I SIMPOSIO NACIONAL de ONCOLOGÍA de PRECISIÓN

Vigo, del **28** de **febrero** al **1** de **marzo** de **2019**

Estrategia Nacional de Medicina de Precisión

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Disclosure of interest

Consulting and advisory services:

Roche, MSD, BMS, Boerhinger Ingelheim, Pfizer, Abbvie, Guardant Health, Novartis, Lilly, Astra-Zeneca, Jansen, Sysmex, Blueprint Medicines, Takeda.

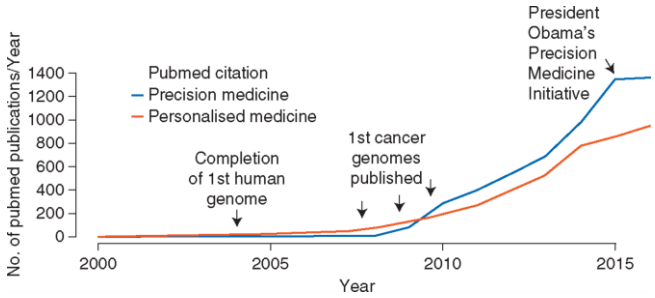
Speaking and public presentations:

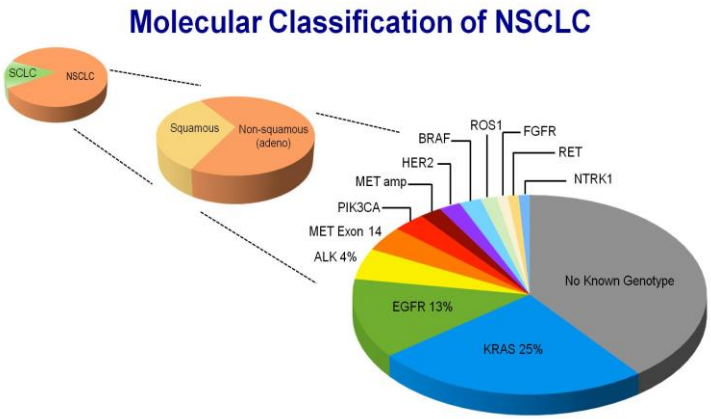
Roche, MSD, BMS, Pfizer, Novartis, BI, Rovi

PRECISION MEDICINE DEFINITION

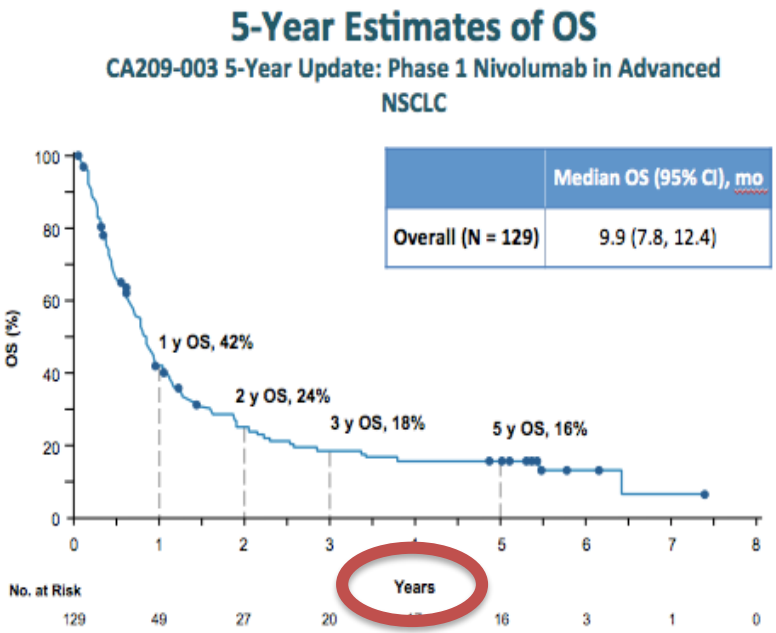
- Although the term "precision medicine" is relatively new, the concept has been a part of healthcare for many years.
- According to the Precision Medicine Initiative (NIH), precision medicine is "an emerging approach for disease treatment and prevention that takes into account individual variability in genes, environment, and lifestyle for each person."

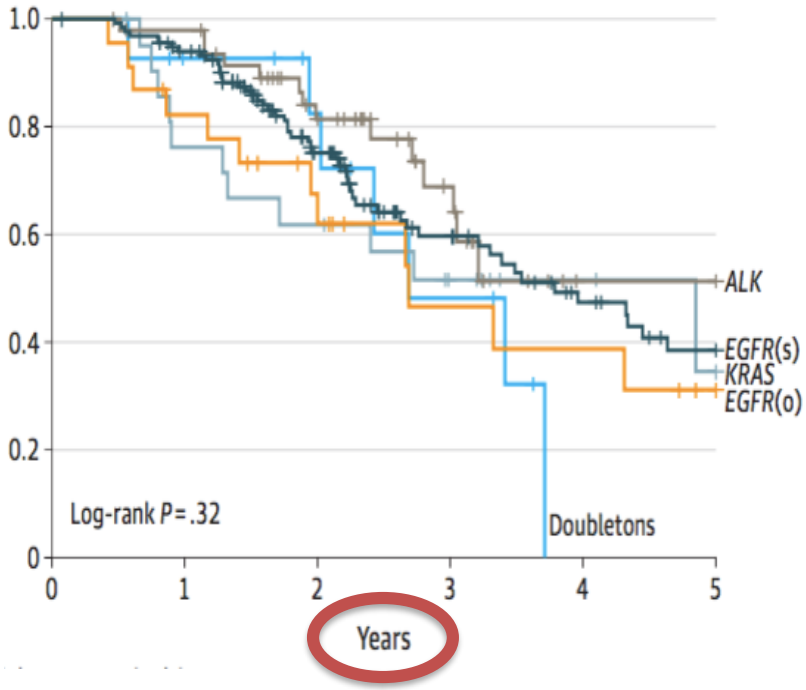
"The right drug for the righ patient at the right time"





Precision medicine is a fact in lung cancer!!!



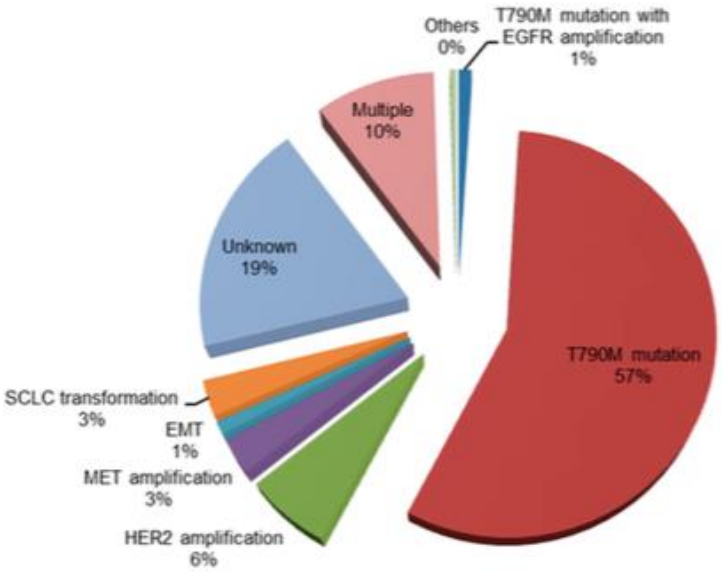


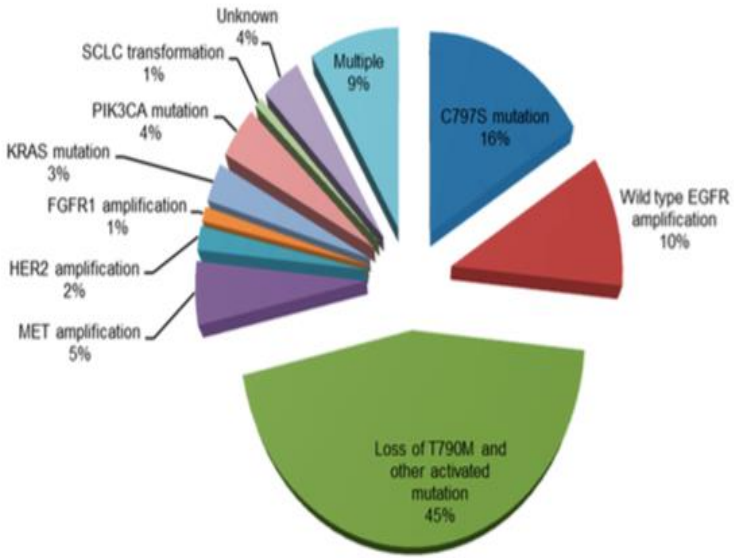
RIGHT DRUGS: ESTABLISH TARGETS

EGFR Mutations

- Found in 10% to 30% of NSCLC patients.
- Predominantly located in *EGFR* exons 18-21
- Specific *EGFR* mutation identified is important
  - There are sensitive mutations, primary resistance mutations (often exon 20), and acquired resistance mutations (T790M)
- We have first, second and third generation approved agents.

