

What's Next: New Agents Under Clinical Development for Colorectal Cancer

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A Comprehensive Cancer Center Designated by the National Cancer Institute

Targets in Metastatic Colorectal Cancer

Where We Are in 2007

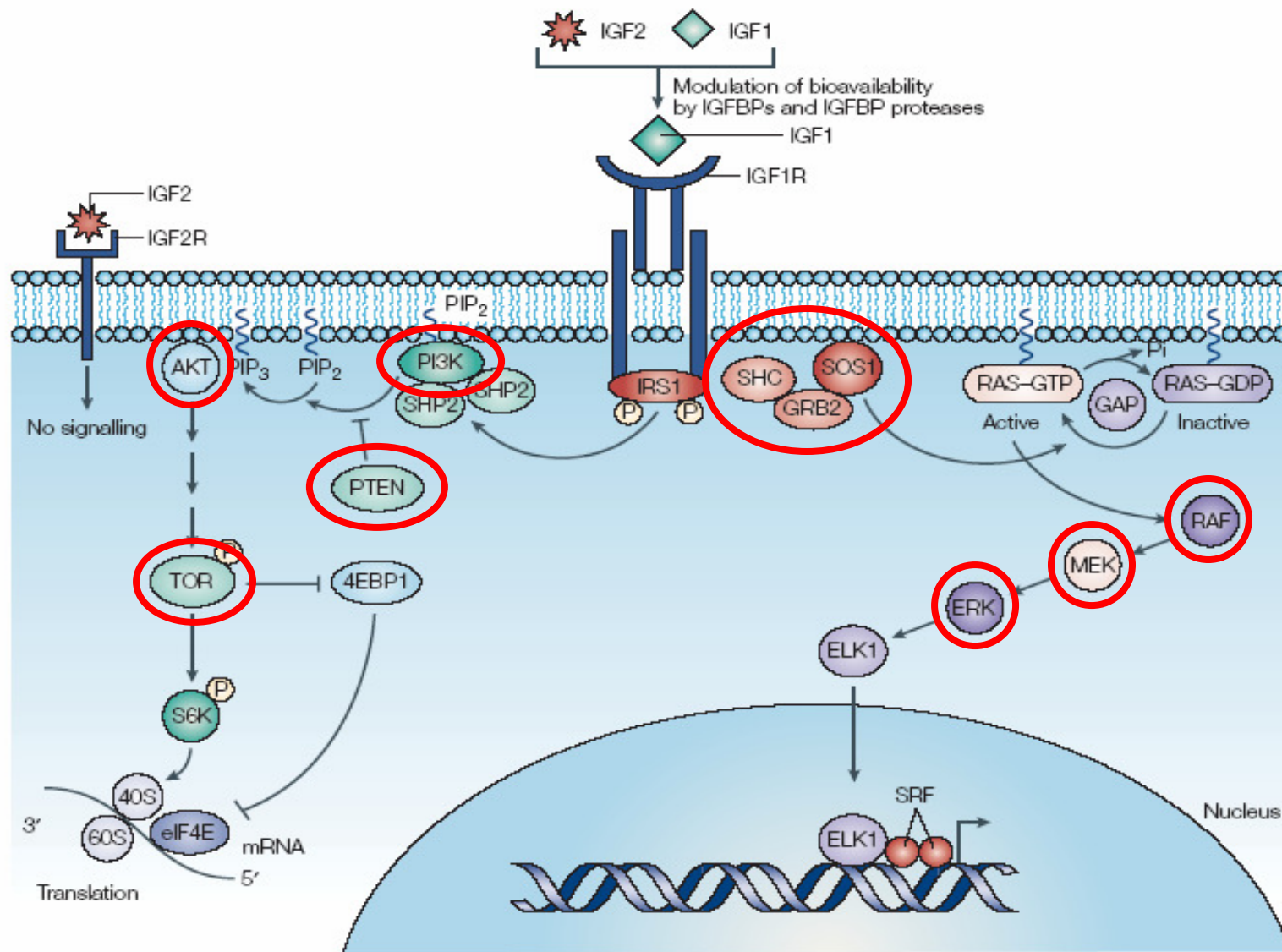
- Survival has more than doubled with the coordinated use of all known effective drugs
- We are currently “filling in the gaps” of our knowledge:
 - Is capecitabine a valid alternative to 5-FU/LV when used as part of combination chemotherapy? Does this hold true when bevacizumab is added to the regimen?
 - Is it better to use chemotherapy with bevacizumab, cetuximab/panitumumab or both as 1st-line treatment for mCRC?
 - Are there “better” VEGF- or EGFR-targeted agents than what we have now?
 - How can we optimize the “stop-and-go” approach? Should all chemotherapy be stopped? Should targeted agents be used during chemotherapy-free breaks?

Targets in Metastatic Colorectal Cancer

Where We Need To Go

- **My prediction:**
 - It is unlikely that any of the current strategies to optimize use of existing therapies will lead to median survival exceeding 28-30 months
 - Colorectal cancer develops as the result of disruption of multiple signaling pathways
 - There is an urgent need for therapies that exploit other targets in colorectal cancer
 - What might those targets be?

Insulin Like Growth Factor 1 Receptor



Insulin-Like Growth Factor-I Receptor (IGF-IR)

Key Features

- **Receptor tyrosine kinase located on the cell surface with extracellular and transmembrane domains**
- **IGF-1 and IGF-2 are major ligands and IGFBP 1-6 regulate these levels in the plasma**
- **Activation of the IGF-IR pathway results in:**
 - **Proliferation**
 - **Transformation**
 - **Evasion from apoptosis**
 - **Tissue invasion and metastases**
 - **Stimulation of angiogenesis**
- **Closely related to the insulin receptor:**
 - **59% sequence homology with IR**
 - **84% homology with the tyrosine kinase domain**
 - **100% homology with the ATP binding pocket**

Insulin-Like Growth Factor-I Receptor (IGF-IR)

A “Drugable” Target

- First report of an *in vivo* model showing antineoplastic activity of an antibody against IGF-1R

Arteaga & Osborne: J Clin Invest 84:1418-1423, 1989

- In a pancreatic cancer model, truncated IGF-1R can function as a dominant negative inhibitor to:
 - block IGF-I and IGF-II-induced receptor activation and activation of Akt
 - suppress tumorigenicity *in vivo*
 - enhance cytotoxic effects of radiation and chemotherapy by up-regulation of apoptosis
 - prolong survival of tumor bearing mice

Min, Adachi, Yamamoto, Ito, Itoh, Lee, Nadaf, Carbone, Imai: Cancer Res 63:6432-6441, 2003

