Precision medicine in cancer: future or illusion?

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Or already present ?

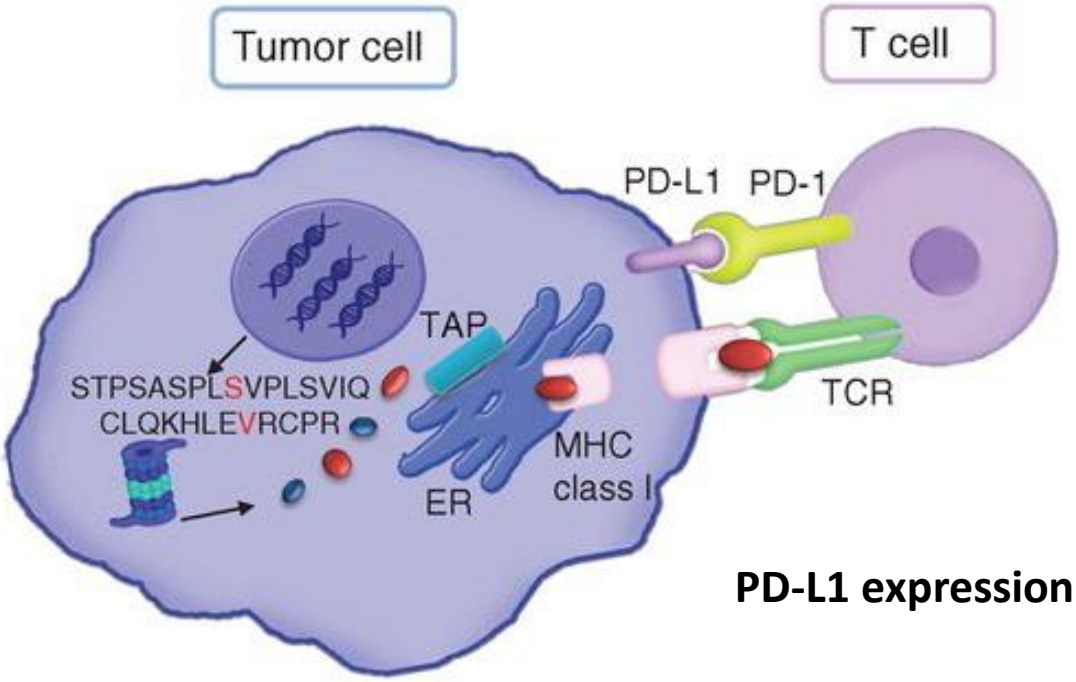
Precision medicine in oncology is already happening, the only question is: *what is affordable?*

1. Patient characteristics
2. Cancer type
3. Immunohistochemical markers (ER)
4. Genotyping (RNA/DNA)
5. Immune biomarkers: TIL/PD-L1 expression for immune checkpoint inhibitors

Current cancer treatments

- Local: surgery and radiotherapy
- **Systemic treatments**
  1. Chemo
  2. Hormonal
  3. **Targeted**
  4. **Immunotherapy**
     1. **Immune checkpoint inhibitor**
     2. **Personalized cell therapies**

Prediction response to immune checkpoint inhibitors

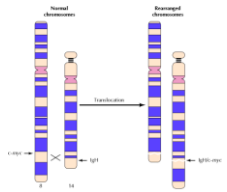


Lymphocytic infiltrates

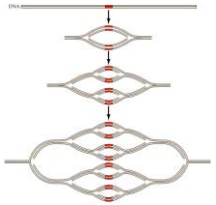
PD-L1 expression

Mutation load and neo-antigens

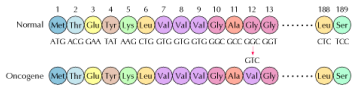
Therapeutic targets: oncogenes that drive the cancer



Translocation



Gene amplification

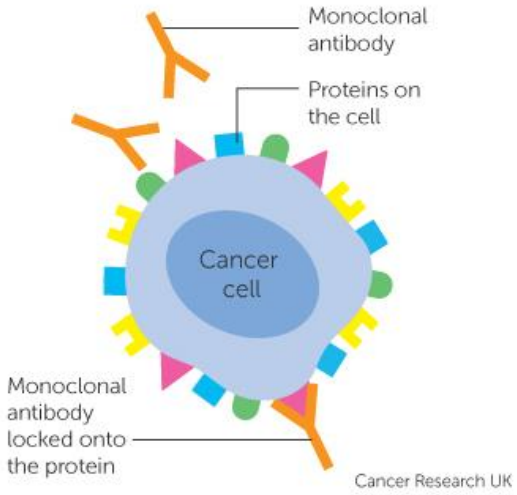


Mutation

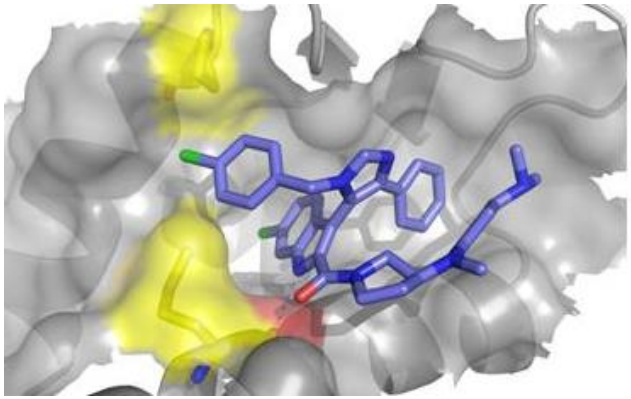
1. Targeted gene sequencing
2. Gene panels
3. Whole exome or genome

Treatments

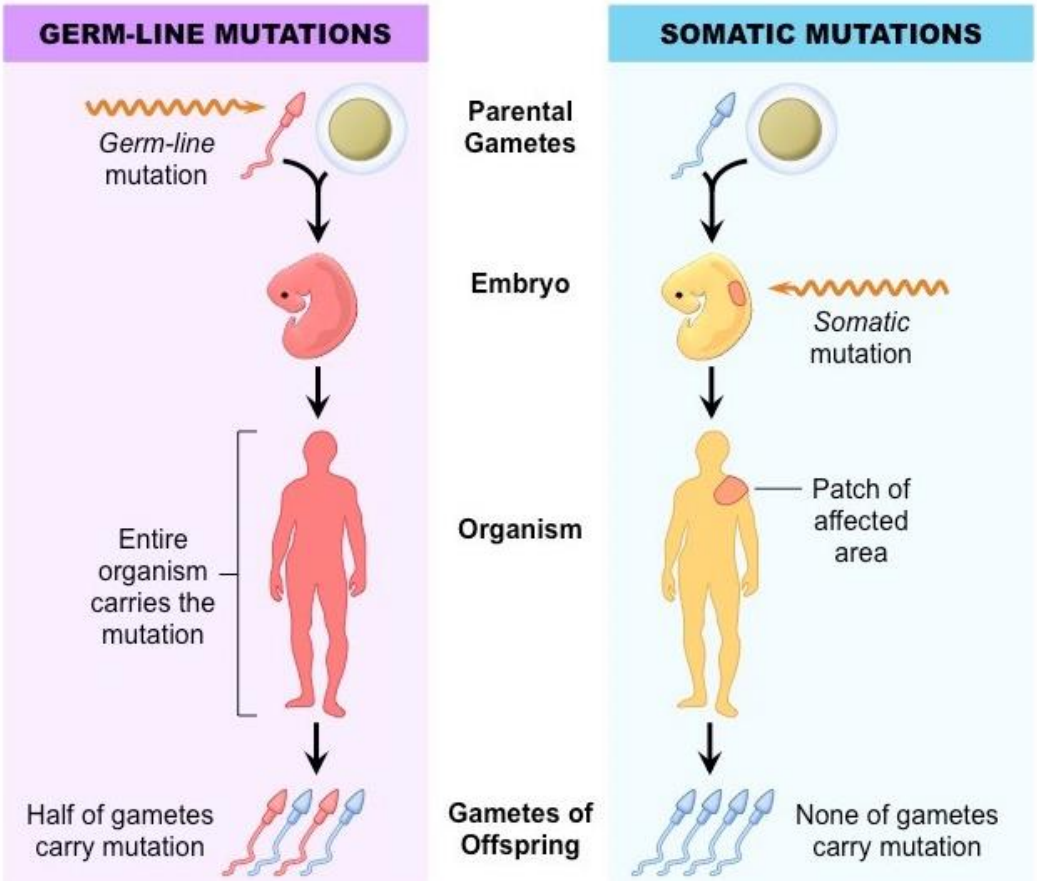
- Monoclonal antibodies
  - Surface oncogenic receptors



- Small molecules
  - Intracellular targets

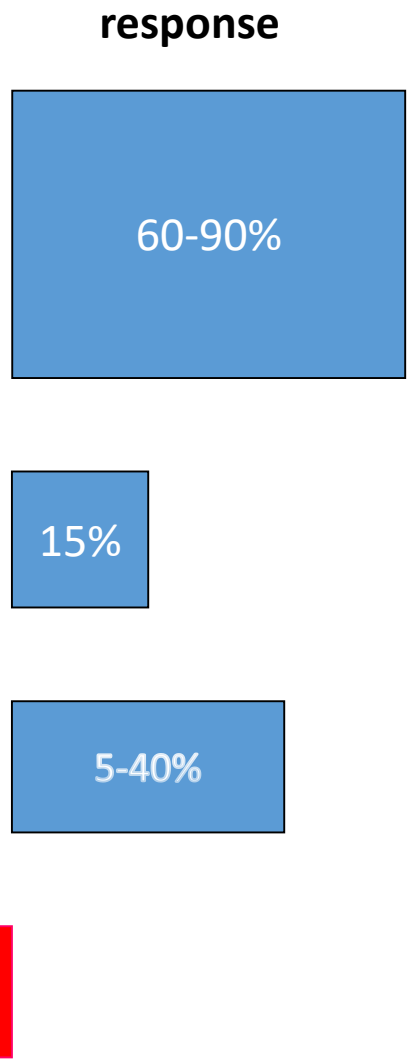


Both somatic mutations in cancer genes and germline mutations in cancer predisposition genes can be therapeutic targets

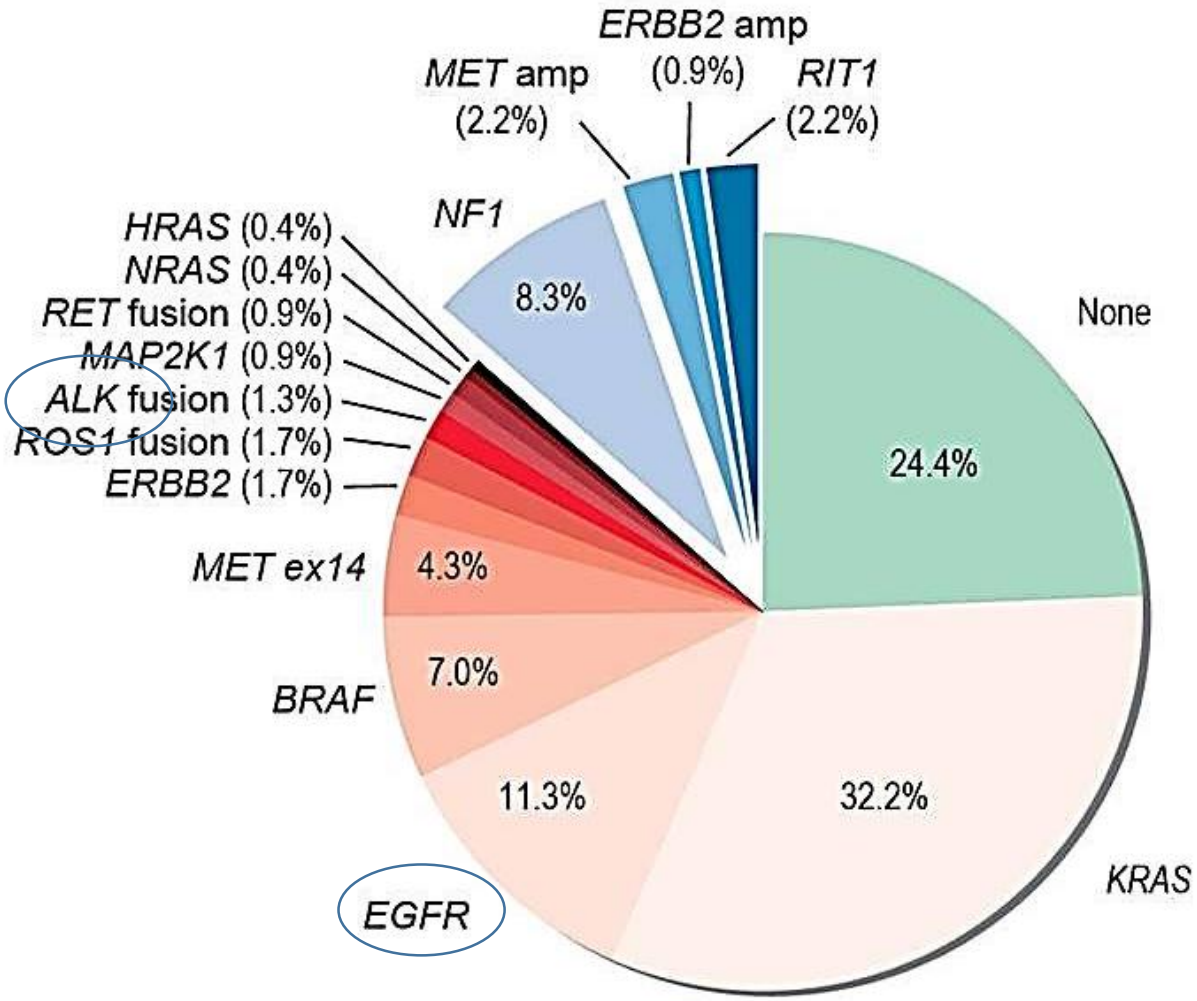


Predictive power of genotyping for targeted treatments: varying magnitude

- **Mutant protein**
  - Mutant c-kit in GIST
  - bcr-abl in CML
  - Mutant EGFR in lung cancer
  - ALK-fusion in lung cancer
  - …..
- **Overexpression < gene amplification**
  - HER-2 in breast cancer
- **Driven expression**
  - VEGF in RCC, brain tumors and OVCA
- **Physiological expression of wild-type protein**
  - EGFR in NSCLC



