VII SIMPÓSIO INTERNACIONAL DE Melanoma

HOTEL PULLMAN VILA OLÍMPIA

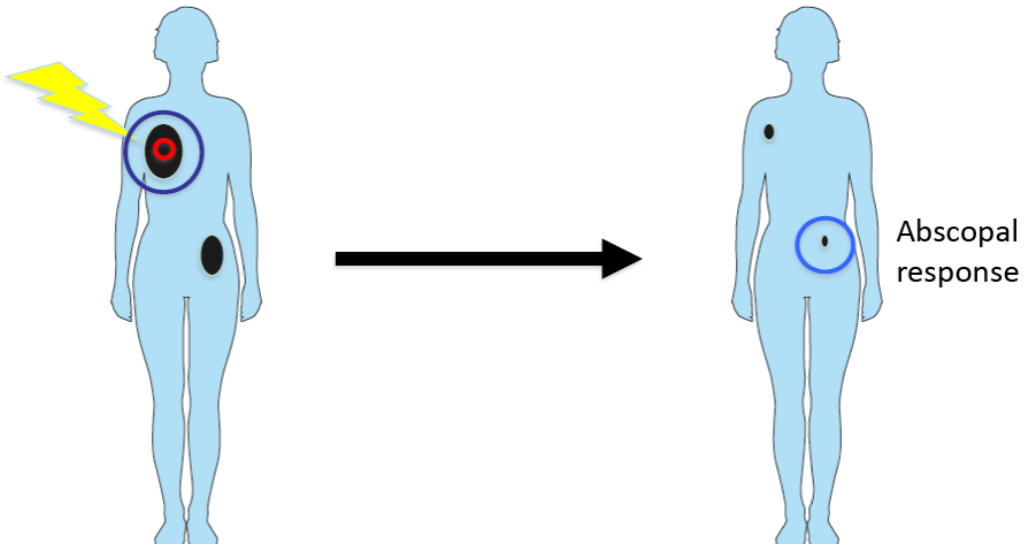
29 E 30 DE NOVEMBRO 2019

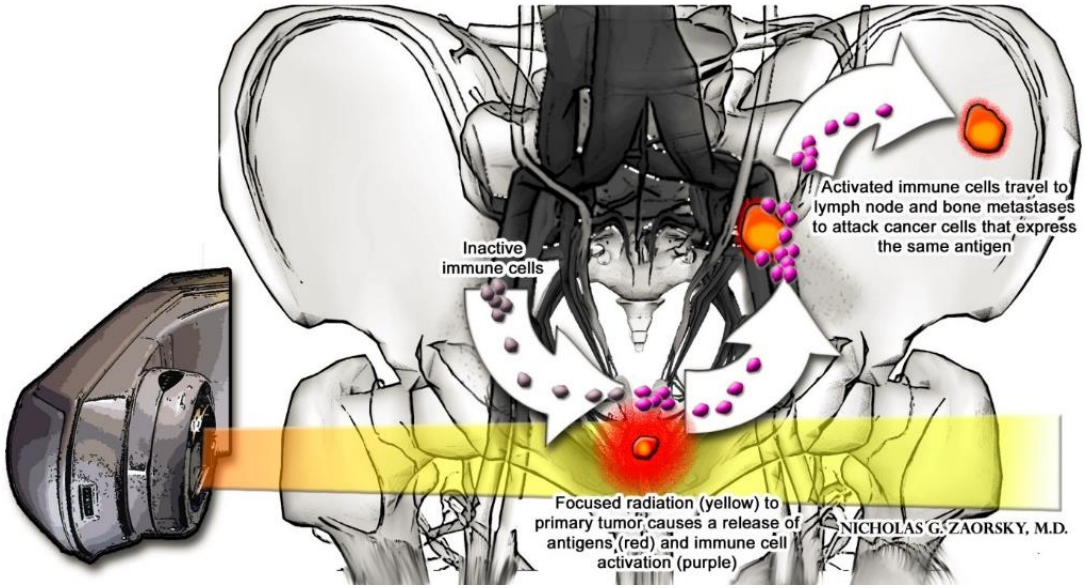
EFEITO ABSCOPAL
Podemos contar com ele?

Erlon Gil

AB = away from e SCOPUS = target

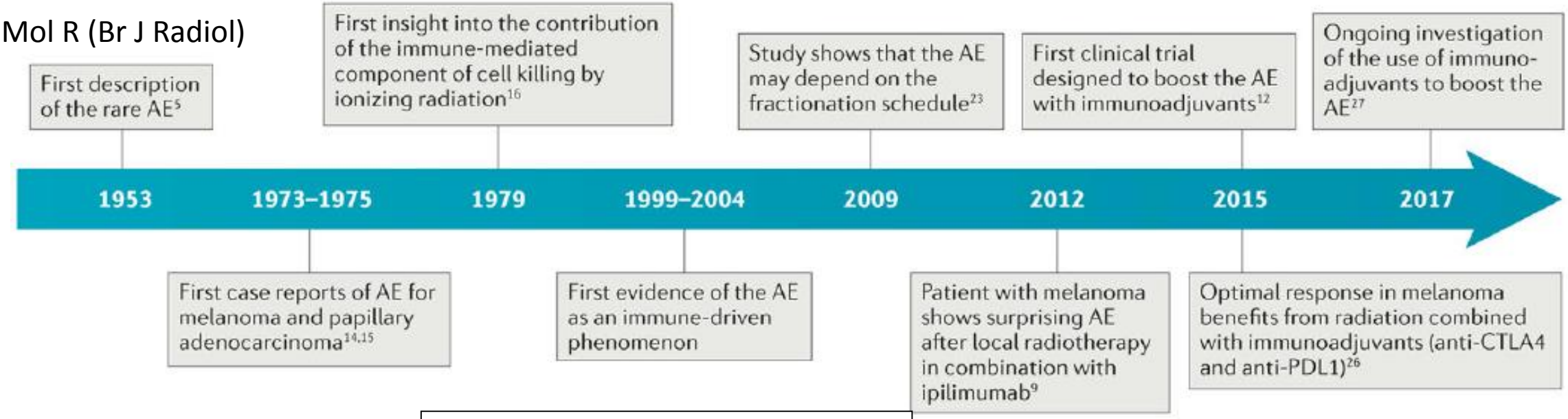
Efeito da radiação que é manifestada em sítio distante do que foi diretamente irradiado

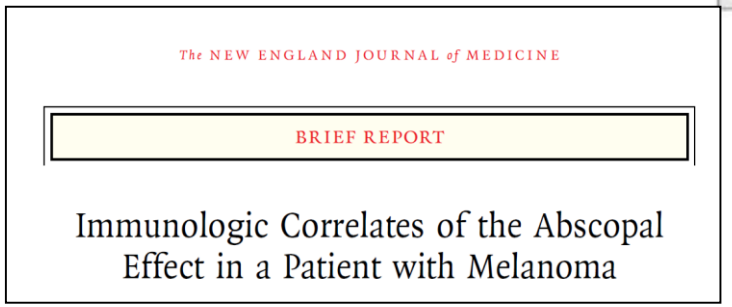




Histórico

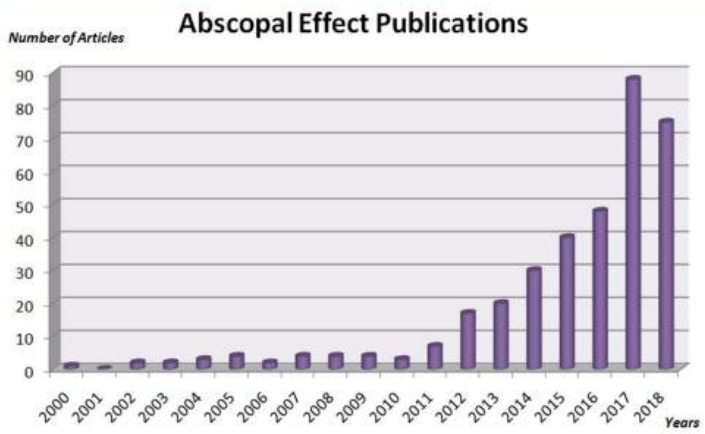
*Mol R (Br J Radiol)

