

Melanoma

Inibidores de BRAF/MEK no tratamento adjuvante

Rafael Aron Schmerling



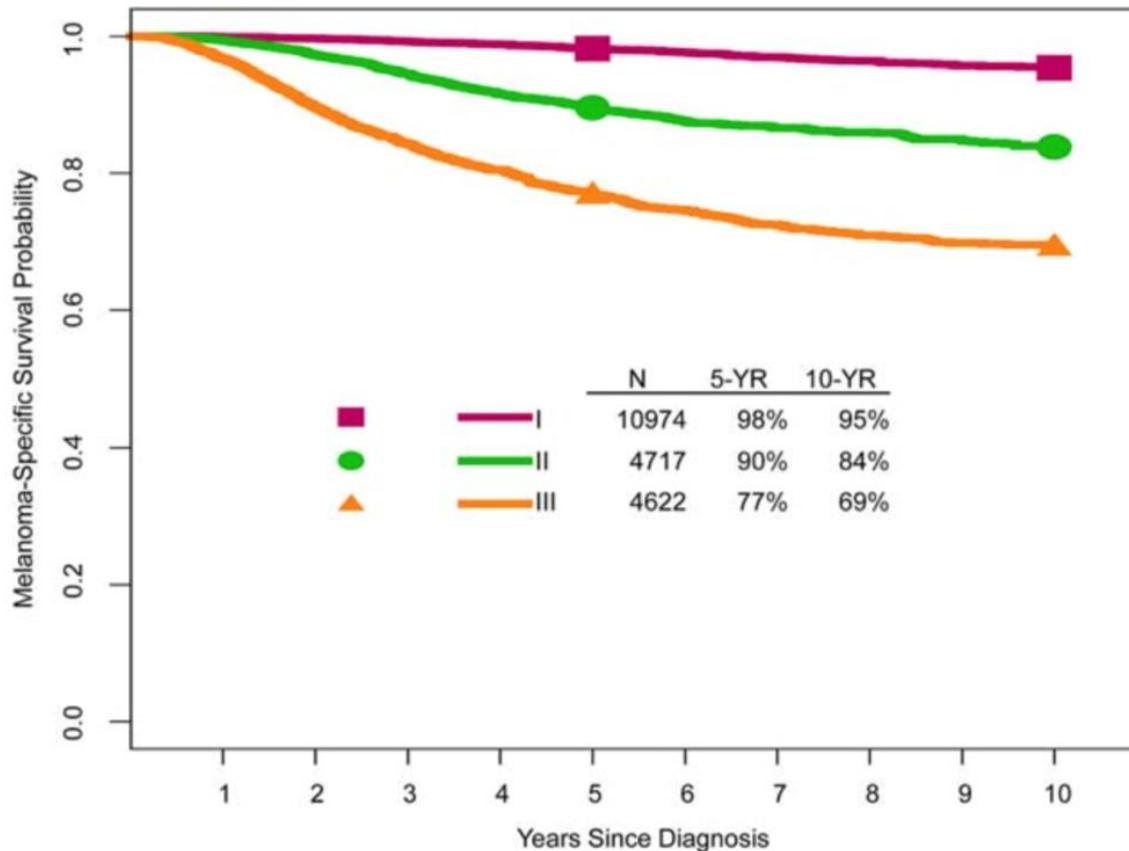
A Beneficência
Portuguesa
de São Paulo

Potenciais Conflitos de Interesse

Bayer	Consultoria, honorários
Bristol-Myers Squibb	Consultoria, honorários, pesquisa, patrocínio
Merck Serono	Consultoria, honorários
Merck Sharp & Dome	Consultoria, honorários, pesquisa
Novartis	Consultoria, honorários, pesquisa
Pierre Fabre	Consultoria, honorários
Roche	Consultoria, honorários, pesquisa, patrocínio
Sanofi Genzyme	Consultoria, honorários

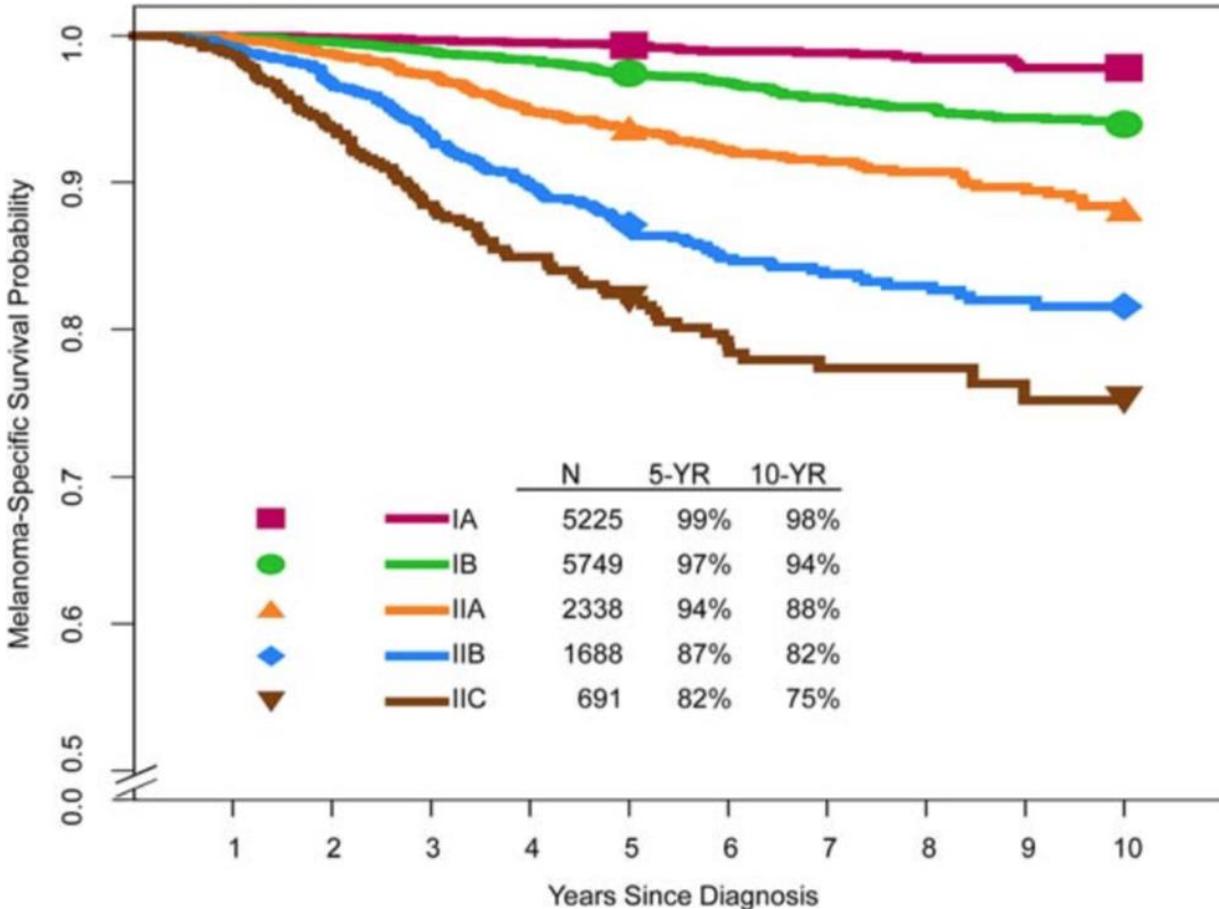
Quem deve ser tratado?