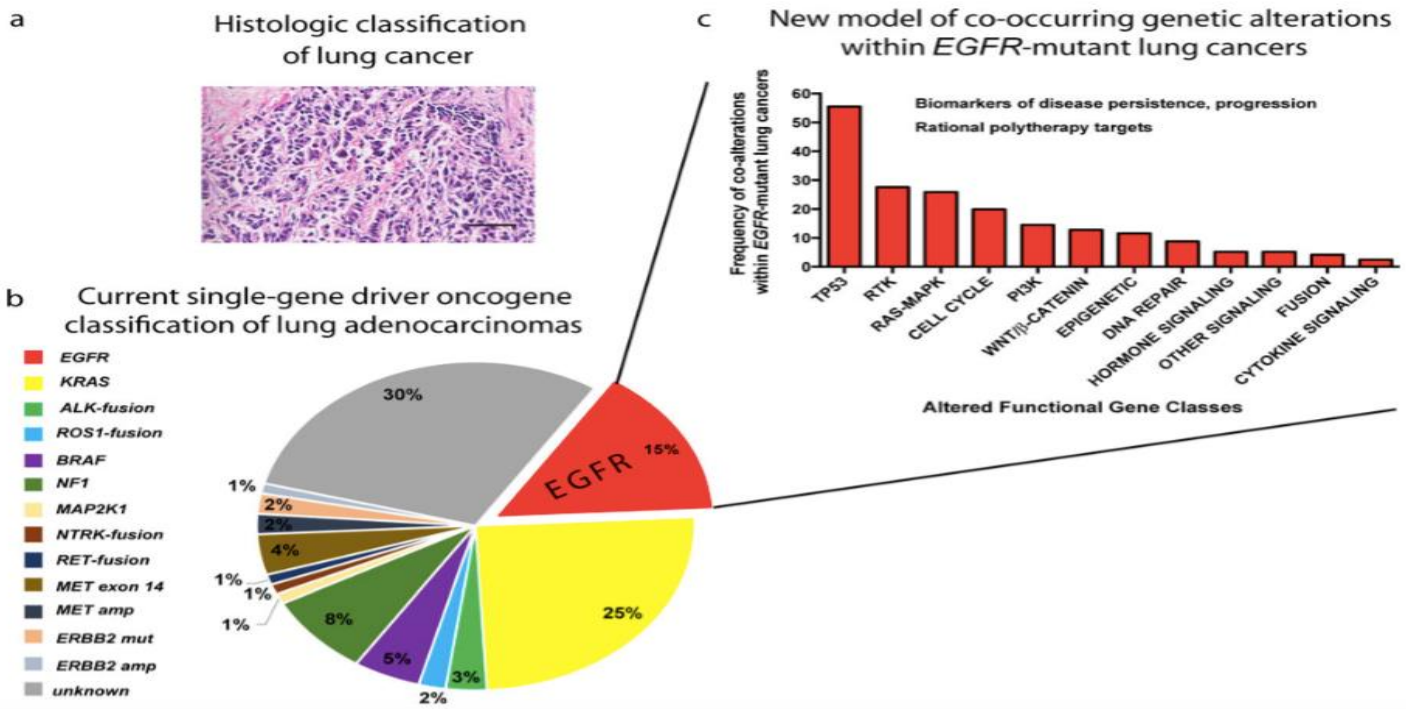
Acquired resistance mechanisms
1st vs 3rd Generation EGFR TKI





1.Ramalingam SS, et al. J Clin Oncol. 2018; 2. Minari T et al. JTO 2018 [Epub ahead of print; 3. Yu HA, et al. Clin Cancer Res. 2013;19(8):2240-2247;

Co-occurring genetics alterations



Blakely, Nat Genet 2017

ALK Gene Rearrangements

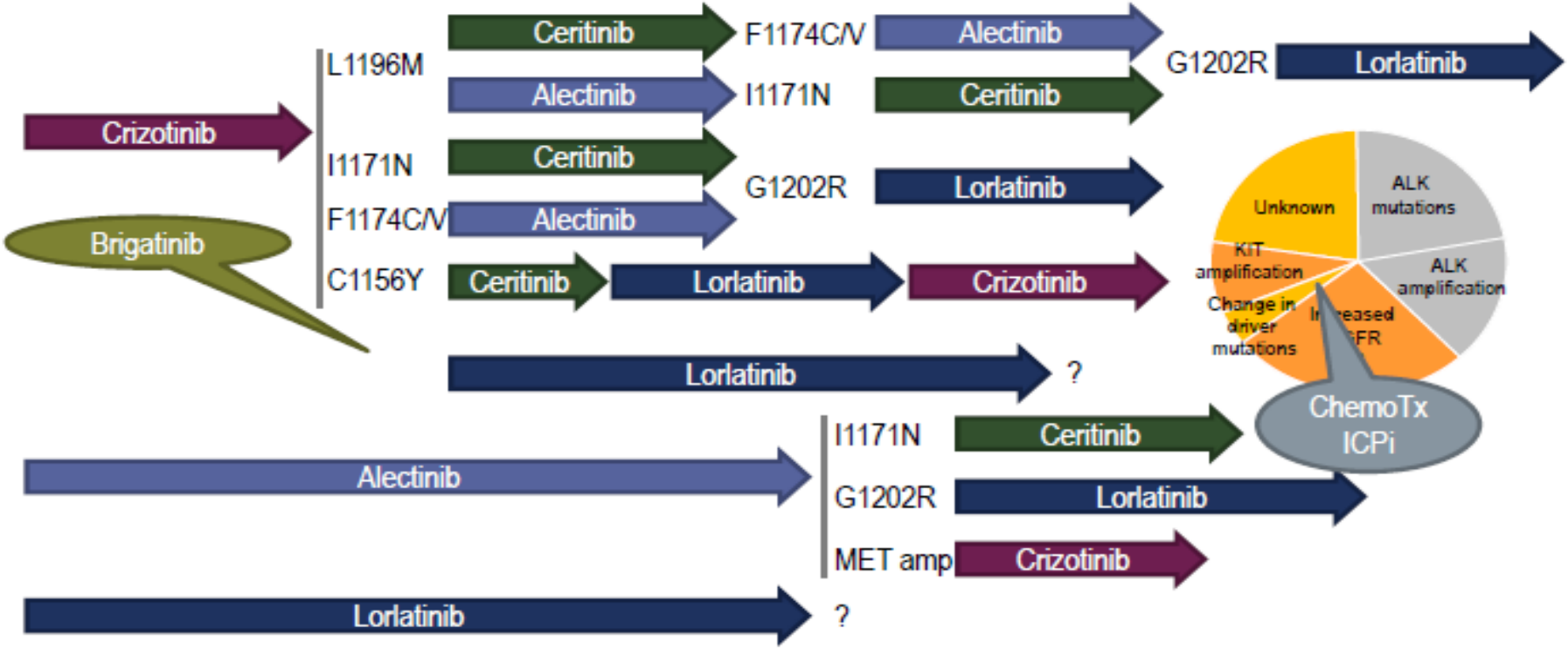
- Frequency: 4% overall, 33% in EGFR-negative never-smokers.
- Several ALK variants identified in NSCLC; clinical significance of each is unknown
- Testing
  - Vysis break apart FISH (> 15% cells with split signal in 50 nuclei scored)
  - ALK IHC
  - NGS
- 4 agents approved for ALK-positive NSCLC (first line and/or after progression):

  Crizotinib, ceritinib, alectinib and brigatinib.

ALK Gene Rearrangements Resistance

ALK mutation	Gainor et al, cancer discovery 2016[19]				Zhang et al, AACR 2015 abstract 781[24]		
	ALK phosphorylation mean IC_{50} (nmol/L)						
	Ceritinib	Alectinib	Brigatinib	Lorlatinib	Ceritinib	Alectinib	Brigatinib
EML4–ALK	5	11	11	2	37	25	14
C1156Y	5	12	5	5	195	67	45
I1171N	8	398	26	49	119	724	124
I1171S	4	177	18	30	ND	ND	ND
I1171T	4	34	6	12	ND	ND	ND
F1174C	38	27	18	8	109	31	58
F1174L	ND	ND	ND	ND	117	44	55
F1174V	ND	ND	ND	ND	121	46	64
V1180L	ND	ND	ND	ND	16	597	11
L1196M	9	118	27	34	67	133	41
L1198F	196	82	14	15	697	84	82
L1152R	ND	ND	ND	ND	437	62	11
L1152p	ND	ND	ND	ND	451	48	20
G1202R	124	707	130	50	354	690	184
G1202R del	50	59	96	5	ND	ND	ND
D1203N	35	28	35	11	159	42	79
E1210K	6	32	24	2	80	59	107
G1269A	0	25	ND	10	29	56	9
D1203N + F1174c	238	75	123	70	ND	ND	ND
D1203N + E1210K	98	83	136	27	ND	ND	ND
T1151Tins	ND	ND	ND	ND	283	201	114

ND = not done	IC_{50} <50	IC_{50} 50–200	IC_{50} >200



SHI Ou, et al. JTO 2014; SHI Ou *et al.* Lung Cancer 2015; Shaw AT, *et al.* NEJM 2016; Friboulet L, *et al.* Cancer Discov 2014; Toyokawa S, *et al.* 2013.
Presented by: Tetsuya Mitsudomi, MD.

ROS 1 Rearrangements

- Found in < 1% of lung adenocarcinomas.
- Drugs used to treat ALK+ tumours including crizotinb, ceritinib and lorlatinib have also shown marked activity in ROS1+[1].

