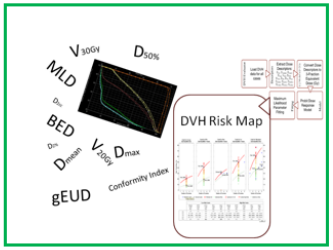
Società Italiana di Radiobiologia

XXVI CONGRESSO NAZIONALE AIRO
XXX CONGRESSO NAZIONALE AIRB
IX CONGRESSO NAZIONALE AIRO GIOVANI

verso ...
i "nuovi" limiti di dose per OARs
in radioterapia ipofrazionata



A cura del
GRUPPO AIRO REGIONALE EMILIA ROMAGNA MARCHE
(coordinatore Giovanna Mantello)

INTEGRAZIONE DELLA RADIOTERAPIA IPOFRAZIONATA CON I NUOVI FARMACI: NUOVA TOSSICITA'?

SERVIZIO SANITARIO REGIONALE
EMILIA-ROMAGNA
Azienda Ospedaliero - Universitaria di Modena
Policlinico

ELISA D'ANGELO

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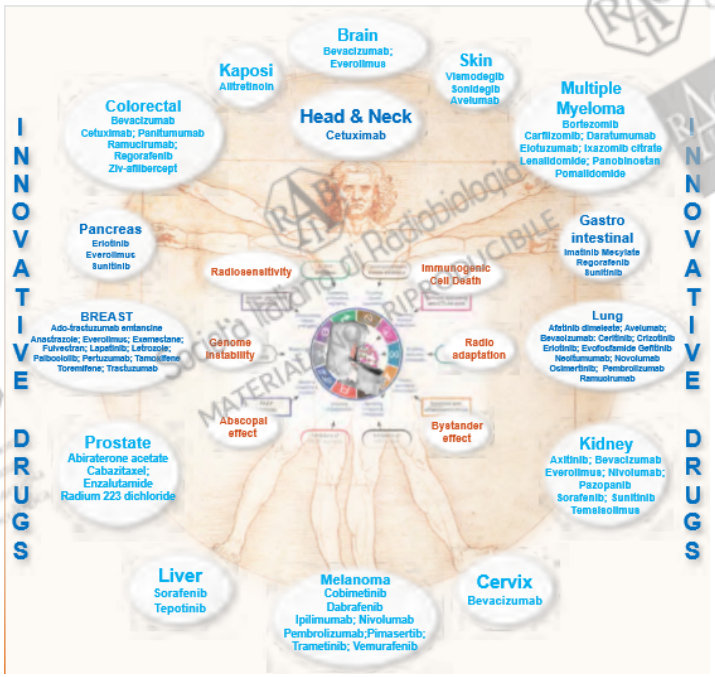
DICHIARAZIONE

Relatore: Elisa D'Angelo

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.

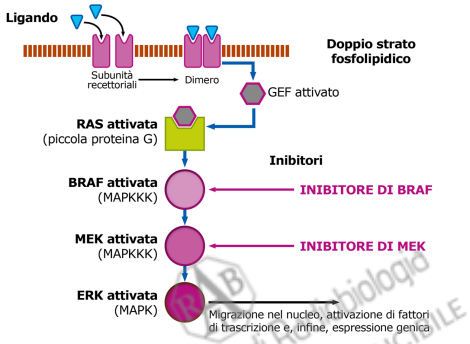
- Posizione di dipendente in aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**
- Consulenza ad aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**
- Fondi per la ricerca da aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**
- 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)**

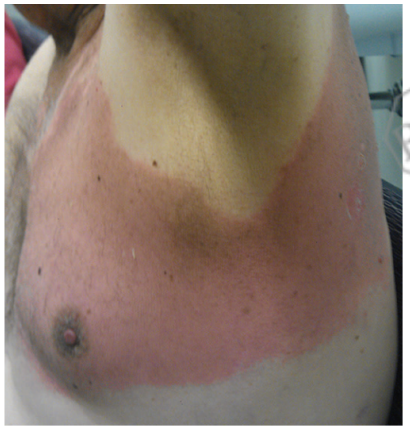
INTEGRAZIONE DELLA RADIOTERAPIA IPOFRAZIONATA CON I NUOVI FARMACI: NUOVA TOSSICITA'?



TARGET THERAPY E RADIOTERAPIA IPOFRAZIONATA

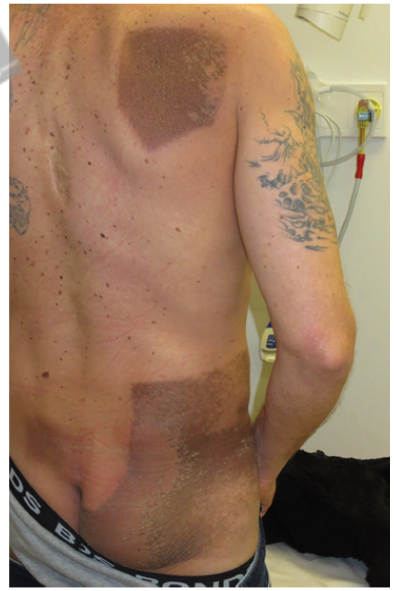
Inibitori BRAF e tox cutanea





RT: 36 Gy (3Gy/fr)
Dabrafenib 150 mg twice a daily concomitante
Comparsa rash maculo-papulare tossicità a 21 Gy

8 Gy
Dabrafenib 150 mg per twice a day (8 settimane)
Comparsa di tox dopo il secondo corso di RT su meta



Pulvirenti T et al., *JCO* **2014**; *32*

Inibitori BRAF e tox cutanea

Research

Case Report/Case Series

Vemurafenib and Radiosensitization

Lise Boussemart, MD; Catherine Boivin, MD; Joël Claveau, MD; Yun Gan Tao, MD; Gorana Tomasic, MD; Emilie Routier, MD; Christine Mateus, MD; Eric Deutsch, MD, PhD; Caroline Robert, MD, PhD

IMPORTANCE The *BRAF* inhibitor, vemurafenib, was recently approved for the treatment of patients with $BRAF^{V600}$ metastatic melanoma. Wider use of this drug and longer follow-up periods of treatment are resulting in the emergence of a growing number of reports detailing new adverse effects. Cutaneous adverse effects are preeminent with UV-A–dependent phototoxicity, hyperkeratotic follicülitis, hand-foot skin reaction, hair changes, verrucous papillomas, keratoacanthomas, and squamous cell carcinomas.

OBSERVATIONS We report 2 cases of dermatitis occurring on a previously irradiated skin area in patients treated with vemurafenib for a $BRAF^{V600}$-mutated metastatic melanoma. The first case occurred 10 days after a low dose of radiation was delivered that usually does not induce any radiodermatitis, suggesting radiosensitization by vemurafenib. The second case occurred 30 days after radiotherapy and was diagnosed as radiation recall dermatitis.

