DRUG LAB 1

Le integrazioni di terapia biologica e radioterapia nel melanoma

Carlo Greco
c.greco@policlinicocampus.it

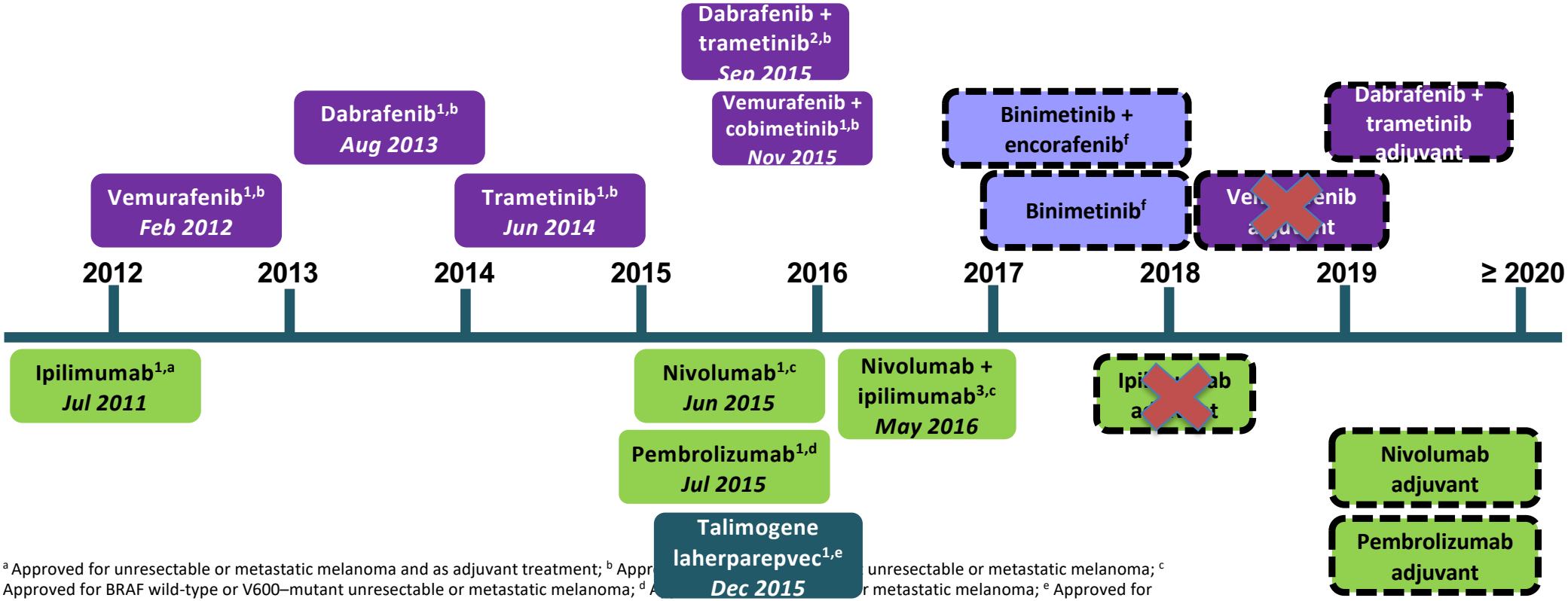
UNIVERSITÀ CAMPUS BIO-MEDICO DI ROMA

DICHIARAZIONE

Come da nuova regolamentazione della Commissione Nazionale per la Formazione Continua del Ministero della Salute, è richiesta la trasparenza delle fonti di finanziamento e dei rapporti con soggetti portatori di interessi commerciali in campo sanitario.

- Posizione di dipendente in aziende con interessi commerciali in campo sanitario
- Consulenza ad aziende con interessi commerciali in campo sanitario (**NIENTE DA DICHIARARE)**
- Fondi per la ricerca da aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**
- Partecipazione ad Advisory Board **(NIENTE DA DICHIARARE)**
- Titolarietà di brevetti in compartecipazione ad aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**
- Partecipazioni azionarie in aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**

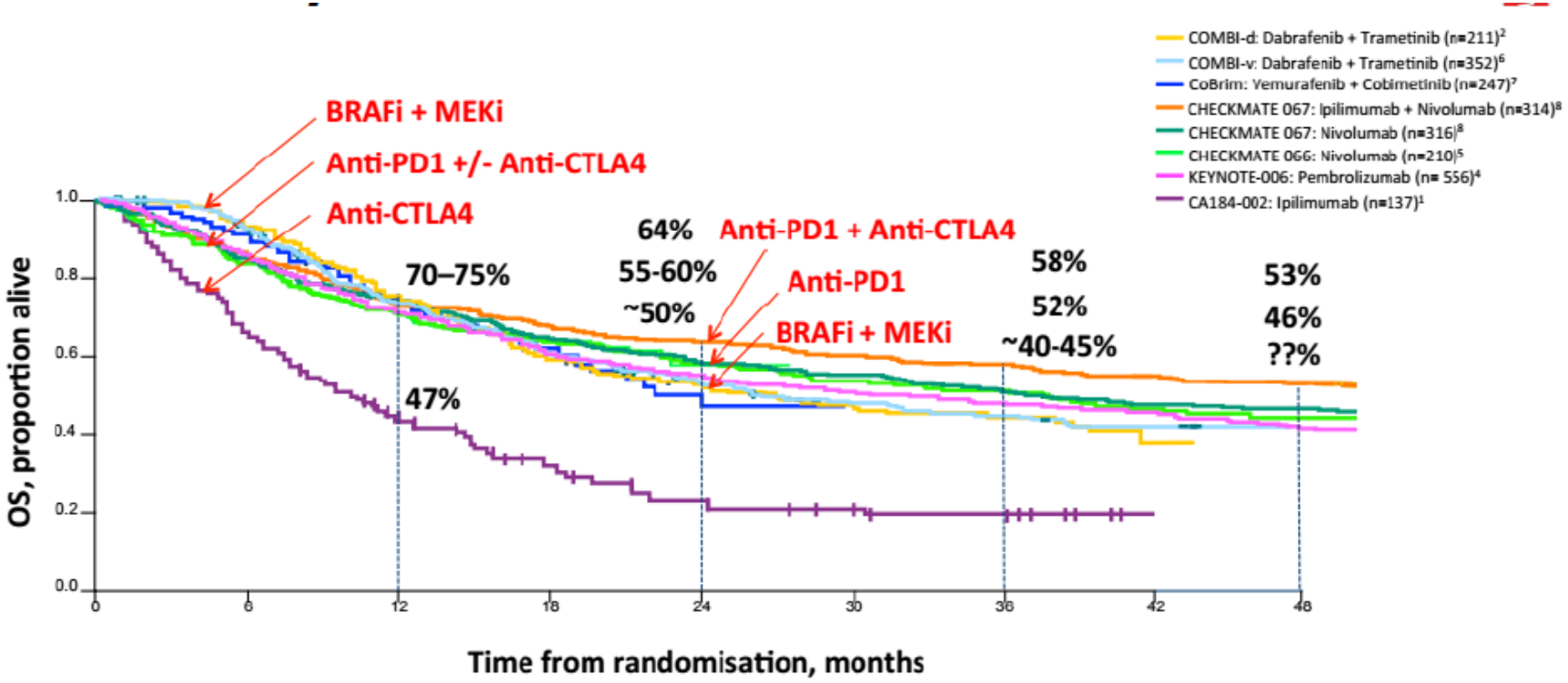
Metastatic Melanoma: Available Treatments 2011 to ≥ 2020



[a] Approved for unresectable or metastatic melanoma and as adjuvant treatment; [b] Appr… unresectable or metastatic melanoma; [c] Approved for BRAF wild-type or V600–mutant unresectable or metastatic melanoma; [d] A… r metastatic melanoma; [e] Approved for unresectable melanoma that is regionally or distantly metastatic, with no bone, brain, lung, or other visceral disease;
[f] These products are not yet approved for use by regulatory authorities.
Dashed line indicates future-looking indications.

1. European Medicines Agency. http://www.ema.europa.eu/ema/. Accessed 13 Sep 2016; 2. Novartis [press release]. https://www.novartis.com/news/media-releases/novartis-receives-eu-approval-tafinlar%C2%AE-and-mekinist%C2%AE-first-combination-approved. Accessed 14 Sep 2016; 3. Bristol-Myers Squibb [press release]. http://investor.bms.com/investors/news-and-events/press-releases. Accessed 14 Sep 2016.

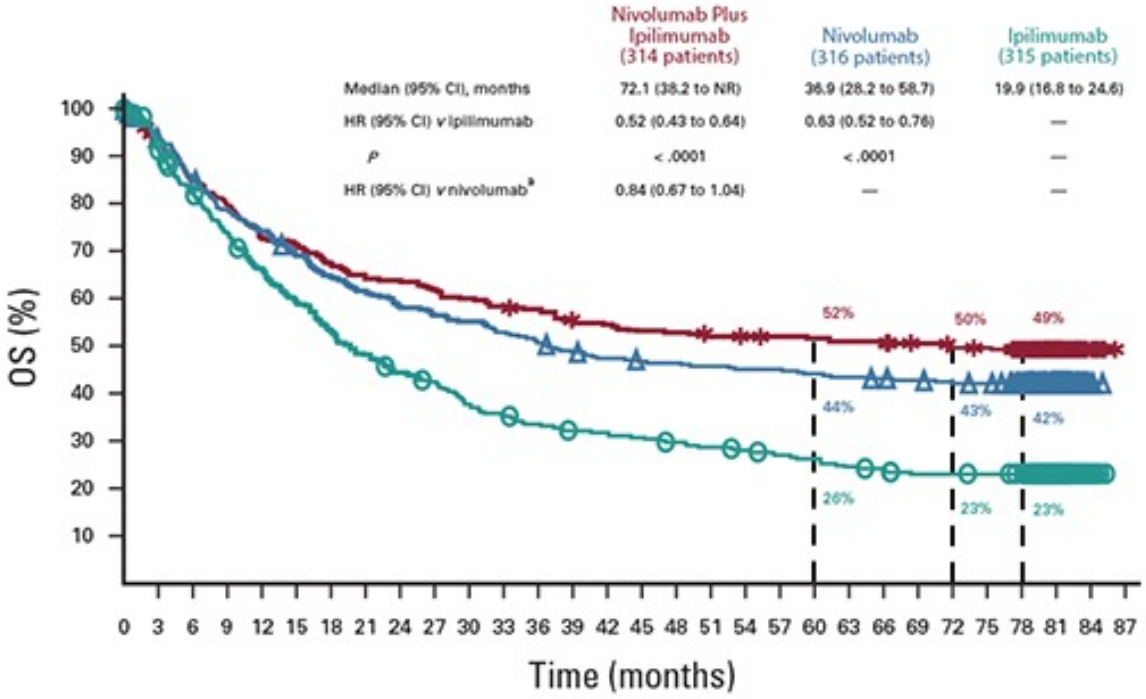
METASTATIC MELANOMA
OVERALL SURVIVAL WITH NEW APPROACHES



CheckMate-067

Table 1. Response to Treatment.*

Variable	Nivolumab plus Ipilimumab (N=314)	Nivolumab (N=316)	Ipilimumab (N=315)
Best overall response — no. (%)†			
Complete response	69 (22)	60 (19)	18 (6)
Partial response	114 (36)	81 (26)	42 (13)
Stable disease	38 (12)	30 (9)	69 (22)
Progressive disease	74 (24)	121 (38)	159 (50)
Unable to determine	19 (6)	24 (8)	27 (9)



Larkin N Engl J Med. 2019

Wolchok JD*J Clin Oncol*. 2021.

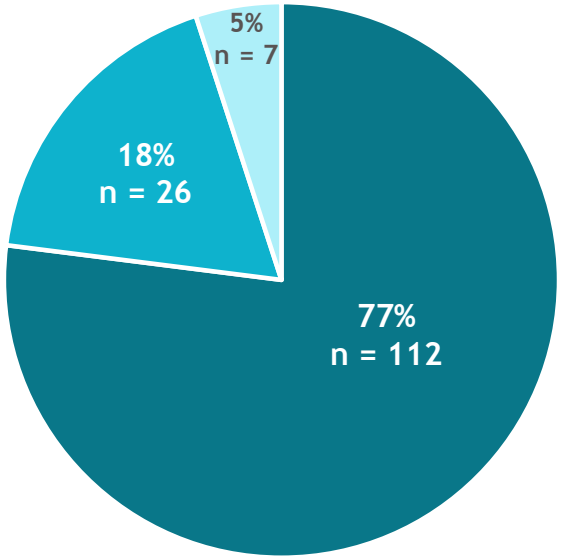
Patients alive and treatment-free at 6.5 years

On study therapy

Received subsequent systemic therapy

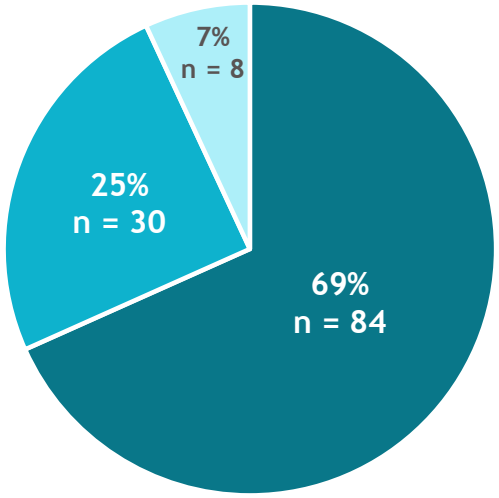
Treatment-free (off study treatment and never received subsequent systemic therapy)

NIVO + IPI (n = 145)



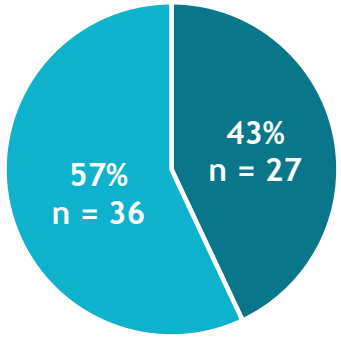
Median follow-up 80.8 mo (range 74.0-86.3)

NIVO (n = 122)



Median follow-up 80.8 mo (range 76.4-85.3)

IPI (n = 63)



Median follow-up 81.0 mo (range 77.0-85.6)

Caso Clinico

2017

- ✓ Uomo, 51 anni
- ✓ 13/7/2017 asportazione di melanoma cutaneo sottoscapolare destra III livello di Clark , Breslow mm 1.5, assenza di segni di regressione; linfonodo sentinella negativo. Stadiazione sistemica negativa.

→ FUP clinico strumentale.

