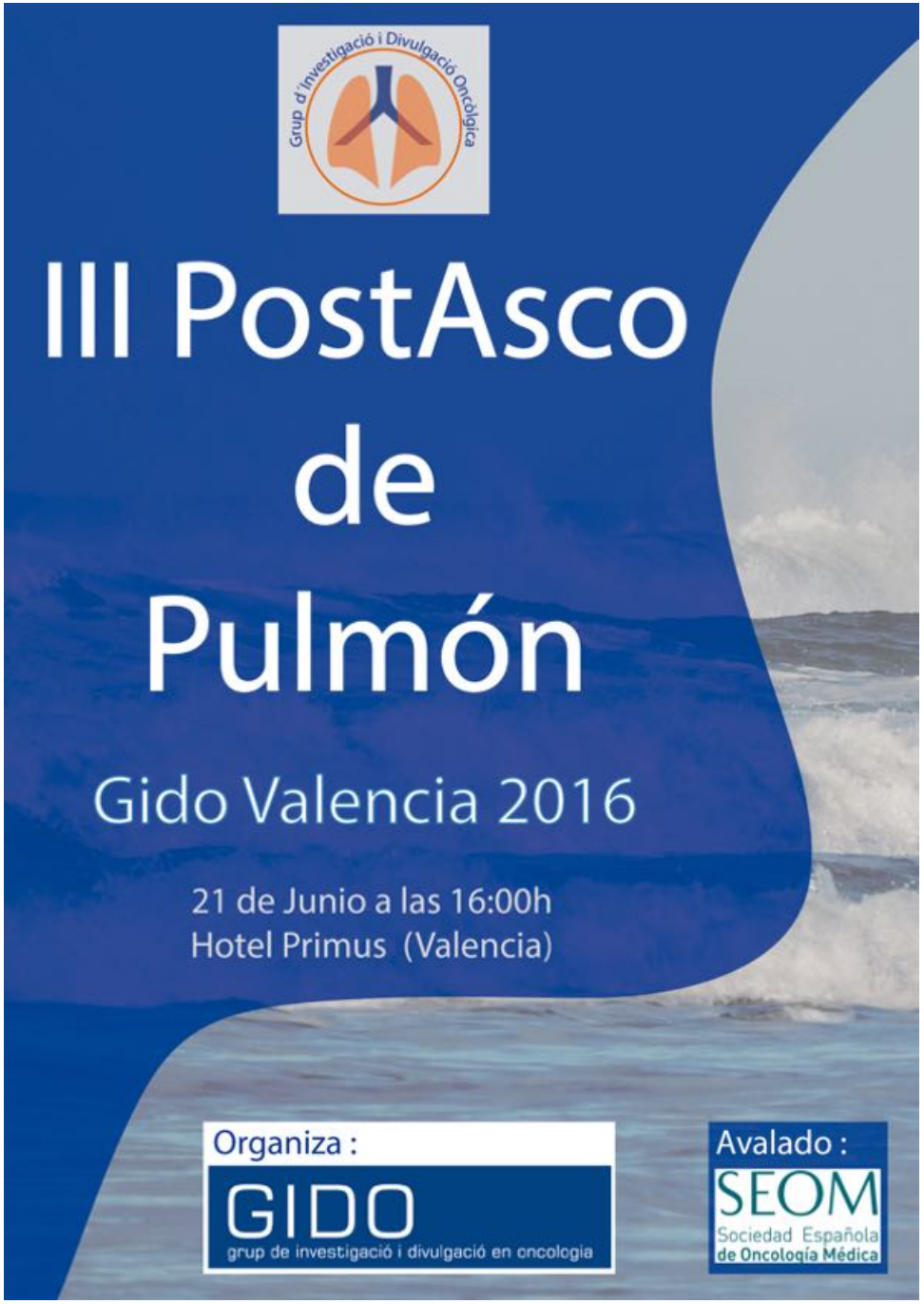
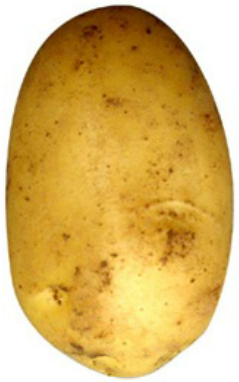
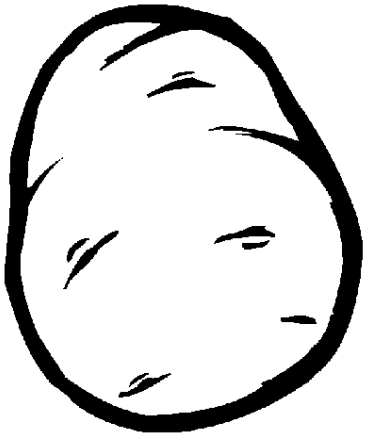
GIDO
grup de investigació i divulgació en oncologia

Aportaciones post asco 2016 EGFR

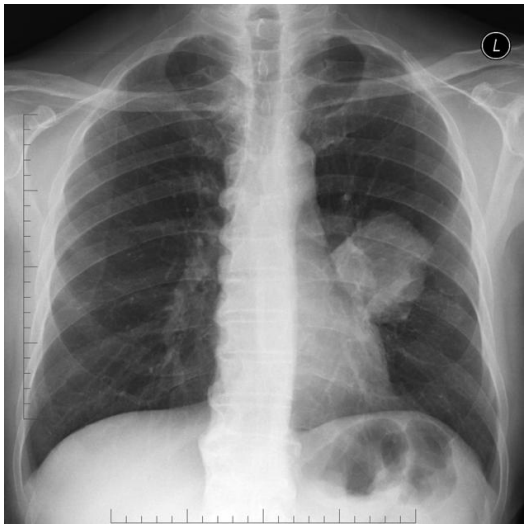
Francisco Aparisi Aparisi
Oncología Médica
H. Virgen de los Lirios de Alcoy
21.06.2016





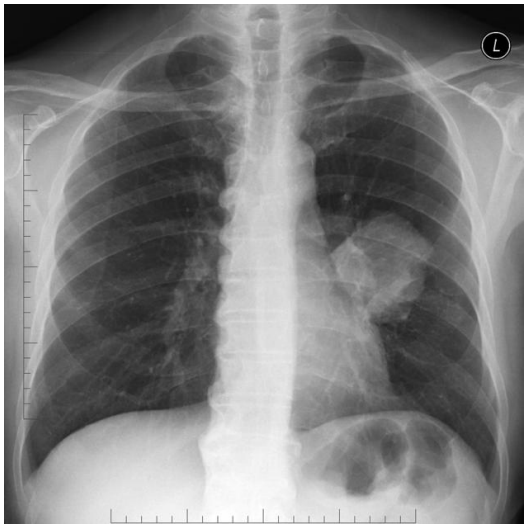


Castellano	Patata
Catalán	Patata
Francés	Pomme de terre
Inglés	Potato
Italiano	Patata
Valenciano	Creïlla



CPNCP EGFR-

CPNCP EGFR+

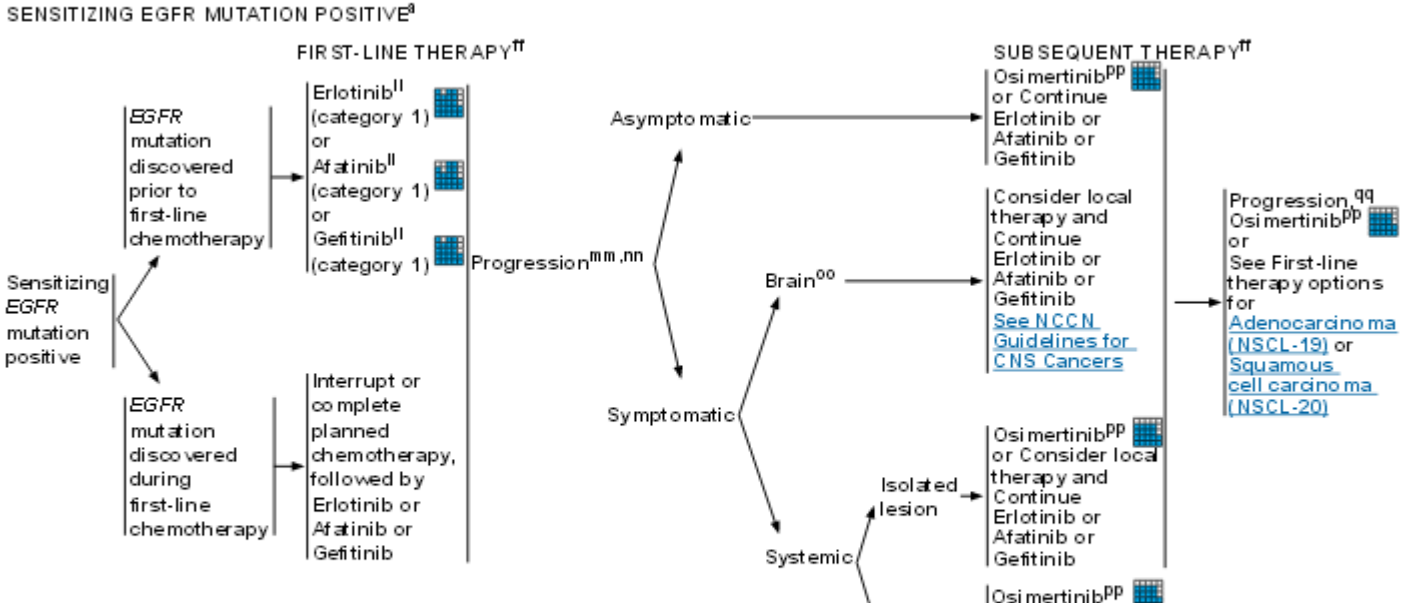


National Comprehensive Cancer Network®

NCCN Guidelines Version 4.2016
Non-Small Cell Lung Cancer
NCCN Evidence Blocks™

E= Efficacy of Regimen/Agent
S= Safety of Regimen/Agent
Q= Quality of Evidence
C= Consistency of Evidence
A= Affordability of Regimen/Agent
E S Q C A

NCCN Guidelines Index
NSCLC TOC
Discussion



Annals of Oncology Advance Access published August 11, 2014

[a] See Principles of Pathologic Review (NSCL-A).
[ff] See Systemic Therapy for Advanced or Metastatic Disease (N
[ll] For performance status 0-4.
[mm] Prior to changing therapy, a biopsy is reasonable to determir
[nn] Beware of flare phenomenon in subset of patients who discon
[oo] Consider pulse erlotinib for carcinomatosis meningitis.
[pp] Osimertinib is approved for patients with metastatic EGFR T7 test performed in a CLIA-approved laboratory.
[qq] Afatinib + cetuximab may be considered in patients with disea

clinical practice guidelines

Annals of Oncology 00: 1–13, 2014

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

M. Reck[1,2], S. Popat[3,4], N. Reinmuth[1,2], D. De Ruysscher[5], K. M. Kerr[6], S. Peters[7] & on behalf of the ESMO Guidelines Working Group*

[1]Department of Thoracic Oncology, LungenClinic, Grosshansdorf; [2]Member of the German Center for Lung Research (DZL), Germany; [3]Royal Marsden Hospital NHS Foundation Trust, London; [4]Royal Marsden Hospital NHS Foundation Trust, Surrey, UK; [5]Department of Radiation Oncology, University Hospitals Leuven/ KU Leuven, Leuven, Belgium; [6]Department of Pathology, Aberdeen Royal Infirmary and Aberdeen University Medical School, Aberdeen, UK; [7]Department of Oncology, Centre Hospitalier Universitaire Vaudois (CHUV), Lausanne, Switzerland

EGFR m+

Author	Study	Agent	N (EGFR mut +)	RR	Median PFS (mo)	PFS HR	OS (mo)	OS HR	Crossover (%)
Mok et al	IPASS	**Gefitinib** (vs carbo/pacli)	261	71.2% vs 47.3%	9.8 vs 6.4	0.48 (0.36-0.64)	21.6 vs 21.9	1.00 (0.76-1.33)	40
Han et al	First-SIGNAL	**Gefitinib** (vs cim/gem)	42	84.6% vs 37.5%	8.0 vs 6.3	0.54 (0.27-1.1)	27.2 vs 25.6	1.04 (0.50-2.18)	75
Mitsud et al									
Maem o et al									
Zhou						0.26)		1.58)	
Rosell et al	EURTAC	**Erlotinib** (vs cis-carbo/doc/gem)	174	58% vs 15%	9.7 vs 5.2	0.47 (0.28-0.78)	19.3 vs 19.5	0.93 (0.64-1.35)	76
Wu et al	ENSURE	**Erlotinib** (vs carbo/gem)	275	62.7% vs 32.6%	11 vs 5.5	0.34 (0.22-0.51)	26.3 vs 25.5	0.91 (0.63-1.31)	NA
Sequist et al	LUX-Lung 3	**Afatinib** (cis/pem)	345	56% vs 23%	11.1 vs 6.9	0.58 (0.43-0.78)	31.6 vs 28.2	0.78 (0.58-1.06)	75

En el tratamiento de 1ª línea en CNMP EGFRm+, los EGFR ITKs de 1ª generación (erlotinib, gefitinib) y 2ª generación (afatinib) **mejoran claramente la SLP** frente a QT basada en platino.

En estos ensayos no han demostrado beneficio en SG debido al empleo de estos ITKs en **2ª línea tras progresión a quimioterapia**

Enfoque pragmático

-TINIB

1º generación

Erlo-	Tarceva	Roche	Aprobado
Gefi-	Iressa	Astra	Aprobado
Ico-		Beta Pharma	Aprobado en China

2º generación

Afa-	Giotrif	Boehringer	aprobado
Daco-		Pfizer	On going
Nera-		Puma Biotechnology	

3º generación

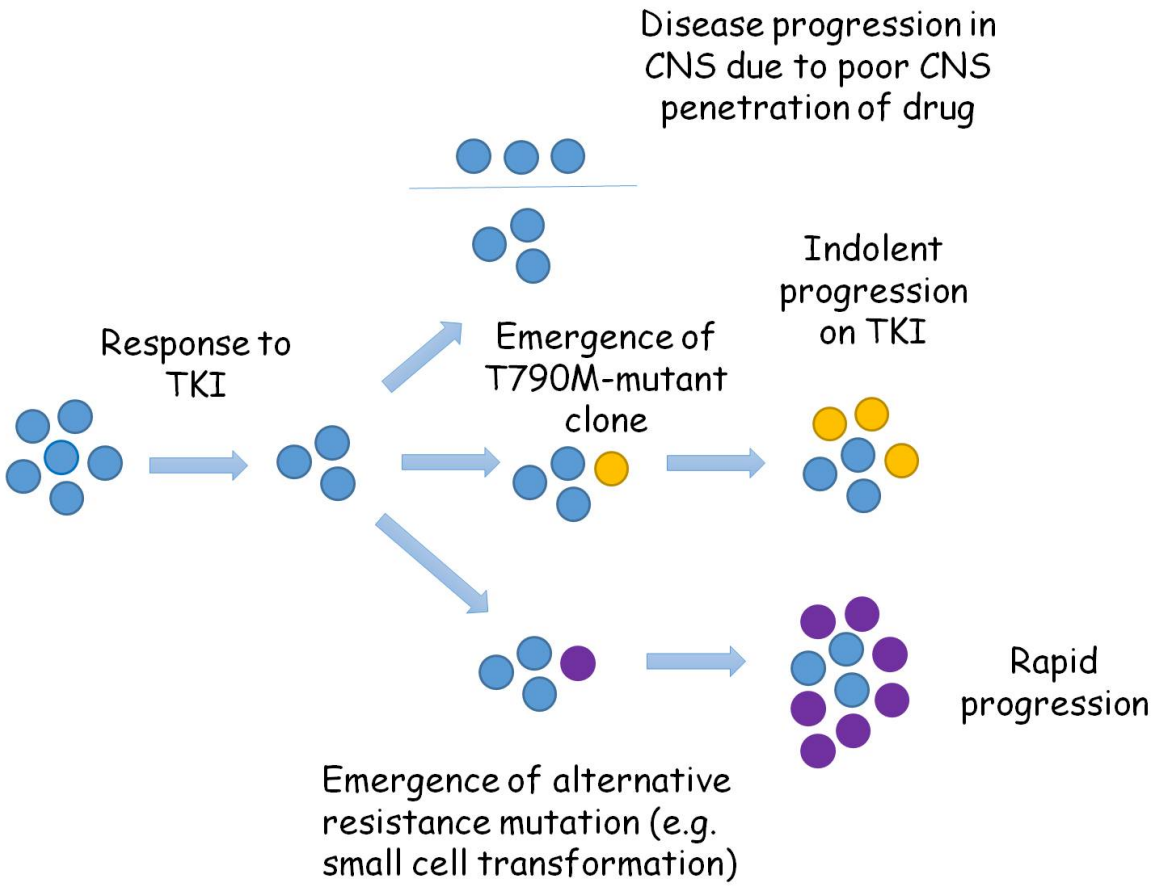
Osimer-	Tagrisso	Astra Zeneca	Pendiente de precio T790M
Rocile-		Clovis Oncology UK	Stop desarrollo
Olmu-		Boehringer	Aprobado en Corea T790M

