I SIMPOSIO NACIONAL
de ONCOLOGÍA de PRECISIÓN

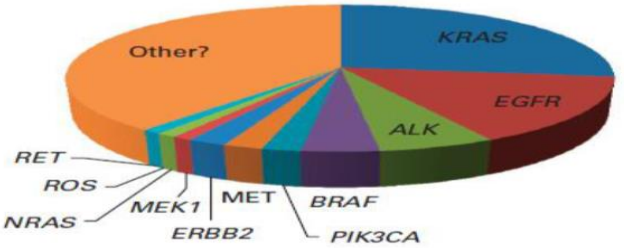
Vigo, del 28 de febrero al 1 de marzo de 2019

Necesidad de rebiopsia para elegir el tratamiento adecuado

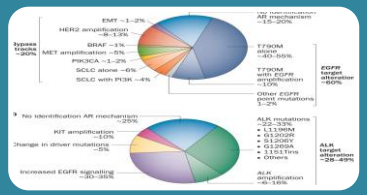
Dr. Marga Majem
Hospital de la Santa Creu i Sant Pau, Barceloan

Introduction

- Rebiopsy means to **biopsy after cancer progression on initial therapy.**
- Not the same concept as **repeated biopsy** → an initial biopsy was not adequate for histologic or molecular diagnosis.
- Several molecular alterations have been discovered with effective targeted therapies but with final progressive disease.



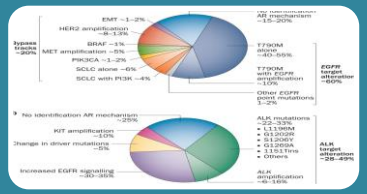
The importance of rebiopsy



To discover the mechanisms of resistance in patients with driver mutations and to develop more effective treatments

- EGFR-TKI

The importance of rebiopsy

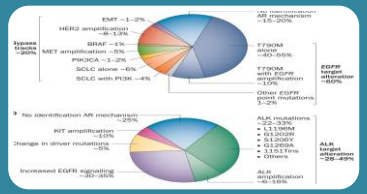


To discover the mechanisms of resistance in patients with driver mutations and to develop more effective treatments

- EGFR-TKI

To administer the best treatment based on the rebiopsy findings

The importance of rebiopsy



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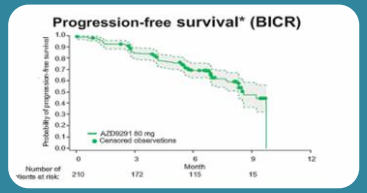


To improve survival of our patients

- Better Quality of life
- Less toxicity

Scenarios for rebiopsy

1. Patients with known genetic alterations.
2. Clinical trial setting → biomarker analysis after progressive disease

- **Not all samples are valid for rebiopsy.**

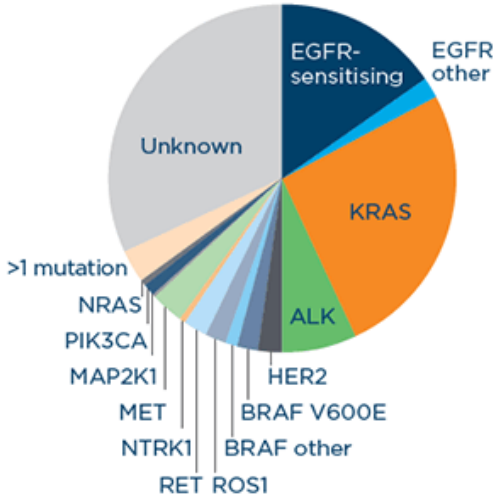
- Biopsy is generally preferred
- Cytology / cell block might not be useful (IHQ, …)

- Rebiopsies need **a multidisciplinary approach** to choose the more appropriate lesion for rebiopsy.
- Medical oncologists must explain the need for rebiopsies to their colleagues.

Patients with known genetic alterations

- All patients will develop resistance to TKI → Rebiopsy to detect acquired resistance mechanism.
  - **Tissue biopsies** to detect driver or AR mutations → NGS platforms.
  - **Liquid biopsies (NGS):** T790M and are being studied in other contexts.

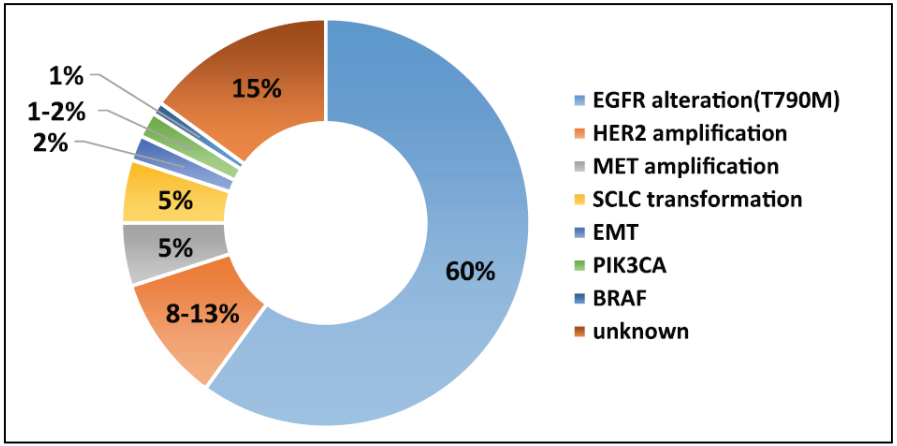
DRIVER MUTATIONS IN LUNG ADENOCARCINOMA

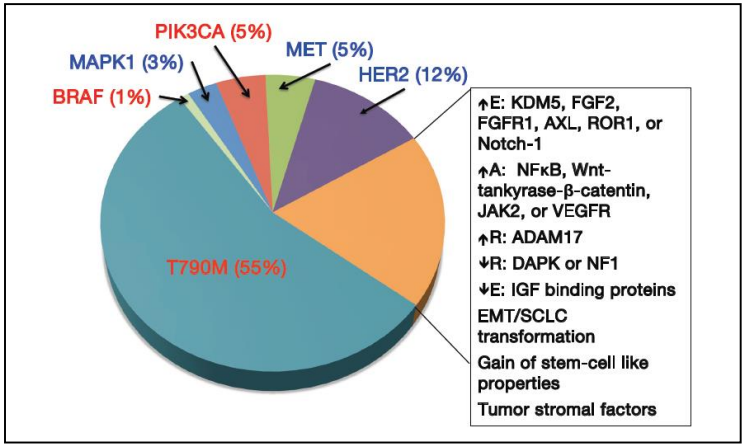


Driver mutations in lung adenocarcinoma	
EGFR-sensitizing	15%
EGFR other	2%
KRAS	25%
ALK	7%
HER2	2%
BRAF V600E	2%
BRAF other	1%
ROS1	2%
RET	2%
NTRK1	0–5%
MET	3%
MAP2K1	0–5%
PIK3CA	1%
NRAS	0–5%
>1 mutation	3%
Unknown	31%

Patients with EGFR mutation in NSCLC

- All patients will develop resistance to EGFR-TKI





T790M: RESISTANCE MUTATION

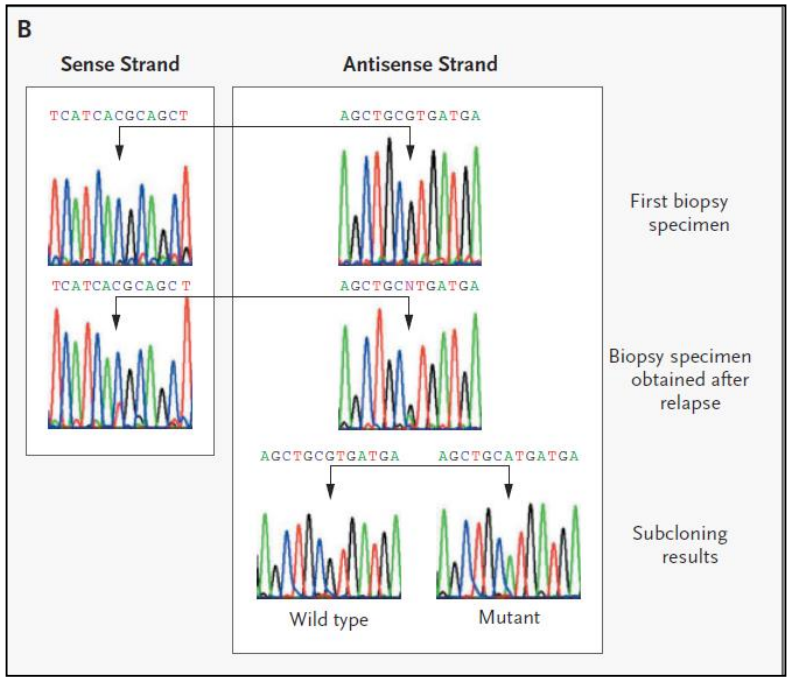
- Substitution at position 790 from a Threonine to a Methionine in exon 20.
- 50% - 60% of EGFR mutant with AR to EGFR-TKI.

