II° CONGRESSO
Gruppo Interregionale
AIRO Piemonte-
Liguria-Valle d'Aosta

Aspetti clinici e tecnici della radioterapia nei tumori del colon-retto
8 ottobre 2011
Castello di Grinzane Cavour

Radioterapia e terapie a bersaglio molecolare

Associazione Italiana Radioterapia Oncologica

Almalina Bacigalupo - Genova

PRE-OPERATIVE COMBINED CHEMORADIATION HAS REPLACED POST-OPERATIVE RTCT AS STANDARD TREATMENT FOR LOCALLY ADVANCED RECTAL CANCER

(Sauer N.Engl.J.Med 2004) (I,A)

-LOCAL RECURRENCES DECREASING FROM 40 TO<10%

-OS INCREASING FROM 50 to 75% IN THE LAST 40 YEARS

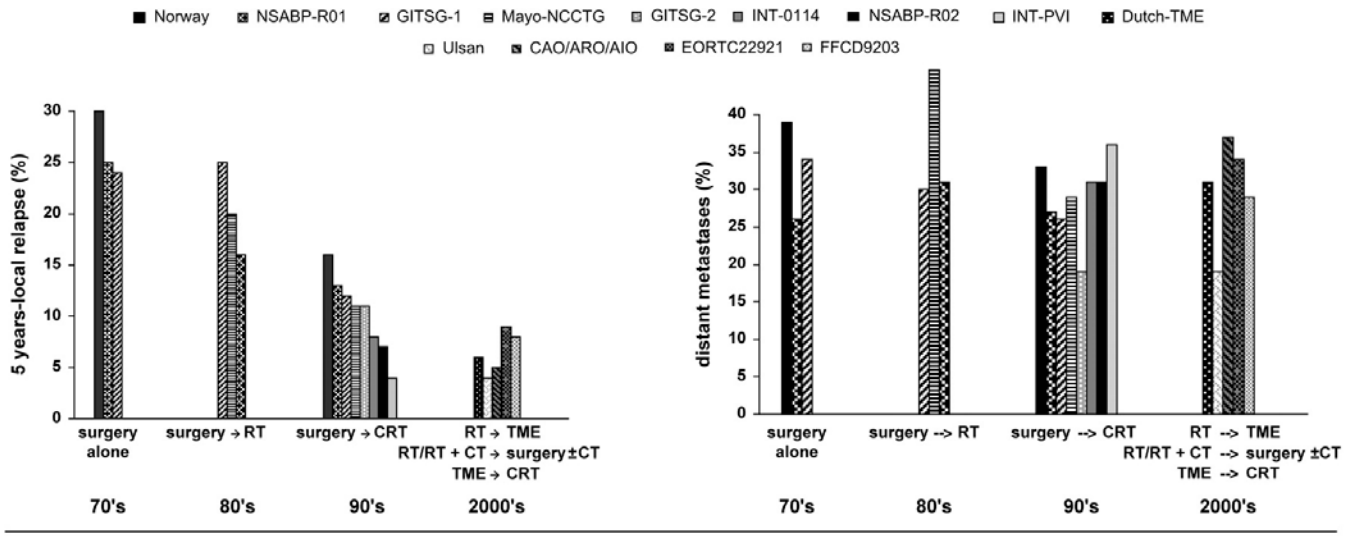
For T3N0 of the mid and upper rectum tumor control rates are satisfactory with combined modality therapy (although improved organ or sphincher-preservation maybe possible for distal T)

For the highest risk pts (T3N+ and T4) significant limitations in pelvic T control remain

METASTASIS REPRESENT THE SITE OF FAILURE FOR UP TO 30% OF PATIENTS DESPITE OPTIMAL SURGERY AND PRE-OR POST- OPERATIVE CTRT

TO ACHIEVE THIS GOAL,
MORE EFFECTIVE CTRT ARE NEEDED

Outcome with standard fluorouracil-based combined modality treatment programs for locally advanced rectal cancer.



RT: radiotherapy; CRT: radiotherapy with concomitant and sequential chemotherapy (except Norway trial where chemotherapy was administered exclusively during radiotherapy); TME: total mesorectal excision; CT: chemotherapy.

Aschele C , Lonardi S Ann Oncol 2007;18:1908-1915

Annals of Oncology

Outcome with standard fluorouracil-based combined modality treatment programs for locally advanced rectal cancer. Differential impact on local failure and distant metastases

STANDARD REGIMENS

INFUSED REGIMENS ARE GENERALLY USED FOR THE ADMINISTRATION OF FU CONCOMITANT TO RADIATION, BASED ON FU PHARMACOKINETICS SENSITIZATION

TREATMENT SIMPLIFICATION

ORAL FLUOROPYRIMIDINES ARE ABLE TO MAINTAIN PROTRACTED PLASMA LEVELS OF FU WITHOUT THE NEED FOR IV ACCESSES AND INFUSION PUMPS

ROLE OF NEW DRUGS

OXALIPLATIN + 5-FU-LEUCOVORIN: SIGNIFICANT ACTIVITY IN METASTATIC COLORECTAL CANCER
(DE GRAMONT J CLIN ONCOL 2000)

MOSAIC TRIAL (ADJUVANT COLON CANCER):
significant improvement in DFS at 5 years (73.3% vs 67.4% P=.003) in favor of FOLFOX4

OS at 6 years: 78.5% vs 76.0% in favor of FOLFOX4P=.046

NSABP-C-07 study confirm the results of MOSAIC trial

ALL THE NEW DRUGS APPROVED FOR USE IN COLORECTAL CANCER IN THE LAST 10 YEARS (IRINOTECAN, OXALIPLATIN, CAPECITABINE, CETUXIMAB AND BEVACIZUMAB) HAVE RADIOSENSITIZING PROPERTIES

Setting	Study	Control arm	Experimental arm
Post-operative[a]	E3201[b]	FU + LV	FOLFIRI/FOLFOX
	E5204	FOLFOX	FOLFOX + bevacizumab
	CHRONICLE	Observation	CAPE + OXA
Pre-operative[c]	STAR	PVI FU	PVI FU + OXA
	NASBP R-04	PVI FU	PVI FU + OXA/ CAPE ± OXA
Pre- and post-operative[d]	PETACC 6	CAPE	CAPE + OXA

[a]Following pre- or post-operative fluoropyrimidine-based chemoradiation. [c]Concomitant to radiation. [d]Concomitant to pre-operative radiation and as adjuvant post-operative treatment. [b]Study accrual closed on April 2005. FU, 5-fluorouracil; LV, leucovorin; FOLFIRI, fluororacil + leucovorin + irinotecan; FOLFOX, fluororacil + leucovorin + oxaliplatin; CAPE, capecitabine; OXA, oxaliplatin; PVI, protracted venous infusion.

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Primary Tumor Response to Preoperative Chemoradiation With or Without Oxaliplatin in Locally Advanced Rectal Cancer: Pathologic Results of the STAR-01 Randomized Phase III Trial

Carlo Aschele, Luca Cionini, Sara Lonardi, Carmine Pinto, Stefano Cordio, Gerardo Rosati, Salvatore Artale, Angiolo Tagliagambe, Giovanni Ambrosini, Paola Rosetti, Andrea Bonetti, Maria Emanuela Negru, Maria Chiara Tronconi, Gabriele Luppi, Giovanni Silvano, Domenico Cristiano Corsi, Anna Maria Bochicchio, Germana Chiaulon, Maurizio Gallo, and Luca Boni

41 ITALIAN CENTERS
2003-2008
747 pts

J Clin Oncol 29. © 2011 by American Society of Clinical Oncology

- SIMILAR RATES OF ABDOMINOPERINEAL RESECTION (20% v 18%, ARM A v ARM B)

- SIMILAR RATES OF pCR :16%

VOLUME 28 · NUMBER 10 · APRIL 1 2010
JOURNAL OF CLINICAL ONCOLOGY
ORIGINAL REPORT

SAME CONCLUSIONS IN ACCORD 12/0405 PRODIGE 2

RT + CAPECITABINE
vs
INTENSIFIED RT/CAPECITABINE PLUS OXALIPLATIN

ypCR RATES WERE NUMERICALLY INCREASED IN THE OXALIPLATIN-CONTAINING ARM BUT THE DIFFERENCE WAS SMALL (13.9% CAP-45 vs 19.3% CAPOX-50)

Merito della RT a 50Gy??

NO STATISTICAL SIGNIFICANCE

DESPITE THE PRECLINICAL RATIONALE AND PROMISING PHASE II DATA,OXALIPLATIN IS NOT A CLINICALLY EFFECTIVE RADIATION SENSITIZER AT LEAST USING THE DOSE AND REGIMEN AS DESCRIBED

THE LACK OF EFFECT ON PRIMARY TUMOR RESPONSE DOES NOT PRECLUDE EFFECT ON SYSTEMIC MICROMETASTASIS (LOWER FREQUENCY OF EXTRAPELVIC MTS FOUND AT SURGERY)

ypCR RATES IN THE CONTROL ARM SEEM TO BE HIGHER IN THESE TWO TRIALS COMPARED WITH THOSE REPORTED IN LESS RECENT STUDIES (OPTIMIZED RT TECHNIQUES AND/OR HIGHER RT DOSES)

NEW STRATEGIES:

*INDUCTION CT

*TARGETED THERAPIES

*IMAGE-GUIDED IMRT TECHNIQUES

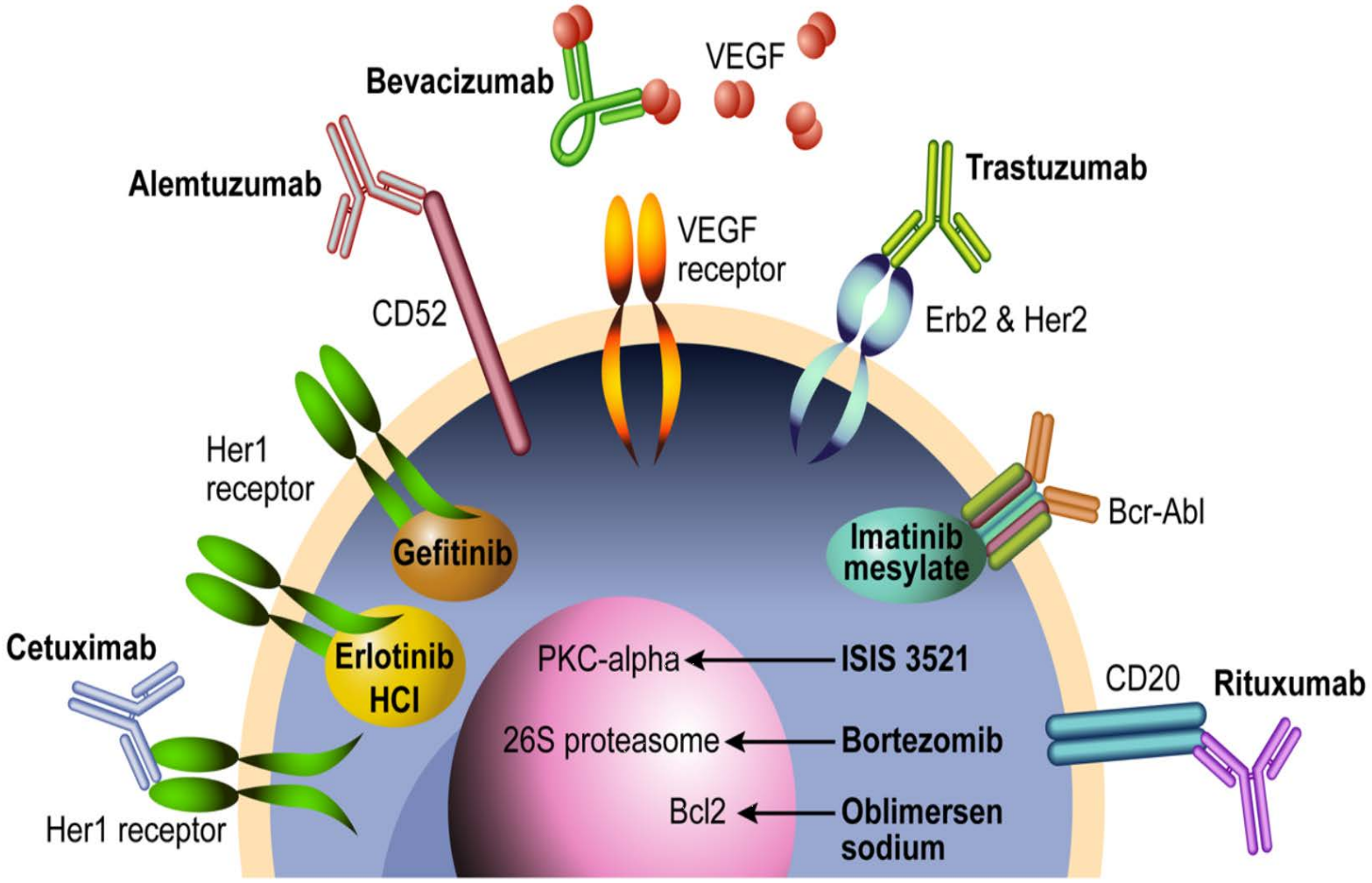
Targeted Therapies

- **Gli “umab”**
- **Monoclonal antibodies**: proteine che si legano a recettore o altra molecola di segnale extracellulare
- **Gli “inib”**
- **Tyrosine Kinase Inhibitors**: molecole che legano e inibiscono attività enzimatiche intracellulari

Farmaci a Bersaglio Molecolare

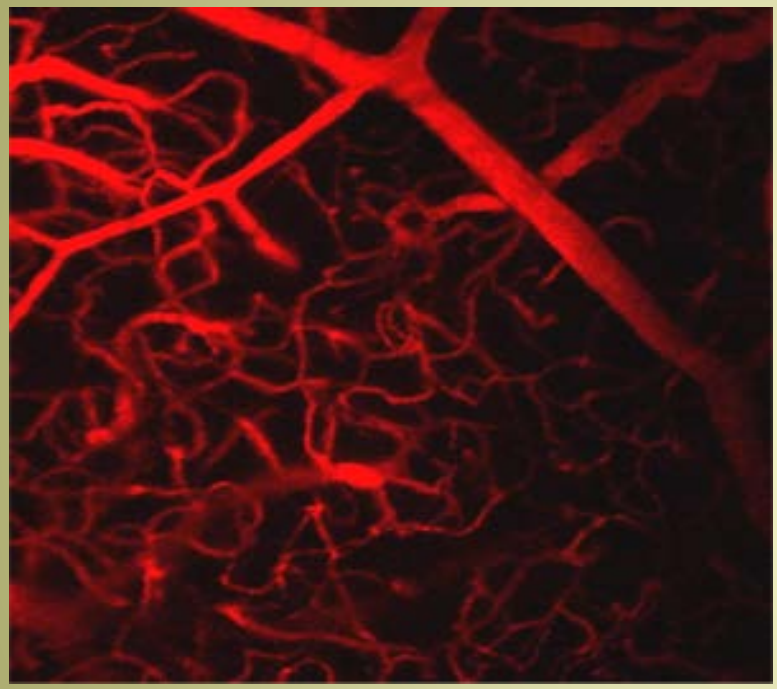
Anticorpi monoclonali ….gli "umab"	Inibitori della trasduzione del segnale …" gli "inib"
Rituximab (→CD20)	Imatinib mesilato (→ bcr-abl -, c-kit-, PDGF-TKs)
Trastuzumab (→HER2)	Gefitinib (→ EGFR-TK)
Panitumumab (→EGFR)	Erlotinib (→ EGFR-TK)
Cetuximab (→EGFR)	Bortezomib (→ proteasoma)
	Sorafenib, Sunitinib
Bevacizumab (→VEGF)	

