GECP lung cancer research

Precision Medicine: Oncologist perspective on the impact of the molecular evaluation of solid tumor

Mariano Provencio

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DISCLOSURES

Employment:

- Universidad Autónoma de Madrid.
- Chair of Medical Oncology Department at Puerta de Hierro Hospital

Research Grants:

AstraZeneca, Roche, BMS, Boerhringer-Ingelheim

Stock holder:

- none

Consultant:

AstraZeneca, BMS, Boerhringer-Ingelheim, Celgene, MSD, Roche, Takeda, Thermo Fisher Scientific

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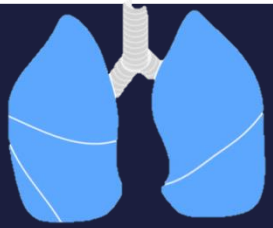
Speaker was provided an honorarium by Thermo Fisher Scientific for this presentation.

Precision Medicine

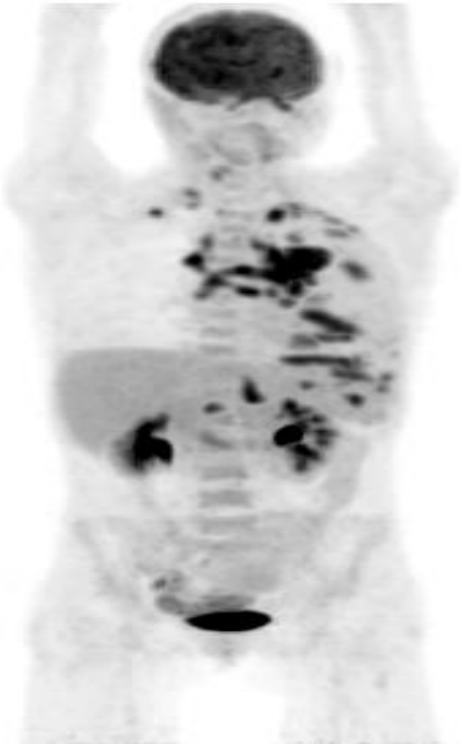
Background & Current Situation

SPAIN ≈ 250.000
Cancer New Cases

REDECAN. Cancer Incidence in Spain 2015. Clin Transl Oncol. DOI 10.1007/s12094-016-1602-9



- Lung Cancer ≈28.000 new cases/year
- 1st Cause of cancer-related death



Clinical Case

Woman: 56 years, no smoker

Diagnosis: lung cancer IV stage- July 2014

Metastasis: bones, ganglions and lung

THE PRECISION MEDICINE INITIATIVE

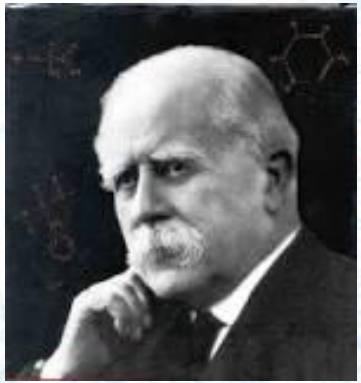
So what is Precision Medicine?

It's health care tailored to you.

In his 2015 State of the Union address, President Obama announced that he's launching the Precision Medicine Initiative — a bold new research effort to revolutionize how we improve health and treat disease.

Until now, most medical treatments have been designed for the "average patient." As a result of this "one-size-fits-all" approach, treatments can be very successful for some patients but not for others. Precision Medicine, on the other hand, is an innovative approach that takes into account individual differences in people's genes, environments, and lifestyles.

President Obama participates in a panel discussion moderated by Dr. James Hamblin of The Atlantic on the importance of PMI at the White House, February 25, 2016.



Genetics inMedicine | COMMENTARY

Archibald E. Garrod: the father of precision medicine

Robert L. Perlman, MD, PhD[1] and Diddahally R. Govindaraju, PhD[2]

Archibald Garrod is best known for his book *Inborn Errors of Metabolism* (1909), in which he argued that four diseases—alkaptonuria, albinism, cystinuria, and pentosuria—were inherited as Mendelian autosomal recessive traits.[2] This pre-

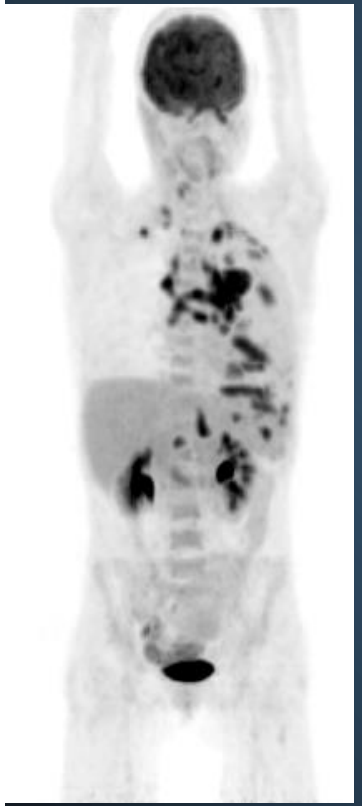
was a commonly used term for gene.) He discussed chemical individuality in the context of Darwin's theory of evolution by natural selection and by considering disease as an "agent of evolution" (p. 53). After calling attention to some of the chemical

prehensive understanding of individual patients, because "The constitution of a man is the sum of *all* his qualities, his bodily form, the structure of his tissues, his coloration, height, weight, blood pressure, and body temperature; … and tricks of gesture and action. In all or some of these respects, each man differs from all his fellows, for even uniovular twins are not exactly

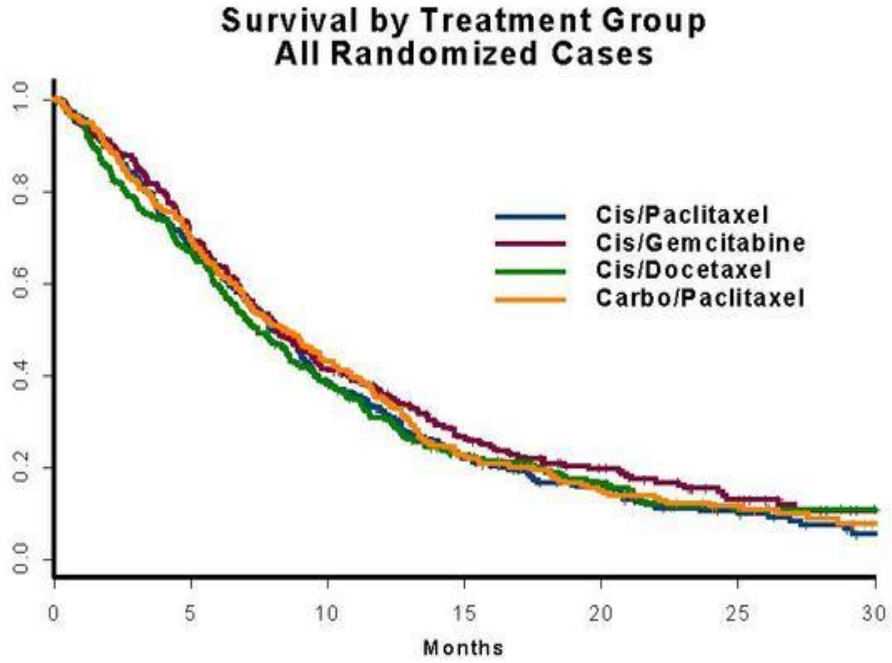
- **Clinical case**

- **Woman**: 56 years, no smoker
- **Diagnosis**: lung cancer IV stage- July 2014
- **Metastasis**: bones, ganglions and lung

5 Years Survival rate with chemotherapy: **0%**



UNSELECTED POPULATION



ORR: 20-30%

mPFS: 5-6 months

mOS: 8-10 months

2 year survival rate: 11%

5 year survival rate: 0%

Schiller J, et al. N Enl J Med 2012

So what is Precision Medicine?

It's health care tailored to you.

In his 2015 State of the Union address, President Obama announced that he's launching the Precision Medicine Initiative — a bold new research effort to revolutionize how we improve health and treat disease.

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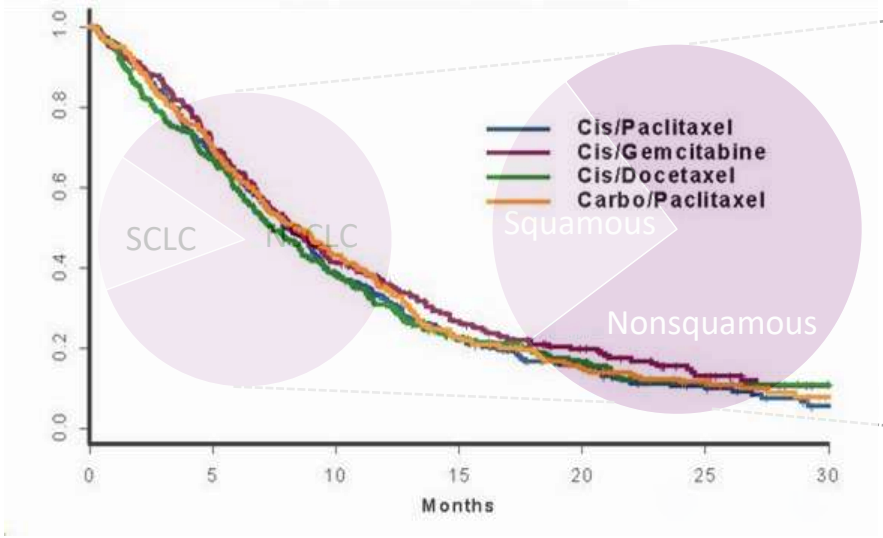
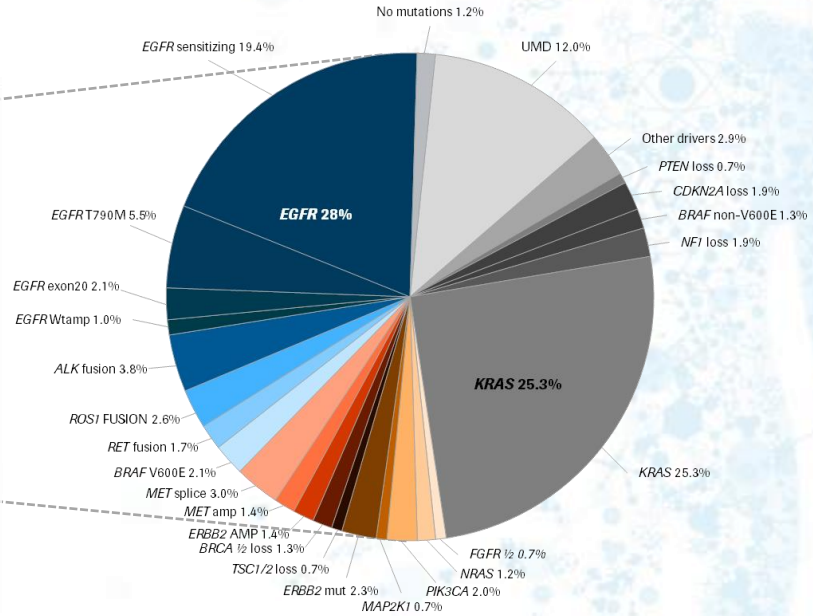
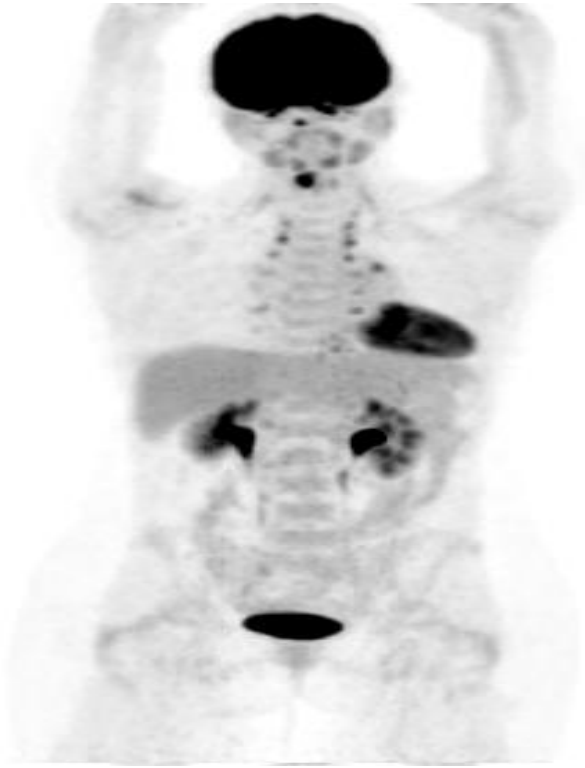




Spectrum of oncogenic drivers associated to 860 patients with lung adenocarcinoma identified by MSK-Impact.

