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MELANOMA

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 o 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".

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CONFLITOS DE INTERESSE

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

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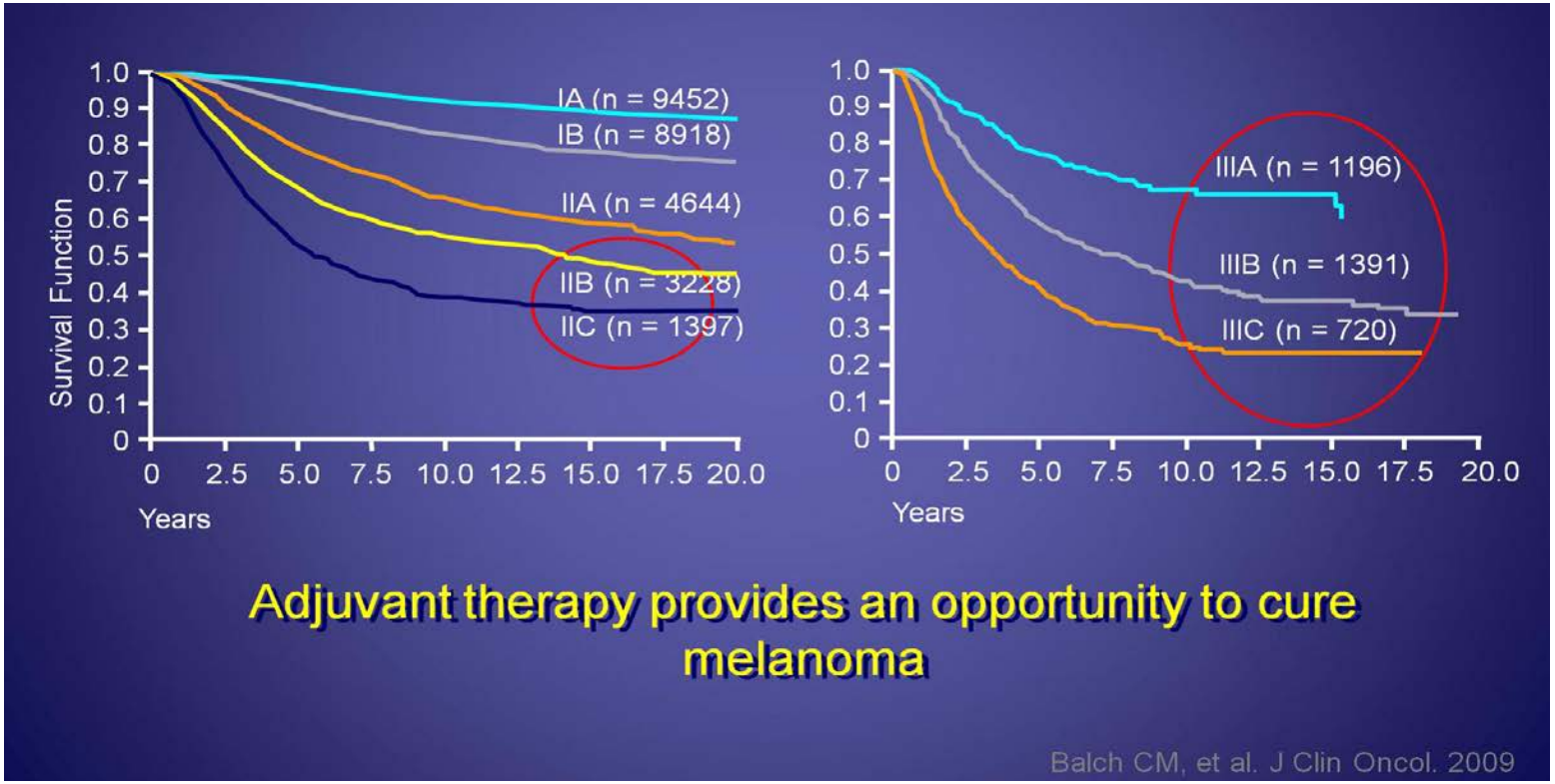
Roteiro

1. Tratamento Adjuvante do Melanoma: Existe um *standard*?
2. Estudos relevantes em adjuvância - ASCO 2017
3. Estudos relevantes em Neoadjuvância - ASCO 2017
4. Estudos relevantes no Melanoma Metastático – ASCO 2017
5. Tratamento da Metástase cerebral – ASCO 2017

Tratamento Adjuvante do Melanoma: Existe um *standard*?

Racional da Terapia Adjuvante

Tratar os pacientes que possuem maior risco de recorrência



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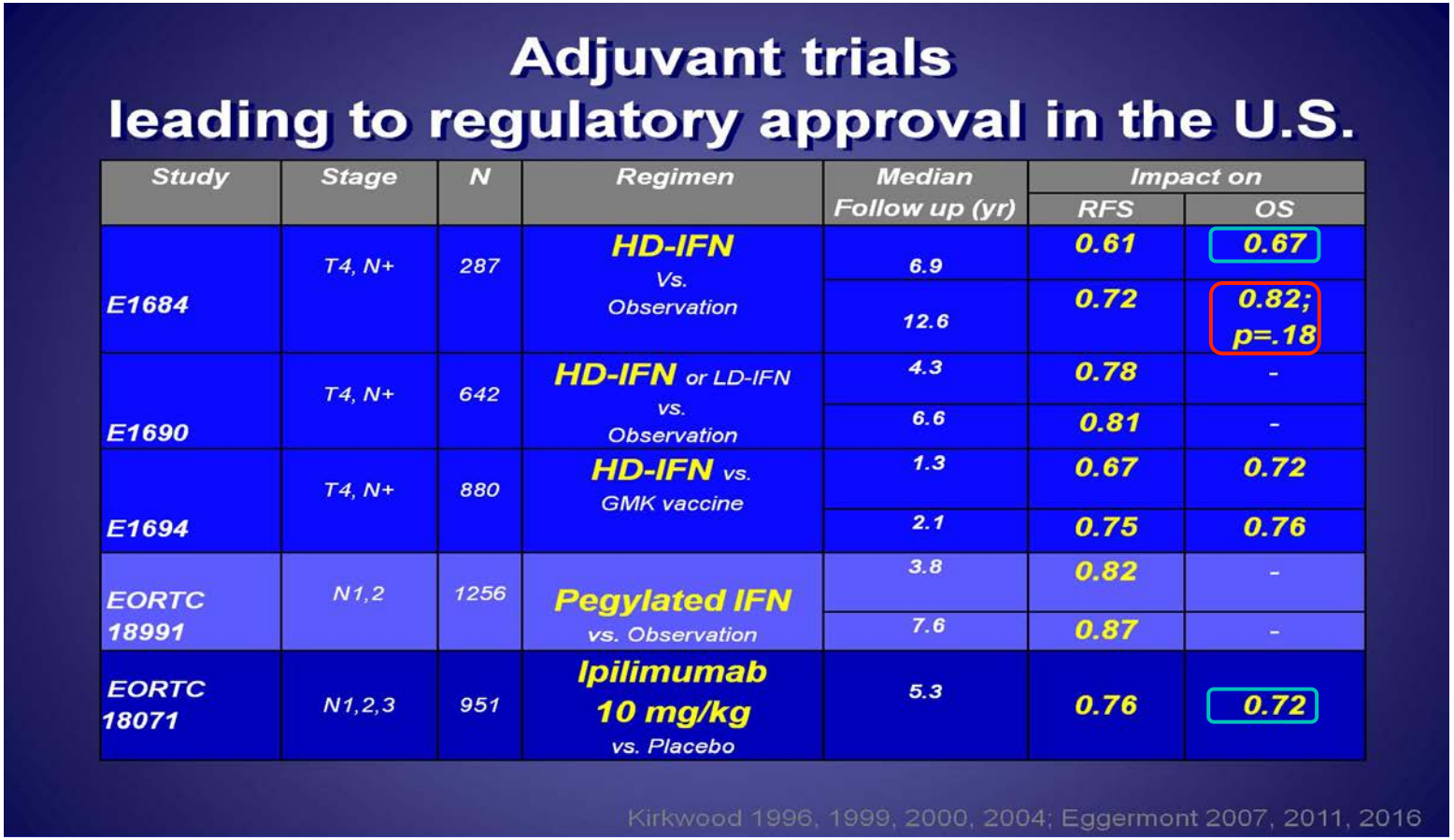
Cenário mundial atual



Adjuvant trials leading to regulatory approval in the U.S.

Study	Stage	N	Regimen	Median Follow up (yr)	Impact on RFS	Impact on OS
E1684	T4, N+	287	HD-IFN Vs. Observation	6.9	0.61	0.67
				12.6	0.72	0.82; p=.18
E1690	T4, N+	642	HD-IFN or LD-IFN vs. Observation	4.3	0.78	-
				6.6	0.81	-
E1694	T4, N+	880	HD-IFN vs. GMK vaccine	1.3	0.67	0.72
				2.1	0.75	0.76
EORTC 18991	N1,2	1256	Pegylated IFN vs. Observation	3.8	0.82	-
				7.6	0.87	-
EORTC 18071	N1,2,3	951	Ipilimumab 10 mg/kg vs. Placebo	5.3	0.76	0.72

Kirkwood 1996, 1999, 2000, 2004; Eggermont 2007, 2011, 2016

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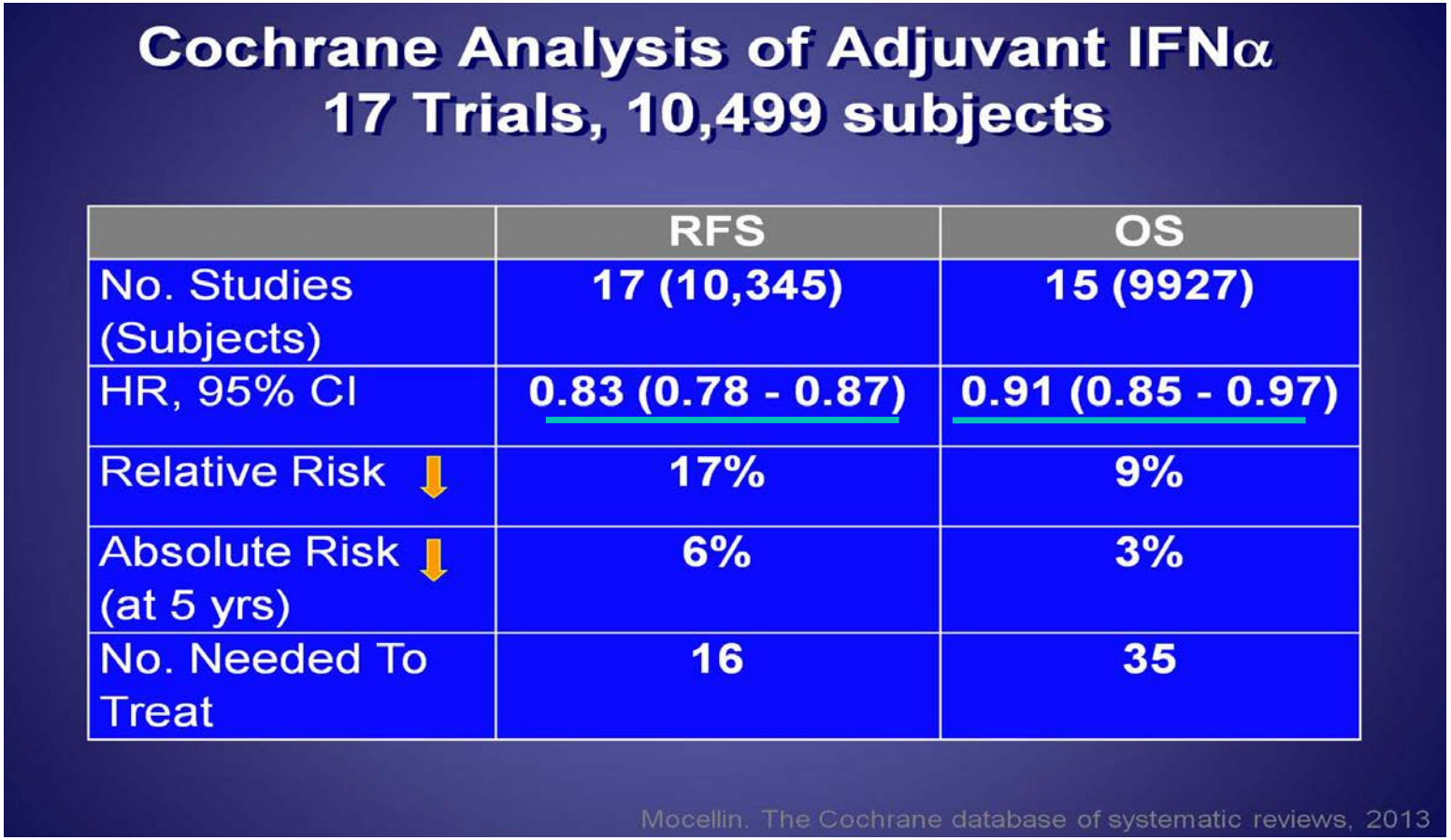
INFα: Discreto efeito positivo em SLR e SG



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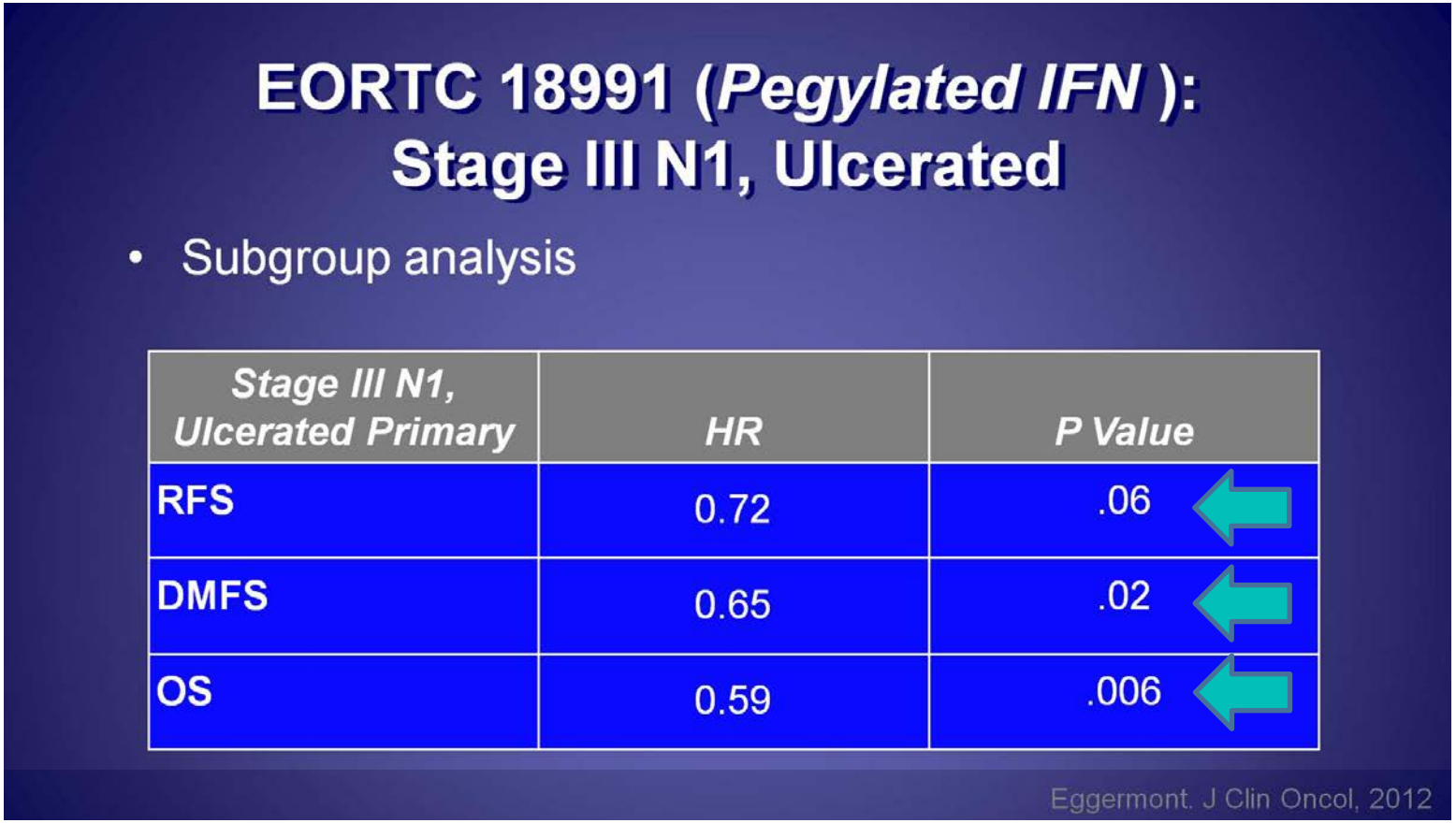
INF-Peguilado: Subgrupo N1, ulcerado



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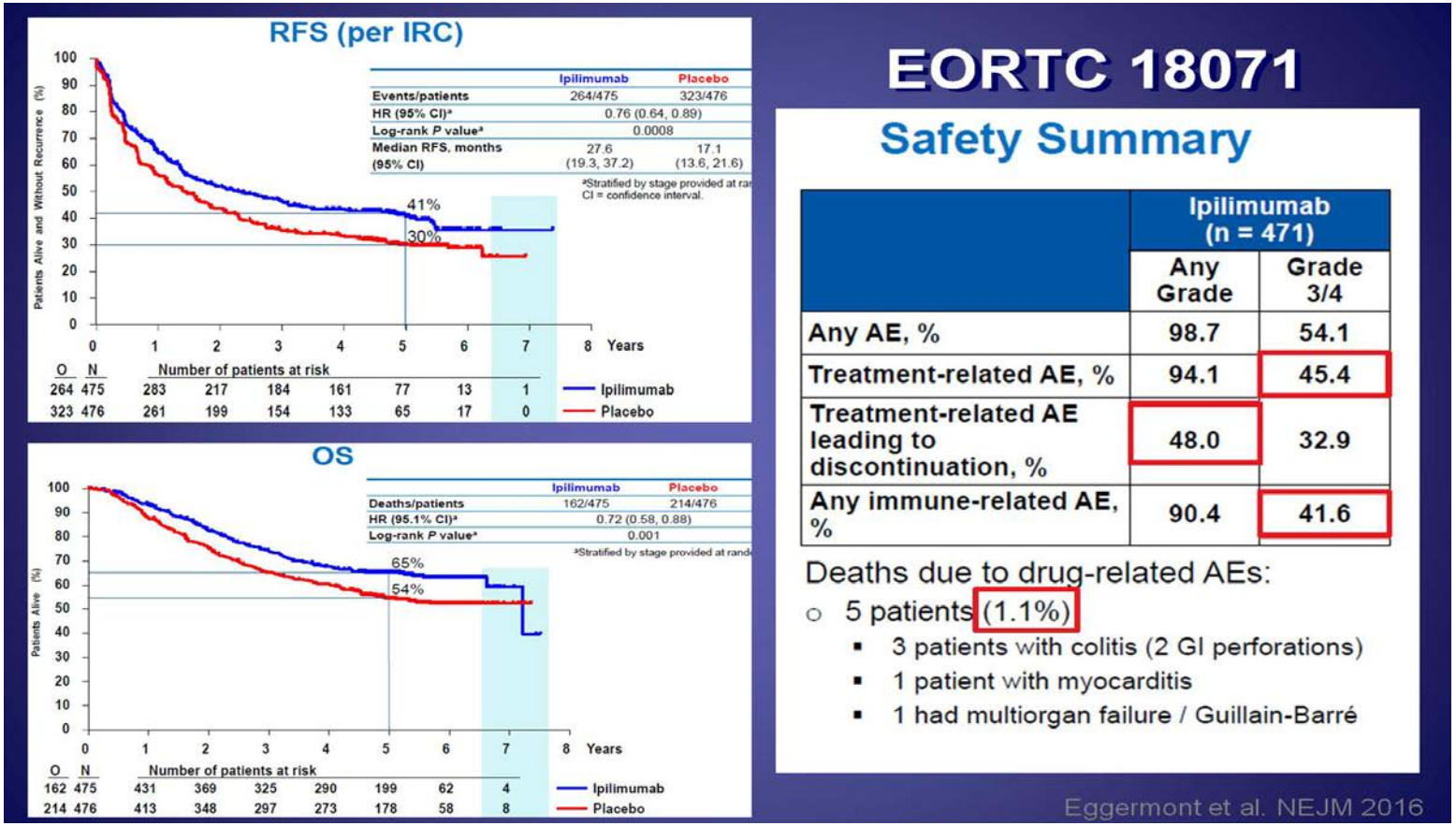
Ipilimumabe: Ganhos *vs* Toxicidade



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O que sabemos hoje?

- INF adjuvante proporciona ganho em Sobrevida Livre de Recorrência (SLR) e em Sobrevida Global (SG).
- O maior benefício de PEG-INF foi observado no subgrupo N1 ulcerado (41% redução do risco de morte)
- Na prática, a minoria dos pacientes tolera mais de 1 ano PEG-INF (mediana de uso de 1,4 ano)
- Ipilimumabe 10 mg/Kg aumenta SLR e SG, porém está associado a toxicidade significativa.

Isso é tudo que podemos oferecer?

Estudos mais relevantes em Adjuvância ASCO 2017

Qual a melhor estratégia adjuvante: Ipilimumabe ou HD-INF?

