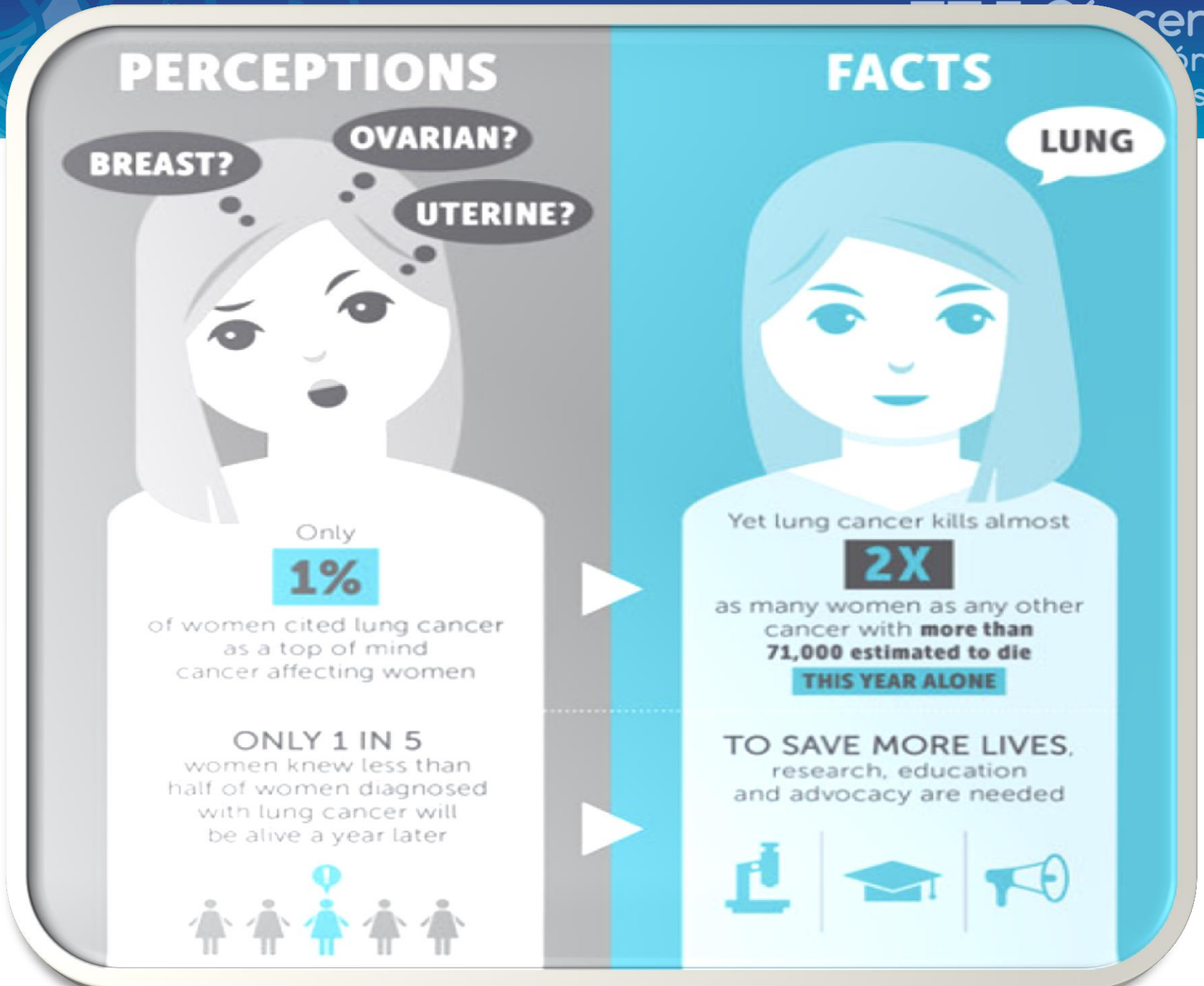
IV Simposio Cáncer de Pulmón en Mujeres

Madrid, 25 de febrero de 2016

Diferencias de género en el tratamiento sistémico: Terapias dirigidas

Rosario García Campelo
Medical Oncology Unit
University Hospital A Coruña, Spain

Anyone can get lung cancer…


PERCEPTIONS
BREAST?
OVARIAN?
UTERINE?
Only
1%
of women cited lung cancer as a top of mind cancer affecting women
ONLY 1 IN 5
women knew less than half of women diagnosed with lung cancer will be alive a year later
FACTS
LUNG
Yet lung cancer kills almost
2X
as many women as any other cancer with more than 71,000 estimated to die
THIS YEAR ALONE
TO SAVE MORE LIVES,
research, education and advocacy are needed

Tumores con más alta Incidencia, Mortalidad y Prevalencia a 5 años en España (Informe GLOBOCAN 2012).

3º incidencia

1º mortalidad

2º incidencia

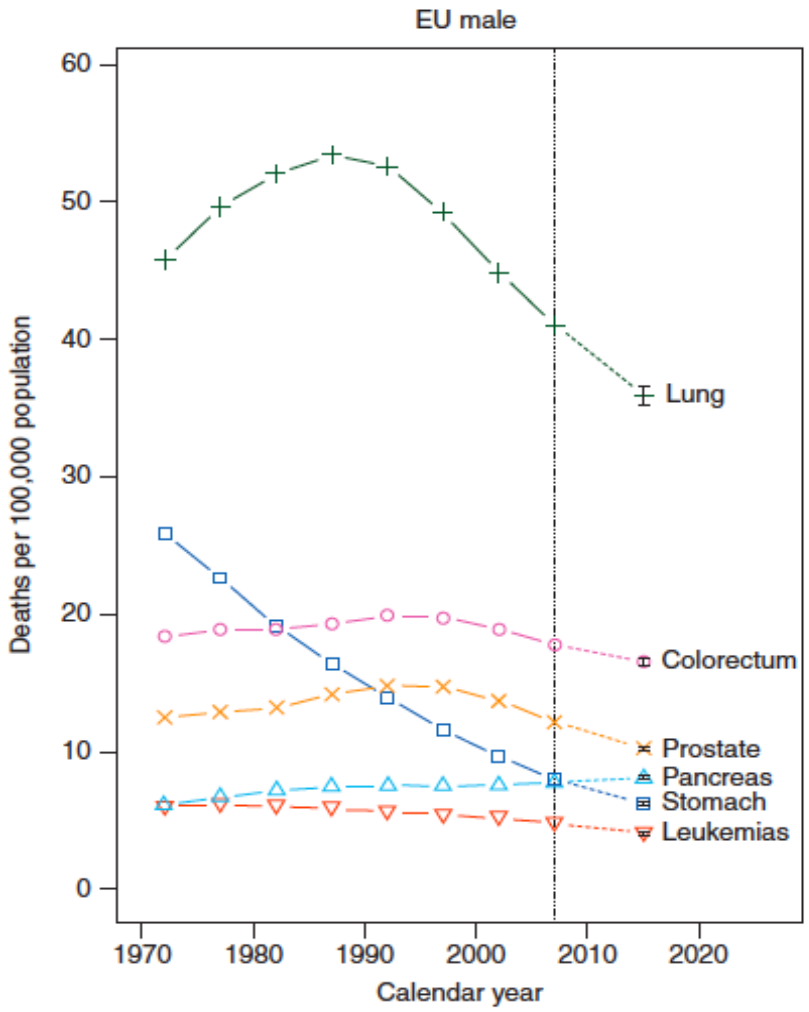
1º mortalidad

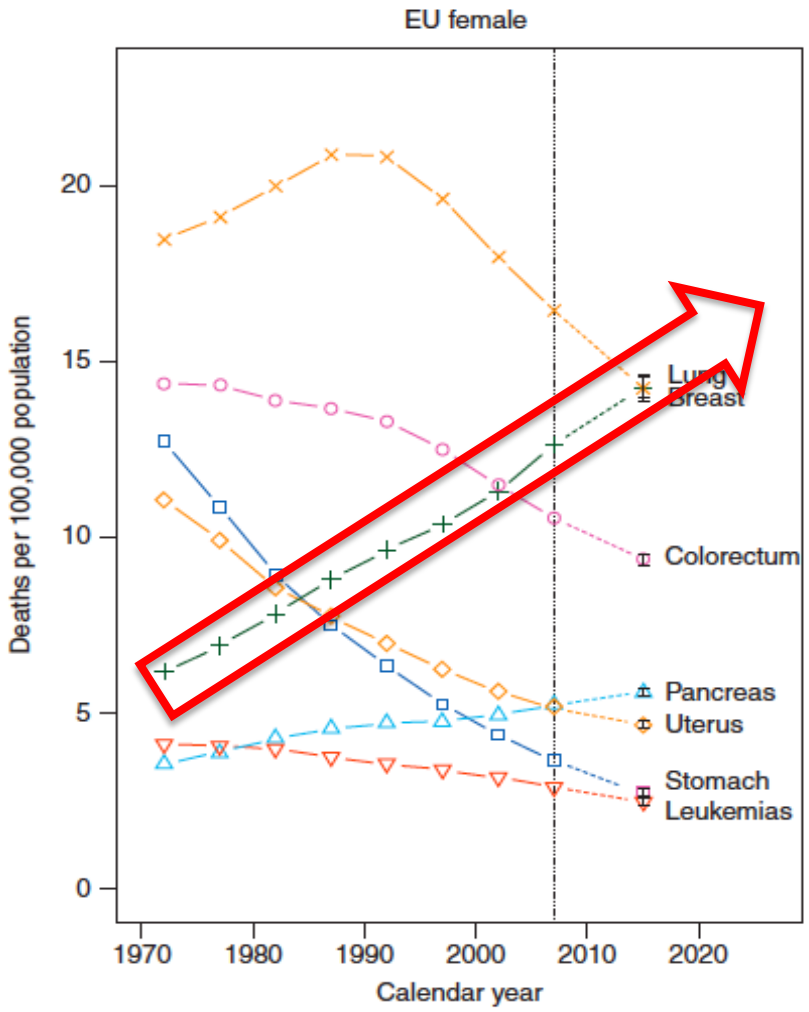
4º incidencia

3º mortalidad

In 2015, for the first time in Europe, lung cancer morality rate in women will be superior to breast cancer mortality rate

IV Simposio Cáncer de Pulmón en Mujeres

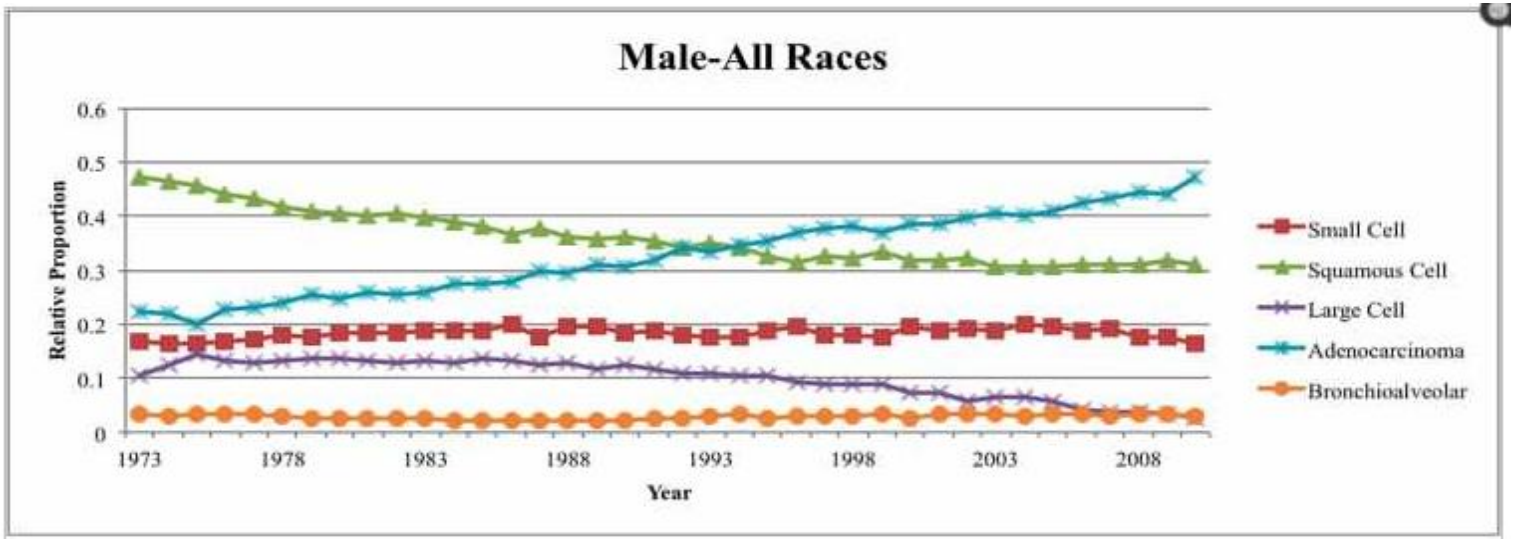


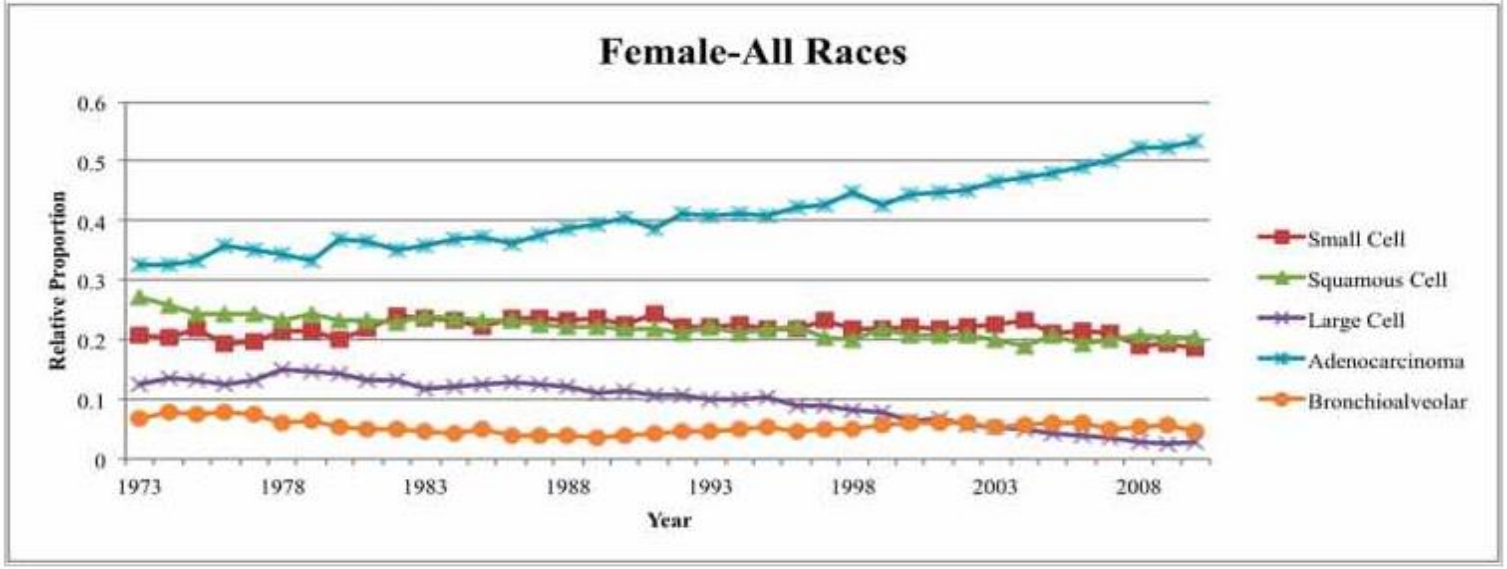


Malvezzi M et al. Ann Oncol 2015

Lung cancer incidence trends by gender, race and histology in the United States, 1973-2010.