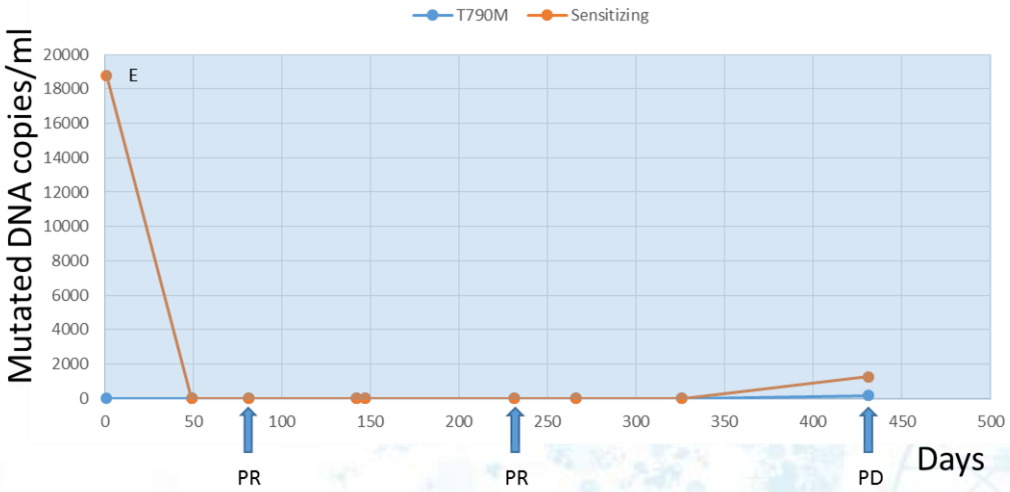
SCLC: small cell lung cancer, NSCLC: non-small cell lung cancer; UMD: no actionable mutation.

1. Bode, A. M., and Dong, Z., (2018) *npj Precision Onc* 2:1; 2. Jordan EJ *et al.* (2017) *Cancer Discov.* 2017; 7: 596-609.



Positive for EGFR del. exon 19 mutation

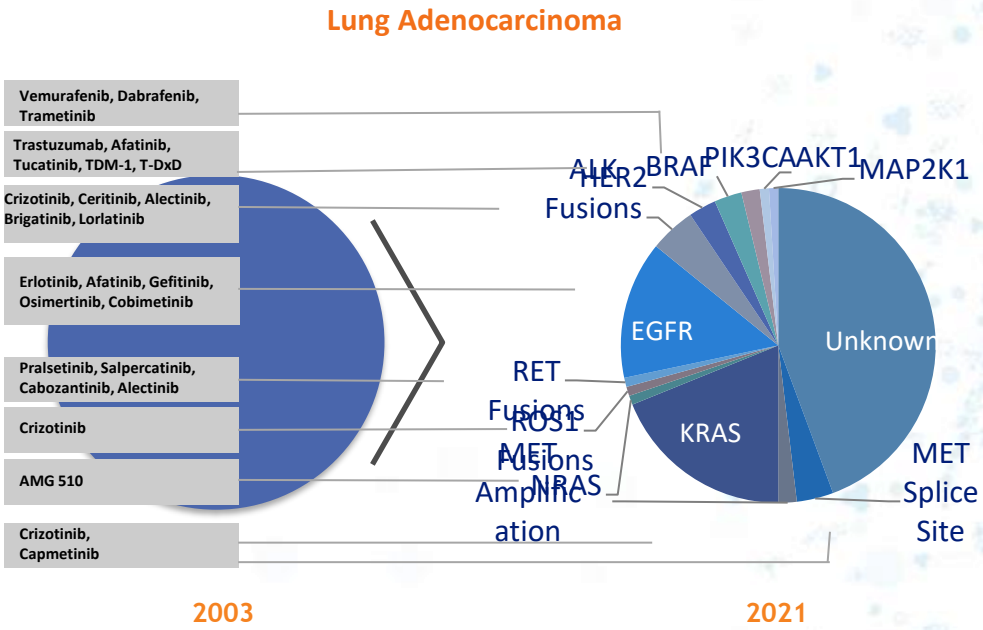
Complete remission after treatment with first generation TKI



Disease progression after 15 months

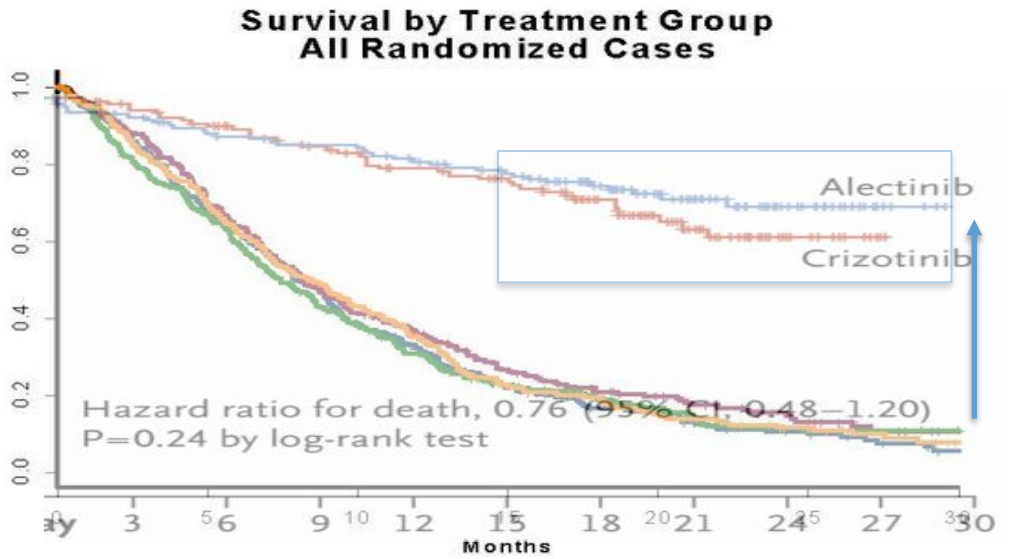
Lung Cancer: poster child for precision medicine

Why is it important to identify molecular biomarkers for every patient?



Modified and updated from Pao and Hutchinson, Nature Medicine. 2012; 18:349-351.

Why is it important to identify molecular biomarkers for every patient?



Targeted therapy: 10 years of progress

2004

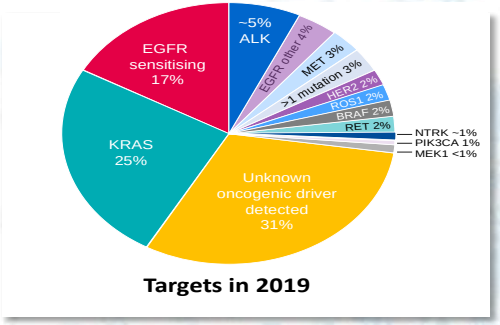
The NEW ENGLAND JOURNAL of MEDICINE

MAY 20, 2004

Activating Mutations in the Epidermal Growth Factor Receptor Underlying Responsiveness of Non–Small-Cell Lung Cancer to Gefitinib

EGFR Mutations in Lung Cancer: Correlation with Clinical Response to Gefitinib Therapy

EGF receptor gene mutations are common in lung cancers from "never smokers" and are associated with sensitivity of tumors to gefitinib and erlotinib



Targets in 2019

Metastatic non-small cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

Originally published in 2018 – Ann Oncol (2018) 29 (suppl 4): iv192–iv237
D. Planchard[1], S. Popat[2], K. Kerr[3], S. Novello[4], E. F. Smit[5], C. Faivre-Finn[6], T. S. Mok[7], M. Reck[8], P. E. Van Schil[9], M. D. Hellmann[10] & S. Peters[11], on behalf of the ESMO Guidelines Committee*

1. Patients with a tumour with a sensitising EGFR mutation should receive first-line EGFR TKIs including erlotinib, gefitinib or afatinib, or dacomitinib. None of the four EGFR TKIs is consensually considered as a preferred option
2. First-line osimertinib is now considered one of the options for patients with a tumour with sensitising EGFR mutations

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Contents lists available at ScienceDirect

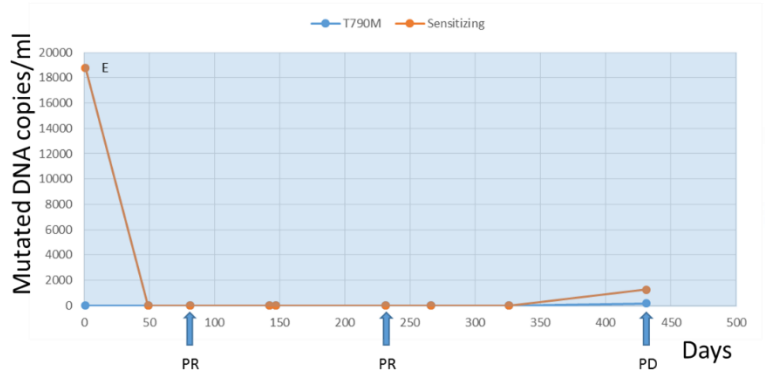
Translational Oncology

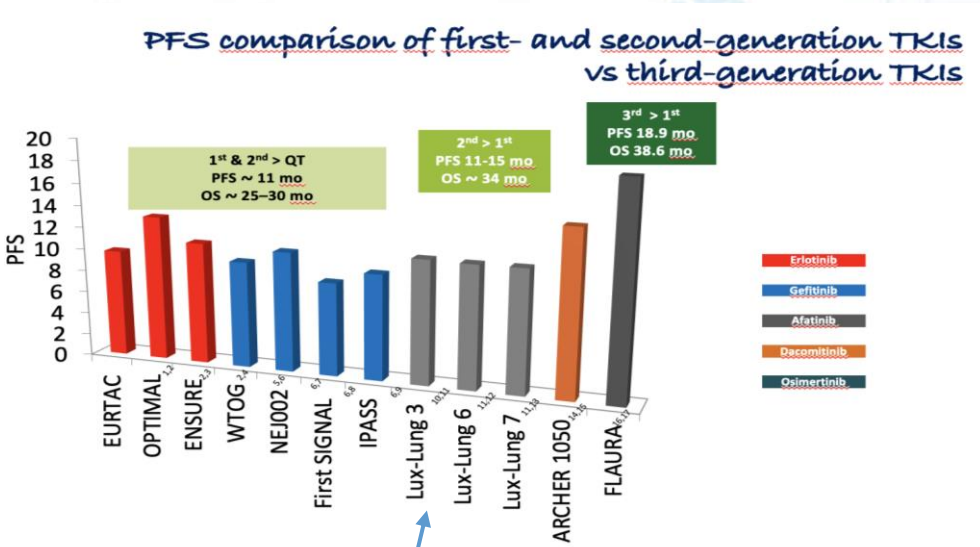
journal homepage: www.elsevier.com/locate/tranon