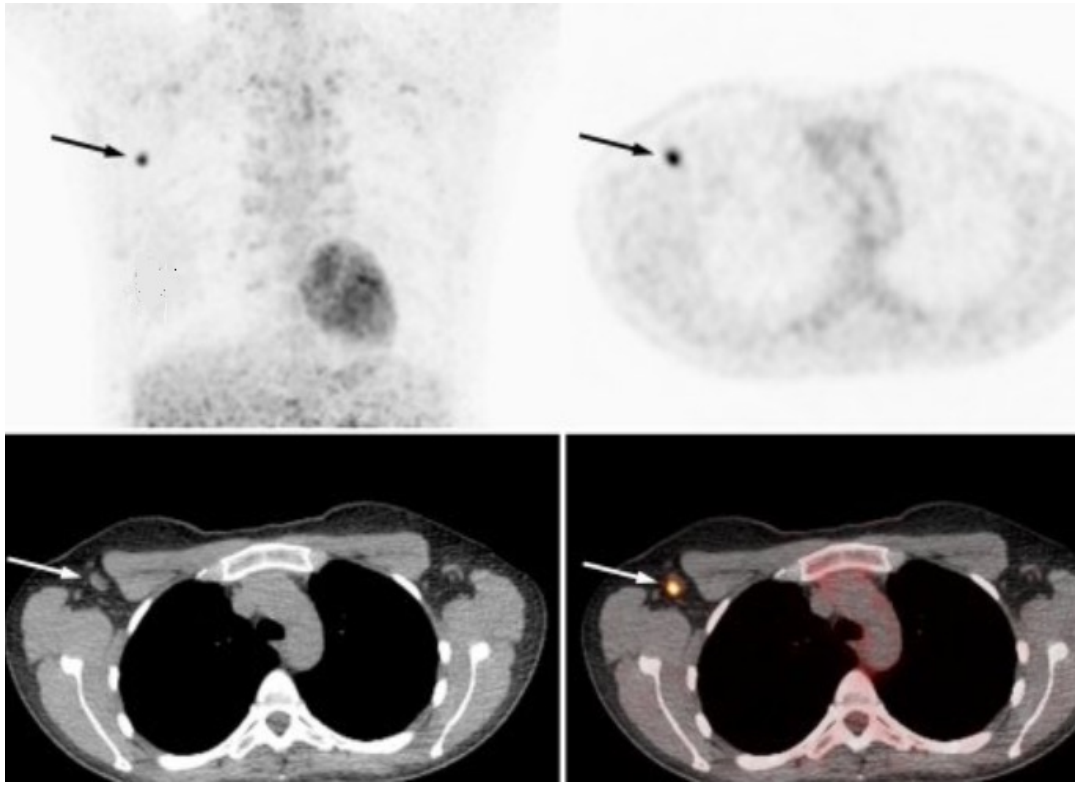
✓15/7/2018 TC TB con mdc comparsa di adenopatia ascellare destra 25 mm
✓25/07/2018 PET/TC captazione patologica a carico di adenopatia (SUV max 9.7)

→ 28/07/2018: Escissione chirurgica

→EI: massiva metastasi di melanoma (HMB 45+) **Braf mutato (V600E)**

→Linfoadenectomia ascellare negativa

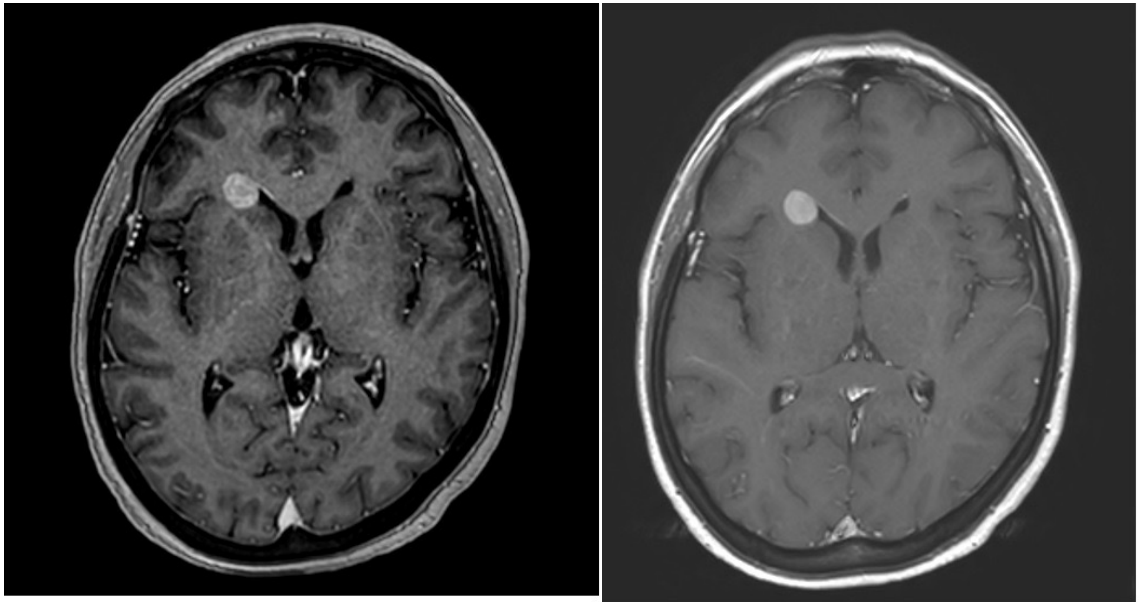
→FUP



2019

✓ **M +** singola encefalica

✓ Stadiazione sistemica negativa



Question Time

a. Proponi inizio della terapia con inibitori di Braf e rivaluti la paziente a 3 mesi con nuova RM

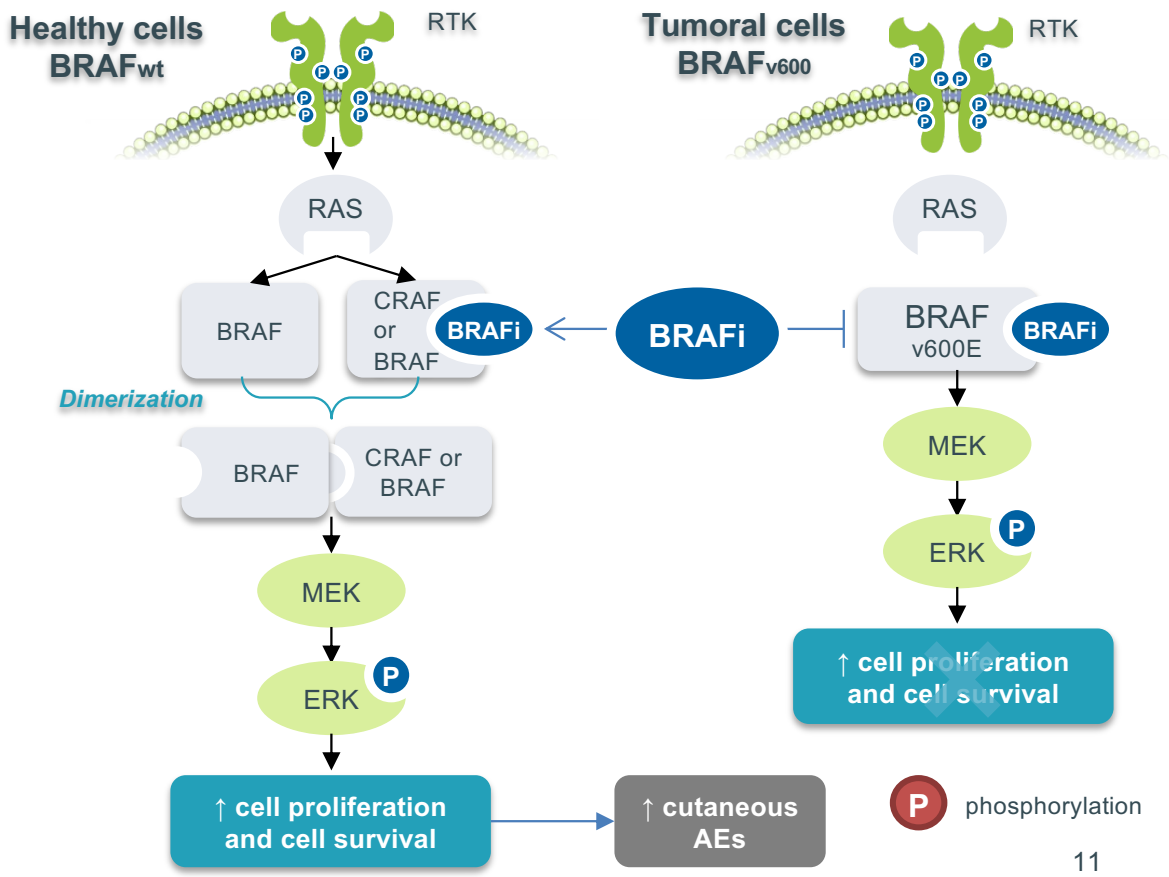
b. Proponi RT whole brain

c. Proponi SRT

Ruolo delle mutazioni *BRAF*

Paradoxical ERK activation and BRAF inhibitors

- **BRAF inhibitors** induce a **conformational change of CRAF or BRAF monomers**, and promote their **dimerization in healthy cells**
- **RAF – RAF dimerization** leads to **the activation of ERK signalling in healthy cells**
- **BRAF inhibitors induce a paradoxical ERK activation in healthy cells**



Poulikakos et al. Nature, 2010
Adelmann et al., 2016, Oncotarget

Treatment Strategies for Metastatic Melanoma 2022- Italy

BRAF wild type

Immunotherapy
1st line
ipilimumab plus nivolumab
nivolumab
pembrolizumab
2nd line
anti CTLA4 ab
ipilimumab or chemotherapy

CT

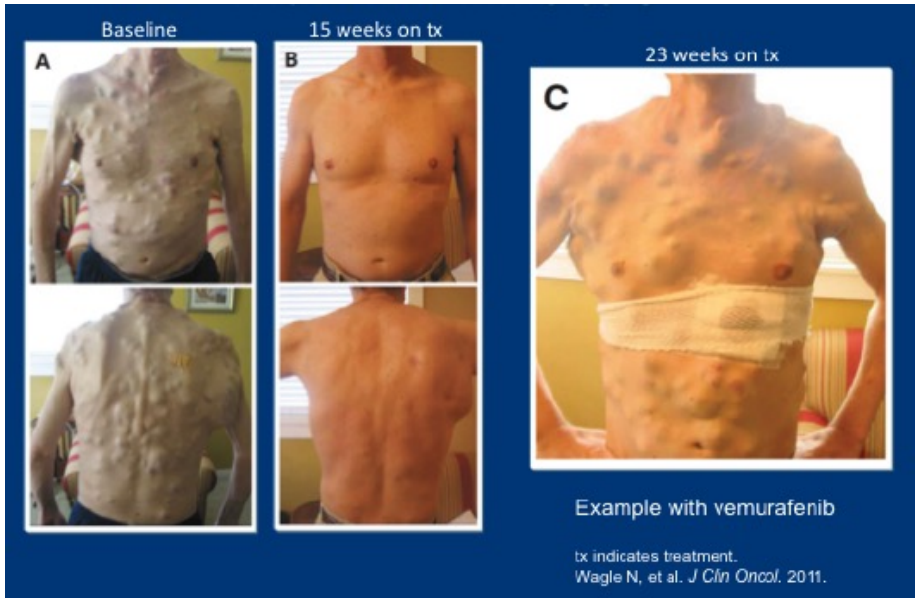
BRAF^{V600} Mutant

BRAF/MEK Inhibition
dabrafenib+trametinib
vemurafenib+cobimetinib
encorafenib+binimetinib

Immunotherapy **1st line**
1st line ipilimumab plus nivolumab
(younger age– PDL1 1% - Brain mets)

nivolumab
pembrolizumab

2nd line
anti CTLA4 ab
ipilimumab

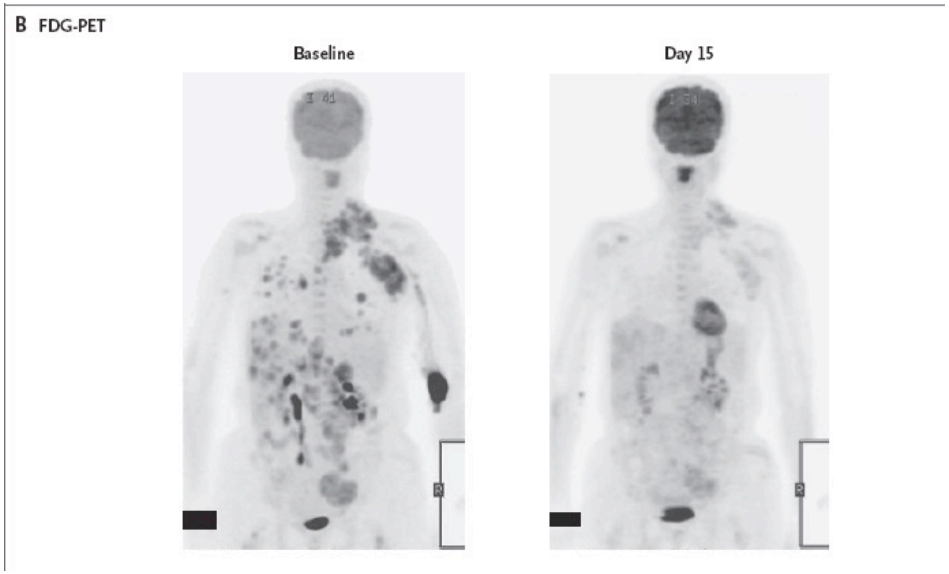


BRAF INHIBITORS

Early and dramatic clinical tumor shrinkage…….

and immediate metabolic responses

"Established" role in highly symptomatic and bulky disease in BRAF mutated patients



Overview of clinical trials of BRAF+MEK inhibitors combination therapy in metastatic melanoma

Phase	Study	Arms
Phase 1	**BRIM-7**	Vemurafenib+cobimetinib
Phase 2	**BRF113220 (part C)**	Dabrafenib Dabrafenib+trametinib (150/1) Dabrafenib+trametinib (150/2)
Phase 3	**coBRIM**	Vemurafenib+placebo Vemurafenib+cobimetinib
	COMBI-d	Dabrafenib+placebo Dabrafenib+trametinib (150/2)
	COMBI-v	Vemurafenib+placebo Dabrafenib+trametinib (150/2)
	Columbus (part 1)	Vemurafenib Encorafenib (300) Encorafenib (450)+binimetinib
	Columbus (part 2)	Encorafenib (300) Encorafenib (300)+Binimetinib

Summary of phase 3 targeted therapy clinical trials

	Clinical Activity		Efficacy				Safety		Study Population		Post-PD Tx
STUDY	**ORR (CR %)**	**Median PFS**	**Median OS**	**2-year OS**	**3-year OS**	**4-year OS**	**G3-4**	**Discontinuation**	**Raised LDH**	**M1c**	**Anti-PD-1**
coBRIM Ascierto Lancet 2016 ASCO 2018	70% (16%)	12.3 months	22.5 months	49%	39%	35%	60%	14%	46%	59%	17%
COMBI-d Long Ann Oncol 2017	69% (16%)	11.0 months	25.1 months	52%	44%	NA	35%	9%	36%	67%	9%
COMBI-v Long JCO 2018	67% (19%)	12.1 months	26.1 months	53%	45%	NA	58%	15%	34%	63%	9%
Columbus Dummer Lancet Oncol 2018 & ASCO 2018	75% (16%)	14.9 months	33.6 months	58%	47%	NA	47%	12%	29%	64%	23%*

Data reported only for combination therapy

*including anti-CTLA-4+anti-PD-1 in 3% of pts

- **More patients in the coBRIM and COMBI trials had baseline LDH>ULN**
- **Less patients in the Columbus trial had baseline LDH>ULN and more patients in the Columbus trial received anti-PD-1 as a post-PD systemic therapy**

BRAF inhibitors single-agent vs BRAF/MEK combinations
Adverse events of interest

Toxicity	vemurafenib	*vemurafenib+ cobimetinib*	*dabrafenib*	*dabrafenib+ trametinib*	*encorafenib*	*encorafenib + binimetinib*
Photosensitivity	++ (15%)	+++ (28%)	+/-	+/- (4%)	+/-	+/- (5%)
Rash	++	++	+/-	+/-	+/-	+/-
Hand-foot skin reaction*	+/-	-	+	-	++ (50%)	+/-
Hyperkeratosis	+	+/-	++	+/-	++	+/-
Keratoacanthoma/ Squamous cell carcinoma	+++ (15-20%)	+/- (3%)	++(9%)	+/- (1-2%)	+ (4%)	+/- (1%)
Pyrexia (+/-chills)	+ (20%)	+(25%)	++ (33%)	+++ (50-55%)	+/-	+ (18%)
Arthralgia	++	+	+	+	+	+
Headache	+	-	+	+	+	+
Fatigue	+	+	+/-	+	+/-	
Gastrointestinal toxicity	+	++	+/-	+/-	++ (30-40%)	++ (30-40%)
Liver toxicity	+	++	-	+/-	+/-	+/-
QTC prolongation	+	+	+/-	-	+/-	-
Hypertension		-		+ (20-25%)		+/- (11%)
Ejection fraction decrease		+/- (5-10%)		+/- (5-10%)		+/- (8%)
Chorioretinopathy		+ (12%)		+/-		+ (20%)

