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Terapia a bersaglio molecolare e personalizzazione del trattamento nei tumori dell'apparato gastroenterico

LA CITTA' DELLE VERBENE FONDAZIONE ONLUS

Numero di nuovi tumori stimati per anno in Italia

In Italia si diagnosticano circa 360.000 nuovi casi all'anno

Sede	Uomini	Donne
Vie aerodigestive superiori	7.200	2.300
Esofago	1.400	600
Stomaco	7.900	5.300
Colon-retto	31.400	23.200
Colon	21.900	17.000
Retto	9.500	6.200
Fegato	8.900	4.300
Colecisti e vie biliari	2.100	2.400
Pancreas	5.800	6.400
Polmone	27.000	11.200
Osso	400	200
Cute (melanomi)	5.300	5.100
Cute (non melanomi)	38.500	32.900
Mesotelioma	1.300	400
S. di Kaposi	500	200
Tessuti molli	1.100	700
Mammella	1.100	46.900
Utero cervice		2.000
Utero corpo		8.200
Ovaio		4.800
Prostata	35.800	
Testicolo	2.200	
Rene, vie urinarie*	8.400	4.300
Parenchima	7.000	3.600
Pelvi e vie urinarie	1.400	700
Vescica**	22.100	5.100
Sistema nervoso centrale	3.200	2.500
Tiroide	4.100	12.200
Linfoma di Hodgkin	1.300	1.000
Linfoma non-Hodgkin	6.900	5.900
Mieloma	2.700	2.500
Leucemie	4.400	3.500
Tutti i tumori, esclusi carcinomi della cute	199.500	166.500

Terapia a bersaglio molecolare nei tumori dell'apparato gastroenterico

- TUMORI DELLO STOMACO
- TUMORI DEL PANCREAS
- TUMORI DEL COLON-RETTO
- TUMORI PRIMITIVI DEL FEGATO

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 interferire con le cellule in rapida divisione
- Principali categorie di farmaci a bersaglio molecolare:
- – Piccole molecole
- – Anticorpi monoclonali

Gli esordi della terapia a bersaglio molecolare

- Scoperta di un farmaco contro un bersaglio apparentemente critico.
- Impiego clinico con risultati variabili (in genere attività rilevante in circa 10% dei pazienti non selezionati).
- Combinazioni con chemioterapici basata sugli standard in uso per una determinata neoplasia (risultati spesso deludenti).

Gli esordi della terapia a bersaglio molecolare

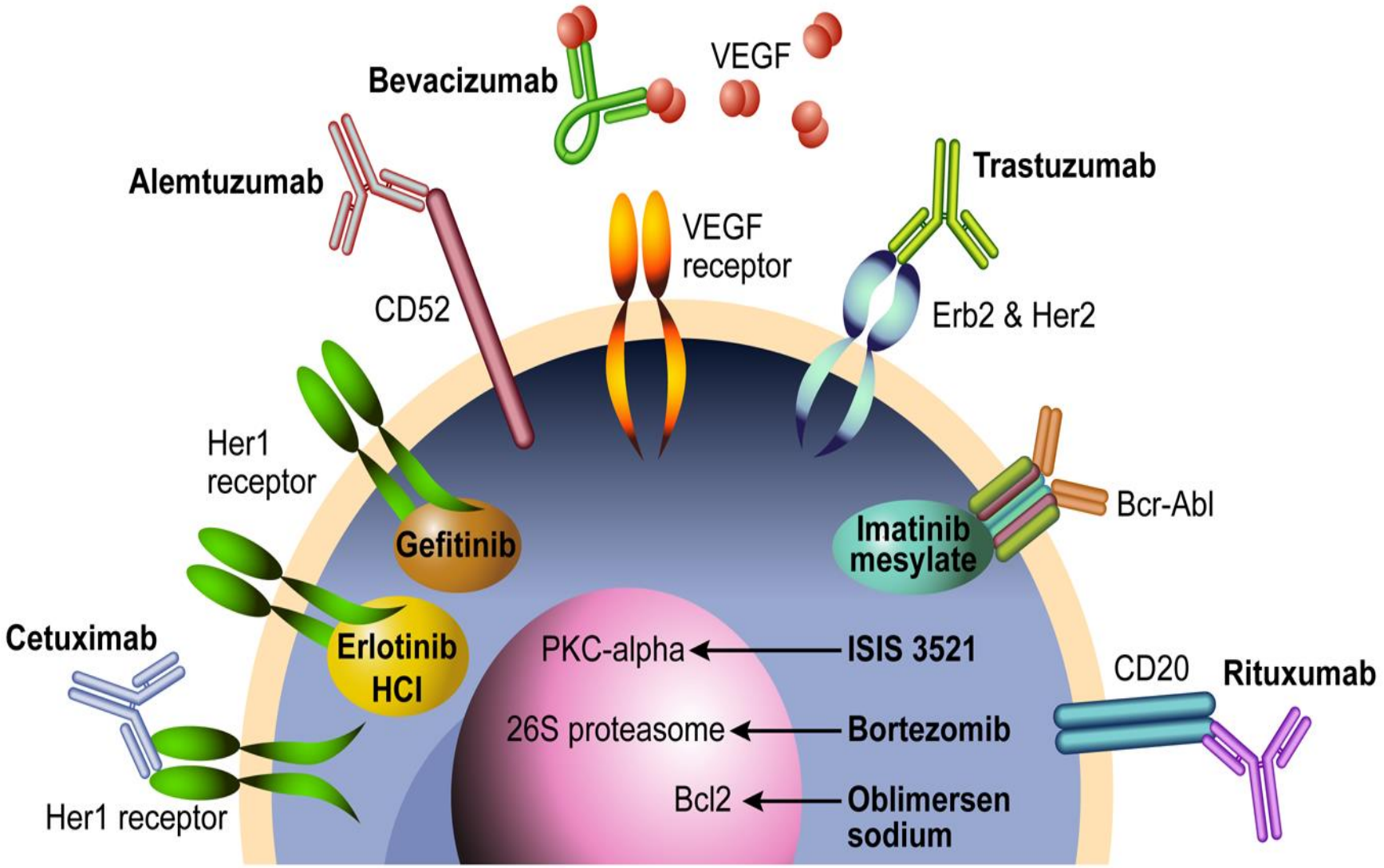
- Piccole percentuali di pazienti ma con elevata possibilità di risposta
- Estensione d'uso a patologie diverse da quelle in indicazione se sono presenti le alterazioni molecolari bersaglio per i farmaci
- Durata dei trattamenti: tossicità, costi ecc.
- Utilizzo di nuove tecnologie e diagnostica per immagini per ridurre tossicità e costi

LE SFIDE DELL'ERA DELLE TERAPIE TARGETED

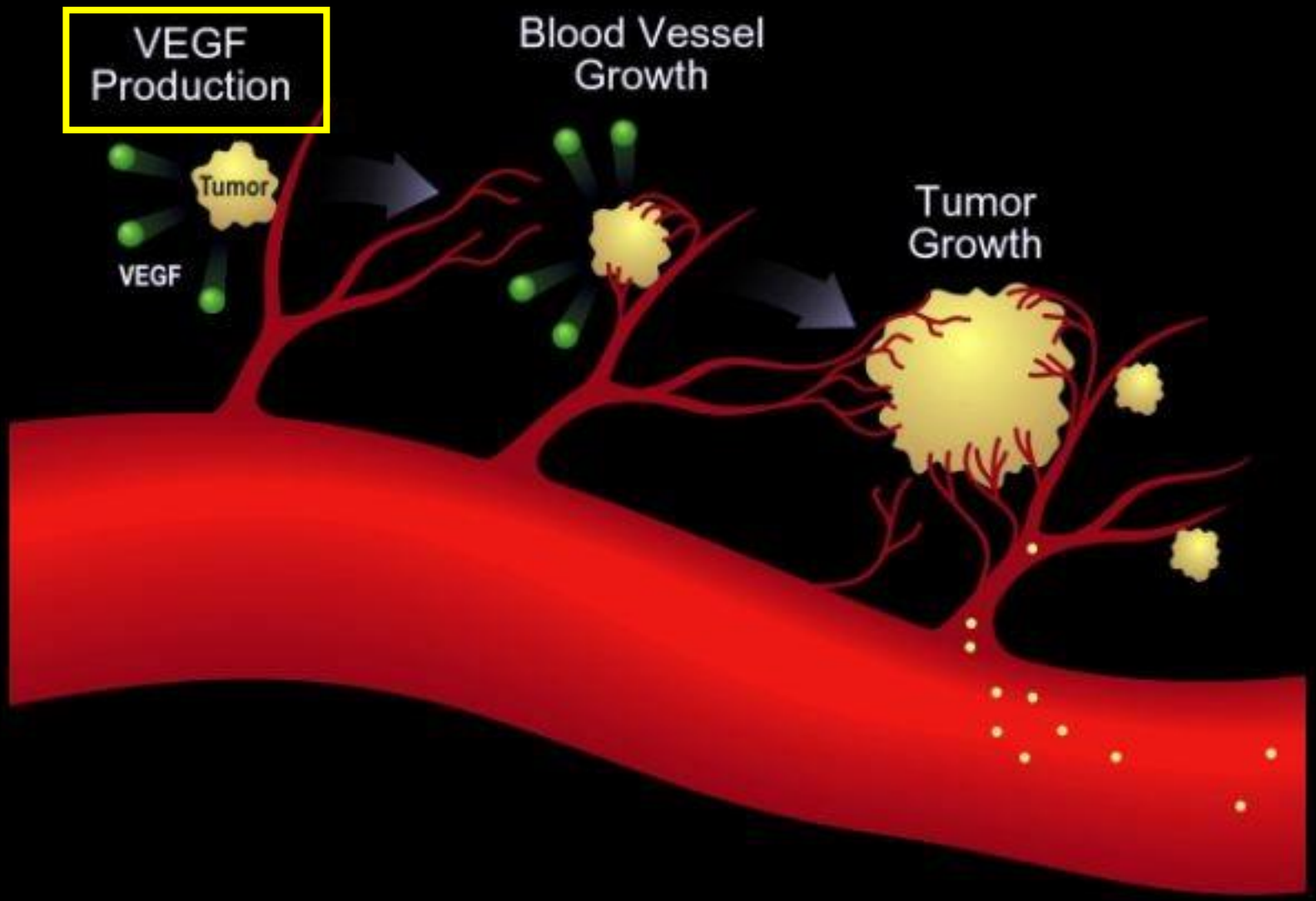
Problematiche

- Attualmente sono in fase di sviluppo circa 800 farmaci antitumorali
- Molti (troppi ?) farmaci
- Sempre più malattie in cui utilizzarli
- Maggiore uso di controlli con placebo
- Maggiore impiego di trial clinici randomizzati
- Più tempo per raggiungere gli endpoints
- Più linee di terapia efficaci
- Documentazioni più costose
- Maggiore complessità delle norme "regolatorie"

Targeted Therapies



Angiogenesis



Farmaci a Bersaglio Molecolare

Anticorpi monoclonali
….gli "umab"

Rituximab (→CD20)

Trastuzumab (→HER2)

Cetuximab (→EGFR)

Bevacizumab (→VEGF)

Inibitori della trasduzione del segnale
…" gli "inib"

Imatinib mesilato (→ bcr-abl -, c-kit-, PDGF-TKs)

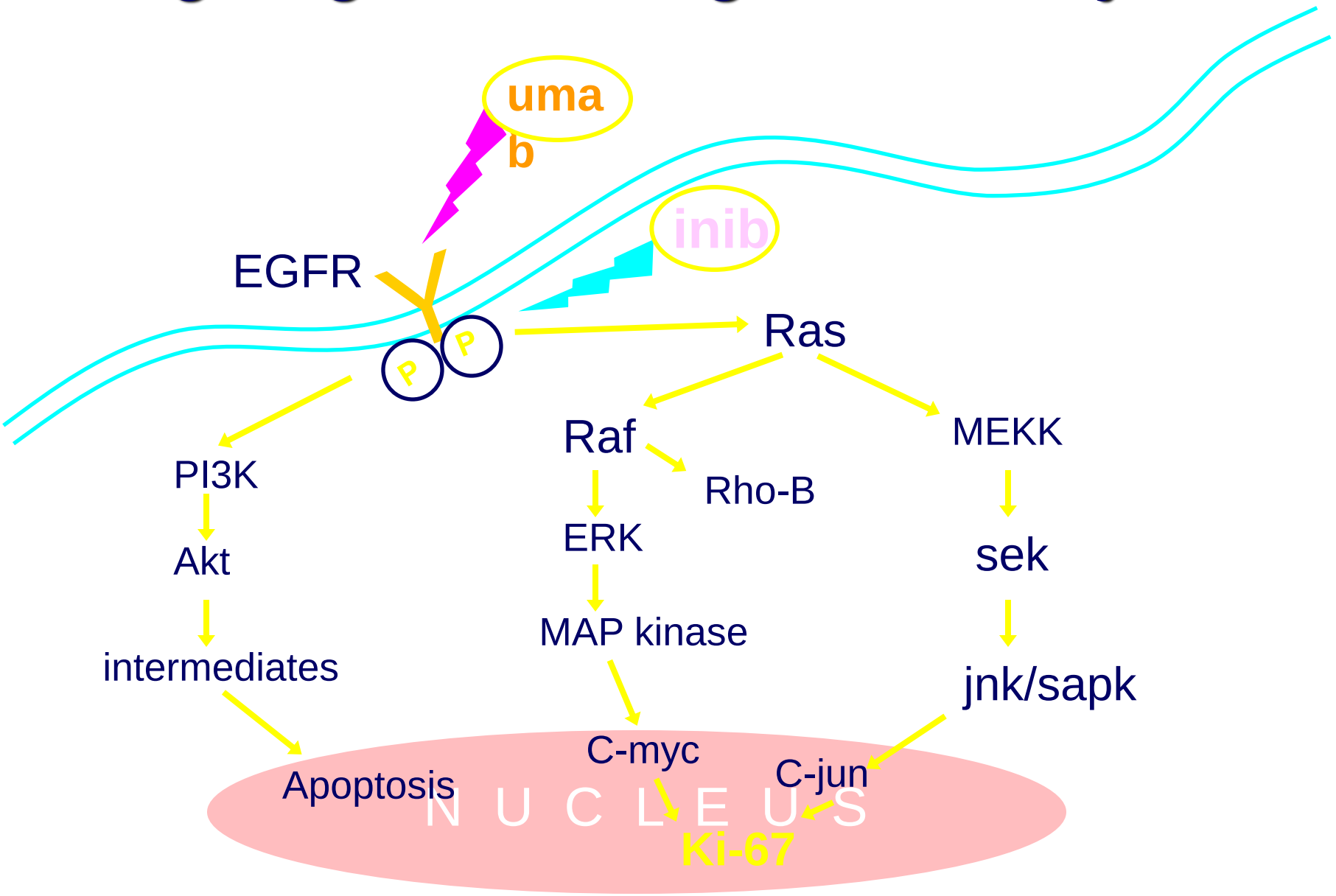
Gefitinib (→ EGFR-TK)

Erlotinib (→ EGFR-TK)

Bortezomib (→ proteasoma)

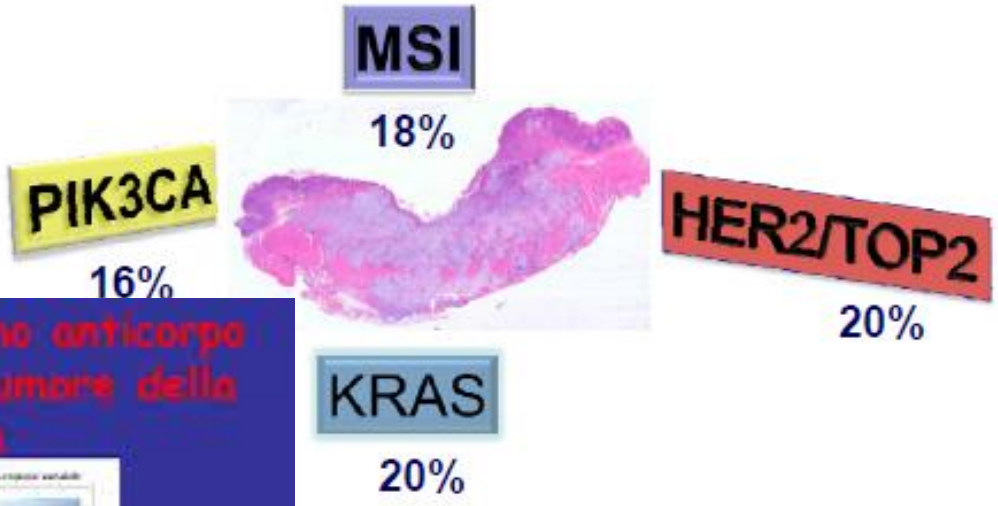
Sorafenib, Sunitinib

Targeting Cellular Signal Pathways

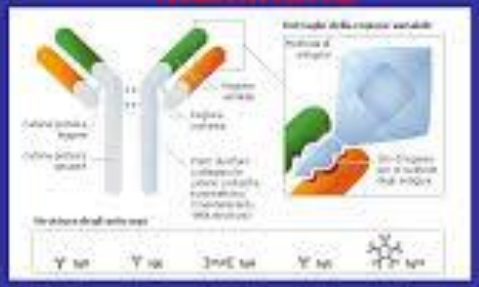


GASTRIC CANCER

Gli studi clinici sui tumori dello stomaco dovrebbero includere la sottoclassificazione molecolare



