



IRCCS Azienda Ospedaliera Universitaria
San Martino – IST
Istituto Nazionale per la Ricerca sul Cancro



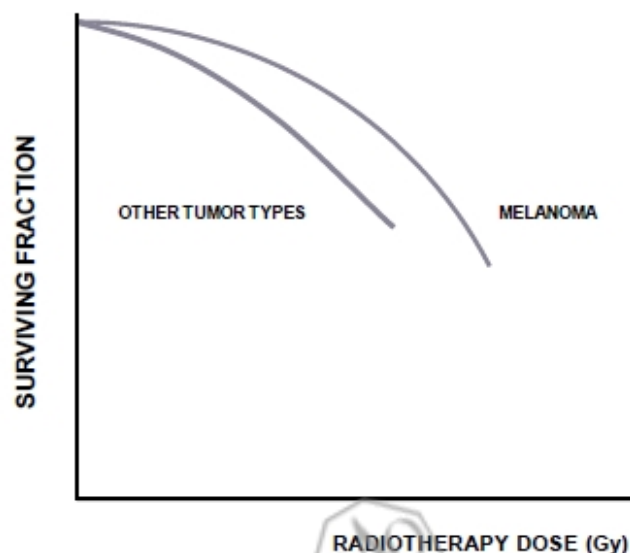
Melanoma

**dati clinici di associazione
su target intra e extracranici**

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Radiation Oncology Department

New therapeutic role of RT in melanoma



Società Italiana di Radiobiologia
MATERIALE NON RIPRODUCIBILE

Radioresistant → Radiosensitive (new techniques/higher fractionation)

Immunosuppressive RT effect → Immunogenic Effect

Palliative setting → enhancing the survival curve



New drugs and potentially enforced role of RT in melanoma

Overall Survival Metastatic Melanoma

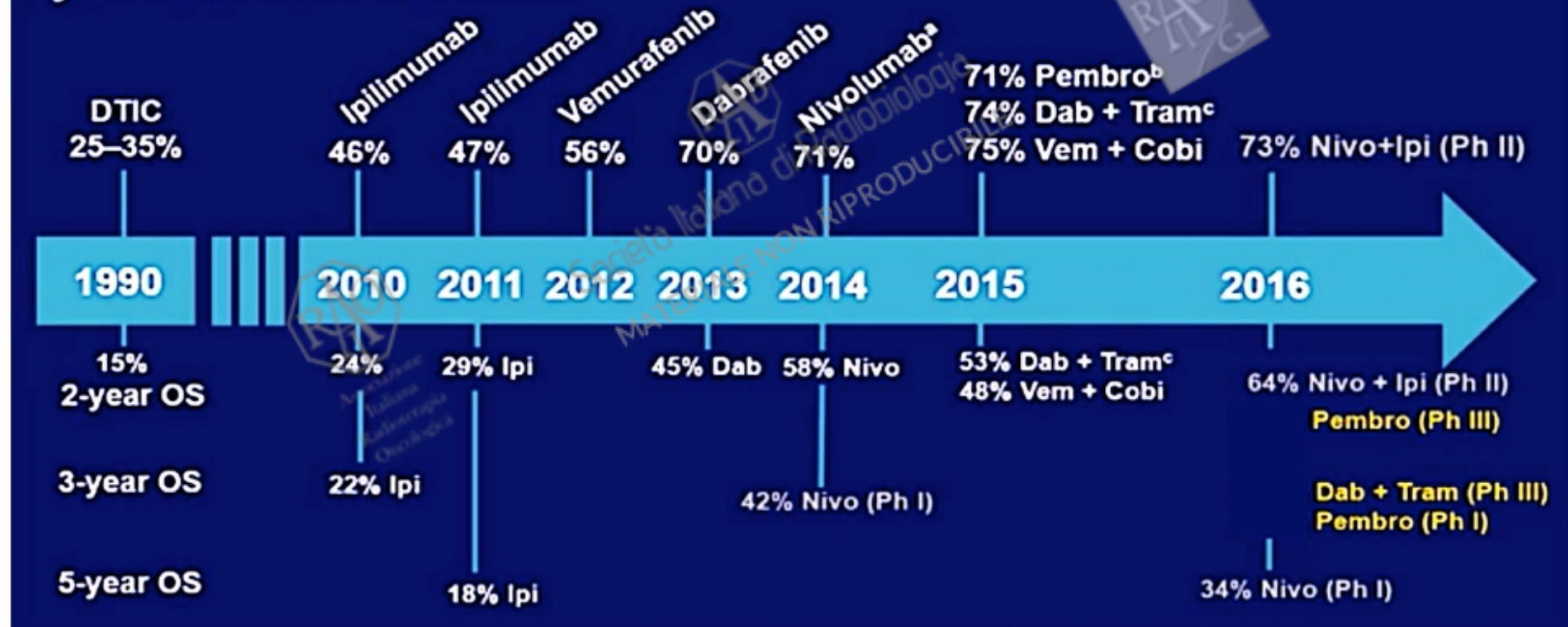
1-year OS Phase III Studies



New drugs and potentially enforced role of RT in melanoma

Overall Survival Metastatic Melanoma

1-year OS Phase III Studies



MBM

Melanoma brain metastases



Società Italiana di Radiobiologia
MATERIALE NON RIPRODUCIBILE



- Up to 40% of melanoma patients develop BM
- MBM median survival is 6 months
- **Systemic treatments**
 - ICI
 - CTLA 4 MoAb: ***Ipilimumab***
 - Anti PD1 MoAb: ***Pembrolizumab, Nivolumab***
 - Target therapy
 - BRAF inhibitors: ***Vemurafenib, Dabrafenib***
 - MEK inhibitors: ***Trematinib, Cobemitinib***
- **Local treatments**
 - Surgery
 - Radiotherapy

Local treatments

SURGERY

Large retrospective study (N > 300) in MBM

Treatment	<i>n</i>	%	Median Survival (Months)
None	83	23.3	2.04
WBRT alone	100	28.2	3.98
RS alone	26	7.3	9.87
Surgery alone	36	10.1	8.16
WBRT + RS	20	5.6	9.44
Surgery + WBRT	58	16.3	8.81
Surgery + RS	20	5.6	13.75
Surgery + WBRT + RS	12	3.4	10.2

Abbreviations: WBRT, whole-brain radiotherapy; RS, radiosurgery.