A phase III randomized study of adjuvant ipilimumab (3 or 10 mg/kg) versus high-dose interferon alfa-2b for resected high-risk melanoma (U.S. Intergroup E1609): ***Preliminary safety and efficacy of the ipilimumab arms.***

Apresentação oral, abstract 9500

Presented By Ahmad Tarhini at 2017 ASCO Annual Meeting

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Racional do E1609

Avaliar redução de dose do Ipilimumabe (Toxicidade)
Comparar Ipilimumabe *vs* HD-INF (e não *vs* placebo)

Status of Ipilimumab 10 mg/kg (Ipi10) & 3 mg/kg (Ipi3)

- MDX1020: Regulatory approval of Ipi3 in unresectable metastatic melanoma
- EORTC 18071: Regulatory approval of Ipi10 in Stage III resected melanoma
- CA184-169: Ipi10 vs. Ipi3 in unresectable metastatic melanoma
  - Improvement in OS with Ipi10 vs. Ipi3 (HR 0.84, 95% CI 0.70, 0.99); p=0.04
  - No known impact on clinical practice, yet

Toxicidade de Ipi é dose dependente

CA184-169 - Safety	Ipi10 n = 364	Ipi3 n = 362
Treatment-related serious AEs, %	37	18
AEs leading to discontinuation, %	31	19
Immune-related Grade 3-4 AEs, %	30	14

Hodi et al. NEJM 2000; Eggermont et al. NEJM 2016; Ascierto et al. Lancet Oncology 2017

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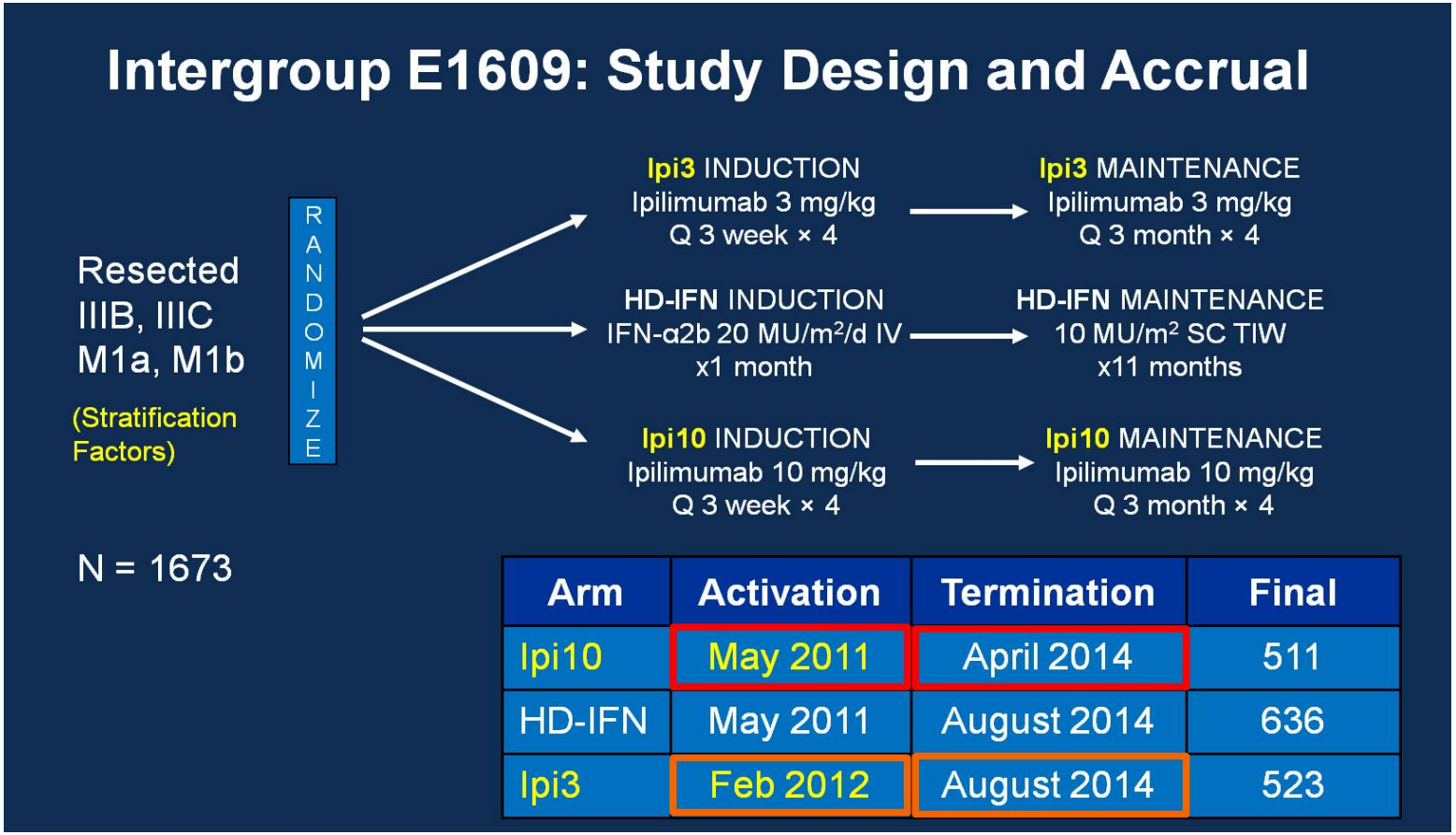
Desenho do E1609



Arm	Activation	Termination	Final
Ipi10	May 2011	April 2014	511
HD-IFN	May 2011	August 2014	636
Ipi3	Feb 2012	August 2014	523

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Endpoints do E1609

- Co-Primary Endpoints
  - Relapse Free Survival (RFS): HR = 0.75, 80% power, type I error rate=0.003
  - Overall survival (OS): HR = 0.75, 80% power, type I error rate = 0.022
  - Planned Two-Step Hierarchical Analysis
    - First Step: Ipi3 vs. HDI (Full info: 416 survival & 655 relapse events)
    - Second Step: Ipi10 vs. HDI
- Secondary Endpoints
  - Quality of Life
  - Biomarkers

Os dados de relevância apresentados na ASCO 2017 foram apenas de segurança e eficácia de Ipilimumabe nas 2 doses.

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Dados demográficos do E1609

Patient & Disease Characteristics

(Concurrently randomized patients)

	Ipi3 (n = 367)	Ipi10 (n = 406)
Age, yrs (median & range)	54 (19-80)	55 (19-80)
Male, %	62.7	66.8
ECOG PS 0/1, %	85.0/15.0	83.5/16.5
Stage, %		
IIIB	52.3	52.7
IIIC	39.8	40.1
M1a	6.0	5.7
M1b	1.9	1.5
Microscopic LN involvement, %	46.7	47.7
Unknown primary, %	14.7	11.3
Ulceration of primary, %	46.9	43.4

ECOG PS = Eastern Cooperative Oncology Group performance status; LN: Lymph Node

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Perfil de segurança de Ipilimumabe

Safety Summary

(Based on all toxicity data as of 3/2/17)

	Ipi3 (n = 516)		Ipi10 (n = 503)	
	Any Grade	Grade 3/4	Any grade	Grade 3/4
Any AE, %	98.4	53.3	100	65.4
Treatment-related AE, %	96.0	36.6	98.8	56.5
Treatment-related AE leading to discontinuation, %	34.9	25.0	53.7	42.9
Any immune-related AE, %	73.6	18.8	86.9	34.0

Treatment and Discontinuation Details

(Based on cases with available data as of 3/2/17)

	Ipi3 (n = 512)	Ipi10 (n = 503)
Discontinuation, %	100	100
Reasons for discontinuation, %		
Completed entire regimen	38.1	21.5
Melanoma relapse	22.9	13.7
AE related to study drug	35.2	55.5
Other reasons[a]	3.9	9.3
Median doses, per patient, n	5	4
Receiving ≥1 maintenance dose, %	53.5	32.8

[a]Includes withdrawal, refusal, other

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Eventos adversos selecionados

	Ipi3 (n = 516)			Ipi10 (n = 503)		
	All grades	Grade 3	Grade 4	All grades	Grade 3	Grade 4
Dermatologic						
Rash	46.5	4.7	0	58.2	8.2	0.2
Gastrointestinal						
Diarrhea / Colitis	50.0	11.6	0.4	55.3	17.1	1.4
Pancreas						
Lipase increased	10.9	2.5	0.1	12.7	3.9	0.1
Endocrine						
Hypophysitis	9.1	3.7	0.2	16.1	7.6	0.2
Adrenal insuff.	9.7	2.1	0	14.5	3.0	0.4
Hypothyroid	10.1	0.6	0	20.9	0.8	0.2
Hyperthyroid	4.1	0	0	6.4	0.2	0

	Ipi3 (n = 516)			Ipi10 (n = 503)		
	All grades	Grade 3	Grade 4	All grades	Grade 3	Grade 4
Hepatic						
ALT increased	18.4	2.1	1.0	32.2	5.4	2.4
Neurologic						
Meningitis	0.4	0.4	0	0.8	0.8	0
Peripheral motor neuropathy	0.8	0.8	0	2.0	0.6	0
Peripheral sensory neuropathy	5.6	0.8	0	5.6	0.2	0
Other						
Pneumonitis	1.2	0.2	0.2	3.6	1.2	0
Myocarditis	0	0	0	0.2	0	0.2
Renal	3.7	0.6	0	5.2	0.2	0

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Mortes relacionadas ao tratamento

Treatment Related Deaths

Ipi3 (2 patients/516; 0.4%)
Colitis / Bowel perforation
Colitis / Death NOS (Colitis requiring steroids & infliximab. C-diff infection. D/C in stable condition. Withdrew consent. Death)

Ipi10 (8 patients/503; 1.6%)
Colitis
Colitis / Colonic perforation
Colitis
Colitis / Ventricular tachycardia (Gr4 Colitis, later rehab, DVT, pneumonia, VT)
Colitis / Nervous system disorder (GI toxicity with subsequent neurologic decline; 81 y.o.)
Pneumonitis
Thromboembolic event / Hypopituitarism
Cardiac arrest (Syncope, sepsis, sudden death)

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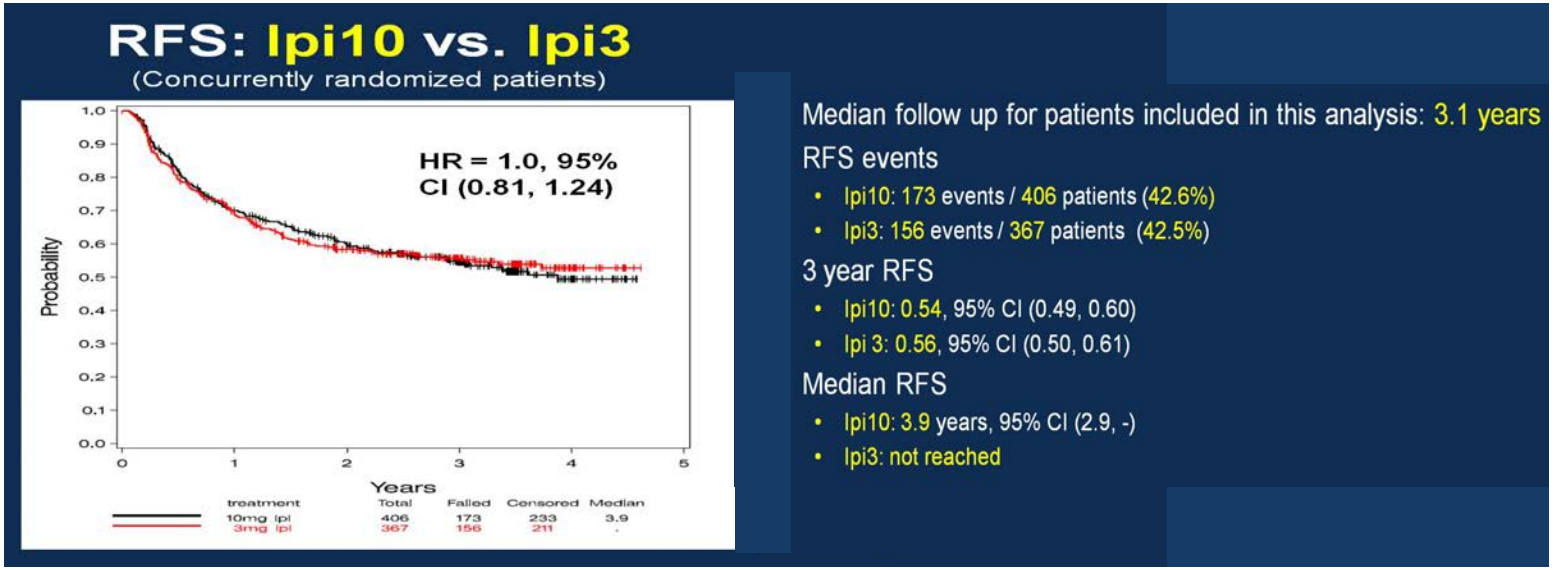
RFS: Análise não-planejada



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Conclusões

- Adjuvant therapy of high-risk melanoma with ipilimumab 10 mg/kg is associated with significantly more toxicity and more treatment-related deaths compared to ipilimumab 3 mg/kg
- Unplanned exploratory analysis of concurrently randomized patients shows no difference in RFS for ipilimumab 10 mg/kg compared to ipilimumab 3 mg/kg at a median follow up of 3.1 years
- Additional follow up is needed to inform the Ipi10 vs. Ipi3 OS comparison
- Analyses of the planned co-primary endpoints of RFS and OS for Ipi3 vs. HD-IFN await maturation of the trial

Presented By Ahmad Tarhini at 2017 ASCO Annual Meeting

Existe algum papel para Bevacizumabe adjuvante?

Adjuvant bevacizumab as treatment for melanoma patients at high risk of recurrence: ***Final results for the AVAST-M trial.***

Apresentação oral, abstract 9501

Presented By Philippa Corrie at 2017 ASCO Annual Meeting

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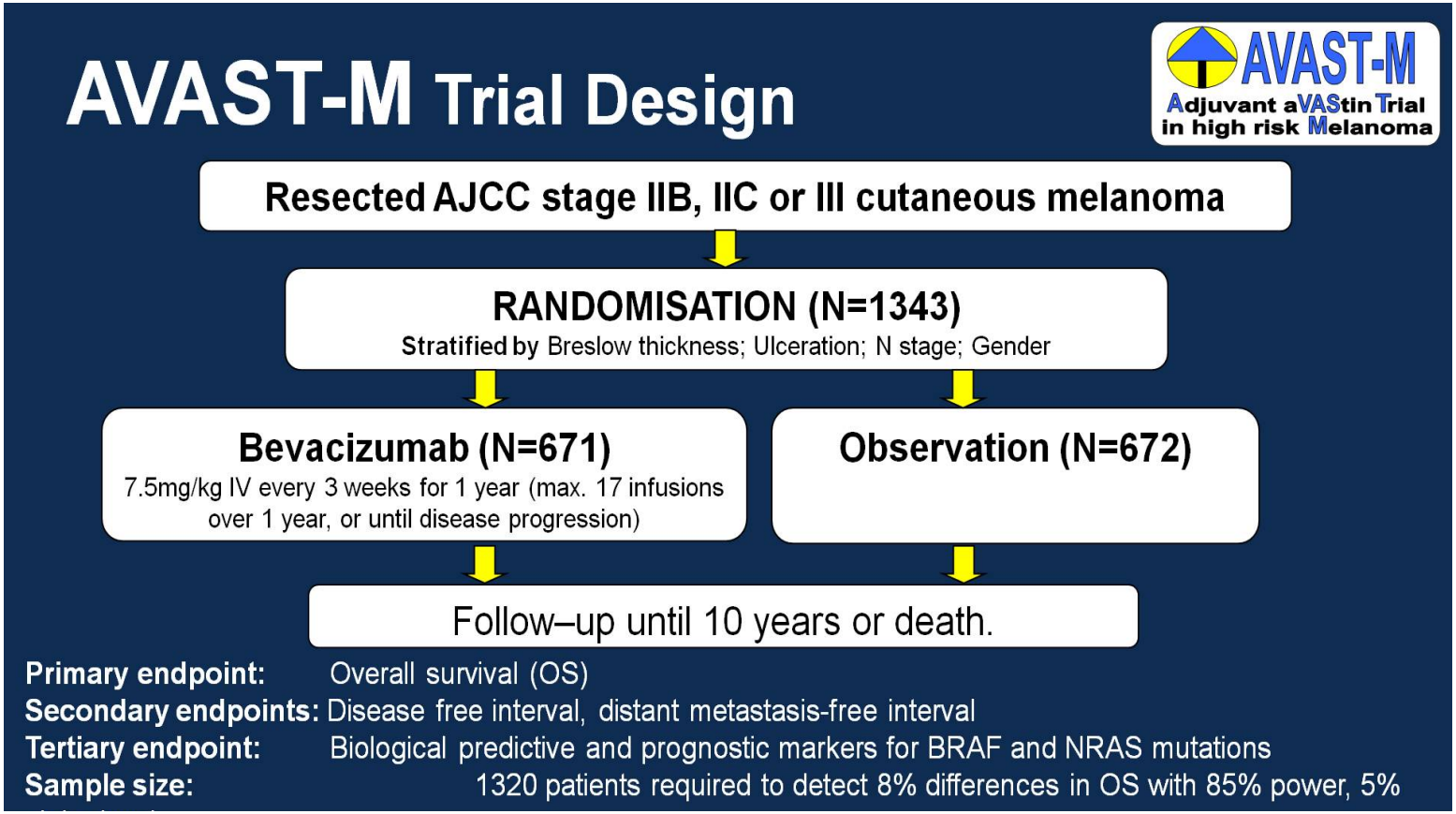
Desenho do AVAST-M



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Características de base

		Bevacizumab (N=671)	Observation (N=672)
Age (years)	Median (range)	56 (18-87)	55 (19-88)
Gender	Male	56%	56%
	Female	44%	44%
ECOG PS	0	90%	88%
	1	10%	12%
AJCC Disease stage	IIB	15%	16%
	IIC	13%	10%
	IIIA	15%	14%
	IIIB	36%	38%
	IIIC	21%	22%
Breslow thickness	≤ 2.0mm	30%	30%
	>2 – 4mm	30%	30%
	>4mm	33%	32%
	Unknown	7%	8%
Ulceration	Present	39%	38%
	Absent	46%	48%
	Unknown	15%	14%
SLNB performed	Yes	32%	32%
N classification	N0	28%	26%
	N1a or N2a	21%	20%
	Other N	51%	54%

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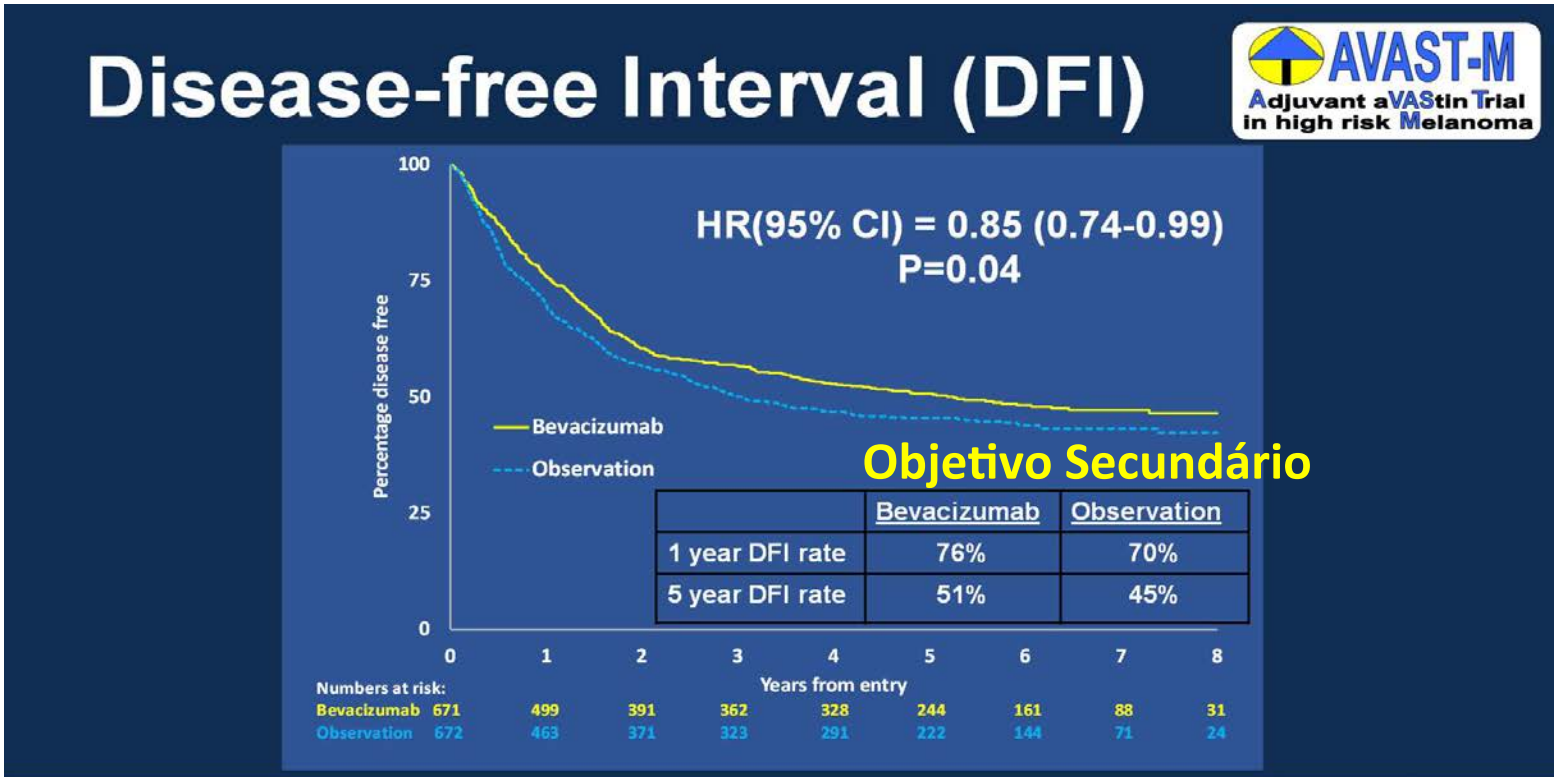
Resultados do AVAST-M

SLD foi estatisticamente superior para o grupo experimental



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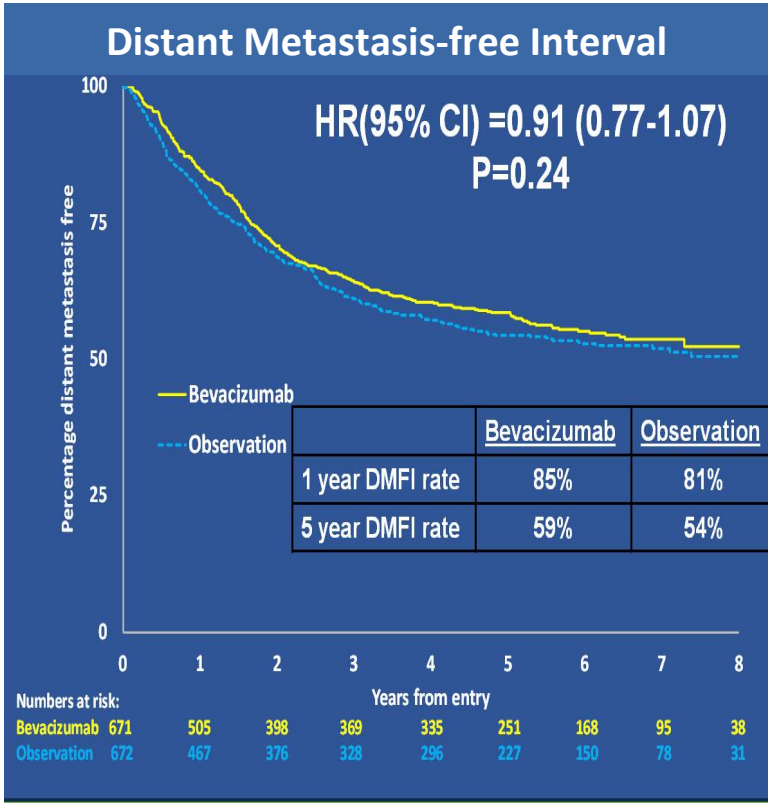
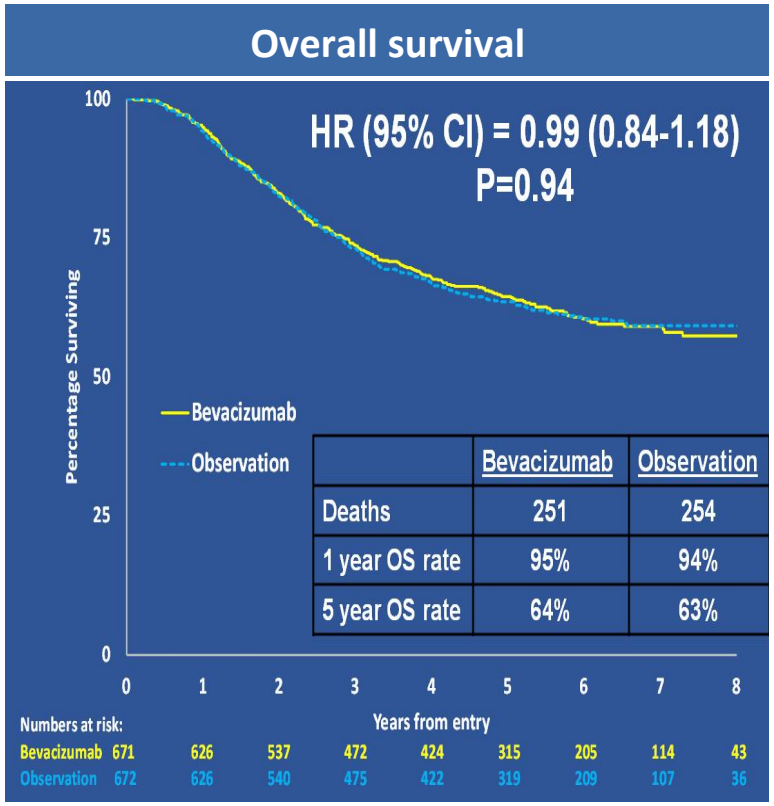
Resultados do AVAST-M

O Objetivo primário (SG) não foi atingido, assim como DMFI.





