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Destaques


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

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

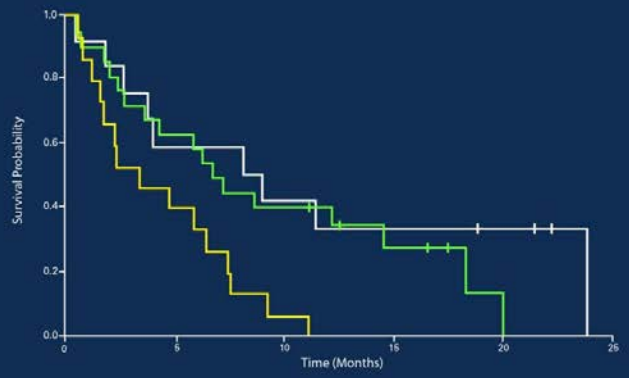
Background: Tumor MET as a Predictive Factor

	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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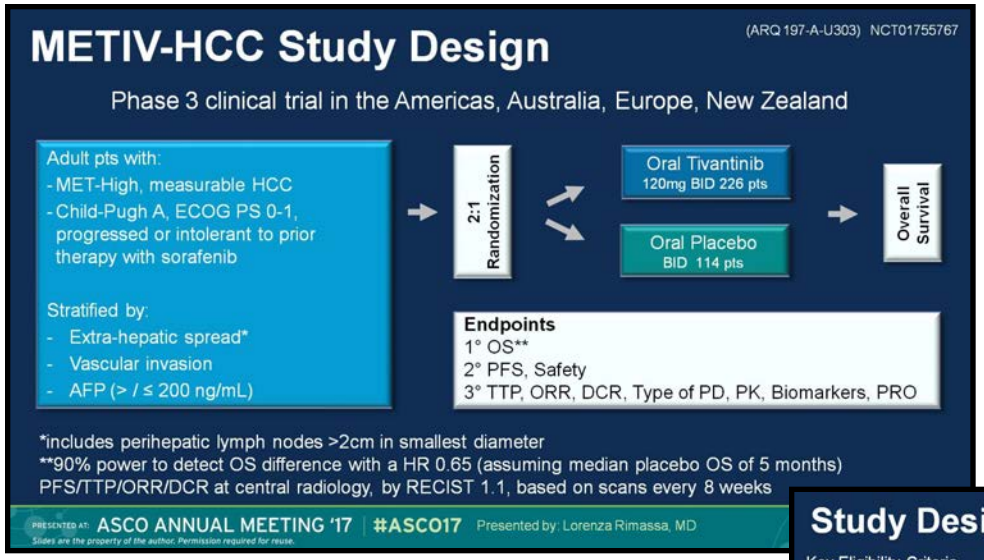
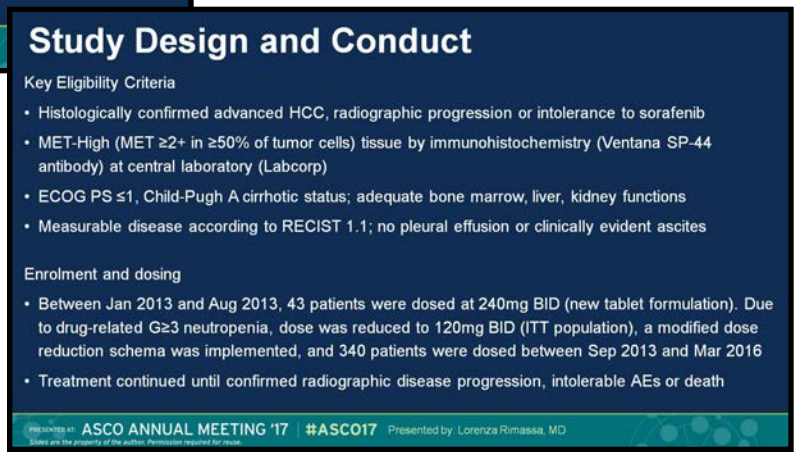
CARCINOMA HEPATOCELULAR

TIVANTINIB EM SEGUNDA LINHA

Desenho do Estudo





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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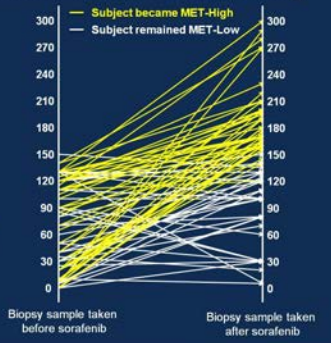
Baseline Tumor MET at Immunohistochemistry

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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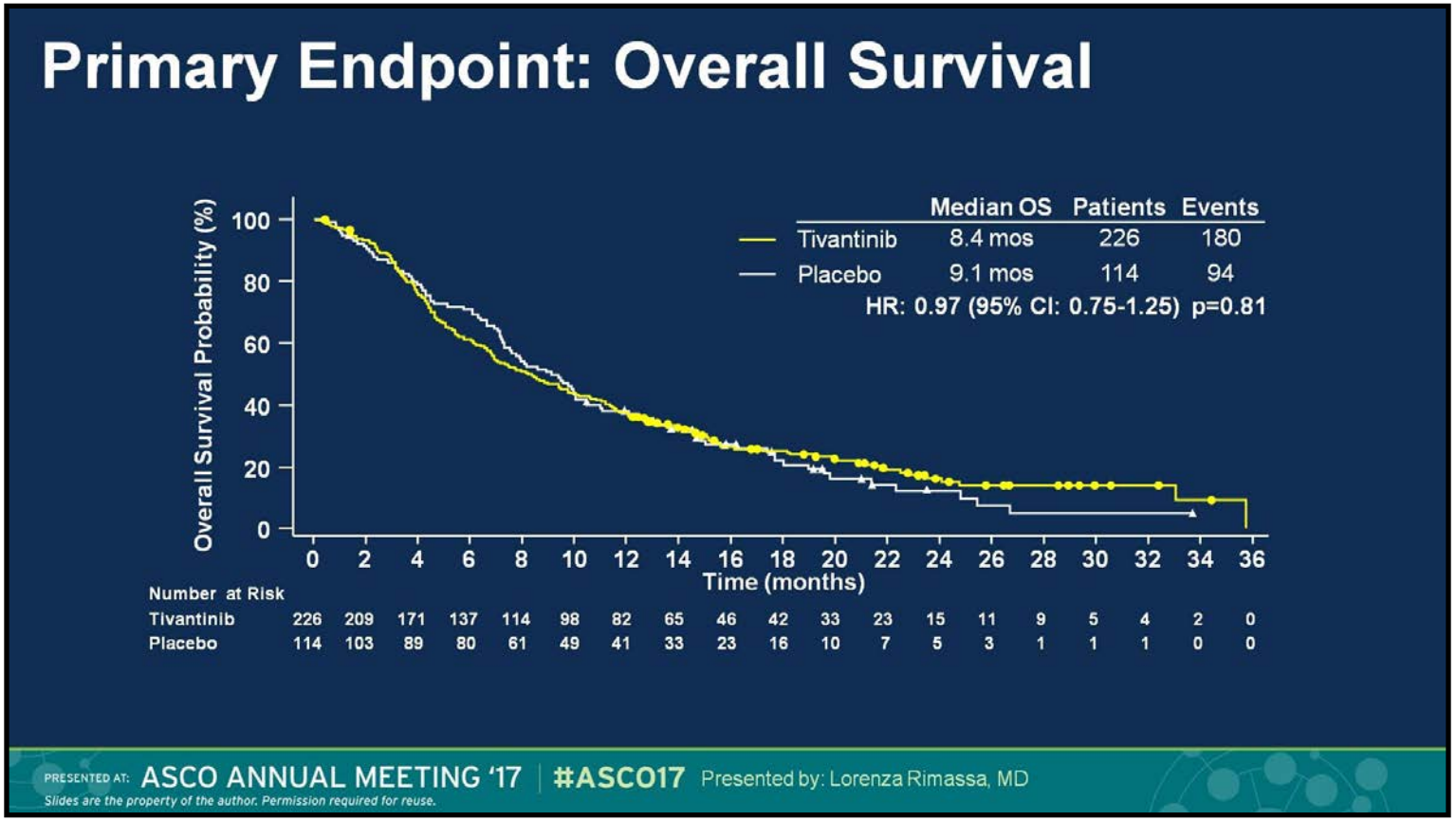
CARCINOMA HEPATOCELULAR

TIVANTINIB EM SEGUNDA LINHA

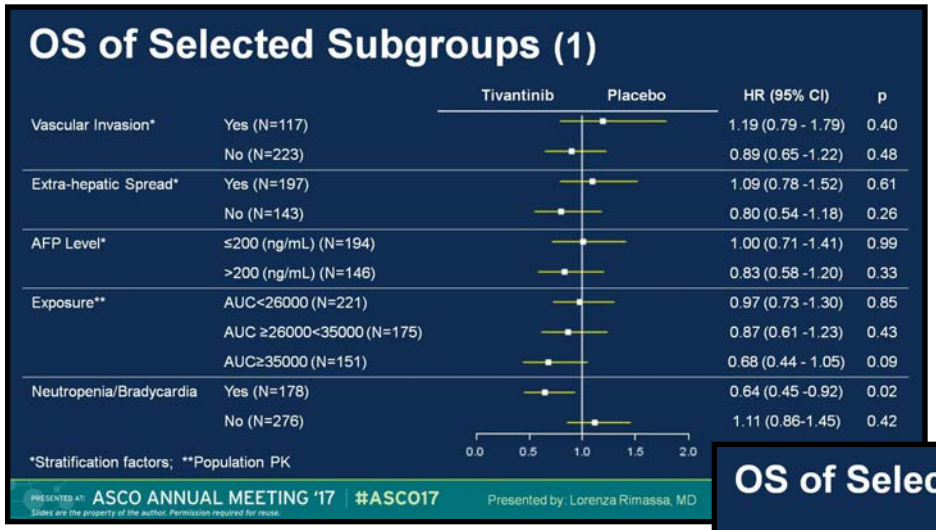
Desfecho Primário

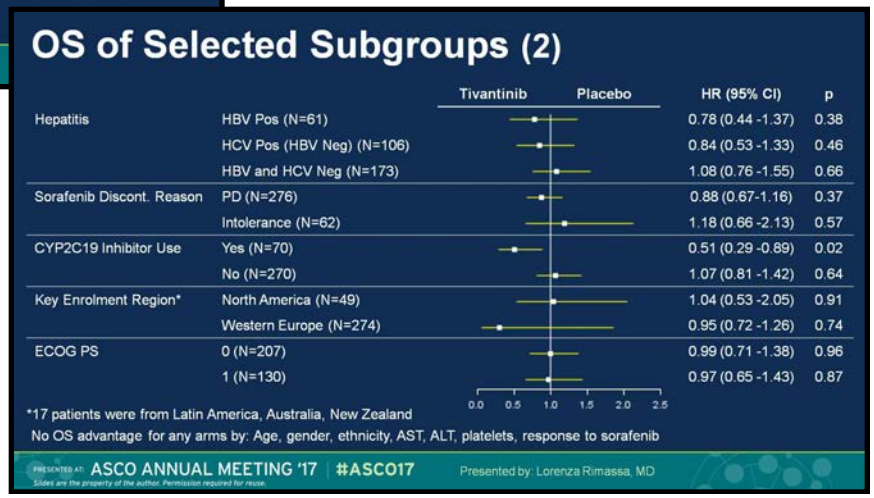


CARCINOMA HEPATOCELULAR

TIVANTINIB EM SEGUNDA LINHA

Desfecho Primário





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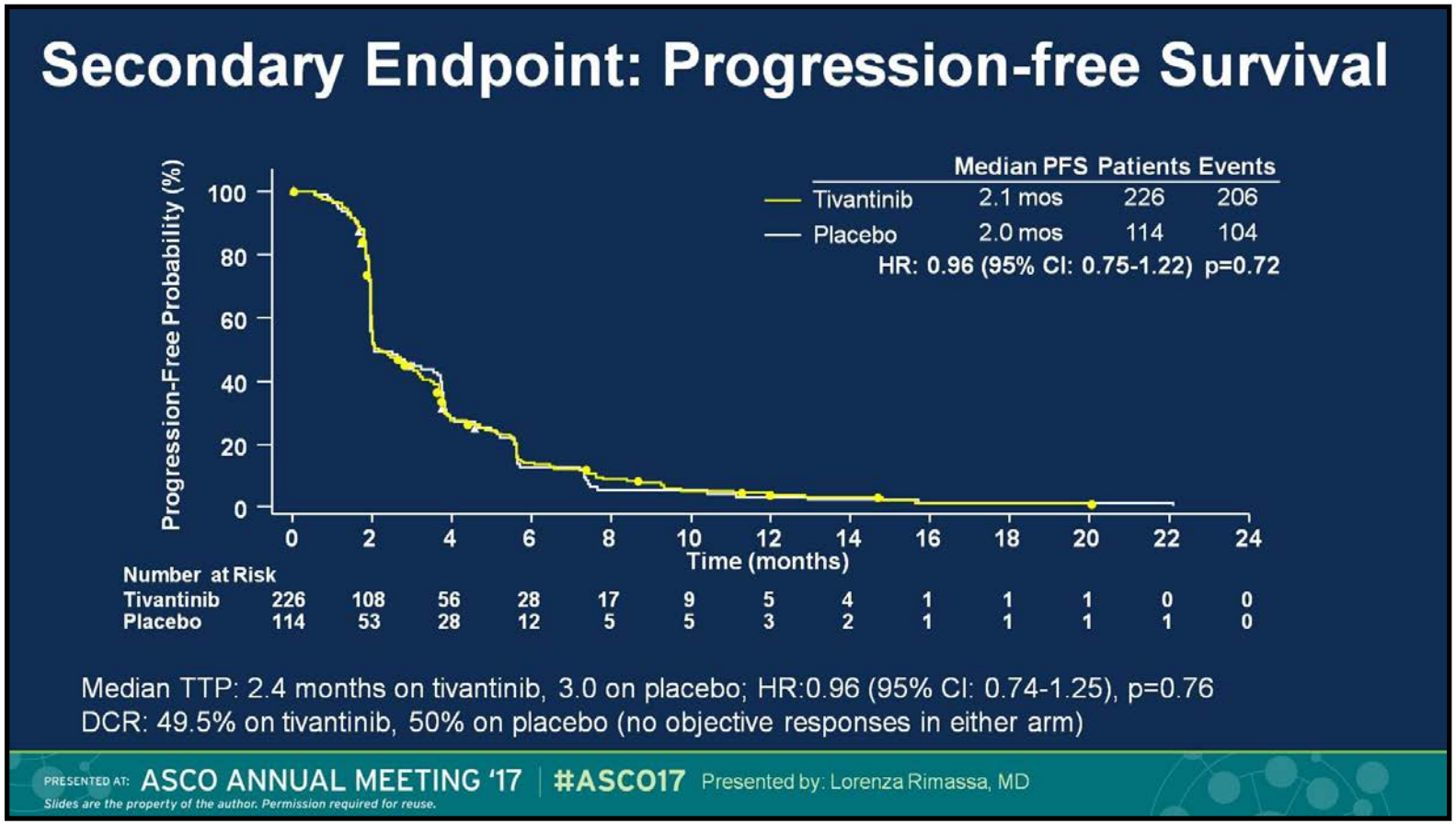
CARCINOMA HEPATOCELULAR

TIVANTINIB EM SEGUNDA LINHA

Desfecho Secundário



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)

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Treatment-Emergent Adverse Events Summary

Most Common (>15%) TEAEs	Tivantinib All grades	Tivantinib Grade ≥3	Tivantinib Grade 5	Placebo All grades	Placebo Grade ≥3	Placebo 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


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

Ann-Lii Cheng,[1] Richard S. Finn,[2] Shukui Qin,[3] Kwang-Hyub Han,[4] Kenji Ikeda,[5] Fabio Piscaglia,[6] Ari Baron,[7] Joong-Won Park,[8] Guohong Han,[9] Jacek Jassem,[10] Jean Frederic Blanc,[11] Arndt Vogel,[12] Dmitry Komov,[13] TR Jeffry Evans,[14] Carlos Lopez,[15] Corina Dutcus,[16] Min Ren,[16] Silvija Kraljevic,[17] Toshiyuki Tamai,[18] Masatoshi Kudo[19]

[1]National Taiwan University Hospital, Taipei, Taiwan; [2]Geffen School of Medicine, UCLA Medical Center, Santa Monica, CA, USA; [3]Nanjing Bayi Hospital, Nanjing, Jiangsu, China; [4]Severance Hospital, Yonsei University, Seoul, S. Korea; [5]Toranomon Hospital, Tokyo, Japan; [6]University of Bologna, Bologna, Italy; [7]California Pacific Medical Center Research Institute, San Francisco, CA, USA; [8]National Cancer Center Korea, Goyang-si, S. Korea; [9]Xijing Hospital, Fourth Military Medical University, Xi'an, China; [10]Medical University of Gdansk, Gdansk, Poland; [11]University of Bordeaux, Bordeaux, France; [12]Hannover Medical School, Hannover, Germany; [13]N.N. Blokhin Cancer Research Center, Moscow, Russia; [14]University of Glasgow, Beatson West of Scotland Cancer Centre, Glasgow, UK; [15]Marqués de Valdecilla University Hospital, Santander, Spain; [16]Eisai Inc., Woodcliff Lake, NJ, USA; [17]Eisai Ltd., Hatfield, UK; [18]Kindai University Faculty of Medicine, Osaka-Sayama, Japan.

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Study Rationale

- Hepatocellular carcinoma (HCC) is the second leading cause of cancer death worldwide and is responsible for nearly 745,000 deaths each year[1]
- Sorafenib is the only systemic therapy proven to extend overall survival when used as first-line treatment for HCC[2]:
  - 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, PDGFRα, RET, and KIT, showed promising clinical activity in a previous phase 2 trial in patients with advanced HCC[7]

FGF, fibroblast growth factor; PDFGRα, 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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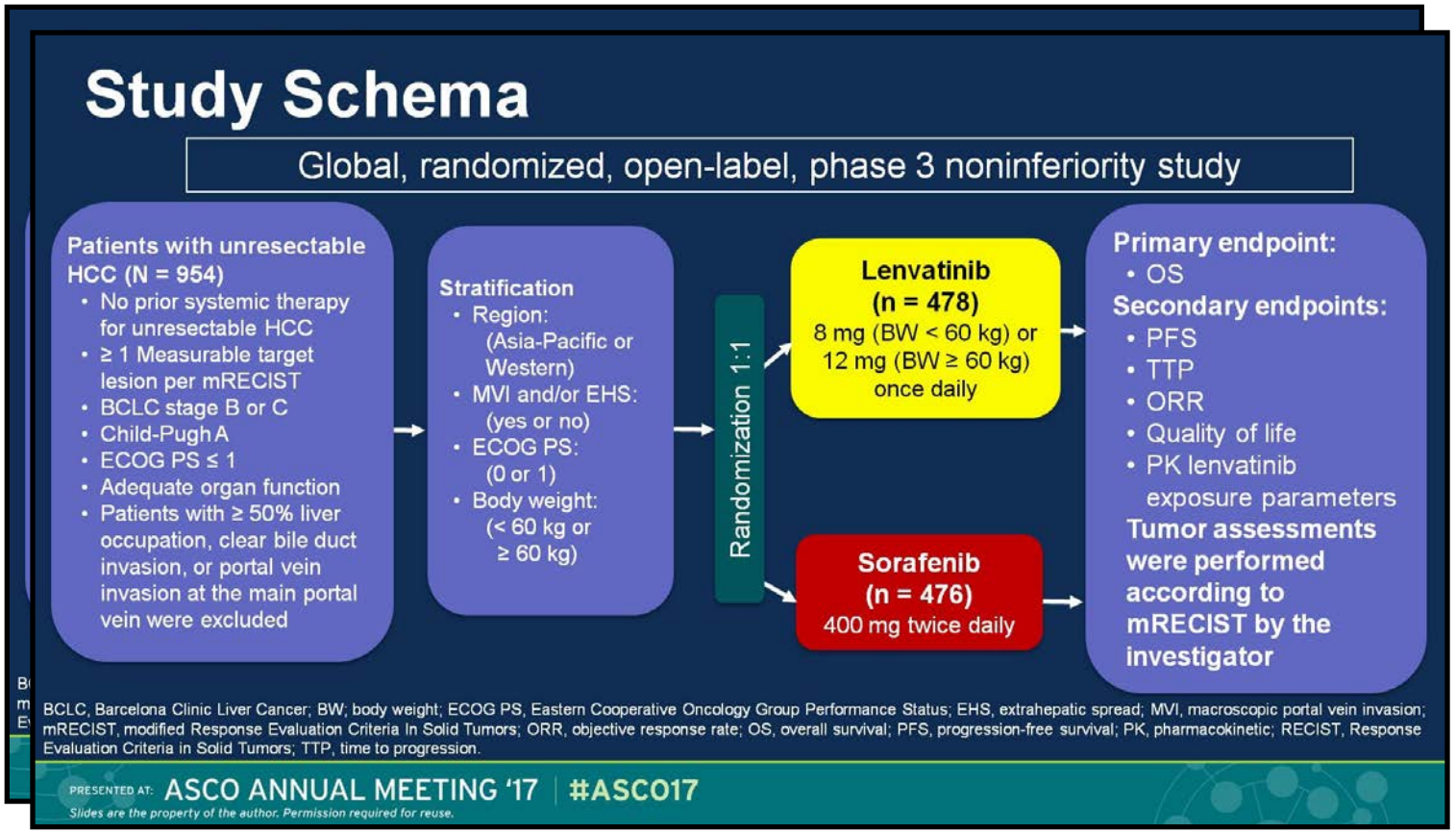
REFLECT STUDY: LENVATINIB VS. SORAFENIBE

Desenho do Estudo



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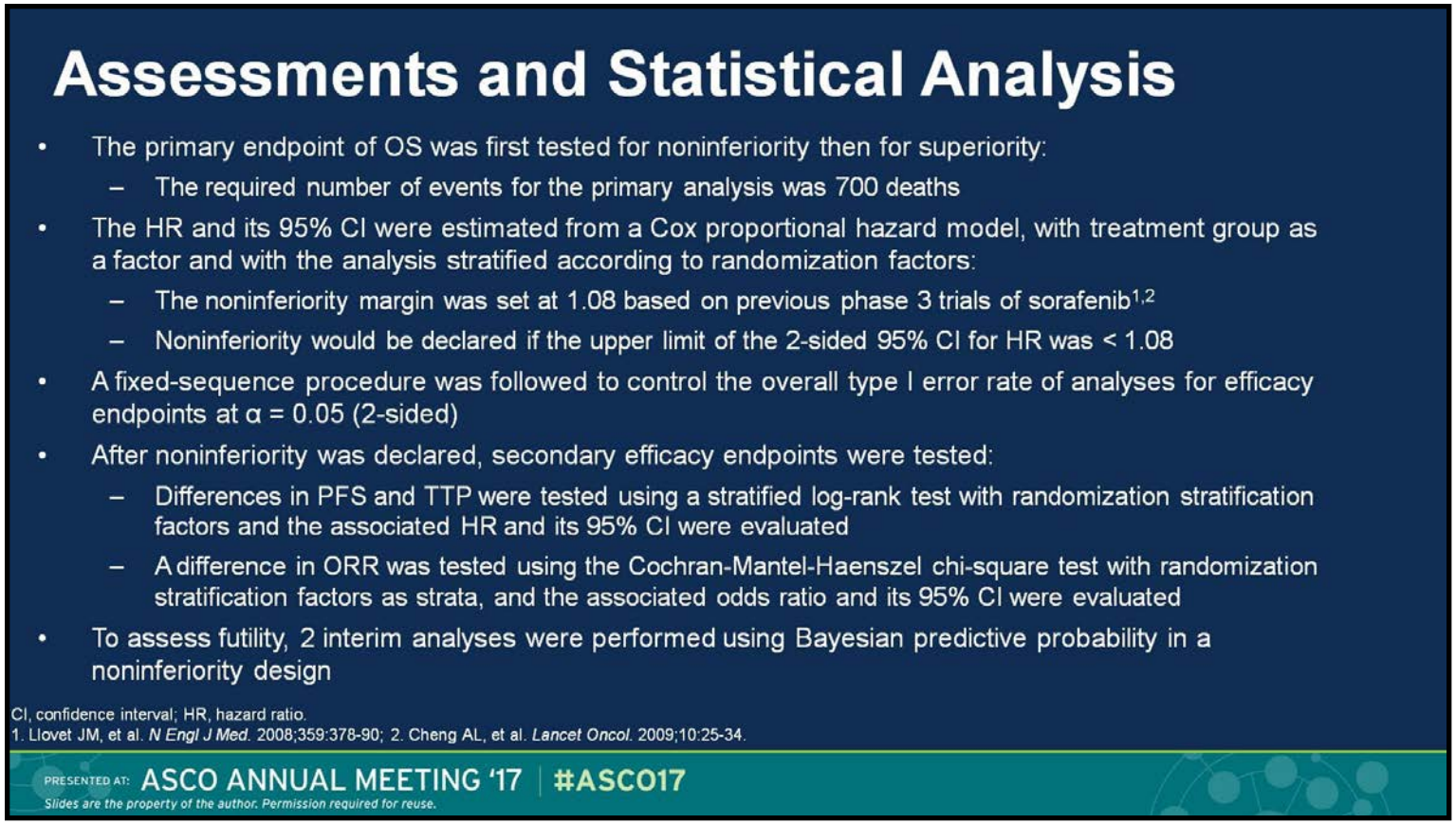
Desenho do Estudo



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)

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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)
	Unknown	62 (13)	69 (15)
Baseline AFP level group (ng/mL), n (%)	< 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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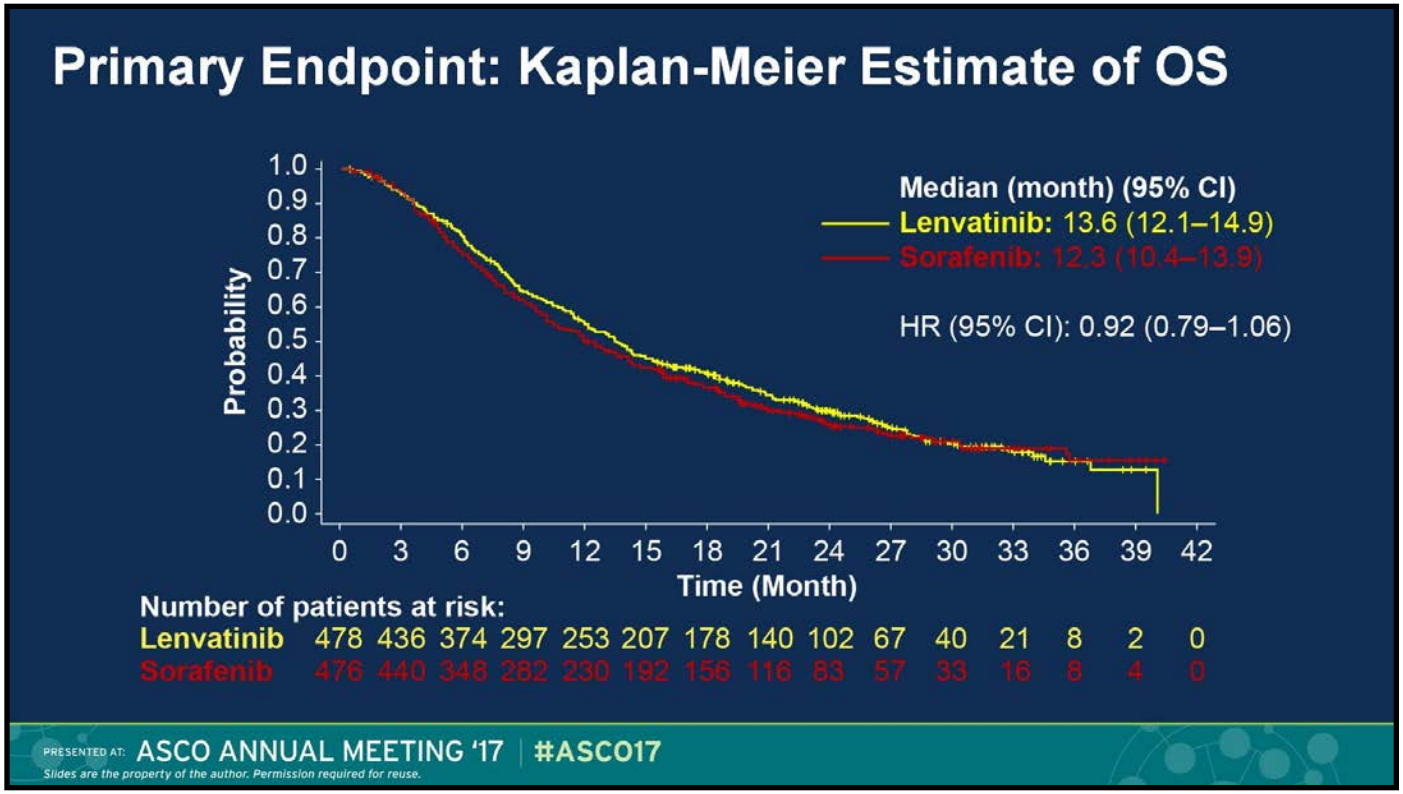
REFLECT STUDY: LENVATINIB VS. SORAFENIBE

Resultados - Desfecho primário



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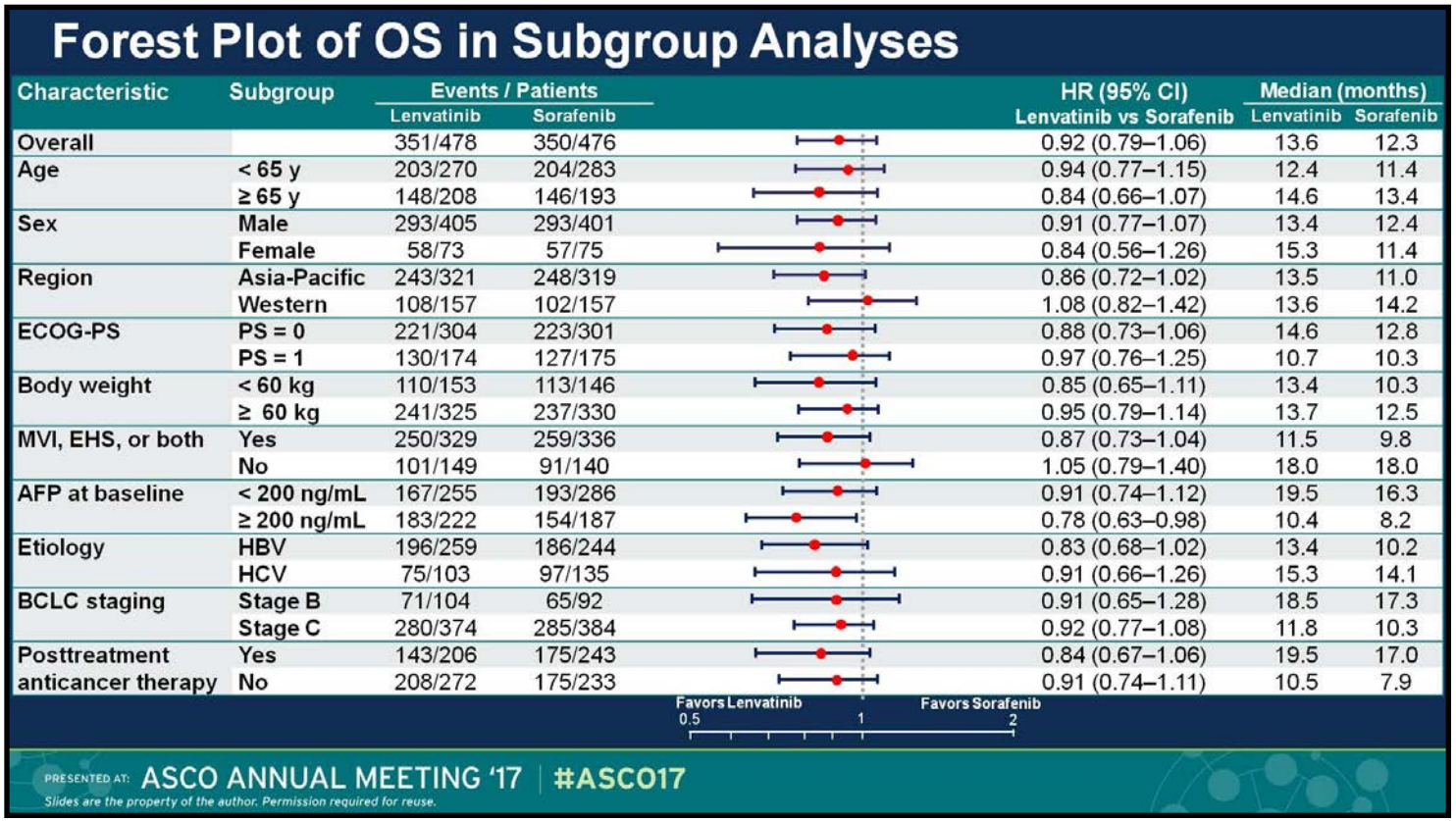
REFLECT STUDY: LENVATINIB VS. SORAFENIBE

