





Destiques ASCO 2017

○ Apresentação

A Sociedade Americana de Oncologia Clínica (ASCO) foi fundada em 1964 e, desde então, tornou-se a principal organização voltada para profissionais que lidam diariamente com o câncer em todo o mundo.

Sua missão é promover o combate à doença, habilitando seus membros a oferecer o que existe de melhor em termos de tratamento para os seus pacientes. Para isso, investe maciçamente em pesquisa e é reconhecida por promover educação continuada de alto nível.

Todos os anos, a ASCO organiza seu Congresso, reunindo os mais renomados profissionais do mundo em todas as áreas da Oncologia. O contato direto com profissionais de destaque, o intenso compartilhamento de informações, assim como a troca de experiências cotidianas criam um ambiente favorável para o aprendizado.

O Grupo Oncoclínicas não poderia deixar de estar presente nesse evento, trazendo para seus pacientes e parceiros todas as novidades apresentadas. Em linha com nosso objetivo de nos transformar no melhor grupo de Oncologia do país, estivemos presentes com mais de 80 Oncologistas em Chicago, coletando os principais e mais atualizados dados científicos.

E por meio do Instituto Oncoclínicas conseguimos compilar as informações mais relevantes, transformando-as em um *slide kit* didático, versátil e inovador. É com prazer que disponibilizamos a vocês, nossos parceiros, o “Melhor da ASCO 2017”.

Instituto Oncoclínicas



CÂNCER COLORRETAL



CONFLITOS DE INTERESSE

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

ROTEIRO

1. COLABORAÇÃO IDEA

- IDEA FRANCE
- TOSCA TRIAL
- SCOT STUDY
- ANÁLISE COMBINADA

2. CALGB/SWOG 80405

- ANÁLISES TRANSLACIONAIS E CORRELATIVAS

3. NOVAS ESTRATÉGIAS TERAPÊUTICAS PARA A DOENÇA METASTÁTICA

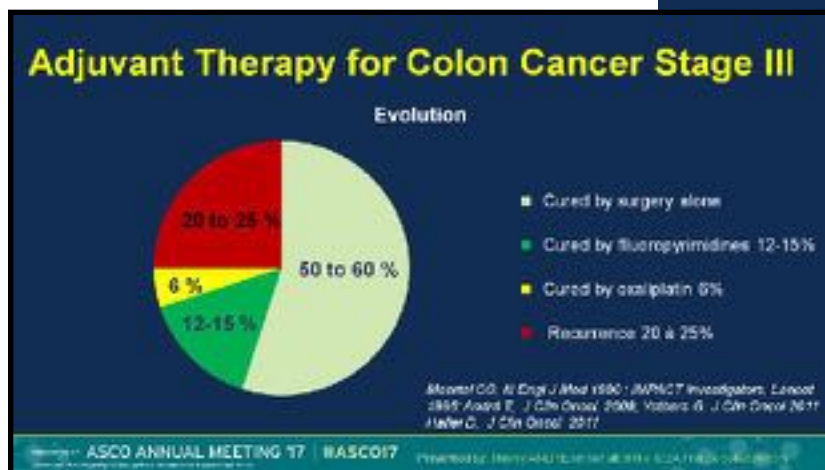
- SWOG S 1406 USO DO VEMURAFENIBE PARA MUTAÇÃO DO BRAF
- SUNSHINE: SUPLEMENTAÇÃO DE VITAMINA D
- FOXFIRE: RADIOTERAPIA SELETIVA INTERNA (SIRT)
- FRESCO TRIAL: SEGURANÇA E EFICÁCIA DO FRUQUINTINIBE

CÂNCER COLORRETAL COLABORAÇÃO IDEA

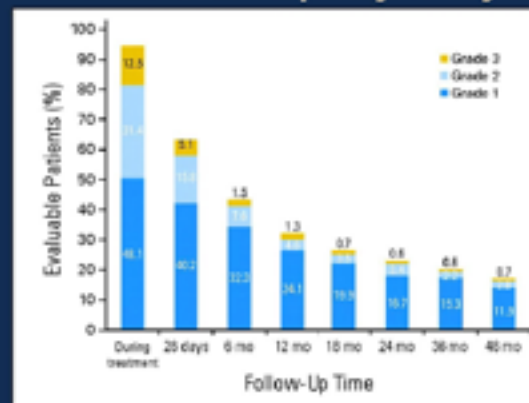


COLABORAÇÃO IDEA

- Câncer colorretal estágio III
 - Quimioterapia adjuvante baseada em oxaliplatina por 6 meses é o tratamento padrão atual (FOLFOX, CAPOX).
- Oxaliplatina no tratamento adjuvante
 - 1/3 do benefício absoluto de sobrevida.
 - Associada a neuropatia cumulativa dose-dependente e residual: 12,5% de neuropatia grau 3 em 6 meses de FOLFOX



The BIG Problem: Large Proportion of Patients with Residual Neuropathy at 4 yrs



COLABORAÇÃO IDEA

- Colaboração acadêmica internacional (12 países) entre membros de seis estudos clínicos randomizados.
- Objetivo: avaliar a não inferioridade de 3 vs. 6 meses de tratamento adjuvante com quimioterapia baseada em oxaliplatina através de uma análise combinada dos seis ECR's.

IDEA Trials Summary			
Trial	Regimen(s)	Stage III Colon Cancer Patients*	Enrolling Country
TOSCA	CAPOX or FOLFOX4	2402	Italy
SCOT	CAPOX or mFOLFOX6	3983	UK, Denmark, Spain, Australia, Sweden, New Zealand
IDEA France	CAPOX or mFOLFOX6	2010	France
C80702	mFOLFOX6	2440	US, Canada
HORG	CAPOX or FOLFOX4	708	Greece
ACHIEVE	CAPOX or mFOLFOX6	1291	Japan

*Only stage III colon cancer patients were included in the pooled primary analysis

Presented at: ASCO ANNUAL MEETING '17 #ASCO17 Presented by: Qian Shi, PhD on behalf of IDEA collaborators

COLABORAÇÃO IDEA

IDEA FRANCE



Oxaliplatin-based chemotherapy for patients with stage III colon cancer: Disease Free Survival results of the three versus six months adjuvant IDEA France Trial.

André T, Bonnetain F, Mineur L, Benhoutha J, Desrame J, Faroux R, Dauba J, Vemerey D, Aissat N, Louvet C, Lepère C, Dupuis O, Becouarn Y, Mabire M, Egret-Orsière J, Bouche O, Desplantes O, Ychou M, de Gramont A, Taieb J

Presented at: ASCO ANNUAL MEETING '17 | #ASCO17

Study Design (Methods)



- Objective: DFS = Time from date of randomization (enrollment) to the earliest date of relapse, secondary colorectal primary tumor, or death due to all causes
- Primary Analysis Population: Modified ITT = Randomized patients who received any dose of treatment

Accrual goal: 2000 patients

Presented at: ASCO ANNUAL MEETING '17 | #ASCO17

Presented by: TRISTY ANDRE on behalf of the IDEA France collaborators

COLABORAÇÃO IDEA

IDEA FRANCE

- Resultados

Results: Overall Patient Characteristics (mITT)

N patients	2010
Median age, years	64
ECOG PS 0/1/2	74%/25%/1%
N1/N2	75%/25%
T1-2	12%
T3	70%
T4	18%
T1-3, N1	62%
T4 and/or N2	38%
mFOLFOX6/CAPOX	90%/10%

Median Follow-up: 4.3 years

Data frozen on March 10, 2017

Presented at ASCO ANNUAL MEETING '17 #ASCO17 Presented by Thierry Tilly, MD, PhD, University of Paris

Results: Patient Characteristics by Arm (mITT)

	3M	6M
N patients	1002	1008
Age, > 70 years	25%	26%
ECOG PS 0/1/2	74%/24%/1%	74%/24%/1%
N1/N2	75%/25%	75%/25%
T1-2	12%	12%
T3	71%	68%
T4	17%	20%
T1-3, N1	63%	61%
T4 or N2	37%	39%
mFOLFOX6/CAPOX	90%/10%	91%/9%

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COLABORAÇÃO IDEA

IDEA FRANCE

- Resultados

Treatment exposure

	3M N=1002	6M N=1008
All drugs		
Mean chemotherapy duration (weeks)	11.8	21.7
Median chemotherapy duration (weeks)	12	24
All drugs		
Received full length chemotherapy (%)	94	78
All drugs/mFOLFOX6/CAPOX		
Mean No. of cycles	5.9/4	10.9/7.1
mFOLFOX6/CAPOX		
Oxaliplatin theoretical dose (mg/m ²)	510/520	1020/1040
Oxaliplatin dose received (mg/m ²)	494/504	732/760
Mean No. of cycle with oxaliplatin	5.7/3.9	8.9/6.1
Median dose-intensity (%)		
5-FU	97	92
Capecitabine	90	83
Oxaliplatin	97	72

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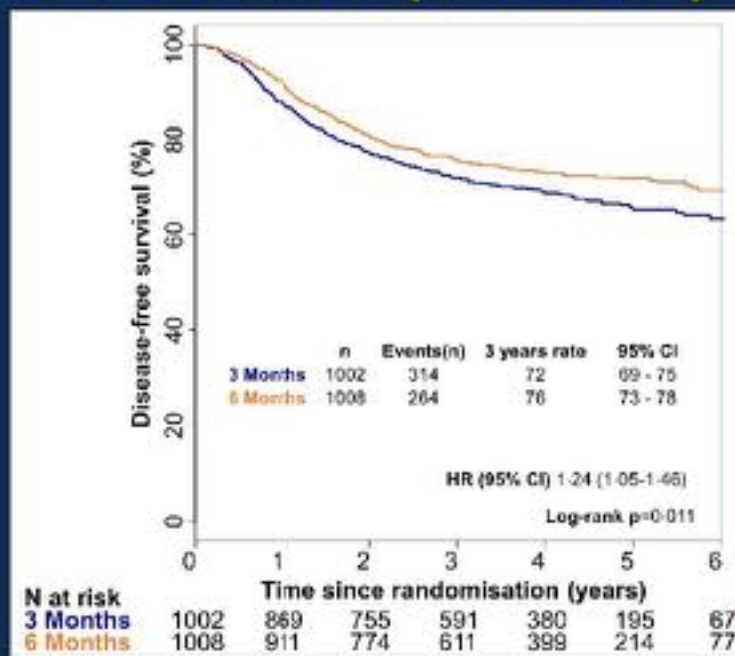
COLABORAÇÃO IDEA

IDEA FRANCE

- Desfecho primário

DFS for mITT (N=2010)

Median follow-up
4.3 years



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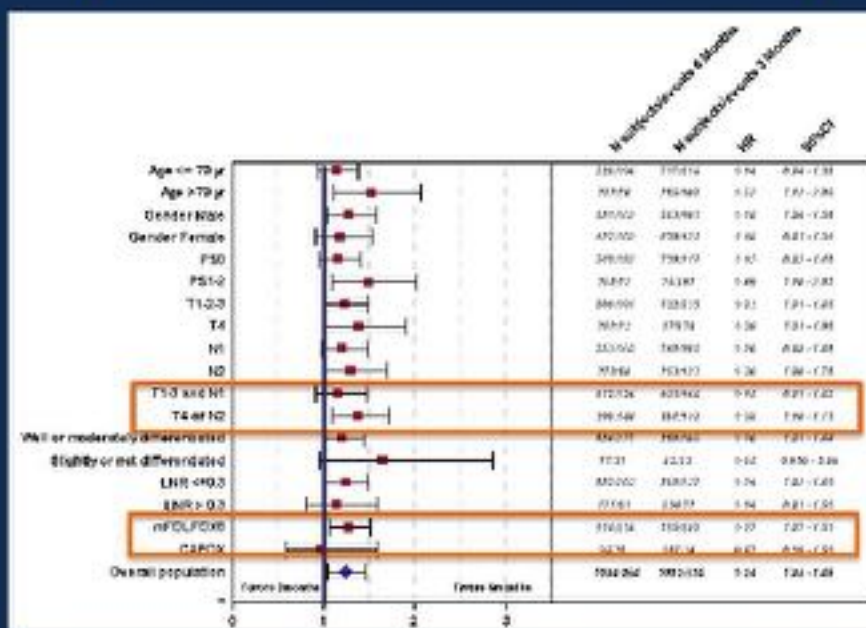
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COLABORAÇÃO IDEA

IDEA FRANCE

- Análises de subgrupo exploratórias

Forest plot - DFS for mITT (N=2010)



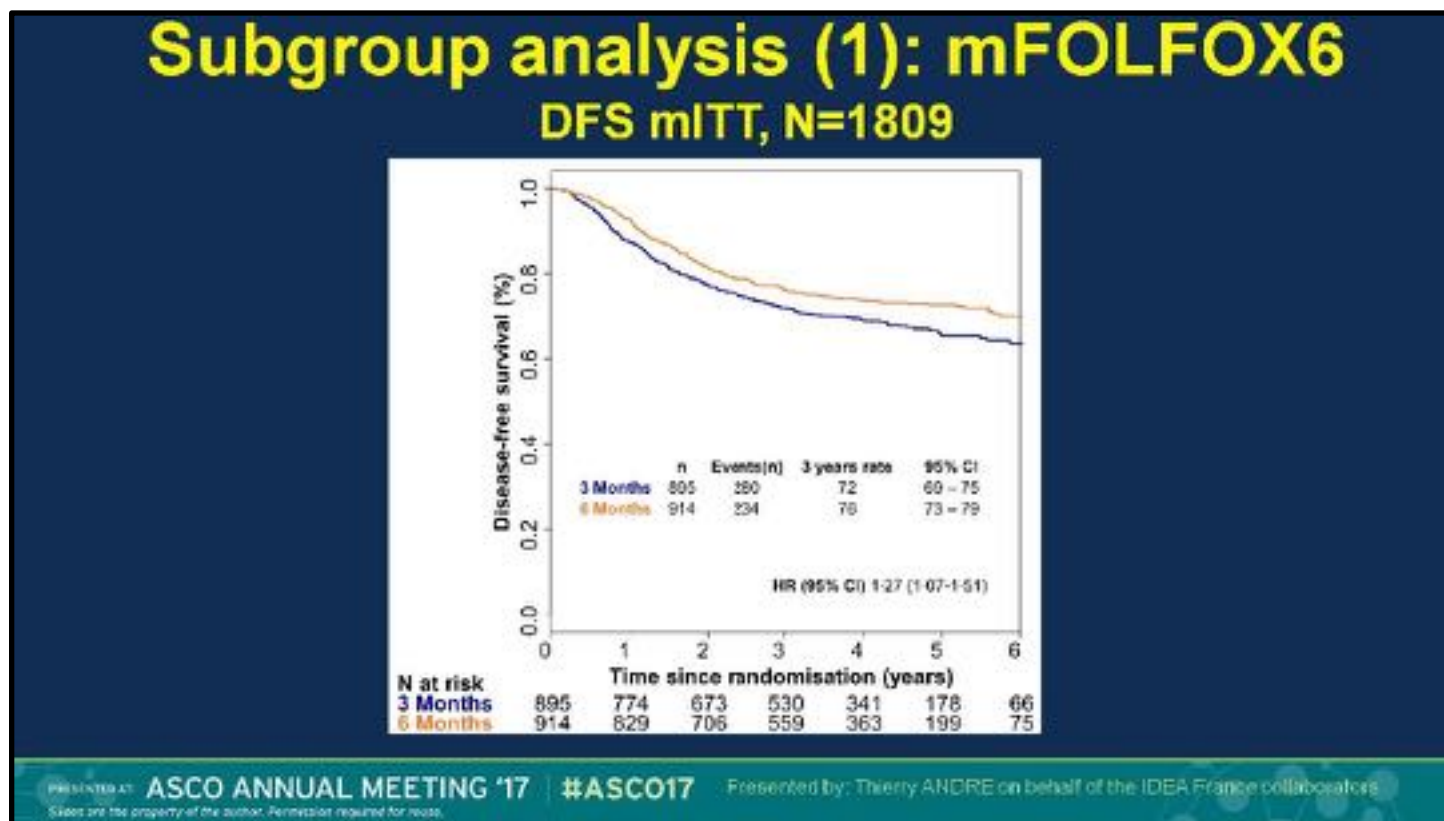
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COLABORAÇÃO IDEA

IDEA FRANCE

- Análises de subgrupo exploratórias



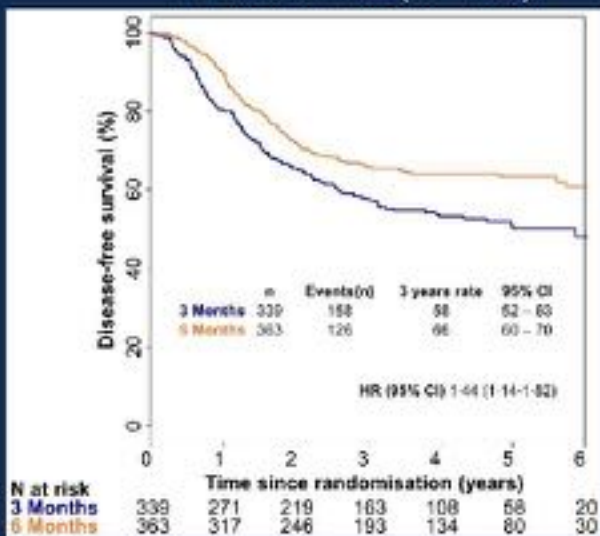
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IDEA FRANCE

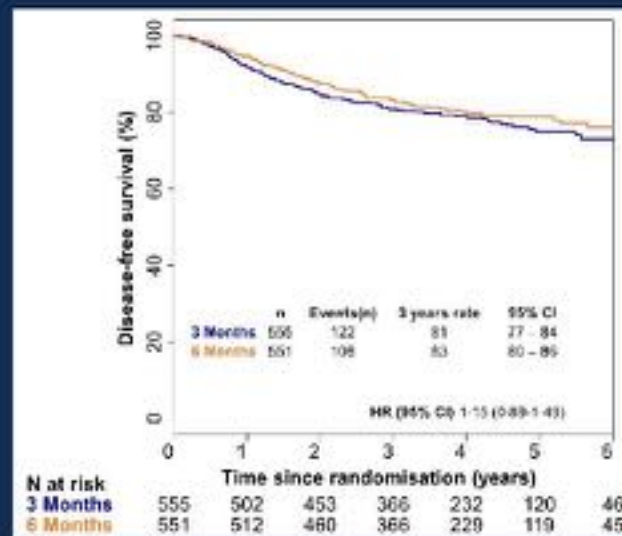
- Análises de subgrupo exploratórias

Subgroup analysis (2): mFOLFOX6 DFS mITT

T4 and/or N2 (N=702)



T1-3 N1



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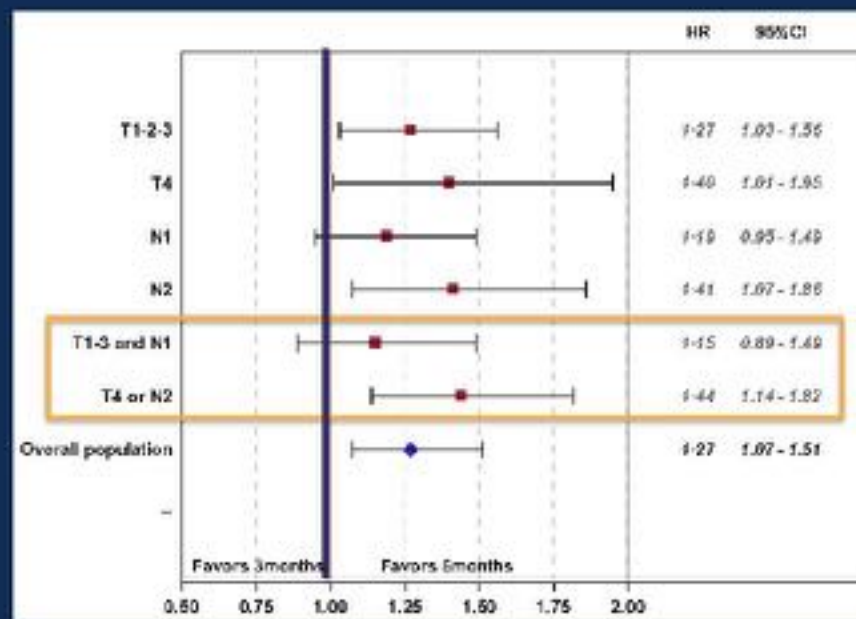
Presented by: Thierry ANDRE on behalf of the IDEA France collaborators.

COLABORAÇÃO IDEA

IDEA FRANCE

- Análises de subgrupo exploratórias

Subgroup analysis(3): mFOLFOX6 DFS mITT



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IDEA FRANCE

- **Segurança**

Safety(1): 3 vs 6 months

	3M N=1002 (%)	6M N=1008 (%)	P
All	29.5	46.4	< 0.001
Neutropenia	12.3	16.7	0.005
Febrile Neutropenia	1.4	1.7	0.595
Thrombocytopenia	1.1	2.8	0.006
Diarrhea	4.8	5.7	0.375
Nausea	1.7	2.3	0.343
Vomiting	2.3	1.9	0.524
Fatigue	2.6	5.2	0.003
Oxaliplatin allergy (grade 3/2)	1.7	4.6	< 0.001

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Neuropathy Grade ≥2 NCI CTCAE v3.0

	3M (%)	6M (%)	P
Maximal neuropathy			
During the first seven months			
2	23	39	
3-4	6	20	< 0.001
On-treatment and follow-up*			
2	28	41	
3-4	8	25	< 0.001
Residual neuropathy at last follow-up visit			
2	2	6	
3-4	0.5	2	< 0.001

* randomization to test follow-up

Median follow-up, 3.5 years after randomisation (IQR 2.6-4.5)

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COLABORAÇÃO IDEA

IDEA FRANCE

- Conclusões
 - 6 meses de tratamento com quimioterapia adjuvante baseada em oxaliplatina é superior a 3 meses em relação a sobrevida livre de doença (90% da população tratada com FOLFOX6).
 - SLD 3 vs. 6 meses: 72% vs. 76%. $p=0,011$
 - Análises de subgrupo (pacientes tratados com FOLFOX 6).
 - T1-3 N1: benefício absoluto de 2% para 6 meses de tratamento (SLD 83% vs. 81% $p=NS$) deve ser balanceado contra um maior risco de neuropatia periférica.
 - T4 e/ou N2: benefício absoluto de 8% para 6 meses de tratamento sugere manutenção do tratamento padrão atual

COLABORAÇÃO IDEA

TOSCA TRIAL

**FOLFOX / CAPOX in stage II–III colon cancer:
efficacy results of the Italian Three Or Six Colon
Adjuvant trial TOSCA. Abstr. 3501**

A. Sobrero, S. Lonardi, G. Rosati, M. Di Bartolomeo, M. Ronzoni, N. Pella, M. Scafrazzi, M. Baiardi, M.G. Zampino, F. Pasini, P. Marchetti, M. Cantore, A. Zaniboni, L. Rimassa, L. Ciuffreda, D. Ferretti, V. Zagonel, E. Maestri, E. Rulli & R. Labianca on behalf of TOSCA investigators

Abstract: ASCO ANNUAL MEETING '17 #ASCO17

Study Design

Stage II/III
Colon
Cancer

R

3 months

6 months

Objective

Non-inferiority of 3 months
compared with 6 months of
adjuvant FOLFOX or CAPOX
(regimen as per physician's choice)

Abstract: ASCO ANNUAL MEETING '17 #ASCO17

Presented by: A. Sobrero on behalf of TOSCA collaborators

COLABORAÇÃO IDEA

TOSCA TRIAL

- Características do estudo

Statistical Design

- **Primary Endpoint: Relapse-free survival (RFS)**
 - Time from date of randomization to the earliest date of relapse or death due to all causes
- **Primary Analysis Population: per protocol**
 - Randomized, no major violation of eligibility criteria and study conduct and received at least 1 dose of the assigned treatment
- **Pre-planned Subgroup Analyses:**
 - By stage

Presented at: ASCO ANNUAL MEETING '17 #ASCO17 Presented by: A. Soares

TOSCA results

• Randomized, n	3759
• ITT population, n	3715
• Per protocol population, n	3614
• Accrual started	June 2007
• Accrual ended	march 2013
• Median follow up	62 months
• CAPOX / FOLFOX	34 / 66

Choice of delta and non-inferiority hypothesis testing

DELTA

- > 5% absolute delta in 3-yr RFS clinically meaningful
- < 2% absolute delta in 3-yr RFS clinically meaningless
- We compromised on < 4 % i.e. HR 1.20 as the non inferiority margin.

HYPOTHESIS TESTING

- The 3 month arm is considered non inferior if the upper margin of the 95% CI is < 1.20. 944 events needed, to have an 80% power to reject the null hypothesis of inferiority.

Presented at: ASCO ANNUAL MEETING '17 #ASCO17

Presented by: A. Soares on behalf of TOSCA collaborators

COLABORAÇÃO IDEA

TOSCA TRIAL

- Resultados

Results: Patient and tumour characteristics

Patient / tumour characteristics	3 Months (N=1775)	6 Months (N=1839)
Age, median years	64.7	64.4
ECOG PS 0	95.2 %	94.5 %
Males	56.3 %	55.1 %
Stage II non T4	27.0 %	26.3 %
Stage II T4	6.2 %	6.2 %
Stage III low risk , T1-3 N1	42.4 %	43.1 %
Stage III high risk, T4 or I and N2	22.4 %	22.3 %
Right colon	41.5 %	40.9 %
G3	29.8 %	29.9 %
Median N of nodes examined	18	18

Reported at ASCO ANNUAL MEETING '17 #ASCO17

Presented by A. Sobrero on behalf of

RESULTS: COMPLIANCE, %

	3 months	6 months
Completed	88	66
Interrupted	8	33
Continued beyond 3 mo	3	-
Never started	1	1
Completed FP w/o oxali	1	10

More than 80% of pts in the control arm completed at least 5 months

Reported at ASCO ANNUAL MEETING '17 #ASCO17

Presented by A. Sobrero on behalf of IEO/IRCC/CCF

COLABORAÇÃO IDEA

TOSCA TRIAL

- Toxicidade

Results: Toxicity

Adverse Events	Grade 1-2, %		Grade 3-4, %		p-value ¹
	3 months	6 months	3 months	6-months	
Neurological	37.0	41.0	9.0*	31.0*	<.0001
Febrile neutropenia	1.7	3.5	1.4	2.7	<.0001
Thrombocytopenia	33.0	47.0	1.6	2.1	<.0001
Diarrhoea	29.0	35.0	5.1	6.4	<.0001
Allergic reactions	3.4	6.4	0.5	2.0	<.0001

¹Chi-squared test for trend ; Total number of grade 5 events: 2 ("possible")
* Clinically relevant neurological toxicity (grade 2 , 3 and 4)

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COLABORAÇÃO IDEA

TOSCA TRIAL

- Desfecho primário

Results: RFS by arm Overall Population



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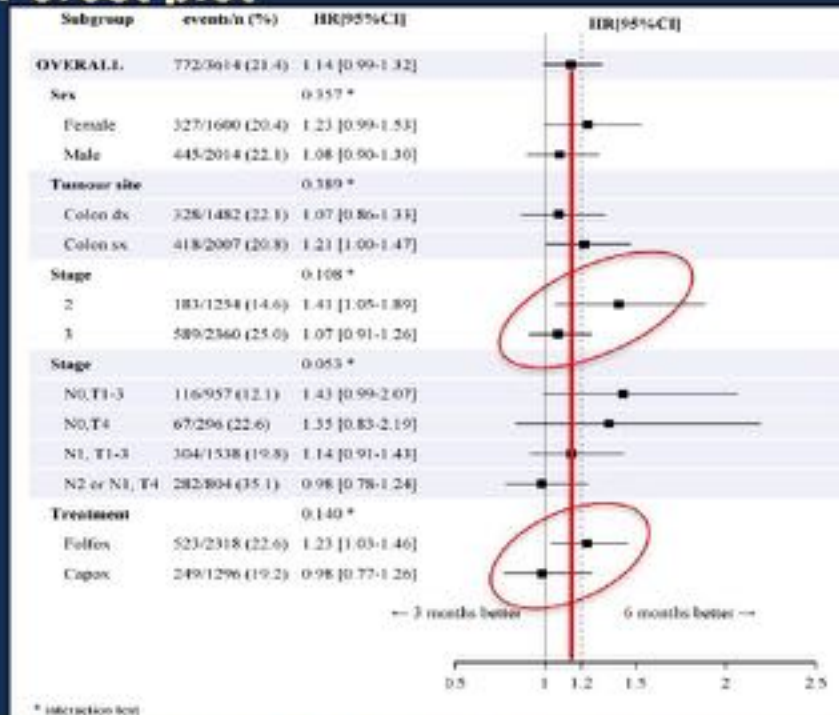
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COLABORAÇÃO IDEA

TOSCA TRIAL

- Desfecho primário

Results: Forest plot



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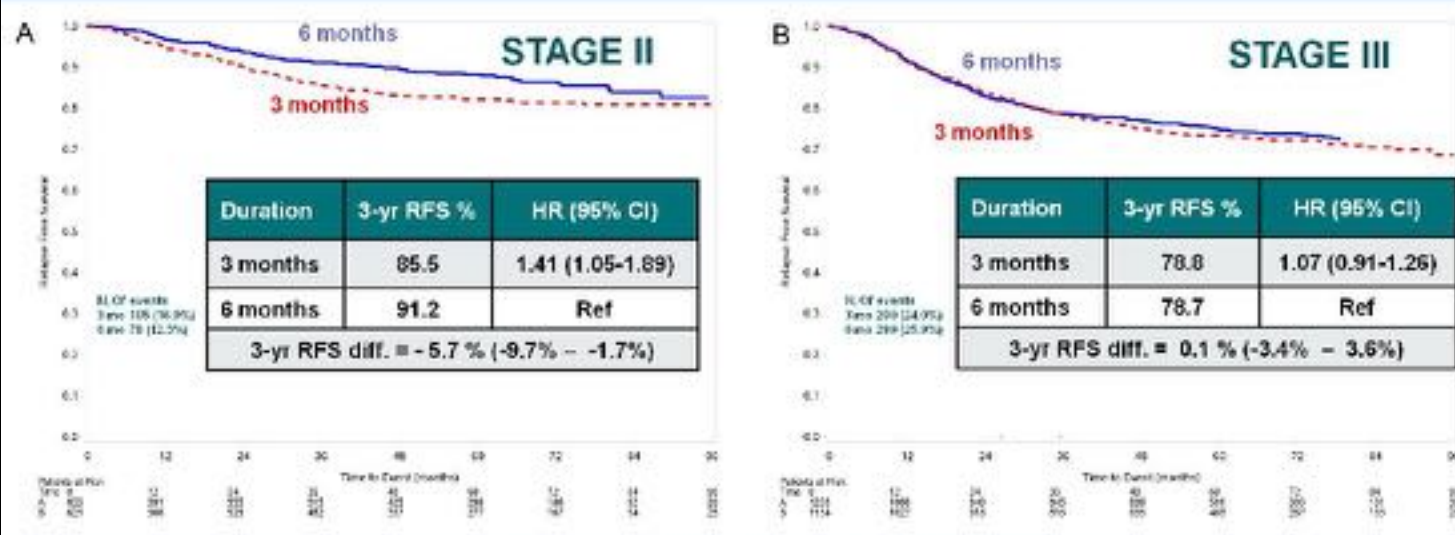
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COLABORAÇÃO IDEA

TOSCA TRIAL

- Desfecho primário

Results: RFS by stage



Interaction p-value = 0.108

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COLABORAÇÃO IDEA

TOSCA TRIAL

- Desfecho primário: o efeito estágio dependente é confiável?