Mecanismos de resistencia

Mechanism	Gene	Alterations	Prevalence	Detection method	References
EGFR-dominant	*EGFR*	SNV: T790M	41-63%	LNA-PCR/Sequencing assay	Hata et al. 2013[13], Yu et al. 2013[14]
		SNV: D761Y, T854A, L747S	<5%	PCR-RFLP	Balak et al, 2006[113]; Bean et al, 2008[114]; Costa DB 2007[115]
		Amplification	8%	FISH	Sequist et al, 2011[12]
Bypass signalling tracts	*PIK3CA*	SNV	5%	SNaPshot	Sequist et al, 2011[12]
	BRAF	SNV	1%	SNaPshot	Ohashi et al, 2012[60]
	MET	Amplification	5%	FISH	Sequist et al, 2011[12]; Yu et al. 2013[14]
	HER2	Amplification	12-13%	FISH	Takezawa et al, 2012[116]; Yu et al. 2013[14]
	AXL	Increased expression	20%	IHC	Zhang et al, 2012[117]
	HGF	Increased expression	61%	IHC	Yano et al, 2011[118]
	PTEN	Loss	10%	IHC	Yamamoto et al, 2010[119]
Phenotypic alterations	*RB1* loss	Transformation to small-cell lung cancer	14%	Histological examination and confirmed by expression of neuroendocrine markers	Sequist et al, 2011[12] Niederst et al 2015[62]
	-	Transition to EMT	16%/20%	IHC stain of vimentin and e-cadherin	Sequist et al, 2011[12]; Zhang et al, 2012[117]

Tan DS J Thorac Oncol. 2016

Enfoque científico

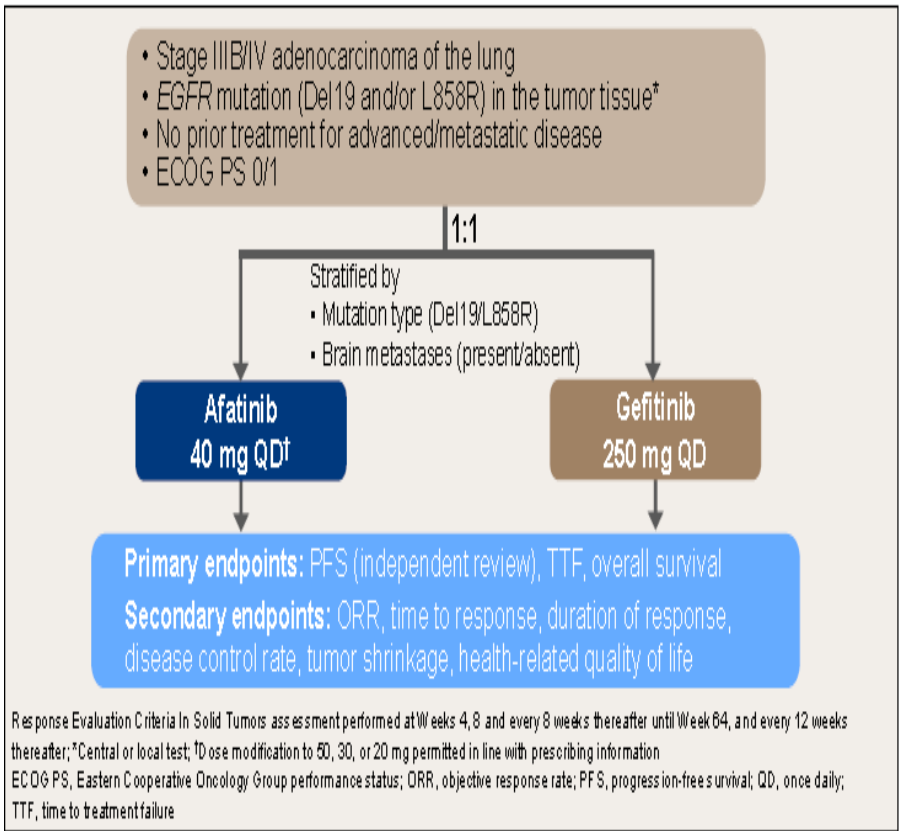


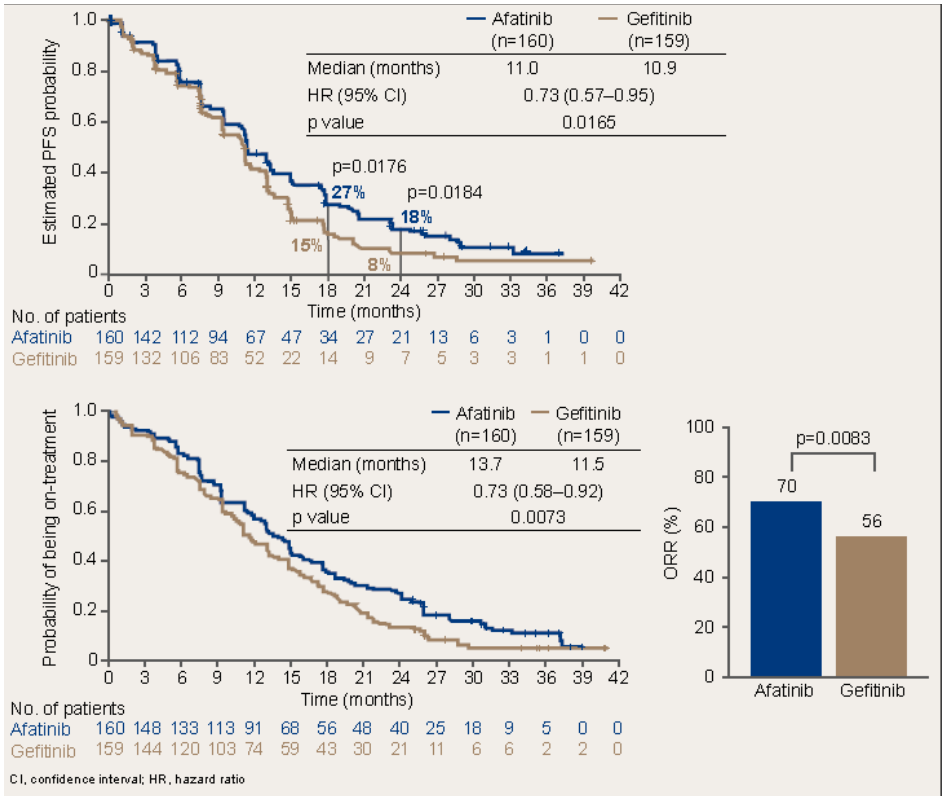
Sacher, Jänne & Oxnard Cancer 2014

1º línea

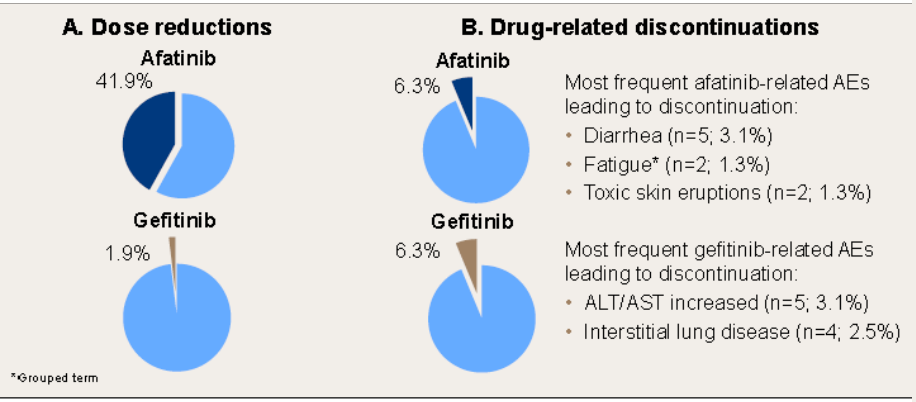
Afatinib

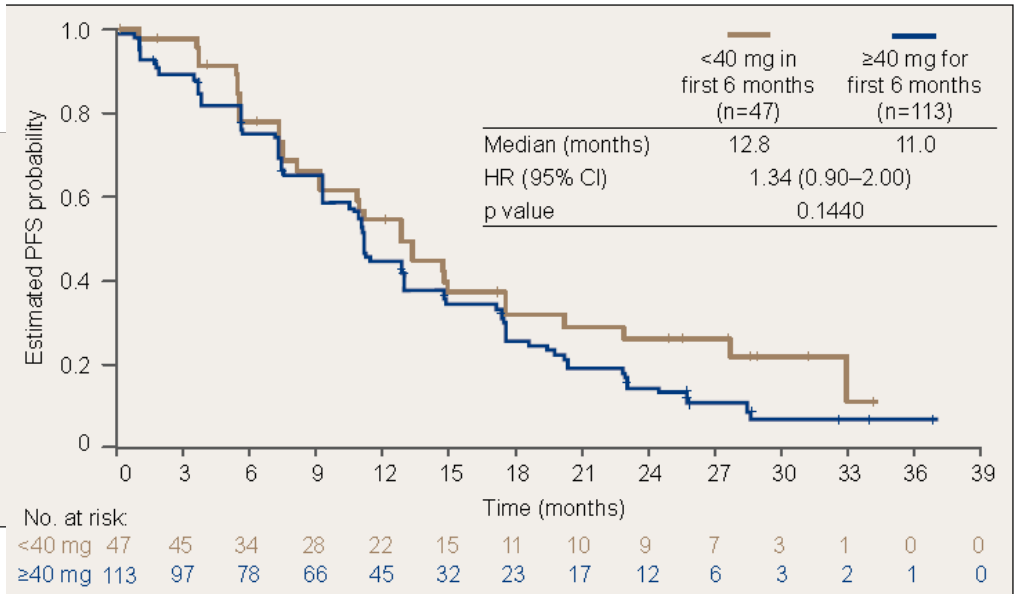
First-line afatinib versus gefitinib for patients with *EGFR* mutation-positive NSCLC (LUX-Lung 7): patient-reported outcomes and impact of dose modifications on efficacy and adverse events



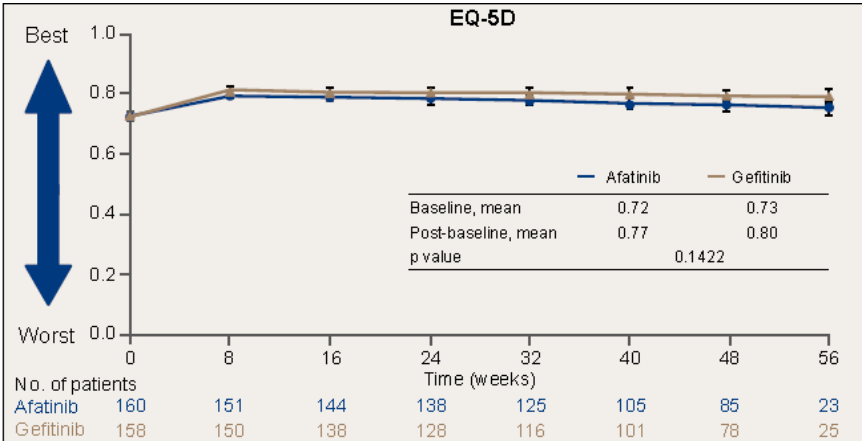


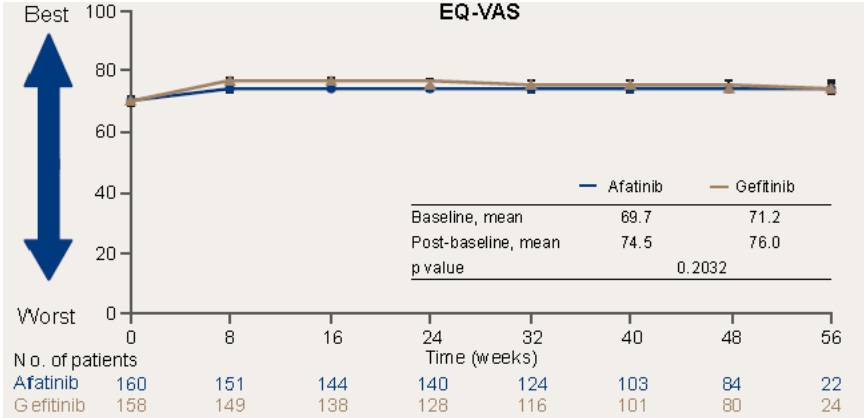
Efecto en PFS de reducción de dosis





Calidad de vida





Otros

- Icotinib:
  - CDDP-pemetrexed vs icotinib 1º línea:
    - EP: SLP: 296 días vs 219 días p = 0.008
- Mutaciones de P53 al inicio:
  - *TP53*, sobretodo mutaciones en exón 8 → disminuye respuesta
- C-MET concomitante a EGFR disminuye respuesta

Concurrent genetic alterations identified by next-generation sequencing in untreated, metastatic EGFR-mutant lung cancers.

Helena A. Yu, Emmet Jordan, Ai Ni, Daniel Feldman, Christopher Rodriguez, Ryan Kim, Mark G. Kris, David Solit, Michael Berger, Marc Ladanyi, Maria Arcila, Gregory J. Riely
Memorial Sloan Kettering Cancer Center, New York, NY

Abstract #9053

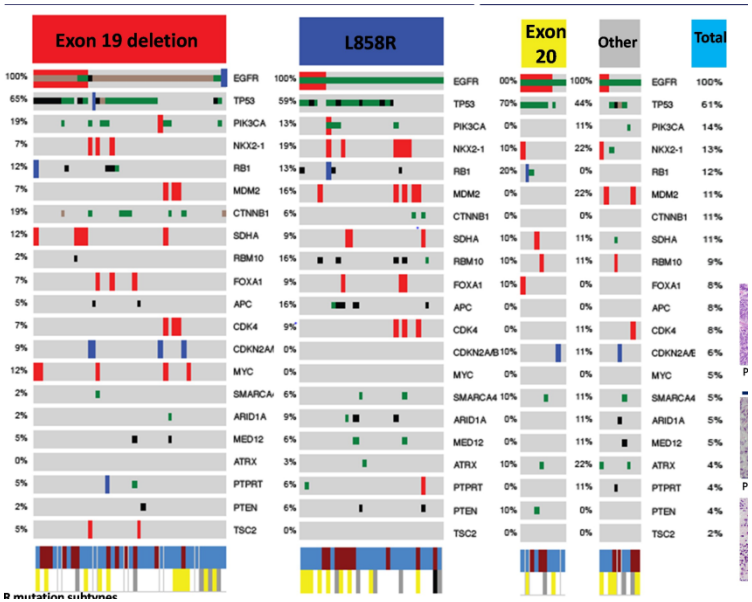
Methods

- We identified all patients with newly diagnosed EGFR-mutant lung cancers that had targeted NGS performed between Jan 2014 and Sept 2015 prior to any EGFR TKI treatment.
- We utilized a hybrid capture, next-generation sequencing based mutation platform that identifies molecular alterations in 341(v1.0) – 410(v2.0) genes (MSK-IMPACT).
- Fisher's exact and log rank tests were used to identify associations between co-mutations and clinical characteristics, sites of disease, and outcomes

Results

Clinical characteristics		N (%)
Total		95
Age	Median (range)	63 (24-89)
Sex	Male	29 (33)
	Female	66 (67)
Smoking	Never-smoker	55 (58)
	Former smoker	40 (42)
	Median pack-yr (range)	6 (1-125)
Histology	Adenocarcinoma	91 (96)
	Squamous	3 (3)
	Small cell	1 (1)

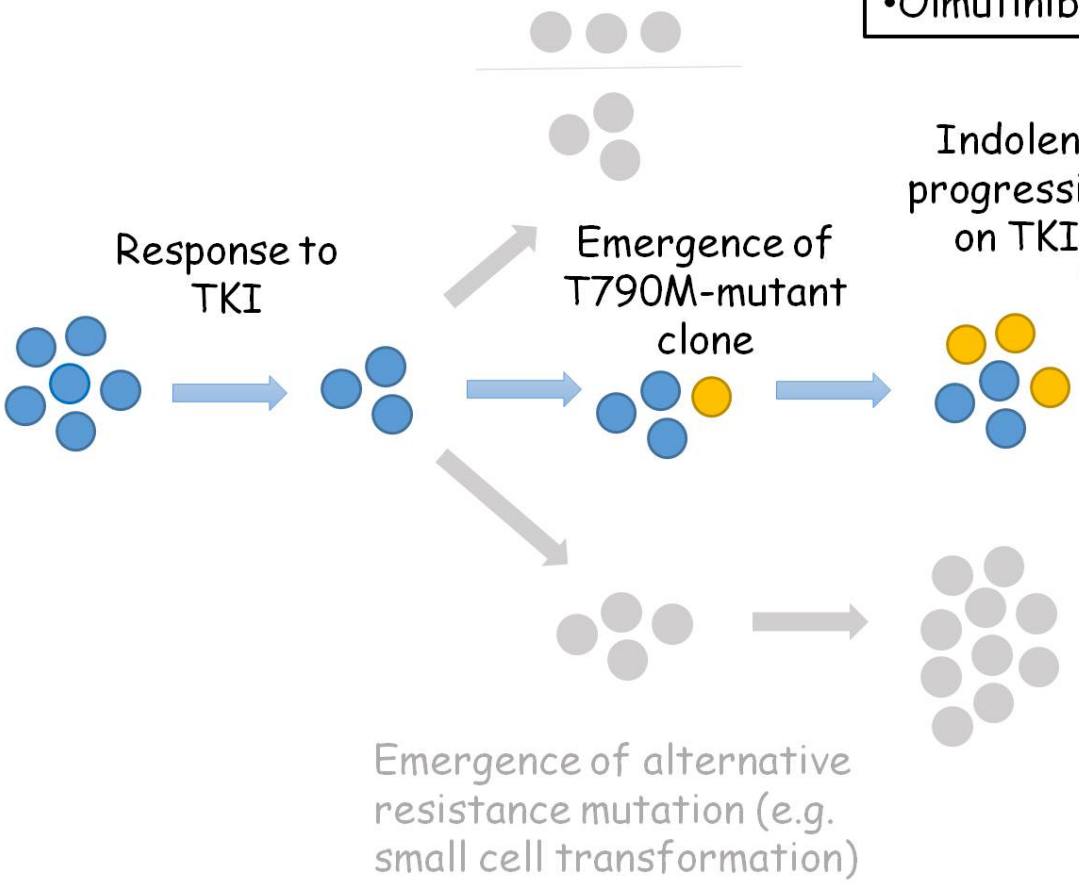
EGFR mutation subtypes	N (%)
Exon 19 deletions	43 (45)
L858R	33 (35)
Exon 20 insertions	10 (11)
G719A/G719S	6 (6)
L861Q	2 (2)
S768I	1 (1)



Conclusions/Future Directions

- Concurrent alterations were commonly seen with activating EGFR mutations; potential therapeutic combinations may be proposed based on the more frequent concurrent alterations present.
- Further study may identify potential associations between concurrent alterations and eventual mechanisms of resistance to EGFR TKI, such as pre-treatment RB1 loss and small cell transformation.
- There is no association between EGFR mutation subtype and concurrent alterations present or mutation count.
- The presence of EGFR amplification, and >5 concurrent mutations were associated with shorter overall survival.
- The presence of p53, RB1, and >5 concurrent mutations were associated with shorter progression-free survival on EGFR TKI.