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Análise molecular

Impact Of Genotype On Overall Survival

AVAST-M
Adjuvant aVASTin Trial in high risk Melanoma

- Tumours from 682 patients were assessed for *BRAF* V600E and *NRAS* mutations
- 303 (44%) of tumours had *BRAF* V600E mutation
- 379 (56%) of tumours were *BRAF* wildtype
  - 134 (20%) tumours had *NRAS* mutation
  - 167 (25%) tumours were *NRAS* wildtype
  - 78 (11%) not assessed for *NRAS*

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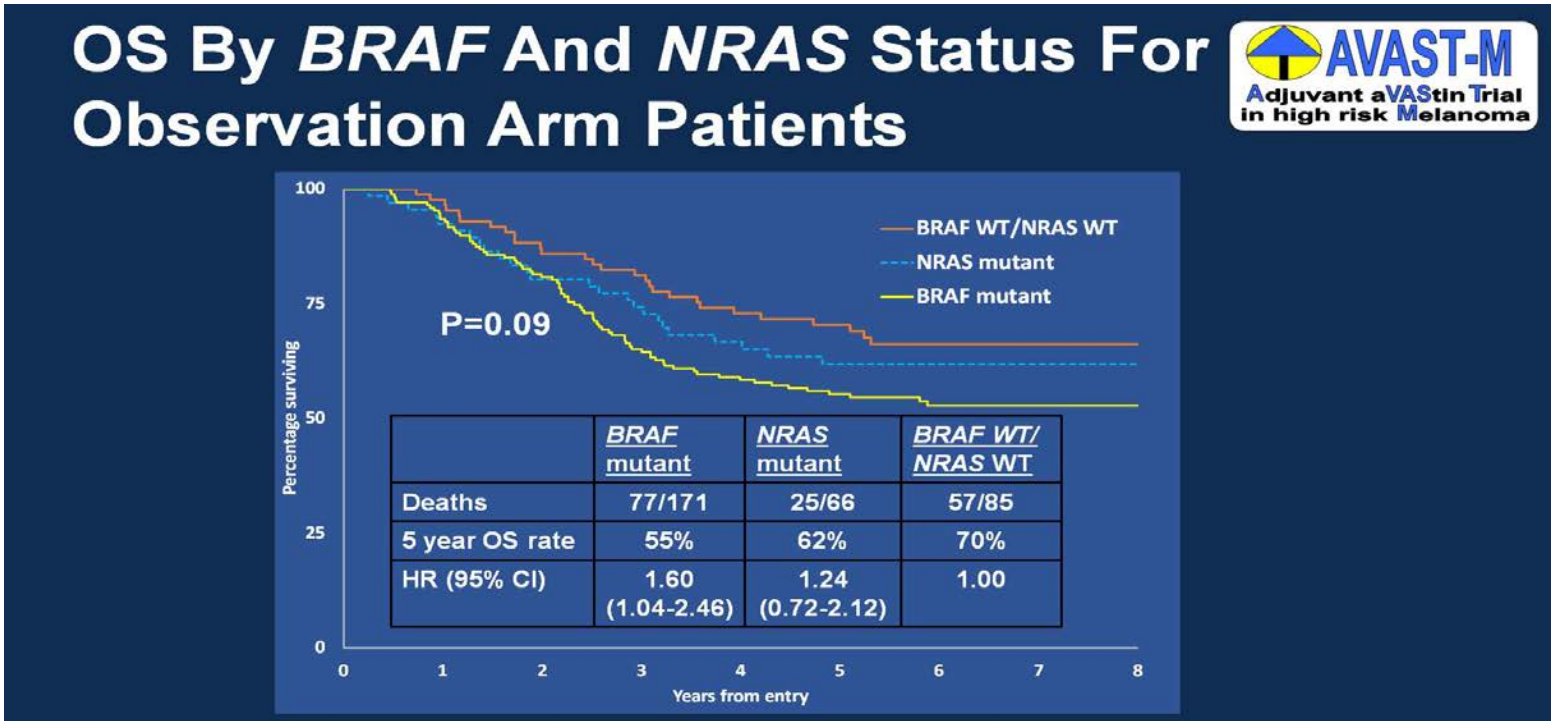
Análise exploratória: SG por *status* mutacional

No braço de observação, a mutação do BRAF parece ser fator de pior prognóstico



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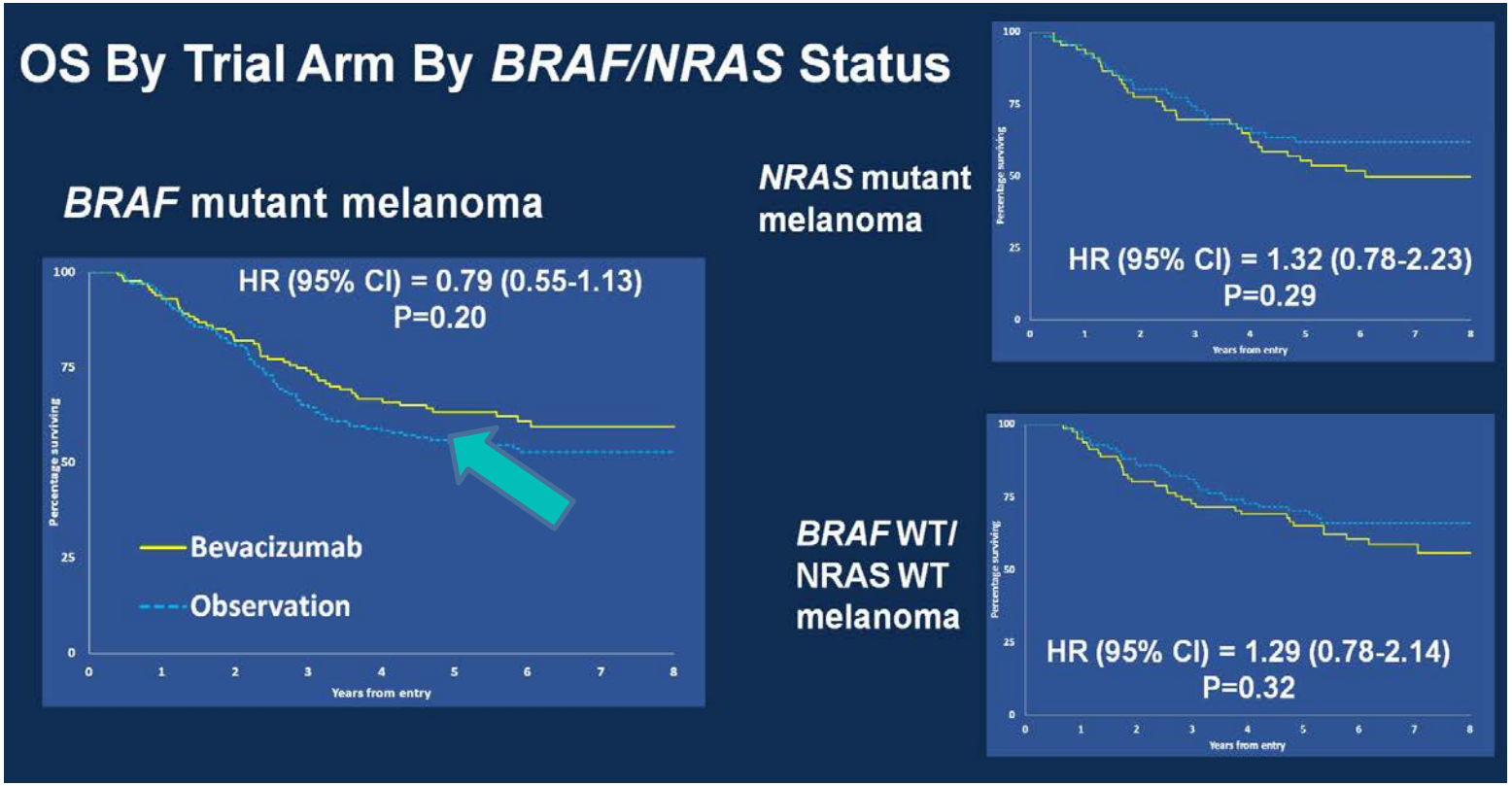
Análise exploratória: SG por *status* mutacional

No subgrupo BRAFm+, Bevacizumabe ”tende”a exercer papel protetor



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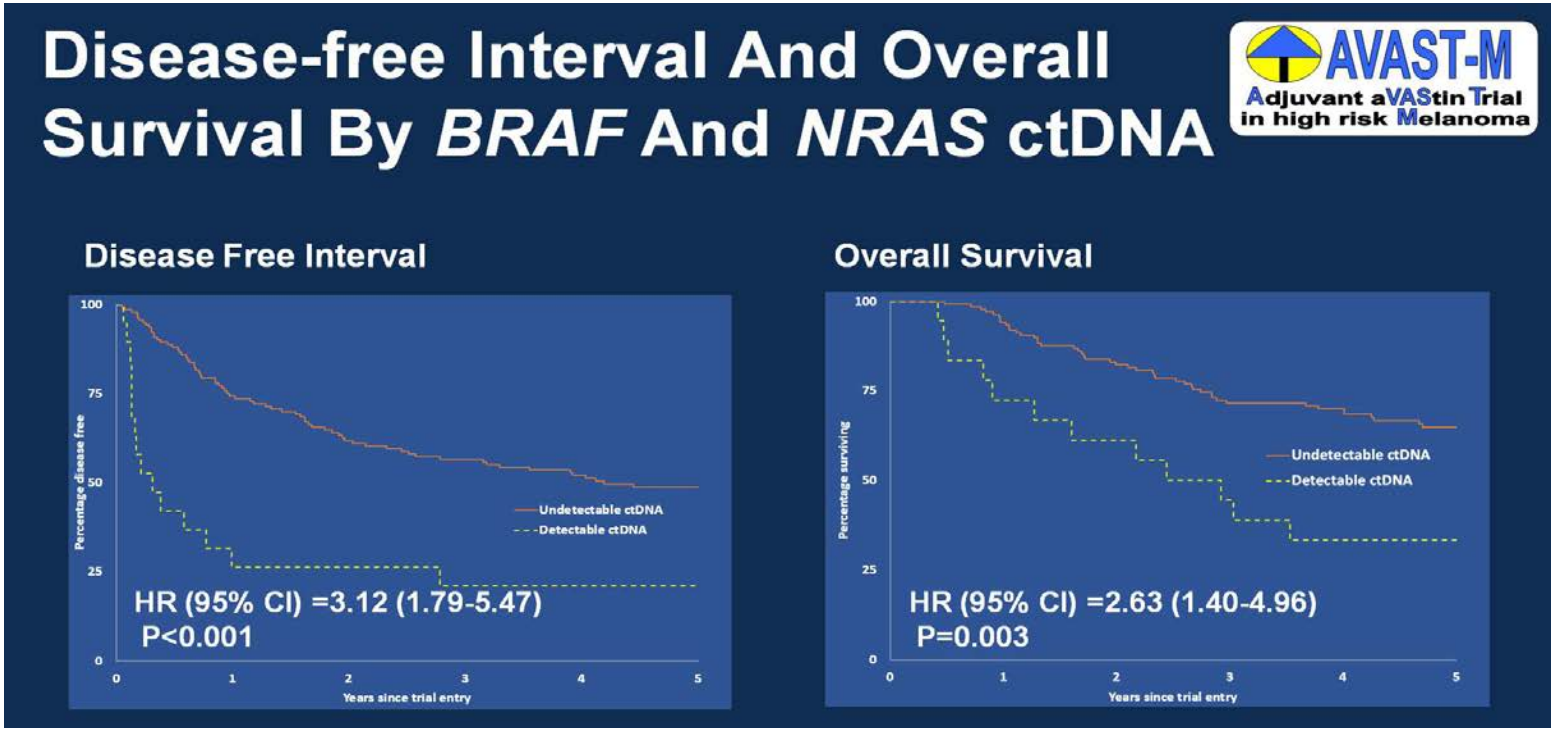
Sobrevida de acordo com ctDNA

Pacientes com mutações detectadas por biópsia líquida tiveram sobrevidas inferiores



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Conclusões

Conclusions

AVAST-M
Adjuvant aVASTin Trial in high risk Melanoma

- AVAST-M is the largest melanoma trial evaluating angiogenesis inhibition
- Adjuvant bevacizumab improves long term disease-free interval
- This did not translate into a significant improvement in distant metastasis free or overall survival
- In the observation arm, *BRAF and NRAS* mutation status appeared to influence overall survival
- Detectable mutant *BRAF* and *NRAS* ctDNA predicted for worse survival, suggesting ctDNA may be a useful method to stratify patients for future adjuvant therapy trials

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Considerações finais sobre Adjuvância

- INF ou Ipilimumabe 10 mg/Kg seguem como únicas opções disponíveis no cenário adjuvante
    - Aguardamos resultados do E1609: Ipi (10 ou 3 mg/Kg) *vs* INF
- Bevacizumabe não se mostrou capaz de aumentar sobrevida global na análise final do AVAST-M
- A detecção de *driver mutations* específicas por biópsia líquida pode ser um importante definidor de conduta
    - Estudos mais robustos tornam-se justificáveis e necessários
    - Biomarcador???
- Há uma tendência entre os debatedores em se direcionarem todos os pacientes para *clinical trials*
- É grande a expectativa pelos resultados de *trials* com anti-PD1/PD-L1 e com inibidores de BRAF/MEK!
    - Cenas dos próximos capítulos

Estudos mais relevantes em Neoadjuvância ASCO 2017

O que esperar de terapia Neoadjuvante?

Preliminary results from the international neoadjuvant melanoma consortium (INMC).

Pôster, abstract 9581

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Taxa de Resposta nos 4 estudos de NAT

Interim data from 4 ongoing trials of immunotherapy or dabrafenib / trametinib (Abstract 9581)

Immunotherapy	Dabrafenib + Trametinib
• N = 18 o ipi/nivo x2 cycles (N = 10) o ipi/nivo x3 cycles (N = 4) o nivo x4 cycles (N = 4)	• N = 40 o DT x2 months (N = 10) o DT x3 months (N = 30)
• 7 (39%) achieved pCR o 0 relapsed	• 22 (55%) achieved pCR o 4/22 (18%) relapsed

Estudos em andamento

OpaCIN (NKI) (MIA)
NA ChPi (MDACC)

Neo-Combi (MIA)
Combi-Neo (MDACC)

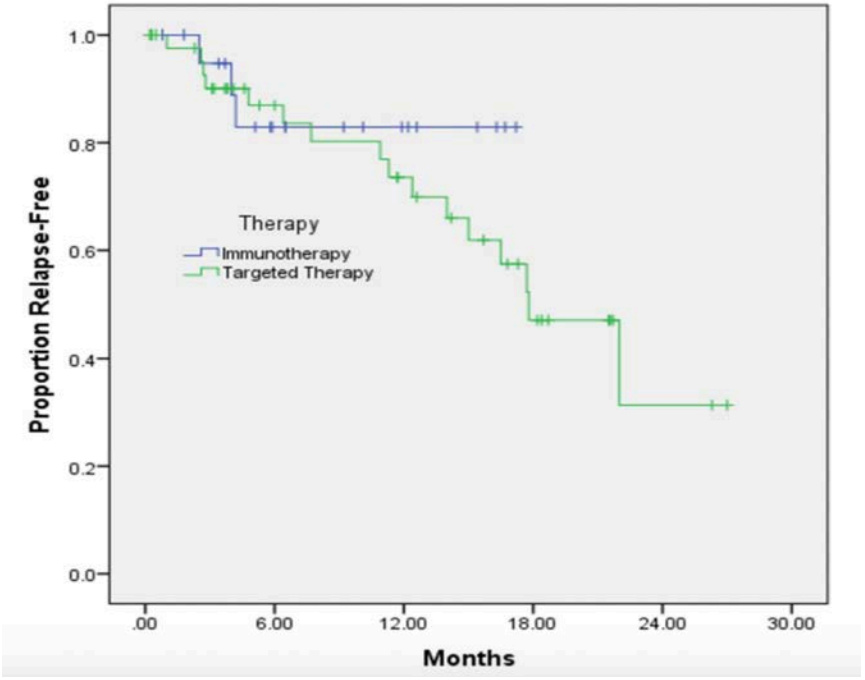
Menzes et al. ASCO 2017. Abstract 9581
Blank et al. SMR 2016;
Amaria et al. SMR 2016;
Saw et al. ASCO 2016

Presented By Alexander M. Menzies at 2017 ASCO Annual Meeting

Presented By Ahmad Tarhini at 2017 ASCO Annual Meeting

Conclusões

- Terapia alvo e Imunoterapia estão associados com altas taxas de resposta completa em pacientes com melanoma em estágio III
- Dados preliminares correlacionam pCR com melhores curvas de SLD, especialmente nos pacientes em imunoterapia



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Duplo bloqueio imunológico no cenário Neoadjuvante

Neoadjuvant ipilimumab + nivolumab (IPI+NIVO) in palpable stage III melanoma: Updated data from the OpACIN trial and first immunological analyses.

Pôster, abstract 9586

Presented By Elisa A. Rozeman at 2017 ASCO Annual Meeting

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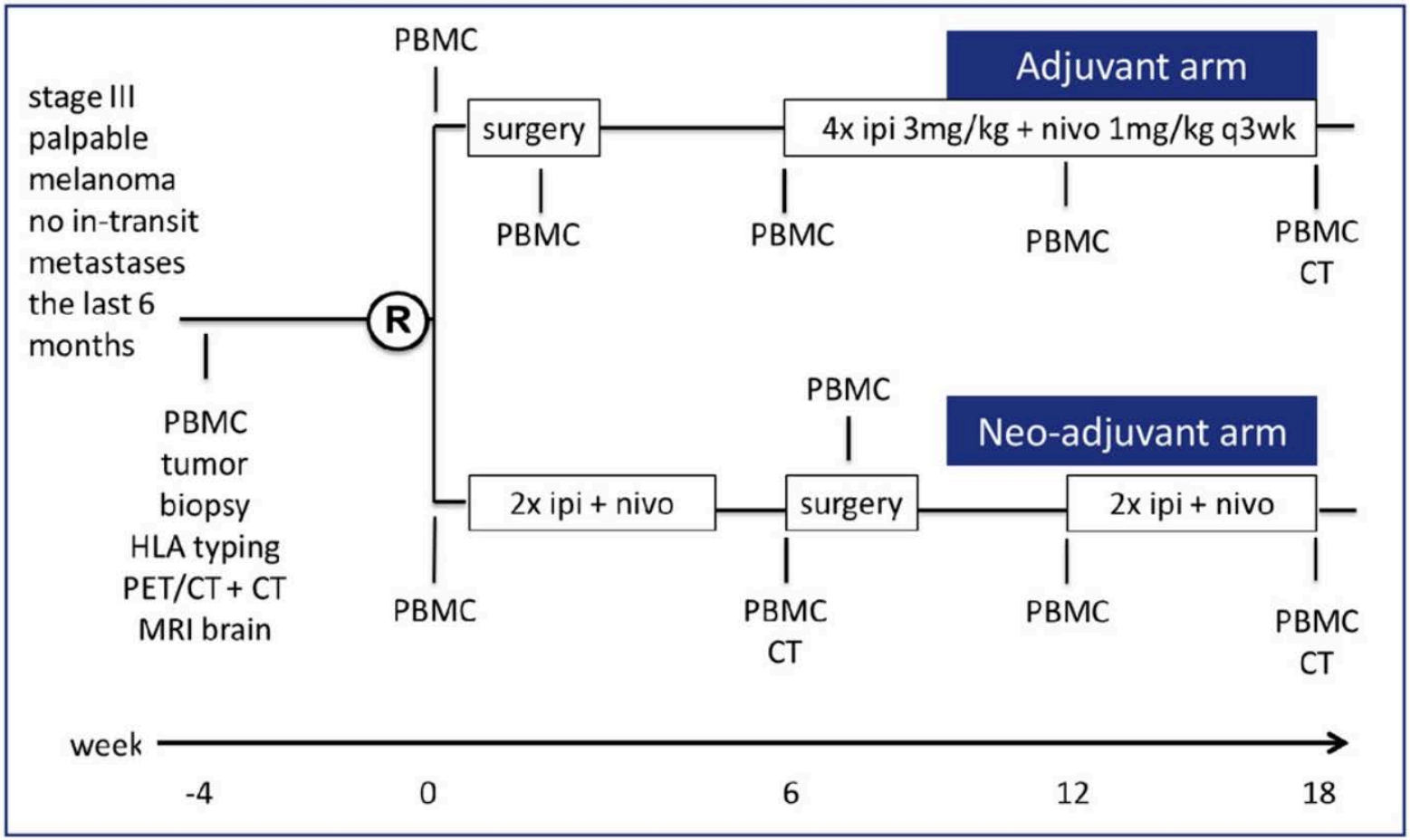
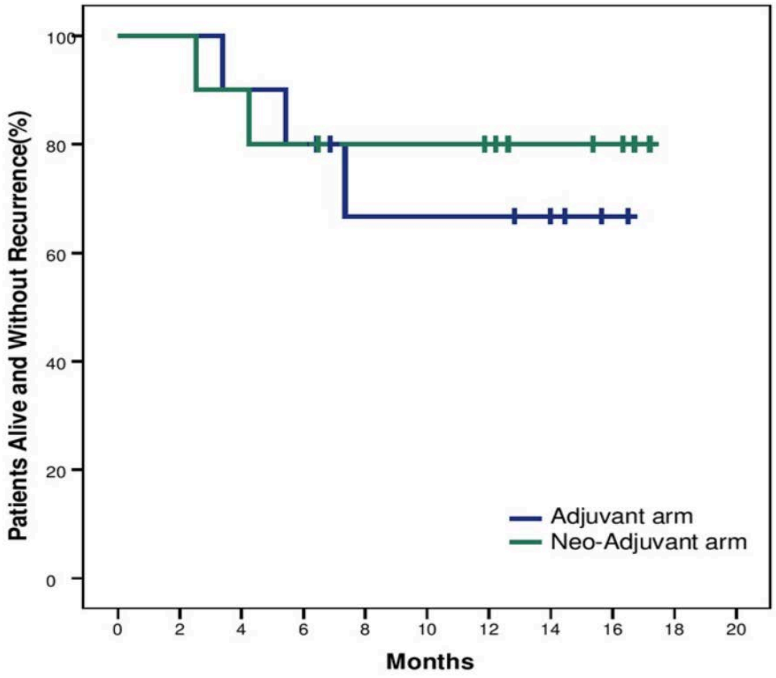
Desenho do *OpaCIN trial*