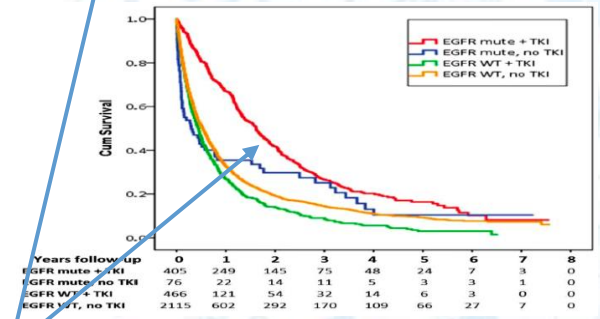
Long term follow-up of EGFR mutated NSCLC cases

Gad Rennert[a,b,c,*], Maya Gottfried[d], Hedy S Rennert[a,b], Flavio Lejbkowicz[a,b], Meira Frank, Ilana Cohen[a,b], Shiri Kelt[a,b], Abed Agbarya[e], Elizabeta Dudnik[f], Julia Dudnik[g], Rivka Katznelson[h], Moshe Mishali[d], Natalie Maimon Rabinovich[d], Hovav Nechushtan[i], Amir Onn[j], Shoshana Keren Rosenberg[k], Mariana Wollner[l], Alona Zer[f], Jair Bar[m,1], Naomi Gronich[a,b,1]

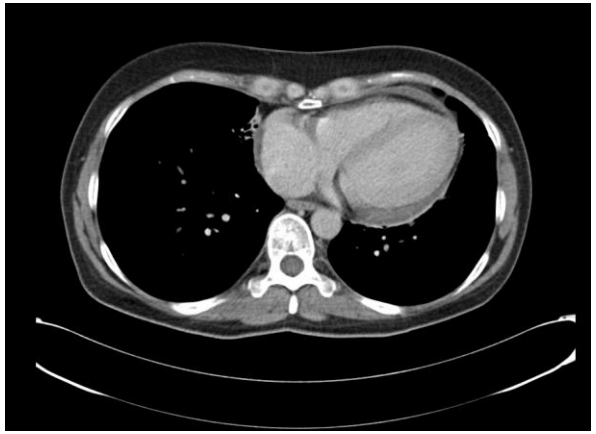
[a] Clalit Health Services National Cancer Control Center and Personalized Medicine Program, Israel







Our patient PFS: 15 months

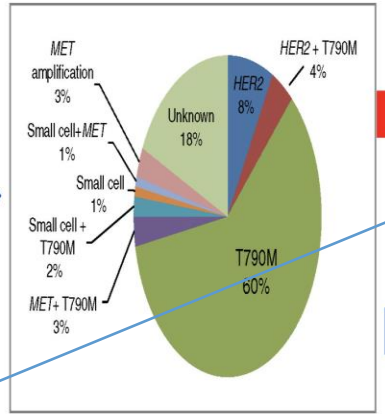


Back to hospital for **Cardiac tamponade**
Poor general condition
Requires surgical evacuation

PFS: 15 months

Plasma negative at T790M

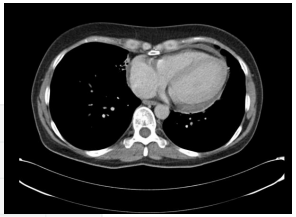
Erlotinib or gefitinib or afatinib

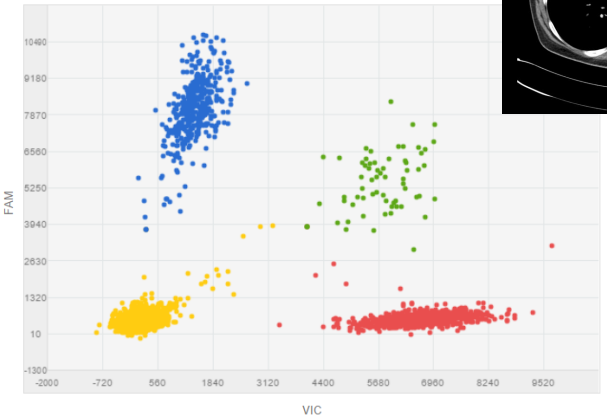


T790M-ve: Chemotherapy

T790M+ve Osimertinib

0% live at 5 years
PFS: 4 months



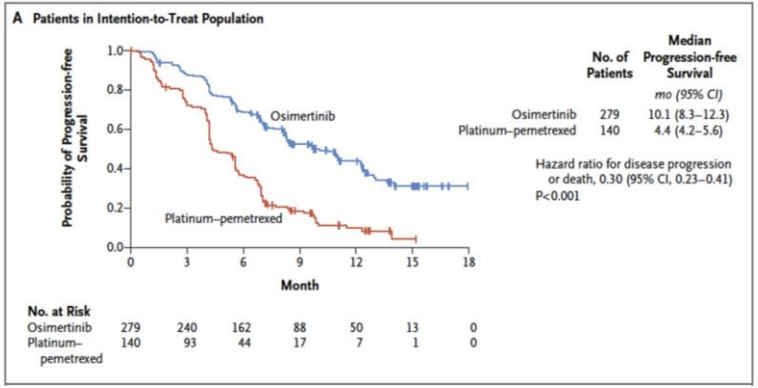


T790M mutation identified in pericardial liquid

Osimertinib treatment started

What to expect from Chemotherapy?

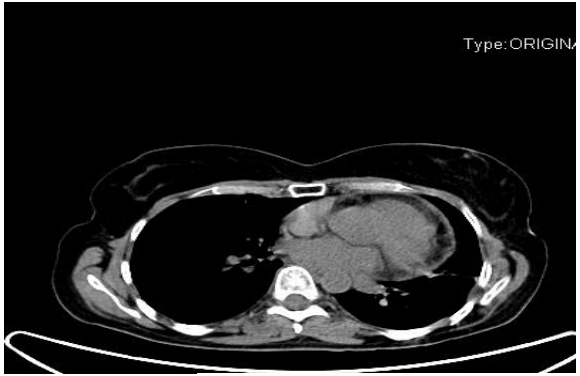
Osimertinib in T790M+ acquired resistance to EGFR TKIs



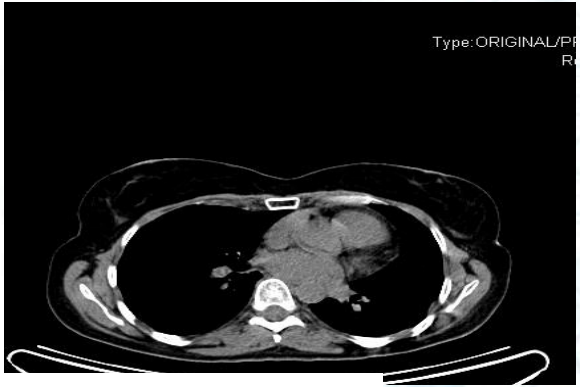
DE GRUYTER Clin Chem Lab Med 2021; aop

Clara Pérez-Barrios*, Estela Sánchez-Herrero, Natalia Garcia-Simón, Miguel Barquín, Mariola Blanco Clemente, Mariano Provencio and Atocha Romero

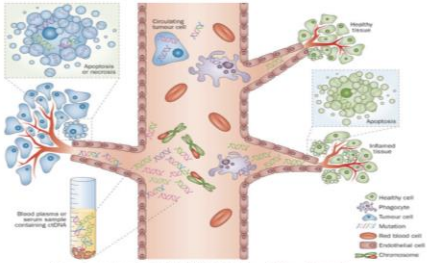
ctDNA from body fluids is an adequate source for *EGFR* biomarker testing in advanced lung adenocarcinoma



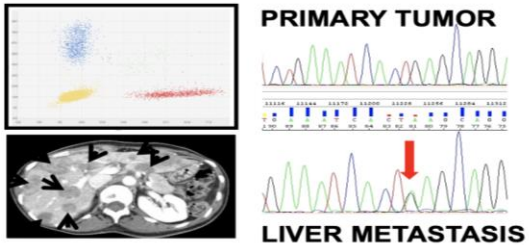
Complete Response



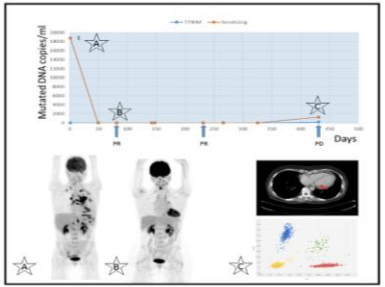
ctDNA



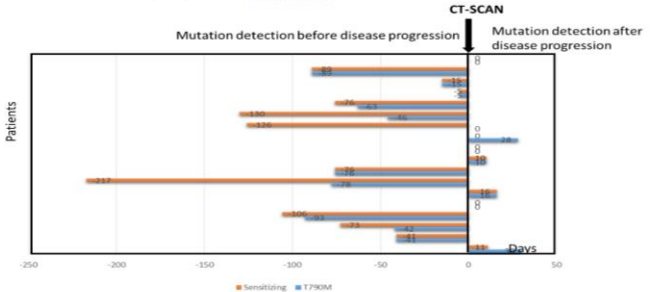
Crowley, E. et al. (2013) Nat. Rev. Clin. Oncol.



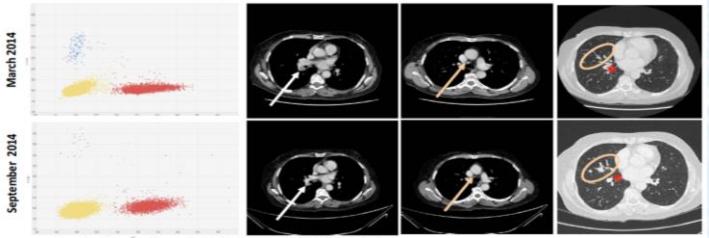
Romero A, et al . Translational Research 2015; 166(6):783-7



Provencio M , et al . Oncotarget. 2017 Aug 7;8(36):60291-6029



Provencio M , et al . Oncotarget. 2017 Nov 16;9(1):488-494



García-Sáenz JA et al. BMC Cancer 2017;17(1):210

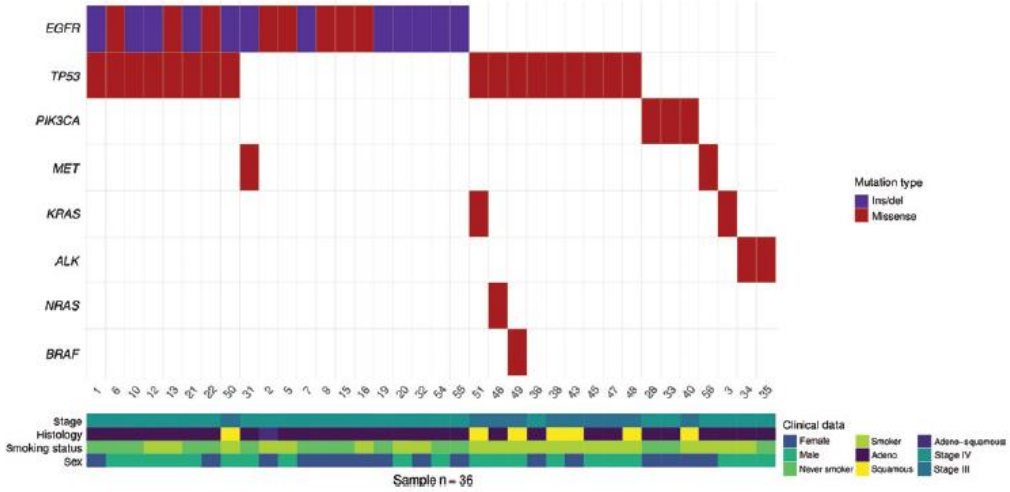
ctDNA NGS profiling is feasible. HPH experience.

