idcsalud

UAM UNIVERSIDAD AUTONOMA DE MADRID

Cáncer de Ovario Platino-Resistente.

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Enfermedad platino-resistente. Definición

- La respuesta obtenida tras una primera línea y el tiempo a la progresión son ambos predictores de respuesta a líneas subsecuentes.
- El intervalo libre de tratamiento ha sido adoptado para la estratificación de los pacientes en grupos de riesgo:

ILP < 4 semanas: P- Refractaria
ILP < 6 meses: P- Resistente
ILP 6-12 meses: P- Sensible parcial
ILP > 12 meses: P- Sensible

GCIG 4th Ovarian Cancer Consensus Meeting

Enfermedad platino-resistente. Intención del tratamiento

- Objetivo principal. ¿Qué queremos conseguir?
  - *Tratamiento paliativo.*
    - Calidad de vida (menor toxicidad).
    - Control de síntomas.
    - Aumento SLP.

Enfermedad platino-resistente. Guías Clínicas

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2014
Epithelial Ovarian Cancer/ Fallopian Tube Cancer/ Primary Peritoneal Cancer

NCCN Guidelines Index
Ovarian Cancer TOC
Discussion

DISEASE STATUS	THERAPY FOR PERSISTENT DISEASE OR RECURRENCE[r,s,t]
Progression, stable, or persistent disease on primary chemotherapy	Clinical trial[u] or Supportive/palliative care only (See NCCN Guidelines for Palliative Care) or Recurrence therapy[r,t]
Complete remission and relapse <6 mo after stopping chemotherapy or Stage II, III, and IV with partial response	Clinical trial[u] or Recurrence therapy[r,t] or Observe (category 2B)
Complete remission and relapse ≥6 mo after stopping chemotherapy — Radiographic and/or clinical relapse	Consider secondary cytoreductive surgery[j] → Clinical trial[u] or Combination platinum-based chemotherapy[r,t] preferred for first recurrence (category 1) or Recurrence therapy[r,t]
Complete remission and relapse ≥6 mo after stopping chemotherapy — Biochemical relapse (rising CA-125 and no radiographic evidence of disease)	Clinical trial[u] or Delay treatment until clinical relapse or Immediate treatment for recurrent disease (recurrence therapy[t]) (category 2B)

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ACCEPTABLE RECURRENCE THERAPIES (1 OF 2)[a]

	Cytotoxic Therapy (In alphabetical order)	Hormonal Therapy	Targeted Therapy	Radiation Therapy
Preferred Single Agents or Combinations	**Platinum-Sensitive Disease**[b,c] Carboplatin[1] Carboplatin/docetaxel[2,3] Carboplatin/gemcitabine[1] Carboplatin/gemcitabine/bevacizumab[d,e] (category 2B)[4] Carboplatin/liposomal doxorubicin[5] Carboplatin/paclitaxel (category 1)[6] Carboplatin/paclitaxel (weekly)[7] Cisplatin[6] Cisplatin/gemcitabine[8] **Platinum-Resistant Disease** Docetaxel[9] Etoposide, oral[10] Gemcitabine[11,12] Liposomal doxorubicin[11,12] Liposomal doxorubicin/bevacizumab[d,e,13] Paclitaxel (weekly)[14] Paclitaxel (weekly)/bevacizumab[d,e,13] Topotecan[15,16] Topotecan/bevacizumab[d,e,13]		Bevacizumab[d,e,17,18]	
Other Potentially Active Agents	**Single Agents**[19] Altretamine Capecitabine Cyclophosphamide Doxorubicin Ifosfamide Irinotecan Melphalan Oxaliplatin Paclitaxel Paclitaxel, albumin bound (nab-paclitaxel) Pemetrexed Vinorelbine	Anastrozole Letrozole Leuprolide acetate Megestrol acetate Tamoxifen		Palliative localized radiation therapy

[a]Patients who progress on two consecutive therapy regimens without evidence of clinical benefits have diminished likelihood of benefitting from additional therapy. (Griffiths RW, et al. Outcomes after multiple lines of chemotherapy for platinum-resistant epithelial cancers of the ovary, peritoneum, and Fallopian tube. Int J Gyn Ca 2011;21:58-65.) Decisions to offer clinical trials, supportive care, or additional therapy should be made on a highly individual basis.

[b]In general, the Panel would recommend combination regimens based on randomized trial data, especially in first relapses.

[c]Platinum-based combination therapy should be considered for platinum-sensitive recurrences.

[d]In patients who have not previously received bevacizumab.

[e]Contraindicated for patients at increased risk of gastrointestinal perforation.

See References (OV-D 2 of 2)

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See References (OV-D 2 of 2)

Enfermedad platino-resistente. Puntos clave:

- El tratamiento en Ca ovario platino-resistente consigue tasas de respuesta inferiores al 15% y un ILP de 3-4 meses.
- Los principales agentes que han demostrado eficacia en Ca ovario P-Resistente:
  - Paclitaxel (semanal o c/3 semanas)
  - Topotecan
  - Doxorrubicina liposomal pegilada
  - Gemcitabina
- Ninguno de estos agentes ha demostrado superioridad con respecto a otro.
- Las terapias en combinación han resultado deletéreas en SLP y con mayor toxicidad.

