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IMMUNOTHERAPY AND RADIOTHERAPY FOR MELANOMA BRAIN METASTASES: IS THERE A SYNERGISM?

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IMMUNOLOGIC EFFECTS OF RADIOTHERAPY

- Increase natural killer (NK) cell activity
- Enhancement of antigen presentation to dendritic cells (radiation-induced cell death generates key molecular signals, that have been shown to promote the uptake and presentation of tumour-derived antigens by DCs)
- Increase of the production of immonostimolatory cytokine
- Augmentation of cluster of differentiation 8(CD8)-positive T cell infiltration

Review Article

Irradiation and Immunotherapy: From Concept to the Clinic

April K. S. Salama, MD[1]; Michael A. Postow, MD[2,3]; and Joseph K. Salama, MD[4]

Cancer June 1, 2016

IMMUNOLOGIC EFFECTS OF RADIOTHERAPY

- Boost of the expression of major histocompatibility complex (MHC)
- Upregulation of vascular cellular adhesion molecule-1 (VCAM-1)on tumor endotelium → facilitation of tumor infiltration by T-cells
- Down-regulation of inhibitory immune signals from suppressor and regulatory T cells

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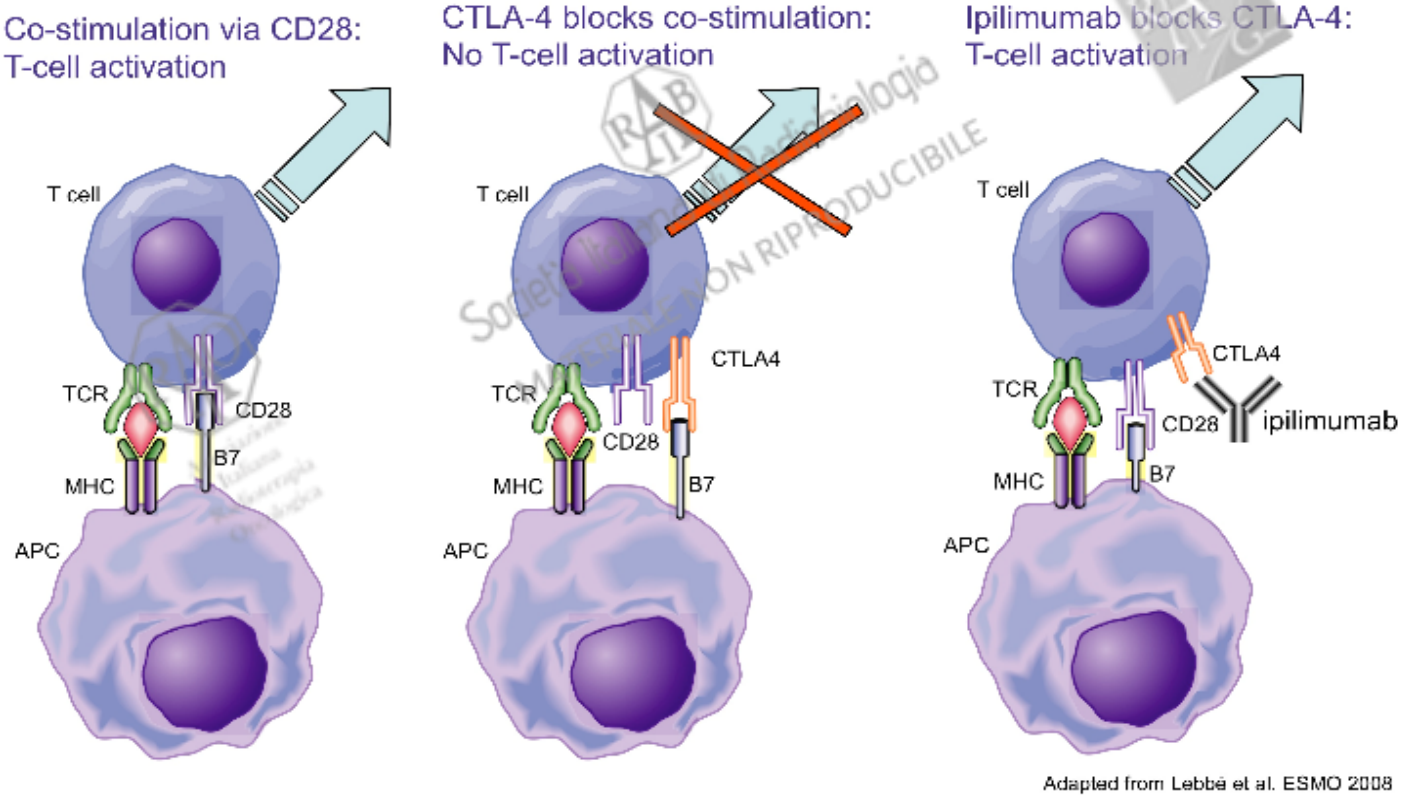
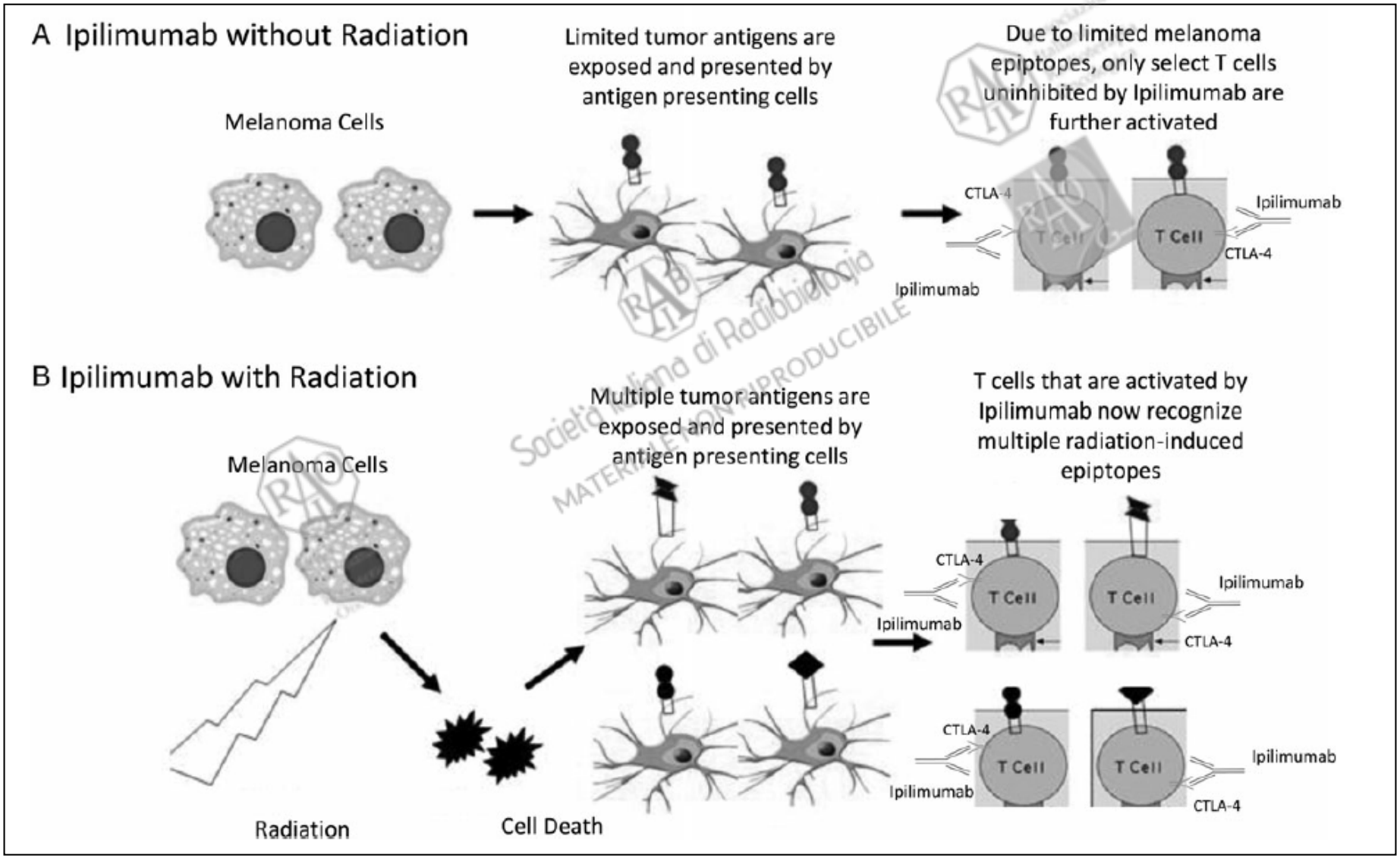
Role of IPILIMUMAB

