Cancer Centre: 'Next generation sequencing in routine clinical practice'

Belgian Society of Medical Oncology

"Precision"

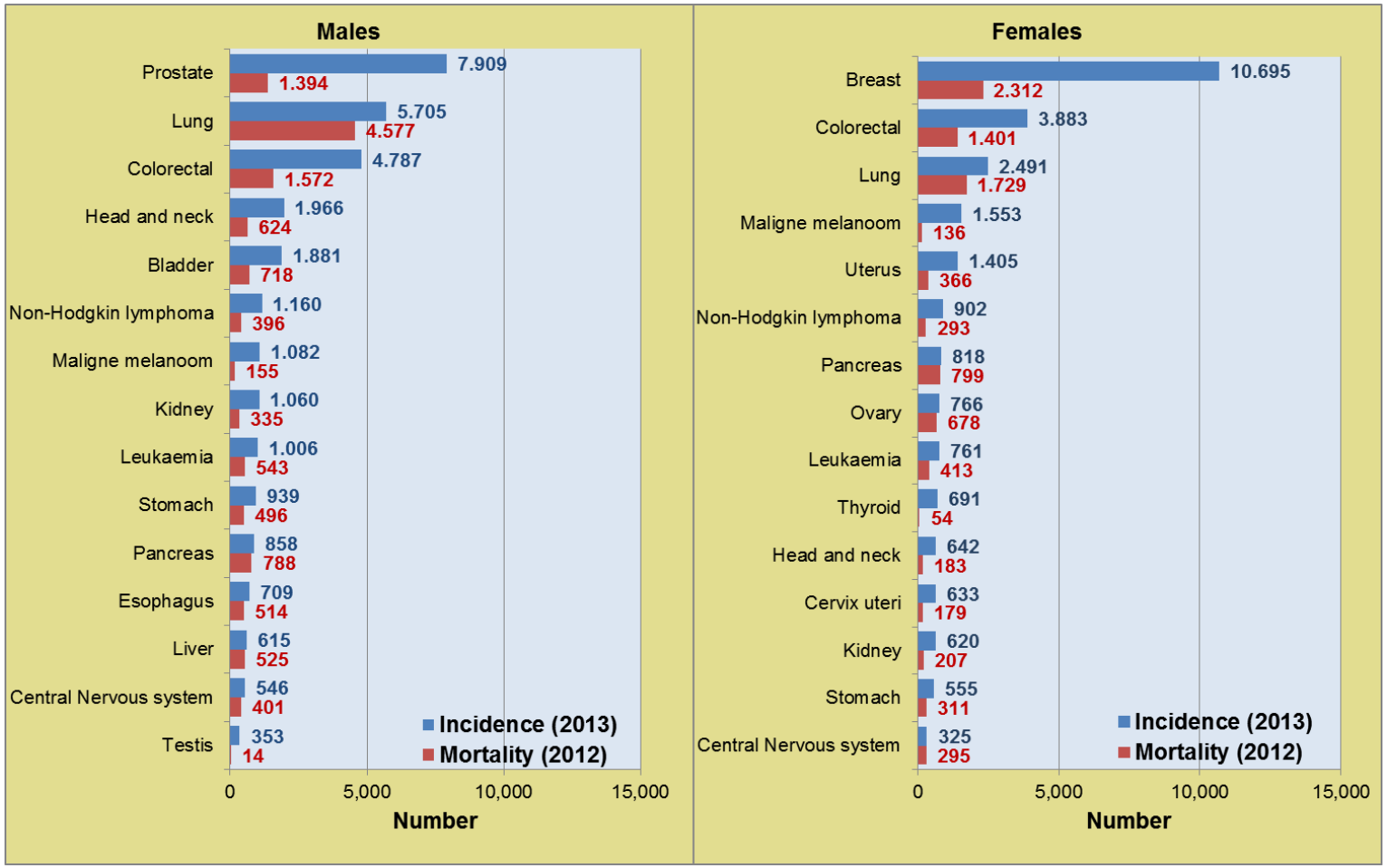
Bringing innovation to the patient

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

Jacques De Grève MD, PhD

For the Precision Steering committee

Cancer, a high medical need



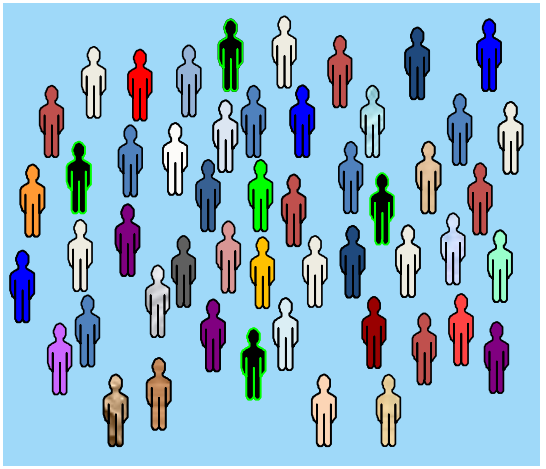
Cancer registry

Cancer

- Second cause of disease related fatality
- Local treatments: surgery and radiotherapy
- **Systemic treatments**
  1. Chemo
  2. Hormonal
  3. **Targeted**
  4. Immunotherapy

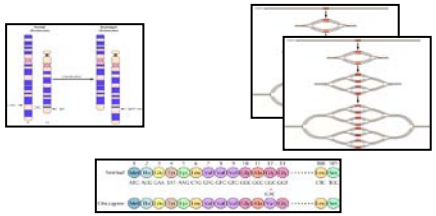
Basis of treatment choices

1. **Clinical criteria**
   - Disease stage
   - Performance status



2. **Pathological criteria**
   - Cancer type
   - Therapeutic target expressed:
     - Estrogen receptor
     - PDL1
     - ….

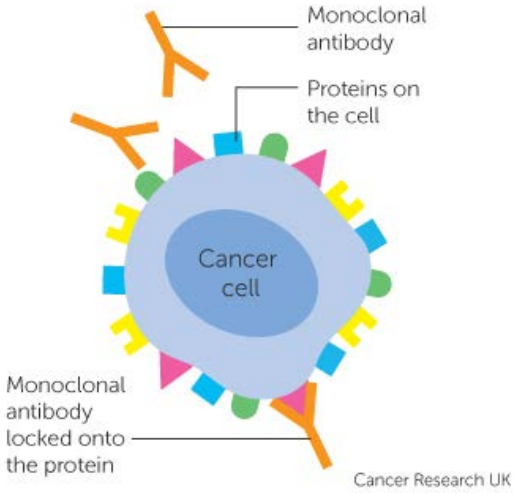
3. **Genomic criteria**
   - **Cancer gene mutations**



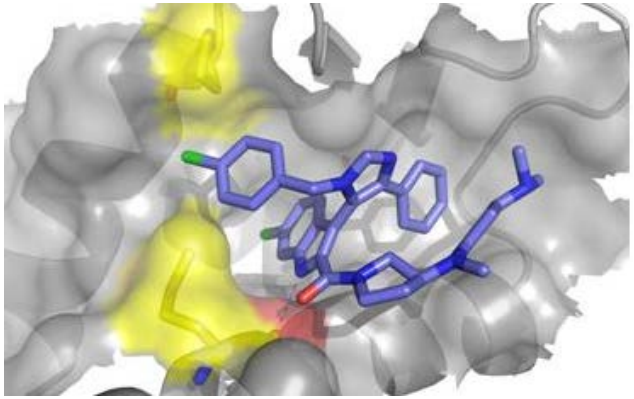
Which drugs can target the aberrant proteins

Targeted therapies

- **Monoclonal antibodies**
  - Surface receptors

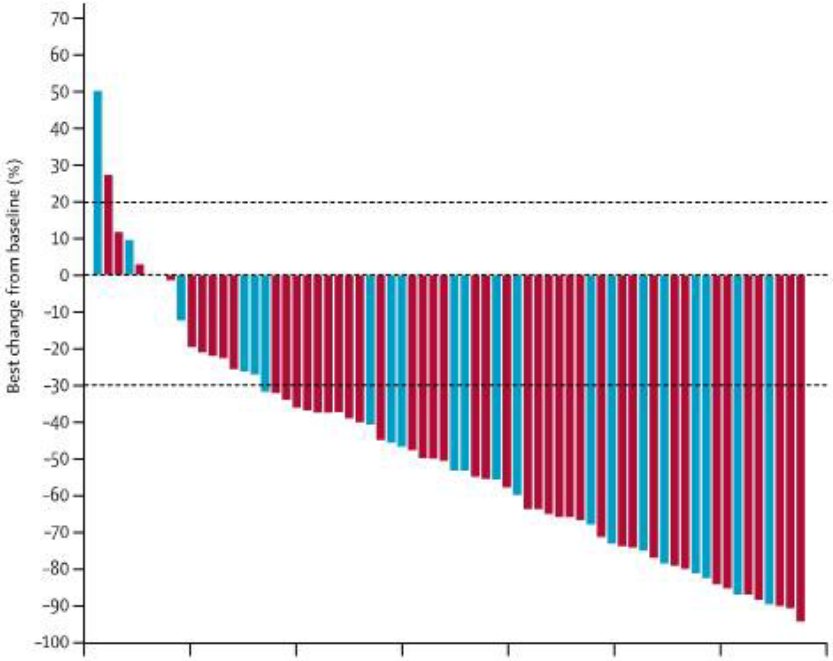


- **Small molecules**
  - Intracellular targets



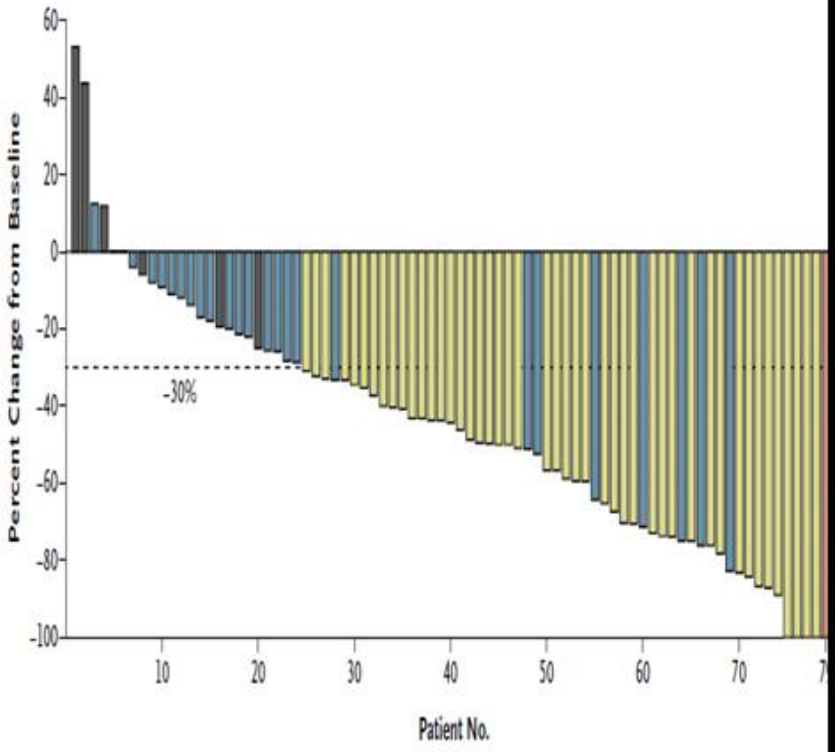
Impressive therapeutic results with targeted therapies