NÃO!

- Pouca plausibilidade
- Ausência de consistência externa
- Poucos eventos (78 vs. 105)
- Teste de interação por estágio não significativo

SIM!

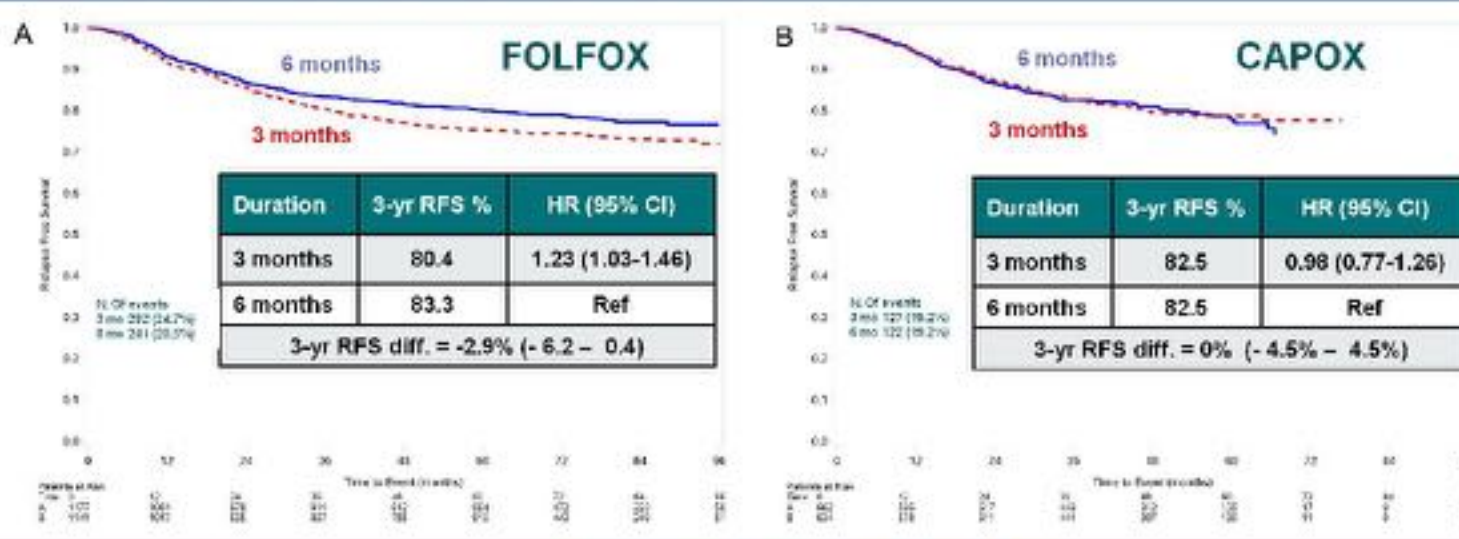
- Dado de uma análise prospectiva pré-planejada
- Estádio II..... Biologia diferente?

COLABORAÇÃO IDEA

TOSCA TRIAL

- Desfecho primário

Results: RFS by treatment



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COLABORAÇÃO IDEA

TOSCA TRIAL

- Conclusões
 - Não inferioridade não foi demonstrada HR 1.14 (0.99 - 1.32)
 - Diferença absoluta de SLD em 3 anos é muito pequena (1,9%)
 - Curvas de SLD idênticas para o estágio III
 - Diferença observada no subgrupo do estágio II.
 - Curvas de SLD idênticas para o esquema CAPOX
 - Diferença observada no subgrupo do FOLFOX.
 - Toxicidade muito inferior no braço de 3 meses de tratamento.

COLABORAÇÃO IDEA

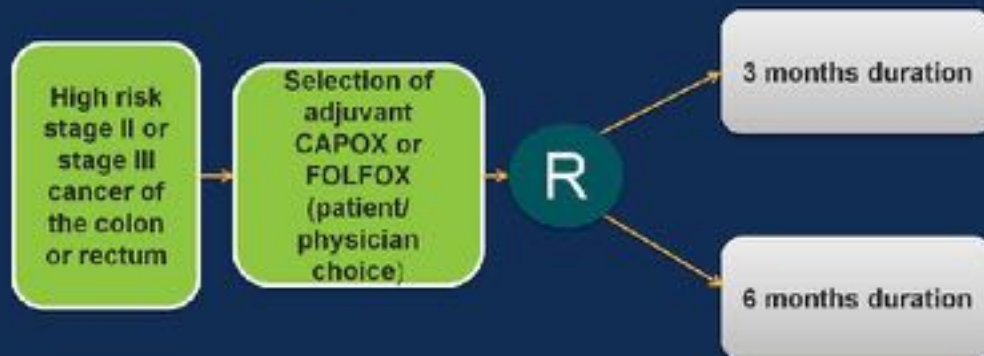
SCOT STUDY

Final DFS results of the SCOT study:
An International Phase III Randomised (1:1) Non-inferiority Trial Comparing 3 versus 6 months of oxaliplatin based adjuvant chemotherapy for colorectal cancer

Timothy Iversen, Rachel S Kerr, Mark P Saunders, Niels Henrik Holander, Josep Tabernero, Andrew Haydon, Bengt Glimelius, Andrea Halkin, Claire Soudder, Kathleen Anne Boyd, Ashita Waterson, Louise Medley, Charles Wilson, Richard Ellis, Sharada Essapen, Amandeep S Dhadia, Mark Harrison, Stephen Falk, Sherif Raouf, James Paul

Abstract: ASCO ANNUAL MEETING '17 #ASCO17 Poster 450, 5th June, 12:00 PM

SCOT Design



Abstract: ASCO ANNUAL MEETING '17 #ASCO17 Poster 450, 5th June, 12:00 PM
Presented by: Tim Iversen, MD on behalf of SCOT Investigators

COLABORAÇÃO IDEA

SCOT STUDY

- Características do estudo

Statistical design

- **Non-inferiority**
 - Designed as a non-inferiority trial aiming to exclude a maximum 2.5% fall in 3-year DFS on the 3 month arm corresponding to a hazard ratio of 1.13
- **Power**
 - For a hazard ratio of 1.13 and 90% power at the 2.5% 1-sided level of statistical significance, 9500 patients and 2750 events needed

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SCOT CONSORT Diagram



SCOT STUDY

- Resultados

Results: Patient characteristics

		3 months	6 months
Gender	Female	39.6%	39.4%
	Male	60.5%	60.6%
PS	0	71.9%	70.4%
	1	28.1%	29.6%
Site	Colon	81.9%	82.0%
	Rectum	18.1%	18.0%
Age	Median (IQ range)	65 (58-70)	65 (58-70)

BY REQUEST, ASCO ANNUAL MEETING '17 #ASCO17 Sponsored by: TIL Pharma, Seattle to West Coast, via ASCO

Results: Treatment regimen

Regimen	3 month duration	6 month duration
CAPOX	2051 (67.4%)	2056 (67.5%)
FOLFOX	993 (32.6%)	988 (32.5%)

Results: Patient characteristics

		3 months	6 months
T stage	0	0.0%	0.1%
	1	3.0%	3.1%
	2	9.3%	9.3%
	3	57.5%	57.4%
	4	30.1%	30.1%
N stage	0	18.4%	18.3%
	1	56.9%	56.9%
	2	24.8%	24.8%

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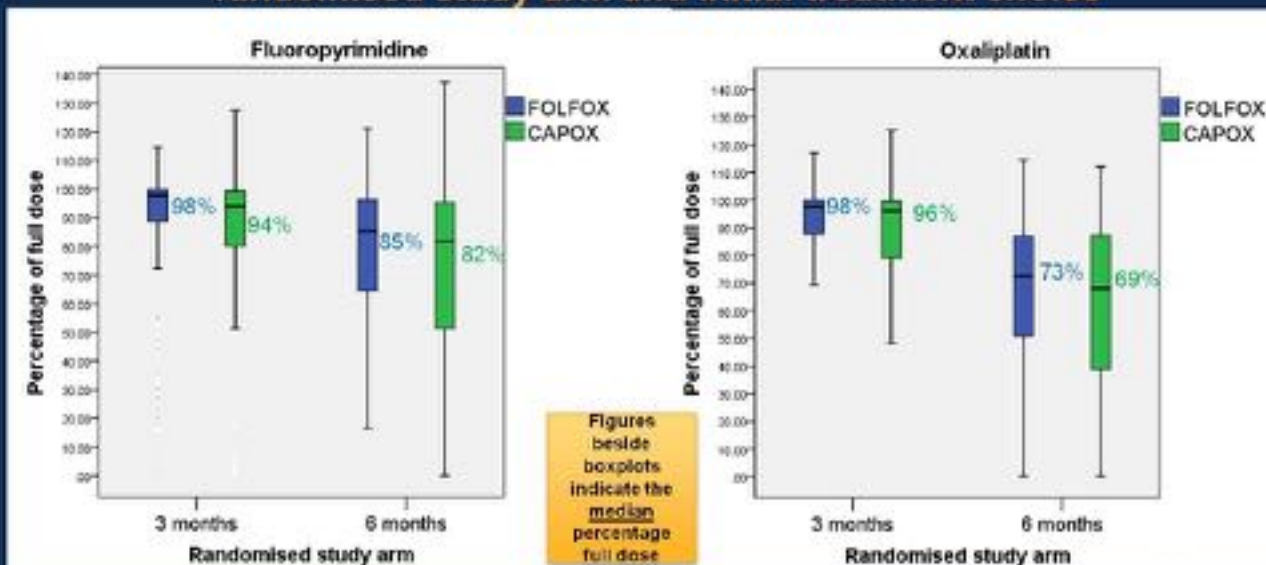
COLABORAÇÃO IDEA

SCOT STUDY

- Resultados

Results: Treatment compliance

Percentage of full oxaliplatin and full fluoropyrimidine dose by randomised study arm and initial treatment choice



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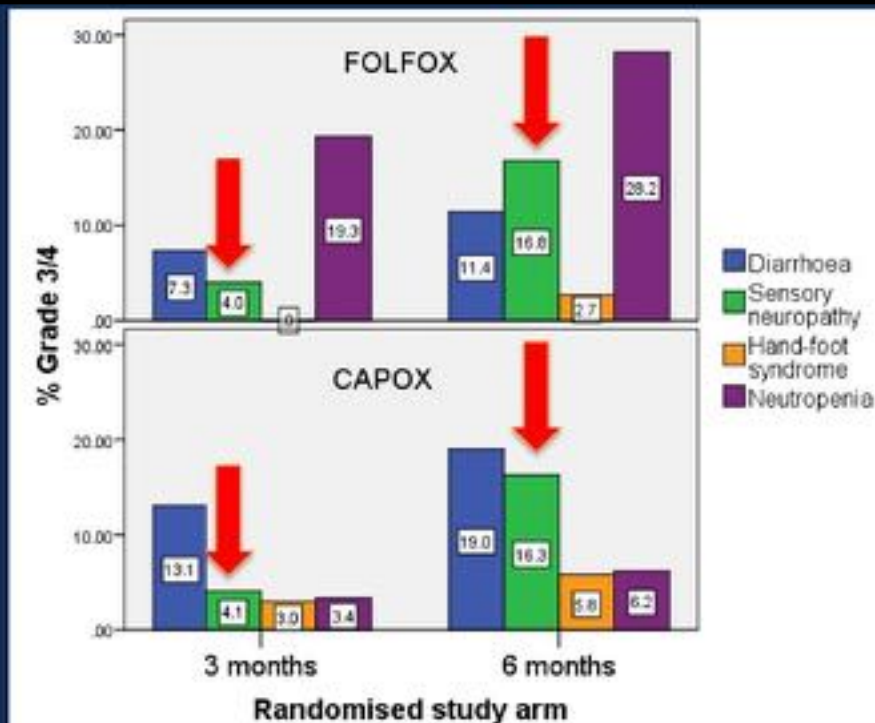
Presented by: Tim Iveson, MD on behalf of SCOT investigators

COLABORAÇÃO IDEA

SCOT STUDY

- Toxicidade

**Results:
Grade 3/4
adverse
events by
Duration and
Regimen**



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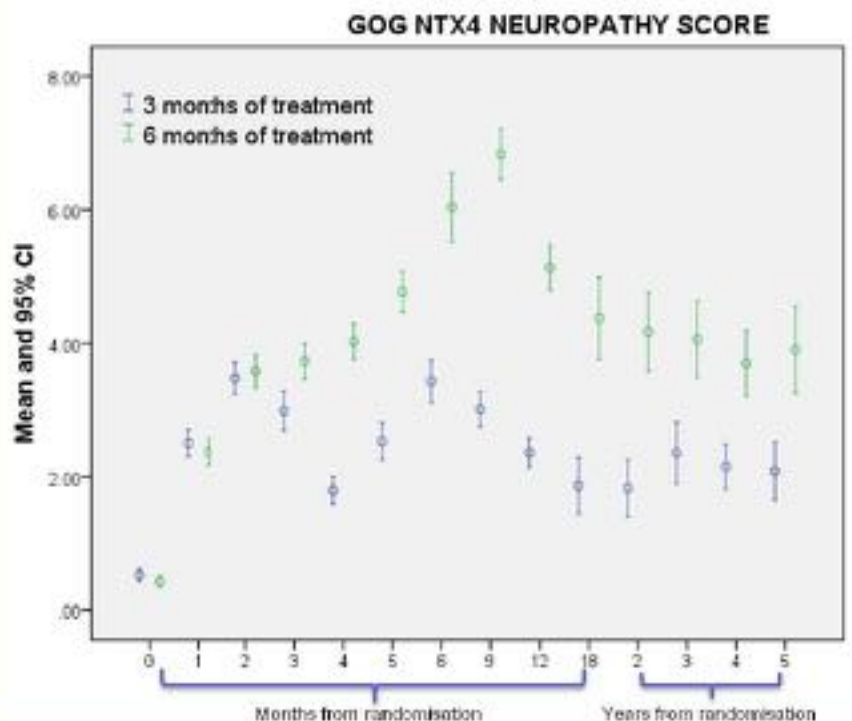
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COLABORAÇÃO IDEA

SCOT STUDY

- Toxicidade

**Results:
Neuropathy
measured by
questionnaire
over time
by treatment
duration**



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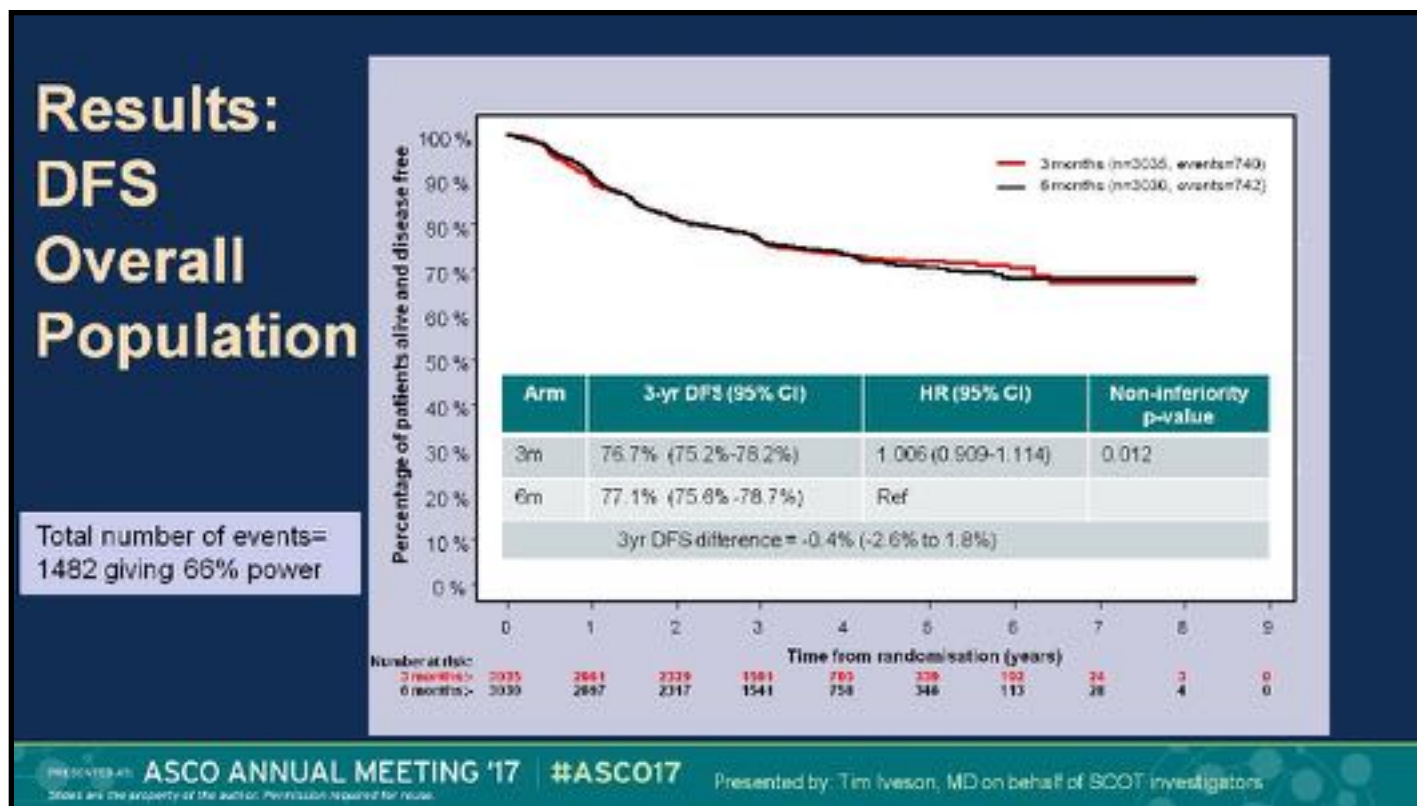
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SCOT STUDY

- Desfecho primário

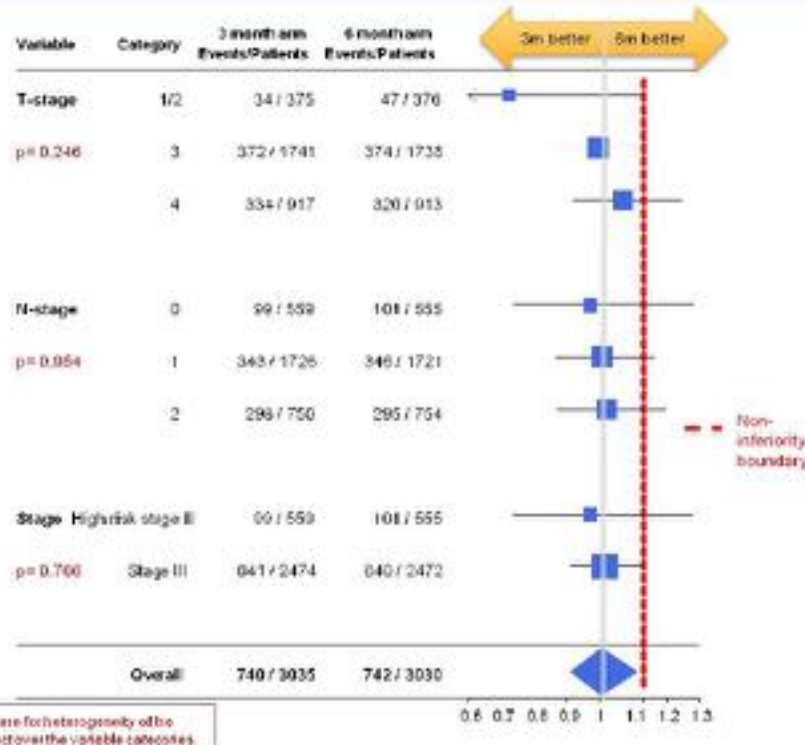


COLABORAÇÃO IDEA

SCOT STUDY

- Desfecho primário

Results: DFS duration comparison by N- and T- Stage



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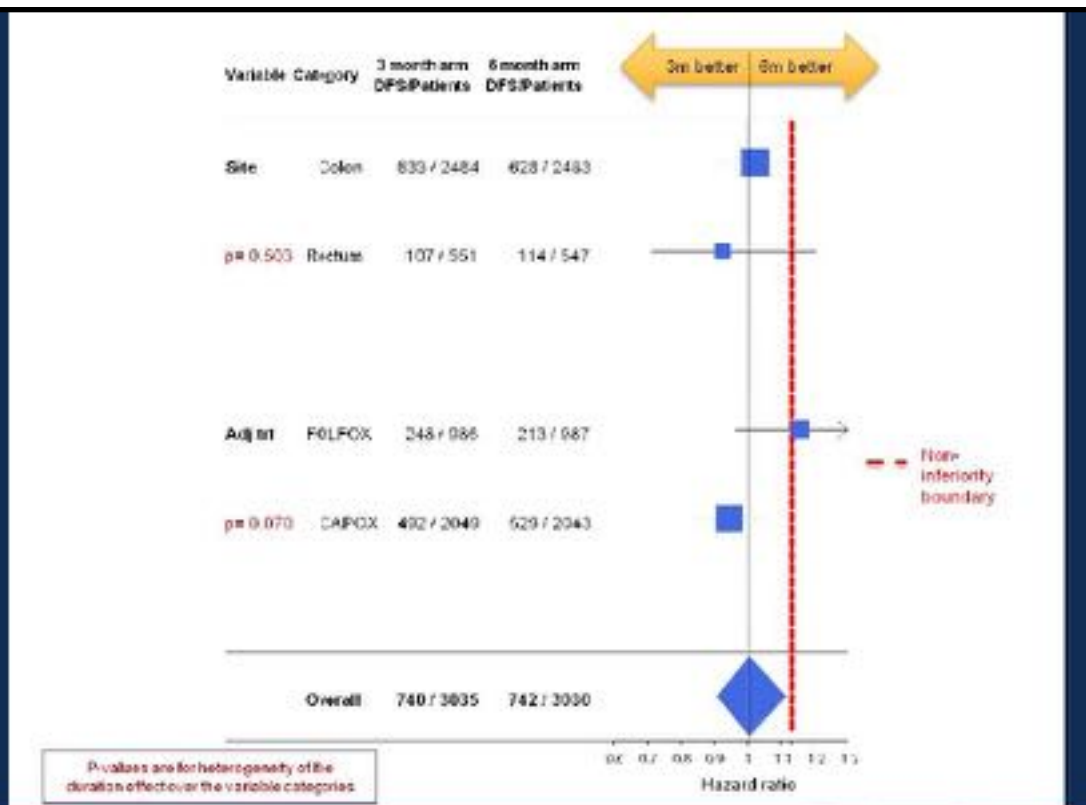
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COLABORAÇÃO IDEA

SCOT STUDY

- Desfecho primário

**Results:
DFS
duration
comparison
by adjuvant
treatment
and site of
disease**



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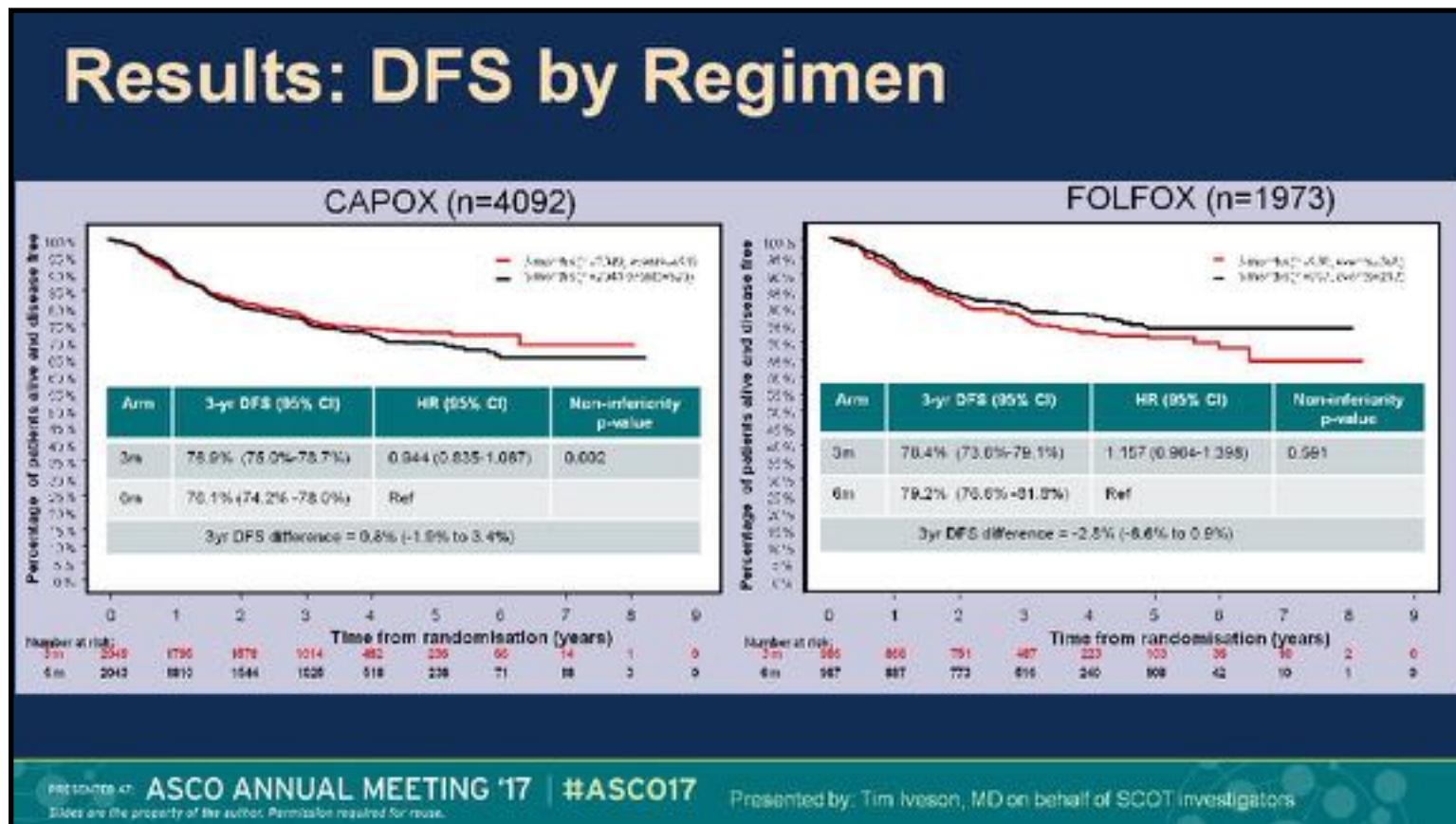
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Presented by: Tim Iveson, MD on behalf of SCOT investigators

