Sociedad Andaluza de Oncología Medica

III REUNIÓN DE TRABAJO

EN CÁNCER DE CABEZA Y CUELLO

Lunes 22 de marzo de 2021

En enfermedad metastásica Extreme vs TPEx

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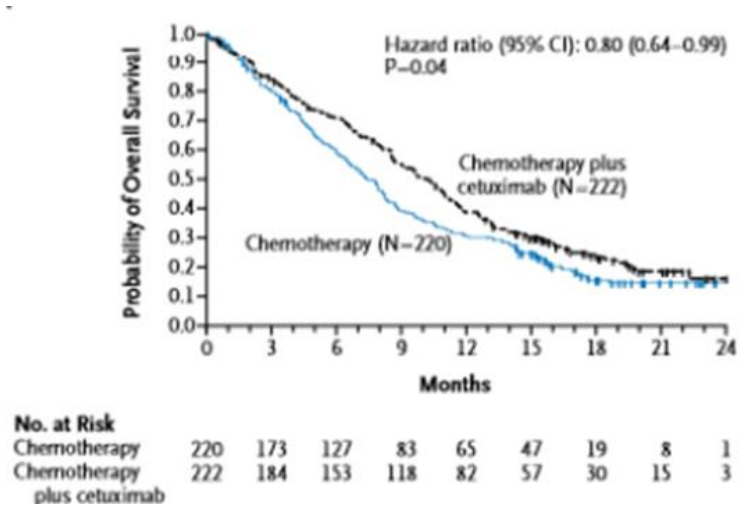
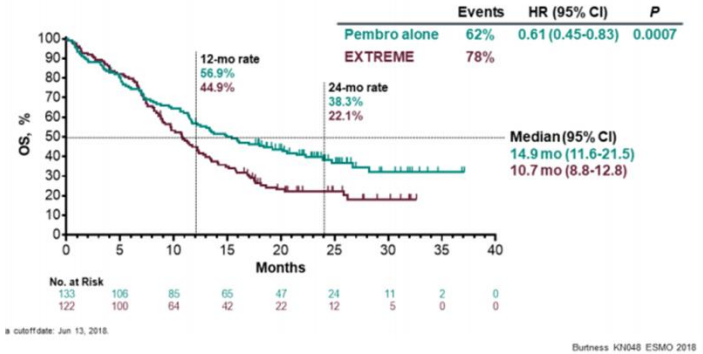
INTRODUCCIÓN

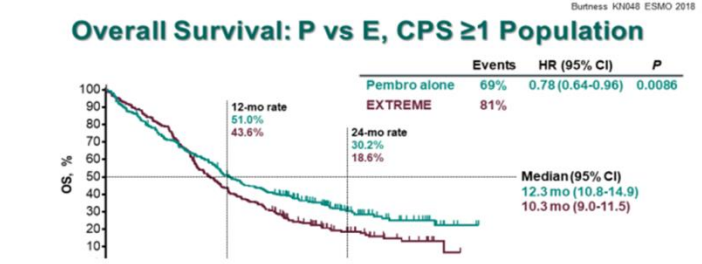
- El régimen EXTREME ha sido el tratamiento estándar de 1ª linea para CCyC R/M



- EXTREME ha sido el único régimen en 35 años que había demostrado un beneficio significativo en supervivencia vs QT sola



- No obstante, el escenario del tratamiento está cambiando debido a los recientes datos de Pembrolizumab.



Pero, no todos los pacientes son candidatos a inmunoterapia

¿Es posible modificar la QT del esquema EXTREME para mejorar los resultados y disminuir toxicidad?

Combinaciones de Cetuximab+Platino+Taxanos

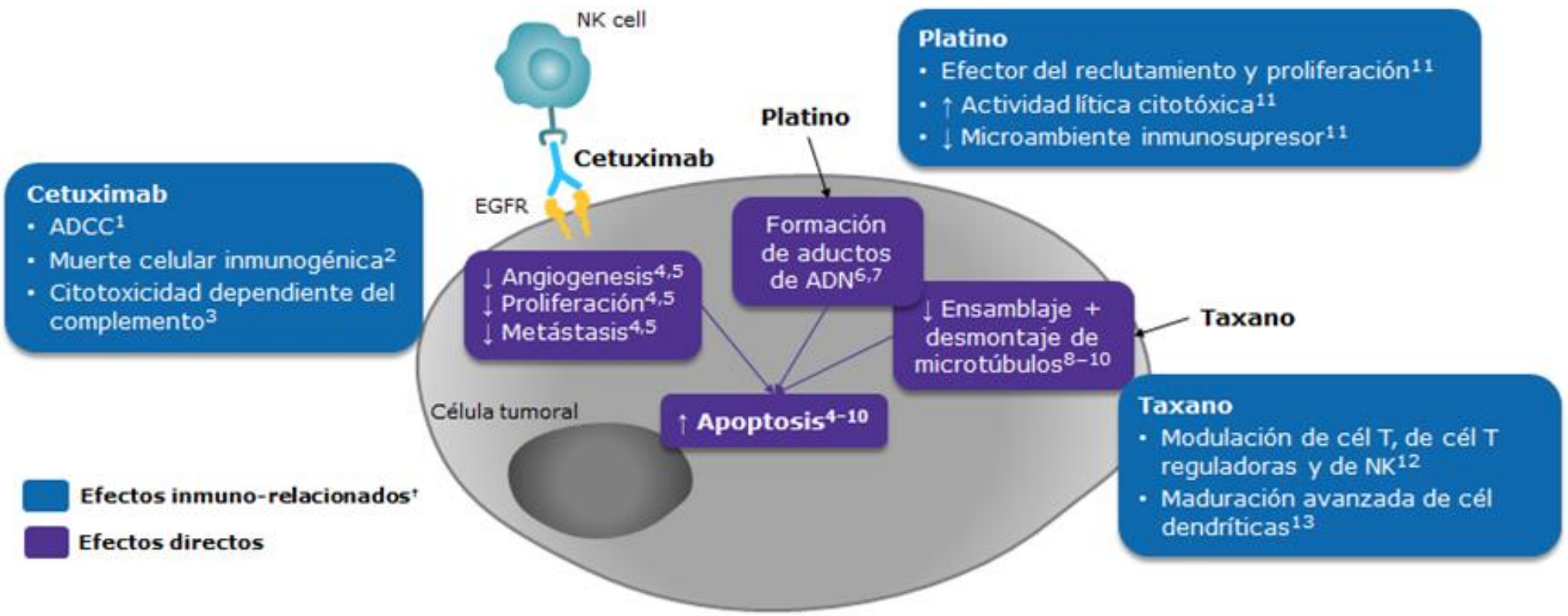
Estudios Fase II de regímenes con Cetuximab + Platino + Taxano en 1ª línea de CECC R/M*

