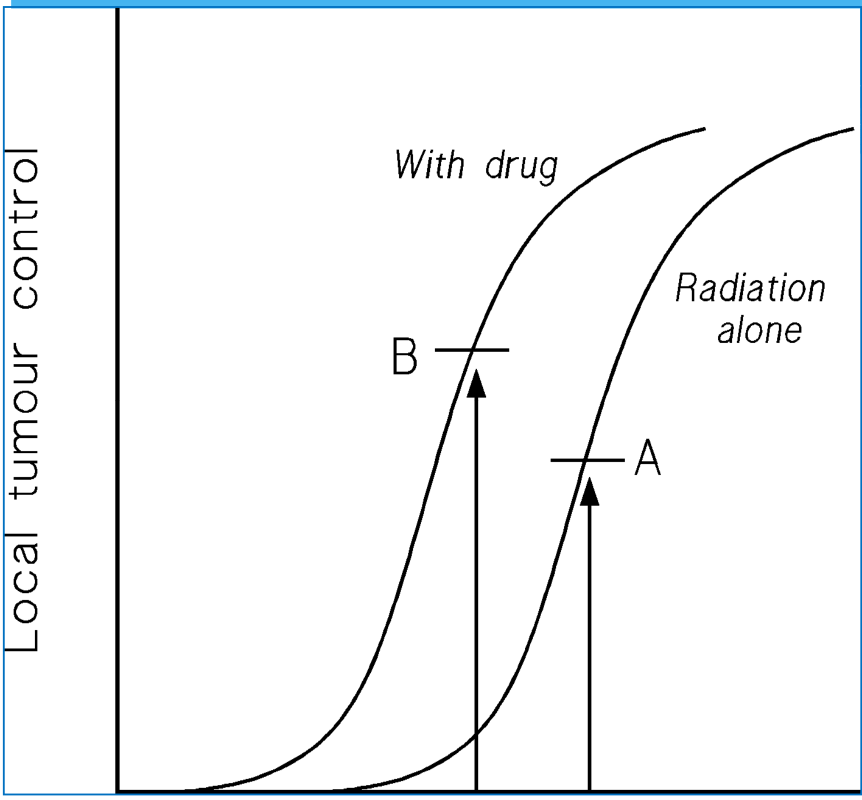
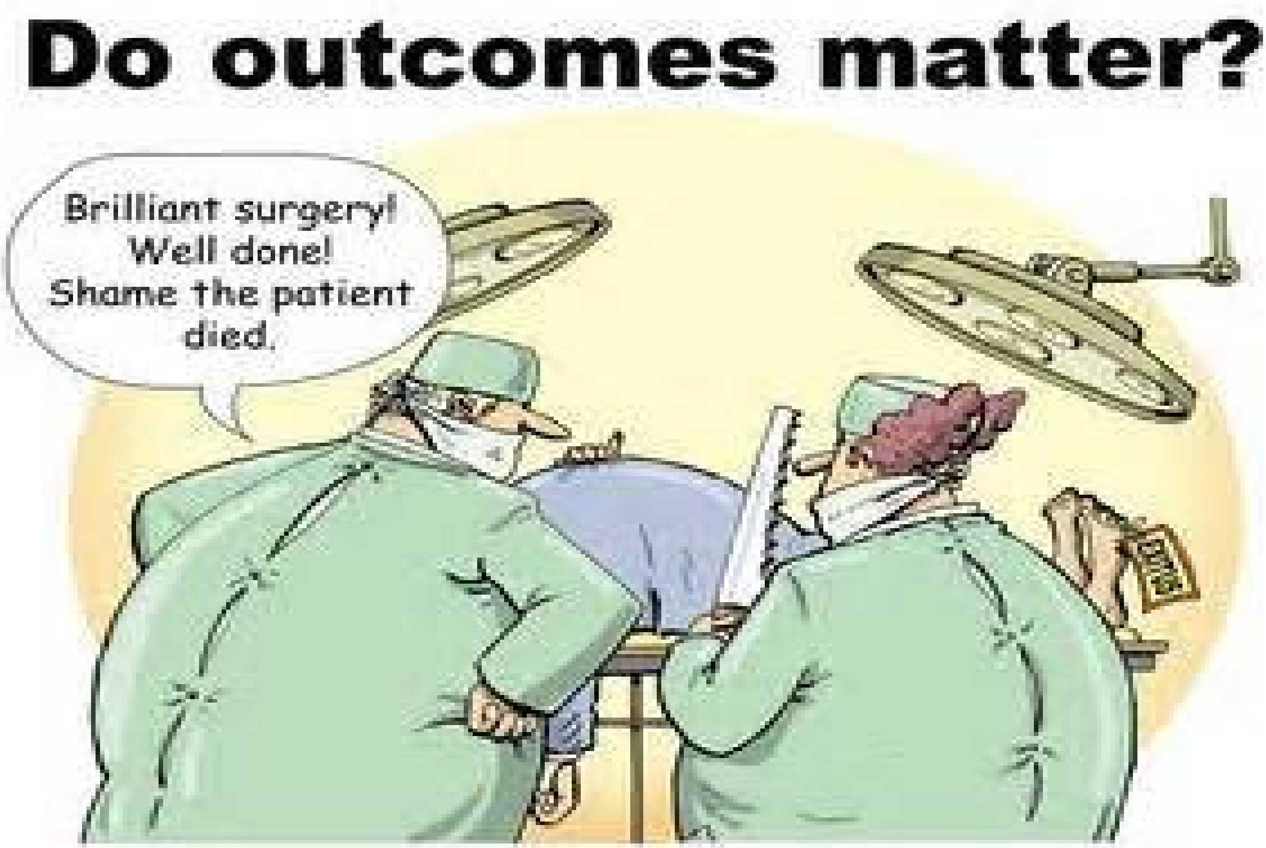
Can targeted therapy help overcome radioresistance?