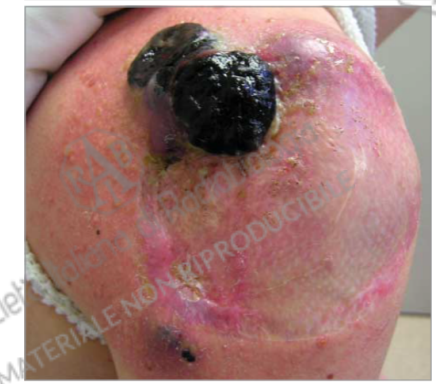
CONCLUSIONS AND RELEVANCE Vemurafenib should be considered a potential cutaneous radiosensitizer and an inducer of radiation recall dermatitis. However, these adverse effects are easily managed with topical corticosteroids. Dose reduction or interruption of vemurafenib is not required. Further studies and reports will enlighten us as to whether this pharmacodynamic interaction between x-rays and vemurafenib is also seen with other *BRAF* or *MEK* inhibitors on the same mitogen-activated protein kinase pathway currently under development.

JAMA Dermatol. 2013;149(7):855-857. doi:10.1001/jamadermatol.2013.4200
Published online May 22, 2013.

Author Affiliations: Department of Medical Oncology, Institut Gustave Roussy, Villejuif, France (Boussemart, Routier, Mateus, Robert); Department of Dermatology, Melanoma and Skin Cancer Clinic, Centre hospitalier universitaire de Quebec–Hôpital Hôtel-Dieu, Quebec City, Quebec, Canada (Boivin, Claveau). Department of Radiation Oncology (Drs Tao and Deutsch), Institut Gustave Roussy, Villejuif, France (Tao, Deutsch); Department of Pathology, Institut Gustave Roussy, Villejuif, France (Tomasic).

Corresponding Author: Caroline Robert, MD, PhD, Department of Medical Oncology, Institut Gustave Roussy, 114 rue Edouard Vaillant, 94800 Villejuif, France (caroline.robert@igr.fr).

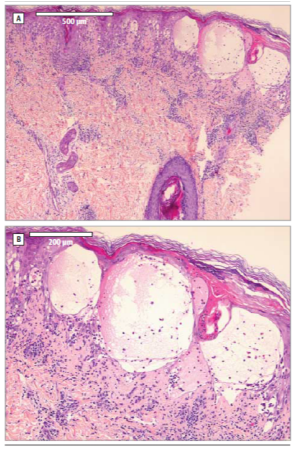
Figure 1. Vesicular Erythematous Dermatitis



Vesicular erythematous dermatitis strictly located around the right shoulder skin metastasis in patient 1.

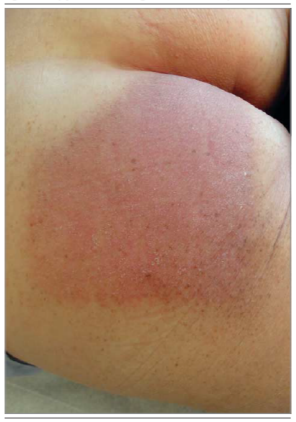
18 Gy (3Gy/fr)
960mg vemurafenib
twice daily iniziato 1 giorno dopo RT
Comparsa dermatite vescicolare 10 gg dopo

20 Gy (4 Gy/fr)
960mg vemurafenib
twice daily iniziato 23 gg dopo fine RT
Comparsa eczema pruriginoso sette gg dopo inizio farmaco (30 dopo rt):RRD



Skin biopsy specimen from the dermatitis observed around the previously irradiated skin metastasis in patient 1 (hematoxylin and eosin, ×5 [A] and ×10 [B]).

Figure 3. Sharply Delimited Rectangular Eczematous Plaque



Sharply delimited rectangular eczematous plaque on the buttock in patient 2, exactly matching the previously irradiated field.

Nota AIFA

19/10/2015

Nell'ambito della variazione II/24G relativa alla specialità medicinale ZELBORAF® (approvata dal CHMP in data 24 settembre 2015), l'EMA ha richiesto l'invio di una DHPC al fine di sensibilizzare gli operatori sanitari riguardo il potenziamento della radiotossicità associata a Zelboraf (vemurafenib). Sono stati riferiti casi severi di lesioni correlate a radiazioni, alcuni con esito fatale, in pazienti sottoposti a radioterapia prima, durante o dopo il trattamento con Zelboraf. La maggior parte dei casi è stata di natura cutanea, ma alcuni casi hanno coinvolto gli organi viscerali. Pertanto Zelboraf deve essere usato con cautela quando è somministrato prima, in concomitanza o in sequenza al trattamento radiante

Case report: Radiation recall da sorafenib

Strahlenther Onkol (2016) 192:342–348
DOI 10.1007/s00066-016-0950-7

CASE STUDY

Radiation recall dermatitis induced by sorafenib

A case study and review of the literature

Sonja Stieb[1,2] · Oliver Riesterer[1] · Cornelia Brüssow[1] · Bernhard Pestalozzi[3] · Matthias Guckenberger[1] · Stefan Weiler[4]

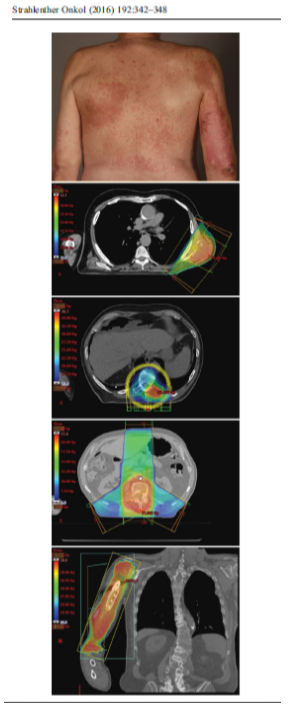
Received: 29 October 2015 / Accepted: 28 January 2016 / Published online: 23 February 2016

Metastasi ossee da HCC

SBRT su meta osso

Sorafenib 400 mg twice daily da metà marzo

Una settimana dopo: febbre, lesion eritematose delle aree precedentemente irradiate



Inattesa tossicità anche dopo lungo tempo?!?

