IV Simposio Cáncer de Pulmón en Mujeres

Madrid, 25 de febrero de 2016

Diferencias de género en el tratamiento sistémico: Otras terapias

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Introducción

- Avances en el tratamiento del ca. de pulmón
  Impacto en la supervivencia

- Género: posible factor pronóstico y predictivo

- Diferencias en el comportamiento de los tumores en función del sexo
  Tratamientos utilizados
  Eficacia
  Toxicidad

Factor pronóstico

- Dos estudios epidemiológicos en Francia

Diferencias clínicas entre 2000 y 2010

Pacientes mayores, más no o poco fumadores, mejor PS

Escamoso (50,3%) → Adenocarcinoma (48,7%)

↑ Estadio IV (56,9 vs 41,6%)

		Varones	Mujeres	HR
Supervivencia 1 año (%)	2000	38,8	41,9	0,81
	2010	43,4	49,1	0,71

Devieuvre, Lung Cancer 2016

Factor predictivo

	Pre-1990	Post-1990	*P*
No. of patients*	1520	1878	
No. of trials	6	3	
Patients on cisplatin regimens, %	79.7	94.8	<.0001
Mean age, y	60.0	60.9	.0048
Male, %	70.1	63.2	<.0001
Performance status 0-1, %	81.8	96.5	<.0001
Stage IIIB, %	0	15	<.0001
Weight loss >10%, %	15.1	12.3	.0197
Adenocarcinoma and adenosquamous carcinoma histology	47.2	57.3	<.0001
Sites of metastases			
≤1 Metastatic site	45.9	29.4	<.0001
Bone disease	37.5	32.3	.0016
Pulmonary metastasis	59.7	79.4	<.0001
Liver metastasis	17.0	20.4	.0138
Brain metastasis	0.2	8.2	<.0001
Pulmonary metastasis ONLY	22.2	25.9	<.0134
Bone metastasis ONLY	8.6	2.8	<.0001
Liver metastasis ONLY	3.0	1.4	.0022

Wakelee, J Thorac Oncol 2006

Factor predictivo

TABLE 4
Cox Proportional Hazards Model: Overall Survival

	Baseline: Date of Study Entry		Baseline: Date of Diagnosis	
Variable	***P***	**Hazard Ratio**	***P***	**Hazard Ratio**
Date of diagnosis: post-1990 vs. pre-1990	<.0001	0.765	<.0001	0.762
Performance status 2 vs. 0-1	<.0001	1.580	<.0001	1.538
Cisplatin-based chemotherapy vs. noncisplatin regimens	.0261	0.882	.0244	0.881
Age ≥70 y vs. <70 y	.6513	0.978	.9120	1.005
Weight loss >10% (6 mo) vs. weight loss ≤10%	<.0001	1.262	<.0001	1.233
Pulmonary metastases ONLY vs. any nonpulmonary metastases	<.0001	0.703	<.0001	0.723
Nonadenocarcinoma histology vs. adenocarcinoma or adenosquamous carcinoma	.4425	1.028	.8075	1.009
Female vs. male	<.0001	0.862	.0001	0.865

Wakelee, J Thorac Oncol 2006

Diferencias en tratamientos

Mujeres: Más cirugía (menos comorbilidad cardiovascular, respiratoria)

Menos neumonectomías (adenocarcinoma)

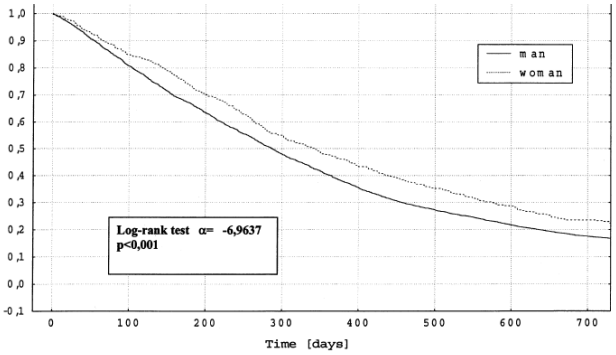
Alexion, Eur J Cardiothorac Surg 2002

Mujeres: ↑ cirugía ± QT-RT

↓ Sintomático/ No tratamiento

Table 5. Treatment of lung cancer patients

	All (%)	Female		Male		*P* value
		Number	%	Number	%	
Treatment	12378 (100)	1710	100	10668	100	
Chemotherapy	3518 (28.5)	512	29.9	3006	28.2	NS
Surgery	2406 (19.4)	397	23.2	2009	18.8	0.0001
Surgery and chemo- and/or radiotherapy	706 (5.7)	125	7.3	681	5.5	0.003
Radiotherapy	1807 (14.6)	247	14.5	1560	14.6	NS
Symptomatically	3345 (27)	376	22	2969	27.9	0.0001
Refused	1807 (4.8)	53	3.1	543	5	0.0005



