Βασικές αρχές στοχεύουσας θεραπείας- Το παράδειγμα του καρκίνου του νεφρού

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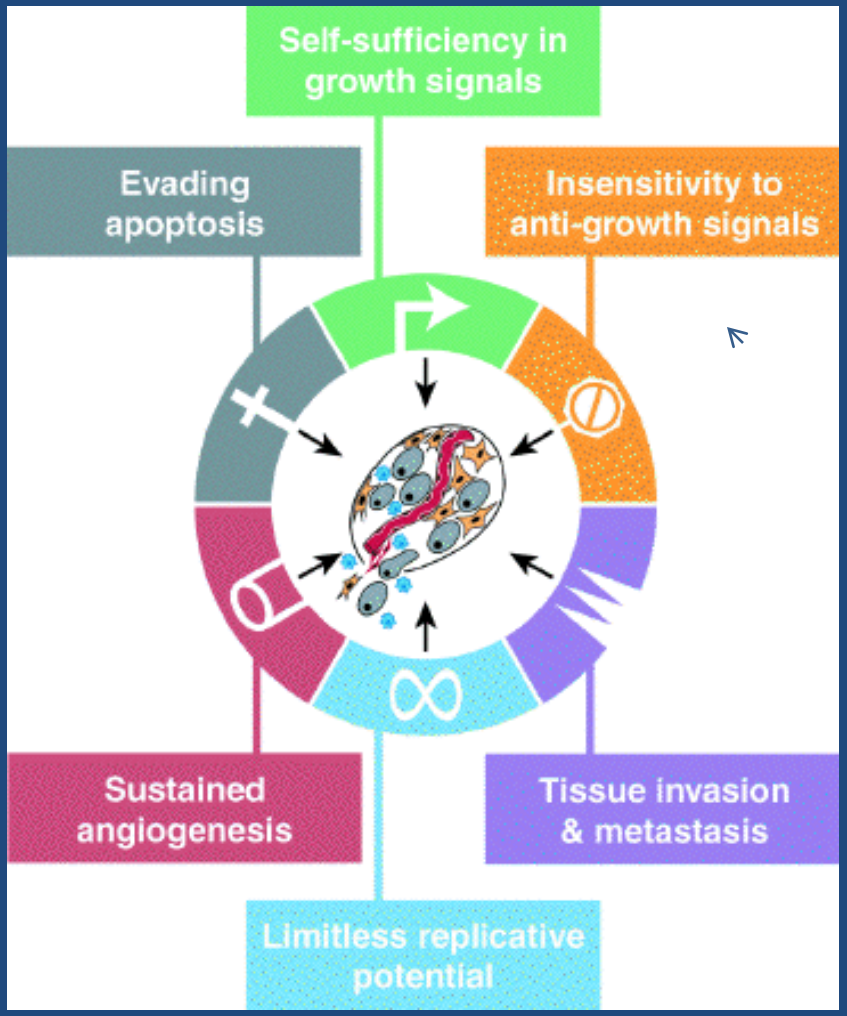
Θεραπευτική Κλινική ΕΚΠΑ

Cell

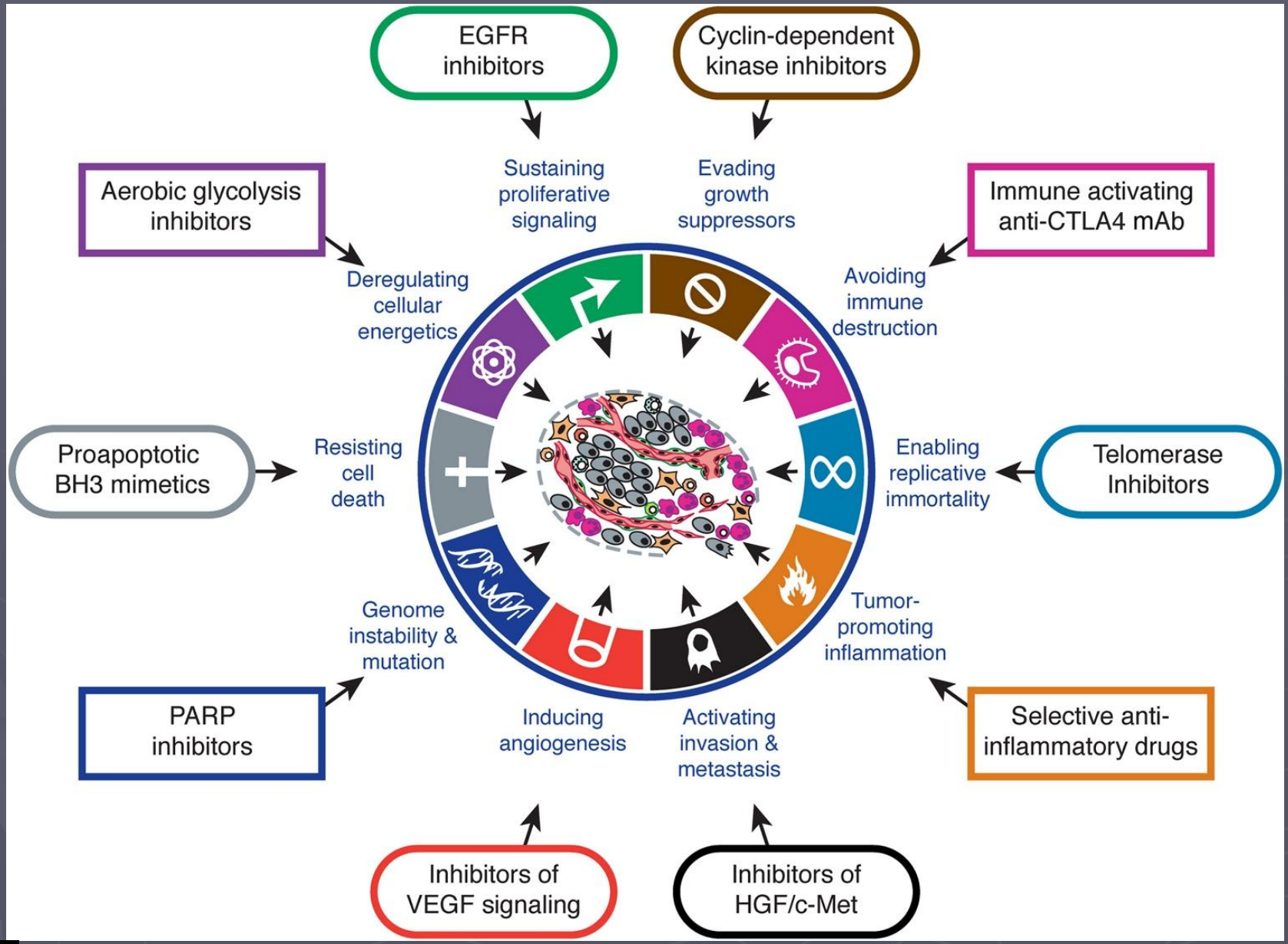
The Hallmarks of Cancer



Hanahan and Weinberg—2000

ΒΙΟΛΟΓΙΑ ΤΩΝ ΟΓΚΩΝ-ΑΝΤΑΠΟΚΡΙΣΗ ΣΤΗ ΧΜΘ

- Πρόσφατα δεδομένα αποδεικνύουν ότι η ανταπόκριση των όγκων στην χημειοθεραπεία εξαρτώνται από την ύπαρξη μοριακών παραγόντων, κάποιοι από τους οποίους σήμερα μπορούν να προσδιοριστούν η και να ποσοτικοποιηθούν



Cell 2011 144, 646-674DOI: (10.1016/j.cell.2011.02.013)

ΘΕΡΑΠΕΙΑ ΚΑΚΟΗΘΩΝ ΝΕΟΠΛΑΣΜΑΤΩΝ

Τοπικοπεριοχική

- Χειρουργική
- Ακτινοθεραπεία

Συστηματική

- Χημειοθεραπεία
- Ορμονοθεραπεία
- Ανοσοθεραπεία
- Στοχευμένη θεραπεία
- Συμπτωματική αγωγή

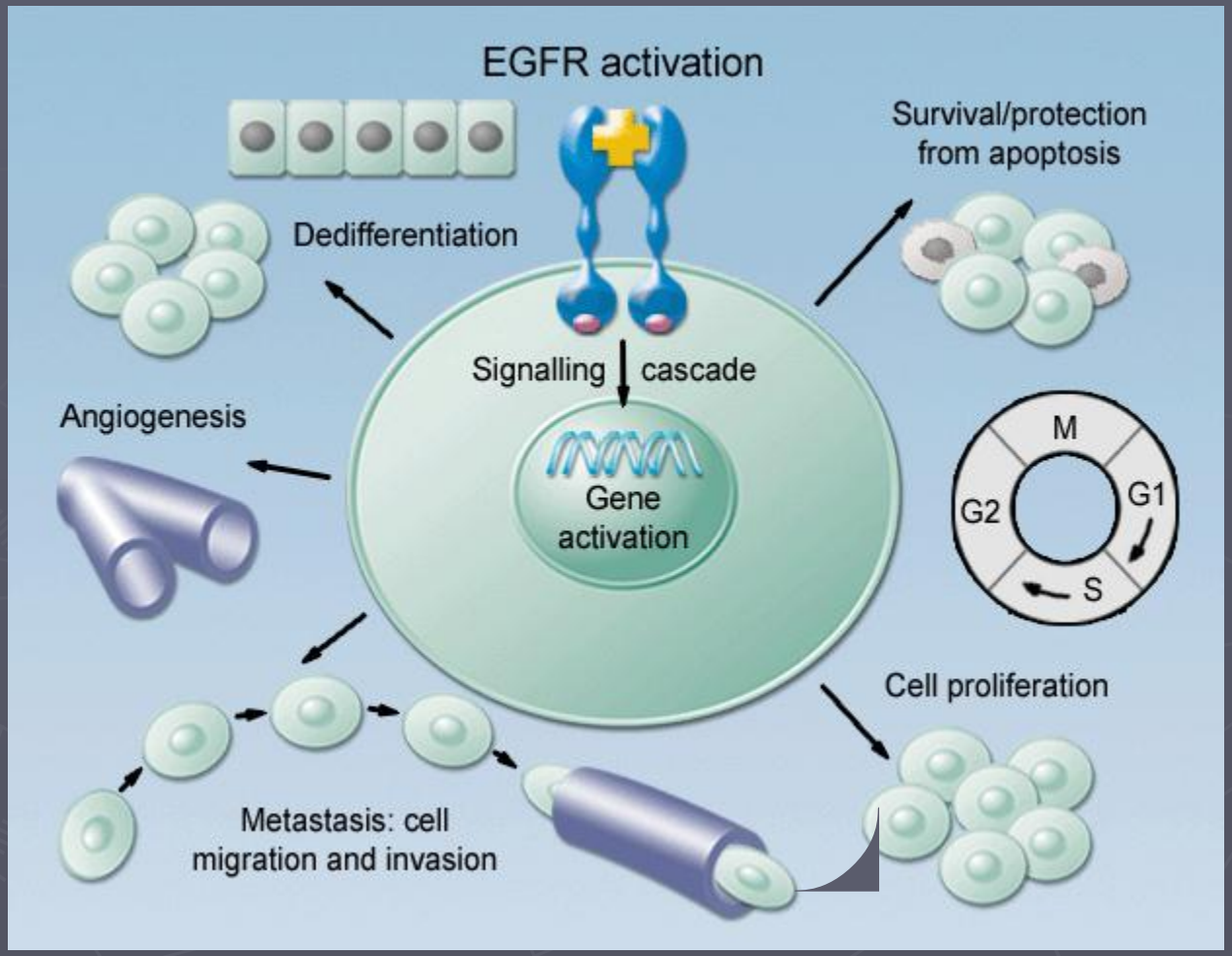
Στοχευμένη θεραπεία

- Η ανάπτυξη του όγκου, η ανθεκτικότητα στην απόπτωση και η ικανότητα για δημιουργία μεταστάσεων εξαρτάται από μοριακούς παράγοντες, οι οποίοι μπορούν να αποτελέσουν στόχους για αντινεοπλασματική θεραπεία