Local treatments **RADIOTHERAPY**

WBRT vs SRS

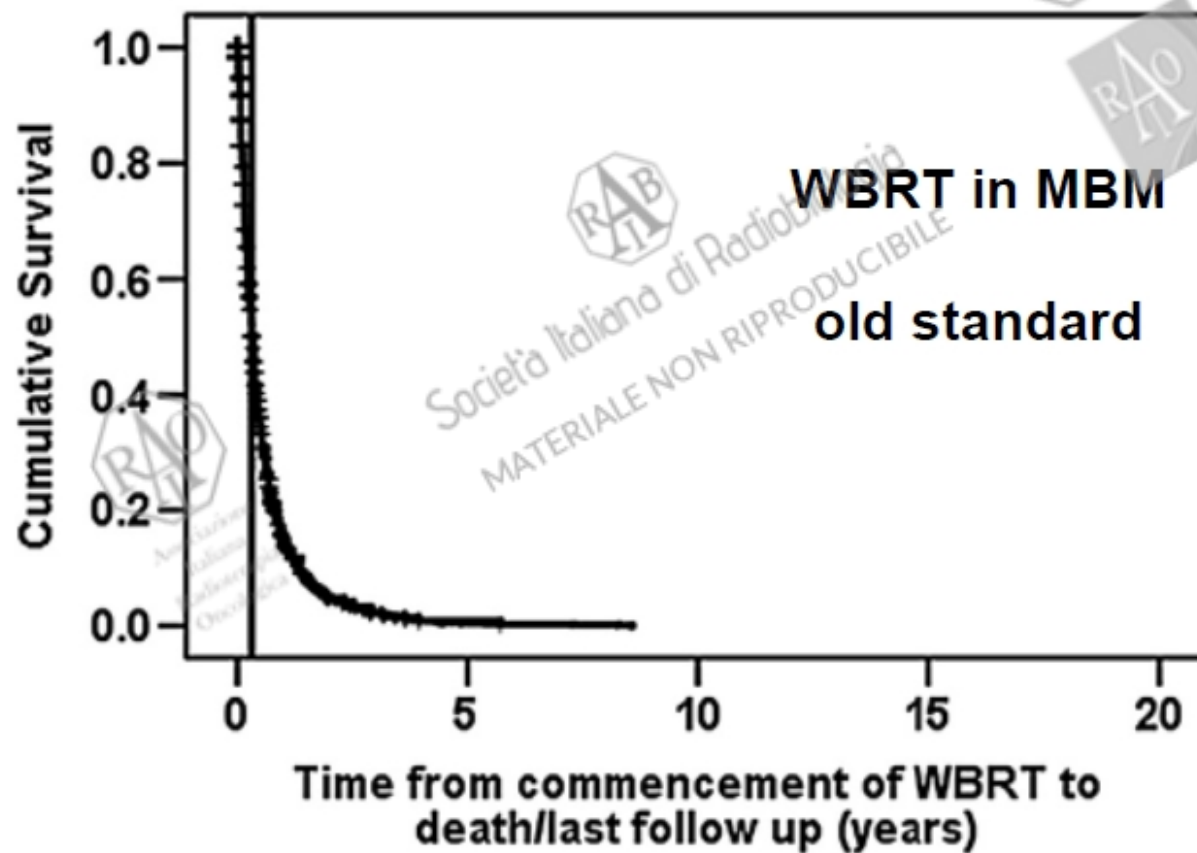


Fig 2. Whole-brain radiotherapy survival.

Local treatments **RADIOTHERAPY**

WBRT old standard

Adjuvant WBRT After SRS

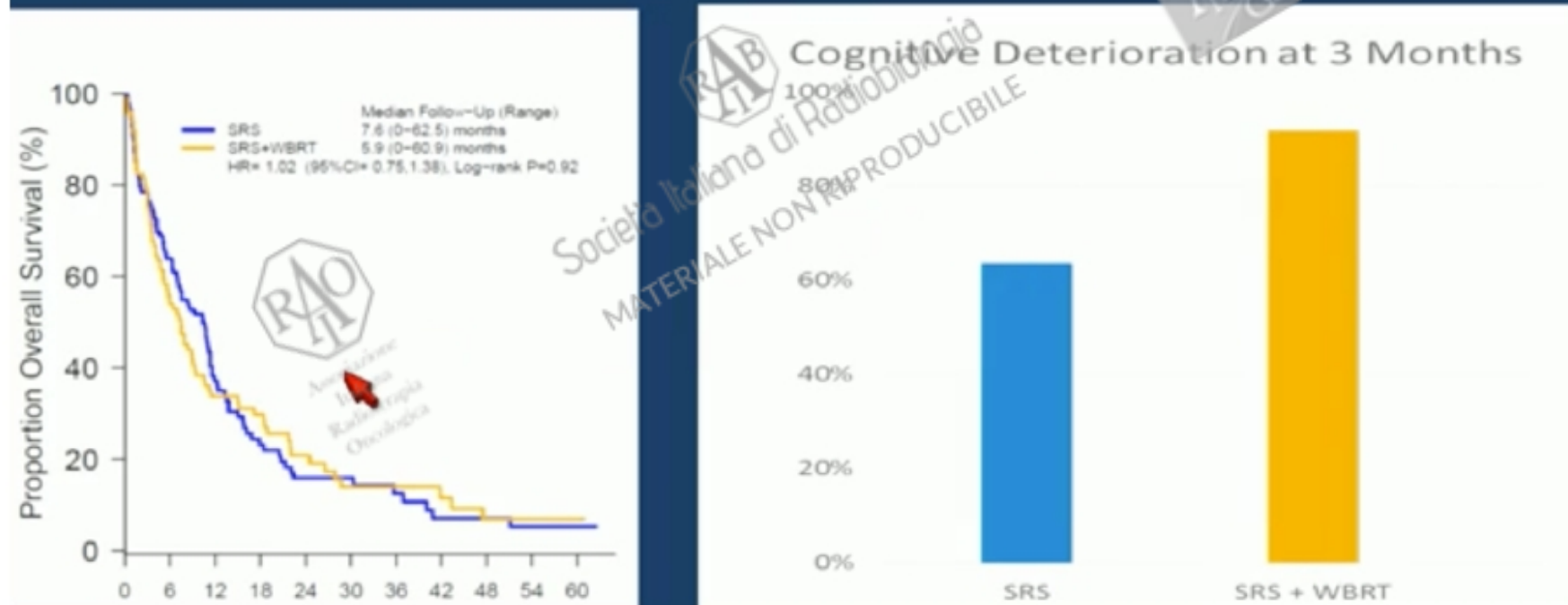
	#	LC	DBC	Med OS
EORTC SRS	199	69%	52%	10.9 mo
+WBRT		81%	67%	10.9 mo
Japan SRS	132	73%	36%	8 mo
+WBRT		89%	58%	7.5 mo
MDACC SRS	58	67%	45%	15.2 mo
+WBRT		100%	73%	5.7 mo

