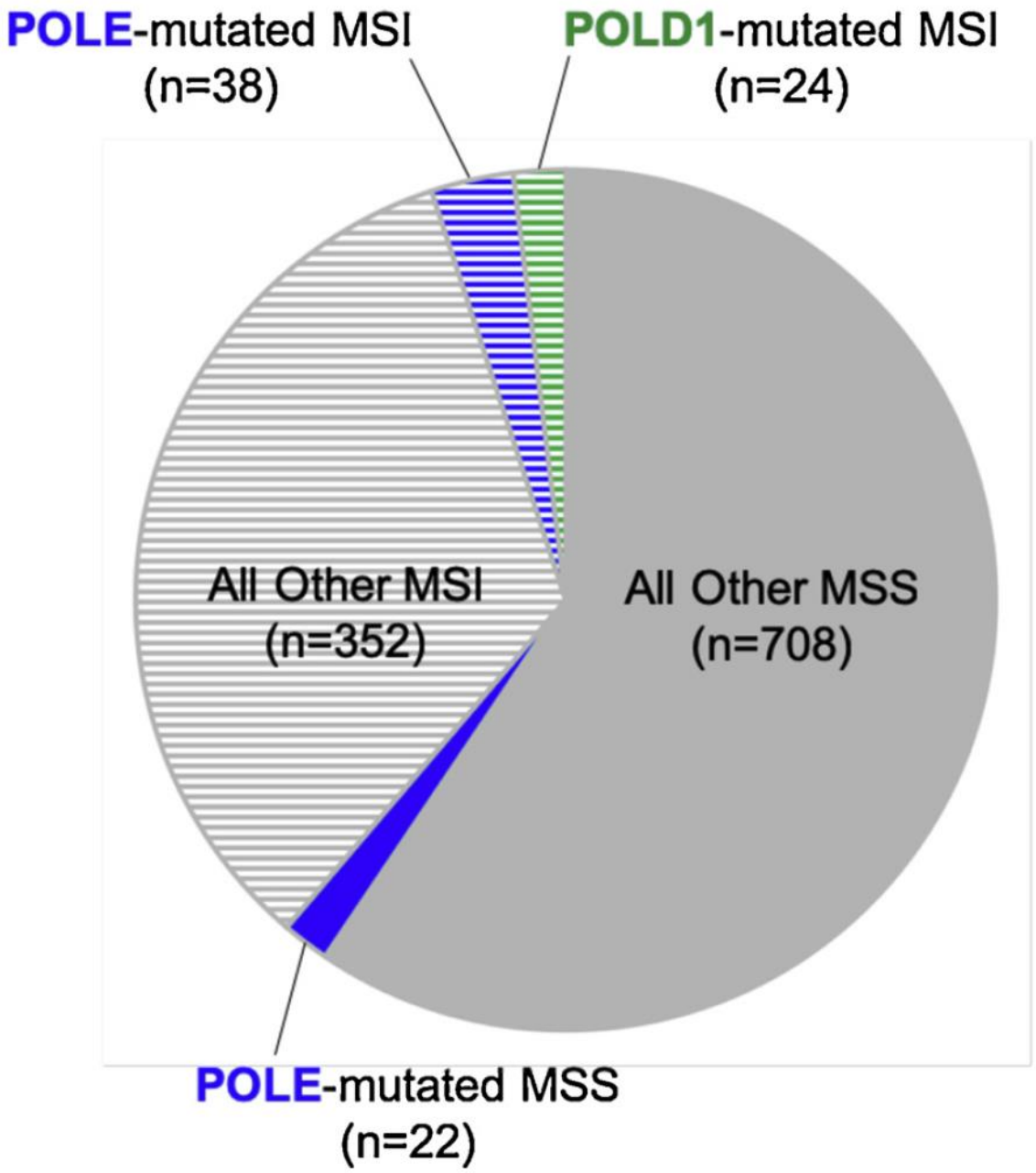
REVIEWS

A panoply of errors: polymerase proofreading domain mutations in cancer

Emily Rayner[1], Inge C. van Gool[2]*, Claire Palles[1], Stephen E. Kearsey[3], Tjalling Bosse[2], Ian Tomlinson[1] and David N. Church[1]*

NATURE REVIEWS | CANCER VOLUME 16 | FEBRUARY 2016

Universiteit Antwerpen UZA



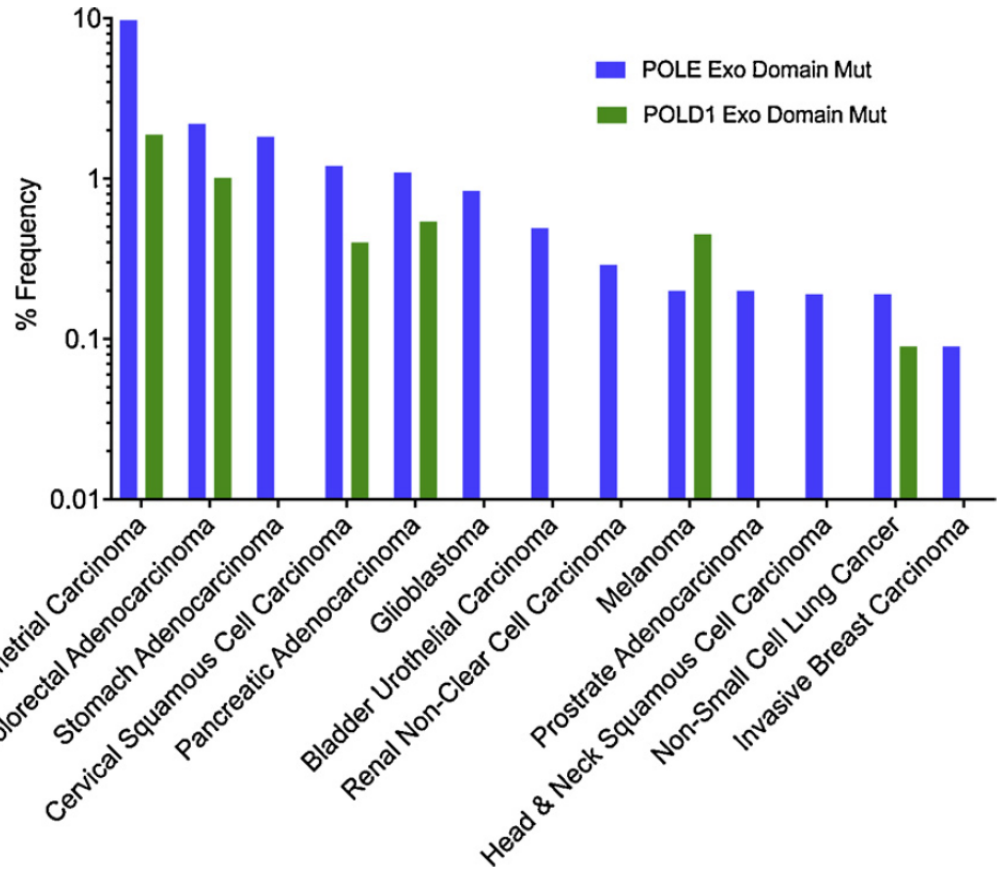


Fig. 1. POLE and POLD1 exonuclease domain mutation frequencies in select cancer types. Frequency data was collected from TCGA PanCancer Atlas studies and included 10,953 patients (10,967 samples) as of November 2018 [50,51]. POLE and POLD1 mutations were scored positive for those with hypermutant tumors (reported tumor mutation burden $\geq$10 mutations/Mb). Hypermutant frequency was determined as a percentage of all TCGA tumors of that particular cancer.