AJCC, 8^a edição



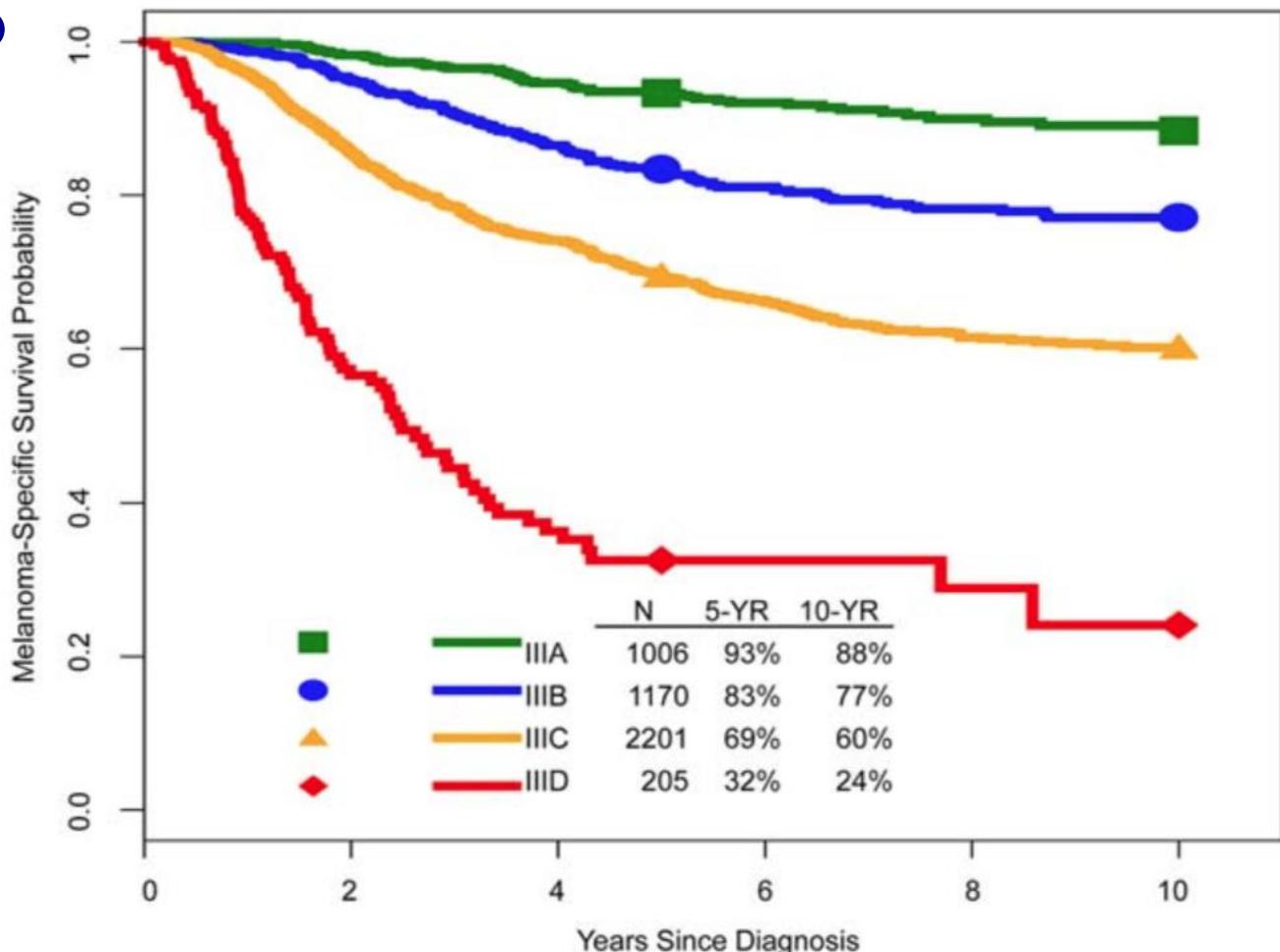
AJCC, 8^a edição

Sobrevida I e II



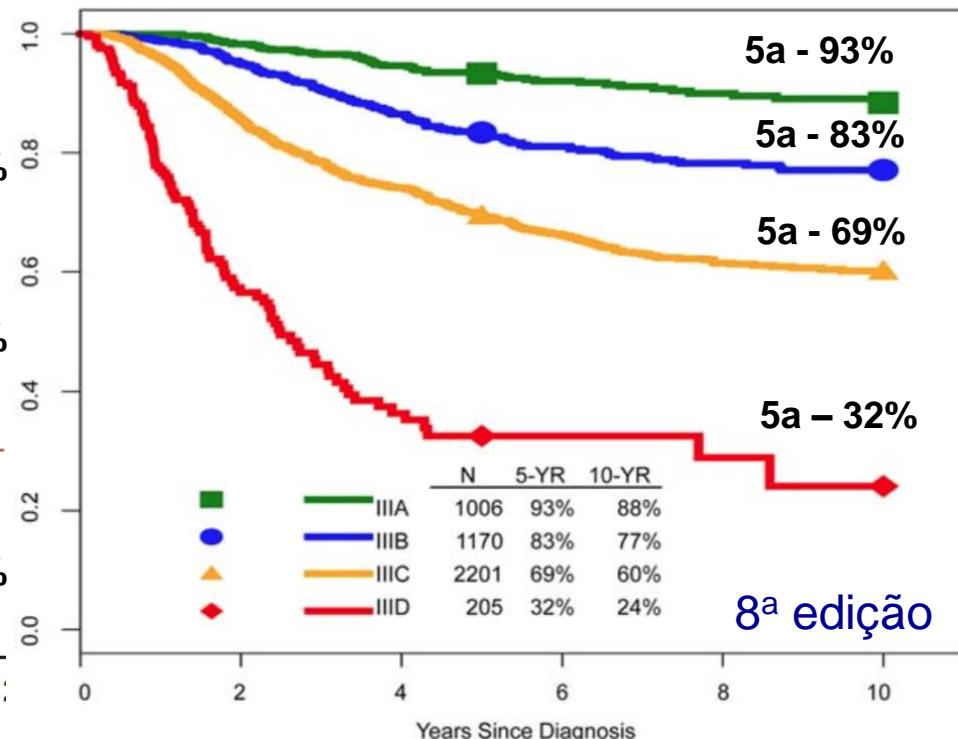
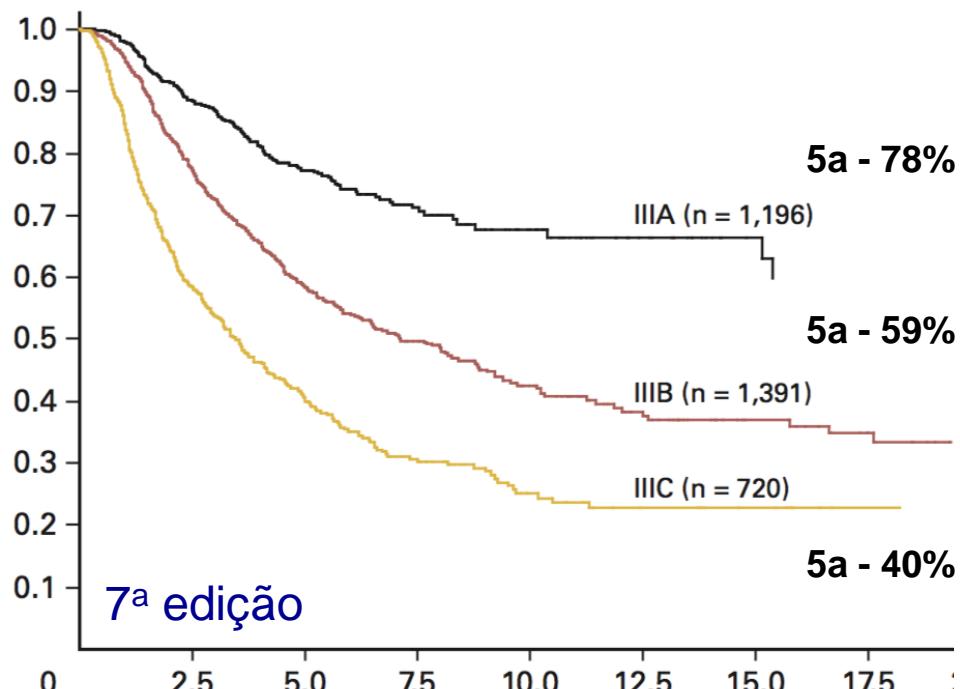
AJCC, 8^a edição

Sobrevida III

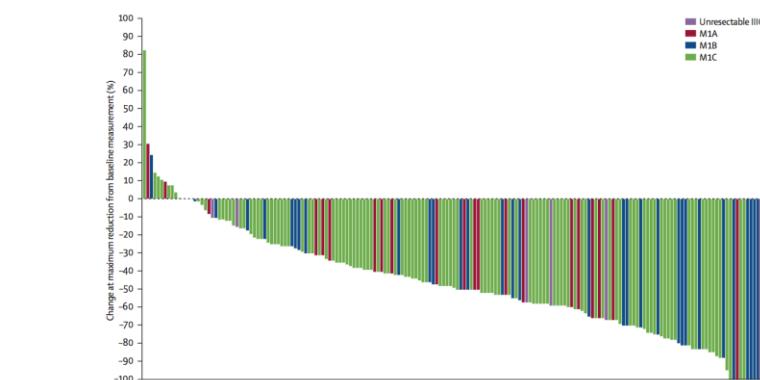
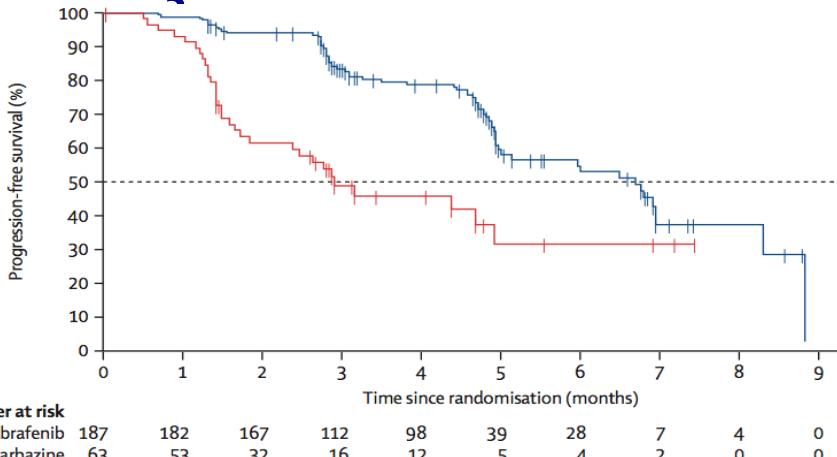
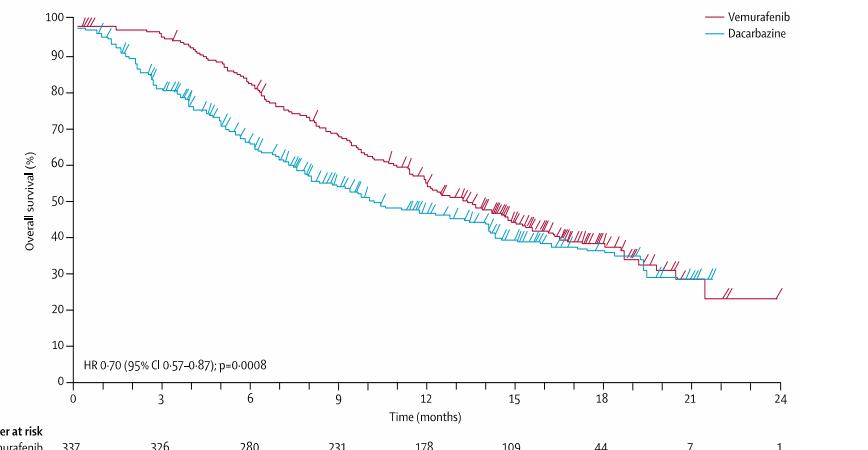
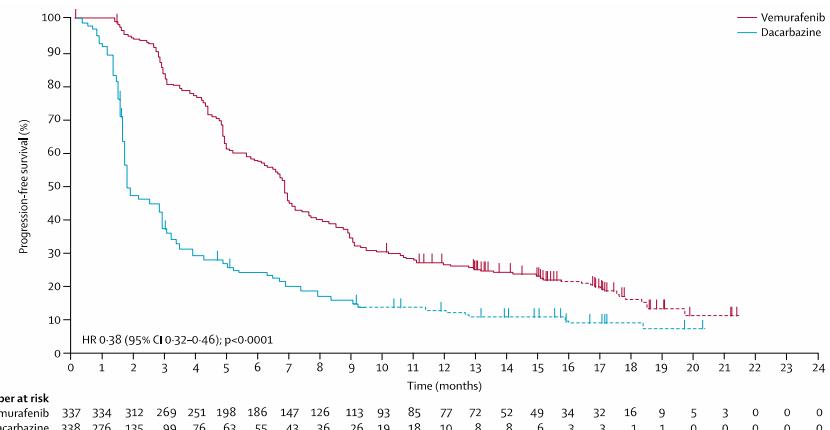