Melanoma Brain Mets (MBM): background

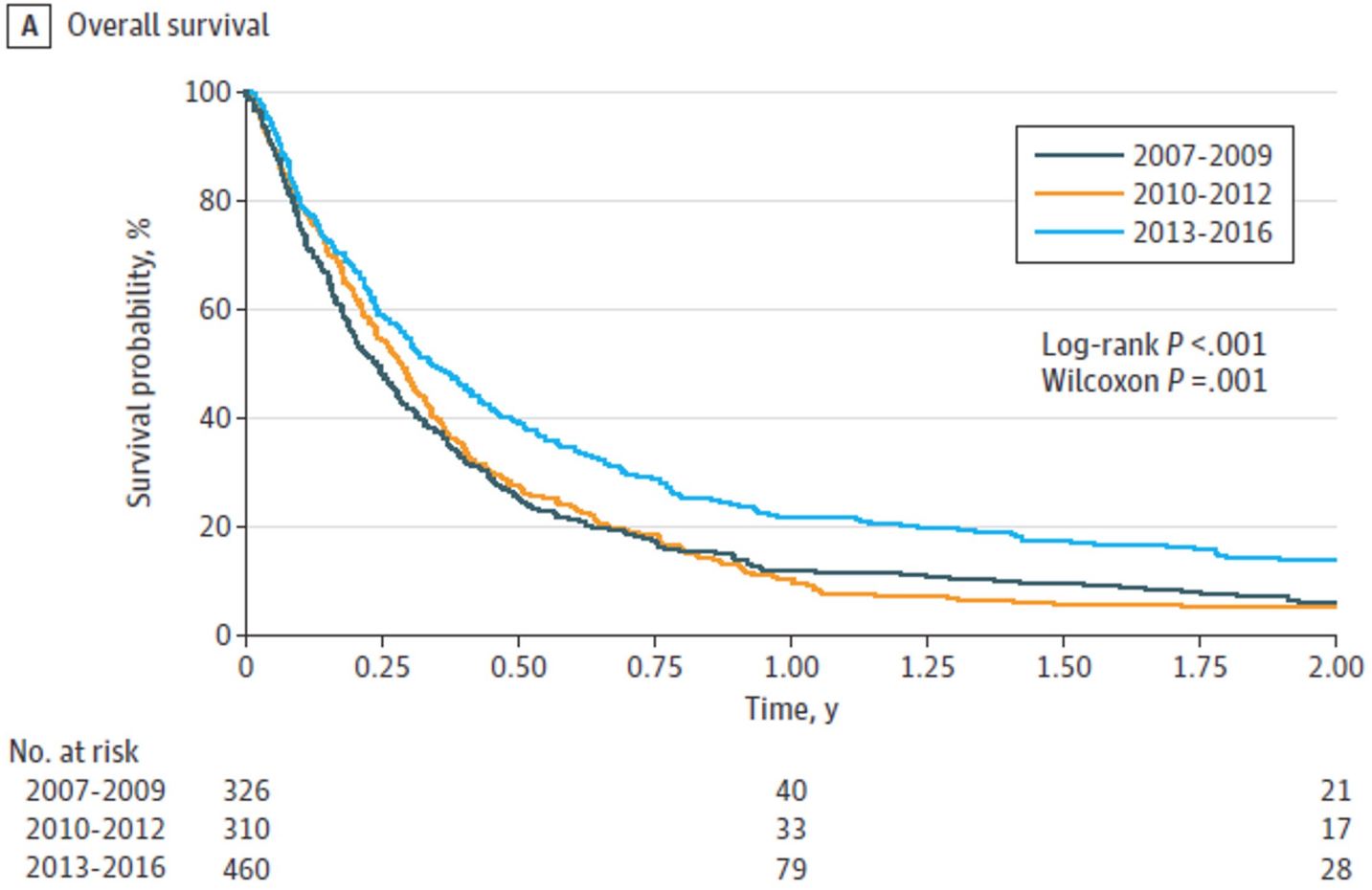
- Melanoma is the 3rd most common cause of brain metastases (after lung and breast)
- ~7% of patients with melanoma have BM at diagnosis
- Melanoma exhibit the highest CNS tropism and 40-50% of stage IV melanoma develop BM (even more among BRAF positive patients)
- Historical median OS for stage IV d was 4 months with a 3-months survival rate of 43%.

AJCC 8th Edition

M Category	Anatomic Site	LDH Level
M1d	**Distant metastasis to CNS with or without M1a, M1b, or M1c sites of disease**	**Not recorded or unspecified**
M1d(0)		Not elevated
M1d(1)		Elevated

Gershenwald et al. CA Cancer J Clin. 2017 Nov;67(6):472-492; Becco P et al. Cancers (Basel) 2020 Jun 21;12(6):1640. Drago et al, Melanoma Research 2019

MBM: survival improvement over time



2-year survival rate

2007-2009: **6,4%**

2010-2012: 5,5%

2013-2016: 13,8%

Brastianos et al. JAMA Network Open, 2020;3(7):e208204. Tawbi et al. EDBK_200819 Am Soc Clin Oncol Educ Book 38 (May 23, 2018) 741-750

BRAFi inhibitors monotherapy in MBM

Study (pretreated)	Trial Design	Drug(s)	No. Patients	IC ORR % (CR + PR)	mPFS (Months)	mOS (Months)
Dummer R. (2014)[1]	Phase II	**Vemurafenib**	24	16	3.9	5.3
Falchook G.S. (2012)[2]	Phase I	**Dabrafenib**	10	NA	4.2	NA
Arance A.M. (2016)[3]	Observational	**Vemurafenib**	66	18	NA	NA
Long G.V. (2012)[4] - **BREAK-MB** (Cohort A: no previous local treatment; cohort B: PD after local treatment)	Phase II	**Cohort A BRAFV600E Dabrafenib**	74	39.2	16.1 wks (≈ 3.7 mo)	33.1 wks (≈7.6 mo)
		Cohort A BRAFV600K Dabrafenib	15	6.7	8.1 wks (≈ 1.9 mo)	16.3 wks (≈3.8 mo)
		Cohort B BRAFV600E Dabrafenib	65	30.8	16.6 wks (≈3.8 mo)	31.4 wks (≈7.2 mo)
		Cohort A BRAFV600K Dabrafenib	18	22.2	15.9 wks (≈ 3.7 mo)	21.9 wks (≈ 5.1 mo)
McArthur G.A. (2017)[5] (Cohort 1: previous untreated BM; cohort 2: previously treated BM)	Phase II	**Cohort 1 Vemurafenib**	90	18	3.7*	8.9
		Cohort 2 Vemurafenib	56	18	4.0*	9.6

Dummer et al. Eur J Cancer 2014. Falchook et al. Lancet. 2012. Arance et al. 2016. Long et al. Lancet Oncol 2012. McArthur et al. Ann Oncol. 2017

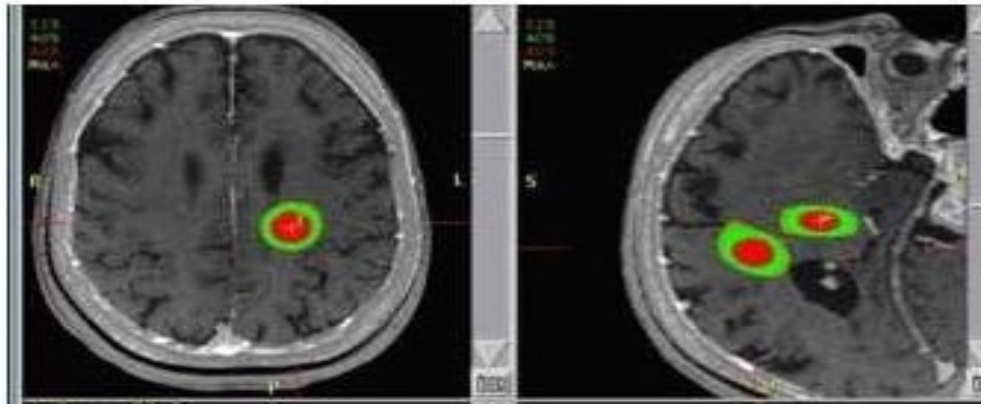
Is radiation delivery safe if target therapy is concurrently administered?

Few clinical data exist on the safety of combination of Radiotherapy with many of the present targeted drugs, and most data are from small patient series with relatively short follow up

The combination of RT and targeted therapies unfortunately might also account for increased toxicity to normal tissue from the combination of the two

Severe radiotherapy-induced EXTRACUTANEOUS TOXICITY under vemurafenib.

The first patient, a female aged 32, treated with vemurafenib for three months, presented a steroid-dependent RADIONECROSIS after brain stereotactic radiosurgery. Symptoms persisted until her death six months later.



Pulvirenti ,J Clinical Oncol Vol 32, 2014

Study	Study year	Study type	*N* (patients/ lesions)	Dose (Gy) (median/ fractions)	Targeted drug	Start of targeted drug	Primary tumor	Treated site	Treatment timing	Follow-up (median months)	Toxicity (⩾3)	Infield Toxicity (⩾3)
Ahmed et al. [54]	2015	Retrospective	24 (80)	21/1	Vemurafenib 960 mg p.o./2xd	Median 5.2 m (0.4–17.1 m) before SRT, paused 2–3 days before/ after SRT	Melanoma	Brain	Oligometastatic disease	5.1	Y	Y
Peuvrel et al. [60]	2013	Case report	1 (2)	20/1	Vemurafenib 960 mg p.o./2xd	3 months before SRT, concurrent	Melanoma	Brain	Oligoprogression	NR	Y	Y
Narayana et al. [57]	2013	Retrospective	6 (14)	20/1	Vemurafenib 960 mg p.o./2xd	Before, concurrent or after SRT median 8.7 w (range 2.6–113.6 w)	Melanoma	Brain	Advanced metastatic	12.2	N	N
Ly et al. [57]	2015	Restrospective	17 (96)	20/1	Vemurafenib 720 mg ($n = 4$) or 960 mg ($n = 3$) p.o./2xd ($n = 4$); Dabrafenib 150 mg p.o./2xd ($n = 9$); unknown BRAF-Inhibitor ($n = 1$)	Before or after SRT, paused during SRT median 7 days, range 1–20 days	Melanoma	Brain	Advanced metastatic	10.5	NR	NR
Liebner et al. [59]	2014	Case report	2 (4)	22, 24, 27/1 or 30/5	Vemurafenib 960 mg p.o./2xd	1–3 m before SRT, paused during SRT	Melanoma	Brain	Advanced metastatic	NR	Y	Y
Stefan et al. [61]	2016	Case report	1 (1)	10/1	Vemurafenib 960 mg p.o./2xd	Concurrent, 1 m before SRT	Melanoma	Spine	Advanced metastatic	NR	N	N
Gaudy et al. [55]	2014	Retrospective	24 (209)	20, 28/1	Vemorafenib ($n = 20$); Dabrafenib ($n = 4$), dosage NR	Concurrent ($n = 20$) 2.5 t1/2 after SRT ($n = 4$)	Melanoma	Brain	Advanced metastatic	4.7	Y	Y
Wolf et al. [53]	2016	Prospective	31 (NR)	18/1	Dabrafenib; Vemurafenib; Dabrafenib and Trametinib, dosage NR	Concurrent ($n = 6$); before and after ($n = 12$); after ($n = 12$) > 1 months after SRT; before SRT ($n = 1$)	Melanoma	Brain	Advanced metastatic	NR	NR	NR
Hecht et al. [4]	2015	Retrospective	19 (NR)	SRS dose NR	Vemurafenib; Dabrafenib, dosage NR	Concurrent	Melanoma	Brain ($n = 18$), Body ($n = 1$)	Advanced metastatic	6.6	N	N
Patel et al. [58]	2016	Retrospective	4 (8)	21/1	Dabrafenib 150 mg p.o./2xd and Trametinib 2 mg p.o./1 d	Concurrent ($n = 3$), paused 2–3 days before/ after SRT, start 0.7 m after SRT ($n = 1$)	Melanoma	Brain	Advanced metastatic	10.6	N	N

Kroeze et al. Cancer Treatment Reviews 53 (2017) 25–37

Critical Review

Avoiding Severe Toxicity From Combined BRAF Inhibitor and Radiation Treatment: Consensus Guidelines from the Eastern Cooperative Oncology Group (ECOG)

Christopher J. Anker, MD,* Kenneth F. Grossmann, MD, PhD,†

There is no conclusive evidence linking BRAFi and RT with intracranial neurotoxicity with either fractionated RT or SRS.

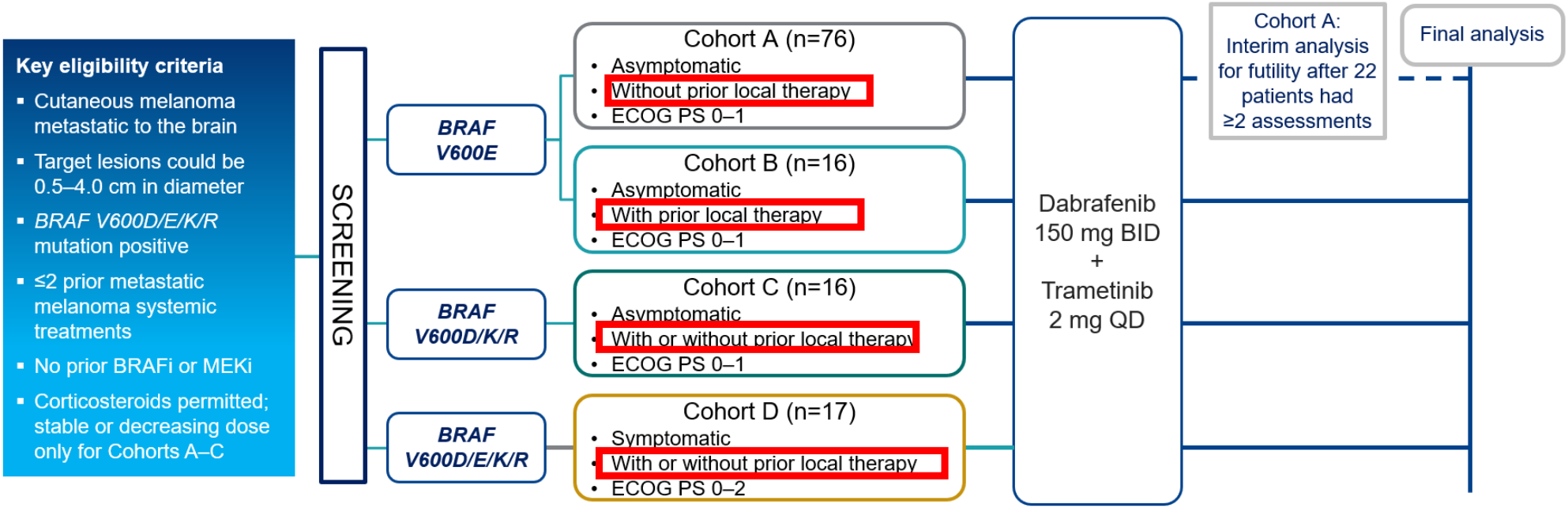
BRAFi and MEKi recommendations (eg, vemurafenib/ dabrafenib and trametinib/cobimetinib)

- Hold ≥1 day before and after SRS.

