

PÓS 2017
ASCO
ANNUAL MEETING
Making a Difference in Cancer Care *WITH YOU*

The graphic features a central dark grey circle with a yellow border. Inside the circle, the text "PÓS 2017" is in yellow, "ASCO" is in large white letters, and "ANNUAL MEETING" is in smaller white letters. Below this, the tagline "Making a Difference in Cancer Care WITH YOU" is written in a smaller white font. To the right of the text is a network diagram consisting of a central white person icon connected to various white icons representing different aspects of cancer care, such as a microscope, a person, a gear, a document, and a globe. The background of the entire slide is a yellow grid of interconnected hexagons.

CÂNCER DO TRATO GASTROINTESTINAL NÃO COLORRETAL



CONFLITOS DE INTERESSE

Esses slides estão isentos de conflitos de interesses e possuem finalidade essencialmente educacional.



ROTEIRO

1. CARCINOMA HEPATOCELULAR

- TIVANTINIB EM SEGUNDA LINHA
- REFLECT STUDY: LENVATINIB VS. SORAFENIBE
- SIRT VS. SORAFENIBE EM TUMORES LOCALMENTE AVANÇADOS

2. CANCER GÁSTRICO

- IMUNOTERAPIA NO CÂNCER GÁSTRICO (KEYNOTE 059 E CHECKMATE 032)
- FLOT 4

3. PÂNCREAS E VIAS BILIARES

- BILCAP: CAPECITABINA ADJUVANTE EM TUMORES DE VIAS BILIARES
- RTOG 0848: ERLOTINIBE + GEMCITABINA NA ADJUVÂNCIA DO CÂNCER DE PÂNCREAS
- HALO 202: PEGPH20 NO TRATAMENTO DE PRIMEIRA LINHA DO CÂNCER DE PÂNCREAS AVANÇADO

CARCINOMA HEPATOCELULAR



CARCINOMA HEPATOCELULAR

TIVANTINIB EM SEGUNDA LINHA

Contexto

- Sorafenibe e regorafenibe são agentes aprovados para o tratamento do carcinoma hepatocelular avançado (CHC).
- MET => Proteína tirosina quinase associada ao receptor do fator de crescimento hepatocitário (HGF).
=> Envolvido na progressão e disseminação do hepatocarcinoma.
- Tivatinib => Inibidor oral da MET
=> Ganho de sobrevida global e sobrevida livre de progressão vs. placebo em um estudo de fase 2 em pacientes com CHC MET-High.

CARCINOMA HEPATOCELULAR

TIVANTINIB EM SEGUNDA LINHA

Contexto

- MET-High: Fator preditivo para atividade de Tivantinib

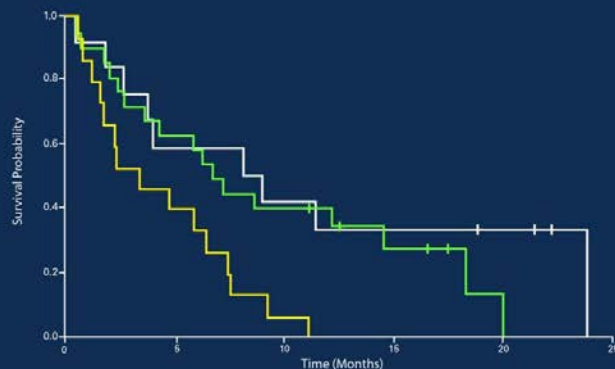
Background: Tumor MET as a Predictive Factor

	Median OS	Patients	Events
— Placebo MET-Low	9.0 mos	13	9
— Placebo MET-High	3.8 mos	15	15

HR: 0.34 (95% CI: 0.13-0.86) p=0.02

	Median OS	Patients	Events
— Placebo MET-Low	9.0 mos	13	9
— Tivantinib MET-High	7.2 mos	22	17

HR: 0.72 (95% CI: 0.30-1.70) p=0.45



Tivantinib vs placebo in 37 MET-High patients: HR: 0.43 (95% CI: 0.19-0.97), p=0.03

Tivantinib vs placebo in 40 MET-Low patients: HR: 1.33 (95% CI: 0.58-3.04), p=0.50

Significant interaction test for tivantinib and tumor MET status in terms of OS (p=0.04)

Rimassa L, GI Cancers Symposium 2016, abstr 197

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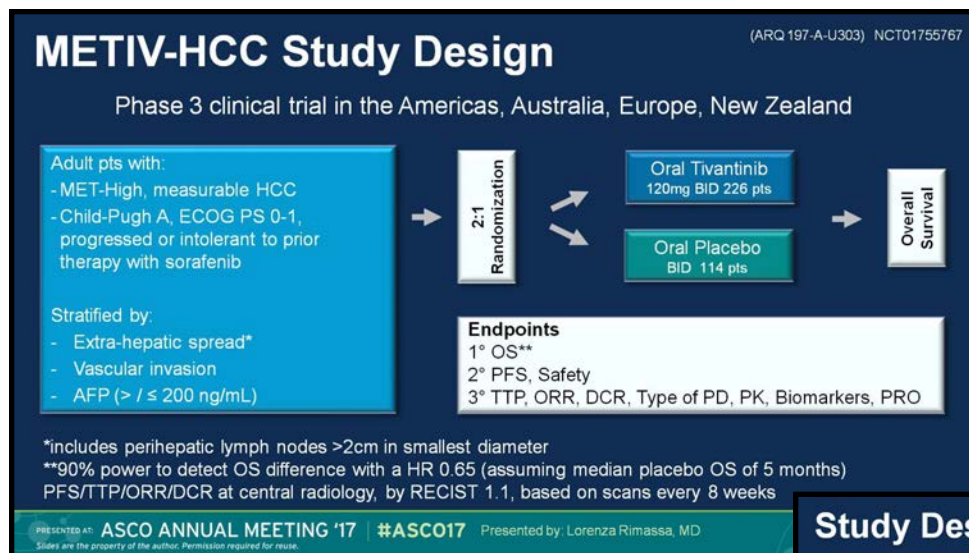
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CARCINOMA HEPATOCELULAR

TIVANTINIB EM SEGUNDA LINHA

Desenho do Estudo



Study Design and Conduct

Key Eligibility Criteria

- Histologically confirmed advanced HCC, radiographic progression or intolerance to sorafenib
- MET-High (MET ≥2+ in ≥50% of tumor cells) tissue by immunohistochemistry (Ventana SP-44 antibody) at central laboratory (Labcorp)
- ECOG PS ≤1, Child-Pugh A cirrhotic status; adequate bone marrow, liver, kidney functions
- Measurable disease according to RECIST 1.1; no pleural effusion or clinically evident ascites

Enrolment and dosing

- Between Jan 2013 and Aug 2013, 43 patients were dosed at 240mg BID (new tablet formulation). Due to drug-related G≥3 neutropenia, dose was reduced to 120mg BID (ITT population), a modified dose reduction schema was implemented, and 340 patients were dosed between Sep 2013 and Mar 2016
- Treatment continued until confirmed radiographic disease progression, intolerable AEs or death

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CARCINOMA HEPATOCELULAR

TIVANTINIB EM SEGUNDA LINHA

Resultados

Baseline Characteristics (1)

	Tivantinib N=226 (%)	Placebo N=114 (%)
Median age (yrs. range)	65.6 (19 - 87)	64.7 (26 - 84)
Males	199 (88.1)	107 (93.9)
Caucasian	162 (71.7)	86 (75.4)
ECOG PS 0	141 (62.4)	66 (57.9)
BCLC stage A / B / C	15 (6.6) / 27 (11.9) / 184 (81.4)	7 (6.1) / 17 (14.9) / 90 (78.9)
Extrahepatic spread*	130 (57.5)	67 (58.8)
Vascular invasion*	79 (35.0)	38 (33.3)
Extrahepatic spread and/or vascular invasion	160 (70.8)	81 (71.1)
AFP >200ng/mL*	97 (42.9)	48 (42.1)
HBV+ / HCV+	40 (17.7) / 73 (32.3)	21 (18.4) / 33 (28.9)
Child-Pugh A	215 (95.1)	108 (94.7)

*Stratification factors

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Baseline Characteristics (2)

	Tivantinib N=226 (%)	Placebo N=114 (%)
Prior sorafenib for <60 days	25 (11.1)	11 (9.6)
Median time on sorafenib (months, range)	6.3 (0.4 - 46.5)	5.8 (0.7 - 65.0)
Median time from last sorafenib dose (months, range)	2.2 (0.43 - 32.4)	2.2 (0.46 - 43.0)
Reason for sorafenib discontinuation		
Intolerance	38 (16.9)	24 (21.1)
Radiographic progression	186 (82.7)	89 (78.1)
Increased size of existing lesions	148 (65.8)	64 (56.1)
New intrahepatic lesions	66 (29.3)	42 (36.8)
New distant metastasis	28 (12.4)	20 (17.5)
New vascular invasion	12 (5.3)	3 (2.6)

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Baseline Tumor MET at Immunohistochemistry

Tested Tumor Samples (overall)	MET-High N (%)	MET-Low N (%)
N=1125	591 (53)	534 (47)
Biopsied before sorafenib (N=558)	197 (35)	361 (65)
Biopsied after sorafenib (N=567)	394 (69)	173 (31)
Median H-score (range)	170 (120 - 300)	90 (0 - 180)

MET-High Tumor Samples	Biopsied Pre-sorafenib N (%)	Biopsied Post-sorafenib N (%)
N=591	197 (33)	394 (67)
Median H-Score (range)	170 (130 - 290)	170 (120 - 300)

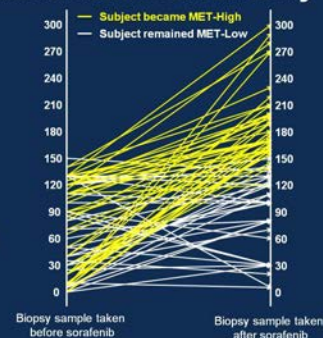
Per-protocol IHC was performed by the central lab; subsequent analysis by an independent lab on a subset of samples was not conclusive due to reader and assay differences; final results are pending

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Baseline Tumor MET at Immunohistochemistry

51 out of 84 (61%) patients who were MET-Low before sorafenib and were re-biopsied after sorafenib (before enrolment in METIV-HCC) converted to MET-High. In these patients, the median H-score increase was 100

A correlation was found between High MET status and treatment with sorafenib ($p < 0.0001$)
No correlation was found between MET status and other factors related to prior therapies



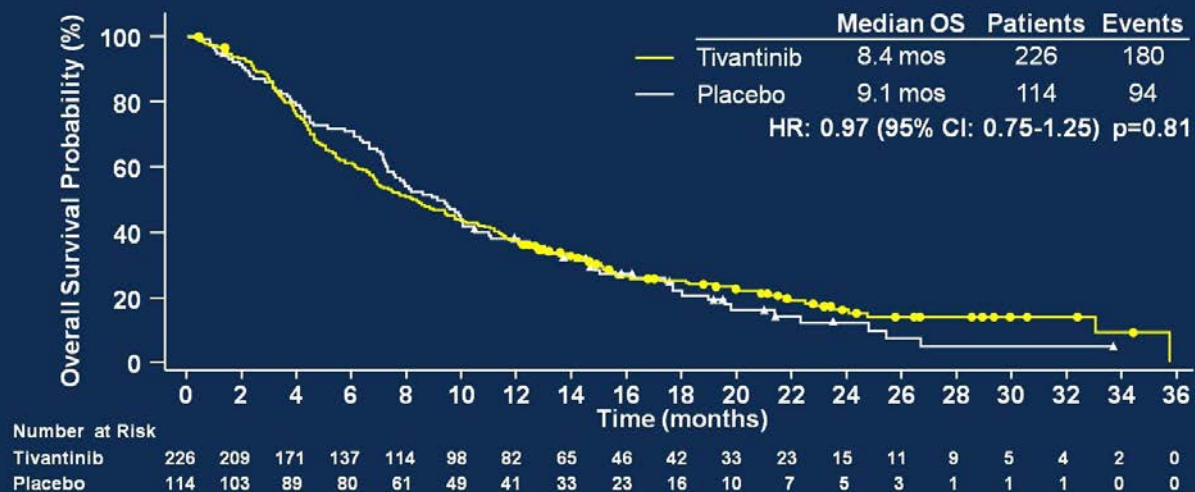
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CARCINOMA HEPATOCELULAR

TIVANTINIB EM SEGUNDA LINHA

Desfecho Primário

Primary Endpoint: Overall Survival



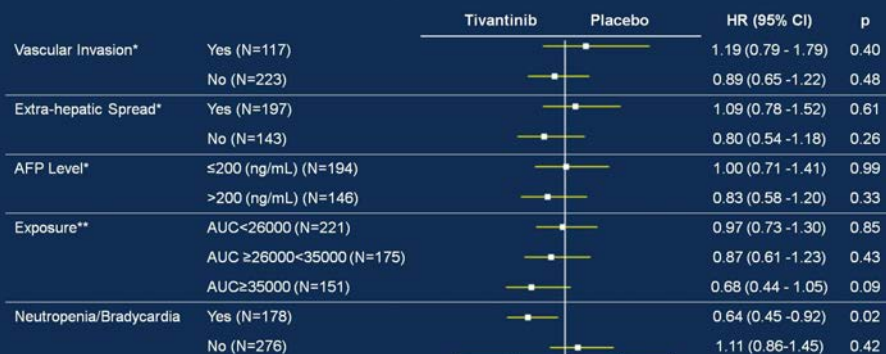
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CARCINOMA HEPATOCELULAR

TIVANTINIB EM SEGUNDA LINHA

Desfecho Primário

OS of Selected Subgroups (1)

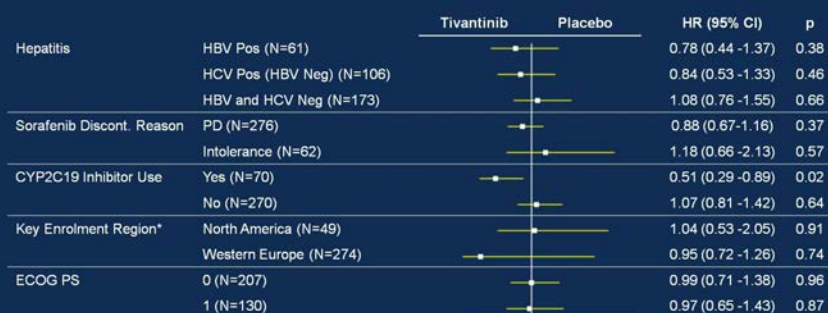


*Stratification factors; **Population PK

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OS of Selected Subgroups (2)



*17 patients were from Latin America, Australia, New Zealand

No OS advantage for any arms by: Age, gender, ethnicity, AST, ALT, platelets, response to sorafenib

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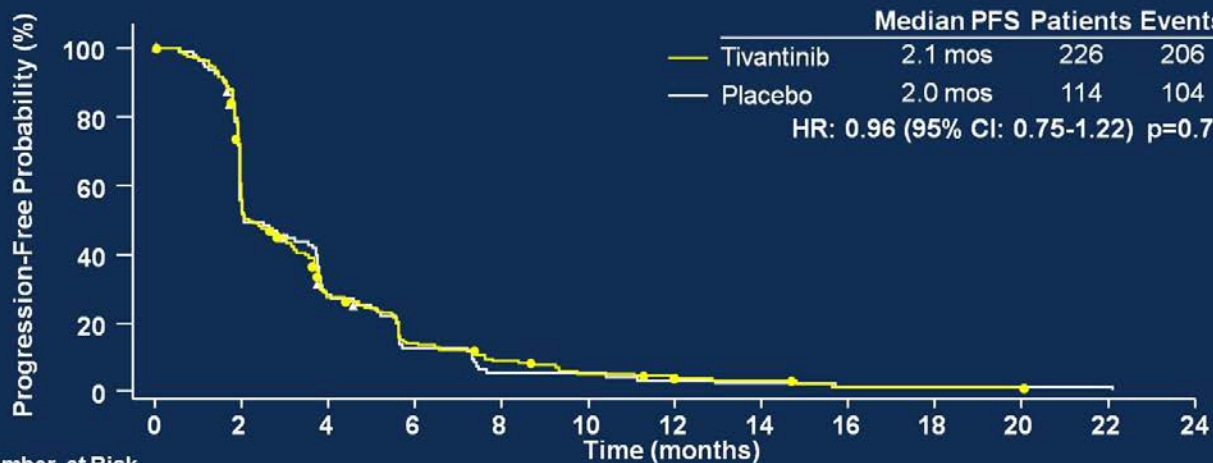
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CARCINOMA HEPATOCELULAR

TIVANTINIB EM SEGUNDA LINHA

Desfecho Secundário

Secondary Endpoint: Progression-free Survival



Number at Risk

Tivantinib	226	108	56	28	17	9	5	4	1	1	1	0	0
Placebo	114	53	28	12	5	5	3	2	1	1	1	1	0

Median TTP: 2.4 months on tivantinib, 3.0 on placebo; HR:0.96 (95% CI: 0.74-1.25), p=0.76
DCR: 49.5% on tivantinib, 50% on placebo (no objective responses in either arm)

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CARCINOMA HEPATOCELULAR

TIVANTINIB EM SEGUNDA LINHA

Segurança

Treatment-Emergent Adverse Events Summary

TEAE Grade	Tivantinib N=225 (%)	Placebo N=114 (%)
Any Grade	214 (95.1)	108 (94.7)
≥3	125 (55.6)	63 (55.3)
5	43 (19.1)	10 (8.8)
4	16 (7.1)	7 (6.1)
3	66 (29.3)	46 (40.4)
2	74 (32.9)	33 (28.9)
1	15 (6.7)	12 (10.5)

G5 TEAEs related to the study drug:

- 1.3% (N=3) on tivantinib, 0 on placebo

Deaths (all causes) within 30 days from last dose:

- 22.1% (N=50) on tivantinib, 15.8% (N=18) on placebo
- Most common G5 TEAEs on tivantinib: general deterioration 3.5% (N=8), hepatic failure 2.6% (N=6)

Treatment-Emergent Adverse Events Summary

Most Common (>15%) TEAEs	Tivantinib			Placebo		
	All grades	Grade ≥3	Grade 5	All grades	Grade ≥3	Grade 5
Abdominal Pain	69 (30.7)	9 (4.0)	0 (0.0)	44 (38.6)	5 (4.4)	0 (0.0)
Fatigue	58 (25.8)	3 (1.3)	0 (0.0)	31 (27.2)	5 (4.4)	0 (0.0)
Asthenia	48 (21.3)	7 (3.1)	1 (0.4)	25 (21.9)	2 (1.8)	0 (0.0)
Ascites	46 (20.4)	16 (7.1)	0 (0.0)	24 (21.1)	9 (7.9)	1 (0.9)
Decreased Appetite	36 (16.0)	2 (0.9)	0 (0.0)	21 (18.4)	3 (0.6)	0 (0.0)
Pruritus	24 (10.7)	3 (1.3)	0 (0.0)	21 (18.4)	0 (0.0)	0 (0.0)
Edema peripheral	54 (24.0)	1 (0.4)	0 (0.0)	19 (16.7)	0 (0.0)	0 (0.0)
Anemia	42 (18.7)	11 (4.9)	1 (0.4)	17 (14.9)	7 (6.1)	0 (0.0)
Diarrhea	50 (22.2)	4 (1.8)	0 (0.0)	17 (14.9)	2 (1.8)	0 (0.0)
Nausea	50 (22.2)	1 (0.4)	0 (0.0)	13 (11.4)	1 (0.9)	0 (0.0)
Other TEAEs of relevance:						
Neutropenia	28 (12.4)	9 (4.0)	0 (0.0)	5 (4.4)	1 (0.9)	0 (0.0)
Bradycardia	31 (13.8)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

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CARCINOMA HEPATOCELULAR

TIVANTINIB EM SEGUNDA LINHA

Conclusões

- Tivatinib na dose de 120 mg BID não foi superior ao placebo em termos de sobrevida global em pacientes com CHC-MET High que progrediram ou foram intolerantes ao sorafenibe.
- A sobrevida dos pacientes com CHC-MET High foi mais longa que o esperado (9,1 meses).
- Os efeitos adversos foram manejáveis na dose de 120 mg BID.

CARCINOMA HEPATOCELULAR

REFLECT STUDY: LENVATINIB VS. SORAFENIBE

Contexto

Study Rationale

- Hepatocellular carcinoma (HCC) is the second leading cause of cancer death worldwide and is responsible for nearly 745,000 deaths each year¹
- Sorafenib is the only systemic therapy proven to extend overall survival when used as first-line treatment for HCC²:
 - Over the past 10 years, 4 global phase 3 trials (of sunitinib, brivanib, linifanib, and erlotinib plus sorafenib) failed to meet their primary endpoints of noninferiority or superiority to sorafenib in overall survival (OS)³⁻⁶
- Lenvatinib, an oral multikinase inhibitor targeting VEGF receptors 1, 2, and 3, FGF receptors 1, 2, 3, and 4, PDGFR α , RET, and KIT, showed promising clinical activity in a previous phase 2 trial in patients with advanced HCC⁷

FGF, fibroblast growth factor; PDGFR α , platelet-derived growth factor receptor α ; VEGF, vascular endothelial growth factor.

1. Ferlay J, et al. *Int J Cancer*. 2015;136:E359-86; 2. Llovet JM, et al. *N Engl J Med*. 2008;359:378-90; 3. Cheng AL, et al. *J Clin Oncol*. 2013;31:4067-75; 4. Johnson PJ, et al. *J Clin Oncol*. 2013;31:3517-24; 5. Cainap C, et al. *J Clin Oncol*. 2015;33:172-9; 6. Zhu AX, et al. *J Clin Oncol*. 2015;33:559-66; 7. Ikeda K, et al. *J Gastroenterol*. 2017;52:512-9.

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A Phase 3 Trial of Lenvatinib vs Sorafenib in First-line Treatment of Patients With Unresectable Hepatocellular Carcinoma (REFLECT Study)

Ann-Li Cheng,¹ Richard S. Finn,² Shukai Qin,³ Kwang-Hyub Han,⁴ Kenji Ikeda,⁵ Fabio Piscaglia,⁶ Ari Baron,⁷ Joong-Won Park,⁸ Guohong Han,⁹ Jaesok Jassem,¹⁰ Jean Frederic Blanc,¹¹ Arndt Vogel,¹² Dmity Komov,¹³ TR Jeffrey Evans,¹⁴ Carlos Lopez,¹⁵ Corina Dulcis,¹⁶ Min Ren,¹⁶ Slijeva Kraljević,¹⁷ Toshiyuki Tamai,¹⁸ Masatoshi Kudo¹⁹

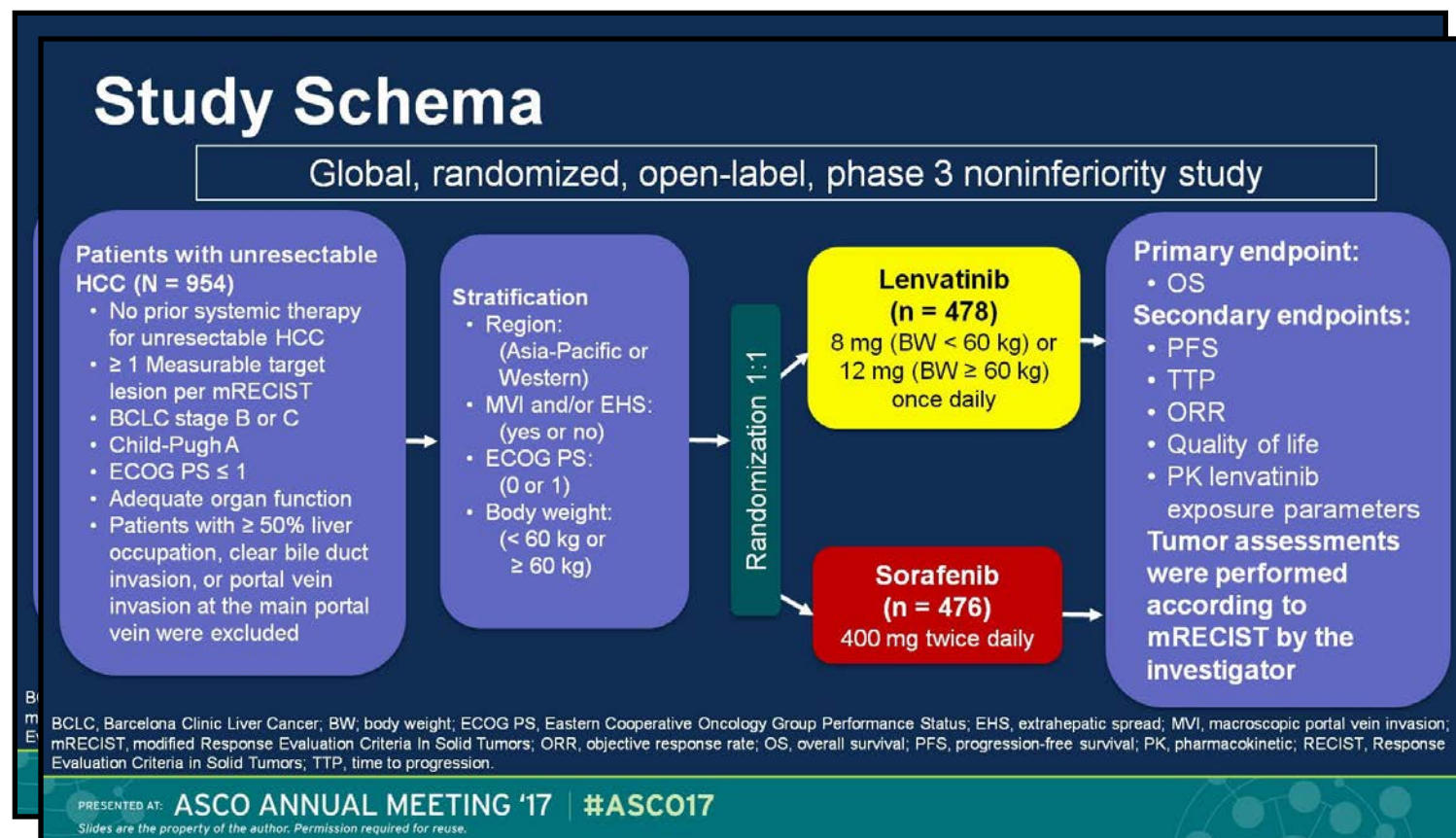
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CARCINOMA HEPATOCELULAR

REFLECT STUDY: LENVATINIB VS. SORAFENIBE

Desenho do Estudo



CARCINOMA HEPATOCELULAR

REFLECT STUDY: LENVATINIB VS. SORAFENIBE

Desenho do Estudo

Assessments and Statistical Analysis

- The primary endpoint of OS was first tested for noninferiority then for superiority:
 - The required number of events for the primary analysis was 700 deaths
- The HR and its 95% CI were estimated from a Cox proportional hazard model, with treatment group as a factor and with the analysis stratified according to randomization factors:
 - The noninferiority margin was set at 1.08 based on previous phase 3 trials of sorafenib^{1,2}
 - Noninferiority would be declared if the upper limit of the 2-sided 95% CI for HR was < 1.08
- A fixed-sequence procedure was followed to control the overall type I error rate of analyses for efficacy endpoints at $\alpha = 0.05$ (2-sided)
- After noninferiority was declared, secondary efficacy endpoints were tested:
 - Differences in PFS and TTP were tested using a stratified log-rank test with randomization stratification factors and the associated HR and its 95% CI were evaluated
 - A difference in ORR was tested using the Cochran-Mantel-Haenszel chi-square test with randomization stratification factors as strata, and the associated odds ratio and its 95% CI were evaluated
- To assess futility, 2 interim analyses were performed using Bayesian predictive probability in a noninferiority design

CI, confidence interval; HR, hazard ratio.

1. Llovet JM, et al. *N Engl J Med*. 2008;359:378-90; 2. Cheng AL, et al. *Lancet Oncol*. 2009;10:25-34.

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CARCINOMA HEPATOCELULAR

REFLECT STUDY: LENVATINIB VS. SORAFENIBE

Resultados

Patient Characteristics

Characteristic	Category	Lenvatinib (n = 478)	Sorafenib (n = 476)
Mean age (years)		61.3	61.2
Sex, n (%)	Male	405 (85)	401 (84)
	Female	73 (15)	75 (16)
Region, n (%)	Western	157 (33)	157 (33)
	Asia-Pacific	321 (67)	319 (67)
Body weight (kg), n (%)	< 60	153 (32)	146 (31)
	≥ 60	325 (68)	330 (69)
ECOG PS, n (%)	0	304 (64)	301 (63)
	1	174 (36)	175 (37)
MVI, EHS, or both, n (%)	Yes	329 (69)	336 (71)
	No	149 (31)	140 (29)
Child-Pugh class, n (%)	A	475 (99)	471 (99)
	B	3 (1)	5 (1)
BCLC stage, n (%)	B (intermediate stage)	104 (22)	92 (19)
	C (advanced stage)	374 (78)	384 (81)

Patient Characteristics (continued)

Characteristic	Category	Lenvatinib (n = 478)	Sorafenib (n = 476)
Involved disease sites per patient, n (%)	1	207 (43)	207 (44)
	2	167 (35)	183 (38)
	≥ 3	103 (22)	86 (18)
Etiology of chronic liver disease, n (%)	Hepatitis B	251 (53)	228 (48)
	Hepatitis C	91 (19)	126 (27)
	Alcohol	36 (8)	21 (4)
	Other	38 (8)	32 (7)
Baseline AFP level group (ng/mL), n (%)	Unknown	62 (13)	69 (15)
	< 200	255 (53)	286 (60)
	≥ 200	222 (46)	187 (39)
Median baseline AFP level (ng/mL)		133.1	71.2
Concomitant systemic antiviral therapy for hepatitis B or C, n (%)		163 (34)	149 (31)

AFP, alpha-fetoprotein.