AJCC, 7^a vs 8^a edição

Sobrevida III

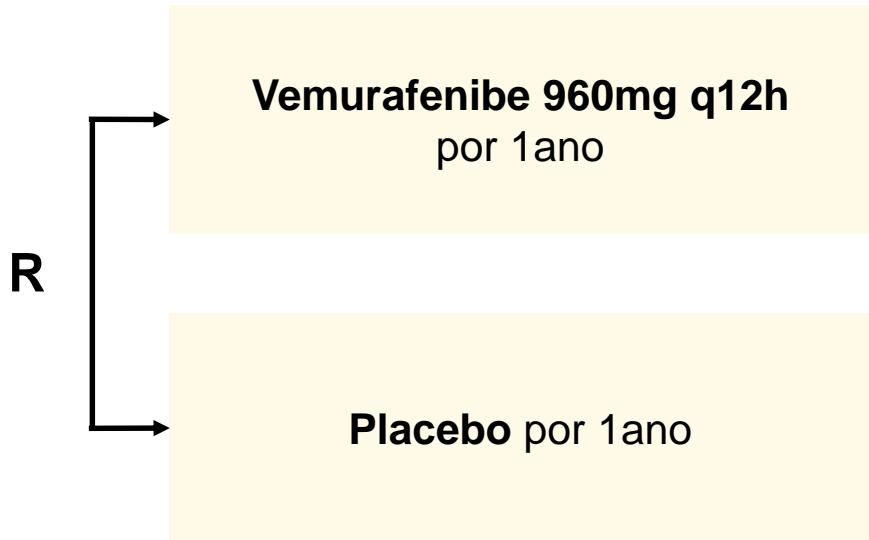


Inibidores de BRAF na doença metastática



Hauschild et al, Lancet, 2012; McArthur et al, Lancet Oncol, 2014

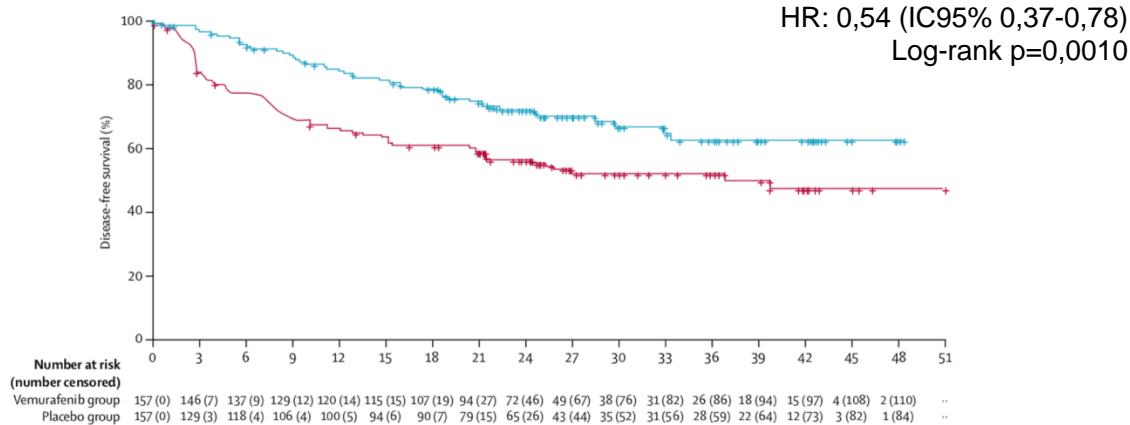
BRIM 8 – Vemurafenibe vs Placebo



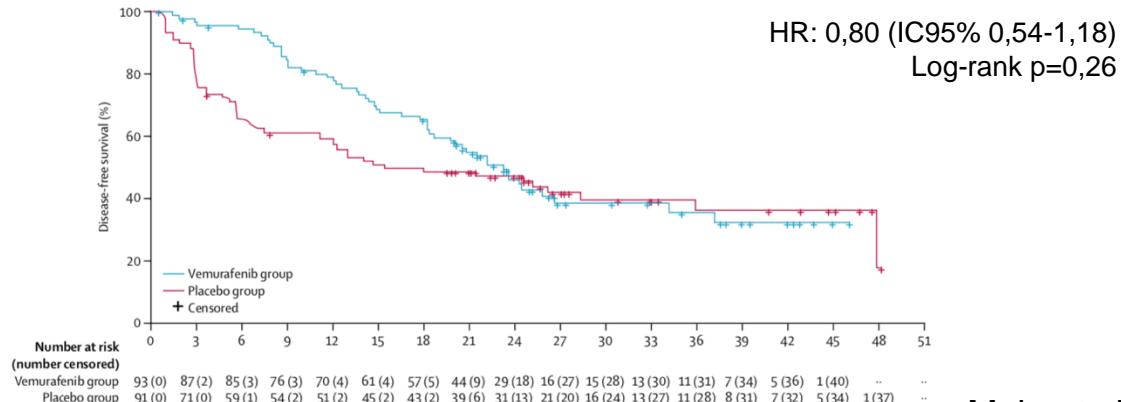
COORTE 1	Vemurafenibe N=157	Placebo N=157
V600E	123 (90%)	129 (93%)
Não-V600E	13 (10%)	9 (7%)
IIC	10%	8%
IIIA	23%	25%
IIIB	68%	68%
COORTE 2	Vemurafenibe N=93	Placebo N=91
V600E	77 (91%)	67 (89%)
Não-V600E	8 (9%)	8 (11%)
IIIC	181 (41%)	166 (38%)