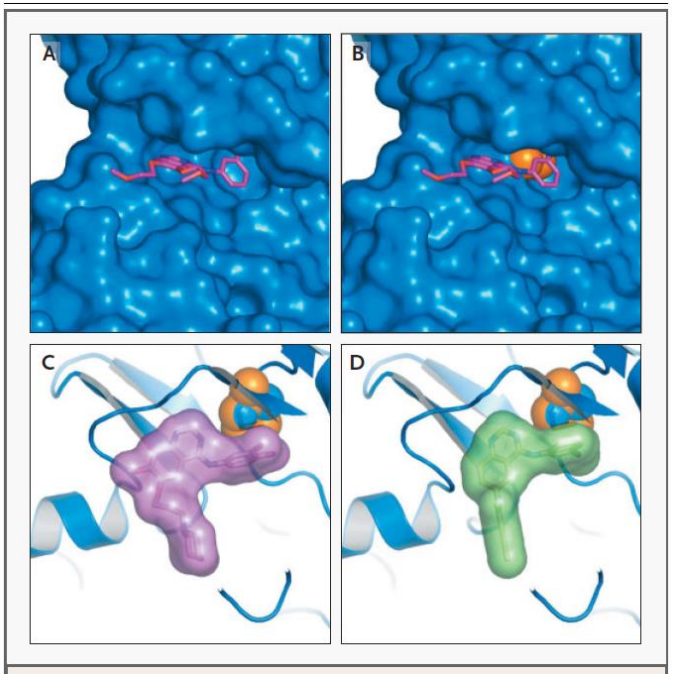
Wu and Shih Molecular Cancer (2018) 17:38; Stewart Transl Lung Cancer Res 2015;4(1):67-81

EGFR Mutation and Resistance of Non–Small-Cell Lung Cancer to Gefitinib

T790M

Susumu Kobayashi, M.D., Ph.D., Titus J. Boggon, Ph.D., Tajhal Dayaram, B.A.,



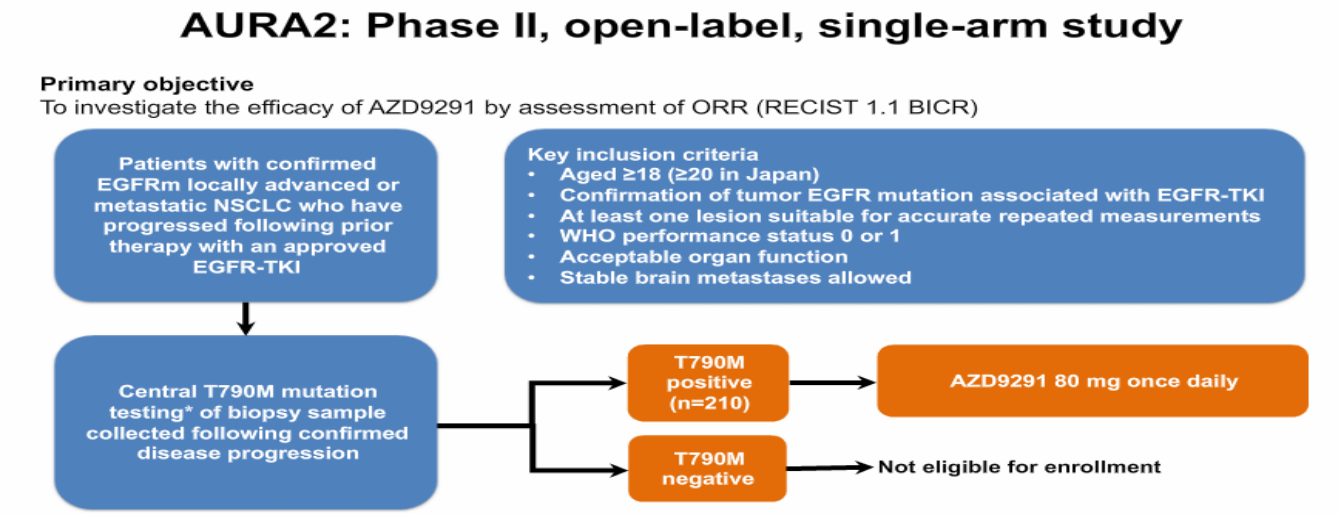


N Engl J Med 2005;352:786-92

REBIOPSY TO DETECT T790M AFTER PROGRESSION TO EGFR-TKI

Osimertinib for pretreated *EGFR* Thr790Met-positive advanced non-small-cell lung cancer (AURA2): a multicentre, open-label, single-arm, phase 2 study

Glenwood Goss, Chun-Ming Tsai, Frances A Shepherd, Lyudmila Bazhenova, Jong Seok Lee, Gee-Chen Chang, Lucio Crino, Miyako Satouchi, Quincy Chu, Toyoaki Hida, Ji-Youn Han, Oscar Juan, Frank Dunphy, Makoto Nishio, Jin-Hyoung Kang, Margarita Majem, Helen Mann, Mireille Cantarini, Serban Ghiorghiu, Tetsuya Mitsudomi



Lancet Oncol 2016

Osimertinib for pretreated *EGFR* Thr790Met-positive advanced non-small-cell lung cancer (AURA2): a multicentre, open-label, single-arm, phase 2 study

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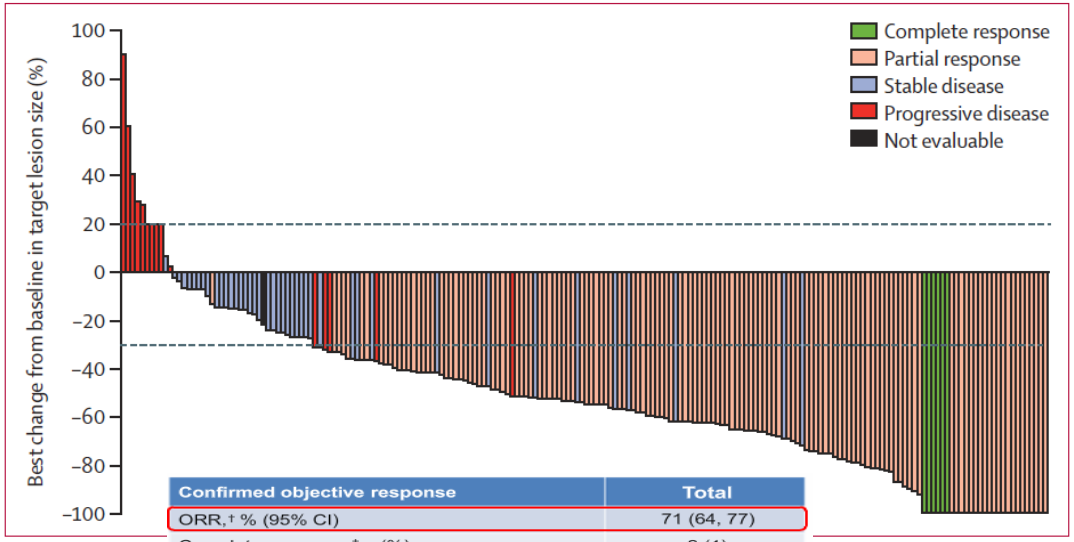


Confirmed objective response	Total
ORR,† % (95% CI)	71 (64, 77)
Complete response,‡ n (%)	2 (1)
Partial response,‡ n (%)	139 (70)
Stable disease ≥6 weeks,§ n (%)	41 (21)
Progressive disease, n (%)	15 (8)
DCR, % (95% CI)	92 (87, 95)