Trastuzumab: il primo anticorpo monoclonale per il tumore della mammella



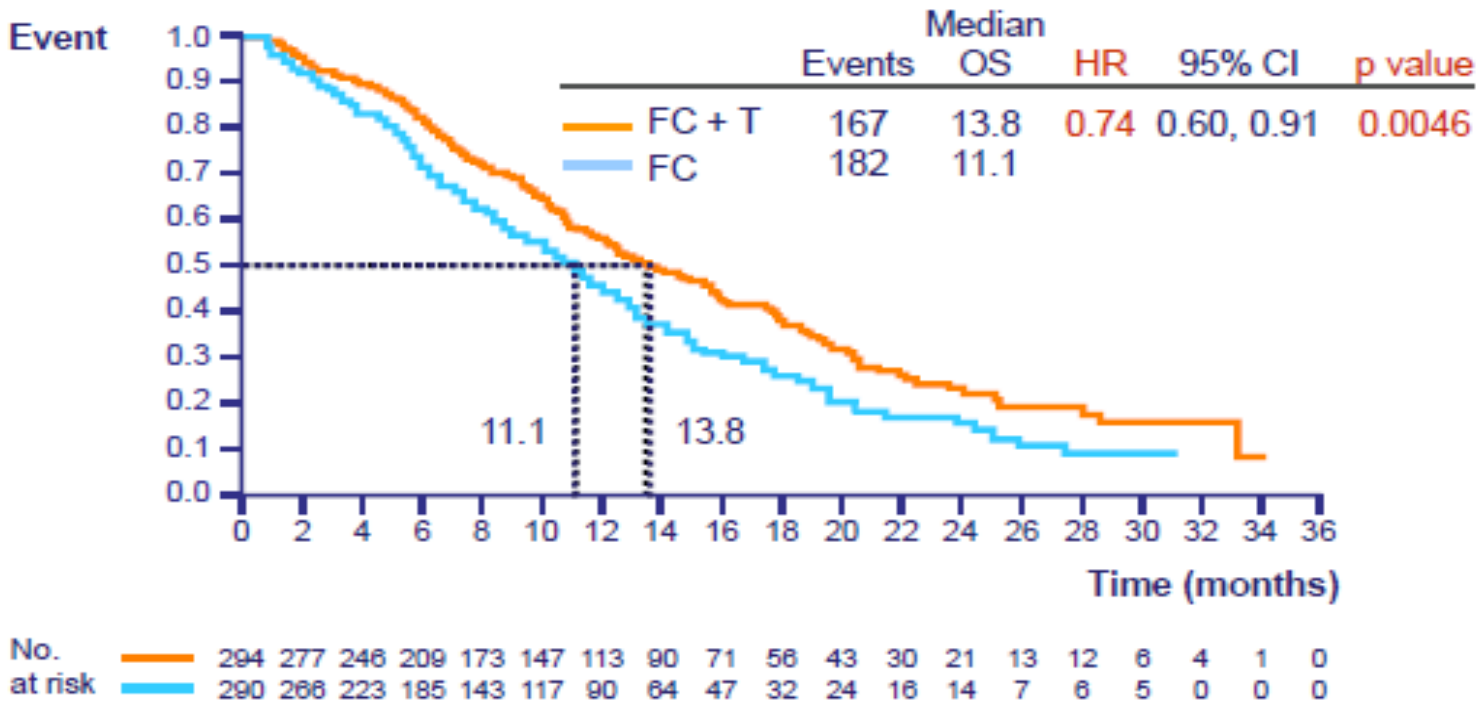
- Un anticorpo monoclonale è un anticorpo concepito per riconoscere e legarsi a una sostanza specifica

IL TRASTUZUMAB BLOCCA HER2

- Specifico per il bersaglio del recettore HER2
- Alta affinità e specificità
- 95% umano, 5% murino
  - Aumentato potenziale per effetto immuno-mediato

INIBITORI DI HER2 (TRASTUZUMAB) NEL CARCINOMA GASTRICO

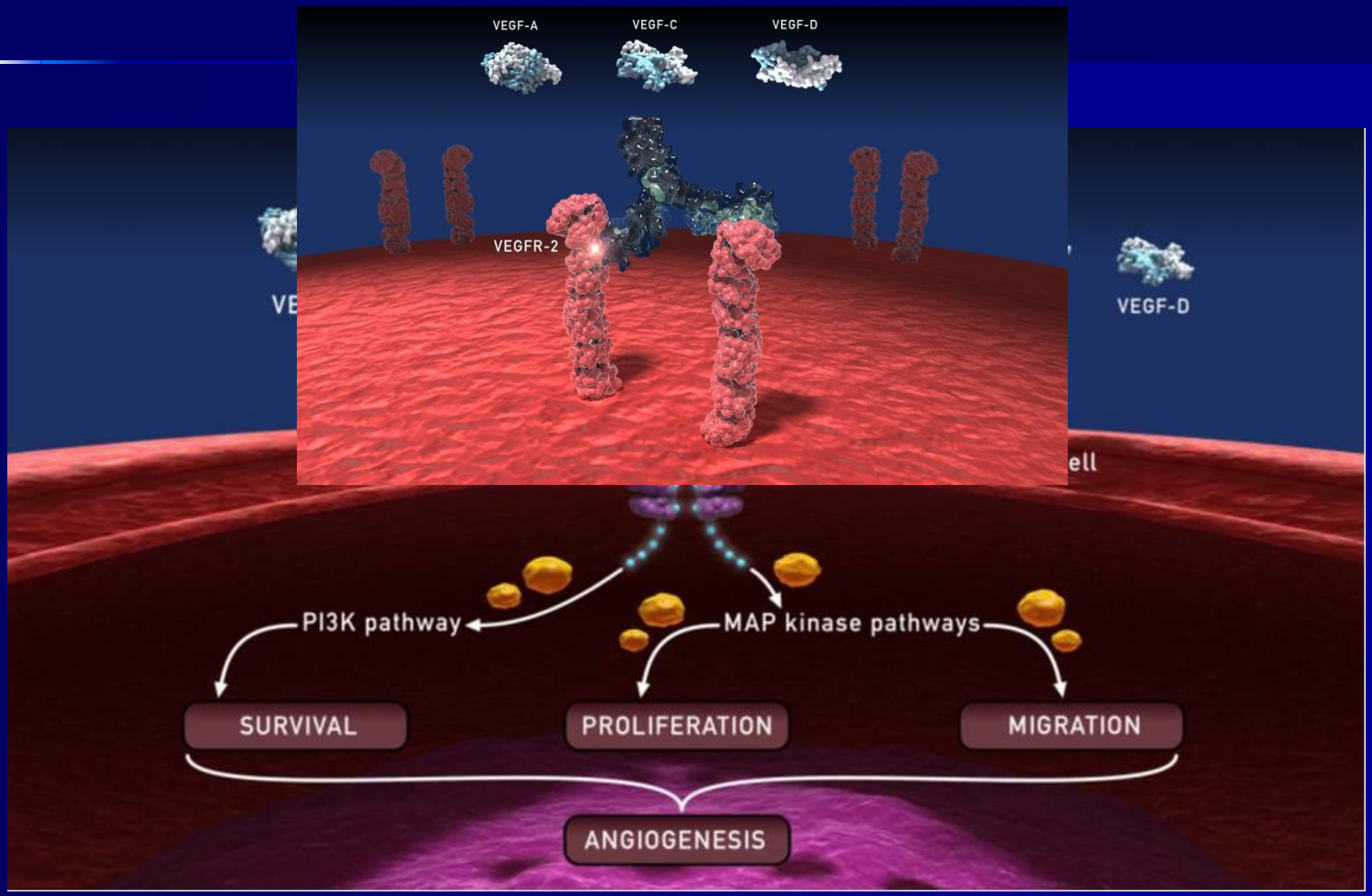
Toga Trial: OS



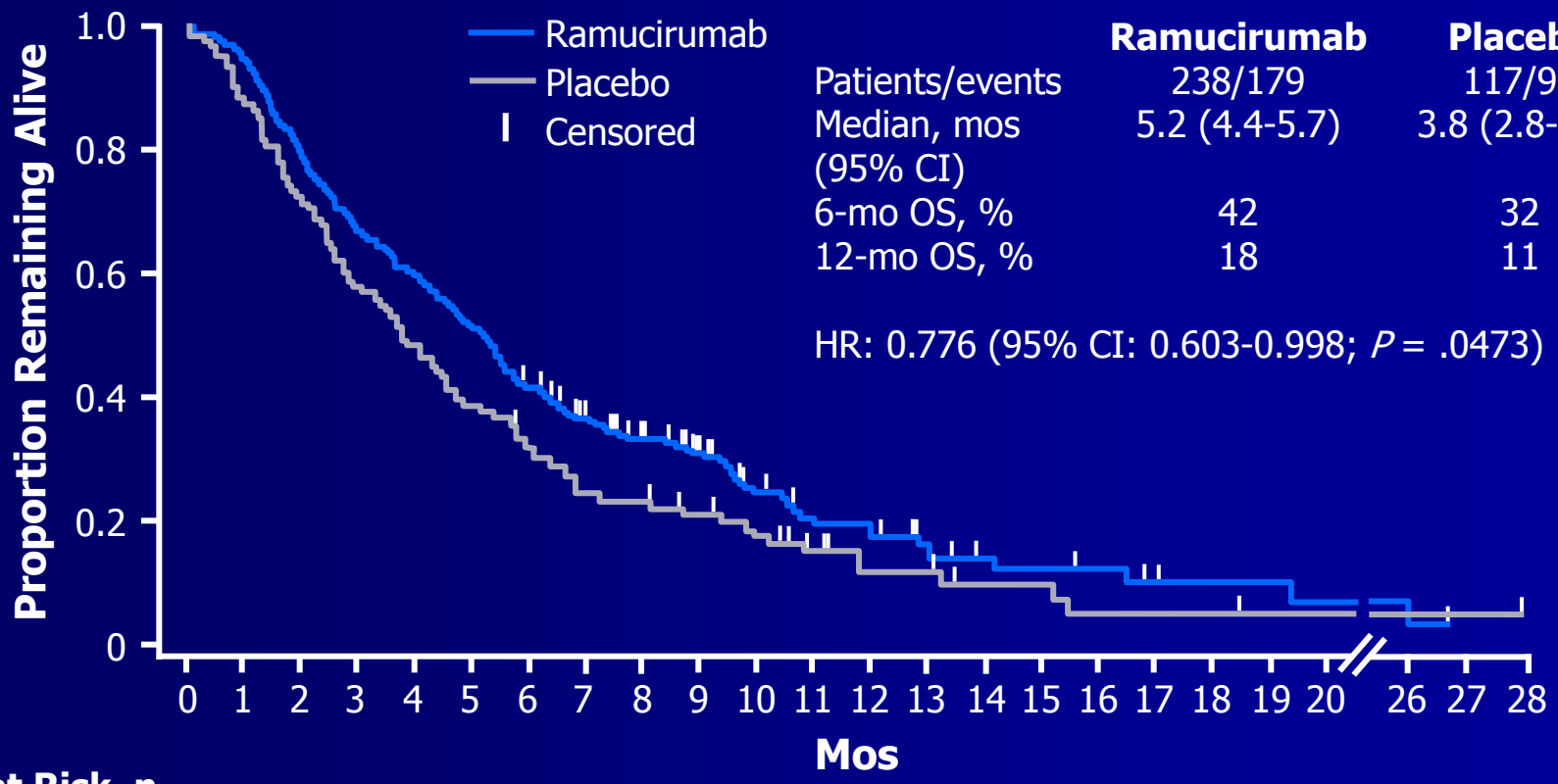
T, trastuzumab

Bang et al; ASCO 2009 and Lancet 2010

Phase III REGARD Trial: BSC ± Ramucirumab in Metastatic Gastric or GEJ Cancer



REGARD Trial of BSC ± Ramucirumab in Metastatic Gastric or GEJ Cancer: OS



	Ramucirumab	Placebo
Patients/events	238/179	117/99
Median, mos (95% CI)	5.2 (4.4-5.7)	3.8 (2.8-4.7)
6-mo OS, %	42	32
12-mo OS, %	18	11

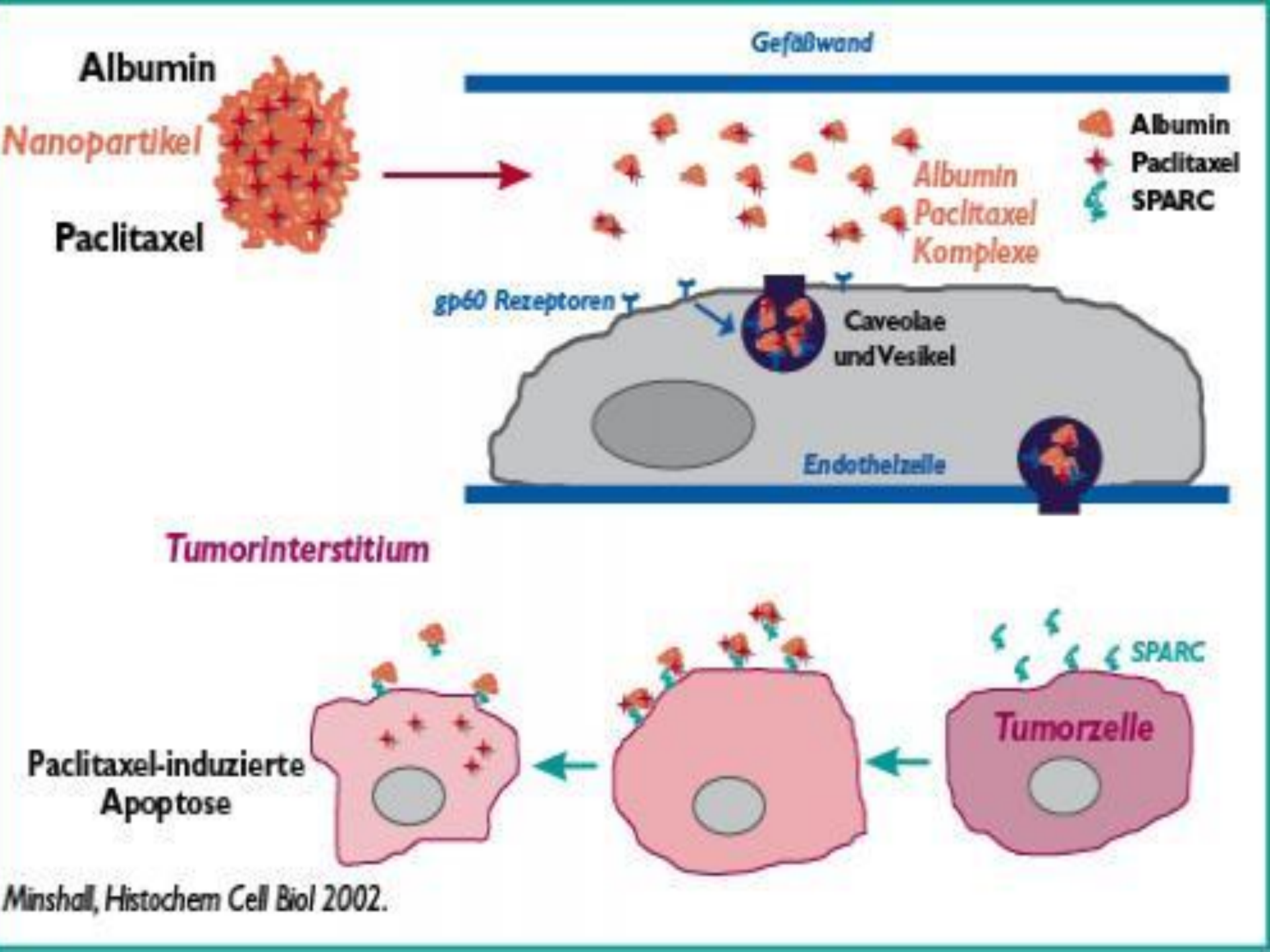
HR: 0.776 (95% CI: 0.603-0.998; *P* = .0473)