Approved Mutant Selective EGFR TKIs
- Osimertinib (US, EU, Japan)
- Olmutinib (South Korea)



Tissue based EGFR T790M Testing

Use of plasma based EGFR T790M testing (Wakelee et al)

Evolution of Resistance (Chabon et al)

Sacher, Jänne & Oxnard Cancer 2014

1-Rociletinib

TIGER-X (Ph 1/2)
- First-in-human study
- Single arm – expansion cohorts
- ≥2nd-line mutant EGFR NSCLC, T790M+

TIGER-1 (Ph 2/3)
- Randomized rociletinib vs erlotinib
- 1st-line, treatment-naïve

TIGER-2 (Ph 2)
- Single-arm, 500 mg BID going forward
- 2nd-line mutant EGFR NSCLC
- Patients progressing on 1st-line EGFR TKI
- Both T790M+ and T790M– cohorts

TIGER-3 (Ph 3)
- Randomized rociletinib vs chemotherapy
- >2nd-line mutant EGFR NSCLC, T790M+ and T790M– (sequential analysis)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Rociletinib in *EGFR*-Mutated Non–Small-Cell Lung Cancer

L.V. Sequist, J.-C. Soria, J.W. Goldman, H.A. Wakelee, S.M. Gadgeel, A. Varga, V. Papadimitrakopoulou, B.J. Solomon, G.R. Oxnard, R. Dziadziuszko, D.L. Aisner, R.C. Doebele, C. Galasso, E.B. Garon, R.S. Heist, J. Logan, J.W. Neal, M.A. Mendenhall, S. Nichols, Z. Piotrowska, A.J. Wozniak, M. Raponi, C.A. Karlovich, S. Jaw-Tsai, J. Isaacson, D. Despain, S.L. Matheny, L. Rolfe, A.R. Allen, and D.R. Camidge

ABSTRACT

BACKGROUND

Non–small-cell lung cancer (NSCLC) with a mutation in the gene encoding epidermal growth factor receptor (*EGFR*) is sensitive to approved EGFR inhibitors, but resistance develops, mediated by the T790M *EGFR* mutation in most cases. Rociletinib (CO-1686) is an EGFR inhibitor active in preclinical models of *EGFR*-mutated NSCLC with or without T790M.

METHODS

In this phase 1–2 study, we administered rociletinib to patients with *EGFR*-mutated NSCLC who had disease progression during previous treatment with an existing EGFR inhibitor. In the expansion (phase 2) part of the study, patients with T790M-positive disease received rociletinib at a dose of 500 mg twice daily, 625 mg twice daily, or 750 mg twice daily. Key objectives were assessment of safety, side-effect profile, pharmacokinetics, and preliminary antitumor activity of rociletinib. Tumor biopsies to identify T790M were performed during screening. Treatment was administered in continuous 21-day cycles.

RESULTS

A total of 130 patients were enrolled. The first 57 patients to be enrolled received the free-base form of rociletinib (150 mg once daily to 900 mg twice daily). The remaining patients received the hydrogen bromide salt (HBr) form (500 mg twice daily to 1000 mg twice daily). A maximum tolerated dose (the highest dose associated with a rate of dose-limiting toxic effects of less than 33%) was not identified. The only common dose-limiting adverse event was hyperglycemia. In an efficacy analysis that included patients who received free-base rociletinib at a dose of 900 mg twice daily or the HBr form at any dose, the objective response rate among the 46 patients with T790M-positive disease who could be evaluated was 59% (95% confidence interval [CI], 45 to 73), and the rate among the 17 patients with T790M-negative disease who could be evaluated was 29% (95% CI, 8 to 51).

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Sequist at the Department of Medicine, Massachusetts General Hospital, 32 Fruit St., Yawkey 7B, Boston, MA 02114, or at lvsequist@partners.org.

N Engl J Med 2015;372:1700-9.
DOI: 10.1056/NEJMoa1413654

Fase I/II
2º línea a progresión
47 pac T790M + → TR: 59%
17pac T790 M- -→ TR: 29%

Inter- and intra-patient heterogeneity of resistance mechanisms to the mutant EGFR selective inhibitor rociletinib

Jacob J. Chabon[1,2], Andrew D. Simmons[3], Aaron M. Newman[1,2], Alexander F. Lovejoy[1,2], Mohammad S. Esfahani[1,2], Henry J. Haringsma[3], David M. Kurtz[2,4], Henning Stehr[1,2], Florian Scherer[2], Kathleen A. Durkin[5], Gregory Otterson[6], Thomas W. Purcell[7], D. Ross Camidge[7], Jonathan W. Goldman[8], Lecia V. Sequist[9], Zofia Piotrowska[9], Heather A. Wakelee[2], Joel W. Neal[2], Ash A. Alizadeh[1,2,10], and Maximilian Diehn[1,2,11]

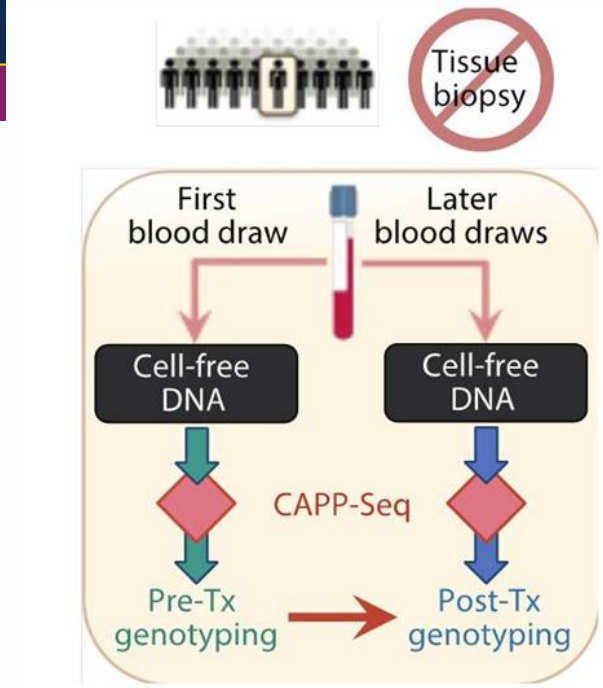
[1]Institute for Stem Cell Biology and Regenerative Medicine, Stanford, California; [2]Stanford Cancer Institute, Stanford, California; [3]Clovis Oncology, Boulder, Colorado; [4]Department of Bioengineering, Stanford, California; [5]Molecular Graphics and Computation Facility, Berkeley, California; [6]The Ohio State University, Columbus, Ohio; [7]Division of Medical Oncology, University of Colorado School of Medicine, Colorado; [8]David Geffen School of Medicine, University of California, Los Angeles, California; [9]Massachusetts General Hospital and Harvard Medical School, Boston, Massachusetts; [10]Division of Hematology, Stanford, California; [11]Department of Radiation Oncology, Stanford, California

PRESENTED AT: ASCO ANNUAL MEETING '16

Presented by: Jake Chabon (Stanford University)

Abstract # 9000

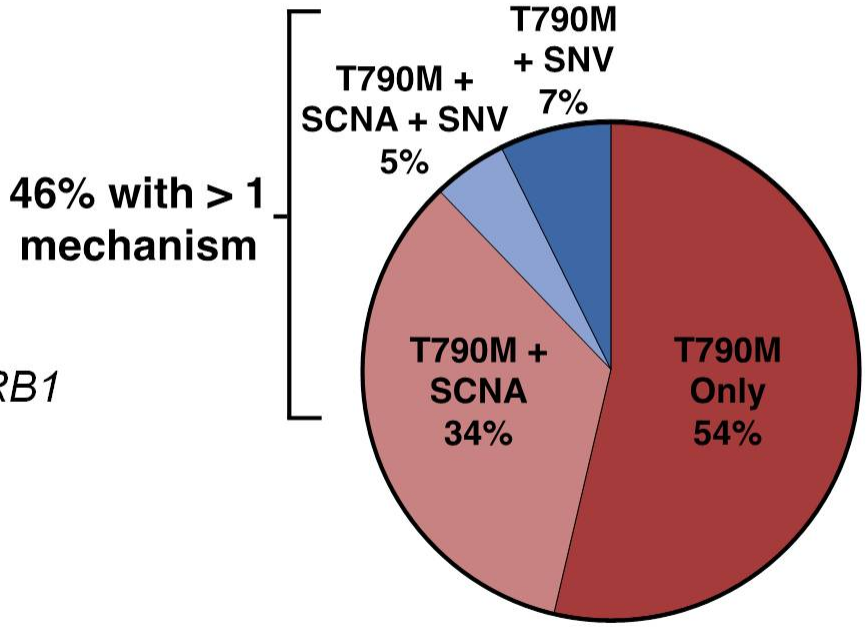
Cancer Personalized Profiling by deep Sequencing (CAPP-Seq)[1,2]



1) Newman & Bratman *et al.* Nature Med 2014
2) Newman, Lovejoy, Klass *et al.* Nature Biotechnol 2016

Intra-patient Heterogeneity of Resistance Mechanisms to First-line EGFR TKIs

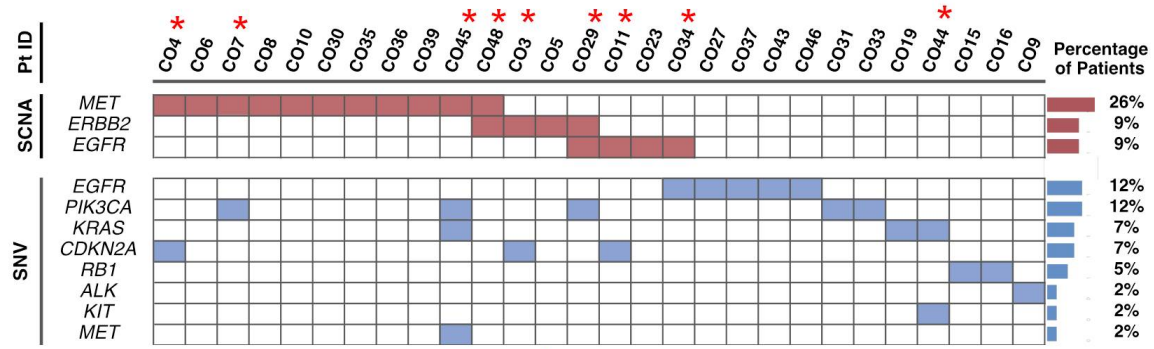
- Baseline rociletinib plasma
  - *n* = 41 patients with detectable T790M
- 34% T790M+SCNA (copy number gain)
  - *MET* or *ERBB2*
- 7% T790M+SNV(s)
  - *EGFR*, *PIK3CA* or *RB1*
- 5% T790M+SCNA+SNV
  - SCNA in *MET* and SNV in *PIK3CA* or *RB1*



SNV=single nucleotide variant, SCNA=somatic copy number alteration

Inter- and Intra-patient Heterogeneity of Resistance to Rociletinib

- Putative resistance mechanism criteria:
  - Emerged at progression
  - Increased from baseline to progression
- Mechanism(s) identified in 65% of patients
  - 9 genes involved
  - 21% of patients develop multiple resistance mechanisms (*)



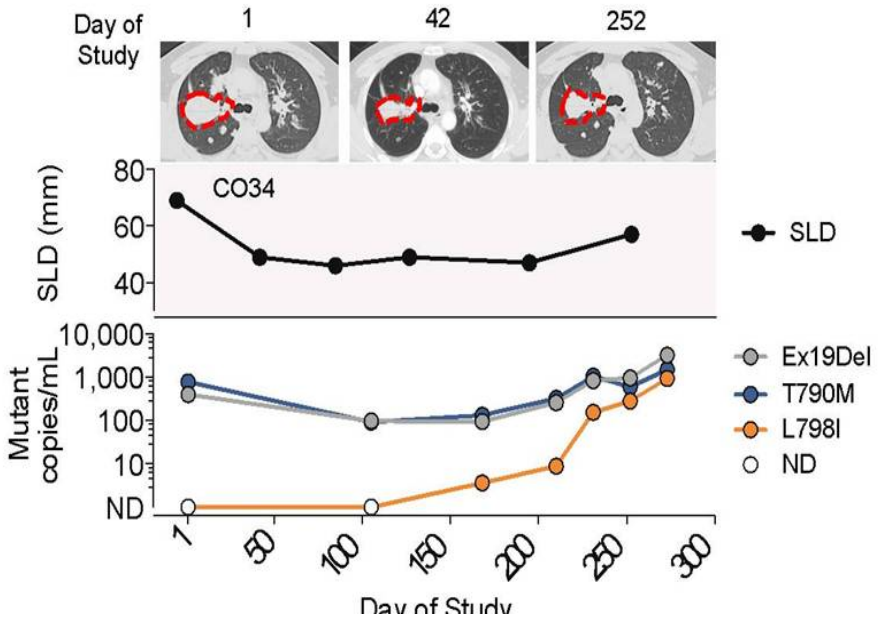
SNV=single nucleotide variant, SCNA=somatic copy number alteration, *=patient with > 1 mechanism identified

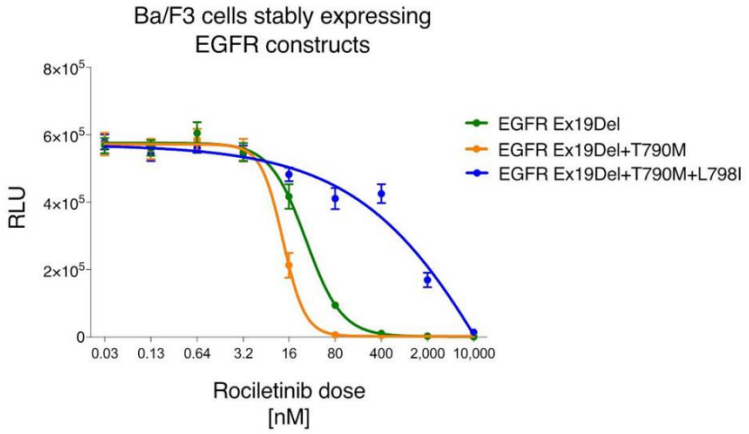
PRESENTED AT: ASCO ANNUAL MEETING '16

Presented by: Jake Chabon (Stanford University)
Abstract # 9000

Gene	Number of Patients	Baseline Alterations	Emergent Alterations
EGFR	5	A750P	C797S L798I L692V E709K
PIK3CA	5	E545K	E542K (3) E545K (3) E81K
KRAS	3		G12A Q61H A146T
CDKN2A	3	D74A	D74A (2)
RB1	2	G587*	R787Q
ALK	1		R1061Q
KIT	1		L576P
MET	1	D1304H	