Estudio		Platino	Taxano	Comparador
Randomizado, no inferioridad **CET-MET[1] (N=85)**	✓	**Carboplatino** Hasta 6 ciclos	Paclitaxel	EXTREME
1 solo brazo **CSPOR–HN02[2] (CARBITAX) (N=45)**	✓	**Carboplatino** Hasta 6 ciclos	Paclitaxel	NA
1 solo brazo (ongoing) **CACTUX[3] (N=70)**	✓	**Carboplatino** o **cisplatino** Hasta 6 ciclos	Nab-paclitaxel‡	NA
Randomizado, no inferioridad **CET-INT[4] (N=201)**	✓	**Cisplatino** Hasta 6 ciclos	Paclitaxel	Cetuximab + cisplatino
1 solo brazo **GORTEC 2008-03 (TPEx)[5] (N=54)**	✓	**Cisplatino** 4 ciclos	Docetaxel	NA

*Cetuximab está indicado en CECC R/M en combinación con QT basada en platino. Los taxanos no están actualmente aprobados para CECC R/M; †Regimen de mantenimiento off-label; ‡Regimen de mantenimiento off-label con cetuximab + nab-paclitaxel; NA, not applicable

1. Friesland S, et al. ASCO 2018 (Abstract 6032); 2. Tahara M, et al. Ann Oncol 2018; doi:10.1093/annonc/mdy040; 3. Adkins D, et al. Oral Oncology 2017;72:26-31; 4. Bossi P, et al. Ann Oncol 2017;28:2820–2826; 5. Guigay J, et al. Ann Oncol 2015;26:1941–1947.

MECANISMO DE ACCIÓN Y RACIONAL



1. Ferris RL, et al. Cancer Treat Rev 2018;63:48-60; 2. Pozzi C, et al. Nat Med 2016;22:624-631; 3. Hsu YF, et al. Mol Cancer 2010;9:139; 4. Lee J, Moon C. Biol Med 2011;236:375-389; 5. Barry SP, et al. Int J Exp Pathol 2010;91:506-514; 6. Siddik ZH. Oncogene 2003;22:7265-7279; 7. Chao SY, et al. BMC Med Genomics 2011;4:23; 8. Abal M, et al. Curr Cancer Drug Targets 2003;3:193-203; 9. de Weger VA, et 2014;25:488-494; 10. Kingston DGI. Chem Commun 2001;0:867-880; 11. de Biasi AR, et al. Clin Cancer Res 2014;20:5384-5391; 12. Garnett CT, et al. Clin Cancer Res 2008;14:3536-3544; 13. Cell Immunol 2010;263:79-87.

	Toxicidades cardiacas	DPD	Reacciones infusionales	Neutropenia
5-FU	EA más comunes: eventos de angina e isquemia. Muerte súbita y tromboembolismo han sido reportados	Contraindicado para pacientes con ausencia de actividad DPD conocida	Ocurren raramente	Reportado comúnmente
Taxanos	EA más comunes: bradiarritmia. No existen casos de tromboembolismo reportados para paclitaxel o docetaxel	La deficiencia de DPD no es un problema	Reacciones en ~10% de los pacientes– se reducen con administración de corticoesteroides	Depende del esquema y de la edad del paciente, soporte con G-CSF puede ser requerido para reducir el riesgo de neutropenia

TPExtreme randomized trial:
TPEx *versus* Extreme regimen in 1st line Recurrent/Metastatic Head and Neck Squamous Cell Carcinoma (R/M HNSCC)

Joël GUIGAY, Jérôme Fayette, Ricard Mesia, Cedrik Lafond, Esma Saada-Bouzid, Lionnel Geoffrois, Laurent Martin, Didier Cupissol, Olivier Capitain, Helene Castanie, Damien Vansteene, Philippe Schafhausen, Catherine Dubos Arvis, Caroline Even, Christian Sire, Melissa Delhommeau, Cecile Michel, Jean Bourhis, Ulrich Keilholz, Anne Auperin,
GORTEC - AIO Studien gGmbH - TTCC - H&N Unicancer

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Hôpital Prive du Confluent S.A.S, Nantes, France; Institut de Cancerologie de l'Ouest-René Gaudducheau, Nantes, France; Universitätsklinikum Ham
Baclesse, Oncology, Caen, France; Gustave Roussy, Villejuif, France; Groupe Hospitalier Bretagne Sud-Radiothérapie-Oncologie, Lorient, France; G
Center, Berlin, Germany

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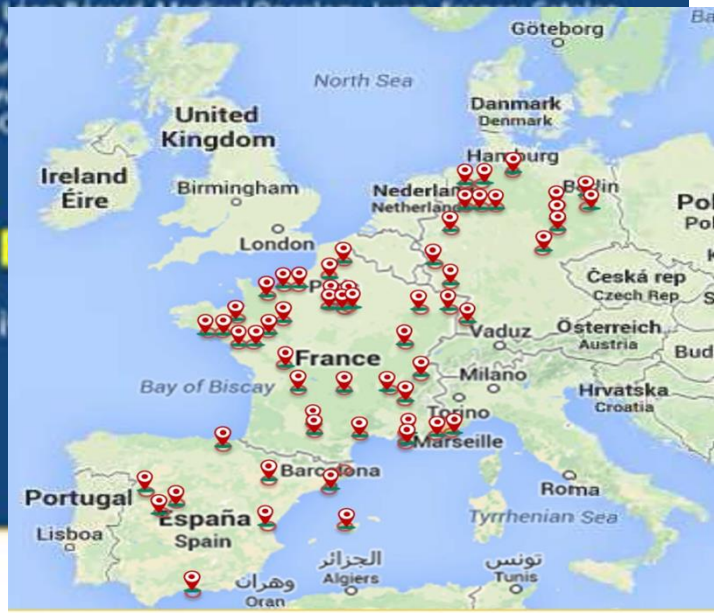