Quimioterapia en Cáncer de Ovario P-Resistente

Autor	ILPlatino	Farmaco	Nº Pacientes (PR)	Tasa de respuesta (PR/PS)	mTTP – semanas (PR/PS)	SG – semanas (PR/PS)
Ten Bokkel Huinink	?¿	Topotecan Paclitaxel	112 (60) 114 (59)	(13/28) (6,7/20)	23 14 P=0,002	61 43
Gordon	6,7 7	Topotecan DLP	235 (124) 239 (130)	17 (8/32) 20 (16/31)	17 (14/23) 16 (9/29) P=0,037	57 (41/71) 69 (35/108)
O'Byrne	6,6 6,7	DLP Paclitaxel	106 (65) 107 (77)	19 24	22 22	46 56
Vermorken	< 12	Oxaliplatino Topotecan	79 (51) 79 (53)	11,4 (4/25) 8,9 (5,7/15)	- -	- -
Rosenberg	?	Paclitaxel sem Paclitaxel c/3 sem	104 104	31 32	5,5 m 8,3 m	14,6 m 19,2 m
Ferrandina	?	DLP Gemcitabina	76 77	16 28	16 20	55 50

Tasas de respuesta. Estudios Fase II en enfermedad platino-resistente (<6m ILP)

Table 4. Response Rates and 95% CIs for Single Agents in Selected Phase II GOG Trials

		Response Rate				PFS (months)	
Study	Agent	No. of Patients With Response	Total No. of Patients	%	95% CI (%)	Median	Range
26LL[25]	Oral etoposide	11	41	27	14.2 to 42.9	5.7	0.8-30.8+
126C[5]	Altretamine	3	30	10	2.1 to 26.5	2.4	0.4-154.8+
126D[6]	Pyrazoloacridine	2	24	8	1.0 to 27.0	2.2	0.7-24.3
126G[8]	CI-958	1	25	4	0.1 to 20.4	1.5	0.5-15.4
126H[9]	24-hr topotecan	1	25	4	0.1 to 20.4	2.1	0.3-29.6
126I[11]	9-aminocamptothecin	8	56	14	6.4 to 26.2	2.9	0.5-46.0
126J[10]	Docetaxel	13	58	22	12.5 to 35.3	2.1	0.5-26.2
126K[12]	Oxaliplatin	1	23	4	0.1 to 21.8	1.7	0.6-13.1
126M	Epothilone-B	7	50	14	5.8 to 26.7	4.4	0.8-32.6+
126N[14]	weekly paclitaxel	10	48	21	10.5 to 35.0	4.8	0.6-62.2+
126Q	Pemetrexed	10	48	21	10.5 to 35.0	2.9	1.0-33.1

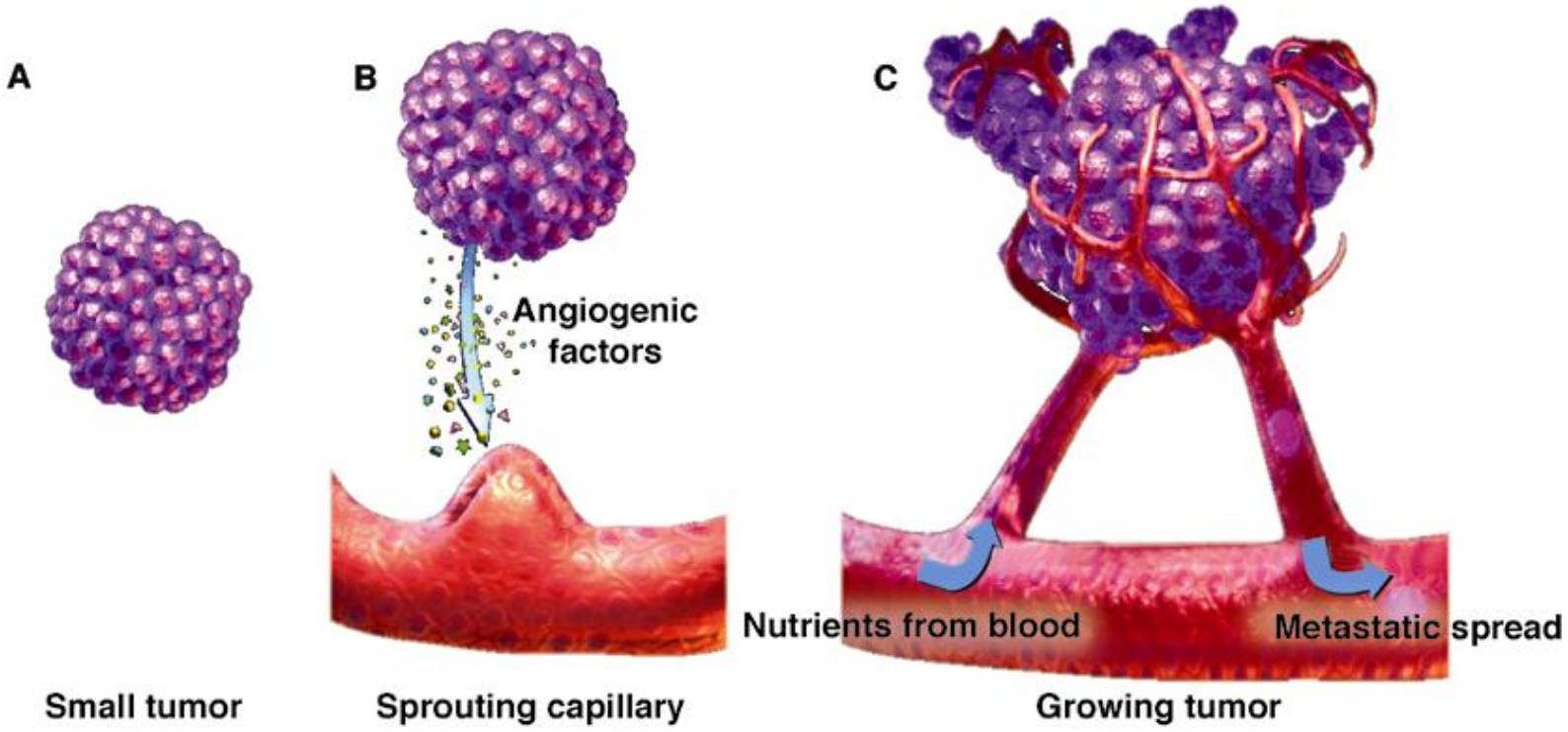
Abbreviations: GOG, Gynecologic Oncology Group; PFS, progression-free survival.

