Percorsi e processi organizzativi nei trattamenti integrati dei tumori gastrointestinali

Associazione Dossetti

Roma, 25-26 ottobre 2011

Stato dell'arte e prospettive della Target Therapy nei Tumori gastroenterici

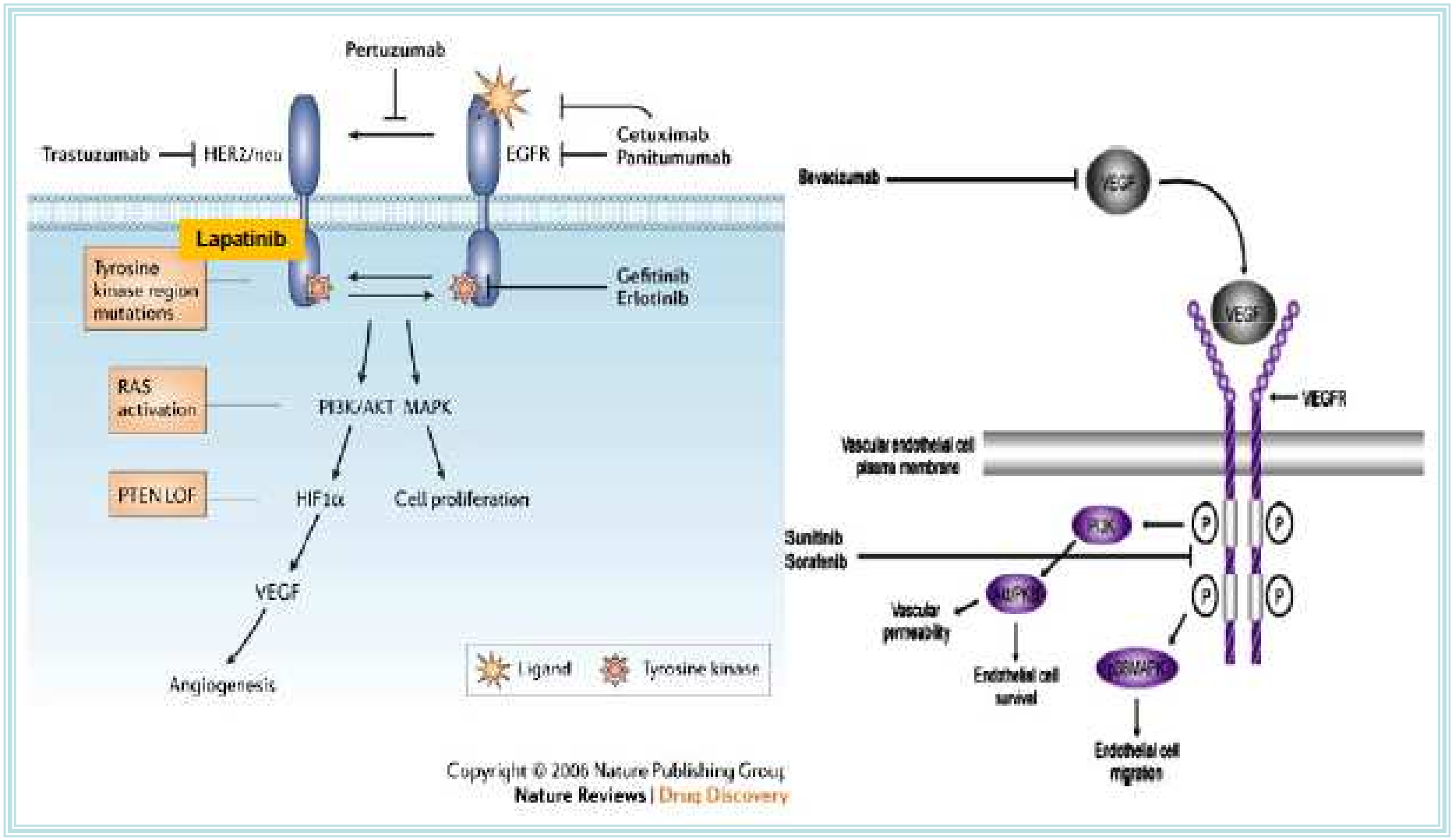
Carlo Barone
Oncologia Medica

Centro Oncologico

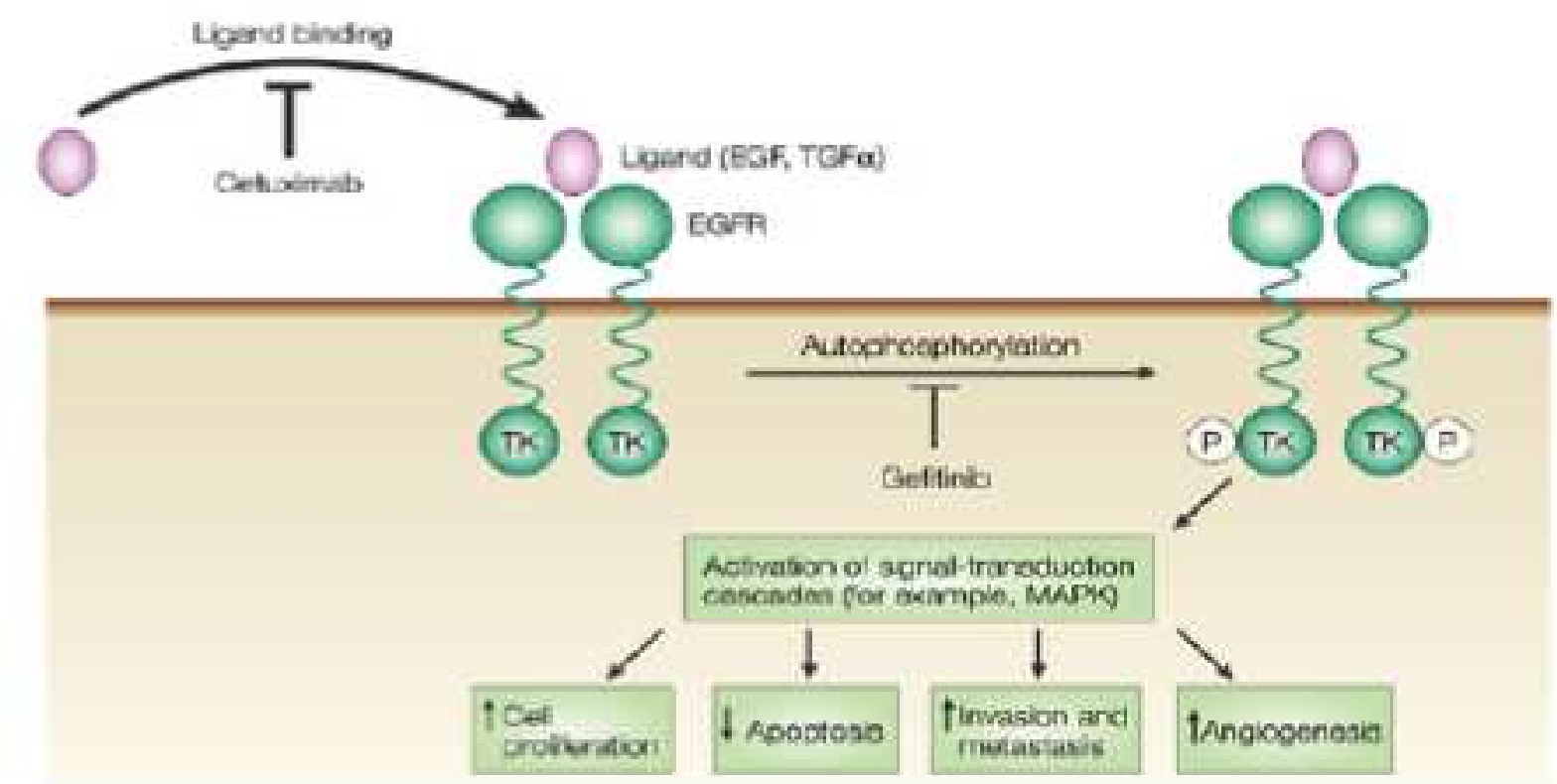
Targeted Therapy

- Trattamento che ha l'obiettivo di bloccare la crescita tumorale ostacolando l'attività di specifiche molecole bersaglio necessarie per la carcinogenesi e la crescita tumorale, piuttosto che interferendo con le cellule in rapida divisione
- Principali categorie di farmaci a bersaglio molecolare
  - Piccole molecole
  - Anticorpi monoclonali