E. Mazzeo
Azienda Ospedaliero-Universitaria di Modena

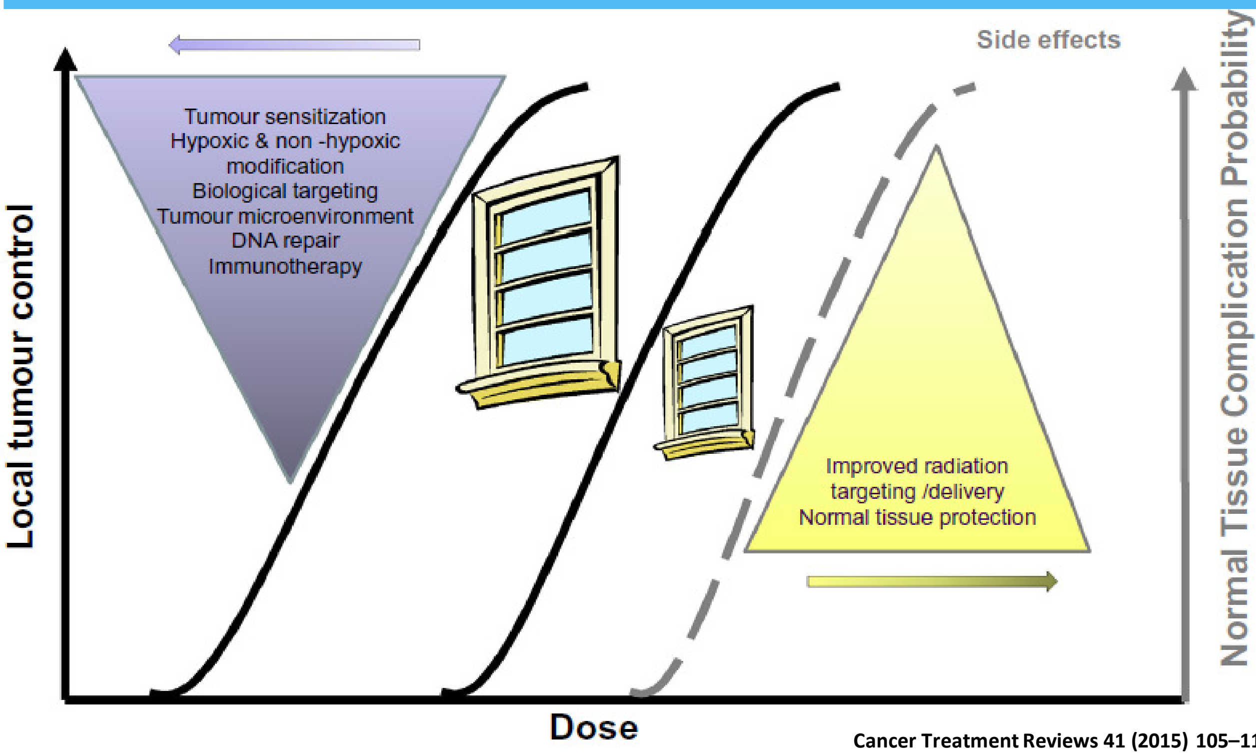
Therapeutic Gain



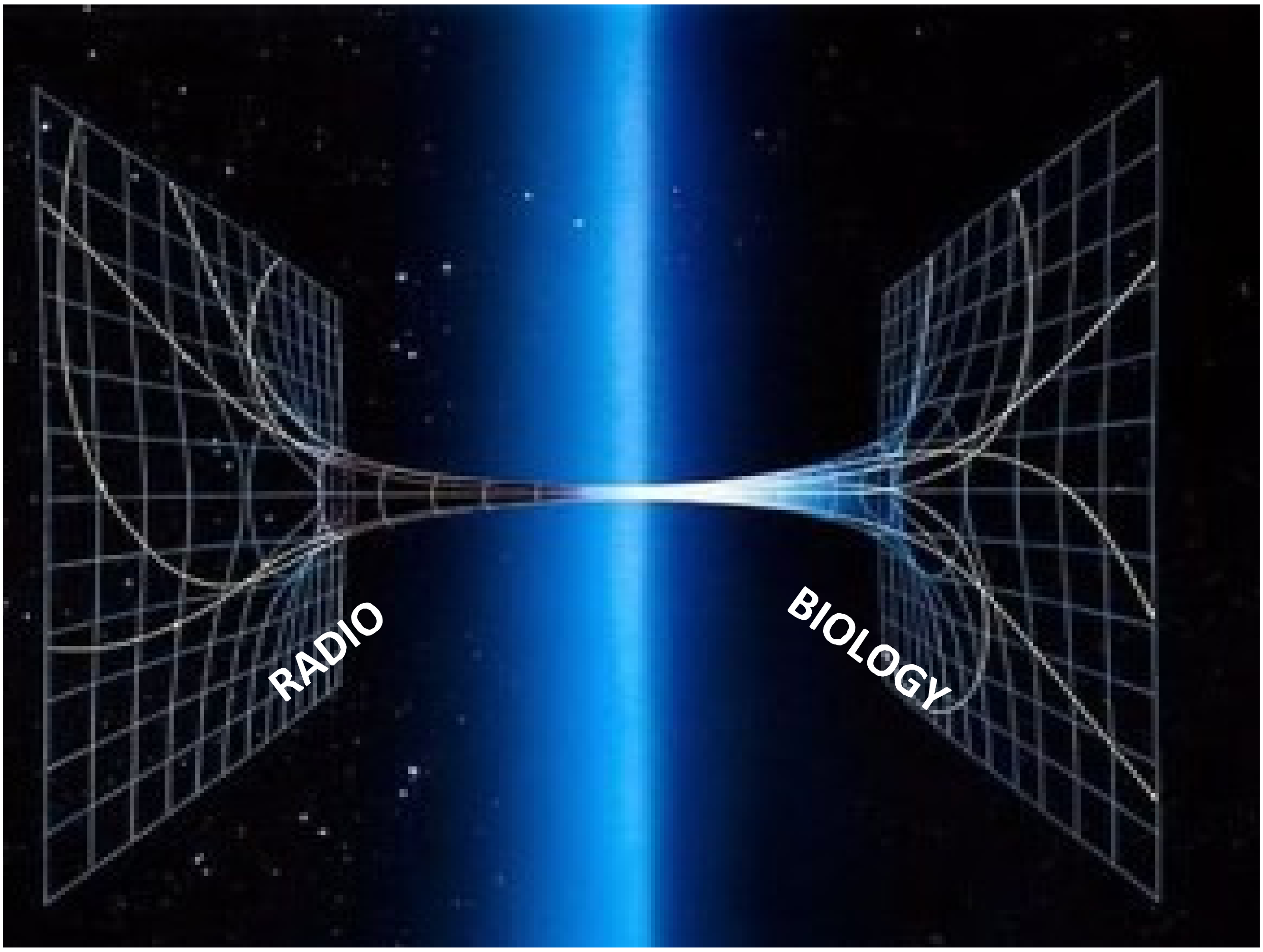
Basic clinical radiobiology, IV edition



How to improve therapeutic gain?



Cancer Treatment Reviews 41 (2015) 105–113



How to improve therapeutic gain?

- **Total dose and fractionation**
- **New technologies:** improvements in instrumentation, machine software and diagnostic techniques enabling more accurate dose delivery to the tumour while minimizing dose to surrounding healthy tissue
- **Protons and other ions**

RADIO

- **Biological response modifiers for normal tissues**
- **Chemotherapy**
- **Targeted therapy**

BIOLOGY

Chemotherapy

- **Concomitant chemotherapy is largely used** and probably represents the most important change in our clinical practice during the last decades
- Only in a relatively small proportion of patients is chemotherapy **sufficiently effective to destroy subclinical metastatic deposits**
- **Normal tissue toxicity is frequently increased** after combined radiochemotherapy, which may limit doses of drugs or radiation

Disease site	References
Glioblastoma	Stupp, 2005
Head & Neck SCC	Budach, 2006; Pignon, 2000; Forastière, 2003; Cooper, 2004; Bernier 2004
Non-small cell lung cancer	Rowell and O'Rourke, 2004
Small-cell lung cancer	Pignon, 1992
Cancer of uterine cervix	Green, 2005; Green, 2001; NACCCMA, 2004
Oesophageal carcinoma	Wong, 2006
Rectal carcinoma	Bosset, 2005; Wolmark, 2000
Anal carcinoma	Bartelink, 1997

Basic clinical radiobiology, IV edition

Chemotherapy

Currently available chemotherapeutic drugs are far from being perfect for combining with Radiotherapy

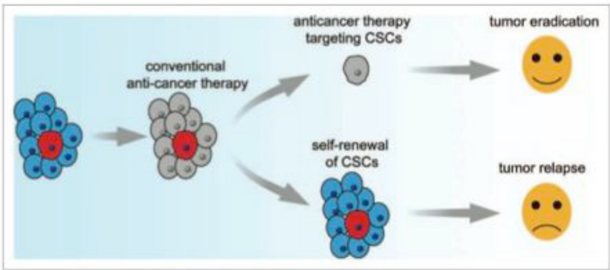
Radioresistance

Capacity of the cells to recover and repair sublethal damage between irradiation fractions

