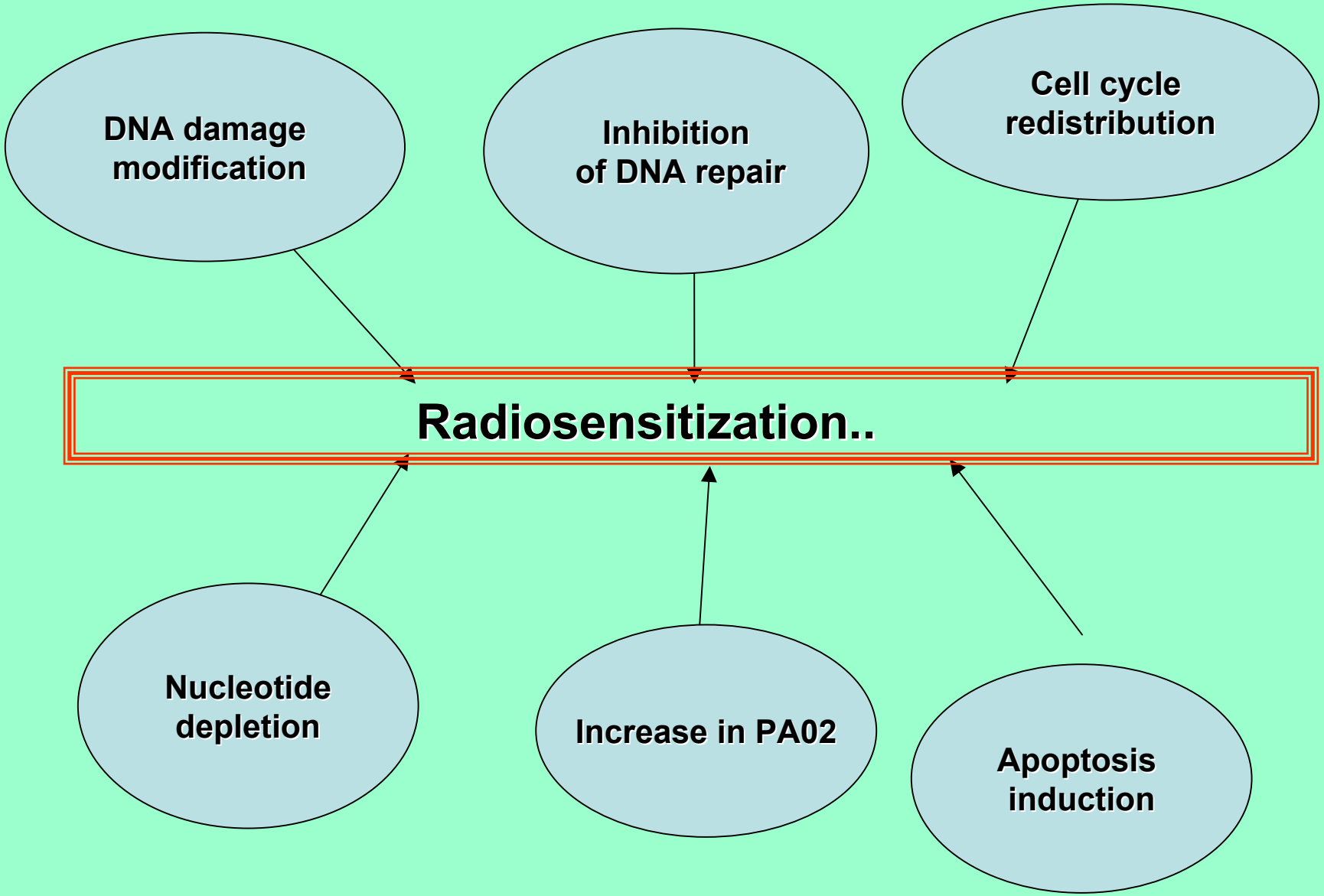
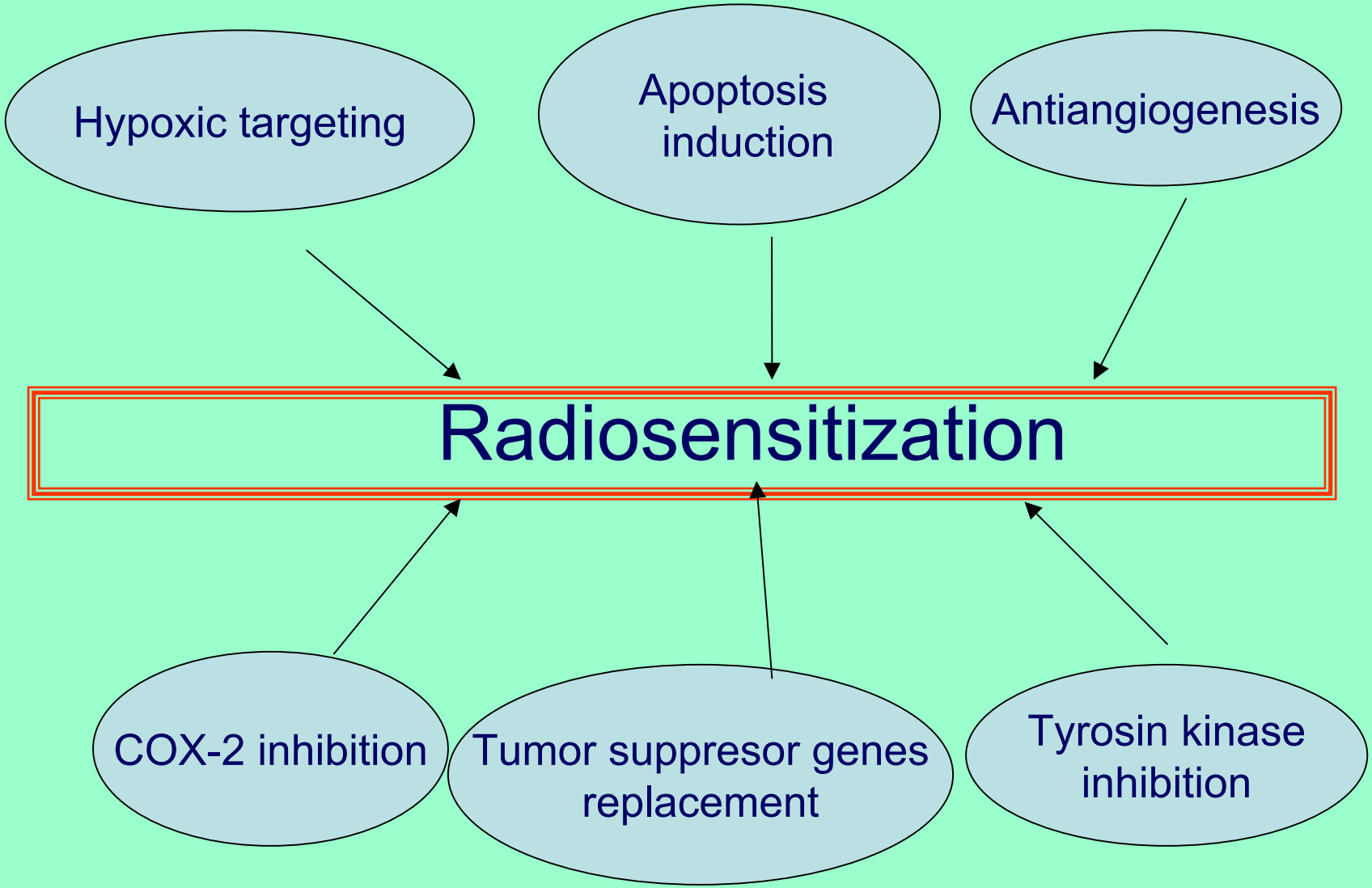
Strategies to improve anti tumor effectiveness of radiotherapy

Eric Deutsch MD PhD
Institut Gustave Roussy
Villejuif, France

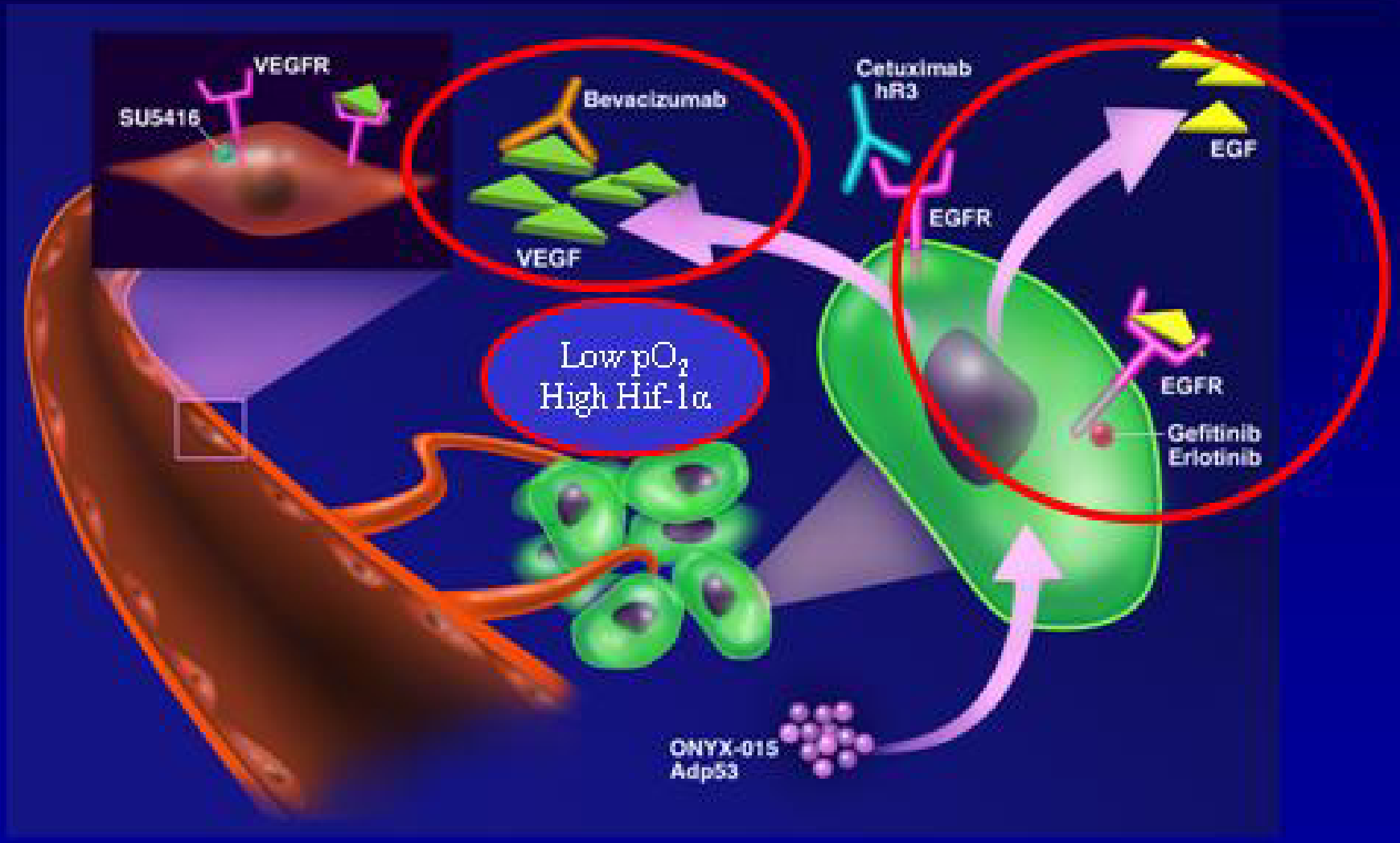
Classical view : radiosensitization….



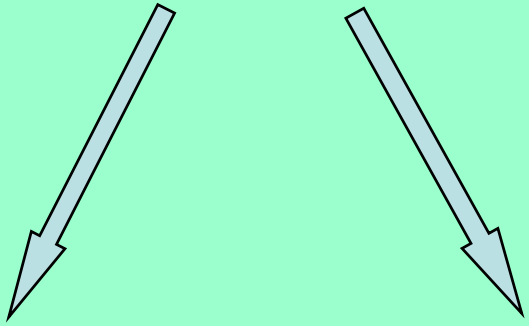
Biological view..



Current Clinical Targets



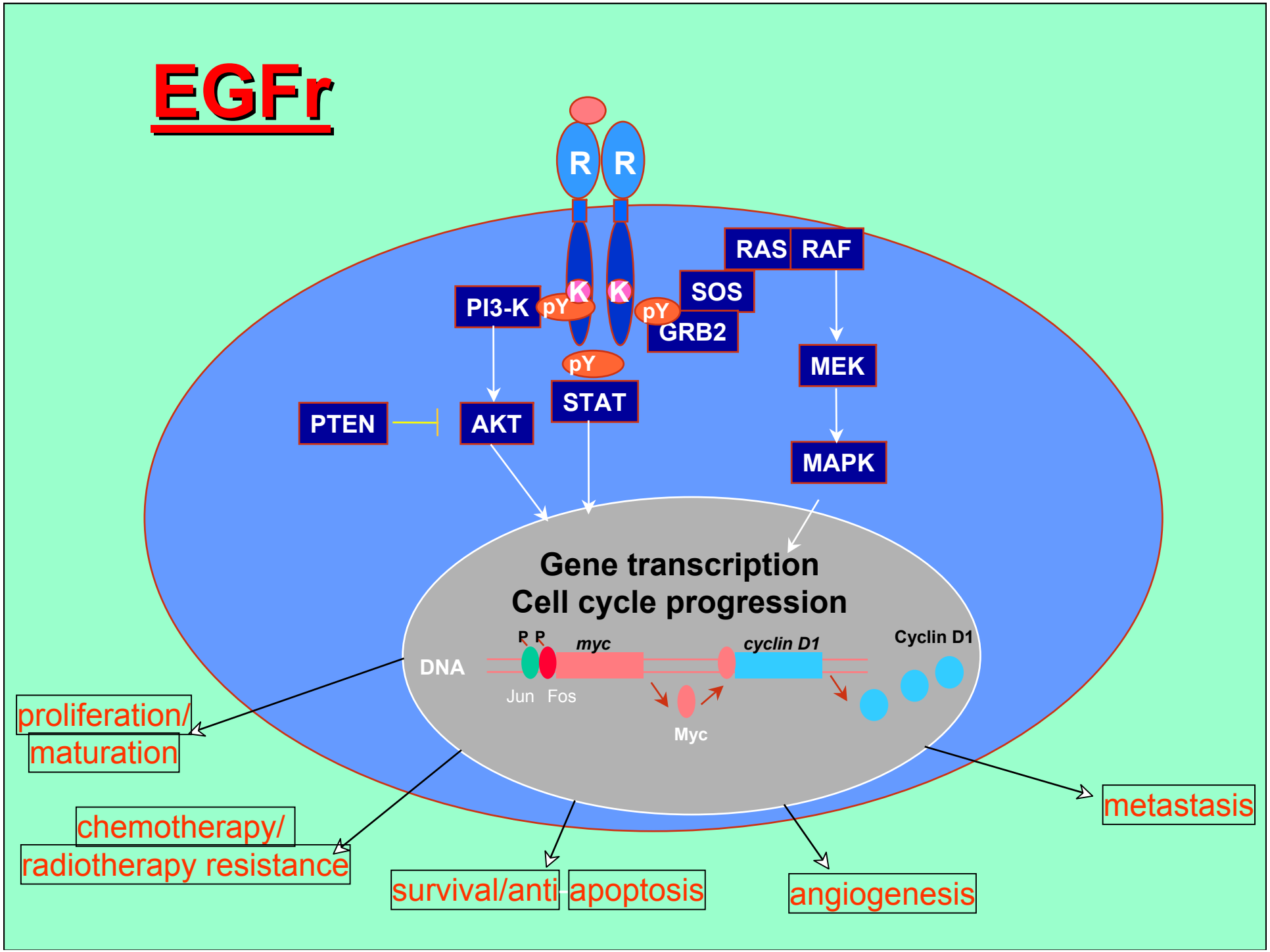
More than 60 new agents tested in phase I or II trials



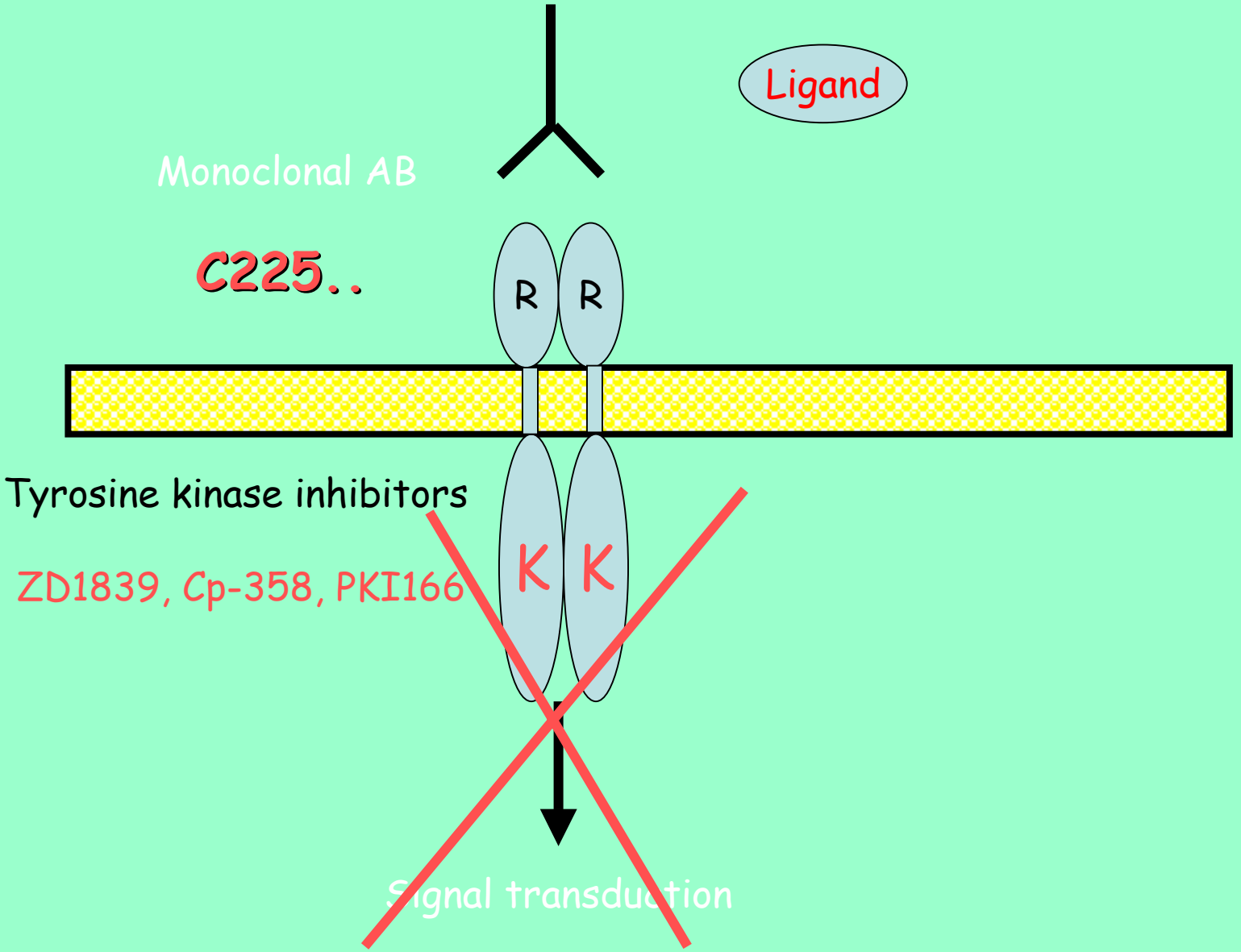
« Intrinsic »
radiation response
Anti EGFr, mTOR, PI3K.. COX-2,
Proteasome inhibitors, TNFr inducers