IV Simposio Cáncer de Pulmón en Mujeres

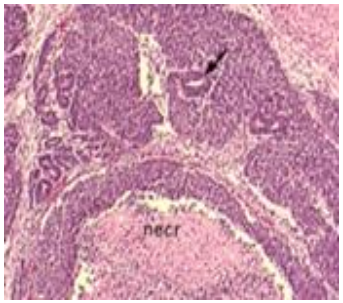




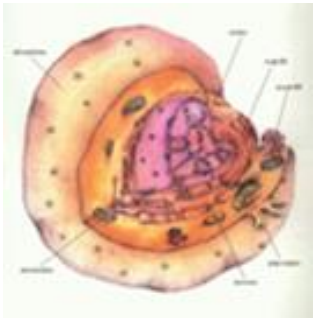
Meza R et al. PLOs One 2015

Molecular profiling is changing our perception of NSCLC

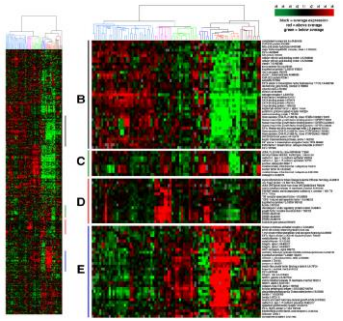
Tumour histology



Molecular biology



Molecular profile



1990s

- Non-specific toxic chemotherapies

2000s

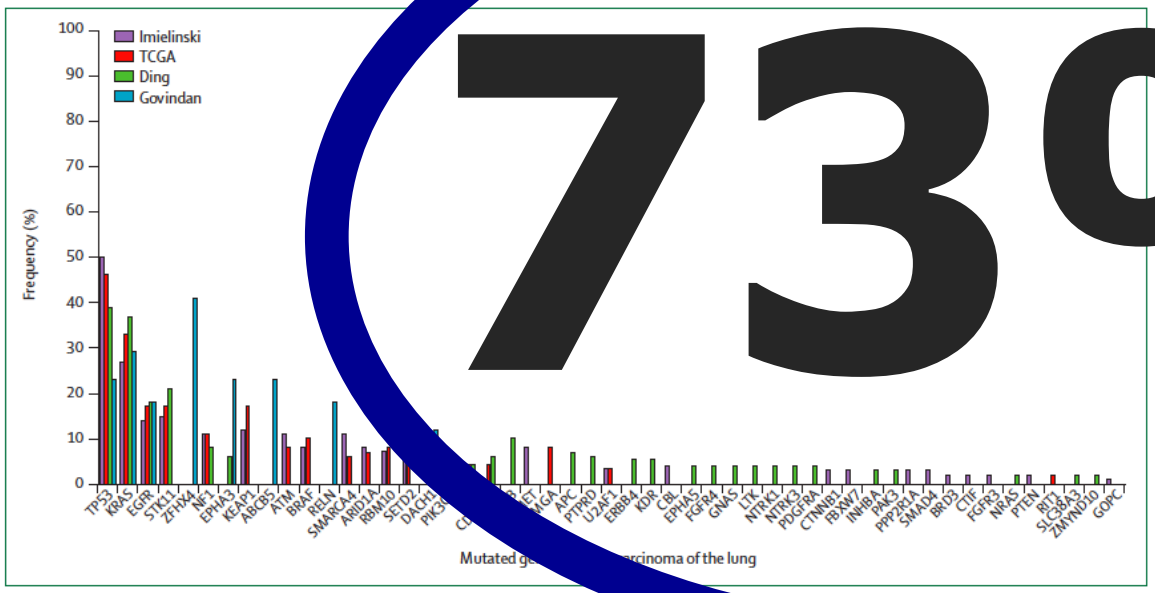
- Targeted therapies with increased benefit and reduced toxicity

Future

- Molecular diagnostics to personalise patient care and increase treatment rates

Genomic alterations in Lung Adenocarcinoma

IV Simposio Cáncer de Pulmón en Mujeres



73%

	Frequency
Mutations	
S	2%
R	%
AF	7
MET 4 skip	4
RIT	2
, NRAS, MAP2K1	%
Translocations	
ROS1	1·7%
ALK	1·3%
RET	0·9%
Amplification	
	2·2%
ERBB2	0·9%

Table 2: Driver alterations in lung adenocarcinoma

Devarakonda S et al. Lancet Oncol 2015

Prevalence and clinical association of gene mutations through Multiplex Mutation Testing in patients with NSCLC: Results from the ETOP Lungscape Project

Study objective

To describe the epidemiology of selected cancer-related mutations and investigate their association to clinicopathological features and patient outcomes

Study design

Multiplex Mutation Testing was performed on patients with resected stage I–III NSCLC with clinical data and FFPE tissue availability

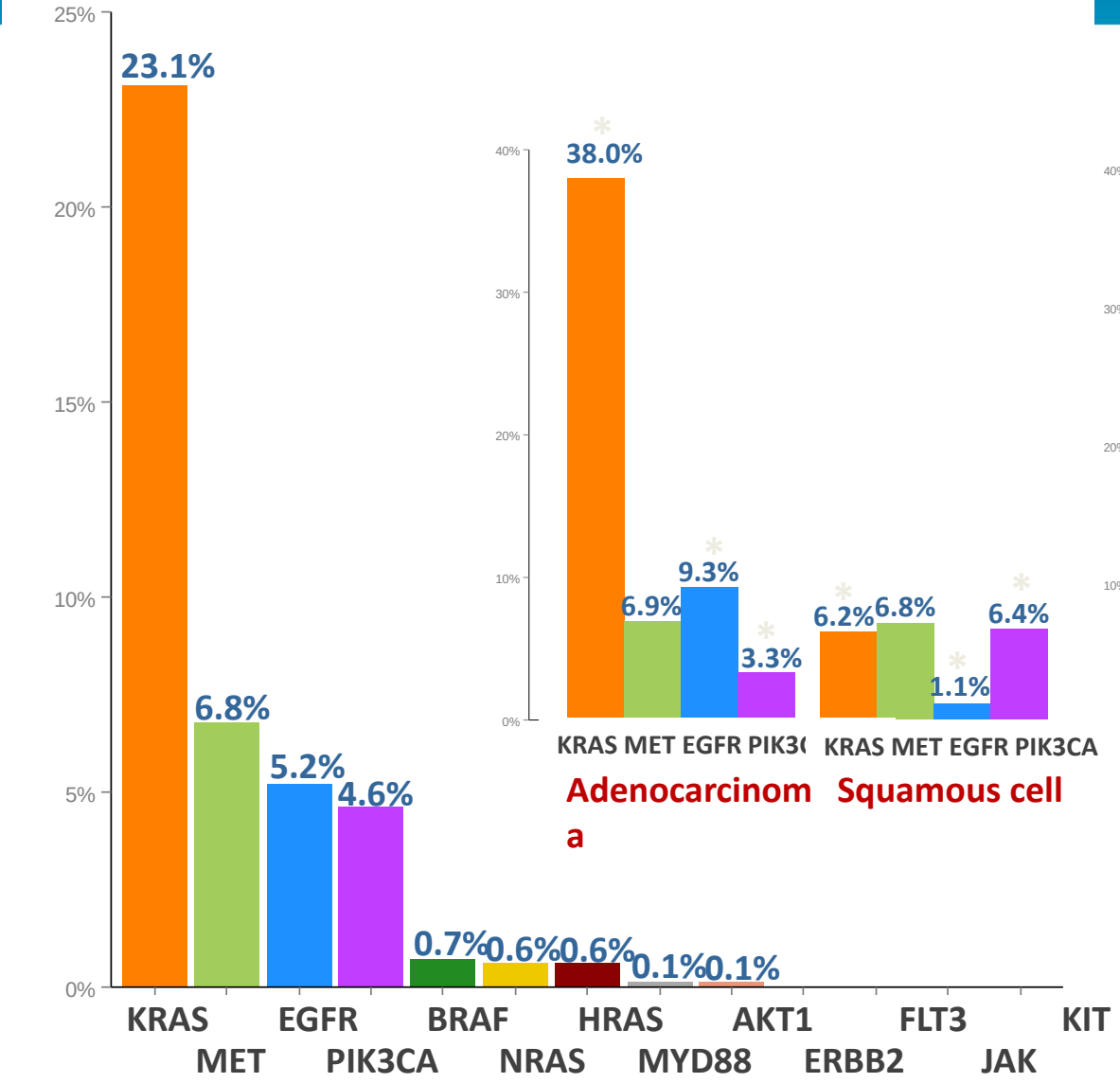
Multiplex testing has been evaluated in 1,801 patients with a median follow-up of 4.7 years; **65.4% were male**; **10.3% never smokers**; and median age was 66.3 years

Kerr et al. Ann Oncol 2015; 26 (suppl 6): abstr 3001

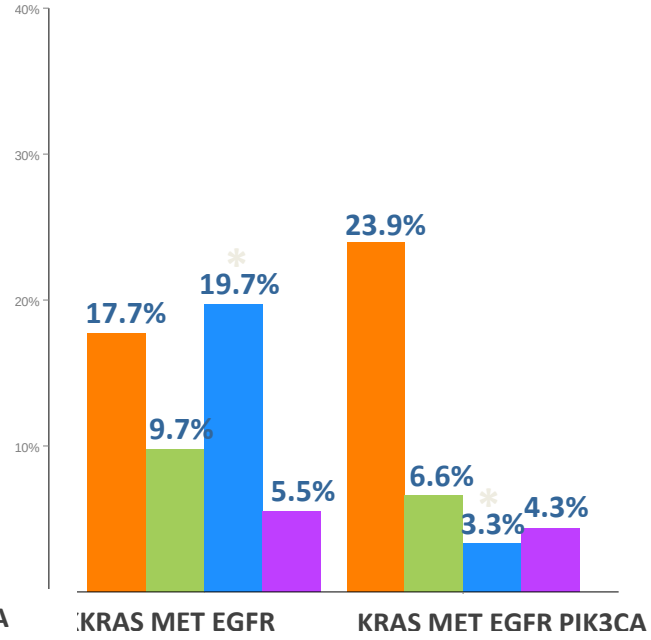
Prevalence of cancer related gene mutations

The most common mutations were KRAS, MET, EGFR and PIK3CA with an overall prevalence of 23.1%, 6.8%, 5.2% and 4.6%, respectively

IV Simposio Cáncer de Pulmón en Mujeres



* Significant at 0.05



Kerr et al. Ann Oncol 2015; 26 (suppl 6): abstr 3001

Gender differences

- **EGFR** mutation prevalence:
  - **Gender: 9.5%** in **females** vs. 2.9% in males; p<0.001
  - **Smoking status: 19.7%** in **non-smokers** vs. 3.3% in smokers; p<0.001

- **KRAS** mutation prevalence:
  - **Gender: 31.4%** in **females** vs. 18.7% in males; p<0.001
  - **Histology: 38.0%** in **adenocarcinoma,** 6.2% in squamous cell, 20.2% in undifferentiated, 26.8% in other; p<0.001

Kerr et al. Ann Oncol 2015; 26 (suppl 6): abstr 3001

Molecular profiling has increased the complexity of the lung cancer treatment paradigm

IV Simposio Cáncer de Pulmón en Mujeres

Treatment is now increasingly driven by molecular profiling…

… which increases the need for molecular testing

ALK = anaplastic lymphoma kinase; EGFR = epidermal growth factor receptor
HER2 = human epidermal growth factor receptor 2; KRAS = Kirsten rat sarcoma viral oncogene homologue
NRAS = neuroblastoma RAS viral (v-ras) oncogene homolog; PD-L1 = programmed death-ligand 1
PIK3CA = phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha

Barlesi, et al. ASCO 2013
Johnson, et al. ASCO 2013
Pao & Girard. Lancet Oncol 2011
Kerr, et al. J Thorac Oncol 2015

The Boston Globe

A drug that works — for some

Researchers try to solve mystery of lung cancer medicine

By Raja Mishra
GLOBE STAFF

CONCORD — Early last year, Kate Robbins started her death journal. It was meant to guide her two children after lung cancer killed her. Robbins poured out advice: on dating, on morality, on family. The things a mother explains to her teens.

