

12º SIMPÓSIO
INTERNACIONAL DE

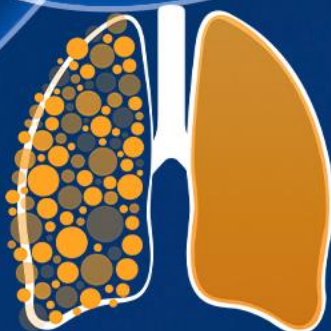
CÂNCER DE PULMÃO

2ª JORNADA ONCONNECTION MULTICARE

2024

GERENCIAMENTO E PRODUÇÃO

RV+
EVENTOS MÉDICOS



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PULMÃO

2ª JORNADA ONCONNECTION MULTICARE

2024

Radioterapia no SNC:

Cérebro total (WBRT) X Radiocirurgia (SRS)

Paula Pratti R F de Arruda

Coordenadora da Radioterapia do Hospital Santa Paula e Hospital Leforte (DASA Oncologia)

GERENCIAMENTO E PRODUÇÃO



- Cirurgia
- Tratamento sistêmico
- Radioterapia
 - Cérebro total (WBRT)
 - Radiocirurgia (SRS)

- Prognóstico
- Sintomático vs Assintomático
- Tumor em área eloquente
- Volume doença
- Perfil molecular

Graded Prognostic Assessment (GPA)

Non-small-cell and small-cell lung cancer		GPA Scoring Criteria			Patient Score	
Prognostic Factor	0	0.5	1.0			
Age, years	> 60	50-60	< 50		—	
KPS	< 70	70-80	90-100		—	
ECM	Present	—	Absent		—	
No. of BM	> 3	2-3	1		—	
Sum total					—	
Median survival (months) by GPA: 0-1.0 = 3.0; 1.5-2.0 = 5.5; 2.5-3.0 = 9.4; 3.5-4.0 = 14.8						
Melanoma		GPA Scoring Criteria			Patient Score	
Prognostic Factor	0	1.0	2.0			
KPS	< 70	70-80	90-100		—	
No. of BM	> 3	2-3	1		—	
Sum total					—	
Median survival (months) by GPA: 0-1.0 = 3.4; 1.5-2.0 = 4.7; 2.5-3.0 = 8.8; 3.5-4.0 = 13.2						
Breast cancer		GPA Scoring Criteria				Patient Score
Prognostic Factor	0	0.5	1.0	1.5	2.0	
KPS	≤ 50	60	70-80	90-100	n/a	—
Subtype	Basal	n/a	LumA	HER2	LumB	—
Age, years	≥ 60	< 60	n/a	n/a	n/a	—
Sum total						—
Median survival (months) by GPA: 0-1.0 = 3.4; 1.5-2.0 = 7.7; 2.5-3.0 = 15.1; 3.5-4.0 = 25.3						
Renal cell carcinoma		GPA Scoring Criteria			Patient Score	
Prognostic Factor	0	1.0	2.0			
KPS	< 70	70-80	90-100		—	
No. of BM	> 3	2-3	1		—	
Sum total					—	
Median survival (months) by GPA: 0-1.0 = 3.3; 1.5-2.0 = 7.3; 2.5-3.0 = 11.3; 3.5-4.0 = 14.8						
GI cancers		GPA Scoring Criteria				Patient Score
Prognostic Factor	0	1	2	3	4	
KPS	< 70	70	80	90	100	—
Median survival (months) by GPA: 0-1.0 = 3.1; 2.0 = 4.4; 3.0 = 6.9; 4.0 = 13.5						

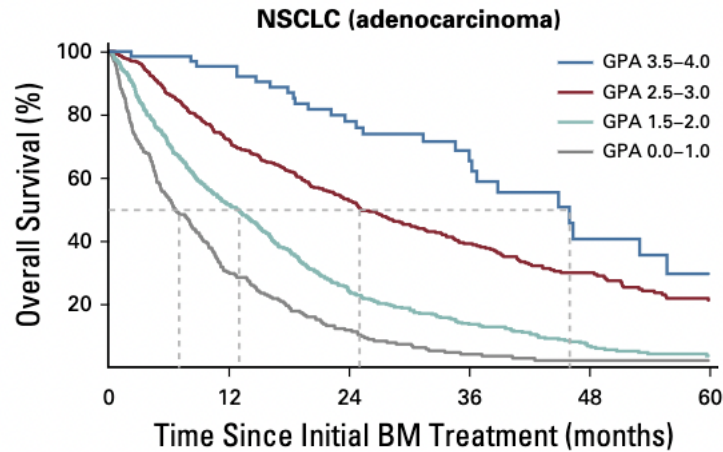
GPA-Lung Cancer Using Molecular Markers (Lung-mol GPA)

NSCLC adenocarcinoma					
KPS	≤ 70	80	90-100	NA	NA
Age, years	≥ 70	< 70	NA	NA	NA
No. of BM	≥ 5	1-4	NA	NA	NA
ECM	Present	NA	Absent	NA	NA
EGFR and ALK	Both negative or unknown	NA	EGFR or ALK positive	NA	NA

Sum = MS (months) by GPA: 0-1 = 7; 1.5-2.0 = 13; 2.5-3.0 = 25; 3.5-4.0 = 46

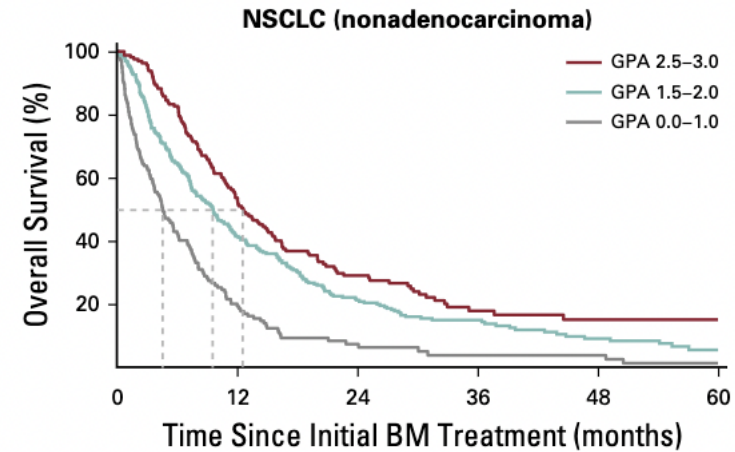
NSCLC nonadenocarcinoma					
KPS	≤ 70	80	90-100	NA	NA
Age, years	≥ 70	< 70	NA	NA	NA
No. of BM	≥ 5	1-4	NA	NA	NA
ECM	Present	NA	Absent	NA	NA

Sum = MS (months) by GPA: 0-1 = 5; 1.5-2.0 = 10; 2.5-3.0 = 13; 3.5-4.0 = NA



No. at risk:

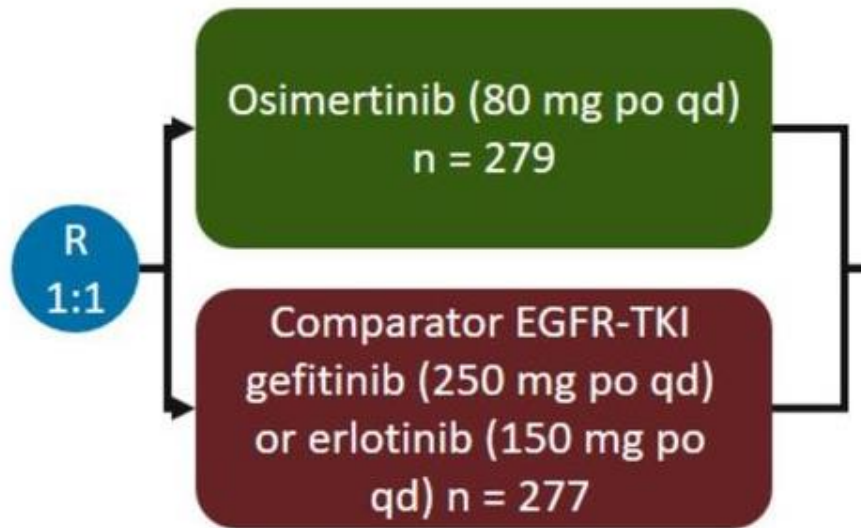
	0	12	24	36	48	60
GPA 3.5-4.0	64	60	39	21	8	
GPA 2.5-3.0	453	302	187	108	61	
GPA 1.5-2.0	616	286	115	49	18	
GPA 0.0-1.0	289	74	24	7	3	



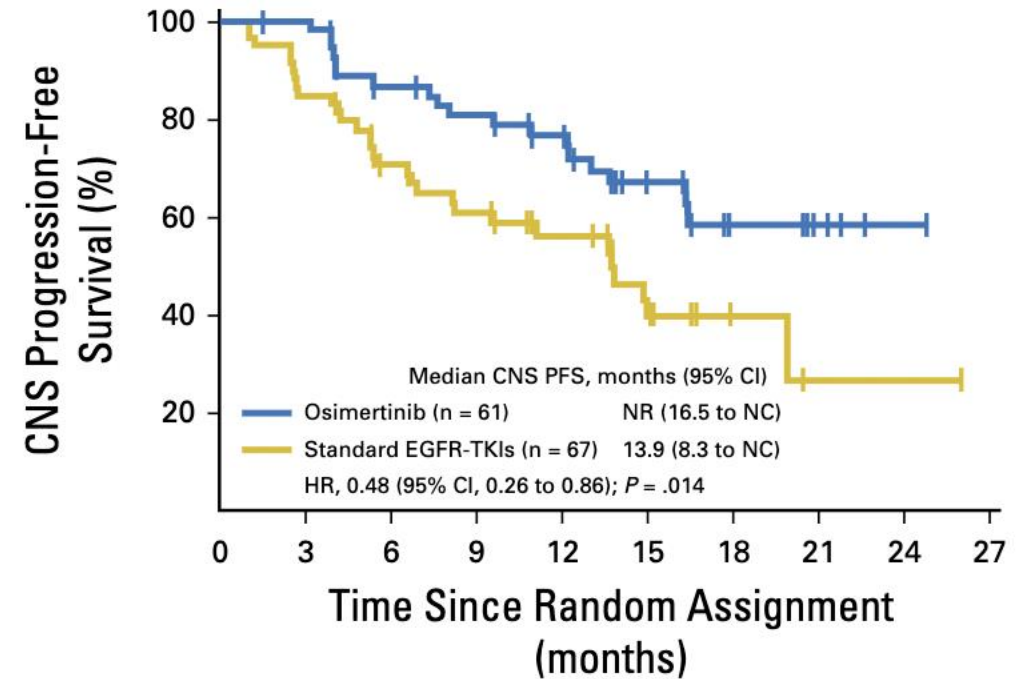
No. at risk:

	0	12	24	36	48	60
GPA 3.5-4.0	0	0	0	0	0	0
GPA 2.5-3.0	164	83	38	15	9	
GPA 1.5-2.0	304	114	49	25	13	
GPA 0.0-1.0	153	26	7	3	3	

FLAURA: Análise de resposta em SNC



A



No. at risk:

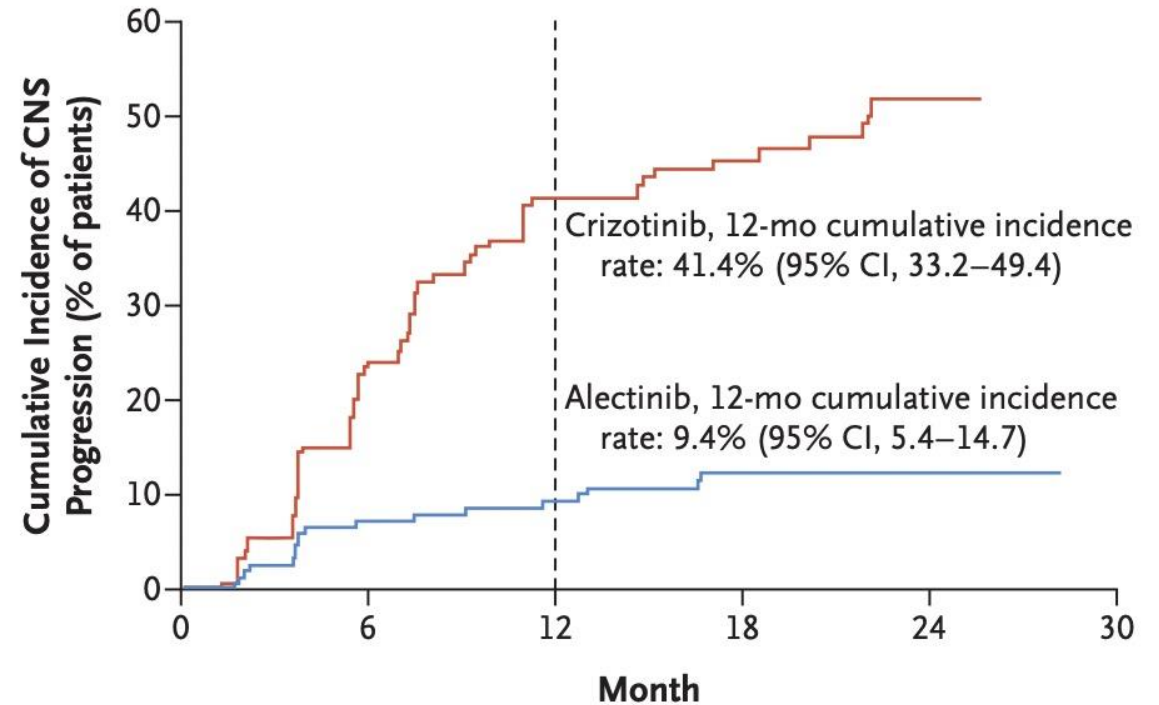
Osimertinib	61	54	44	40	34	21	8	4	1	0
Standard EGFR-TKIs	67	50	37	31	21	13	4	1	1	0

CNS ORR: 66% versus 43% favorecendo osimertinib

Alectinib versus Crizotinib in Untreated ALK-Positive Non-Small-Cell Lung Cancer

Solange Peters, M.D., Ph.D., D. Ross Camidge, M.D., Ph.D.,
Alice T. Shaw, M.D., Ph.D., Shirish Gadgeel, M.D., Jin S. Ahn, M.D.,
Dong-Wan Kim, M.D., Ph.D., Sai-Hong I. Ou, M.D., Ph.D., Maurice Pérol, M.D.,
Rafal Dziadziuszko, M.D., Rafael Rosell, M.D., Ph.D., Ali Zeaiter, M.D.,
Emmanuel Mitry, M.D., Ph.D., Sophie Golding, M.Sc., Bogdana Balas, M.D.,
Johannes Noe, Ph.D., Peter N. Morcos, Pharm.D., and Tony Mok, M.D.,
for the ALEX Trial Investigators*

C Cumulative Incidence of CNS Progression

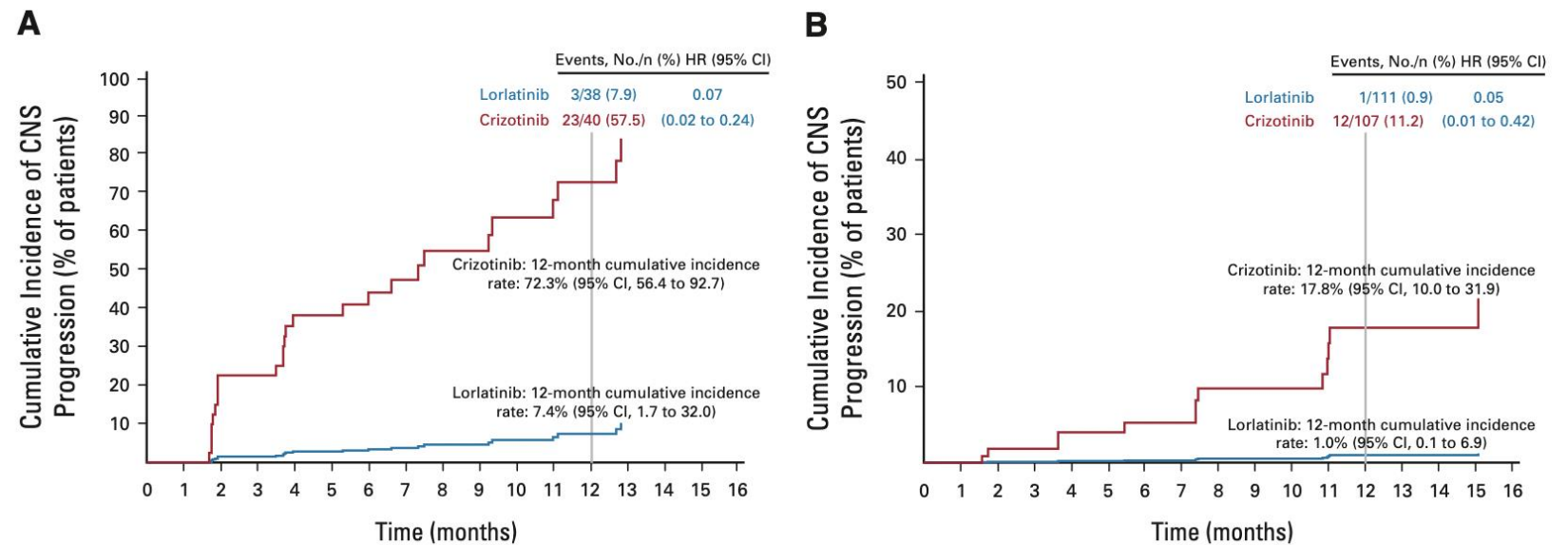


ALK

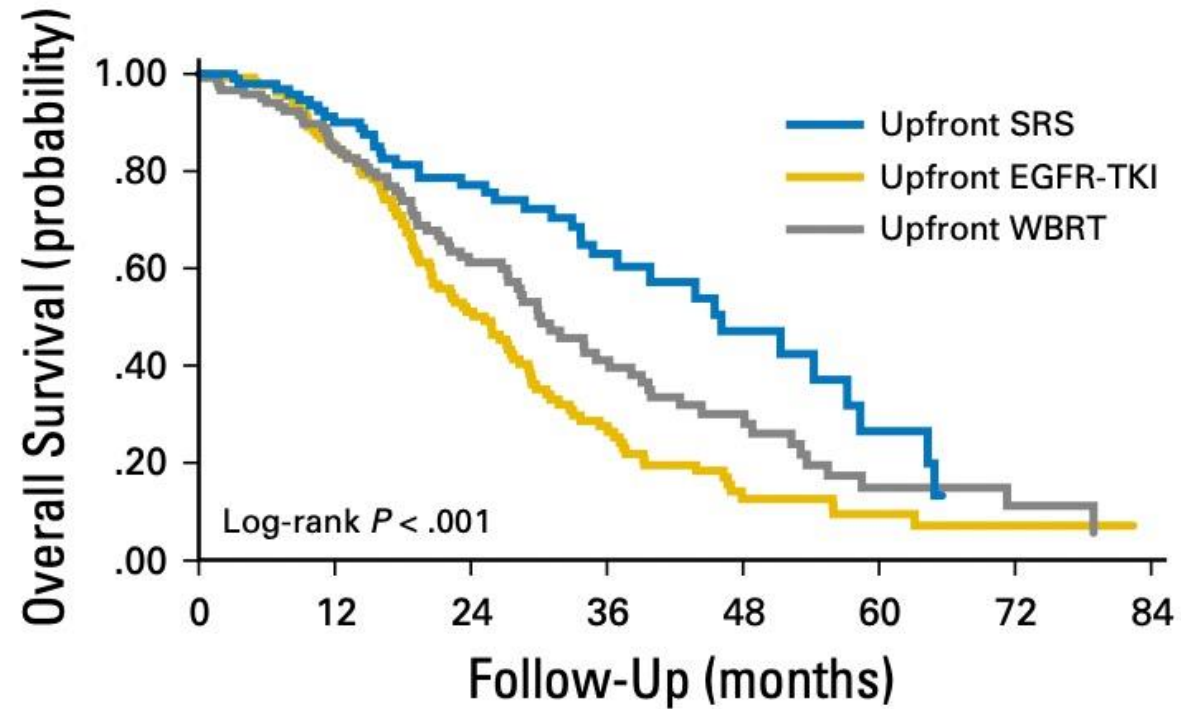
Lorlatinibe vs Crizotinibe

Post Hoc Analysis of Lorlatinib Intracranial Efficacy and Safety in Patients With ALK-Positive Advanced Non-Small-Cell Lung Cancer From the Phase III CROWN Study

Benjamin J. Solomon, MB, BS, PhD¹; Todd M. Bauer, MD²; Sai-Hong Ignatius Ou, MD, PhD³; Geoffrey Liu, MD⁴;
Hidetoshi Hayashi, MD, PhD⁵; Alessandra Bearz, MD⁶; Konstantin Penkov, MD, PhD⁷; Yi-Long Wu, MD⁸; Oscar Arrieta, MD⁹;
Jacek Jassem, MD, PhD¹⁰; Anna M. Calella, PhD¹¹; Gerson Peltz, MD, MPH¹²; Anna Polli, BSc¹¹; Holger Thurm, MD¹³; and
Tony Mok, MD¹⁴



Inibidores de TKI e Radioterapia



No. at risk		0	12	24	36	48	60	72	84
Upfront SRS	100	76	51	29	13	5	1	1	
Upfront WBRT	120	97	52	27	15	6	3	1	
Upfront EGFR-TKI	131	103	54	24	8	4	2	0	

Treatment for Brain Metastases: ASCO-SNO-ASTRO Guideline

Recommendation 2.3. Osimertinib or icotinib may be offered to patients with asymptomatic brain metastases from *EGFR*-mutant non–small-cell lung cancer (NSCLC). If these agents are used, local therapy may be delayed until there is evidence of intracranial progression (Type: informal consensus; Evidence quality: low; Strength of recommendation: weak).