LC = Local Control
DBC = Distant Brain Control

Local treatments **RADIOTHERAPY**

WBRT old standard

Adjuvant WBRT-N0574

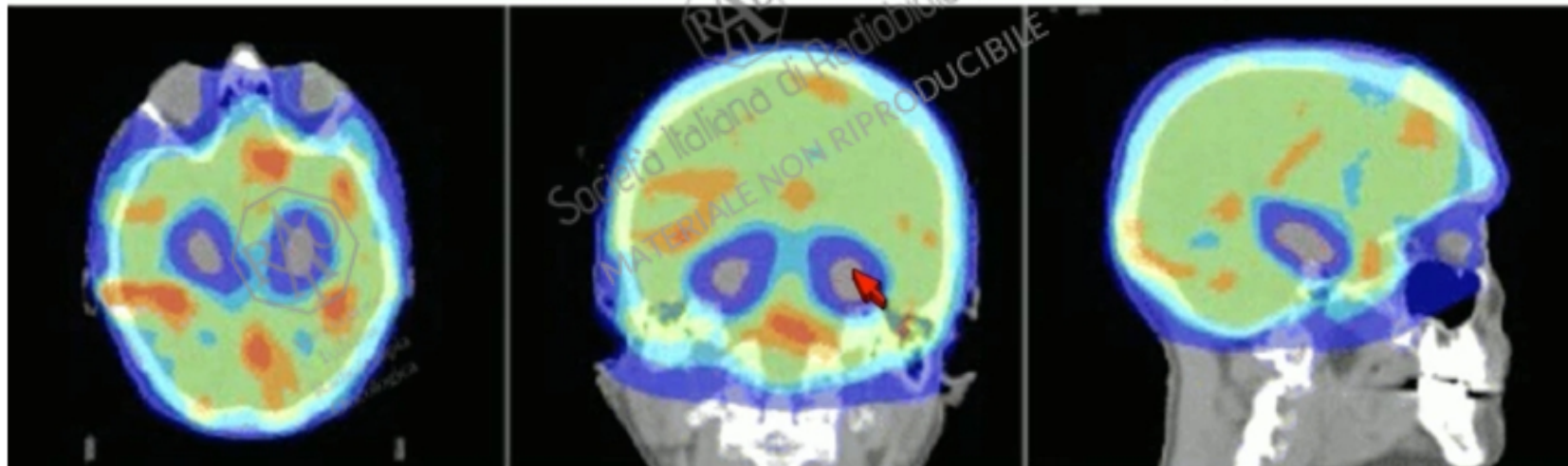


WBRT old standard

Hippocampal neurogenesis vital to memory

Cognitive Function

Hippocampal Avoidance Phase II RTOG 0933



Memory deficits reduced from 30% to 7%

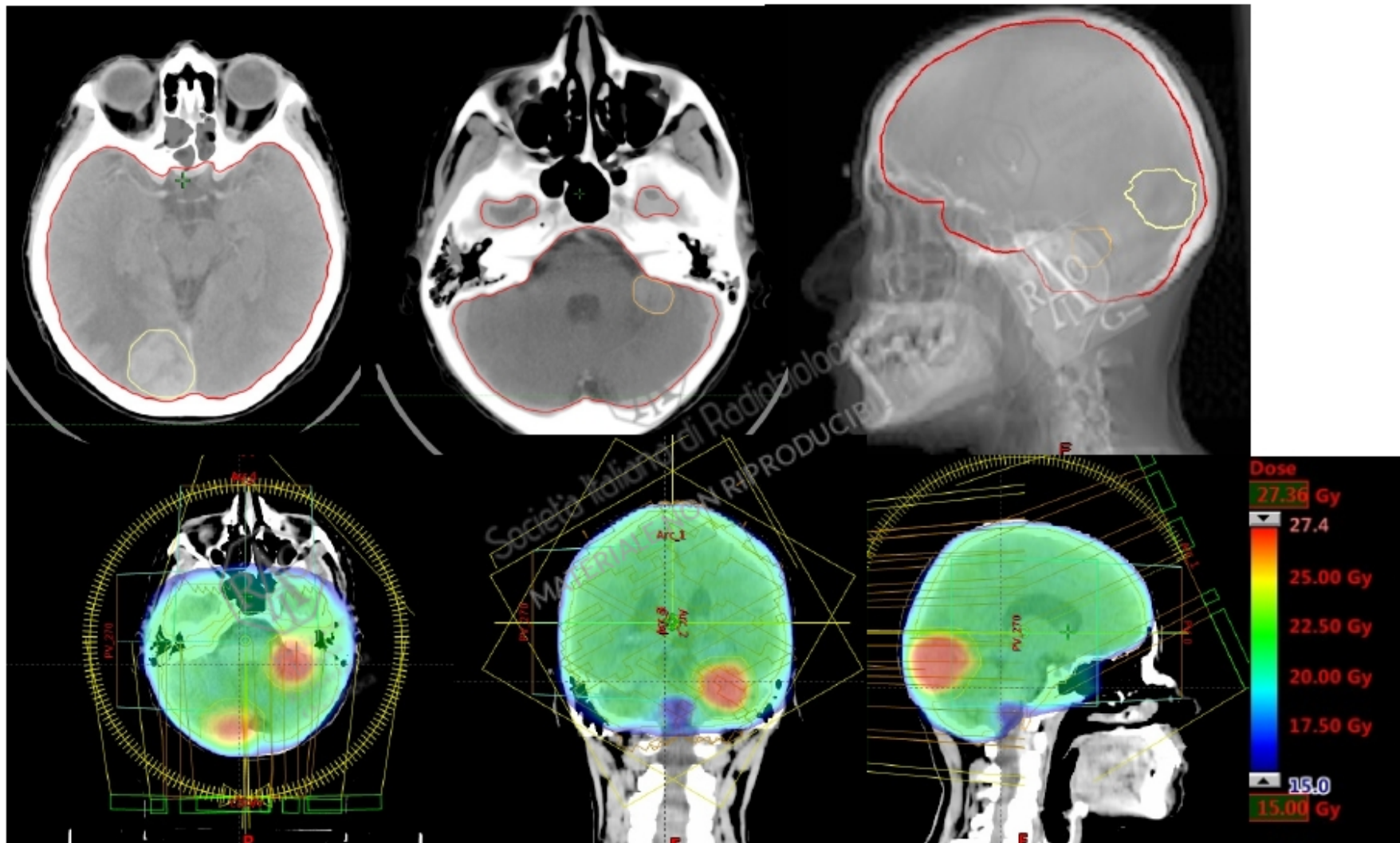
Local treatments **RADIOTHERAPY**

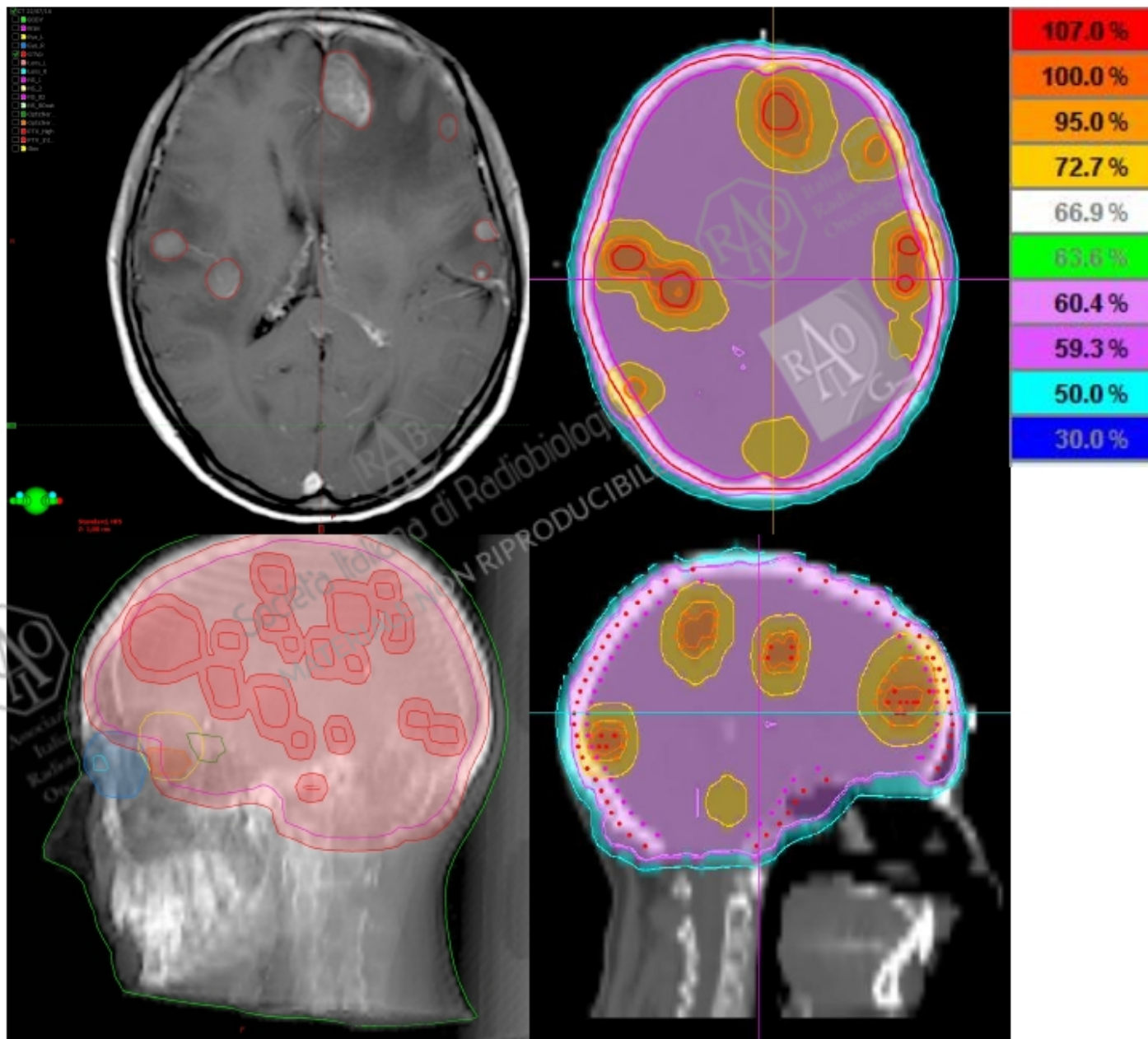
SRS

JLGK0901 Prospective SRS Trial

- 1194 brain met pts
 - 1-10 brain mets
 - <10cc + <3cm
 - Total vol <15 cc
- SRS alone
- 92% Died Systemic Disease Progression