Insulin-Like Growth Factor-I Receptor (IGF-IR)

Relationship to and Role in CRC

- IGF-IR is overexpressed in colon cancer, but activation rather than overexpression may most important
- High levels of circulating IGF-1 found in patients with colorectal cancer
- IGF-IR promoter polymorphisms may be related to earlier age of onset of CRC in pts with HNPCC

Strategies for Blockade of IGF-IR

Monoclonal Antibodies:

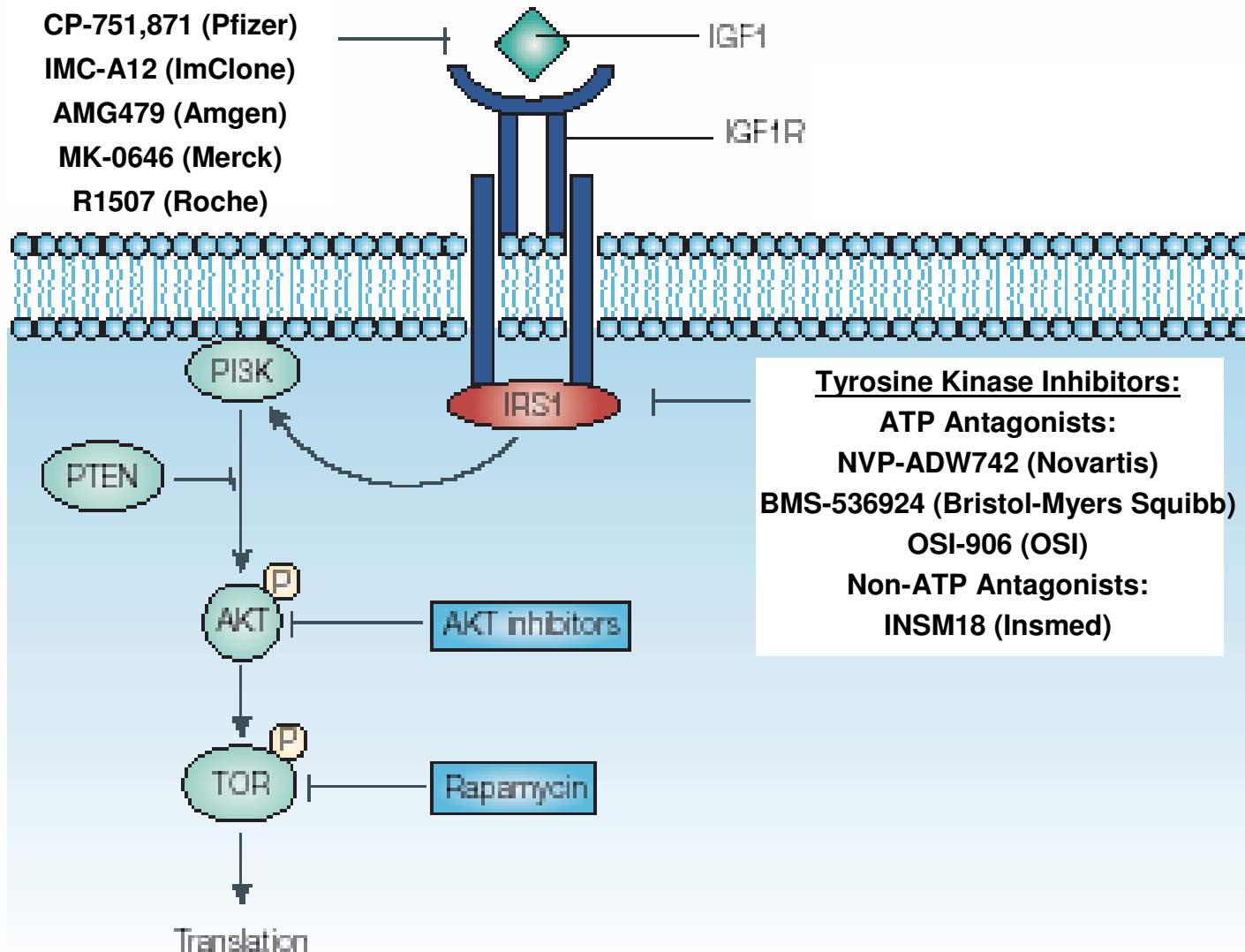
CP-751,871 (Pfizer)

IMC-A12 (ImClone)

AMG479 (Amgen)

MK-0646 (Merck)

R1507 (Roche)



Tyrosine Kinase Inhibitors:

ATP Antagonists:

NVP-ADW742 (Novartis)

BMS-536924 (Bristol-Myers Squibb)

OSI-906 (OSI)

Non-ATP Antagonists:

INSM18 (Insmed)

Adapted from Pollak, Schernhammer, & Hankinson – Nat Rev Cancer - 2004
Hofmann & Garcia-Echaverria - Drug Discovery Today - 2005