Repopulation capacity between fractions

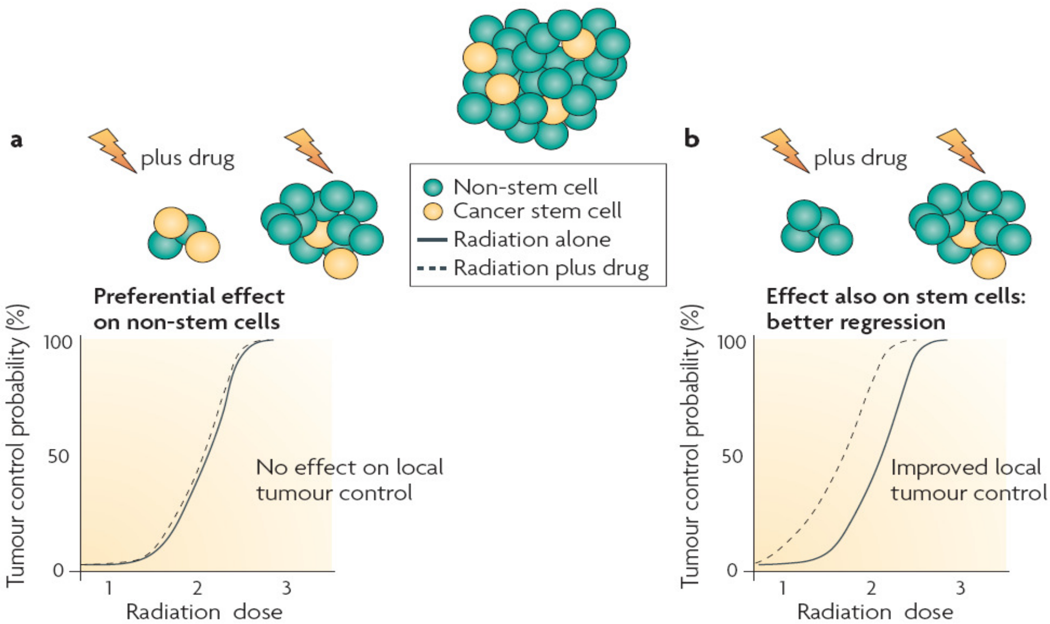
Tumor hypoxia

Microenvironmental factors



Clarke et al., *Cancer Res* 66: 9339-9344, 2006

CSCs (cancer stem cells) & radioresistance

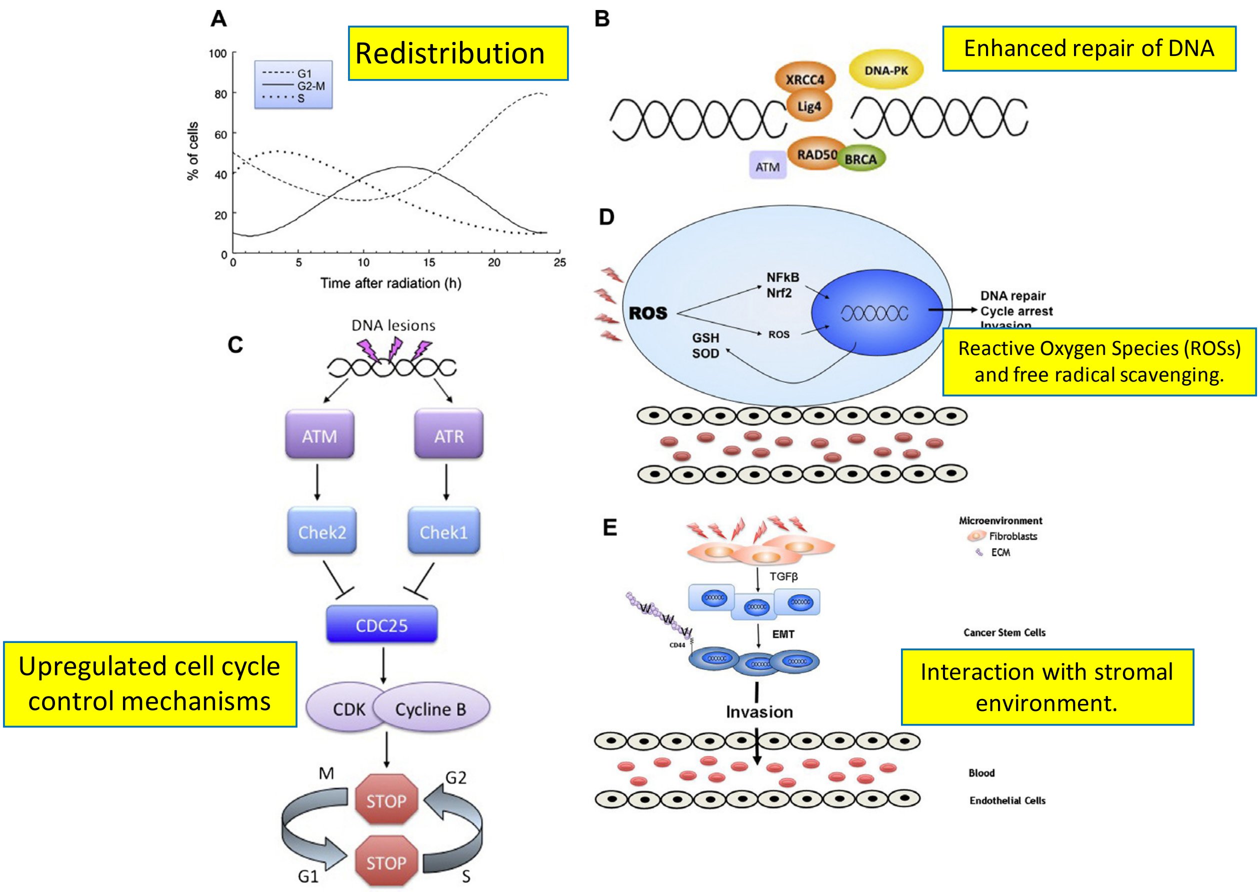


Baumann et al., *Nature Rev Cancer* 545-554, 2008

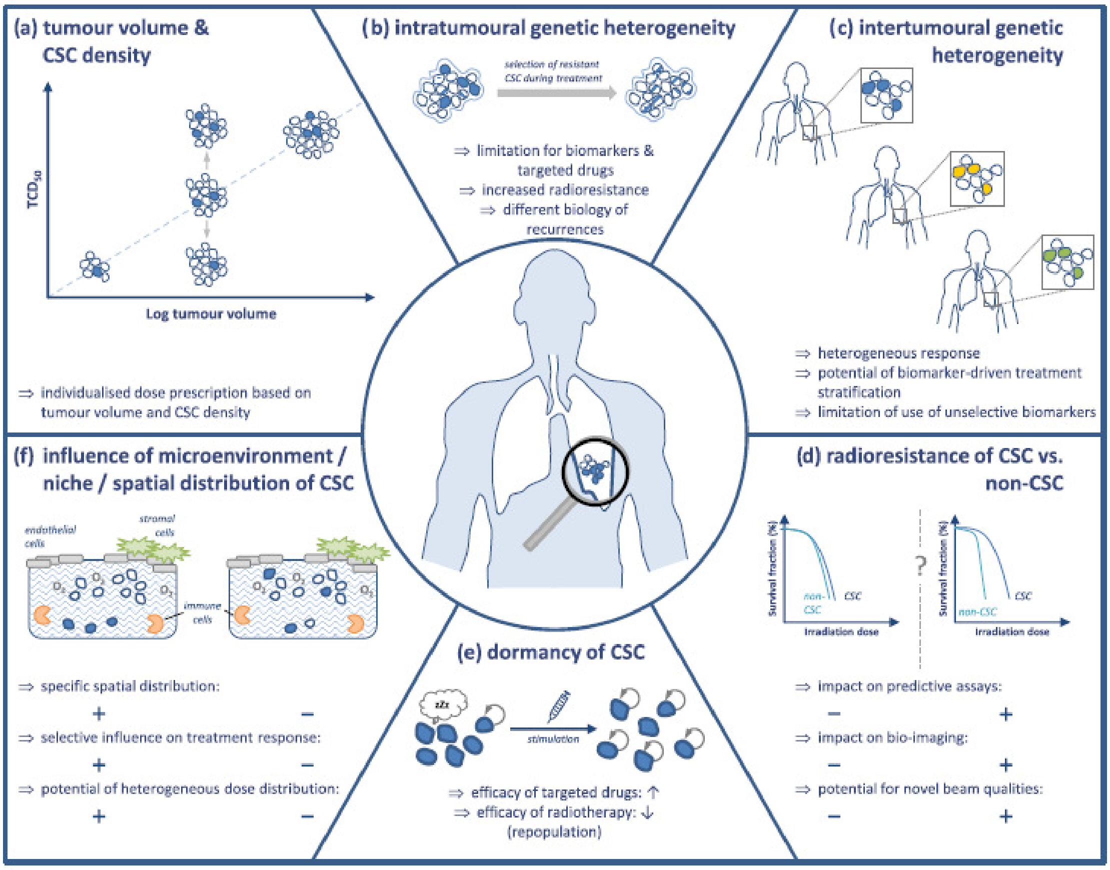
Cancer stem cells: CSCs

- CSCs are **small subpopulations of all tumor cells**
- Capacity to **selfrenew**
- Capacity to **generate the heterogenous lineages of cancer cells** that comprise the tumour
- Anticancer therapy can **cure** a **tumor only if all cancer stem cells are killed**
- CSCs may be **resistant subset of tumor cells,** while nontumorigenic cells constitute **bulk** of tumor cells
- **Radiotherapy is efficient to kill CSCs,** much more than CTx
- Only **combinations which enhance radiotherapy** killing of CSCs have better curative potential
- In the context of radiotherapy a CSC translates into a cell which has the capacity to cause a recurrence

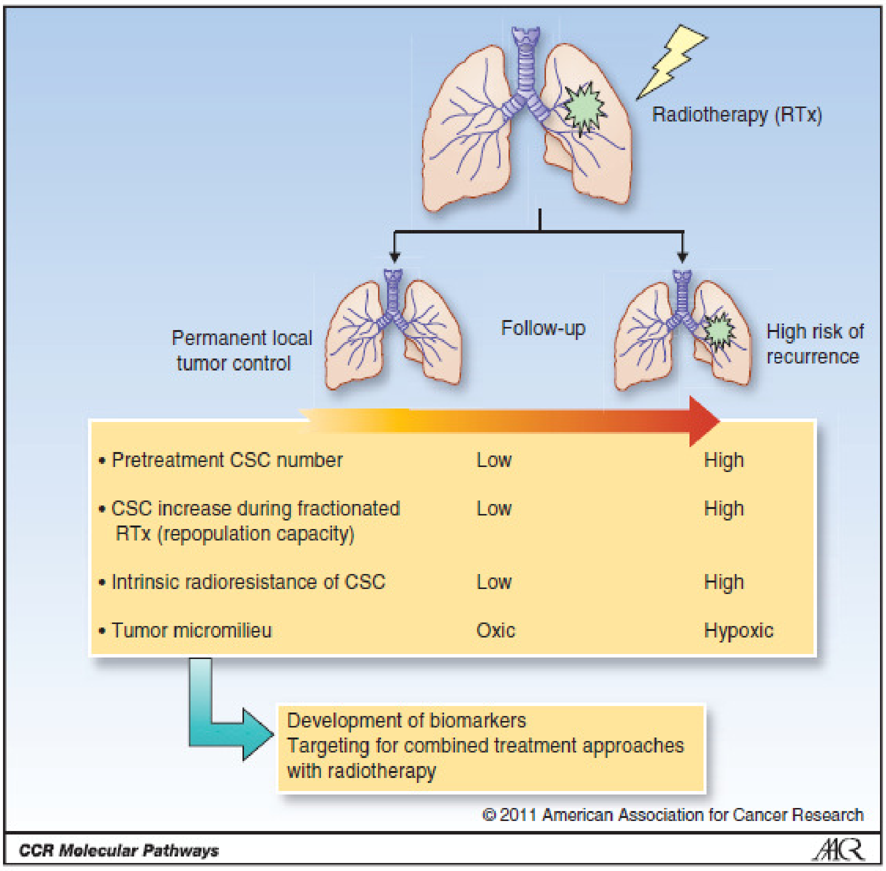
Clarke et al., *Cancer Res* 66: 9339-9344, 2006
Baumann et al., *Nature Rev Cancer* 545-554, 2008
Krause M. et al, Clin Cancer Res; 17(23) December 1, 2011



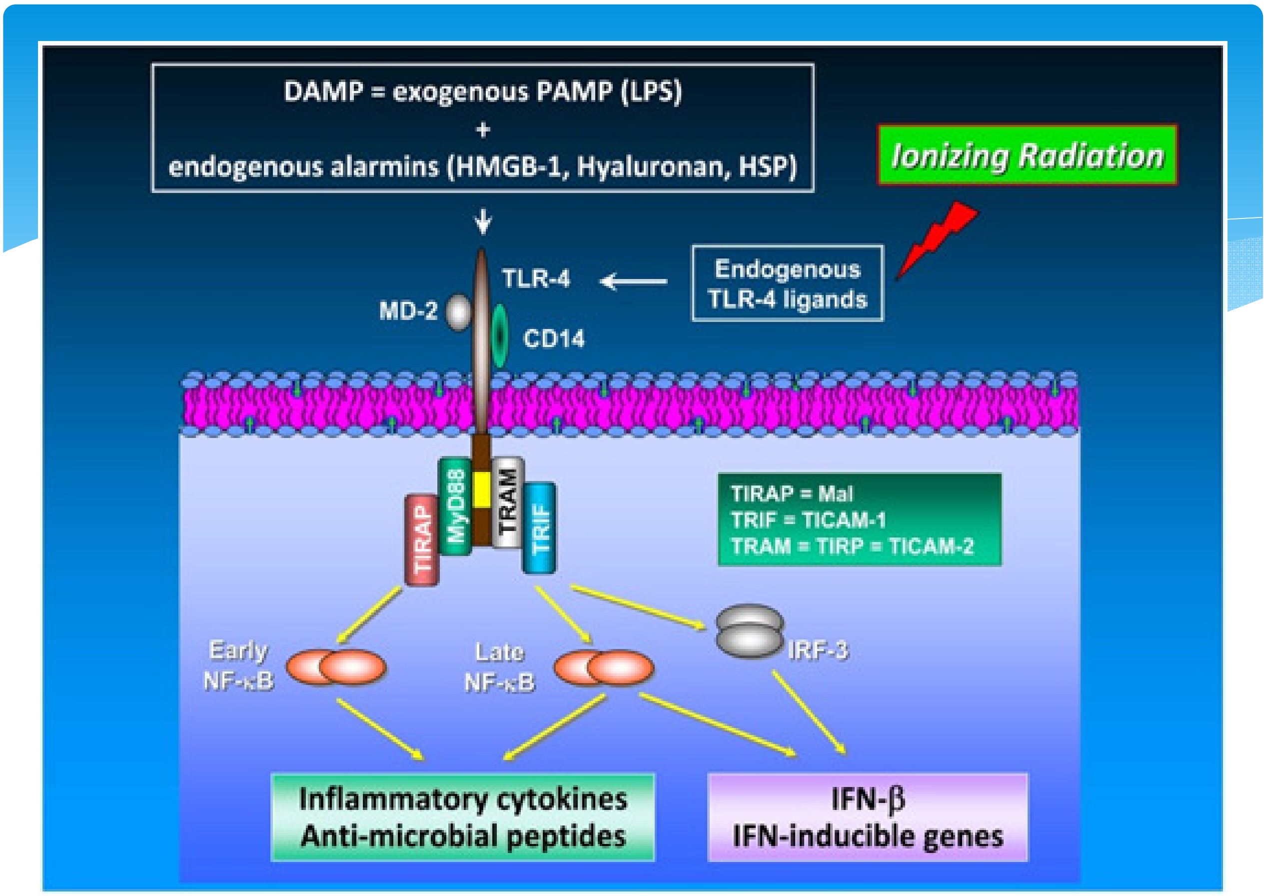
Moncharmont C. et al, Cancer Letters 322 (2012) 139–147