	Median OS
1 met	14 months
2-4 mets	11 months
5-10 mets	11 months





Selected clinical trials (N>40) in MBM *iBRAF*

Study	Year	Study design	Therapeutic intervention	Number	Median PFS (months)	Intracranial RR	Median OS (months)
Long et al (BREAK-MB)	2012	Phase 2	Dabrafenib	Cohort A 74	4.0	39.2%	8.2
				Cohort B 65	4.1	30.8%	7.8
Kefford et al	2015	Phase 2	Vemurafenib	Cohort I 90	4.0	18%	7.0
				Chorth II 56	4.3	20%	6.9

Cohort A: *V600E New*
 Cohort B: *V600 Recurrent*
 Cohort I: *Recurrent*
 Cohort II: *New*



Selected clinical trials ICI in MBM

Study	Year	Study design	Therapeutic intervention	Number	Median PFS (months)	Median OS (months)
Margolin et al.	2012	Phase 2	Ipilimumab	Cohort A 51	4.0	7.0
				Cohort B 21	4.1	3.7
Queirolo et al.	2014	Phase 2	Ipilimumab	146	2.8	4.3

Cohort A: *Asimptomatic (no steroid)*

Cohort B: *Simptomica (steroids)*

Combination of SRS and ICI treatments

- ◆ SRS might increase permeability of blood-brain barrier
- ◆ High dose fractionated schedule of SRS might be better than single fraction (24Gy/3Fx more effective than 20Gy/1Fx)
- ◆ Immunogenic
- ◆ Most of clinical data are small and retrospective

Combination of SRS and ICI treatments

Authors	No. of patients	Arm(s) (No. of patients)	Type of RT	Immunotherapy	Median survival	Local control	Freedom from new brain met.
Knisely et al.	77	SRS alone SRS + Ipilimumab	SRS	Ipilimumab	4.9 months 21.3 months	n.a.	n.a.
Silk et al.	70	RT alone RT + Ipilimumab	SRS or WBRT	Ipilimumab 3 mg/kg every 3 weeks for a planned four doses	5.3 months 18.3 months		
Mathew et al.	58	SRS alone (33) SRS + Ipilimumab (25)	SRS	Ipilimumab 3 mg/kg every 3 weeks for a planned four doses	5.9 months (whole series)	65% at 6 months 63% at 6 months	47% at 6 months 35% at 6 months
Patel et al.	54	SRS alone (34) SRS + Ipilimumab (20)	SRS	Ipilimumab 3 mg/kg every 3 weeks for a planned four doses	38.5% OS at 1 year 37.1% OS at 1 year	92.3% at 1 year 71.4% at 1 year	29.1% at 1 year 12.1% at 1 year
Kiess	46	SRS + Ipilimumab (46)	SRS	Ipilimumab 3 mg/kg or 10 mg/kg every 3 weeks for a planned four doses + maintenance therapy every 3 months	12.4 months	87–100 % at 1 year according to timing of SRS	8–36% at 1 year according to timing of SRS
Ahmed et al.	26	SRS + Nivolumab	SRS	Nivolumab	11.8–12 months	91% and 85% at 6 and 12 months	66% and 53% at 6 and 12 months



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Enforced the role of SRS vs WBRT in association with ICI

Ipilimumab and radiation therapy for melanoma brain metastases.

Cancer Med 2013 Dec;2(6):899–906

IPILIMUMAB + RT

Median OS 18.3 months
(95% C.I. 8.1-25.5)

IPILIMUMAB + SRS

Median OS 19.9 months

RT

median OS 5.3 months
(95% C.I. 4.0-7.6)

SRS alone

Median OS 4.0 months

No advantages in WBRT group



Combination of SRS and ICI treatments

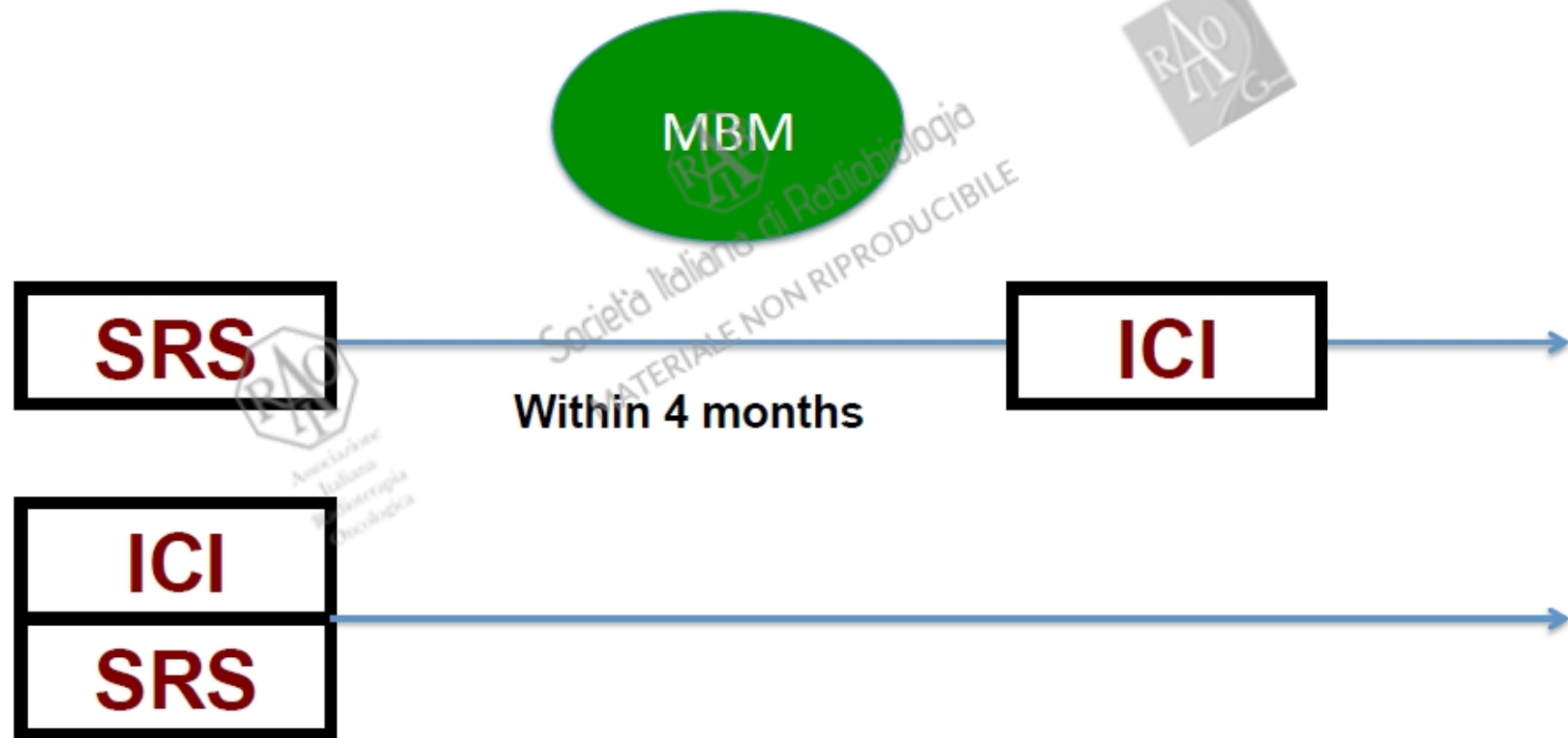
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Emerging role of Timing between ICI and RT

Stereotactic radiosurgery for melanoma brain metastases in patients receiving ipilimumab: safety profile and efficacy of combined treatment.