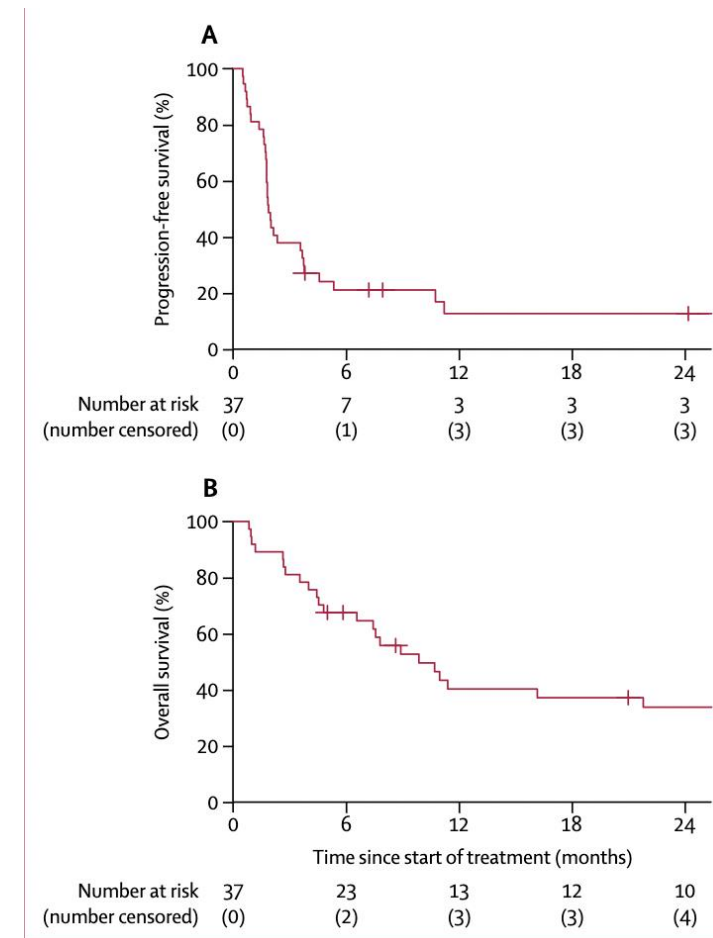
Qualifying Statement: The expert panel recognizes that as of this publication, icotinib is not approved by the US Food and Drug Administration or the European Medicines Agency.

Recommendation 2.4. Alectinib, brigatinib, or ceritinib may be offered to patients with asymptomatic brain metastases from *ALK*-rearranged NSCLC. If these agents are used, local therapy may be delayed until there is evidence of intracranial progression (Type: informal consensus; Evidence quality: low; Strength of recommendation: weak).

Pembrolizumab for management of patients with NSCLC and brain metastases: long-term results and biomarker analysis from a non-randomised, open-label, phase 2 trial

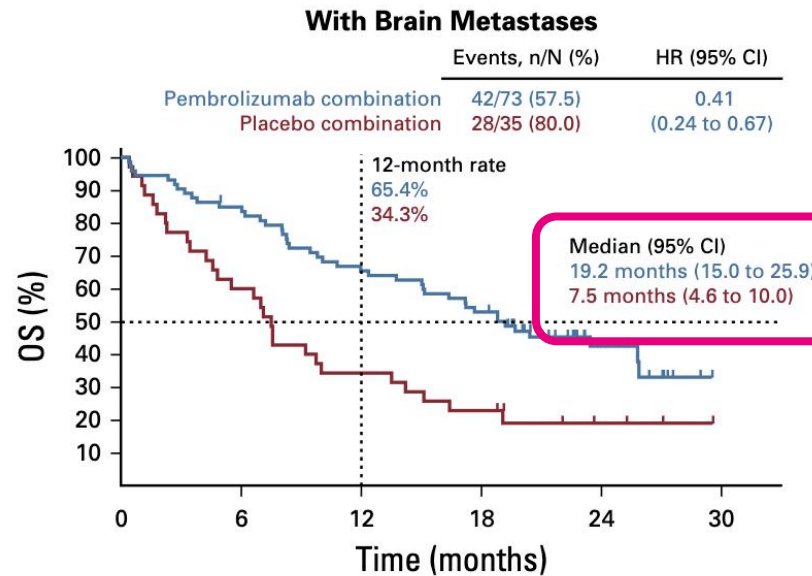
Sarah B Goldberg, Kurt A Schalper, Scott N Gettinger, Amit Mahajan, Roy S Herbst, Anne C Chiang, Rogerio Lilenbaum, Frederick H Wilson, Sacit Bulent Omay, James B Yu, Lucia Jilaveanu, Thuy Tran, Kira Pavlik, Elin Rowen, Heather Gerrish, Annette Komlo, Richa Gupta, Hailey Wyatt, Matthew Ribeiro, Yuval Kluger, Geyu Zhou, Wei Wei, Veronica L Chiang, Harriet M Kluger

- 29,7% dos pac com PD-L1 tiveram resposta intracraniana
- SG (2 anos): 34% (dados históricos 14.3%)



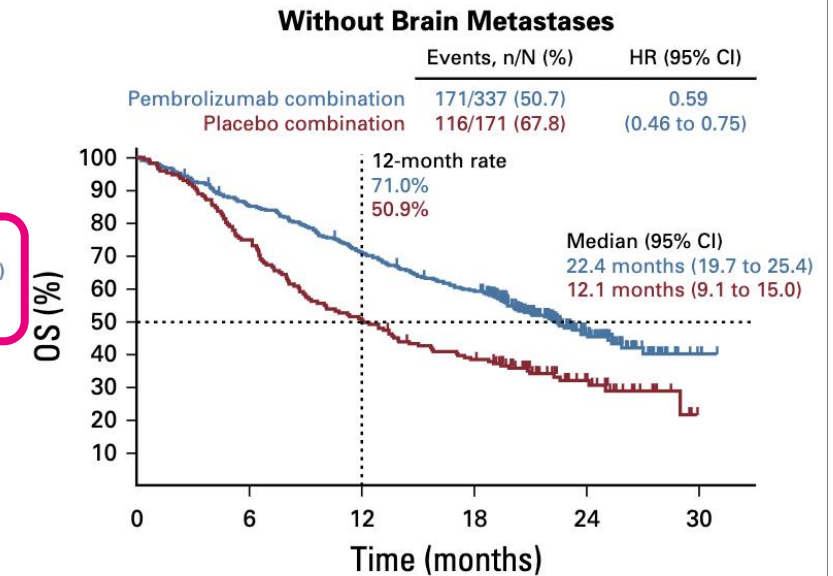
Updated Analysis From KEYNOTE-189: Pembrolizumab or Placebo Plus Pemetrexed and Platinum for Previously Untreated Metastatic Nonsquamous Non-Small-Cell Lung Cancer

Shirish Gadgeel, MB, BS¹; Delvys Rodríguez-Abreu, MD²; Giovanna Speranza, MD, MSc³; Emilio Esteban, MD⁴; Enriqueta Felip, MD, PhD⁵; Manuel Dómine, MD, PhD⁶; Rina Hui, MB, BS, PhD⁷; Maximilian J. Hochmair, MD⁸; Philip Clingan, MB, BS⁹; Steven F. Powell, MD¹⁰; Susanna Yee-Shan Cheng, MD¹¹; Helge G. Bischoff, MD¹²; Nir Peled, MD, PhD¹³; Francesco Grossi, MD¹⁴; Ross R. Jennens, MB, BS¹⁵; Martin Reck, MD¹⁶; Edward B. Garon, MD¹⁷; Silvia Novello, MD, PhD¹⁸; Belén Rubio-Viqueira, MD¹⁹; Michael Boyer, MB, BS, PhD²⁰; Takayasu Kurata, MD, PhD²¹; Jhanelle E. Gray, MD²²; Jing Yang, PhD²³; Tuba Bas, PhD²³; M. Catherine Pietanza, MD²³; and Marina C. Garassino, MD²⁴



No. at risk:

	0	6	12	18	24	30
Pembro	73	61	47	38	14	0
Placebo	35	21	12	8	3	0



No. at risk:

	0	6	12	18	24	30
Pembro	337	285	236	196	65	2
Placebo	171	128	87	64	23	0

Treatment for Brain Metastases: ASCO-SNO-ASTRO Guideline

Recommendation 2.5. Pembrolizumab may be offered to patients with asymptomatic brain metastases from immunotherapy-naïve, programmed death-ligand 1–NSCLC who are also receiving pemetrexed and a platinum agent (Type: informal consensus; Evidence quality: low; Strength of recommendation: weak). *NOTE: See Recommendation 2.2 regarding local therapy.*

that local therapy could be delayed in Recommendations 2.3 and 2.4, the Panel did not reach consensus regarding delay of local therapy when pembrolizumab plus pemetrexed and a platinum agent are used. Some on the Panel believed that the PFS and OS benefits reported in the Keynote 189 trial¹⁶⁶ were sufficient to make that recommendation, and others believed that in the absence of a full reporting of intracranial control rates, a recommendation to defer local therapy was premature. In the absence of consensus, no recommendation regarding deferring local therapy was made. The potential

