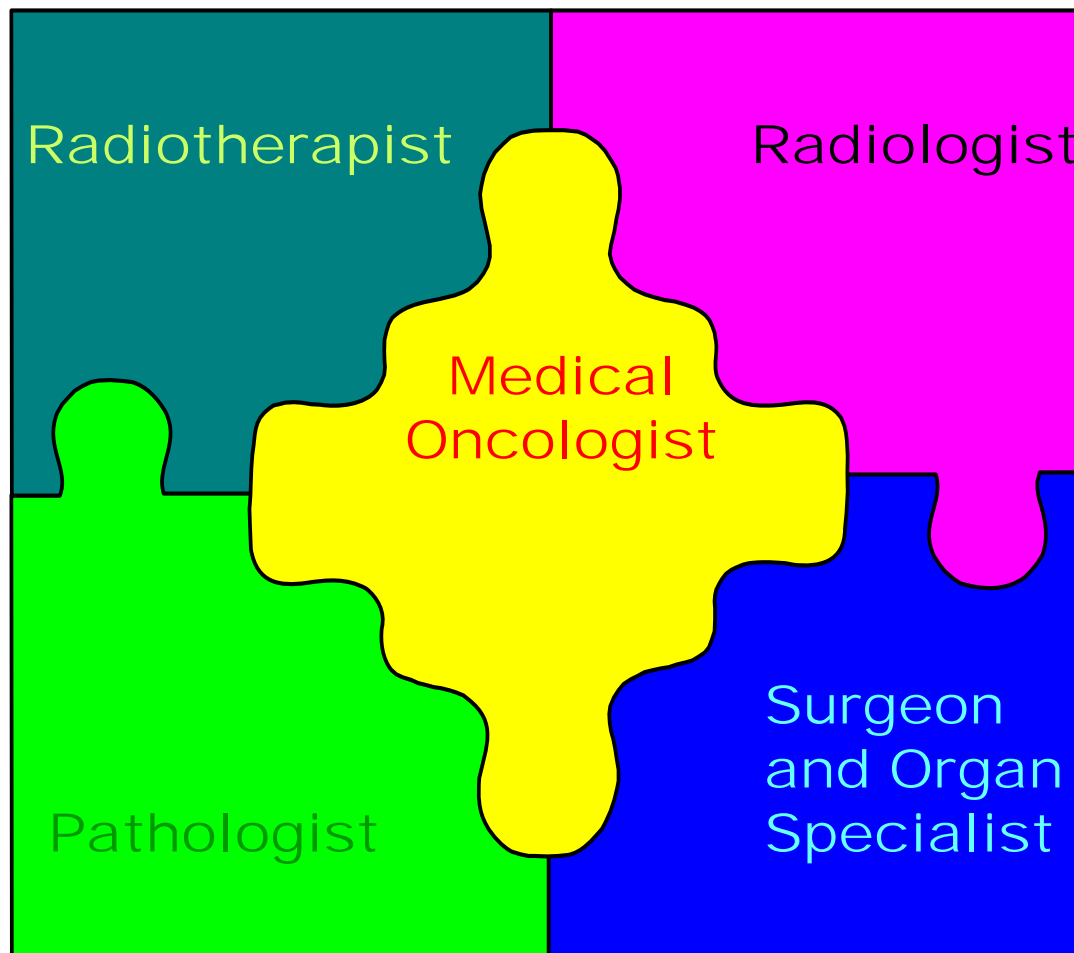


Medical Oncology

Multidisciplinary Cancer Management Course

Multidisciplinary Approach



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ASCO/ESMO Global Oncology Curriculum

“The management of malignant diseases requires the expertise of many different medical subspecialties, and the majority of patients with malignant diseases are best managed in a multidisciplinary approach with **integration of the various subspecialties** because of increasing complexity of modern treatment. The trainee should **recognize the contributions of each of these subspecialties** in making the diagnosis, assessing disease stage, and treating the underlying disease and its complications.”

J Clin Oncol. 2004;22:4616-4625.

Role of Medical Oncologist

- Coordinate care of patients with cancer, especially stage III and IV cancers
- Administer systemic agents (drugs, biologic agents, hormone therapy, etc.)
- Manage symptoms of systemic therapies
- Manage symptoms of stage IV cancers, including end-of-life care

Role of Medical Oncologist (cont.)

- Enter patients into clinical trials
- Provide for counseling, including psychosocial, genetic, and preventive interventions
- Discuss/provide screening for relapse
- Manage cancer as a chronic disease
- Counsel patients about multidisciplinary care plans and treatment options

Primary Indications for Chemotherapy for Solid Tumors

- Neoadjuvant and adjuvant treatment of operable disease
- In combination with radiation therapy for locally advanced disease
- Palliative therapy for metastatic disease

Response of Advanced Solid Tumors to Chemotherapy

The following cancers are curable by chemotherapy

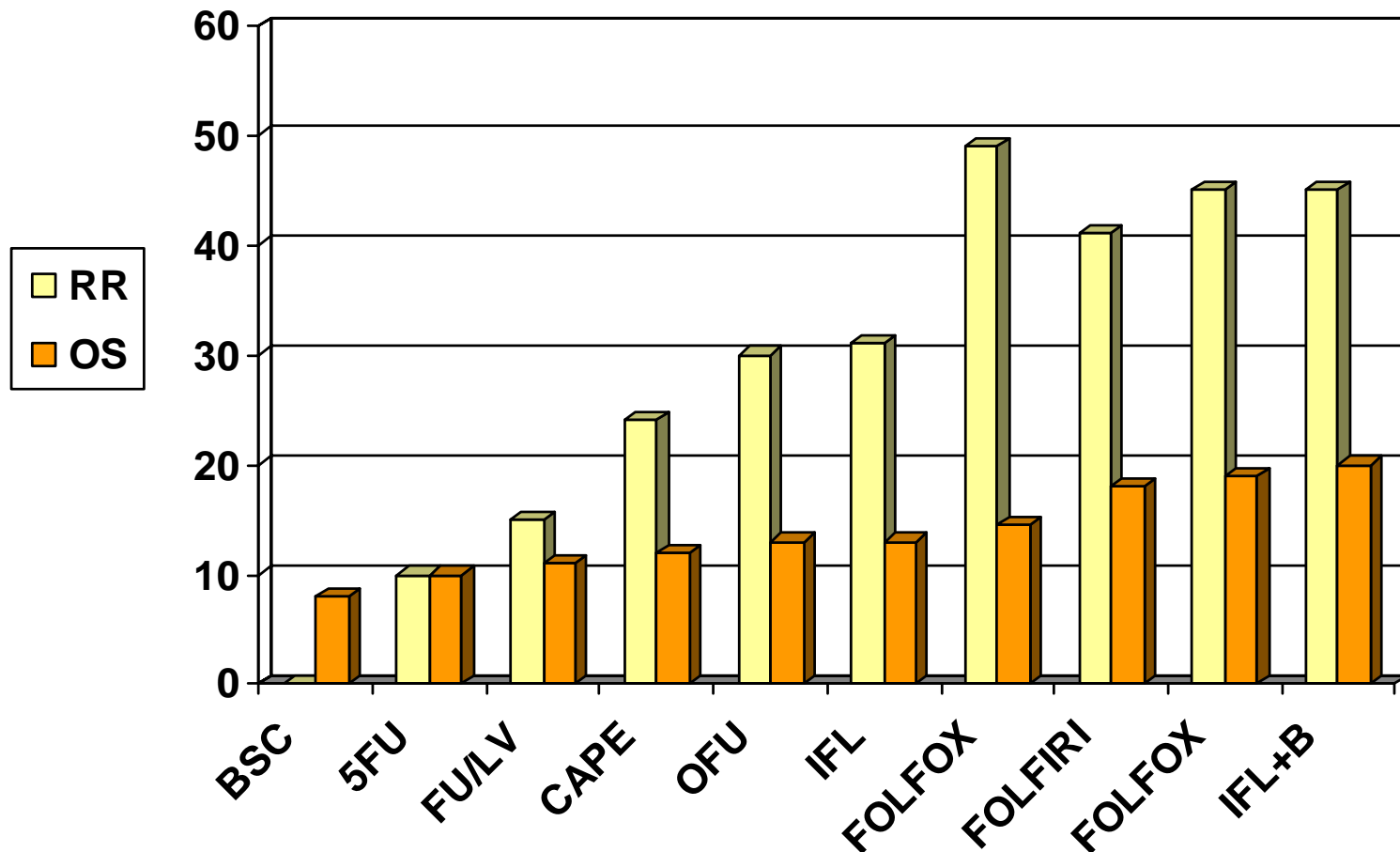
- Ewing's sarcoma
- Rhabdomyosarcoma
- Wilms tumor
- Lymphoma (Hodgkin's and non-Hodgkin's)
- Gestational trophoblastic cancer
- Testicular cancer

Response of Advanced Solid Tumors to Chemotherapy (cont.)

Chemotherapy has significant activity in other cancers, such as

- Colorectal cancer
- Breast cancer
- Head and neck cancer
- Lung cancer
- Ovarian cancer
- Bladder cancer

First-Line Chemotherapy for Colorectal Cancer: Benefit and Evolution



Response of Advanced Solid Tumors to Chemotherapy (cont.)

Chemotherapy has minor activity in some cancers:

Brain tumors (astrocytoma)

Melanoma

Cervical cancer

Pancreatic cancer

Hepatocellular cancer

Prostate cancer

Kaposi's sarcoma

Soft tissue sarcoma

The Case of “Noncurative” Chemotherapy

- Quality of life as main endpoint of treatment
- Involvement of patients in decisions about their care
- Systematic and continuous integration with the palliative care experts and in the home setting

“Good Points” for Chemotherapy of Solid Tumors Today

- Many options with different toxicity profiles
- Possibility to customize treatment (also for elderly or unfit patients and opportunity for second-line treatment)
- Better integration of chemotherapy in the combined modality

Response of Solid Tumors to Chemotherapy (cont.)

Adjuvant chemotherapy is effective

- Breast cancer
- Colorectal cancer (stage III)
- Ovarian cancer
- Lung cancer (stage II and III)

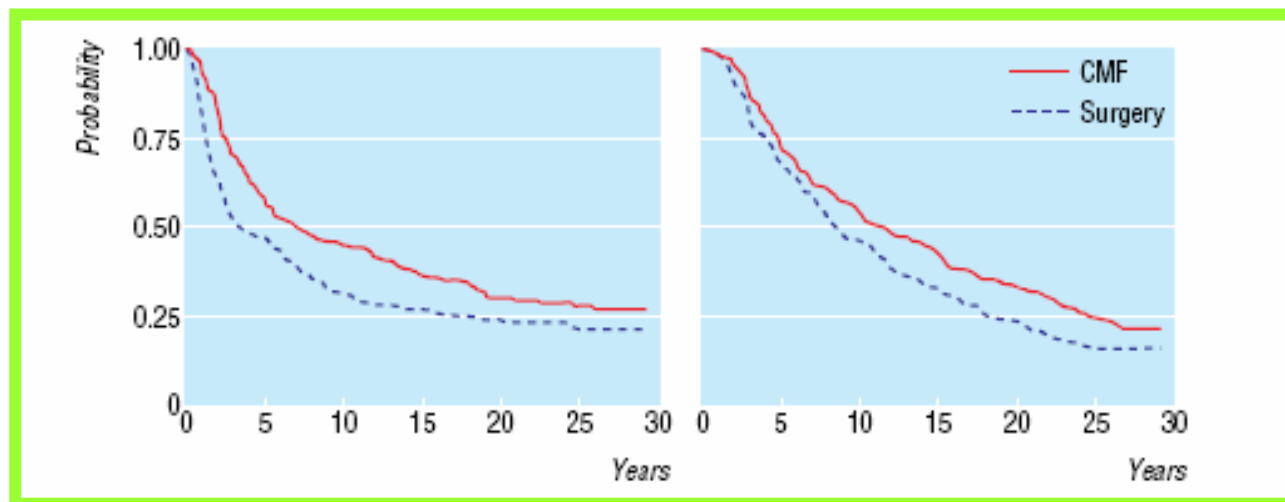
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30 years' follow up of randomised studies of adjuvant CMF in operable breast cancer: cohort study

Gianni Bonadonna, Angela Moliterni, Milvia Zambetti, Maria Grazia Daidone, Silvana Pilotti, Luca Gianni, Pinuccia Valagussa

Relapse-free Survival

Overall Survival



Bonadonna et al. *BMJ*. 2005; 330: 217-223.