Miller et al; Pemetrexed in platinum-resistant ovarian cancer. JCO.June, 2009

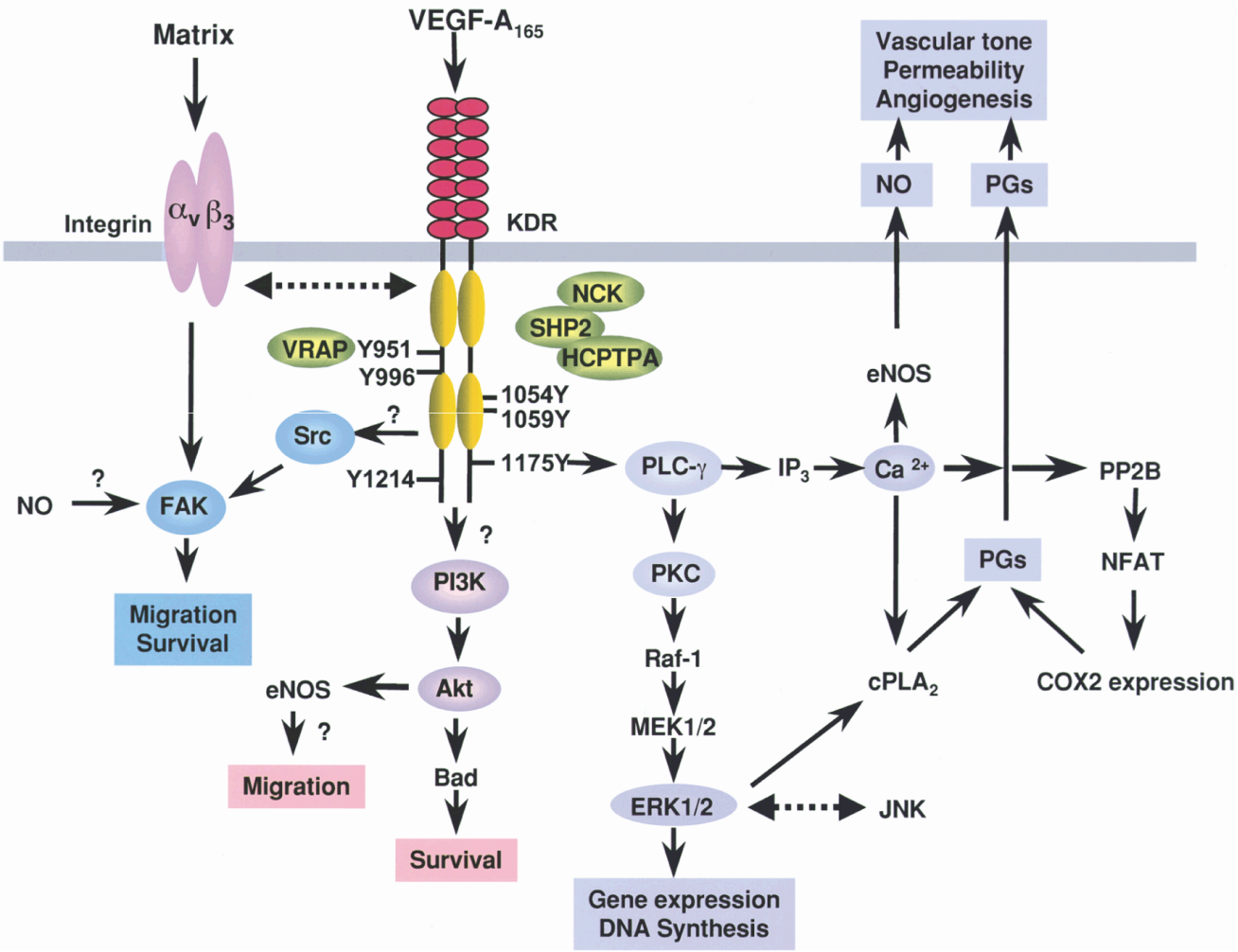
Perfil de toxicidad de los principales agentes