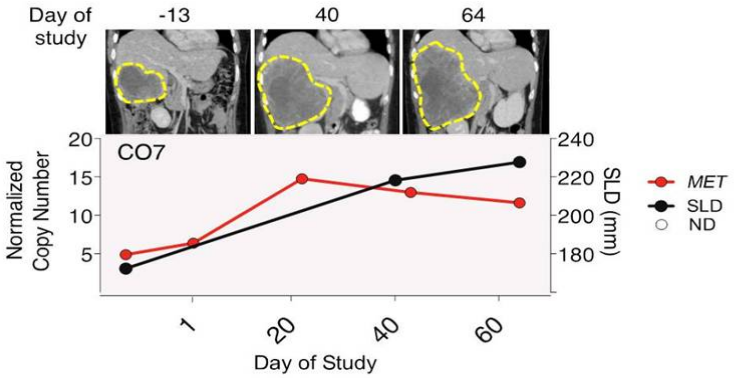
Novel EGFR L798I Resistance Mutation



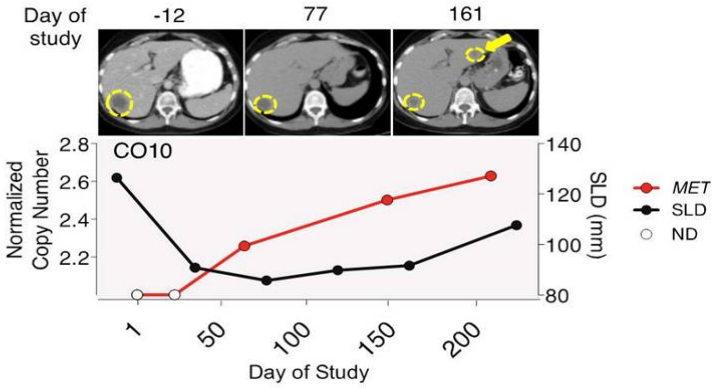


MET Copy Number Gain Mediates Innate and Acquired Resistance to Rociletinib

Innate Resistance



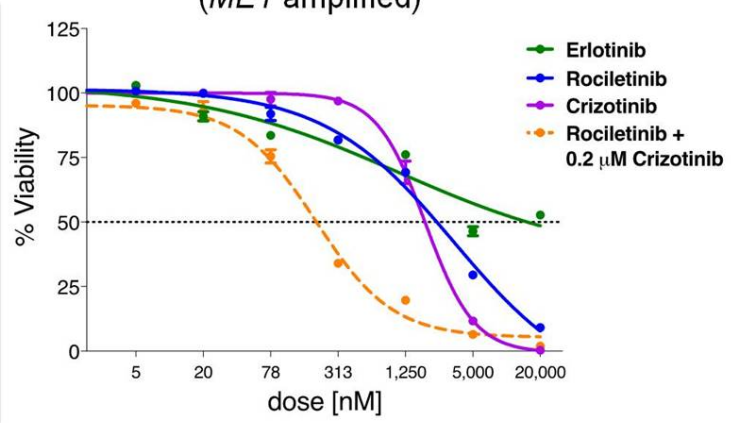
Acquired Resistance



MET Pathway Inhibition Restores Sensitivity to Rociletinib Treatment

- Preclinical models of acquired rociletinib resistance
- PC-9 (EGFR del19) xenografts chronically dosed with rociletinib
- Rociletinib-resistant xenografts reproducibly developed *MET* amplification
- *MET* mediated resistance could be overcome by concurrent EGFR and MET inhibition

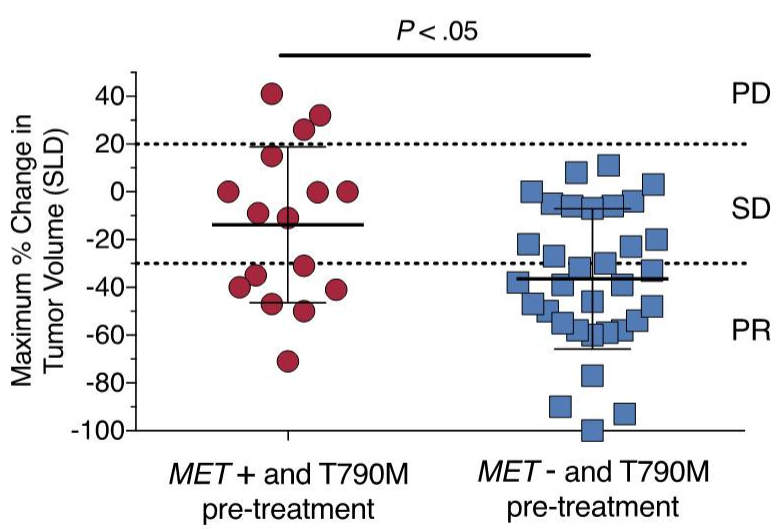
PC-9
rociletinib-resistant
(*MET* amplified)

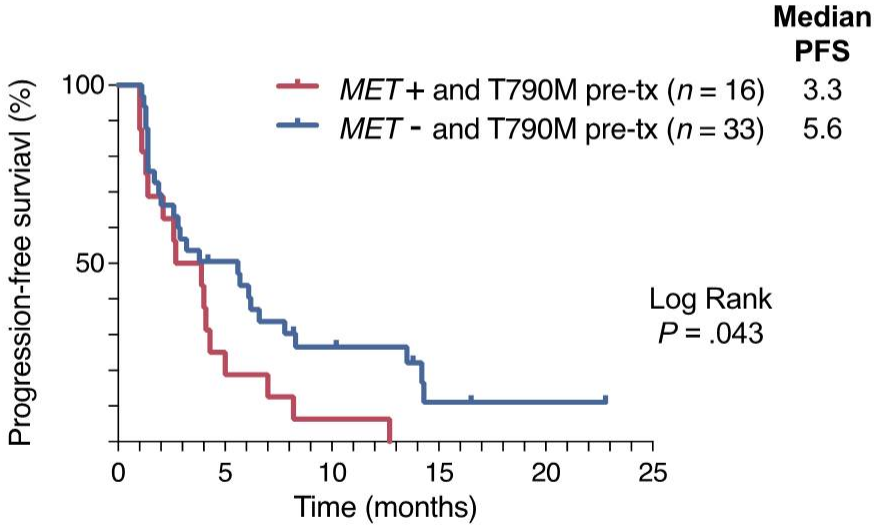


Presence of Multiple Resistance Mechanisms is Associated with Poor Outcome

Expanded cohort with pre-treatment *MET* assessment[1]

Group A: *MET*+ & T790M+ Patients (*n* = 16)
Group B: *MET*- & T790M+ Patients (*n* = 33)





[1]*MET* status was determined by CAPP-Seq ctDNA analysis, FISH on tumor biopsy, or prior patient history

Presented By Jacob Chabon at 2016 ASCO Annual Meeting

Epidermal growth factor receptor genotyping of matched urine, plasma and tumor tissue from non-small cell lung cancer patients treated with rociletinib

Heather Wakelee,[1] Shirish Gadgeel,[2] Jonathan Goldman,[3] Karen Reckamp,[4] Chris Karlovich,[5] Vlada Melnikova,[6] Jean-Charles Soria,[7] Helena Yu,[8] Benjamin Solomon,[9] Maurice Pérol,[10] Joel Neal,[1] Stephen Liu,[11] Mitch Raponi,[5] Darrin Despain,[5] Mark Erlander,[6] Shannon Matheny,[5] Sergey Yurasov,[5] D. Ross Camidge,[12] Lecia Sequist[13]

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PRESENTED AT: ASCO ANNUAL MEETING '16

Abstract 9001
Presented by: Heather A. Wakelee

TIGER-X: Tissue, Plasma, and Urine *EGFR* Test Platforms

	FFPE tissue	Plasma	Urine
EGFR test platform	Real-Time PCR (*therascreen*®)	Digital PCR + Flow Cytometry (BEAMing)	Mutation Enrichment NGS (trovera)
Company	Qiagen	Sysmex-Inostics	Trovagene
Specimen collection	Mandatory	Mandatory	Optional
Test specimen input	Two 5 μm slides	2 mL	100 mL
EGFR mutations detected	T790M, Ex19del, L858R, G719X, L861Q, S768I, Ex20ins	T790M, Ex19del, L858R, G719X, L861Q	T790M, Ex19del, L858R

FFPE, formalin-fixed, paraffin-embedded; NGS, next-generation sequencing; PCR, polymerase chain reaction.

Plasma Detection Is Sensitive and Can Complement Tissue T790M Testing

- Plasma sensitivity=**80.9% (313/387)** with tissue as reference
  - Plasma identifies almost as many T790M-positive patients (n=374) as tissue (n=387) when inadequate biopsies (n=55) are included

Plasma vs Tissue

T790M		Tissue			*total*
		Positive	Negative	Inadequate	
Plasma (BEAMing)	Positive	313	23	38	374
	Negative	74	17	17	108
total		387	40	55	482

*Includes cases where tissue biopsy had no tumor cells, tissue *EGFR* test result was invalid, or tissue was unavailable for central laboratory testing.

Urine Detection Is Equally Sensitive and Can Complement Tissue T790M Testing

- Urine sensitivity=**81.1% (142/175)** with tissue as reference
  - Urine identifies almost as many T790M-positive patients (n=169) as tissue (n=175) when inadequate biopsies (n=22) are included
- 4/11 (36%) T790M urine-positive/tissue-negative patients had PR as best confirmed response

Urine vs Tissue

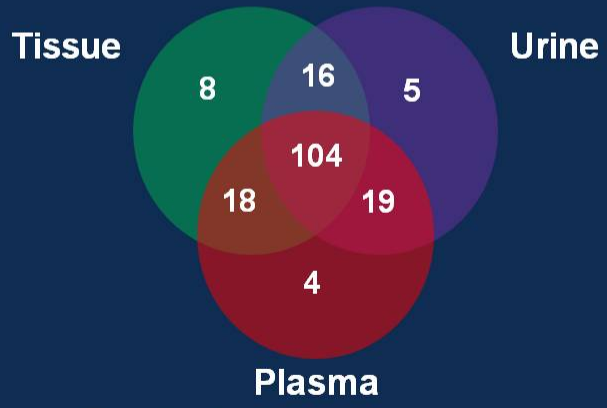
T790M		Tissue			*total*
		Positive	Negative	Inadequate*	
Urine	Positive	142	11	16	169
	Negative	31	5	6	42
	Inadequate	2	0	0	2
total		175	16	22	213

* Includes cases where tissue biopsy had no tumor cells, tissue *EGFR* test result was invalid, or tissue was unavailable for central laboratory testing.

Plasma, Tissue, and Urine Identify Unique and Overlapping Subsets of T790M-Positive Patients

- 181 samples had matched pretreatment T790M results in plasma, tissue, and urine
  - 7 were T790M-negative or inadequate by all 3 sample types (4%)
  - 174 were T790M-positive by at least 1 sample type (96%)

T790M-Positive Cases



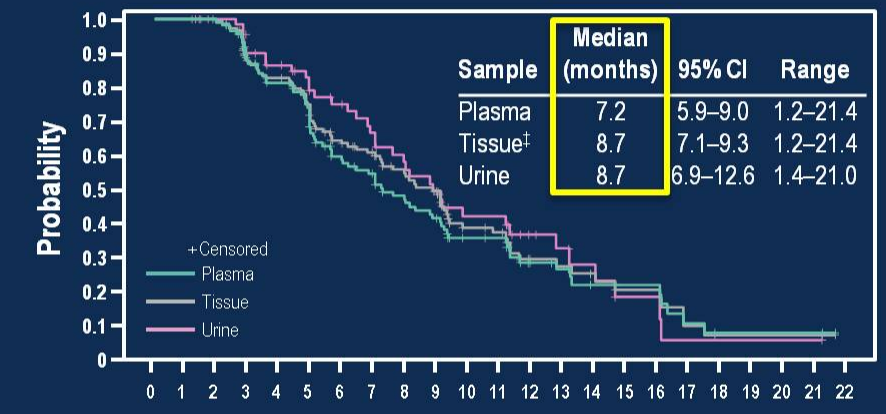
Proportion of patients in diagram not to scale.

- Total positive by tissue: 146 of 181
- Total positive by plasma: 145 of 181
- Total positive by urine: 144 of 181

104 (57%) were positive by all 3 sample types

Duration of Response and Progression-Free Survival: Results Independent of Sample Type Used to Identify T790M Positivity

Duration of Response*†

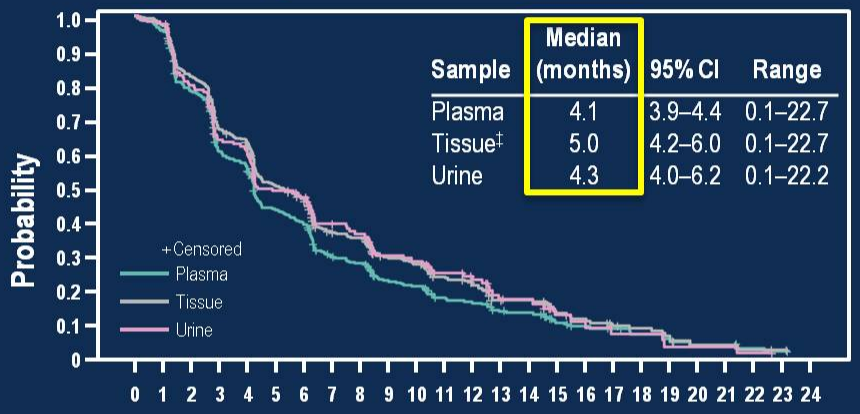


Sample	Median (months)	95% CI	Range
Plasma	7.2	5.9–9.0	1.2–21.4
Tissue‡	8.7	7.1–9.3	1.2–21.4
Urine	8.7	6.9–12.6	1.4–21.0

Patients at Risk

Plasma	120	116	89	59	43	28	16	9	8	2	2	0
Tissue	150	143	110	73	53	29	15	11	8	2	2	0
Urine	62	60	49	36	27	17	10	6	3	1	1	0

Progression-Free Survival†



Sample	Median (months)	95% CI	Range
Plasma	4.1	3.9–4.4	0.1–22.7
Tissue‡	5.0	4.2–6.0	0.1–22.7
Urine	4.3	4.0–6.2	0.1–22.2

Patients at Risk

Plasma	370	283	194	136	91	62	42	31	16	10	5	3	0
Tissue	440	355	261	185	126	83	52	35	19	12	4	2	0
Urine	168	132	97	74	49	35	24	13	5	4	2	1	0

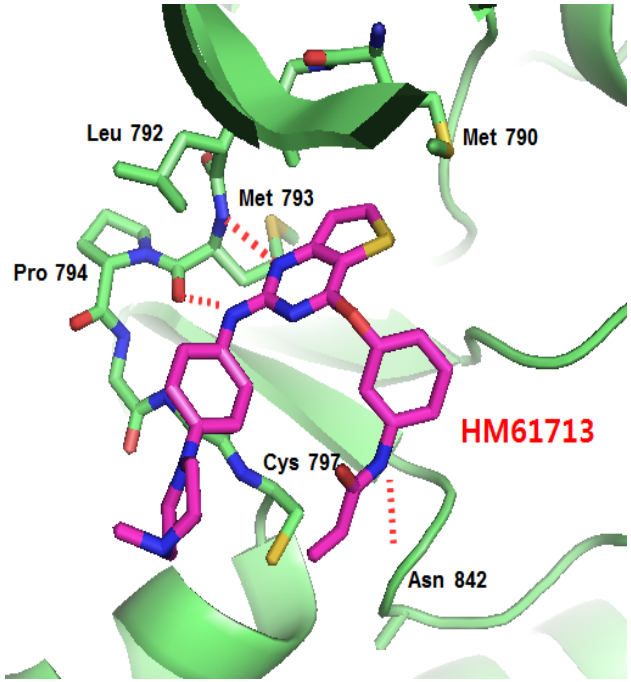
Data cutoff date: April 15, 2016.
*Investigator-assessed confirmed response (RECIST v1.1).
†Combined dosing groups (500, 625, and 750 mg BID).
‡Overall median (95% CI) duration of response and overall median (95% CI) progression-free survival for TIGER-X is equivalent to the result for tissue.

Presented By Heather Wakelee at 2016 ASCO Annual Meeting

Abstracts

- **9042**:Rociletinib-associated cataracts in EGFR-mutant NSCLC:
  - phase I/II TIGER-X
  - 53%
  - median latency of 15 mos from initial drug exposure to surgery.
- **9045**: Updated results from TIGER-X, a phase I/II open label study of rociletinib in patients (pts) with advanced, recurrent T790M-positive non-small cell lung cancer (NSCLC).