Anker Int J Radiation Oncol Biol Phys, Vol. 95, No. 2, pp. 632e646, 2016

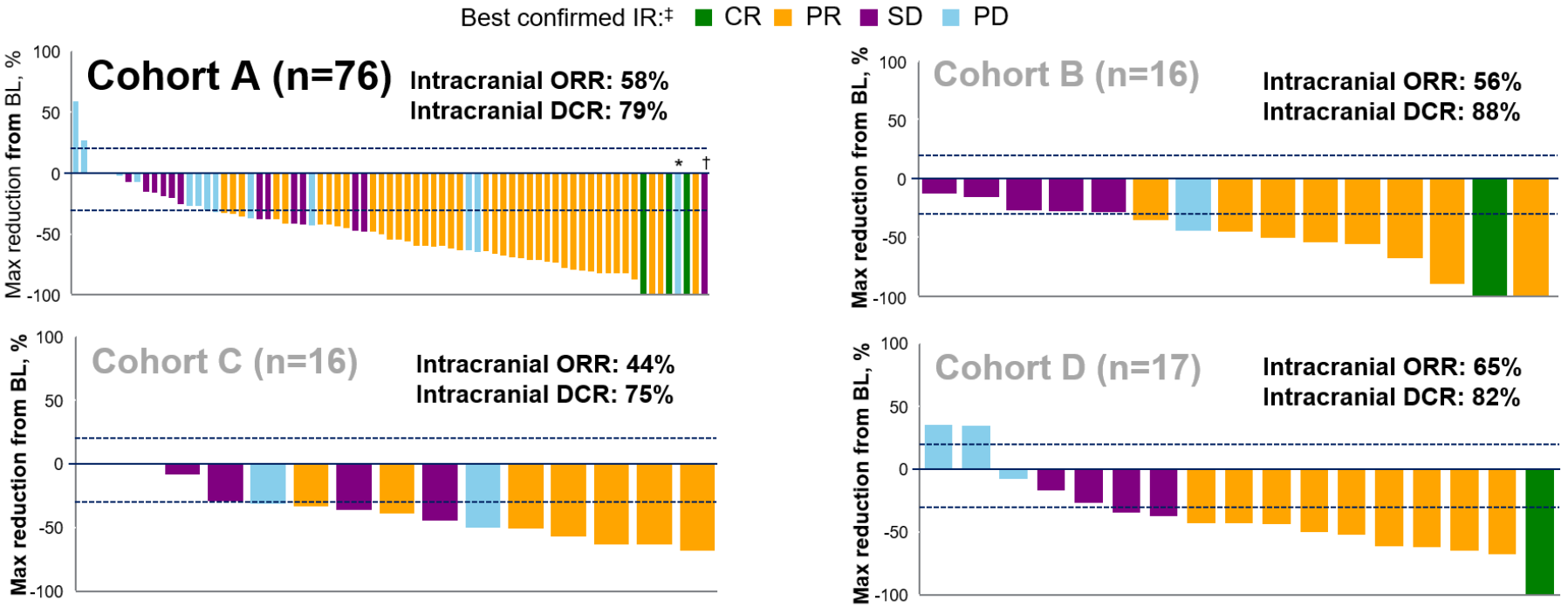
Dabrafenib/trametinib: COMBI-MB

A Phase II, open-Label, multicentre study of dabrafenib + trametinib in subjects with *BRAF* mutation-positive melanoma that has metastasized to the brain.



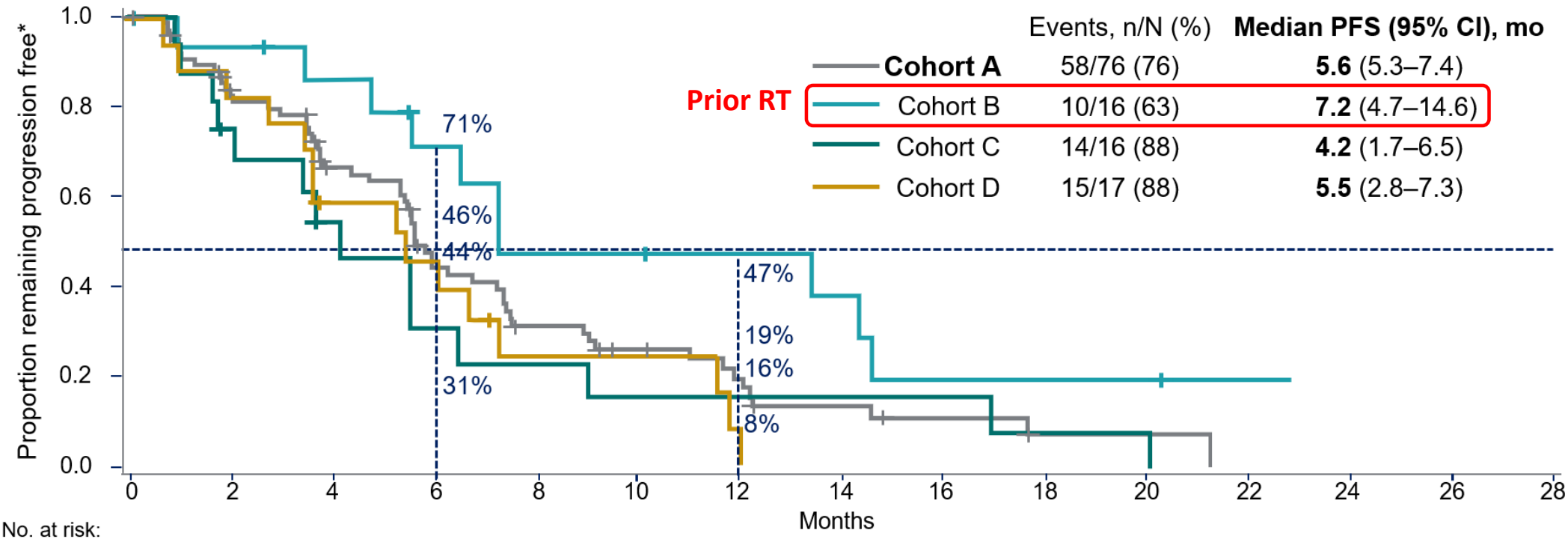
Davies MA, et al. Lancet Oncol. 2017. Davies et al. J Clin Oncol 2017; 35(15)_suppl.9506

Dabrafenib/trametinib: COMBI-MB



Davies MA, et al. Lancet Oncol. 2017. Davies et al. J Clin Oncol 2017; 35(15)_suppl.9506

Dabrafenib/trametinib: COMBI-MB



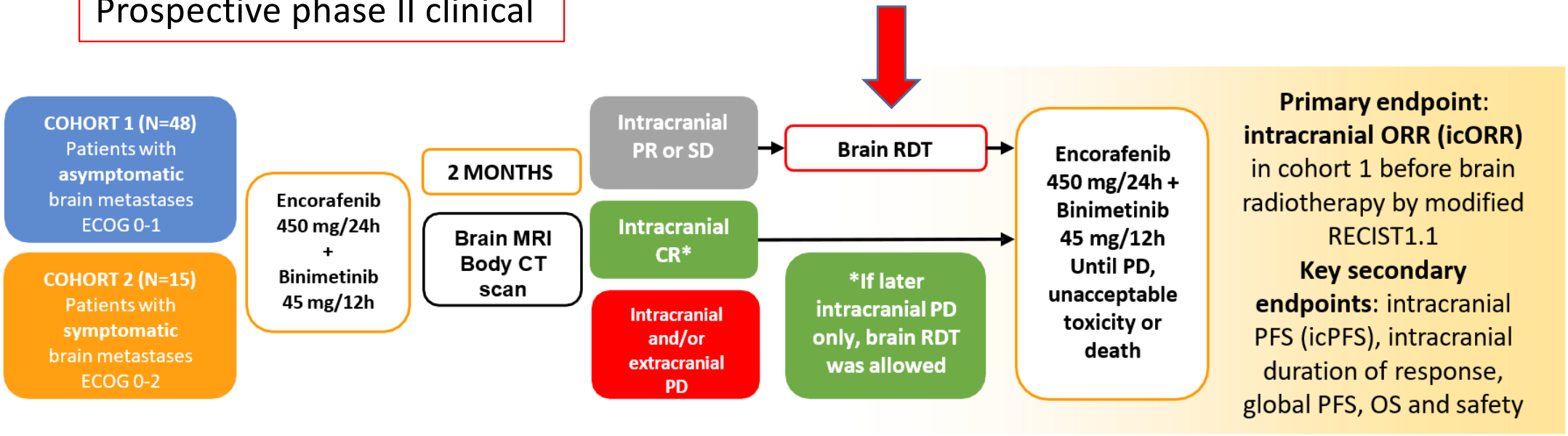
No. at risk:

Cohort A	76	58	43	27	18	13	9	5	3	1	1	0	0	0	0
Cohort B	16	14	12	9	6	6	5	4	2	2	2	1	0	0	0
Cohort C	16	11	7	4	3	2	2	2	2	1	1	0	0	0	0
Cohort D	17	14	9	7	3	3	1	0	0	0	0	0	0	0	0

Davies MA, et al. Lancet Oncol. 2017. Davies et al. J Clin Oncol 2017; 35(15)_suppl.9506

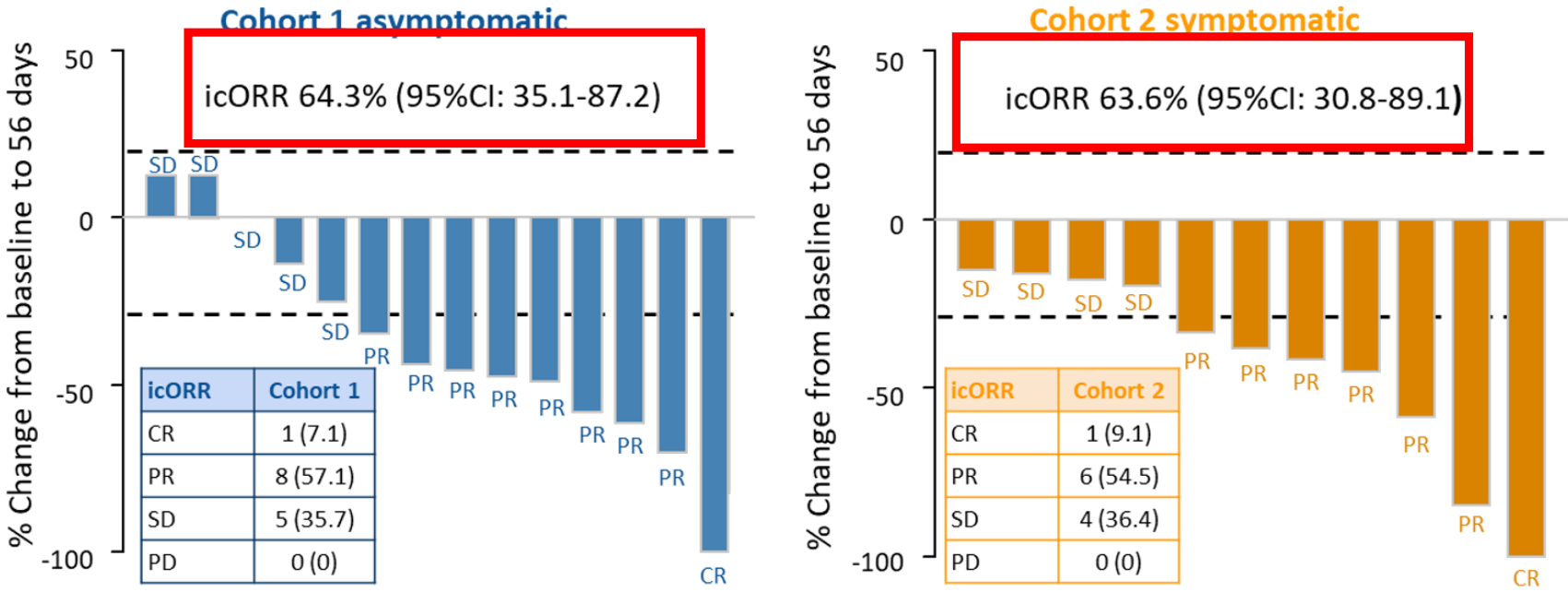
Encorafenib/binimetinib: GEM1802 trial

Prospective phase II clinical



Márquez-Rodas I, et al. ESMO 2021

Encorafenib/binimetinib: GEM1802 trial



icORR	Cohort 1
CR	1 (7.1)
PR	8 (57.1)
SD	5 (35.7)
PD	0 (0)

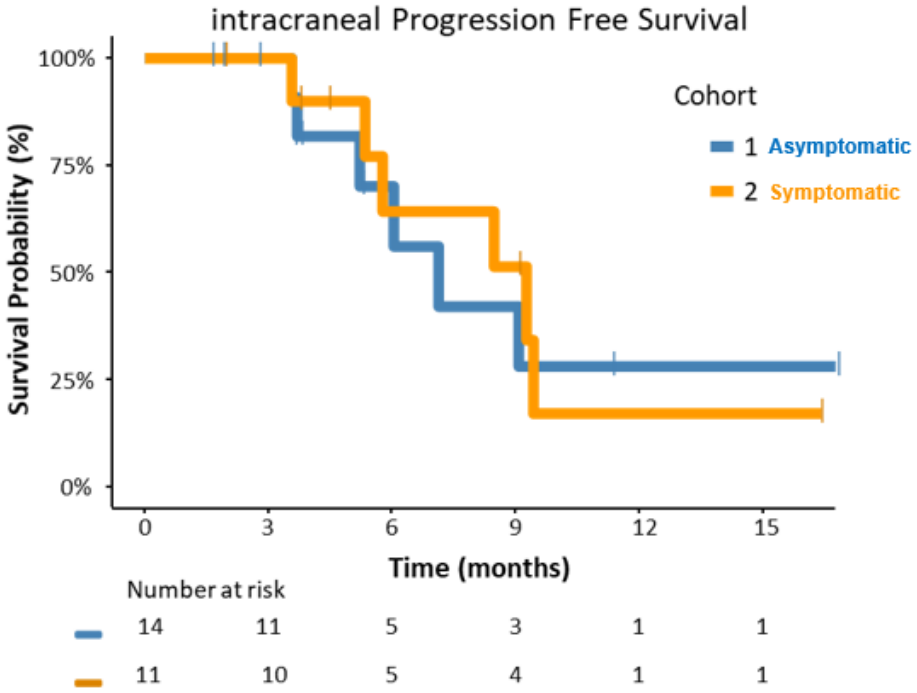
icORR	Cohort 2
CR	1 (9.1)
PR	6 (54.5)
SD	4 (36.4)
PD	0 (0)

Radiotherapy after 2 mo EB	Cohort 1	Cohort 2
RT any, n (%)	10 (71.4)	8 (72.7)
Whole Brain RT, n (%)	4 (40)	5 (63)
Radiosurgery/SRS, n (%)	6 (60)	3 (37)

Márquez-Rodas I, et al. ESMO 2021

Encorafenib/binimetinib: GEM1802 trial

icPFS	6m rate, % (95% CI)	Median (95% CI), m
Cohort 1	70.1 (46.5-100)	7.1 (5.2-NA)
Cohort 2	64.3 (38.5-100)	9.3 (5.8-NA)



TOXICITY

Safety population	Cohort 1 (Asymptomatic)	Cohort 2 (Symptomatic)
	n = 17	n = 15
Toxicities EB related, n (%)	14 (82.4)	9 (60)
Toxicities RT related, n (%)	0 (0)	1 (6.7)
G3-4 Toxicities EB related, n (%)	4 (23.5)	2 (13.3)
G3-4 Toxicities RT related, n (%)	0 (0)	1 (6.7)*
SAE related	1 (5.9)#	1 (6.7)*

*vomiting and #pancreatitis that required hospitalization

There were no deaths associated to EB treatment or RT.