COLABORAÇÃO IDEA

SCOT STUDY

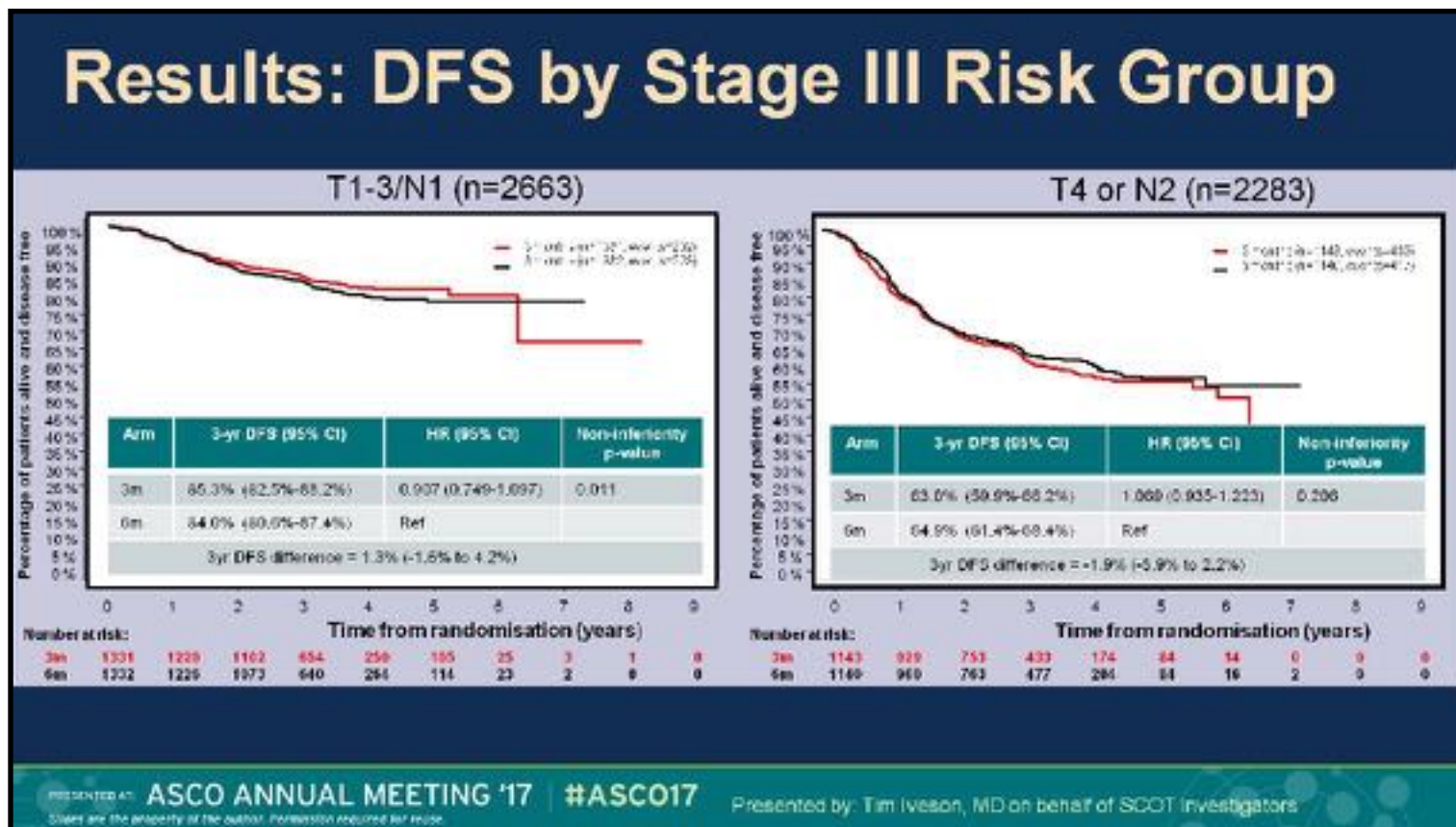
- Desfecho primário



COLABORAÇÃO IDEA

SCOT STUDY

- Desfecho primário

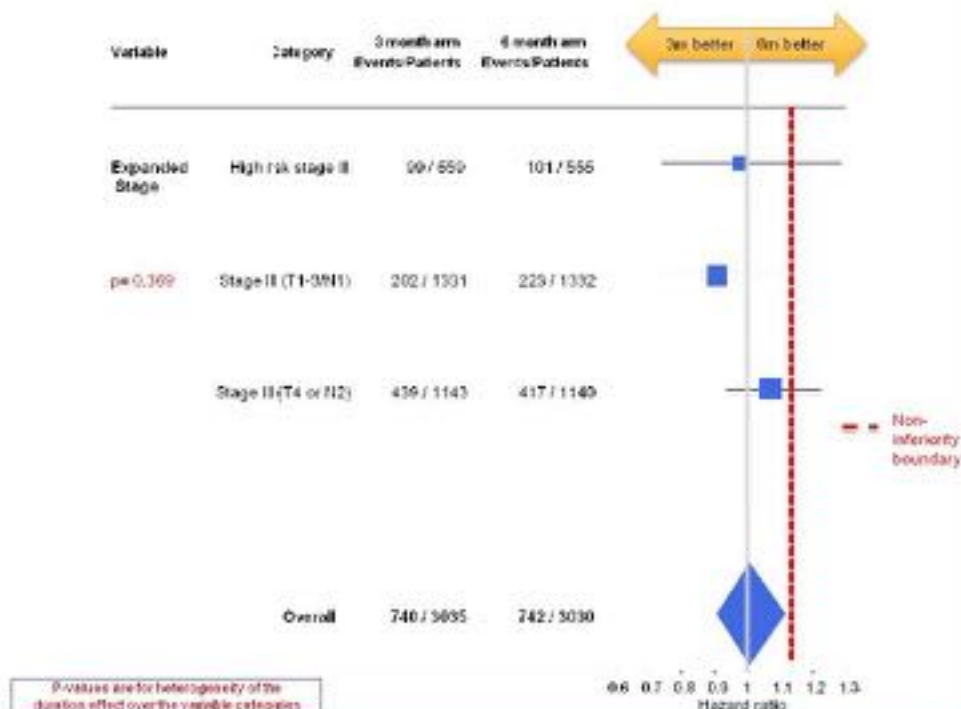


COLABORAÇÃO IDEA

SCOT STUDY

- Desfecho primário

**Results:
DFS
duration
comparison
by
expanded
stage**



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COLABORAÇÃO IDEA

SCOT STUDY

- Desfecho primário

Results: 3-year DFS by risk group and regimen

Risk Group	Regimen	3-yr DFS Difference (95% CI) 3m minus 6m		HR (95% CI) 3m versus 6m	
T1-3,N1	CAPOX (n=1774)	3.4%	(-0.1%, 6.9%)	0.76	(0.60 – 0.96)
	FOLFOX (n=889)	-2.9%	(-7.7%, 1.9%)	1.27	(0.91 – 1.78)
T4 or N2	CAPOX (n=1515)	-1.4%	(-6.4%, 3.6%)	1.05	(0.89 – 1.23)
	FOLFOX (n=768)	-2.7%	(-9.6%, 4.1%)	1.13	(0.89 – 1.44)

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SCOT STUDY

- Conclusões
- O estudo atingiu seu o desfecho de não inferioridade previamente estabelecido na comparação 3 vs. 6 meses de tratamento na população global.
- Tratamento por 3 meses é menos tóxico e melhor tolerado.
- 3 meses de CAPOX foi não inferior a 6 meses de CAPOX.
- 3 meses de FOLFOX não foi não inferior a 6 meses de FOLFOX.
- Estádio III de baixo risco (T1-3 N1): 3m não inferior a 6m.
- Estádio III de alto risco (T4 e/ou N2): 3m inferior a 6m.

COLABORAÇÃO IDEA

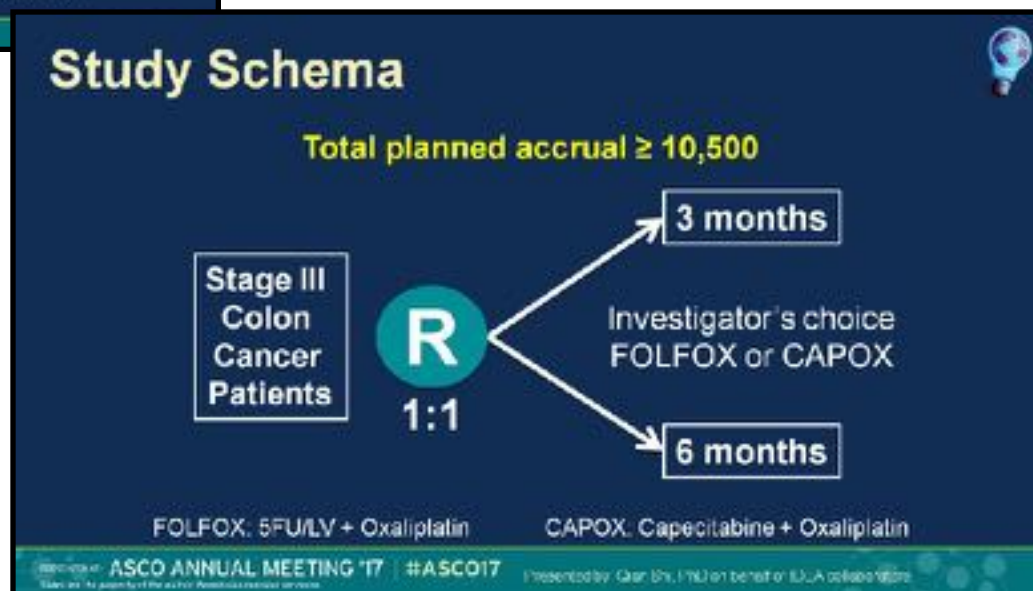
ANÁLISE COMBINADA



Prospective Pooled Analysis of Six Phase III Trials Investigating Duration of Adjuvant Oxaliplatin-based therapy (3 vs. 6 months) for Patients with Stage III Colon Cancer: The IDEA (International Duration Evaluation of Adjuvant Chemotherapy) Collaboration

Qian Shi, Alberto F. Sobrero, Anthony F. Shields, Takayuki Yoshino, James Paul, Julie Taleb, Ioannis Sfragidakis, Rachel Kerr, Roberto Labianca, Jeffrey A. Meyerhardt, Franck Bonnetain, Toshiko Watanabe, Ioannis Boukovinas, Lindsay A. Rentfro, Axel Grothey, Dorota Niedzwiecki, Walter Totti, Thierry André, Daniel J. Sargent, Timothy J. Iversen

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COLABORAÇÃO IDEA

ANÁLISE COMBINADA

- Características do estudo

Study Overview

- **Objective**

To evaluate the *non-inferiority (NI)* of 3m compared with 6m of adjuvant oxaliplatin-based treatment in stage III colon cancer

- **Approach**

Prospectively-designed, pooled analysis of individual patient data from six concurrently conducted phase III randomized trials

Trial	Regimen(s)	Stage III Colon Cancer Patients*	Enrolling Country
TOSCAs	CaPOX or FOLFFOX4	2402	Italy
SCOT	CaPOX or mFOLFFOX6	3383	UK, Germany, Spain, Australia, Sweden, New Zealand
IDEA France	CaPOX or mFOLFFOX6	2010	France
C80703	mFOLFFOX6	3440	US, Canada
HORG	CaPOX or FOLFFOX4	708	Greece
ACHIEVE	CaPOX or mFOLFFOX6	1291	Japan

*Only stage III colon cancer patients were included in the pooled primary analysis

Statistical Design

- **Primary Endpoint: Disease-free survival (DFS)**

- Time from date of randomization (enrollment) to the earliest date of relapse, secondary colorectal primary tumor, or death due to all causes

- **Primary Analysis Population: Modified Intent-To-Treat**

- Randomized and received any dose of treatment
- Analysis according to patients' original randomization assignment

- DFS Hazard ratio (HR; 3m vs. 6m) and two-sided 95% confidence interval (CI) were estimated by Cox model **stratified by study**

- **Pre-planned Subgroup Analyses: By regimen and T/N stage**

COLABORAÇÃO IDEA

ANÁLISE COMBINADA

- Características do estudo

Rationale for Non-inferiority Margin

Historical Data from MOSAIC

5FU/LV + Oxaliplatin vs. 5FU/LV

24% relative risk reduction

IDEA Consensus (Oncologists and Patient Advocates)

Oxaliplatin-based Treatment: 3m vs. 6m

12% relative risk increase (upper 95% CI)

→ NI Margin: DFS HR = 1.12

Andre et al. N Engl J Med 2004; Andre et al. Curr Colorectal Cancer Rep 2013

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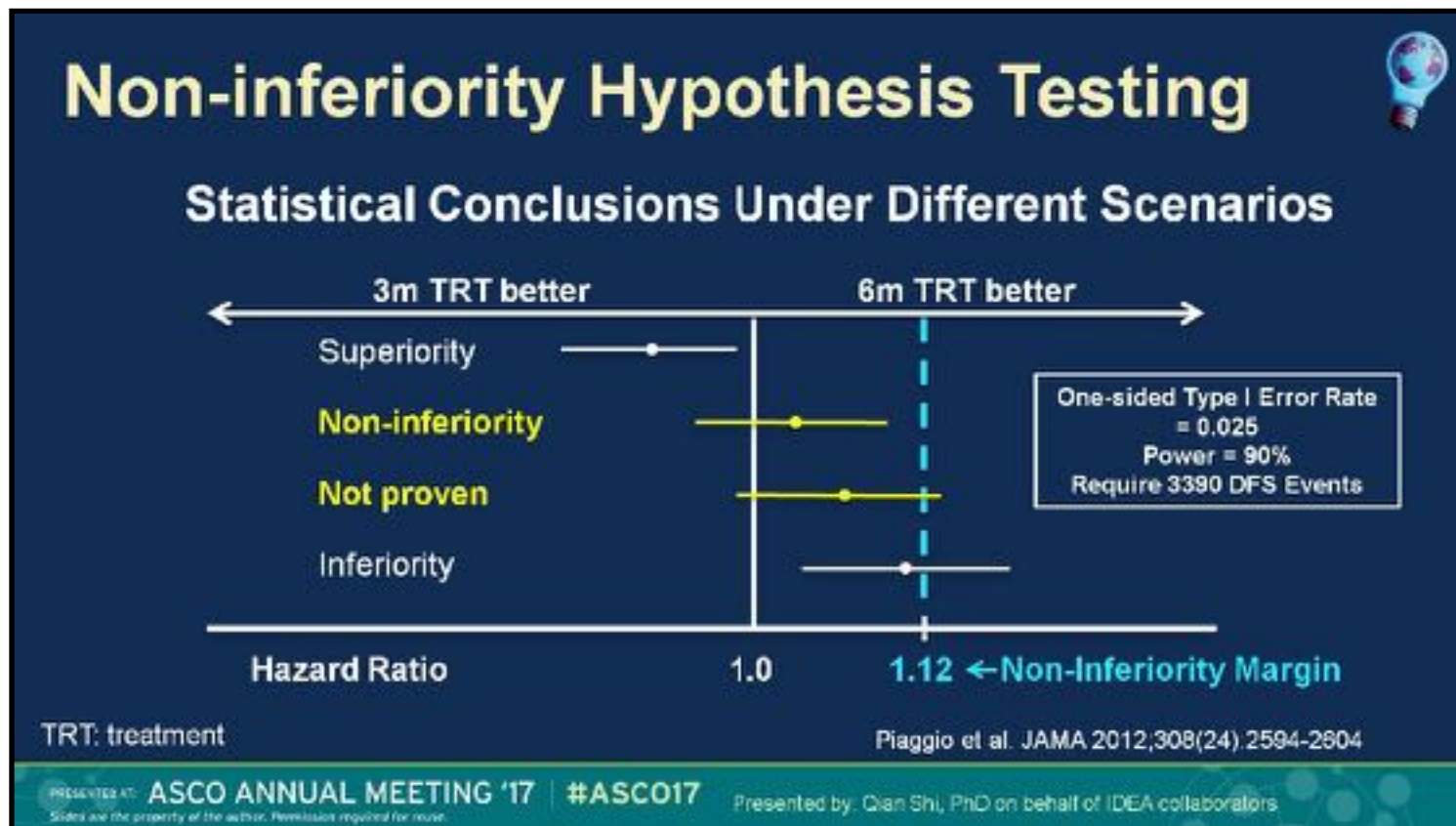
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COLABORAÇÃO IDEA

ANÁLISE COMBINADA

- Características do estudo



COLABORAÇÃO IDEA

ANÁLISE COMBINADA

- Resultados

Patient Characteristics	TOSCANA (N=2492)	SCOT (N=3993)	IDEA France (N=2910)	C89702 (N=2440)	HORG (N=768)	ACHIEVE (N=1291)
Median Age, years	64	65	64	61	67	66
ECOG PS*						
0	99%		74%	71%	82%	
1	5%		26%	29%	18%	
T4	12%	29%	18%	15%	14%	28%
N Stage						
N1	73%	69%	75%		67%	
N2	27%	31%	25%		33%	
Median follow-up time, m	62	37	51	35	48	37

*1% of PS 2 in IDEA France and C89702 trials

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N patients	12,834
Total DFS events	3,263 (96% of planned)
ECOG PS 0 / 1	79% / 21%
N1 / N2	72% / 28%
T1-2	13%
T3	66%
T4	21%
FOLFOX / CAPOX	60% / 40%

Data frozen on Feb 1st, 2017

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ANÁLISE COMBINADA

- Resultados

Treatment Compliance				
Treatment Compliance	FOLFOX		CAPOX	
	3m Arm	6m Arm	3m Arm	6m Arm
Total no. weeks received treatment	12 (12-12)	24 (20-24)	12 (12-12)	24 (18-24)
Median (Q1-Q3)				
Reached the planned last cycle ¹	90%	71%	86%	65%
% of dose actually delivered, Mean (Standard Deviation)				
5FU ²	92.4 (22.7)	81.6 (26.6)	---	---
Capecitabine	---	---	91.2 (23.5)	78.0 (29.4)
Oxaliplatin	91.4 (19.9)	72.8 (25.6)	89.8 (21.7)	69.3 (28.3)

¹ 1% of patients assigned to 3m treatment (both FOLFOX and CAPOX) received > 3m of treatment; ² combining infusion and bolus

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ANÁLISE COMBINADA

- Toxicidade

Adverse Events



Adverse Events	FOLFOX			CAPOX		
	3m Arm	6m Arm	p-value ¹	3m Arm	6m Arm	p-value ¹
Overall						
G2	32%	32%	<.0001	41%	48%	<.0001
G3-4	38%	57%		24%	37%	
Neurotoxicity						
G2	14%	32%	<.0001	12%	36%	<.0001
G3-4	3%	16%		3%	9%	
Diarrhea						
G2	11%	13%	<.0001	10%	13%	0.0117
G3-4	5%	7%		7%	9%	

¹Chi-squared test for trend; Total of 19 grade 5 events; Adverse events only collected on first 617 patients enrolled to SCOT trial

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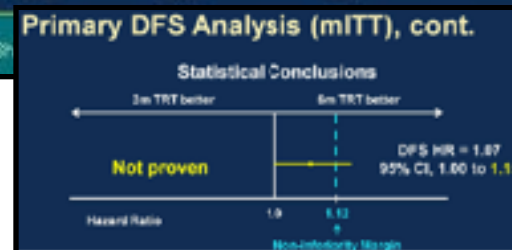
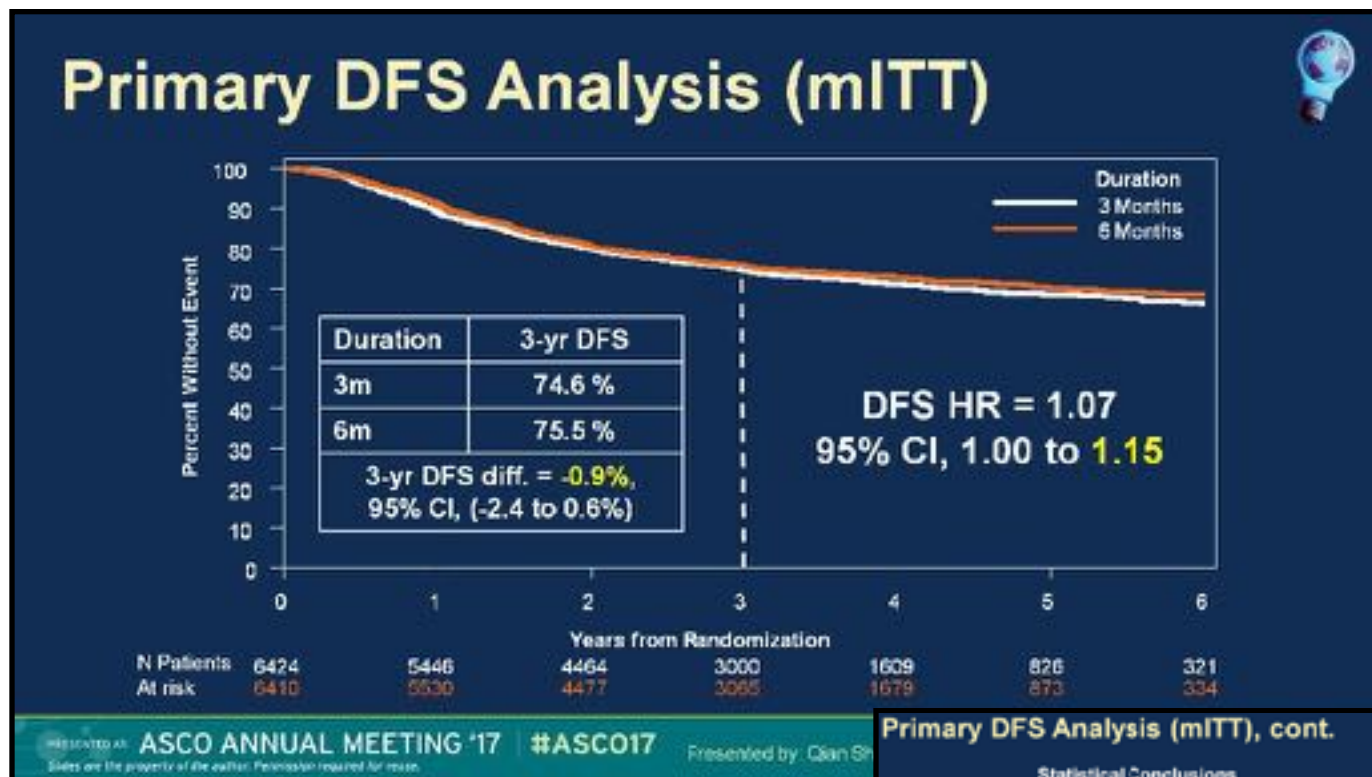
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ANÁLISE COMBINADA

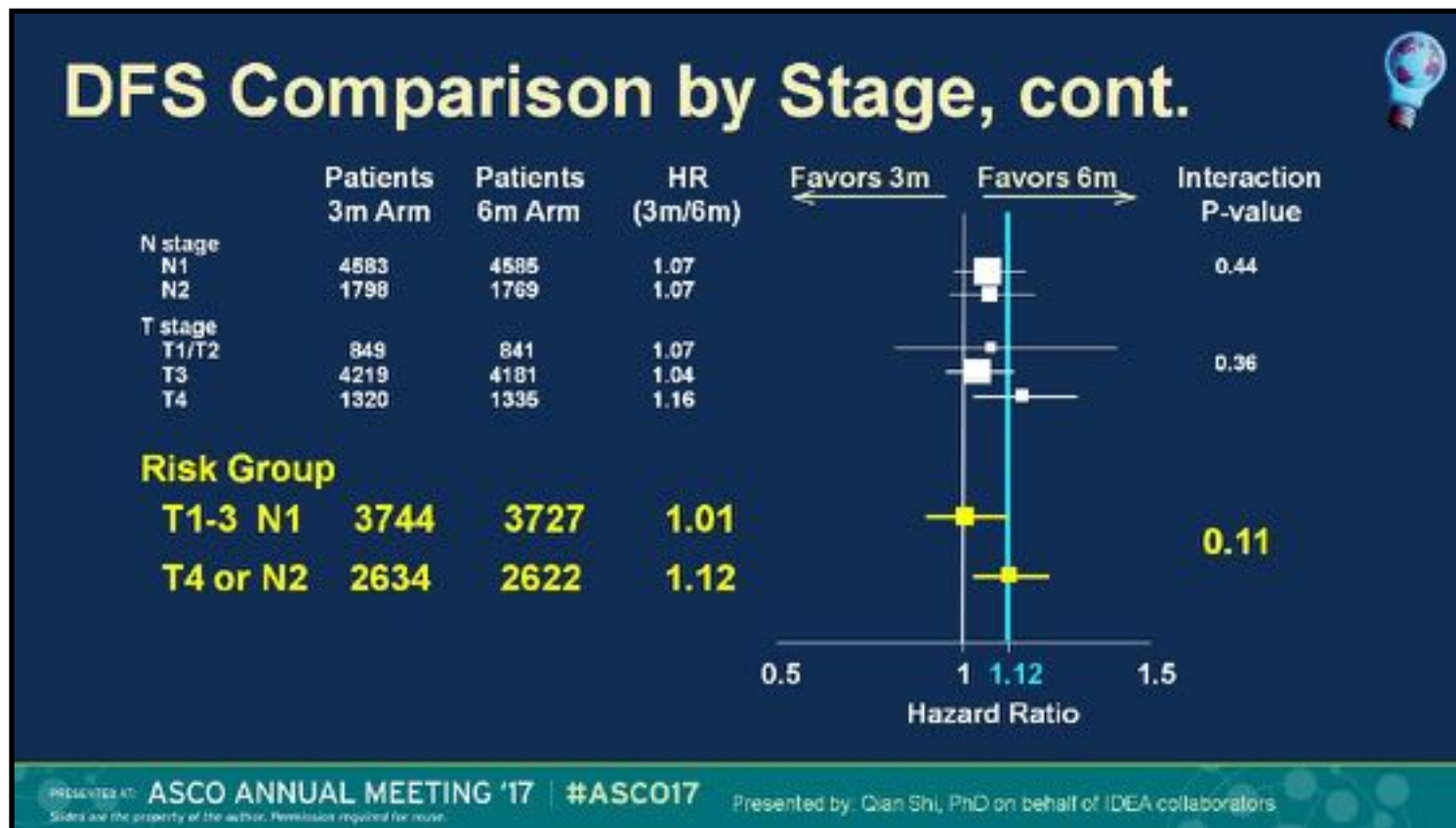
- Desfecho primário



COLABORAÇÃO IDEA

ANÁLISE COMBINADA

- Desfecho primário



COLABORAÇÃO IDEA

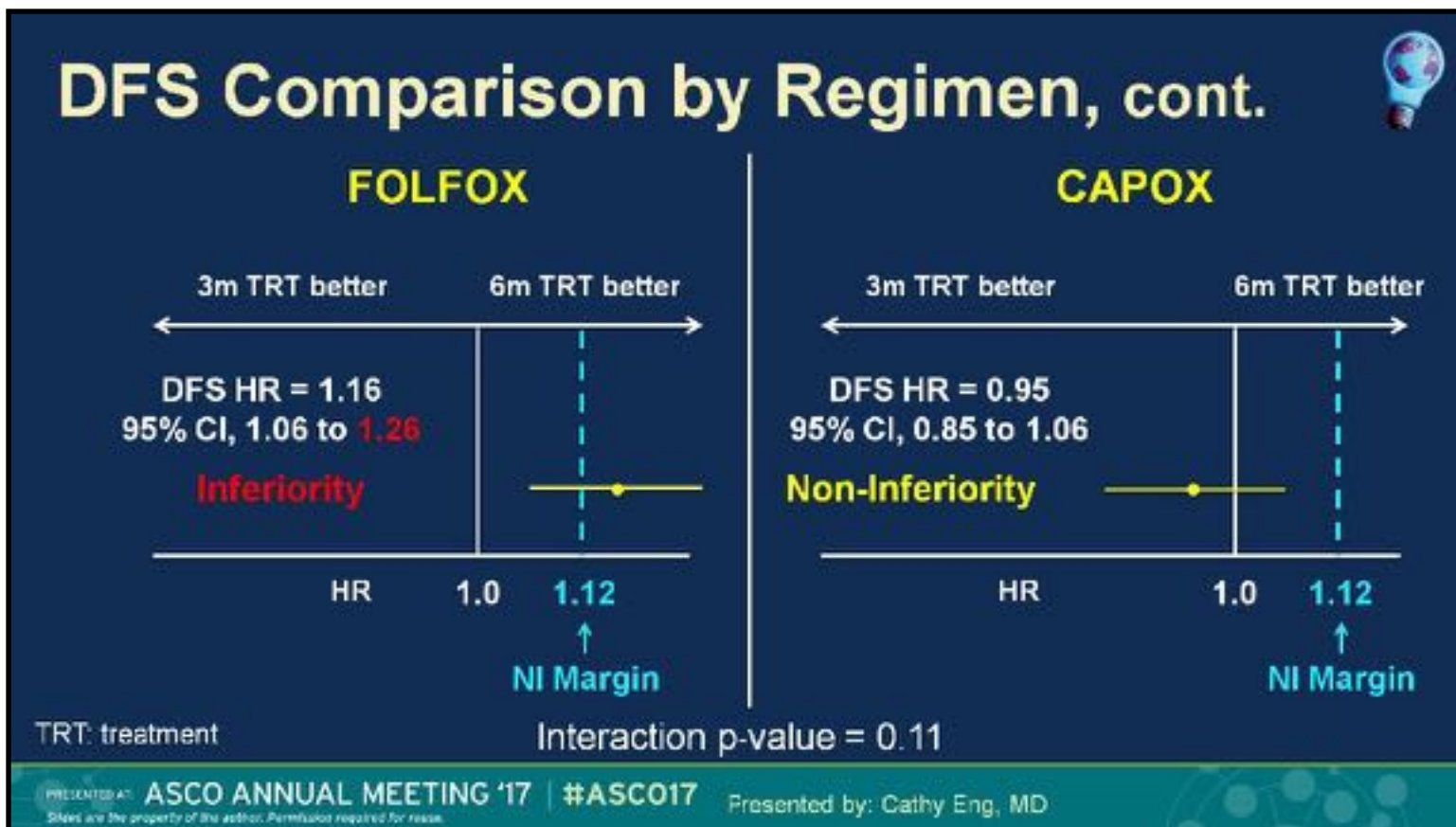
ANÁLISE COMBINADA

- Desfecho primário
 - Grande diferença de prognóstico observado entre grupos T1-3N1 vs. T4 e/ouN2: 20% δ em SLD 3 anos.
 - Análise "*post ad-hoc*" entre estes grupos.
- Dois regimens distintos utilizados: XELOX e FOFLOX.
 - Análise "*ad hoc*" 3m vs. 6m por regime.
 - Análise "*pos hoc*" entre regimes.