« **ex**trinsic »
micro environment
Anti VEGFr, FGFr

**Source : www.clinicaltrials.gov*

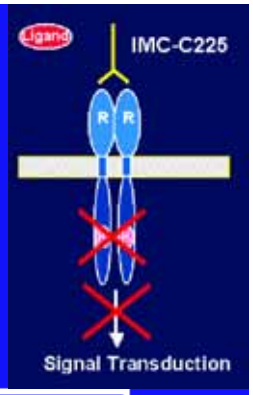

EGFr
R
R
K
K
pY
pY
pY
PI3-K
SOS
GRB2
RAS
RAF
MEK
MAPK
PTEN
AKT
STAT
Gene transcription
Cell cycle progression
DNA
P P
myc
Jun Fos
Myc
cyclin D1
Cyclin D1
proliferation/
maturation
chemotherapy/
radiotherapy resistance
survival/anti-apoptosis
angiogenesis
metastasis

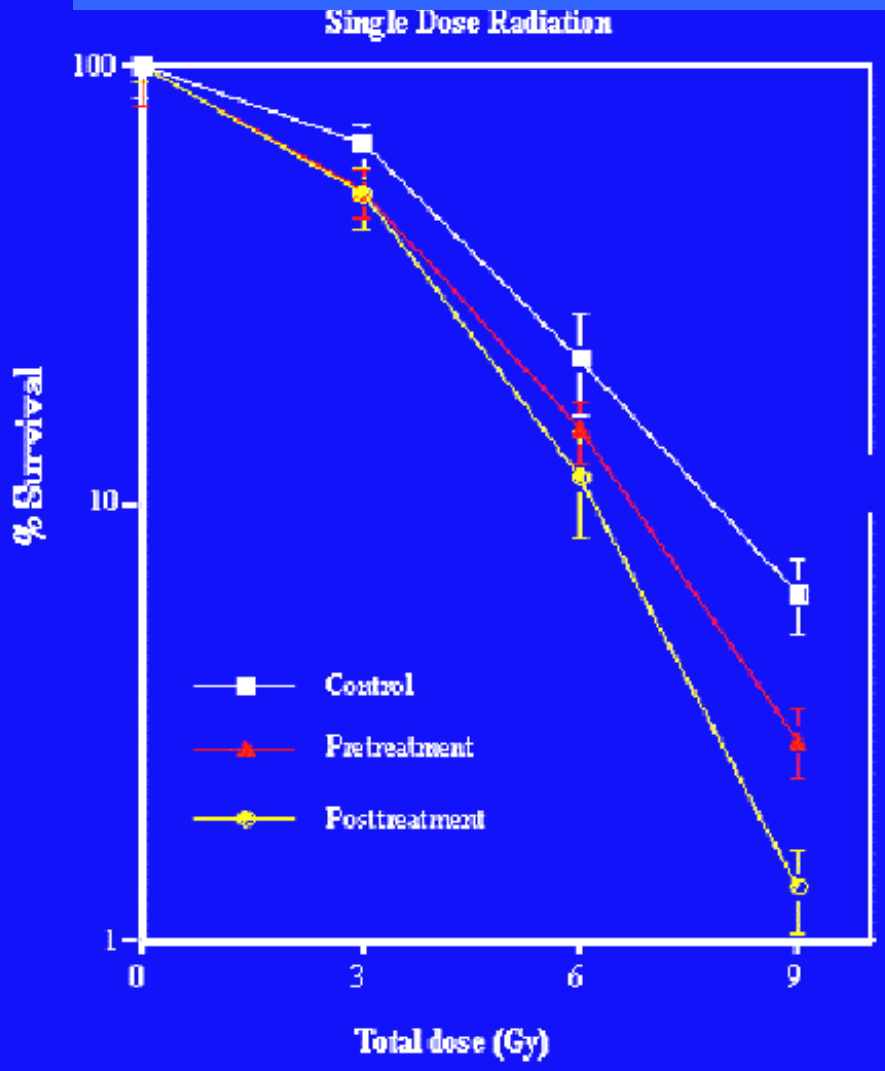
SPECIFIC EGFr INHIBITORS :

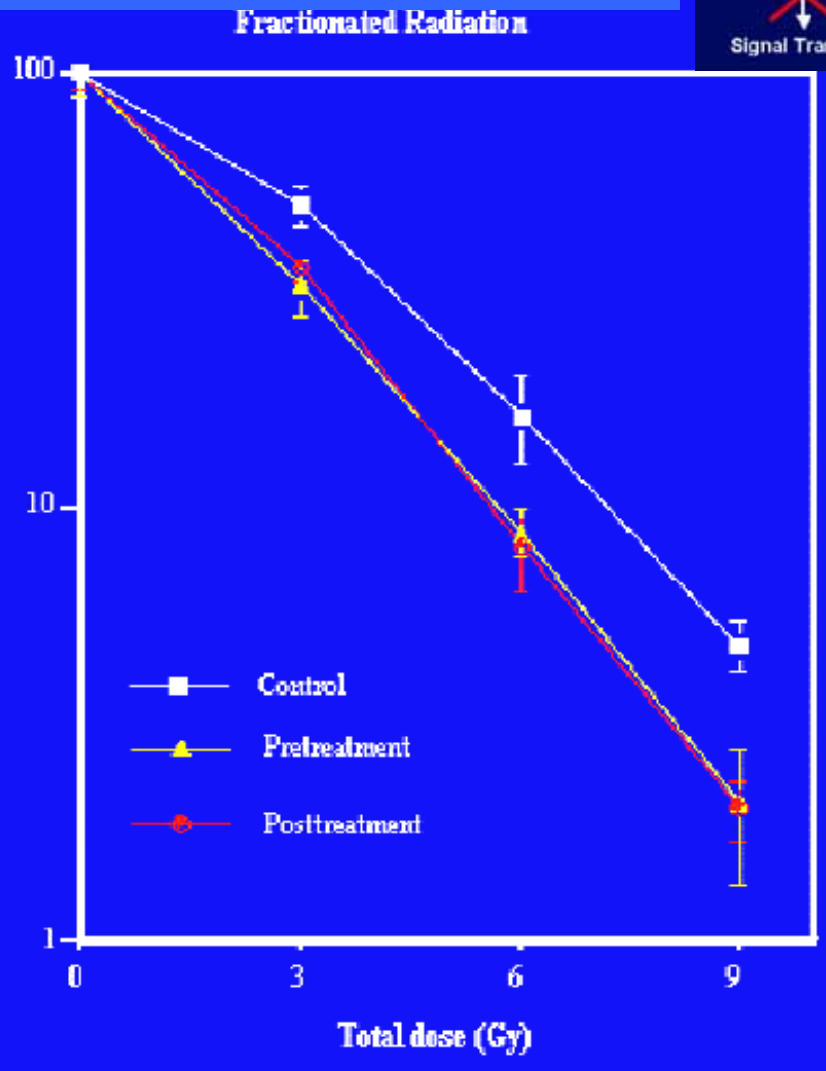


C225 + irradiation

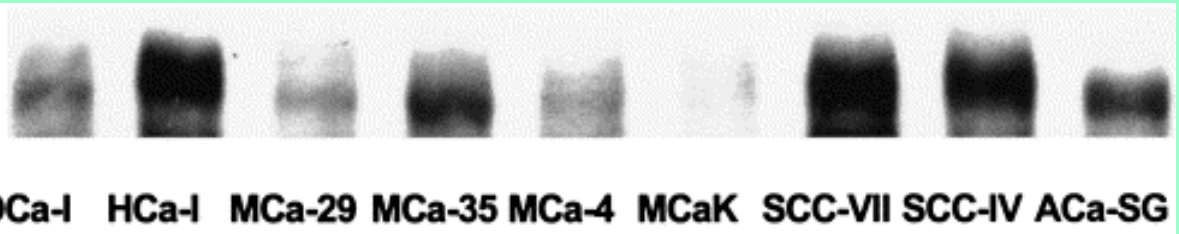
in vitro





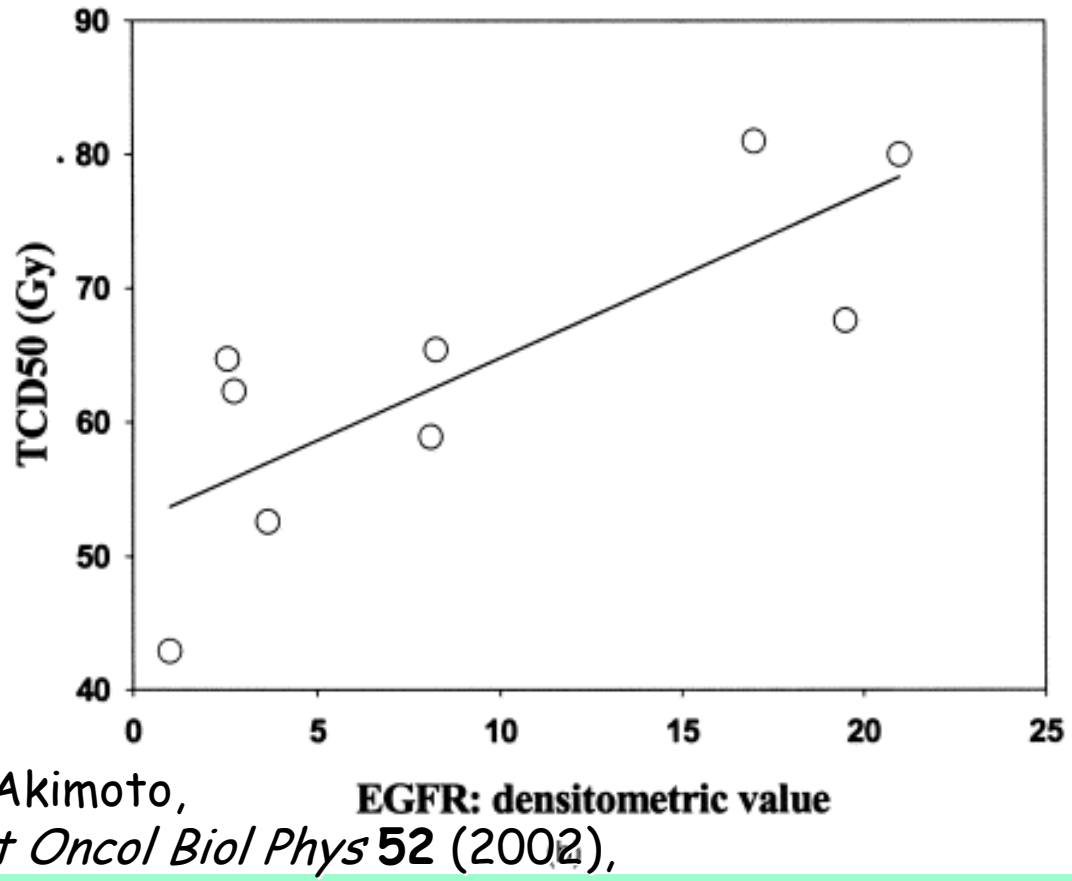


P. Harari



(a)

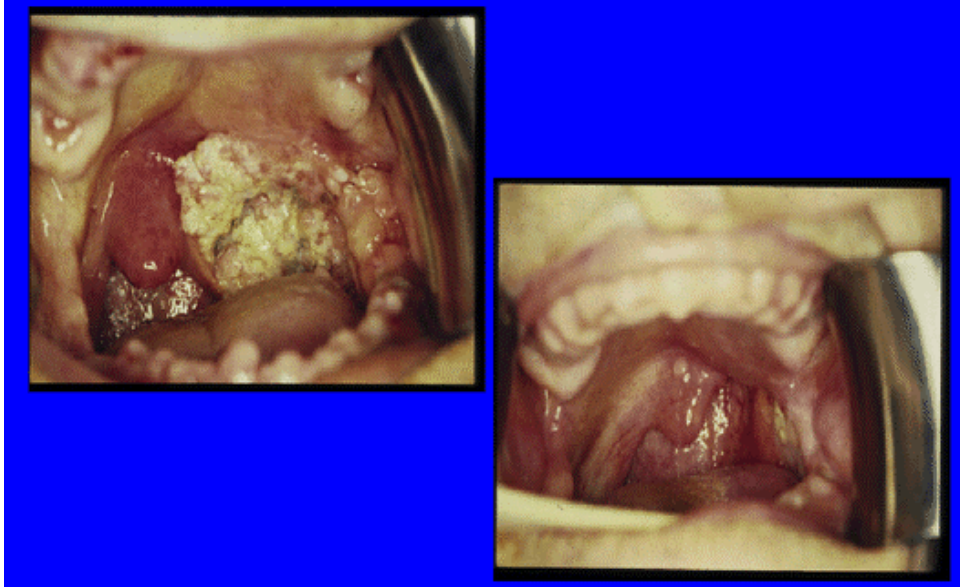
EGFr expression : Dose effect relationship

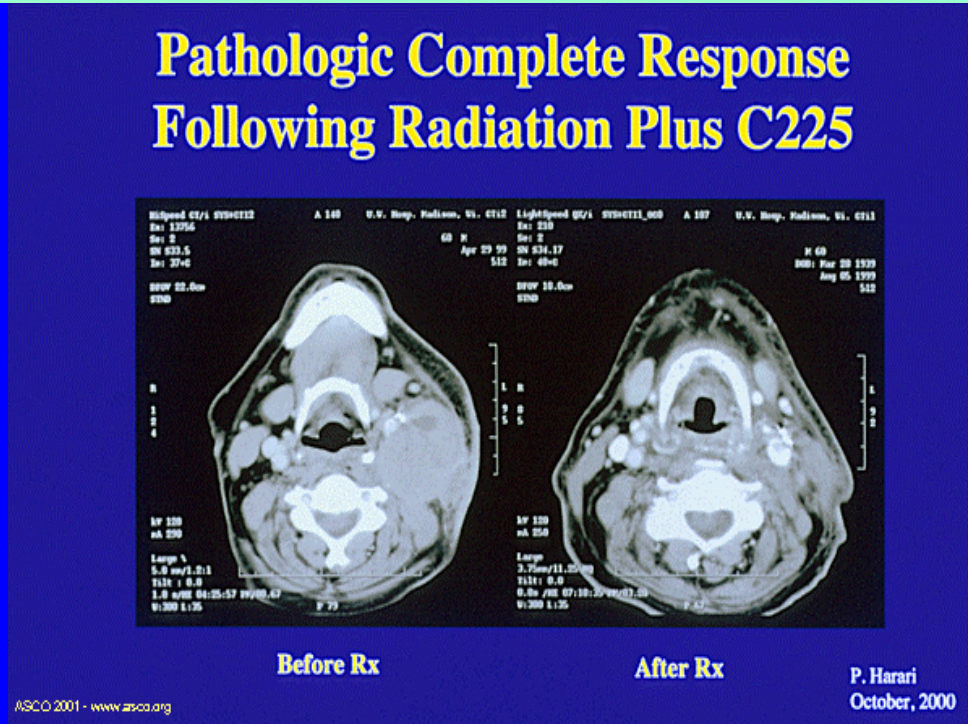


L. Milas, T. Akimoto,
Int J Radiat Oncol Biol Phys **52** (2002),

C225 & irradiation :

transfert from bench to clinic





EGFR & radiotherapy : First clinical evidence of the value of target agents combined to radiotherapy

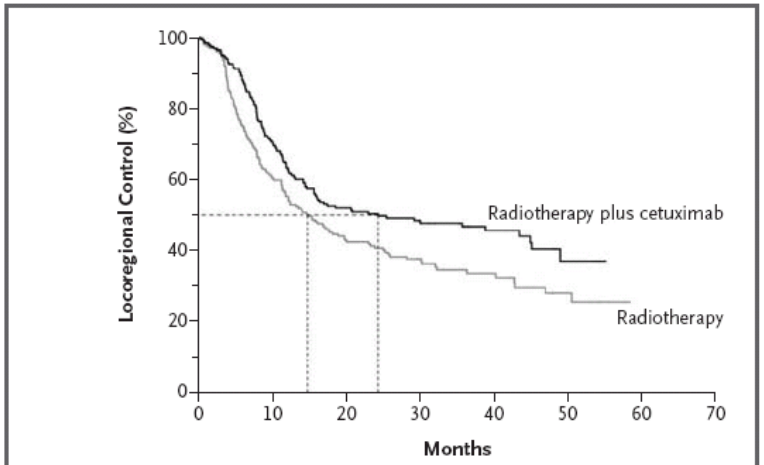


Figure 1. Kaplan–Meier Estimates of Locoregional Control among All Patients Randomly Assigned to Radiotherapy plus Cetuximab or Radiotherapy Alone.

The hazard ratio for locoregional progression or death in the radiotherapy-plus-cetuximab group as compared with the radiotherapy-only group was 0.68 (95 percent confidence interval, 0.52 to 0.89; P=0.005 by the log-rank test). The dotted lines indicate the median durations of locoregional control.

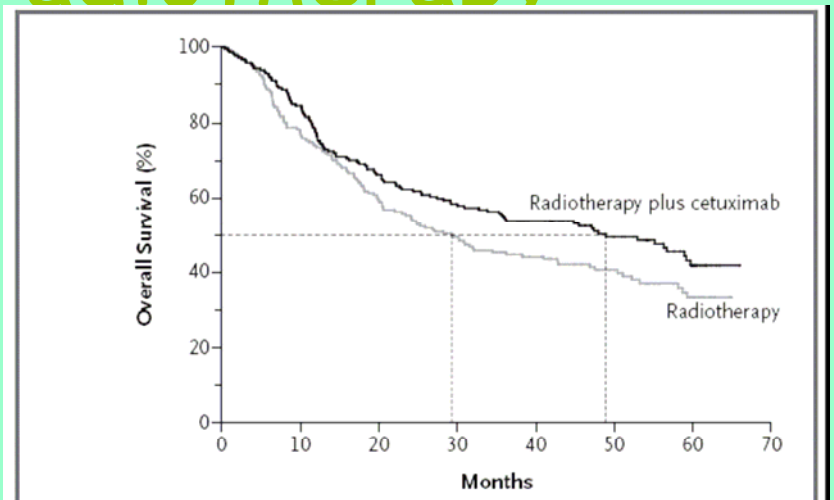
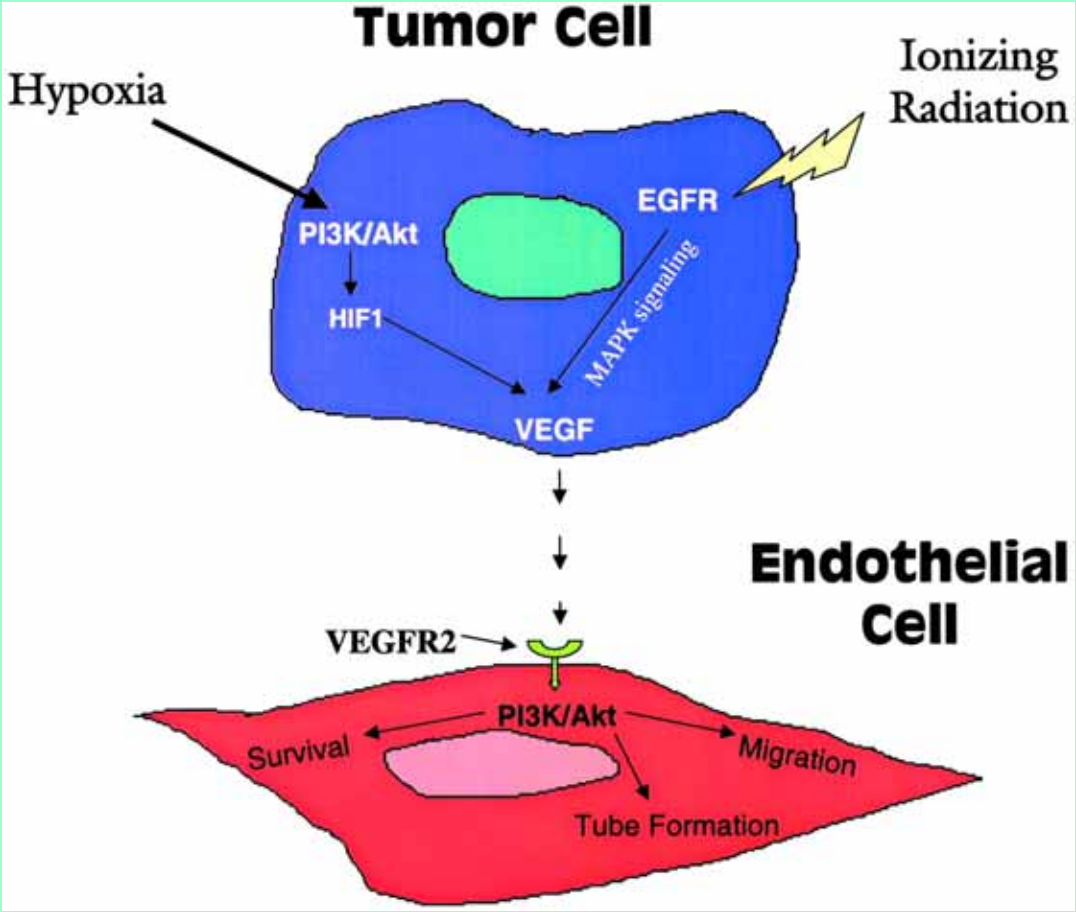


Figure 2. Kaplan–Meier Estimates of Overall Survival among All Patients Randomly Assigned to Radiotherapy plus Cetuximab or Radiotherapy Alone.