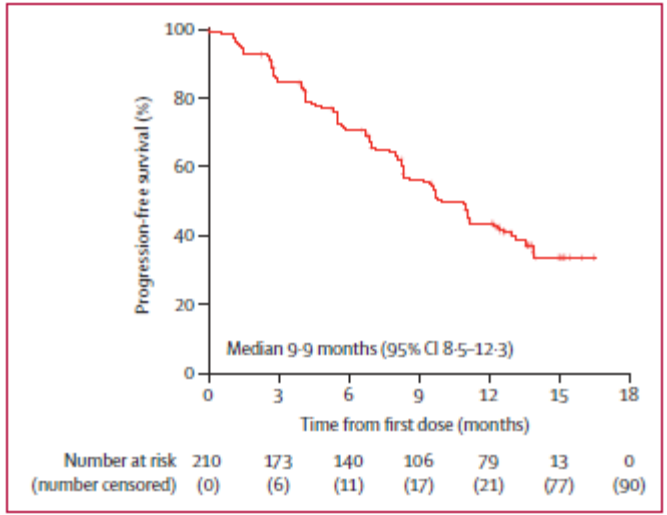


Figure 4: Kaplan-Meier curve for progression-free survival in all patients

Lancet Oncol 2016

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Osimertinib or Platinum–Pemetrexed in *EGFR* T790M–Positive Lung Cancer

T.S. Mok, Y.-L. Wu, M.-J. Ahn, M.C. Garassino, H.R. Kim, S.S. Ramalingam, F.A. Shepherd, Y. He, H. Akamatsu, W.S.M.E. Theelen, C.K. Lee, M. Sebastian, A. Templeton, H. Mann, M. Marotti, S. Ghiorghiu, and V.A. Papadimitrakopoulou, for the AURA3 Investigators*

AURA3 study design

Key eligibility criteria

- ≥18 years (≥20 years in Japan)
- Locally advanced or metastatic NSCLC
- Evidence of disease progression following first-line EGFR-TKI therapy
- Documented EGFRm and central confirmation of tumour *EGFR* T790M mutation from a tissue biopsy taken after disease progression on first-line EGFR-TKI treatment
- WHO performance status of 0 or 1
- No more than one prior line of treatment for advanced NSCLC
- No prior neo-adjuvant or adjuvant chemotherapy treatment within 6 months prior to starting first EGFR-TKI treatment
- Stable* asymptomatic CNS metastases allowed

• Patients were stratified at randomisation based on ethnicity (Asian/Non-Asian)

R 2:1

Osimertinib (n=279)
80 mg orally QD

Platinum-pemetrexed (n=140)
Pemetrexed 500 mg/m² + carboplatin AUC5 *or* cisplatin 75 mg/m² Q3W for up to 6 cycles + optional maintenance pemetrexed#

Endpoints

Primary:

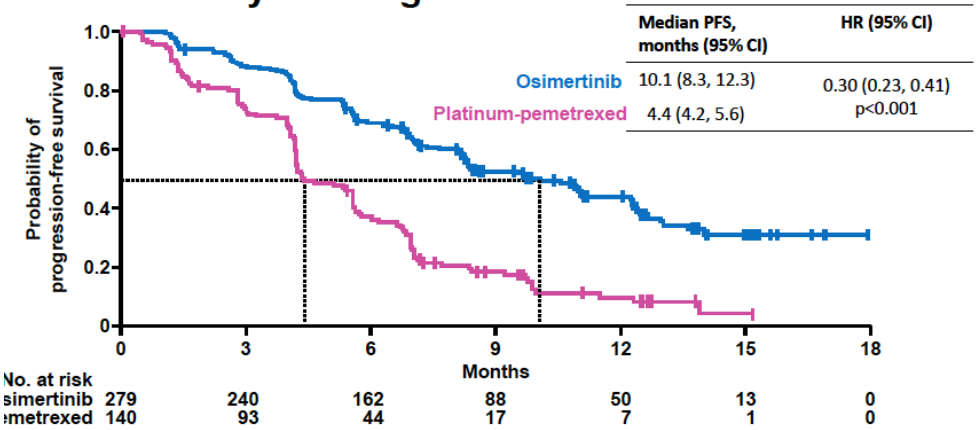
- **PFS by investigator assessment (RECISTv1.1)**

Secondary and exploratory:

- Overall survival
- Objective response rate
- Duration of response
- Disease control rate
- Tumour shrinkage
- BICR-assessed PFS
- Patient reported outcomes
- Safety and tolerability

Optional crossover
Protocol amendment allowed patients on chemotherapy to begin post-BICR confirmed progression open-label osimertinib treatment

AURA3 primary endpoint: PFS by investigator assessment



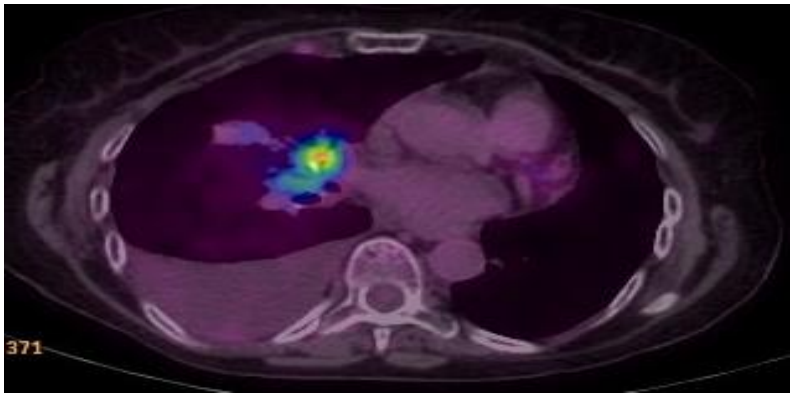
s of PFS by BICR was consistent with the investigator-based analysis: **HR 0.28** (95% CI 0.20, 0.38), p<0.001; PFS 11.0 vs 4.2 months.

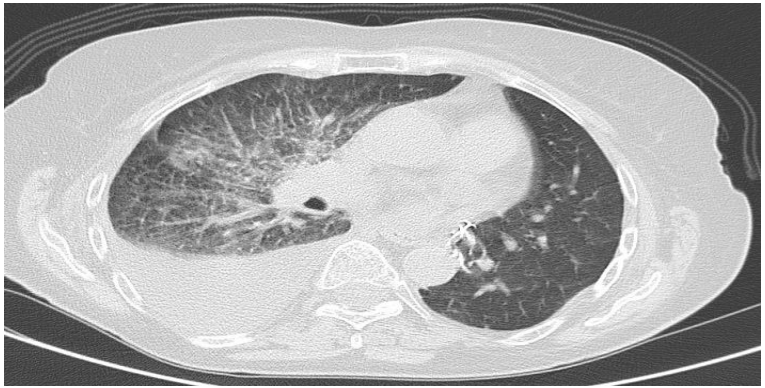
NEJM 2017

To determine T790M is not always easy

CLINICAL HISTORY

- 71-y woman, never smoker. Stage IV NSCLC with Ex19del EGFR mutation.
- PD after 1st gen EGFR-TKI and Chemotherapy.
- Lung biopsy with Bronchoscopy could not determine EGFR mutation status.
- Pleural biopsy with **VATS** → **Exon 19 del & Exon 20 T790M**
- Osimertinib 80 mg from 8/2014 (AURA2 Trial)
- Clinical benefit from the first week, partial response, still on treatment (2/2019).