Targeted Therapies

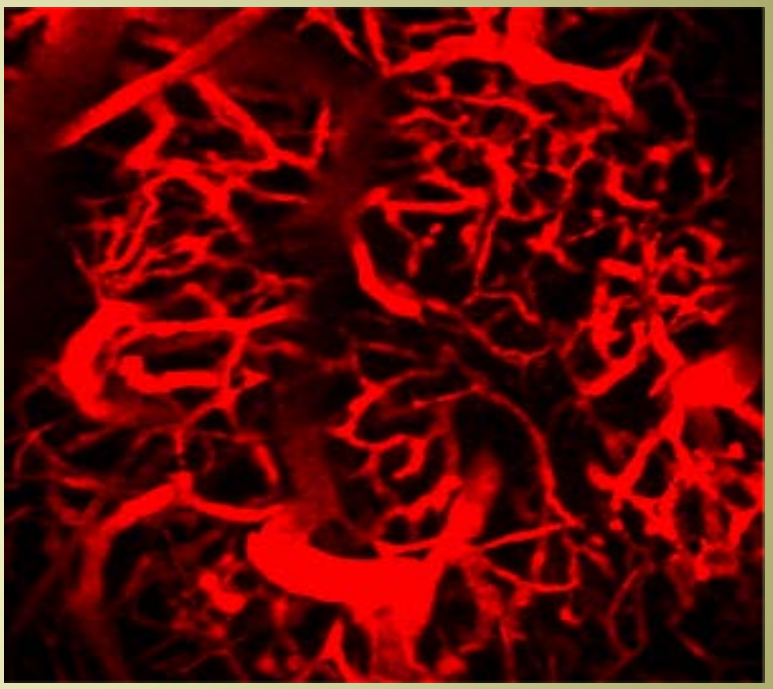


ANTICORPI MONOCLONALI INIBITORI DELL'ANGIOGENESI ANTI-VEGFR2

Neo-angiogenesi tumorale



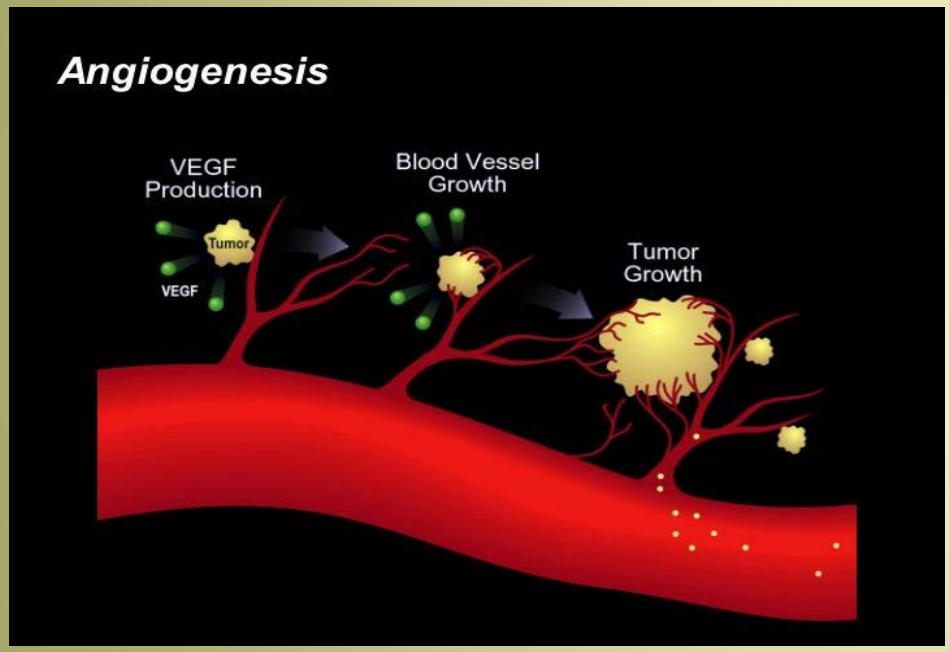
Normal tissue



Tumor tissue

Jain: Science; 307: 58-62, 2005

VEGF



- **è il più potente e specifico fattore mitogeno per le cellule endoteliali;**

- **è un fattore di sopravvivenza per le cellule dei vasi neoformati;**

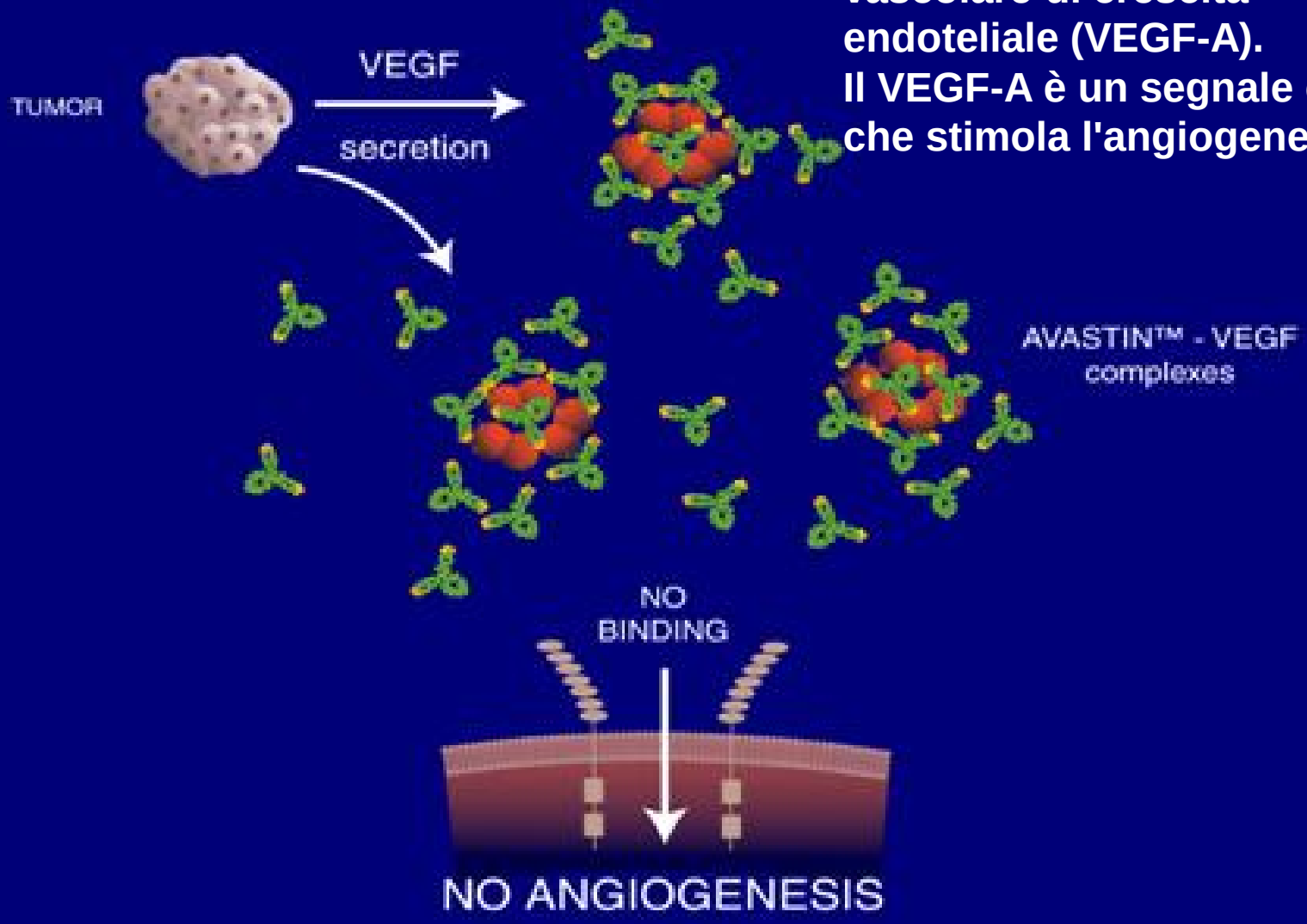
- **induce un aumento della permeabilità vasale, facilitando l'immissione delle cellule neoplastiche nel torrente circolatorio.**

Bevacizumab (Avastin™): rhuMAb VEGF

- Recombinant Humanized Monoclonal Antibody to VEGF
- 93% human, 7% murine
- Recognizes all isoforms of VEGF, Kd = 8 x 10-10 M
- Terminal half life 17-21 days

AVASTIN™ Blocks Angiogenesis

Bevacizumab si lega al fattore vascolare di crescita endoteliale (VEGF-A).
Il VEGF-A è un segnale chimico che stimola l'angiogenesi



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JUNE 3, 2004 VOL. 350 NO. 23

Bevacizumab plus Irinotecan, Fluorouracil, and Leucovorin for Metastatic Colorectal Cancer

Herbert Hurwitz, M.D., Louis Fehrenbacher, M.D., William Novotny, M.D., Thomas Cartwright, M.D., John Hainsworth, M.D., William Heim, M.D., Jordan Berlin, M.D., Ari Baron, M.D., Susan Griffing, B.S., Eric Holmgren, Ph.D., Napoleone Ferrara, M.D., Gwen Fyfe, M.D., Beth Rogers, B.S., Robert Ross, M.D., and Fairooz Kabbinavar, M.D.

813 pts randomized study

CONCLUSIONS

The addition of bevacizumab to fluorouracil-based combination chemotherapy results in statistically significant and clinically meaningful improvement in survival among patients with metastatic colorectal cancer.

BEVACIZUMAB / RADIOSENSITIVITY

It has been suggested that anti-VEGF therapy results in destruction of immature nonfunctional vessels leading to a vascular “normalization” and a better blood flow provided by the remnant mature vessels, which may improve drug distribution and reduce tumor hypoxia.

MORTE CELLULARE DEL T

RADIOSENSIBILITA’

Direct evidence that the VEGF-specific antibody bevacizumab has antivascular effects in human rectal cancer (phase I study)

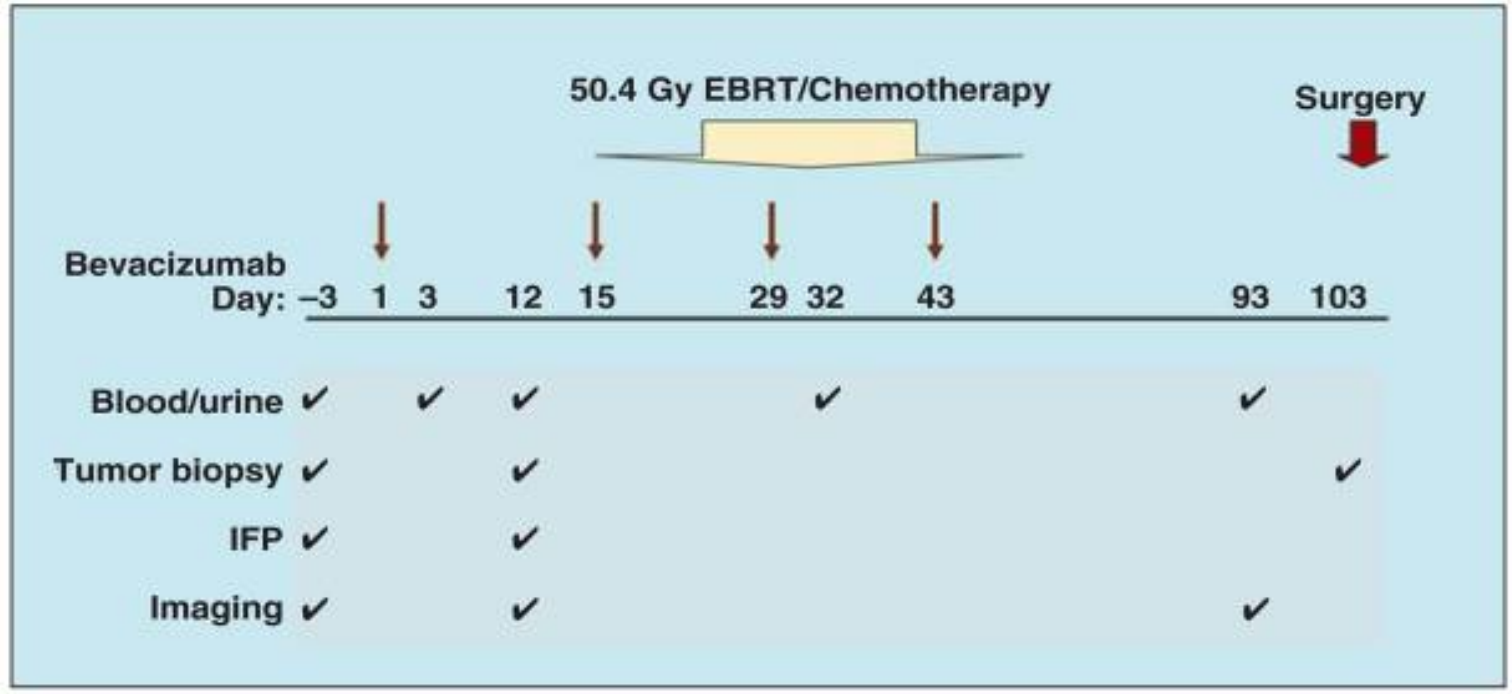
Christopher G Willett, Nat Med 2004

to evaluate the effects of bevacizumab alone on

(i) tumor physiology (blood perfusion, blood volume, permeability–surface area product, microvascular density (MVD), perivascular coverage, interstitial fluid pressure (IFP) and 18-fluorodeoxyglucose (FDG) uptake);

(ii) systemic response (VEGF level in blood, number of circulating endothelial cells (CECs) and progenitor cells);