2-Olmutinib



- EGFR mutation-specific, i.e. sparing wild type EGFR
- Activity against sensitizing EGFR mutations (Del19, L858R, L861Q etc)
- Activity against T790M resistance mutation

BI1482694 (HM61713): Mechanism of Action

Oral EGFR mutant -specific TKI

- Potent and irreversible inhibition of sensitizing (Del19, L858R) and resistance (T790M) EGFR mutations
- More than 200 fold selectivity over wild type EGFR

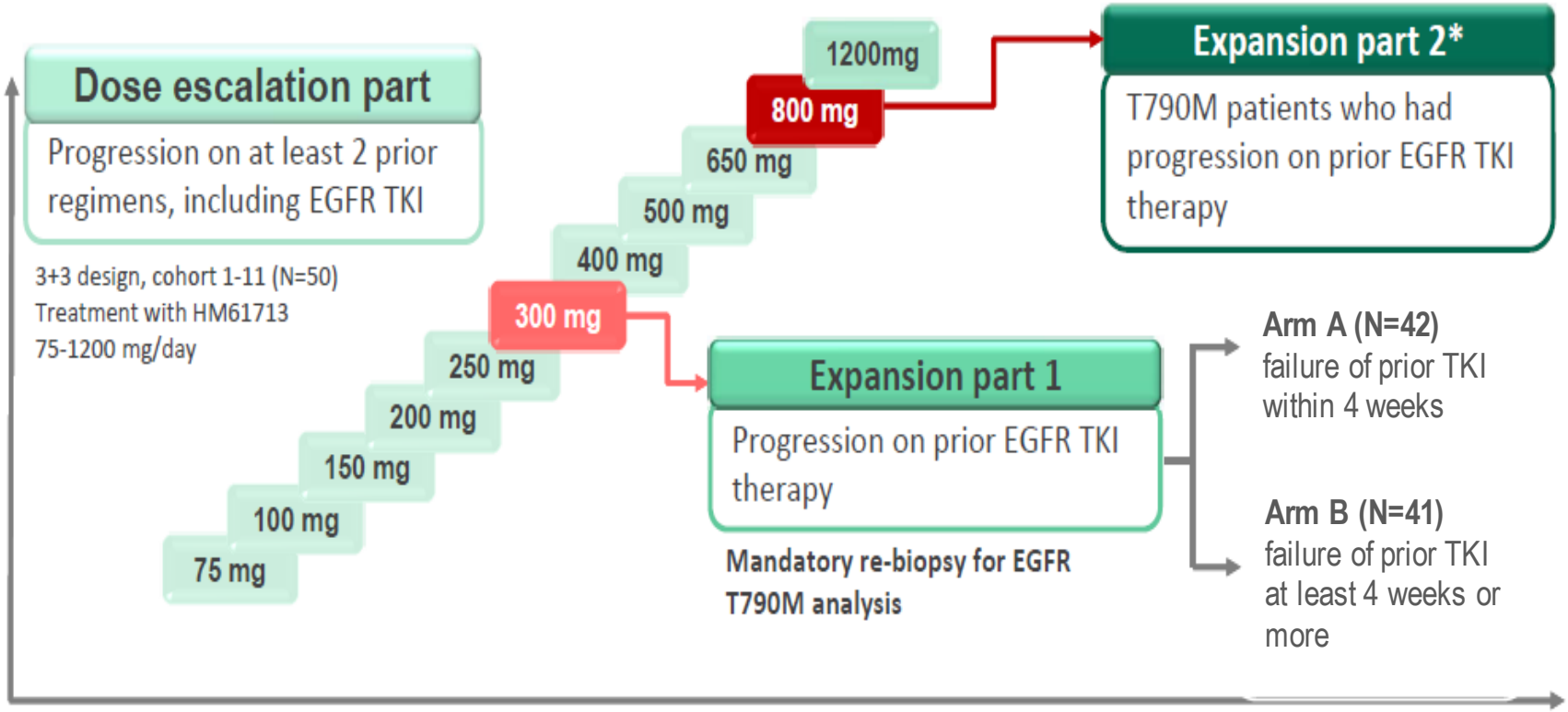
***In vitro* cell growth inhibition in NSCLC**

	Inhibition concentration (IC_{50}, nM)		
	H358	HCC827	H1975
	EGFR WT	$EGFR^{exon\ 19\ del}$	$EGFR^{L858R/T790M}$
Erlotinib	449	3.2	2,253
Afatinib	31	1.8	53
BI1482694 /HM61713	2,225	9.2	10

Park K. WCLC 2015

HM-EMSI-101 Phase I/II Trial

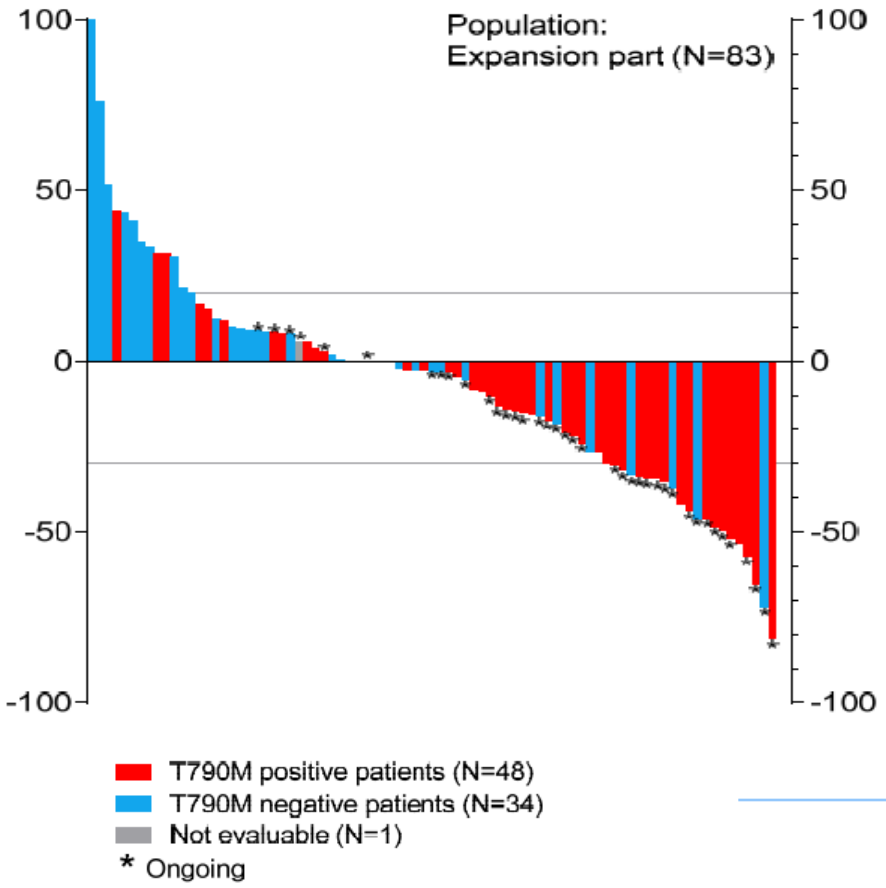
- Korean patients with EGFR M+ NSCLC
- Previously treated with at least one EGFR TKI and could receive additional lines of chemotherapy or other systemic treatments
- At RP2D (**800 mg qd**) all eligible patients had to have confirmed T790M+ status



Park K, et al. J Thorac Oncol 2015;33(Suppl. 15); Abstract 8084

Expansion Part 1: Activity at 300 mg QD (ASCO 2014)

T790M positive and negative patients



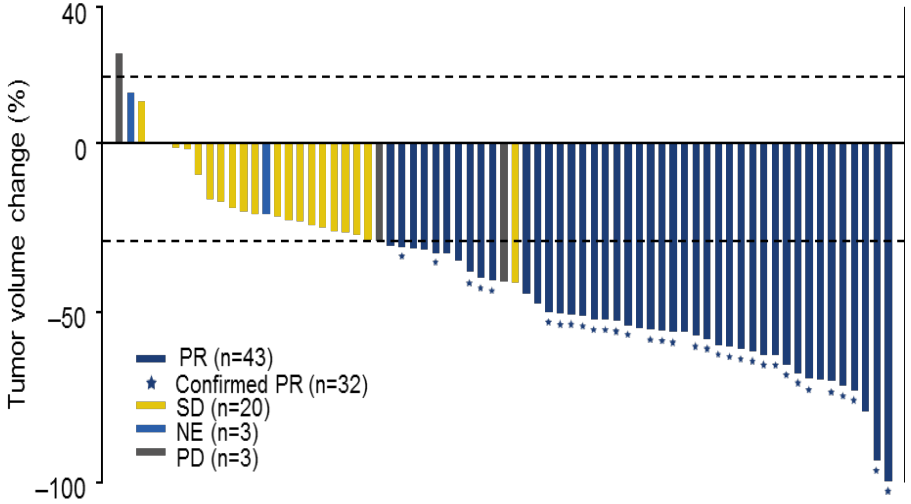
T790M+ and T790M-	N=83
PR	22%
SD	46%
DCR	68%
PD	32%

ORR in T790M+ = 29.2%

Kim DW, et al., *J Clin Oncol* 2014. 32: Abstract 8011.

Activity in T790M+ patients at 800 mg QD (ESMO Asia 2015)

Expansion Part 2: Data cut-off 30 June 2015



	Evaluable patients (n=69)
OR (confirmed and unconfirmed), n (%)	43 (62)
Disease control, n (%)	63 (91)
Confirmed OR, n (%)	32 (46)
SD, n (%)	31 (45)
PD, n (%)	3 (4)
NE, n (%)	3 (4)

- Of 76 treated patients, 69 were evaluable for response by independent assessment
- ORR 62%, including 32 (46%) pts whose response had been confirmed by the time of data cut-off
- DCR 91%

NE, not evaluable; OR, objective response; PD, progressive disease; PR, partial response; QD, once daily; SD, stable disease; DCR, disease control rate

Lee JS, et al. ESMO Asia 2015; #425PD

Actualización de eficacia y seguridad

Characteristic	Patients (N=76)
Gender, n (%)	
Female	44 (58)
Median age, years (range)	60 (32–85)
ECOG PS, n (%)	
0 / 1 / 2	5 (7) / 56 (74) / 15 (20)
Smoking history, n (%)	
Never / former / current	53 (70) / 21 (28) / 2 (3)
Previous lines of systemic treatment*, n (%)	
1 / 2 / ≥3	19 (25) / 27 (36) / 30 (39)
Previous EGFR TKI†, n (%)	
Gefitinib	58 (76)
Erlotinib	21 (28)
Afatinib	11 (14)
Poziotinib	2 (3)
Median interval from last EGFR TKI, days	61
T790M mutation, n (%)	
Positive (local test)	76 (100)
Positive (central test)	73 (96)

*Including EGFR TKIs; †Patients may have received more than one EGFR TKI
ECOG PS, Eastern Cooperative Oncology Group performance status

Response, n (%)	Evaluable for response (n=70)
OR (confirmed and unconfirmed)	43 (61)
Disease control	63 (90)
Confirmed OR	38 (54)
SD / unconfirmed PR	20 (29) / 5 (7)
PD	3 (4)
NE	4 (6)

NE, not evaluable; PD, progressive disease; SD, stable disease

- Median PFS among all treated patients (n=76) by independent review was 6.9 months (95% confidence interval [CI]: 5.36, 9.49)
  - Median PFS was 8.8 months (95% CI: 3.98, 11.07) in patients with one prior systemic treatment (n=19) and 6.8 months (95% CI: 4.21, 8.35) in patients with two or more prior regimens (n=57)

Treatment-related AEs in >20% of patients

AE, n (%)	Treated patients (N=76)	
	All grades	Grade ≥3
Diarrhea	45 (59)	0
Pruritus	32 (42)	1 (1)
Rash	31 (41)	4 (5)
Nausea	30 (39)	0
Palmar-plantar erythrodysesthesia syndrome	23 (30)	3 (4)
Decreased appetite	23 (30)	0
Dry skin	21 (28)	1 (1)
Skin exfoliation	20 (26)	1 (1)

No AEs of QT prolongation or hyperglycemia and no drug-related deaths

AE, adverse event; DRAE, drug related adverse events; 4 (5%) patients discontinued due to DRAEs (Upper abdominal pain and vomiting [n=1], interstitial lung disease [n=1], peripheral neuropathy [n=1] and skin exfoliation [n=1]); 11 (14%) patients had serious DRAEs

Park K, et al. ASCO 2016; Poster #378

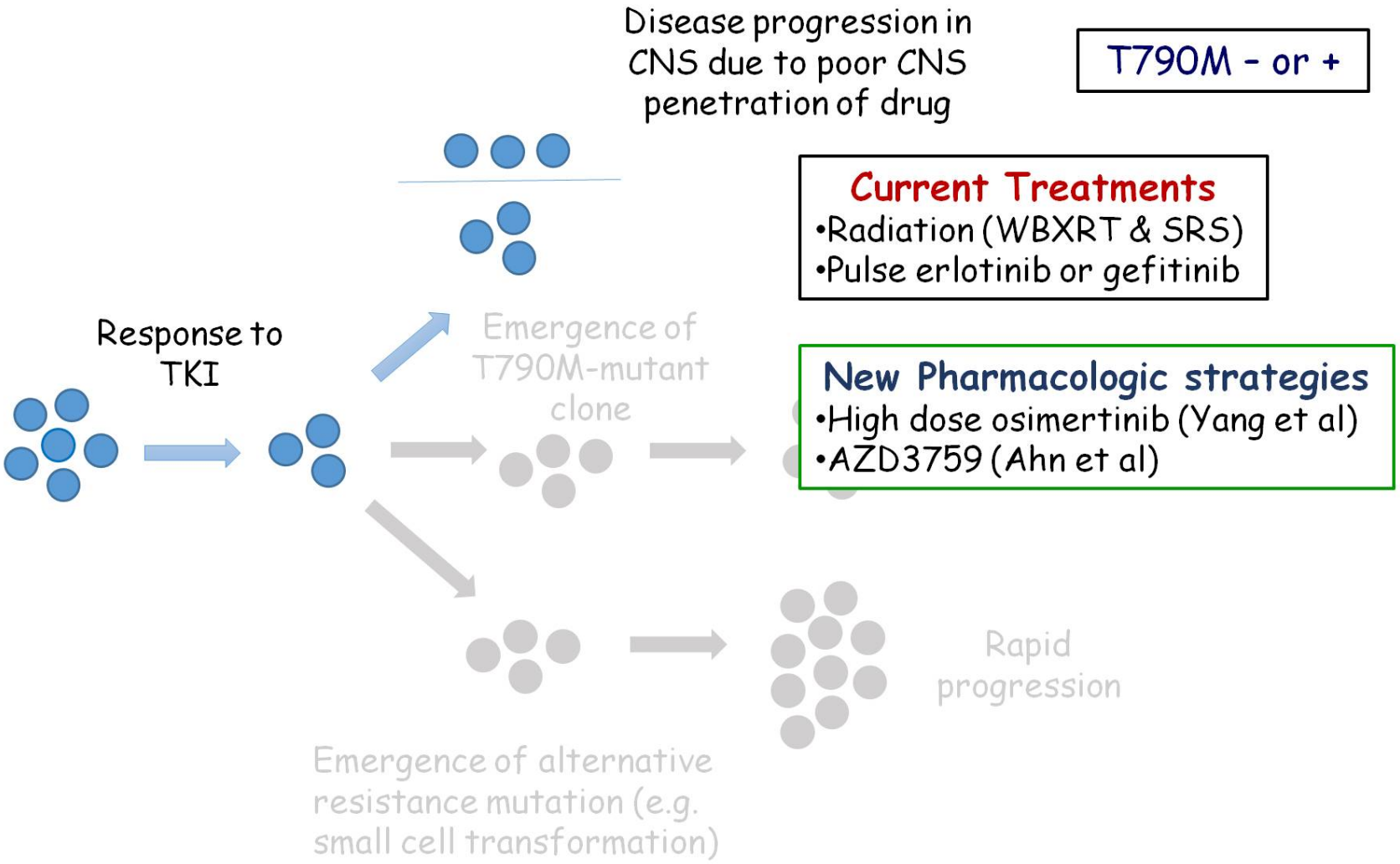
HM-EMSI-101 Trial conclusions

- The MTD and RP2D was determined as 800 mg QD
- Olmutinib showed meaningful clinical activity in EGFR TKI-resistant NSCLC harbouring a T790M mutation, at the RP2D
  - ORs by independent assessment were observed in 61% of the patients
  - 38 (54%) patients had confirmed partial response with a median duration of response of 8.3 months
- The most common treatment-related AEs included typically mild-to-moderate gastrointestinal (diarrhoea, nausea) and dermatologic (rash, pruritus) disorders
- An ongoing global Phase II trial, **ELUXA 1** (NCT02485652), is further assessing the efficacy and safety of olmutinib in patients with T790M+ NSCLC

Park K, et al. ASCO 2016; Poster #378
Lee JS, et al. Annals of Oncology (2015) 26 (suppl_9): ix128-ix129