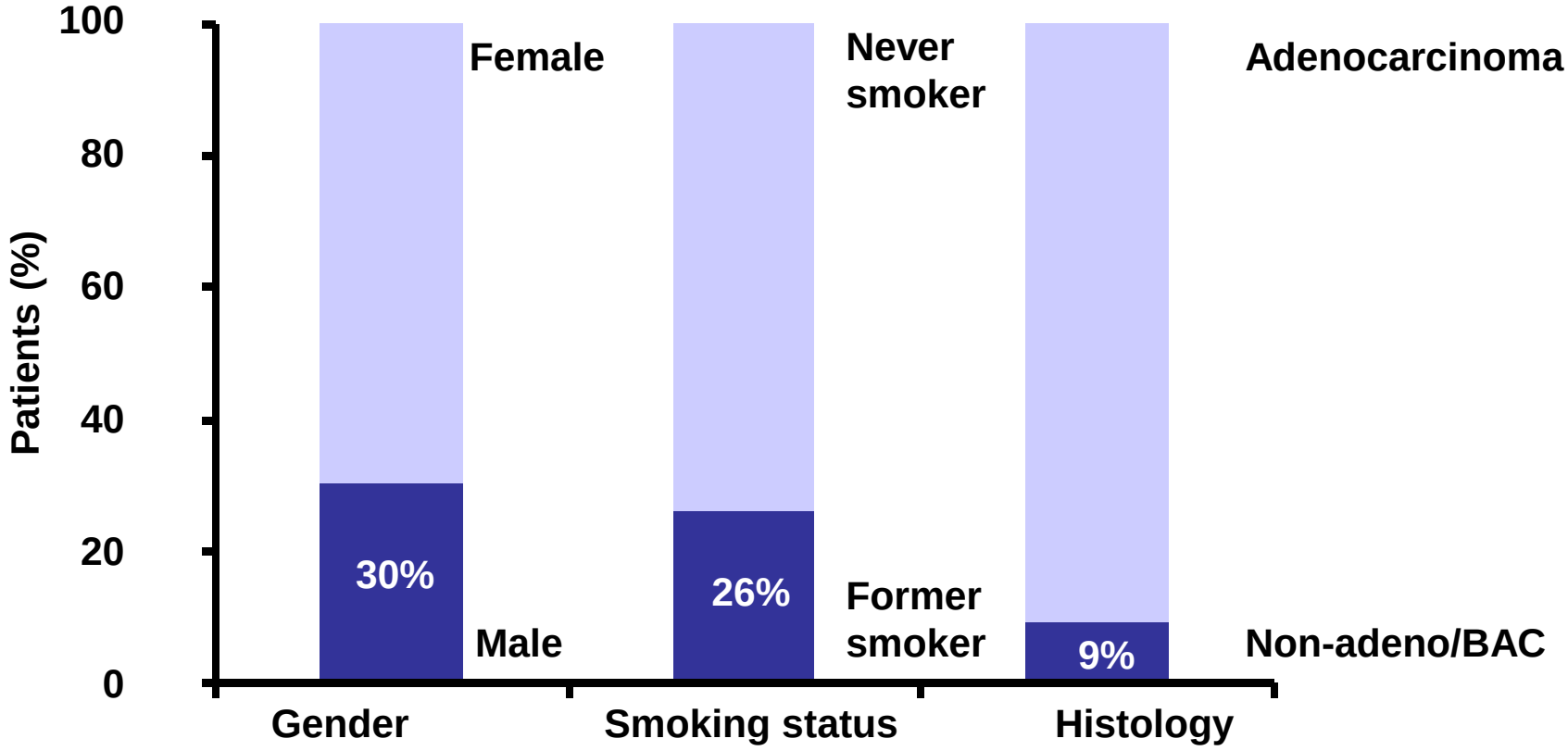
She also memorialized quiet, poignant moments. One rainy day, watching 10-year-old Hillary board the school bus, Robbins began weeping. She wrote simply, "You looked really pretty today." The kids would read the journal years later, she hoped, and feel their mother's love.

Advanced lung cancer patients rarely live one year. Robbins had months left. Then, last autumn, she began taking an experimental drug called Iressa, as did hundreds of other patients in the United States. Most continued to worsen.

But a small group, including Robbins, thrived.

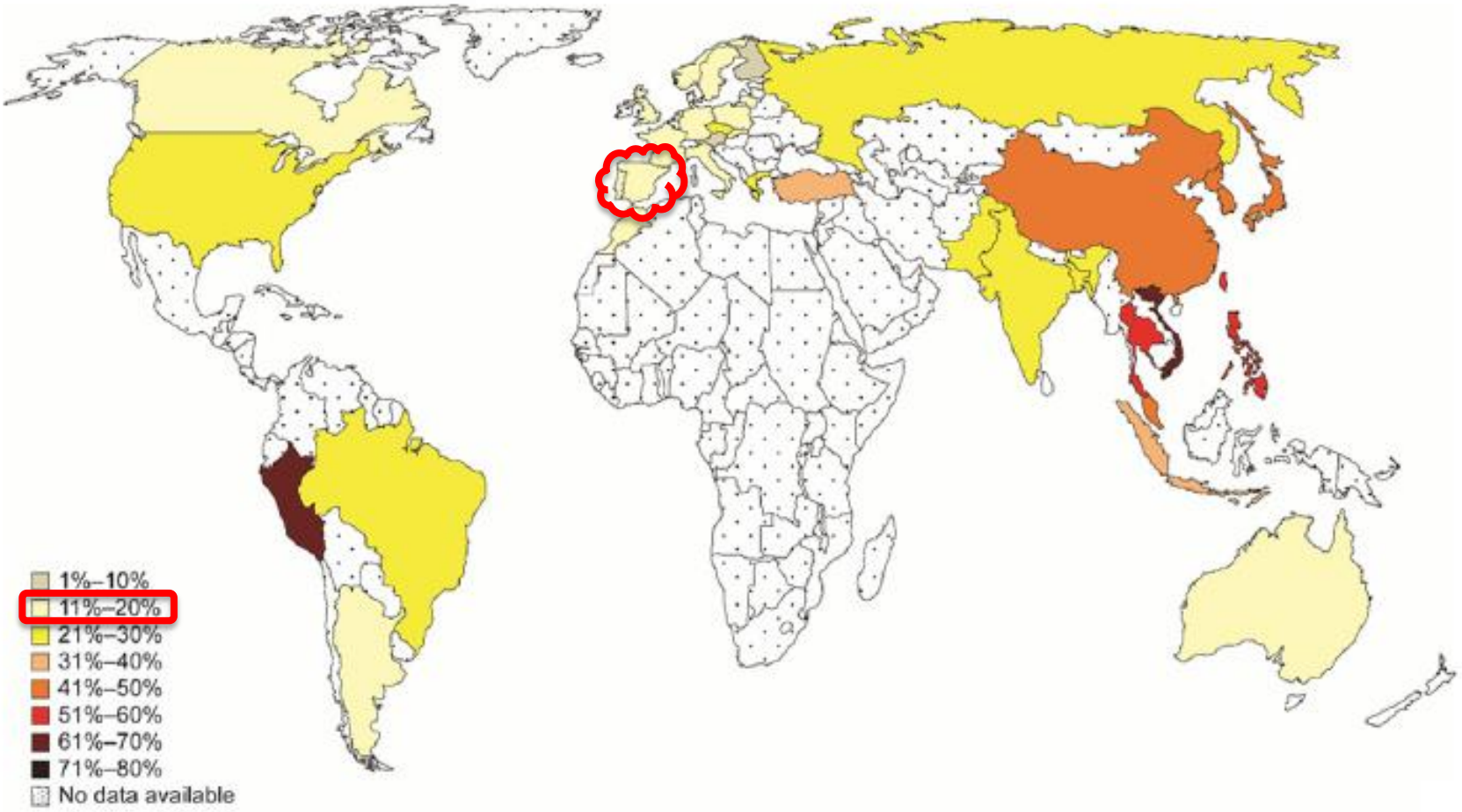
Female…EGFR mutated related disease

Spanish Lung Cancer Group trial in advanced NSCLC patients with *EGFR* mutations (n=350)



Rosell, et al. NEJM 2009

EGFR MUT INCIDENCE



Midha et al. Am J Cancer Res 2015

Table 2. Frequency of *EGFR* mutations in patients with NSCLC of ADC histology by gender and country

Country	No. studies	*EGFR* mutation frequency					
		Males			Females		
		No. patients with an *EGFR* mutation/ total no. patients	Overall *EGFR* mutation frequency (%)	*EGFR* mutation frequency range (%)	No. patients with an *EGFR* mutation/ total no. patients	Overall *EGFR* mutation frequency (%)	*EGFR* mutation frequency range (%)
Asia-Pacific							
Overall	20	473/1250	37	20-80	763/1263	60	0-83
China	4 [36, 40, 46, 49]	41/86	48	25-80	43/62	69	29-83
Hong Kong	1 [51]	28/84	33	N/A	87/131	66	N/A
Japan	10 [60, 61, 65, 68, 69, 74, 76, 77, 80, 82]	345/893	39	34-67	534/866	62	0-76
Republic of Korea	4 [87, 89, 94, 95]	41/152	27	20-36	75/162	46	38-80
Taiwan	1 [111]	18/35	51	N/A	24/42	57	N/A
Europe							
Overall	9	88/1035	9	4-18	133/616	22	3-35
Austria	1 [113]	3/58	5	N/A	4/38	11	N/A
Germany	2 [118, 120]	15/211	7	4-12	27/163	17	14-23
Greece	1 [125]	3/17	18	N/A	1/3	33	N/A
Italy	3 [127, 133, 135]	26/323	8	6-13	49/215	23	13-35
Poland	1 [140]	25/310	8	N/A	30/121	25	N/A
Russia	1 [143]	16/116	14	N/A	22/76	29	N/A
North America							
Overall	2	175/923	19	8-20	459/1656	28	21-28
USA	2 [7, 157]	175/923	19	8-20	459/1656	28	21-28
Indian subcontinent							
Overall	3	160/689	23	23-26	99/318	31	14-33
Bangladesh	1 [167]	12/47	26	N/A	2/14	14	N/A
India	2 [168, 169]	148/642	23	23	97/304	32	32-33
Africa							
Overall	1	7/91	8	N/A	22/46	48	N/A
Morocco	1 [177]	7/91	8	N/A	22/46	48	N/A

Midha et al. Am J Cancer Res 2015

Change in clinical trial populations

Sex differences in lung Cancer Trials… The past

IV Simposio Cáncer de Pulmón en Mujeres

Table 1. Trials Demonstrating Gender-based Differences in Age, Histology, and Smoking Status in NSCLC

	Year	No. of Patients	% Female	Age at Diagnosis (y)		% Adenocarcinoma		% Nonsmokers	
				Male	Female	Male	Female	Male	Female
Ferguson[24]	1990	772	38	60	57	35	45	6	16
de Perrot[25]	2000	1037	19	61	62	26	54	2	27
Minami[26]	2000	1242	27	64	62.5	48	86	8.6	87
Radzikowska[27]	2002	20,561	14	62	60	9.6	21.6	2.4	18.8
Visbal[20]	2004	4618	41	68	66	48	59.5	7.6	19.6

Donington J et al. Semin Thoracic Surg 2011

EGFR mutation…
a very good example

IV Simposio Cáncer de Pulmón en Mujeres

Table 1. Characteristics of Patients in Constituent Trials

Study Name, Year	Treatment Comparison	Median PFS (months)	No. of Patients	Exon 19 Deletion (%)	Exon 21 L858R Substitution (%)	Age < 65 Years (%)	ECOG PS 0 and 1 (%)	Asian (%)	Women (%)	Never-Smoker (%)	Adenocarcinoma (%)
NEJ002, 2010, 2013[2,15*]	Gefitinib *v* CP	10.8 *v* 5.4	224†	51	43	49	99	100	63	62	93
WJTOG 3405, 2010, 2012[3,16]	Gefitinib *v* CisD	9.6 *v* 6.5	172	51	49	53	100	100	69	69	97
OPTIMAL, 2011, 2012[4,18]	Erlotinib *v* CG	13.1 *v* 4.6	154	53	47	75	94	100	59	71	87
EURTAC, 2012[5]	Erlotinib *v* platinum-G or platinum-D	9.7 *v* 5.2	173	66	34	49	86	0	73	69	92
LUX-Lung 3, 2013[6*]	Afatinib *v* CisPem	11.1 *v* 6.9	345	49	40	61	100	72	65	68	100
LUX-Lung 6, 2014[7*]	Afatinib *v* CisG	11.0 *v* 5.6	364	51	38	76	100	100	65	77	100
ENSURE, 2014[8]‡	Erlotinib *v* CisG	11.0 *v* 5.5	217	54	45	79	94	100	61	71	94

Abbreviations: CG, carboplatin-gemcitabine; CisD, cisplatin-docetaxel; CisG, cisplatin-gemcitabine; CisPem, cisplatin-pemetrexed; CP, carboplatin-paclitaxel; ECOG, Eastern Cooperative Oncology Group; EURTAC, European Tarceva Versus Chemotherapy; NEJ002, North East Japan 002; PFS, progression-free survival; PS, performance status; WJTOG, West Japan Thoracic Oncology Group.

*Includes patients with uncommon mutations of the *EGFR* gene.

†NEJ002 recruited a total of 228 patients; PFS outcome was only reported for 224 patients.

‡Reported in abstract only.

Lee C, et al. J Clin Oncol 2015

Table 3. Association Between Baseline Characteristics and Exon 19 Deletion or Exon 21 L858R Substitution: Pooled Data From Four Clinical Trials

Characteristic	Exon 19 Deletion (n = 401) No.	%	Exon 21 L858R Substitution (n = 313) No.	%	*P*
Age, years					.20
< 65	233	58	166	53	
≥ 65	168	42	147	47	
ECOG PS					.32
0	186	46	136	44	
1	191	48	164	52	
2	24	6	13	4	
Sex					.81
Female	268	67	206	66	
Male	133	33	107	34	
Smoking					.81
Never	268	67	212	68	
Ever	133	33	101	32	
Histologic subtype					.11
Adenocarcinoma	377	94	284	91	
Other	24	6	29	9	

Abbreviations: EGOG, Eastern Cooperative Oncology Group; PS, performance status.