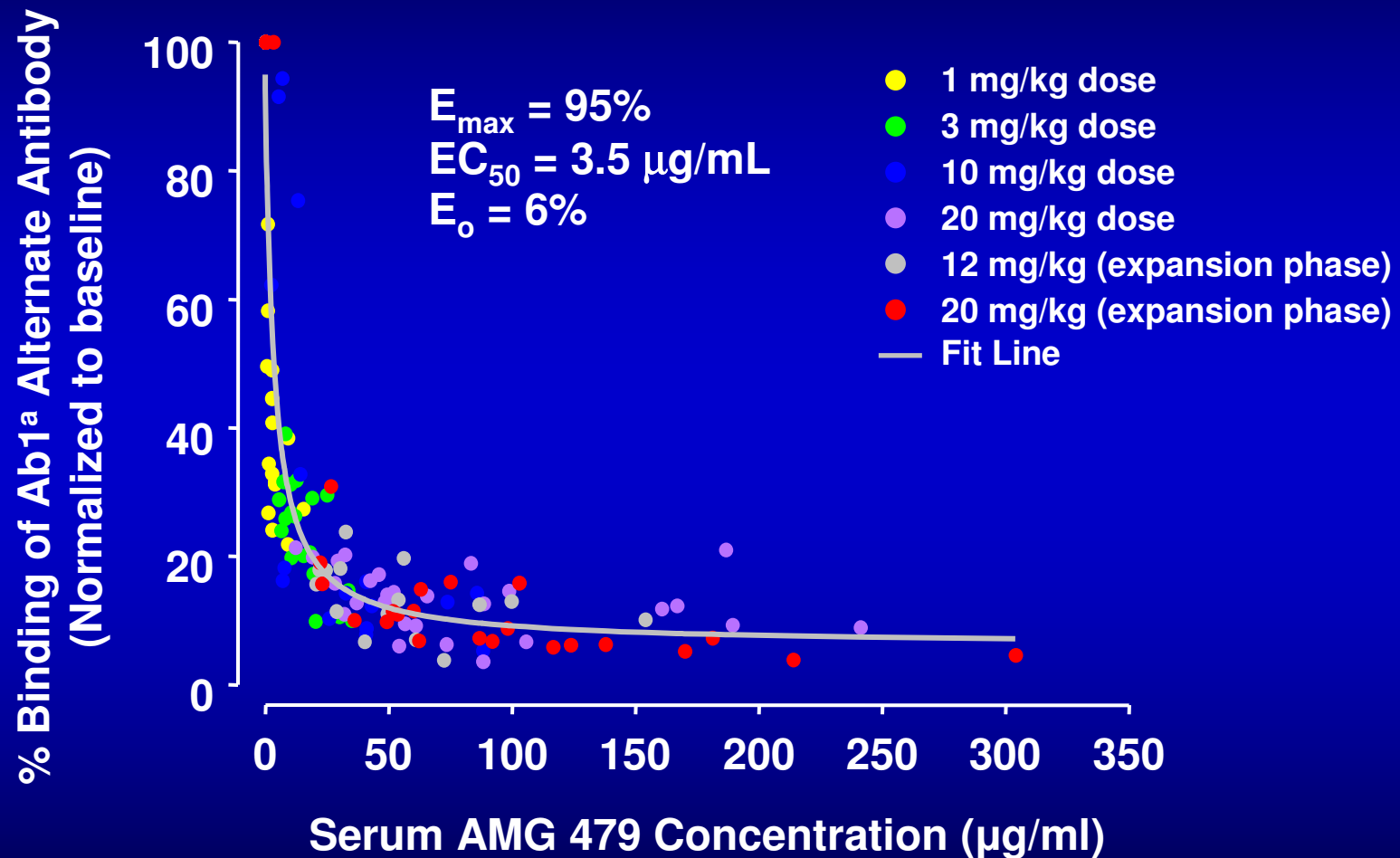
A Phase 1 Pharmacokinetic and Pharmacodynamic Study of AMG 479, a Fully Human Monoclonal Antibody Against IGF-1R, in Advanced Solid Tumors

**A.W. Tolcher,¹ M.L. Rothenberg,² J. Rodon,³
D. Delbeke,² A. Patnaik,¹ L. Nguyen,⁴ F. Young,⁴ Y. Hwang,⁴
C. Haqq,⁴ and I. Puzanov²**

**¹South Texas Accelerated Research Therapeutics, San Antonio, TX;
²Vanderbilt University, Nashville, TN; ³Cancer Therapy and Research
Center, Institute for Drug Development, San Antonio, TX; ⁴Amgen Inc.,
Thousand Oaks, CA**

AW Tolcher, ML Rothenberg, et al: J Clin Oncol 25(18S):118s, 2007 (Abst# 3002)

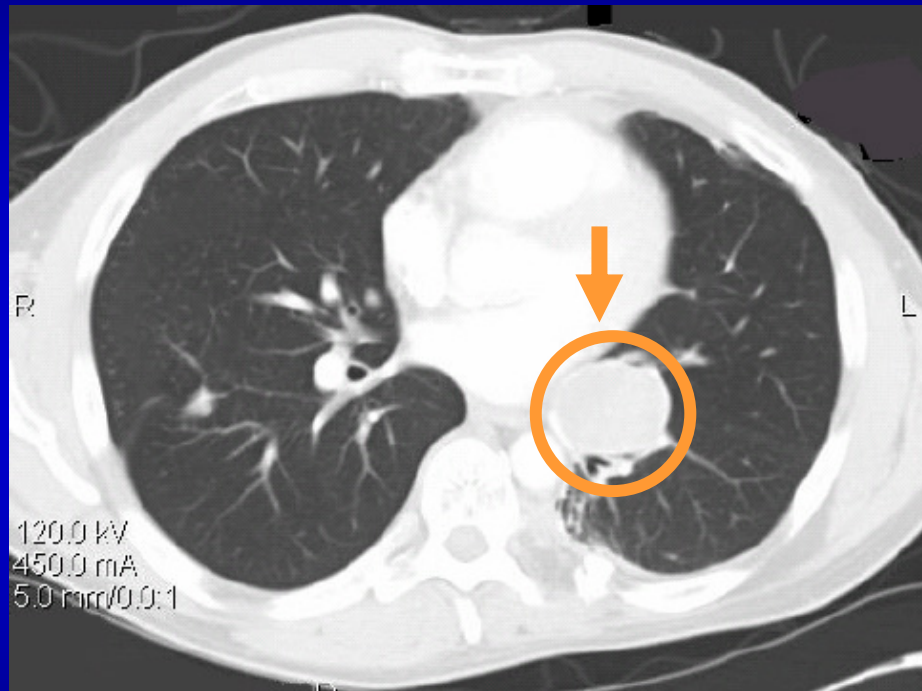
IGF-1R Occupancy on Neutrophils



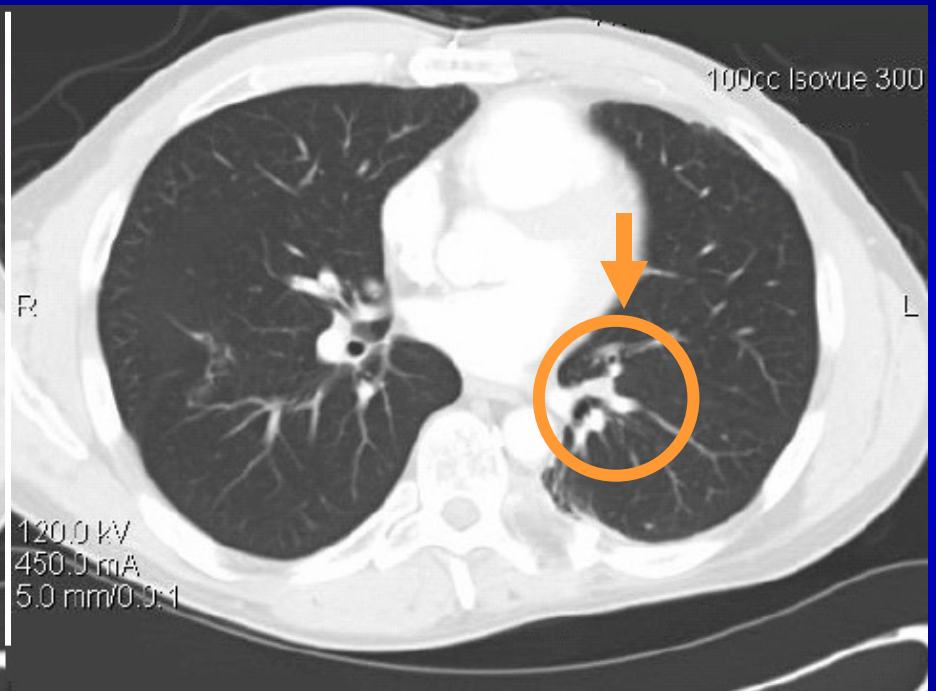
^aAb1 is a monoclonal antibody to IGF-1R, which competes for the same external-binding domain as AMG 479