BRIM 8 – Vemurafenibe vs Placebo

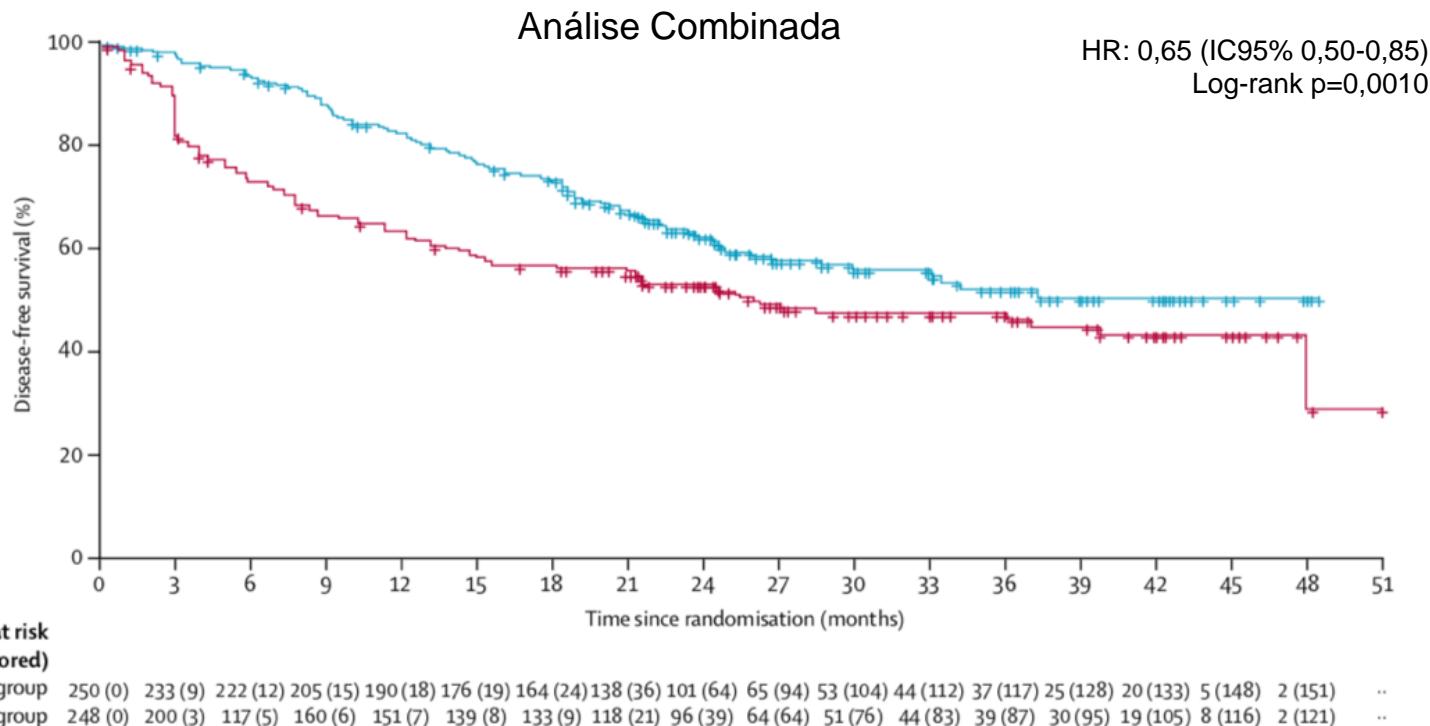
IIC, IIIA, IIIB



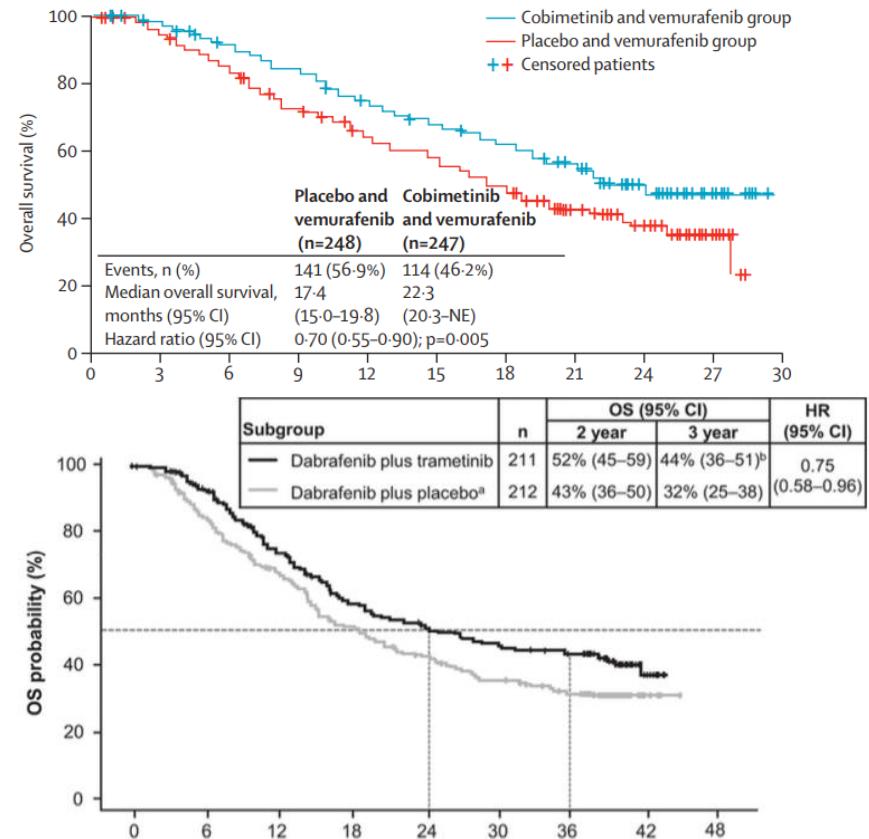
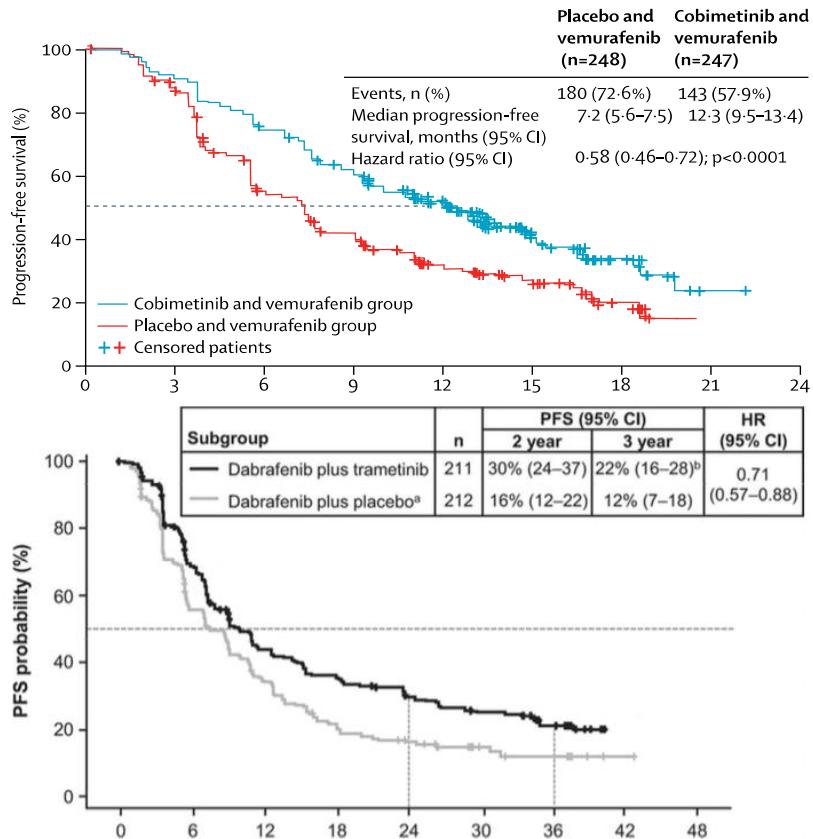
IIIC



BRIM 8 – Vemurafenibe vs Placebo



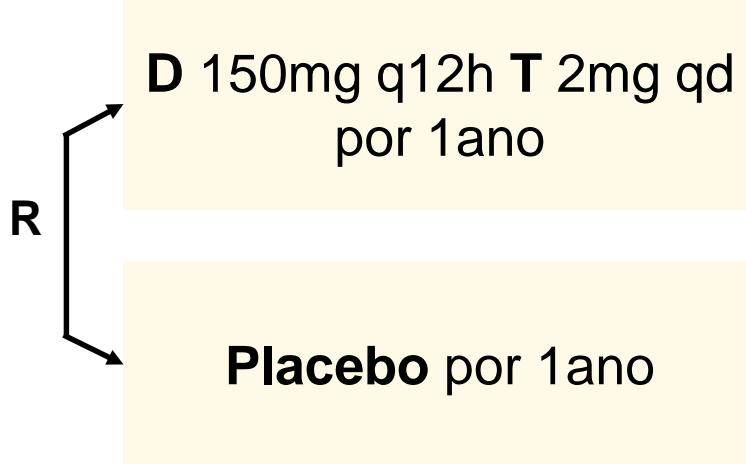
Inhibidores de BRAF/MEK vs. BRAF



Ascierto et al, Lancet Oncol 2016; Lon et al. Ann Oncol, 2017

Dabrafenibe/Trametinibe vs. Placebo

	Dab/Tram N=438	Placebo N=432
V600E	397 (91%)	395(91%)
V600K	41 (9%)	37 (9%)