Pts at Risk, n

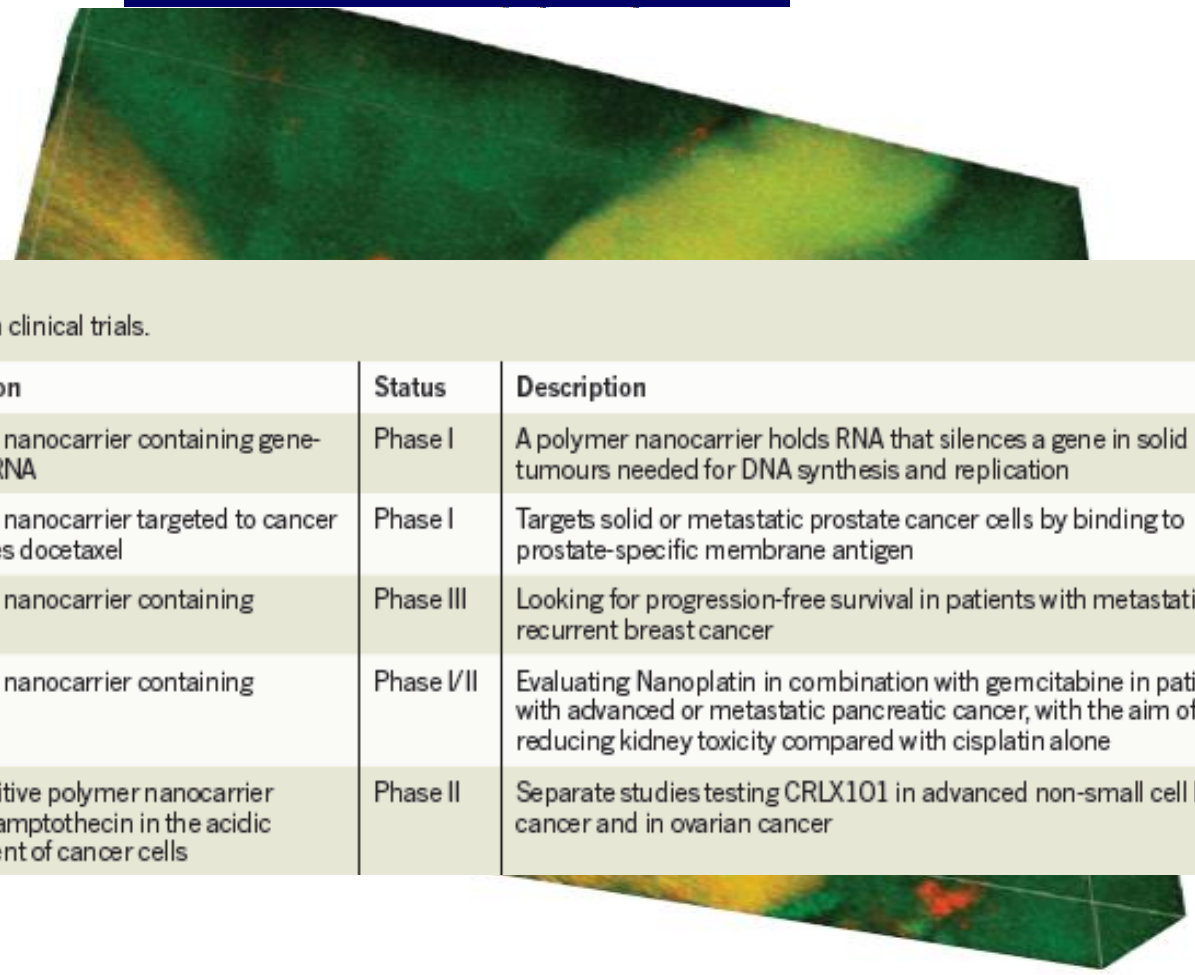
Ramucirumab	238	154	92	49	17	7	3	0	0
Placebo	117	66	34	20	7	4	2	1	0

FATTORI DETERMINANTI PER LA CRESCITA TUMORALE E NUOVI BERSAGLI TERAPEUTICI

- • Microambiente e Stroma
- • Target epigenetici
- • Metabolismo
- • miRNA


Albumin
Nanopartikel
Paclitaxel
Gefäßwand
Albumin
Paclitaxel
SPARC
Albumin
Paclitaxel
Komplexe
gp60 Rezeptoren
Caveolae
und Vesikel
Endothelzelle
Tumorinterstitium
SPARC
Tumorzelle
Paclitaxel-induzierte
Apoptose
Minshall, Histochem Cell Biol 2002.

Nanomedicine has the potential to address one of the biggest problems in cancer therapy: how to get enough of the right drug to the right place, without causing side effects or inducing resistance.



NANOMEDICINE IN CLINICAL TRIALS

Several nanoscale drug carriers are currently in clinical trials.

Company	Drug	Formulation	Status	Description
Calando Pharmaceuticals	CALAA-01	A polymer nanocarrier containing gene-silencing RNA	Phase I	A polymer nanocarrier holds RNA that silences a gene in solid tumours needed for DNA synthesis and replication
BIND Biosciences	BIND-014	A polymer nanocarrier targeted to cancer cells carries docetaxel	Phase I	Targets solid or metastatic prostate cancer cells by binding to prostate-specific membrane antigen
Nippon Kayaku	NK105	A polymer nanocarrier containing paclitaxel	Phase III	Looking for progression-free survival in patients with metastatic or recurrent breast cancer
NanoCarrier	Nanoplatin (NC-6004)	A polymer nanocarrier containing cisplatin	Phase I/II	Evaluating Nanoplatin in combination with gemcitabine in patients with advanced or metastatic pancreatic cancer, with the aim of reducing kidney toxicity compared with cisplatin alone
Cerulean Pharma	CRLX101	A pH-sensitive polymer nanocarrier releases camptothecin in the acidic environment of cancer cells	Phase II	Separate studies testing CRLX101 in advanced non-small cell lung cancer and in ovarian cancer

A reconstructed 3D image showing the accumulation of 30-nm nanoparticles (green) in a pancreatic tumour.

GEMCITABINA

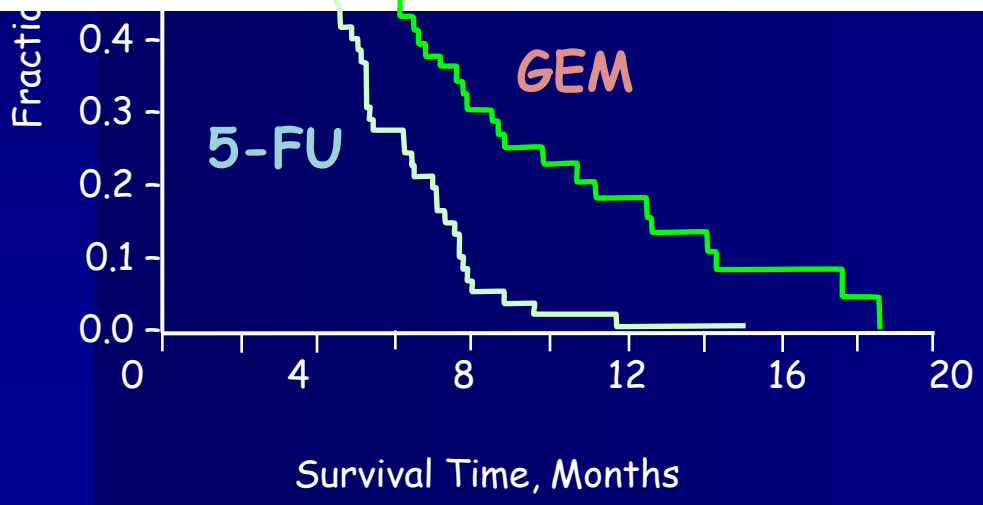
Improvements in Survival and Clinical Benefit With Gemcitabine as First-Line Therapy for Patients With Advanced Pancreas Cancer: A Randomized Trial

5-FU 4.41 2%

By Howard A. Burris III, Malcolm J. Moore, John Andersen, Mark R. Green, Mace L. Rothenberg, Manuel R. Modiano, M. Christine Cripps, Russell K. Portenoy, Anna Maria Storniolo, Peter Tarassoff, Robert Nelson, F. Andrew Dorr, C.D. Stephens, and Daniel D. Von Hoff

GEM 5.65 18%

J Clin Oncol 15:2403-2413.



N	126
Stadio	IV
KPS	50-70

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

This article was published on October 16, 2013, at NEJM.org.

N Engl J Med 2013.
DOI: 10.1056/NEJMoa1304369

Increased Survival in Pancreatic Cancer with nab-Paclitaxel plus Gemcitabine

Daniel D. Von Hoff, M.D., Thomas Ervin, M.D., Francis P. Arena, M.D., E. Gabriela Chiorean, M.D., Jeffrey Infante, M.D., Malcolm Moore, M.D., Thomas Seay, M.D., Sergei A. Tjulandin, M.D., Wen Wee Ma, M.D., Mansoor N. Saleh, M.D., Marion Harris, M.D., Michele Reni, M.D., Scot Dowden, M.D., Daniel Laheru, M.D., Nathan Bahary, M.D., Ramesh K. Ramanathan, M.D., Josep Tabernero, M.D., Manuel Hidalgo, M.D., Ph.D., David Goldstein, M.D., Eric Van Cutsem, M.D., Xinyu Wei, Ph.D., Jose Iglesias, M.D., and Markus F. Renschler, M.D.

DISEGNO dello STUDIO

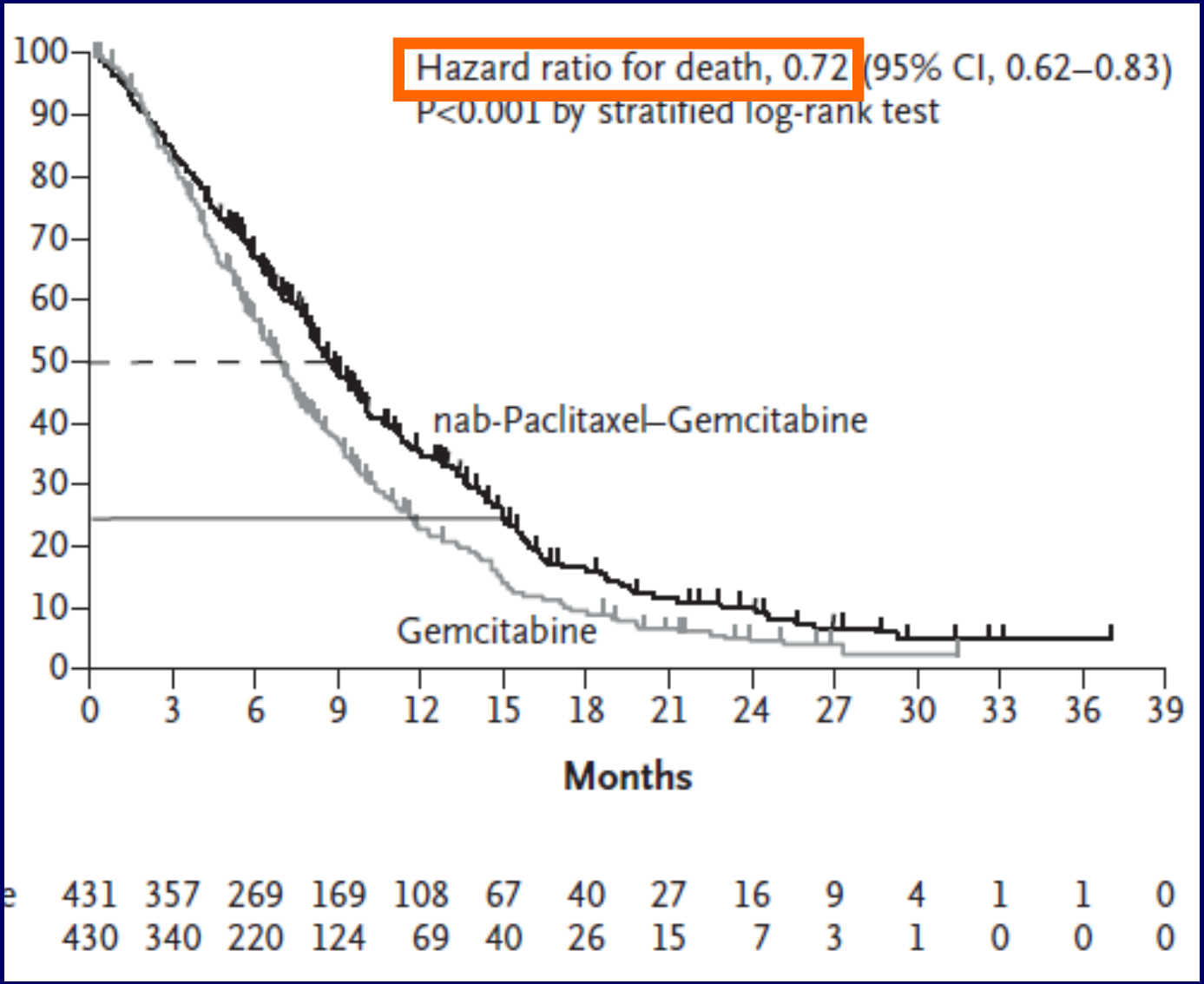
N = 842

- Stadio IV
- No precedente terapia
- KPS ≥70

nab-Paclitaxel
125 mg/m^2 ogni 3/4 settimane
+
Gemcitabina
1000 mg/m^2 IV ogni 3/4 settimane

Gemcitabina
1000 mg/m^2 ogni settimana x 7/8 settimane
poi ogni 3/4 settimane

SOPRAVVIVENZA



FRONT-LINE THERAPY

Phase III Nab-Paclitaxel + Gemcitabine vs Gemcitabine (MPACT), N= 861

Outcomes	Nab-P + Gem	Gemcitabine
Median Overall Survival	8.5 mths	6.7 mths
	HR 0.72, p= 0.000015	
1-Year Survival	35%	22%
Progression-Free Survival	5.5 mths	3.7 mths
Response Rate	23%	7%
Toxicity	**Nab-P+ Gem**	**Gemcitabine**
AE death	4%	4%
Neutropenia (Gd 3-4)	38%	27%
Fatigue (Gd 3-4)	17%	7%
Neuropathy (Gd 3-4)	17%	<1%