DE GRUYTER

Clin Chem Lab Med 2019; aop

Mariano Provencio[a], Clara Pérez-Barrios[a], Miguel Barquin[a], Virginia Calvo, Fabio Franco, Estela Sánchez, Ricardo Sánchez, Daniel Marsden, Juan Cristóbal Sánchez, Paloma Martin Acosta, Raquel Laza-Briviesca, Alberto Cruz-Bermúdez and Atocha Romero*

Next-generation sequencing for tumor mutation quantification using liquid biopsies



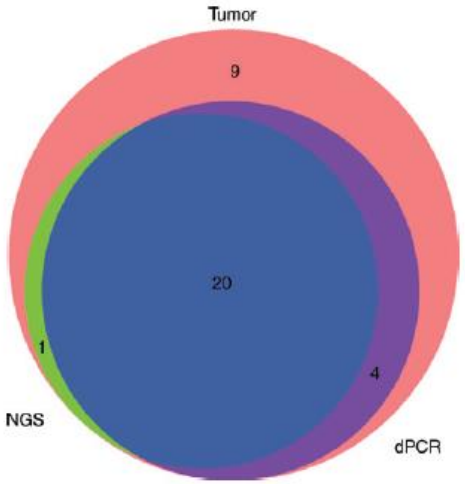


Figure 3: Venn diagram summarizing the number of mutations identified by NGS (green), dPCR (purple) and reported according to pathologist report (pink) and overlapping results (blue).

Clinical Utility of Comprehensive Cell-free DNA Analysis to Identify Genomic Biomarkers in Patients with Newly Diagnosed Metastatic Non–small Cell Lung Cancer

…ria M. Raymond[3], Davey B. Daniel[4], …[6], Miguel A. Villalona-Calero[7], Daniel Dix[3], …n[3], and Vassiliki A. Papadimitrakopoulou[8]

Table 2. Genotype-tailored therapies and their outcomes in patients with actionable alterations in ctDNA

Patient	Highest-level actionable alteration	VAF (%)	Co-mutations	Line of therapy	Treatment	Treatment context	Best response	mPFS (months)	mOS (months)
1	*EGFR* (exon 19 del)	5.5	Yes	First line	Erlotinib ± Ramucirumab	Clinical trial (NCT02411448)	Partial response	*11.8*	*14.1*
2	*EGFR* (exon 19 del)	6.4	Yes	Second line	Afatinib	Standard care	Stable disease	*10.8*	*11.9*
3	*EGFR* (exon 19 del)	11.6	Yes	First line	Afatinib	Standard care	Partial response	*5*	*6.1*
4	*EGFR* (exon 19 del)	0.08	No	First line	Erlotinib	Standard care	Partial response	*7.7*	*11*
5	*EGFR* (L858R)	35.2	Yes	First line	Gefitinib	Standard care	Partial response	*7.2*	*10*
6	*EGFR* (L858R)	0.3	Yes	First line	Gefitinib	Standard care	Not evaluable[a]	*0.7*	1.1
7	*EGFR* (L858R)	10.3	Yes	First line	Afatinib	Standard care	Partial response	*8.1*	*8.2*
8	*ROS1* (SDC4-ROS1)	1.3	Yes	Second line	Crizotinib	Standard care	Partial response	3.6	5.2
9	*BRAF* (V600E)	0.3	No	Forth line	Dabrafenib + trametinib	Compassionate use	Partial response	3.7	*13.4*
10	*MET* (exon 14 skip)	8	Yes	Second line	Crizotinib	Compassionate use	Progressive disease	0.5	1.9
11	*HER2* (S310F)	2.2	Yes	Third line	Paclitaxel + trastuzumab	Compassionate use	Stable disease	2.9	10.4
12	*FGFR1* (AMP)		Yes	Second line	Docetaxel + nintedanib	Standard care	Partial response	2.8	*13.8*

Italicized numbers correspond to censored events.

[a]This patient died of septicemia and the disease could not be evaluated for response.

VAF, variant allele frequency; AMP, amplification; mPFS, median progression-free survival; mOS, median overall survival.

…ping is chal-
…ts with newly
…r (mNSCLC)
… biomarkers
…med to dem-
…ll-free DNA
…ndard-of-care
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…patients with
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Results: Among 282 patients, physician discretion SOC tissue genotyping identified a guideline-recommended biomarker in 60 patients versus 77 cfDNA identified patients (21.3% vs. 27.3%; $P \leq 0.0001$ for noninferiority). In tissue-positive patients, the biomarker was identified alone (12/60) or concordant with cfDNA (48/60), an 80% cfDNA clinical sensitivity for any guideline-recommended biomarker. For FDA-approved targets (*EGFR*, *ALK*, *ROS1*, *BRAF*) concordance was >98.2% with 100% positive predictive value for cfDNA versus tissue (34/34 *EGFR*-, *ALK*-, or *BRAF*-positive patients). Utilizing cfDNA, in addition to tissue, increased detection by 48%, from 60 to 89 patients, including those with negative, not assessed, or insufficient tissue results. cfDNA median turnaround time was significantly faster than tissue (9 vs. 15 days; $P < 0.0001$). Guideline-complete genotyping was significantly more likely (268 vs. 51; $P < 0.0001$).

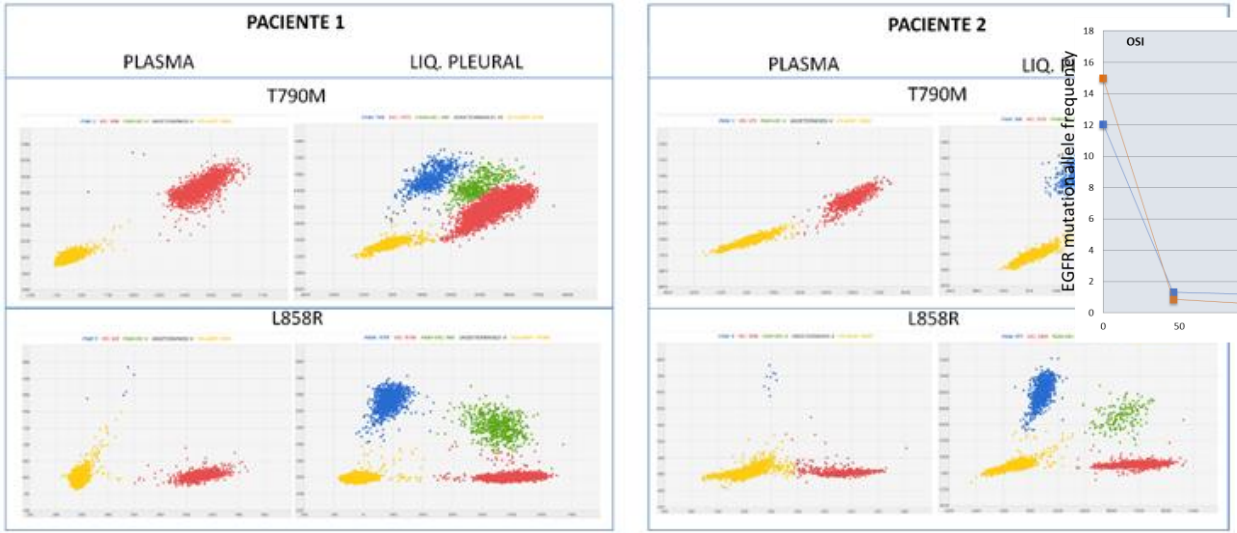
Conclusions: In the largest cfDNA study in previously untreated mNSCLC, a validated comprehensive cfDNA test identifies guideline-recommended biomarkers at a rate at least as high as SOC tissue genotyping, with high tissue concordance, more rapidly and completely than tissue-based genotyping.

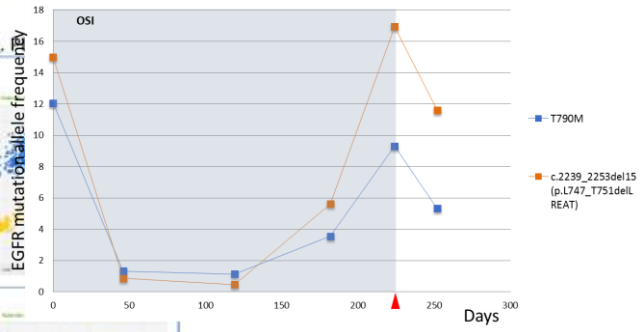
See related commentary by Meador and Oxnard, p. 4583

Zugazagoitia J et al. Clinical utility of plasma-based digital next-generation sequencing in patients with advance-stage lung adenocarcinomas with insufficient tumor samples for tissue genotyping.Ann Oncol. 2019 Feb 1;30(2):290-296

Testing. EXPERIENCE FROM HPH

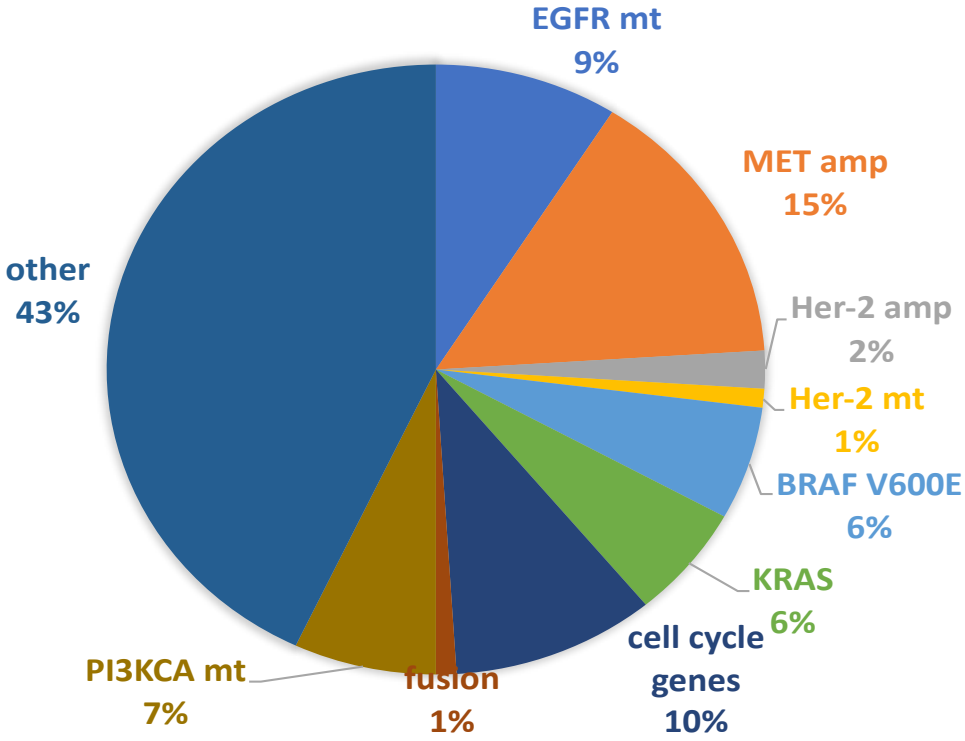
- Malignant effusions are very informative
- AF increases over time. T790M detection rate increases when more than one sample is tested. Changes can be seen within days.