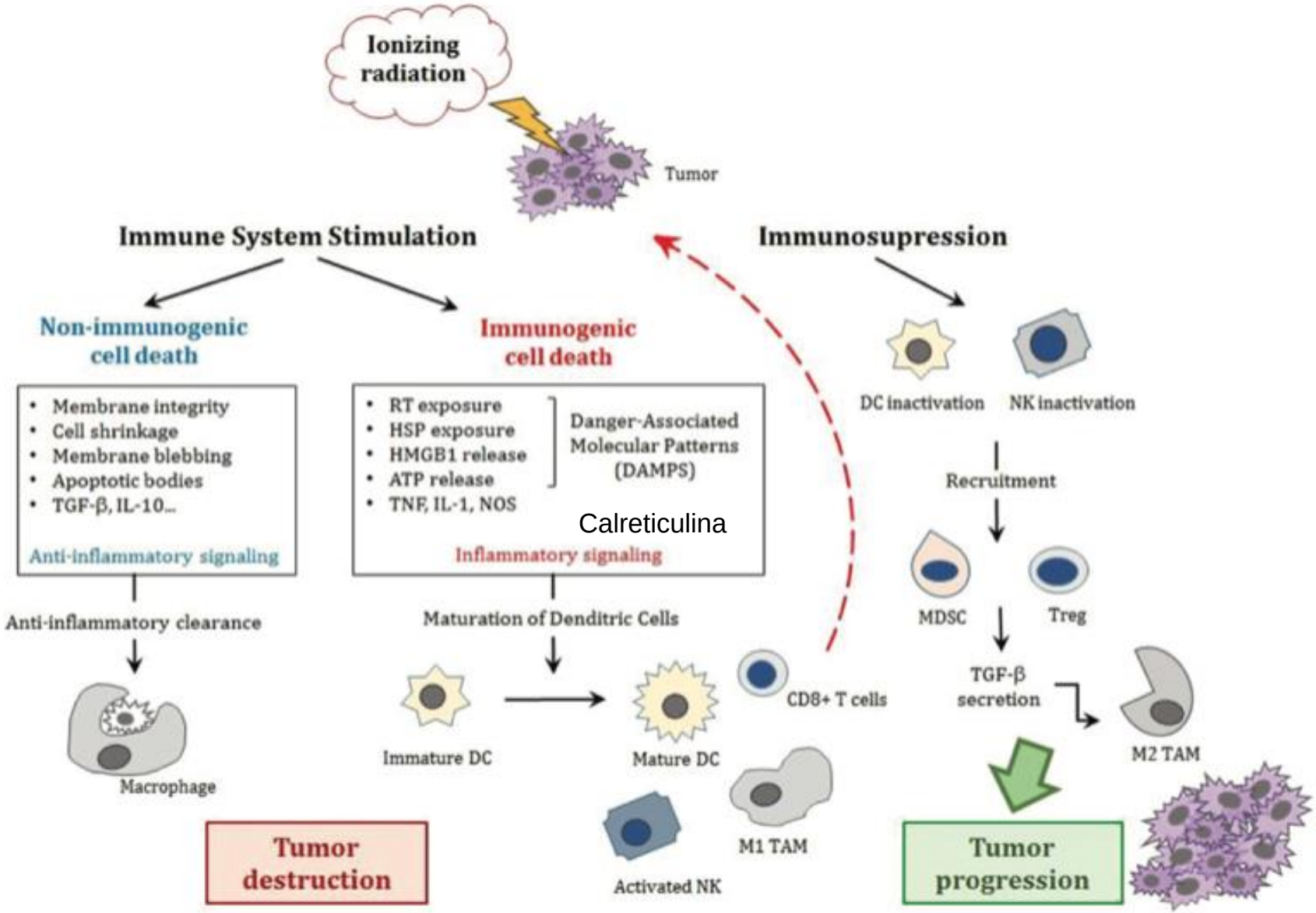


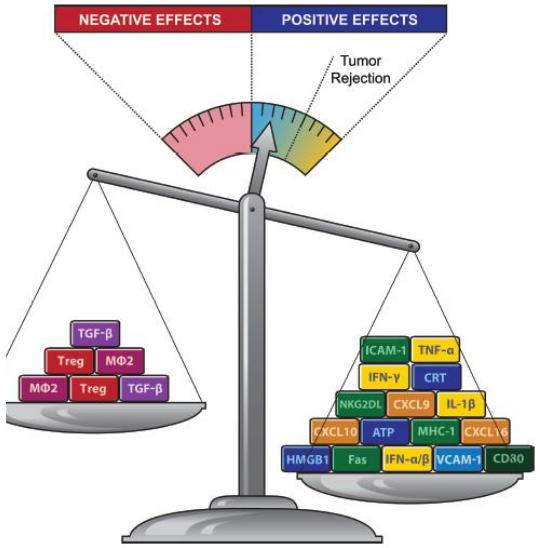

The NEW ENGLAND JOURNAL of MEDICINE

BRIEF REPORT

Immunologic Correlates of the Abscopal Effect in a Patient with Melanoma



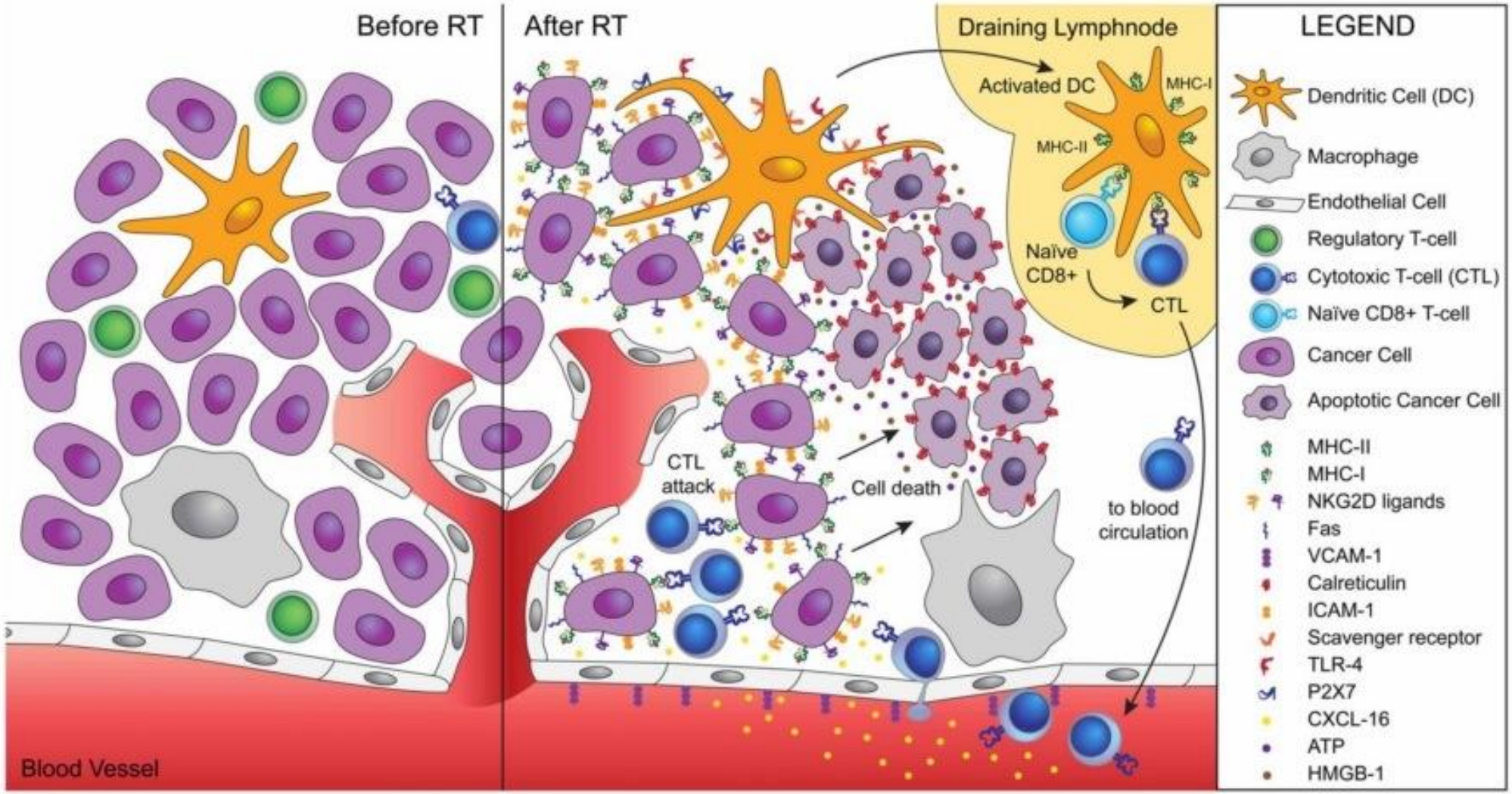




Tipo de tecido e histologia dependente

Formenti S, J Natl Cancer Inst 2013
Carvalho HA et al, Clinics 2018

Radioterapia e Micro ambiente Tumoral



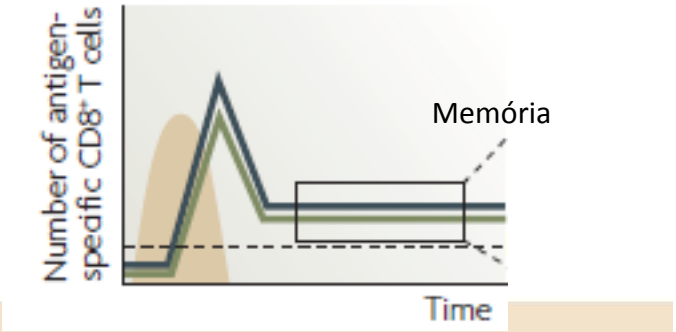
Radioterapia e Efeito Abscopal

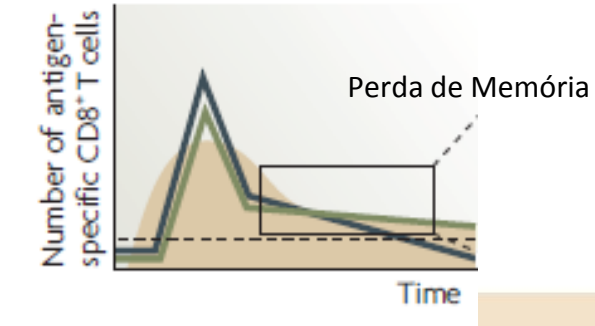
Evento RARO - 46 casos reportados (1969 – 2014)