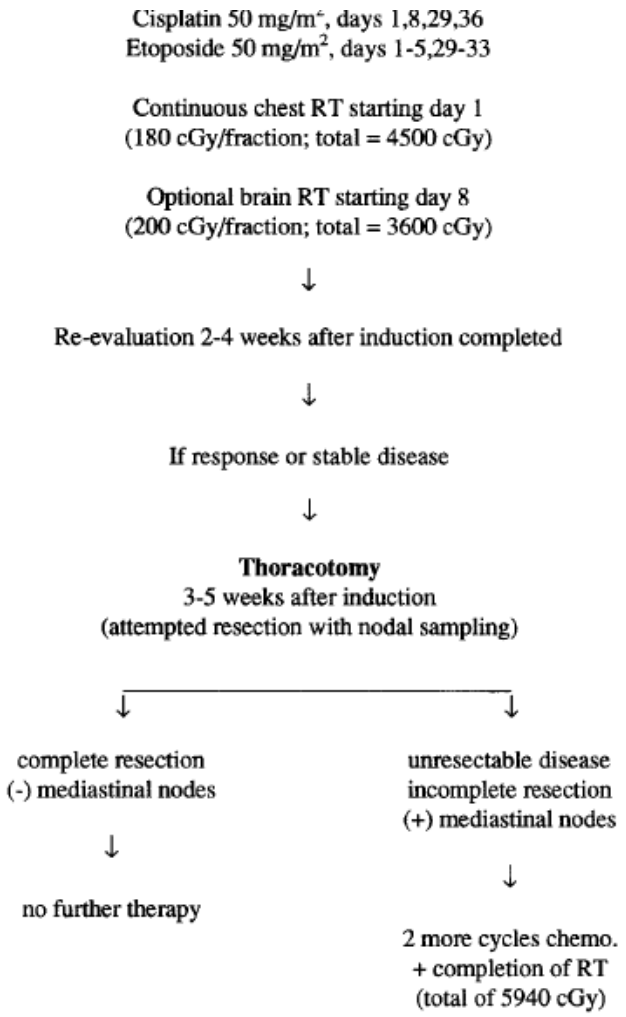
Radzikowska, Ann Oncol 2013

Enfermedad localmente avanzada

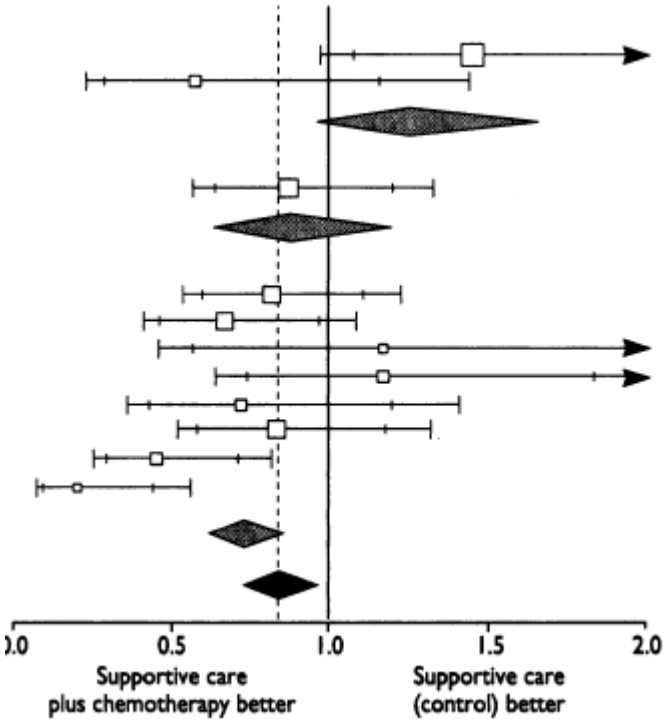
Table 5. Exploratory Univariate Survival Analyses of Prestudy Characteristics

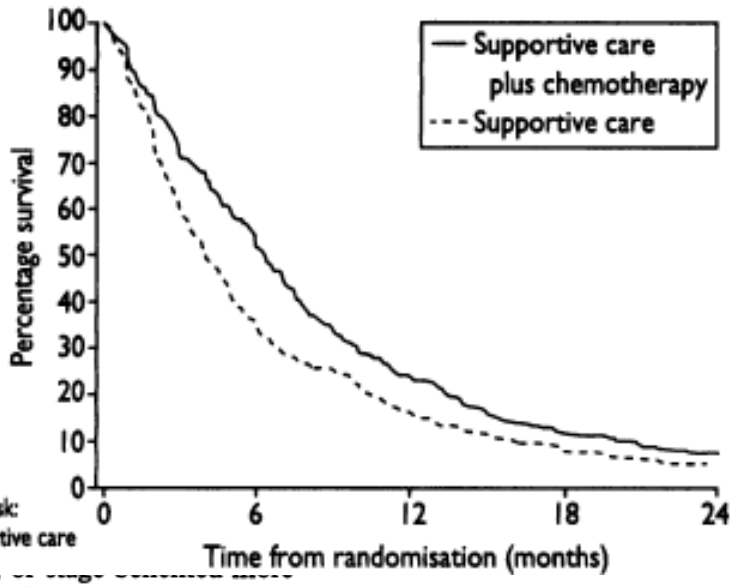
Prestudy Factor*	Median Survival (months)	P
Female v male	21 v 12	.08
T4N0, N1, or NX v all others	28 v 13	.07
T4N0, N1, NX or T1N2 v all others†	32 v 12	.03