Στόχοι αντινεοπλασματικής θεραπείας

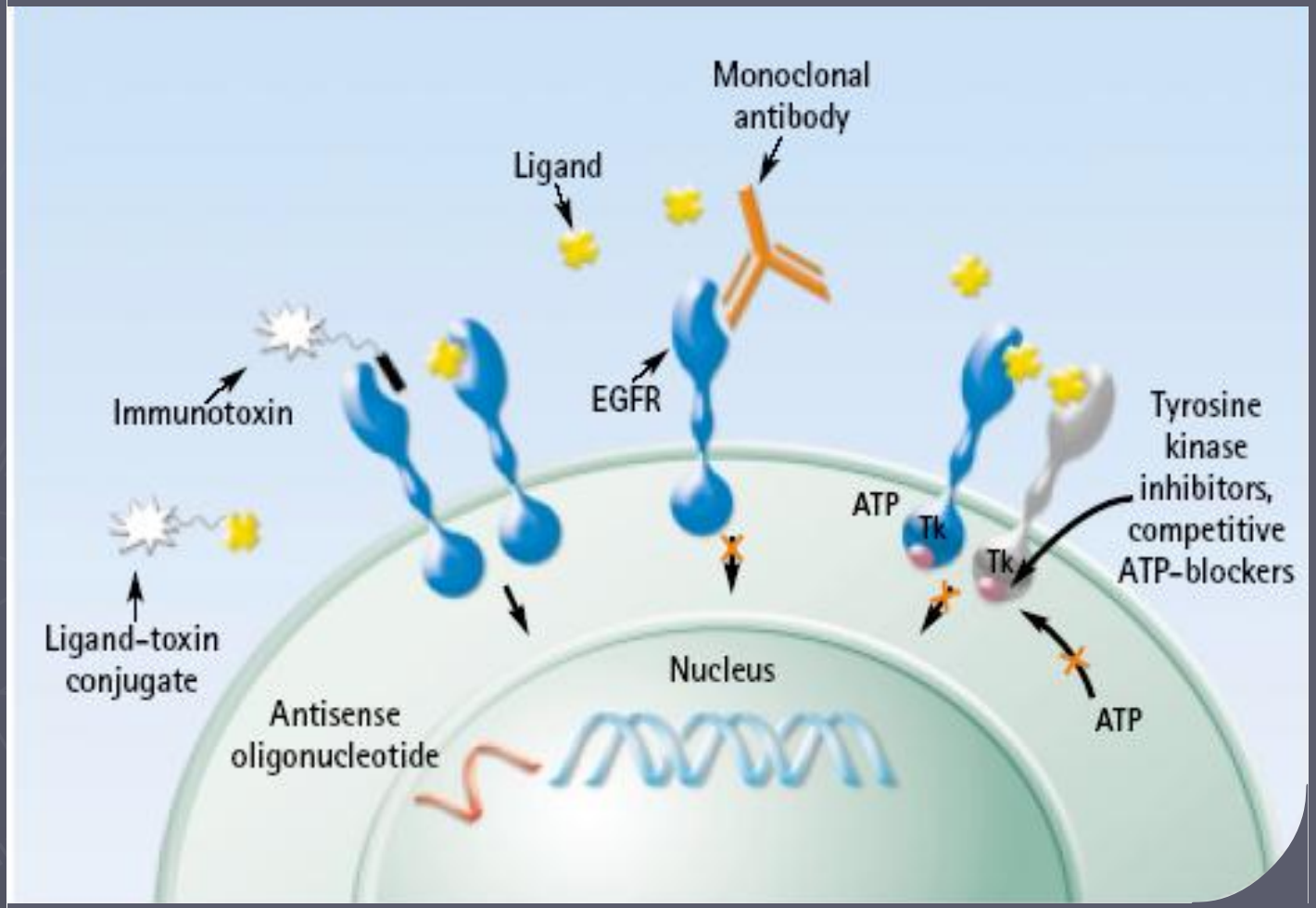
- ER, PgR
- Androgen Receptors
- HER-2
- KIT
- VEGF
- EGFR

EGFR

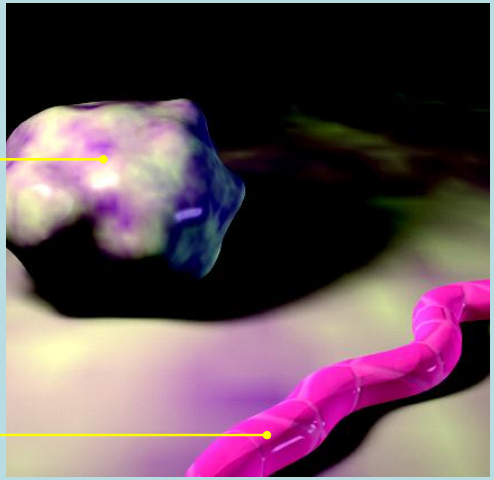


Baselga. Eur J Cancer 2001: 37 Suppl 4:S16-S22.

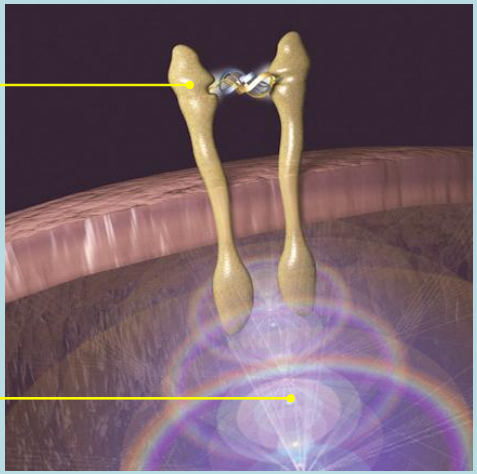
TKI-targeting approaches



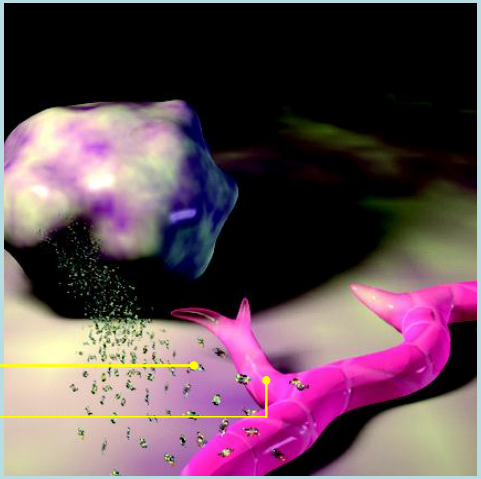
MALIGNANT TUMORS NEED A BLOOD SUPPLY TO GROW



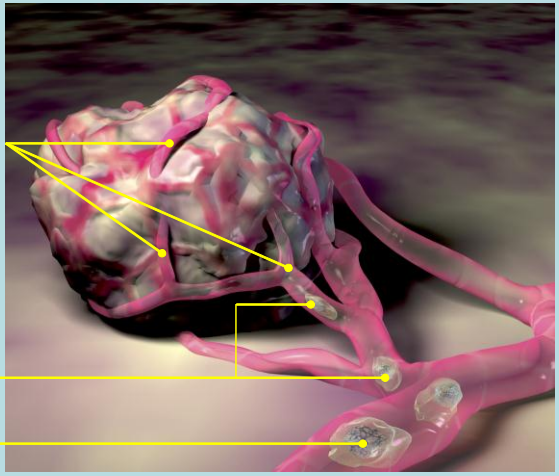
VEGF TRIGGERS MULTIPLE DOWNSTREAM SIGNALS THAT PROMOTE ANGIOGENESIS



THE ANGIOGENIC SWITCH TRIGGERS GROWTH OF NEW VESSELS



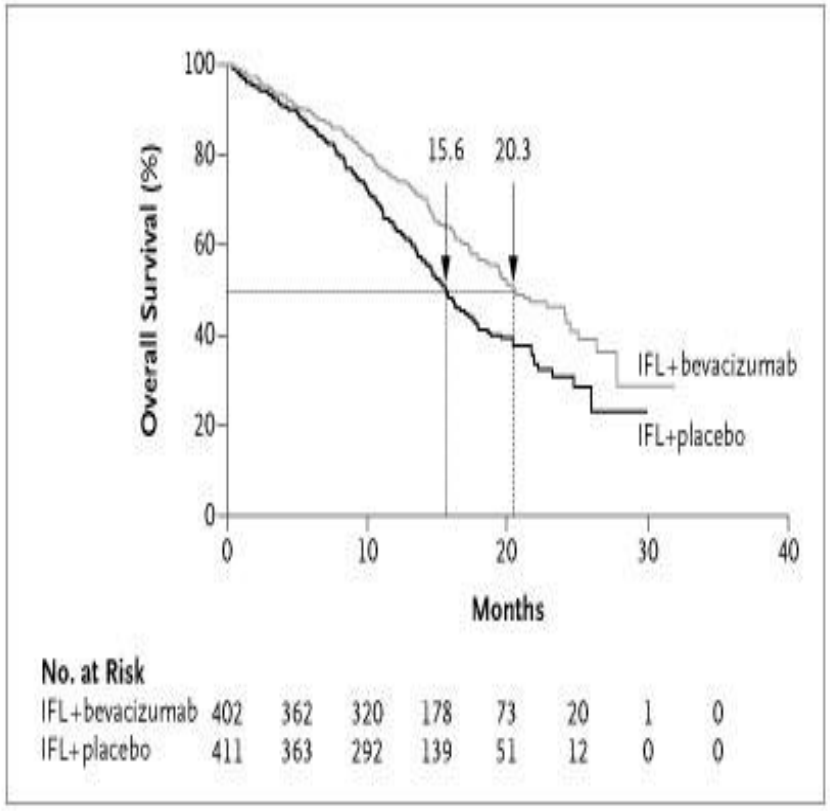
ANGIOGENESIS AND VASCULARIZATION SUPPORT TUMOR GROWTH AND METASTASIS

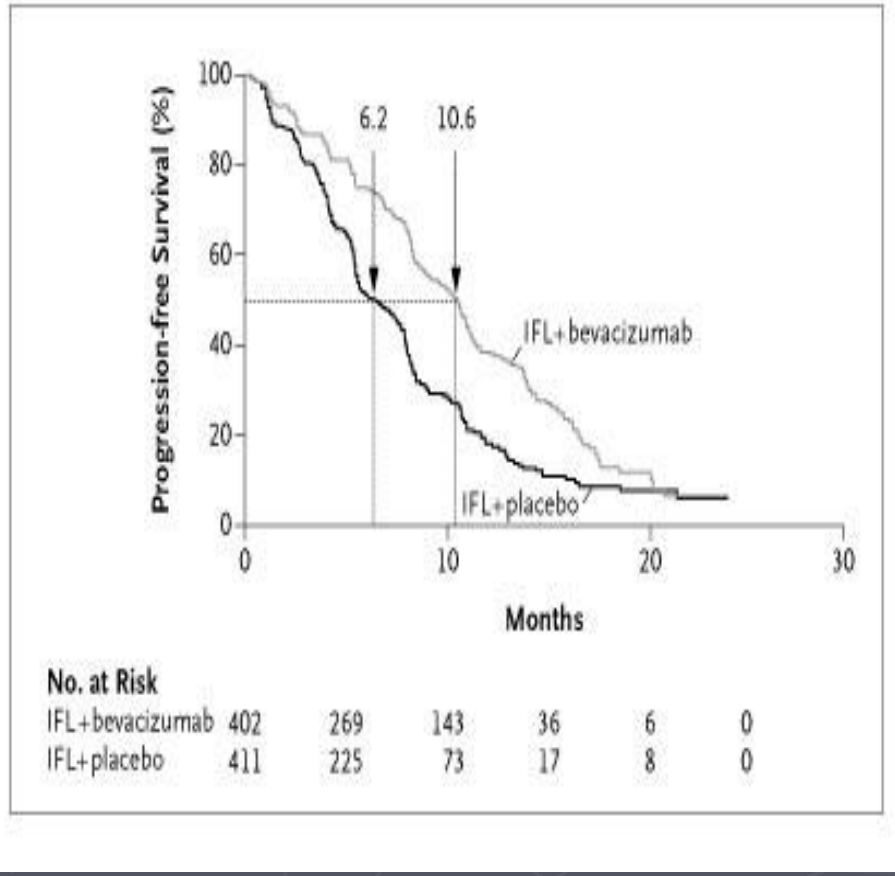


Πλεονεκτήματα συνδυασμού στοχευμένης θεραπείας και χημειοθεραπείας

- Διαφορετικοί μηχανισμοί δράσης
- Διαφορετική τοξικότητα
- Συνέργεια σε πειραματικά μοντέλα