1. A Radioterapia por si só não é suficiente para vencer os efeitos imunossupressores no microambiente tumoral

2. Alta concentração de células T funcionais

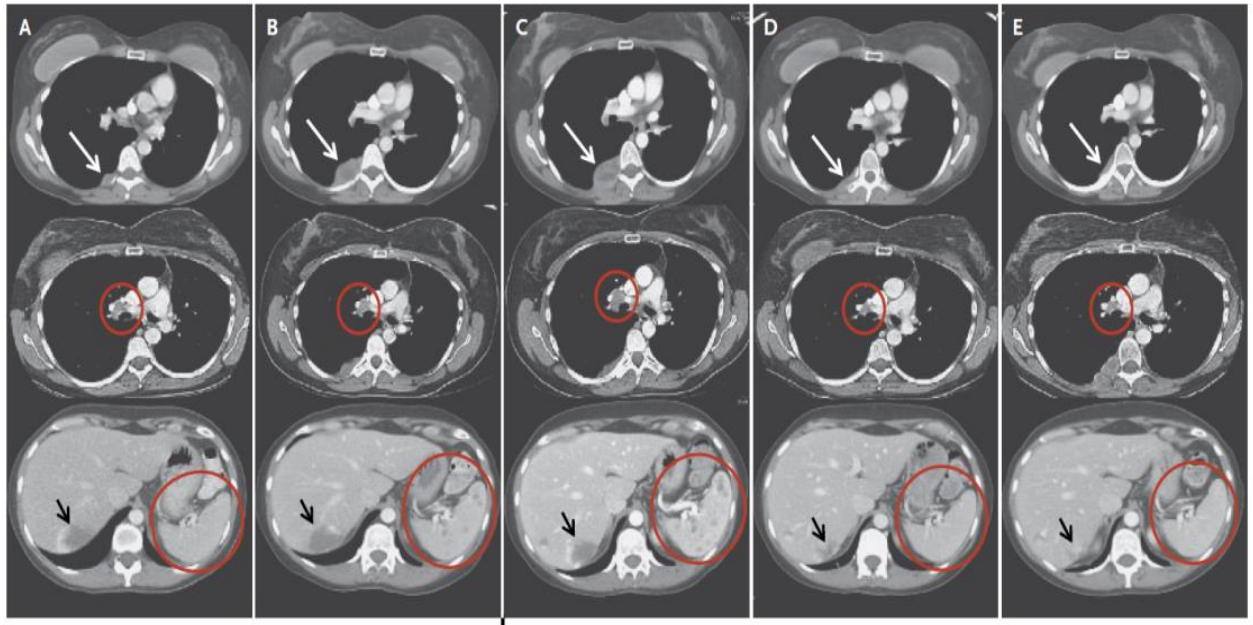
3.Persistência da exposição de antígenos pode levar a exaustão de células T

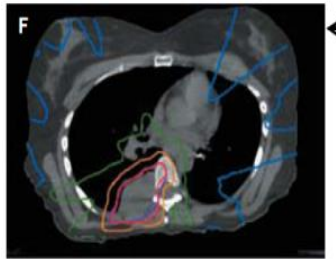




Nature Rev Immunol 2008

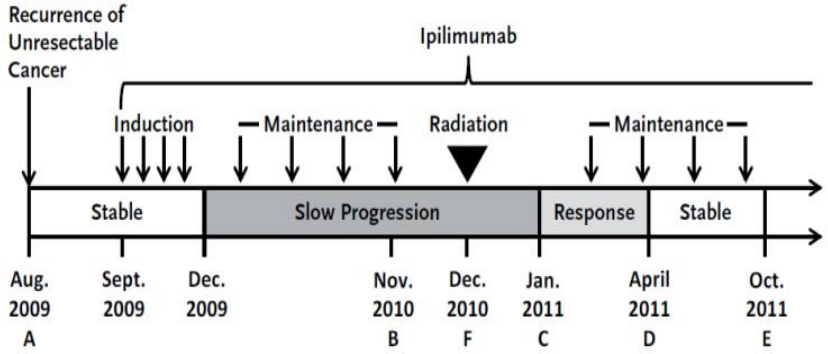
Radioterapia e Inibidores de Check Points





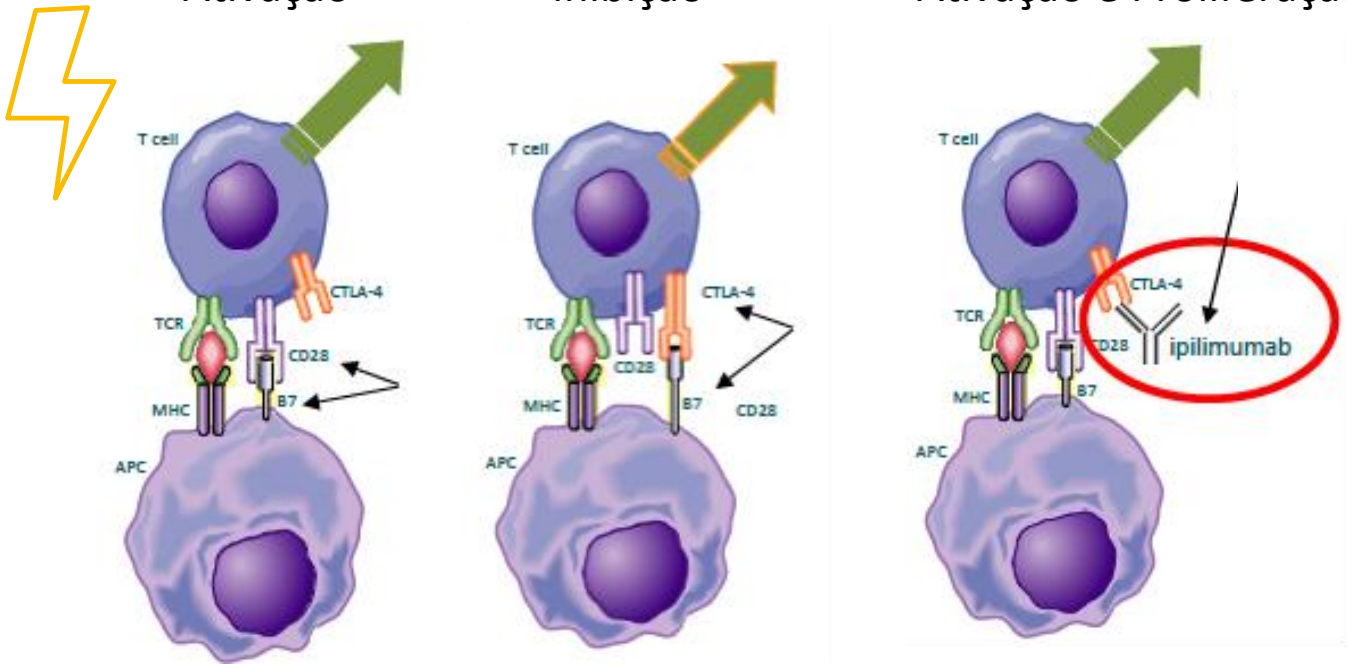
December 2010

3 x 9,5 Gy

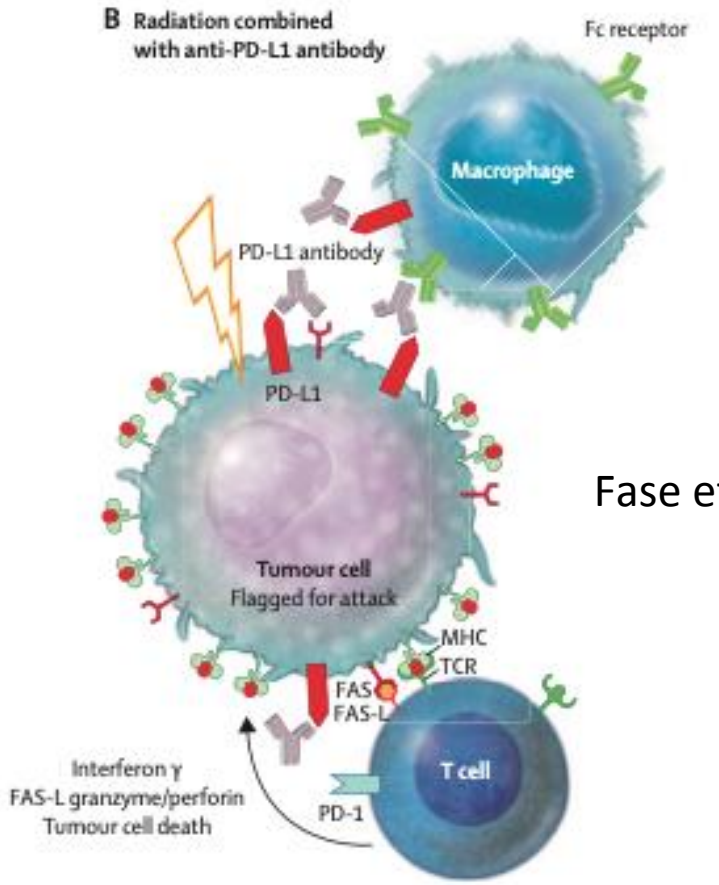


Postow M et al N Engl J Med 2012

Radioterapia e Inibidores de Check Points



Anti CTLA-4



Fase efetora

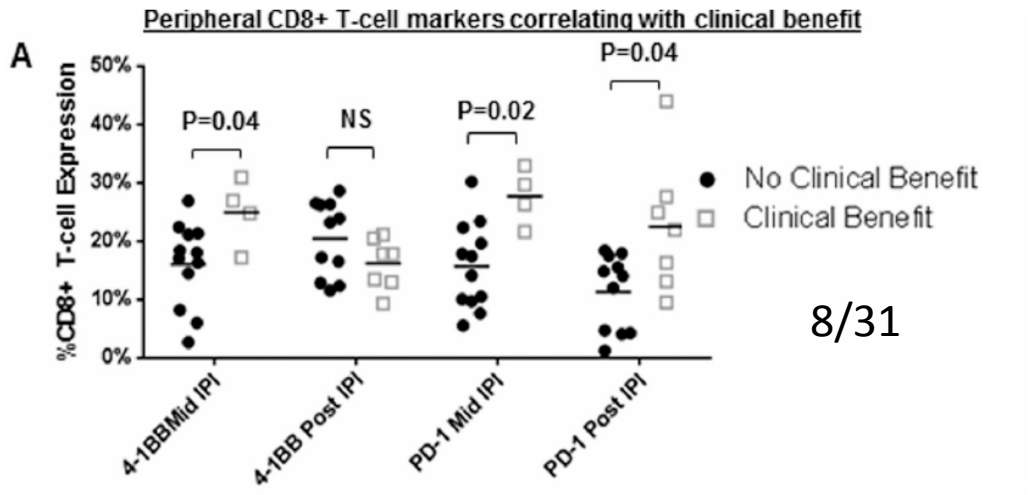
Anti PDL1

??????.....