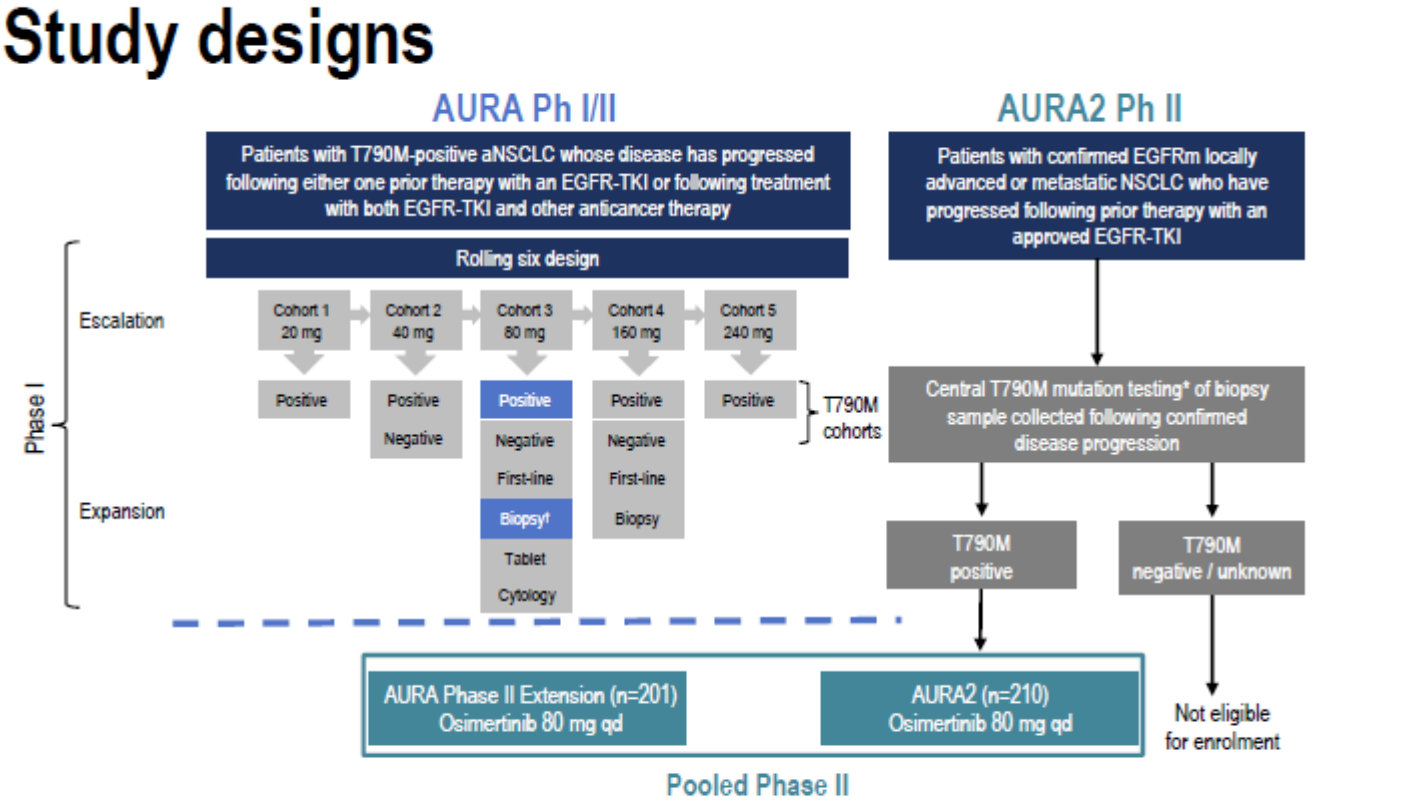
Otros

- Fase I EGF816→ datos de 111 pacientes
- Retrospectivo T790M a la recaida
  - 135 casos rebiopsiados
  - 50% T790M a la recaida
  - Más frecuente cuanto más tardia es la recaida
- Fase I ASP8273 300 mg



Sacher, Jänne & Oxnard Cancer 2014

Osimertinib (AZD9291) Tagrisso

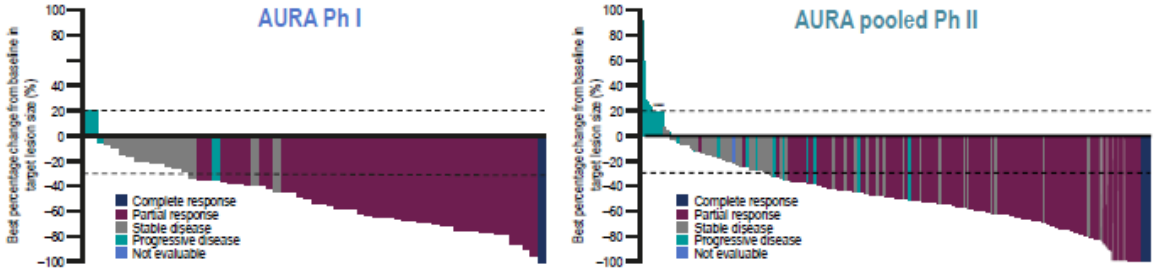


AURA Ph I data cut-off 4 January 2016; AURA pooled Ph II data cut-off 1 November 2015

*The EGFR T790M mutation status of the patient's tumour was prospectively determined by the designated central laboratory using the Cobas® EGFR Mutation Test (Roche Molecular Systems) by biopsy taken after confirmation of disease progression on the most recent treatment regimen; †Paired biopsy cohort patients with T790M positive tumours; safety and efficacy data only reported here; Data from cohorts in grayed out boxes are not included in the analyses reported here.

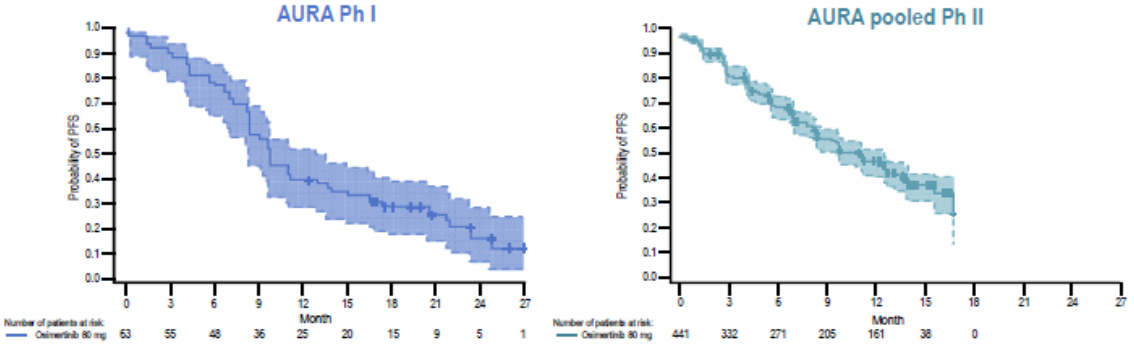
aNSCLC, advanced NSCLC; qd, once daily

Tumour response to osimertinib treatment



	AURA Ph I (80 mg) N=61	AURA pooled Ph II (80 mg) N=397
Confirmed ORR	71% (95% CI 57, 82)	66% (95% CI 61, 71)
Disease control rate†	93% (95% CI 84, 98)	91% (95% CI 88, 94)
Best objective response		
Complete response	1	6
Partial response	42	256
Stable disease ≥6 weeks	14	99
Progressive disease	2	25

Progression-free survival with osimertinib



	AURA Ph I (80 mg) N=63	AURA pooled Ph II (80 mg) N=411
Median PFS,* months (95% CI)	9.7 (8.3, 13.6)	11.0 (9.6, 12.4)
Remaining alive and progression-free,† % (95% CI)		
12 months	41 (29, 53)	48 (42, 53)
18 months	29 (18, 41)	NC
24 months	17 (8, 30)	NC

AURA Ph I data cut-off 4 January 2016; population: safety analysis set; assessment: investigator assessed;

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 APRIL 30, 2015 VOL. 372 NO. 18

AZD9291 in EGFR Inhibitor–Resistant Non–Small-Cell Lung Cancer

Pasi A. Jänne, M.D., Ph.D., James Chih-Hsin Yang, M.D., Ph.D., Dong-Wan Kim, M.D., Ph.D., David Planchard, M.D., Ph.D., Yuichiro Ohe, M.D., Suresh S. Ramalingam, M.D., Myung-Ju Ahn, M.D., Ph.D., Sang-We Kim, M.D., Ph.D., Wu-Chou Su, M.D., Leora Horn, M.D., Daniel Haggstrom, M.D., Enriqueta Felip, M.D., Ph.D., Joo-Hang Kim, M.D., Ph.D., Paul Frewer, M.Sc., Mireille Cantarini, M.D., Kathryn H. Brown, Ph.D., Paul A. Dickinson, Ph.D., Serban Ghiorghiu, M.D., and Malcolm Ranson, M.B., Ch.B., Ph.D.

ABSTRACT

BACKGROUND

The EGFR T790M mutation is the most common mechanism of drug resistance to epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors in patients who have lung cancer with an EGFR mutation (EGFR-mutated lung cancer). In preclinical models, the EGFR inhibitor AZD9291 has been shown to be effective against both EGFR tyrosine kinase inhibitor–sensitizing and T790M resistance mutations.

METHODS

We administered AZD9291 at doses of 20 to 240 mg once daily in patients with advanced lung cancer who had radiologically documented disease progression after previous treatment with EGFR tyrosine kinase inhibitors. The study included dose-escalation cohorts and dose-expansion cohorts. In the expansion cohorts, prestudy tumor biopsies were required for central determination of EGFR T790M status. Patients were assessed for safety, pharmacokinetics, and efficacy.

RESULTS

A total of 253 patients were treated. Among 31 patients enrolled in the dose-escalation cohorts, no dose-limiting toxic effects occurred at the doses evaluated. An additional 222 patients were treated in five expansion cohorts. The most common all-cause adverse events were diarrhea, rash, nausea, and decreased appetite. The overall objective tumor response rate was 51% (95% confidence interval [CI], 45 to 58). Among 127 patients with centrally confirmed EGFR T790M who could be evaluated for response, the response rate was 61% (95% CI, 52 to 70). In contrast, among 61 patients without centrally detectable EGFR T790M who could be evaluated for response, the response rate was 21% (95% CI, 12 to 34). The median progression-free survival was 9.6 months (95% CI, 8.3 to not reached) in EGFR T790M–positive patients and 2.8 months (95% CI, 2.1 to 4.3) in EGFR T790M–negative patients.

CONCLUSIONS

AZD9291 was highly active in patients with lung cancer with the EGFR T790M mutation who had had disease progression during prior therapy with EGFR tyrosine kinase inhibitors. (Funded by AstraZeneca; ClinicalTrials.gov number, NCT01802632.)

From the Lowe Center for Thoracic Oncology and the Belfer Institute for Applied Cancer Science, Dana–Farber Cancer Institute, Boston (P.A.J.); National Taiwan University and National Taiwan University Hospital (J.C.-H.Y.) and Cheng Kung University Hospital (W.-C.S.) — both in Taipei, Taiwan; Seoul National University Hospital (D.-W.K.), Samsung Medical Center (M.-J.A.), Asan Medical Center (S.-W.K.), and Yonsei Cancer Center, Yonsei University Health System (J.-H.K.) — all in Seoul, South Korea; Institut Gustave Roussy, Villejuif, France (D.P.); National Cancer Center Hospital, Tokyo (Y.O.); Winship Cancer Institute of Emory University, Atlanta (S.S.R.); Vanderbilt Ingram Cancer Center, Nashville (L.H.); Levine Cancer Institute, Carolinas Healthcare System, Charlotte, NC (D.H.); Vall d'Hebron University Hospital and Vall d'Hebron Institute of Oncology, Barcelona (E.F.); and AstraZeneca, Macclesfield (P.F., M.C., K.H.B., P.A.D., S.G.), and University of Manchester, Christie Hospital, Manchester (M.R.) — both in the United Kingdom. Address reprint requests to Dr. Jänne at Dana–Farber Cancer Institute, Lowe Center for Thoracic Oncology, 450 Brookline Ave., HIM 223, Boston, MA 02215, or at pasi_janne@dfci.harvard.edu.

N Engl J Med 2015;372:1689-99.
DOI: 10.1056/NEJMoa1411817

4.1 Indicaciones terapéuticas

TAGRISSO está indicado para el tratamiento de pacientes adultos con cáncer de pulmón no microcítico (CPNM) localmente avanzado o metastásico con mutación positiva del receptor del factor de crecimiento epidérmico (EGFR) T790M.

4.2 Posología y forma de administración

El tratamiento con TAGRISSO se debe iniciar y supervisar por un médico con experiencia en el uso de terapias antineoplásicas.

Al valorar el uso de TAGRISSO como un tratamiento para el CPNM localmente avanzado o metastásico, es necesario que se determine el estado de la mutación del EFGR T790M. El estado de la mutación del EFGR T790M se debe determinar usando un método test validado (ver sección 4.4).

Posología

La dosis recomendada es de 80 mg de osimertinib una vez al día, hasta progresión de la enfermedad o toxicidad inaceptable.

Pendiente de precio en nuestro país

Phase I study (BLOOM) of AZD3759, a CNS penetrable EGFR inhibitor, for the treatment of non-small-cell lung cancer (NSCLC) with brain metastasis (BM) and leptomeningeal metastasis (LM)

Myung-Ju AHN[1], Dong-Wan KIM[2], Tae Min KIM[2], Chia-Chi LIN[5], Jayantha RATNAYAKE[5], David J CARLILE[3], Xiaolu YIN[4], Zhenfan YANG[4], Haiyi JIANG[5], James Chih-Hsin YANG[6]

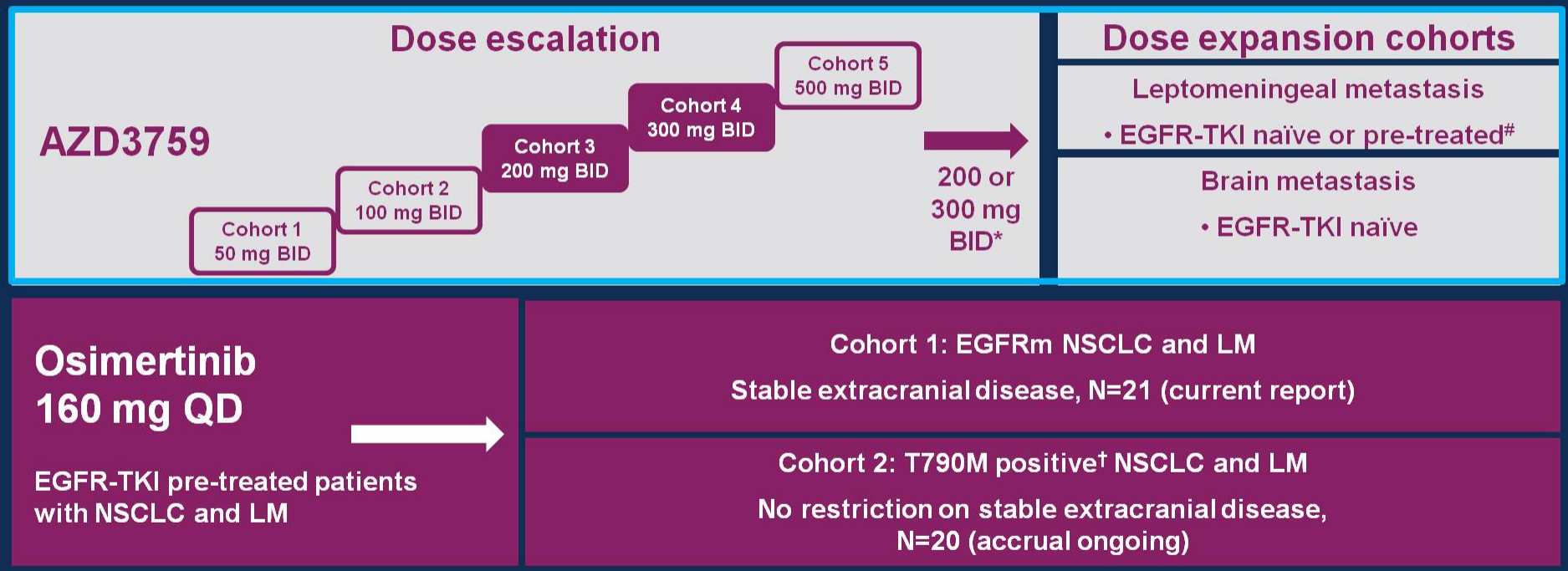
1. Samsung Medical Center, South Korea; 2. Seoul National University Hospital, South Korea; 3. Early Clinical Development, AstraZeneca; 4. Asia & Emerging Markets iMed, AstraZeneca; 5. Global Medicine Development, AstraZeneca; 6. National Taiwan University Hospital, Taiwan

PRESENTED AT: ASCO ANNUAL MEETING '16

Presented by: Myung-Ju Ahn

BLOOM study design overview

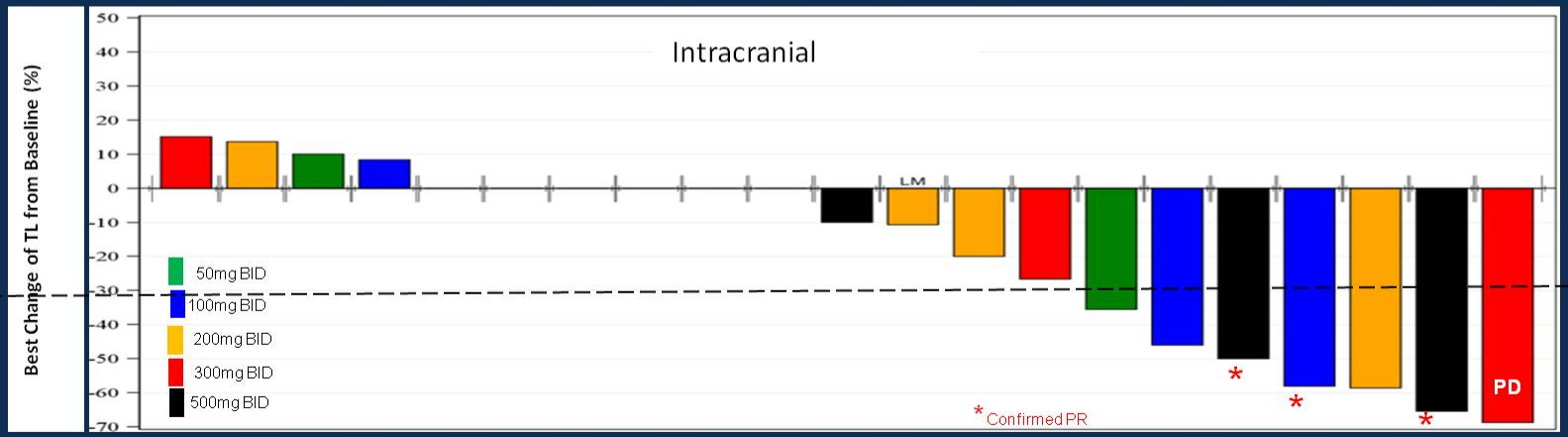
Phase I study to assess the safety, tolerability, pharmacokinetics and preliminary anti-tumor activity of AZD3759 or osimertinib in patients with EGFRm advanced NSCLC



*Both AZD3759 200 mg and 300 mg BID were explored to evaluate long-term tolerability and efficacy; #Requires stable extracranial disease if EGFR TKI pre-treated; †T790M status is based on testing of an extracranial tumor or plasma sample. BID, twice daily; QD, once daily

Anti-tumor activity

- 21 patients with measurable BM lesions were heavily pre-treated and had progressed both extracranially and intracranially on entering the study. 13 out of 21 patients had EGFR TKI as immediate prior treatment.
- Tumor shrinkage in the brain (target lesion) was observed in 11 patients at doses ≥50mg BID, with 3 confirmed PR and 3 unconfirmed PR by IA.
- 8 out of 22 patients with measurable extracranial lesions had tumor shrinkage, with one unconfirmed PR by IA.