The hazard ratio for death in the radiotherapy-plus-cetuximab group as compared with the radiotherapy-only group was 0.74 (95 percent confidence interval, 0.57 to 0.97; P=0.03 by the log-rank test). The dotted lines indicate the median survival times.

C225 + radiotherapie : Bonner NEJM 2006

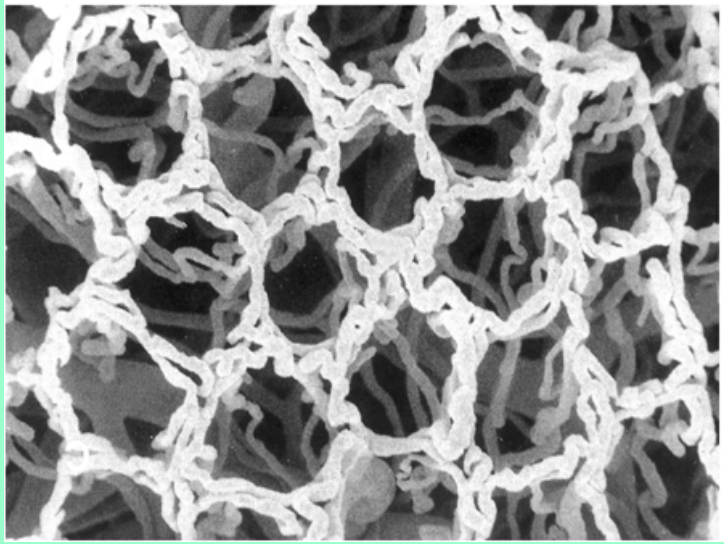
On the other side : the endothelial cell



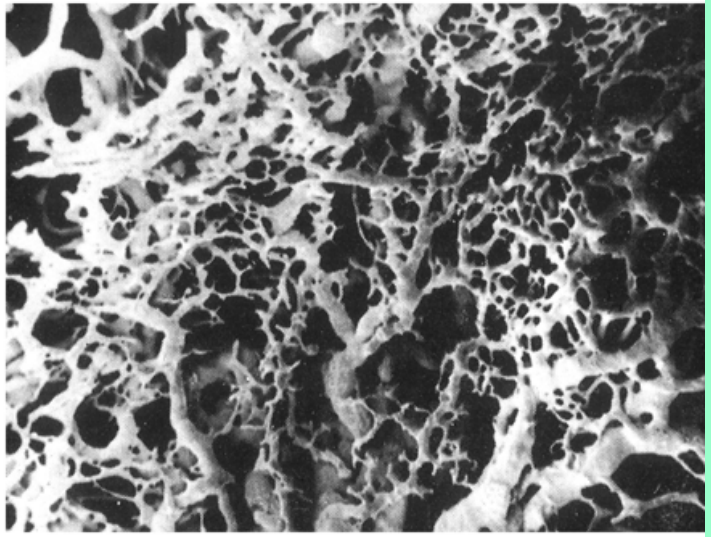
Wachsberger, Clinical Cancer Research Vol. 9, 1957-1971, June 2003

Tumor Neovasculature: Comparative Tortuosity and Disorganization

Normal colorectal mucosa



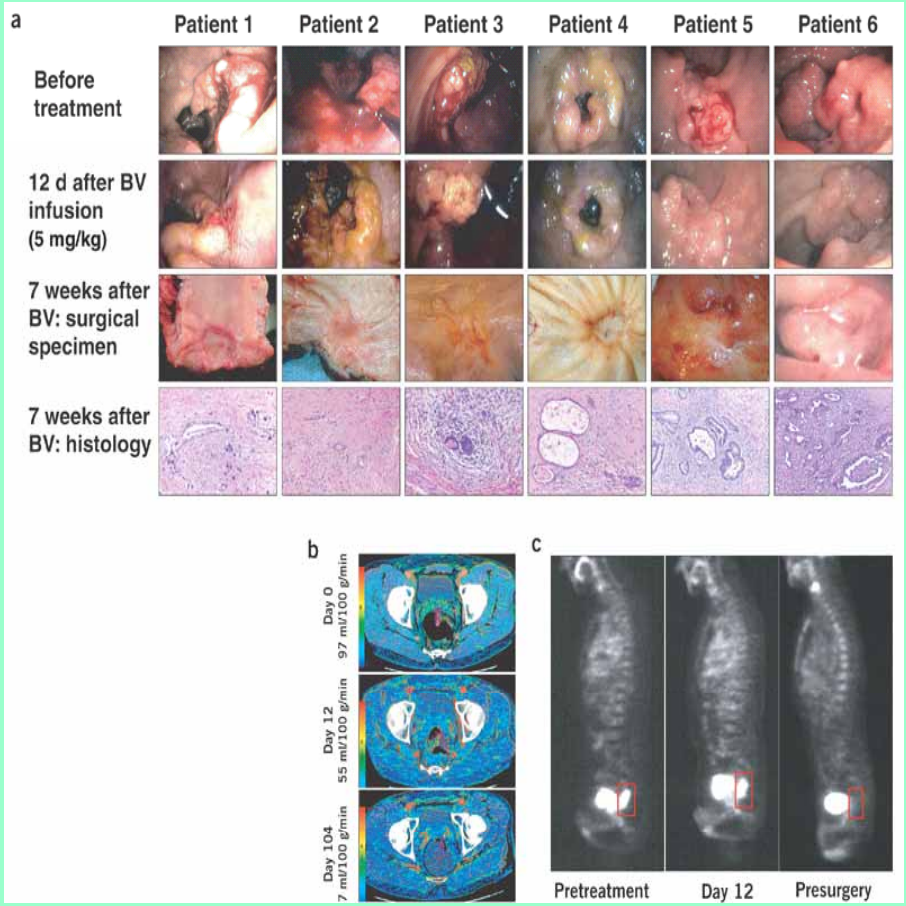
Nearby colorectal cancer



From Konerding et al. In Molls and Vaupel, eds. *Blood Perfusion and Microenvironment of Human Tumors*, 2002.

Antivascular agents :

a way to increase RT efficacy?



Wilett, Nature Medicine 05

Genentech
IN BUSINESS FOR LIFE

April 2007

IMPORTANT DRUG WARNING
Regarding AVASTIN® (bevacizumab)

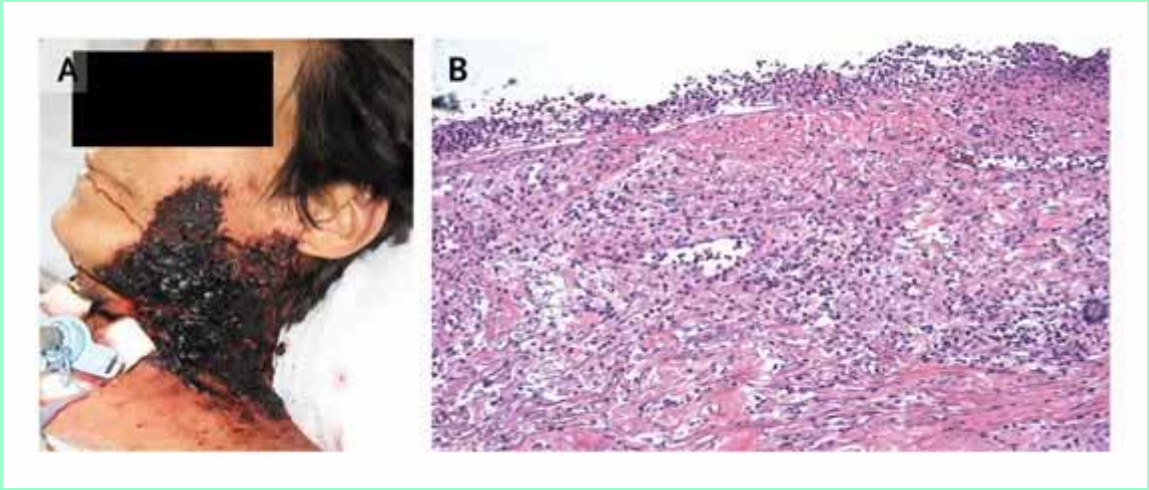
Dear Healthcare Provider:

Genentech, Inc. would like to inform you of important new safety information regarding AVASTIN® (bevacizumab). This information concerns **tracheoesophageal (TE) fistula** that occurred in a study combining concurrent chemotherapy and radiation plus AVASTIN in patients with limited-stage small cell lung cancer (SCLC). AVASTIN is not indicated for use in SCLC.

In an investigator-sponsored multicenter, single-arm phase II trial, patients with limited-stage SCLC received four cycles of concurrent irinotecan, carboplatin, radiation therapy, and AVASTIN followed by maintenance AVASTIN for up to 6 months. There have been two confirmed serious adverse events of TE fistula (one fatal) reported in the first 29 patients enrolled in the study. A third, fatal event (upper aerodigestive tract hemorrhage and death of unknown cause), was also reported, in which TE fistula was suspected but not confirmed. All three events occurred during the AVASTIN maintenance phase of the study in the context of persistent esophagitis. As of March 22, 2007, six cases of TE fistula have also been reported in other lung and esophageal cancer studies involving the use of AVASTIN and chemotherapy alone or with concurrent radiation treatment.