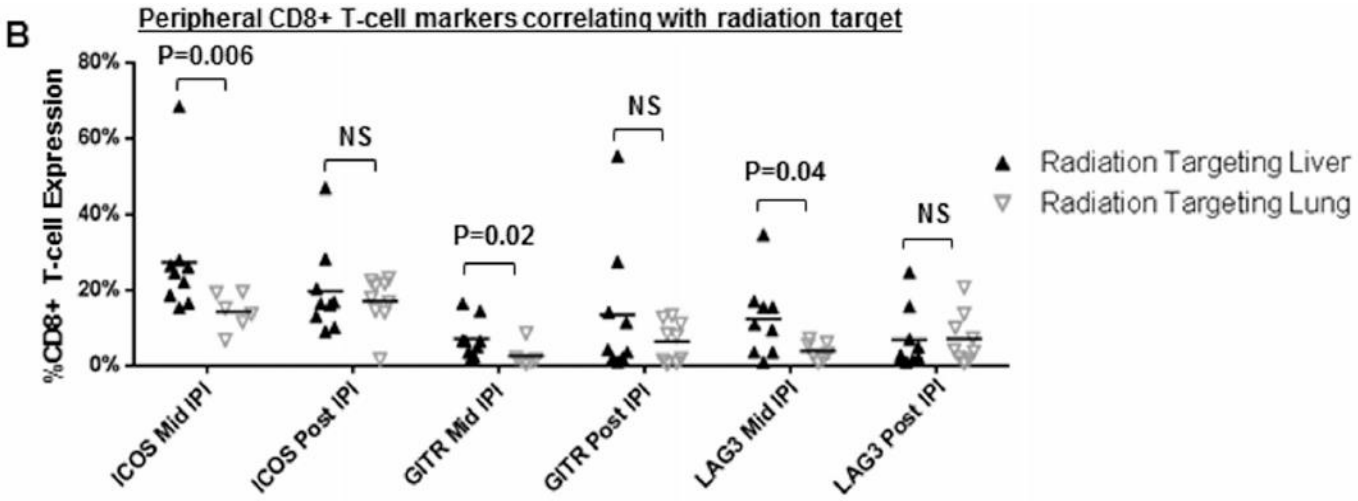
- Sitio metastático a ser irradiado ?
- Dose e fracionamento da Radioterapia ?
- Sequencia da Radio/imunoterapia ?
- Seleção de pacientes/biomarcadores ?

Sitio Metastático

Radioterapia (5 x 10 Gy) Figado e pulmão + ipilimumab 3mg/kg – 3 sem (4 doses)
Concomitante e sequencial
Resposta fora da área irradiada : ≥ resposta parcial ou estável mantido por 6 meses
Correlação com linfócitos T periféricos