Next generation ALK and ROS1 Inhibitors : Better CNS penetration, more potent, active against resistance kinase domain mutations

Cellular ALK Phosphorylation Mean IC50 (nM)

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

Gainor et al. Cancer Discovery 2016

IC50 ≤ 50 nM
IC50 > 50 <200 nM
IC50 ≥ 200 nM

ALK G1202R Lorlatinib > Ropotrectinib

ROS1 G2032R Ropotrectinib > Lorlatinib

Table 1. Ropotrectinib Potently Inhibited WT and Mutant ALK/ROS1/TRK in Ba/F3 Cell Proliferation IC_{50} (nM

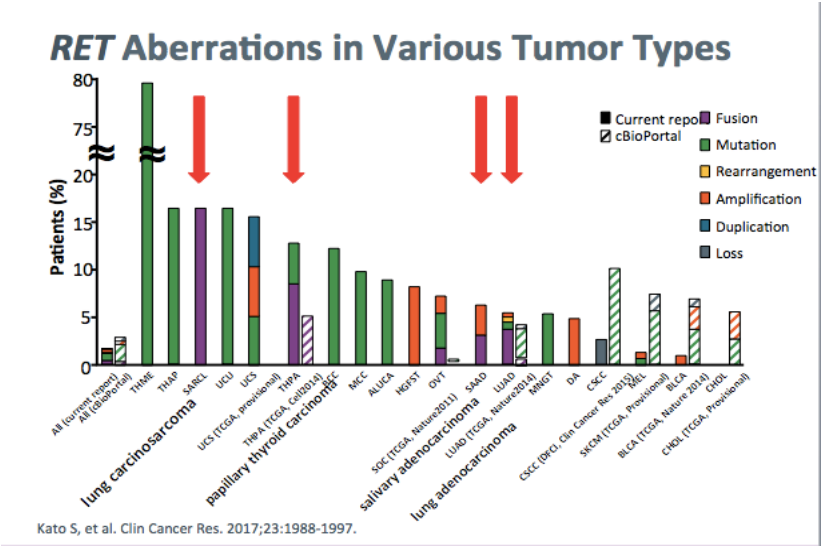
	EML4-ALK V1		CD74-ROS1			LMNA-TRKA		ETV6-TRKB		ETV6-TRKC		
Inhibitor	WT	G1202R	WT	G2032R	G2033N	WT	G595R	WT	G639R	WT	G623R	G623I
Ropotrectinib	27	63.6	<0.2	3.3	1.3	<0.2	0.4	<0.2	0.6	<0.2	3	1.4
Crizotinib	55.7	400	14.6	266.2	200.9							
Ceritinib	7.1	965	42.8	1813	169.2							
Alectinib	11.6	417										
Brigatinib	10.9	190.5	21	1172	128.4							
Lorlatinib	0.5	41.5	0.2	160.7	3.3							
Ensartinib			39.5	371.8	401.9							
Entrectinib			10.5	1813	169.2	0.5	705	<0.5	1384	0.6	1623	1351
Larotrectinib						4	1024	10.9	3000	10.2	3293	742.3

[1]Herbst R. Nature 2018

EMERGING TARGETS: BEYOND *EGFR*, *ALK* AND *ROS*

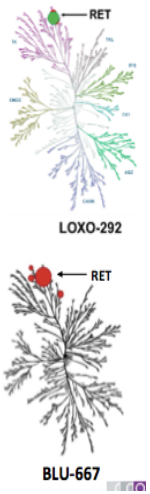
RET rearrangements

- Observed in 1-2% NSCLC
- Most common in never smokers and advanced disease.
- Promised clinical results with highly selected RET inhibitors



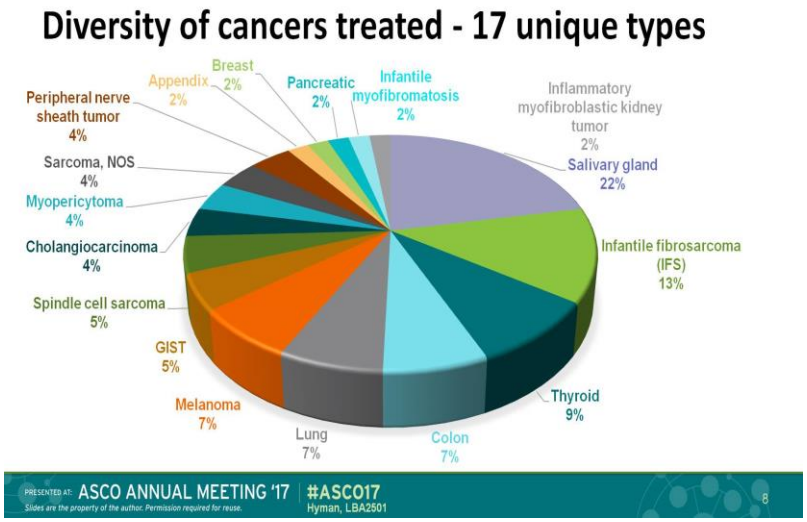
Emerging RET Therapies in Clinical Trials

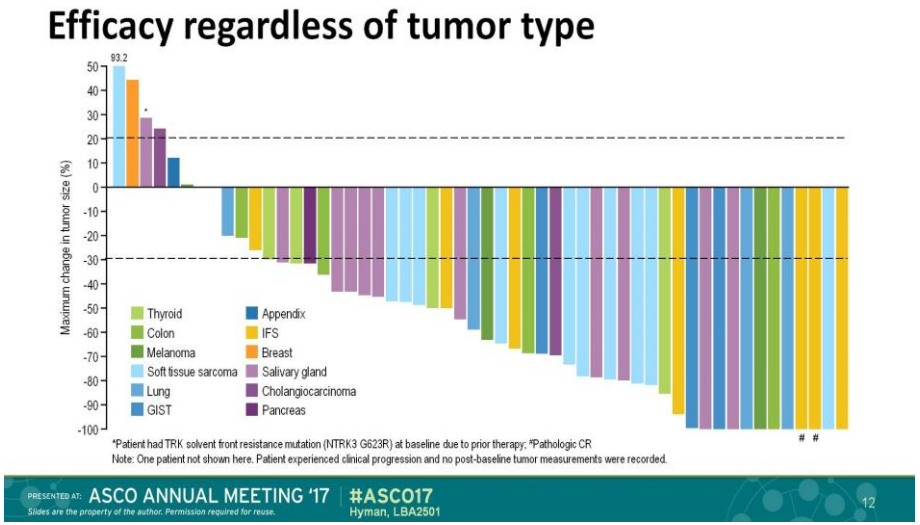
- LOXO-292:
  - Phase I/II study (LIBRETTO)[1]
    - Primary endpoint: determination of MTD, recommended dose for further study
    - Secondary endpoints: PK, safety/tolerability, ORR (RECIST v1.1), DoR
- BLU-667
  - Phase I/II study(ARROW)[2]
    - Primary endpoint: determination of MTD, recommended phase II dose, AEs, ORR
    - Secondary endpoints: DoR, DCR, PFS, and OS



NTRK rearrangements

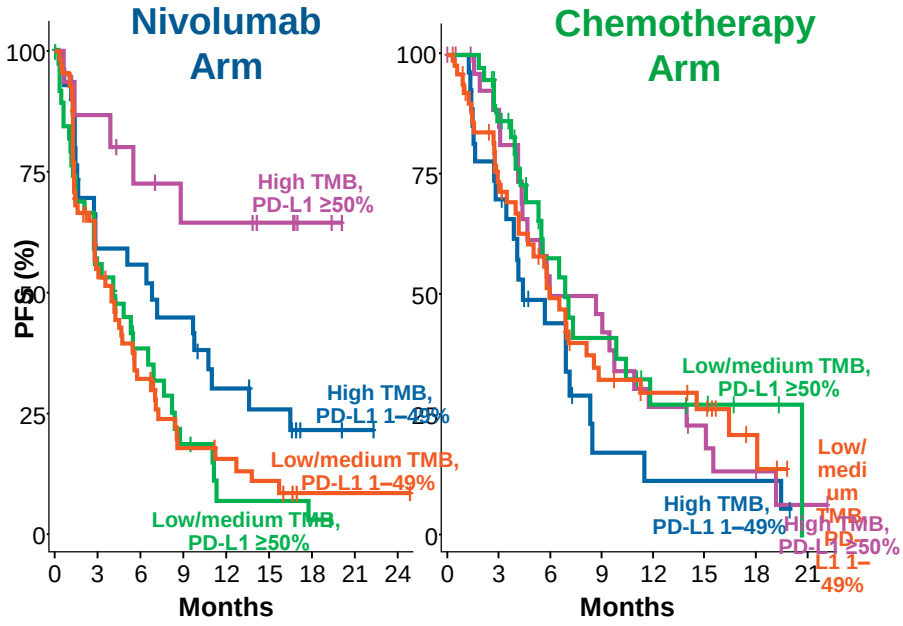
- TRK fusions occur rarely but broadly in appendiceal cancer, breast cancer, cholangiocarcinoma, colorectal cancer, GIST, infantile fibrosarcoma, lung cancer, mammary analogue secretory carcinoma of the salivary gland, melanoma, pancreatic cancer, thyroid cancer, and various sarcomas.
- Several TRK inhibitors are now in clinical development including Larotrectinib and Entrectinib.





“Right drug” also means upfront PDL-1 IHC in advanced NSCLC

- For some NSCLC patients IO is truly a life changing treatment.
- However, durable effects have only been demonstrated in a subset of patients
- Key next steps are
  - To identify the patients most likely to benefit from IO.
  - To understand mechanisms of resistance
- Different biomarkers under research: PDL1 IHC, TMB, immune signatures…
  - Currently, PDL1 status is key to select Pembrolizumab upfront!



KRAS co-mutation impact clinical response to IO?

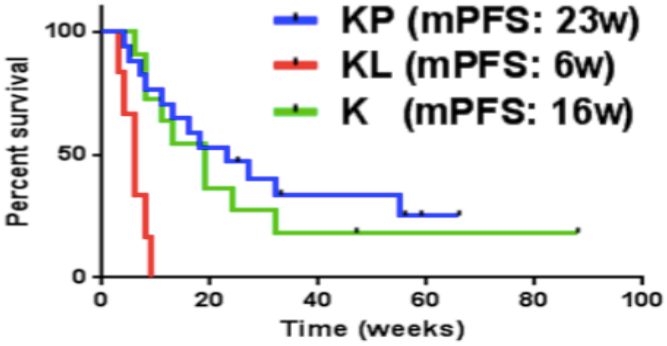
Datasets:

- 229 *KRAS*-mutant NSCLC patients enrolled in the MDACC Moon Shot Gemini Protocol
- 35 patients received immunotherapy and had robust clinical data and at least 46-gene NGS molecular panel

Co-mutations	n=35
STK11/LKB1	6 (17%)
TP53	17 (49%)
Neither (*KRAS* only)	12 (34%)

KRAS alleles	n=35
G12D	7 (20%)
G12V	9 (26%)
G12C	11 (31%)