Estágios – n (%)		
IIIA	93 (19%)	71 (16%)
IIIB	169 (39%)	187 (43%)
IIIC	181 (41%)	166 (38%)
III inespecífico	5 (1%)	8 (2%)



* relacionado ao tratamento

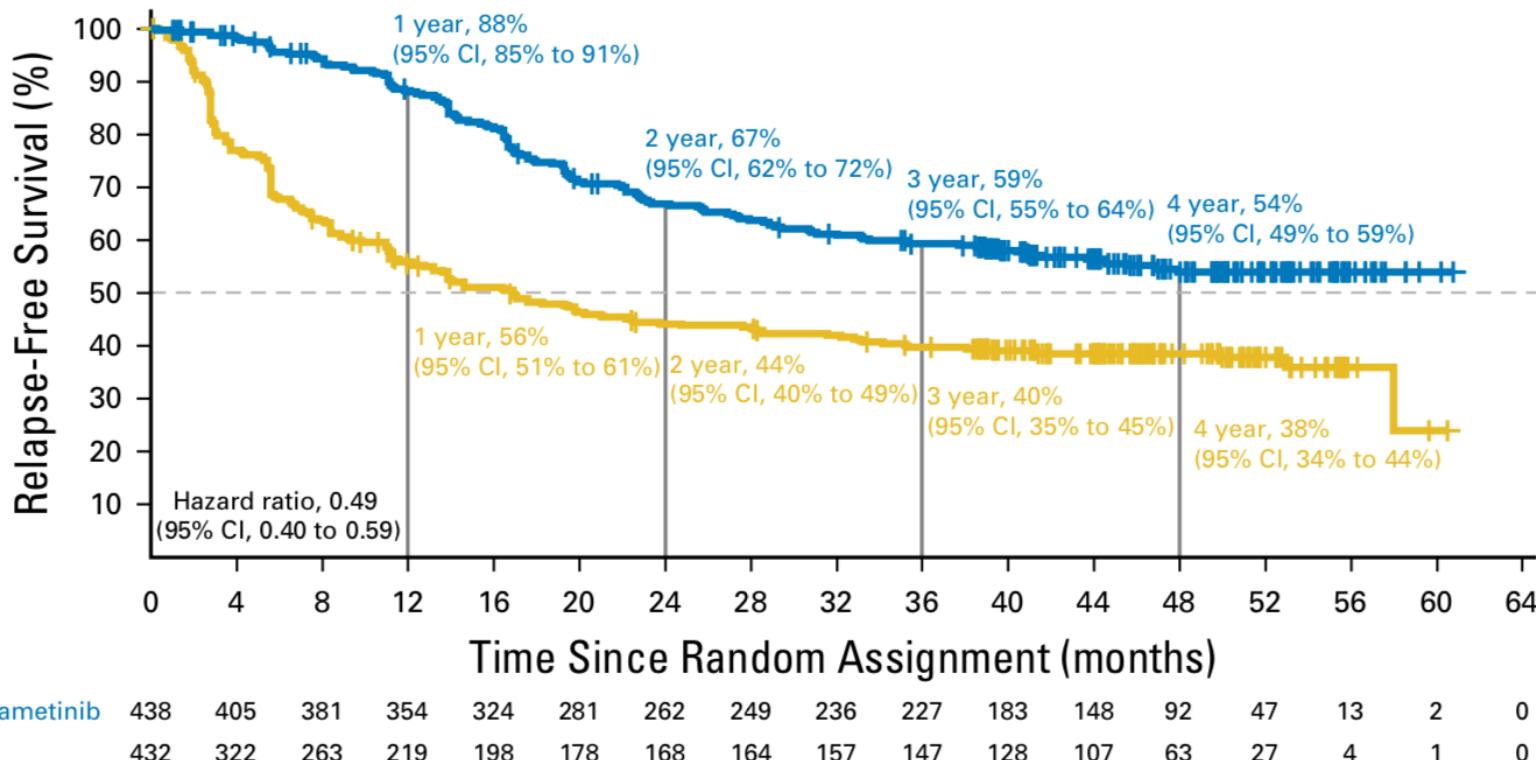
Dabrafenibe/Trametinibe vs. Placebo

Dabrafenibe / Trametinibe		
	Qualquer Grau	G3 / G4
Qualquer Evento*	97%	41%
Febre	63%	5%
Fadiga	47%	4%
Náusea	40%	1%
Cefaléia	39%	1%
Diarréia	33%	1%
Vômito	28%	1%
Artralgia	24%	0
Evento* que levasse a descontinuação	26%	

