

Anti-EGFr compounds and radiation in the clinic

- Brescia 2007 -

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Combining RT with molecular target agents

- **Radiotherapy** = now well equipped (high precision RT, IGRT ...)
- **None of the next step forward** = integrating the potential of new molecular targeted drugs in combination with RT

Molecular targeted therapies

- The term "**targeted therapies**" refers to treatment strategies directed against molecular targets considered to be involved in the process of neoplastic transformation
- **This is not a new concept** in oncology; hormonal manipulation

Targeted therapies: which target ?

- **Causal mutation** (eg: bcr-abl, mutated activated KIT)
 - Early
 - Constant
- **« Late »** molecular alterations
(eg: HER2 amplification, EGFr overexpression)
 - Occuring late (?) in the oncogenic process
 - Inconstant
 - Prognostic
- **« Bystander » target** (eg: PDGFR, HER1 expression)
 - Role in transformation?

Targeting EGFr : rational

- EGFr : expressed at high level in several human cancers

ex : in > 90% of HNSCC cases

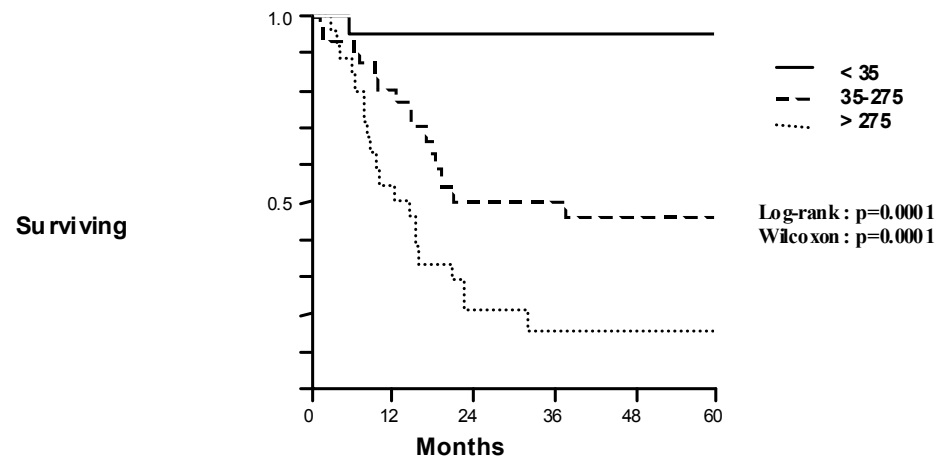
Lung, rectal, cervical carcinomas etc...

- Is the expression of EGFr a marker of poor prognosis ?

Prognostic value of EGFr : quantitative evaluation

: assay using 125 labeled EGFr : fmol of bound EGF / mg of membrane protein

Figure 1 Overall survival curves according to the 3 sub-groups of EGFR tumoral levels

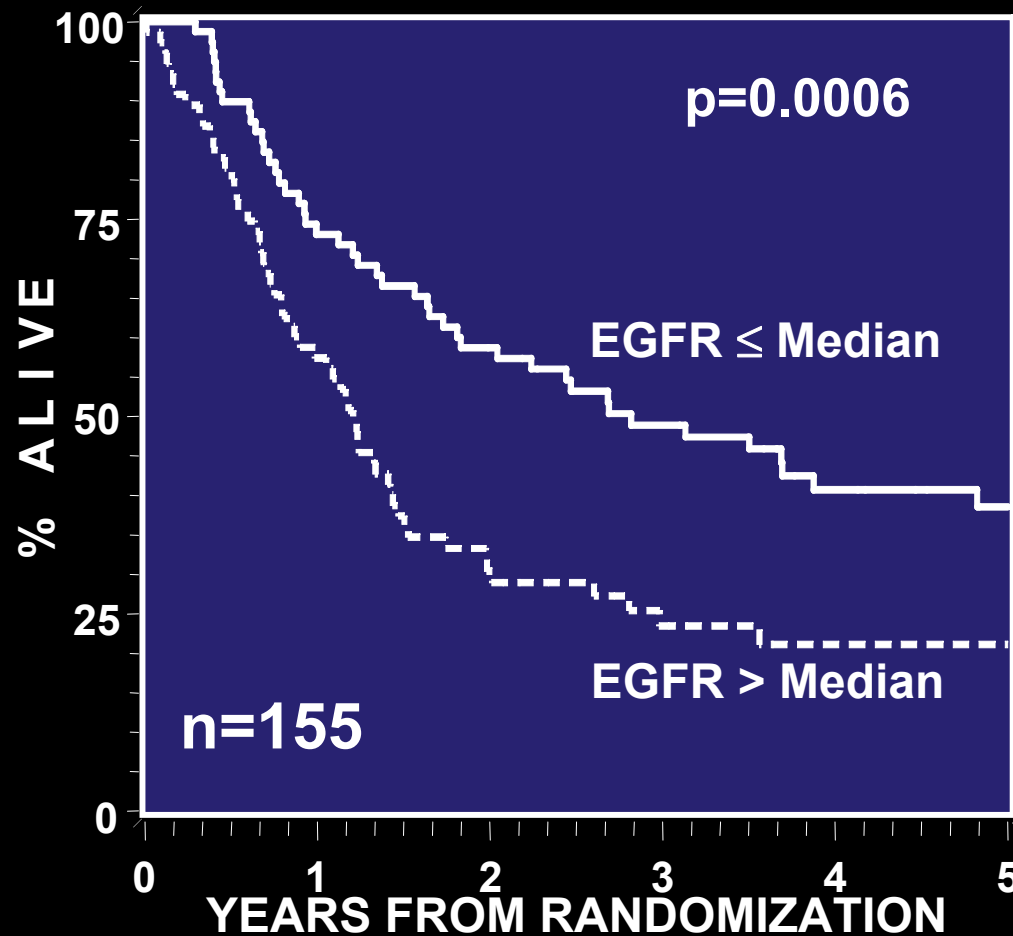


Time in months		0	12	24	36	48
EGFR < 35	N	20	19	19	19	19
	Censored	0	2	4	3	3
35 < EGFR < 275						
	N	37	27	19	18	17
	Censored	0	3	4	1	5
EGFR > 275	N	20	13	6	3	2
	Censored	0	1	0	1	1

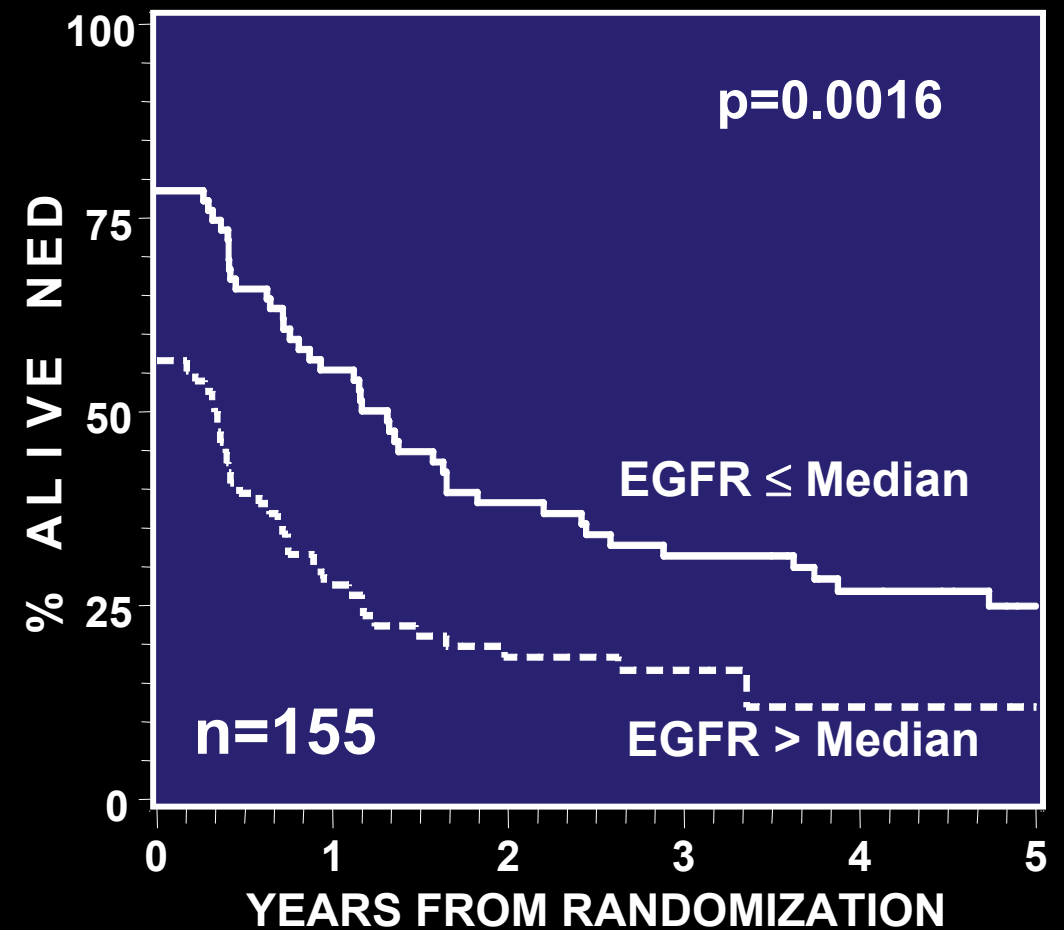
(N = 92 HNSCC, *Milano et al*)