COLABORAÇÃO IDEA

ANÁLISE COMBINADA

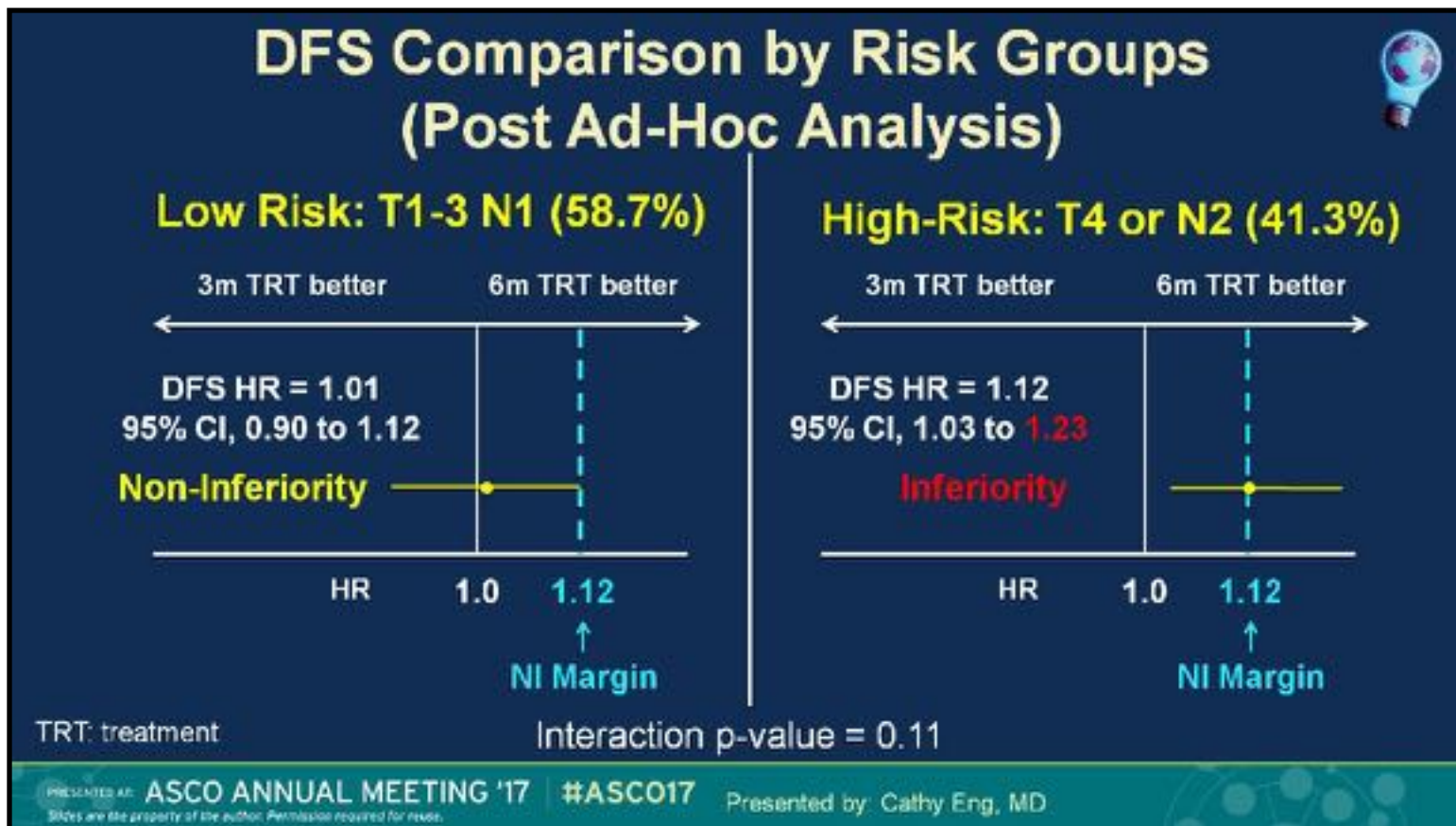
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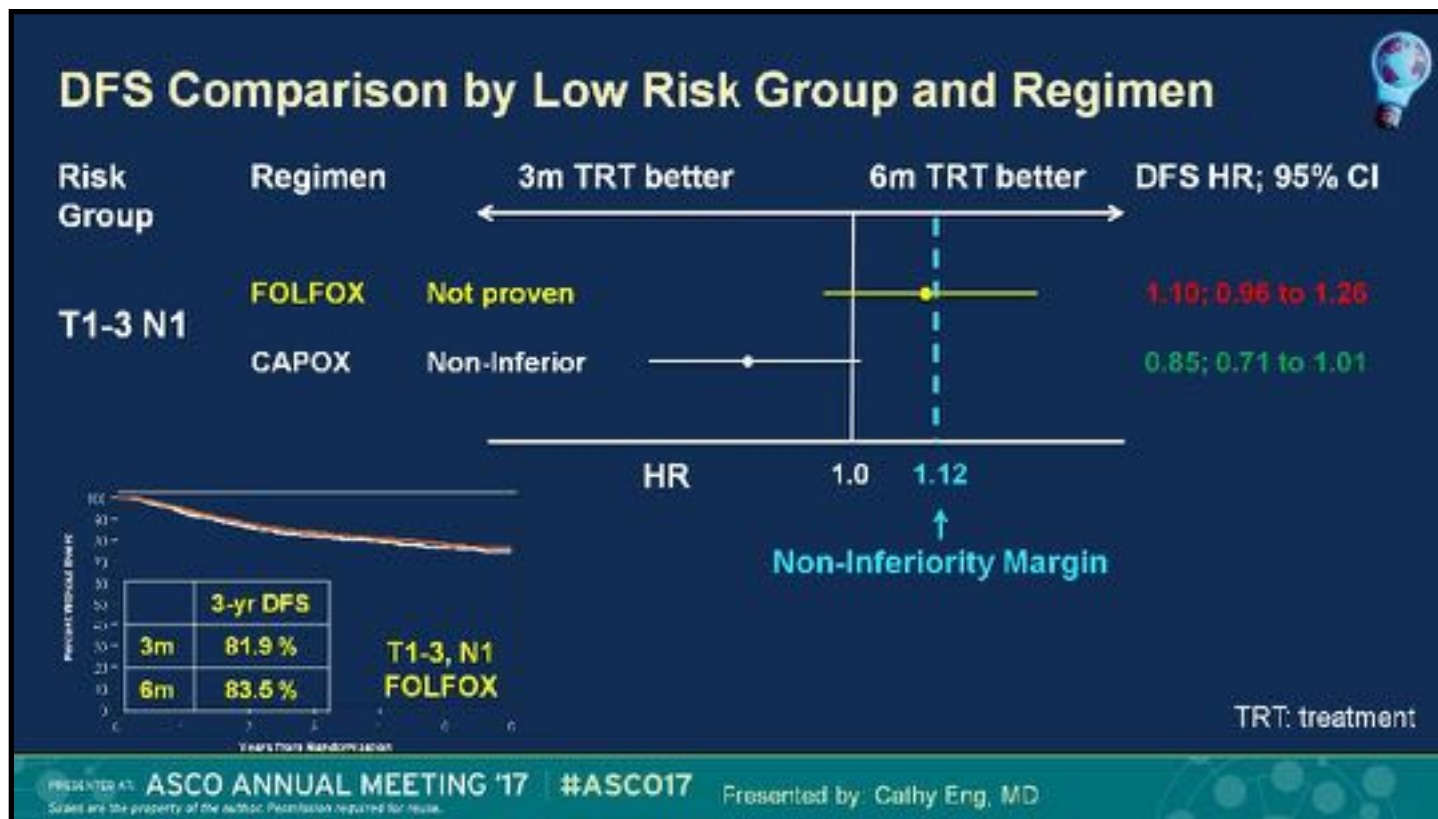
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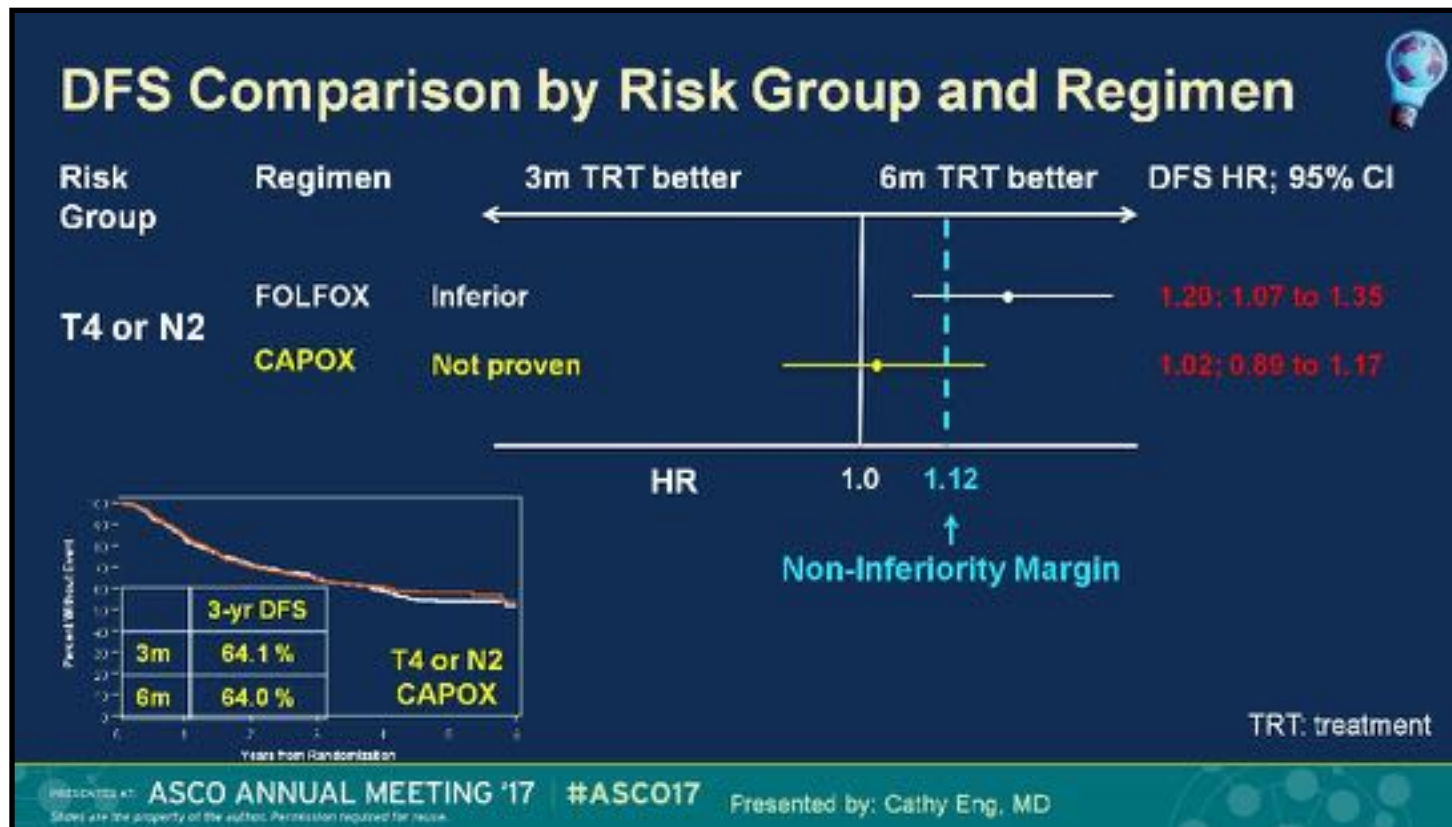
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ANÁLISE COMBINADA

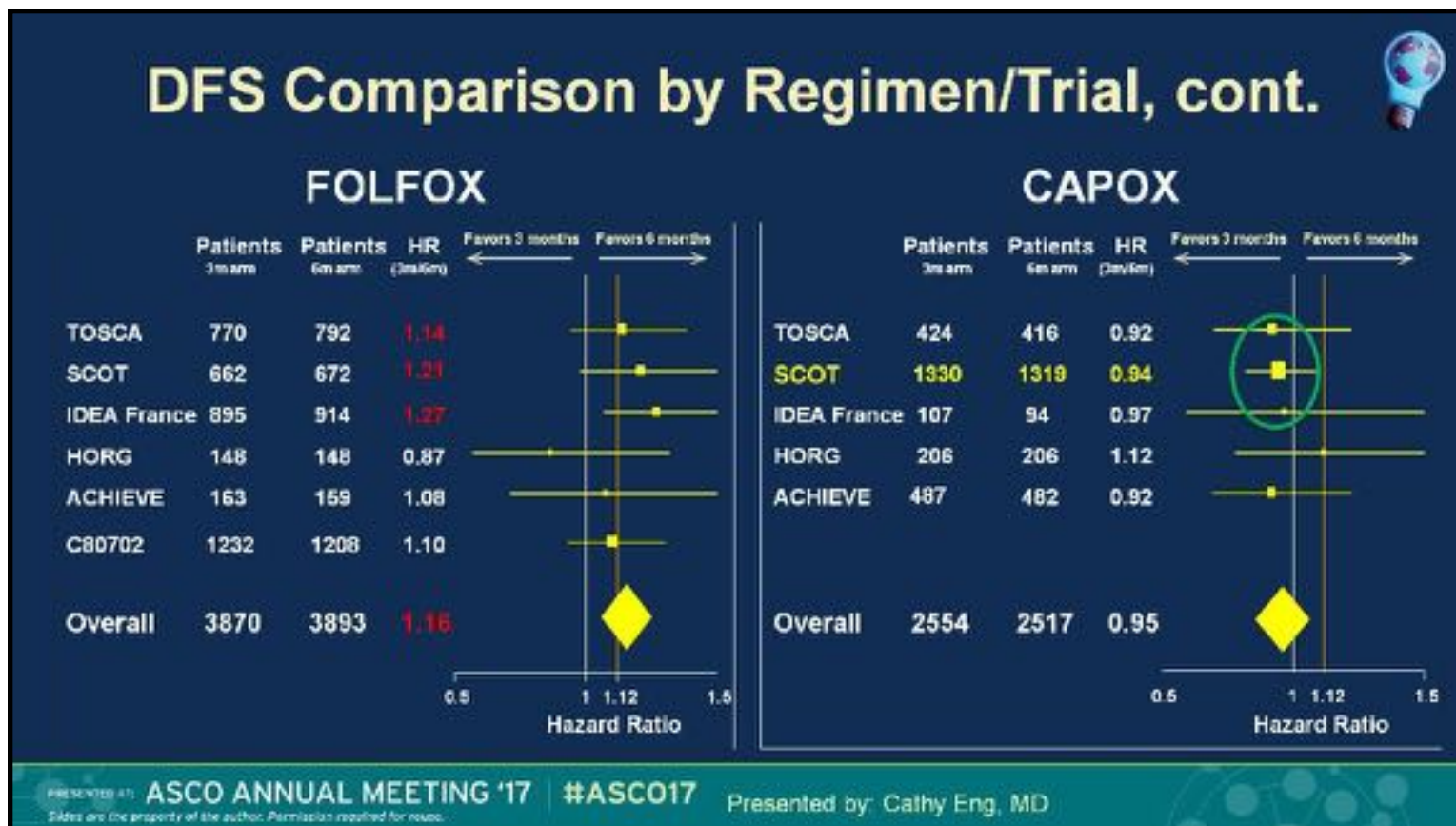
- Desfecho primário



COLABORAÇÃO IDEA

ANÁLISE COMBINADA

- Desfecho primário



COLABORAÇÃO IDEA

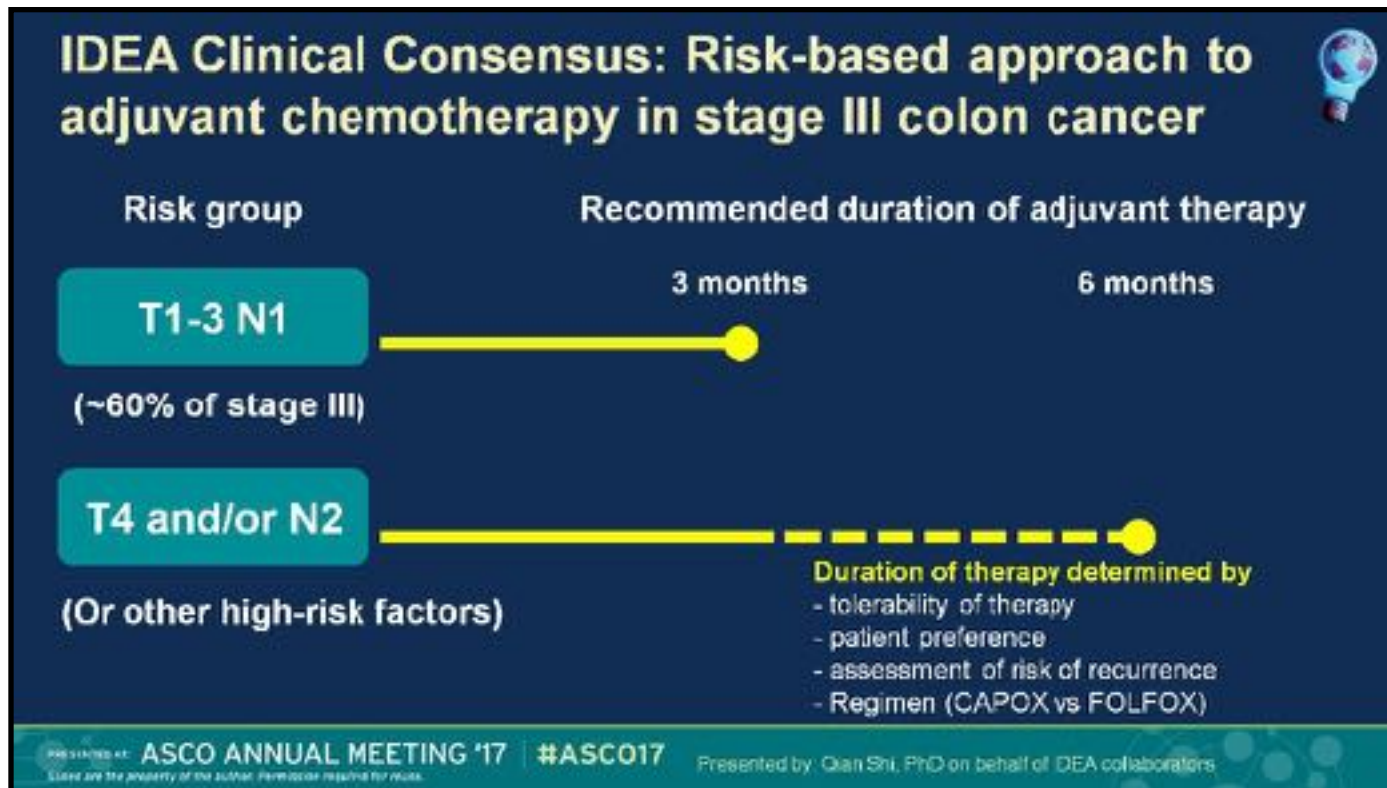
ANÁLISE COMBINADA

- Conclusões
 - 3m vs. 6m: maior conformidade no tratamento; redução na toxicidade.
 - Desfecho primário na população geral não alcançado
 - Análises secundárias de acordo com risco e regime de tratamento podem estabelecer subgrupos de efetividade.
 - Duração de tratamento: balanço entre potencial perda de efetividade em SLD em 3 anos e redução da neurotoxicidade.
 - SLD em 3 anos é um desfecho substitutivo validado para sobrevida global nesta população

COLABORAÇÃO IDEA

ANÁLISE COMBINADA

- Conclusões



COLABORAÇÃO IDEA

ANÁLISE COMBINADA

- Críticas ao estudo
 - Análise combinada de 6 estudos independentes heterogêneos
 - 3 estudos (ACHIEVE, CALGB 80702, HORG) ainda sem apresentação de dados finais.
 - Pacientes com MSI-H não foram excluídos.
 - Resultados ainda não publicados. SG imatura.

Plenary Discussion:
International Duration Evaluation
of Adjuvant Chemotherapy (IDEA)
A Pooled Analysis –
A Change in Treatment Paradigm?

Cathy Eng, B.S., F.A.C.R.
The University of Texas MD Anderson Cancer Center
Stephanie Caroline Steves Distinguished Professor in Cancer Research
Professor, Dept of Medical Oncology
June 4, 2017
Contact info: cathy@mdanderson.org Twitter: @cathyengmd

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Conclusions:

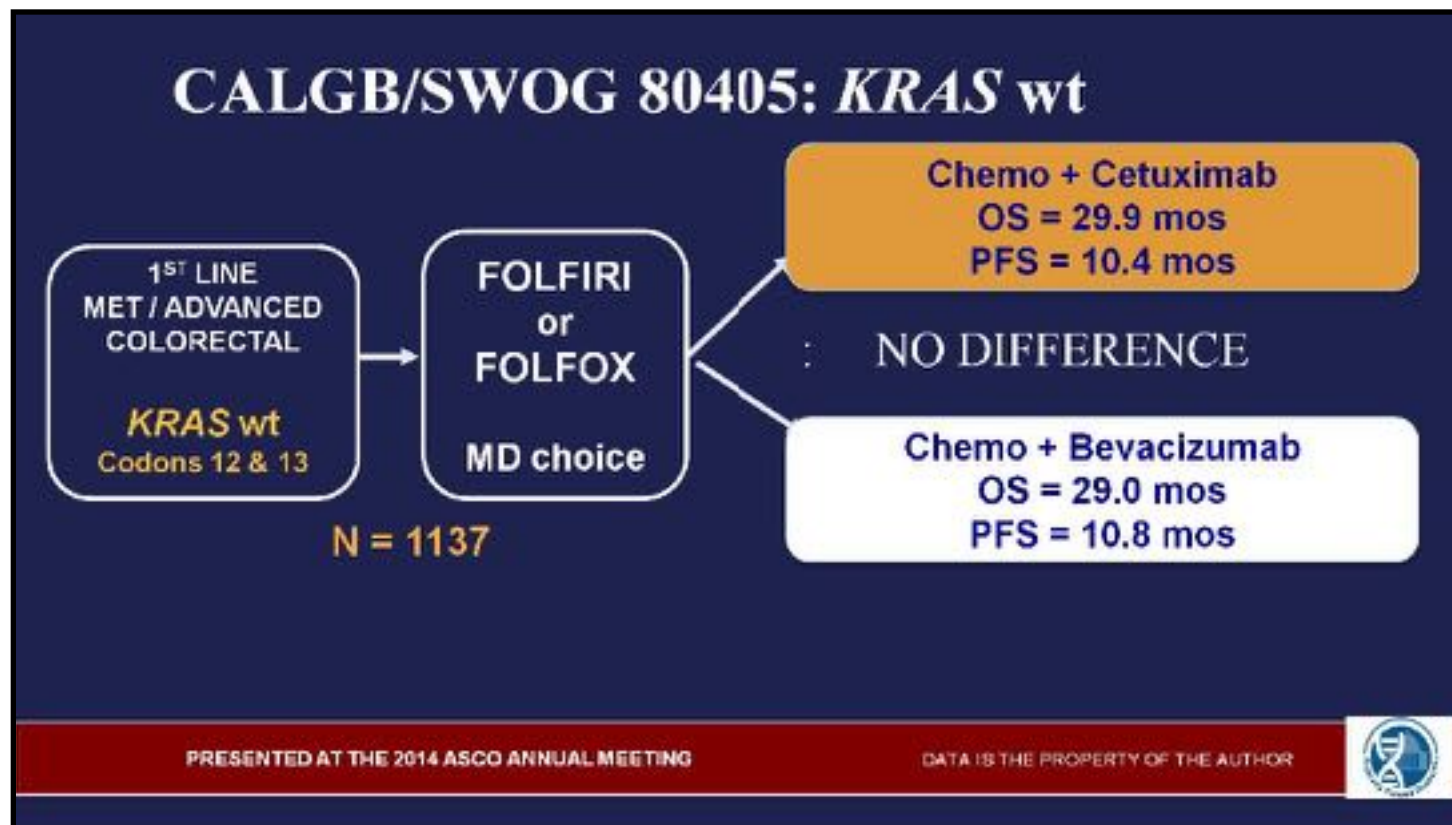
- To date, based on the information provided from the IDEA pooled analysis, 3M of adjuvant oxaliplatin-based chemotherapy is not non-inferior to 6M for DFS.
 - CAPOX appears non-inferior in T1-3N1 patients, but is largely based on one trial (SCOT) with incomplete capture of SAE's
 - Furthermore, CAPOX is not a regimen for all patients.
- Six months of adjuvant oxaliplatin-based chemotherapy for stage III colon cancer remains the standard of care.
 - Reality: Few patients are able to receive all 6 months of oxaliplatin-based chemotherapy due to treatment-related SAE's (e.g., dose-limiting neuropathy)
 - The final duration of oxaliplatin-based therapy should be a continuous matter of discussion between the physician and the patient based on existing toxicities of therapy.

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CÂNCER COLORRETAL CALGB/SWOG 80405

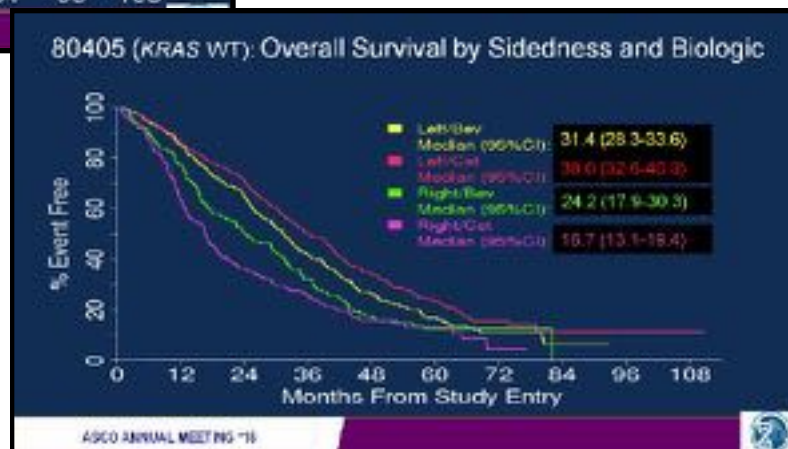
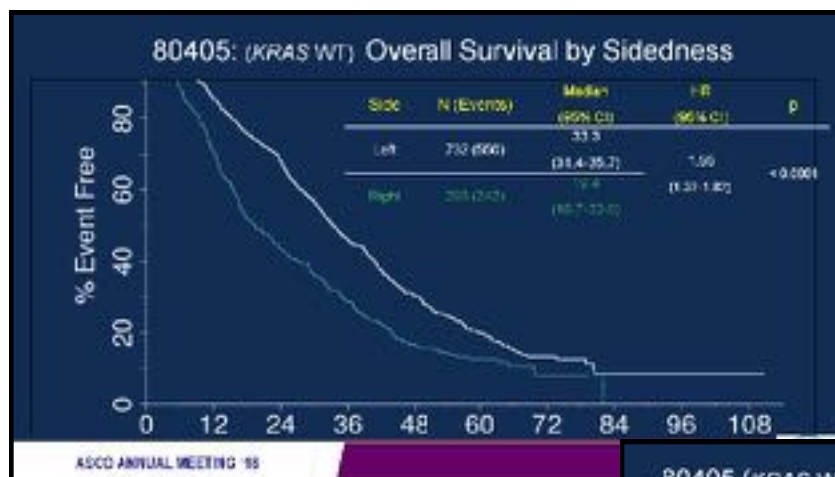
CALGB/SWOG 80405

- Desenho original e resultado final



CALGB/SWOG 80405

- Análises exploratórias indicaram que a lateralidade é prognóstica e preditiva.



CALGB/SWOG 80405

ANÁLISES TRANSLACIONAIS E CORRELATIVAS

CALGB/SWOG 80405 (Alliance)- Translational & Correlative studies

- Abstract 3503
Primary (1°) tumor location as an independent prognostic marker from molecular features for OS in patients mCRC.
Alan P. Venook, MD, FASCO, et al.
- Abstract 3504
Somatic DNA mutations, MSI status, mutational load: Association with OS in patients with mCRC.
Federico Innocenti, MD, PhD, et al.
- Abstract 3511 (Tuesday 9:45 AM, CSS – Making sense of Consensus Molecular Subtypes)
Impact of Consensus Molecular Subtyping on OS and PFS in patients with mCRC.
Heinz-Josef Lenz, MD, FACP, et al.

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ANÁLISES TRANSLACIONAIS E CORRELATIVAS

- ABSTRACT 3503
 - Lateralidade persiste prognóstica mesmo quando ajustada pelas características avaliadas.

Factors included in multivariate analysis

- Age
- Race
- Gender
- Synchronous v metachronous
- Consensus Molecular Subtypes
- MSI, BRAF, NRAS, KRAS, HRAS

Cox proportional hazard stratified: prior XRT, +/- adj chemotherapy

$HR = 1.392 (1.032, 1.878), p = 0.031$

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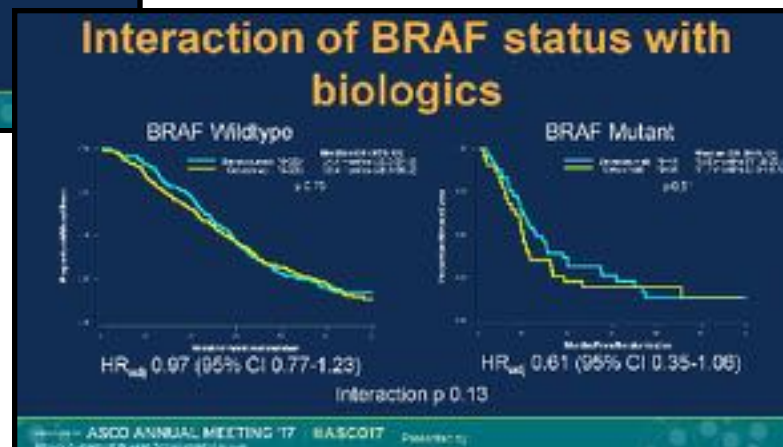
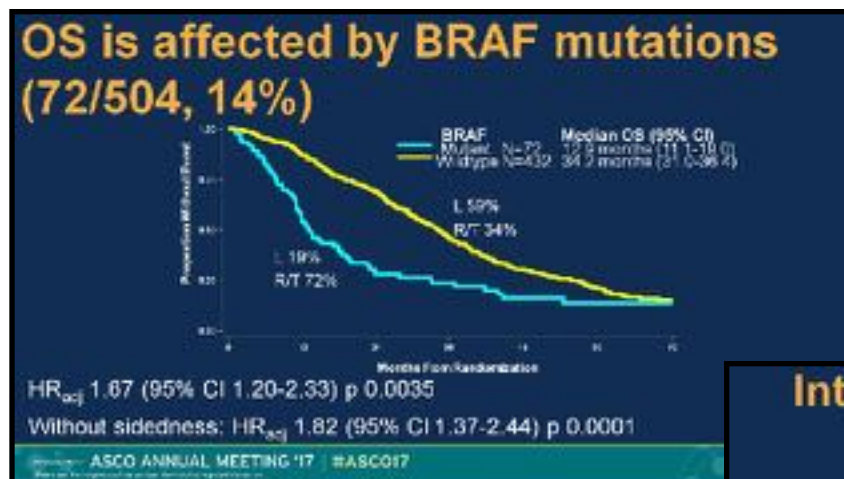
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ANÁLISES TRANSLACIONAIS E CORRELATIVAS

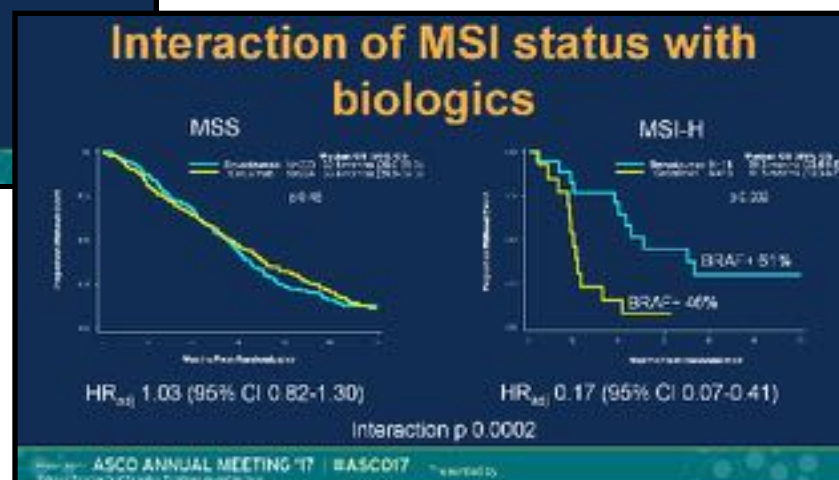
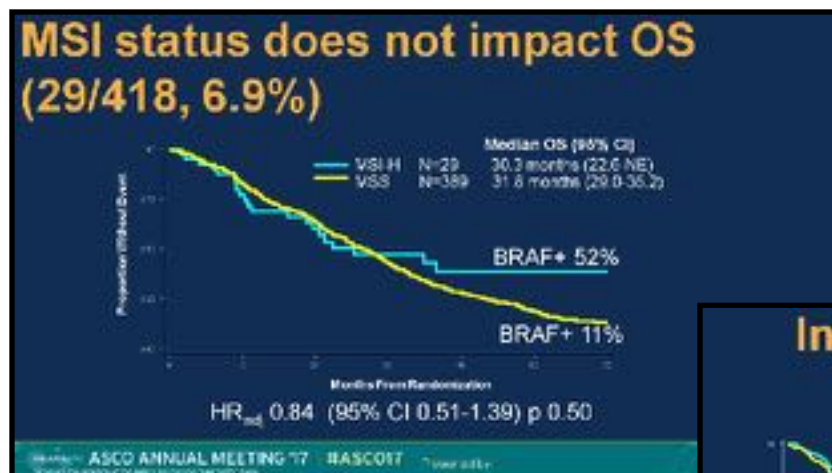
- ABSTRACT 3504
 - Mutação do BRAF: fortemente prognóstica mas não é preditiva.