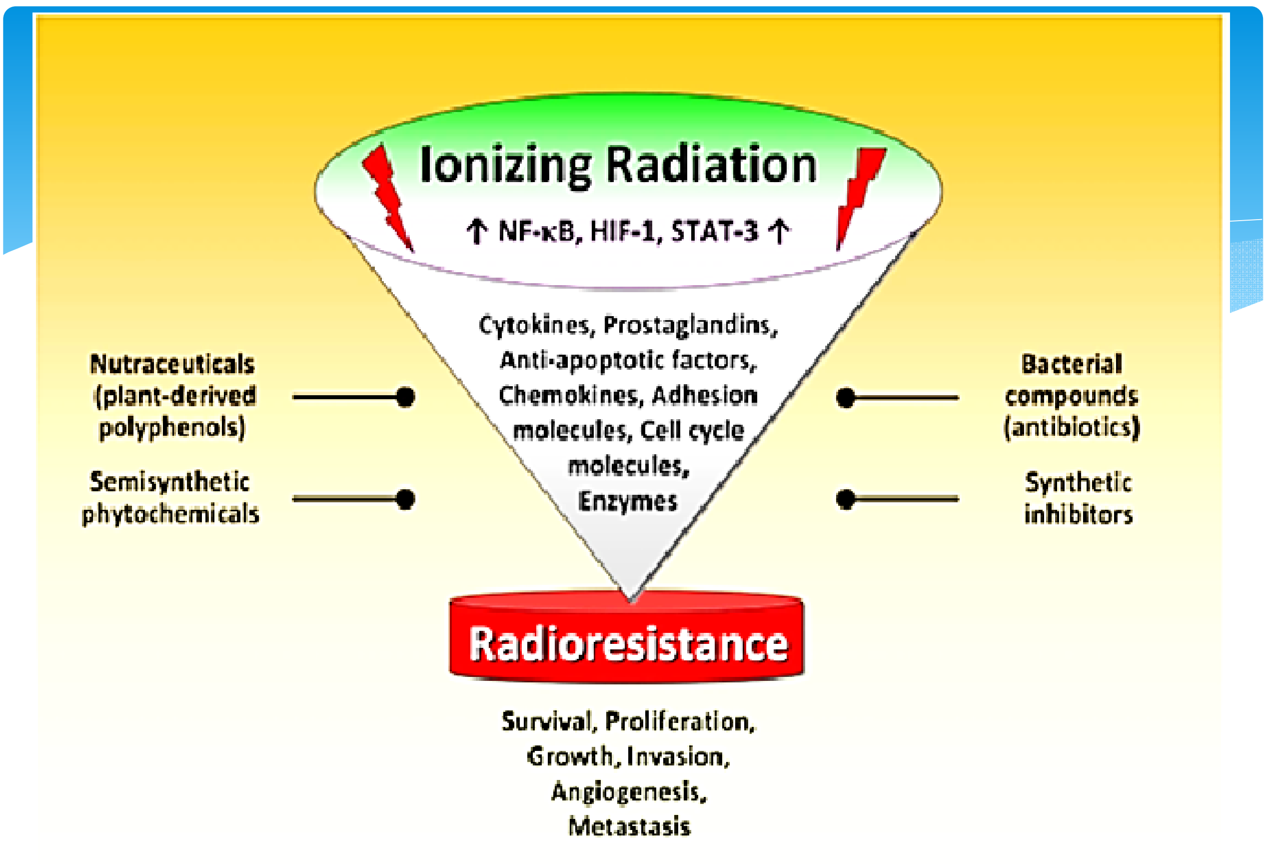
Krause M. et al, Clin Cancer Res; 17(23) December 1, 2011



Krause M. et al, Clin Cancer Res; 17(23) December 1, 2011



Gabriele Multhoff and Jürgen Radons, Frontiers in oncology - 2012



Gabriele Multhoff and Jürgen Radons, Frontiers in oncology - 2012

Need for new scenarios

More effective and less toxic substances are needed to further improve the results of systemic therapies combined with radiation

The best targeted therapy

Attractive targets for drugs to be used specifically within the context of radiotherapy:

- A "perfect" targeted drug for radiotherapy may have no impact on the survival of cancer cells when given without irradiation, but effectively decreases mechanisms of radiation resistance, thereby improving local tumour control.
- Would be(Over)expressed in a high proportion of tumours frequently treated by radiation
- Would be not expressed by normal tissues surrounding the tumour
- Would be linked to poor locoregional tumour control after radiotherapy alone
- Would ideally be associated with known radiobiological mechanisms of tumour radioresistance

Krause M. et al., 2006

Literature

Contents lists available at ScienceDirect

Cancer Treatment Reviews

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

Anti-Tumour Treatment

Drug radiotherapy combinations: Review of previous failures and reasons for future optimism

Geoff S. Higgins [a,b,*], Sean M. O'Cathail [b], Ruth J. Muschel [a], W. Gillies McKenna [a,b]

[a] Cancer Research UK/MRC Oxford Institute for Radiation Oncology, Gray Laboratories, Department of Oncology, University of Oxford, Oxford, UK
[b] Oxford University Hospitals NHS Trust, Department of Oncology, Churchill Hospital, Oxford, UK

Cancer Treatment Reviews 41 (2015) 105–113

Clinical trials

combining radiosensitising drugs with radiotherapy

Hypoxic Modifiers	Nimorazole	Head and Neck (SCC)	Phase 3
	Tirapazamine	Head and Neck (SCC)	Phase 3
		Cervical	Phase 3
		SCLCa	Phase 2
		NSCLCa	Phase 1
	TH-302	-	Pending
	Metformin	NSCLCa	Phase 2
		CNS	Phase 1
VEGF inhibition	Bevacizumab	Glioblastoma Mulitforme	Phase 3
		Pancreas	Phase 2
		NSCLCa	Phase 2
		Prostate	Phase 2
		Rectum	Phase 2
		Head and Neck (SCC)	Phase 2
		Endometrial	Phase 2
		Sarcoma	Phase 2
		Cervical	Phase 2
		Oesophagus/GOJ	Phase 2
		Nasopharyngeal	Phase 2
	Cediranib	Rectum	Phase 1

Cancer Treatment Reviews 41 (2015) 105–113

Clinical trials

combining radiosensitising drugs with radiotherapy

PI3K inhibition	BKM120	Lung	Phase 1
		CNS	Phase 1
mTOR inhibition	Everolimus	Prostate	Phase 1
		Head and Neck (SCC)	Phase 1
		CNS	Phase 1/2
		Cervical	Phase 1
		NSCLCa	Phase 1
	Temsirolimus	NSCLCa	Phase 1
		CNS	Phase 2
		Prostate	Phase 1
	Rapamycin	Rectum	Phase 1/2
AKT inhibition	Nelfinavir	Pancreas	Phase 1
		Cervical	Phase 1
		NSCLCa	Phase 1/2
		Oligometastases	Phase 2
		Pancreas	Phase 2/3
		CNS	Phase 1

Cancer Treatment Reviews 41 (2015) 105–113

Clinical trials

combining radiosensitising drugs with radiotherapy

MEK inhibiton	AZD6244	NSCLCa	Phase 1
		Rectum	Phase 1
	Trametinib	Rectum	Phase 1
c-MET inhibition	Ficlatuzumab	Head and Neck (SCC)	Phase 1
PARP inhibition	Olaparib	Breast	Phase 1
		Head and Neck (SCC)	Phase 1
		Oesophagus	Phase 1
		NSCLCa	Phase 1
	Veliparib	Rectum	Phase 1
		Breast	Phase 1
	Iniparib	Brain mets	Phase 1
ATR inhibition	AZD6738	Any	Phase 1
CTLA-4 blockade	Ipilimumab	Prostate	Phase 3
		Melanoma	Phase 2
		NSCLCa	Phase 2
		Liver	Phase 2
		Lymphoma	Phase 2
		Brain metastases	Phase 2
		Head and Neck (SCC)	Phase 1
	Tremelimumab	Pancreas	Phase 1
PD-1 blockade	Pembrolizumab	Any	Phase 1
	AMP-224	Colorectal	Phase 1
PDL-1 blockade	MEDI4736	Pancreas	Phase 1

Cancer Treatment Reviews 41 (2015) 105–113

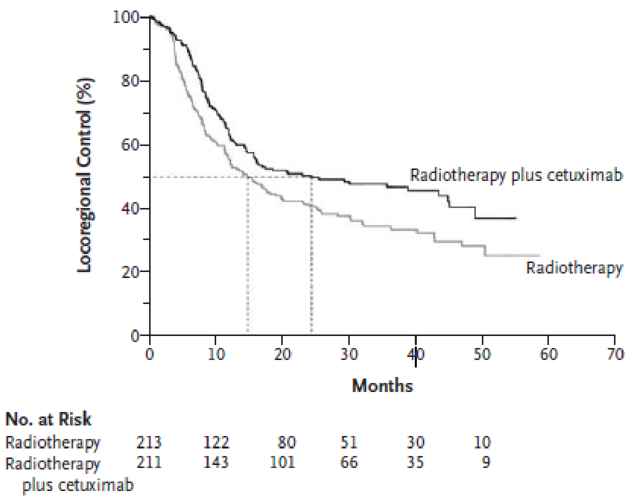
Clinical trials

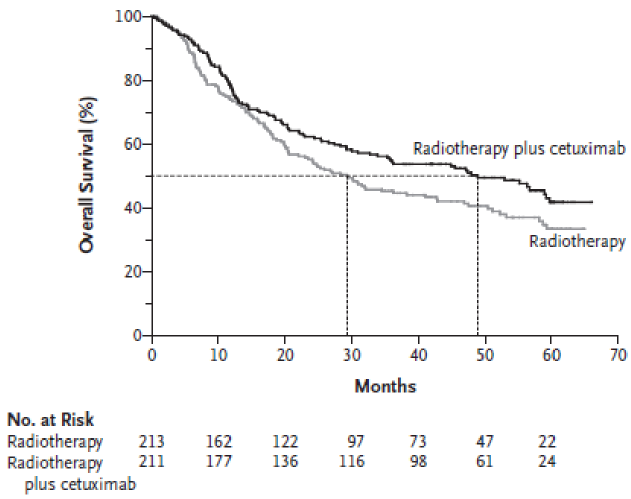
combining radiosensitising drugs with radiotherapy