EGFR Expression (IHC) vs survival *(K. Ang et al)*

Overall Survival

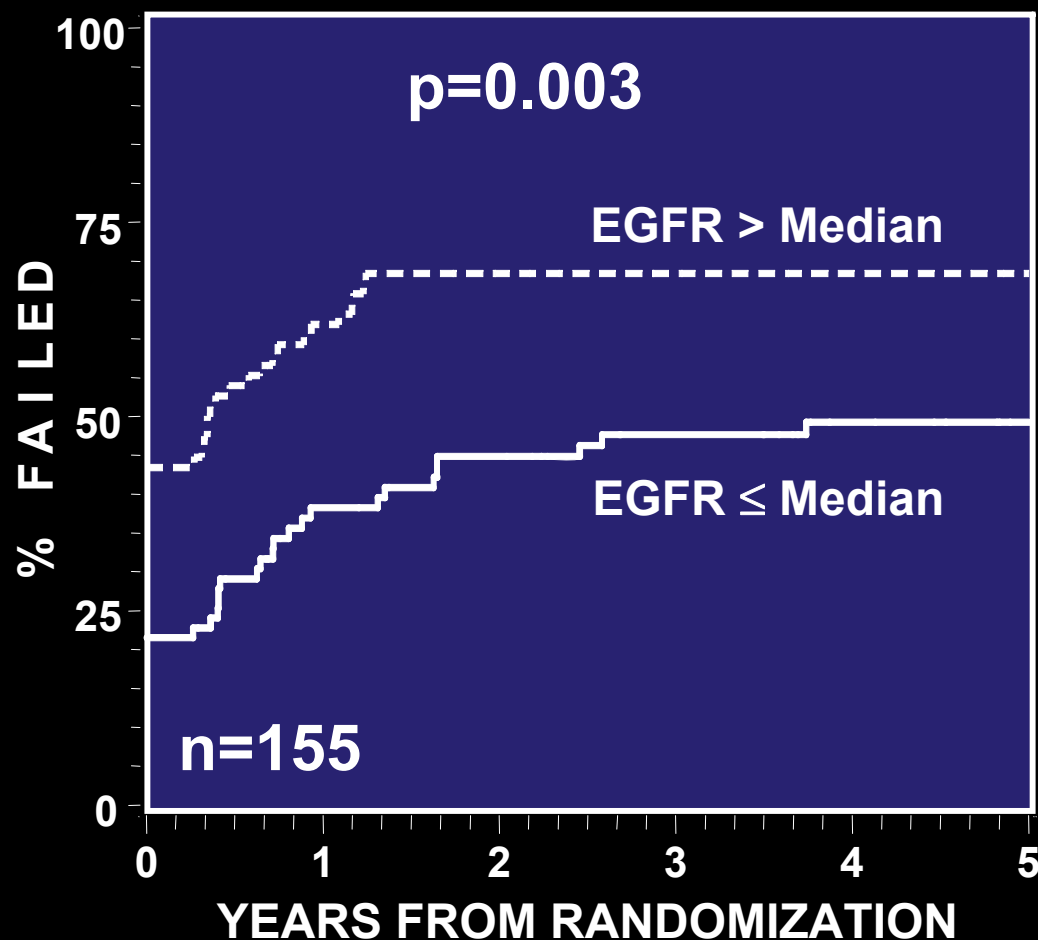


Disease-Free Survival

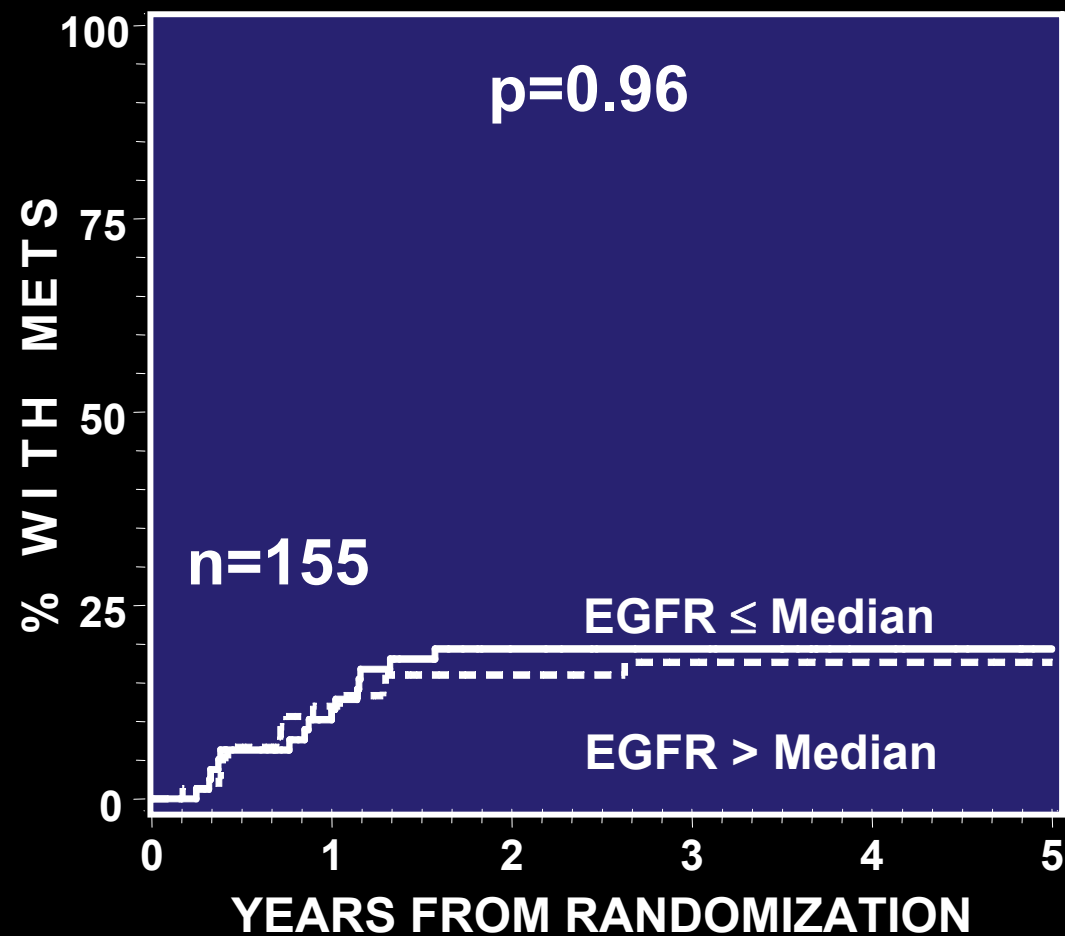


EGFR expression : pattern of failure

Local-Regional Relapse

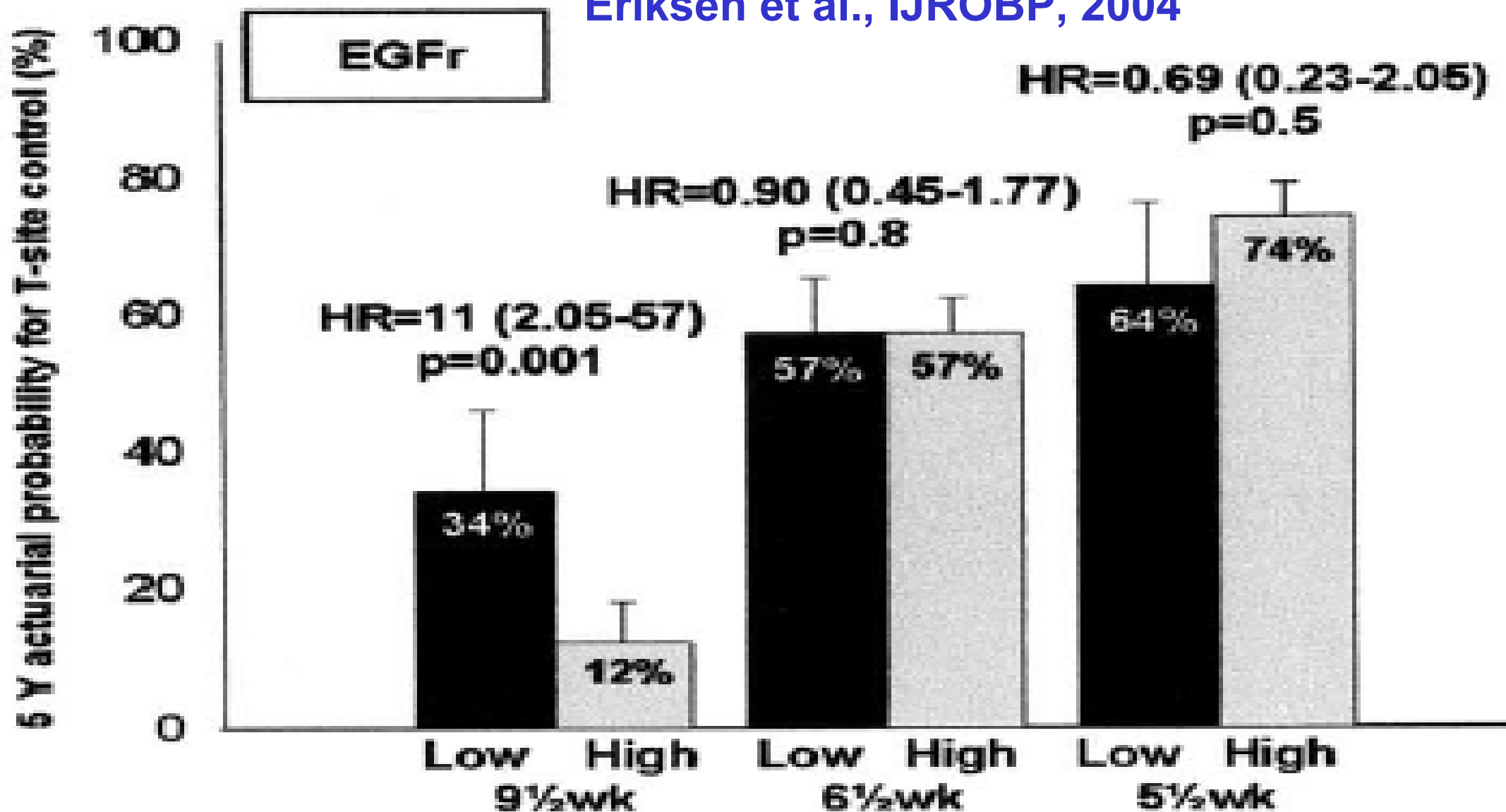


Distant Metastasis



Impact of EGFr expression / overall time of RT (HNSCC)