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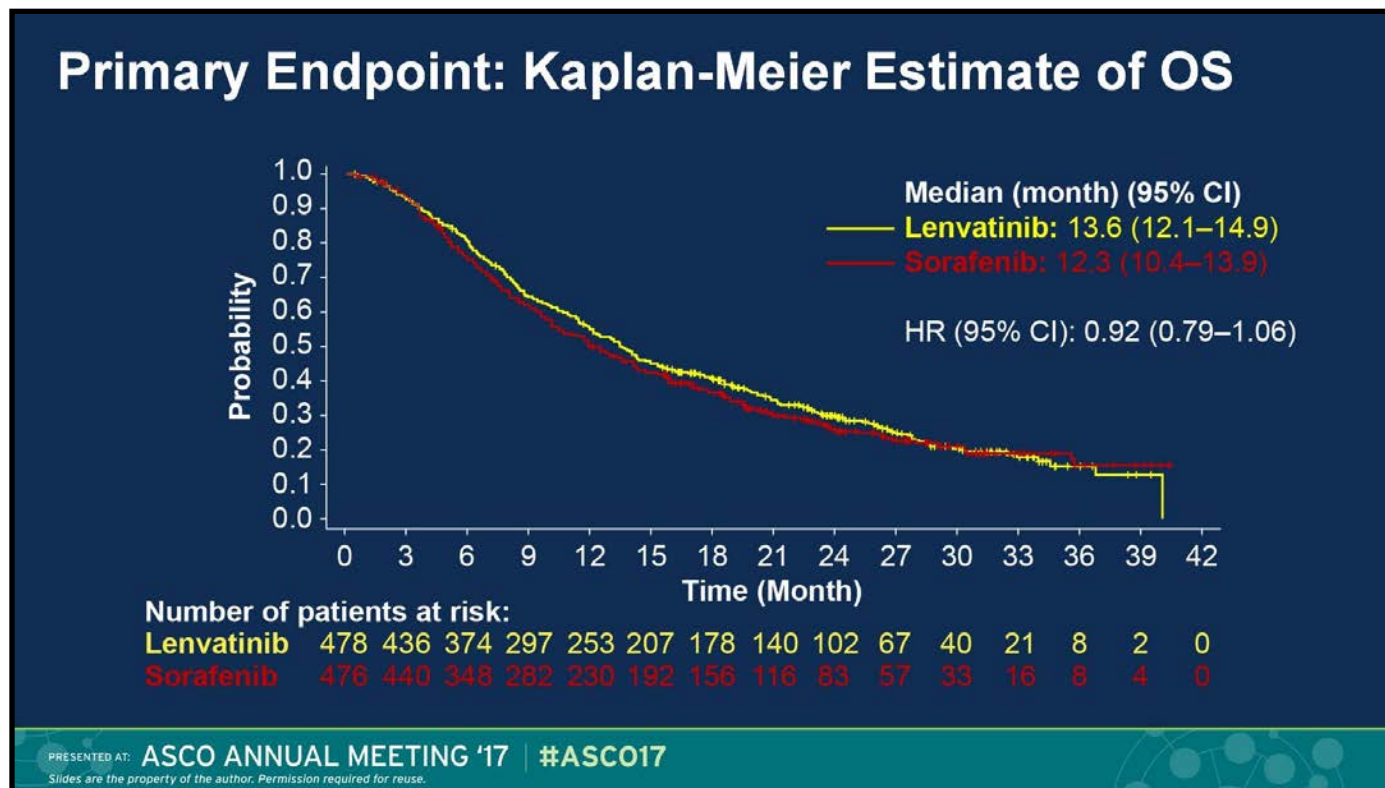
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REFLECT STUDY: LENVATINIB VS. SORAFENIBE

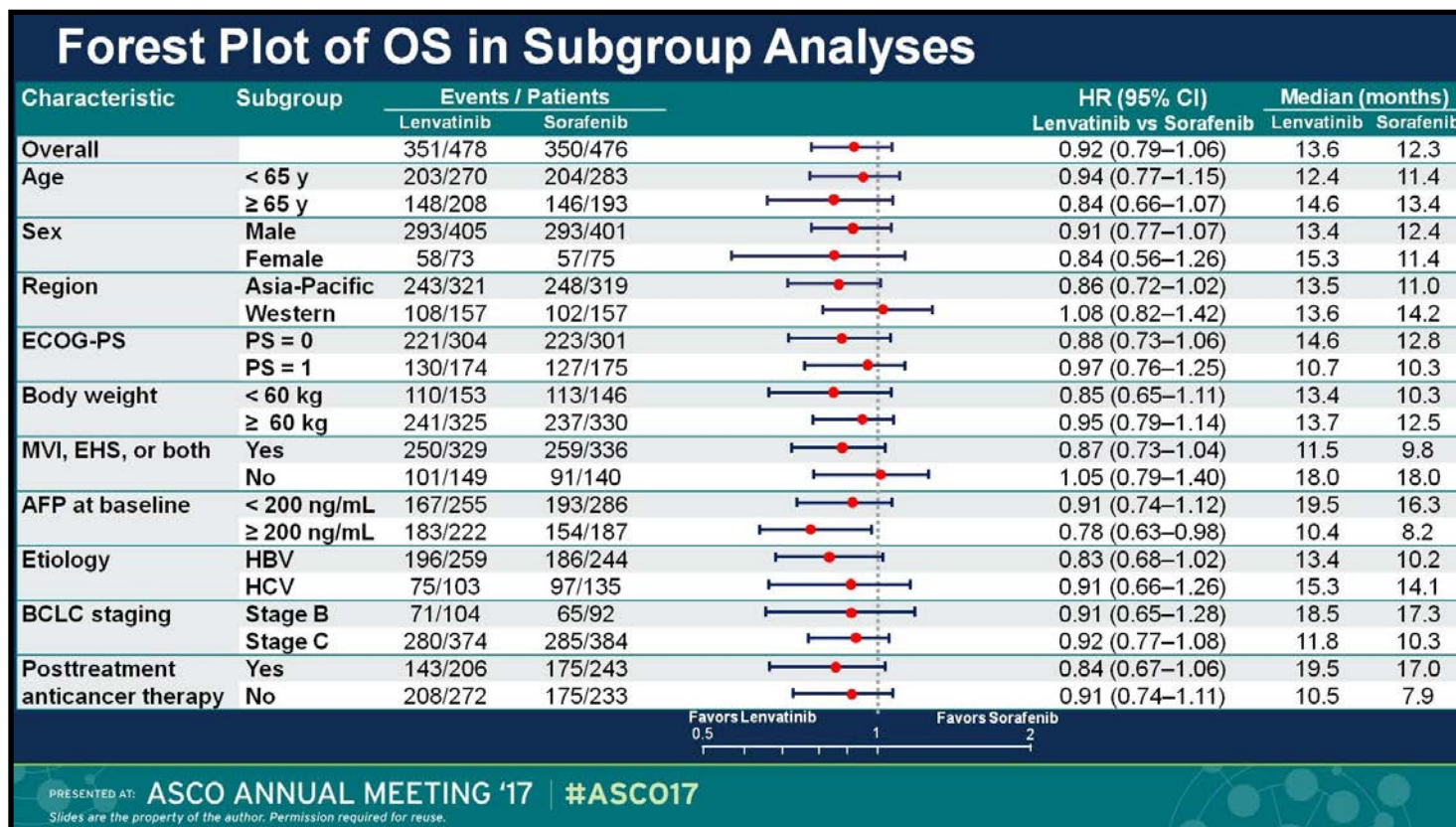
Resultados - Desfecho primário



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REFLECT STUDY: LENVATINIB VS. SORAFENIBE

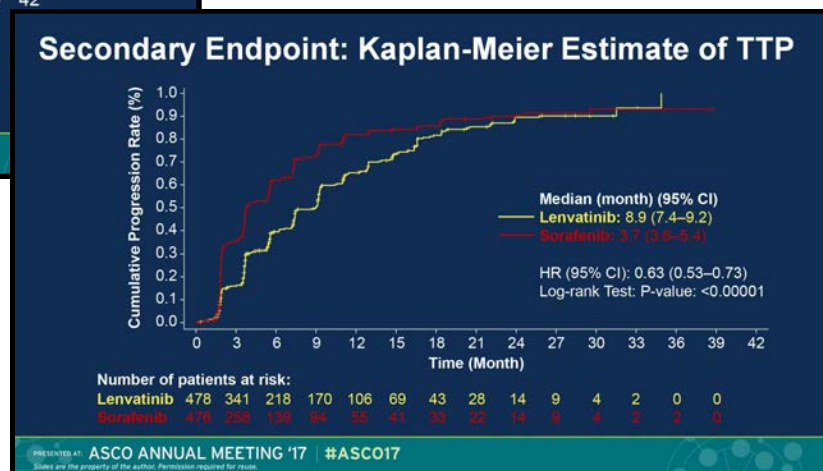
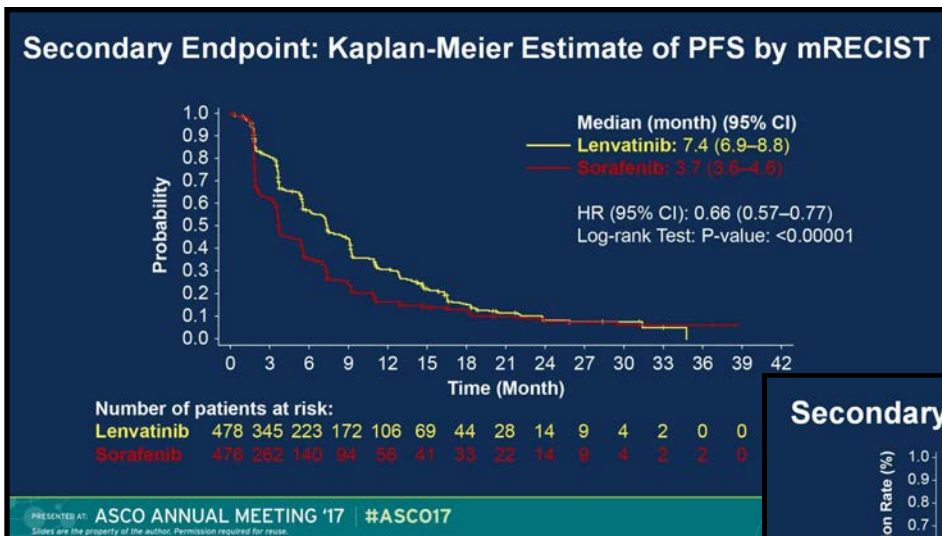
Resultados - Desfecho primário



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REFLECT STUDY: LENVATINIB VS. SORAFENIBE

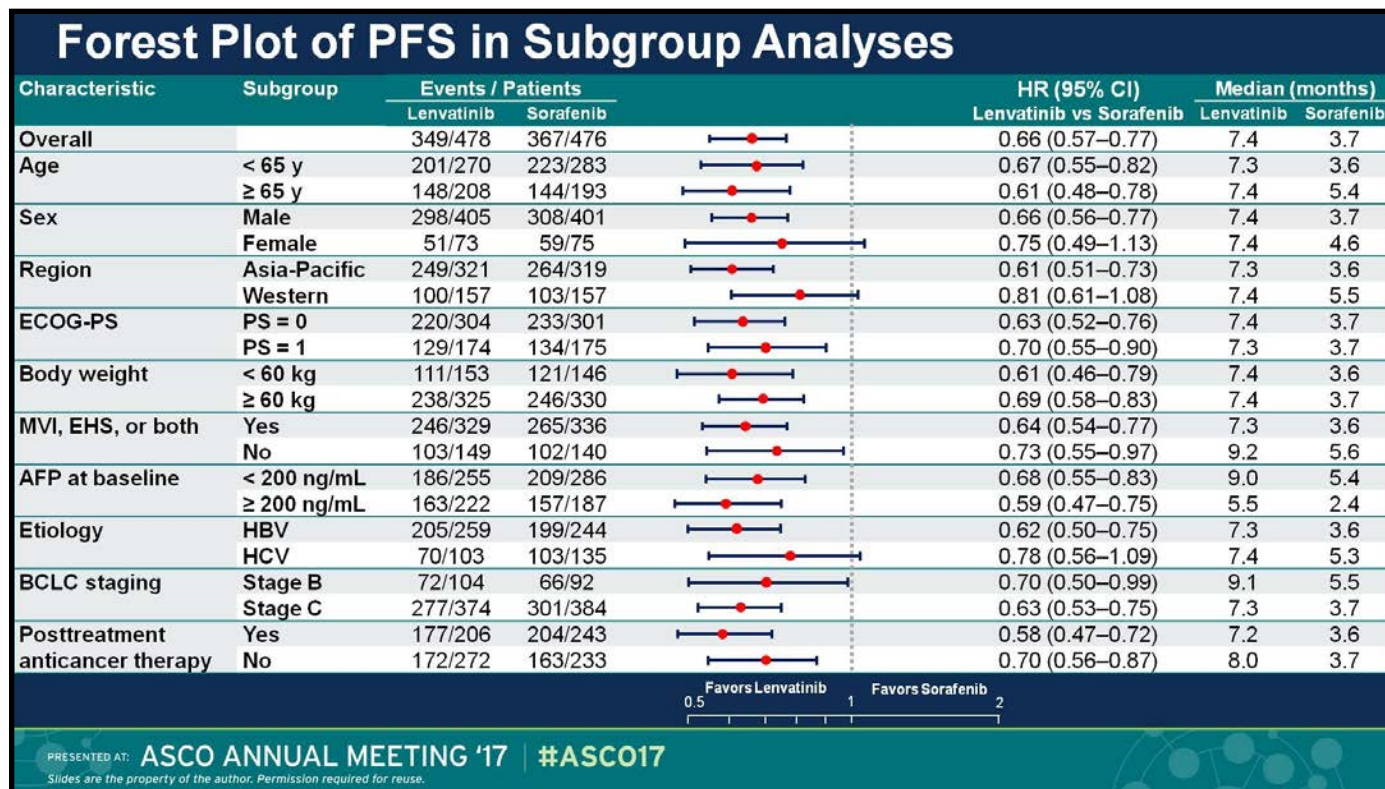
Resultados - Desfechos secundários



CARCINOMA HEPATOCELULAR

REFLECT STUDY: LENVATINIB VS. SORAFENIBE

Resultados - Desfechos secundários



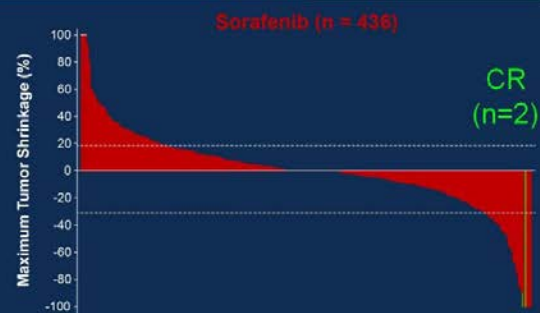
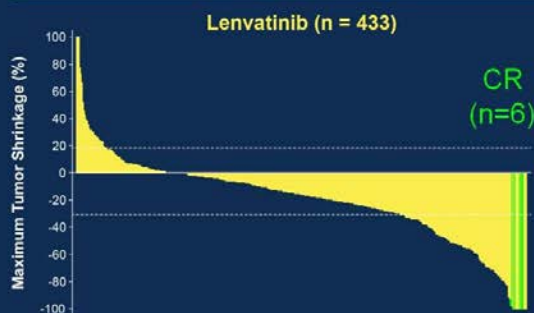
CARCINOMA HEPATOCELULAR

REFLECT STUDY: LENVATINIB VS. SORAFENIBE

Resultados - Desfechos secundários

Maximum Change in Tumor Size by mRECIST

n, (%)	Lenvatinib (n = 478)	Sorafenib (n = 476)	Odds Ratio (95% CI)
ORR	115 (24.1)	44 (9.2)	3.13 (2.15–4.56)
95% CI	20.2–27.9	6.6–11.8	<i>P</i> < 0.00001
CR	6 (1.3)	2 (0.4)	
PR	109 (22.8)	42 (8.8)	
SD	246 (51.5)	244 (51.3)	
Durable SD	167 (34.9)	139 (29.2)	
PD	71 (14.9)	147 (30.9)	
Unknown/NE	46 (9.6)	41 (8.6)	
DCR	361 (75.5)	288 (60.5)	
95% CI	71.7–79.4	56.1–64.9	



Percentage change in tumor size is truncated at 100% (rectangles). ORR is defined as CR+PR, according to mRECIST; durable SD is defined as SD lasting \geq 23 weeks. CR, complete response; NE, not evaluable; PD, progressive disease; PR, partial response; SD, stable disease.

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CARCINOMA HEPATOCELULAR

REFLECT STUDY: LENVATINIB VS. SORAFENIBE

Conclusões

Conclusions

- Lenvatinib has demonstrated noninferiority versus sorafenib in OS in patients with unresectable HCC (13.6 months for lenvatinib versus 12.3 months for sorafenib)
- Lenvatinib has achieved statistically significant and clinically meaningful improvement in PFS, TTP, and ORR versus sorafenib in this population
- The safety profiles of lenvatinib and sorafenib in this study appear consistent with those previously reported in patients with HCC
- Based on these results, lenvatinib may be a potential treatment option in patients with advanced HCC

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CARCINOMA HEPATOCELULAR

SIRT VS. SORAFENIBE EM TUMORES LOCALMENTE AVANÇADOS

Contexto

Background

The majority of patients with Hepatocellular Carcinoma (HCC) have **locally advanced disease** (+/- PVT) at diagnosis.

Both **SIRT** and **sorafenib** have demonstrated efficacy in this group of patients but have different mechanisms of actions.

A definitive RCT comparing these 2 promising therapies in locally advanced HCC will impact on outcomes in a large number of patients and potentially change clinical practice.

¹ Llovet JM et al. *N Engl J Med*. 2008; **359**: 378-90. ² Llovet JM et al. *Lancet* 2002; **359**: 1734-9. ³ Lo CM et al. *Hepatology* 2002; **35**: 1164-71. ⁴ Llovet JM et al. *Hepatology* 2003; **37**: 429-42. ⁵ Oliveri RS et al. *Cochrane Database Syst Rev* 2011;(3):CD004787. ⁶ Sangro B et al. *Hepatology* 2011; **54**: 868-78. ⁷ Salem R et al. *Gastroenterology* 2010; **138**: 52-64. Khor et al. *Hepatology International* 2014; **8**:395-404

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Phase III multi-centre open-label randomized controlled trial of selective internal radiation therapy (SIRT) versus sorafenib in locally advanced hepatocellular carcinoma: The SIRveNIB study.

Pierce K.H. Chow
National Cancer Center Singapore, Singapore
DukeNUS Medical School, Singapore

Mihir Gandhi
Singapore Clinical Research Institute, Singapore
DukeNUS Medical School, Singapore

On behalf of

The Asia-Pacific Hepatocellular Carcinoma Trials Group

(<http://www.scri.edu.sg/cm/asia-pacific-hepatocellular-carcinoma-ahcc-trials-group/about-ahcc/>)
ClinicalTrials.gov: NCT01135056

Asia-Pacific
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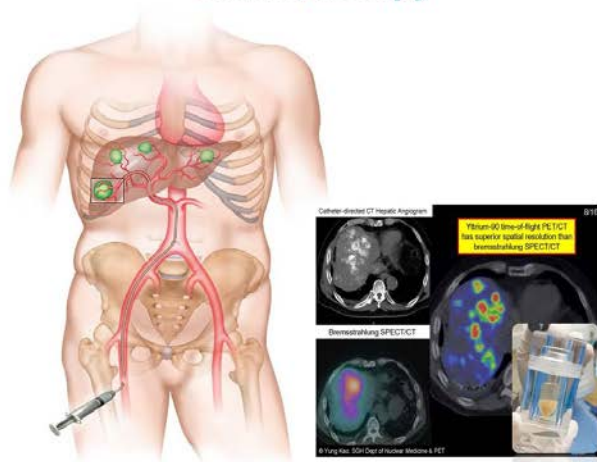
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SIRT VS. SORAFENIBE EM TUMORES LOCALMENTE AVANÇADOS

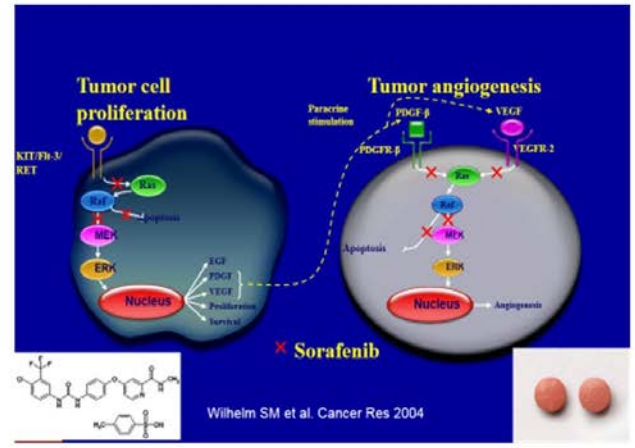
Contexto

Different Therapeutic Classes

SIRT:
Brachytherapy



Sorafenib:
Oral molecular targeted therapy



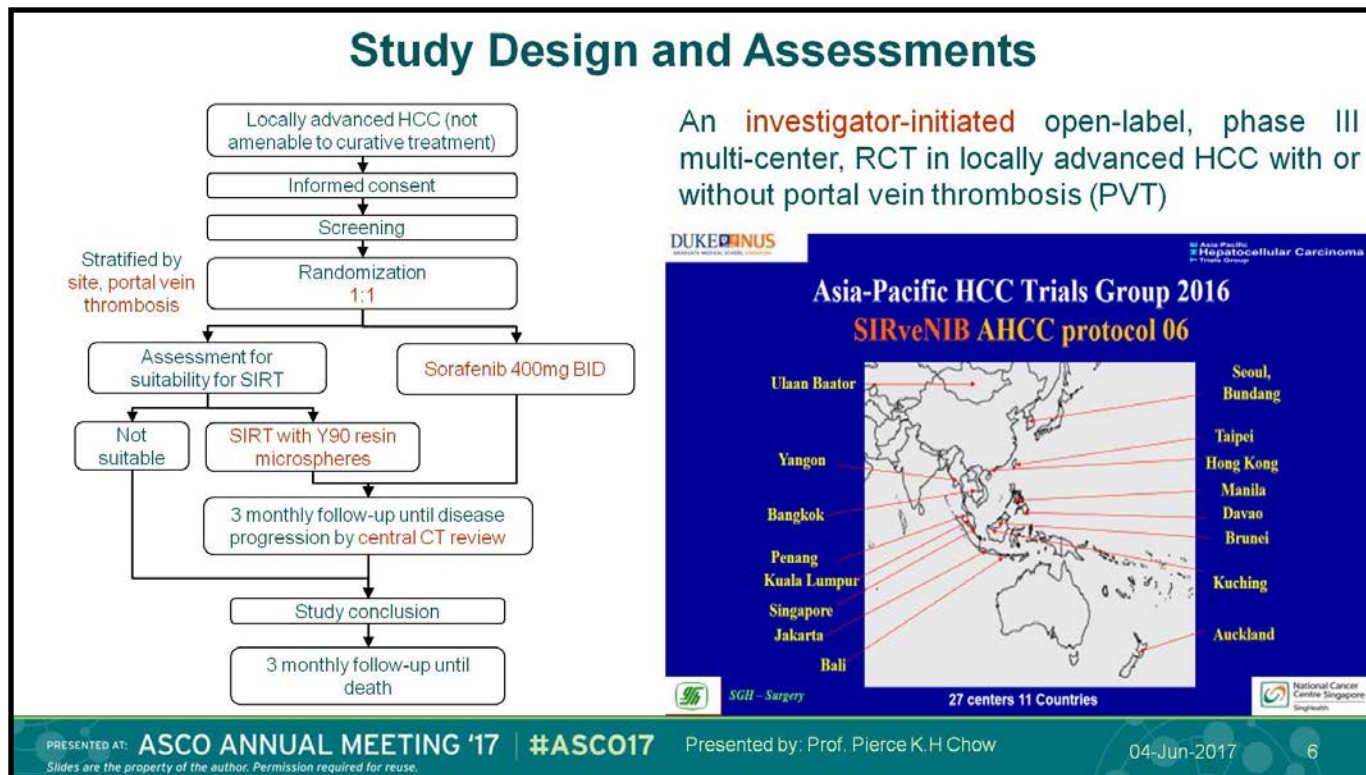
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Desenho do Estudo



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SIRT VS. SORAFENIBE EM TUMORES LOCALMENTE AVANÇADOS

Desenho do Estudo

Objectives

Primary objective

To assess the efficacy of **SIRT** with Y90 resin microspheres compared with **sorafenib** in patients with locally advanced liver cancer not amenable to curative therapies, with respect to overall survival (OS).

