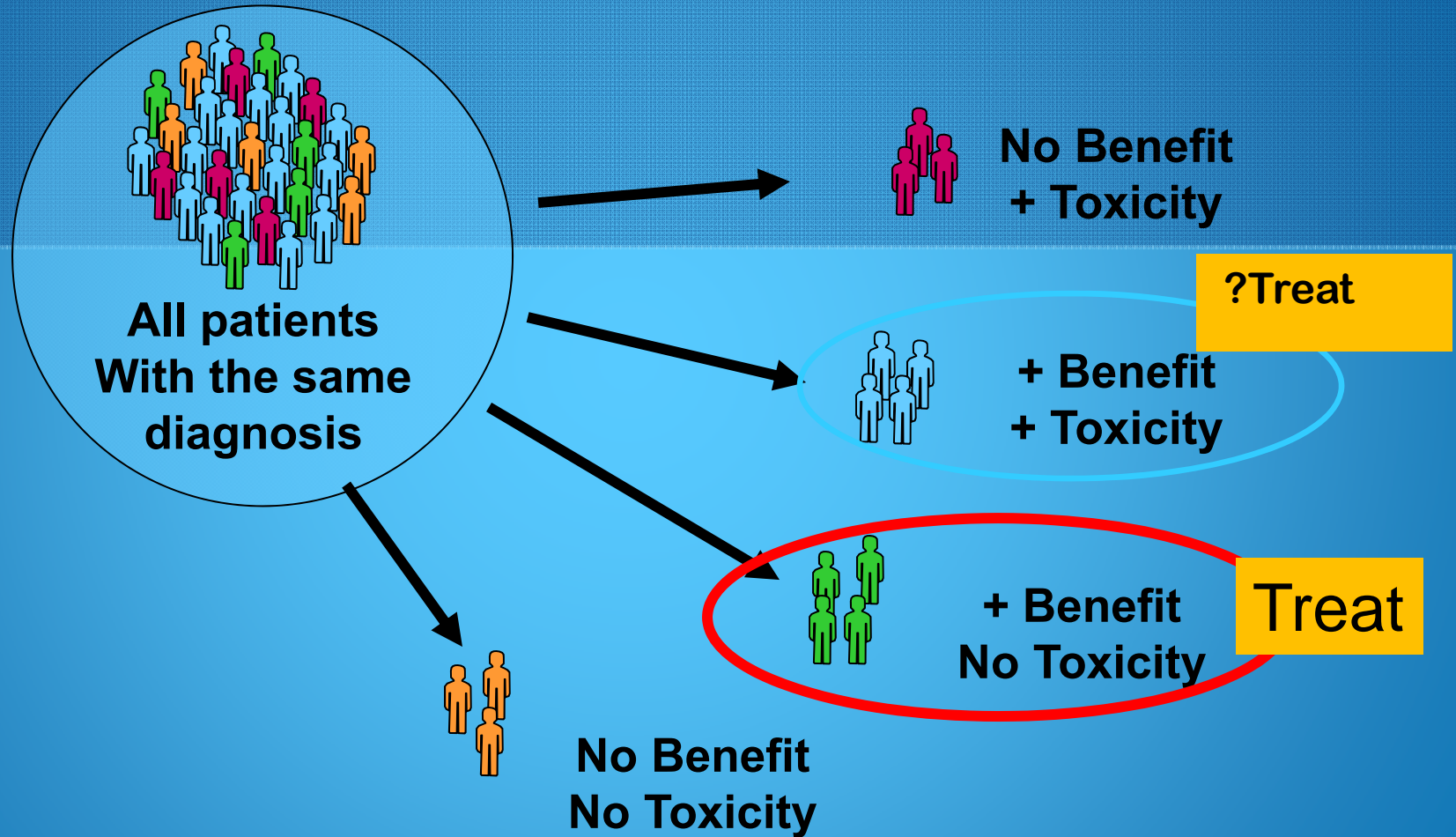




Emerging trend in cancer treatment: Systemic therapy

Assist. Prof. Ekaphop Sirachainan
Vice president
Thai Society of Clinical Oncology
(TSCO)