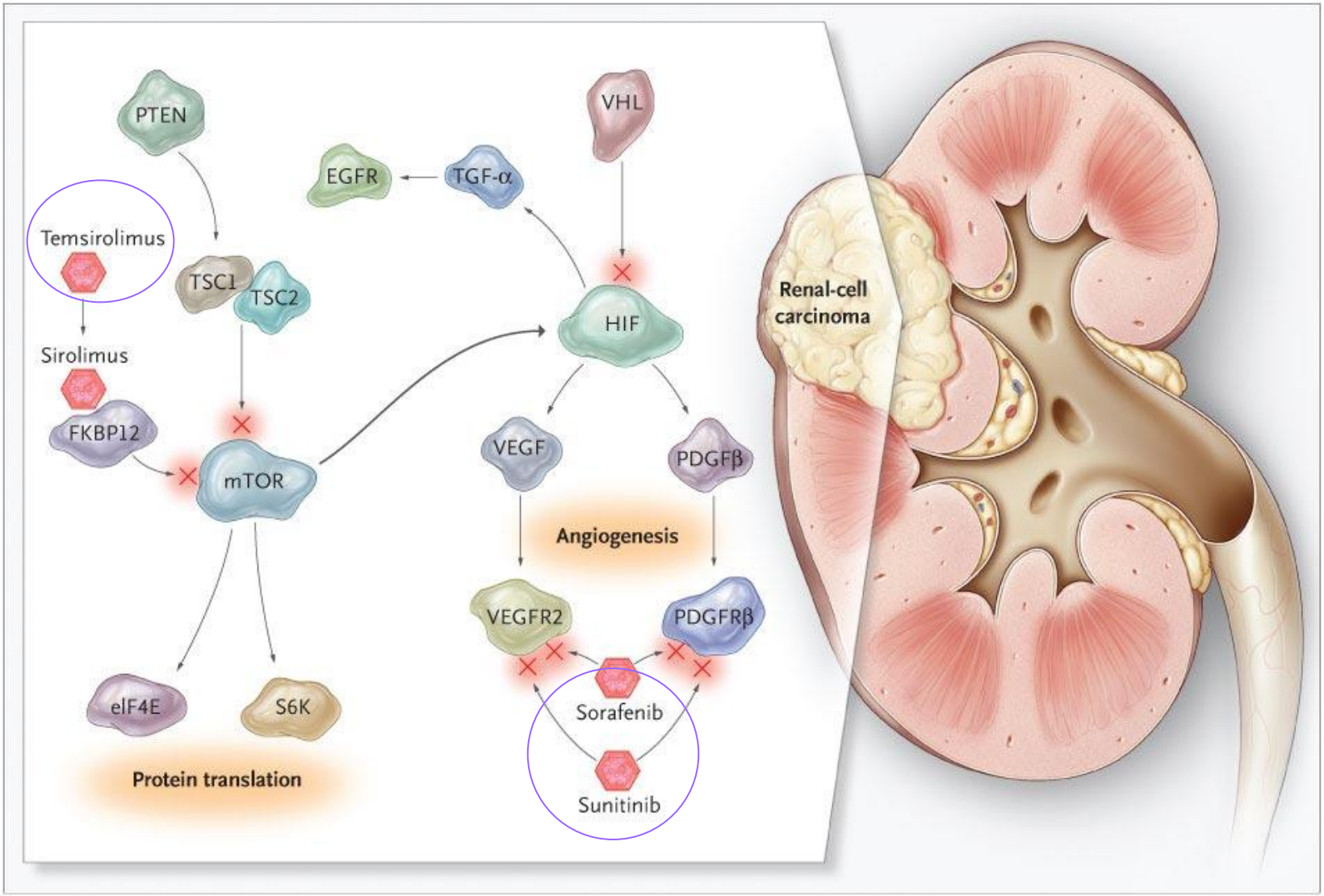
Kaplan-Meier Estimates of Survival and **Progression-free Survival**





The NEW ENGLAND JOURNAL of MEDICINE

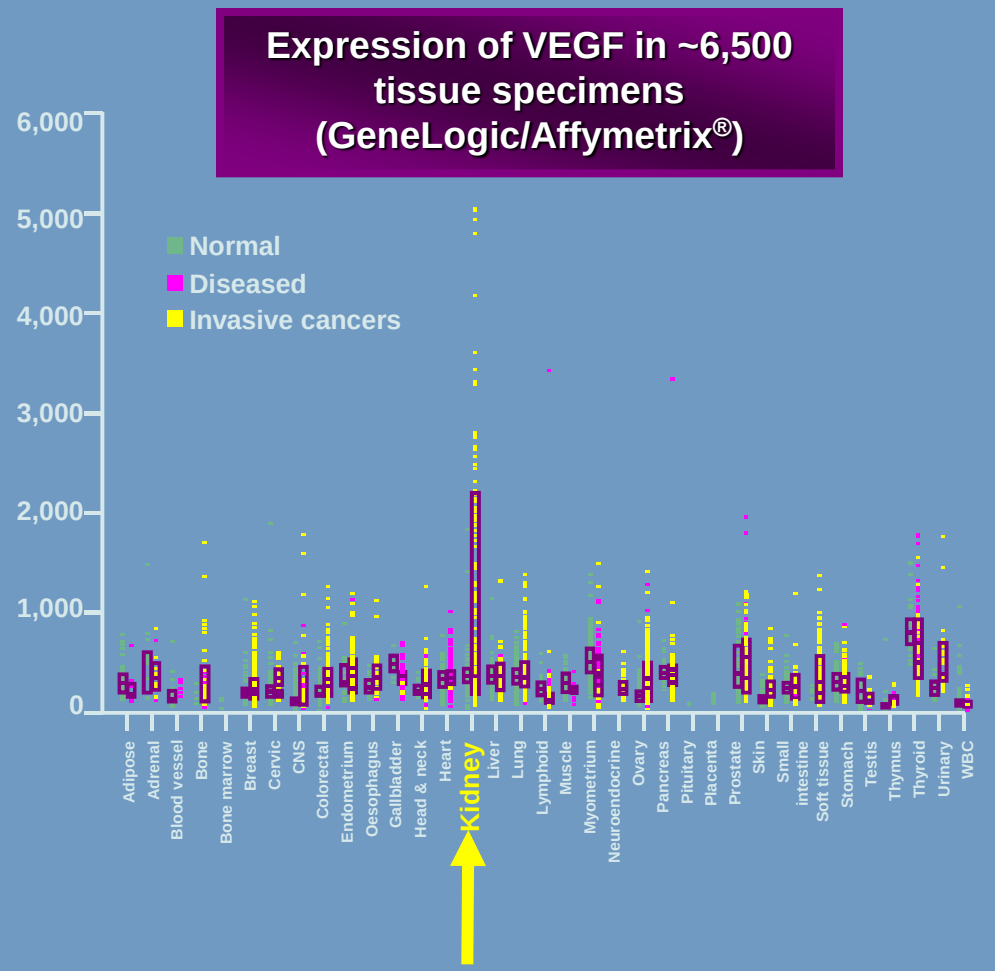
Molecular Pathways and Targeted Therapies in Renal-Cell Carcinoma

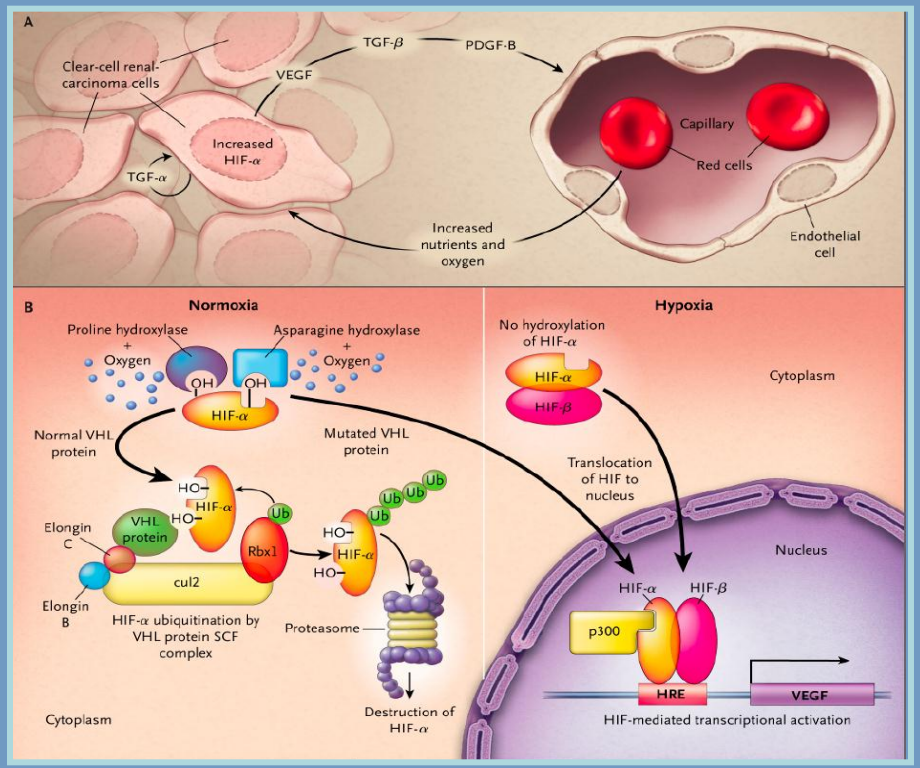


Brugarolas J. N Engl J Med 2007;356:185-187

The NEW ENGLAND JOURNAL of MEDICINE

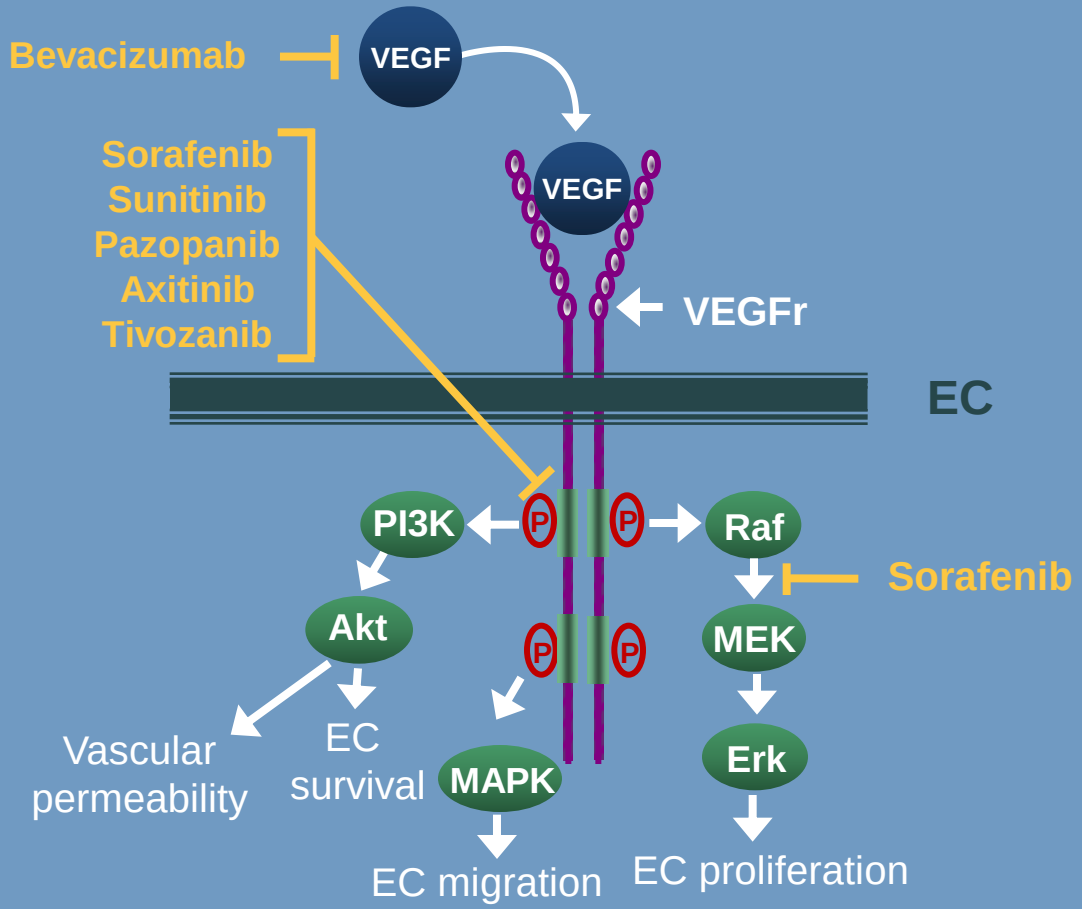
RCC Is a Highly Vascularized and VEGF-Expressing Tumor





Abbreviations: RCC, renal cell carcinoma; VEGF, vascular endothelial growth factor.
Adapted from Cohen and McGovern. *N Engl J Med.* 2005;353:2483.