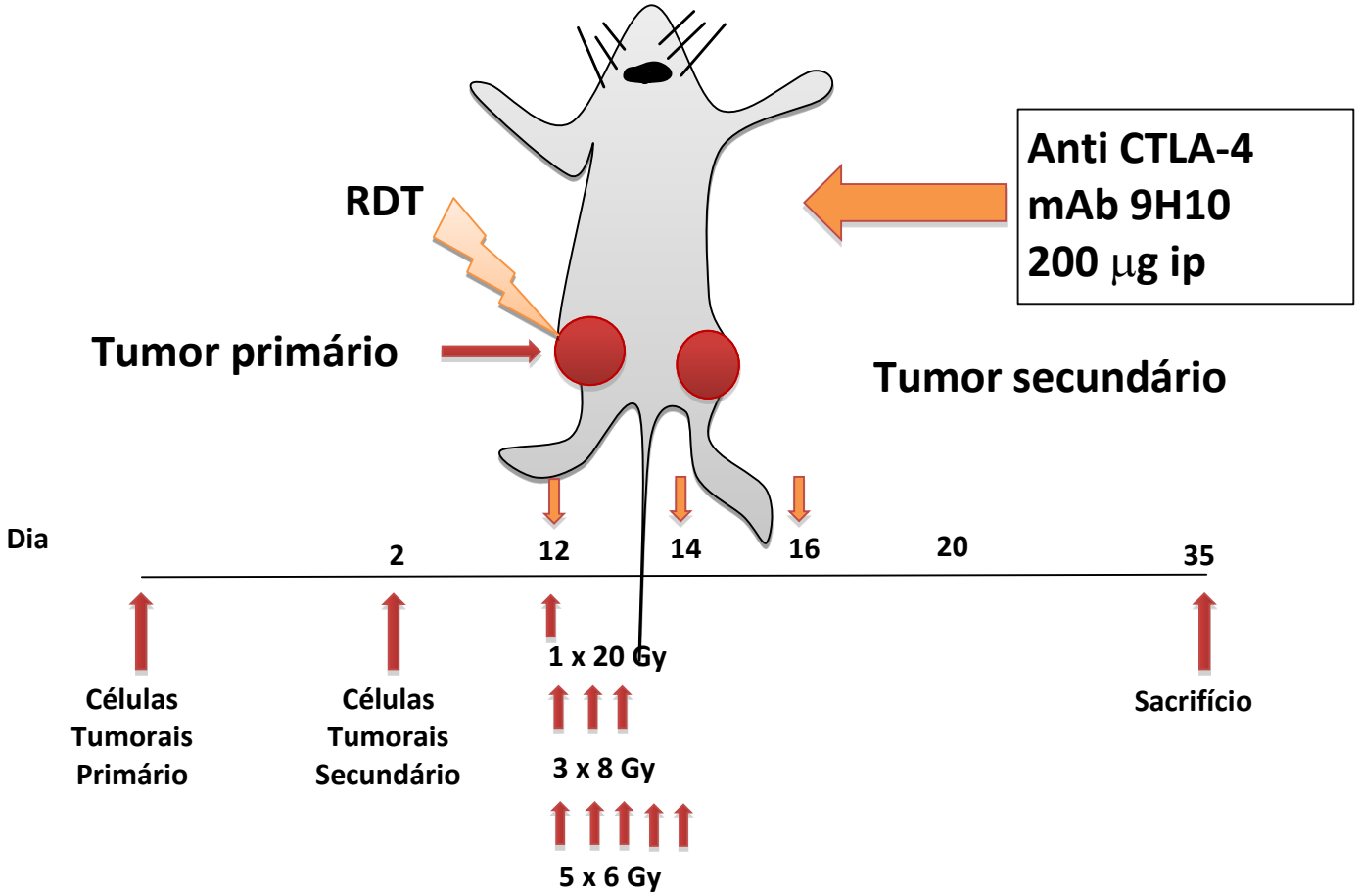


8/31

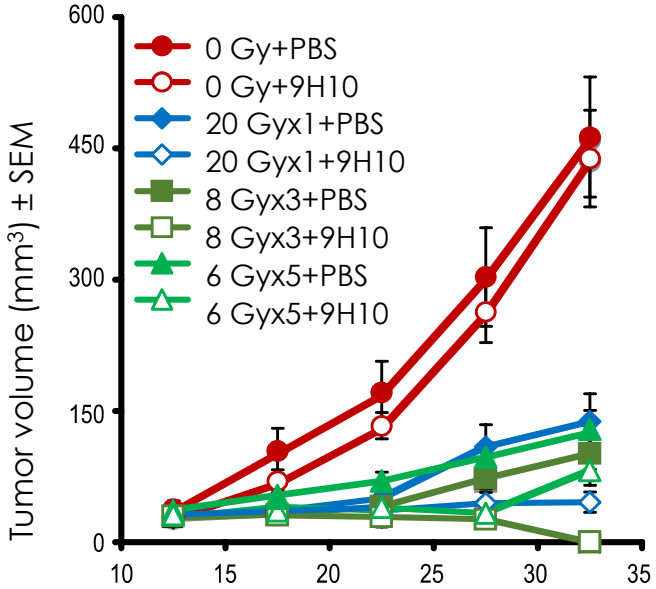


Tang C et al; Clin Cancer Res 2017

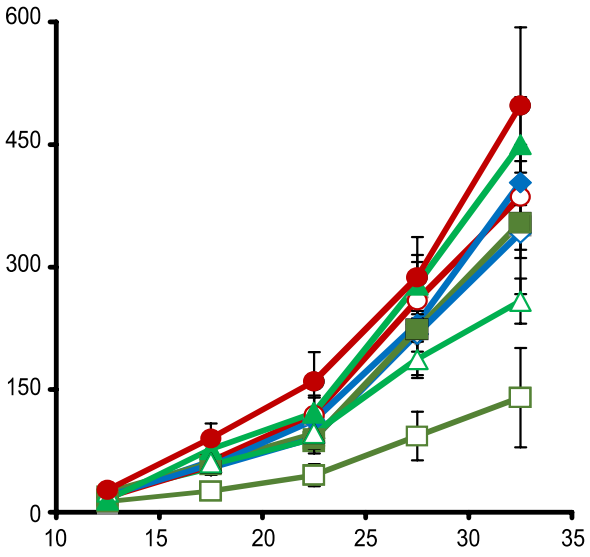
Dose e Fracionamento



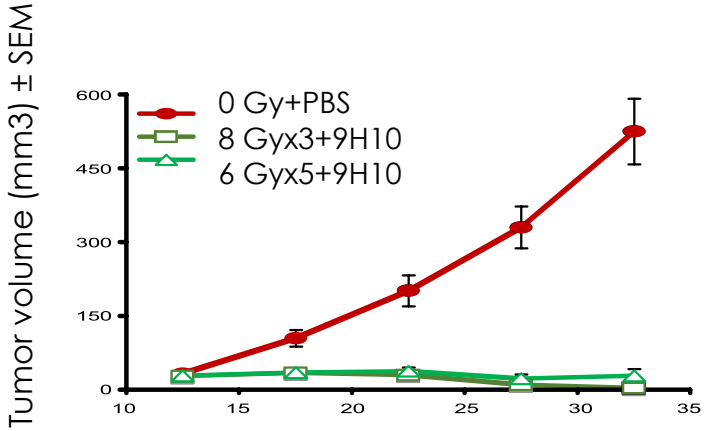
Dewan MZ et al. Clin Cancer Res 2009



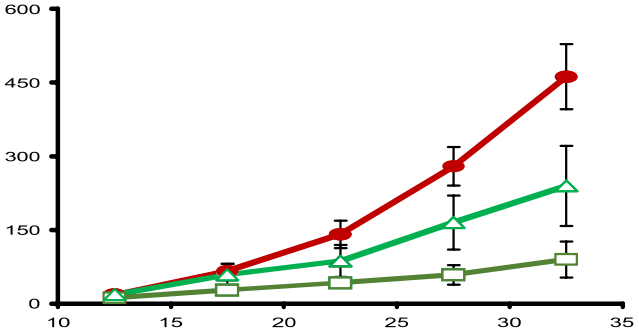
Tumor primário



Tumor secundário



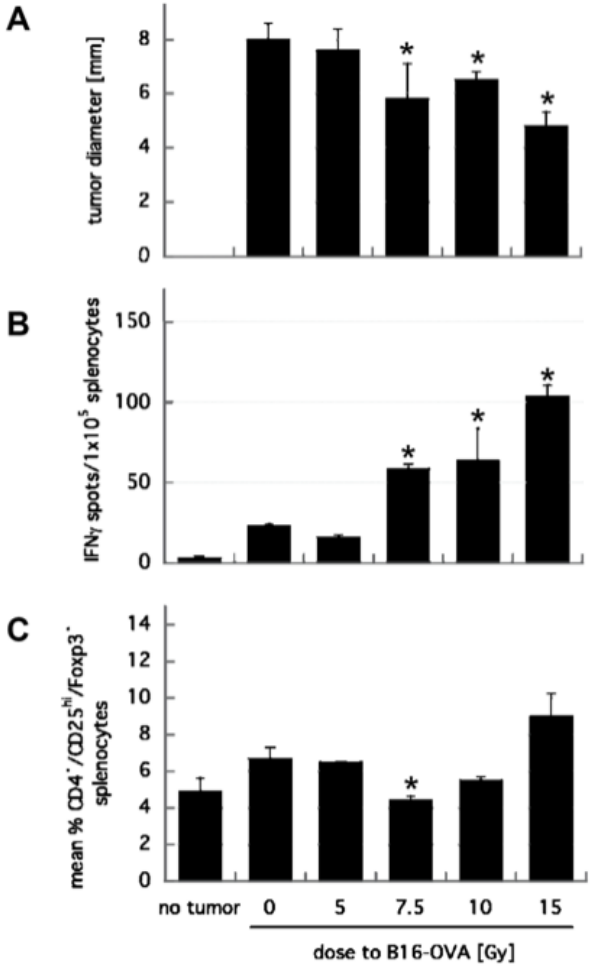
Tumor primário

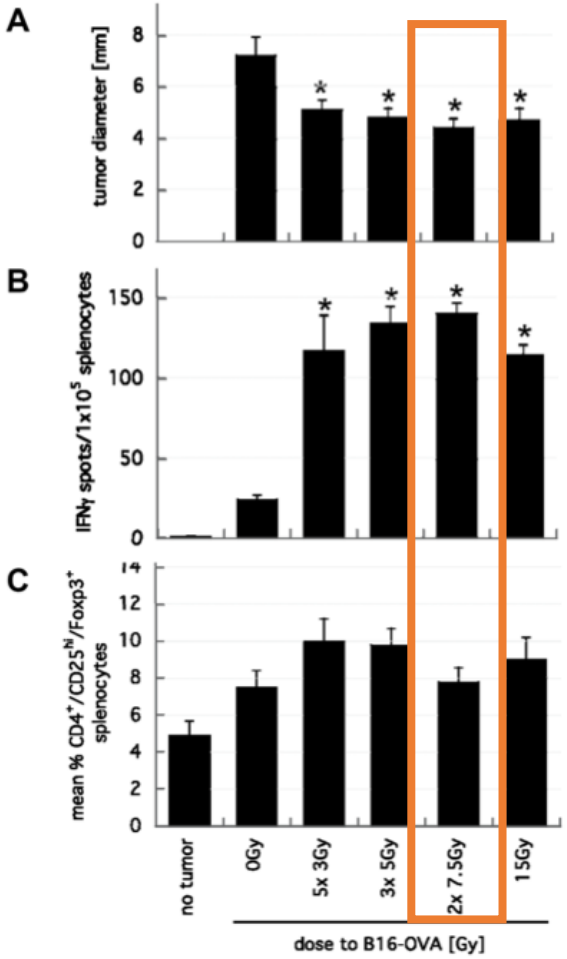


Tumor secundário

Dewan MZ et al. Clin Cancer Res 2009

Dose e Fracionamento





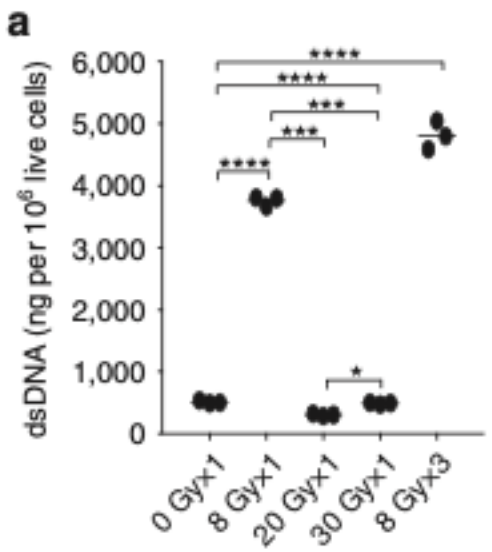
Melanoma em murinos

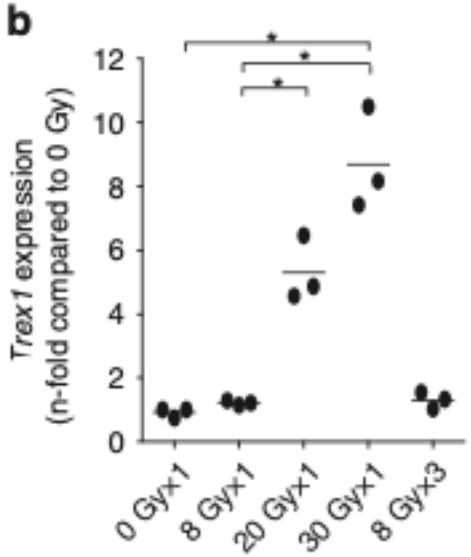
Controle tumoral aumenta de acordo com o aumento da dose, assim como o numero de linfócitos T reativos ao tumor e também o numero de linfócitos T reguladores (Treg)