The Promise of Pharmacogenomic Testing Personalized treatment





Targeted therapy in cancer

- Antiangiogenesis
- Anti EGFR & HER2
- mTOR inhibitor
- Immunotherapy



Antiangiogenesis

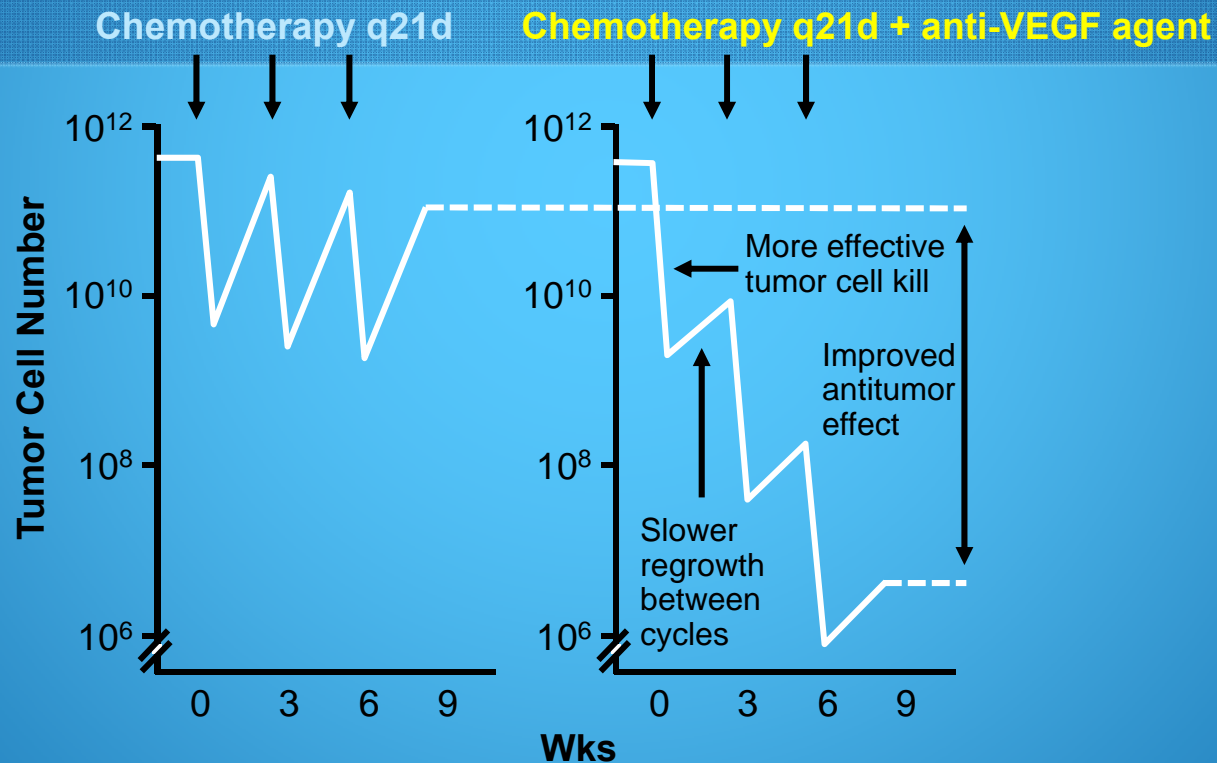
Bevacizumab



- 93% human, 7% murine
- recognizes all major isoforms of human VEGF, $K_d = 8 \times 10^{-10}M$
- terminal half-life 17–21 days