PRESENTED AT: 2019 ASCO ANNUAL MEETING #ASCO19

PRESENTED BY: Pr Joël GUIGAY

TPExtreme study design (NCT 02268695)

KEY ELIGIBILITY CRITERIA

- → R/M HNSCC not suitable for locoregional treatment
- → Age 18-70 years
- → PS 0-1
- → Creatinine clearance >60 mL/min
- → Prior cisplatin ≤300 mg/m²
- → No Anti-EGFR for 1 year

MINIMIZATION FACTORS

- → PS
- → Metastatic status
- → Previous cetuximab
- → Country

R 1:1

N = 270

EXTREME
(Reference arm)

6 cycles Q3W CT

CISPLATIN → 100 mg/m² IV
5FU → 4000 mg/m² 96h continuous infusion
CETUXIMAB → 400 mg/m² (loading dose), then 250 mg/m² IV weekly

- → Maintenance cetuximab 250 mg/m²
- → WEEKLY
- → until progression or unacceptable toxicity

N = 269

TPEx
(Experimental arm)

4 cycles Q3W CT

CISPLATIN → 75 mg/m² IV
DOCETAXEL → 75 mg/m² IV
CETUXIMAB → 400 mg/m² (loading dose), then 250 mg/m² IV weekly
+ G CSF after each cycle

- → Maintenance cetuximab 500 mg/m²
- → EVERY 2 WEEKS
- → until progression or unacceptable toxicity

Study Endpoints

PRIMARY

Overall survival (OS)

SECONDARY

Progression-free survival (PFS)

Objective response rate (ORR) 12 weeks

Tolerance

Compliance

EXPLORATORY

OS/prognostic factors

HPV

Quality of Life (QoL)

Medico-economic study

ORR: Objective Response Rate assessed by RECIST 1.1 locally and by central review

Characteristics, ITT Population

Patient characteristics:

	EXTREME N=270	TPEx N=269
Age, median (range)	60 years (23-71)	60 years (38-70)
Male	231 (86%)	240 (89%)
PS ECOG 1	184 (68%)	183 (68%)
Current/former smoker	243 (90%)	255 (95%)
Prior platin	140 (52%)	156 (58%)
Prior cetuximab (stop ≥1 year before inclusion)	27 (10%)	31 (12%)

Tumor initial characteristics:

	EXTREME	TPEx
Hypopharynx	63 (23%)	54 (20%)
Oral cavity	52 (19%)	57 (21%)
Larynx	57 (21%)	34 (13%)
Oropharynx (OPC)	96 (36%)	120 (45%)
OPC p16 positive	17 (6%)	37 (14%)
OPC HPV DNA positive	14 (5%)	19 (7%)
Metastatic at initial diagnosis	56 (21%)	46 (17%)

Tumor characteristics at inclusion:

	EXTREME	TPEx
Metastatic alone	118 (44%)	110 (41%)
Locoregional relapse alone	98 (36%)	94 (35%)
Metastatic and locoregional relapse	54 (20%)	65 (24%)

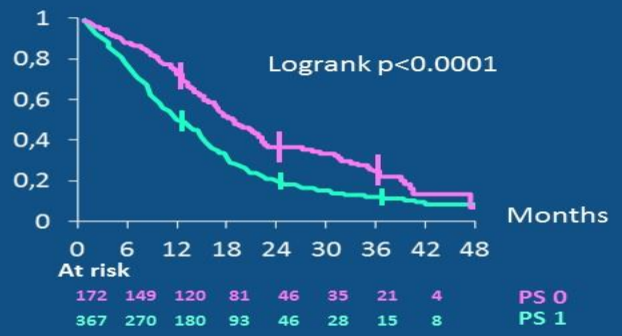
Overall Survival

Median OS higher than expected:
14.5 months in TPEx arm and
13.4 months in EXTREME arm

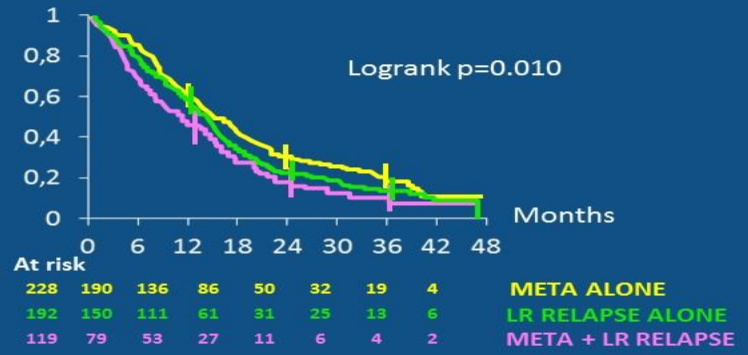
Hazard ratio TPEx vs EXTREME:
HR=0.87 (95% CI: 0.71-1.05)
p-value=0.15

Overall Survival: prognostic factors

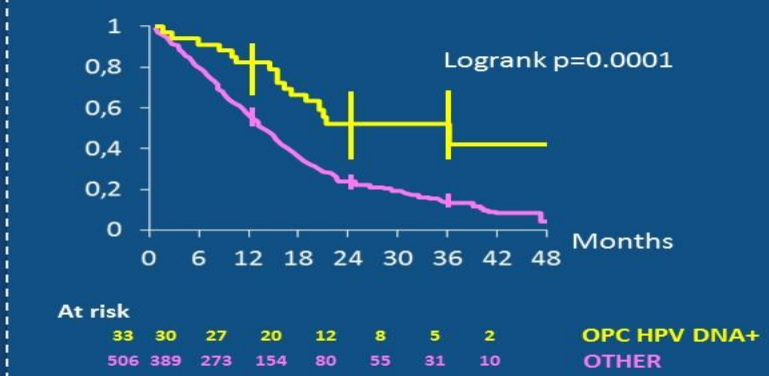
- **Performance status**



- **Type of evolution at inclusion**



- **Tumor location and HPV DNA status**



Progression Free Survival and ORR 12 wks

- 486 events, 247 in the EXTREME arm and 239 in the TPEx arm
- **HR = 0.88 (95%CI:0.74-1.06), p-value = 0.17**