Radiation recall dermatitis

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4 pazienti presenti in letteratura con RRD da sorafenib

Table 2 Present case and summary of reported cases of radiation recall dermatitis (RRD) in [a]MEDLINE and the [b]WHO pharmacovigilance database "VigiBase®" [22]

Author, year	Age, gender	Diagnosis	Radiotherapy	Daily sorafenib dosage	Onset of RRD after start of sorafenib	Symptoms	RRD treatment	Outcome
Stieb, 2015	77, m	HCC	Bone metastases 20–36 Gy	2×400 mg	1 week	Erythematous rash, eczematous dissemination, pruritus	Topical steroids and oral antihistamines, Sorafenib discontinued	Skin reaction decreased within 2 weeks
Hsieh[a], 2014	63, m	HCC	Liver SBRT 6×8 Gy	300 mg	1 week	RRD grade 2	Topical steroids, Sorafenib discontinued	Symptoms resolved after 10 days
Oh[a], 2013	50, m	HCC	Chest wall mass 13×3 Gy	2×400 mg	2 weeks	Erythematous patch, dry desquamation, dissemination, pruritus	Oral antihistamines, Sorafenib discontinued	Sorafenib was restarted, no recurrent RRD
Chung[a], 2010	38, m	HCC	Liver SBRT 6×5 Gy	2×200 mg	Several days	Progressive pruritus, fatigue, patchy hyperpigmentation, dry desquamation	Topical steroids, Sorafenib continued	Pruritus and skin changes resolved after 2–3 weeks, Sorafenib was escalated without exacerbation of RRD
n.a.[b], 2008	51, m	RCC	n.a.	n.a.	n.a.	Vesicular rash, swelling, tenderness, pain	n.a.	n.a.

HCC hepatocellular carcinoma, *m* male, *n.a.* not available, *RCC* renal cell carcinoma, *RRD* radiation recall dermatitis, *SBRT* stereotactic radiotherapy

VEGF Inibitori e SBRT

International Journal of Radiation Oncology biology • physics
www.redjournal.org

Clinical Investigation: Gastrointestinal Cancer

Increased Bowel Toxicity in Patients Treated With a Vascular Endothelial Growth Factor Inhibitor (VEGFI) After Stereotactic Body Radiation Therapy (SBRT)

Brandon M. Barney, MD,* Svetomir N. Markovic, MD, PhD,† Nadia N. Laack, MD,* Robert C. Miller, MD,* Jann N. Sarkaria, MD,* O. Kenneth Macdonald, MD,‡ Heather J. Bauer, RN,* and Kenneth R. Olivier, MD*

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Received Mar 29, 2013, and in revised form May 3, 2013. Accepted for publication May 5, 2013

Table 3 Summary of clinical findings in patients who had SBI

Patient No.	Age (y)	Primary tumor	Site treated with SBRT	RT dose (Gy/fraction)	Maximum bowel dose (Gy)	Time from SBRT to VEGFI (mo)	Time from VEGFI to SBI (mo)	VEGFI regimen	SBI
1	54	HCC	Liver	30/3	30.0	1.3	3.3	Sorafenib, 400 mg twice a day	Gastric ulcer, grade 3
2	71	CRC	Liver	60/5	44.9	0.5	4.0	FOLFOX-6 every 3 wk Bevacizumab, 5 mg/kg every 2 wk	Gastric perforation, grade 4
3	66	Pancreas	Pancreas	42/5	46.2	7.0	3.4	Capecitabine, 1000 mg twice a day Bevacizumab, 15 mg/kg every 3 wk	Duodenal perforation, grade 5
4	67	Melanoma	Liver	60/3	18.3	2.0	3.1	Carboplatin, AUC = 6 every 3 wk Paclitaxel, 200 mg/m^2 every 3 wk Bevacizumab, 15 mg/kg every 3 wk	Small bowel perforation, grade 4
5	75	RCC	Lymph node	40/5	39.7	16.3	0.9	Bevacizumab, 10 mg/kg every 2 wk	Duodenal ulcer, grade 3
6	52	Melanoma	Liver	60/3	37.6	0.0	3.1	Carboplatin, AUC = 2 every wk Paclitaxel, 100 mg/m^2 every week Bevacizumab, 10 mg/kg every 2 wk	Gastric ulcer, grade 3
7	55	Melanoma	Liver	60/5	36.2	2.3	0.4	Bevacizumab, 10 mg/kg every 2 wk	Gastric ulcer, grade 4

Abbreviations: AUC = area under curve; CRC = colorectal adenocarcinoma; FOLFOX-6 = folinic acid, fluorouracil, and oxaliplatin; HCC = hepatocellular carcinoma; RCC = renal cell carcinoma; RT = radiation therapy; SBI = serious bowel injury; SBRT = stereotactic body radiation therapy; VEGFI = vascular endothelial growth factor inhibitor.

- SBRT: RT 3D-CONFORMAL O IMRT, 1-5 FRAZIONI, DOSI TRA 28 Gy E 60 Gy
- **TOX INTESTINALE GRADO≥3 : 7/76 (9%),**
- **TUTTI AVEVANO ESEGUITO TERAPIA CON VEGFI (6 PZ BEVACIZUMAB, 1 PZ SORAFENIB) DOPO LA RT, MEDIANA DI COMPARSA 4,6 MESI**
- **BEVACIZUMAB DOSE DI 10 mg/Kg ogni 2 sett; 15 mg/Kg ogni 3 sett**
- 13/76 PAZIENTI NONOSTANTE INTEGRAZIONE TRA SBRT E VEGFI NON HANNO MANIFESTATO TOX SEVERA

Antiangiogenetici

Int J Radiat Oncol Biol Phys. 2015 July 1; 92(3): 568–576. doi:10.1016/j.ijrobp.2015.02.016.

Gastrointestinal Toxicities With Combined Antiangiogenic and Stereotactic Body Radiation Therapy

Erqi L. Pollom, MD[*], **Lei Deng, MBBS**[*], **Reetesh K. Pai, MD**[†], **J. Martin Brown, PhD**[*], **Amato Giaccia, PhD**[*], **Billy W. Loo Jr, MD, PhD**[*], **David B. Shultz, MD, PhD**[*], **Quynh Thu Le, MD**[*], **Albert C. Koong, MD, PhD**[*], and **Daniel T. Chang, MD**[*]

[*]Department of Radiation Oncology, Stanford University School of Medicine, Stanford, California

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Clinical reports of luminal GI toxicity with SBRT and hypofractionated radiation therapy and anti-VEGF agents