Von Hoff, D. NEJM, 2013

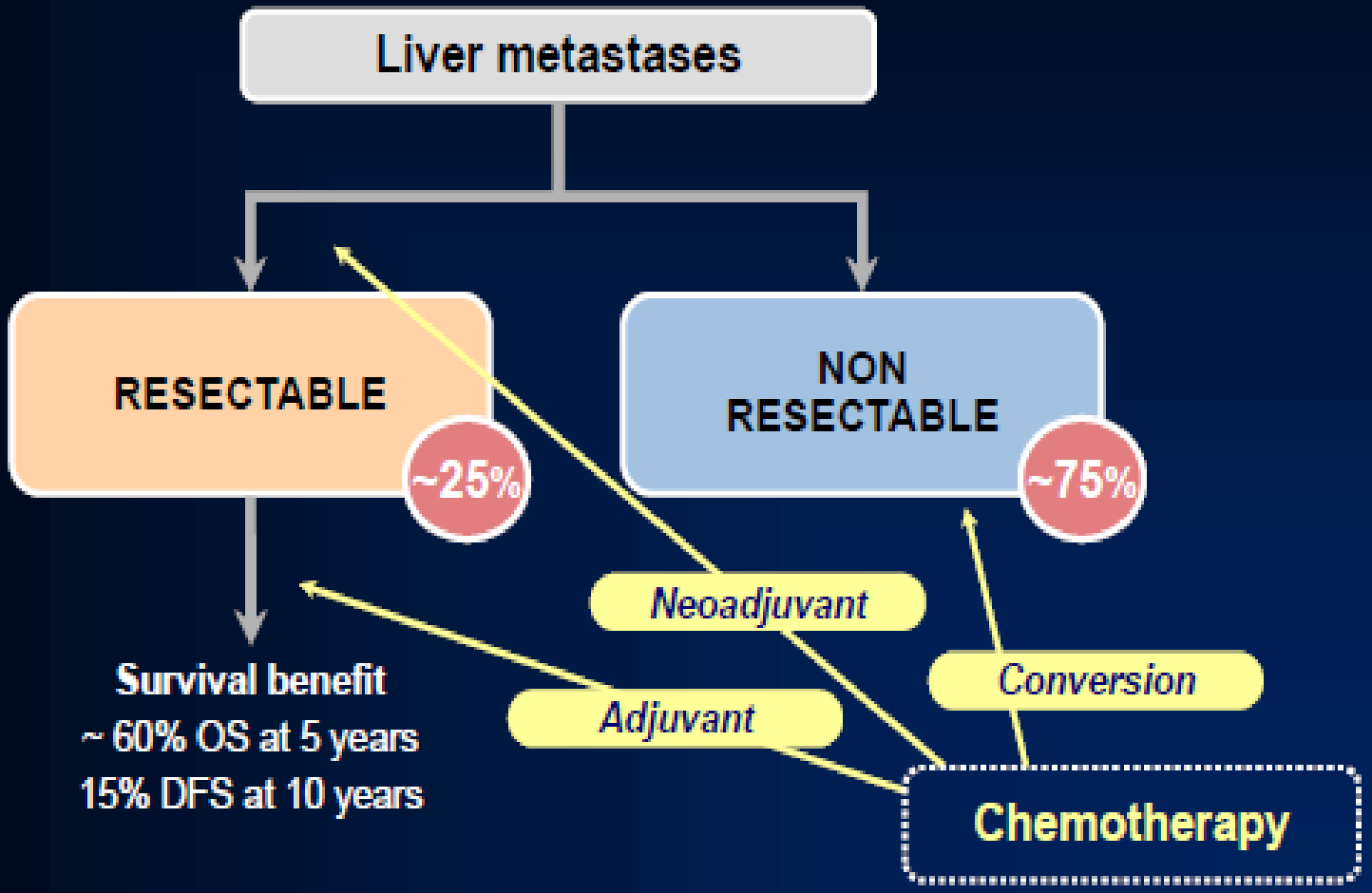
FRONT-LINE THERAPY

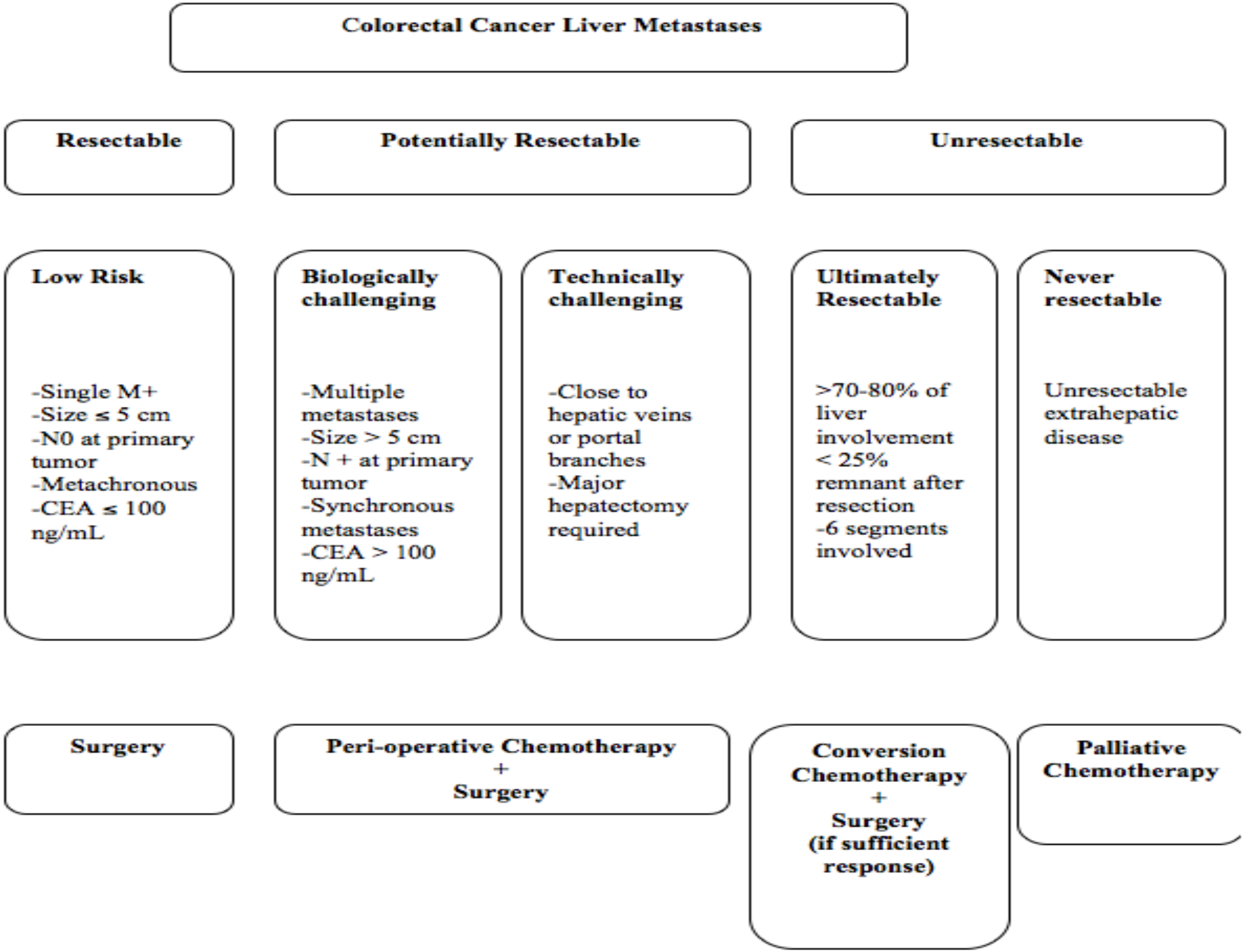
Similarities and Differences

	FOLFIRINOX N= 167	Nab-P + Gem N= 431
Patient population	Metastatic only	Metastatic only
Median age	61 years	62 years
Age limit	< 76 years	No upper limit
Performance Status	ECOG 0-1	KPS 70-100%
Recruitment	France	US (63%), Europe, Aust Academic, Community
Trial Conduct	Stopped Interim analysis	Increased N
Control Gemcitabine	Med OS 6.8 mths	Med OS 6.7 mths
Experimental arm	Med OS 11.1 mths	Med OS 8.5 mths
HR, p-value	HR 0.57, p< 0.001	HR 0.72, p= 0.001
Quality of Life	Yes	-
Growth factors	42%	26%

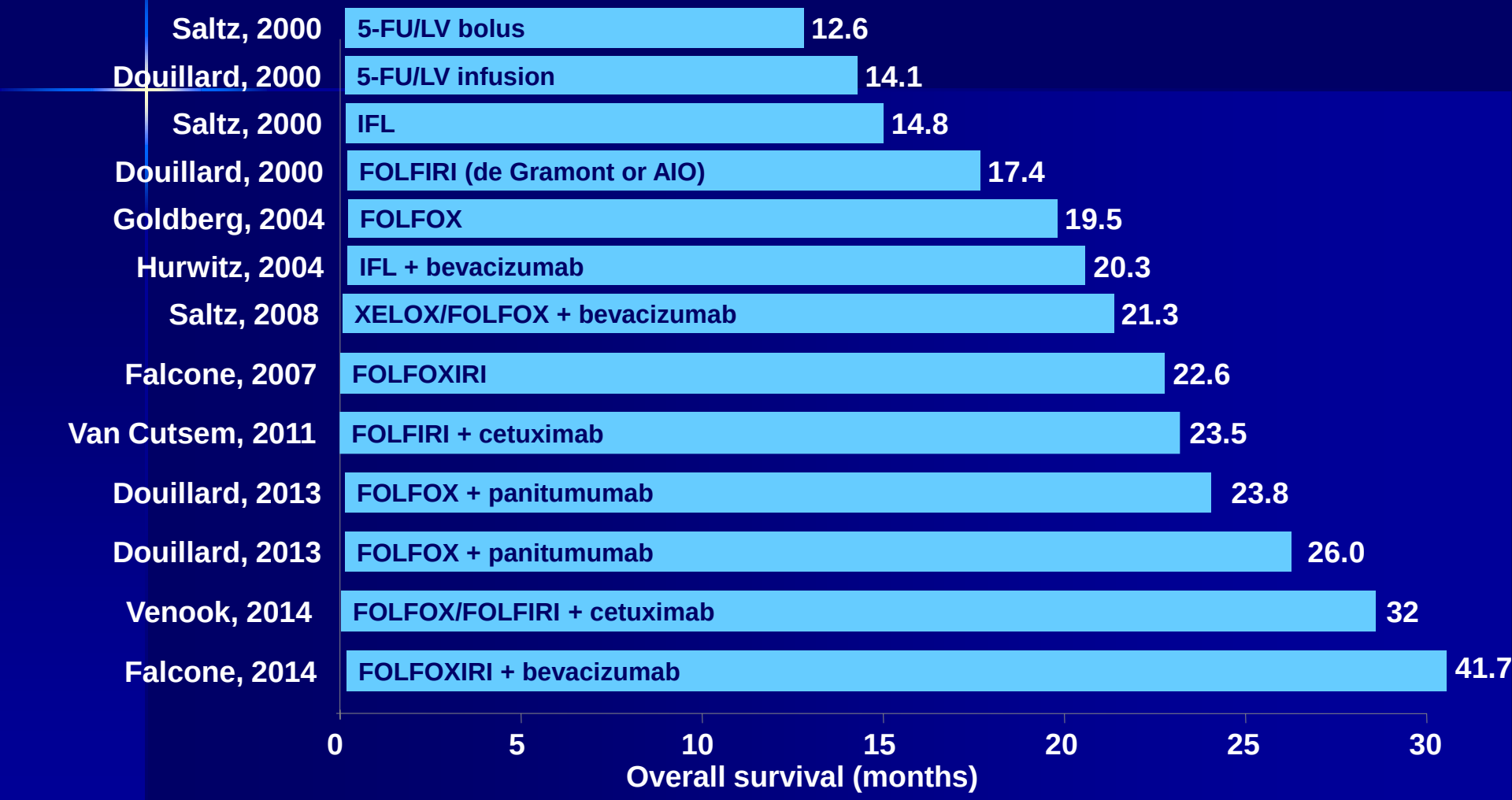
- **I farmaci a bersaglio molecolare possono modificare le modalità e la sequenza degli interventi terapeutici**
- **L'esempio della resecabilità delle metastasi epatiche da carcinoma del colon-retto metastatico**

Integrating Chemotherapy and Liver Surgery for Metastatic Colorectal Cancer

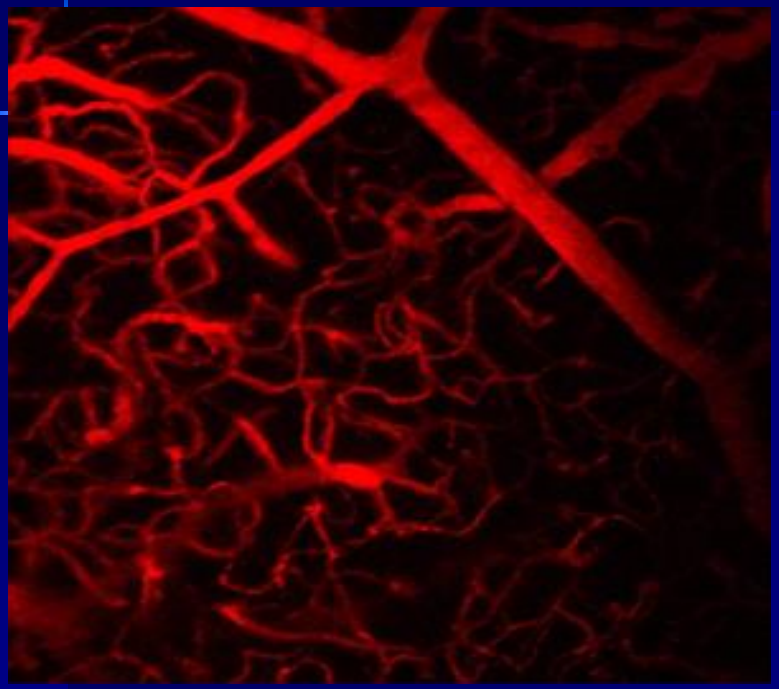



Colorectal Cancer Liver Metastases
Resectable
Potentially Resectable
Unresectable
Low Risk
-Single M+
-Size ≤ 5 cm
-N0 at primary tumor
-Metachronous
-CEA ≤ 100 ng/mL
Biologically challenging
-Multiple metastases
-Size > 5 cm
-N + at primary tumor
-Synchronous metastases
-CEA > 100 ng/mL
Technically challenging
-Close to hepatic veins or portal branches
-Major hepatectomy required
Ultimately Resectable
>70-80% of liver involvement
< 25% remnant after resection
-6 segments involved
Never resectable
Unresectable extrahepatic disease
Surgery
Peri-operative Chemotherapy
+
Surgery
Conversion Chemotherapy
+
Surgery
(if sufficient response)
Palliative Chemotherapy

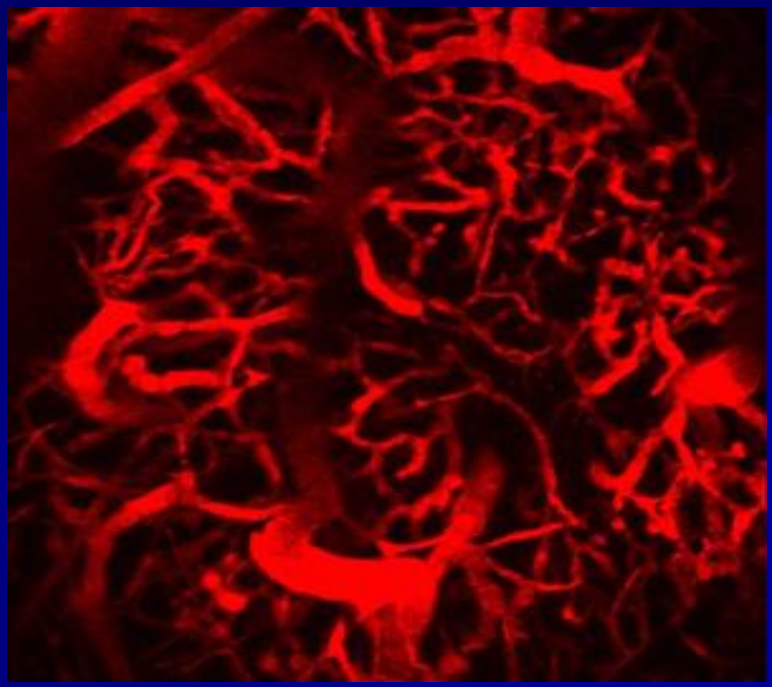
Incremental improvements in OS in mCRC over the past decade