Albain,J Clin Oncol 1995



QT: Metanálisis 1995





% of patients.
atients specifiertive care
rmance status,
chemotherapy (figure 9 shows stage,

Non-small Cell Lung Cancer Collaborative Group, BMJ 1995

ELCWP

Análisis retrospectivo

1.052 pacientes

7 ensayos

QT basada en platino

Table 4. Best-Fitted Cox Multivariate Regression Model

Variable	Coefficient	SD	RR	95% CI	P
Disease extent					
Limited	0.44	0.10	1.55	1.28-1.89	< .0001
Disseminated					
Karnofsky performance status					
	−0.36	0.10	0.70	0.58-0.85	.0003
≤ 70					
≥ 80					
WBC count	0.29	0.10	1.33	1.10-1.63	.0003
Normal					
Abnormal					
Skin metastases	1.03	0.27	2.80	1.65-4.76	.008
No					
Yes					
Serum calcium level	0.50	0.19	1.65	1.14-2.39	.007
Normal					
Abnormal					
Neutrophil count	0.27	0.10	1.31	1.08-1.59	.02
Normal					
Abnormal					
Age (years)	0.24	0.10	1.27	1.04-1.55	.02
≤ 60					
> 60					
Sex	−0.36	0.15	0.70	0.52-0.94	.03
Male					
Female					

Paesmans, J Clin Oncol 1995

DNA repair capacity

Menor en tumores de mujeres

mayor susceptibilidad a carcinógenos

mayor efectividad de QT

Ensayo en 377 pacientes (171 con QT)

Nucleotide Escision Repair (NER)

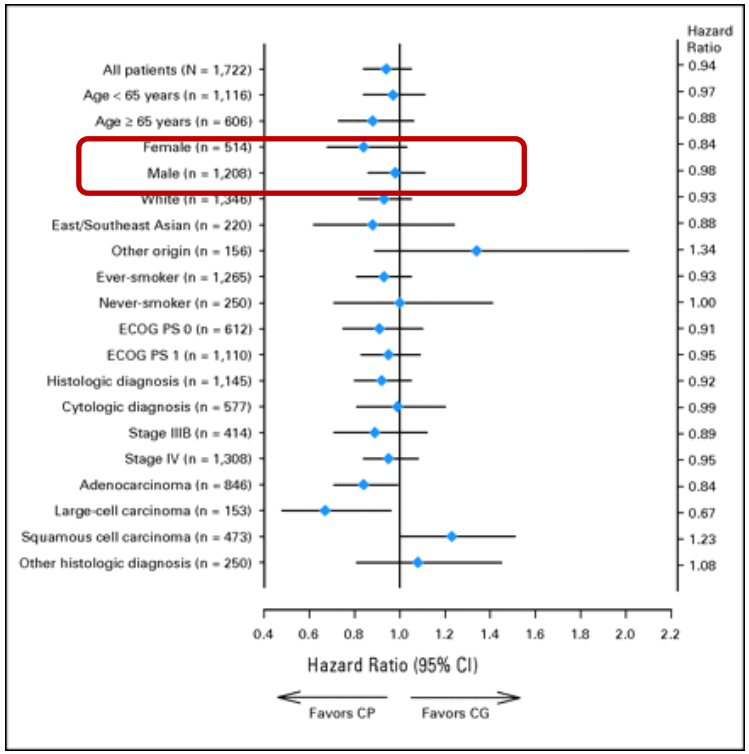
↓ riesgo de muerte (RR 2,72 primer vs cuarto cuartil)