Important genomic stratification of lung cancer

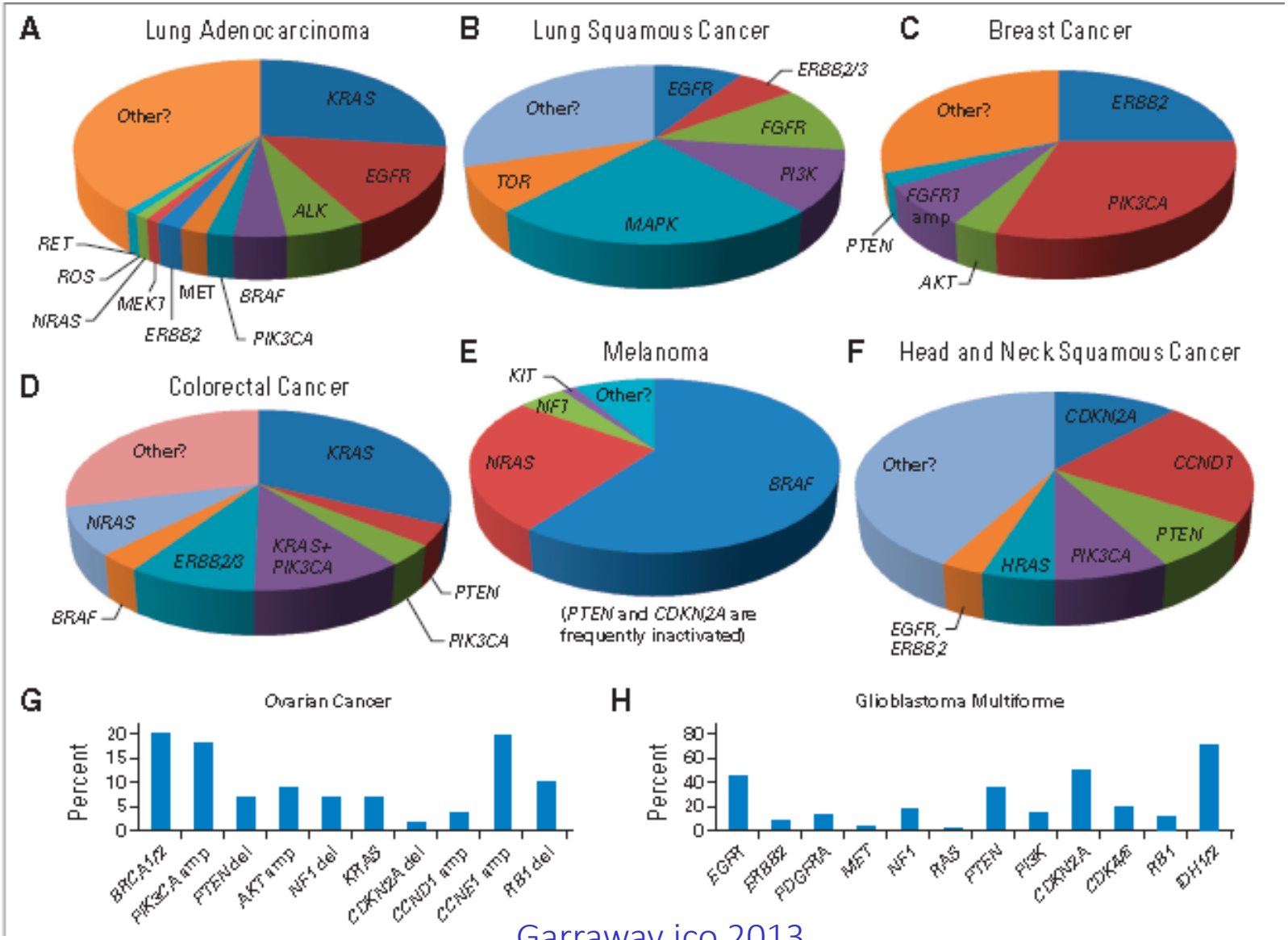


Memorial Sloan Kettering Cancer Center

TCGA Research Network

All actionable (routine or investigational)

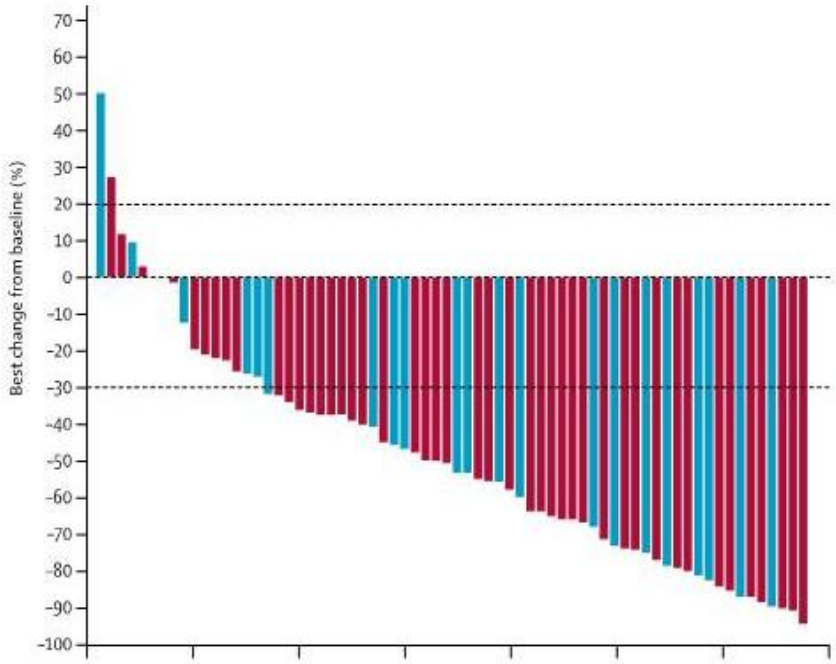
But also in many other cancers



Garraway jco 2013

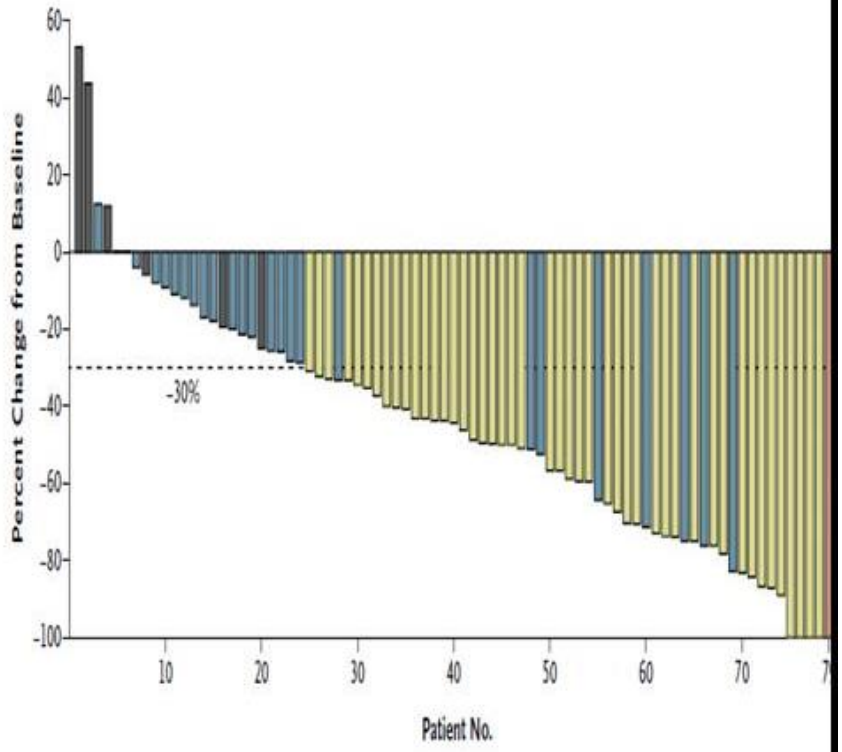
Impressive therapeutic results

Erlotinib in EGFR mutant lung cancers



Rosell et al., *Lancet Oncol* 2012

Crizotinib in ALK mutant lung cancers

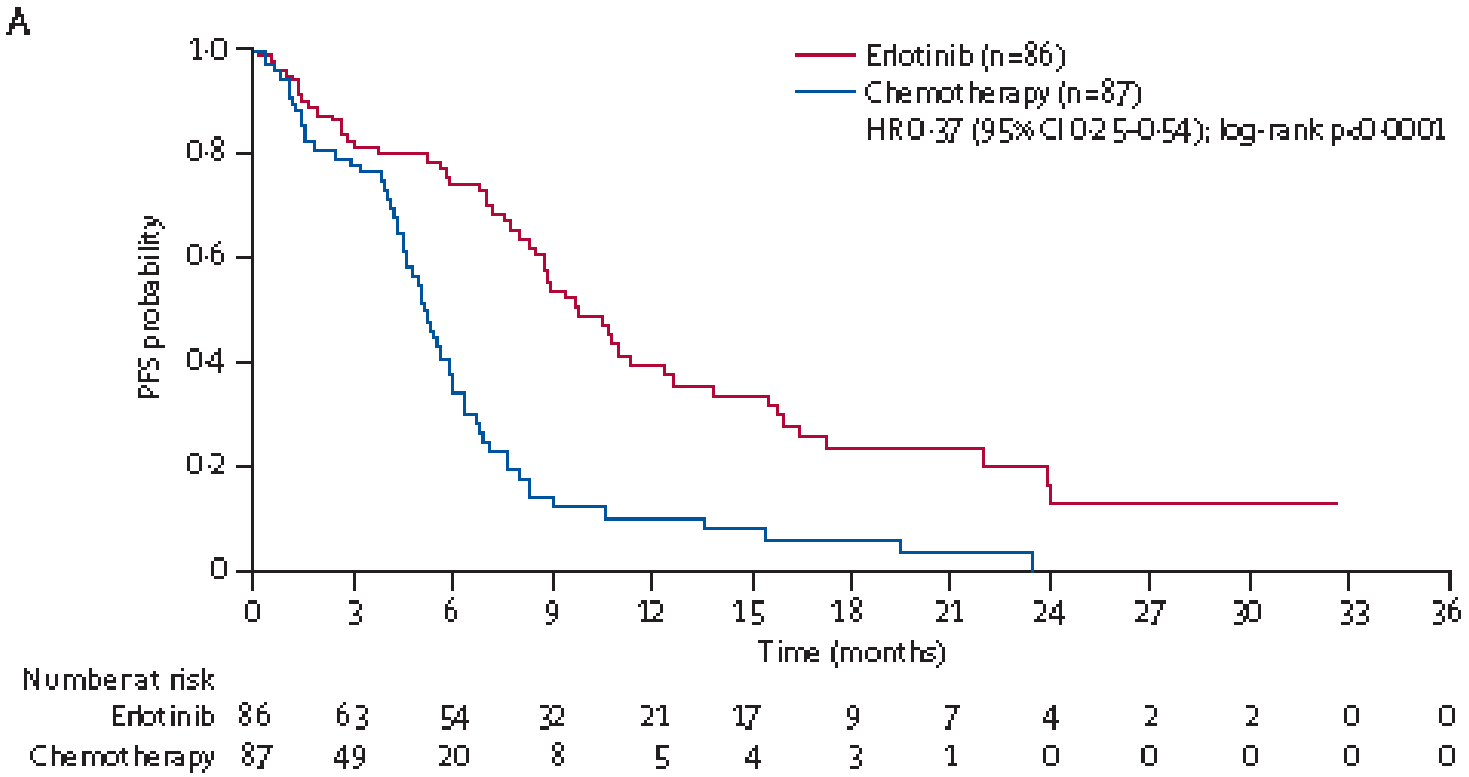


Kwak et al., *N Engl J Med* 2010

Memorial Sloan Kettering Cancer Center

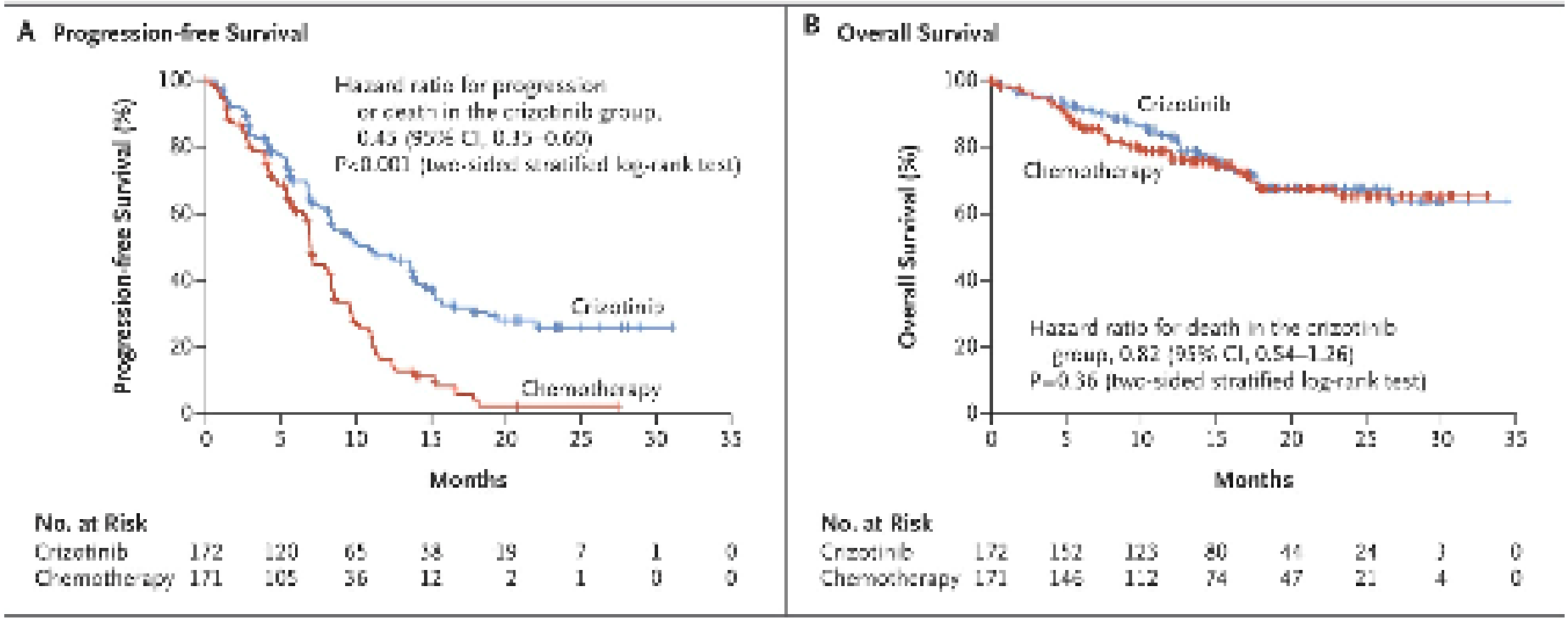
Presented By Charles Rudin at 2014 ASCO Annual Meeting

