XXIV SIMPOSIO DE REVISIONES EN CÁNCER

"Tratamiento médico del cáncer en el año 2022"

Tratamiento del Cáncer Gástrico con **Antiangiogénicos**

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Disclousures

- Employment: Complexo Hospitalario Universitario Ourense
- Consultant or Advisory Role:BMS, Amgen, MSD, Eisai,Sanofi,Servier,Roche,Bayer,Lilly
- Speaking:Amgen,Servier,AstraZeneca,Lilly,Eisai,Sanofi,Bayer,Seagen

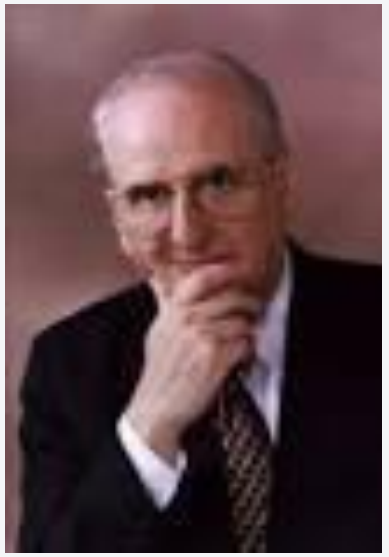
Índice

- Introducción
- Revisiones en 1L
- Revisiones en 2L
- Revisiones en 3L
- Futuro
- Conclusiones

INTRODUCCIÓN: "Nuevos Conceptos en Angiogénesis"

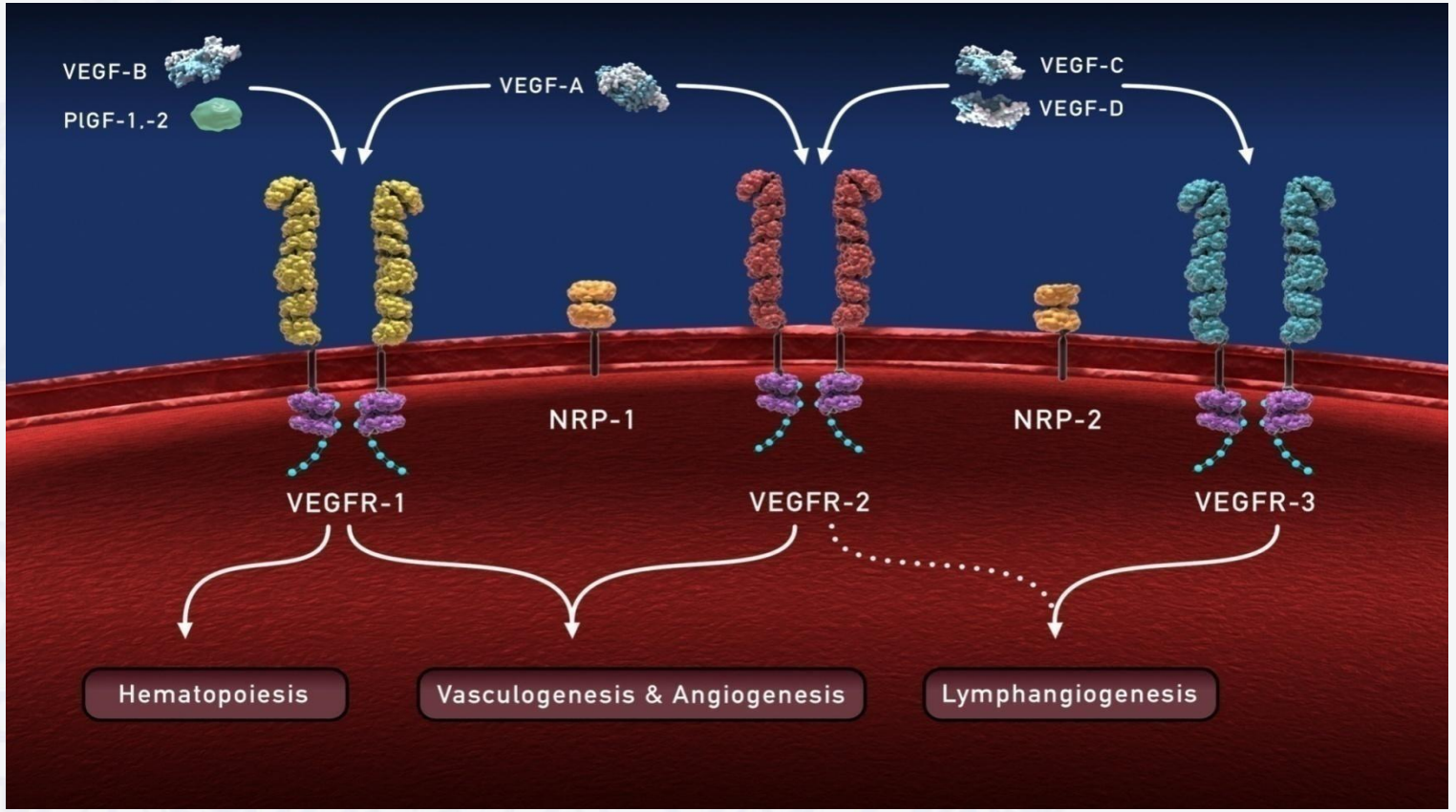
1. Angiogénesis diferente de vasculogénesis (descrita ya en 1971) y es el mecanismo por el que crecen los tumores

'En ausencia de vascularización, los tumores sólidos permanecen latentes y de un tamaño de 2–3mm^3 , estando su tamaño limitado por la capacidad del oxígeno y los nutrientes para difundirse en el interior del tumor'



Folkman J. N Engl J Med. 1971 Nov 18;285(21):1182-6.

2. Los "actores principales" son **VEGF y VEFR**

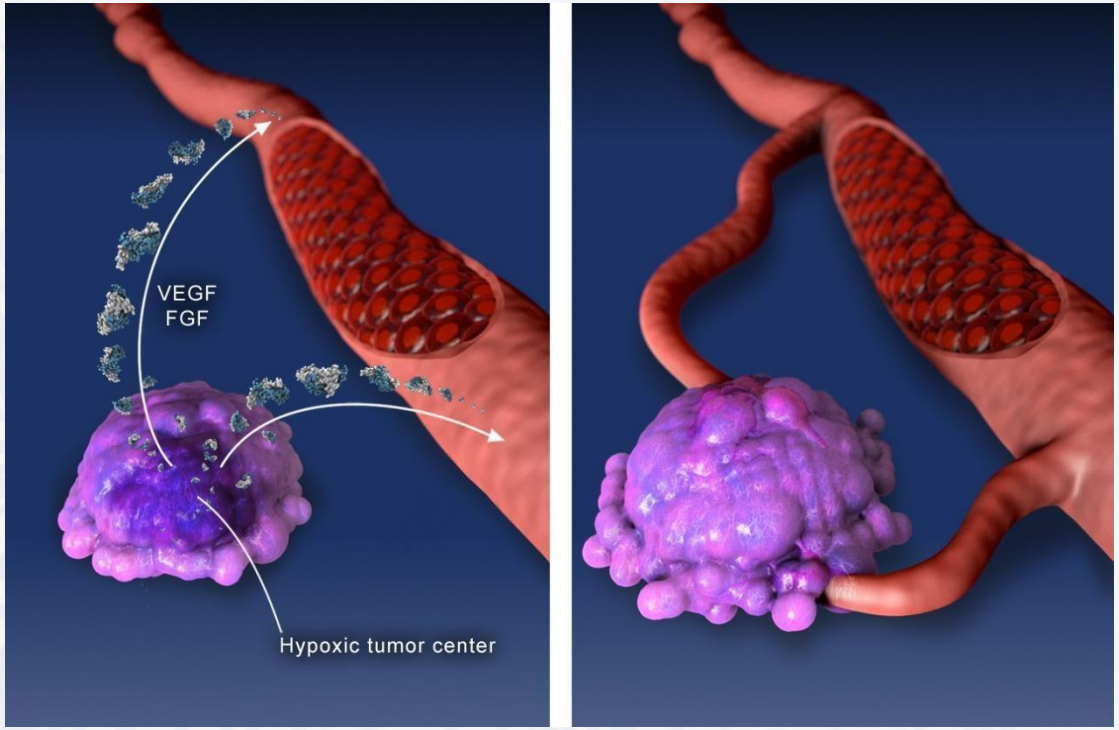


Cada inhibidor actúa en una diana diferente

1. Revisado en Adams and Alitalo. *Nat Rev Mol Cell Biol* 2007;8(6):464-78.
2. Reviewed in Hicklin and Ellis. *J Clin Oncol* 2005;23(5):1011-27.

3. La **Hipoxia** tumoral es el principal estímulo para la secreción de **VEGF**

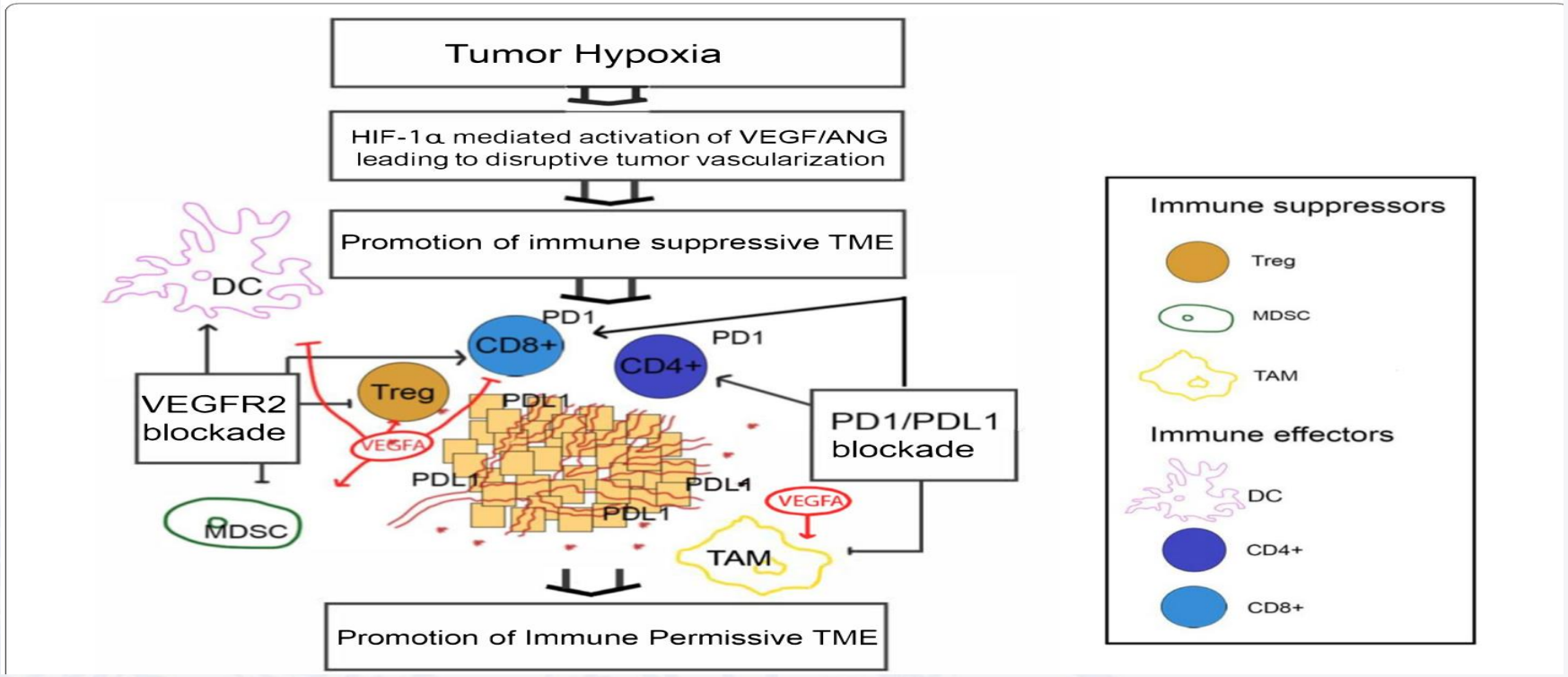
Un exceso de VEGF inicia el proceso angiogénico tumoral



1. Revisado en Adams and Alitalo. *Nat Rev Mol Cell Biol* 2007;8(6):464-78.
2. Reviewed in Hicklin and Ellis. *J Clin Oncol* 2005;23(5):1011-27.

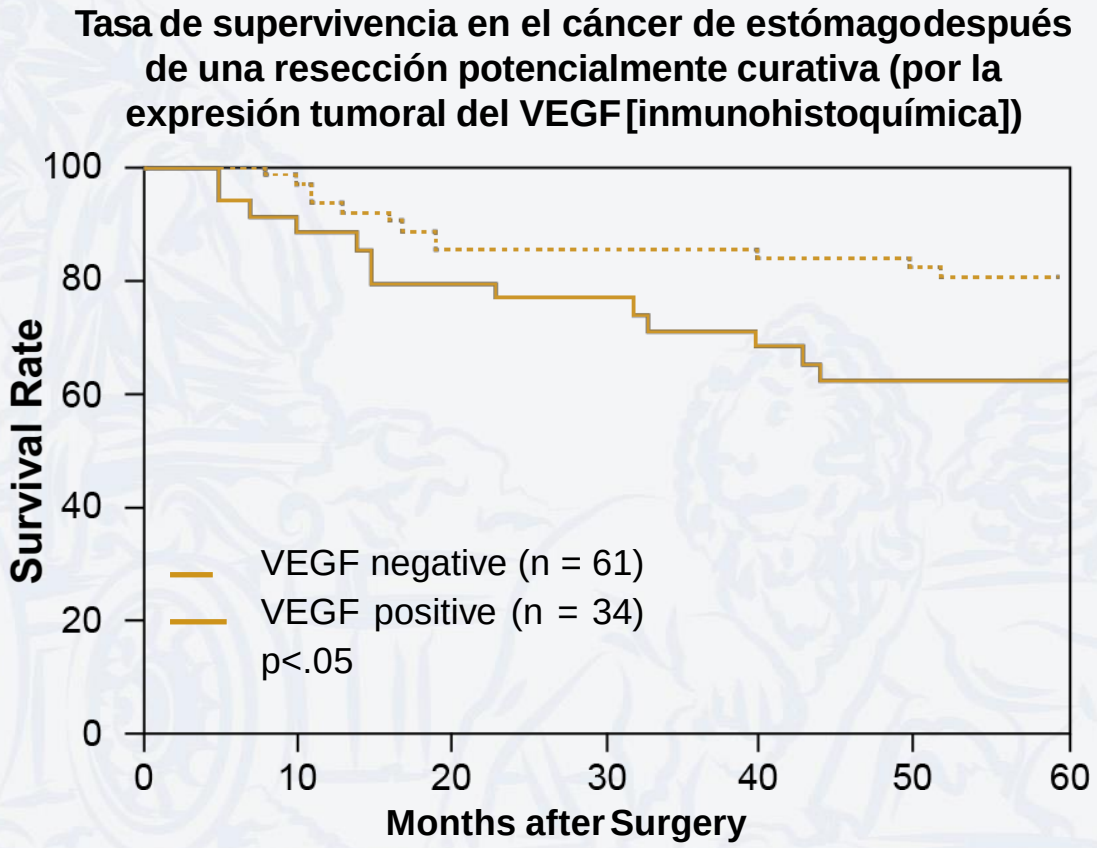
4. La Hipoxia tumoral conduce a un **microambiente (TME) "inmunosupresor"**

- **Con la secreción de VEGFA se inhibe la función de CD8+,maduración células dendríticas**
- **Establece potencial sinergia entre anti PD-1/PD-L1 y antiangiogénicos**



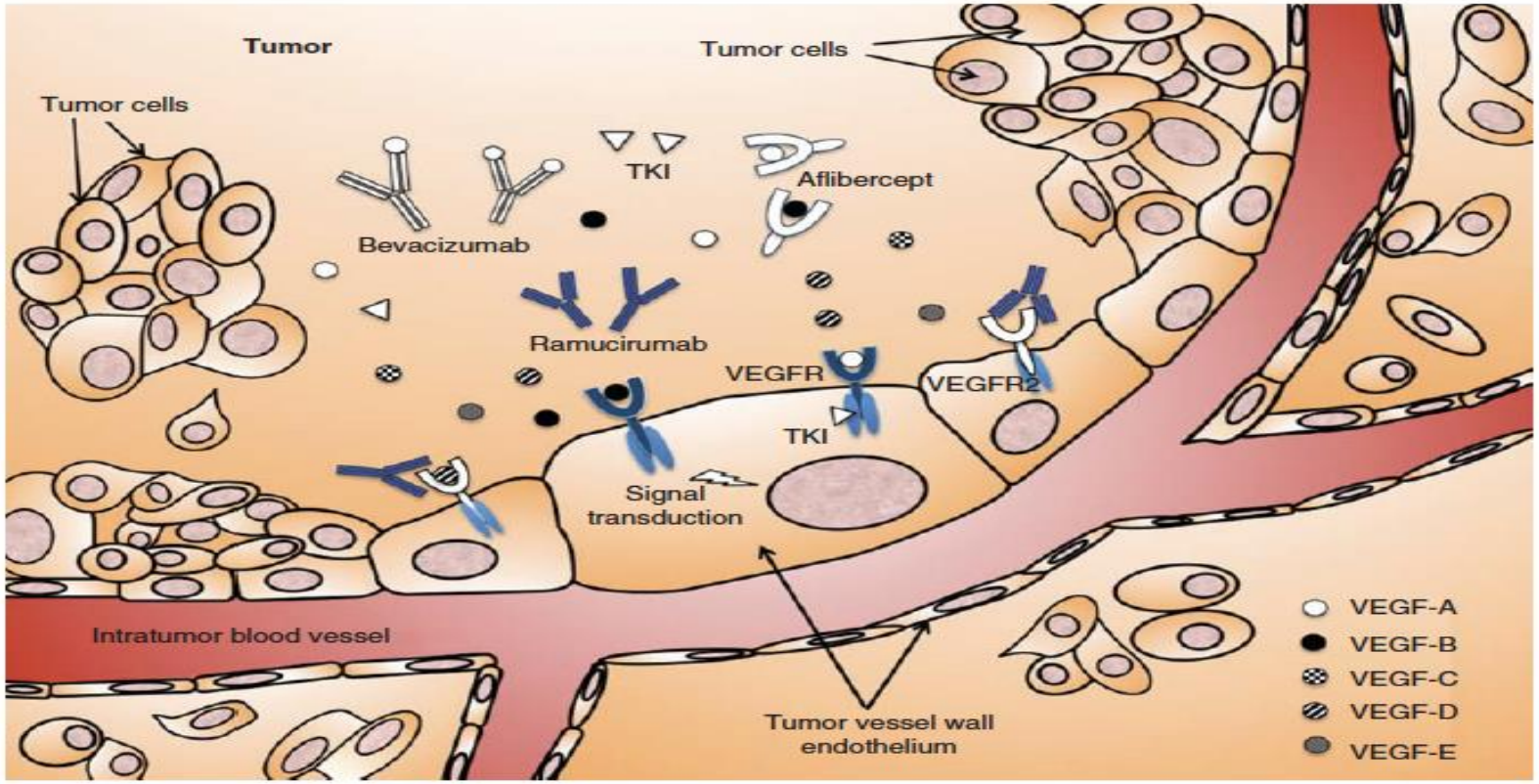
Adaptado. Saeed A, J Hematol Oncol. 2021 Jan 12;14(1):13.