RT e Imunoterapia

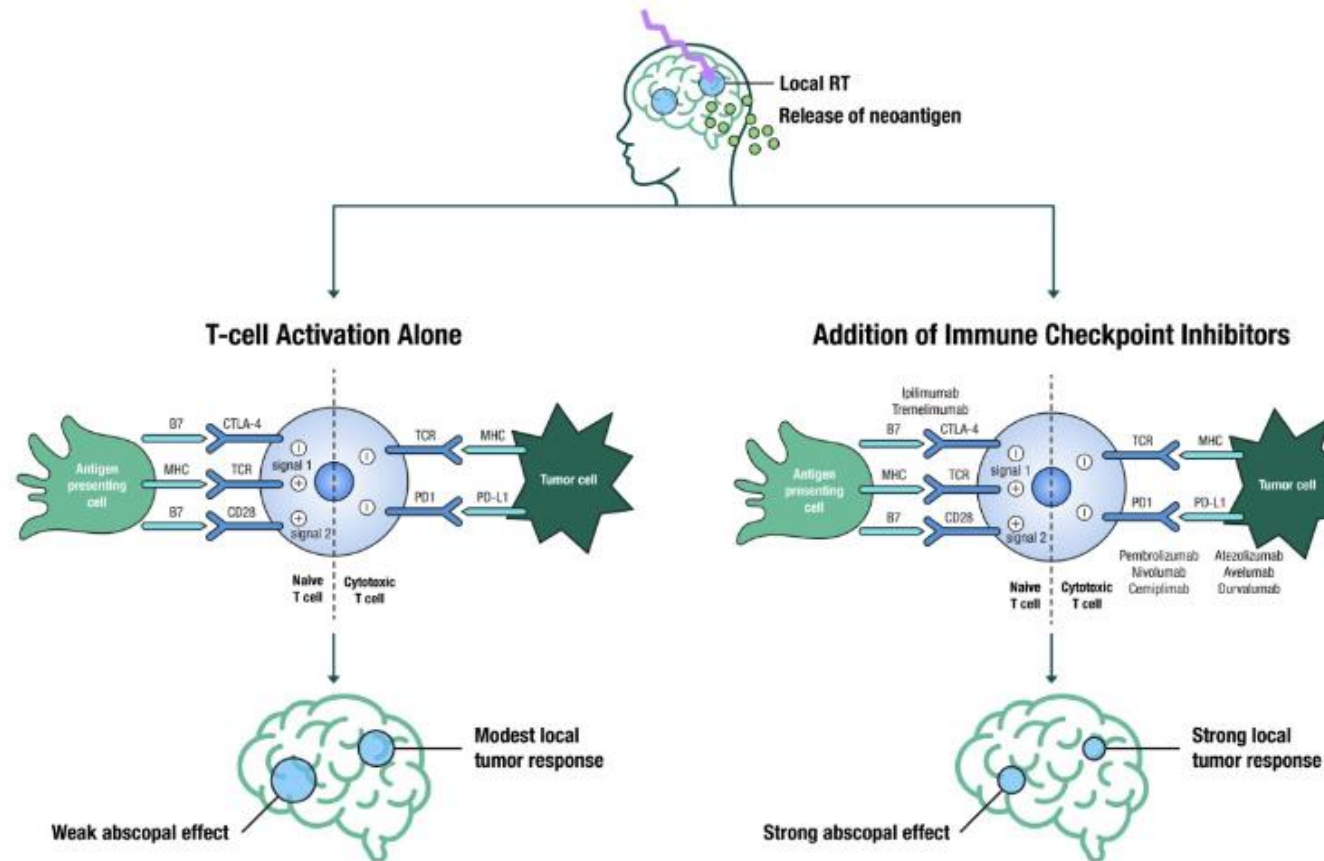


Figure 2. Illustration of the immune stimulatory effects of SRS leading to a localized breakdown and permeability of the BBB, causing the release of tumor associated neoantigens, ultimately leading to T-cell activation by antigen presenting cells (modest local tumor response and a weak abscopal effect); in contrast, the addition of immune checkpoint inhibitors (anti-CTLA4, anti-PD1 and anti-PDL1) to SRS leads to strong local tumor response and a strong abscopal effect (abscopal effect is defined as tumor shrinkage or elimination in sections of the body not directly targeted by local therapy).

Radiocirurgia (SRS)

- Radiocirurgia isolada
- Radiocirurgia associada a WBRT
- Radiocirurgia do leito operatório

RTOG 95-08

S
T
R
A
T
I
F
Y

Number of
Metastases

1. Single
2. 2-3

Extent of Extracranial
Disease

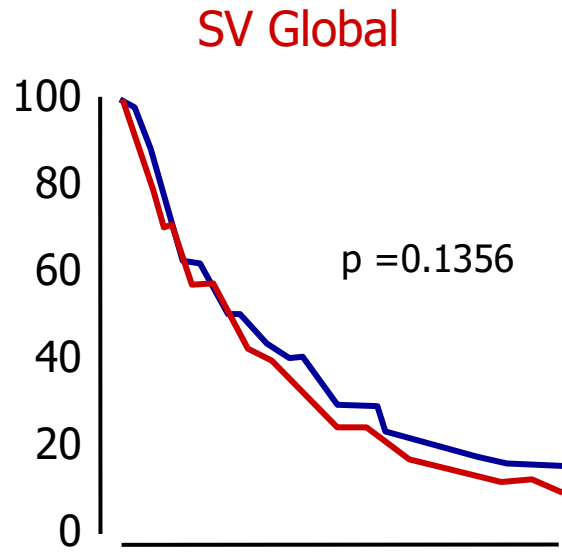
1. None
2. Present

R
A
N
D
O
M
I
Z
E

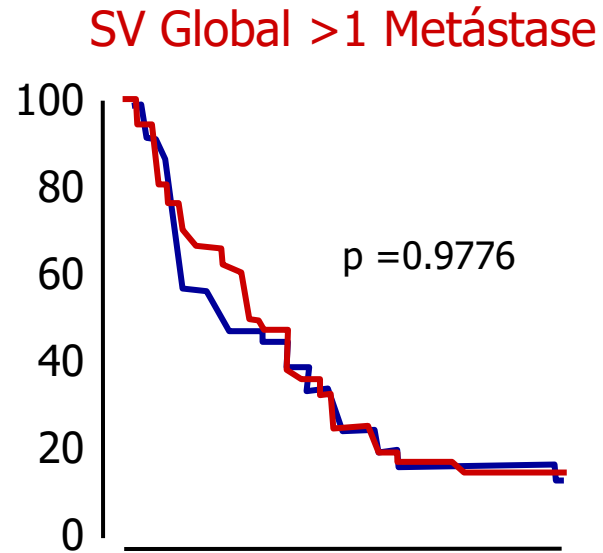
Arm 1: Whole brain RT to 37.5 Gy/15 fractions/2.5 Gy once daily, 5 days/week followed by radiosurgery to all (1-3) metastase(i)s