Neo-angiogenesi tumorale



Normal tissue



Tumor tissue

Jain: Science; 307: 58-62, 2005

ANGIOGENESI:
formazione di nuovi vasi sanguigni
a partire da pre-esistenti
vasi capillari normali

aggressività della malattia

esito clinico sfavorevole

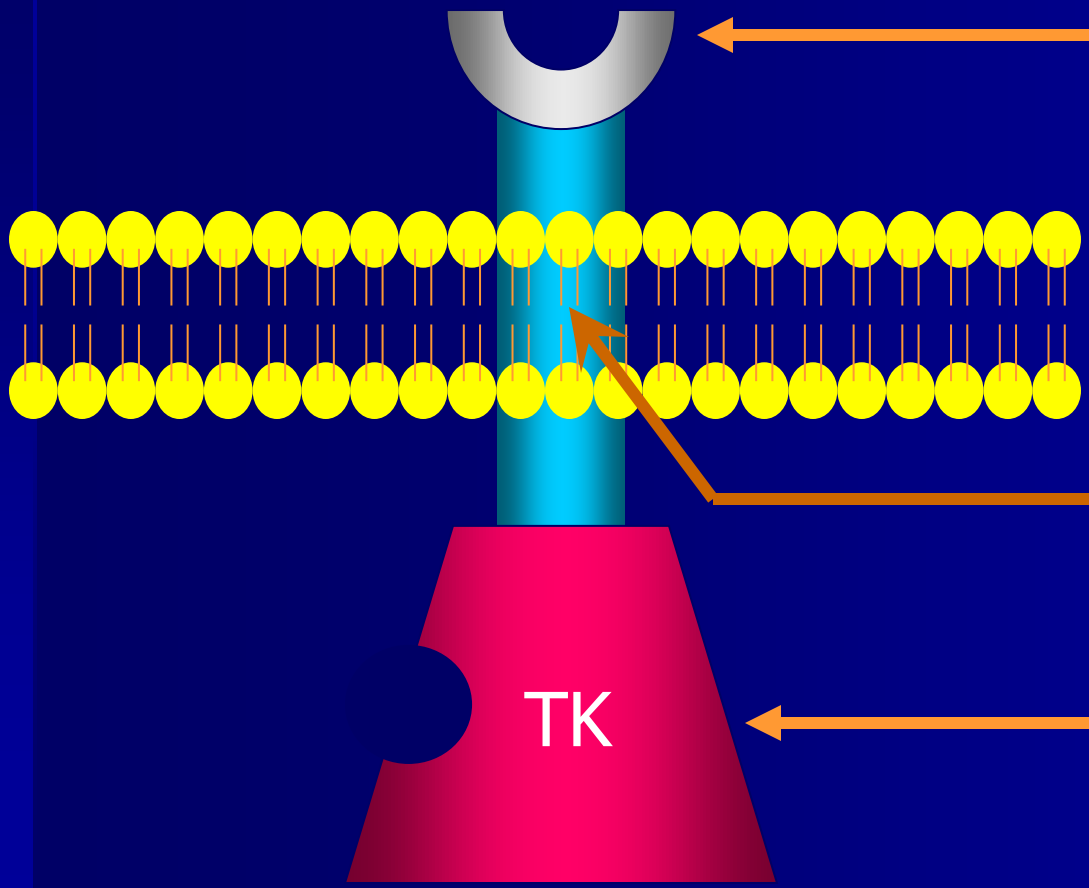
ridotta sopravvivenza globale

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

EGFR

Epidermal Growth Factor Receptor



Extracellular Domain

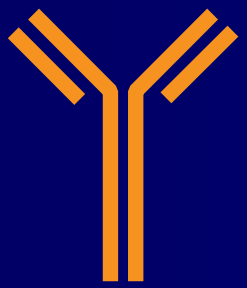
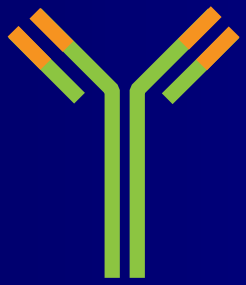
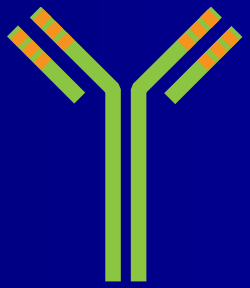
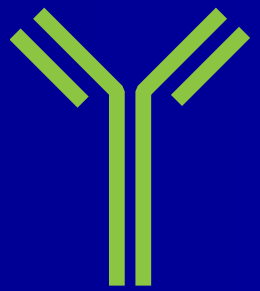
Transmembrane Domain

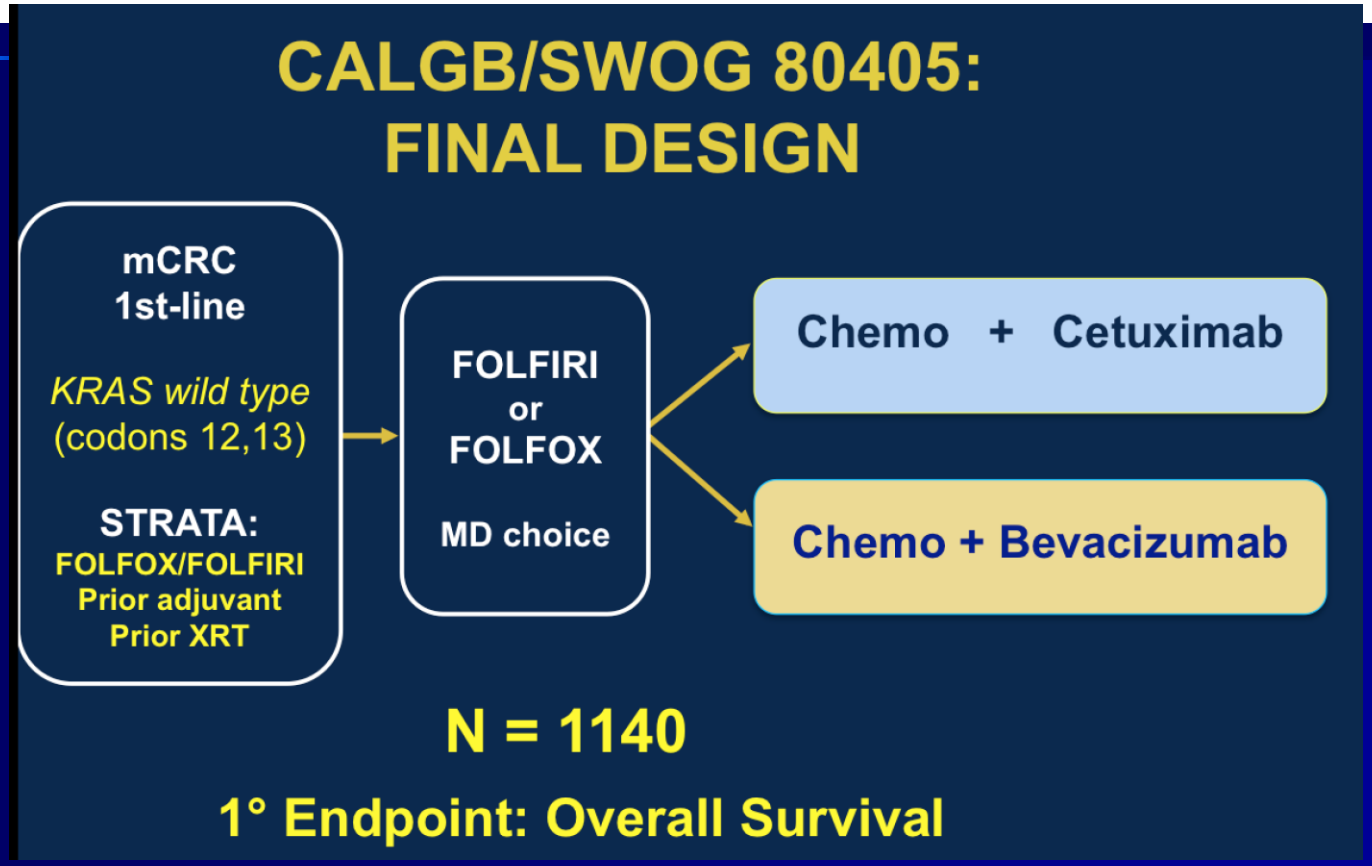
Intracellular Domain

Anti-EGFR

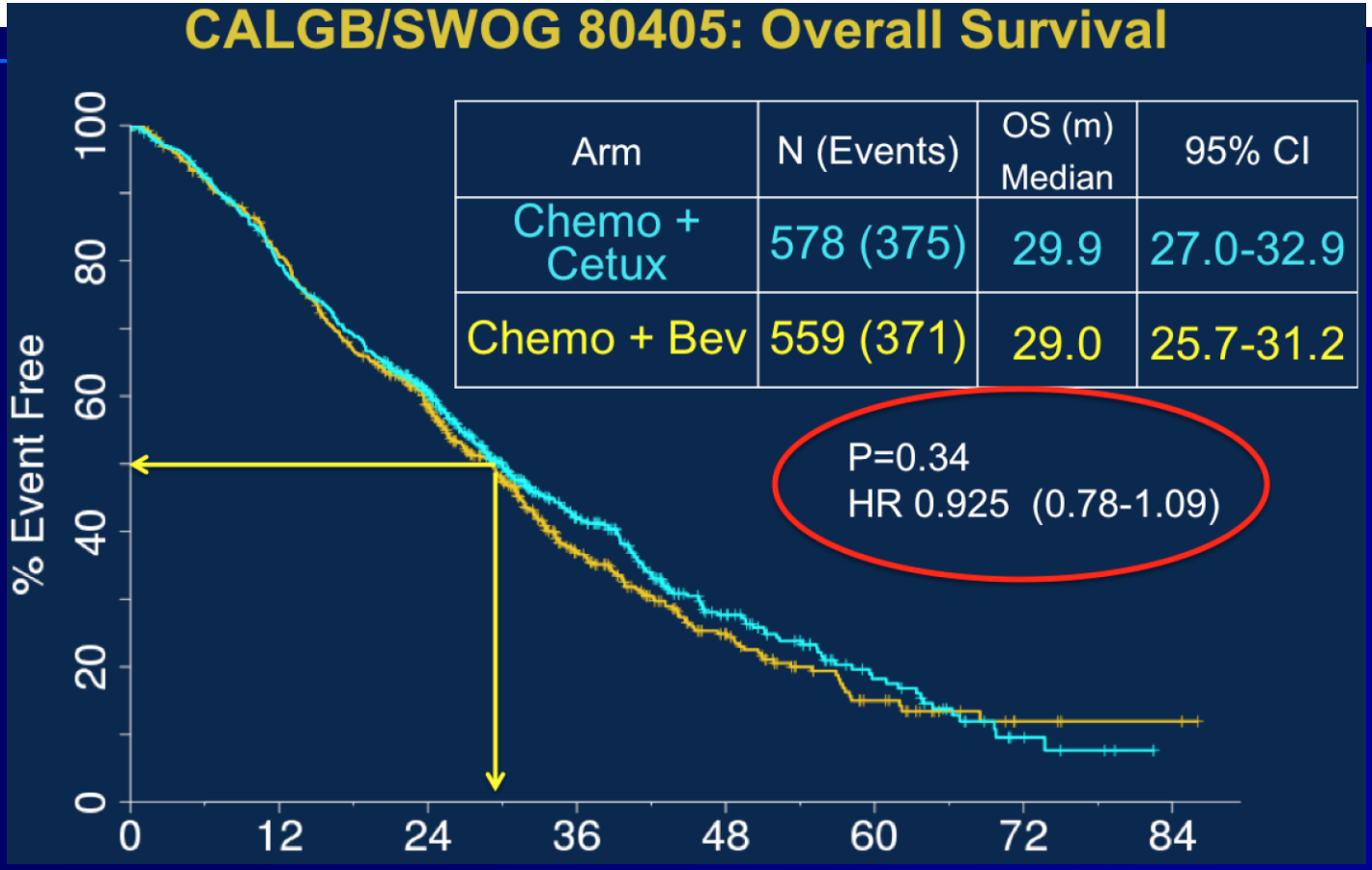
Cetuximab
Panitumumab

} Anti EGFR antibody

Mouse	Chimeric	Humanized	Fully Human
			
100% Mouse	34% Mouse cetuximab	10% Mouse matuzumab	100% Human panitumumab


CALGB/SWOG 80405:
FINAL DESIGN
mCRC
1st-line
KRAS wild type
(codons 12,13)
STRATA:
FOLFOX/FOLFIRI
Prior adjuvant
Prior XRT
FOLFIRI
or
FOLFOX
MD choice
Chemo + Cetuximab
Chemo + Bevacizumab
N = 1140
1° Endpoint: Overall Survival

CALGB/SWOG 80405: Overall Survival



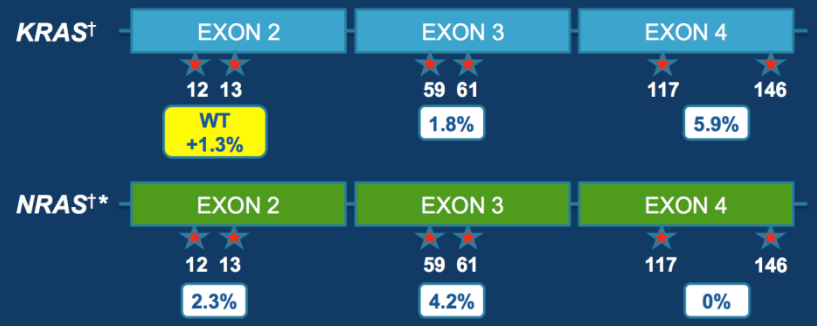
Arm	N (Events)	OS (m) Median	95% CI
Chemo + Cetux	578 (375)	29.9	27.0-32.9
Chemo + Bev	559 (371)	29.0	25.7-31.2

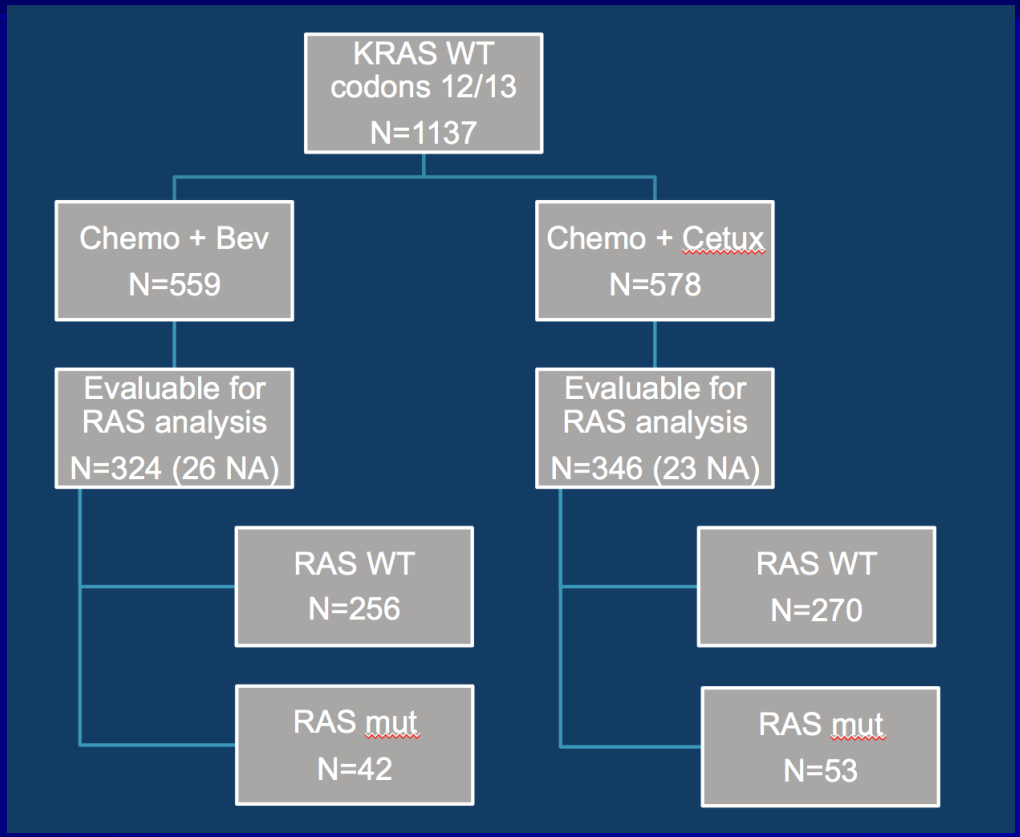
P=0.34
HR 0.925 (0.78-1.09)

Venook A et Al

CALGB/SWOG 80405 RAS Analysis

670/1137 patients (59%) with *KRAS* codon 12/13 WT tumors evaluable
621/1137 analyzed (55%) analyzed
95/621 (15.3%) patients new ras mutation identified