Erlotinib in EGFR mutant lung cancers



Rosell et al., *Lancet Oncol* 2012

Crizotinib in ALK mutant lung cancers

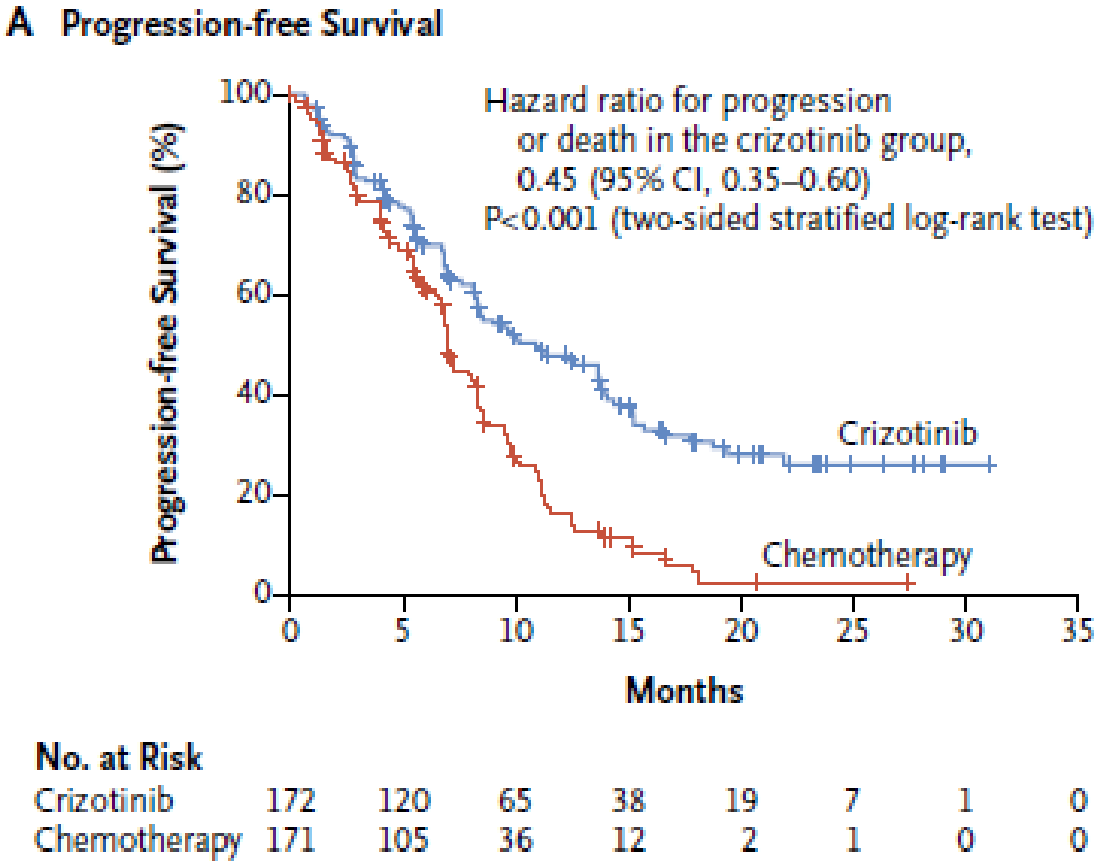


Kwak et al., *N Engl J Med* 2010

Memorial Sloan Kettering Cancer Center

Presented By Charles Rudin at 2014 ASCO Annual Meeting

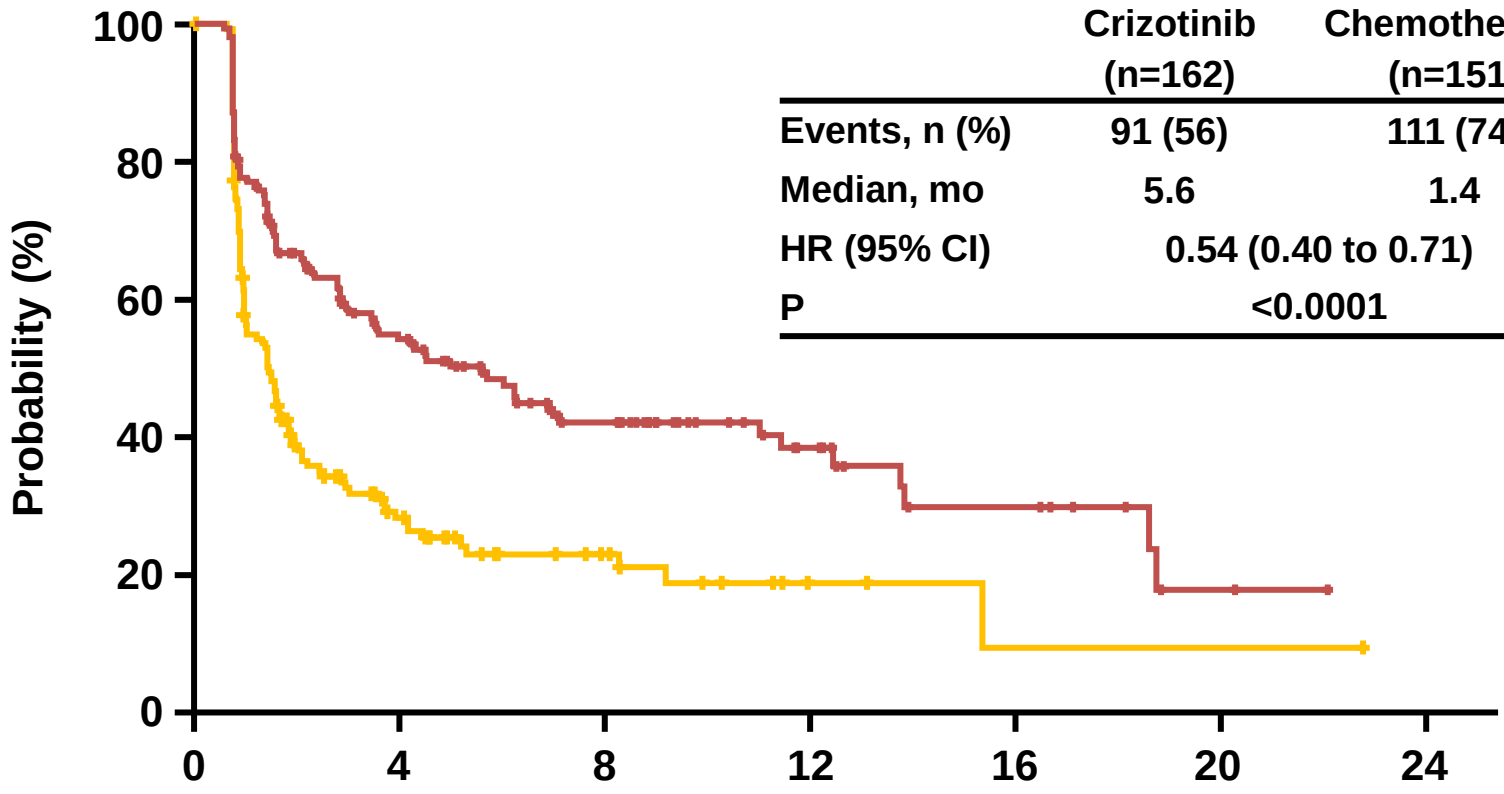
Crizotinib in ALK translocated NSCLC



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]