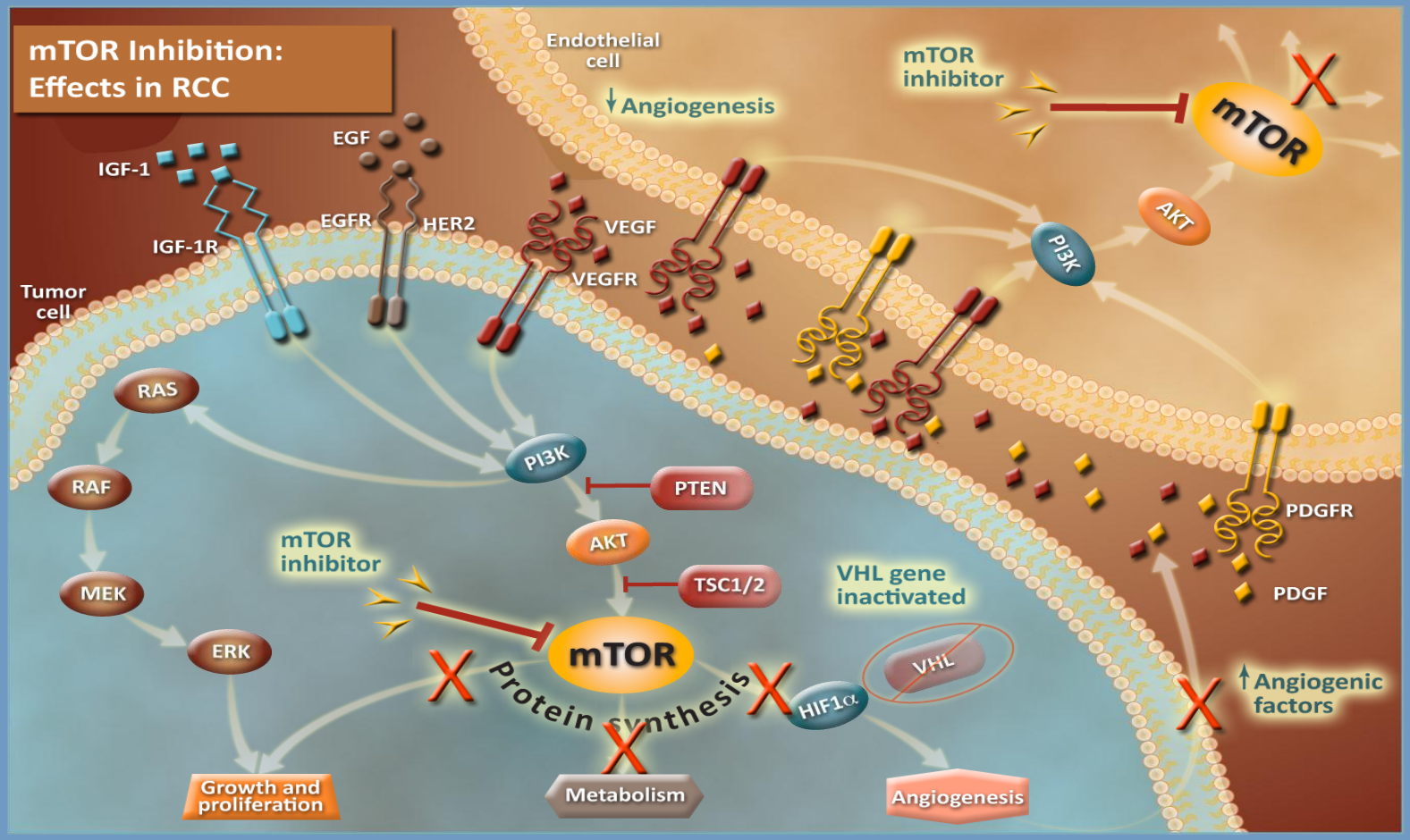
VEGF Signaling Pathway Inhibitors: Approved and Investigational Agents



EC, endothelial cell; Erk, extracellular signal-regulated kinase; MAPK, mitogen-activated protein kinase; MEK, mitogen-activated protein/extracellular signal-regulated kinase; PI3K, phosphatidylinositol 3-kinase; Akt, protein kinase B

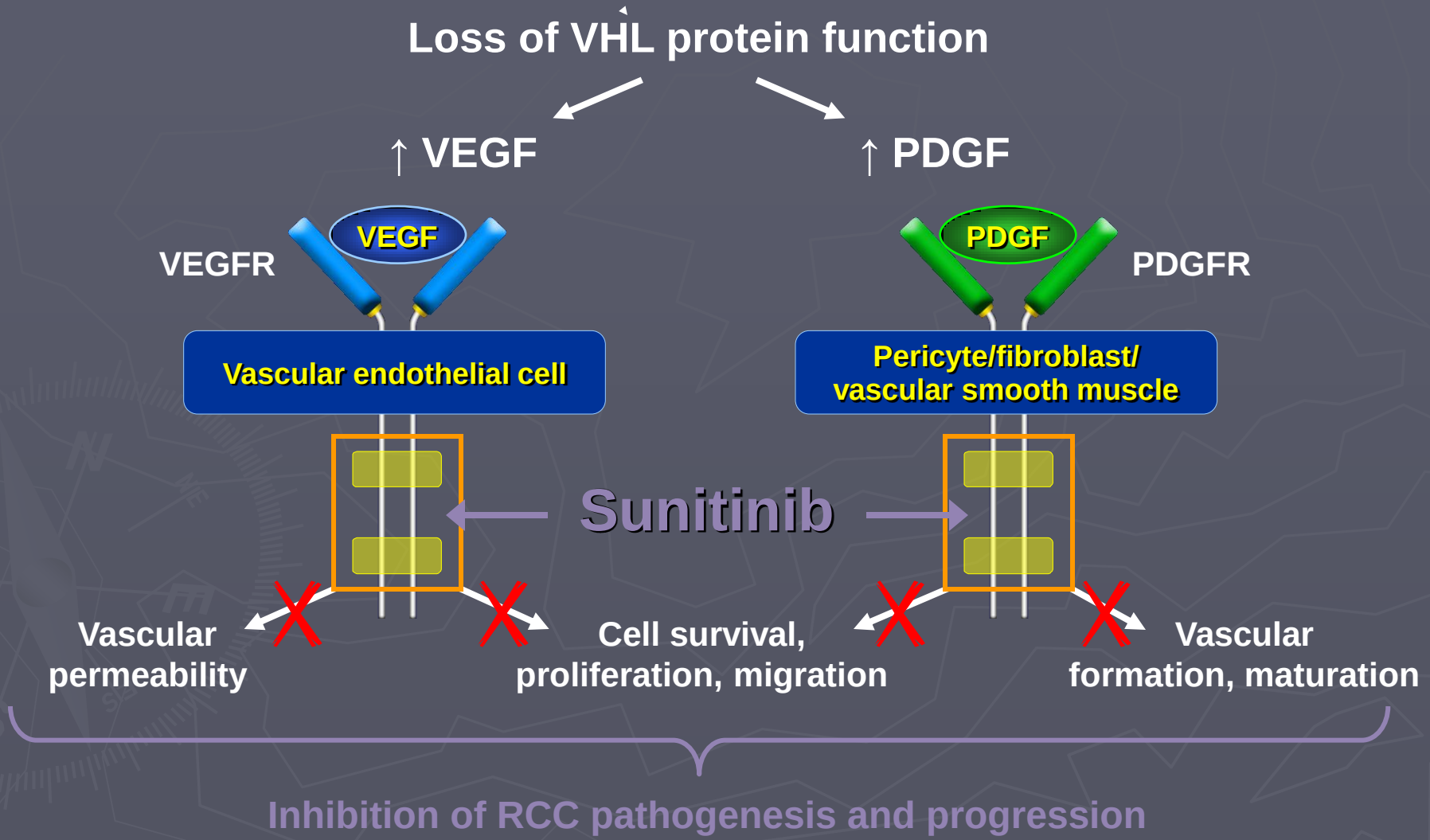
Modified with permission from: Garcia JA, Rini BI. *CA Cancer J Clin*. 2007;57:112-125.

mTOR Signaling Pathway Inhibition



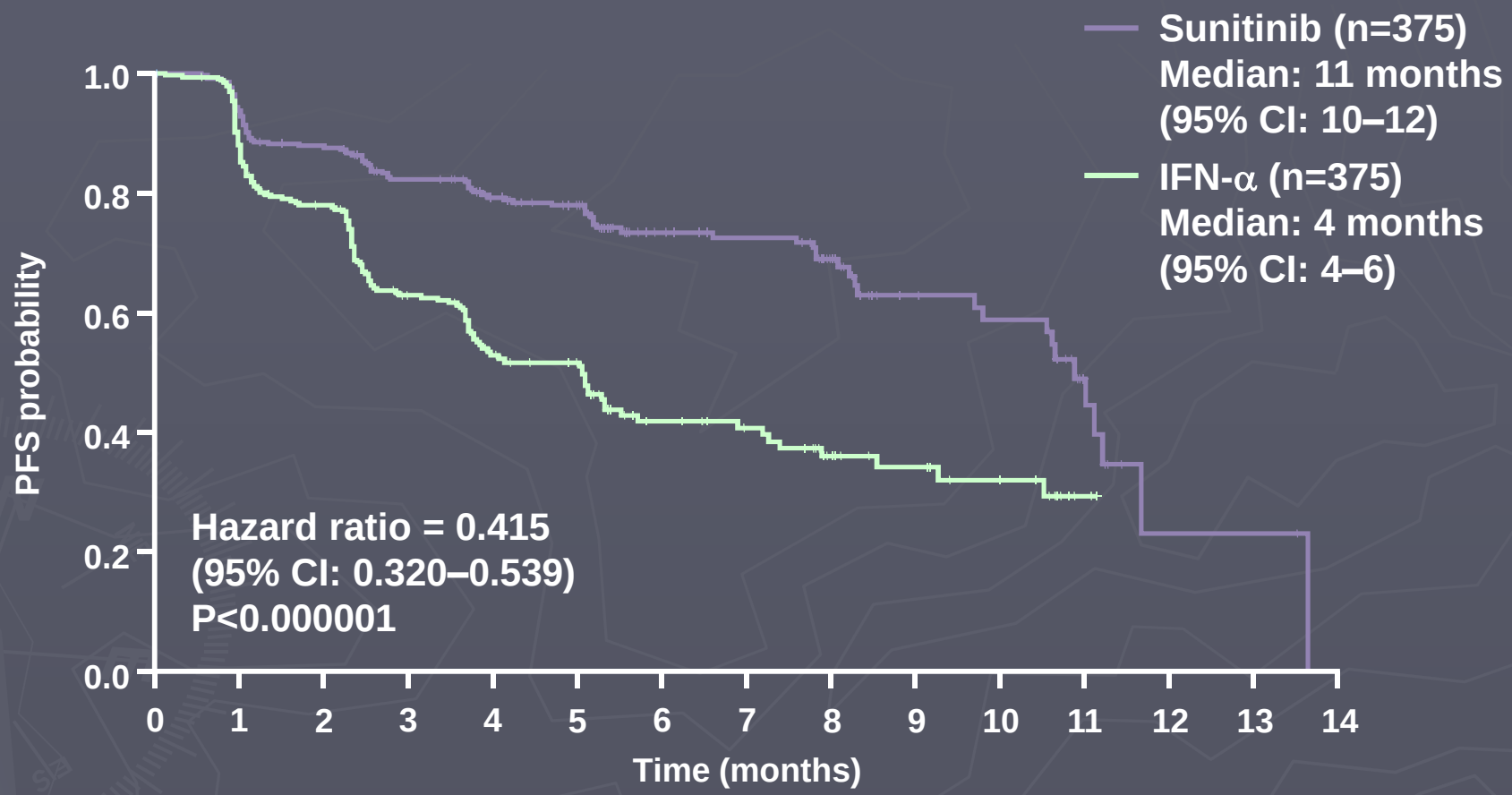
EGFR, epidermal growth factor receptor; HER2, human epidermal growth factor receptor 2; HIF-1α, hypoxia-inducible factor 1α; IGF-1R, insulin-like growth factor receptor; PDGFR, platelet-derived growth factor receptor; PTEN, phosphatase and tensin homolog; TSC1/2, tuberous sclerosis type 1/2; VHL, Von Hippel-Lindau