5. La **sobreexpresión de VEGF** se correlaciona con mayor agresividad y peor pronóstico en Adenocarcinomas gástricos y de la UEG



Lieto E, Ann Surg Oncol. 2008 Jan;15(1):69-79.

6. Sabemos que los diferentes antiangiogénicos (TKIs o anticuerpos) tienen **diferente mecanismos de acción**



Fase III
- Bevacizumab
- Ramucirumab
- Apatinib

Adaptado.Barzi A, Thara E. Angiogenesis in esophageal and gastric cancer: a paradigm shift in treatment. Expert Opin Biol Ther. 2014 Sep;14(9):1319-32.

PRIMERA LÍNEA: Una historia de fracasos…

1. **Bevacizumab (AntiVEGF - A)** no impacta en SG (Fase III AVAGAST; n: 774; **19% Panaméricanos**)

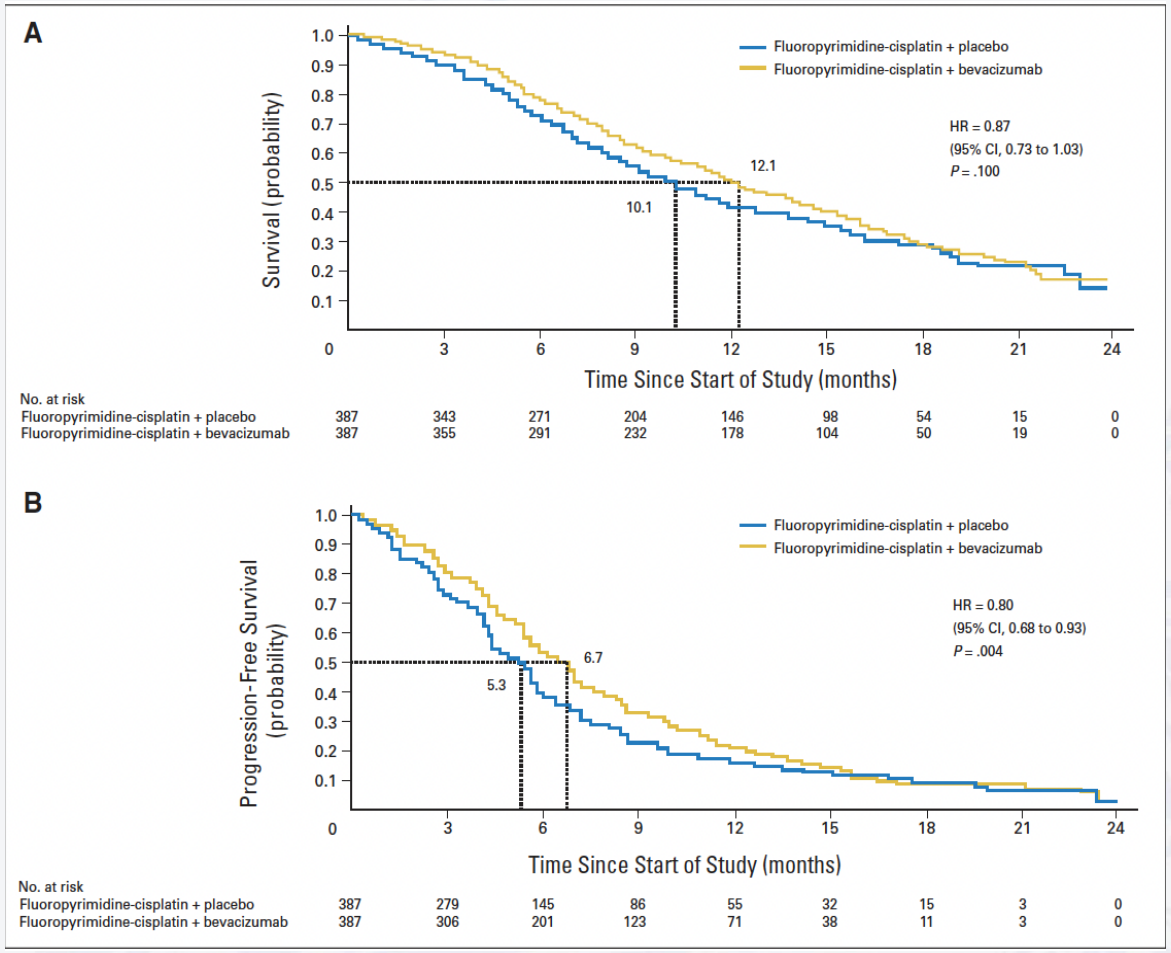
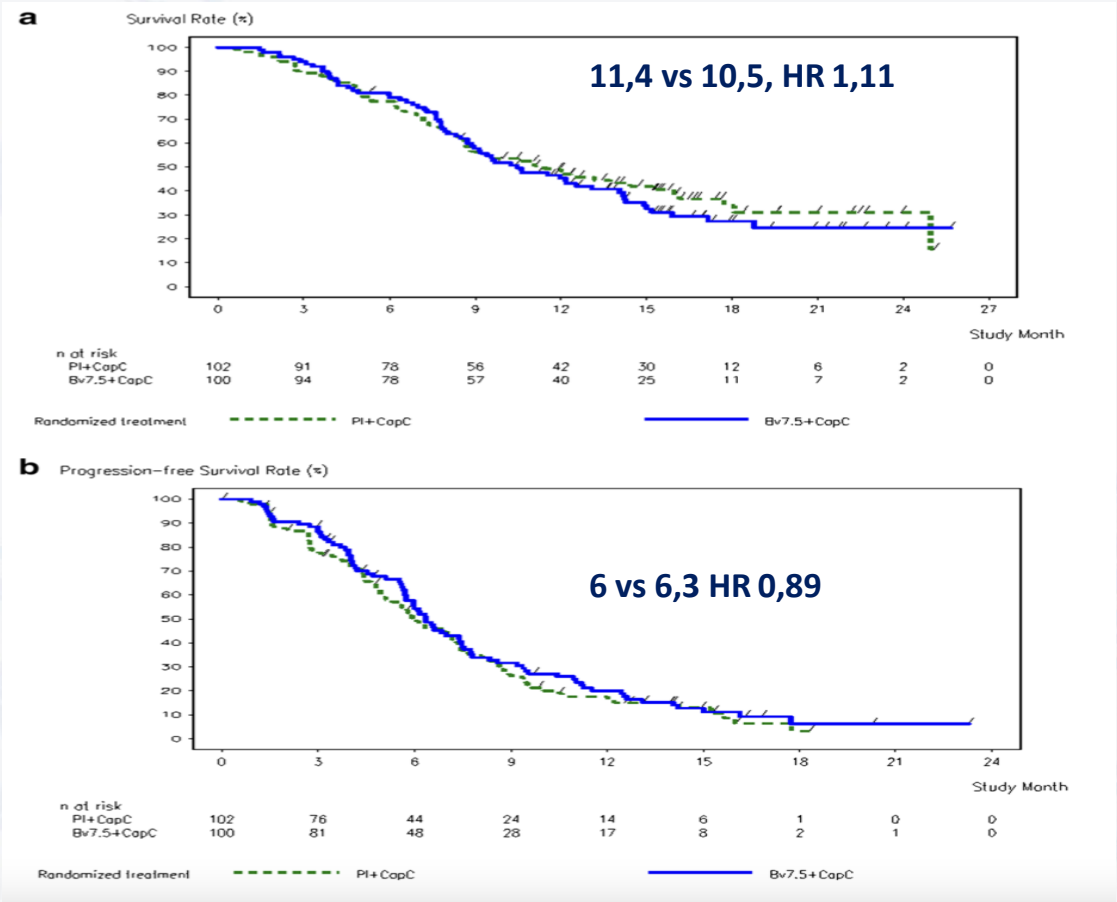


Table 4. Baseline Characteristics and Efficacy by Region (intention-to-treat population)

	Asia				Europe				Pan-America			
	Fluoropyrimidine-Cisplatin +				Fluoropyrimidine-Cisplatin +				Fluoropyrimidine-Cisplatin +			
	Bevacizumab (n = 188)	Placebo (n = 188)			Bevacizumab (n = 125)	Placebo (n = 124)			Bevacizumab (n = 74)	Placebo (n = 75)		
Efficacy												
Median overall survival, months	13.9	12.1	0.97	0.75 to 1.25	11.1	8.6	0.85	0.63 to 1.14	11.5	6.8	0.63	0.43 to 0.94
Median progression-free survival, months	6.7	5.6	0.92	0.74 to 1.14	6.9	4.4	0.71	0.54 to 0.93	5.9	4.4	0.65	0.46 to 0.93
Response rate	142	132			109	110			60	55		
Overall response rate	47.9	45.5	1.10	0.69 to 1.77	41.3	28.2	1.79	1.02 to 3.15	50.0	36.4	1.75	0.83 to 3.69

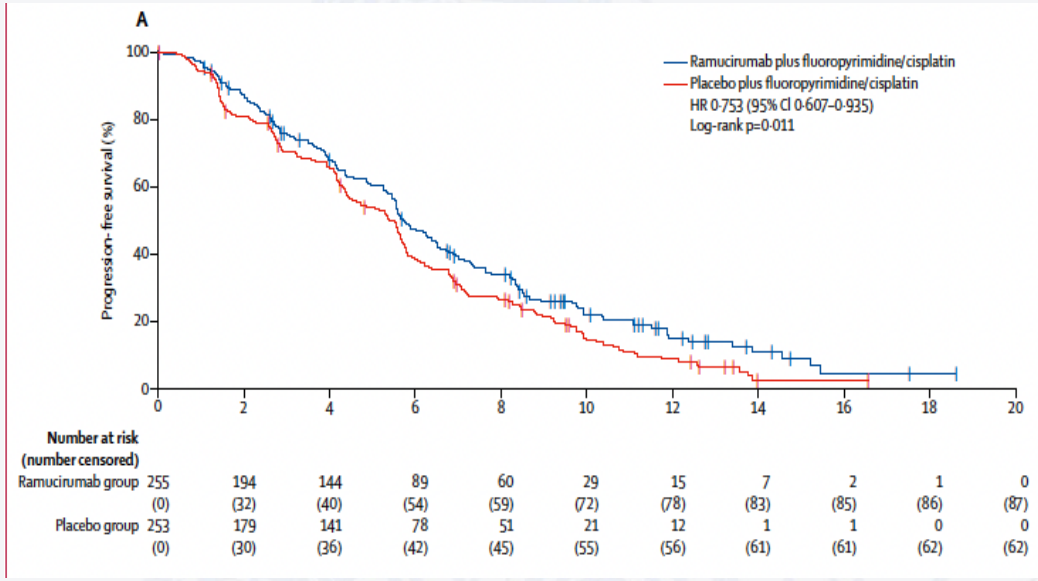
Ohtsu A, J Clin Oncol. 2011 Oct 20;29(30):3968-76

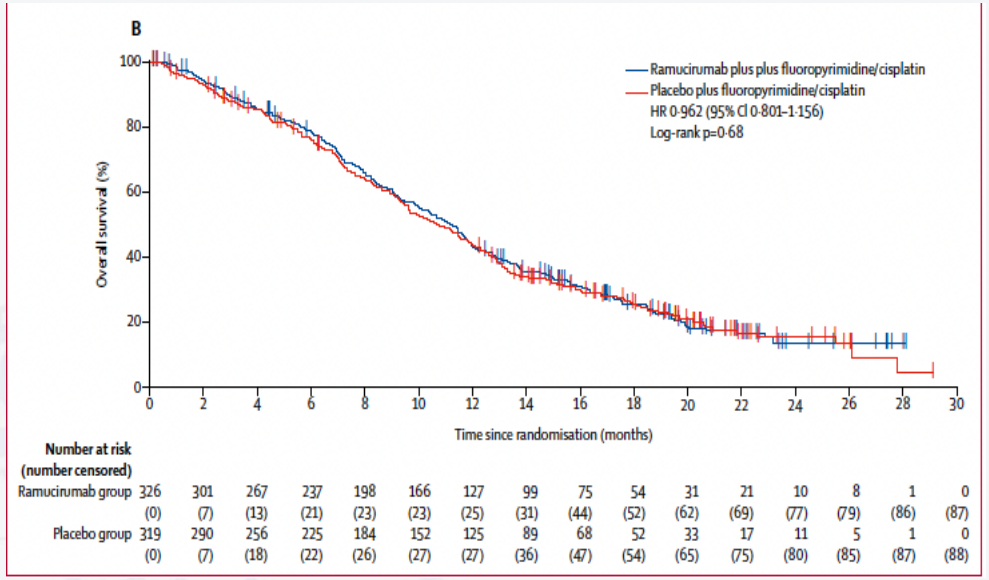
1. **Bevacizumab (AntiVEGF - A)** no impacta en SG (Fase III AVATAR, China; n:202)



Shen L, Gastric Cancer. 2015 Jan;18(1):168-76.

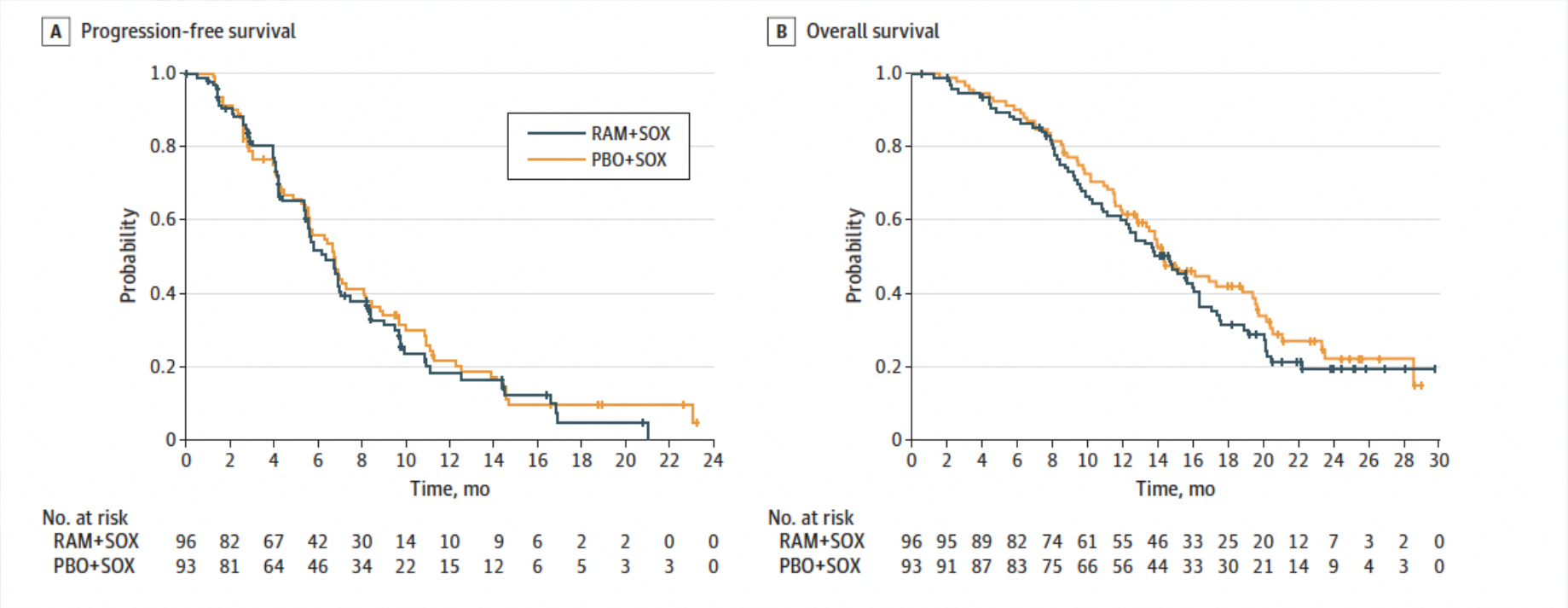
2. **Ramucirumab (AntiVEGFR - 2)** no impacta en SG (Fase III RAINFALL, n:645)





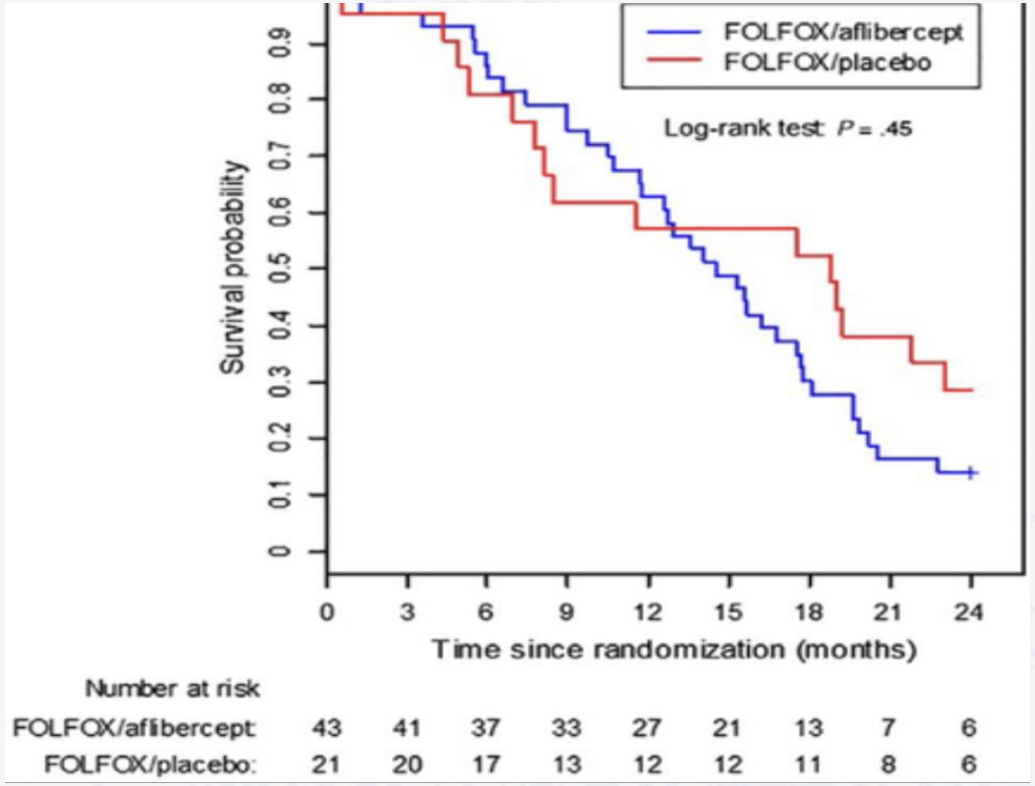
Fuchs CS, Lancet Oncol. 2019 Mar;20(3):420-435.