Arm 2: Whole brain RT to 37.5 Gy/15 fractions/2.5 Gy once daily, 5 days/week

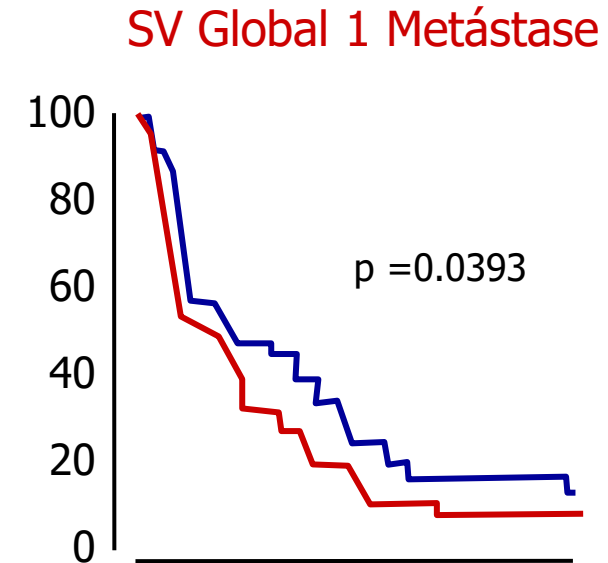
WBRT vs WBRT + SRS RTOG 95-08



— WBRT+SRS MST 6.5 m
— WBRT MST 5.7 m



— WBRT+SRS MST 5.8 m
— WBRT MST 6.7 m



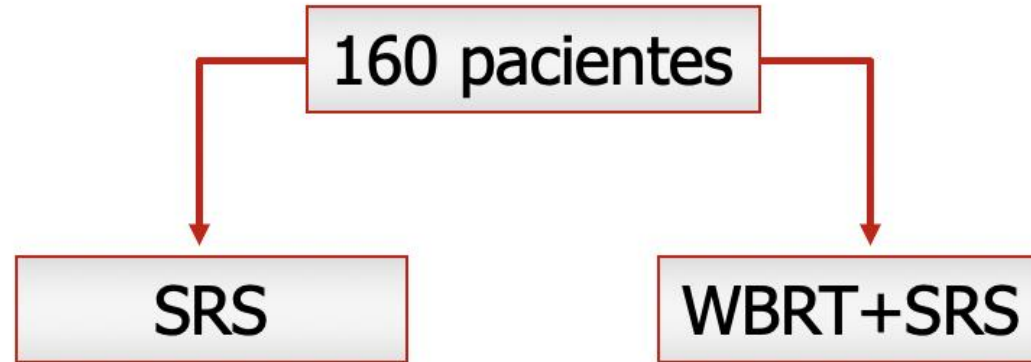
— WBRT+SRS MST 6.5 m
— WBRT MST 4.9 m

WBRT+SRS: ↑ LC, ↓ uso de esteróides

Sem ≠ morte neurológica, falha intracraniana regional

SRS vs WBRT + SRS

JROSG 99-1



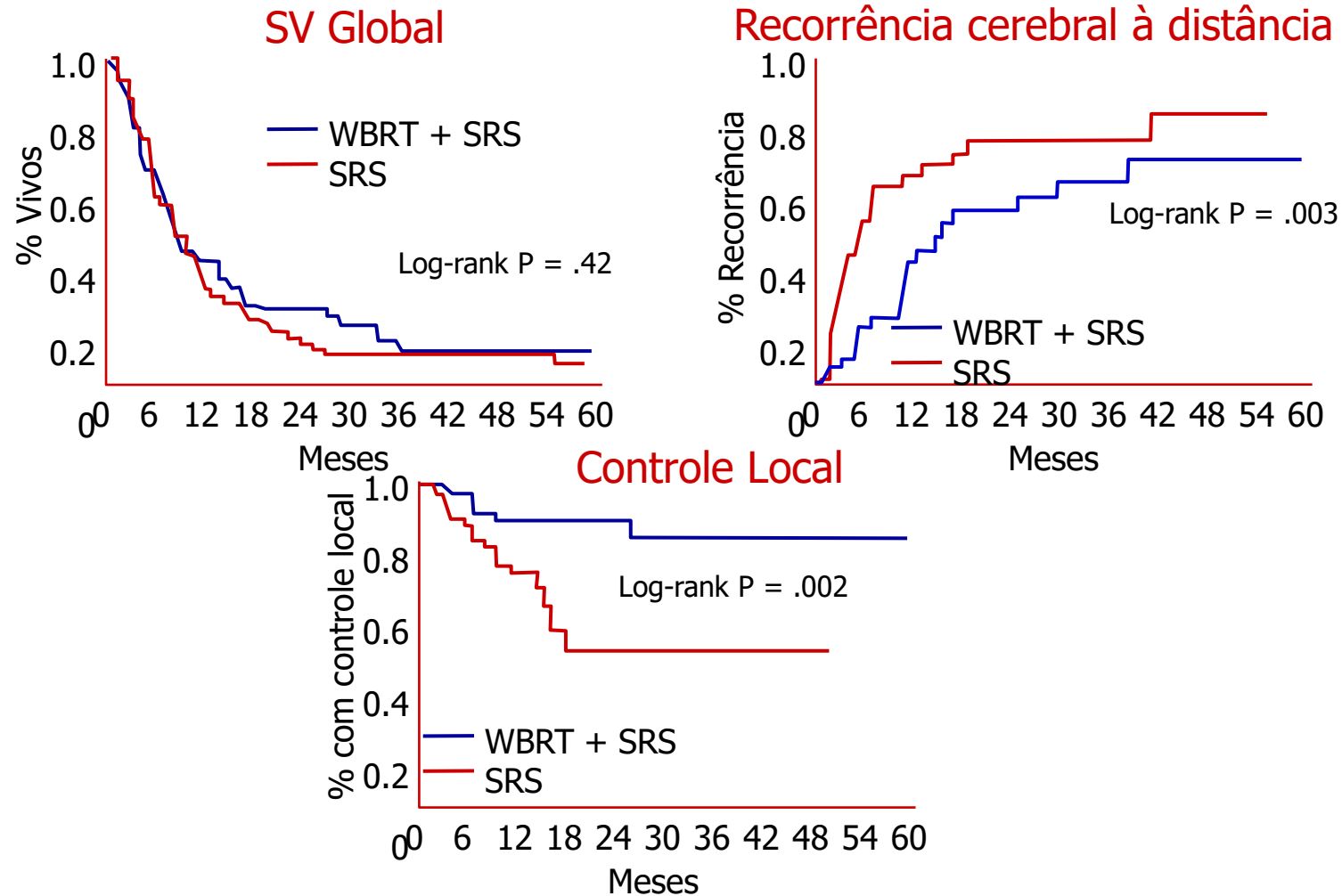
1-4 metástases <3cm

80-90% RPA classe 2

60% doença estável abaixo do pescoço

SRS vs WBRT + SRS

JROSG 99-1

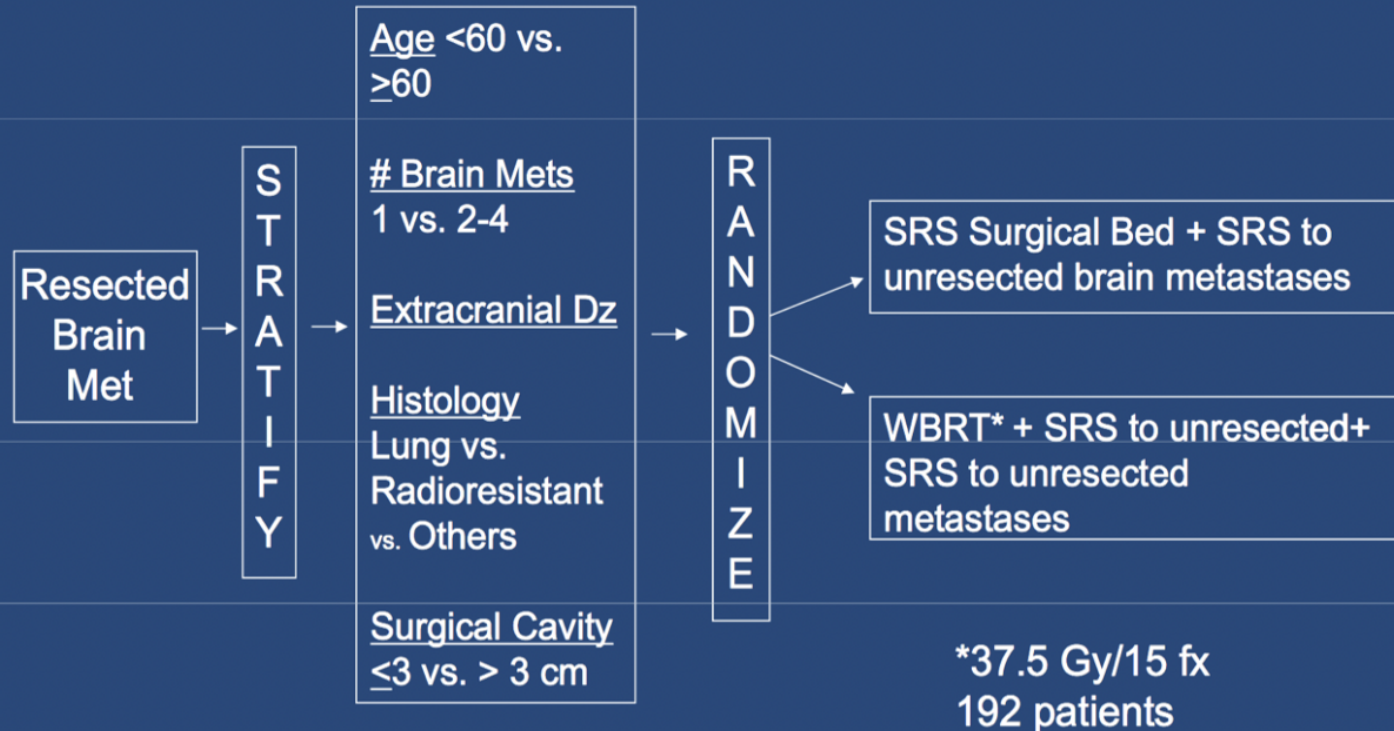


Radiocirurgia de leito operatório

N107C

SRS vs. WBRT Resected Brain Mets

Determine if neurocog progression less at 6 months with SRS



NCCTG N107C

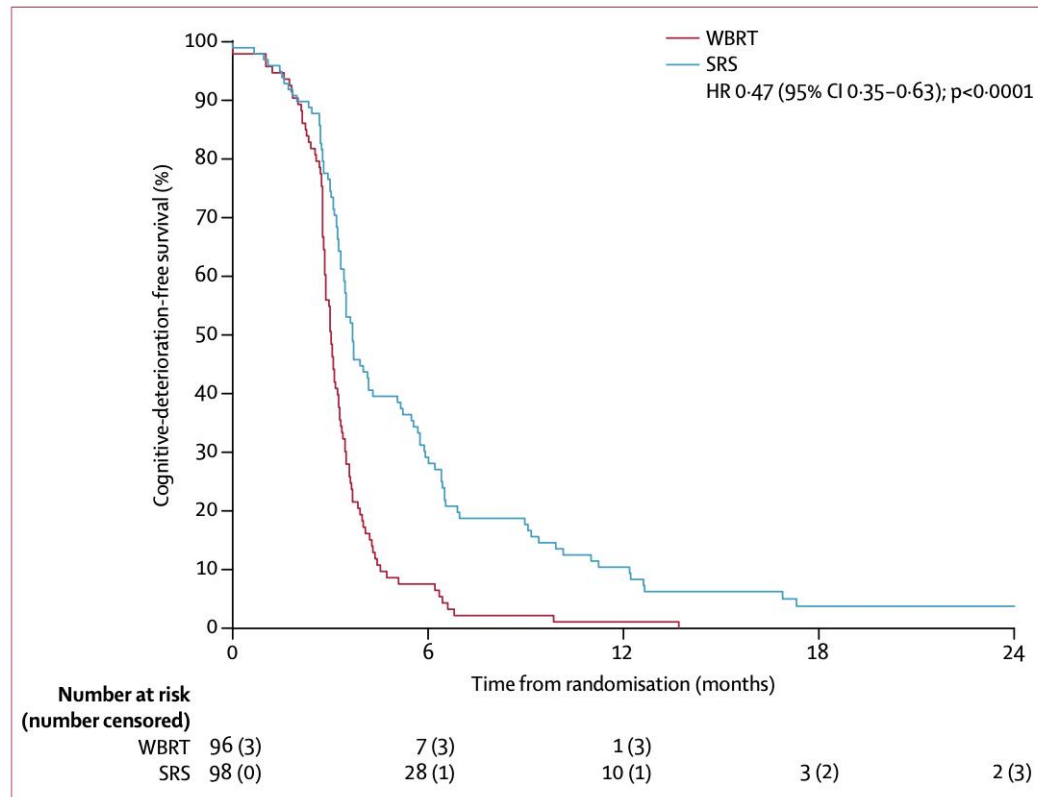


Figure 2: Cognitive-deterioration-free survival
WBRT=whole brain radiotherapy. SRS=stereotactic radiosurgery.