Sunitinib


Loss of VHL protein function
↑ VEGF
↑ PDGF
VEGFR
VEGF
PDGF
PDGFR
Vascular endothelial cell
Pericyte/fibroblast/
vascular smooth muscle
Sunitinib
Vascular
permeability
Cell survival,
proliferation, migration
Vascular
formation, maturation
Inhibition of RCC pathogenesis and progression

PFS

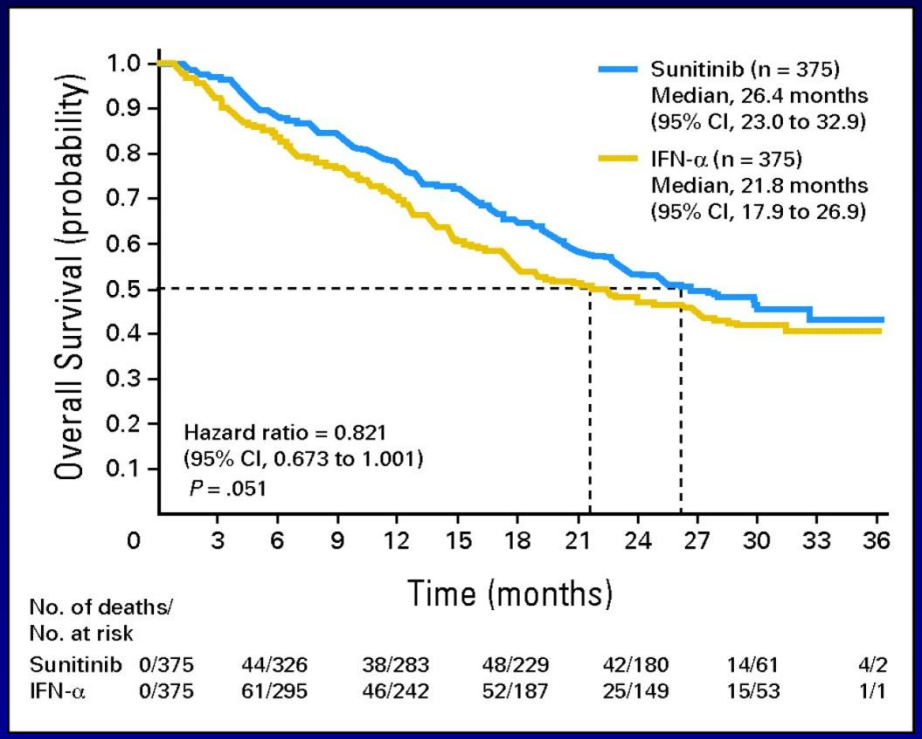
Independent central review



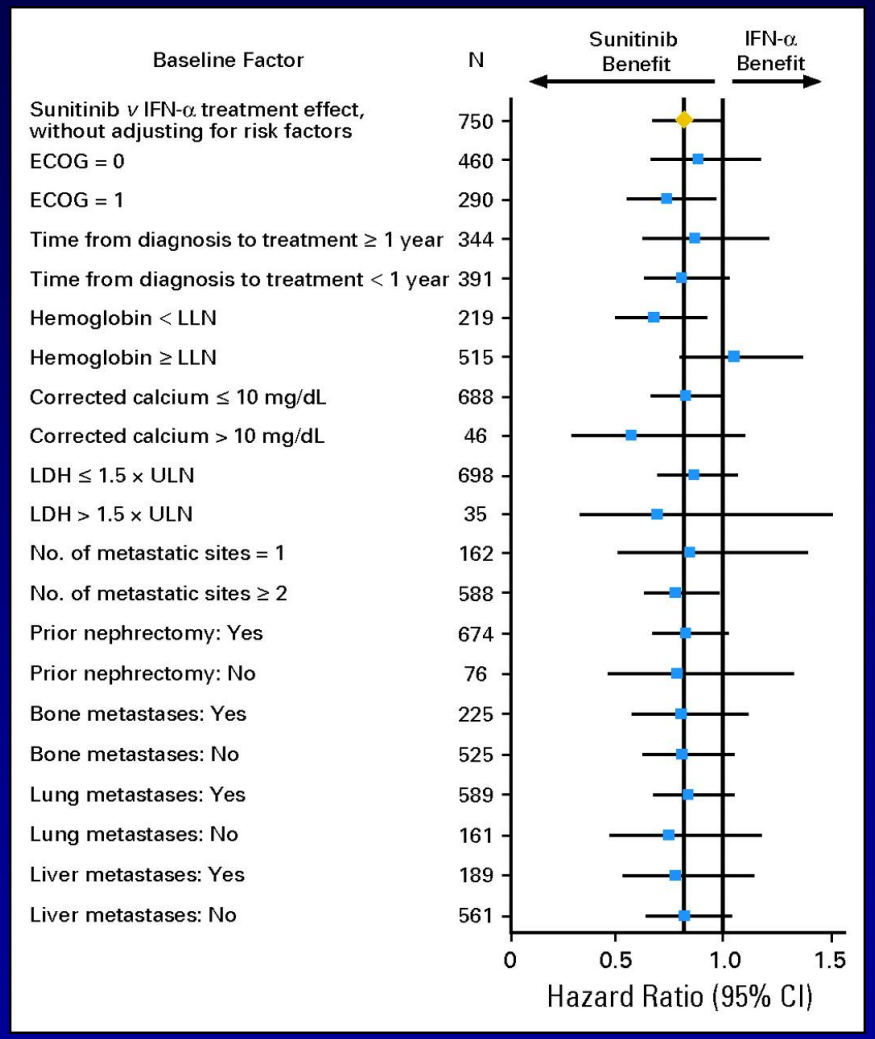
No. of subjects at risk					
Sunitinib:	375	235	90	32	2
IFN-α:	375	152	42	18	0

Motzer RJ, et al. NEJM 2007

Kaplan-Meier estimates of overall survival

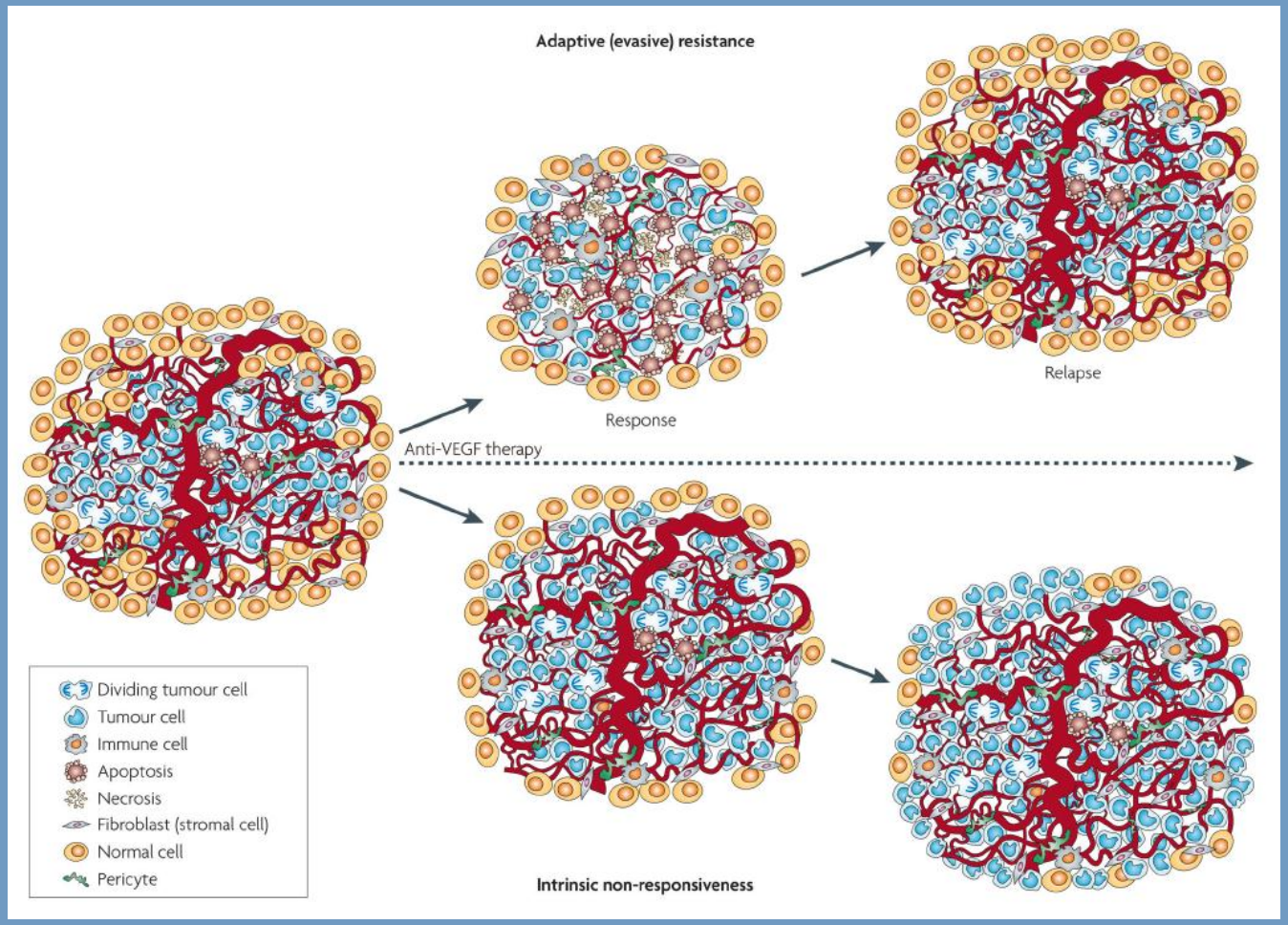


Overall survival subgroup analysis by individual baseline factors



Motzer, R. J. et al. J Clin Oncol; 27:3584-3590 2009

Resistance to VEGF-Targeted Therapy Is a Key Clinical Issue



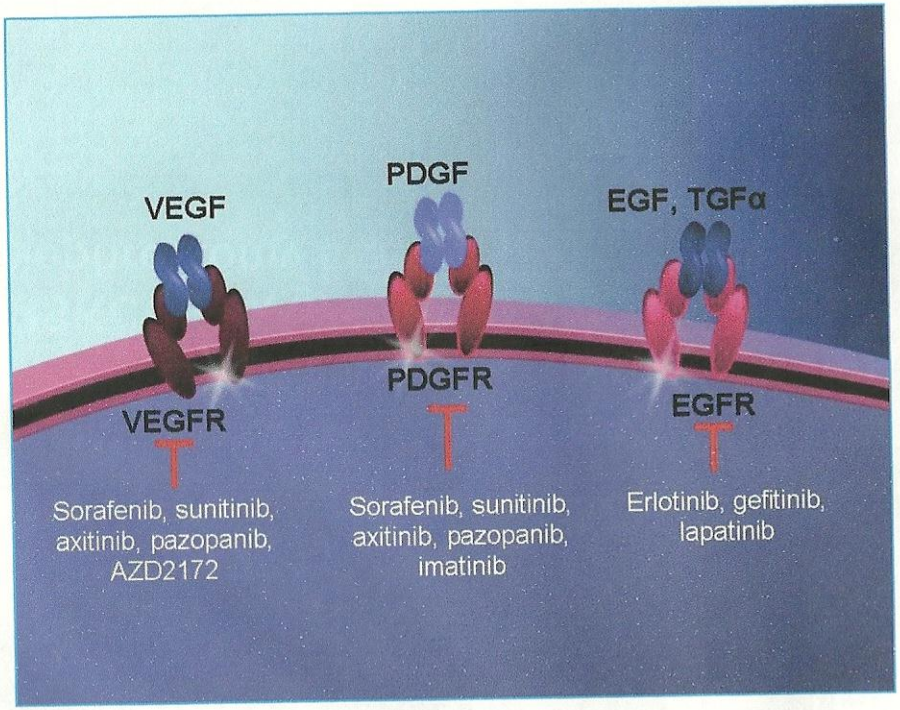
Adaptive resistance: VEGF-targeted agents fail to produce enduring clinical responses in most patients

Intrinsic resistance: No predictive biomarkers available to date

Bergers G, Hanahan D. *Nat Rev Cancer*. 2008;8:592-603.