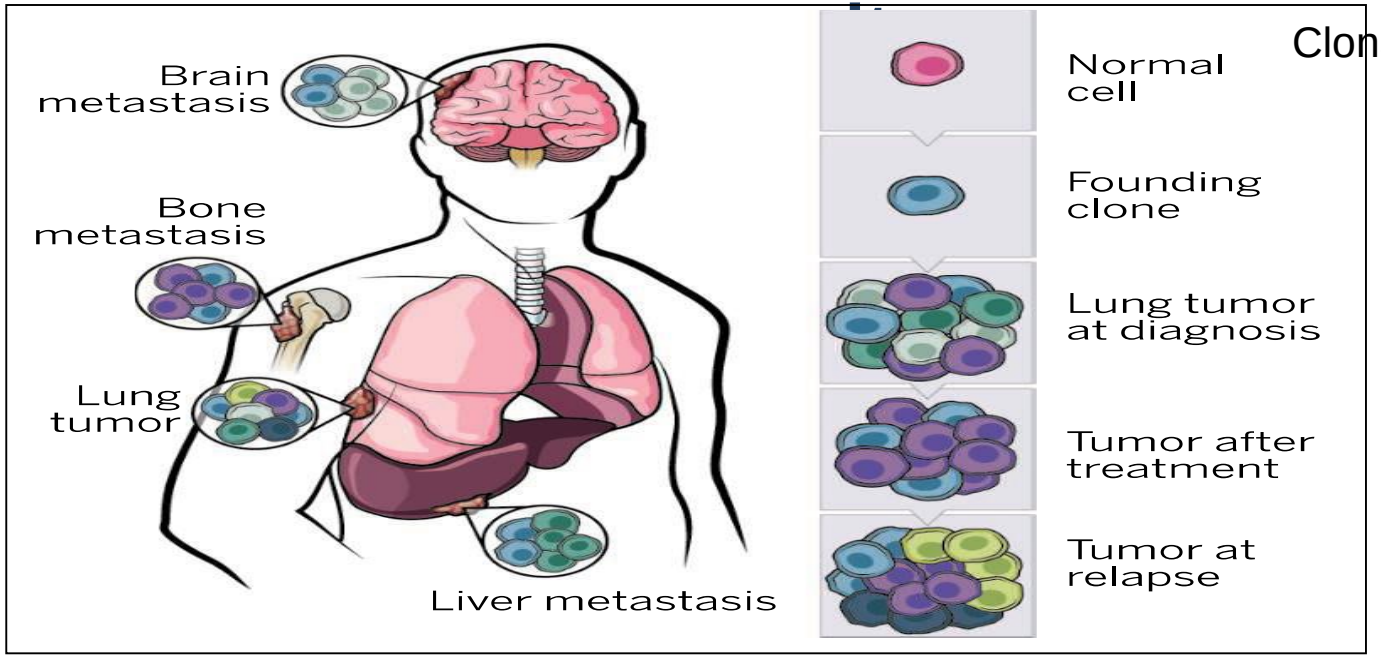
Significantly shorter median PFS with immunotherapy in the KL subgroup



Skoulidis WCLC 2016

PERSONALIZED TREATMENT: CHALLENGES

Tumor heterogeneity: different clones may drive different metastatic

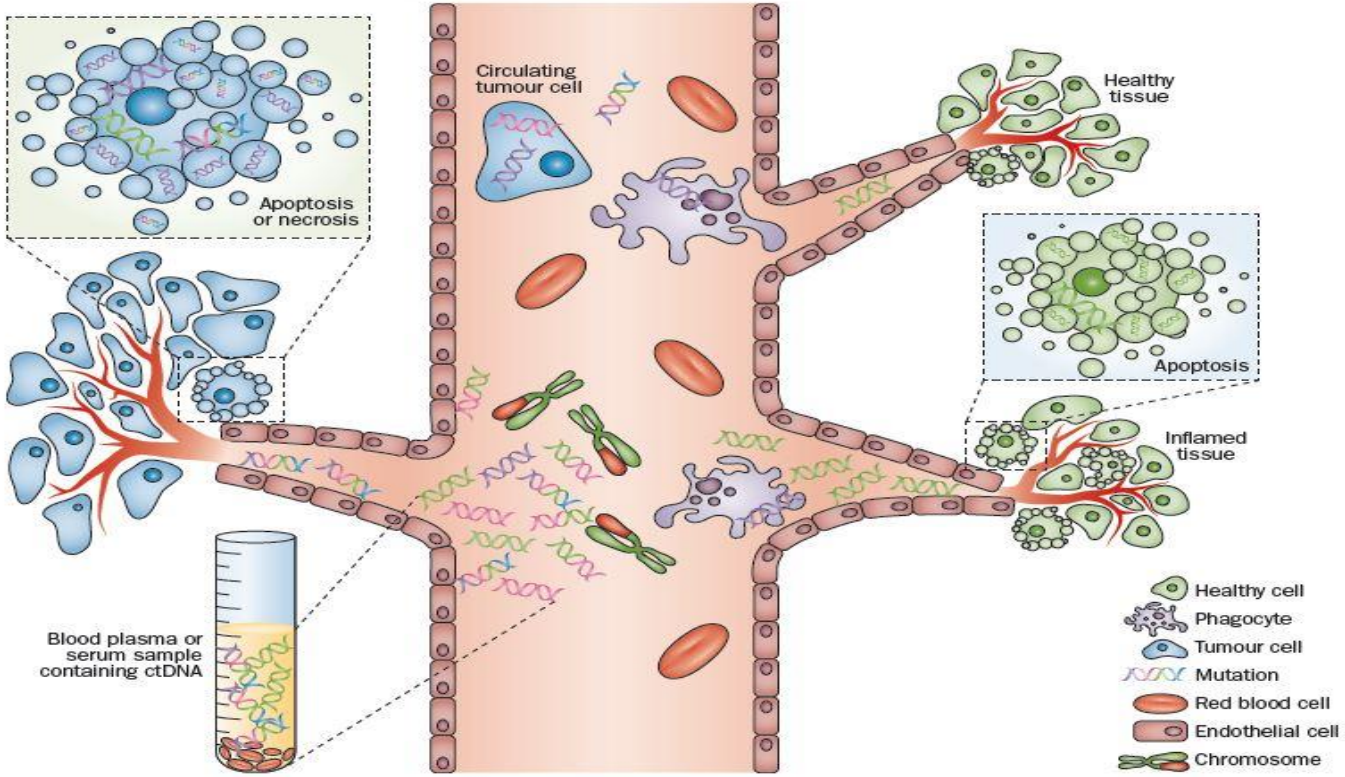


Clonal heterogeneity over time

Spatial heterogeneity at given timepoint

Govindan, Science 2014

Can we find genomic changes from the blood ?



Crowley E et al. Nat Rev Clin Oncol. 2013;10(8):472-84.

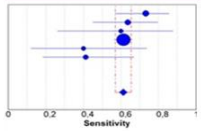
EGFR Liquid Biopsy as an alternative to tissue at progression

- Several factors, including difficulty of repeat solid biopsy, frailty of patients with more advanced disease, and higher ctDNA concentrations after progression, render liquid biopsies a good alternative
- However, **validation of negative results is still needed**

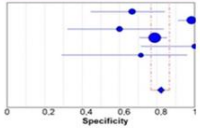
Overall pooled accuracy of ctDNA analysis:

- Sensitivity = 0.67
- Specificity = 0.80

RT-PCR

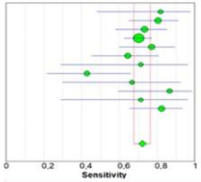


No. of studies: 6
Pooled sensitivity:
0.61 (95% CI 0.57-0.65)
Inconsistency: 31.5%

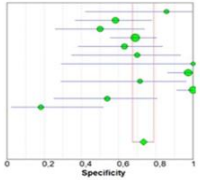


Pooled specificity:
0.82 (95% CI 0.77-0.87)
Inconsistency: 83.5%

dPCR/ddPCR
Higher sensitivity, lower specificity vs nondigital PCR

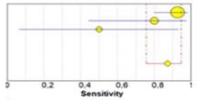


No of studies: 12
Pooled sensitivity:
0.72 (95% CI 0.68-0.76)
Inconsistency: 28.8%

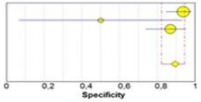


Pooled specificity:
0.73 (95% CI 0.67-0.79)
Inconsistency: 84.1%

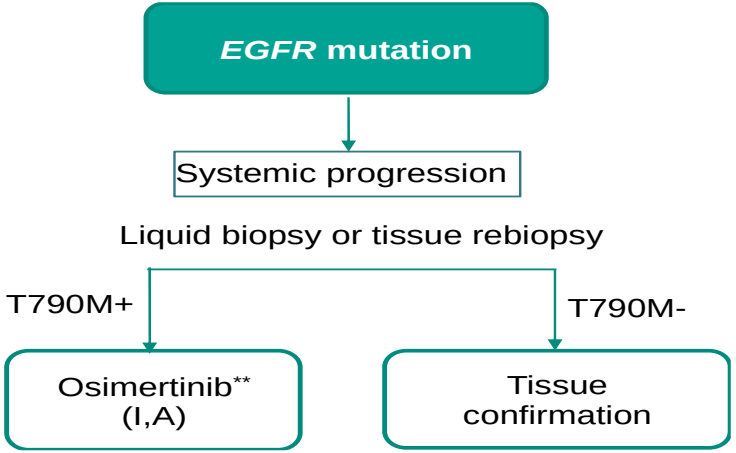
NGS
Highest sensitivity



No of studies: 3
Pooled sensitivity:
0.87 (95% CI 0.76-0.95)
Inconsistency: 59.3%