Erlotinib in EGFR mutated lung cancer



***Rosell et al, Lancet Oncol* 2012; 13: 239–46**

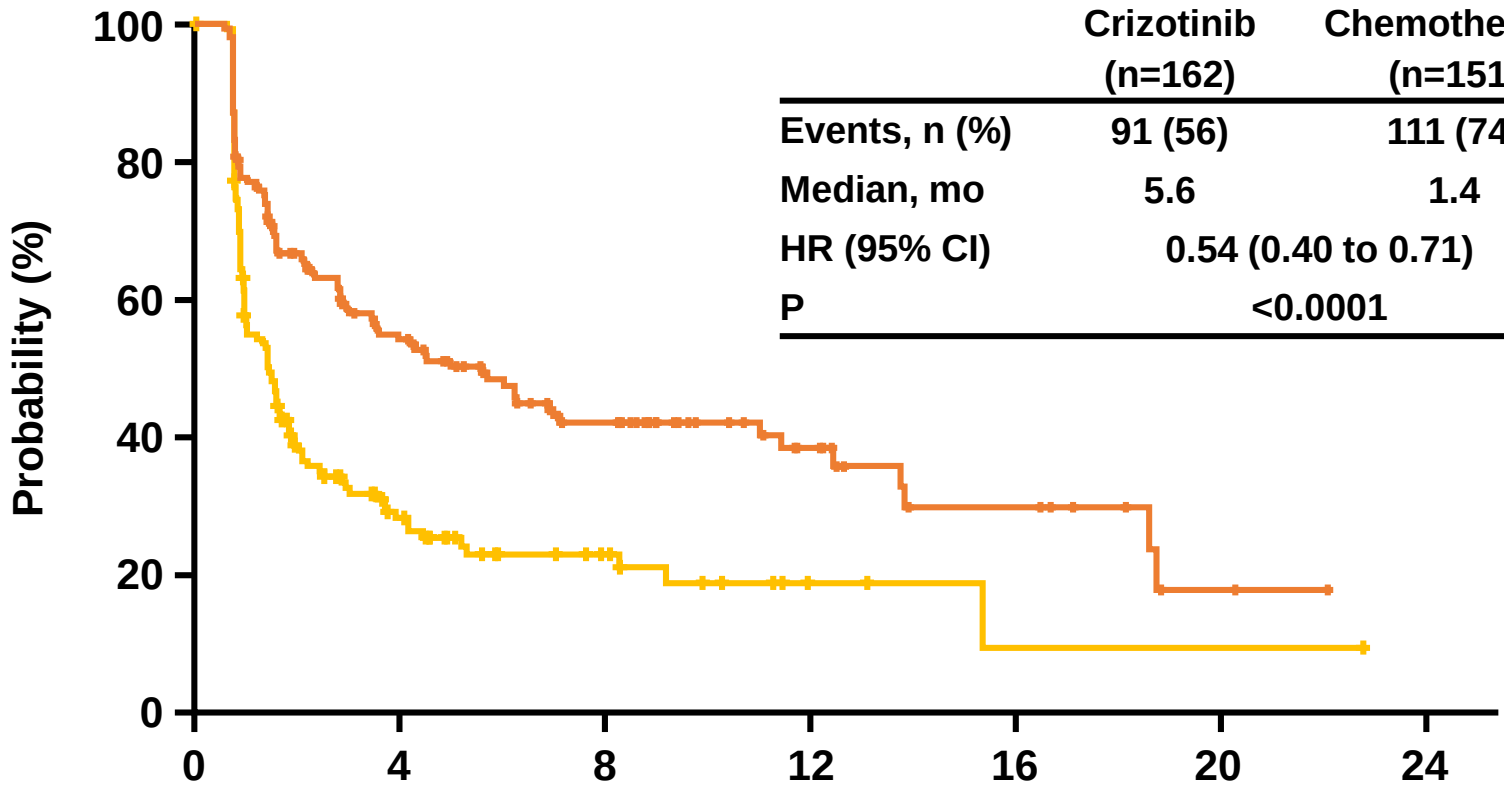
Alk targeting: crizotinib



Shaw et al N Eng J Med; Solomon et al N Eng J Med

Improved quality of life

Time to Deterioration in Lung Cancer Symptoms[a]



	Crizotinib (n=162)	Chemotherapy (n=151)
Events, n (%)	91 (56)	111 (74)
Median, mo	5.6	1.4
HR (95% CI)	0.54 (0.40 to 0.71)	
P	<0.0001	

No. at risk							
Crizotinib	162	71	40	17	9	2	0
Chemotherapy	151	30	13	3	1	1	0

[a]Composite of chest pain, cough, and dyspnea

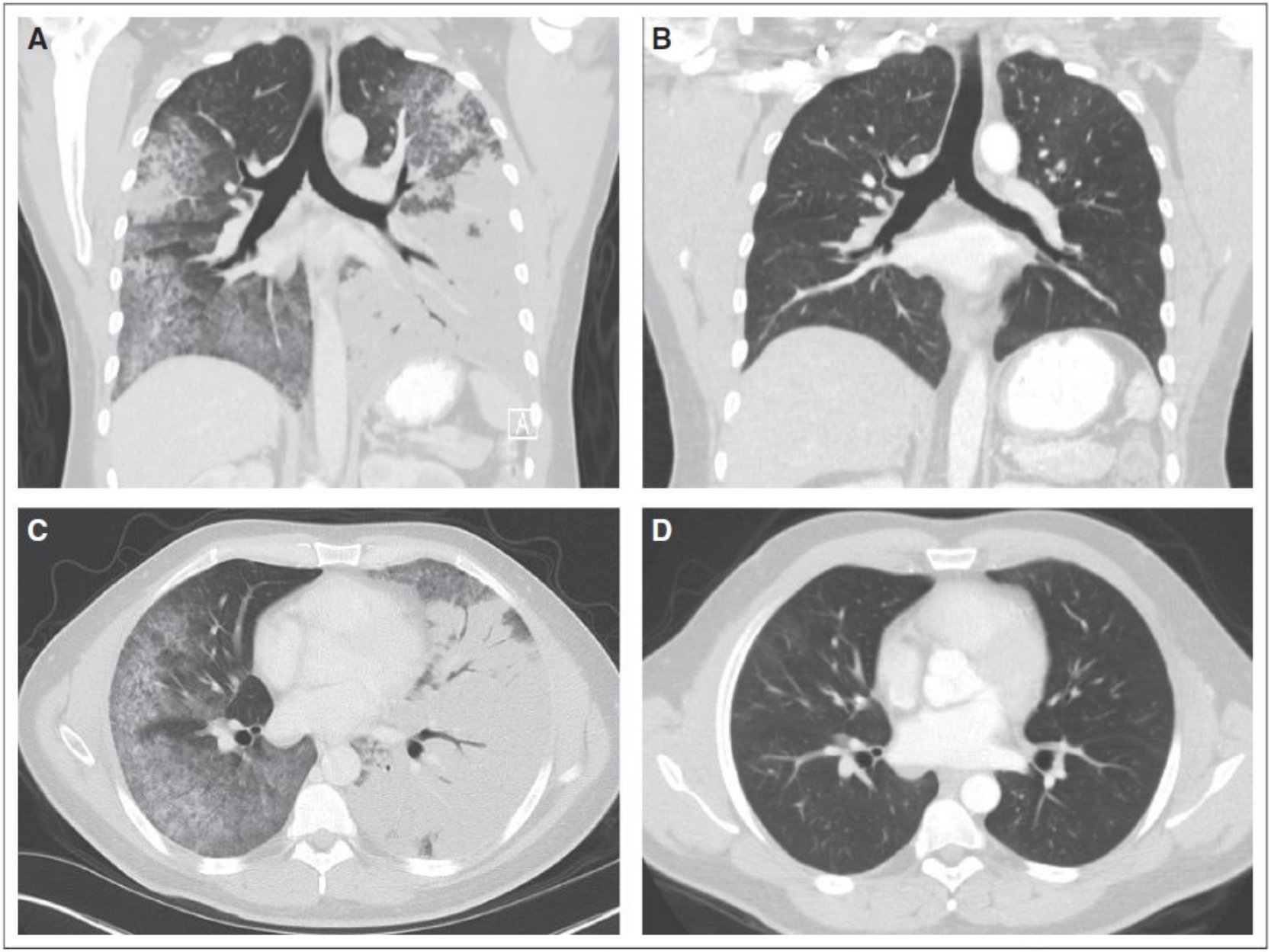
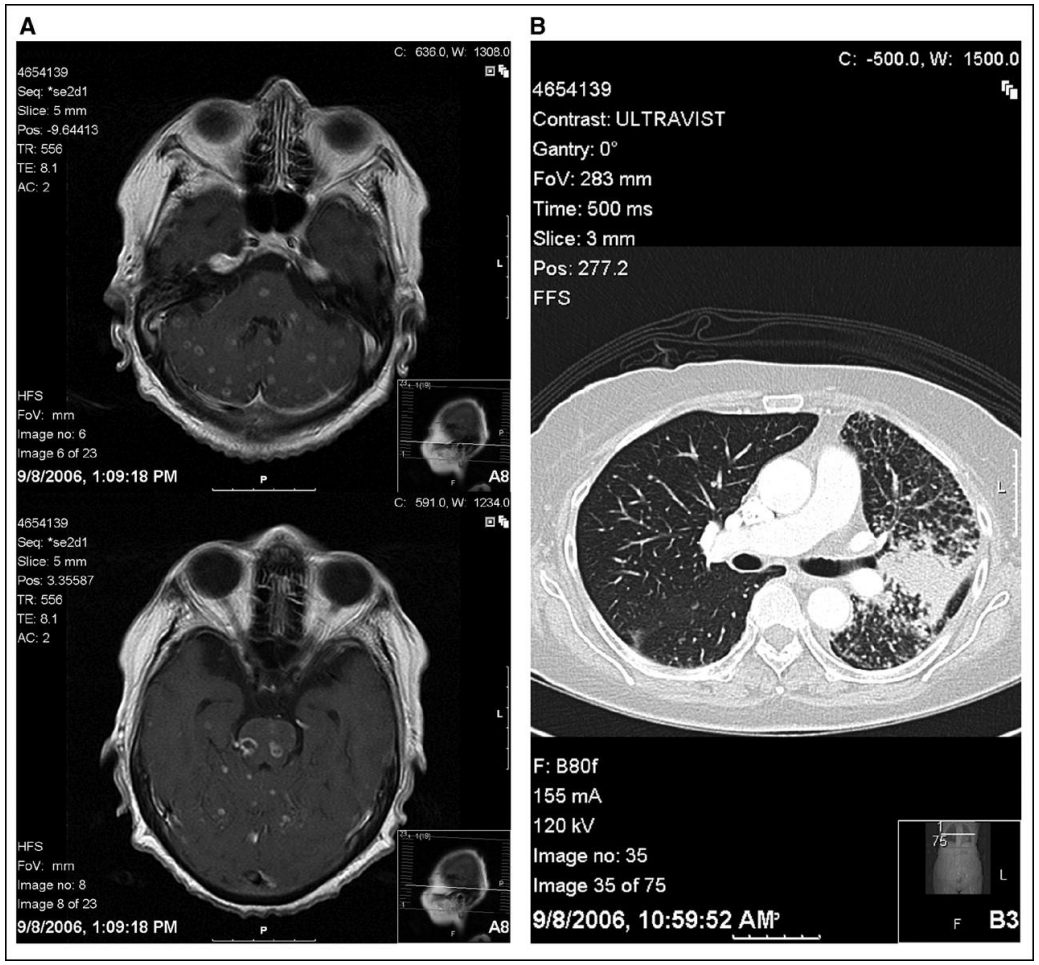
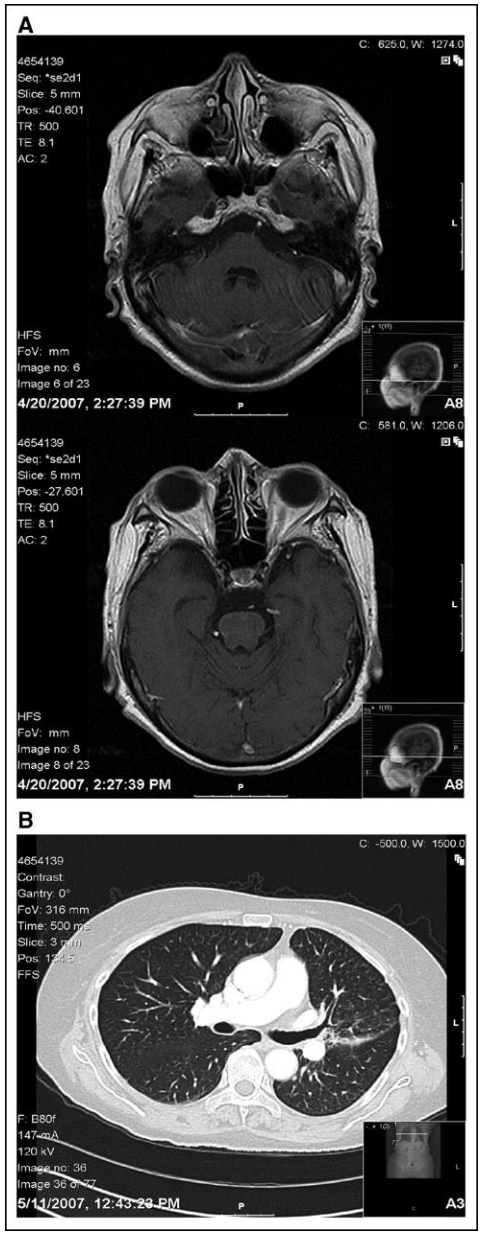


Fig 4. Response of an *ROS1*-positive patient with advanced non–small-cell lung cancer to crizotinib. Computed tomography scans of the chest were obtained (A and C) at baseline and (B and D) after 12 weeks of crizotinib. Shown are (A and B) coronal reconstructions and (C and D) axial slices.