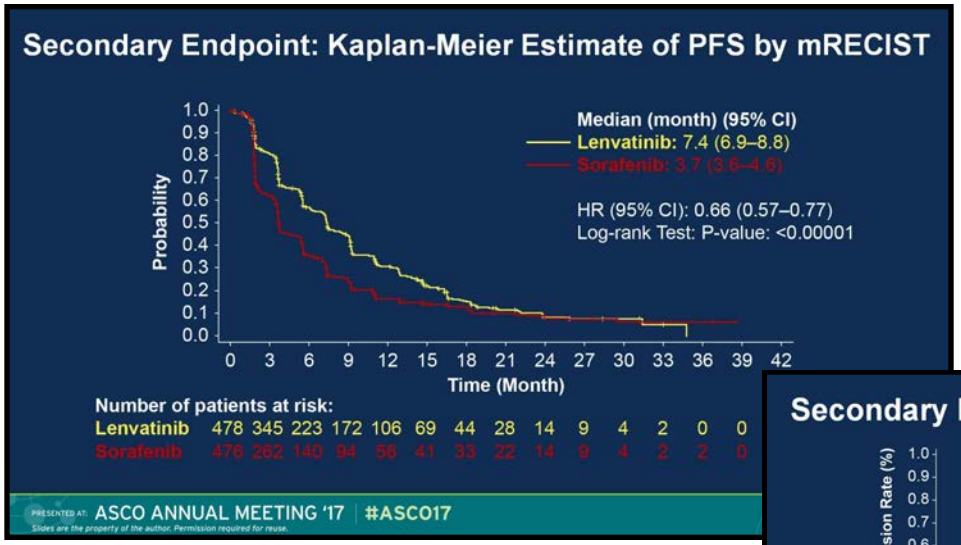
Resultados - Desfecho primário

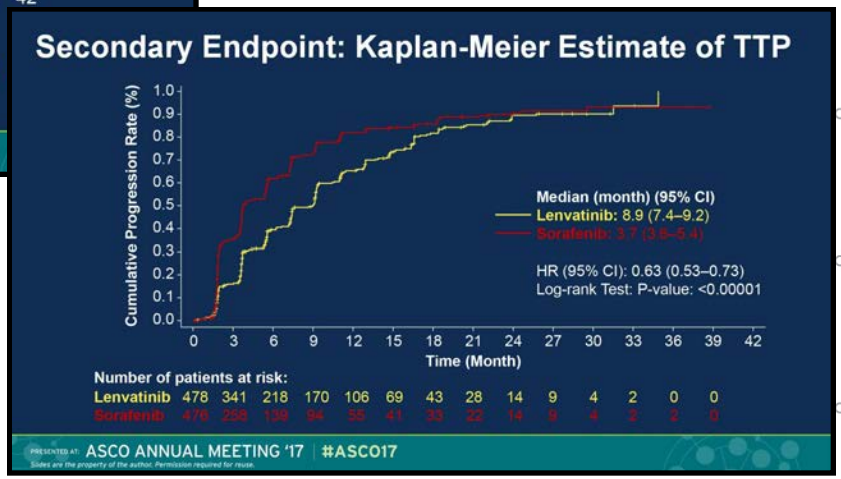


CARCINOMA HEPATOCELULAR

REFLECT STUDY: LENVATINIB VS. SORAFENIBE

Resultados - Desfechos secundários





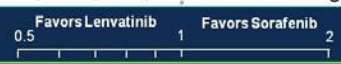
CARCINOMA HEPATOCELULAR

REFLECT STUDY: LENVATINIB VS. SORAFENIBE

Resultados - Desfechos secundários

Forest Plot of PFS in Subgroup Analyses

Characteristic	Subgroup	Events / Patients		HR (95% CI)	Median (months)	
		Lenvatinib	Sorafenib	Lenvatinib vs Sorafenib	Lenvatinib	Sorafenib
Overall		349/478	367/476	0.66 (0.57–0.77)	7.4	3.7
Age	< 65 y	201/270	223/283	0.67 (0.55–0.82)	7.3	3.6
	≥ 65 y	148/208	144/193	0.61 (0.48–0.78)	7.4	5.4
Sex	Male	298/405	308/401	0.66 (0.56–0.77)	7.4	3.7
	Female	51/73	59/75	0.75 (0.49–1.13)	7.4	4.6
Region	Asia-Pacific	249/321	264/319	0.61 (0.51–0.73)	7.3	3.6
	Western	100/157	103/157	0.81 (0.61–1.08)	7.4	5.5
ECOG-PS	PS = 0	220/304	233/301	0.63 (0.52–0.76)	7.4	3.7
	PS = 1	129/174	134/175	0.70 (0.55–0.90)	7.3	3.7
Body weight	< 60 kg	111/153	121/146	0.61 (0.46–0.79)	7.4	3.6
	≥ 60 kg	238/325	246/330	0.69 (0.58–0.83)	7.4	3.7
MVI, EHS, or both	Yes	246/329	265/336	0.64 (0.54–0.77)	7.3	3.6
	No	103/149	102/140	0.73 (0.55–0.97)	9.2	5.6
AFP at baseline	< 200 ng/mL	186/255	209/286	0.68 (0.55–0.83)	9.0	5.4
	≥ 200 ng/mL	163/222	157/187	0.59 (0.47–0.75)	5.5	2.4
Etiology	HBV	205/259	199/244	0.62 (0.50–0.75)	7.3	3.6
	HCV	70/103	103/135	0.78 (0.56–1.09)	7.4	5.3
BCLC staging	Stage B	72/104	66/92	0.70 (0.50–0.99)	9.1	5.5
	Stage C	277/374	301/384	0.63 (0.53–0.75)	7.3	3.7
Posttreatment anticancer therapy	Yes	177/206	204/243	0.58 (0.47–0.72)	7.2	3.6
	No	172/272	163/233	0.70 (0.56–0.87)	8.0	3.7



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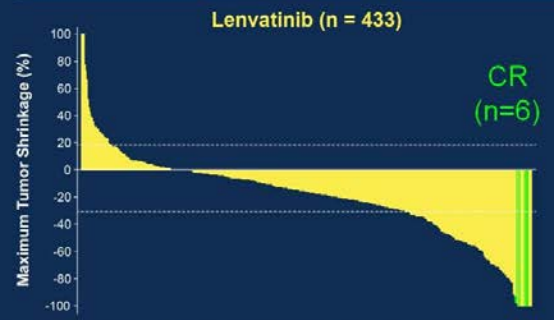
CARCINOMA HEPATOCELULAR

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	*P* < 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 ≥ 23 weeks.
CR, complete response; NE, not evaluable; PD, progressive disease; PR, partial response; SD, stable disease.

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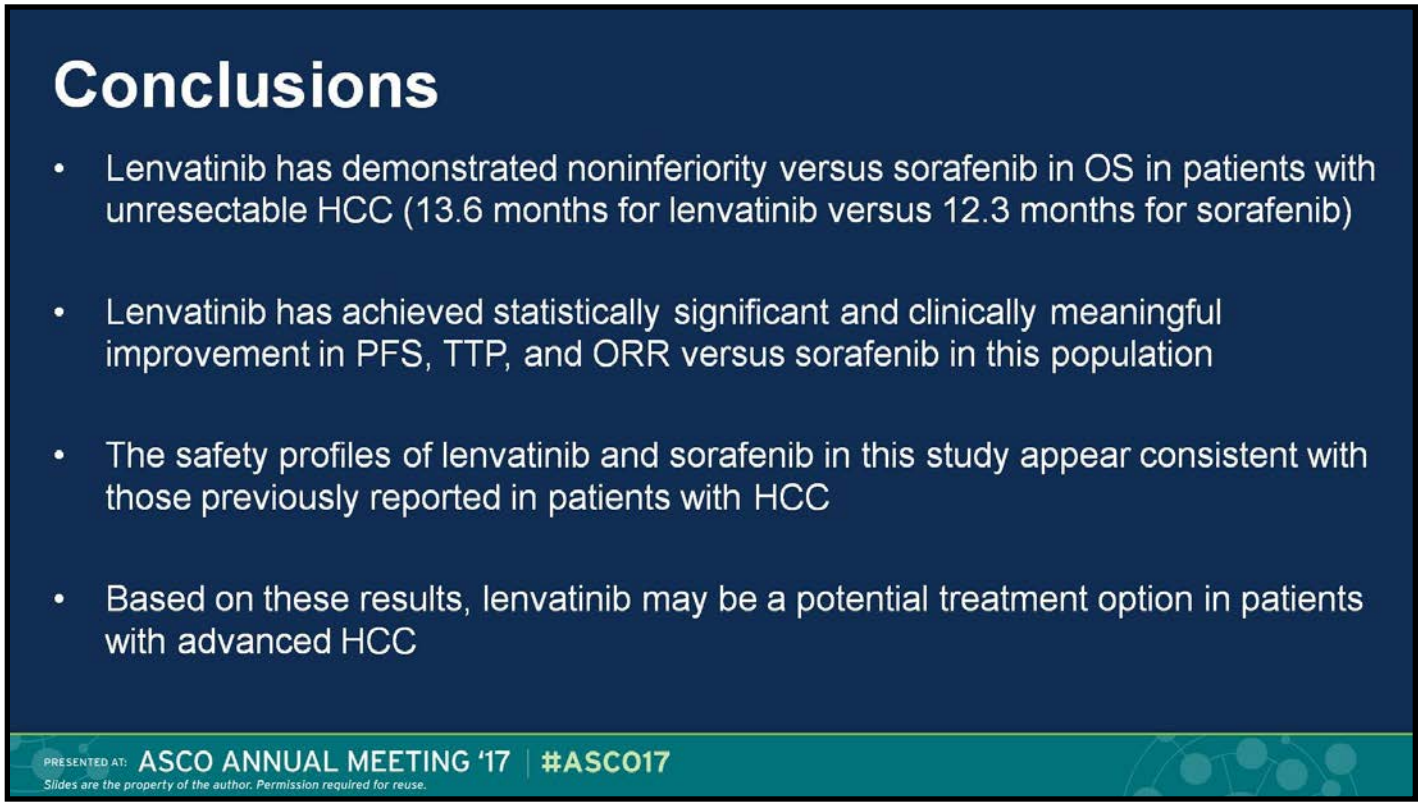
REFLECT STUDY: LENVATINIB VS. SORAFENIBE

Conclusões



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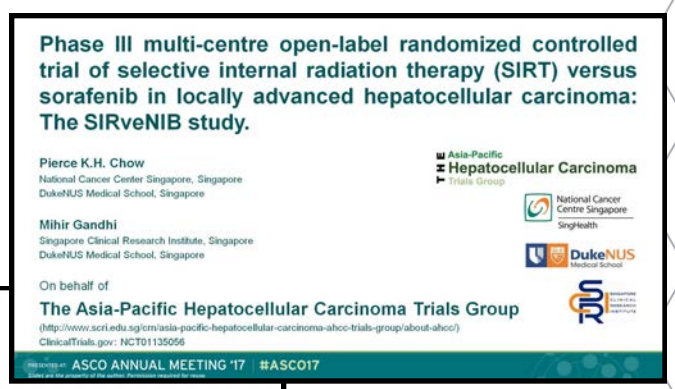
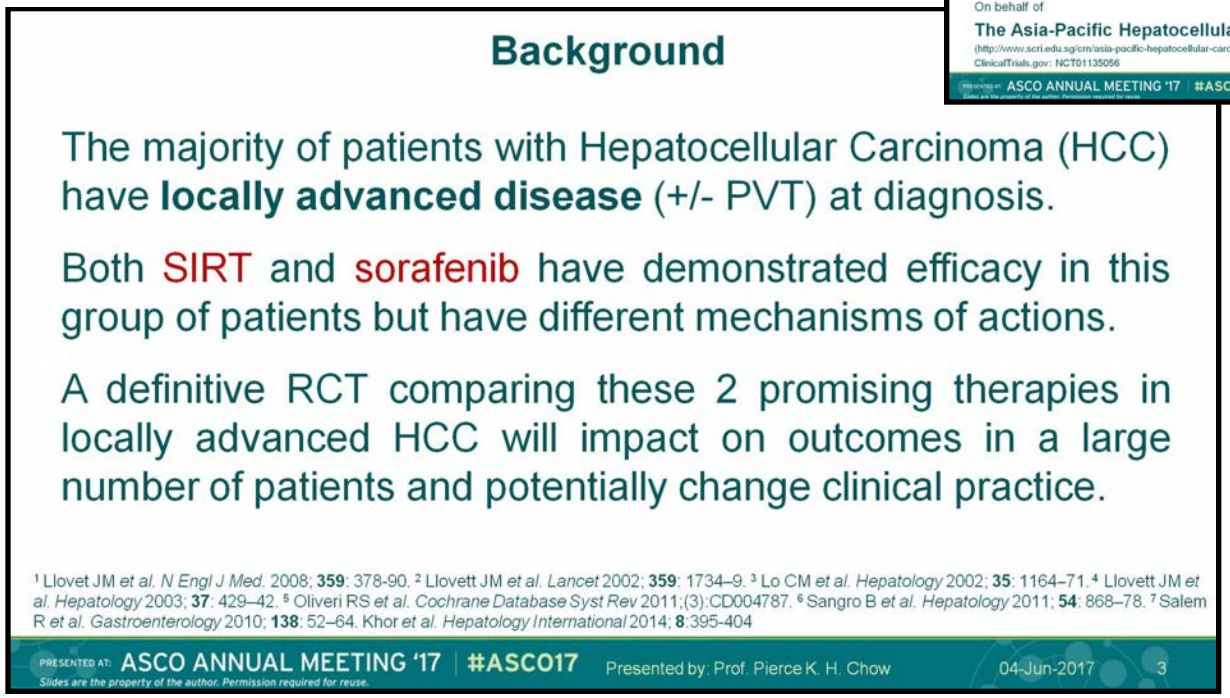
SIRT VS. SORAFENIBE EM TUMORES LOCALMENTE AVANÇADOS

Contexto





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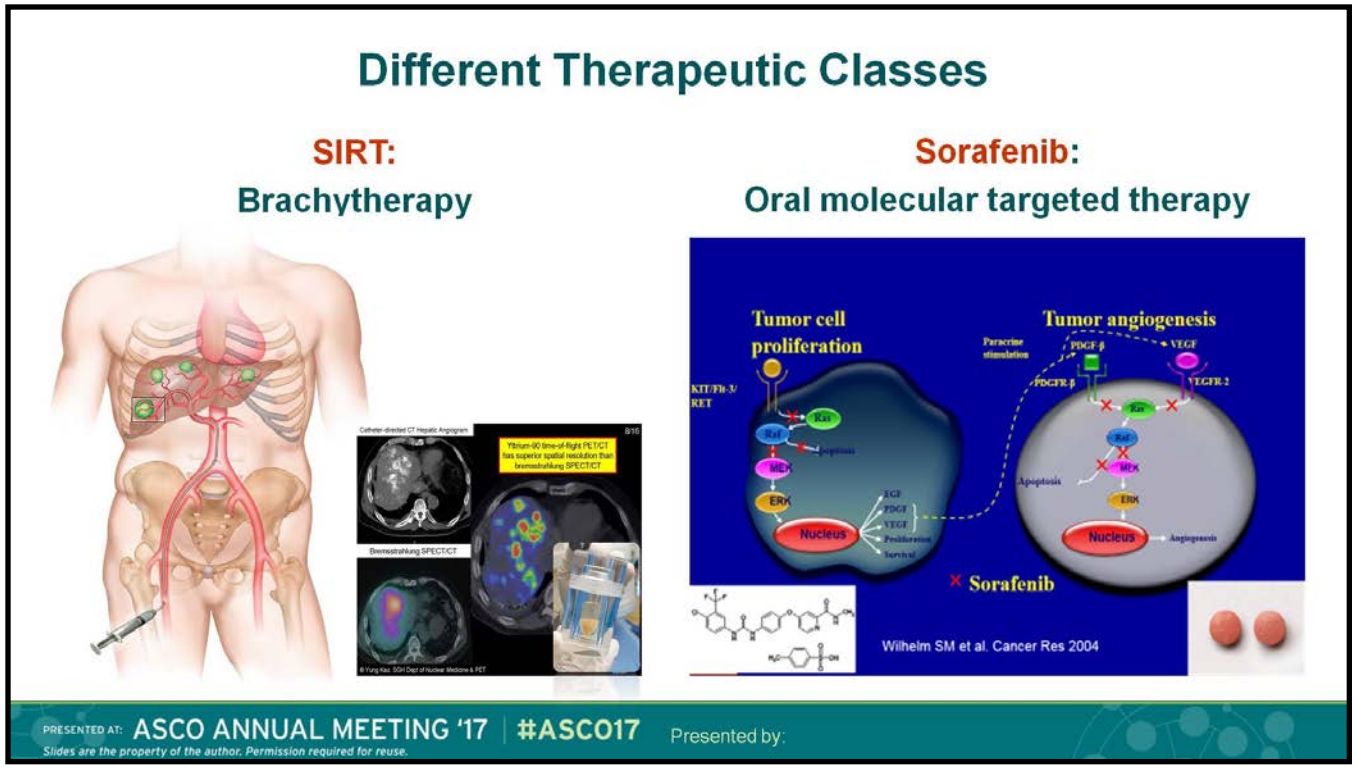
SIRT VS. SORAFENIBE EM TUMORES LOCALMENTE AVANÇADOS

Contexto



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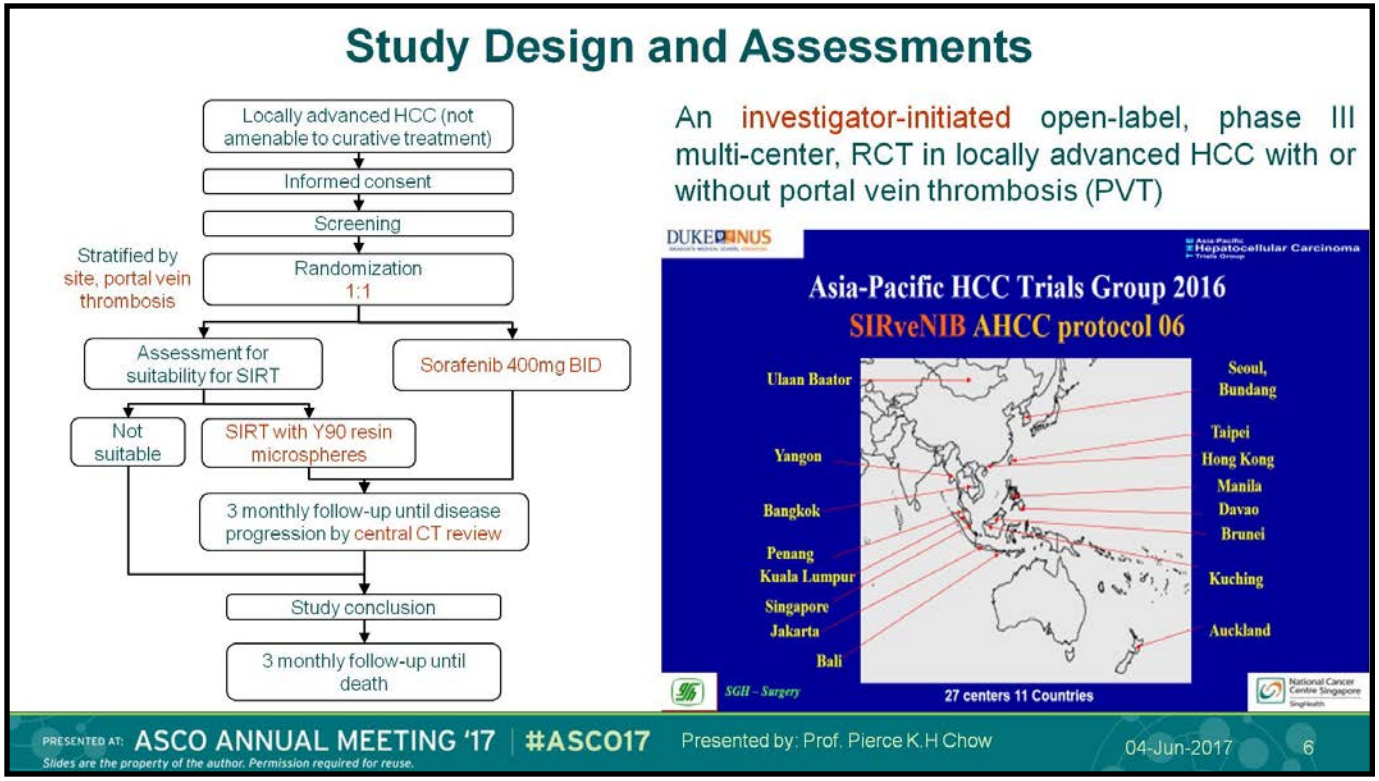
SIRT VS. SORAFENIBE EM TUMORES LOCALMENTE AVANÇADOS

Desenho do Estudo



CARCINOMA HEPATOCELULAR

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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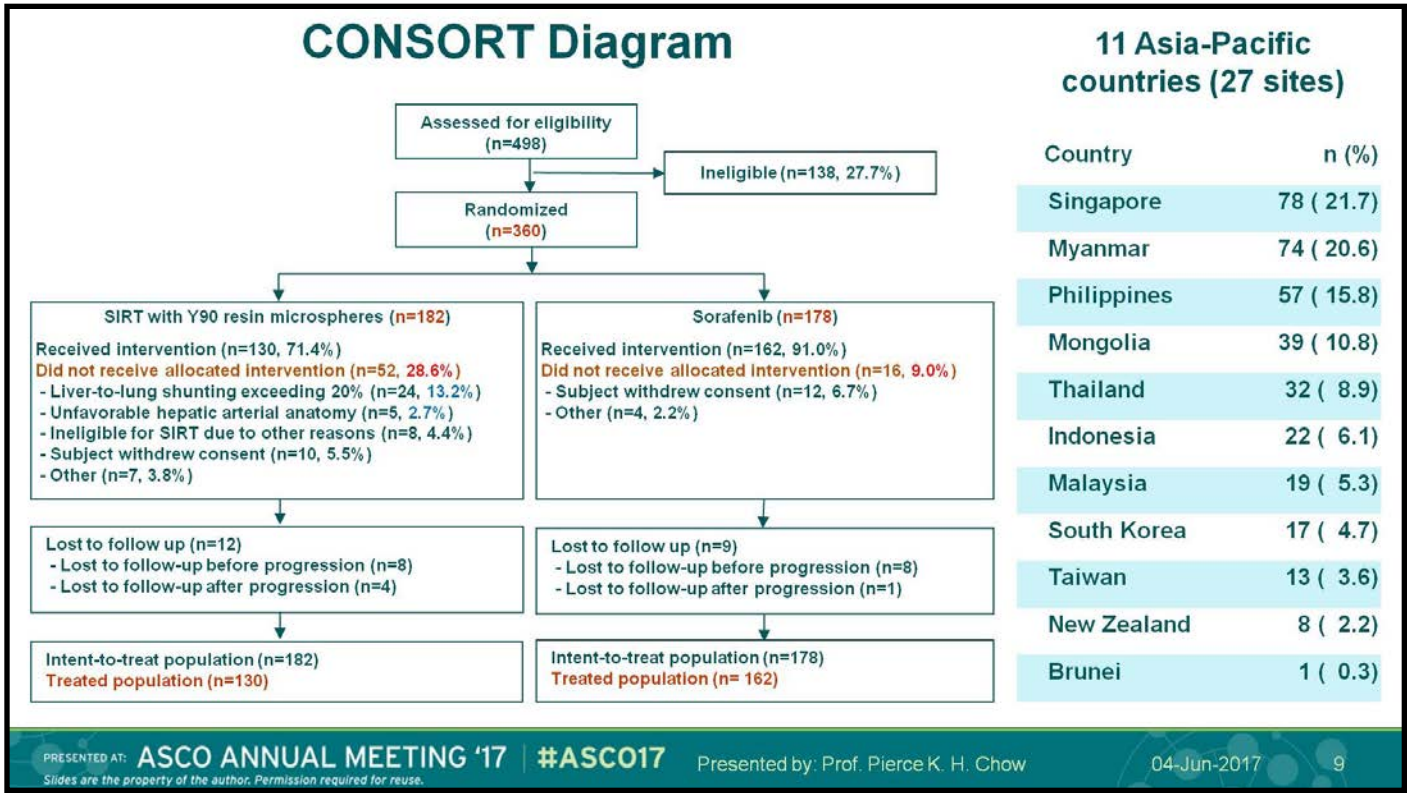
SIRT VS. SORAFENIBE EM TUMORES LOCALMENTE AVANÇADOS

Resultados



CARCINOMA HEPATOCELULAR

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 ≥ 80% adherence to planned doses: 88.9%

SIRT Treatment Centers

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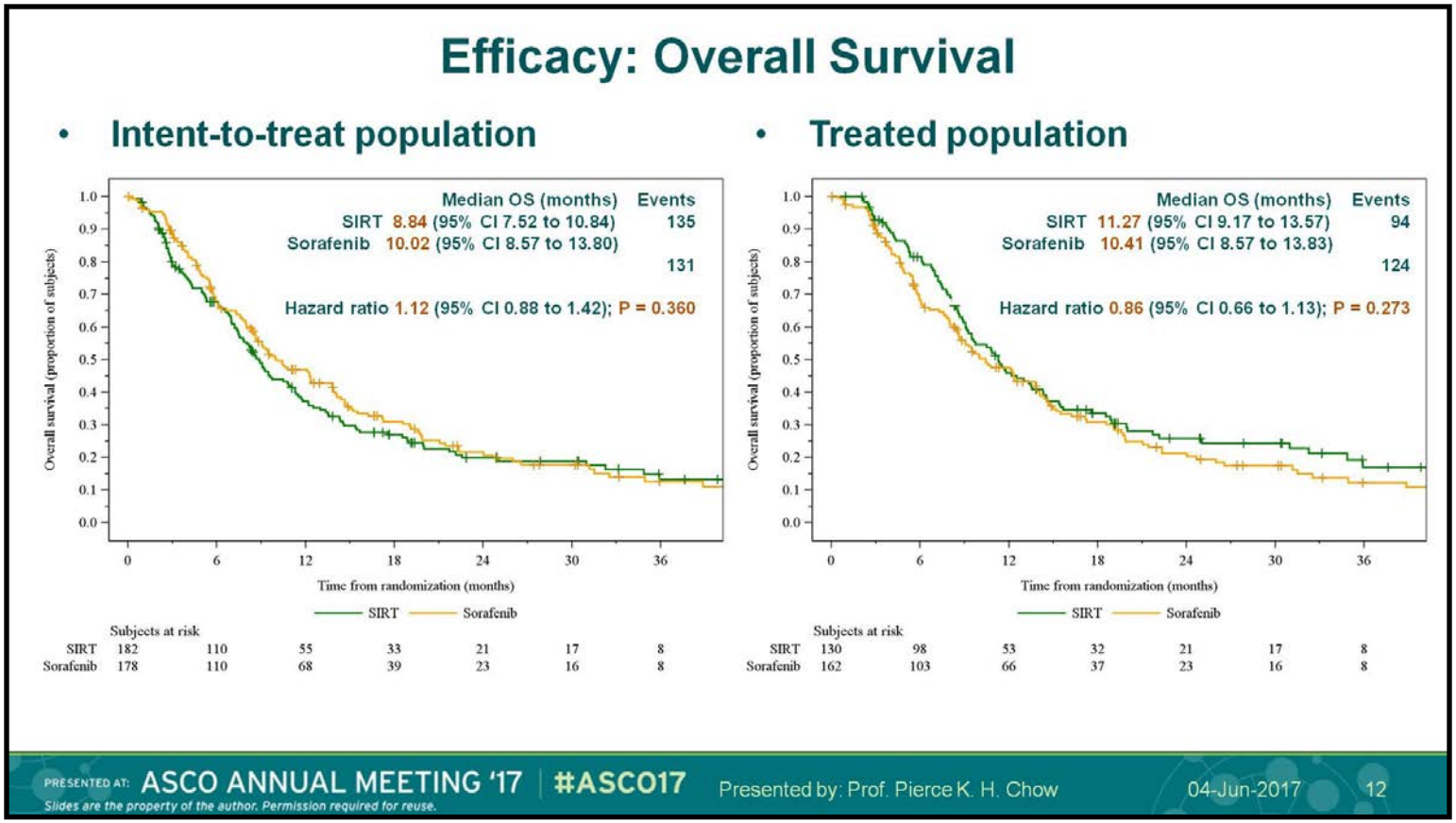
SIRT VS. SORAFENIBE EM TUMORES LOCALMENTE AVANÇADOS

Resultado - Desfecho Primário



CARCINOMA HEPATOCELULAR

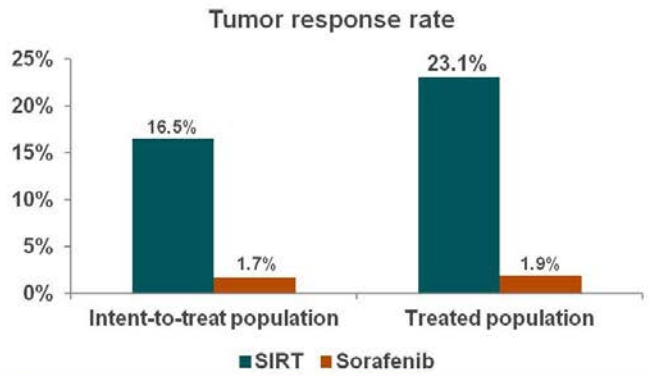
SIRT VS. SORAFENIBE EM TUMORES LOCALMENTE AVANÇADOS