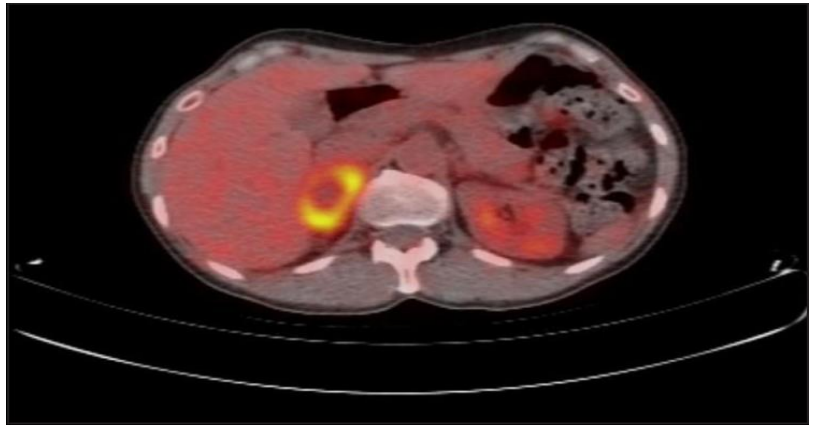




To determine T790M is not always easy

CLINICAL HISTORY

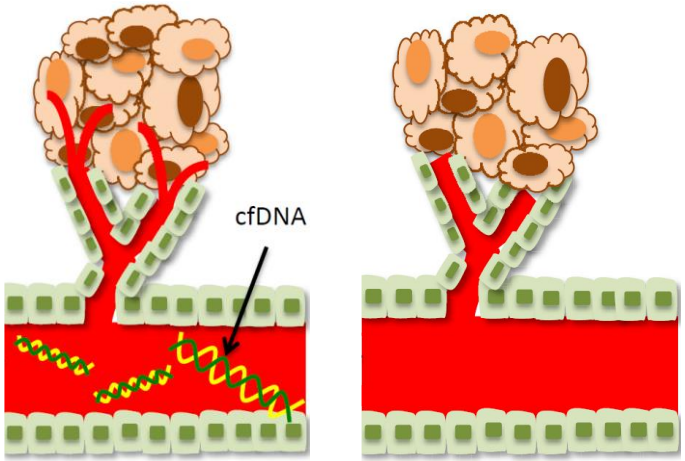
- 69-y woman, never smoker. Stage IV NSCLC with Ex19del EGFR mutation.
- Progression after 1st gen EGFR-TKI with adrenal met as unique accessible lesion to rebiopsy.
- 5/2014 Right **Suprarenalectomy → Exon 19 del & Exon 20 T790M**
- Osimertinib 80 mg from 6/2014 (AURA 2 Trial)
- Complete response, still on treatment (2/2019)



Liquid biopsy

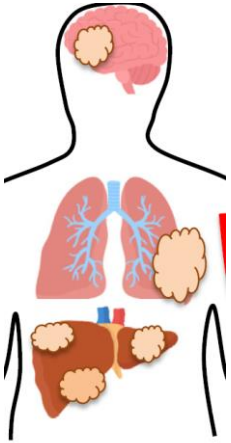
Factors that may influence sensitivity and specificity of ctDNA detection

Shedding vs. Non-shedding

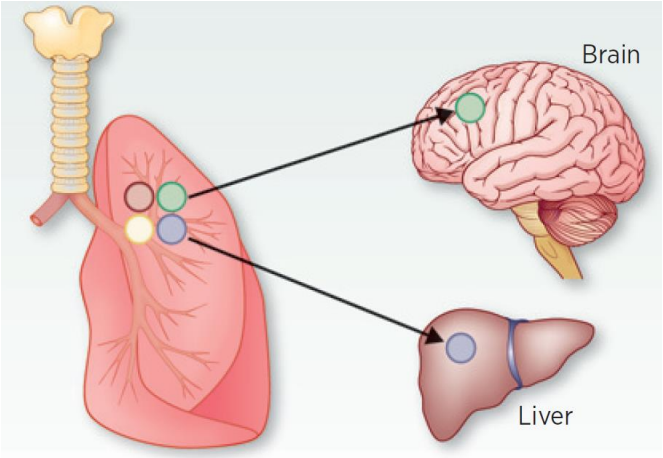


Sacher AG, et al. J Thorac Oncol 2017;12:1344-56

Stage

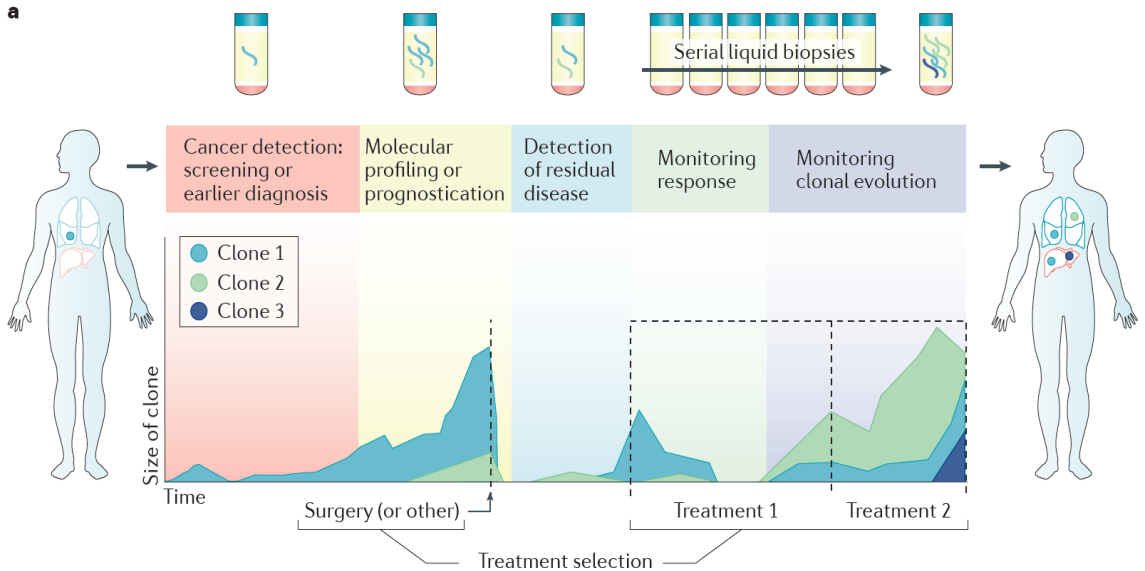


Inter-metastatic heterogeneity



Jamal-Hanjani et al. CCR 2015;21:1258-66

Potential application of circulating tumor DNA



1. Cancer early detection
2. Monitoring of minimal residual disease, tumor dynamics and recurrence
3. Estimation of tumor and mutation burden and for prognostication
4. Identification of driver mutations for targeted therapy
5. Identification of resistant mutation (mechanism) and real time assessment of evolution of resistance
6. Evaluation of early treatment response

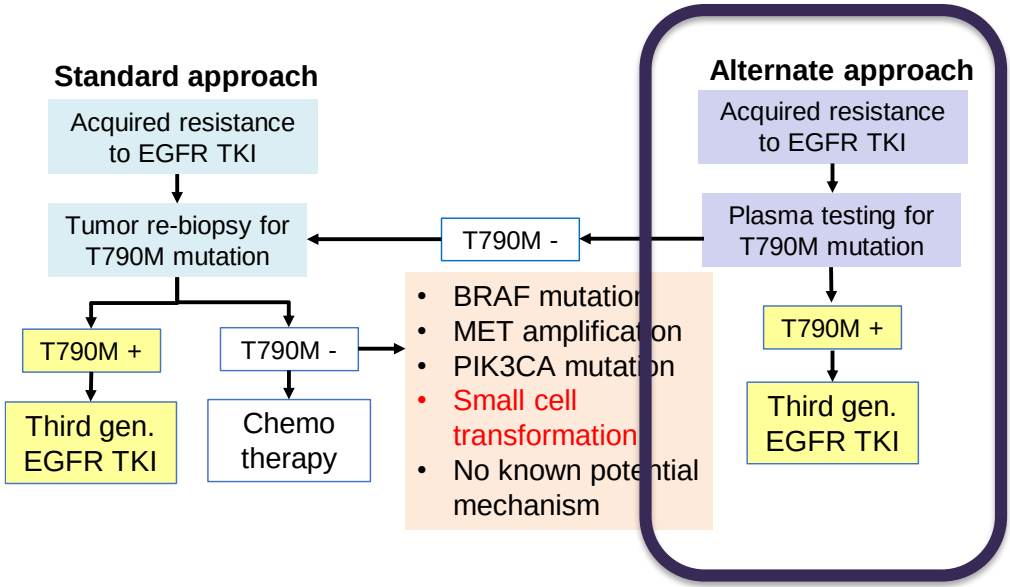
- *Wan JCM, et al. Nat Rev Cancer 2017;17:223-8*

Use of liquid biopsy for identification of resistant mutation and driver mutations for targeted therapy

2018 updated CAP/IASLC/AMP Guideline

Expert consensus opinions:

Cell-free plasma DNA methods can be used to identify **EGFR T790M** mutations in patients who responded then progress on EGFR TKI; **testing of tumor sample is recommended if the plasma result is negative.**



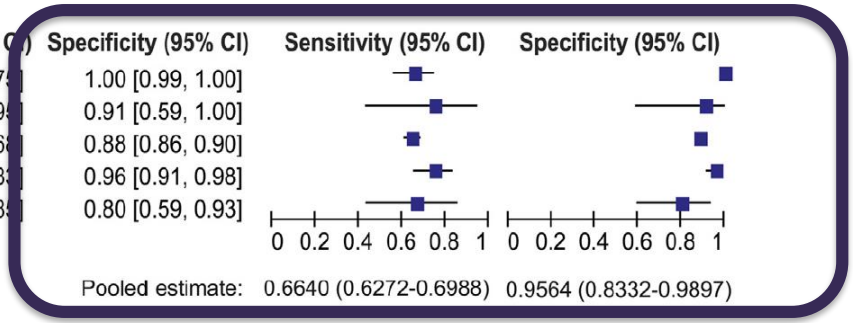
Lindeman NI, et al. J Thorac Oncol 2018; 13: 323-358

Use of liquid biopsy for identification of resistant mutation and driver mutations for targeted therapy

2018 updated CAP/IASLC/AMP Guideline

- **Recommendation:** In some clinical settings in which **tissue is limited and/or insufficient** for molecular testing, physicians may use a cfDNA assay to identify EGFR mutations.