High activity of Nivolumab in patients with pathogenic exonucleasic domain POLE mutated mismatch repair proficient advanced tumors

First results of the program AcSé Nivolumab POLE cohort

Benoît Rousseau, MD PhD

Solid Tumor Division, Luis Diaz' Lab, Memorial Sloan Kettering Cancer Center, New York, USA

I. Bieche, E. Pasmant, V. Simmet, N. Hamzaoui, J. Masliah-Planchon, D. Pouessel, A. Bruyas, P. Augereau, J-J. Grob, F. Rolland, E. Saada-Bouzid, R. Cohen, O. Bouche, N. Hoog-Labouret, F. Legrand, C. Simon, A. Lamrani-Ghaouti, S. Chevret, A. Marabelle

ESMO 2020

Universiteit Antwerpen

UZA

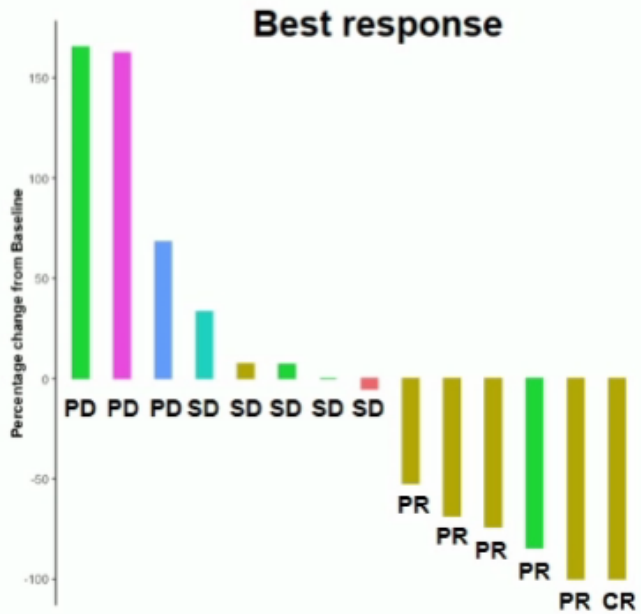
50 POLE mutated patients screened between 01/2018 and 07/2020 => 16 patients included

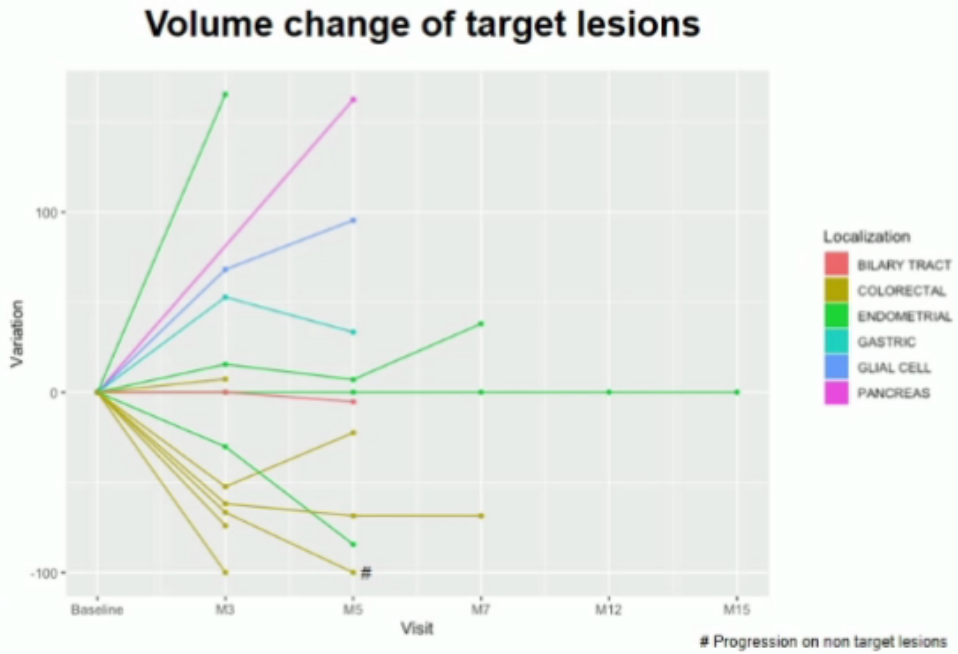
		Pathogenicity	
	All 16 patients	No/Unknown 8 patients	Yes 8 patients
Age, years	57 ± 16	63 ± 10	51 ±20
Male sex	11, 69%	7, 87.5%	4, 50%
PS (ECOG) at 1	12, 75%	6, 75%	6, 75%
Primitive tumor			
Colorectal*	7, 44%	4, 50%	3, 37.5%
Endometrial	4, 25%	0	4, 50%
Gastric	2, 12.5%	2, 25%	0
Glial cell	1, 6%	0	1, 12.5%
Biliary tract	1, 6%	1, 12.5%	0
Pancreas	1, 6%	1, 12.5%	0
No previous lines	2.6 ± 2.1	4 ± 2	1 ± 0.8

Results – Primary endpoint

RECIST 1.1	Response at 84 days % (n/N=16)	Best Response % (n/N=16)
CR	0% (0)	6% (1)
PR	38% (6)	32% (5)
ORR (PR+CR)	**38% (6)**	**38% (6)**
DCR (SD+PR+CR)	62% (10)	69% (11)
PD*	38% (6)	31% (5)

* Two patients progressed clinically and didnt have radiologic assessment and are not represented on the figures





