<u>II Sessione</u>

Focus sulle integrazioni Radioterapia – Nuovi Farmaci: che cosa cambia nella pratica clinica?

Radioterapista - Oncologo Medico: un punto di vista interdisciplinare

Moderatori: M. Buglione – C. Verusio

Melanoma

C. Fallai – C. Cimminiello
Fondazione IRCCS Istituto Nazionale Tumori Milano

Radiation Therapy for Melanoma

Wenyin Shi

Definitive radiation therapy

For certain well-defined situations, including medical inoperability, lentigo maligna melanoma (LMM), mucosal melanoma, and ocular melanoma

Adjuvant radiation therapy

For patients with node - positive disease, (RT) following lymphadenectomy effectively to prevent local and regional recurrence

Symptom palliation

For patients with advanced stage and metastatic disease, RT is highly effective in providing symptom relief

Cutaneous Melanoma Etiology & Therapy . Ward WH and Farma JM eds 2017 Codon Publications

The emerging role of radiotherapy for desmoplastic melanoma and implications for future research

Daniel E. Oliver[a,d], Kirtesh R. Patel[d], Douglas Parker[b,c], Keith A. Delman[e], David H. Lawson[f], Ragini R. Kudchadkar[f] and Mohammad K. Khan[d]

Melanoma Research 2015, 25:95–102

Review Article

Experience with Treating Lentigo Maligna with Definitive Radiotherapy

Gerald B. Fogarty,[1,2,3,4] Angela Hong,[1,2] Alex Economides,[4] and Pascale Guitera[1]

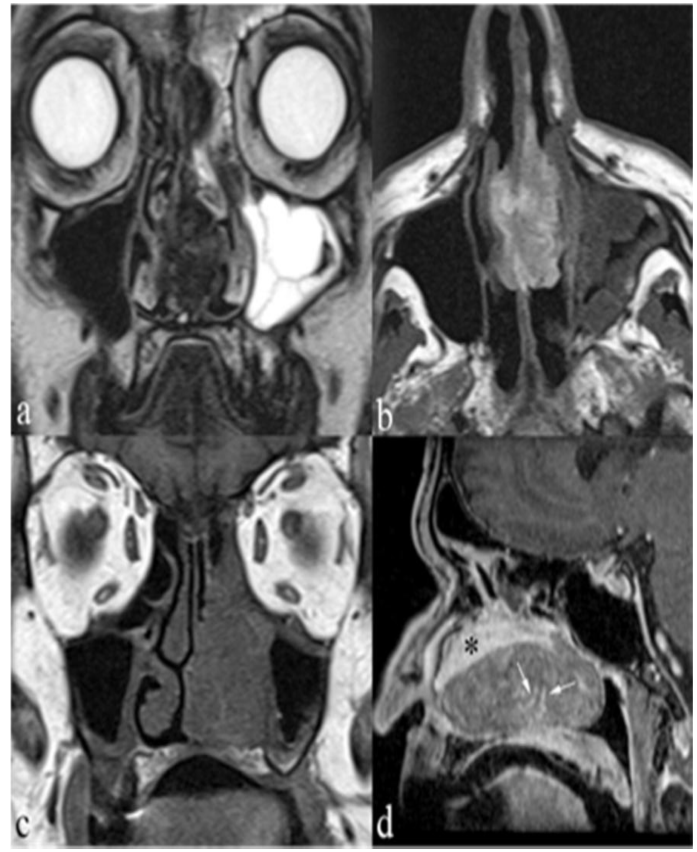
[1] *Melanoma Institute Australia, Poche Centre, Crows Nest, Australia*
[2] *Genesis Cancer Care, Mater Hospital, Crows Nest, Australia*
[3] *Genesis Cancer Care, St. Vincent's Hospital, Darlinghurst, Australia*
[4] *Australia and New Zealand Melanoma Trials Group, Sydney, Australia*

Correspondence should be addressed to Alex Economides; alex.economides@melanoma.org.au

Received 19 March 2018; Accepted 7 June 2018; Published 15 July 2018

Mucosal Melanoma: a Literature Review

•Oral
•Sinonasal
•Respiratory Tract
•Gastrontestinal tract
•Female Genitourinary Tract
•Male Genitourinary Tract



Head & Neck:
The most frequent site of mucosal MM
Aggressive behaviour
Severe prognosis

The use of immunotherapy gains ground as for other subsets of melanoma

Skovsted Yde S et al. Current Oncology Reports (2018) 20: 28

Mucosal melanoma of the head and neck
Radiotherapy synthetic recommendations

- **Postoperative radiotherapy** to the tumour bed is recommended on a type 3 basis (evidence fron non randomised studies) as standard option in all patients *with advanced disease stage*

- **Primary RT** is recommended, on a type-3 basis, as standard option for patients who refuse surgery or who are suffering from an inoperable/unresectable tumour

- **Exclusive RT with heavy particles** (Hadron therapy) can be considered as experimental treatment within clinical trials, on a type R basis (rational inference), even for operable patients

- **RT** is recommended as individualized treatment on a type R basis for the **salvage** of local recurrence

- **Palliative RT** is recommended on a type R basis as standard treatment of symptomatic metastatic disease

Ascierto PA et al. Critical Reviews in Oncology/Hematology 112 (2017) 136–152

OCULAR MELANOMA

- Local control is exceptionally good with RT delivered by either episcleral plaque brachytherapy or external beam radiation therapy (EBRT) while preserving the eye and vision(°)
- Collaborative Ocular Melanoma Study: 125I plaque BCT (85 Gy) is equivalent to enucleation in the prevention of metastatic melanoma for medium sized choroidal melanoma, with local control being achieved in 90% of patients. Only 5% of the patients require enucleation due to radiation-induced toxicities (°°)
- Currently, iodine-125 (125I) and ruthenium-106/rhodium-106 are the most commonly used isotopes in USA and Europe
- In terms of EBRT, proton therapy is most commonly used for the treatment of ocular melanoma. Compared to plaque therapy, proton therapy has advantages in treating larger tumors
- A large, single institution study comparing proton beam with enucleation showed no apparent difference in long-term survival (*,**). Favorable 10-year local failure rates of 4.3% were observed (**)