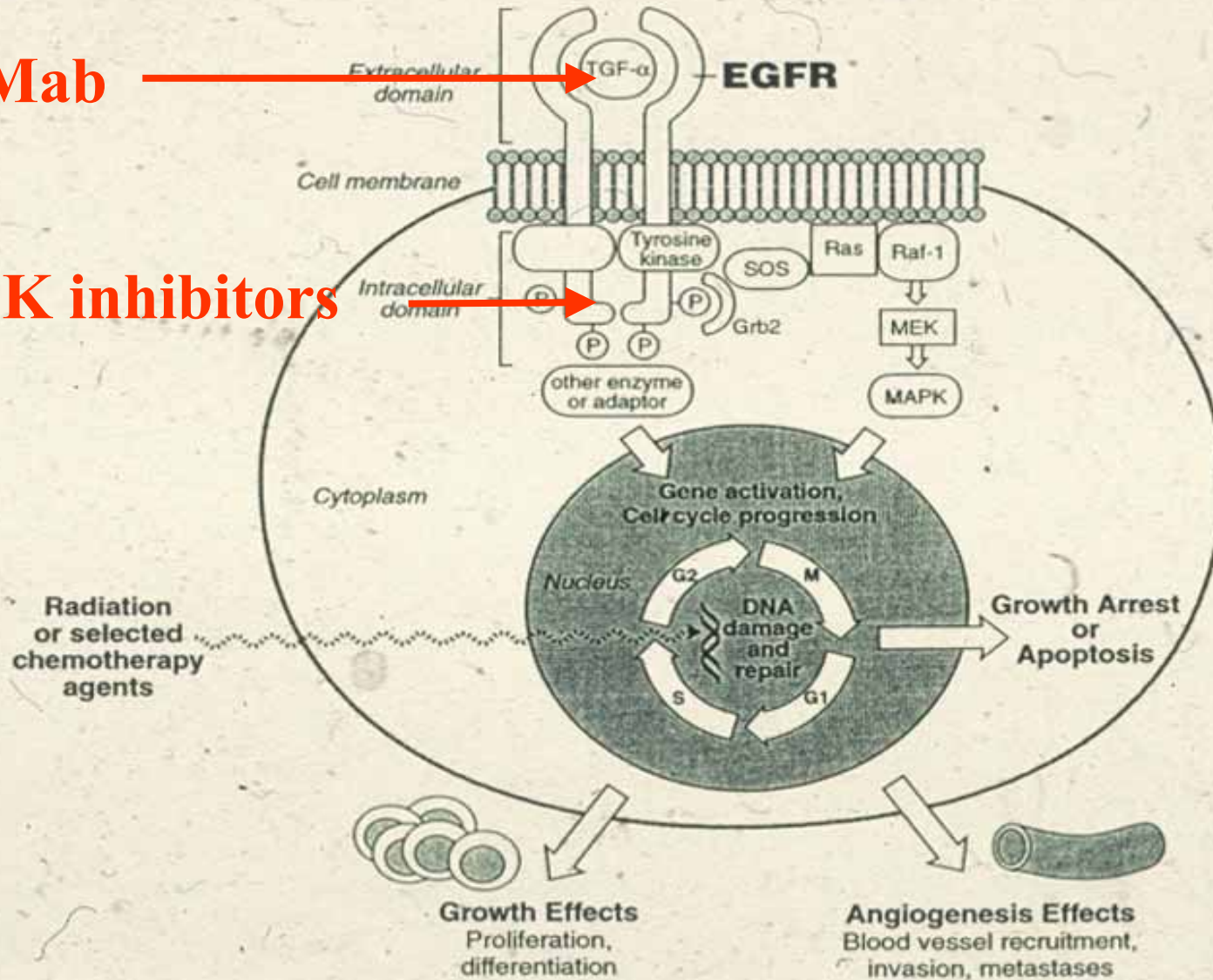
Eriksen et al., IJROBP, 2004



What are the tools for targeting EGFR ?

Mab

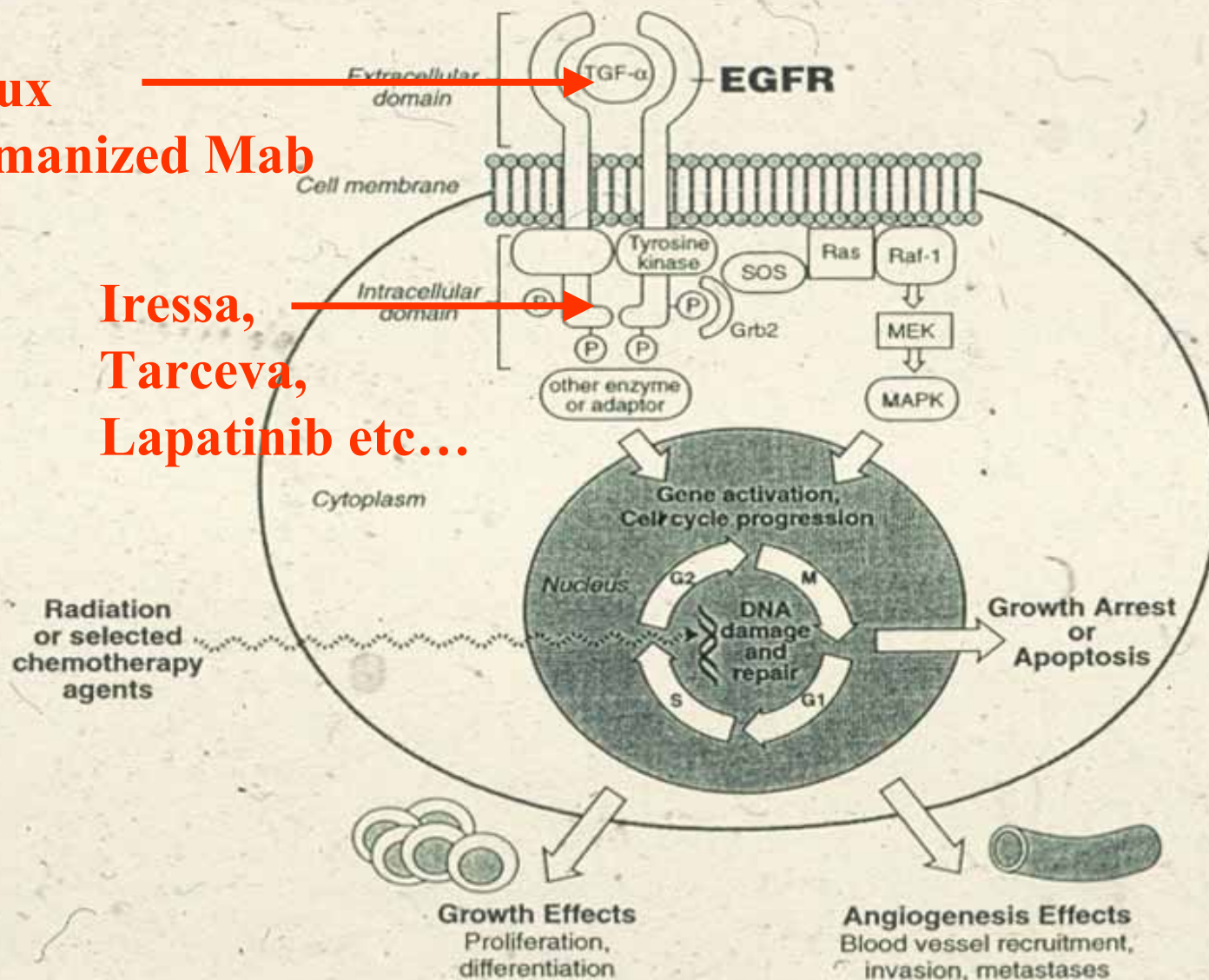
TK inhibitors



What are the tools for targeting EGFr ?

**Erbix
& humanized Mab**

**Iressa,
Tarceva,
Lapatinib etc...**



Targeting EGFr has some clinical activity ?

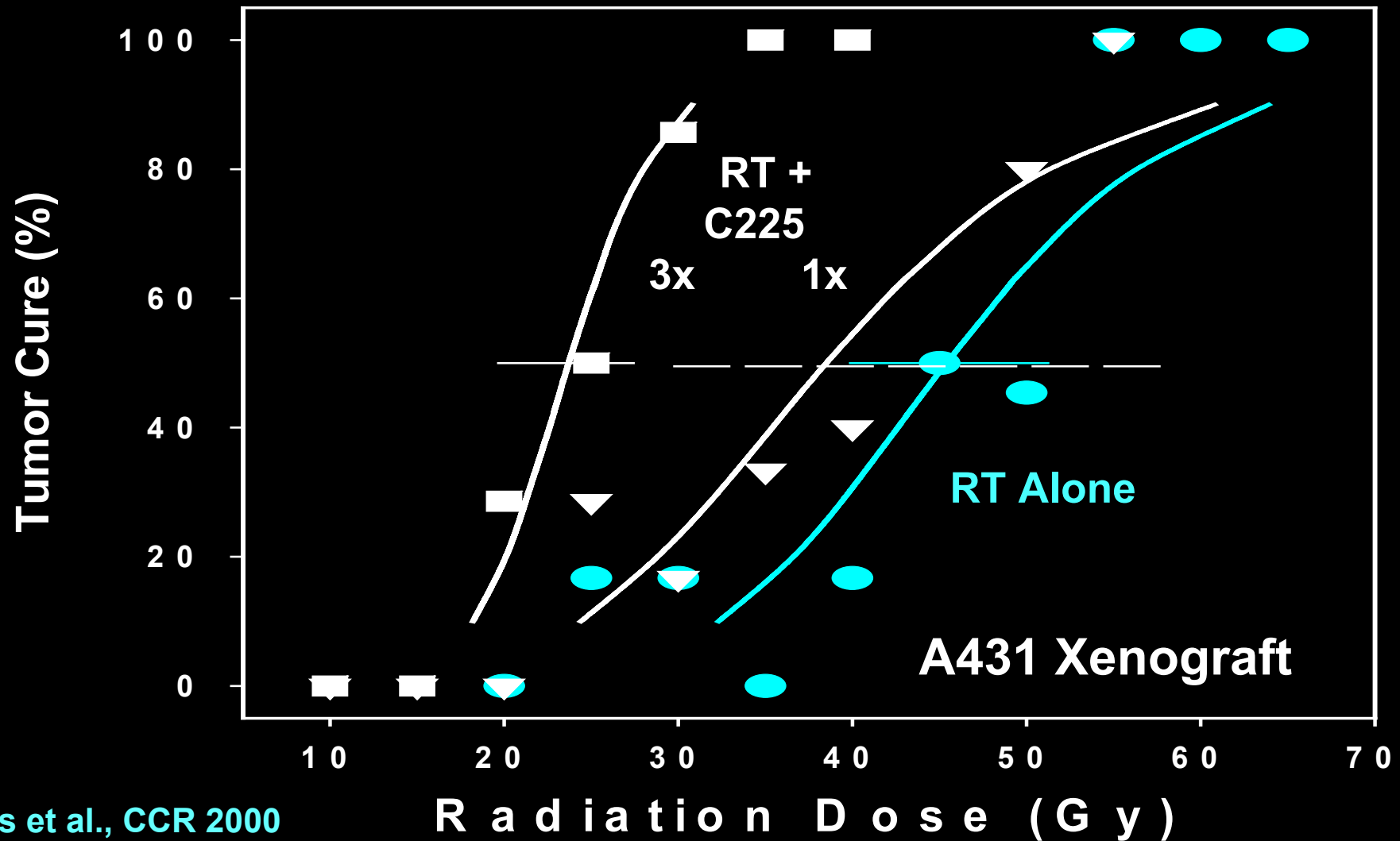
example : in refractory HNC

- **Erbix in Recurrent / Metastatic HNSCC, with documented progression under CDDP based CT (*Baselga, 96 patients JCO 2005*)**
- **10% response rate**
- **Strong suggestion of improved survival : 6.1 months versus < 2.7 months for matched historical cases ++**