Study	TP	FP	FN	TN	Detection System	Sensitivity (95% CI)	Specificity (95% CI)
Douillard 2014[242]	69	1	36	546	ARMs	0.66 [0.56, 0.7	1.00 [0.99, 1.00]
Kukita 2013[234]	9	1	3	10	PNA/LNA clamp	0.75 [0.43, 0.9	0.91 [0.59, 1.00]
Li 2014[243]	389	114	214	874	Multiple	0.65 [0.61, 0.6	0.88 [0.86, 0.90]
Mok 2015[235]	72	6	24	136	allele-specific PCR	0.75 [0.65, 0.8	0.96 [0.91, 0.98]
Oxnard 2014[232]	14	5	7	20	ddPCR	0.67 [0.43, 0.8	0.80 [0.59, 0.93]



Evidence demonstrated that, although positive EGFR testing results may effectively be used to guide therapy, undetected results should be confirmed with analysis of a tissue sample, if possible.

Lindeman NI, et al. J Thorac Oncol 2018; 13: 323-358

P2.13-24

Prospective efficacy of osimertinib in circulating tumour DNA (ctDNA) *T790M*-mutant non-small cell lung cancer (NSCLC) patients

J. Remon[1], C. Jovelet[2], L. Lacroix[2], D. Planchard[1], L. Mezquita[1], K. Howarth[3], E. Green[3], V. Plagnol[3], C Morris[3], N Rosenfeld[3], C. Caramella[4], C. Le Péchoux C[5], F. Aboubakar Nana[1], E. Auclin[1], A. Botticella[5], J. Adam[6], R. Ferrara[1], A. Gazzah[1], M. Ngocamus[1], JC. Soria[1,7], B. Besse[1,7]

[1]Gustave Roussy, Université Paris-Saclay, Department of Oncology Medicine, France; [2]Laboratoire de Recherche Translationnelle, AMMICA, INSERM US23/CNRS UNS3655, Gustave Roussy, France; [3]Inivata Ltd., Cambridge, United Kingdom; [4]Gustave Roussy, Université Paris-Saclay, Department of Radiology, France; [5]Gustave Roussy, Université Paris-Saclay, Department of Oncology Radiotherapy, France; [6]Gustave Roussy, Université Paris-Saclay, Department of Pathology, France; [7]University Paris-Sud and Gustave Roussy Cancer Campus, France

IASLC 19th World Conference on Lung Cancer
September 23–26, 2018 Toronto, Canada

P2.13-24
Abstract #14031

Long-term efficacy of osimertinib in T790M + only by ctDNA (without tissue information) has not been fully validated.

Objectives:
- **% of patients with acquired ctDNA-T790M positive.**
- **OS of the overall advanced EGFR-mutant population, as well as, OS comparison for T790M positive vs. negative.**

METHODS

Prospective study in non feasible tissue re-biopsy *EGFR*-mutant advanced NSCLC patients with acquired resistance to EGFR TKI who received osimertinib (80 mg daily, EAP or approval) at RECIST progression according to *ct*DNA *T790M* mutational status using InVisionSeq™ results.

- We recruited 76 patients (71% female, median age 64 years, 72% *Del19* EGFR mutation, 71% never-smokers).

The *ct*DNA *T790M* mutation was detected in 56% (N=43) of NSCLC patients.

- Median OS of advanced *EGFR*-mutant population was 42.4 months (mo.) (95% CI:38.6 - 49.8) (Figure 1)
  - According to T790M status, median OS was 46.6 mo. (95% CI: 38.8 - 55.5) and 40.0 mo. (95% CI: 29.8 - NR) for *T790M*-positive and *T790M*-negative NSCLC patients, respectively (p=0.21). Both cohorts had already received a median of 3 previous treatment lines (Figure 2).

- In 36 *T790M*-positive NSCLC patients who received osimertinib:
  - The RR was 55% (PR: 55%, SD 27.5% and PD: 12.5%)
  - The median PFS was 7.9 months (95% CI: 5.6-12.3).
  - Median OS on osimertinib among 10 patients with brain and / or leptomeningeal metastases at baseline was of 18 mo. (95%: 12-NR).

Figure 1.

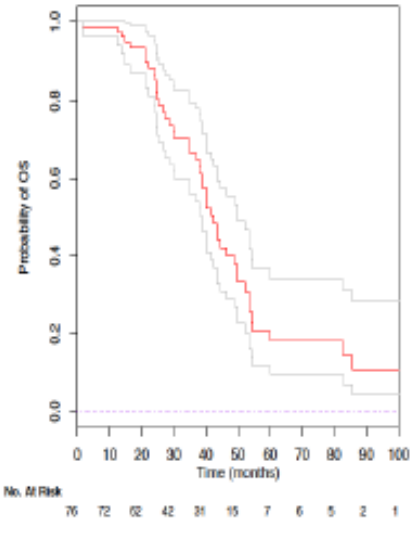
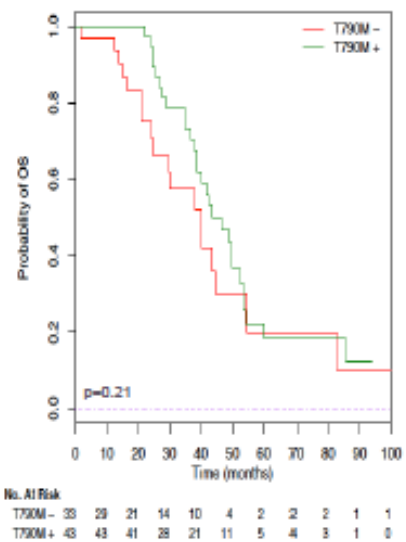


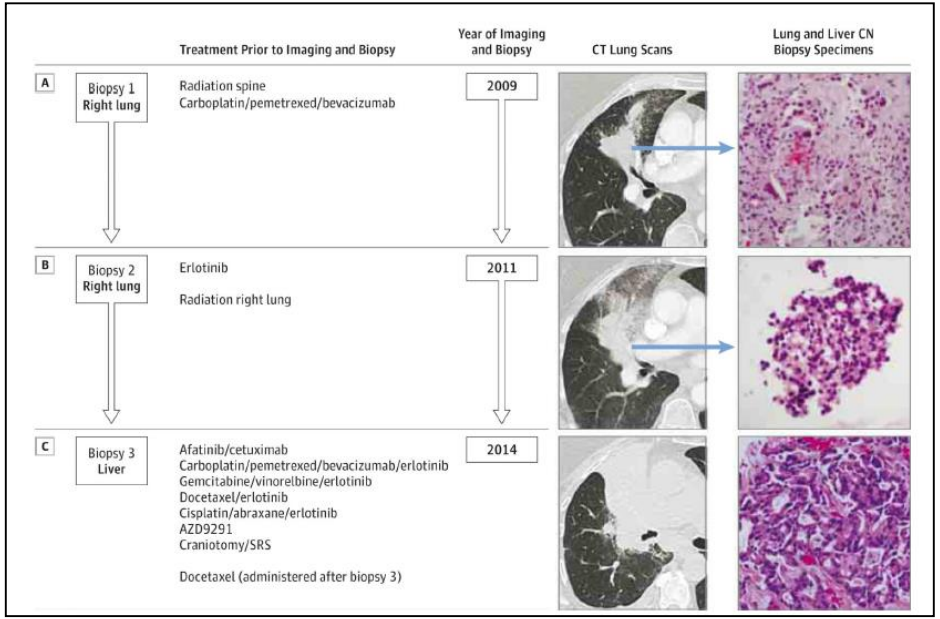
Figure 2.