(iii) tumor response



6pz+ 5pz

At day 12: 1 of 11 patients exhibited a partial clinical response, and a number of antivascular effects induced by bevacizumab were observed

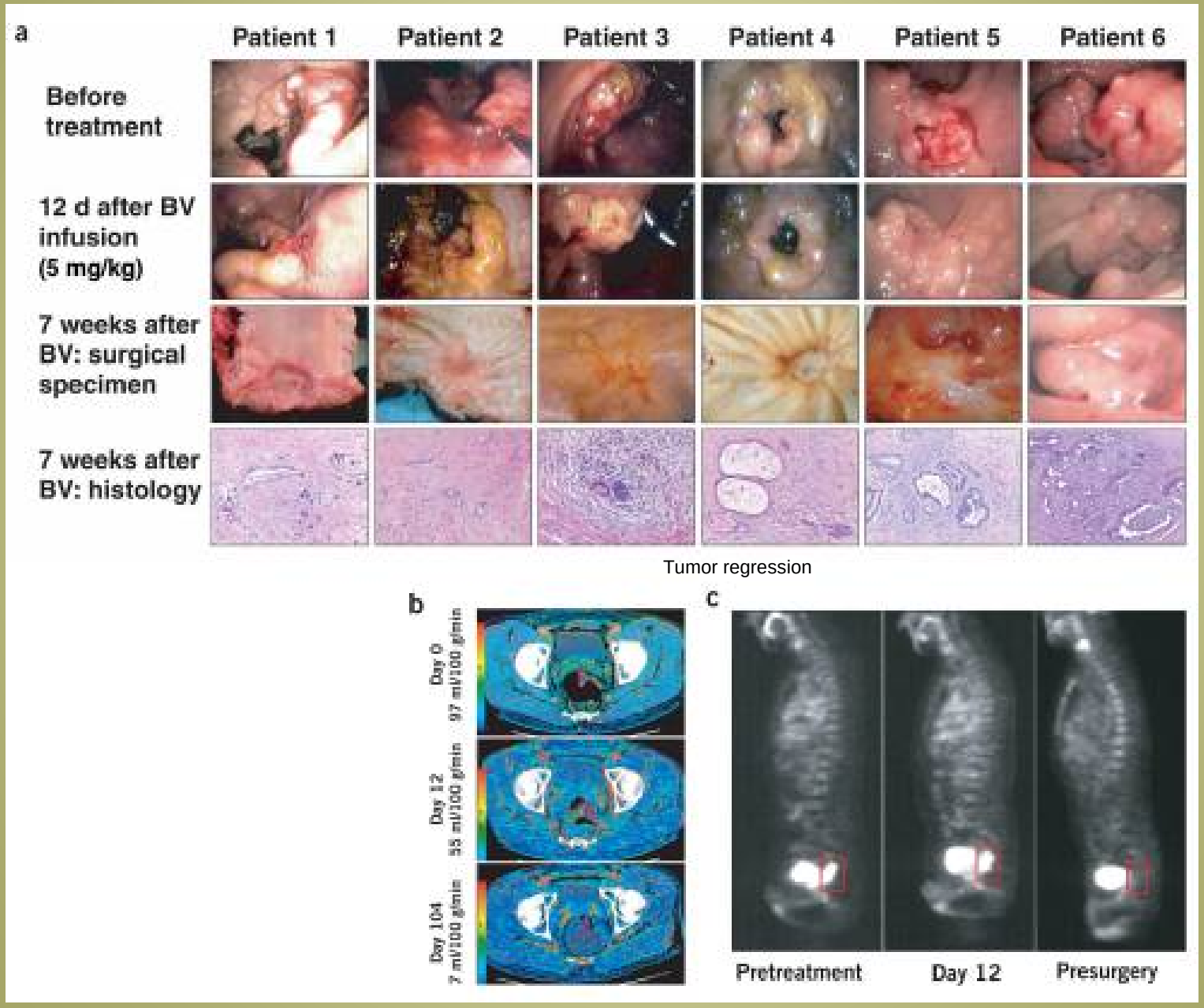
Tumor responses evaluated by endoscopy, CT, and PET at 7 weeks after completion of the combined treatment are encouraging with evidence of tumor regression and decreased FDG activity

↓ Perfusione tumorale

↓ Pressione interstiziale tumorale

Con 5 mg/ Kg: no eventi avversi
no complicanze chirurgiche

Con 10 mg/kg 2 pz diarrea G3-4
2 pz complicanze postchirurgiche
(embolia polmonare,occlusione)


a
Patient 1
Patient 2
Patient 3
Patient 4
Patient 5
Patient 6
Before treatment
12 d after BV infusion (5 mg/kg)
7 weeks after BV: surgical specimen
7 weeks after BV: histology
Tumor regression
b
Day 0
97 mV/100 g/min
Day 12
55 mV/100 g/min
Day 104
7 mV/100 g/min
c
Pretreatment
Day 12
Presurgery

Patient 1

VOLUME 27 · NUMBER 18 · JUNE 20 2009

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Efficacy, Safety, and Biomarkers of Neoadjuvant Bevacizumab, Radiation Therapy, and Fluorouracil in Rectal Cancer: A Multidisciplinary Phase II Study

Christopher G. Willett, Dan G. Duda, Emmanuelle di Tomaso, Yves Boucher, Marek Ancukiewicz, Dushyant V. Sahani, Johanna Lahdenranta, Daniel C. Chung, Alan J. Fischman, Gregory Y. Lauwers, Paul Shellito, Brian G. Czito, Terence Z. Wong, Erik Paulson, Martin Poleski, Zeljko Vujaskovic, Rex Bentley, Helen X. Chen, Jeffrey W. Clark, and Rakesh K. Jain

32 pts ypT0 16%

ACTUARIAL 5-YEAR LOCAL CONTROL 100%
OVERALL S 100%
ACTUARIAL 5-YEAR DFS 75% for metastases

with bevacizumab at 10 mg/kg)

Adverse Event	Grade 1	Grade 2	Grade 3
GI			
Anorexia	6	1	1
Constipation	8	1	1
Dehydration	—	2	1
Diarrhea	12	5	7
Mucositis	7	8	1
Perirectal abscess	—	—	1
Proctalgia/proctitis	1	5	—
Colitis	—	—	1
GU			
Frequency/urgency	13	5	—
Hesitancy	2	—	—
Hypertension	7	1	3
Hand foot	3	1	1
Infection	1	8	—
Skin, radiation dermatitis	13	5	2
Neurologic	4	0	1
Wound, separation	—	—	1

NOTE. There were no grade 4 events.
Abbreviation: GU, genitourinary.

PHASE II STUDY OF PREOPERATIVE RADIATION WITH CONCURRENT CAPECITABINE,OXALIPLATIN AND BEVACIZUMAB FOLLOWED BY SURGERY AND POSTOPERATIVE 5-FU, LEUCOVORIN,OXALIPLATIN (FOLFOX) AND BEVACIZUMAB IN PTS WITH LOCALLY ADVANCED RECTAL CANCER ECOG 3204
J.C. Landry **ASTRO 2009**

Bev 5mg/kg i.v. days 1-15-29 preop
16 pts
TOXICITY: neutropenia, leucopenia, diarrhea
GRADE III: 6/16 (38%)
GRADE IV: 2/16 (13%)
pCR 33%

NEOADJUVANT BEVACIZUMAB DOES NOT APPEAR TO CONTRIBUTE TO POSTOPERATIVE COMPLICATIONS AFTER SURGERY OF RECTAL CANCER
M.M. Shah **ASTRO 2009**

Comparable postoperative complication profile for locally advanced rectal cancer patients who underwent neoadjuvant CTRT with and without bevacizumab

Int. J. Radiation Oncology Biol. Phys., Vol. 76, No. 3, pp. 824–830, 2010

0360-3016/10/$–see front matter

ELSEVIER

doi:10.1016/j.ijrobp.2009.02.037

CLINICAL INVESTIGATION **Rectum**

PHASE II TRIAL OF NEOADJUVANT BEVACIZUMAB, CAPECITABINE, AND RADIOTHERAPY FOR LOCALLY ADVANCED RECTAL CANCER

Christopher H. Crane, M.D.,* Cathy Eng, M.D.,† Barry W. Feig, M.D.,‡ Prajnan Das, M.D.,* John M. Skibber, M.D.,‡ George J. Chang, M.D.,‡ Robert A. Wolff, M.D.,† Sunil Krishnan, M.D.,* Stanley Hamilton, M.D.,§ Nora A. Janjan, M.D.,* Dipen M. Maru, M.D.,§ Lee M. Ellis, M.D.,‡ and Miguel A. Rodriguez-Bigas, M.D.‡

Departments of *Radiation Oncology, †Gastrointestinal Medical Oncology, ‡Surgical Oncology, and §Pathology, The University of Texas M. D. Anderson Cancer Center, Houston, TX

Table 5. Worst acute toxicity during chemoradiation

Toxicity	No. of Patients (%)
Grade 2 gastrointestinal	3 (12%)
Grade 3 perianal desquamation	1 (4%)
Grade 2 hand-foot syndrome	6 (24%)
Fatigue	4 (16%)

Table 6. Pathologic response to chemoradiation

Characteristic ($n = 25$)	No. of Patients (%)
Pathologic complete response	8 (32%)
Microscopic residual disease (≤ 10% viable cells)	6 (24%)
T downstaging	16 (64%)
N downstaging*	15 (79%)
T or N downstaging or both	21 (84%)

* This analysis is based on 19 patients with node-positive disease at the time of clinical workup who had mesorectal excision.