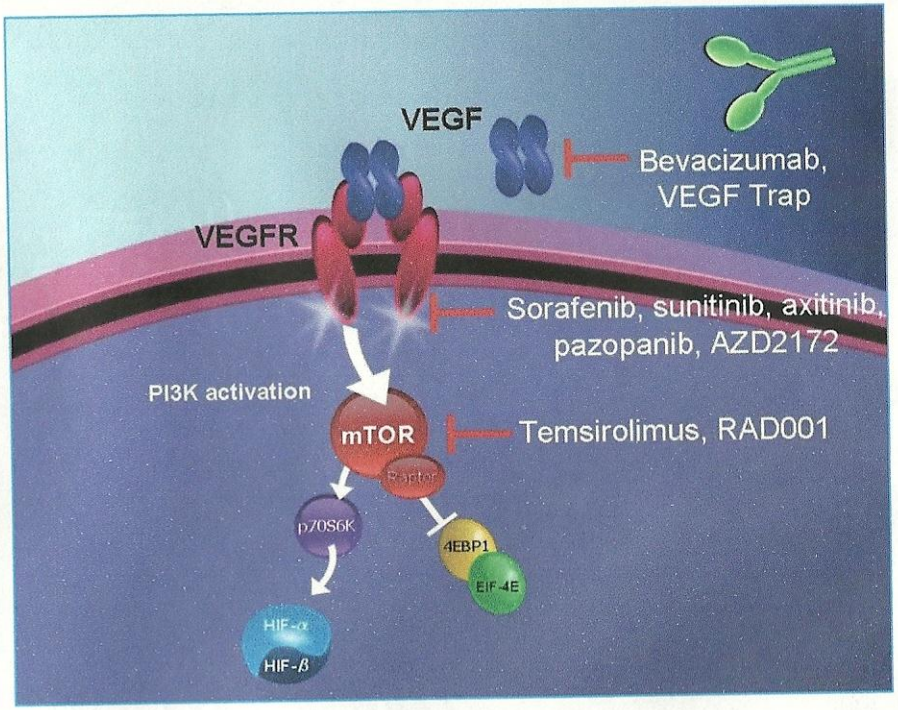
Combination of targeted Agents: Horizontal versus Vertical Blockade

Horizontal Blockade

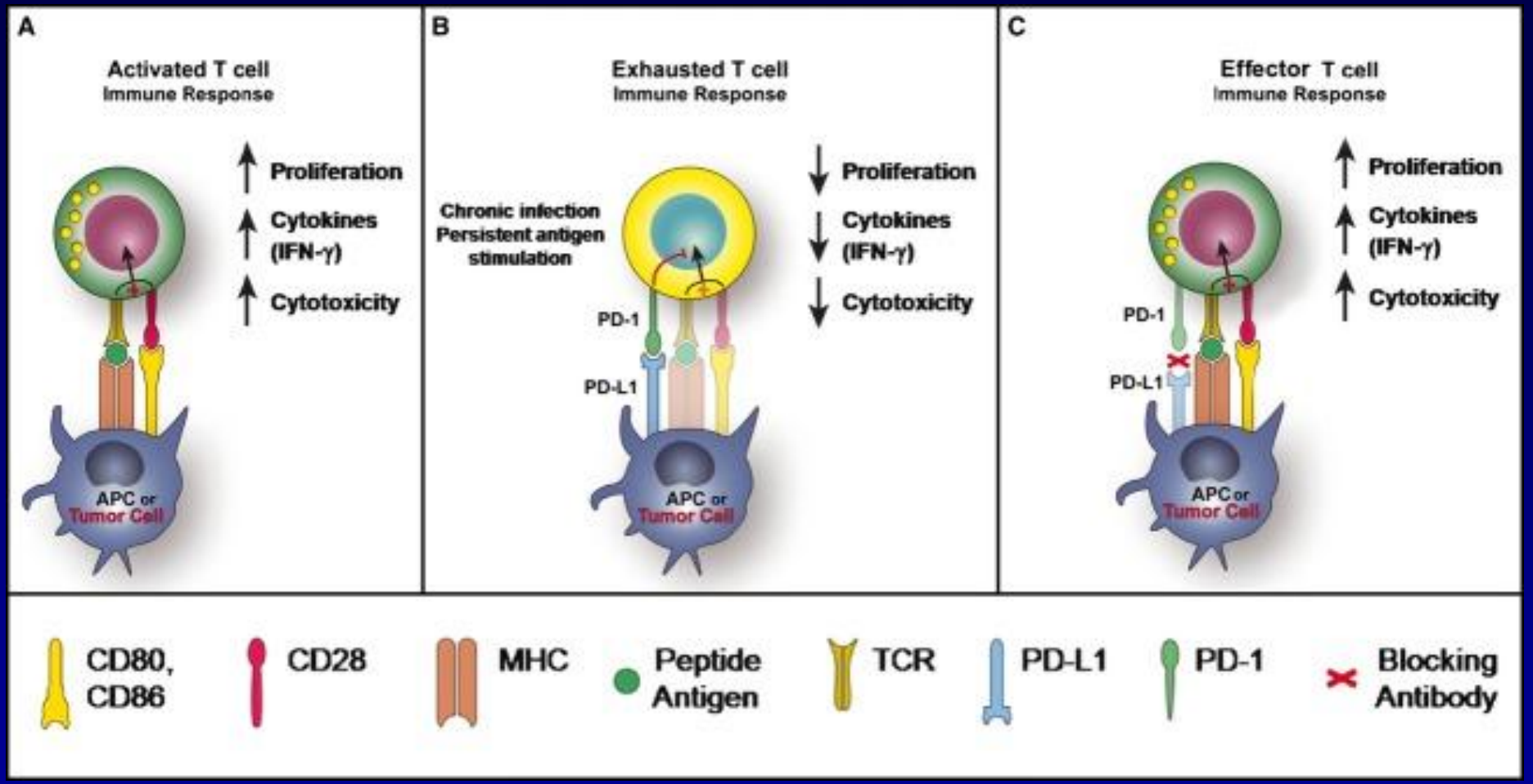


Multiple different signaling pathways are targeted

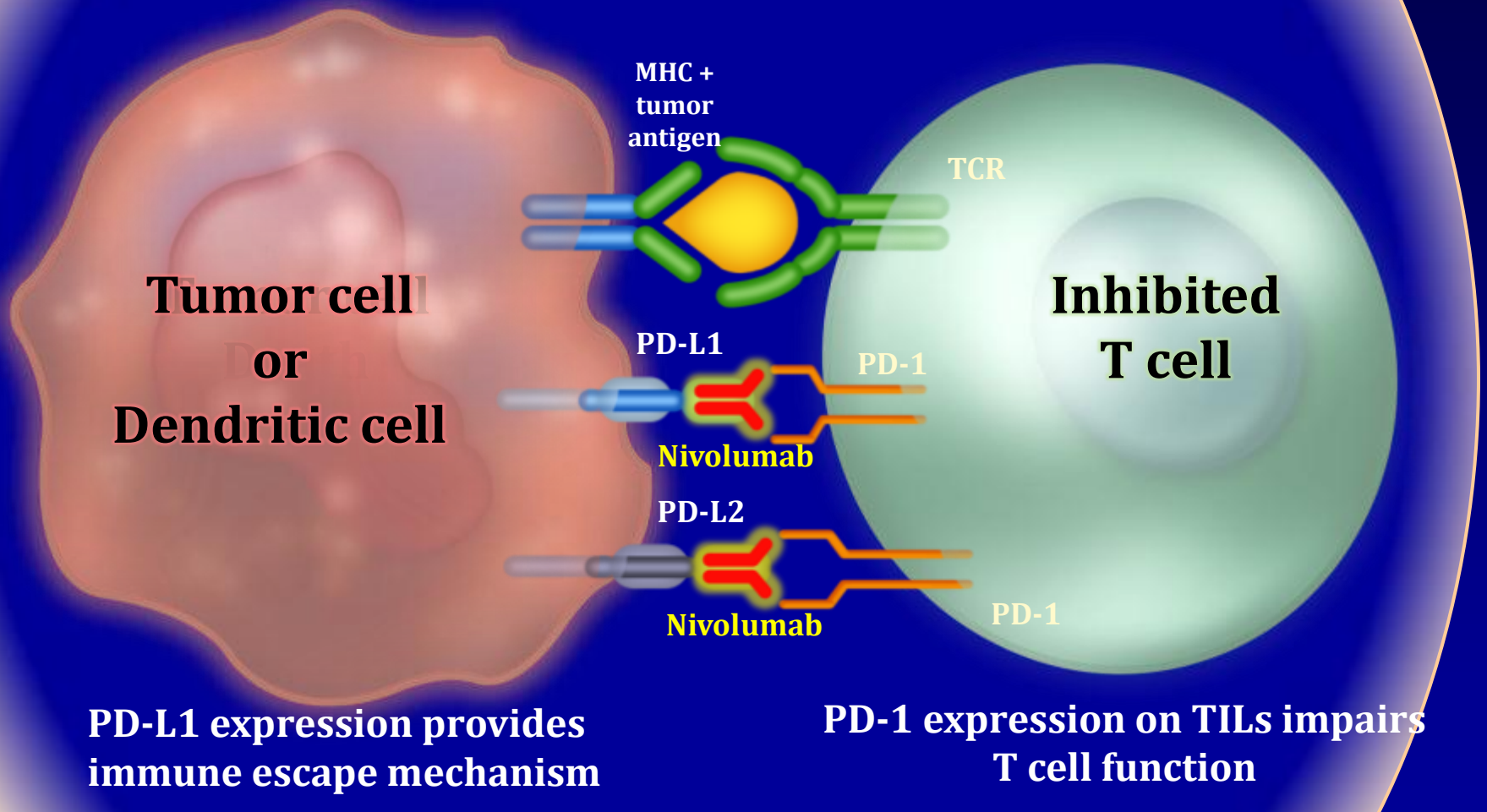
Vertical Blockade



A single signaling pathway e.g. VEGF is targeted in ≥ levels


A
Activated T cell
Immune Response
Proliferation
Cytokines
(IFN-γ)
Cytotoxicity
APC or
Tumor Cell
B
Exhausted T cell
Immune Response
Chronic infection
Persistent antigen
stimulation
PD-1
PD-L1
Proliferation
Cytokines
(IFN-γ)
Cytotoxicity
APC or
Tumor Cell
C
Effector T cell
Immune Response
PD-1
PD-L1
Proliferation
Cytokines
(IFN-γ)
Cytotoxicity
APC or
Tumor Cell
CD80,
CD86
CD28
MHC
Peptide
Antigen
TCR
PD-L1
PD-1
Blocking
Antibody

Immunosuppressive tumor microenvironment



PD-1, programmed death-1; PD-L1, programmed death ligand-1.