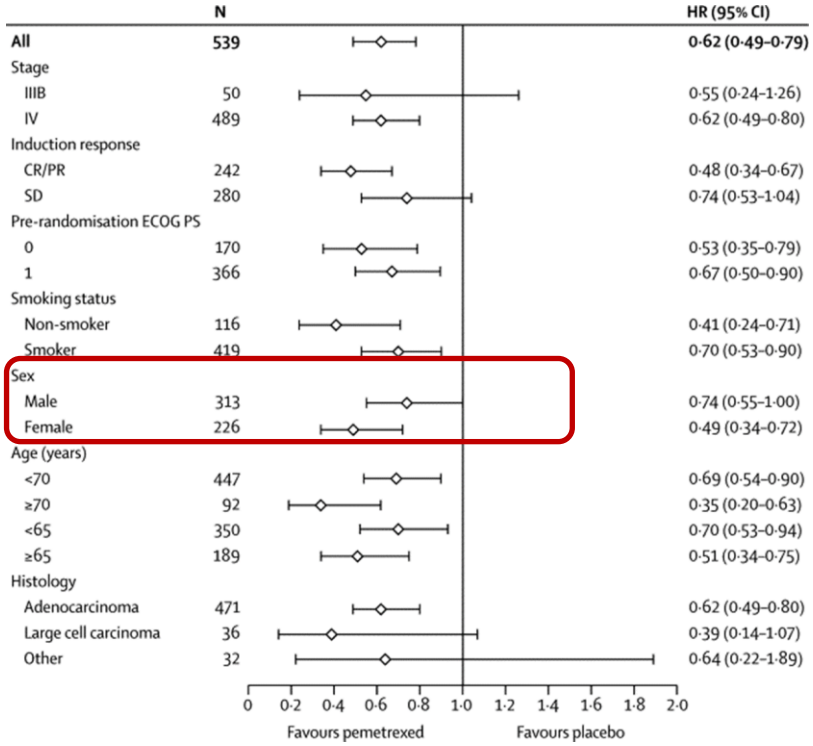
Sin relación con otros factores

Sólo en pacientes con QT

Bosken, J Natl Cancer Inst 2002

Pemetrexed

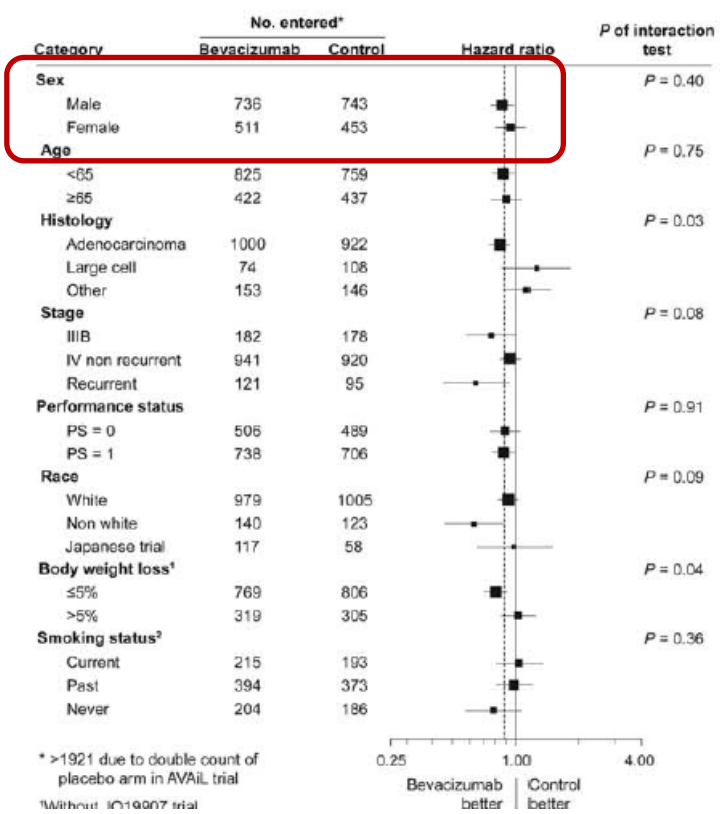


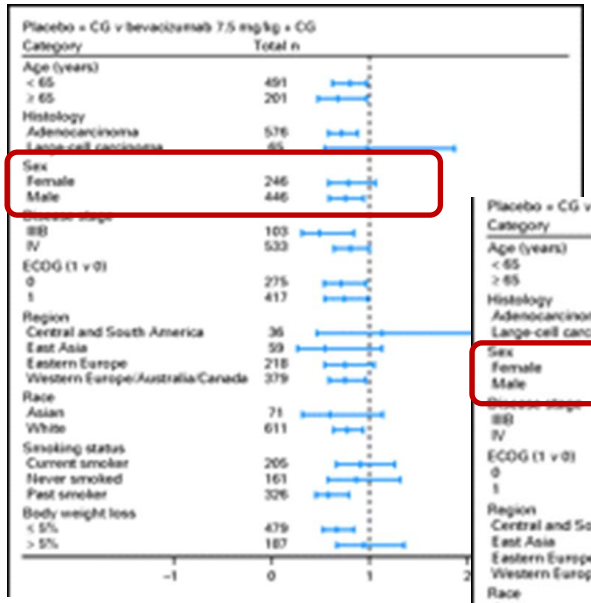


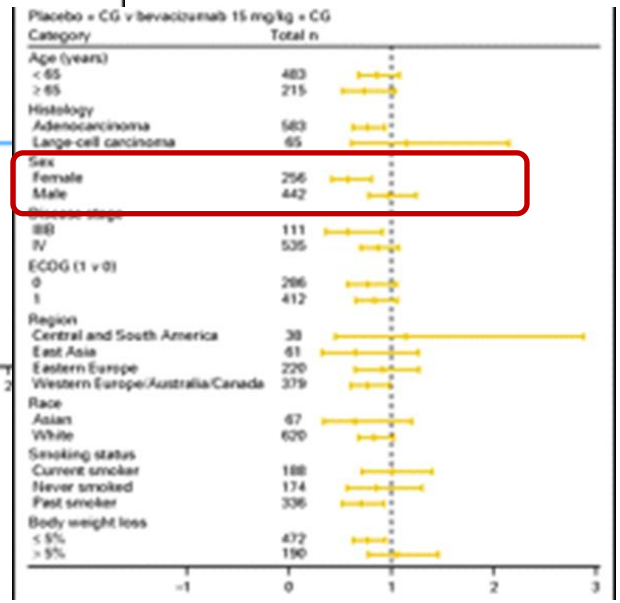
Scagliotti, J Clin Oncol 2008

Paz Ares, J Clin Oncol 2013

Bevacizumab



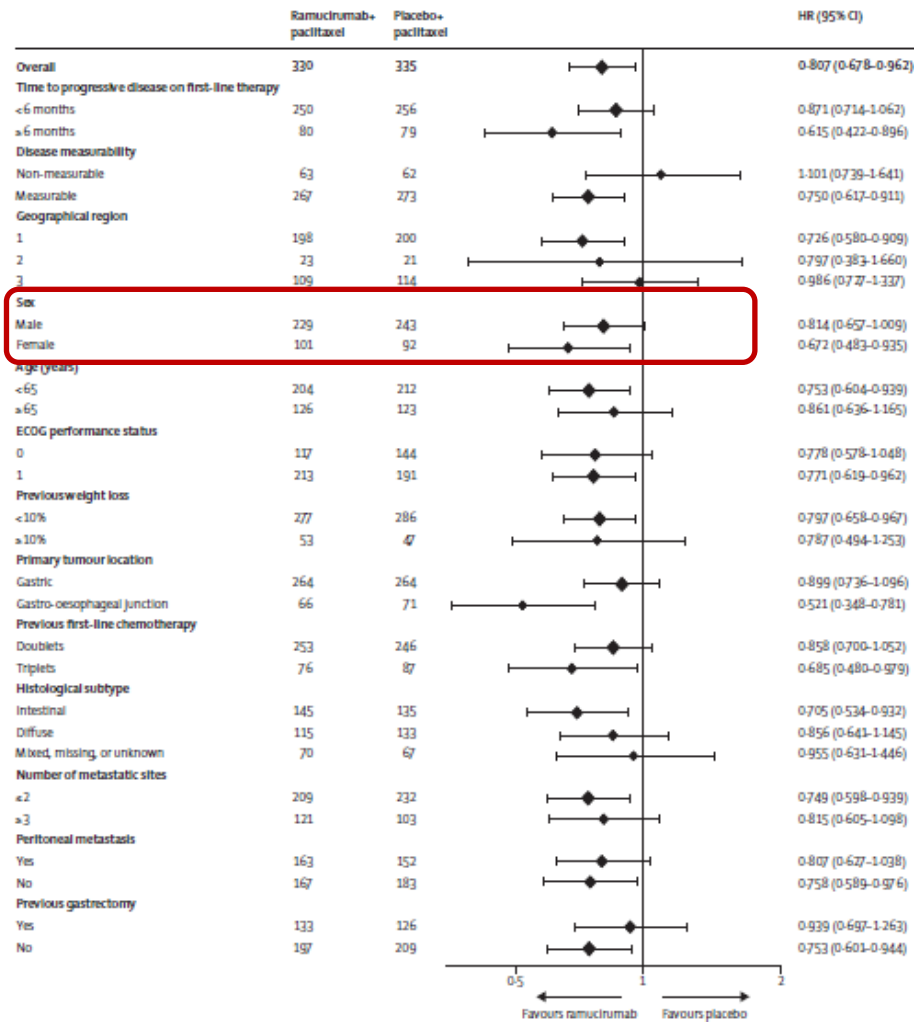




Soria, Ann Oncol 2013

Reck, Ann Oncol 2010

Ramucirumab

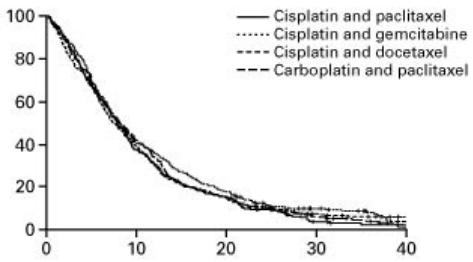