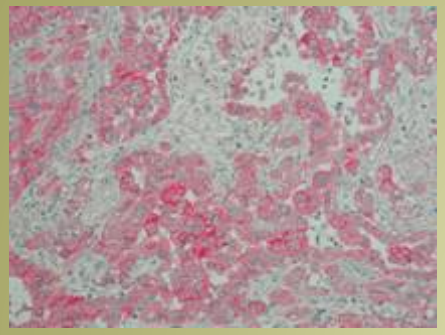
Table 7. Surgical procedures performed and perioperative complications

Procedure*	No. of patients	Minor complications	Major complications†	Total
Low anterior resection	10	2: anastomotic leaks, resolved	None	2/10 (20%)
Proctectomy with coloanal anastomosis	8	1: superficial wound abscess	1: anastomotic dehiscence	2/8 (25%)
Abdominoperineal resection	6	2: delayed perineal wound healing	2: perineal wound dehiscence	4/6 (67%)
Transanal resection	1	None	None	0/1 (0%)
Total	25	5/25 (20%)	3/25 (12%)	8/25 (32%)

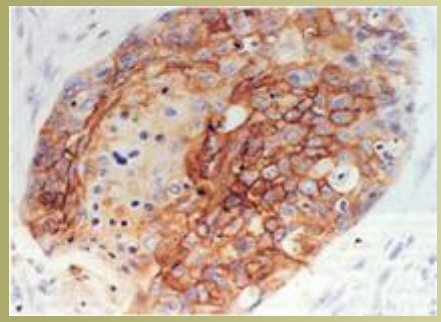
Conclusions: The addition of bevacizumab to neoadjuvant chemoradiation resulted in encouraging pathologic complete response without an increase in acute toxicity. The impact of bevacizumab on perineal wound and anastamotic healing due to concurrent bevacizumab requires further study.

Neoadjuvant, Chemoradiation, Rectal cancer, Bevacizumab.

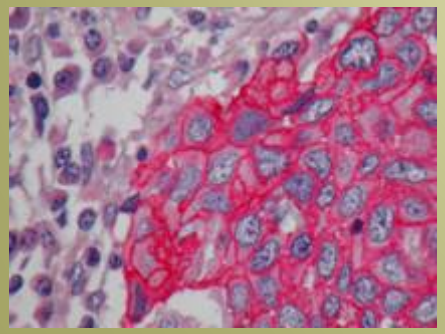
EGFR expression in solid tumors



Colorectal



Lung (NSCLC)



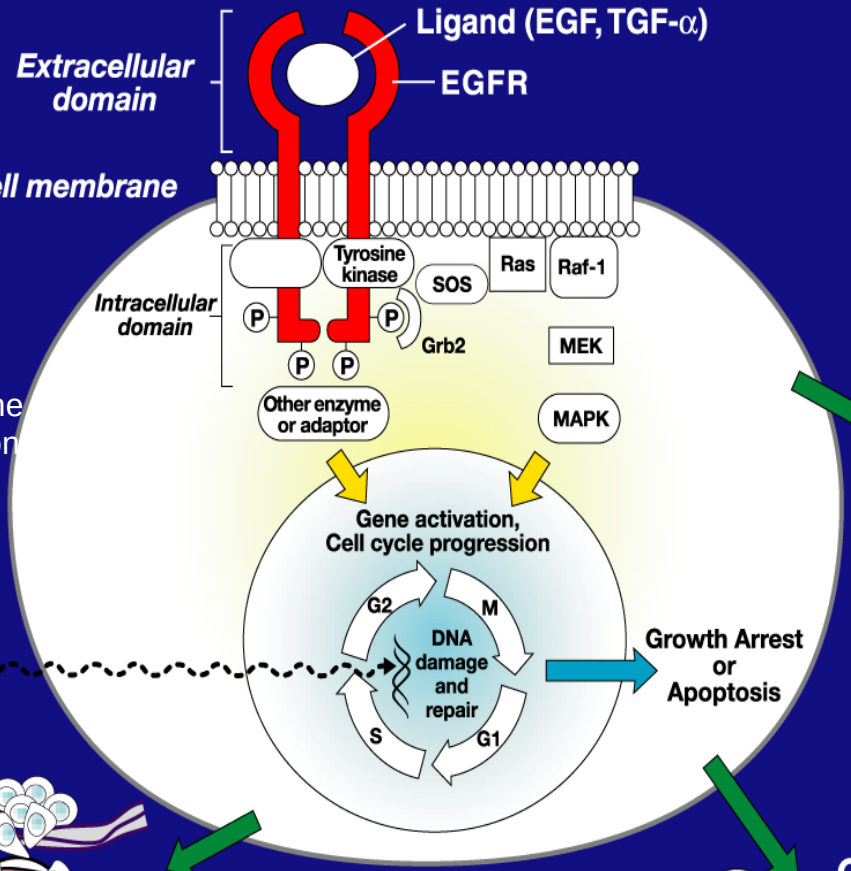
Head & Neck (SCC)

EGFR is expressed in a variety of solid tumors

Colorectal cancer (advanced)	75-82%
Lung cancer (NSCLC)	40-91%
Head & neck cancer (SCCHN)	90-100%
Gastric cancer	33-74%
Ovarian cancer	35-70%

Role of the EGFR in Signal Transduction and Tumor Progression

-Proteina transmembrana
con attività tirosino-kinasica intrinseca
-Iperespressa nell'80% delle neoplasie del colon-retto
-Ruolo nella differenziazione e proliferazione cell, nell'angiogenesi, nella metastatizzazion



Harari PM, Huang S-M. *Clin Cancer Res*. 6:323, 2000

CORRELATION OF TUMOR REGRESSION GRADE (TRG), CIRCUMFERENTIAL MARGIN (CM), AND EPIDERMAL GROWTH FACTOR RECEPTOR EXPRESSION WITH DFS IN LOCALLY ADVANCED RECTAL CANCER PATIENTS (LARC) TREATED WITH PREOPERATIVE RTCT

EGFR overexpression associated with radioresistance and poor prognosis

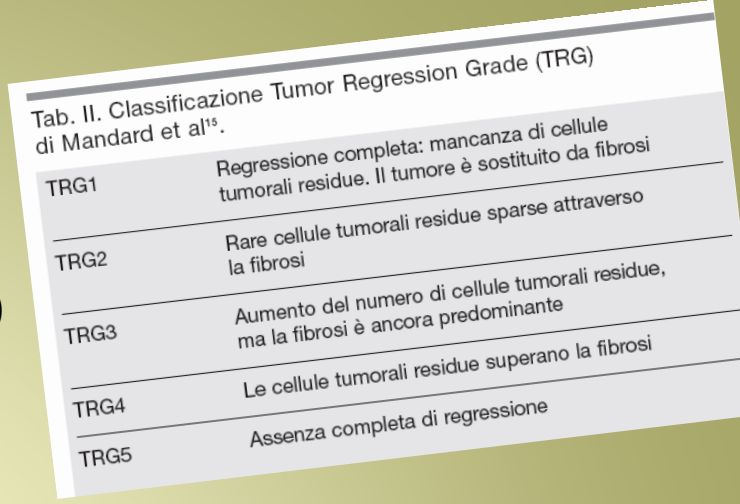
EGFR was determinated at the preRT biopsy, using EGFR monoclonal antibody and was evaluated according to extension and intensity
It was defined positive (EGFR+) as extension of 10% or more.

EGFR
FATTORE PROGNOSTICO

Arias F.-ASCO 2011

RESULTS

PATHOLOGIC COMPLETE REMISSION 13 pts (14%)
DOWNSTAGING 43 pts



Tab. II. Classificazione Tumor Regression Grade (TRG) di Mandard et al[15].

TRG1	Regressione completa: mancanza di cellule tumorali residue. Il tumore è sostituito da fibrosi
TRG2	Rare cellule tumorali residue sparse attraverso la fibrosi
TRG3	Aumento del numero di cellule tumorali residue, ma la fibrosi è ancora predominante
TRG4	Le cellule tumorali residue superano la fibrosi
TRG5	Assenza completa di regressione

EGFR+ in 62/92 tumors (67.4%) not associated with T-stage or N-stage

	3yDFS	
TRG0-1	100%	
TRG 2-3	71%	p.0.001
CM< 1mm	86%	
CM>1mm	70%	p=0.1
EGFR -	85%	
EGFR+	81%	p=0.5

CONCLUSION

EGFR is significantly expressed but is not predictive factor for response

TRG is the strongest prognostic factor

Arias F.-ASCO 2011

ErbB Inhibition as a Therapeutic Strategy

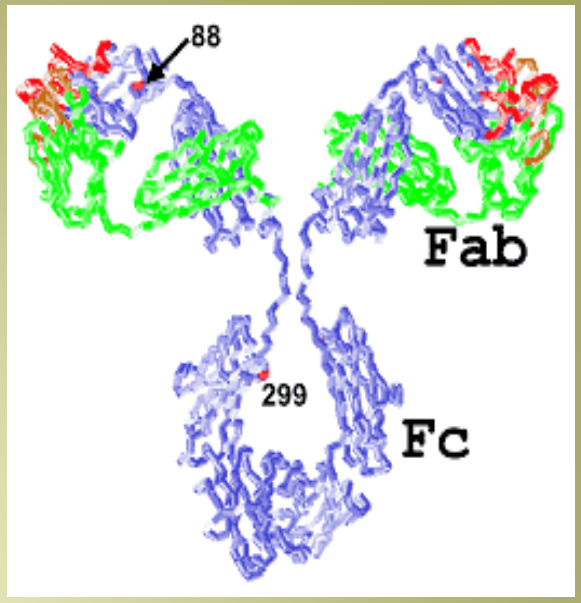
EGFR overexpression is associated with tumor repopulation during fractionated radiotherapy

Decreased repopulation as well as increased reoxygenation contribute to the improvement in local control after targeting of the EGFR by C225 during fractionated irradiation