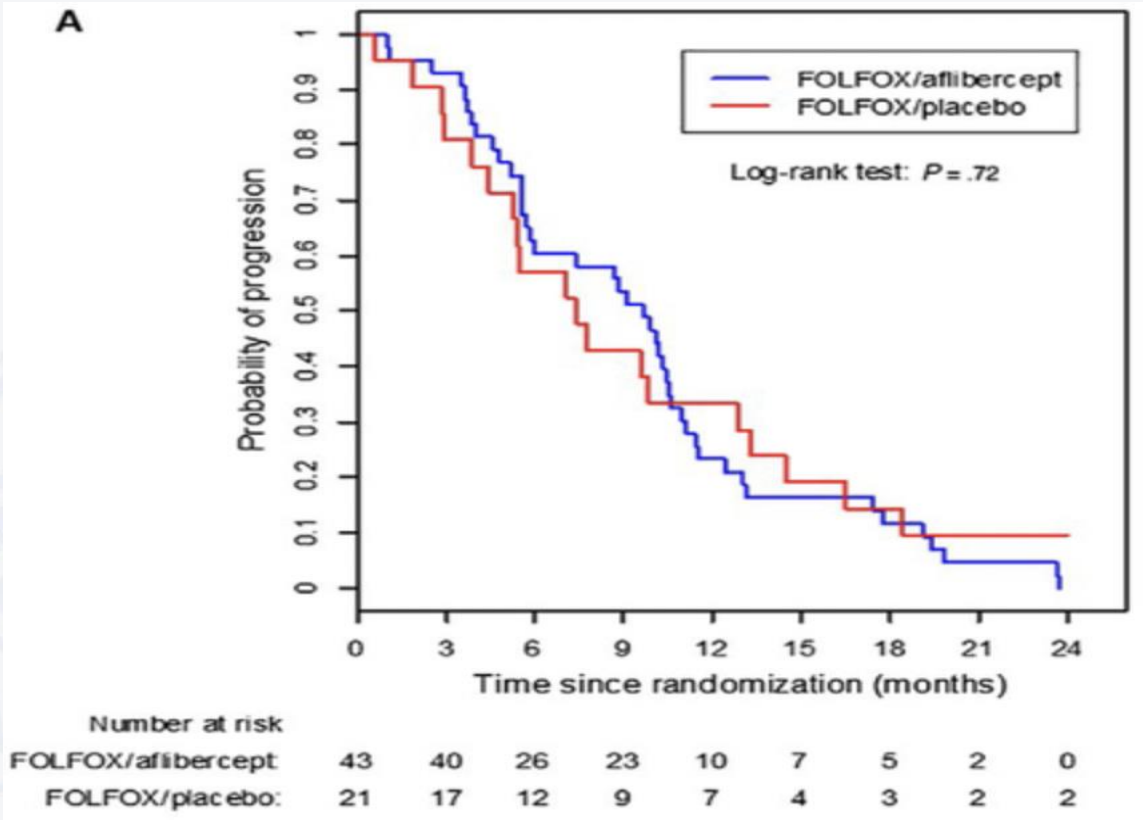
2. **Ramucirumab (AntiVEGFR - 2)** no impacta en SG (Fase II RAINSTORM, China, n:189)



Yoshikawa T,. JAMA Netw Open. 2019 Aug 2;2(8):e198243.

3. **Aflibercept,** combinado con FOLFOX no impacta en SG (Fase II) no impacta ni en SG ni en SLP (n:64)





Cleary JM, Cancer. 2019 Jul 1;125(13):2213-2221

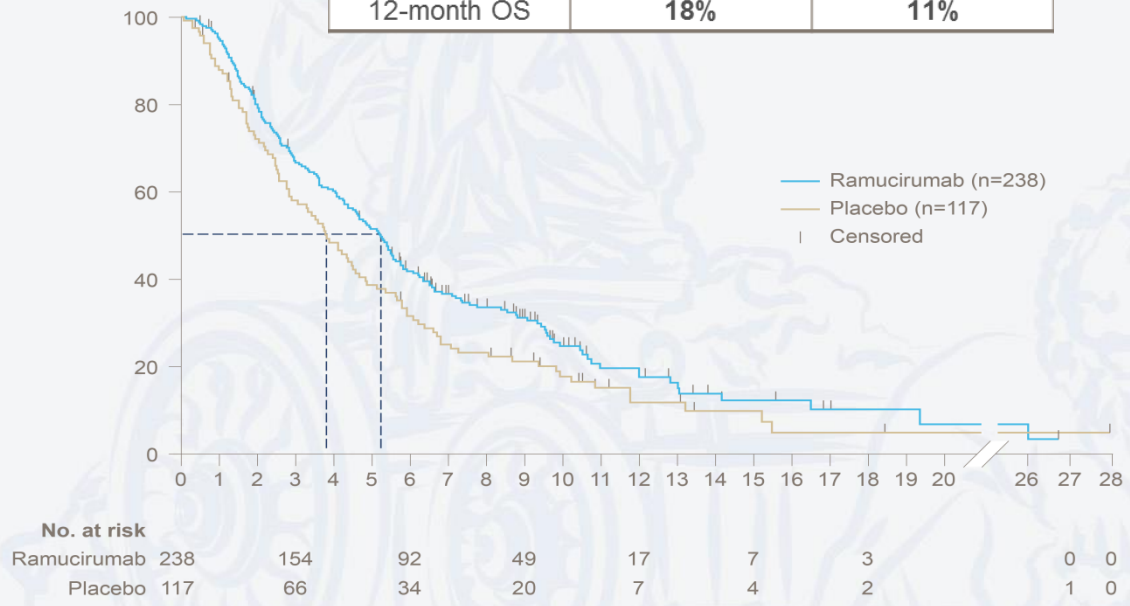
SEGUNDA LÍNEA: ¡Éxito !

1. Un 40% llegarán a 2L y diferentes citotóxicos demostraron beneficio frente a PLACEBO.

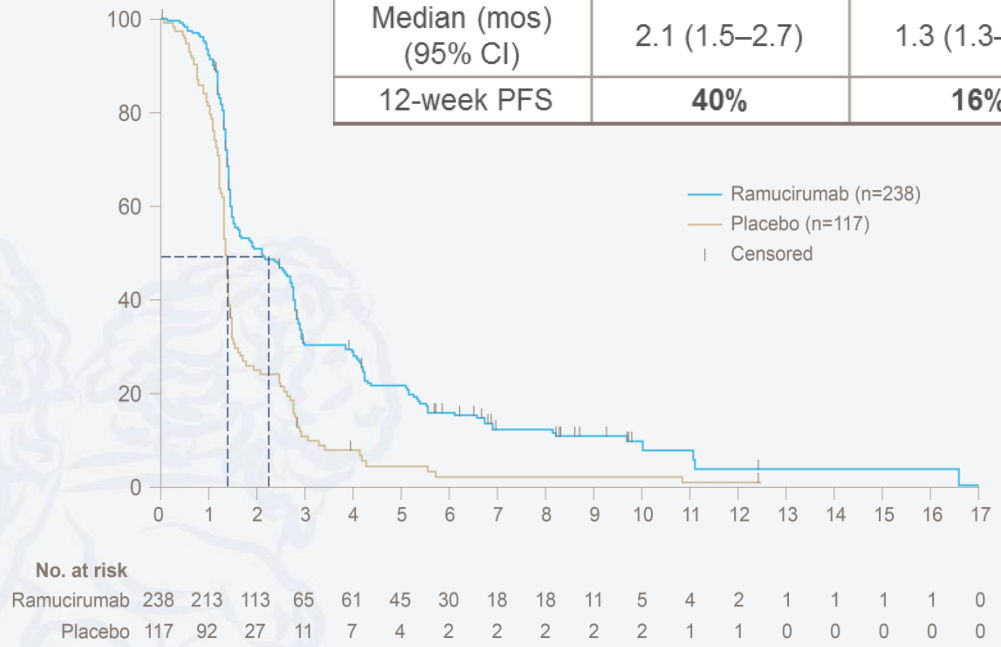
Publicación	Estudio, País	N	Droga	SG	Incremento
Thuss-Patience PC. Eur J Ca 2011	AIO Alemania	40	Irinotecan Vs **BSC**	4 vs 2.4 P 0.012	HR 0.48 1.6 meses
Kang JH. JCO 2012	Corea	202	Irino/Docetaxel Vs **BSC**	5.3 vs 3.8 P 0.007	HR 0.66 1.5 meses
Ford HE. Lancet Oncol 2014	COUGAR02 Reino Unido	168	Docetaxel Vs **BSC**	5.2 vs 3.6 P 0.01	HR 0.67 1.6 meses
Hironaka JCO 2013	WJOG 4007	223	Paclitaxel vs Irinorecán	9.5 vs 8.4 P:0.38	HR 1.13 Menos tóxico paclitaxel

2. **Ramucirumab (antiVEGFR2) es superior a placebo** (Fase III, REGARD, n:355).

HR (95% CI)=0.776 (0.603–0.998) *p* value=0.047		
	Ramucirumab	Placebo
Patients / Events	238 / 179	117 / 99
Median (mos) (95% CI)	5.2 (4.4–5.7)	3.8 (2.8–4.7)
6-month OS	**42%**	**32%**
12-month OS	**18%**	**11%**



HR (95% CI)=0.483 (0.376–0.620)		
Log rank *p* value (stratified) <0.0001		
	Ramucirumab	Placebo
Patients / Events	238 / 199	117 / 108
Median (mos) (95% CI)	2.1 (1.5–2.7)	1.3 (1.3–1.4)
12-week PFS	**40%**	**16%**



Fuchs CS et al. Lancet 2014;383:31–39

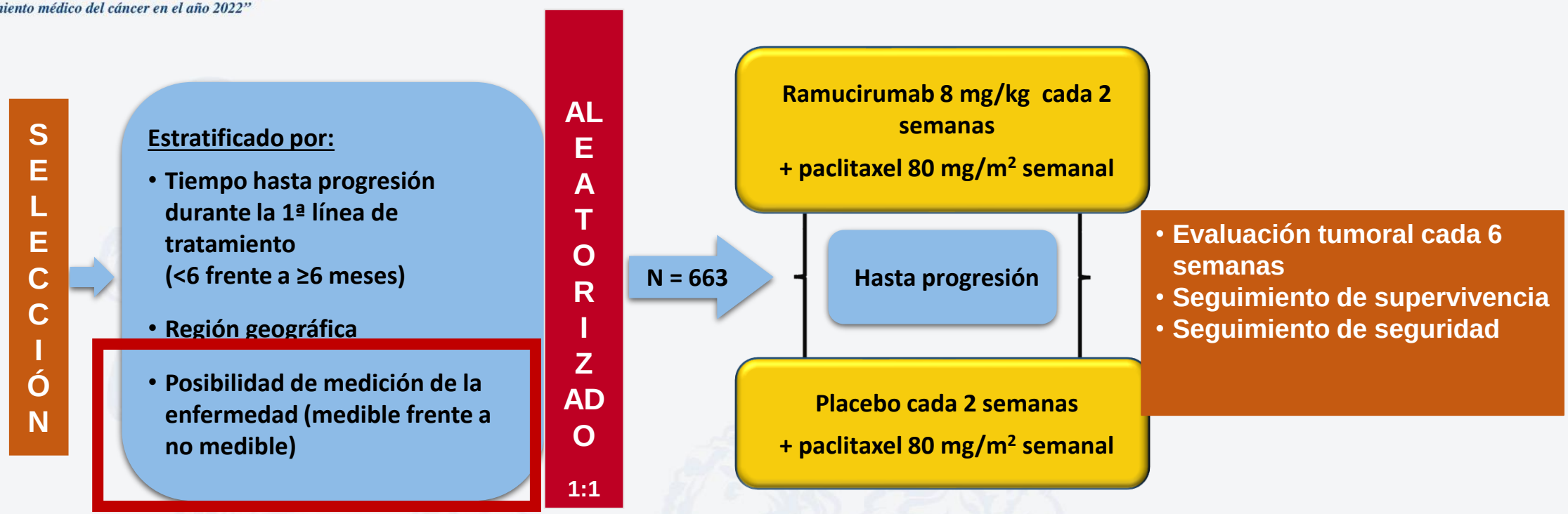
2. **Ramucirumab (antiVEGFR2) es superior a placebo** (Fase III, REGARD, n:355).

	Ramucirumab (n=238)	Placebo (n=117)
Respuesta Completa	1 (<1 %)	0
Respuesta Parcial	7 (3 %)	3 (3%)
Enfermedad Estable	108 (45 %)	24 (21%)
Enfermedad Progresiva	78 (33%)	63 (54%)
Sin evaluación	44 (18 %)	27 (23%)

Fuchs CS et al. Lancet 2014;383:31–39

2. **Ramucirumab (antiVEGFR2)/paclitaxel es superior a paclitaxel en SG,SLP y TR** (Fase III, RAINBOW, n:665).

RAINBOW : Diseño



Población de pacientes

- Adenocarcinoma gástrico o de la UGE (metastásico o localmente avanzado y no resecable)
- Tratamiento de primera línea con doblete platino / fluoropirimidina con o sin una antraciclina
- Los pacientes experimentaron progresión durante la primera línea de tratamiento o en los 4 meses siguientes
- EG ECOG 0/1
- Sin metástasis en el SNC

Wilke H et al. Lancet Oncol 2014;15:1224–1235

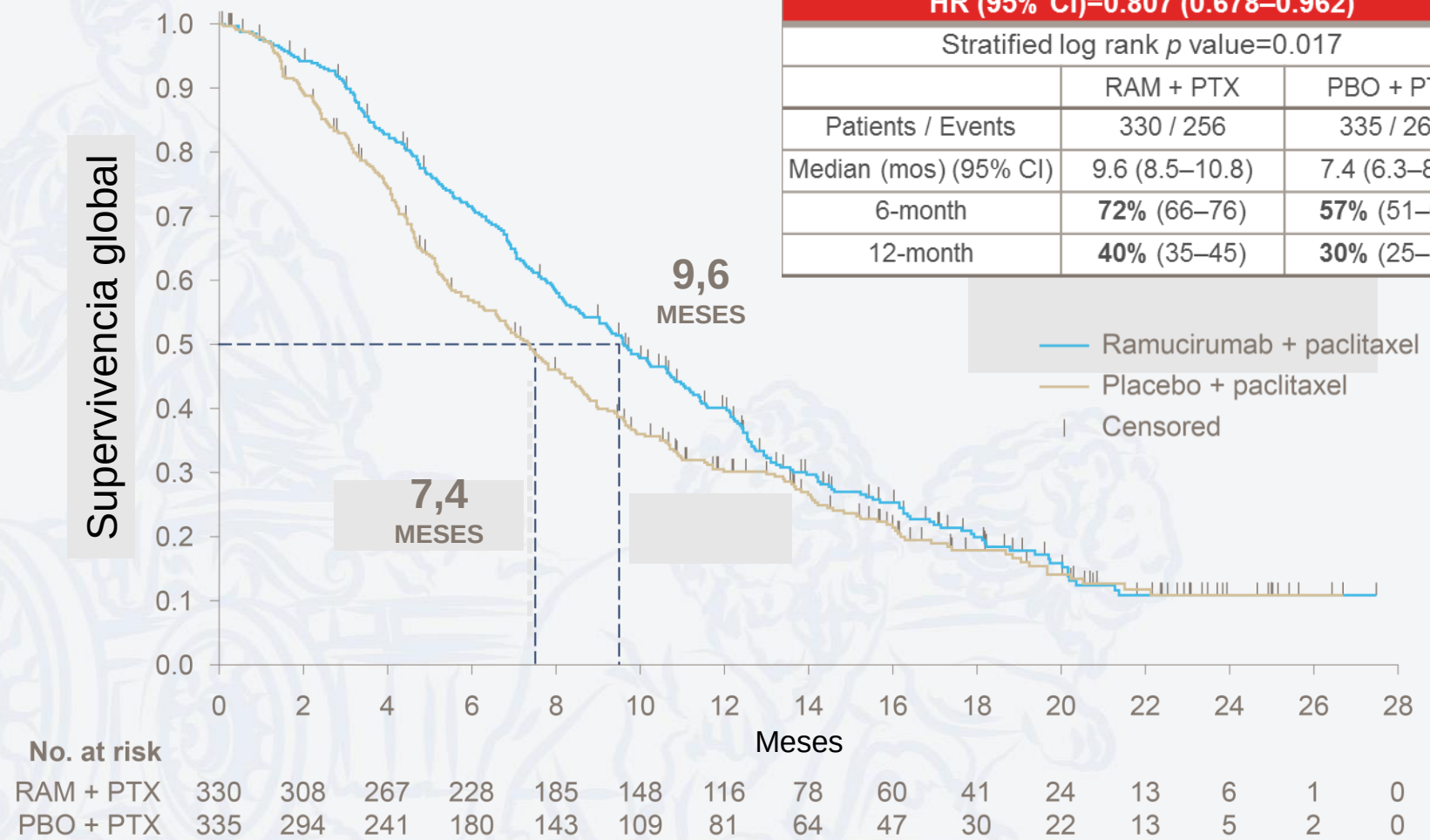
RAINBOW :Características basales

		Ram+Pac N=330 n (%)		Plc+Pac N=335 n (%)	
Tipo de cáncer	**Gástrico**	**264**	**(80,0)**	**264**	**(78,8)**
	UGE	**66**	**(20,0)**	**71**	**(21,2)**
Subtipo histológico	**Intestinal**	**145**	**(43,9)**	**135**	**(40,3)**
	Difuso	**115**	**(34,8)**	**133**	**(39,7)**
	Mixto	**21**	**(6,4)**	**14**	**(4,2)**
	Desconocido/ausente	**49**	**(14,8)**	**53**	**(15,8)**
Tumor primario	**Presente**	**209**	**(63,3)**	**209**	**(62,4)**
Número de sitios metastásicos	**0-2**	**209**	**(63,3)**	**232**	**(69,3)**
	≥ 3	**121**	**(36,7)**	**103**	**(30,7)**
Metástasis peritoneales	**Sí**	**163**	**(49,4)**	**152**	**(45,4)**
Extensión de la enfermedad	**Metastásica**	**324**	**(98,2)**	**324**	**(96,7)**
Pérdida de peso (Pasados 3 meses)	**< 10 %**	**277**	**(83,9)**	**286**	**(85,4)**
	≥ 10 %	**53**	**(16,1)**	**47**	**(14,0)**