Int J Radiat Oncol Biol Phys 2015 Jun 1;92(2):368–75



Combination of SRS and ICI treatments

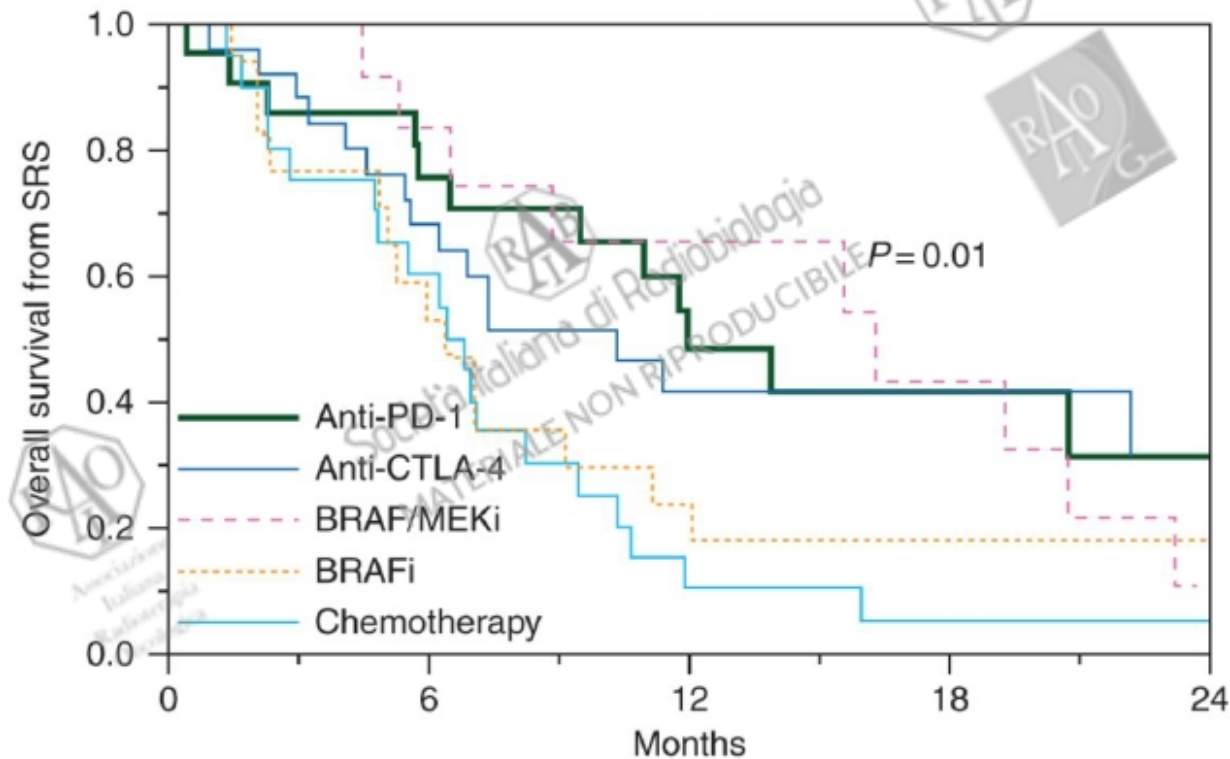
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SRS and ICI and Combo therapy

Clinical outcomes of melanoma brain metastases treated with stereotactic radiosurgery and anti-PD-1 therapy, anti-CTLA-4 therapy, BRAF/MEK inhibitors, BRAF inhibitor, or conventional chemotherapy.

Annals of Oncology Sept 2016



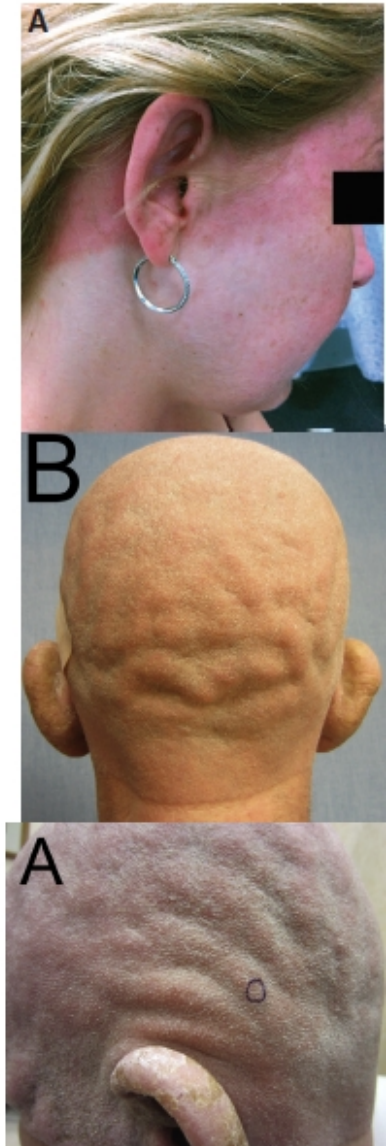
No. at risk	0	6	12	18	24
Anti-PD-1	21	16	10	5	4
Anti-CTLA-4	25	18	9	8	4
BRAF/MEKi	12	10	7	5	2
BRAFi	18	10	5	4	4
Chemotherapy	20	13	3	2	1

Toxicity

Avoiding Severe Toxicity From Combined BRAF Inhibitor and Radiation Treatment: Consensus Guidelines from ECOG

- Combination of BRAFi and RT for melanoma 27 publications
- 7 publications noted potential intracranial neurotoxicity
- Rates of radionecrosis, hemorrhage from WBRT, SRS, or both do not appear increased with concurrent or sequential administration of BRAFi

Hold BRAFi 3 days before & after fractionated RT
Hold BRAFi 1 day before and after SRS



Systemic metastasis

Extracranial targets



General properties of target therapies vs checkpoint immunotherapy

	Targeted Therapy	Immunotherapy
PK	Short (hours)	Long (weeks)
PD	Short (hours)	Long (years)
What kills the cancer	The small molecule stopping an oncogenic signal	A body system designed to kill its targets anywhere in the body
Body distribution	Passive (blood distribution)	Active (T cells searching for antigen)
Memory	No	Yes