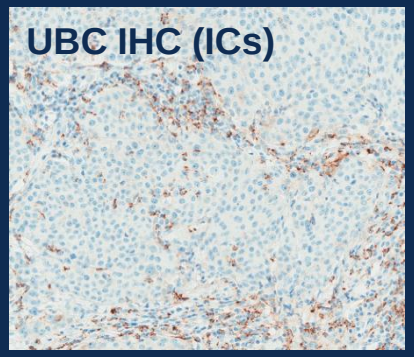
Gabrilovich D, et al. *Nat Med.* 1996;2:1096-103; Gabrilovich D, et al. *Nat Rev Immunol.* 2009;9:162-74; Bronte V, et al. *J Immunother*. 2001;24:431-46; Finke JH, et al. *Clin Cancer Res.* 2008;14:6674-82; Ko JS, et al. *Clin Cancer Res.* 2009;15:2148-57; Thompson RH, et al. *Clin Cancer Res.* 2007;13:1757-61; Thompson RH, et al. *Proc Natl Acad Sci U S A.* 2004;101:17174-9.

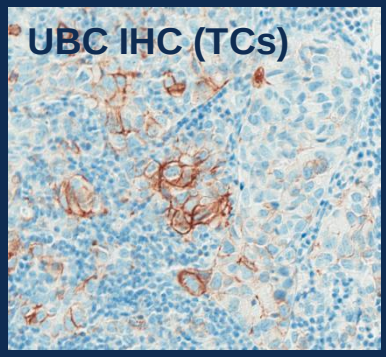
Υποδοχέας HER-2 και Trastuzumab (Herceptin^{R})

- Διαμεμβρανική γλυκοπρωτείνη 185 kDa
- Ενίσχυση του γονιδίου σε 15-25% καρκίνων μαστού
- Η ενίσχυση έχει σαν αποτέλεσμα επιθετική συμπεριφορά του όγκου και βράχυνση της επιβίωσης
- Μονοκλωνικό αντίσωμα έναντι του υποδοχέα HER-2
- Ανθρωποποιημένο (95%)
- Αποτελεσματικό σε πειραματικά μοντέλα

PD-L1 Prevalence in Solid Tumors

Indication	PD-L1+ (IC)	PD-L1+ (TC)
NSCLC (n = 184)	26%	24%
UBC (n = 205)	**27%**	**11%**
RCC (n = 88)	25%	10%
Melanoma (n = 59)	36%	5%
HNSCC (n = 101)	28%	19%
Gastric cancer (n = 141)	18%	5%
CRC (n = 77)	35%	1%
Pancreatic cancer (n = 83)	12%	4%





ICs; tumor-infiltrating immune cells.
TCs; tumor cells.
PD-L1+ if ≥ 5% ICs or TCs were positive for PD-L1 staining (Genentech/Roche PD-L1 IHC).

MPDL3280A: Summary of ORR in UBC

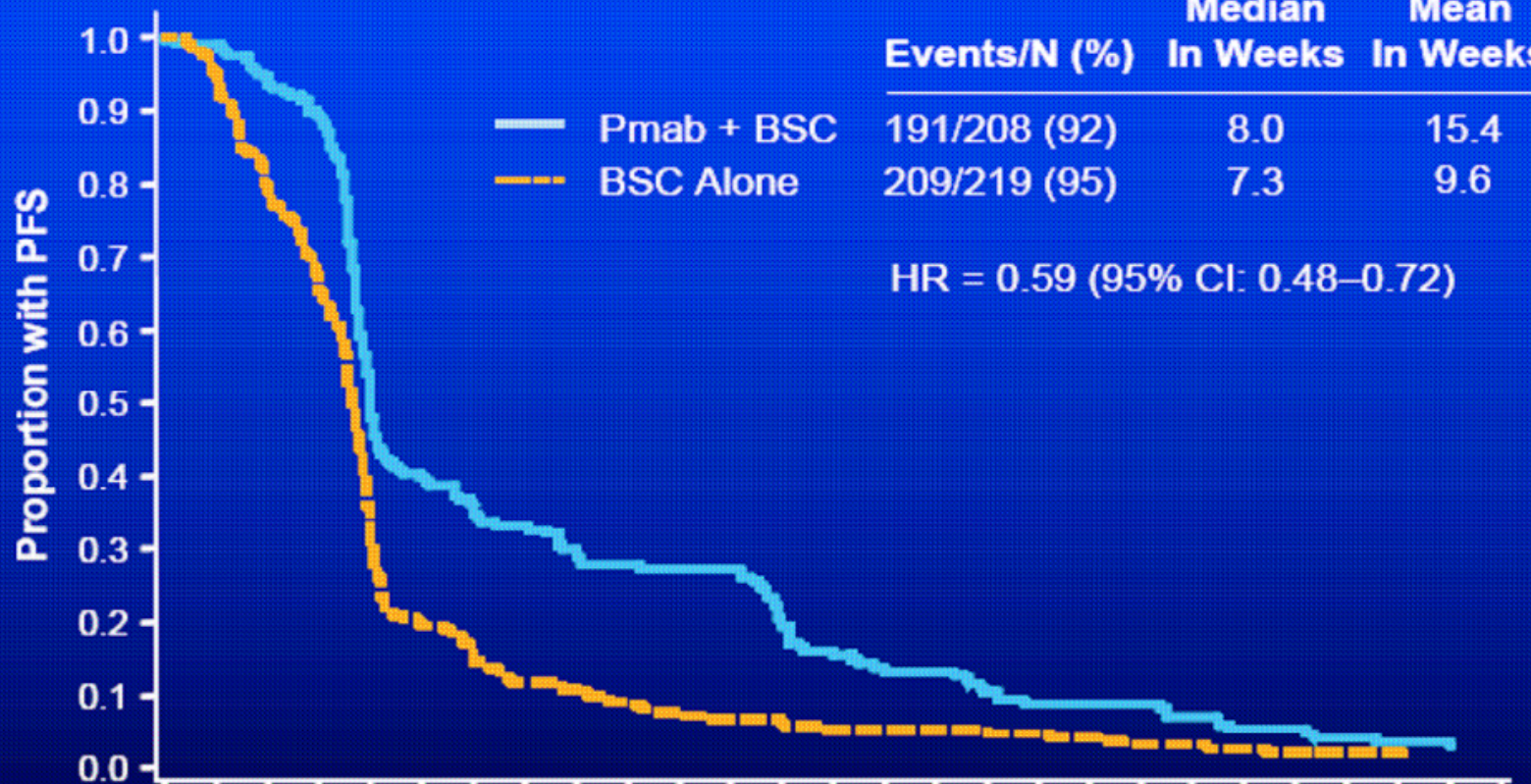
Efficacy-evaluable population with UBC in Phase I expansion

PD-L1 IHC **Tumor-infiltrating immune cells (ICs)**	**ORR** **% (95% CI)**	**Dx+ vs Dx− ORR** **% (95% CI)**
IHC **3** (n = 10)	**50%** (22-78)	**43%** (26-63)
IHC **2** (n = 20)	**40%** (21-64)	
IHC 1 (n = 23)	**13%** (4-32)	**11%** (4-26)
IHC 0 (n = 12)	**8%** (0.4-35)	

- 2 CRs (1 IHC 2, 1 IHC 3)
- 16 of 17 responding patients had ongoing responses at the time of data cutoff
- ORR = 52% (95% CI, 32-70) for Dx+ with ≥ 12 weeks of follow-up

Investigator-assessed ORRs unconfirmed) per RECIST v1.1.
2 pts with unknown IHC status are not included in table.
Diagnostic (Dx)/PD-L1+: IHC 3 (≥ 10% of ICs PD-L1+) and IHC 2 (≥ 5% but < 10% of ICs PD-L1+).
Diagnostic (Dx)/PD-L1–: IHC 1 (≥ 1% but < 5% ICs PD-L1+) and IHC 0 (<1% ICs PD-L1+).
Patients dosed by Nov 20, 2013 (≥ 6 wk follow-up) with measurable disease at baseline. Clinical data cutoff was Jan 1, 2014.

KRAS Evaluable Patients: PFS by Treatment



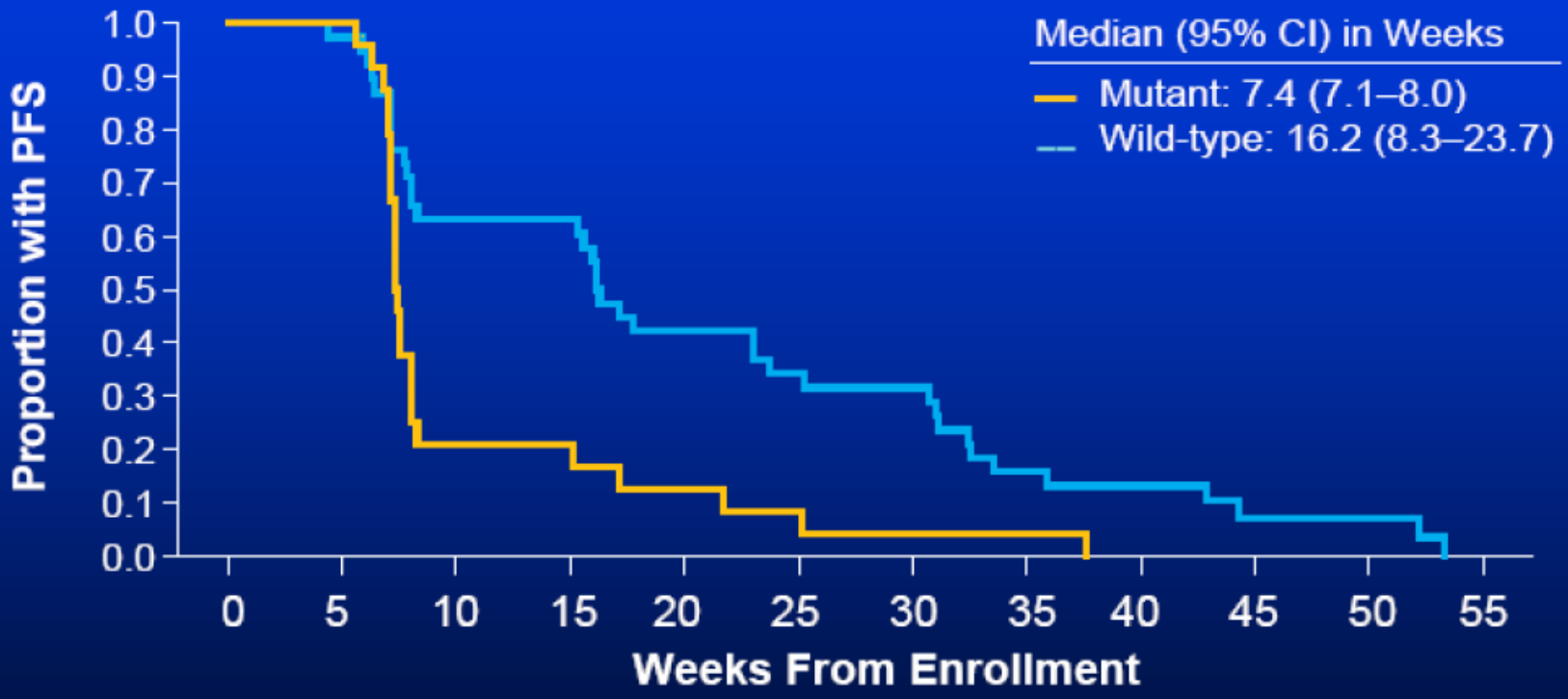
	Events/N (%)	Median In Weeks	Mean In Weeks
Pmab + BSC	191/208 (92)	8.0	15.4
BSC Alone	209/219 (95)	7.3	9.6

HR = 0.59 (95% CI: 0.48–0.72)

Patients at Risk

Pmab + BSC	208	197	188	178	106	79	71	64	55	50	49	49	37	29	25	24	19	15	15	15	12	9	9	7	6	6
BSC Alone	219	200	168	142	75	42	34	25	23	19	16	14	14	10	10	10	10	9	8	6	6	5	4	4	4	3