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ANÁLISES TRANSLACIONAIS E CORRELATIVAS

- ABSTRACT 3504
 - Instabilidade de microsatélites: não é prognóstica mas pode ser preditiva.



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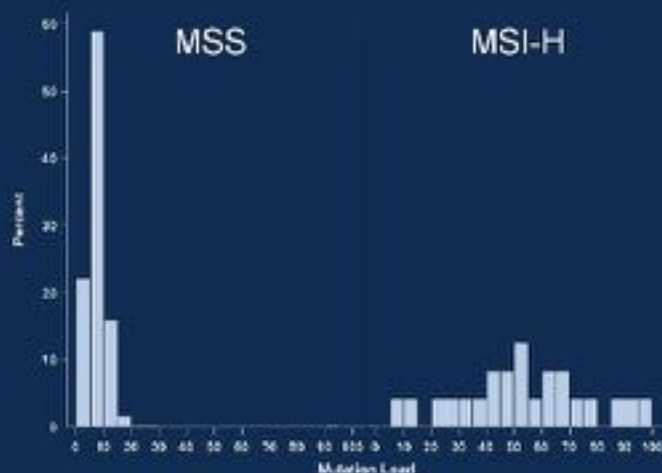
ANÁLISES TRANSLACIONAIS E CORRELATIVAS

- ABSTRACT 3504
 - Carga mutacional

Mutational Load (ML) by MSI status (N=319)

2 MSS excluded: high ML of 93 and 361

Median ML in MSS: 6 (range 0.5 – 85)



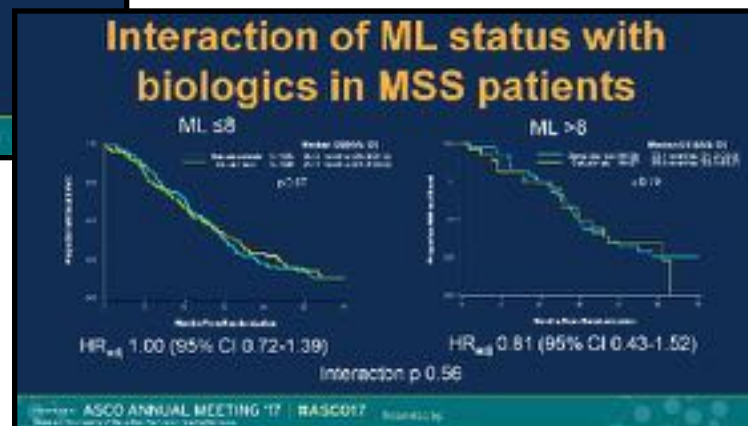
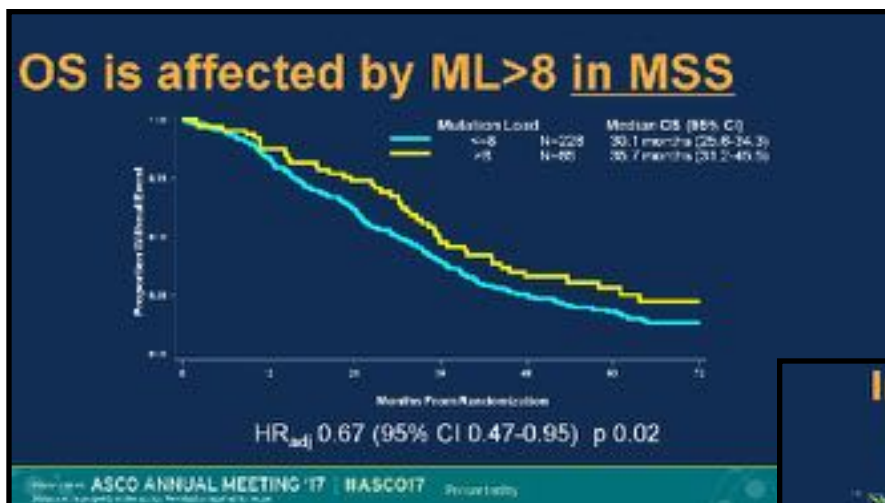
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ANÁLISES TRANSLACIONAIS E CORRELATIVAS

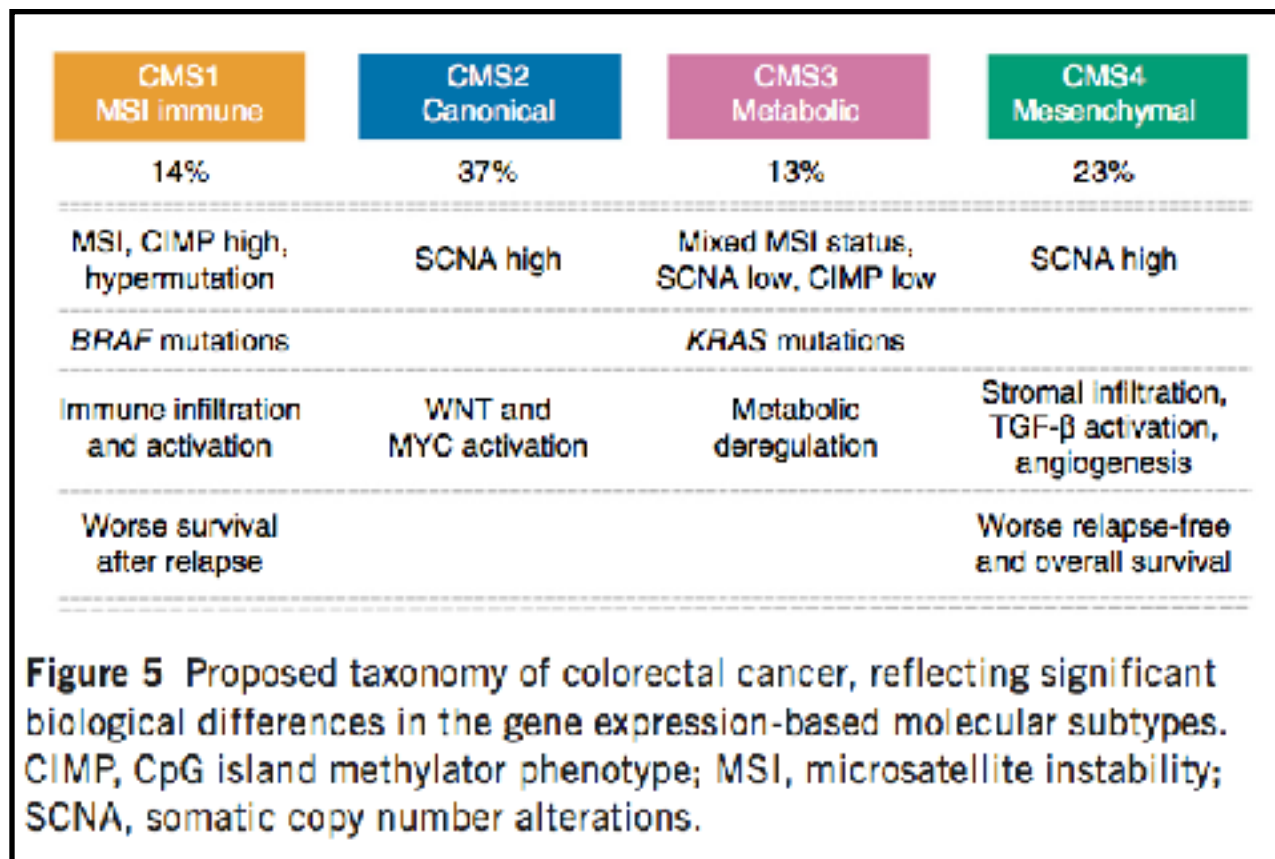
- ABSTRACT 3504
 - Carga mutacional em pacientes com fenótipo de estabilidade de microsatélites pode ser prognóstica mas não é preditiva.



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ANÁLISES TRANSLACIONAIS E CORRELATIVAS

- ABSTRACT 3511
 - Consenso de Subtipos Moleculares do Câncer de Cólon (CMS)



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ANÁLISES TRANSLACIONAIS E CORRELATIVAS

- ABSTRACT 3511
 - Consenso de Subtipos Moleculares do Câncer de Cólon (CMS)

My CMS Cheat-sheet

- **CMS1**: MSI/BRAF, CIMP, Immune
 - **CMS2**: Supposed to have 2 copies
Copy number alterations, “canonical”, Myc/Wnt (2 genes)
 - **CMS3**: Metabolic, KRAS mut’n enriched
 - **CMS4**: Mesenchymal, stromal, TGFβ
- Remember, CMS types were developed on biology, not outcome.



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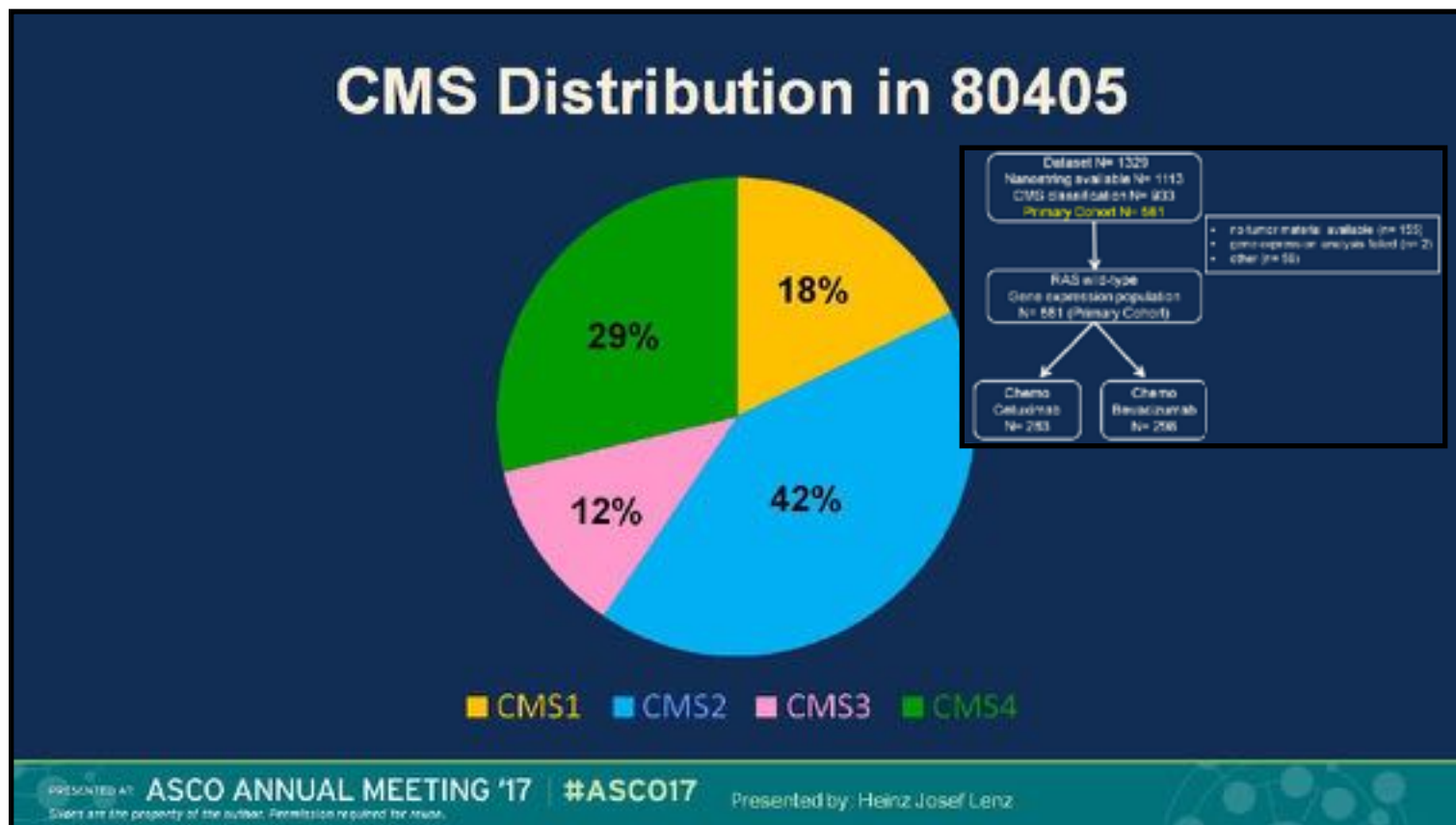
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Presented by: Wells Messersmith, MD (Colorado)

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ANÁLISES TRANSLACIONAIS E CORRELATIVAS

- ABSTRACT 3511
 - Consenso de Subtipos Moleculares do Câncer de Cólon (CMS)



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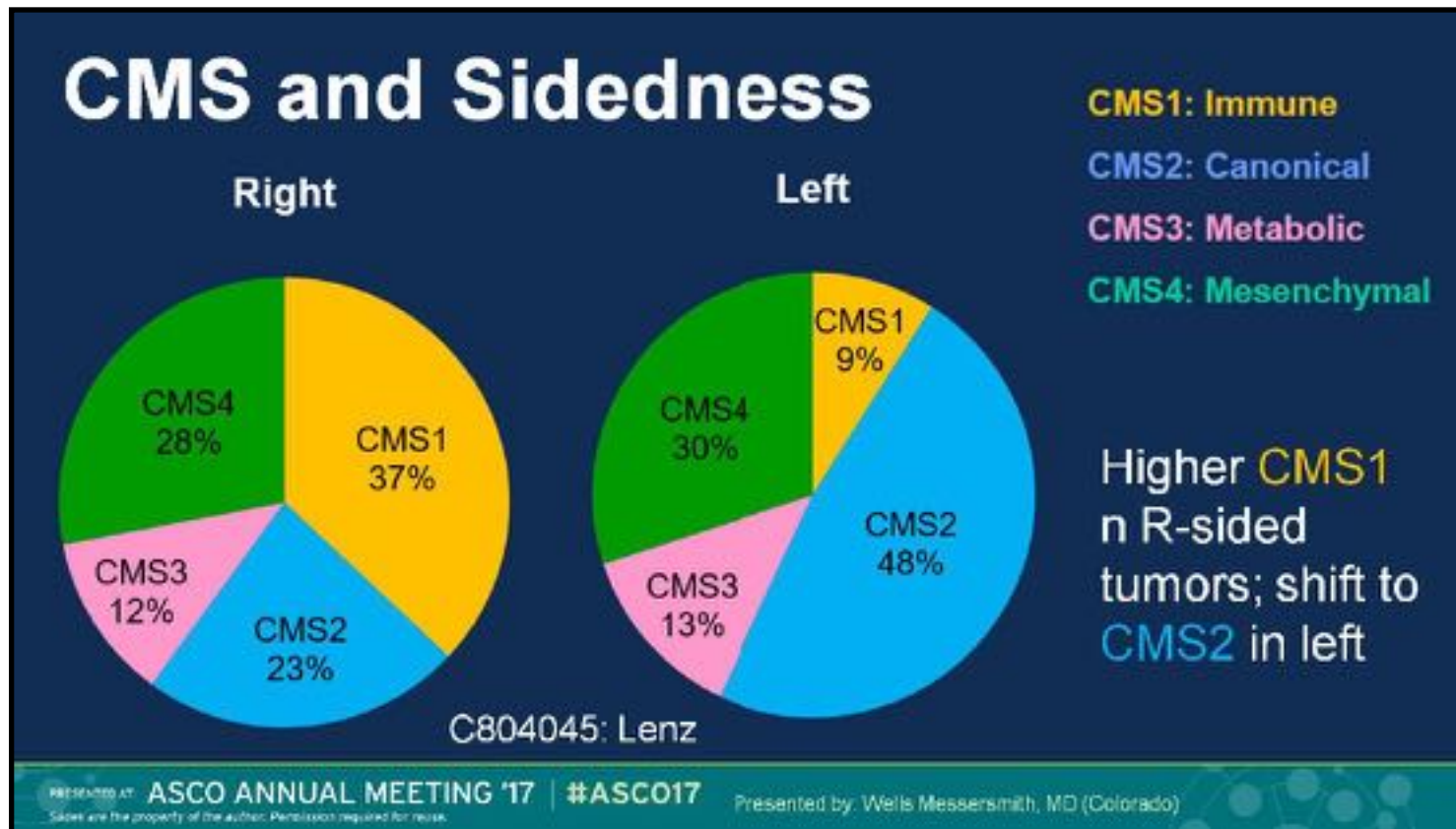
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Presented by: Heinz Josef Lenz

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ANÁLISES TRANSLACIONAIS E CORRELATIVAS

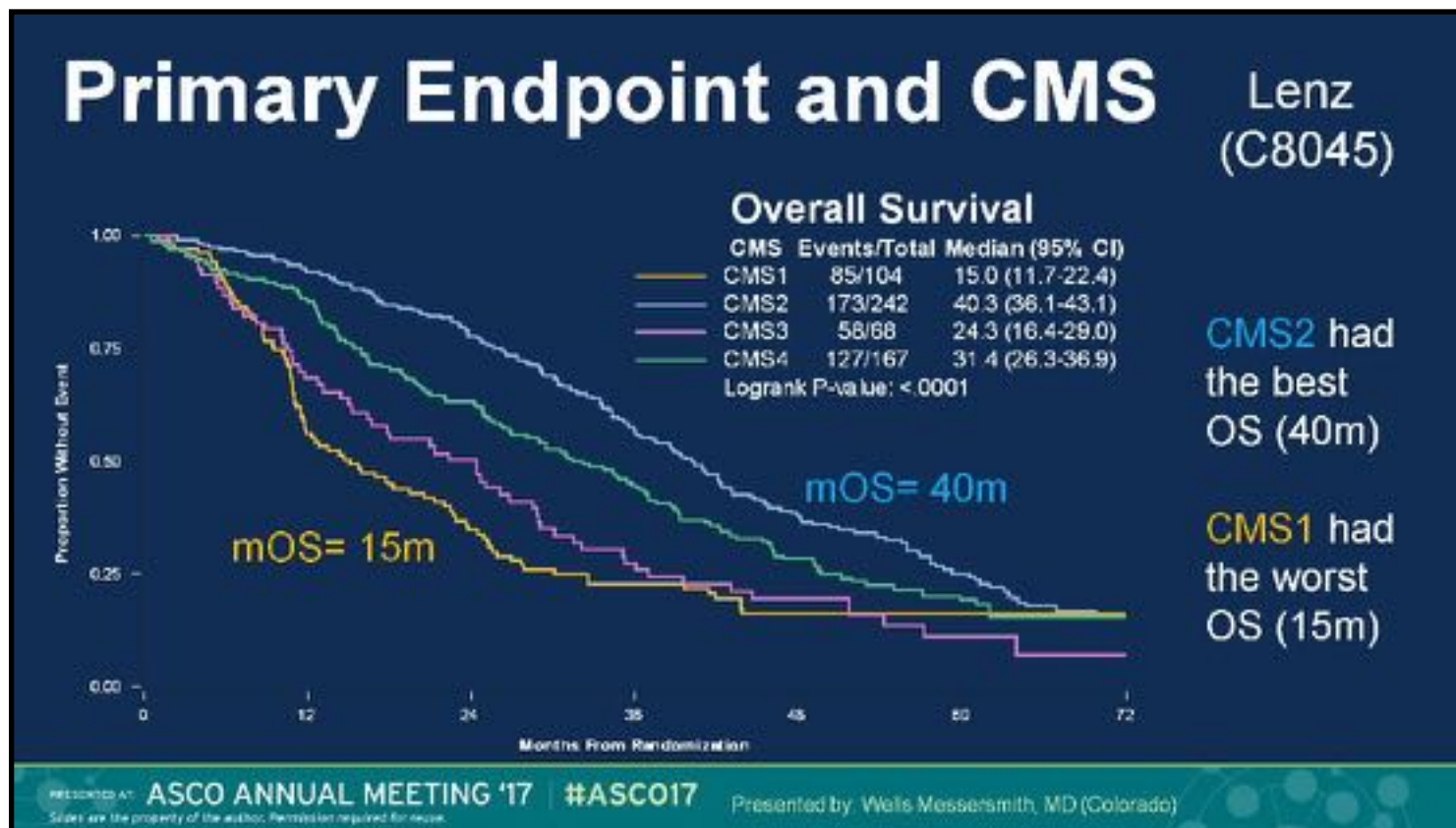
- ABSTRACT 3511
 - CMS e lateralidade



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ANÁLISES TRANSLACIONAIS E CORRELATIVAS

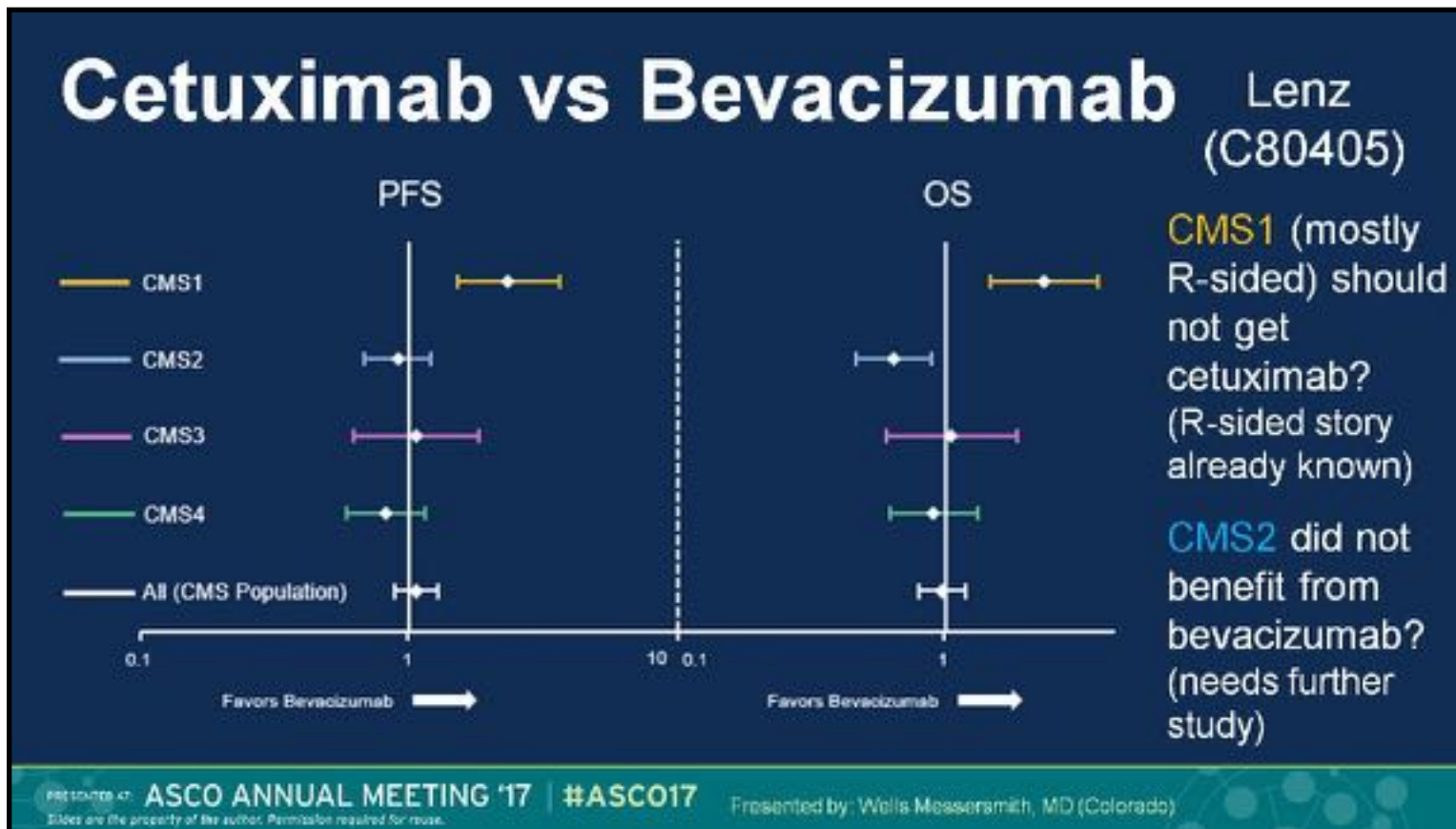
- ABSTRACT 3511
 - A classificação do CMS é altamente prognóstica



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ANÁLISES TRANSLACIONAIS E CORRELATIVAS

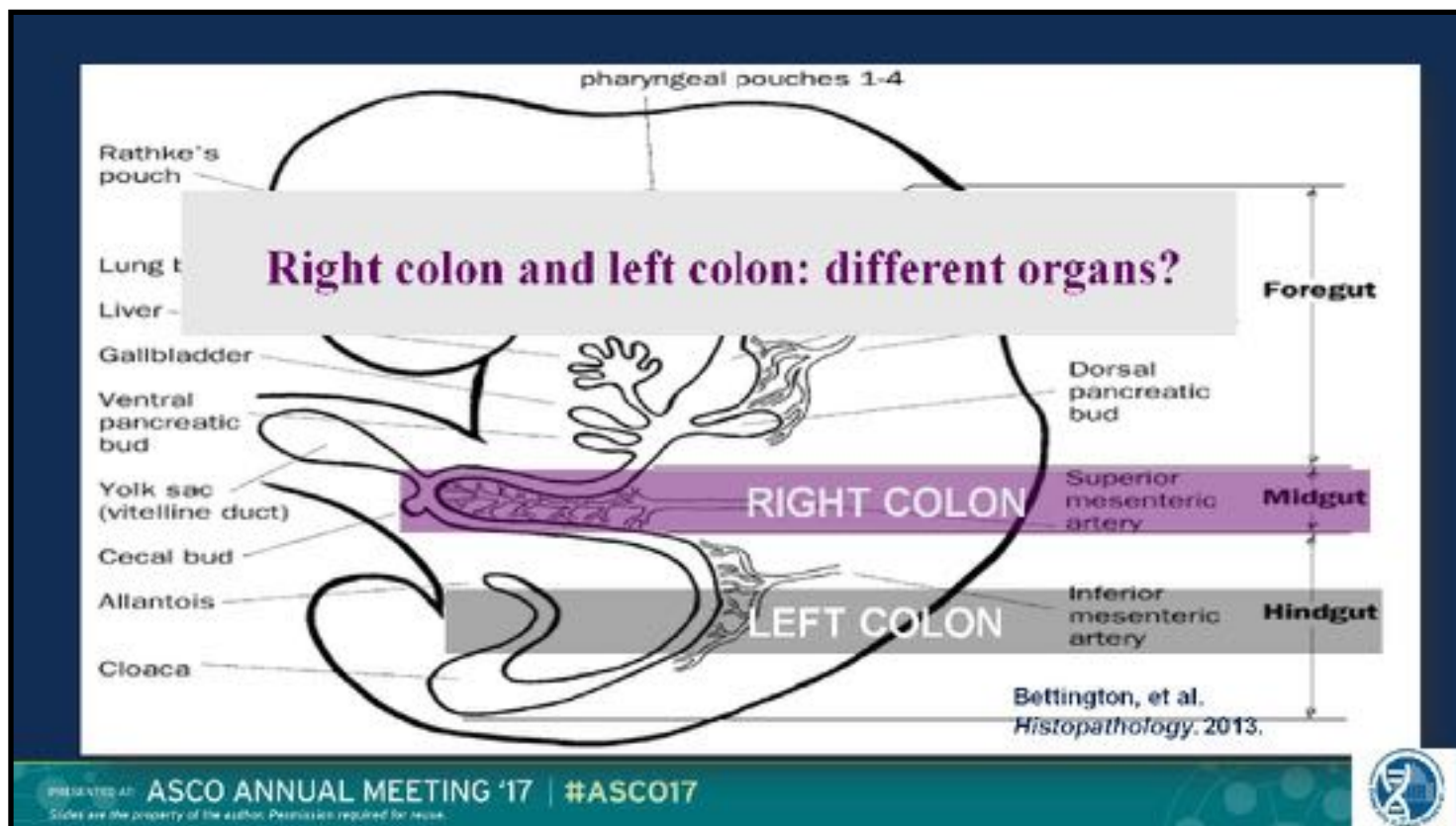
- ABSTRACT 3511
 - A classificação do CMS pode ser preditiva



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ANÁLISES TRANSLACIONAIS E CORRELATIVAS