Lee C, et al. J Clin Oncol 2015

What about outcome? The past…

IV Simposio Cáncer de Pulmón en Mujeres

Table 4. Clinical Series Demonstrating NSCLC Survival Benefit in Women

	Author	Year	No. of Patients	% Female	Median Survival (Months) Male	Median Survival (Months) Female	*P* Value
Population	Radzikowska[27]	2002	20,561	14	RR, 1.15		0.001
	Wisnivesky (SEER)[71]	2007	18,67	43	38% (5-y survival)	46% (5-y survival)	0.001
	Cetin (SEER)[93]	2011	51,749	40	14% (1-y survival)	18% (1-y survival)	N/R
Surgery	Ferguson[76]	2000	451	41	26.9	41.8	0.006
	De Perrot[25]	2000	1037	19	24	30	0.004
	Minami[26]	2000	1242	27	65	121	0.05
	Alexiou[73]	2002	833	30	34% (5-y survival)	47% (5-y survival)	0.001
	Batevick[74]	2005	351	32		RR, 0.54	0.001
	Cerfolio[75]	2006	1085	38	50% (5-y survival)	60% (5-y survival)	0.001
Multimodality	Albain[83]	1995	126	36	12	21	0.08
	Werner-Wasik[84]	2000	1999	28	9.9	11.4	0.001
	Keller[94]	2002	488	42	35	41	0.12
	Albain[95]	2009	429	36	RR, 1.42		0.009
Chemotherapy	O'Connell[86]	1986	378	30	8.8	12.4	0.001
	Albain[85]	1991	2531	23	4.8	5.7	0.0005
	Paesmans[87]	1995	1052	10		RR, 0.70	0.03
	Wakelee[88]	2006	1207	37	7.3	9.2	0.004
All	Visbal[20]	2004	4618	41	12	16.8	0.01

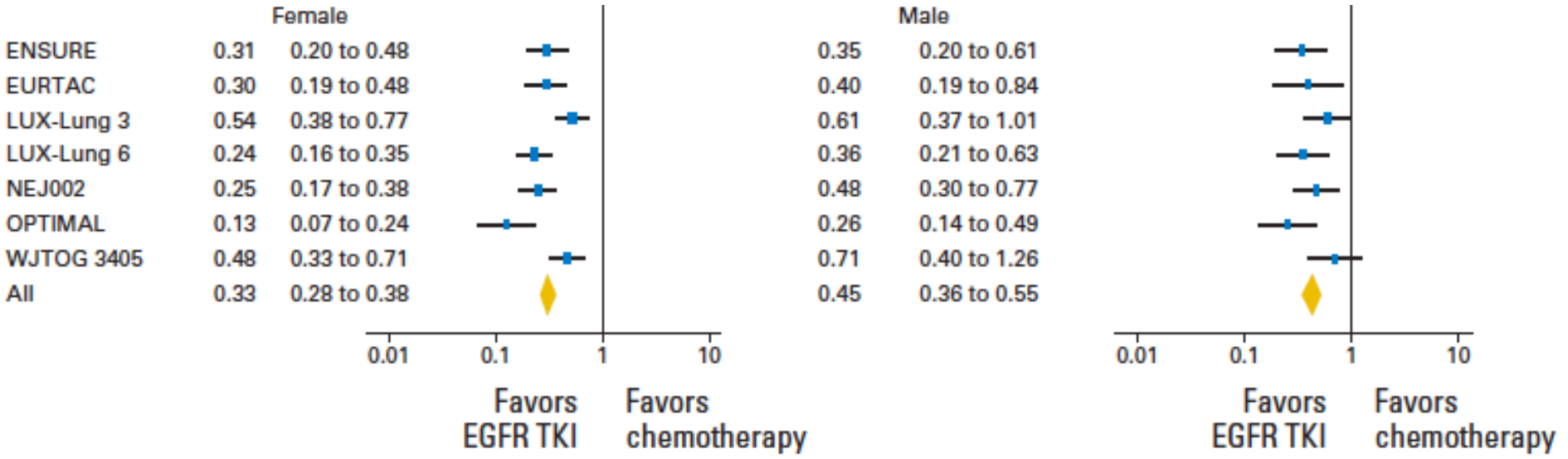
N/R, not reported; RR, relative risk.

Donington J et al. Semin Thoracic Surg 2011

Is the same effect for EGFR mutant NSCLC women?

IV Simposio Cáncer de Pulmón en Mujeres

HR 0.33 vs HR 0.45



Lee C, et al. J Clin Oncol 2015

Women had a 27% greater PFS benefit with EGFR TKIs than men

Predictive effect of sex is largely independent of smoking status and EGFR mutation type

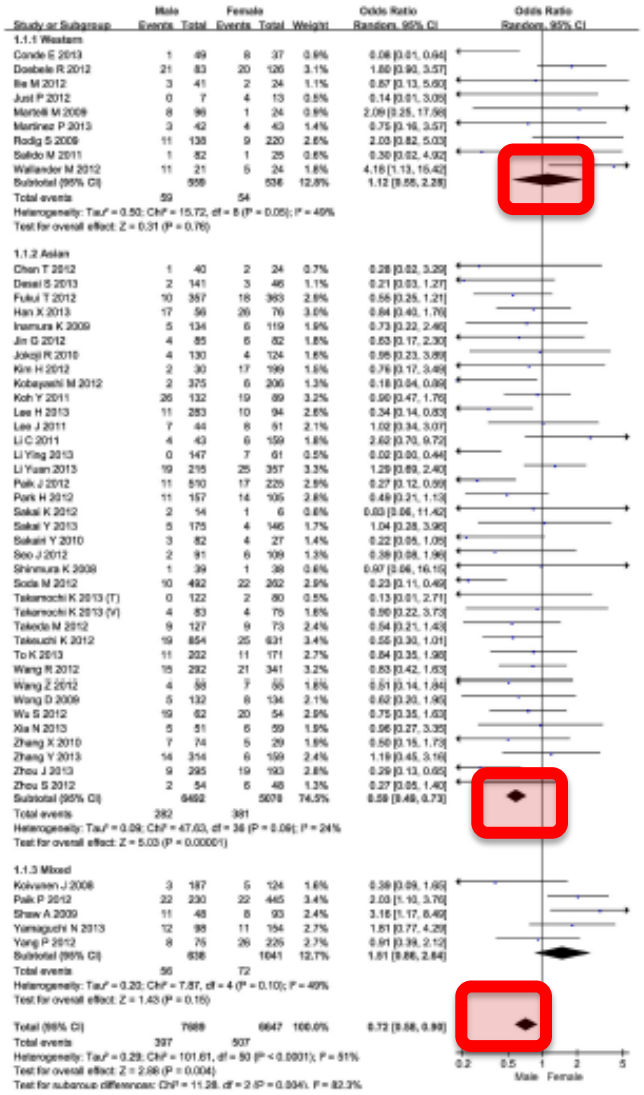
OPEN ACCESS Freely available online

PLOS ONE

Clinicopathological and Demographical Characteristics of Non-Small Cell Lung Cancer Patients with ALK Rearrangements: A Systematic Review and Meta-Analysis

CrossMark

Cáncer de Pulmón en Mujeres



Lower risk of carrying ALK rearrangements in males than females OR 0.72

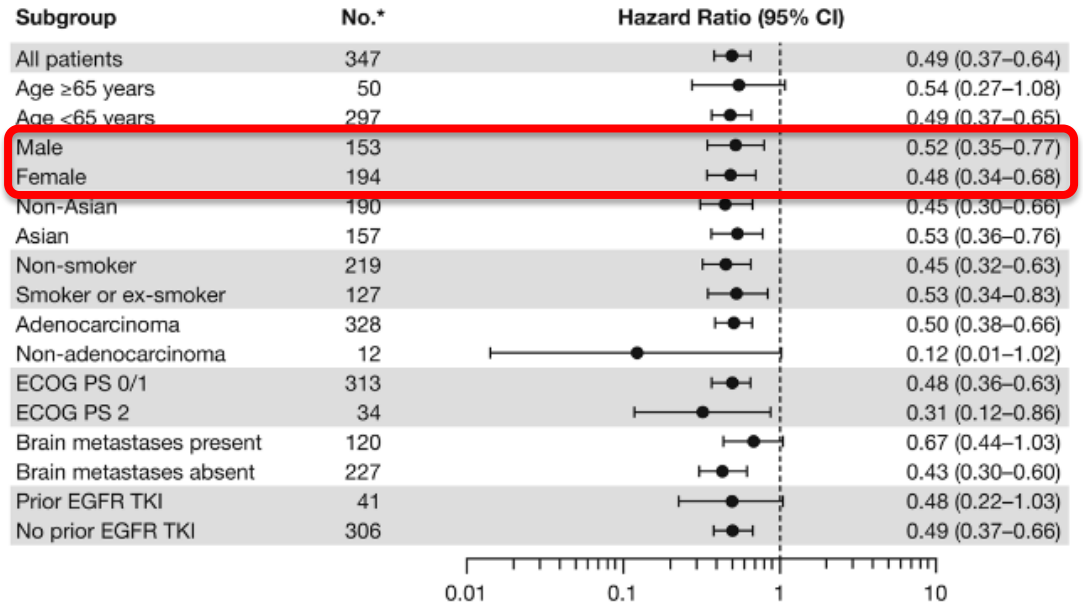
Lian F. Plos One 2014

Profile 1007

Table 1. Baseline Clinical Characteristics of Patients in the Intention-to-Treat Population.*

Characteristic	Crizotinib (N=173)	Chemotherapy (N=174)
Age — yr		
Median	51	49
Range	22–81	24–85
Age distribution — no. (%)		
<65 yr	146 (84)	151 (87)
≥65 yr	27 (16)	23 (13)
Male sex — no. (%)	75 (43)	78 (45)

HR 0.52 vs 0.48



Profile1014

Table 1. Baseline Characteristics in the Intention-to-Treat Population.*

Characteristic	Crizotinib (N=172)	Chemotherapy (N=171)
Age — yr		
Median	52	54
Range	22–76	19–78
Male sex — no. (%)	68 (40)	63 (37)
Race — no. (%)†		
White	91 (53)	85 (50)
Asian	77 (45)	80 (47)
Other	4 (2)	6 (4)
Smoking status — no. (%)		
Never smoked	106 (62)	112 (65)
Former smoker	56 (33)	54 (32)
Current smoker	10 (6)	5 (3)

HR 0.54 vs 0.45

C Progression-free Survival, According to Subgroup

Subgroup	No. of Patients	Hazard Ratio (95% CI)
Crizotinib vs. chemotherapy	343	0.45 (0.35–0.60)
Age		
≥65 yr	55	0.37 (0.17–0.77)
<65 yr	288	0.51 (0.38–0.68)
Male	131	0.54 (0.36–0.82)
Female	212	0.45 (0.32–0.63)

Solomon B, et al. NEJM 2014

European population

Table 4
Cox regression analysis for mortality according to *Anaplastic Lymphoma Kinase* (ALK) status.

	Univariate analyses		Multivariate analyses ($n = 109$)	
	Hazard ratio (HR) (95% confidence interval, CI)	*p*-Value	HR (95% CI)	*p*-Value
ALK rearrangement				
Positive	1*		1	
Negative	2.30 (1.06–5.01)	0.04	2.98 (1.29–6.90)	0.01
Gender				
Female	1*		1	
Male	2.89 (1.83–4.55)	<0.001	3.36 (2.07–5.49)	<0.001

Fallet V. European J Cancer 2014

What about toxicity?

- ***Hypogonadism*** should be discussed with male patients prior to initiating crizotinib treatment

- 30% of crizotinib-treated patients experience grade 1-2 edema, which was associated with a rather late onset.

  Peripheral edemas is most commonly observed, particularly in women.