Profile of acquired resistance to osimertinib in 1st

1st line osimertinib



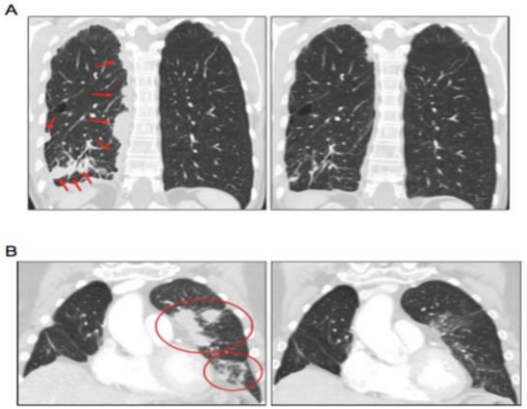
Ramalingam ESMO 18

Cancer Discov. 2018 Sep 26. doi: 10.1158/2159-8290.CD-18-1022. [Epub ahead of print]

Final Version Cancer Discovery

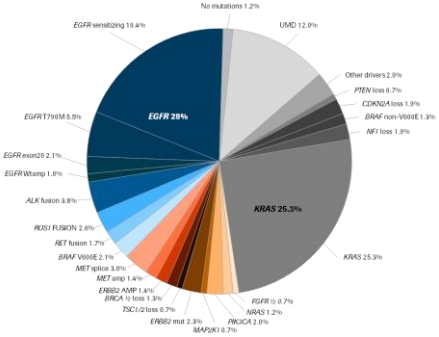
Landscape of Acquired Resistance to Osimertinib in *EGFR*-Mutant NSCLC and Clinical Validation of Combined EGFR and RET Inhibition with Osimertinib and BLU-667 for Acquired *RET* Fusion.

Piotrowska Z[#1], Isozaki H[#1], Lennerz JK[2], Gainor JF[1], Lennes IT[1], Zhu VW[3], Marcoux N[1], Banwait MK[1],



Responses observed in the two patients treated with osimertinib and BLU-667

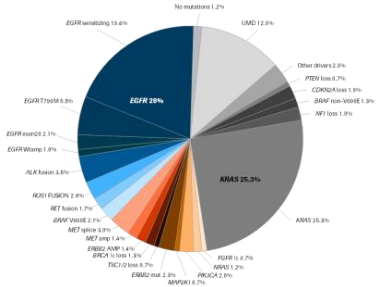
Selpercatinib vs. Pralsetinib



	Pralsetinib (BLU-667)		Selpercatinib (LOXO–292)	
	Prior Platinum	Tx Naive	Prior Platinum	Tx Naive
n (ITT response)	92	29	105	39
ORR (%)	61% (55%)	73% (66%)	64%	85%
CNS Evaluable Response (n)	9		22	
CNS ORR (%)	56%		82%	
DOR	NR (11.3 - NR)		18	NR (12-NR)
Median follow-up (mo)	7.5	3.7	14	9
PFS (mo)	-	-	17	NE
Dosing	400 mg daily		160 mg BID	

PRESENTED AT: 2020 ASCO ANNUAL MEETING #ASCO20 Slides are the property of the author, permission required for reuse. PRESENTED BY: Ryan Gentzler, MD, MS

Gainor J, et al. ASCO 2020
Subbiah et al. ASCO 2020

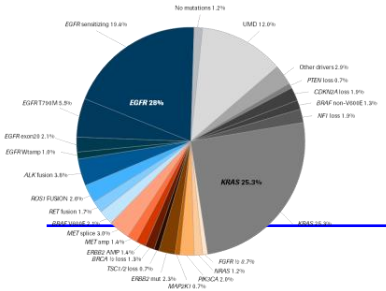


MET TKI in *MET*ex^{14} NSCLC

	Dose	Line	N	RR (%)	PFS (mo.)
CRIZOTINIB (PROFILE 1001)	250 mg BID	**Naïve**	**24**	**25**	**7.3**
CAPMATINIB (GEOMETRY)	400 mg BID	**Naïve (cohort 5B)**	**28**	**68**	**12.4**
TEPOTINIB (VISION)	500 mg QD FDA priority review	**Naïve**	**43**	**44**	**8.5**
SAVOLITINIB	600 mg QD (≥ 50 Kg) 400 mg QD (< 50 Kg)	**Naïve**	**28**	**46**	**5.6**

Capmatinib: icRR 54% (7/13)

Drilon- Nature Med 20202 * Wolf –NEJM 2020 * Garon – AACR 2020 * Groen –ASCO 2020 * Paik- NEJM 2020 * Lu – ASCO 2020



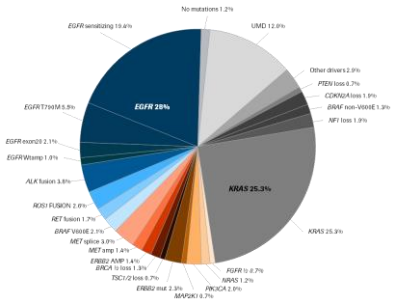
MET TKI in *MET* amp NSCLC

	Ampl	N	RR(%)	PFS (mo.)	OS (mo.)
CRIZOTINIB (PROFILE 1001)	GCN≥4	20	40	6.7	
	GCN >2.2 - <4	14	14	1.9	NR
	GCN <2.2	3	33	1.8	
CRIZTONIB (AcSé)	GCN ≥ 6	25	16	3.2	5.7
CRIZOTINIB (METROS)	GCN ≥ 2	16	31	5.0	NR

Higher efficacy as higher is the MET amplification
However, even in high MET (≥ 10) EFFICACY is MODEST
Therefore, are MET TKI the best approach for MET amp NSCLC?

CAPMATINIB (GEOMETRY)	MET/CEP7 ≥10 Naïve	14	40	4.2	9.6
	MET/CEP7 ≥ 10 Pre	55	29	4.1	10.6
SYM105	MET/CEP7 ≥2 Naïve	7	29	5.5	NR
	MET/CEP7 ≥ 2 Pre	1	NR	5.4	

Camidge –ASCO 2018 * Moro-Sibilot –AoO 2019 * Landi – CCR 2019 * Schuler – AoO 2020 * Wolf- ASCO 2020 * Camidge – ASCO 2020



- **Clinical Case**
- **Woman**: 56 years, no smoker
- **Diagnosis**: lung cancer IV stage- July 2014
- **Metastasis**: bones, ganglions and lung

ORIGINAL REPORT

Economic Impact of Next-Generation Sequencing Versus Single-Gene Testing to Detect Genomic Alterations in Metastatic Non–Small-Cell Lung Cancer Using a Decision Analytic Model

Nathan A. Pennell, MD, PhD[1]; Alex Mutebi, PhD[2]; Zheng-Yi Zhou, PhD[3]; Marie Louise Ricculli, MSc[3]; Wenxi Tang, MS[3]; Helen Wang[3]; ...

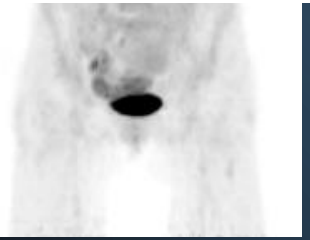
- Compared sequential or simultaneous testing of single gene tests for EGFR-ALK-ROS1-BRAF to up-front NGS.
- Used CMS and commercial payer reimbursement rates for testing in a hypothetical cohort of NSCLC patients.

NGS versus Single Gene Results

- Up-front NGS saved between $127K and $1.5M compared to single gene testing
- Time to test results was fastest with NGS and more pts were successfully tested than with single-gene

Pennell N et al. JCO Prec Oncol 2019

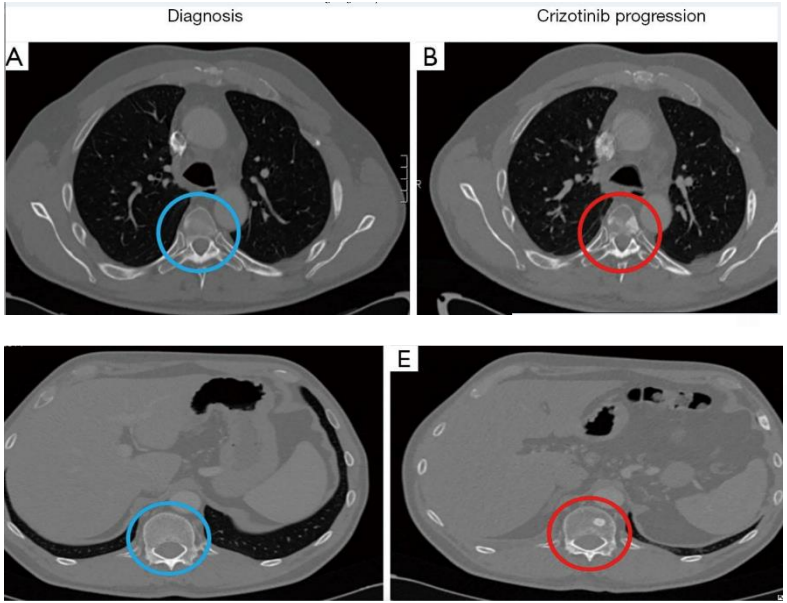
5 Years Survival rate with chemotherapy: **0%**



The need to determine precisely what happens is not important only during the initial diagnosis….

Next-generation sequencing to dynamically detect mechanisms of resistance to *ALK* inhibitors in *ALK*-positive NSCLC patients: a case report

Estela Sánchez-Herrero[1], Mariola Blanco Clemente[2], Virginia Calvo[2], Mariano Provencio[1,2], Atocha Romero[1,2]



Mutation status	Cellular ALK Phosphorylation Mean IC_{50} (nM)				
	Crizotinib	Ceritinib	Alectinib	Brigatinib	Lorlatinib
EML4-ALK	38.6	4.9	11.4	10.7	2.3
C1156Y	61.9	5.3	11.6	4.5	4.6
I1171N	130.1	8.2	397.7	26.1	49.0
I1171S	94.1	3.8	177.0	17.8	30.4
I1171T	51.4	1.7	33.6	6.1	11.5
F1174C	115.0	38.0[a]	27.0	18.0	8.0
L1196M	339.0	9.3	117.6	26.5	34.0
L1198F	0.4	196.2	42.3	13.9	14.8
G1202R	381.6	124.4	706.6	129.5	49.9
G1202del	58.4	50.1	58.8	95.8	5.2
D1203N	116.3	35.3	27.9	34.6	11.1
E1210K	42.8	5.8	31.6	24.0	1.7
G1269A	117.0	0.4	25.0	ND	10.0

A plasma sample was obtained at this time and sequenced on an Ion S5™ Sequencer (Thermo Fisher, Palo Alto, CA) using the Oncomine™ Lung cfDNA Assay NGS panel (Thermo Fisher, Palo Alto, CA) to examine circulating tumor DNA (ctDNA).