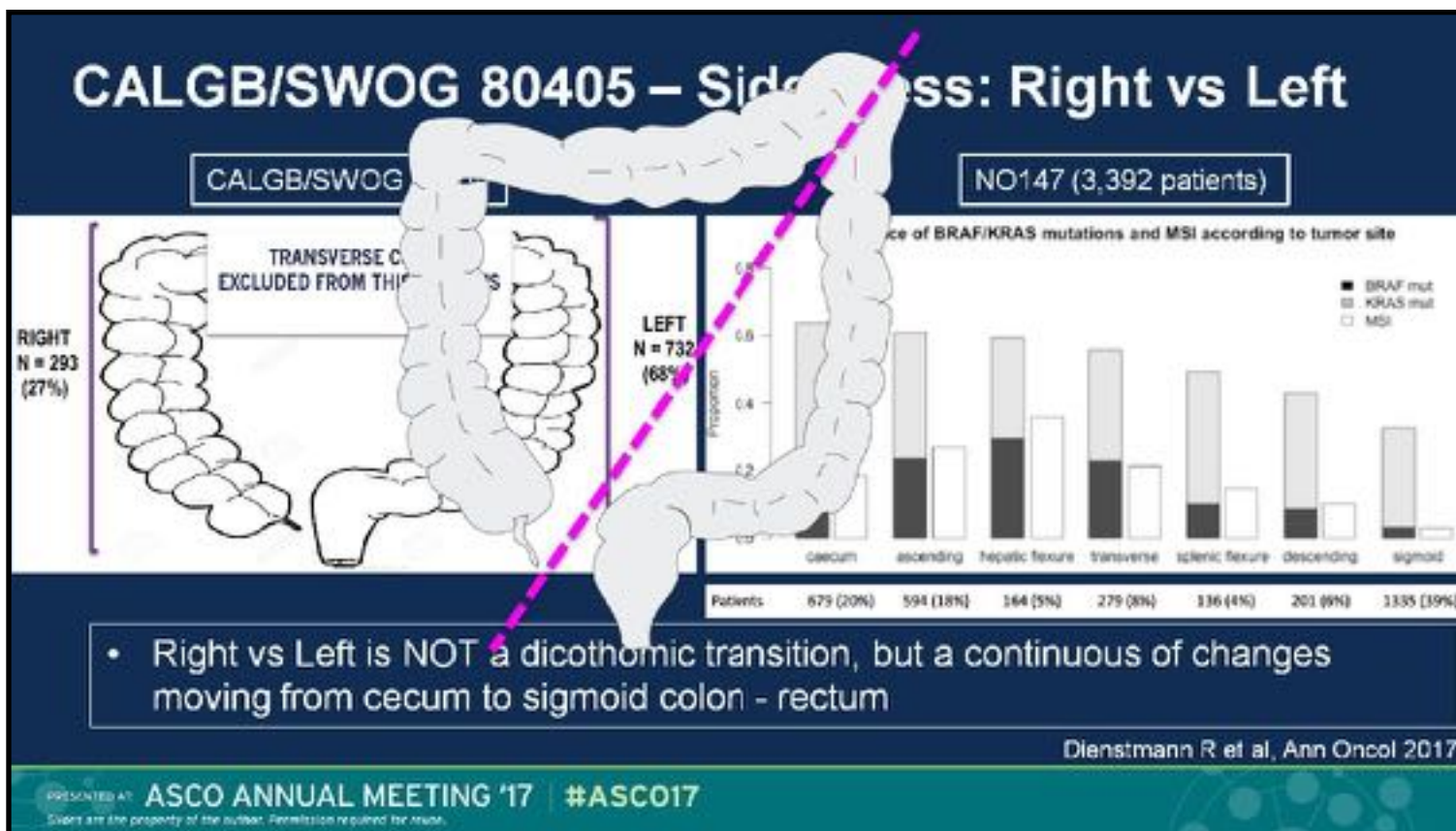
- CONCLUSÕES



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ANÁLISES TRANSLACIONAIS E CORRELATIVAS

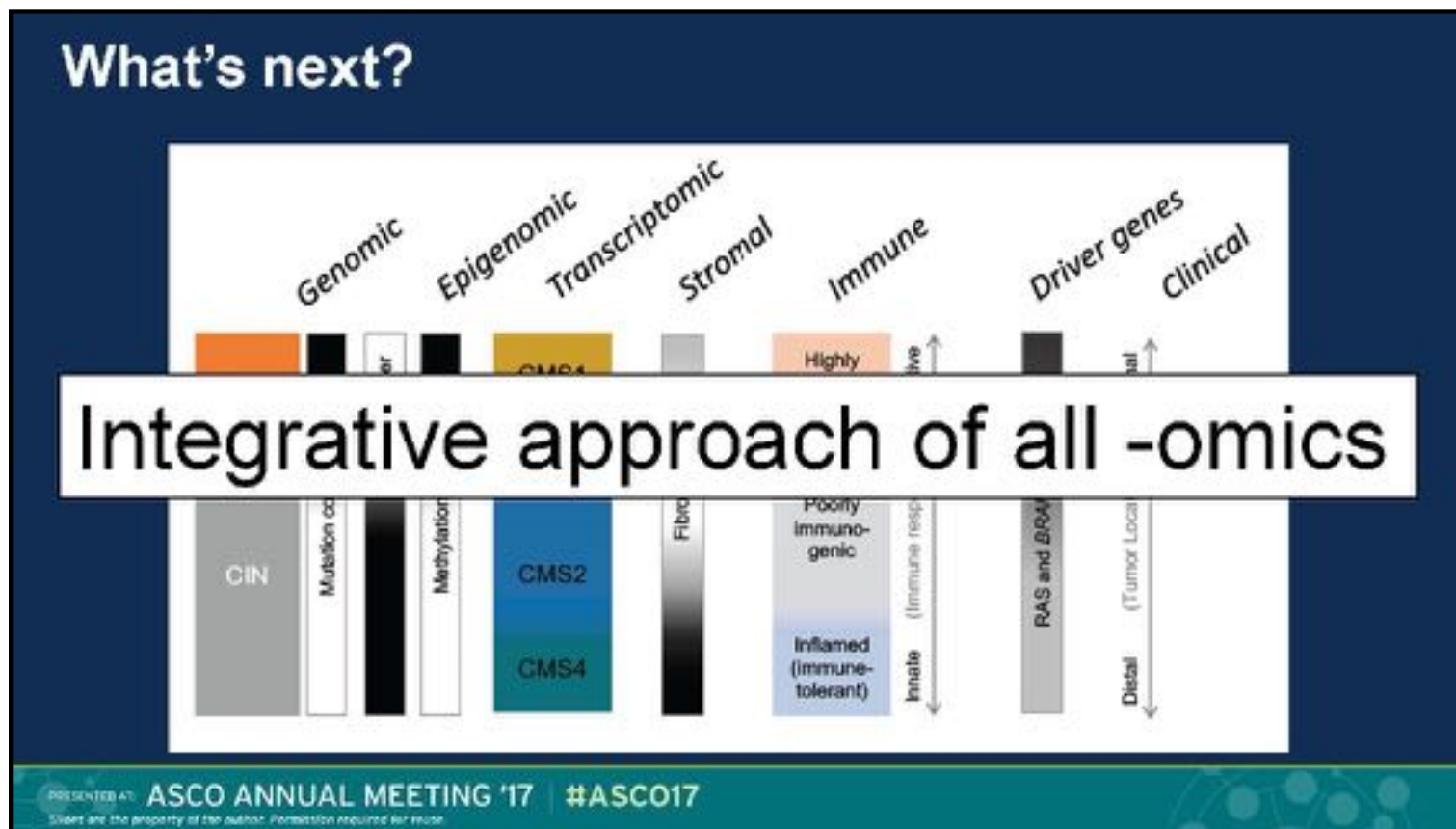
- CONCLUSÕES



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ANÁLISES TRANSLACIONAIS E CORRELATIVAS

- CONCLUSÕES



CÂNCER COLORRETAL METASTÁTICO NOVAS ESTRATÉGIAS TERAPÊUTICAS

CCR METASTÁTICO: NOVAS ESTRATÉGIAS

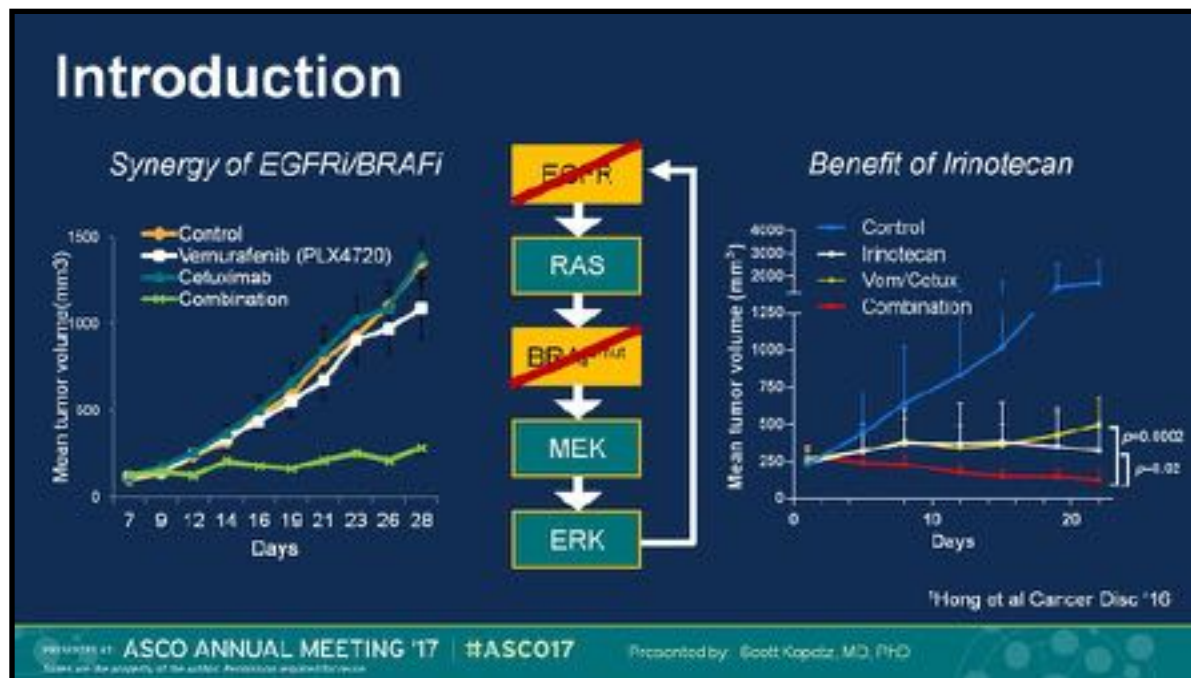


- Mutação BRAF V600E é presente em 7% dos pacientes com CCR metastático.
- Ativação constitucional da via de sinalização MAPK-quinase.
- Associado a biologia agressiva e refratariedade aos tratamentos disponíveis.

CCR METASTÁTICO: NOVAS ESTRATÉGIAS

SWOG S 1406 USO DO VEMURAFENIBE PARA MUTAÇÃO DO BRAF

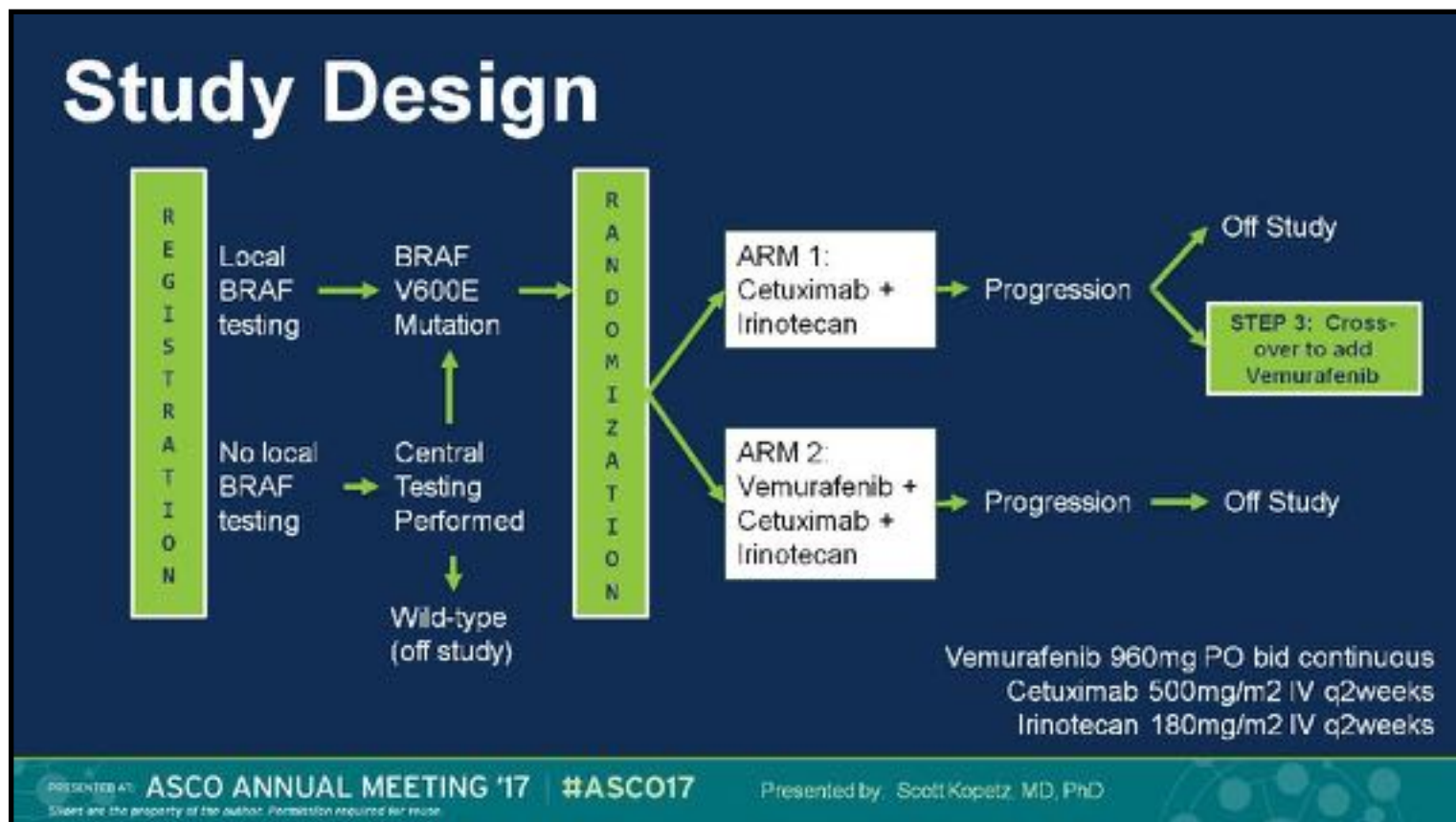
- Vemurafenibe é um inibidor específico da mutação do BRAF V600E
 - Atividade limitada como agente isolado
 - Efeito sinérgico quando associado ao anti-EGFR e irinotecano



CCR METASTÁTICO: NOVAS ESTRATÉGIAS

SWOG S 1406 USO DO VEMURAFENIBE PARA MUTAÇÃO DO BRAF

- Desenho do estudo



CCR METASTÁTICO: NOVAS ESTRATÉGIAS

SWOG S 1406 USO DO VEMURAFENIBE PARA MUTAÇÃO DO BRAF

- Desenho do estudo

Key inclusion and exclusion criteria

Inclusion Criteria

- Measurable or non-measurable metastatic disease
- BRAF V600E mutation and have tissue available for central BRAF V600E testing
- Extended RAS wild type
- Must have had one or two prior regimens of systemic chemotherapy for metastatic disease or locally advanced, unresectable disease
- Performance status of 0 or 1

Exclusion Criteria

- Prior cetuximab or panitumumab
- Prior BRAF or MEK inhibitor
- Chemotherapy within 14 days of registration

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Objectives

Primary Objective:

- Progression-free survival

Key Secondary Objectives:

- Frequency and severity of treatment-related toxicity
- Overall survival
- Overall response rate, including confirmed and unconfirmed, complete and partial response in the subset of patients with measurable disease

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SWOG S 1406 USO DO VEMURAFENIBE PARA MUTAÇÃO DO BRAF

- Resultados

Demographics	Cetuximab + Irinotecan (n=50)*	Vemurafenib + Cetuximab + Irinotecan (n=49)*
Median age, years (range)	62 (31–83)	60 (34–83)
Female, n (%)	37 (74%)	21 (43%)
Race, n (%)		
White	49 (98%)	43 (88%)
Black	0 (0%)	1 (2%)
Asian	1 (2%)	4 (8%)
Hispanic Ethnicity, n (%)	2 (4%)	2 (4%)
ECOG PS, n (%)		
0	23 (46%)	24 (49%)
1	27 (54%)	25 (51%)
Prior irinotecan treatment (%)	19 (38%)	20 (41%)
Prior regimens: 1 prior regimen for mCRC	26 (52%)	27 (55%)
2 prior regimens for mCRC	17 (34%)	19 (39%)
Failed adjuvant within 6 months	7 (14%)	3 (6%)
*106 patients were randomized; 7 patients were deemed ineligible due to: inadequate hematologic function (3), not having BRAF V600E mutation (3), and receiving chemotherapy within 14 days prior to randomization (1). In the eligible patients, BRAF V600E was centrally confirmed by NGS in all tested patients (n=72).		

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CCR METASTÁTICO: NOVAS ESTRATÉGIAS

SWOG S 1406 USO DO VEMURAFENIBE PARA MUTAÇÃO DO BRAF

- Toxicidade

Grade 3/4 Adverse Events

	Cetuximab + Irinotecan (n=46)*	Vemurafenib + Cetux + Irino (n=46)*
Anemia	0 (0%)	6 (13%)
Dehydration	3 (7%)	5 (11%)
Diarrhea	6 (13%)	11 (24%)
Febrile Neutropenia	2 (4%)	5 (11%)
Fatigue	7 (15%)	7 (15%)
Neutropenia	3 (7%)	15 (33%)
Rash	3 (7%)	2 (4%)
Hypomagnesemia	2 (4%)	0 (0%)
Nausea	1 (2%)	9 (20%)
Arthralgia	0 (0%)	3 (7%)
Discontinued due to AE	3/50 (6%)	8/49 (16%)

*Seven patients did not start treatment, primarily due to decline in PS before treatment initiated, and are not included in the safety cohort.

*Median duration of treatment is 47 days and 58 days

April 18, 2017 data cutoff

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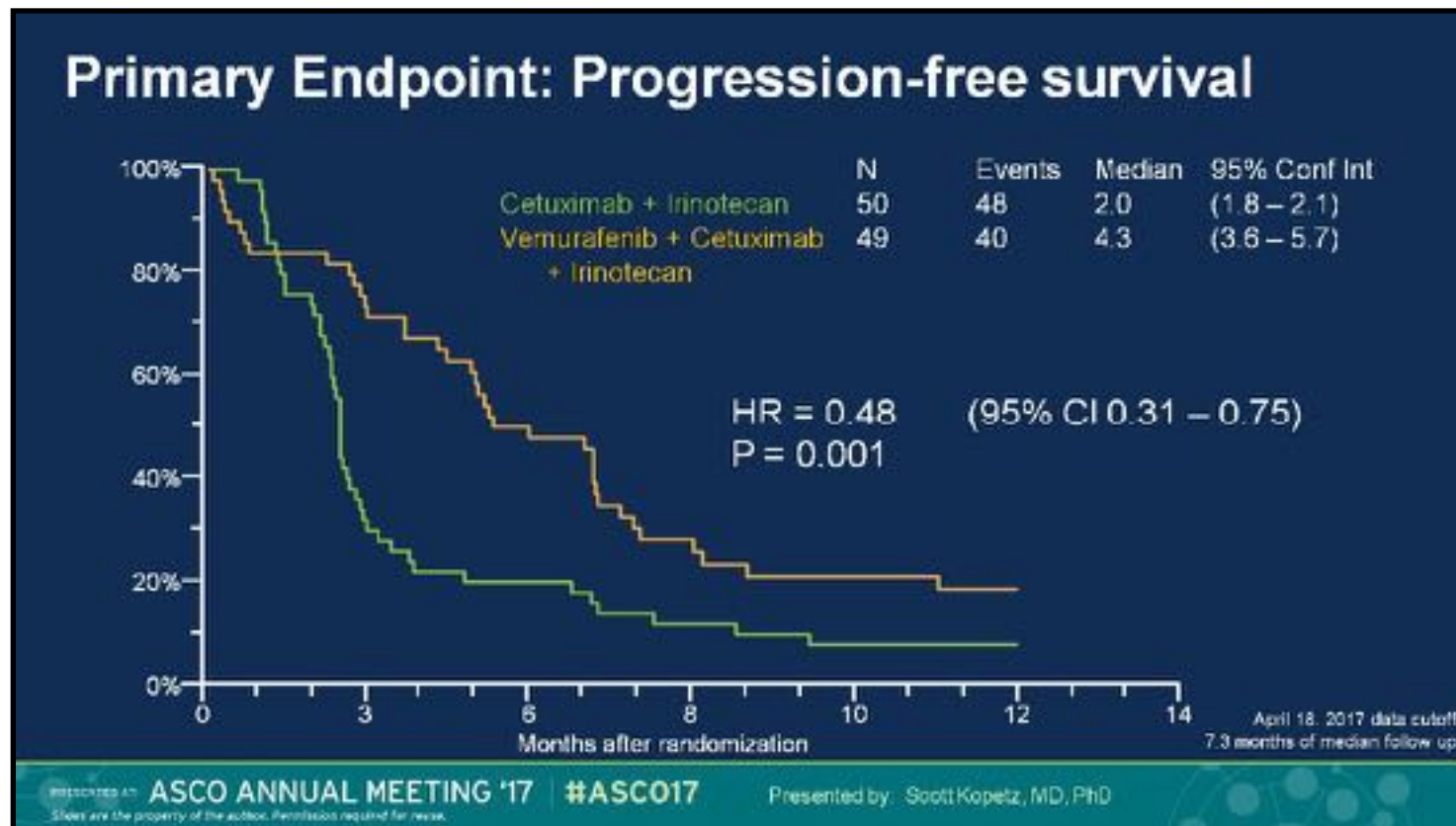
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CCR METASTÁTICO: NOVAS ESTRATÉGIAS

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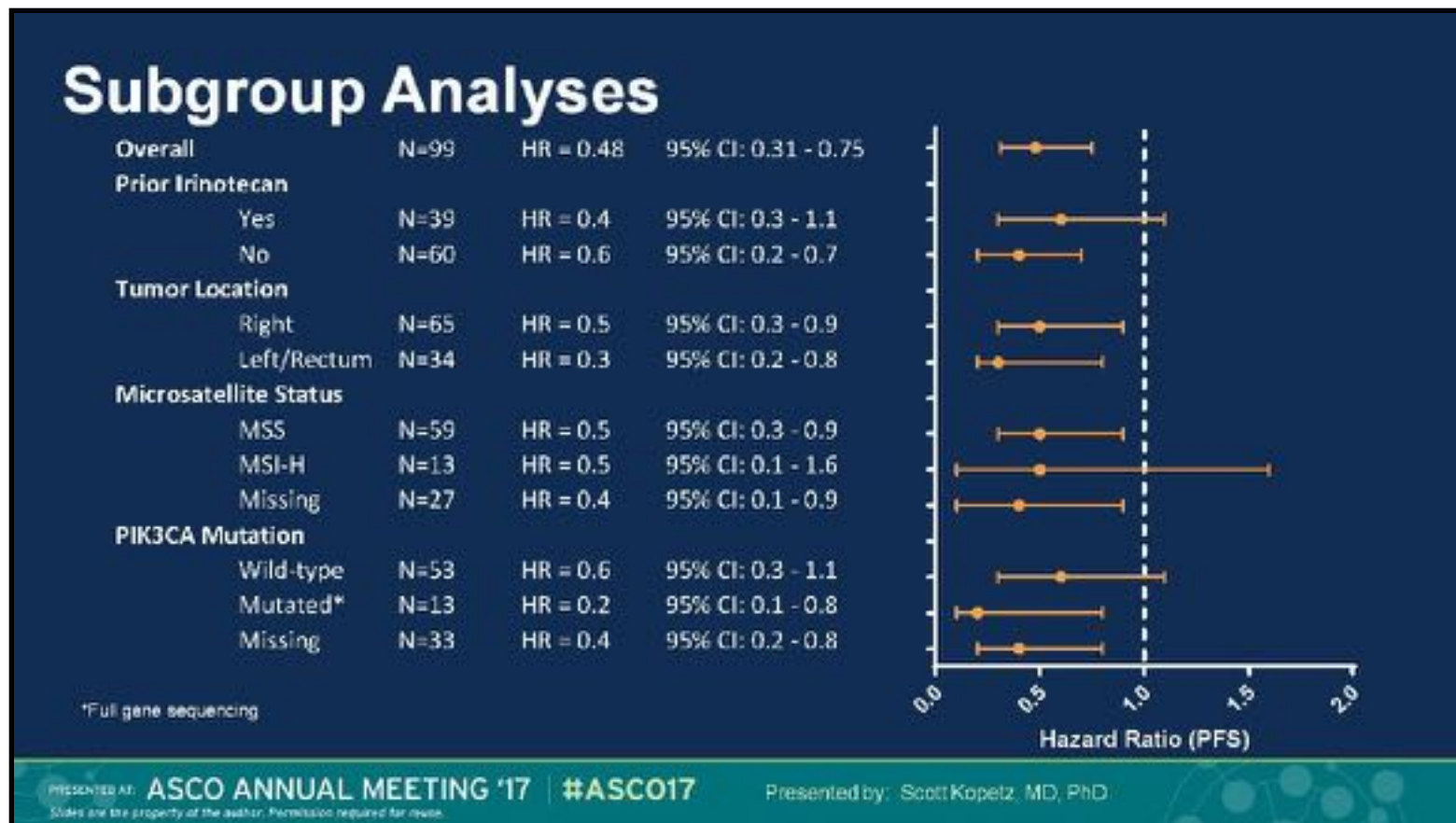
- Desfecho Primário



CCR METASTÁTICO: NOVAS ESTRATÉGIAS

SWOG S 1406 USO DO VEMURAFENIBE PARA MUTAÇÃO DO BRAF

- Desfecho Primário



CCR METASTÁTICO: NOVAS ESTRATÉGIAS

SWOG S 1406 USO DO VEMURAFENIBE PARA MUTAÇÃO DO BRAF

- Desfecho Secundário

Response Rate

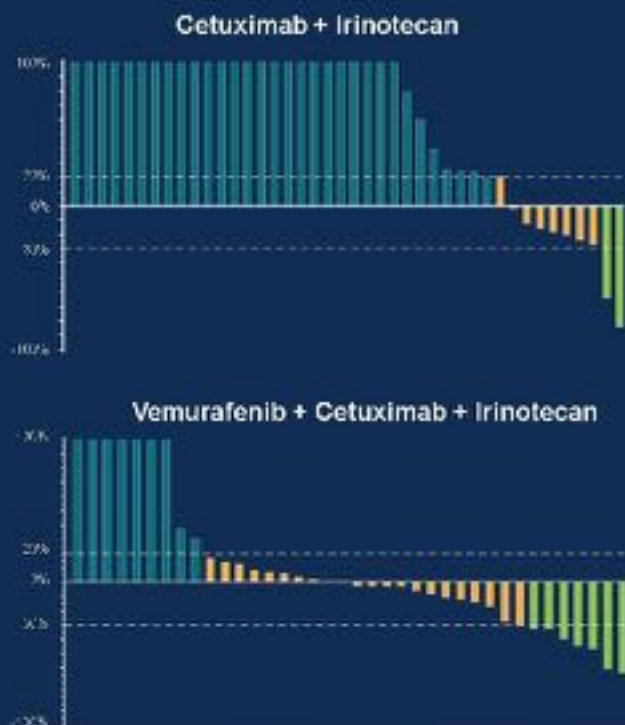
	Cetuximab + Irinotecan (n=47) ^a	Vemurafenib + Cetuximab + Irinotecan (n=44) ^a	P-value ^c
Partial response ^b	4%	16%	P=0.001
Stable disease	17%	50%	
Progression ^c	66%	18%	

Disease Control Rate

22%

67%

^a98 patients had measurable disease; ^bConfirmed and unconfirmed; PR for patients previously treated with irinotecan was 0% and 18%, respectively; ^cIncluding symptomatic deterioration; ^dChi-squared



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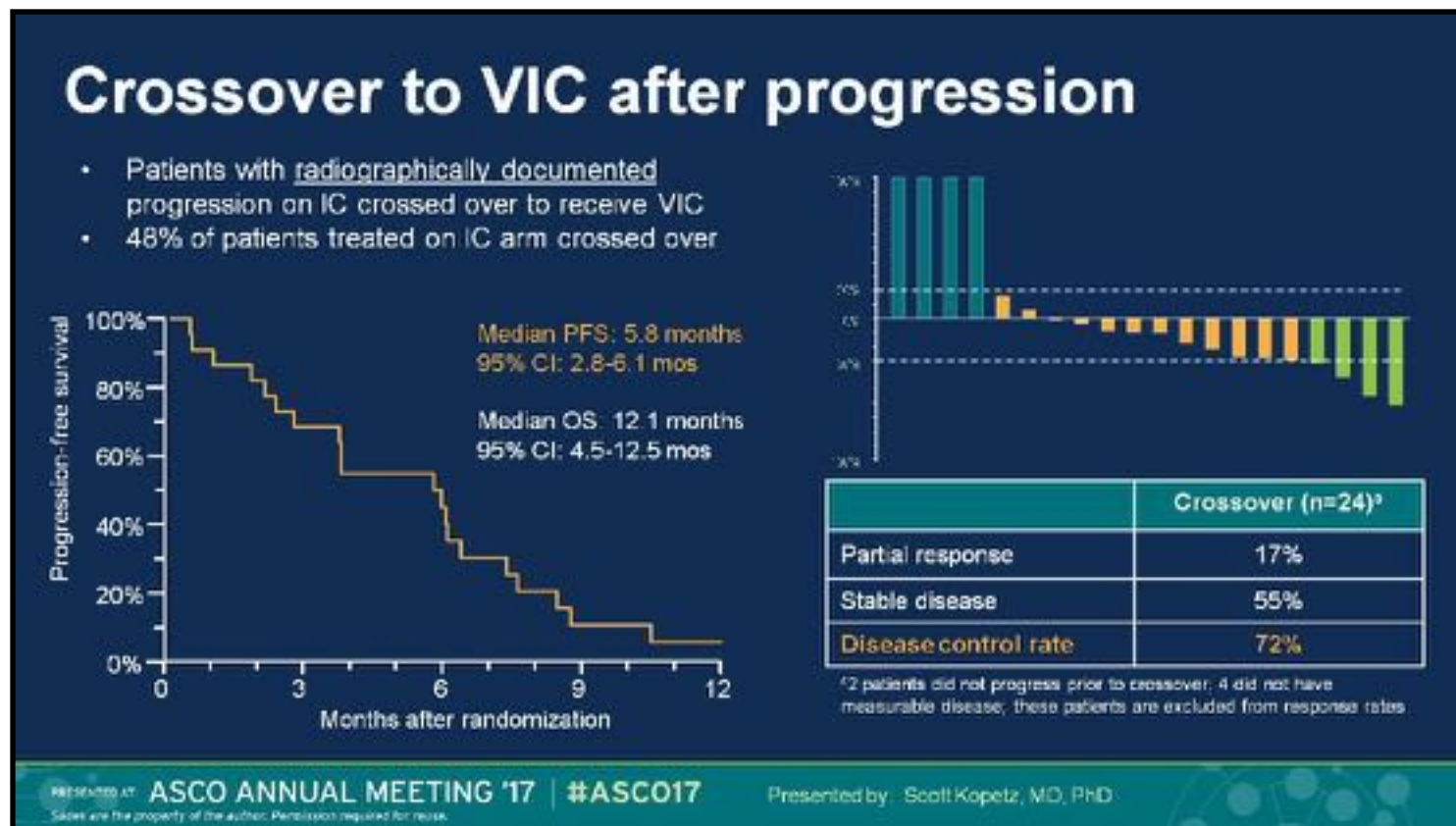
Presented by: Scott Kopetz, MD, PhD