And rebiopsies continue …
acquired resistance to Osimertinib

Acquired Resistance of *EGFR*-Mutant Lung Cancer to a T790M-Specific EGFR Inhibitor: Emergence of a Third Mutation (C797S) in the EGFR Tyrosine Kinase Domain

Helena A. Yu, MD, Shaozhou K. Tian, MD, Alexander E. Drilon, MD, Laetitia Borsu, PhD, Gregory J. Riely, MD, PhD, Maria E. Arcila, MD, and Marc Ladanyi, MD



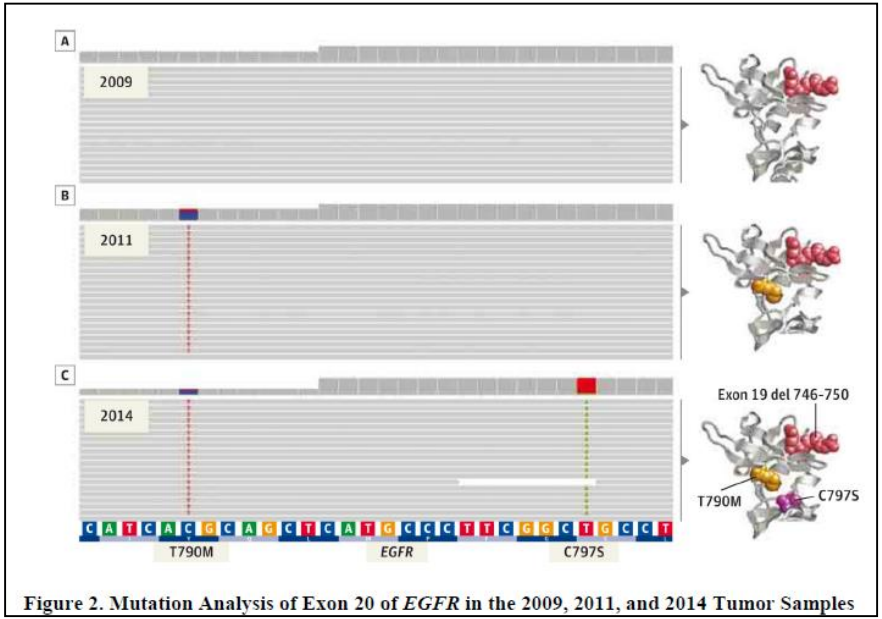
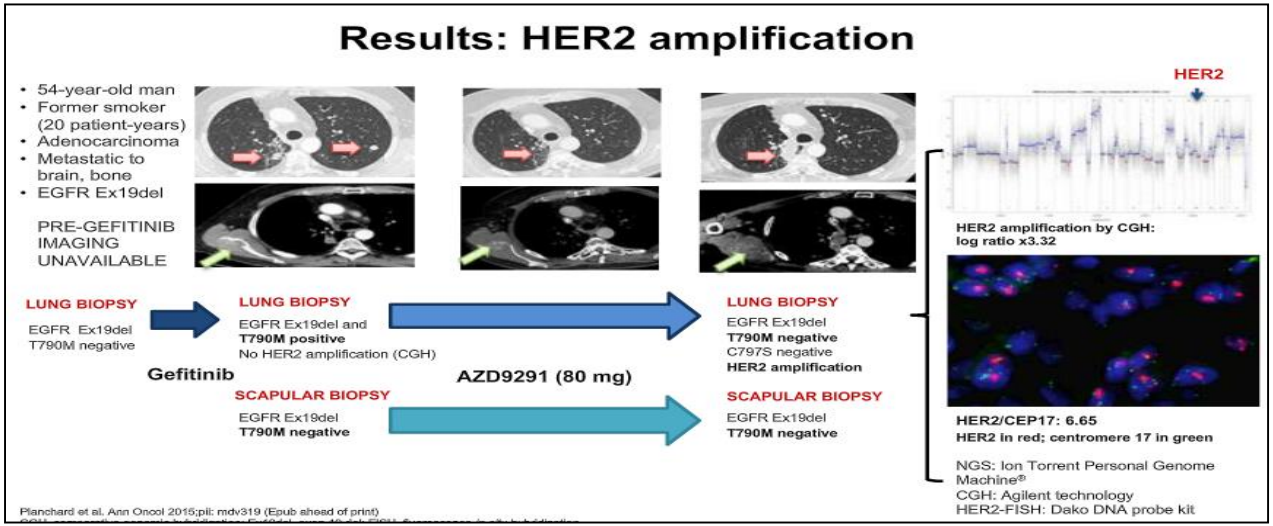


Figure 2. Mutation Analysis of Exon 20 of *EGFR* in the 2009, 2011, and 2014 Tumor Samples

JAMA Oncol. 2015 October 1; 1(7): 982–984.

AR to Osimertinib → role for liquid biopsies

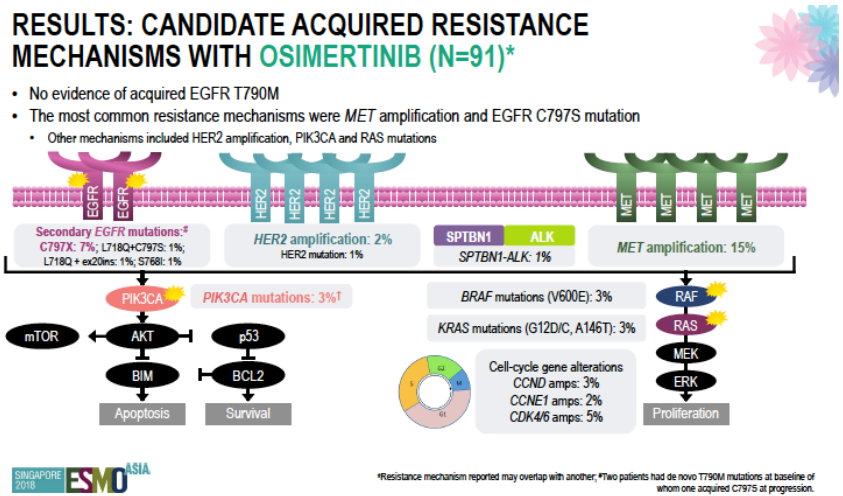
- 22% had **detectable C797S** on PCR, all with detectable T790M.
- 48% had no detectable T790M in plasma → overgrowth of an **alternate resistance mechanism.**
- Her-2 amplification
- MET amplification
- BRAF V600E mutation

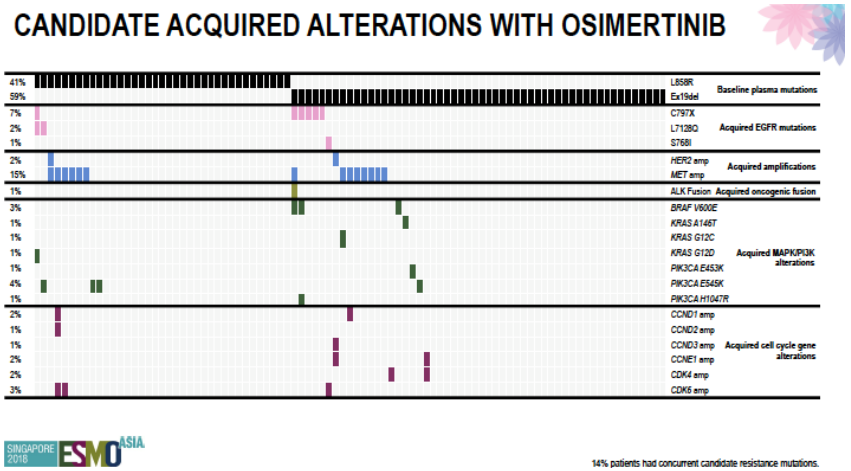


Oxnard et al. J Thorac Oncol 2015; 10 (suppl 2): ORAL17.07

FLAURA TRIAL.
Acquired alterations WITH OSIMERTINIB

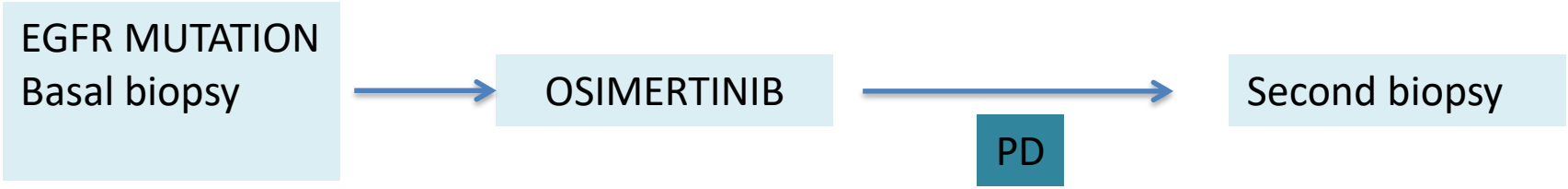
- Paired samples from baseline and at progression / discontinuation
- Plasma NGS (Guardanth Health)