Progression-Free Survival for Panitumumab-Treated Patients by *KRAS* Status



Patients at Risk:

Mutant	24	24	6	6	4	3	2	2			
Wild-type	38	38	25	25	17	14	13	7	6	3	3

Αντιαγγειογενετικοί παράγοντες

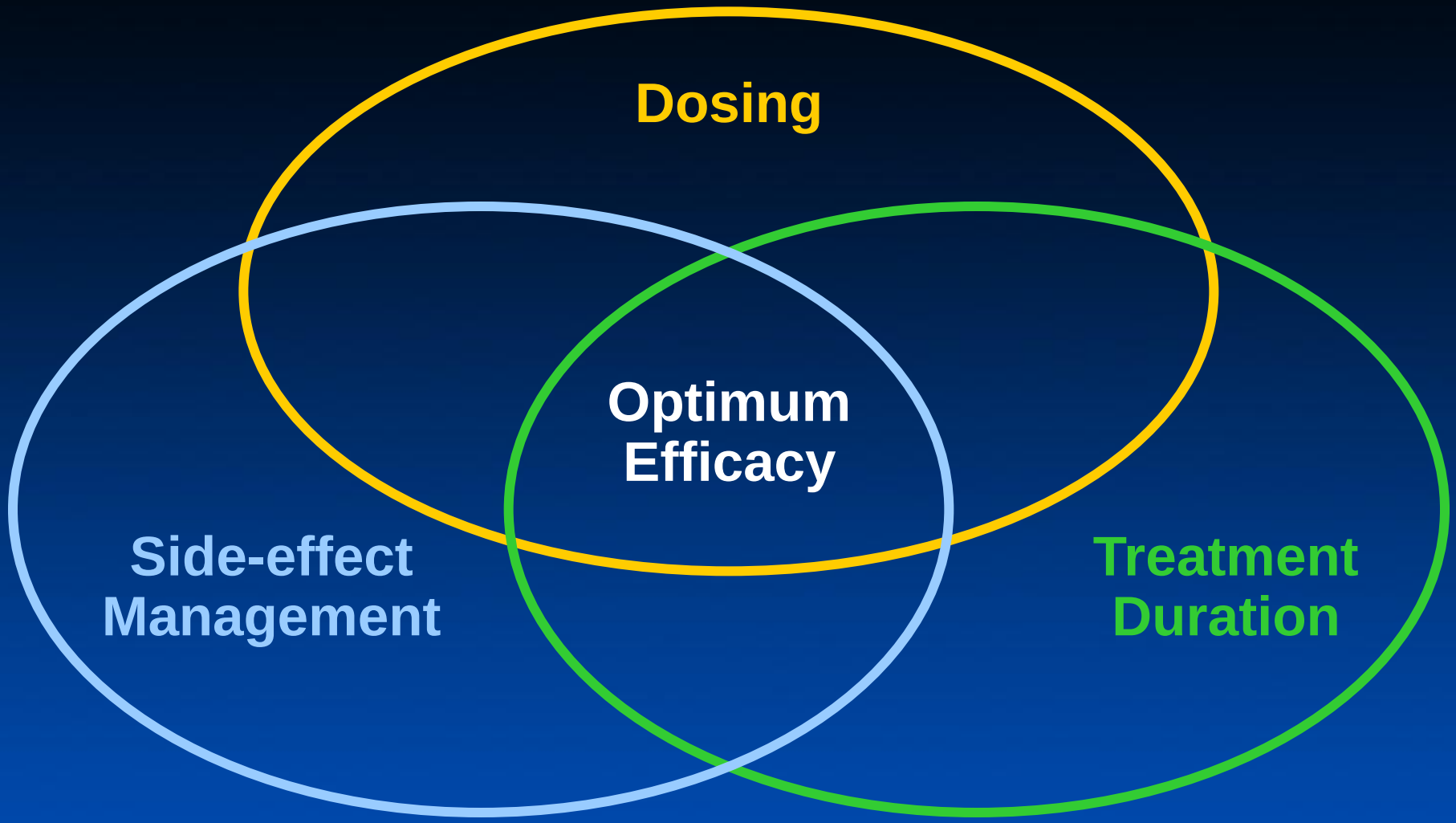
- Το μονοκλωνικό αντίσωμα Bevacizumab (Avastin) επιμήκυνε την επιβίωση σε ασθενείς με μεταστατικό καρκίνο π. εντέρου, οι οποίοι έλαβαν χημειοθεραπεία
- Επίσης αύξησε την ελεύθερη-προόδου νόσου επιβίωση σε ασθενείς με μεταστατικό καρκίνο νεφρού μετά από θεραπεία με κυτταροκίνες και βελτίωσε τα αποτελέσματα της χημειοθεραπείας σε μη μικροκυτταρικό καρκίνο πνεύμονος.
- Τοξικότητα: υπέρταση, αιμορραγία πεπτικού η πνευμόνων (σπάνια), διάτρηση εντέρου (σπάνια)
- Είναι εγκεκριμένο για την θεραπεία μεταστατικού καρκίνο π. εντέρου σε συνδυασμό με ιρινοτεκάνη και φθοριοουρακίλη

Most Common Side-effects (≥20%) Reported with the Four Licensed Agents for mRCC

Sunitinib[1]	Fatigue, gastrointestinal disorders, dysgeusia, decreased appetite, hypertension, HFS, skin discolouration, mucosal inflammation, rash
Sorafenib[2]	Diarrhea, rash, alopecia
Temsirolimus[3]	Asthenia, anemia, rash, gastrointestinal, disorders, oedema, metabolic disorders, dyspnea, pain, cough, bacterial infections
Bevacizumab/IFN-α[4,5]	Anorexia, fatigue/asthenia, hemorrhage, hypertension, influenza-like illness, headache, diarrhea

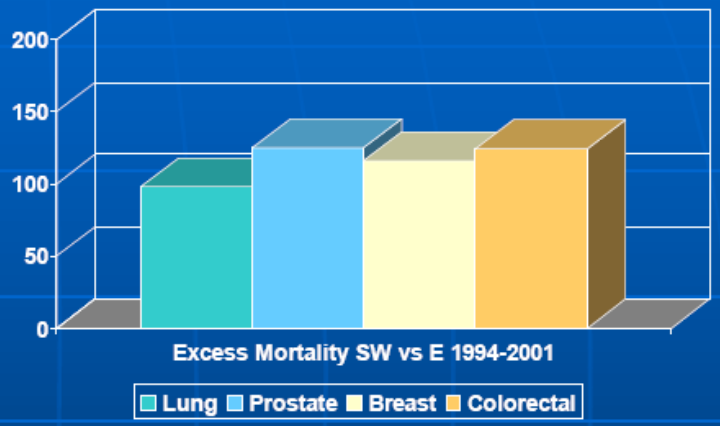
1. Pfizer Inc. SUTENT® (sunitinib) Summary of Product Characteristics, February 2009; 2. Bayer Healthcare. Nexavar® (sorafenib) Summary of Product Characteristics, 2008; 3. Wyeth Pharmaceuticals. Torisel® (Temsirolimus) Summary of Product Characteristics, 2009; 4. Escudier B, et al. *Lancet* 2007; 5. Roche Products Ltd. Avastin® (bevacizumab) Summary of Product Characteristics, 2008

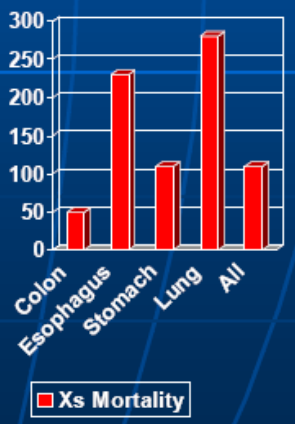
Three Key Factors for Successful Therapy Management in mRCC



Cancer in Ireland 2007: What affects your outcome?

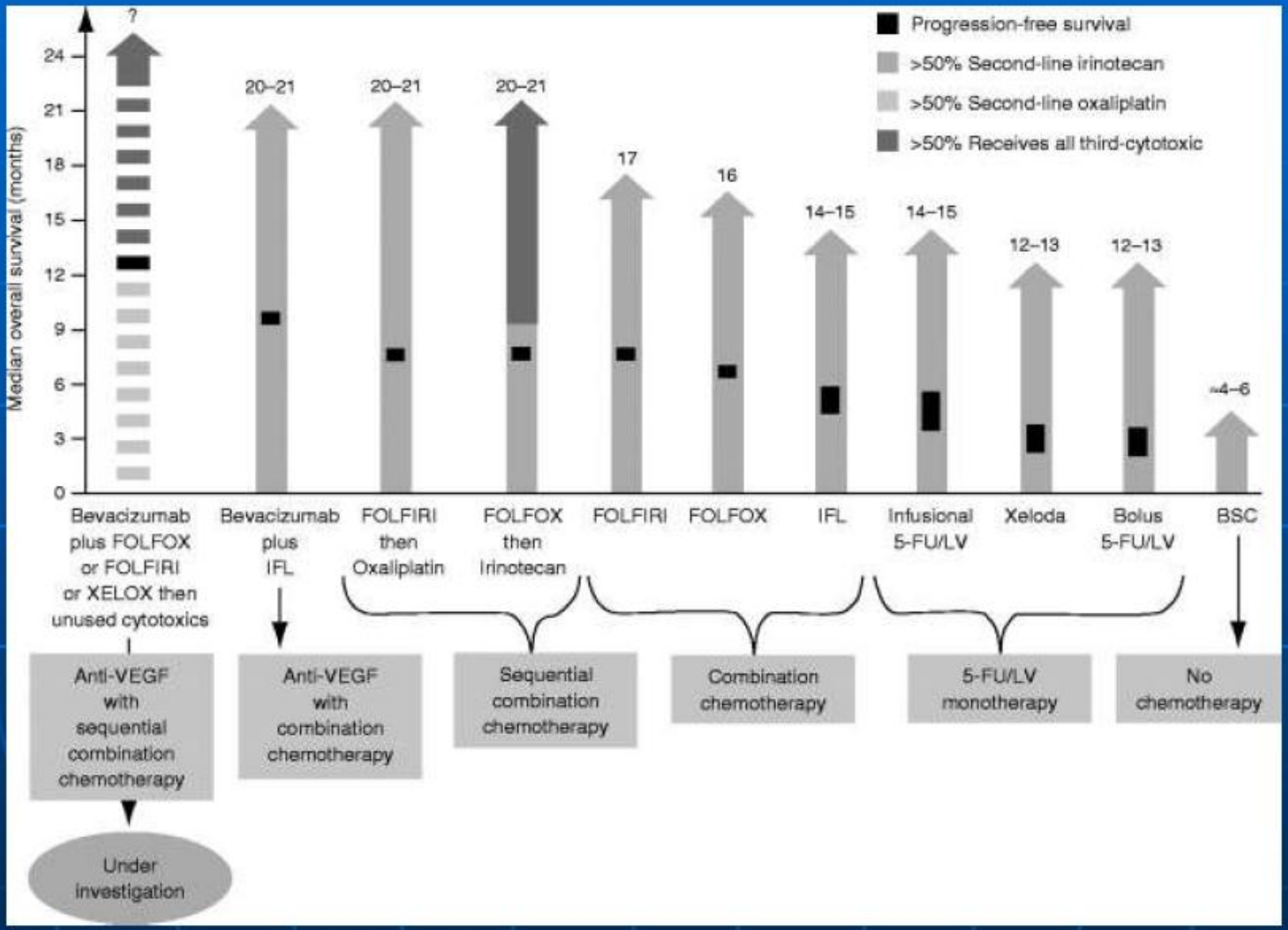
- What cancer you have and how extensive it is
- Where you live
- Where you are treated
- Who treats you
- How much you earn





Cancer Care 2007

- Doctor- surgeon, radiotherapist, medical oncologist
- Nurse specialist
- Pathologist
- Radiologist
- Psychooncologist
- Social worker
- Interventional pain
- GP
- Occupational Therapist
- Physiotherapist
- Dietician
- Palliative care
- Public health nurse
- Business manager
- Secretary
- Pharmacist
- Pastoral care
- IT



Venook, A. Oncologist 2005;10:250-261