Study	Patient	% of patients treated with anti-VEGF agent and SBRT	Radiation schedule	Anti-VEG F agent	Toxicity	In-field toxicity?
Peters et al (30)	1 patient with renal cell carcinoma	N/A	8 Gy in 1 fraction	Sorafenib 400 mg twice daily for 5 weeks before and 3 days after RT	Grade 5 colon perforations, 1 week after SBRT	Yes
Lodick et al (31)	1 patient with renal cell carcinoma	N/A	28 Gy in 7 fractions	Bevacizumab 10 mg/kg every other week, 4 months after RT	Grade 5 cecal perfomtion, 3.5 months after SBRT	Yes
Stephans et al (32)	2 patients with lung/liver tumors near esophagus	29%	50 Gy in 5 fractions	Not specified, received anti-VEGF agent within 2 months of completing SBRT	≥Grade 3 esophageal fistula at median time of 8.4 months after SBRT	Yes
Barney et al (33)	1 patient with hepatocellular carcinoma	35%	30 Gy in 3 fractions	Sorafenib 400 mg BID, 1.3 months after SBRT	Grade 3 gastric ulcer, 4.6 months after SBRT	Yes
	1 patient with colorectal carcinoma		60 Gy in 5 fractions	Bevacizumab 5 mg/kg every 2 weeks, 0.5 months after SBRT	Grade 4 gastric perforation, 4.5 months after SBRT	Yes
	1 patient with pancreas cancer		42 Gy in 5 fractions	Bevacizumab 15 mg/kg every 3 weeks, 7 months after SBRT	Grade 5 duodenal perforation, 10.4 months after SBRT	Yes
	1 patient with melanoma		60 Gy in 3 fractions	Bevacizumab 15 mg/kg every 3 weeks, 2 months after SBRT	Grade 4 small bowel perforation, 5.1 months after SBRT	Yes
	1 patient with renal cell carcinoma		40 Gy in 5 fractions	Bevacizumab 10 mg/kg every 2 weeks, 16.3 months after SBRT	Grade 3 duodenal ulcer, 17.2 months after SBRT	Yes
	1 patient with melanoma		60 Gy in 3 fractions	Bevacizumab 10 mg/kg every 2 weeks, with SBRT	Grade 3 gastric ulcer, 3.1 months after SBRT	Yes
	1 patient with melanoma		60 Gy in 5 fractions	Bevacizumab 10 mg/kg every 2 weeks, 2.3 months after SBRT	Grade 4 gastric ulcer, 2.7 months after SBRT	Yes
Dawson et al (34)	1 patient with hepatocellular carcinoma	12.5%	33 Gy in 6 fractions	Sorafenib 400 mg daily, with SBRT	Grade 4 acute on chronic small bowel obstruction, 27 days after SBRT	Yes
	1 patient with hepatocellular carcinoma		30 Gy in 6 fractions	Sorafenib 400 mg daily, with SBRT	Grade 3 GI bleed, 51 days after SBRT	Yes

Abbreviations: GI = gastrointestinal, SBRT = stereotactic body radiation therapy, VEGF = vascular endothelial growth factor.

Quali meccanismi???

Antiangiogenetici

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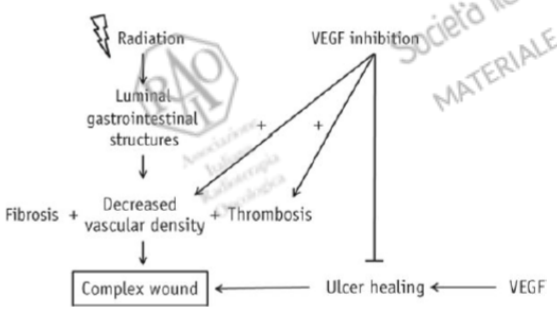


Fig. 2.
Vascular endothelial growth factor inhibition combined with radiation results in nonhealing complex wound.

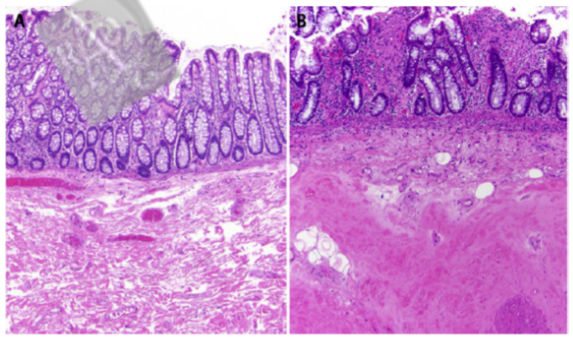
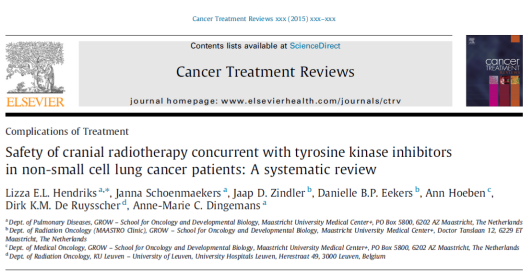


Fig. 1.
(A) Unirradiated colon showing normal-appearing glands overlying loose fibrovascular submucosa (hematoxylin and eosin, ×40). (B) The colon in this patient with chronic radiation injury demonstrates hyalinized collagen (fibrosis) replacing the submucosa. The overlying mucosa also demonstrates distorted crypt architecture and patchy lamina propria fibrosis (hematoxylin and eosin, ×40).

PERCHE' ASSOCIARE E CON CHE TIMING?

Inibitori tyr K e RT encefalica



Cancer Treatment Reviews xxx (2015) xxx–xxx

Contents lists available at ScienceDirect

Cancer Treatment Reviews

journal homepage: www.elsevierhealth.com/journals/ctrv

Complications of Treatment

Safety of cranial radiotherapy concurrent with tyrosine kinase inhibitors in non-small cell lung cancer patients: A systematic review

Lizza E.L. Hendriks [a,*], Janna Schoenmaekers [a], Jaap D. Zindler [b], Danielle B.P. Eekers [b], Ann Hoeben [c], Dirk K.M. De Ruysscher [d], Anne-Marie C. Dingemans [a]

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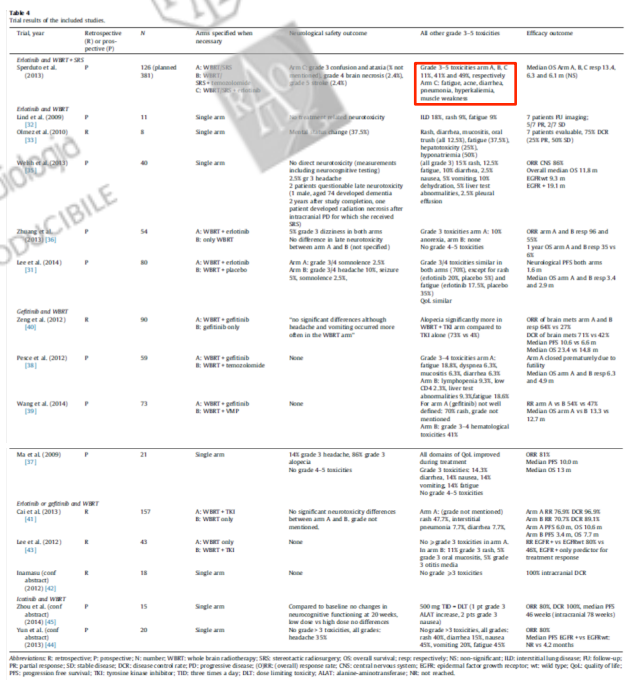

Table 4
Trial results of the included studies.