Agent	ORR (%)	Toxicity (Grade 3 and 4)
Paclitaxel	21–53	Neutropenia, anemia, GI, neurologic, fatigue, dyspnea, infection, pulmonary
Gemcitabine	14–22	Neutropenia, anemia, thrombocytopenia, nausea/vomiting, fatigue
PLD	11–28	Hand-foot syndrome, stomatitis
Topotecan	15–32	Neutropenia, anemia, thrombocytopenia
Vinorelbine	3–29	Neutropenia, anemia, worsening paresthesia
Oral etoposide	18–27	Neutropenia, leukopenia, anemia, thrombocytopenia
Docetaxel	7–28	Neutropenia, leukopenia
Ifosfamide	10	Myeolosuppression, nephrotoxicity, central nervous system toxicity
Pemetrexed (Alimta)	21	Myelosuppression

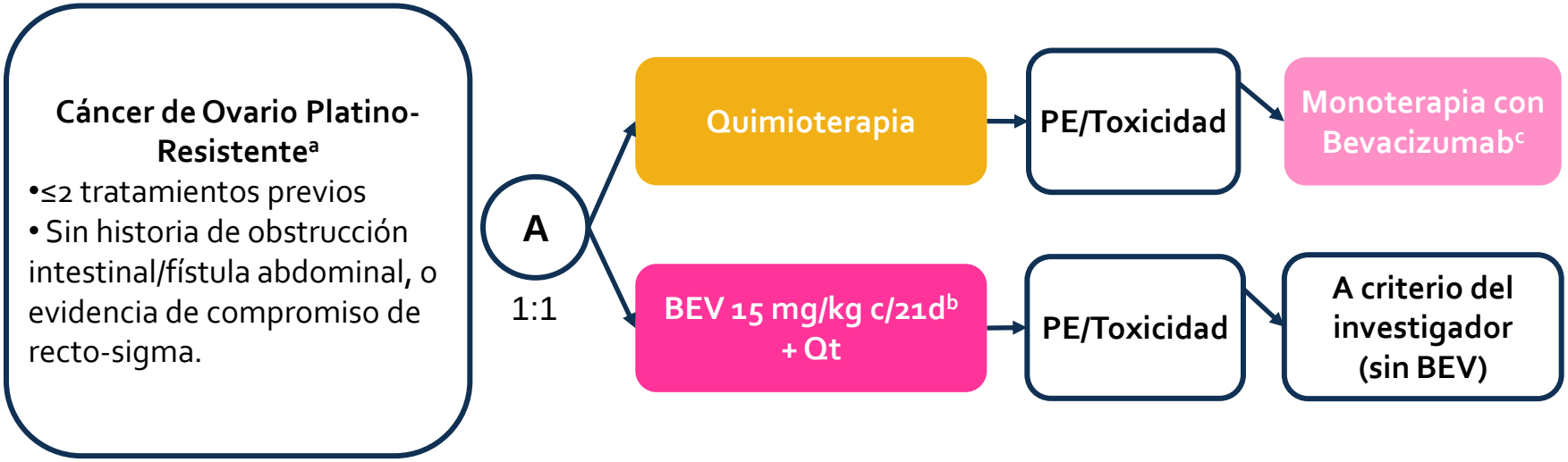
Angiogénesis.



Antiangiogénicos y Ca de ovario.



Ensayo clínico AURELIA. Diseño:



Factores de estratificación

- Quimioterapia elegida
- Tratamiento antiangiogénico previo
- Intervalo libre de tratamiento (< 3 m; 3-6 m)

Opciones de quimioterapia (a criterio del investigador).