Theoretical Advantages of Neoadjuvant Chemotherapy

- Better patient tolerance and compliance
- Reduces tumor burden
 - Downstaging
 - Conservative surgery
- Earliest treatment of micrometastatic disease
 - Survival
- In vivo testing of new agents

Indications for Neoadjuvant Chemotherapy

- Initial treatment for locally advanced or inflammatory breast cancer
- Allows breast conservation for patients with large primary tumors
- Used to treat patients with ovarian cancers who are not candidates for surgery
- Used to treat patients with osteosarcoma to make conservative surgery possible

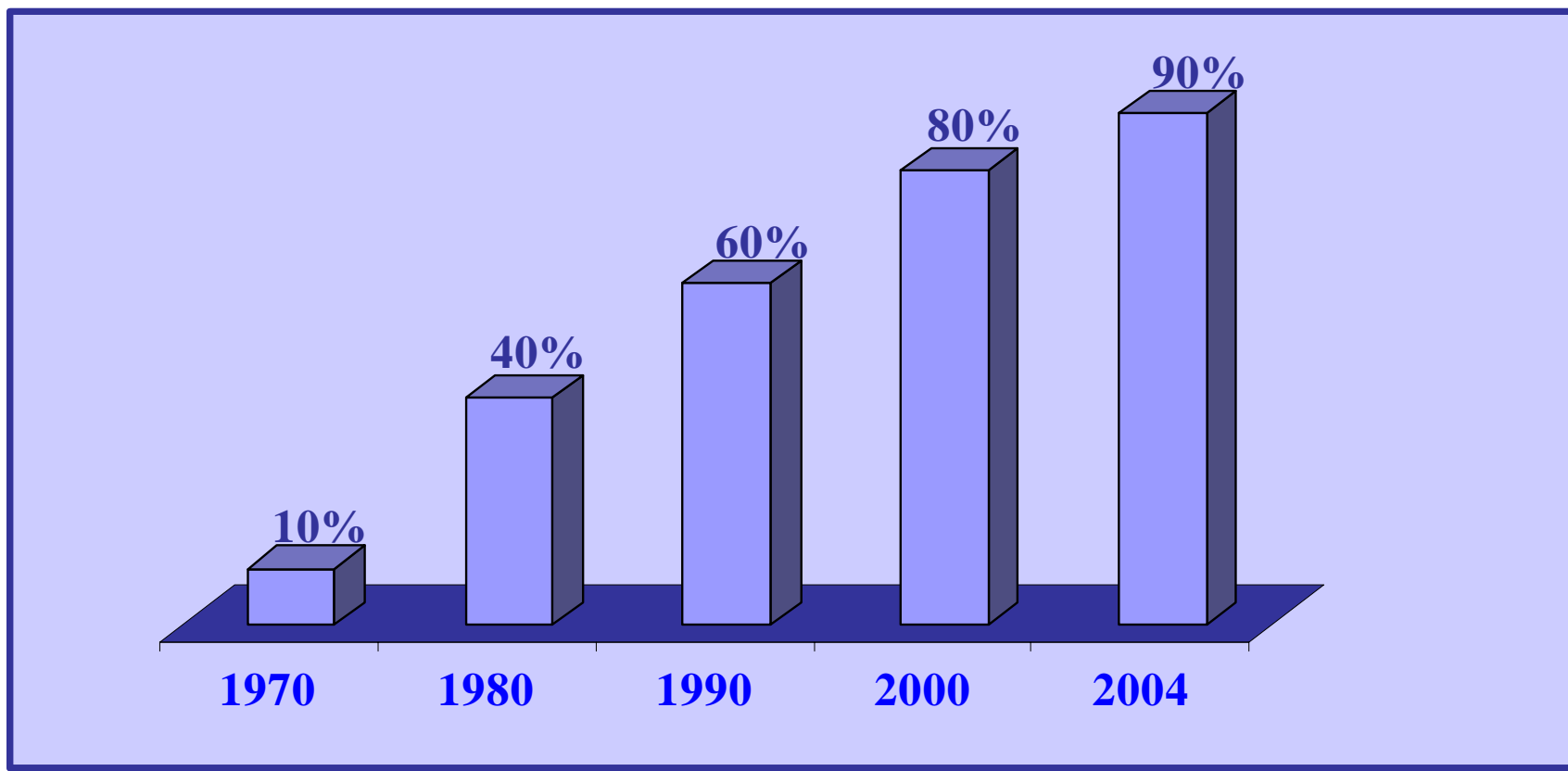
Supportive Care

Progress in the following supportive measures has had a major impact on clinical practice

- Antiemetic therapy
- Analgesic drugs
- Diphosphonates
- Growth factors

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Progress in the Control of Acute Cisplatin-Induced Nausea and Vomiting



Consensus Recommendations and Guidelines for Antiemetic Therapy

The combination of a 5-HT₃ antagonist plus a corticosteroid, plus a NK-1 antagonist represents the standard of care for patients receiving chemotherapy of high emetic risk

MASCC. Perugia Consensus Conference, March 29-31, 2004

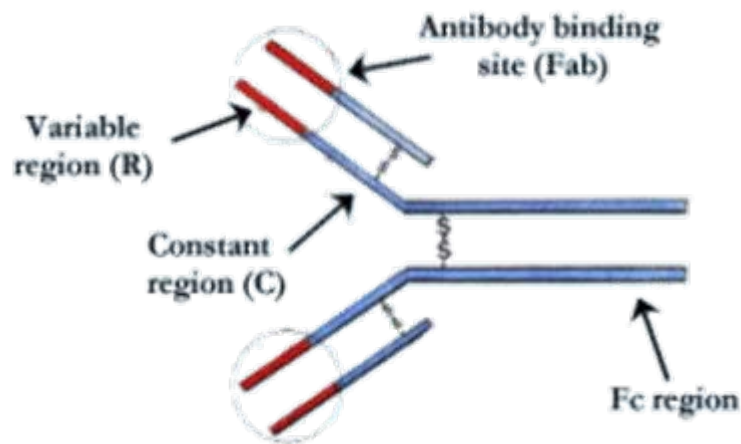
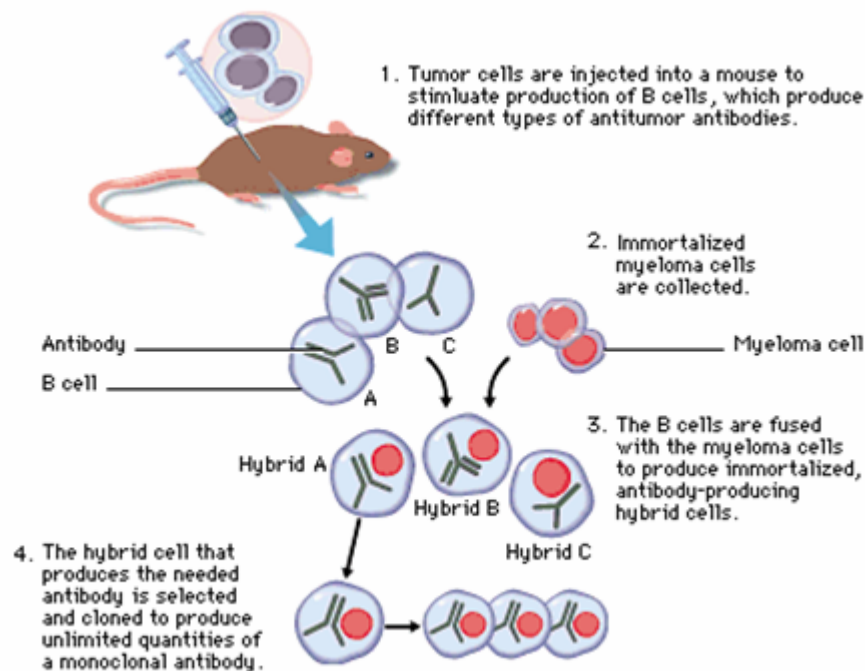
ASCO. *J Clin Oncol*. 2006;24(18):2932-2947

New Therapies for Solid Tumors

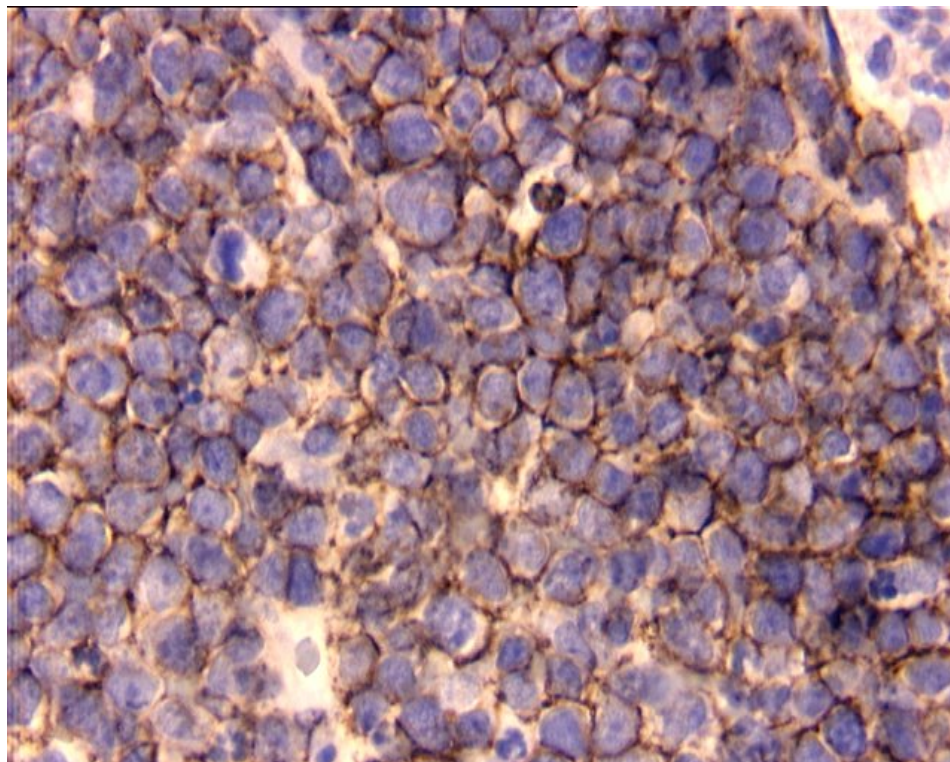
- Signal transduction inhibitors
- Cyclo-oxygenase-2 (COX-2) inhibitors
- Retinoids
- Matrix metalloprotease inhibitors
- Gene therapy
- Vaccine therapy
- Angiogenesis inhibitors

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Monoclonal antibody: The concept