Conclusion

- AZD3759 was well-tolerated up to 300mg BID
- Drug-related adverse events are mainly skin rash and diarrhea
- Adverse events related to AZD3759 are similar to those reported with approved EGFR TKIs
- AZD3759 achieved concentrations above IC50 for target inhibition in CSF in all patients ≥200mg BID
- Encouraging intracranial anti-tumor activity was observed with AZD3759 treatment
- LM and BM expansion cohorts are ongoing

BLOOM study design: osimertinib LM cohort 1

Study cohort objectives – cohort 1: EGFRm NSCLC and LM

To assess the safety and tolerability of osimertinib in patients with LM

First patient dosed: April 14, 2015

Data cut-off: March 10, 2016

Osimertinib LM cohort 1

Advanced or metastatic EGFRm NSCLC and confirmed diagnosis of LM by positive CSF cytology

Key inclusion criteria:

- Primary tumor with EGFR L858R or exon 19 deletion
- Prior EGFR-TKI treatment
- ECOG PS 0–2
- Stable extracranial disease
- At least one LM lesion by MRI scan

Osimertinib 160 mg QD

Assessments

- Adverse events*
- Efficacy assessment:
  - OS
  - Brain MRI and extracranial MRI or CT scan*†
  - CSF cytology
  - Neurological exam*
  - CNS symptoms*
- PK in CSF
- Quantification of EGFRm DNA in CSF

*As assessed by study investigator; †modified RECIST for CNS disease; RECIST 1.1 for extracranial disease.
CT/MRI, CSF cytology and neurological exam frequency every 6 weeks. 1 cycle = 21 days of continuous dosing.
CSF, cerebrospinal fluid; CT, computed tomography; ECOG, Eastern Cooperative Oncology Group Performance Status
MRI, magnetic resonance imaging; RECIST, Response Evaluation Criteria In Solid Tumors

NCT02228369

Patient demographics: osimertinib LM cohort 1

- All 21 patients were Asian with adenocarcinoma histology
- Two patients had T790M detected in CSF at study entry; 6 patients had T790M detected in plasma
- Duration of treatment: 1–49 weeks ongoing
- Twenty-one patients dosed; 15 patients are ongoing treatment
  - Safety analysis: n=21
  - Efficacy analysis n=21*

Characteristic, n	N=21
Gender: male / female	6 / 15
Age: median (range), years	59.0 (44–75)
Smoking status: current / former / never	1 / 5 / 15
ECOG PS: 0 / 1 / 2	1 / 11 / 9
Neurological assessment at baseline: normal / abnormal	11 / 10
Prior lines of systemic therapy: median (range)	3.0 (1–8)
Prior whole brain radiotherapy	11
Prior EGFR-TKIs†: gefitinib / erlotinib / dacomitinib / HM61713 (BI 1482694)	16 / 3 / 1 / 1
Prior systemic response to EGFR-TKI: partial response / stable disease / progressive disease	14 / 6 / 1
Tumor tissue EGFRm mutation status (local test)‡: Ex19Del / L858R	9 / 13

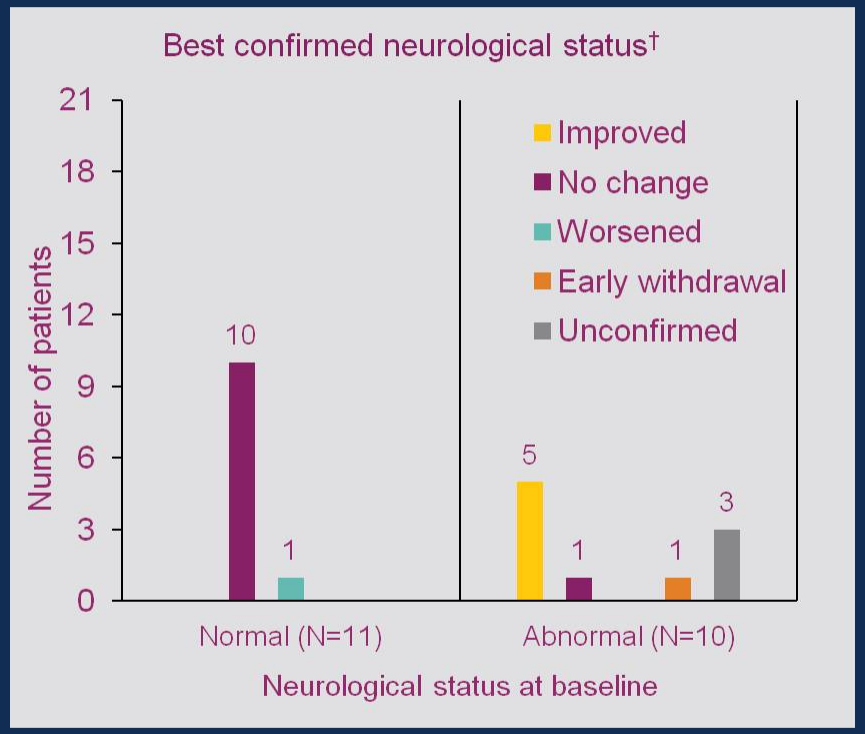
*Efficacy analysis set included all dosed patients; †One patient received two lines of therapy: gefitinib and HM61713; ‡One patient had both Ex19Del and L858R detected at baseline. Ex19del, exon 19 deletion

Osimertinib activity across LM assessments

Efficacy assessments were conducted on 21 patients

- Seven patients had confirmed* radiological improvement
- Two patients had confirmed* CSF cytology clearance; no tumor cells were detected in two consecutive CSF samples
- Five patients had confirmed* improved neurological function

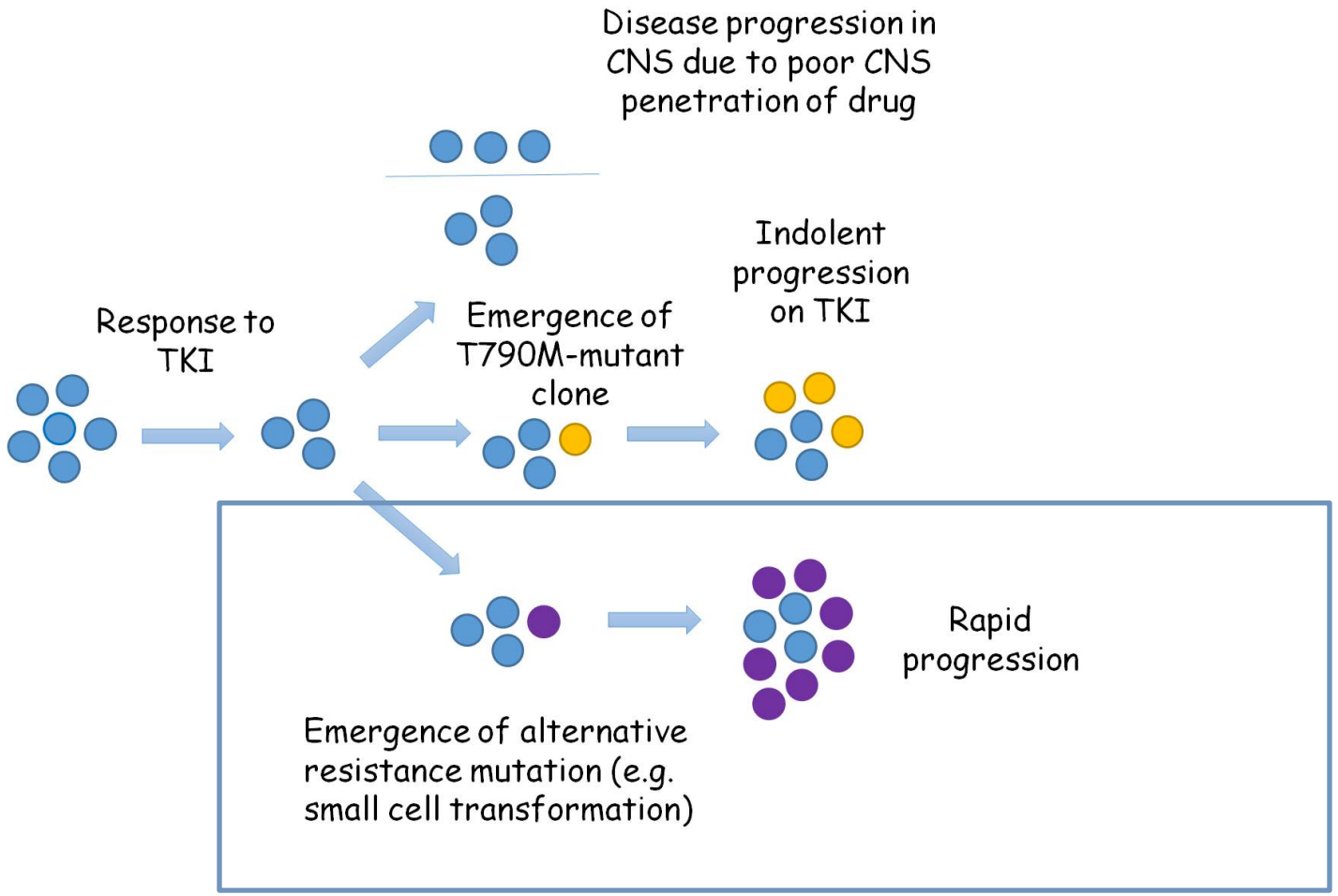
Best MRI imaging intracranial response, n (%)	N=21	
	Confirmed*	Unconfirmed
Responding	7 (33)	1 (5)
Stable disease	9 (43)	2 (10)
Early withdrawal	2 (10)	



Population: efficacy, n=21.*Response confirmation was done at least 4 weeks after the initial response; †Response assessed by neurological examination

Conclusions

- Preclinical data indicate that osimertinib crosses the BBB
- Osimertinib shows encouraging preliminary safety, tolerability and activity in pre-treated patients with EGFRm advanced NSCLC and LM
  - The AE profile is as expected and manageable
  - Neurological function improved from baseline in 5 patients
  - Radiological improvements in LM were seen in 7 patients
  - Clearance of tumor cells from the CSF occurred in 2 patients at 2 consecutive visits
  - Time on treatment suggests durable clinical benefit, with 15 patients remaining on treatment, 7 of whom have been on treatment for >9 months
- Further evaluation of osimertinib in this setting is warranted
- The BLOOM study is ongoing and a cohort enrolling patients with T790M positive NSCLC and LM is open; T790M status is based on testing of an extracranial tumor or plasma sample



Sacher, Jänne & Oxnard Cancer 2014

Phase II safety and efficacy results of a single-arm Phase Ib/II study of capmatinib (INC280) + gefitinib in patients with *EGFR*-mutated, cMET+ non-small cell lung cancer

Yi-Long Wu[1], Dong-Wan Kim[2], Enriqueta Felip[3], Li Zhang[4], Xiaoqing Liu[5], Cai Cun Zhou[6], Dae Ho Lee[7], Ji-Youn Han[8], Alexander Krohn[9], Rachel Lebouteiller[10], Sabine Glaser[11], Matthew Squires[11], Mikhail Akimov[11], Daniel Tan[12].

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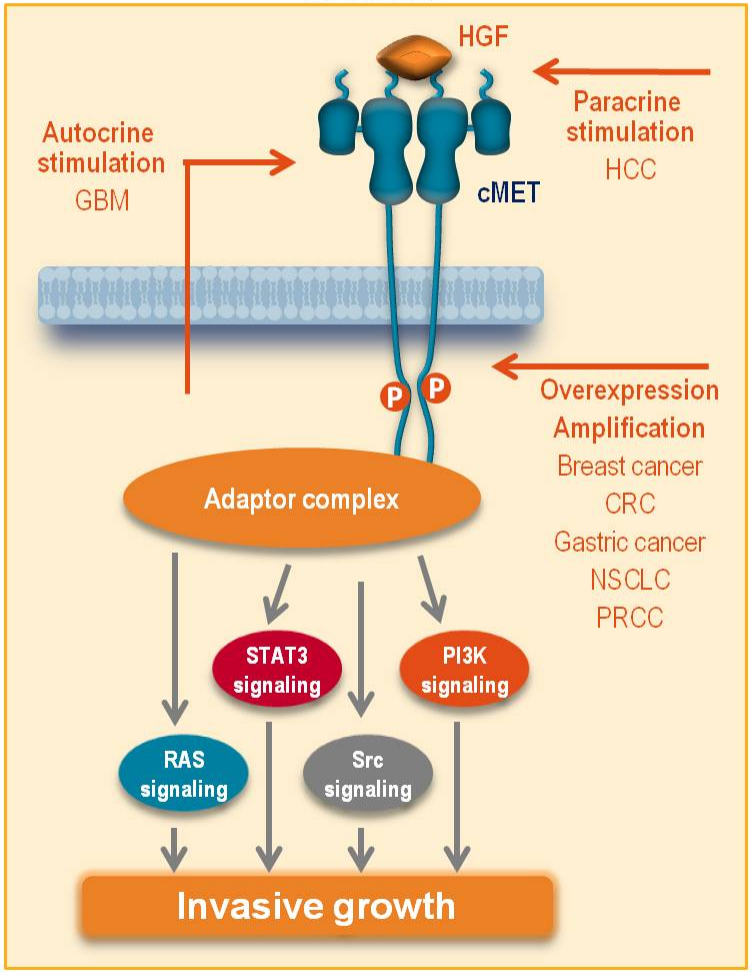
INTRODUCTION

- Amplification and overexpression of cMET has been described in multiple tumor types, including lung, breast, colon, and gastric cancers.[1]
- Downstream signaling pathways following cMET activation include the RAS/MAPK, PI3K/AKT **(Figure 1)**, and Rac/Rho pathways which promote cell proliferation, survival, and metastasis.[1]
- Aberrant activation of the cMET pathway may result from high-level *cMET* gene amplification (GCN ≥5),[2] gene mutations, or cMET overexpression and is associated with poor clinical outcomes in cancer patients.
  - ***cMET* amplification** as an independent driver (3–5%) can cause resistance to EGFR inhibitors and may account for approximately 20% of relapses in patients with NSCLC receiving EGFR-targeted therapy.[3,4]
  - ***cMET* mutations** have been identified in primary tumors as well as metastatic lesions of several cancers, including head and neck, liver, and NSCLC (2–5%).[5,6]
  - **Overexpression of cMET** is often associated with resistance to chemo- and radiotherapy.[7,8]

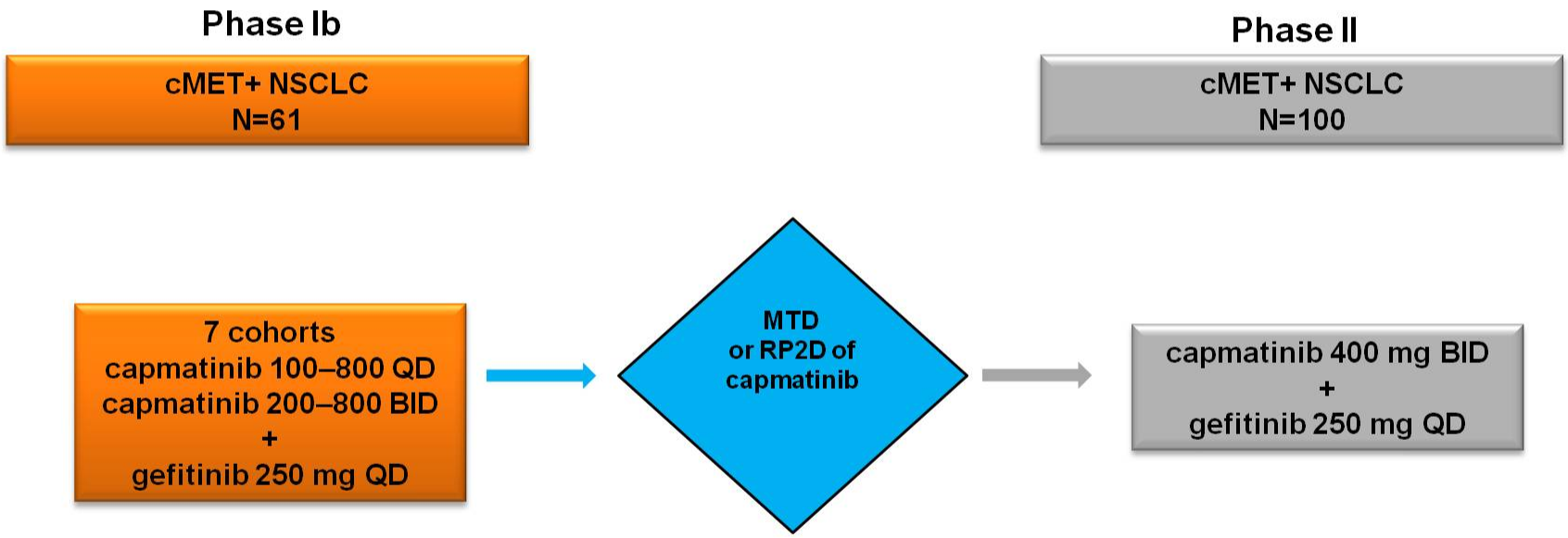
Figure 1. Signaling Pathways Activated by cMET in Cancer



CRC, colorectal cancer; EGFR, epidermal growth factor receptor; HCC, hepatocellular carcinoma; GBM, glioblastoma; HGF, hepatocyte growth factor; NSCLC, non-small cell lung cancer; PI3K, phosphatidylinositol 3-kinase; PRCC, papillary renal cell carcinoma; RTK, receptor tyrosine kinase; STAT3, signal transducer and activator of transcription 3.