Progression on non target lesions

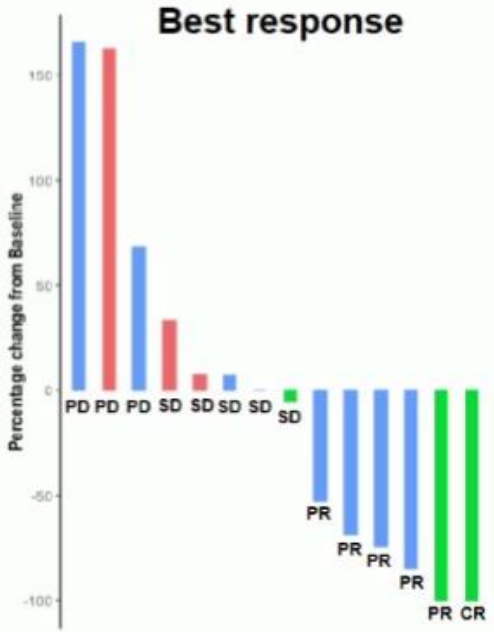
Universiteit Antwerpen

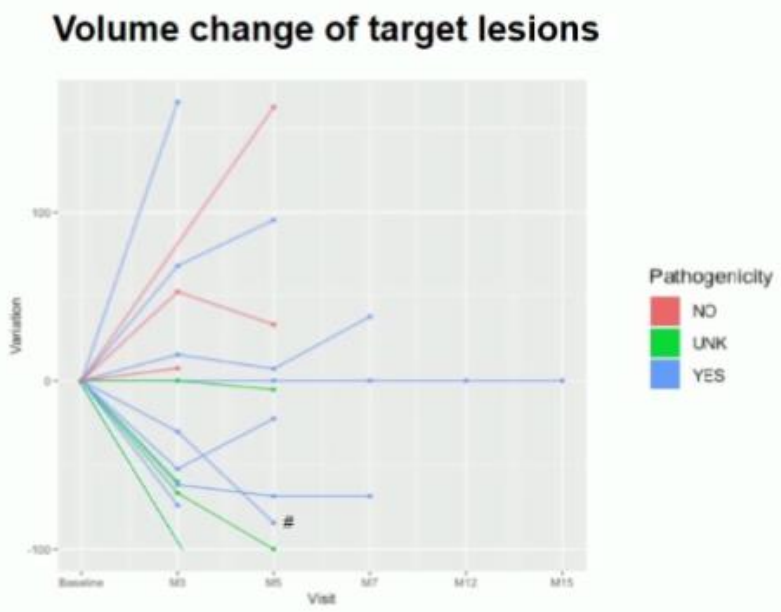
UZA

Results – Response according to pathogenicity

RECIST 1.1	Non pathogenic Response at 84 days % (n/N=5)	Unknow significance Response at 84 days % (n/N=3)	Pathogenic Response at 84 days % (n/N=8)
CR	0%	33% (1)	0%
PR	0%	33% (1)	50% (4)
ORR (PR+CR)	**0%**	**66% (2)**	**50% (4)**
DCR (SD+PR+CR)	0%	100% (3)	75% (6)
PD*	100% (5)*	0%	25 % (2)

* Two patients with non pathogenic mutations progressed clinically and didnt have radiologic assessment and are not represented on the figures





Progression on non target lesions

Universiteit Antwerpen

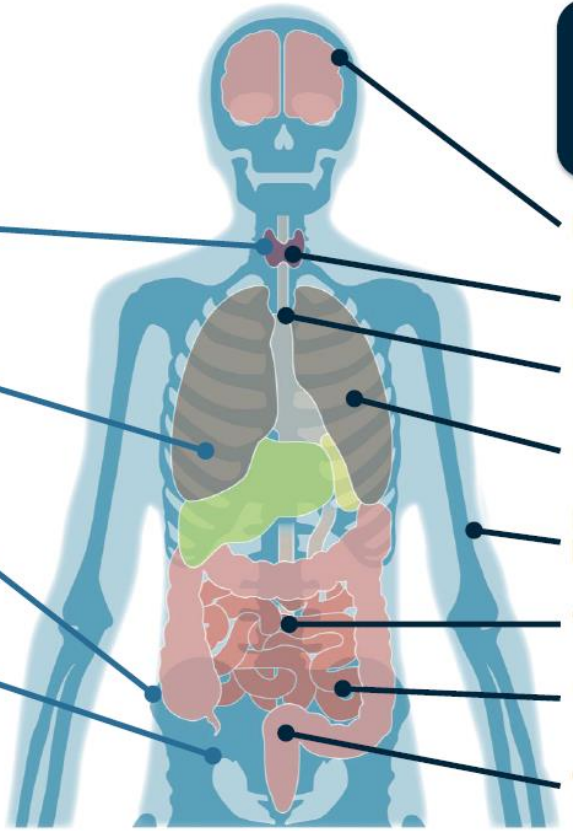
UZA

AGNOSTIC ONCOLOGY: Context independent

The prevalence of *RET* alterations varies by tumor type[1,2]

RET fusions
- NSCLC (≈1% to 2%)[1]
- PTC (≈10%)[1,2]

RET mutations
- MTC (Approx. 60%)[1]



PTC (≈10%)[1,2]
NSCLC (≈1% to 2%)[1]
CMML[3]
Ovarian epithelial carcinoma (1.9%)[2]

Meningioma (5.6%)[2]
MTC (≈60%)[1]
Esophageal adenocarcinoma (1.4%)[2]
Breast carcinoma (0.2%)[2]
Melanoma (0.7%) and basal cell carcinoma (12.5%)[2]
Gastric adenocarcinoma (0.7%)[2]
Ureter urothelial carcinoma (16.7%)
Colorectal adenocarcinoma (0.7%)[2]