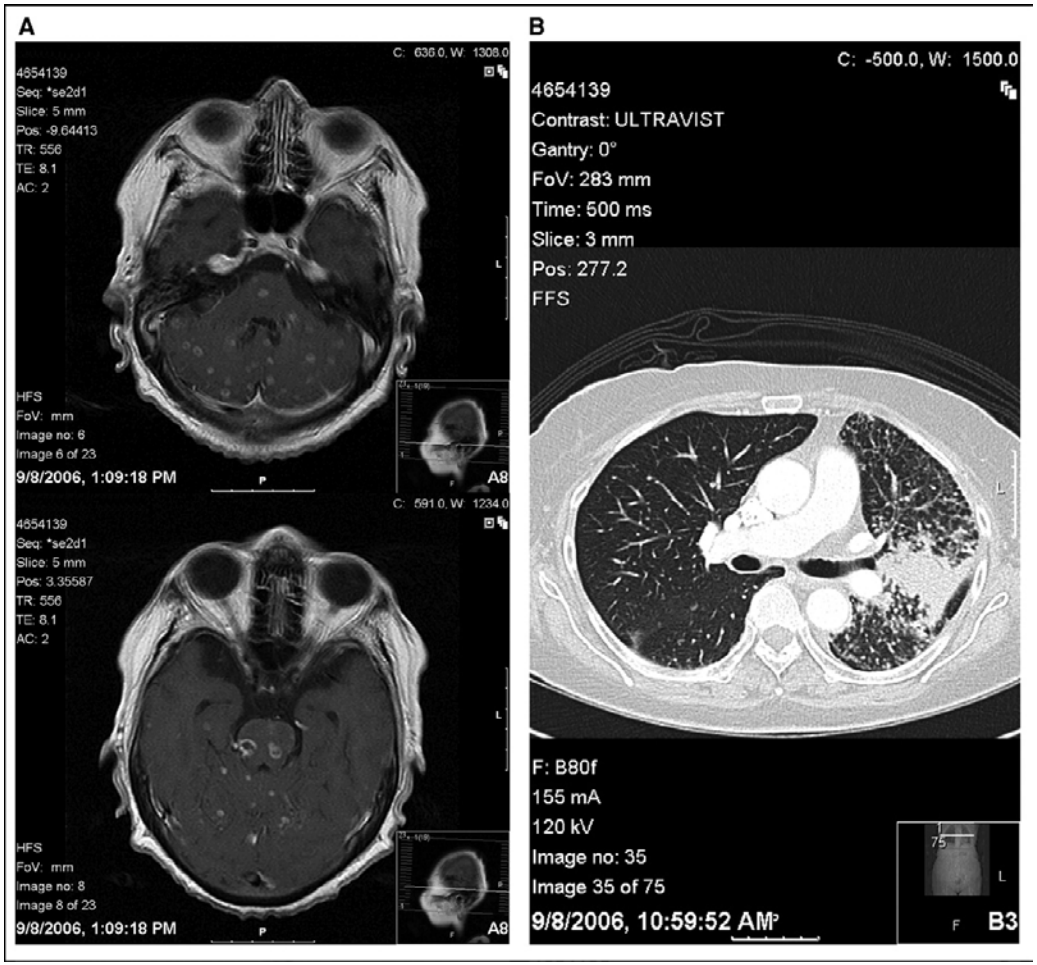


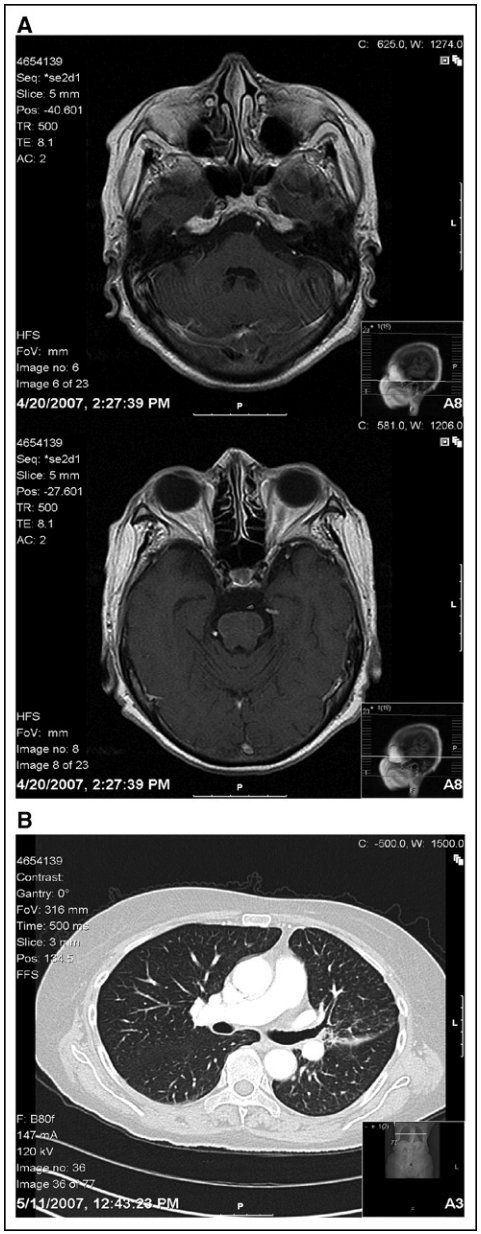
	Crizotinib (n=162)	Chemotherapy (n=151)
Events, n (%)	91 (56)	111 (74)
Median, mo	5.6	1.4
HR (95% CI)	0.54 (0.40 to 0.71)	
P	<0.0001	

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

Also active in brain metastases

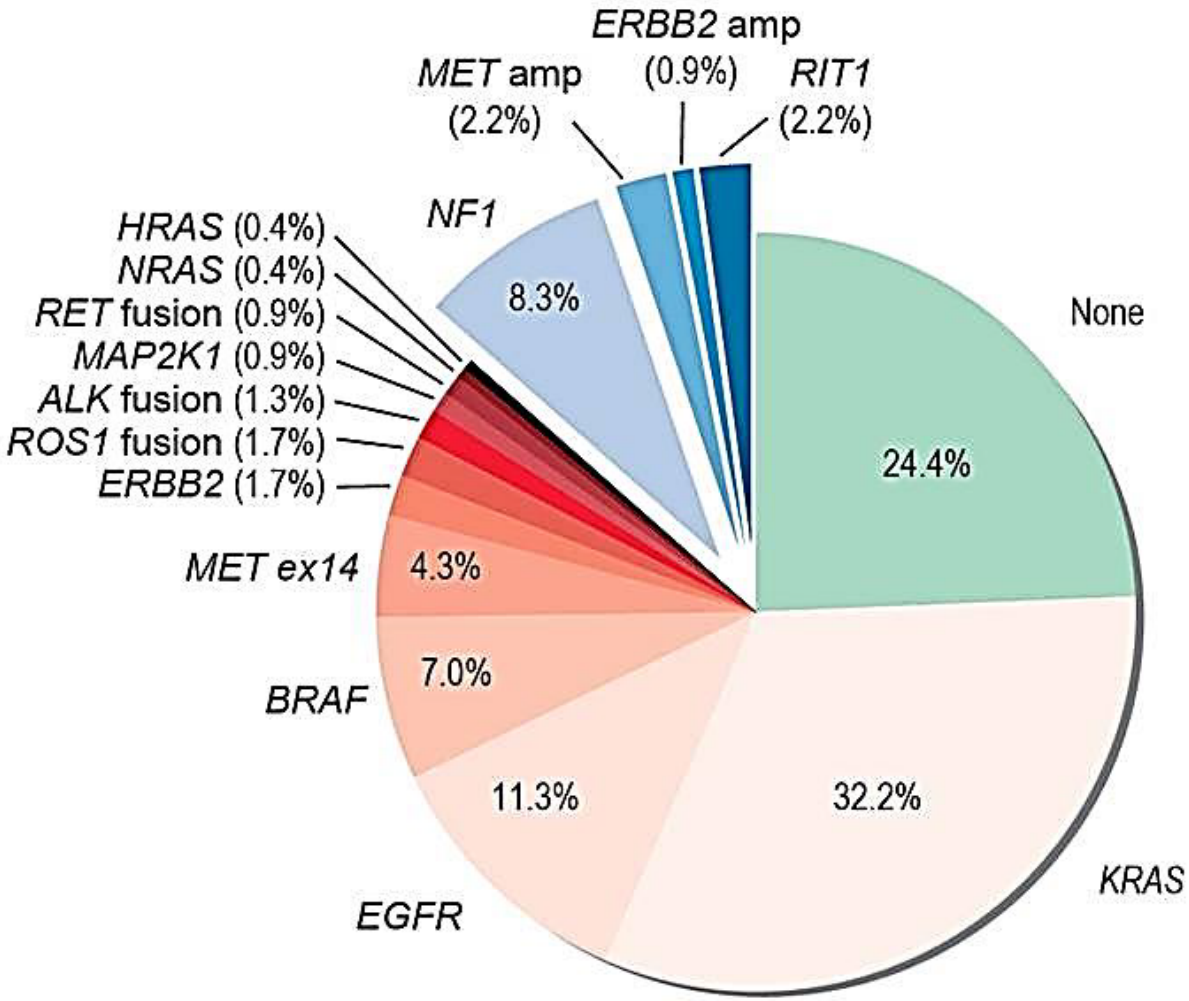




Response in 1 mth; 8+ mth

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

Many targets in lung cancer

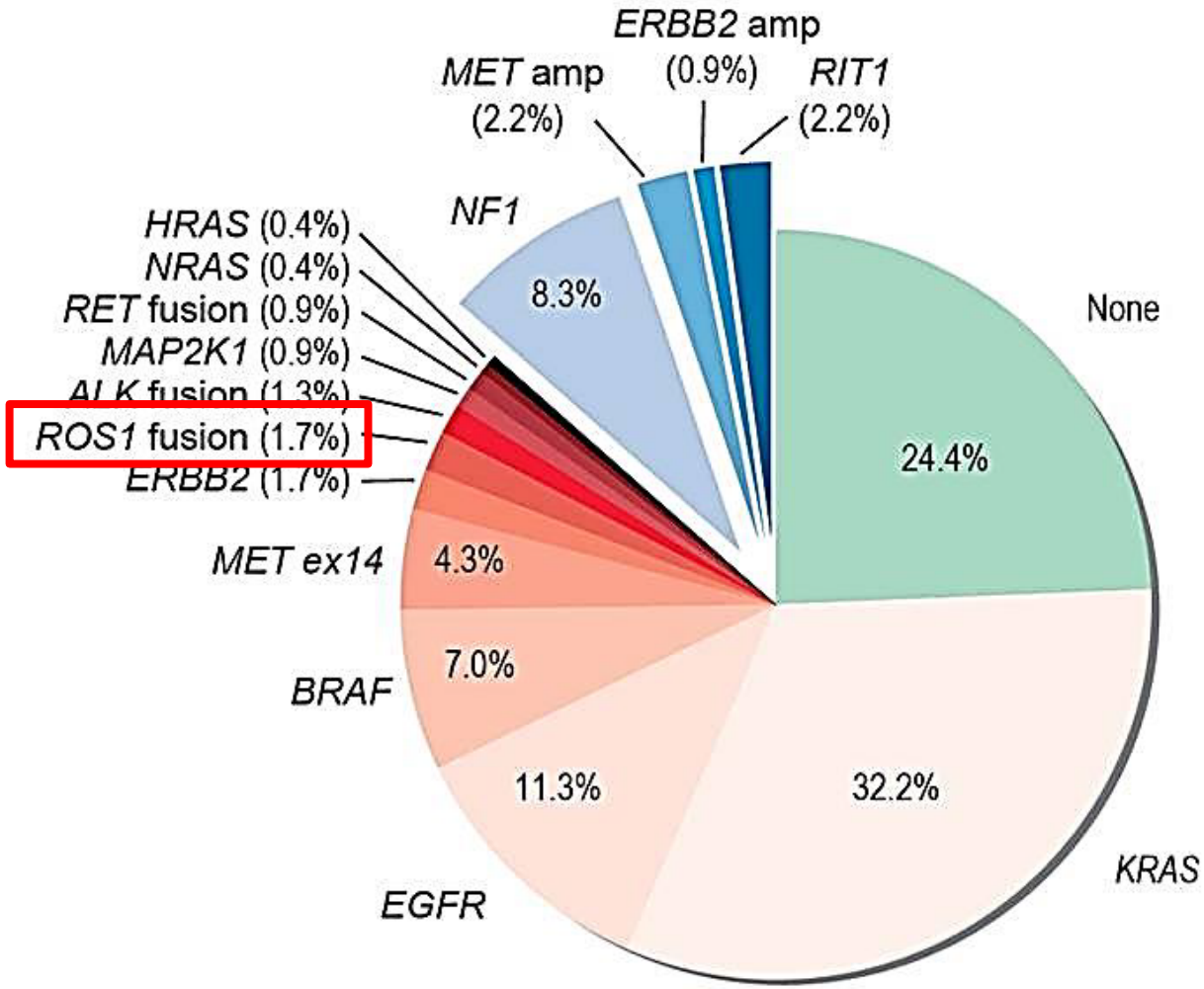


Memorial Sloan Kettering Cancer Center

TCGA Research Network

All targetable (routine or investigational)