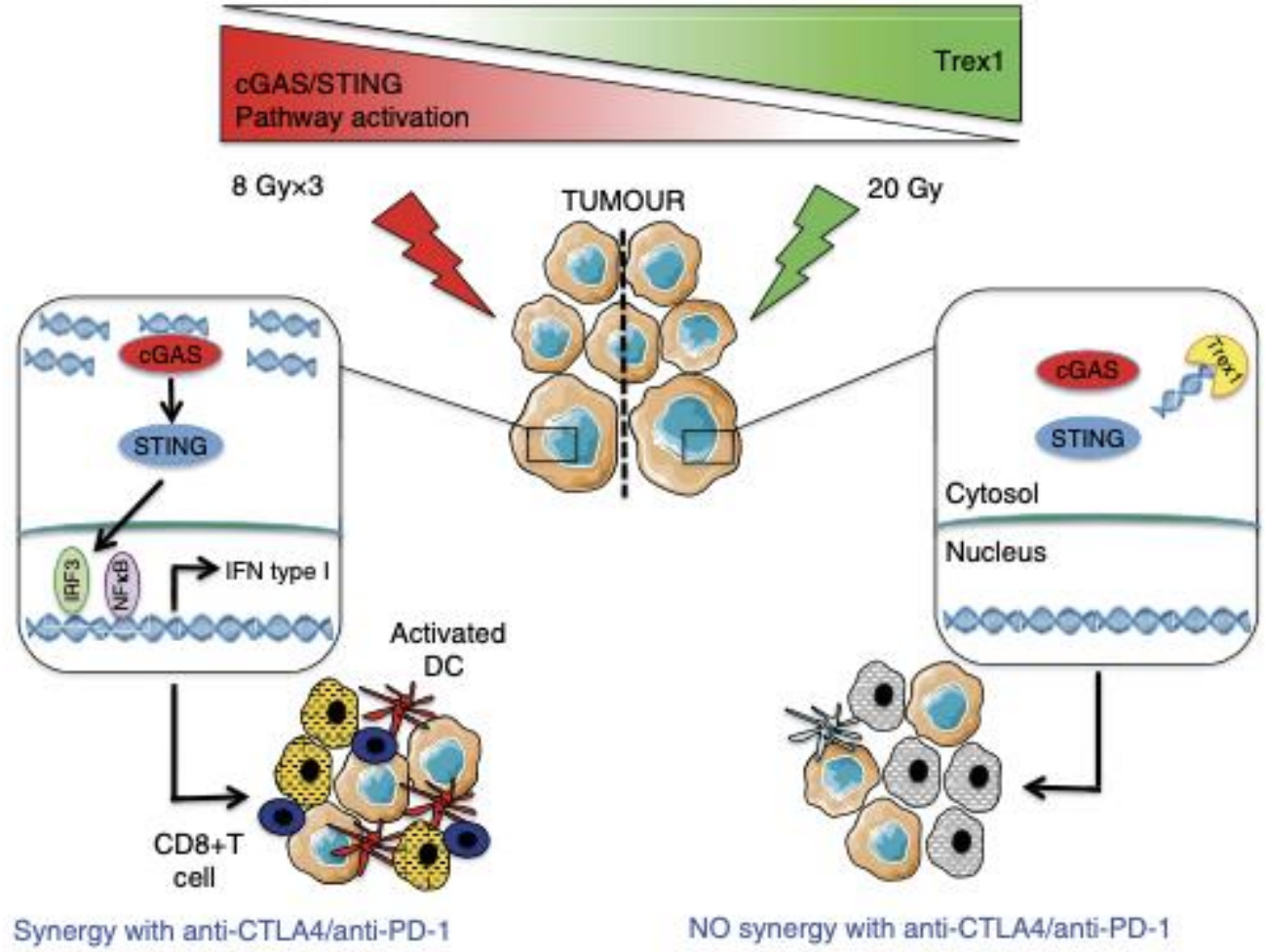
Tratamento fracionado com dose de 7,5 Gy promove melhor controle tumoral, assim como menor numero de Linfócitos Treg

Shaue D et al IJROBP 2012

Dose e Fracionamento







Vanpouille-Box C, Nat Commun 2017

Sequencia Radioterapia/Imuno

Radioterapia antes…
Preparação imunológica mais eficaz (mais antígeno tumoral é liberado durante a morte celular induzida por radiação)

Radioterapia após…
O sistema imunológico está adaptado para responder ao antígeno liberado pela morte celular induzida por radiação

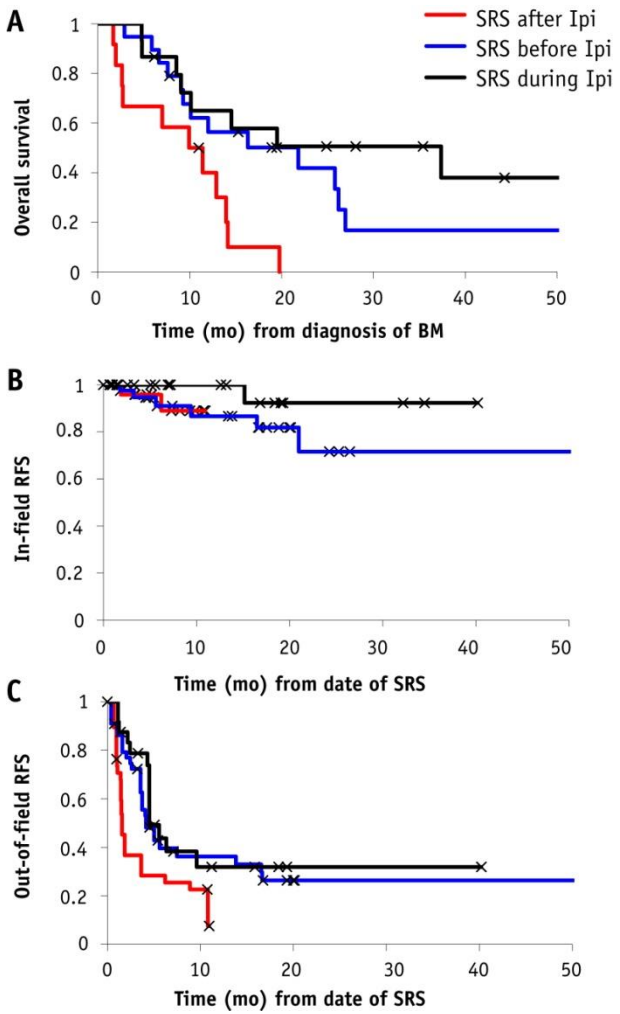
Campbell A et al, Oncology 2018

Anti CTLA-4 - simultaneamente
Anti PDL-1 - logo depois da Radio

46 pacientes com Melanoma
Metástase em SNC
Ipilimumab e Radiocirurgia

15 pacientes concomitante
19 antes
12 após

SG e efeito abscopal associado com o “timing" da associação

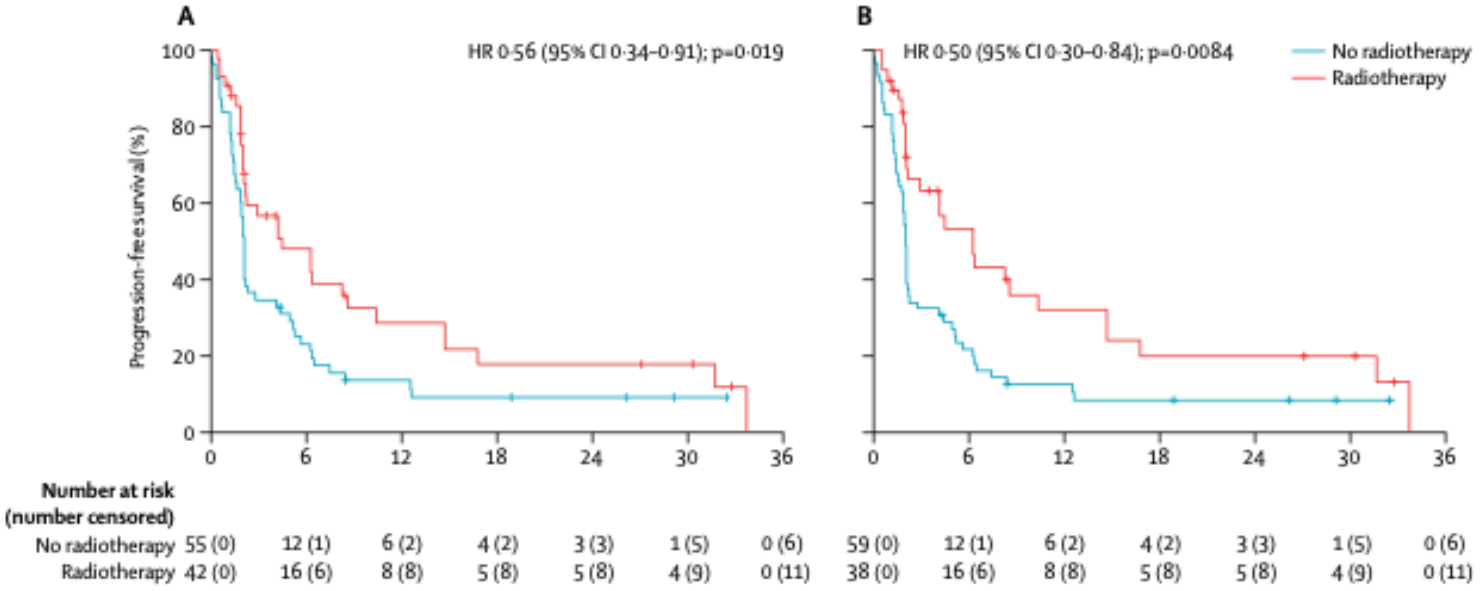


Int J Radiat Oncol Bio Phys 2015

Previous radiotherapy and the clinical activity and toxicity of pembrolizumab in the treatment of non-small-cell lung cancer: a secondary analysis of the KEYNOTE-001 phase 1 trial

Narek Shaverdian*, Aaron E Lisberg*, Krikor Bornazyan, Darlene Veruttipong, Jonathan W Goldman, Silvia C Formenti, Edward B Garon†, Percy Lee†

42 (43%) of 97 pacientes foram submetidos a Radioterapia ANTES do primeiro ciclo de Pembrolizumab



Narek Shaverdian, Lancet Oncol 2017

Biomarcadores

- Satus do p53

Abscopal effect of radiation therapy: interplay between radiation dose and p53 status. Strigari L et al Int; J Radiat Biol. 2014

- Correlação com resposta local/Contagem absoluta de linfócitos prévio a RDT

Abscopal effects of radiotherapy on advanced melanoma patients who progressed after ipilimumab immunotherapy.
Grimald AM et al; Oncoimmunology. 2014

- Expressão da Calreticulina

Calreticulin exposure dictates the immunogenicity of cancer cell death. Obeid M et al; Nat Med. 2007