Wilke H et al. Lancet Oncol 2014;15:1224–1235

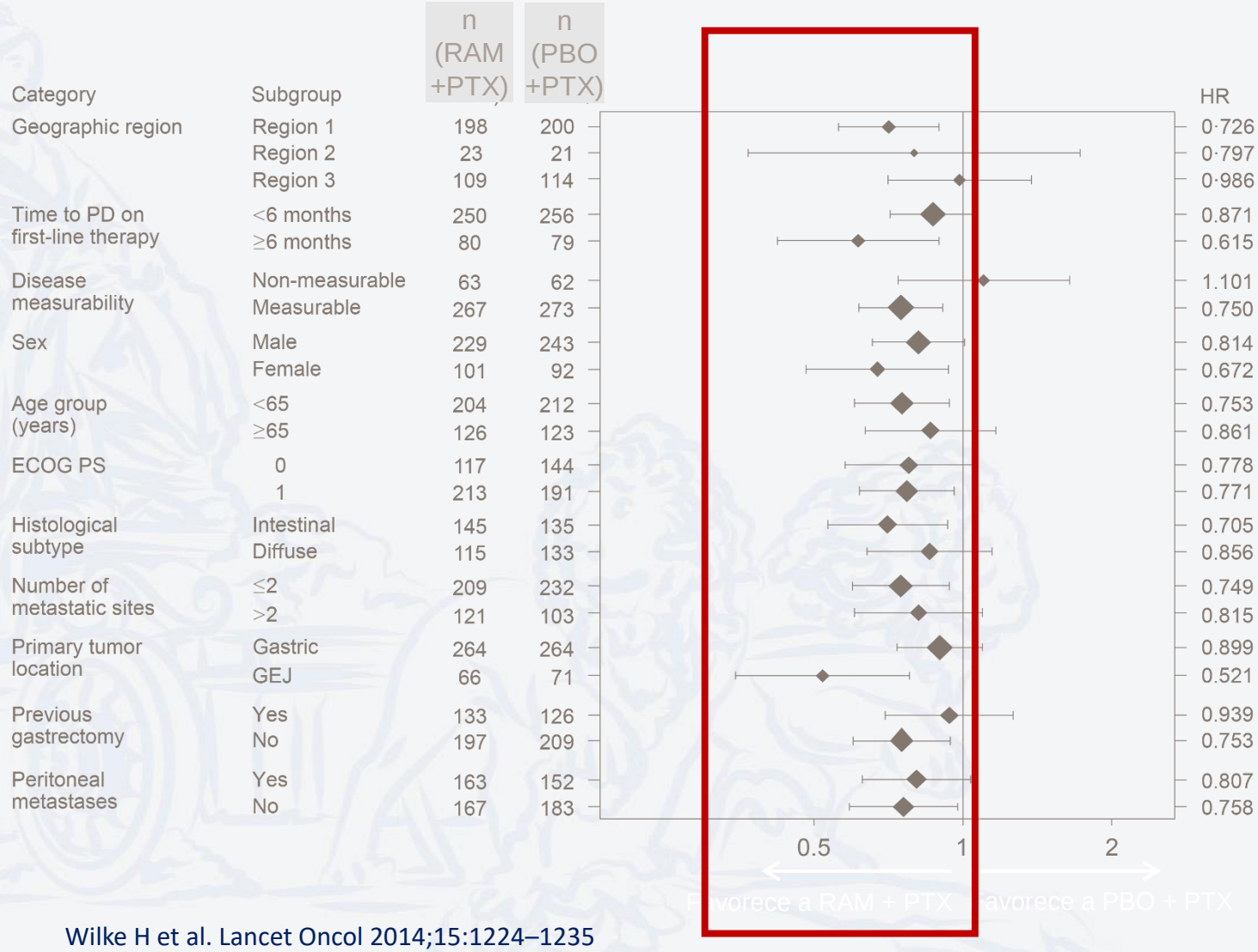
RAINBOW : SG

HR (95% CI)=0.807 (0.678–0.962)		
Stratified log rank *p* value=0.017		
	RAM + PTX	PBO + PTX
Patients / Events	330 / 256	335 / 260
Median (mos) (95% CI)	9.6 (8.5–10.8)	7.4 (6.3–8.4)
6-month	**72%** (66–76)	**57%** (51–62)
12-month	**40%** (35–45)	**30%** (25–35)



Wilke H et al. Lancet Oncol 2014;15:1224–1235

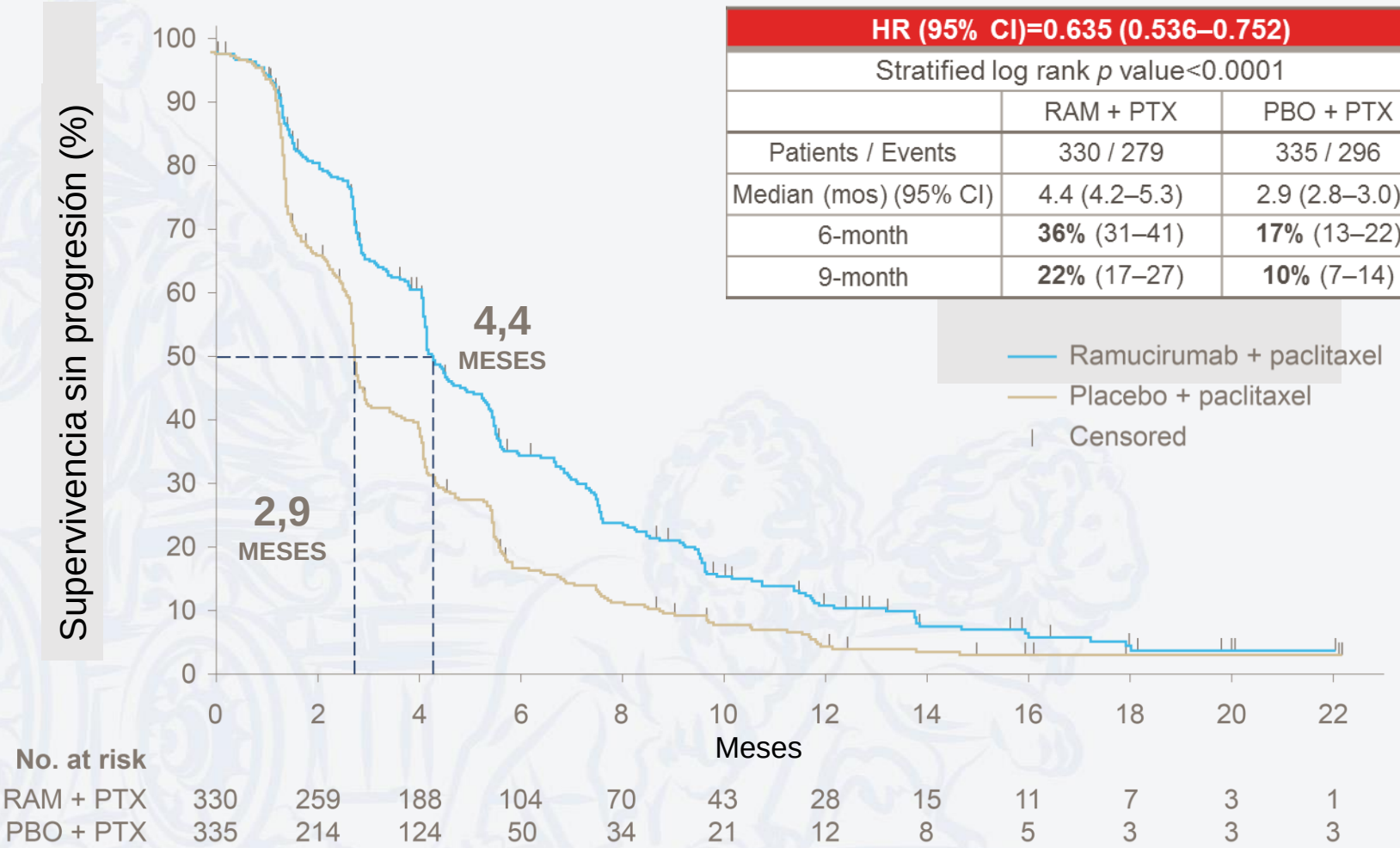
RAINBOW : Todos los subgrupos se benefician



Wilke H et al. Lancet Oncol 2014;15:1224–1235

RAINBOW : SLP

HR (95% CI)=0.635 (0.536–0.752)		
Stratified log rank *p* value<0.0001		
	RAM + PTX	PBO + PTX
Patients / Events	330 / 279	335 / 296
Median (mos) (95% CI)	4.4 (4.2–5.3)	2.9 (2.8–3.0)
6-month	**36%** (31–41)	**17%** (13–22)
9-month	**22%** (17–27)	**10%** (7–14)

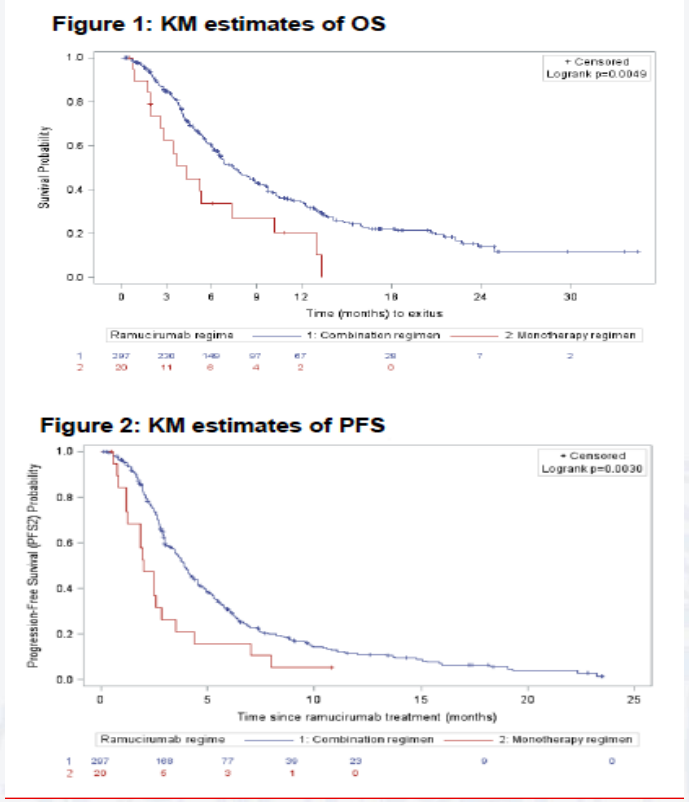


WHAT ELSE….?

SEGUNDA LÍNEA: lecciones aprendidas

1.Estudios de Vida Real:RAMIS y RAMOSS

1. Los **estudios de vida real (RAMIS, n:317)** corroboran los hallazgos de los Fase III **RAINBOW y REGARD**



SG 7.2 ms (7.4 combinación vs 4.3 monoterapia)

SLP 3.8 ms (3.9 combinación vs 2 monoterapia)

Tpo a PE (TTP) 4.3ms (4.5 combinación y 2.5 monoterapia)

RR medible (2.9% CR y 17.6% PR):19.2% . RAINBOW 28%

RR no medible: 35.3% no progresión

Solo 2.2% ajustes de dosis de ramucirumab

Longo F et al. Future Oncol. 2021 Feb 16. doi: 10.2217/fon-2020-1216.

P43

Ramucirumab effectiveness in patients with advanced gastric cancer (AGC) or gastro-esophageal junction (GEJ) adenocarcinoma in clinical practice in Spain: *Sub-analysis of RAMIS study*

N:173

Subanálisis en pacientes tratados en combinación, ECOG 0/1

SG mediana: 10.3 meses

SLP mediana : 4.9 meses

Figure 1. KM estimates for OS

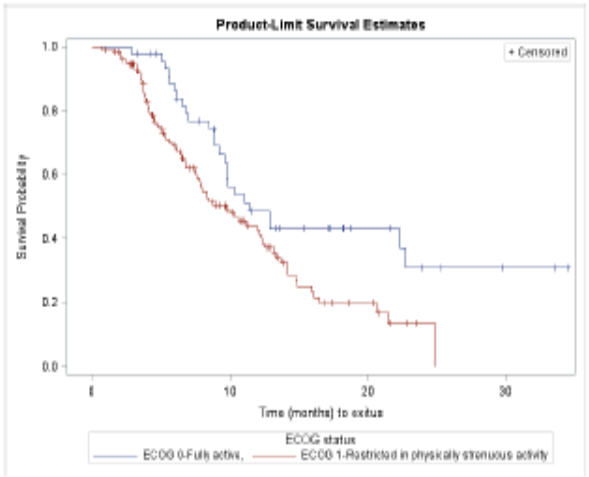
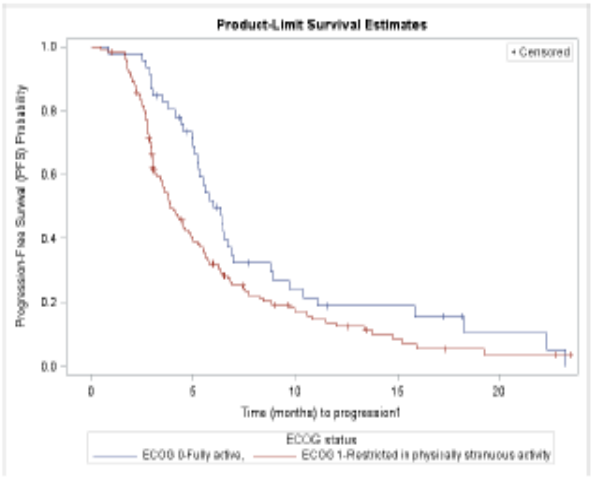


Figure 2. KM estimates for PFS



Longo et al. ESMOWGI 2020

1. Los **estudios de vida real (RAMOSS, n:177)** corroboran los hallazgos de los Fase III **RAINBOW y REGARD**

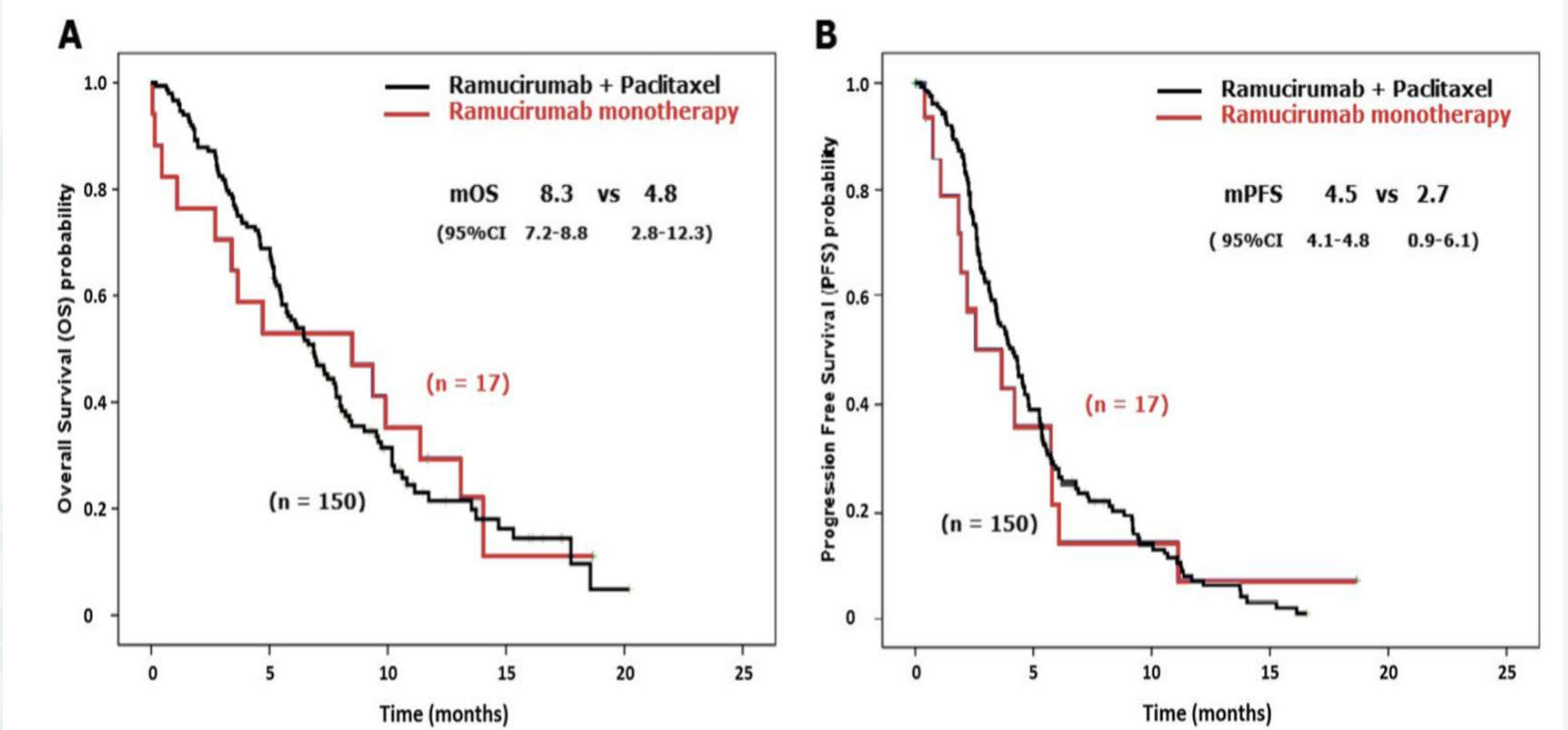


Fig. 3 Kaplan–Meier plots for OS (A) and PFS (B) according to treatment

Di Bartolomeo M,. Target Oncol. 2018 Apr;13(2):227-234.