AW Tolcher, ML Rothenberg, et al: J Clin Oncol 25(18S):118s, 2007 (Abst# 3002)

Chemo-Refractory Ewing's Sarcoma: Metabolic Complete Response



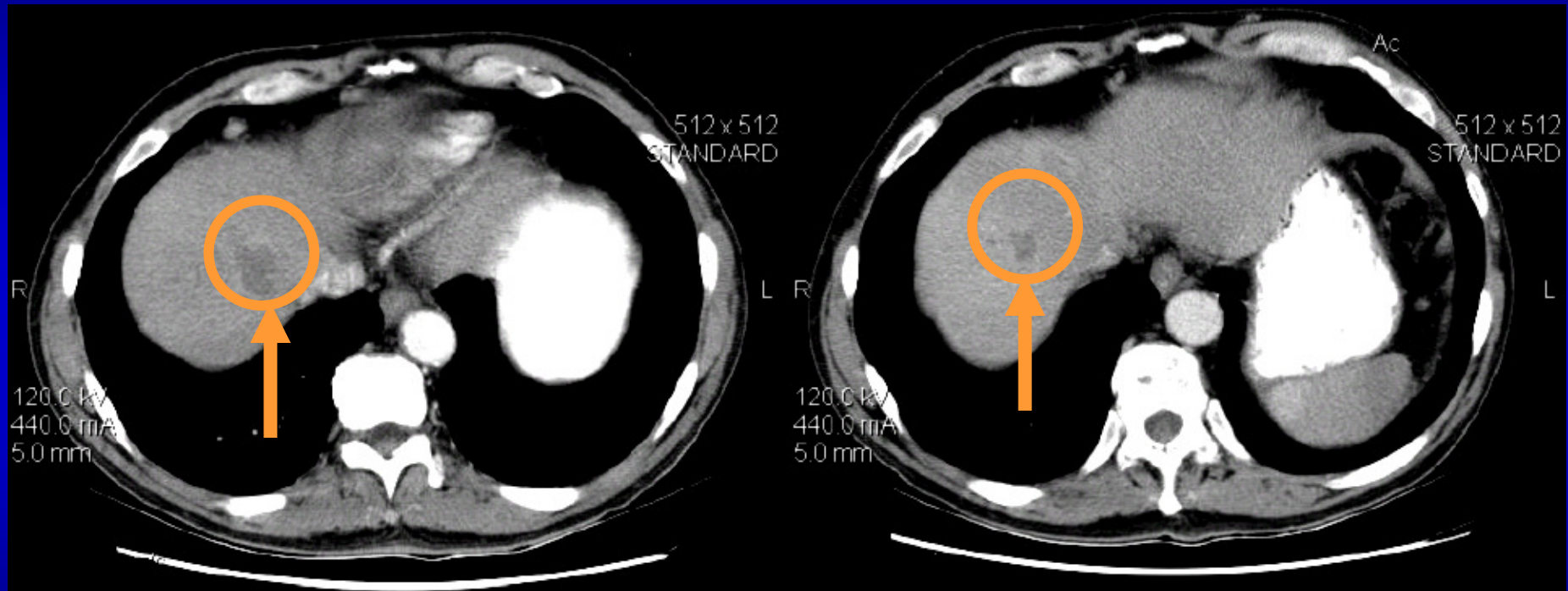
Baseline



Day 80: -100% shrinkage
(Day 50: ¹⁸FDG PET/CT [metabolic CR])

AW Tolcher, ML Rothenberg, et al: J Clin Oncol 25(18S):118s, 2007 (Abst# 3002)