* relacionado ao tratamento

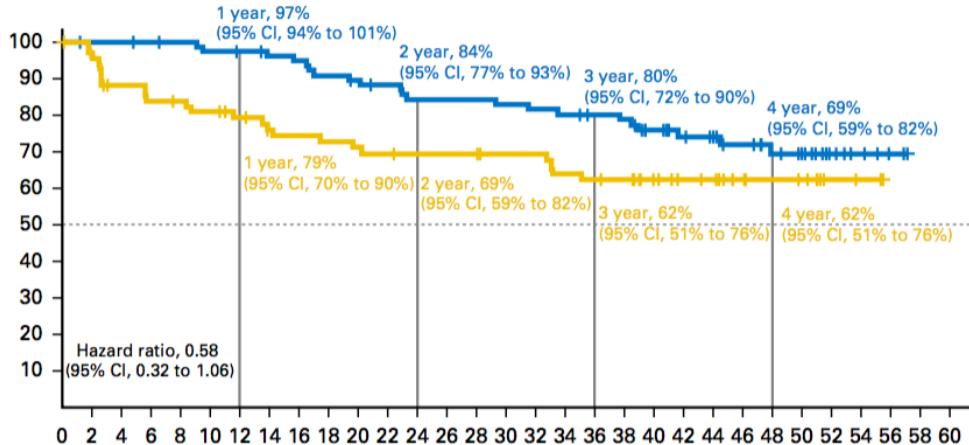
Long et al. N Engl J Med, 2017

Dabrafenibe e Trametinibe

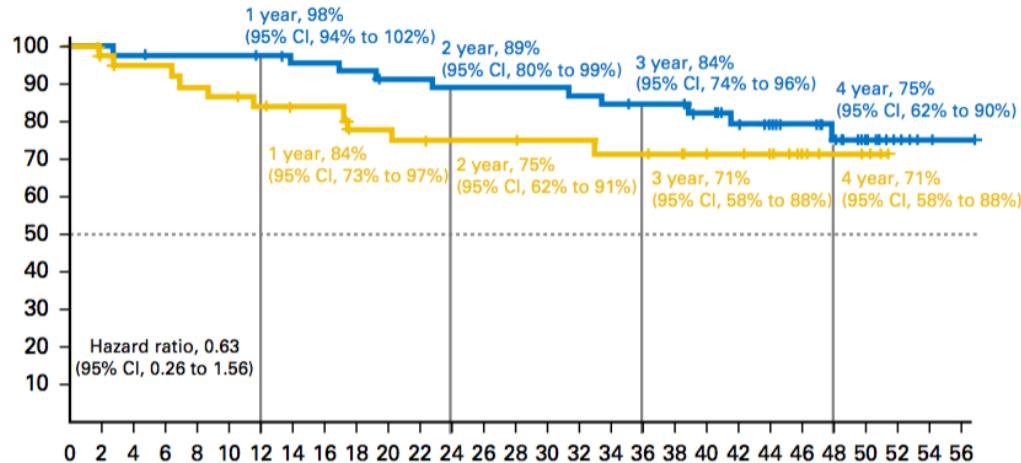


Dabrafenibe e Trametinibe

IIIA, 7^a ed

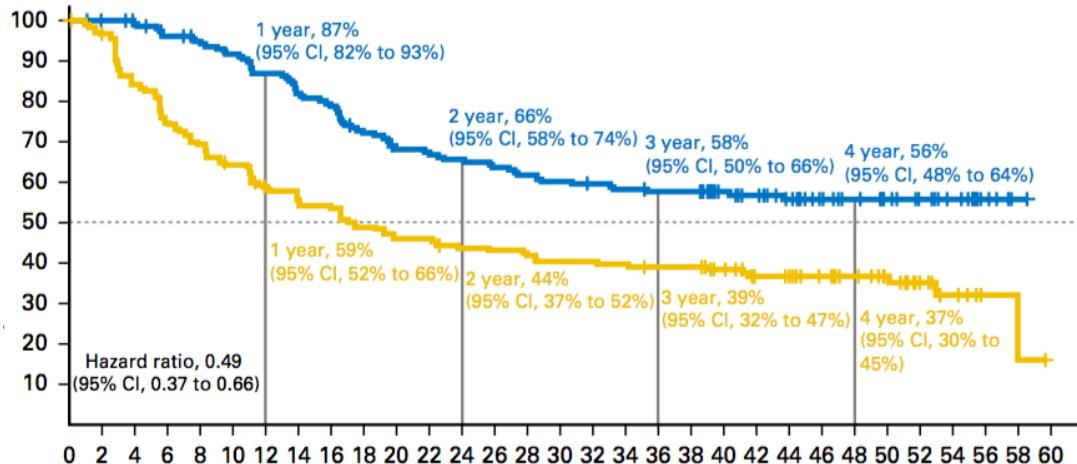


IIIA, 8^a ed

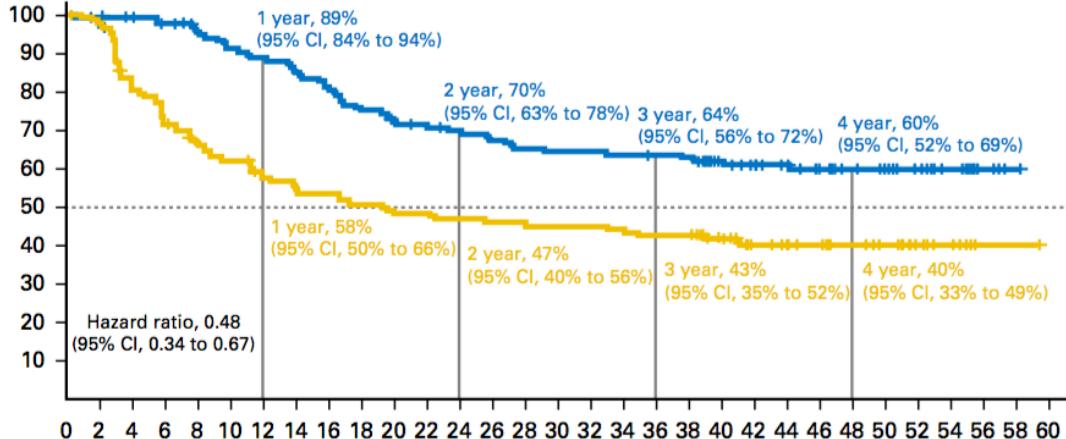


Dabrafenibe e Trametinibe

IIIB, 7^a ed

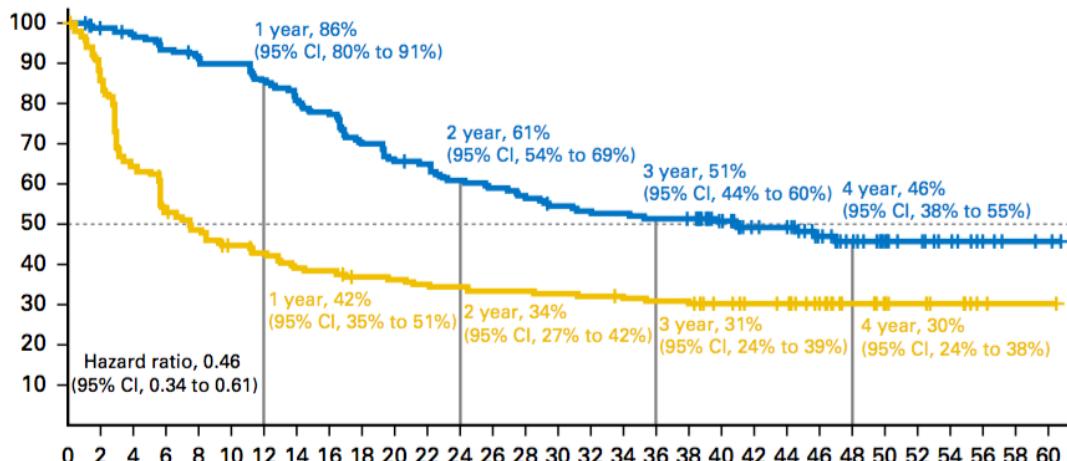


IIIB, 8^a ed

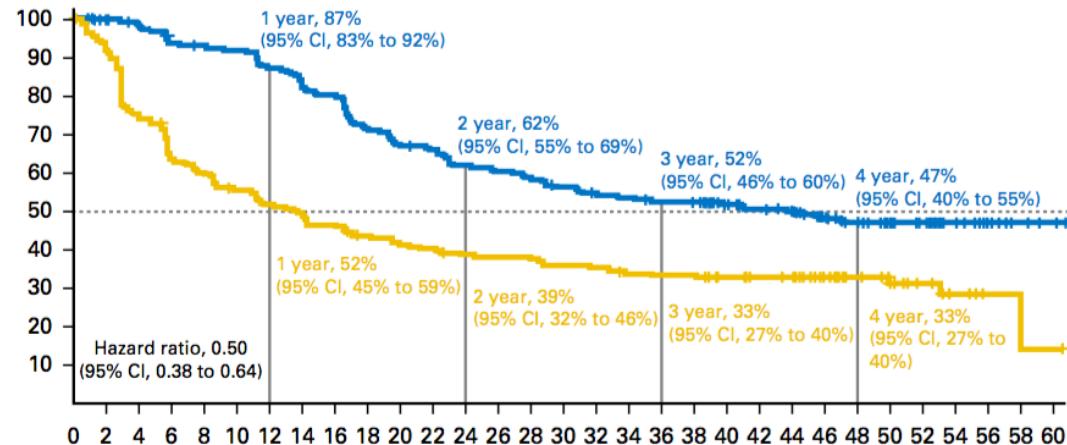


Dabrafenibe e Trametinibe

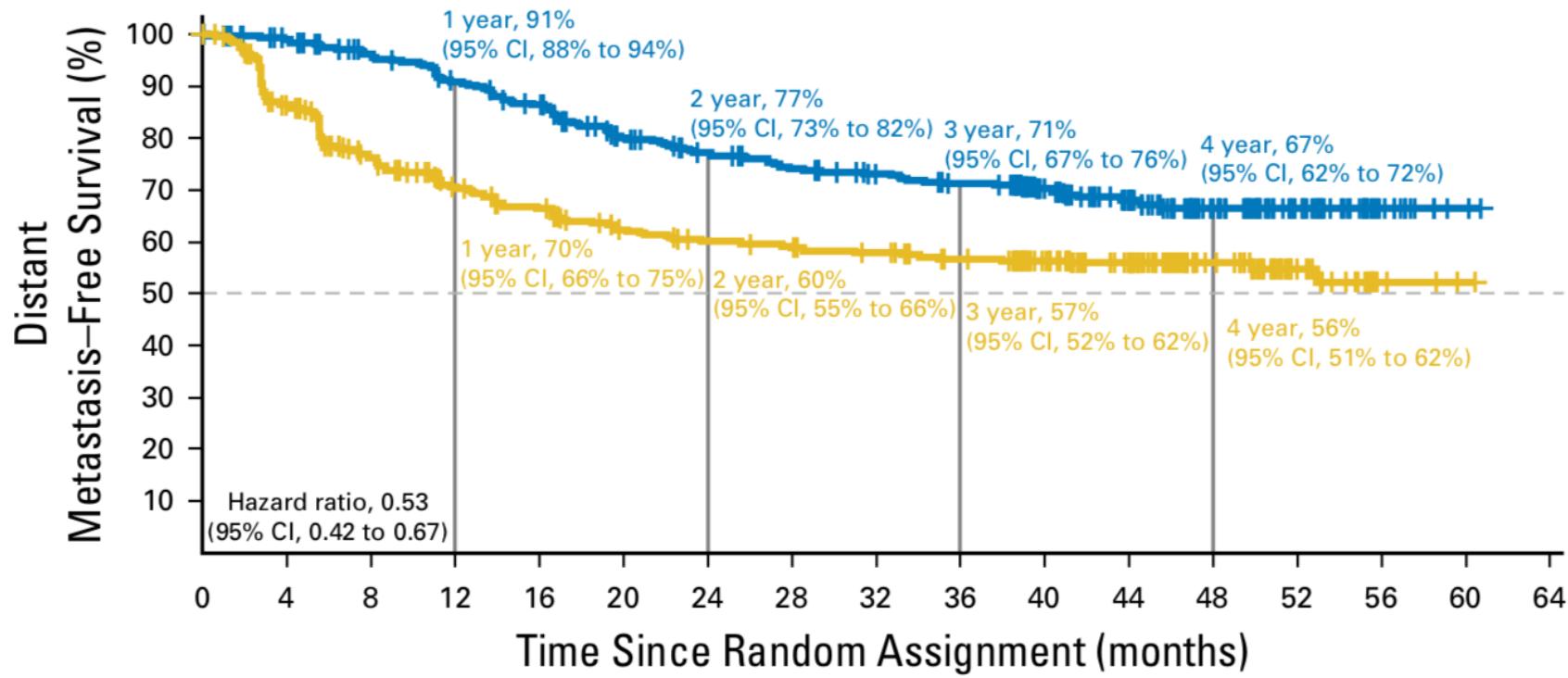
IIIC, 7^a ed



IIIC, 8^a ed



Dabrafenibe e Trametinibe



No. at risk

	438	407	381	352	327	285	265	252	238	229	185	150	92	47	13	2	0
Dabrafenib plus trametinib	438	407	381	352	327	285	265	252	238	229	185	150	92	47	13	2	0
Placebo	432	330	265	221	201	179	169	165	159	149	130	108	64	28	4	1	0