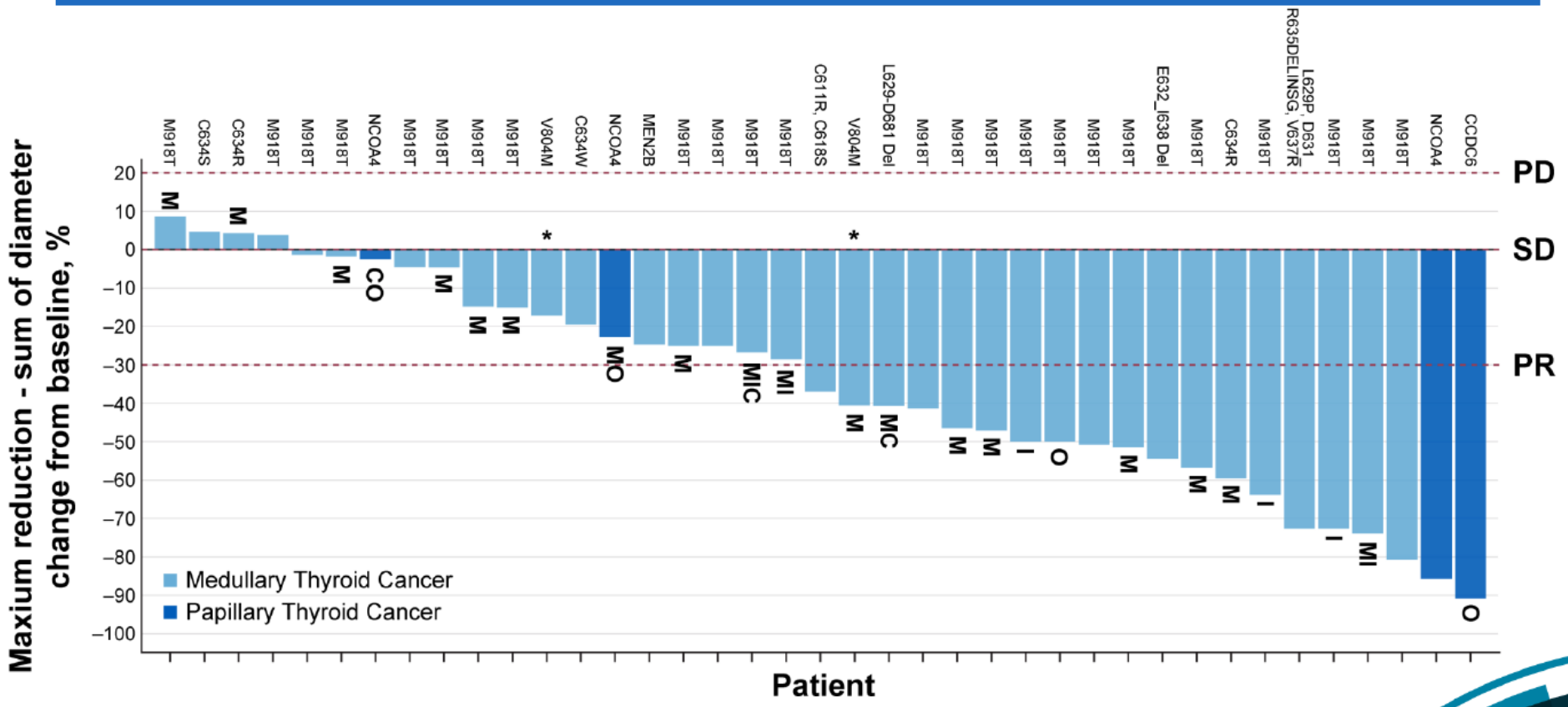
MTC, medullary thyroid cancer; NSCLC, non-small cell lung cancer; PTC, papillary thyroid cancer.

1. Drilon A et al. *Nat Rev Clin Oncol*. 2018;15(3):151-167. 2. Kato S et al. *Clin Cancer Res*. 2017;23(8):1988-1997.
3. Ballerini P et al. *Leukemia*. 2012;26(11):2384-2389.

Activity of Pralsetinib

BLU-667 has profound activity in *RET*-altered thyroid cancer

90% of evaluable *RET*-altered thyroid cancer patients had tumor shrinkage



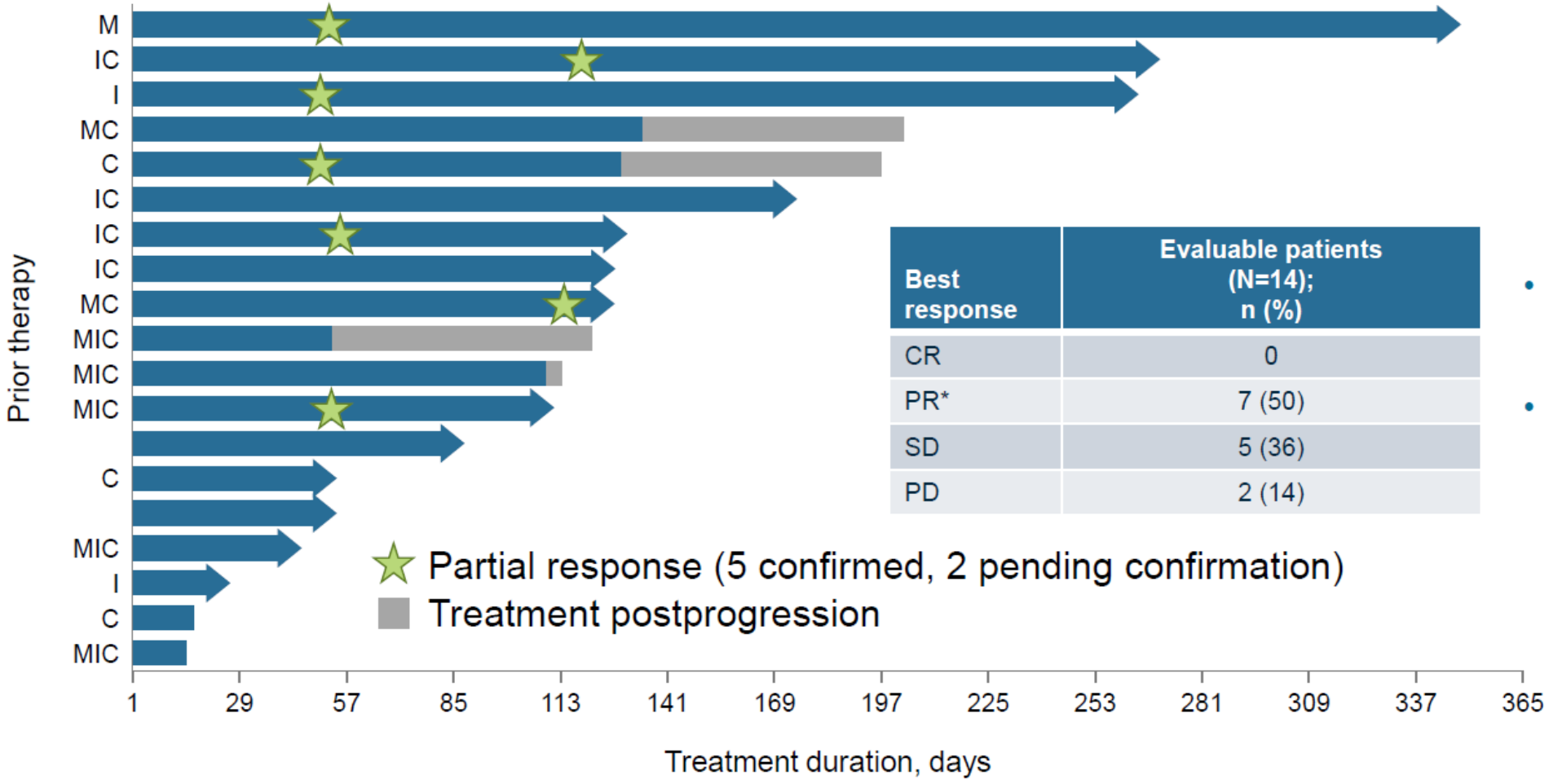
Responses seen regardless of RET alteration, including RET V804M,* or prior treatment

NCO4A, nuclear receptor coactivator 4; CCDC6, coiled-coil domain containing 6; M, prior MKI therapy; C, prior chemotherapy; O, other therapy; I, prior immunotherapy; PD, progressive disease; SD, stable disease; PR, partial response.