Paclitaxel 80 mg/m^2 semanal

Topotecan 4 mg/m^2 dias 1, 8, y 15 c/4s

PLD 40 mg/m^2 day 1 c/4s

Objetivo Primario: Comparar SLP con Qt sola Vs Qt + Bvz según criterios RECIST v1.0

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The latest version is at http://jco.ascopubs.org/cgi/doi/10.1200/JCO.2013.51.4489

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Bevacizumab Combined With Chemotherapy for Platinum-Resistant Recurrent Ovarian Cancer: The AURELIA Open-Label Randomized Phase III Trial

Eric Pujade-Lauraine, Felix Hilpert, Béatrice Weber, Alexander Reuss, Andres Poveda, Gunnar Kristensen, Roberto Sorio, Ignace Vergote, Petronella Witteveen, Aristotelis Bamias, Deolinda Pereira, Pauline Wimberger, Ana Oaknin, Mansoor Raza Mirza, Philippe Follana, David Bollag, and Isabelle Ray-Coquard

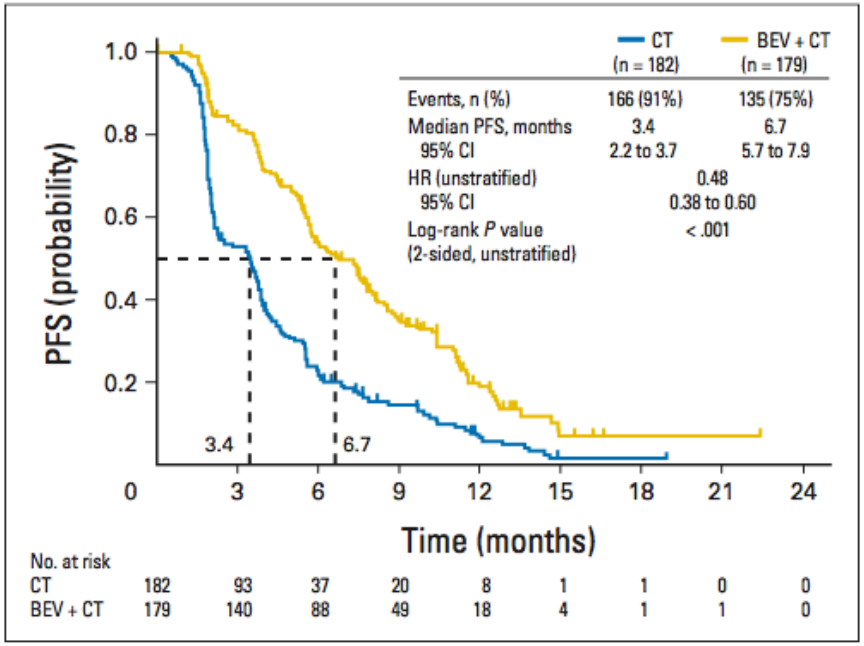


Fig 2. Progression-free survival (PFS). BEV, bevacizumab; CT, chemotherapy; HR, hazard ratio.

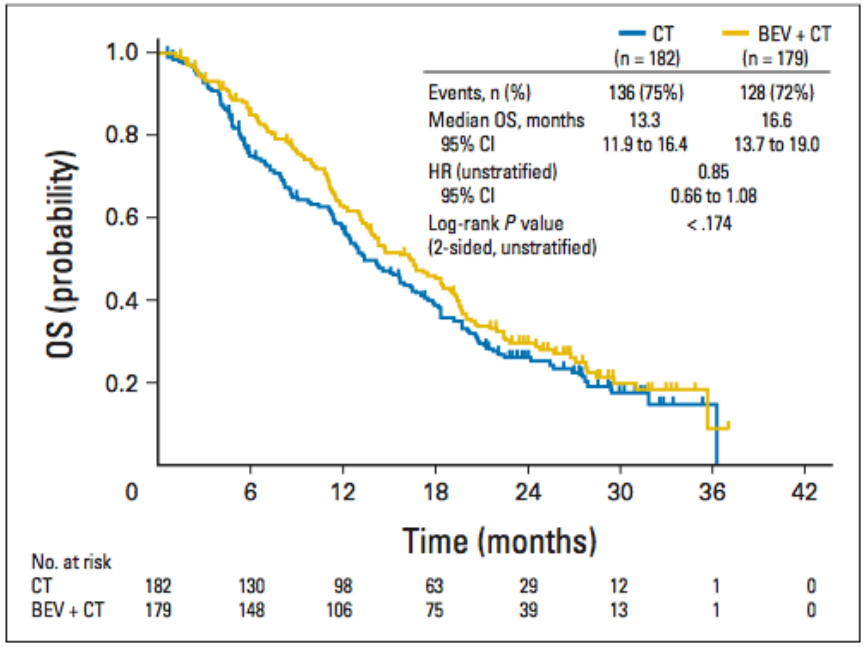


Fig 3. Overall survival (OS). BEV, bevacizumab; CT, chemotherapy; HR, hazard ratio.

Ensayo Clínico AURELIA

- El estudio AURELIA demostró un aumento significativo en SLP (HR, 0.48; 95% CI, 0.38 to 0.60) y un incremento en la tasa de respuestas según criterios RECIST del 15% (11.8% versus 27.3%).