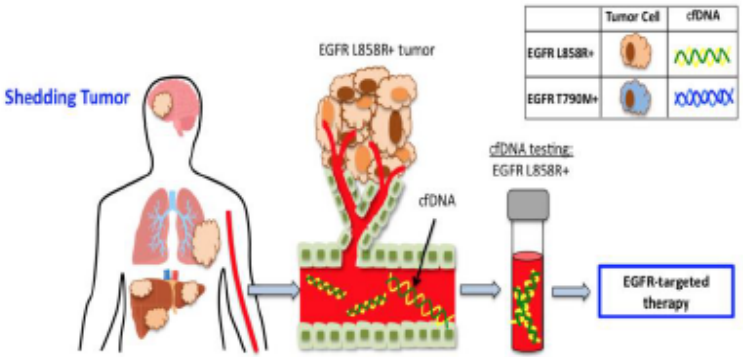


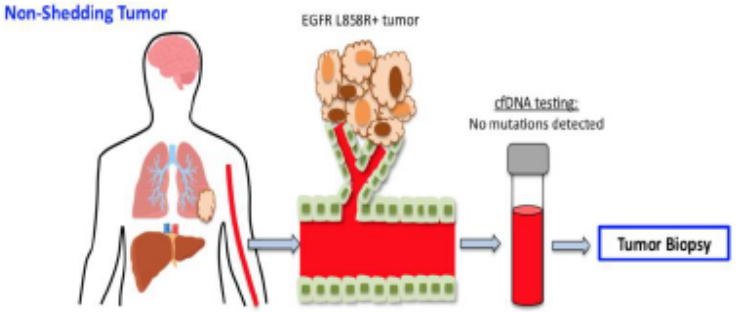
Pooled specificity:
0.89 (95% CI 0.82-0.94)
Inconsistency: 64.5%

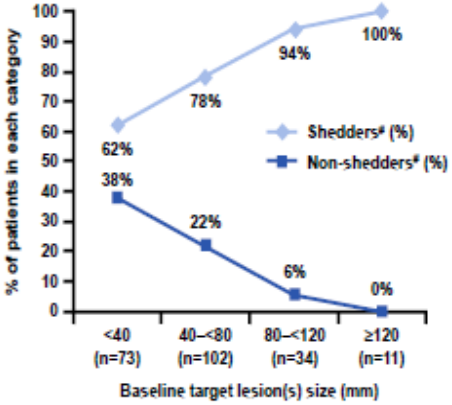


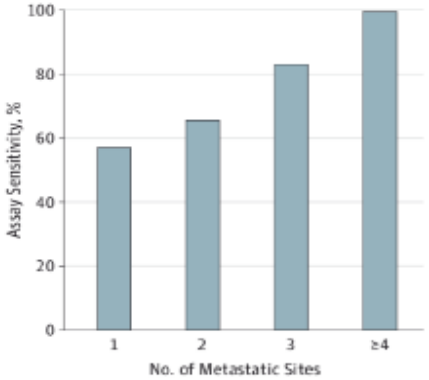
Passiglia et al. Sci Rep. 2018;8:13379; Adapted form SEOM guidelines, Majem CTO 2018.

Shedding and tumor burden in the resistant setting







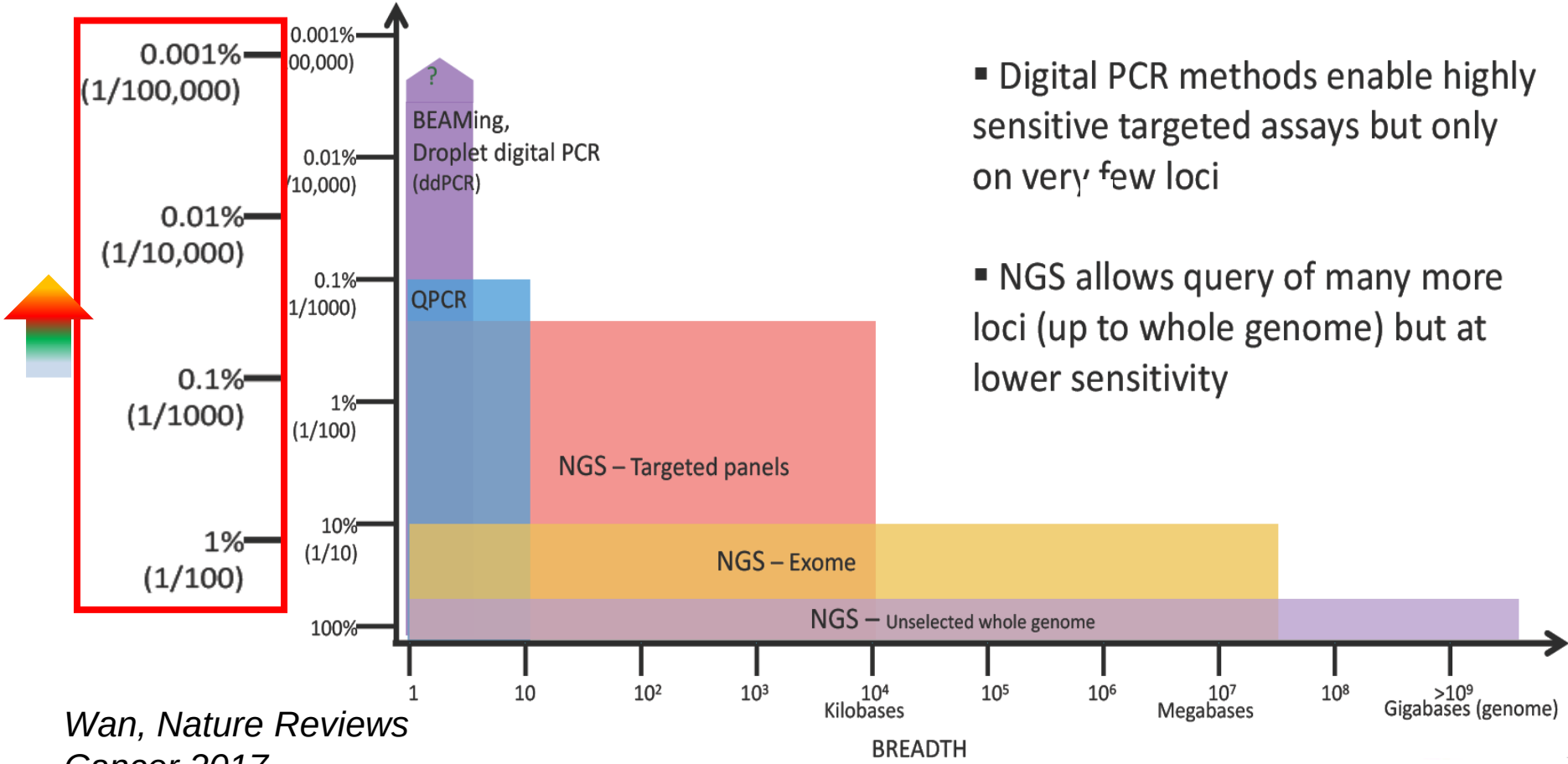


25% of patients non-shedders (AURA 3)

Assay sensitivity increases with tumor burden

Sacher A.G et al. JTO 2017; Sacher, JAMA Oncol 2017
Ahn et al. WCLC 2017

New quantitative assays are in the AF range to detect ctT790M



- Digital PCR methods enable highly sensitive targeted assays but only on very few loci
- NGS allows query of many more loci (up to whole genome) but at lower sensitivity

Wan, Nature Reviews Cancer 2017

Several Technologies for ctDNA testing

cobas® EGFR Mutation Test v2 (CE-IVD)

BIO-RAD

Droplet Digital™ PCR: A Breakthrough in Quantitative PCR

GUARDANT360™

PGD

BIOCARTIS

FOUNDATIONACT®

ThermoFisher SCIENTIFIC

ion torrent

sysmex

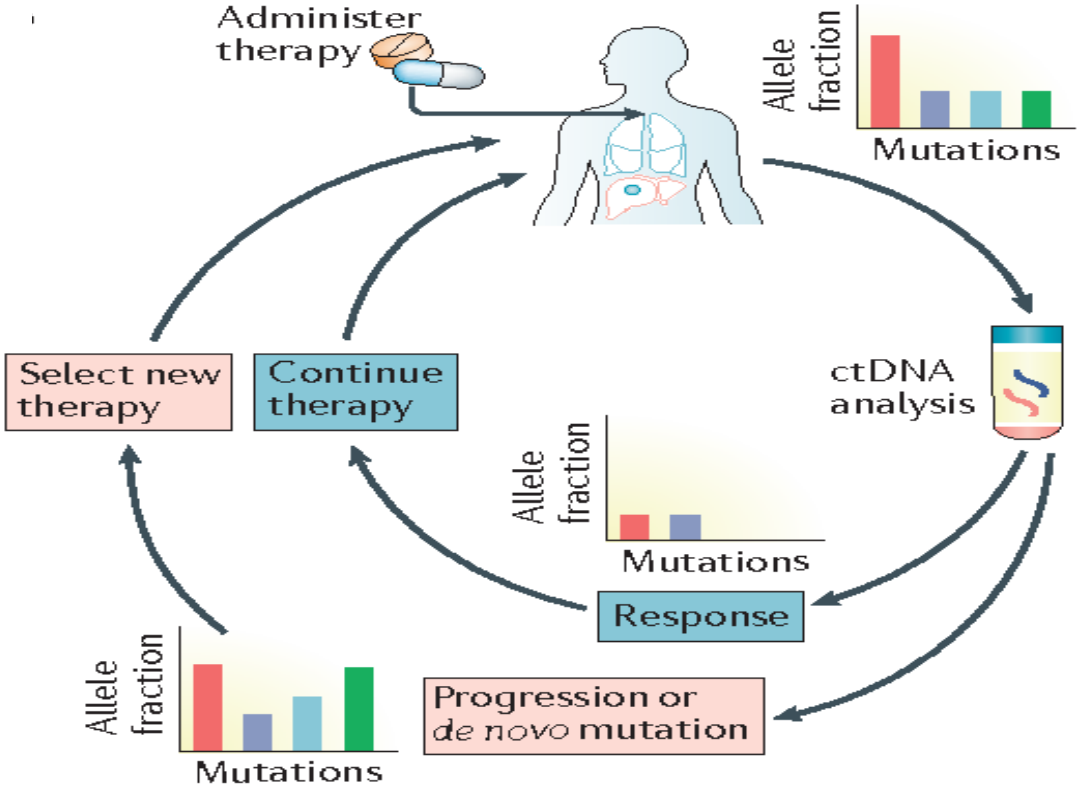
Inivata

The OncoBEAM™ Advantage:
The Latest on Cell-Free Tumor DNA Liquid Biopsies

BARCELONA Hospital Universitari

IDIBAPS

Treating earlier, treating better?