Patients Enrolled as of 9 May 2018, Follow-up as of 14 Sep 2018

Activity of Pralsetinib

BLU-667 has durable activity and high response rates in *RET*-altered NSCLC

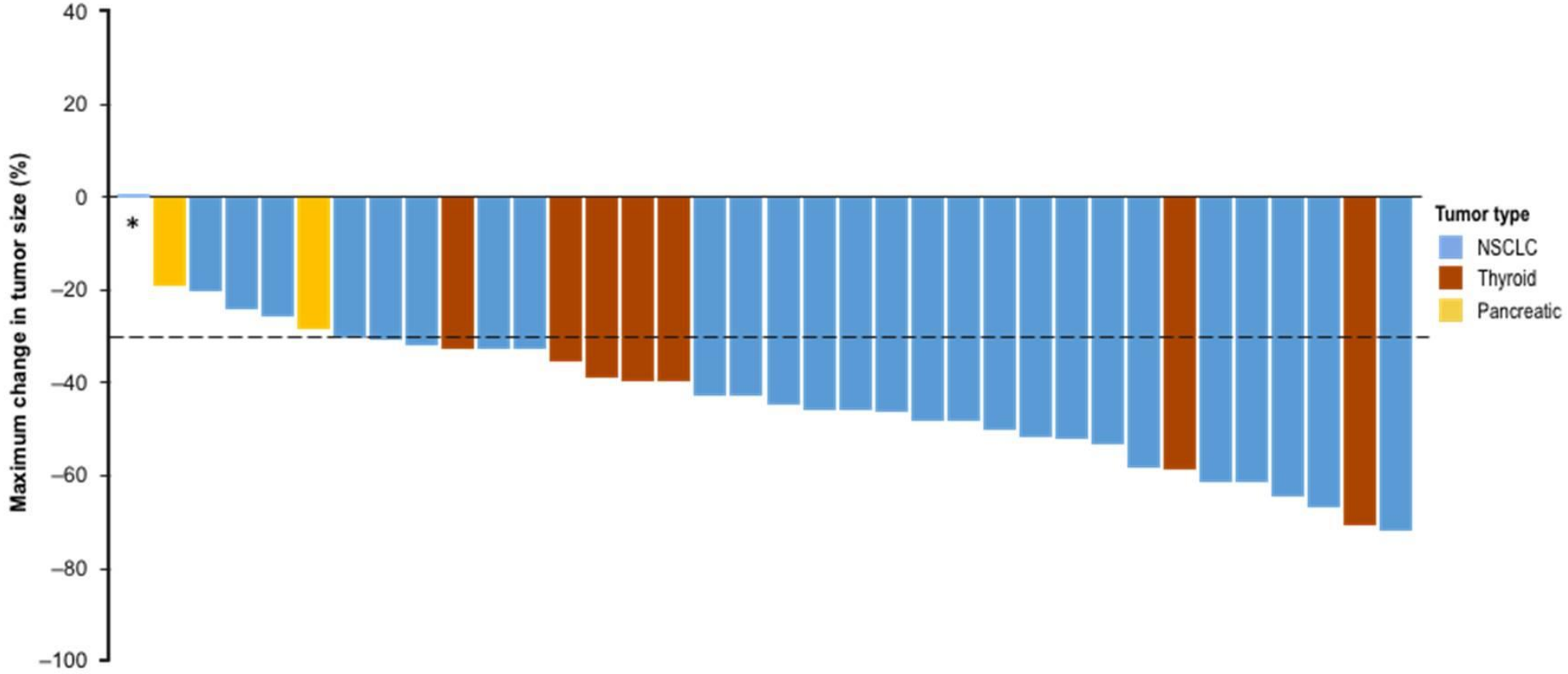


Best response	Evaluable patients (N=14); n (%)
CR	0
PR*	7 (50)
SD	5 (36)
PD	2 (14)

- **Treatment duration up to 11.4 months and ongoing**
- **13/19 (68%) remain on treatment**

Activity of Selpercatinib

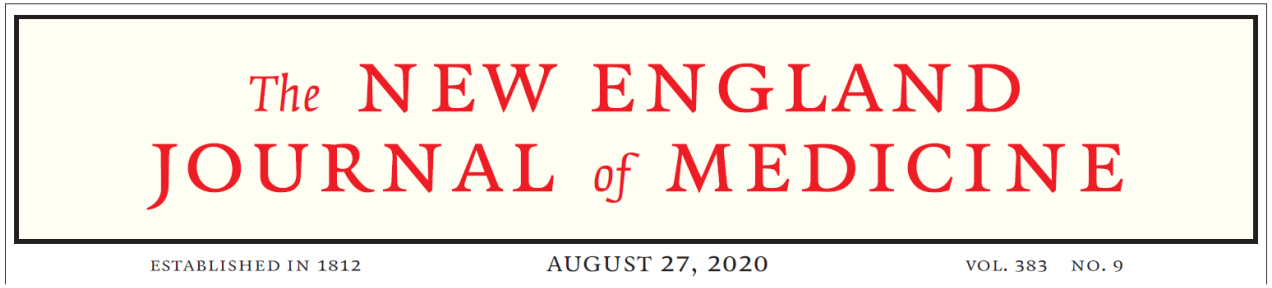
Histology-agnostic activity of LOXO-292 in RET fusion^{+} cancers



AGNOSTIC ONCOLOGY: Context independent RET Alterations

- **RET fusions**
  - Oncogenic drivers in 1-2% of NSCLC
  - Associated with high risk of brain M+
  - Usually mutually exclusive with other drivers

- Results part of the **LIBRETTO-001 trial**, a phase ½ trial of selpercatinib in solid tumors harbouring activating RET alterations (ie. Fusions or mutations)



- **Results**
  - 105 pts with RET fusion pos advanced NSCLC
  - Most heavily pretreated but also untreated were included
  - PRETREATED GROUP: 64% ORR, median duration of response 17.5 months !!!!
  - UNTREATED GROUP: 85% ORR.