2.Población Her 2

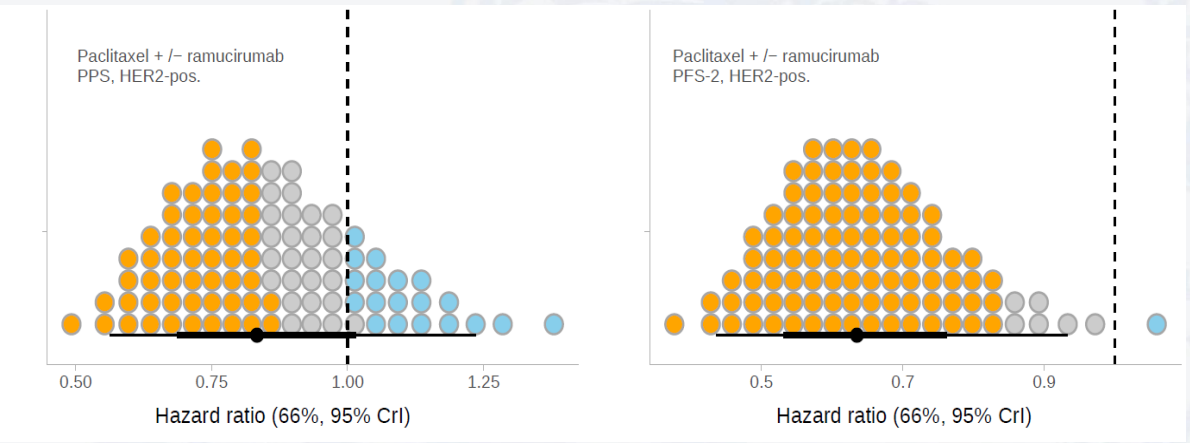
2. La **población Her 2** se beneficia del empleo de paclitaxel y ramucirumab

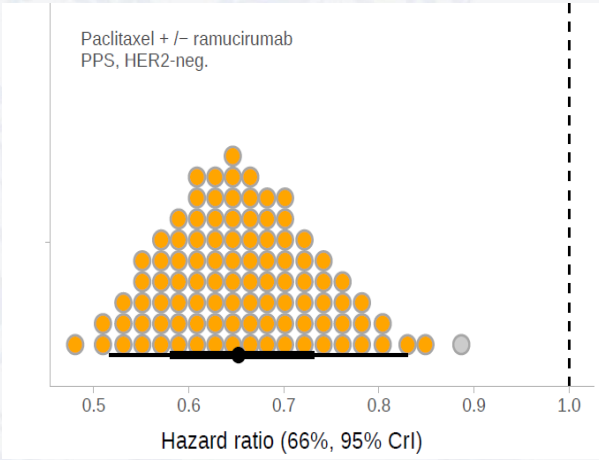
Bayesian models: **HER2-positive tumors.**

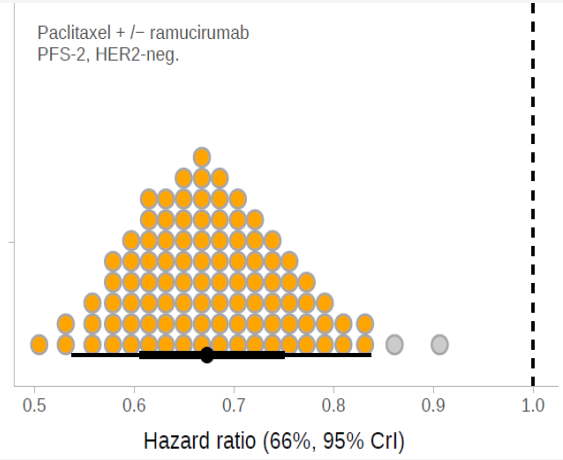
The posterior probability of benefit (HR <1) with **paclitaxel-ramucirumab** vs paclitaxel in terms of **OS-2** is **81%,** with **HR 0.83** (95% CrI, 0.56-1.23). The dot plot shows the posterior probability distribution for OS. For **PFS-2,** the probability of benefit (HR<1) with paclitaxel-ramucirumab vs paclitaxel is **99%**, with HR 0.63 (95% CrI, 0.43-0.92).

Bayesian models: **HER2-negative tumors.**

The posterior probability of benefit (HR <1) with **paclitaxel-ramucirumab** vs paclitaxel in terms of **OS-2** is **100%**, with **HR 0.65** (95% CrI, 0.51-0.82). The dot plot shows the posterior probability distribution for OS. For PFS-2, the probability of benefit (HR<1) with paclitaxel-ramucirumab vs paclitaxel is **100%,** with HR 0.67 (95% CrI, 0.54-0.83).



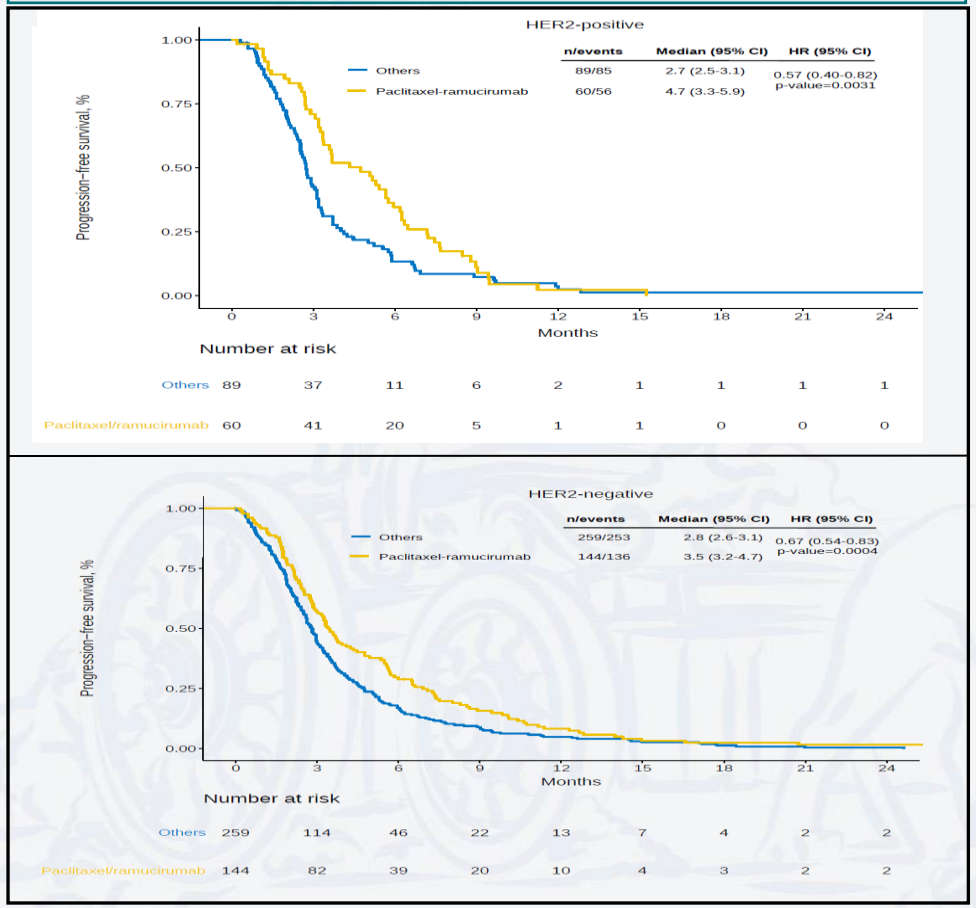


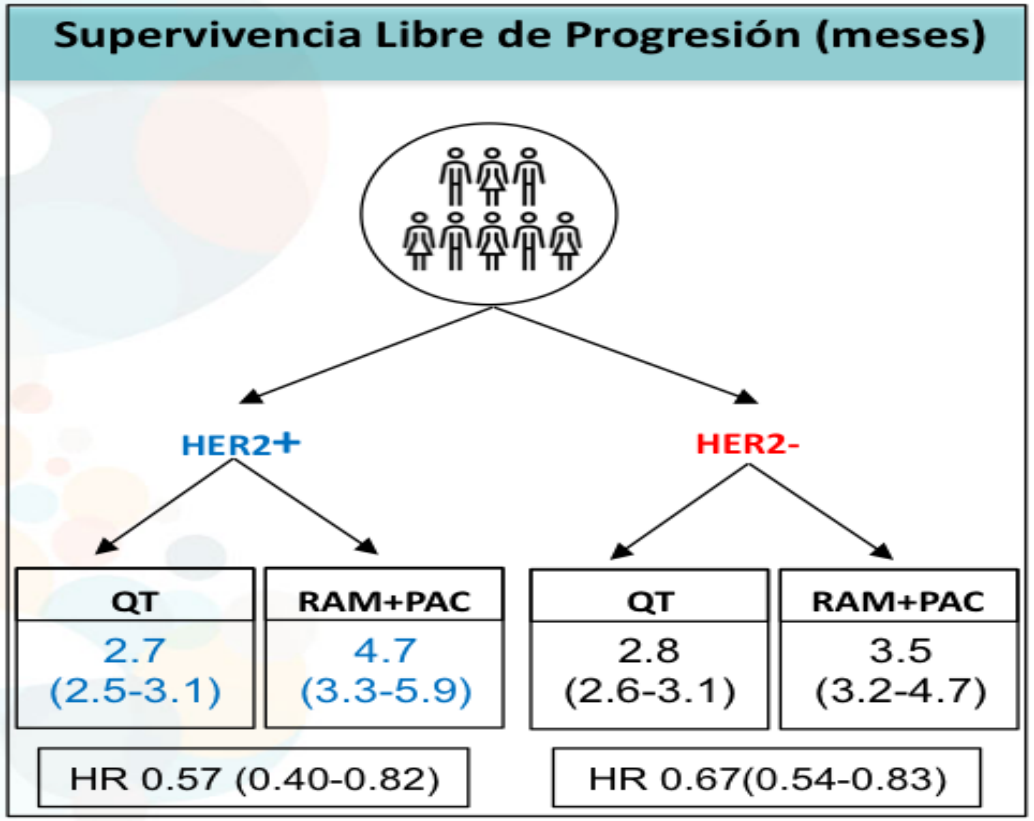


Cotes Sanchis A. PLOSone 2020; 15(7):e0235848.

3. El beneficio es independiente del estatus HER 2 (estudio RAINHER,SLP)

Supervivencia Libre de Progresión (SLP2)



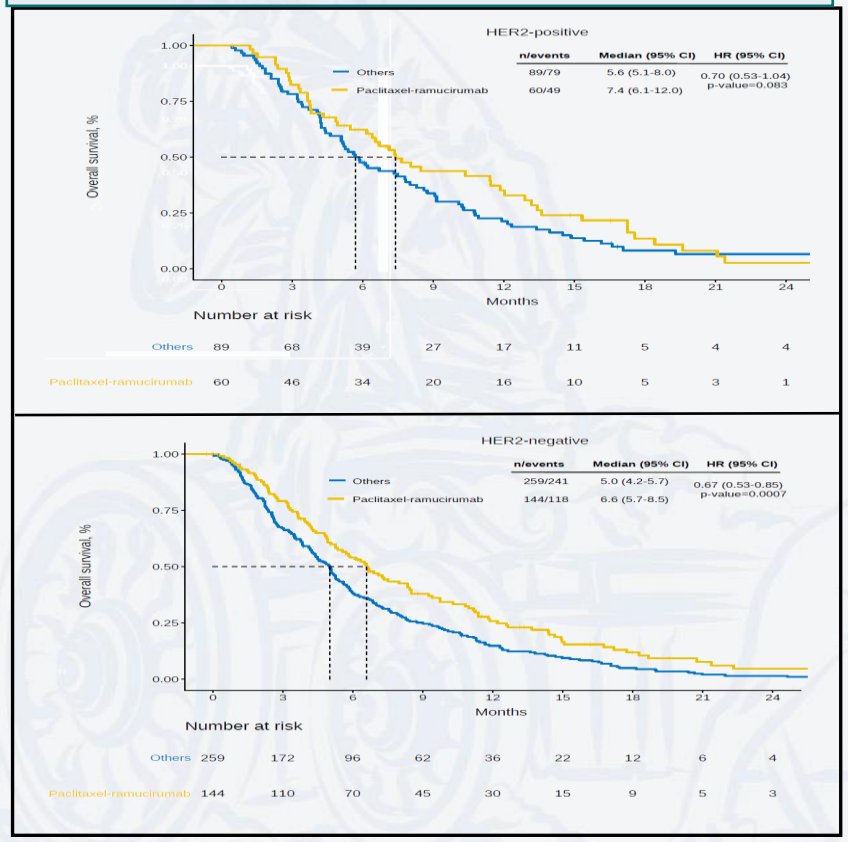


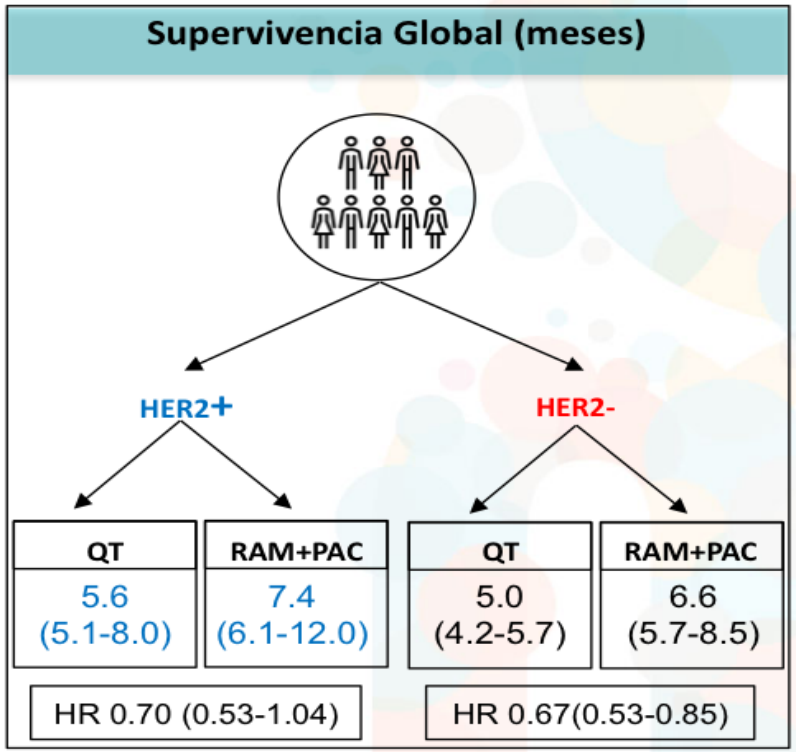
No se encontró interacción entre el estado de **HER2** y el efecto del tratamiento **en SLP2 (p=0.459)**

Gallego J, et al. Oral Presentation, SEOM 2021

3. El beneficio es independiente del estatus HER 2 (estudio RAINHER, SG)

Supervivencia Global (SG2)





No se encontró interacción entre el estado de **HER2** y el efecto del tratamiento **en SG2 (p=0.822)**

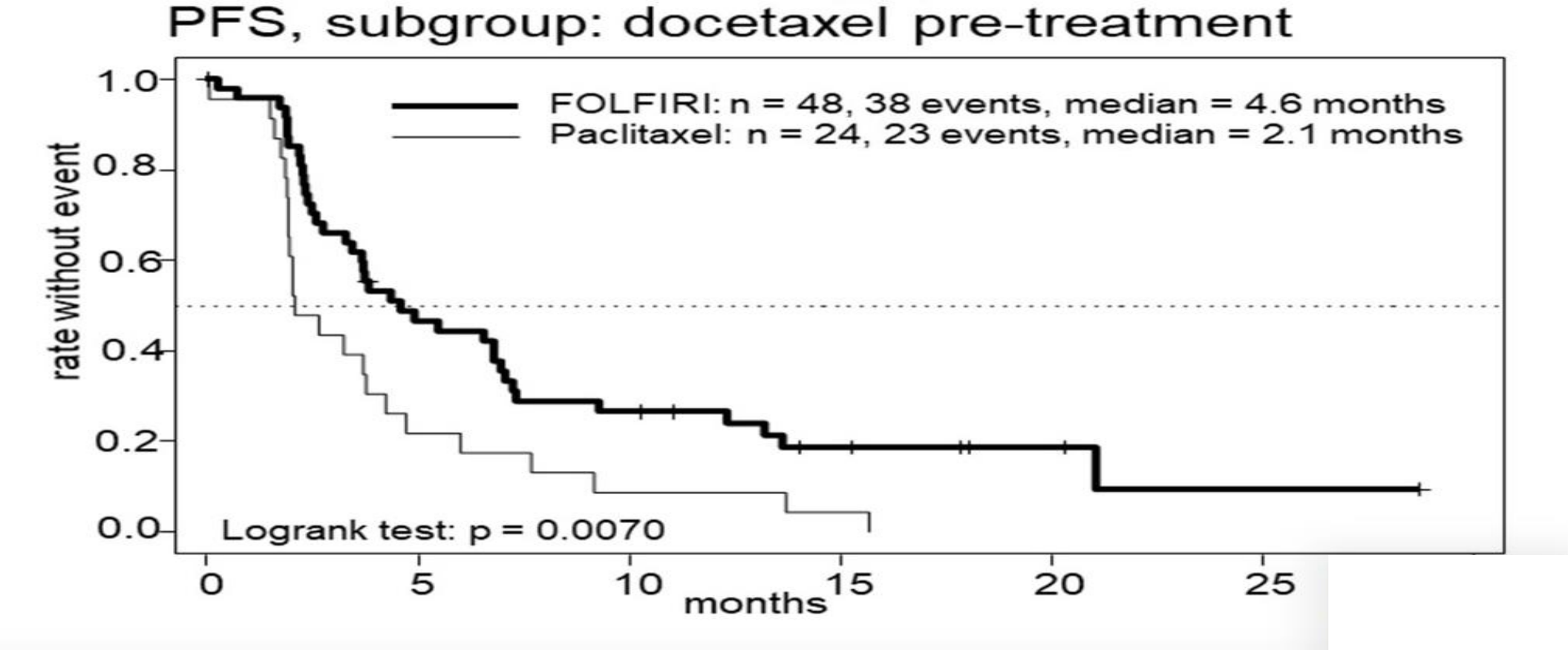
Gallego J, et al. Oral Presentation, SEOM 2021

Los resultados sugieren que el **beneficio en supervivencia del tratamiento de 2L** en AG y de UEG avanzado, RAM+PAC o QT, es **independiente** del estado de **HER2**

El presente análisis **complementa** con datos de **práctica clínica real** los resultados del ensayo clínico **RAINBOW**.