"the safety profile of adding radiotherapy could make this approach feasible, although longer follow-up is needed in order to better characterized this strategy"

Márquez-Rodas I, et al. ESMO 2021

Question Time

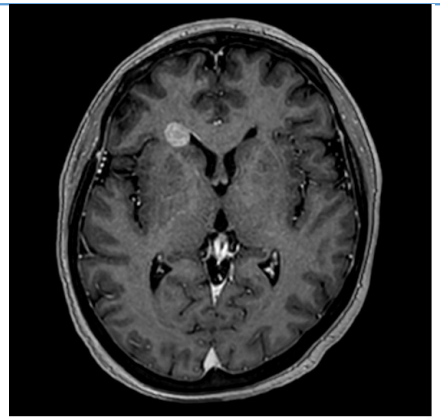
a. Proponi inizio della terapia con inibitori di Braf e rivaluti la paziente a 3 mesi con nuova RM

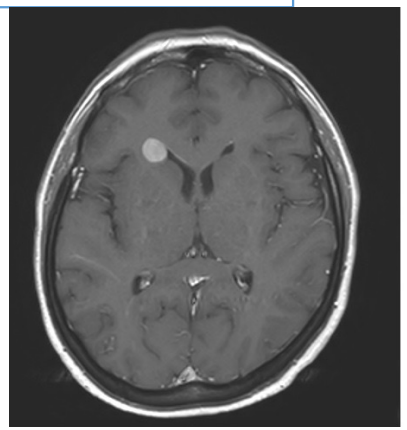
b. Proponi RT whole brain

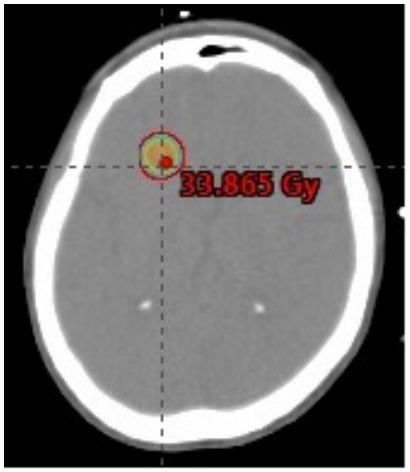
c. Proponi SRT

Dal **14 al al 17 Agosto 2019**

SRT lesione cerebrale 27 Gy (3 fr, disomogeneità 80%) SRT 9Gy x 3 fr



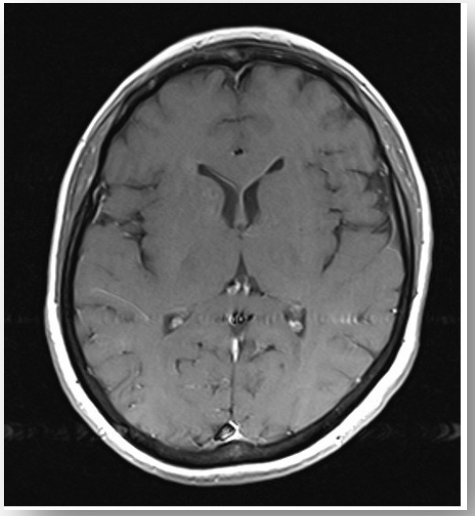




1/9/2018 inizia terapia con **dabrafenib** (150 mg (2 capsule da 75 mg) due volte al giorno (dose giornaliera 300 mg) un'ora prima dei pasti o almeno 2 ore dopo il pasto e **trametimib** 2 mg /die

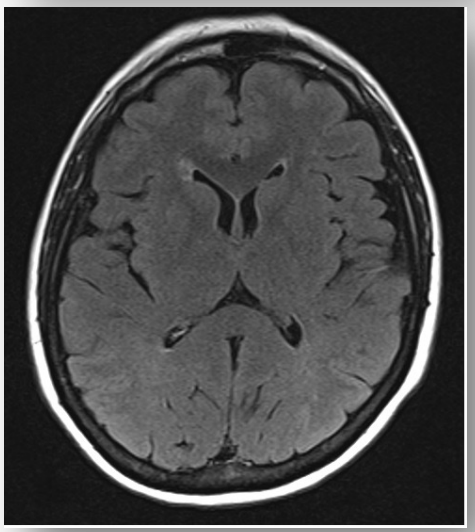
✓Prima rivalutazione:

RM : “*residua area rotondeggiante iperintensa in T1 ed ipointensa in T2/GRE, priva di significativo CE, di 6 mm in adiacenza al corno frontale del ventricolo laterale dx*



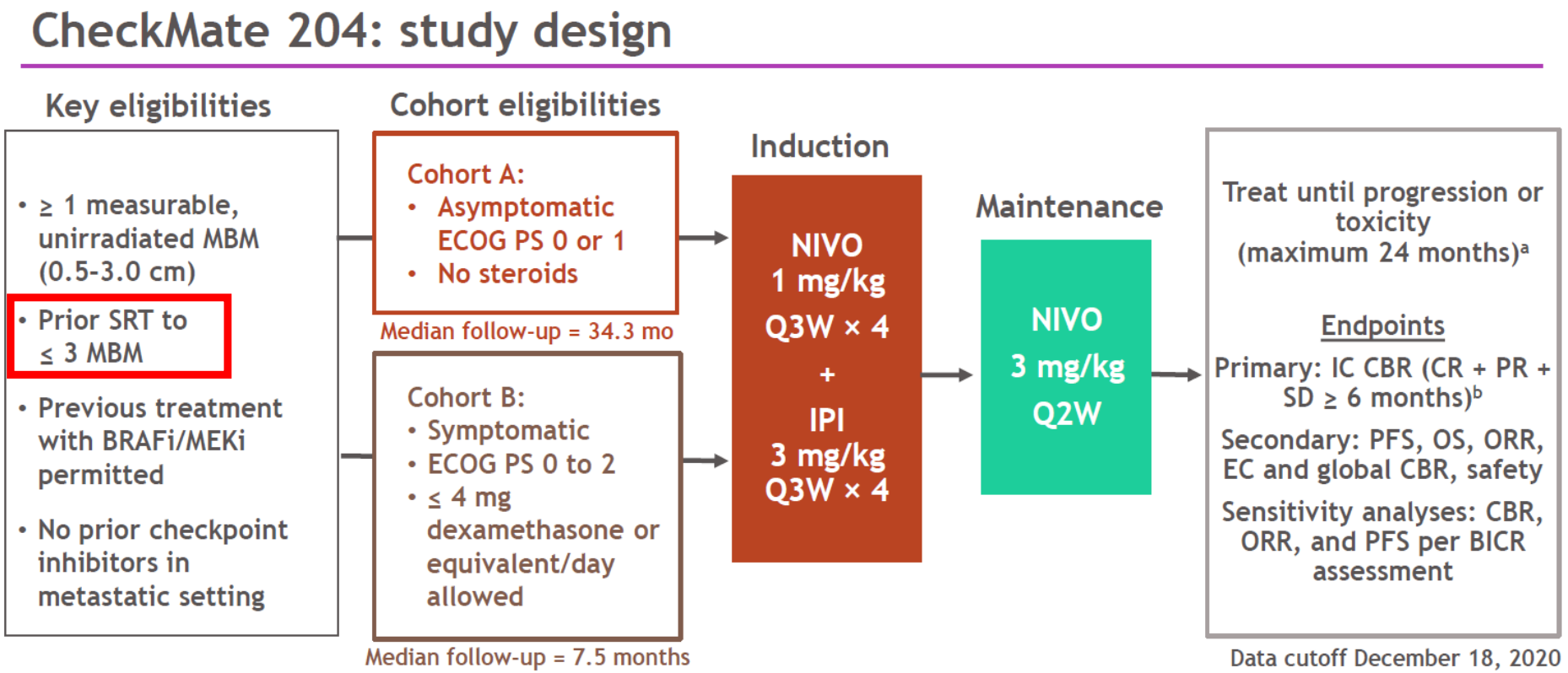
Settembre 2022

✓ RM e TC TB negative



E se il paziente fosse stato BRAF WT?

Nivo/Ipi: Checkmate 204



Minimum follow-up 34.2 months

- Still in follow up: 59 patients in cohort A and 5 patients in cohort B

Tawbi HA, et al. ESMO 2021

Fondazione
Policlinico Universitario
Campus Bio-Medico

Nivo/Ipi: Checkmate 204

Asymptomatic patients' intracranial response to treatment

	Investigator (n = 101)	BICR (n = 101)
Best overall response, n (%)		
Complete response	33 (33)	26 (26)
Partial response	21 (21)	24 (24)
Stable disease ≥6 months	4 (4)	4 (4)
Progressive disease	30 (30)	30 (30)
Not evaluable for CBR[a]	13 (13)	11 (11)
CBR, n/N (%; 95% CI)	58/101 (57; 47-67)	54/101 (53; 43-64)
ORR, n/N (%; 95% CI)	54/101 (53; 43-64)	50/101 (50; 39-60)
Ongoing responders/patients with objective response (%)	46/54 (85)	42/50 (84)

- Median duration of response was not yet reached at 36 months

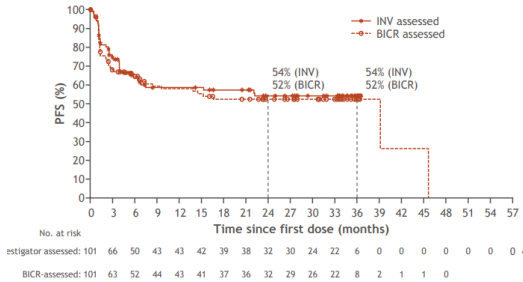
Symptomatic patients' intracranial response to treatment

	Investigator (n = 18)	BICR (n = 18)
Best overall response, n (%)		
Complete response	3 (17)	3 (17)
Partial response	0	1 (6)
Stable disease ≥6 months	0	0
Progressive disease	11 (61)	10 (56)
Not evaluable for CBR[a]	4 (22)	3 (17)
CBR and ORR, n/N (%; 95% CI)	3/18 (17; 4-41)	4/18 (22; 6-48)
Ongoing responders/patients with objective response (%)	3/3 (100)	4/4 (100)

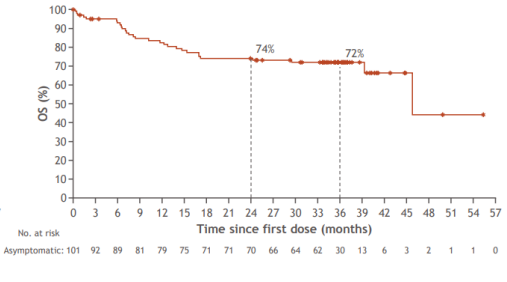
- Median duration of response was not yet reached at 36 months

Survival in asymptomatic patients

Intracranial PFS



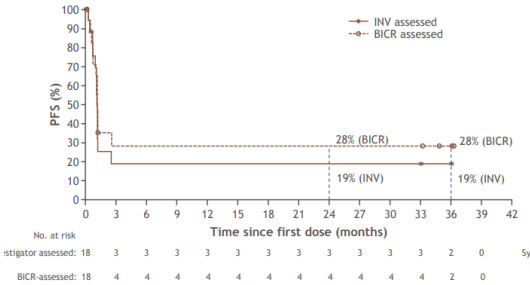
OS



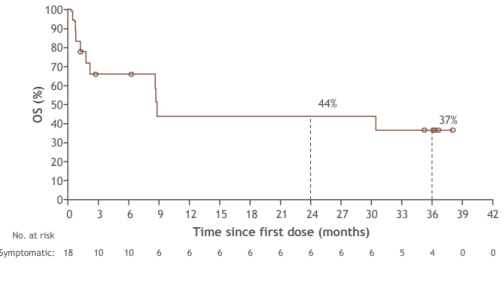
- PFS rates for extracranial and global disease were similar
  - Extracranial 24-month rates were 59% (INV) and 62% (BICR); 36-month rates were 53% and 62%
  - Global 24-month rates were 50% (INV) and 48% (BICR); 36-month rates were 45% and 48%

Survival in symptomatic patients

Intracranial PFS



OS



- PFS rates for extracranial and global disease were similar
  - Extracranial 24- and 36-month rates were 28% (INV) and 36% (BICR)
  - Global 24- and 36-month rates were 24% (INV) and 26% (BICR)

Tawbi HA, et al. ESMO 2021

Local and distant brain control in melanoma and NSCLC brain metastases with concurrent radiosurgery and immune checkpoint inhibition

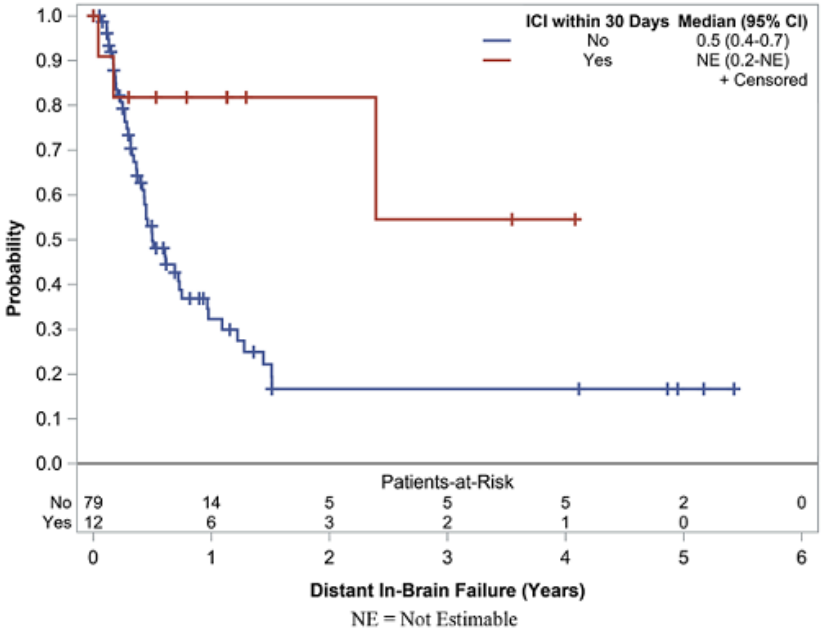
Amy Le[1] · Homan Mohammadi[2] · Toka Mohammed[1] · Heather Burney[3] · Yong Zang[3] · Douglas Frye[4] · Kevin Shiue[1] · Tim Lautenschlaeger[1] · James Miller[5]

144 pts, 95 NSCLC, 49 (34%) Melanoma [477 lesions]

Table 4 Distant in-brain failure univariate and multivariate analysis

Univariate analysis	n	Hazard ratio	95% Confidence interval	p-value
SRS within 30 days of ICI				
Concurrent vs. non-concurrent or no ICI	455	0.21	0.07–0.62	0.0051*
SRS within 60 days of ICI				
Concurrent vs. non-concurrent or no ICI	455	0.74	0.32–1.70	0.4775
SRS within 90 days of ICI				
Concurrent vs. non-concurrent or no ICI	455	1.37	0.59–3.18	0.4564

Fig. 2 Distant in-brain failure



Journal of Neuro-Oncology (2022) 158:481–488

Immune checkpoint inhibitor therapy may increase the incidence of treatment-related necrosis after stereotactic radiosurgery for brain metastases: a systematic review and meta-analysis

Pyeong Hwa Kim [1] · Chong Hyun Suh [1] · Ho Sung Kim [1] · Kyung Won Kim [1] · Dong Yeong Kim [2] · Ayal A. Aizer [3]
Rifaquat Rahman [3] · Jeffrey P. Guenette [4] · Raymond Y. Huang [4]

16 studies (14 on melanoma, 2 on NSCLC)

The incidence of treatment-related **necrosis** was higher inSRS+ICI than SRS alone(16.0%vs.6.5%; p =0.065;OR,2.35).