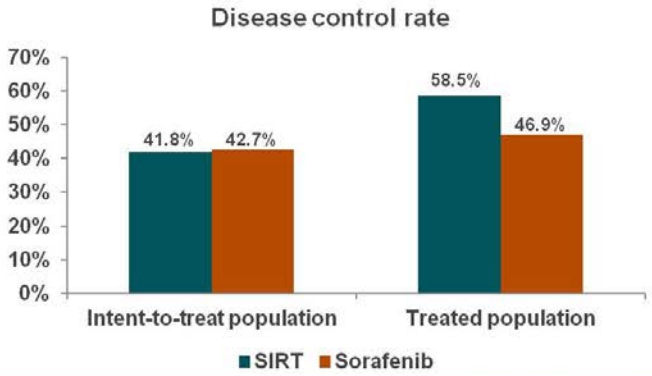
Resultados - Desfechos secundários

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

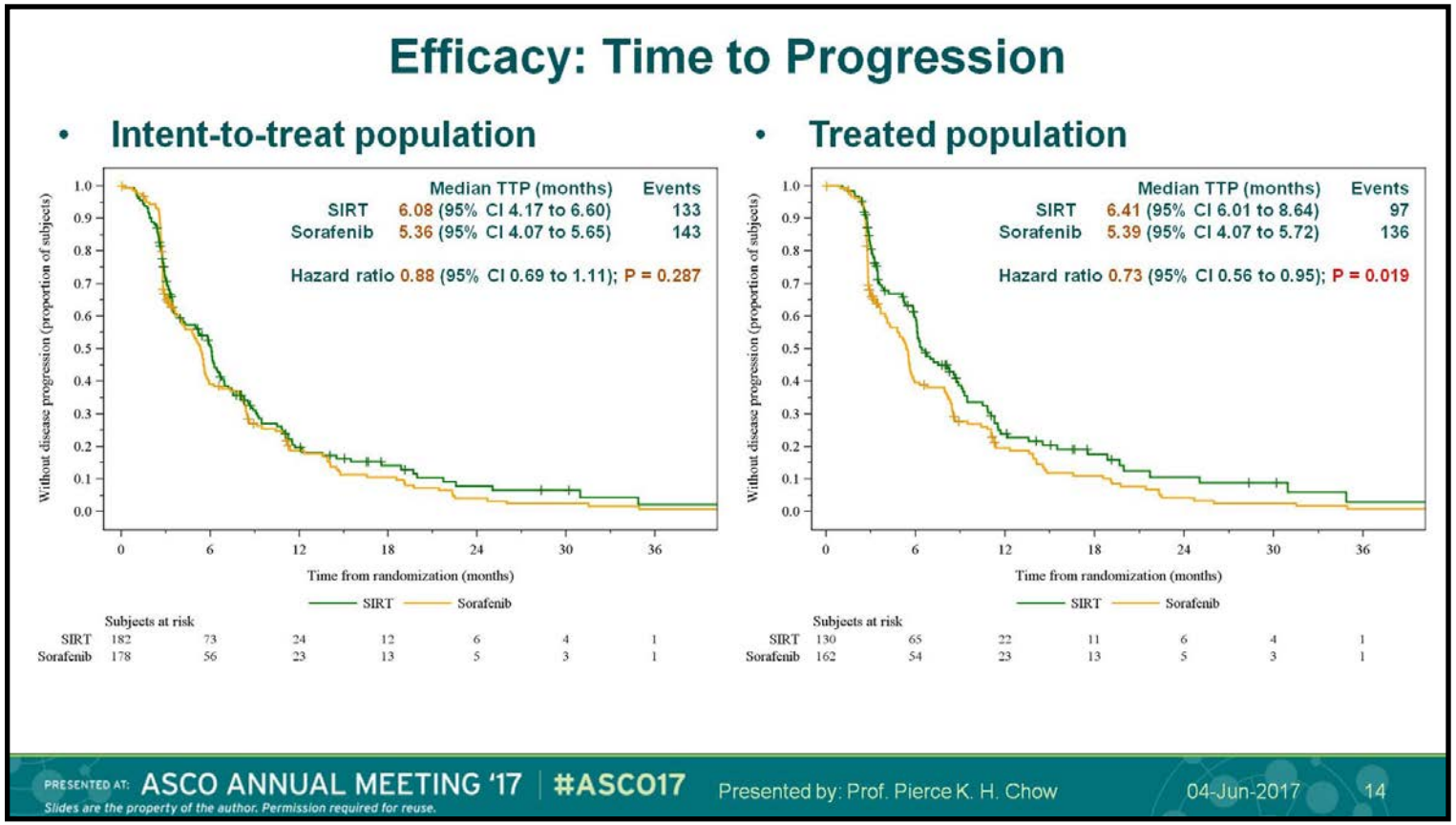




CARCINOMA HEPATOCELULAR

SIRT VS. SORAFENIBE EM TUMORES LOCALMENTE AVANÇADOS

Resultados - Desfechos secundários



CARCINOMA HEPATOCELULAR

SIRT VS. SORAFENIBE EM TUMORES LOCALMENTE AVANÇADOS

Resultados - Desfechos secundários

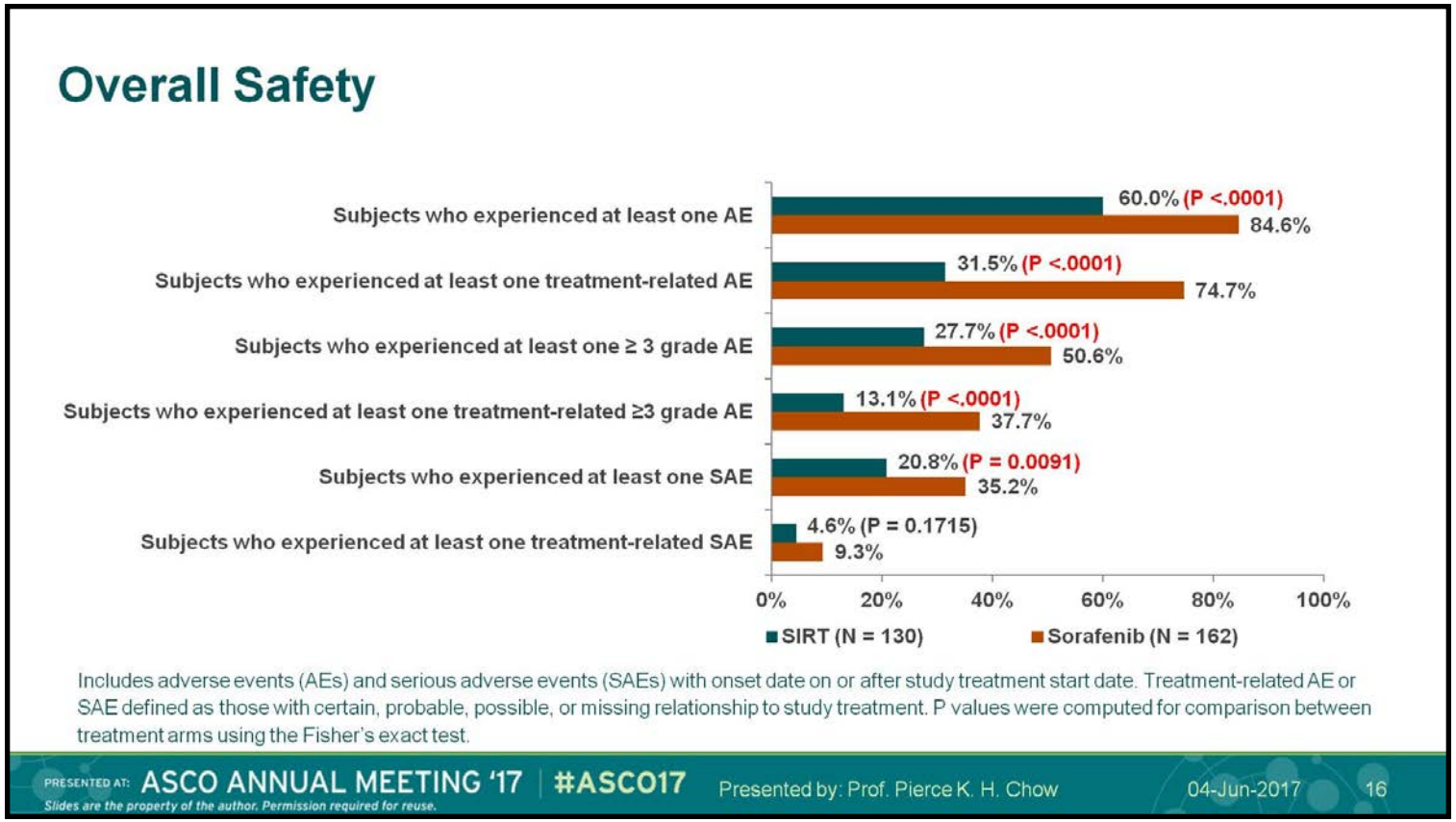
Efficacy: Secondary Outcomes

	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**

CARCINOMA HEPATOCELULAR

SIRT VS. SORAFENIBE EM TUMORES LOCALMENTE AVANÇADOS

Resultados - Segurança



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) Grade 1 - 2	SIRT (N = 130) Grade ≥ 3	Sorafenib (N = 162) Grade 1 - 2	Sorafenib (N = 162) Grade ≥ 3	P Grade 1 - 2	P 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) Grade 1 - 2	SIRT (N = 130) Grade ≥ 3	Sorafenib (N = 162) Grade 1 - 2	Sorafenib (N = 162) Grade ≥ 3	P Grade 1 - 2	P 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 erythrodysaesthesia 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.

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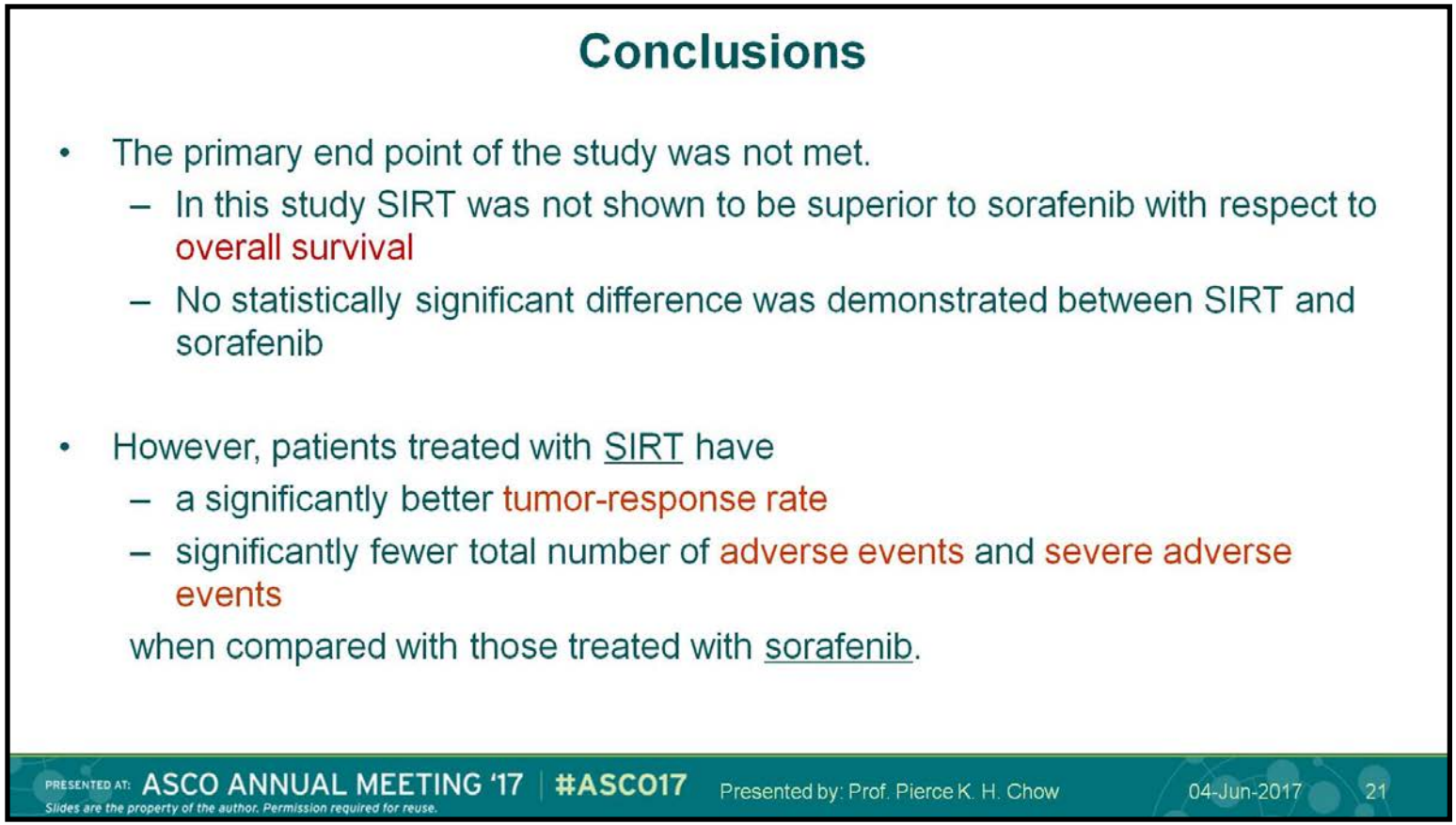
SIRT VS. SORAFENIBE EM TUMORES LOCALMENTE AVANÇADOS

Conclusões



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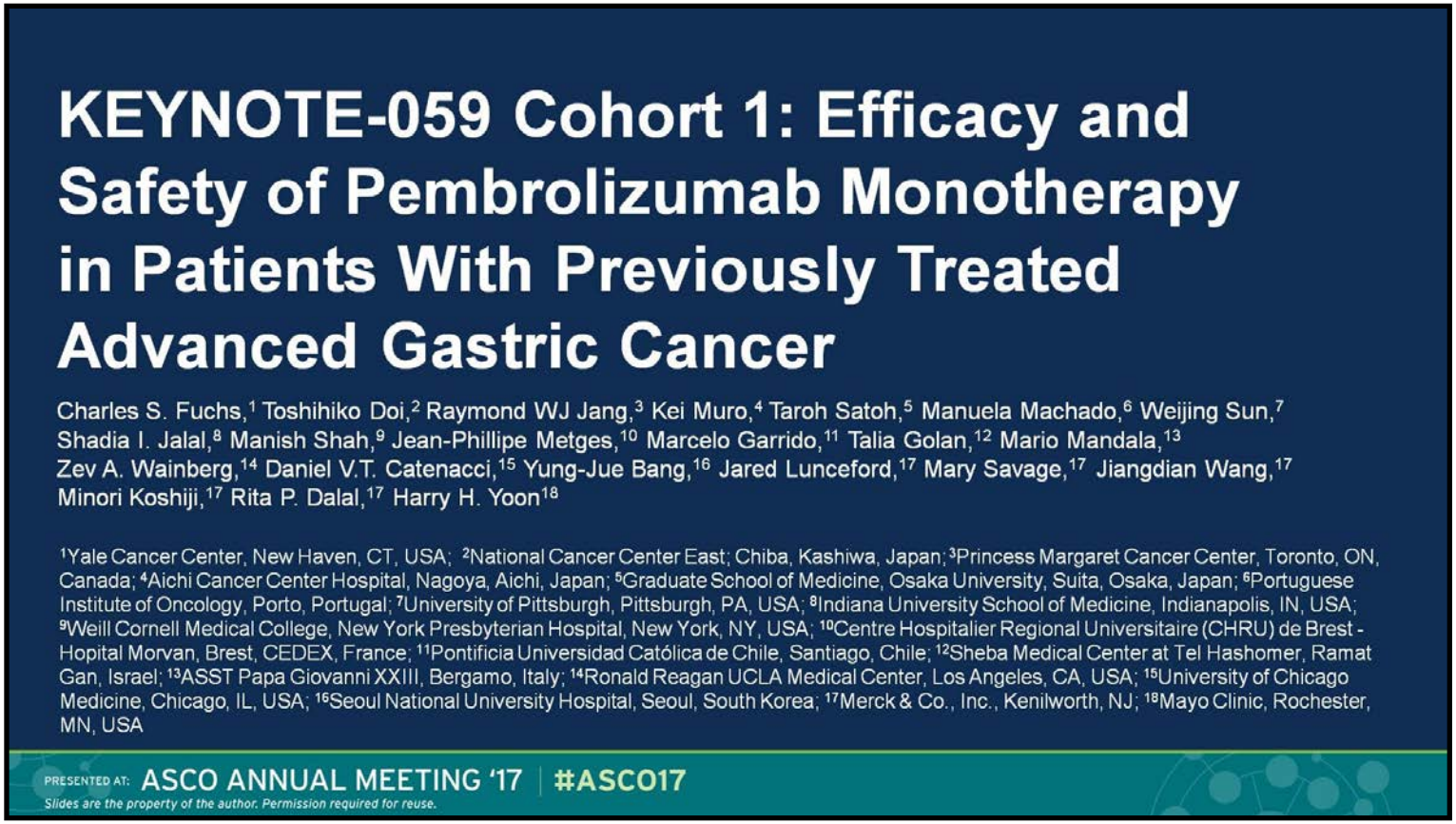

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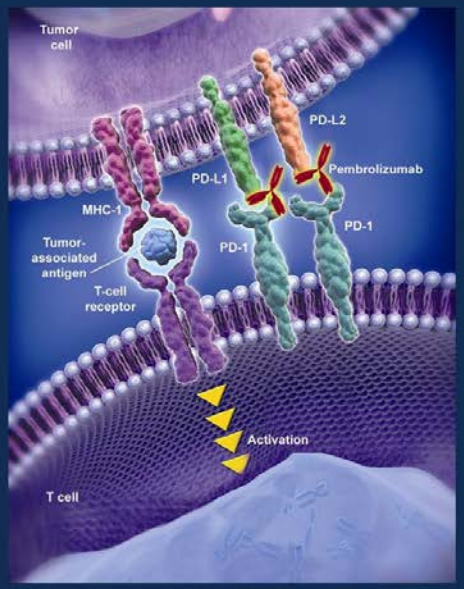
Contexto

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 cancers[1-3]
- Pembrolizumab is a selective, humanized high-affinity immunoglobulin G4-κ monoclonal antibody that blocks the interaction between PD-1 and its ligands[4]
- In a phase 1b trial, pembrolizumab demonstrated promising antitumor activity in advanced G/GEJ cancer[5]



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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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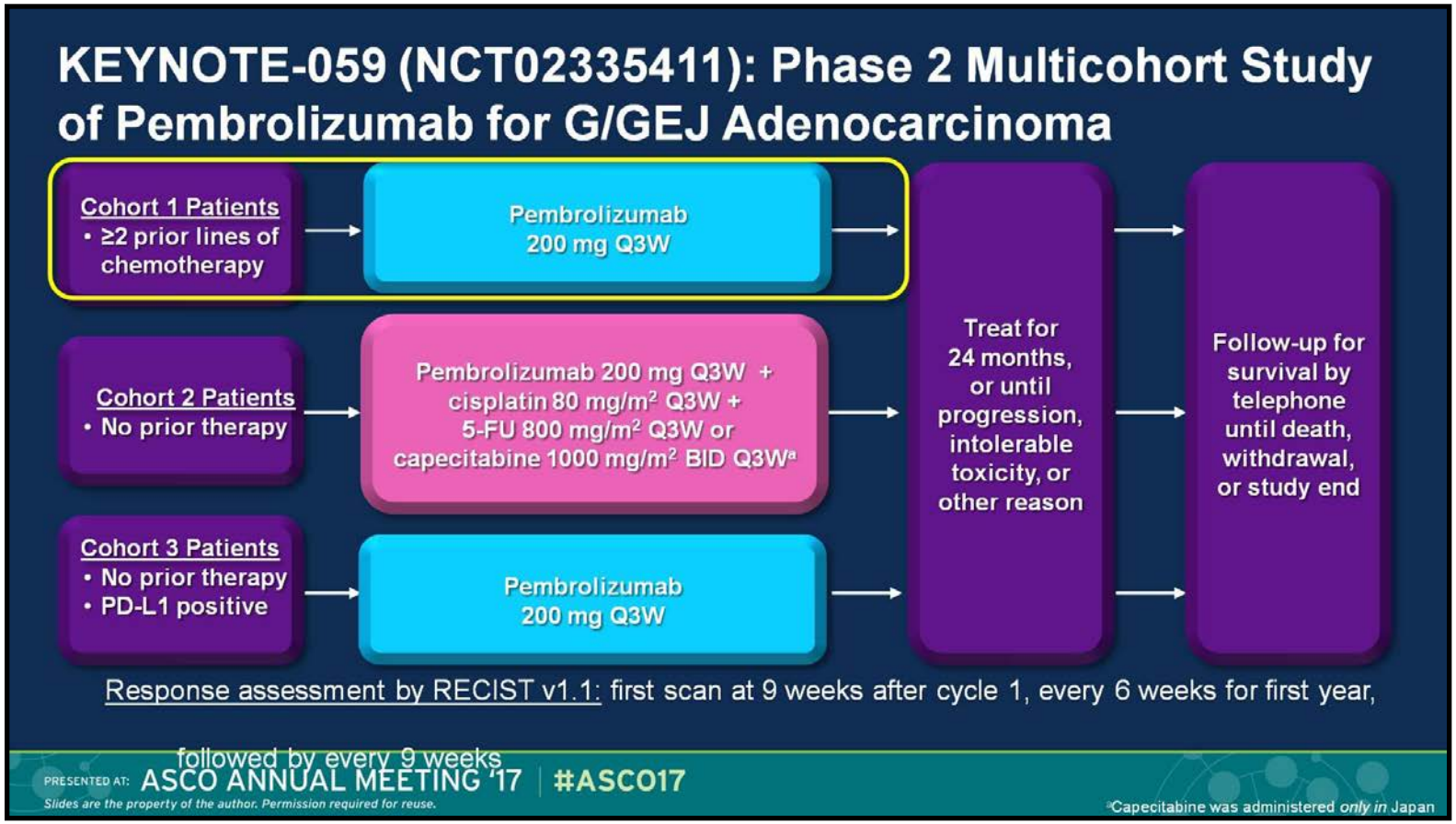
Contexto



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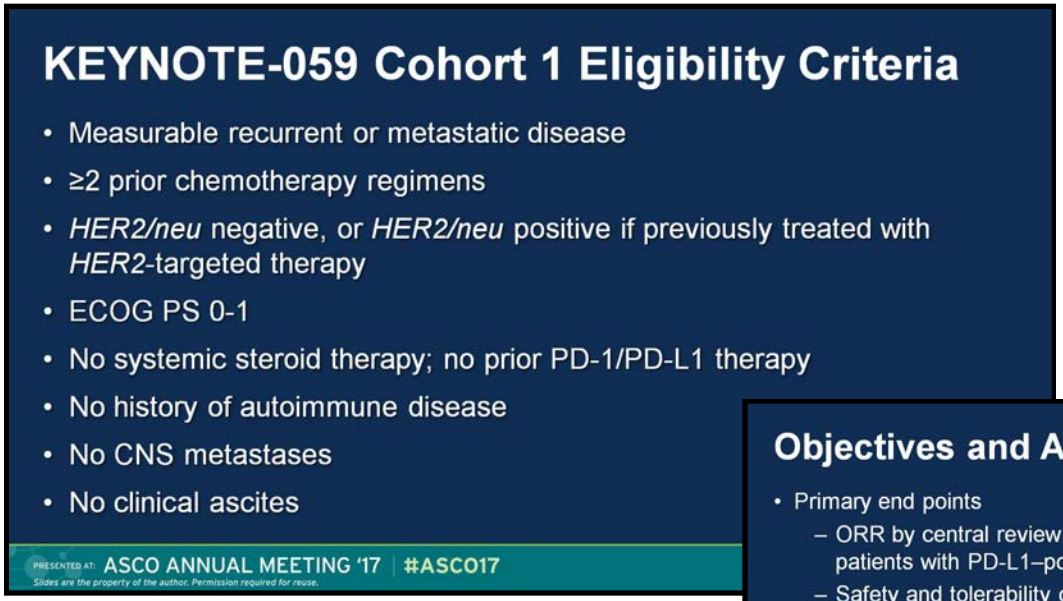
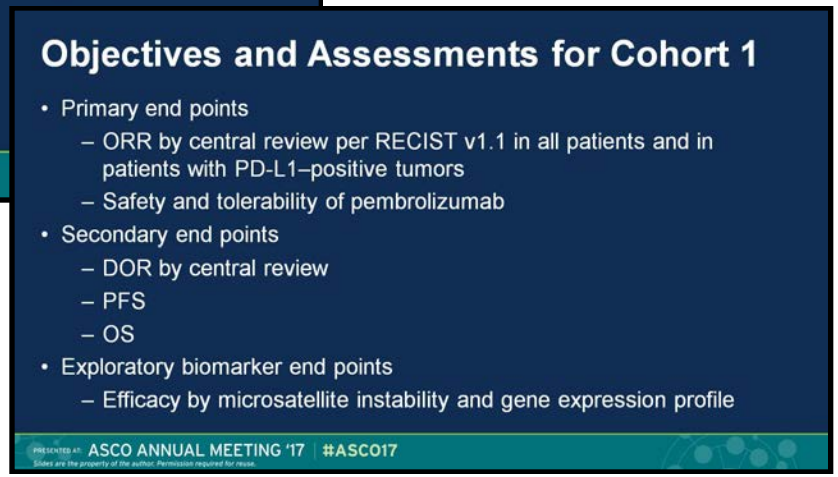
Desenho do Estudo





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Desenho do Estudo

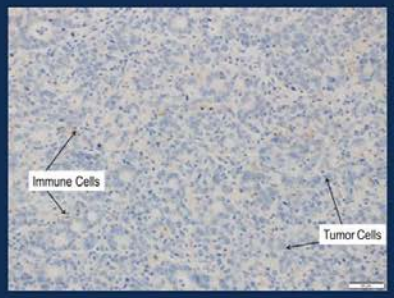
PD-L1 Expression IHC[a]

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

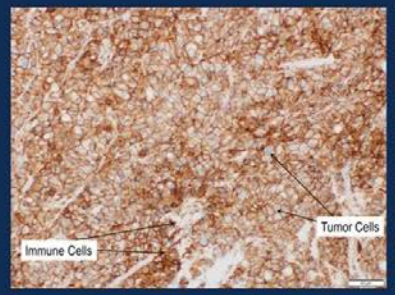
$$\text{CPS} = \frac{\text{No. of PD-L1 staining cells (tumor cells, lymphocytes, macrophages)}}{\text{Total No. of viable tumor cells}} \times 100$$

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

PD-L1 negative



PD-L1 positive



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[a]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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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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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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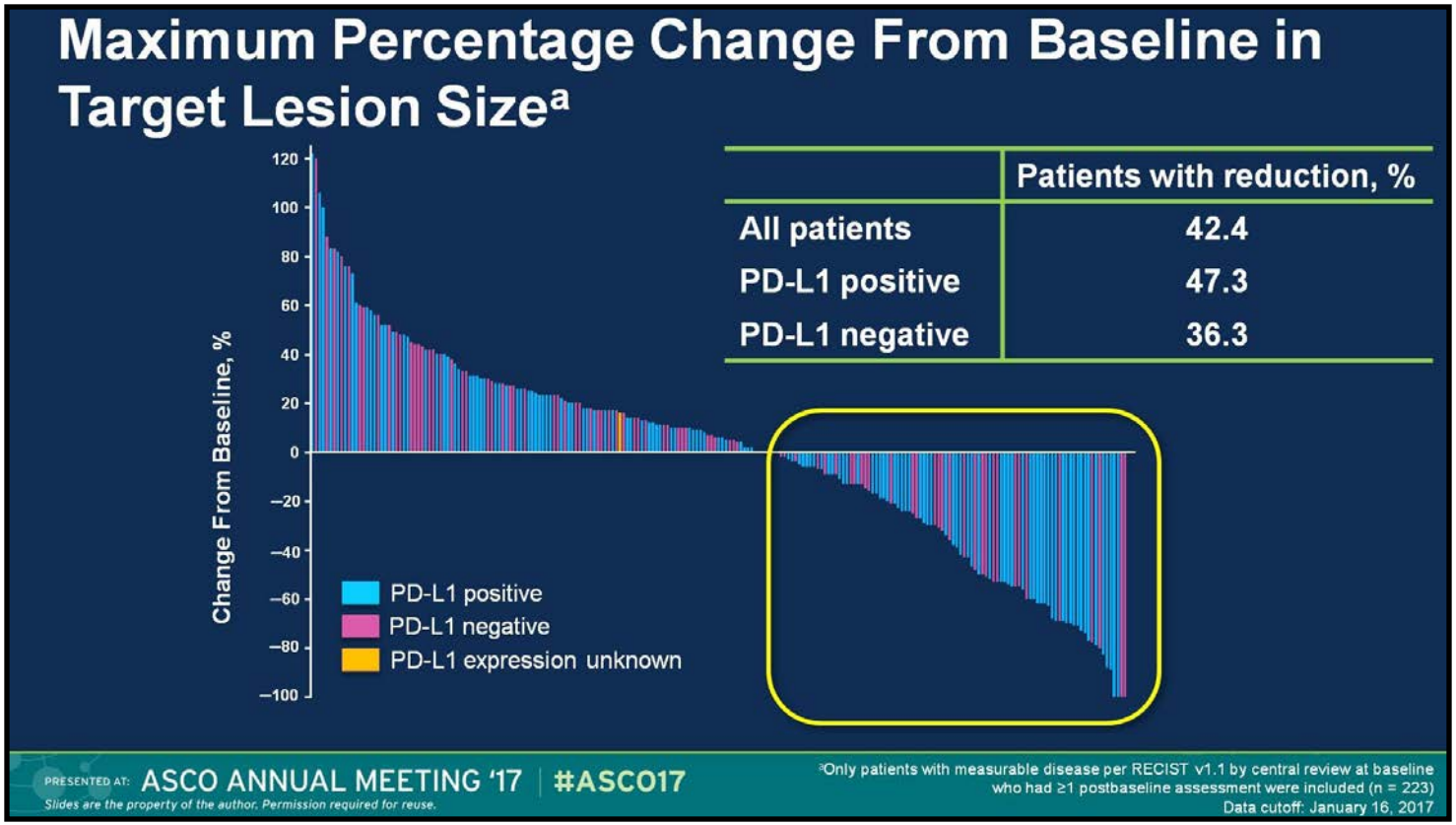
Resultados - Desfecho Primário



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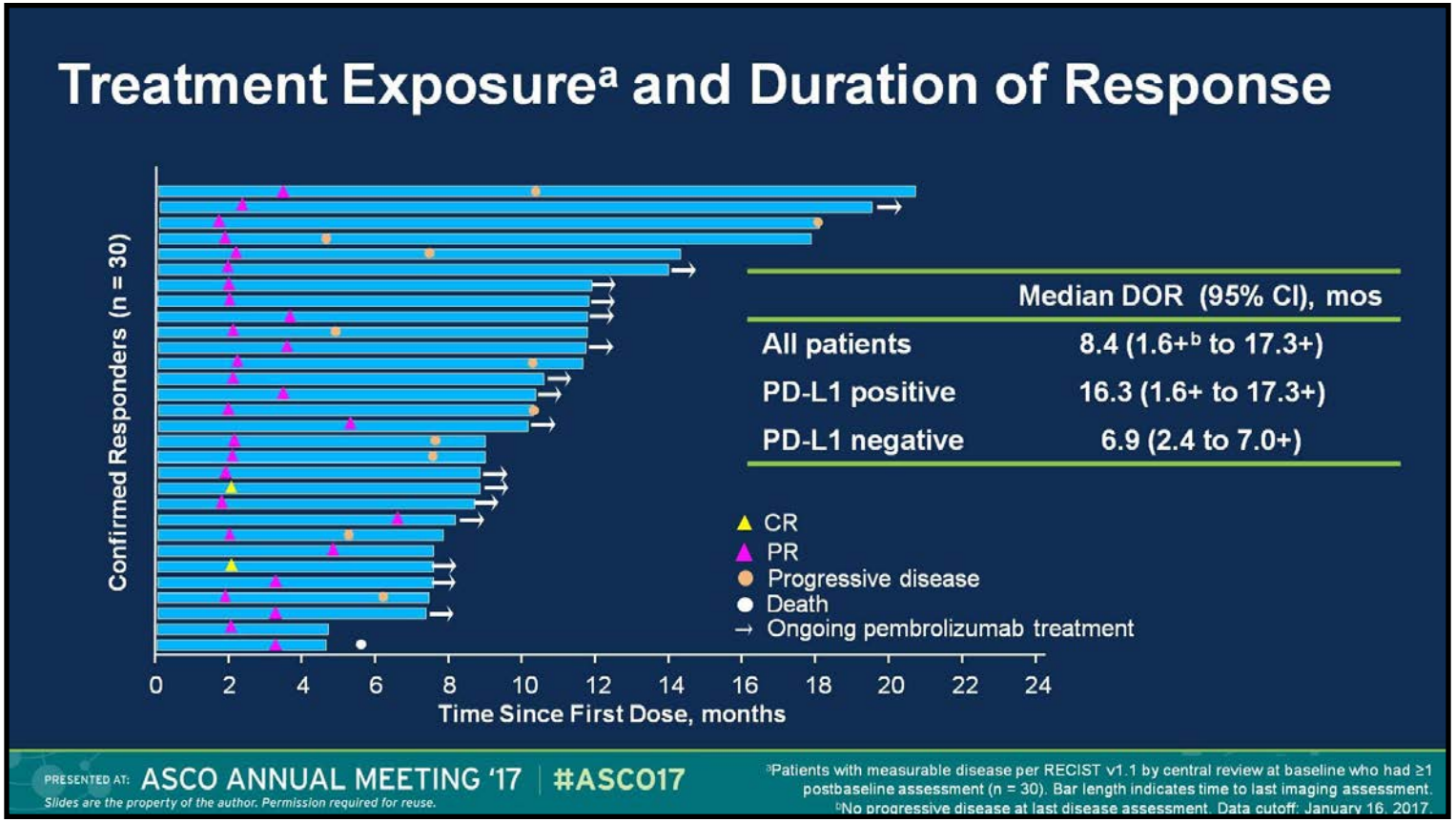
IMUNOTERAPIA - KEYNOTE 059