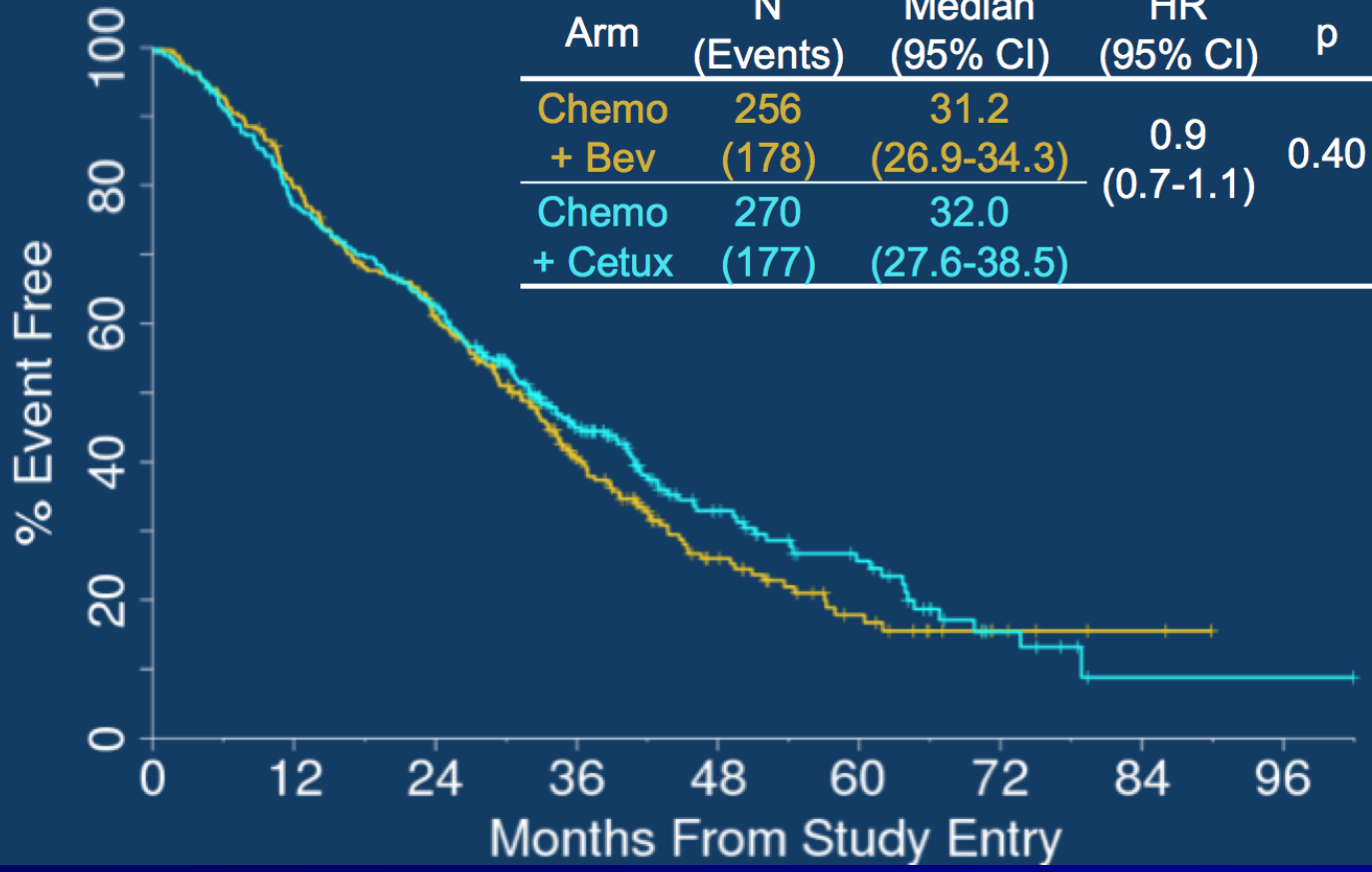


Lenz HJ et Al, ESMO 2014

CALGB/SWOG 80405 RAS Analysis

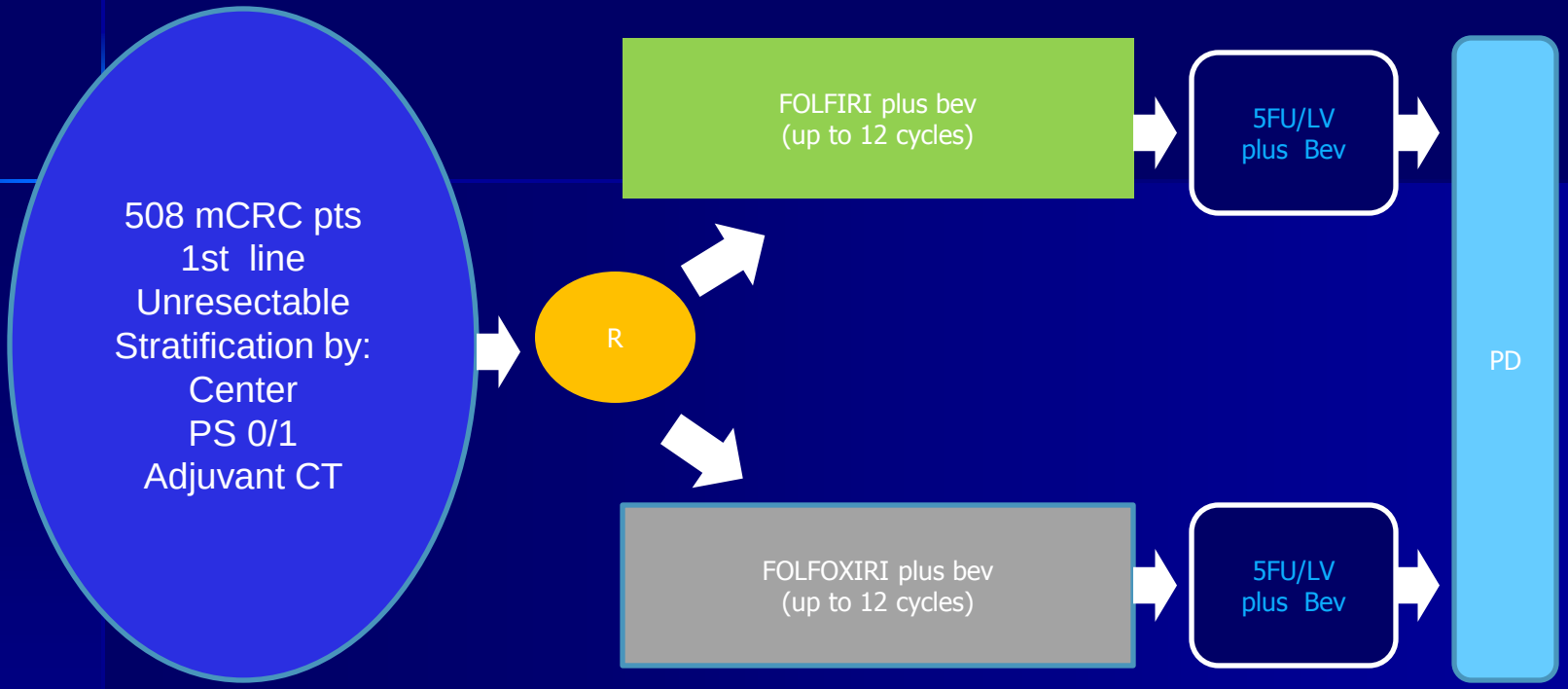
Overall Survival By Arm
(*All RAS Wild Type Patients*)

Arm	N (Events)	Median (95% CI)	HR (95% CI)	p
Chemo + Bev	256 (178)	31.2 (26.9-34.3)	0.9 (0.7-1.1)	0.40
Chemo + Cetux	270 (177)	32.0 (27.6-38.5)		



Lenz HJ et Al, ESMO 2014

TRIBE study design



Primary end-point

PSF

to detect a HR for PFS of 0.75 in favour of FOLFOXIRI+bev with a 2-sided typt 1 error =0.05; Power =80%, 379 events required

Secondary end-points:

RR,secondary R0-resection rate , overall survival,safety profile, biomarkes evaluation

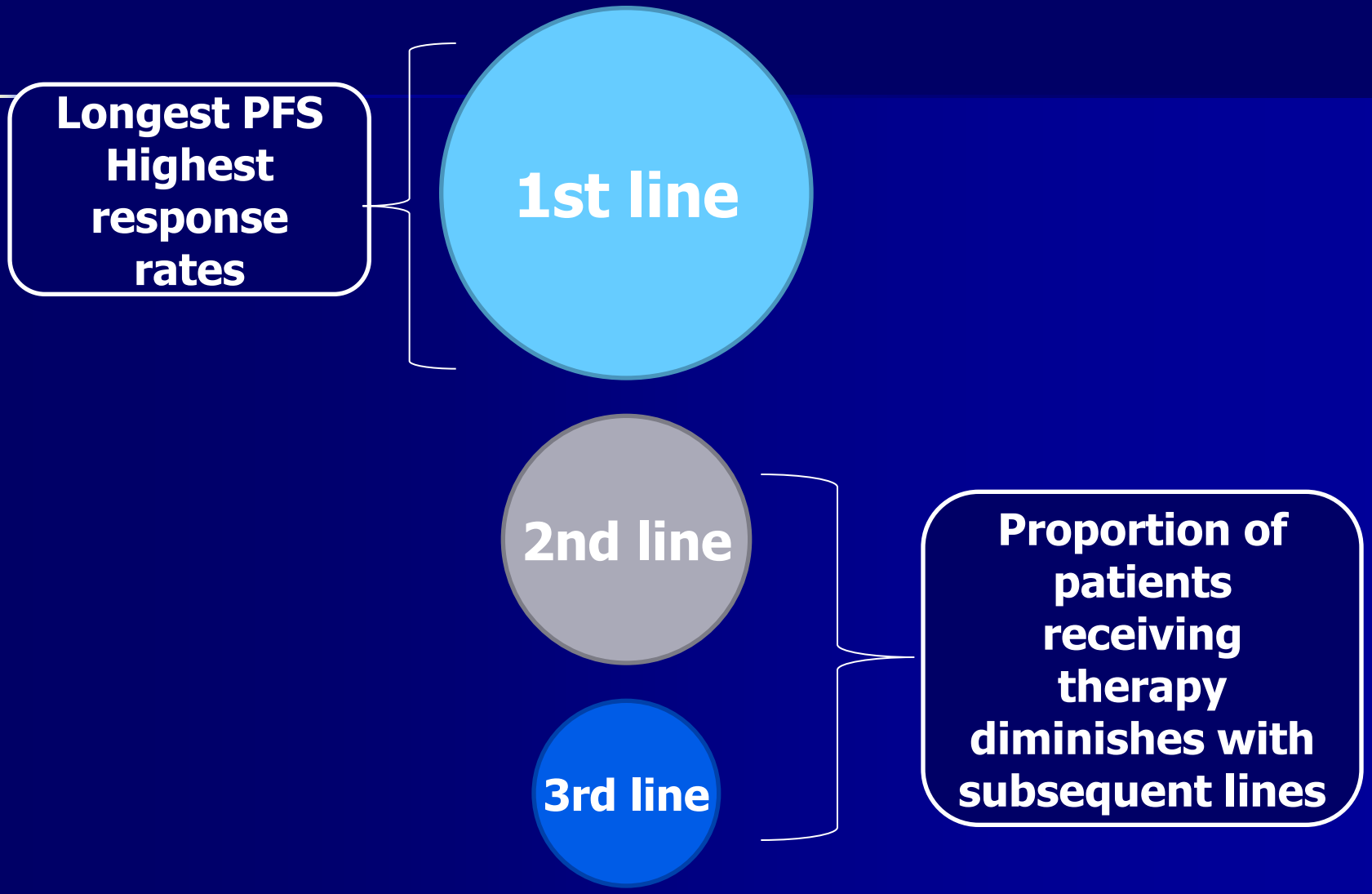
Falcone A et al. ASCO 2013 abs 3505

TRIBE study

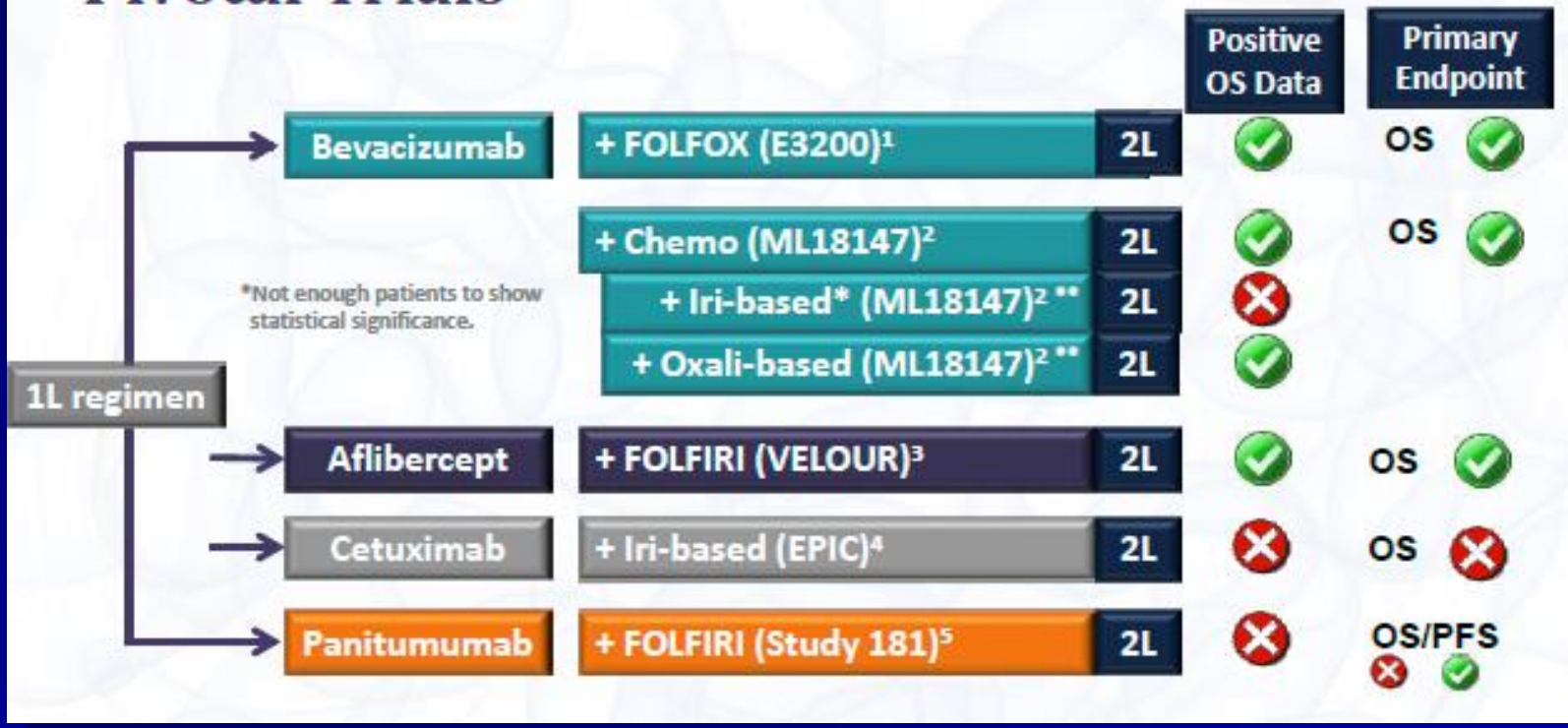
RAS and BRAF mutations' predictive impact

	N	FOLFIRI + bev Arm A Median PFS	FOLFOXIRI + bev Arm B Median PFS	HR [95% CI]	FOLFIRI + bev Arm A Median OS	FOLFOXIRI + bev Arm B Median OS	HR [95% CI]
ITT population	508	9.7	12.1	0.75 [0.62-0.90]	25.8	31.0	0.79 [0.63-1.00]
RAS and BRAF evaluable population	375	10.3	12.1	0.80 [0.64-0.99]	25.8	31.0	0.86 [0.65-1.12]
RAS mutated	218	9.5	12.0	0.82 [0.61-1.09]	23.1	30.8	0.86 [0.60-1.22]
BRAF mutated	28	5.5	7.5	0.55 [0.26-1.18]	10.8	19.1	0.55 [0.24-1.23]
All wt patients	129	11.3	13.3	0.75 [0.52-1.10]	34.4	41.7	0.85 [0.52-1.39]

Importance of 1st line treatment decision in mCRC



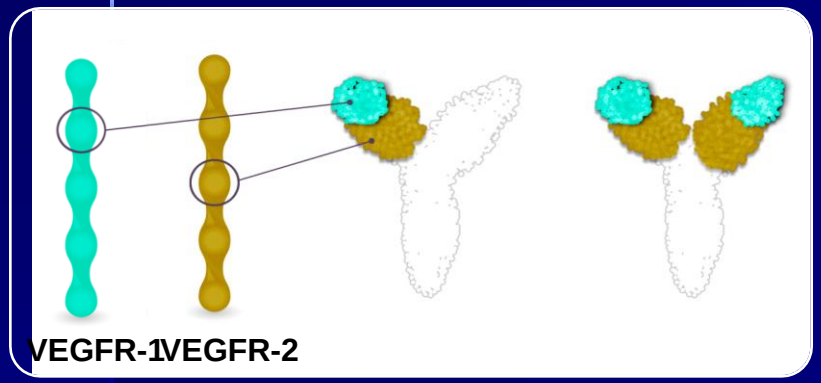
Second-Line Biologic + Chemo Options: Pivotal Trials