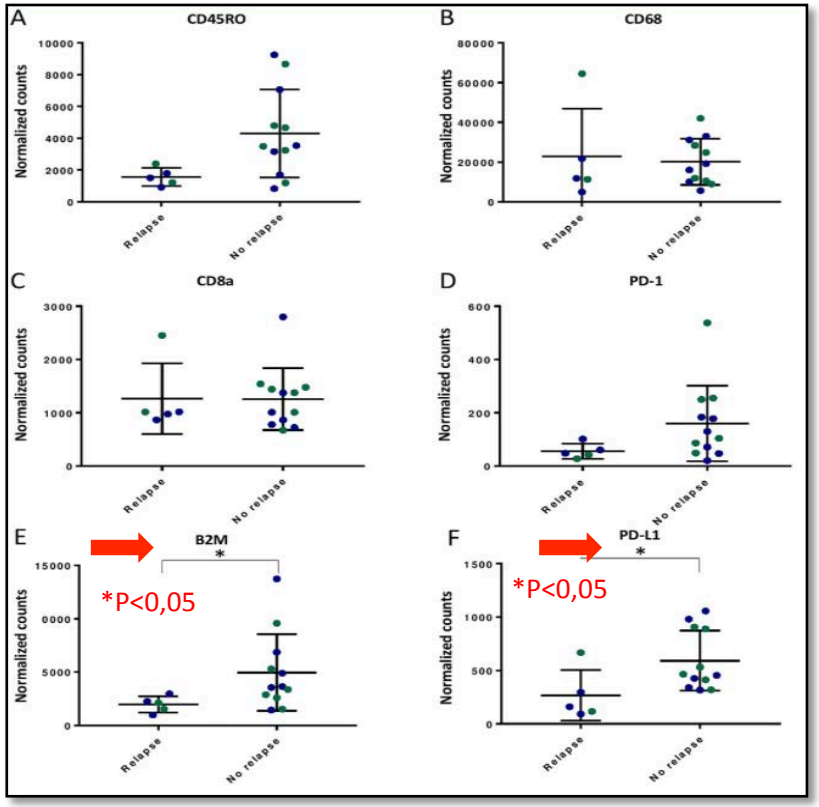
Presented By Elisa A. Rozeman at 2017 ASCO Annual Meeting

Resultados preliminares: *OpaCIN trial*

Sobrevida livre de recorrência



Análise Molecular de potenciais Biomarcadores



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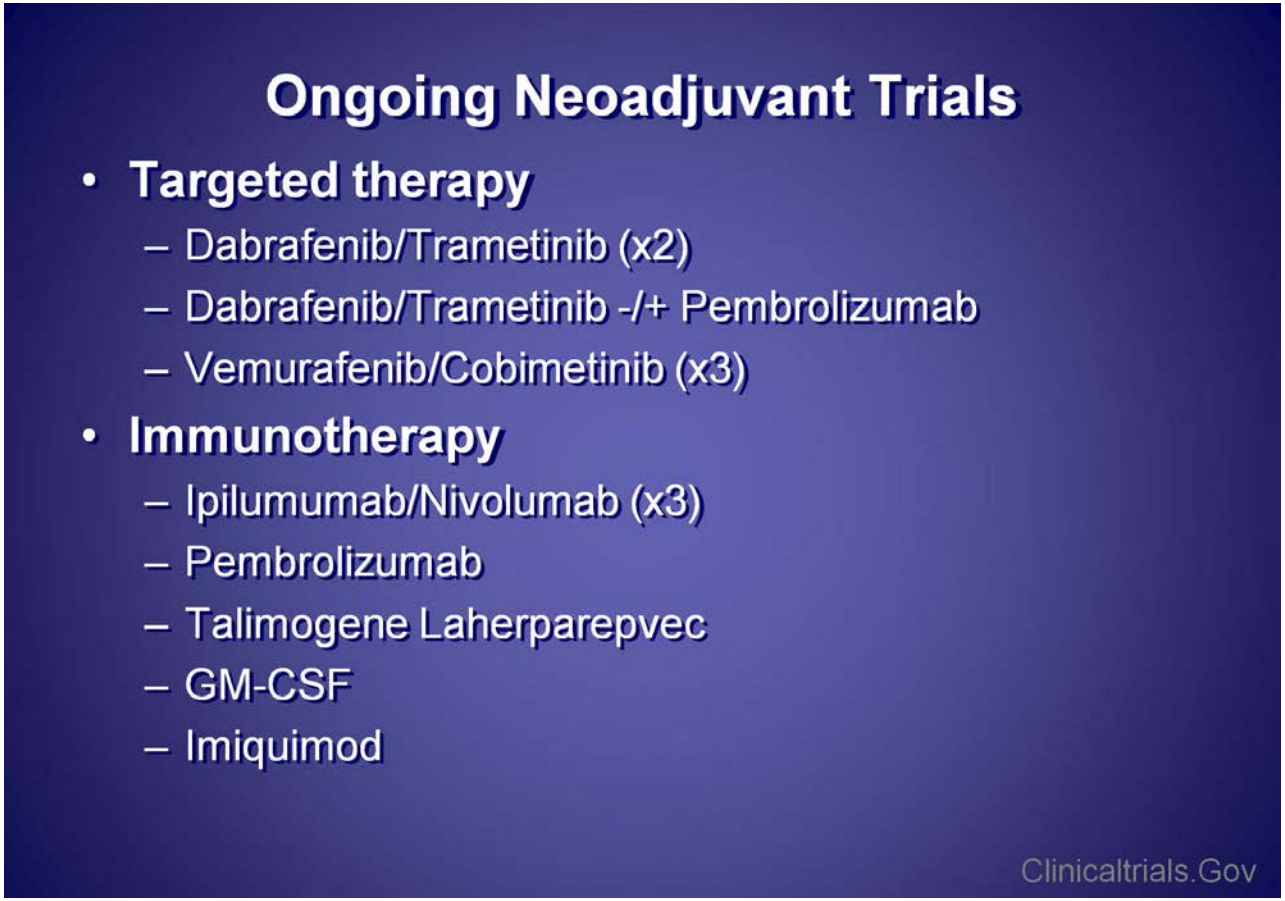
Conclusões: *OpaCIN trial*

- Ipi + Nivo Neoadjuvante induzem a elevados índices de resposta (80%)
- Porém às custas de toxicidade
    - Apenas 2 pacientes dos 20 concluíram os 4 ciclos propostos
- Até o momento, nenhum dos respondedores progrediu, no braço da neoadjuvância
- PD-L1 e B2M são possíveis biomarcadores dos pacientes que melhor respondem ao duplo bloqueio imunológico.
    - Testes multiparamétricos podem aumentar a especificidade

Presented By Elisa A. Rozeman at 2017 ASCO Annual Meeting

Futuro...



Melanoma Metastático ASCO 2017

Dados de sobrevida de longo prazo com Pembrolizumabe

Long-term outcomes in patients (pts) with ipilimumab (ipi)-naive advanced melanoma in the phase 3 KEYNOTE-006 study who completed pembrolizumab (pembro) treatment.

Apresentação oral, abstract 9504

Presented By Caroline Robert at 2017 ASCO Annual Meeting

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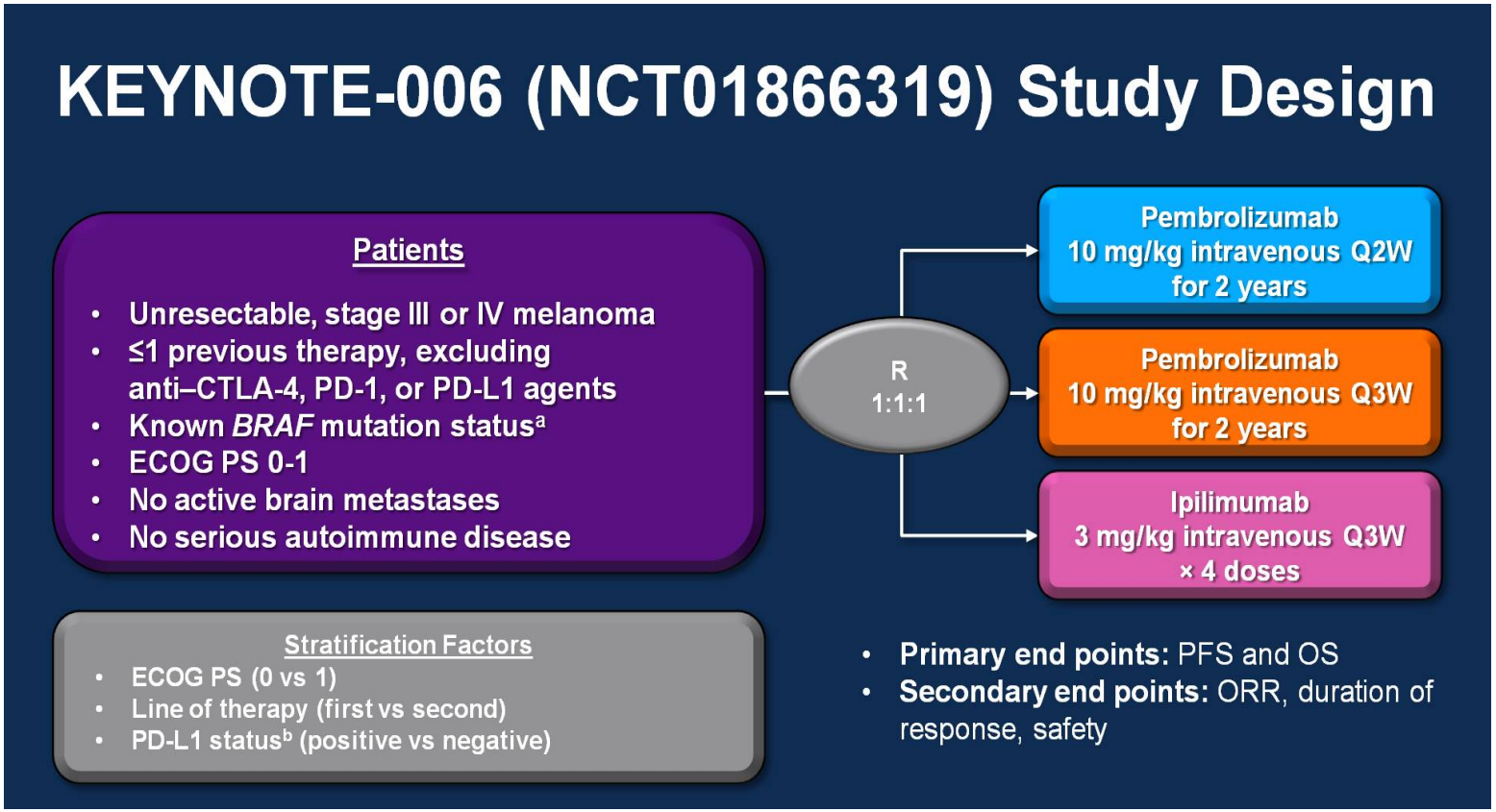
Desenho: KEYNOTE-006



Presented By Caroline Robert at 2017 ASCO Annual Meeting

Características de base: KEYNOTE-006

Os grupos estavam bem balanceados

Characteristic	Pembrolizumab N = 556	Ipilimumab N = 278
Age, median (range), years	62 (18-89)	62 (18-88)
Men, n (%)	335 (60)	162 (58)
ECOG PS 0, n (%)	384 (69)	188 (68)
Elevated LDH, n (%)	179 (32)	91 (33)
BRAF^{V600} mutant, n (%)	195 (35)	107 (38)
PD-L1 positive,[a] n (%)	446 (80)	225 (81)
M1c disease, n (%)	368 (66)	178 (64)
1 previous therapy,[b] n (%)	187 (34)[c]	97 (35)

Apresentação oral, abstract 9504

Presented By Caroline Robert at 2017 ASCO Annual Meeting

Características de base: KEYNOTE-006

Post Study Antineoplastic Therapy

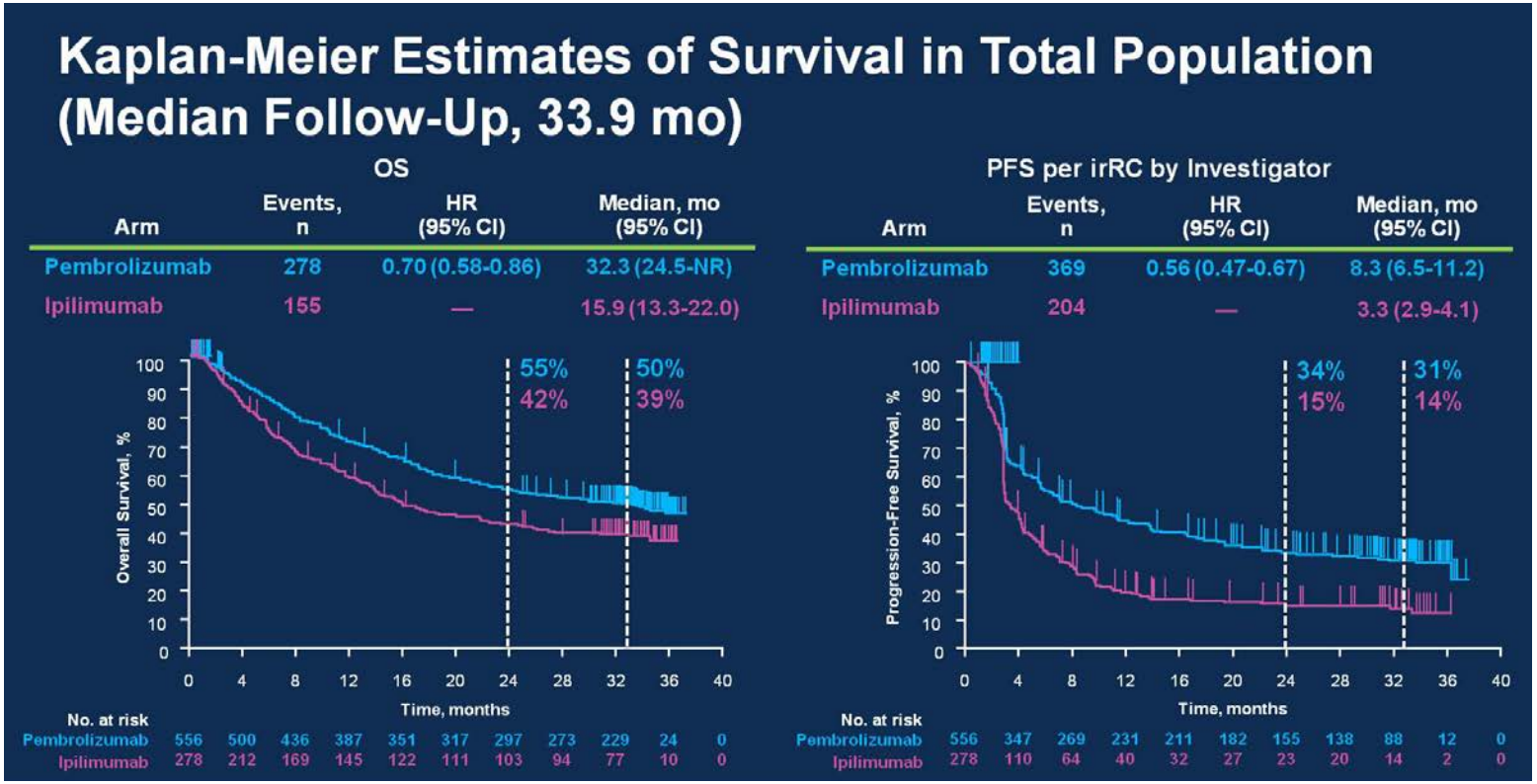
Therapy, n (%)	Pembrolizumab N = 555	Ipilimumab N = 256
Any[a]	247 (44)	138 (54)
Immunotherapy	172 (31)	97 (39)
Anti–CTLA-4	137 (25)	13 (5)
Anti–PD-1	49 (9)[b]	86 (34)[c]
Anti–PD-L1	3 (<1)	2 (<1)
Anti–CLTA-4 + anti–PD-1	0	1 (<1)
BRAF inhibitor ± MEK inhibitor	130 (23)	81 (32)
Chemotherapy	64 (11)	32 (12)
Other therapy	11 (4)	13 (5)

- O grupo de Pembro recebeu mais anti-CTLA4
- O grupo de Ipi recebeu mais anti-PD1
- O grupo de Ipi recebeu mais terapia alvo

Presented By Caroline Robert at 2017 ASCO Annual Meeting

Resultados de longo termo: KEYNOTE-006

Pembro comprovou superioridade frente a Ipi



Apresentação oral, abstract 9504

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Resultados de longo termo: KEYNOTE-006

Taxas de Respostas objetivas favoreceram Pembro

Tumor Response (irRC, investigator)

	Pembrolizumab N = 556	Ipilimumab N = 278
ORR, % (95% CI)	42 (38-46)	16 (12-21)
Best overall response, % (95% CI)		
CR	13 (11-16)	3 (1-6)
PR	29 (25-33)	14 (10-18)
SD	21 (18-25)	25 (20 -31)
PD	29 (26-33)	39 (33-45)

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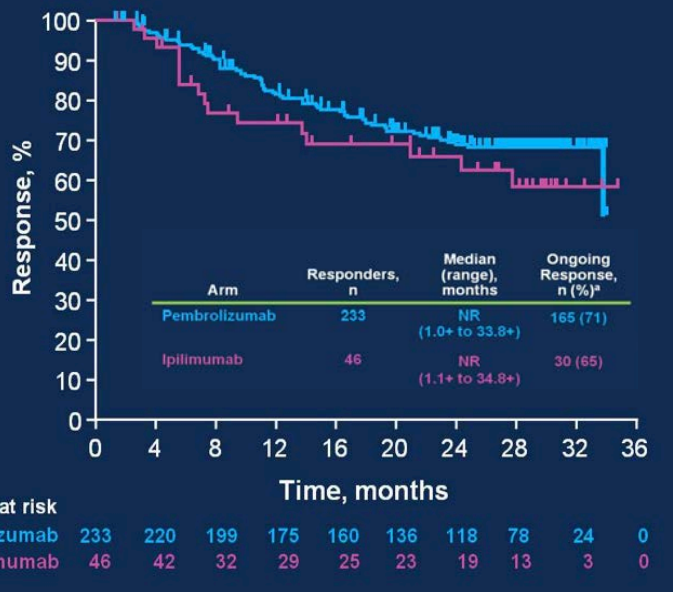
Resultados de longo termo: KEYNOTE-006

Pembro demonstrou taxas de respostas superiores e mais duradouras

Tumor Response (irRC, investigator)

	Pembrolizumab N = 556	Ipilimumab N = 278
ORR, % (95% CI)	42 (38-46)	16 (12-21)
Best overall response, % (95% CI)		
CR	13 (11-16)	3 (1-6)
PR	29 (25-33)	14 (10-18)
SD	21 (18-25)	25 (20 -31)
PD	29 (26-33)	39 (33-45)



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Toxicidade: KEYNOTE-006

Pembrolizumabe: Mais alterações tireoidianas
Ipilimumabe: Mais colites

Immune-Mediated AEs[a]

n (%)	Pembrolizumab N = 555	Ipilimumab N = 256
Any grade	144 (26)	48 (19)
Grade 3/4	50 (9)	31 (12)
Led to death	0	0
Led to discontinuation	28 (5)	14 (5)
Immune-mediated AEs occurring in >2% patients		
Hypothyroidism	60 (11)	5 (2)
Hyperthyroidism	29 (5)	6 (2)
Colitis	17 (3)	19 (7)
Skin disorders	15 (3)	5 (2)
Pneumonitis	13 (2)	1 (<1)

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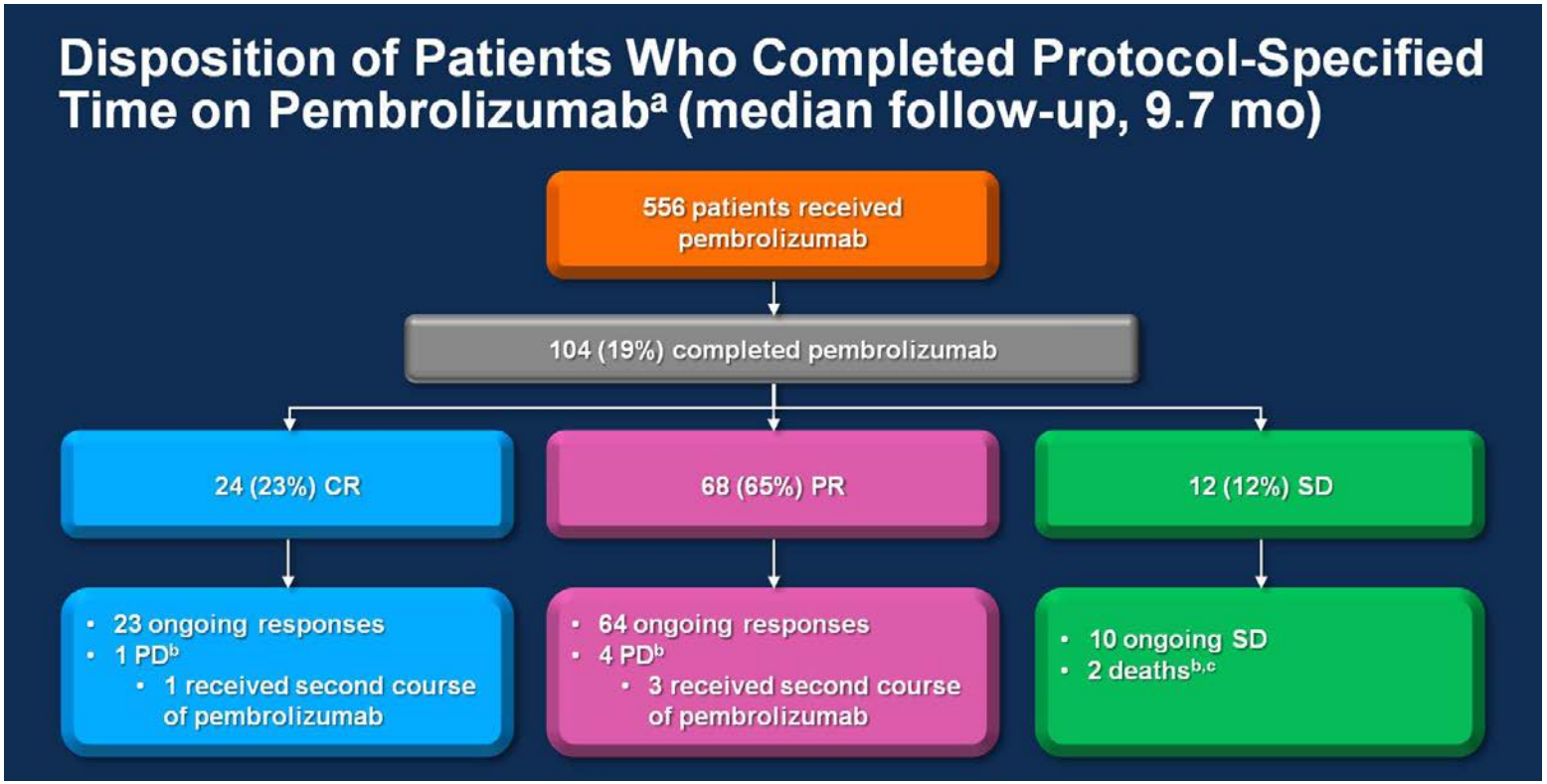
KEYNOTE-006

O que aconteceu com os pacientes que completaram 2 anos de tratamento?