Potenziali bersagli nei tumori gastrointestinali



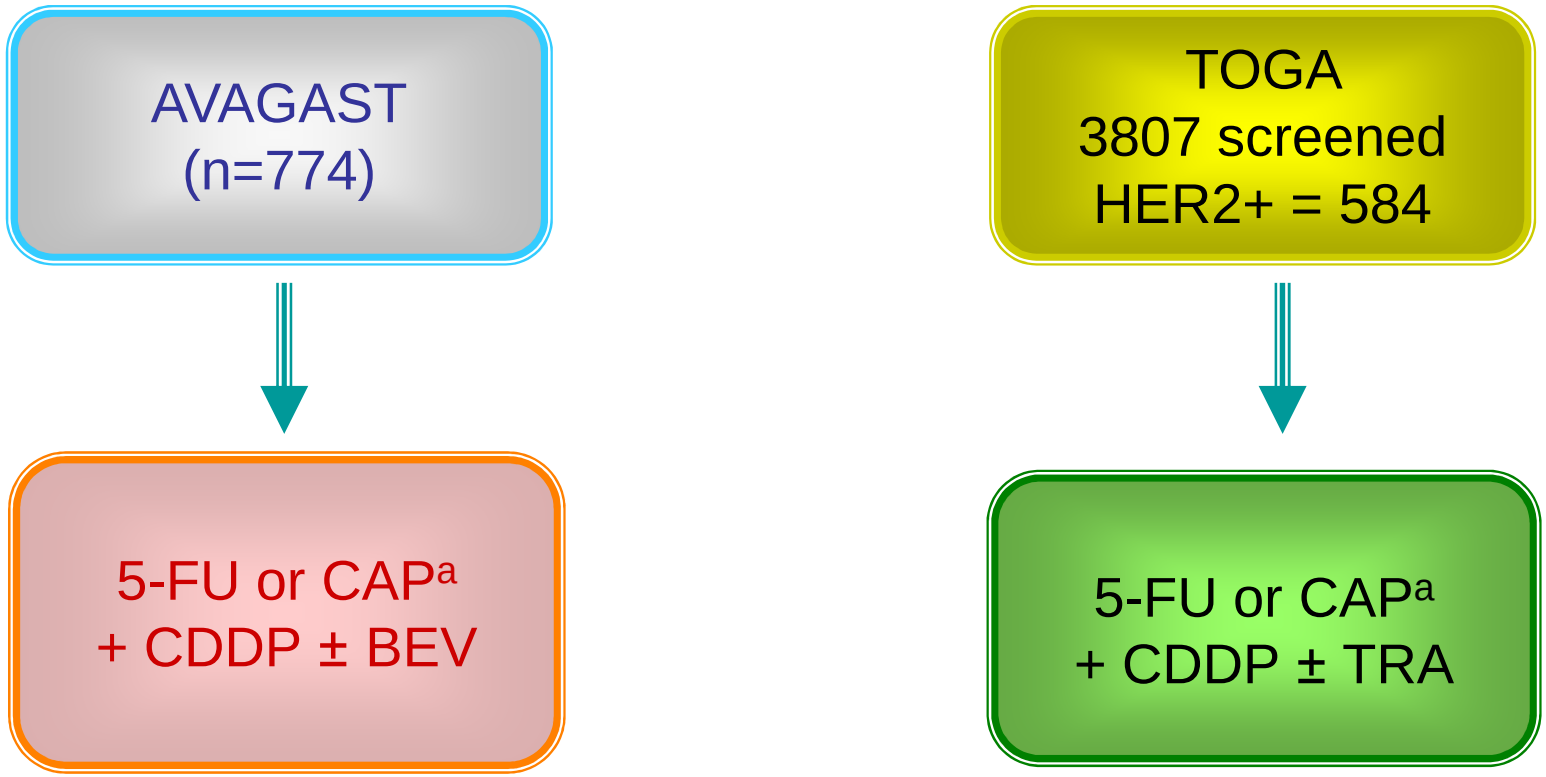
Inibitori di EGFR: mAbs and TKIs:
Cetuximab è il più studiato sinora nel CG



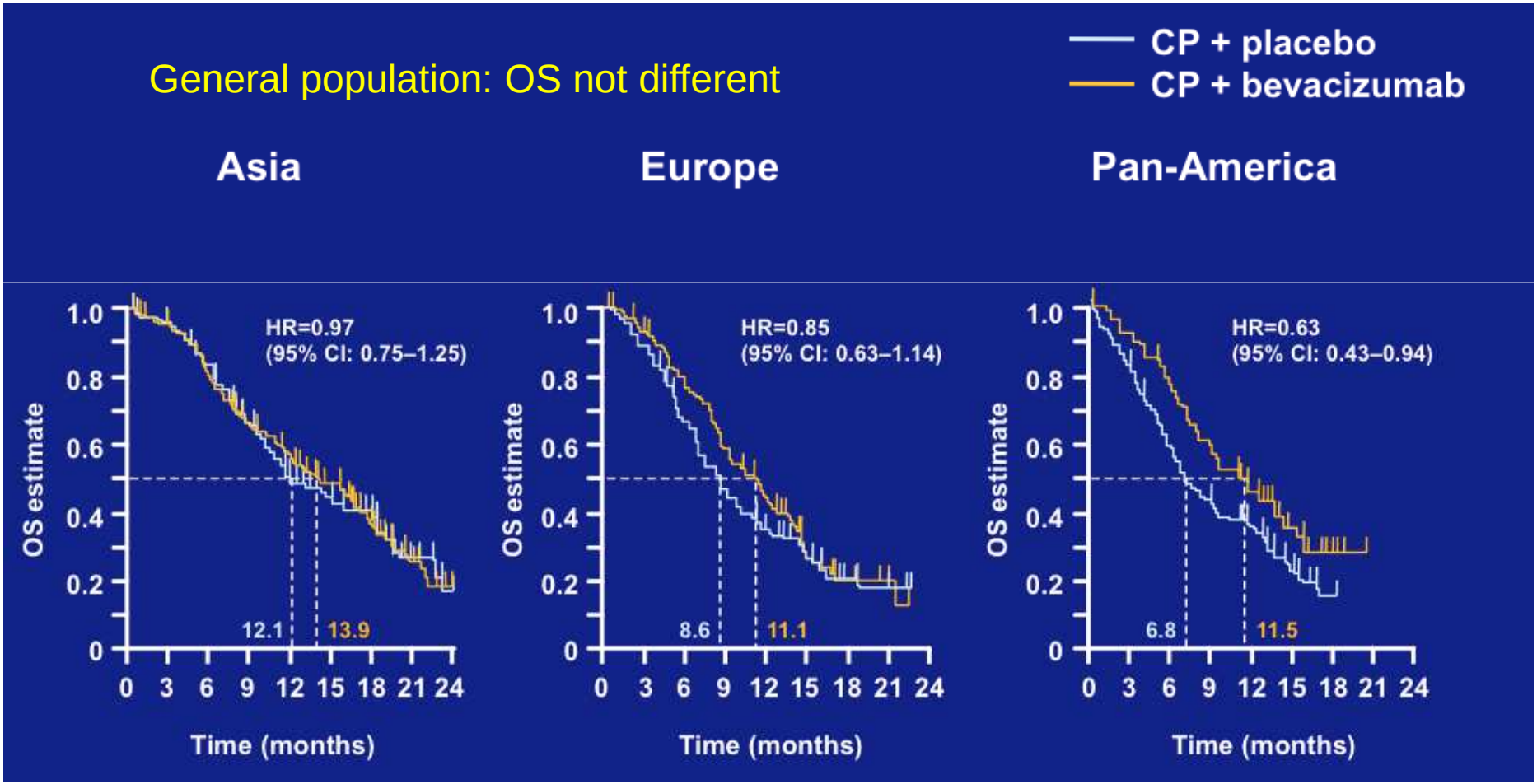
Cetuximab nel cancro gastrico

Author	Regimen	Ph	n	Site	RR	OS
Pinto ‘07	C+FOLFIRI	II	38	89% GC	44%	12 m
Moehler ‘11	C+FUFAIRI	II	49	69% GC	42%	16.6 m
Han ’09	C+FOLFOX	II	38	100% GC	50%	9.9 m
Kim ‘11	C+XELOX	II	44	95% GC	52%	11.8 m
Lordick ’07	C+FOLFOX	II	52	52% GC	65%	9.5 m
Pinto ’08	C+Cis/TXT	II	72	82% GC	41%	9 m
Woell ‘09	C+OXA/IRI	II	51		63%	9.5 m
Yeh ’10	C+FUci/Cis	II	35		69%	14.5 m