Rare mutations



Memorial Sloan Kettering Cancer Center

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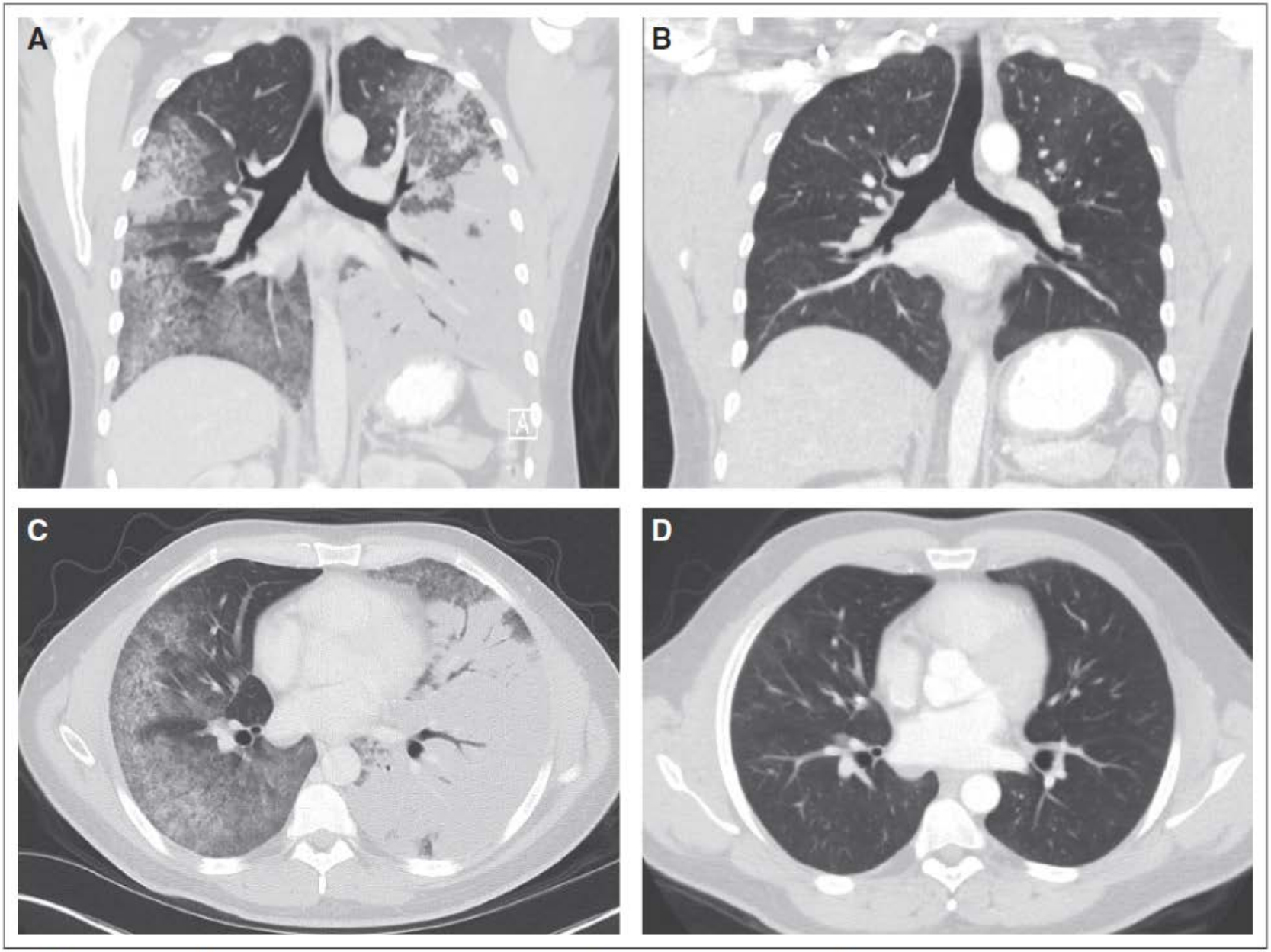
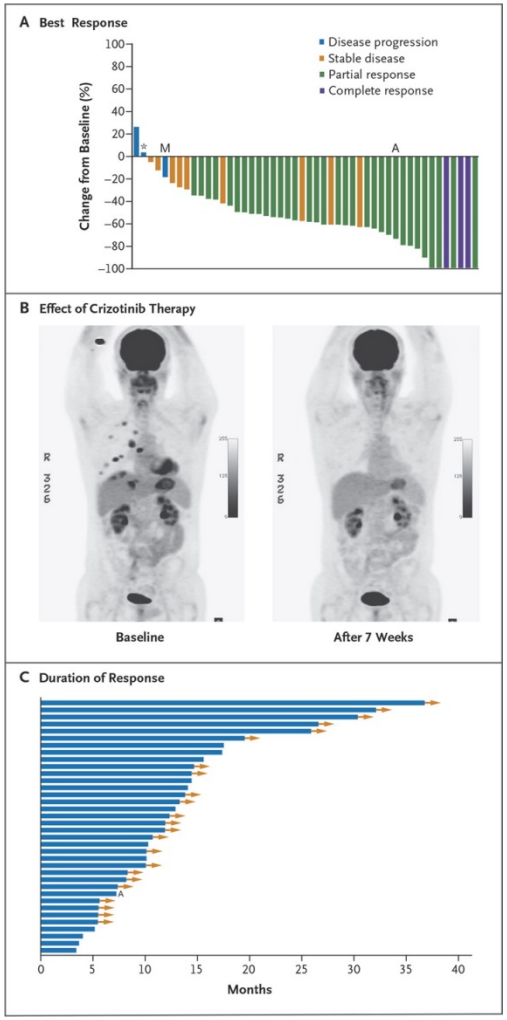


Fig 4. Response of an *ROS1*-positive patient with advanced non–small-cell lung cancer to crizotinib. Computed tomography scans of the chest were obtained (A and C) at baseline and (B and D) after 12 weeks of crizotinib. Shown are (A and B) coronal reconstructions and (C and D) axial slices.

Rare mutations respond as well



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

Same mutations also occur in children

Pediatric patients in trial

11 patients (7 boys)
Median age 9 y [3 – 16]

	n	molecular alterations
ALCL	2	2 ALK trans
Neuroblastoma	2	2 ALK mt
IMT	2	1 ALK trans, 1 ROS1 trans
High Grade Glioma	3	1 MET amp, 1 MET trans, 1 MET amp+trans
Mesothelioma	1	ALK trans
Atypical meningioma	1	ROS1 trans
Total	11	6 ALK+, 3 MET+, 2 ROS1

Disease characteristic	Total N=11 (%)
Primary tumor still in place at inclusion	
No	4 (40%)
Yes	6 (60%)
Missing or not applicable	1
Metastatic disease at inclusion	
No	6 (60%)
Yes	4 (40%)
Missing or not applicable	1
If Yes, (n=4)	
Time between metastatic diagnosis and inclusion (months)	
Median	25 (10 ; 37)
Number of Metastatic sites at inclusion	
2	2 (50%)
3	1 (25%)
4	1 (25%)

ALCL, anaplastic large cell lymphoma
IMT, inflammatory myofibroblastic tumor

Same mutations also occur in children

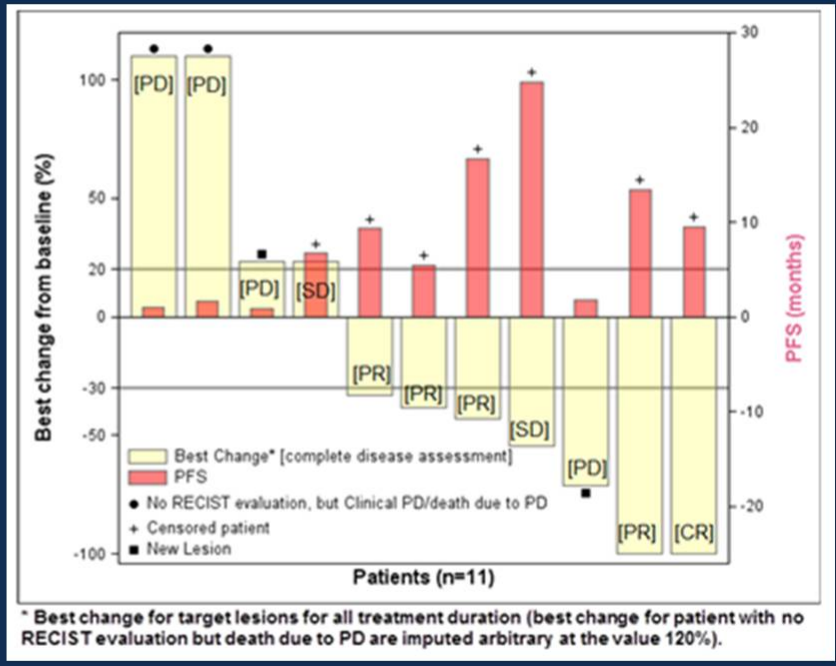
Efficacy: best response

1 CR, 4 PR, 2 SD, 4 PD

ORR = 5/11 ; 0,45 [0.17 – 0.77]

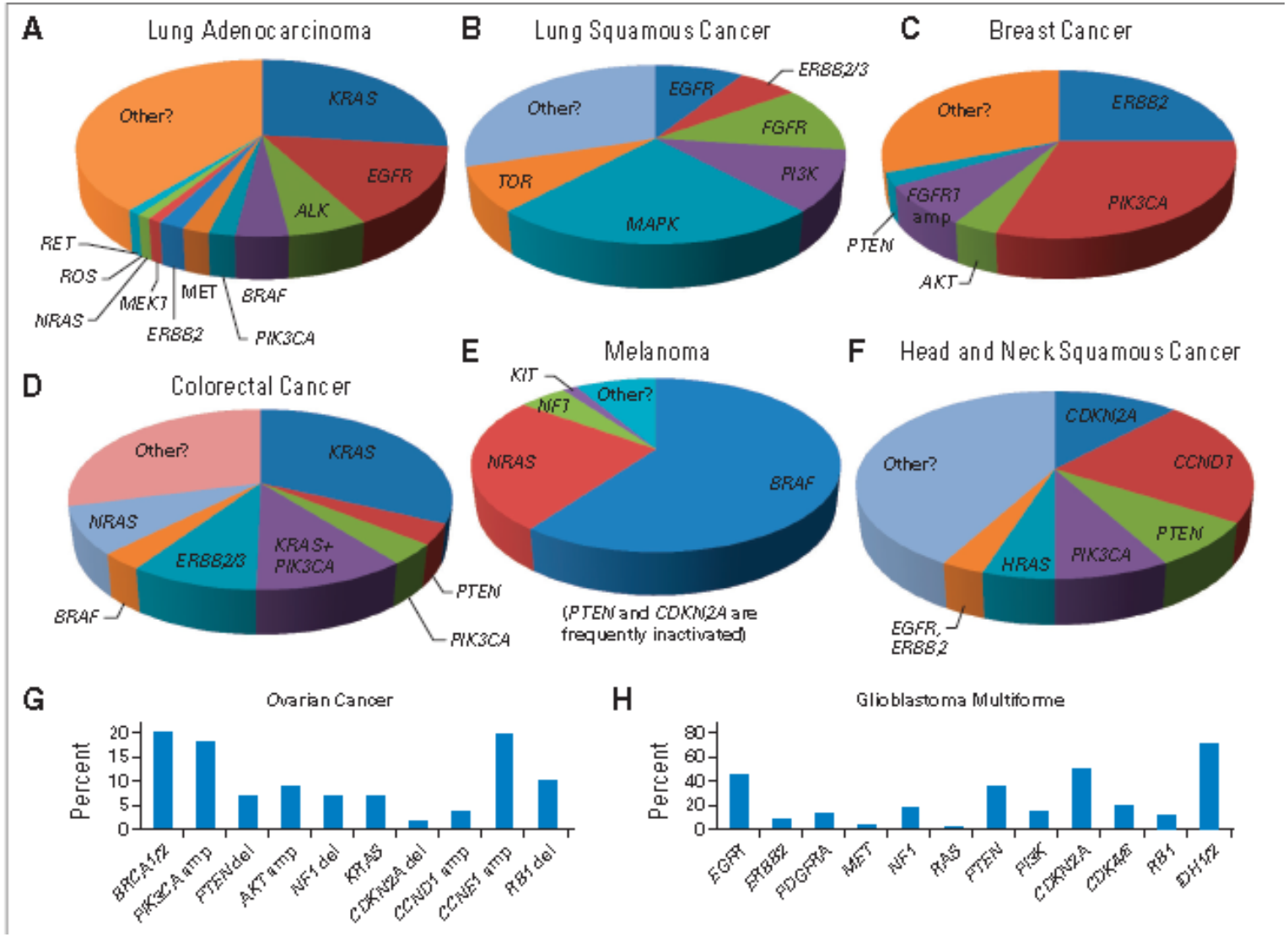
	Best response	PFS (months)
ALCL	CR	9.5+
ALCL	PR	13.4+
IMT ROS1 trans	PR	16.7+
IMT ALK trans	PR	5.5+
Meningioma ROS1 trans	PR	9.3+
Mesothelioma ALK trans	SD	24.8+
HGG MET trans+amp	SD	6.7+