METHODS

Figure 3. Study Design (NCT01610336)



MTD, maximum-tolerated dose; RP2D, recommended Phase II dose.

METHODS

- The objectives and endpoints of the study are shown in **Table 2.**

Table 2. Study Objectives and Endpoints (Phase II)

Objectives	Endpoints
Primary	
• Estimate overall clinical activity of capmatinib in combination with gefitinib in NSCLC patients with *cMET* gene dysregulation	• ORR per RECIST v1.1
Secondary	
• Estimate time-dependent clinical activity of capmatinib in combination with gefitinib	• OS, DoR and PFS
• Determine safety and tolerability of capmatinib in combination with gefitinib	• Frequency, duration, and severity of AEs and SAEs, changes in physical examination, clinical laboratory parameters, vital signs and ECGs
• Characterize PK profile of capmatinib in combination with gefitinib	• Plasma concentration of capmatinib and gefitinib, PK parameters

AE, adverse events; DoR, duration of response; ECGs, electrocardiograms; ORR, overall response rate; OS, overall survival; PK, pharmacokinetics; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors; SAEs, serious adverse events.

RESULTS

Patient Demographics and Characteristics

- As of March 01, 2016 (data cut-off date), 100 patients were enrolled in the Phase II part of the study **(Table 3).**
- 95% of patients were diagnosed with adenocarcinoma of the lung.
- 59% of patients had 1 prior line of therapy; 41% had ≥2 lines of therapy.
- All patients were pretreated with an EGFR TKI
  - An EGFR TKI was the last antineoplastic therapy administered in 74% of patients
  - 83% of patients received either an EGFR TKI alone or in combination with chemotherapy as the last antineoplastic regimen prior to the study
- The molecular status of patients included in the study is shown in **Table 4**.

RESULTS

Efficacy

- As of March 01, 2016, 90% of patients with a baseline (BL) assessment had at least one post-BL assessment for efficacy.
  - Overall, the objective response rate (ORR) and the disease control rate (DCR) were 31% and 81%, respectively **(Table 6)**.
    - In the GCN ≥6 molecular subgroup the ORR and DCR were 50% and 84%, respectively
  - Partial responses were observed in all molecular subgroups **(Table 6 and Figures 4 and 5)**.
- Overall (in all 100 patients), median progression-free survival (mPFS) was 24 weeks (95% CI 16.6–24.1).
  - mPFS data for the molecular subgroups are not yet mature.

RESULTS

Table 7. Adverse Events, Regardless of Causality (Any Grade Occurring in ≥10% of All Patients – Safety Set*)

AE, preferred term	All patients N=100	
	All grades, (>10%) n (%)	Grades 3/4 (5%) n (%)
Total	98 (98)	55 (55)
Nausea	33 (33)	5 (5)
Peripheral edema	32 (32)	5 (5)
Hypoalbuminemia	31 (31)	1 (1)
Decreased appetite	28 (28)	3 (3)
Fatigue	22 (22)	5 (5)
Anemia	20 (20)	2 (2)
Diarrhea	20 (20)	1 (1)
Rash	20 (20)	2 (2)
Vomiting	20 (20)	3 (3)
Cough	19 (19)	0
Amylase increased	17 (17)	6 (6)
Blood creatinine increased	16 (16)	0

*Safety set consists of all patients who received at least one dose of study drug and had at least one valid post-baseline safety assessment.
A patient with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment;
a patient with multiple adverse events is counted only once in the total row;
only AEs occurring during treatment or within 30 days of the last study medication are reported.

CONCLUSIONS

- Preliminary clinical activity was observed in patients treated with capmatinib plus gefitinib, particularly in those with high GCN expression.
- Capmatinib in combination with gefitinib is well tolerated.
  - The most common study drug-related all grade and grade 3/4 AEs were nausea and increased lipase, respectively.
- No drug-drug interactions were reported.
- Preliminary data suggest that capmatinib in combination with gefitinib is a promising treatment option for *EGFR*-mutated, *cMET*-amplified (cMET+) NSCLC patients.
- This study is ongoing but not recruiting participants.
- A randomized Phase II study of capmatinib in combination with erlotinib is ongoing.

HER2 Amplification in *EGFR* mutant NSCLC After Acquired Resistance to EGFR-Directed Therapies

Bing Xia, Anna Wurtz, Scott N. Gettinger, Roy S. Herbst, Anne C. Chiang, Mimi Wan, Jeffrey Sklar, Veronique Neumeister, Katerina A. Politi and Sarah B. Goldberg
Yale Cancer Center, New Haven, CT; Yale School of Medicine, New Haven, CT; Smilow Cancer Hospital, New Haven, CT

Yale CANCER CENTER
A Comprehensive Cancer Center Designated by the National Cancer Institute

Figure 2: Relative frequencies of *HER2* amplification, T790M status, *MET* amplification, and small cell transformation at time of resistance to TKI.

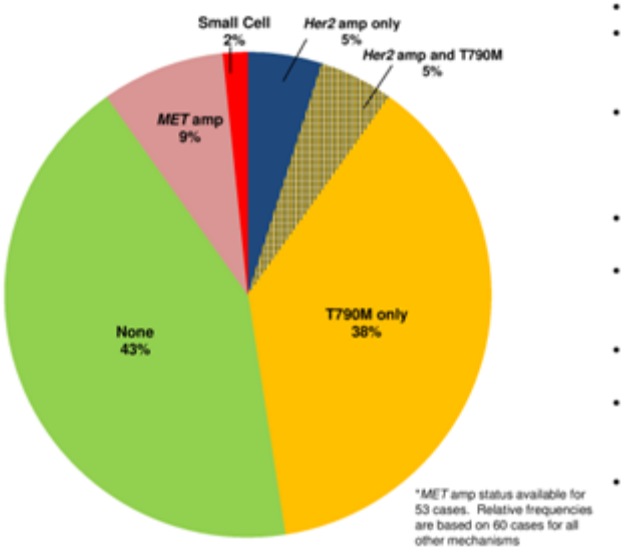
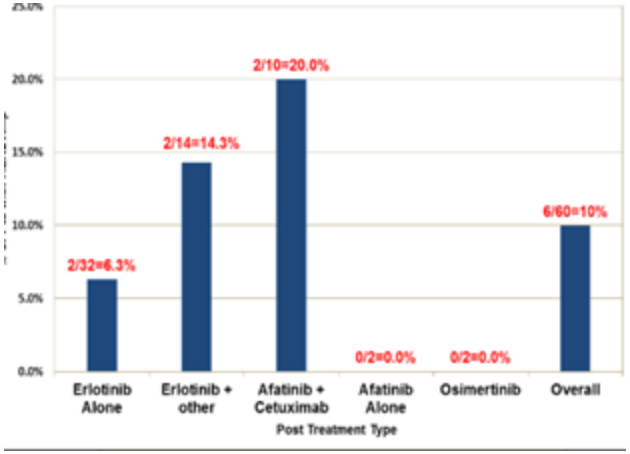


Figure 3: Subjects with *HER2* amplification after resistance to erlotinib alone, second line erlotinib + other agents, afatinib + cetuximab, afatinib alone, and osimertinib



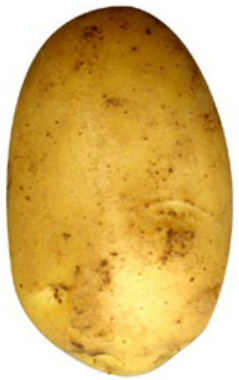
Conclusions

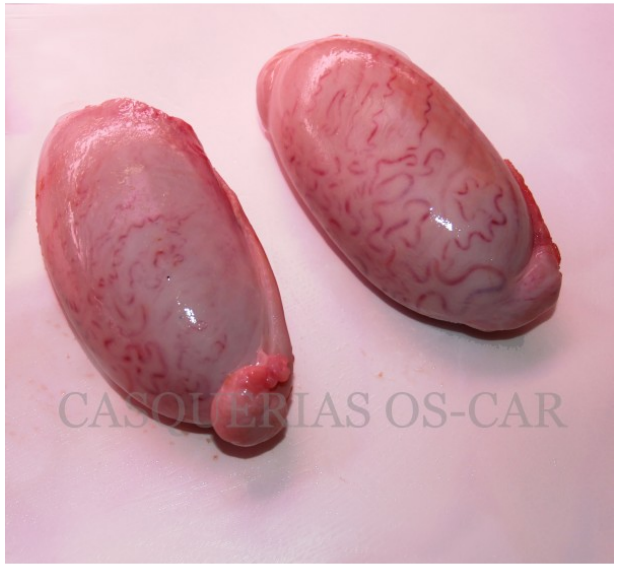
We demonstrate that *HER2* amplification may be a mechanism of resistance to first-line erlotinib alone, second-line erlotinib + other agents, and second-line afatinib + cetuximab, as it was detected in 6.3%, 14.3%, and 20.0% of cases respectively after acquired resistance to these agents. We further show that in the erlotinib alone cases, low level *HER2* amplification was present pre-treatment and increased at acquired resistance. These findings support further investigation into HER2-directed therapies in *EGFR* mutant tumors that harbor *HER2* alterations.

Otros

- A randomized, open-label, phase 2 study of emibetuzumab plus erlotinib (LY+E) and emibetuzumab monotherapy (LY) in patients with acquired resistance to erlotinib and MET diagnostic positive (MET Dx+) metastatic NSCLC.
  - 111 pacientes
  - ORR was 3.8% for LY+E and 4.8% for LY.

Creïlla





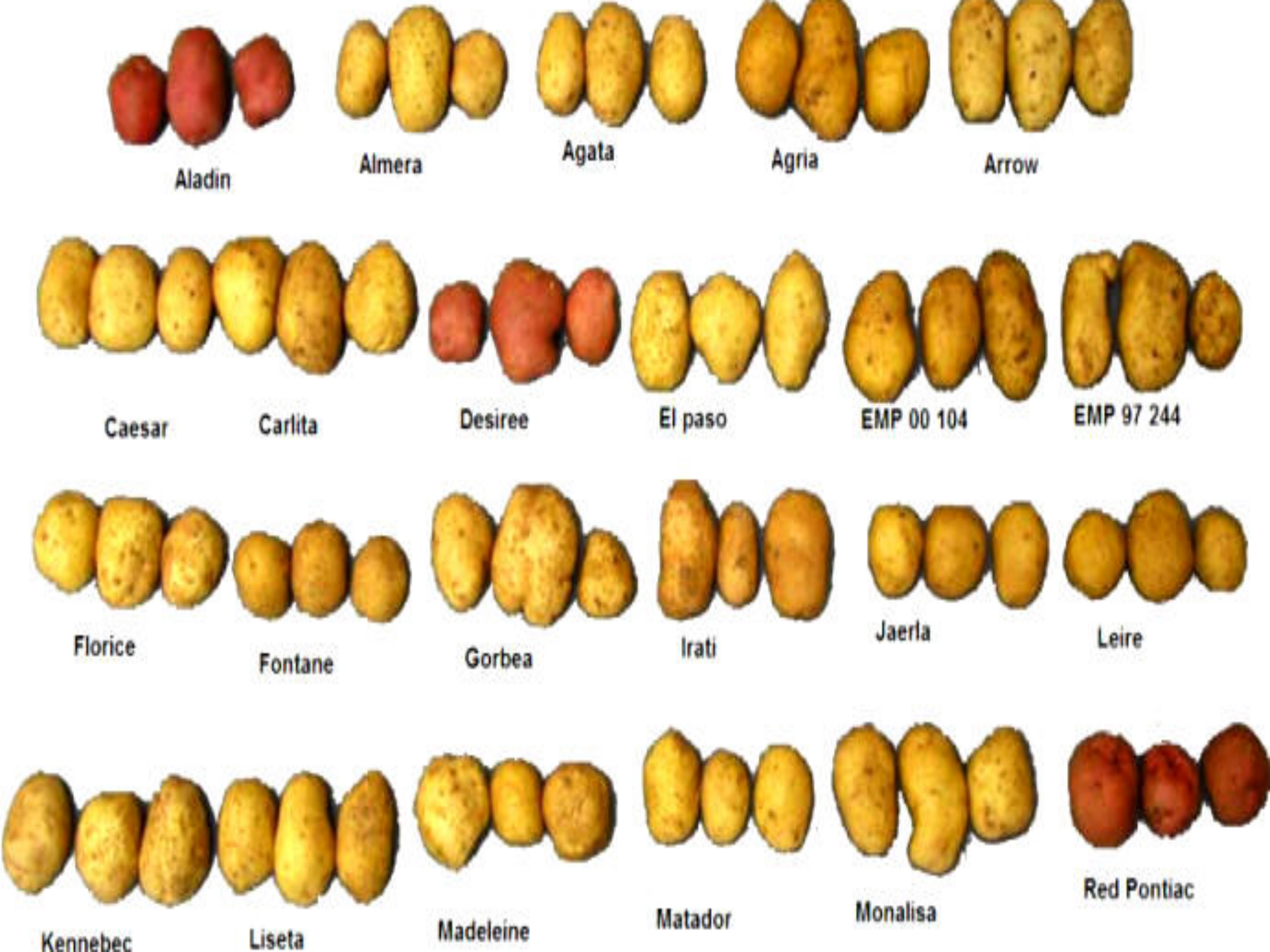
Criadilla → Creadilla → Creïlla

Conclusiones

- CPCNCP avanzado EGFR mutado:
  - Ampliamente asumido el papel de los ITK de 1º y 2º generación
  - El arsenal de ITK de 3º generación para tratar el principal mecanismo de resistencia (T790M) va aumentando:
    - Osimertinib 80 mg : TR: 66%, SLP: 11 meses
    - Olmutinib 800 mg : Corea, TR: 61%
    - Rociletinib: suspendido su desarrollo
  - Otras formas de detección en aumento:
    - Plasma
    - Orina

Conclusiones

- La progresión cerebral es uno de los principales mecanismos de progresión:
  - Asociar a los tratamientos locales RT, RadioQx o Qx:
    - Osimertinib a dosis de 160 mgr en estudio
    - AZD 3759
- Otros mecanismos de progresión en estudio


Aladin
Almera
Agata
Agria
Arrow
Caesar
Carlita
Desiree
El paso
EMP 00 104
EMP 97 244
Florice
Fontane
Gorbea
Irati
Jaerla
Leire
Kennebec
Liseta
Madeleine
Matador
Monalisa
Red Pontiac

Todos los cánceres.
Lavanda

Cáncer de riñon.
naranja

Cáncer de Páncreas.
púrpura

Cáncer de vejiga.
amarillo

Cáncer sarcoma.
purpura

Cáncer de Próstata.
azul claro

Cáncer de cerebro.
gris

Cáncer / leucemia.
naranja

Sarcoma / cáncer de hueso.
amarillo

Cáncer de mama.
rosa

Cáncer de hígado.
esmeralda

Cáncer de Estómago.
Lavanda

Cáncer de cuello uterino.
azul / blanco

Cáncer de pulmón.
blanco

Cáncer de testicular.
orquídea

Cáncer en la infancia.

Linfoma.

Cáncer de tiroides.


Kazbeji Georgia abril 2016
Moltes gràcies