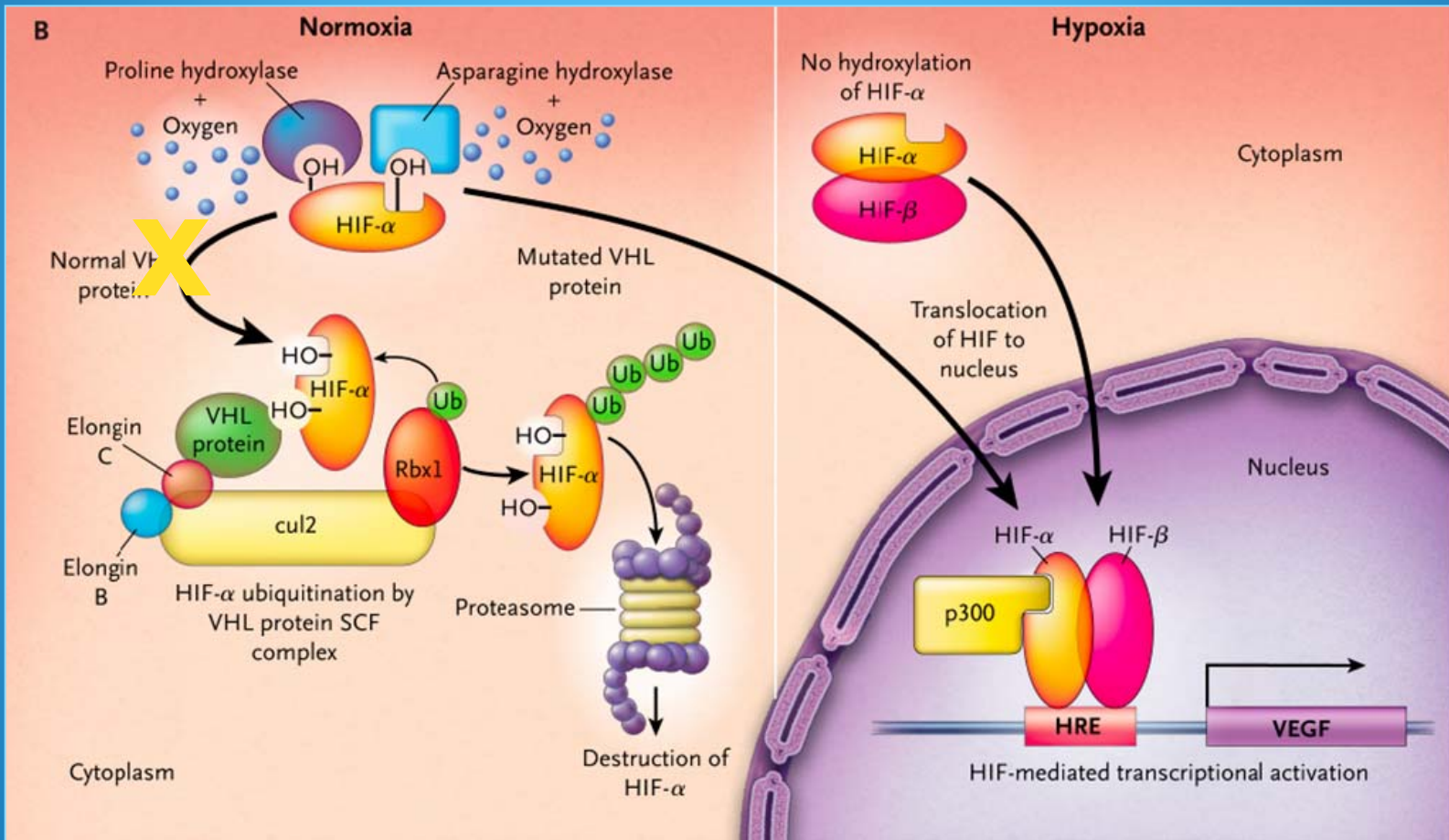
How Does Bev Enhance Chemo Efficacy?