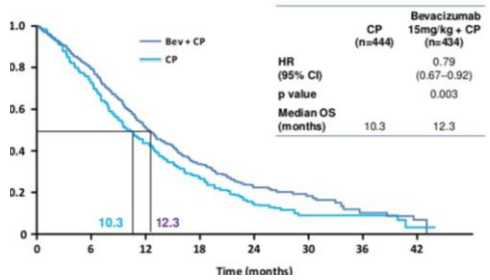
Wilke, Lancet Oncol 2014

E1594 + QT E4599

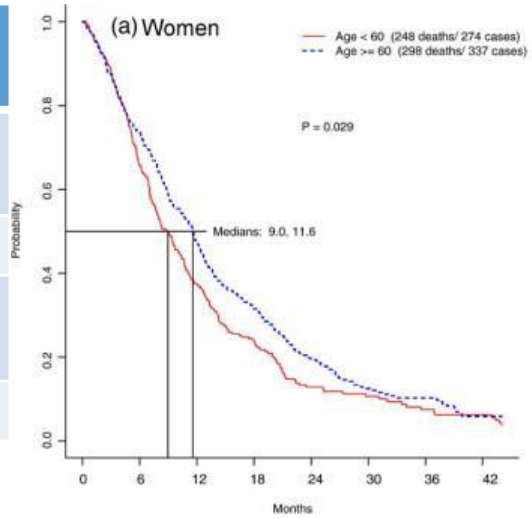
1590 pacientes (1157 + 433)

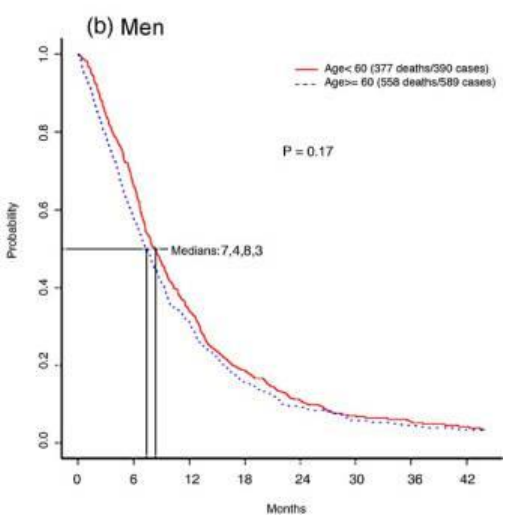
Análisis de subgrupos no planificado
≥60 vs < 60 años como subrogado de menopausia





		PFS (m)	Supervivencia (m)
Mujeres	<60 años	4,7	9,0
	≥60 años	3,8	11,6
Varones	<60 años	3,4	8,3
	≥60 años	4,0	7,4





Wakelee, Lung Cancer 2012

E4599 Bevacizumab

850 pacientes