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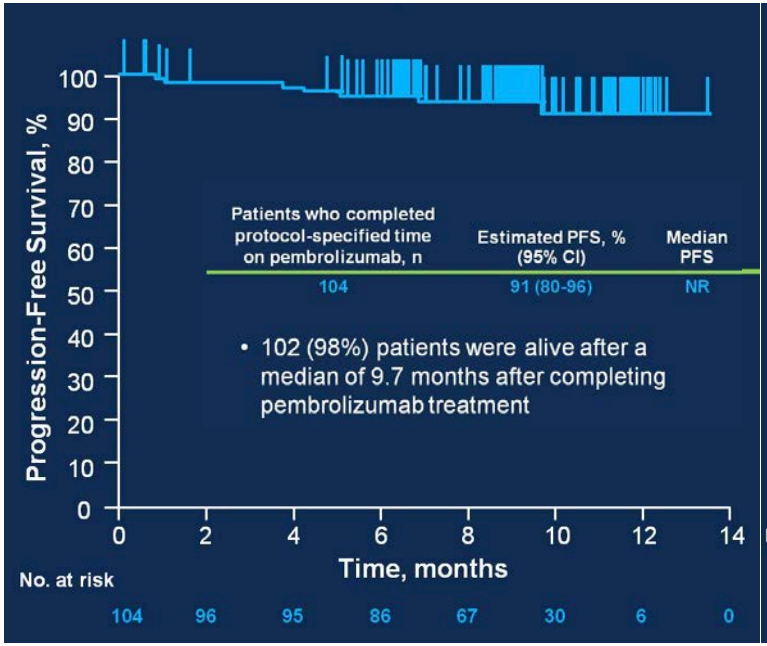
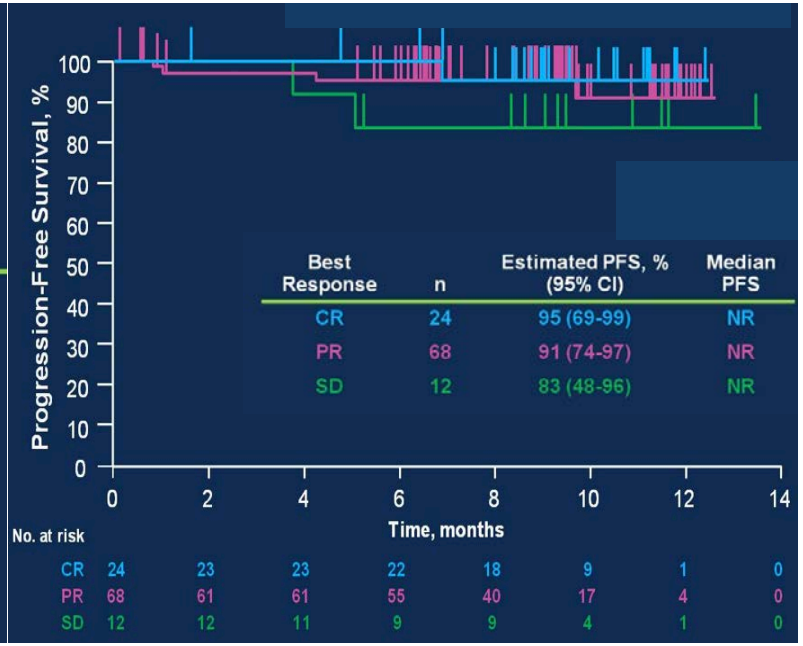
SLP após completar 2 anos: KEYNOTE-006

SLP na população geral



SLP de acordo com grau de resposta



Mesmo os pacientes que tiveram doença estável (SD) mantiveram-se livres de progressão após interrupção de Pembro

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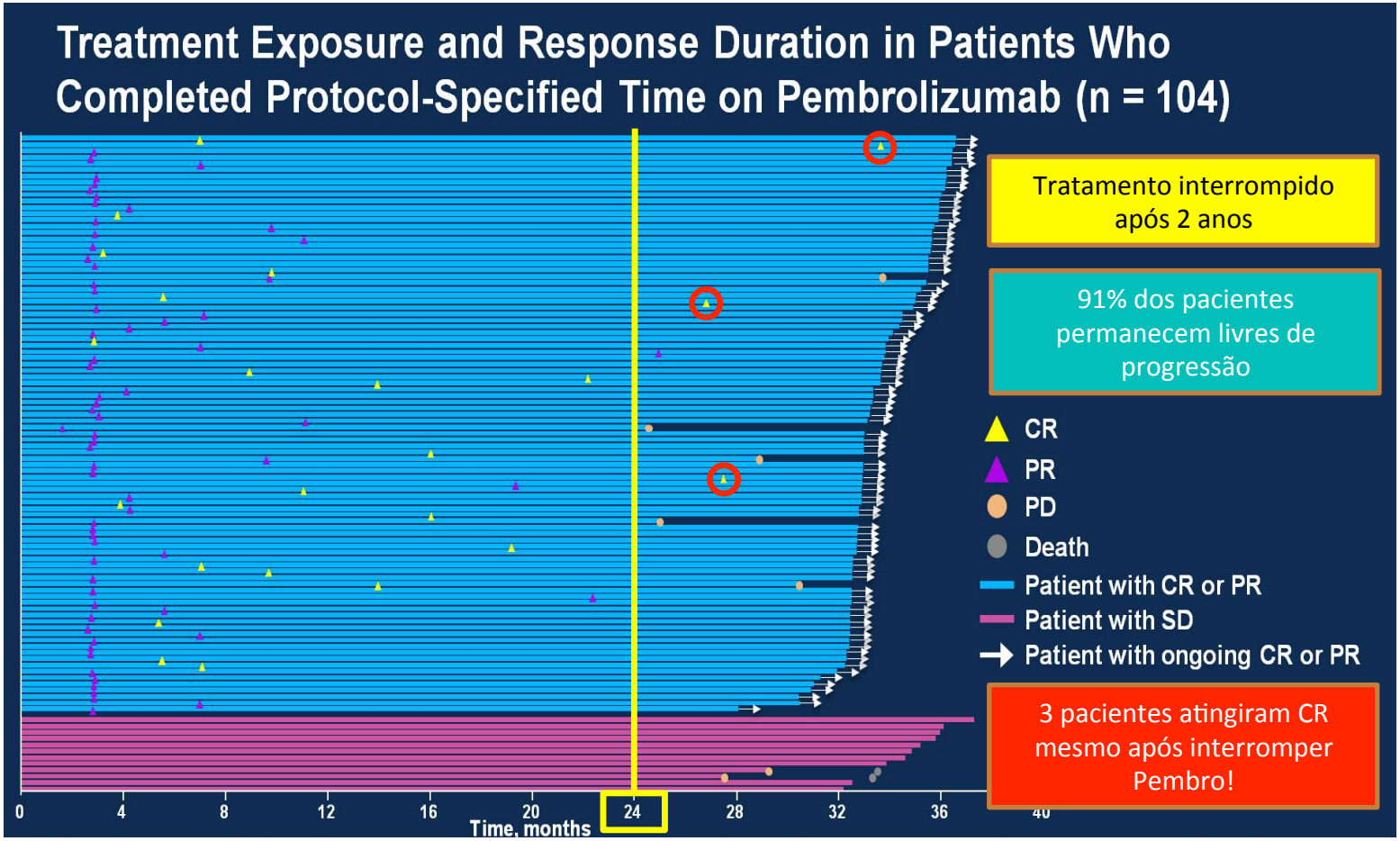
Respostas mantidas: KEYNOTE-006



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Conclusões: KEYNOTE-006

Summary and Conclusions

- After a median follow-up of nearly 3 years, superiority of pembrolizumab over ipilimumab was confirmed
  - Median OS: 32.3 vs 15.9 months
  - Median PFS: 8.3 vs 3.3 months
  - Favorable safety profile
- 91% of patients who completed 2 years of pembrolizumab treatment are progression free after a median follow-up of 9.7 months
- Data further support use of pembrolizumab as standard of care for patients with advanced melanoma

Presented By Caroline Robert at 2017 ASCO Annual Meeting

Dados de sobrevida de longo prazo com duplo bloqueio BRAF/MEK no melanoma metastático BRAF mutado

Five-year overall survival (OS) update from a phase II, open-label trial of dabrafenib (D) and trametinib (T) in patients (pts) with BRAF V600–mutant unresectable or metastatic melanoma (MM).

Apresentação oral, abstract 9505

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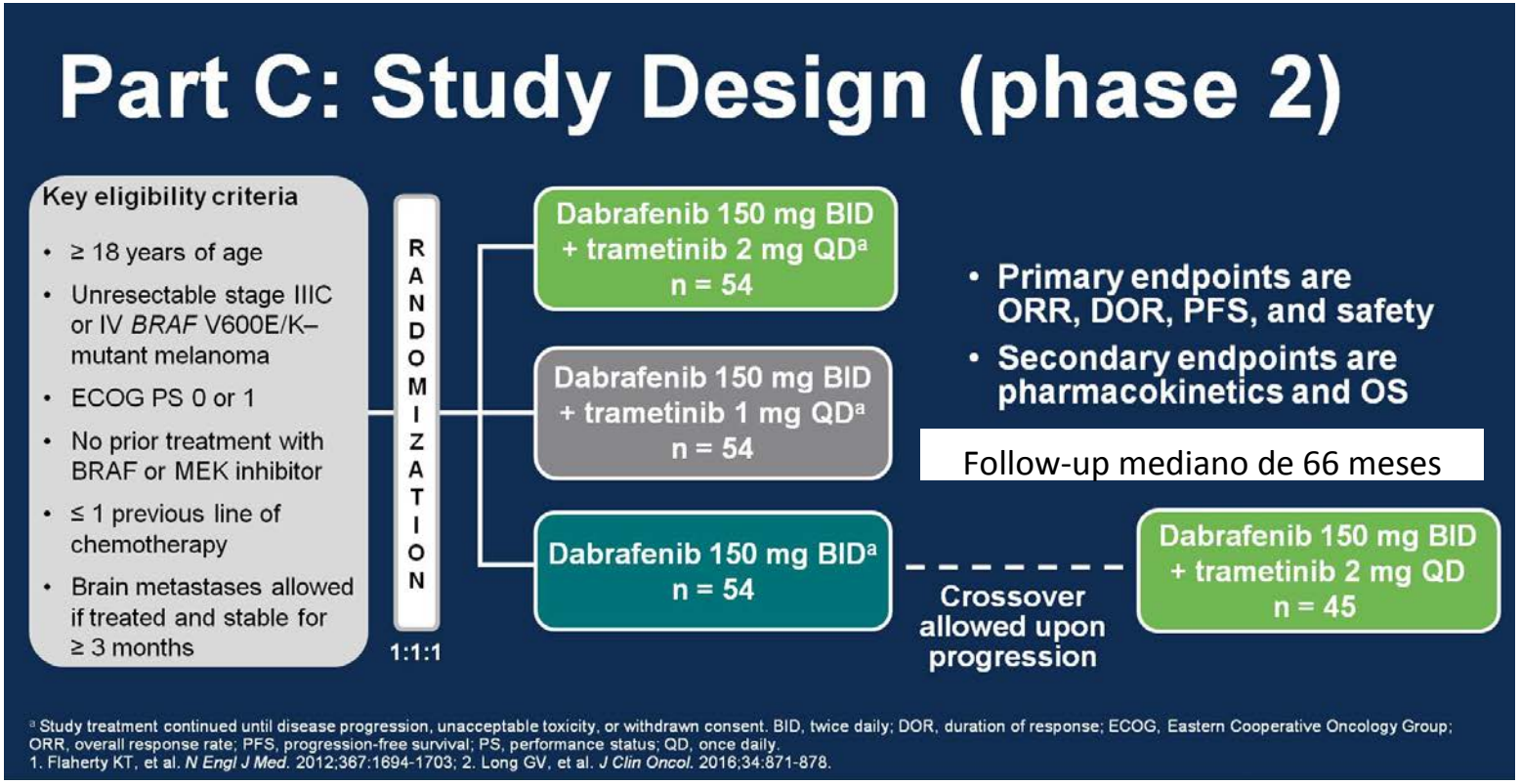
Desenho do Estudo



Demonstrar dados de longo prazo (5 anos) com uso de iBRAF + iMEK

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Características de base

Characteristic	D+T 150/2 (n = 54)	D+T 150/1 (n = 54)	D Monotherapy (n = 54)
Median age (range), years	58 (27-79)	49 (23-85)	50 (18-82)
Male sex, n (%)	34 (63)	30 (56)	29 (54)
ECOG PS 1, n (%)	19 (35)	16 (30)	20 (37)
Stage, n (%)			
IIIC/M0	0	1 (2)	1 (2)
M1a	6 (11)	9 (17)	11 (20)
M1b	10 (19)	11 (20)	5 (9)
M1c	38 (70)	33 (61)	37 (69)
Treatment naive, n (%)	41 (76)	38 (70)	42 (78)
History of brain metastases, n (%)	2 (4)	7 (13)	4 (7)
***BRAF* mutation, n (%)**			
V600E	47 (87)	45 (83)	45 (83)
V600K	7 (13)	9 (17)	9 (17)
LDH level > ULN, n (%)	22 (41)	25 (46)	27 (50)
≥ 3 Organ sites with metastasis, n (%)	28 (52)	27 (50)	34 (63)
Previous chemotherapy, n (%)	7 (13)	15 (28)	12 (22)
Previous immunotherapy, n (%)	13 (24)	16 (30)	8 (15)

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Resultados

Os grupos foram bem balanceados

Confirmed Response Rates and Duration

	D+T 150/2 (n = 54)	D+T 150/1 (n = 54)	D Monotherapy (n = 54)
Best response, n (%)			
Complete response	9 (17)	5 (9)	2 (4)
Partial response	32 (59)	22 (41)	27 (50)
Stable disease	13 (24)	24 (44)	22 (41)
Progressive disease	0	2 (4)	3 (6)
Not evaluable	0	1 (2)	0
Response rate (CR+PR), n (%) [95% CI]	**41 (76) [62-87]**	**27 (50) [36-64]**	**29 (54) [40-67]**
Duration of response	n = 41	n = 27	n = 29
Progressed or died, n (%)	33 (80)	21 (78)	27 (93)
Median (95% CI), months	10.5 (7.4-19.2)	11.1 (7.6-13.2)	5.6 (4.1-7.4)

CR, complete response; PR, partial response.

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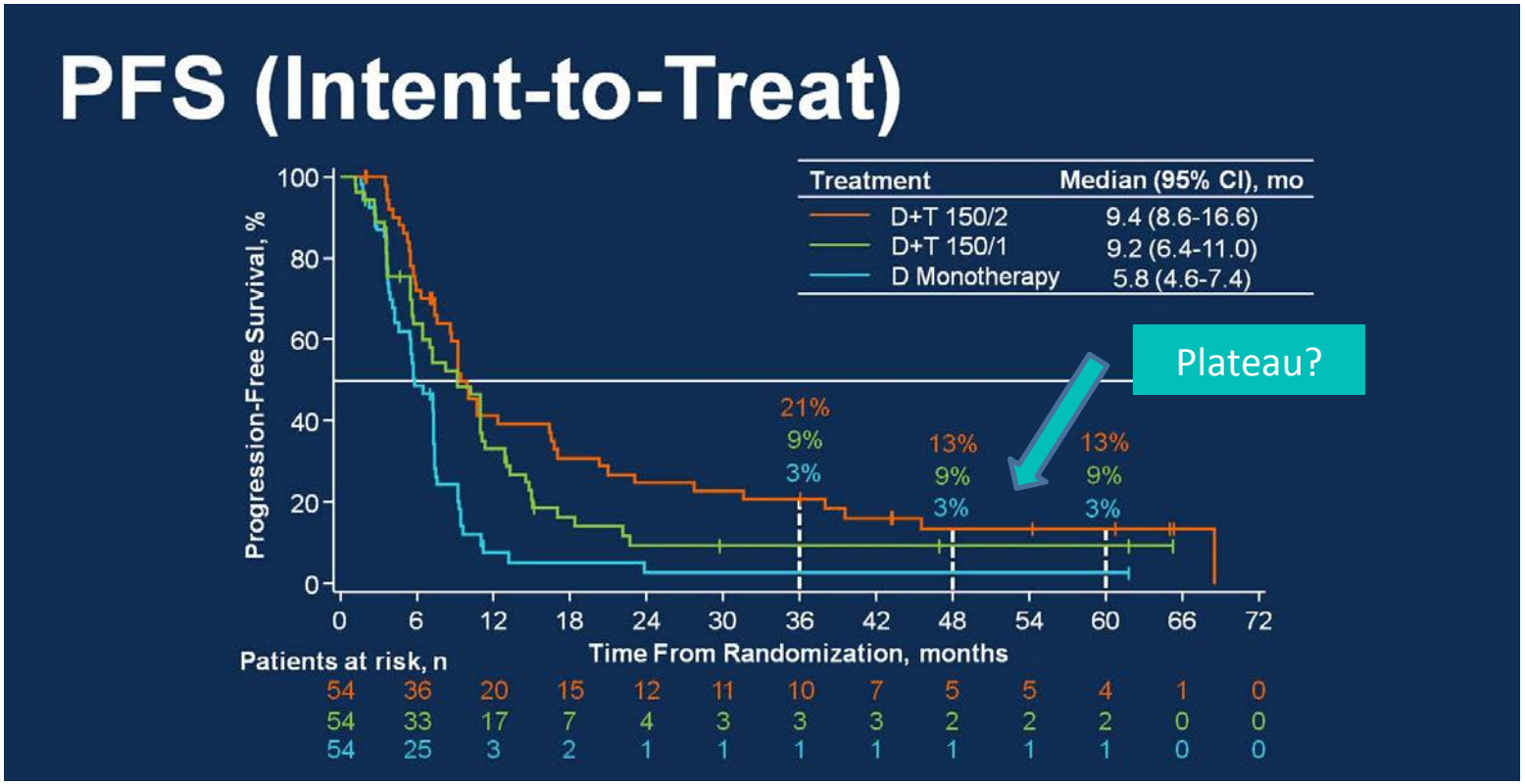
Resultados

É possível que nem todos os pacientes desenvolvam resistência adquirida



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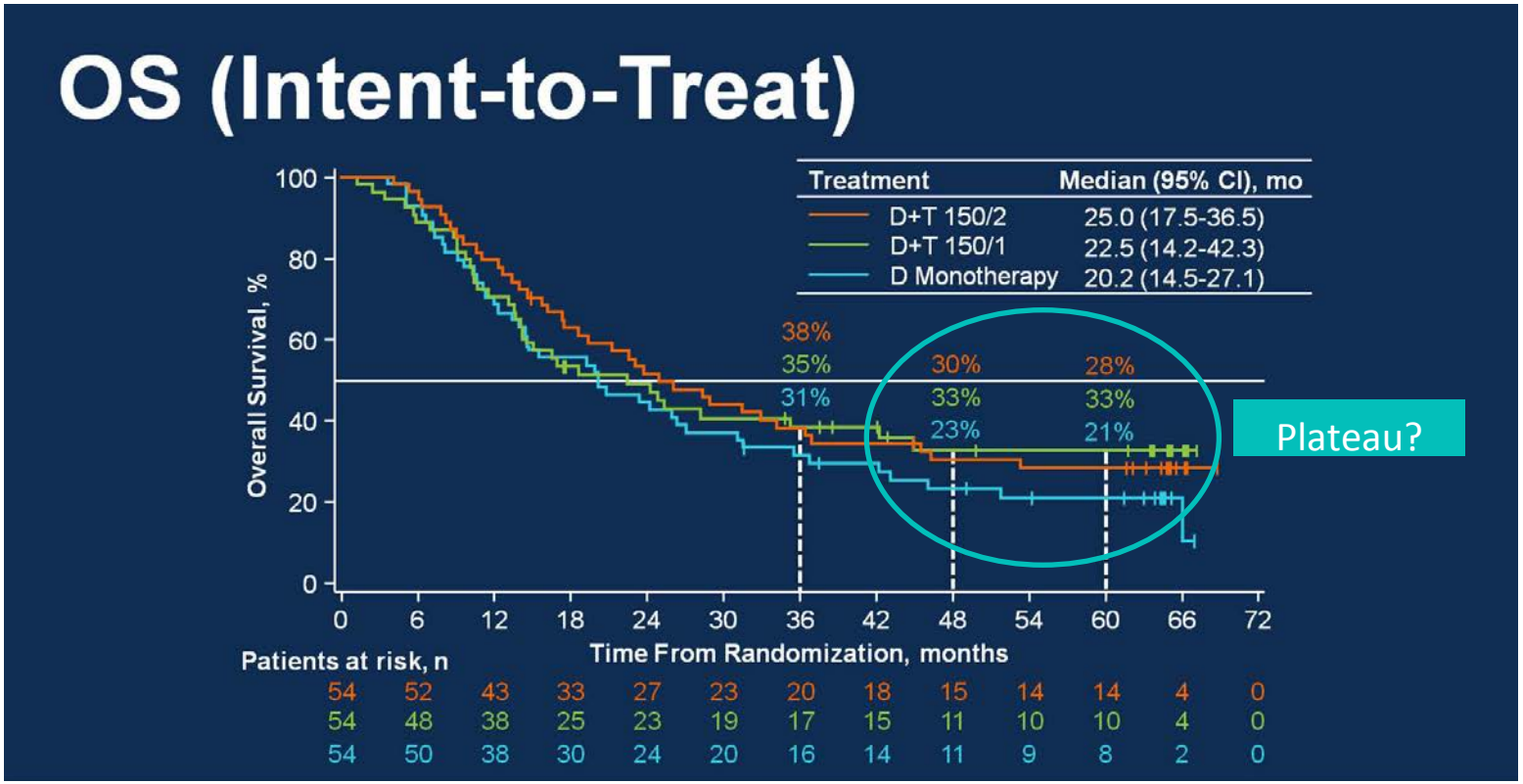
Resultados

Há uma significativa proporção de pacientes vivos em 4 e 5 anos.
O plateau das curvas de sobrevida lembra o da imunoterapia



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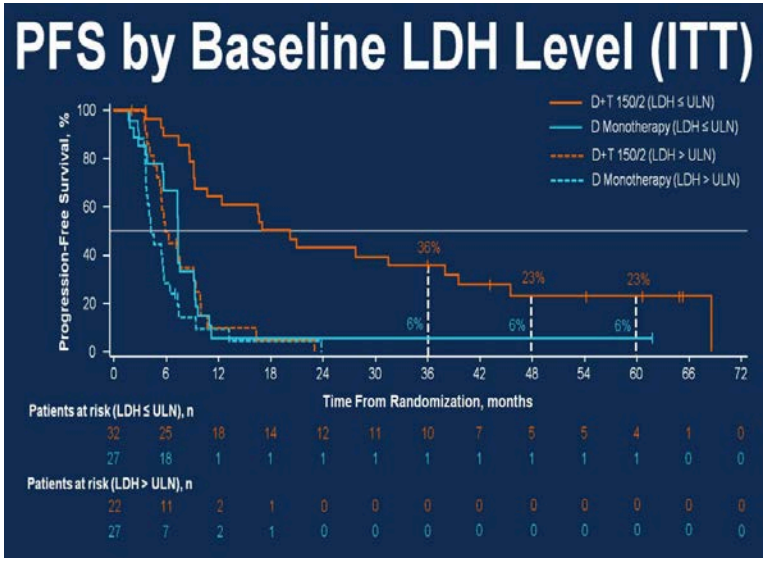
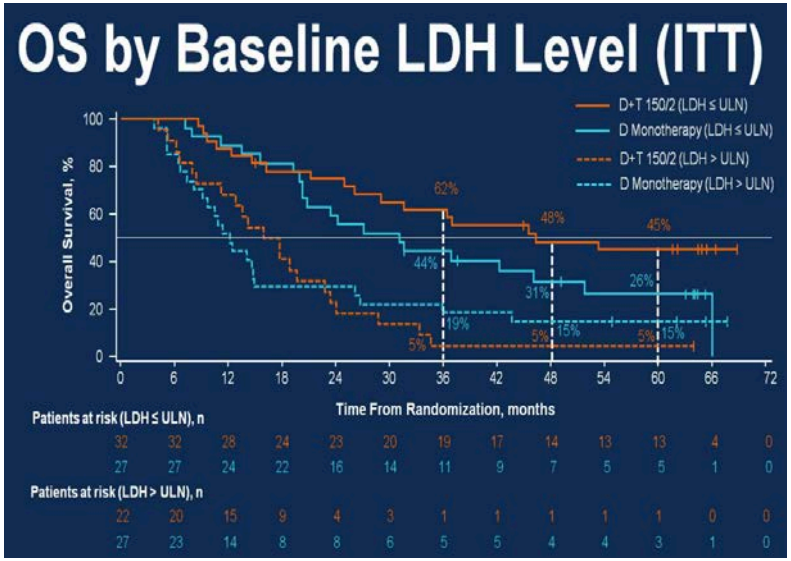
Sobrevida de acordo com LDH