Resultados - Desfecho Primário



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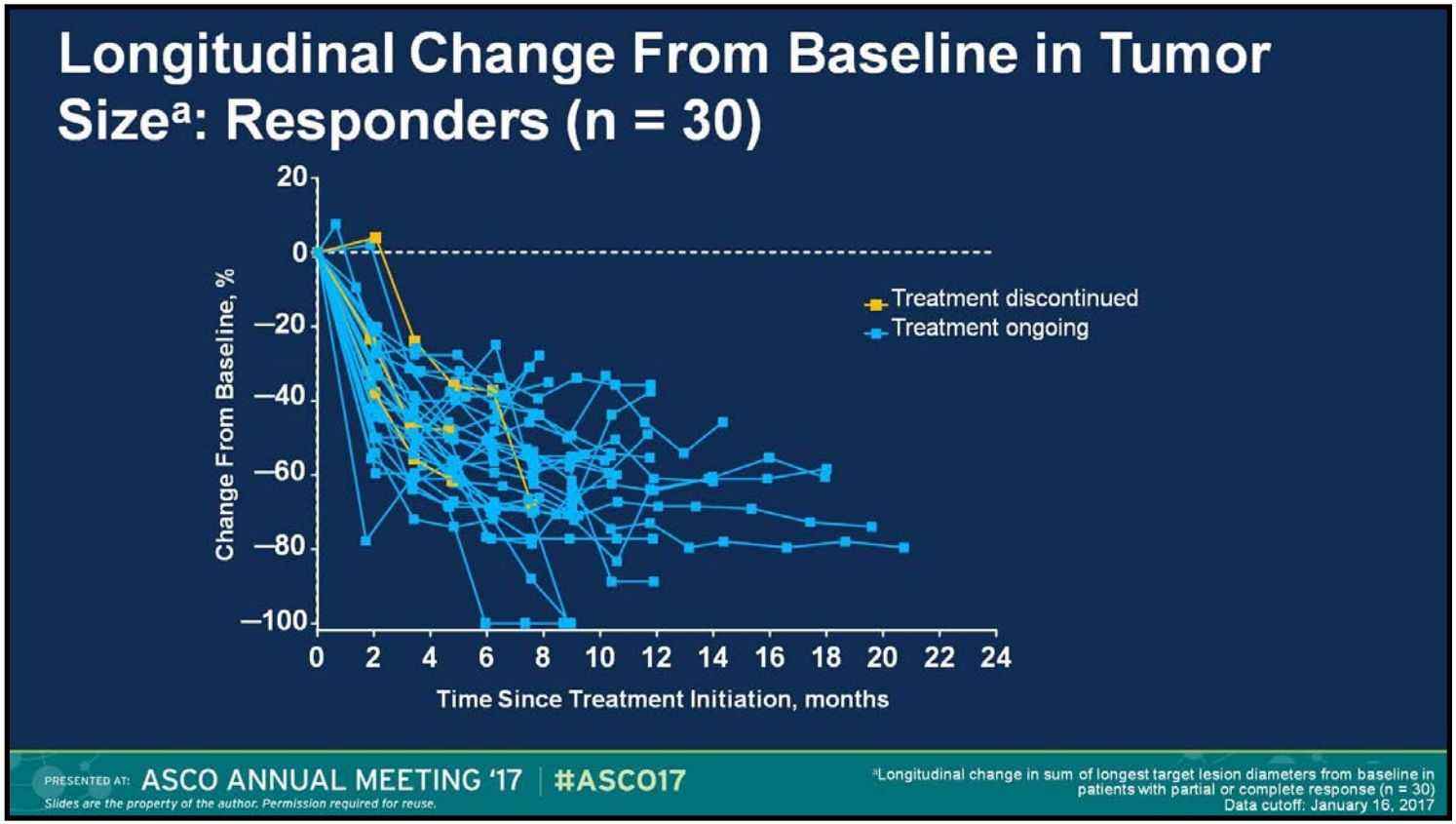
IMUNOTERAPIA - KEYNOTE 059

Resultados - Desfecho Primário



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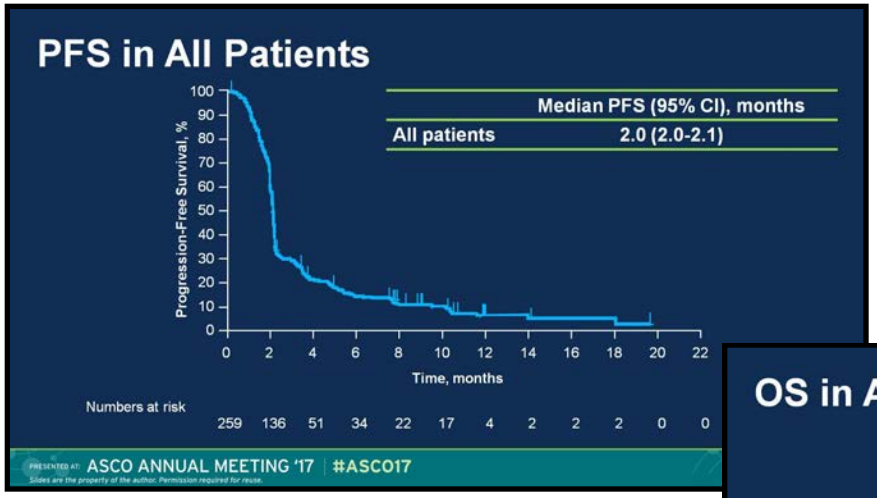
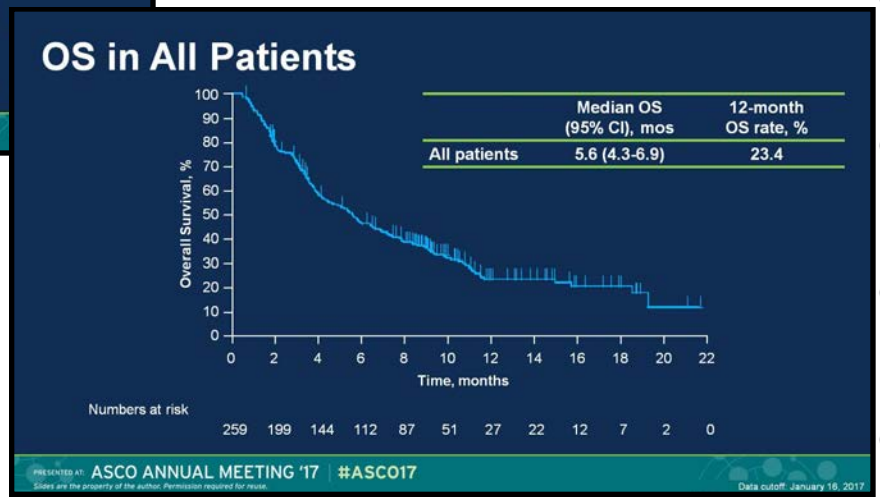
IMUNOTERAPIA - KEYNOTE 059

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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[a]Only confirmed responses were included
[b]CR + PR + SD≥2 months
Data cutoff: January 16, 2017

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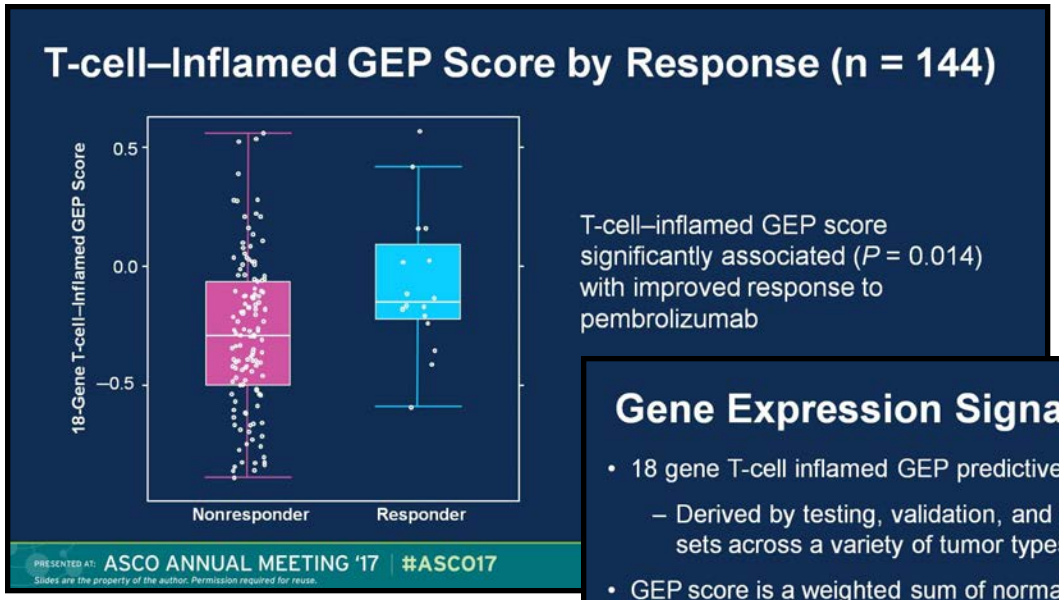
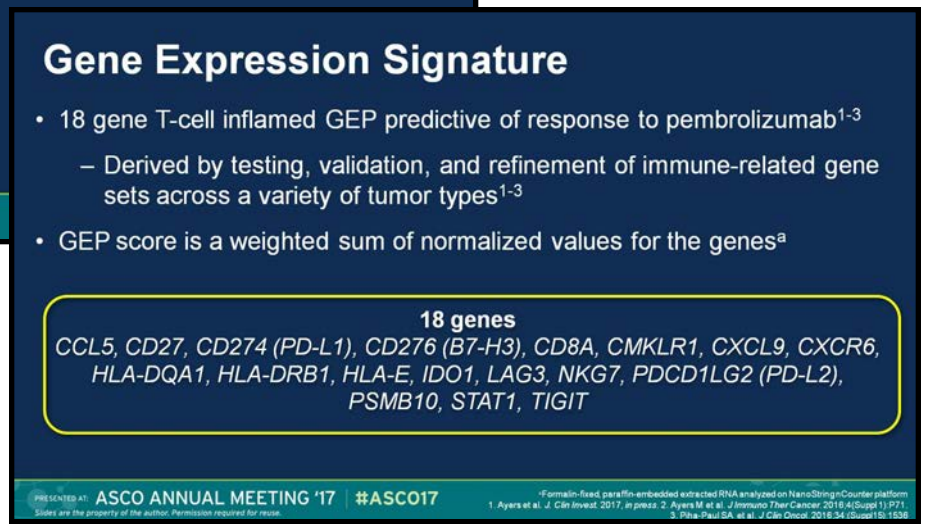
Resultados - Desfechos Secundários





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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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[a]Includes erythema multiforme, jaundice, rash, maculopapular rash

Data cutoff: January 16, 2017

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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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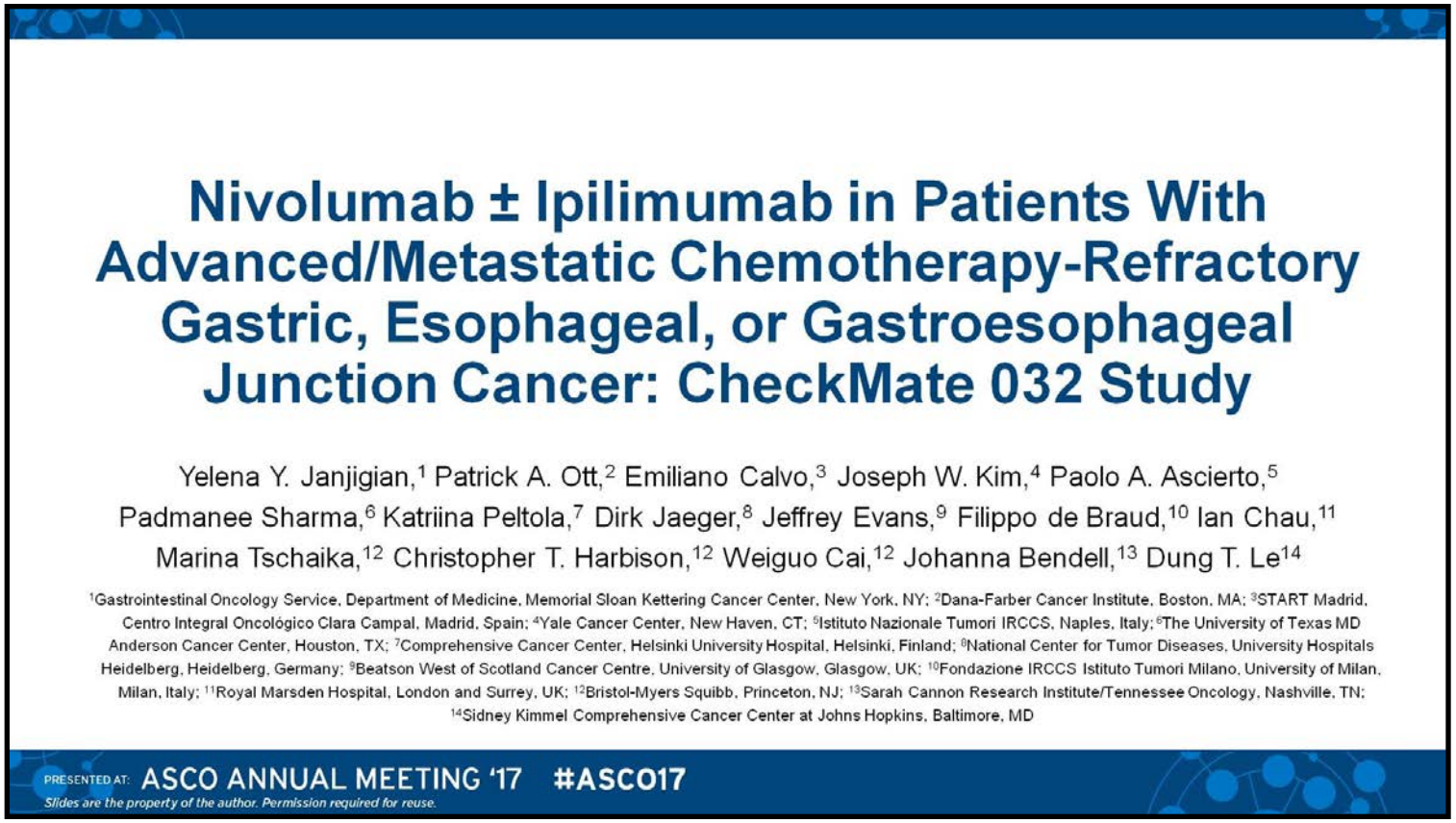
IMUNOTERAPIA - CHECKMATE 032



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

Yelena Y. Janjigian,[1] Patrick A. Ott,[2] Emiliano Calvo,[3] Joseph W. Kim,[4] Paolo A. Ascierto,[5] 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. Le[14]

[1]Gastrointestinal Oncology Service, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY; [2]Dana-Farber Cancer Institute, Boston, MA; [3]START Madrid, Centro Integral Oncológico Clara Campal, Madrid, Spain; [4]Yale Cancer Center, New Haven, CT; [5]Istituto Nazionale Tumori IRCCS, Naples, Italy; [6]The University of Texas MD Anderson Cancer Center, Houston, TX; [7]Comprehensive Cancer Center, Helsinki University Hospital, Helsinki, Finland; [8]National Center for Tumor Diseases, University Hospitals Heidelberg, Heidelberg, Germany; [9]Beatson West of Scotland Cancer Centre, University of Glasgow, Glasgow, UK; [10]Fondazione IRCCS Istituto Tumori Milano, University of Milan, Milan, Italy; [11]Royal Marsden Hospital, London and Surrey, UK; [12]Bristol-Myers Squibb, Princeton, NJ; [13]Sarah Cannon Research Institute/Tennessee Oncology, Nashville, TN; [14]Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, MD

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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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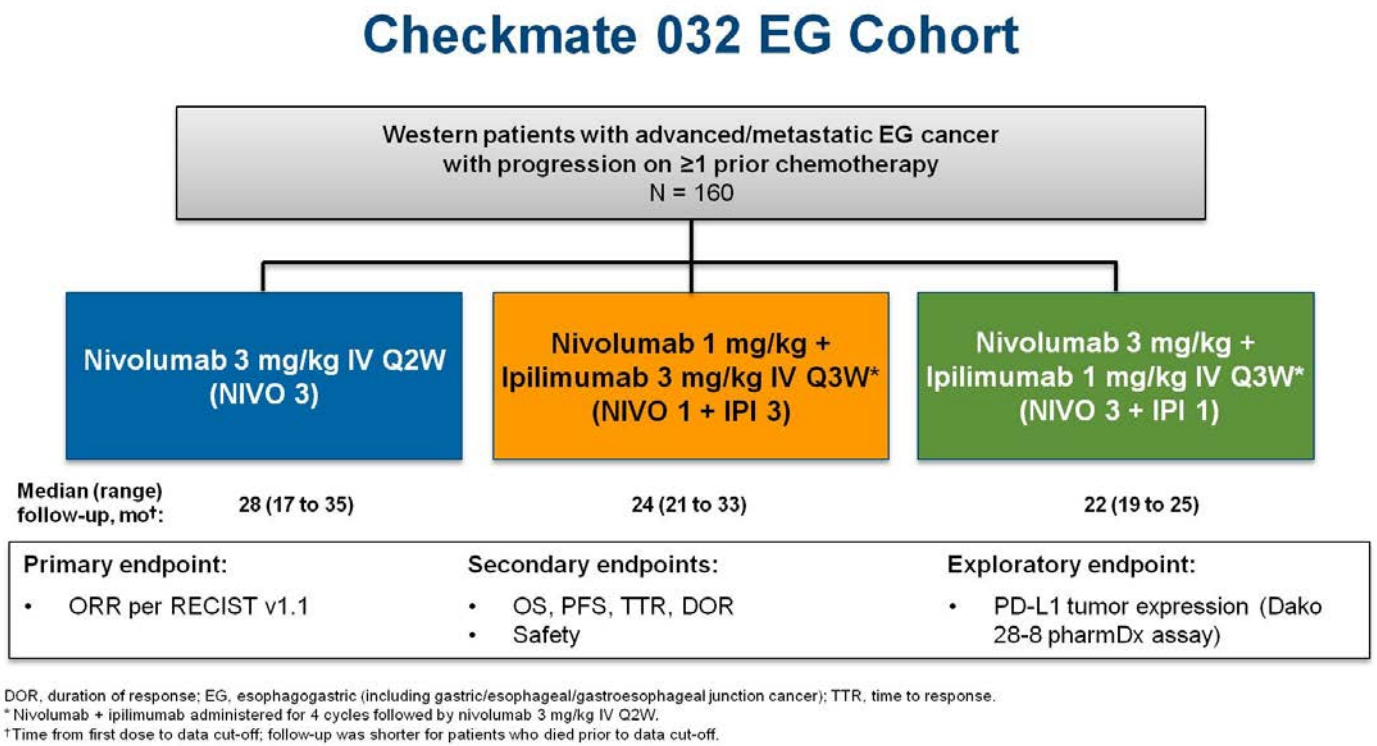
Desenho do Estudo



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 (%)*	**7 (12)**	**12 (24)**	**4 (8)**
[95% CI]	[5, 23]	[13, 39]	[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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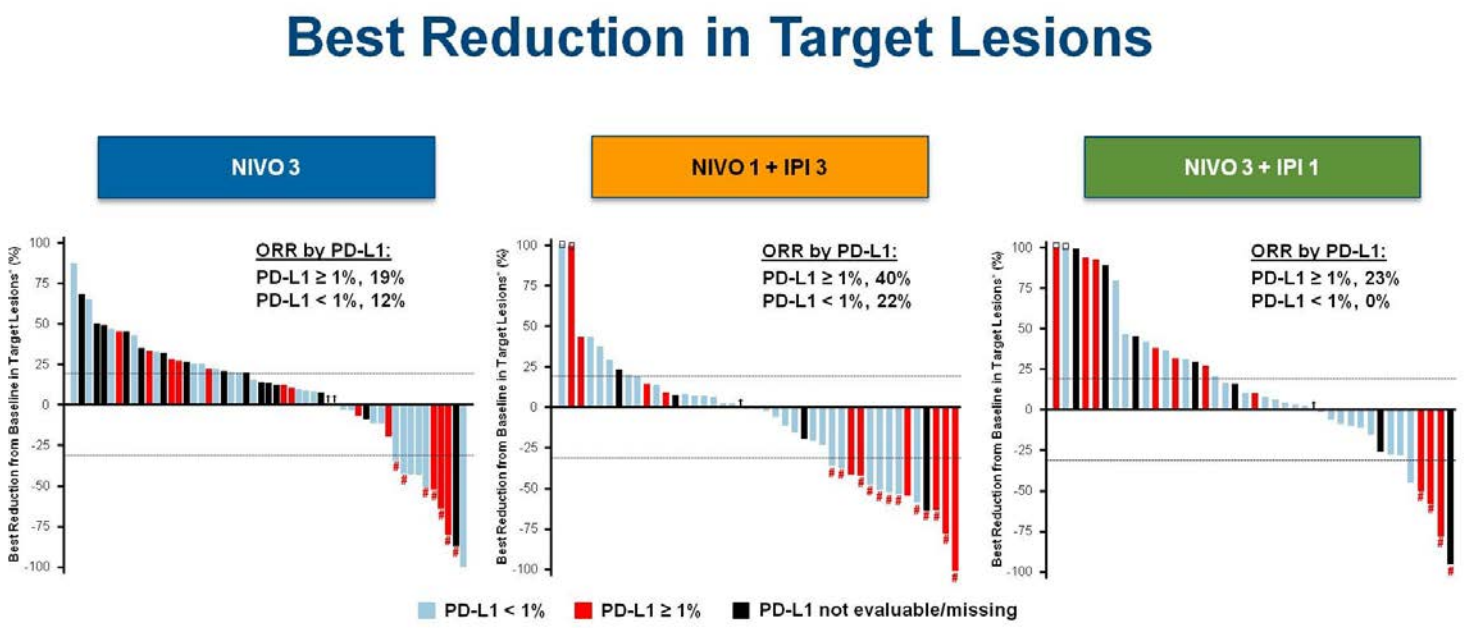
IMUNOTERAPIA - CHECKMATE 032

Resultados - Desfecho Primário



- 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).
□ change truncated to 100%

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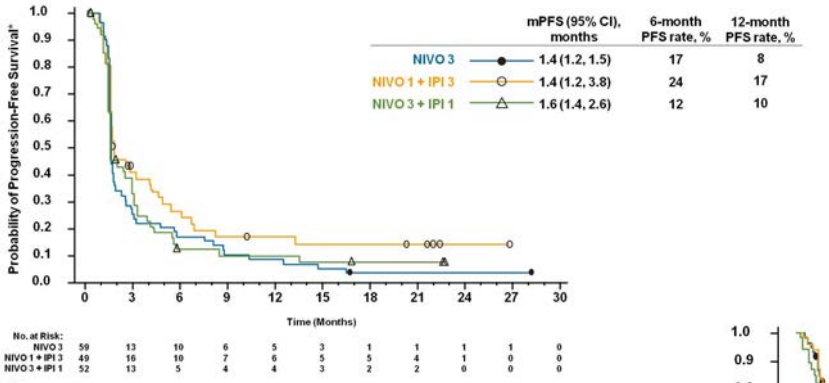
IMUNOTERAPIA - CHECKMATE 032

Resultados - Desfechos Secundários

Progression-Free Survival



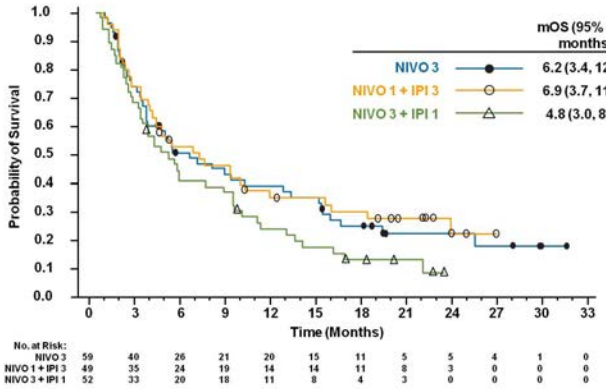
	mPFS (95% CI), months	6-month PFS rate, %	12-month PFS rate, %
NIVO 3	1.4 (1.2, 1.5)	17	8
NIVO 1 + IPI 3	1.4 (1.2, 3.8)	24	17
NIVO 3 + IPI 1	1.6 (1.4, 2.6)	12	10

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



	mOS (95% CI), months	12-month OS rate, %	18-month OS rate, %
NIVO 3	6.2 (3.4, 12.4)	39	25
NIVO 1 + IPI 3	6.9 (3.7, 11.5)	35	28
NIVO 3 + IPI 1	4.8 (3.0, 8.4)	24	13

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 reports[1-4]
- 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

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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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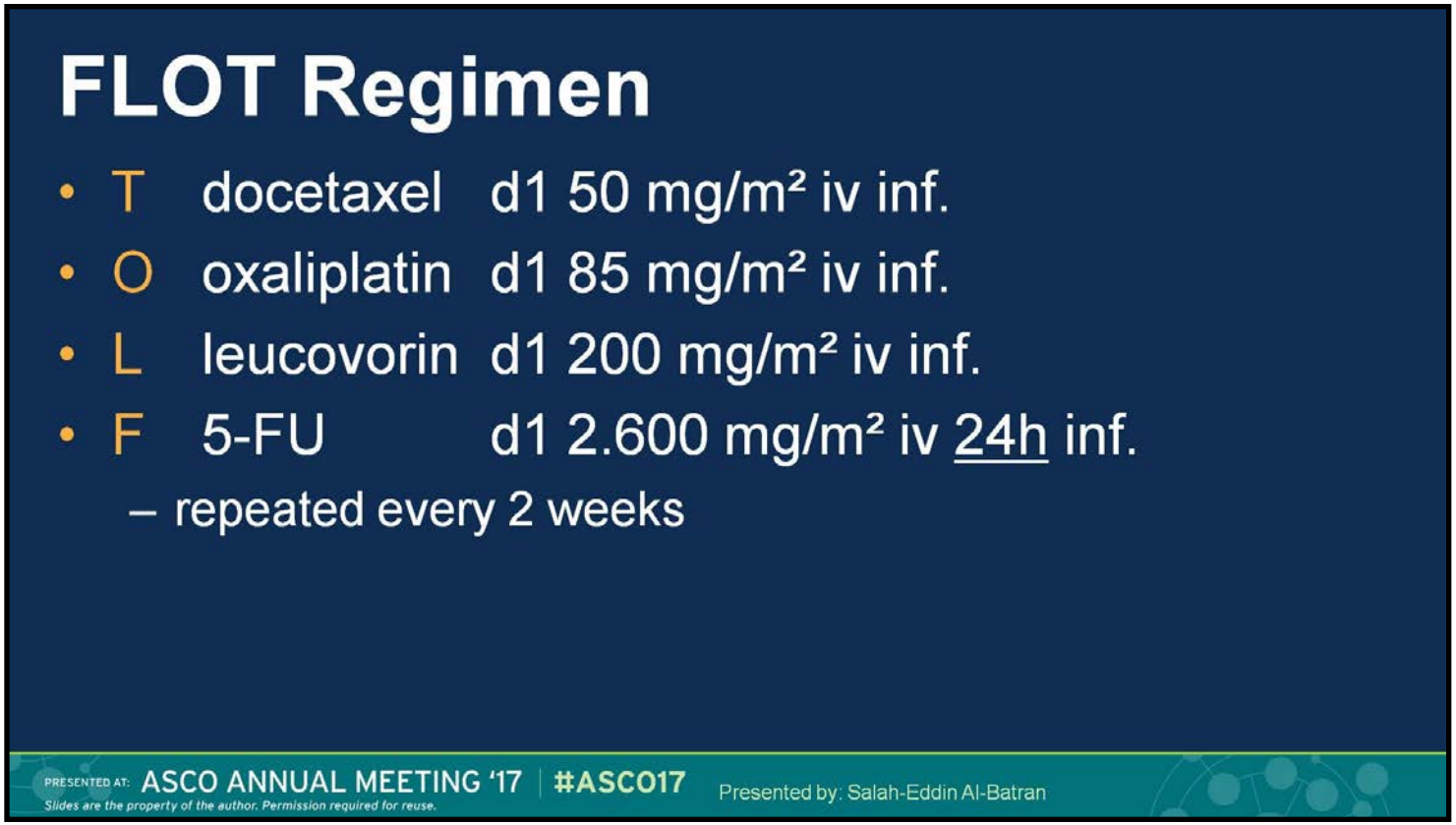
FLOT 4

Contexto



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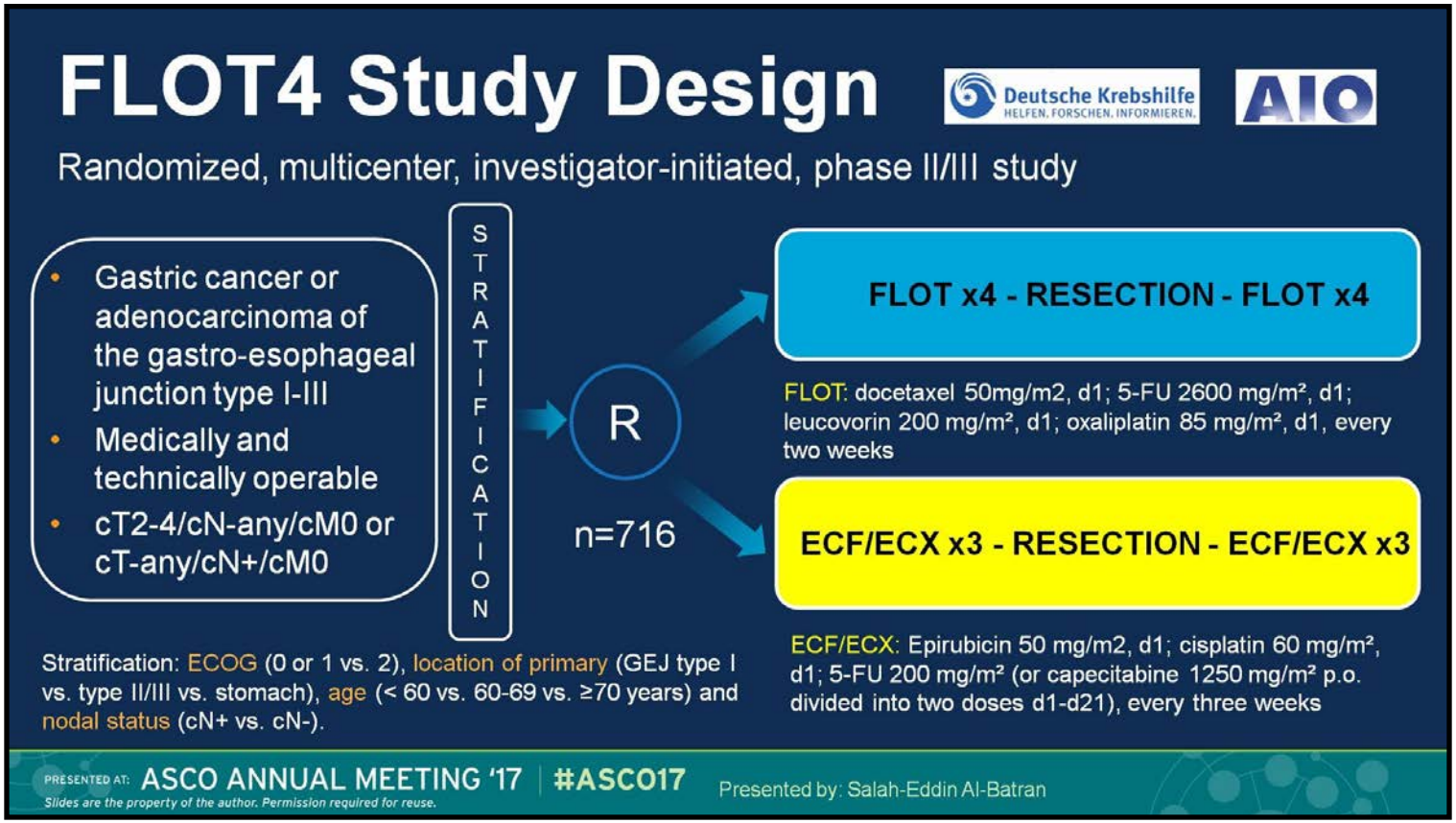
FLOT 4