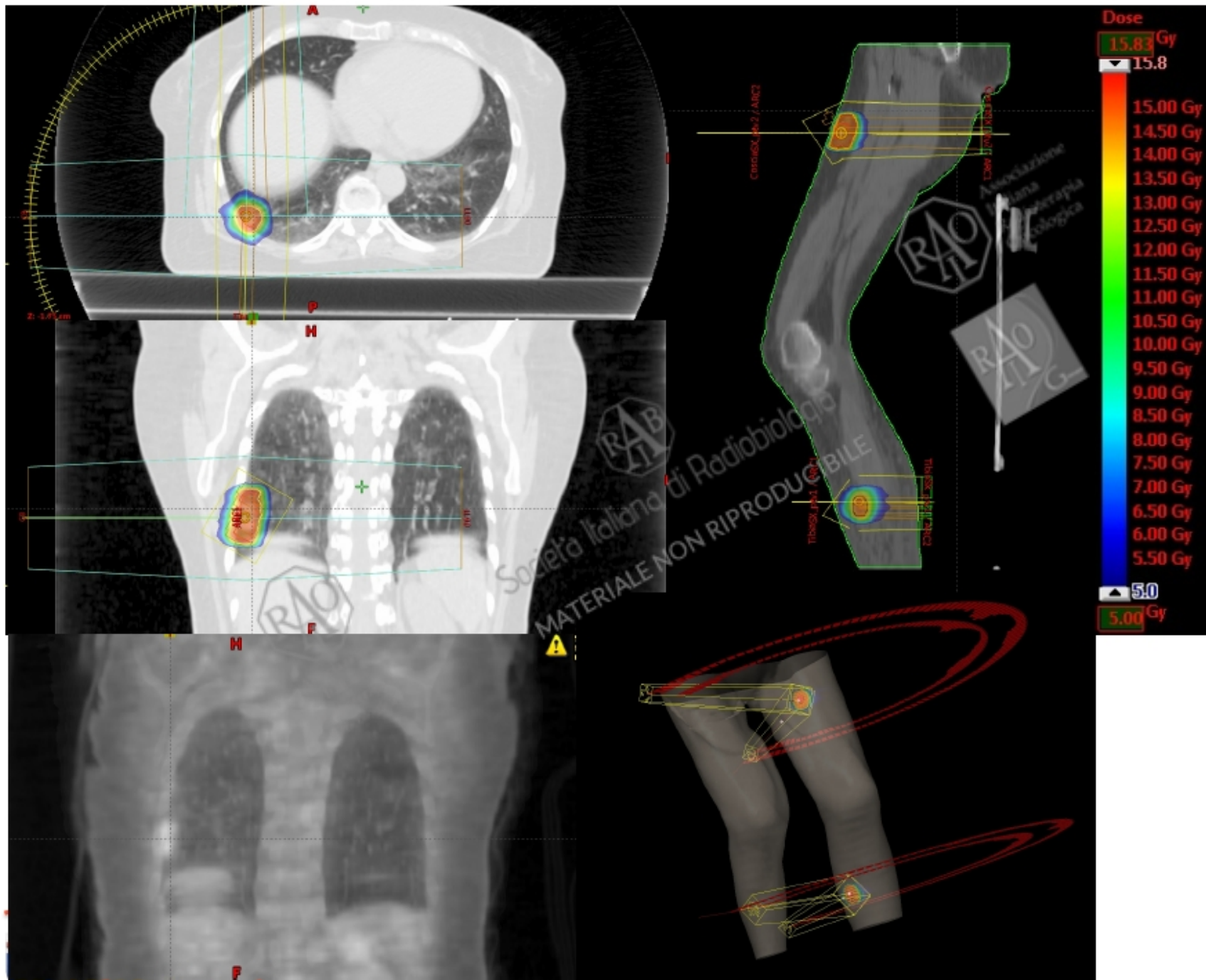
Abscopal effect in clinic

Postow 2012 New England : Case Report of PD under IPI -> Palliative RT on paraspinal mass with systemic response. (CD4+ T and NY-ESO-1)

Reynders 2015 Canc Treat Review: 23 clinical case and time to abscopal response was 5 months and median PFS 13 months.

Chandra 2015 Oncoimmunology: 47 patients. AE related to low and fractionated dose (controversial with other data)

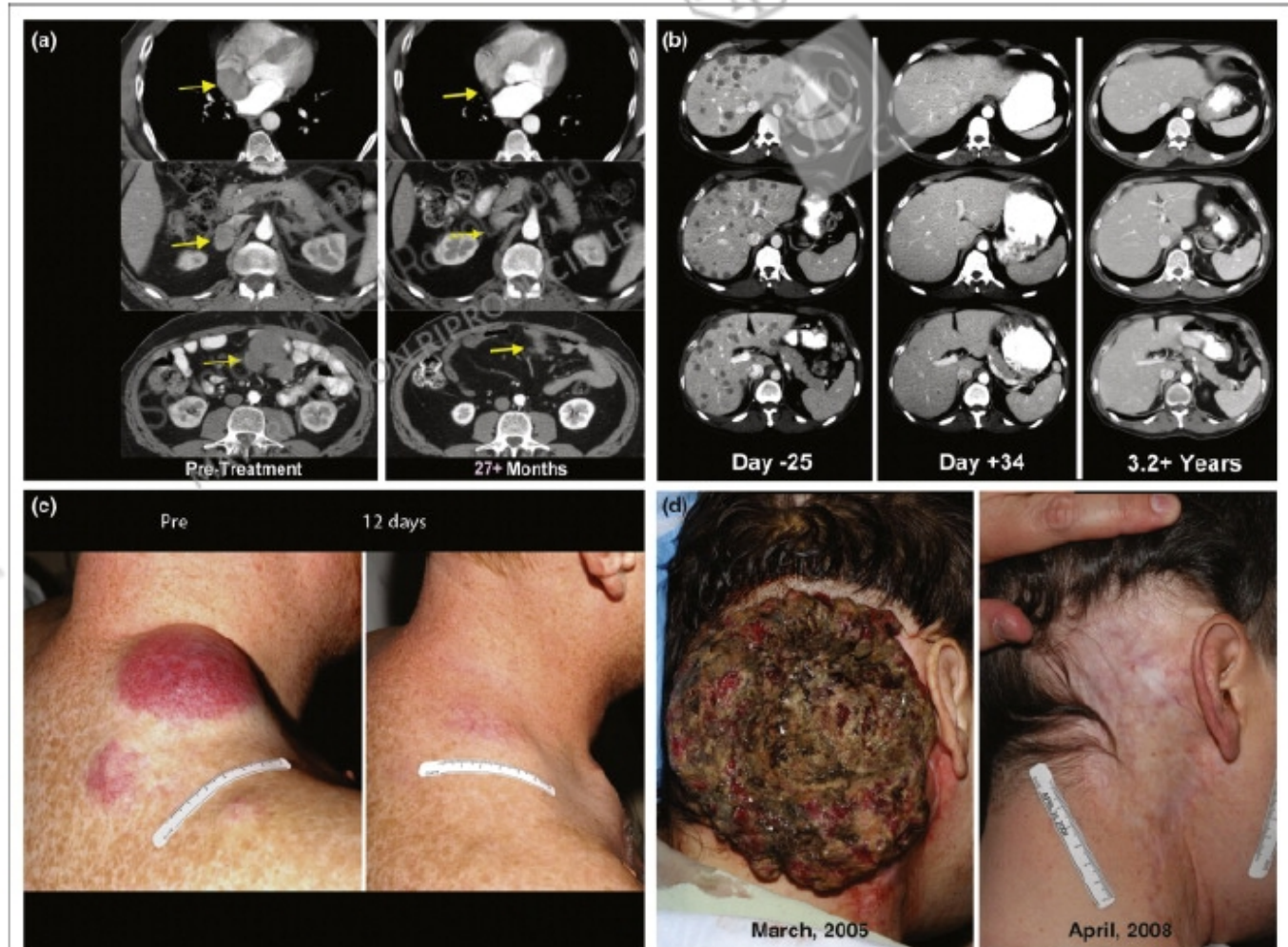
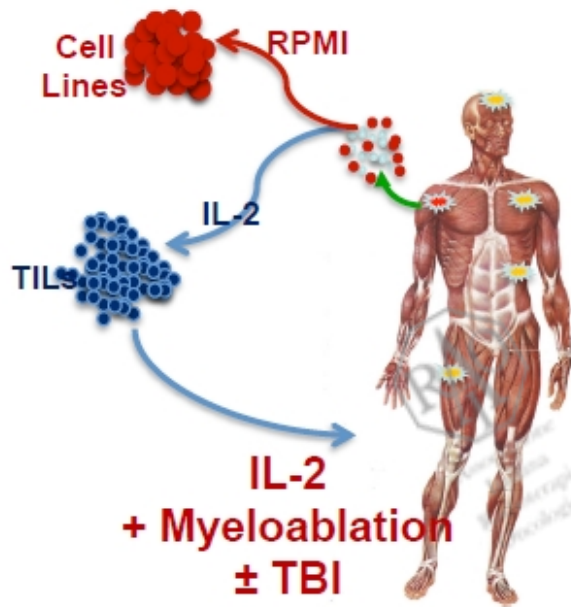
Radiation treatment field	# of RT courses (%)	Total RT dose, median (range), Gy	RT fraction size, median (range), Gy
Whole brain	15 (23)	30 (30, 37.5)	3 (2.5, 3)
Brain directed stereotactic radiosurgery / therapy	18 (28)	20 (18, 25)	19.5 (5, 25)
Spine	7 (11)	30 (20, 37.5)	3 (2, 4)
Intrathoracic	3 (5)	24 (24, 30)	4 (3, 4)
Bone	8 (12)	30 (8, 36)	3.5 (3, 8)
Soft tissue	13(20)	35 (24, 66)	3 (2, 6)
Abdominovisceral	1 (2)	36(36, 36)	3 (3, 3)