Paciente que tinham LDH normal tiveram maior benefício





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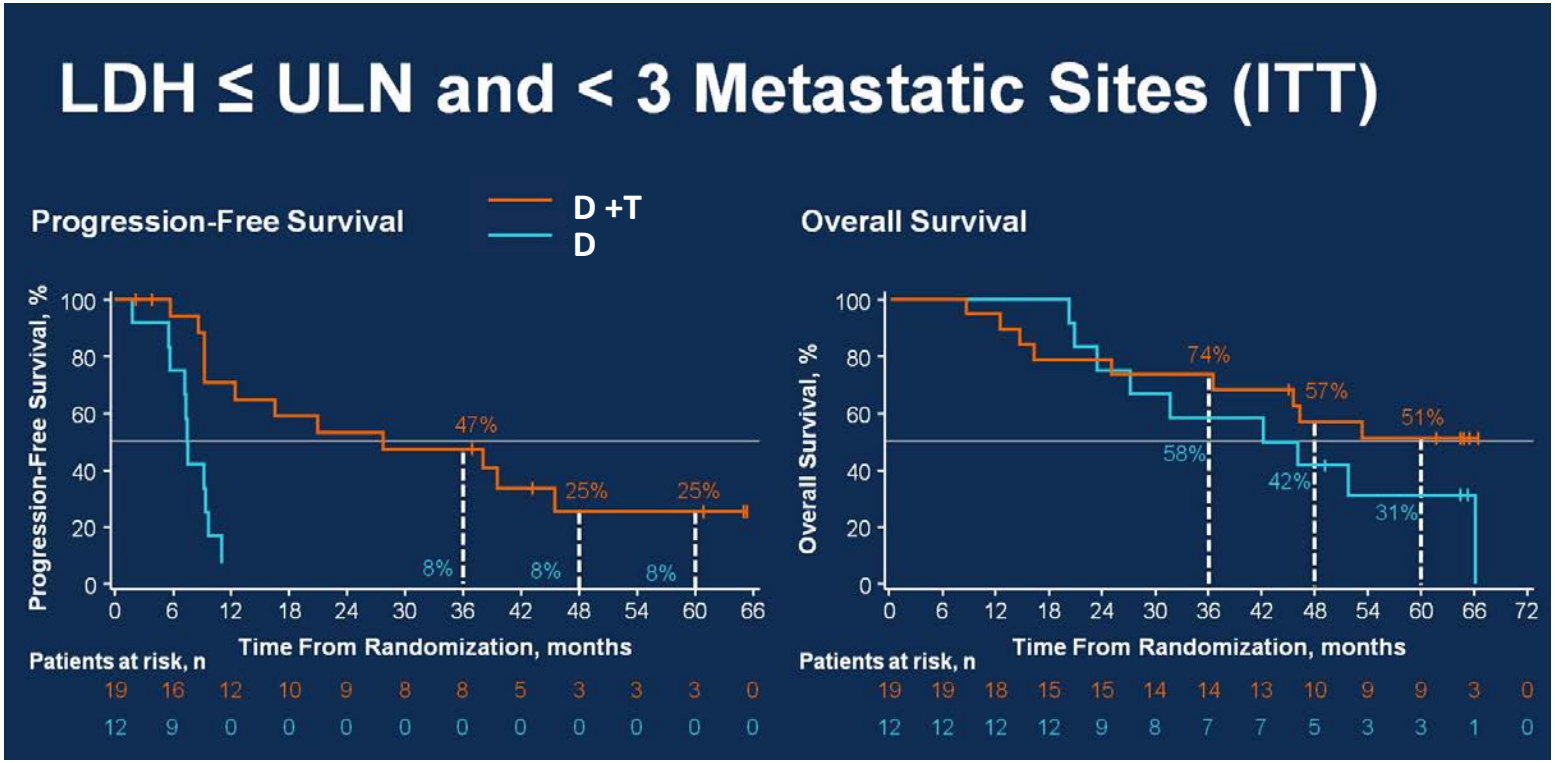
Sobrevida de acordo com LDH e Volume

51% dos pacientes com LDH normal e baixo volume de metástases estavam vivos em 5 anos



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Toxicidade

AE, n (%)	D+T 150/2 (n = 55)		D+T 150/1 (n = 54)		D Monotherapy (n = 53)[a]	
	Any Grade	Grade 3/4	Any Grade	Grade 3/4	Any Grade	Grade 3/4
Pyrexia	38 (69)	4 (7)	39 (72)	6 (11)	14 (26)	0
Diarrhea	27 (49)	1 (2)	18 (33)	2 (4)	15 (28)	0
Nausea	26 (47)	2 (4)	30 (56)	4 (7)	11 (21)	0
Vomiting	26 (47)	1 (2)	24 (44)	4 (7)	8 (15)	0
Arthralgia	19 (35)	0	28 (52)	0	18 (34)	0
Rash	18 (33)	0	13 (24)	0	19 (36)	0
Hyperkeratosis	9 (16)	0	4 (7)	0	15 (28)	0
Squamous cell carcinoma of the skin[b]	4 (7)	3 (5)	1 (2)	1 (2)	7 (13)	6 (11)
Ejection fraction decrease	8 (15)	2 (4)	4 (7)	1 (2)	0	0
Alopecia	3 (5)	0	8 (15)	0	19 (36)	0
Photosensitivity	2 (4)	0	3 (6)	0	3 (6)	0
Chorioretinopathy	1 (2)	0	0	0	0	0
Retinal vein occlusion	0	0	0	0	0	0

	D+T 150/2 (n = 55)	D+T 150/1 (n = 54)	D Monotherapy (n = 53)[a]
Treatment-related AEs, n (%)	55 (100)	52 (96)	51 (96)
Grade 3/4 treatment-related AE	23 (42)	23 (43)	13 (25)
Discontinuations due to AEs, n (%)	9 (16)	4 (7)	1 (2)

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Conclusões

Conclusions

- This is the longest follow-up for any randomized trial evaluating a BRAF inhibitor combined with a MEK inhibitor
- Long-term survival is achievable with D+T in patients with *BRAF* V600–mutant metastatic melanoma, particularly those with favorable baseline factors:
  - 5-year OS with D+T 150/2: 28% (95% CI, 17%-41%)
  - 5-year OS (normal baseline LDH and < 3 organ sites with metastasis) with D+T 150/2: 51% (95% CI, 27%-71%)
- No new safety signals identified with long-term D+T treatment
- These data support the use of D+T as a treatment option that can achieve long-term survival in *BRAF* V600E/K–mutated melanoma

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Metástase Cerebral
ASCO 2017

Presented By Lynn Schuchter at 2017 ASCO Annual Meeting

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É seguro usar Nivolumabe + Ipilimumabe em pacientes com metástases cerebrais?

Efficacy and safety of nivolumab (NIVO) plus ipilimumab (IPI) in patients with melanoma (MEL) metastatic to the brain: Results of the phase II study CheckMate 204.

Apresentação oral, abstract 9507

Presented By Hussein Tawbi at 2017 ASCO Annual Meeting

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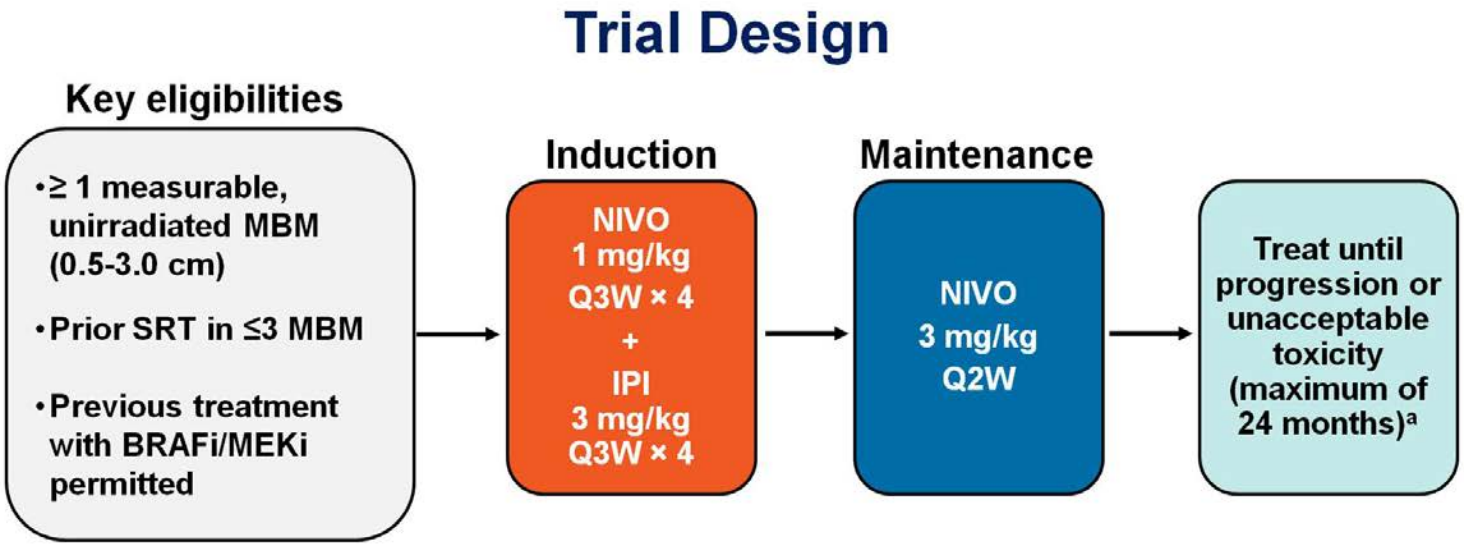
Desenho: *CheckMate* 204



- Exclusion criteria included neurological symptoms; steroids > 10 days; WBRT; prior treatment with checkpoint inhibitors; leptomeningeal disease
- Original planned enrollment of 110 asymptomatic patients

Q2W = every 2 weeks; Q3W = every 3 weeks

[a]Patients with grade 3-4 adverse events (AEs) during NIVO+IPI induction could resume NIVO when toxicity resolved; all patients who discontinued proceeded to follow-up

Presented By Hussein Tawbi at 2017 ASCO Annual Meeting

Características de base: *CheckMate* 204

	All patients (N = 75)
Male, n (%)	53 (71)
Median age, years (range)	59 (22–79)
***BRAF* mutation, n (%)**	41 (55)
***NRAS* mutation, n (%)**	5 (7)
LDH > ULN, n (%)	31 (41)
LDH > 2x ULN, n (%)	11 (15)
Prior systemic cancer therapy, n (%)	12 (16)
Dabrafenib/Trametinib	6 (8)
Vemurafenib	2 (3)
Prior SRT, n (%)	7 (9)
Median of median target lesion diameters, mm (IQR)	9.0 (6.5–14.0)
Target lesions, n (%)	
1-2 lesions	59 (79)
>3 lesions	16 (21)

IQR = interquartile range

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Resultados: *CheckMate* 204

Response to Treatment – All Patients (N = 75)

	Global	Intracranial	Extracranial
Best overall response, n (%)			
Complete response	4 (5)	16 (21)	5 (7)
Partial response	36 (48)	25 (33)	32 (43)
Stable disease	4 (5)	4 (5)	2 (3)
Progressive disease[a]	18 (24)	18 (24)	16 (21)
Not evaluable[b]	13 (17)	12 (16)	20 (27)
Objective response rate, % (95% CI)	53 (41–65)	55 (43–66)	49 (38–61)
Clinical benefit rate[c], % (95% CI)	59 (47–70)	60 (48–71)	52 (40–64)

[a]Confirmed and unconfirmed progressive disease
[b]Includes unconfirmed responses
[c]Clinical benefit rate = complete response + partial response + stable disease ≥ 6 months

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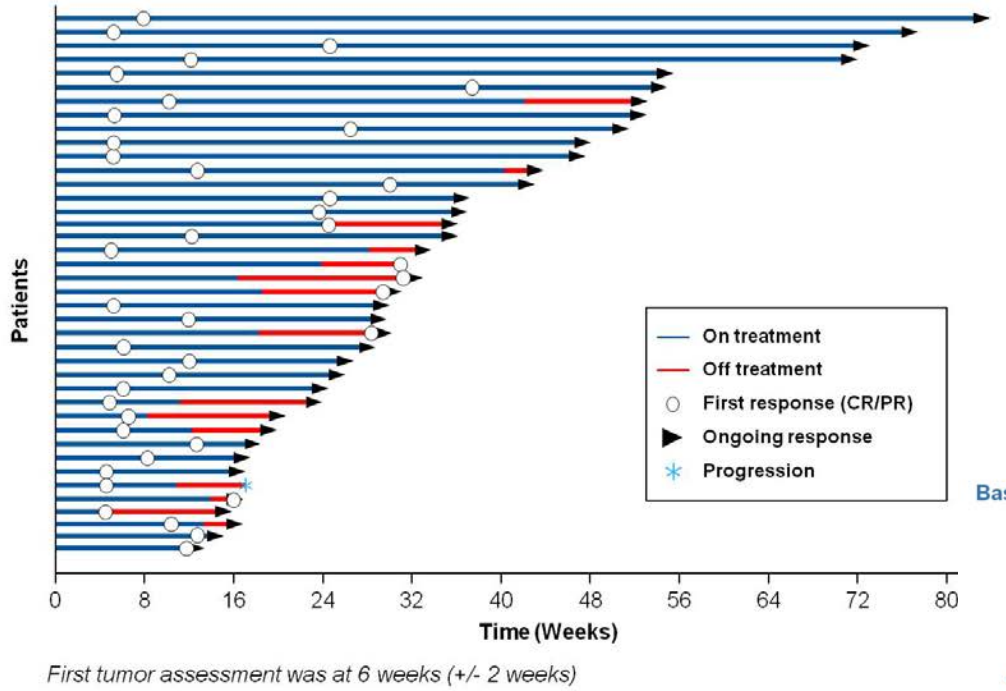
Resultados: *CheckMate* 204

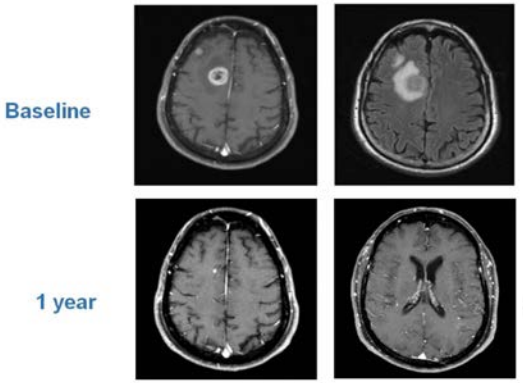
Swimmer Plot: Time to and Duration of Intracranial Response



First tumor assessment was at 6 weeks (+/- 2 weeks)

	N = 41
Time to response,[a] median (range), months	2.8 (1.0–11.0)
Duration of response,[a] median (95% CI), months	NR (NR-NR)
Ongoing response among responders[a]	38/41 (93%)

[a]Minimum follow-up of 6 months from date of first dose; 1 patient undergoing further evaluation and not



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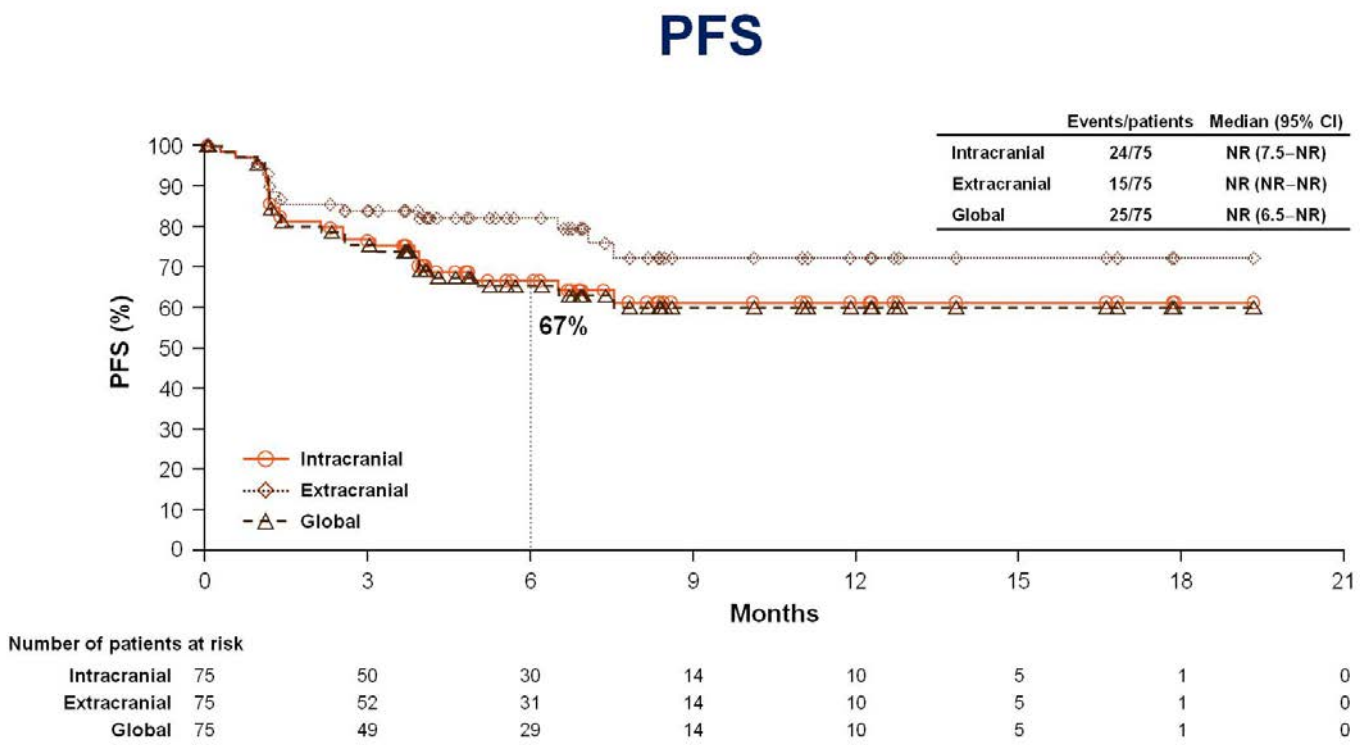
Resultados: *CheckMate* 204



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Toxicidade sistêmica: *CheckMate* 204

Treatment-related AEs

Events reported in at least 5% of patients, n (%)[a]	All patients (N = 75)	
	Any grade	Grade 3–4
Patients with an event	72 (96)	39 (52)
Skin	57 (76)	6 (8)
General disorders	45 (60)	5 (7)
Gastrointestinal	44 (59)	10 (13)
Endocrine	29 (39)	8 (11)
Nervous system	28 (37)	6 (8)
Musculoskeletal	25 (33)	1 (1)
Metabolism	18 (24)	4 (5)
Respiratory	13 (17)	2 (3)
Eye	11 (15)	1 (1)
Blood	6 (8)	0
Hepatobiliary	4 (5)	2 (3)
Psychiatric	4 (5)	0
Patients who discontinued due to an AE	23 (31)	19 (25)

[a]One death reported: treatment-related grade 5 myocarditis

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Toxicidade no SNC: *CheckMate* 204

Treatment-related Nervous System AEs

n (%)	All treated patients (N = 75)	
	Any grade	Grade 3–4
Patients with an event	28 (37)	6 (8)
Headache	19 (25)	3 (4)
Paresthesia	3 (4)	0
Aphasia	2 (3)	0
Dysgeusia	2 (3)	0
Peripheral sensory neuropathy	2 (3)	0
Seizure	2 (3)	0
Brain edema	1 (1)	1 (1)
Carpal tunnel syndrome	1 (1)	0
Dizziness	1 (1)	0
Intracranial hemorrhage	1 (1)	1 (1)
Peripheral motor neuropathy	1 (1)	1 (1)
Polyneuropathy	1 (1)	0
Syncope	1 (1)	1 (1)
Tremor	1 (1)	0
Visual field defect	1 (1)	0

- Median time to onset of grade 3–4 nervous system AEs was 33 days (n=6)
- Median time to resolution of grade 3–4 nervous system AEs was 4 days (3/3)

Presented By Hussein Tawbi at 2017 ASCO Annual Meeting

Conclusões: *CheckMate* 204

- In patients with advanced MEL and untreated brain metastases, NIVO+IPI demonstrates clinically meaningful efficacy, and can become a new treatment option
- With over 9 months of follow-up, NIVO+IPI resulted in an intracranial ORR of 55%, with 21% of patients achieving a complete response
  - Median PFS is not reached; 6-month PFS rate > 60%
- The safety profile was consistent with earlier experience in patients without MBM[1,2]
- Further investigations of systemic therapy should consider
  - Patients who are symptomatic/requiring steroids: cohort of 20 is actively enrolling
  - Approaches to incorporate and sequence radiation therapy
  - Earlier inclusion of this MBM population into randomized studies of novel combinations to accelerate drug development for MBM

1. Larkin J et al. *N Engl J Med.* 2015;373:23-34. 2. Hodi FS et al. *Lancet Oncol.* 2016;17:1558-1568.

Presented By Hussein Tawbi at 2017 ASCO Annual Meeting

Estudos com imunoterapia no paciente com metástase cerebral – *ABC trial*

A randomized phase II study of nivolumab or nivolumab combined with ipilimumab in patients (pts) with melanoma brain metastases (mets): The Anti-PD1 Brain Collaboration (ABC).