Ipilimumab Blocks Negative Signaling From CTLA-4



Adapted from Lebbé et al. ESMO 2008

APC, antigen-presenting cell; CTLA-4, cytotoxic T-lymphocyte antigen-4; MHC, major histocompatibility complex; TCR, T-cell receptor.



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Patel et al, Neuro-Oncology, 2015

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Humanitas Cancer Center experience

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PATIENTS AND METHODS (1)

- 34 patients (2010 – 2015)

17 patients

Radiotherapy on brain +
IPILIMUMAB
(Immunotherapy group – IG)

MEAN AGE: 53.3 ys (range 30-81)

17 patients

Radiotherapy on brain +
OTHER THERAPIES*
(Control Group– CG)

MEAN AGE: 54.8 ys (range 32-80)

* BRAF, TMZ, Fotemustine

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PATIENTS AND METHODS (2)

EXTRACRANIAL DISEASE	N° of pts (IG group)	N° of pts (CG group)
Yes	15 (88%)	8 (47%)
No	2 (12%)	9 (53%)

TIMING OF IMMUNOTHERAPY (IG)	N° of pts (IG group)
BEFORE RT	7 (41%)
CONCOMITANTLY	6 (35%)
AFTER RT	4 (24%)

NUMBER OF LESIONS	N° of pts (IG group)	N° of pts (CG group)
1	7 (41%)	12 (70%)
2	2 (12%)	3 (18%)
≥3	8 (47%)	2 (12%)

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PATIENTS AND METHODS (3)

KIND OF RADIOTHERAPY	N° of pts (IG group)	**Mean dose (Gy)**	**Range / fractions**
Radiosurgery	10 (59%)	19.4	18-25 / 1
Hypofractionated RT	3 (18%)	31.25	25-40 / 3-5
Whole Brain Irradiation	4 (24%)	30	- /10

KIND OF RADIOTHERAPY	N° of pts (CG group)	**Mean dose (Gy)**	**Range / fractions**
Radiosurgery	10 (59%)	24.4	24-25 / 1
Hypofractionated RT	2 (12%)	36	30-42 / 5
Whole Brain Irradiation	5 (29%)	30	- /10

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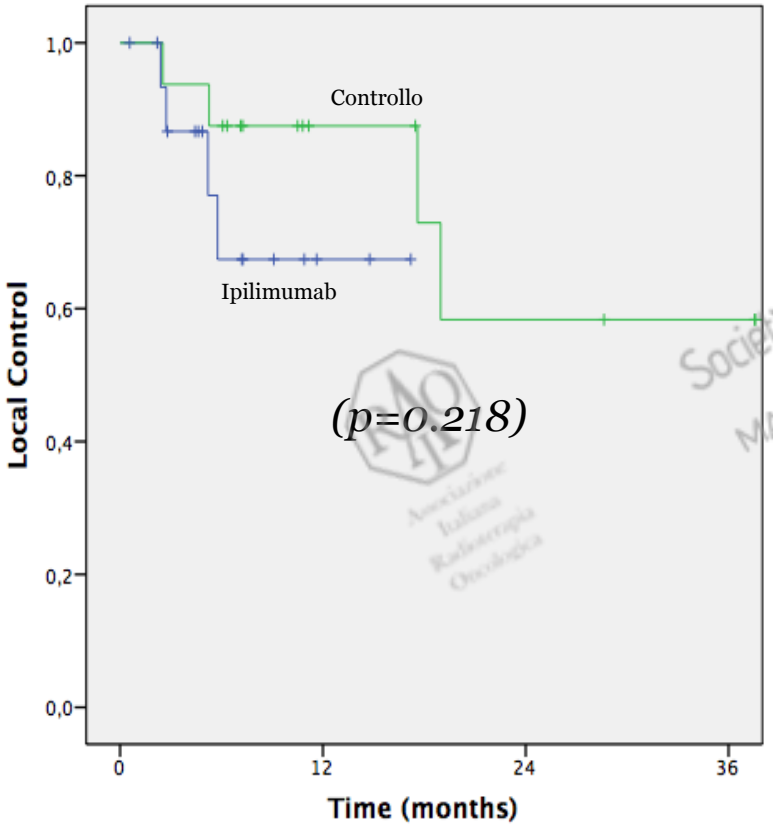
RESULTS: RECIST response