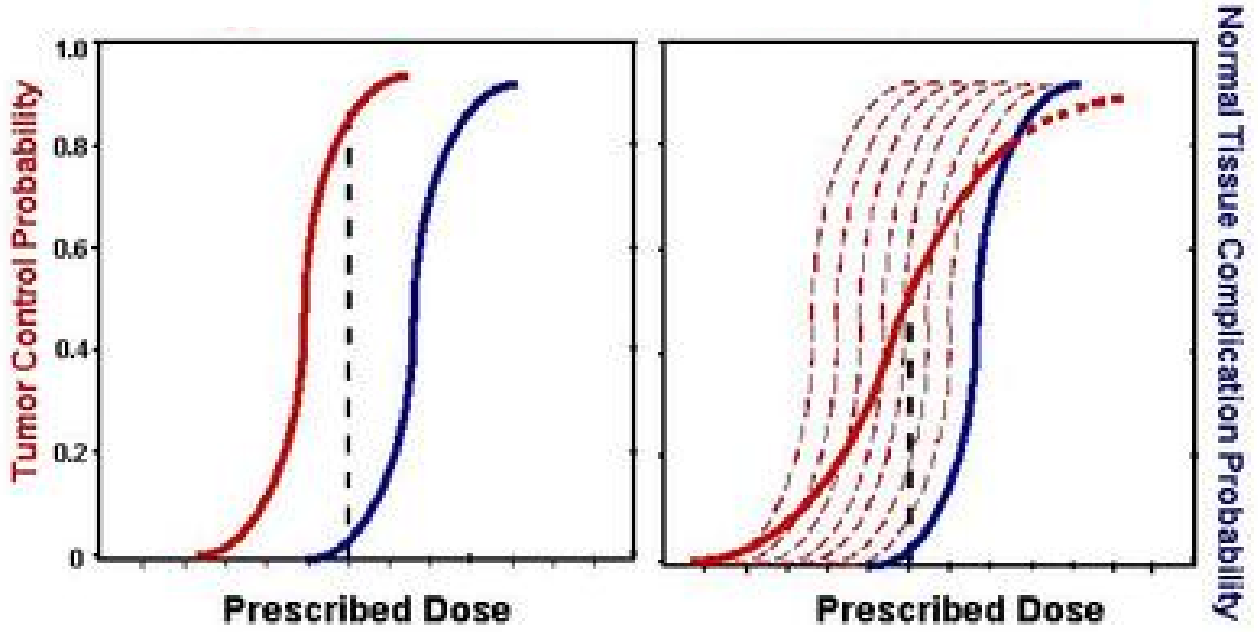
Toxicities of new agents

Anti EGFr + Radiotherapy :
One (unusual) case of grade IV skin necrosis

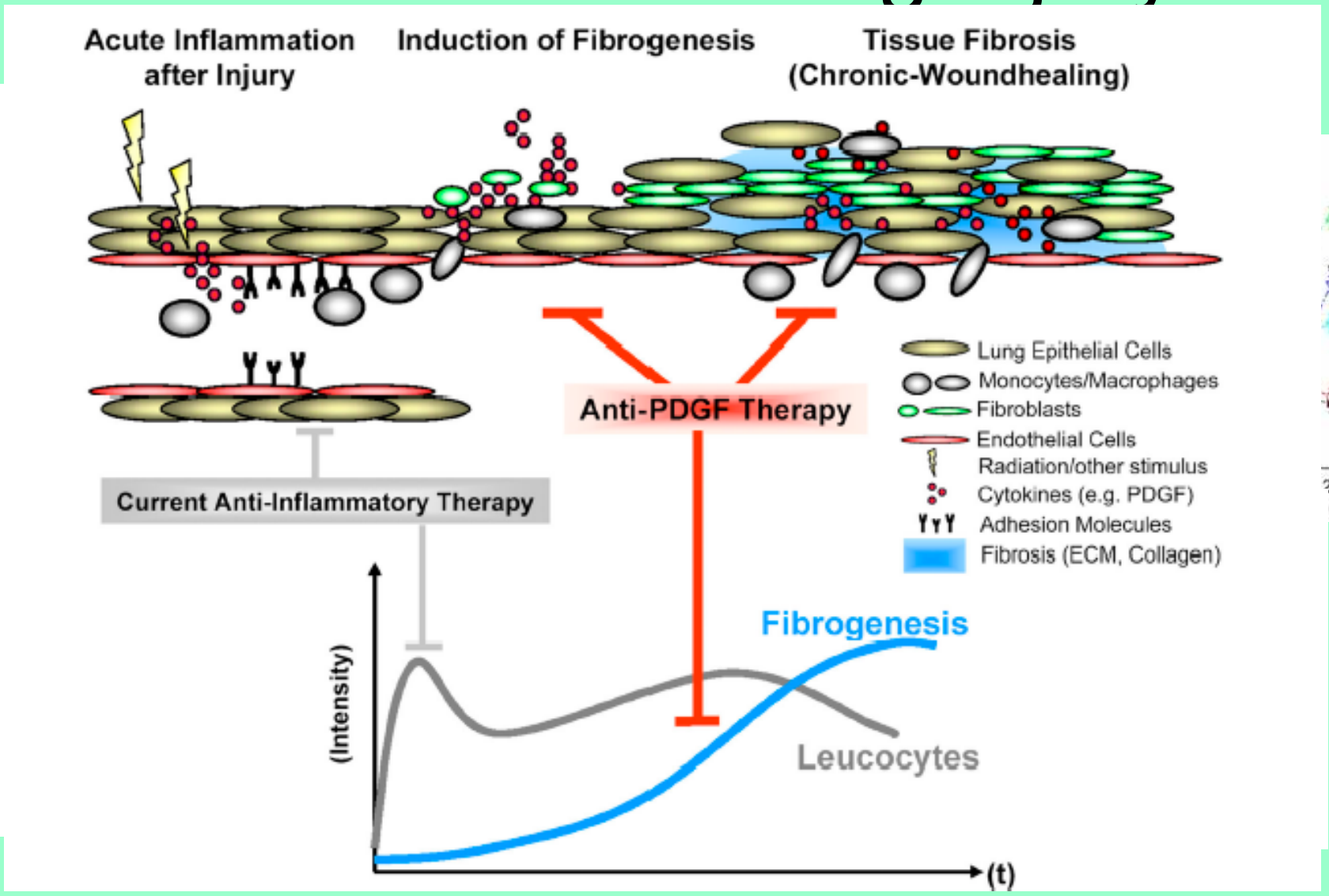


Budach W, New England Journal of Medicine, 2007

TCP/NTCP Model of Radiotherapy

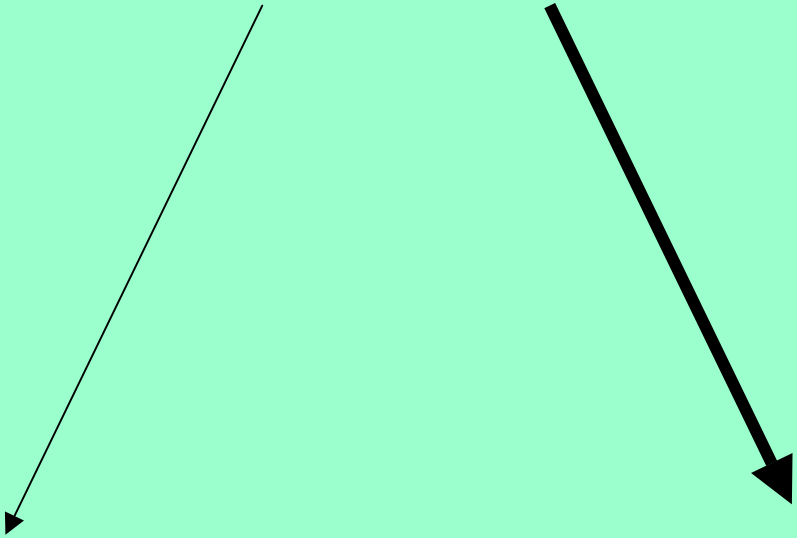


Modulation of lung injury



Abdollahi JEM 2005

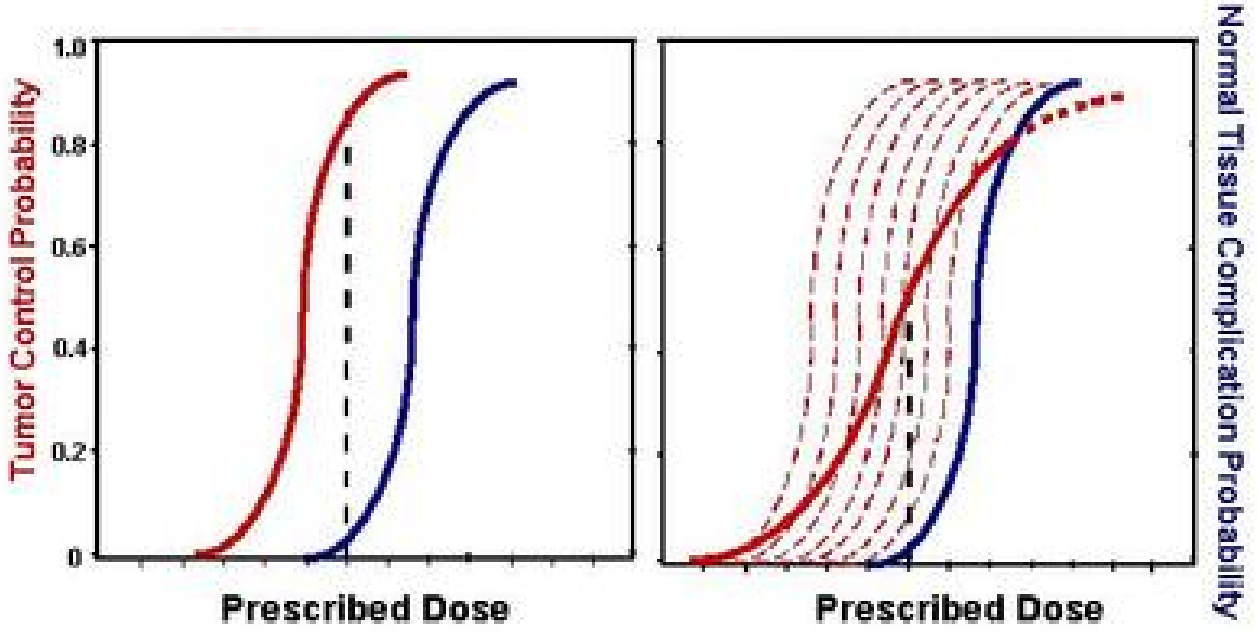
DEVELOPMENTS in RADIOTHERAPY



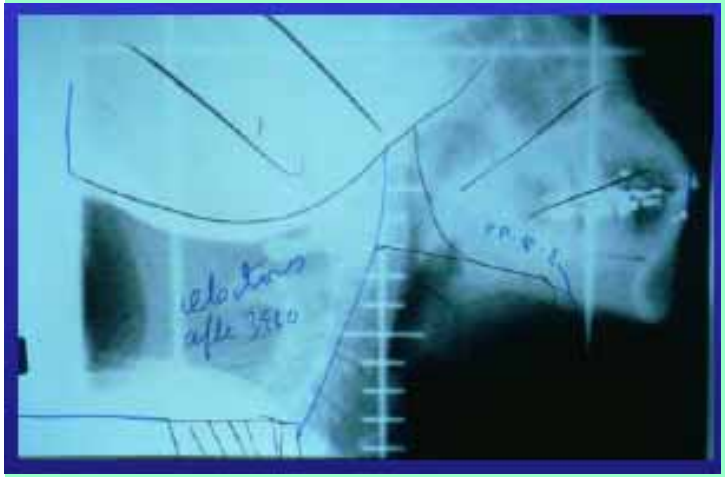
TECHNICAL

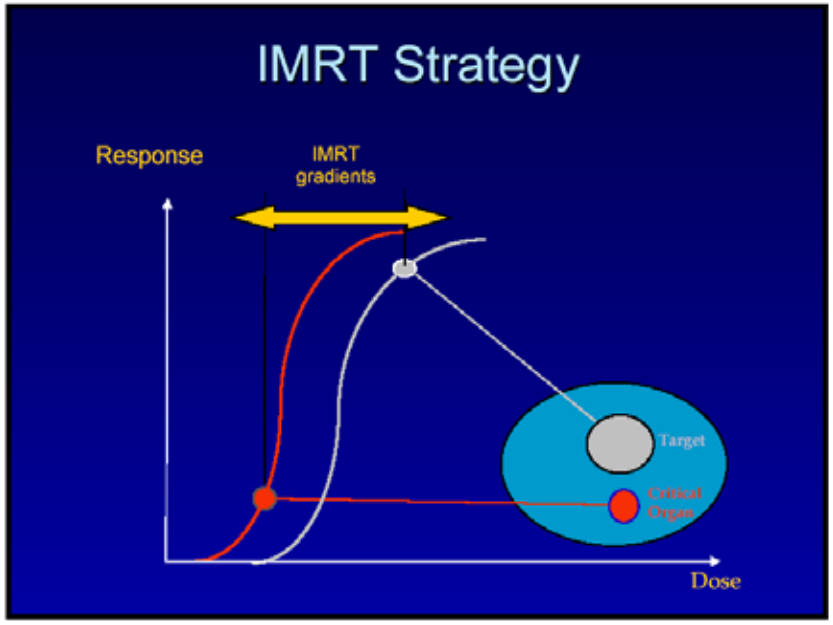
BIOLOGY

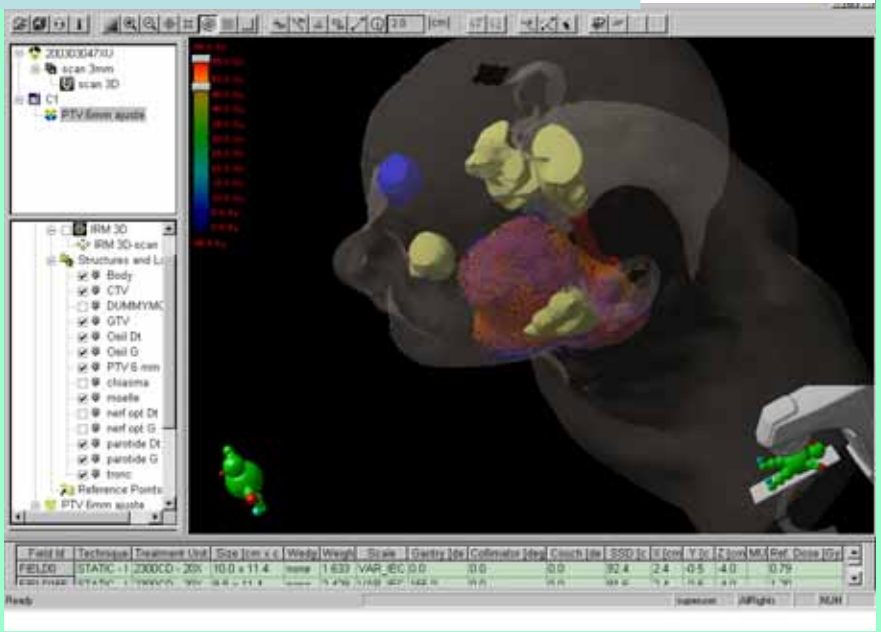
TCP/NTCP Model of Radiotherapy

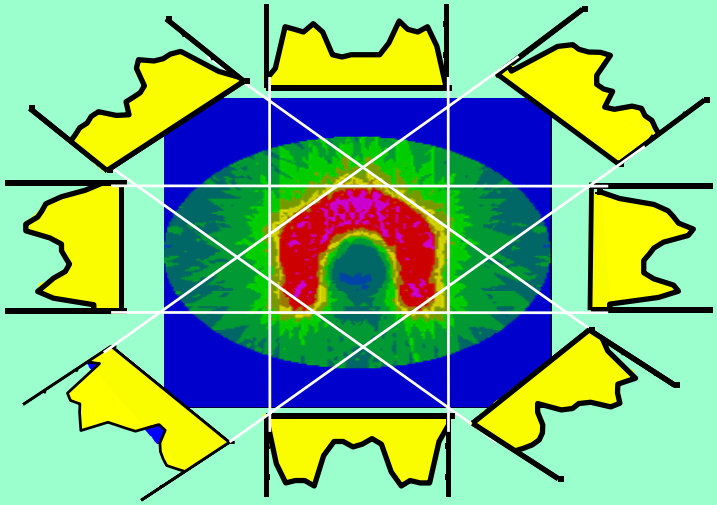


BALISITICS OPTIMIZATION : IMRT









IMRT allows better accuracy

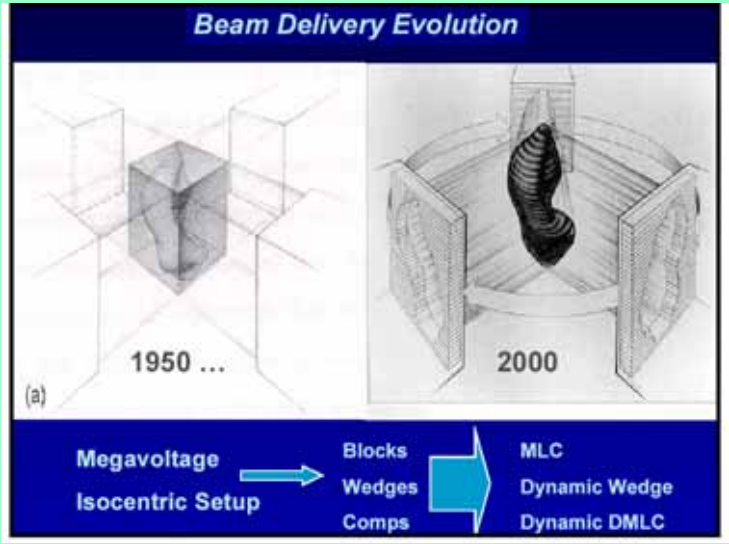
IMRT
In HNSCC

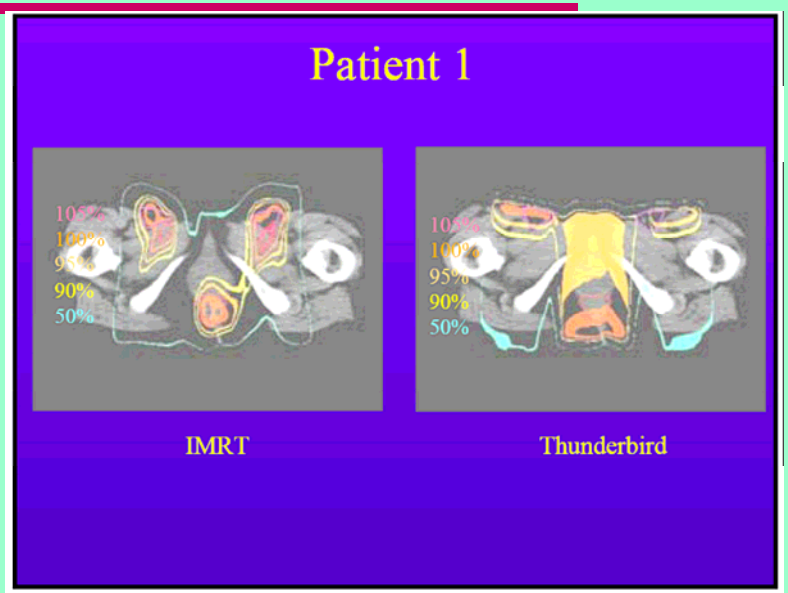
1) **Normal tissues sparing**

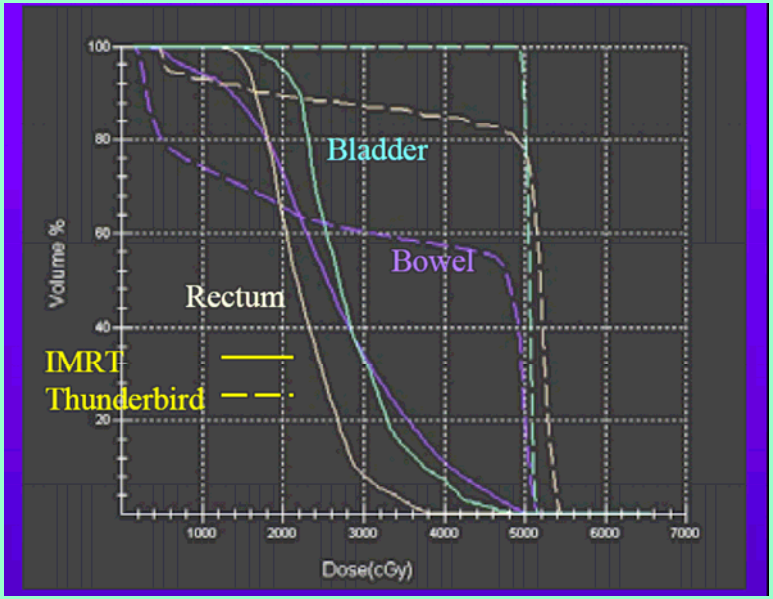
2) **Dose escalation**

OPTIMIZED RADIOTHERAPY in GI TUMORS :

Toward a better therapeutic index..

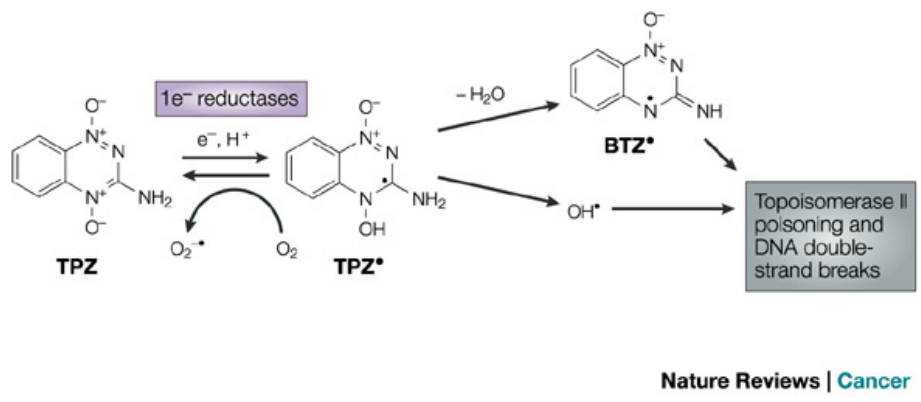






The usefulness of functionnal imaging : the example of tyrapazamine

- Bioreductive agent when hypoxic
- Radiosensitizer



Randomized phase III

→ **RT + CDDP**

→ **RT + CDDP + Tyrapazamine**

<u>Overall results : 2 arms similar!!</u>

Tirapazamine :
Hypoxia PET to select the patients?

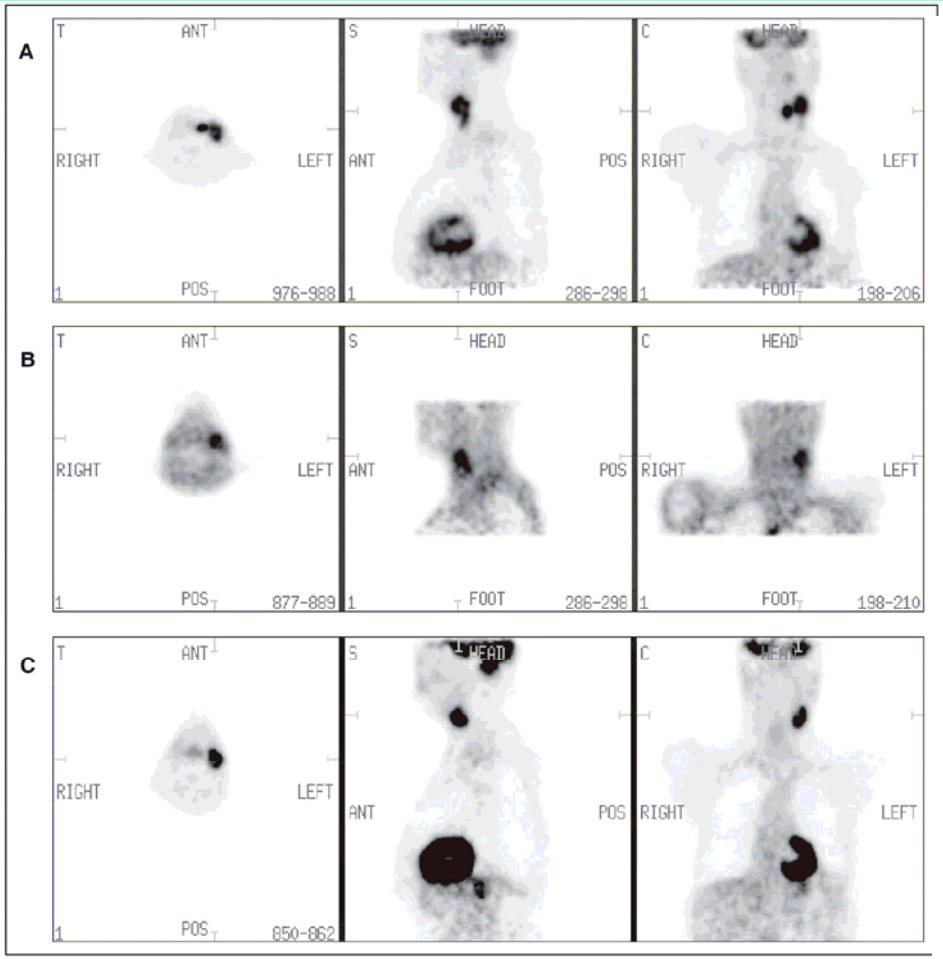


Fig 1. (A) Baseline [^{18}F]-fluorodeoxyglucose (FDG) positron emission tomography (PET) of patient with T2N2b squamous cell carcinoma of the pyriform fossa with left nodal mass. (B) [^{18}F]-fluoromisonidazole (FMISO) -PET at baseline, nonhypoxic primary tumor, and hypoxic node. (C) FDG-PET 12 weeks after chemoboost, complete response in nonhypoxic primary tumor, and poor response in hypoxic node. Residual tumor in nodal mass was confirmed pathologically after neck dissection.

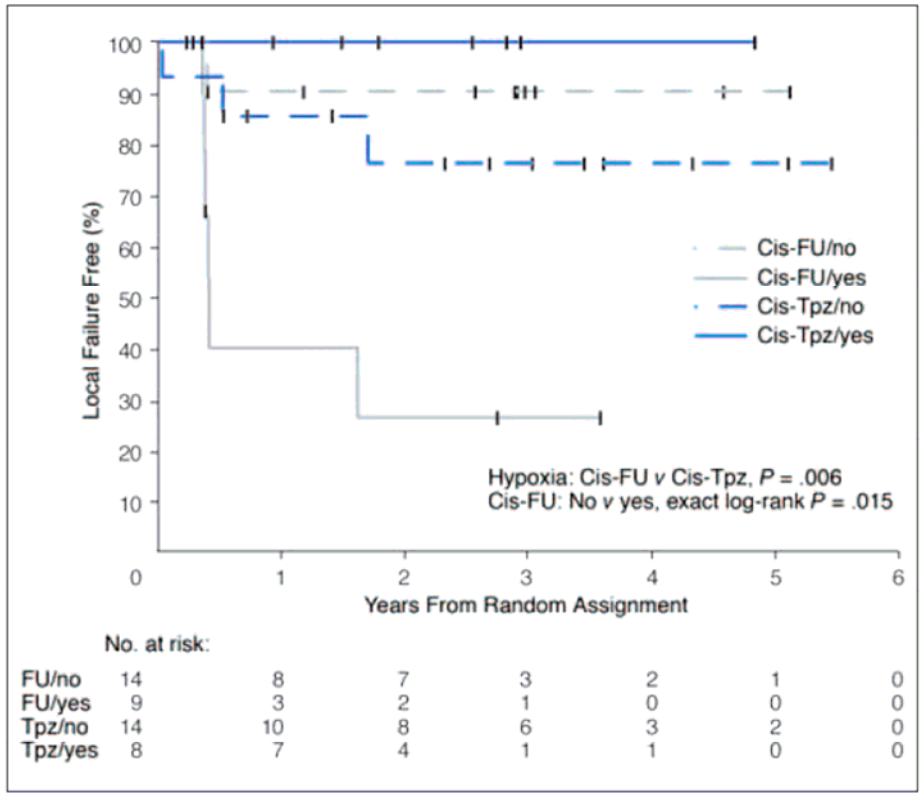
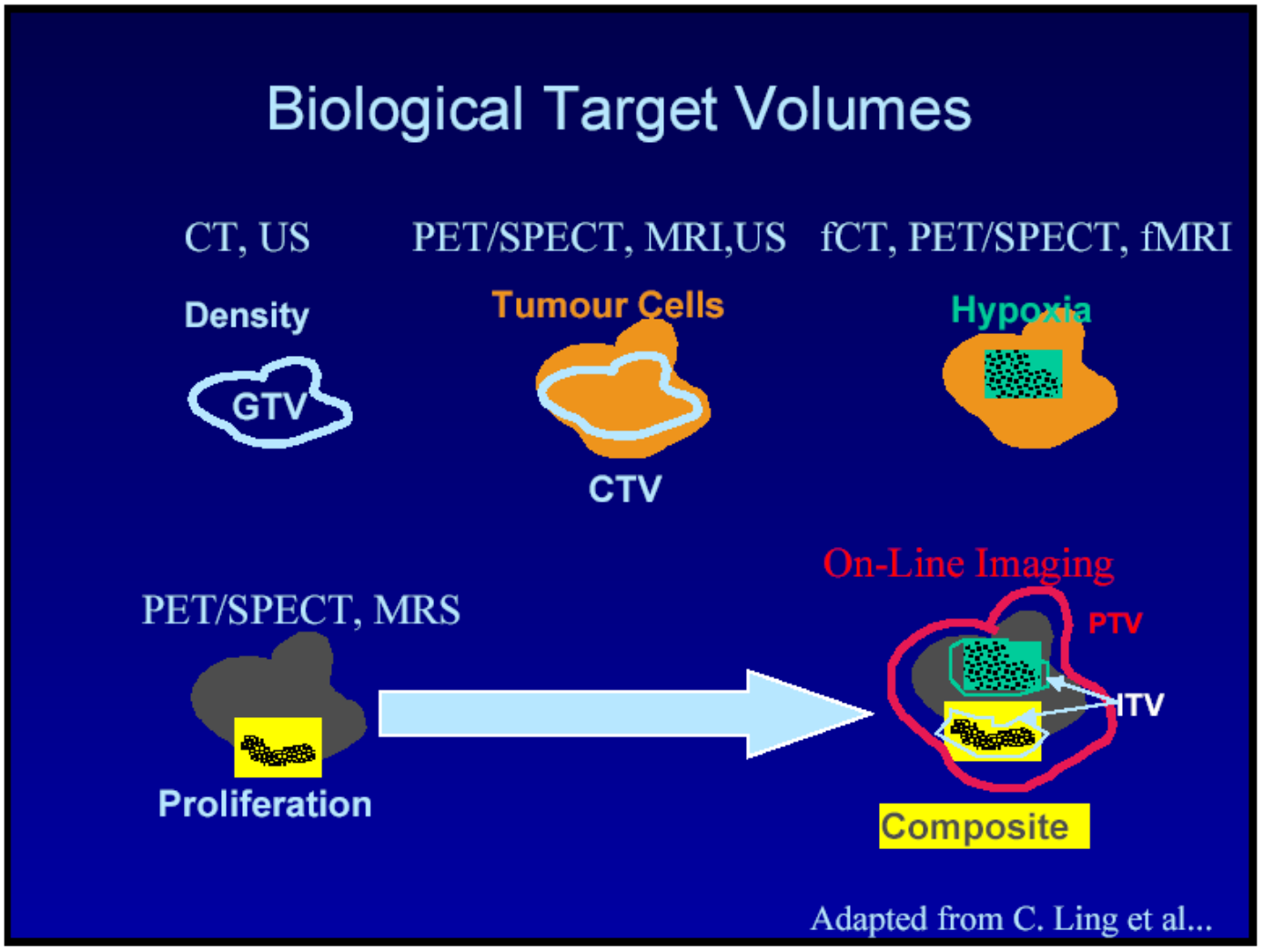