5 patients are still on treatment



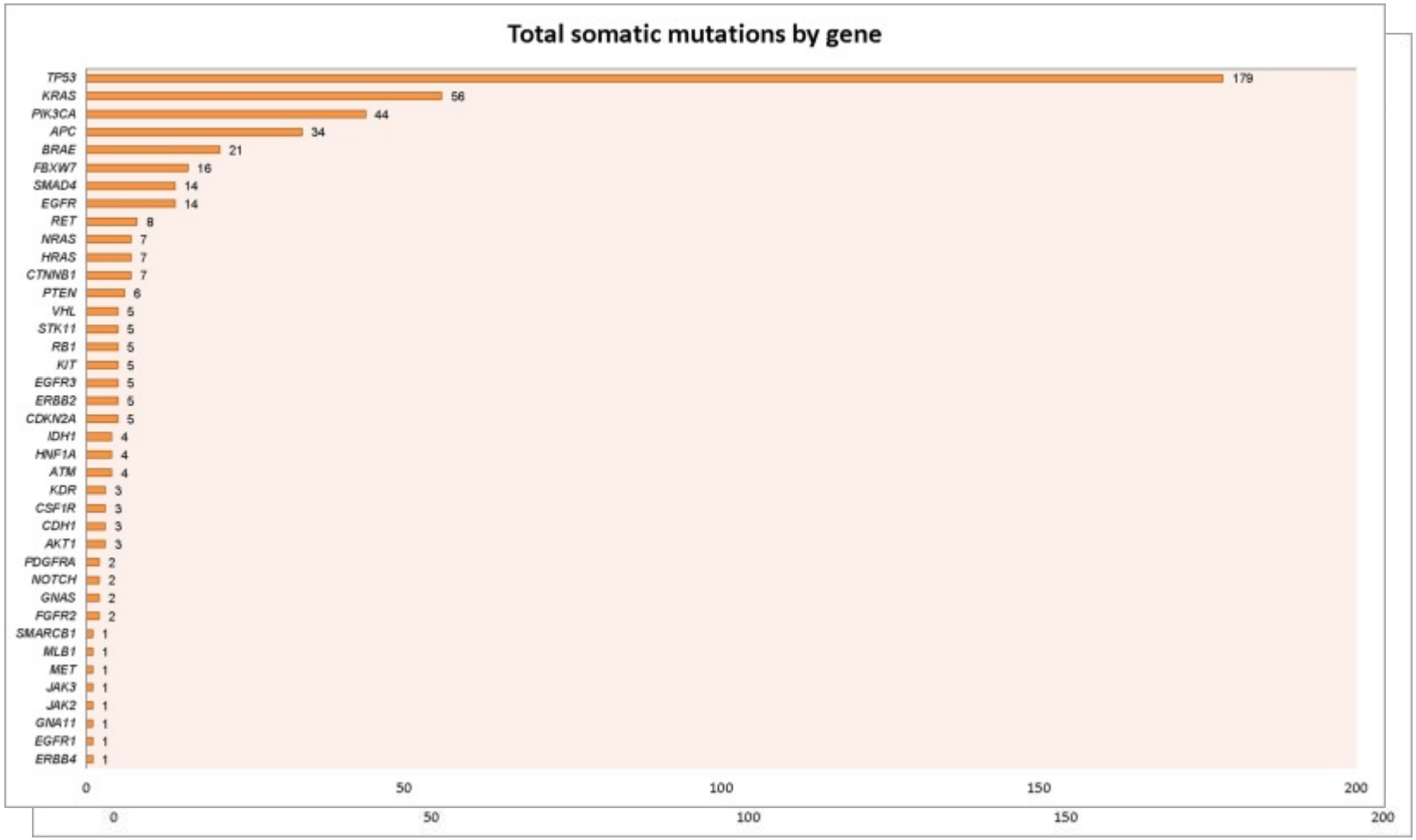
* Best change for target lesions for all treatment duration (best change for patient with no RECIST evaluation but death due to PD are imputed arbitrary at the value 120%).

Such actionable mutations are found in all cancer types



Garraway ASCO & JCO 2013

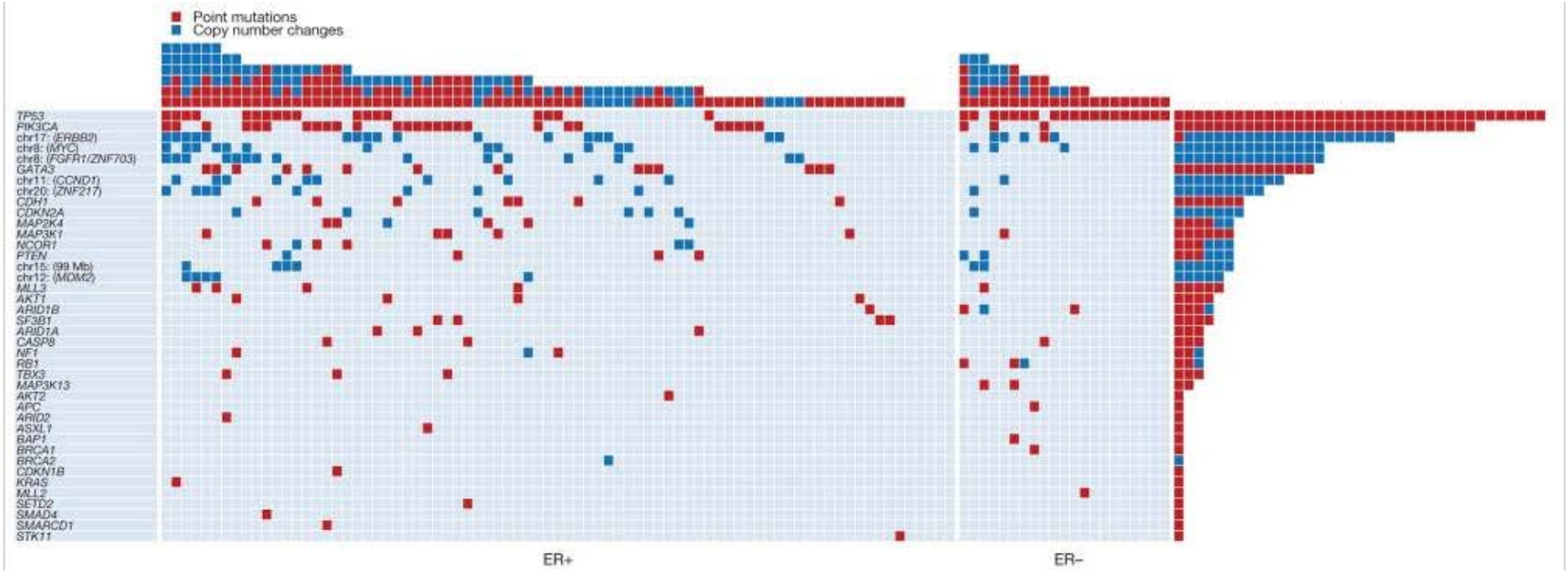
Actionable mutations are frequent or rare across cancer types



Boland, Oncotarget. 2015 Aug 21;6(24):20099-110

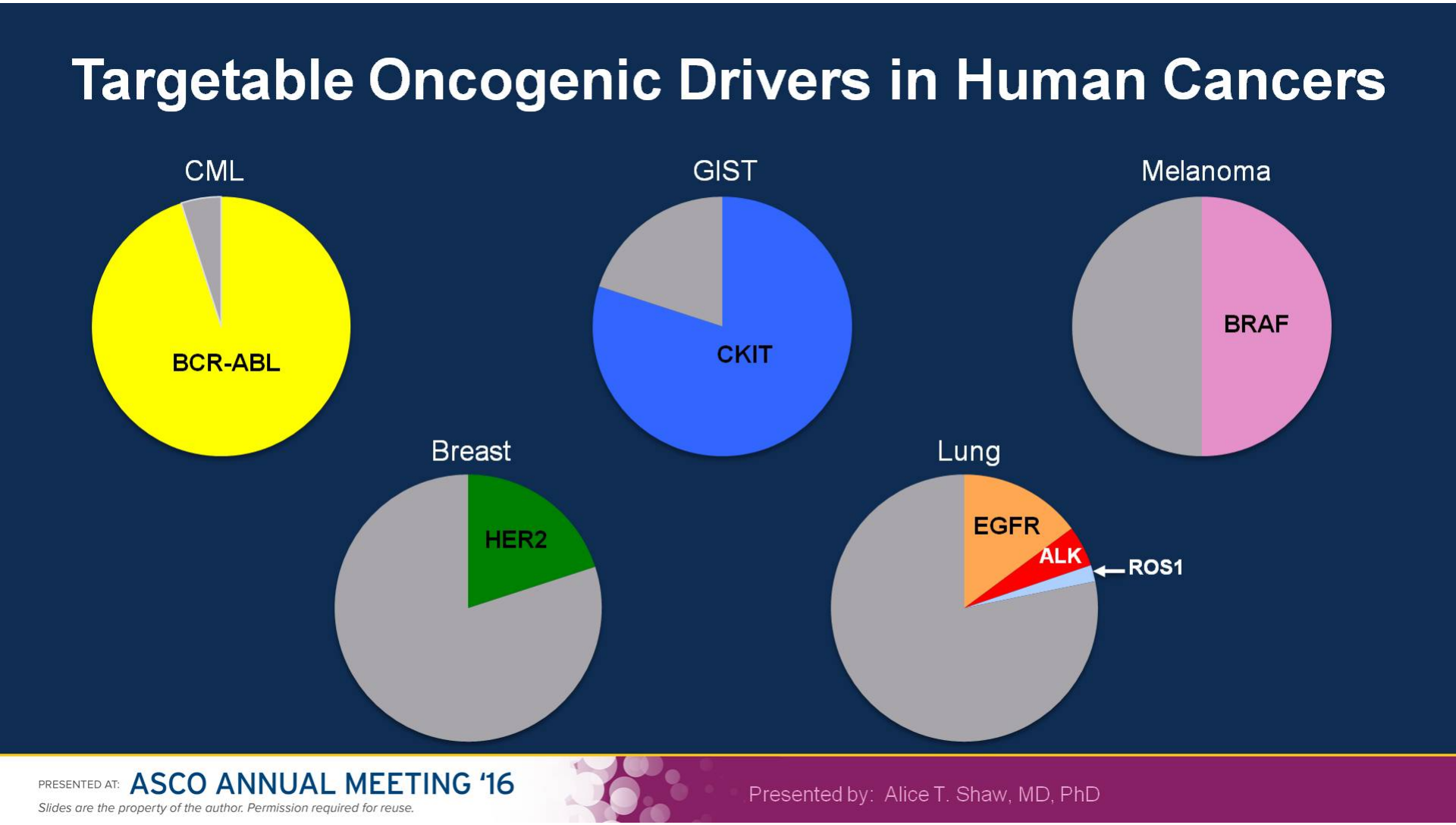
Actionable mutations are frequent or rare in frequent cancers