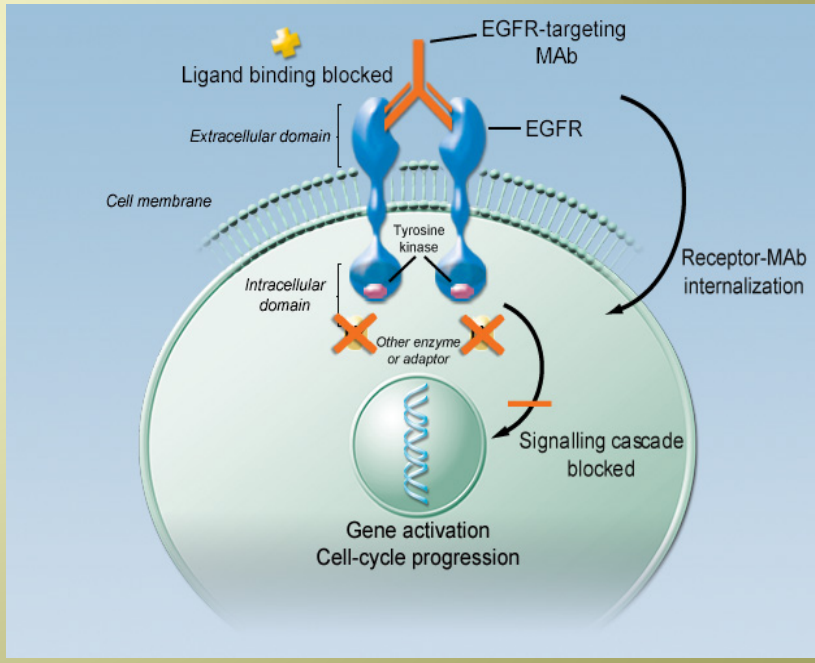
Mechthild Krause[a], Gernot Ostermann[a], Cordula Petersen[a], Ala Yaromina[a], Franziska Hessel[a], Andreas Harstrick[c], Albert J van der Kogel[d], Howard D Thames[e], Michael Baumann[a,b,*]

Radiotherapy and Oncology 76 (2005) 162-167
www.thegreenjournal.com

CETUXIMAB



- Cetuximab is a chimeric human/murine immunoglobulin G1 (IgG1) MAB targeting the EGFR, that was initially developed from the murine antibody m225.
- The drug achieves its anticancer effect by binding to the extracellular endogenous binding domain of EGFR with an affinity greater than natural EGFR ligands.
- Subsequently, cetuximab downregulates EGFR expression and interferes with a number of signaling pathways, including Ras-Raf-MAP, phosphatidylinositol 3-kinase, Akt, JAK/STAT kinases, and protein kinase C.
- Prevents binding of EGF or TGF- to EGFR and prevents activation of intracellular tyrosine kinase



COLORECTAL CANCER

- RANDOMIZED PHASE III STUDY OF IRINOTECAN AND 5FU/FA WITH OR WITHOUT CETUXIMAB IN THE FIRST LINE TREATMENT OF PATIENTS WITH COLORECTAL CANCER: THE CRYSTAL STUDY
  Van Cutsem- ASCO 2007

Response-Rate: 46.9% vs 38.7% BETTER PFS

- PHASE III TRIAL OF CETUXIMAB PLUS IRINOTECAN AFTER FLUOROPYRIMIDINE AND OXALIPLATIN FAILURE IN PATIENTS WITH METASTATIC COLORECTAL CANCER.
  Sobrero 2008

Response rate: 16.4% vs 4.2% BETTER PFS

- MULTICENTER PHASE II AND TRANSLATIONAL STUDY OF CETUXIMAB IN METASTATIC COLORECTAL CARCINOMA REFRACTORY TO IRINOTECAN, OXALIPLATIN AND FLUOROPYRIMIDINES
  Lenz JCO 2006

S 6.6 months

- CETUXIMAB MONOTHERAPY AND CETUXIMAB PLUS IRINOTECAN IN IRINOTECAN REFRACTORY METASTATIC COLORECTAL CANCER
  Cunningham N Engl J med 2004

Response rate 22.9% vs 10.8%

Phase I/II Studies of Cetuximab With Radiation Therapy and Chemotherapy for Rectal Cancer

Study	N	EBRT Dose	Chemotherapy	Cetuximab	pCR Rate
MSKCC[38]	20	50.4 Gy/1.8 Gy/5.5 wk	5-FU IV CI, 225 mg/m²/d	400 mg/m² d 1, then 250 mg/m² weekly	12%
Heibelberg[39]	20	50.4 Gy/1.8 Gy/5.5 wk	Irinotecan, 40–50 mg/m² (weekly) Capecitabine, 400–500 mg/m² bid	400 mg/m² d 1, then 250 mg/m² weekly	7%*
Louvain[40]	40	45 Gy/1.8 Gy/5 wk	Capecitabine, 625–825 mg bid	400 mg/m²/1 wk before RT, then 250 mg/m² weekly during RT	5%
German Multisite Study[41]	60	50.4 Gy/1.8 Gy/5.5 wk	Oxaliplatin, 50 mg/m² (d1, 8, 22, 26) Capecitabine, 500–825 mg/m² bid	400 mg/m²/1 wk before RT, then 250 mg/m² weekly during RT	9%

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CLINICAL INVESTIGATION **Rectum**

NEOADJUVANT TREATMENT WITH SINGLE-AGENT CETUXIMAB FOLLOWED BY 5-FU, CETUXIMAB, AND PELVIC RADIOTHERAPY: A PHASE II STUDY IN LOCALLY ADVANCED RECTAL CANCER

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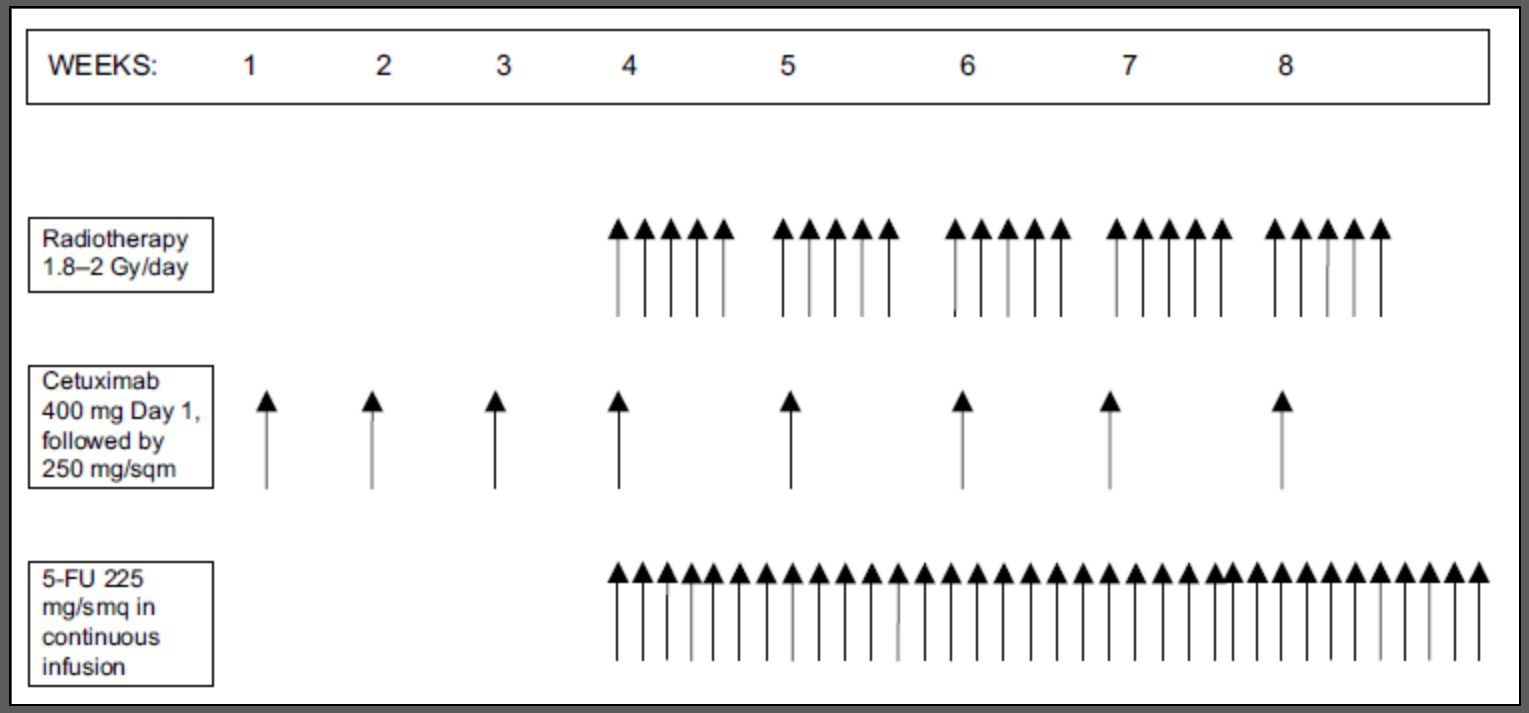
TREATMENT SCHEDULE



TOXICITY

	Grade		
	1–2	3–4	Total
Skin rash	28 (70%)	3 (7.5%)	31 (77.5%)
Hypersensitivity reactions	5 (13%)	3 (7.5%)	8 (20.5%)
Gastrointestinal	19 (47%)	5 (13%)	24 (60%)
Diarrhea	13 (32%)	3 (7.5%)	16 (39.5%)
Stomatitis	1 (2.5%)	1 (2.5%)	2 (5%)
Nausea/vomiting	0 (0%)	0 (0%)	0 (0%)
Liver enzyme	2 (5%)	1 (2.5%)	3 (7.5%)
Anal/rectal pain	3 (7.5%)	0 (0%)	3 (7.5%)
Haematologic	1 (2.5%)	1 (2.5%)	2 (5%)
Anemia	1 (2.5%)	0 (0%)	1 (2.5%)
Trombocytopenia	0 (0%)	0 (0%)	0 (0%)
Neutropenia	0 (0%)	0 (0%)	0 (0%)
Febrile neutropenia	0 (0%)	1 (2.5%)	1 (2.5%)
Sistemic symptoms	2 (5%)	0 (0%)	2 (5%)
Fatigue	2 (5%)	0 (0%)	2 (5%)
Urologic toxicity	1 (2.5%)	0 (0%)	1 (2.5%)
Cystitis	1 (2.5%)	0 (0%)	1 (2.5%)

35/40 PTS COMPLETED NEOADJUVANT TREATMENT:

5 pts (12%) STOPPED PERMANENTLY CETUXIMAB AFTER ONE ADMINISTRATION (3 hypersensitivity reactions, 1 rapid PD , 1 purulent arthritis)

6 pts INTERRUPT TEMPORARILY FOR CETUX RELATED TOXICITY

DOWN-STAGING IN 23 PTS (60.5%)

pT0N0 IN 3 PTS (8%)

Conclusions: Preoperative treatment with 5-FU, cetuximab, and pelvic RT is feasible with acceptable toxicities; however, the rate of pathologic responses is disappointingly low.