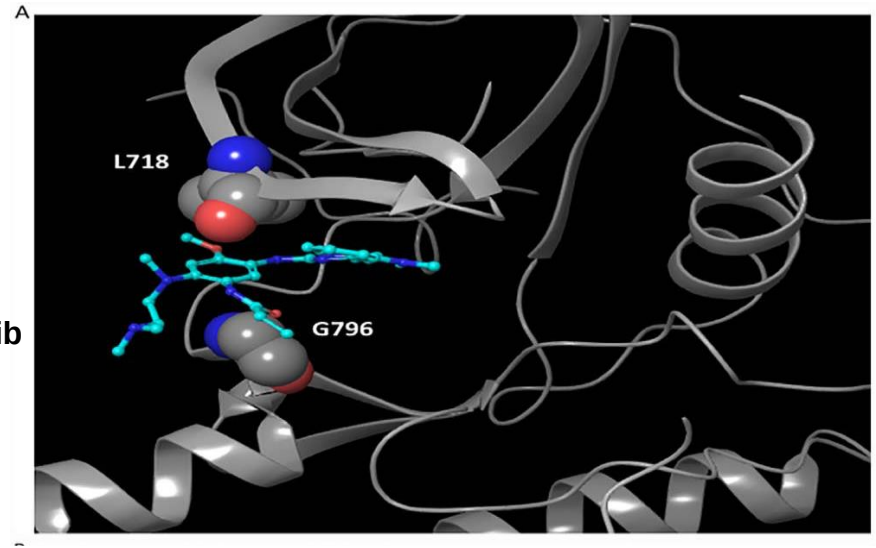
Wan, Nature Reviews Cancer 2017

Novel dominant EGFR solvent-front mutations in AR to osimertinib

Detection by plasma testing of a 69y old Caucasian female with AR to osimertinib:

- **L858R (MAF 17.9%)**
- **T790M (MAF 18.2%)**
- **G796S/R (MAF 14.4%)**
- **C797S/G (MAF 2.26%)**
- L792F/H (MAF 0.35%)
- V802F (MAF 0.36%)

disables osimertinib binding by sterical interference



Ou et al, Lung Cancer 2017

Healthcare stakeholders are unclear about the clinical utility of NGS

- Concerns:
  - Only a subset of patients have tumours harbouring specific actionable alterations that directly influence the choice of treatment.
  - Cost: it could be an expense addition rather than an affordable alternative.
  - Definition of "actionability" varies widely across studies and institutions (30% - 94%)[1].
  - Organized information: without the organized collection of efficacy or AEs, **each patient could be a clinical trial of a patient[2]**

[1]Berger M, Nat Rev 2018, [2]*Stinchcombe T. et al, Ann Oncol 2017*

Clinical applicability and cost of a 46-gene panel: retrospective validation and prospective audit in the UK National Health Service

- 46-gene hotspot cancer panel assay
- 351 patients (108 NSCLC, 88 colorectal and 109 melanoma)
- Median TAT 7 working days
- A locally actionable mutation (available targeted treatment or clinical trial) 35% but targeted treatment only 15%
- **At a cost of £339 per patient, the panel was less expensive locally than performing more than 2 o 3 single gene tests**

Hamblin A et al. PLOS Medicine 2017

Ensuring equity of access to innovation: France organisation of molecular centres for personalized medicine

Provides nationwide molecular diagnostic tests

The programme is operated by INCa/Ministry of Health *since 2006!!!!!*

➢ Objectives

- Perform molecular testing for all patients;
- Whatever the healthcare institution status (public hospitals, private hospitals…);
- Perform high quality tests;
- leukemia, solid tumours

➢ 28 regional centres

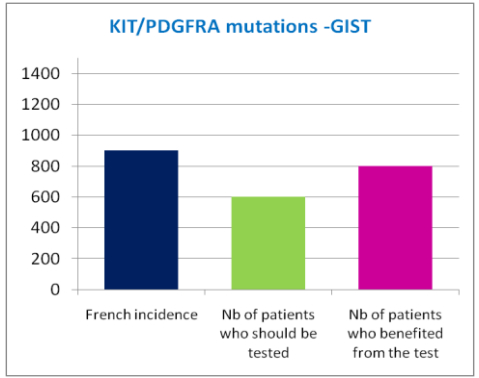
- Partnerships between several laboratories located in University hospitals and cancer centres
- Regional organization
- Cooperation between pathologists and biologists

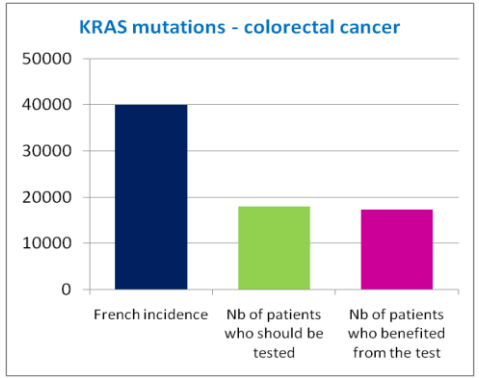
Benefit for all patients

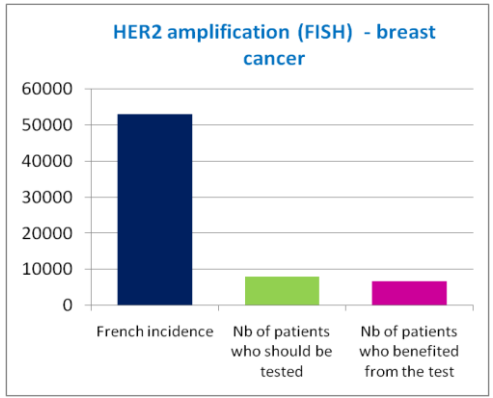
Molecular tests are performed :

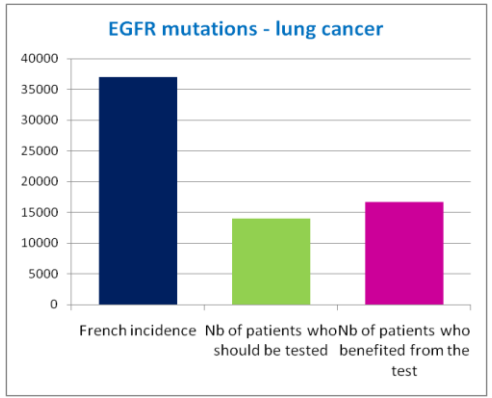
- For all patients
- free of charge for patients & hospitals
- With compensation of local pathologists for sample shipments

➔ Ensure that all patients effectively benefit from molecular testing







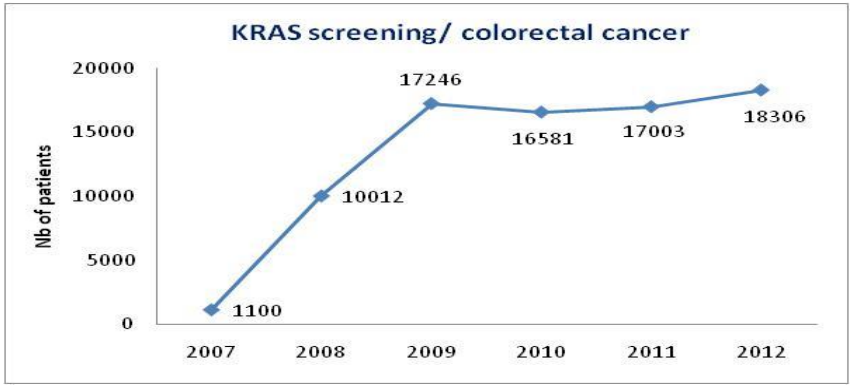


Rapid access to innovation

Offer each patient in France an equal access to molecular tests as soon as a therapy is available

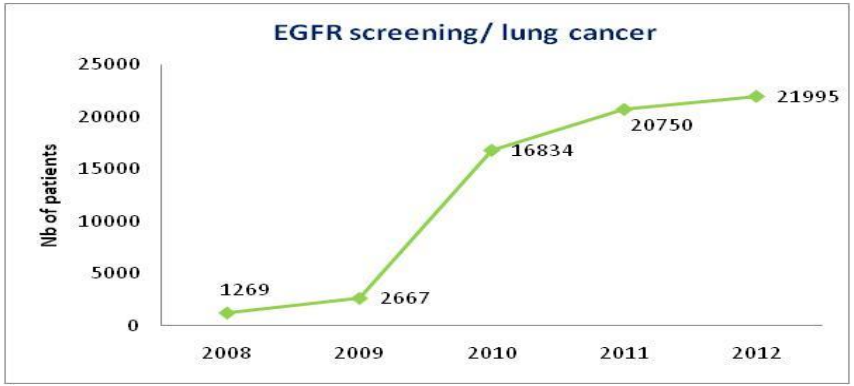
Mid 2008 : EMA approvals for panitumumab and cetuximab for patients with **wild type KRAS tumours**

⇒ INCa started to allocate €2.5M to the 28 centres at the end of 2008



June 2009 : gefitinib approvals by EMA for patients with **activating mutations of EGFR in their tumours**

=> INCa started to allocate €1.7M to the 28 centres at the end of 2009

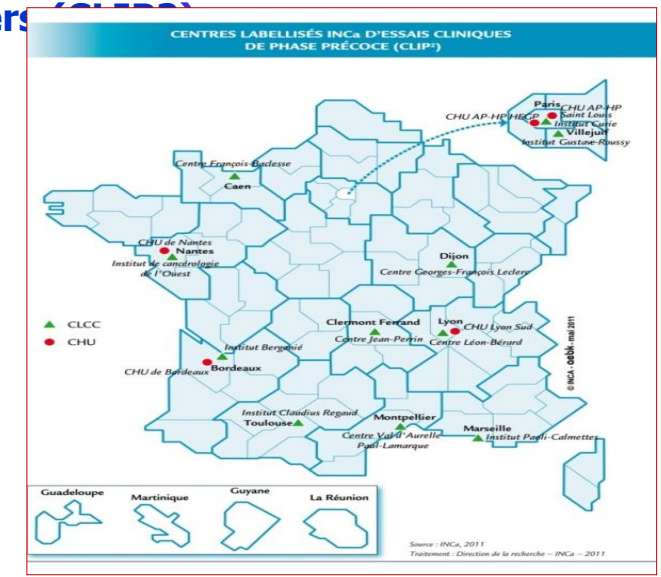


Leveraging the nationwide screening initiative

- **Increase patient access to innovative drugs**
- **Promote the development of new targeted therapies**