RESPONSE of the IRRADIATED LESIONS	N° of pts (IG group)	N° of pts (CG group)
Complete Response	1 (5%)	1 (5%)
Partial Response	5 (29%)	8 (47%)
Stable disease	9 (53%)	4 (24%)
Progressive Disease	2 (12%)	4 (24%)

RESULTS : Local Control (LC)



LC	IG group	CG group
6 months	67.4%	87.5%
12 months	67.4%	58.3%

Any difference in terms of LC

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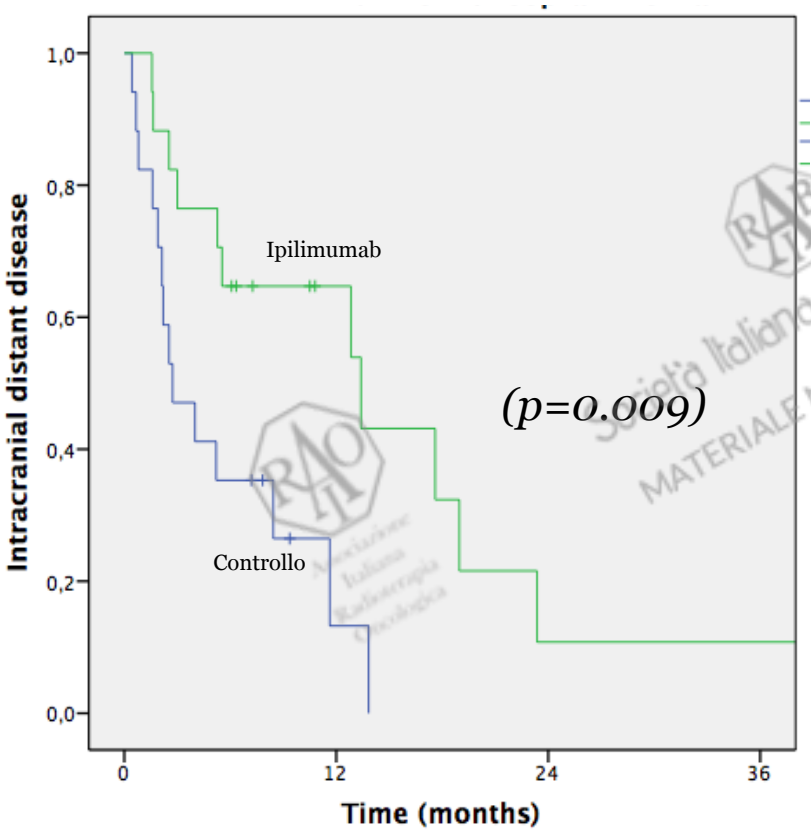
RESULTS: Intracranial Distant Disease Control (IDDC)