Carcinoid Tumor: Partial Response

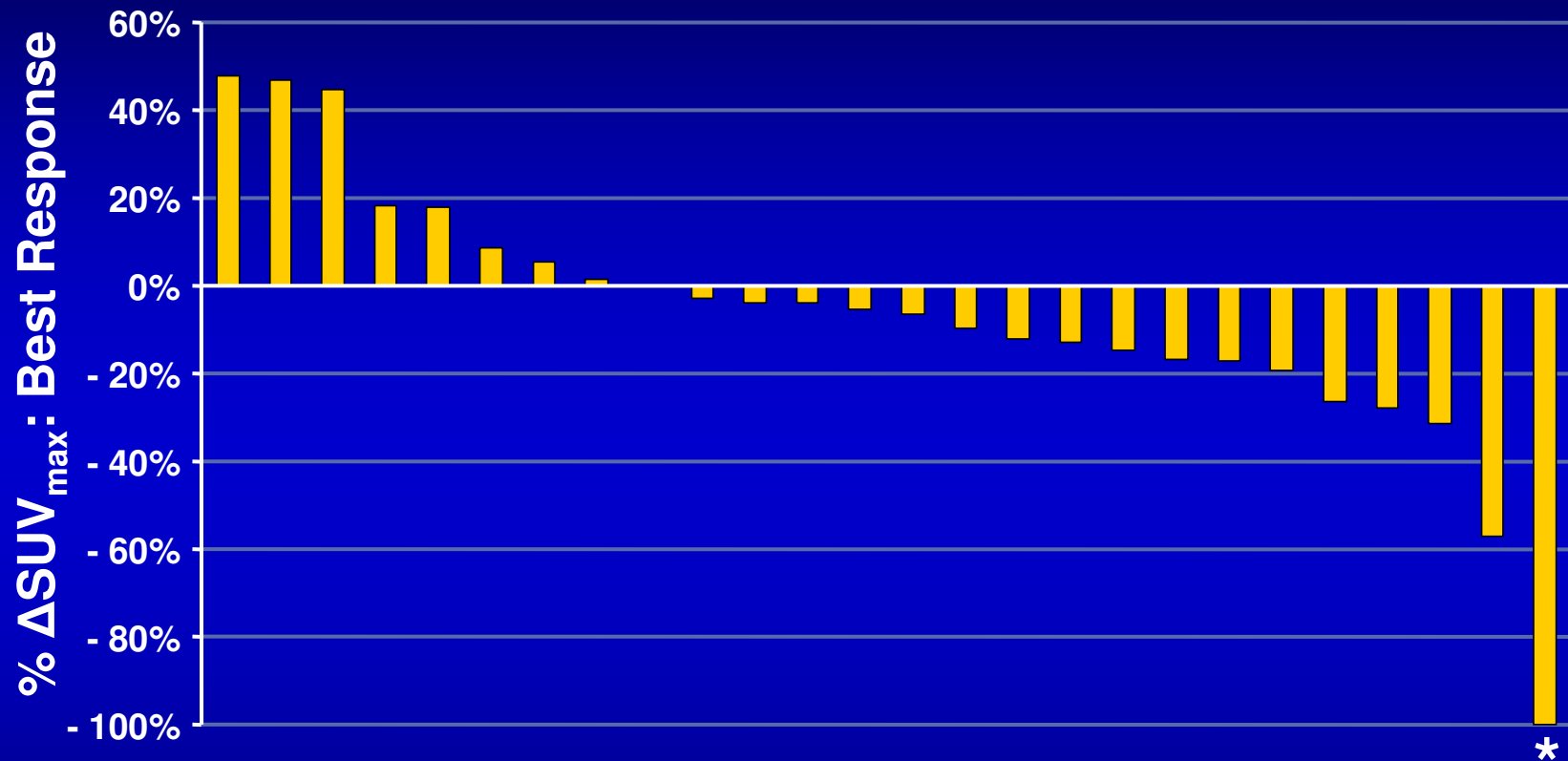


Baseline

Day 336: -48% shrinkage

AW Tolcher, ML Rothenberg, et al: J Clin Oncol 25(18S):118s, 2007 (Abst# 3002)

AMG 479 ¹⁸F-DG-PET/CT: Best Response



- 17/26 patients had some decrease in metabolic activity
- All PET/CT scans were analyzed by a central reader (including metabolic CR*)

AW Tolcher, ML Rothenberg, et al: J Clin Oncol 25(18S):118s, 2007 (Abst# 3002)

Are there alternative ways of reducing IGF-I?

Lycopene



Lycopene and IGF-I

Colon cancer (pre-op)

Lycopene 15 mg bid
(n = 30)

Placebo bid
(n = 26)

	Placebo	Lycopene	p-value
IGF-I	+3 ± 11%	-25 ± 5%	.02
IGF-II	0 ± 6%	+2 ± 6	NS
IGFBP-3	-4 ± 3%	-7 ± 5%	NS
IGF-1/IGFBP-3	+7 ± 13%	-24 ± 6%	.03
Lycopene	+18 ± 10%	+103 ± 33%	.04

Toll-Like Receptor 9

Key Features

- **First described and best understood for role in immune regulation in the gastrointestinal tract**
 - Expressed by both intestinal epithelial cells and immune cells within the GI tract
- **Transmembrane receptor**
- **TLR 9 recognizes unmethylated CpG motifs**
- **Stimulation of TLR 9 by oligonucleotides promotes**
 - Activation of macrophages, dendritic cells, and NK cell activity
 - Secretion of cytokines including IL-6, IL-12, TNF α , and IFN
 - Up-regulation of co-stimulatory molecules

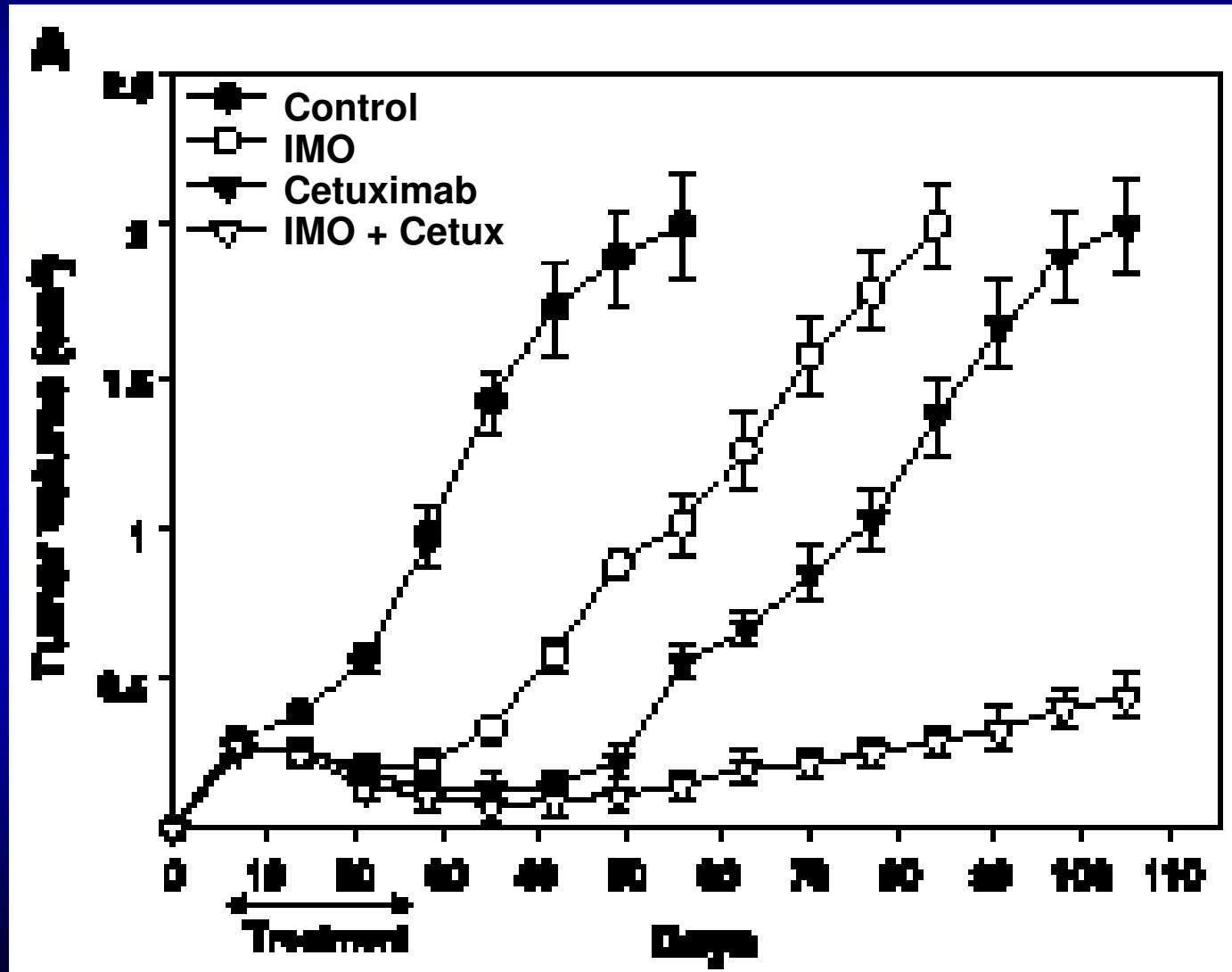
Toll-Like Receptor 9 Agonists

Potential Role in Treatment of CRC

- “Escape” of tumor from EGFR inhibition may occur due to overexpression of downstream signaling molecules including
 - ϕ MAP Kinase
 - ϕ Akt
 - COX-2
 - VEGF
- TLR 9 oligonucleotide agonist can block expression of these downstream signals