The NGS study revealed the presence of the p.**Gly1269A** (c.3806G>C) resistance mutation in the *ALK* gene (MAF =0.88%)

Next, using dPCR, we analyzed the p.Gly1269Ala (c.3806G>C) mutation in a plasma sample collected previously than the former. This technique **did not detect the p.Gly1269Ala** (c.3806G>C) mutation

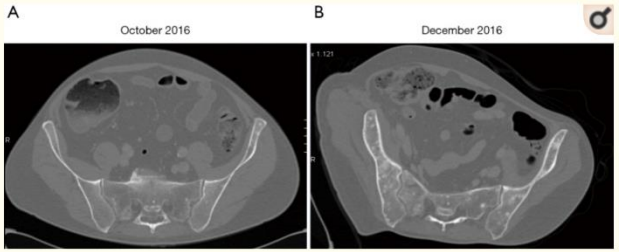
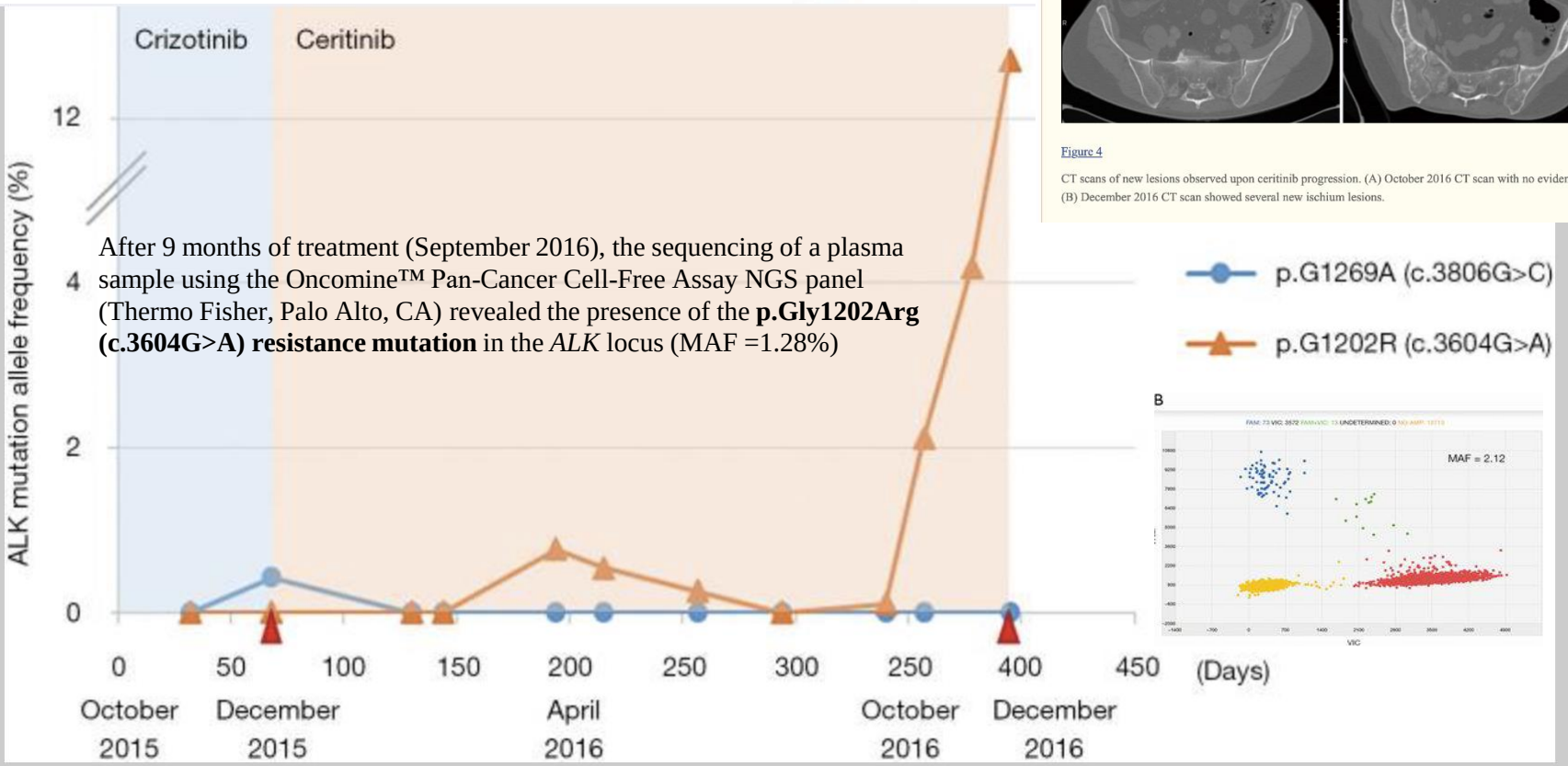


Figure 4

CT scans of new lesions observed upon ceritinib progression. (A) October 2016 CT scan with no evidence of PD; (B) December 2016 CT scan showed several new ischium lesions.

After 9 months of treatment (September 2016), the sequencing of a plasma sample using the Oncomine™ Pan-Cancer Cell-Free Assay NGS panel (Thermo Fisher, Palo Alto, CA) revealed the presence of the **p.Gly1202Arg (c.3604G>A) resistance mutation** in the *ALK* locus (MAF =1.28%)

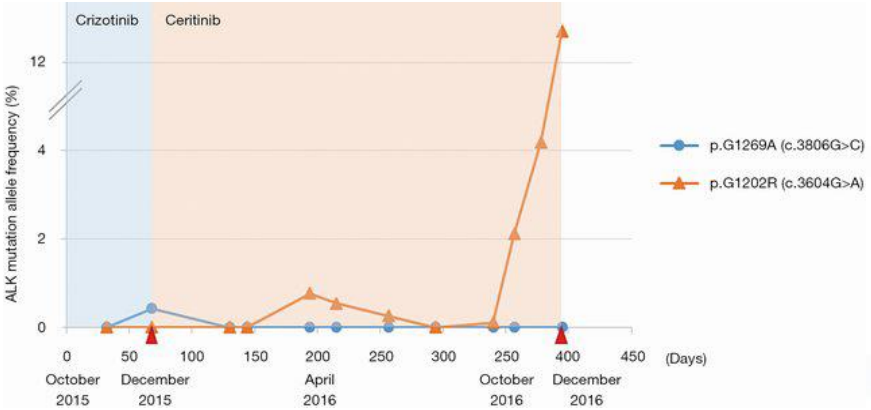


Next-generation sequencing to dynamically detect mechanisms of resistance to *ALK* inhibitors in *ALK*-positive NSCLC patients: a case report

Estela Sánchez-Herrero[1], Mariola Blanco Clemente[2], Virginia Calvo[2], Mariano Provencio[1,2], Atocha Romero[1,2]

[1]Molecular Oncology Laboratory, Biomedical Sciences Research Institute, [2]Medical Oncology Department, Puerta de Hierro-Majadahonda University Hospital, Madrid, Spain

Retrospective analysis of all 12 plasma samples collected by dPCR revealed that the p.Gly1202Arg (c.3604G>A) mutation was not present during the crizotinib treatment,
but appeared between the fourth and sixth months (April-June 2016) after the start of the ceritinib treatment.



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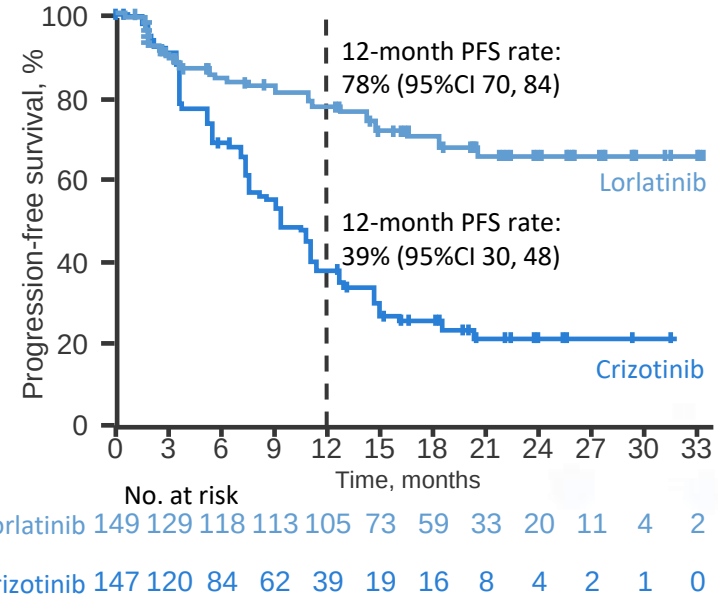
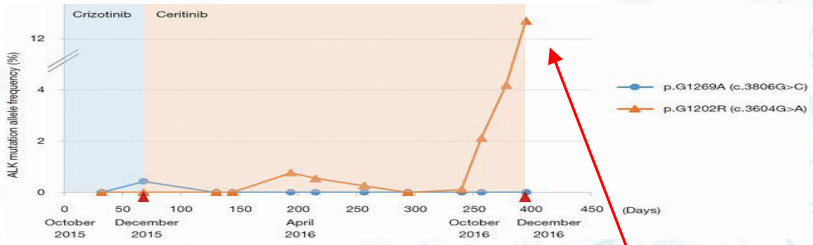
LBA2: Lorlatinib vs crizotinib in the first-line treatment of patients (pts) with advanced ALK-positive non-small cell lung cancer (NSCLC): Results of the Phase 3 CROWN study – Solomon B, et al

- **Key results**

PFS by BICR



*By stratified log-rank test



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Solomon B, et al. Ann Oncol 2020;31(suppl):Abstr LBA2

Emerging KRAS inhibitors as a potential treatment for KRAS-mutated NSCLC

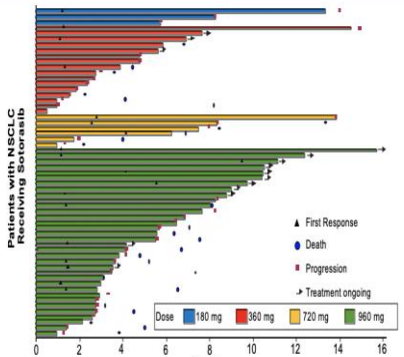
CodeBreak™ 100: Responses in Patients With NSCLC

Emerging KRAS inhibitors as a potential treatment for KRAS-mutated NSCLC
CodeBreak™ 100: Responses in Patients With NSCLC

	960 mg (n = 34)	All Patients (n = 59)
Best Overall Response per Investigators' Assessment, n (%)		
Confirmed Partial Response	12 (35.3)	19 (32.2)
Stable Disease	19 (55.9)	33 (55.9)
Progressive Disease	2 (5.9)	5 (8.5)
Not Evaluable	1 (2.9)	1 (1.7)
Not Done*	0	1 (1.7)
Confirmed Objective Response Rate†, % (95% CI)	35.3 (19.8, 53.5)	32.2 (20.6, 45.6)
Disease Control Rate‡, % (95% CI)	91.2 (76.3, 98.1)	88.1 (77.1, 95.1)

- Tumor shrinkage of any magnitude from baseline was observed in 42 patients (71.2%) at the first week 6 assessment
- At the 960 mg dose (n = 34), confirmed ORR was 35.3% and DCR was 91.2%
  - 960 mg dose was identified as the Phase II dose in NSCLC

Emerging KRAS inhibitors as a potential treatment for KRAS-mutated NSCLC
CodeBreak™ 100: Duration of clinical benefit and progression-free survival

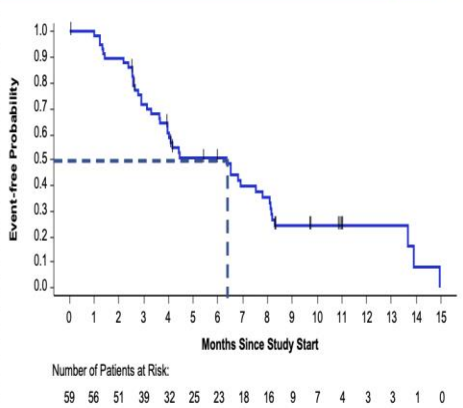


Confirmed PR, n = 19

Patients with SD, n = 33

Duration of response*	Duration of stable disease‡
Median of 10.9 (1.1+ to 13.6) months	Median of 4.0 (1.4 to 10.9+) months

10/19 responders still in response†



Median PFS: 6.3 (range 0.0+ to 14.9) months

*Duration of response was measured from first evidence of PR/CR to disease progression or death due to any cause, whichever was earlier. †At data cutoff of June 1, 2020. ‡Duration of SD was measured from the start of the treatment until the criteria for disease progression were met or death, whichever was earlier. + Indicates censored value. Median follow-up time was 11.7 (range 4.8-21.2) months.