The incidence of t necrosis ***was significantly lower when analysis was restricted to the studies only including*** ***symptomatic*** *treatment-related necrosis compared to that restricted to the studies including both symptomatic and asymptomatic (8.9% vs. 27.9%; p < 0.001)*

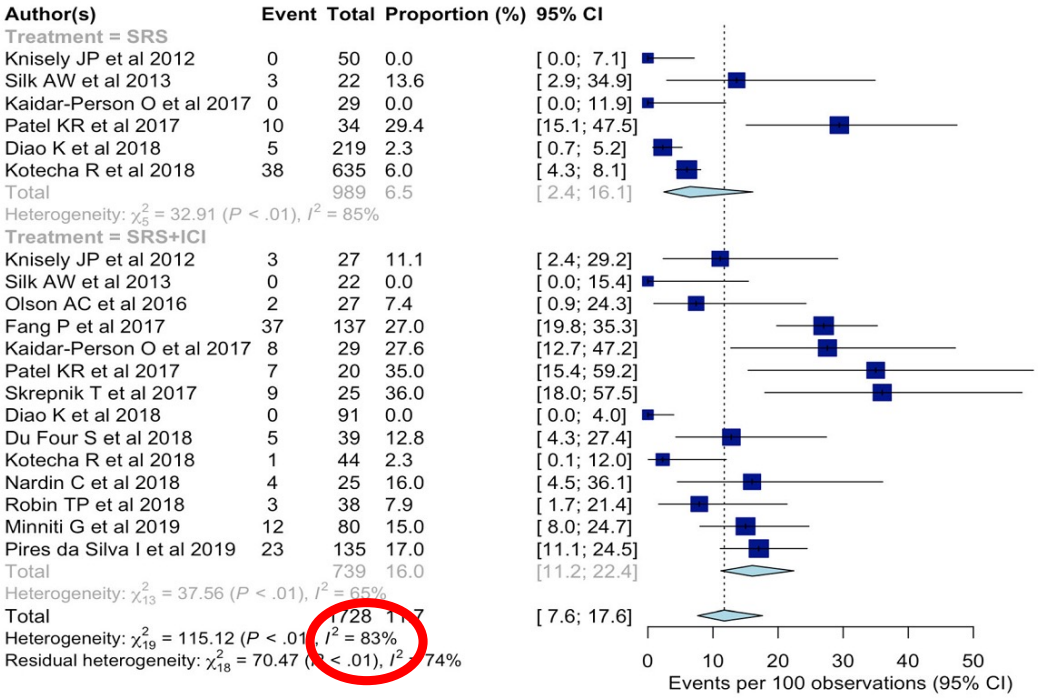
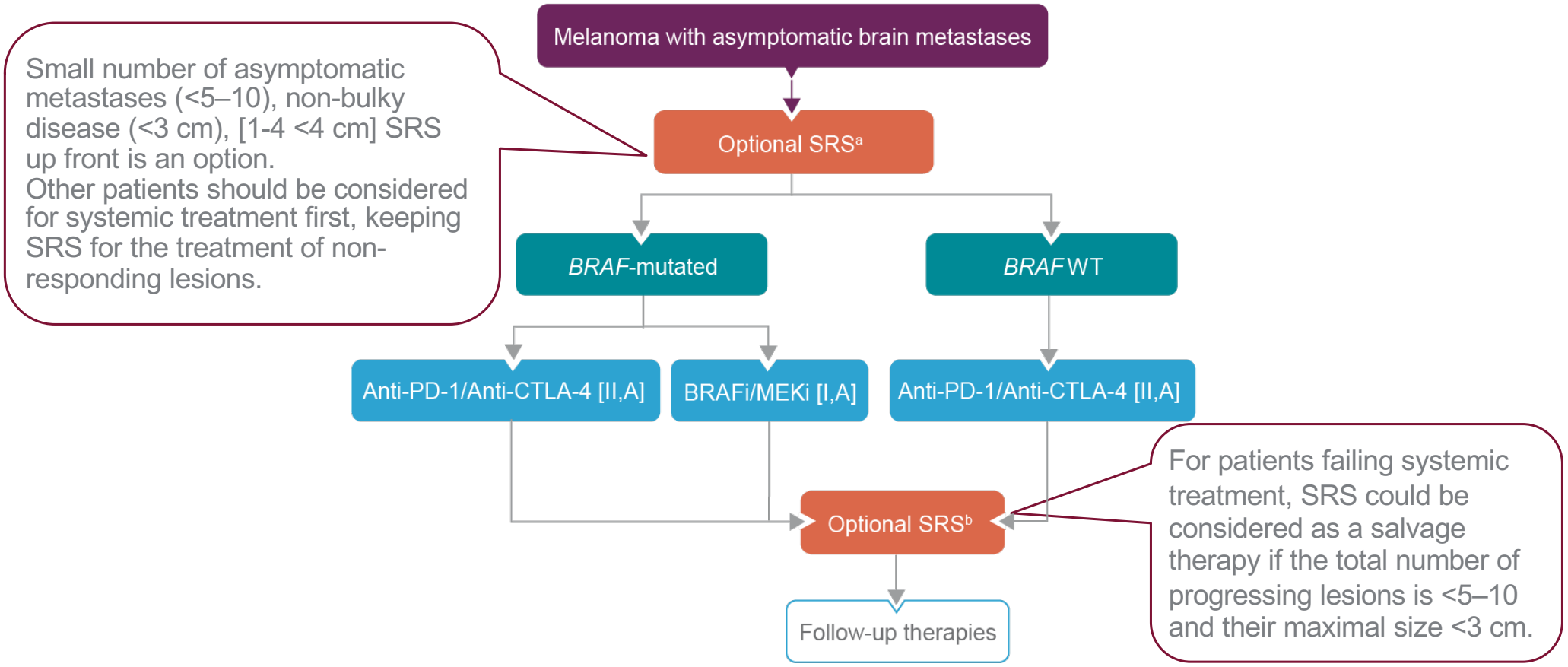


Fig. 2 Forest plot for the incidence of the treatment-related necrosis after the use of stereotactic radiosurgery (SRS) with or without immune checkpoint inhibitor (ICI) in melanoma brain metastasis

European Radiology 2020

Asymptomatic MBM



Any room for induction systemic therapy before SBRT?

Michielin et al. Ann Oncol. 2019

Ongoing clinical trials

EBRAIN-MEL

A Phase 2
multicentre clinical trial

evaluating the activity
of encorafenib + binimetinib
administered
before local treatment
in patients with
BRAF-mutated melanoma metastatic
to the brain.

NCT03898908 – Sponsor: GEM

BEPCOME-MB

A Phase 2
multicentre clinical trial

testing the addition
of upfront stereotactic radiosurgery
to encorafenib + binimetinib +
pembrolizumab
in comparison with
encorafenib + binimetinib +
pembrolizumab alone in patients with
BRAF^{V600} mutation-positive melanoma
with brain metastasis.

NCT04074096 – Sponsor: UNICANCER/EADO

ABC-X

MBM
≥5mm and
≤40mm
Asymptomatic
No prior systemic

nivolumab
+
ipilimumab>>
nivolumab

nivolumab
+
Ipilimumab>>
nivolumab

SRS

NCT03340129

SWOG S2000

BRAF-V600 mutant brain mets

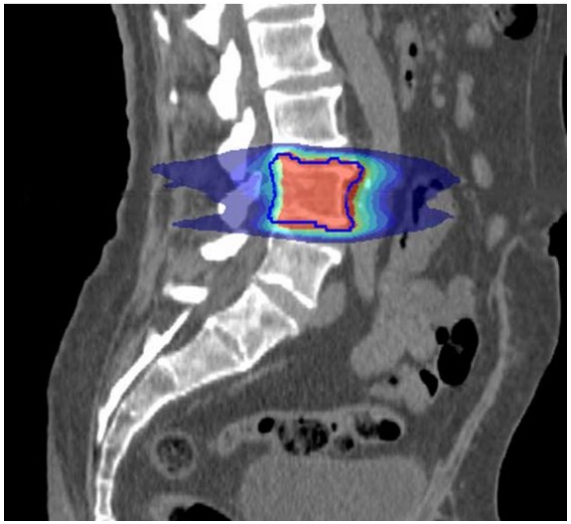
symptomatic
prior adjuvant
allowed

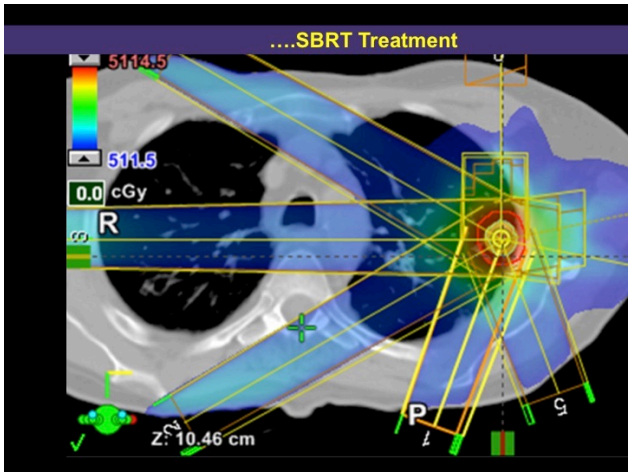
Arm A (n = 50)
Encorafenib (450 mg qday) + **binimetinib** (45 mg PO BID) + **nivolumab 480** mg q4 weeks

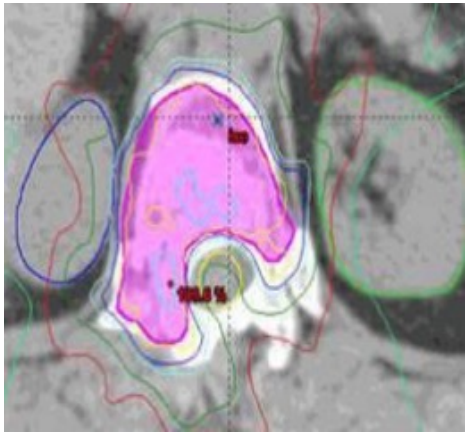
Arm B (n = 50)
Ipilimumab at 3 mg/kg + **nivolumab** 1 mg/kg q3 weeks x4 cycles → nivolumab 480 mg q4 wks

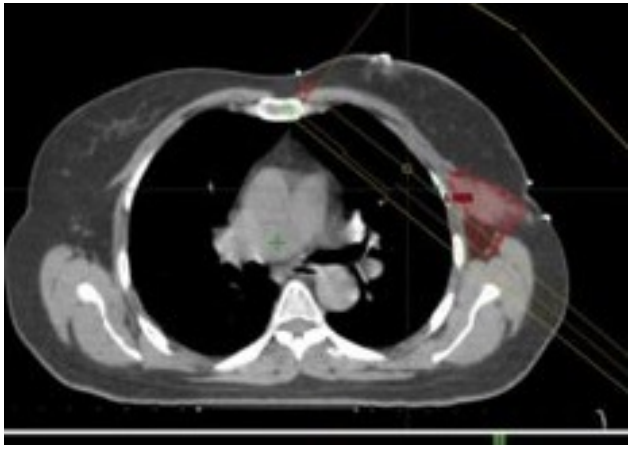
NCT04511013

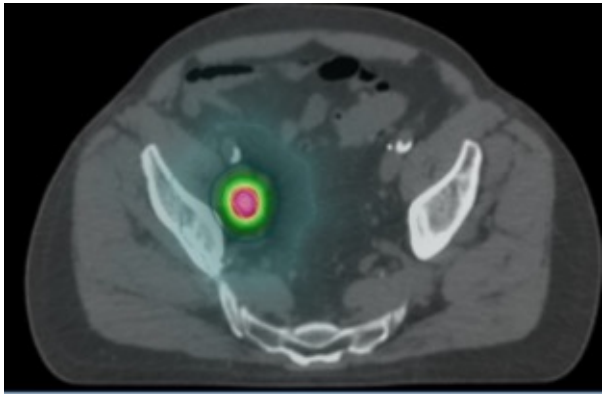
Extracranial palliative radiation therapy











NOTA INFORMATIVA IMPORTANTE
CONCORDATA CON LE AUTORITA' REGOLATORIE EUROPEE
E L'AGENZIA ITALIANA DEL FARMACO (AIFA)

19 Ottobre 2015

Potenziamento della radiotossicità associata a Zelboraf® (vemurafenib)

Sintesi

- Casi severi di lesioni correlate a radiazioni, alcuni con esito fatale, sono stati riferiti in pazienti sottoposti a radioterapia prima, durante o dopo il trattamento con Zelboraf

- 20 casi di lesioni da radiazioni diagnosticate come recall da radiazioni (n = 8 casi) e sensibilizzazione alle radiazioni (n = 12 casi)

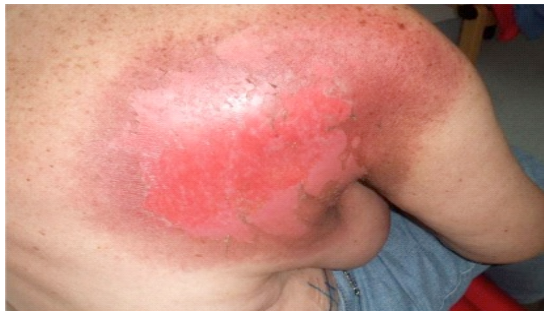
- La maggior parte dei casi è stata **di natura cutanea**, ma alcuni casi hanno coinvolto gli **organi viscerali**

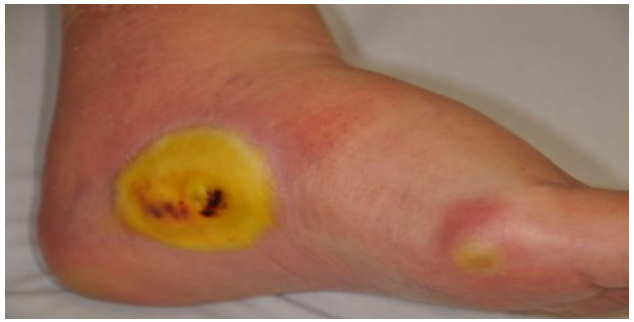
- 8 casi di recall da radiazioni hanno evidenziato un'infiammazione acuta confinata all'area precedentemente irradiata, innescata dalla somministrazione di Zelboraf, 7 o più giorni dopo il completamento della radioterapia.

Zelboraf deve essere usato con cautela quando è somministrato prima, in concomitanza o in sequenza al trattamento radiante.