Desenho do Estudo



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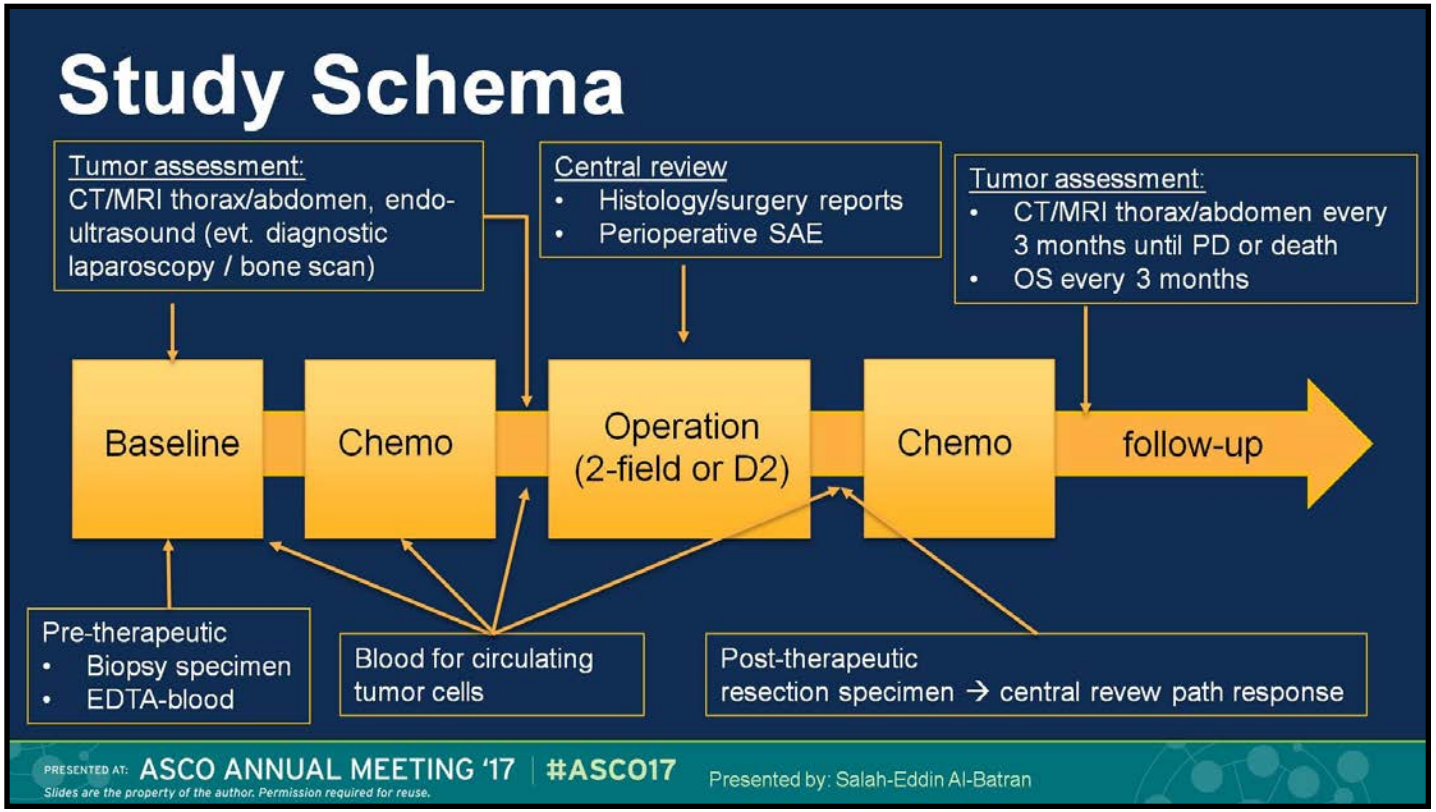
FLOT 4

Desenho do Estudo



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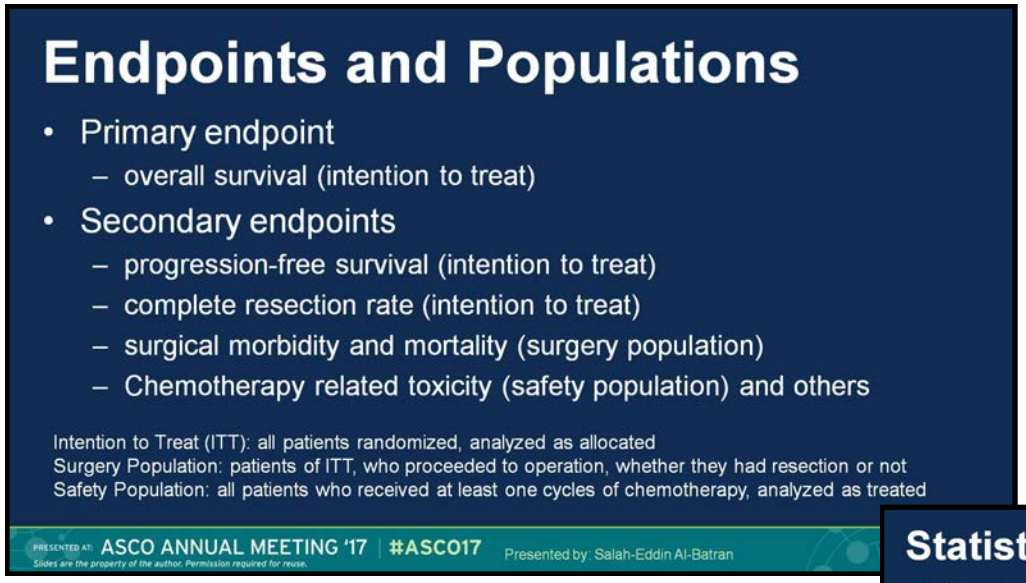
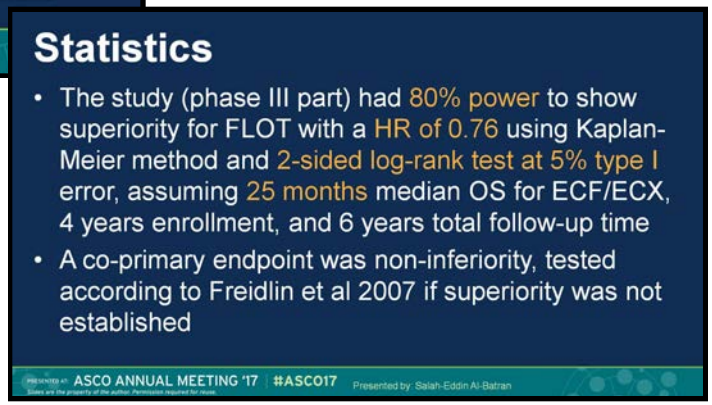
FLOT 4

Desenho do Estudo





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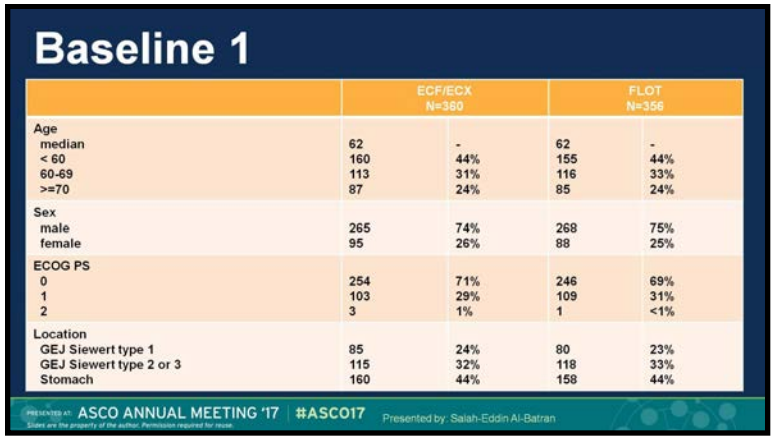
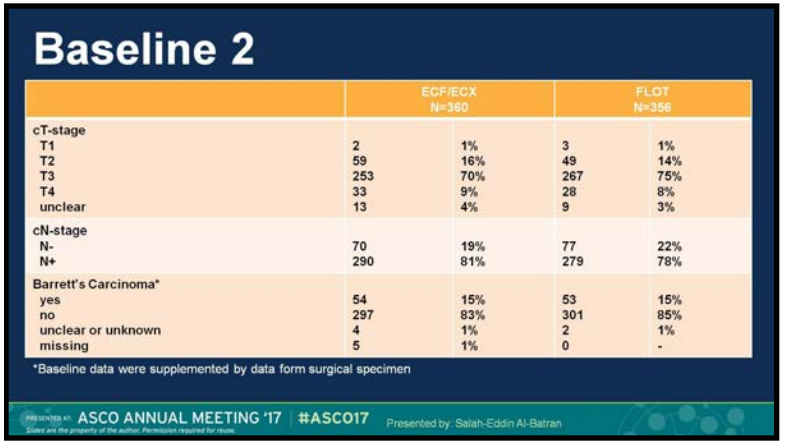
FLOT 4

Resultados



Baseline 1

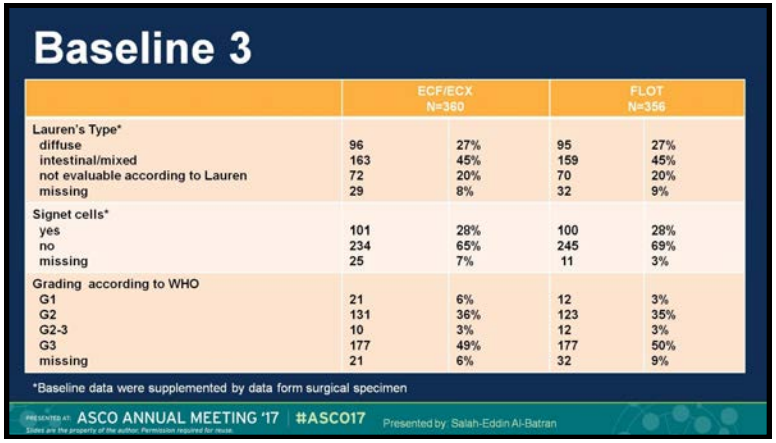
	ECF/ECX N=360		FLOT N=356	
Age				
median	62	-	62	-
< 60	160	44%	155	44%
60-69	113	31%	116	33%
>=70	87	24%	85	24%
Sex				
male	265	74%	268	75%
female	95	26%	88	25%
ECOG PS				
0	254	71%	246	69%
1	103	29%	109	31%
2	3	1%	1	<1%
Location				
GEJ Siewert type 1	85	24%	80	23%
GEJ Siewert type 2 or 3	115	32%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



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 form surgical specimen



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 form 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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CÂNCER GÁSTRICO

FLOT 4

Resultados

Histopathology (ypTN)

ypT-stage	ECF/ECX (360)	FLOT (356)	P-value§
≤T1	53 (15%)	88 (25%)	0.001
T2	44 (12%)	44 (12%)	
T3	175 (49%)	165 (46%)	
T4	47 (13%)	37 (10%)	
NA*	41 (11%)	22 (6.2%)	

ypT-stage	ECF/ECX (360)	FLOT (356)	P-value§
N0	146 (41%)	174 (49%)	0.029
N1	44 (12%)	55 (16%)	
N2	54 (15%)	47 (13%)	
N3	73 (20%)	57 (16%)	
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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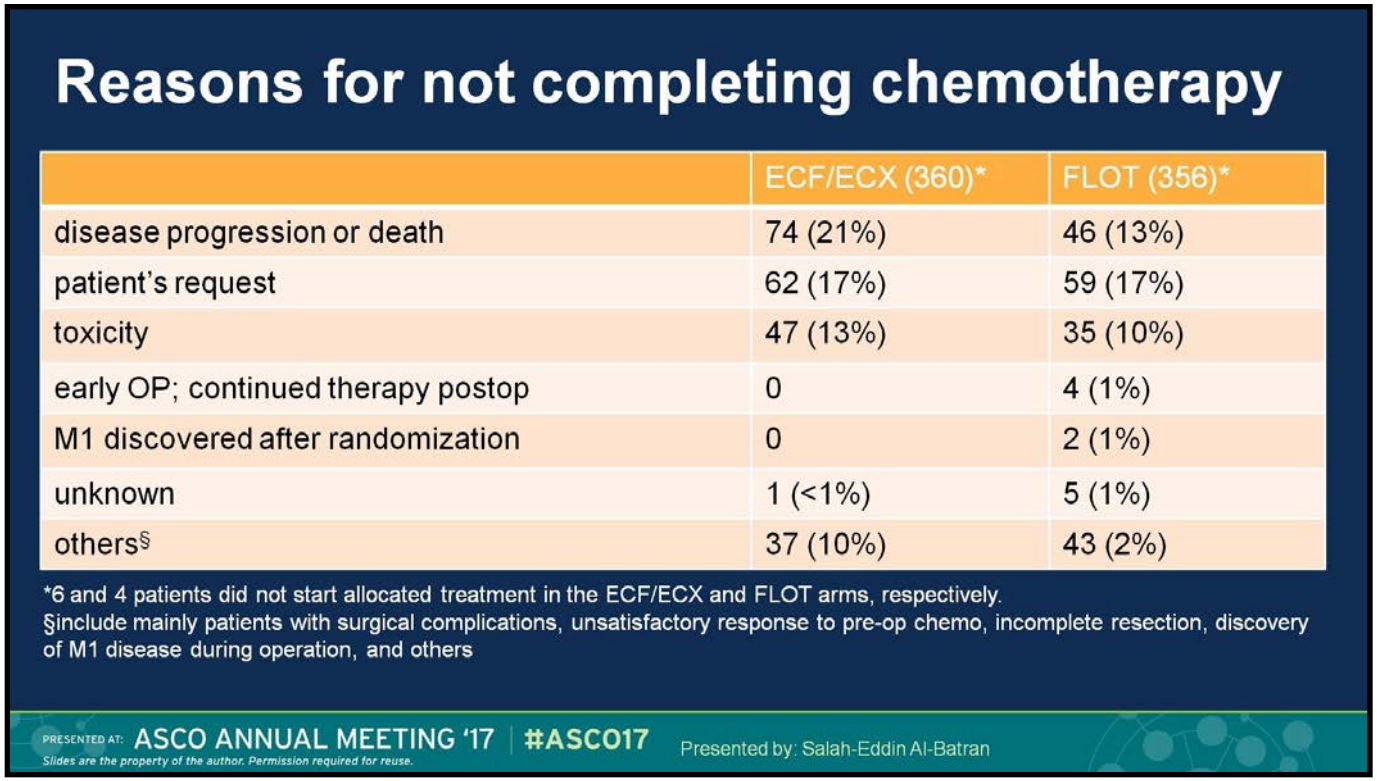
CÂNCER GÁSTRICO

FLOT 4

Resultados - Segurança



Reasons for not completing chemotherapy

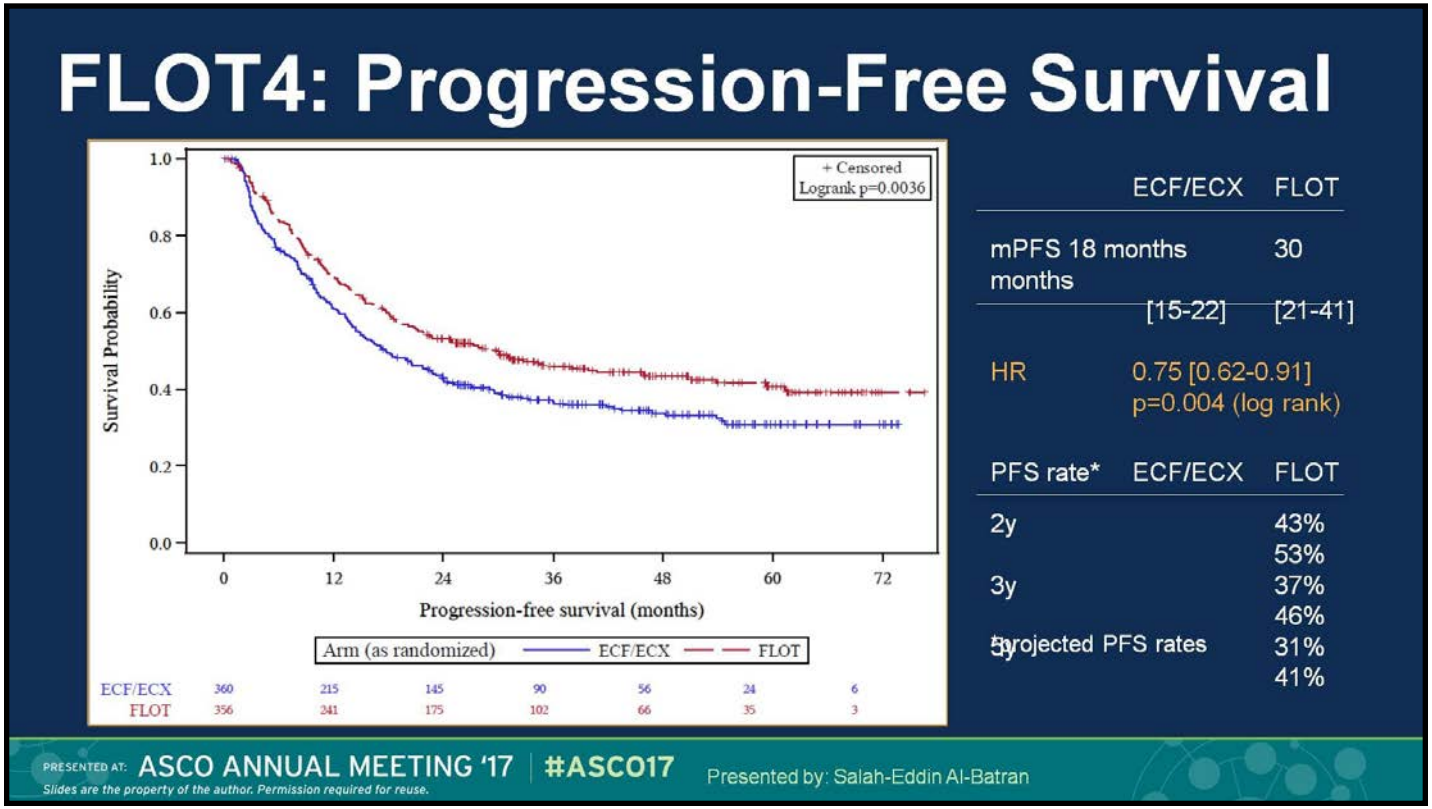
	ECF/ECX (360)*	FLOT (356)*
disease progression or death	74 (21%)	46 (13%)
patient's request	62 (17%)	59 (17%)
toxicity	47 (13%)	35 (10%)
early OP; continued therapy postop	0	4 (1%)
M1 discovered after randomization	0	2 (1%)
unknown	1 (<1%)	5 (1%)
others§	37 (10%)	43 (2%)

*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

CÂNCER GÁSTRICO

FLOT 4

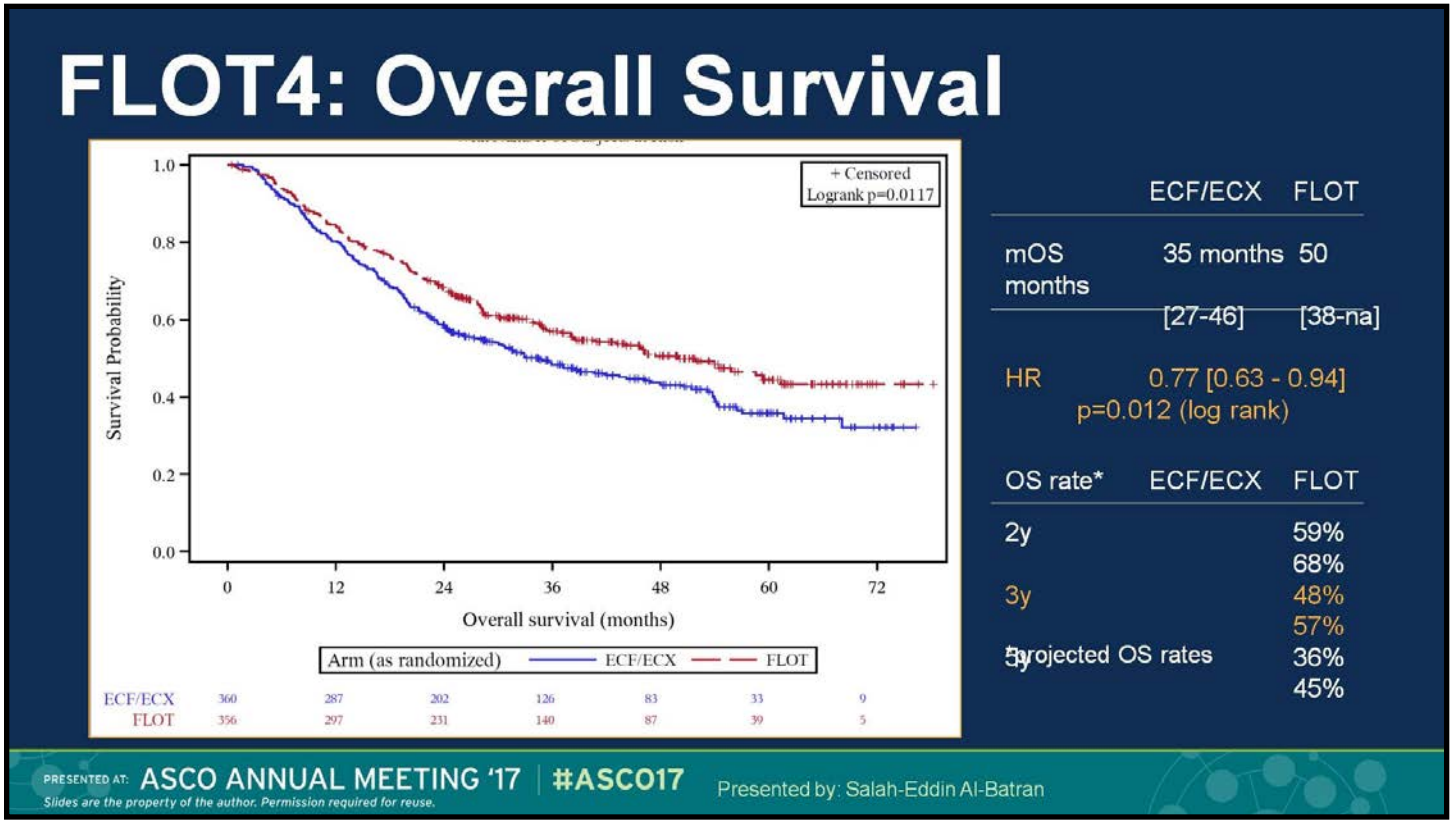
Resultados



CÂNCER GÁSTRICO

FLOT 4

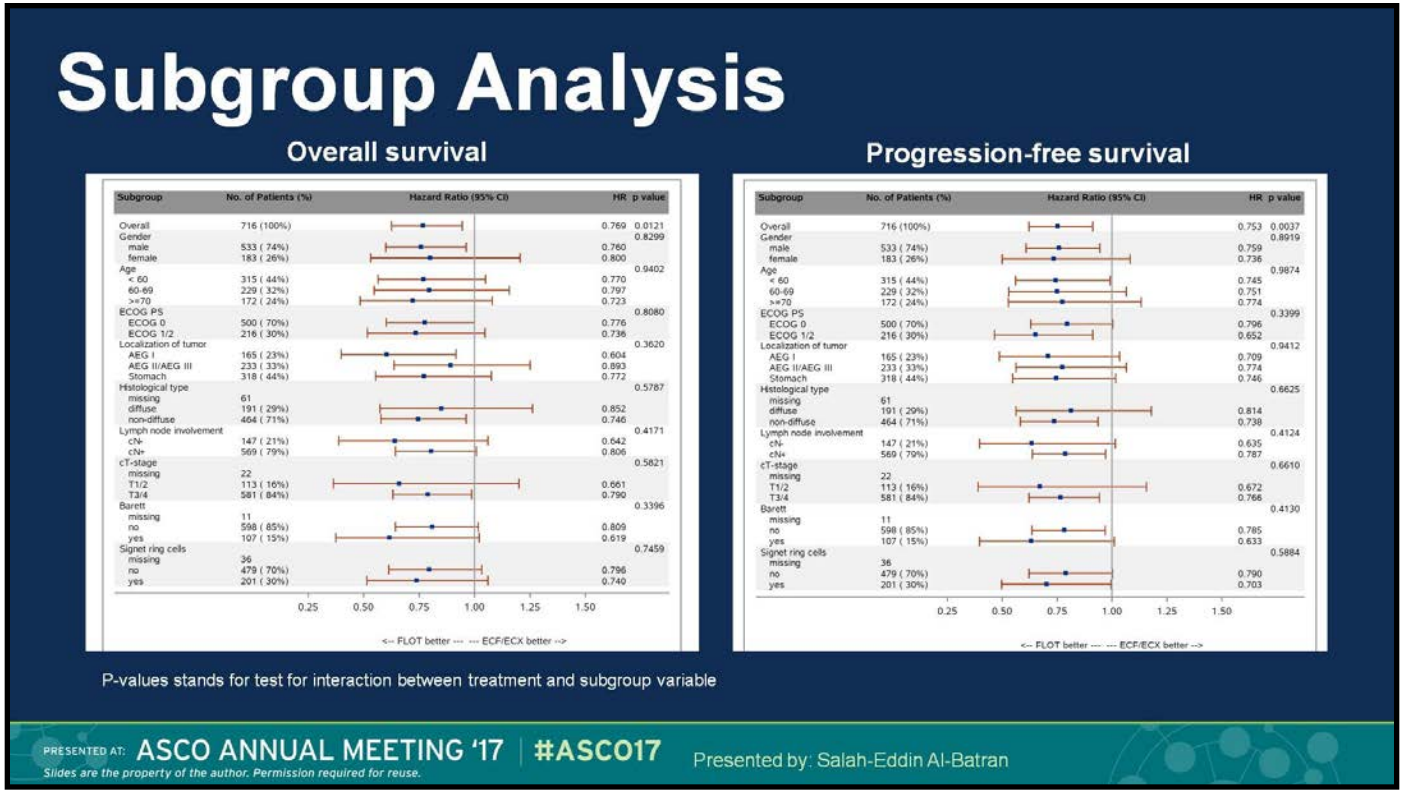
Resultado - Desfecho Primário



CÂNCER GÁSTRICO

FLOT 4

Resultado - Desfecho Primário



CÂNCER GÁSTRICO

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.

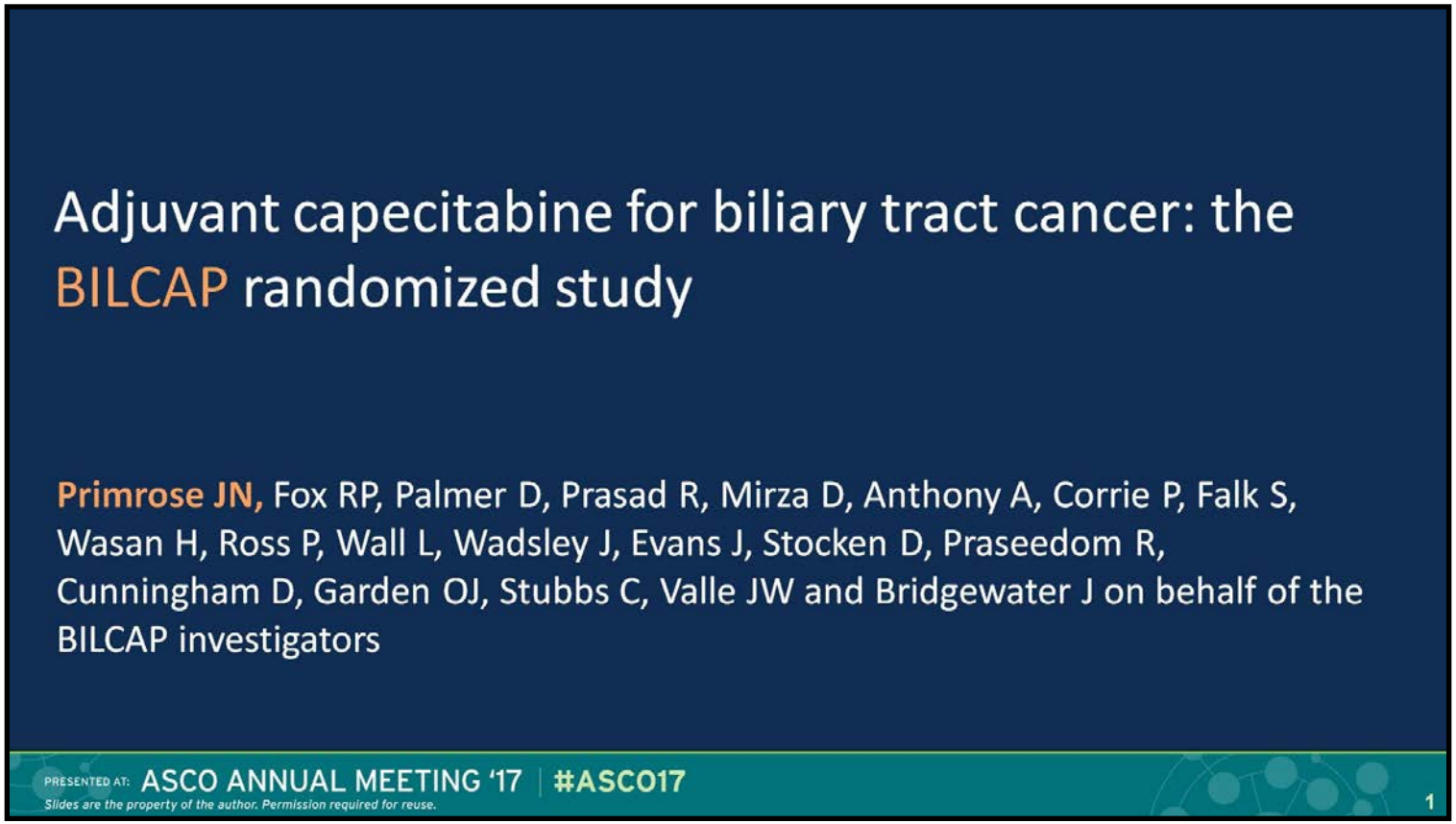
- Não houve aumento de morbidade cirúrgica, mortalidade, necessidade de novas intervenções e tempo de hospitalização.