EGFR inhibition	Cetuximab	Head and Neck (SCC)	Phase 3**
		NSCLCa	Phase 3
		Oesophagus	Phase 3
		Pancreatic	Phase 2
		Nasopharyngeal	Phase 2
		Colorectal	Phase 2
		Anal	Phase 2
		CNS	Phase 2
		Cervical	Phase 2
		Gastric	Phase 2
	Panitumumab	Head and Neck (SCC)	Phase 3
		Rectal	Phase 2
		Anus	Phase 2
		Cervical	Phase 2
		Oesophagus	Phase 2
		Pancreatic	Phase 2
	Gefitinib	NSCLCa	Phase 3
		CNS	Phase 1/2
		Oesophagus/GOJ	Phase 2
		Head and Neck (SCC)	Phase 2
		Gastric	Phase 1/2
		Pancreas	Phase 1/2
		Prostate	Phase 2
	Erlotinib	Pancreas	Phase 2/3
		Head and Neck (SCC)	Phase 3
		NSCLCa	Phase 3
		Oesophagus/GOJ	Phase 3
		Oesophagus	Phase 3
		NSCLCa Brain mets	Phase 3
		Rectum	Phase 1/2
		CNS	Phase 2
		Skin SCC	Phase 2
		Cervical	Phase 1

Cancer Treatment Reviews 41 (2015) 105–113

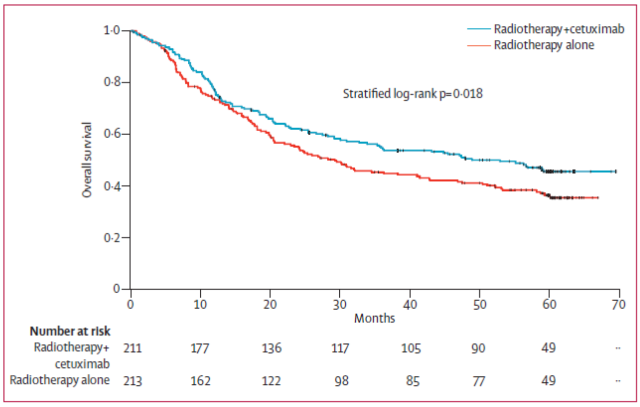
Cetuximab



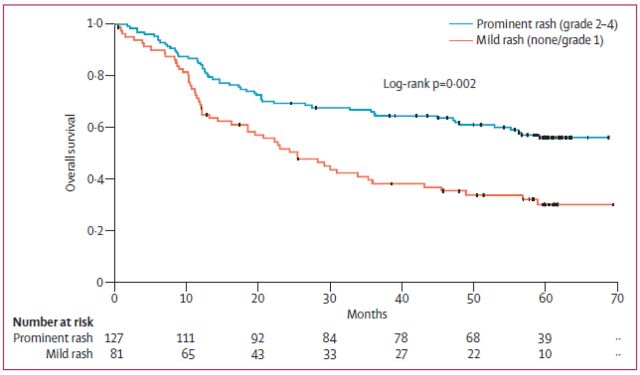


Bonner JA et al., N Engl J Med 2006;354:567-78.

Cetuximab



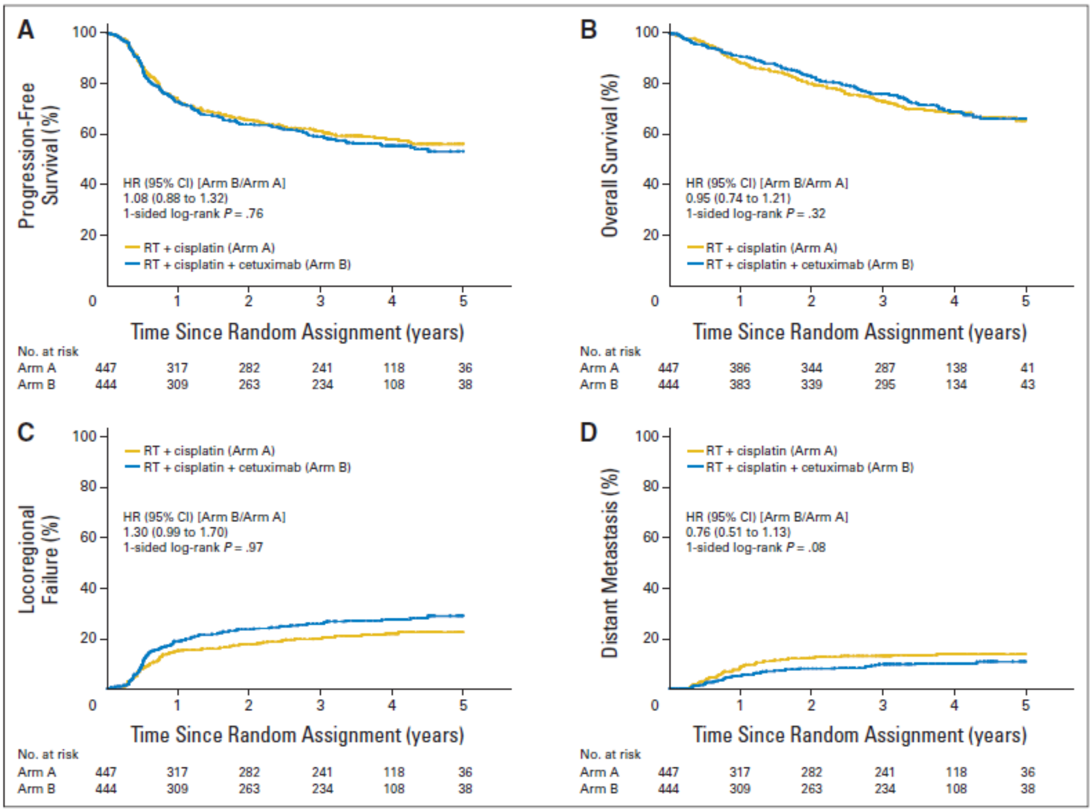
Overall survival by treatment: 5-year update (median follow-up 60 months)



Overall survival by severity of rash in cetuximab-treated patients

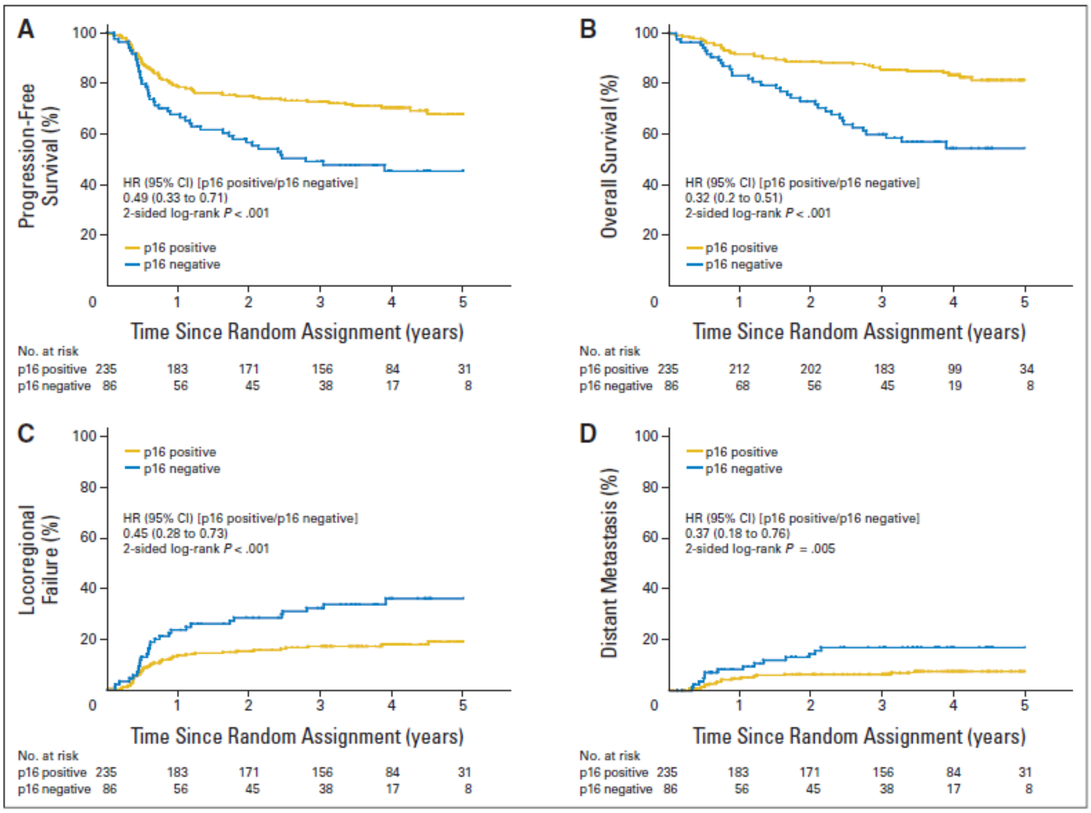
Bonner JA et al., Lancet Oncol 2010; 11:21-28