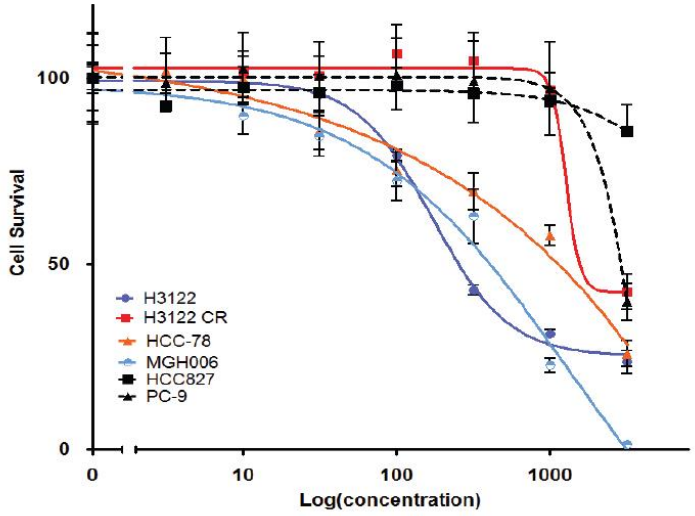
VOLUME 30 · NUMBER 8 · MARCH 10 2012

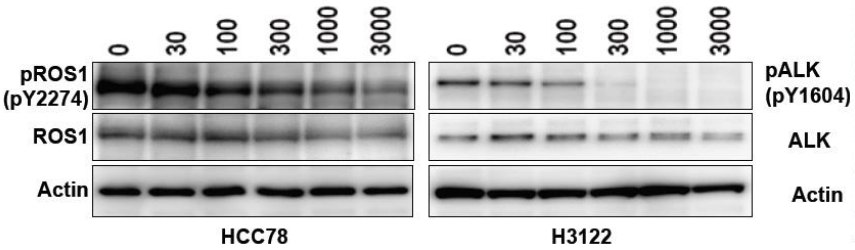
JOURNAL OF CLINICAL ONCOLOGY

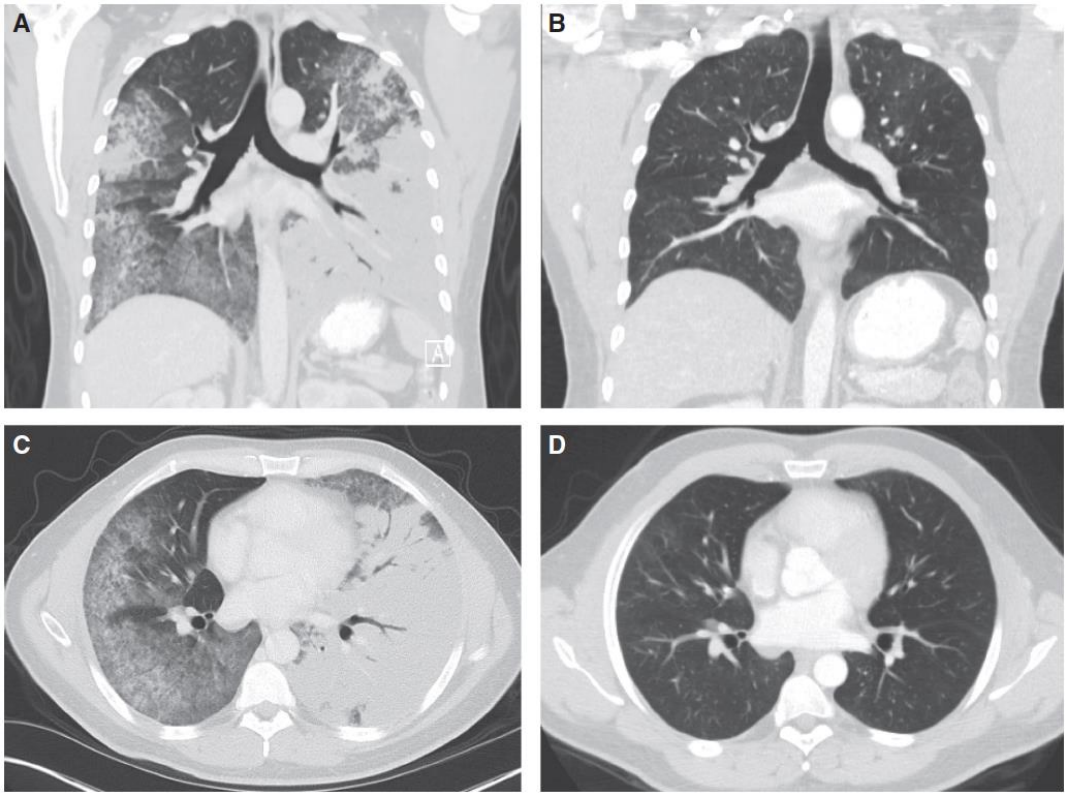
ORIGINAL REPORT

ROS1 Rearrangements Define a Unique Molecular Class of Lung Cancers

Kristin Bergethon, Alice T. Shaw, Sai-Hong Ignatius Ou, Ryohei Katayama, Christine M. Lovly, Nerina T. McDonald, Pierre P. Massion, Christina Siwak-Tapp, Adriana Gonzalez, Rong Fang, Eugene J. Mark, Julie M. Batten, Haiquan Chen, Keith D. Wilner, Eunice L. Kwak, Jeffrey W. Clark, David P. Carbone, Hongbin Ji, Jeffrey A. Engelman, Mari Mino-Kenudson, William Pao, and A. John Iafrate





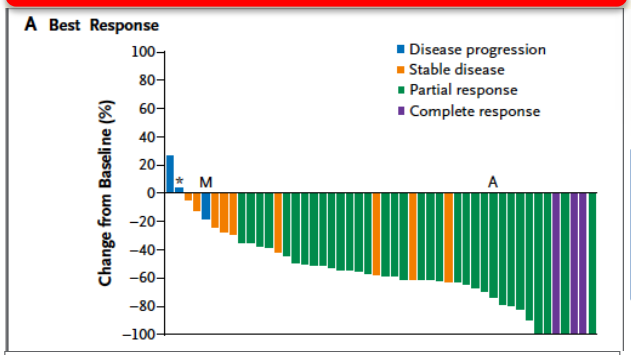


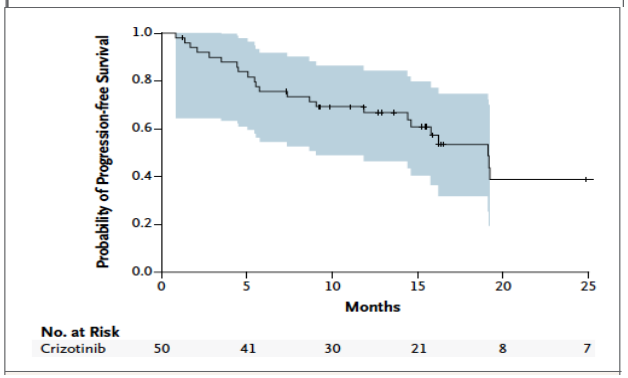
The US and European experience

IV Simposio Cáncer de Pulmón en Mujeres

Table 1. Characteristics of the Patients at Baseline.

Characteristic	ROS1 Cohort (N=50)
Age — yr	
Median	53
Range	25–77
Sex — no. (%)	
Male	22 (44)
Female	28 (56)

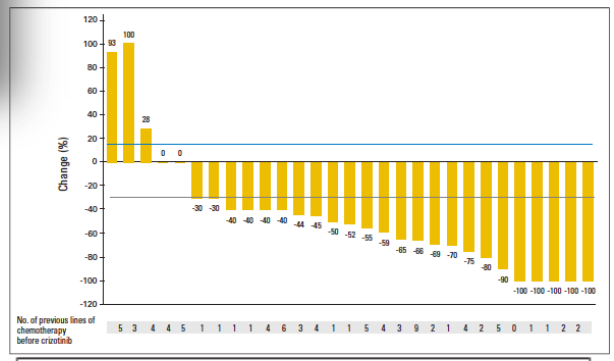


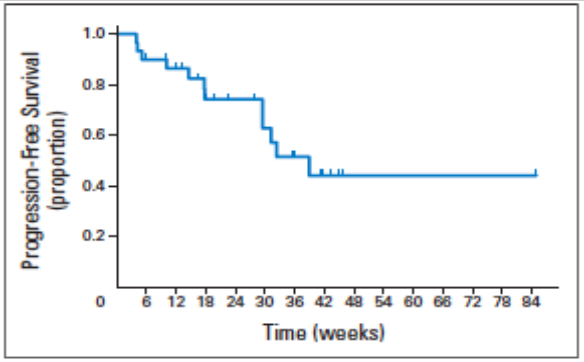


RR	72%	80%
PFS	19.2	9.1

Table 1. Clinical and Biologic Characteristics of Patients With Lung Cancer and a *ROS1* Rearrangement

Characteristics	No. of Patients (N = 31)	%
Age at diagnosis, years		
Mean	53.4	
Standard deviation	11.9	
Median	50.5	
F	20	64.5
Tobacco use		
Never	22	71
Former	6	19.3
Current	3	9.7
Unknown	0	





Shaw A, et al. NEJM 2014

Mazieres J et al. J Clin Oncol 2015

VOLUME 29 · NUMBER 26 · SEPTEMBER 10 2011

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Clinical Features and Outcome of Patients With Non–Small-Cell Lung Cancer Harboring *BRAF* Mutations

Antonio Marchetti, Lara Felicioni, Sara Malatesta, Maria Grazia Sciarrotta, Luigi Guetti, Antonio Chella, Patrizia Viola, Carmela Pullara, Felice Mucilli, and Fiamma Buttitta

1046 NSCLC

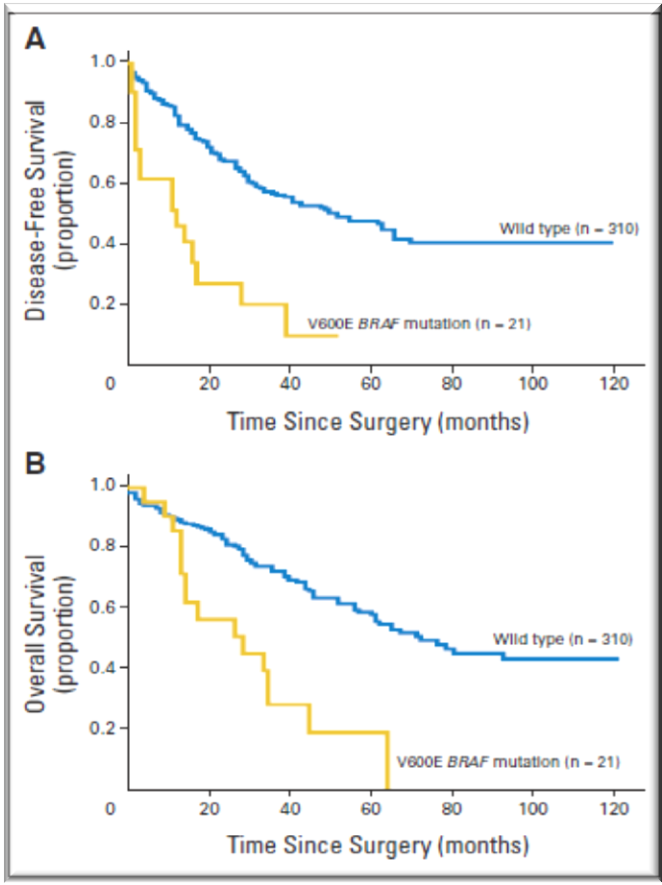
- **4.9% ADC**
- 0.3% SCC

V600E 56.8%

V600E more prevalent in females: **8.6% vs 0.9%**

V600E showed agressive histotype and shorter PFS and OS

Non V600E mut: smokers, no prognostic implications



Marchetti A, et al. J Clin Oncol 2011

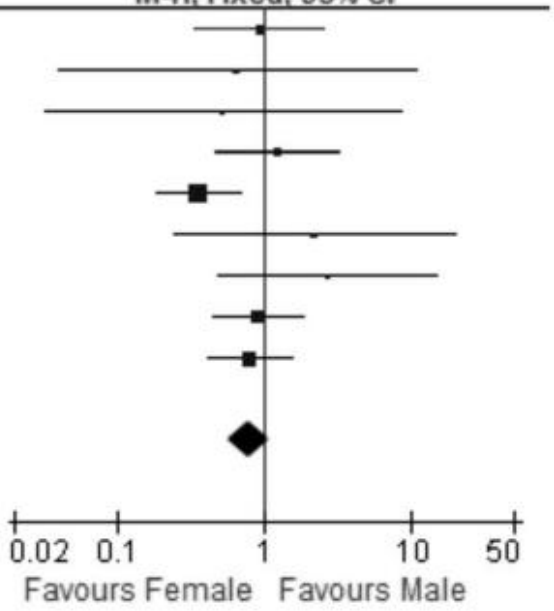
BRAF: Review and MA

A

Study or Subgroup	Male Events	Male Total	Female Events	Female Total	Weight	Odds Ratio M-H, Fixed, 95% CI	Year
Pratilas 2008	6	339	11	577	9.9%	0.93 [0.34, 2.53]	2008
Schmid 2009	1	58	1	38	1.5%	0.65 [0.04, 10.70]	2009
Lee 2010	1	113	1	60	1.6%	0.53 [0.03, 8.57]	2010
Paik 2011	7	235	11	452	9.0%	1.23 [0.47, 3.22]	2011
Marchetti 2011	19	552	17	187	30.3%	0.36 [0.18, 0.70]	2011
Kobayashi 2011	4	377	1	204	1.6%	2.18 [0.24, 19.61]	2011
Sasaki 2012	4	113	2	148	2.1%	2.68 [0.48, 14.89]	2012
Cardarella 2013	17	145	19	148	20.5%	0.90 [0.45, 1.81]	2013
Ilie 2013	24	292	16	158	23.6%	0.79 [0.41, 1.54]	2013
Total (95% CI)		**2224**		**1972**	**100.0%**	**0.79 [0.57, 1.10]**	
Total events	83		79				

Heterogeneity: $Chi^2 = 9.23$, $df = 8$ ($P = 0.32$); $I^2 = 13\%$

Test for overall effect: $Z = 1.41$ ($P = 0.16$)



Chen D, et al. Plos One 2014

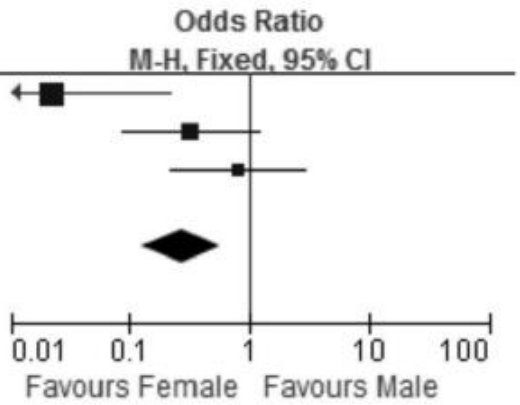
BRAF V600E

A

Study or Subgroup	Male Events	Male Total	Female Events	Female Total	Weight	Odds Ratio M-H, Fixed, 95% CI	Year
Marchetti 2011	5	19	16	17	49.5%	0.02 [0.00, 0.21]	2011
Ilie 2013	10	24	11	16	30.6%	0.32 [0.09, 1.23]	2013
Cardarella 2013	8	17	10	19	19.9%	0.80 [0.22, 2.97]	2013
Total (95% CI)		**60**		**52**	**100.0%**	**0.27 [0.12, 0.59]**	
Total events	23		37				

Heterogeneity: $Chi^2 = 7.37$, $df = 2$ ($P = 0.03$); $I^2 = 73\%$

Test for overall effect: $Z = 3.31$ ($P = 0.0009$)

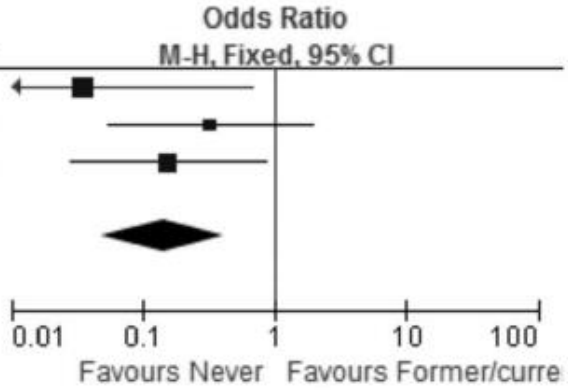


B

Study or Subgroup	Former/current Events	Former/current Total	Never Events	Never Total	Weight	Odds Ratio M-H, Fixed, 95% CI	Year
Marchetti 2011	11	26	10	10	41.5%	0.04 [0.00, 0.67]	2011
Cardarella 2013	13	29	5	7	21.5%	0.33 [0.05, 1.96]	2013
Ilie 2013	12	29	9	11	37.0%	0.16 [0.03, 0.86]	2013
Total (95% CI)		**84**		**28**	**100.0%**	**0.14 [0.05, 0.42]**	
Total events	36		24				

Heterogeneity: $Chi^2 = 1.69$, $df = 2$ ($P = 0.43$); $I^2 = 0\%$

Test for overall effect: $Z = 3.50$ ($P = 0.0005$)



Chen D et al. PlOs One 2014

Vemurafenib in NSCLC BRAF V600

IV Simposio Cáncer de Pulmón en Mujeres

Table 1. Demographic and Clinical Characteristics of th

Characteristic	NSCLC (N=20)
Sex — no. (%)	
Male	14 (70)
Female	6 (30)
Yr of age — median (range)	61 (48–83)
ECOG performance status†	
0 or 1	16 (80)
≥2	4 (20)
Prior systemic therapies — no. (%)‡	
Any	19 (95)
None	1 (5)
1	10 (50)
2	4 (20)
≥3	5 (25)
Prior radiation — no. (%)	4 (20)
BRAF V600 mutation — no. (%)	
V600E	18 (90)
V600G	1 (5)
V600 unknown	1 (5)

* ECD denotes Erdheim–Chester disease, ECOG Eastern
† Tumor types in this cohort included breast cancer, cer tumors of unknown type.
‡ Prior systemic therapies were determined on the basis

Table 2. Preliminary Best Response According to Cohort.*

Variable	NSCLC (N=20)
Patients with ≥1 postbaseline assessment — no.	19
Complete response — no. (%)	0
Partial response — no. (%)	8 (42)
Stable disease — no. (%)	8 (42)
Progressive disease — no. (%)	2 (11)
Missing data — no. (%)†	1 (5)
Overall response — no. (%) [95% CI]	8 (42) [20–67]

* The denominator for patients with a complete or partial re postbaseline assessment or early withdrawal. Of the 19 pa sponse but was included in the denominator for the effica
† All patients with missing data withdrew early.