°Munzenrider JE. Hematol Oncol Clin North Am. 2001;15(2):389–402
°°Melia BM. Ophthalmology. 2001;108(2):348–66
*Gragoudas ES, Arch Ophthalmol. 2002;120(12):1665–71
**Gragoudas ES, Trans Am Ophthalmol Soc. 2002;100:43–8; discussion 8–9
*** Wang Z, Nabhan M. Int J Radiat Oncol Biol Phys. 2013;86(1):18–26

Adjuvant radiation therapy

- Adjuvant radiation therapy can reduce local recurrence for certain high-risk primary melanomas, including lentigo maligna, desmoplastic/neurotropic features, and mucosal melanomas (head and neck and anorectal)
- There are retrospective and limited prospective data to support adjuvant radiation following lymphadenectomy for nodal metastatic disease at high risk for regional recurrence
- Radiation therapy is associated with increased potential toxicity, such as lower extremity lymphedema, and may negatively interact with concurrent adjuvant interferon therapy

Table 2
Selected published studies of regional control for adjuvant radiation therapy following lymph node dissection for nodal metastatic melanoma

			Number of Patients				Regional Control Rate			
Authors,[Ref.] Year	Type	Nodal Basin	RT	No RT	RT Dose (Gy)	Median F/U (mo)	RT (%)	No RT (%)		*P* Value
Adjuvant Radiation										
Ballo et al,[58] 2003	Retro	C	160		30	78	94		[10 y]	
Ballo et al,[64] 2002	Retro	A	89		30	63	87		[5 y]	
Ballo et al,[59] 2004	Retro	I	40		30	22.5	74		[3 y]	
Burmeister et al,[51] 2006	Pro	C, A, I	234		48	58.4	91		[5 y]	
Adjuvant Radiation vs LND Alone										
Moncrieff et al,[48] 2008	Retro	C	129	587	33	34.7	89.9	93.9	[6 y]	.20
Strojan et al,[49] 2010	Retro	C	43	40	60	25	78	56	[2 y]	.015
Pinkham et al,[50] 2013	Retro	A	121	156	48	23	86	87		
Gojkovic-Horvat et al,[65] 2012	Retro	I	37	64	50.6		86	91	[2 y]	.395
Bibault et al,[60] 2011	Retro	C, A, I	60	26	50	73	C 85 A 90 I 80	50 70 72		.4
Agrawal et al,[52] 2009	Retro	C, A, I	509	106	30	60	89.8	59.4	[5 y]	<.0001
Creagan et al,[53] 1978	Pro		27	29	50		88.9	96.6		
Burmeister et al,[54] 2012	Pro	C, A, I	109	108	48	40	81	69	[3 y]	.041

Abbreviations: A, axillary; C, cervical; F/U, follow-up; I, inguinal; LND, lymph node dissection; mo, months; Pro, prospective; Retro, retrospective; RT, radiation therapy; y, year.

Oxenberg et al. Surg Clin N Am 94 (2014) 1031–1047

COMBI-AD: STUDY DESIGN—EXTENDED FOLLOW-UP ANALYSIS

Key eligibility criteria

- Completely resected stage IIIA (lymph node metastasis > 1 mm), IIIB, or IIIC cutaneous melanoma
- *BRAF* V600E/K mutation
- ECOG performance status 0 or 1
- No prior radiotherapy or systemic therapy
- Tissue collection was mandatory at baseline and optional upon recurrence

Stratification

- ***BRAF*** **mutation status (V600E, V600K)**
- **Disease stage (IIIA, IIIB, IIIC)**

RANDOMIZATION

N = 870

1:1

Dabrafenib 150 mg BID + trametinib 2 mg QD (n = 438)

2 matched placebos (n = 432)

Treatment duration: 12 months

Primary analysis
D+T median FU, 33 months

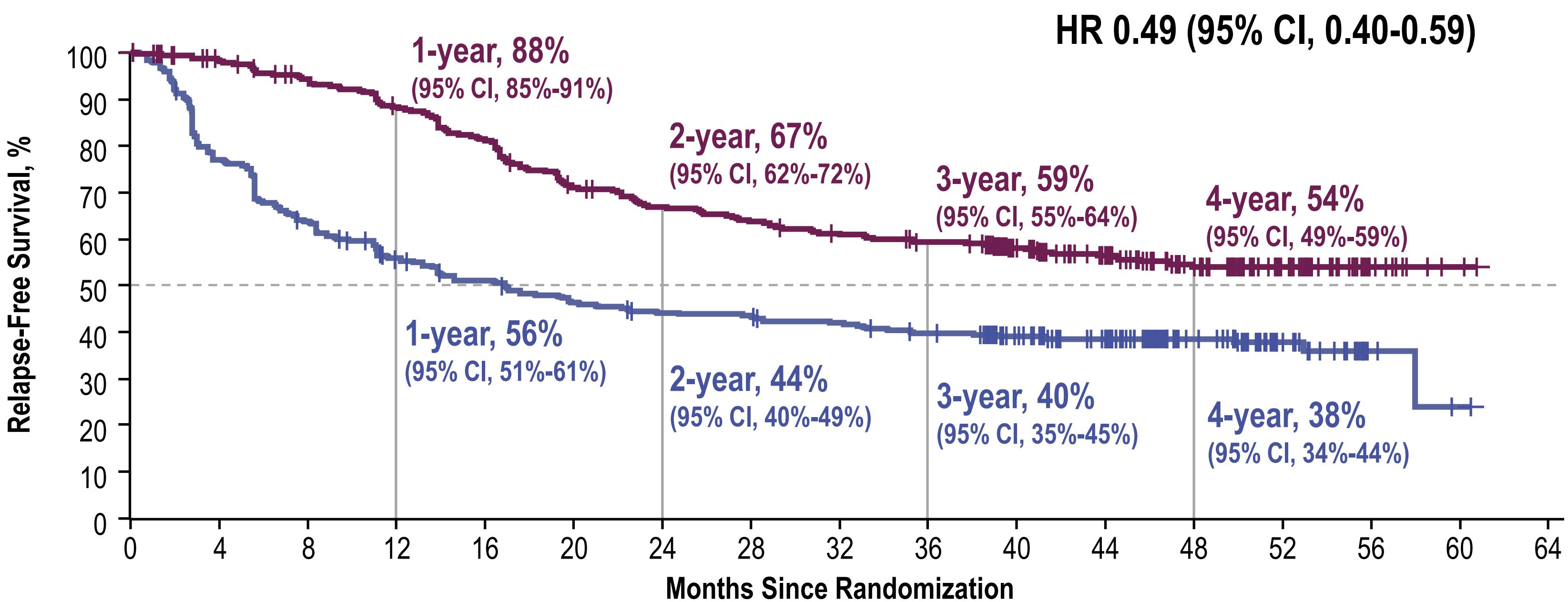
Updated analysis
D+T median FU, 44 months