Secondary objectives

To compare SIRT with sorafenib for:

- Tumour response rate (RECIST 1.1)
- Disease control rate
- Time to disease progression (overall and in liver)
- Progression free survival (overall and in liver)
- Toxicity and safety (CTCAE 4.02)

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Sample size

Assumptions

Median OS for SIRT = **14 months** [Sangro et al. *Hepatology*. 2011;54(3):868-78]

Median OS for sorafenib = **9.35 months** [Kang et al. *Ann Oncol*. 2008;19(Supplement 8):177]

Hazard ratio = **0.67**

Type I error (two-sided) = **5%**

Power = **90%**

Built-in drop-out rate = **20%**

Accrual period = **3 years**

Follow-up period = **2 years**

Sample size (Using the Log-rank test)

180 + 180 = **360 subjects** (Final analysis at **266 deaths**)

Eligibility Criteria

- Unequivocal diagnosis of HCC (**AASLD Criteria** or **histology**) that is locally advanced but without extra-hepatic metastases
 - With or without **portal vein thrombosis**
 - BCLC B and BCLC C without distant metastases
- At least one lesion with dimension ≥ 10 mm
- Age 18 years and above
- ECOG performance status **0 - 1**
- Child-Pugh A-B (up to **7 points**)
- Adequate hematological, renal and hepatic function
- Life expectancy of at least 3 months
- Not having > 2 **prior** administrations of hepatic artery directed therapy
- No prior hepatic artery directed therapy within **past 4 weeks**

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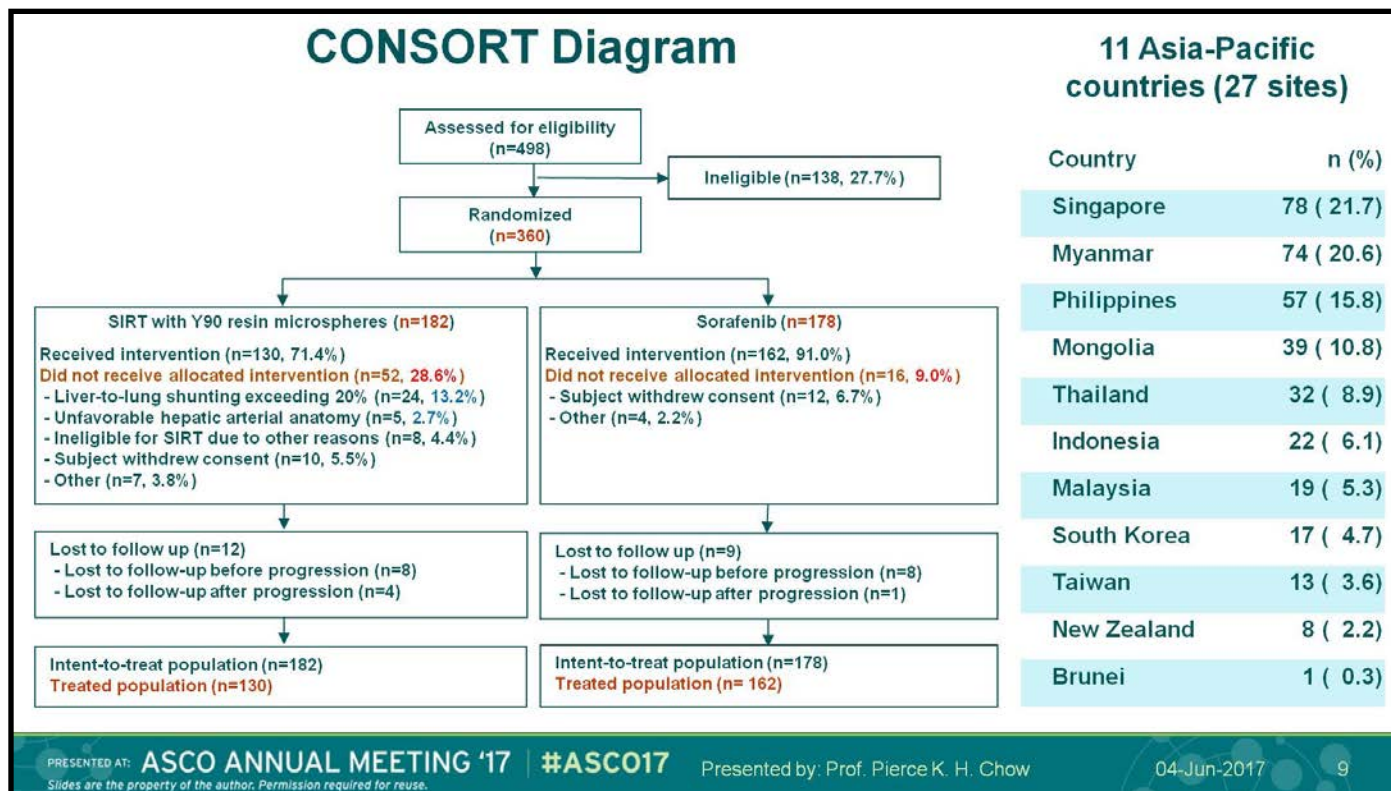
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CARCINOMA HEPATOCELULAR

SIRT VS. SORAFENIBE EM TUMORES LOCALMENTE AVANÇADOS

Resultados



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SIRT VS. SORAFENIBE EM TUMORES LOCALMENTE AVANÇADOS

Resultados

Baseline Characteristics

Characteristics	Intent-to-treat population			Treated population		
	SIRT (N = 182)	Sorafenib (N = 178)	P	SIRT (N = 130)	Sorafenib (N = 162)	P
Age (years), Mean (SD)	59.5 (12.9)	57.7 (10.6)	0.154	60.9 (11.5)	57.5 (10.6)	0.009
Male, n (%)	147 (80.8)	151 (84.8)	0.331	107 (82.3)	138 (85.2)	0.525
Body mass index (kg/m ²), Mean (SD)	23.2 (4.2)	24.0 (4.6)	0.089	23.2 (4.3)	24.1 (4.7)	0.089
Portal vein thrombosis, n (%)	56 (30.8)	54 (30.3)	1.000	30 (23.1)	48 (29.6)	0.232
ECOG status, n (%)			0.265			0.559
0	135 (74.2)	141 (79.2)		106 (81.5)	127 (78.4)	
1	47 (25.8)	37 (20.8)		24 (18.5)	35 (21.6)	
Child-Pugh stage, n (%)			0.613			0.455
A	163 (89.6)	156 (87.6)		117 (90.0)	142 (87.7)	
B	18 (9.9)	21 (11.8)		12 (9.2)	20 (12.3)	
BCLC stage, n (%)			0.239			0.427
A		0 1 (0.6)			0 1 (0.6)	
B	100 (54.9)	109 (61.2)		83 (63.8)	95 (58.6)	
C	81 (44.5)	68 (38.2)		46 (35.4)	66 (40.7)	
Tumor size >50% of liver, n (%)	43 (23.6)	43 (24.2)	1.000	23 (17.7)	35 (21.6)	0.462
Hepatitis, n (%)			0.484			0.653
B	93 (51.1)	104 (58.4)		68 (52.3)	94 (58.0)	
C	26 (14.3)	19 (10.7)		20 (15.4)	19 (11.7)	
B and C	4 (2.2)	5 (2.8)		3 (2.3)	2 (1.2)	

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SIRT VS. SORAFENIBE EM TUMORES LOCALMENTE AVANÇADOS

Resultados

Study Treatments Exposure

- **SIRT (n = 130)**
 - Median time from randomization to treatment: **21.0 days**
 - n=52 (28.6%) did not receive allocated SIRT
 - All subjects received single dose
 - Mean activity administered: **1.8 GBq**
- **Sorafenib (n = 162)**
 - Median time from randomization to treatment start: **3.0 days**
 - n=16 (9%) did not receive allocated sorafenib
 - Mean daily dose per subject: **644.5 mg**
 - Median treatment duration: 13.8 weeks
 - Subjects with $\geq 80\%$ adherence to planned doses: **88.9%**

SIRT Treatment Centers



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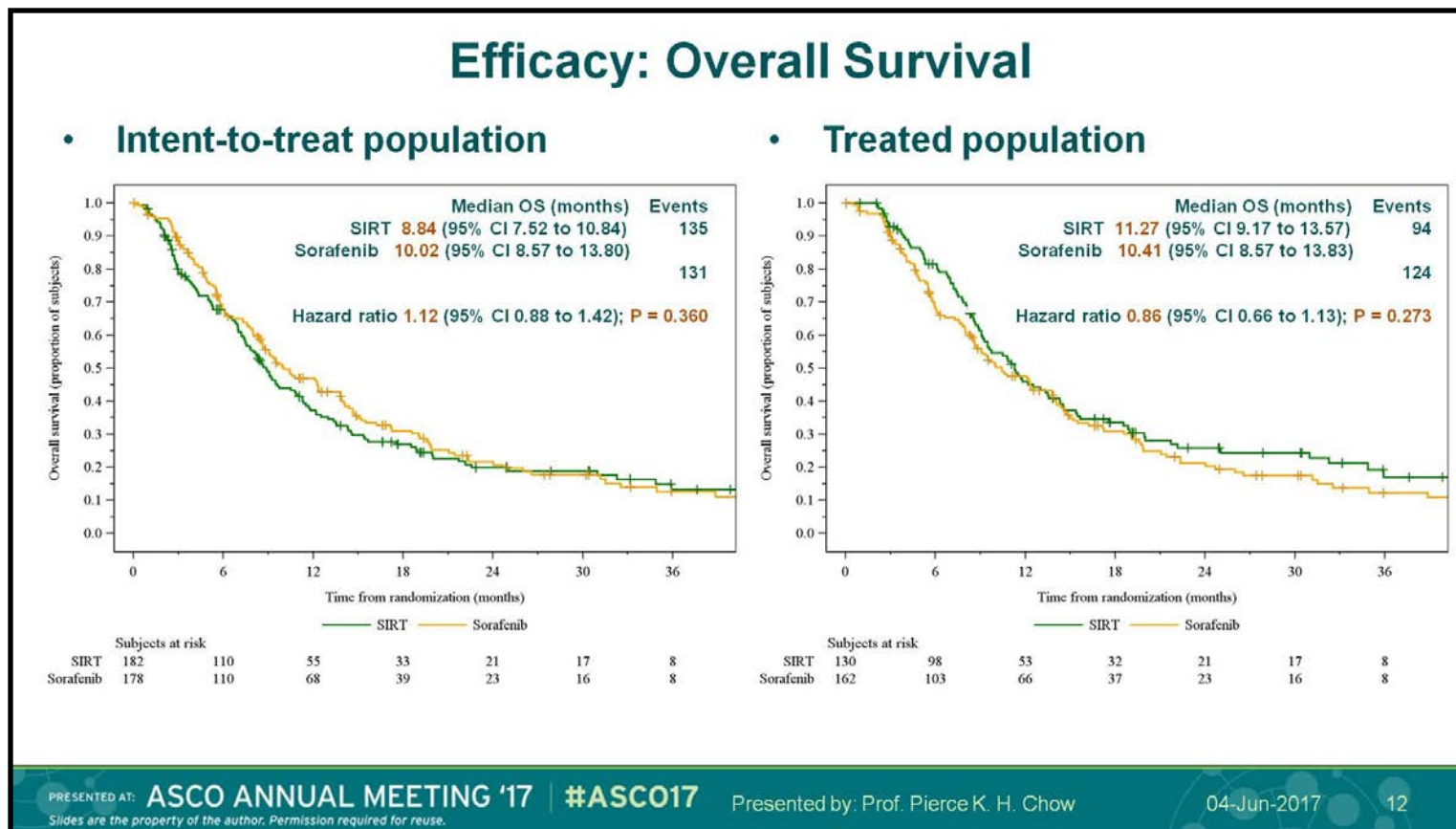
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SIRT VS. SORAFENIBE EM TUMORES LOCALMENTE AVANÇADOS

Resultado - Desfecho Primário



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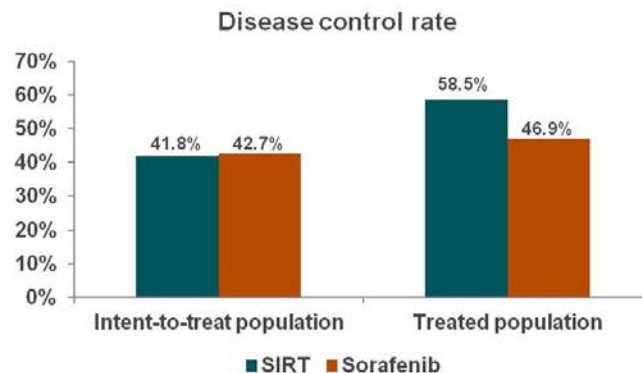
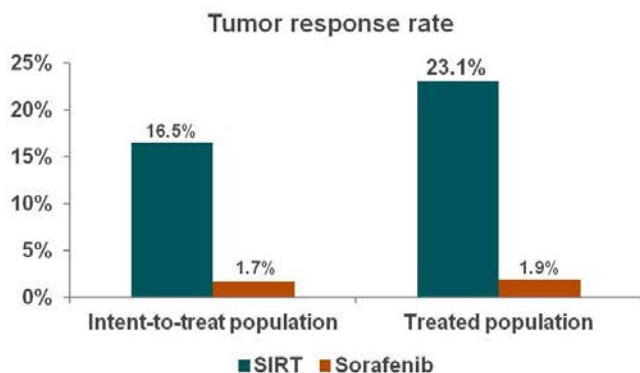
SIRT VS. SORAFENIBE EM TUMORES LOCALMENTE AVANÇADOS

Resultados - Desfechos secundários

Efficacy: Tumor Response Rate and Disease Control Rate

	Intent-to-treat population			Treated population		
	SIRT (N = 182)	Sorafenib (N = 178)	P-value	SIRT (N = 130)	Sorafenib (N = 162)	P-value
Tumor response rate (CR + PR), n (%)	30 (16.5)	3 (1.7)	<.001	30 (23.1)	3 (1.9)	<.001
Disease control rate (CR + PR + SD), n (%)	76 (41.8)	76 (42.7)	0.915	76 (58.5)	76 (46.9)	0.059

CR: Complete response; PR: Partial response; SD: Stable disease



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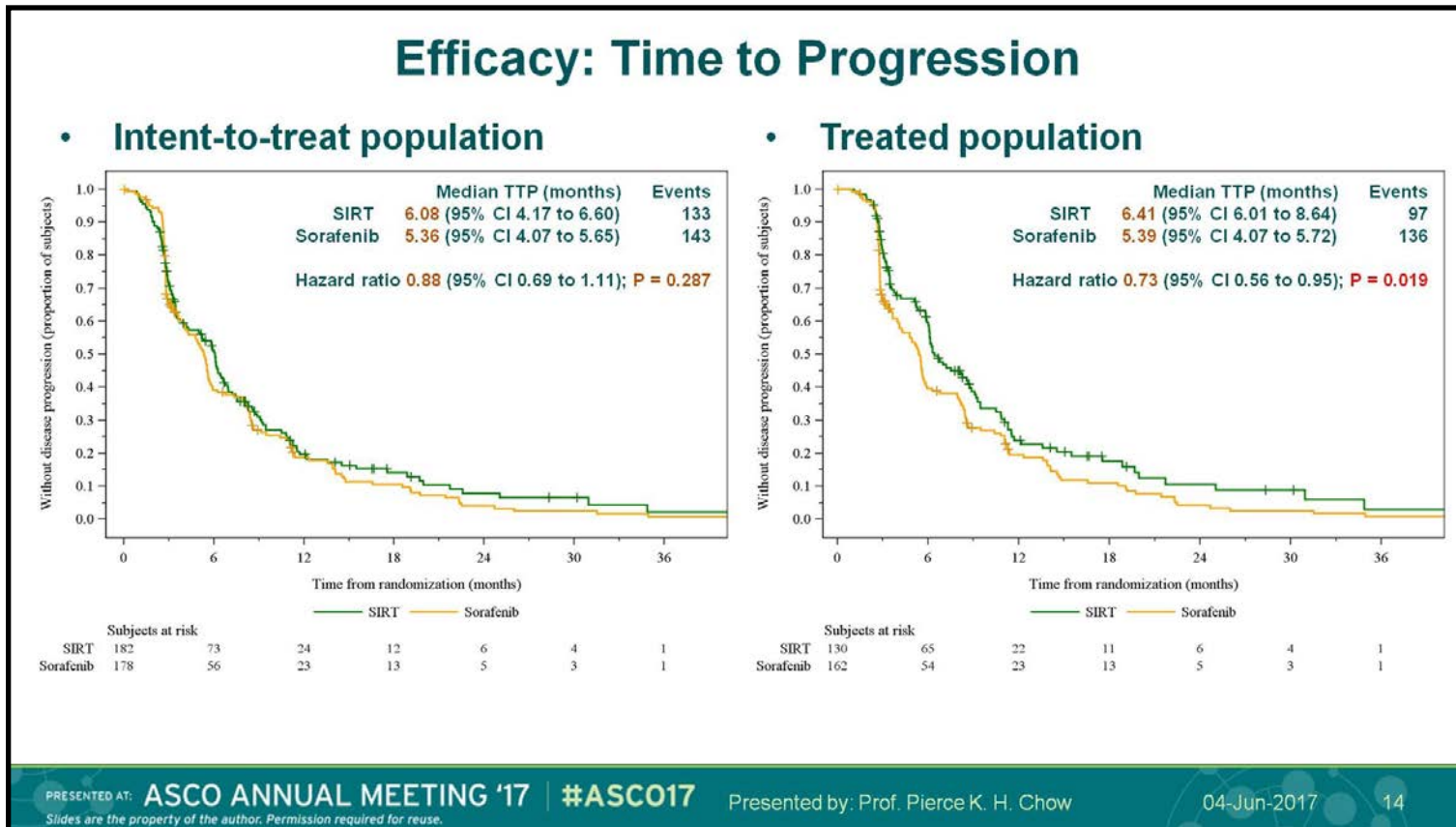
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SIRT VS. SORAFENIBE EM TUMORES LOCALMENTE AVANÇADOS

Resultados - Desfechos secundários



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SIRT VS. SORAFENIBE EM TUMORES LOCALMENTE AVANÇADOS

Resultados - Desfechos secundários

Efficacy: Secondary Outcomes

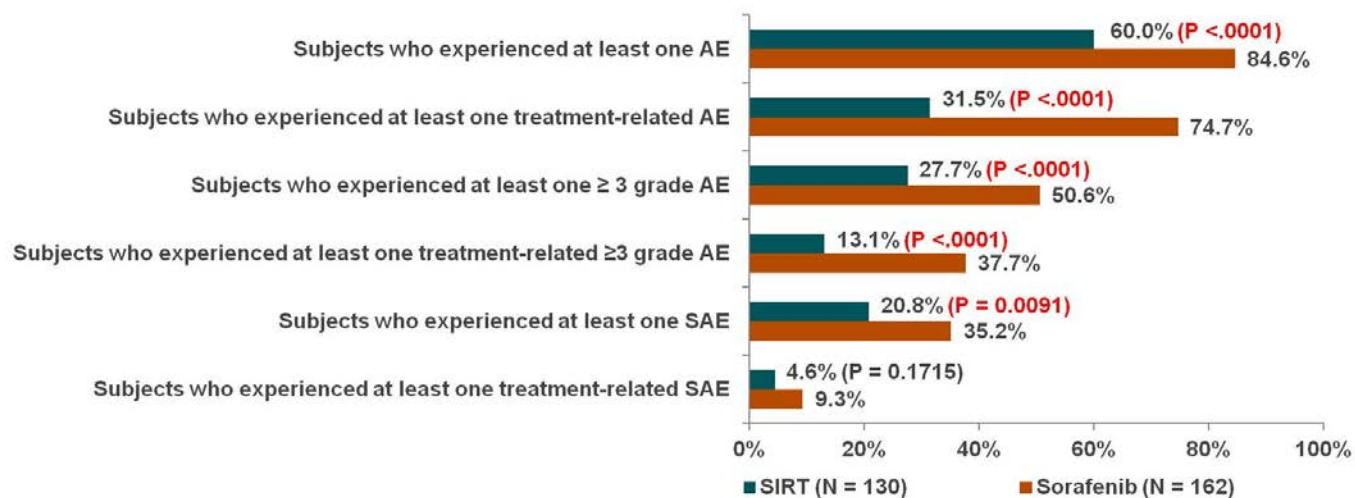
	Intent-to-treat population			Treated population		
	SIRT (N = 182)	Sorafenib (N = 178)	P-value	SIRT (N = 130)	Sorafenib (N = 162)	P-value
Time-to-tumor progression (months)						
Median	6.08	5.36		6.41	5.39	
Hazard ratio (95% confidence interval)	0.88 (0.69, 1.11)		0.287	0.73 (0.56, 0.95)		0.019
Time-to-tumor progression in liver (months)						
Median	6.11	5.39		6.77	5.45	
Hazard ratio (95% confidence interval)	0.87 (0.68, 1.10)		0.241	0.72 (0.55, 0.93)		0.013
Progression-free survival (months)						
Median	5.85	5.06		6.28	5.22	
Hazard ratio (95% confidence interval)	0.89 (0.71, 1.12)		0.306	0.73 (0.56, 0.93)		0.013
Progression-free survival in liver (months)						
Median	6.01	5.06		6.67	5.22	
Hazard ratio (95% confidence interval)	0.88 (0.70, 1.10)		0.259	0.71 (0.55, 0.92)		0.009

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SIRT VS. SORAFENIBE EM TUMORES LOCALMENTE AVANÇADOS

Resultados - Segurança

Overall Safety



Includes adverse events (AEs) and serious adverse events (SAEs) with onset date on or after study treatment start date. Treatment-related AE or SAE defined as those with certain, probable, possible, or missing relationship to study treatment. P values were computed for comparison between treatment arms using the Fisher's exact test.

CARCINOMA HEPATOCELULAR

SIRT VS. SORAFENIBE EM TUMORES LOCALMENTE AVANÇADOS

Resultados - Segurança

Selected Adverse Events Graded with CTCAE 4.02

System Organ Class Preferred term, Number of subjects (%)	SIRT (N = 130)		Sorafenib (N = 162)		P	
	Grade 1 - 2	Grade ≥ 3	Grade 1 - 2	Grade ≥ 3	Grade 1 - 2	Grade ≥ 3
Blood and lymphatic system disorders						
Anaemia	4 (3.1)	0	5 (3.1)	4 (2.5)	1.0000	0.1315
Gastrointestinal disorders						
Abdominal pain	11 (8.5)	3 (2.3)	9 (5.6)	2 (1.2)	0.3585	0.6588
Ascites	5 (3.8)	5 (3.8)	14 (8.6)	4 (2.5)	0.1505	0.5179
Constipation	0	0	9 (5.6)	0	0.0051	-
Diarrhoea	2 (1.5)	0	42 (25.9)	6 (3.7)	<0.001	0.0353
Nausea	10 (7.7)	1 (0.8)	10 (6.2)	0	0.6466	0.4452
General disorders and administration site conditions						
Fatigue	5 (3.8)	0	19 (11.7)	6 (3.7)	0.0175	0.0353
Oedema peripheral	10 (7.7)	0	5 (3.1)	1 (0.6)	0.1082	1.0000
Pyrexia	6 (4.6)	0	17 (10.5)	1 (0.6)	0.0804	1.0000
Metabolism and nutrition and disorders						
Decreased appetite	11 (8.5)	0	20 (12.3)	1 (0.6)	0.3412	1.0000
Hypoalbuminaemia	6 (4.6)	1 (0.8)	7 (4.3)	1 (0.6)	1.0000	1.0000

Includes adverse events which were experienced by at least 5% of treated subjects in either arm and have onset date on or after study treatment start date. P values were computed for comparison between treatment arms using the Fisher's exact test.

CARCINOMA HEPATOCELULAR

SIRT VS. SORAFENIBE EM TUMORES LOCALMENTE AVANÇADOS

Resultados - Segurança

Selected Adverse Events Graded with CTCAE 4.02

System Organ Class Preferred term, Number of subjects (%)	SIRT (N = 130)		Sorafenib (N = 162)		P	
	Grade 1 - 2	Grade ≥ 3	Grade 1 - 2	Grade ≥ 3	Grade 1 - 2	Grade ≥ 3
Respiratory, thoracic and mediastinal disorders						
Cough	8 (6.2)	0	8 (4.9)	0	0.7969	-
Skin and subcutaneous tissue disorders						
Alopecia	0	0	16 (9.9)	0	<.0001	-
Palmar-plantar erythrodysesthesia syndrome	1 (0.8)	0	62 (38.3)	27 (16.7)	<.0001	<.0001
Rash	0	0	18 (11.1)	0	<.0001	-
Vascular disorders						
Hypertension	0	0	22 (13.6)	2 (1.2)	<.0001	0.5043
AEs typically associated with SIRT						
Gastric ulcer	0	1 (0.8)	0	0	-	0.4452
Upper gastrointestinal haemorrhage	1 (0.8)	1 (0.8)	0	3 (1.9)	0.4452	0.6315
Jaundice	1 (0.8)	1 (0.8)	1 (0.6)	2 (1.2)	1.0000	1.0000
Hepatic cirrhosis	0	0	1 (0.6)	1 (0.6)	1.0000	1.0000
Portal hypertension	0	0	0	1 (0.6)	-	1.0000
Radiation hepatitis	0	2 (1.5)	0	0	-	0.1974

Includes adverse events which were experienced by at least 5% of treated subjects in either arm, or known to be associated with SIRT and have onset date on or after study treatment start date. P values were computed for comparison between treatment arms using the Fisher's exact test.

CARCINOMA HEPATOCELULAR

SIRT VS. SORAFENIBE EM TUMORES LOCALMENTE AVANÇADOS

Conclusões

Conclusions

- The primary end point of the study was not met.
 - In this study SIRT was not shown to be superior to sorafenib with respect to **overall survival**
 - No statistically significant difference was demonstrated between SIRT and sorafenib
- However, patients treated with SIRT have
 - a significantly better **tumor-response rate**
 - significantly fewer total number of **adverse events** and **severe adverse events**when compared with those treated with sorafenib.

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IMUNOTERAPIA - KEYNOTE 059

KEYNOTE-059 Cohort 1: Efficacy and Safety of Pembrolizumab Monotherapy in Patients With Previously Treated Advanced Gastric Cancer

Charles S. Fuchs,¹ Toshihiko Doi,² Raymond WJ Jang,³ Kei Muro,⁴ Taroh Satoh,⁵ Manuela Machado,⁶ Weijing Sun,⁷ Shadia I. Jalal,⁸ Manish Shah,⁹ Jean-Phillipe Metges,¹⁰ Marcelo Garrido,¹¹ Talia Golan,¹² Mario Mandala,¹³ Zev A. Wainberg,¹⁴ Daniel V.T. Catenacci,¹⁵ Yung-Jue Bang,¹⁶ Jared Lunceford,¹⁷ Mary Savage,¹⁷ Jiangdian Wang,¹⁷ Minori Koshiji,¹⁷ Rita P. Dalal,¹⁷ Harry H. Yoon¹⁸

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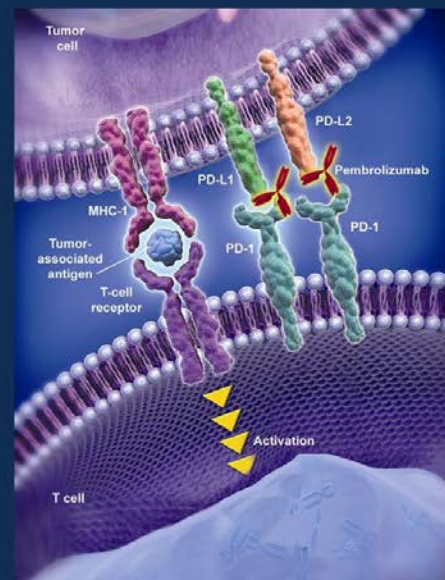
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IMUNOTERAPIA - KEYNOTE 059

Contexto

Pembrolizumab in Gastric and Gastroesophageal (G/GEJ) Cancer

- PD-L1 and its ligands PD-L1 and PD-L2 have been shown to be overexpressed in gastric cancers¹⁻³
- Pembrolizumab is a selective, humanized high-affinity immunoglobulin G4-κ monoclonal antibody that blocks the interaction between PD-1 and its ligands⁴
- In a phase 1b trial, pembrolizumab demonstrated promising antitumor activity in advanced G/GEJ cancer⁵



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1. Kim JW et al. *Gastric Cancer*. 2016;19:42-52.
2. Qing Y et al. *Drug Des Devel Ther*. 2015;9:901-909. 3. Dong M et al. *Hum Path*.2016;53:25-34.
4. Keytruda [package insert]. Whitehouse Station, NJ, USA: Merck Sharp & Dohme Corp.; May 2017.
5. Muro K et al. *Lancet Oncol*. 2016;17:717-726.