Toll-Like Receptor 9 Agonists

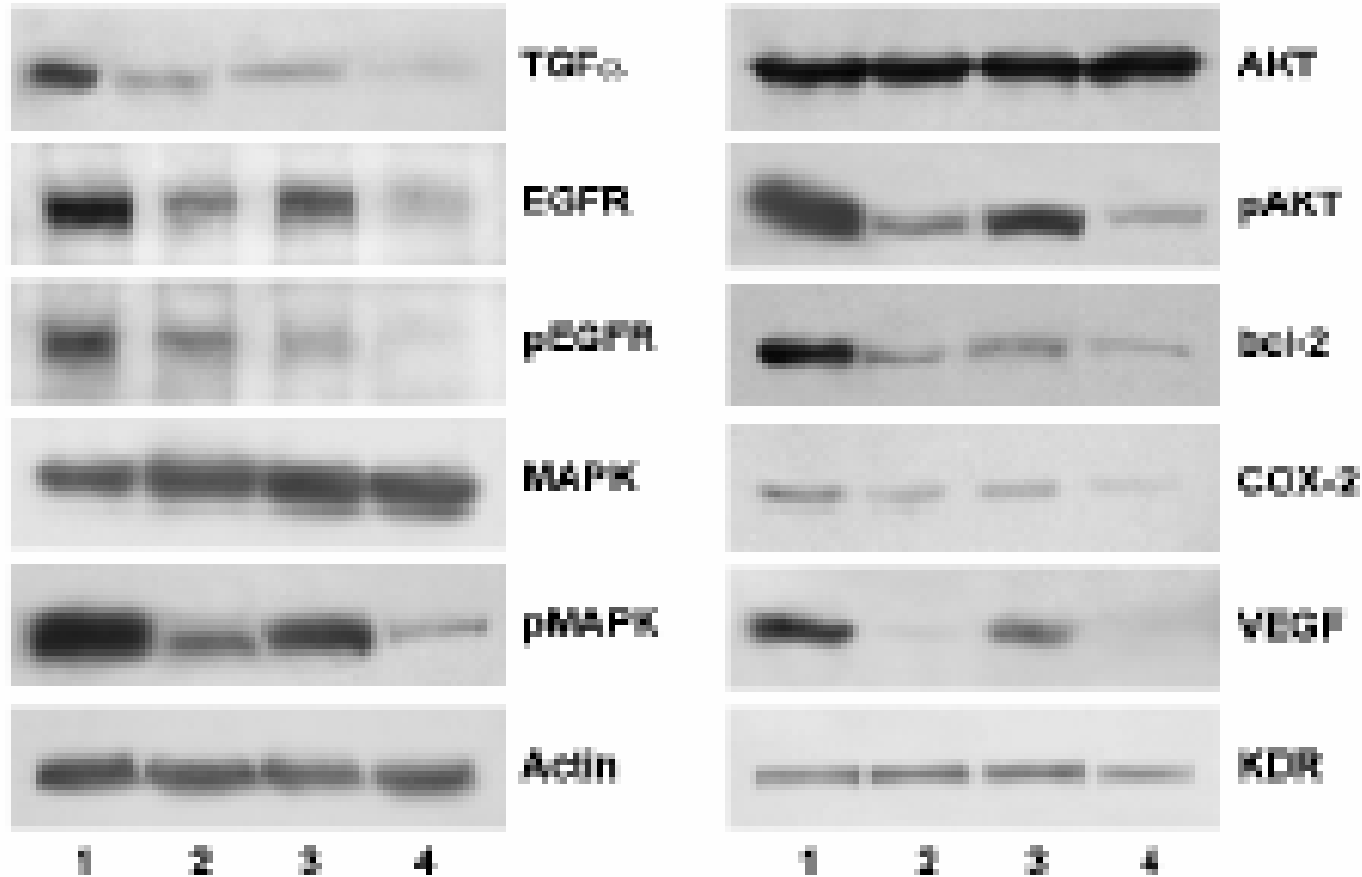
Human Tumor Xenograft Model of CRC



Damiano et al: Clin
Cancer Res 12:577-
583, 2006

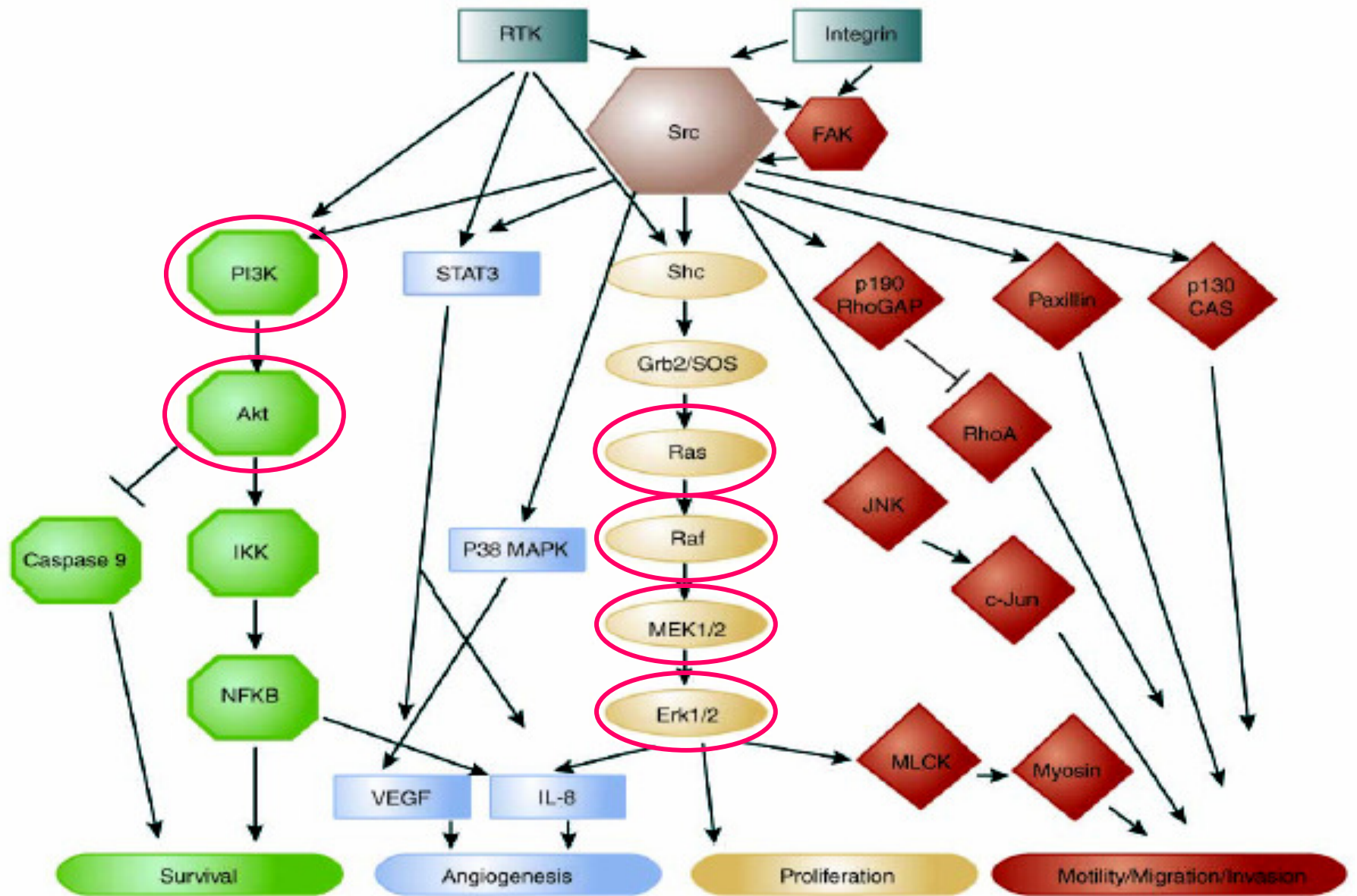
Toll-Like Receptor 9 Agonists

Human Tumor Xenograft Model of CRC



Src: New Insights into an Old Target

- First oncogene discovered
- Non-receptor tyrosine kinase found on intracellular portion of cell membrane
- Normal Src is activated/phosphorylated by a variety of stimuli:
 - Growth factor pathways: EGFR, PDGF
 - Steroid hormones
 - Stress
 - Cell cycle progression
- Promotes angiogenesis, up-regulates VEGF and IL-8 expression, and increases vascular permeability
- Site of Src phosphorylation is key to activity:
 - COOH-terminal Y530 → inactive conformation
 - Y418 → Src activation