- Expressão de Trex1

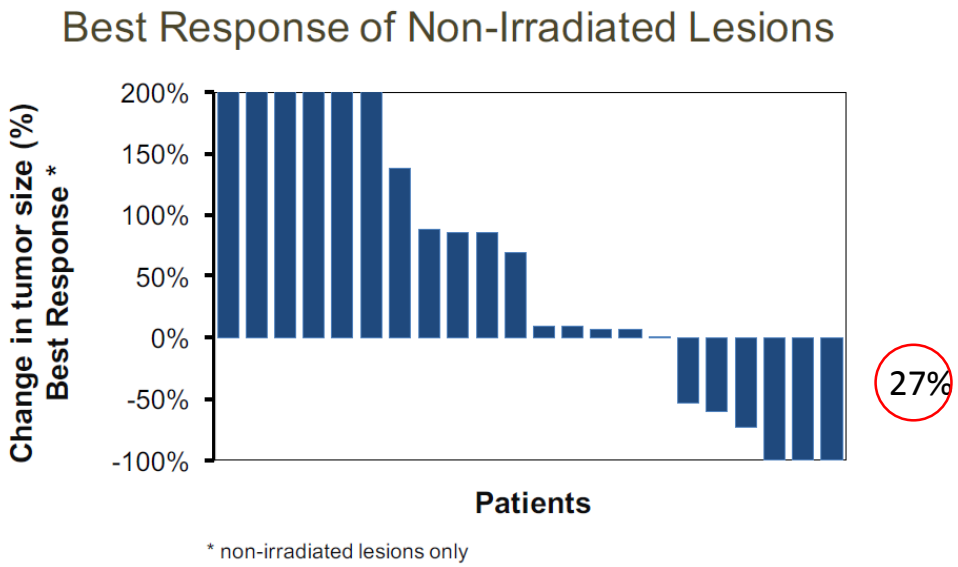
DNA exonuclease Trex1 regulates radiotherapy-induced tumour immunogenicity. Vanpouille-Box C et al; Nat Commun. 2017

- Expressão de PDL-1

Pembrolizumab versus chemotherapy for PD-L1-positive non-small-cell lung cancer. Reck M et al ; N Engl J Med. 2016

A Prospective Clinical Trial Combining Radiation Therapy with Systemic Immunotherapy in Metastatic Melanoma

22 pacientes;
RDT 5 dias após IPI



- 3 (14%) RC – 55 semanas de seguimento médio
- 3 (14%) RP – 40 semanas de seguimento médio

Hiniker SM, Int J Radiat Oncol Biol Phys. 2016

Improved survival and complete response rates in patients with advanced melanoma treated with concurrent ipilimumab and radiotherapy versus ipilimumab alone

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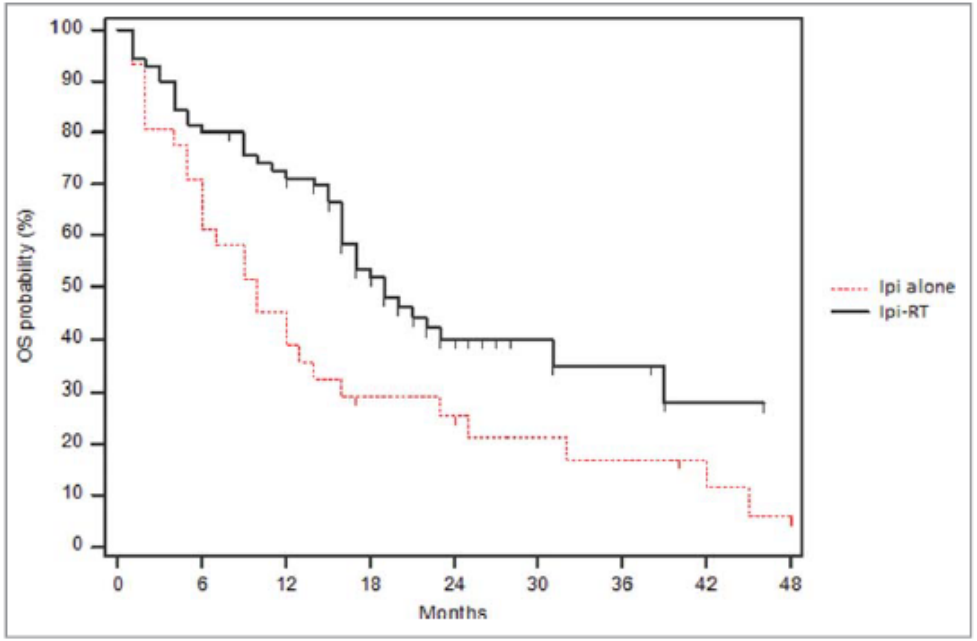
101 pacientes com melanoma metástatico
2011 a 2015 - FU 19 meses
31 Ipi
70 RDT + Ipi

Outcome	Ipilimumab/RT	Ipilimumab alone	p-value
N	70	31	
Median overall survival, months	19	10	0.01*
Progression free survival, months	5	3	0.20
Overall response rate, n (%)	26 (37.1)	6 (19.4)	0.11
Complete response	18 (25.7) 35%	2 (6.5)	0.04*
Partial response	7 (10.0)	3 (9.7)	0.96
Mixed response	1 (1.4)	1 (3.2)	0.56



Koller KM, CANCER BIOLOGY & THERAPY 2017

Combining radiotherapy and ipilimumab induces clinically relevant radiation-induced abscopal effects in metastatic melanoma patients: A systematic review

Rodolfo Chicas-Sett [a,*], Ignacio Morales-Orue [a], Delvys Rodriguez-Abreu [b], Pedro Lara-Jimenez [a]

[a] Department of Radiation Oncology, "Dr. Negrín" University Hospital of Gran Canaria, Barranco de la Ballena s/n, 35010 Las Palmas de Gran Canaria, Spain
[b] Department of Medical Oncology, Insular University Hospital of Gran Canaria, Plaza Doctor Pasteur s/n, 35016 Las Palmas de Gran Canaria, Spain

R. Chicas-Sett et al. / Clinical and Translational Radiation Oncology 9 (2018) 5–11

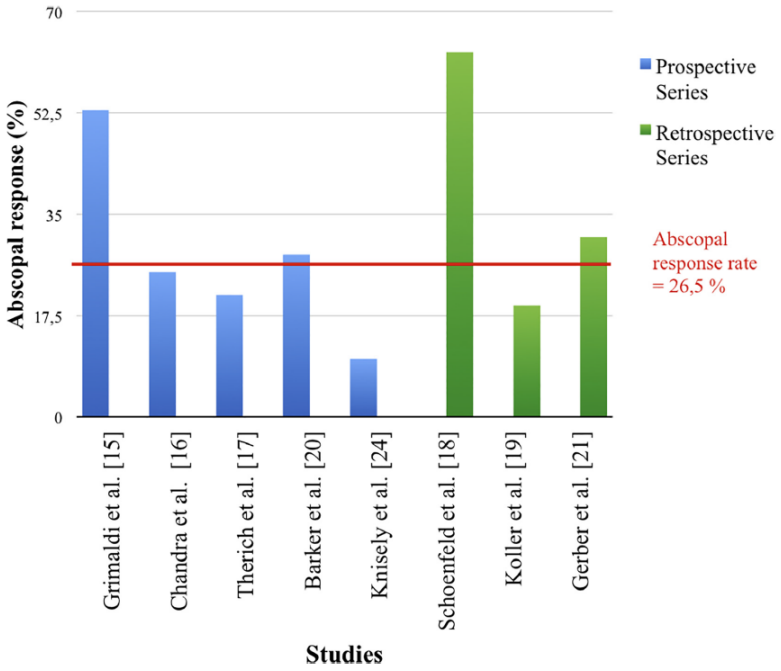


Fig. 2. Prospective and retrospective studies quantifying the abscopal responses.

R. Chicas-Sett et al. / Clinical and Translational Radiation Oncology 9 (2018) 5–11

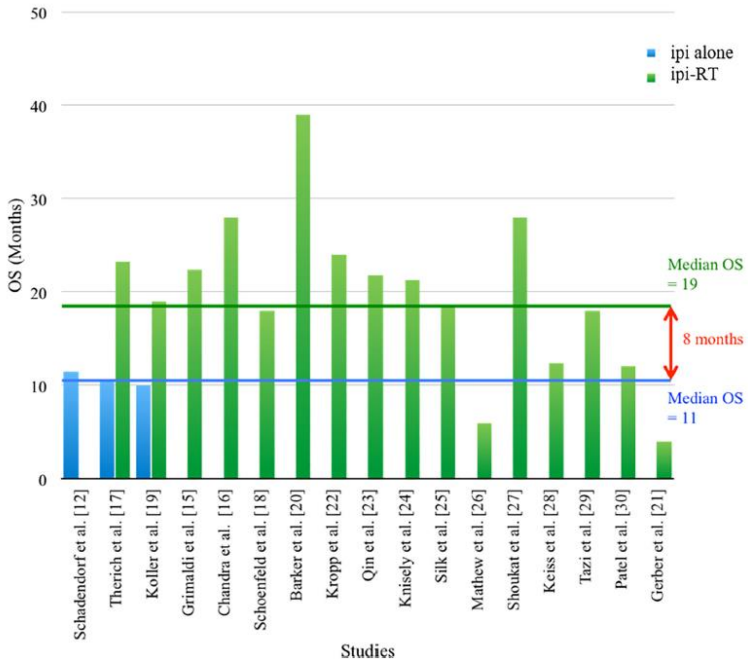


Fig. 3. Overall survival outcomes reported in prospective and retrospective studies using ipi-RT versus ipi alone.