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IMUNOTERAPIA - KEYNOTE 059

Contexto

KEYNOTE-059 (NCT02335411): Phase 2 Multicohort Study of Pembrolizumab for G/GEJ Adenocarcinoma

Cohort 1 Patients
• ≥ 2 prior lines of chemotherapy

Pembrolizumab
200 mg Q3W

Cohort 2 Patients
• No prior therapy

Pembrolizumab 200 mg Q3W +
cisplatin 80 mg/m² Q3W +
5-FU 800 mg/m² Q3W or
capecitabine 1000 mg/m² BID Q3W^a

Cohort 3 Patients
• No prior therapy
• PD-L1 positive

Pembrolizumab
200 mg Q3W

Treat for
24 months,
or until
progression,
intolerable
toxicity, or
other reason

Follow-up for
survival by
telephone
until death,
withdrawal,
or study end

Response assessment by RECIST v1.1: first scan at 9 weeks after cycle 1, every 6 weeks for first year,

followed by every 9 weeks

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^aCapecitabine was administered *only* in Japan

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IMUNOTERAPIA - KEYNOTE 059

Desenho do Estudo

KEYNOTE-059 Cohort 1 Eligibility Criteria

- Measurable recurrent or metastatic disease
- ≥ 2 prior chemotherapy regimens
- *HER2/neu* negative, or *HER2/neu* positive if previously treated with *HER2*-targeted therapy
- ECOG PS 0-1
- No systemic steroid therapy; no prior PD-1/PD-L1 therapy
- No history of autoimmune disease
- No CNS metastases
- No clinical ascites

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Objectives and Assessments for Cohort 1

- Primary end points
 - ORR by central review per RECIST v1.1 in all patients and in patients with PD-L1–positive tumors
 - Safety and tolerability of pembrolizumab
- Secondary end points
 - DOR by central review
 - PFS
 - OS
- Exploratory biomarker end points
 - Efficacy by microsatellite instability and gene expression profile

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IMUNOTERAPIA - KEYNOTE 059

Desenho do Estudo

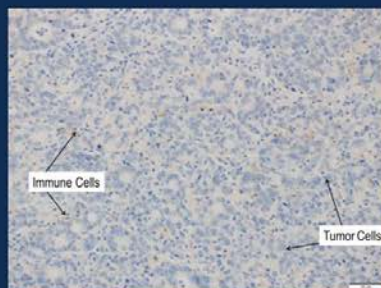
PD-L1 Expression IHC^a

- PD-L1 expression is determined by combined positive score (CPS)

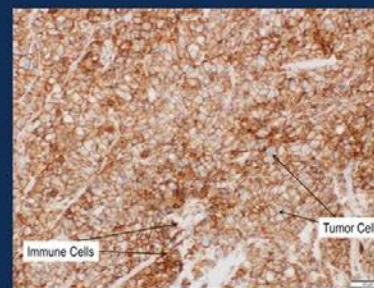
$$\text{CPS} = \frac{\text{No. of PD-L1 staining cells (tumor cells, lymphocytes, macrophages)}}{\text{Total No. of viable tumor cells}} \times 100$$

- **A specimen is considered to have positive PD-L1 expression if CPS ≥1%**

PD-L1
negative



PD-L1
positive



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®22C3 pharmDx IHC, Agilent Technologies, Carpinteria, CA

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IMUNOTERAPIA - KEYNOTE 059

Resultados

Baseline Disease Characteristics

Characteristic, n (%)	N = 259
ECOG PS	
0	107 (41.3)
1	151 (58.3)
Location of primary tumor	
Gastric	125 (48.3)
GEJ	133 (51.4)
Number of prior therapies	
2	134 (51.7)
3	75 (29.0)
≥4	50 (19.3)

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Data cutoff: January 16, 2017

Baseline Demographics

Characteristic	N = 259
Median age (range), years	62 (24-89)
Male, n (%)	198 (76.4)
Geographic region, n (%)	
United States	124 (47.9)
East Asia	34 (13.1)
Rest of world	101 (39.0)

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Data cutoff: January 16, 2017

Baseline Disease Characteristics

Characteristic, n (%)	N = 259
Previous surgery for gastric cancer	
Yes (gastrectomy, other)	66 (25.5)
No	193 (74.5)
HER2 positive	63 (24.3)
PD-L1 expression	
Positive	148 (57.1)
Negative	109 (42.1)

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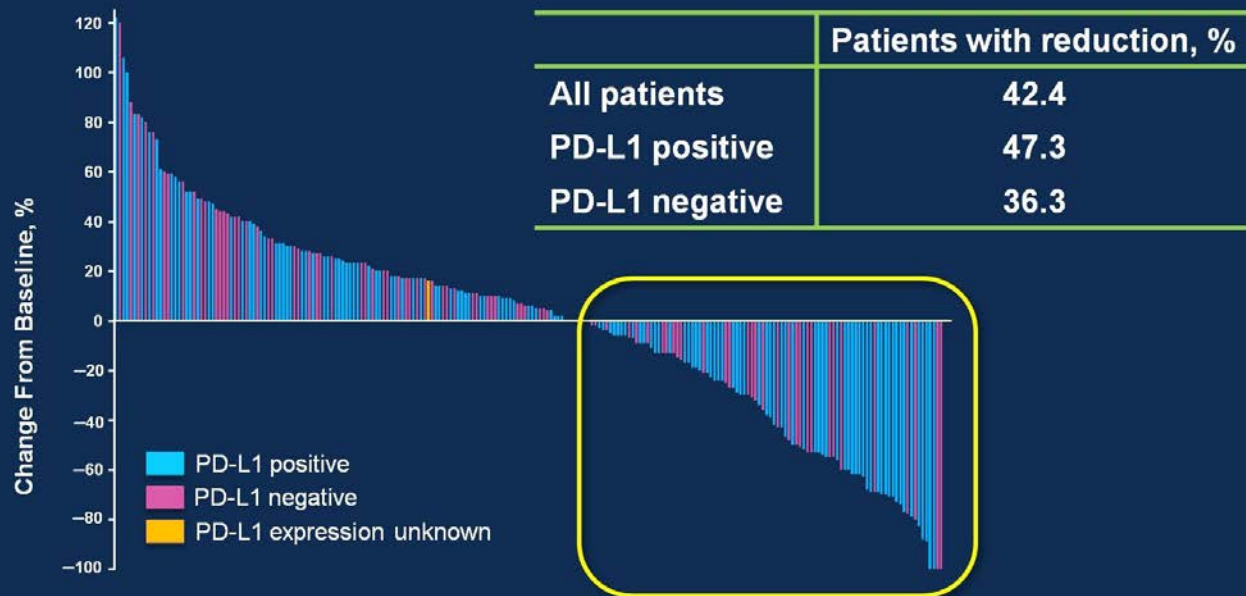
Data cutoff: January 16, 2017

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IMUNOTERAPIA - KEYNOTE 059

Resultados - Desfecho Primário

Maximum Percentage Change From Baseline in Target Lesion Size^a



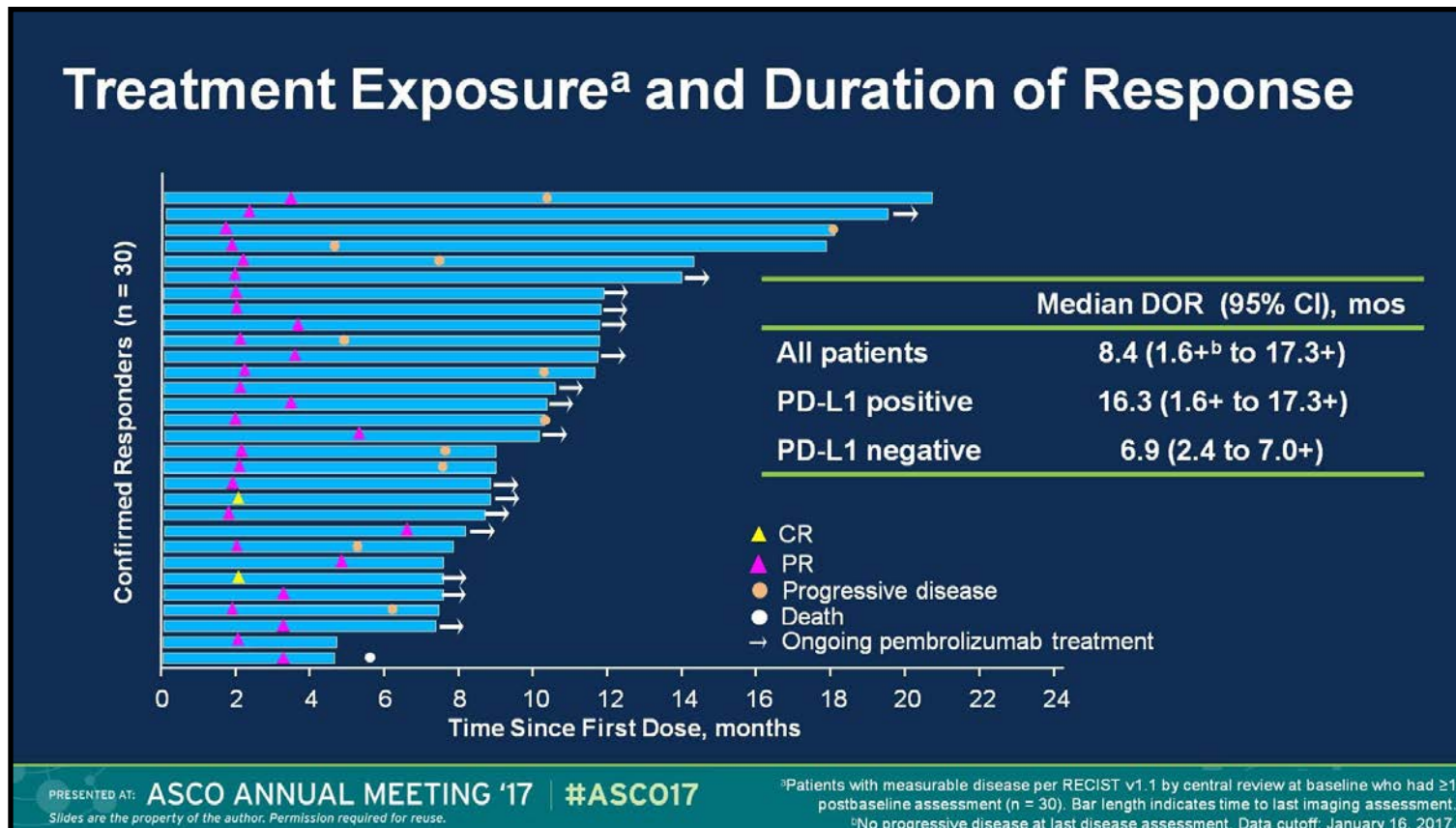
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^aOnly patients with measurable disease per RECIST v1.1 by central review at baseline who had ≥ 1 postbaseline assessment were included (n = 223)
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IMUNOTERAPIA - KEYNOTE 059

Resultados - Desfecho Primário

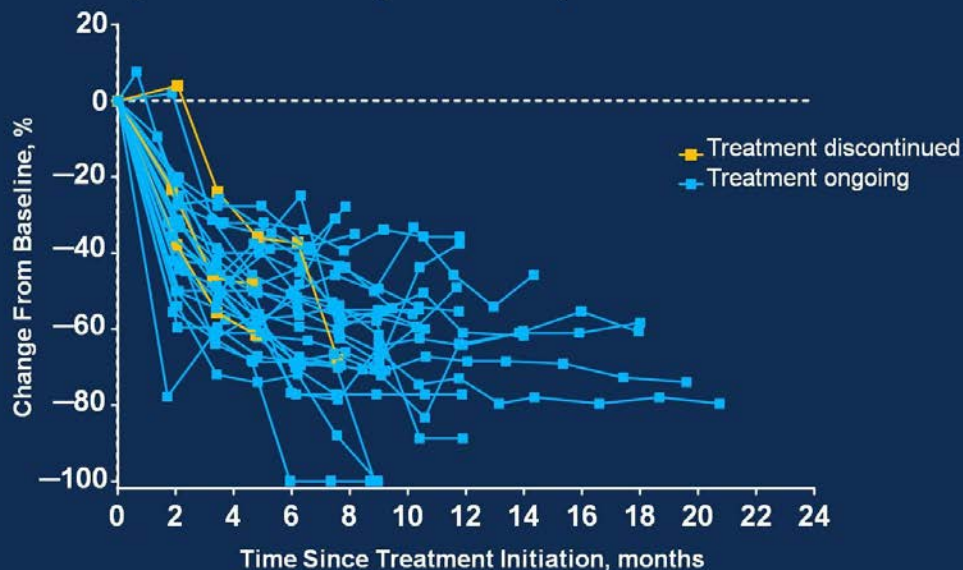


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IMUNOTERAPIA - KEYNOTE 059

Resultados - Desfecho Primário

Longitudinal Change From Baseline in Tumor Size^a: Responders (n = 30)



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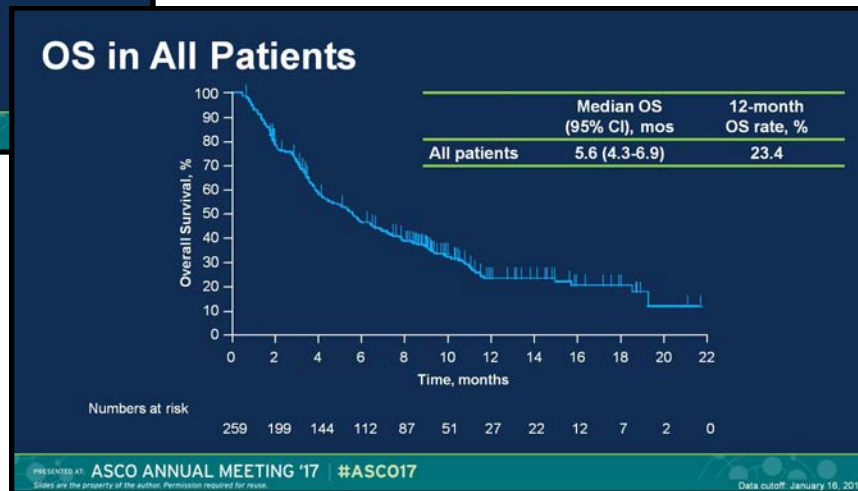
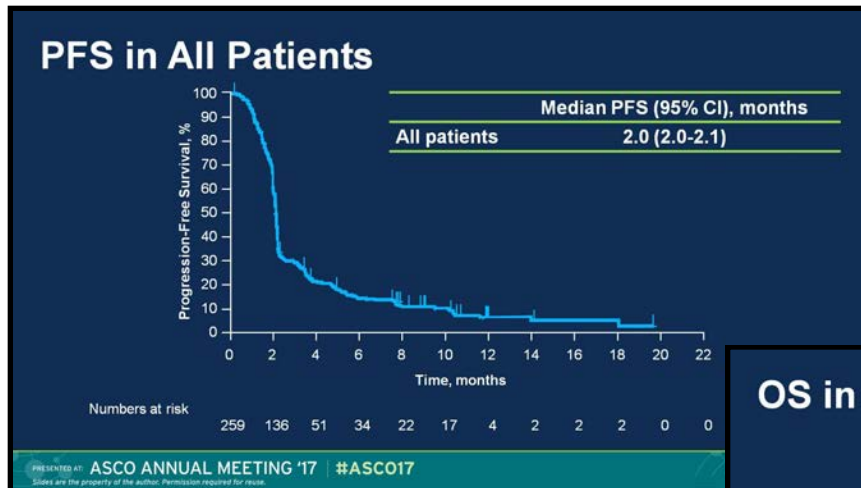
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^aLongitudinal change in sum of longest target lesion diameters from baseline in patients with partial or complete response (n = 30)
Data cutoff: January 16, 2017

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IMUNOTERAPIA - KEYNOTE 059

Resultados - Desfechos Secundários



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IMUNOTERAPIA - KEYNOTE 059

Resultados - Desfechos Secundários

Response by MSI Status (n = 174)

4.0% of patients were MSI-High

Response ^a	MSI-High (n = 7)		Non-MSI-High (n = 167)	
	%	95% CI	%	95% CI
ORR	57.1	18.4-90.1	9.0	5.1-14.4
CR	14.3	0.4-57.9	2.4	0.7-6.0
PR	42.9	9.9-81.6	6.6	3.3-11.5
DCR ^b	71.4	29.0-96.3	22.2	16.1-29.2

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^aOnly confirmed responses were included

^bCR + PR + SD ≥ 2 months

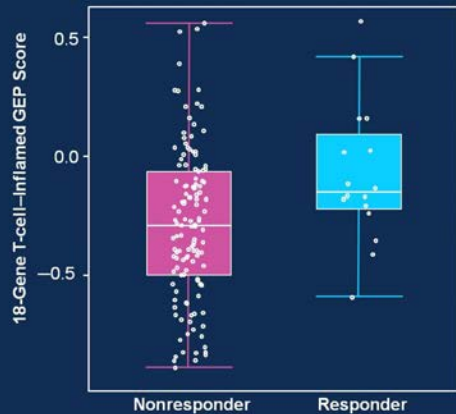
Data cutoff: January 16, 2017

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IMUNOTERAPIA - KEYNOTE 059

Resultados - Desfechos Secundários

T-cell-Inflamed GEP Score by Response (n = 144)



T-cell-inflamed GEP score significantly associated ($P = 0.014$) with improved response to pembrolizumab

Gene Expression Signature

- 18 gene T-cell inflamed GEP predictive of response to pembrolizumab¹⁻³
 - Derived by testing, validation, and refinement of immune-related gene sets across a variety of tumor types¹⁻³
- GEP score is a weighted sum of normalized values for the genes^a

18 genes

CCL5, CD27, CD274 (PD-L1), CD276 (B7-H3), CD8A, CMKLR1, CXCL9, CXCR6, HLA-DQA1, HLA-DRB1, HLA-E, IDO1, LAG3, NKG7, PDCD1LG2 (PD-L2), PSMB10, STAT1, TIGIT

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^aFormalin-fixed, paraffin-embedded extracted RNA analyzed on NanoString[®]Counter platform
1. Ayers et al. J Clin Invest. 2017, in press. 2. Ayers M et al. J Immunother Cancer. 2016;4(Suppl 1):P71.
3. Pihla-Paul SA, et al. J Clin Oncol. 2016;34(Suppl 16):1636

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IMUNOTERAPIA - KEYNOTE 059

Resultados - Segurança

Treatment-Related Adverse Events

Event	All Patients (N = 259)	
	All Grades (in >5%), %	Grades 3/4, %
Fatigue	18.9	2.3
Pruritus	8.9	0
Rash	8.5	0.8
Hypothyroidism	7.7	0.4
Decreased appetite	7.3	0
Anemia	6.9	2.7
Nausea	6.9	0.8
Diarrhea	6.6	1.2
Arthralgia	5.8	0.4

- 2 patients discontinued treatment because of treatment-related AEs (abnormal hepatic function and bile duct stenosis)
- Grade 5 treatment-related adverse events occurred in 2 patients (acute kidney injury and pleural effusion)

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Data cutoff: January 16, 2017.

Immune-Mediated Adverse Events

Event	All Patients (N = 259)	
	All Grades (in >1), %	Grades 3/4, %
Any	17.8	4.6
Hypothyroidism	8.9	0.4
Hyperthyroidism	3.5	0
Colitis	2.3	1.2
Pneumonitis	1.9	0.8
Thyroiditis	1.5	0.4
Infusion reaction	1.5	0
Severe skin reactions ^a	1.5	1.5

- 13 (28.3%) patients received systemic corticosteroids for immune-mediated AEs
- 10 (3.8%) patients experienced treatment interruption because of immune-mediated AEs

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^aIncludes erythema multiforme, jaundice, rash, maculopapular rash
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IMUNOTERAPIA - KEYNOTE 059

Conclusões

Conclusions

- Pembrolizumab demonstrated promising antitumor activity and durable responses in patients with advanced G/GEJ cancer progressing after ≥ 2 prior lines of therapy
- ORR was higher in patients with PD-L1–positive tumors, but responses were also observed in patients with PD-L1–negative tumors
- Treatment was well tolerated

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Conclusions

- Pembrolizumab represents a potential treatment option for patients with G/GEJ cancer who have progressed after ≥ 2 prior lines of therapy
- Ongoing randomized clinical trials are now assessing pembrolizumab in earlier lines of therapy and in combination with chemotherapy regimens for patients with advanced G/GEJ cancer

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IMUNOTERAPIA - CHECKMATE 032

Nivolumab ± Ipilimumab in Patients With Advanced/Metastatic Chemotherapy-Refractory Gastric, Esophageal, or Gastroesophageal Junction Cancer: CheckMate 032 Study

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Padmanee Sharma,⁶ Katriina Peltola,⁷ Dirk Jaeger,⁸ Jeffrey Evans,⁹ Filippo de Braud,¹⁰ Ian Chau,¹¹
Marina Tschaika,¹² Christopher T. Harbison,¹² Weiguo Cai,¹² Johanna Bendell,¹³ Dung T. Le¹⁴

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IMUNOTERAPIA - CHECKMATE 032

Contexto

Background

- Nivolumab improved OS vs placebo in Asian patients with gastric/GEJ cancer with ≥ 2 prior treatments (ATTRACTION-2 phase 3 study)¹
 - **27% vs 11% of patients alive at 1 year (HR, 0.63; $P < 0.0001$)**
- Nivolumab alone or in combination with ipilimumab led to encouraging results in a similar population of Western patients (CheckMate 032 phase 1/2 study)^{2,3}
- Here we present **longer-term updated survival, efficacy, and safety data from CheckMate 032**

GEJ, gastroesophageal junction.

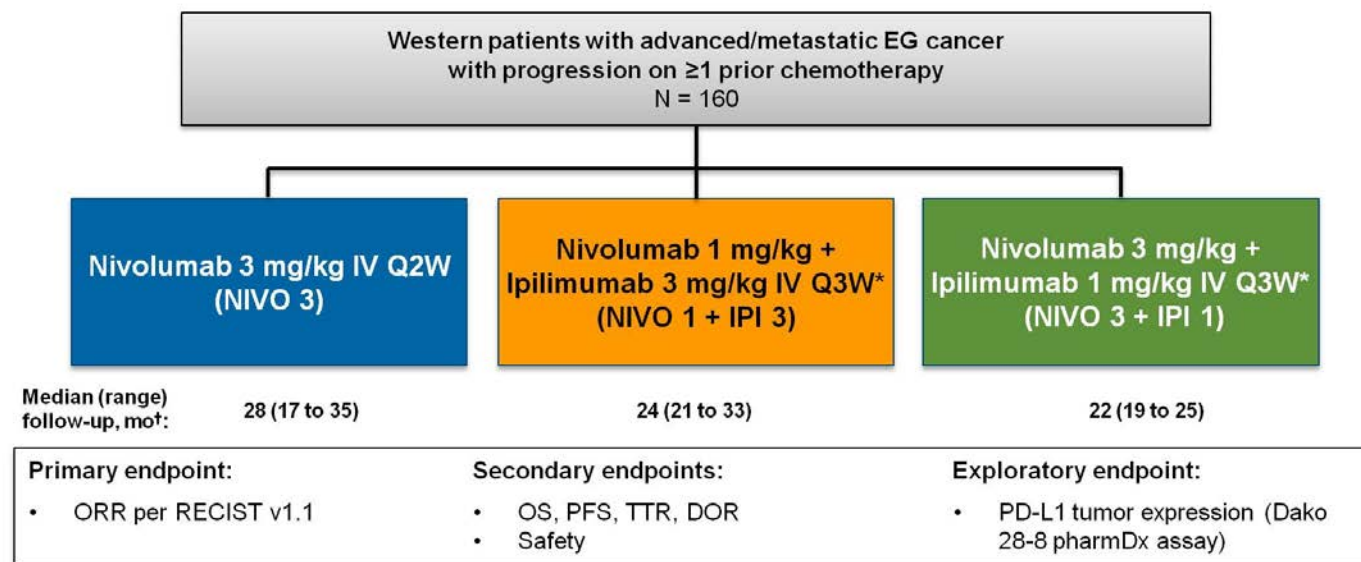
1. Kang YK, et al. ASCO-GI 2017 [abstract 2]; 2. Janjigian YY, et al. ASCO 2016 [abstract 4010]; 3. <https://clinicaltrials.gov/ct2/show/study/NCT01928394> (Accessed April 21, 2017).

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IMUNOTERAPIA - CHECKMATE 032

Desenho do Estudo

Checkmate 032 EG Cohort



DOR, duration of response; EG, esophagogastric (including gastric/esophageal/gastroesophageal junction cancer); TTR, time to response.

* Nivolumab + ipilimumab administered for 4 cycles followed by nivolumab 3 mg/kg IV Q2W.

† Time from first dose to data cut-off; follow-up was shorter for patients who died prior to data cut-off.

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IMUNOTERAPIA - CHECKMATE 032

Resultados

Patient Disposition

Patients, n (%)	NIVO 3 n = 59	NIVO 1 + IPI 3 n = 49	NIVO 3 + IPI 1 n = 52
Continuing on study treatment	2 (3)	6 (12)	3 (6)
Not continuing on study treatment	57 (97)	43 (88)	49 (94)
Disease progression	50 (85)	25 (51)	38 (73)
AE related to study drug	2 (3)*	9 (18)†	7 (13)‡
AE unrelated to study drug	3 (5)	5 (10)	1 (2)
Patient withdrawal/noncompliance	2 (3)	4 (8)	3 (6)

* Increased ALT/AST (n=1); pneumonitis (n=1).

† Increased ALT/AST (n=3); colitis (n=2); diarrhea (n=2); colitis, cystitis, and transaminitis (n=1); diarrhea and hyperthyroidism (n=1).

‡ Acute renal failure, autoimmune hepatitis, diarrhea, enteritis, increased ALT/AST, lymphocytic myocarditis, and pneumonitis (n=1 each).

Baseline Characteristics

Patients, n (%)	NIVO 3 n = 59	NIVO 1 + IPI 3 n = 49	NIVO 3 + IPI 1 n = 52
Age, median (range), years	60 (29 to 80)	53 (27 to 77)	58 (19 to 81)
≥65 years	17 (29)	10 (20)	17 (33)
Male	45 (76)	34 (69)	45 (87)
Race			
White	56 (95)	46 (94)	50 (96)
Black	3 (5)	1 (2)	1 (2)
Asian/other	0	2 (4)	1 (2)
Primary site			
Gastric	19 (32)	22 (45)	18 (35)
GEJ/esophageal	40 (68)	27 (55)	34 (65)
Number of prior regimens			
0	0	1 (2)	0
1	10 (17)	6 (12)	16 (31)
2	20 (34)	19 (39)	16 (31)
3	19 (32)	11 (22)	13 (25)
>3	10 (17)	12 (24)	7 (13)
PD-L1 tumor expression, n/N (%)†			
≥1%	16/42 (38)	10/42 (24)	13/43 (30)
<1%	26/42 (62)	32/42 (76)	30/43 (70)

* PD-L1 tumor expression rates reported according to the number of patients with quantifiable samples. PD-L1 was quantifiable in 71%, 86%, and 83% of patients in the NIVO 3, NIVO 1 + IPI 3, and NIVO 3 + IPI 1 treatment groups, respectively.

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IMUNOTERAPIA - CHECKMATE 032

Resultados - Desfecho Primário

Objective Response

	NIVO 3 n = 59	NIVO 1 + IPI 3 n = 49	NIVO 3 + IPI 1 n = 52
ORR, n (%)* [95% CI]	7 (12) [5, 23]	12 (24) [13, 39]	4 (8) [2, 19]
BOR, n (%)*			
Complete response	1 (2)	1 (2)	0
Partial response	6 (10)	11 (22)	4 (8)
Stable disease	12 (20)	8 (16)	15 (29)
Progressive disease	34 (58)	23 (47)	24 (46)
Not evaluable	6 (10)	6 (12)	9 (17)
DCR, n (%)†	19 (32)	20 (41)	19 (37)
Median TTR (range), months	1.6 (1.2 to 4.0)	2.7 (1.2 to 14.5)	2.6 (1.3 to 2.8)
Median DOR (95% CI), months	7.1 (3.0, 13.2)	7.9 (2.8, NE)	NR (2.5, NE)

BOR, best objective response; DCR, disease control rate; NR, not reached; NE, not estimable.

* Investigator review.

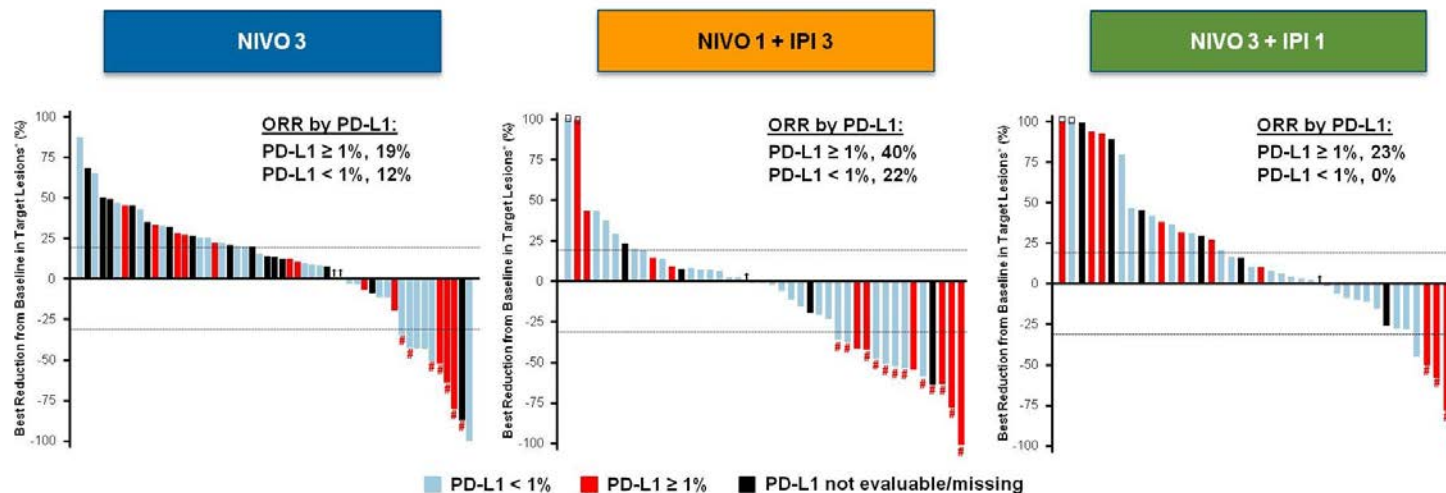
† Patients with a BOR of complete response, partial response, or stable disease.

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IMUNOTERAPIA - CHECKMATE 032

Resultados - Desfecho Primário

Best Reduction in Target Lesions



- Responses were observed regardless of PD-L1 expression

* Investigator review.

Patients with confirmed response (complete or partial response).

† Patients with 0% best reduction in target lesion, including 3 patients with PD-L1 ≥ 1% (NIVO 3, n=2; NIVO 3 + IPI 1, n=1) and 1 patient with PD-L1 < 1% (NIVO 1 + IPI 3).

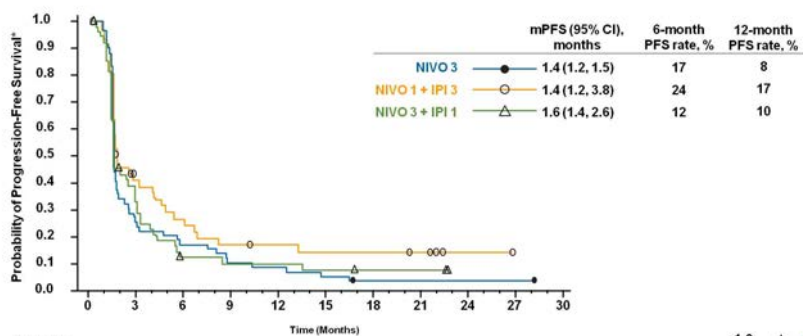
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IMUNOTERAPIA - CHECKMATE 032

Resultados - Desfechos Secundários

Progression-Free Survival



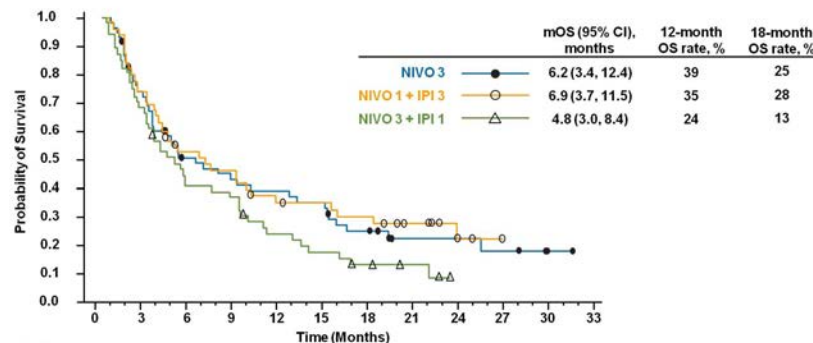
No. at Risk:	0	3	6	9	12	15	18	21	24	27	30
NIVO 3	59	13	10	6	5	3	1	1	1	1	0
NIVO 1 + IPI 3	49	16	10	7	6	5	5	4	1	0	0
NIVO 3 + IPI 1	52	13	5	4	4	3	2	2	0	0	0

mPFS, median PFS
* Investigator review.