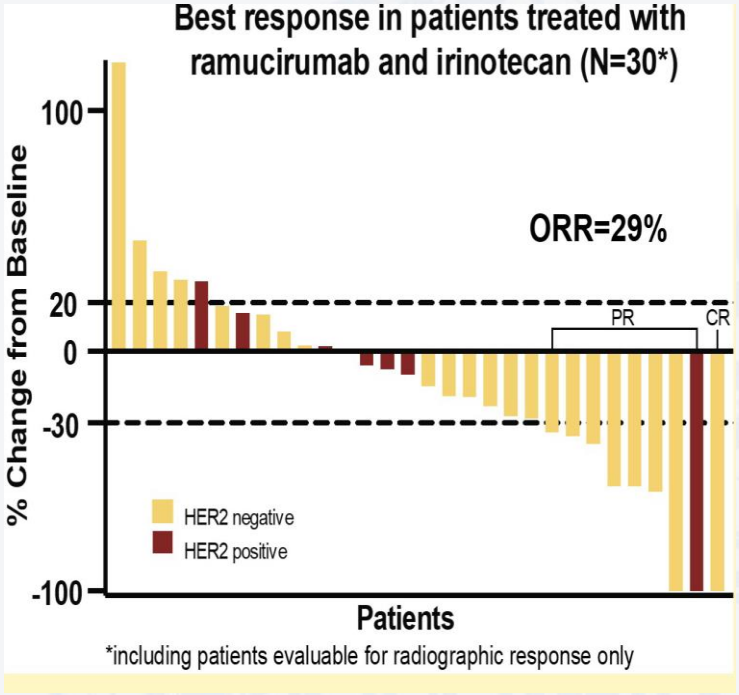
3.Otras quimioterapias de Combinación

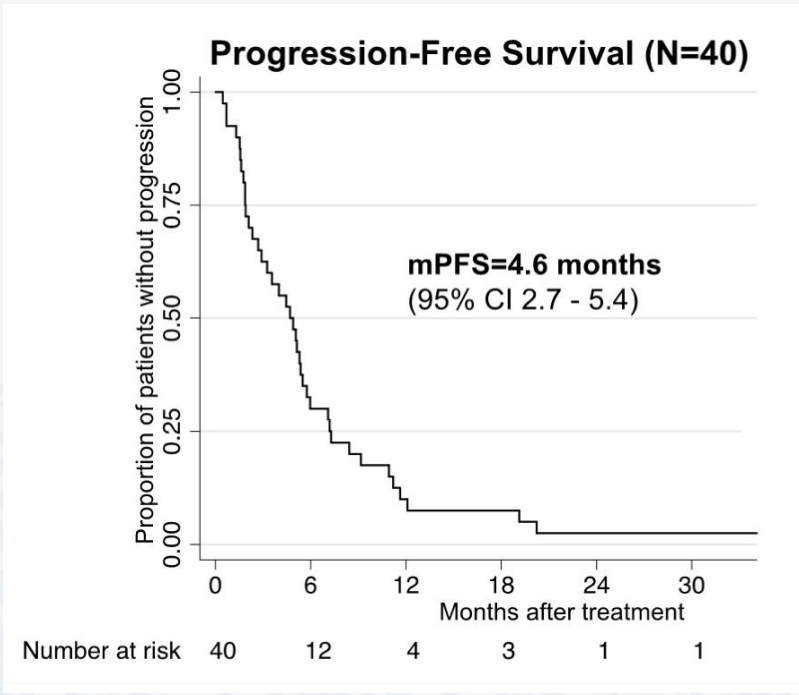
4. FOLFIRI/ramucirumab (Fase II RAMIRIS, n:101) no difiere en eficacia (SG, SLP) comparado con paclitaxel /ramucirumab

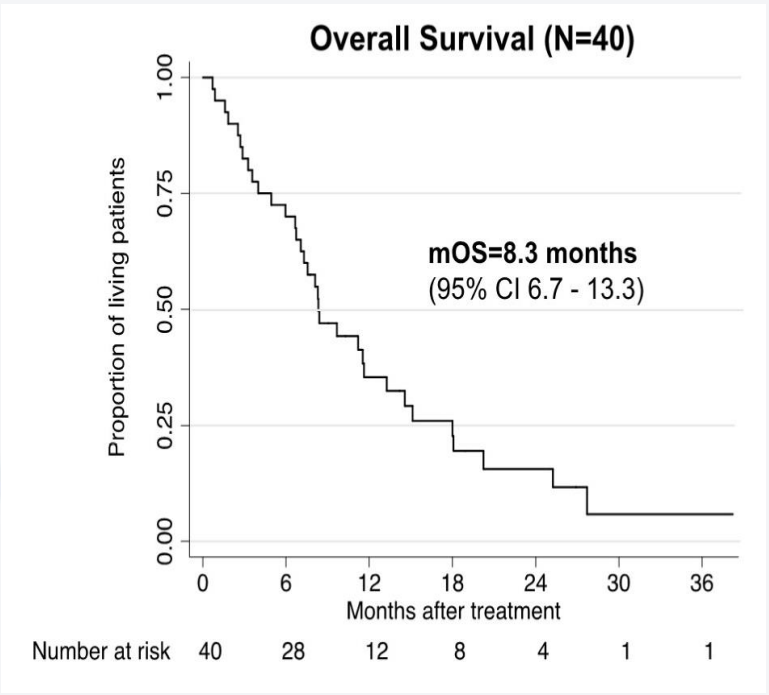


Lorenzen.J Clin Oncol 38: 2020 (suppl; abstr 4514)

4. Ramucirumab/Irinotecán (Fase II), es eficaz y opción a consideran en pacientes con neurotoxicidad g≥2 (n:40)



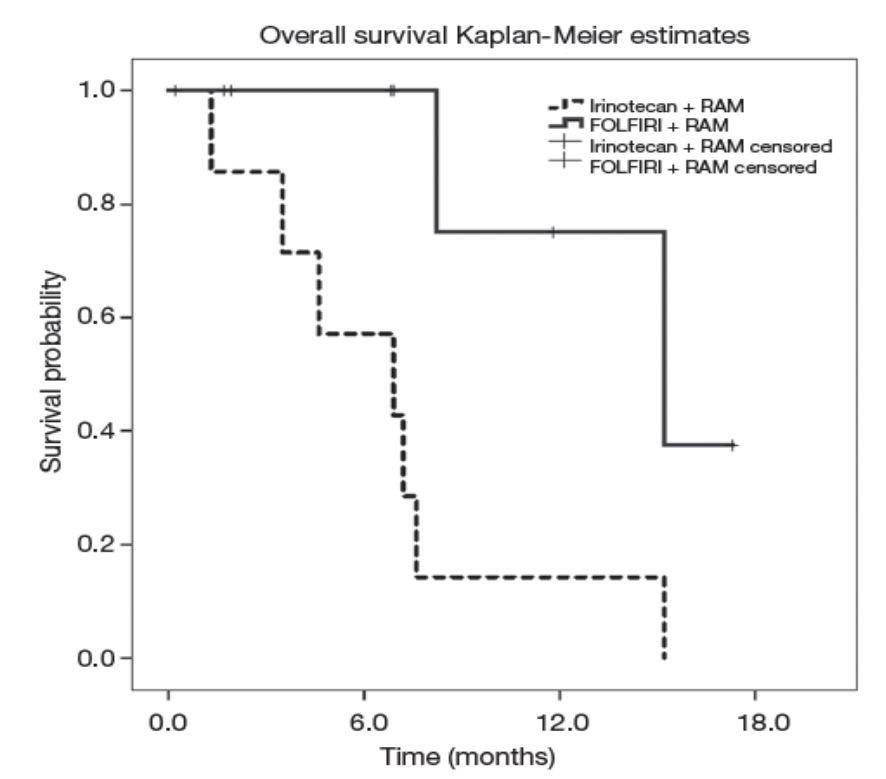




Park et al. ASCOGI 2022.Abstract 284.F3

Ramucirumab plus FOLFIRI or irinotecan as second-line therapy in advanced or metastatic gastric or gastroesophageal junction adenocarcinoma

Verena Schlintl, Florian Huemer, Richard Greil, Lukas Weiss



N:16

FOLFIRI-RAM **mayor SG** comparado con irinotecan- RAM **15.2 meses (95% CI: 4.7–25.7) *vs*. 6.9 meses** (95% CI: 1.0–12.8), P=0.01

No diferencia estadísitica en SLP (5.4 *vs*. 4.6 months, P=0.19).

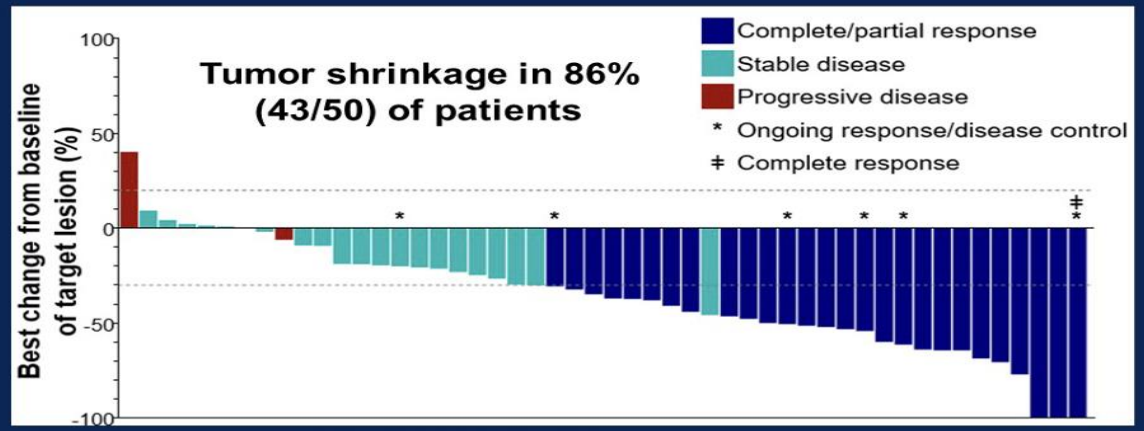
Schlintl V, Huemer F, Greil R, Weiss L. *Journal of Gastrointestinal Oncology*. 2021;12(2).

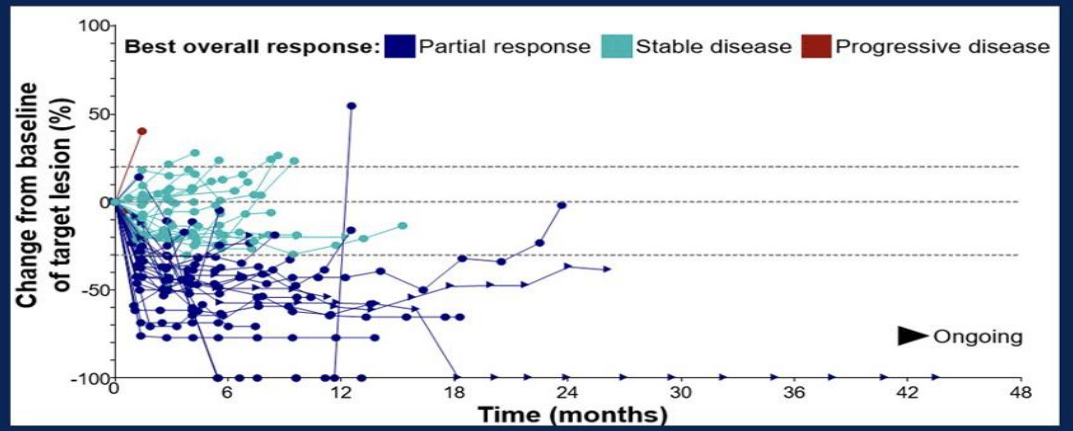
4. Estudio HER/RAM (Asiático) fase I/II que combina paclitaxel/ramucirumab y trastuzumab (n:50)

Updated Efficacy

Best response	No	%
Complete response	1	2
Partial response	26	52
Stable disease	21	42
Progressive disease	2	4
Objective response	**27**	**54**
Disease control	**48**	**96**

- Median follow-up duration (range): 27.5 months (17.4-37.6)
- mPFS: 7.1months (95% CI= 4.8-9.4)
  Met the primary end point
- mOS: 13.6months (95% CI=9.4-17.7)
- mDOR: 6.8months (95% CI=1.5-11.9)

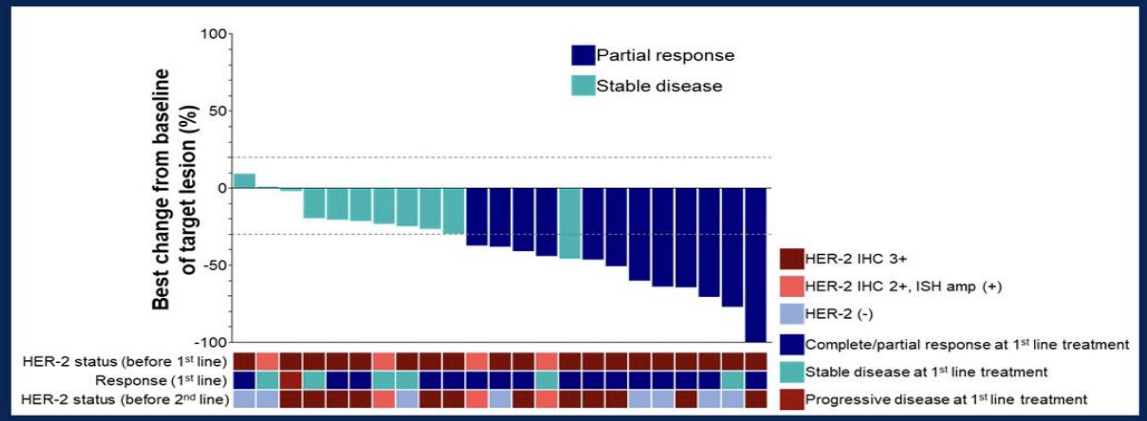


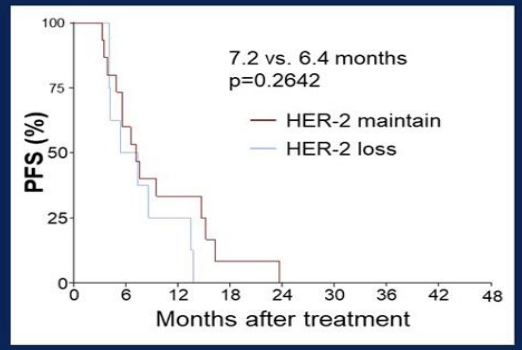


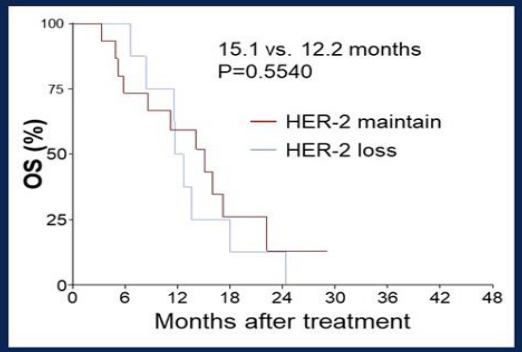
- Data cut off date: 2021- 09-07

4. Estudio HER/RAM fase I/II que combina paclitaxel/ramucirumab y trastuzumab (n:50)

Tumor response and survival according to HER-2 expression changes (n=23)







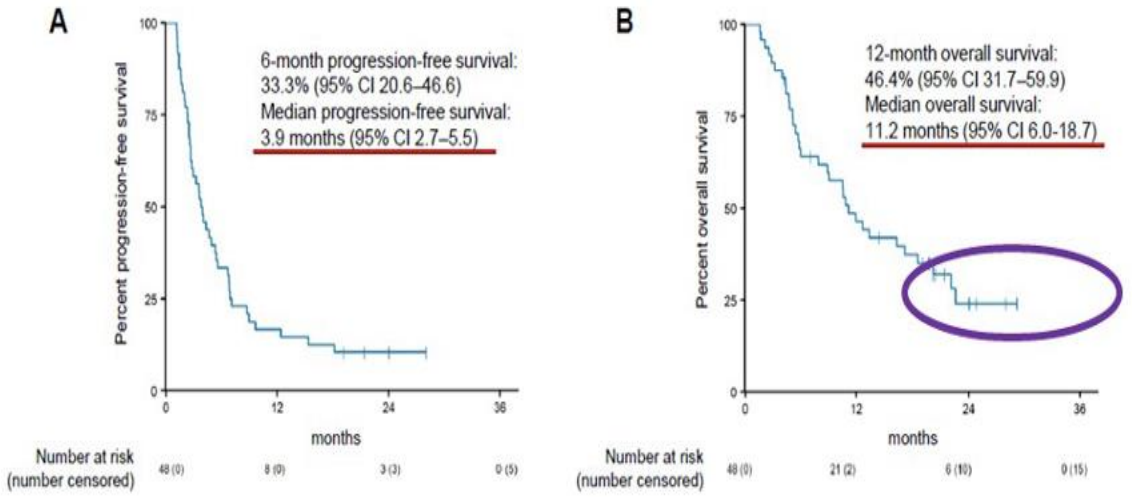
- Her-2 loss after 1st line treatment was 8/23 (34.7%).
- There was no association of tumor response or survival according to Her-2 loss, suggesting Trastuzumab/Ramucirumab/Paclitaxel triplet regimen might cover various tumor clones.