Table 2. Summary of Grade ≥ 3 (and selected grade ≥ 2) AEs of Special Interest

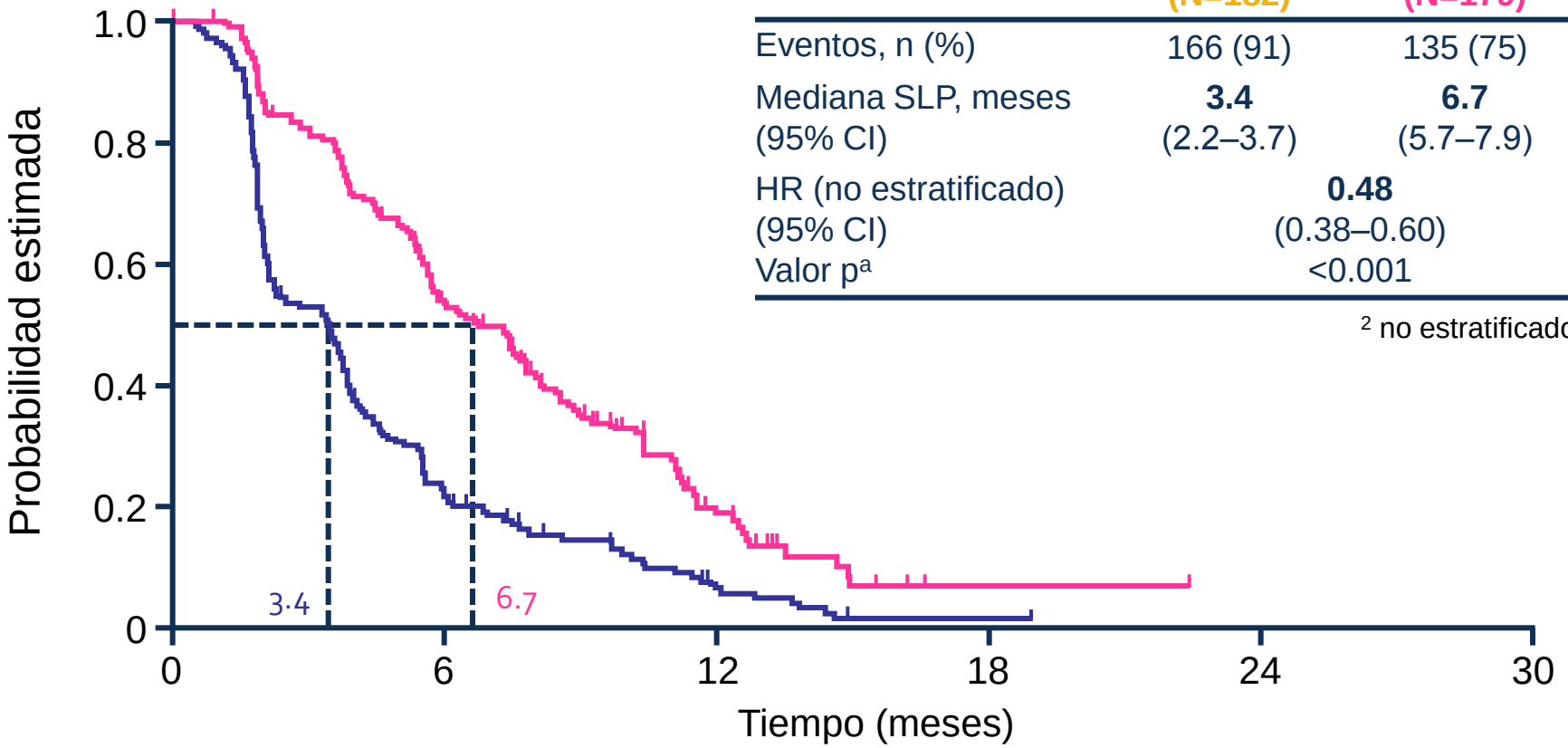
	Chemotherapy Alone (n = 181)		Bevacizumab Plus Chemotherapy (n = 179)	
AE	No.	%	No.	%
Hypertension	2	1	13	7
Grade ≥ 2	12	7	36	20
Proteinuria	0	0	3	2
GI perforation	0	0	3	2
Grade ≥ 2	0	0	4	2
Fistula/abscess	0	0	2	1
Grade ≥ 2	0	0	4	2
Bleeding	2	1	2	1
Thromboembolic event	8	4	9	5
Arterial	0	0	4	2
Venous	8	4	5	3
Wound-healing complication	0	0	0	0
Reversible posterior leukoencephalopathy syndrome	0	0	1	1
Congestive heart failure	1	1	1	1
Cardiac disorders (excluding congestive heart failure)	0	0	0	0

Abbreviation: AE, adverse event.

Supervivencia libre de progresión: Población global.