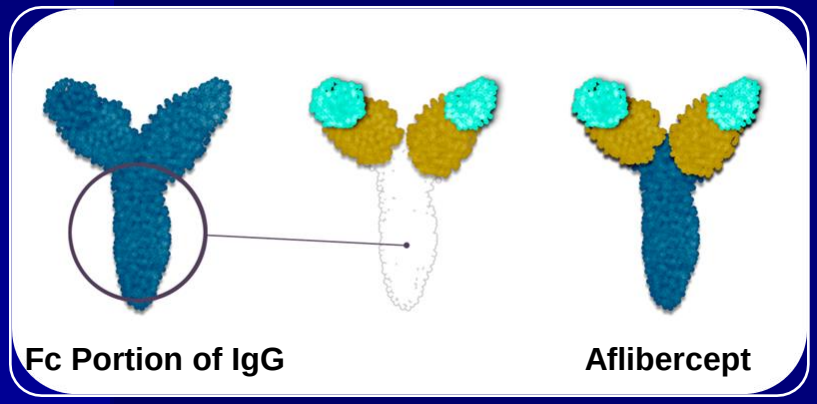


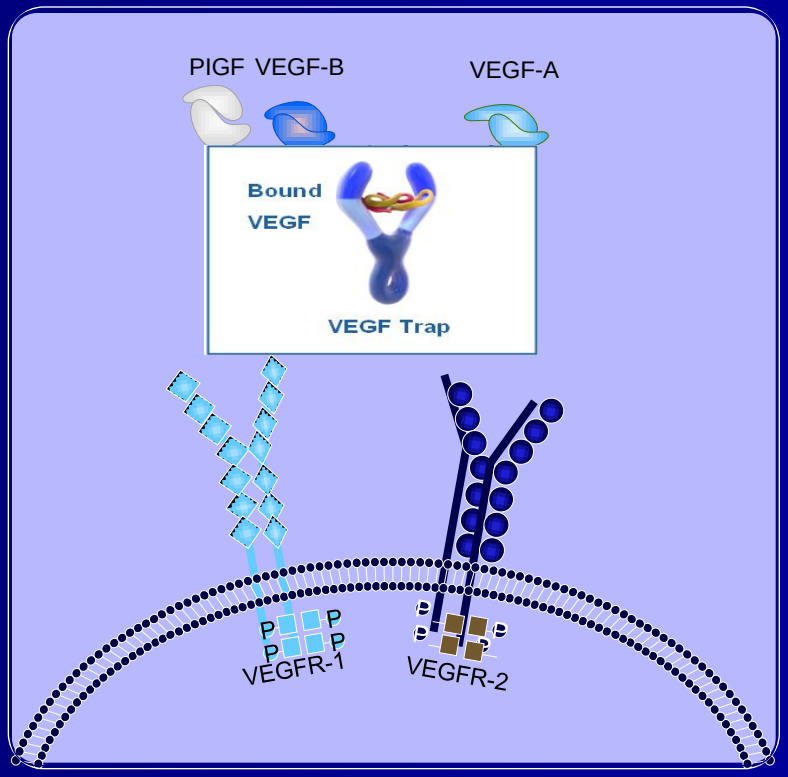
Aflibercept is a novel multiple angiogenic factor trap that binds VEGF-A and also uniquely targets VEGF-B and placental growth factor (PlGF)

ZALTRAP is a novel recombinant fusion protein that combines the VEGFR-1 and VEGFR-2 binding domains and the Fc region of the human IgG1 antibody

ZALTRAP binds VEGF-A with a higher affinity than its native receptors and potentially blocks the activation of VEGFR-1 and VEGFR-2

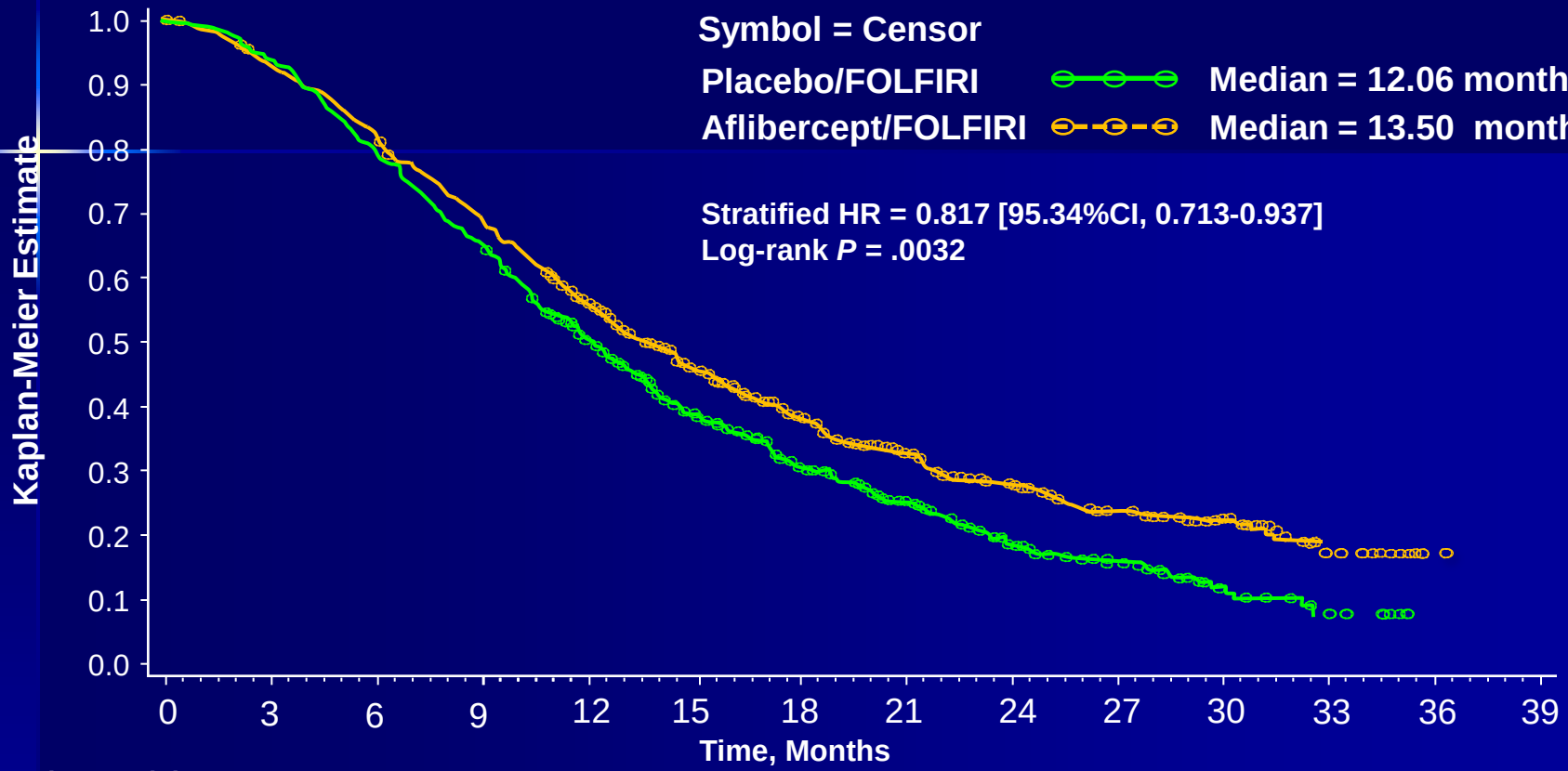






1.Adapted from Holash. Proc Natl Acad Sci. 2002;99:11393-11398. 2. Adapted from Tew. Clin Cancer Res. 2010;16:358-366.

VELOUR: OS (ITT Population)



Number at Risk

Placebo	614	573	485	401	286	193	131	87	51	31	14
AFLI	612	566	498	416	311	216	148	104	75	49	33

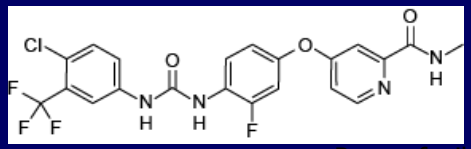
Survival probability, %

Placebo	79.1	50.3	30.9	18.7	12.0
AFLI	81.9	56.1	38.5	28.0	22.3

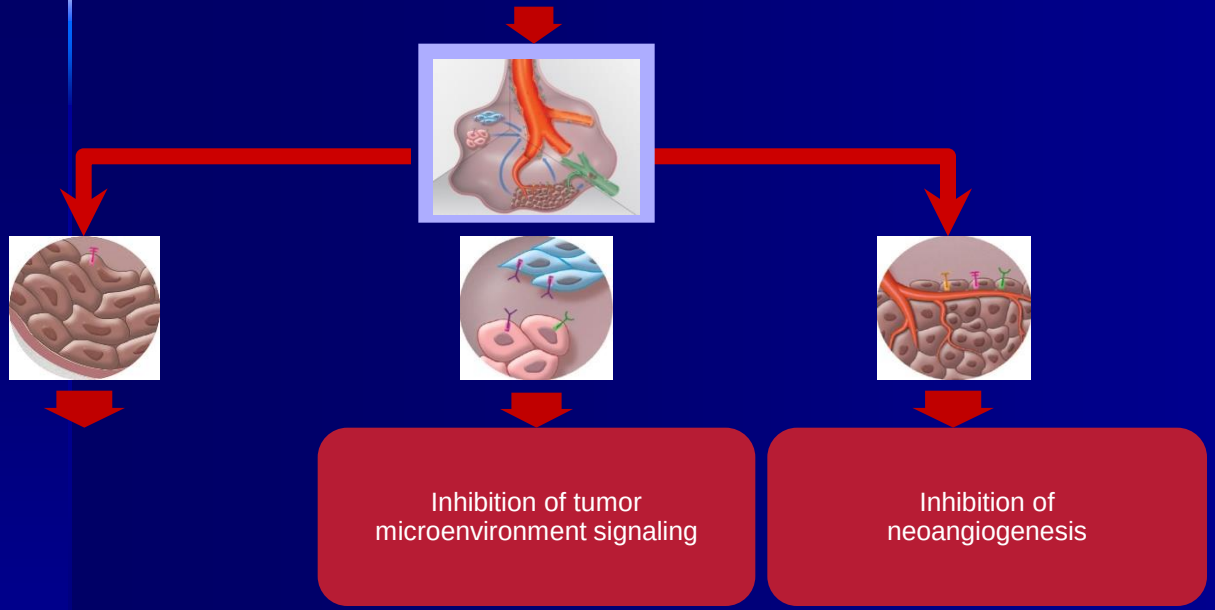
Van Cutsem E, et al. *Ann Oncol.* 2011;22(Suppl 5). Abstract O-0024.
Allegra C, et al. *J Clin Oncol.* 2012;30(15S): Abstract 3505.

Cut-off date = February 7, 2011;
Median follow-up = 22.28 months

Regorafenib: multi-kinase inhibitor

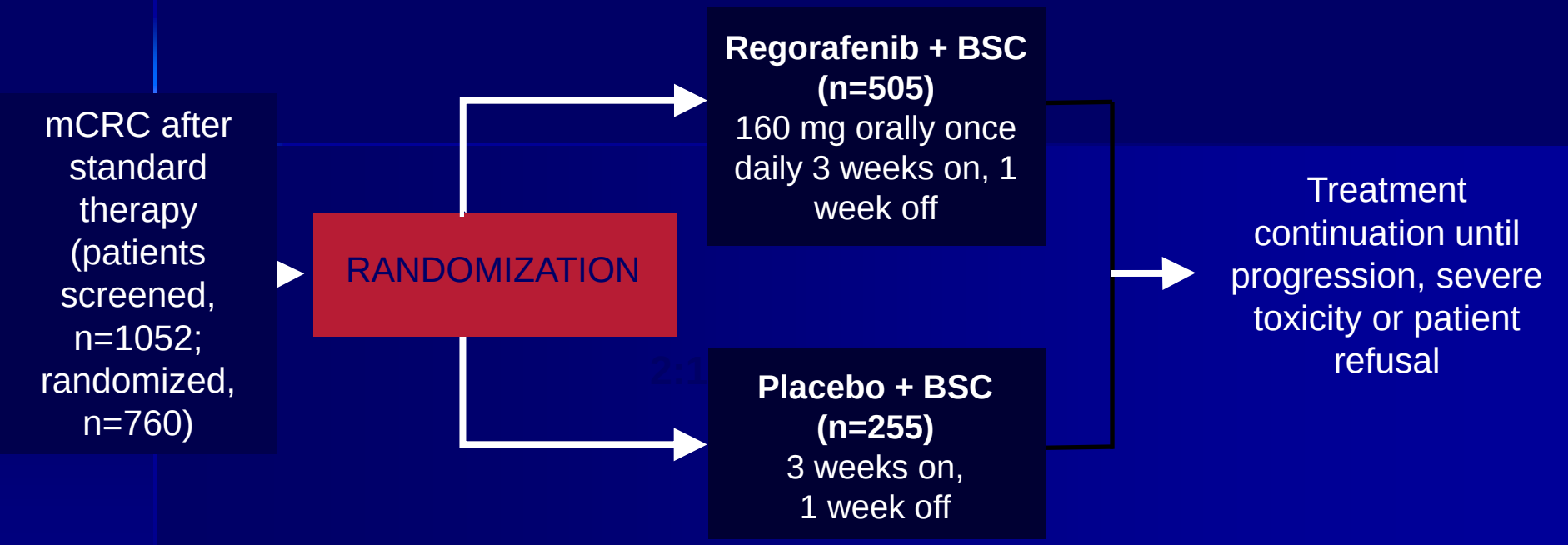


Regorafenib



Biochemic activity	Regorafenib IC_{50} mean ± SD nmol/l (n)	
VEGFR1	13 ± 0.4	(2)
Murine VEGFR2	4.2 ± 1.6	(10)
Murine VEGFR3	46 ± 10	(4)
TIE2	311 ± 46	(4)
PDGFR-β	22 ± 3	(2)
FGFR1	202 ± 18	(6)
KIT	7 ± 2	(4)
RET	1.5 ± 0.7	(2)
RAF-1	2.5 ± 0.6	(4)
B-RAF	28 ± 10	(6)
$B\text{-}RAF^{V600E}$	19 ± 6	(6)

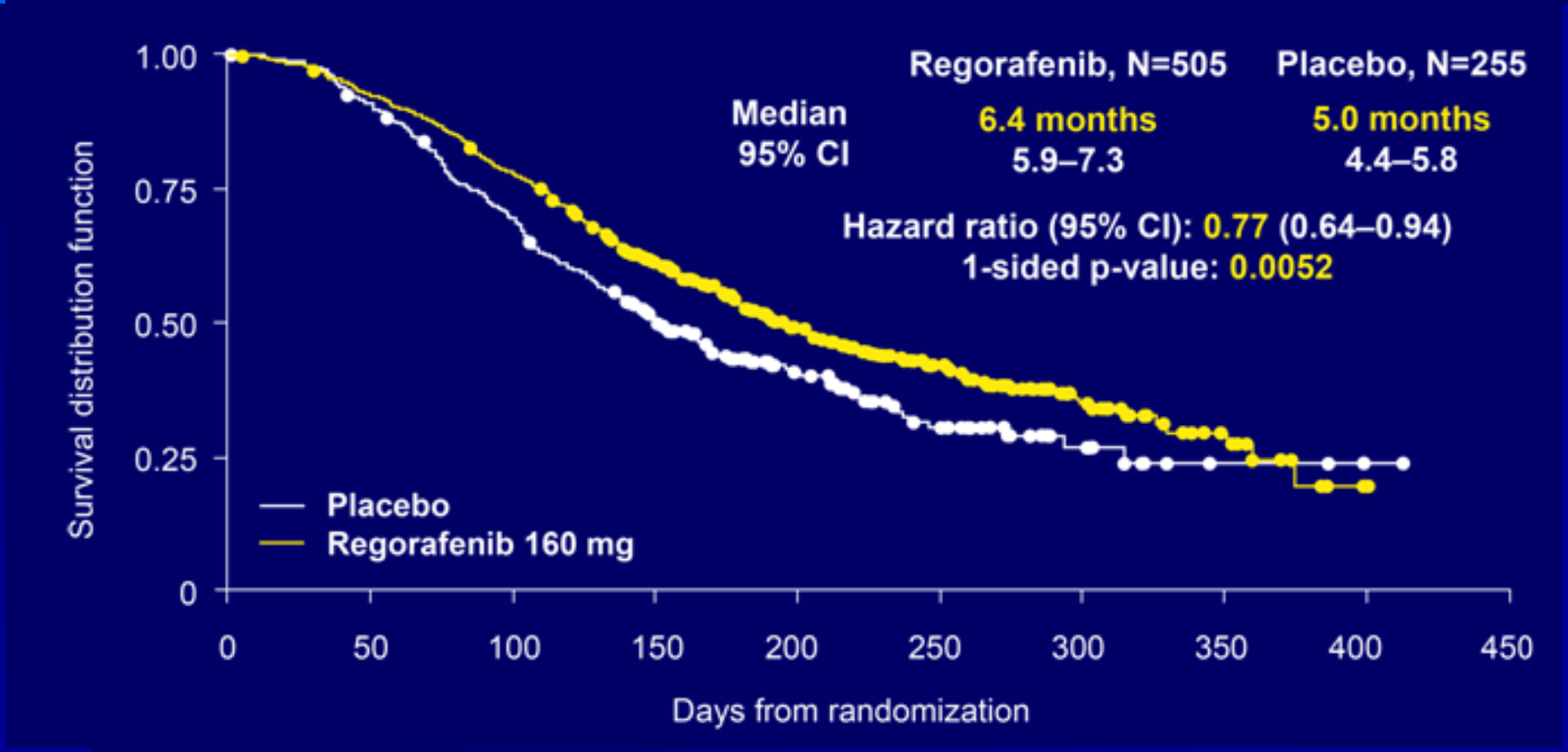
Phase III CORRECT trial



- Multicenter, randomized, double-blind, placebo-controlled, phase III
- Stratification: prior anti-VEGF therapy, time from diagnosis of metastatic disease, geographical region
- Global trial: 16 countries, 114 centers
- Recruitment: May 2010 to March 2011