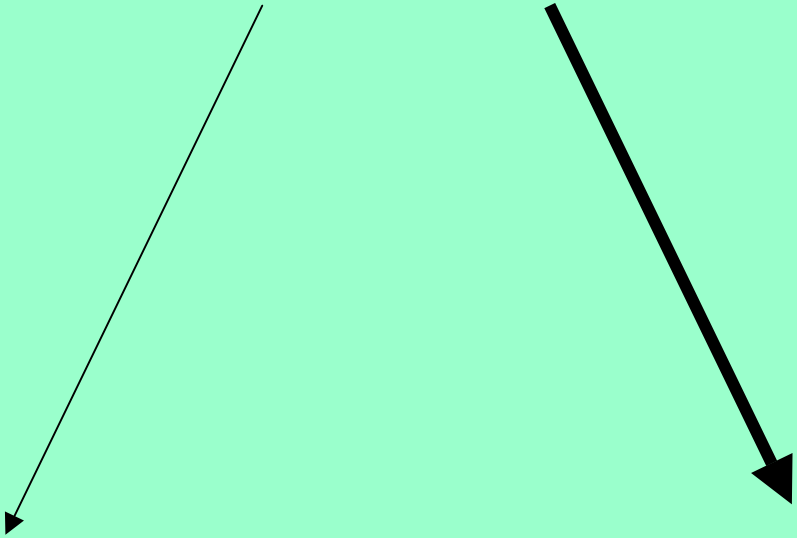
Fig 2. Time to local failure (Kaplan-Meier method) by treatment arm and hypoxia in the primary tumor (censored times are indicated as tick marks on the curves). Cis, cisplatin; FU, fluorouracil; TPZ, tirapazamine.

Rischin, JCO 2006

THE NEXT STEP :
IMAGE GUIDED RADIOTHERAPY
(PET as a tool for radiotherapy)



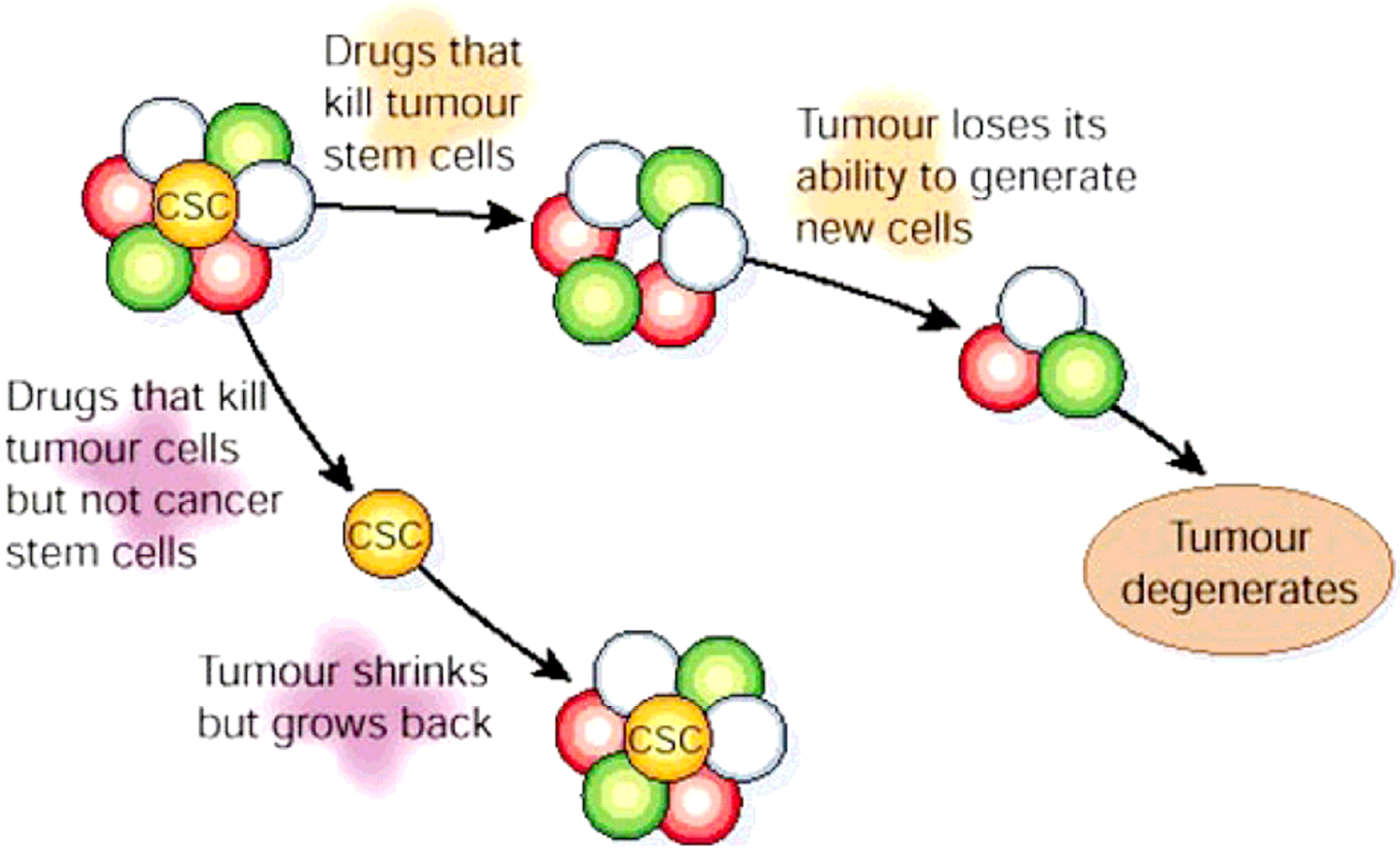
DEVELOPMENTS in RADIOTHERAPY



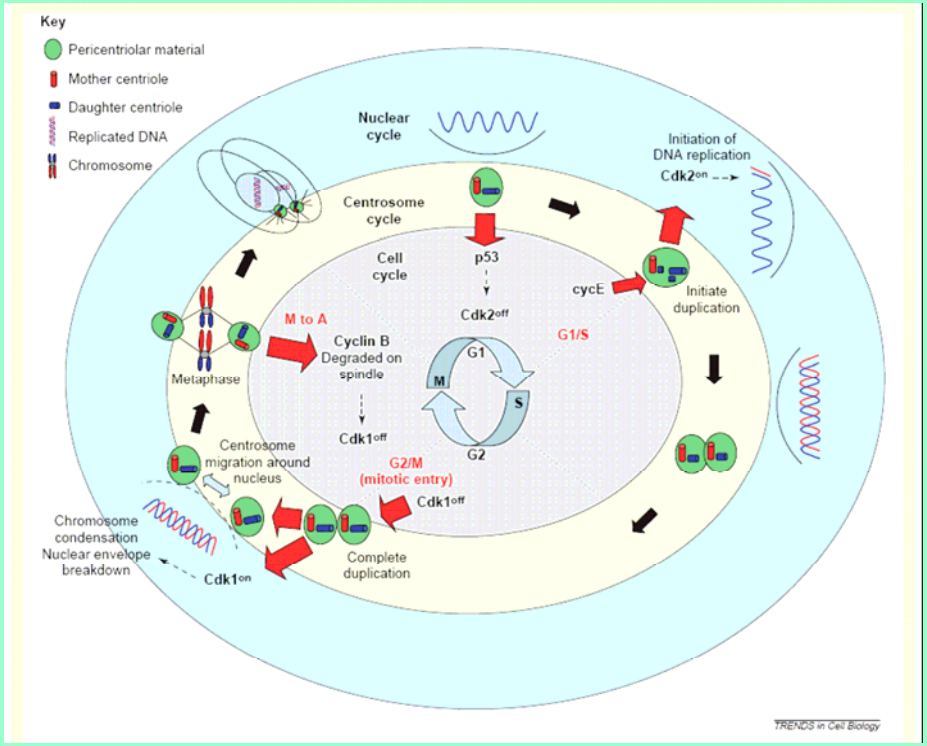
TECHNICAL

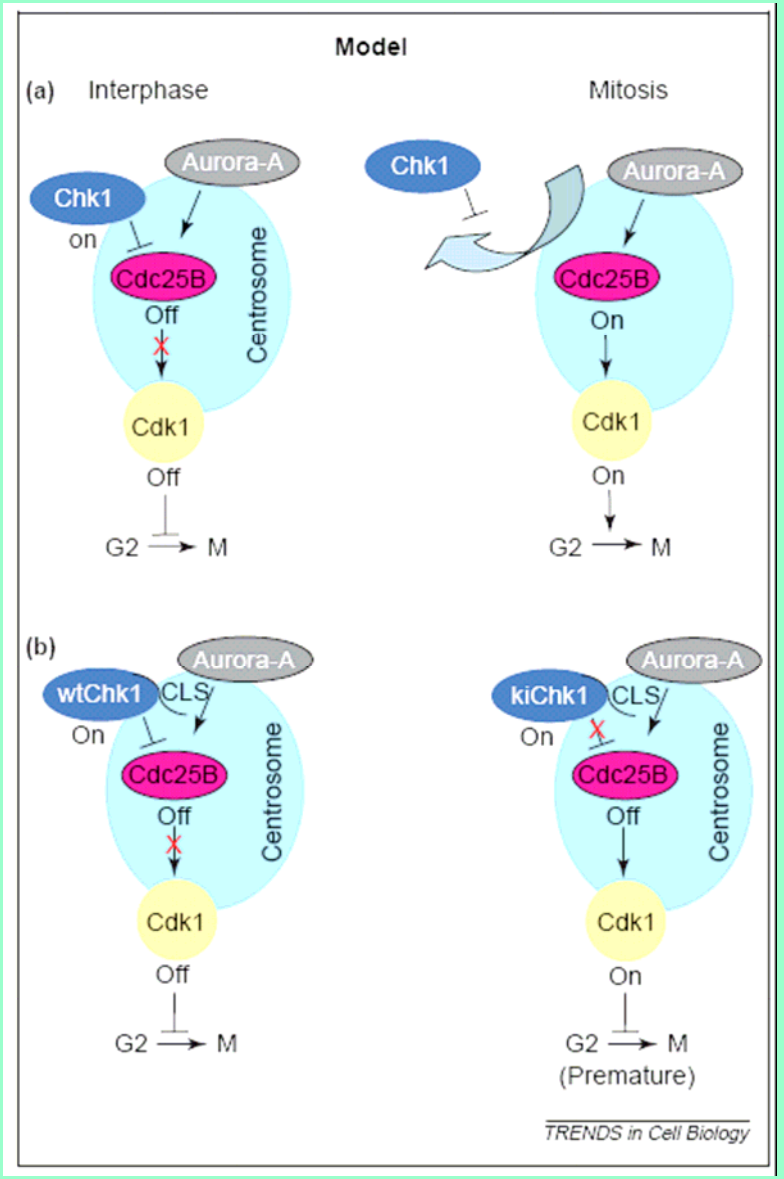
BIOLOGY

Tumor stem cells :

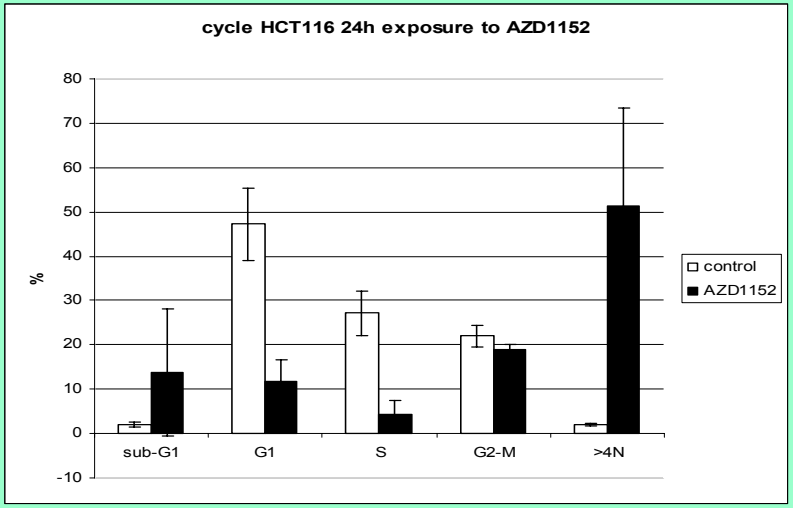


Stem cells radioresistance : G2/M arrest

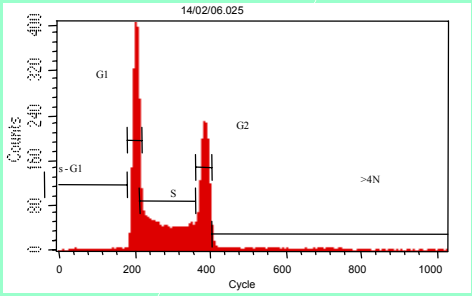




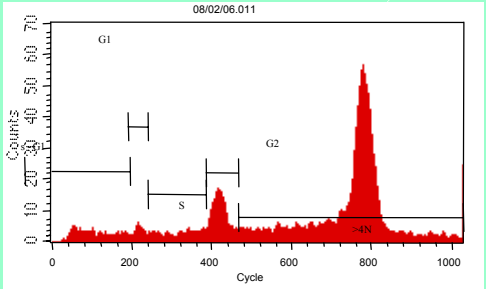
Induction polyploidy in p53-/-HCT116 cells by AZD1152



p53-/- control

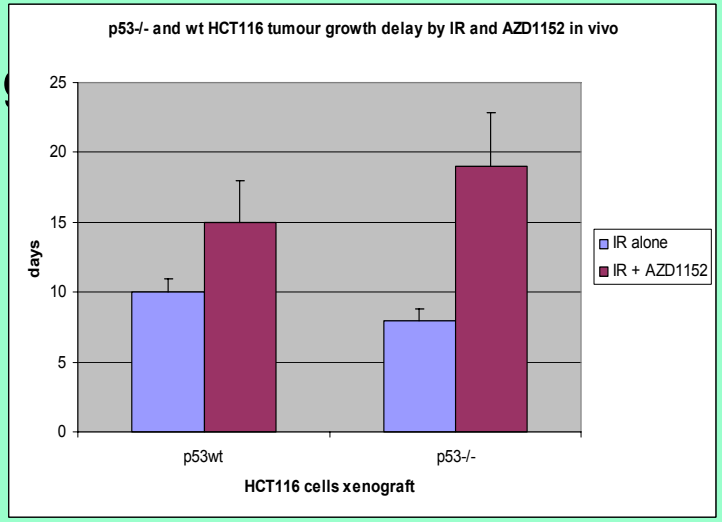


p53-/- AZD1152

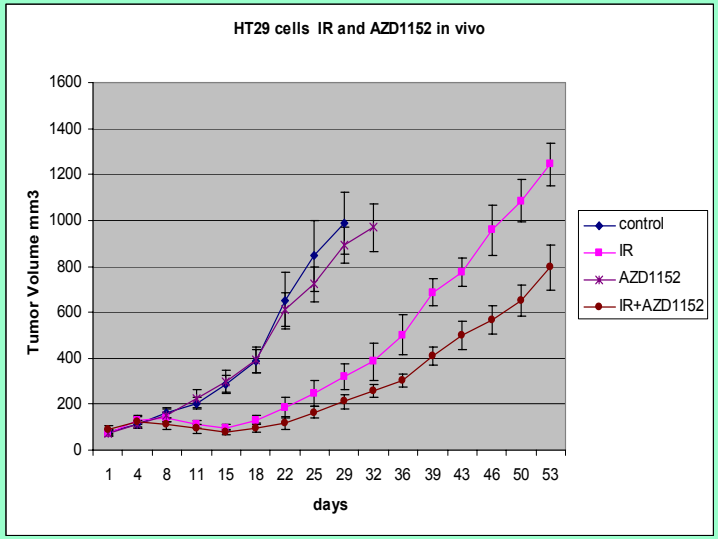


Fi

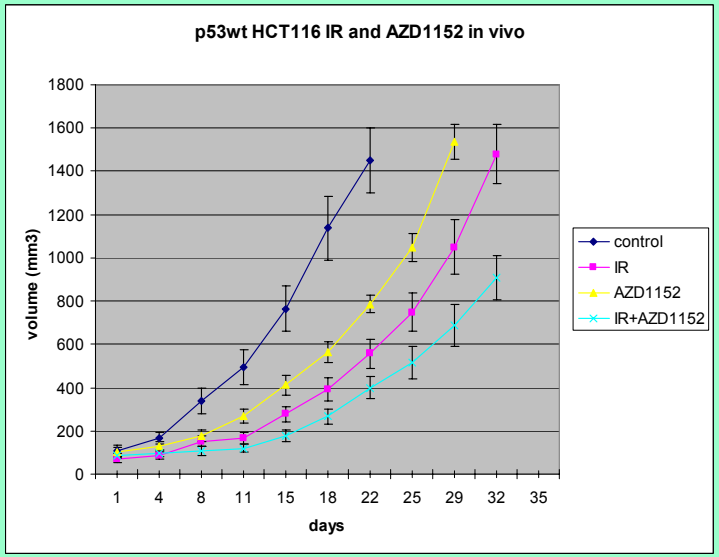
6a



6d



6b



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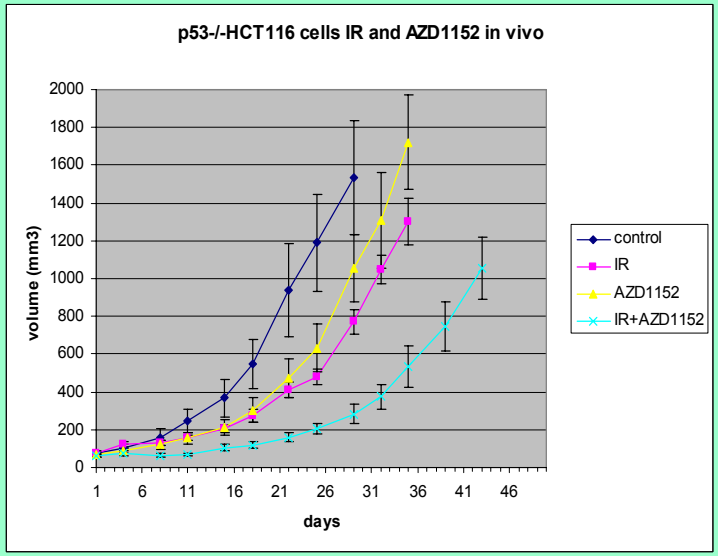
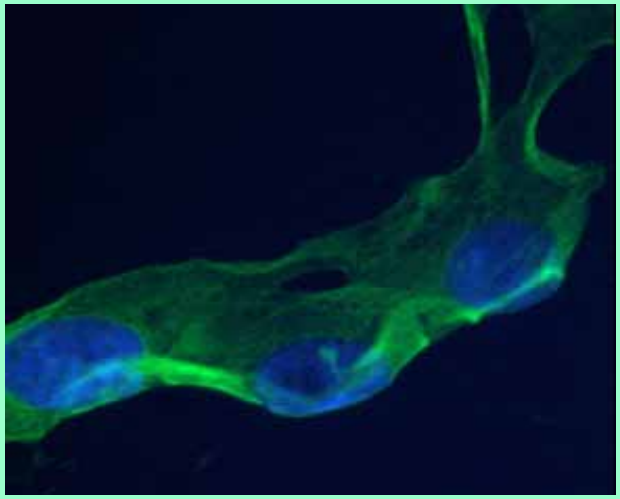