Targeting EGFr + irradiation : pre-clinical studies

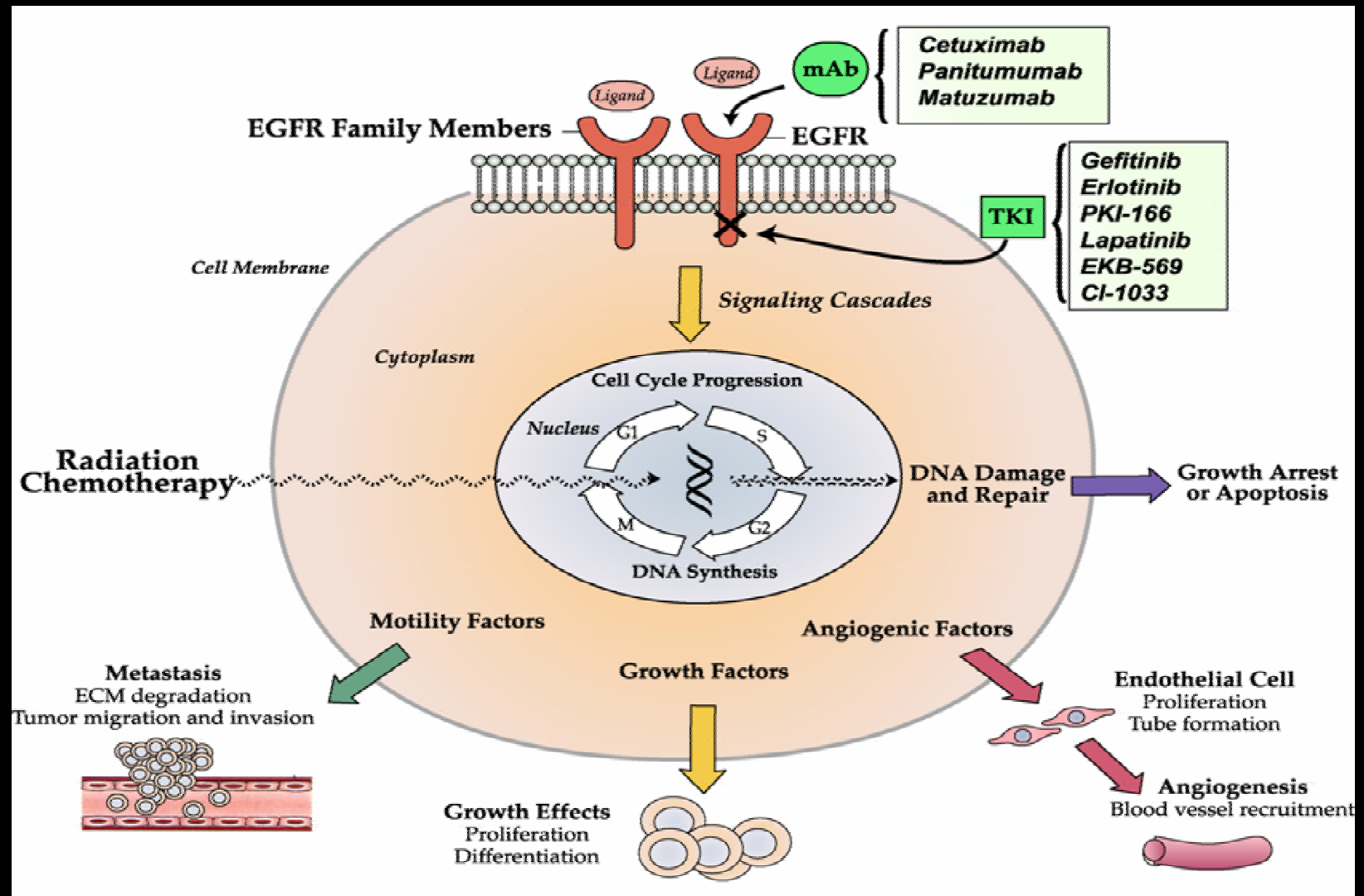
Solomon IJROBP 2003	Iressa	+
Wakeling Cancer Res 2002	Iressa	+
Chakravarti Cancer Res 2002	AG1478	+
Raben Semin Oncol 2002	Iressa	+
Huang Cancer Res 2002	Iressa	+
Huang Cancer Res 2001	C225	+
Milas Clin cancer Res 2001	C225	+
Harari Cancer Res 2000	C225	+

RT + erbitux *in vivo* (tumor cure experiments) : *...from bench to bedside*



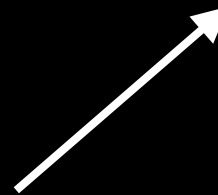
Milas et al., CCR 2000

How does EGFr targeting and irradiation works ?

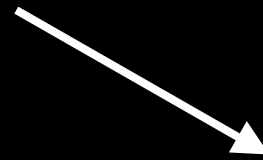


RT +/- erbitux : Proof of concept in a randomized Phase III trial (*Bonner New Eng J Med 2006*) (pivotal study)

HNSCC
Locally advanced
N = 424 patients



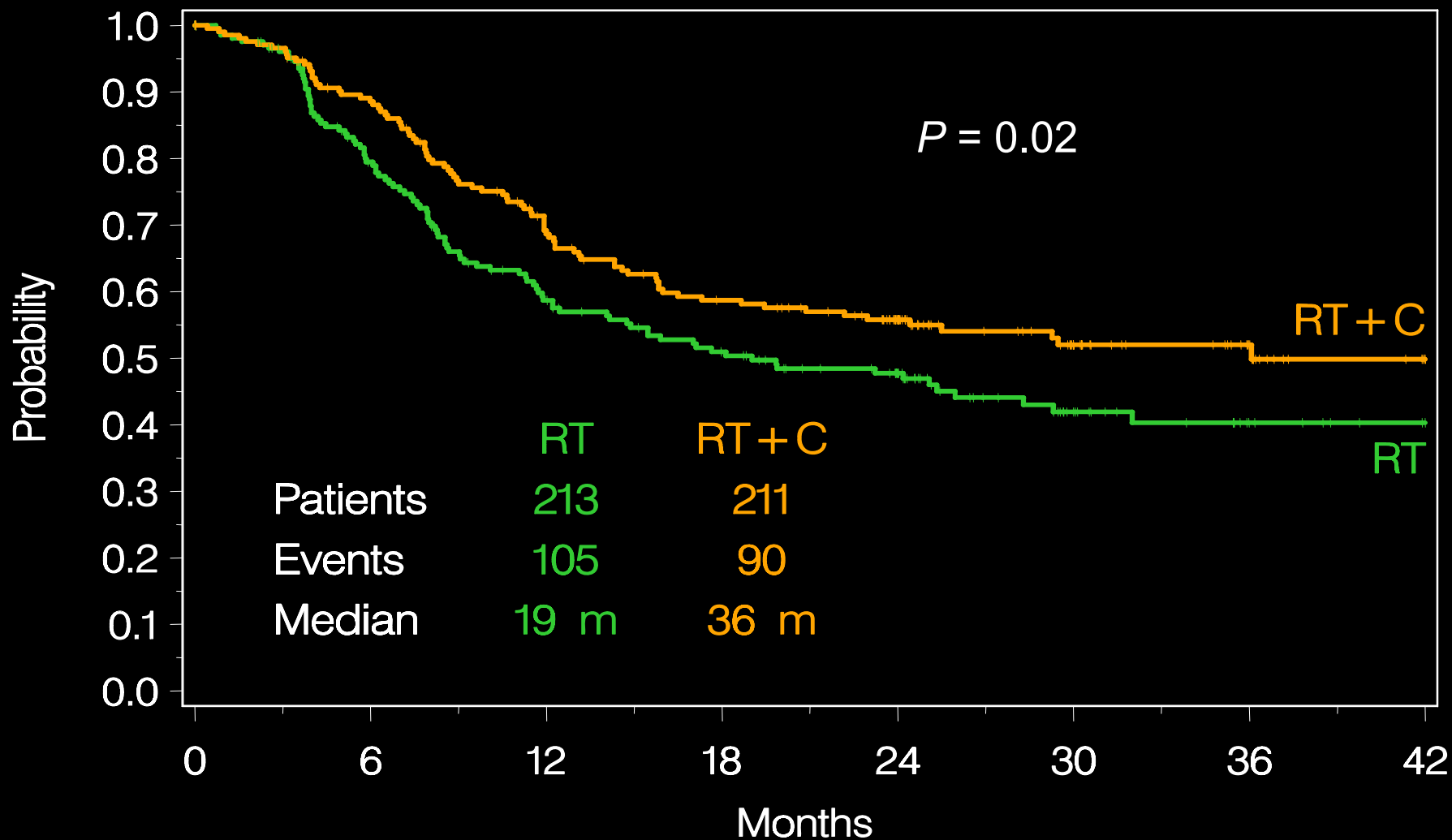
RT + Erbitux



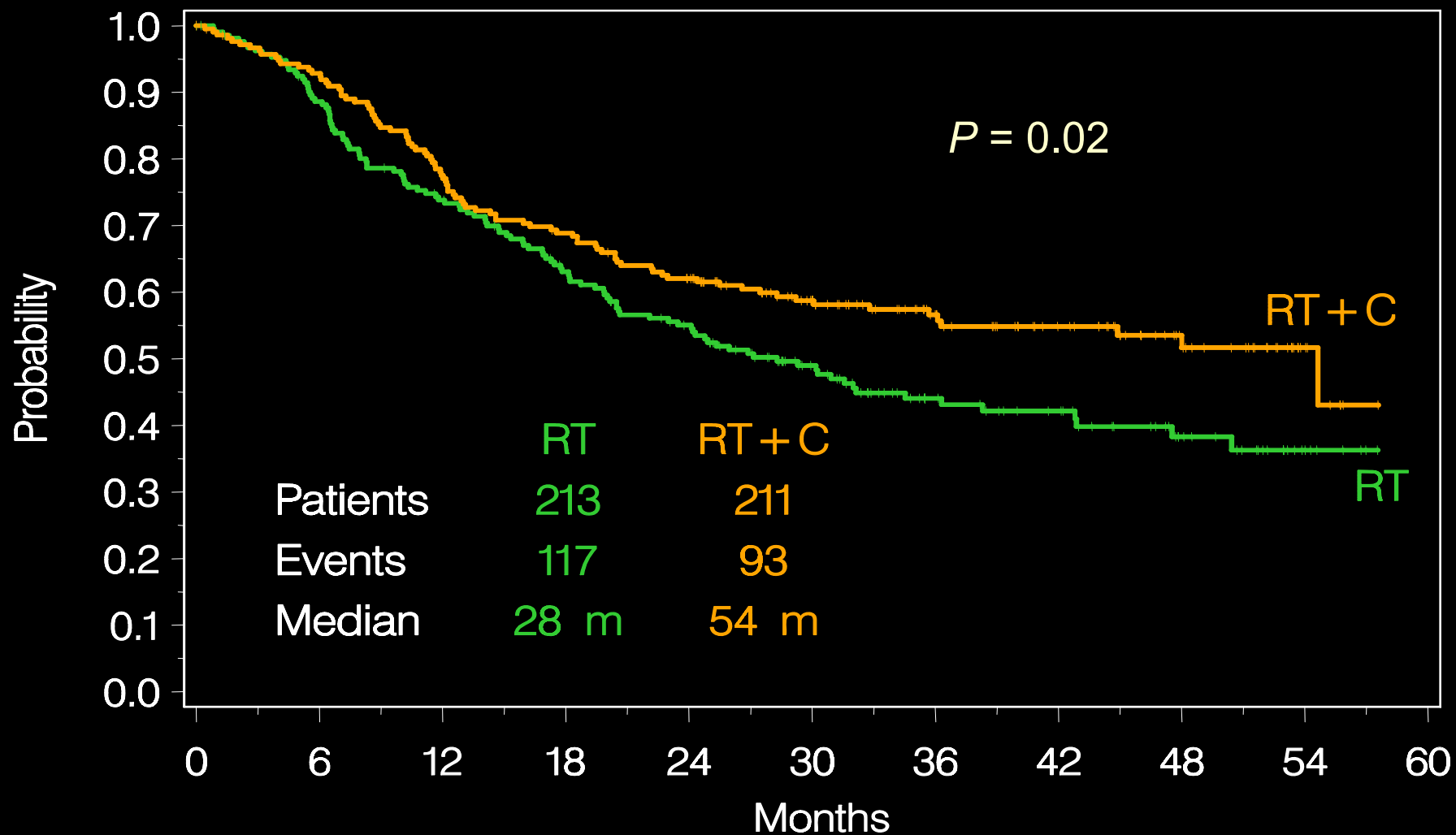
RT

Erbitux +/- RT in HNSCC : loco-regional control *(Bonner New*

Eng J Med 2006)