Trial, year	Retrospective (R) or prospective (P)	N	Arms specified when necessary	Neurological safety outcome	All other grade 3–5 toxicities	Efficacy outcome
Erlotinib and WBRT + SRS						
Sperduto et al. (2013)	P	126 (planned 381)	A: WBRT+SRS B: WBRT+SRS + temozolomide C: WBRT+SRS + erlotinib	Arm C: grade 3 confusion and ataxia (3 not mentioned), grade 4 brain necrosis (2.4%), grade 5 stroke (2.4%)	Grade 3–5 toxicities arm A, B, C: 11%, 4.1% and 49%, respectively Arm C: fatigue, acne, diarrhea, pneumonia, hyperkalaemia, muscle weakness	Median OS Arm A, B, C resp 13.4, 6.3 and 6.1 m (NS)
Erlotinib and WBRT						
Lind et al. (2009) [32]	P	11	Single arm	No treatment related neurotoxicity	ILD 18%, rash 9%, fatigue 9%	7 patients PD imaging; 5/7 PR, 2/7 SD
Olmez et al. (2010) [33]	R	8	Single arm	Mental status change (37.5%)	Rash, diarrhea, mucositis, oral trush (all 12.5%), fatigue (37.5%), hepatotoxicity (25%), hyponatremia (50%)	7 patients evaluable, 75% DCR (25% PR, 50% SD)
Welsh et al. (2013) [34]	P	40	Single arm	No direct neurotoxicity (measurements including neurocognitive testing) 2.5% gr 3 headache 2 patients questionable late neurotoxicity (1 male, aged 74 developed dementia 2 years after study completion, one patient developed radiation necrosis after intracranial PD for which she received SRS)	(all grade 3) 15% rash, 12.5% fatigue, 10% diarrhea, 2.5% nausea, 5% vomiting, 10% dehydration, 5% liver test abnormalities, 2.5% pleural effusion	ORR CNS 86% Overall median OS 11.8 m EGFRwt 9.3 m EGFR + 19.1 m
Zhuang et al. (2013) [36]	P	54	A: WBRT + erlotinib B: only WBRT	5% grade 3 dizziness in both arms No difference in late neurotoxicity between arm A and B (not specified)	Grade 3 toxicities arm A: 10% anorexia, arm B: none No grade 4–5 toxicities	ORR arm A and B resp 96 and 55% 1 year OS arm A and B resp 35 vs 6%
Lee et al. (2014) [31]	P	80	A: WBRT + erlotinib B: WBRT + placebo	Arm A: grade 3/4 somnolence 2.5% Arm B: grade 3/4 headache 10%, seizure 5%, somnolence 2.5%,	Grade 3/4 toxicities similar in both arms (70%), except for rash (erlotinib 20%, placebo 5%) and fatigue (erlotinib 17.5%, placebo 35%) QoL similar	Neurological PFS both arms 1.6 m Median OS arm A and B resp 3.4 and 2.9 m
Gefitinib and WBRT						
Zeng et al. (2012) [40]	R	90	A: WBRT + gefitinib B: gefitinib only	"no significant differences although headache and vomiting occurred more often in the WBRT arm"	Alopecia significantly more in WBRT + TKI arm compared to TKI alone (73% vs 4%)	ORR of brain mets arm A and B resp 64% vs 27% DCR of brain mets 71% vs 42% Median PFS 10.6 vs 6.6 m Median OS 23.4 vs 14.8 m
Pesce et al. (2012) [38]	P	59	A: WBRT + gefitinib B: WBRT + temozolomide	None	Grade 3–4 toxicities arm A: fatigue 18.8%, dyspnea 6.3%, mucositis 6.3%, diarrhea 6.3% Arm B: lymphopenia 9.3%, low CD4 2.3%, liver test abnormalities 9.3%,fatigue 18.6%	Arm A closed prematurely due to futility Median OS arm A and B resp 6.3 and 4.9 m
Wang et al. (2014) [39]	P	73	A: WBRT + gefitinib B: WBRT + VMP	None	For arm A (gefitinib) not well defined: 70% rash, grade not mentioned Arm B: grade 3–4 hematological toxicities 41%	RR arm A vs B 54% vs 47% Median OS arm A vs B 13.3 vs 12.7 m
Ma et al. (2009) [37]	P	21	Single arm	14% grade 3 headache, 86% grade 3 alopecia No grade 4–5 toxicities	All domains of QoL improved during treatment Grade 3 toxicities: 14.3% diarrhea, 14% nausea, 14% vomiting, 14% fatigue No grade 4–5 toxicities	ORR 81% Median PFS 10.0 m Median OS 13 m
Erlotinib or gefitinib and WBRT						
Cai et al. (2013) [41]	R	157	A: WBRT + TKI B: WBRT only	No significant neurotoxicity differences between arm A and B, grade not mentioned.	Arm A: (grade not mentioned) rash 47.7%, interstitial pneumonia 7.7%, diarrhea 7.7%,	Arm A RR 76.9% DCR 96.9% Arm B RR 70.7% DCR 89.1% Arm A PFS 6.0 m, OS 10.6 m Arm B PFS 3.4 m, OS 7.7 m
Lee et al. (2012) [43]	R	43	A: WBRT only B: WBRT + TKI	None	No >grade 3 toxicities in arm A. In arm B: 11% grade 3 rash, 5% grade 3 oral mucositis, 5% grade 3 otitis media	RR EGFR + vs EGFRwt 80% vs 46%, EGFR + only predictive for treatment response
Inamasu (conf abstract) (2012) [42]	R	18	Single arm	None	No grade >3 toxicities	100% intracranial DCR
Icotinib and WBRT						
Zhou et al. (conf abstract) (2014) [45]	P	15	Single arm	Compared to baseline no changes in neurocognitive functioning at 20 weeks, low dose vs high dose no differences	500 mg TID + DLT (1 pt grade 3 ALAT increase, 2 pts grade 3 nausea)	ORR 80%, DCR 100%, median PFS 46 weeks (intracranial 78 weeks)
Yun et al. (conf abstract) (2013) [44]	P	20	Single arm	No grade > 3 toxicities, all grades: headache 35%	No grade >3 toxicities, all grades: rash 40%, diarrhea 15%, nausea 45%, vomiting 20%, fatigue 45%	ORR 80% Median PFS EGFR + vs EGFRwt: NR vs 4.2 months

Abbreviations: R: retrospective; P: prospective; N: number; WBRT: whole brain radiotherapy; SRS: stereotactic radiosurgery; OS: overall survival; resp: respectively; NS: non-significant; ILD: interstitial lung disease; FU: follow-up; PR: partial response; SD: stable disease; DCR: disease control rate; PD: progressive disease; (O)RR: (overall) response rate; CNS: central nervous system; EGFR: epidermal factor growth receptor; wt: wild type; QoL: quality of life; PFS: progression free survival; TKI: tyrosine kinase inhibitor; TID: three times a day; DLT: dose limiting toxicity; ALAT: alanine-aminotransferase; NR: not reached.

WBRT: Dose totale tra 20 e 50 Gy in 4 (20 Gy) to 25 (50 Gy) frazioni

Non sembra esserci tossicità aggiuntiva di rilievo

Attenzione al T½!!!