Apresentação oral, abstract 9508

Presented By Georgina Long at 2017 ASCO Annual Meeting

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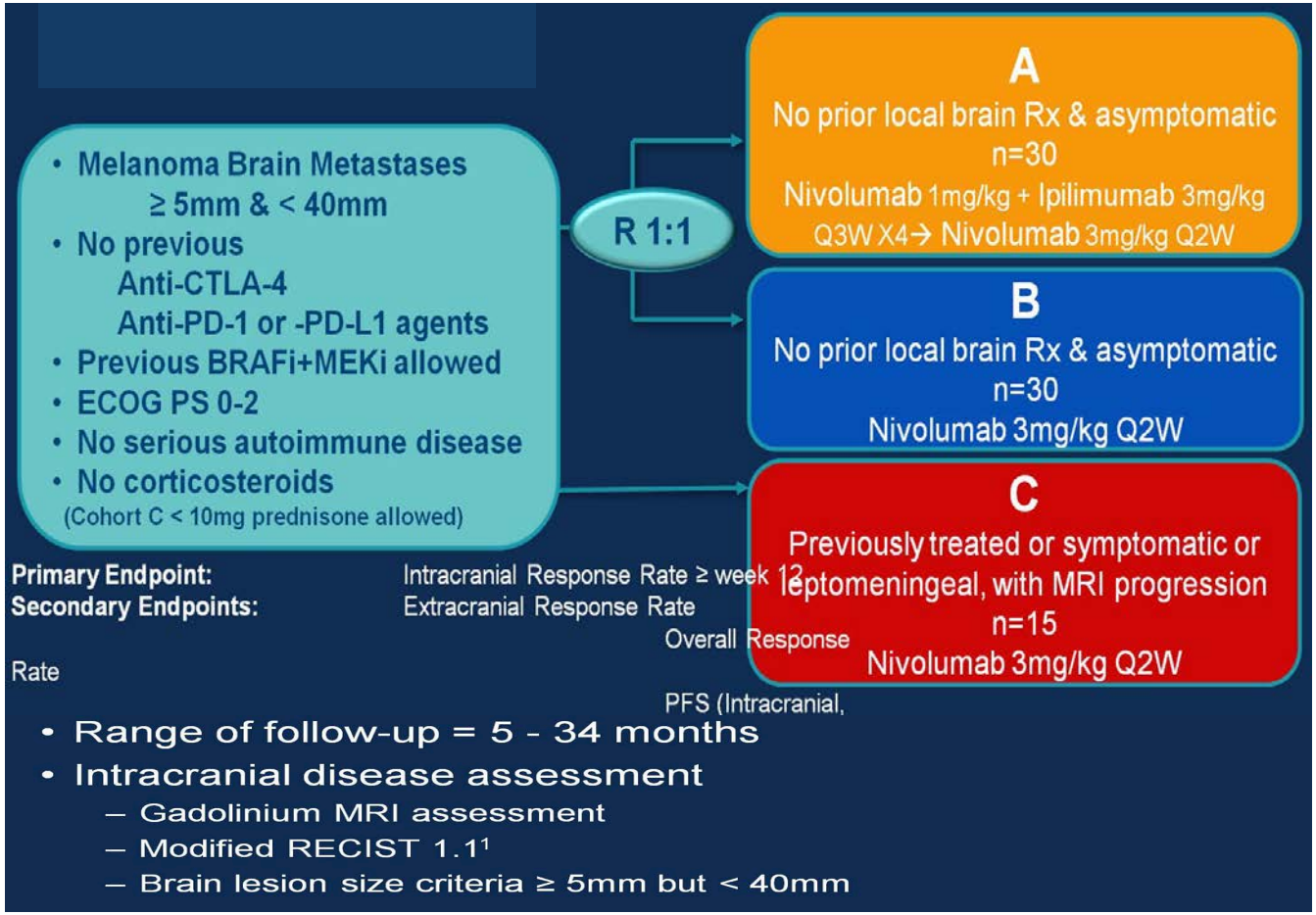
Desenho: ABC *trial*



Presented By Georgina Long at 2017 ASCO Annual Meeting

Características de base: ABC *trial*

	A: Ipi+Nivo N=26	B: Nivo N=25	C: Nivo† N=16
Age, median (range)	61 (29-76)	62 (31-86)	54 (28-73)
Sex, male n (%)	22 (85%)	19 (76%)	11 (69%)
ECOG performance status, n (%)			
1	6 (23%)	9 (36%)	7 (44%)
2	1 (4%)	0	1 (6%)
LDH > ULN, n (%)	11 (42%)	14 (58%)	6 (38%)
V600 BRAF mutation-positive, n (%)	12 (46%)	14 (56%)	13 (81%)
Target brain metastases, n (%)			
1	5 (19%)	5 (20%)	1 (6%)
2-4	9 (35%)	15 (60%)	7 (44%)
>4	12 (46%)	5 (20%)	8 (50%)
Extracranial metastases, n(%)	21 (81%)	20 (80%)	12 (75%)
Prior BRAFi+MEKi	6 (23%)	6 (24%)	12 (75%)
Prior local brain therapy	0	0	16 (100%)

†Leptomeningeal, previous local treatment or symptoms

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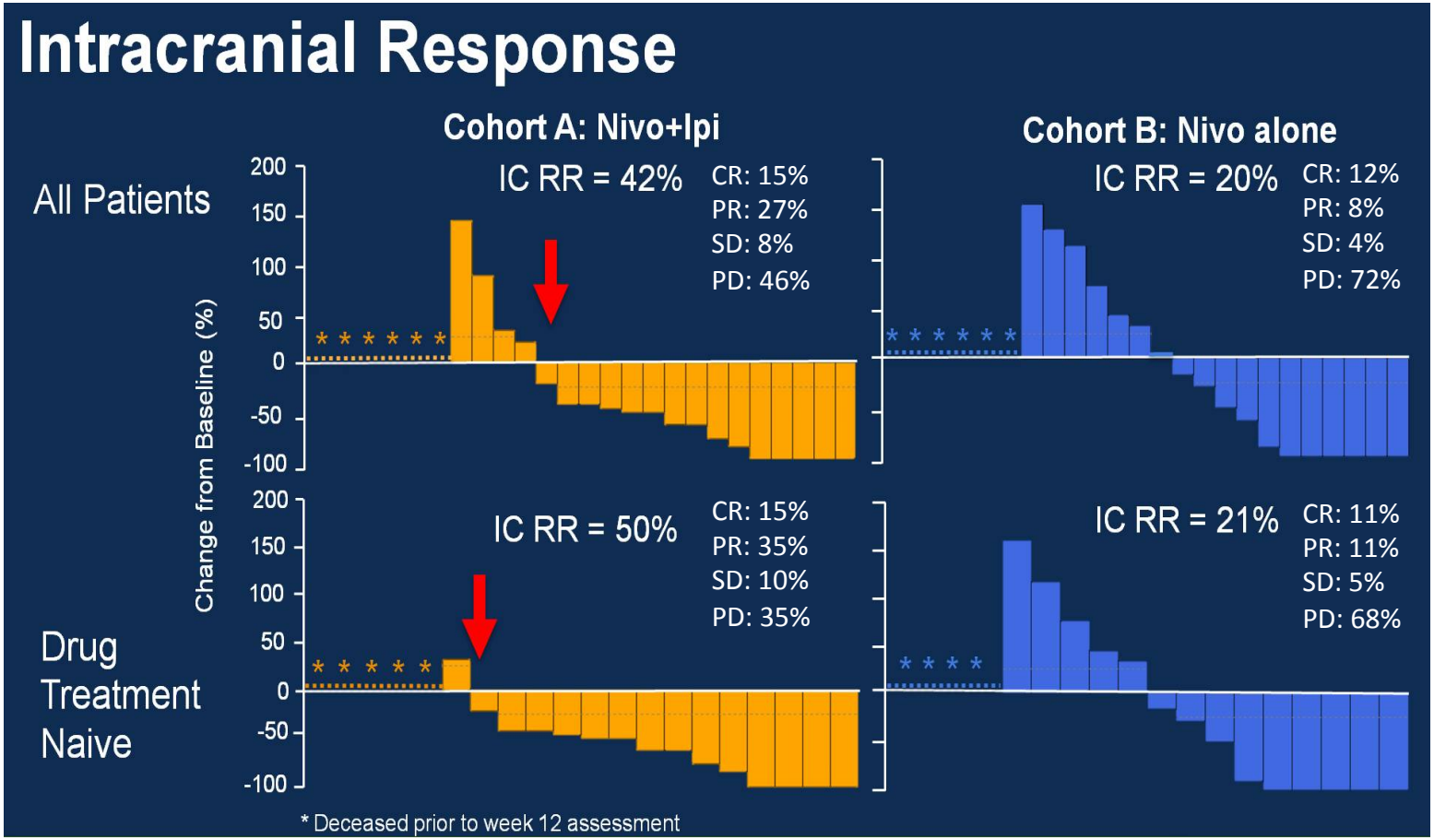
Resultados: ABC *trial*



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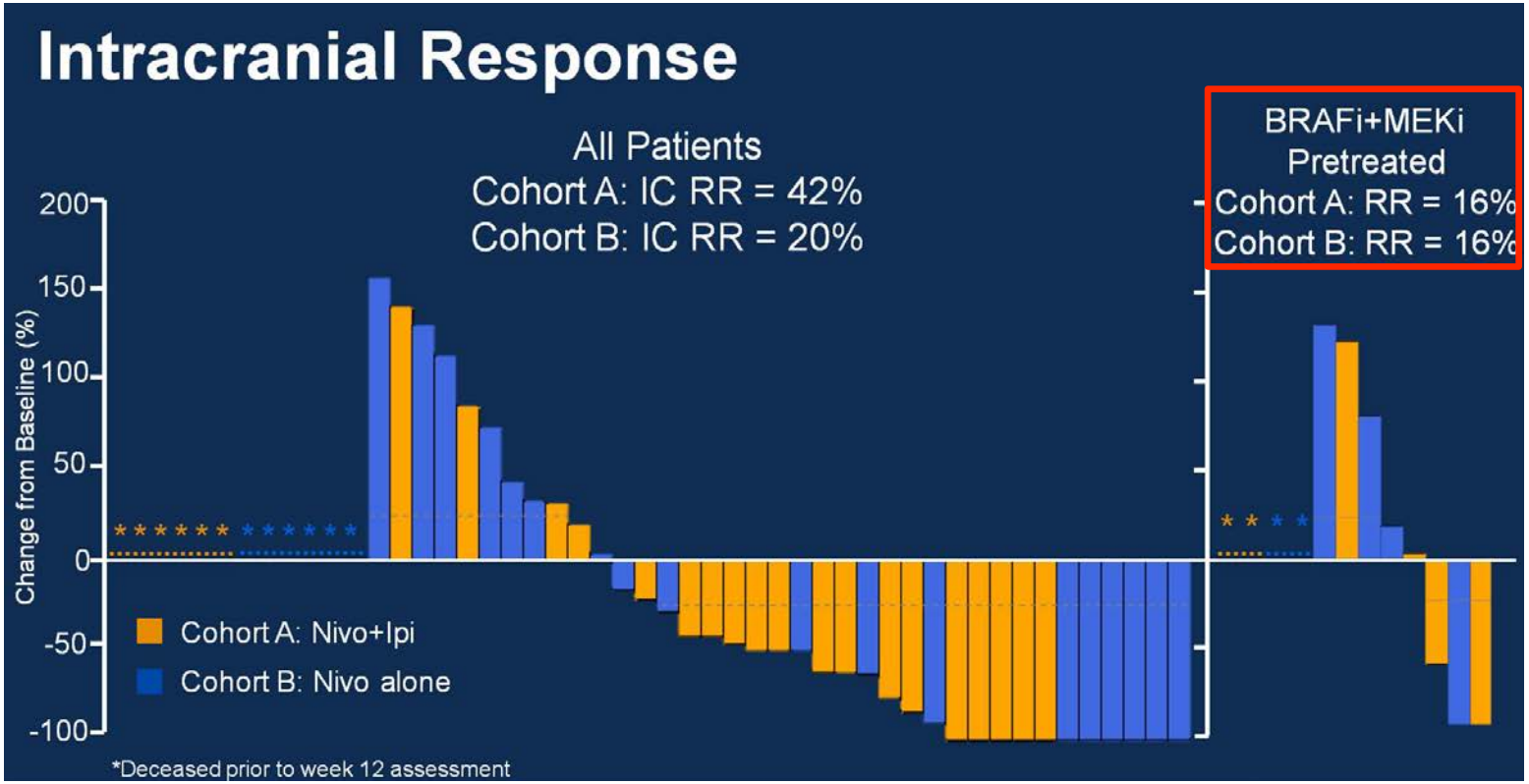
Resultados: ABC *trial*

Pacientes previamente tratados com terapia alvo tiveram respostas inferiores aos virgens de tratamento



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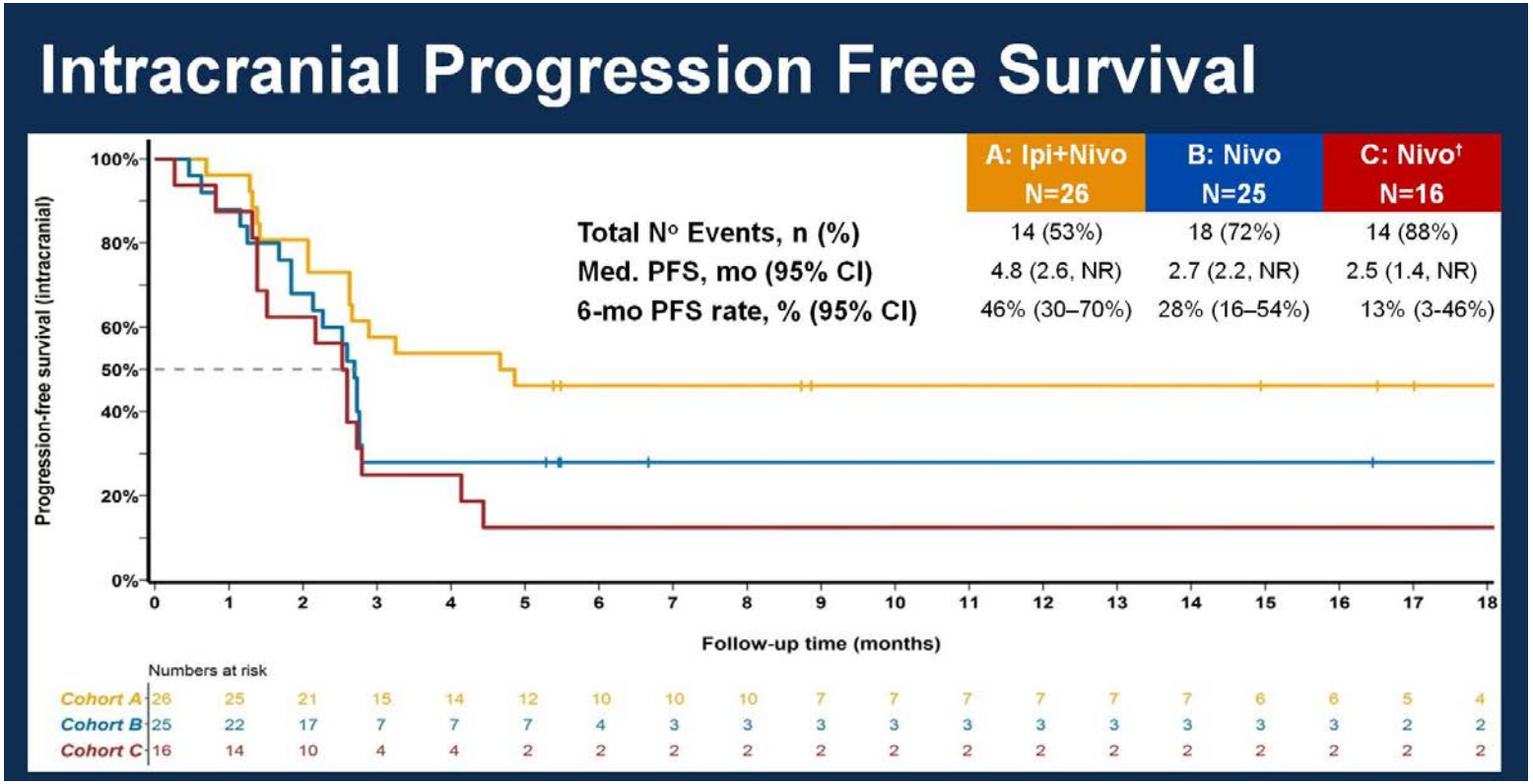
Resultados: ABC *trial*



A SLP intracraniana foi melhor para a combinação

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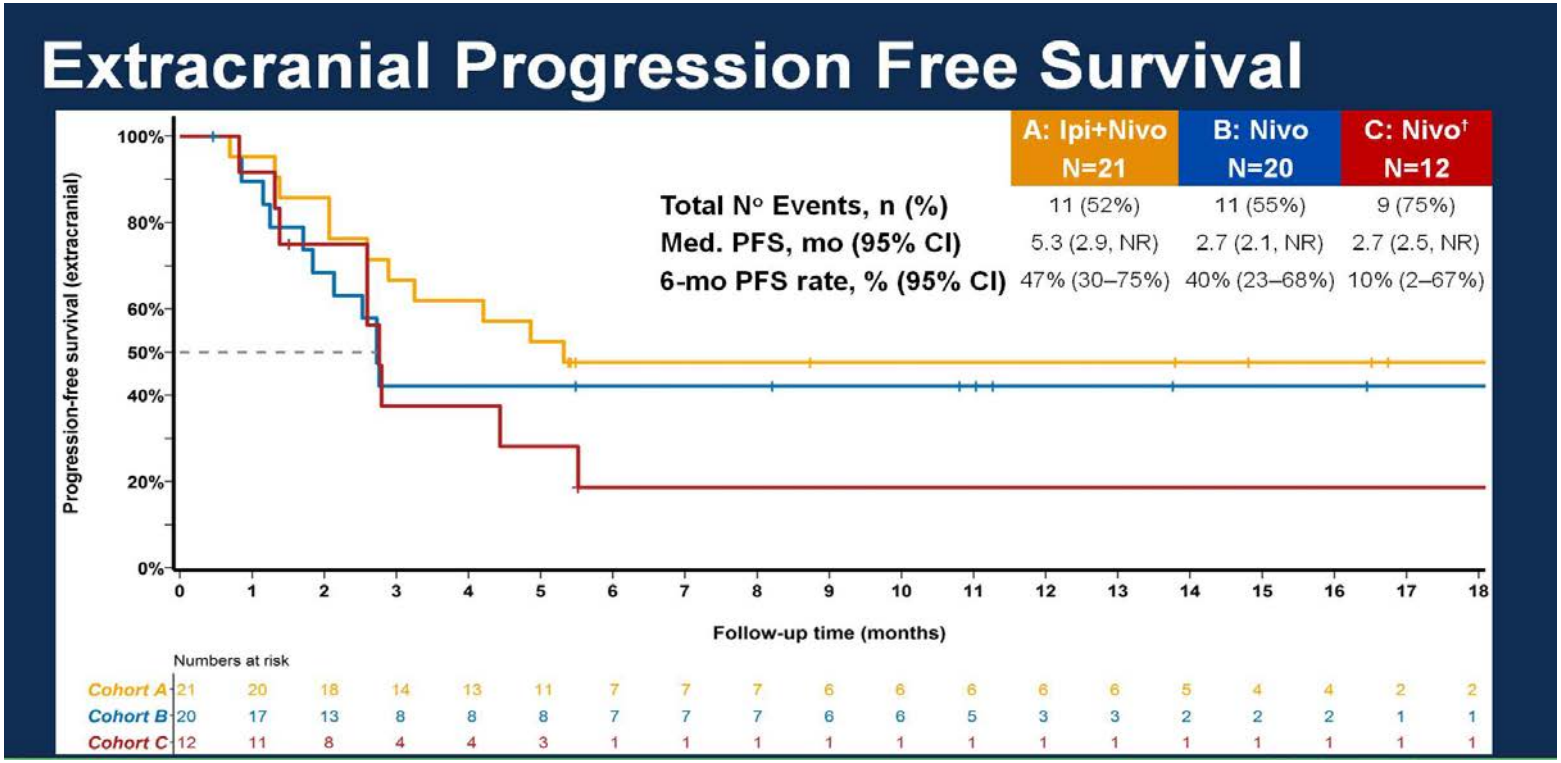
Resultados: ABC *trial*

A combinação também proporcionou melhor controle da doença extracraniana



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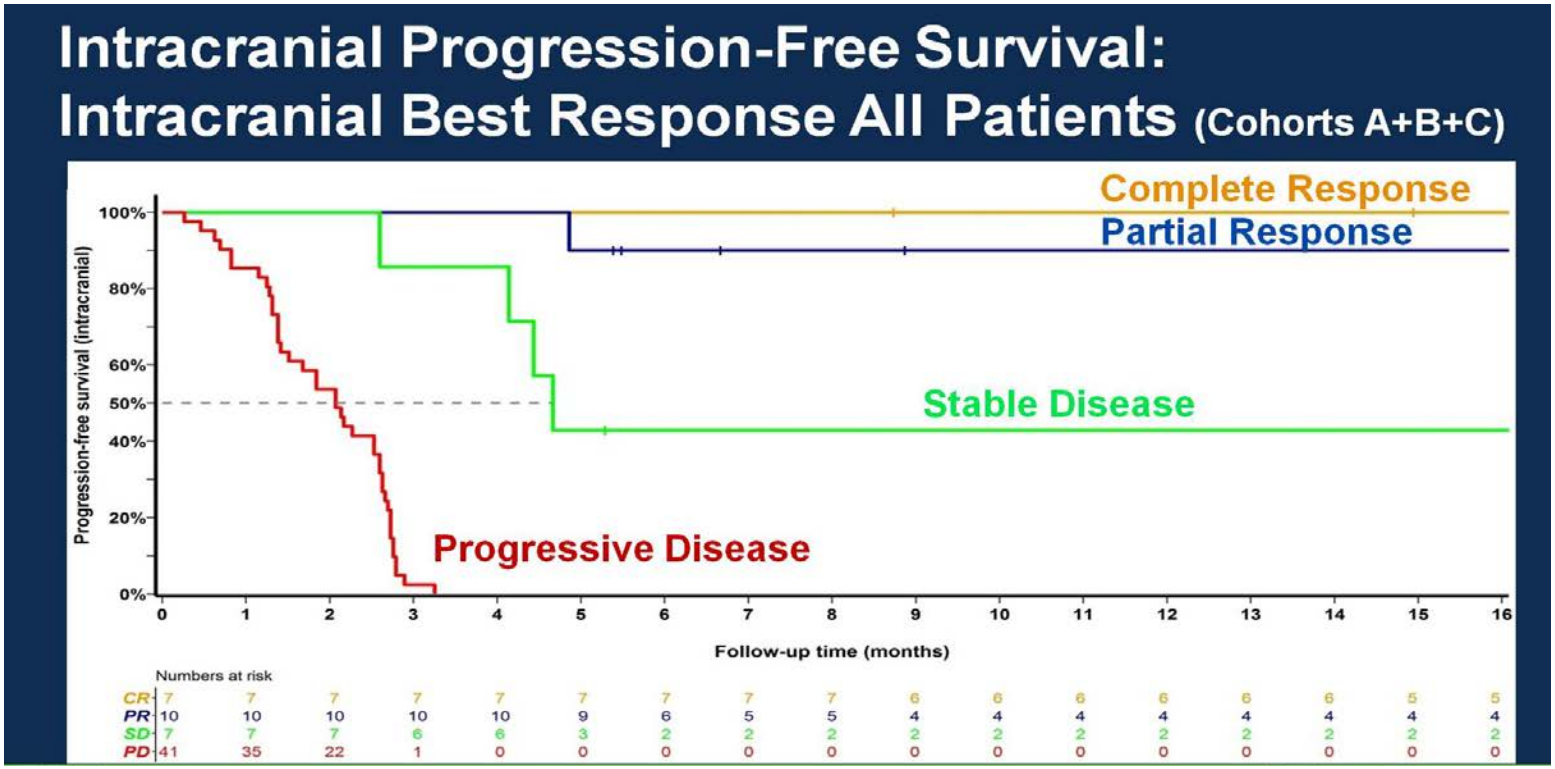
Resultados: ABC *trial*

Pacientes que obtiveram CR e PR foram os maiores beneficiados



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Toxicidade: ABC *trial*

Treatment-Related Adverse Events

	A: Ipi+Nivo N=26	B: Nivo N=25	C: Nivo† N=16
Treatment-related AEs, n (%)	25 (96%)	17 (68%)	9 (56%)
Grade 3/4 treatment-related AEs, n (%)	12 (46%)	6 (24%)	3 (19%)
Treatment-related SAE, n (%)	12 (46%)	3 (12%)	4 (25%)
Discontinuation due to AE*	7 (27%)	1 (4%)	1 (6%)
Death due to treatment-related AE	0	0	0

- No new or unexpected AEs
- 4/67 (6%) pts had neurological AE: 1 radionecrosis, 1 seizure, 2 headache

SAE; Serious Adverse Event
*Pts with grade3/4 treatment related AE in Cohort A were allowed to continue nivolumab monotherapy if recovered and deemed due to ipilimumab

No grupo da combinação: 27% de descontinuação

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Conclusões: ABC *trial*

- Nivolumab combined with ipilimumab or nivolumab alone have activity in active, asymptomatic melanoma brain metastases, without prior local therapy
  - Nivo+Ipi Intracranial: Response Rate = 42%; 6-month PFS 46%
  - Nivo alone Intracranial: Response Rate = 20%; 6-month PFS 29%
- Activity is **high** when nivo+ipi given upfront
  - Nivo+Ipi: Intracranial Response Rate = 50%
- Intracranial and extracranial responses were mostly concordant
- Activity is **low** following BRAFi+MEKi
  - Nivo+Ipi: Intracranial Response Rate = 16%
  - Nivo alone: Intracranial Response Rate = 16%
- Activity of nivo monotherapy is **low** after multiple modality therapy or in leptomeningeal melanoma
  - Nivo alone: Intracranial Response Rate = 6%
- There were no unexpected toxicities

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Duplo bloqueio BRAF/MEK no tratamento de metástases cerebrais do melanoma

COMBI-MB: A phase II study of combination dabrafenib (D) and trametinib (T) in patients (pts) with BRAF V600–mutant (mut) melanoma brain metastases (MBM).