- **ORR (CR+PR) at 12 weeks according to local evaluation**

→ **46% (123 / 269) in the TPEx arm**
→ **40% (109 / 270) in the EXTREME arm**

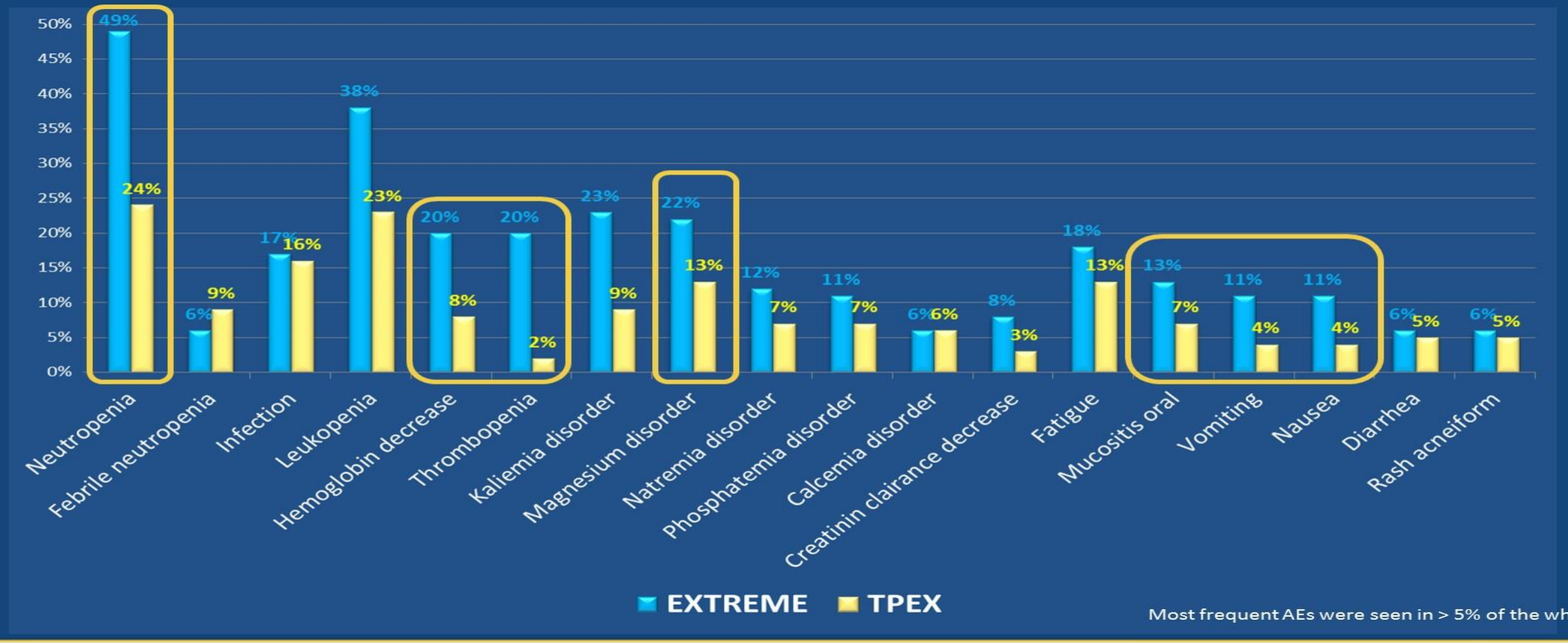
Adverse events (AEs) during chemotherapy phase

Maximal grade of AEs	EXTREME	TPEx
% patients with no AE or AE grade 1-2	8%	19%
% patients with AEs grade 3	41%	45%
% patients with AEs grade 4	44%	30%
% patients with AEs grade 5	7%	6%

Toxicity was lower in the TPEx arm:

36% pts had grade ≥4 AEs during CT vs 51% in EXTREME (p<0.001)

Most frequent AEs grade ≥ 3



Most frequent AEs were seen in > 5% of the whole population

Compliance

	EXTREME	TPEx	P-value
Median number of CT cycles delivered	5	4	
% of pts who received all planned cycles of CT	44%	72%	<0.0001
% of cycles administered with delay	27%	10%	<0.0001
% of pts switched to carboplatin	34%	9%	<0.0001
% of pts who received G-CSF	43%	98%	<0.0001
% of pts who received the planned number of Cx injections during CT phase	30%	51%	<0.0001

CT : chemotherapy ; Cx : cetuximab ; pts : patients

Maintenance

		EXTREME	TPEx	P-value
% of pts who started maintenance		52%	72%	<0.0001
% of pts without maintenance		48%	28%	
Main reasons:	Progression or death	21%	13%	
	Toxicity	11%	6%	
	Patient refusal	6%	2%	
	Other reasons	10%	7%	
Dose of Cx received during maintenance (median in mg/m²)		3 246	3 858	0.015
Duration of maintenance (median)		12 weeks	14 weeks	
Duration of treatment (CT + maintenance) (median)		18 weeks	21 weeks	

Cx: cetuximab; patients:pts

TPExtreme randomized trial: Quality of Life (QoL) and survival according to second-line treatments in patients with recurrent/metastatic head and neck squamous cell carcinoma (R/M HNSCC)

Joël Guigay, Jérôme Fayette, Ricard Mesia Sr., Esma Saada-Bouzid, Cedrik Lafond, Lionnel Geoffrois, Laurent Martin, Olivier Capitain, Didier Cupissol, Helene Castanie, Alison Claire Johnson, Damien Vansteene, Caroline Even, Christian Sire, Raissa Kapso, Melissa Delhommeau, Cecile Chevassus-Clement, Ulrich Keilholz, Jean Bourhis, Anne Auperin, GORTEC - AIO Studien gGmbH - TTCC - Unicancer H&N