- **Primary endpoint: RFS**
- **Secondary endpoints: OS, DMFS, FFR, safety**

BID, twice daily; DMFS, distant metastasis–free survival; D+T, dabrafenib + trametinib; ECOG, Eastern Cooperative Oncology Group; FFR, freedom from relapse; FU, follow-up; QD, once daily.

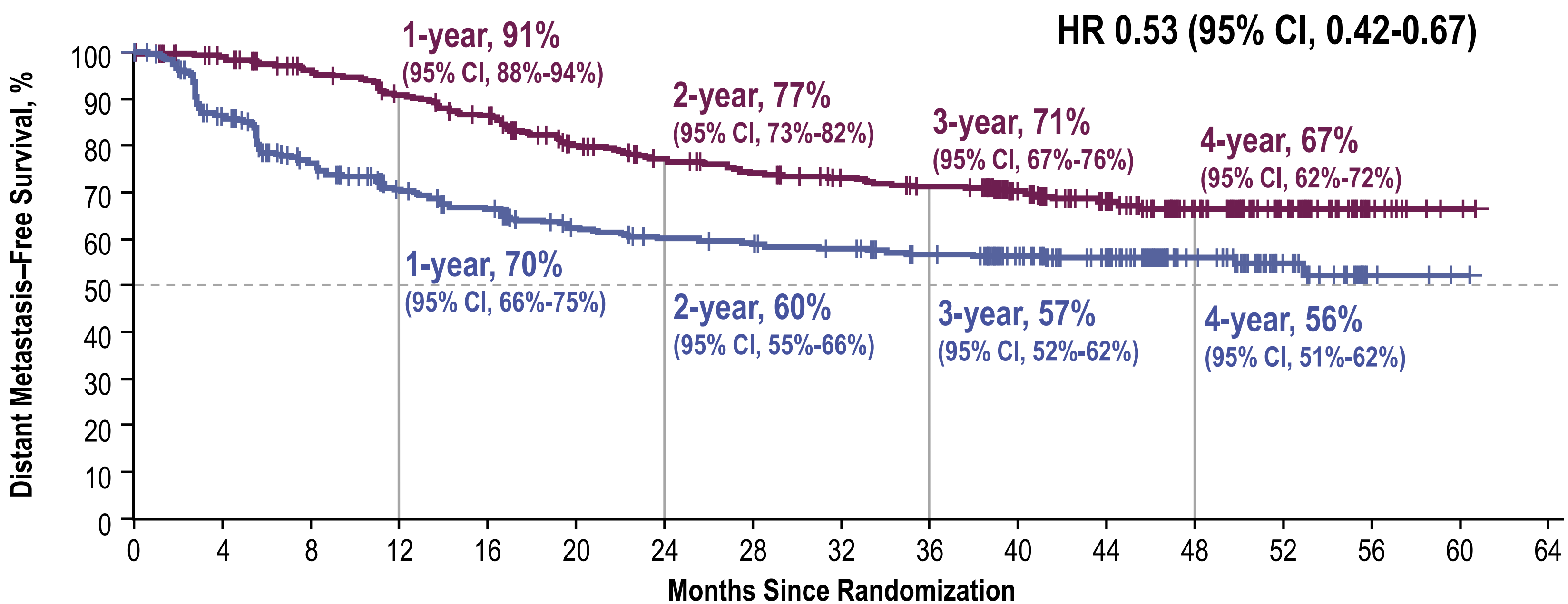
Long GV, et al. *N Engl J Med*. 2017;377:1813-1823.

RELAPSE-FREE SURVIVAL



No. at risk																	
Dabrafenib + trametinib	438	405	381	354	324	281	262	249	236	227	183	148	92	47	13	2	0
Placebo	432	322	263	219	198	178	168	164	157	147	128	107	63	27	4	1	0

DISTANT METASTASIS–FREE SURVIVAL



No. at risk																	
Dabrafenib + trametinib	438	407	381	352	327	285	265	252	238	229	185	150	92	47	13	2	0
Placebo	432	330	265	221	201	179	169	165	159	149	130	108	64	28	4	1	0

CheckMate 238: Study Design

Patients with:

- High-risk, completely resected stage IIIB/IIIC or stage IV (AJCC 7th edition) melanoma
- No prior systemic therapy
- ECOG 0-1

1:1

n = 453

NIVO 3 mg/kg IV Q2W
and
IPI placebo IV
Q3W for 4 doses
then Q12W from week 24

n = 453

IPI 10 mg/kg IV
Q3W for 4 doses
then Q12W from week 24
and
NIVO placebo IV Q2W

Follow-up

Maximum treatment duration of 1 year

Stratified by:

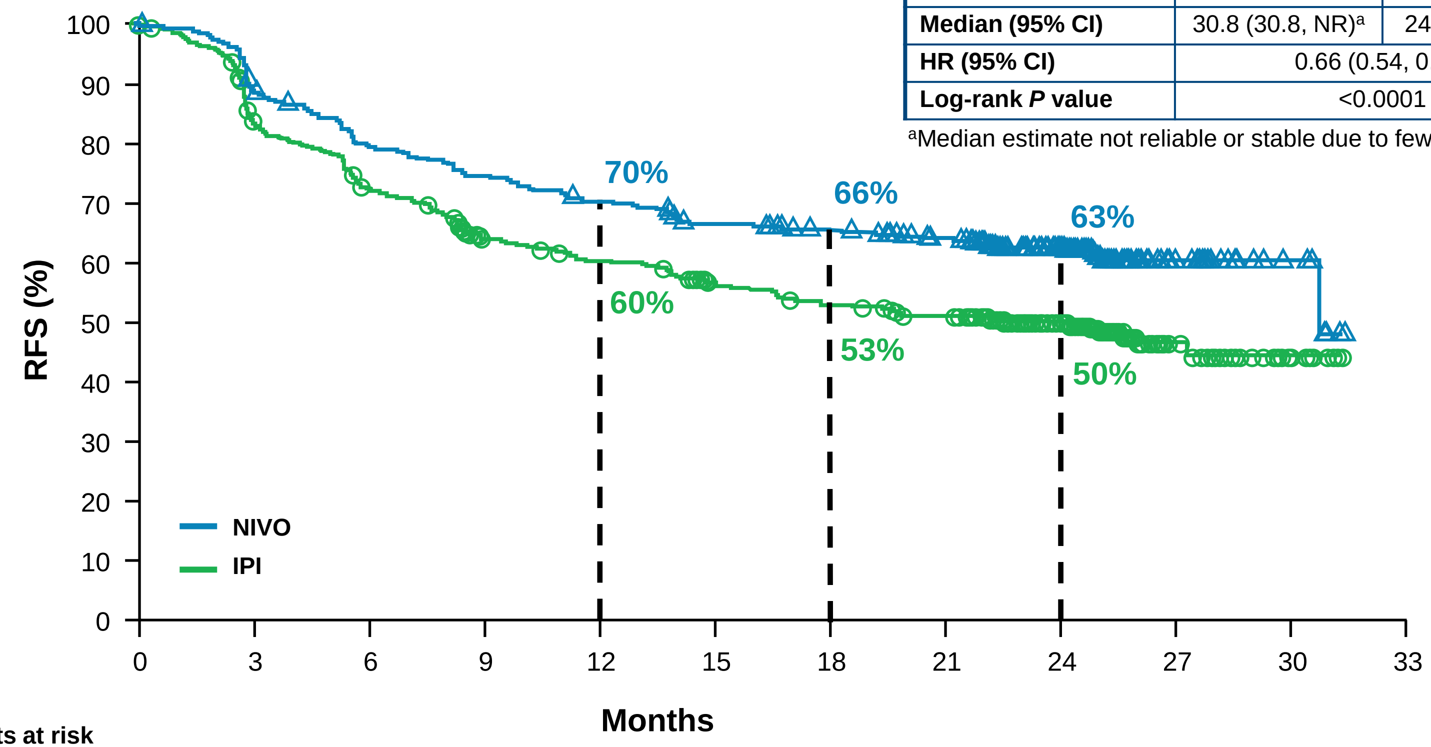
1) Disease stage: IIIB/C vs IV M1a-M1b vs IV M1c
2) PD-L1 status at a 5% cutoff in tumor cells

Enrollment period: March 30, 2015 to November 30, 2015

Primary Endpoint: RFS in All Patients

	NIVO	IPI
Events/patients	171/453	221/453
Median (95% CI)	30.8 (30.8, NR)[a]	24.1 (16.6, NR)
HR (95% CI)	0.66 (0.54, 0.81)	
Log-rank *P* value	<0.0001	

[a]Median estimate not reliable or stable due to few patients at risk.

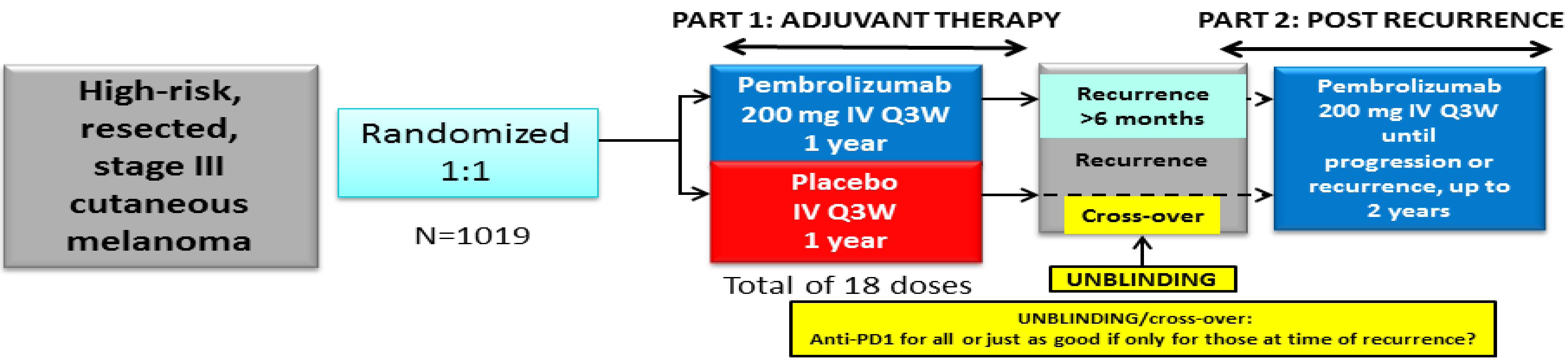


Number of patients at risk

NIVO	453	394	353	331	311	291	280	264	205	28	7	0
IPI	453	363	314	270	251	230	216	204	149	23	5	0

MUNICH 2018 ESMO congress

EORTC 1325/KEYNOTE-54: Study Design



Stratification factors:

- ✓ **Stage**: IIIA (>1 mm metastasis) vs. IIIB vs. IIIC 1-3 positive lymph nodes vs. IIIC ≥4 positive lymph nodes
- ✓ **Region**: North America, European countries, Australia/New Zealand, other countries

Primary Endpoints:

- **RFS (per investigator) in overall population,** and **RFS in patients with PD-L1-positive tumors**

Secondary Endpoints:

- **DMFS and OS** in all patients, and in patients with PD-L1-positive tumors; **Safety, Health-related quality of life**

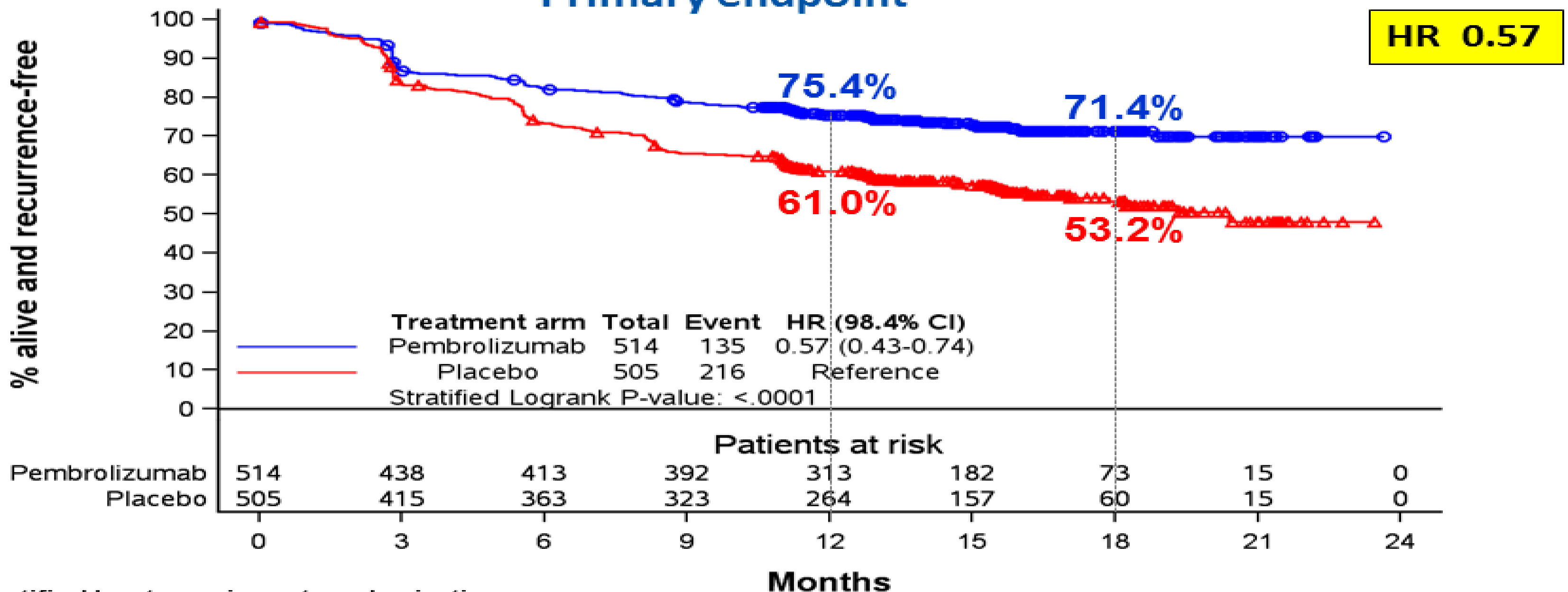
EORTC

The future of cancer therapy

Pr Proprietary

Recurrence-Free Survival in the ITT Population

Primary endpoint



*Stratified by stage given at randomization

EORTC

The future of cancer therapy

Pr Proprietary

MUNICH 2018 ESMO congress

Advanced extracranial MM IPILIMUMAB ± RT OUTCOME

Clinical and Translational Radiation Oncology 9 (2018) 5–11

Contents lists available at ScienceDirect

Clinical and Translational Radiation Oncology

journal homepage: www.elsevier.com/locate/ctro

Review Article

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]