Hyman et al. NEJM 2015

European EUORAF

TABLE 1. Patient Characteristics	
Sample size (N)	35
Age at diagnosis	
Median years (range)	63 (42–85)
Gender	
Male	18 (51%)
Female	17 (49%)
Smoking status	
Never	14 (40%)
Former/current	16 (46%)
Unknown	5 (14%)
Country	
France	13 (37%)
Switzerland	10 (28%)
Germany	7 (20%)
The Netherlands	4 (11%)
Austria	1 (3%)
Systemic therapy	
Median lines (range)	3 (1–6)
Platinum-based frontline therapy	30 (86%)

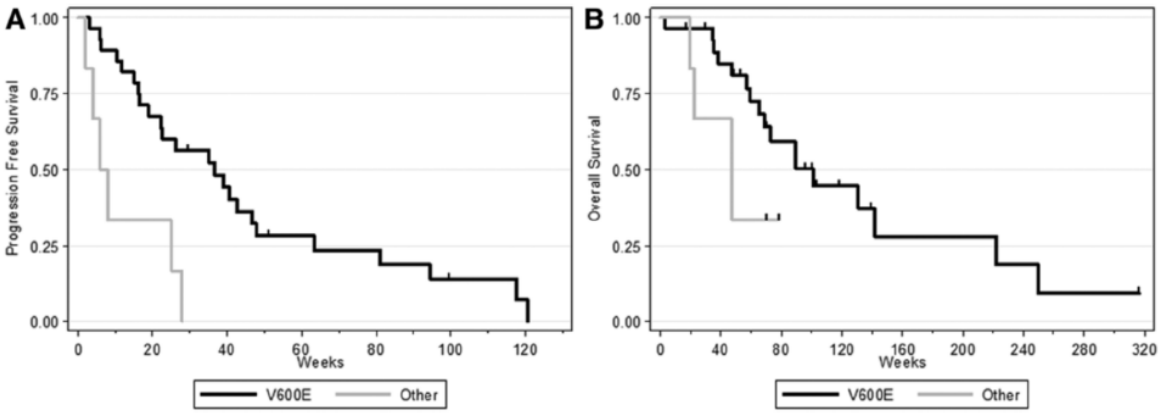
Gautschi O et al. J Thorac Oncol 2015

European EUORAF

TABLE 4. Best Response with BRAF Inhibitor

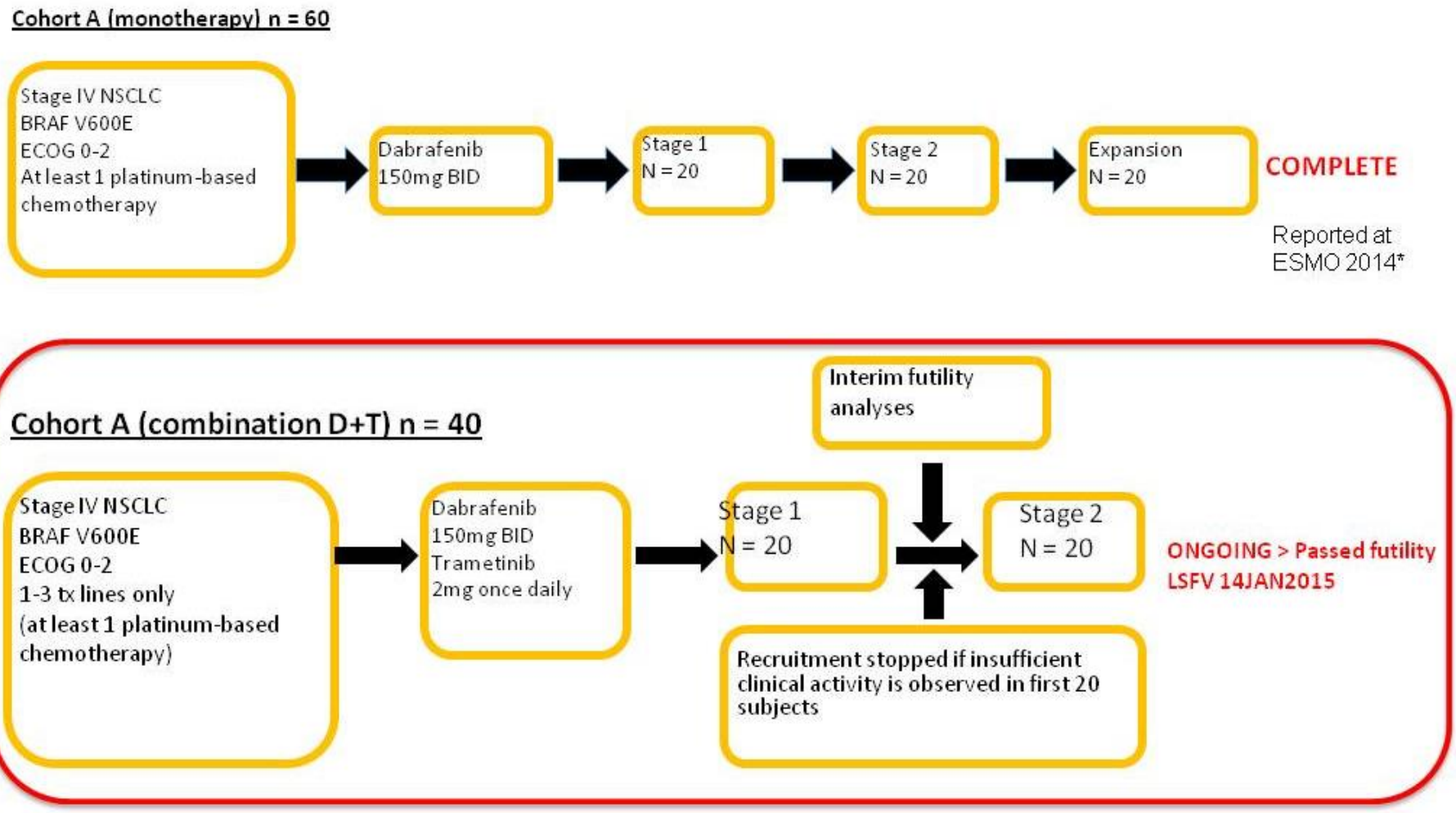
	All Patients (N = 35)	V600E and Vemurafenib Subgroup (N = 25)
Data missing	1	1
Not measurable	1 (3%)	1 (4%)
CR	2 (6%)	2 (8%)
PR	16 (47%)	11 (46%)
SD	11 (32%)	10 (42%)
PD	4 (12%)	0
ORR	18 (53%; 95% CI: 35–70)	13 (54%; 95% CI: 33–74)
DCR	29 (85%; 95% CI: 69–95)	23 (96%; 95% CI: 79–100)

CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; ORR, overall response rate; DCR, disease control rate; CI, confidence interval.



Gautschi O et al. J Thorac Oncol 2015

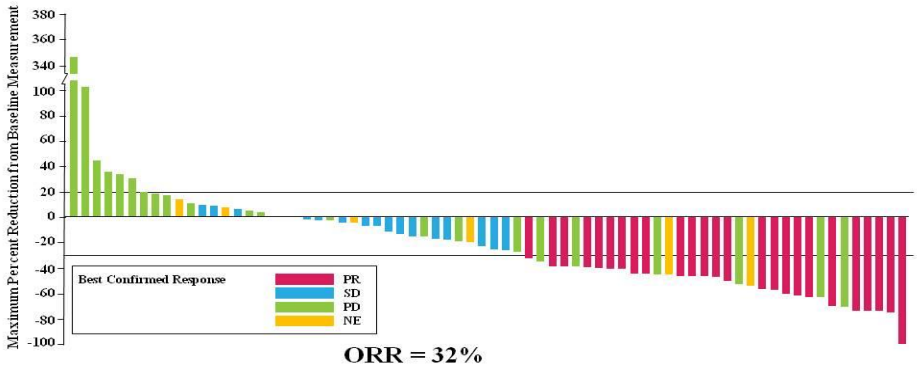
Interim results of a phase II study of the BRAF inhibitor dabrafenib in combination with the MEK inhibitor trametinib in patients with *BRAF* V600E mutated metastatic non-small cell lung cancer



Planchard D et al. ASCO 2015

BRAF V600E Mutant NSCLC - Best Confirmed Response in ≥ 2nd Line (N = 78)

Single-Agent Dabrafenib

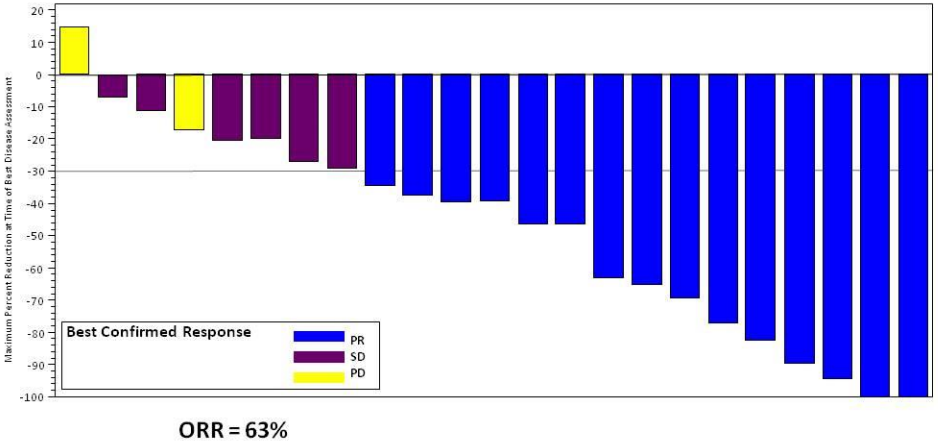


ORR 32%

D Planchard, ESMO 2014

BRAF V600E Mutant NSCLC - Best Confirmed Response in ≥ 2nd Line (N = 24)

Dabrafenib + Trametinib



ORR 63%

The median duration of response was not reached

Planchard D et al. ASCO 2015

Epidemiology HER2 mutation

- 403 stage I-III adenocarcinomas in caucasian patients: mutation in 9 **(2.2%).**
- 78% in frame duplications **insertions in exon 20**
- Frequency higher in females and in **never smokers**

- 394 adenocarcinoma, HER2 mutations preferentially in oriental ethnicity (**3.9% vs 0.7%**)
- All HER2 mutations were in-frame **insertions in exon 20**, significantly more frequent in **never smokers and adenocarcinoma**

- **6%** of EGFR/KRAS/ALK-negative specimens
- More frequent among **never-smokers** but no associations with sex, race, or stage
- **HER2 mutation was not associated with concurrent HER2 amplification**

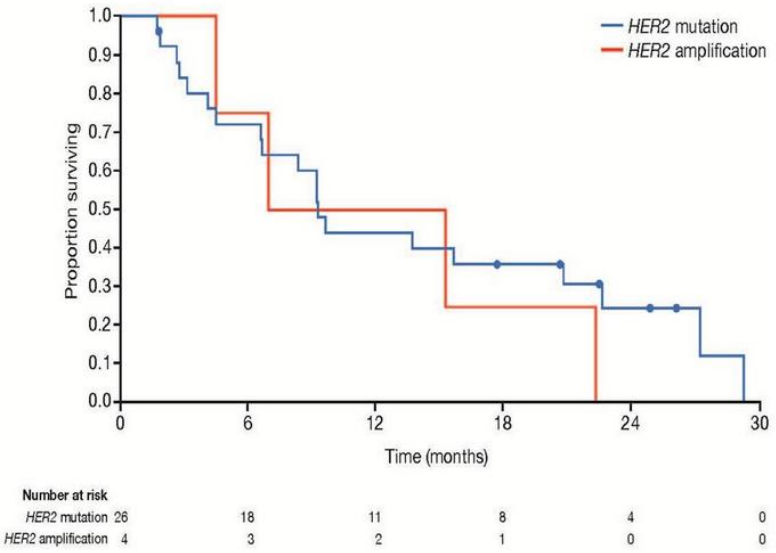
- 3.800 p: HER2 mut in 1.7%, **all insertions in exon** 20, 69% women, never-smokers 52.3%