BC.Cho, ESMO ASIA 2018

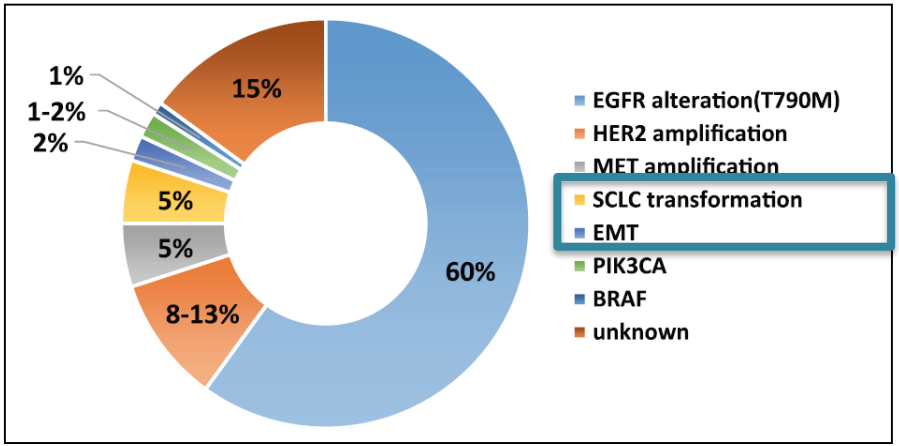
ELIOS TRIAL

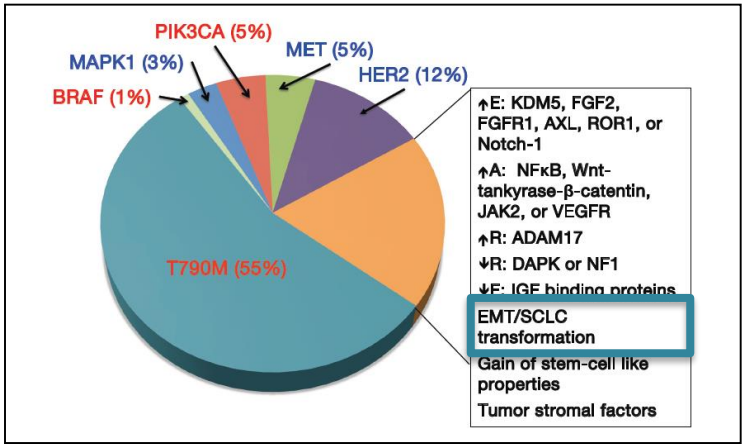


Phase 2 trial
N: 150 pts
Primary endpoint: to characterize % of genetic or proteomic markers at PD

Patients with known EGFR mutations: Histology transformation

- All patients will develop resistance to EGFR-TKI





HISTOLOGY TRASNFORMATION AS AR to EGFR-TKI

- Also described in ALK traslocation patients

Wu and Shih Molecular Cancer (2018) 17:38; Stewart Transl Lung Cancer Res 2015;4(1):67-81

Patients with known ALK traslocations

Table 1. Molecular characteristics of second-generation *ALK* inhibitors.

Drugs	Targets other than *ALK*	Activity against L1196M resistance mutation	Activity against C1156Y resistance mutation	Activity against G1202R resistance mutation	Activity against other crizotinib-resistant mutations	Lack of activity against resistance mutations
Ceritinib	IGF-R1, InsR, ROS1	Yes	No	No	G1269A, I1171T, S1206Y, L1152R, F1174L, V1180L	G1202R, F1174C
Alectinib	LTK, GAK	Yes	Yes	No	G1269A, S1206Y, L1152R, F1174L, 1151T-ins	G1202R, V1180L, I1171T
Brigatinib	ROS1, EGFR	Yes	Yes	Yes	G1269A, S1206Y, 1151T-ins, F1174C, I1171T, D1203N, E1210K, F1245C	NA
Entrectinib	TrkA, TrkB, TrkC, ROS1	Yes	Yes	NA	NA	NA
PF-06463922	ROS1	Yes	NA	Yes	G1269A	NA
TSR-011	TrkA, TrkB, TrkC	Yes	NA	NA	NA	NA
ASP3026	ROS1, ACK	Yes	NA	NA	F1174L	NA
X-396	MET	Yes	Yes	NA	NA	NA
CEP-37440	FAK	NA	NA	NA	NA	NA

ALK, anaplastic lymphoma kinase; NA, not available.

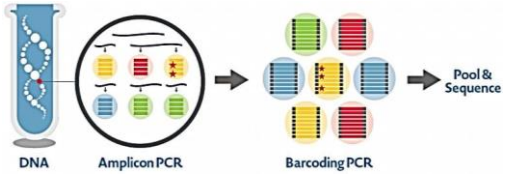
I. Sullivan, Ther Adv Med Oncol 2016, Vol. 8(1) 32–47

WLCC 2018: Feasibility and clinical relevance of ALK- and ROS1-fusion variant detection using liquid biopsy in advanced NSCLC

Aurélie Swalduz1*, Laura Mezquita2*, Sandra Ortiz-Cuaran3, Cécile Jovelet2, Virginie Avrillon1, David Planchard2, Solène Marteau3,Gonzalo Recondo2, Séverine Martinez3, Frank De Kievit4, Vincent Plagnol4, Karen Howarth4, Clive Morris4, Emma Green4, Luc Odier4, Ludovic Lacroix2, Pierre Fournel6, Etienne Rouleau2, Claire Tissot7, Caroline Caramella2, Stéphane Hominal8,Luc Friboulet2, Maurice Pérol1, Benjamin Besse2, Pierre Saintigny1

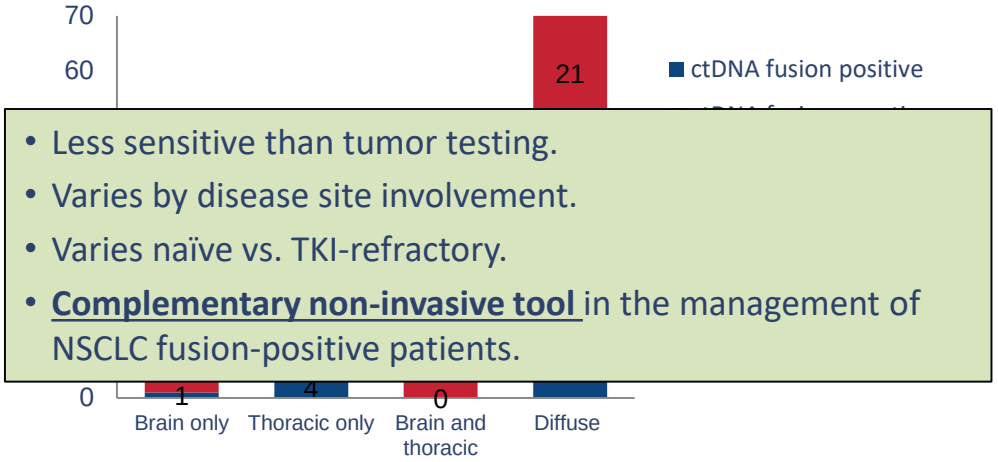
N: 128 advanced NSCLC (101 ALK, 27 ROS1)

Inivata InVision Sequencing



EML4-ALK v1 v2 v3	AKT1	ALK	BRAF	CCND1	CDKN2A	CTNNB1
	EGFR	ERBB2	ESR1	FGFR1	FGFR2	FGFR3
CD74-ROS1	GATA3	GNA11	GNAQ	GNAS	HRAS	IDH1
SLC34A2-	IDH2	KIT	KRAS	MAP2K1	MET	MYC
SDC4-ROS1	NFE2L2	NRAS	NTRK1	NTRK3	PDGF RA	PIK3CA
EZR-ROS1	PPP2R1A	PTEN	ROS1	STK11	TP53	U2AF1