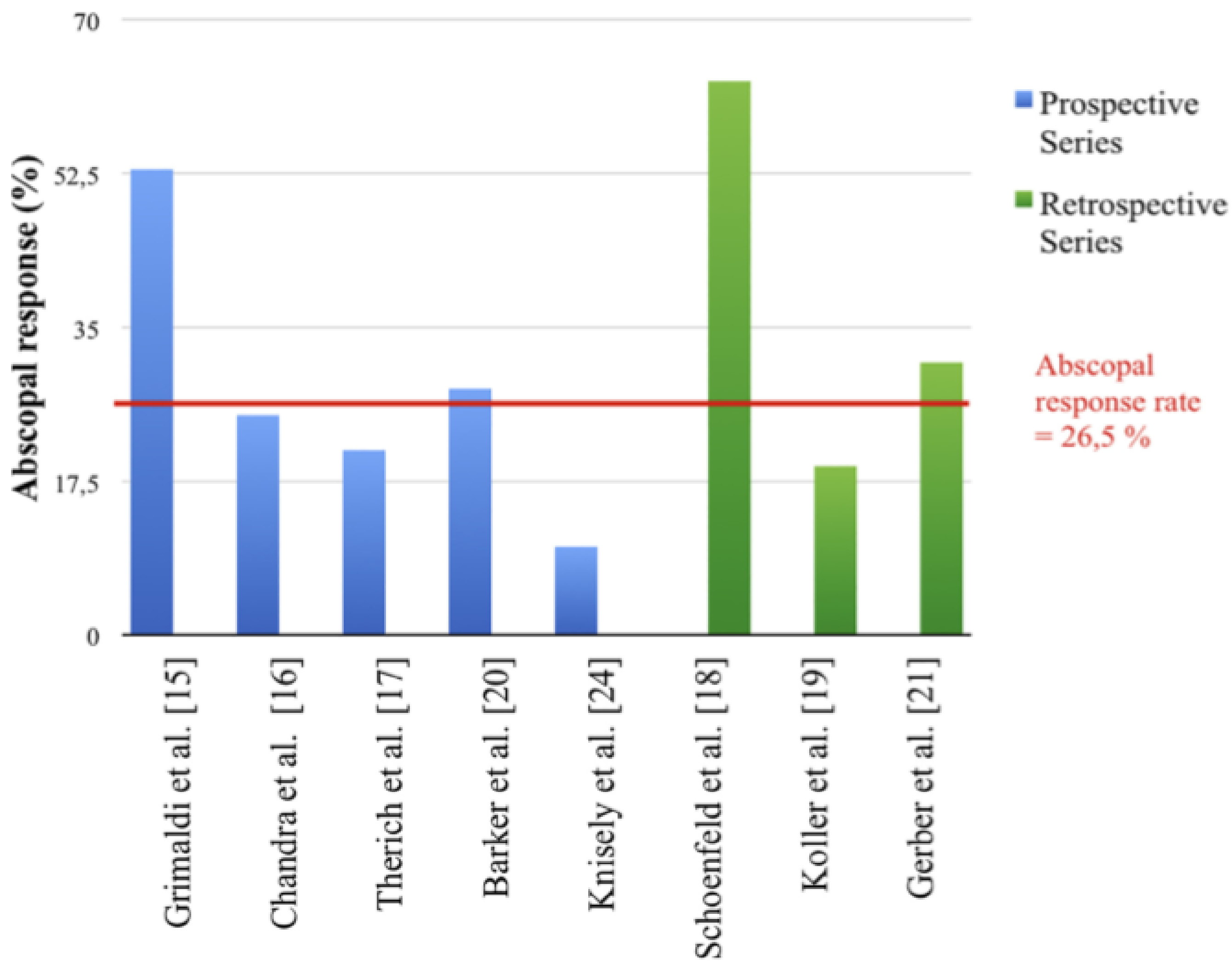
[a] Department of Radiation Oncology, "Dr. Negrín" University Hospital of Gran Canaria, Barranco de la Ballena s/n, 35010 Las Palmas de Gran Canaria, Spain
[b] Department of Medical Oncology, Insular University Hospital of Gran Canaria, Plaza Doctor Pasteur s/n, 35016 Las Palmas de Gran Canaria, Spain

Table 1
Clinical outcomes and abscopal responses in clinical studies of melanoma with the combination of ipi and radiotherapy.

	Study type	N	Location	Modality	RT dose (Gy)/Fractions	ipi dosage	Median OS (months)	Abscopal response (%)	Toxicity ≥ Grade 3
Grimaldi [15]	Prospective	21	Various	SRS	30/10; 20–24/1	3 mg/kg/3 w	22,4	53	NR
Chandra [16]	Prospective	25	Various	SRS	26/4	3 mg/kg/3 w	28	25	NR
Theurich [17]	Prospective	45	Various	SBRT	Various	3 mg/kg/3 w	23,25	21	18,30%
Barker [20]	Prospective	29	Various	SBRT	24/1 (SBRT); Various (EBRT)	3–10 mg/kg/3 w	39	28	Not increased
Knisely [24]	Prospective	27	Brain	SRS	Not reported	NR	21,3	10	NR
Schoenfeld [18]	Retrospective	16	Brain	SRS	36 (WBRT); 22 (SRS)	3–10 mg/kg/3 w	18	63	Not increased
Koller [19]	Retrospective	70	Various	SBRT	NR	3 mg/kg/3 w	19	19,2	Not increased
Gerber [21]	Retrospective	13	Brain	WBRT	27–37.5/9–15	3–10 mg/kg/3 w	4	31	Not increased
Kropp [22]	Retrospective	16	Various	SBRT	Various	3 mg/kg/3 w	24	NR	Not increased
Qin [23]	Retrospective	44	Various	SBRT	Various	NR	21,8	NR	Not increased
Silk [25]	Retrospective	33	Brain	SRS	30–37/10–13 (WBRT); 14–24/1–5 (SRS)	3 mg/kg/3 w	18,3	NR	Not increased
Mathew [26]	Retrospective	25	Brain	SRS	15–20/1	3–10 mg/kg/3 w	5,9	NR	NR
Shoukat [27]	Retrospective	11	Brain	SRS	NR	NR	28	NR	Not increased
Kiess [28]	Retrospective	46	Brain	SRS	15–24/1	3–10 mg/kg/3 w	12,4	NR	20%
Tazi [29]	Retrospective	10	Brain	SRS	NR	NR	18	NR	10%
Patel [30]	Retrospective	20	Brain	SRS	15–21/1–5	3 mg/kg/3 w	12	NR	Not increased

RT = radiation therapy; ipi = ipilimumab; SBRT = stereotactic body radiation therapy; SRS = stereotactic radio surgery; NR = not reported.

Prospective and retrospective studies quantifying the abscopal responses



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

Toxicity

Adverse events produced by ipilimumab in patients with metastatic melanoma includes immune-related adverse events , which affect the skin, colon, endocrine organs, liver, and lungs with a 10–27% with severe grade 3 toxicity

In the present review, the prevalence of side effects (detailed only in four trials) ranged from 10% to 20 %. The most common complications of combined treatment included colitis, local skin or mucosal effects, and/or diarrhea

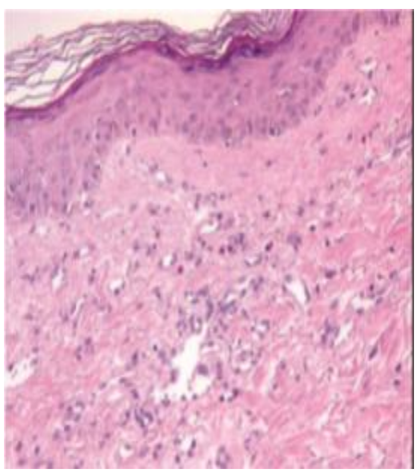
These results were very similar to those obtained in the majority of trials evaluating IPI in monotherapy

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

Ipilimumab may increase the severity of cutaneous toxicity related to radiotherapy

As a result of upregulation of immune system with ipilimumab, many immune-related adverse effects, such as dermatitis, colitis, hepatitis, and hypophysitis, have been previously reported

At the time of treatment with radiotherapy (IMRT)concurrent ipilimumab.