Also active in the brain

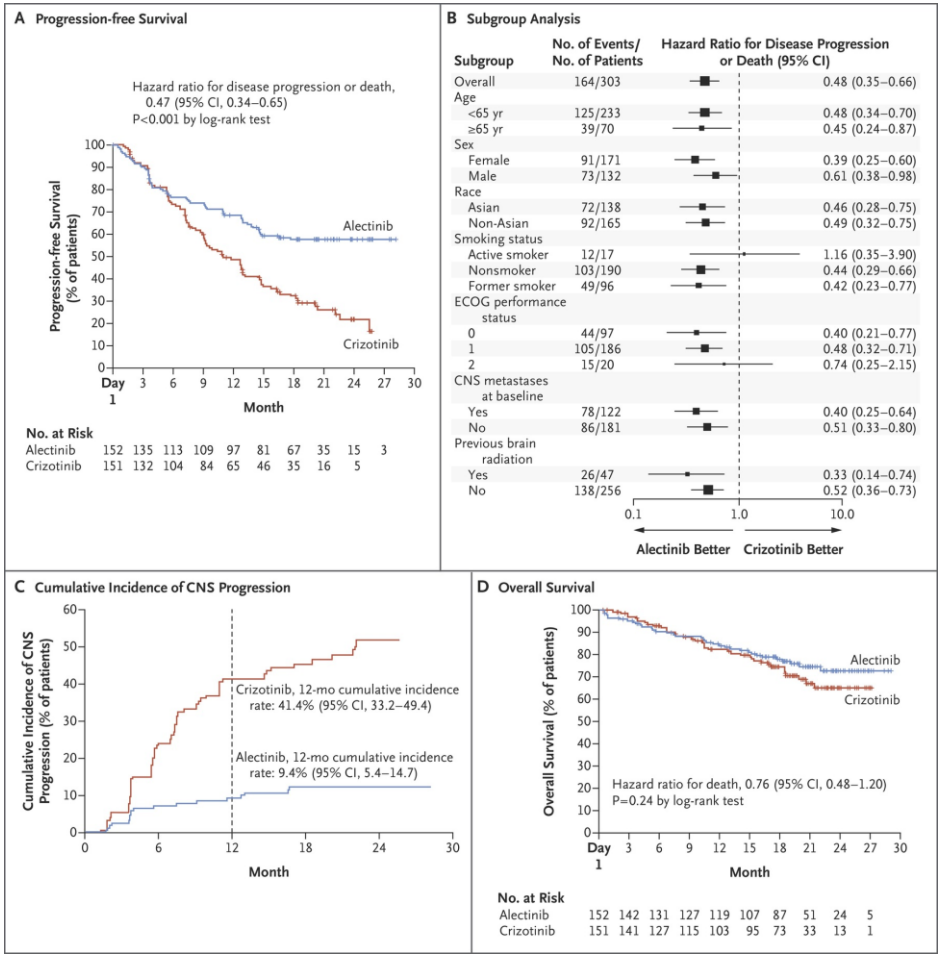




Response in 1 mth; 8+ mth

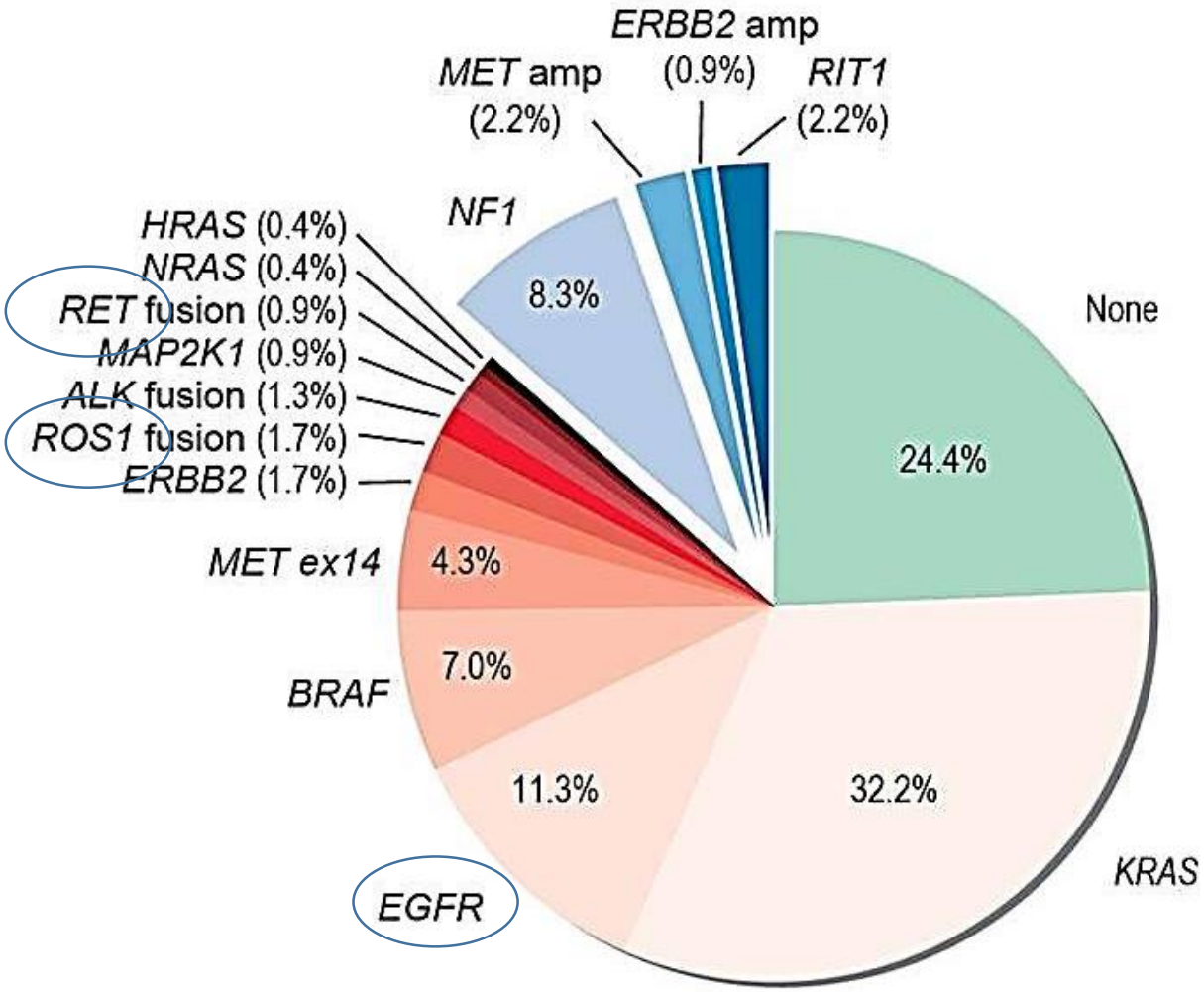
J Clin Oncol. 2008;26(4):686

Second generation: alectinib



Peters et al, NEJM 2017

Some targets are rare



Memorial Sloan Kettering Cancer Center

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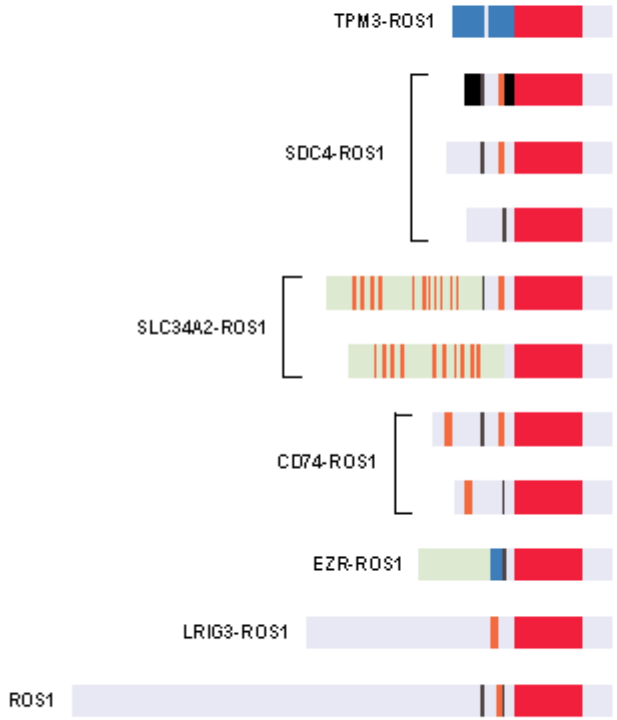
Alle actionable (routine or investigational)

Some targets are rare

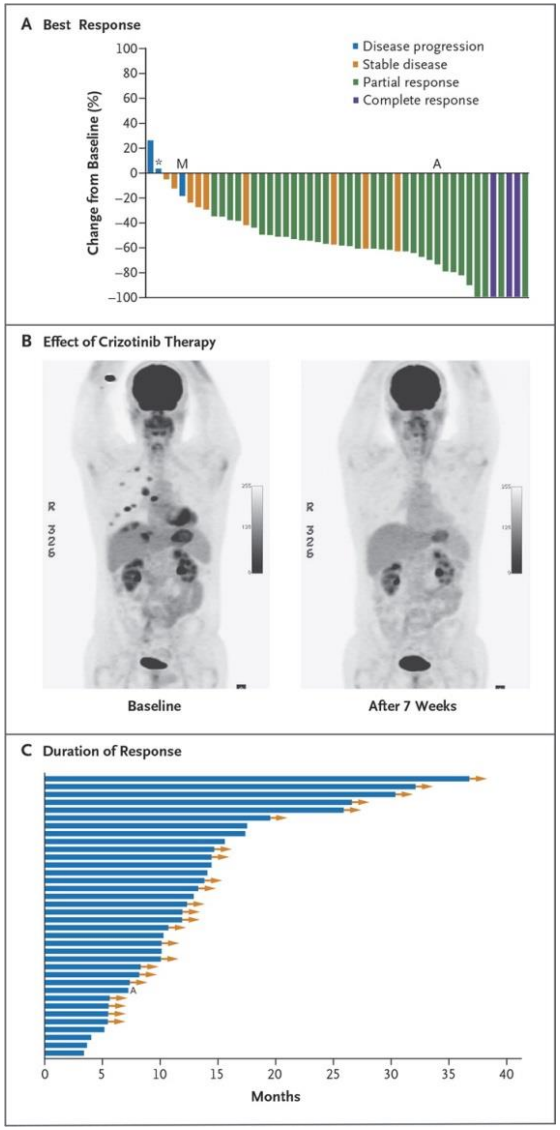
ROS1 rearrangements in NSCLC 1%



- ROS1 is receptor tyrosine kinase of the insulin receptor family
- *ROS1* gene fusions are potential driver mutations and are present in ~1% of NSCLC cases
- Enriched in younger never or light smokers with adenocarcinoma histology
- No overlap with other oncogenic drivers

Bergethon et al., JCO 30(8): 863-70, 2012; Takeuchi et al., Nat Med 18(3): 378-81, 2012

But they respond as well



Shaw AT et al. N Engl J Med 2014;371:1963-1971.