	QT (N=182)	BEV + QT (N=179)
Eventos, n (%)	166 (91)	135 (75)
Mediana SLP, meses (95% CI)	**3.4** (2.2–3.7)	**6.7** (5.7–7.9)
HR (no estratificado) (95% CI)	**0.48** (0.38–0.60)	
Valor p[a]	<0.001	

[2] no estratificado



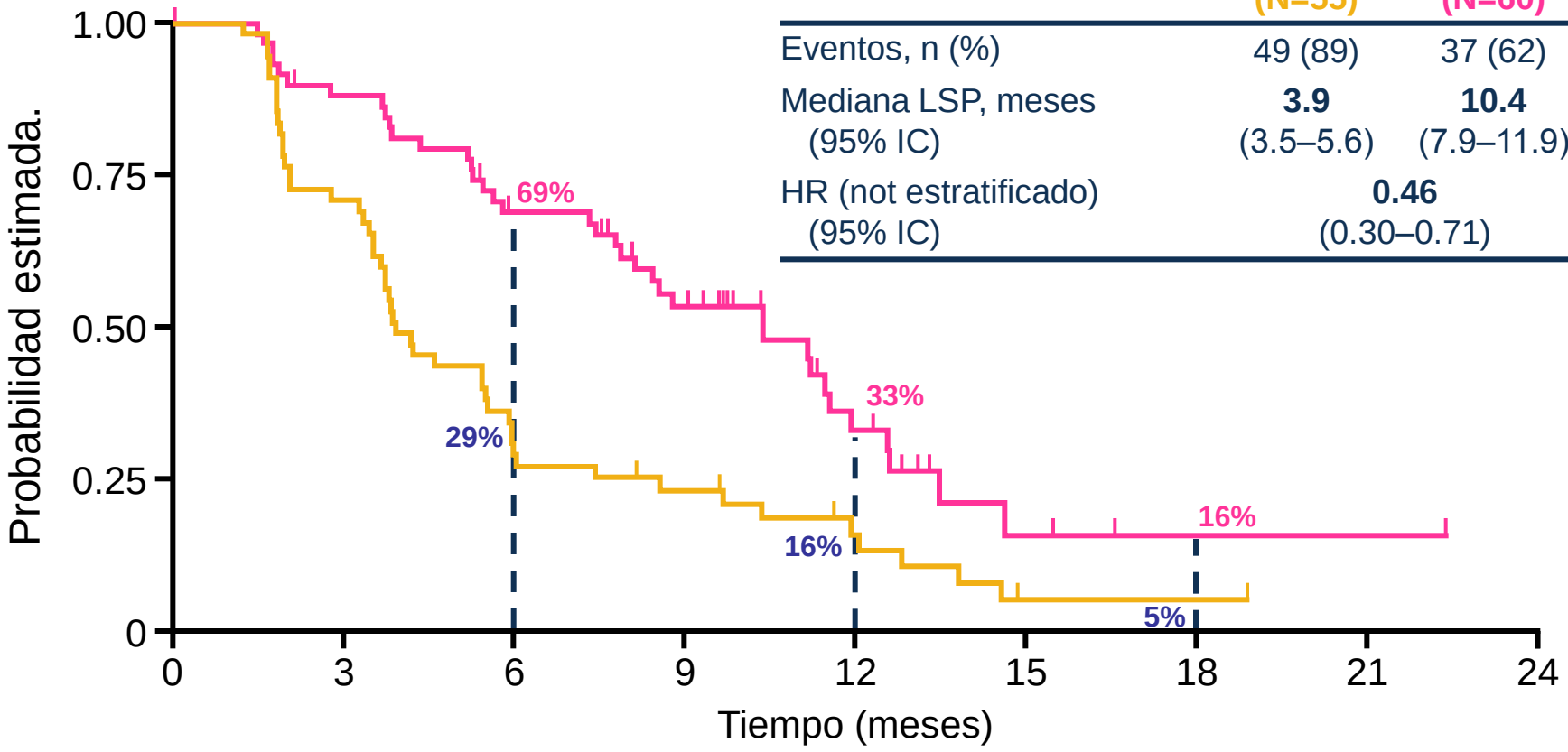
No. at risk:

QT	182	93	37	20	8	1	1	0	0
BEV + QT	179	140	88	49	18	4	1	1	0

Duración de seguimiento (mediana): 13.9 meses (brazo QT) vs 13.0 meses (BEV + QT)

SLP: Cohorte tratada con paclitaxel

	QT (N=55)	BEV + QT (N=60)
Eventos, n (%)	49 (89)	37 (62)
Mediana LSP, meses (95% IC)	**3.9** (3.5–5.6)	**10.4** (7.9–11.9)
HR (not estratificado) (95% IC)	**0.46** (0.30–0.71)	