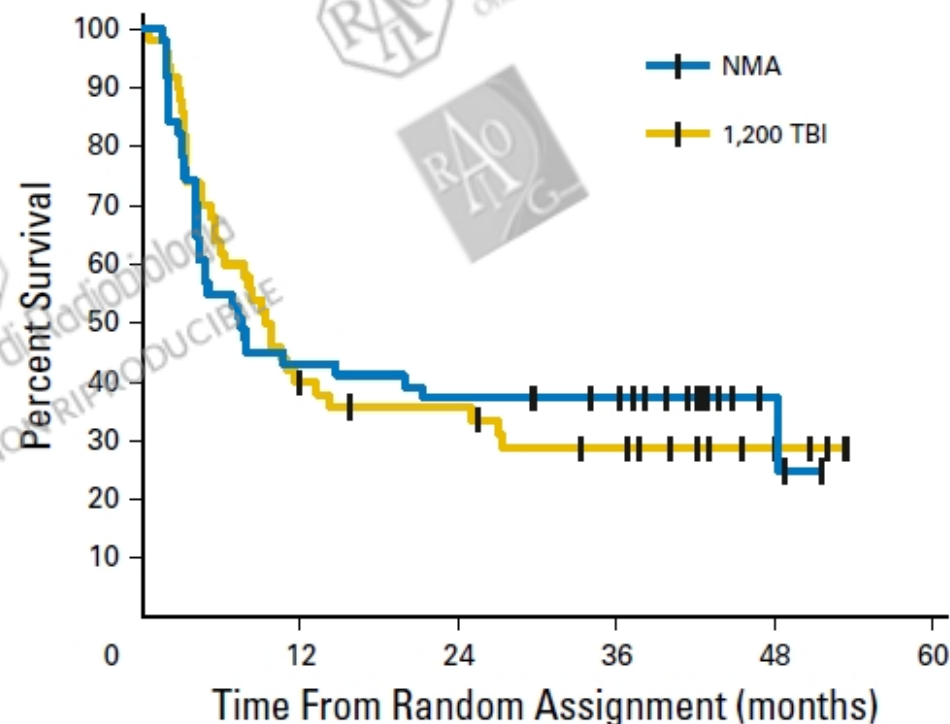
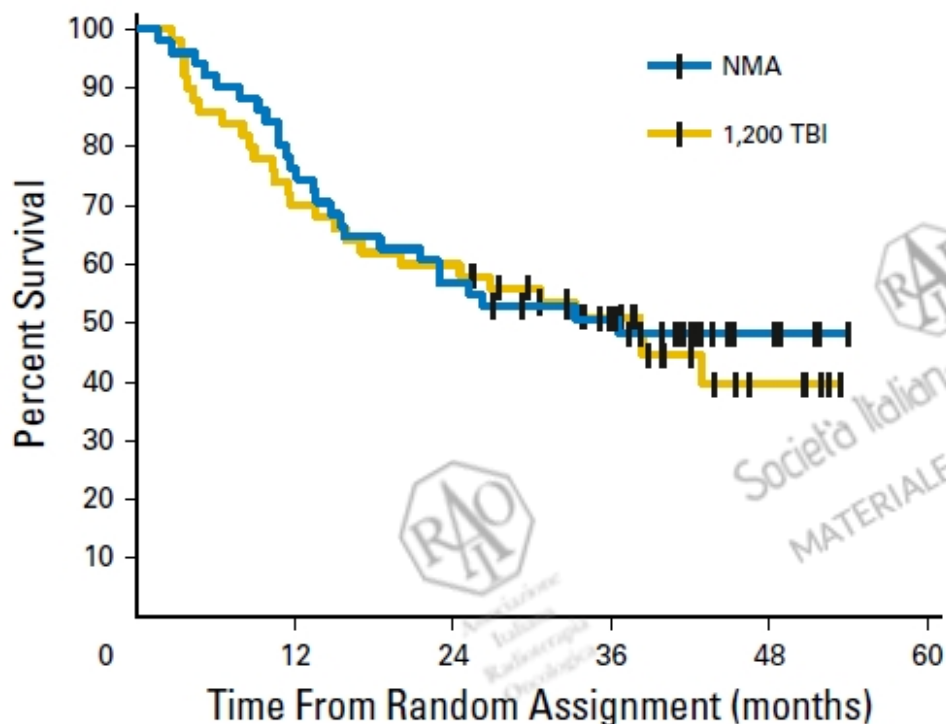
Toxicity



Adoptive immunotherapy with Autologous T cells



Adoptive immunotherapy with Autologous T cells



Adoptive Cell Therapy for Melanoma: Randomized Lymphodepletion



News from ASTRO 2016 Annual meeting

Between more than 1200 abstracts 11
where on clinical melanoma treatment

7 oral presentation
4 ePoster

6 on RT and immunemodulation
3 on adjuvant role of RT



Ongoing RT- combo Trials

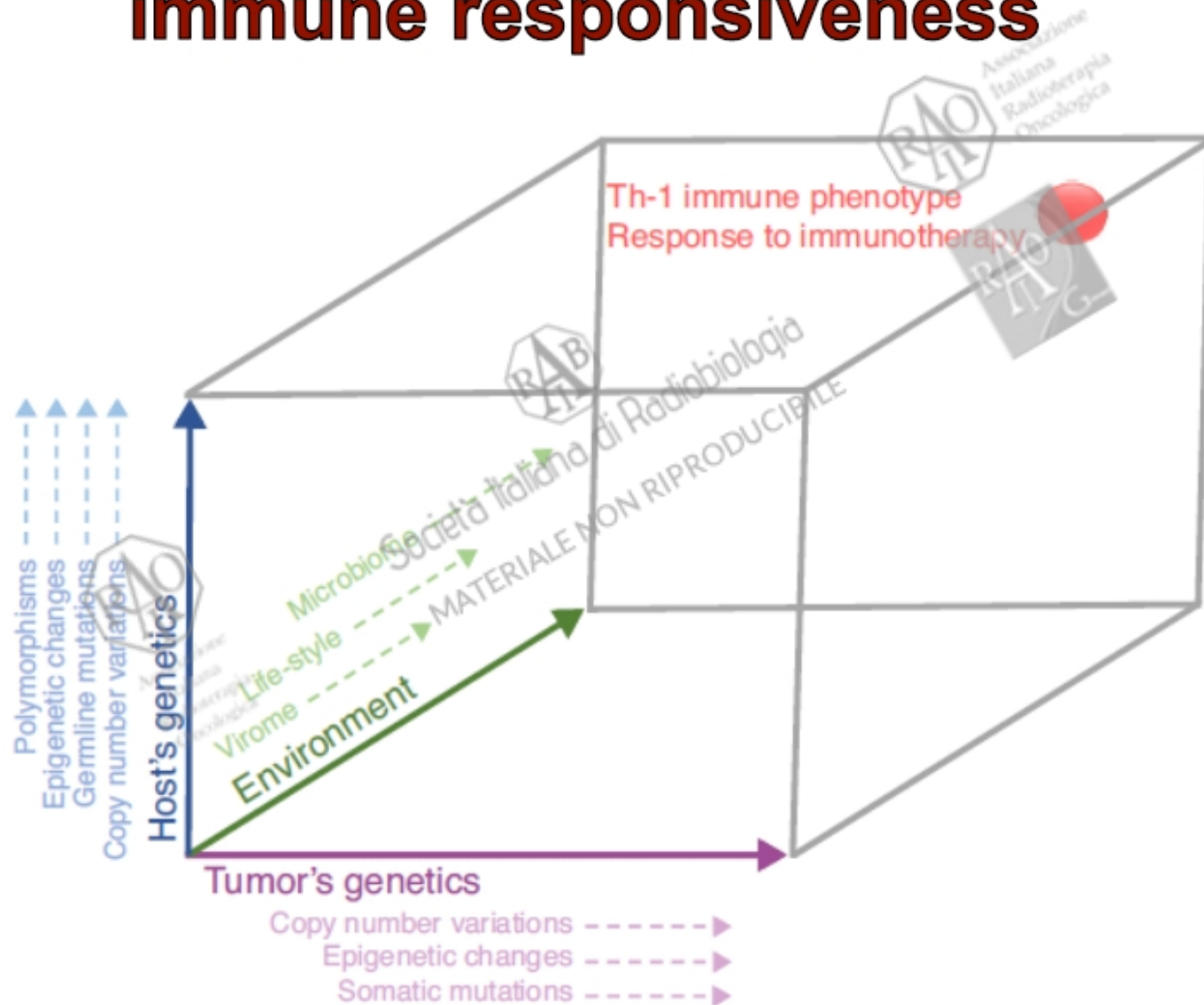
Prospective clinical trials combining either anti-CTLA-4 or anti-PD-1 agents and radiotherapy for advanced melanoma (from www.clinicaltrials.gov, December 2015, in order of estimated completion date).