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Sponsor: GORTEC

National Cooperative Groups coordination

FRANCE Pr J. BOURHIS | SPAIN Pr R. MESIA | GERMANY Pr U. KEILHOLZ

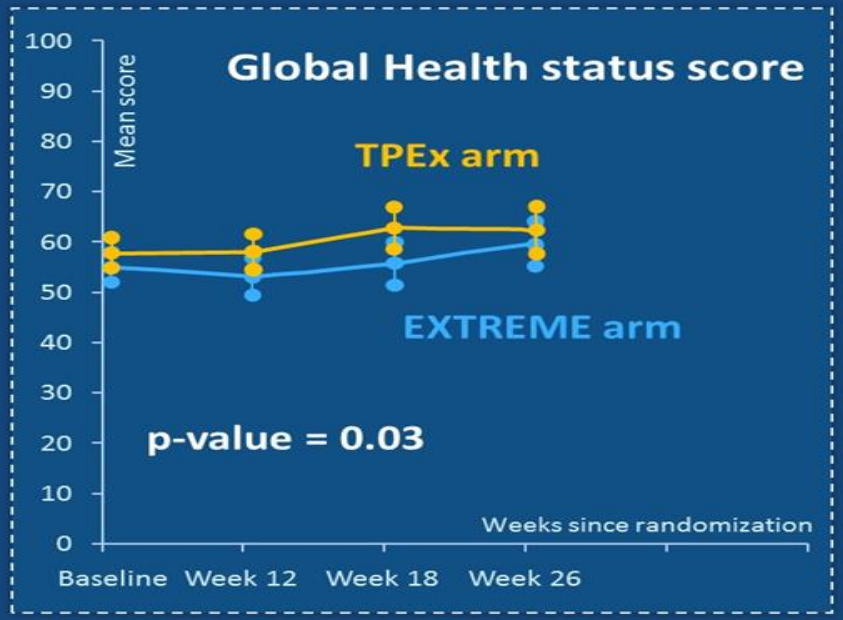
PRESENTED AT: 2020 ASCO ANNUAL MEETING #ASCO20

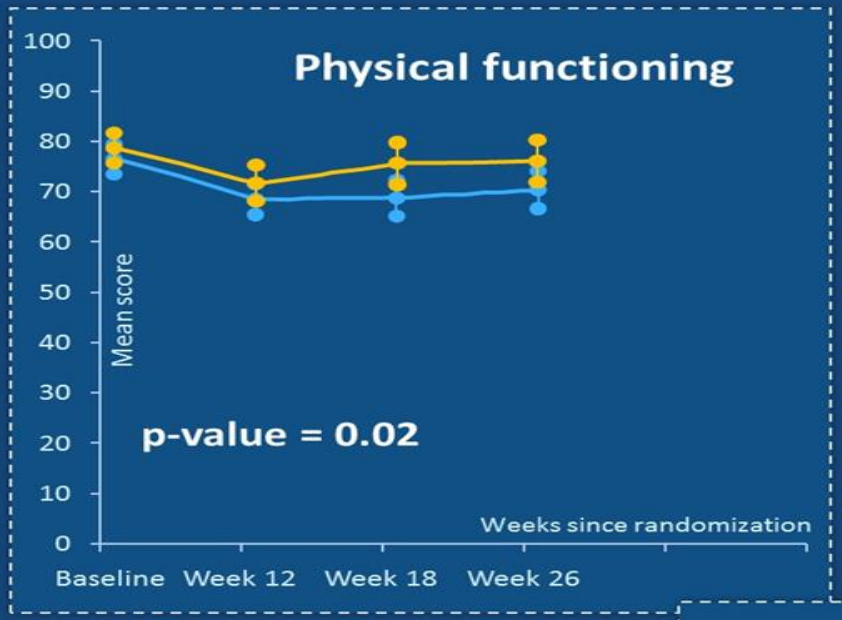
PRESENTED BY: Pr Joël GUIGAY

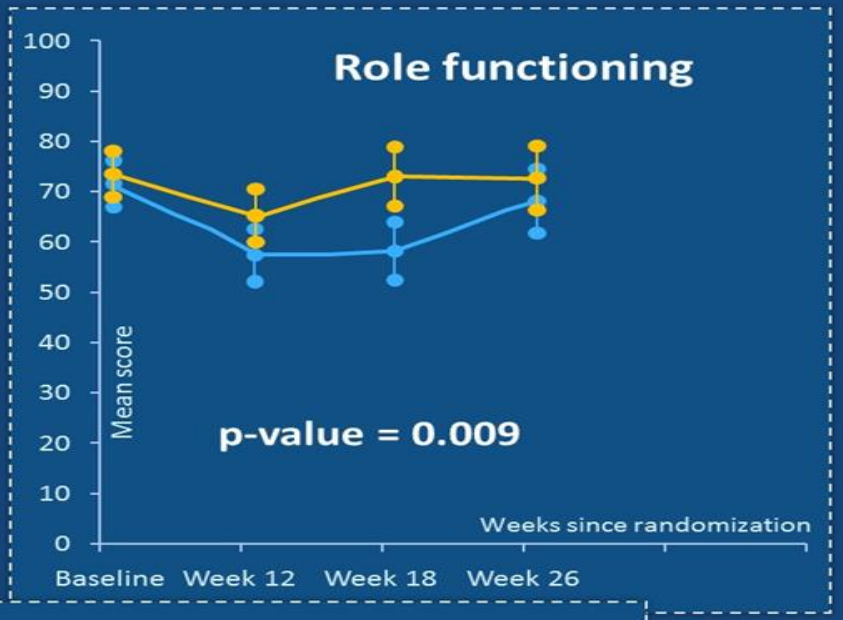
Primary QoL endpoint, physical and functioning scales

Mean and 95% confidence interval of QoL scores by treatment arm, from baseline until Week 26