Monoclonal antibody: The target



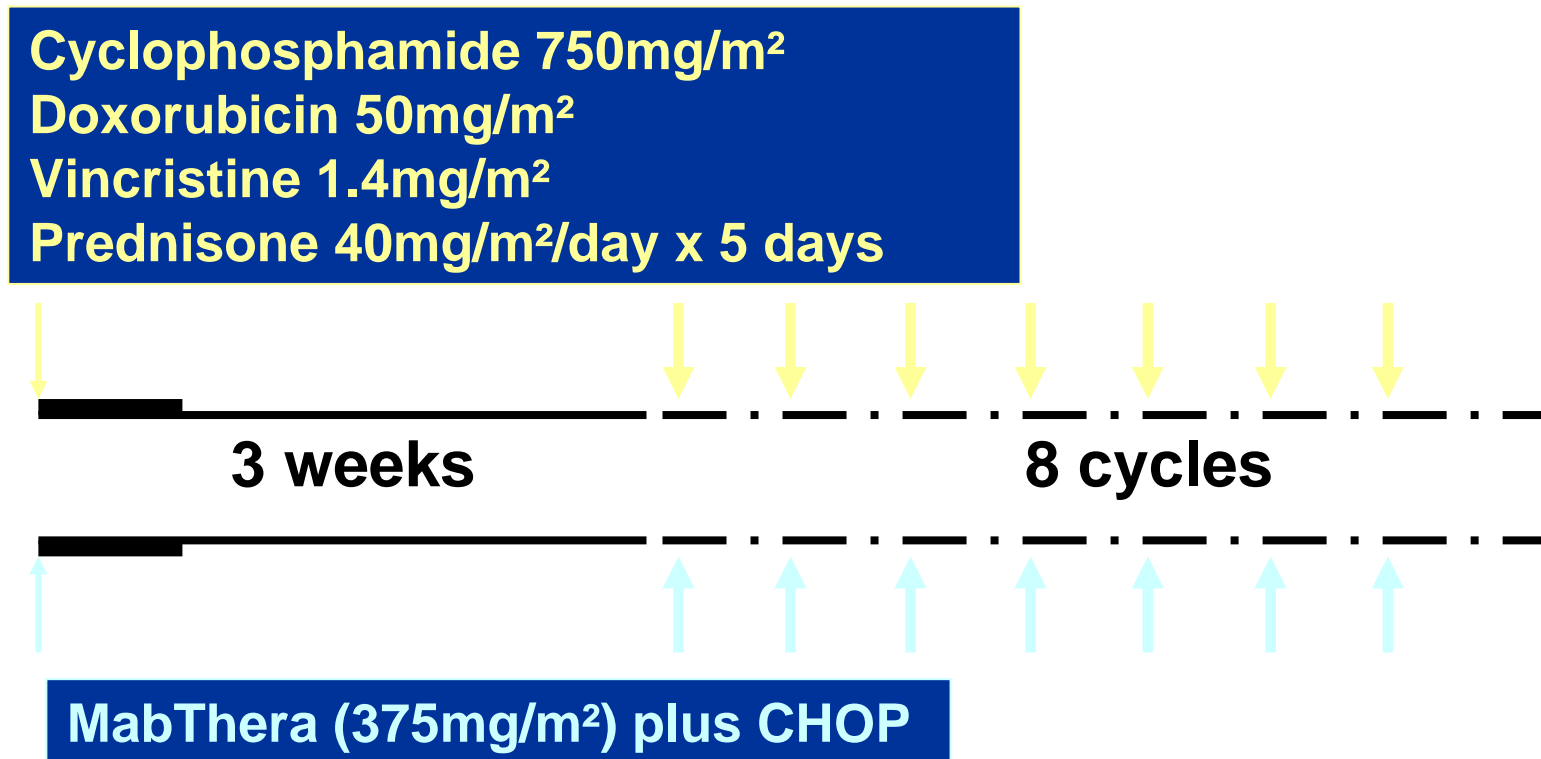
CD 20 Antigen on B-Leukocyte

Monoclonal antibody: The drug

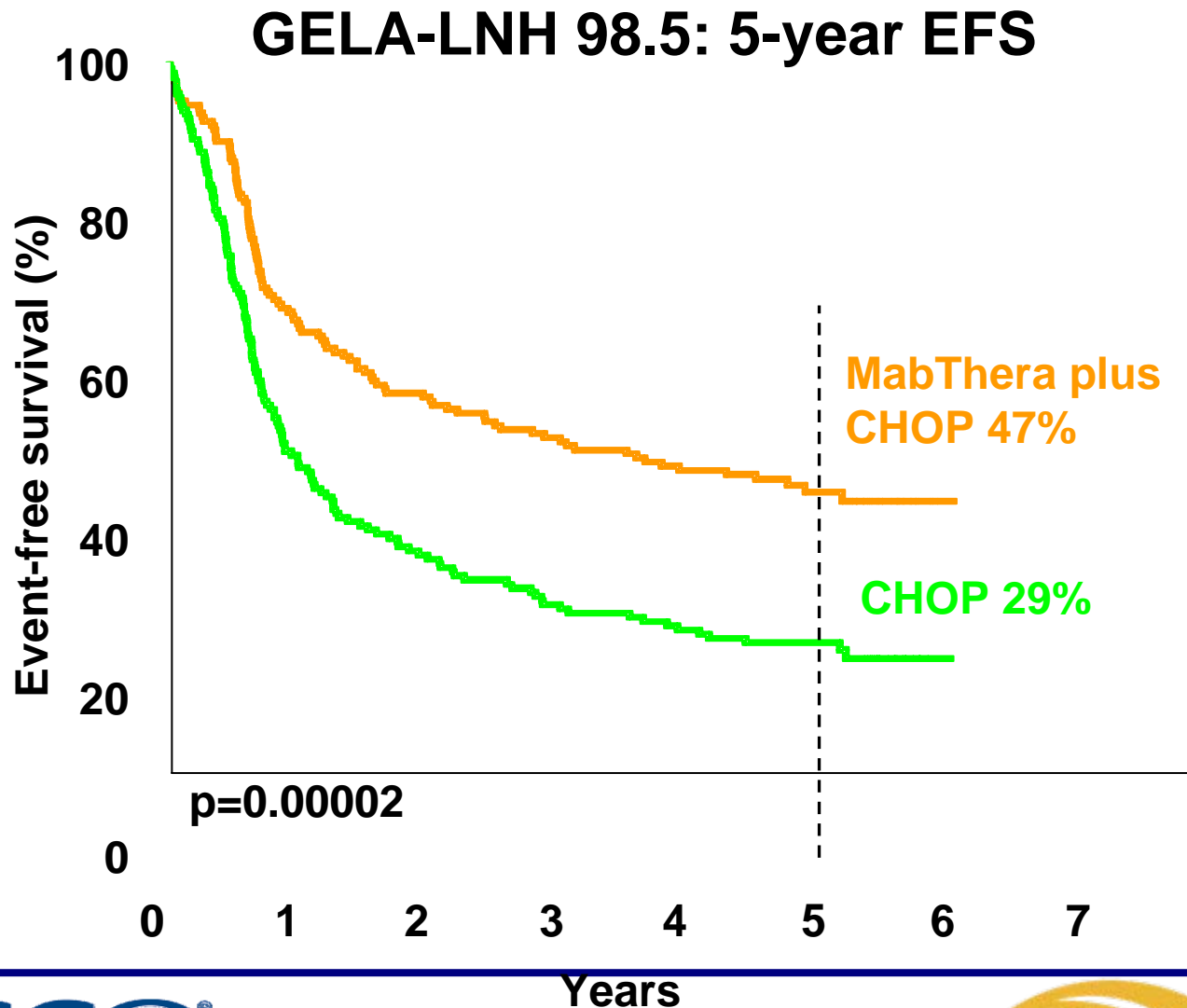
- Rituximab (Mabthera)
- Chimeric anti-CD 20 monoclonal antibody
- For CD-20 positive low grade lymphoma or diffuse large B-cell lymphoma

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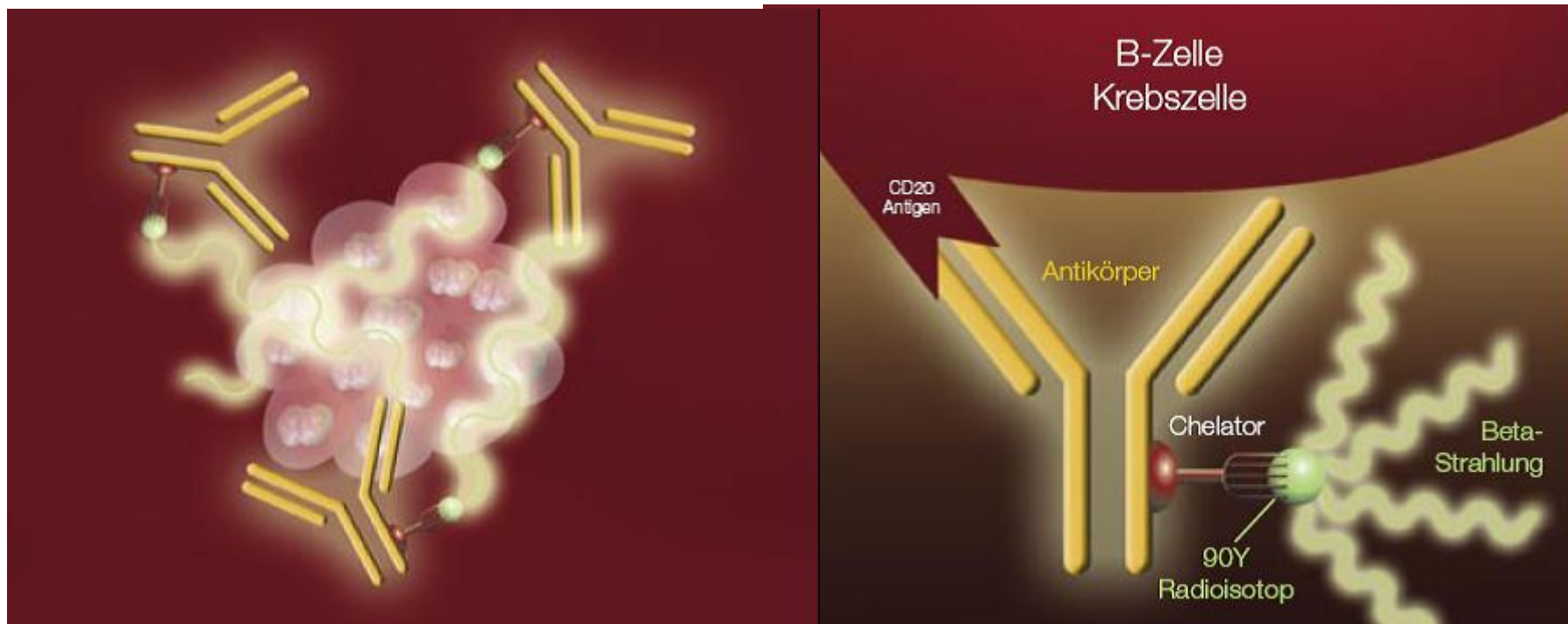
MabThera plus CHOP versus CHOP in elderly patients with DLBCL: **GELA phase III trial**