Dabrafenibe e Trametinibe

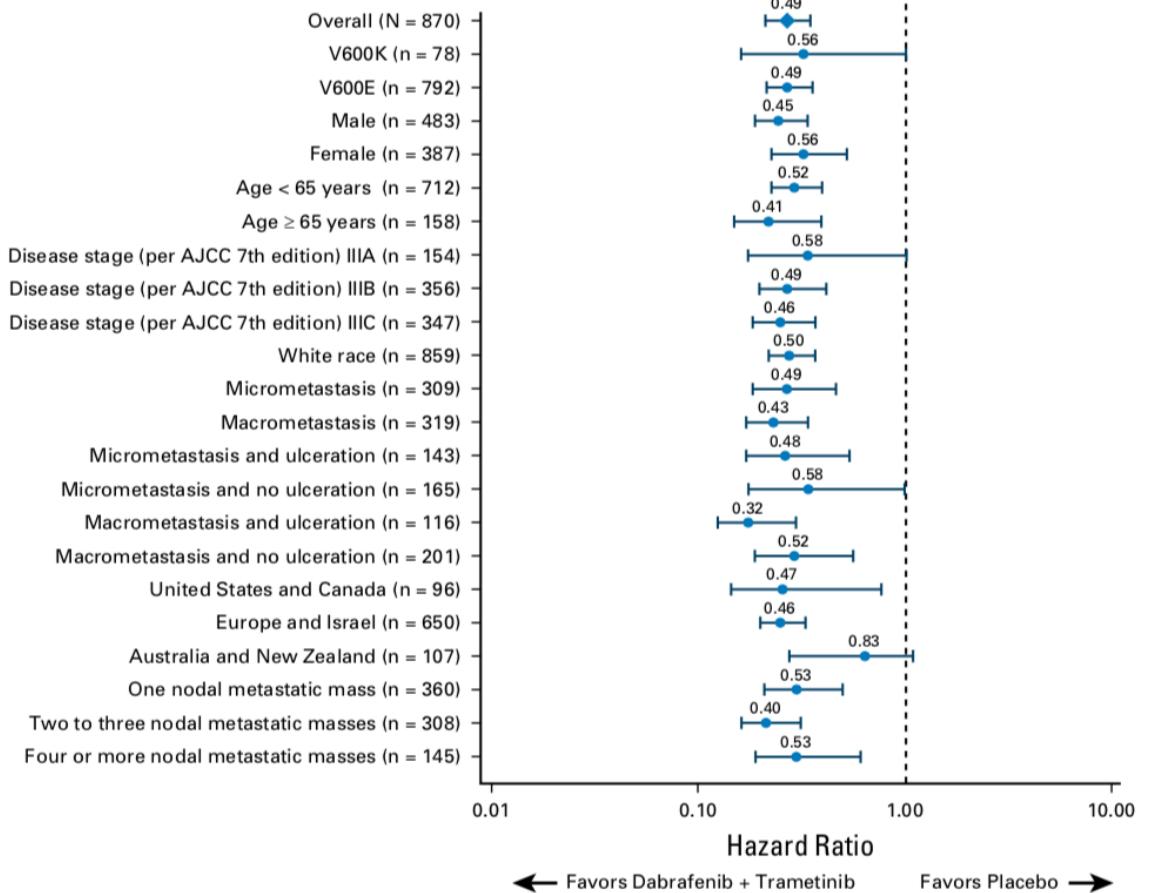


Table 2. Therapy after Melanoma Recurrence (Safety Population).^a

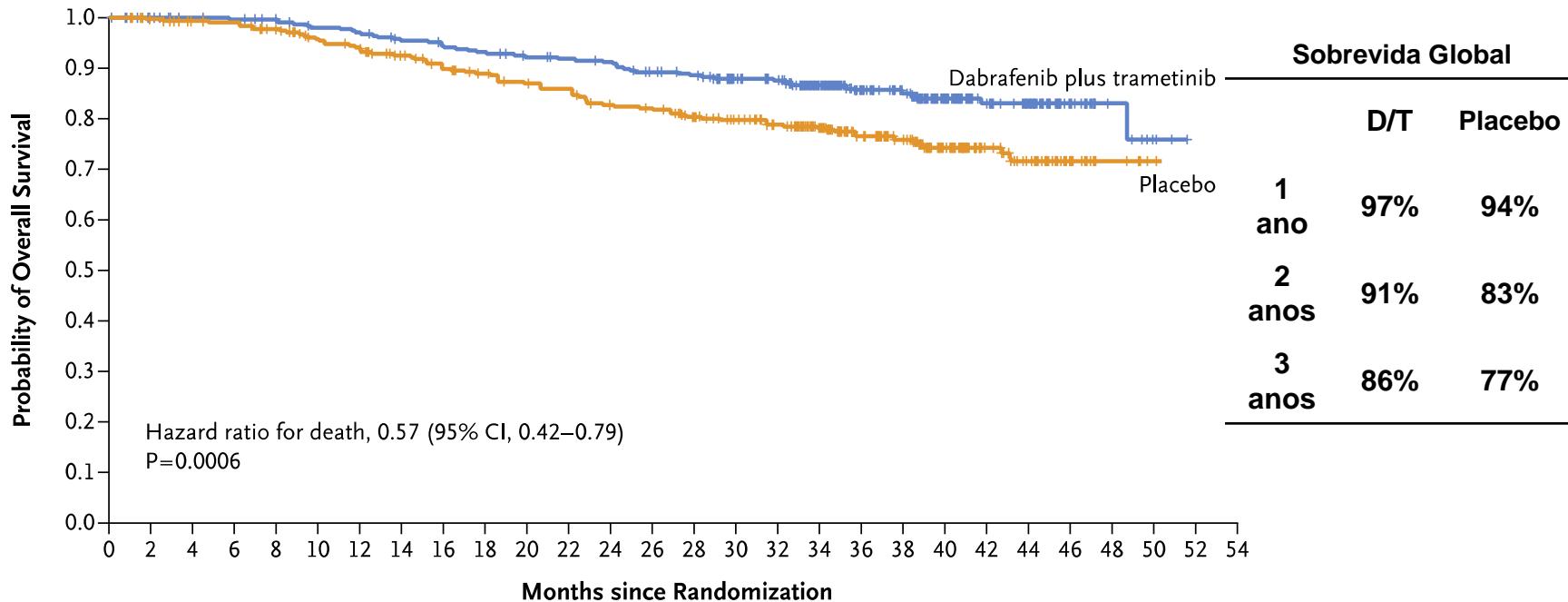
Type of Therapy	Dabrafenib plus Trametinib (N=435)	Placebo (N=432)
no. (%)		
Any anticancer therapy	148 (34)	217 (50)
Surgery	78 (18)	131 (30)
Radiotherapy	60 (14)	72 (17)
Any systemic therapy [†]	120 (28)	183 (42)
Small-molecule targeted therapy	63 (14)	137 (32)
Any BRAF inhibitor	63 (14)	137 (32)
Dabrafenib	44 (10)	86 (20)
Vemurafenib	29 (7)	59 (14)
Encorafenib	0	16 (4)
Any MEK inhibitor	47 (11)	77 (18)
Trametinib	28 (6)	48 (11)
Cobimetinib	20 (5)	18 (4)
Binimatinib	2 (<1)	15 (3)
Immunotherapy	89 (20)	103 (24)
Anti-PD-1 or PD-L1	71 (16)	68 (16)
Anti-CTLA-4	53 (12)	68 (16)
Interferon	6 (1)	11 (3)
T-VEC	0	1 (<1)
Biologic therapy	1 (<1)	1 (<1)
Chemotherapy	20 (5)	23 (5)
Investigational treatment	6 (1)	19 (4)
Other systemic therapy	2 (<1)	0

Long et al, NEJM 2017;

Hauschild et al, J Clin Oncol 2018

Dabrafenibe e Trametinibe

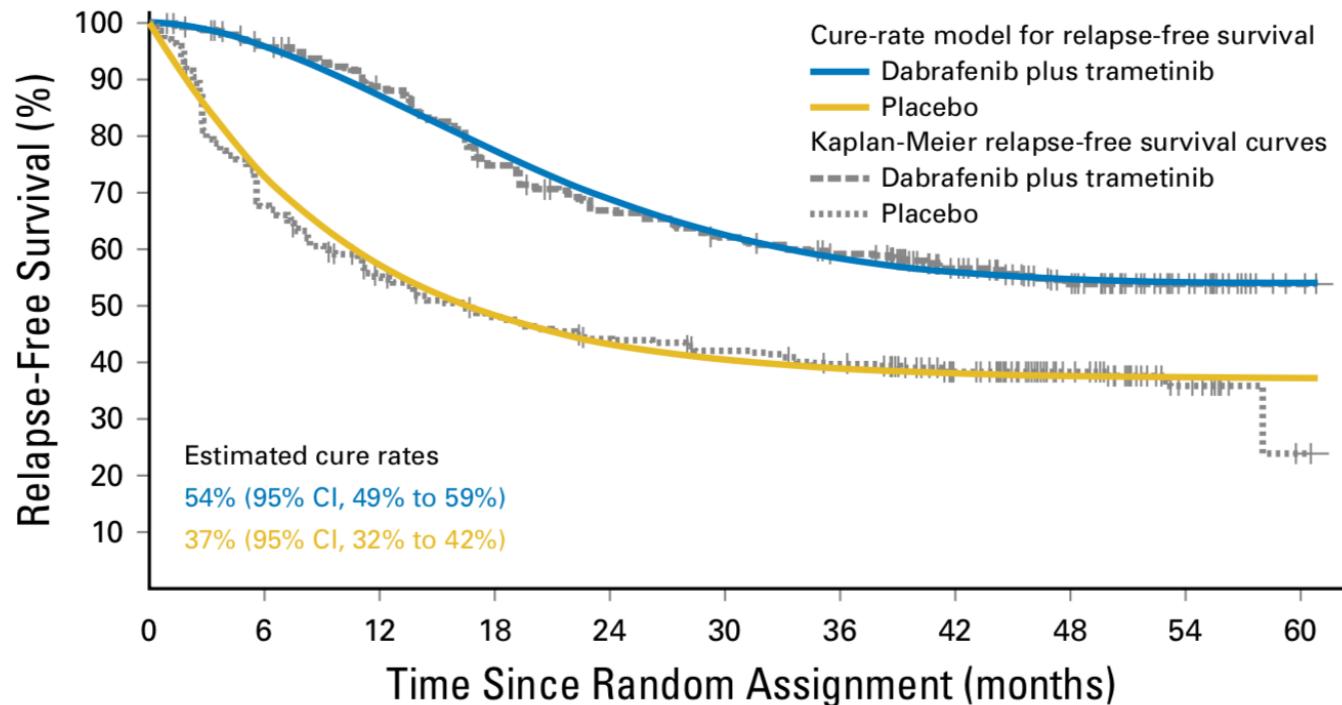
Overall Survival



No. at Risk

Dabrafenib plus trametinib	438 426 416 414 408 401 395 387 381 376 370 366 362 352 328 301 291 233 180 164 105 82 67 28 12 5 0 0
Placebo	432 425 415 410 401 386 378 362 346 337 328 308 303 284 269 252 202 164 152 94 64 51 17 7 1 0 0

Dabrafenibe e Trametinibe



No. at risk

Dabrafenib plus trametinib	438	391	354	298	262	242	227	161	92	34	2
Placebo	432	280	219	185	168	158	147	112	63	18	1

Dabrafenibe/Trametinibe vs. Placebo

COMBI AD

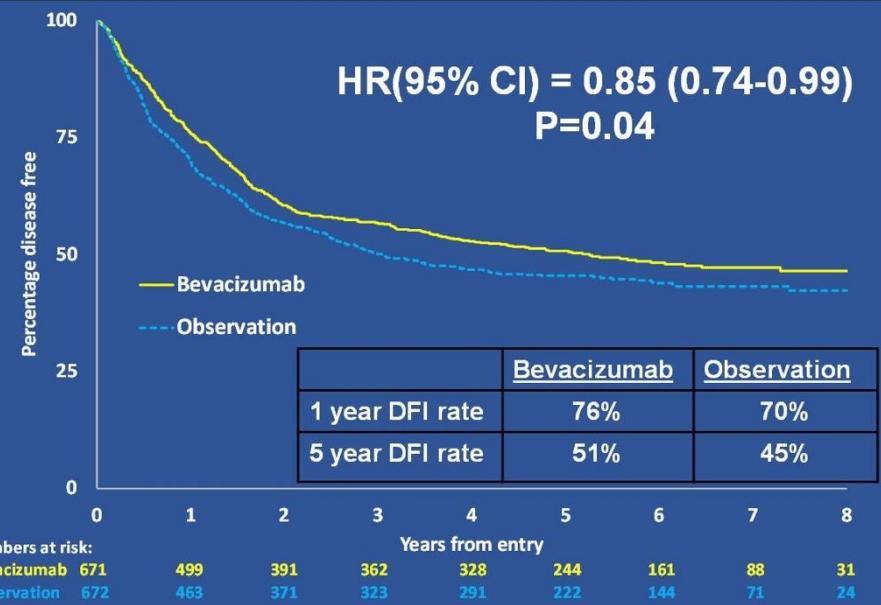
	Dabrafenibe / Trametinibe	
	Qualquer Grau	G3 / G4
Qualquer Evento*	97%	41%
Febre	63%	5%
Fadiga	47%	4%
Náusea	40%	1%
Cefaléia	39%	1%
Diarréia	33%	1%
Vômito	28%	1%
Artralgia	24%	0
Evento* que levasse a interrupção de dose	66%	
Evento* que levasse a redução de dose	38%	
Evento* que levasse a descontinuação	26%	