Overall Survival by PD-L1 Status

OS rate (95% CI), %	NIVO 3	NIVO 1 + IPI 3	NIVO 3 + IPI 1
Patients with PD-L1 ≥1%	n = 16	n = 10	n = 13
12 months	34 (12, 57)	50 (18, 75)	23 (6, 47)
Patients with PD-L1 <1%	n = 26	n = 32	n = 30
12 months	45 (25, 6)	32 (16, 48)	25 (11, 42)

Overall Survival



No. at Risk:	0	3	6	9	12	15	18	21	24	27	30	33
NIVO 3	59	40	26	21	20	15	11	5	5	4	1	0
NIVO 1 + IPI 3	49	35	24	19	14	14	11	8	3	0	0	0
NIVO 3 + IPI 1	52	33	20	18	11	8	4	3	0	0	0	0

mOS, median OS.

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IMUNOTERAPIA - CHECKMATE 032

Resultados - Segurança

Treatment-Related Adverse Events

Patients, n (%)	NIVO 3 n = 59		NIVO 1 + IPI 3 n = 49		NIVO 3 + IPI 1 n = 52	
	Any grade	Grade 3/4	Any grade	Grade 3/4	Any grade	Grade 3/4
Any TRAE	41 (69)	10 (17)	41 (84)	23 (47)	39 (75)	14 (27)
Serious TRAEs	6 (10)	3 (5)	21 (43)	17 (35)	13 (25)	9 (17)
TRAEs leading to treatment discontinuation	2 (3)	2 (3)	10 (20)	10 (20)	7 (13)	5 (10)
TRAEs in ≥15% of patients in any treatment arm						
ALT increased	5 (8)	2 (3)	8 (16)	7 (14)	5 (10)	2 (4)
AST increased	7 (12)	3 (5)	8 (16)	5 (10)	2 (4)	1 (2)
Decreased appetite	9 (15)	0	5 (10)	0	3 (6)	0
Diarrhea	9 (15)	1 (2)	15 (31)	7 (14)	5 (10)	1 (2)
Fatigue	20 (34)	1 (2)	14 (29)	3 (6)	10 (19)	0
Pruritus	10 (17)	0	9 (18)	1 (2)	12 (23)	0
Rash	5 (8)	0	10 (20)	0	8 (15)	0

- One grade 5 TRAE was reported (tumor lysis syndrome in a patient treated with NIVO 3 + IPI 1)

TRAE, treatment-related adverse event.

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IMUNOTERAPIA - CHECKMATE 032

Conclusões

Conclusions

- Nivolumab alone or in combination with ipilimumab demonstrates clinical activity in patients with chemotherapy-refractory EG cancer irrespective of PD-L1 status
- Safety profile is consistent with prior reports¹⁻⁴
- Nivolumab alone and in combination with ipilimumab are being investigated in phase 3 studies in patients with advanced EG cancer

1. Janjigian YY, et al. ASCO 2016 [abstract 4010]; 2. Larkin J, et al. *N Engl J Med.* 2015;373:23-34; 3. Wolchok JD, et al. *N Engl J Med.* 2013;369:122-133; 4. Antonia SJ, et al. *Lancet Oncol.* 2016;17:883-895.

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FLOT 4

Perioperative chemotherapy with docetaxel, oxaliplatin, and fluorouracil/leucovorin (FLOT) versus epirubicin, cisplatin, and fluorouracil or capecitabine (ECF/ECX) for resectable gastric or gastroesophageal junction (GEJ) adenocarcinoma (FLOT4): A multicenter, randomized phase 3 trial

Al-Batran SE, Homann N, Schmalenberg H, Kopp HG, Haag GM, Luley KB, Schmiegel WH, Folprecht G, Probst S, Prasnikar N, Thuss-Patience P, Fischbach W, Trojan J, Koenigsmann M, Pauligk C, Goetze TO, Jaeger E, Lindig U, Kasper S, Hozaeel W, Meiler J, Schuler MH, Hofheinz RD for the German Gastric Study Group at AIO

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FLOT 4

Contexto

- ECF: esquema quimioterápico padrão no tratamento perioperatório do câncer gástrico desde a publicação do MAGIC TRIAL.
- Resultado permanece insatisfatório: sobrevida em 5 anos de 36%.
- Estudo de fase 2 com esquema FLOT demonstrou previamente resultados promissores.



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FLOT 4

Contexto

FLOT Regimen

- **T** docetaxel d1 50 mg/m² iv inf.
- **O** oxaliplatin d1 85 mg/m² iv inf.
- **L** leucovorin d1 200 mg/m² iv inf.
- **F** 5-FU d1 2.600 mg/m² iv 24h inf.
– repeated every 2 weeks

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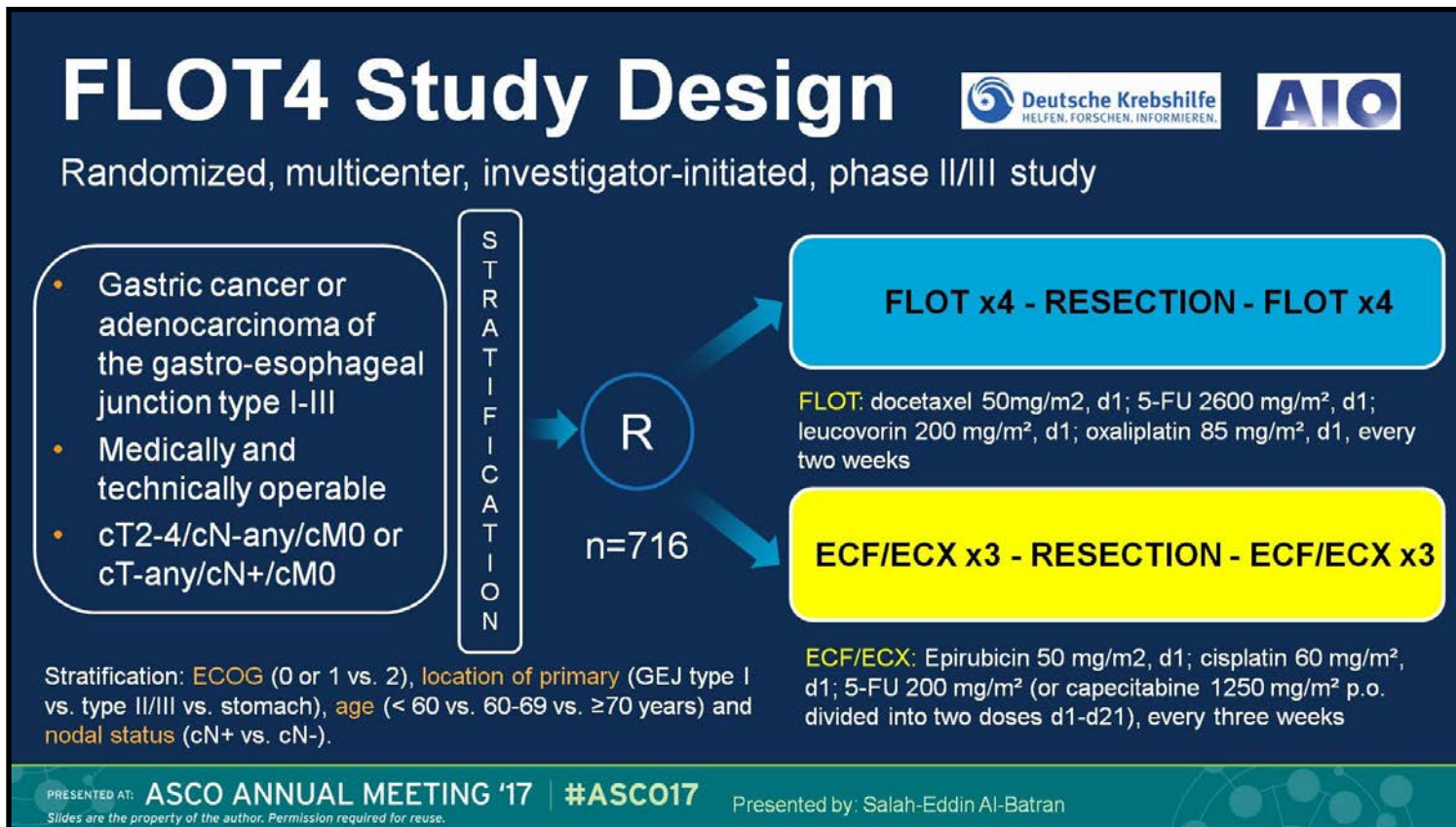
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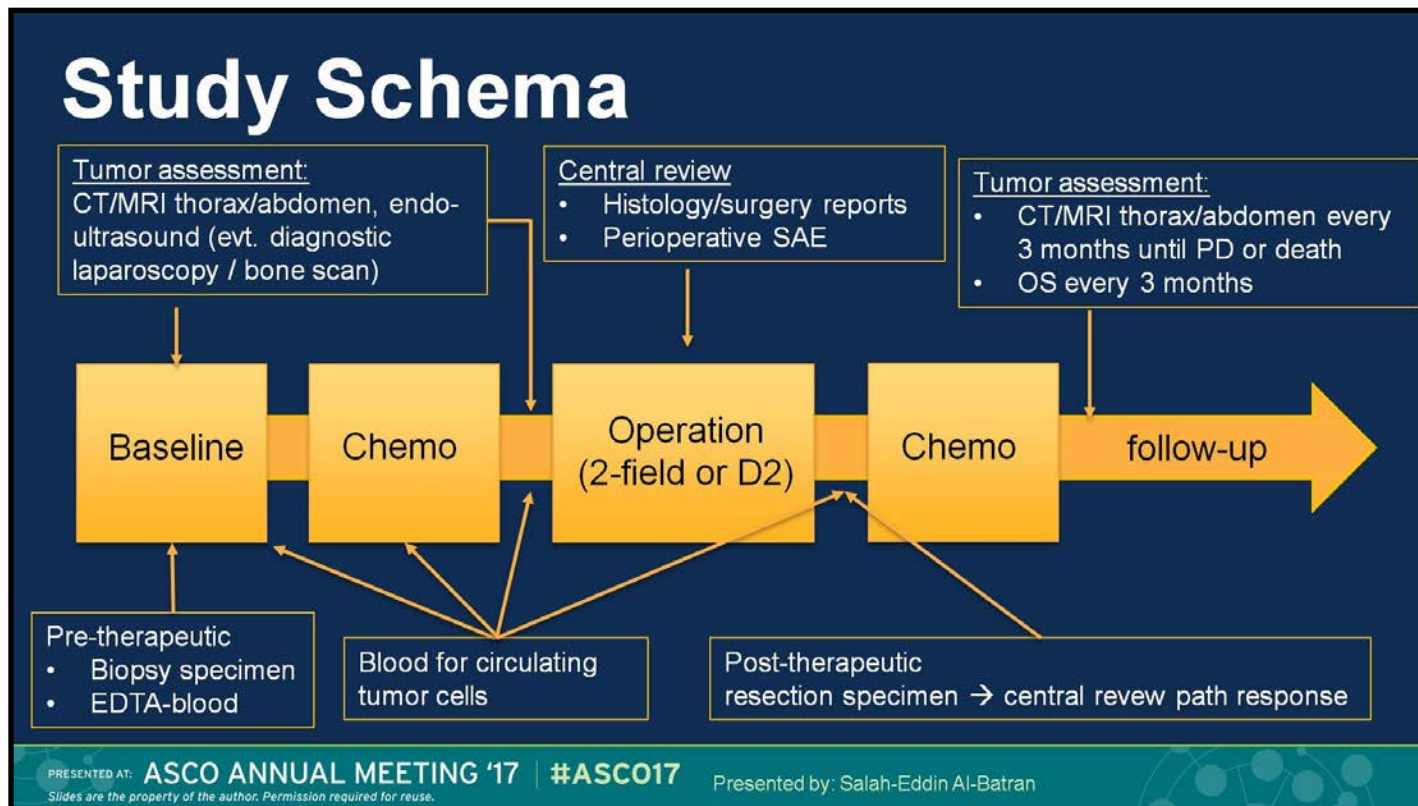
Desenho do Estudo



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FLOT 4

Desenho do Estudo



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Desenho do Estudo

Endpoints and Populations

- Primary endpoint
 - overall survival (intention to treat)
- Secondary endpoints
 - progression-free survival (intention to treat)
 - complete resection rate (intention to treat)
 - surgical morbidity and mortality (surgery population)
 - Chemotherapy related toxicity (safety population) and others

Intention to Treat (ITT): all patients randomized, analyzed as allocated

Surgery Population: patients of ITT, who proceeded to operation, whether they had resection or not

Safety Population: all patients who received at least one cycles of chemotherapy, analyzed as treated

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Statistics

- The study (phase III part) had 80% power to show superiority for FLOT with a HR of 0.76 using Kaplan-Meier method and 2-sided log-rank test at 5% type I error, assuming 25 months median OS for ECF/ECX, 4 years enrollment, and 6 years total follow-up time
- A co-primary endpoint was non-inferiority, tested according to Freidlin et al 2007 if superiority was not established

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FLOT 4

Resultados

Baseline 1

	ECF/ECX N=360		FLOT N=356	
Age				
median	62	-	62	-
< 60	160	44%	155	44%
60-69	113	31%	116	33%
>=70	87	24%	85	24%
Sex				
male	265	74%	268	75%
female	95	26%	88	25%
ECOG PS				
0	254	71%	246	69%
1	103	29%	109	31%
2	3	1%	1	<1%
Location				
GEJ Siewert type 1	85	24%	80	23%
GEJ Siewert type 2 or 3	115	32%	118	33%
Stomach	160	44%	158	44%

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Baseline 2

	ECF/ECX N=360		FLOT N=356	
cT-stage				
T1	2	1%	3	1%
T2	59	16%	49	14%
T3	253	70%	267	75%
T4	33	9%	28	8%
unclear	13	4%	9	3%
cN-stage				
N-	70	19%	77	22%
N+	290	81%	279	78%
Barrett's Carcinoma*				
yes	54	15%	53	15%
no	297	83%	301	85%
unclear or unknown	4	1%	2	1%
missing	5	1%	0	-

*Baseline data were supplemented by data from surgical specimen

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Baseline 3

	ECF/ECX N=360		FLOT N=356	
Lauren's Type*				
diffuse	96	27%	95	27%
intestinal/mixed	163	45%	159	45%
not evaluable according to Lauren	72	20%	70	20%
missing	29	8%	32	9%
Signet cells*				
yes	101	28%	100	28%
no	234	65%	245	69%
missing	25	7%	11	3%
Grading according to WHO				
G1	21	6%	12	3%
G2	131	36%	123	35%
G2-3	10	3%	12	3%
G3	177	49%	177	50%
missing	21	6%	32	9%

*Baseline data were supplemented by data from surgical specimen

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FLOT 4

Resultados

Surgery 1

	ECF/ECX (360)	FLOT (356)	P-value
Enrolled	360 (100%)	356 (100%)	
Proceeded to surgery	340 (94%)	345 (97%)	
Rate of resectional tumor surgery (ITT)	313 (87%)	336 (94%)	0.001
Rate of margin-free (R0)-resection (ITT)	276 (77%)	300 (84%)	0.011
Type of surgery			
transthoracic esophagectomy	98 (27%)	109 (31%)	
gastrectomy with or without transhiatal esophagectomy	199 (55%)	208 (58%)	
multivisceral resection	10 (3%)	15 (4%)	
other resectional tumor surgery	6 (2%)	4 (1%)	
palliative (non-curative) resection	6 (2%)	0 (0%)	
non-resectional surgery	22 (6%)	9 (3%)	
no surgery	19 (5%)	11 (3%)	

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Surgery 2

	ECF/ECX (360)	FLOT (356)
#LN removed (25%;75% Quantile)*	25.0 (19;33)	24.0 (18;32)
Lymphadenectomy		
2-Field	106 (29%)	113 (32%)
D2	192 (53%)	204 (57%)
3-Field	2 (1%)	1 (<1%)
D3	5 (1%)	10 (3%)
D1	7 (2%)	5 (1%)
missing	7 (2%)	3 (1%)
not applicable/D0	41 (11%)	20 (6%)

*numbers related to patients with resectional surgery only

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Chemotherapy

	ECF/ECX (360)*	FLOT (356)
Started allocated pre-op chemo	354 (98%) [§]	352 (99%) [§]
Completed allocated pre-op chemo	327 (91%)	320 (90%)
Started allocated post-op chemo	187 (52%)	213 (60%)
Completed allocated post-op chemo	133 (37%)	162 (46%)
Completed post-chemo any [§]	157 (44%)	182 (51%)

*69% of patients in the ECF/ECX arm received ECX

[§]Numbers also exclude 2 patients in each arm who crossed over to the other arm by mistake. These patients were analyzed as allocated in the ITT population and as actually treated in the safety and per protocol populations

[§]Chi-Square Test

[§]Include patients who had major modifications in postoperatively

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FLOT 4

Resultados

Histopathology (ypTN)

ypT-stage	ECF/ECX (360)	FLOT (356)	P-value [§]	ypT-stage	ECF/ECX (360)	FLOT (356)	P- value [§]
≤T1	53 (15%)	88 (25%)	0.001	N0	146 (41%)	174 (49%)	0.029
T2	44 (12%)	44 (12%)		N1	44 (12%)	55 (16%)	
T3	175 (49%)	165 (46%)		N2	54 (15%)	47 (13%)	
T4	47 (13%)	37 (10%)		N3	73 (20%)	57 (16%)	
NA*	41 (11%)	22 (6.2%)		NA*	43 (12%)	23 (7%)	

*NA, not applicable and include patients who could not be staged due to no operation, non-resectional surgery, or tumor regression
§Chi-Square Test

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CÂNCER GÁSTRICO

FLOT 4

Resultados - Segurança

Chemo Related Toxicity 1

Grade 3-4 >5%	ECF/ECX (N=354)	FLOT (N=354)	P-value (Chi-Square)
Diarrhea	13 (4%)	34 (10%)	0.002
Vomiting	27 (8%)	7 (2%)	<0.001
Nausea	55 (16%)	26 (7%)	0.001
Fatigue	38 (11%)	25 (7%)	
Infections	30 (9%)	63 (18%)	<0.001
Leukopenia	75 (21%)	94 (27%)	
Neutropenia	139 (39%)	181 (51%)	0.002
Sensory	7 (2%)	24 (7%)	0.002
Thromboembolic	22 (6%)	9 (3%)	0.03
Anemia	20 (6%)	9 (3%)	0.04

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Chemo Related Toxicity 2

Toxic event	ECF/ECX (N=354)	FLOT (N=354)	P-value (Chi-Square)
SAE any	220 (62%)	215 (61%)	
SAE w relation to treatment	137 (34%)	139 (35%)	
toxic death	2 (<1%)	2 (<1%)	

SAE, serious adverse events

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Operative Morbidity/Mortality

	ECF/ECX (N=341)	FLOT (N=345)	P-value
complication any	188 (55%)	188 (55%)	
surgical w/o medical	66 (19%)	53 (20%)	
medical	104 (31%)	105 (30%)	
Re-operations	37 (11%)	34 (10%)	
death in hospital	15 (4%)	8 (2%)	
death 30-days	10 (3%)	6 (2%)	
death 90-days	26 (8%)	16 (5%)	
hospitalization days [median (25%;75%Q)]	16 (13;23)	15 (12;21)	

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FLOT 4

Resultados - Segurança

Reasons for not completing chemotherapy

	ECF/ECX (360)*	FLOT (356)*
disease progression or death	74 (21%)	46 (13%)
patient's request	62 (17%)	59 (17%)
toxicity	47 (13%)	35 (10%)
early OP; continued therapy postop	0	4 (1%)
M1 discovered after randomization	0	2 (1%)
unknown	1 (<1%)	5 (1%)
others§	37 (10%)	43 (2%)

*6 and 4 patients did not start allocated treatment in the ECF/ECX and FLOT arms, respectively.

§include mainly patients with surgical complications, unsatisfactory response to pre-op chemo, incomplete resection, discovery of M1 disease during operation, and others

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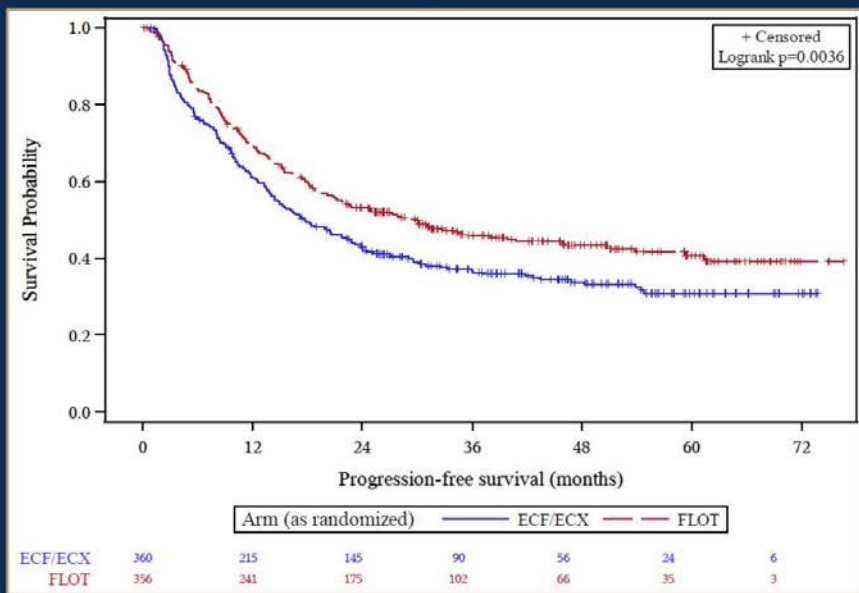
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FLOT 4

Resultados

FLOT4: Progression-Free Survival



	ECF/ECX	FLOT
mPFS 18 months months	[15-22]	[21-41]
HR	0.75 [0.62-0.91] p=0.004 (log rank)	
PFS rate*	ECF/ECX	FLOT
2y		43%
3y		37%
Projected PFS rates		46%
		31%
		41%

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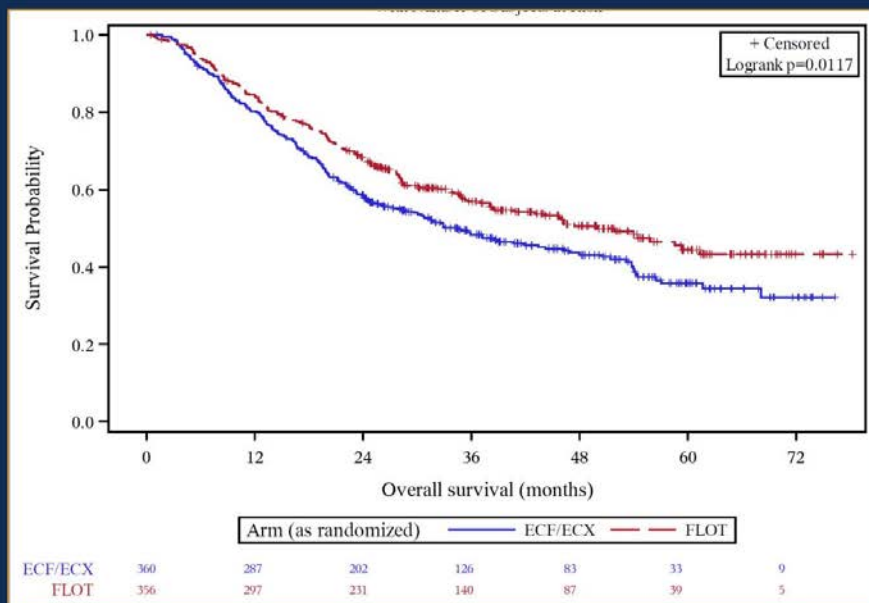
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FLOT 4

Resultado - Desfecho Primário

FLOT4: Overall Survival



ECF/ECX FLOT

mOS
months

35 months 50

[27-46] [38-na]

HR

0.77 [0.63 - 0.94]
p=0.012 (log rank)

OS rate*

ECF/ECX FLOT

2y

59%

68%

3y

48%

57%

5y projected OS rates

36%

45%

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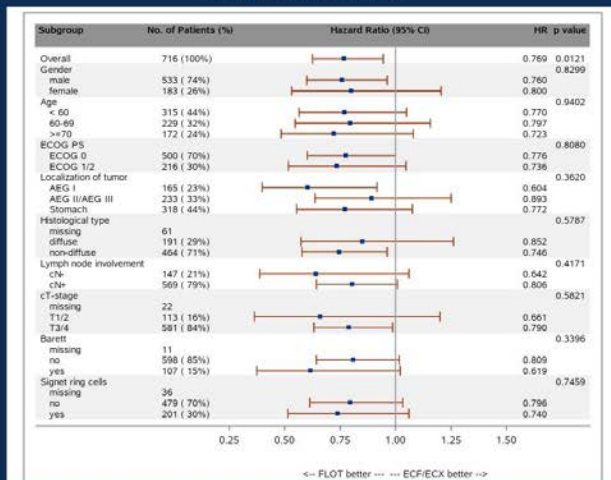
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FLOT 4

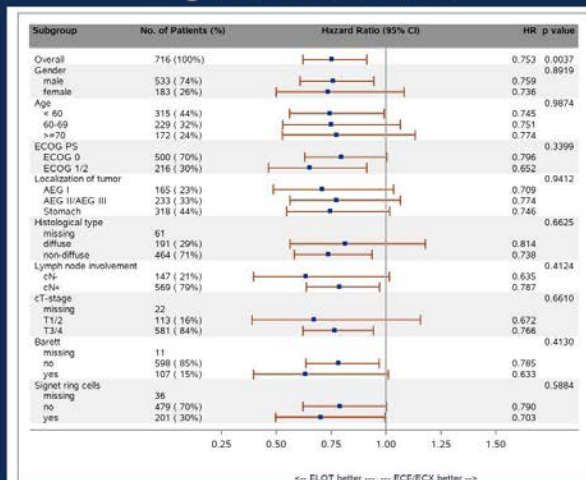
Resultado - Desfecho Primário

Subgroup Analysis

Overall survival



Progression-free survival



P-values stands for test for interaction between treatment and subgroup variable

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FLOT 4

Conclusões

- FLOT aumentou as taxas de cirurgia curativa, sobrevida livre de progressão e sobrevida global quando comparado com ECF/ECX.
- Efeito relativo o FLOT foi consistente em todos os subgrupos e análises de sensibilidade.
- Não houve aumento de morbidade cirúrgica, mortalidade, necessidade de novas intervenções e tempo de hospitalização.
- **FLOT é o novo esquema padrão para o tratamento quimioterápico perioperatório do câncer gástrico!**

CÂNCER DE PÂNCREAS E VIAS BILIARES



○ CÂNCER DE PÂNCREAS E VIAS BILIARES

BILCAP

Adjuvant capecitabine for biliary tract cancer: the **BILCAP** randomized study

Primrose JN, Fox RP, Palmer D, Prasad R, Mirza D, Anthony A, Corrie P, Falk S, Wasan H, Ross P, Wall L, Wadsley J, Evans J, Stocken D, Praseedom R, Cunningham D, Garden OJ, Stubbs C, Valle JW and Bridgewater J on behalf of the BILCAP investigators

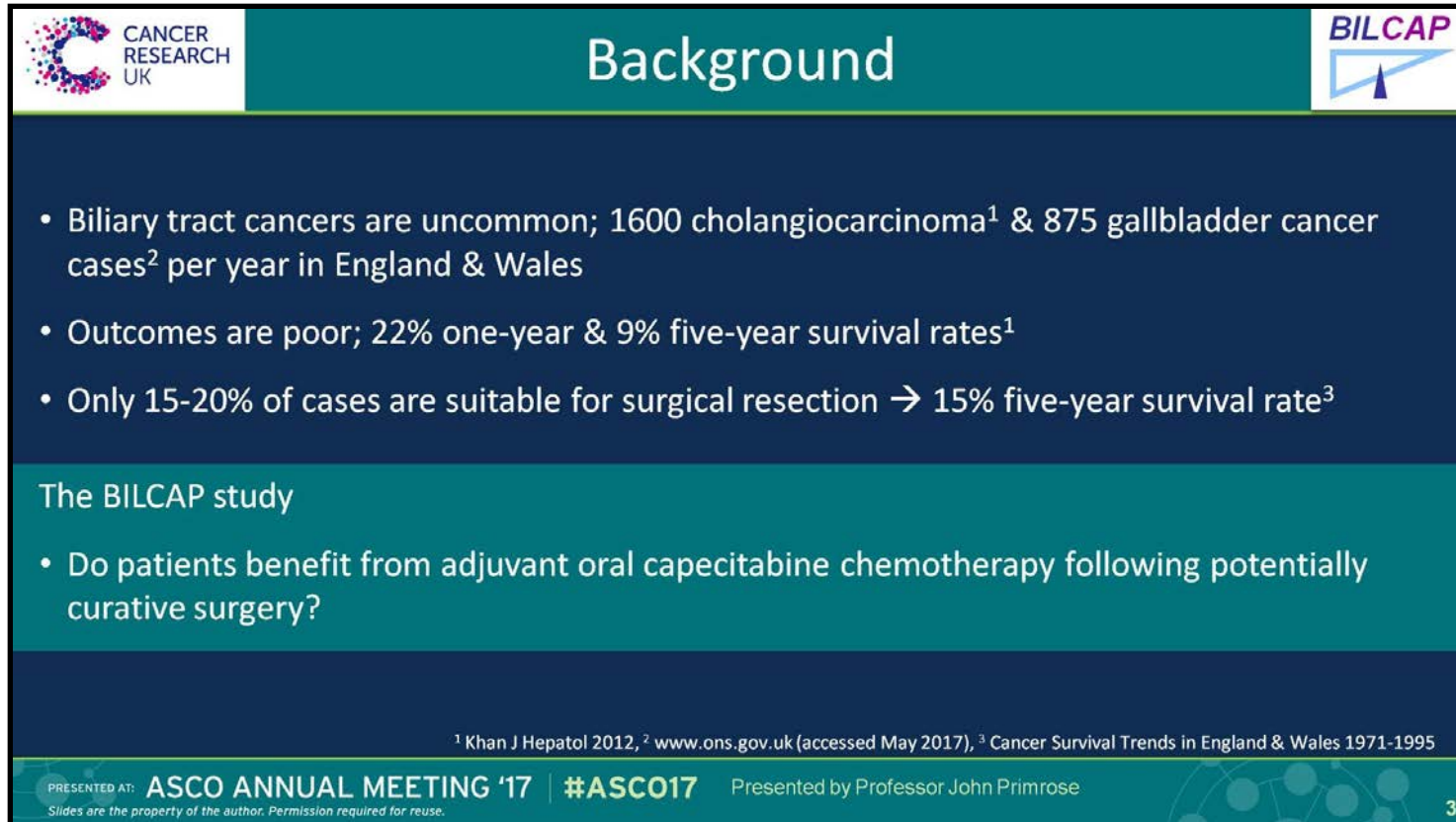
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BILCAP

Contexto



The slide features a teal header with the Cancer Research UK logo on the left and the BILCAP logo on the right. The main content area is dark blue with white text. A teal bar at the bottom contains the text 'The BILCAP study' and a bullet point. The footer is a dark teal bar with white text.