RTOG 0522



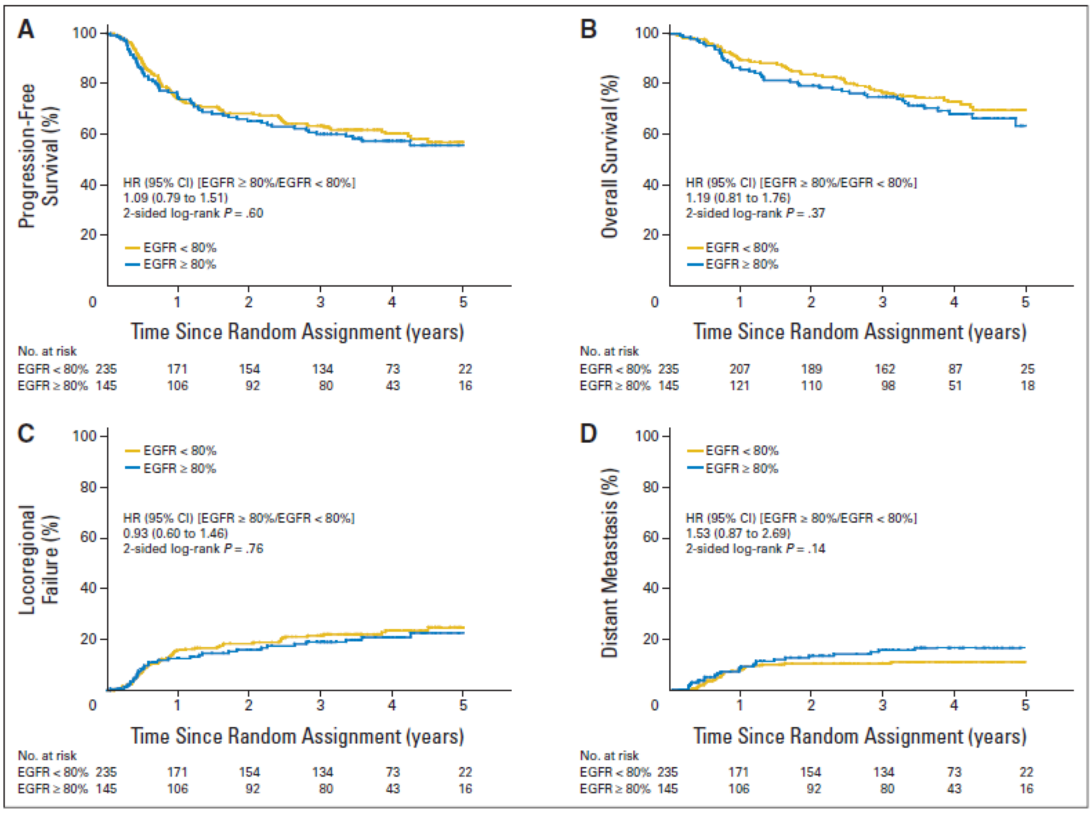
Ang KK. et al. JCO 2014

RTOG 0522



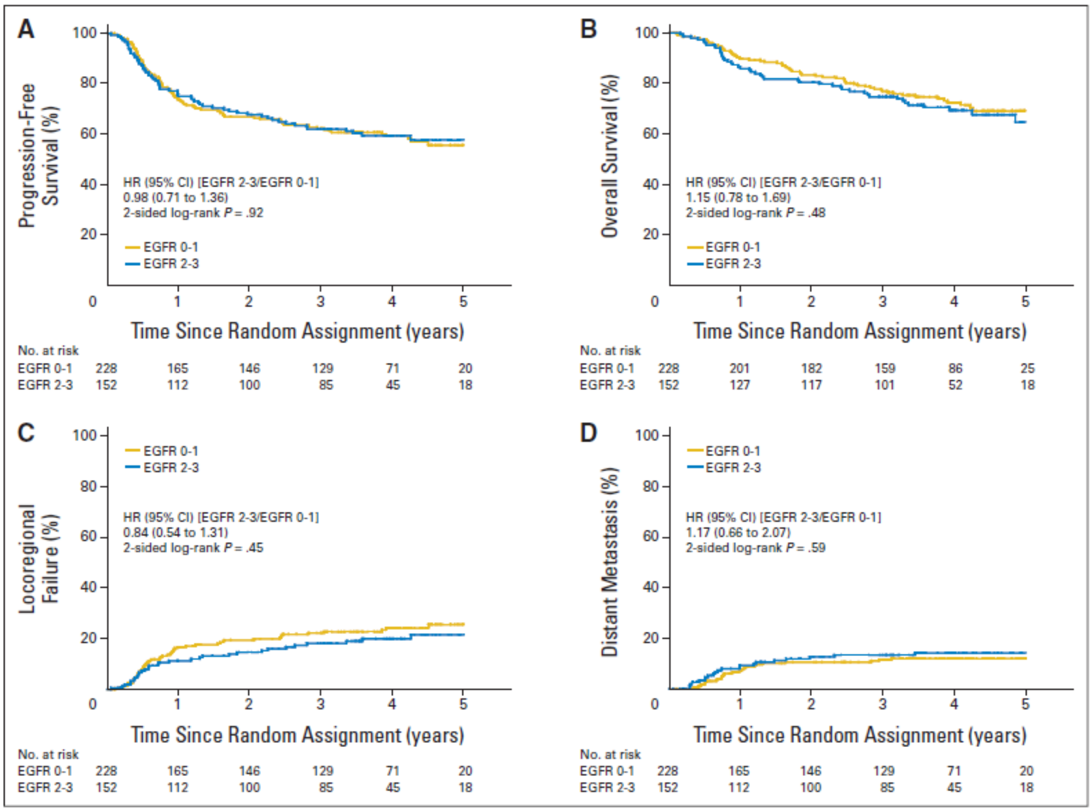
Ang KK. et al. JCO 2014

RTOG 0522



Ang KK. et al. JCO 2014

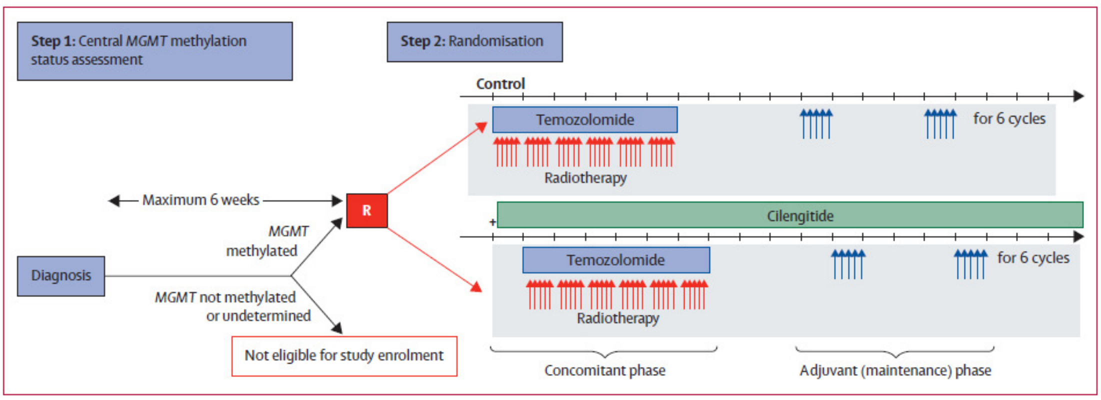
RTOG 0522



Ang KK. et al. JCO 2014

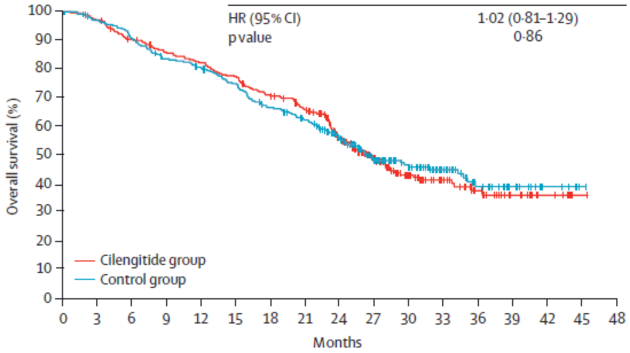
Integrin Inhibition

Cilengitide combined with standard treatment for patients with newly diagnosed glioblastoma with methylated *MGMT* promoter (CENTRIC EORTC 26071-22072 study): a multicentre, randomised, open-label, phase 3 trial

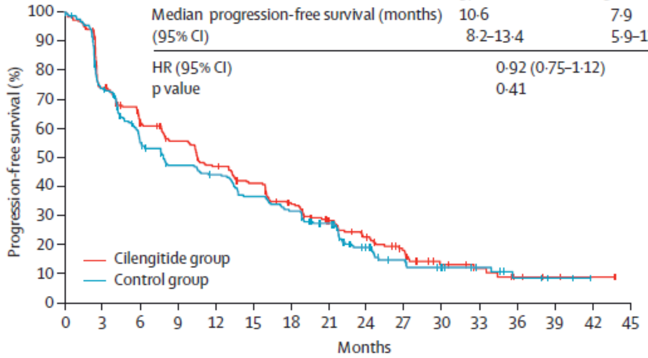


Lancet Oncol 2014; 15: 1100–08

	Cilengitide group (n=272)	Control group (n=273)
Number of events	144	138
Median overall survival (months)	26·32	26·32
(95% CI)	23·8–28·8	23·9–34·7
HR (95% CI)	1·02 (0·81–1·29)	
p value	0·86	



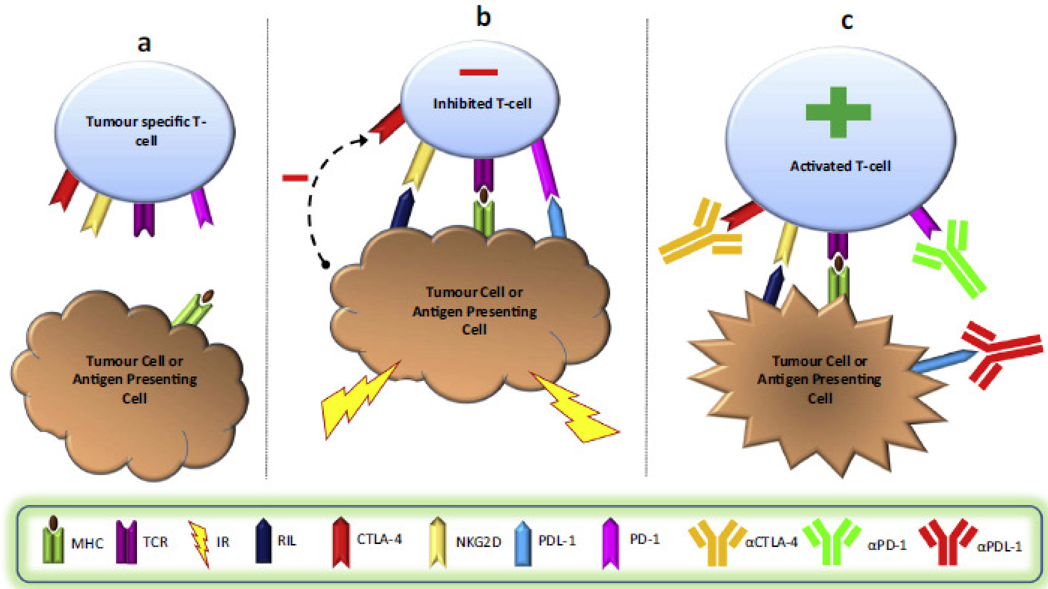
	Cilengitide group (n=272)	Control group (n=273)
Number of events	197	192
Median progression-free survival (months)	10·6	7·9
(95% CI)	8·2–13·4	5·9–12·5
HR (95% CI)	0·92 (0·75–1·12)	
p value	0·41	



Lancet Oncol 2014; 15: 1100–08

Interpretation The addition of cilengitide to temozolomide chemoradiotherapy did not improve outcomes; cilengitide will not be further developed as an anticancer drug. Nevertheless, integrins remain a potential treatment target for glioblastoma.