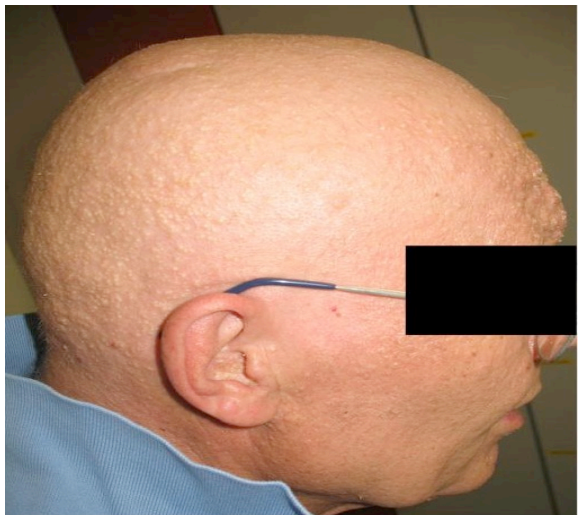
Radiosensitization by BRAF inhibitor therapy – mechanism and frequency of toxicity in melanoma patients

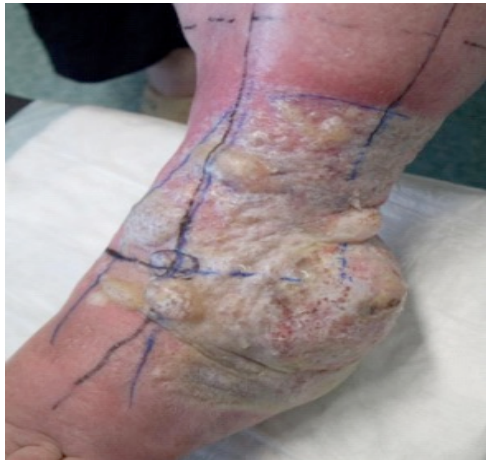
161 melanoma patients were evaluated for acute and late toxicity, of whom 70 consecutive patients received 86 series of radiotherapy with concomitant BRAF inhibitor therapy





43% of acute or late toxicities





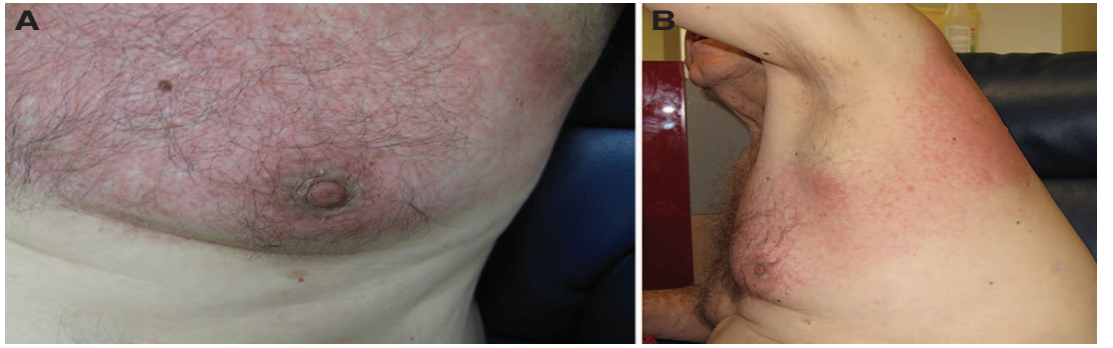
Hecht et al. Annals of Oncology 2014

JOURNAL OF CLINICAL ONCOLOGY | DIAGNOSIS IN ONCOLOGY

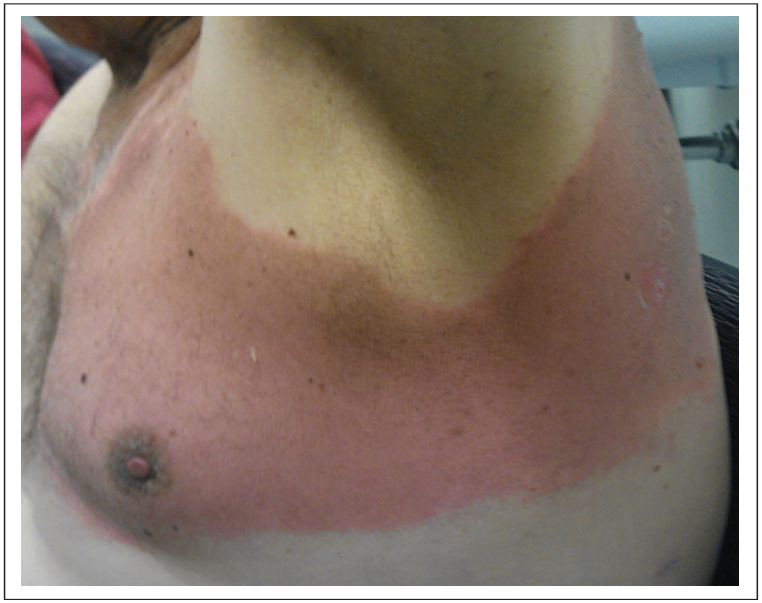
ACUTE RADIATION SKIN TOXICITY ASSOCIATED WITH BRAF INHIBITORS

A 71-year-old man with widespread metastatic melanoma

Disease progression in the axilla was treated with palliative radiotherapy of 36 Gy in 12 fractions and Vemurafenib.



21 Gy to the dose prescription point, 14 Gy to skin



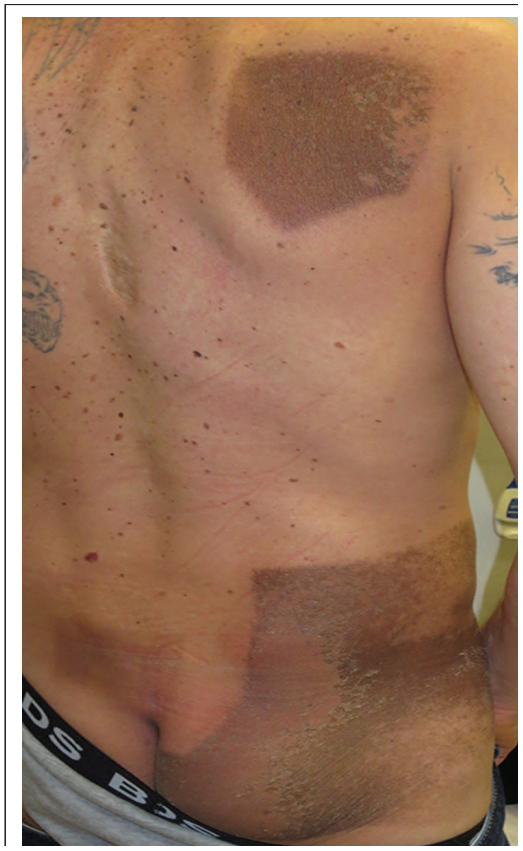
27 Gy to the dose prescription point, 18 Gy to skin

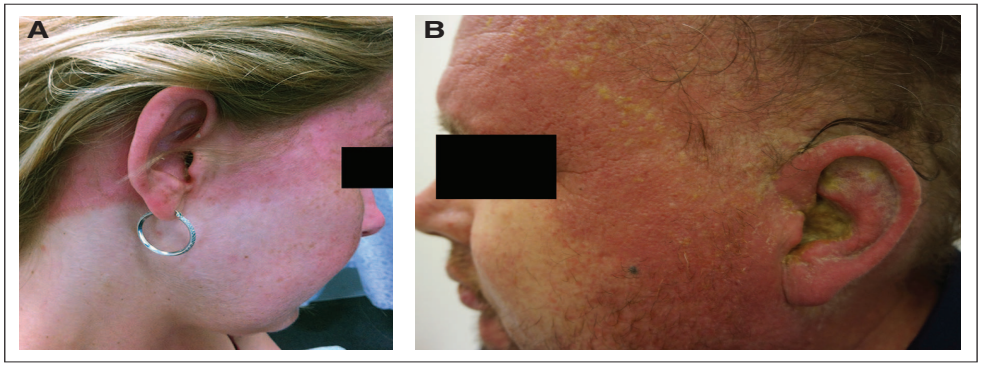
Pulvirenti ,J Clinical Oncol Vol 32, 2014

JOURNAL OF CLINICAL ONCOLOGY | DIAGNOSIS IN ONCOLOGY

ACUTE RADIATION SKIN TOXICITY ASSOCIATED WITH BRAF INHIBITORS

RT 8 Gy to painful bony metastases in the left humerus, left ribs, and sacrum. **After** radiotherapy, he began receiving dabrafenib. He underwent 8 Gy to these new sites of metastatic disease, concurrently with dabrafenib. There was no overlap with his previous radiotherapy fields.

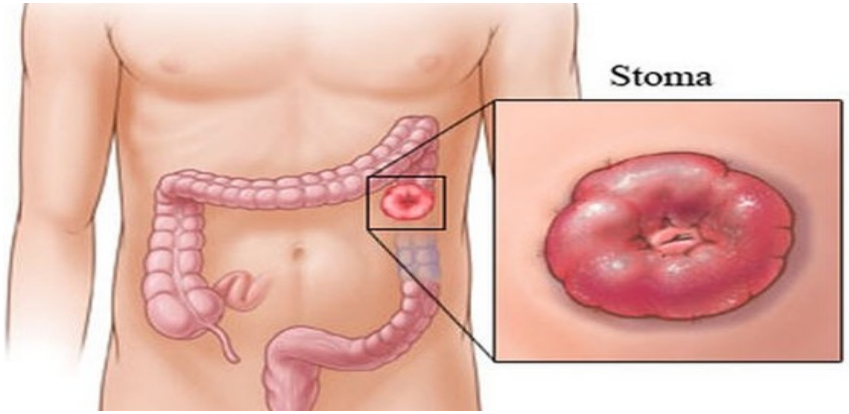




Whole-brain radiotherapy at a dose of 30 Gy in 10 fractions concurrent with dabrafenib

Pulvirenti ,J Clinical Oncol Vol 32, 2014

Severe radiotherapy-induced EXTRACUTANEOUS TOXICITY under vemurafenib.



The second patient, a male aged 64 and treated with vemurafenib for nineteen days, presented a radiation-induced ANORECTITIS complicated by diarrhoea, anorexia and weight loss following the concomitant radiation of a primary rectal tumour. A colostomy was needed after ten months in order to improve local status and general health.

Avoiding Severe Toxicity From Combined BRAF Inhibitor and Radiation Treatment: Consensus Guidelines from the Eastern Cooperative Oncology Group (ECOG)

Christopher J. Anker, MD*, Kenneth F. Grossmann, MD, PhD†, Michael B. Atkins, MD‡, Gita Suneja, MD§, Ahmad A. Tarhini, MD, PhD‖, and John M. Kirkwood, MD‖

Summary

BRAFi increase the risk of grade 2 and 3 dermatitis with RT.

The severity of the reaction appears dependent on the dose of RT but not BRAFi, and all but 1 grade 3 dermatitis incident was reported in the setting of concurrent RT and BRAFi administration.

RT recommendations

- Consider dose per fraction <4 Gy unless using a stereotactic approach or the patient has very poor prognosis/performance status.
- For adjuvant nodal basin RT, consider a dose ≤ 48 to 50 Gy in 20 fractions
- For spine metastases, consider posterior oblique RT fields when feasible and safe to minimize exit dose through visceral organs

➢ **Hold ≥3 days before and after fractionated RT.** Int J Radiat Oncol Biol Phys. 2016 June

Table 2 Treatment of BRAFi-related and radiation therapy–related toxicities

Toxicity	Treatment*	Expected outcome
Dermatitis	Dry desquamation: barrier creams (eg, Aquaphor, Calmoseptine, Desitin, Balneol); topical steroids† (20, 29) Consider urea cream (31) Moist desquamation: silvadene cream (19)	Resolution in wk (18) to 1-2 mo (27, 37)
CVG	Recommended: topical steroids† (21, 24) (IV steroids unnecessary) (24) Consider: retinoids & antibiotics (21)	Resolution in wk (24) to 5 mo (Current)
FCP	Ulcers: calcium alginate dressings (36) Folliculocentric eruptions: topical steroids† (36)	Resolution in wk (28) to mo (31); with some cases unresolved for beyond 1 y (23)
Pneumonitis	Prednisolone with or without IV antibiotics (20)	Prompt improvement in symptoms (20)
Anorectitis‡	Oral prednisone (26) Discontinue BRAFi (26) If refractory: consider colostomy (26)	Slow improvement over mo (26)
Mucositis/esophagitis‡	Supportive care & TPN if needed (34) Discontinue BRAFi (34)	Slow improvement over mo (34)

Abbreviations: BRAFi = BRAF inhibitor; CVG = cutaneous verrucous gyrata; FCP = follicular cystic proliferation; IV = intravenous; TPN = total parenteral nutrition.

Numbers in parentheses indicate references.

*Analgesics should be considered for all patients as needed.

† Examples of topical steroids include betamethasone (18), aclometasone (21), and triamcinolone (36).

‡ All reported grade 3 gastrointestinal tract toxicity including mucositis, esophagitis, and anorectitis occurred with concurrent BRAFi and radiation therapy.

Anker et al. ,Int J Radiat Oncol Biol Phys. 2016 June

Phase I/II trial of concurrent extracranial palliative radiation therapy with Dabrafenib and Trametinib in metastatic BRAF V600E/K mutation-positive cutaneous Melanoma

Dabrafenib and Trametinib before and during palliative RT to **soft tissue, nodal or bony metastases.**

6 patients were treated at level 1 (20 Gy in 5fr) and 4 patients at level 2a (30 Gy in 10 fr) - June 2016 to October 2019-

Table 3
RT related immediate and delayed skin toxicity (all Grade 1 or 2).

Characteristic	Immediate (<3 months)		Delayed (>3 months)	
	# Participants (N = 10)	# Events	# Participants (N = 10)	# Events
Rash maculo-papular	5	7	0	0
Skin atrophy	1	2	0	0
Dermatitis radiation	8	22	0	0
Skin hyperpigmentation	1	2	1	2
Superficial soft tissue fibrosis	2	2	2	2

Wang et al. Clinical and Translational Radiation Oncology 30 (2021) 95–99

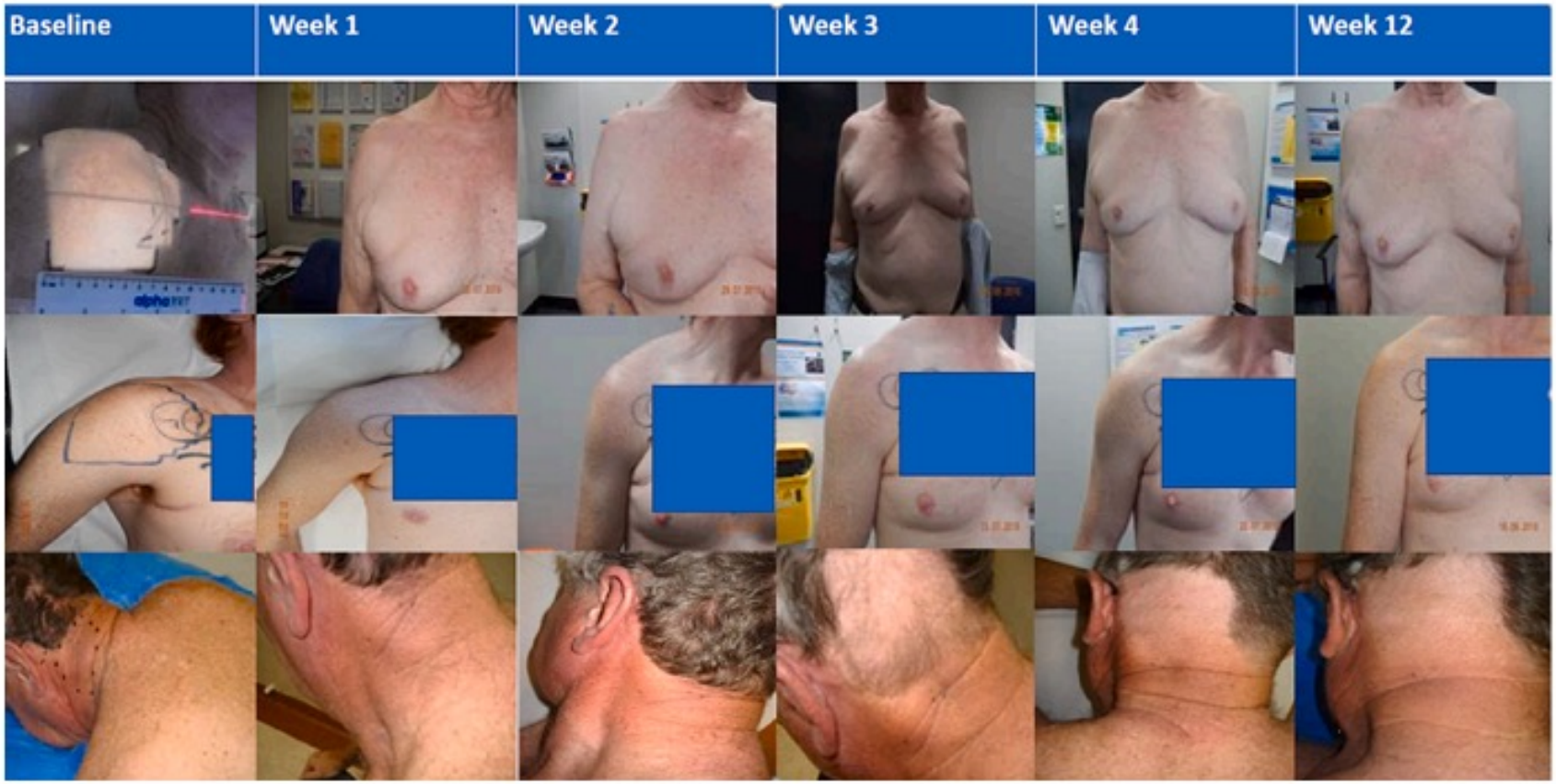


Fig. 1. Clinical photographs of irradiated area for select patients on dose level I.