⇒ **guide patients with specific molecular alterations towards clinical trials**

⇒ **strengthen collaboration between molecular centres and accredited early phases clinical trials centers (CLIP2)**



CLIP2 clinical activity - 2011
166 early phase trials
1788 patients included

The 16 CLIP2 cover all pathologies (including hematology, pediatric, rare diseases…)

Routine molecular profiling is the only way to identify all potential patients candidates to receive targeted treatment

- Routine molecular profiling in France shows **improvement in the survival of about 50% of patients**

NOWAK, CALVO, AND SORIA

Europe Does It Better: Molecular Testing across a National Health Care System—The French Example

Frédérique Nowak, PhD, Fabien Calvo, MD, PhD, and Jean-Charles Soria, MD, PhD

OVERVIEW

Drug approvals for molecularly stratified tumor subgroups make molecular testing mandatory and require that molecular diagnostics be performed nationwide. To this end, the French National Cancer Institute (INCa) and the French Ministry of Health have set up a national network of 28 regional molecular genetics centers. Selective molecular tests are performed in these facilities. They are free of charge for all patients in their region, irrespective of the type of establishment in which they are receiving treatment. A specific program has also been implemented to anticipate the launch of new targeted therapies and to accelerate the time-to-access to new drugs and experimental therapies. The initiative has been operational for 5 years and has been successful in meeting its initial aims of uniform nationwide test provision and fast implementation of molecular tests for new tumor biomarkers.

Routine molecular profiling of patients with advanced non-small-cell lung cancer: results of a 1-year nationwide programme of the French Cooperative Thoracic Intergroup (IFCT)

*Fabrice Barlesi, Julien Mazieres, Jean-Philippe Merlio, Didier Debieuvre, Jean Mosser, Hervé Lena, L'Houcine Ouafik, Benjamin Besse, Isabelle Rouquette, Virginie Westeel, Fabienne Escande, Isabelle Monnet, Antoinette Lemoine, Rémi Veillon, Hélène Blons, Clarisse Audigier-Valette, Pierre-Paul Bringuier, Régine Lamy, Michèle Beau-Faller, Jean-Louis Pujol, Jean-Christophe Sabourin, Frédérique Penault-Llorca, Marc G Denis, Sylvie Lantuejoul, Franck Morin, Quin Tran, Pascale Missy, Alexandra Langlois, Bernard Milleron, Jacques Cadranel, Jean-Charles Soria, Gérard Zalcman, for the Biomarkers France contributors**

The NEW ENGLAND JOURNAL of MEDICINE

Perspective

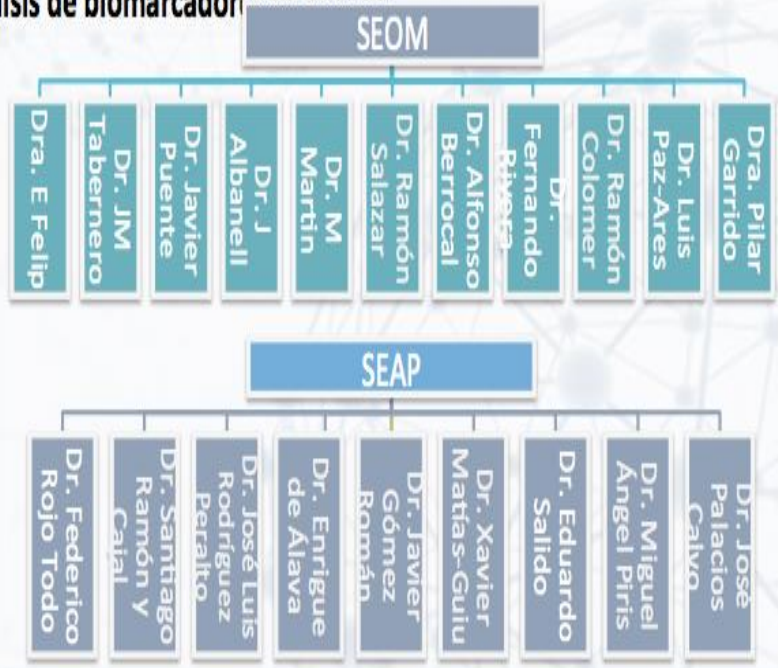
Biomarker Tests for Molecularly Targeted Therapies — The Key to Unlocking Precision Medicine

Gary H. Lyman, M.D., M.P.H., and Harold L. Moses, M.D.

Barlessi F. et al, Lancet 2016

PBC Plataforma de Biomarcadores en Cáncer

Las sociedades SEAP-SEOM constituyeron el Grupo de Trabajo en Biomarcadores, con el fin de explorar iniciativas conjuntas para el desarrollo del análisis de biomarcadores en cáncer



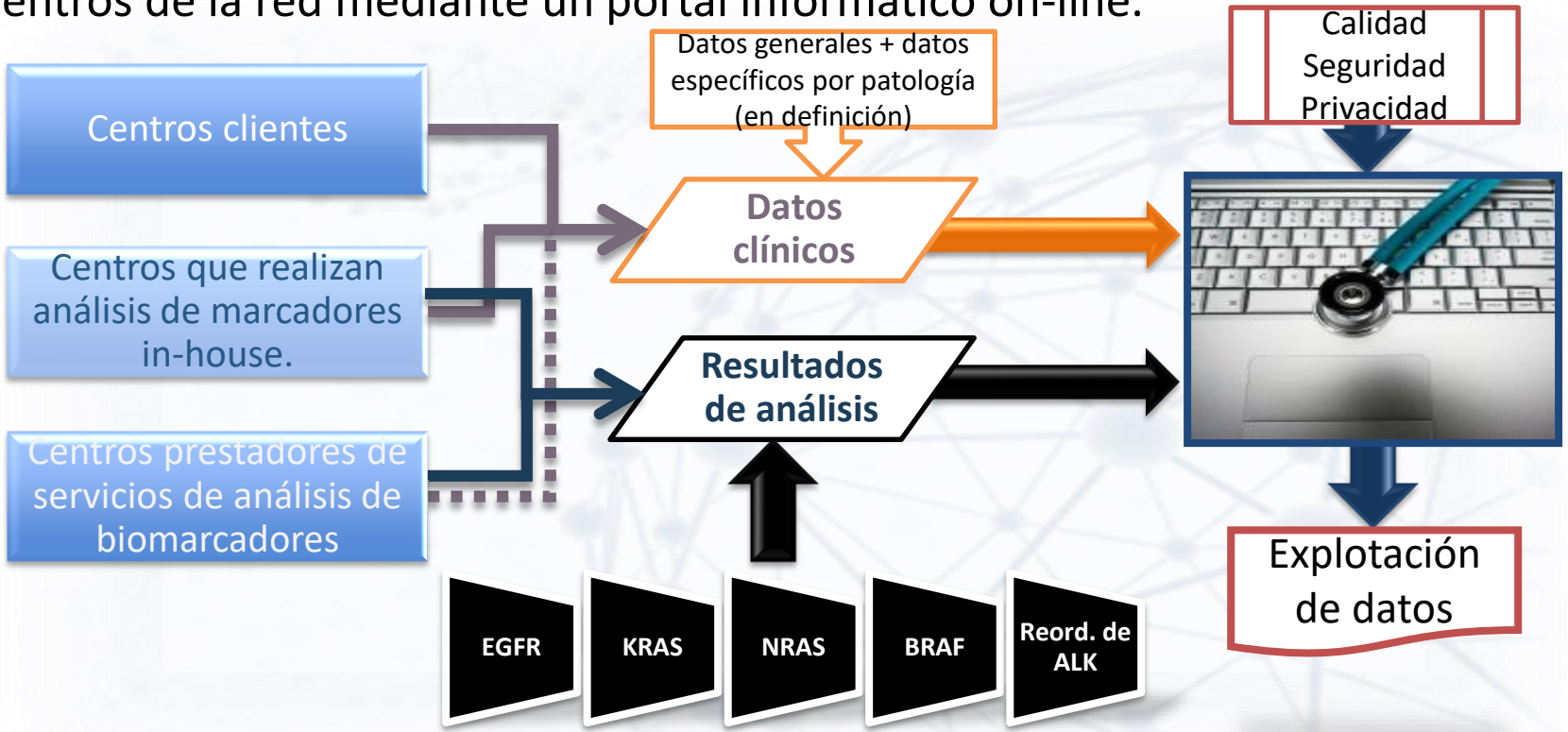
Se presentan agrupados por patologías, los marcadores iniciales sobre los que trabajará la Plataforma.

Biomarcadores iniciales

TIPO DE CÁNCER	BIOMARCADOR	*PACIENTE*	
Pulmón	EGFR	CPNM avanzado a) carcinoma no-escamoso, b) no fumadores.	11.000
	Reordenamientos ALK	CPNM avanzado y EGFR no mutado.	1.375
Colo-rectal	KRAS	CCR metastásico	7.000
	NRAS	CCR metastásico	
Melanoma	BRAF	Melanoma metastásico	900

*Se contemplarán los **mecanismos necesarios para la implementación de nuevos análisis** conforme se acredite su aplicación a la práctica clínica.*

La Plataforma desarrollará una base de datos única, accesible a todos los centros de la red mediante un portal informático on-line.