- **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



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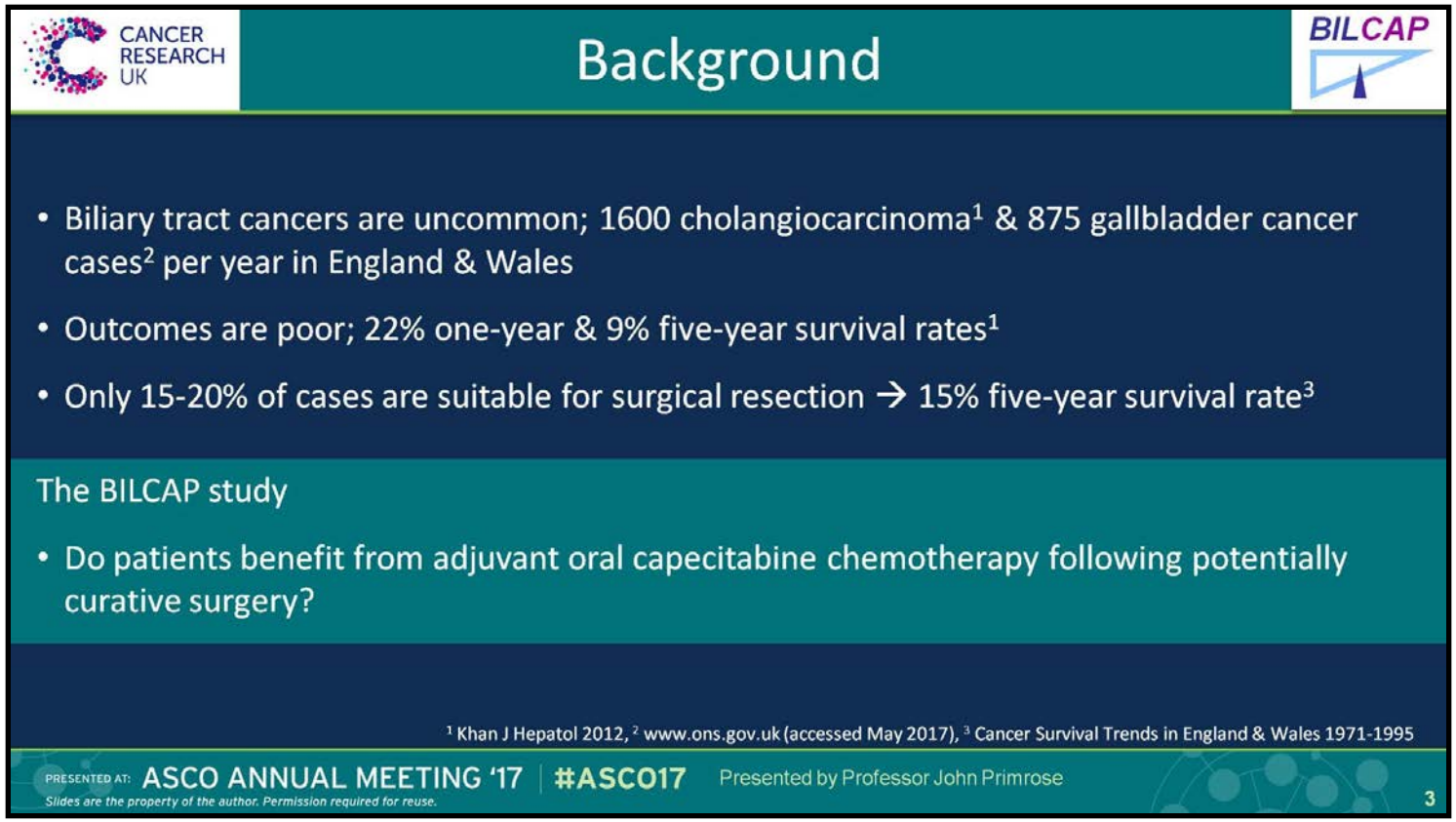
Contexto



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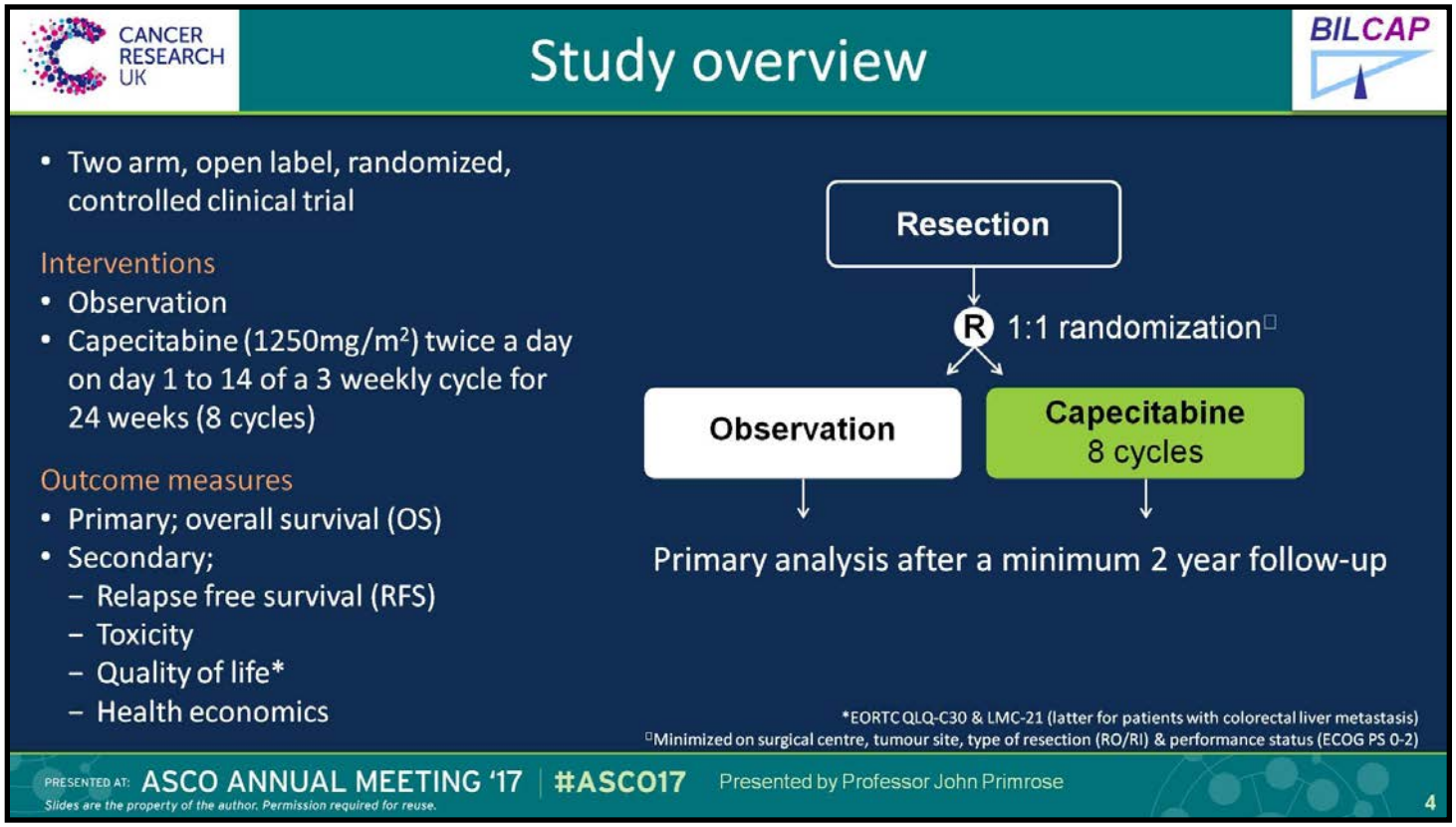
BILCAP

Desenho do Estudo



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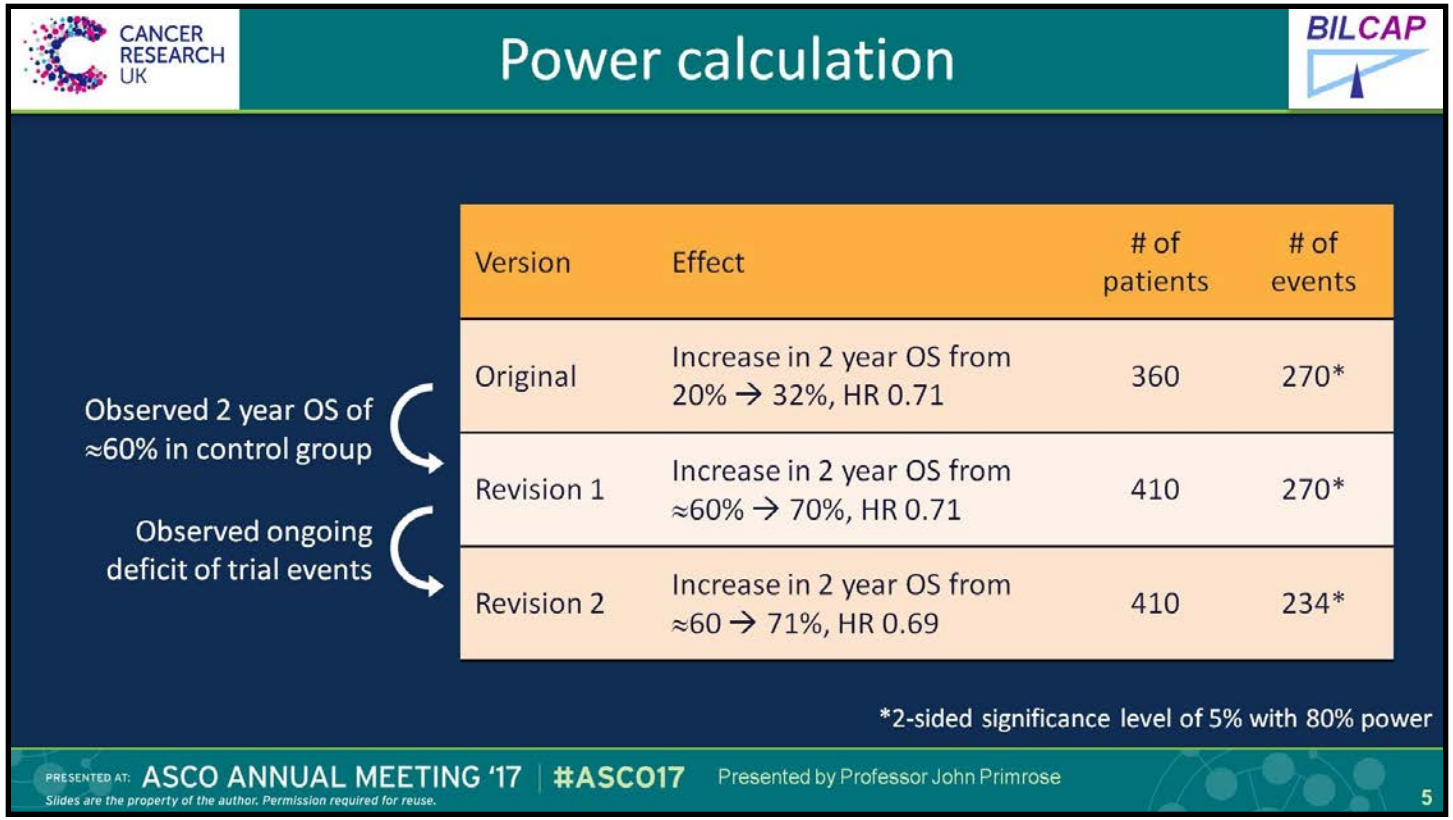
Desenho do Estudo



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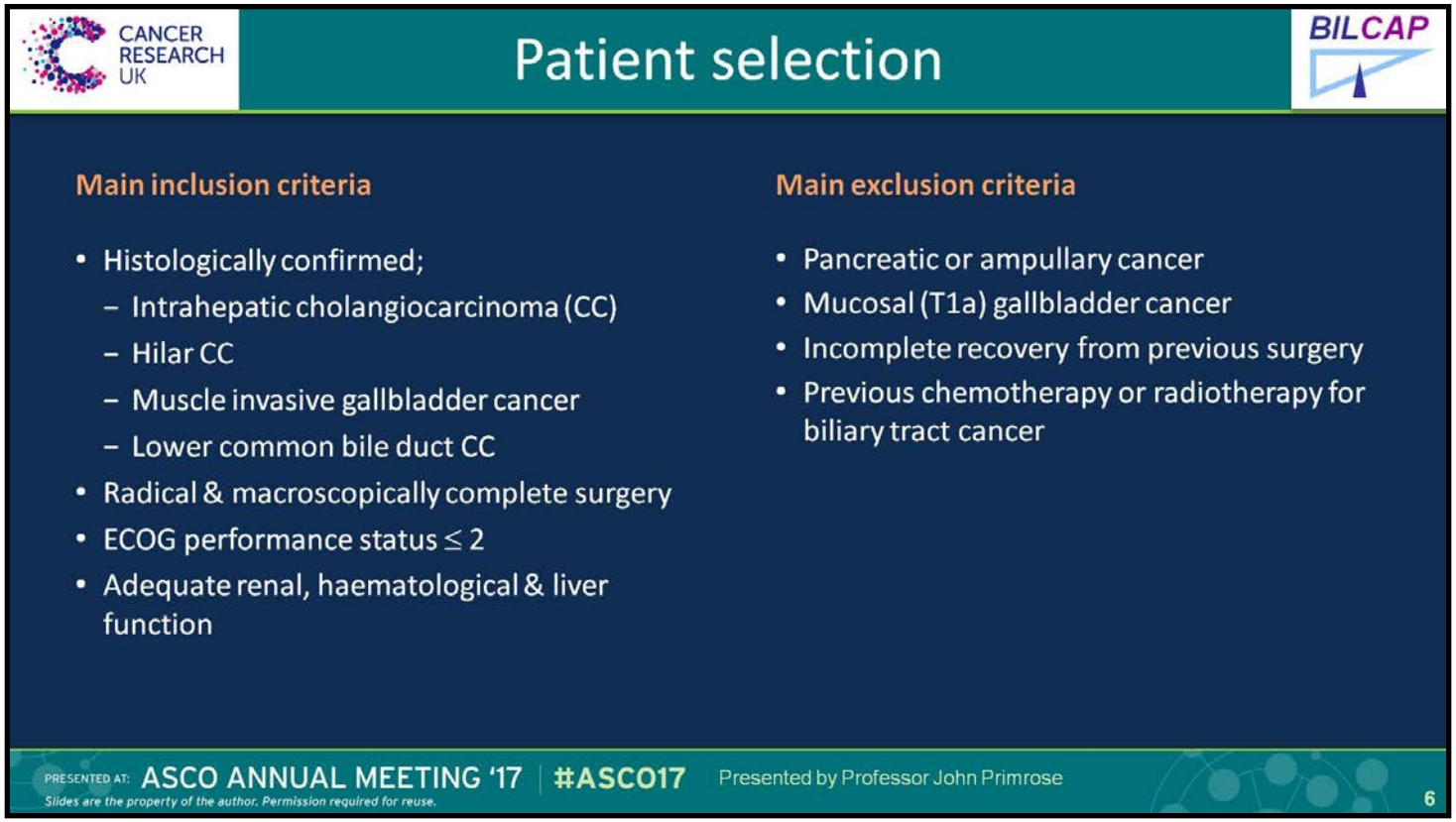
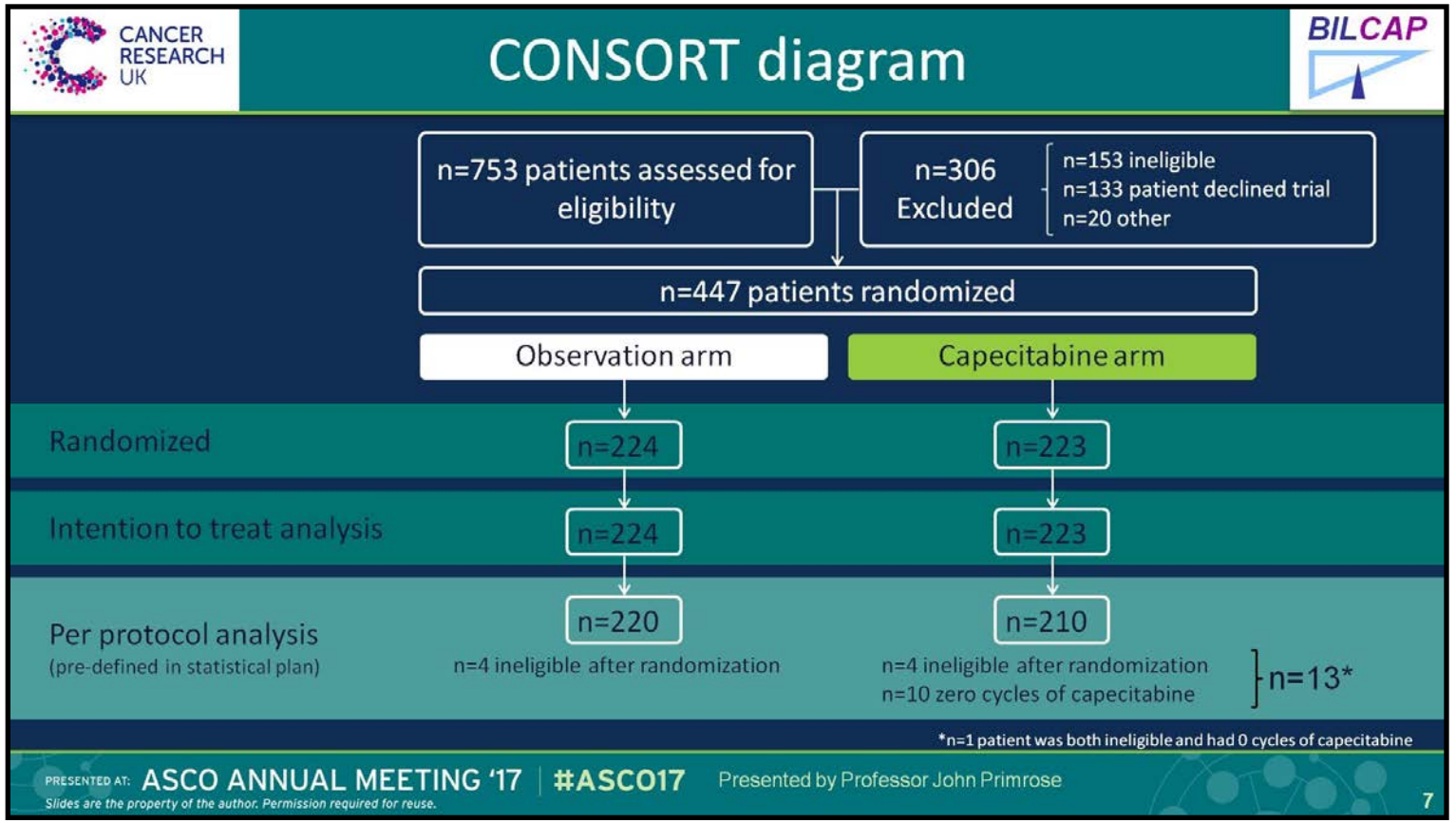
Desenho do Estudo



CÂNCER DE PÂNCREAS E VIAS BILIARES

BILCAP

Resultados



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BILCAP

Resultados

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Baseline characteristics

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		Observation arm (n=224)	Capecitabine arm (n=223)
Gender	Male	113 (50%)	111 (50%)
Age	Median years (inter-quartile range)	64 (55-69)	62 (55-68)
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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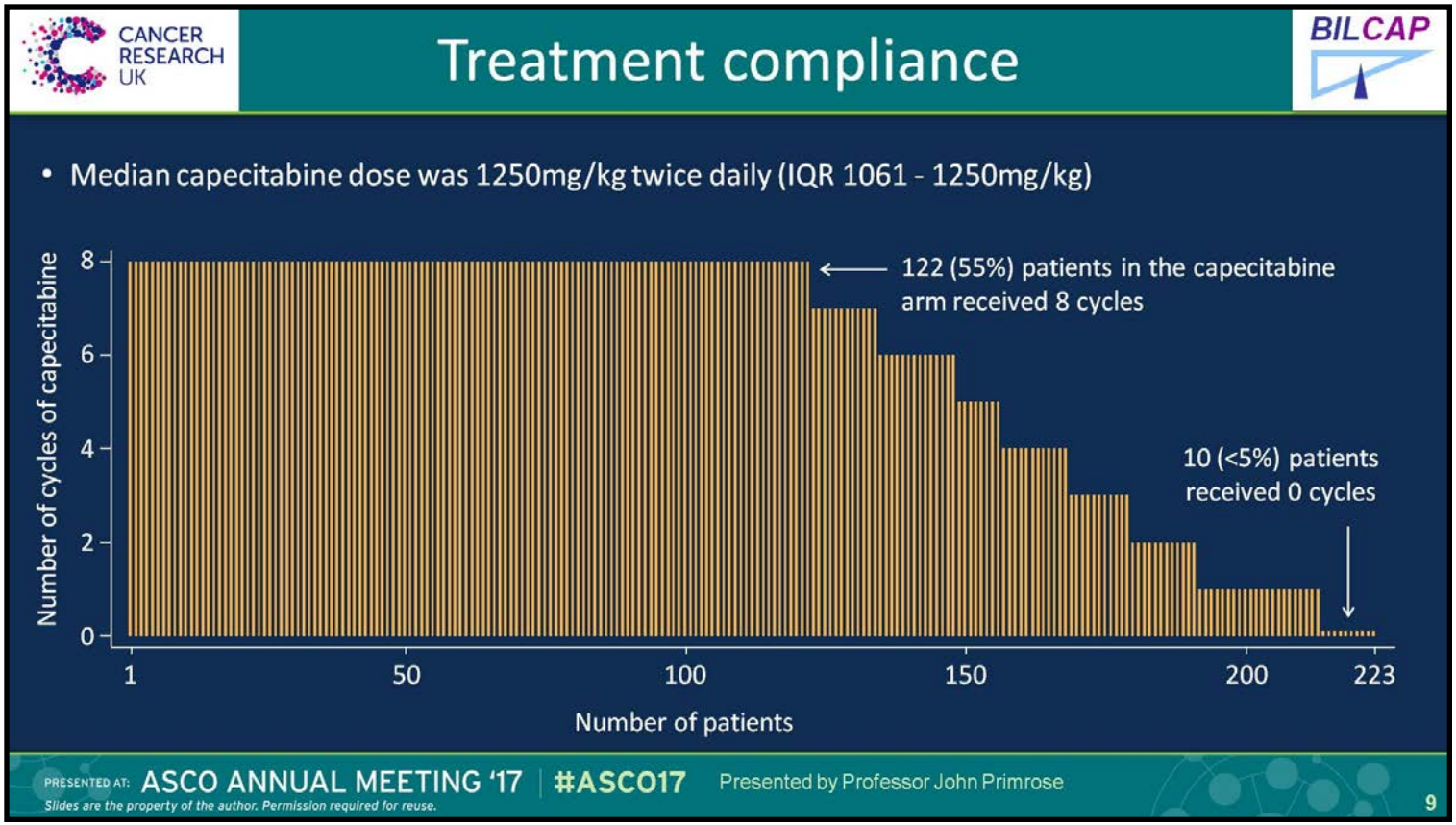
Resultados



CÂNCER DE PÂNCREAS E VIAS BILIARES

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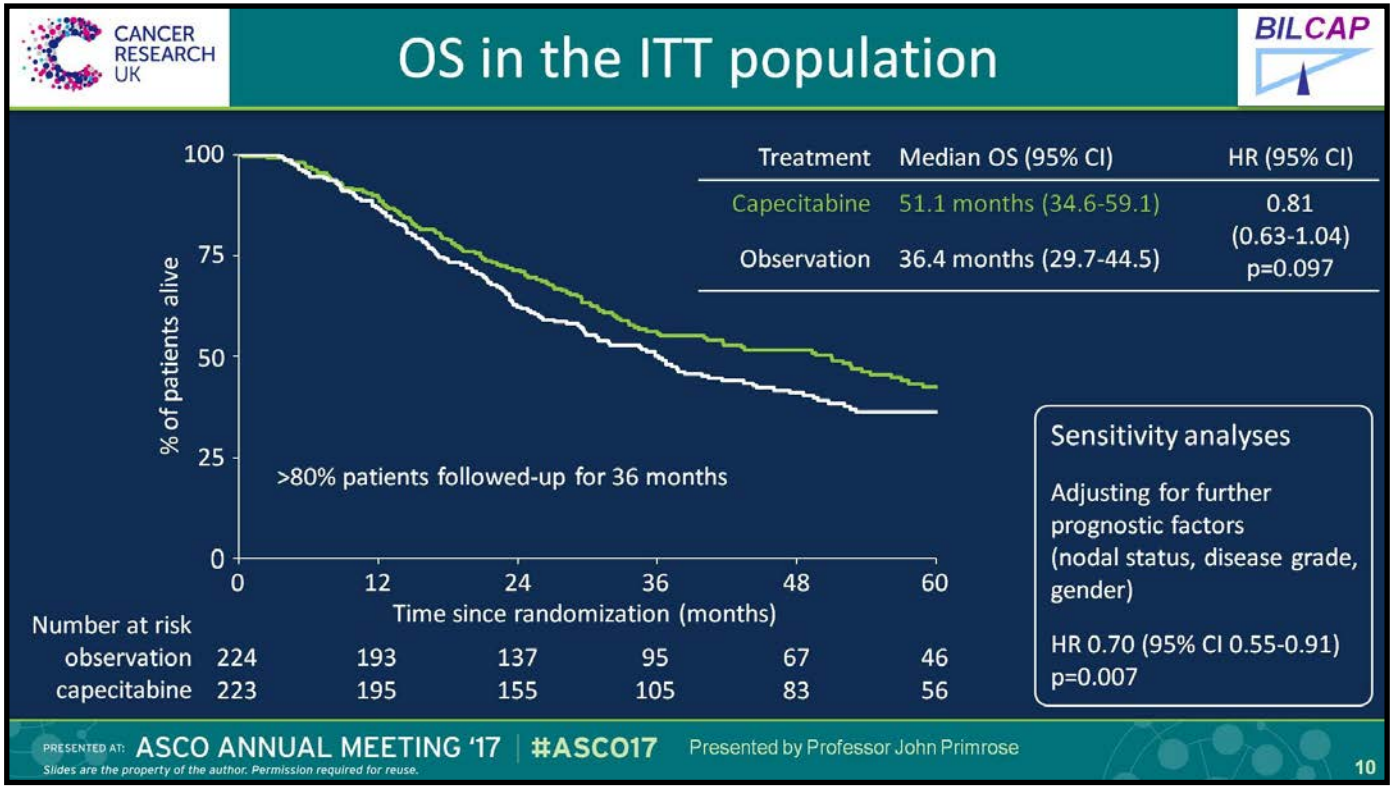
Resultados - Desfecho Primário



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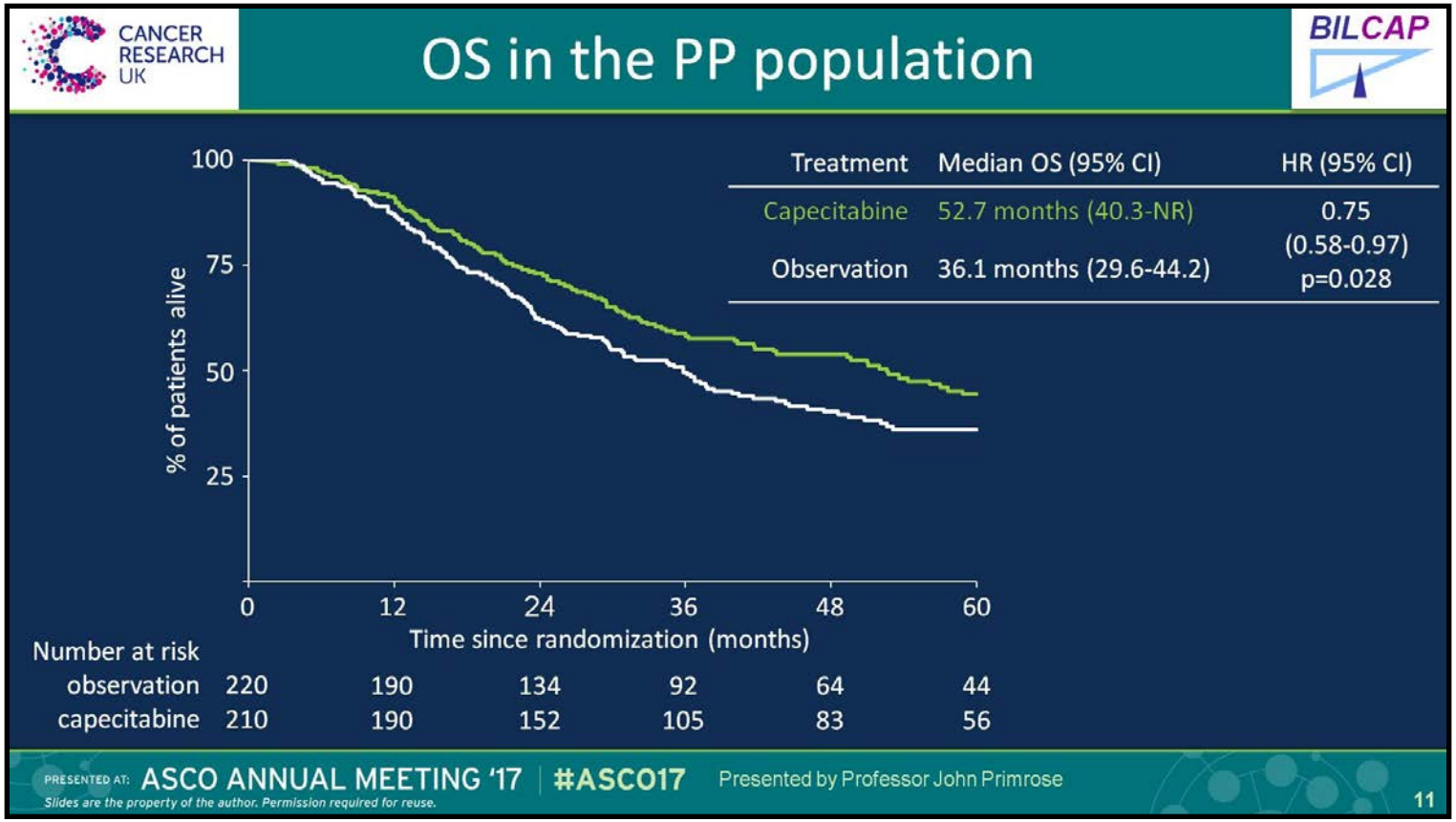
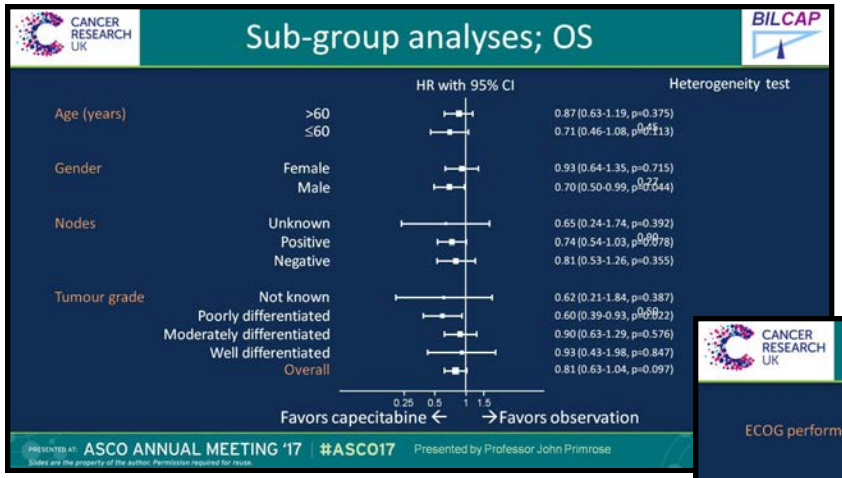
Resultados - Desfecho Primário