Tao et al BJC 2008,
Tao et al Oncogene 2008

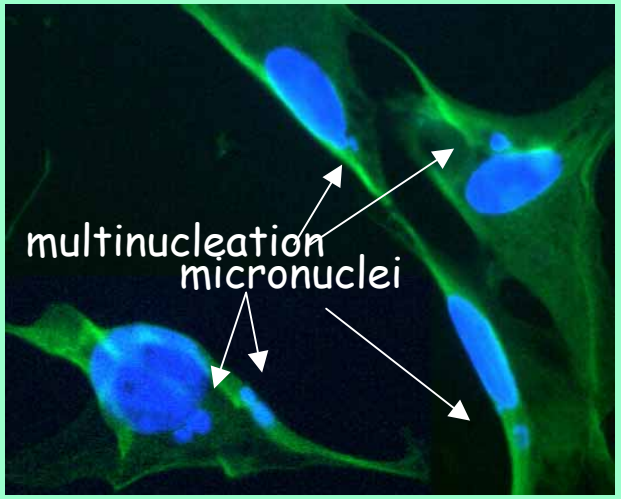
Institut de cancérologie
GUSTAVE ROUSSY
VILLEJUIF - www.igr.fr

Cell death mecanims as targets for radiosensitization
Morphology of mitotic catastrophe (MC)

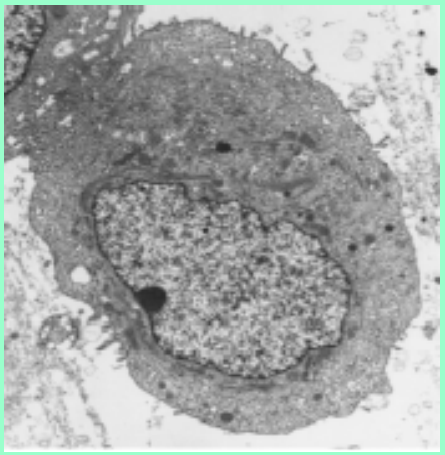
control

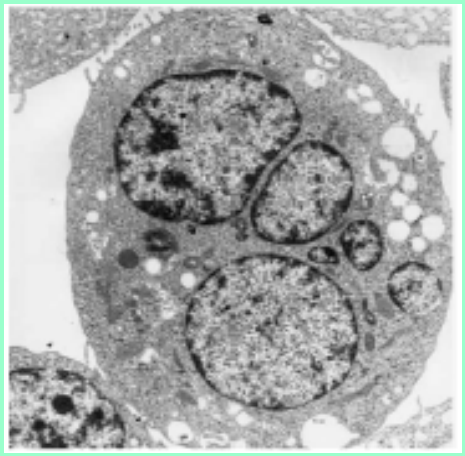


MC



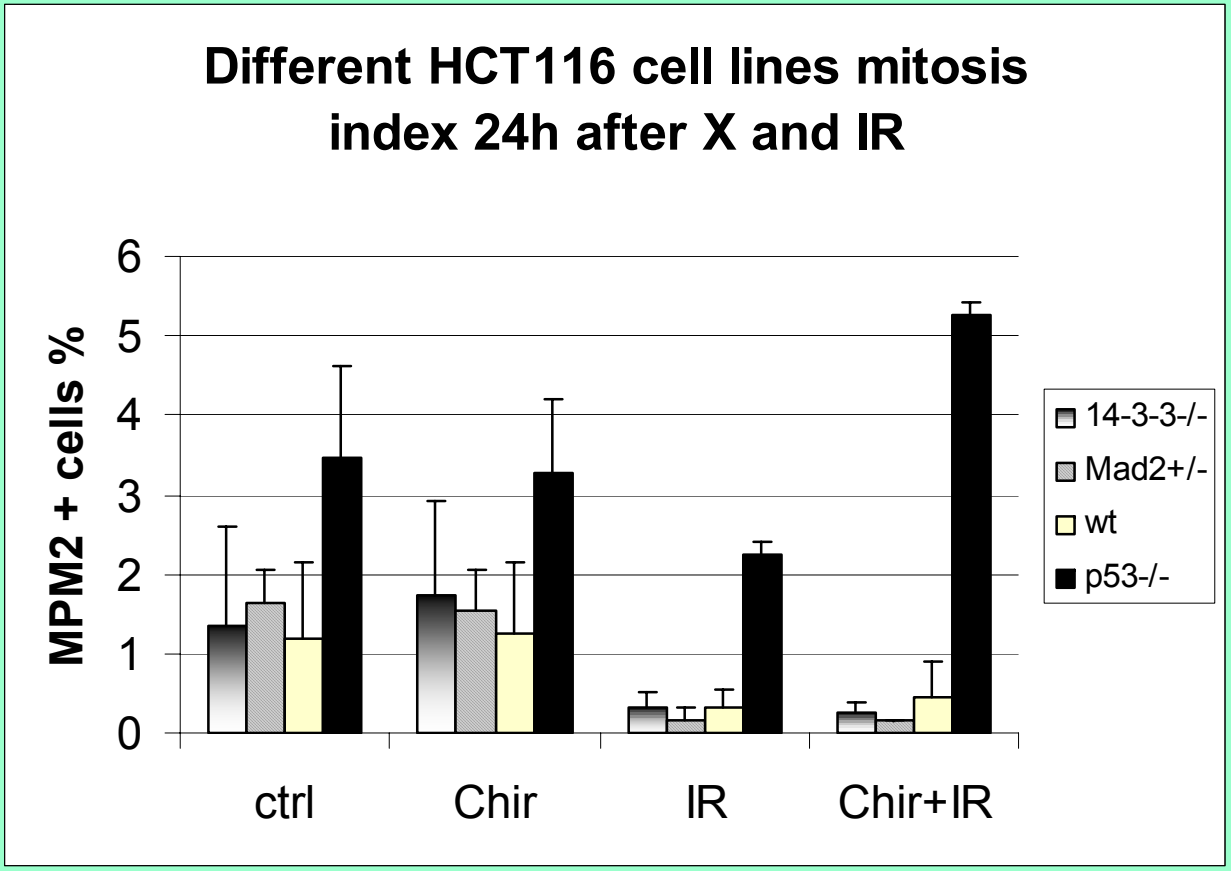
Hoechst/β-tubulin





Morse et al, 2005

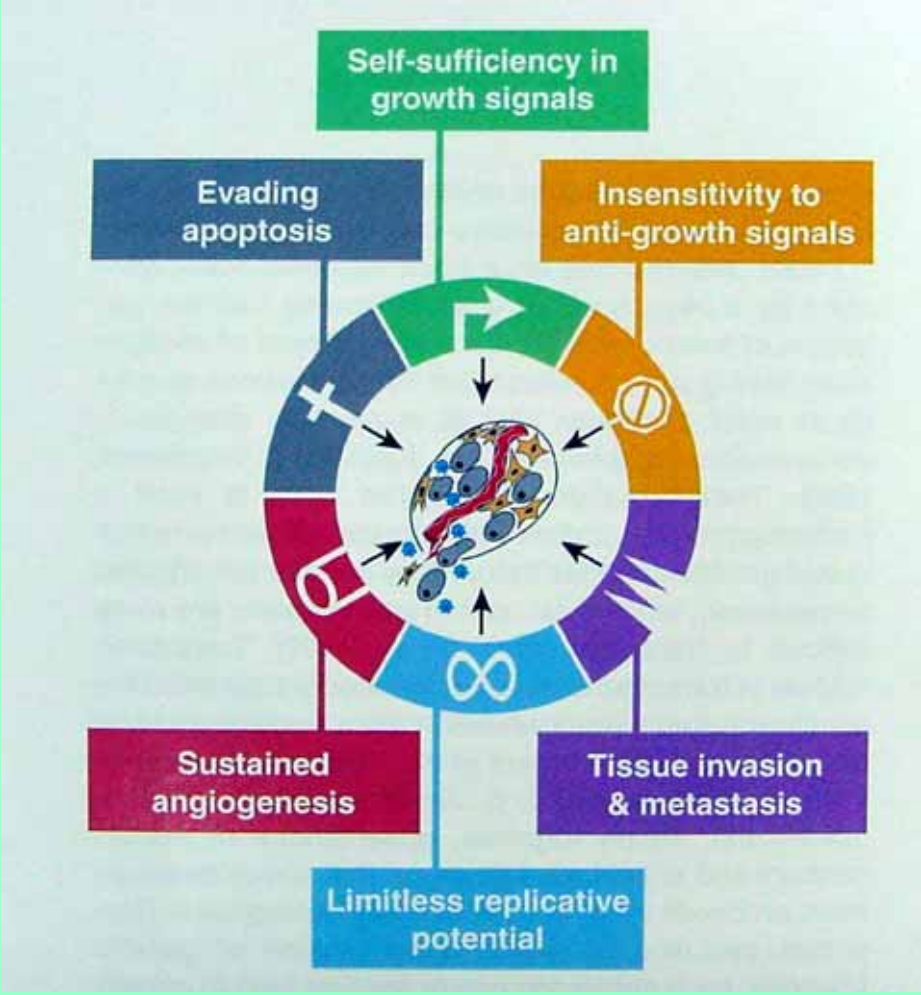
Preferential mitotis entry for P53 deficient cells after irradiation



Genes involved in cancer

- **Oncogenes**
  - Activated from protooncogenes
  - Usually enhance cell proliferation
- **Tumor suppressor genes**
  - Inactivated by mutation or deletion
  - Usually arrest cell proliferation
- **Genes regulating apoptosis**
  - Control cell survival
  - Overexpression,mutation or deletion can enhance cell survival
- **Genes regulating metastasis**
  - Control cell motility and interaction with the environment
  - Both activating and inactivating mutations

Hanahan and Weinberg 2000
The hallmarks of cancer
Cell 100, 57-70.



From the benchmark to the patients…

Drug	Vitro	Vivo	Normal tissue	XRT Phase I	Publication
NS398	+	+	+/-	Ongoing	J Urol 2003
AG1024	+	+	+/-	??	BJC 2003
Omega-3	+	+	+	Abbott	BJC 2003
Tirapazamine	+	+	-	Ongoing Sanofi	BJC, IJROBP <1995
Cidofovir	+	+	-	Ongoing	Oncogene 2003 Lancet Oncol
Ritonavir	+	+	-	??	
Metastat	+	+	-		AACR 2003
Roscovitine	+	+	-	??	Can Res 2003
Aurora B	+	+	?		Oncogene 2007
Statins	+	+	++	Pfizer	IJROBP CCR

Future challenges :
Organ specific drug targeting

Shift

What **might** → What **does** cause cancer

Gène	Cancer	Drogue
Brca1	Sein	
K-RAS PIKCA APC	Colon	FTI PI3K inhibitors
p53	Li Fraumeni	
PTEN	Colon/Poumon	Akt inhibitors
C-Kit	GIST	Gllevec, Sutent, Sorafenib
RB	Retinoblastome	
Bcr-Abl FLT-3 PML-RAR	LMC LAM LAM	Gleevec, Dasatinib CEP701
B-RAF	Mélanome	Sorafenib, Chiron 265
RET	Thyroïde	AZD compounds
JAK	Polyglogulies	AZD compounds

« oncogene addiction »

Table 1. Oncogene addiction: studies in mice, studies in human cancer cell lines, and clinical evidence

Studies in mice*

Targeted oncogene	Cancer type
c-myc	T cell and acute myeloid Leukemia
Bcr-Abl	Leukemia
H-ras	Melanoma
K-ras	Lung
c-myc	Pancreatic β-cell
c-myc	Osteogenic sarcoma
Her-2/neu	Breast
c-myc	Breast
Wnt-1	Breast

Studies in human cancer cell lines†

Targeted oncogene	Cancer cell line
Her-2	Breast
Cyclin D1	Esophagus, colon, pancreatic, squamous, nasopharyngeal
K-ras^{mut}	Pancreatic
K-rasv^{12}	Pancreatic
β-Catenin	Colon
Cyclin E	Liver
Mutant β-Raf	Melanoma
MITF	Melanoma

Clinical evidence

Targeted oncogene (s)	Disease	Agent ‡
HER-2	Breast§,‖	Trastuzumab (combination)
BCR/ABL	Chronic myeloid leukemia§	Imatinib (monotherapy)
C-KIT	Gastrointestinal stromal tumor§	Imatinib (monotherapy)
EGFR	NSCLC§	Gefitinib, erlotinib§ (monotherapy)
EGFR	Head and neck, colorectal§	Cetuximab (combination)
EGFR	Pancreas§	Erlotinib (combination)
VEGF	Breast, colorectal§,‖, kidney	Bevacizumab (combination)
VEGFR, RAF	Kidney§	Sorafenib (monotherapy)

NOTE: For specific references and further details, see ref. 6.
*Switching off the indicated oncogene led to growth inhibition, differentiation, apoptosis and/or tumor regression.
†Treatment of these cell lines with an antisense oligonucleotide or a RNAi directed to the respective oncogene caused growth inhibition, and in some cases, decreased tumorigenicity and increased chemosensitivity.
‡Treatment regimen indicates agent alone (monotherapy) or in combination with cytotoxic agents (combination).
§Food and Drug Administration–approved.
‖Phase III evidence shows improved disease-free or overall survival rates.

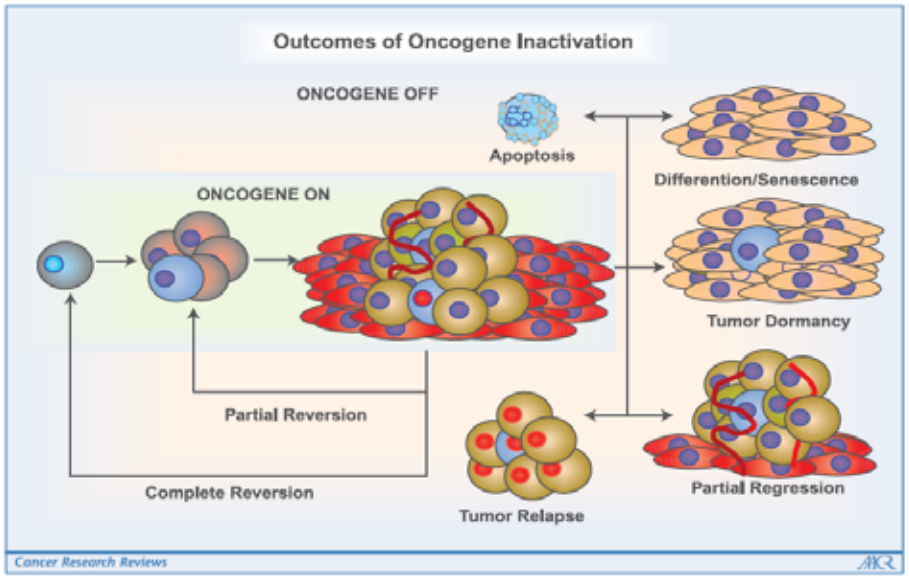
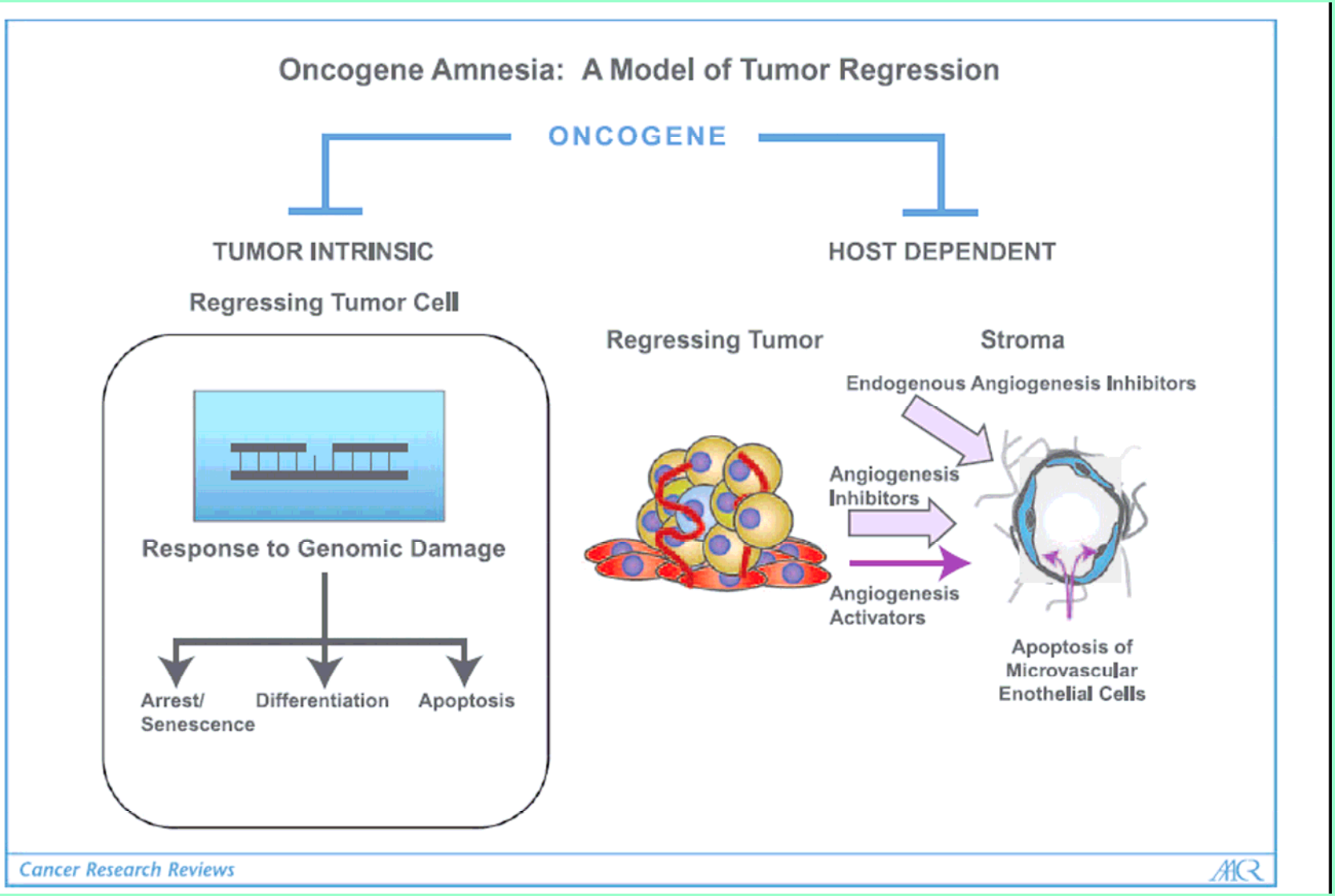


Figure 1. Many possible outcomes to oncogene inactivation: no effect, complete, or partial tumor reversion. Tumor death, dormancy, differentiation, or relapse.