Chicas-Sett R, et al.; Clin Transl Radiat Oncol. 2018

JAMA Oncology | Original Investigation

Effect of Pembrolizumab After Stereotactic Body Radiotherapy vs Pembrolizumab Alone on Tumor Response in Patients With Advanced Non-Small Cell Lung Cancer

Results of the PEMBRO-RT Phase 2 Randomized Clinical Trial

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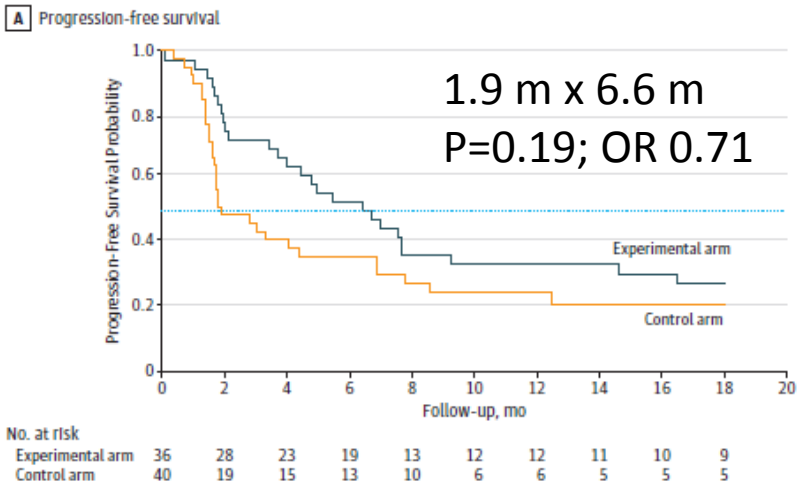
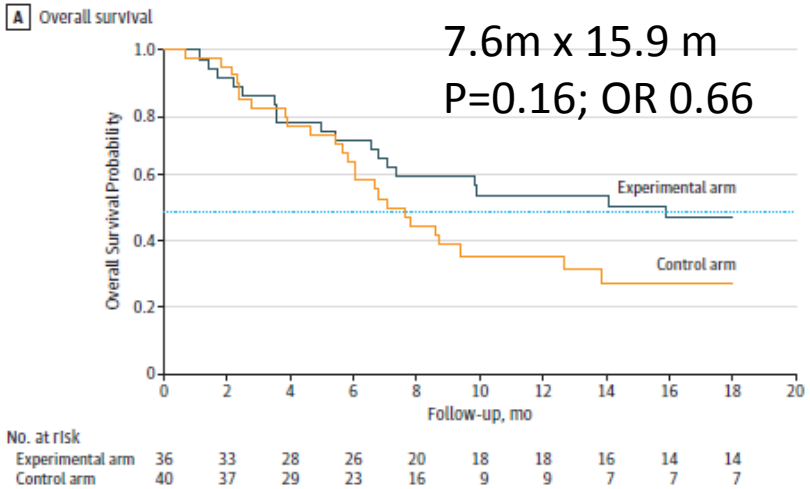
Pembrolizumabe (200mg/3 sem) vs 3 x 8 Gy - Pembrolizumabe

Response	Experimental Arm, No./Total No. (%) (n = 36)[a]	Control Arm, No./Total No. (%) (n = 40)[b]
Best overall response, No.		
Complete response	3	1
Partial response	14	8
Stable disease	9	10
Progressive disease	10	21
Objective response rate at 12 wk		
Overall[c]	13/36 (36)	7/40 (18)
PD-L1 TPS, %		
0	4/18 (22)	1/25 (4)
1-49	3/8 (38)	3/8 (38)
≥50	6/10 (60)	3/5 (60)
Disease control rate at 12 wk[d]	23/36 (64)	16/40 (40)





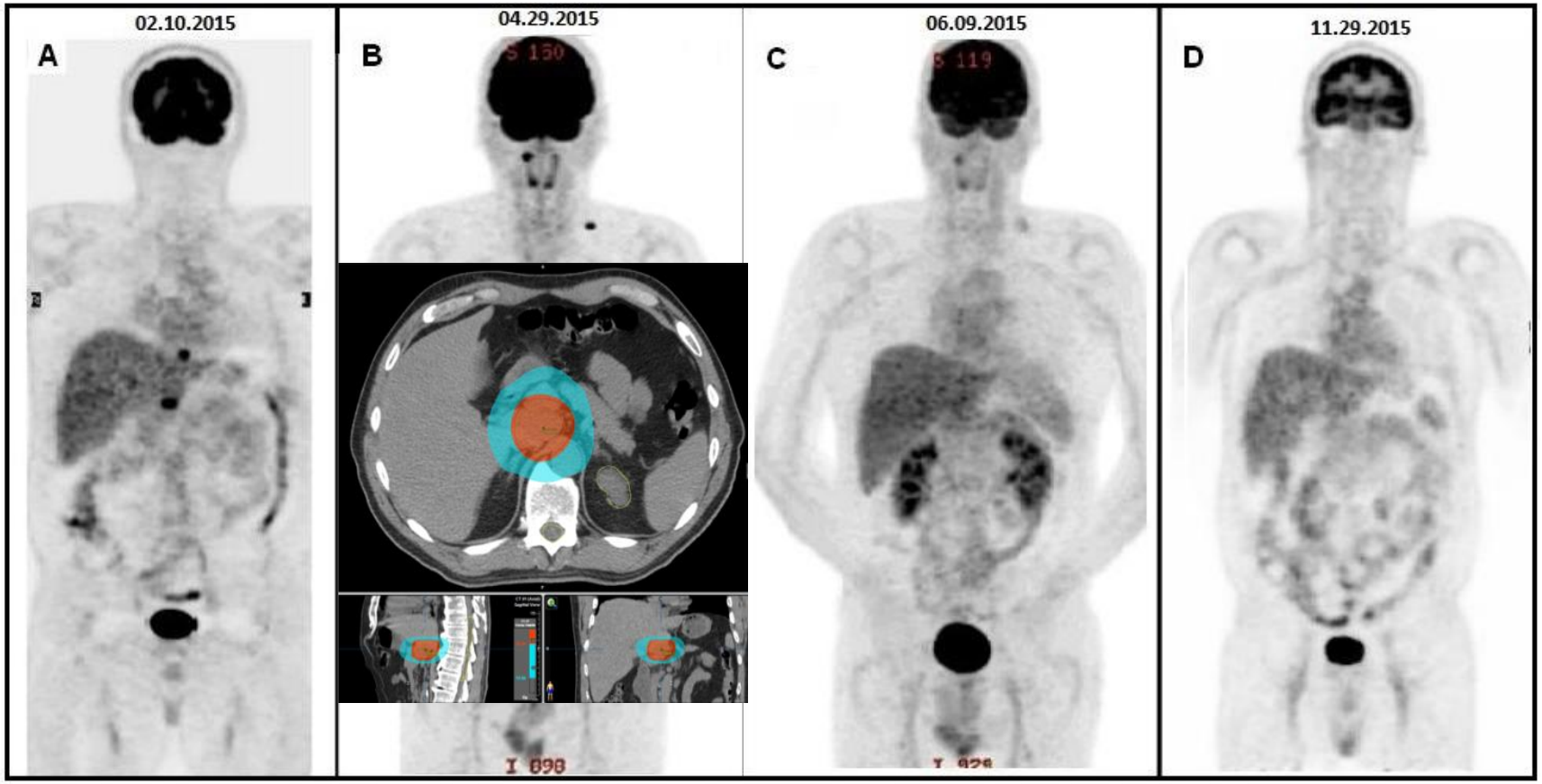
Willemijn SME et al JAMA Oncology 2019

Experiência BP

Droga	RT	Abscopal	Contrôle local	Sítio
PEMBRO	3 x 8 Gy	NA	X	Gânglio
NIVO	4 x 10 Gy		X	Pulmão
NIVO	3 x 8 Gy			Osso
NIVO	3 x 8 Gy			Gânglio
PEMBRO	3 x 8 Gy		X	Pulmão
NIVO	10 x 3,5 Gy		X	Mama
IPI	3 x 8 Gy			Fígado
NIVO	3 x 8 Gy		X	Vagina
NIVO	3 x 8 Gy			Estômago
NIVO	3 X 10 Gy		X	Parede torácica
NIVO	3 x 8 Gy		X	Partes moles
IPI	3 x 8 Gy		X	Partes moles
IPI + PEMBRO	3 x 8 Gy	X	X	Fígado
IPI	3 x 8 Gy	X	X	Gânglio
NIVO	4 x 10 Gy	X	X	Pulmão
NIVO	3 x 8 Gy	X	X	Subcutâneo
NIVO	4 x 10 Gy	X	X	Pulmão
NIVO	3 x 8 Gy	X	X	Gânglio

33%

Progressão de doença após 6 doses de Nivolumab seguida de RT (3 x 8 Gy)



Efeito Abscopal:

- Podemos contar com ele?

SIM (chance de 25% a 35 % quando associado a um inibidor de chekpoint)
- depende do tipo de tumor
- resposta tardia pode ser um fator de confusão para determinar a verdadeira incidência -
Chance de pseudoprogressão baixa - 8%

- 3 x 8 Gy tem se comprovado o melhor fracionamento (sítio metastático deve ser escolhido com base na segurança, volume e sintomas do paciente)

- Sequência do tratamento

- Biomarcadores para selecionar o melhor paciente

- Estudos randomizados para melhor avaliação