- **Primary QoL endpoint**



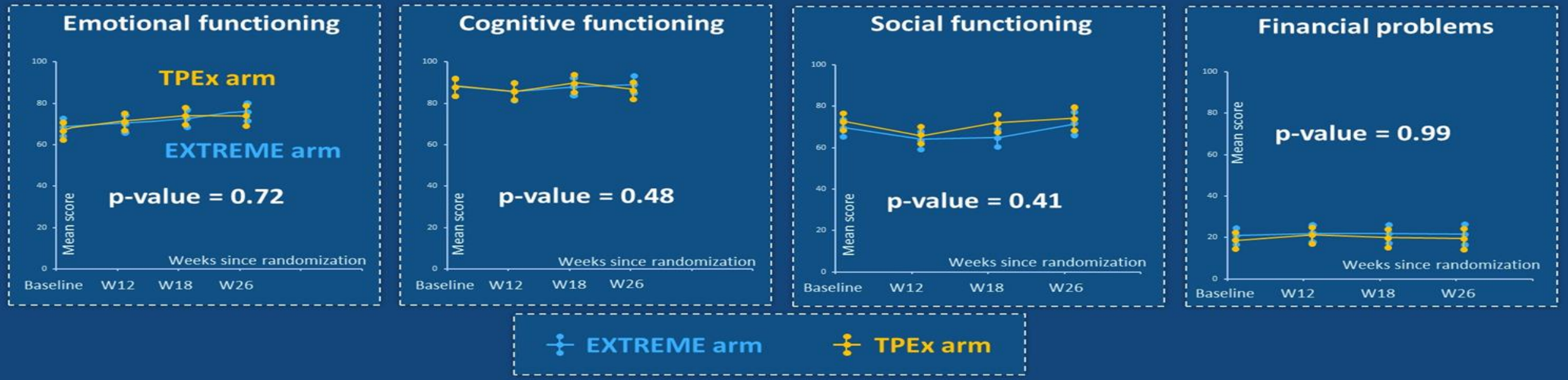




EXTREME arm TPEx arm

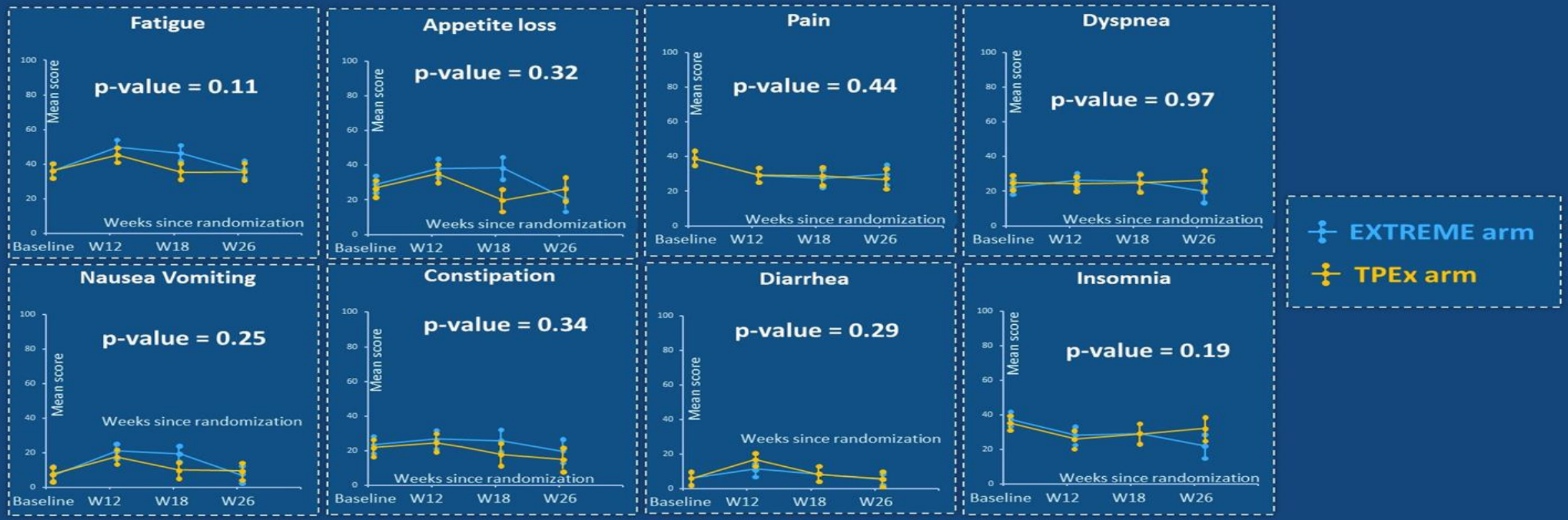
QoL: other functional scales & financial problems

Mean and 95% confidence interval of QoL scores by treatment arm, from baseline until Week 26



QoL: scores related to symptoms

Mean and 95% CI of QoL scores by treatment arm, from baseline until Week 26



2nd line treatment

	EXTREME arm		TPEx arm	
Patients with 2nd line data available	256		245	
2nd line received	164 (64%)		157 (64%)	
Type of 2nd line				
IO (anti PD-1/PDL-1)	41 (16%)		41 (17%)	
Taxane based chemotherapy	56 (22%)	120 (47%)	30 (12%)	109 (44%)
Other chemotherapy	40 (16%)		61 (25%)	
Cetuximab +/- chemotherapy	24 (9%)		18 (7%)	
Radiotherapy	3 (1%)		7 (3%)	

- 79% and 85% of the 2nd line treatments were given after progression in EXTREME and TPEx arms, respectively.