WHICH IS THE BETTER SEQUENCE OF ADMINISTRATION OF CETUXIMAB AND RADIOTHERAPY?

WHICH PATIENTS ???

SEVERAL MECHANISMS MAY CONTRIBUTE TO THE APPARENTLY SUBADDITIVE INTERACTION BETWEEN RCT AND CETUXIMAB, INCLUDING:

- G1 cell cycle arrest
- A less critical role of repopulation using a non curative radiation dose
- Antagonistic effects on 5-FU-based CTRT and Oxaliplatin (different sequence??)
- K-ras mutation status (a negative predictor for response)

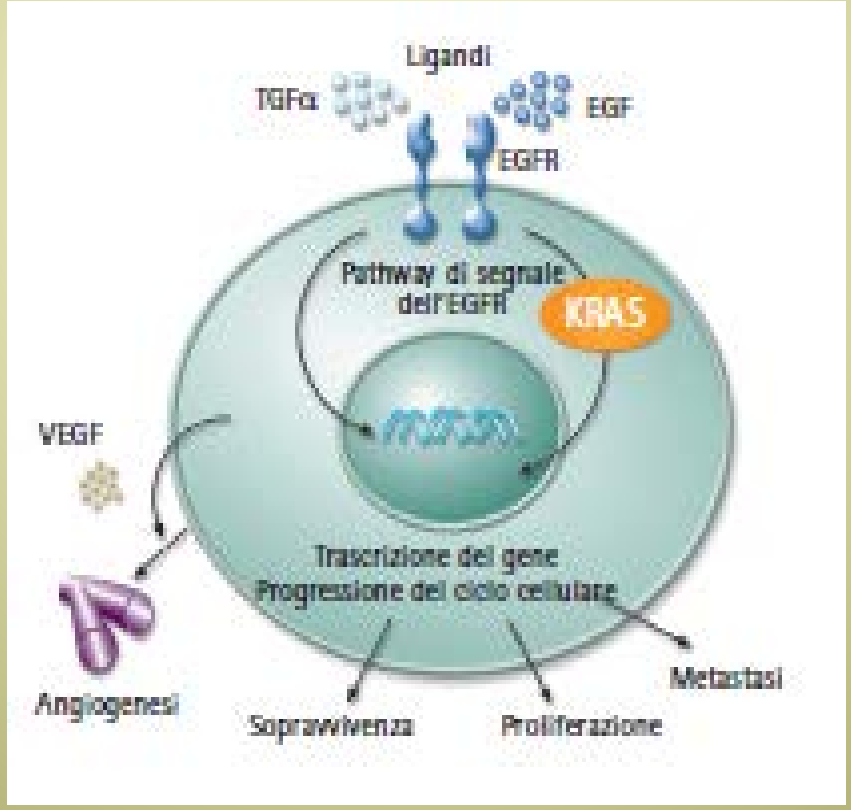
Cos'è il KRAS?

Il KRAS è un gene che codifica una proteina che gioca un ruolo chiave nella via di trasduzione del segnale intracellulare del recettore del fattore di crescita epidermico (EGFR)

Questa via di trasduzione del segnale intracellulare è importante nello sviluppo e nella progressione tumorale

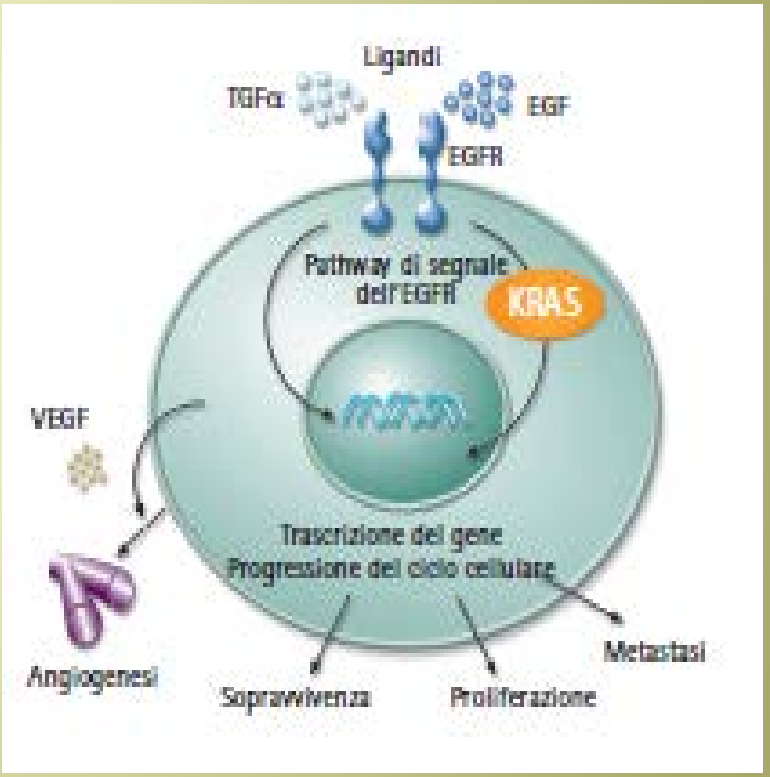
La proteina KRAS agisce nella parte iniziale della cascata di trasduzione del segnale

La proteina KRAS svolge un ruolo cruciale nello sviluppo del tumore, attraverso la regolazione di proteine a valle che sono coinvolte nella proliferazione, sopravvivenza cellulare, diffusione delle metastasi ed angiogenesi



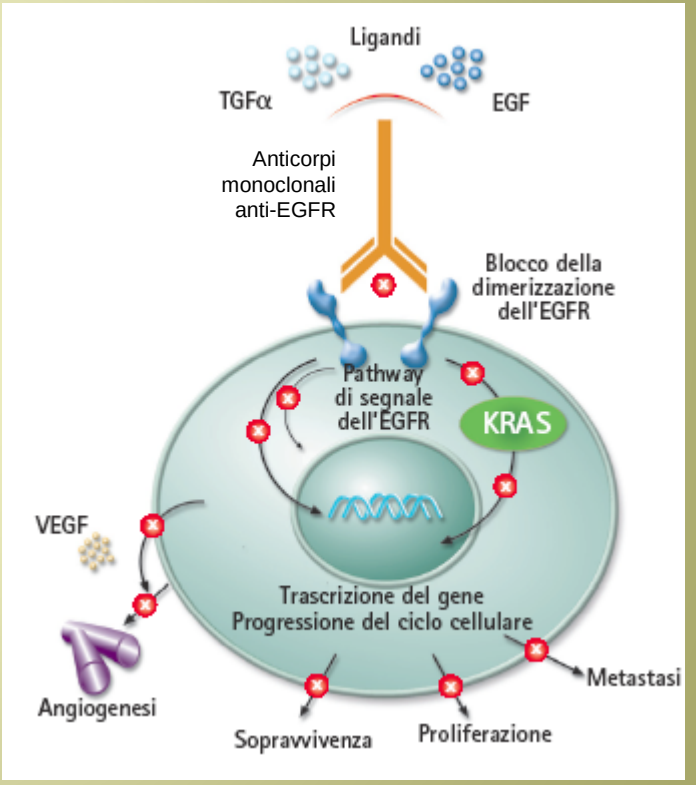
La via dell'EGFR e l'importanza dello stato di KRAS

- Il gene KRAS può essere normale (wild-type) o mutato
- **La proteina KRAS wild-type** è **temporaneamente** attivata, in risposta al segnale indotto dall'EGFR
  - **Gli effetti della proteina sono ben controllati**
- **La proteina KRAS mutata** **è attivata costituzionalmente**, anche in assenza del segnale mediato dall'EGFR
  - **Gli effetti del KRAS** sulla proliferazione cellulare e sulla diffusione del tumore **proseguono senza controllo**
- Lo stato di KRAS di un tumore può avere significato prognostico ed essere predittivo di risposta ad un determinato trattamento



Uso di anticorpi monoclonali anti-EGFR per bloccare le vie di trasduzione del segnale intracellulare

- Gli anticorpi monoclonali diretti contro l'EGFR bloccano la trasduzione del segnale mediata dal recettore e inibiscono i successivi eventi a cascata, inclusi gli effetti mediati dal KRAS
- Quando il KRAS è mutato la proteina è sempre "attivata" e, probabilmente, bloccando l'EGFR non si hanno effetti sulla trasduzione del segnale
  - Il tumore continua a crescere, proliferare e diffondersi
- Pertanto, l'inibizione dell'EGFR con un anticorpo monoclonale potrebbe essere più efficiente nei tumori KRAS wild-type
  - Nel CRC metastatico, più del 65% dei pazienti ha cellule tumorali con gene KRAS wild-type
  - Esistono sei mutazioni del KRAS a livello dei codoni 12/13 nel CRC : G12A, G12V, G12D, G12C, G12S, G13D e G12R



I vantaggi del test di KRAS

- Conoscere lo stato di KRAS del tumore di un paziente permette di individualizzare il trattamento

- I pazienti con KRAS wild type trattati con inibitori anti-EGFR hanno un maggior beneficio clinico rispetto ai pazienti con KRAS mutato[1,2]

Il test dello stato di KRAS permette di personalizzare la terapia

1) Bokemeyer *et al*. ASCO Annual Meeting 2008: abstract 4000. 2) Van Cutsem *et al*. ASCO Annual Meeting 2008: abstract 2.