CR, complete response; **NSCLC,** non-small cell lung cancer; **PFS,** progression-free survival; **PR,** partial response; **SD,** stable disease.

Hong DS. Oral presentation at European Society of Medical Oncology 2020 Virtual Congress, September 19-21, 2020.

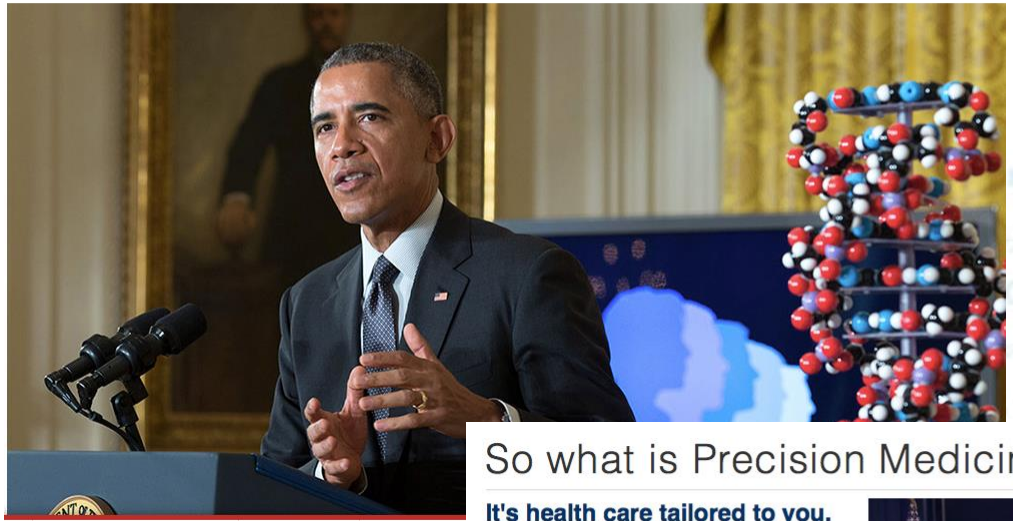
The NEW ENGLAND JOURNAL of MEDICINE

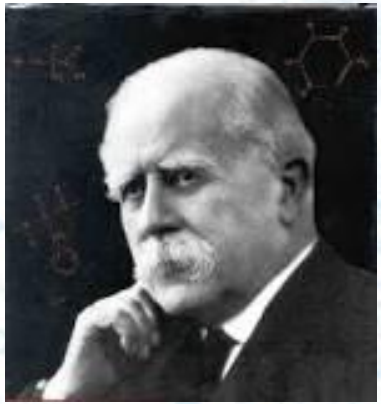
ORIGINAL ARTICLE

$KRAS^{G12C}$ 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

THE PRECISION MEDICINE INITIATIVE





PRECISION MEDICINE | INITIATIVE | PRINCIPLES

So what is Precision Medicine?

It's health care tailored to you.

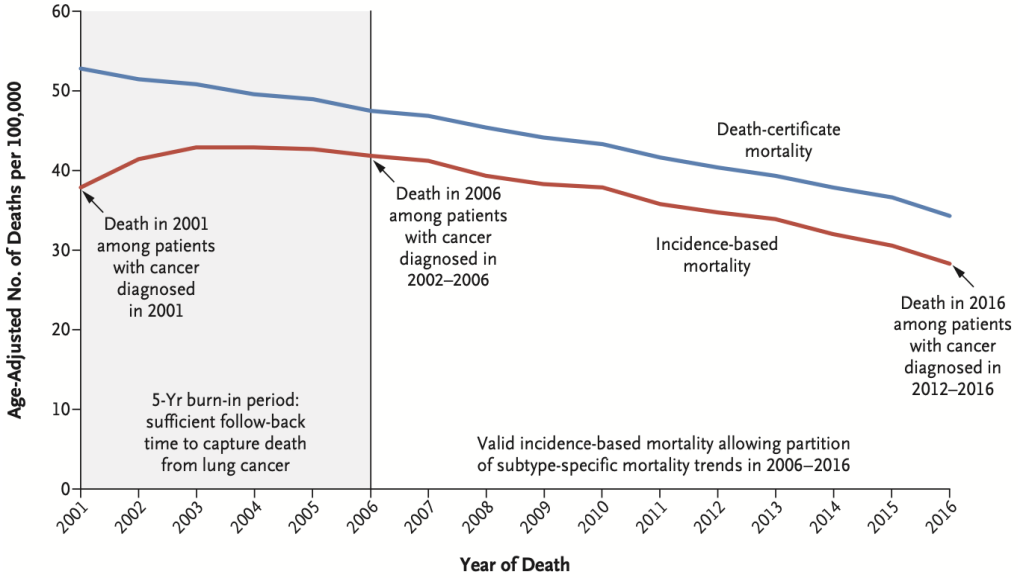
In his 2015 State of the Union address, President Obama announced that he's launching the Precision Medicine Initiative — a bold new research effort to revolutionize how we improve health and treat disease.

Until now, most medical treatments have been designed for the "average patient." As a result of this "one-size-fits-all" approach, treatments can be very successful for some patients but not for others. Precision Medicine, on the other hand, is an innovative approach that takes into account individual differences in people's genes, environments, and lifestyles.

President Obama participates in a panel discussion moderated by Dr. James Hamblin of The Atlantic on the importance of PMI at the White House, February 25, 2016.

The Effect of Advances in Lung-Cancer Treatment on Population Mortality

Nadia Howlader, Ph.D., Gonçalo Forjaz, D.V.M., Meghan J. Mooradian, M.D., Rafael Meza, Ph.D., Chung Yin Kong, Ph.D., Kathleen A. Cronin, Ph.D., Angela B. Mariotto, Ph.D., Douglas R. Lowy, M.D., and Eric J. Feuer, Ph.D.



Howlader N,. N Engl J Med. August 13, 2020

The Era of Precision in Medicine…

- ***Cancer: it's more than just a disease***
  - We are achieving incredible survival rates
  - NGS: mandatory

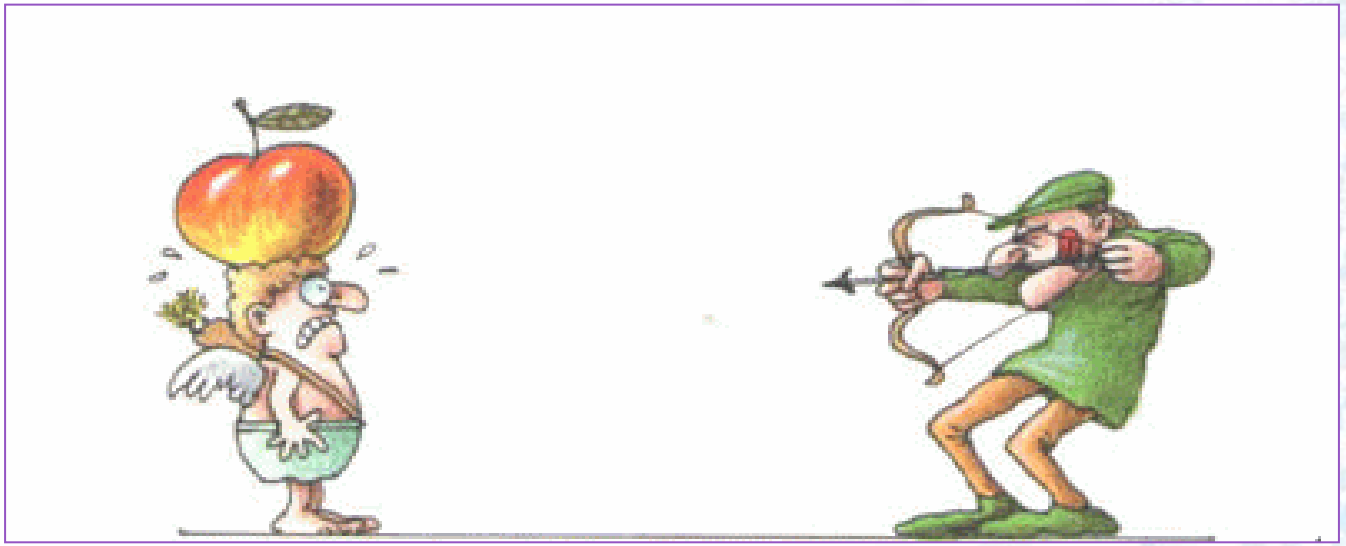
- ***Genomic testing***: it's a real revolution
  - If we do not look for molecular alterations ... we will not find them ...and it is not precision medicine
  - Explosion of liquid biopsy related publications
  - Resistance mecanisms to known actionable mutations