COMBI-D

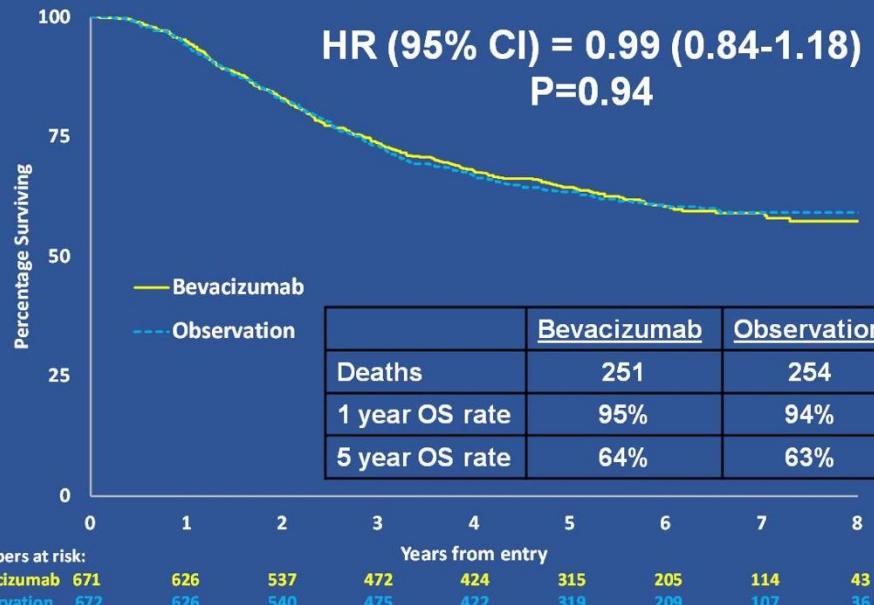
	Dabrafenibe / Trametinibe	
	Qualquer Grau	G3 / G4
Qualquer Evento*	95%	32%
Febre	51%	6%
Fadiga	35%	2%
Náusea	30%	0
Cefaléia	30%	1%
Diarréia	24%	1%
Vômito	20%	1%
Artralgia	24%	1%
Evento* que levasse a interrupção de dose	49%	
Evento* que levasse a redução de dose	25%	
Evento* que levasse a descontinuação	9%	

Bevacizumabe Adjuvante

Intervalo Livre de Doença



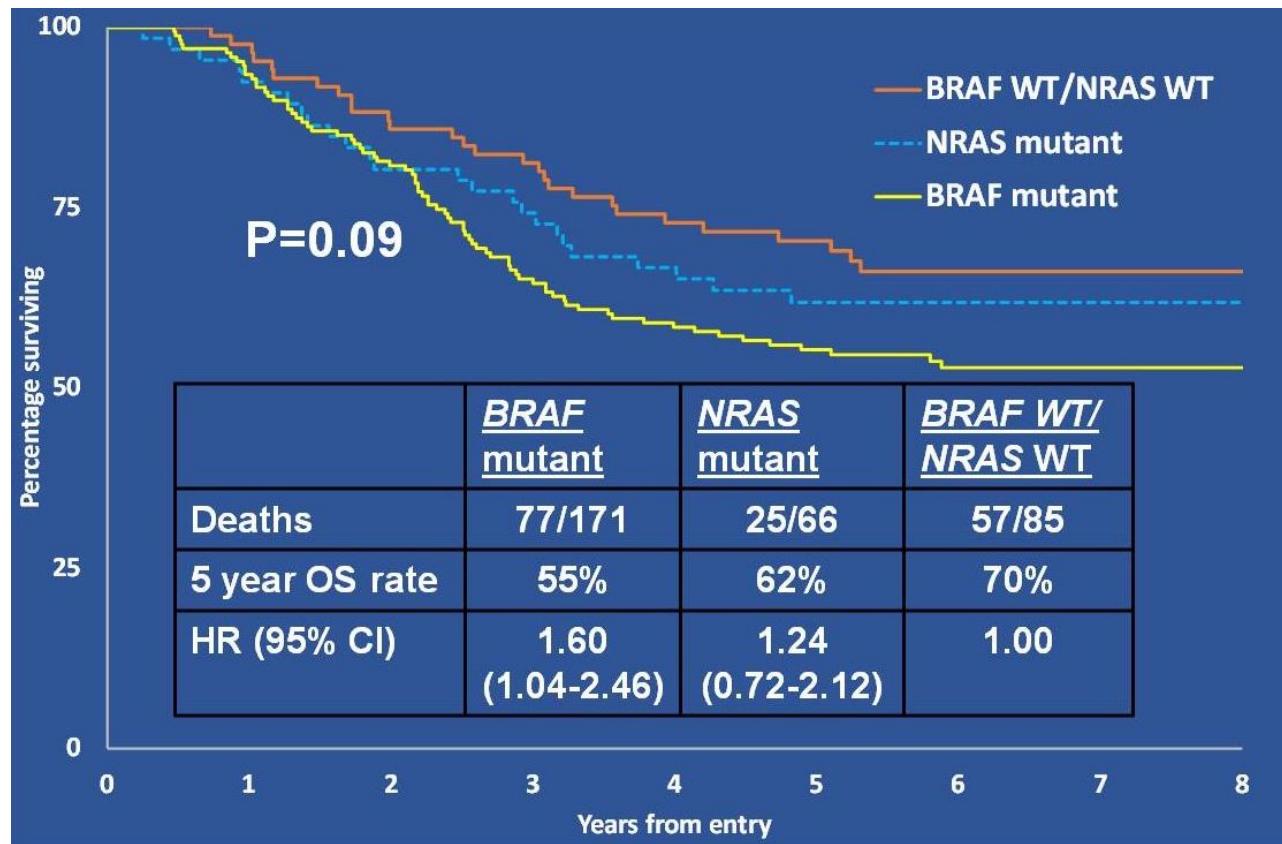
Sobrevida Global



Sobrevida segundo Status de BRAF/NRAS

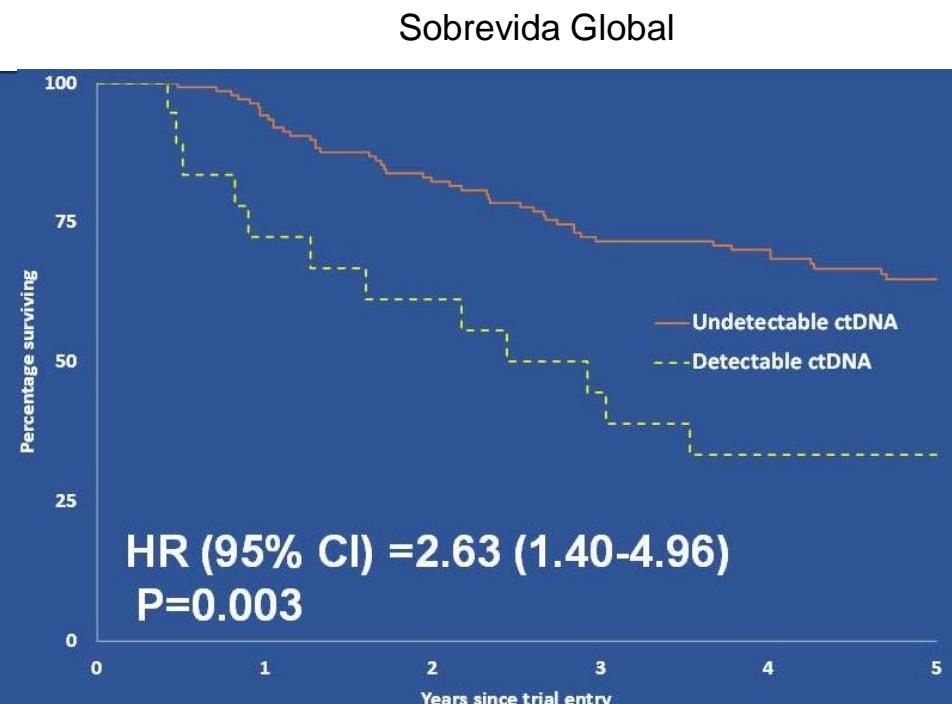
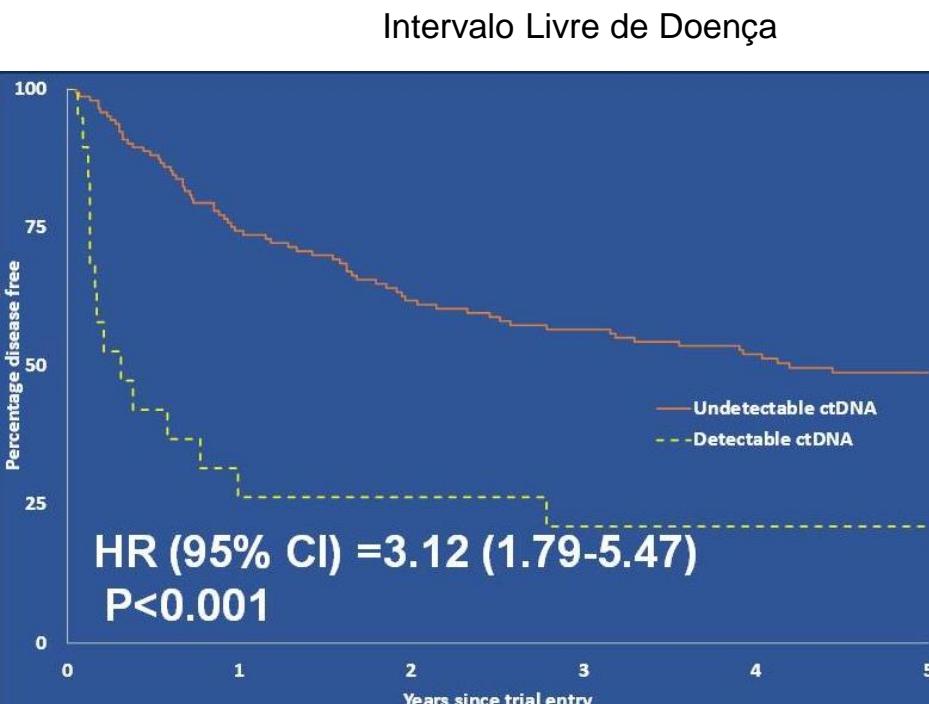
Pacientes do Braço Controle

Sobrevida Global



Sobrevida e ILD segundo ctDNA

Pacientes do Braço Controle



Quem deve ser tratado?

Em Resumo...

HR 0,49 DFS Risco Abs -16% em 4 anos

“platô” em DFS

ganho sustentado depois do fim do tratamento

Estimativa de ganho de cura: 17% em 4 anos

26% de interrupção do tratamento por toxicidade



**Dabrafenibe
Trametinibe**

**Nivolumabe
Pembrolizumabe**

Obrigado!!
@MelanomaSarcoma