Importanza del bersaglio nel ca. gastrico
Confronto inter-trial: ToGA vs AVAGAST

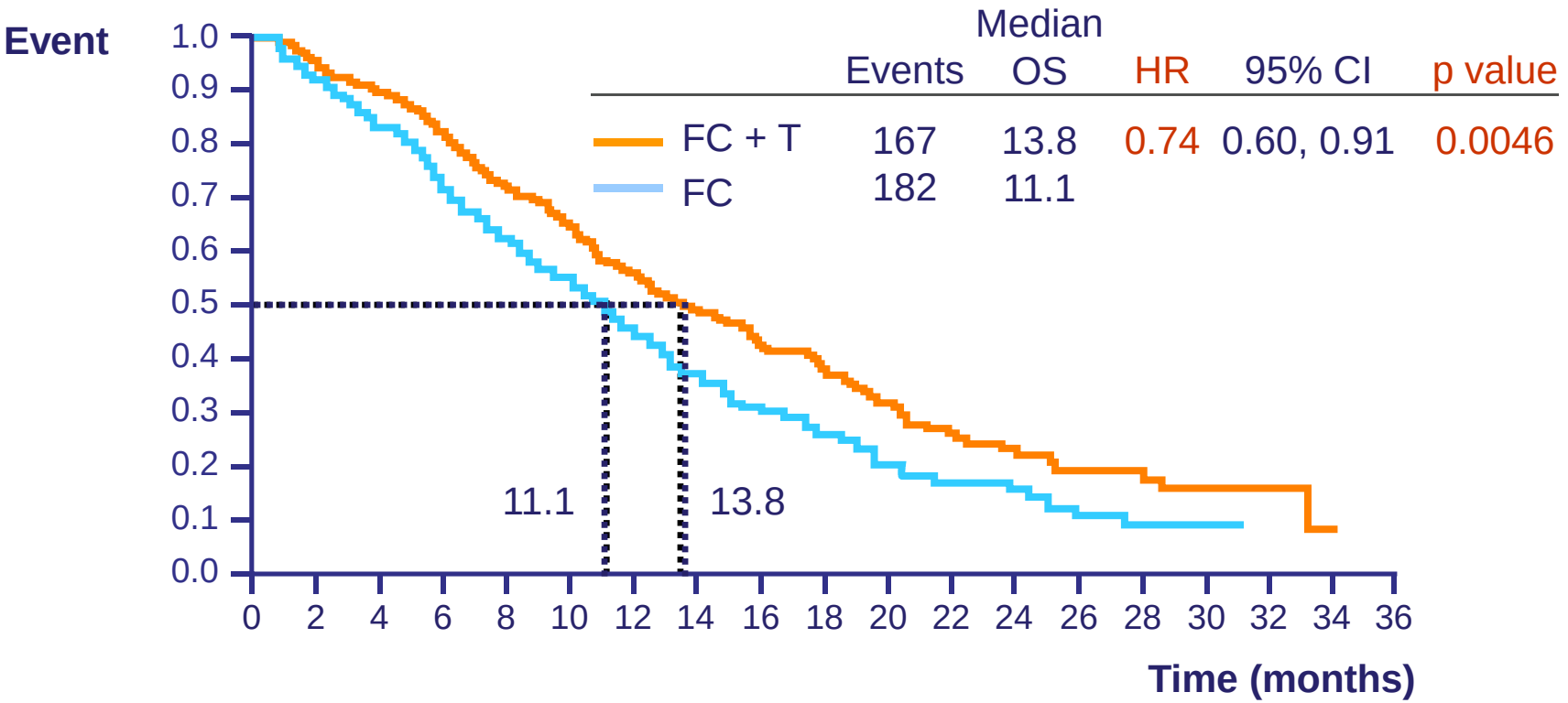


AVAGAST Trial: OS by Region



Van Cutsem et al, Proc ESMO 2010

Toga Trial: OS



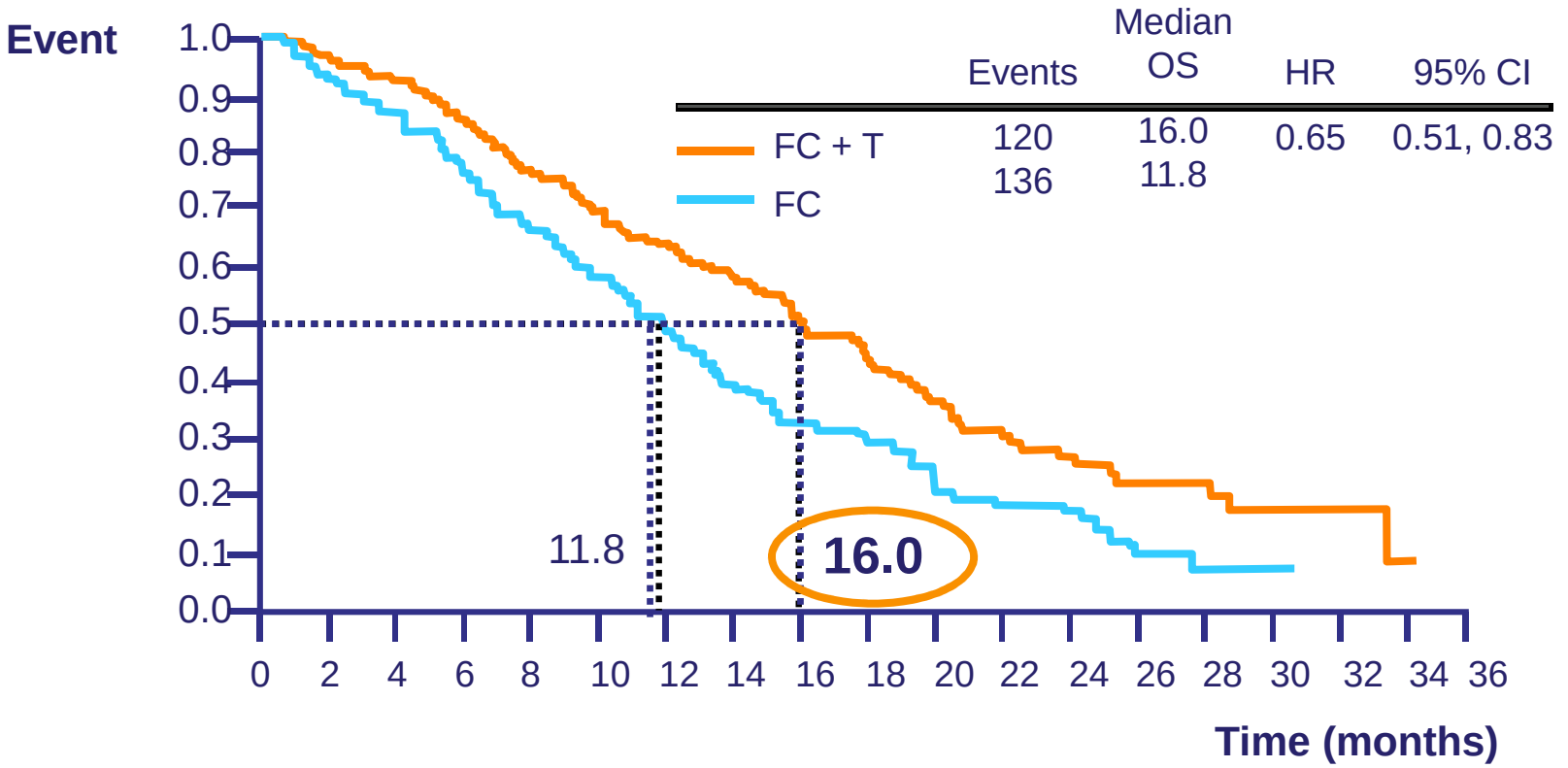
	Events	Median OS	HR	95% CI	p value
FC + T	167	13.8	0.74	0.60, 0.91	0.0046
FC	182	11.1			

No. at risk																			
FC + T	294	277	246	209	173	147	113	90	71	56	43	30	21	13	12	6	4	1	0
FC	290	266	223	185	143	117	90	64	47	32	24	16	14	7	6	5	0	0	0

T, trastuzumab

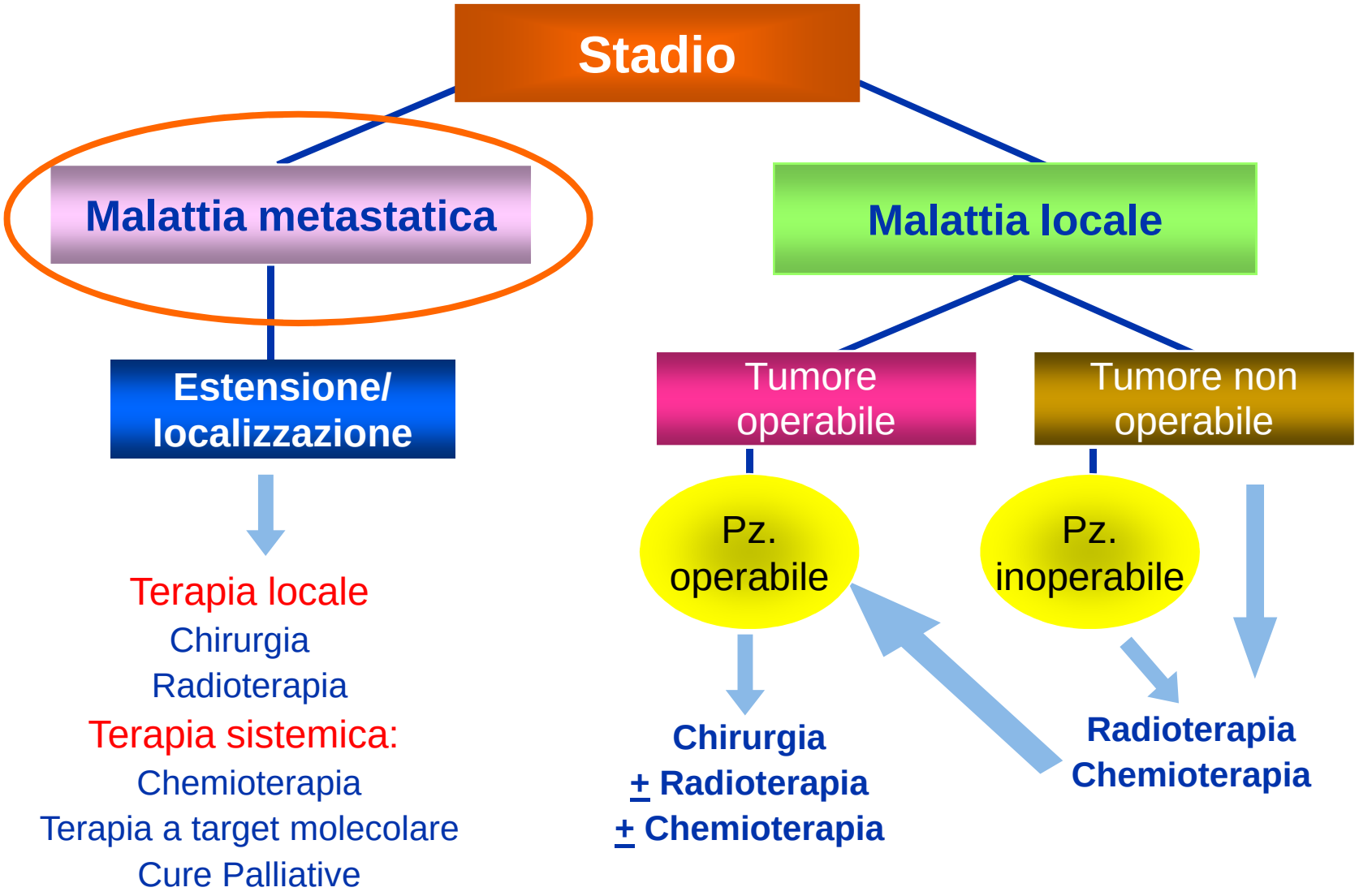
Bang et al; ASCO 2009 and Lancet 2010

OS in IHC2+/FISH+ or IHC3+ (analisi esplorativa)