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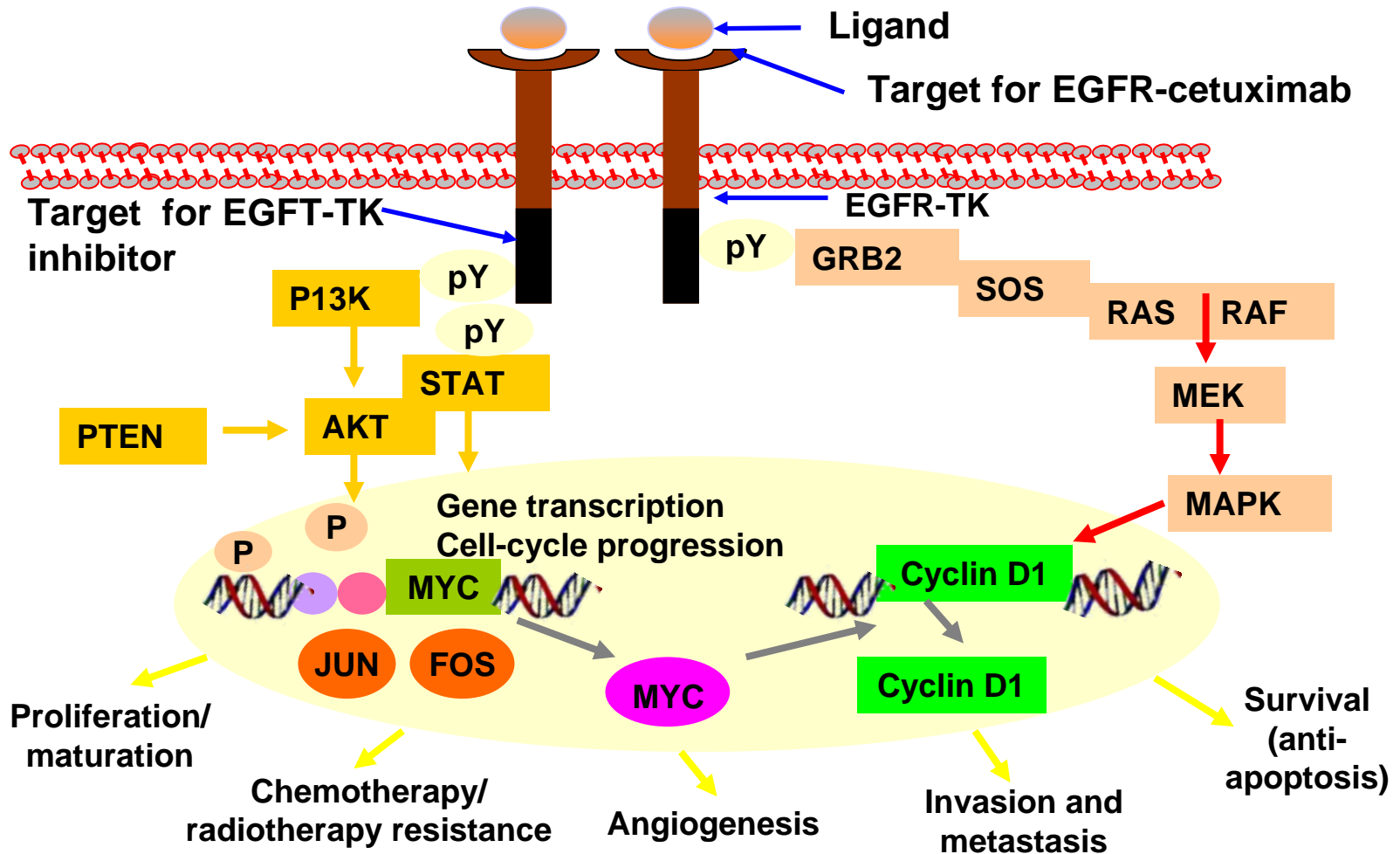


New weapon: Zevalin



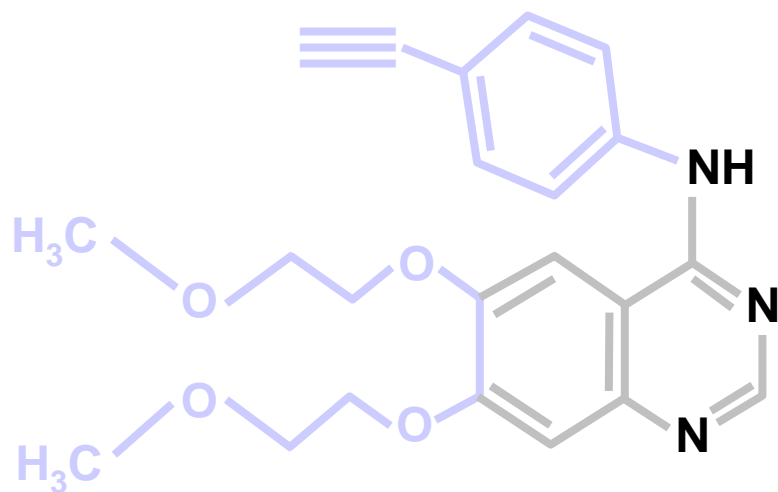
EGFR Pathway

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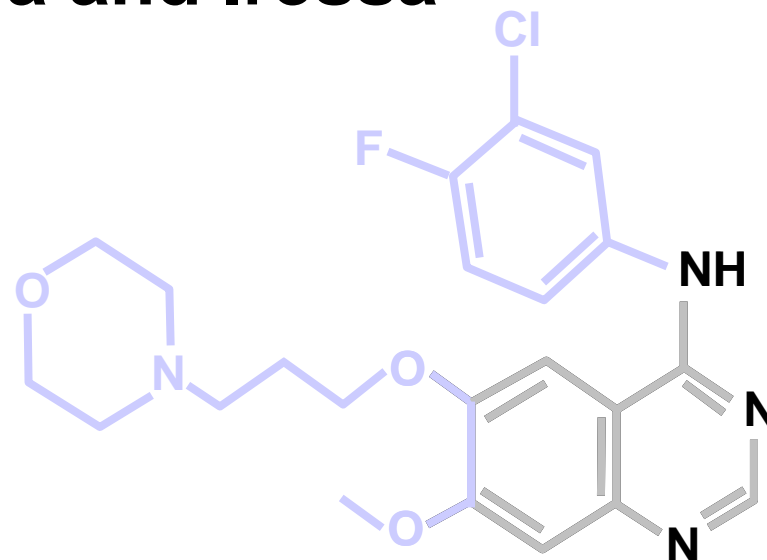
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EGFR TKI: Tarceva and Iressa



Tarceva

$K_i = 0.4 \text{ nM}$



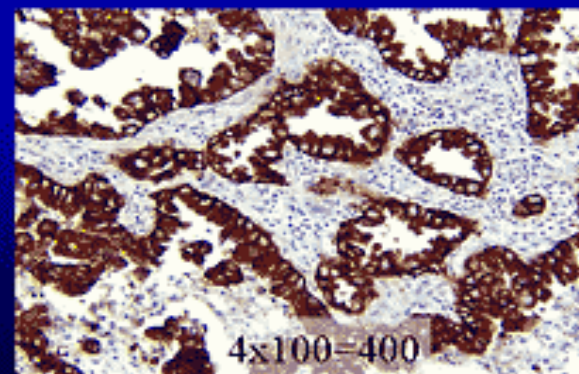
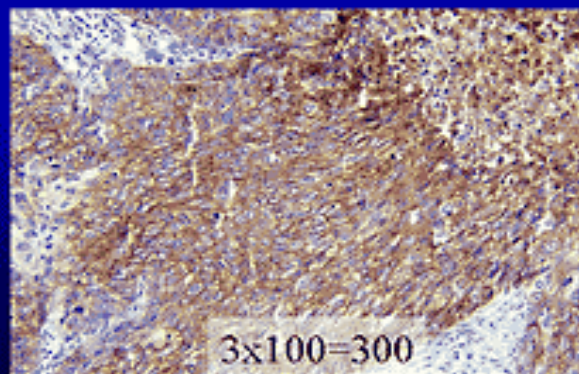
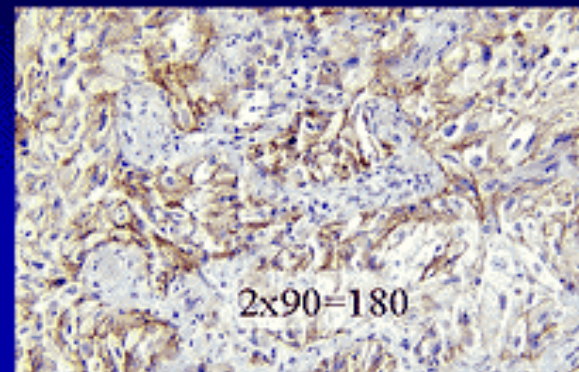
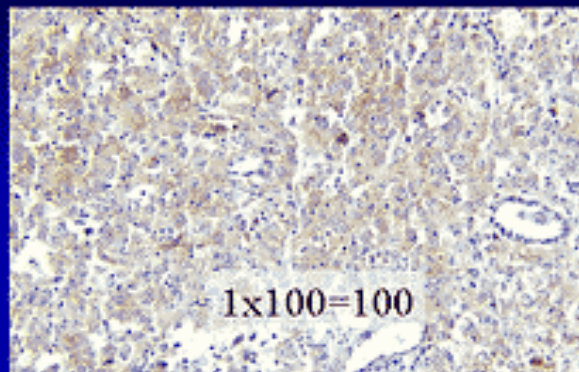
Iressa

$K_i = 3 \text{ nM}$

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What is the target?

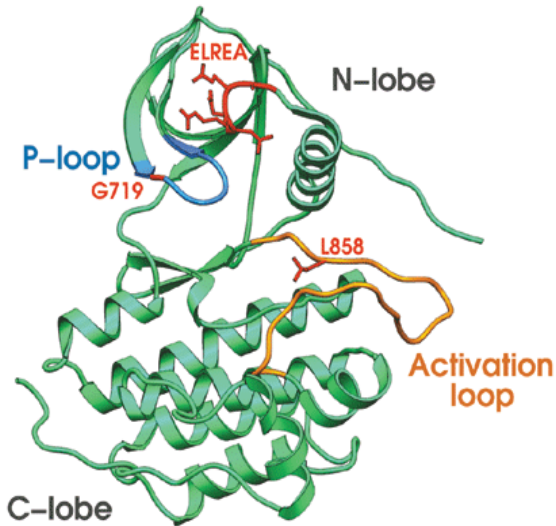
IHC Scoring for EGFR Expression (*Franklin, Colorado Lung Spore*)





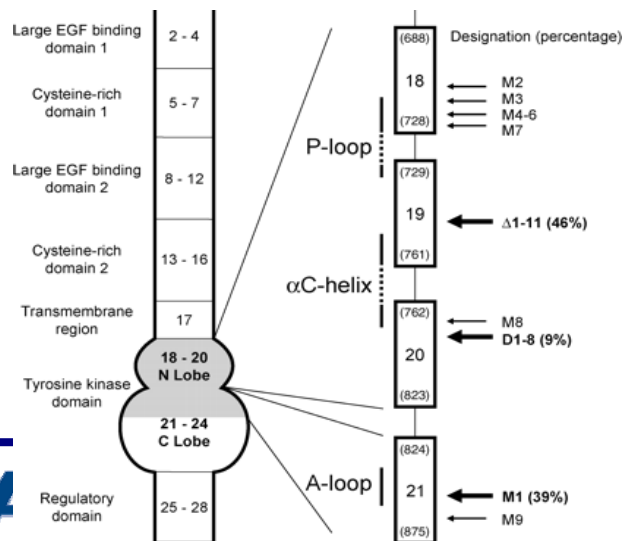
Hitting the target is not an easy job!!!