breast cancer



Stephens, Nature 2012

Currently approved major targeted therapies



Presented By Alice Shaw at 2016 ASCO Annual Meeting

Many more genes are currently actionable

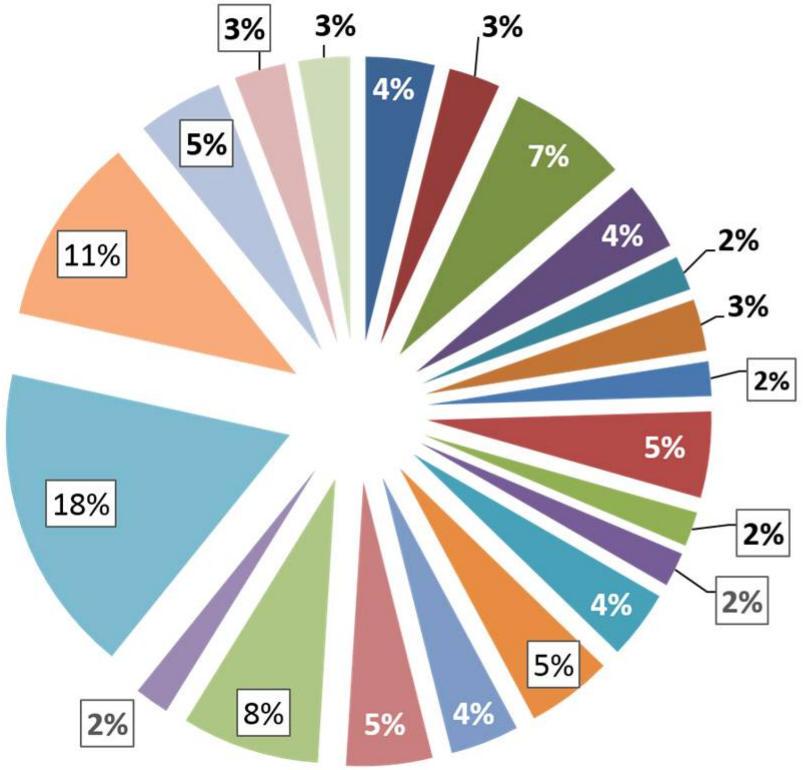
Drug	Molecular Aberration
Afatinib	EGFR Activating Mutations
Afatinib	HER2 Activating Mutations
AZD9291	EGFR Mutations (T790M/Rare Activating)
Crizotinib	ALK Translocations
Crizotinib	ROS1 Translocations
Dabrafenib and Trametinib	BRAF V600K/V600E Mutations
GDC-0032 (taselisib)	PIK3CA Mutations
GSK2636771	PTEN Mutation or Deletion w/ PTEN Expression on IHC
GSK2636771	PTEN Loss by IHC
T-DM1	HER2 Amplification
Trametinib	BRAF Fusions or non-V600K/non-V600E Mutations
Trametinib	NF1 Mutations
Trametinib	GNAQ/GNA11 Mutations
Vismodegib	SMO/PTCH1 Mutations
Defactinib	NF2 Loss
Sunitinib	cKIT Mutations
Dasatinib	DDR2 Mutations
Crizotinib	MET Amplification
Crizotinib	Exon 14 Skipping
AZD4547	FGFR Fusions, Mutations, and Amplifications
AZD5363	AKT Mutations
Binimetinib	NRAS Mutations Awaiting CRADA.
Palbociclib	CCND1,2,3 Amplification(and Rb protein expression by IHC)
Nivolumab	MMR deficiency (IHC: MLH1, MSH2

24 genes

Presented By Lillian Siu at 2016 ASCO Annual Meeting

Many more genes are actionable

Actionable Mutations of Interest in NCI-MATCH and Estimated Prevalence



aMOIs (actionable mutations of interest):

- ALK translocations - (4%)
- BRAF fusions or non-V600E, non-V600K mutations - (2.79%)
- BRAF V600E or V600K - (1-12%)
- cKIT mutations - (4%)
- DDR2 mutations - (2%)
- EGFR activating mutations - (1-4%)
- EGFR T790M mutations - (1-2%)
- FGFR amplifications or FGFR mutations - (5%)
- GNA11 mutations - (1.6%)
- GNAQ mutations - (2%)
- HER2 activating mutations - (2-5%)
- HER2 amplifications - (5%)
- MET amplifications - (4%)
- mTOR mutations - (5%)
- NF1 mutations - (7.7%)
- NF2 loss - (2%)
- PIK3CA mutations or amplifications - (17-18%)
- PTEN mutations or deletions - (11%)
- ROS1 translocations - (5%)
- SMO or PTCH1 mutations - (2.63 and 3.76%)
- TSC1 or TSC2 mutations - (2.6-3.5%)

Courtesy Barbara Conley

reopened in May 2016 with a total of 24 treatment arms. Each arm expects to enroll a maximum of 35 patients

NCI-**M**olecular **A**nalysis for **T**herapy **Ch**oice

https://www.cancer.gov/about-cancer/treatment/clinical-trials/nci-supported/nci-match

Why Precision ?

- Targeted drugs follow a path of development addressing most frequent **genotype-cancer type** associations and **are registered and marketed** in these indications
  - In rare cancers if homogeneously mutated

- The **same actionable mutations can occur in any cancer type**, not just in the registered cancer type

- **Rare mutations or rare cancer type-genotype** associations do not enter a development path easily

- Although there is a **high plausibility that the same drugs will work in these off-label indications**, the patients concerned remain without access to these treatments for a very long time (years)

Precision Belgium components

- **Implementing gene panel sequencing**
  - Ongoing evaluation of NEXTgen platforms
  - Sequencing all established and emerging actionable genes
  - Cancer Centre > RIZIV/INAMI
- **Establish national real-time shared database**
  - Clinical data
  - Genomic data

  } **Healthdata**
  - Connected to e-health and Cancer Registry
  - Accessible to all investigators/oncologists

- **Precision 1**
  - Investigate benefits of approach
  - **Interinstitutional Molecular tumor board**
- **Precision 2**
  - Establish **new evidence on efficacy in specific genotype-cancer type associations**

Philippe Aftimos

Lore Decoster

NGS part

- Cancers systematically sequenced
- Consensus gene panel (Compermed)
- National database healthdata
  - Storage of anonymous information
  - Sequencing results: stored as VCF files
  - Clinical data
- Automated upload from centers

Gene panel proposition

Tumor types	Nomenclature (example)	Gene panels		
		Tumor specific gene panels		ComPerMed gene panel
Tumor A	300.1	Gene 1 Gene 2 Gene 3	OR	Gene 1 Gene 2 Gene 3 Gene 4 Gene 5 Gene 6 Gene 7 Gene 8 Gene 9 Gene 10
Tumor B	300.2	Gene 4 Gene 5		
Tumor C	300.3	Gene 4 Gene 3 Gene 6 Gene 7		
Tumor D	300.4	Gene 5 Gene 8 Gene 9 Gene 10		

Laboratory can choose to use either a tumor specific gene panel or the ComPerMed gene panel. The ComPerMed gene panel contains all the genes included in the different tumor specific gene panels.

1. Genes which **MUST be** analyzed for the analyzed tumor: (level 1 & 2)

2. Laboratories **are allowed** to analyze more genes

3. Laboratories are allowed to use **either**:
(a) A tumor specific gene panel **or**
(b) The ComPerMed gene panel

4. For the reimbursement:
(a) If < xx kb (calculated on the basis of the minimal set of genes for the analyzed tumor (level 1&2) → amount to be discussed (INAMI/RIZIV)
(b) If > xx kb (calculated on the basis of the minimal set of genes for the analyzed tumor (level 1&2)
OR the ComPerMed gene panel
→ Reimbursement higher than (a) → amount to be discussed (INAMI/RIZIV)

NB: If laboratories add more genes than those which are present in the ComPerMed gene panel, these will not be reimbursed.