Crizotinib in Ros mutated lung

Levels of genomic analysis

1. *Companion diagnostics* for individual reimbursed drugs

2. Next Generation Sequencing (NGS)
   - Organ-oriented panels for reimbursed drugs
     - Aline Herbrant, Els Vanvalckenborg, Sciensano
     - Anouk Waeytens, Compermed & RIZIV
   - Organ-agnostic panels (independent of tumor type)
   - Broad panels for all actionable genes
     - Including investigational drugs in development
   - Panels also including explorative targets

3. Whole genome/exome

Current Clinical practice

1. *Companion diagnostics* for reimbursed drugs

2. NGS (not yet reimbursed)
   - Organ-oriented panels for reimbursed drugs
     - Aline Herbrant, Els Vanvalckenborg, Sciensano
   - Agnostic panels (independent of tumor type)
   - Broad panels for all actionable genes
     - Including investigational drugs in development
   - Panels also including explorative targets

3. Whole genome/exome

Current Clinical practice

1. *Companion diagnostics* for rei drugs

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   - Panel ng explorative targets

3. Whol ome/exome

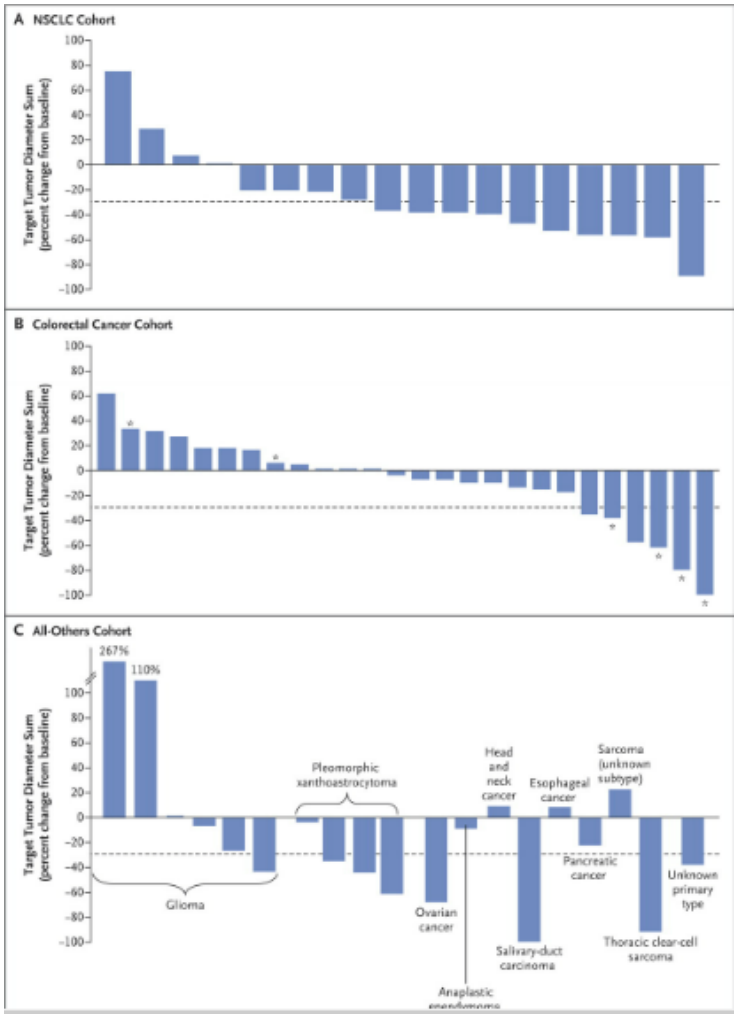
Insufficient !

Everything that is missed

- Other cancer types (than the ones specifically foreseen for reimbursement) can carry the same mutations

- Mutations selecting for novel therapies
  - Ad hoc searching for patients that have these mutations in their tumor or germline is like looking for a needle in a haystack & severely hampers accrual in genotype-driven clinical trials

Mutations that are typically associated with particular cancer types also can be found an many other cancer types with variable therapeutic sensitivity



BRAF targeting

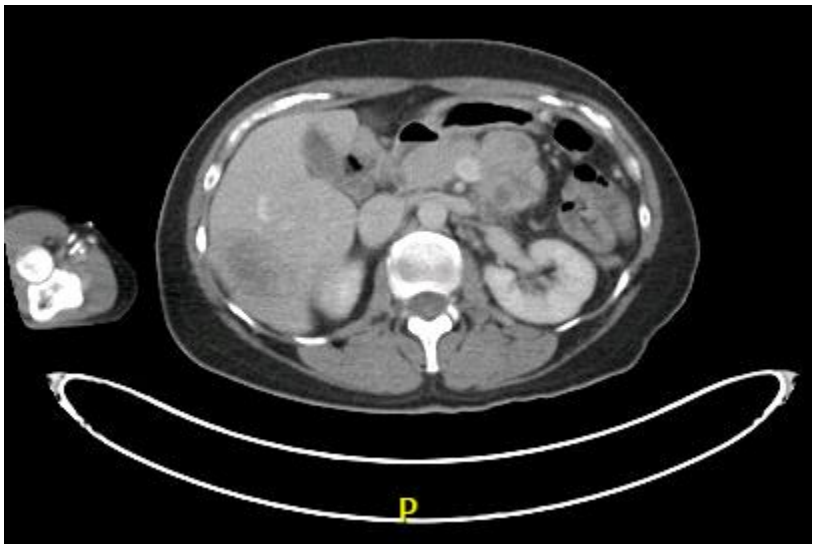
Heyman et al n engl j med 373;8, 2015

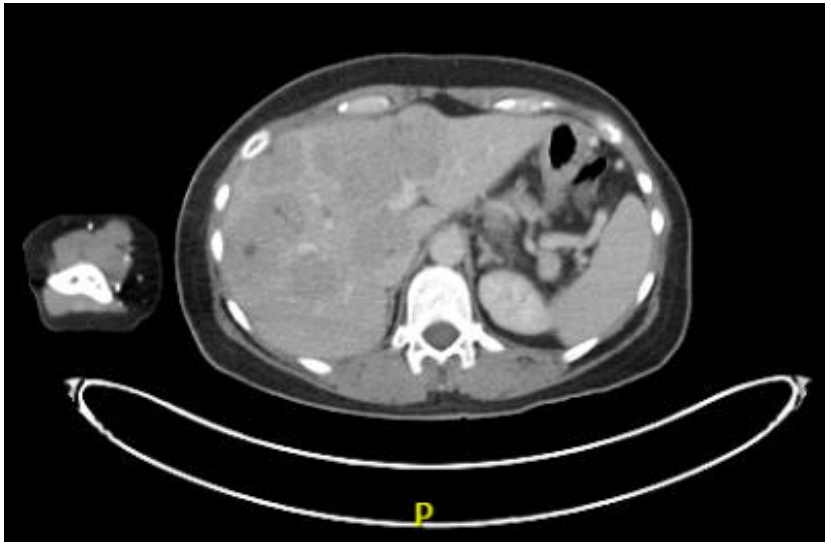
- Yes, they are all rare, but there are *many* different ones
- Many rare ones together make a big one
- Even rare patients have a right to the most effective therapy

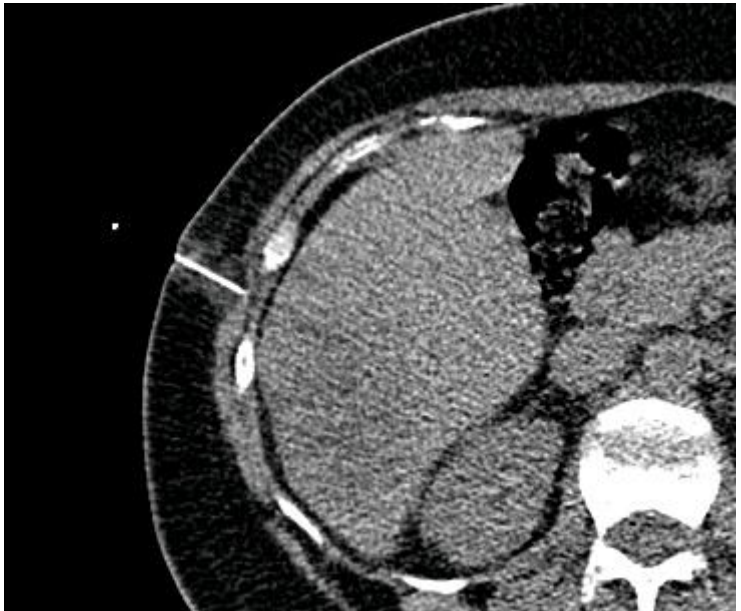
Example of rare mutation

- SN, female, 50 yrs
- Pancreatic cancer, 6 cm with diffuse liver mets
  - Pain and pressure on the stomach > feeding problems
- **Molecular typing**
  - **KRAS : no mutation**
  - **Academic NGS sequencing (50+ genes): no mutations**
- Chemotherapy
  - Response with disappearance of symptoms
  - Disease progression after 5 months

Example of rare mutation







Example of rare mutation

- Broader sequencing (FoundationOne) (> 300 genen)
  - **RET rearrangement**
  - **RET mutated/rearranged in 1% of pancreatic cancers**

Example of rare mutation

Genomic Alterations Identified[†]

RET GP2-RET fusion
CDKN2A loss
GATA1 L136* – subclonal[#]
SPTA1 Q2384K

Additional Findings[†]

Microsatellite status MS-Stable

Tumor Mutation Burden TMB-Low; 5 Muts/Mb

[†] For a complete list of the genes assayed and performance specifications, please refer to the Appendix

[#] See Appendix for details

Example of rare mutation

Genomic Findings Detected	FDA-Approved Therapies (in patient's tumor type)	FDA-Approved Therapies (in another tumor type)	Potential Clinical Trials
RET GP2-RET fusion	None	Cabozantinib Lenvatinib Ponatinib Sorafenib Sunitinib Vandetanib	Yes, see clinical trials section
CDKN2A loss	None	None	None
GATA1 L136* - subclonal	None	None	None
Microsatellite status MS-Stable	None	None	None
SPTA1 Q2384K	None	None	None

Example of rare mutation

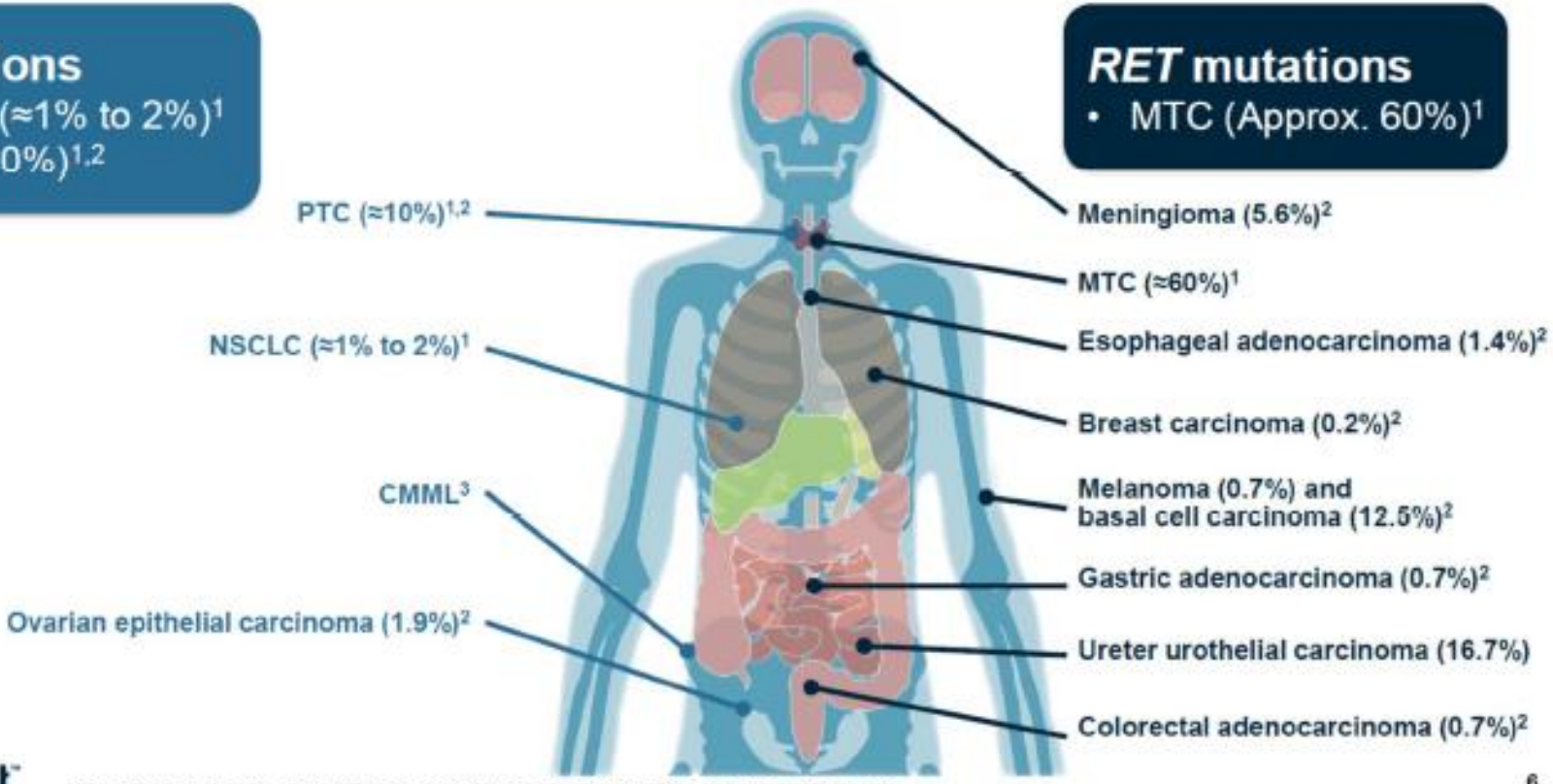
- R/ Alectinib
  - PR> focal progression> chemo-embolisation> alectinib continued
  - Now nine months symptom-free

RET mutations/rearrangements occur in many other cancer types

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]



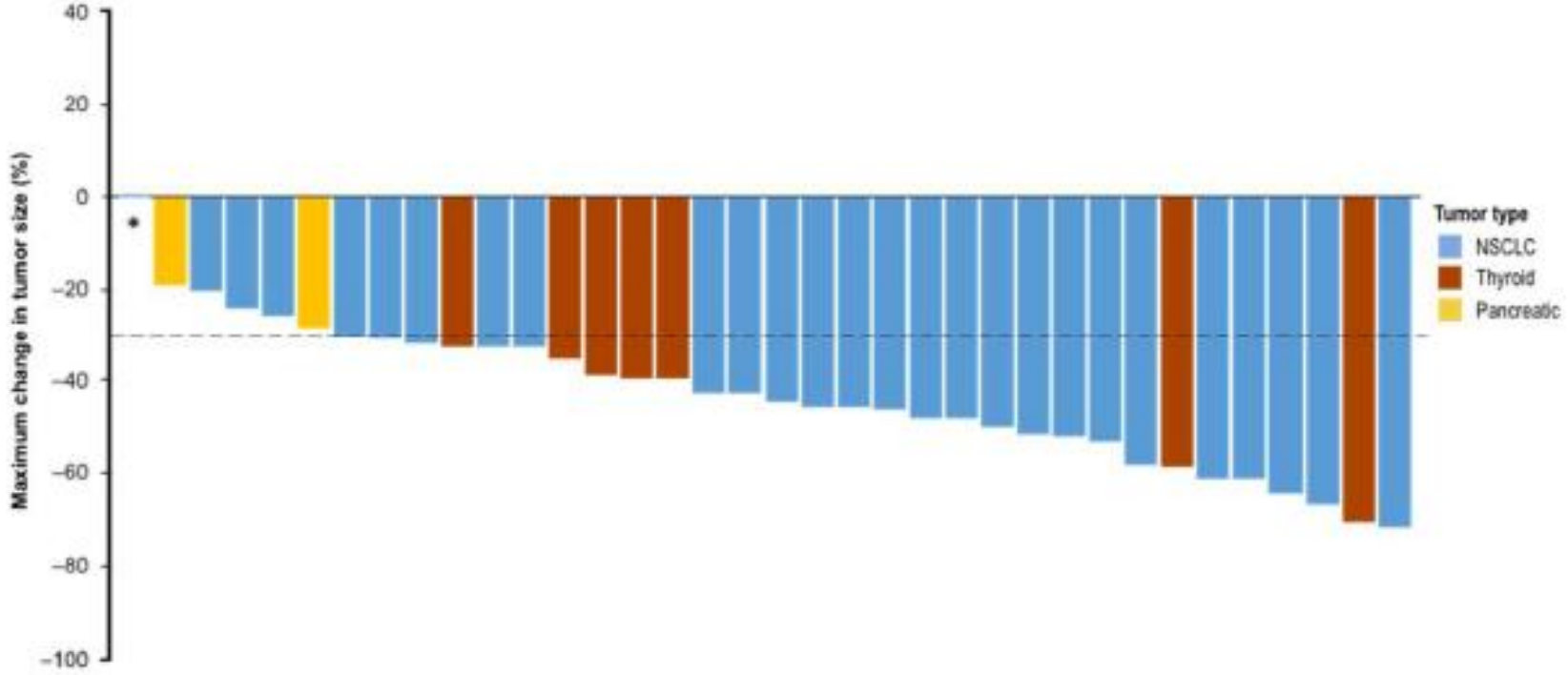
MTC, medullary thyroid cancer; NSCLC, non-small cell lung cancer; PTC, papillary thyroid cancer.