Erbitux +/- RT in HNSCC : overall survival *(Bonner New Eng J Med 2006)*



Pivotal phase III study: relevant grade 3–5 side effects

Side effect	RT (n=212)	ERBITUX + RT (n=208)	p-value ^a
Mucositis / stomatitis	52%	56%	0.44
Dysphagia	30%	26%	0.45
Radiation dermatitis	18%	23%	0.27
Xerostomia	3%	5%	0.32
Fatigue / malaise	5%	4%	0.64
Acne-like rash	1%	17%	<0.001
Infusion-related reactions ^b	0%	3%	0.01

^aFisher's exact test

^bListed for its relationship to ERBITUX

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TPF + RT-Erbitux^o (after 6 injections)

**Severe skin reactions
can be observed
(10-15%)**



TPF + RT-Erbitux^o (after 6 injections)

**However,
90% of the
Patients
Received
The planned
Erbitux dose
In the Bonner's Study**



Radiation dermatitis : general management

Do's

Patients should:

- ✓ Ensure skin is clean and dry before RT
- ✓ Keep the irradiated area clean, even when ulcerated
- ✓ Drying pastes, gels, creams and hydrophilic dressings may be beneficial as post-RT treatment approaches

Don'ts

Patients should avoid :

- ✗ sun exposure (wherever possible)
- ✗ skin irritants (perfumes, deodorants or alcohol-based lotions)
- ✗ scratching the skin in the affected area and the use of topical moisturisers etc. before RT

Radiation dermatitis: grade-specific management

Grade 1^a

Moisturisers
(optional)
Antibacterial
moisturisers
(occasionally)

Grade 2^a

Non-infected: use ≥ 1 topical approaches:

- Drying gels (topical antiseptic)
- Anti-inflammatory emulsion +++
- Hyaluronic acid cream
- Hydrophilic dressings
- Zinc oxide paste (if easily removed)
- Silver sulfadiazine or beta glucan cream

Where infection is suspected:

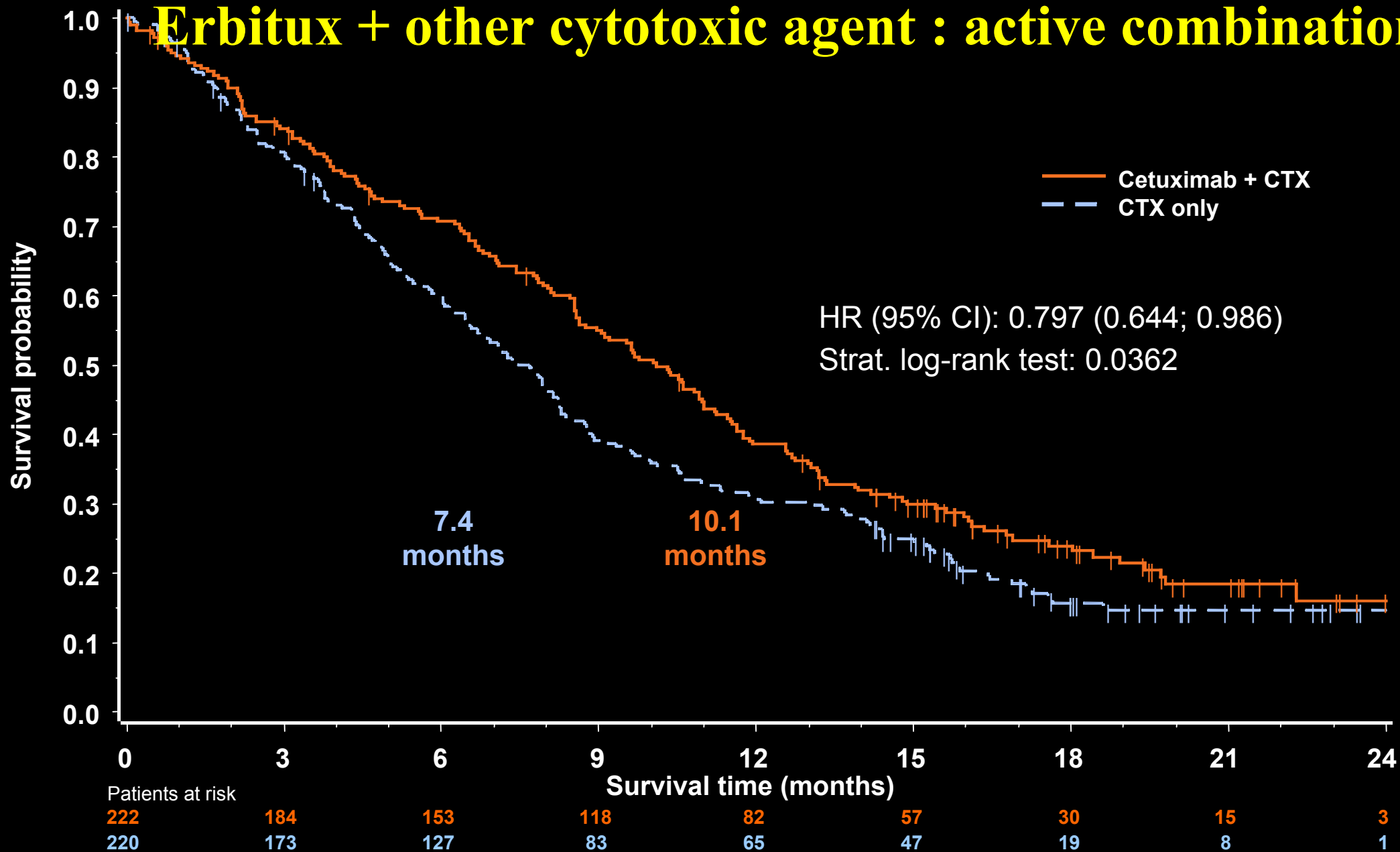
- Try to identify infectious agent
- Topical antibiotics (not prophylactic)
- Doxycycline is not recommended
- Check blood granulocyte counts (particularly with CRT)
- Carry out blood cultures if there are additional signs of sepsis and / or fever

Grade 3^a

Grade 4^a

Verify radiation
dose / distribution
Requires specialized wound
care

Erbix + other cytotoxic agent : active combination



What are the next steps in the clinic ?

Example : in locally advanced HNSCC

1) Intermediate & moderately advanced cases :

?

RT + Anti-EGFr = **RT-CT**
... and less toxic ??

2) Other (more) locally advanced :

RT-CT + Anti-EGFr > **RT-CT** ??

3) After surgery in high risk post-op patients :

RT-CT + Anti-EGFr > **RT-CT** ??

4) **Anti-EGFr** as maintenance therapy after the local treatment ??

Anti-EGFr in the Post-operative setting : a Phase III randomised trial evaluating Iressa (GORTEC 2004-01)