Apresentação oral, abstract 9506

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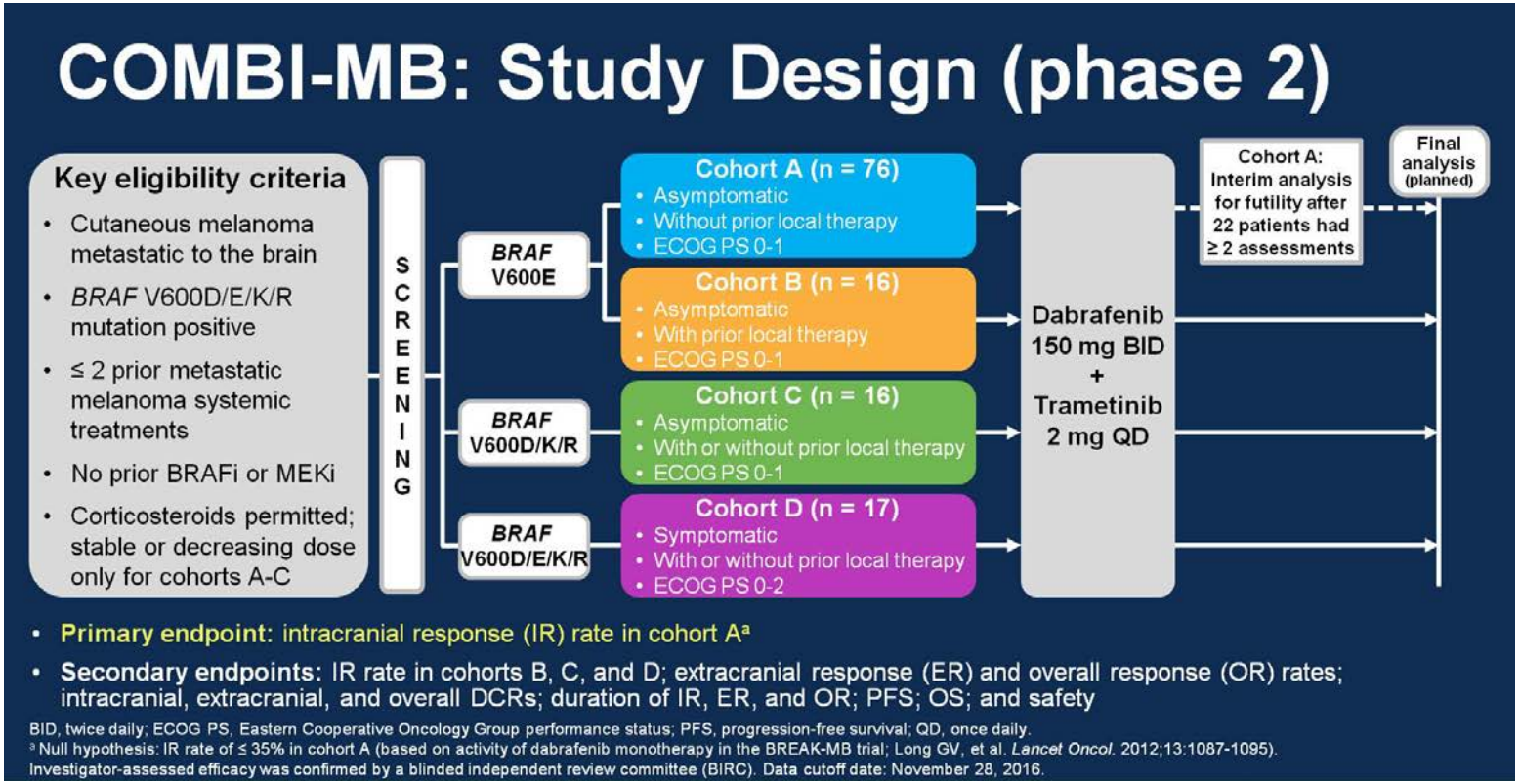
Desenho: COMBI-MB

A coorte A é a de maior interesse pela maior amostragem



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Características de base: COMBI-MB

	Cohort A (n = 76)	Cohort B (n = 16)	Cohort C (n = 16)	Cohort D (n = 17)
Median age (range), y	52.0 (23-84)	54.5 (36-74)	63.0 (44-84)	46.0 (23-68)
Male, n (%)	40 (53)	10 (63)	11 (69)	11 (65)
ECOG PS 0, n (%)	50 (66)	11 (69)	12 (75)	9 (53)
***BRAF* genotype, n (%)**				
V600E	73 (96)	16 (100)	0	15 (88)
V600K/D/R	3 (4)	0	16 (100)	2 (12)
Target brain metastases, n (%)				
1	41 (54)	7 (44)	7 (44)	7 (41)
2	20 (26)	7 (44)	6 (38)	7 (41)
≥ 3	15 (20)	2 (13)	3 (19)	3 (18)
Median SLD of target and nontarget intracranial lesions (range), mm	19.5 (6-117)	14.0 (5-40)	20.0 (5-61)	33.0 (10-84)
Extracranial metastases present, n (%)	68 (89)	12 (75)	16 (100)	12 (71)
Elevated LDH level (> ULN), n (%)	28 (37)	3 (19)	6 (38)	5 (29)
Steroid use at baseline, n (%)	13 (17)	3 (19)	4 (25)	11 (65)
Previously treated with systemic anticancer treatment, n (%)	17 (22)	5 (31)	3 (19)	7 (41)

LDH, lactate dehydrogenase; SLD, sum of lesion diameters; ULN, upper limit of normal.

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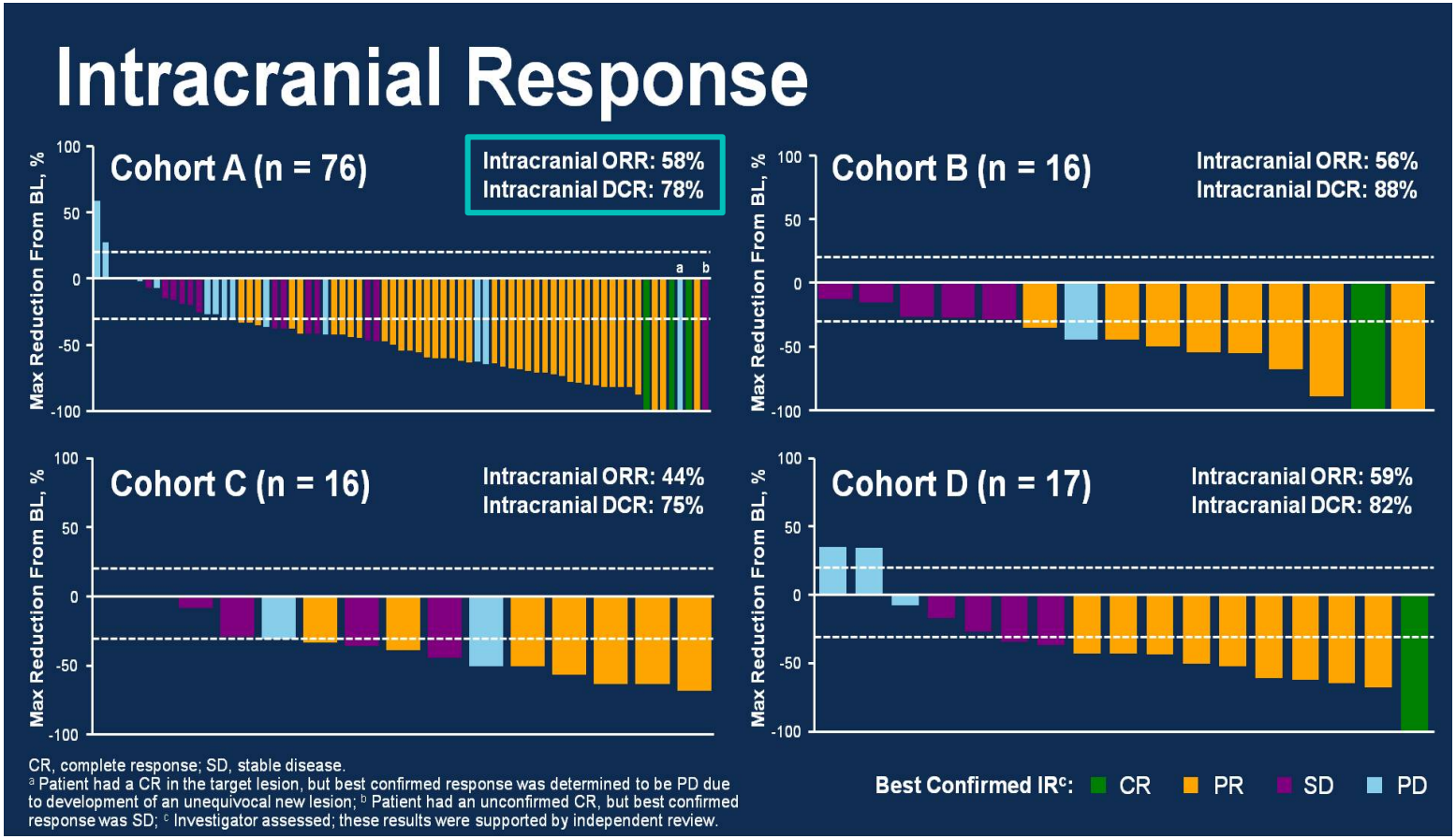
Resultados: COMBI-MB



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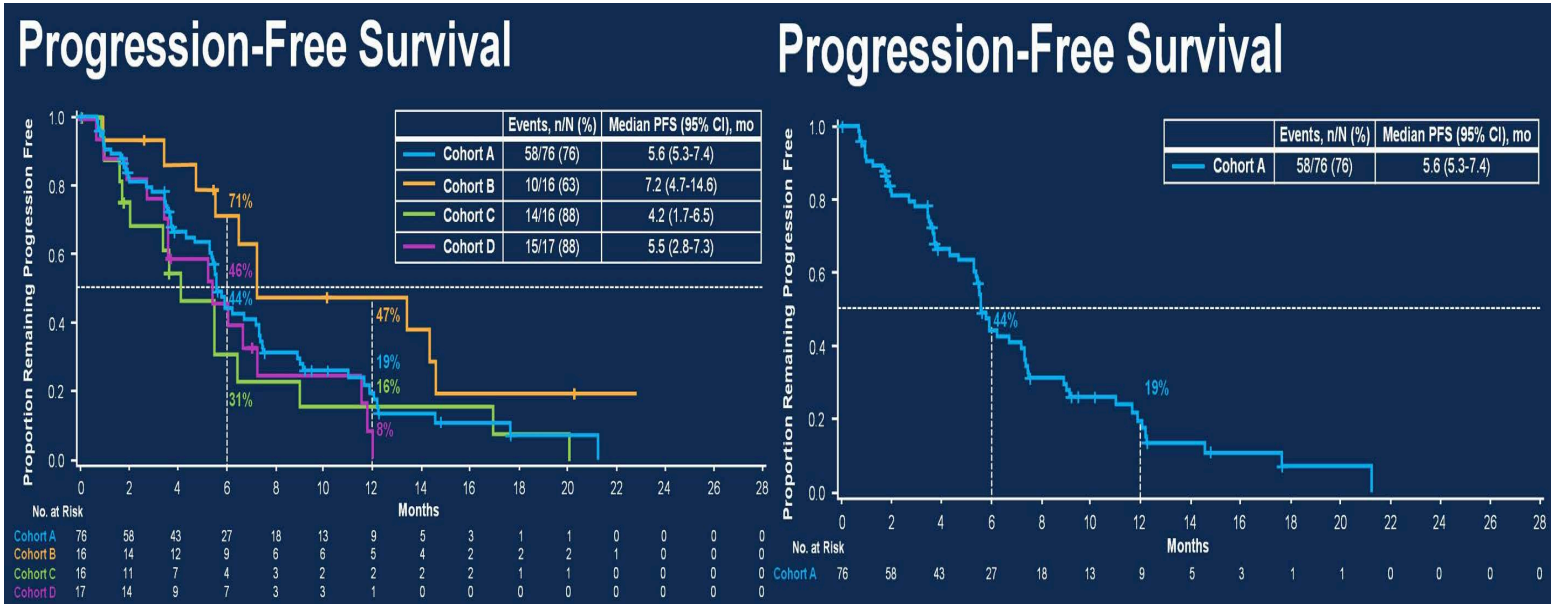
Resultados: COMBI-MB



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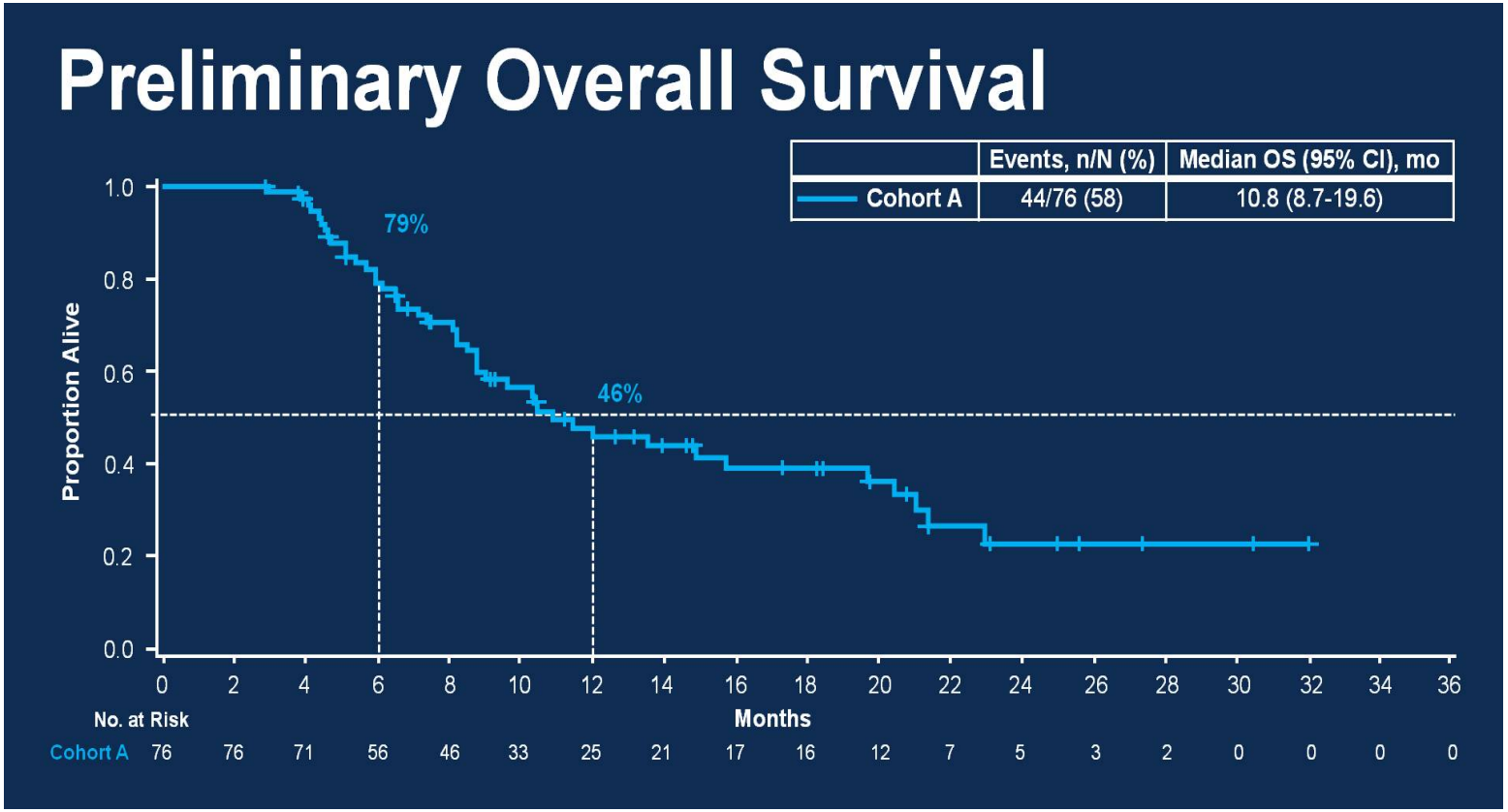
Resultados: COMBI-MB



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Toxicidade: COMBI-MB

Category, n (%)	Cohort A (n = 76)
AEs	74 (97)
Related to study treatment	62 (82)
Leading to discontinuation	6 (8)
Leading to dose reduction	17 (22)
Leading to dose interruption	35 (46)
Serious AEs (SAEs)	26 (34)
Related to study treatment	11 (14)
Fatal SAEs	1 (1)[a]

AE, n (%)	Cohort A (n = 76)	
	Any Grade	Grade 3/4
Any	74 (97)	34 (45)
Pyrexia	44 (58)	2 (3)
Asthenia	27 (36)	0
Headache	27 (36)	1 (1)
Nausea	23 (30)	0
Diarrhea	22 (29)	0
Vomiting	22 (29)	1 (1)
Chills	16 (21)	0
Arthralgia	15 (20)	0
Myalgia	13 (17)	0

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Conclusões: COMBI-MB

- First report of a phase 2 trial evaluating BRAFi + MEKi in patients with melanoma brain metastases
- Clinical benefit and tolerability were achievable with dabrafenib + trametinib in some patients with *BRAF* V600–mutant melanoma metastasized to the brain
  - IR rate of 58% (95% CI, 46%-69%) in cohort A patients; primary endpoint was met
  - Median duration of OR (eg, 6.5 months in cohort A) was generally shorter than that observed in patients without melanoma brain metastases (12-14 months)[1-3]
  - No unexpected safety issues were observed with the combination
- These results support:
  - Use of dabrafenib + trametinib as a treatment option for patients with brain metastases
  - Need for continued research to improve outcomes in this advanced melanoma population

1. Long GV, et al. *Lancet*. 2015;386:444-451; 2. Long GV, et al. *Ann Oncol*. 2017 May 5. [Epub ahead of print]; 3. Robert C, et al. *Ann Oncol*. 2016;27(suppl 6) [abstract LBA40].

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Studies report fantastic results….

50%	60%	75%
ABC	CheckMate 204	COMBI MB

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Studies report fantastic results….

But still most patients progress. 25%-50% of patients enrolled on the studies have died.

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Clinical implications

Question	YES	NO
Are these data sufficient to warrant up front systemic therapy for CNS mets?	✓	
Are the results practice changing?	✓	
Do we know which treatment to give first?		✗
Do we know the best sequence of therapy?		✗
Do we know how to best combine systemic and local therapy?		✗

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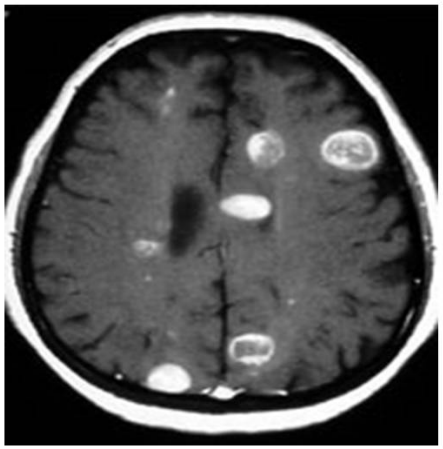
What is the right sequence?



BRAF mutant

Ipi/Nivo → Dab/Tram

Dab/Tram → Ipi/Nivo Nivo

Nivo → Dab/Tram

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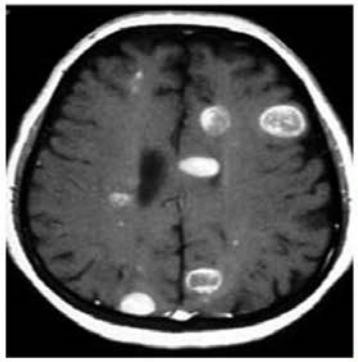
What is the right sequence?



BRAF mutant

Ipi/Nivo → Dab/Tram

Dab/Tram → ~~Ipi/Nivo Nivo~~

Nivo → Dab/Tram

ABC
16% RR

Numbers small. Longer follow up and ongoing studies to address

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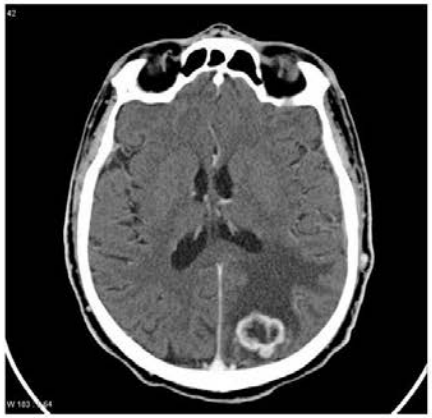
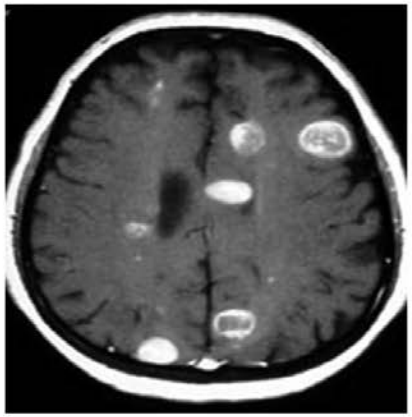
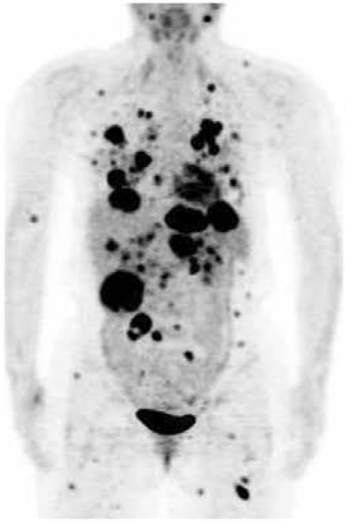
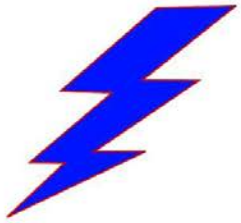
Many Variables in the Selection of RX







- BRAF mutation
- Prior Therapy
- Performance Status



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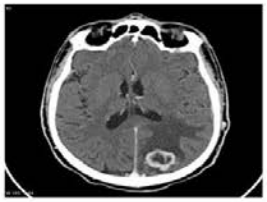
Comments

1. Studies well done, asked critically important questions, in clinically relevant patient population (though most patients asymptomatic).
2. Sample sizes modest, very small in some of the cohorts.
3. No unexpected toxicities.
4. Safe to give Ipi/Nivo in patients with brain metastases.
5. In general, concordant responses- brain and extra- CNS disease.
6. Early results. Short follow up.



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