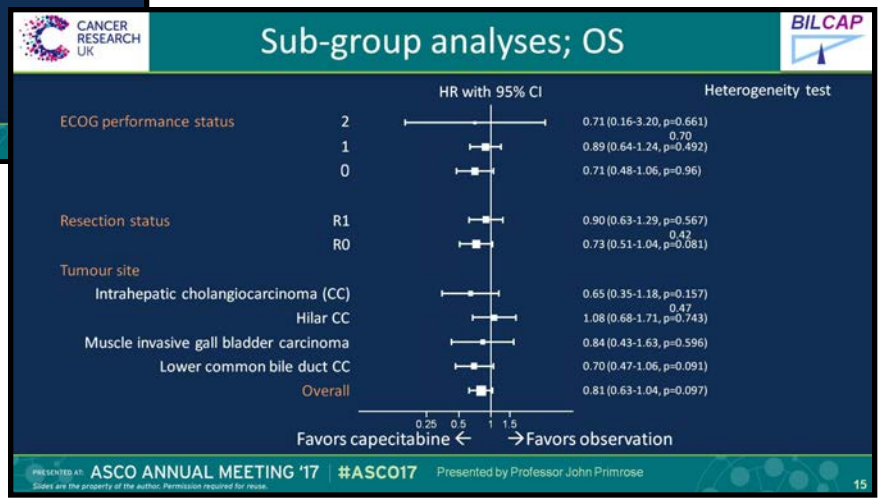


CÂNCER DE PÂNCREAS E VIAS BILIARES

BILCAP

Resultados - Desfecho Primário

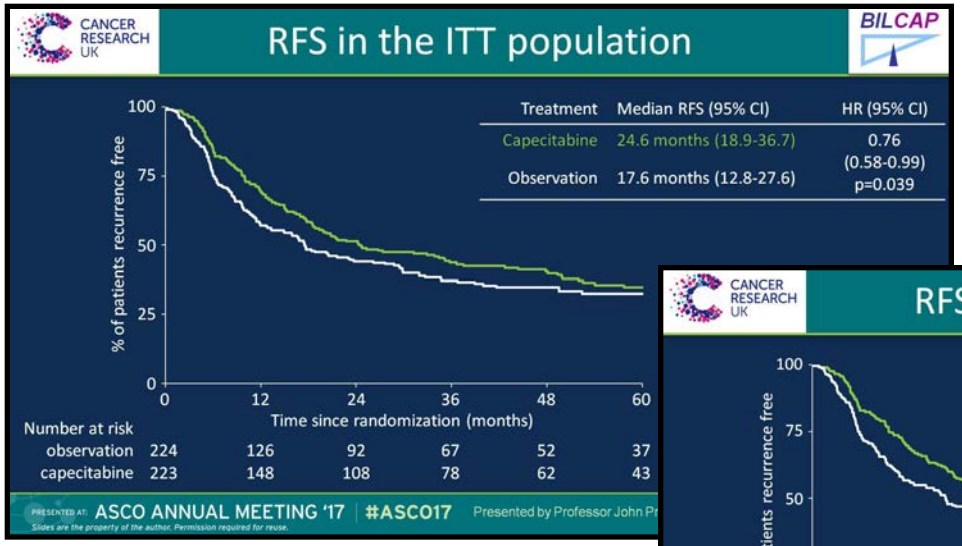


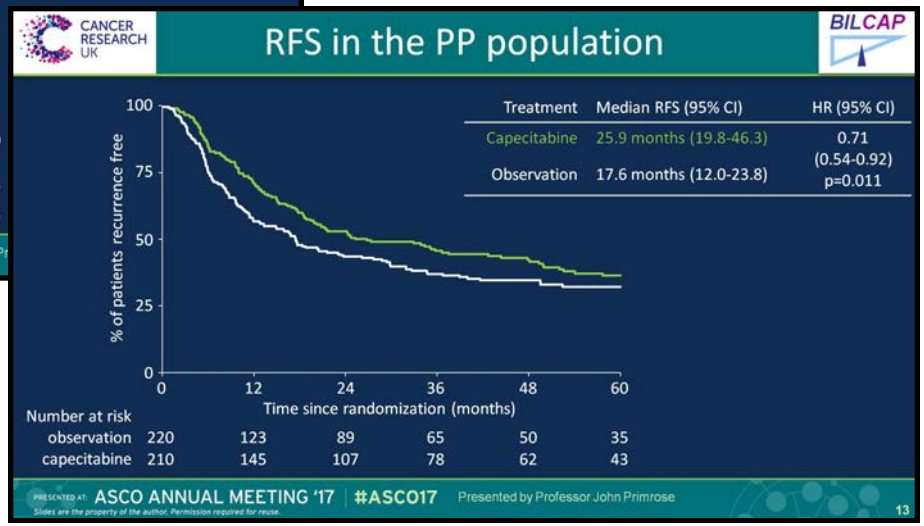


CÂNCER DE PÂNCREAS E VIAS BILIARES

BILCAP

Resultados - Desfechos Secundários

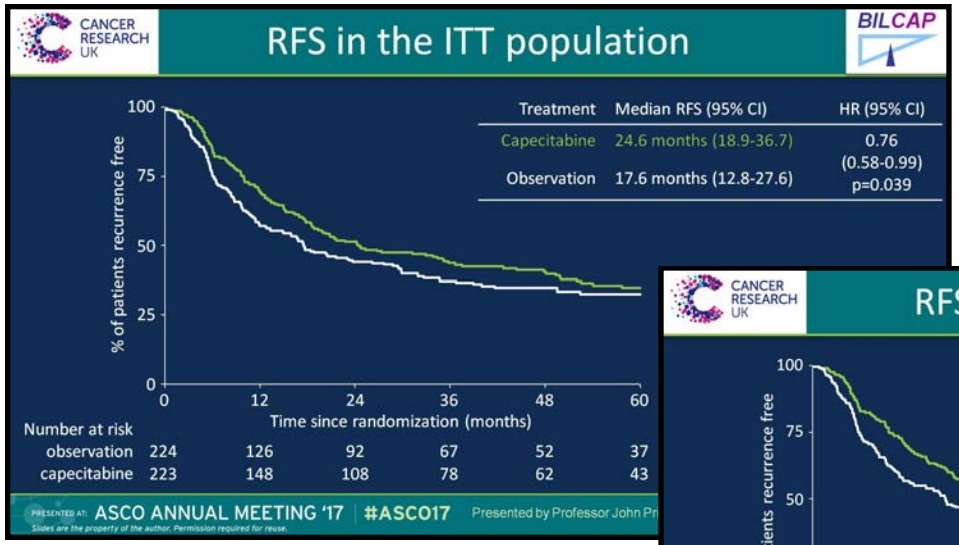


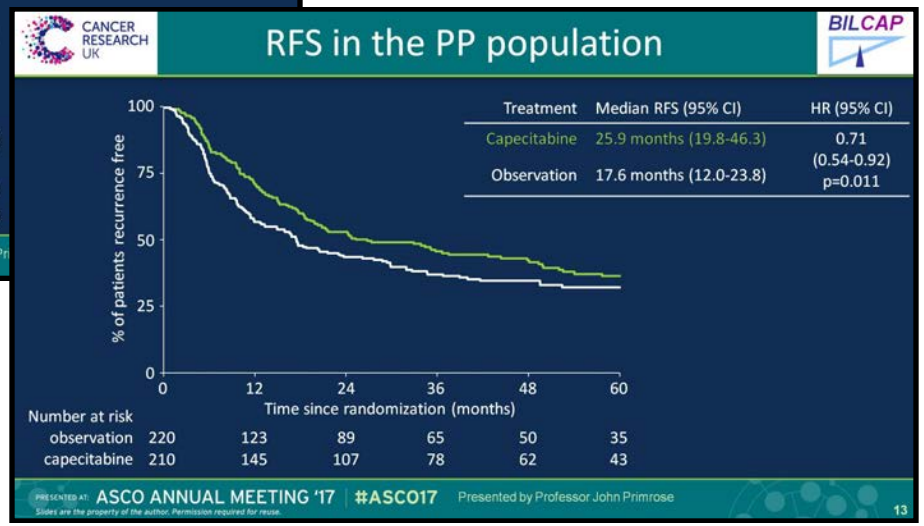


CÂNCER DE PÂNCREAS E VIAS BILIARES

BILCAP

Resultados - Desfechos Secundários





CÂNCER DE PÂNCREAS E VIAS BILIARES

BILCAP

Resultados - Segurança

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Toxicity

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Toxicity type	All grades n	All grades %	Grades 1 & 2 n	Grades 1 & 2 %	Grades 3&4 n	Grades 3&4 %
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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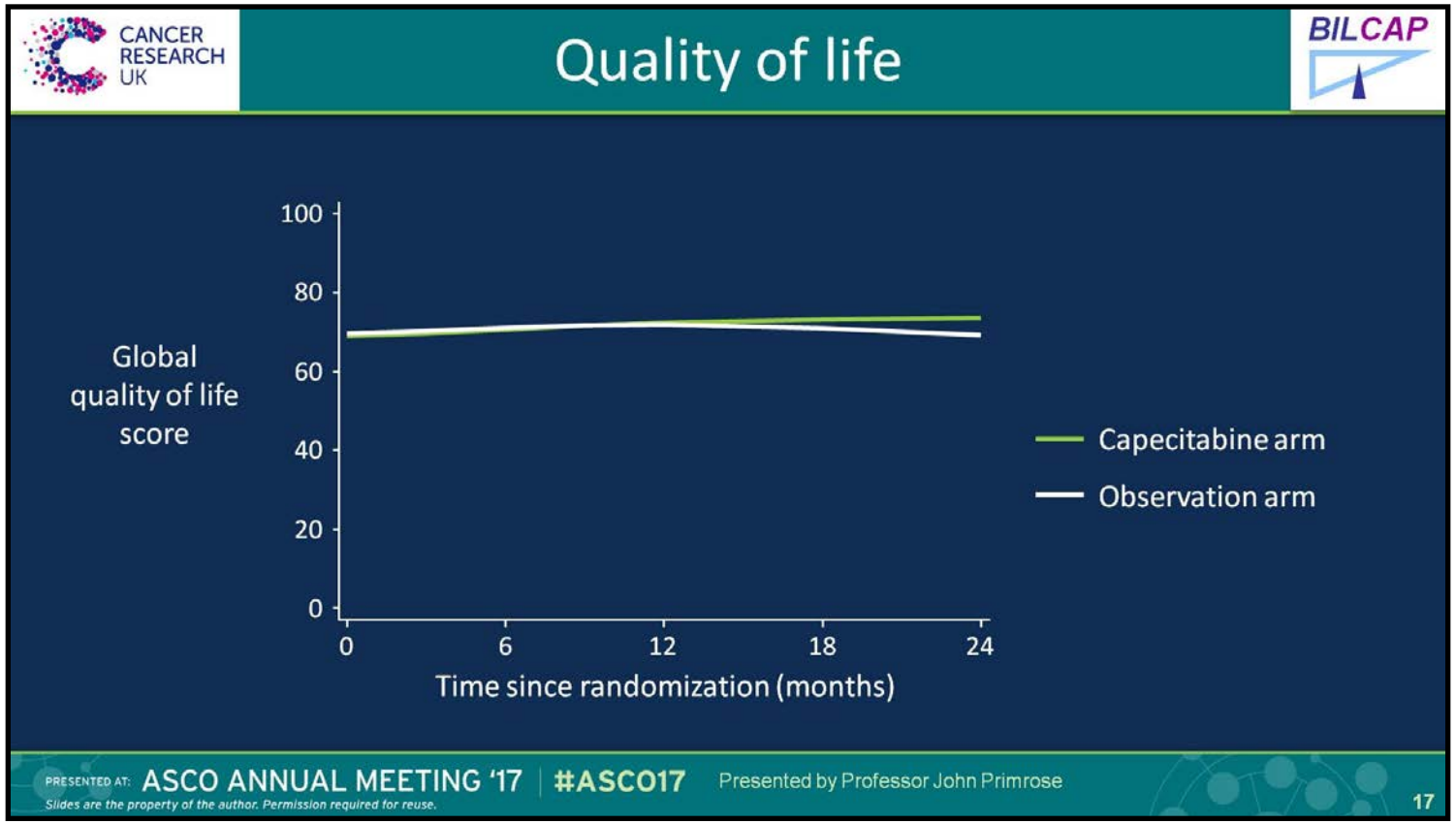
BILCAP

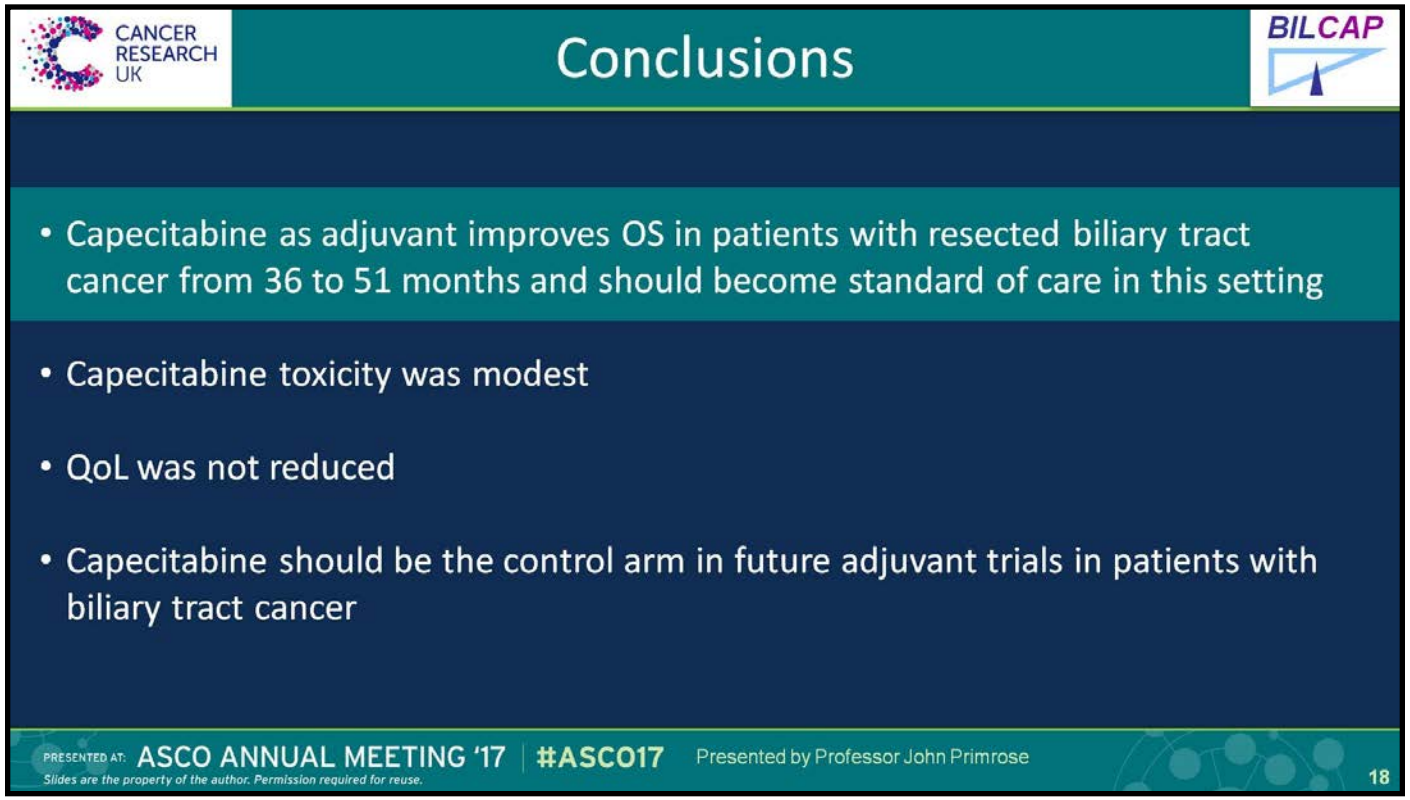
Resultados - Qualidade de Vida



CÂNCER DE PÂNCREAS E VIAS BILIARES

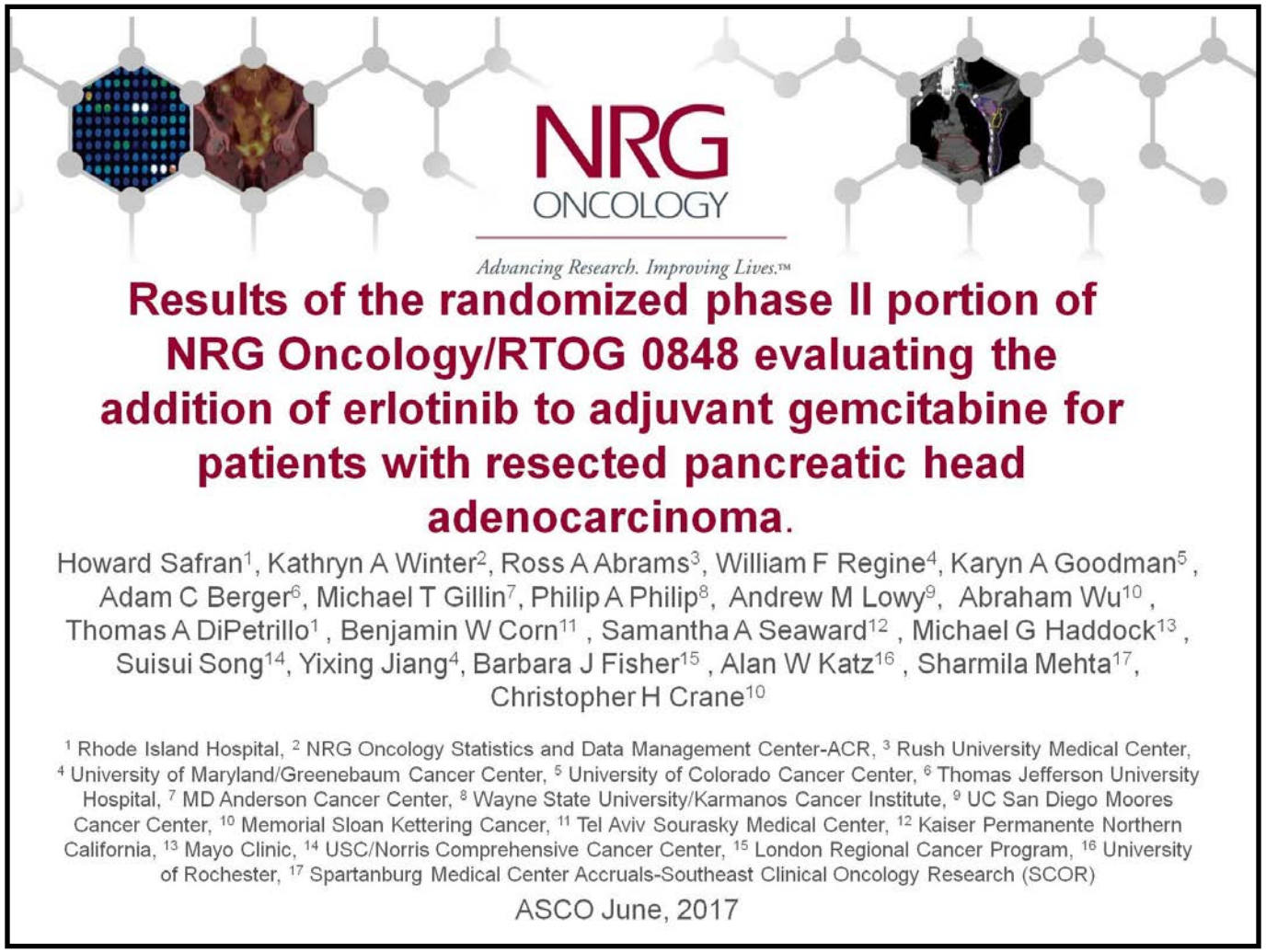
BILCAP

Resultados - Conclusões



CÂNCER DE PÂNCREAS E VIAS BILIARES

RTOG 0848



CÂNCER DE PÂNCREAS E VIAS BILIARES

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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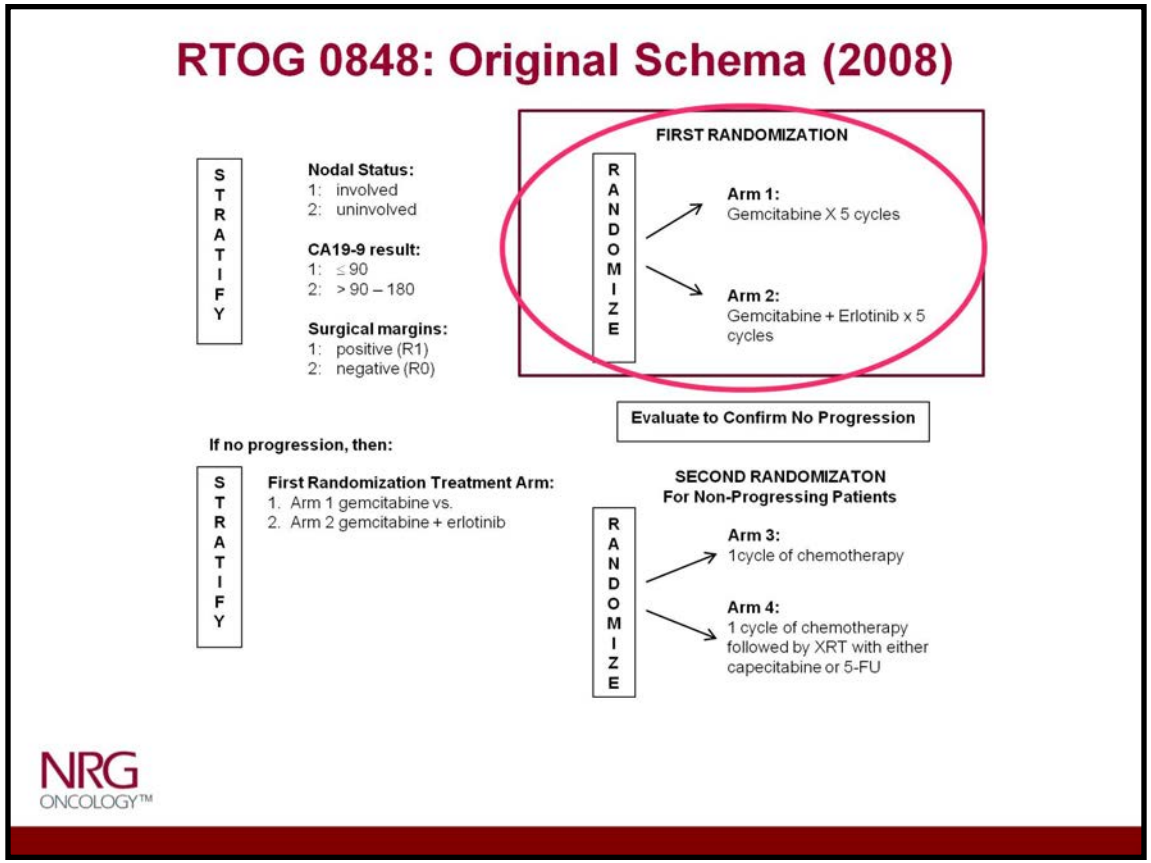
RTOG 0848

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 ≤ 180 units/mL**
- ANC ≥ 1,500 cells/mm^3 , platelets ≥ 100,000 cells/mm^3, serum total bilirubin ≤ 2x ULN, creatinine < 2x ULN, SGOT ≤ 2.5 ULN
- CT of abdomen and chest CT/x-ray

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RTOG 0848

Desenho do Estudo

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 α = 0.05.

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 and15.3 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

Desenho do Estudo

RTOG 0848: Study Objectives

Phase IIR: 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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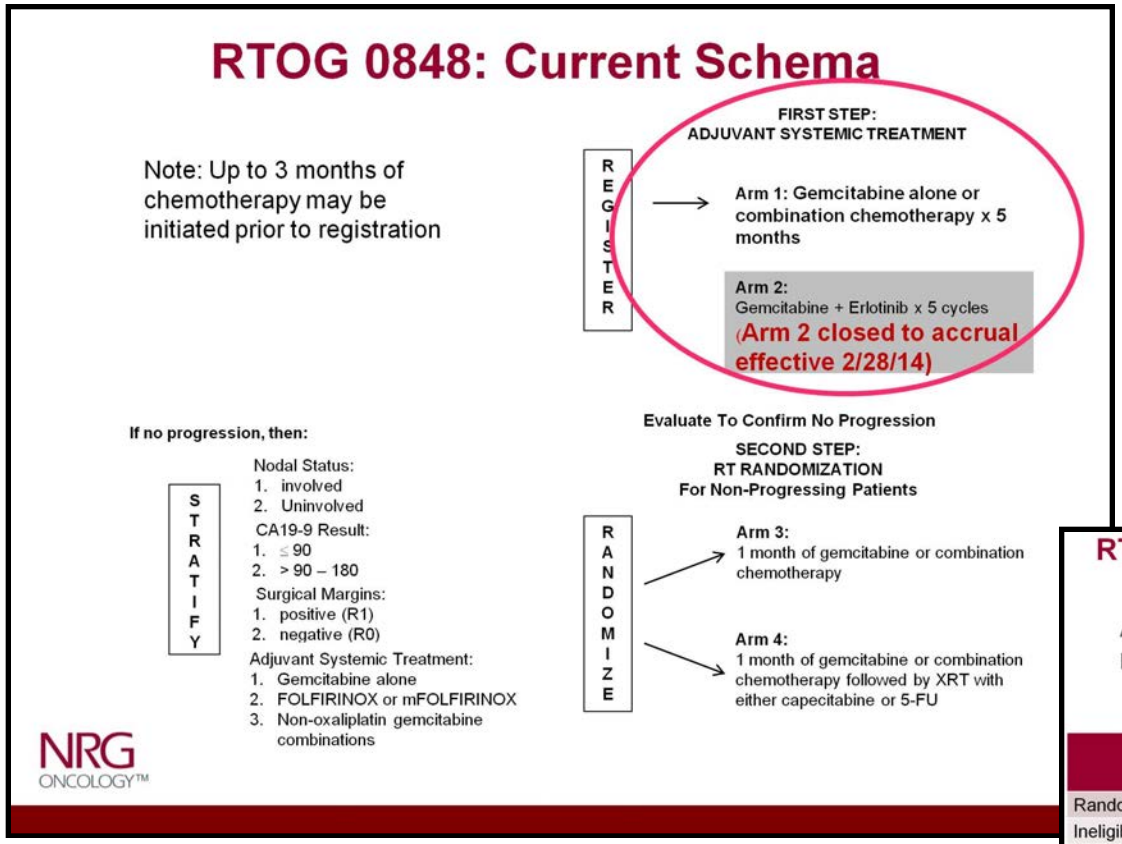
RTOG 0848

Desenho do Estudo



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

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)
Diarrhea	*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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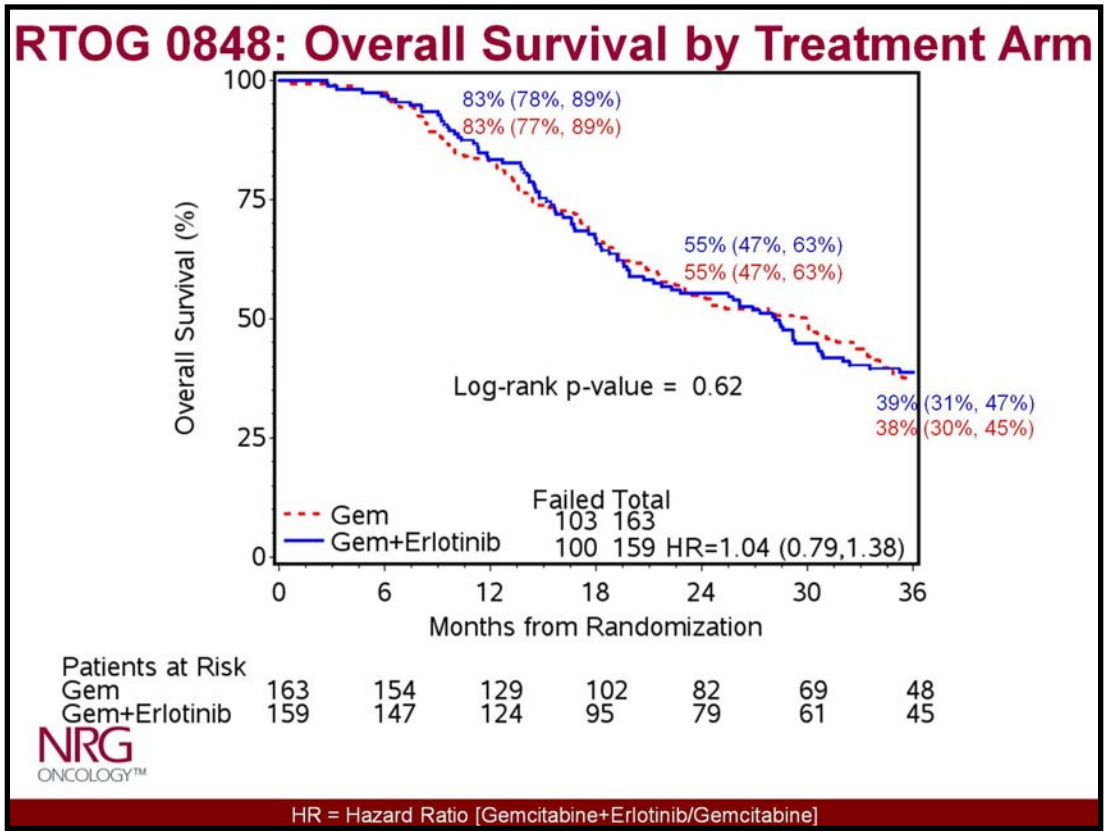
RTOG 0848

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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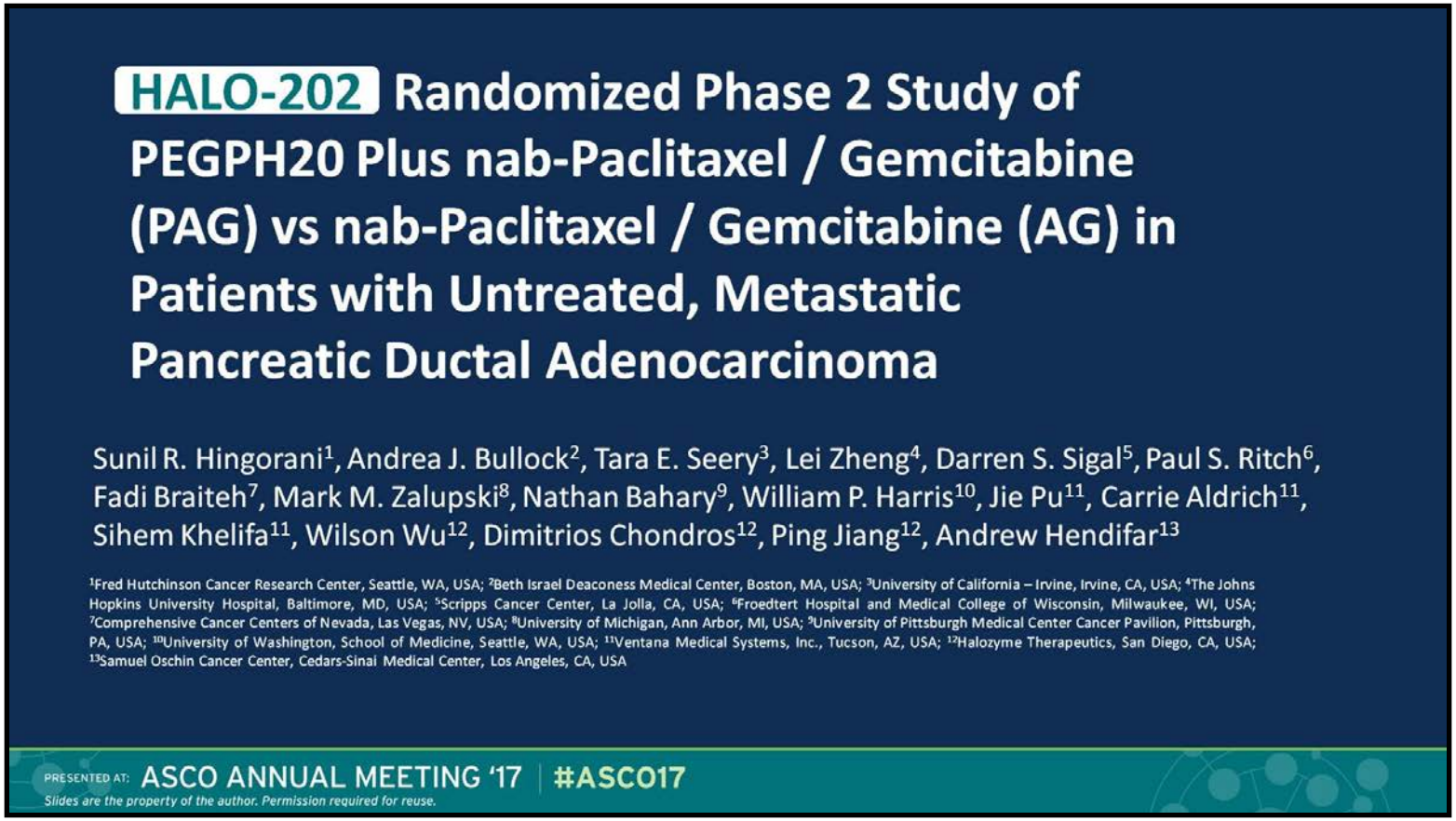
HALO 202



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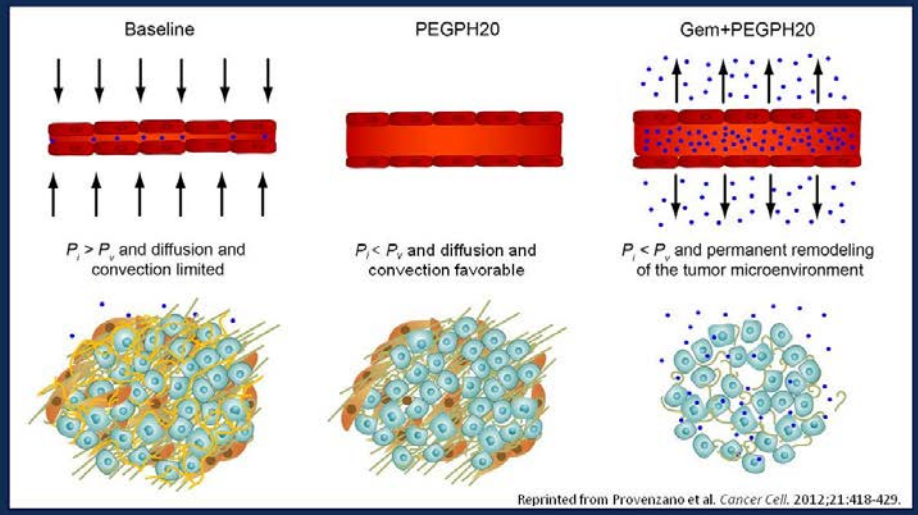
HALO 202

Contexto

PEGPH20 Degrades Hyaluronan in the Tumor Microenvironment

Hyaluronan (HA)

- Naturally occurring, linear, megadalton polysaccharide and major component of the tumor stroma[1]
- 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 PDA[4]



Reprinted from Provenzano et al. *Cancer Cell*. 2012;21:418-429.