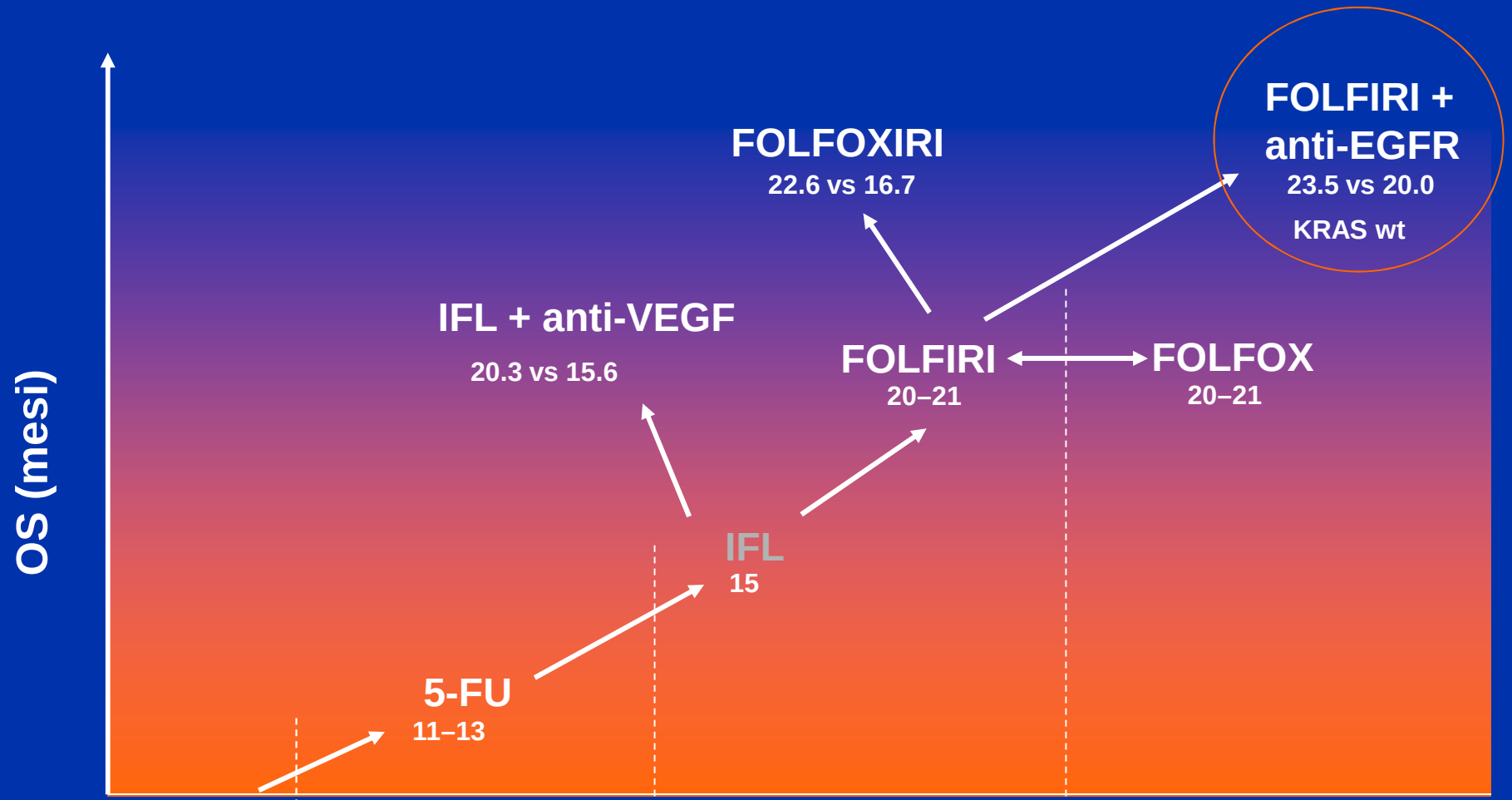


Bang et al; ASCO 2009 and Lancet 2010

Ca. colo-rettale: Strategia articolata



La terapia sistemica: le nuove terapie prolungano la sopravvivenza



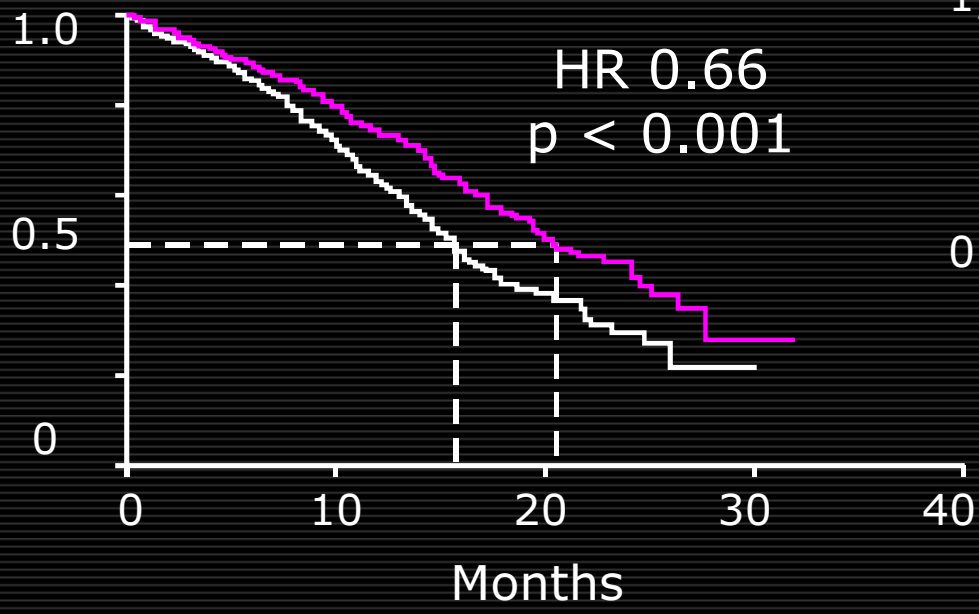
BSC, Terapia di supporto

Hurwitz H, et al. N Engl J Med 2004;350:2335–42
Goldberg RM, et al. J Clin Oncol 2004;22:23–30;
Tournigand C, et al. J Clin Oncol 2004;22:229–37
Van Cutsem E, et al. J Clin Oncol 2011;29:2011–2019

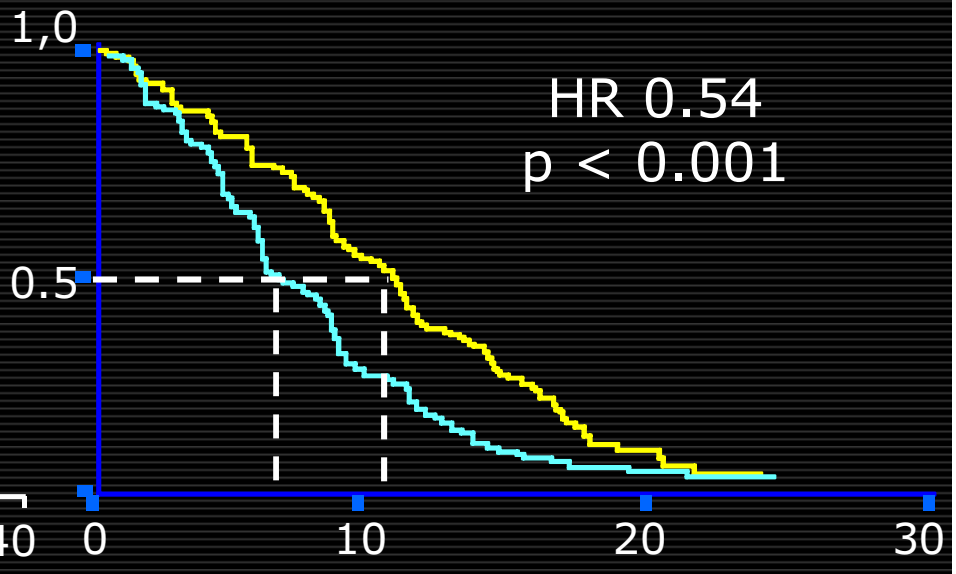
Scheithauer W, et al. Br Med J 1993;306:752–5;
Saltz LB, et al. N Engl J Med 2000;343:905–14;
Hoff PM, et al. J Clin Oncol 2001;19:2282–92;
Falcone A, et al. J Clin Oncol 2007;25:1670–76

Il Bevacizumab migliora l'efficacia di una terapia non ottimale

Median Survival



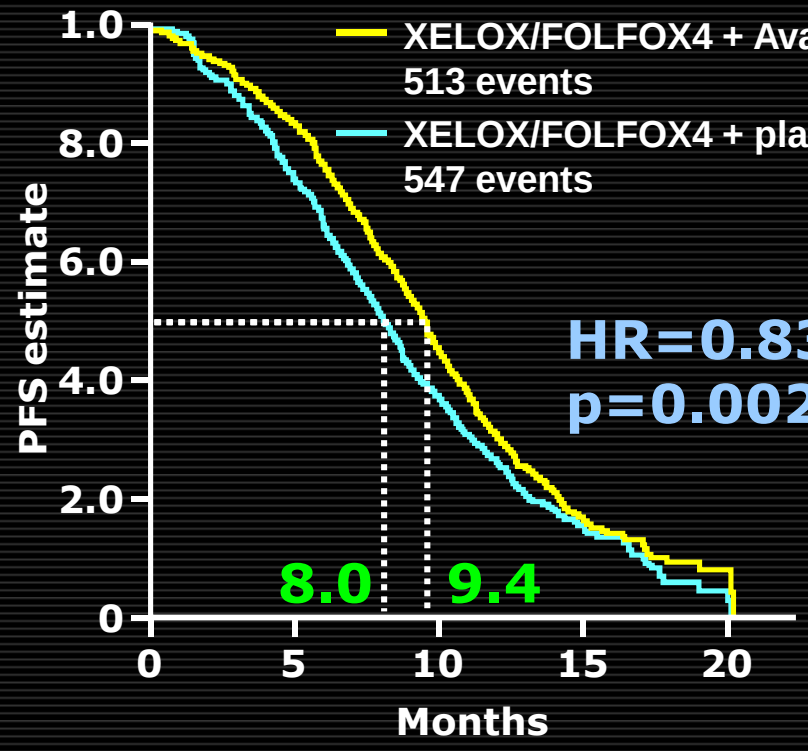
Med Progr-Free Surv



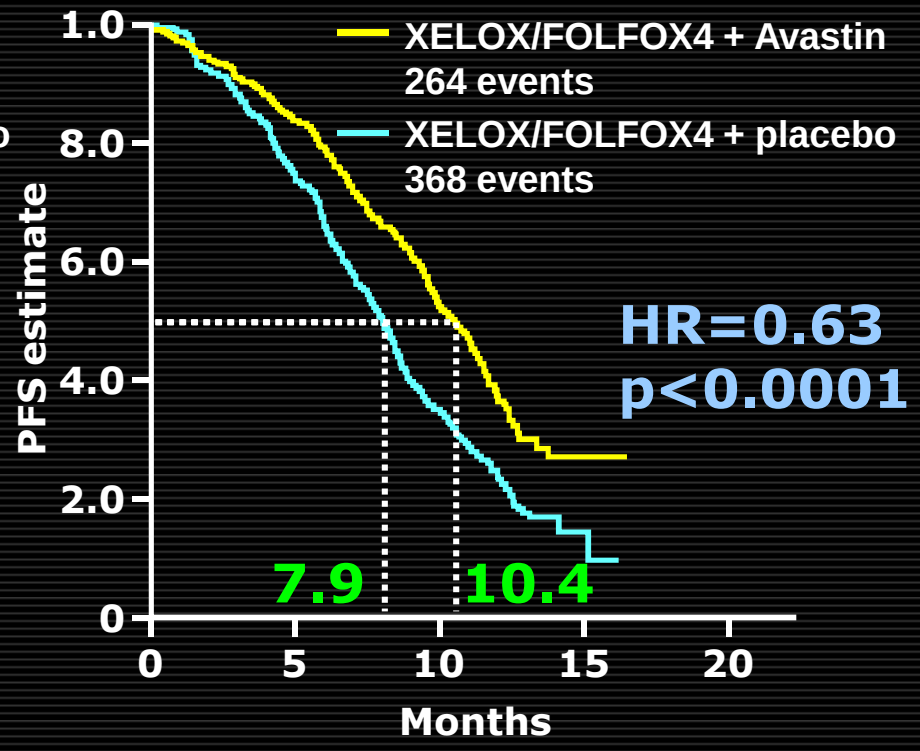
Hurwitz H, et al. N Engl J Med 2004;350:2335–42