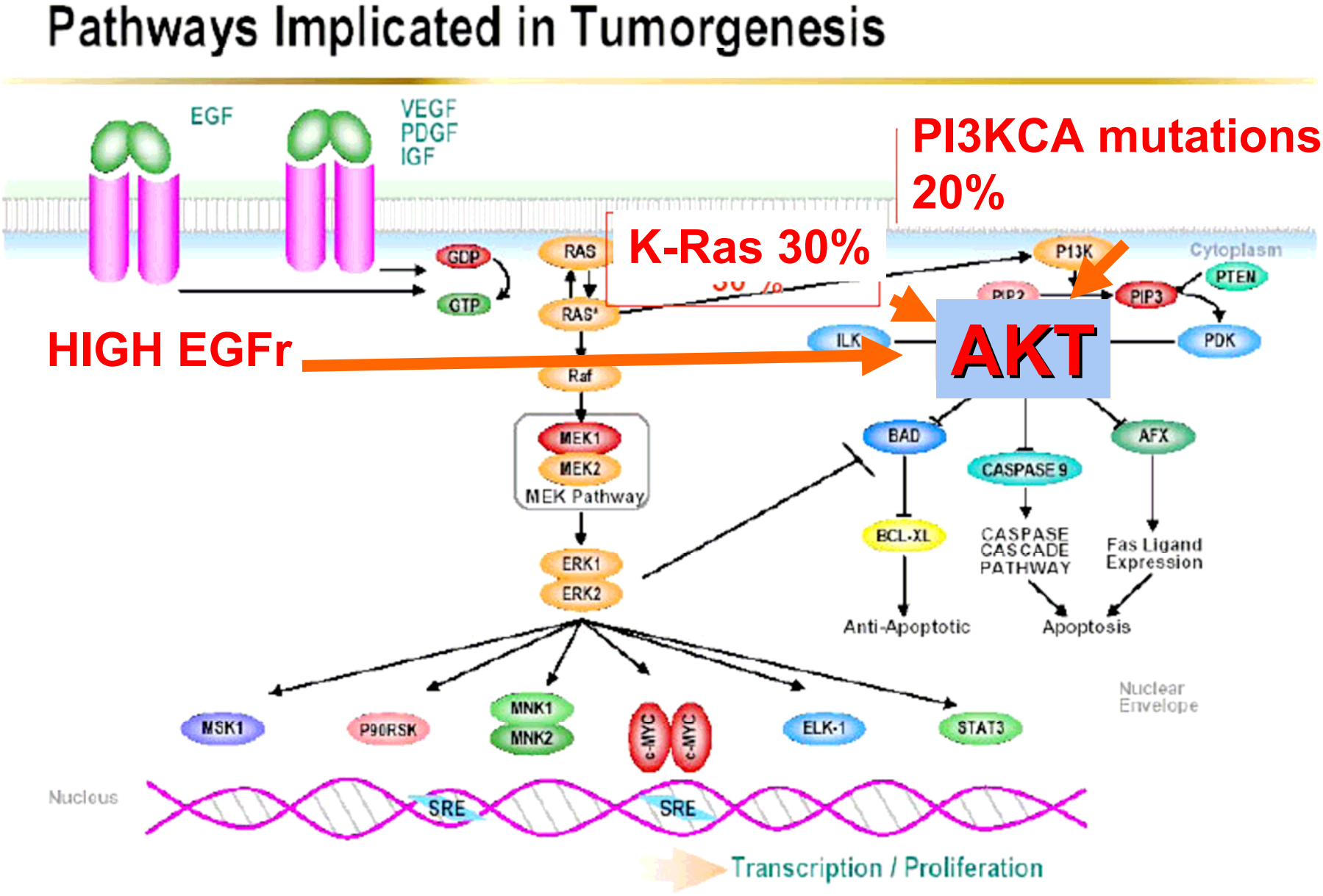
Weinstein Can Res 08

Molecular pathology into radiation practice ?

TNM « ultra staging »

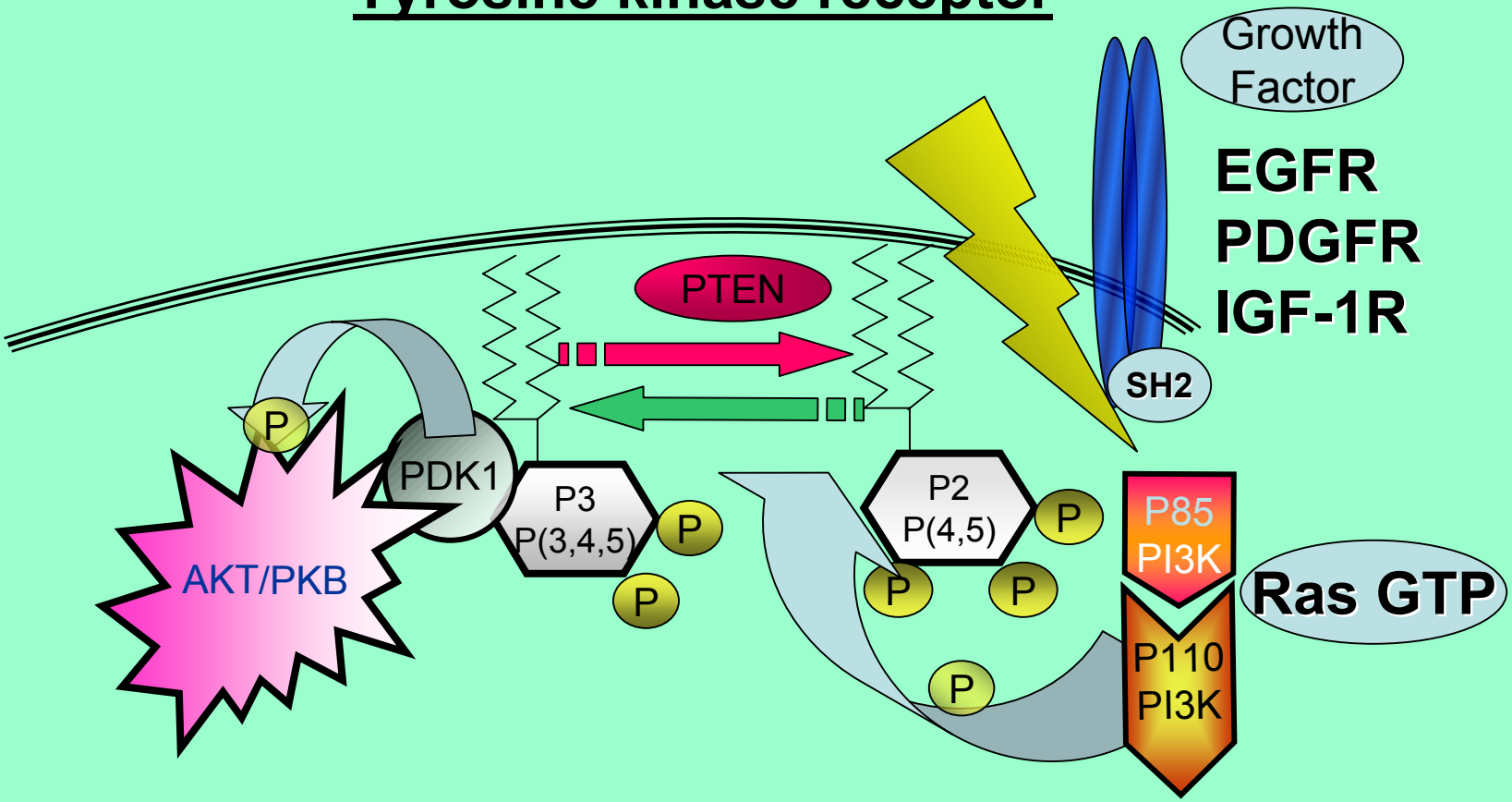
- -GI tumors
- -Cervical cancer
- -Lung tumors

Targeted therapies for RECTUM PRE OP RT?

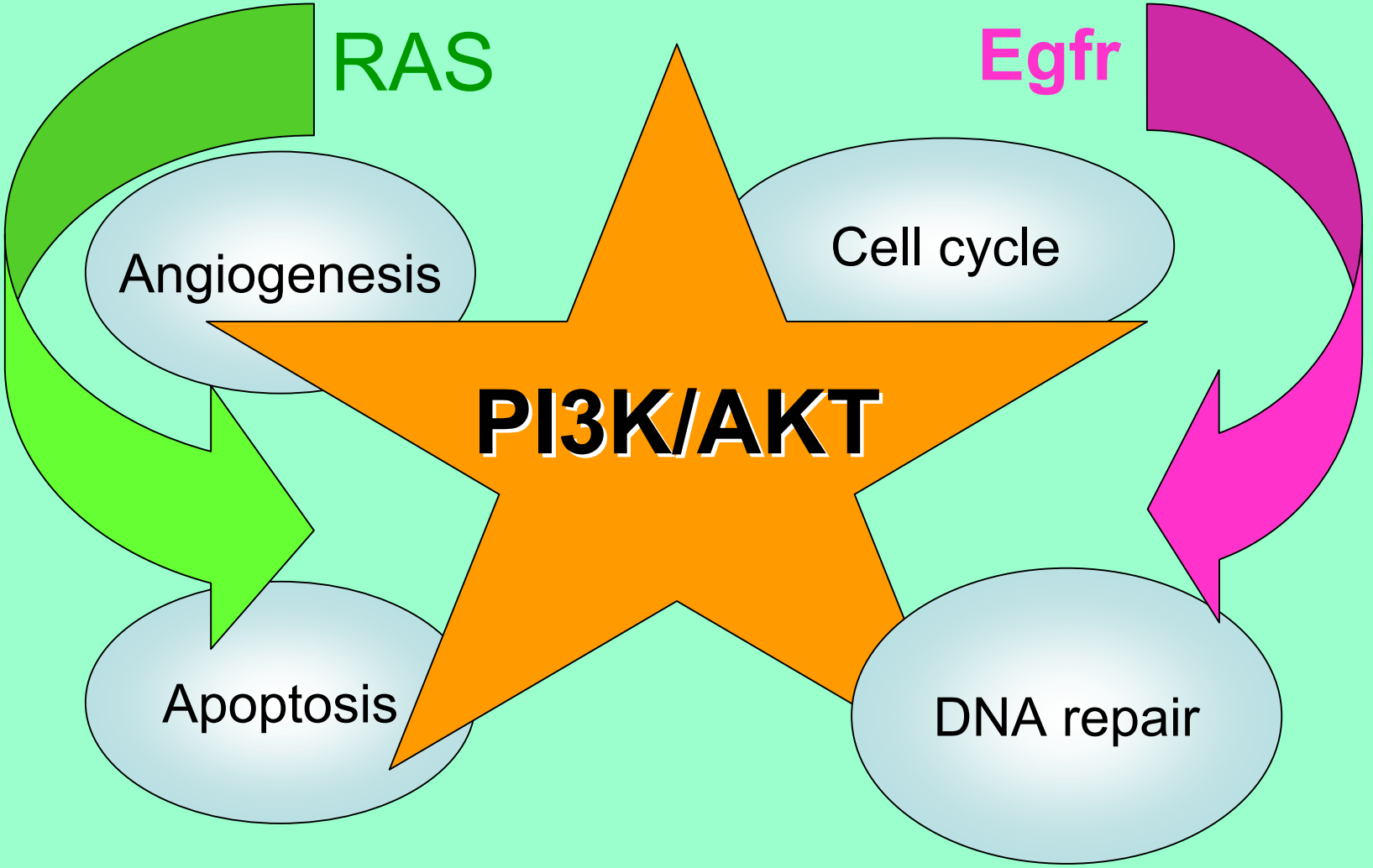


PI3K AKT the main pathway for radiation response

Tyrosine kinase receptor



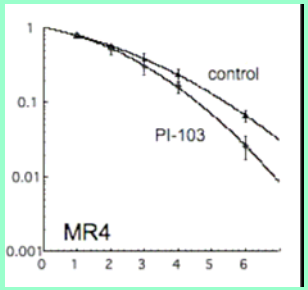
AKT the main *AKTor*

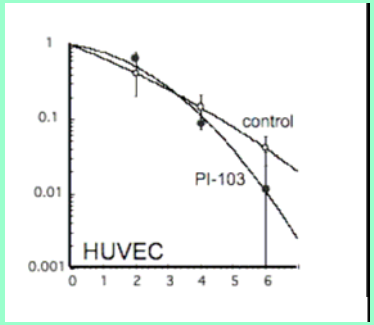


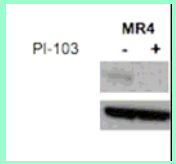
The PI3K and mTOR inhibitor selectively sensizites « addicted tumor cells »

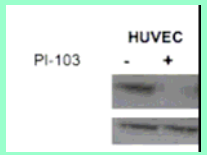
Non tumor cells no/low PI3K activation

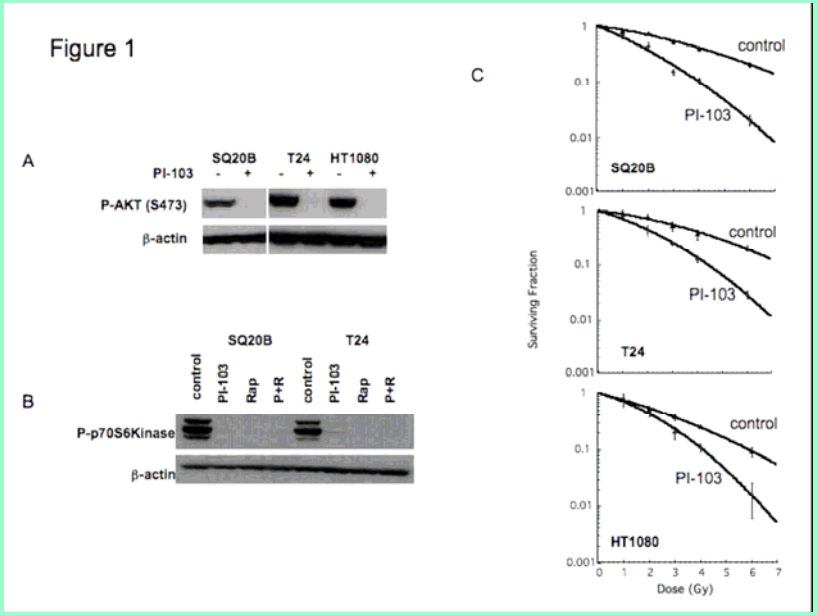
Tumor cells with PI3K activation











Cancer Res in press

Virus related cancers

(15% of cancers wordwide and 7% in western countries)…

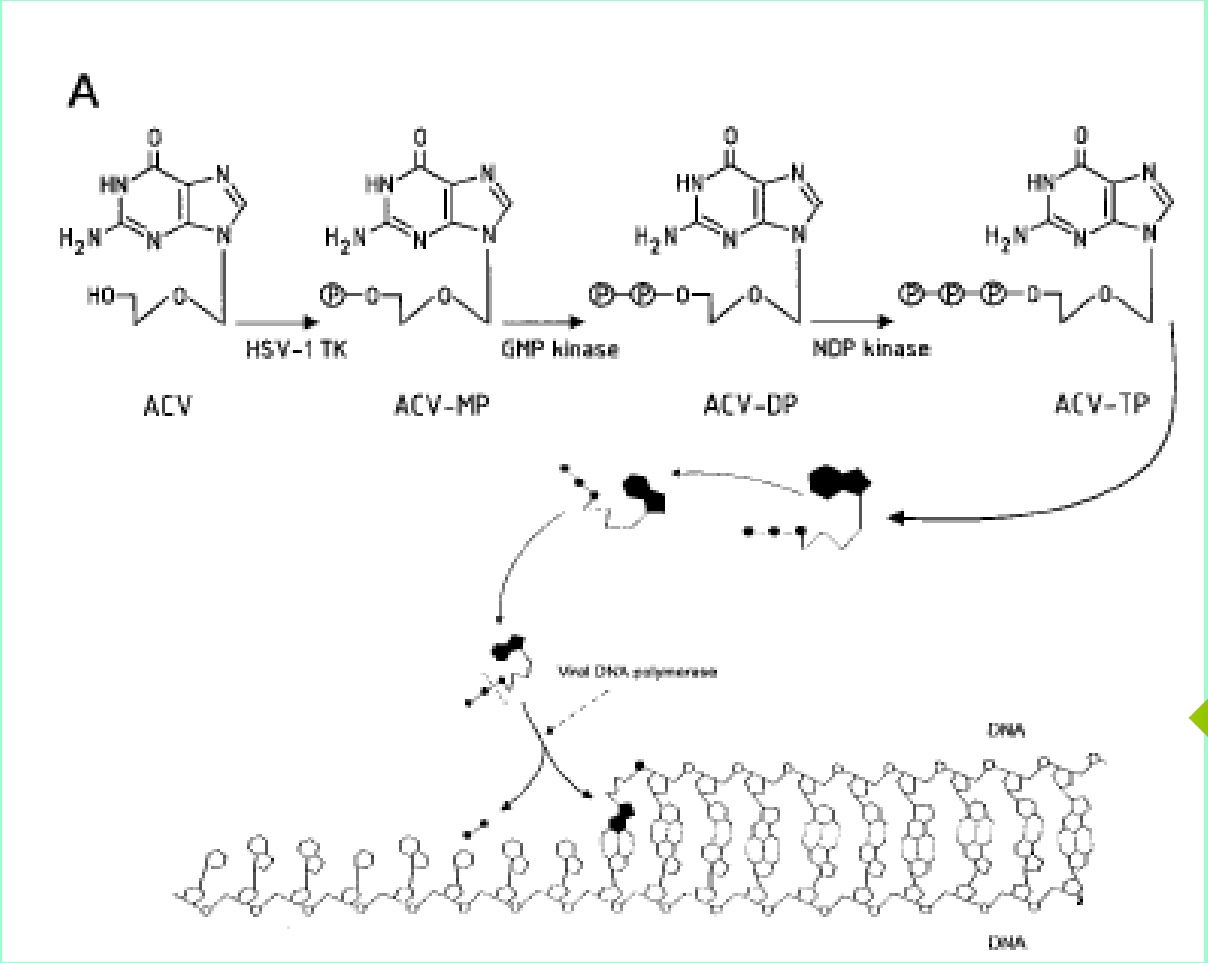
- Epstein-Barr virus (EBV) : Lymphoma, Nasopharynx…
- Human papilloma virus (HPV) : Carcinoma of the cervix, HNSCC, anal cancer

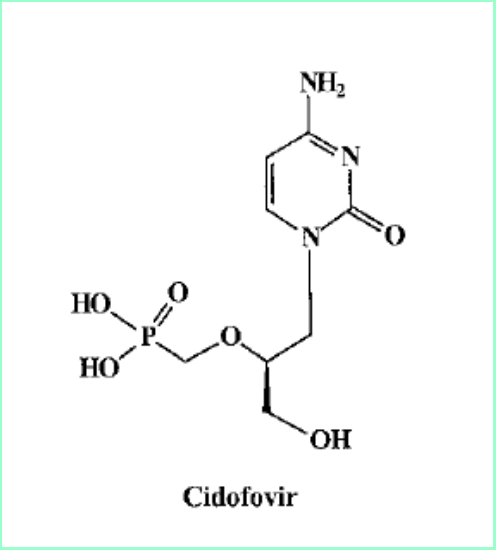
Uterine cervix carcinoma : HPV 16 & 18 …

➔ 500 000 cases / year (3.700 in France)

Cidofovir (HPMPC)