CANCER RESEARCH UK

Background

BILCAP

- Biliary tract cancers are uncommon; 1600 cholangiocarcinoma¹ & 875 gallbladder cancer cases² per year in England & Wales
- Outcomes are poor; 22% one-year & 9% five-year survival rates¹
- Only 15-20% of cases are suitable for surgical resection → 15% five-year survival rate³

The BILCAP study

- Do patients benefit from adjuvant oral capecitabine chemotherapy following potentially curative surgery?

¹ Khan J Hepatol 2012, ² www.ons.gov.uk (accessed May 2017), ³ Cancer Survival Trends in England & Wales 1971-1995

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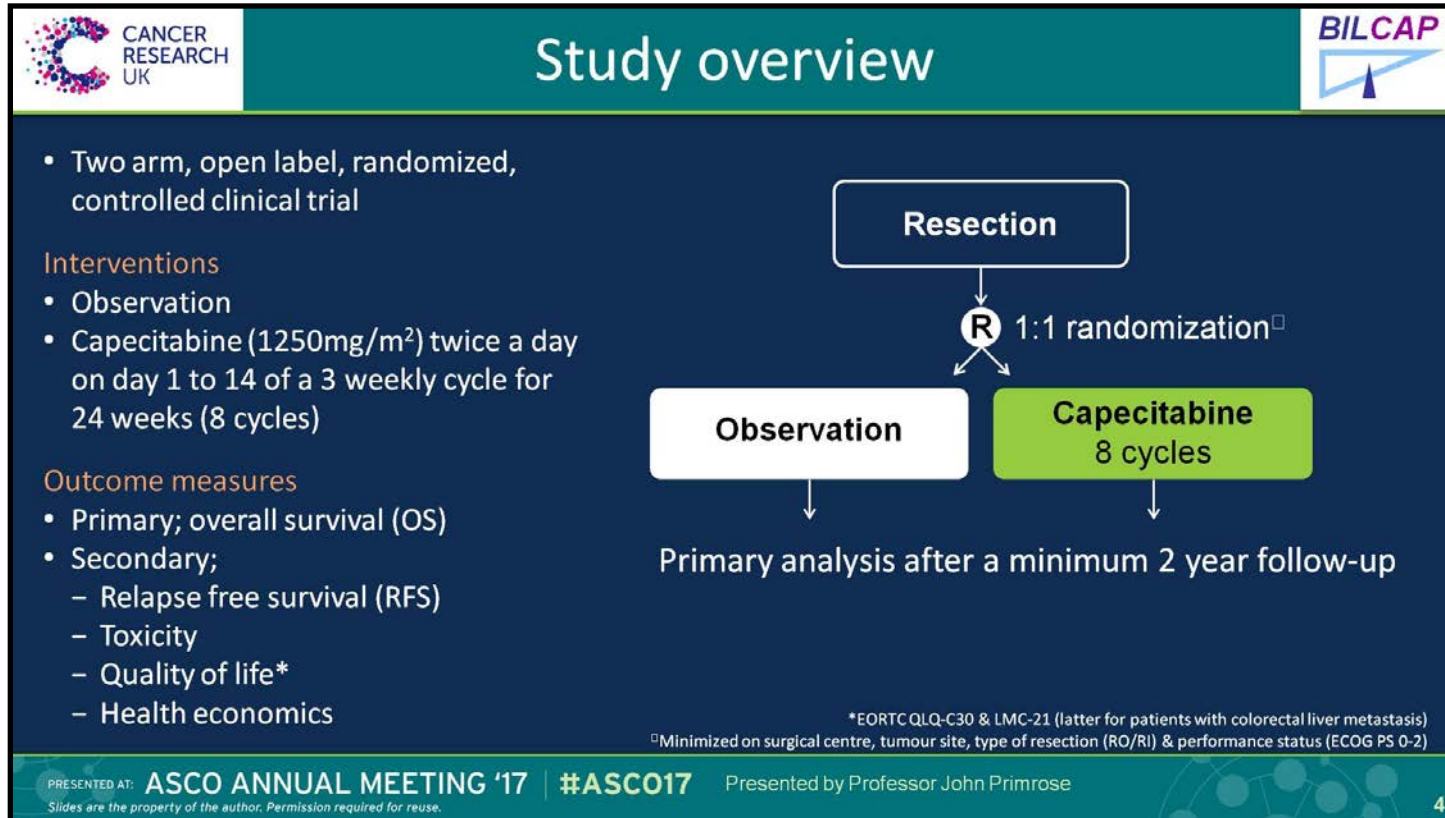
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Desenho do Estudo



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Desenho do Estudo

Power calculation

Version	Effect	# of patients	# of events
Original	Increase in 2 year OS from 20% → 32%, HR 0.71	360	270*
Revision 1	Increase in 2 year OS from ≈60% → 70%, HR 0.71	410	270*
Revision 2	Increase in 2 year OS from ≈60 → 71%, HR 0.69	410	234*

Observed 2 year OS of ≈60% in control group

Observed ongoing deficit of trial events

*2-sided significance level of 5% with 80% power

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BILCAP

Desenho do Estudo



Patient selection

Main inclusion criteria

- Histologically confirmed;
 - Intrahepatic cholangiocarcinoma (CC)
 - Hilar CC
 - Muscle invasive gallbladder cancer
 - Lower common bile duct CC
- Radical & macroscopically complete surgery
- ECOG performance status ≤ 2
- Adequate renal, haematological & liver function

Main exclusion criteria

- Pancreatic or ampullary cancer
- Mucosal (T1a) gallbladder cancer
- Incomplete recovery from previous surgery
- Previous chemotherapy or radiotherapy for biliary tract cancer

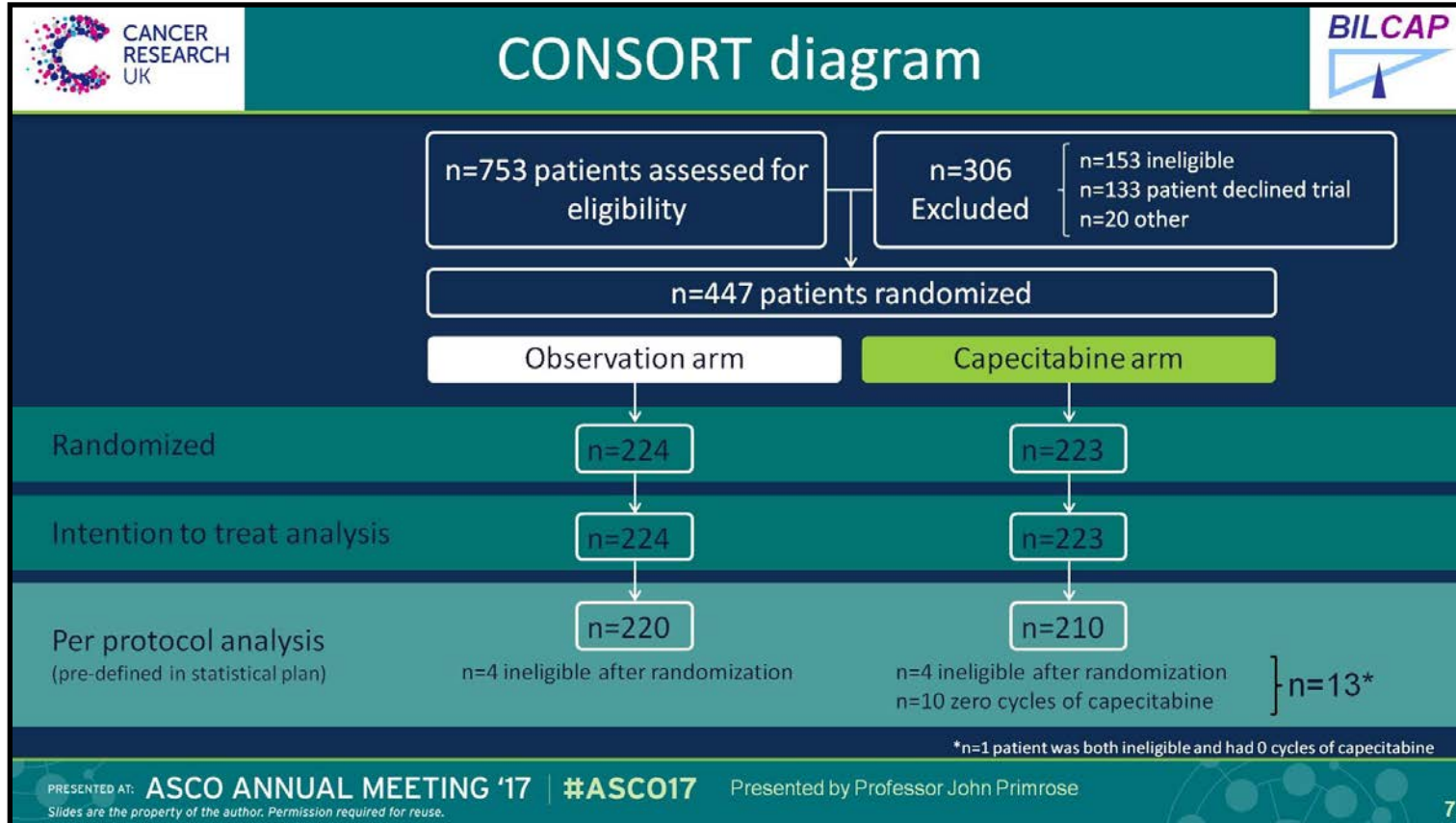
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Resultados



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BILCAP

Resultados

		Observation arm (n=224)	Capecitabine arm (n=223)
Gender	Male	113 (50%)	111 (50%)
	Female	111 (50%)	112 (50%)
Age	Median years (inter-quartile range)	64 (55-69)	62 (55-68)
	Range	22-90	22-90
Tumour site	Intrahepatic CC	41 (18%)	43 (19%)
	Hilar CC	63 (28%)	65 (29%)
	Muscle invasive gall bladder carcinoma	40 (18%)	39 (17%)
	Lower common bile duct CC	80 (36%)	76 (34%)
Resection status	R0	140 (63%)	139 (62%)
	R1	84 (38%)	84 (38%)
ECOG performance status	0	101 (45%)	100 (45%)
	1	116 (52%)	116 (52%)
	2	7 (3%)	7 (3%)
Tumour size	Median mm (inter-quartile range)	25 (20-44)	25 (19-45)
Lymph node status	N0	108 (48%)	100 (45%)
	N1	102 (46%)	108 (48%)
	NX	14 (6%)	15 (7%)

Values shown are n (%) for categorical data, and median (IQR) for continuous measures

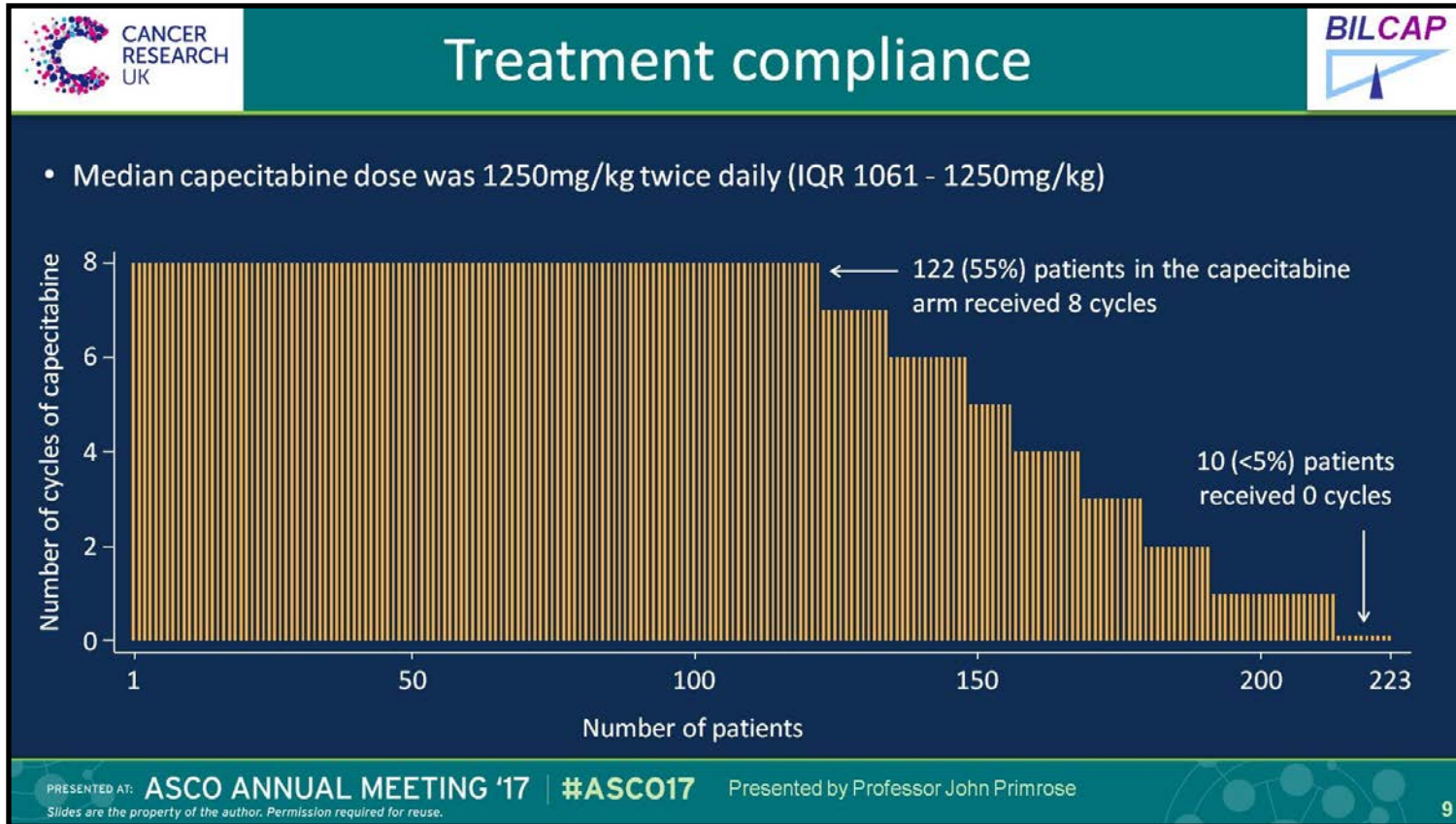
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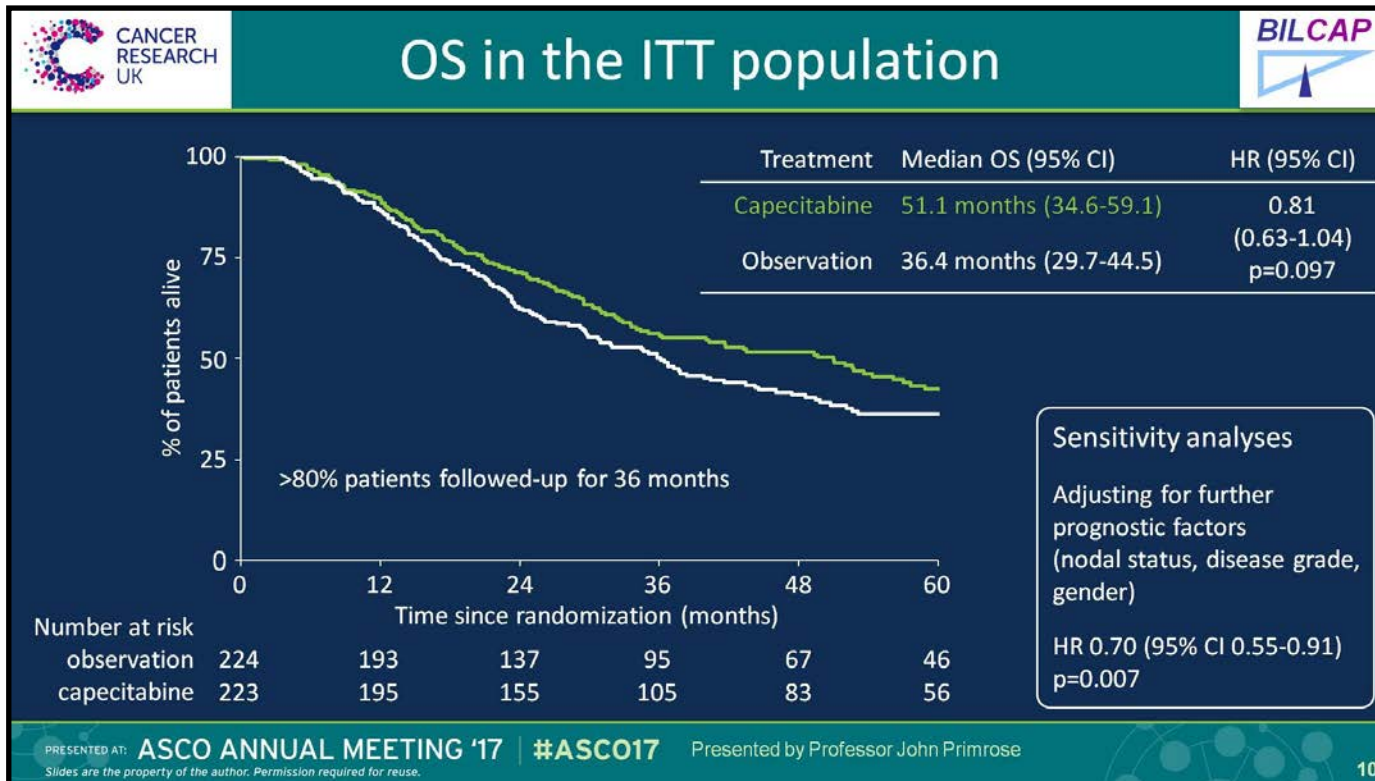
Resultados



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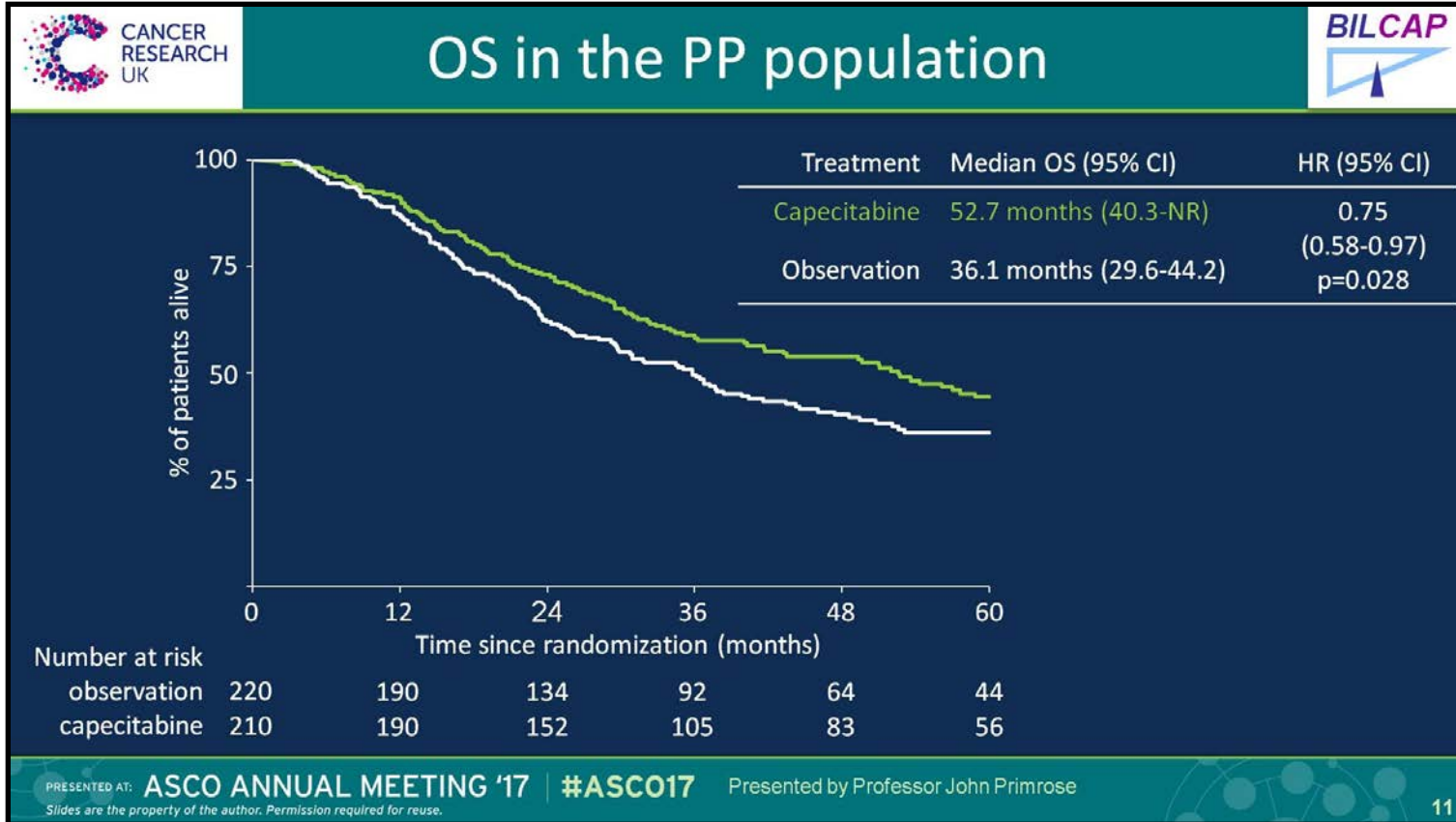
Resultados - Desfecho Primário



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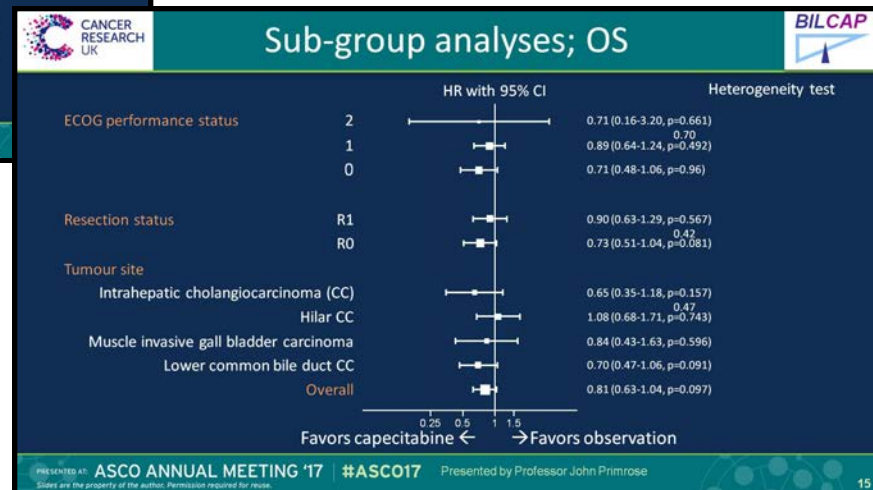
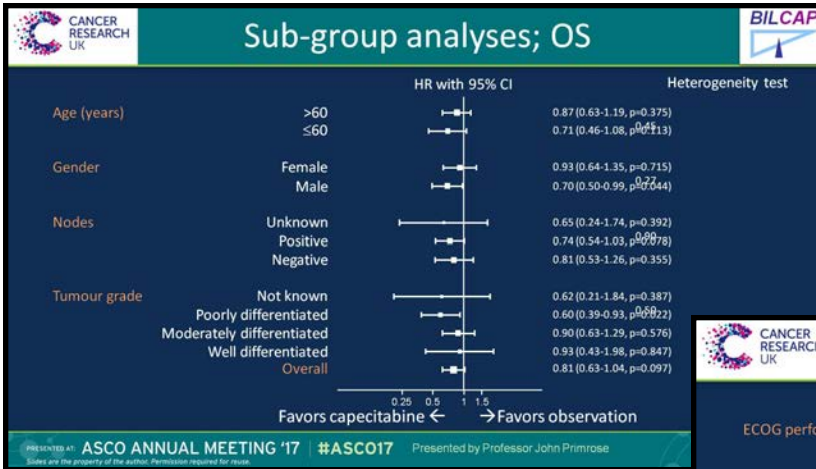
Resultados - Desfecho Primário



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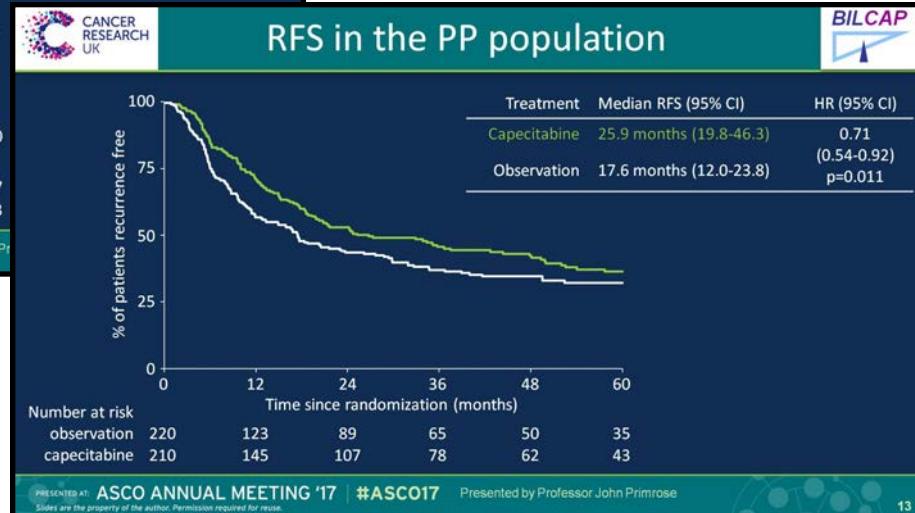
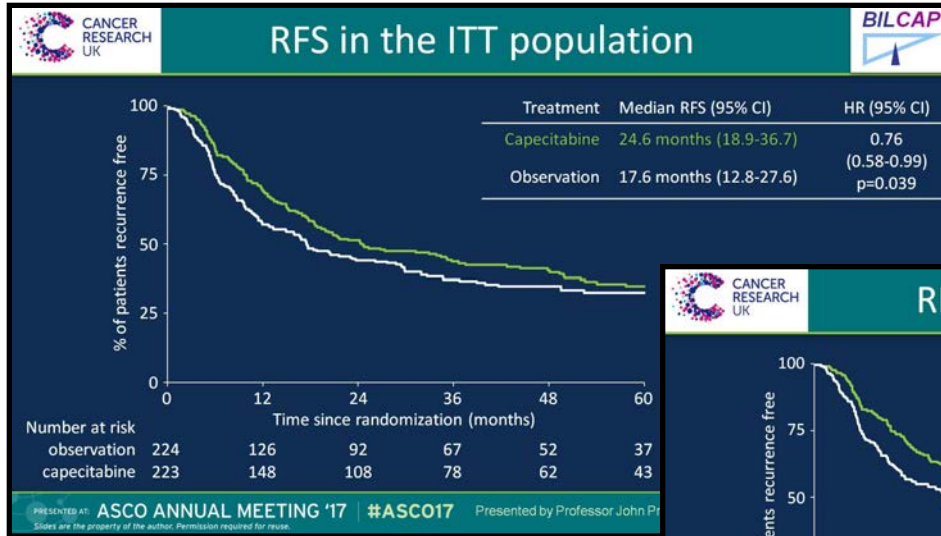
Resultados - Desfecho Primário