Src

Relationship to and Role in CRC

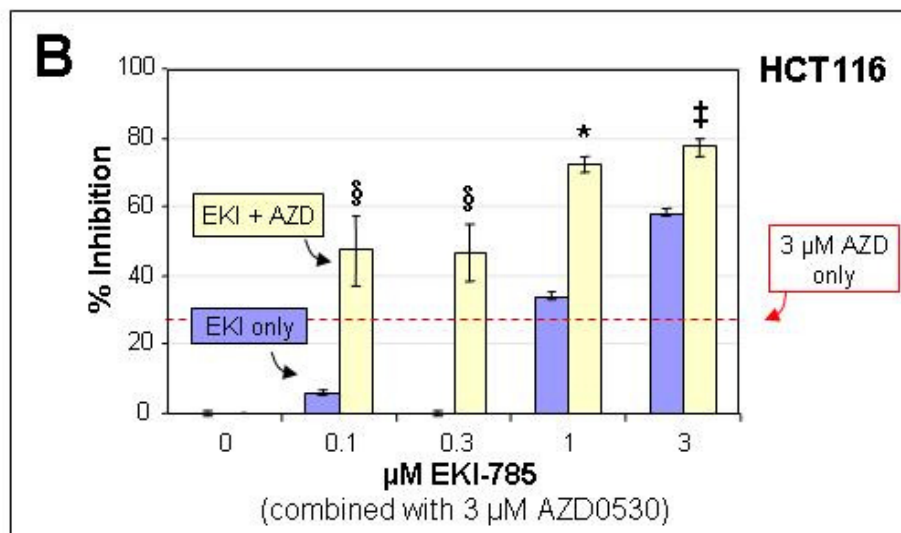
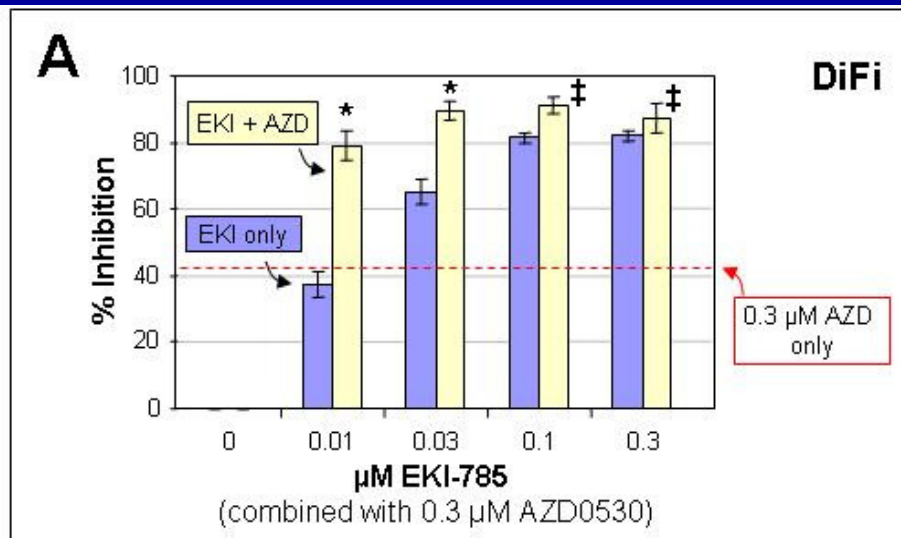
- **Overexpressed in > 80% of human CRC**
- **Src activity increases with cancer progression**
 - ↑ levels in metastases compared to primary tumors
- **High expression levels associated with EMT and poorer prognosis**
- **Interacts with a number of growth factor signaling pathways, including EGFR (pTyr 845)**
 - Src can be an upstream activator and/or a downstream mediator of EGFR activity
 - Src activation may be a mechanism of escape from EGFR inhibition
- **Disrupts sites at cell periphery involved in migration and cell-cell adhesion**
 - Cadherin-associated cell-cell junctions
 - Integrin-mediated cell-intercellular junction focal adhesion sites