HNSCC
Operated,
High risk



+

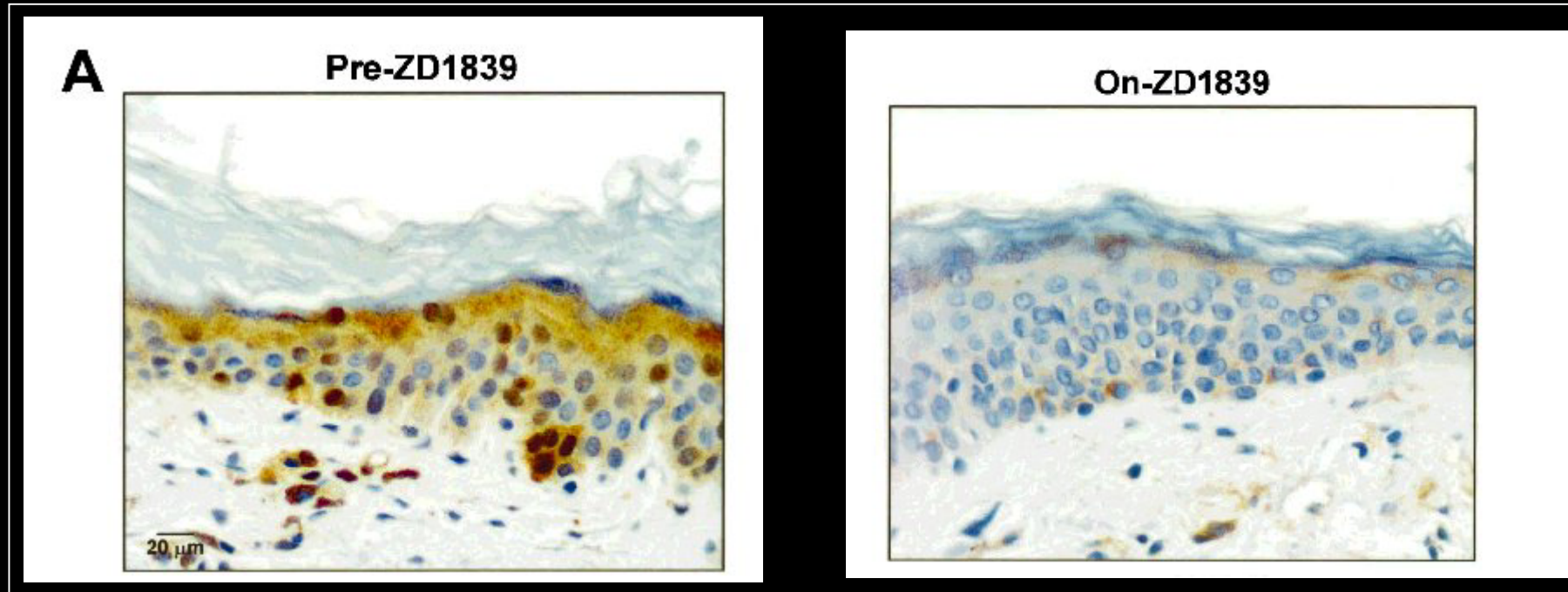
CDDP-66 Gy
+ Iressa 500 mg/day

CDDP-66 Gy

Biological markers of response : Gortec 2004-01 randomized trial

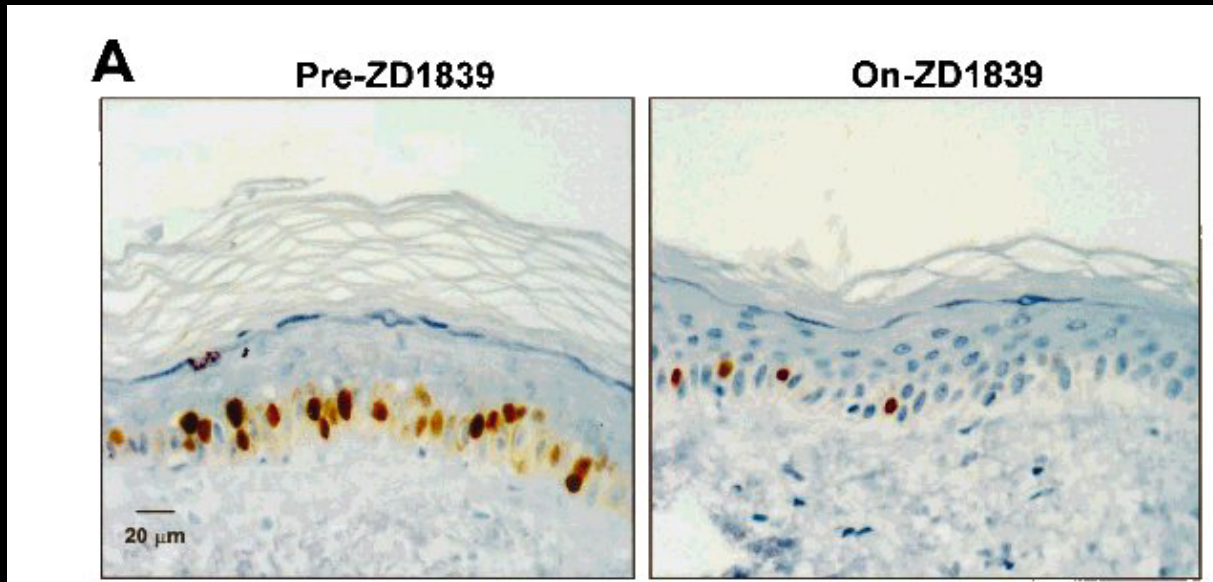
	Tumeur	Peau saine
REGF par technique biochimique	X	
REGF et effecteurs de la voie de signalisation par Western blot : <ul style="list-style-type: none"> - REGF et phosphoREGF - AKT et phosphoAKT - ERK et phosphoERK - Bax et Bcl2 - Caspases 3 et 9 - PTEN 	X	
REGF et effecteurs de la voie de signalisation par IHC : <ul style="list-style-type: none"> - REGF et phosphoREGF - AKT et phosphoAKT - ERK et phosphoERK - Bax et Bcl2 - Caspases 3 et 9 - TGFα et EGF - HER2, 3 et 4 	X	X
Polymorphisme du gène REGF	X	X
Recherche des Mutations Somatiques du REGF	X	
DNA array	X	

Effect of Iressa on EGFr signaling pathway



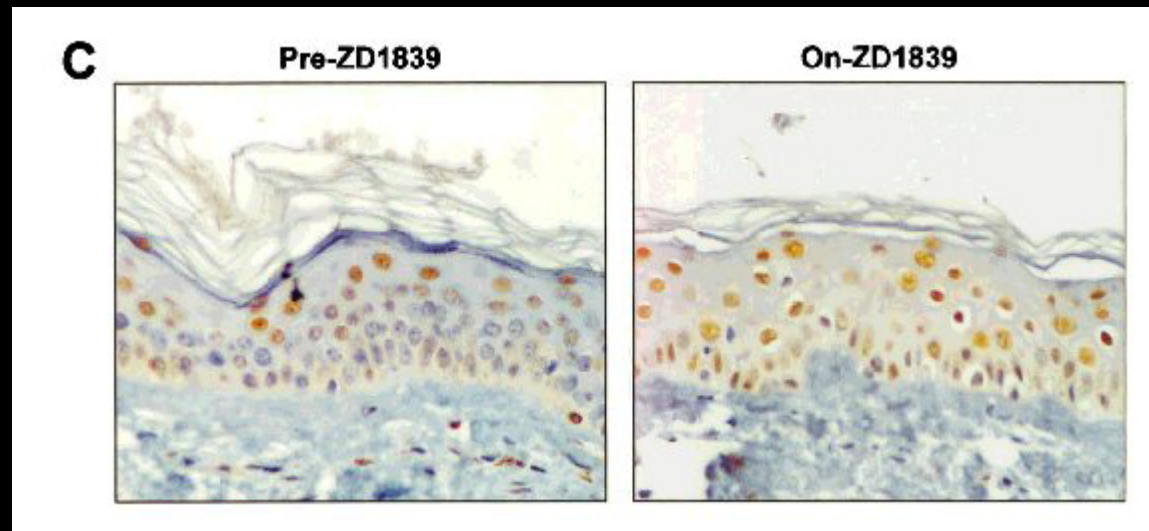
Marked decrease of activated MAPK, expression

Effect of Iressa on cell proliferation ?



- Ki67 : decrease $p < 0.001$

- p27 : increase
- $p < 0.001$

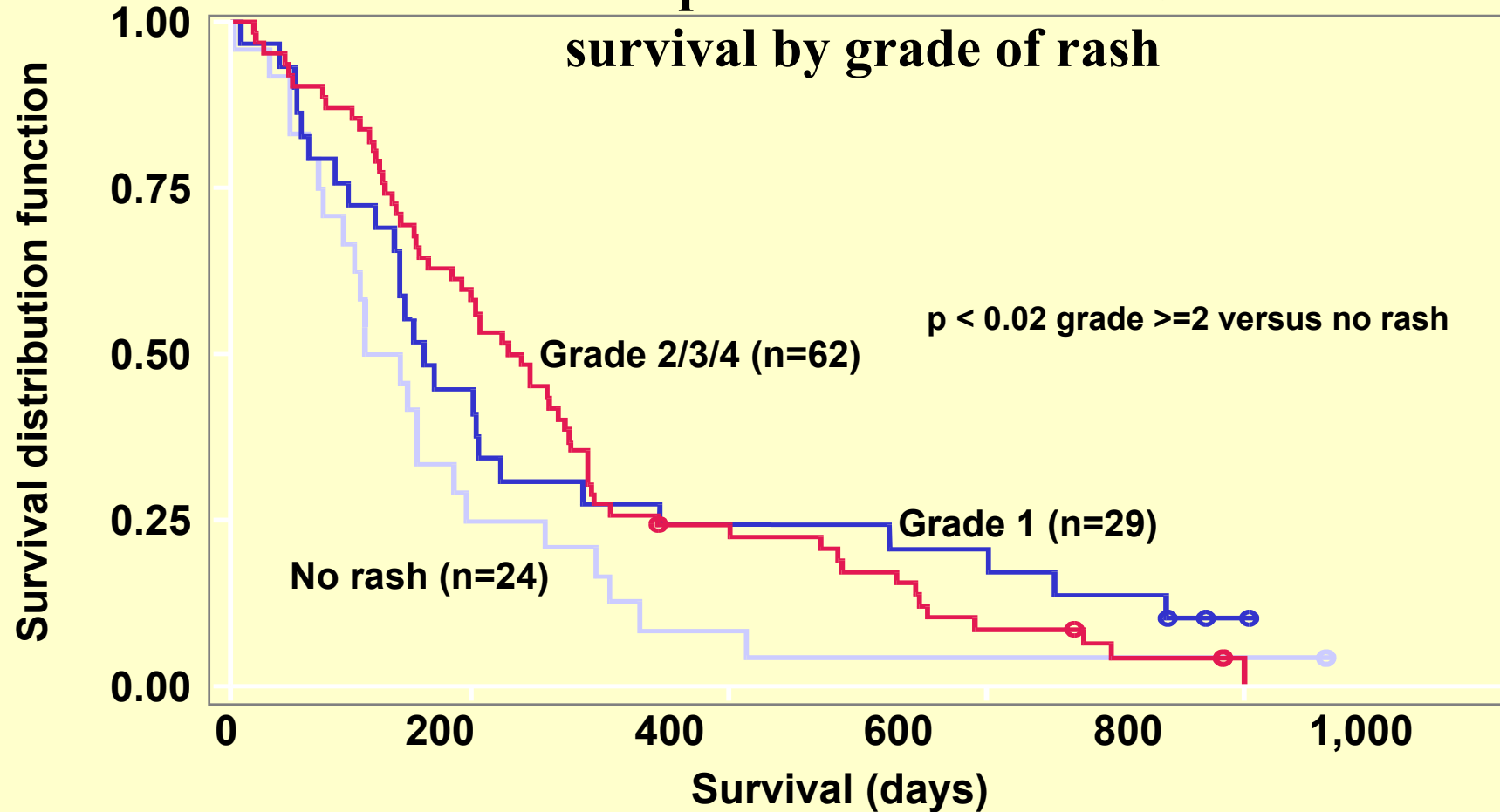


Molecular markers of response to EGFr targeting + irradiation ?

- **Immunohistochemistry of EGFr ?** : unlikely
- **FISH / EGFr amplification**, could predict disease outcome : to be evaluated
- **Mutations in the kinase domain** : small category of patients with NSCLC with spectacular response to gefitinib. Not relevant for other cancers (HNC)
- **Polymorphism of EGFr in intron 1** : associated with skin toxicity and response to gefitinib et erlotinib in vitro
- **Role for ADCC ?** (Erbbitux)

Skin toxicity : predictive of tumor response, when combined with irradiation ?

Tarceva™ phase II trial in HNSCC :



Hidalgo M. Consort Novel Targeted Therapies Head and Neck Cancer 2003
Data on file, OSI Pharmaceuticals Inc. 2003

RT-CT + erbitux *versus* RT-CT ?

RTOG H0522 Phase III randomized trial

Stage III & IV* HNSCC

Stratify :

- Larynx ~ Others
- N0~N1,2a,2b~N2c-3
- KPS
60-80 ~ 90-100
- 3-D vs IMRT*

R
A
N
D
O
M
I
Z
E

1.

Accelerated FX* +
CDDP: 100 mg/m², q3W X 2

2.