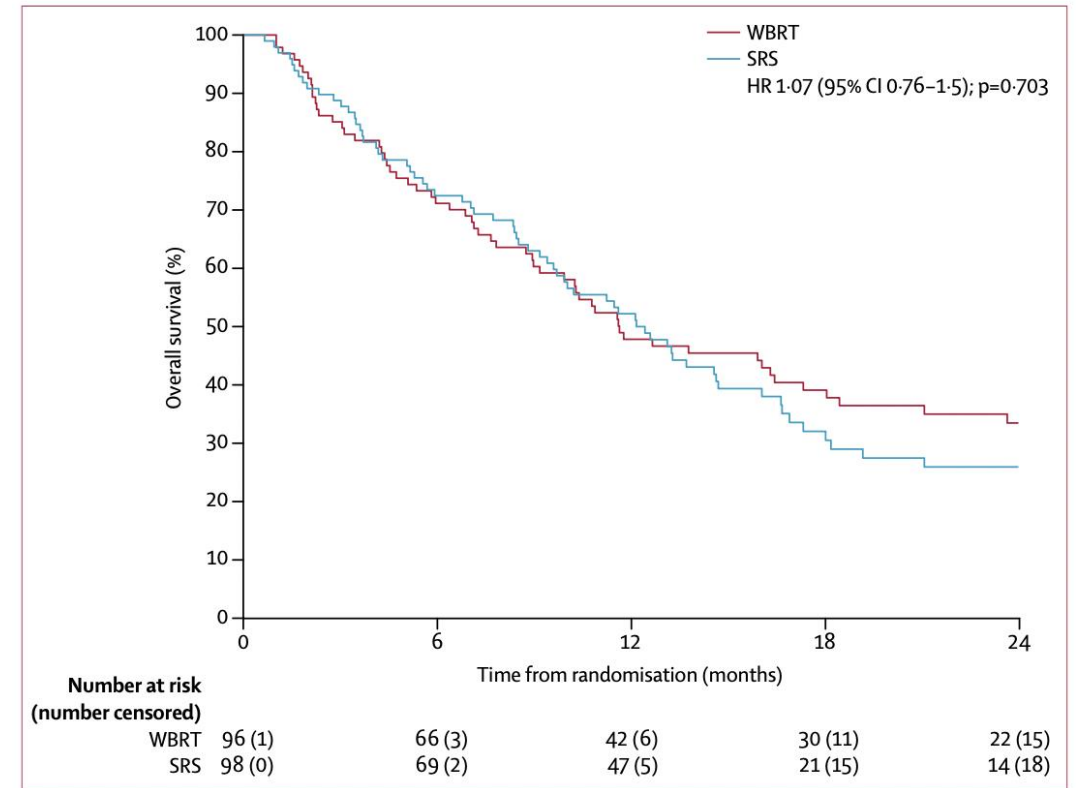
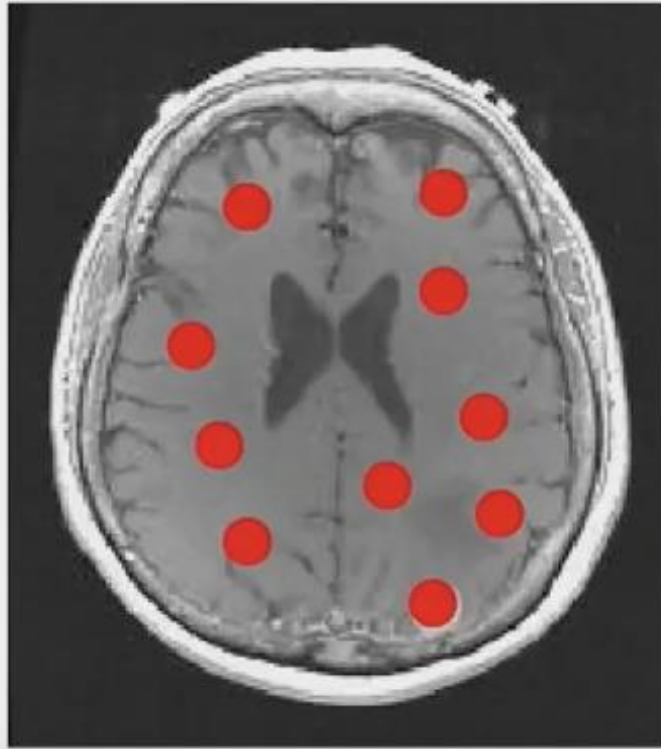


Figure 3: Overall survival
WBRT=whole brain radiotherapy. SRS=stereotactic radiosurgery.

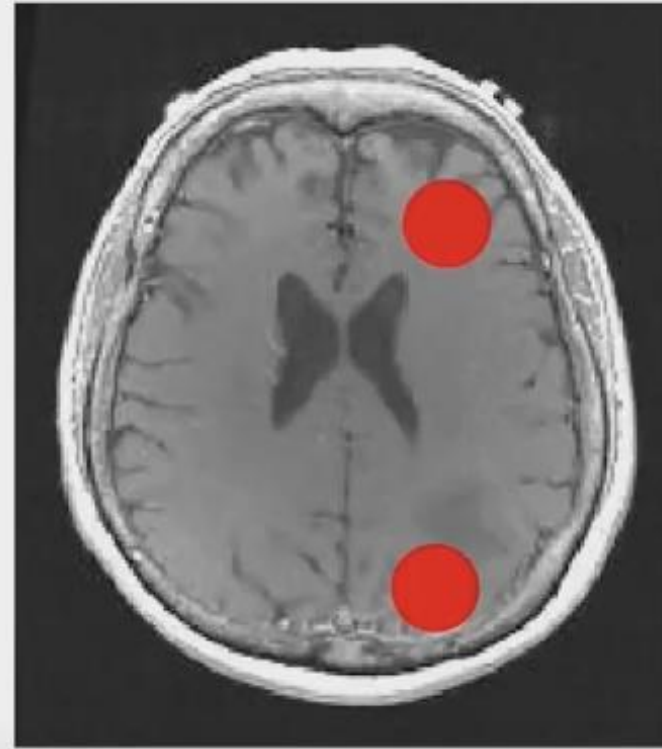
Radiocirurgia isolada

- 5 estudos randomizados comparando SRS/FSRS vs WBRT + SRS/FSRS
- SRS isolada deve ser oferecida para pacientes com 1-4 metástases cerebrais (< 4cm)
 - Sem diferença em SG quando comparada a WBRT
 - SRS vs WBRT (sem estratégias de radioproteção): menor deterioração cognitiva
 - WBRT: maior controle intracraniano

Controvérsia: Número ou volume?



10 mets x 1 cm = **5 cc**



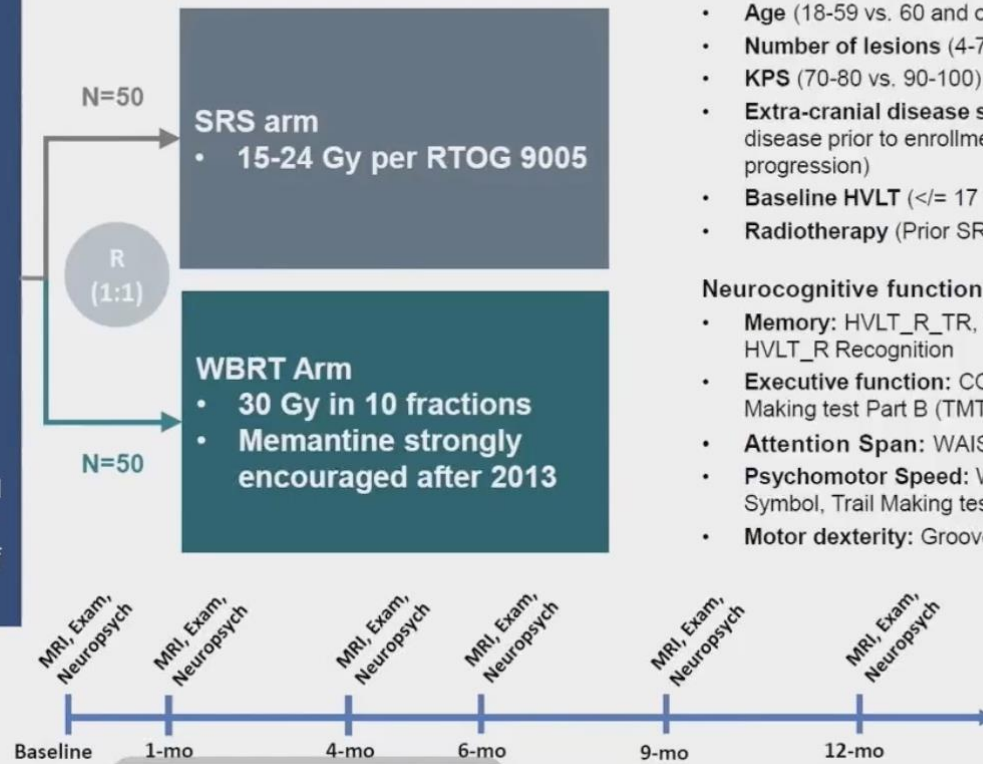
2 mets x 2cm = **8.4 cc**

SRS vs WBRT em 4-15 lesões: Estudo fase III

Trial Design (Schema)

Key Eligibility Criteria:

- Adult patient with 4-15 untreated brain mets confirmed by neuroradiology (up to 20 lesions allowed at the time of treatment)
- All lesions amenable to SRS treatment
- KPS \geq 70
- No LMD (radiographic or cytological)
- No prior WBRT
- Prior SRS to 1-3 brain mets with $>$ 6 weeks intervals allowed
- Excluded prior surgical resection of brain mets
- Excluded histology: melanoma, small cell carcinoma, lymphoma/leukemia, or germ cell histology
- Systemic therapy allowed at the discretion of treating oncologist



Stratification factors:

- **Histology** (breast vs. other)
- **Age** (18-59 vs. 60 and over)
- **Number of lesions** (4-7 vs. 8-15)
- **KPS** (70-80 vs. 90-100)
- **Extra-cranial disease status** (progressive disease prior to enrollment vs. no progression)
- **Baseline HVLt** (\leq 17 vs. \geq 28)
- **Radiotherapy** (Prior SRS vs. no prior SRS)

Neurocognitive function tests:

- **Memory:** HVLt_R_TR, HVLt_R_DR, HVLt_R Recognition
- **Executive function:** COWA, and Trail Making test Part B (TMTB)
- **Attention Span:** WAIS-III Digit Span
- **Psychomotor Speed:** WAIS-III Digit Symbol, Trail Making test Part A (TMTA)
- **Motor dexterity:** Grooved Pegboard