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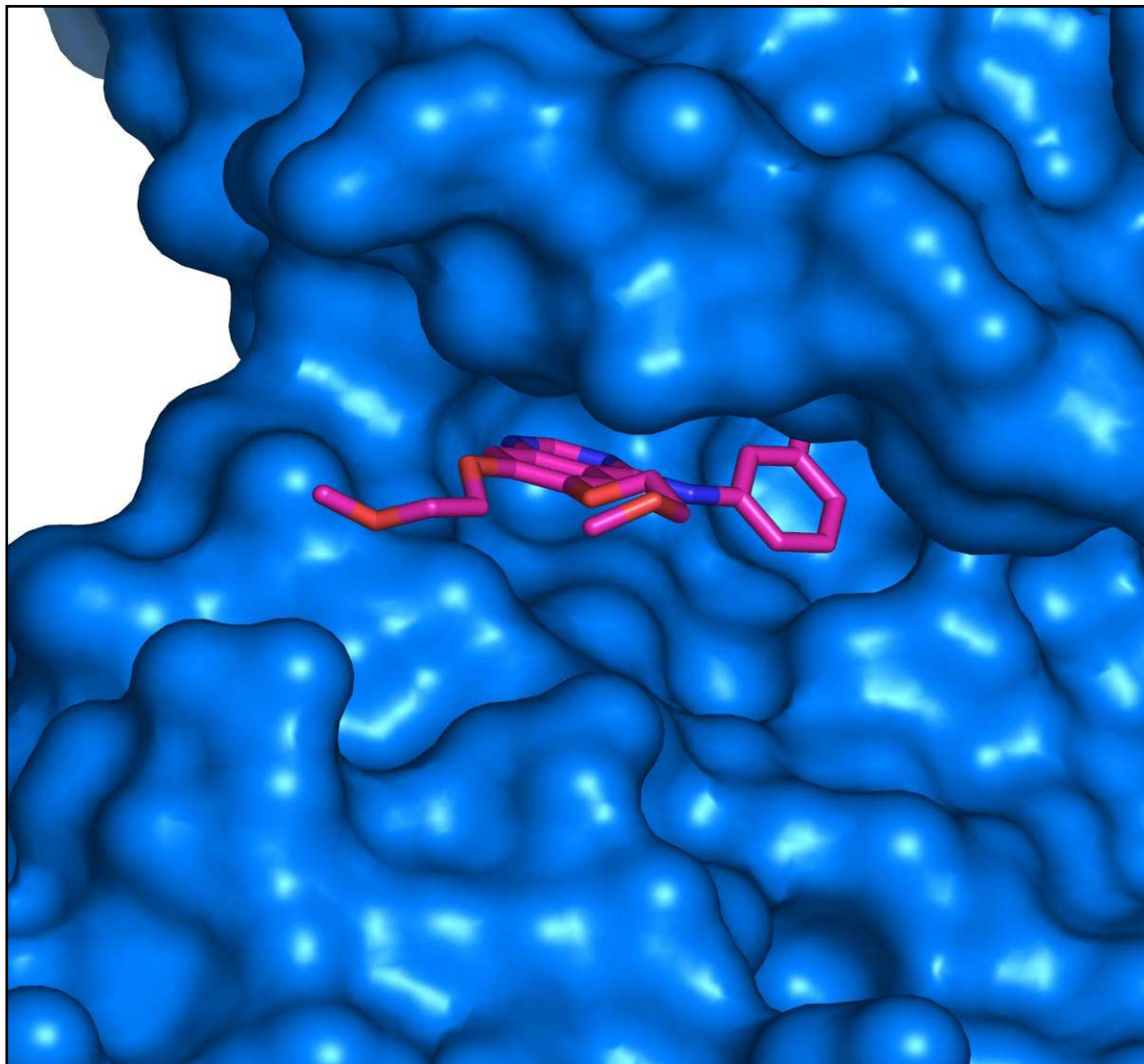
EGFR mutation: A real target?

- Three type of mutations
- Missense mutation at exons 18 and 21
 - G719A (4%)
 - L858R (38%)
- Deletions at exon 19
 - E746_A750 (45%)



Paez Science 304:1497, 2004

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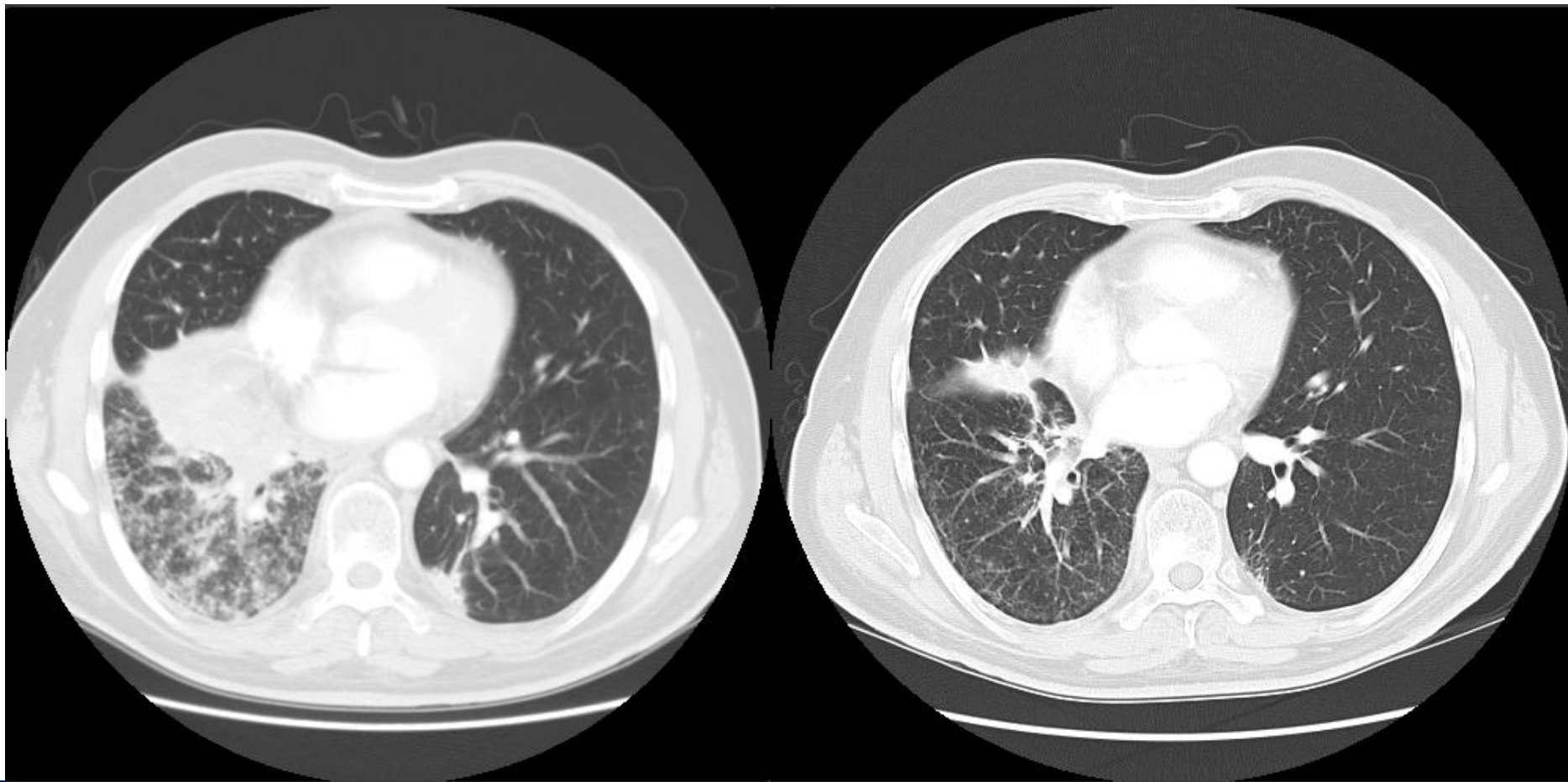


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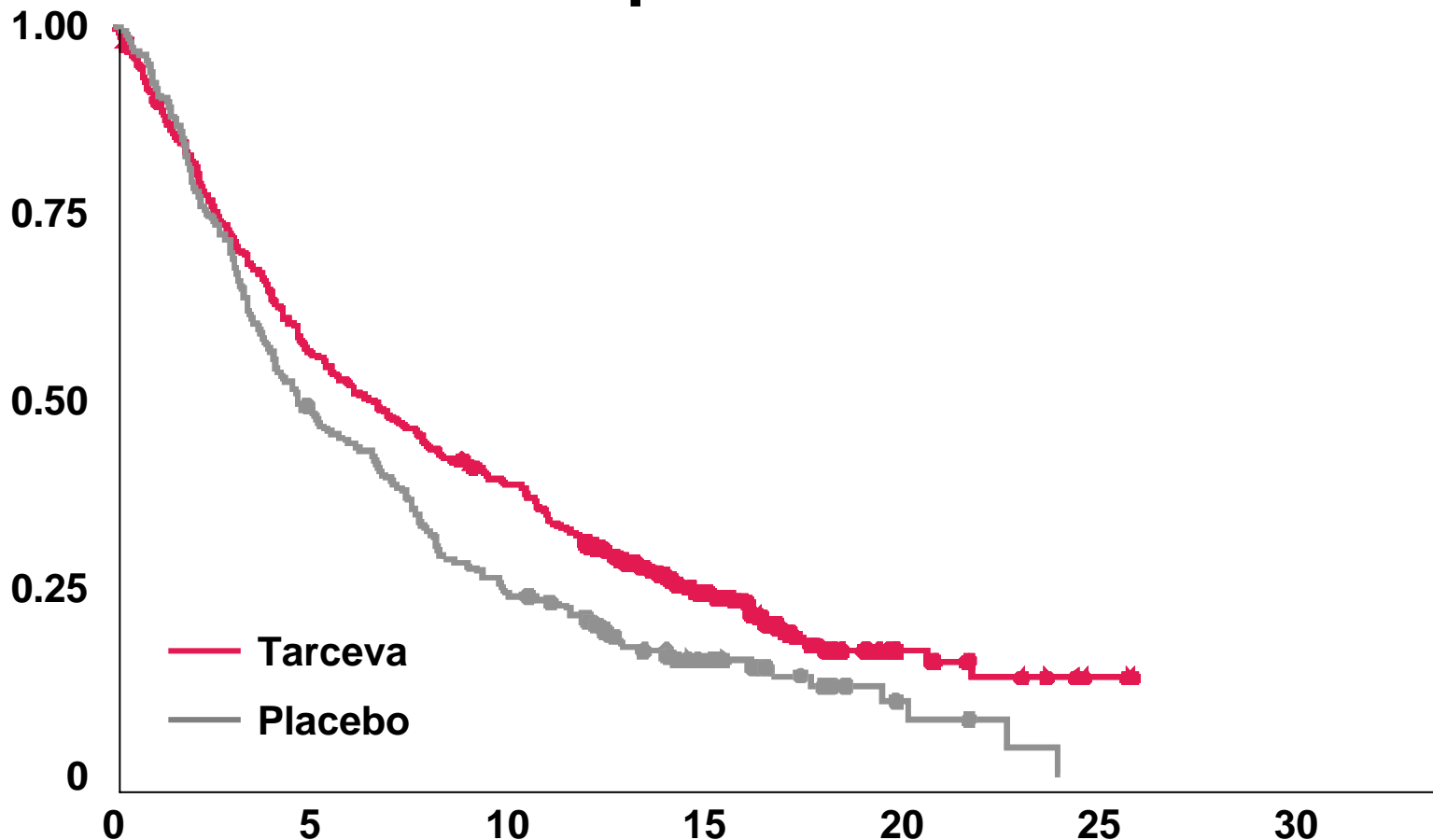
Publication	n	Mutation positive		Wild type	
		n (%)	n (%) responders	n (%)	n (%) responders
Zhang et al 2005	30	12 (40)	8 (89)	18 (60)	1 (11)
Shih et al 2006	62	29 (47)	20 (69)	34 (54)	3 (9)
Mitsudomi 2005	59	33 (56)	19 (56)	26 (44)	1 (4)
Han et al 2005	90	17 (19)	11 (65)	73 (81)	10 (14)
Takano et al 2005	66	39 (59)	32 (82)	27 (41)	3 (11)
Tokumo et al 2005	21	9 (43)	8 (89)	12 (57)	2 (17)
Kosaka et al 2004	59	33 (56)	24 (73)	26 (44)	2 (8)
Koyama et al 2004	21	8 (38)	8 (100)	13 (62)	6 (46)
Kodo et al 2004	7	3 (43)	3 (100)	4 (57)	1 (25)
Total	415	183 (44)	133 (73)	233 (56)	29 (12)