April 18, 2017 data cutoff

CCR METASTÁTICO: NOVAS ESTRATÉGIAS

SWOG S 1406 USO DO VEMURAFENIBE PARA MUTAÇÃO DO BRAF

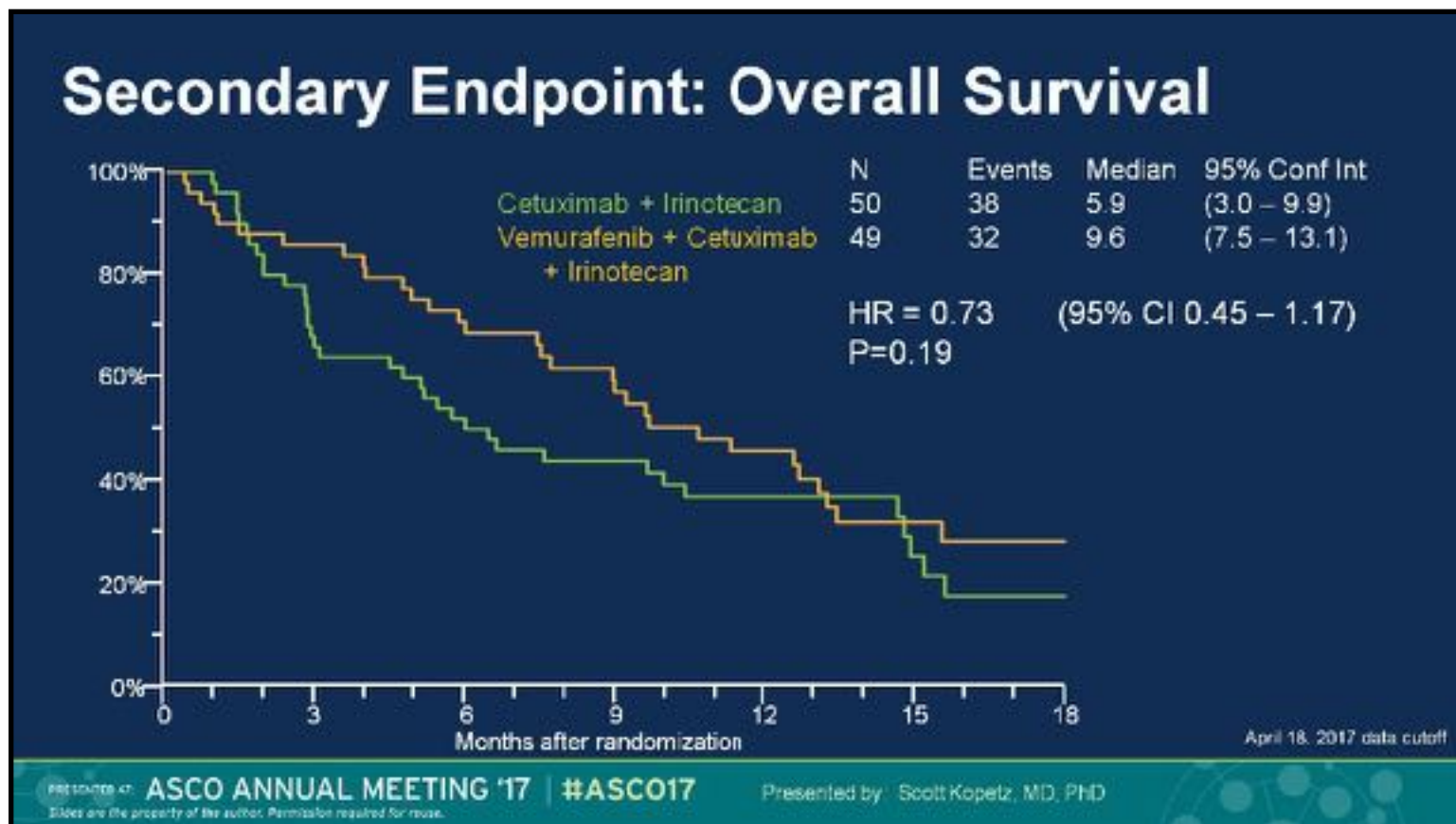
- Desfecho Secundário



CCR METASTÁTICO: NOVAS ESTRATÉGIAS

SWOG S 1406 USO DO VEMURAFENIBE PARA MUTAÇÃO DO BRAF

- Desfecho Secundário



CCR METASTÁTICO: NOVAS ESTRATÉGIAS

SWOG S 1406 USO DO VEMURAFENIBE PARA MUTAÇÃO DO BRAF

- Conclusões

Conclusions

- The combination of vemurafenib, cetuximab, and irinotecan (VIC) met its primary endpoint demonstrating improved progression-free survival in patients with BRAF^{V600E} CRC
- Activity of VIC combination did not differ by prior irinotecan, MSI status, PIK3CA mutations, or sidedness.
- Addition of Vemurafenib to IC showed activity even after progression on IC.
- Overall survival showed a trend that VIC decreased risk of death compared to IC. This analysis is limited by a high rate of crossover to VIC after progression on IC.
- VIC represents a new treatment for metastatic BRAF^{V600E} colorectal cancer.

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Presented by: Scott Kopetz, MD, PhD

CCR METASTÁTICO: NOVAS ESTRATÉGIAS

SUNSHINE: SUPLEMENTAÇÃO DE VITAMINA D

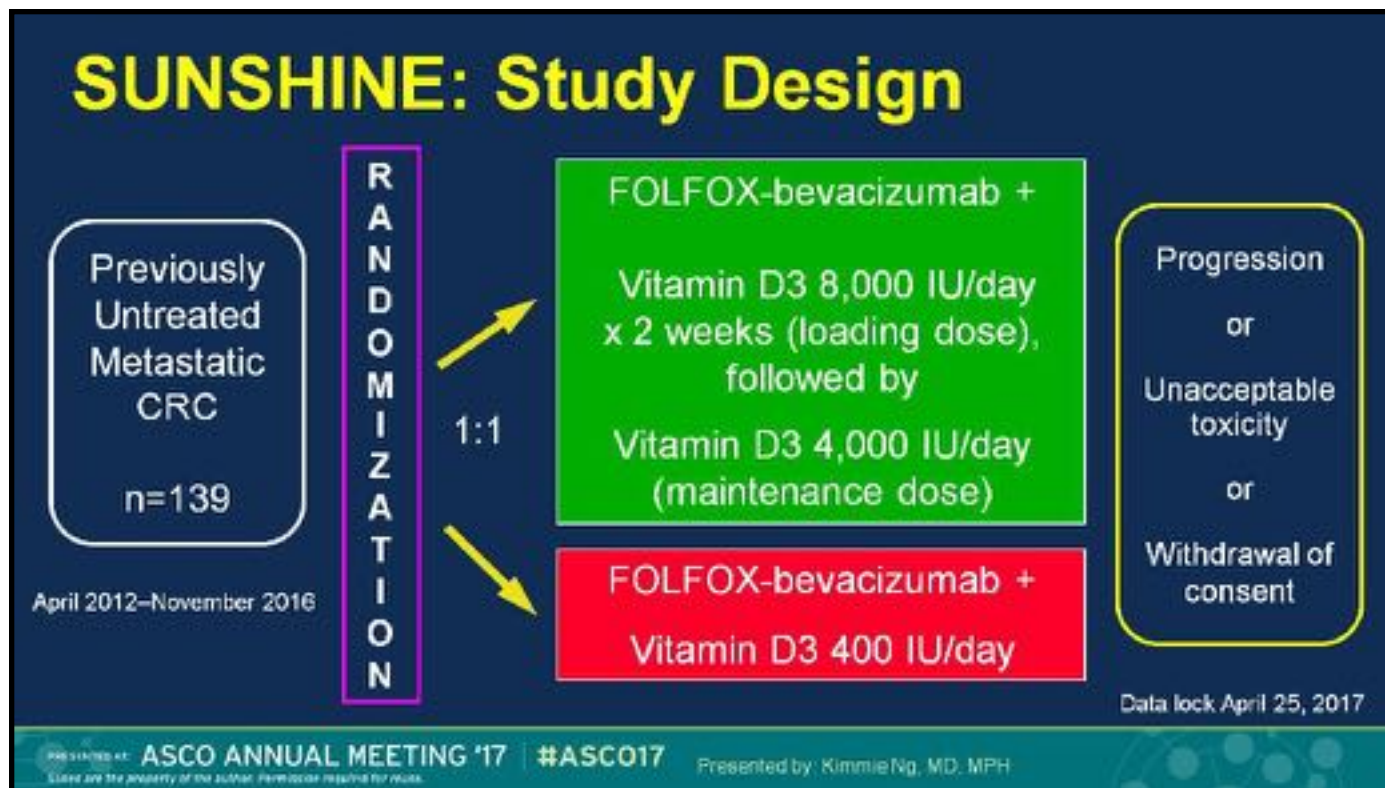


- Vitamina D tem propriedades anti-neoplásicas.
- As células de CCR expressam o receptor de vitamina D.
- Modelos pré-clínicos evidenciam atividade anti-proliferativa.
- Altos níveis plasmáticos de vitamina D são associados a aumento de sobrevida no CCR.

CCR METASTÁTICO: NOVAS ESTRATÉGIAS

SUNSHINE: SUPLEMENTAÇÃO DE VITAMINA D

- Desenho do estudo



CCR METASTÁTICO: NOVAS ESTRATÉGIAS

SUNSHINE: SUPLEMENTAÇÃO DE VITAMINA D

- Desenho do estudo

Study Objectives

- Primary objective
 - Progression-free survival (PFS) by intent-to-treat analysis
- Secondary objectives
 - Objective response rate
 - Overall survival (OS)
 - Toxicity
 - Incidence of vitamin D deficiency
 - Association between plasma 25(OH)D levels and PFS and OS
 - Time course of change in plasma 25(OH)D levels

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Statistical Methods

- Prospective, randomized, double-blinded, phase II clinical trial
 - Plasma banked for future 25(OH)D assays to maintain blinding
 - Blinded central radiology review of restaging scans
- Planned enrollment of 140 subjects to obtain 130 evaluable subjects (65 per arm)
 - One-sided log rank test provides 80% power at 20% significance level to detect HR 0.73 for PFS

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Key Eligibility Criteria

- Histologically confirmed, metastatic colorectal adenocarcinoma
- No prior systemic treatment for metastatic disease
- Measurable disease per RECIST v1.1
- ECOG performance status 0-1
- No regular use of vitamin D supplements $\geq 2,000$ IU/day in past year
- No pre-existing hypercalcemia or predisposing conditions

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CCR METASTÁTICO: NOVAS ESTRATÉGIAS

SUNSHINE: SUPLEMENTAÇÃO DE VITAMINA D

- Resultados

Baseline Characteristics

CHARACTERISTIC	CONTROL (n=70)	HIGH-DOSE (n=69)	P
Median age, years (range)	56 (28-83)	54 (24-81)	0.72
Gender, No. (%)			0.54
Male	38 (54)	41 (59)	
Female	32 (46)	28 (41)	
Race, No. (%)			0.66
White	55 (79)	52 (75)	
Black	6 (9)	4 (6)	
Other	9 (12)	13 (19)	
ECOG performance status, No. (%)			0.07
0	40 (57)	29 (42)	
1	30 (43)	40 (58)	
Received prior adjuvant therapy, No. (%)	5 (7)	6 (9)	0.73
Median no. metastatic sites (range)	2 (1-4)	2 (1-5)	0.65

Treatment Exposure

VARIABLE	CONTROL (n=70)	HIGH-DOSE (n=69)	P
Median (range)			
Follow-up time, months	17.5 (0-52)	16.9 (0-47.9)	0.41
No. chemotherapy cycles*	15 (0-52)	14 (0-53)	0.41
No. cycles with bevacizumab	11 (0-49)	11 (0-40)	0.28
No. cycles with oxaliplatin	9 (0-26)	11 (0-35)	0.09
Compliance with vitamin D [†] , %	98 (0-100)	98 (0-100)	0.83

*One cycle = 14 days. [†]Compliance calculated as % of expected vitamin D exposure dates.

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Patient Disposition

REASON OFF TREATMENT (No. (%))	CONTROL (n=70)	HIGH-DOSE (n=69)	P
Disease progression	35 (50)	30 (44)	0.44
Death	1 (1)	1 (1)	1.00
Curative-intent surgery	6 (8)	11 (16)	0.19
Toxicity or prolonged treatment delay	8 (11)	4 (6)	0.75
Intercurrent illness	1 (2)	0	1.00
Non-compliance	2 (3)	3 (4)	0.69
Withdrawal of consent	9 (13)	11 (16)	0.60
Physician decision	5 (7)	4 (6)	1.00
Not receiving treatment as of 4/20/17	0 (0)	0 (0)	1.00

Primary Tumor Location

LOCATION No. (%)	CONTROL (n=70)	HIGH-DOSE (n=69)	P
Right colon (cecum, ascending colon, hepatic flexure)	13 (27)	18 (23)	0.59
Transverse colon	6 (11)	4 (6)	0.24
Left colon (splenic flexure, descending colon, sigmoid, rectosigmoid, rectum)	43 (61)	46 (71)	0.23

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CCR METASTÁTICO: NOVAS ESTRATÉGIAS

SUNSHINE: SUPLEMENTAÇÃO DE VITAMINA D

- Segurança

Common Grade 3/4 Adverse Events

ADVERSE EVENT No. (%)	CONTROL (n=67)	HIGH-DOSE (n=68)	P
Neutropenia	25 (37)	30 (44)	0.53
Hypertension	13 (19)	13 (19)	0.97
Peripheral neuropathy	5 (7)	5 (7)	0.98
Fatigue	5 (7)	4 (6)	0.74
Thromboembolic event	4 (6)	5 (7)	1.00
Diarrhea	8 (12)	1 (1)	0.02
Vomiting	6 (9)	2 (3)	0.16
Anemia	5 (7)	2 (3)	0.27
Hyperglycemia	3 (5)	5 (7)	0.72
Hypokalemia	3 (5)	4 (6)	1.00
Hyperphosphatemia*	0 (0)	1 (1)	1.00
Kidney stone*	1 (1)	0 (0)	0.50

* Possibly related to vitamin D3

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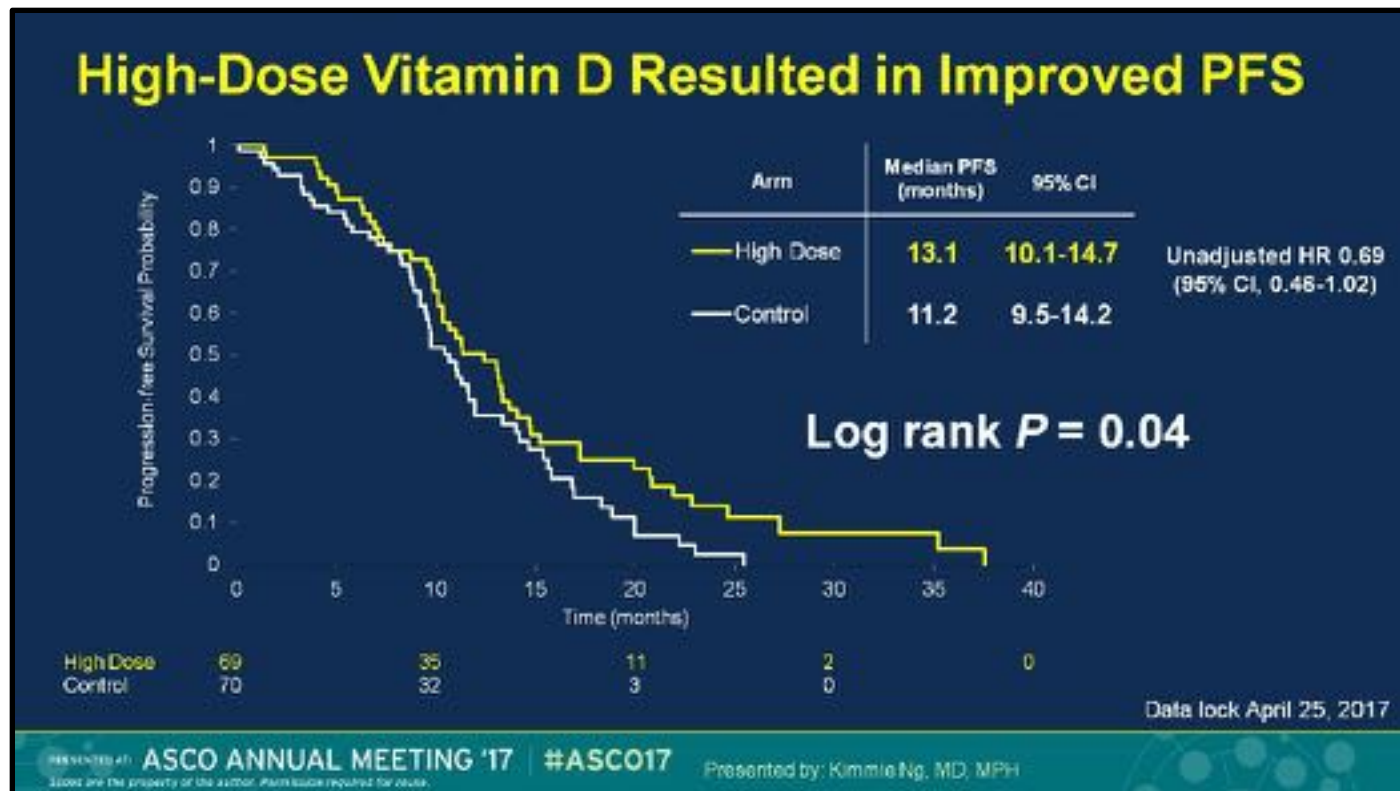
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CCR METASTÁTICO: NOVAS ESTRATÉGIAS

SUNSHINE: SUPLEMENTAÇÃO DE VITAMINA D

- Desfecho primário



CCR METASTÁTICO: NOVAS ESTRATÉGIAS

SUNSHINE: SUPLEMENTAÇÃO DE VITAMINA D

- Desfecho primário

Multivariate Analysis of PFS

VARIABLE	HR	95% CI	P*
High-dose vitamin D3	0.67	0.45 – 0.99	0.02
Age (years)	1.01	0.99 – 1.03	0.17
Female (vs. male)	1.04	0.70 – 1.56	0.42
White (vs. non-white)	1.11	0.69 – 1.79	0.33
ECOG PS 1 (vs. 0)	1.28	0.87 – 1.88	0.10
No. metastatic sites	0.95	0.76 – 1.18	0.31

* One-sided P-value

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CCR METASTÁTICO: NOVAS ESTRATÉGIAS

SUNSHINE: SUPLEMENTAÇÃO DE VITAMINA D

- Desfecho secundário

Objective Response Rate

VARIABLE No. (%)	CONTROL (n=70)	HIGH-DOSE (n=69)	P
Complete response (CR)	0	0	1.00
Partial response (PR)	39 (55)	38 (55)	1.00
Stable disease (SD)	20 (29)	28 (41)	0.16
Progressive disease	3 (4)	0	0.24
Inevaluable for response	8 (11)	3 (4)	0.21

Disease control rate
96%

84%

(CR+PR+SD)

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CCR METASTÁTICO: NOVAS ESTRATÉGIAS

SUNSHINE: SUPLEMENTAÇÃO DE VITAMINA D

- Conclusões

Conclusions

- First completed, randomized, double-blinded, controlled clinical trial of vitamin D supplementation in colorectal cancer patients
- In combination with first-line chemotherapy, high-dose vitamin D3 supplementation significantly improved PFS in metastatic colorectal cancer patients
- High-dose vitamin D3 did not lead to any added toxicity, and resulted in significantly less grade 3/4 diarrhea
- A larger confirmatory phase III trial is warranted

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CCR METASTÁTICO: NOVAS ESTRATÉGIAS

FOXFIRE: RADIOTERAPIA SELETIVA INTERNA (SIRT)

Overall survival analysis of the FOXFIRE
prospective randomized studies of first-line
selective internal radiotherapy (SIRT) in patients
with liver metastases from colorectal cancer

Professor Ricky Sharma

Chair of Radiation Oncology, University College London, United Kingdom

on behalf of the FOXFIRE, SIRFLOX and FOXFIRE-Global Investigators



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Presented by: Ricky Sharma

Selective Internal Radiation Therapy (SIRT)

- SIRT involves injection of millions of yttrium-90 labelled resin microspheres directly in to the blood supply of primary or secondary liver tumors
 - A single large radiation dose
 - FDA approved in 2002 for unresectable liver tumors
 - Supported by NCCN Guidelines (Category 2A) and ESMO Guidelines (II,B)
 - Commissioned in several countries for mCRC patients refractory to chemotherapy



Hendriks A et al. *J Clin Oncol* 26: 3687-3694, 2010.
NCCN Guidelines: Rectal Cancer v1.2017.

NCCN Guidelines: Colon Cancer v1.2017
Van Cutsem E et al. *Ann Oncol* 27: 1386-1422, 2016

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Presented by: Ricky Sharma

CCR METASTÁTICO: NOVAS ESTRATÉGIAS

FOXFIRE: RADIOTERAPIA SELETIVA INTERNA (SIRT)

- Desenho do estudo

Three prospective randomized studies planned for combined analysis of overall survival

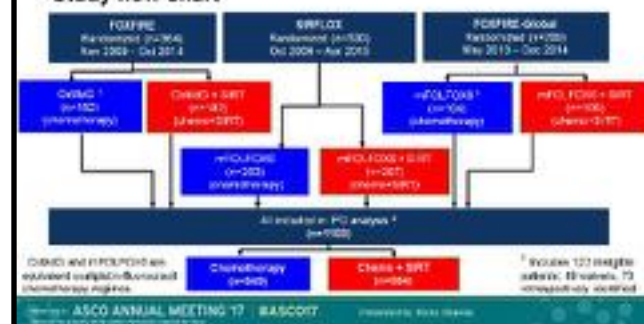
Study name	Geographic region	Recruitment completed	Patients recruited
SIRFLOX	ANZ, EME, USA	2013	530
FOXFIRE	UK	2014	364
FOXFIRE Global	ANZ, AP, EME, USA	2014	209
Total recruitment			1,103

Wides PS et al. JBR Res Protocol 28: e43, 2017

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Presented by: Dr. Jo. Stenman

Study flow chart



Key eligibility criteria

- Adenocarcinoma of the colon or rectum
- Liver metastases not surgically resectable or ablatable
- Eligible for systemic chemotherapy as first-line treatment for metastatic CRC
- WHO Performance Status 0 – 1
- Limited extra-hepatic metastases
- Permitted to have primary tumor in situ
- No evidence of ascites, cirrhosis, portal hypertension

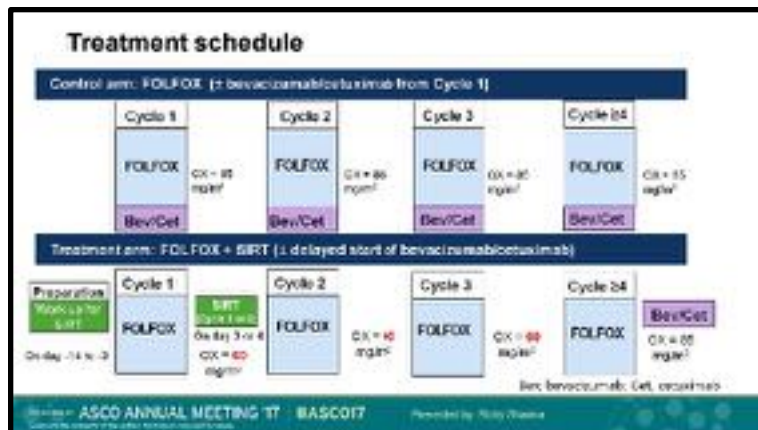
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Presented by: Dr. Jo. Stenman

CCR METASTÁTICO: NOVAS ESTRATÉGIAS

FOXfire: RADIOTERAPIA SELETIVA INTERNA (SIRT)

- Desenho do estudo



Study endpoints

Primary endpoint

- Overall survival (time from randomization to all-cause death)

Secondary endpoints

- PFS at any site (independent central imaging review)
- Liver-specific PFS (independent central imaging review)
- Objective tumor response rate at any site (RECIST v1.0)
- Hepatic resection rate
- Toxicity & safety (NCI CTCAE v3.0)
- Health-related quality of life

Source: ASCO ANNUAL MEETING 17 | ASCO17

Presented by: Nicky Oliveira

CCR METASTÁTICO: NOVAS ESTRATÉGIAS

FOX FIRE: RADIOTERAPIA SELETIVA INTERNA (SIRT)

Resultados

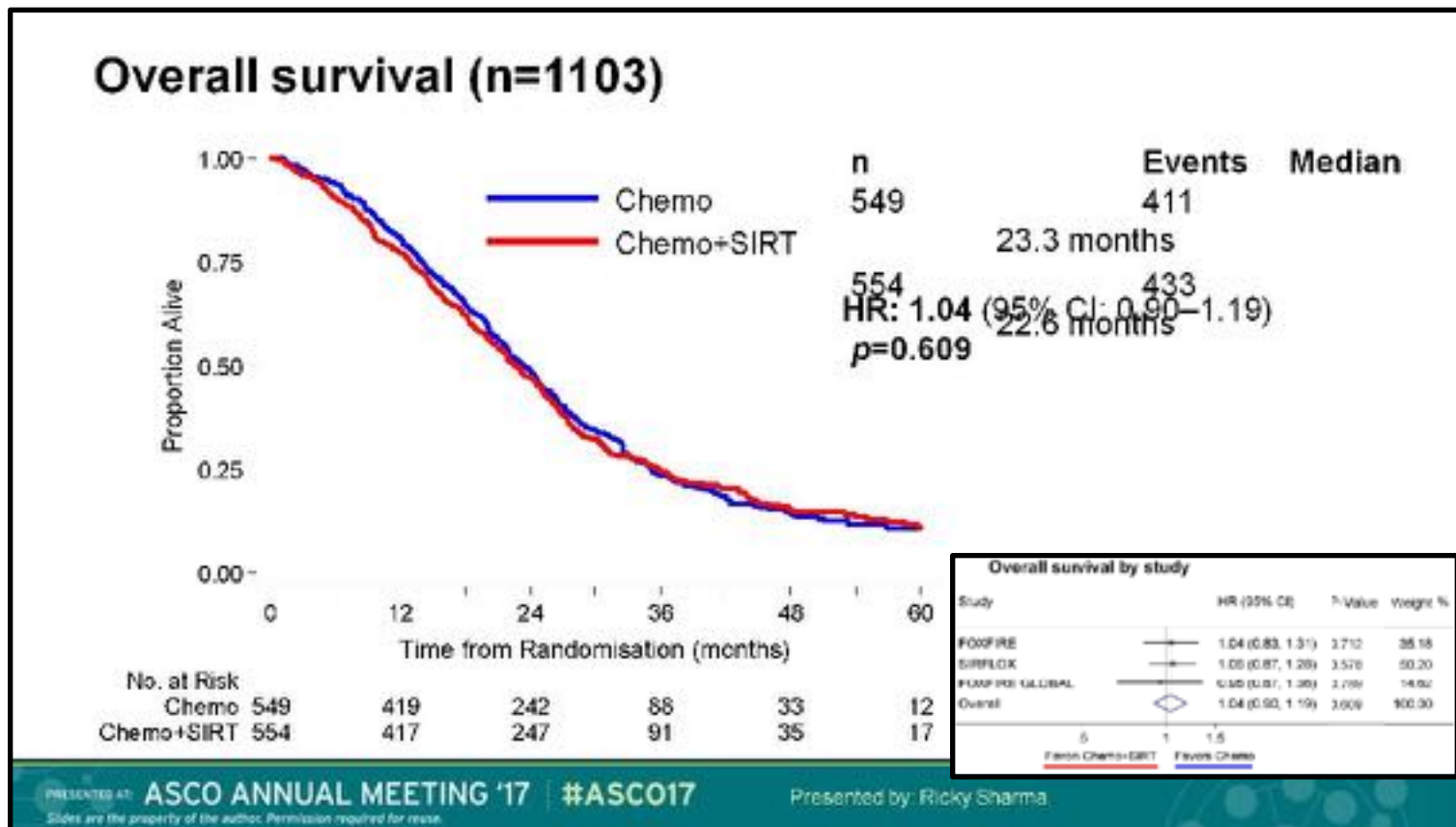
Characteristic	Chemo (n = 549)	Chemo+SIRT (n = 554)
Median age in years (range)	68 (23 – 89)	63 (28 – 92)
Male	65.8%	66.6%
WHO performance status		
0	63.2%	63.9%
1	36.4%	35.7%
Extra-hepatic metastases	34.8%	36.9%
>25% liver involvement	30.6%	32.3%
Intent to treat with biologicals	54.6%	53.8%
Synchronous presentation with liver metast	88.6%	87.2%
Primary tumor in situ	55.0%	50.2%

Characteristic	Chemo (n = 549)	Chemo+SIRT (n = 554)
Did not receive SIRT: Total	-	8.6%
Reasons in FOX FIRE:		
- Clinical deterioration	-	(33.3%)
- Aberrant vascular anatomy/ang shunting	-	(43.6%)
- Withdrew consent to SIRT	-	(23.0%)
Cycles of oxaliplatin received at full protocol dose	49.1%	43.8%
Median (Q/R) number of cycles of FOLFOX chemotherapy	12 (7-12)	12 (7-15)
Patients receiving bevacizumab	46.6%	35.6%
Patients receiving cetuximab	1.8%	0.7%

CCR METASTÁTICO: NOVAS ESTRATÉGIAS

FOX FIRE: RADIOTERAPIA SELETIVA INTERNA (SIRT)