Rha.Póster 330.ASCOGI2022

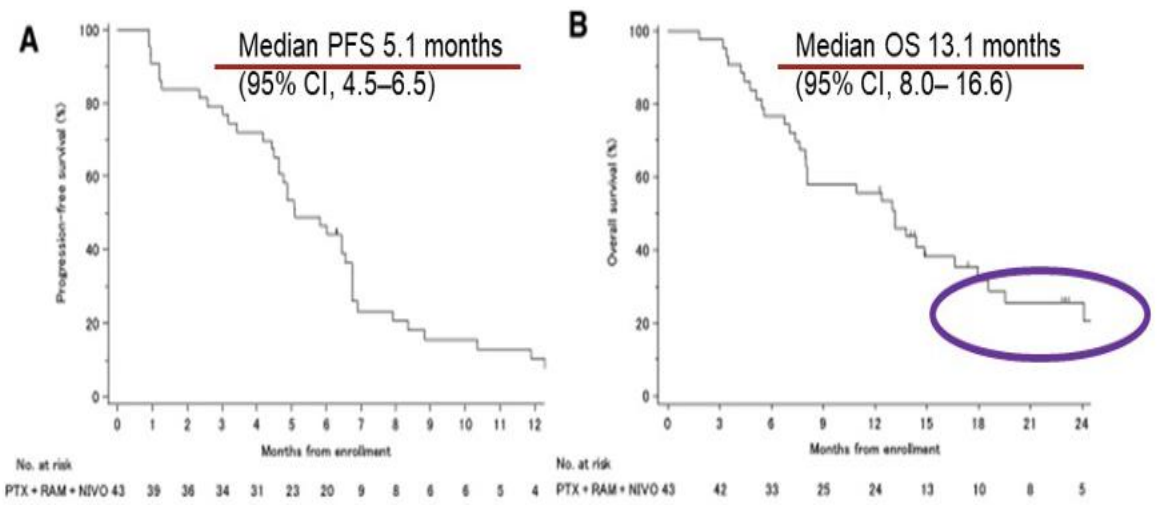
4.Combinación con Inmunoterapia

1. Fase II Combinación (triplete) Ramucirumab/nivolumab y paclitaxel muy prometedora (ASIÁTICOS)

phase I/II Paclitaxel + Nivolumab (n=48)



phase I/II Paclitaxel + Ramucirumab + Nivolumab (n=43)

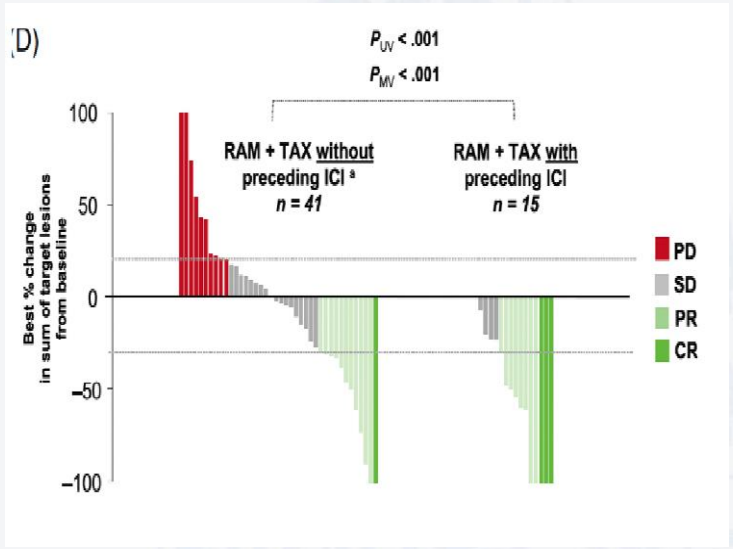


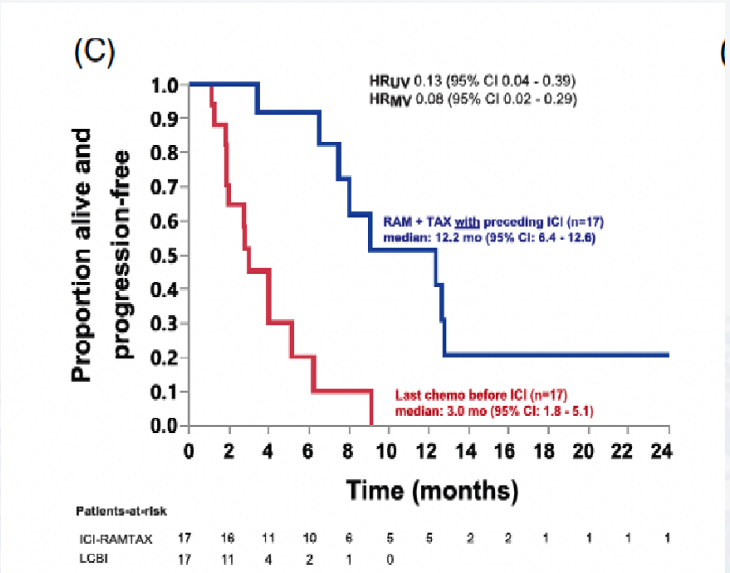
Lee. AACR 2021
Nakajima TE,. Clin Cancer Res. 2021 Feb 15;27(4):1029-1036.

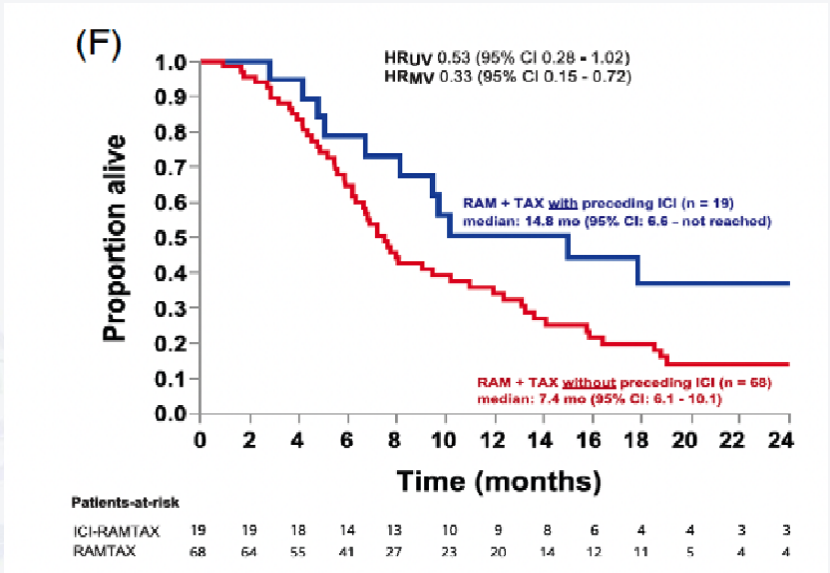
60% CPS ≥1
13.8 months (95% CI, 8.0-19.5 months) in patients with CPS ≥ 1
8.0 months (95% CI, 4.8-24.1 months) in patients with CPS < 1
ORR: 37.2%; DCR:83.7%

5.¿La IO y después antiangiogénicos?

1. Análisis retrospectivo de casos (n:19 IC previa; n;41 no IO previa) mas RR 58%, PFS 12.2 ms, SG 14.8 ms







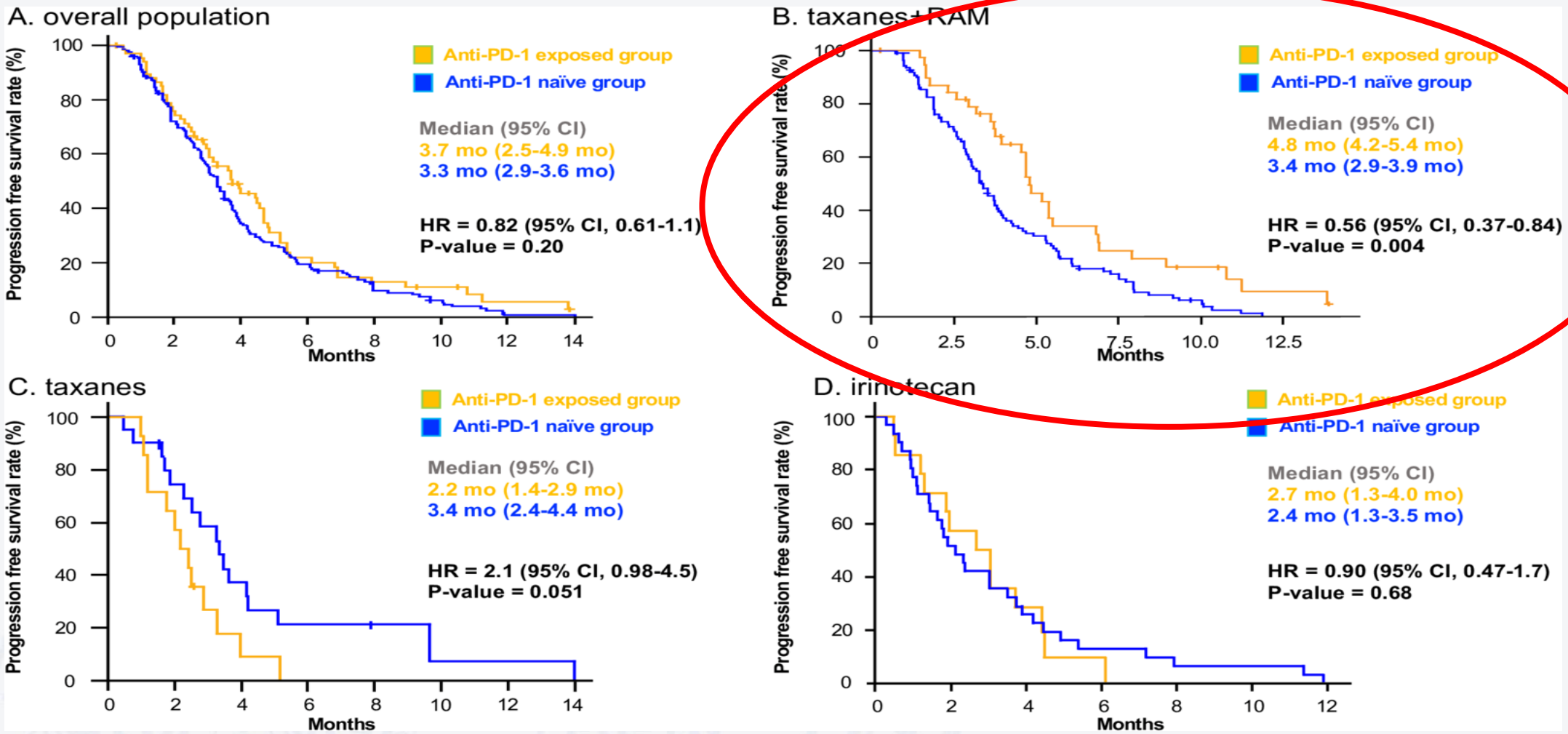
Kankeu Fonkoua. Int J Cancer. 2021 Jul 15;149(2):378-386.

2. Análisis retrospectivo de casos el beneficio de IO previa "aplica " a todas las QT en respuesta pero en SLP Pacli/ramu

Table 2 Tumour responses

	Anti-PD-1-exposed group	Anti-PD-1-naive group	P value
Overall population	**n=56**	**n=138**	
CR	0	0	
PR	25 (45.5%)	27 (19.6%)	
SD	20 (35.7%)	68 (49.3%)	
PD	10 (17.9%)	43 (31.2%)	
NE	1 (1.8%)	0 (0.0%)	
ORR (%)	44.6	19.6	0.001
DCR (%)	80.6	68.8	0.12
Taxanes+RAM	**n=33**	**n=85**	
CR	0	0	
PR	20 (60.6%)	17 (20.0%)	
SD	9 (27.3%)	40 (47.1%)	
PD	4 (12.1%)	28 (32.9%)	
ORR (%)	60.6	20.0	<0.001
DCR (%)	87.9	67.1	0.023

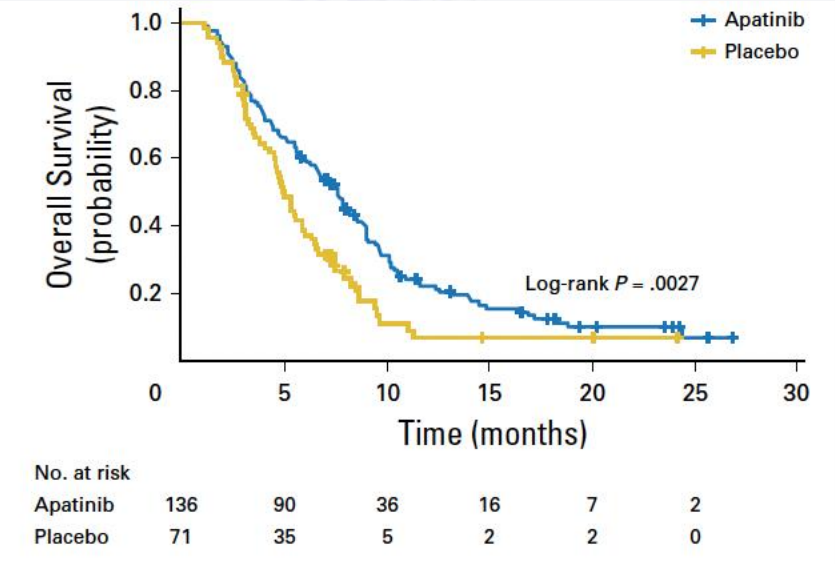
Sasaki A. ESMO Open. 2020 Jul;4(Suppl 2):e000775.

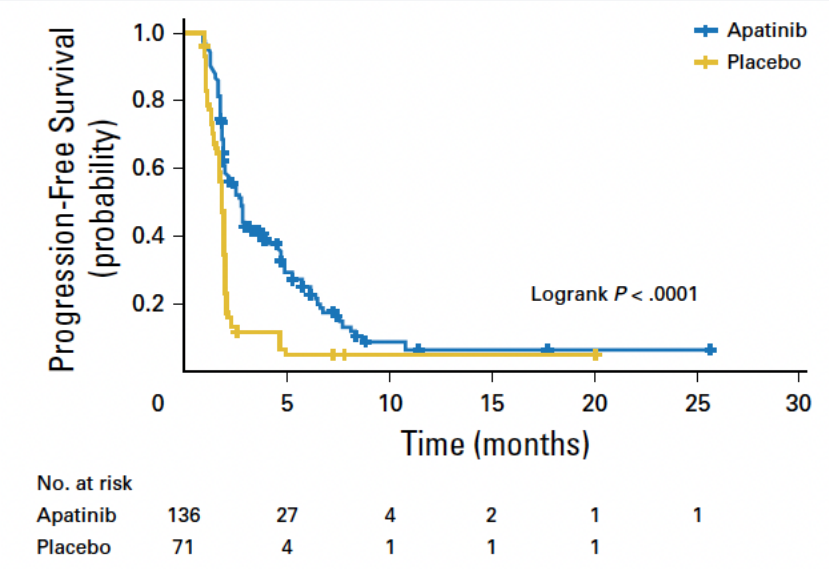


Sasaki A. ESMO Open. 2020 Jul;4(Suppl 2):e000775.

TERCERA LÍNEA: "no hay evidencia"

1. **Apatinib (TKI anti VEGFR-2)** es superior a placebo en población China (Fase III, n 267) en 3L o sucesivas

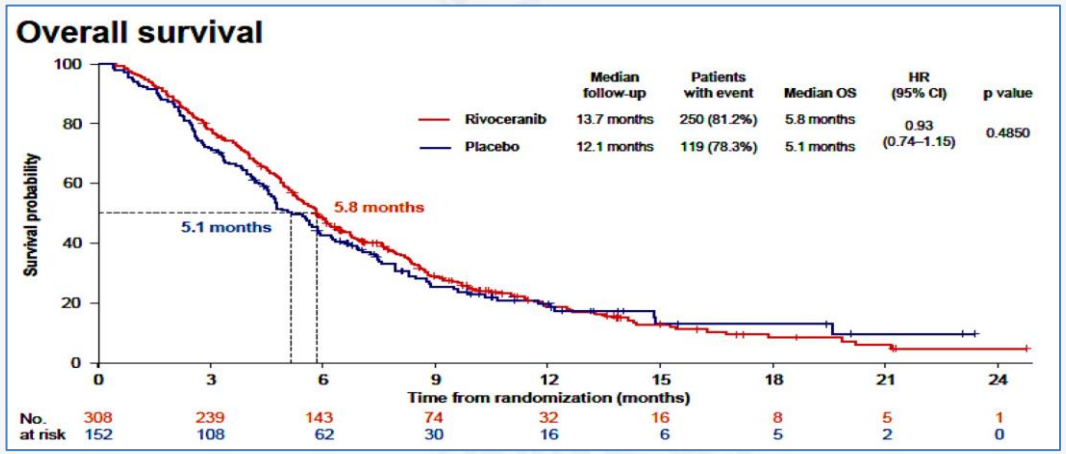


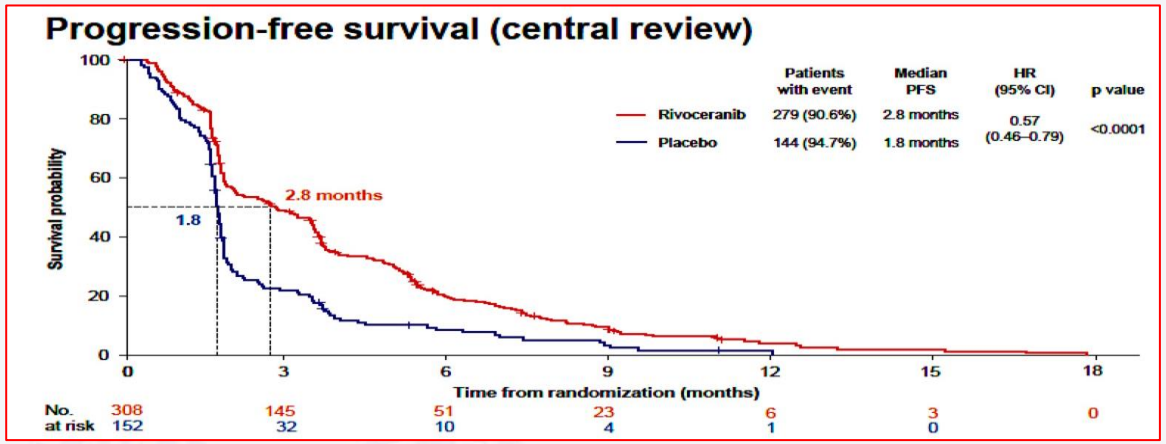


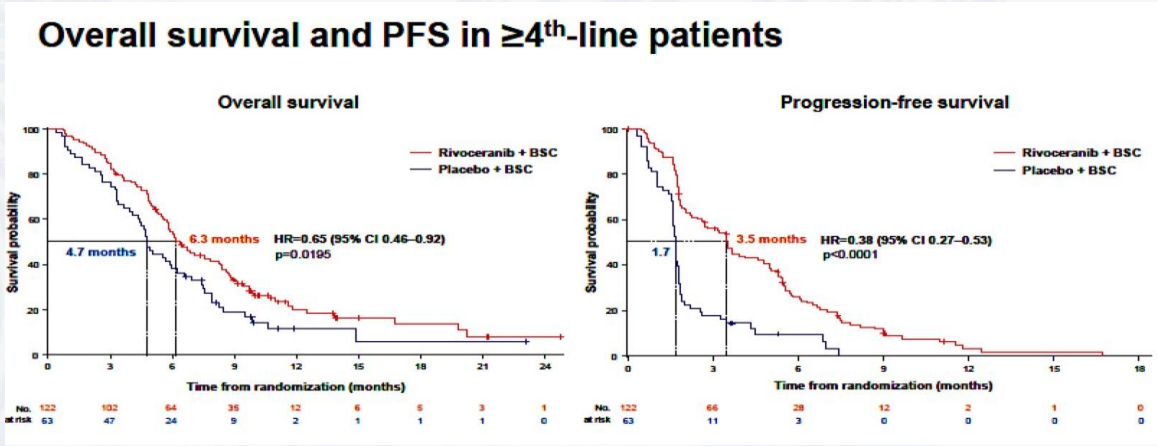
SG: 7.6 ms vs 5.0 ms
SLP 2.6 ms vs 1.8 ms

Li J.J Clin Oncol. 2016 May 1;34(13):1448-54.