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Dramatic response in patient with EGFR mutation



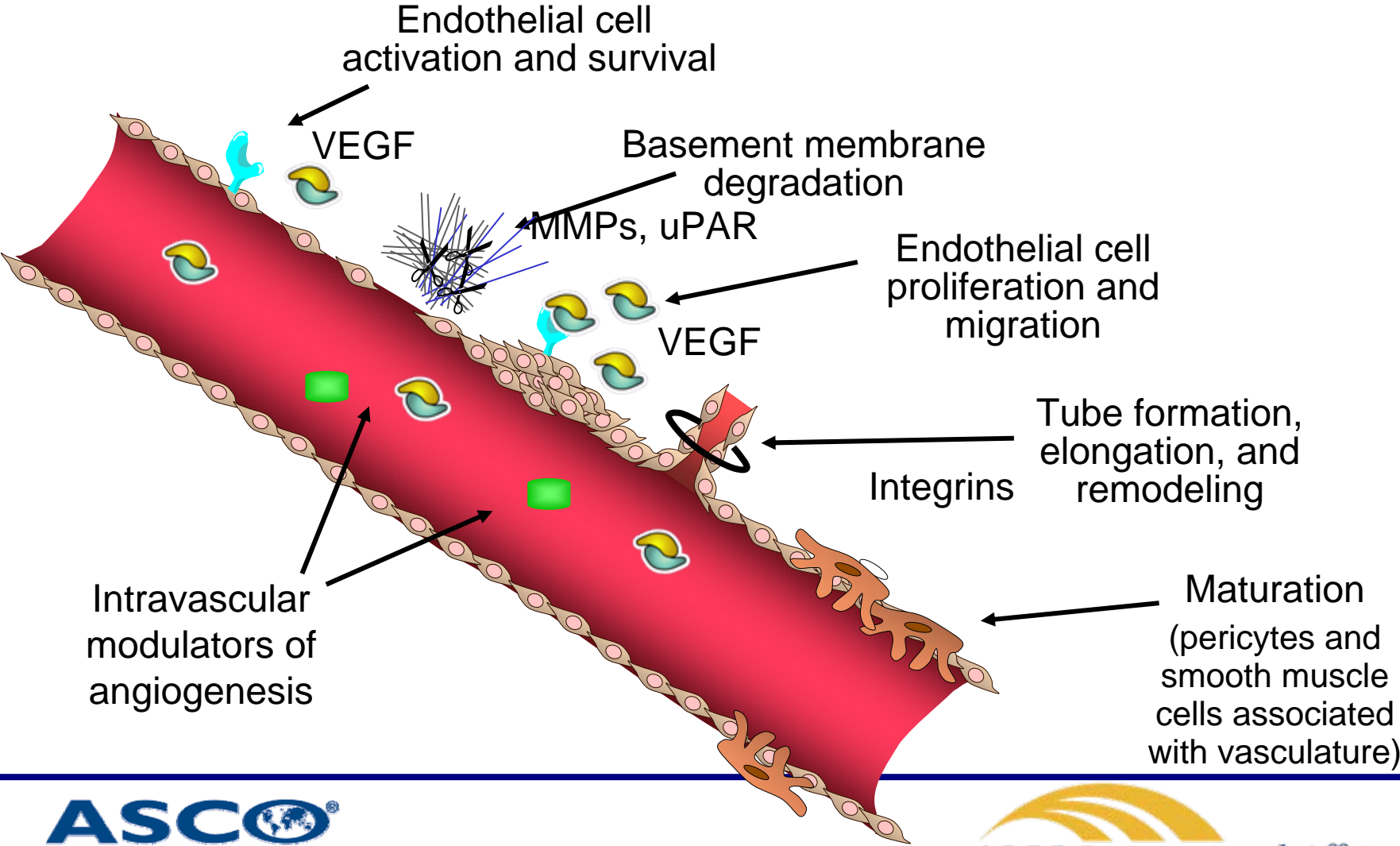
BR 21: Survival Improvement with Tarceva



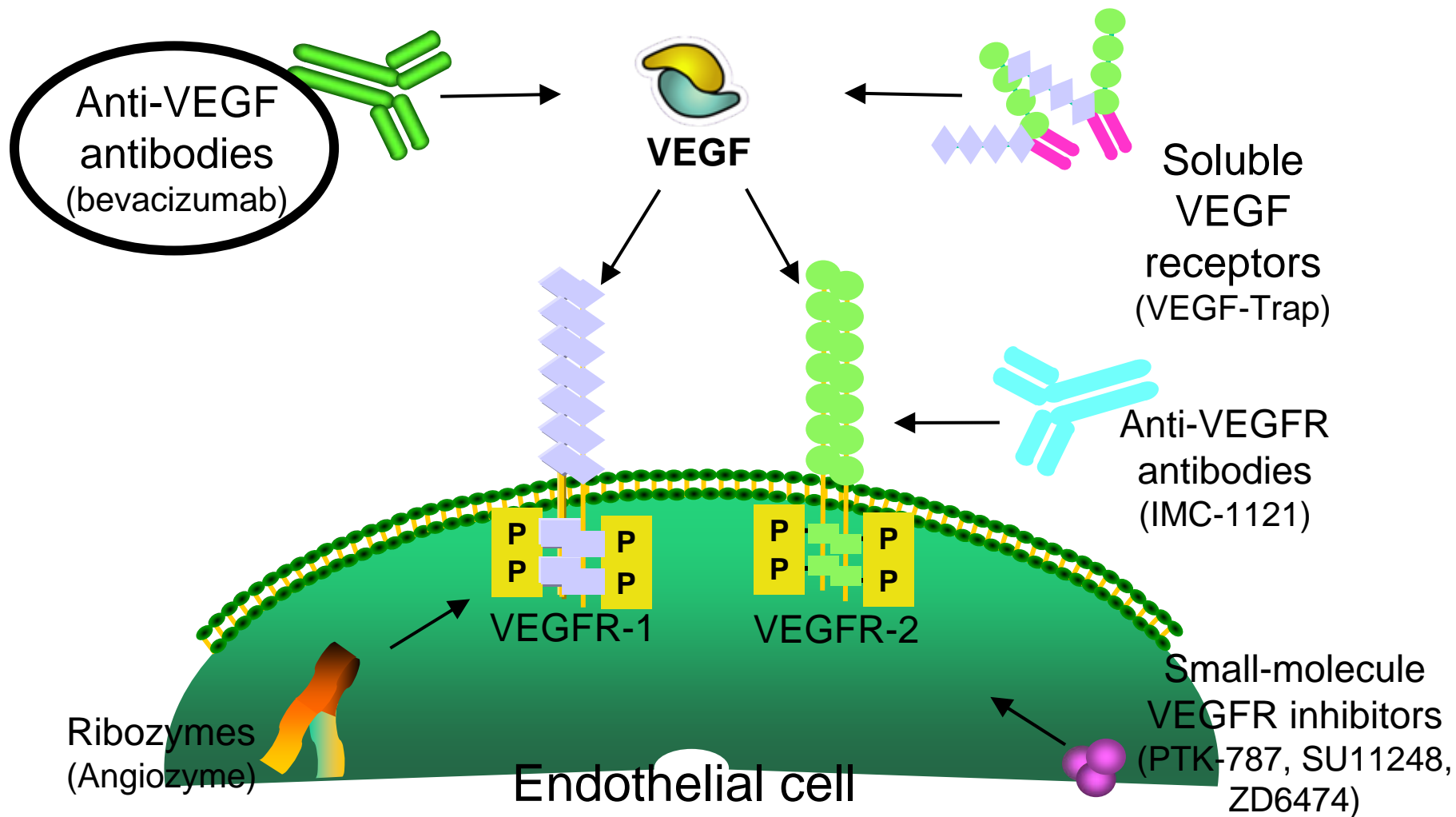
*HR and p (log-rank test) adjusted for stratification factors at randomisation and EGFR status

Angiogenic Pathway

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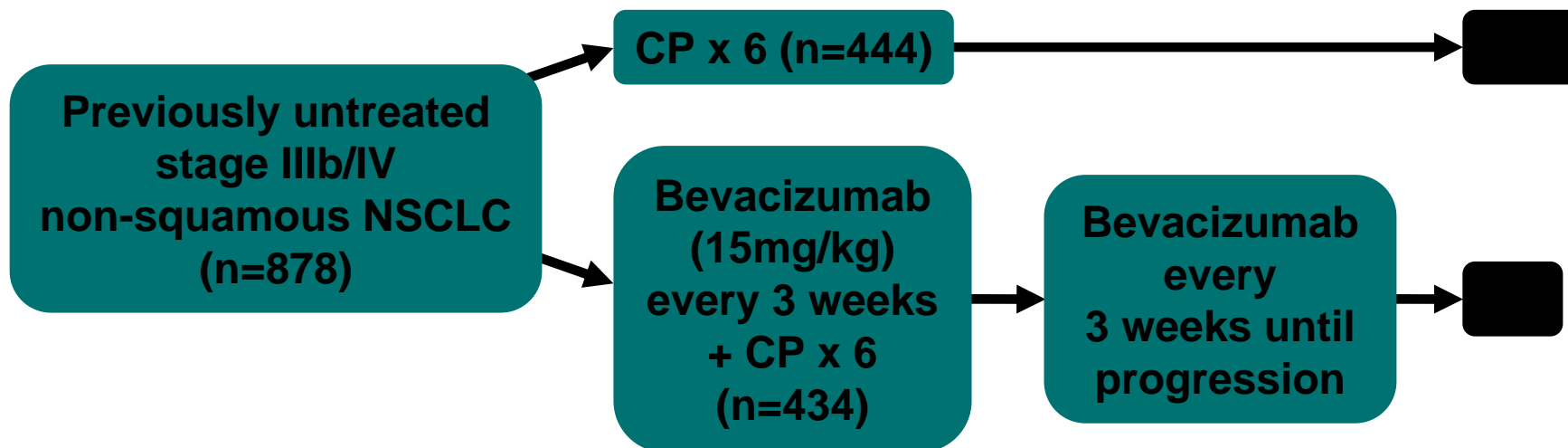