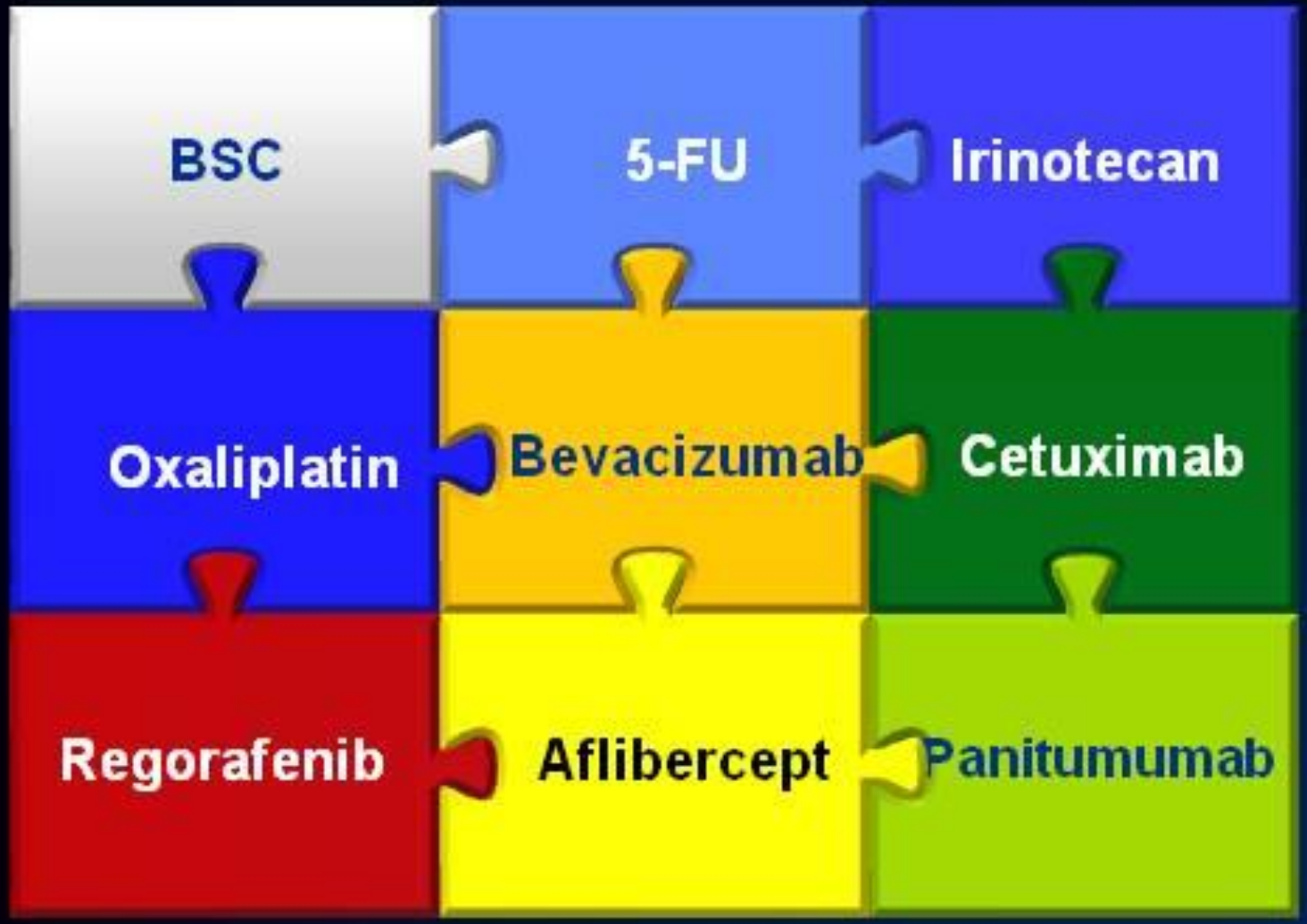
Phase III CORRECT: OS

Primary endpoint met prespecified stopping criteria at interim analysis (1-sided p<0.009279 at approximately 74% of events required for final analysis)

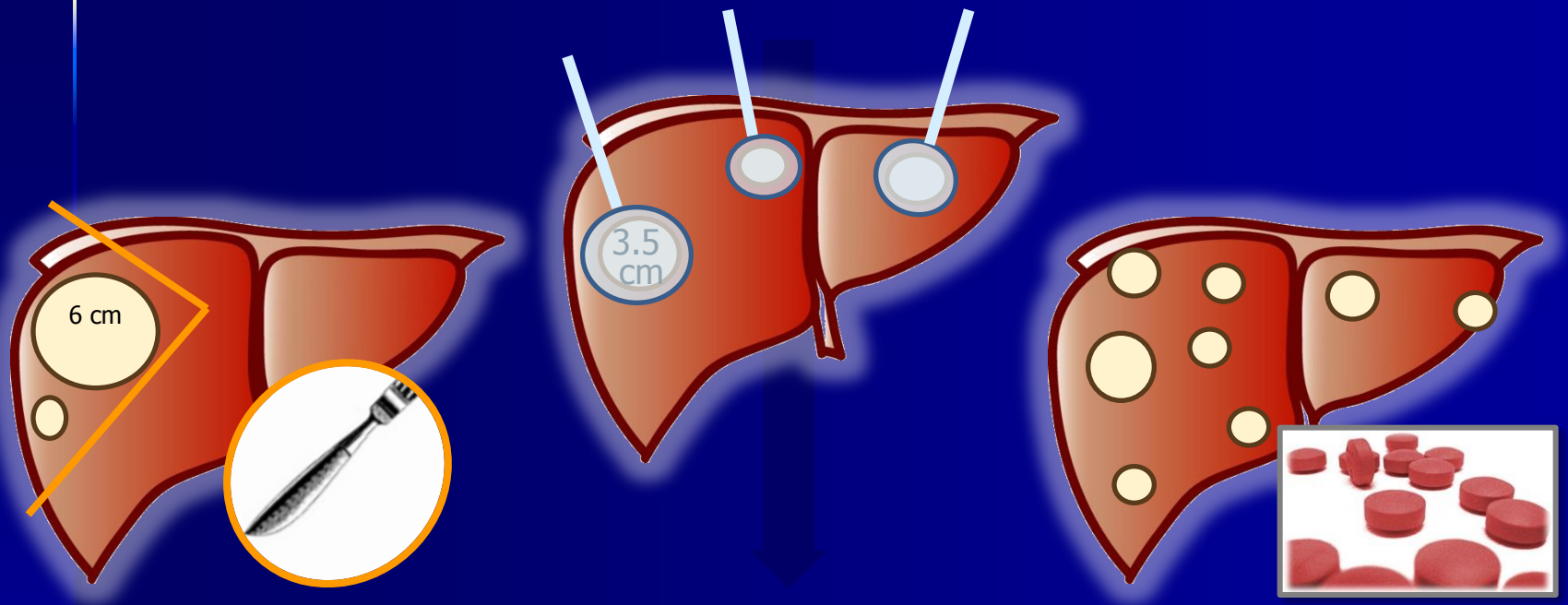


Grothey A et al. Lancet 2013

A high number of agents is currently available for the treatment of mCRC



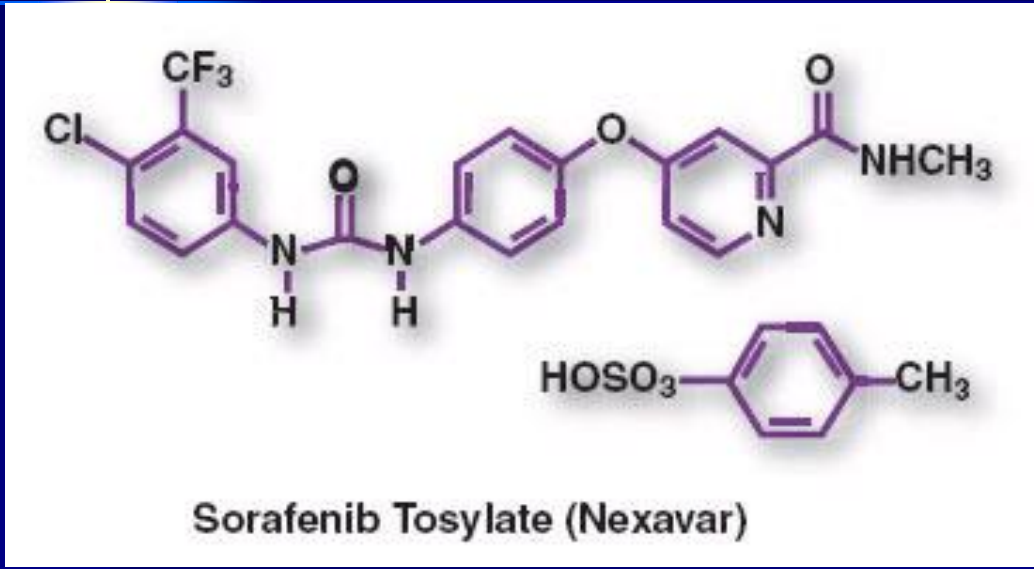
EPATOCARCINOMA



TACE (sempre?)/
TARE (sperimentale)?

Trevisani F. Comunicazione personale.

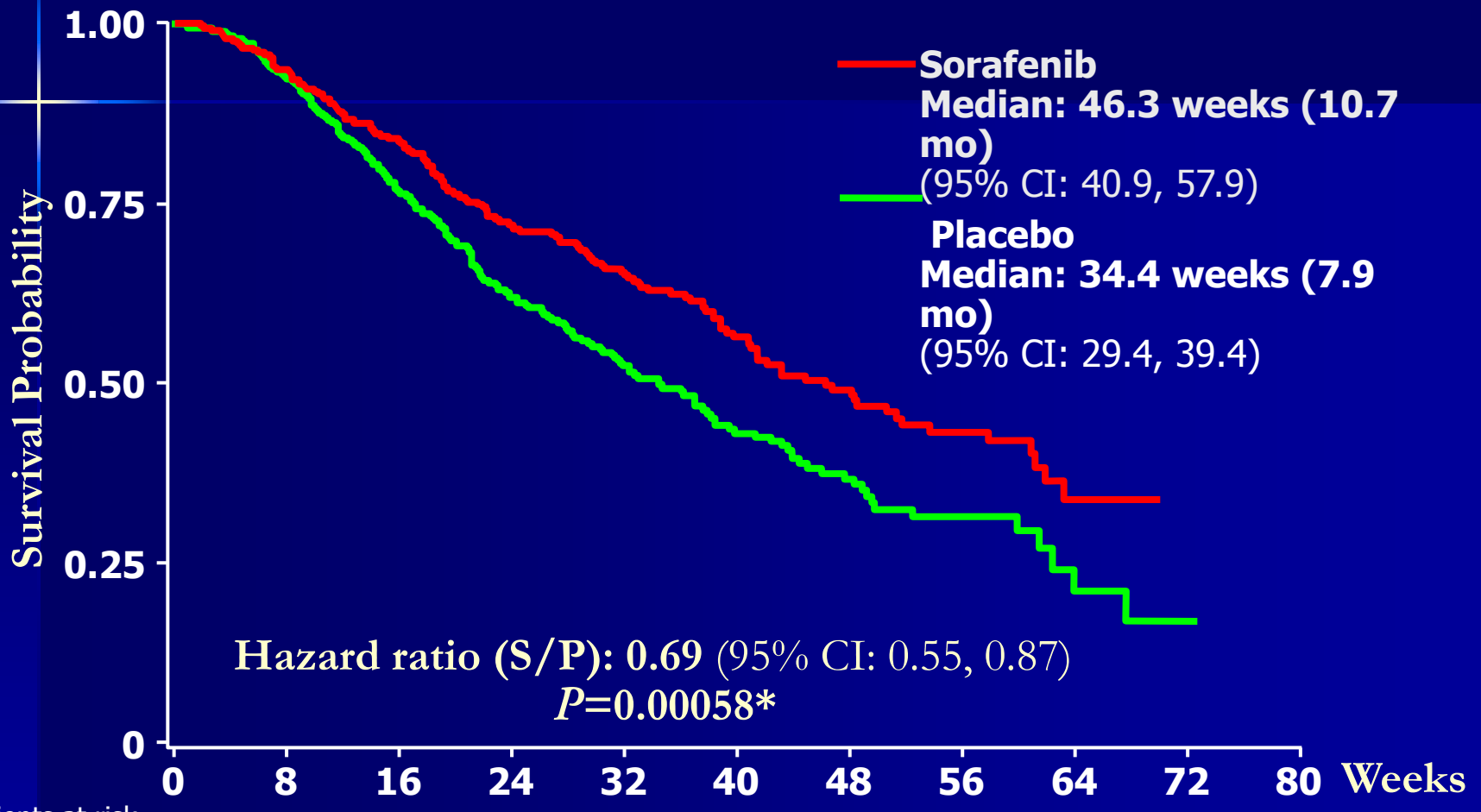
The turning-point in the management of advanced HCC



Sorafenib Tosylate (Nexavar)

Sorafenib (BAY 43-9006, Nexavar): a multikinase inhibitor with activity against Raf, VEGFR-2, VEGFR-3, PDGFR, c-Kit

Phase III SHARP Trial
Overall survival (Intention-to-treat)



Patients at risk

Sorafenib:	299	274	241	205	161	108	67	38	12	0	0
Placebo:	303	276	224	179	126	78	47	25	7	2	0

*O'Brien-Fleming threshold for statistical significance was P=0.0077

Llovet JM et al. Presented at: ECCO; September 23-27, 2007; Barcelona, Spain

Obiettivi della Ricerca sul Genoma del Cancro

- Identificare nel genoma dei tumori alterazioni responsabili della progressione tumorale
- Identificare nuovi bersagli terapeutici
- Selezionare farmaci basati sulle caratteristiche genomiche dei tumori

Terapia medica

- Riduttiva (o neoadiuvante)
- Concomitante
- Precauzionale(o adiuvante)
- Terapeutica: nuove combinazioni e nuovi farmaci
- Approccio multidisciplinare al paziente oncologico (chirurgia, ortopedia, endoscopia, radioterapia, anestesiologia, infettivologia, etc.)

Gruppo Interdisciplinare Cure (G.I.C.)

- Il Gruppo Interdisciplinare Cure (GIC) riunisce al proprio interno medici di diversa specializzazione appartenenti a differenti Unità Operative che,attraverso una visione complessiva della persona malata e dunque grazie all'interdisciplinarità dell'approccio clinico, stabiliscono i percorsi di cura più appropriati.

  Il GIC, nello svolgimento del proprio compito di cura della persona malata, si ispira ai protocolli procedurali attualmente in vigore, ma può anche stabilire collegialmente di ricorrere a protocolli sperimentali purché regolarmente approvati.

Gruppo Interdisciplinare Cure (G.I.C.)

- Il principale vantaggio che deriva da una presa in carico multidisciplinare è rappresentato da una maggiore tempestività e dal coordinamento degli interventi: i diversi professionisti coinvolti nelle fasi di diagnosi e cura, che naturalmente cambiano in base alla patologia e alle specifiche condizioni di salute della persona malata, non incontrano il paziente in successione, frammentando i percorsi diagnostico-terapeutici e allungando i tempi di attesa, ma si presentano come una vera e propria équipe medica che basa la propria operatività sulla comunicazione e la condivisione interdisciplinare.

In conclusione:

- Miglioramenti notevoli nelle percentuali di guarigione
- Netto miglioramento della durata della sopravvivenza
- Significativo miglioramento della qualità di vita

Grazie per l’attenzione!