Universiteit Antwerpen UZA

AGNOSTIC ONCOLOGY: Context independent RET Alterations

- **RET mutations**
  - Occur in 70% of medullary cancers
  - Associated with more agressive disease
  - CAVE: RET fusions rare in thyroid cancers

- Results part of the **LIBRETTO-001 trial**, a phase ½ trial of selpercatinib in solid tumors harbouring activating RET alterations (ie. Fusions or mutations)

- **Results**
  - 162 pts with RET mutant thyroid cancer
  - PRETREATED RET MUTANT: 69% RR
  - UNTREATED RET MUTANT: 73% RR
  - RET FUSION (small group): 79% RR

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Efficacy of Selpercatinib in *RET*-Altered Thyroid Cancers

LONG RESPONSES AND BEAUTIFUL WATERFALL PLOTS !!!!!!!!

AGNOSTIC ONCOLOGY: NRG fusions ??

Table 2 Case reports and retrospective case series of *NRG1* gene fusions positive NSCLC treated with HER2/HER3 inhibitors

Age (yrs)	Sex	Smoking habits	Histology	NRG1 Fusion	Treatment	Line(s) of therapy	Response	PFS (mos)	Treatment duration (mos)	Ref.
Case reports with HER2/HER3 inhibitors										
43	F	Never smoker	Adenocarcinoma	SDC4-NRG1	Afatinib	3rd	PR	12	12	(40)
62	F	Never smoker	IMA	CD74-NRG1	Afatinib	2nd	PR	6	6	(41)
42	M	Never smoker	Adenocarcinoma	SLC3A2-NRG1	Afatinib	2nd	PR	12	18	(35)
62	M	Never smoker	Mucinous adenocarcinoma	CD74-NRG1	Afatinib	1st	PR	10	>10	(35)
70	F	Never smoker	Non-mucinous adenocarcinoma	NR	Afatinib	15th	PR	24	24	(42)
66	F	Never smoker	Non-mucinous adenocarcinoma	CD74-NRG1	Afatinib	5th	PR	19+	19+	(42)
68	M	Former smoker	Non-mucinous adenocarcinoma	SDC4-NRG1	Afatinib	3rd	SD	4	4	(42)
43	F	Never Smoker	IMA	CD74-NRG1	Afatinib	4th	PR	18+	18+	(42)
81	M	Former cigar use	IMA	CD74-NRG1	Afatinib	1st	SD	3	3	(21)
52	F	Current smoker	IMA	SDC4-NRG1	Afatinib	2nd	PD	1	1	(21)
51	M	Former smoker	IMA	CD74-NRG1	Afatinib	1st	PD	2	2	(21)
86	M	N.R.	IMA	CD74-NRG1	GSK2849330	5th	PR	19	N.R.	(21)
55	F	Never Smoker	IMA	SLC3A2-NRG1	Lumretuzumab + erlotinib	6th	SD	3.8	3.8	(43)
42	F	Never Smoker	IMA	SLC3A2-NRG1	Lumretuzumab + erlotinib	6th	SD	3.8	3.8	(43)
Retrospective studies with HER2/HER3 inhibitors in *NRG1* gene fusions positive NSCLC										
12 (number of pts)					Afatinib*	1–15	ORR 33%, DCR 50%	PFS 2.0 months, OS not reached		(38)

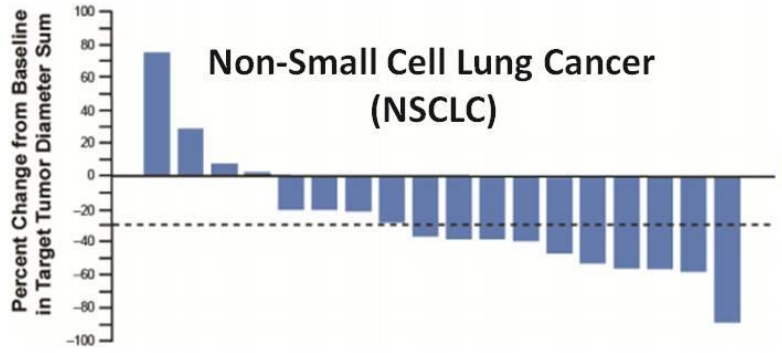
*, one patient was treated with afatinib in combination with docetaxel-ramucirumab. *NRG1, neuregulin-1*; NR, not reported; mos, months; yrs, years; ORR, overall response rate; DCR, disease control rate; PFS, progression free survival; OS, overall survival; pts, patients; IMA, invasive mucinous adenocarcinoma; NSCLC, non-small cell lung cancer; PR, partial response; SD, stable disease; PD, progressive disease.

Universiteit Antwerpen

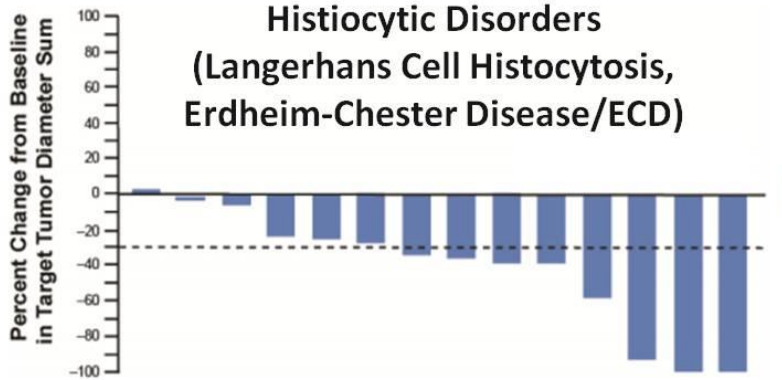
UZA

AGNOSTIC ONCOLOGY: Context dependent

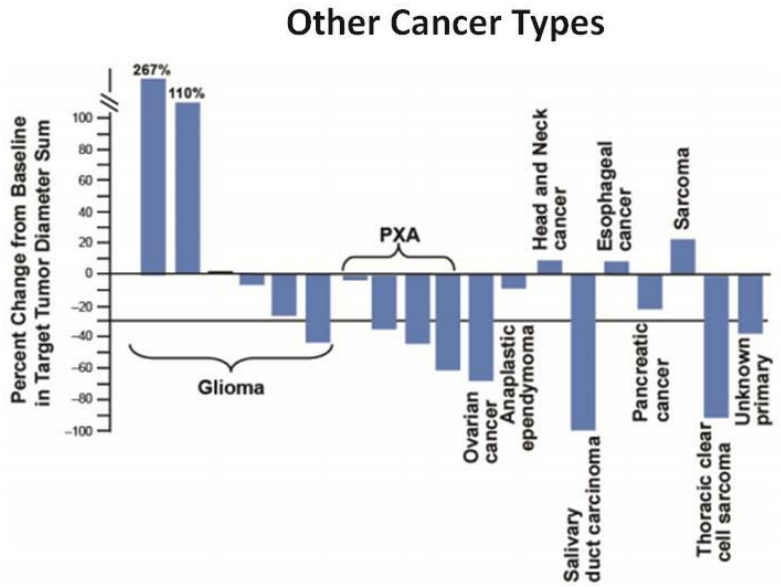
Vemurafenib basket addresses the long tail of BRAF^{V600E} alterations



NCCN Guidelines for NSCLC



FDA Approval for ECD

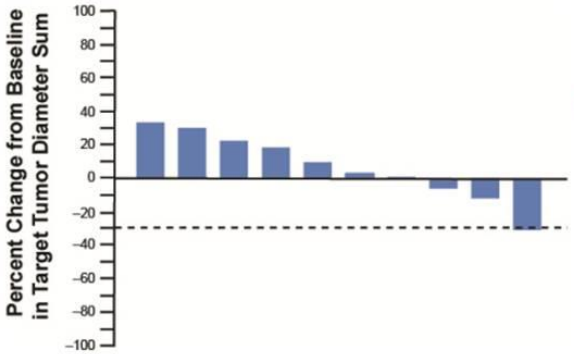


Hyman DM et al. N Engl J Med 2015;373:726-736.