Accelerated FX* +
CDDP: 100 mg/m², q3W X 2
C225: 400 mg/m², Week -1
250 mg/m²/w, Wks 2-8

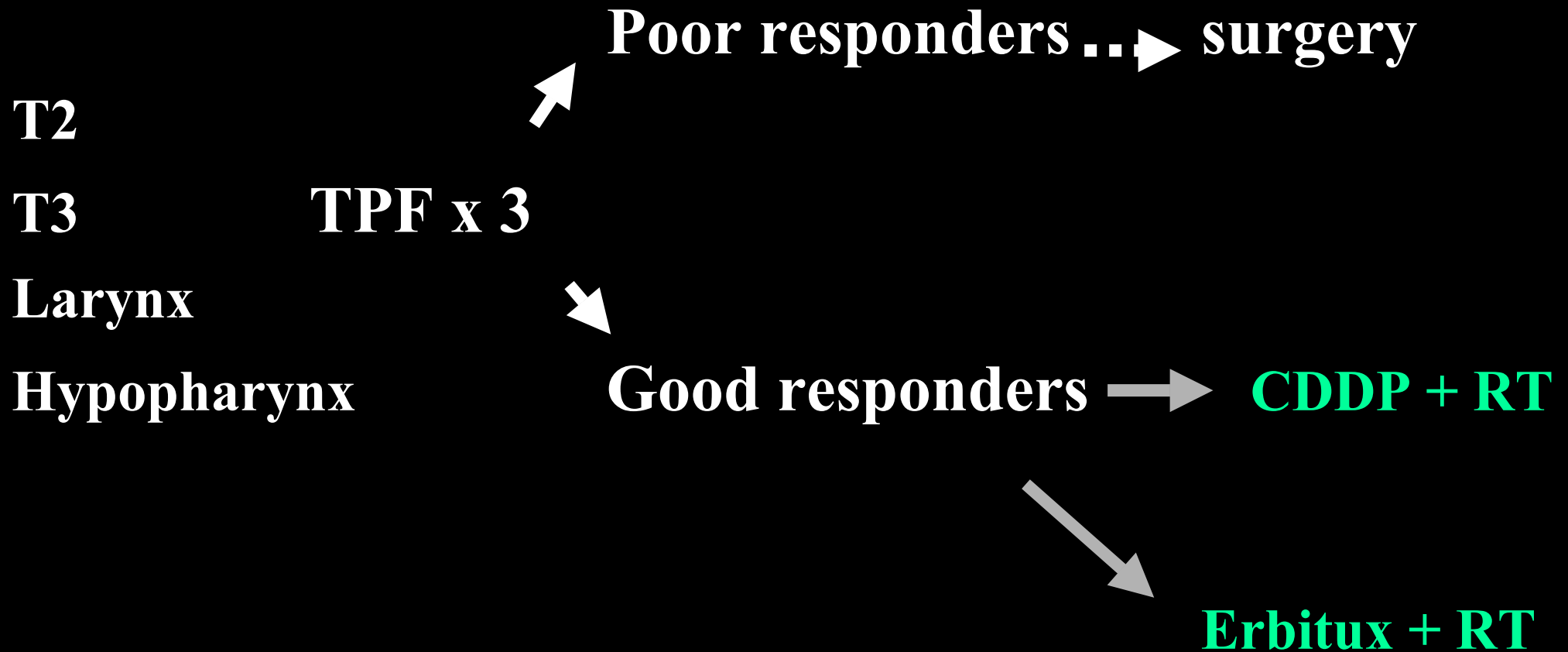
Is there a need to add concurrent chemotherapy,
when treating with RT-Erbitux ?



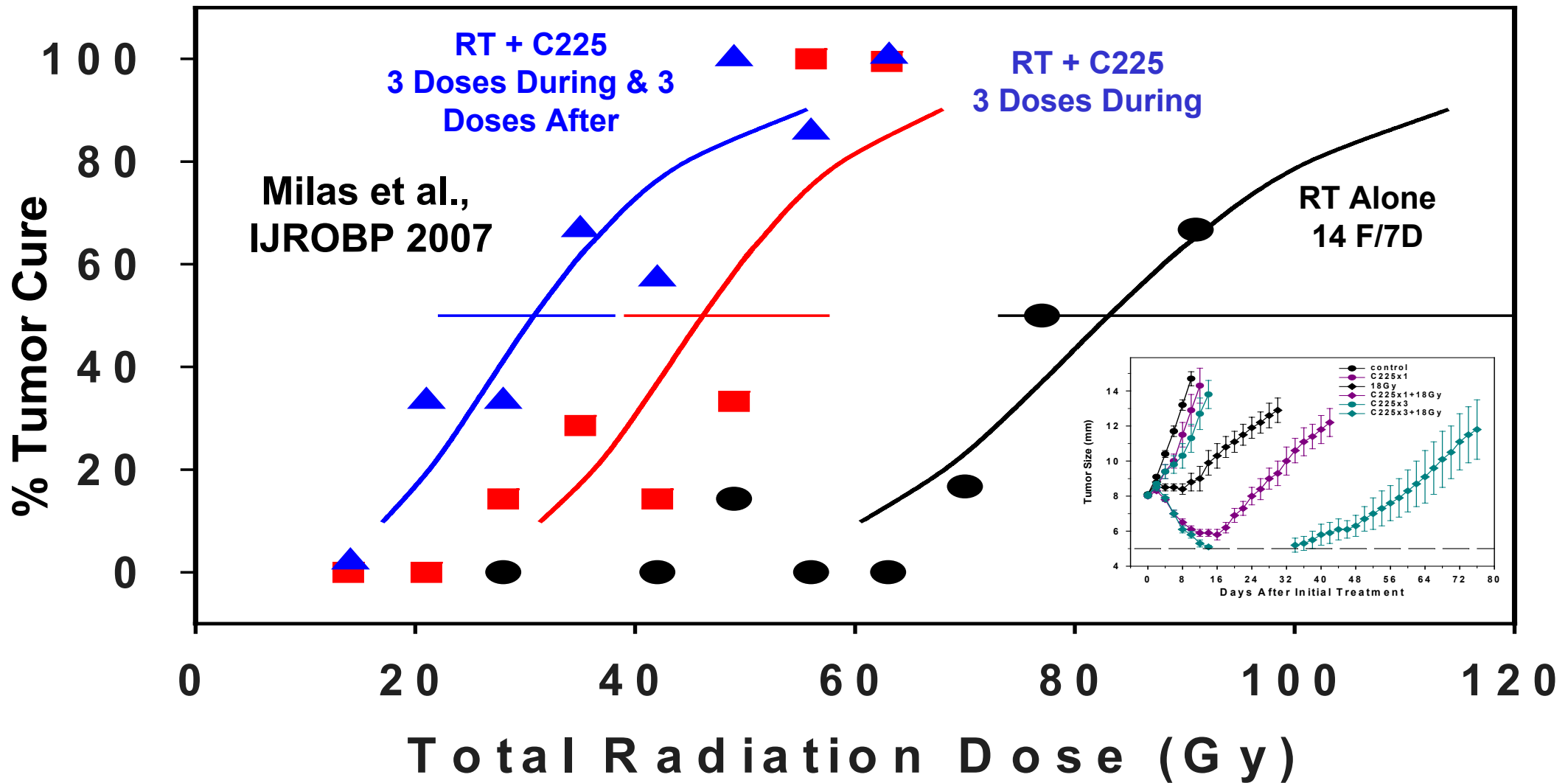
GORTEC 2007-01 randomized trial in locally advanced HNSCC

Replacing chemotherapy by an anti-EGFr :

GORTEC 2004-02 : Phase II randomized : Larynx preservation



Adjuvant EGFr targeting ? : from Bench to the patient *Bonner New Eng J Med 2006 and back to the Bench....*



Single *versus* multiple molecular targeting ?



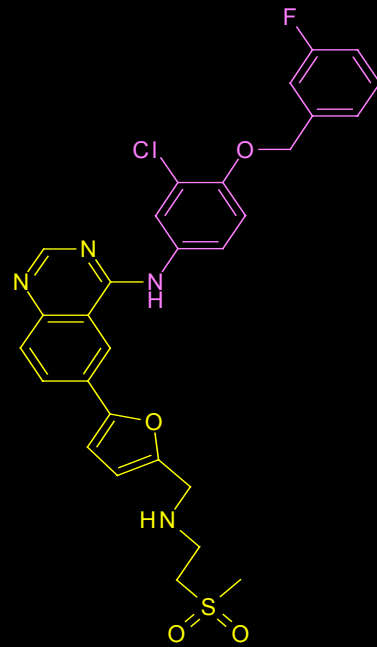
Multiple

>

Single ??

Ex : Tykerb (Lapatinib)

- Quinazoline
- Orally-bioavailable
- Dual-TK inhibitor of ErbB1 and ErbB2



Lapatinib

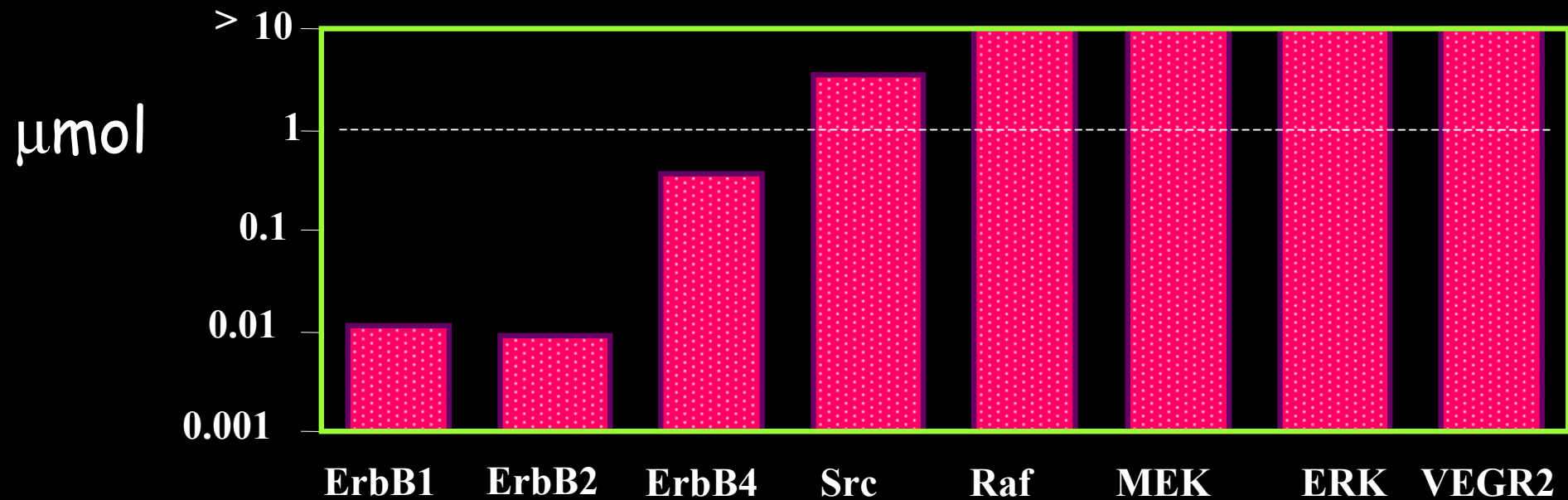
Phase I combined with RT – CDDP

Completed (Gustave Roussy & Royal Marsden
DMT : 1500 mg/m² day)