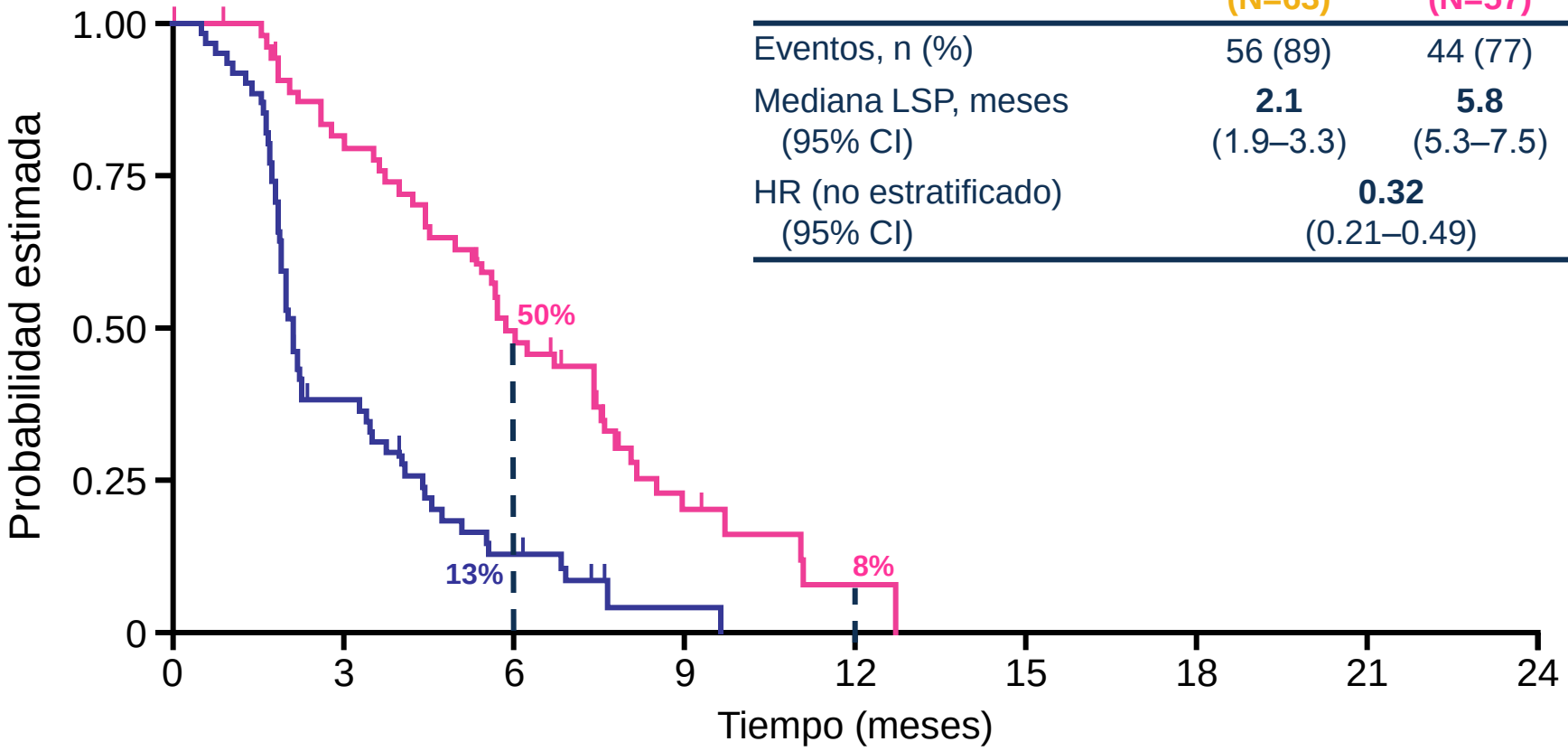


Pob en riesgo									
QT	55	39	16	11	6	1	1	0	0
BEV + QT	60	51	38	27	11	3	1	1	0

Duración mediana de seguimiento:12.7 meses (brazo Qt) vs 12.8 meses (BEV + QT arm)

LSP: Cohorte tratada con topotecan

	QT (N=63)	BEV + QT (N=57)
Eventos, n (%)	56 (89)	44 (77)
Mediana LSP, meses (95% CI)	**2.1** (1.9–3.3)	**5.8** (5.3–7.5)
HR (no estratificado) (95% CI)	**0.32** (0.21–0.49)	



Nº en riesgo:

CT	63	22	7	1	0	0	0	0	0
BEV + CT	57	43	26	8	1	0	0	0	0

Mediana de seguimiento: 9 meses (brazo Qt) vs 10.5 meses (brazo BEV + QT)

Consideraciones especiales

- Elevación del CA125 como único dato de progresión.
  - Considerar observación (no hay beneficio en la supervivencia en iniciar tratamiento de forma precoz).
  - Valorar tratamiento hormonal (tamoxifeno), por su menor toxicidad.
- Ascitis – En el que el papel de la quimioterapia es limitado.
- Obstrucción intestinal – Tratamiento sintomático exclusivo.

CONCLUSIONES:

- Mono-quimioterapia secuencial en pacientes con recidiva platino-resistente de su Ca. Ovario.
- Individualizar según perfil de toxicidad de los agentes quimioterápicos.
- Inicio con Paclitaxel en pacientes que no lo han recibido previamente, o con PLD en aquellas que si lo han recibido, aunque ningún agente ha demostrado ser superior a otro.
- El tratamiento con Bevacizumab en combinación con quimioterapia ha conseguido lo que ningún otro agente hasta ahora.

Muchas gracias