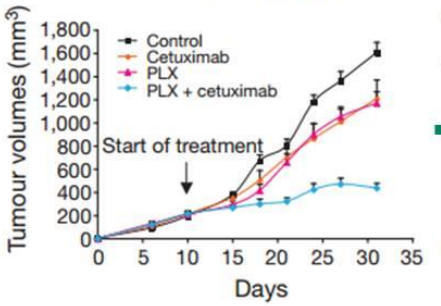
AGNOSTIC ONCOLOGY: Context dependent

Basket trials are adaptable: the platform trial concept

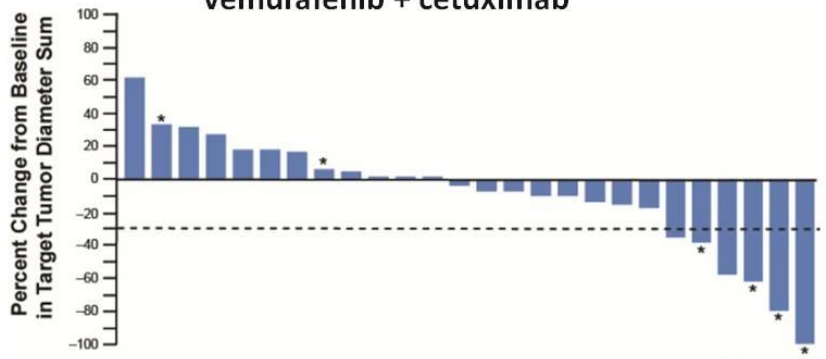
Colorectal Cancer
vemurafenib monotherapy



WiDr xenografts



Colorectal Cancer
vemurafenib + cetuximab



Former therapeutic strategy leaves the study design

Novel therapeutic strategy enters the study design

Prahallad A et al, Nature. 2012 Jan 26;483(7387):100-3.
Hyman DM et al. N Engl J Med 2015;373:726-736.

REVIEWS

RAS-targeted therapies: is the undruggable drugged?

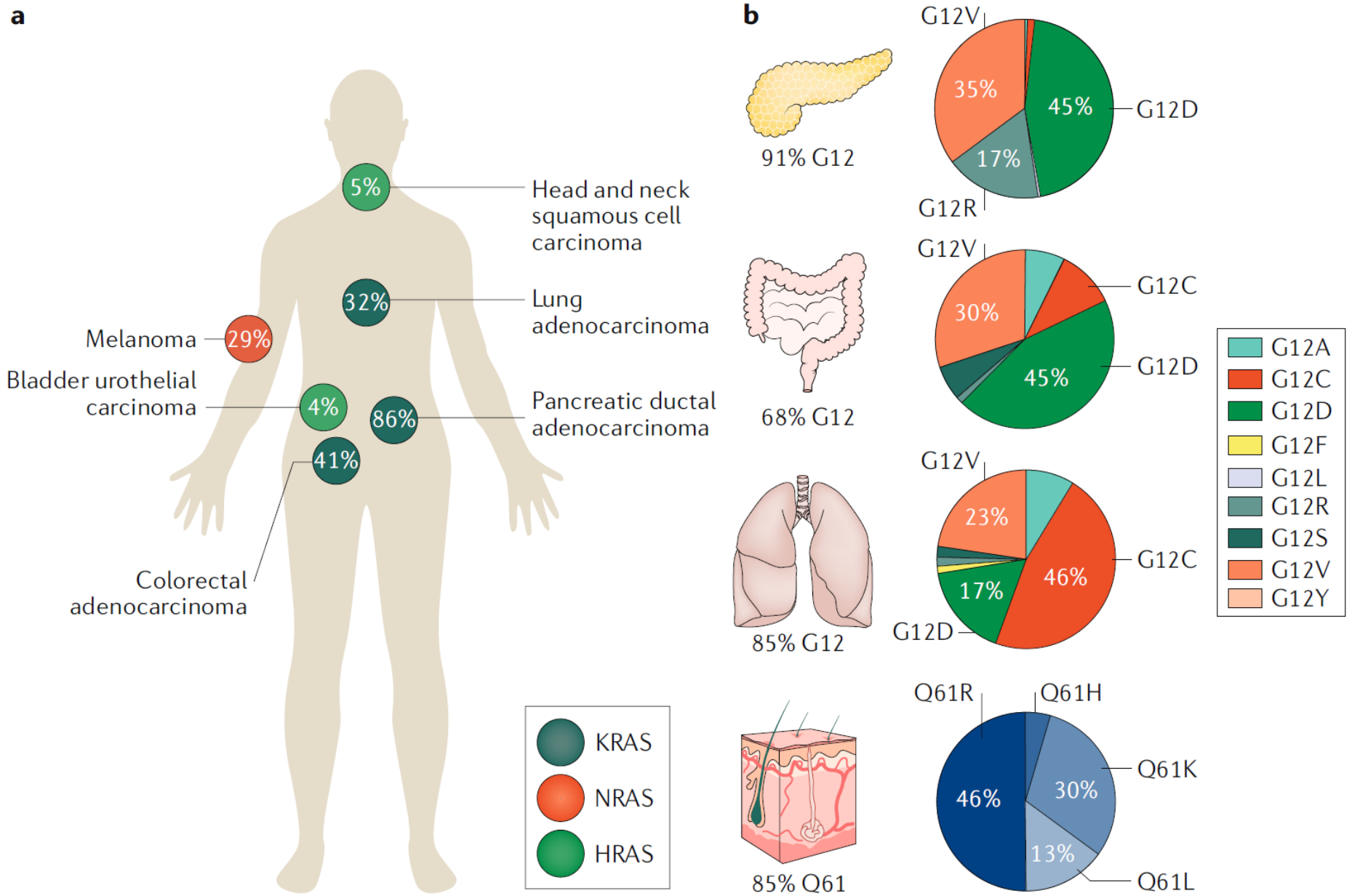
Amanda R. Moore[1], *Scott C. Rosenberg*[1], *Frank McCormick*[2] *and Shiva Malek*[1] ✉