CETUXIMAB IS THE ONLY AGENT THAT HAS BEEN APPROVED AS A RADIOSENSITIZER; ON THE BASIS OF A PHASE III TRIAL (BONNER'STUDY)

BUT

CETUXIMAB AND RT IN NEOADJUV SETTING IN RECTAL CANCER HAS NOT RESULTED IN DRAMATIC INCREASE IN pCR(5%-12%)

IT IS POSSIBLE THAT THE BENEFIT TO CETUXIMAB WAS RESTRICTED TO PTS WITHOUT ACTIVATING K-RAS MUTATIONS

INDUCTION CHEMOTHERAPY

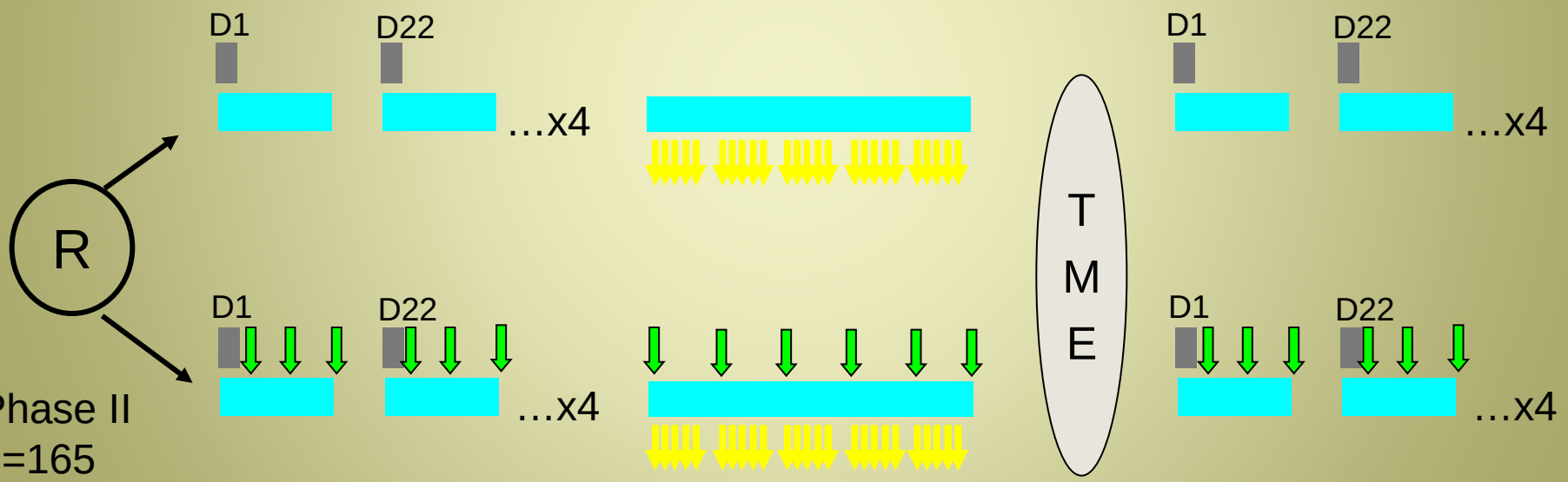
+

TARGET THERAPY

EXPERT-C:EUROPEAN MULTICENTER TRIAL

Patients with MRI defined poor-risk rectal cancer (CRM threatened or involved, low T3,

T extending 5mm or more into perirectal fat,T4, T1-4N2)



Phase II
n=165
15 EUROPEAN CENTRES

Oxa: 130 mg/m^2/d
Cape: 1700 mg/m^2/d

Cape: 1650 mg/m^2/d
RT:45 Gy+ 5.4Gy boost

Oxa: 130 mg/m^2/d
Cape: 2000 mg/m^2/d

Cetuximab: 400 mg/m^2 D1 than 250 mg/m^2 weekly

EXPERT-C

PRIMARY ENDPOINTS: CR (pCR or RADIOLOGICAL CR) **IN KRAS AND BRAF WILD TYPE TUMOURS**

SECONDARY ENDPOINTS: RADIOLOGICAL RESPONSE; CR IN BOTH KRAS WILD TYPE AND MUTANT PATIENTS, R0 RESECTION RATES, PFS, S, SAFETY

RESULTS

	CAPOX+ C	CAPOX	
Radiological response after CT	70%	50%	P=0.038
Radiological response after CTRT	89%	72%	P=0.028
pCR	11%	7%	
PFS	80%	81%	
OS3y	96%	81%	P=0.035
Molecular analysis 149pts			
KRAS/BRAF wild type	46	44	
In 15pts no sufficient tissue for analysis: 9/15 pCR, 6/9 in arm with Cetuximab			

No increased toxicities with Cet

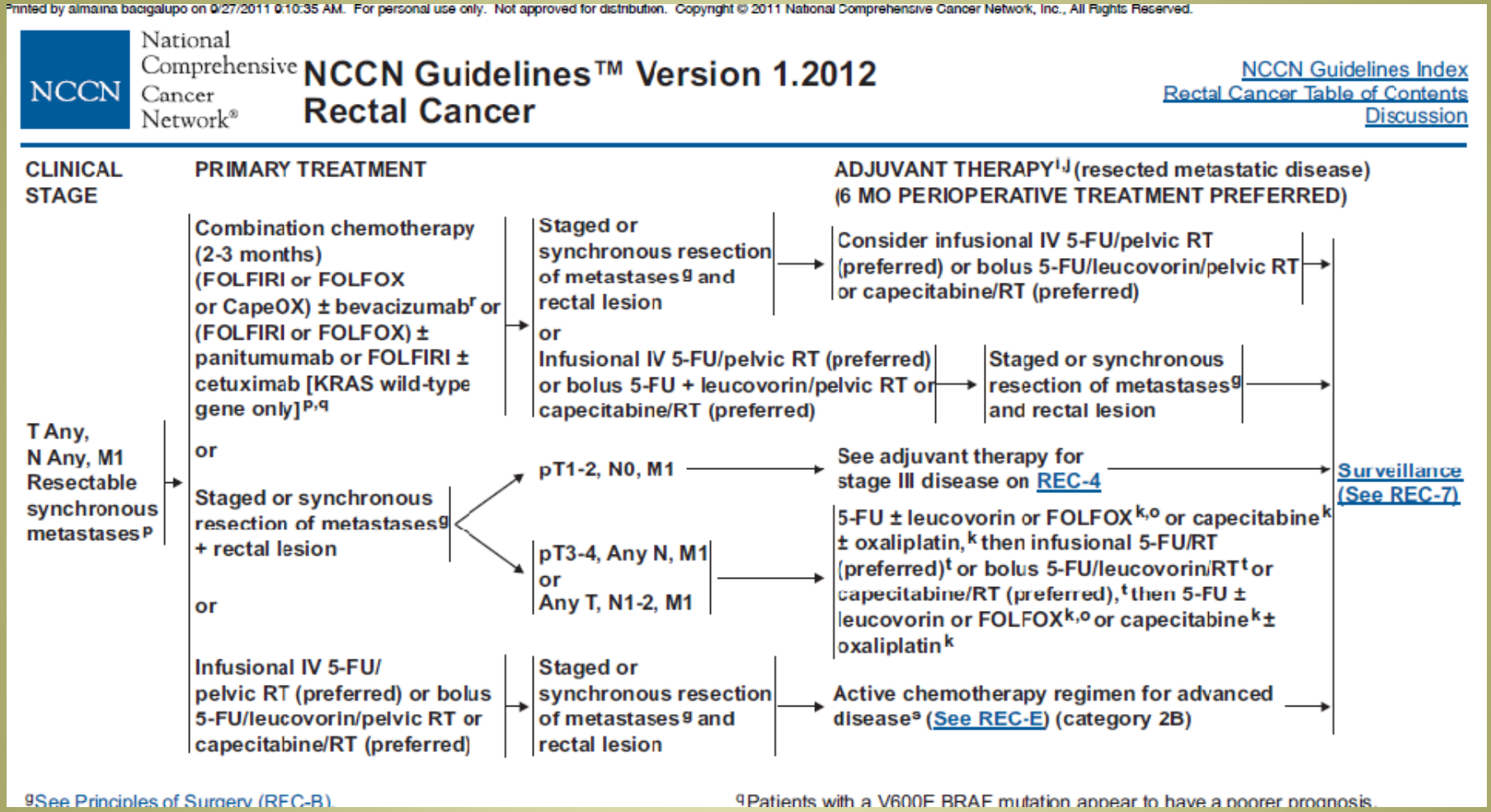
ALTHOUGH THESE DIFFERENCES ARE SMALL, THIS TRIAL IS THE FIRST SINCE THE 1997 SWEDISH TRIAL THAT SHOWED A BENEFIT IN OS

MORE-VIGOROUS VALIDATION OF THESE RESULTS IS REQUIRED IN LARGER PHASE III TRIALS

CONCLUSIONS 1

NEED OF FUTURE TRANSLATIONAL RESEARCH WILL BE TO CHARACTERIZE PTS AND TUMORS WHICH WILL BENEFIT MOST FROM TARGETED THERAPIES

CONCLUSIONS 2



«The panel strongly recommends genotyping of tumor *tissue* ***in all pts with metastatic colorectal cancer at the time of diagnosis of stage IV.*** The recommendation is not mean to indicate a preference regarding regimen selection in the first line setting but rather in order to plan for the treatment continuum»