1. Rivoceranib - Apatinib (TKI anti VEGFR-2) Negativo en población global (Fase III ANGEL) en refractarios (n:369)



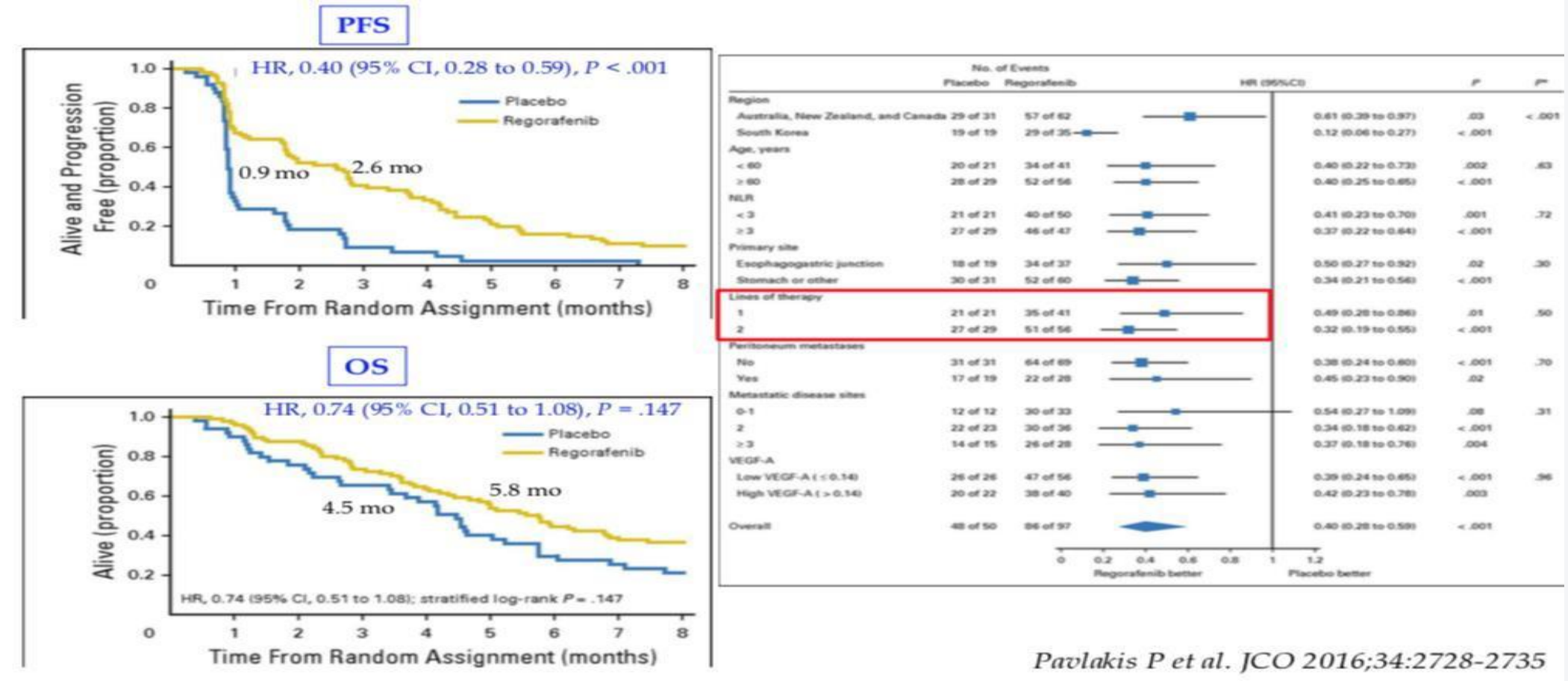




Kang Y-K et al. ESMO 2019. LBA43

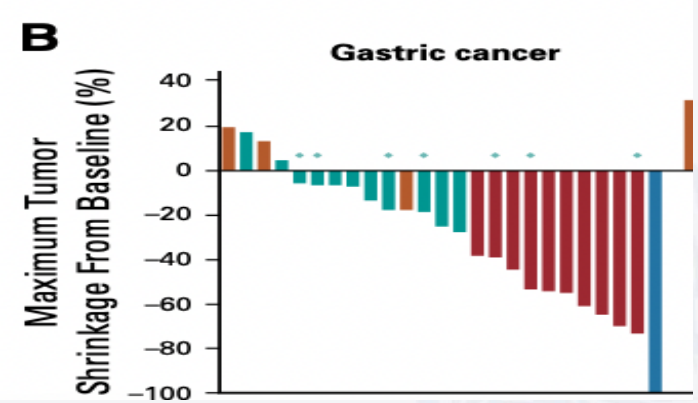
FUTURO

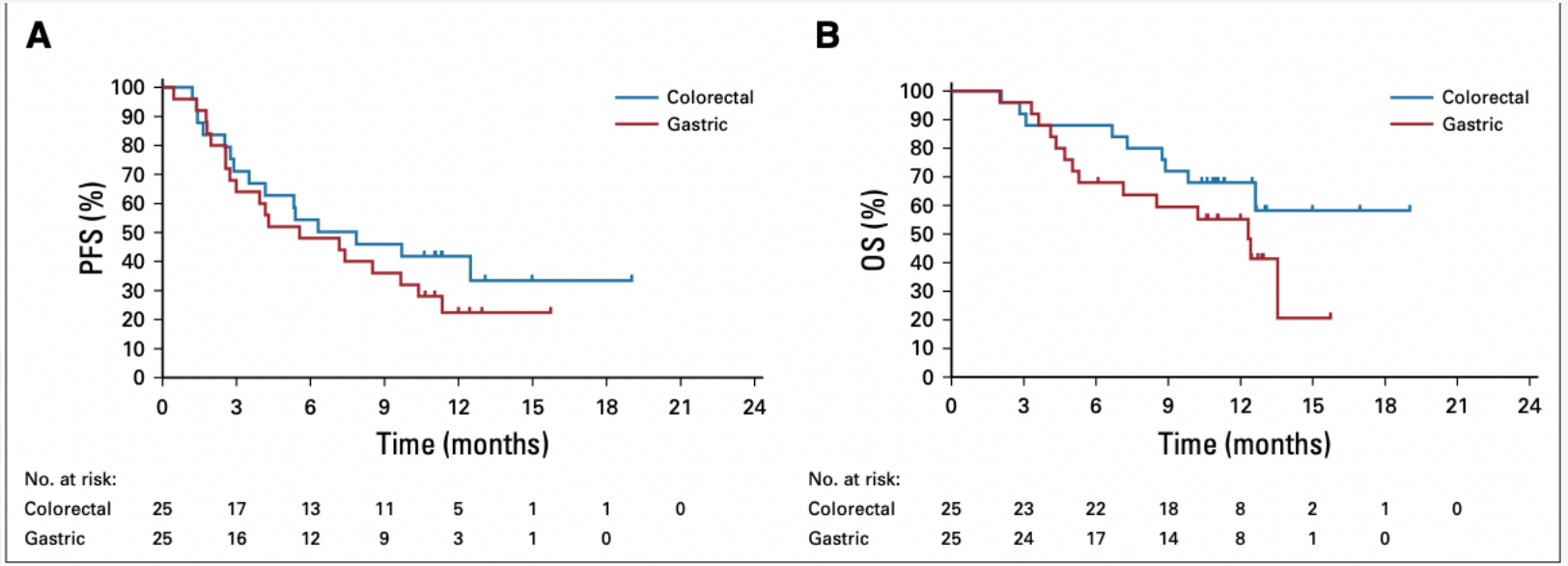
1. **Regorafenib (TKI VEGFR 1-3)** , Fase II frente a placebo (INTEGRATE),resultados prometedores.



FUTURO: "Antiangiogénicos e Inmunomoduladores"

1. Regorafenib (TKI VEGFR 1-3) y Nivolumab (n:25) en refractarios (36% 3L y 64% 4L o sucesiva) (Asia)





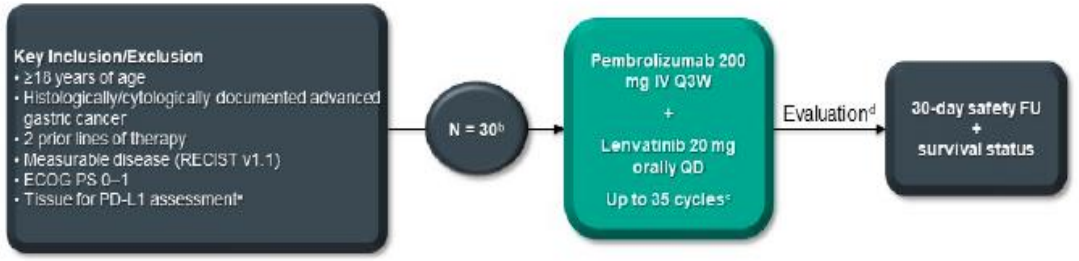
- SLP 5.6 meses
- SG 12.3 meses
- RR 44%

Fukuoka S, J Clin Oncol. 2020 Jun 20;38(18):2053-2061.

2. Lenvatinib (TKI VEGFR 1-3) y Pembrolizumab (n:31) en refractarios, LEAP 005

Chung MK-7902 LEAP-005 ASCO-GI 2021

LEAP-005 (NCT03797326)
Gastric Cancer Cohort



Primary endpoints: ORR (RECIST v1.1, BICR)[e], safety/tolerability
Key secondary endpoints: DCR, DOR, PFS (RECIST v1.1, BICR)[e], OS

Response assessed Q9W until week 54; then Q12W until week 102; then Q24W thereafter

Antitumor Activity

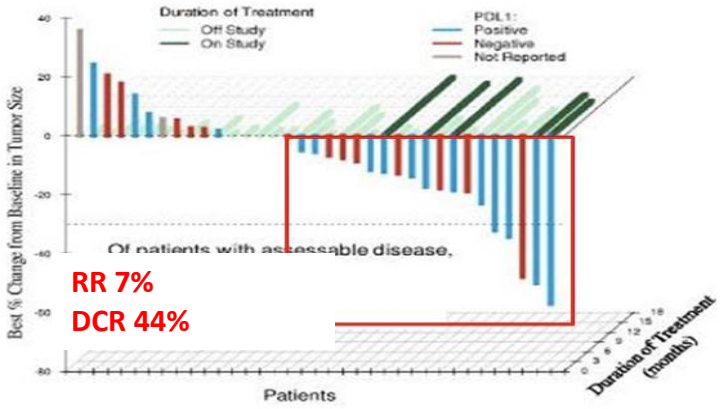
	N = 31
ORR, % (95% CI)	10 (2–26)
DCR,[a] % (95% CI)	48 (30–67)
Best overall response, n (%)[b]	
CR	1 (3)
PR	2 (6)
SD	12 (39)
PD	11 (35)
No assessment[c]	5 (16)
DOR, median (range), mo	NR (2.1+ to 2.3+)

- SLP 2.5 meses
- SG 5.9 meses
- RR 10%, Control 30%

Chung HC, et al. J Clin Oncol 2021;39(suppl):abstr 230

3. Actividad de Ramucirumab combinado con IO (Fase I, pocos pacientes)

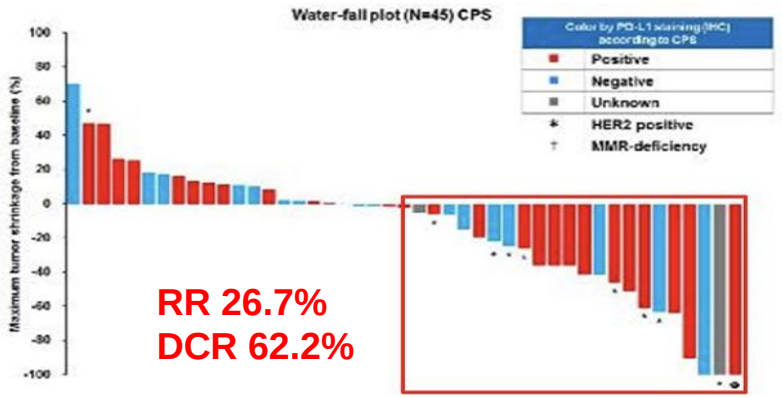
Ph1 Pembrolizumab + Ramucirumab



RR 7%
DCR 44%

N:41
Politratados

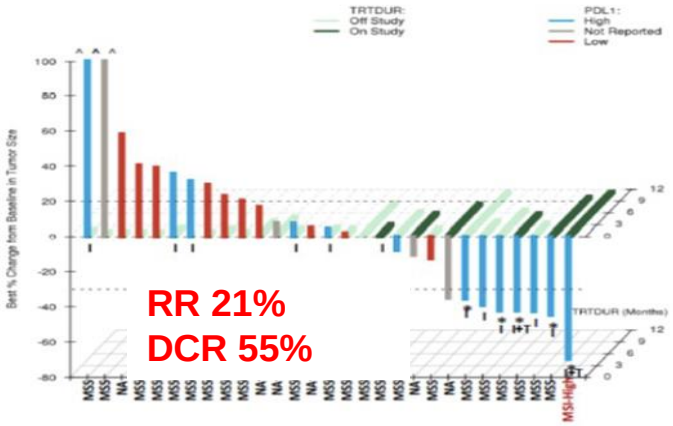
Ph1/2 Nivolumab + Ramucirumab



RR 26.7%
DCR 62.2%

N:46

Ph1 Durvalumab + Ramucirumab



RR 21%
DCR 55%

N:29

Table 3. Response, as confirmed per RECIST, and survival.

	All [1] N = 28	PD-L1-Negative (CPS < 1) N = 6	PD-L1-Positive (CPS ≥ 1) N = 19	CPS ≥ 10 [2] N = 10
Best overall response, *n* (%)				
Complete response	1 (4)	0	1 (5)	0
Partial response	6 (21)	1 (17)	5 (26)	4 (40)
Stable disease	12 (43)	3 (50)	7 (37)	4 (40)
Progressive disease	7 (25)	1 (17)	6 (32)	2 (20)
Not evaluable	2 (7)	1 (17)	0	0
Objective response rate, % (95% CI)	25 (10.7–44.9)	17 (0.4–64.1)	32 (12.6–56.6)	40 (12.2–73.8)
Disease control rate, % (95% CI)	68 (47.6–84.1)	67 (22.3–95.7)	68 (43.4–87.4)	80 (44.4–97.5)
Time to response, median months (95% CI)	2.7 (1.3–2.8)	2.8 (NC)	2.1 (1.3–9.8)	1.4 (1.3–2.8)
Duration of response, median months (95% CI)	NR (9.7–NC)	NR (NC)	NR (9.7–NC)	NR (9.7–NC)
Duration of stable disease, median months (95% CI)	5.6 (3.9–12.3)	5.1 (4.3–5.8)	8.6 (4.1–13.5)	5.0 (4.1–13.5)
Progression-free survival				
Number of events	20	4	14	8
Median duration, months (95% CI)	5.6 (2.7–11.5)	4.3 (2.4–NR)	8.6 (1.5–13.5)	8.3 (1.2–13.5)
6-month rate, % (95% CI)	42.9 (23.9–60.6)	20.8 (0.9–59.5)	52.6 (28.7–71.9)	50.0 (18.4–75.3)
12-month rate, % (95% CI)	30.3 (14.0–48.4)	20.8 (0.9–59.5)	35.5 (15.2–56.6)	30.0 (7.1–57.8)
18-month rate, % (95% CI)	20.8 (7.3–38.9)	20.8 (0.9–59.5)	22.2 (6.3–44.0)	20.0 (3.1–47.5)
Overall survival				
Number of events	17	3	11	5
Median duration, months (95% CI)	14.6 (5.4–27.7)	11.3 (2.4–NR)	17.3 (8.6–NR)	24.7 (5.4–NR)
6-month rate, % (95% CI)	69.4 (48.0–83.4)	62.5 (14.2–89.3)	77.8 (51.1–91.0)	90.0 (47.3–98.5)
12-month rate, % (95% CI)	54.0 (33.4–70.7)	41.7 (5.6–76.7)	66.7 (40.4–83.4)	80.0 (40.9–94.6)
18-month rate, % (95% CI)	40.9 (21.7–59.2)	41.7 (5.6–76.7)	48.1 (23.6–69.0)	57.1 (21.7–81.5)

Herbst RS,. Lancet Oncol. 2019 Aug;20(8):1109-1123.Chau I,. Cancers. 2020;12(10):2985. Hara JCO 2019. 37(4_suppl):129Bang YJ, Eur J Cancer. 2020 Sep;137:272-284.

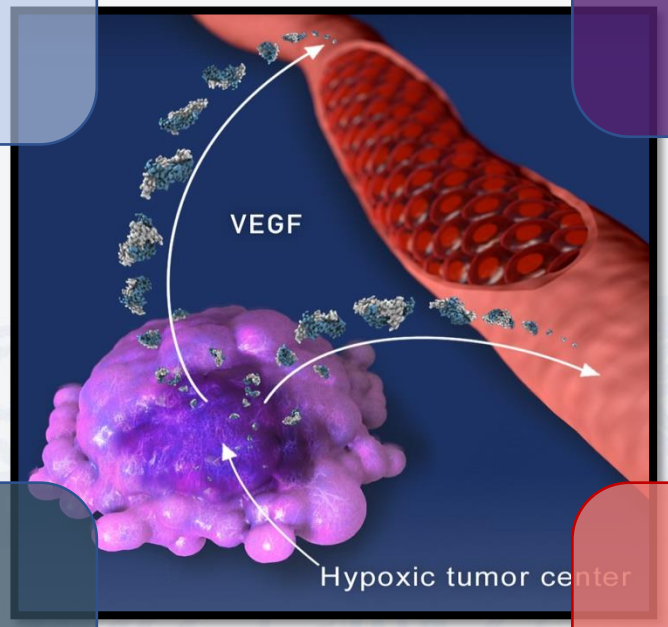
4. Combinaciones Futuras de Ramucirumab

+ inmunoterapia

- pembrolizumab - NCT02443324
- Nivolumab + paclitaxel -UMIN000025947
- Durvalumab - NCT02572687.
- avelumab + paclitaxel - NCT03966118
- nivolumab + rucaparib – NCT0399017
- después de IO (SEQUEL) - NCT04069273

Otros (dianas, TKIs)

- TAS102 NCT03686488 / NCT04660760
  Ipatasertib - NCT04739202



+ QT

- FOLFIRI (RAMIRIS) - NCT03081143
- irinotecan - NCT03141034
- Docetaxel - jRCTs011200010
- Oraxol (Paclitaxel and P-gpi) -NCT02970539
- FLOT (RAMSES) -NCT02661971

HER2+

- trastuzumab + paclitaxel (HER-RAM) - NCT04888663
- tucatinib + trastuzumab + paclitaxel (Mountaineer-02) - NCT04499924

Conclusiones

- Los antiangiogénicos no han demostrado beneficio en "occidente" en 1L y 3L

- Su lugar es 2L

- Resultados reproducibles en estudio vida real
- Nuevas combinaciones: FOLFIRI/irinotecán en estudio
- Beneficio en Her 2 +++
- Beneficio combinando triple terapia

- **Futuro:**

TKI+ Inmunomoduladores

Antiangiogénicos+ Inmunomoduladores

XXIV Simposio de Revisiones en Cáncer

"Tratamiento médico del cáncer en el año 2022"

Gracias

ARÁN