Fast track : No specific pre-clinical data on the
Combined treatment

Tykerb is Selective for ErbB1 and ErbB2

50% Inhibition of in vitro activity



Rusnak et al, *Molecular Cancer Therapeutics*, 1:85-94, 2001

Exemple of multiple molecular targeting + RT-CT :

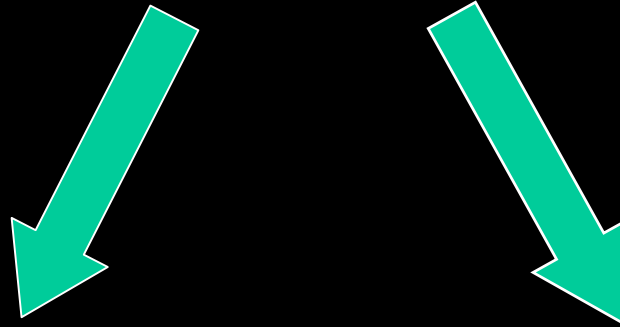
Phase I in HNSCC (IGR/Royal Marsden) :

Anti-EGF + Anti c-erbB2 (Lapatinib/Tykerb)
+ 70 Gy + CDDP

MTD = not reached, recommended dose = 1500 mg/m² daily

Ongoing phase III clinical study

Multiple targeting ...



Intrinsic signaling pathways
modulating radiosensitivity
EGFr, Cox-2, AKT/PI3K ...
DNA repair, apoptosis

Extrinsic modulation of
Radiosensitivity
hypoxia
Angiogenesis,
ECM
Antivascular agents

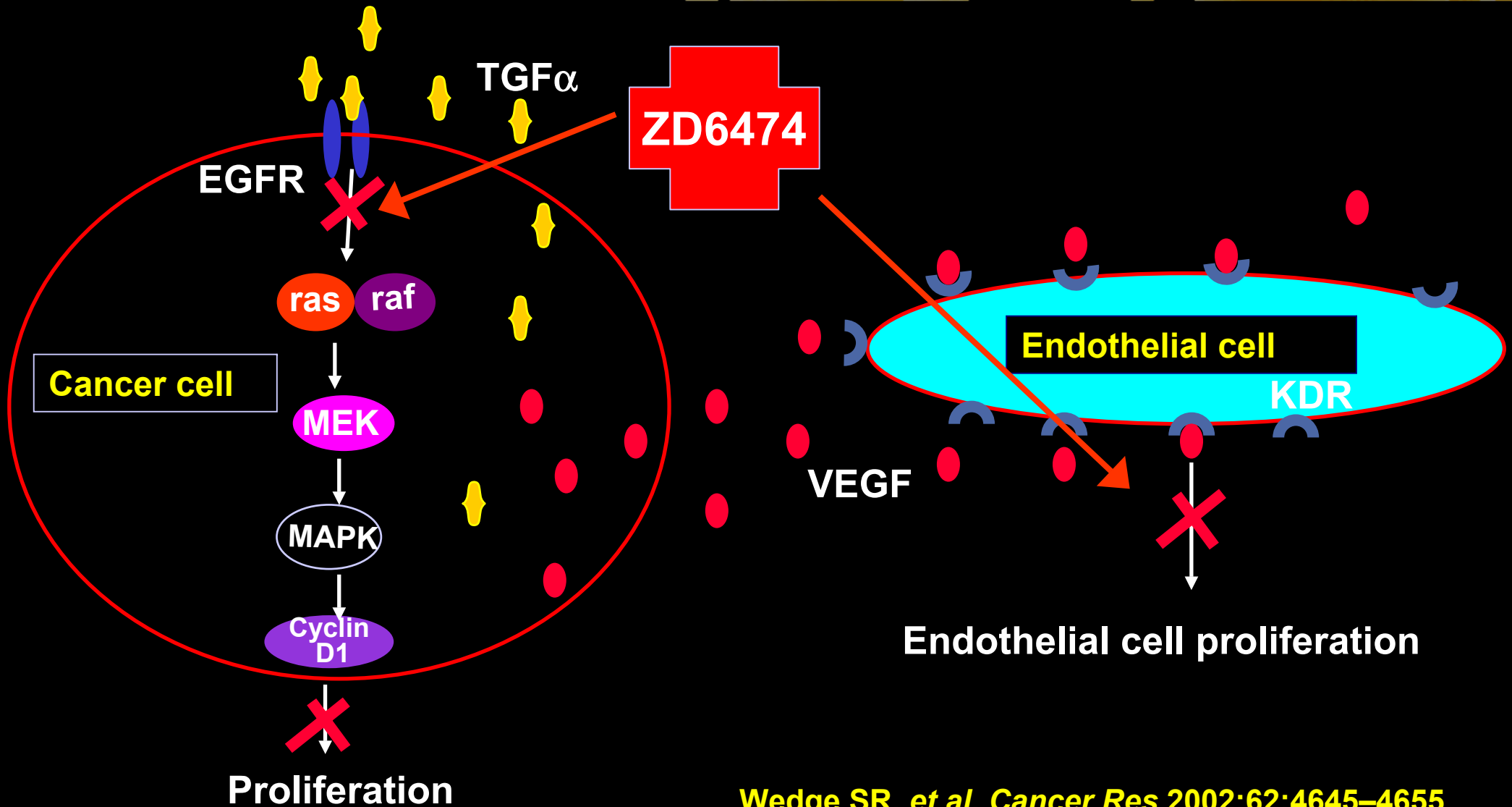
Combining intrinsic + extrinsic targeting ?

Ongoing Phase I (Locally advanced HNC)

Brizel, 2007



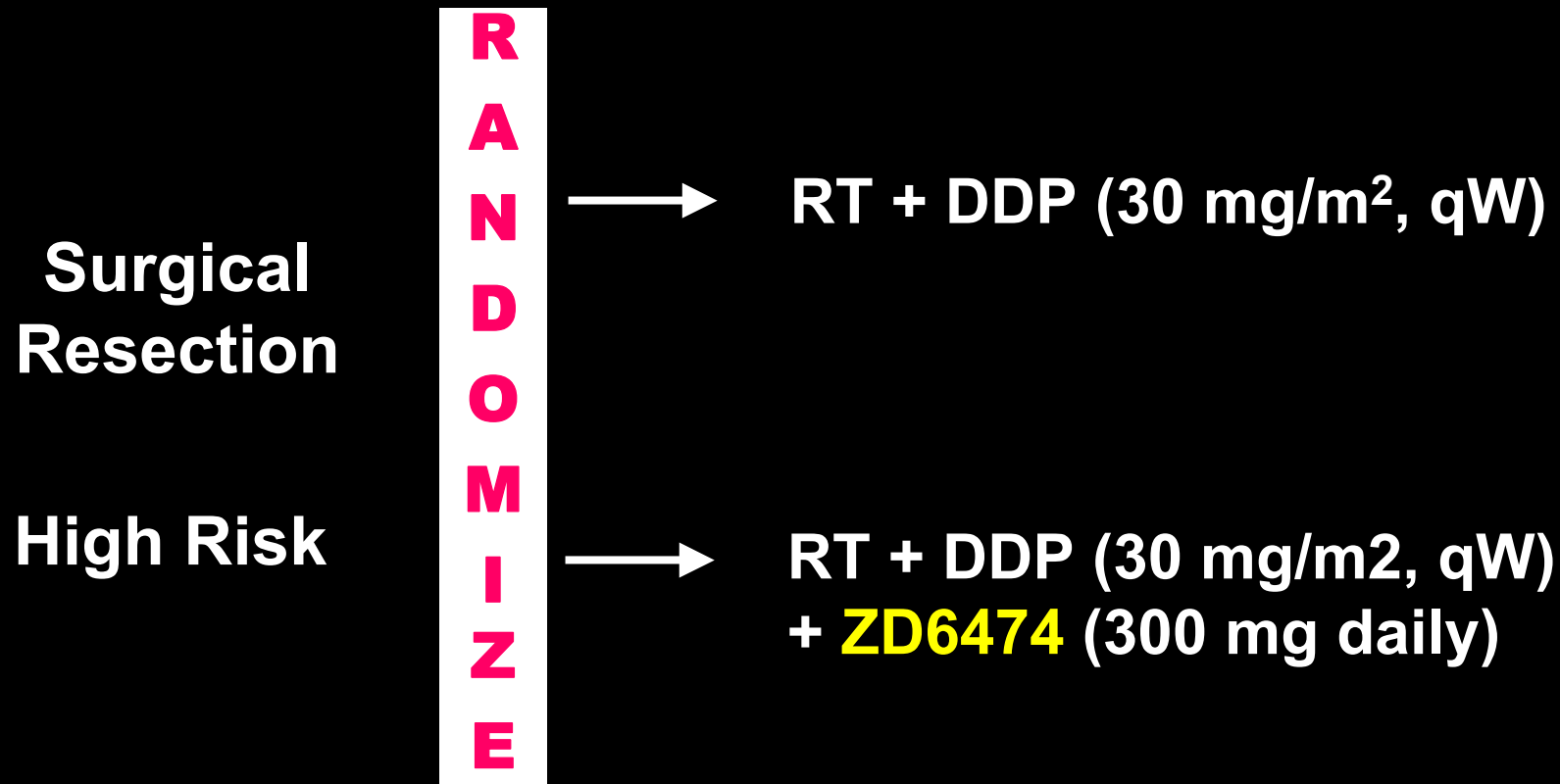
Combining intrinsic + extrinsic targeting : ZD6474, an oral dual EGFR-VEGFR TKI



Wedge SR, et al. *Cancer Res* 2002;62:4645-4655

RTOG 0619 : head & neck Post-op Adjuvant

Phase II-R in Planning, PI: David Raben



Anti-EGFr compounds and radiation in the clinic

- conclusions -

- **EGFr expression** generally associated with resistance to therapy & poor prognosis
- **Erbitux : clinical activity** demonstrated in HN refractory cancers, and when combined with RT or CT
- **Increase of in field radiation toxicity (skin) ?** when erbitux is combined with RT
- **Further studies :**
 - Better define the role of Erbitux & other EGFr inhibitors in HNC and other cancers (/ RT-CT ?)
 - Methods to predict the tumor likely to respond
 - Multiple targeting ?