Primary Endpoints

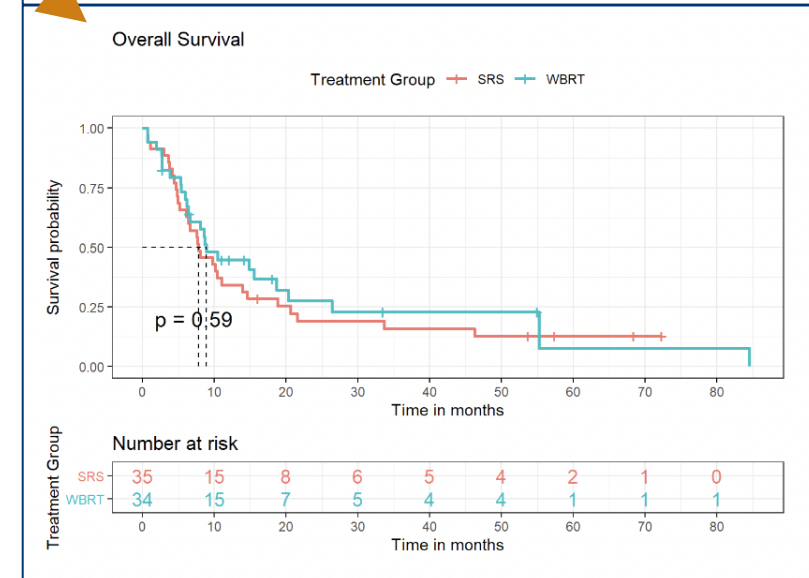
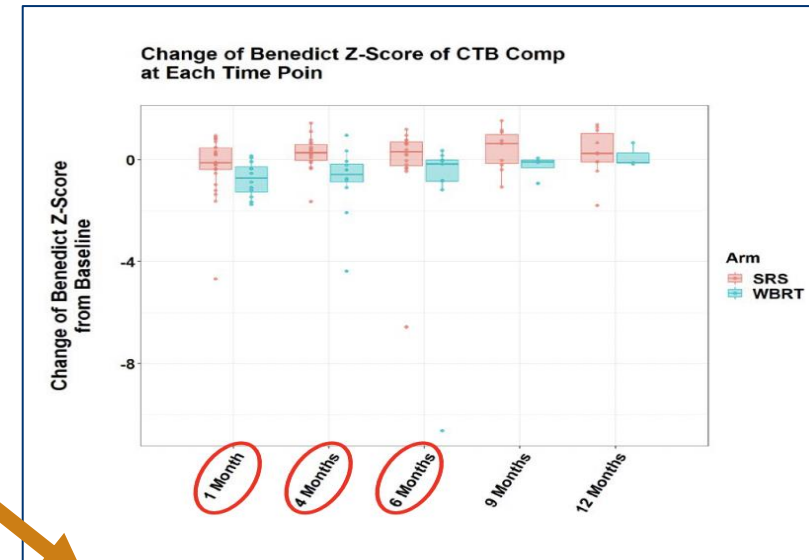
- Memory function at 4 mo (HVLt_R_TR)
- Local control at 4 mo

SRS vs WBRT em 4-15 lesões: Estudo fase III

- 6 Scores avaliados: Mean Z-score from HVLT_R_TR, HVLT_R_DR, HVLT_R Rec, COWA, TMTA e TMTB

Melhor desfecho cognitivo no score combinado com SRS

Follow up Time Point	SRS	WBRT	p
1-mo (median [IQR])	-0.12 [-0.38, 0.47]	-0.71 [-1.26, -0.28]	0.024
4-mo (median [IQR])	0.28 [-0.03, 0.60]	-0.57 [-0.88, -0.17]	0.004
6-mo (median [IQR])	0.31 [-0.23, 0.70]	-0.16 [-0.84, -0.01]	0.027
9-mo (median [IQR])	0.64 [-0.16, 1.00]	-0.08 [-0.32, -0.01]	0.153
12-mo (median [IQR])	0.25 [-0.09, 1.03]	-0.12 [-0.14, 0.27]	0.823



TOXICIDADE

- **Radionecrose:** depende do volume de tratamento, volume de parênquima cerebral sadio que recebem SRS e se dose única/fracionada
- Dose única: V12
 - Risco de radionecrose 10-25%
- Taxas de radionecrose + ICI parecem similares a SRS isolada- Aguardar estudos prospectivos
- Timing/sequência de tratamento também não parece impactar na toxicidade

SRS e Imunoterapia

Table 1. Table of Ongoing Prospective Trials With ICI and Concurrent SRS in Brain Metastases

Trial	Phase	NCT	Condition	Arm(s)	Primary End-point	Enrollment	Status
Durvalumab (MEDI4736) and radiosurgery (fSRT vs PULSAR) for the treatment of nonsmall cell lung cancer brain metastases	II	NCT04889066	NSCLC	Durvalumab + standard fSRS (three fractions every other day) vs durvalumab + PULSAR (3 fractions every 4 weeks)	Intracranial clinical benefit (CR, PR, or SD by brain-modified RECIST)	46 (estimated)	Active, not yet recruiting
Radiosurgery dose reduction for brain metastases on immunotherapy (RADREMI): a prospective pilot study (RADREMI)	I	NCT04047602	1-10 BMs with biopsy-confirmed primary	Dose reduced SRS based on tumor size concurrent with standard of care ICI	Symptomatic RN	42 (estimated)	Active, recruiting
Single vs multi-fraction SRS patients on immunotherapy (MIGRAINE)	II	NCT04427228	1-10 BMs with biopsy-confirmed primary	Three fraction SRS (27 Gy) vs single-fraction SRS (18–20 Gy)	Rate of RN	74 (estimated)	Active, recruiting
Anti-PD-1 brain collaboration + radiotherapy extension (ABC-X Study) (ABC-X)	II	NCT03340129	Melanoma	Nivolumab + ipilimumab vs nivolumab + ipilimumab with concurrent SRS	Neurological-specific cause of death	218 (estimated)	Active, recruiting
Comparing single vs multiple dose radiation for cancer patients with brain metastasis and receiving immunotherapy (HYPOGRYPHE)	III	NCT05703269	NSCLC, Renal cell carcinoma, breast Carcinoma, Melanoma, NSCLC	Single-fraction SRS vs fSRS over 3-5 treatments	Grade 2+ adverse events	244 (estimated)	Active, recruiting
Stereotactic radiosurgery and immune checkpoint inhibitors With NovoTTF-100M for the treatment of melanoma brain metastases	I	NCT05341349	Melanoma	SRS + pembrolizumab + TTFs vs SRS + nivolumab + ipilimumab + TTFs	Grade 3 + CNS toxicity	10 (estimated)	Active, recruiting

fSRS: fractionated stereotactic radiosurgery; PULSAR: personalized ultra-fractionated stereotactic adaptive radiotherapy; RN: radionecrosis; TTFs: tumor treatment fields.

Radioterapia de Cérebro total (WBRT)

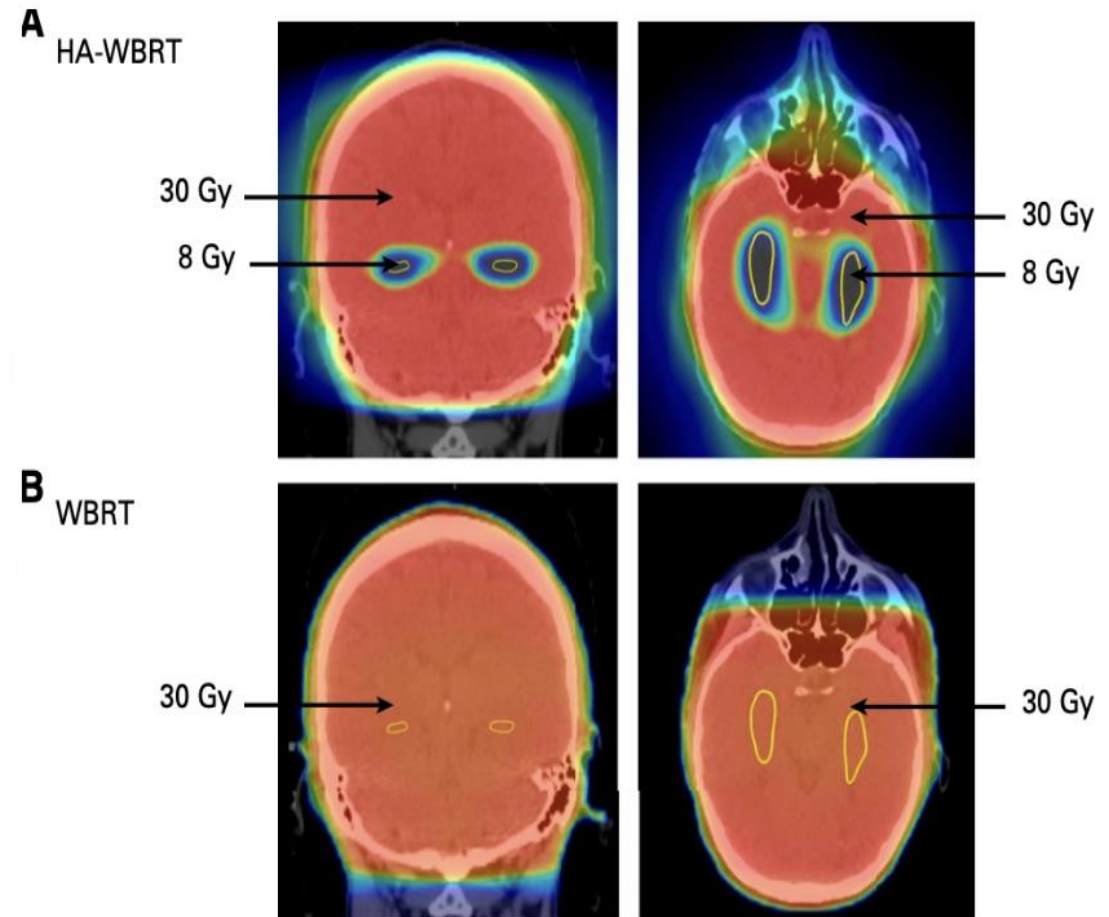
- WBRT já foi o tratamento padrão
- Capacidade de controlar lesões visíveis e microscópicas, melhora os sintomas
- EFEITOS COLATERAIS
 - Fadiga
 - Dificuldade de aprendizado e memória

WBRT + Memantina

- *N*-methyl-d-aspartate (NMDA) é um receptor ativado pelo glutamato
 - Envolvido na memória e aprendizado
 - Se super estimulado: morte neuronal (RT)
- MEMANTINA: agonista receptor NMDA
- RTOG 0614: WBRT vs WBRT + Memantina
 - Tendência a um menor declínio de HVL (p=0.059)