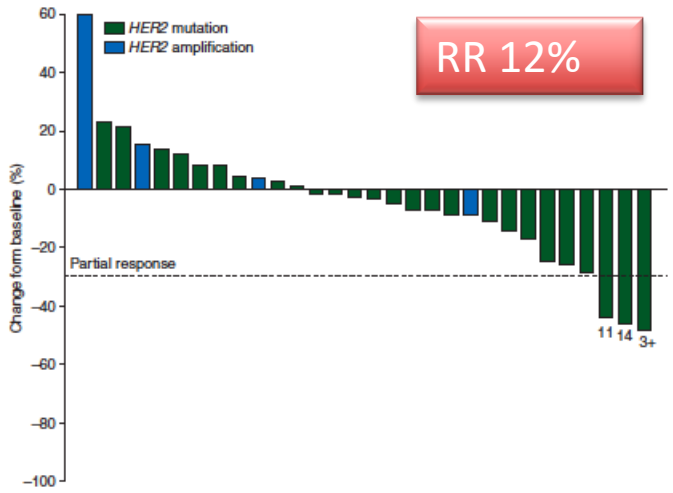
Buttitta, Int J Cancer 2006, Shigematsu, CCR 2005, Arcila CCR 2012, Mazieres JCO 2013

HER2: USA experience
Dacomitinib activity

IV Simposio Cáncer de Pulmón en Mujeres

	HER2-Mutant exon 20 insYVMA (*n*=13)	*HER2*-Mutant exon 20 others (*n*=13)	*HER2*-Amplified (*n*=4)
Median Age (range)	60 (43-75)	58 (33-73)	50 (42-72)
ECOG Performance Status			
0	2 (15%)	7 (54%)	1 (25%)
1	11 (85%)	6 (46%)	3 (75%)
Women	9 (69%)	6 (46%)	0 (0%)
Stage IIIB Adenocarcinoma	0 (0%)	2 (15%)	0 (0%)
Stage IV Adenocarcinoma	13 (100%)	11 (85%)	4 (100%)
Never Smoked Cigarettes	9 (69%)	8 (62%)	1 (25%)
Caucasion (White)	9 (69%)	12 (92%)	3 (75%)
African American (Black)	0 (0%)	0 (0%)	1 (25%)
Asian	3 (23%)	1 (8%)	0 (0%)
Other	1 (8%)	0 (0%)	0 (0%)





RR 12%

Kris M et al. Ann Oncol 2015

Her 2 mut: European experience

IV Simposio Cáncer de Pulmón en Mujeres

Table 1. Clinical and biological characteristics of patients with an *HER2* mutation ($n = 101$)

	Number	Value
Age at initial diagnosis, years ($n = 101$)		
Median		61
Range		30–87 years
Gender		
Male	38	37.6%
Female	63	62.4%
Tobacco use		
Never	61	60.4%
Former	36	35.6%
Current	4	4%

RR: 50%

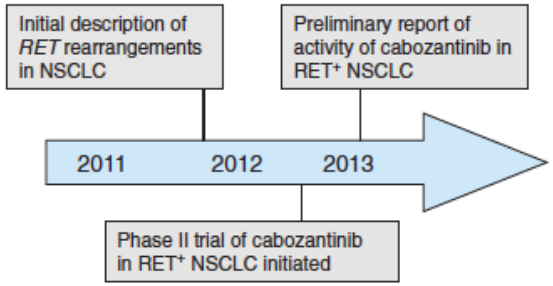
Table 2. Overall response rate (ORR), disease control (DC), progression-free survival (PFS, weeks), and overall survival (OS, weeks) according to drug type

Treatment	*n*	ORR	DC	PFS median (95% CI)	OS median (95% CI)
First-line: without HER2-targeting treatment	93	43.5%	70.7%	6 (5; 7.1)	24 (19.1; 36.4)
Second-line: without HER2-targeting treatment	52	10%	36%	4.3 (3.1; 5)	19.4 (9.6; 24.7)
EGFR-TKI[a]	26	7.6%	26.8%	2.99 (1.87; 4.47)	20.14 (7.14; 32.95)
Trastuzumab combination, T-DM1[a]	58	50.9%	75.5%	4.8 (3.4; 6.5)	13.3 (8.1; 15)
Neratinib, lapatinib, and afatinib[a]	29	7.4%	55.5%	3.4 (2.4; 4)	6.5 (4.7; 30.6)

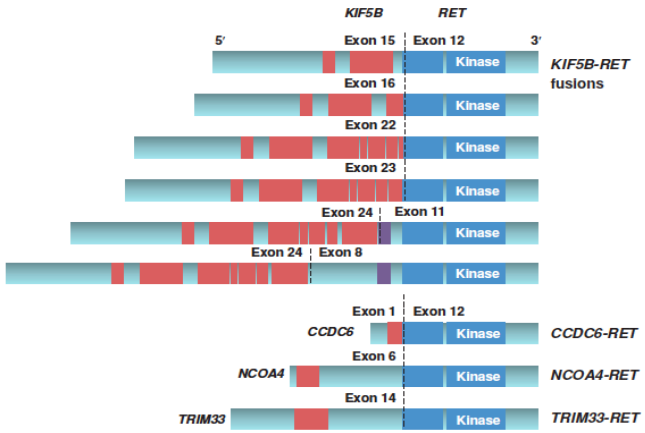
[a]If the same drug has been given more than one time, the results presented here are from their first administration.

Mazieres J et al. Ann Oncol 2016

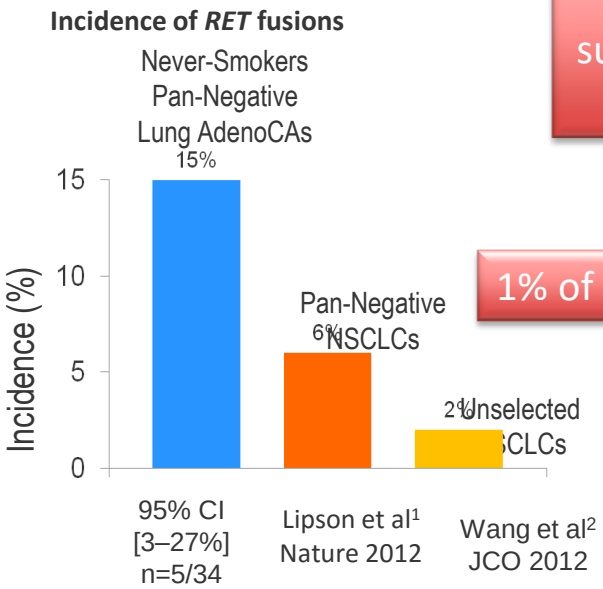
RET: a new kid on the rock



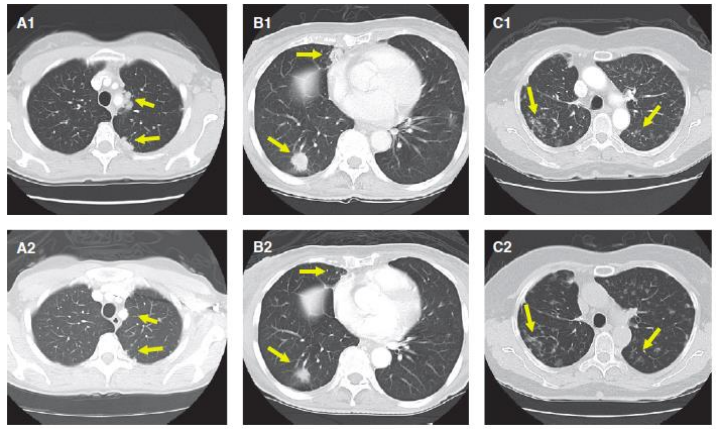
KIF5B, CCDC6



Vandetanib, sorafenib, sunitinib, cabozantinib have RET activity



1% of lung cancer



Drilon et al Cancer Discovery 2013

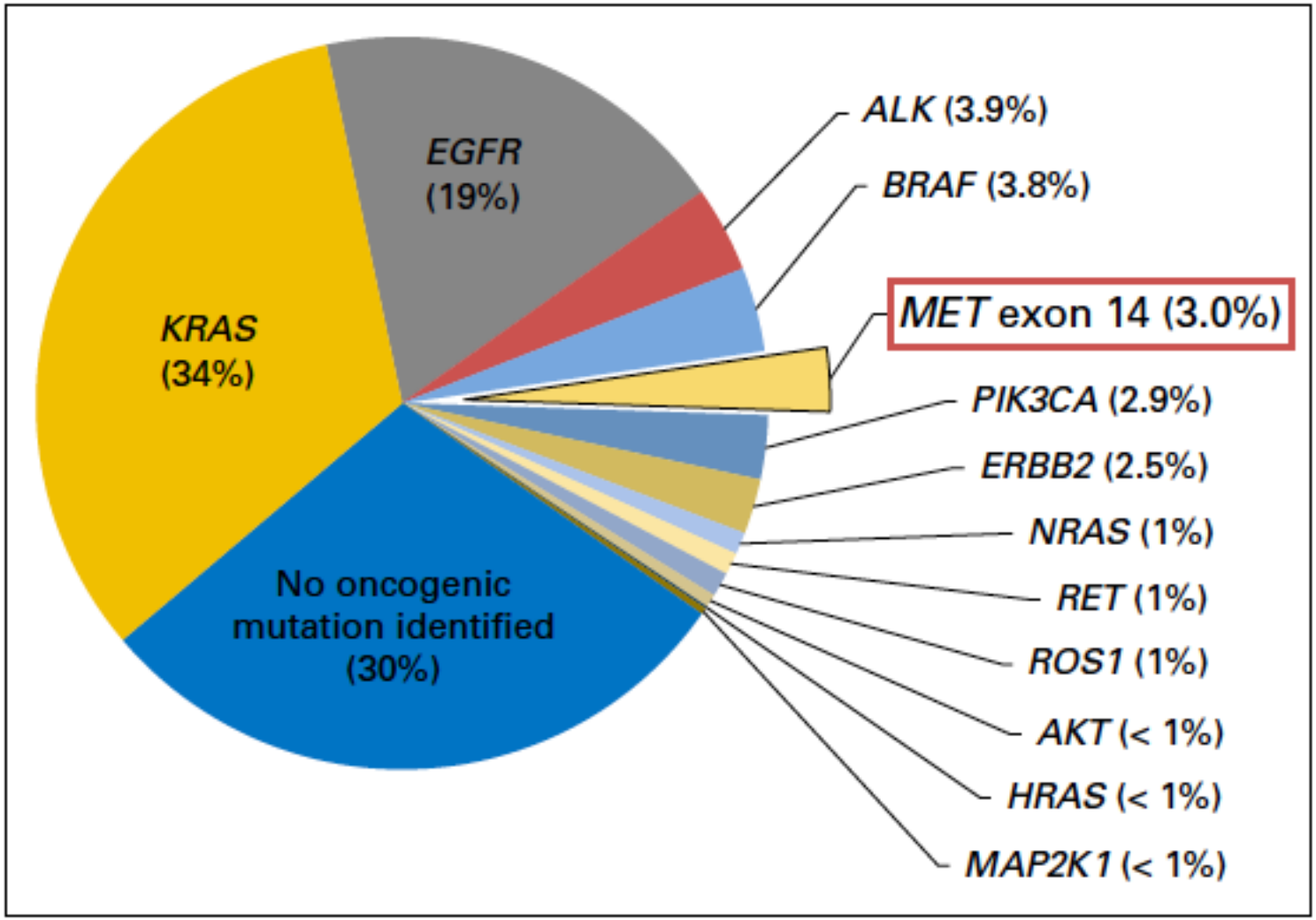
RET: European experience

Table 2. Clinical characteristics of patients with *RET* rearranged non-small cell lung cancer (N = 22)

Characteristics	No.	%
Age at first diagnosis (y)	22	100
Mean ± SD	61 ± 11.7	
Median (range)	62 (39-80)	
Sex		
Female	9	41
Male	13	59
Smoking history		
Never	12	54.6
Former	7	31.8
Current	3	13.6

Michels S et al. J Thorac Oncol 2016

Met Exon 14 Mut



Awad M et al. J Clin Oncol 2016

Table 1. Clinical Characteristics of Patients With Lung Cancers Harboring *MET* Exon 14 Versus *EGFR* or *KRAS* Mutations

Characteristic	No. (%)		
	MET Exon 14 (n = 28)	*EGFR* (n = 99)	*KRAS* (n = 169)
Median age (range), years	72.5 (59-84)	61 (30-93)	65 (42-93)
Sex			
Male	9 (32)	30 (30)	62 (37)
Female	19 (68)	69 (70)	107 (63)
Smoking history, pack-years*			
Never-smoker	10 (36)	57 (58)	6 (4)
≤ 10	3 (11)	10 (10)	11 (7)
> 10	15 (53)	28 (28)	152 (90)
Race			
White, non-Hispanic	28 (100)	79 (80)	157 (93)
Asian	0 (0)	15 (15)	0 (0)
Black	0 (0)	1 (1)	5 (3)
White, Hispanic	0 (0)	3 (3)	3 (2)
Unknown	0 (0)	1 (1)	4 (2)
Histology			
Adenocarcinoma	18 (64)	92 (93)	150 (89)
Pleomorphic with adenocarcinoma component	4 (14)	0 (0)	3 (2)
NSCLC, poorly differentiated	5 (18)	4 (4)	10 (6)
Squamous	0 (0)	2 (2)	5 (3)
Adenosquamous	1 (4)	1 (1)	1 (1)
Stage at diagnosis			
I	13 (46)	9 (9)	12 (7)
II	2 (7)	3 (3)	12 (7)
III	4 (14)	9 (9)	44 (26)
IV	9 (32)	78 (79)	101 (60)

NOTE. Percentages may not add up to 100% because of rounding.
Abbreviation: NSCLC, non–small-cell lung cancer.
*Number of smoking pack-years was not available for four patients with *EGFR* mutations.