IDDC	IG group	CG group
6 months	64.7%	53.9%
12 months	35.3%	10.8%

Ipilumumab improves IDDC

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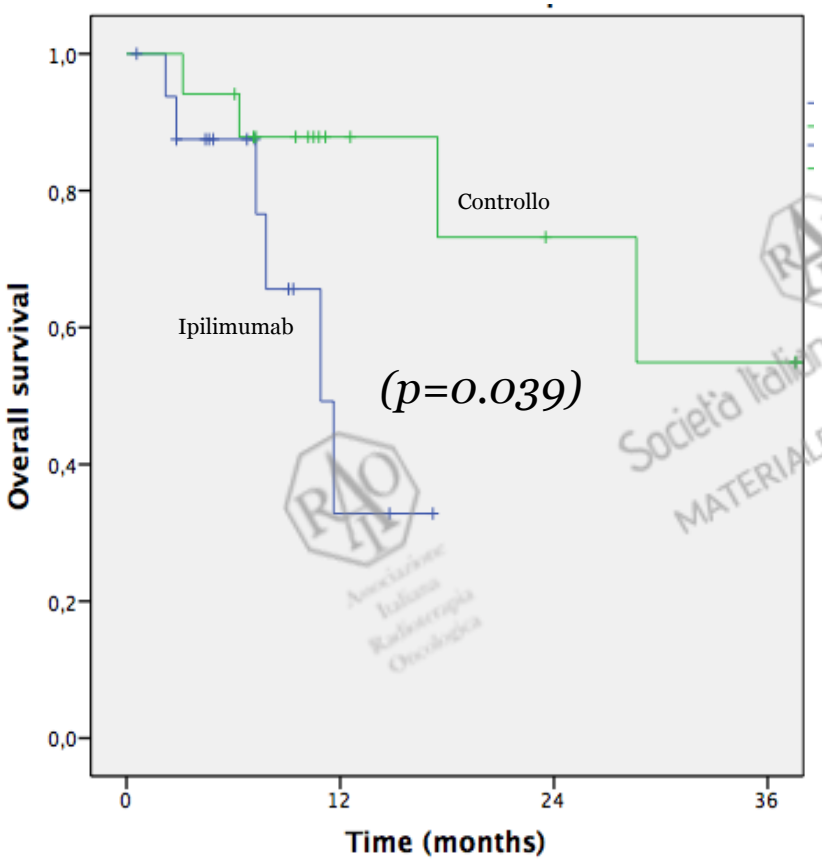
RESULTS: OVERALL SURVIVAL (OS)



OS	IG group	CG group
6 months	87.5%	87.8%
12 months	32.8%	73.2%

Ipilimumab does not improve OS

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RESULTS: Toxicity

- Majority of patients were asymptomatic
- Radionecrosis was observed during follow-up in 2 cases (CG)

For those patients receiving ipilimumab concomitantly, RT did not exacerbate the typical systemic immune-related adverse events associated with ipilimumab

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Ipilimumab in patients with melanoma and brain metastases: an open-label, phase 2 trial

Kim Margolin, Marc S Ernstoff, Omid Hamid, Donald Lawrence, David McDermott, Igor Puzanov, Jedd D Wolchok, Joseph I Clark, Mario Sznol, Theodore F Logan, Jon Richards, Tracy Michener, Agnes Balogh, Kevin N Heller, F Stephen Hodi

Lancet Oncol 2012; 13: 459–65

without brain metastases. Further investigations could assess combinations of ipilimumab and chemotherapy (eg, fotemustine in the NIBIT-M1 trial[23]) and others, such as molecularly targeted small molecules and other immunomodulatory strategies (eg, new checkpoint-blocking antibodies alone or in combination).[31,32]

Melanoma GPA score	Expected median survival	Observed median survival
0-1	3.4 mo	5.9 mo
2	4.7 mo	7.6 mo
3	8.8 mo	11.0 mo
4	13.2 mo	Not reached
All	6.7 mo	12.4 mo

GPA = graded prognostic assessment score.

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tereotactic Radiosurgery for Melanoma Brain Metastases in atients Receiving Ipilimumab: Safety Profile and Efficacy of ombined Treatment

na P. Kiess, MD, PhD[1,3], Jedd D. Wolchok, MD, PhD[2], Christopher A. Barker, MD[3], Michael . Postow, MD[2], Viviane Tabar, MD[4], Jason T. Huse, MD, PhD[5], Timothy A. Chan, MD, PhD[3], oshiya Yamada, MD[3], and Kathryn Beal, MD[3]

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CONCLUSIONS

- The combination of immunotherapy and radiotherapy for melanoma brain metastases did not result in a significant advantage in our experience in terms of local control and survival
- Statistically significant the result of disease control extra-field
- Need of more heterogeneus cohorts for perspective trials
- Further prospective studies are recommended to better exploit this combined treatment


Grazie per
l'attenzione...