Dr Aline Herbrant
Cancer center

One gene panel that covers all actionable mutations (established, emerging) in all cancers should be strongly favored

- Currently only 24 genes
- Not that more expensive than tumor-specific panels
- Identification of rare mutations
- Avoids resequencing[2] efforts
  - Not timely for the patient
  - Added cost
  - Cfr. germline management
- **Precision Belgium impossible without the comprehensive panel**
- **Budgetary concerns to be relativized:**
  - **10K pts x 500€ = 5.000K€**
  - **Pembrolizumab in first -line lung cancer: 30-50,000K€ (modest estimate)**

Actionable mutation identified

1. Eligible for registered/marketed drug

2. Eligible for ongoing pharma-sponsored trial

   Precision 1

3. Creation of multicohort basket trials
   1. **Precision 2**
   2. Open in each centre > ease of patient access

Multicohort basket trials

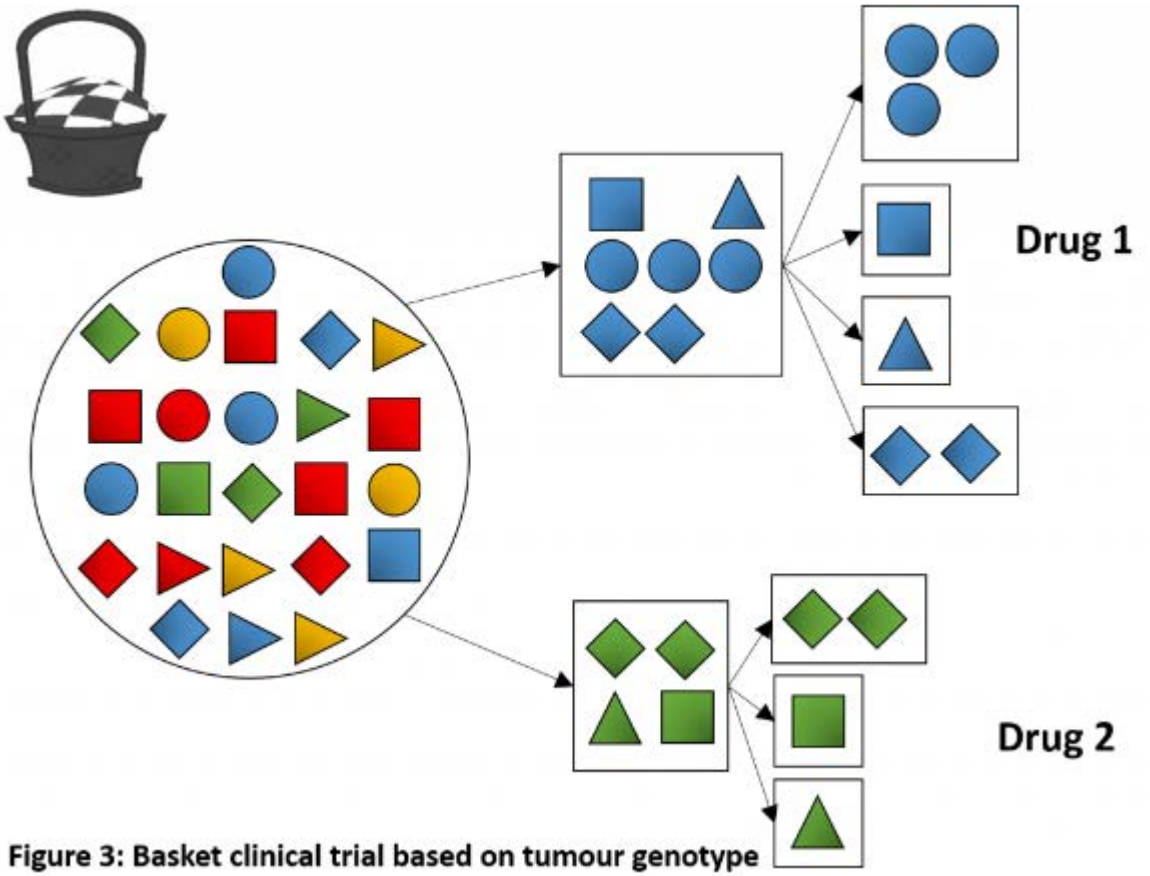
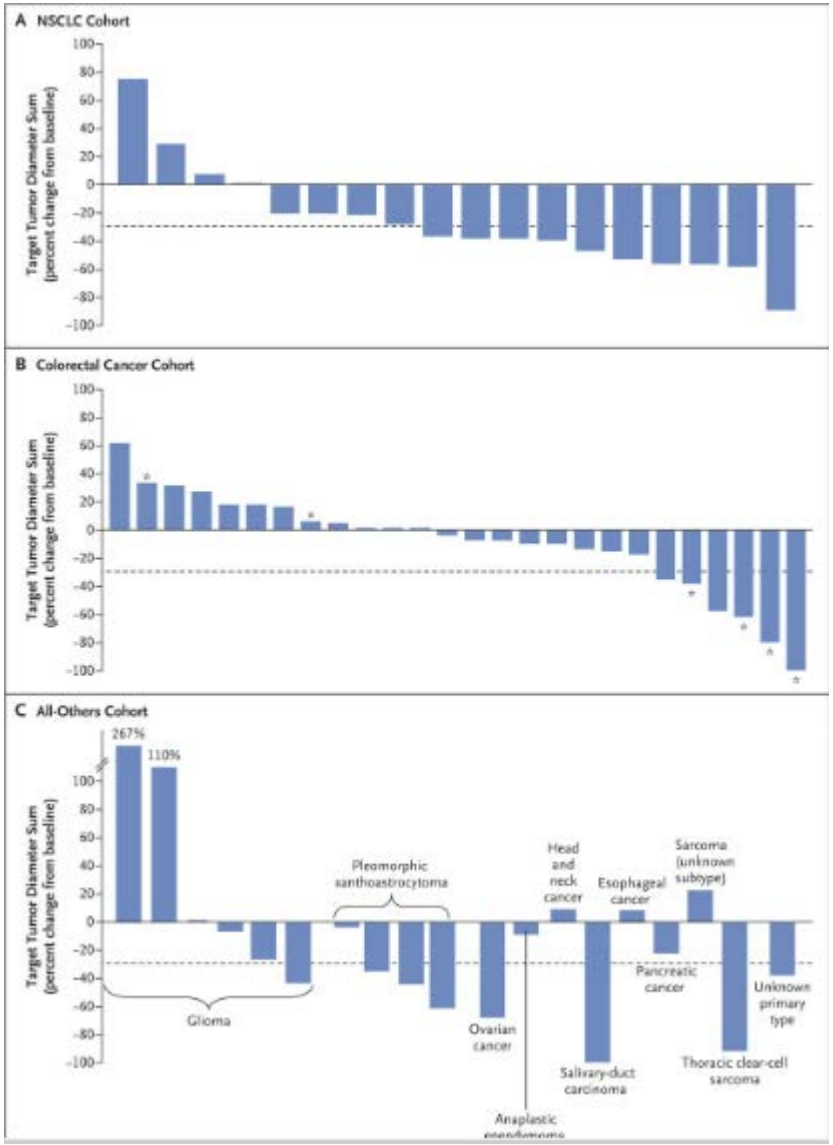


Figure 3: Basket clinical trial based on tumour genotype

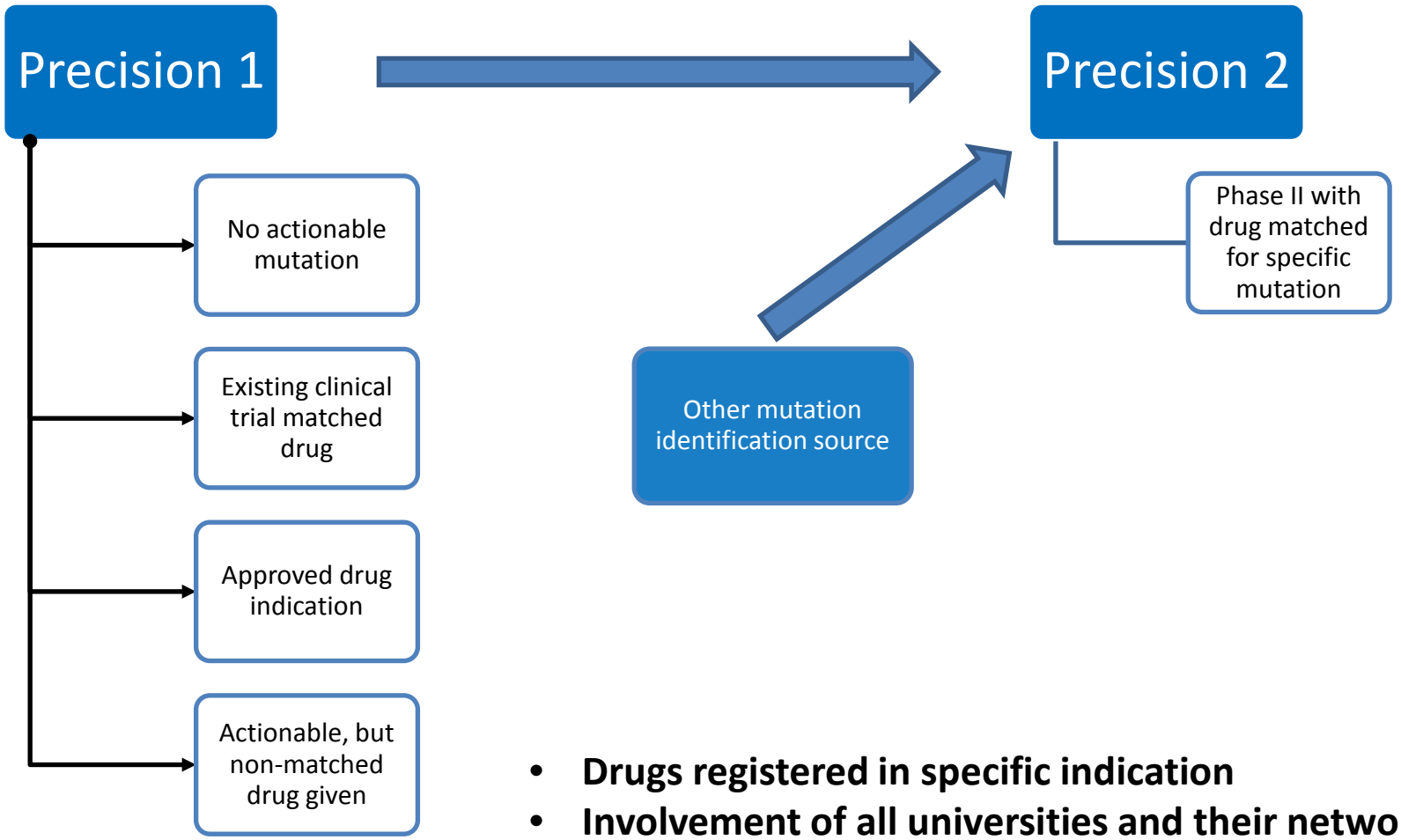
Source: http://www.bhdsyndrome.org/forum/bhd-research-blog/genetic-sequencing-approaches-to-cancer-clinical-trials