Multidisciplinary Targeting the VEGF Pathway Course



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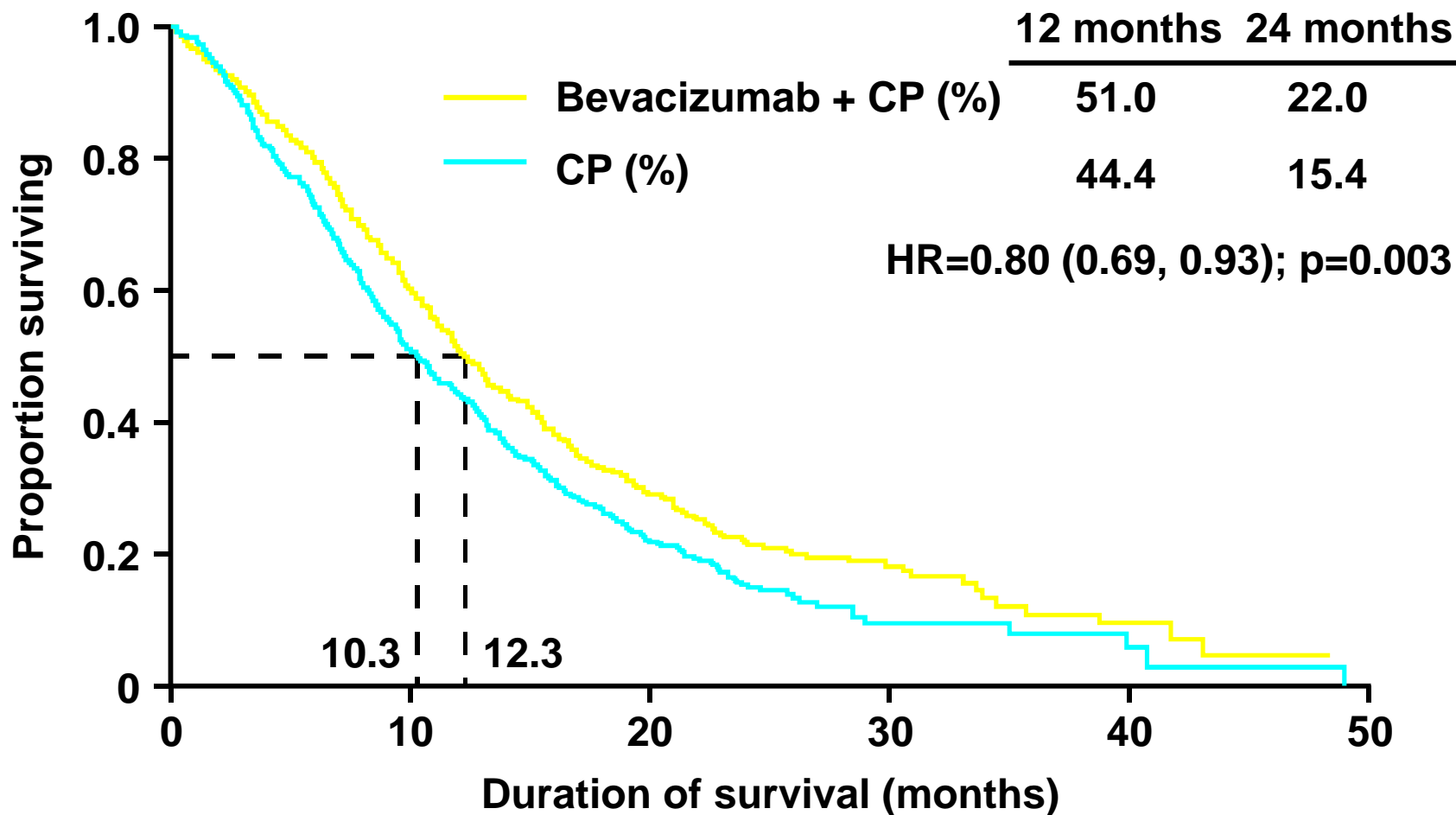
Phase III trial of bevacizumab in NSCLC (E4599)



- Primary endpoint: duration of survival
- Secondary endpoint: overall response rate
- Bevacizumab 15mg/kg i.v. administered every 3 weeks
- Patients in the bevacizumab plus CP arm may receive single-agent bevacizumab until disease progression

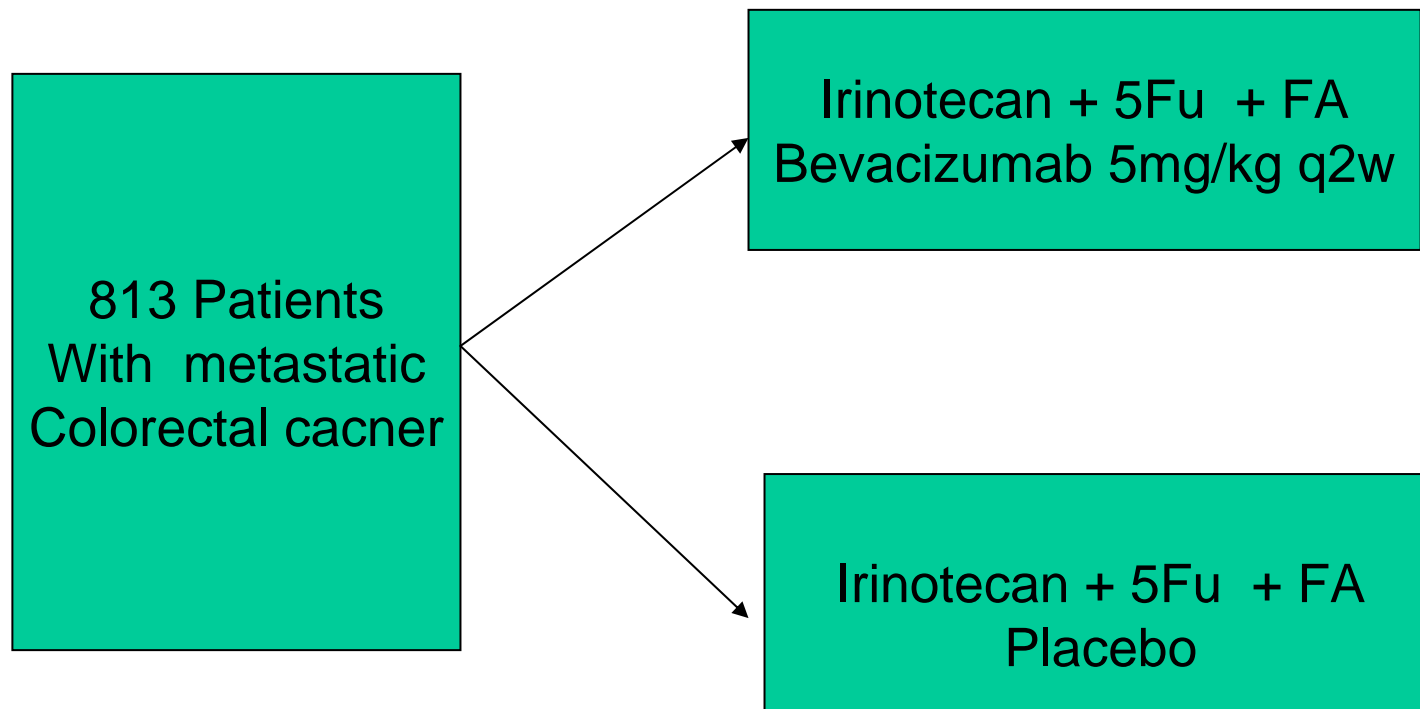
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Present Standard at USA: ECOG 4599 for Non-Squamous Cell Carcinoma



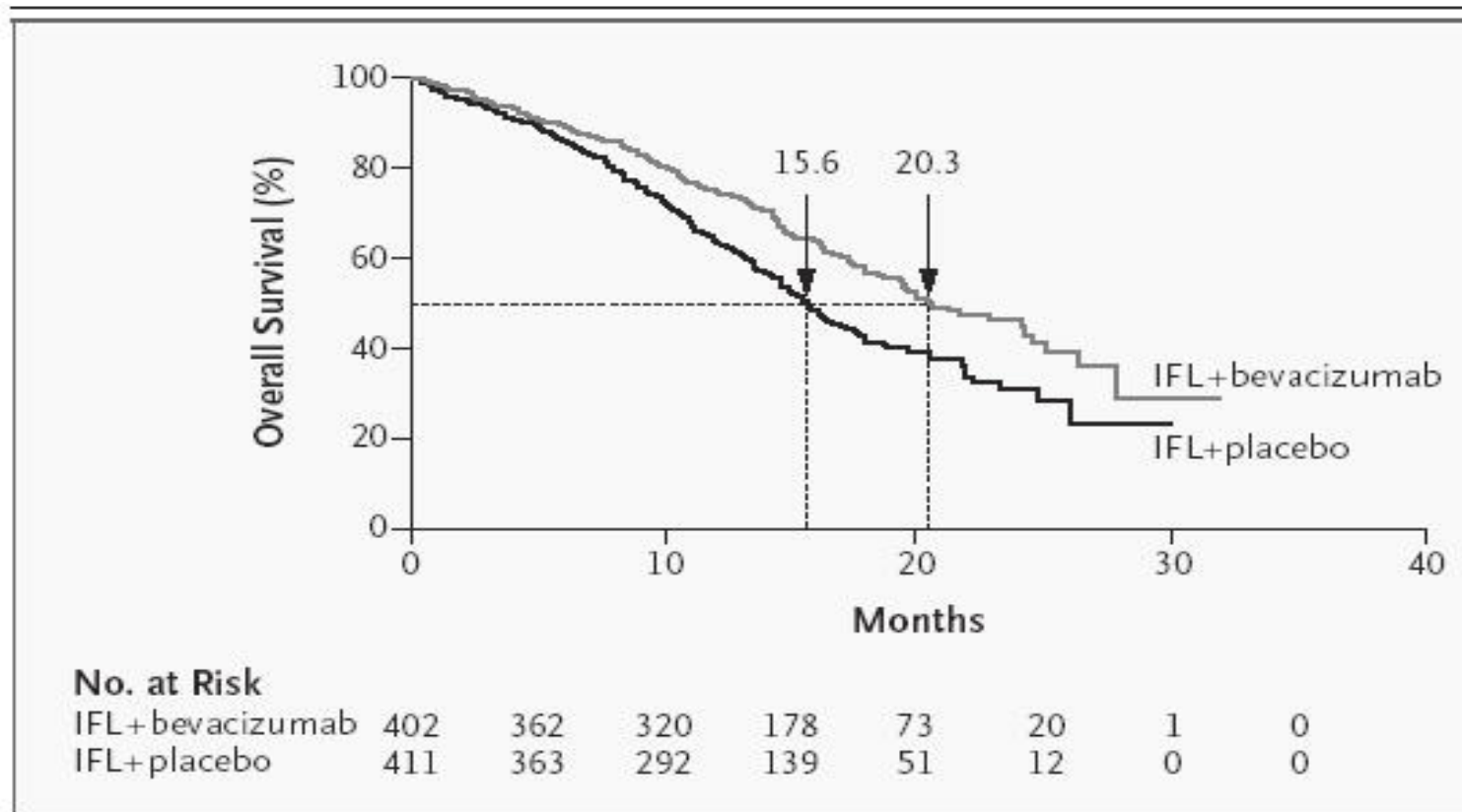
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Bevacizumab in colorectal cancer