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.

RET mutations/rearrangements are actionable independent of cancer type

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

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



PRESENTED AT: 2018 ASCO ANNUAL MEETING #ASCO18

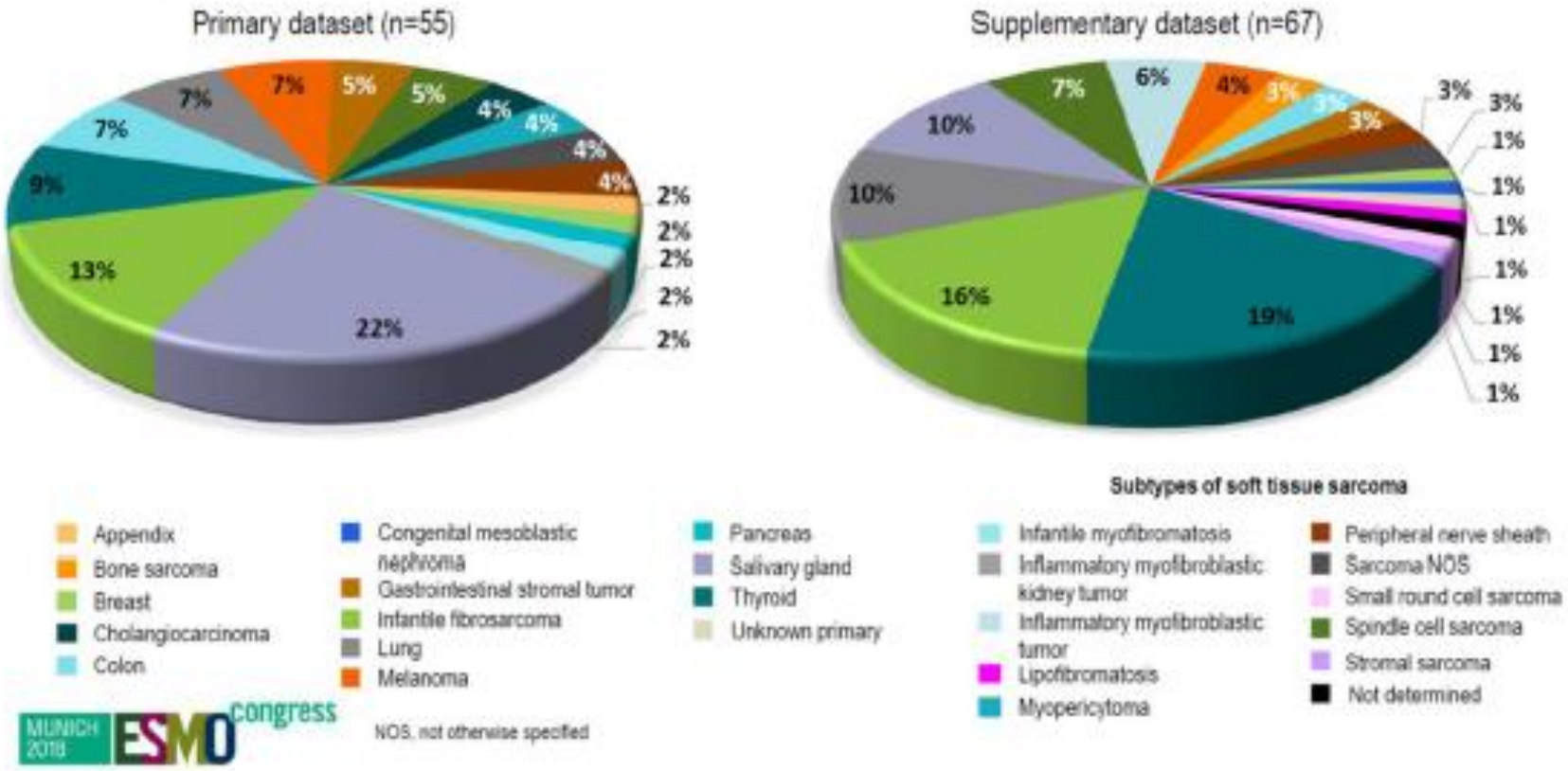
PRESENTED BY: Dr. Alexander Drilon

Drilon A et al, ASCO Annual Meeting 2018

TRK rearrangements

Larotrectinib efficacy and safety in TRK fusion cancer: an expanded clinical dataset showing consistency in an age and tumor agnostic approach

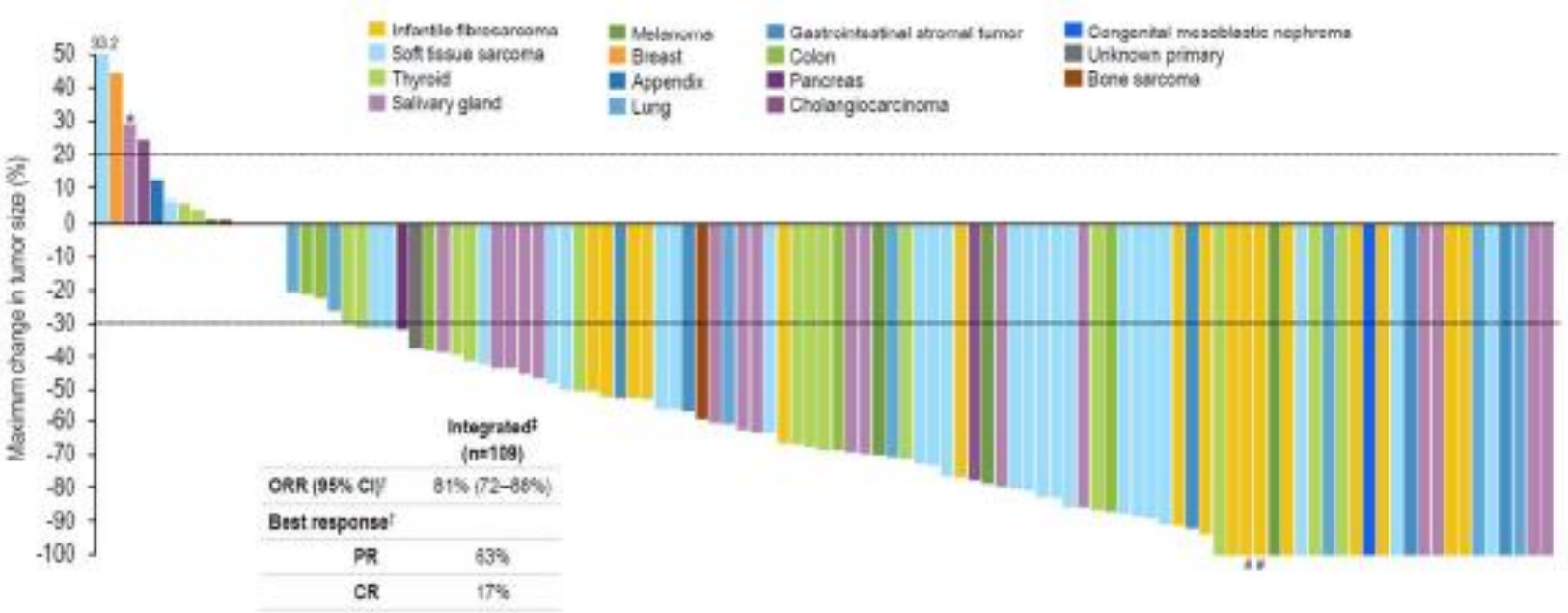
Diversity of cancers treated



TRK rearrangements

Larotrectinib efficacy and safety in TRK fusion cancer: an expanded clinical dataset showing consistency in an age and tumor agnostic approach

Integrated dataset: Larotrectinib is efficacious regardless of tumor type



†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

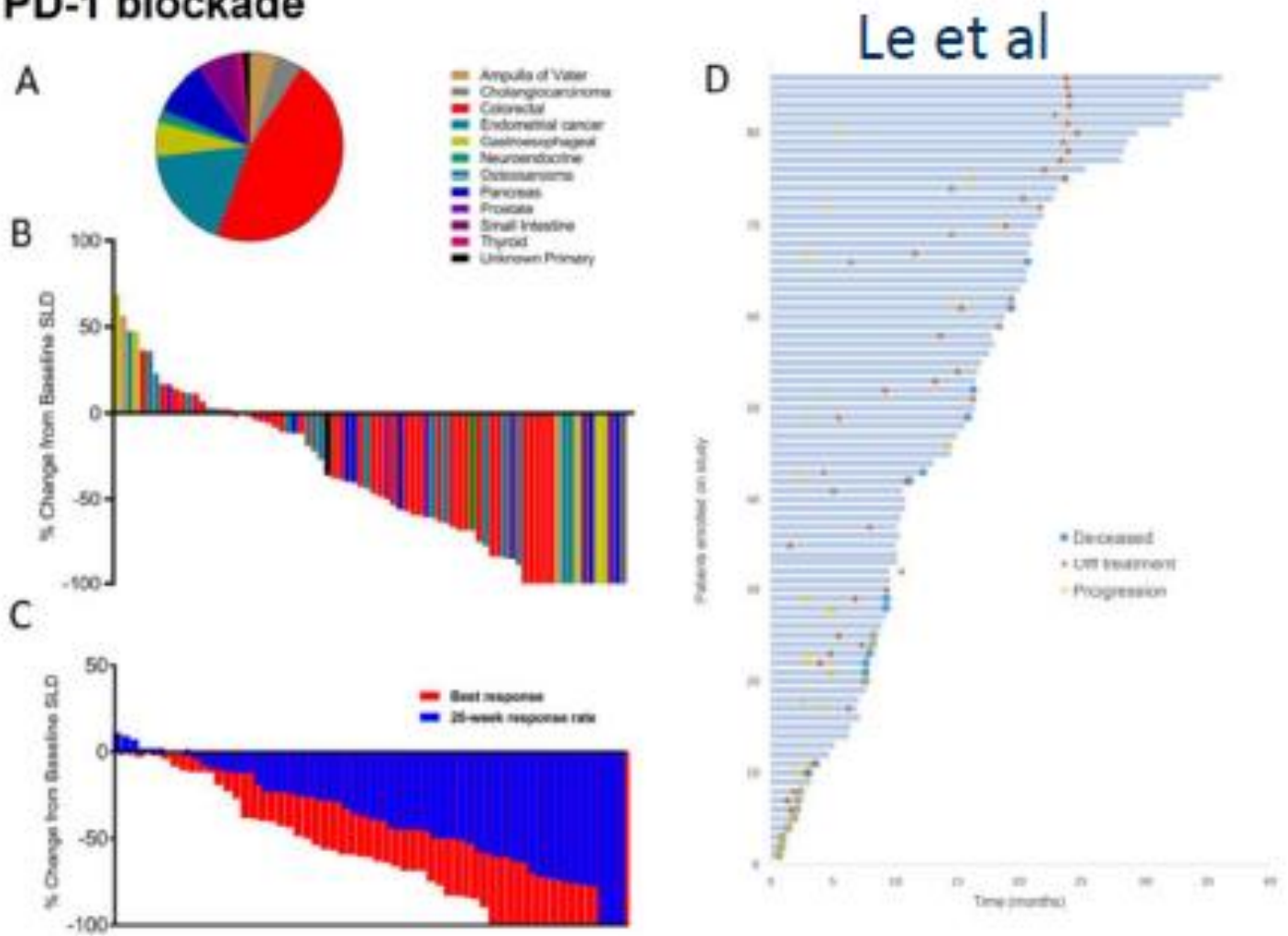
MUNICH 2018 ESMO congress

Investigator response assessments, as of 30 July 2018

Pembrolizumab: agnostic activity in MSI-high cancers

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

Table 1. Cancers with an MSI-H frequency greater than 10%

Tumor type	Frequency, % (*n*)	Study
Colorectal cancer	13% (1066)	Hampel et al. (72)
Endometrial	22% (543), 33% (446)	Zighelboim et al. (73), Hampel et al. (74)
Gastric	22% (295)	TCGA (75)
Hepatocellular carcinoma	16% (37)[a]	Chiappini et al. (76)
Ampullary carcinoma	10% (144)	Ruemmele et al. (77)
Thyroid	63% (30)[a]	Mitmaker et al. (78)
Skin (sebaceous tumors)	35% (20)[a], 60% (25)[a]	Cesinaro et al. (79), Kruse et al (80)
Skin (melanoma)	11% (56)[a]	Palmieri et al. (81)

[a]Studies of less than 100 patients.