Basket trial can demonstrate activity in off-label indications



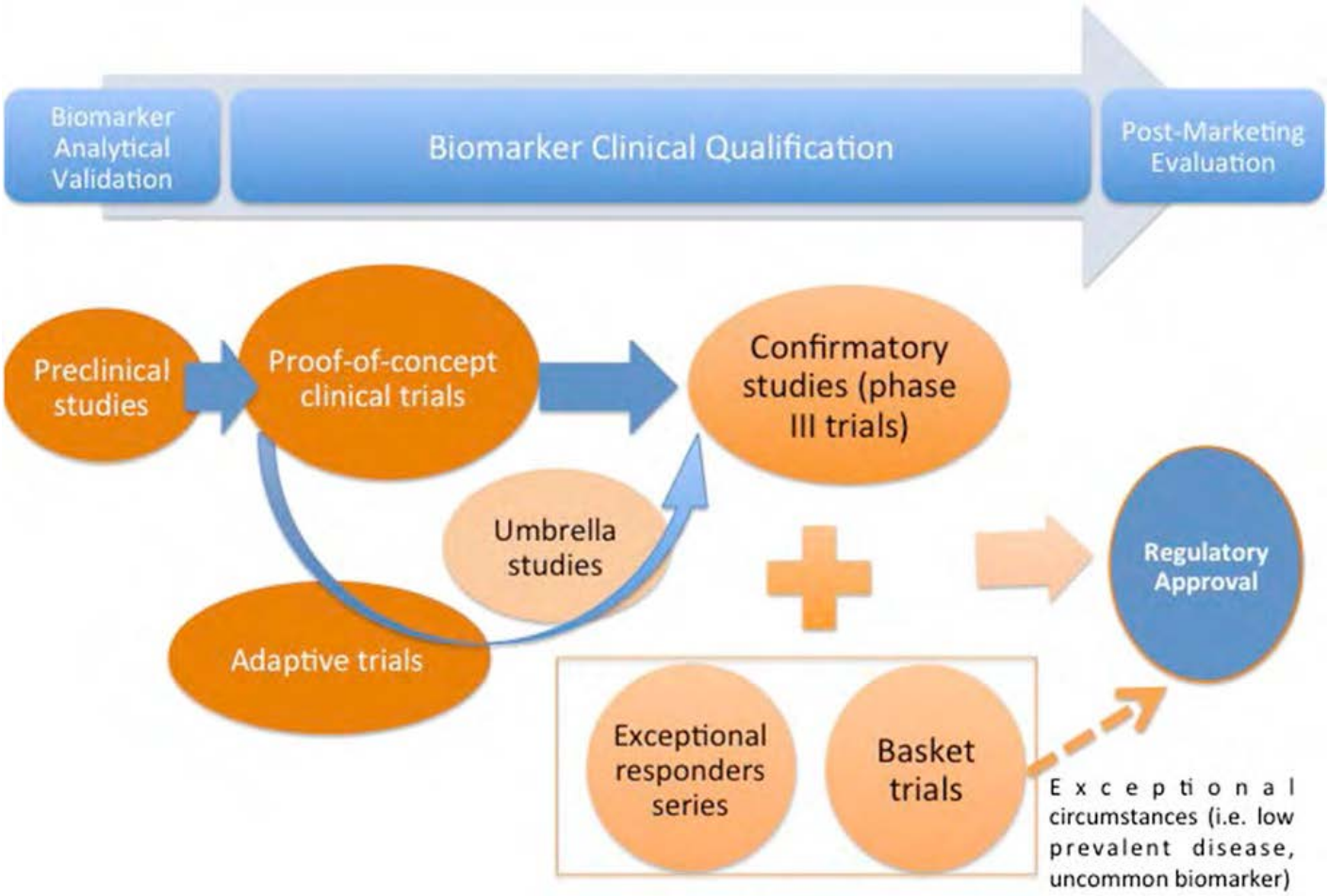
Heyman et al n engl j med 373;8 August 20, 2015

Precision Belgium



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

Clinical Trials in the Era of Genomics and Personalized Medicine



Mateo, ASCO edu 2016

Examples of precision 2 studies in process of activation

- **Afatinib in HER1,2 or 3 mutations in any cancer type**
  - **Boehringer Ingelheim**
  - **Activation ongoing**
- **Imatinib in KIT, PDGFR, bcr-abl mutated cancers**
  - **Novartis**
  - **In negotiation**
- **Olaparib in cancers with HRD gene mutations**
  - **Astrazeneca**
  - **In development**
- **Dabrafenib/Trametinib in non-V600 BRAF mutant cancers**
  - **Novartis**
  - **In negotiation**
- **Other trials in development**

Precision 2: an open explorative phase 2, open label study on afatinib in the treatment of advanced cancer carrying an EGFR, HER2 or HER3 mutation

Study objectives

- Primary:
  - Response rate on afatinib in cancers harboring an EGFR mutation, a HER2 mutation or a HER3 mutation
- Secondary:
  - Disease control rate
  - PFS and OS
  - Safety
  - To study resistance mechanisms
  - Response and PFS on the combination of afatinib and paclitaxel after progression on afatinib

Main in- and exclusion criteria

- Histologically confirmed advanced cancer harbouring an EGFR, HER2 or HER3 mutation
- Failure of at least one previous line of standard treatment
  - No restriction to the number of previous lines
- No other genomic driven trial for the specific tumor type or patient not eligible
- Age ≥18
- ECOG PS ≤2
- Life expectancy > 3 months
- Adequate organ function
- Measurable lesion
- No EGFR mutant non squamous NSCLC

Treatment

- Treatment period 1
  - All patients treated with afatinib until progression, unacceptable toxicity or withdrawal of consent
- At progression
  - Preferable rebiopsy to study resistance mechanisms
  - Fulfill all eligibility criteria for treatment period 2
- Treatment period 2
  - All patients treated with afatinib in combination with paclitaxel weekly until progression, unacceptable toxicity or withdrawal of consent

Deliverables of Precision

- Large genotype-tumor type cohorts
  - Create evidence for drug registration
- Small genotype-tumor type cohorts
  - > pool evidence with similar international efforts
- Create a platform for scientific collaboration
  - Also fundamental research
- Systematic sequencing makes our population more attractive for pharma-sponsored trials

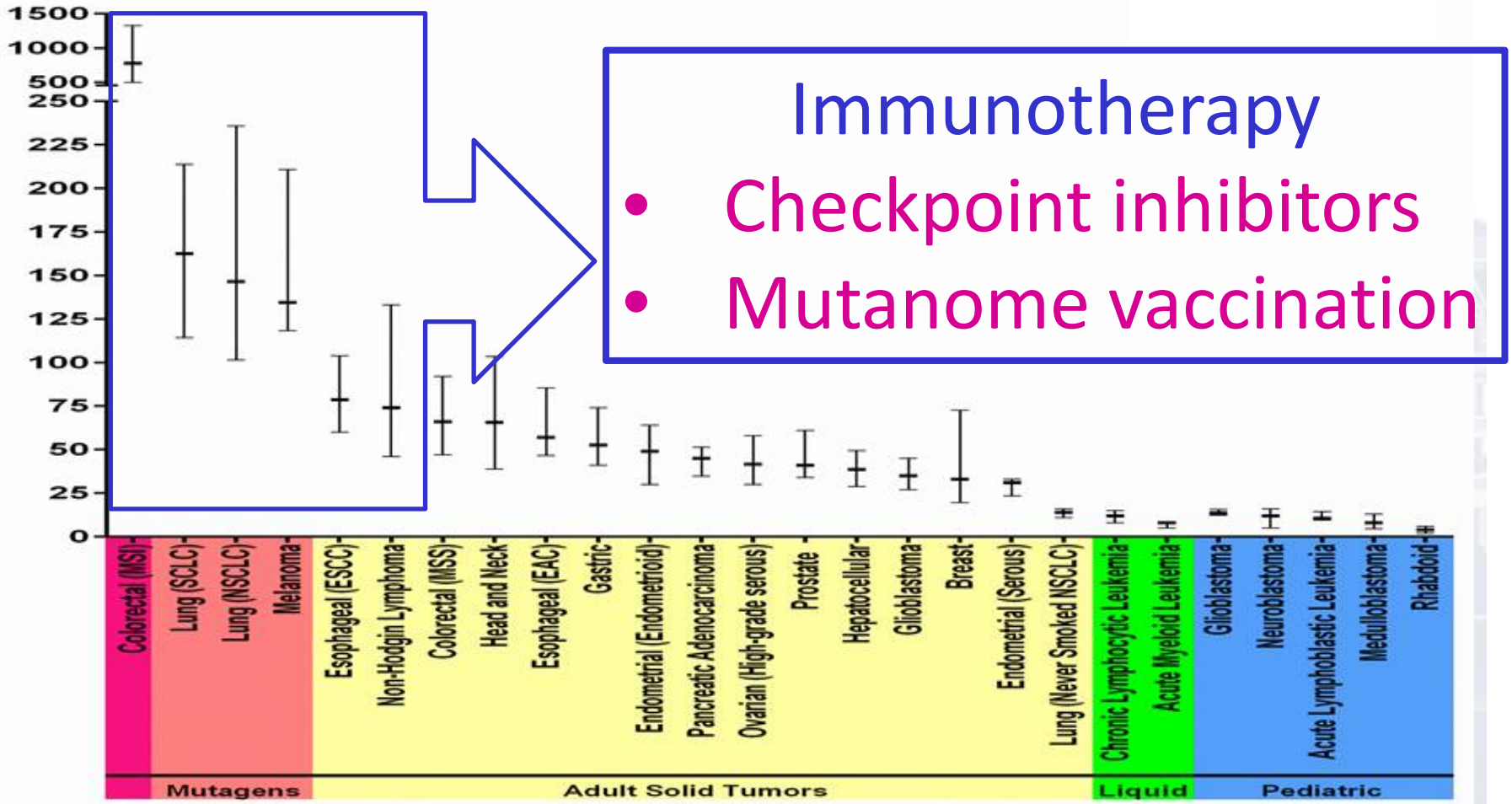
Advantages for all stakeholders

- Patients
  - Access to additional therapeutic options
- Pharma
  - Access to new evidence created on off-label drug activity
- Research
  - Broad cooperation will generate a platform on which more fundamental projects can be grafted

Other applications of sequencing

- Determine sensitivity/resistance to classical therapies
  - Olaparib: targeted agent and chemotherapy
  - Hormonal therapy breast cancer
    - ESR1 mutations
- Sequencing of circulating tumor DNA
  - Following disease response easily
  - Early detection of cancer
  - Selection for immunotherapies

Cancers with high mutation rate



Acknowledgements

- BSMO initiative
- Seven University Medical Oncology departments and their networks
  - Including pediatric oncology and hematology
  - Including Luxemburg
- Supported by the Foundation against cancer
- In collaboration with the Cancer Centre
  - Maggie De Block investment in sequencing
- In collaboration with pharma (drugs)

Current infrastructure

- Coordinator
- Part-time datamanagers in each university and its network
- Cancer Centre support

Precision executive committee

- Roberto Salgado 
- Lore Decoster, Philippe Aftimos
- Marc Vanden Bulcke (Cancer Centre)
- Jacques De Grève (BSMO)

Precision steering committee

- Ahmad Awada - Bordet
- Philippe Aftimos – Precision 1
- Cauwelier Barbara – Hemato-oncology
- Guy Berchem – CH Luxembourg
- Joelle Collignon - CHU Liege
- Lore Decoster – Precision 2
- Jacques De Grève – UZ Brussel, Precision Chair
- Francois Duhoux - UC Louvain
- Sandra Jacobs - Pediatric oncology
- Kevin Punie- KU Leuven
- Christian Rolfo - UZ Antwerpen
- Sylvie Rottey – UZ Gent
- Roberto Salgado –Molecular pathology
- Marc Van den Bulcke - Cancer Centre
- Didier Vandersteichele - STK/FCC