Registration number	Study design	Eligibility criteria	Intervention	Primary endpoint	Estimated enrolment	Estimated study completion date
NCT01689974	Phase II	Locally unresectable, metastatic melanoma, with at least 2 distinct measurable metastatic sites, one of at least 1 cm or larger	Arm A: IPI alone Arm B: IPI and RT	Response rate	10	Completed in March 2015
NCT01497808	Phase I/II	Metastatic melanoma	IPI and SBRT	Dose-limiting toxicity	40	June 2015 (ongoing, not recruiting)
NCT01557114	Phase I	Unresectable locally advanced or metastatic melanoma with at least one melanoma metastasis accessible to radiation therapy	Induction IPI (4 courses), →RT→ Maintenance IPI	Maximum Tolerated Dose of RT in combination with IPI	30	March 2016
NCT01449279	Single institution, open-label, pilot study	Stage IV melanoma	IPI and palliative radiation therapy	Percentage of patients experiencing serious adverse events in the first 4 months of treatment	20	June 2016
NCT01996202	Phase I	Resected patients at high risk of recurrence/ Neoadjuvant- definitive approach for locally advanced patients	RT and IPI	Incidence of immune related adverse events associated with IPI, acute and late radiation toxicities	24	June 2016
NCT01970527	Phase II	Recurrent/stage IV Melanoma Index lesion between 1 and 5 cm	SBRT (3 fractions) between days 1 and 13 → IPI every 3 weeks (4 courses)	Late toxicity, immune-related clinical response, immune-related PFS, OS	40	September 2016
NCT02115139	Phase II	Melanoma brain metastases	Whole brain RT with concurrent IPI	1-year OS	66	October 2016
NCT02097732	Phase II	Melanoma brain metastases	Standard arm: SRS → IPI (4 cycles) Experimental arm: IPI (2 cycles) → SRS → IPI (2 cycles)	Local control rate	40	May 2017
NCT02107755	Phase II	Oligo-metastatic melanoma	SBRT with concurrent IPI	PFS	32	June 2017
NCT02406183	Phase I	Metastatic melanoma with at least 3 extra-cranial measurable lesions	SBRT with concurrent IPI	Maximum Tolerated dose, with dose-limiting toxicity in 25% of patient	21	July 2017
NCT01565837	Phase II	Oligo-metastatic but unresectable melanoma	SBRT with concurrent IPI	OS, safety and tolerability (acute and subacute toxicity)	50	November 2017
NCT02407171	Phase IIa (expansion cohort)	Metastatic melanoma (with at least one site of measurable disease suitable for SBRT)	SBRT (at maximum tolerated dose discovered in phase I) and Pembro (200 mg every 2 weeks)	Overall response rate	60	December 2018
NCT02562625	Phase II	Unresectable or stage IV melanoma with 1-3 lesions targets for high dose radiotherapy and at least one other lesion which will not be irradiated to assess the abscopal effect of the treatment	Arm 1: Pembro alone Arm 2: Pembro and RT (24 Gy/ 3 fr)	Abscopal effect	234	October 2019
NCT01703507	Phase I	Melanoma brain metastases	Arm A: IPI and WBRT Arm B: IPI and SRS	Maximum tolerated dose of IPI	24	November 2019
NCT02318771	Phase I	Metastatic melanoma (among other tumour types)	• RT (8 Gy/1 fr → 20 Gy/5 fr) → re-biopsy → Pembro • Pembro → RT → Pembro	Change in PD-L1 levels	40	January 2020

Abbreviations: SRS: stereotactic radiosurgery; SBRT: stereotactic body radiation therapy; PFS: progression-free survival; OS: overall survival; IPI: ipilimumab; Pembro: pembrolizumab; NA: not applicable; NR: not reported.

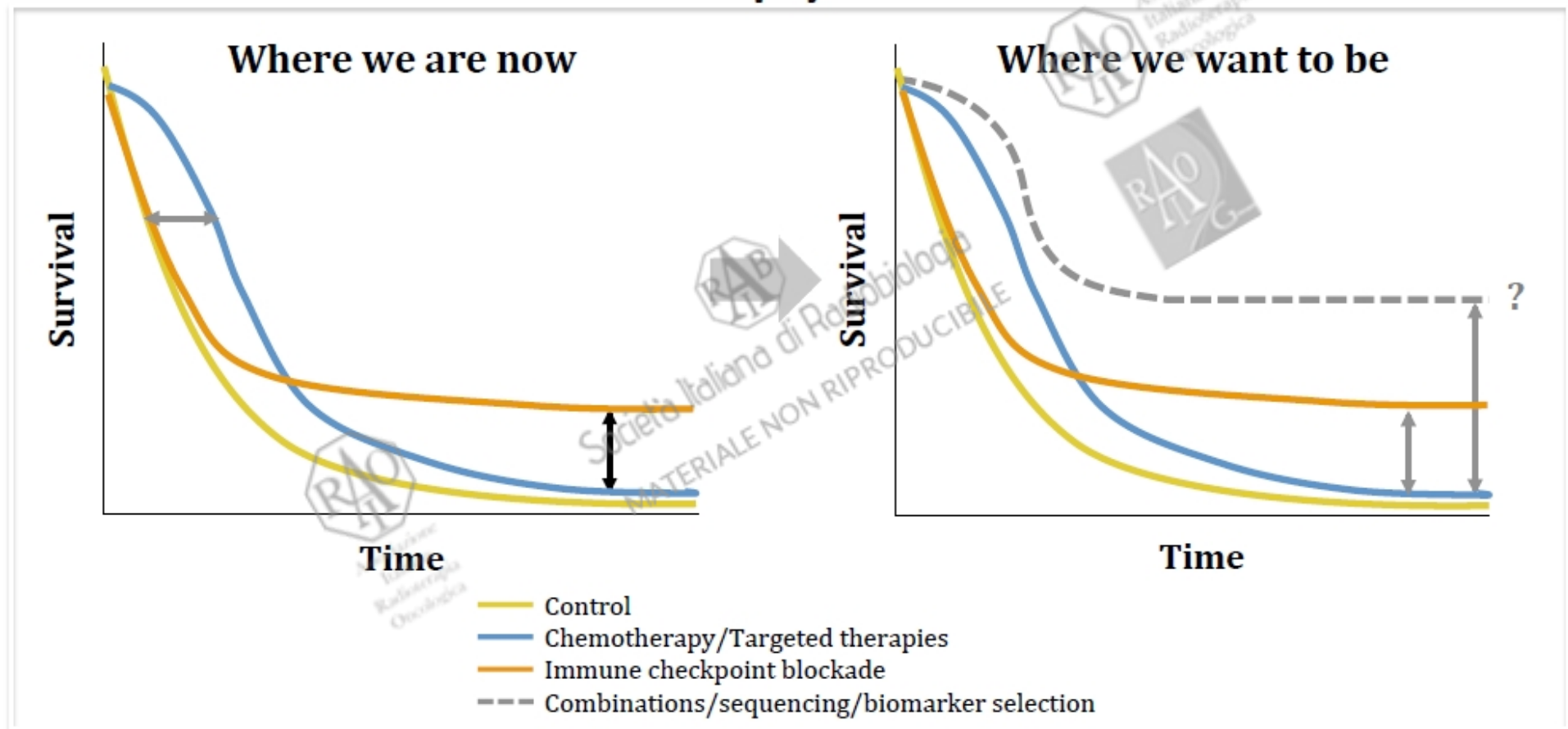


Classes of factors influencing immune responsiveness





Lessons learned :Targeted therapy vs Immunotherapy in melanoma



1. Adapted from Ribas A, presented at WCM, 2013
2. Ribas A, et al. *Clin Cancer Res* 2012;18:336-341
3. Drake CG. *Ann Oncol* 2012;23(suppl 8):



Thank you