Criterios establecidos por el Grupo de Trabajo para la realización de servicios de análisis de biomarcadores de indicación terapéutica a terceros en el marco de la Plataforma

Centro interesado en participar bajo esta modalidad

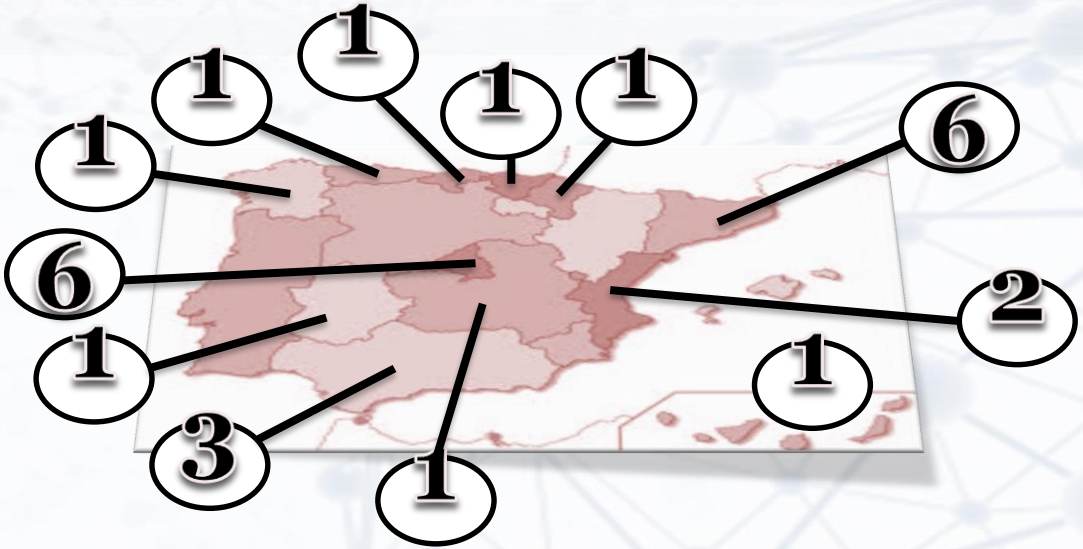
Haber participado de forma activa en algún sistema de intercomparación (SEAP, EMQN,..) con un resultado satisfactorio, o haber estado acreditado o certificado

Ser un Centro Asistencial Público o Privado

Cumplir al menos 3 de las siguientes 4 condiciones

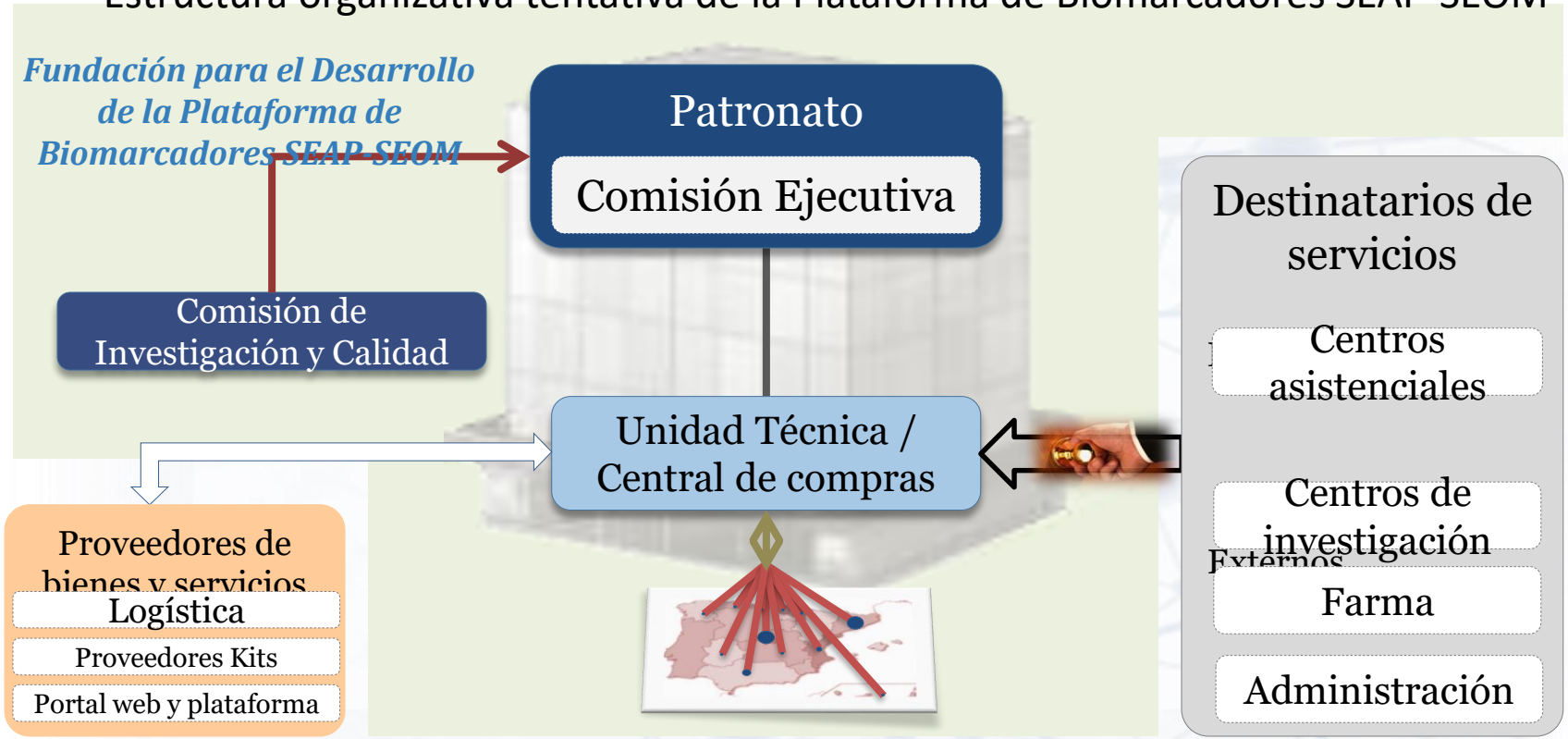
- Haber realizado más de 120 determinaciones de BRAF en los últimos 5 años
- Haber realizado más de 240 determinaciones de EGFR en los últimos 5 años
- Haber realizado más de 350 determinaciones de KRAS en los últimos 5 años
- Haber realizado más de 80 determinaciones de ALK en los últimos 5 años

Se estima, en función de las expresiones de interés recibidas, que el número de centros prestadores de servicios de análisis en el marco de la Plataforma superará inicialmente los 25, con una importante cobertura a nivel estatal.



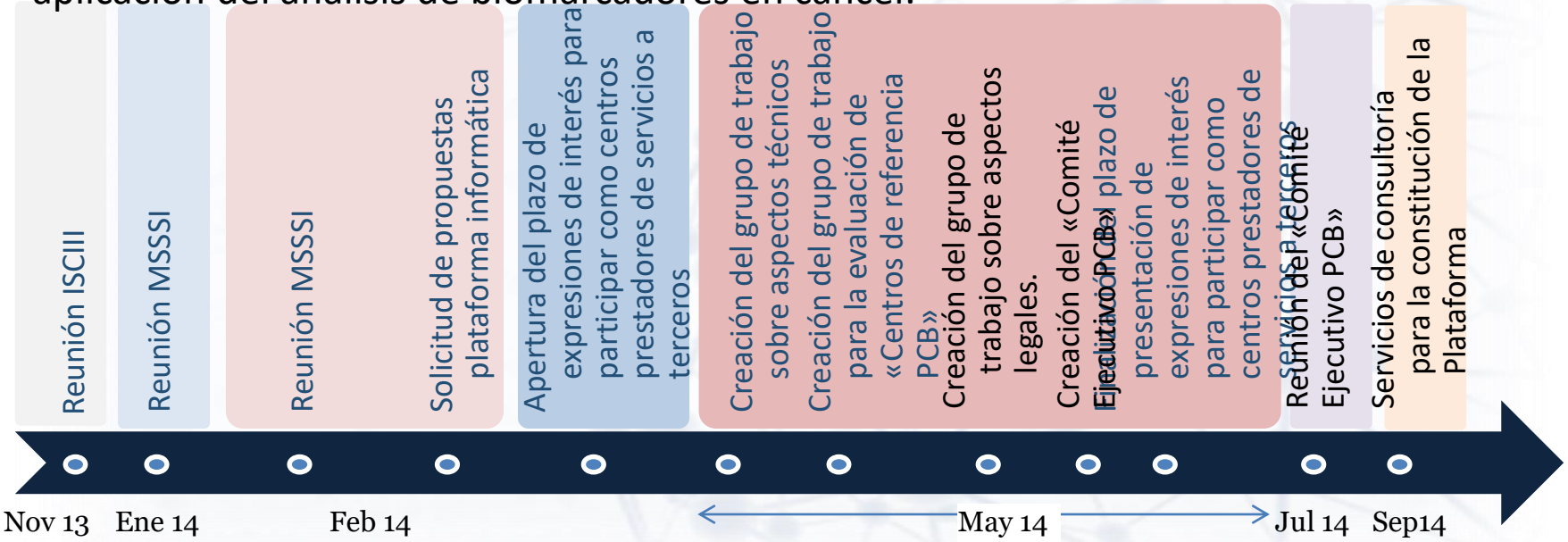
Se arbitrarán los procedimientos *necesarios para la* ***incorporación de centros,*** *que permita la participación de aquellos que lo deseen* ***en las distintas modalidades*** *con el objetivo de* ***sumar esfuerzos en el desarrollo de este ambicioso proyecto.***

Estructura organizativa tentativa de la Plataforma de Biomarcadores SEAP-SEOM



Hasta el momento se han realizado diversas acciones para la puesta en marcha y desarrollo de la Plataforma PCB SEAP-SEOM

Incluyendo actividades de **difusión externa**, contacto con los principales **agentes** involucrados en los **aspectos regulatorios, sanitarios y productivos** del desarrollo y aplicación del análisis de biomarcadores en cáncer.



Próximos pasos previstos en el desarrollo de la Plataforma de Biomarcadores SEAP-SEOM durante 2014-2015

….AND NOW????