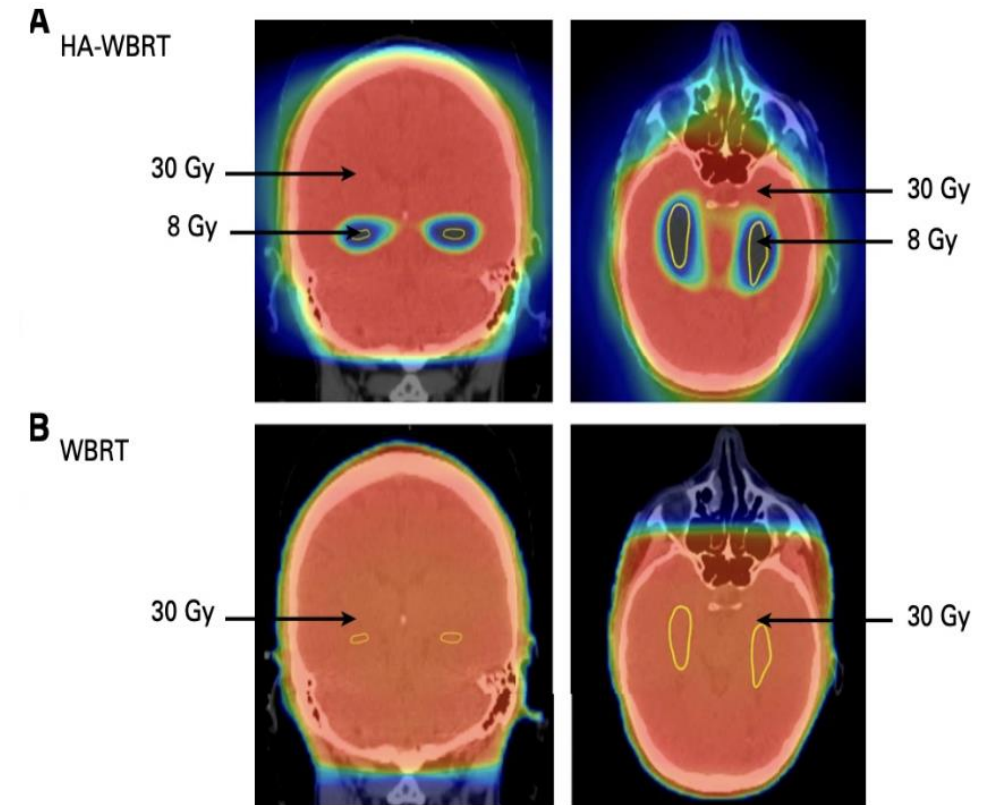
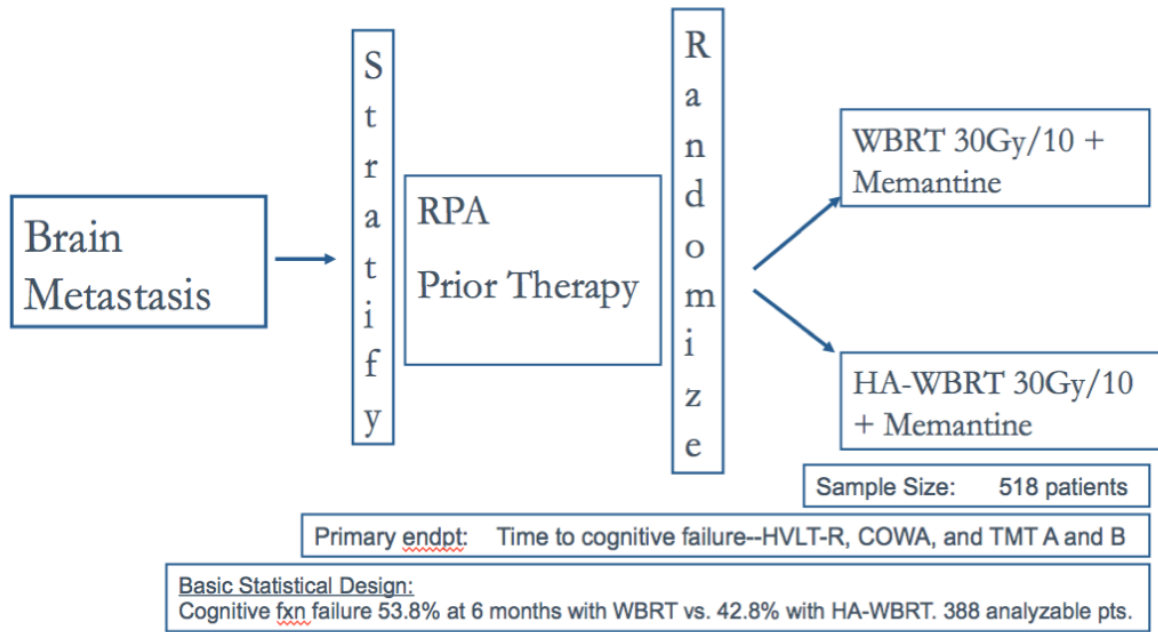
WBRT + Proteção de Hipocampo

- Stem cells no hipocampo são responsáveis pela formação da memória recente
- **RTOG 0933**
 - Estudo fase II
 - HA-WBRT melhorou os desfechos cognitivos quando comparados a controle histórico (7% vs 30%)

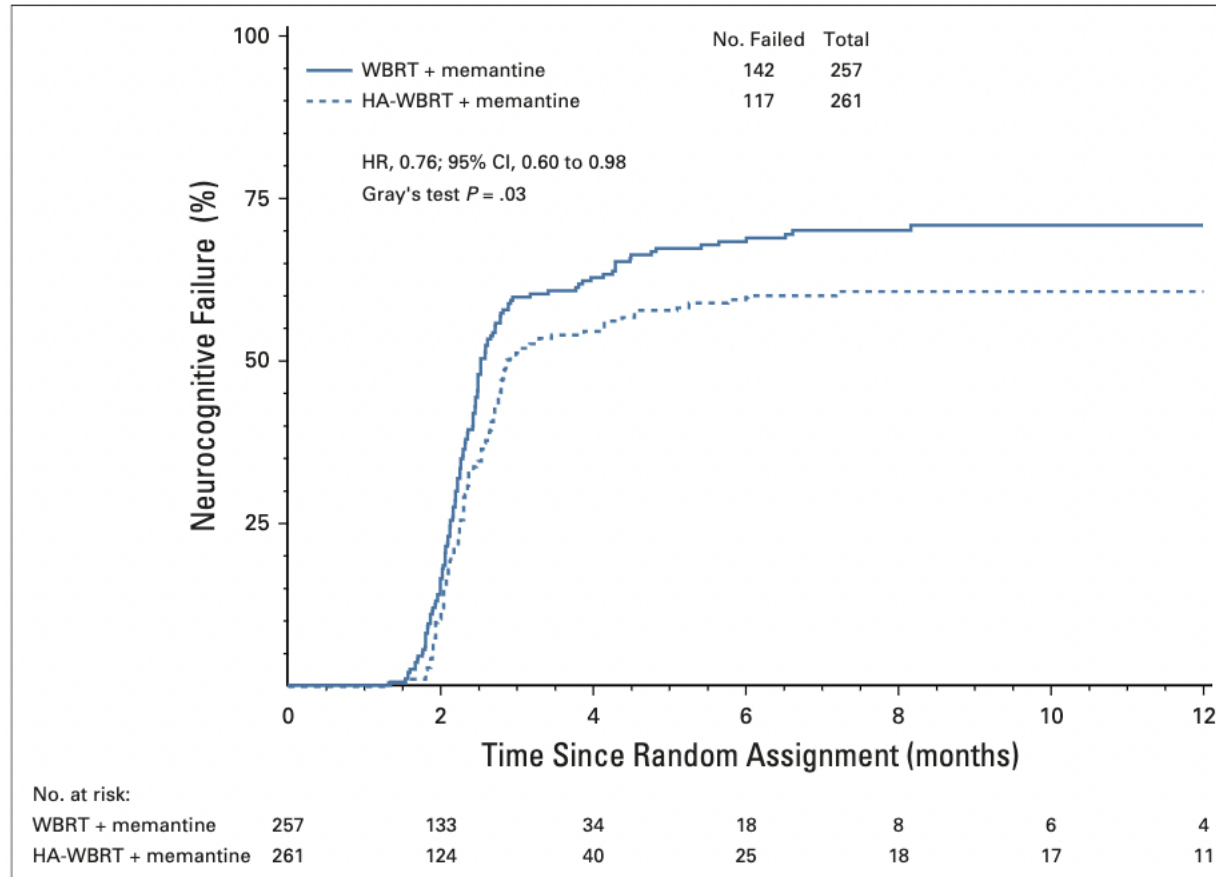


NRG-CC-001

Basic Eligibility: Brain Mets 5mm outside hippocampus; KPS \geq 70; MRI scan



NRG-CC-001



ASCO special articles

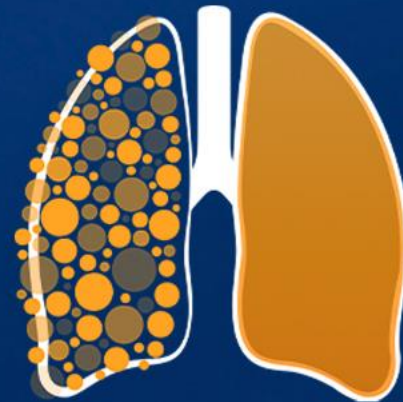
Treatment for Brain Metastases: ASCO-SNO-ASTRO Guideline

Michael A. Vogelbaum, MD, PhD¹; Paul D. Brown, MD²; Hans Messersmith, MPH³; Priscilla K. Brastianos, MD⁴; Stuart Burri, MD⁵; Dan Cahill, MD, PhD⁴; Ian F. Dunn, MD⁶; Laurie E. Gaspar, MD, MBA^{7,8}; Na Tosha N. Gatson, MD, PhD^{9,10}; Vinai Gondi, MD¹¹; Justin T. Jordan, MD⁴; Andrew B. Lassman, MD¹²; Julia Maues, MA¹³; Nimish Mohile, MD¹⁴; Navid Redjal, MD¹⁵; Glen Stevens, DO, PhD¹⁶; Erik Sulman, MD, PhD¹⁷; Martin van den Bent, MD¹⁸; H. James Wallace, MD¹⁹; Jeffrey S. Weinberg, MD²⁰; Gelareh Zadeh, MD, PhD²¹; and David Schiff, MD²²

- Memantina e proteção hipocampo devem ser oferecidas aos pacientes que receberão WBRT e não têm lesões a 5mm do hipocampo, com sobrevida esperada de 4 meses ou mais

Conclusões

- Considerar postergar RT em pacientes assintomáticos com mutação drive
- Existe um benefício da combinação de imunoterapia e RT
- SRS oferece excelente controle local no tratamento de metástases cerebrais, sendo padrão para tratamento de até 4 lesões
- Temos dados para realizar radiocirurgia até 15 lesões
- WBRT tem um bom controle tumoral intracraniano as custas de uma piora da função cognitiva
 - Considerar em casos com alto volume ou alta velocidade de aparecimento de metástases cerebrais
 - Considerar poupar hipocampo e utilização de memantina



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2ª JORNADA ONCONNECTION MULTICARE

2024

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GERENCIAMENTO E PRODUÇÃO