NATURE REVIEWS | DRUG DISCOVERY

https://doi.org/10.1038/s41573-020-0068-6

Universiteit Antwerpen

UZA


a
5%
Head and neck squamous cell carcinoma
32%
Lung adenocarcinoma
Melanoma
29%
Bladder urothelial carcinoma
4%
86%
Pancreatic ductal adenocarcinoma
41%
Colorectal adenocarcinoma
KRAS
NRAS
HRAS
b
91% G12
G12V
35%
45%
G12D
17%
G12R
68% G12
G12V
30%
G12C
45%
G12D
85% G12
G12V
23%
G12C
46%
17%
G12D
G12A
G12C
G12D
G12F
G12L
G12R
G12S
G12V
G12Y
85% Q61
Q61R
Q61H
46%
30%
Q61K
13%
Q61L

24 Sept 2020

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

KRAS^{G12C} Inhibition with Sotorasib in Advanced Solid Tumors

D.S. Hong, M.G. Fakih, J.H. Strickler, J. Desai, G.A. Durm, G.I. Shapiro, G.S. Falchook, T.J. Price, A. Sacher, C.S. Denlinger, Y.-J. Bang, G.K. Dy, J.C. Krauss, Y. Kuboki, J.C. Kuo, A.L. Coveler, K. Park, T.W. Kim, F. Barlesi, P.N. Munster, S.S. Ramalingam, T.F. Burns, F. Meric-Bernstam, H. Henary, J. Ngang, G. Ngarmchamnanrith, J. Kim, B.E. Houk, J. Canon, J.R. Lipford, G. Friberg, P. Lito, R. Govindan, and B.T. Li

We conducted a phase 1 trial of sotorasib in patients with advanced solid tumors harboring the *KRAS* p.G12C mutation. Patients received sotorasib orally once daily. The primary end point was safety. Key secondary end points were pharmacokinetics and objective response, as assessed according to Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1.

Universiteit Antwerpen

UZA

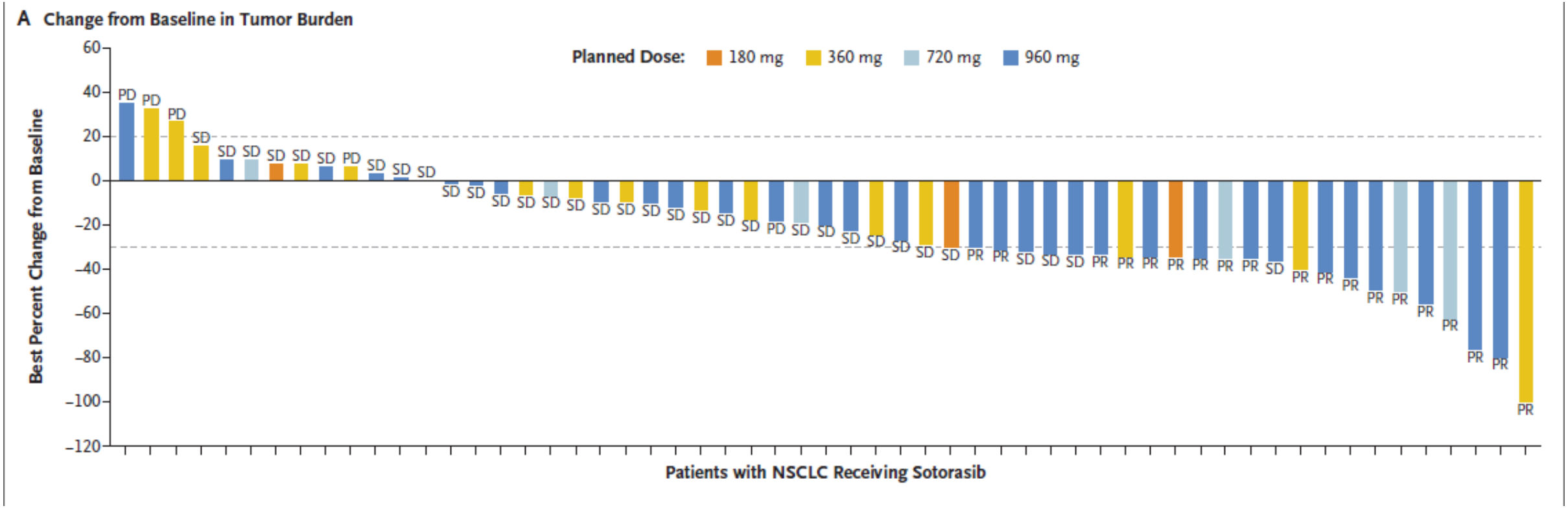
AGNOSTIC ONCOLOGY: Context dependent KRAS G12C

Table 3. Efficacy of Sotorasib in All Tumor Types.

	NSCLC (N=59)	Colorectal Cancer (N=42)	Other (N=28)
Best overall response — no. (%)			
Confirmed complete response	0	0	0
Confirmed partial response	19 (32.2)	3 (7.1)	4 (14.3)
Stable disease	33 (55.9)	28 (66.7)	17 (60.7)
Progressive disease	5 (8.5)	10 (23.8)	4 (14.3)
Could not be evaluated	1 (1.7)	0	1 (3.6)
No assessment*	1 (1.7)	1 (2.4)	2 (7.1)
Objective response — % (95% CI)†	32.2 (20.62–45.64)	7.1 (1.50–19.48)	14.3 (4.03–32.67)
Disease control — % (95% CI)‡	88.1 (77.07–95.09)	73.8 (57.96–86.14)	75.0 (55.13–89.31)

Universiteit Antwerpen UZA

AGNOSTIC ONCOLOGY: Context dependent KRAS G12C



Universiteit Antwerpen

UZA

TMB: biomarker for immune therapy?

- Promising biomarker independent of MSI or PD-L1 status
- Typically reported as:
  - total number of mutations per tumor (when assessed by WES)
  - Normalized to mutations per megabase by gene panel assays

- No clear cutoff to define high versus low (consensus of 10 Mut/mb)
- Prospective trials needed in PDL1 positive or negative tumors.

CHALLENGES: TUMOR AGNOSTIC APPROACH

- Value of conducting multipanel NGS
  - Cost and reimbursement barriers
  - Multiple approved panels
  - ….
- Model is not going to universally work: no « one size fits all »
- Often single arm data
- Importance of real world evidence
- Soon more drugs than patients, so which one to use???
- Selective versus broad inhibitors?

THANKS !!

BSMO

Universiteit Antwerpen

UZA