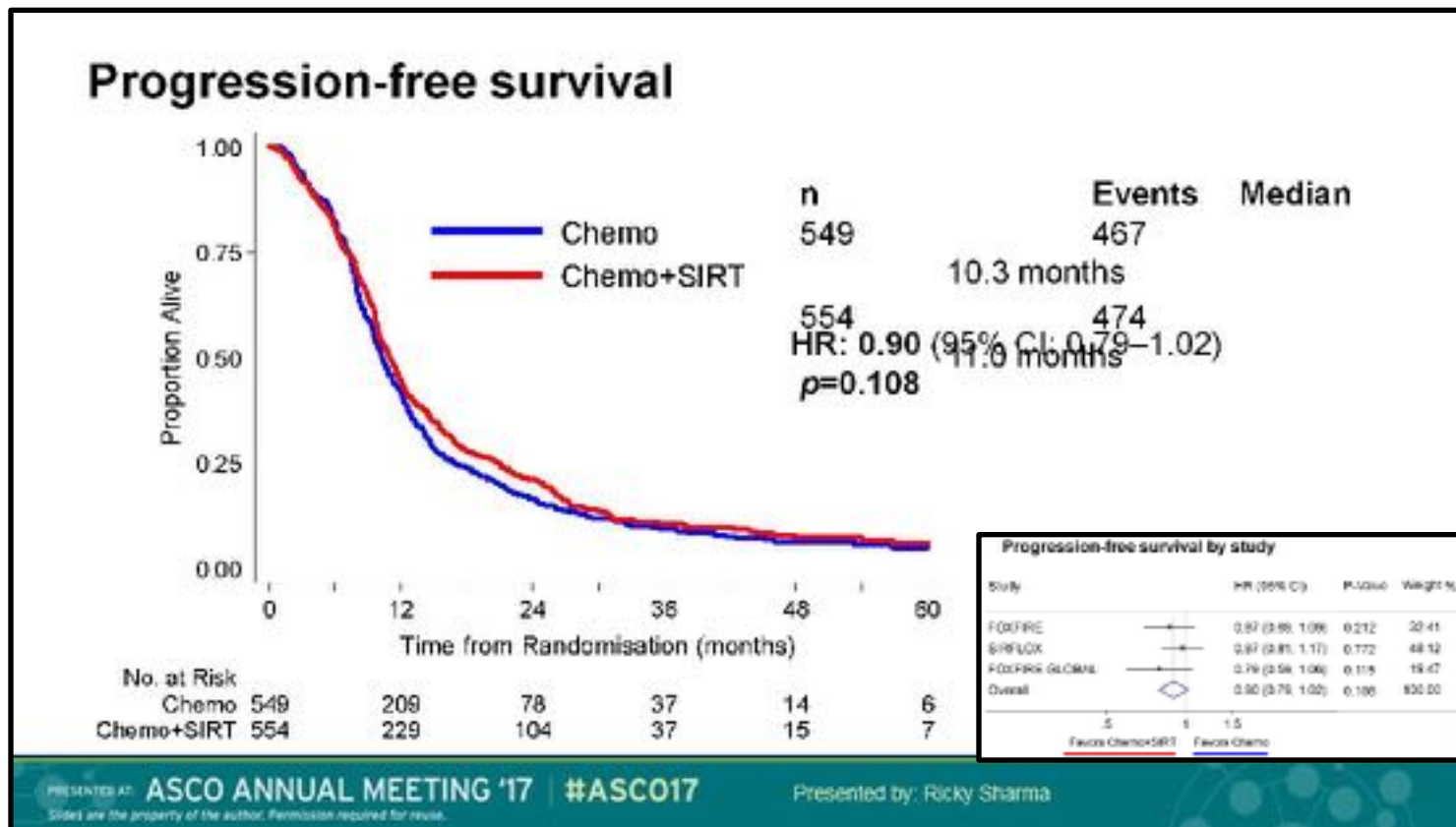
- Desfecho Primário



CCR METASTÁTICO: NOVAS ESTRATÉGIAS

FOXFIRE: RADIOTERAPIA SELETIVA INTERNA (SIRT)

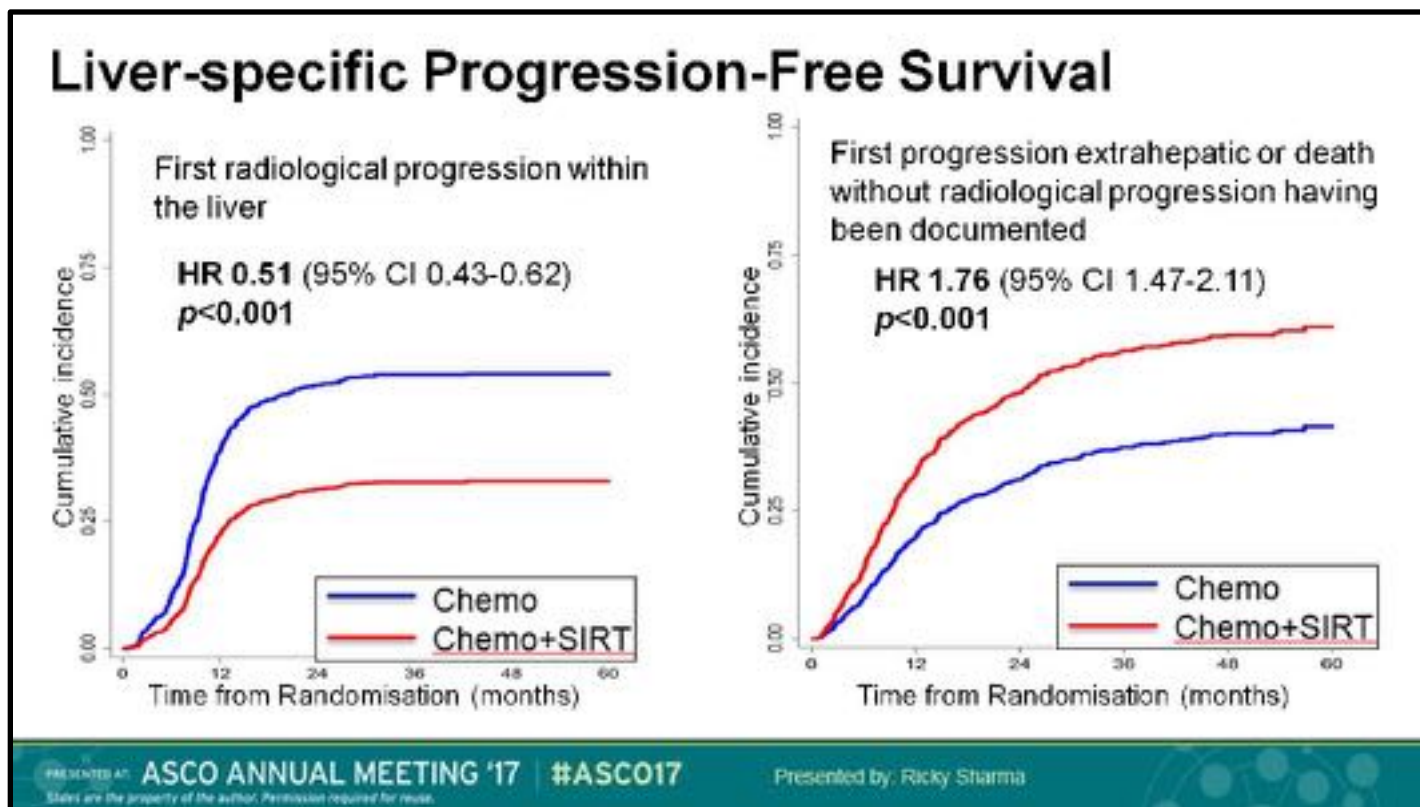
- Desfecho Secundário



CCR METASTÁTICO: NOVAS ESTRATÉGIAS

FOXFIRE: RADIOTERAPIA SELETIVA INTERNA (SIRT)

- Desfecho Secundário



CCR METASTÁTICO: NOVAS ESTRATÉGIAS

FOXFIRE: RADIOTERAPIA SELETIVA INTERNA (SIRT)

- Segurança

Selected all-cause adverse events (safety population)		
Adverse events	Chemo (n = 571)	Chemo+SIRT (n = 507)
All patients any grade	99.6%	99.8%
All patients grade ≥3	66.5%	74.0%
All patients grade 5	1.9%	2.0%
Hematological (grade ≥3)		
Neutropenia	24.2%	36.7%
Febrile neutropenia	2.8%	6.5%
Thrombocytopenia	1.2%	7.7%
Leukopenia	2.3%	5.9%
Non-hematological (grade ≥3)		
Fatigue	4.9%	8.5%
Abdominal pain	2.3%	6.1%
Diarrhea	6.5%	6.7%
Peripheral neuropathy	5.8%	3.6%
Radiation hepatitis	-	0.8%

CCR METASTÁTICO: NOVAS ESTRATÉGIAS

FOXFIRE: RADIOTERAPIA SELETIVA INTERNA (SIRT)

- Conclusões

Conclusions

- Addition of SIRT to FOLFOX first-line chemotherapy in patients with liver-only or liver-dominant mCRC did not improve OS or PFS
- Significant benefit in liver-specific PFS and radiological response rate was achieved by the addition of SIRT
- Toxicity was higher in FOLFOX+SIRT group, particularly hematological
- FOLFOX+SIRT patients were less likely to receive bevacizumab and to receive subsequent post-protocol systemic therapy
- Liver metastases from right-sided primary merit evaluation in other datasets as a subgroup who may derive additional clinical benefit from SIRT

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Presented by: Ricky Sharma

FRESCO TRIAL: SEGURANÇA E EFICÁCIA DO FRUQUINTINIBE

FRESCO: A Phase II trial evaluating Fruquintinib efficacy and safety in 3+ line colorectal cancer patients

Jin LI, Shukul QIN, Rui-Hua XU, Jian-Ming XU, Lin SHEN, Yuxian BAI, Yanhong DENG, Lei YANG, Zhen-Dong CHEN, Haijin ZHONG, Hongmin PAN, Weijian GUO, Yongqian SHU, Ying YUAN, Jianfeng ZHOU, Nong XU, Tianshu LIU, Dong MA, Changping WU, Ying CHENG, Donghui CHEN, Wei LI, Sanyuan SUN, Zhuang YU, Peiguo CAO, Huihui CHEN, Jiejun WANG, Shubin WANG, Hongbin WANG, Shenghua FAN, Ye HUIA, Wei GUO SU

On behalf of the FRESCO Investigators

Poster # 450 - ASCO ANNUAL MEETING 17 / ASCO17

Fruquintinib
VEGFR

Fruquintinib: an oral, potent and highly selective VEGFR inhibitor

Fruquintinib kinase profile

Kinase assay	IC ₅₀ (nM)
BIOCHEMICAL ACTIVITY	
VEGFR2 (PDKC)	39 (2)
VEGFR3 (P84)	0.6
VEGFR1 (P81)	25
Bcr	157
FGFR1	187
Etk	459
Pdg	>2,000
PDGFRA	>2,000
FGFR3	>20,000
Akt	>2,000
G-MET	>2,000
R-Ras	>3,000
Abl	>5,000
CHK1	>2,000
CHK2	>2,000
CDK2	>2,000
LKMT	>2,000

Kinase assay	IC ₅₀ (nmol/L) or inhibition rate (%)
CELL-BASED ACTIVITY	
BRCA-impacted p-POR1 vs HNRV	>1,000
VEGFA stimulated p-VEGFR2 in HDCC9	0.5 ± 0.2, n = 3
VPR-C stimulated p-VEGFR3 in HUCC	1.0
VEGFA dependent HUCC proliferation	1.7
VEGFC dependent HUCC proliferation	4.2
HUCC tube formation	94% at 300 nmol/L
ANTI-ANGIOGENESIS ACTIVITY	
Chondralytic Membrane (CAM)	strong inhibition at 0.1 & 1 nmol/kg

- Potent anti-VEGFR-1, 2 and 3
- Highly selective against other kinases
- High drug exposures at recommended clinical dose resulting in expected full and sustained target coverage
- Clean CYP profile suitable for combinations

Full & sustained target inhibition above 4 mg dose

Time (Days)	Day 1, 4mg QD	Day 1, 2mg QD	Day 1, 1mg QD	Day 1, 400mg QD
1	~100	~100	~100	~100
5	~450	~350	~250	~150
7	~400	~300	~200	~150
14	~350	~250	~150	~150
28	~300	~200	~100	~150

Legend:
— Day 1, 4mg QD
— Day 1, 2mg QD
— Day 1, 1mg QD
— Day 1, 400mg QD

Detailed description: The graph illustrates the pharmacokinetic profile of Fruquintinib, showing that higher doses lead to more pronounced and sustained target inhibition. The 400 mg QD group shows significantly higher protein concentrations compared to lower doses throughout the study period.

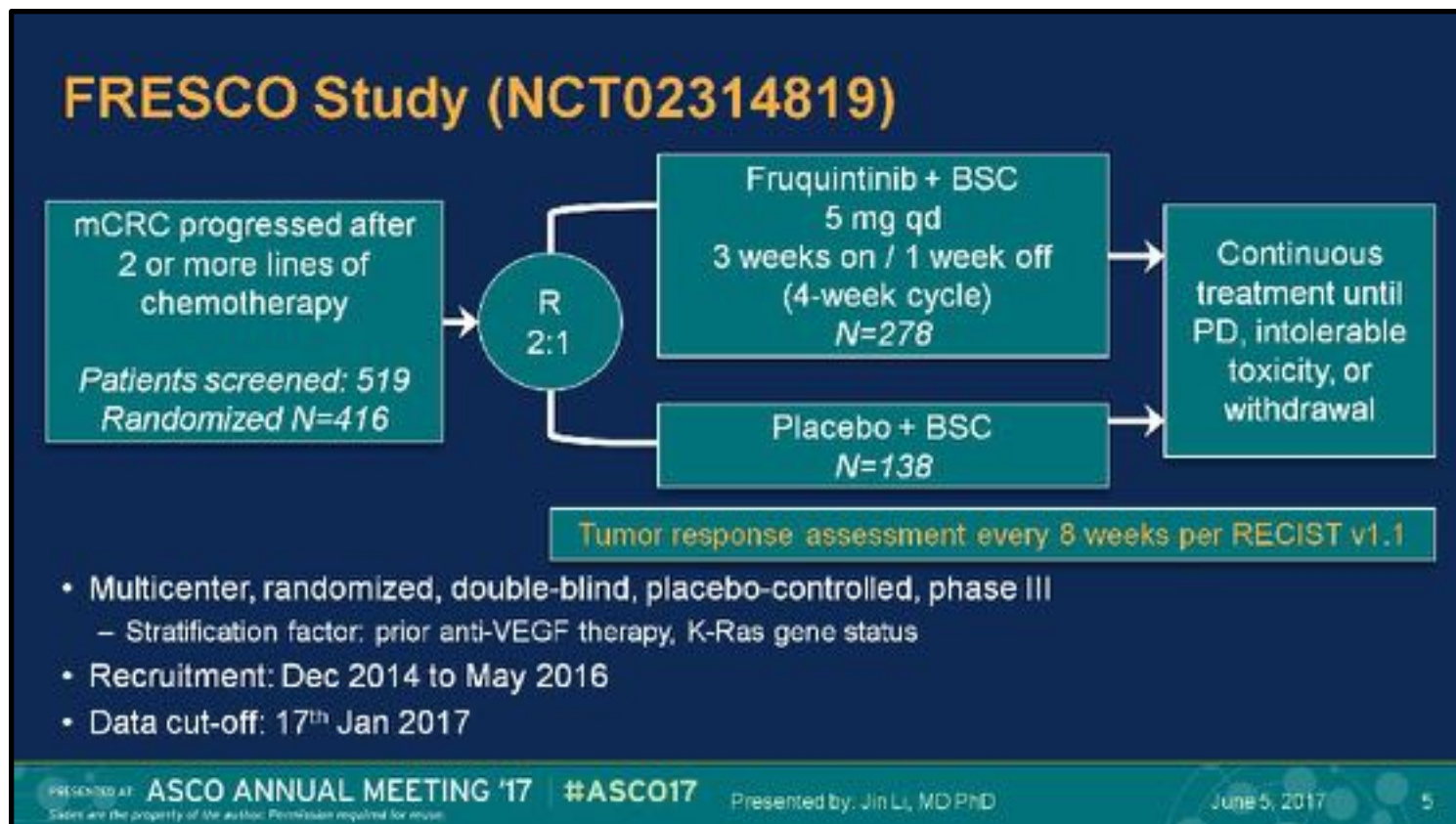
Cancer J Clin Oncol. 2017; 35(12):1642-1649 (2017)

Presented by: Jin Li, MD PhD | June 5, 2017 | 4

CCR METASTÁTICO: NOVAS ESTRATÉGIAS

FRESCO TRIAL: SEGURANÇA E EFICÁCIA DO FRUQUINTINIBE

- Desenho do estudo



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FRESCO Endpoints

- **Primary endpoint: overall survival (OS)**

- 80% power to detect a hazard ratio of 0.7 (corresponding to a median OS improvement from 6.3 months to 9 months), 2-sided overall $\alpha=0.05$
- Planned Sample size: 400

- **Key secondary endpoints:**

- Progression-free survival (PFS)
- Overall response rate (ORR)
- Disease control rate (DCR)

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Patient Eligibility: key inclusion criteria

- Histologically and/or cytologically diagnosed with metastatic CRC (Stage IV)
- Had failed 2 prior treatments with fluoropyrimidine, oxaliplatin, and irinotecan
- Prior anti-VEGF or anti-EGFR targeted therapy allowed, but not mandatory
- Age 18-75 years, Eastern Cooperative Oncology Group performance status (ECOG PS) 0-1, life expectancy ≥ 3 months
- Measurable disease according to Response Evaluation Criteria in Solid Tumors (RECIST) v1.1
- Adequate bone marrow, liver and renal function
- Signed informed consent

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- Resultados

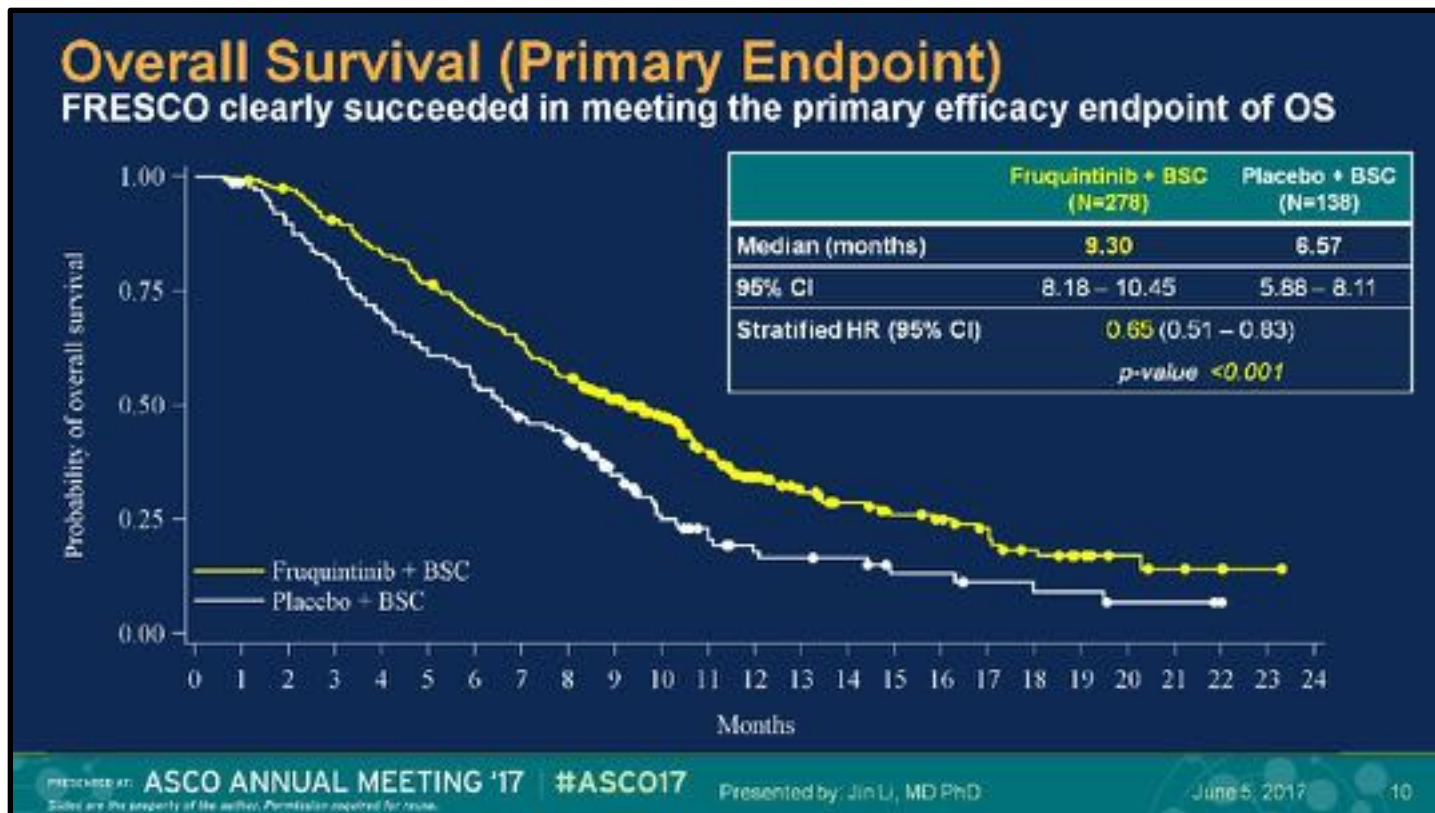
Demographics		Fruquintinib (N=278) n (%)	Placebo (N=138) n (%)
Age	<65 Years	228 (82.0)	110 (79.7)
	≥65 Years	50 (18.0)	28 (20.3)
Sex	Male	158 (56.8)	97 (70.3)
	Female	120 (43.2)	41 (29.7)
Ethnicity	Han	272 (97.8)	135 (97.8)
	Not Han	6 (2.2)	3 (2.2)
ECOG	0	77 (27.7)	37 (26.8)
	1	201 (72.3)	101 (73.2)

Disease Characteristics		Fruquintinib (N=278) n (%)	Placebo (N=138) n (%)
Primary site of the disease	Colon	147 (52.9)	70 (50.7)
	Rectal	125 (45.0)	60 (43.5)
	Colon-Rectal	9 (3.2)	7 (5.1)
	Other ^a	0	1 (0.7)
Primary location of tumor	Left	214 (77.0)	110 (80.3)
	Right	56 (20.1)	21 (15.2)
	Both or Unknown	0 (0.0)	2 (1.5)
K-RAS Gene status	Wild type	157 (56.5)	74 (53.6)
	Mutant	121 (43.5)	64 (46.4)
Prior use of VEGF inhibitor	Yes	88 (31.3)	41 (29.7)
	No	190 (68.6)	97 (70.3)
Prior use of EGFR inhibitor	Yes	40 (14.4)	16 (11.6)
	No	238 (85.6)	122 (88.4)
Liver Metastasis	Yes	185 (66.5)	102 (73.9)
	No	93 (33.5)	36 (26.1)

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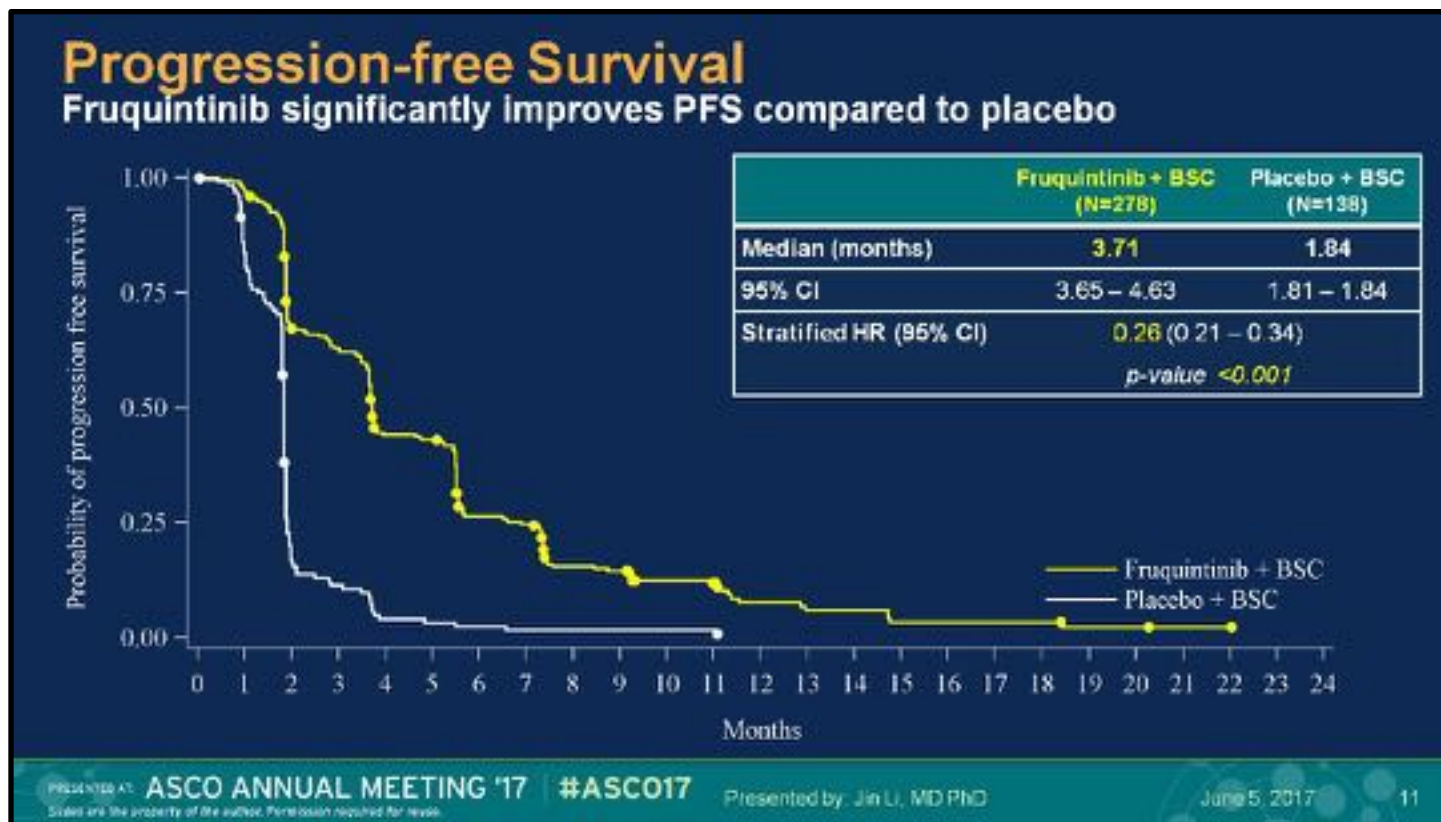
- Desfecho primário



CCR METASTÁTICO: NOVAS ESTRATÉGIAS

FRESCO TRIAL: SEGURANÇA E EFICÁCIA DO FRUQUINTINIBE

- Desfecho secundário



CCR METASTÁTICO: NOVAS ESTRATÉGIAS

FRESCO TRIAL: SEGURANÇA E EFICÁCIA DO FRUQUINTINIBE

- Desfecho secundário

Tumor Response

Best response	Fruquintinib (N=278) n (%)	Placebo (N=138) n (%)
Complete Response (CR)	1 (0.4)	0
Partial Response (PR)	12 (4.3)	0
Stable Disease (SD)	160 (57.6)	17 (12.3)
Progressive Disease (PD)	87 (31.3)	98 (71.0)
Not done / not evaluated	18 (6.4)	23 (16.7)
ORR	13 (4.7)	0
DCR	173 (62.2)	17 (12.3)

ORR = CR + PR (≥ 8 weeks confirmed); $p=0.012$

DCR = CR + PR + SD (≥ 8 weeks after randomization); $p<0.001$

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CCR METASTÁTICO: NOVAS ESTRATÉGIAS

FRESCO TRIAL: SEGURANÇA E EFICÁCIA DO FRUQUINTINIBE

- Segurança

Treatment-emergent Adverse Events Overview (safety population)		
Adverse Events	Fruquintinib (N=278) n (%)	Placebo (N=137) n (%)
Any Grade	274 (88.6)	121 (88.3)
Grade 3	149 (53.6)	23 (16.8)
Grade 4	12 (4.3)	2 (1.5)
Grade 5	0 (0.0)	2 (1.5)
Grade ≥ 3	170 (61.1)	27 (19.7)
SAE	43 (15.5)	8 (5.8)
Leading to		
dose interruption	88 (31.3)	14 (10.2)
dose reduction	67 (24.1)	6 (4.4)
dose interruption or reduction	131 (47.1)	18 (13.1)
treatment discontinuation	42 (15.1)	8 (5.8)

Drug-related Treatment-emergent Adverse Events (safety population; occurring in >15% patients)						
Preferred Term	Fruquintinib (N=278) n (%)			Placebo (N=137) n (%)		
	All grades	Grade 3-4	Grade 5	All grades	Grade 3-4	Grade 5
Hypertension	154 (55.4)	58 (21.2)	0	21 (15.3)	3 (2.2)	0
PPS (or HFBR)	137 (49.3)	30 (10.8)	0	4 (2.9)	0	0
Proteinuria	117 (42.1)	8 (2.9)	0	34 (24.8)	0	0
Dysphagia	100 (36.0)	0	0	2 (1.5)	0	0
TSH increased	81 (29.1)	0	0	3 (2.2)	0	0
AST increased	54 (19.4)	1 (0.4)	0	14 (10.2)	1 (0.7)	0
Weight decreased	50 (18.0)	4 (1.4)	0	12 (8.8)	0	0
Alkaline phosphatase increased	50 (18.0)	4 (1.4)	0	10 (7.3)	2 (1.5)	0
Diarrhea	50 (18.0)	0 (0.0)	0	3 (2.2)	0	0
ALT increased	50 (18.0)	2 (0.7)	0	12 (8.8)	2 (1.5)	0
Stomatitis	42 (15.1)	1 (0.4)	0	0	0	0
Decreased appetite	40 (14.4)	3 (1.1)	0	11 (8.0)	0	0
Hypothyroidism	43 (15.5)	0	0	3 (2.2)	0	0

CCR METASTÁTICO: NOVAS ESTRATÉGIAS

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- Conclusões

Conclusions

- Fruquintinib significantly extended survival time in mCRC patients who have had failed at least 2 lines of systemic therapy
- Clinically meaningful and statistically significant benefits are also shown in PFS, ORR, DCR
- Fruquintinib is well tolerated in mCRC patients with a good safety profile that is consistent to other fruquintinib trials
- Fruquintinib demonstrated favorable risk-to-benefit balance in patients with mCRC

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