Perivascular eosinophilic mononuclear inflammatory cell infiltration in the dermis with melanin pigment increase in the basal layer not compatible with RT dermatitis

After steroid treatment

Eryılmaz MK. J Oncol Pharm Practice 2016, Vol. 22(3) 533–536

Advanced extracranial MM anti-PD-1 mAbs ± RT

- As anti-PD-1 mAbs are associated with ORR ranging from 20 to 40% and a median PFS of 4.1 to 6.9 months in melanoma patients, depending on the line of therapy, there is need for improvement

- Moreover, contrary to the rapid onset of responses obtained with targeted therapies blocking BRAF+MEK proteins in BRAFV600-mutant melanoma, responses to anti-PD-1 mAb are rarely achieved before 3 months of treatment, which may be challenging in patients with very rapid disease kinetics or threatening metastases

- Melanoma patients who have progressed on anti-PD-1 monotherapy also remain challenging, as only some patients treated beyond progression experience a delayed partial response

- The association of anti-PD-1 mAb with radiotherapy was only investigated in small retrospective series, although it is a promising combination

ONCOIMMUNOLOGY
2018, VOL. 7, NO. 7, e1442166 (8 pages)
https://doi.org/10.1080/2162402X.2018.1442166

Taylor & Francis
Taylor & Francis Group

ORIGINAL ARTICLE

OPEN ACCESS Check for updates

Efficacy of combined hypo-fractionated radiotherapy and anti-PD-1 monotherapy in difficult-to-treat advanced melanoma patients

Anissa Roger[a], Adeline Finet[a], Blandine Boru[b], Alain Beauchet[c], Jean-Jacques Mazeron[d], Yves Otzmeguine[e], Astrid Blom[a], Christine Longvert[a], Marie-Florence de Maleissye[a], Magali Fort[a], Elisa Funck-Brentano[a], and Philippe Saiag[a]

- In this study twenty-five patients with stage IIIC-IV melanoma received concomitant mainly hypo-fractioned radiotherapy to a limited number of sites and anti-PD-1 therapy

- The aim of the study was tumor response on radiated and non-radiated sites in two clinical situations: 1) early on in patients with very rapid disease kinetics or with life-threatening locations (“emergency group”); 2) later, in patients experiencing late progression while on anti-PD-1 mAb and proceeding on anti-PD-1 mAb beyond progression (“late radiotherapy group”)

- The 15 patients of the “emergency group” had their first radiotherapy session after a median of 24 days (range -11-59) on anti-PD-1 mAb, including the 6 patients who received stereotactic radiosurgery (SRS) to the brain

Toxicity

Number of patients $N = 25$	Grade 1/2	Grade 3	Grade 4
Skin reactions			
Bullous dermatosis, localized	*1* (4%)	*0*	*0*
Pruritus	*1* (4%)	*0*	*0*
Vitiligo-like depigmentation	*4* (16%)	*0*	*0*
Non-cutaneous adverse events:			
Asthenia	*5* (20%)	*0*	*0*
Diarrhea	*5* (20%)	*1* (4%)*	*0*
Dyspnea	*1* (4%)	*0*	*0*
Reduced/elevated thyroid hormones	*4* (16%)	*0*	*0*
Elevated liver enzymes	*4* (16%)	*0*	*0*
Eosinophilia	*1* (4%)	*0*	*0*
Peripheral neuropathy	*2* (8%)	*0*	*0*
Hypotension	*1* (4%)	*0*	*0*
Vomiting	*1* (4%)	*0*	*0*
Weight loss	*1* (4%)	*0*	*0*
Radiotherapy toxicity			
Radiation-induced dermatitis	*1* (4%)	*0*	*0*
Central nervous system necrosis	*1* (4%)	*0*	*0*

* Occurred in a patient with known Crohn disease.

Adverse events were graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. The case of biopsy-proven local bullous pemphigoid was treated with local steroids without interruption of anti-PD-1. In addition to this table, one patient developed sarcoidosis-like cutaneous granulomas.

- Radiotherapy did not seem to induce unusual or severe anti-PD-1-related adverse events
- It was observed vitiligo-like depigmentation after radiotherapy in 16% of patients, a feature associated with longer survival in advanced melanoma patients treated with immunotherapy

Clinical Oncology 30 (2018) 201–203

Contents lists available at ScienceDirect

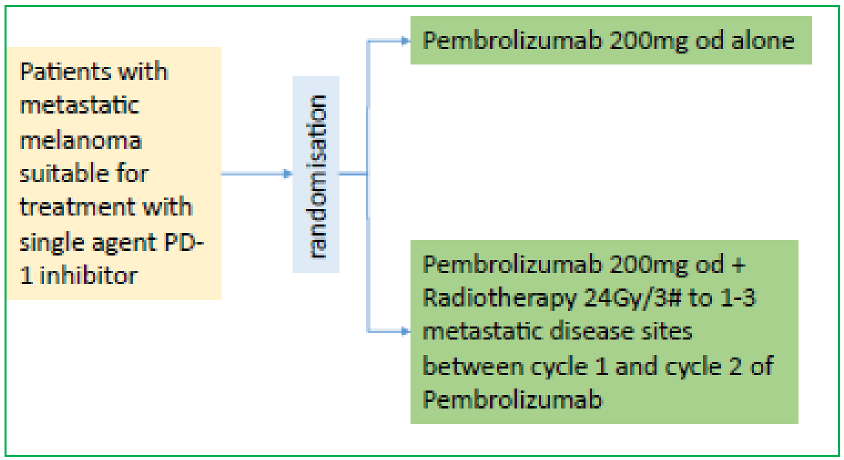
Clinical Oncology

journal homepage: www.clinicaloncologyonline.net

Editorial

Pembrolizumab in Combination with Radiotherapy for Metastatic Melanoma — Introducing the PERM Trial