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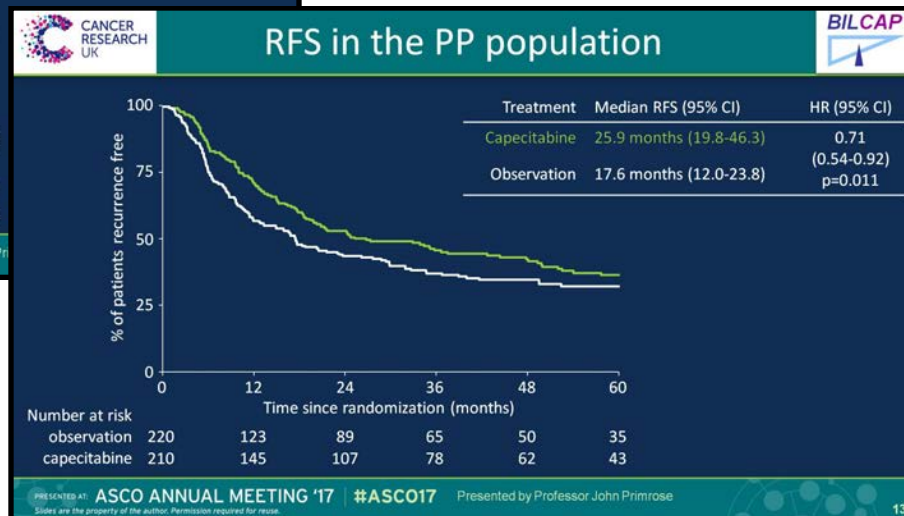
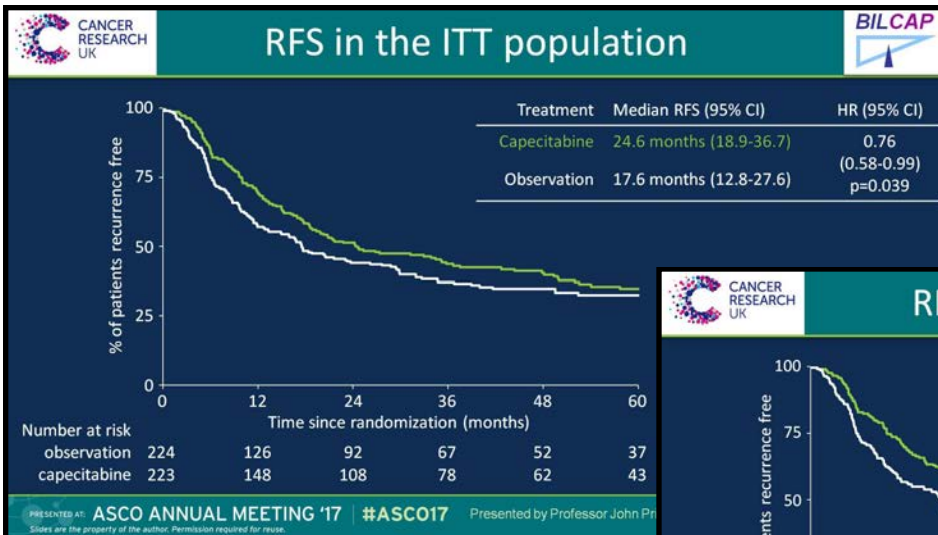
Resultados - Desfechos Secundários



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Resultados - Desfechos Secundários




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Resultados - Segurança



Toxicity



Toxicity type	All grades		Grades 1 & 2		Grades 3&4	
	n	%	n	%	n	%
Fatigue	175	82	159	75	16	8
Plantar palmar erythema	174	82	130	61	44	21
Diarrhoea	137	64	121	57	16	8
Nausea	108	51	106	50	2	1
Mucositis/stomatitis	96	45	94	44	2	1
Vomiting	50	24	49	23	1	0.5
Neutropenia	49	23	45	21	4	2
Bilirubin	45	21	42	20	3	1
Thrombocytopenia	26	12	25	12	1	0.5
Alopecia	20	9	20	9	0	0

- Safety population* n=213 patients

Serious adverse events

- 93 SAEs reported
- ≥1 SAE in 69 (32%) of all patients
- Capecitabine arm; 64 in 47 patients
- Observation arm; 29 in 22 patients (of which 3 resulted in death)

Serious adverse reactions

- Capecitabine arm; 33 in 30 patients

*conditional on receiving capecitabine

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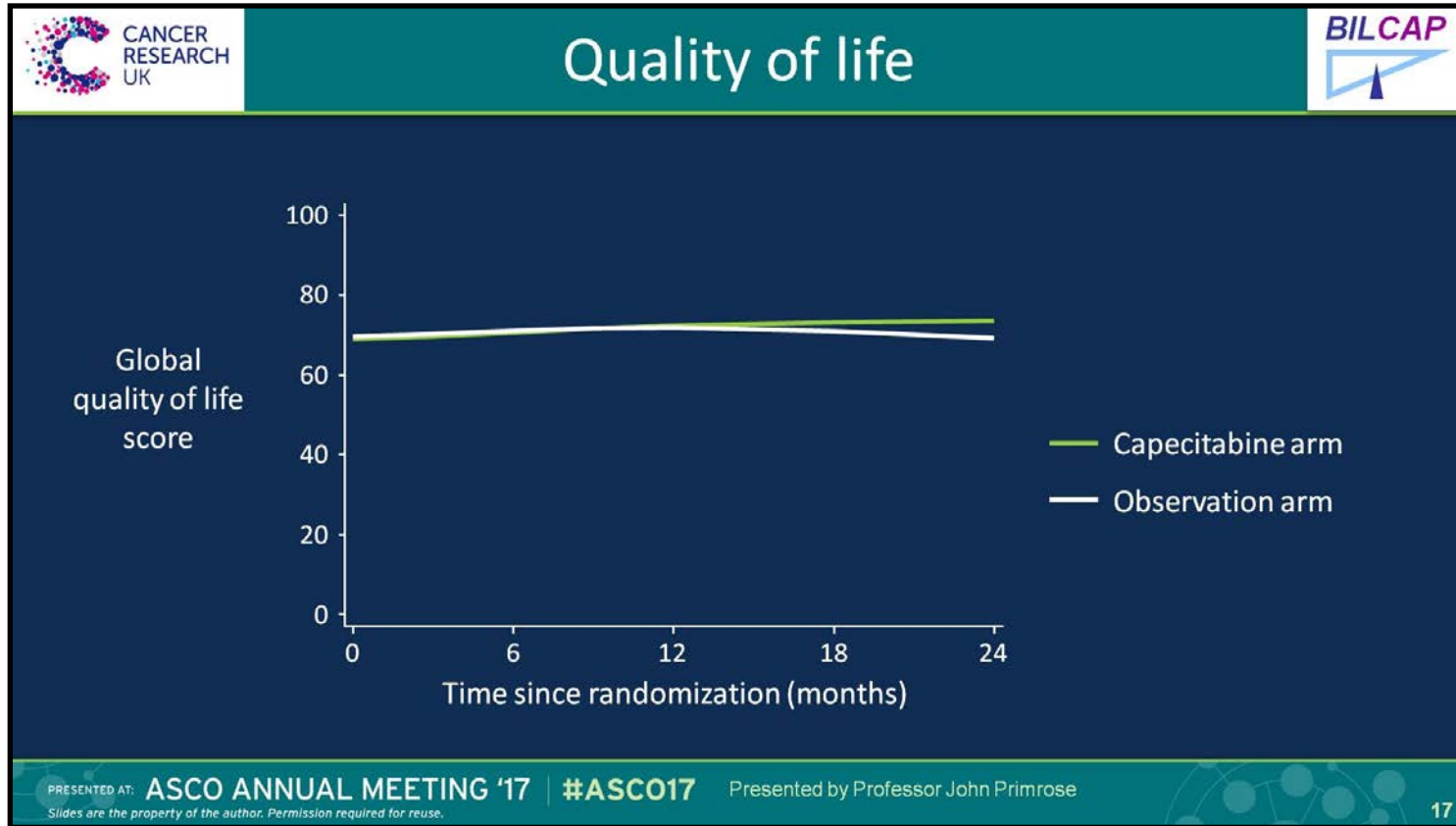
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Resultados - Qualidade de Vida



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Resultados - Conclusões



Conclusions


- Capecitabine as adjuvant improves OS in patients with resected biliary tract cancer from 36 to 51 months and should become standard of care in this setting
- Capecitabine toxicity was modest
- QoL was not reduced
- Capecitabine should be the control arm in future adjuvant trials in patients with biliary tract cancer

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CÂNCER DE PÂNCREAS E VIAS BILIARES

RTOG 0848



Results of the randomized phase II portion of NRG Oncology/RTOG 0848 evaluating the addition of erlotinib to adjuvant gemcitabine for patients with resected pancreatic head adenocarcinoma.

Howard Safran¹, Kathryn A Winter², Ross A Abrams³, William F Regine⁴, Karyn A Goodman⁵, Adam C Berger⁶, Michael T Gillin⁷, Philip A Philip⁸, Andrew M Lowy⁹, Abraham Wu¹⁰, Thomas A DiPetrillo¹, Benjamin W Corn¹¹, Samantha A Seaward¹², Michael G Haddock¹³, Suisui Song¹⁴, Yixing Jiang⁴, Barbara J Fisher¹⁵, Alan W Katz¹⁶, Sharmila Mehta¹⁷, Christopher H Crane¹⁰

¹ Rhode Island Hospital, ² NRG Oncology Statistics and Data Management Center-ACR, ³ Rush University Medical Center, ⁴ University of Maryland/Greenebaum Cancer Center, ⁵ University of Colorado Cancer Center, ⁶ Thomas Jefferson University Hospital, ⁷ MD Anderson Cancer Center, ⁸ Wayne State University/Karmanos Cancer Institute, ⁹ UC San Diego Moores Cancer Center, ¹⁰ Memorial Sloan Kettering Cancer, ¹¹ Tel Aviv Sourasky Medical Center, ¹² Kaiser Permanente Northern California, ¹³ Mayo Clinic, ¹⁴ USC/Norris Comprehensive Cancer Center, ¹⁵ London Regional Cancer Program, ¹⁶ University of Rochester, ¹⁷ Spartanburg Medical Center Accruals-Southeast Clinical Oncology Research (SCOR)

ASCO June, 2017

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RTOG 0848

Contexto

Background: Adjuvant trials at time of RTOG 0848 conception (2008)

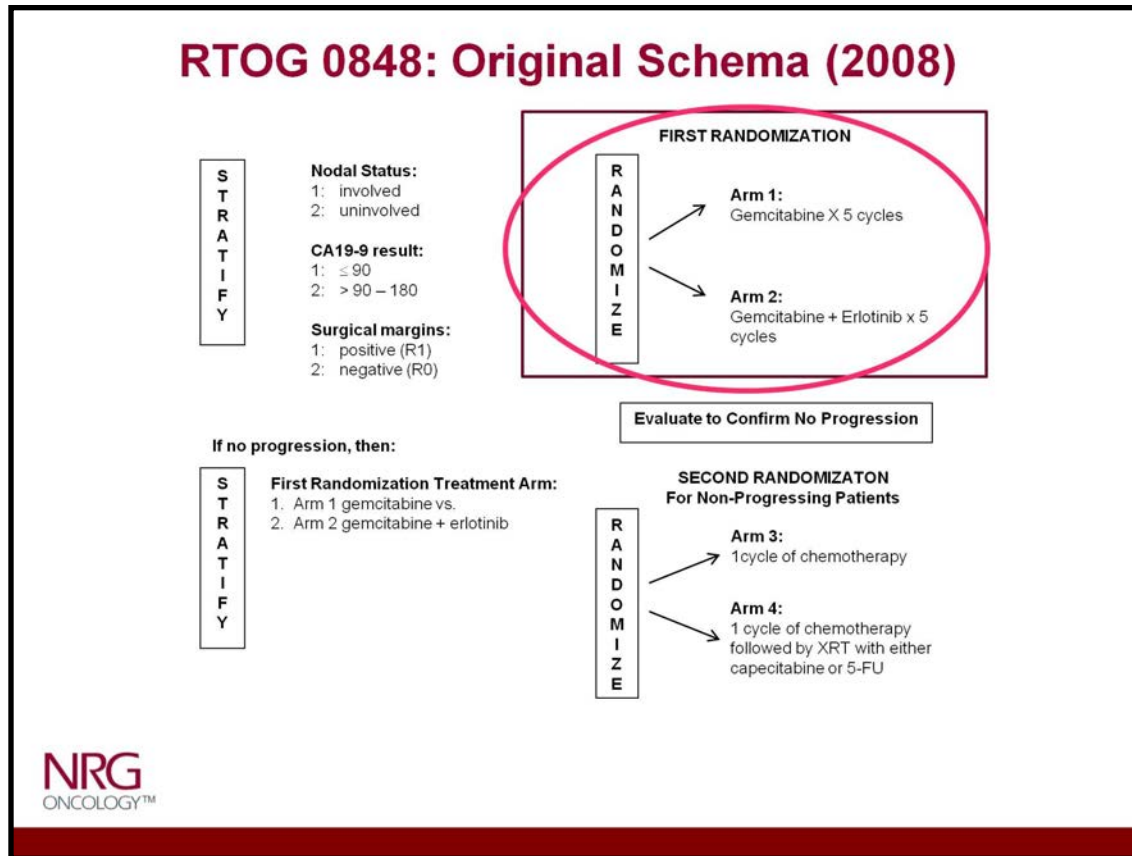
- **GITSG**: Adjuvant RT + 5-FU helpful. **(1985)**
- **ESPAC 1**: Adjuvant RT + 5-FU not helpful. **(2001, 2004)**
- **CONKO-001**: Adjuvant gemcitabine improved median OS vs. observation: 22.8 vs. 20.2 months, (p=0.005). **(2007)**
- **NCIC**: Erlotinib + gemcitabine improves median survival (6.4 vs. 5.9 months) and 1-year survival (17% vs. 24%) and compared to gemcitabine alone. **(2007)**

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RTOG 0848

Desenho do Estudo



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RTOG 0848

Desenho do Estudo

RTOG 0848: Key Eligibility

- **Pancreatic head** adenocarcinoma managed with a **potentially curative resection** (removal of all gross tumor), microscopic margin positivity allowed.
- Stage T1-3, N0-1, M-0
- **CA19-9 \leq 180 units/mL**
- ANC \geq 1,500 cells/mm³, platelets \geq 100,000 cells/mm³, serum total bilirubin \leq 2x ULN, creatinine $<$ 2x ULN, SGOT \leq 2.5 ULN
- CT of abdomen and chest CT/x-ray

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RTOG 0848

Desenho do Estudo

RTOG 0848: Statistical Revision After LAP07

LAP07 Trial

- Evaluated induction single agent gemcitabine (gem) vs gem + erlotinib in *locally advanced* pancreatic cancer
- OS: 16.5 mths for gem and 15.3 mths for gem + erlotinib

2014 RTOG 0848 Design Revision

- Stopped erlotinib randomization
- Changed erlotinib question to a phase IIR study for analysis
- 1-sided alpha of 0.15, with analysis at 200 events (deaths)
- 80% power to detect a signal for an increase in MST from 22 to 28.8 months (HRs = 0.76)
- 90% power to detect a signal for an increase in MST from 22 to 30.6 months (HRs = 0.72)

This analysis reports results of the Ph-IIR erlotinib question.

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RTOG 0848: Original Statistical Assumptions

Overall Sample Size (n=950)

- Based on 640 pts needed for RT question primary endpoint
- 25% progress prior to RT randomization
- **Still accruing to RT question**

Erlotinib Question – Primary Endpoint:

- 856 eligible pts (up to 10% of 950 ineligible)
- Provide 90% power to detect increase MST from 22 to 28 months (HR=0.79), with 1-sided $\alpha = 0.05$.

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RTOG 0848

Desenho do Estudo

RTOG 0848: Study Objectives

Phase II: Erlotinib Question – To determine whether the addition of erlotinib to gemcitabine adjuvant chemotherapy shows a signal for improved survival as compared to gemcitabine alone following R0 or R1 resection of head of pancreas adenocarcinoma

Phase III: Radiation Question (*still accruing*) – To determine whether the use of concurrent fluoropyrimidine and radiotherapy following adjuvant gemcitabine based chemotherapy or non-gemcitabine based chemotherapy such as modified FOLFIRINOX further enhances survival for such patients who are without evidence of progressive disease after 5 months of adjuvant chemotherapy.

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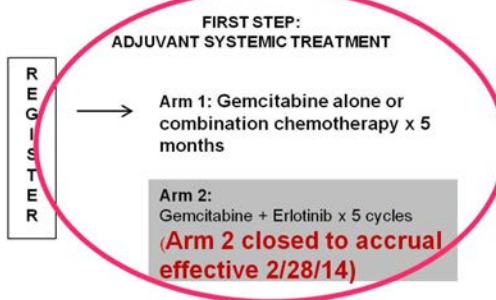
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RTOG 0848

Desenho do Estudo

RTOG 0848: Current Schema

Note: Up to 3 months of chemotherapy may be initiated prior to registration



If no progression, then:

STRATIFY

- Nodal Status:
- involved
 - Uninvolved
- CA19-9 Result:
- ≤ 90
 - > 90 – 180
- Surgical Margins:
- positive (R1)
 - negative (R0)
- Adjuvant Systemic Treatment:
- Gemcitabine alone
 - FOLFIRINOX or mFOLFIRINOX
 - Non-oxaliplatin gemcitabine combinations

Evaluate To Confirm No Progression

RANDOMIZE

- SECOND STEP: RT RANDOMIZATION For Non-Progressing Patients**
- Arm 3: 1 month of gemcitabine or combination chemotherapy
- Arm 4: 1 month of gemcitabine or combination chemotherapy followed by XRT with either capecitabine or 5-FU

RTOG 0848: Accrual Summary

Activated: November 7, 2009
Phase IIR Closed: February 28, 2014

	Gemcitabine	Gemcitabine +Erlotinib	Total
Randomized	169	167	336
Ineligible	6	8	14
Eligible	163	159	322

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CÂNCER DE PÂNCREAS E VIAS BILIARES

RTOG 0848

Resultados

RTOG 0848: Patient and Tumor Characteristics

	Gemcitabine (n=163)		Gemcitabine+ Erlotinib (n=159)		Total (n=322)	
	n	%	n	%	n	%
Median Age (Years) (Min-Max)	63 (39-86)		63 (39-85)		63 (39-86)	
Gender						
Male	88	54	96	60	184	57
Female	75	46	63	40	138	43
Pathologic T-Stage						
T1/T2	37	23	33	21	70	22
T3	126	77	126	79	252	78
Pathologic N-Stage						
N0	52	32	45	28	97	30
N1	111	68	114	72	225	70
CA19-9 Results						
≤ 90	152	93	148	93	300	93
>90-180	11	7	11	7	22	7
Surgical Margins						
Positive (R1)	28	17	27	17	55	17
Negative (R0)	135	83	132	83	267	83

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RTOG 0848

Resultados

RTOG 0848: Adverse Events*

	Gemcitabine (n=161)				Gemcitabine+ Erlotinib (n=157)			
	n and (%) of Patients by Grade				n and (%) of Patients by Grade			
	2	3	4	5	2	3	4	5
Overall Highest Grade	21 (13)	99 (62)	32 (20)	2 (1)	23 (15)	101 (64)	27 (17)	3 (2)
Blood and lymphatic system disorders	56 (35)	30 (19)	1 (1)	0 (0)	48 (31)	32 (20)	2 (1)	0 (0)
Gastrointestinal disorders	62 (39)	35 (22)	0 (0)	0 (0)	54 (34)	42 (27)	2 (1)	0 (0)
<i>Diarrhea</i>	26 (16)	3 (2)	0 (0)	0 (0)	29 (19)	16 (10)	0 (0)	0 (0)
Hepatobiliary disorders	1 (1)	3 (1.9)	1 (1)	0 (0)	0 (0)	1 (1)	0 (0)	1 (1)
Infections and infestations	24 (15)	10 (6)	9 (6)	0 (0)	21 (13)	24 (15)	6 (4)	1 (1)
Metabolism and nutrition disorders	43 (27)	39 (22)	3 (2)	0 (0)	39 (25)	42 (27)	4 (3)	0 (0)

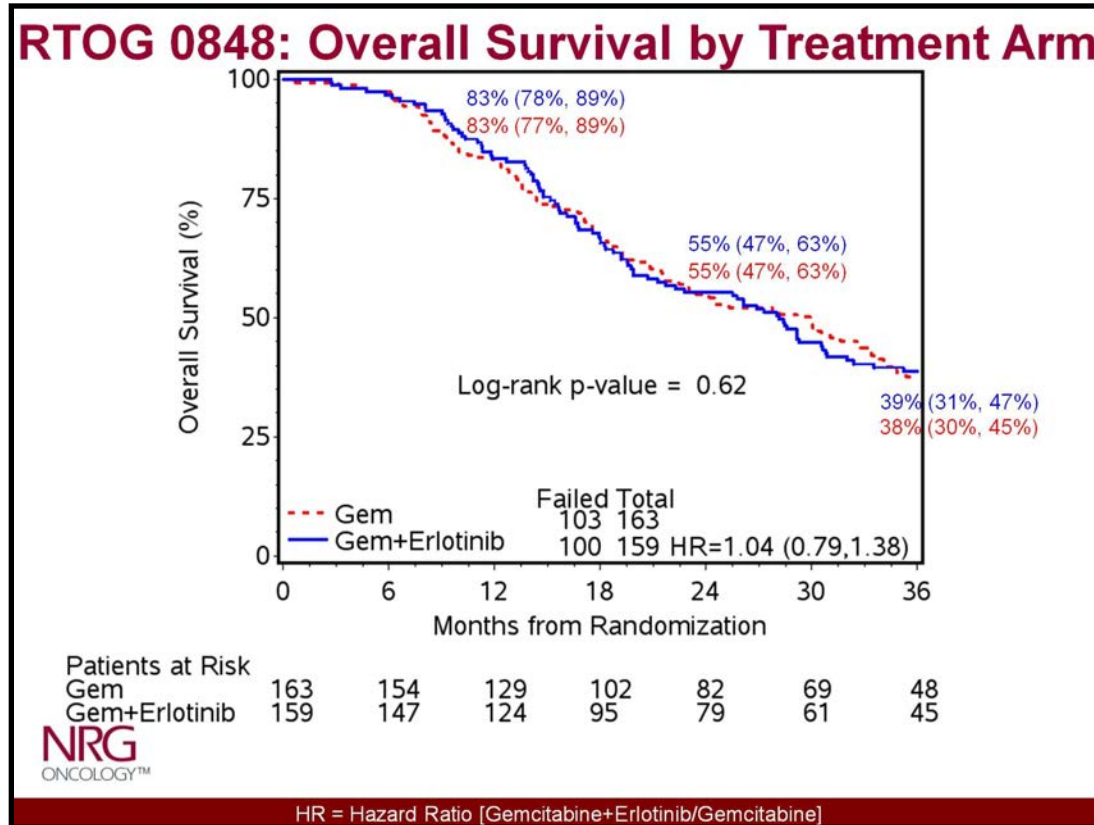
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*Adverse events without regard to attribution

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RTOG 0848

Resultados



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RTOG 0848

Conclusões

RTOG 0848: Conclusions

- The addition of erlotinib to gemcitabine did not provide a signal for increased overall survival compared to gemcitabine alone.
- Minimally higher grade 3 GI toxicity, mainly diarrhea, with the addition of erlotinib.
- Fewer patients on erlotinib received at least 85% of the planned gemcitabine dose.
- **Accrual is continuing to answer the phase III radiation question.**

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HALO 202

HALO-202 Randomized Phase 2 Study of PEGPH20 Plus nab-Paclitaxel / Gemcitabine (PAG) vs nab-Paclitaxel / Gemcitabine (AG) in Patients with Untreated, Metastatic Pancreatic Ductal Adenocarcinoma

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¹Fred Hutchinson Cancer Research Center, Seattle, WA, USA; ²Beth Israel Deaconess Medical Center, Boston, MA, USA; ³University of California – Irvine, Irvine, CA, USA; ⁴The Johns Hopkins University Hospital, Baltimore, MD, USA; ⁵Scripps Cancer Center, La Jolla, CA, USA; ⁶Froedtert Hospital and Medical College of Wisconsin, Milwaukee, WI, USA; ⁷Comprehensive Cancer Centers of Nevada, Las Vegas, NV, USA; ⁸University of Michigan, Ann Arbor, MI, USA; ⁹University of Pittsburgh Medical Center Cancer Pavilion, Pittsburgh, PA, USA; ¹⁰University of Washington, School of Medicine, Seattle, WA, USA; ¹¹Ventana Medical Systems, Inc., Tucson, AZ, USA; ¹²Halozyme Therapeutics, San Diego, CA, USA; ¹³Samuel Oschin Cancer Center, Cedars-Sinai Medical Center, Los Angeles, CA, USA

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HALO 202

Contexto

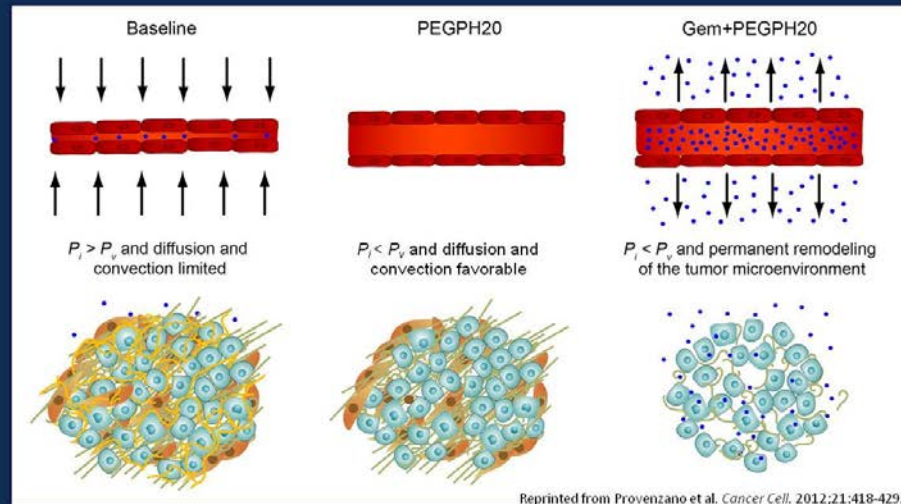
PEGPH20 Degrades Hyaluronan in the Tumor Microenvironment

Hyaluronan (HA)

- Naturally occurring, linear, megadalton polysaccharide and major component of the tumor stroma¹
- HA accumulation increases tumor interstitial gel-fluid pressure, which in turn compresses blood vessels and compromises blood flow^{2,3}
- HA accumulation is associated with accelerated tumor growth and is an independent negative predictor of survival in PDA⁴

PEGPH20 (pegvorhyaluronidase alfa)

- A PEGylated form of recombinant human hyaluronidase PH20, which degrades HA and remodels the tumor stroma



1. Minchinton AJ, et al. *Nat Rev Cancer*. 2006;6:582-592; 2. Thompson CB, et al. *Mol Cancer Ther*. 2010;9:3052-3064; 3. Provenzano PP, et al. *Cancer Cell*. 2012;21:418-429; 4. Whatcott CJ, et al. *Clin Cancer Res*. 2015;21:151.