El grupo de edad no influye en las pacientes que reciben bevacizumab

	Age		*p* value-age
	<60 years	**≥60 years**	
Women − Bev	11.0 mo (8.2–14.2) *N* = 75	13.8 mo (12.4–19.6) *N* = 105	0.11
Women + Bev	15.5 mo (11.0–21.0) *N* = 85	12.8 mo (10.8–17.0) *N* = 122	0.18
Men − Bev	9.3 mo (7.3–10.8) *N* = 95	8.5 mo (7.1–10.3) *N* = 158	0.85
Men + Bev	12.4 mo (10.2–15.2) *N* = 73	11.0 mo (9.3–14.4) *N* = 137	0.59
p value-sex/treatment	0.0006	<0.0001	

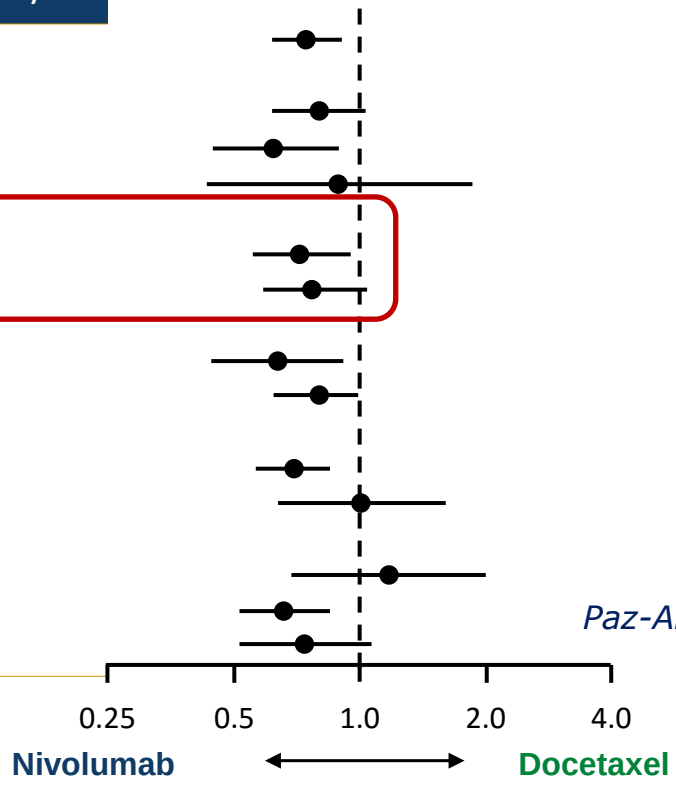
Posibles diferencias:

Hormonales
Diferente capacidad de reparación del ADN
Interacción con VEGF

Wakelee, Lung Cancer 2012

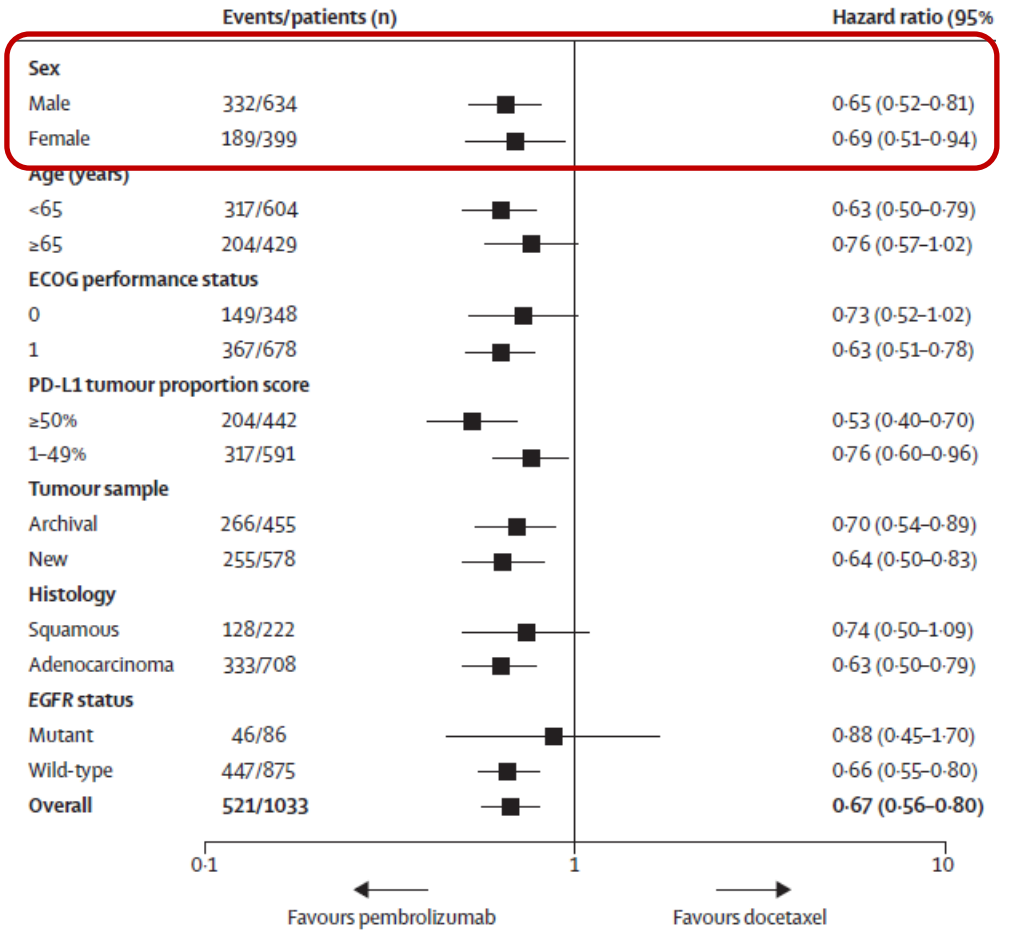
Inmunoterapia: Nivolumab

	N	Unstratified HR (95% CI)
Overall	582	0.75 (0.62, 0.91)
Age Categorization (years)		
<65	339	0.81 (0.62, 1.04)
≥65 and <75	200	0.63 (0.45, 0.89)
≥75	43	0.90 (0.43, 1.87)
Gender		
Male	319	0.73 (0.56, 0.96)
Female	263	0.78 (0.58, 1.04)
Baseline ECOG PS		
0	179	0.64 (0.44, 0.93)
≥1	402	0.80 (0.63, 1.00)
Smoking Status		
Current/Former Smoker	458	0.70 (0.56, 0.86)
Never Smoked	118	1.02 (0.64, 1.61)
***EGFR* Mutation Status**		
Positive	82	1.18 (0.69, 2.00)
Not Detected	340	0.66 (0.51, 0.86)
Not Reported	160	0.74 (0.51, 1.06)



Paz-Ares, ASCO 2015

Pembrolizumab



Herbst, Lancet 2016 (in press)

CMP

- 1006 pacientes, 4 ensayos

Mujeres:

Más toxicidad hematológica

Anemia G3-4: 16,3 vs 5,6%

Leucopenia G3-4: 80,4 vs 69,2%

Más estomatitis y vómitos

16,8 vs 8,3 y 76,8 vs 67,2

No diferencias en supervivencia

Mayor tasa de respuestas y supervivencia

	Female Patients (n = 319)		Male Patients (n = 564)		*P*
	No.	%	No.	%	
Response					< .0001
Overall	256	80.3	377	66.9	
Complete response	169	53.0	186	33.0	
Partial response	87	27.3	191	33.9	
Stable disease	11	3.4	47	8.3	
Progressive disease	52	16.3	140	24.8	
Survival					< .0001
Median, years	1.31		0.91		
95% CI	1.17 to 1.43		0.87 to 0.97		

Singh, J Clin Oncol 2005

Diferencias en Toxicidad

Influencia en la toxicidad

- Análisis retrospectivo NCCTG

1053 pacientes en 7 ensayos (1985-2001)

– Efectos secundarios hematológicos y no hematológicos

(también edad, PS)

Magnitud similar con (46%)

y sin platino

Diferente farmacodinámica

(composición corporal

Absorción

Función hepática

Eliminación renal) en muchos

fármacos

TABLE 6. Multivariate Results

	Grade 3+ Heme[a]			Grade 3+ Non-Heme[b]		
Factor	**Odds ratio**	***p* value**	**95% confidence limits**	**Odds ratio**	***p* value**	**95% confidence limits**
Age (yr) (10-yr increase)	(1.50)	<0.0001	(1.26, 1.78)	(1.23)	0.01	(1.04, 1.44)
Gender						
Male	(1.00)	—	—	(1.00)	—	—
Female	(1.60)	0.007	(1.14, 2.26)	(1.71)	0.0009	(1.25, 2.35)
PS						
0	—	—	—	(1.00)	—	—
1	—	—	—	(1.44)	0.03	(1.03, 2.00)
2/3	—	—	—	(2.29)	0.01	(1.20, 4.39)
WBC (10^9/L) (1-unit increase)	(0.89)	<0.0001	(0.85, 0.94)	—	—	—
Hgb (g/dL)	(0.95)	0.28	(0.86, 1.05)	—	—	—
PLT (10^9/L)	(0.92)	0.22	(0.80, 1.05)	—	—	—

Mandrekar, J Thorac Oncol 2006

Antiemesis

Ond + Dexa → Dexa vs Ond + Dexa → Ond + Dexa

Mujeres: Menos RC en ambos brazos

Varones: Más hipo

	Arm A (n = 363)					Arm B (n = 358)				
	No. of patients	C.R. for vomiting on days 1 through 6		C.R. for nausea on days 1 through 6		No. of patients	C.R. for vomiting on days 1 through 6		C.R. for Nausea on days 1 through 6	
		n (%)	P-value	n (%)	P-value		n (%)	P-value	n (%)	P-value
Total	363	253 (69.7%)		212 (58.4%)		358	255 (71.3%)		218 (60.9%)	
Gender			<0.0001		0.0004			<0.0001		<0.0001
Male	233	181 (77.7%)		152 (65.2%)		228	181 (79.4%)		157 (68.9%)	
Female	130	72 (55.4%)		60 (46.2%)		130	74 (56.9%)		61 (46.9%)	
Age group			0.18		0.22			0.11		0.55
16–49	121	80 (66.1%)		64 (52.9%)		121	80 (66.1%)		69 (57.0%)	
50–64	130	88 (67.7%)		78 (60.0%)		126	88 (69.8%)		80 (63.5%)	
65–82	112	85 (75.9%)		70 (62.5%)		111	87 (78.4%)		69 (62.2%)	
Cisplatin dose (mg/m^2)			0.51		0.24			0.25		0.06
50 or 60	332	233 (70.2%)		197 (59.3%)		329	237 (72.0%)		205 (62.3%)	
75 or 100	31	20 (64.5%)		15 (48.4%)		29	18 (62.1%)		13 (44.8%)	
Tumor type			0.38		0.30			0.16		0.83
GI	97	71 (73.2%)		61 (62.9%)		95	73 (76.8%)		57 (60.0%)	
Others	266	182 (69.5%)		151 (56.8%)		263	182 (69.2%)		161 (61.2%)	
Treatment cycle			0.89		0.49			0.13		0.70
1st cycle	200	140 (70.0%)		120 (60.0%)		200	136 (67.5%)		120 (60.0%)	
2nd cycle	163	113 (69.3%)		92 (56.4%)		158	119 (75.9%)		98 (62.0%)	

Liaw, Support Care Cancer 2001

Resumen

- El género un aspecto importante en esta era de "medicina personalizada"
- Factor pronóstico

  A considerar en la estratificación de ensayos clínicos
- Factor predictivo reproducible con QT

  Menos claro con tratamientos dirigidos
- A tener en cuenta en lo que se refiere a toxicidad
- Campo para la investigación

Are you flirting with me?