Awad M et al. J Clin Oncol 2016

NF1 mutant NSCLC

IV Simposio Cáncer de Pulmón en Mujeres

	NF1 (n=60)	*KRAS* (n=141)	p value
Median age (range)	62 (44-83)	65 (42-86)	0.14
Sex			
Female	31 (52%)	83 (58%)	0.36
Male	29 (48%)	58 (41%)	
Smoking status			
Never-smoker	7 (12%)	6 (4%)	0.06
Former/current	53 (88%)	135 (96%)	
Stage at diagnosis			
I	17 (28%)	55 (39%)	0.34*
II	5 (8%)	14 (10%)	
III	10 (17%)	19 (13%)	
IV	27 (47%)	53 (38%)	
Tumor Histology			
Squamous cell carcinoma	10 (17%)	2 (1%)	
Adenocarcinoma	36 (60%)	136 (96%)	p<0.001
Large cell neuroendocrine	2 (3%)	1 (1%)	
Giant cell carcinoma	1 (2%)	2 (1%)	
Poorly differentiated carcinoma	11 (18%)	0 (0%)	
Distant Metastases			
Bone	13 (22%)	28 (20%)	0.81
Brain	5 (8%)	14 (10%)	0.58
Visceral	25 (42%)	48 (34%)	1.0
% of total NSCLC cohort	10%	24%	

Redig A, et al. CCR 2016

Women appear to be at higher risk for smoking-related lung cancer than men. Genetic mutations associated with more aggressive lung cancers in smokers (KRAS G12C) occur in women at a younger age and who have smoked less than men.

JAMA Oncol 2015

What about IO?

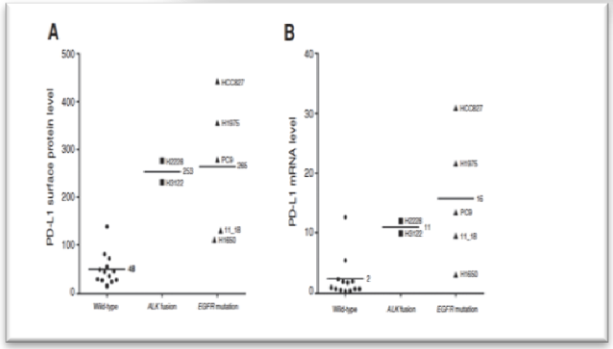
Inmuno checkpoints inhibitors

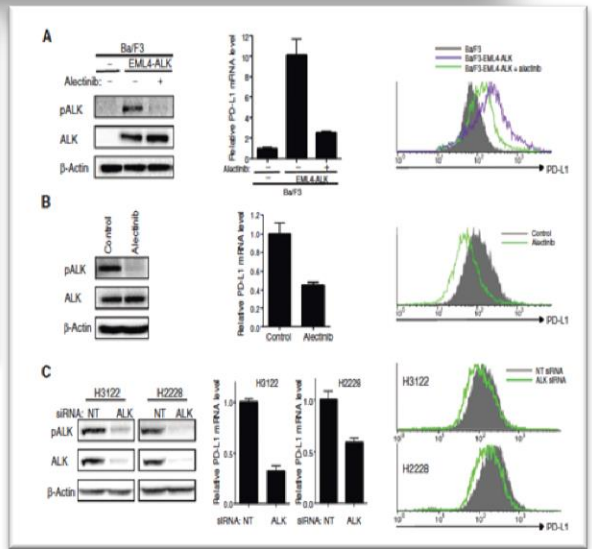
Biology of Human Tumors

Clinical Cancer Research

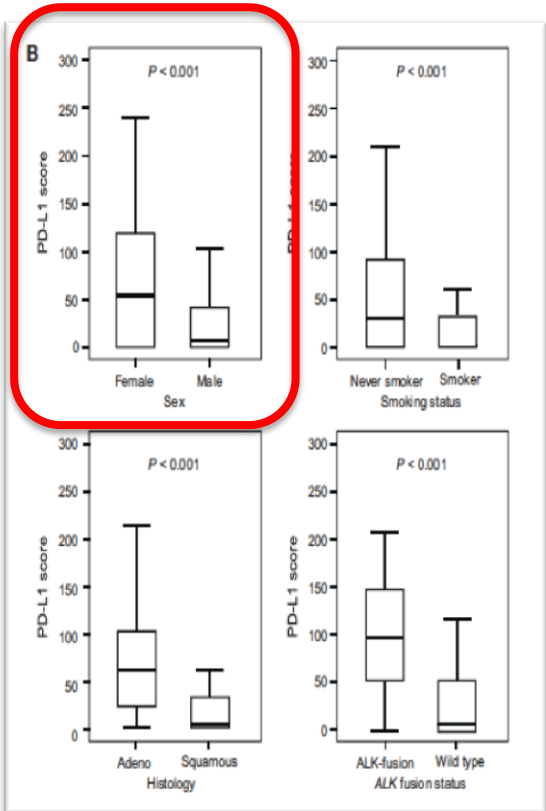
Induction of PD-L1 Expression by the EML4–ALK Oncoprotein and Downstream Signaling Pathways in Non–Small Cell Lung Cancer

Keiichi Ota[1], Koichi Azuma[2], Akihiko Kawahara[3], Satoshi Hattori[4], Eiji Iwama[1,5], Junko Tanizaki[6], Taishi Harada[1], Koichiro Matsumoto[1], Koichi Takayama[1], Shinzo Takamori[7], Masayoshi Kage[3], Tomoaki Hoshino[2], Yoichi Nakanishi[1,8], and Isamu Okamoto[1,8]





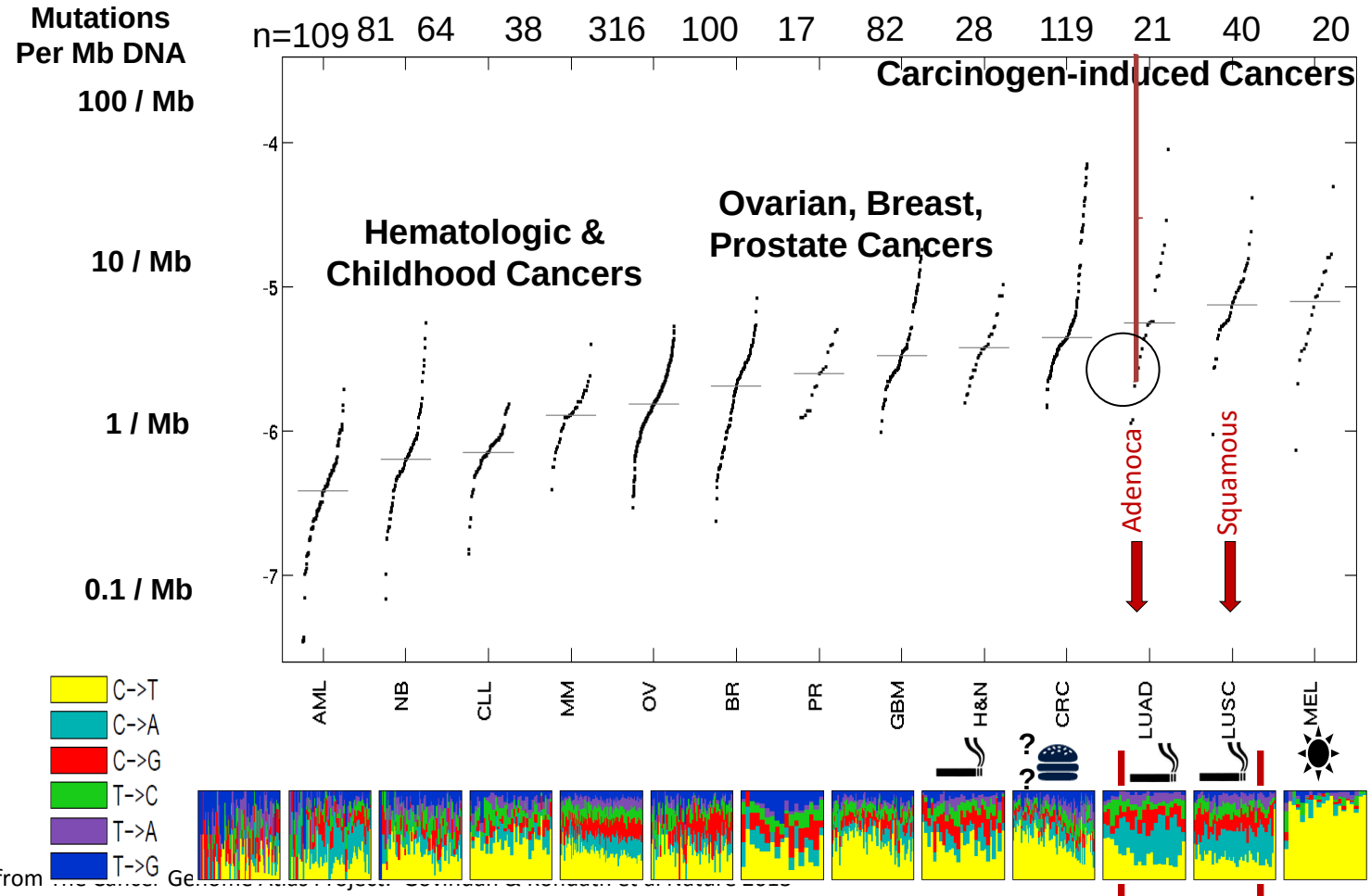
Otta K et al. CCR 2015



Phase III trials: IO vs CT
MEN/ FEMALE

	CheckMate 017	CheckMate 057	KeyNote 010
M/F (%)	76% vs 24%	55% vs 45%	62% vs 38%
HR OS M/F	0.57 vs 0.67	0.73 vs 0.78	0.65 vs 0.69

Magnitude of Genomic Derangement Is Greatest in Lung Cancer. This may contribute to increased inmunogenicity



Adapted from

Some notes to conclude…

- Lung Cancer in women seems to be a biologically specific disease, with a high rate of women diagnosed with lung cancer who have never smoked.
- Oncogenic alterations have been described in this specific population with potential and different personalized therapeutic strategies under evaluation.
- ALK and ROS1 rearrangements tend to occur at younger ages of 50 to 60 years. KRAS, EGFR, and BRAF mutations tend to occur at the ages of 61 to 66 years. cMET mut seems to occur in older adults
- Different activity and toxicity patterns to targeted agents may exist according to gender and need to be explored

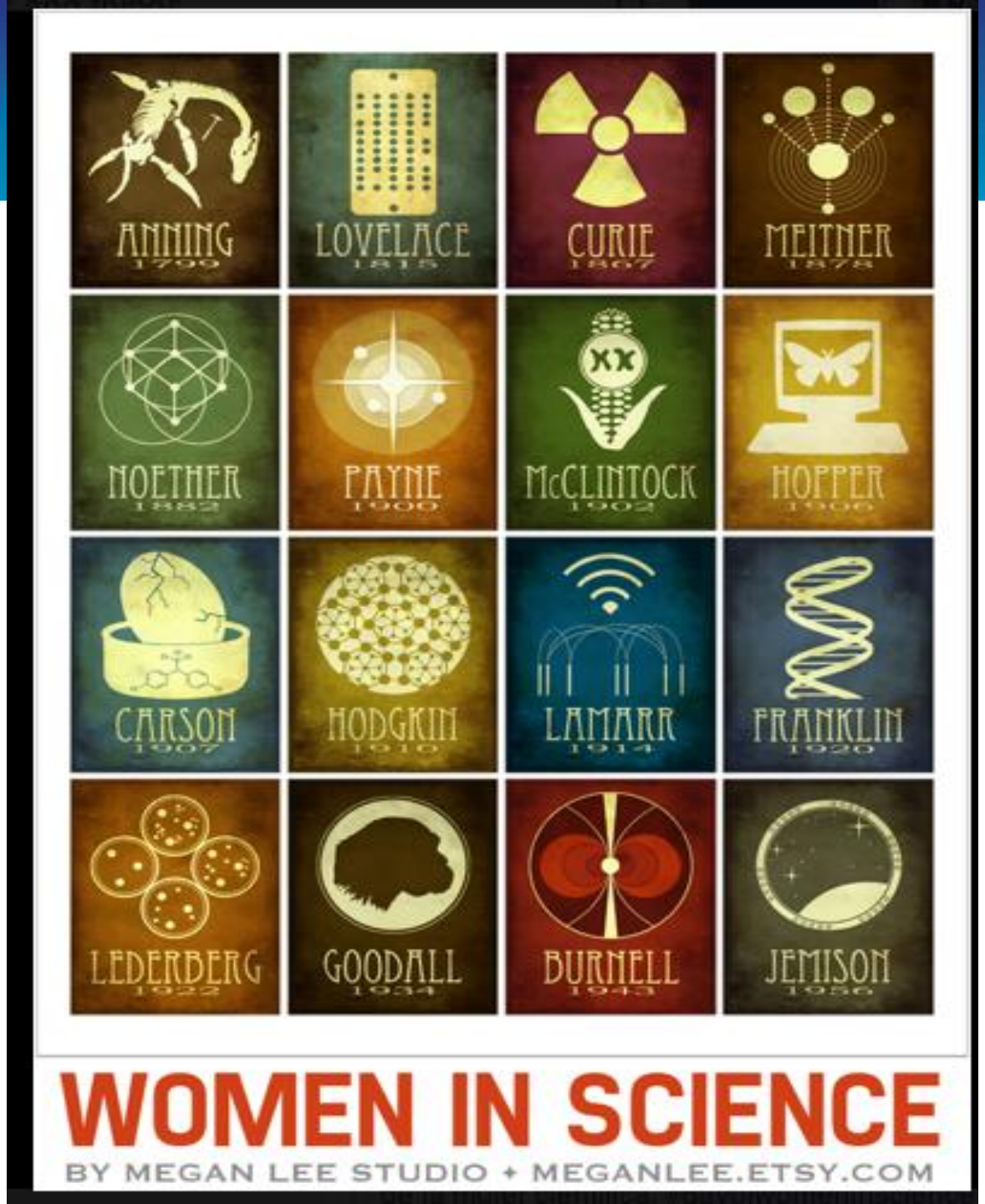
Estudio: IMPULSO **Código: ICA-QUI-2014-01**

VALORACIÓN DE LAS DIFERENCIAS DE GÉNERO EN EL IMPACTO PSICOSOCIAL Y ECONÓMICO EN PACIENTES CON CÁNCER NO MICROCÍTICO DE PULMÓN AVANZADO

Código del Estudio: ICA-QUI-2014-01

Promotor: ICAPEM

Coordinadores: **Dra. Pilar Garrido López**
H. Universitario Ramón y Cajal
Dra. Mª Rosario García Campleo
Complejo Hospitalario A Coruña
Dra. Nuria Viñolas Segarra
Hospital Clínic i Provincial de Barcelona



11 Febrero
Día de la Mujer Científica