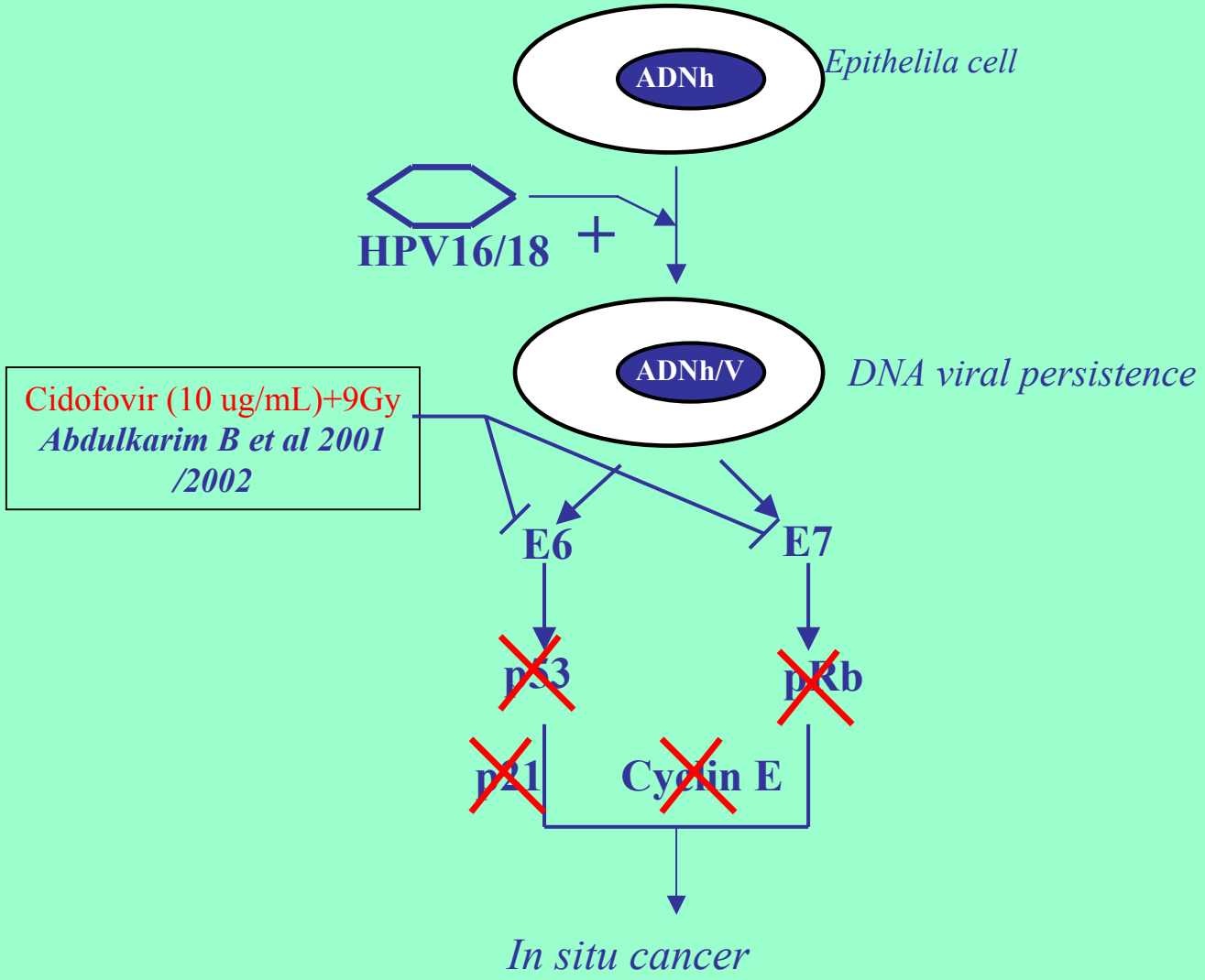
- (*S*)-9-(3-hydroxy-2-phosphonylmethoxypropyl)Cytosine: [(*S*)-HPMPC]
- Phosphonates nucléoside acyclique
- Demi-vie de la drogue *in vivo* : 48 h





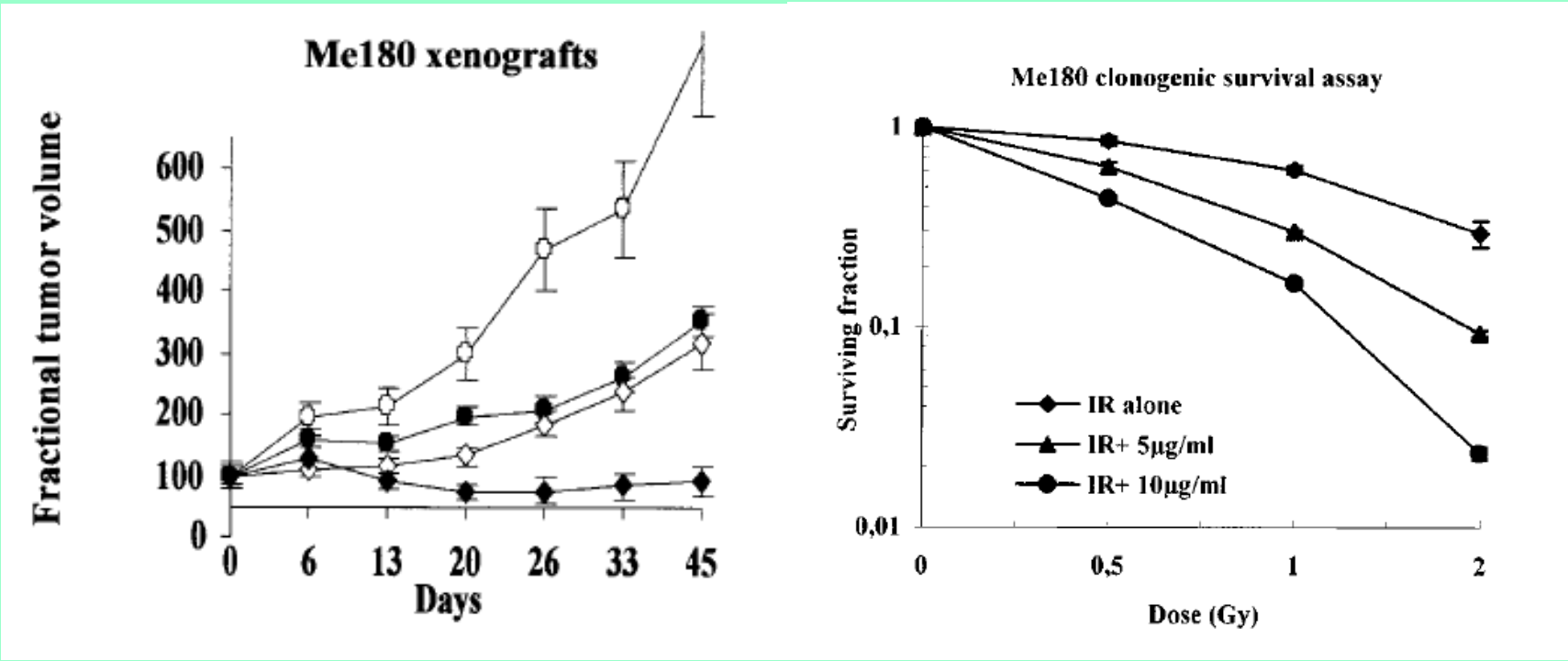
Mécanisme d'action du Cidofovir

Cervical cancer



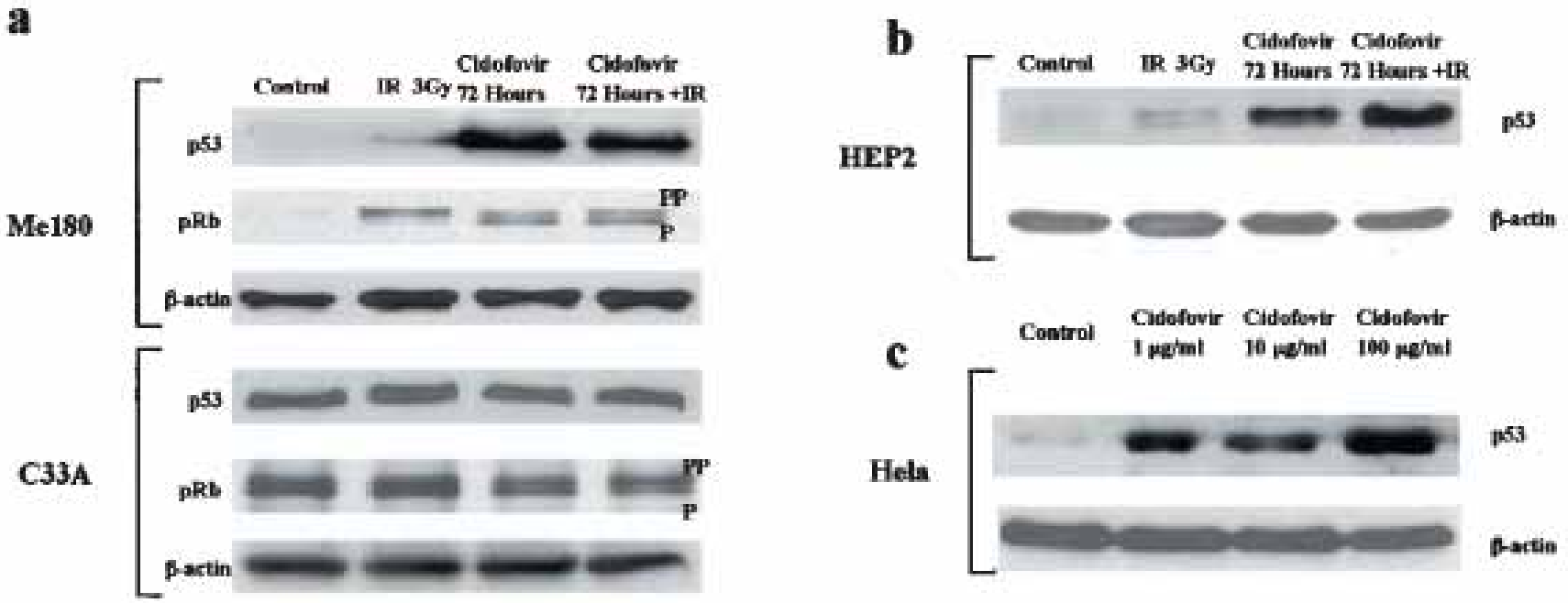
(Abdulkarim et al 2001 oncogene)

HPC positive : Me180 cell line



Abdulkarim et al. Oncogene, 2002

HPV postivie tumors : restoration of p53 and pRB



Oncogenes alterated in lung cancer :

NSCLC vs SCLC

RAS
C-Myc
EGFR
HER2/neu
IGF1

C-myc
Myb
IGF-1
BCL2

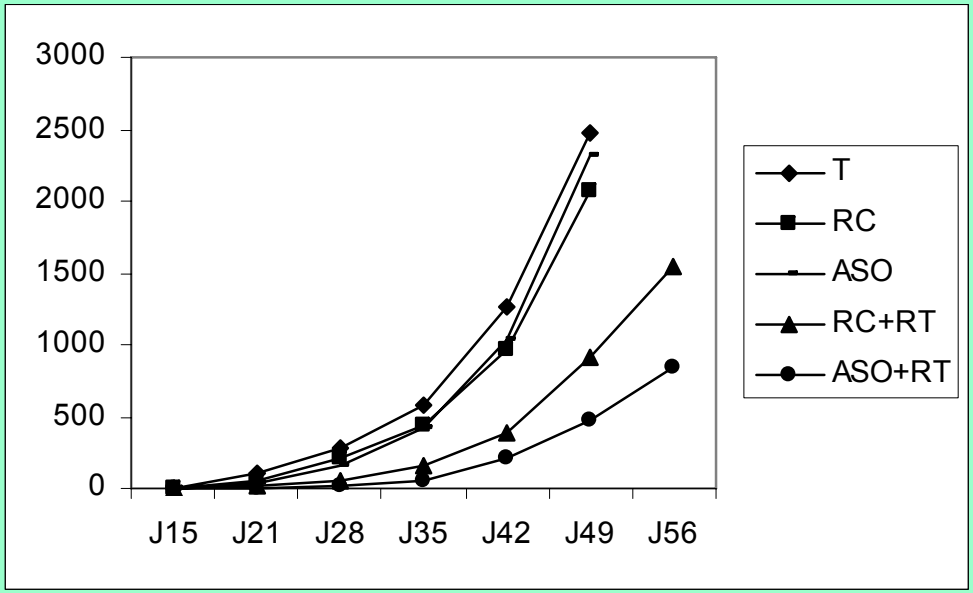
Lung cancer :

BCL2 inhibition :

NSCLC :

No moderate/zero effect

SCLC

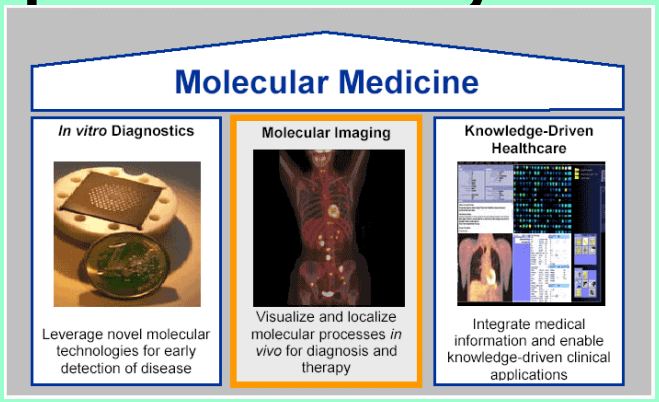


Increase in radiation response in SCLC

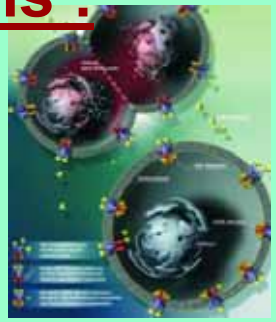
Loriot et al NCI EORTC 2007

Looking toward the future..

Personalised medicine : Challenges rely on tumor response probability



Poor prognosis :

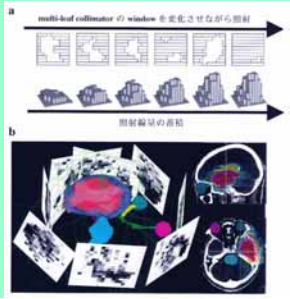


Radiation sensitizer

Tumor « response » profile

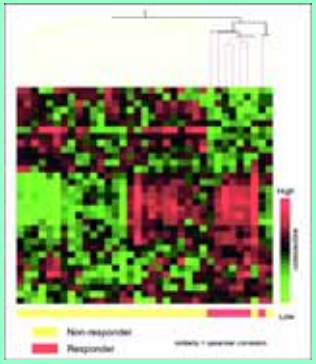
Optimise radiotherapy

Decrease late effects

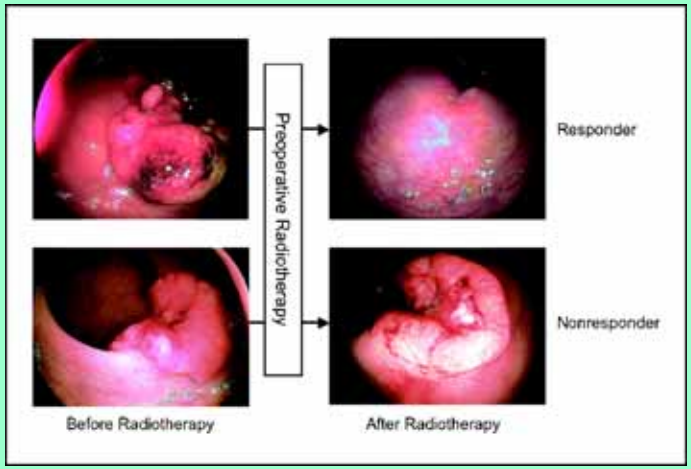


Toward molecular profiling?

- Preoperative Radiotherapy in rectal cancer



responders

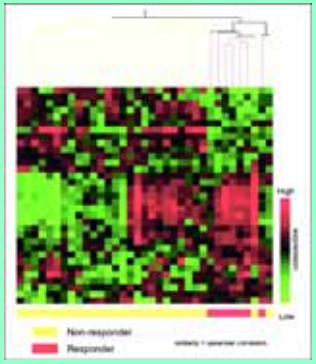


non responders

Watanade Can Res 2006

Toward molecular profiling?

- Preoperative Radiotherapy in rectal cancer



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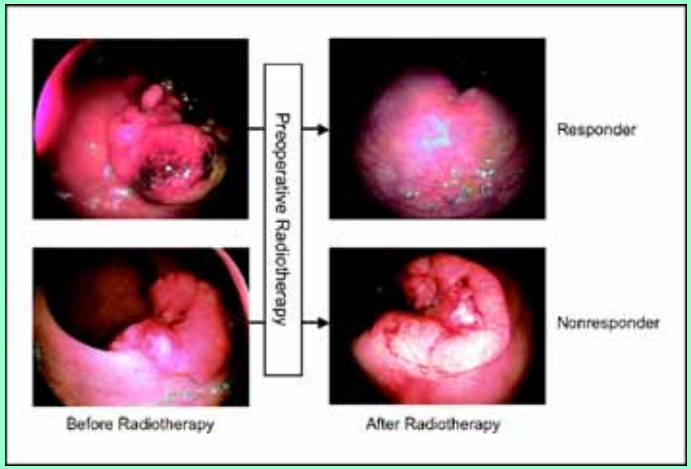
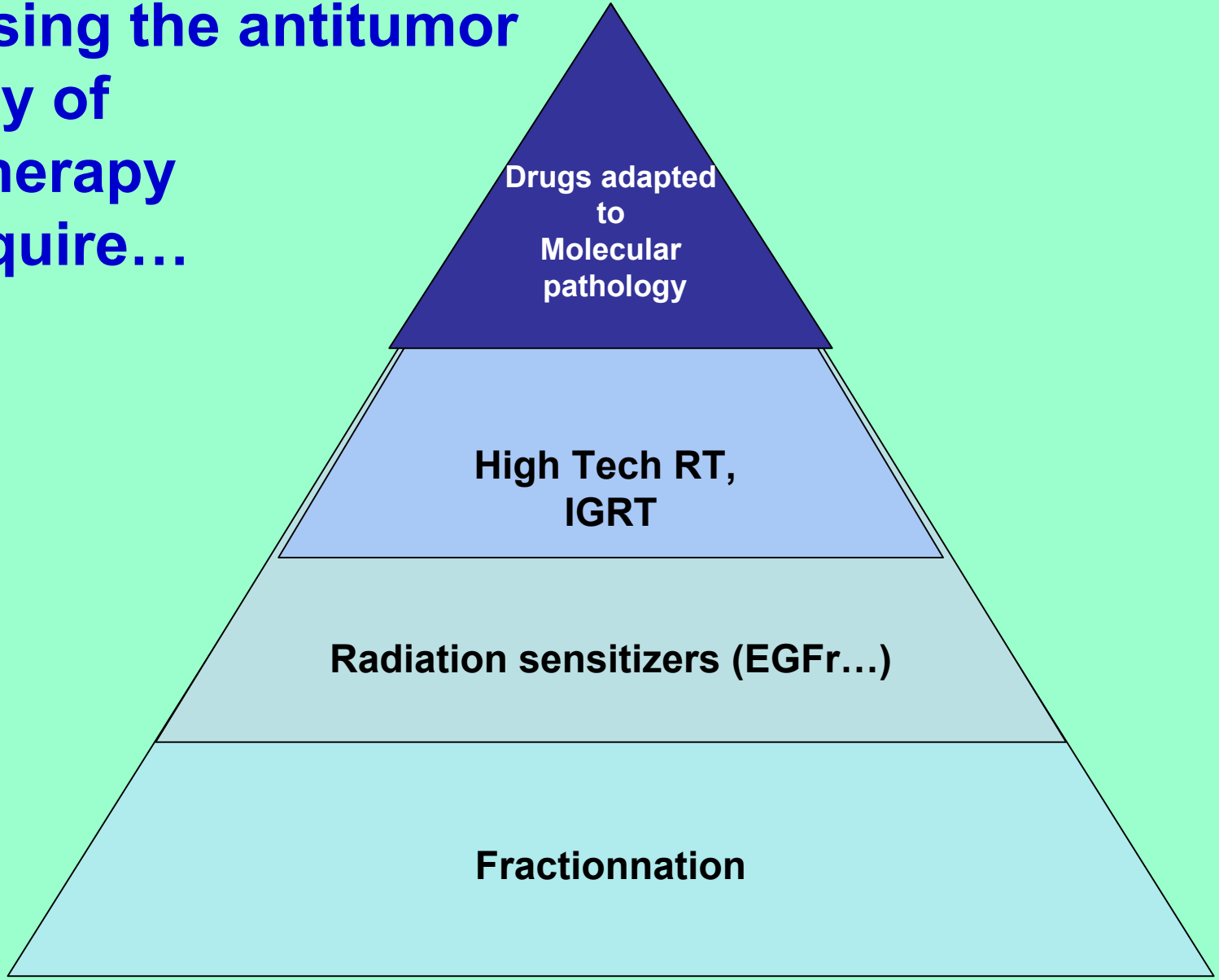


non responders

Watanade Can Res 2006

Increasing the antitumor efficacy of radiotherapy will require…



..integration of all aspects of radiation biology