Targeted therapy and SRS

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Stereotactic radiosurgery (SRS) in the modern management of patients with brain metastases

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Keywords: *stereotactic radiosurgery, brain metastases, whole brain radiation, targeted therapy*

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ABSTRACT

"Although, randomized evidence is still lacking, there is suggestion from retrospective data that the combination may lead to improved outcome, However, caution needs to be exercised as concurrent targeted therapy and radiation treatment may not be as innocuous as previously Thought"

Targeted therapy in combination with radiation							
Staehler et al.[70] Brain (N=51) Spine (N=55)	Sorafenib or sunitinib and SRS	RCC spine and brain SRS ECOG 0 or 1	Local Control	98% at 15 mos	2 asymptomatic tumour hemorrhage	NA	11.1 mos in brain pts
Lin et al.,[71] Phase 1 study (N=35)	Lapatinib dose escalating and WBRT (35Gy in 14 fractions)	Her2-positive breast cancer	CNS objective response	Response rate 79%	7/27 pts had DLTs a 1250mg of lapatinib	46% PFS at 6 mos	NR
Welsh et al.[72] Phase II trial (N=40)	Erlotinib plus WBRT (35Gy in 14 fractions)	NSCLC regardless of EGFR status	CNS objective response according to RECIST	ORR was 86%	Most common Grade 3 toxicity: fatigue (12.5%) and rash (15%)	8.0 mos	Overall 11.8 mos EGFR mutant 19.2 mos
Lee et al.[73] Phase III trial (N=80)	Arm 1: WBRT and placebo Arm 2: WBRT and erlotinib	NSCLC KPS>70 Multiple brain mets 1/35 EGFR mutant	nPFS	No difference in nPFS	Grade 3 or 4 similar in both arms at 70%	nPFS 1.6 mos in both arms	Arm 1: 2.9 mos Arm 2: 3.4 mos
Sperduto et al.[74] Phase III trial (N=126)	Arm 1: WBRT and SRS alone Arm 2: WBRT, SRS and TMZ Arm 3: WBRT, SRS and erlotinib	NSCLS with 1-3 brain metastases. No stratification based on predictive biomarkers	Compare OS for TMZ and erlotinib groups versus WBRT and SRS alone group	NA	Grade 3-5 toxicity Arm 1=11%, Arm 2=41%, Arm 3=49% (p<0.001)	Median PFS: Arm1= 8.1 mos Arm 2= 4.6 mos Arm 3= 4.8 mos	Median OS: Arm1: 13.4 mos Arm 2: 6.3 mos Arm 3: 6.1 mos
Knisely et al.[75] Retrospective review (N=77)	Non-randomized comparison of SRS alone or in combination with ipilimumab	Melanoma brain metastases initially treated with SRS	Compare 2-year and median OS	2-year OS ipilimumab: 47.2% no ipilimumab: 19.7%	NR	NR	Median OS ipilimumab: 21.3mos no ipilimumab: 4.9mos

PFS: progression free survival, nPFS: neurologic progression free survival, OS: overall survival, NSCLC: non-small cell lung cancer, EGFR: epidermal growth factor receptor, WBRT: whole brain radiotherapy, SRS: stereotactic radiosurgery, mos: months, wks: weeks, NS: not significant, NR: not recorded, NA: not applicable

IMMUNOTERAPIA E RADIOTERAPIA IPOFRAZIONATA

Farmaci immunoterapici

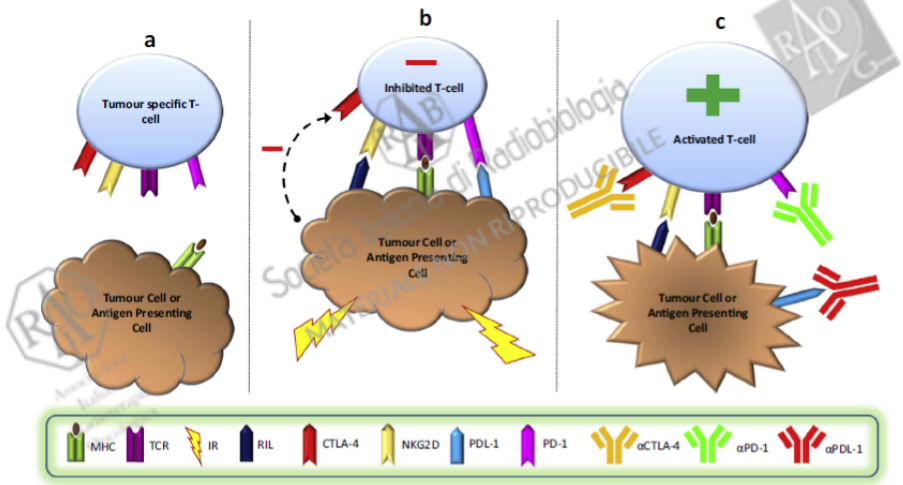

Fig. 2. Simplified summary of the synergistic interaction between ionising radiation and immune checkpoint blockade in inducing an immune response. (A) Tumour cell avoiding T-cell immunosurveillance due to lack of expression of stimulating ligands results in poor T-cell activation. (B) Ionising radiation (IR) of cell leads to upregulation of RAE-1 and other radiation induced ligands (RIL) allowing recognition by T-cells. However, CTLA-4 may negatively regulate this pathway muting the T-cells ability to kill the cancer cell. (C) Addition of CTLA-4 antibody binds CTLA-4, removing this inhibitory signal which thus allows the MHC-T cell receptor complex (TCR) to cause T-cell activation and cell killing. PD-1 and PDL-1 inhibitors are likely to exert similar effects seen with CTLA-4 inhibitors of increasing the activation of T-cell response to irradiated tumour cells.

Anti CTLA-4

Lancet Oncol. 2014 June ; 15(7): 700–712. doi:10.1016/S1470-2045(14)70189-5.