PEGPH20 (pegvorhyaluronidase alfa)

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

1. Minchinton AI, 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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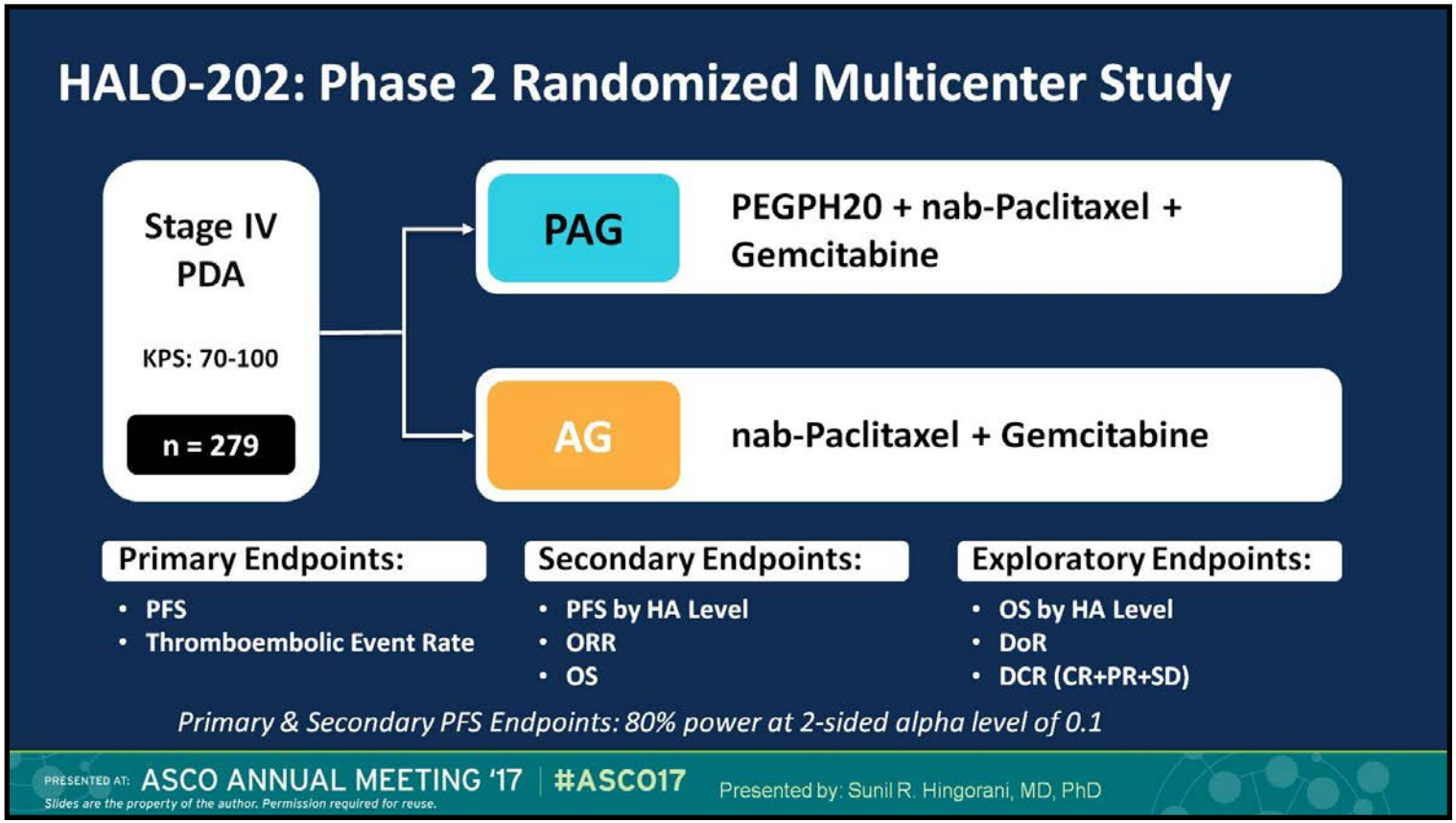
Desenho do Estudo



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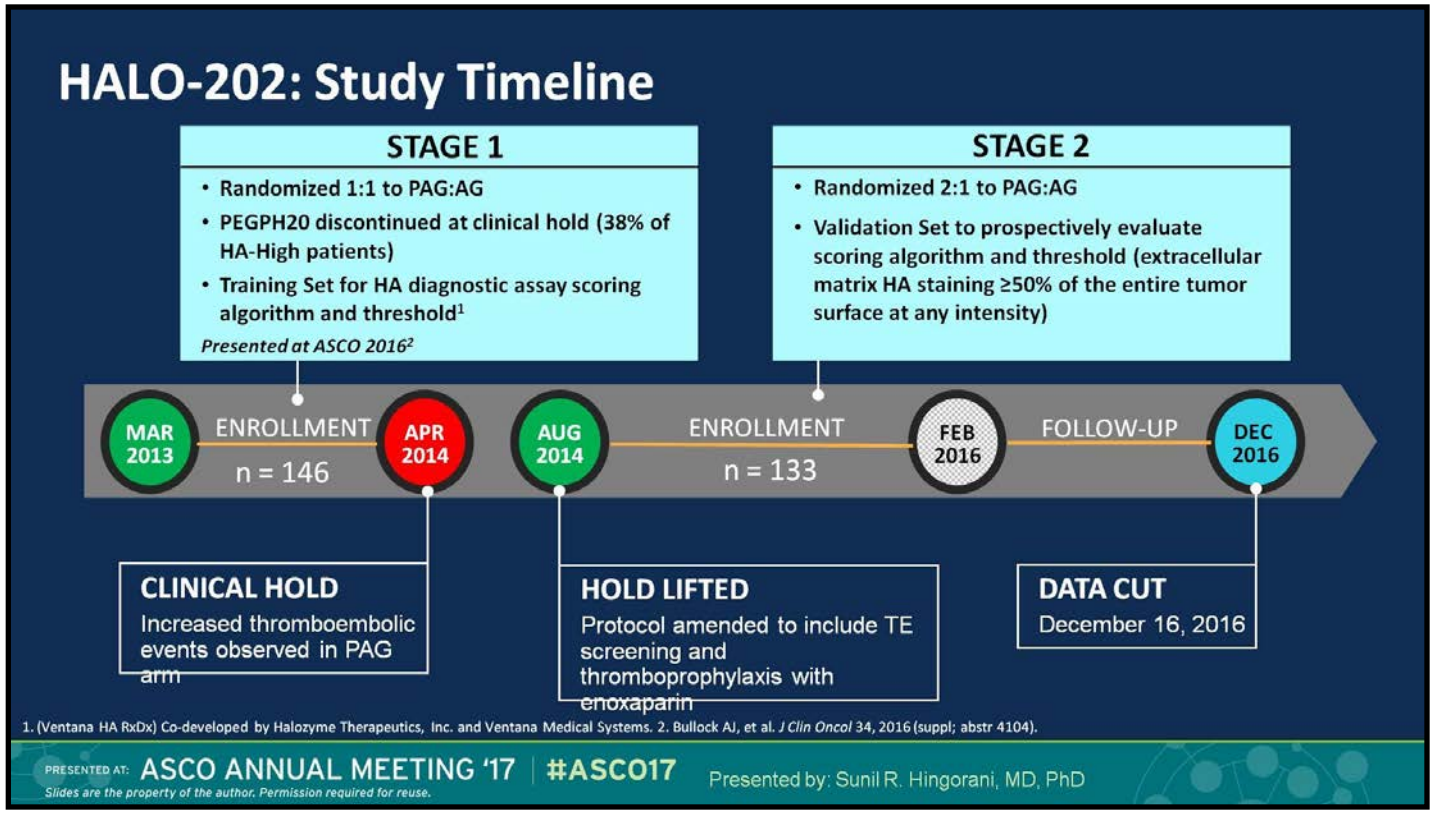
Desenho do Estudo



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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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HALO 202

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 ± SD	64 ± 10	65 ± 9	66 ± 9	67 ± 7
	≥65, n (%)	88 (53)	62 (55)	33 (67)	22 (63)
Gender, n (%)	Male	101 (61)	55 (49)	26 (53)	15 (43)
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)

[a]In 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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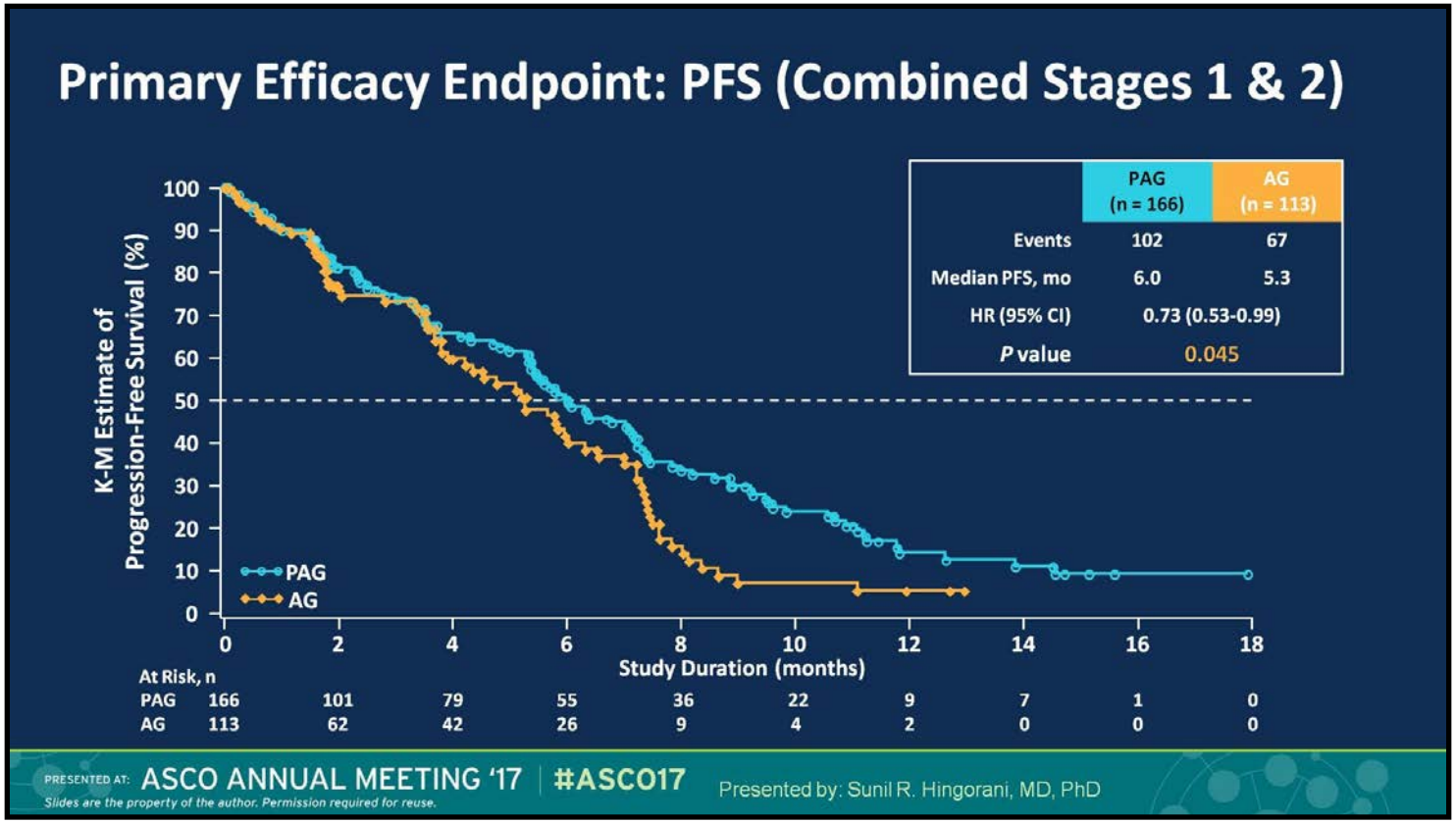
HALO 202

Resultados - Desfecho Primário



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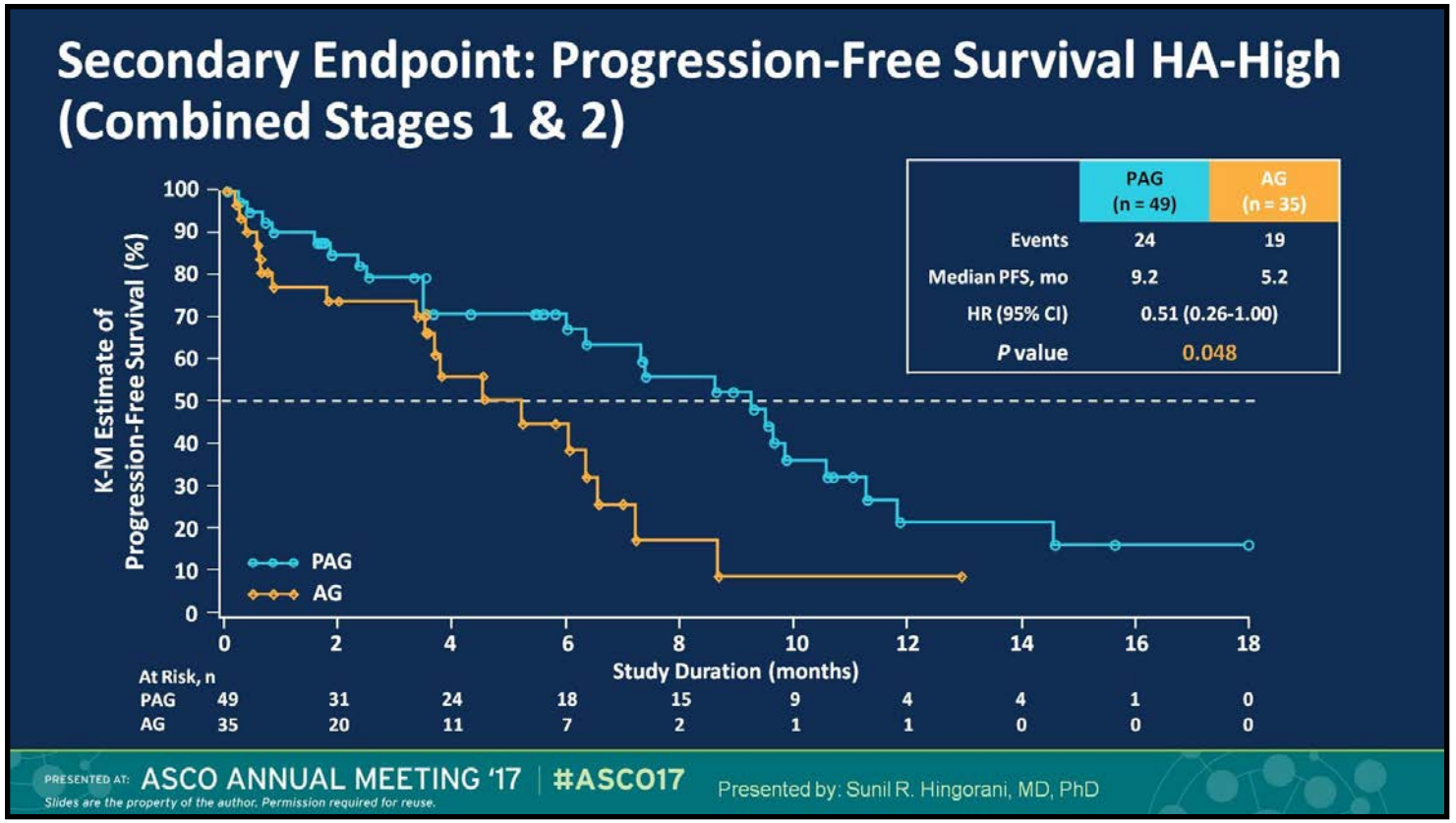
Resultados - Desfecho Secundário



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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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Resultados - Segurança

Treatment-Related Adverse Events in ≥25% of Patients

	PAG (n=160)		AG (n=100)	
n (%)	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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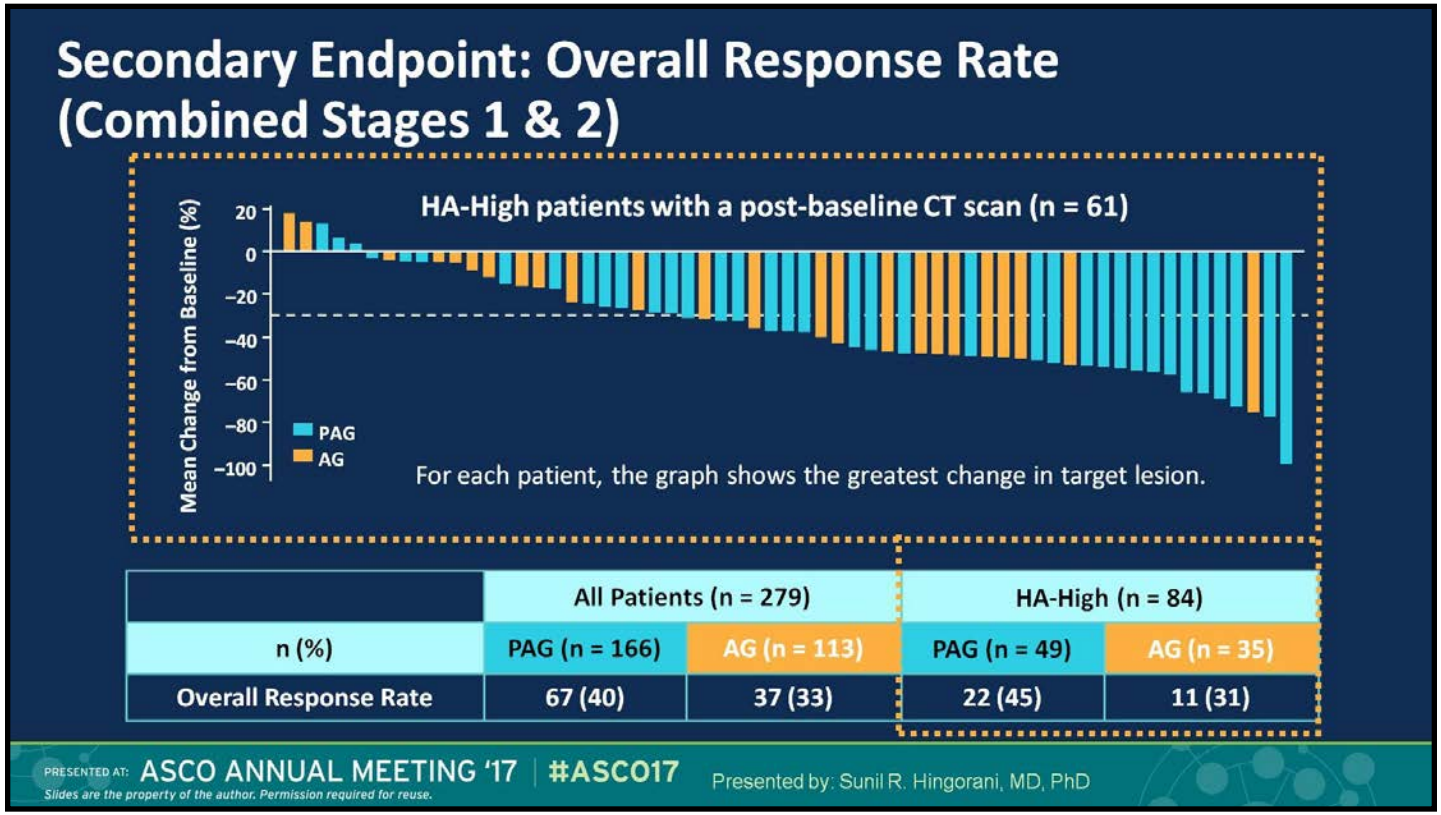
Resultados - Desfecho secundário



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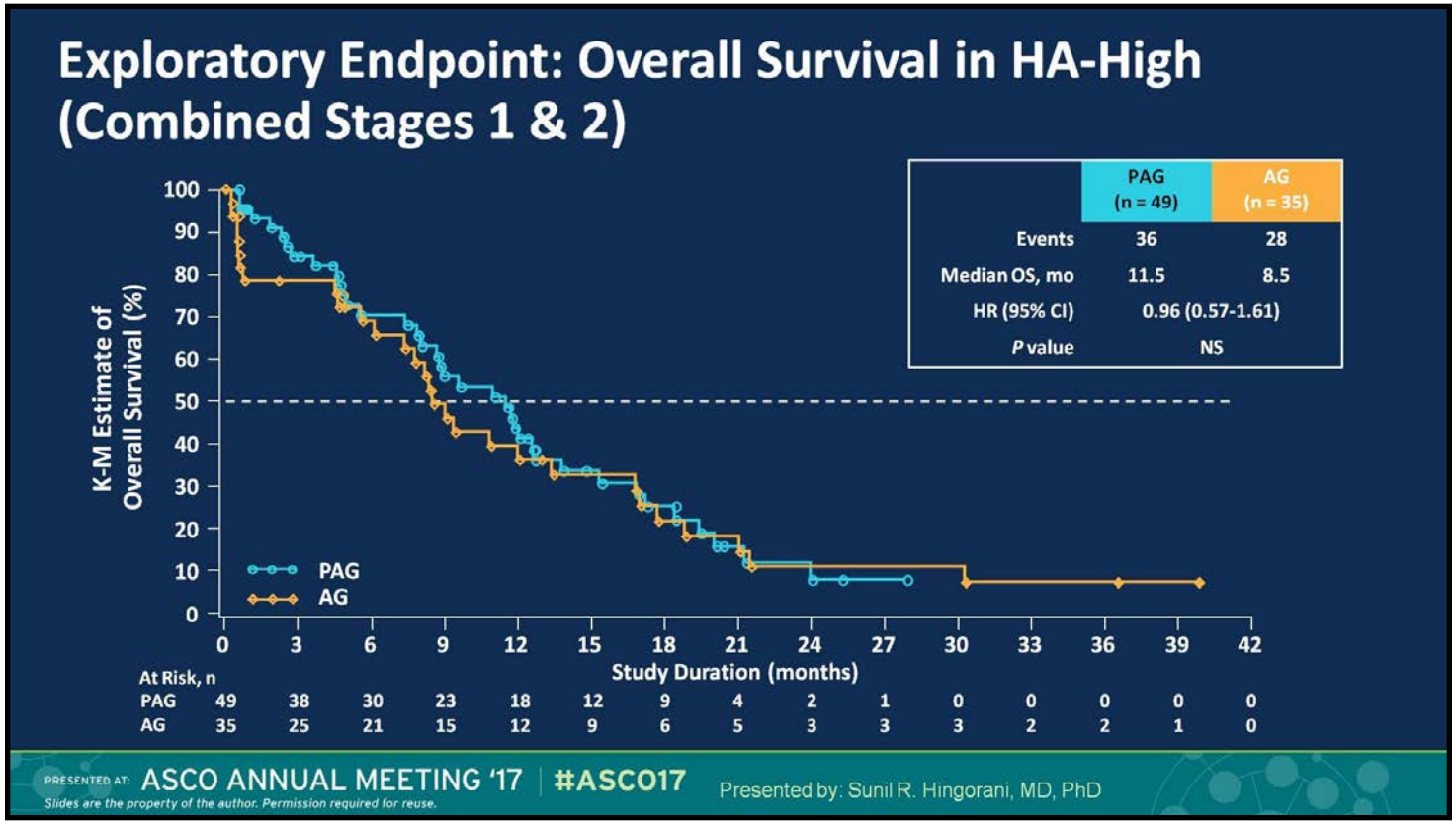
Resultados - Desfecho secundário



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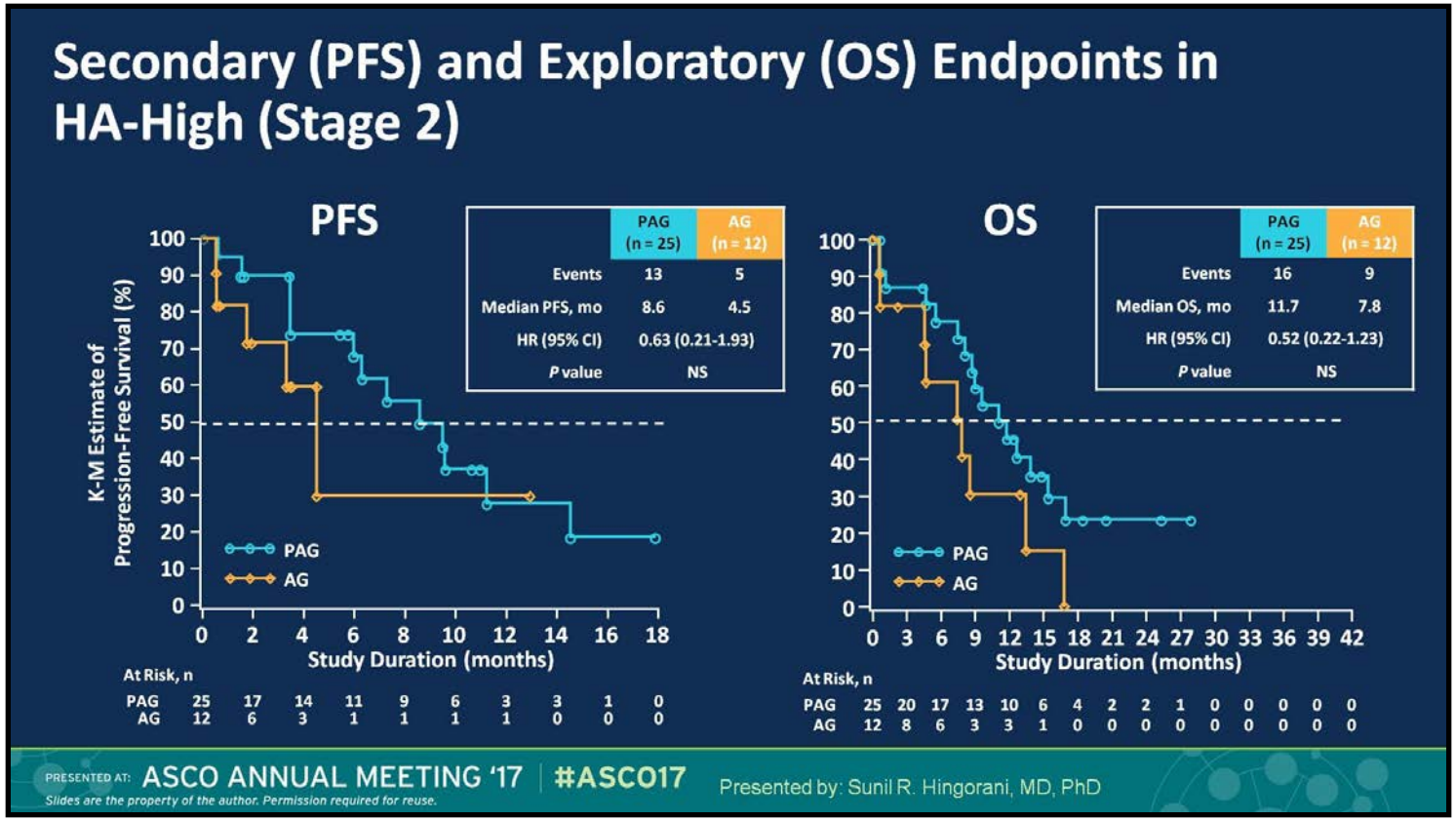
Resultados - Desfecho secundário



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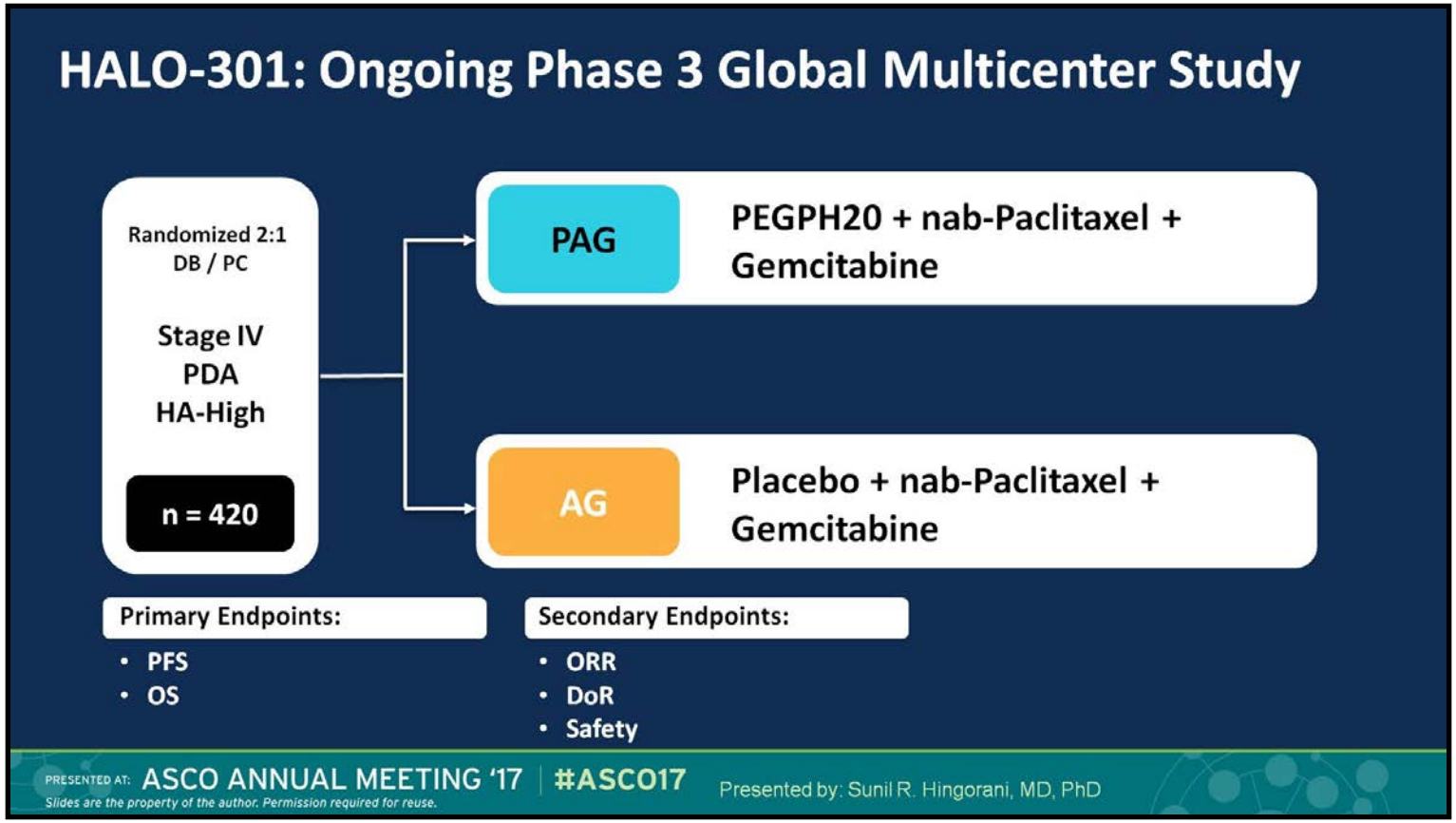
Resultados - Desfecho secundário



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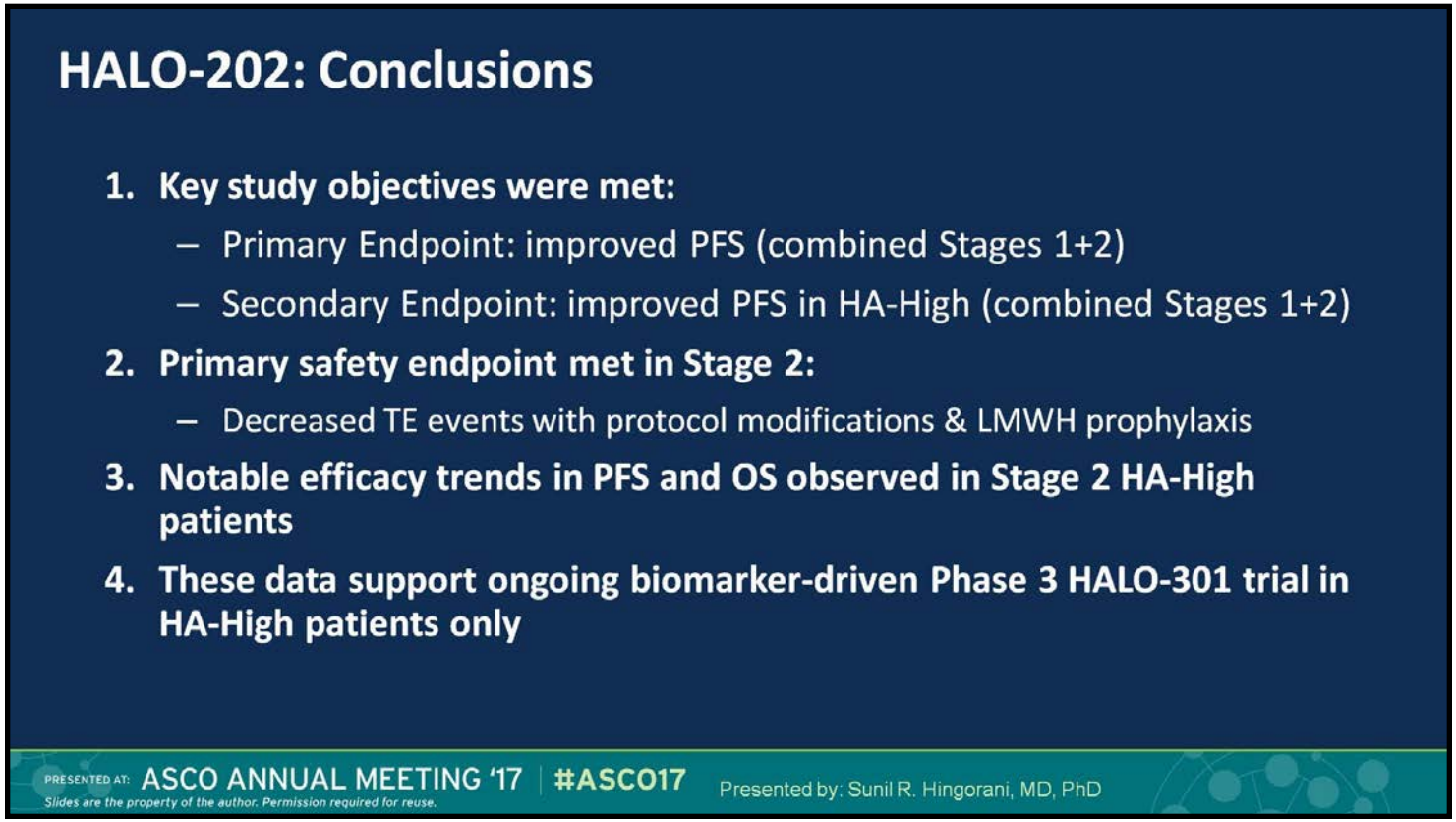
Conclusões



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