Overall Survival

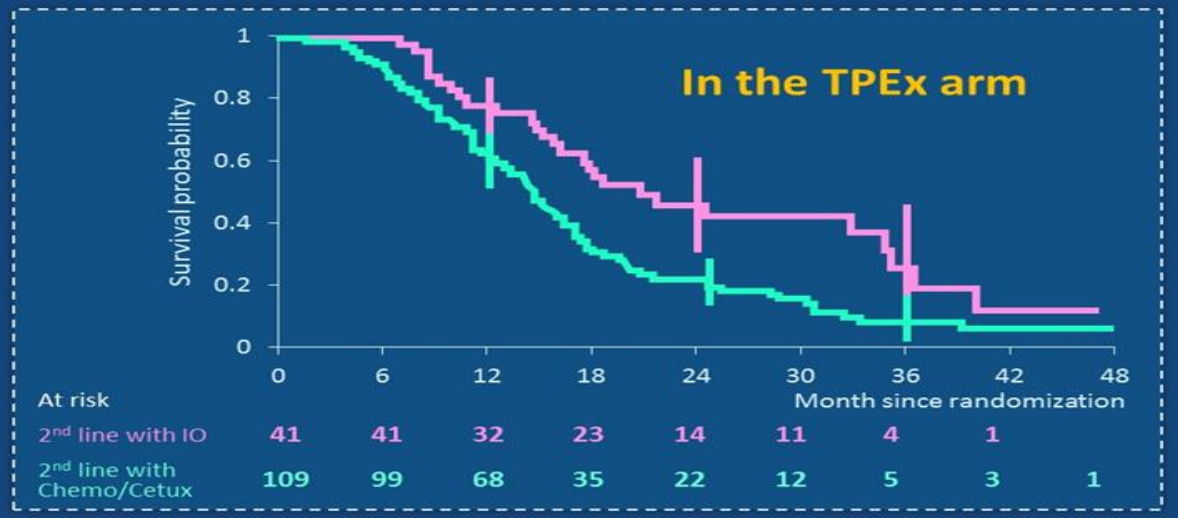
Median OS higher than expected:
14.5 months in TPEx arm and
13.4 months in EXTREME arm

Hazard ratio TPEx vs EXTREME:
HR=0.89 (95% CI: 0.74-1.08)
p-value=0.23

2nd line treatment: Overall Survival since randomization according to Chemo +/- Cetux vs IO

OS rate at	2nd line with chemo/cetux	2nd line with IO
12 months	66.8%	78.1%
24 months	26.8%	36.9%
36 months	12.6%	23.2%
Median OS (95%CI)	16.2 months (14.8 – 17.3)	19.5 months (15.9 – 22.8)

2nd line treatment: Overall Survival since randomization in each arm according to Chemo +/- Cetux vs IO

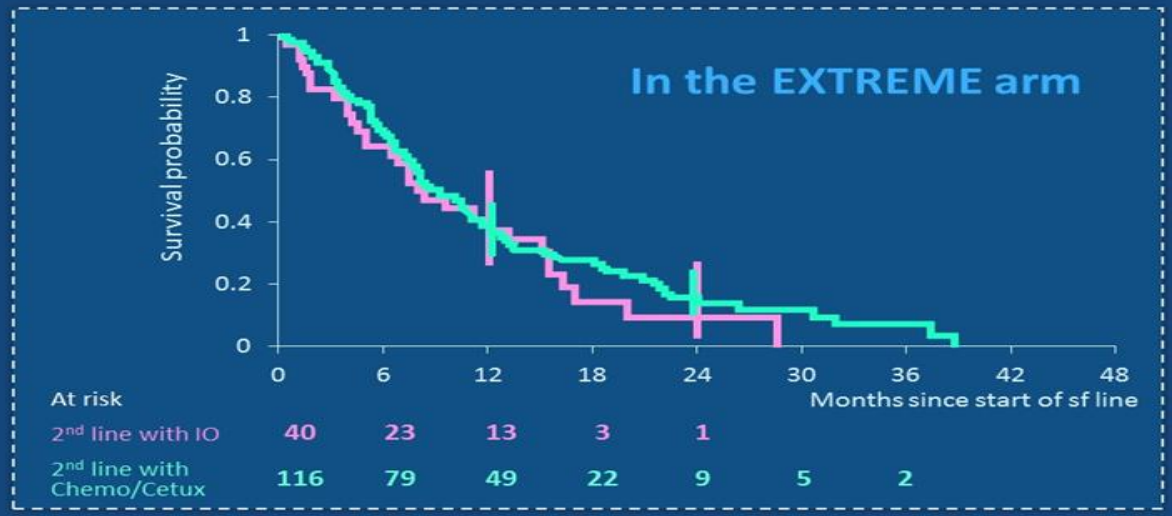


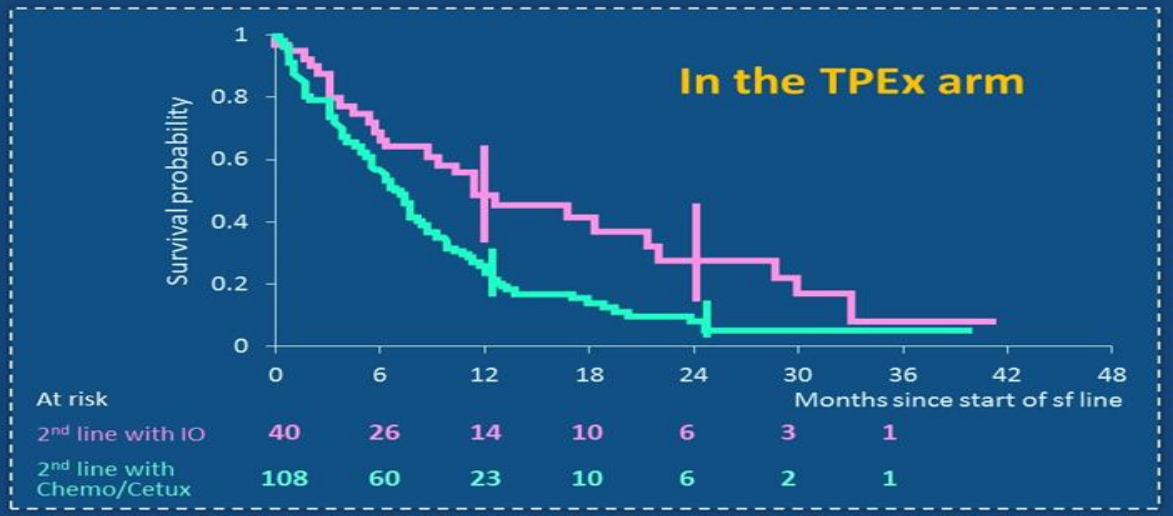
- **Interaction test p = 0.077**

2nd line treatment: Overall Survival since randomization in each arm according to Chemo +/- Cetux vs IO