- **New therapy options**
  - The really are life changer

BIOLOGICAL BASES

BIOMARKER IDENTIFICATION

RIGHT DRUG RIGHT PATIENT



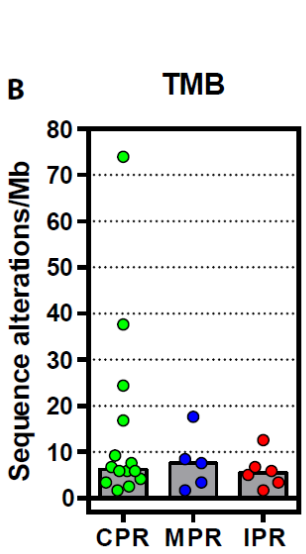
The enemy to fight

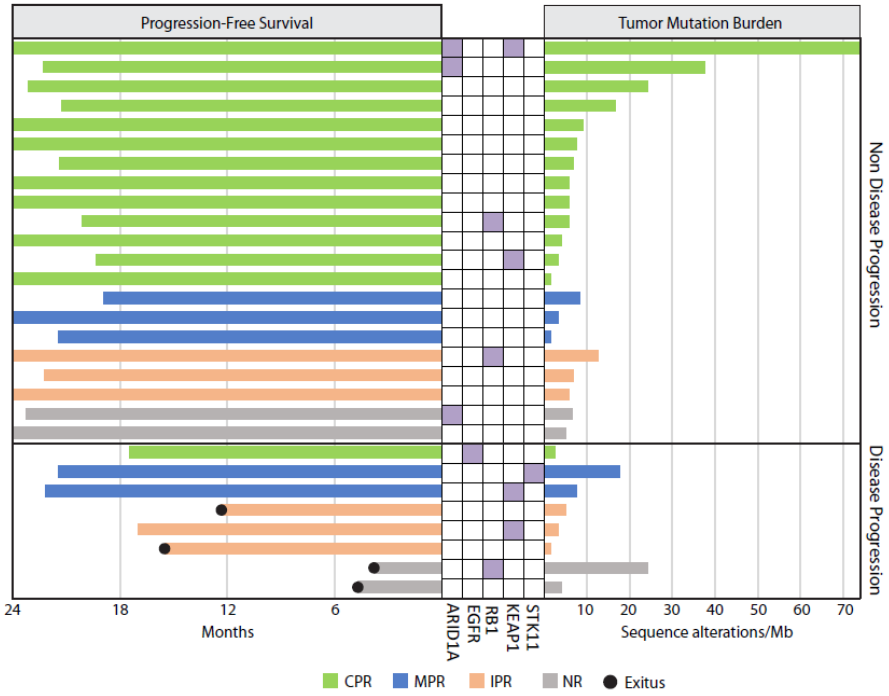
EXTRA SLIDES

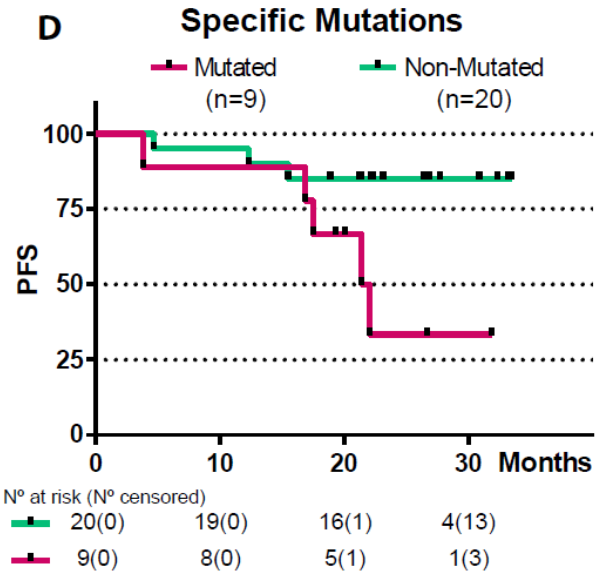
PRECISION MEDICINE STRATEGY

NADIM RESULTS

Specific Mutations

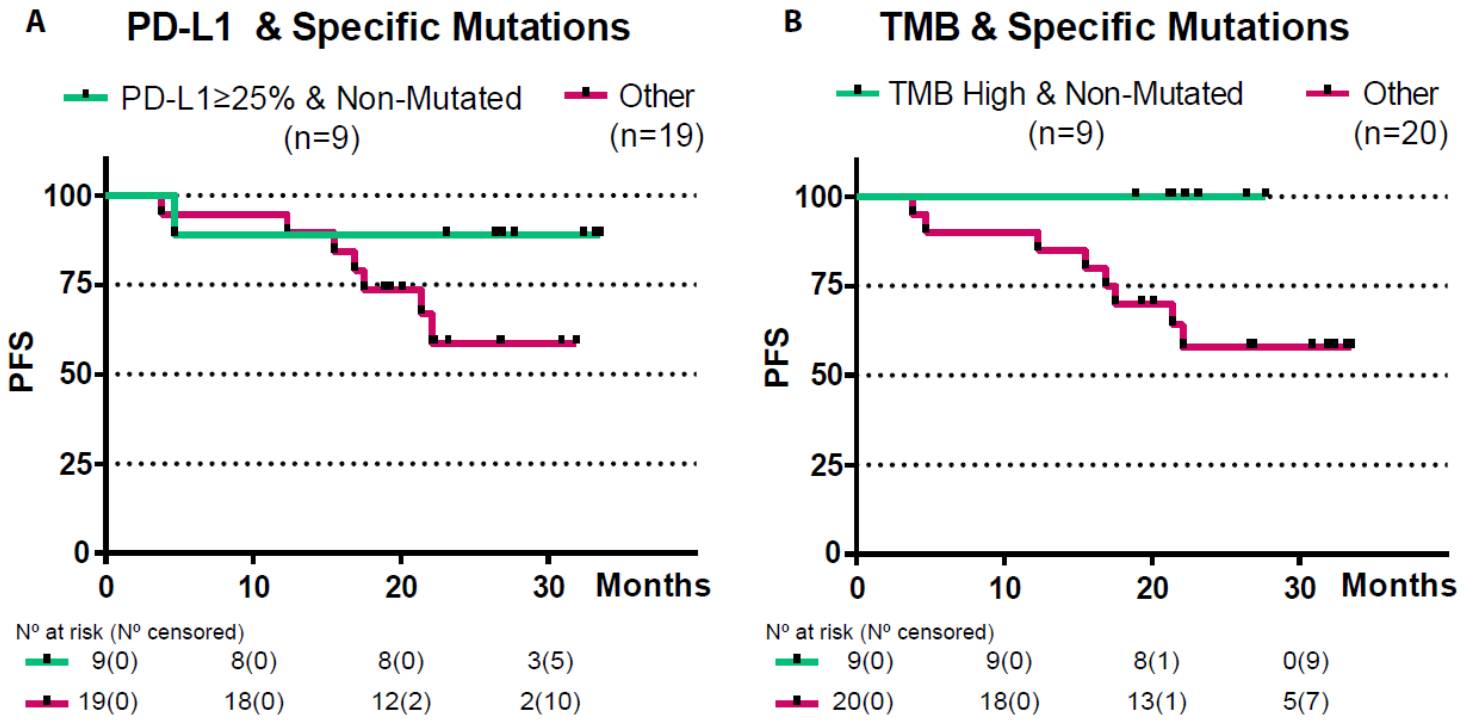






TMB was not associated to pR or PFS/OS but specific mutations were associated to PFS

Provencio et. al., Lancet Oncology 2020. in press



Provencio et. al., Lancet Oncology 2020. in press

PRECISION MEDICINE STRATEGY

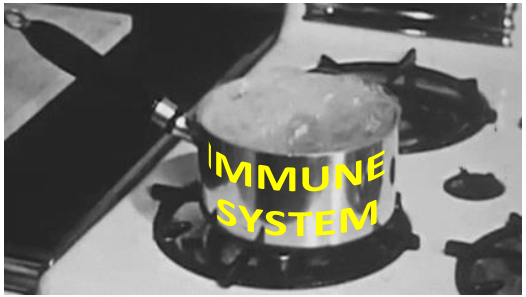
NADIM RESULTS

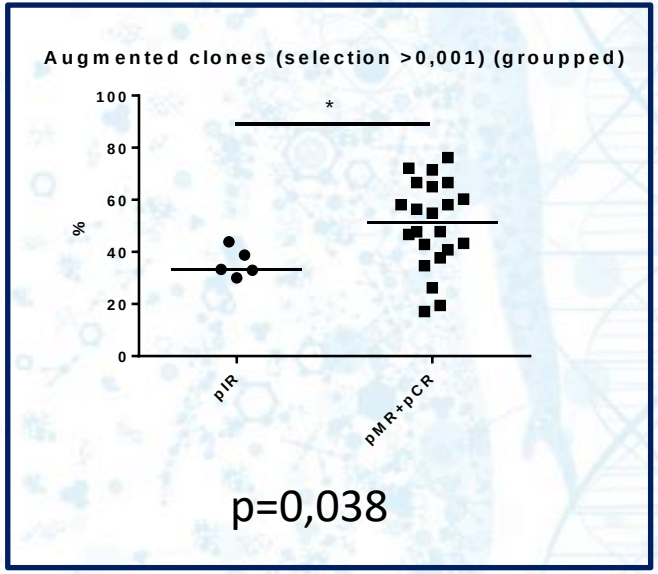
TCR Blood

Prediction of Response & TRAEs

TMB, PD-L1 TPS,
Tumor infiltrating Lymphocytes (TILs)
PBMCs populations & Soluble Factors
T-cell & B-Cell Repertoire
Microbiome & Gene expression RNA-seq

% of clones that vary its frequency between post and pre treatment samples





The % of clones higher than >0,001 that increase their frequency is associated with pathological responses > 90%

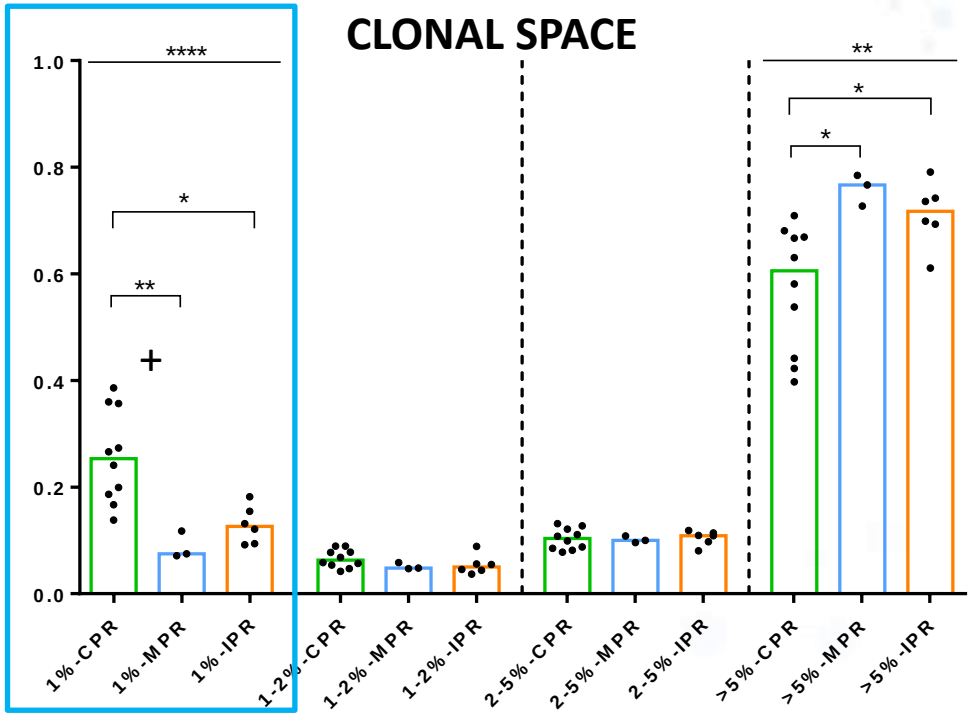
n=27

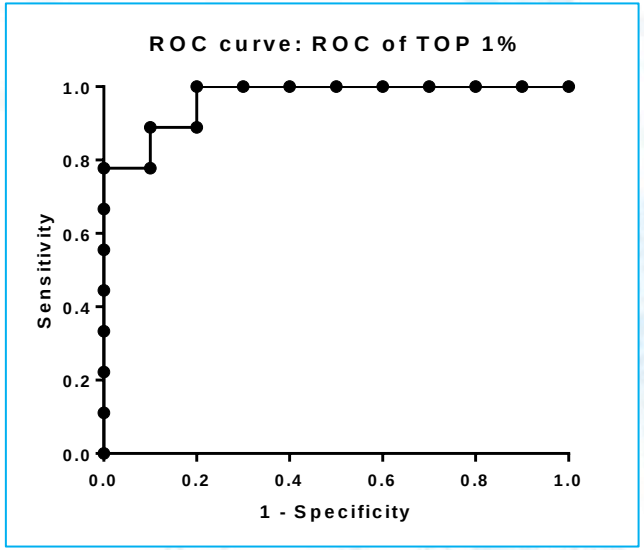
Casarrubios M et. al., 2020. Manuscript in preparation

PRECISION MEDICINE STRATEGY

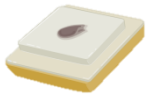
NADIM RESULTS

TCR Tissue





Area under the ROC curve	
Area	0.9667
Std. Error	0.03539
95% confidence interval	0.8973 to 1.036
P value	0.0006101



TOP1% Clonal space from Diagnostic FFPE predicts CPR with an AUC of 0.966

Casarrubios M et. al., 2020. Manuscript in preparation

PRECISION MEDICINE STRATEGY

CONCLUSIONS

More than 800 Molecular PARAMETERS ANALYSED from NADIM Study:

- PD-L1 TPS
- Tumor Mutational Burden
- Hemograms
- **Specific somatic Mutations**
- **Multiplex ImmunoFluorescence**
- **Immunophenotyping of PBMCs**
- **Cytokines**
- **T-Cell Receptor repertoire**
- **RNAseq expression profile**
- Microbiome
- ctDNA & MRD