Il Bevacizumab migliora la PFS di una terapia comprendente OXA

PFS general
Primary endpoint



PFS on-treatment
Secondary endpoint

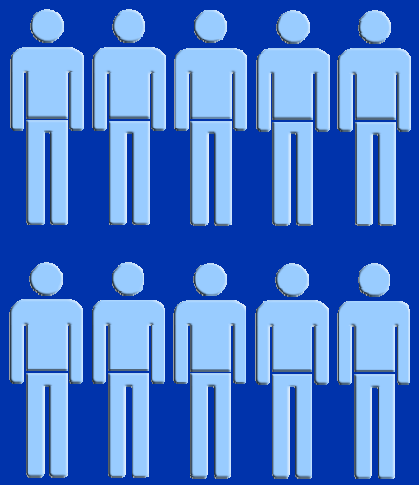


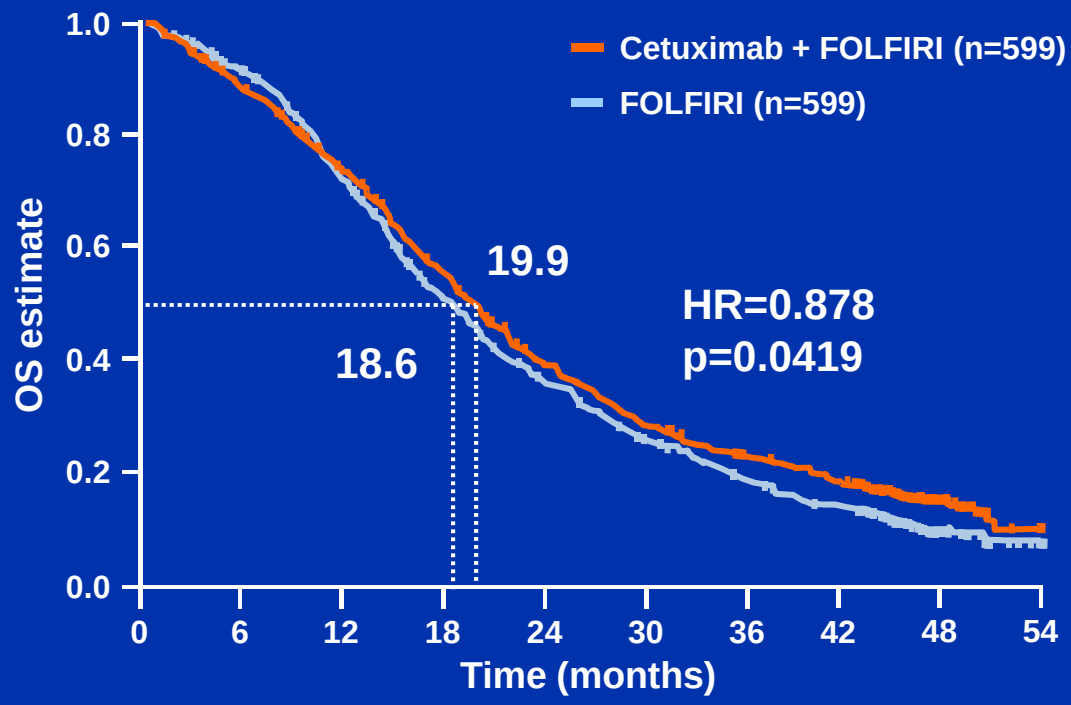
Saltz J Clin Oncol 26:2013, 2008

L’uso di marcatori molecolari ottimizza l’esito della terapia

Tutti I pazienti affetti da mCRC

Es. Studio CRYSTAL

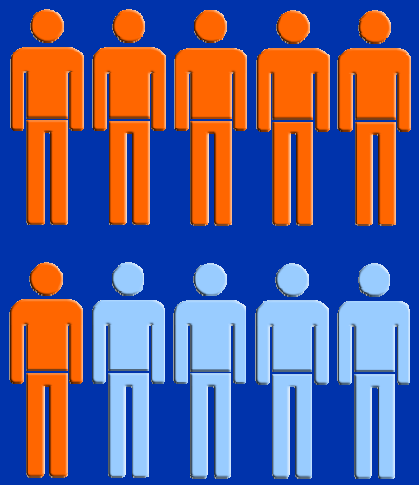




Van Cutsem E, et al. J Clin Oncol 2011;29:2011–2019

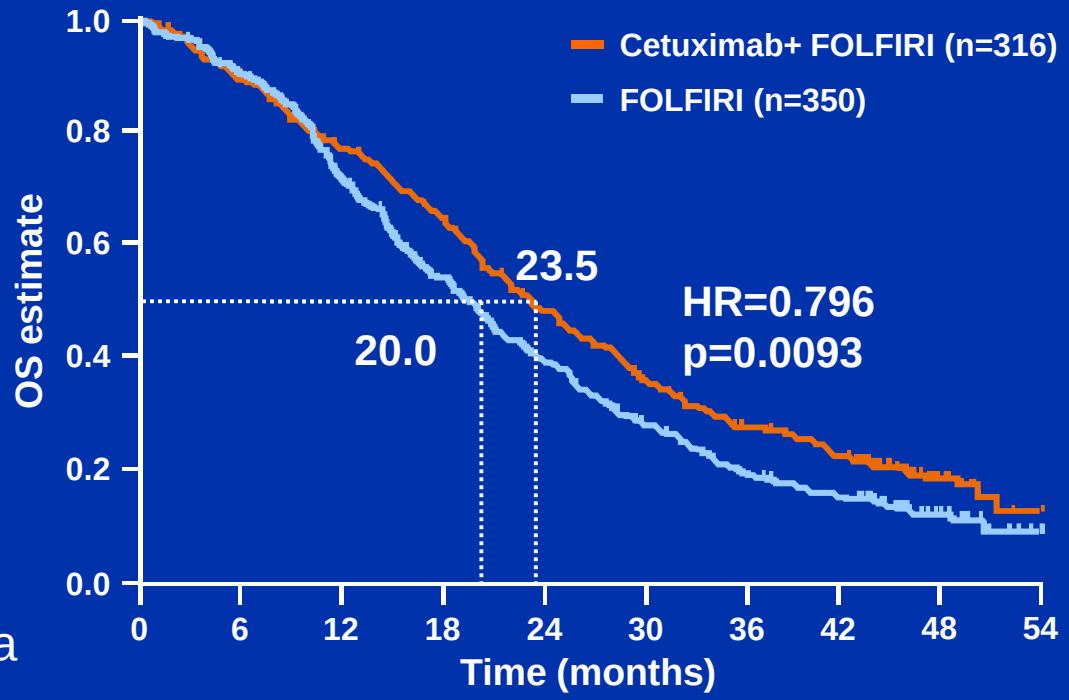
L’uso di marcatori molecolari ottimizza l’esito della terapia