Ipilimumab versus placebo after radiotherapy in patients with metastatic castration-resistant prostate cancer that had progressed after docetaxel chemotherapy (CA184-043): a multicentre, randomised, double-blind, phase 3 trial

Eugene D Kwon, **Charles G Drake**, **Howard I Scher**, **Karim Fizazi**, **Alberto Bossi**, **Alfons J M van den Eertwegh**, **Michael Krainer**, **Nadine Houede**, **Ricardo Santos**, **Hakim Mahammedi**, **Siobhan Ng**, **Michele Maio**, **Fabio A Franke**, **Santhanam Sundar**, **Neeraj Agarwal**, **Andries M Bergman**, **Tudor E Ciuleanu**, **Ernesto Korbenfeld**, **Lisa Sengeløv**, **Steinbjorn Hansen**, **Christopher Logothetis**, **Tomasz M Beer**, **M Brent McHenry**, **Paul Gagnier**, **David Liu**, **Winald R Gerritsen**, and **for the CA184-043 Investigators**[*]

Summary of on-study adverse events

	Ipilimumab (n=393)				Placebo (n=396)			
	Any grade	Grade 3	Grade 4	Grade 5	Any grade	Grade 3	Grade 4	Grade 5
Any adverse event*								
Diarrhoea	199 (51%)	63 (16%)	1 (<1%)	0	97 (24%)	7 (2%)	0	0
Fatigue	150 (38%)	34 (9%)	6 (2%)	0	123 (31%)	31 (8%)	4 (1%)	0
Nausea	127 (32%)	11 (3%)	0	0	106 (27%)	7 (2%)	0	0
Decreased appetite	120 (31%)	15 (4%)	0	0	98 (25%)	12 (3%)	0	0
Vomiting	111 (28%)	7 (2%)	0	0	85 (21%)	9 (2%)	0	0
Pruritus	99 (25%)	1 (<1%)	0	0	22 (6%)	0	0	0
Anaemia	90 (23%)	37 (9%)	3 (1%)	0	88 (22%)	35 (9%)	8 (2%)	0
Decreased weight	90 (23%)	5 (1%)	0	0	56 (14%)	1 (<1%)	0	0
Pyrexia	89 (23%)	5 (1%)	0	0	51 (13%)	1 (<1%)	0	0
Rash	83 (21%)	2 (1%)	0	0	27 (7%)	0	0	0
Asthenia	82 (21%)	25 (6%)	1 (<1%)	0	68 (17%)	12 (3%)	1 (<1%)	0
Constipation	69 (18%)	2 (1%)	0	0	83 (21%)	3 (1%)	0	0
Back pain	59 (15%)	14 (4%)	0	0	77 (19%)	17 (4%)	3 (1%)	0
Peripheral oedema	51 (13%)	0	0	0	37 (9%)	2 (1%)	0	0
Dyspnoea	50 (13%)	15 (4%)	3 (1%)	0	36 (9%)	5 (1%)	2 (1%)	0
Arthralgia	44 (11%)	6 (2%)	0	0	58 (15%)	7 (2%)	0	0
Headache	39 (10%)	2 (1%)	0	0	32 (8%)	2 (1%)	0	0
Dehydration	38 (10%)	21 (5%)	0	0	24 (6%)	8 (2%)	1 (<1%)	1 (<1%)
Pain	37 (9%)	8 (2%)	2 (1%)	0	49 (12%)	15 (4%)	2 (1%)	0
Cough	36 (9%)	2 (1%)	0	0	27 (7%)	0	0	0
Abdominal pain	36 (9%)	6 (2%)	0	0	26 (7%)	7 (2%)	0	0
Increased aspartate aminotransferase	36 (9%)	12 (3%)	2 (1%)	0	21 (5%)	6 (2%)	1 (<1%)	0
Bone pain	34 (9%)	9 (2%)	0	0	55 (14%)	13 (3%)	0	0
Decreased haemoglobin	34 (9%)	10 (3%)	3 (1%)	0	23 (6%)	8 (2%)	1 (<1%)	0
Musculoskeletal pain	32 (8%)	1 (<1%)	0	0	47 (12%)	9 (2%)	0	0
Pain in legs or arms	32 (8%)	4 (1%)	0	0	43 (11%)	9 (2%)	0	0
Insomnia	31 (8%)	0	0	0	34 (9%)	3 (1%)	0	0
Urinary tract infection	31 (8%)	12 (3%)	1 (<1%)	0	27 (7%)	4 (1%)	0	0
Increased alanine aminotransferase	29 (7%)	9 (2%)	0	0	9 (2%)	3 (1%)	0	0
Colitis	27 (7%)	15 (4%)	3 (1%)	0	3 (1%)	0	0	0
Pneumonia	24 (6%)	11 (3%)	1 (<1%)	4 (1%)	9 (2%)	2 (1%)	1 (<1%)	0
Dizziness	25 (6%)	1 (<1%)	0	0	18 (5%)	1 (<1%)	0	0
Hypokalaemia	22 (6%)	10 (3%)	1 (<1%)	0	10 (3%)	4 (1%)	0	0
Hypertension	20 (5%)	1 (<1%)	0	0	13 (3%)	1 (<1%)	0	0
General deterioration of physical health	19 (5%)	12 (3%)	2 (1%)	3 (1%)	15 (4%)	7 (2%)	1 (<1%)	2 (1%)
Chest pain	15 (4%)	1 (<1%)	0	0	18 (5%)	2 (1%)	0	0
Immune-related adverse events								
Diarrhoea	155 (39%)	58 (15%)	1 (<1%)	0	55 (14%)	3 (1%)	0	0
Pruritus	80 (20%)	1 (<1%)	0	0	15 (4%)	0	0	0
Rash	68 (17%)	2 (1%)	0	0	16 (4%)	0	0	0
Colitis	27 (7%)	15 (4%)	3 (1%)	0	3 (1%)	0	0	0
Increased aspartate aminotransferase	22 (6%)	8 (2%)	1 (<1%)	0	13 (3%)	3 (1%)	1 (<1%)	0
Increased alanine aminotransferase	20 (5%)	6 (2%)	0	0	8 (2%)	3 (1%)	0	0
Hypothyroidism	9 (2%)	2 (1%)	0	0	1 (<1%)	0	0	0
Adrenal insufficiency	6 (2%)	2 (1%)	0	0	2 (1%)	1 (<1%)	0	0
Hepatitis	3 (1%)	1 (<1%)	0	0	0	0	0	0
Increased lipase	2 (1%)	0	1 (<1%)	0	2 (1%)	2 (1%)	0	0
Hepatotoxicity	2 (1%)	2 (1%)	0	0	0	0	0	0
Motor dysfunction	1 (<1%)	1 (<1%)	0	0	0	0	0	0

Data are number of patients (%); patients could have had more than one event.

[*] Only events that occurred at a frequency of 5% or higher (as rounded to the nearest 1%) in either group are shown.

Ipilimumab e radioterapia extracranica

TOSSICITA' DI GRADO 3-4 ALTA MA IN LINEA CON LAVORI DI SOLA SRS

NEED FURTHER REPORTS!!!