Src Inhibitors

Current Status and Strategy for Development

- **3 small molecule ATP antagonists of Src are in clinical development:**
 - **Dasatinib (Sprycel™) (Bristol-Myers Squibb) (approved by FDA for refractory CML)**
 - **AZD 0530 (Astra-Zeneca)**
 - **SKI-606 (Wyeth)**
- **When used alone, most likely to influence tumor progression, invasion and metastases**
- **Unlikely to result in shrinkage of primary tumor**
- **How will “activity” be determined in Phase II?**
- **Most likely strategy in CRC will be to combine with:**
 - **Cytotoxic chemotherapy**
 - **Growth factor antagonists**

Combined EGFR axis and Src blockade: *in vitro* Synergy



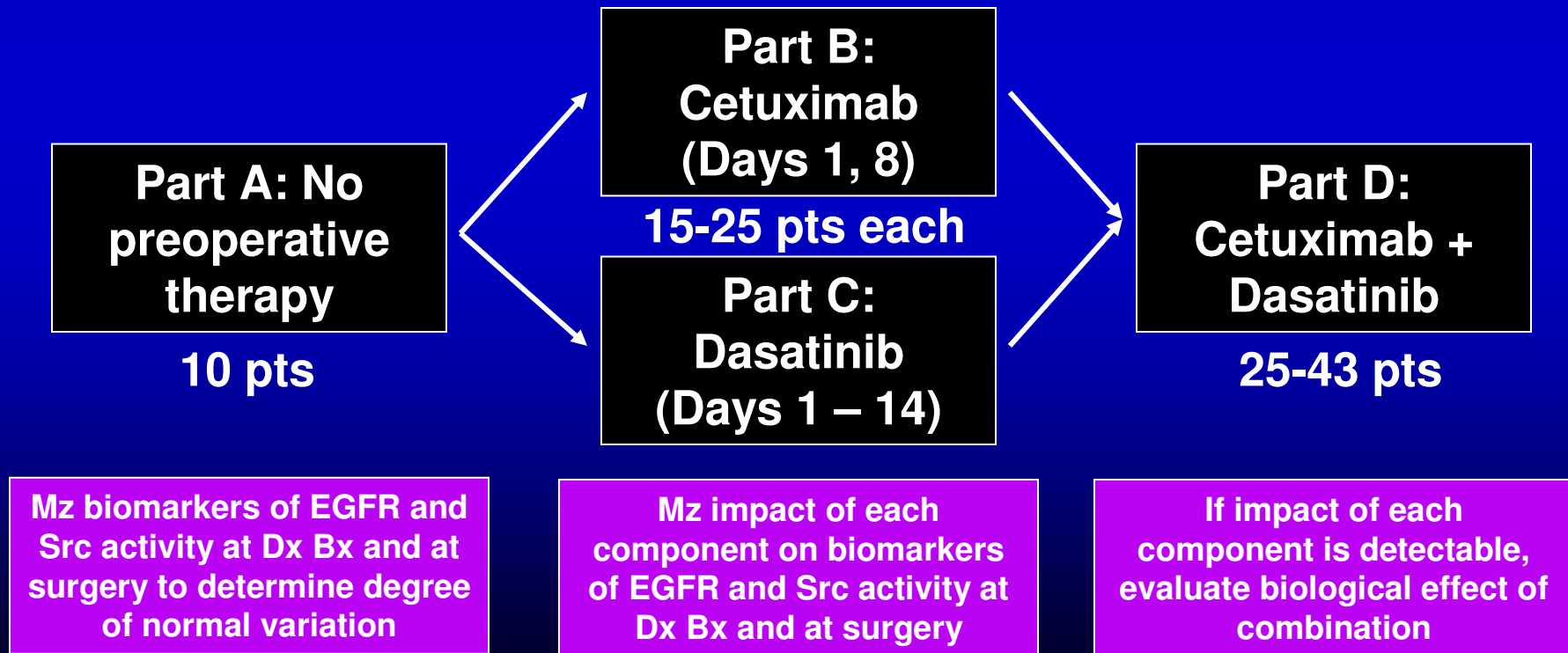
**Cooperative
Effects of
Irreversible EGFR
TKI (EKI-785) and
Src Inhibitor
(AZD0530) on Two
CRC Cell lines:
MTT Assay**

**Data Courtesy of Nipun
Merchant and Bob Coffey**

NCI 8069: Preoperative Trial of Cetuximab + Dasatinib

Clinical Design and Endpoints

- **Eligibility:** patients with liver-limited, potentially resectable liver metastases from CRC



Objectives

Primary Biochemical:

To determine the biochemical response of cetuximab, dasatinib, and the combination in CRC liver metastases following preoperative therapy

Primary Clinical:

To determine the frequency, severity, and duration of AEs during Rx and within 30 days following surgery

Biochemical Endpoints

Pathway	Target	Quantitation	Biological Response (post-Rx compared to pre-Rx)
EGFR	ϕEGFR (Tyr ¹⁰⁶⁸)	IHC: score 0 – 3	Decrease of at least one level
Src	ϕEGFR (Tyr ⁸⁴⁵)	IHC: score 0 – 3	Decrease of at least one level
	ϕ FAK(Tyr ⁸⁶¹)	IHC: score 0 – 3	Decrease of at least one level
	ϕ paxillin(Tyr ⁸⁶¹)	IHC: score 0 – 3	Decrease of at least one level
	ϕ Src(Tyr ⁸⁶¹)	IHC: score 0 – 3	Decrease of at least one level
Both	ϕ Akt	IHC: score 0 – 3	Decrease of at least one level
	Ki67	IHC: % positive cells	25% decrease
	ϕ MAPK	IHC: % positive cells	15% decrease

What's Next: Emerging Agents for mCRC

Conclusions

- Significant advances in the treatment of metastatic CRC will require agents that inhibit targets beyond VEGF and EGFR
- Several promising targets and inhibitors of those targets have been identified
- Unfortunately, most of these agents are still in Phase I or Ib
- The existence of multiple active agents against mCRC increases the difficulty of clinical trial design and the evaluation of these new agents
- These challenges must be overcome if we are to make additional, meaningful progress in the treatment of mCRC