Popolazione analizzata con il test del KRAS



I pazienti KRASwt beneficiano della terapia; i pazienti con KRASm no

Es. Studio CRYSTAL



Van Cutsem E, et al. J Clin Oncol 2011;29:2011–2019

La terapia personalizzata è l’approccio più efficace

Obiettivi diversi nel CRC metastatico

Pazienti con metastasi inizalmente non operabili

Pazienti destinati a cure palliative, con metastasi non operabili

Forte carica tumorale e/o sintomi correlati al tumore

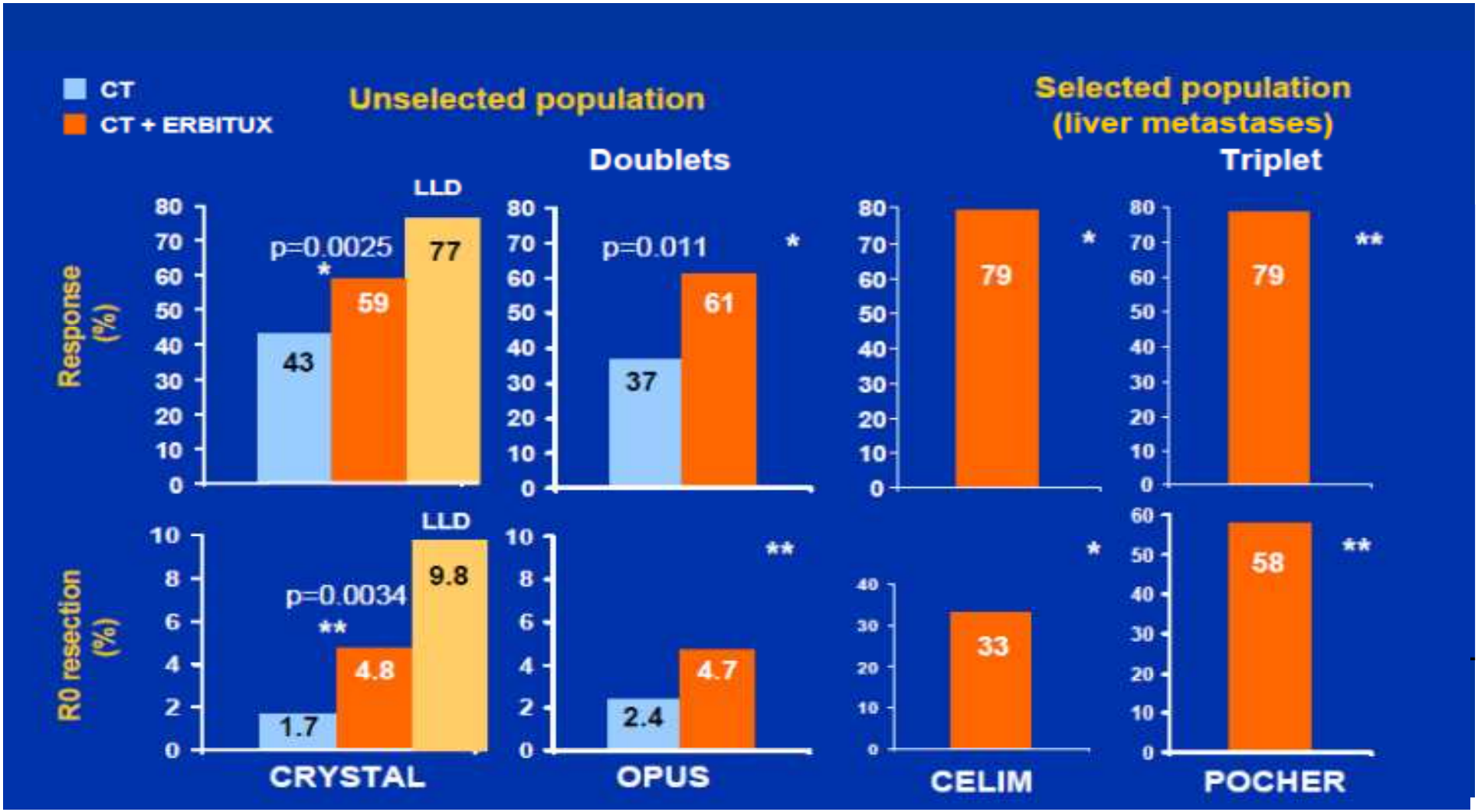
Inizialmente non sintomatici e con malattia meno aggressiva

Cura

Sollievo dei sintomi

Prolungamento della Sopravvivenza

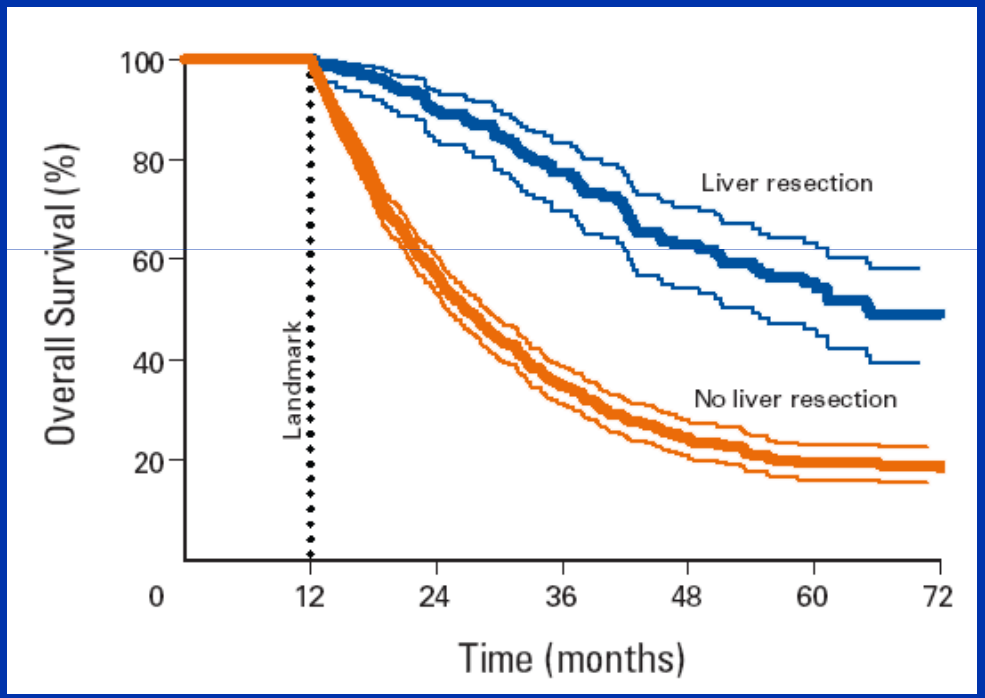
Cetuximab aumenta i pazienti portati a resezione epatica



* *KRAS* WT ** ITT LLD=malattia limitata al fegato

La chirurgia epatica aumenta la sopravvivenza

- ***Landmark analysis*** **della sopravvivenza dei pazienti vivi a 12 mesi dalla diagnosi (70% della popolazione iniziale)**



	OS mediana (mesi)	OS a 5 anni
Pazienti operati	65,3	55%
Pz non operati	26,7	19,5%
HR	0,35	

70% della popolazione inclusa

Error bars represent 95% CLs

Aumento sensibile della sopravvivenza a lungo termine: reale possibilità di cura

Kopetz S et al. J.Clin.Onc. 2009;27:3677-3683

Strategie: Linee Guida Europee 2010

clinical practice guidelines

Annals of Oncology 21 (Supplement 5):
doi:10.1093/

Advanced colorectal cancer: ESMO Clinical Practice Guidelines for treatment

Strategy according to treatment aim

Clinical situation	What is needed?	Tre in
• liver (lung) metastases ✓ potentially resectable	Maximal tumour shrinkage required	Upf t m
• multiple metastases with ✓ rapid progression ✓ tumour related symptoms ✓ risk for rapid deterioration	Control of progressive disease	
• unresectable metastases ✓ no option for resection ✓ no symptoms ✓ risk for rapid deterioration ✓ comorbidity	Tumour shrinkage less relevant Control of further progression Prevention from toxicity	

clinical practice guidelines

Annals of Oncology 21 (Supplement 5): v93–v97, 2010
doi:10.1093/annonc/mdq222

Advanced colorectal cancer: ESMO Clinical Practice Guidelines for treatment

E. Van Cutsem[1], B. Nordlinger[2] & A. Cervantes[3]
On behalf of the ESMO Guidelines Working Group*
[1]Digestive Oncology Unit, University Hospital Gasthuisberg, Leuven, Belgium; [2]Ambroise Paré Hospital, Boulogne, France; [3]Department of Hematology and Medical Oncology, INCLIVA, University of Valencia, Valencia, Spain

incidence

In 2006 there were 412 900 new cases of colorectal cancer (CRC) in Europe. This is 12.9% of all cancer cases. CRC was responsible for 217 400 deaths in Europe in 2006. This represents 12.2% of all cancer deaths. Approximately 25% present with metastases at initial diagnosis and almost 50% of patients with CRC will develop metastases, contributing to the high mortality rates reported for CRC.

diagnosis

Clinical or biochemical suspicion of metastatic disease should always be confirmed by adequate radiological imaging [usually a computed tomography (CT) scan or alternatively magnetic resonance imaging (MRI) or ultrasonography]. Fluorodeoxyglucose-positron emission tomography (FDG-PET) scan can be useful in determining the malignant characteristics of tumoral lesions, especially when combined with CT scan. FDG-PET scan is especially useful to characterize the extent of metastatic disease when the metastases are potentially resectable. Histology of the primary tumour or metastases is always needed before chemotherapy is started. For metachronous metastases histopathological or cytological confirmation of metastases should be obtained, if the clinical or radiological presentation is atypical or very late after the initial diagnosis of the primary tumour. Resectable metastases do not need histological or cytological confirmation before resection because of a low chance of seeding. Evaluation of the general condition, organ function and concomitant non-malignant diseases determines the therapeutic strategy for patients with metastatic CRC.

determination of the treatment strategy

The optimal treatment strategy of patients with metastatic CRC should be discussed in a multidisciplinary team.

In order to identify the optimal treatment strategy for patients with metastatic CRC, the staging should include at least clinical examination, blood counts, liver and renal function tests, carcinoembryonic antigen (CEA), CT scan of the abdomen and chest (alternatively, MRI). The general condition and performance status of the patient are strong prognostic factors and predictive factors. Known biochemical prognostic factors are white blood cell count, alkaline phosphatase level, lactate dehydrogenase, serum bilirubin and albumin. Additional examinations as clinically needed, are recommended before major abdominal or thoracic surgery with potentially curative intent. An FDG-PET can give additional information on equivocal lesions before resection of metastatic disease or can identify new lesions in the case of planned resection of metastases.

treatment of metastatic CRC

The majority of patients have metastatic disease that initially is not suitable for resection. It is, however, important to select patients in whom the metastases are suitable for resection and those with initially unresectable disease in whom the metastases can become suitable for resection after a major response has been achieved with combination chemotherapy. The aim of the treatment in the last group of patients may therefore be to reverse initially unresectable metastatic CRC to resectable CRC.

unresectable metastatic CRC

The optimal treatment strategy for patients with clearly unresectable metastatic CRC is rapidly evolving. The treatment of patients should be seen as a continuum of care in which the determination of the goal of the treatment is important: prolongation of survival, cure, improving tumour-related symptoms, stopping tumour progression and/or maintaining quality of life.

The outcome of patients with metastatic CRC has clearly improved during the last years with median survival now reaching almost 24 months.

The backbone of first-line palliative chemotherapy consists of a fluoropyrimidine [intravenous (i.v.) 5-fluorouracil (5-FU) or

*Correspondence to ESMO Guidelines Working Group, ESMO Head Office, Via L. Taddei 4, CH-6962 Viganello-Lugano, Switzerland.
E-mail: clinicalrecommendations@esmo.org

Approved by the ESMO Guidelines Working Group: April 2002, last update March 2010. This publication supercedes the previously published version: Ann Oncol 2009; 20 (Suppl 4): 61–63.

Conflict of interest: Prof. Van Cutsem has reported that he has received research funding from Amgen, MerckSerono, Pfizer, Roche and Sanofi-Aventis. Prof. Nordlinger has reported no conflicts of interest. Dr Cervantes has reported that he is currently conducting research sponsored by Roche, Amgen and MerckSerono and that he is a member of the speakers' bureau for MerckSerono.