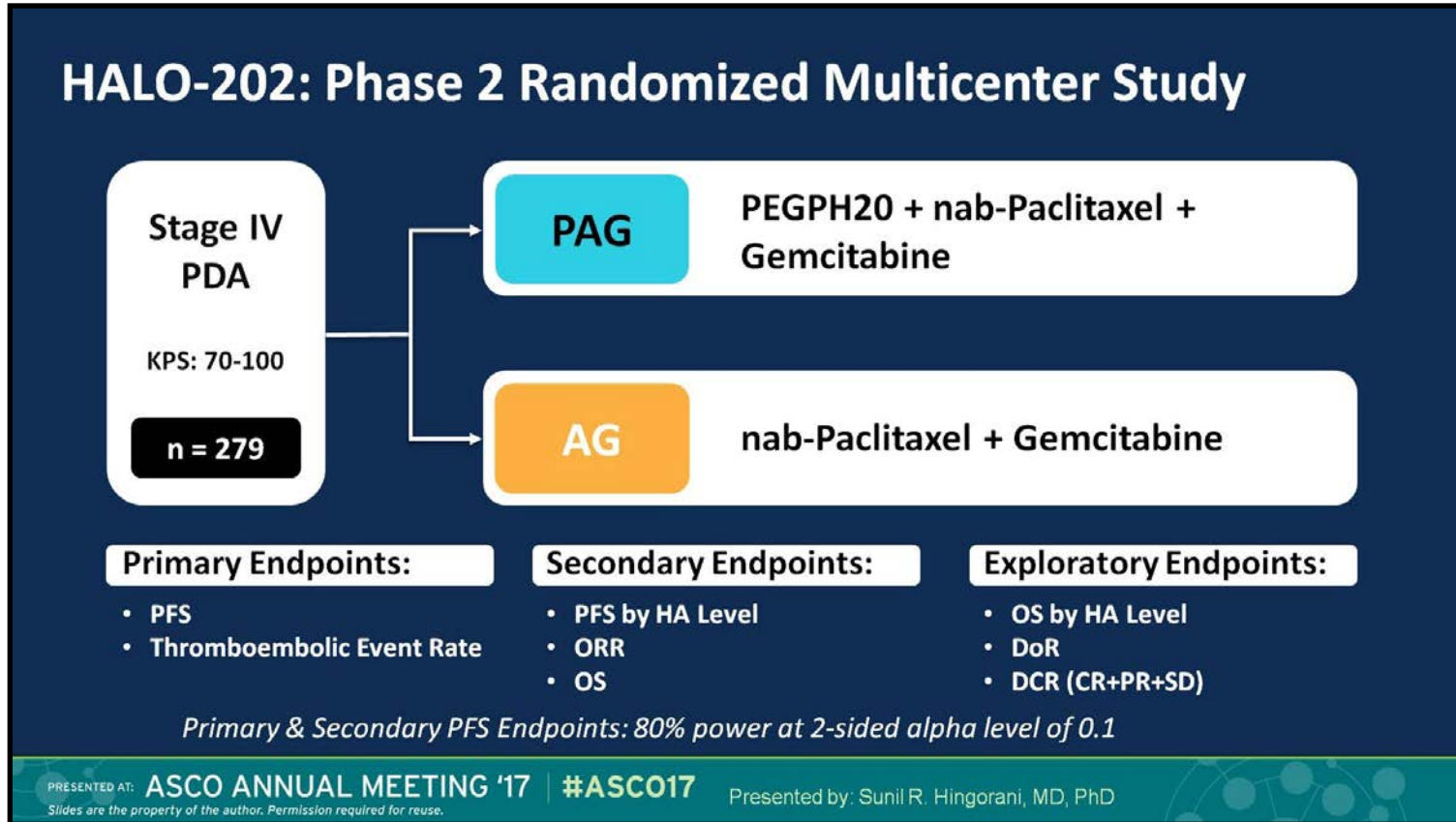
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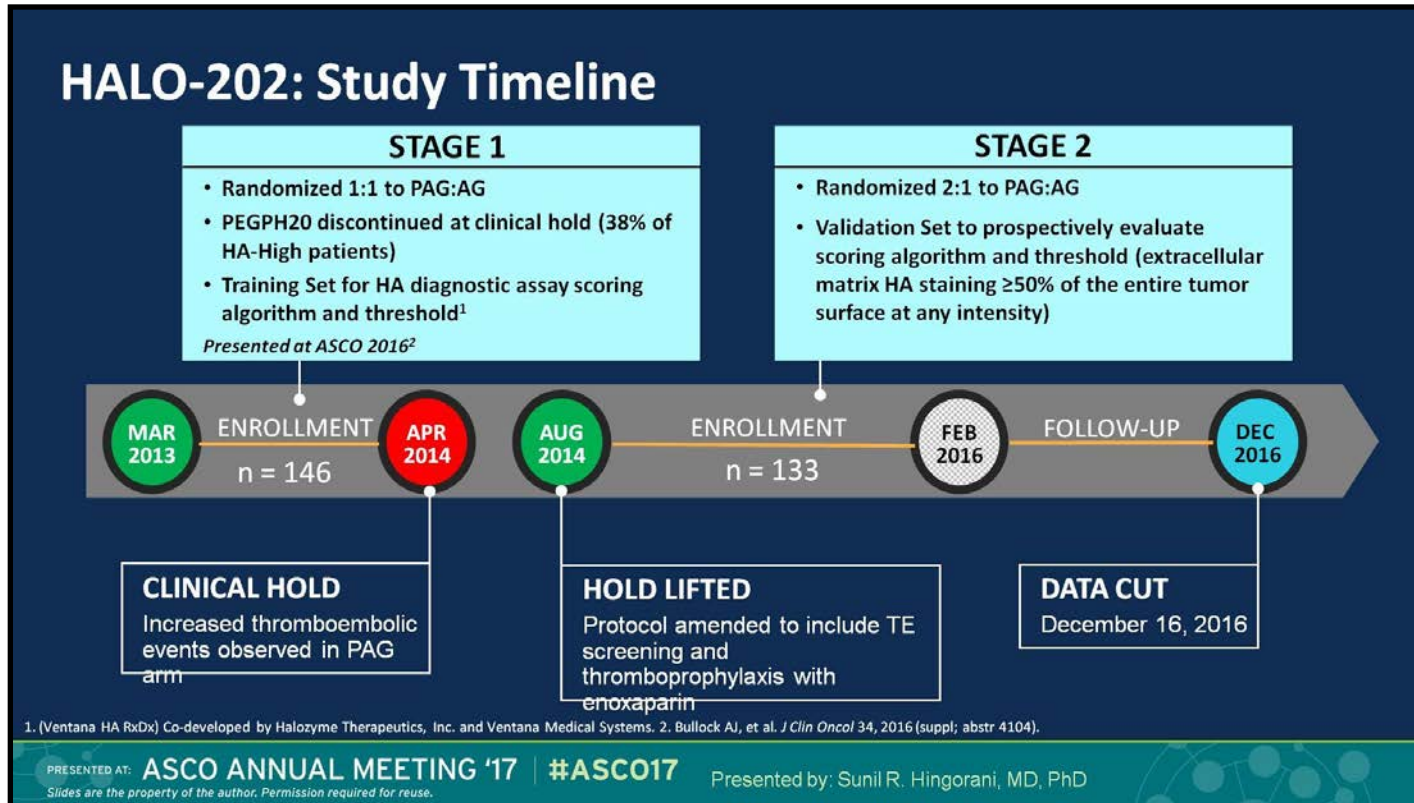
Desenho do Estudo



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HALO 202

Desenho do Estudo



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HALO 202

Resultados

HALO-202: Analysis Populations (Combined Stages 1 & 2)

Population		Stage 1 (n)	Stage 2 (n)	Combined (n)
Intent-To-Treat (Baseline, Efficacy)	Total	146	133	279
	HA-High	47	37	84
Treated (Safety)	Total	135	125	260
	HA-High	45	35	80

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Resultados

HALO-202: Baseline Characteristics (Combined Stages 1 & 2)

		All Patients (n = 279)		HA-High (n = 84)	
		PAG	AG	PAG	AG
Patients		n = 166	n = 113	n = 49	n = 35
Age, years	Mean \pm SD	64 \pm 10	65 \pm 9	66 \pm 9	67 \pm 7
	≥ 65 , n (%)	88 (53)	62 (55)	33 (67)	22 (63)
Gender, n (%)	Male	101 (61)	55 (49)	26 (53)	15 (43)
	Female	65 (39)	58 (51)	23 (47)	20 (57)
KPS, n (%)	70-80	53 (32)	41 (36)	16 (33)	13 (37)
	≥ 90	113 (68)	72 (64)	33 (67)	22 (63)
Primary Pancreatic Tumor Location, n (%)	Head	71 (43)	40 (35)	12 (25)	20 (57)
	Body	63 (38)	58 (51)	23 (47)	10 (29)
	Tail	32 (19)	14 (12)	14 (29)	4 (11)
Site of Metastasis, n (%)	Liver	153 (92)	97 (86)	44 (90)	26 (74)
	Lung	43 (26)	31 (27)	16 (33)	11 (31)
Serum CA 19-9^a [U/mL], n (%)	<37	24 (15)	17 (15)	10 (20)	4 (11)
	≥ 37	140 (84)	93 (82)	39 (80)	30 (86)

^aIn the HA-High group, Serum CA19-9 values are measured for 49 patients in the PAG arm and 34 in the AG arm.

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HALO 202

Resultados

HALO-202: Treatment Exposure (Combined Stages 1 & 2)*

	PAG	AG
Treated Population (n = 260)	160	100
Duration of treatment, months Median (range)	3.3 (0.1 – 18.2)	3.3 (0.1 – 12.9)
Treated patients (HA-High)	n = 48	n = 32
Duration of treatment, months Median (range)	3.3 (0.1 – 18.2)	3.2 (0.03 – 12.9)
≥6 months, n (%)	19 (40)	3 (9)
≥12 months, n (%)	6 (13)	1 (3)

*Exposure defined as first to last dose of any study medication.

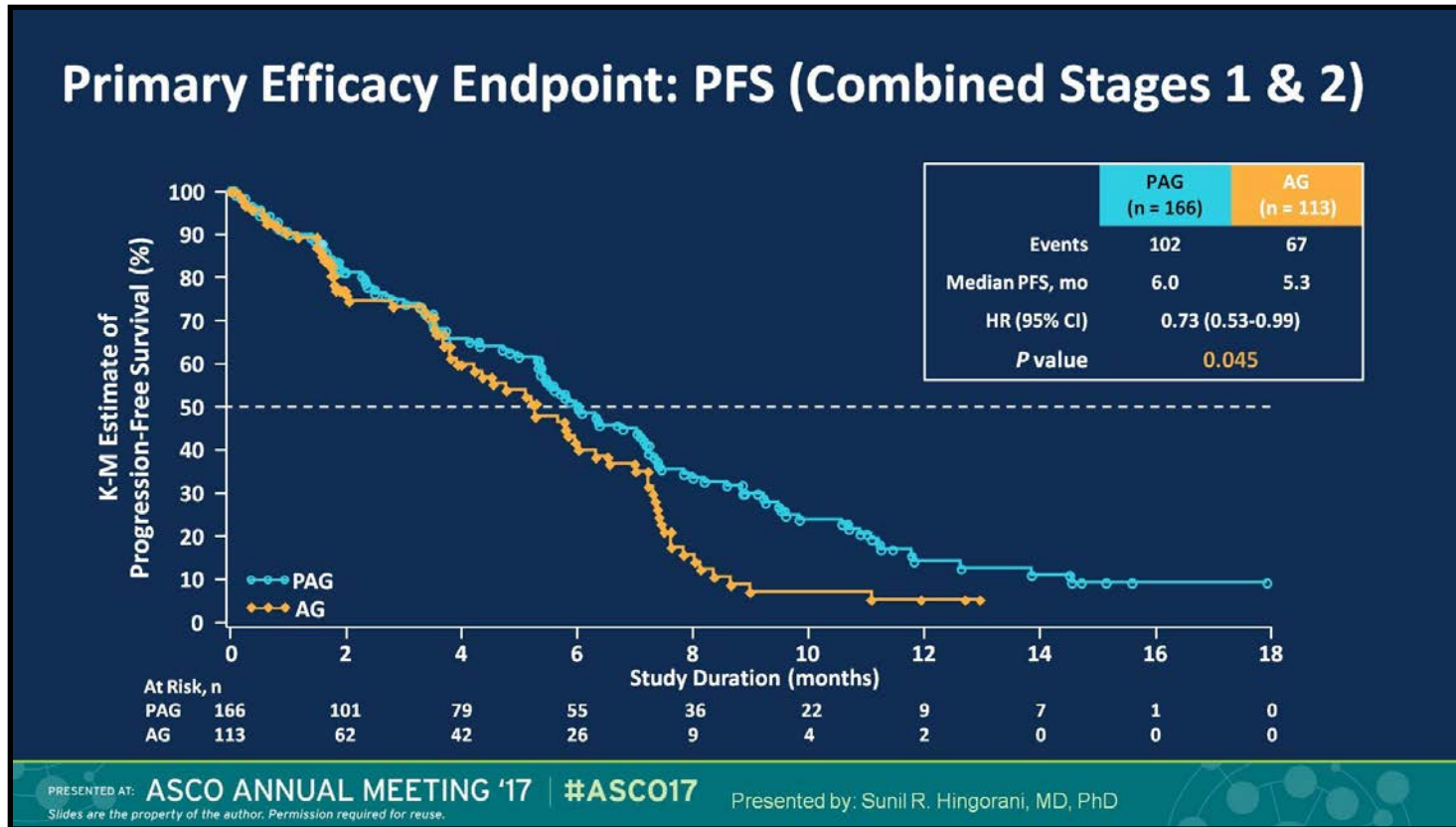
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Resultados - Desfecho Primário

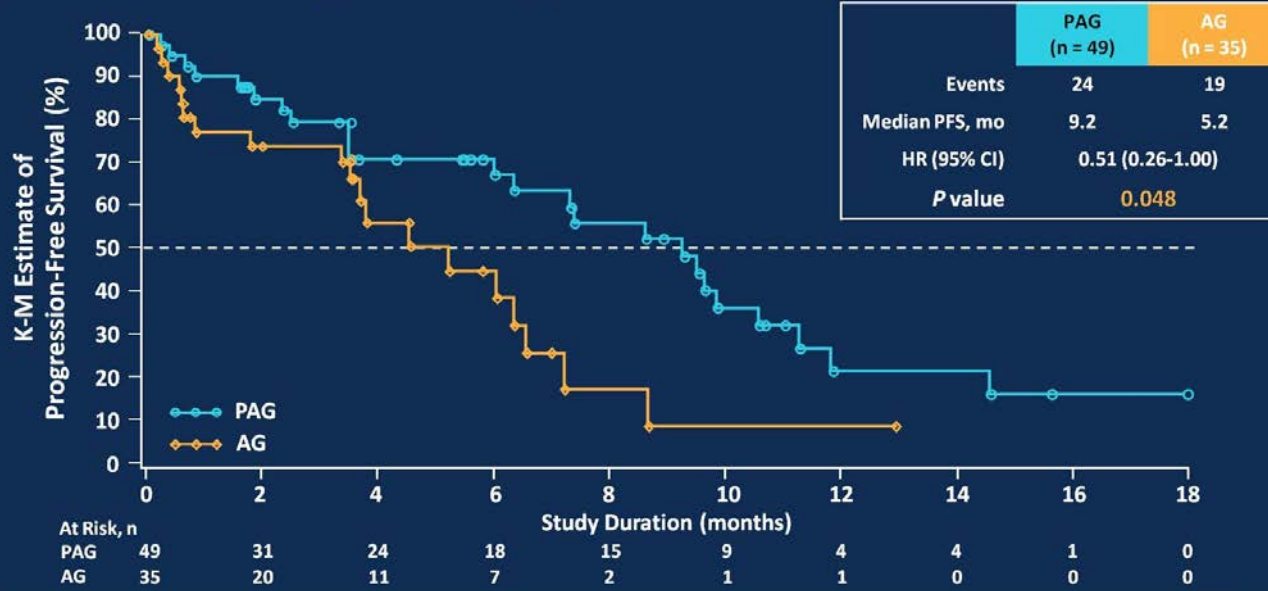


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Resultados - Desfecho Secundário

Secondary Endpoint: Progression-Free Survival HA-High (Combined Stages 1 & 2)



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HALO 202

Resultados - Segurança

Primary Safety Endpoint: TE Rate (Stages 1 and 2)

	Enoxaparin Prophylaxis Dose	TE Rate, %	
		PAG	AG
Stage 1	N/A	43% (32/74)	25% (15/61)
Stage 2*	40 mg/day	28% (5/18)	29% (2/7)
	1 mg/kg/day	10% (7/68)	6% (2/32)

*TE rates for all stage 2 patients are 14% (12/86) in PAG arm and 10% (4/39) in AG arm

- No difference in TE event rate observed by tumor HA level
- No difference in bleeding events by treatment arm

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HALO 202

Resultados - Segurança

Treatment-Related Adverse Events in ≥25% of Patients

n (%)	PAG (n=160)		AG (n=100)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Fatigue	115 (72)	33 (21)	66 (66)	16 (16)
Peripheral edema	101 (63)	8 (5)	26 (26)	4 (4)
Muscle spasms	89 (56)	20 (13)	3 (3)	1 (1)
Nausea	79 (49)	8 (5)	47 (47)	4 (4)
Diarrhea	64 (40)	11 (7)	39 (39)	5 (5)
Anemia	62 (39)	27 (17)	38 (38)	20 (20)
Alopecia	60 (38)	1 (0.6)	39 (39)	0
Decreased appetite	59 (37)	7 (4)	25 (25)	2 (2)
Neutropenia	54 (34)	47 (29)	19 (19)	18 (18)
Neuropathy peripheral	47 (29)	10 (6)	31 (31)	8 (8)
Vomiting	46 (29)	5 (3)	27 (27)	2 (2)
Dysgeusia	45 (28)	0	19 (19)	0
Myalgia	41 (26)	8 (5)	7 (7)	0
Thrombocytopenia	41 (26)	26 (16)	17 (17)	9 (9)

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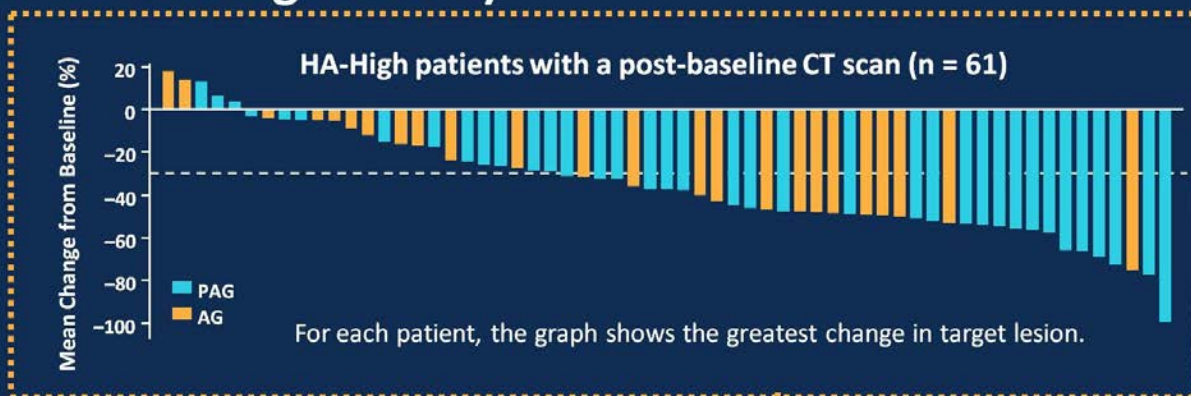
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Resultados - Desfecho secundário

Secondary Endpoint: Overall Response Rate (Combined Stages 1 & 2)



	All Patients (n = 279)		HA-High (n = 84)	
n (%)	PAG (n = 166)	AG (n = 113)	PAG (n = 49)	AG (n = 35)
Overall Response Rate	67 (40)	37 (33)	22 (45)	11 (31)

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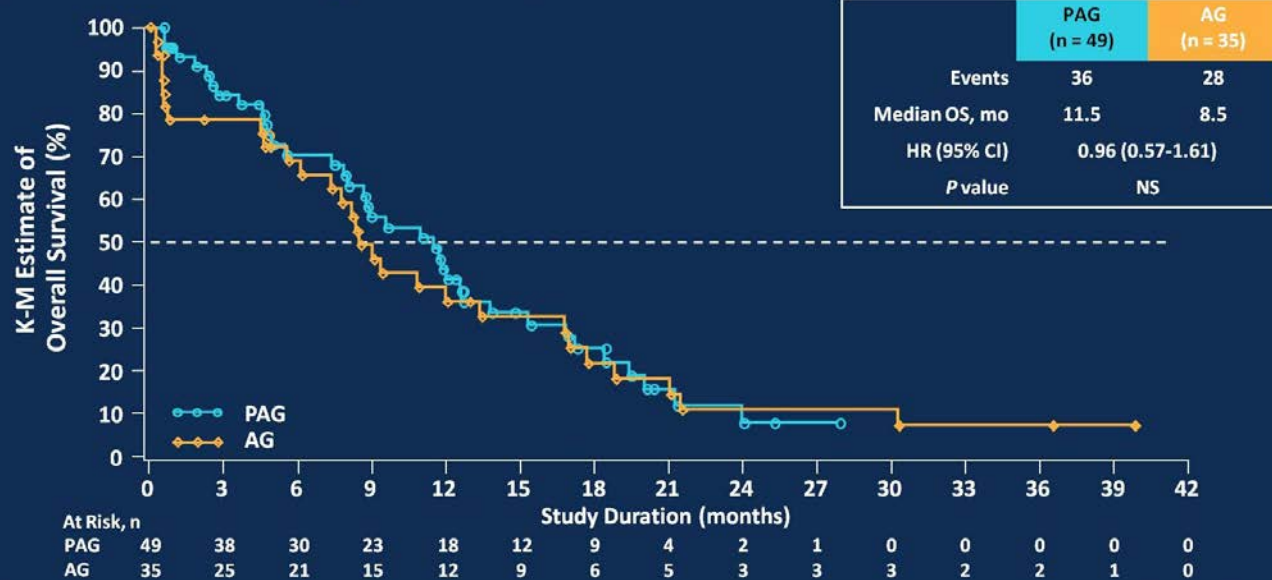
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Resultados - Desfecho secundário

Exploratory Endpoint: Overall Survival in HA-High (Combined Stages 1 & 2)



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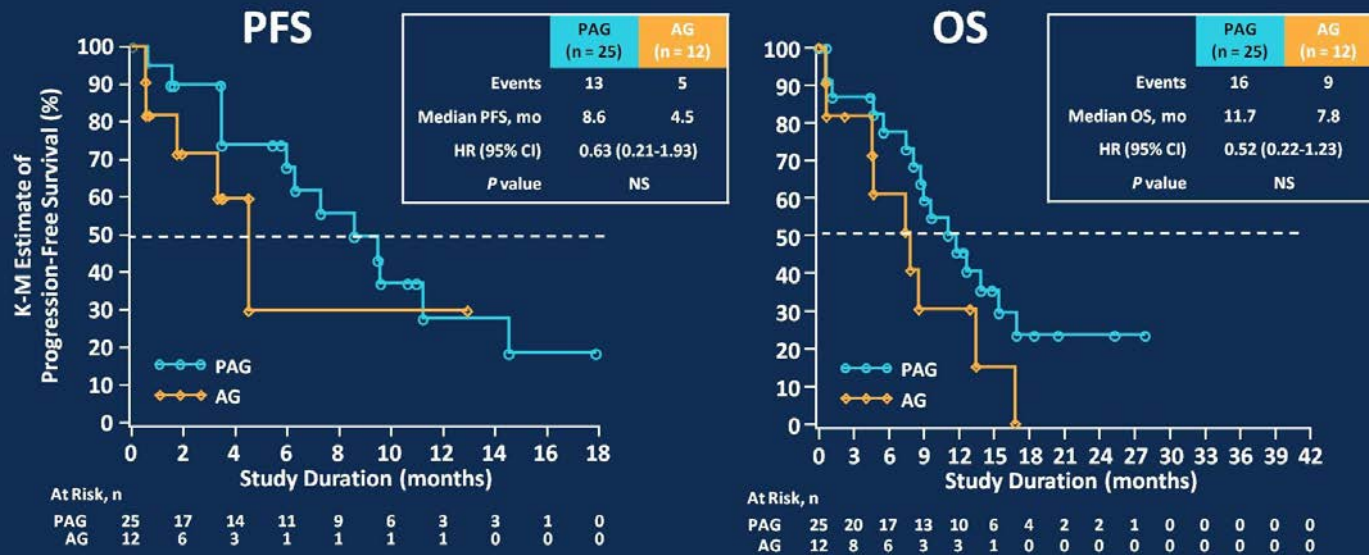
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Resultados - Desfecho secundário

Secondary (PFS) and Exploratory (OS) Endpoints in HA-High (Stage 2)



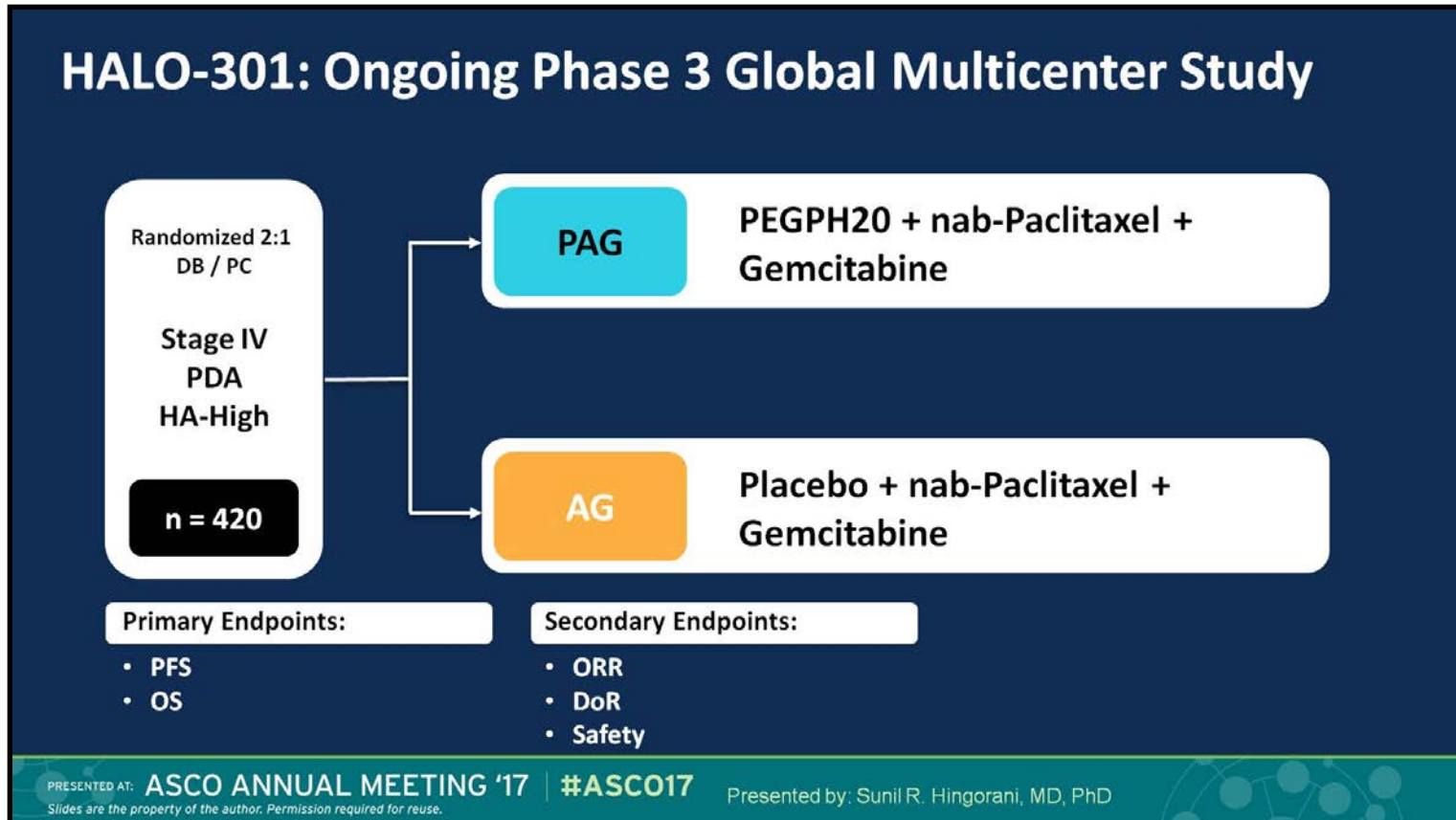
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Resultados - Desfecho secundário



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HALO 202

Conclusões

HALO-202: Conclusions

1. Key study objectives were met:

- Primary Endpoint: improved PFS (combined Stages 1+2)
- Secondary Endpoint: improved PFS in HA-High (combined Stages 1+2)

2. Primary safety endpoint met in Stage 2:

- Decreased TE events with protocol modifications & LMWH prophylaxis

3. Notable efficacy trends in PFS and OS observed in Stage 2 HA-High patients

4. These data support ongoing biomarker-driven Phase 3 HALO-301 trial in HA-High patients only

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