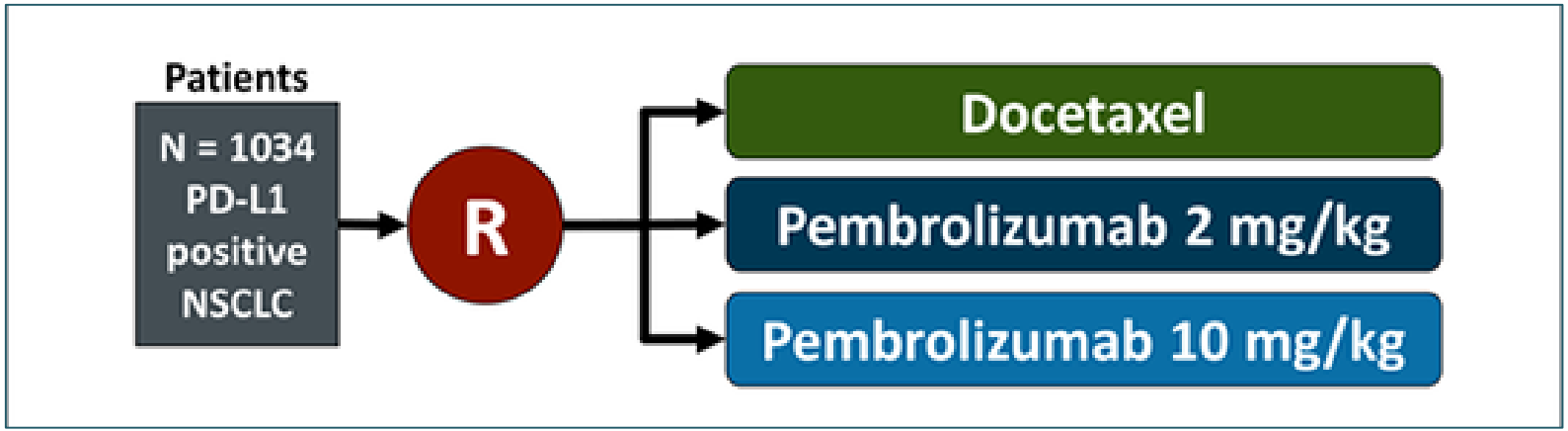
SNVs + Indels - Hotspot Regions
Fusions + SNVs + Indels
CNVs + SNVs + Indels
CNVs only
SNVs + Indels - Exon Coverage 70% for PTEN, 88-100% for TP53, STK11 and CDKN2A



- Less sensitive than tumor testing.
- Varies by disease site involvement.
- Varies naïve vs. TKI-refractory.
- **Complementary non-invasive tool** in the management of NSCLC fusion-positive patients.

- **At diagnosis (TKI-naïve patients):** sensitivity was **67% (n=18/27)**[1]
- **At progression**: ctDNA fusion was detected in 47% of patients (n=47/100)
- 86.4% with thoracic and/or cerebral exclusive disease have non detectable ctDNA fusion.
- 92.4% of patients with detectable ctDNA fusions had diffuse metastatic disease.

PD-L1 status after first line CT.

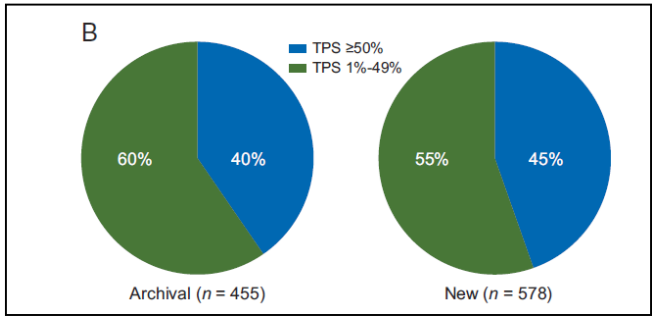


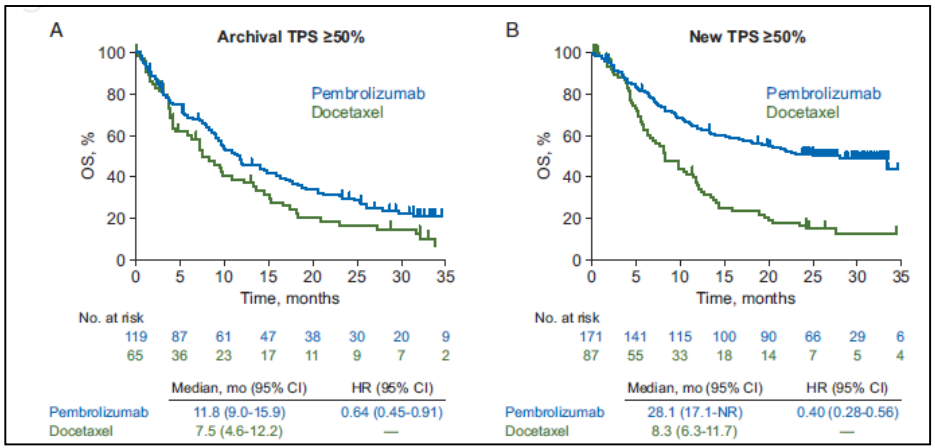
KEYNOTE-010 → PD-L1 after PD in a biopsy in 60% of pts
(Cytology not a valid sample).

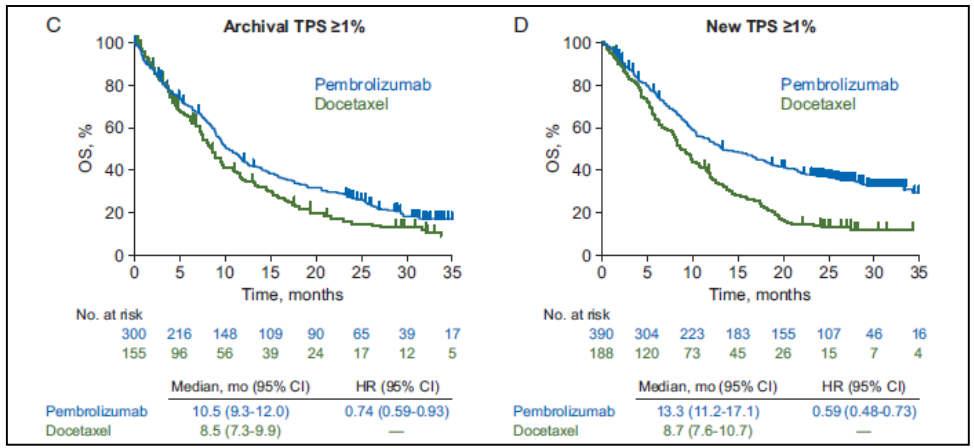
PD-L1 status after first line CT.

Use of archival versus newly collected tumor samples for assessing PD-L1 expression and overall survival: an updated analysis of KEYNOTE-010 trial

R. S. Herbst[1*], P. Baas[2], J. L. Perez-Gracia[3], E. Felip[4,5], D.-W. Kim[6], J.-Y. Han[7], J. R. Molina[8], J.-H. Kim[9], C. Dubos Arvis[10], M.-J. Ahn[11], M. Majem[12], M. J. Fidler[13], V. Surmont[14], G. de Castro Jr[15], M. Garrido[16], Y. Shentu[17], K. Emancipator[17], A. Samkari[17], E. H. Jensen[17], G. M. Lubiniecki[17] & E. B. Garon[18]







Annals of Oncology 30: 281–289, 2019

Personal comments

- Rebiopsy is mandatory to understand **resistance mechanisms and to develop future therapeutic approaches & improve OS and QoL.**
- Multidisciplinary approach is necessary to determine the more accessible lesion to rebiopsy.
- In a near future, **liquid biopsies** might displace tumor rebiopsies in some cases.
  - **Identification of resistant mutation and driver mutations (Negative results does not exclude the presence of mutation).**
  - Need to validate in prospective trials.
  - In the meantime, used if a tissue biopsy is not safe / feasible.
  - Be aware of histological transformation

Lo fácil aburre, lo difícil atrae y lo imposible, solo tarda un poco más.