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Figure 1. Strategy for the treatment of metastatic CRC (modified from Expert discussion ESMO/WCGIC Barcelona june 2009)

Van Cutsem E, et al. Ann Oncol 2010;21(Suppl. 5):v93–v97;
Van Cutsem E, et al. Ann Oncol 2010;21(Suppl. 6):vi1–vi10

KRAS: progresso importante nella terapia del cancro del colon

ASCO® American Society of Clinical Oncology

VOLUME 27 · NUMBER 5 · FEBRUARY 10 2009

JOURNAL OF CLINICAL ONCOLOGY

ASCO SPECIAL ARTICLE

Clinical Cancer Advances 2008: Major Research Advances in Cancer Treatment, Prevention, and Screening—A Report From the American Society of Clinical Oncology

Eric Winer, Julie Gralow,* Lisa Diller,† Beth Karlan,† Patrick Loehrer,† Lori Pierce,† George Demetri,‡ Patricia Ganz,‡ Barnett Kramer,‡ Mark Kris,‡ Maurie Markman,‡ Robert Mayer,‡ David Pfister,‡ Derek Raghavan,‡ Scott Ramsey,‡ Gregory Reaman,‡ Howard Sandler,‡ Raymond Sawaya,‡ Lynn Schuchter,‡ John Sweetenham,‡ Linda Vahdat,‡ and Richard L. Schilsky§*

Personalized medicine: ... “KRAS status and colon cancer treatment: A multinational team of investigators found that in patients with newly diagnosed advanced colorectal cancer, adding the monoclonal antibody cetuximab to chemotherapy was beneficial only when tumors contained the normal (wild-type) form of the gene KRAS ... These findings will help guide treatment for each patient, increasing efficacy while eliminating unnecessary adverse effects in those who will not benefit from the treatment.”

NCCN®

November 2008:
“Determination of KRAS gene status of either the primary tumor or the site of metastasis should be part of the pre-treatment work-up for all patients diagnosed with mCRC.”

L’uso di marcatori molecolari ottimizza l’esito della terapia: la terapia personalizzata



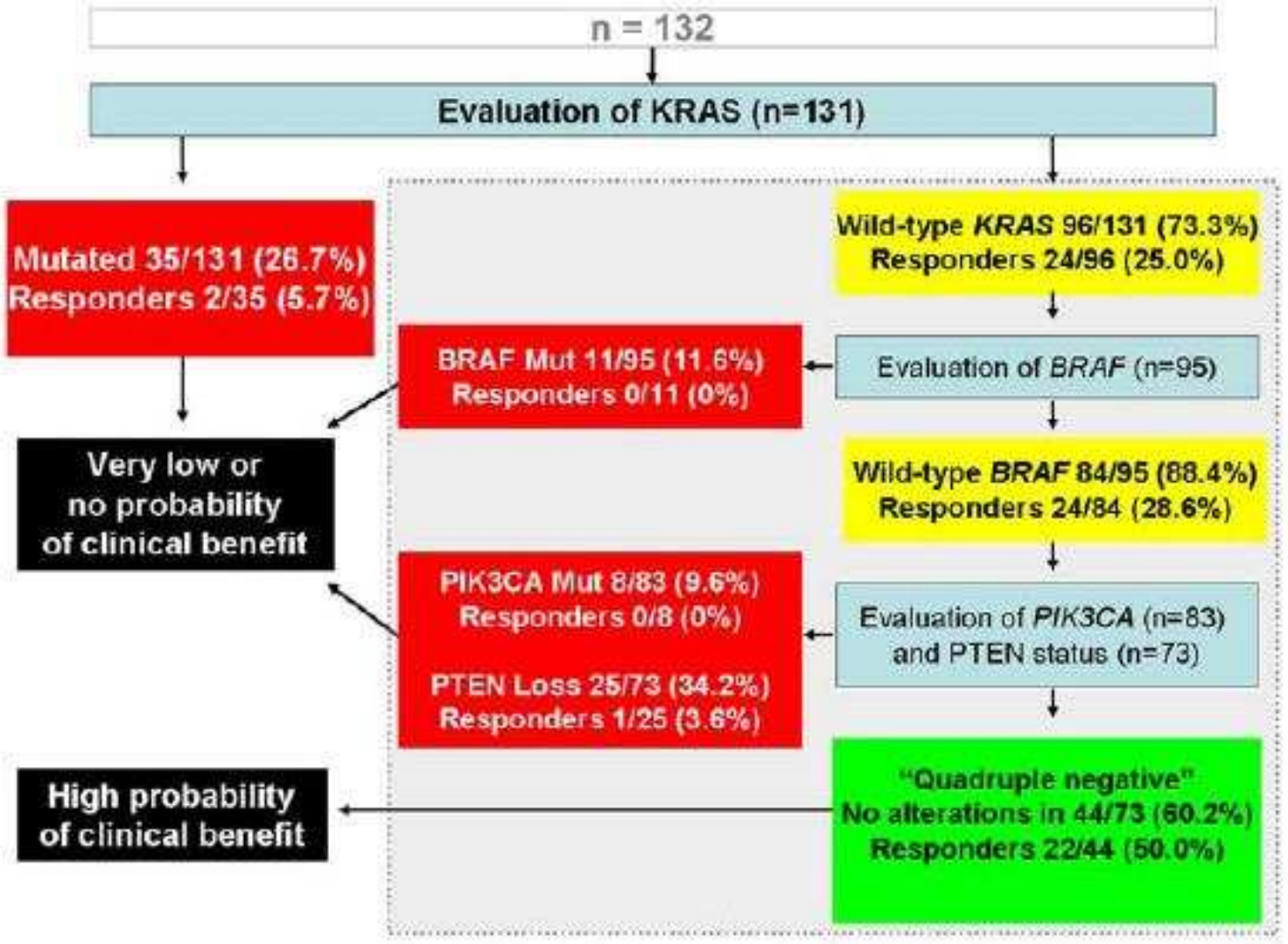
Nei pazienti K-RASwt l’associazione della terapia target anti-EGFR alla chemioterapia



Rispetto alla sola chemioterapia

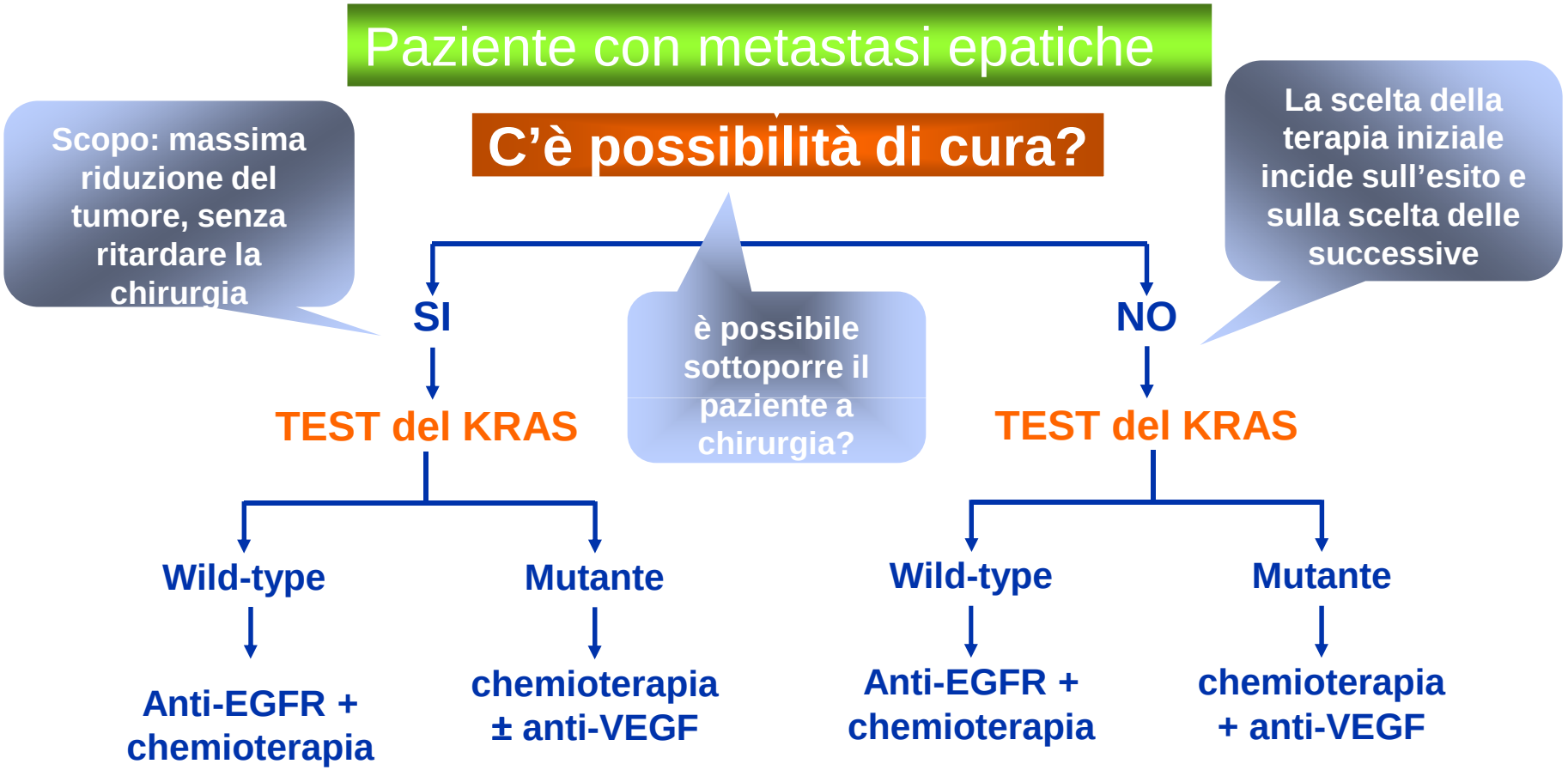
V. Cutsem, NEJM 2008; Bokemeyer C, JCO 2009; Folprecht et al., Lancet 2010