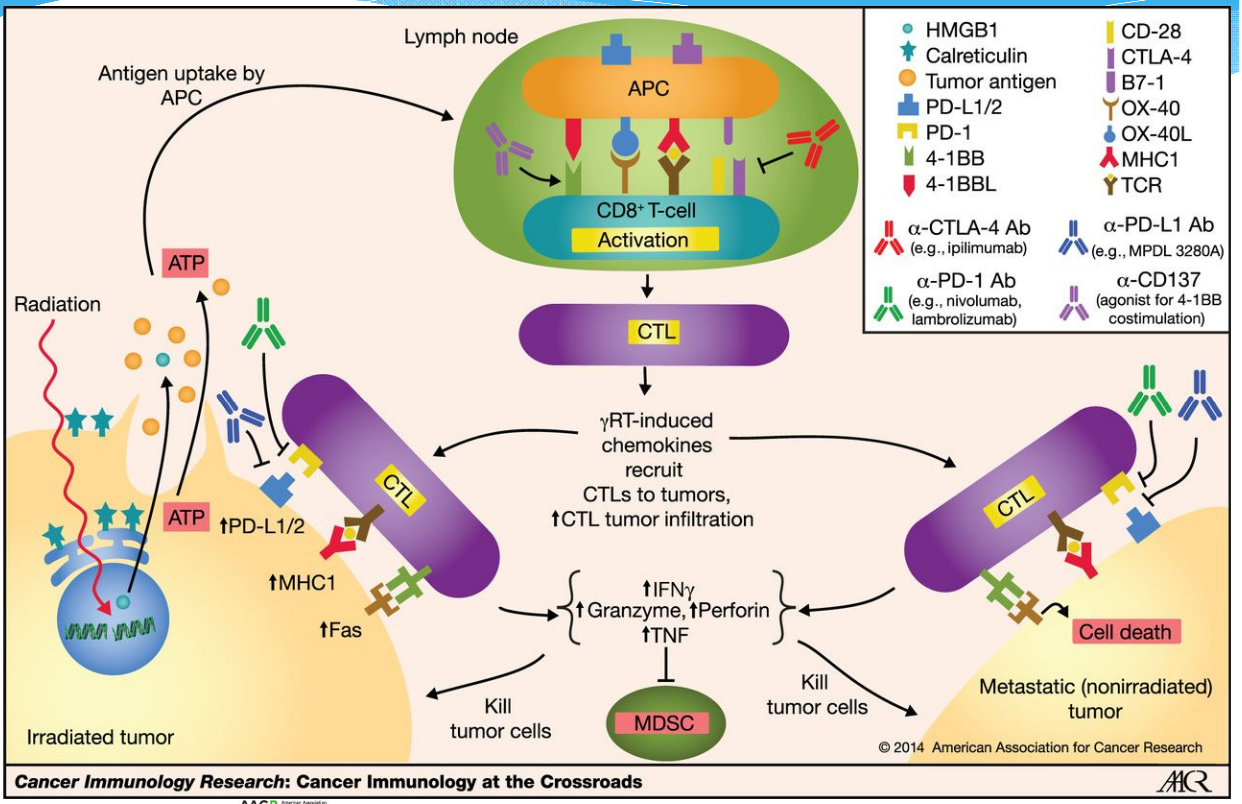
Combined radiotherapy and immunotherapy



Synergistic interaction between ionizing radiation and immune checkpoint blockade in inducing an immune response

The abscopal effect refers to the ability of radiation delivered to a local site to minimize or eradicate metastases at distant sites.

Schematic diagram outlining the antitumor activity and abscopal effect in combining checkpoint inhibitors with radiation-induced immune response



Cancer Immunology Research

Chad Tang et al. Cancer Immunol Res 2014;2:831-838

Laboratory

I step

<u>The initial evaluation is typically performed on **cells in culture**</u>

- Endpoints include: inhibition of cell proliferation, and colony formation after irradiation with and without drug.

- It should be kept in mind that effects in vitro do not necessarily translate into the same effect in vivo.

- Typical problems are that
  - higher drug concentrations can be achieved in vitro than in vivo,
  - the expression of target molecules may be different in vitro and in vivo,
  - cell culture conditions may significantly influence cell survival
  - many microenvironmental factors which are present in tumours (*e.g.* hypoxia, low pH, cell-cell interactions) are usually not reflected in cell culture

No practical alternative to initially screening molecular-targeted drugs combined with radiation using in vitro models

Krause *et al.*, 2006

Laboratory

II step

<u>Experiments on **tumour models in vivo**</u>

*It is important to discriminate **volume-dependent endpoints** such as **tumour regression** or **tumour growth delay** from **local tumour control**.*

* Cancer stem cells, constitute only a small proportion of all cancer cells, whereas the bulk of tumour cells are non-tumourigenic
* Changes in tumour volume after therapy are governed by the changes in the mass of tumour cells, that is primarily by the non-stem cells.

* **Tumour control** is dependent on the complete inactivation of the subpopulation of cancer stem cells

Basic clinical radiobiology, IV edition

Laboratory

Moreover

* The majority of current preclinical studies in cancer research use volume-dependent endpoints.

* Substantial risk that new treatments may be optimized for their effect on the bulk of non-stem cancer cells, with no improvement in the curative potential.

* Several studies have shown a dissociation of tumour volume dependent endpoints and tumour control

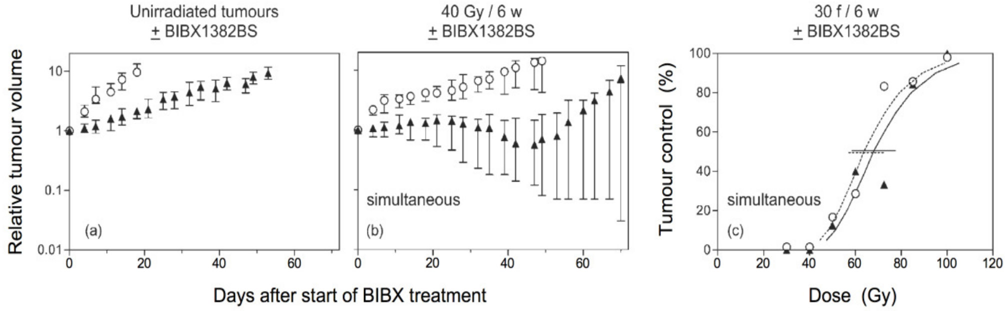
Basic clinical radiobiology, IV edition

Laboratory

Moreover

- Radiotherapy-specific preclinical research strategies need to be applied to test the efficacy of molecular targeted drugs combined with radiation and that cancer stem-cell specific endpoints such as ***local tumour control*** should be used whenever possible

- Today's laboratory mass screening of candidate anticancer drugs is usually done in the absence of radiotherapy. Thus, candidate compounds that are not effective alone, but could be promising for radiosensitising tumour cells, will not be selected.



Basic clinical radiobiology, IV edition

Conclusion

- Previous trials combining drugs with radiotherapy have failed to live up to expectations:
  - unacceptable side effects
  - lack of reliable predictive biomarkers
  - failure to select the most appropriate patients for clinical studies.
- Biomarker development should begin with pre-clinical testing of the compounds and be explored in the earliest clinical studies.

Conclusion

In the future, the combination of more accurate and complete

* molecular diagnostic methods
* development of a wider range of radiosensitising treatment options (drugs, antibodies or genetic manipulation, targeted to a range of pathways affecting the radiation response), will allow treatments tailored to the individual, maximizing tumour cell kill and minimizing normal tissue damage