K. Yip [*], A. Melcher [†‡], K. Harrington [†‡], T. Illidge [§¶], J. Nobes [||], A. Webster [**], D. Smith [‡], P. Lorigan [§¶], P. Nathan [††], J. Larkin [‡]



- In the combination arm patients received 24 Gy in three fractions to the target lesion between cycle 1 and cycle 2 of pembrolizumab
- The primary end point for this study is the response rate as assessed by RECIST criteria 12 weeks from the start of pembrolizumab treatment

FULL PAPER

BJC

British Journal of Cancer (2018) 118, 785–792 | doi: 10.1038/bjc.2017.489

Keywords: radiation; radiotherapy; BRAF; vemurafenib; dabrafenib

Clinical outcome of concomitant vs interrupted BRAF inhibitor therapy during radiotherapy in melanoma patients

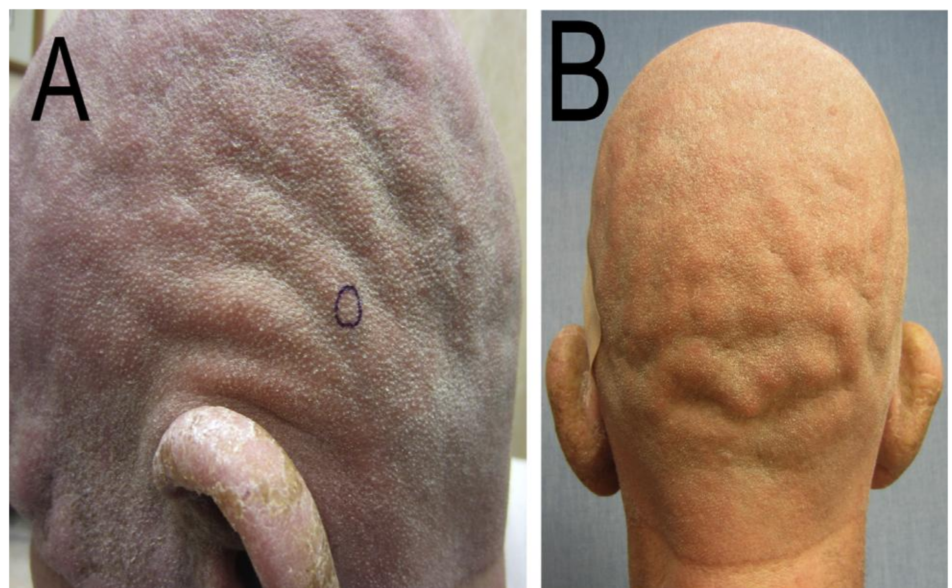
- A total of 155 patients with BRAF-mutated melanoma from 17 European skin cancer centres were retrospectively analysed. Out of these, 87 patients received concomitant radiotherapy and BRAFi (59 vemurafenib, 28 dabrafenib), while in 68 patients BRAFi therapy was interrupted during radiation (51 vemurafenib, 17 dabrafenib)
- Interruption of vemurafenib treatment during radiation was associated with better survival and less toxicity compared to concomitant treatment. Due to lower number of patients, the relevance of treatment interruption in dabrafenib treated patients should be further investigated
- The results of this analysis indicate that treatment with the BRAFi vemurafenib should be interrupted during radiotherapy

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

Increased skin toxicity: BRAFi increase the risk of grade 2 and 3 dermatitis with RT
Dose: The severity of the reaction appears dependent on the dose of RT but not BRAFi
Timing: all but 1 grade 3 dermatitis incident was reported in the setting of concurrent RT and BRAFi administration

Nondermatitis skin toxicity

RT and BRAFi may cause painful and disfiguring nondermatitis reactions, the most common of which are FCP (follicular cystic proliferation) an CVG (cutis verticis gyrata)



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

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

Increased Mucosal toxicity from BRAFi with RT appears low, but → The GI organs should not intentionally be targeted with RT during BRAFi therapy; their concurrent use should be minimized

Hearing toxicity Not increased concern specifically for ototoxicity with concurrent BRAFi administration

Lung toxicity (Recall Radiation Pneumonitis RRP, pleural hemorrhage)
Low probability but → vigilance in detecting symptoms of RRP (cough, fever, shortness of breath, and chest pain) for at-risk patients
Prompt administration of corticosteroids may prevent the need for cessation or dose reduction of BRAFi

Epatotoxicity
Very low probability , but the consequences may be severe → care to minimize liver dose

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

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

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

- Hold 3 days before and after fractionated RT
- Hold 1 day before and after SRS

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

Optimizing combination dabrafenib and trametinib therapy (CombiDT) in BRAF mutation-positive advanced melanoma patients: Guidelines from Australian melanoma medical oncologists

- BRAF inhibitor monotherapy may cause radiosensitization (Anker 2013, Pulvirenti 2016)
- In australian experience combination therapy does not increase skin toxicity compared with single agent BRAF inhibition
- The addition of a MEK inhibitor to a BRAF inhibitor may ameliorate skin toxicity seen with concomitant BRAF inhibition and RT

- Vemurafenib was associated with significantly higher levels of acute radiodermatitis than dabrafenib (40% vs 26%, *P = 0.07)*
- Whole brain radiation therapy (WBRT) with concomitant BRAF inhibitor therapy acute dermatitis was higher than in 91 patients treated with WBRT only (44% vs 8%, *P < 0.001)*
- There was no radiodermatitis > *grade 1 seen with SRS*

Hecht M, et al. Radiosensitization by BRAFi. *Ann Oncol*

Atkinson V et al, Asia-Pacific Journal of Clinical Oncology 2016; 12(Suppl. 7): 5–12