La ricerca continua … marcatori multipli



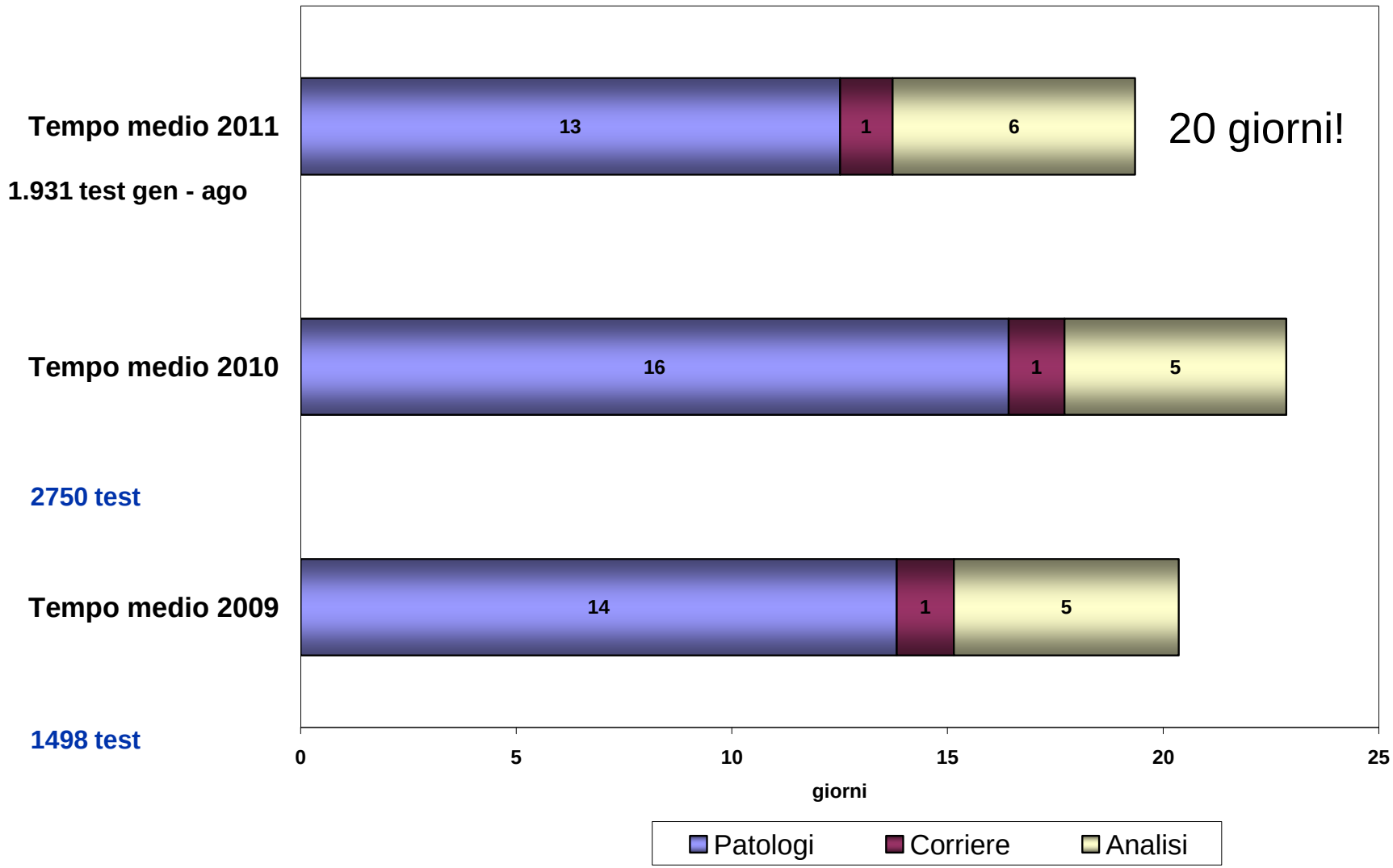
Sartore-Bianchi A, Plos-One 2010

Prospettive: ottimizzare il trattamento del paziente con tumore al colon-retto metastatico

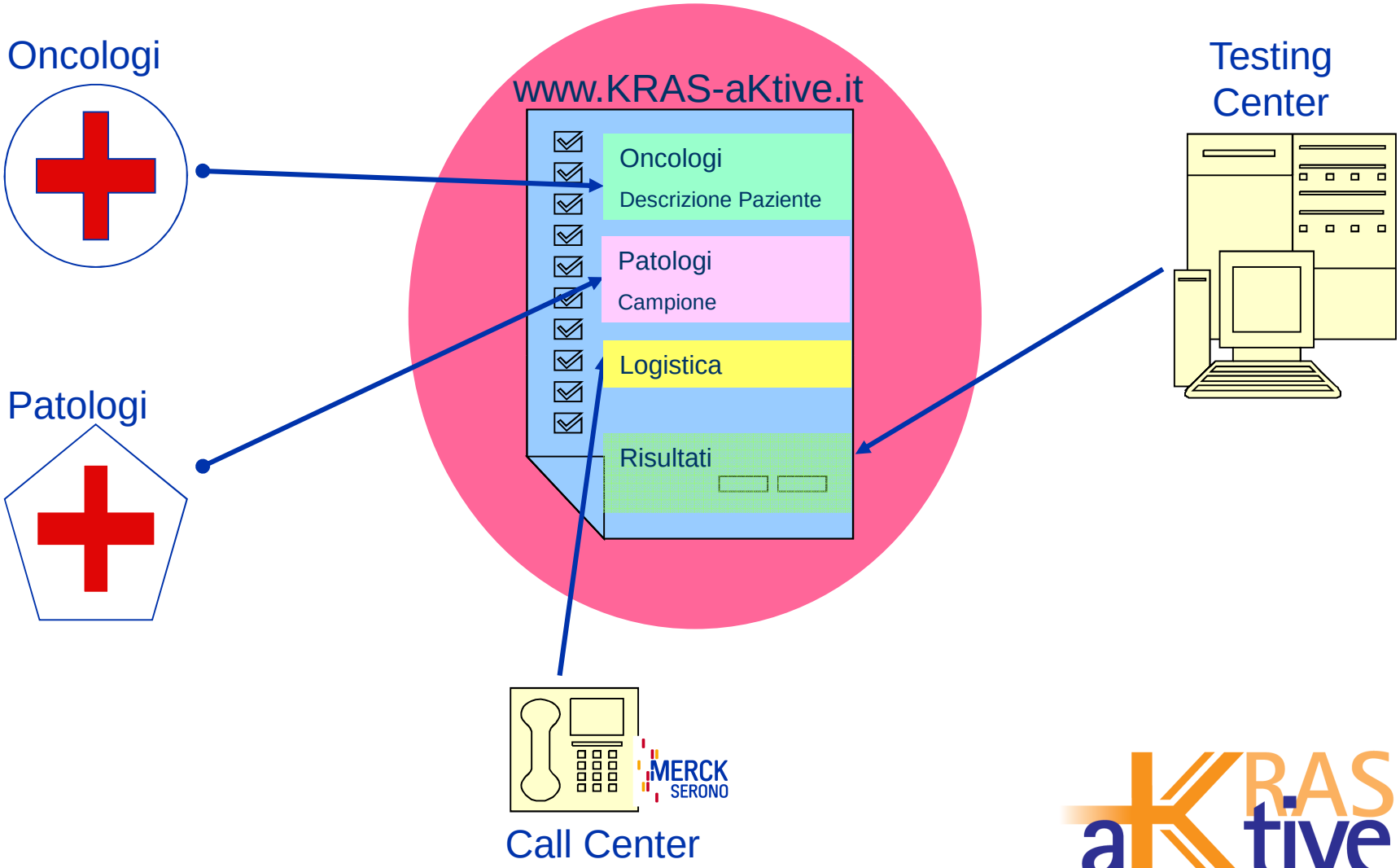


Adam R, et al. Ann Oncol 2010;21:1579–1584

Criticità


Tempo medio 2011
1.931 test gen - ago
13
1
6
20 giorni!
Tempo medio 2010
2750 test
16
1
5
Tempo medio 2009
1498 test
14
1
5
0
5
10
15
20
25
giorni
Patologi
Corriere
Analisi

Il progetto aKtive in collaborazione con le aziende

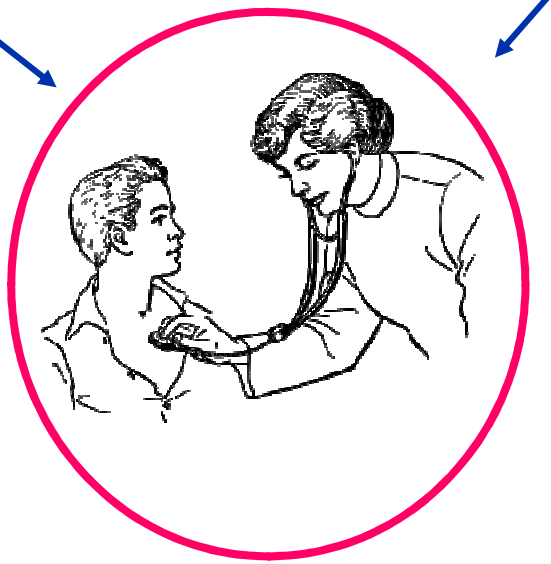


Soluzione 2: anticipazione del test

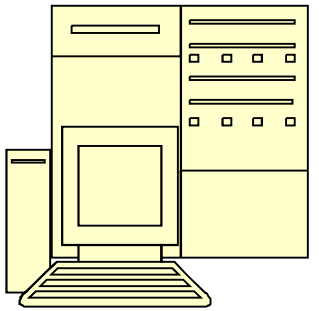
Oncologi

Patologi

Chirurghi



Test nei pazienti con diagnosi di tumore al colon-retto ad alto rischio di ricaduta/metastasi



Conclusioni

- L’identificazione del bersaglio è cruciale per l’efficacia del trattamento
- Le terapie a bersaglio molecolare devono essere primariamente inserite in una strategia che consenta un “outcome” vantaggioso
- Il test deve essere immediatamente disponibile quando la terapia a bersaglio molecolare deve essere utilizzata
- Il futuro dell’oncologia medica e il miglioramento della sopravvivenza dei pazienti dipende dallo sviluppo delle conoscenze su nuovi bersagli e sui farmaci attivi