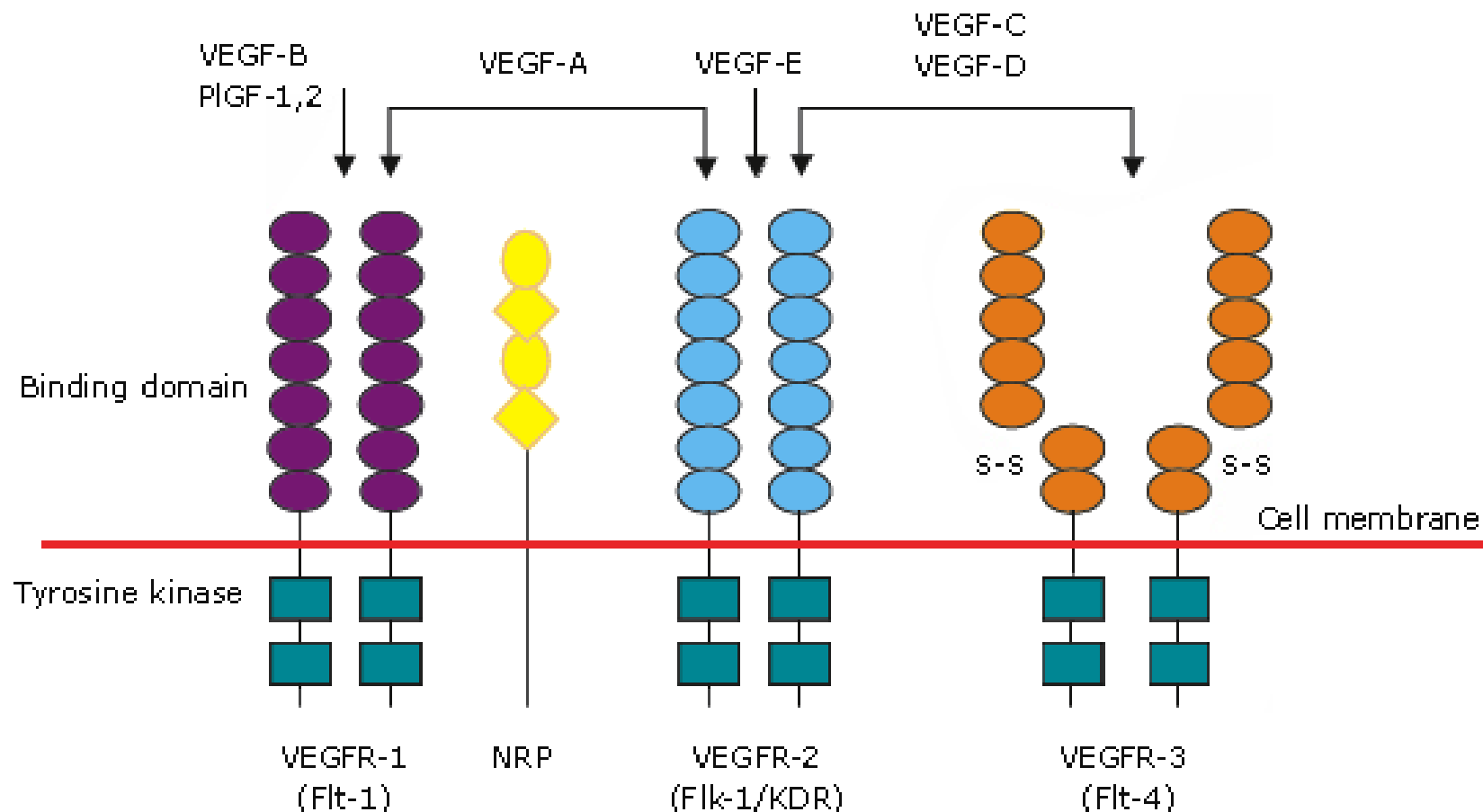
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Bevacizumab in colorectal cancer



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Another Way to Inhibit Angiogenesis: VEGFR TKI



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Rush in a Pack



VEGFR TKI (Vascular Endothelial Growth Factor Receptor Tyrosine Kinase Inhibitors)

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Drug	Target	Study (n)	Result	Toxicity
Sunitinib	VEGFR PDGFR KIT FLT3	II (62)	PR: 11.3% PFS: 11.3 weeks	Neutropenia Hypertension
Sorafenib	VEGFR2 VEGFR3 PDGFR FLT2 c-KIT	II (52)	PR 0 SD 59%	Tumor cavitation Hypertension
PTK/ZK	VEGFR 1,2,3	Randomized Ph II Daily n=54 BDS n=53	PR, 2 and 7% TTP 2.6 and 3.0 M	Vomiting Hypertension Fatigue
AMG 706	VEGFR 1,2,3 PDGFR	I/II (71)	PR 7%	Hyponatremia Hypertension
	c-Kit			Fatigue Diarrhea

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Sutent for RCC

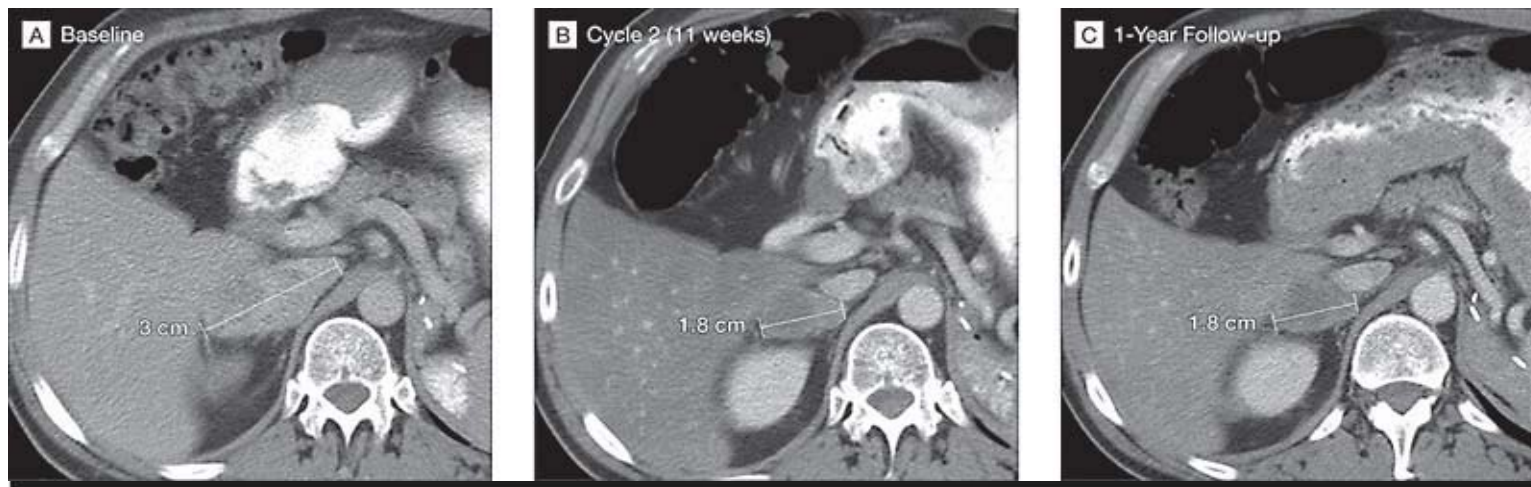


Table 3. Best Response to Sunitinib Treatment

Response	Patients Assessed, No. (%) [*]	
	Independent Third Party [†]	Investigator [‡]
Complete response	0	1 (1)
Partial response	36 (34)	45 (43)
Stable disease for ≥ 3 mo	30 (29)	23 (22)
Progressive disease, stable disease for < 3 mo, or not evaluable	39 (37)	36 (34)

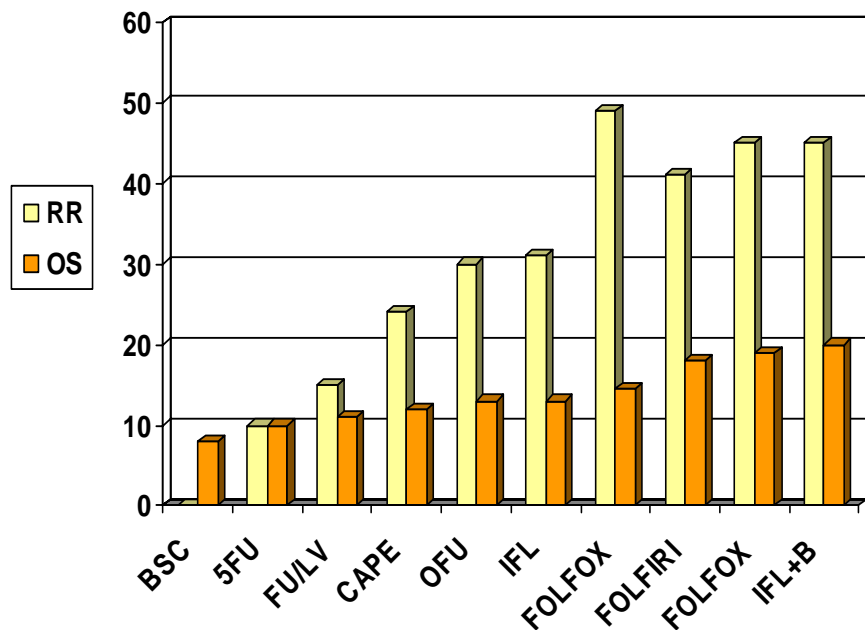
^{*}N = 105 (1 patient enrolled with a diagnosis of clear-cell renal cell carcinoma was withdrawn after a repeat biopsy showed a diagnosis of a different type of cancer).

[†]Assessed by independent third-party core imaging laboratory.

[‡]Assessed by treating physician.

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Progress and Perspectives



Estimated drug costs for 8 weeks of treatment for metastatic colorectal cancer

Regimen	Drug Costs (\$)
Mayo Clinic	63
LV5FU	263
IFL	9,539
FOLFOX	9,581
FOLFIRI	11,889
FOLFIRI + bevacizumab	21,399
FOLFOX + bevacizumab	21,033
Irinotecan + cetuximab	30,790
FOLFIRI + cetuximab	30,570
FOLFOX + cetux/bevacizumab	40,000

Schrag et al. N Engl J Med. 2004;

Conclusion

- Cancer is now viewed as a molecular illness
- Modern technology has made it possible to use molecular marker as a diagnostic and prognostic tool
- Targeted therapies are efficacious if there is a target
- Targeting the molecular pathway with monoclonal antibody or small molecule tyrosine kinase inhibitor has improved survival in many cancer types including lung, colorectal, renal cell and lymphoma.

Two Possible Scenarios

- Treatments are individualized on the basis of genetic characteristics of the patient and of the validated predictive factors
- National outcome studies are needed to better define the cost-effectiveness and the sustainability of every new expensive therapy

Multidisciplinary Care

Principles of multidisciplinary care emphasize the need for the following:

A **team approach**, involving core disciplines integral to the providing of good care, including general practice, with input from other specialities as required

Communication among team members regarding treatment planning

Multidisciplinary Care for Breast Cancer in Australia

In 2000, the National Breast Cancer Centre conducted a survey about multidisciplinary care practice among clinicians at 60 hospitals throughout Australia with various caseloads of women with breast cancer (high, medium, and low)

National Breast Cancer Centre, Australia, November 2003

Multidisciplinary Care for Breast Cancer in Australia (cont.)

- 95% of respondents agreed that it is essential for clinicians to communicate about the care of women with breast cancer; however, 30% of high-case-load hospitals did not have regular multidisciplinary treatment planning meetings
- Opportunities remain for improvement in its implementation, particularly in areas with low caseloads

Perceived Barriers to the Implementation of Multidisciplinary Care

- Inadequacy of infrastructure resources (both human and technologic)
- Difficulty in communication between specialists and general practice physicians
- Resistance to change
- Staffing issues
- Fear of loss of clinical independence

Motivational Factors

- Streamlining of referral pathways

- Opportunity for peer interaction in a friendly and inclusive atmosphere

- Opportunity for education/professional development

- Perceived benefits of multidisciplinary care for both clinicians and their patients



Fotoğraf: George Steinmetz

Dev Develer

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National Geographic Türkiye, Şubat 2005

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Perugia Regional Cancer Center