Table 2. Cancers with an MSI-H frequency between 2% and 10%

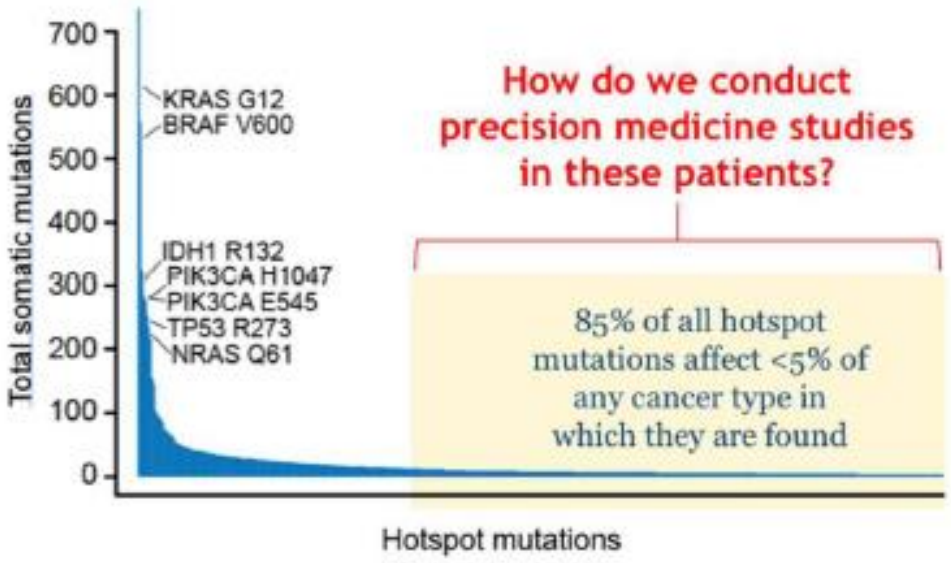
Tumor type	Frequency, % (*n*)	Study
Ovarian	10% (1234)	Murphy and Wentzensen (82)
Cervical	8% (344)[a]	Lazo (83)
Esophageal adenocarcinoma	7% (76)	Farris et al. (84)
Soft-tissue sarcoma	5% (40)	Kawaguchi et al. (85)
Head and neck SCC	3% (153)[b]	Glavac et al. (86)
Renal cell carcinoma	2% (152)	Hammerschmied et al. (87)
Ewing sarcoma	2% (55)	Alldinger et al. (88)

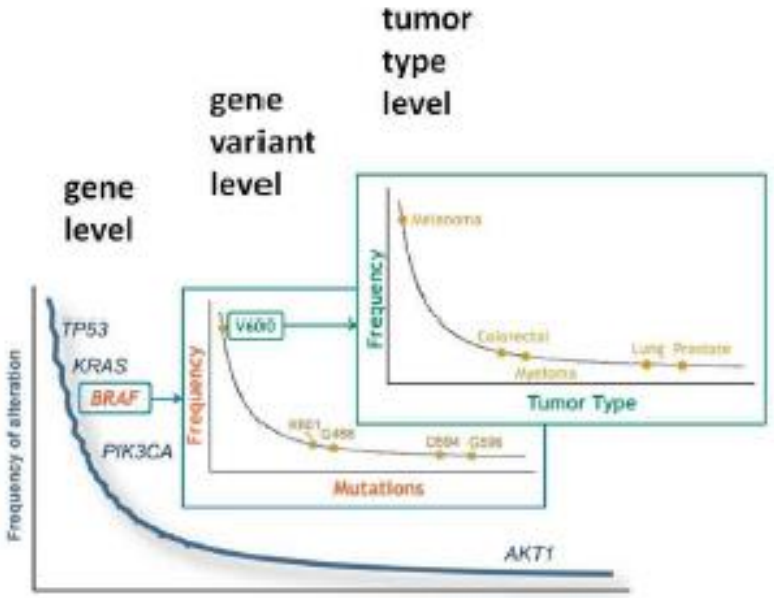
Table 3. Cancers with an MSI-H frequency less than 2%

Tumor type	Frequency, % (*n*)	Study
Skin (squamous cell)	0% (30), 0% (56)	Reuschenbach et al. (89)[a]
Skin (basal cell)	0% (53), 2% (104)	Reuschenbach et al. (89)[a]
Prostate	1% (79)	Burger et al. (90)
Lung	0% (80), 2% (55)	Okuda et al. (91), Ninomiya et al. (92)
Osteosarcoma	0% (68)	Entz-Werle et al. (93)
Glioblastoma	0% (109)	Martinez et al. (94)
Pancreatic ductal adenocarcinoma	0%–2% (338)	Laghi et al (95)
Breast	0% (267), 0% (34), 0% (52), 1% (100)	Anbazhagan et al. (96), Adem et al. (97), Kuligina et al. (98), Toyama et al. (99)
Bladder	1% (84)	Catto et al. (100)
Testicular germ cell	0% (100)	Mayer et al. (70)

Many rare ones together make a big one

There is a 'long tail' of hotspot mutations across different cancers

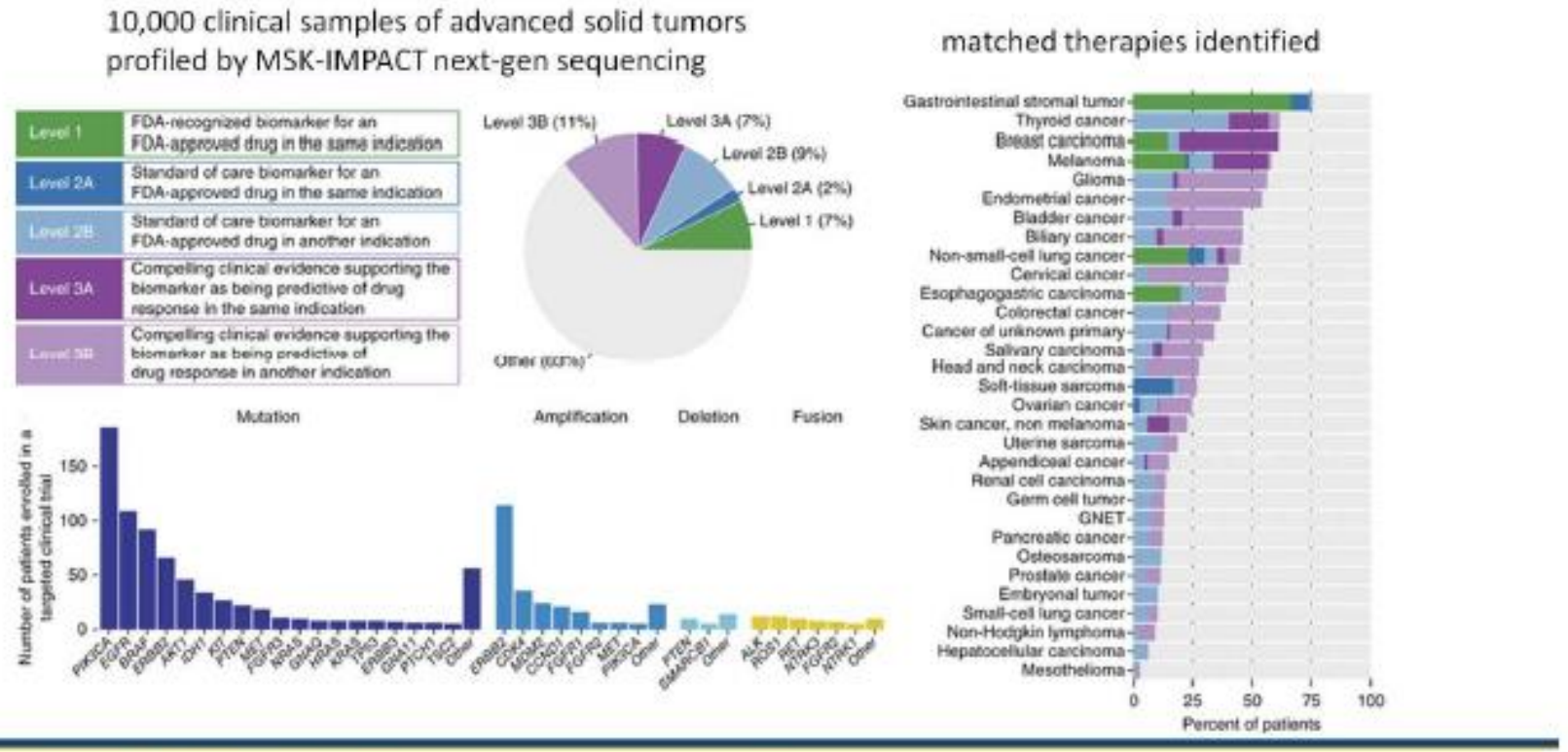




Chang, MT et al. Nat Biotechnol. 2016 Feb;34(2):155-63

Broad agnostic sequencing and clinical translation needed

Actionable alterations can be detected across cancers in the clinic



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PRESENTED BY: Dr. Alexander Drilon

Zehir et al, Nature Med 2017

Presented By Alexander Drilon at 2018 ASCO Annual Meeting

Further validation of yet unexplored cancer type-genotype associations

Tumor agnostic therapy = targeting oncogenic drivers regardless of tissue histology

Tumor agnostic drug development can address the 'long tail'

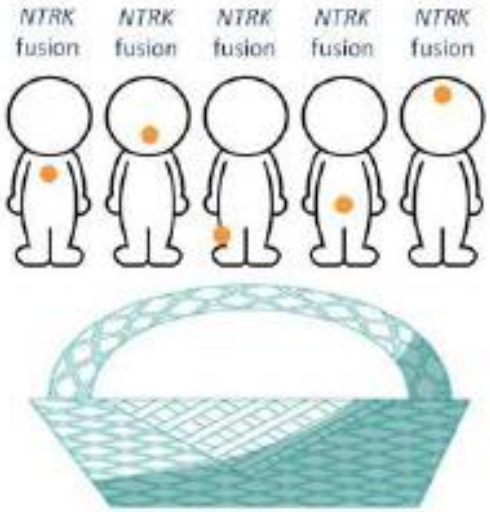
Histology-specific drug development

- Traditional designs
- Umbrella trials

Alteration-specific drug development (agnostic of tumor type)

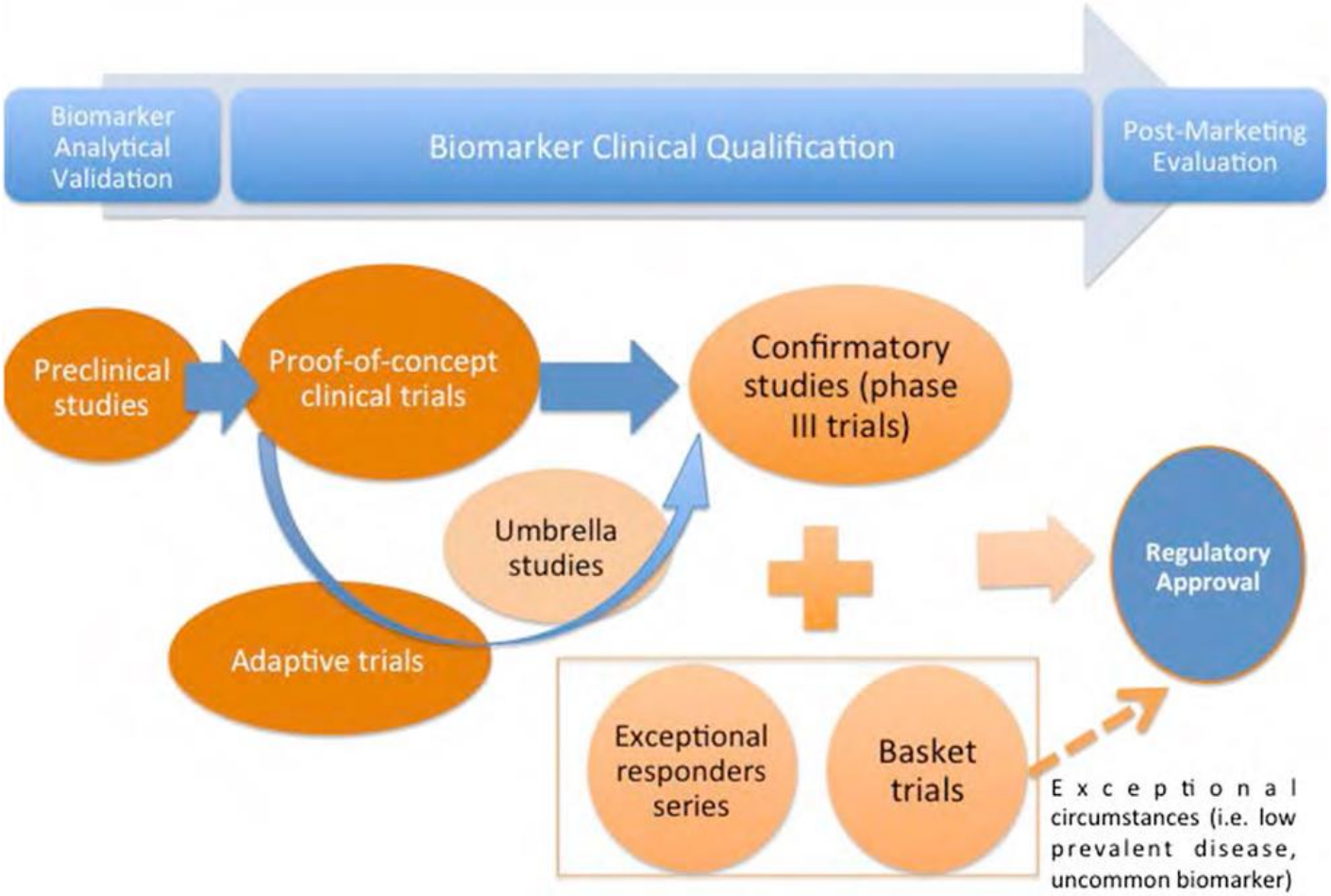
BASKET TRIAL

- One qualifying group of alterations
- Tumor agnostic patient accrual



Drillon A ASCO 2018

Clinical Trials in the Era of Genomics and Personalized Medicine



Mateo, ASCO edu 2016

Belgian Society of Medical Oncology

The Precision initiative

a collaboration between Belgian university hospitals and pharmaceutical industry to give cancer patients access to a broader spectrum of cancer medicines