	EXTREME arm		TPEx arm	
	2nd line with chemo/cetux	2nd line with IO	2nd line with chemo/cetux	2nd line with IO
Overall survival at 12 months	70.8%	78.1%	62.4%	78.1%
Overall survival at 24 months	29.9%	27.5%	23.2%	46.9%
Overall survival at 36 months	15.6%	18.9%	9.9%	27.5%
Median OS (95%CI)	17.6 months (15.2 – 19.5)	19.4 months (13.4 – 22.3)	14.9 months (13.0 – 16.3)	21.9 months (15.9 – 35.0)

2nd line treatment: Overall Survival since start of 2nd line in each arm according to Chemo +/- Cetux vs IO





- **Interaction test p = 0.008**

2nd line treatment: Overall Survival since start of 2nd line in each arm according to Chemo +/- Cetux vs IO

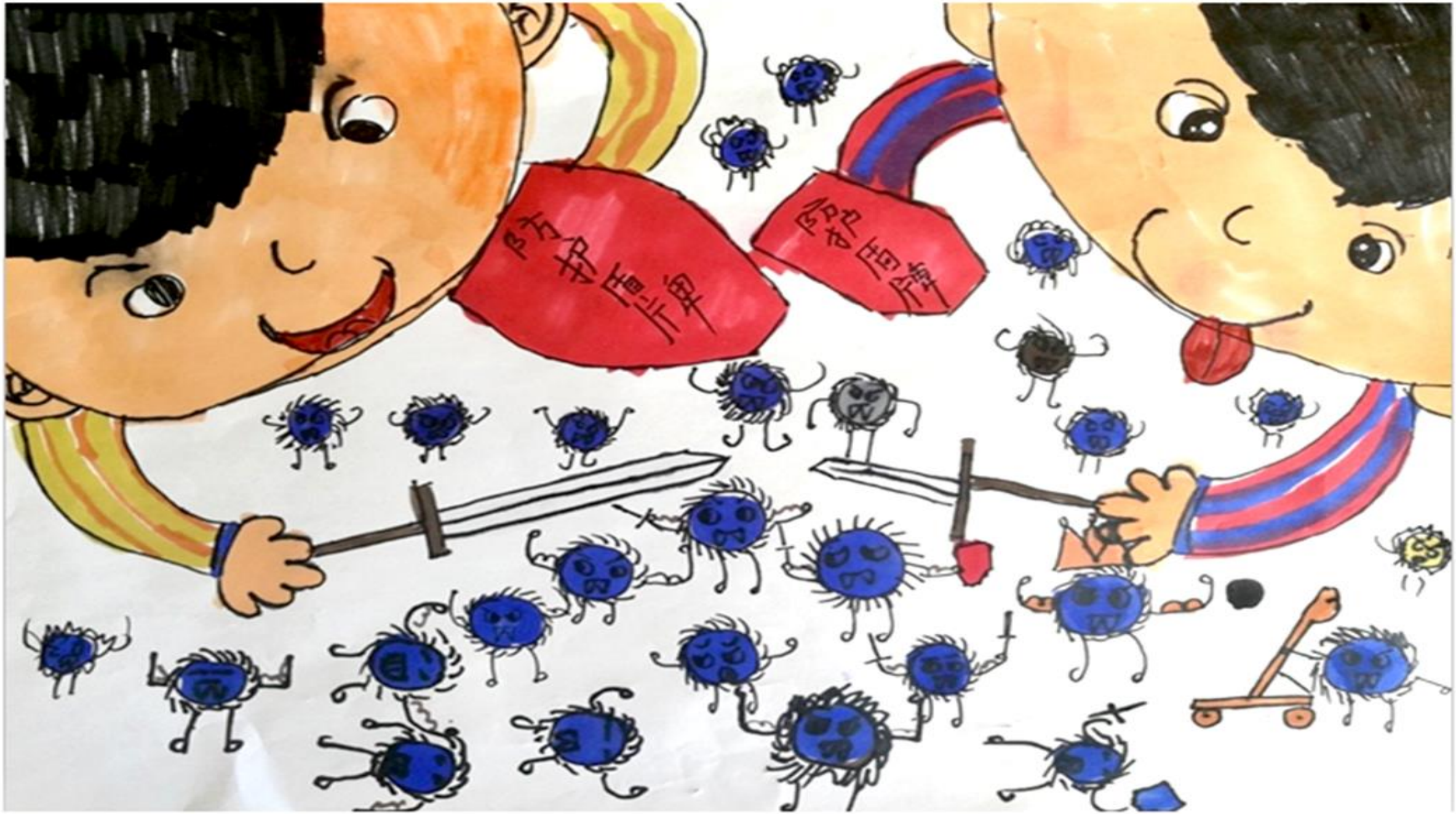
	EXTREME arm		TPEx arm	
	2nd line with chemo/cetux	2nd line with IO	2nd line with chemo/cetux	2nd line with IO
Overall survival at 12 months	39.4%	41.0%	25.1%	49.1%
Overall survival at 24 months	15.9%	9.8%	8.7%	27.8%
Overall survival at 36 months	7.3%	0%	5.8%	8.3%
Median OS (95%CI)	9.3 months (7.7 – 11.6)	8.3 months (5.0 – 15.0)	7.1 months (5.6 – 8.2)	11.6 months (6.0 – 21.4)

CONCLUSIONES

- Los taxanos pueden suponer una alternativa a EXTREME con una eficacia similar, mejor perfil de toxicidad y menor numero de ciclos de QT

- Mejor calidad de vida TEPex

- Los pacientes tratados con inmunoterapia tras TEPex o EXTREME tienen mejor Superviencia que con QT +/- cetuximab
  - Los pacientes tratados con inmunoterapia tras TPEex tienen mejores datos de supervivencia que inmunoterapia tras EXTREME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