TABLE 2. Summary of Selected Studies of Patients Who Received Treatment With Extracranial Radiotherapy and Ipilimumab

Institution (Reference)	No. of Patients Receiving Combination RT and CTLA-4 Inhibition	Median Follow-Up, mo	Ipilimumab	RT Dose	Toxicity Grade ≥ 3	Outcomes
Memorial Sloan-Kettering (Barker 2013[66])	29[a]	11	3 mg/kg or 10 mg/kg every 3 wk up to 4 doses	Median, 30 Gy	irAEs: 10 mg/kg, 43%; 3 mg/kg, 20%	Induction ipilimumab: Median OS, 9 mo; maintenance ipilimumab: median OS, 39 mo
Duke University (Qin 2015[67])	44	23	3 mg/kg every 3 wk up to 4 doses	Ablative: median, 16 Gy; conventional, median, 35 Gy	Not increased with combination	Median OS, 18 mo; OS at 1 y, 64%; ablative: median OS, 20 mo; OS at 1 y, 80%
Multi-institutional phase 1/2 (Slovin 2013[68])	41	16	3 mg/kg or 10 mg/kg every 3 wk up to 4 doses	8 Gy	irAEs: 3 mg/kg, 43% (3/7); 10 mg/kg, 18% (6/34)	Median OS, 17.4 mo
Multi-institutional phase 3 (Kwon 2014[69])	399 (of 799 randomized)	10	10 mg/kg every 3 wk up to 4 doses	8 Gy (up to 5 metastases)	–	Median OS, 11.2 mo; OS at 1 y, 46.8 %; PFS at 6 mo, 30.7%
University of Pennsylvania (Twyman-Saint Victor 2015[70])	22	21	3 mg/kg every 3 wk up to 4 doses	Lung/bone, 16-24 Gy (8 Gy × 2-3); liver/SQ, 12-18 Gy (6 Gy × 2-3)	18 at 24 Gy: 2 grade 3, 0 grade 4	Median PFS, 3.8 mo; median OS, 10.7 mo
New York University[71]	53	NR	NR	NR	NR	NR
Stanford University (Hiniker 2015[72])	20	NR	3 mg/kg every 3 wk up to 4 doses	NR	NR	NR

Abbreviations: CTLA-4, cytotoxic T-lymphocyte-associated protein 4; Gy, gray; irAEs, immune-related adverse events; NR, not reported; OS, overall survival; PFS, progression-free survival; RT, radiotherapy; SQ, subcutaneous.
[a] In total, 166 patients received RT before, during, or after ipilimumab administration.

Salama AK , Cancer 2016

Conclusioni

- Meccanismi della tossicità non sono ancora completamente noti
- Dati disomogenei e casistiche piccole
- Attenzione alla valutazione della tossicità tardiva

British Journal of Cancer (2011) 105, 628–639
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www.bjcancer.com

Guideline

Guidelines for preclinical and early phase clinical assessment of novel radiosensitisers

KJ Harrington[*,1], LJ Billingham[2], TB Brunner[3], NG Burnet[4], CS Chan[5], P Hoskin[6], RI Mackay[7], TS Maughan[8], J Macdougall[9], WG McKenna[3], CM Nutting[1], A Oliver[9], R Plummer[10], IJ Stratford[10] and T Illidge[11] NCRI Clinical and Translational Radiotherapy Research Working Group

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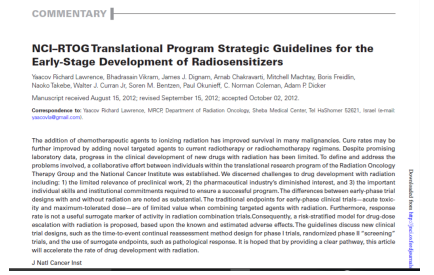
Translational



COMMENTARY

NCI–RTOG Translational Program Strategic Guidelines for the Early-Stage Development of Radiosensitizers

Yaacov Richard Lawrence, Bhadrasain Vikram, James J. Dignam, Arnab Chakravarti, Mitchell Machtay, Boris Freidlin, Naoko Takebe, Walter J. Curran Jr, Soren M. Bentzen, Paul Okunieff, C. Norman Coleman, Adam P Dicker

Manuscript received August 15, 2012; revised September 15, 2012; accepted October 02, 2012.

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The addition of chemotherapeutic agents to ionizing radiation has improved survival in many malignancies. Cure rates may be further improved by adding novel targeted agents to current radiotherapy or radiochemotherapy regimens. Despite promising laboratory data, progress in the clinical development of new drugs with radiation has been limited. To define and address the problems involved, a collaborative effort between individuals within the translational research program of the Radiation Oncology Therapy Group and the National Cancer Institute was established. We discerned challenges to drug development with radiation including: 1) the limited relevance of preclinical work, 2) the pharmaceutical industry's diminished interest, and 3) the important individual skills and institutional commitments required to ensure a successful program. The differences between early-phase trial designs with and without radiation are noted as substantial. The traditional endpoints for early-phase clinical trials—acute toxicity and maximum-tolerated dose—are of limited value when combining targeted agents with radiation. Furthermore, response rate is not a useful surrogate marker of activity in radiation combination trials. Consequently, a risk-stratified model for drug-dose escalation with radiation is proposed, based upon the known and estimated adverse effects. The guidelines discuss new clinical trial designs, such as the time-to-event continual reassessment method design for phase I trials, randomized phase II "screening" trials, and the use of surrogate endpoints, such as pathological response. It is hoped that by providing a clear pathway, this article will accelerate the rate of drug development with radiation.

J Natl Cancer Inst

CONCLUSIONI

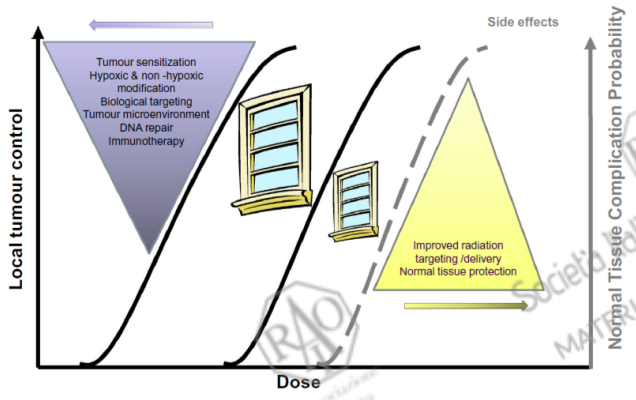
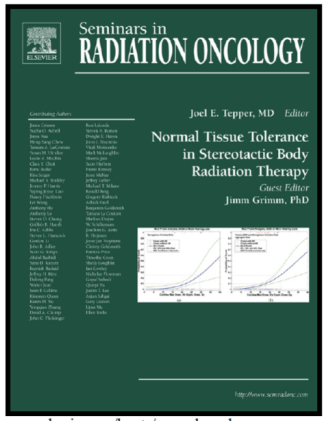


Fig. 1. Strategies to 'open' the therapeutic window by widening the gap between 'local tumour control' and 'normal tissue complication probability' dose–response curves. The tumour control curve can be shifted to the left by specifically rendering tumours more sensitive to radiation. The normal tissue complication curve may be shifted to the right by improved radiotherapy targeting and delivery, or the use of normal tissue 'radioprotectors'.

" Firstly, one important caveat from clinical experience is that significant late effects may not occur for years or decades as seen with standard fractionation so the impact of large doses per fraction may take a while longer to elucidate." Makinde AY



«Alea iacta est»