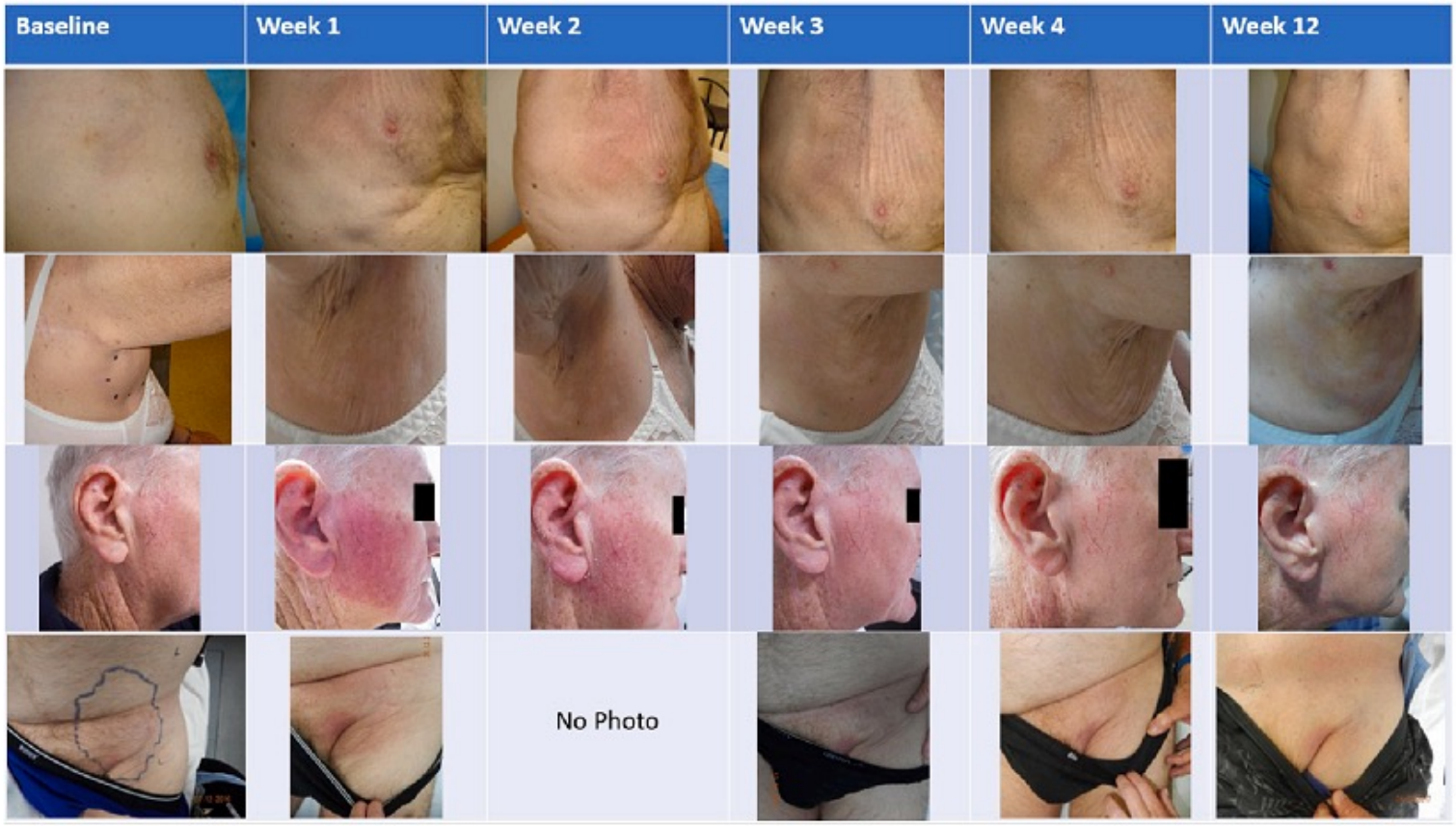


Fig. 2. Clinical photographs of irradiated area for patients on dose level IIa.

Melanoma is highly radioresistant

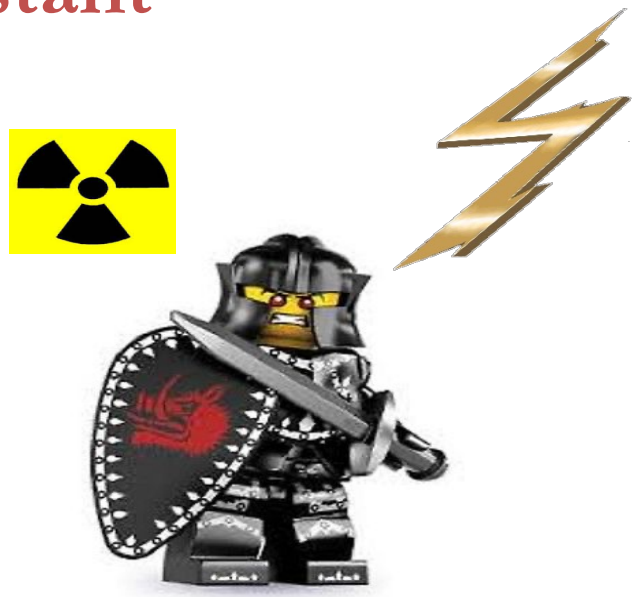
- **High repair capacity**

- **High proliferation capacity**

- **Poor cell differentiation**

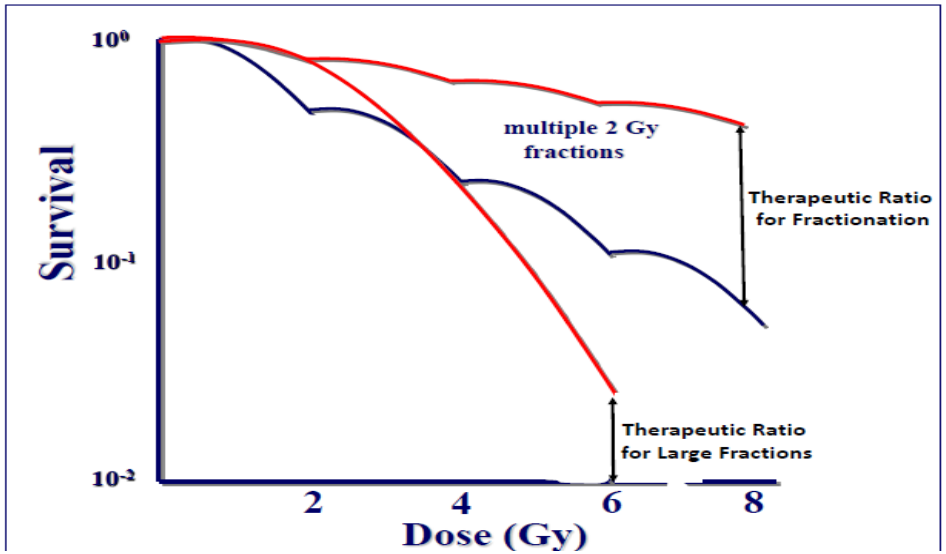
- **Hypoxic cell pools**

- **Abnormal apoptosis (p53 attenuation is common)**



Espenel S, Critical Reviews in Oncology and Hematology 2017

Benefit from large fractions



-Saturation of tumor DNA repair mechanisms

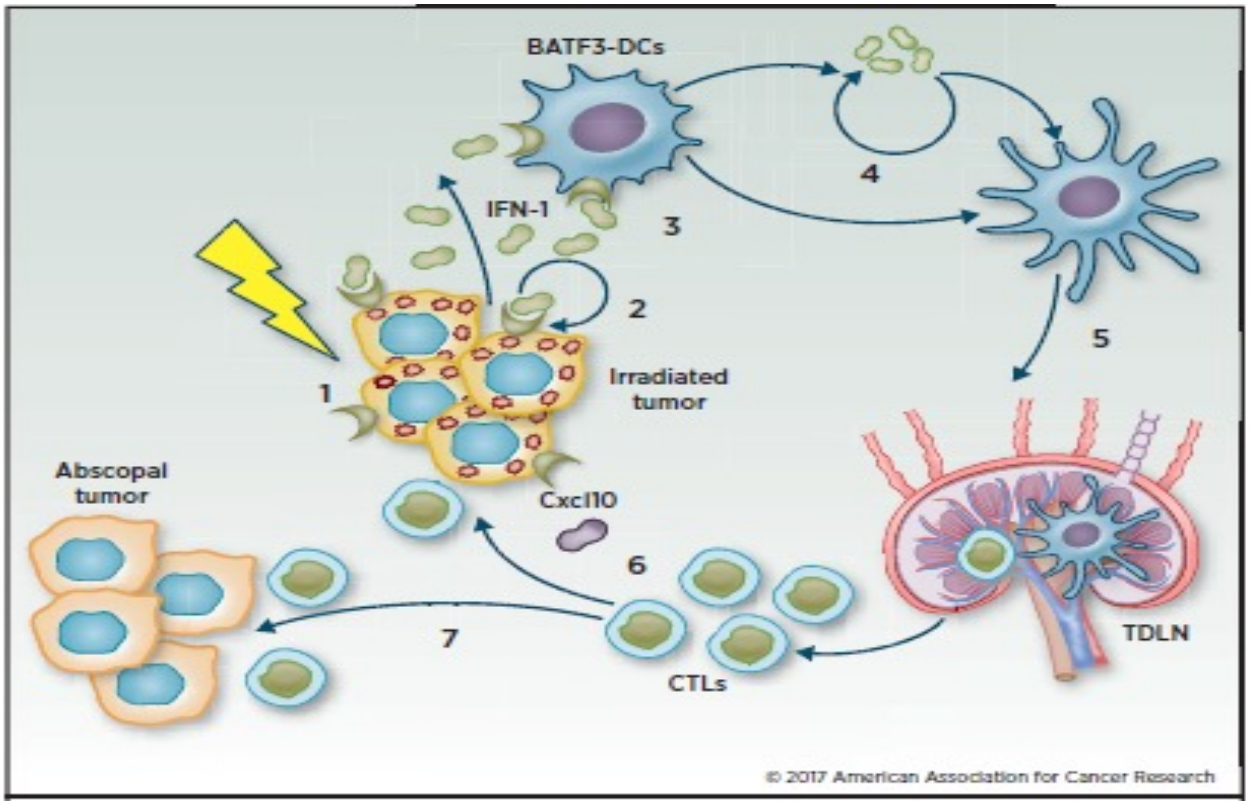
-More lethal and less reparation on sublethal damages on DNA

- Less repopulation

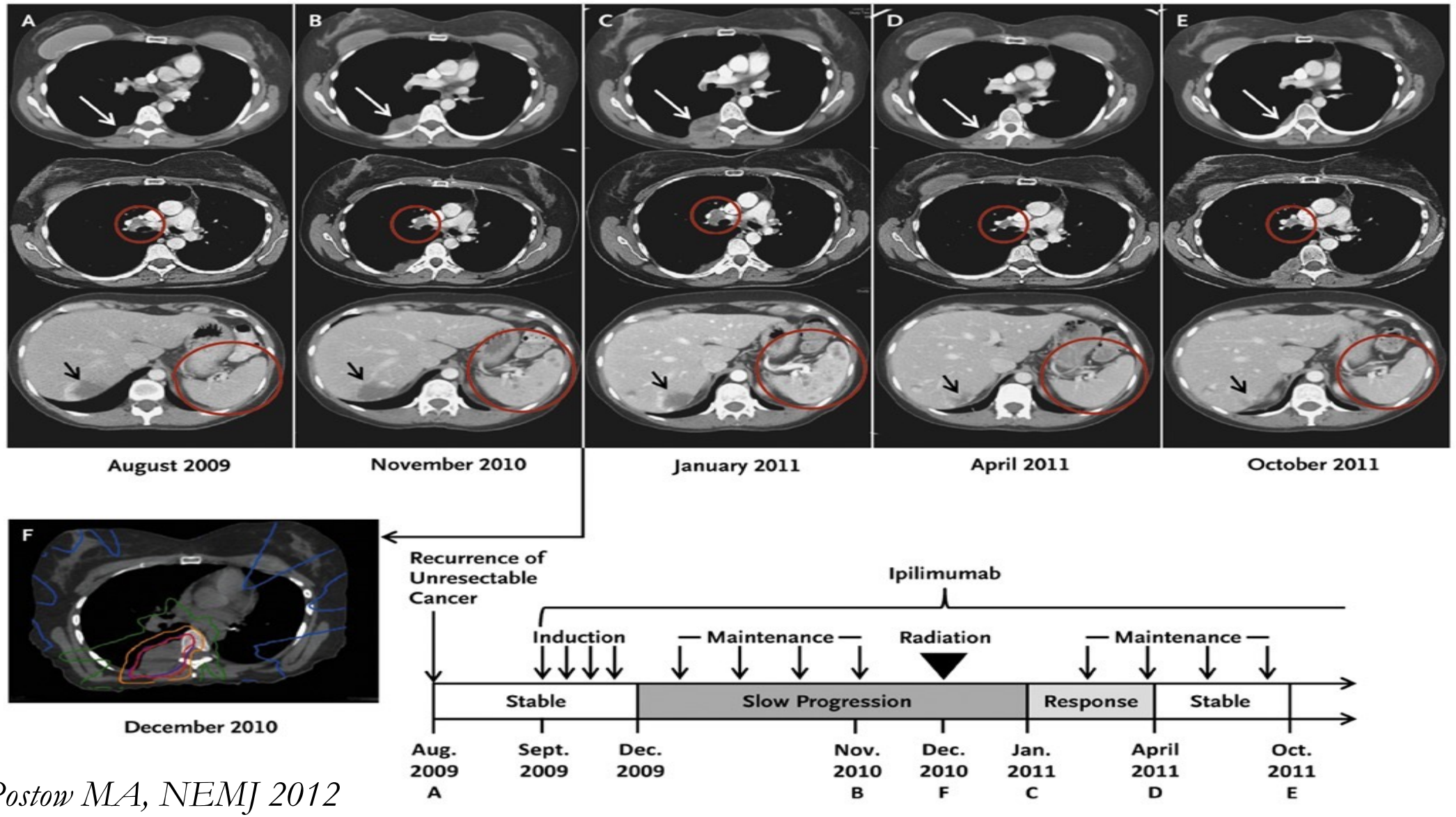
-High endothelial cell apoptosis

Espenel S, Critical Reviews in Oncology and Hematology 2017

RT can convert the tumor in an in situ vaccine…



Vanpouille-Box, Nat Commun 2017



Postow MA, NEMJ 2012

Conclusions

- Data on RT concurrent with BRAF/MEK-inhibitors and ICis is very limited (retrospective studies)

- The combination of immunotherapy and radiotherapy seems to be a safe and effective therapeutic option

- Concurrent treatment with BRAF inhibitors and palliative radiation therapy (RT) could be associated with increased toxicity, especially skin toxicity (theoretical synergism), the concomitant association is not recommended

- The bar has been raised for patients with MBM (combination of new therapies and radiotherapy)

- How to integrate RT and TT/IO in a proper sequence?

Grazie!

UNIVERSITA' CAMPUS BIO-MEDICO DI ROMA