Kom op tegen Kanker

Stichting tegen Kanker

Fondation contre le Cancer

Precision steering committee

- Philippe Aftimos - Bordet, Precision 1
- Cauwelier Barbara – Hemato-oncology
- Joelle Collignon - CHU Liege
- Francois Duhoux - UC Louvain
- Sandra Jacobs - Pediatric oncology
- Jacques De Grève - Chair
- Lore Decoster - UZBrussel, precision 2
- Kevin Punie- KU Leuven
- Marika Rasschaert- UZ Antwerpen
- Sylvie Rottey - UGent
- Roberto Salgado - Molecular pathology
- Marc Van den Bulcke - Cancer Centre
- Didier Vandersteichele - STK/FCC

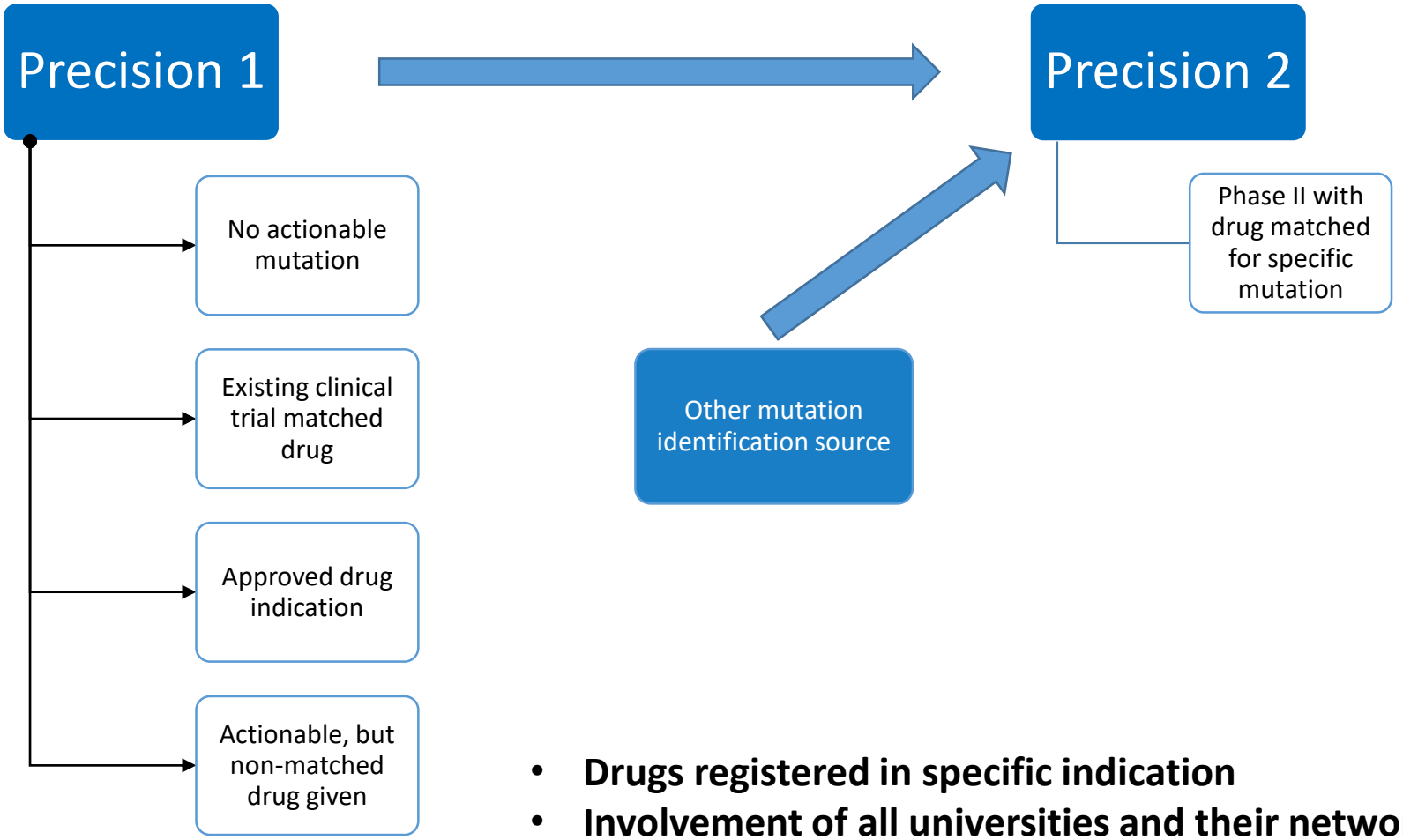
Precision Belgium components

- **Implementing gene panel sequencing**
  - Ongoing evaluation of NEXTgen platforms
  - Sequencing all established and emerging actionable genes
  - Cancer Centre (Sciensano)> RIZIV/INAMI
- **Establish shared national real-time database**
  - Clinical data
  - Genomic data
  - Healthdata & Sciensano
  - Connected to e-health and Cancer Registry
  - Accessible to all investigators/oncologists
- **Precision 1**
  - Establish benefits of genotype driven treatment
  - Interinstitutional Molecular tumor board
- **Precision 2**
  - Establish new evidence on efficacy in specific genotype-cancer type associations

Philippe Aftimos

Lore Decoster

Precision Belgium



- **Drugs registered in specific indication**
- **Involvement of all universities and their networks**
- **National coordinator**

Ongoing Precision studies

- Afatinib in HER1,2 or 3 mutations in any cancer type
  - Recruiting
- Olaparib in cancers with HRD gene mutations
  - Activated

Proposed Precision studies

- Imatinib in KIT, PDGFR, bcr-abl mutated cancers
- Dabrafenib/Trametinib in non-V600 BRAF mutant cancers
- Alpelisib in Pi3K mutant cancers
- Ret inhibitor in RET mutant/rearranged cancers

Advantages (of tissue-agnostic testing) for stakeholders

- Patients
  - Access to additional therapeutic options
- Pharma
  - Patient selection (for trials)
  - Data on efficacy in rare cancer-genotype associations
- Academic research
  - Platform also for scientific collaborators
- Authorities
  - Better insights in real world

To be able to conduct these trials or serve patients in whose disease the specific gene already has been validated as actionable, we need a systematic tissue-agnostic approach to sequencing

What we need: broad agnostic somatic gene panel

1. *Companion diagnostics* for reimbursed drugs

2. NGS
   - Organ-oriented panels for reimbursed drugs
     - Aline Herbrant, Els Vanvalckenborg, Sciensano
   - Agnostic panels (independent of tumor type)
   - **Broad panels for all actionable genes**
     - **Including investigational drugs in development**
   - Panels also including explorative targets

3. Whole genome/exome

Obstacles for Precision

- Content
  - Absence of tumor-agnostic sequensing
  - Absence of many actionable genes, even in academic gene panels
  - Amount of tissue

- Politics
  - Conservative attitude in pathology and genetics
    - **A genomic test is NOT research, only the subsequent use *could* be research**
  - Budget

Staged agnostic sequencing in cancer
proposal

Belgian Precision study

BSMO in collaboration with the Cancer Centre

Rationale

- ***Broader panels*** *applied by some Belgian platforms (+/- 50 genes), sometimes in an agnostic approach, do not cover all potentially actionable genes or not all types of sensitizing mutations in these genes*

- ***Rearrangements*** *which are highly actionable are not systematically covered in NGS testing, but rely on less sensitive immunohistochemistry (if done at all)*

- ***Belgian NGS labs*** *are accredited but have heterogeneous methodology and it has been reported that the mutation detection rate varies from one region to another, pointing possibly towards methodological issues*

Rationale

- ***More comprehensive commercial platforms*** *that cover all actionable genes (up to hundreds of genes) and the various types of mutations in these genes: sequence alterations, rearrangements, resulting in fusion genes, and gene amplifications*
  - *These commercial vendors have adequate comprehensive methodology but are currently too expensive (at their current public pricing) for general application*

- *Example: Foundation Medicine (FoundationOne)*
  - *builds on a large experience in variant annotation in the US and includes probably most if not all current actionable targets including gene mutations, fusions, MSI, a surrogate for tumor mutational burden etc., all at once in one result*
  - *Report actionability and indicates established or clinical trial treatment options*

Hypothesis

- *We expect that up to 20 % of patients who failed in the reimbursed organ-specific NGS could have a mutation that is someway actionable*

- *Test would be applicable to an estimated 5-10K patients with advanced cancer per year*
  - *high attrition rate after baseline diagnostics and standard therapies, as many patients are not eligible for further line therapies*
  - *no utility of genotype targeted therapies in end-stage patients or patients with a poor performance status*

Study

- *Eligibility*
  - *Advanced cancer patients that have failed at least one first-line standard treatment*
  - *Patients have had a reimbursed organ-specific sequencing panel that was negative*
  - *Life expectancy of at least 3 months*
  - *Open to all patients*

- *Eligible patients will*
  - *Have FoundationOne sequencing (epithelial/sarcoma) on their tumor*
  - *Treatment based on the FoundationOne result*

- *Explorative study in 1000 patients*

- *24 months for recruitment through the Precision network*

- *The commercial partner would provide the testing at a reduced rate (compared to public pricing)*
  - *increases the potential for maximizing the return on investment*

Measurable outcomes

- ***What is the added value of comprehensive and agnostic NGS after reimbursed NGS***
  - *Document magnitude of the real life need & the utility of this approach*
  - *Provide an estimate of the budgetary implications*
  - *Comparator is the first-line genomic testing using reimbursed NGS*
  - *Quality and sensitivity control on reimbursed NGS*

- ***The study would inform the authorities (RIZIV) about the amplitude and cost-effectiveness of comprehensive sequencing***

- ***Academic platforms would gain knowledge from the exercise***

Example

- Male patient, 30 years with ultrarare disease
  - Multiple fibroblastic tumors
  - One cervical spine location, next to CNS: needs carbon therapy in Heidelberg
- Academic panel sequencing: no mutations
- FoundationOne: PDGFRβ pathogenic mutation
- Can be treated with imatinib

Conclusion

- Precision medicine is there
- Routine genomic diagnosis does not implement all what is possible, withholding significant treatments for patients and severely hampering clinical trial accrual
- Because of budgetary concerns we propose a prospective staged large panel sequencing project that could inform about the utility and improve current practice

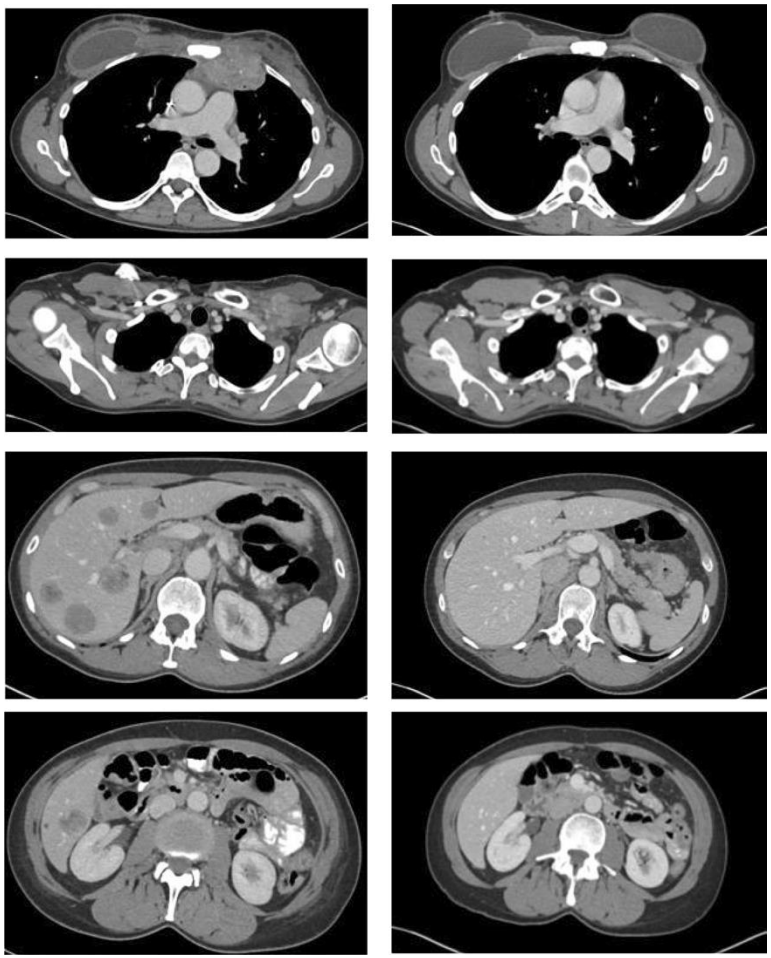
Current routine standard for every cancer patient should be:

1. Broad agnostic tumor panel sequencing of the tumor DNA/RNA

2. Whole genome sequencing of the germline DNA with cancer gene panel analysis

Personalized application of sequencing: mutanome

- Immune therapy (TMB)
- Mutanome vaccination
- Expansion of mutation-directed TILS



Zacharakis, Nature medicine 2018

Future: whole genome

- 9,423 tumor exomes en 26 computational tools to catalog driver genes and mutations
- 299 driver genes with therapeutic/clincial implications

- >3,400 putative missense driver mutations
  - 60%–85% of predicted mutations likely drivers
  - 300 MSI tumors are associated with high PD-1/PD-L1,

- **57% of tumors analyzed harbor putative clinically actionable events**

Bailey et al., 2018, Cell 173, 371–385