An experience

OXFORD

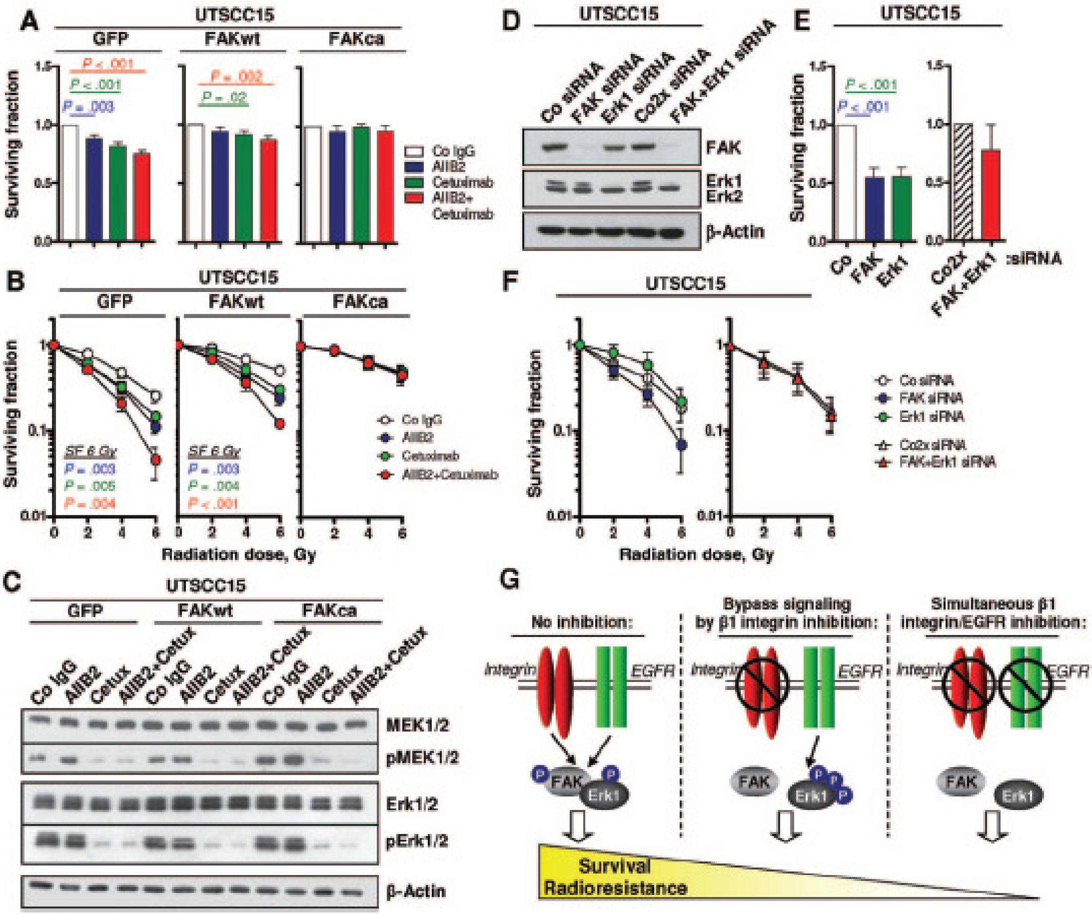
ARTICLE

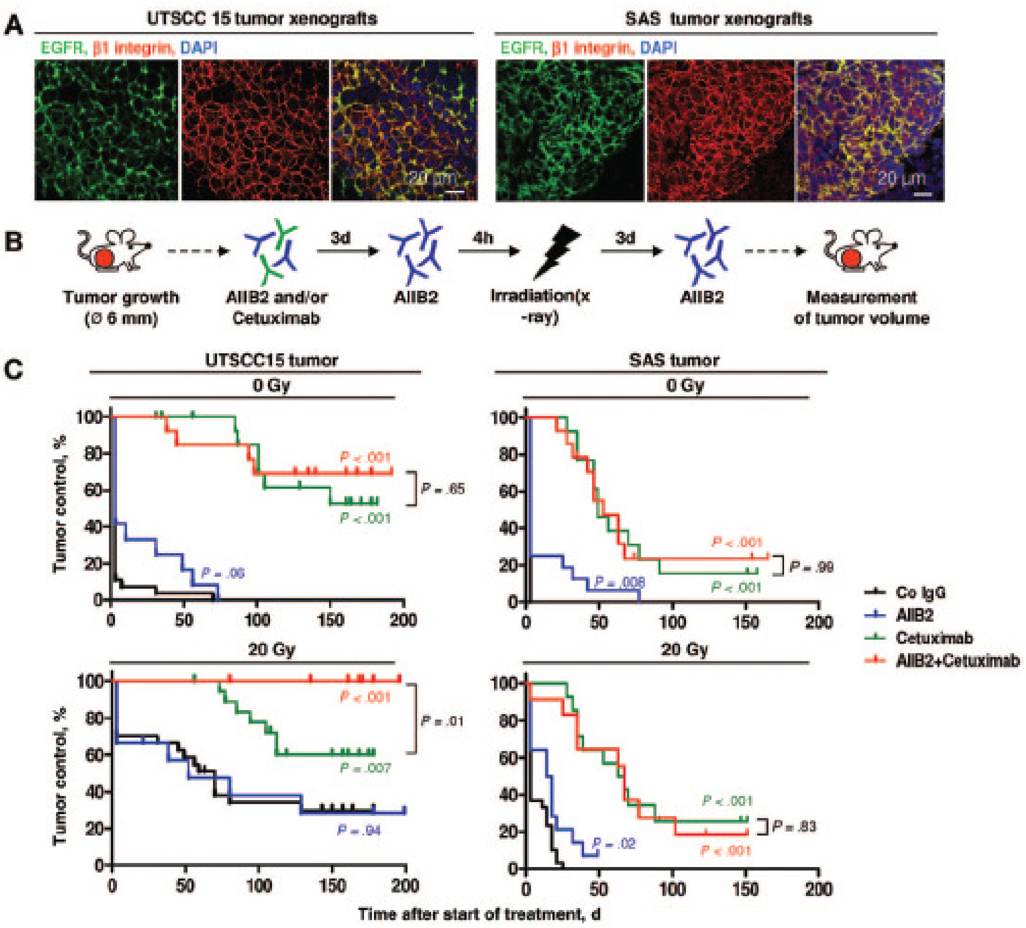
JNCI J Natl Cancer Inst, 2015, 1–11

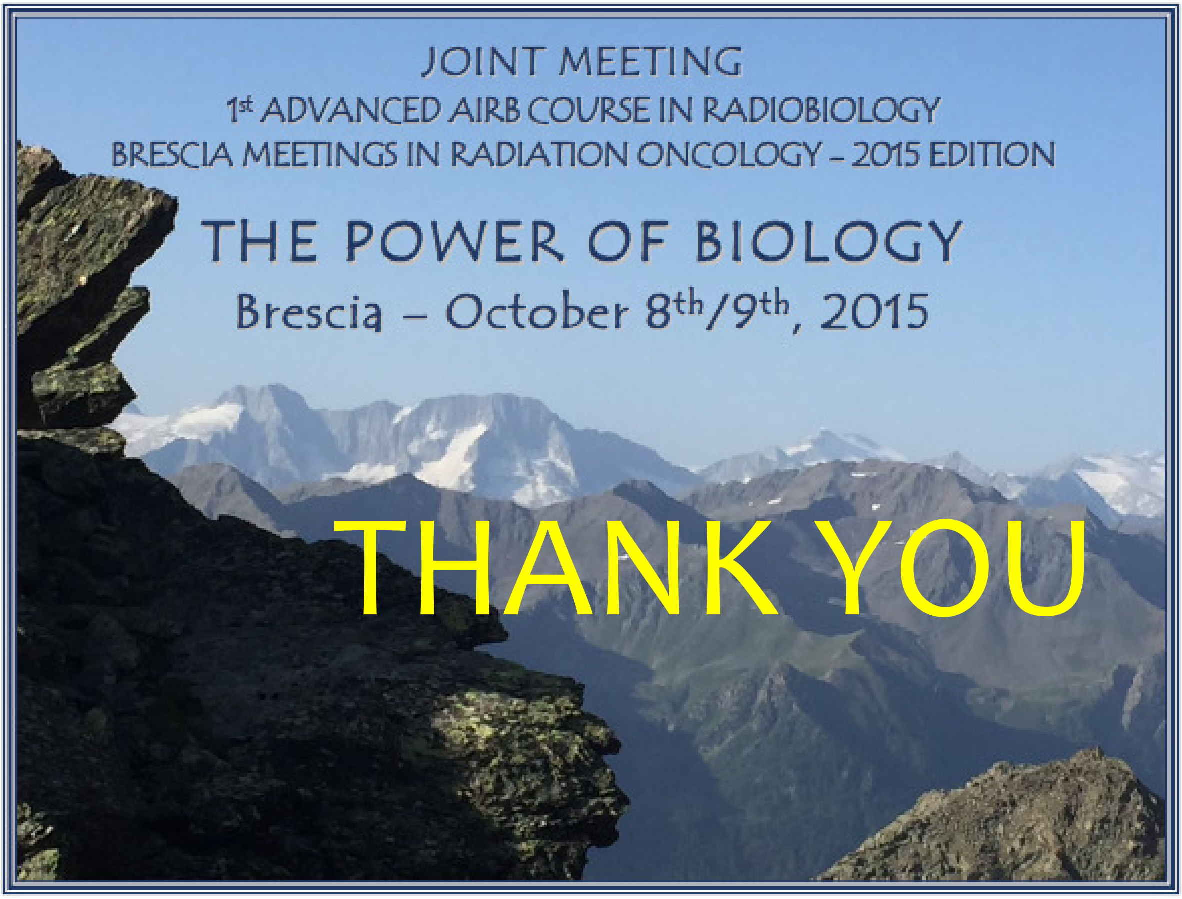
doi:10.1093/jnci/dju419
First published online February 6, 2015
Article

Simultaneous β1 Integrin-EGFR Targeting and Radiosensitization of Human Head and Neck Cancer

Iris Eke, Katja Zscheppang, Ellen Dickreuter, Linda Hickmann, Ercole Mazzeo, Kristian Unger, Mechthild Krause, Nils Cordes


A
UTSCC15
GFP
FAKwt
FAKca
Surviving fraction
P < .001
P < .001
P = .003
P = .002
P = .02
Co IgG
AIIB2
Cetuximab
AIIB2+ Cetuximab
B
UTSCC15
GFP
FAKwt
FAKca
Surviving fraction
SF 6 Gy
P = .003
P = .005
P = .004
SF 6 Gy
P = .003
P = .004
P < .001
Co IgG
AIIB2
Cetuximab
AIIB2+Cetuximab
Radiation dose, Gy
C
UTSCC15
GFP
FAKwt
FAKca
Co IgG
AIIB2
Cetux
AIIB2+Cetux
MEK1/2
pMEK1/2
Erk1/2
pErk1/2
β-Actin
D
UTSCC15
Co siRNA
FAK siRNA
Erk1 siRNA
Co2x siRNA
FAK+Erk1 siRNA
FAK
Erk1
Erk2
β-Actin
E
UTSCC15
Surviving fraction
P < .001
P < .001
Co
FAK
Erk1
Co2x
FAK+Erk1
:siRNA
F
UTSCC15
Surviving fraction
Radiation dose, Gy
Co siRNA
FAK siRNA
Erk1 siRNA
Co2x siRNA
FAK+Erk1 siRNA
G
No inhibition:
Bypass signaling by β1 integrin inhibition:
Simultaneous β1 integrin/EGFR inhibition:
Integrin
EGFR
FAK
Erk1
P
Survival
Radioresistance


A
UTSCC 15 tumor xenografts
EGFR, β1 integrin, DAPI
20 µm
SAS tumor xenografts
EGFR, β1 integrin, DAPI
20 µm
B
Tumor growth (Ø 6 mm)
AIIB2 and/or Cetuximab
3d
AIIB2
4h
Irradiation(x -ray)
3d
AIIB2
Measurement of tumor volume
C
UTSCC15 tumor
0 Gy
Tumor control, %
P < .001
P = .65
P < .001
P = .06
SAS tumor
0 Gy
P < .001
P = .99
P = .008
P < .001
Co IgG
AIIB2
Cetuximab
AIIB2+Cetuximab
20 Gy
Tumor control, %
P < .001
P = .01
P = .007
P = .94
20 Gy
P < .001
P = .83
P = .02
P < .001
Time after start of treatment, d


JOINT MEETING
1st ADVANCED AIRB COURSE IN RADIOBIOLOGY
BRESCIA MEETINGS IN RADIATION ONCOLOGY – 2015 EDITION
THE POWER OF BIOLOGY
Brescia – October 8th/9th, 2015
THANK YOU