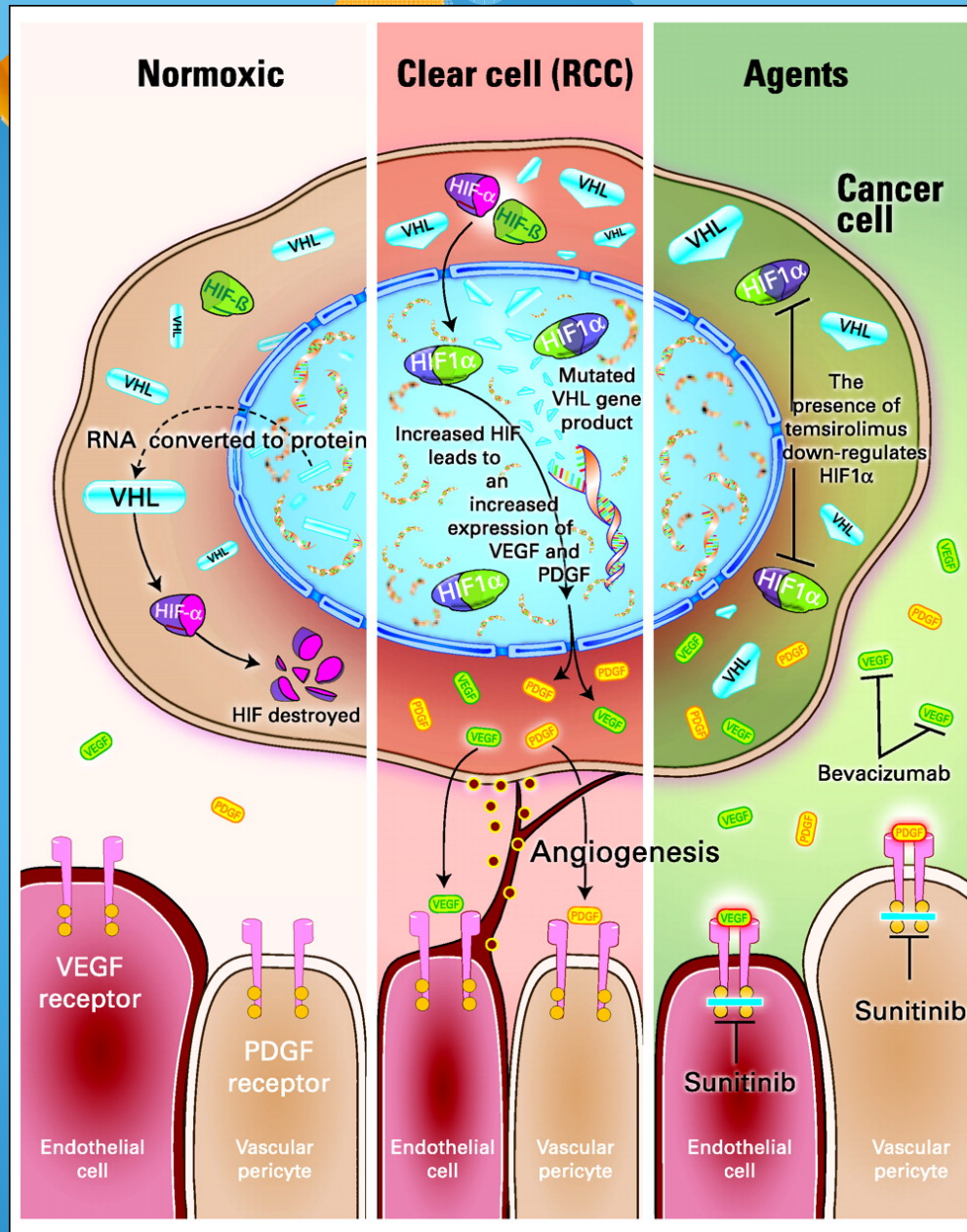
Applying a Brake During the Break



- Clinical implications of antiangiogenic therapies

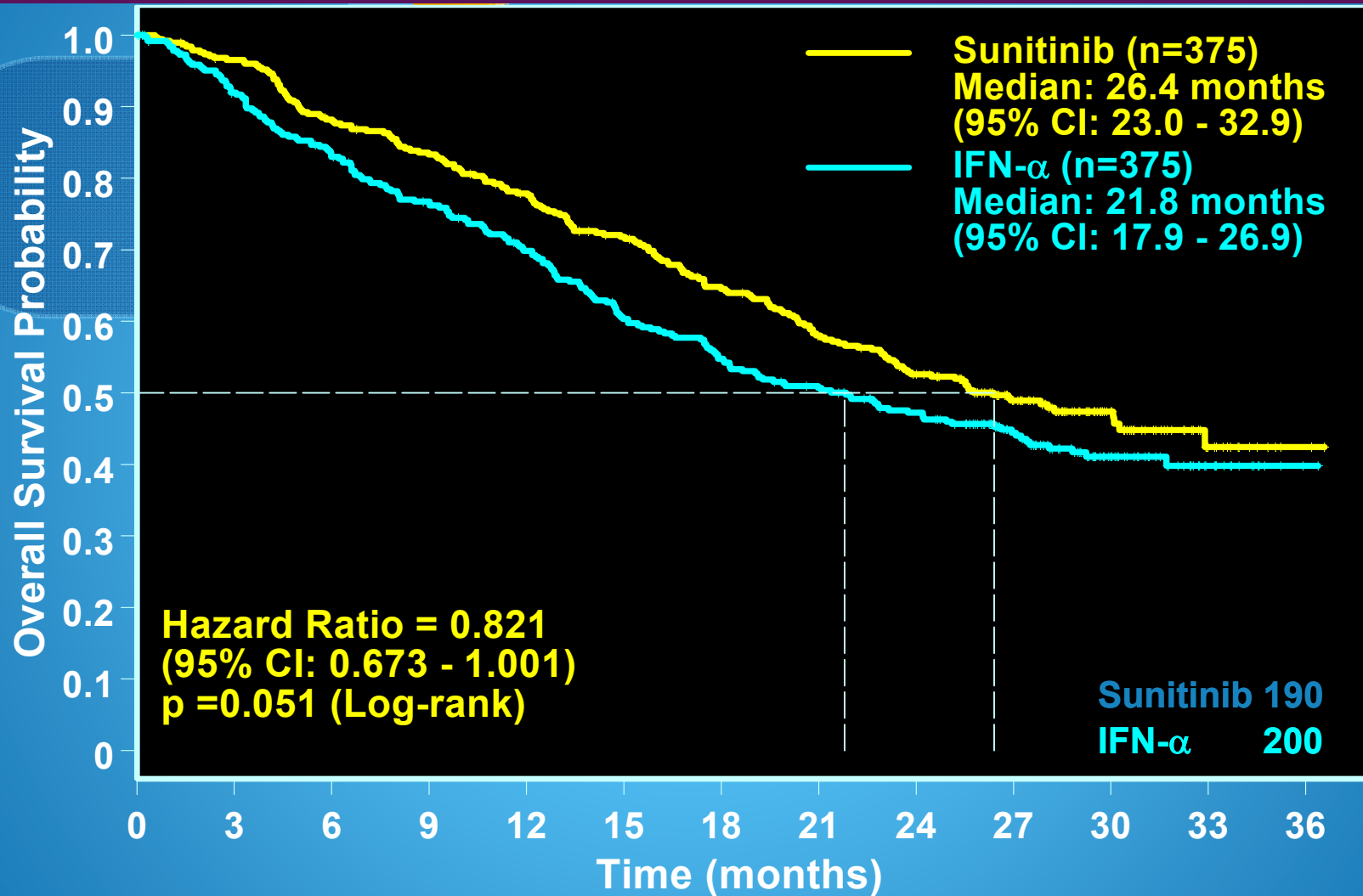
Molecular Mechanisms of the Development of Clear Cell RCC





Motzer, R. J. et al. J Clin Oncol; 24:5601-5608 2006

Final Overall Survival

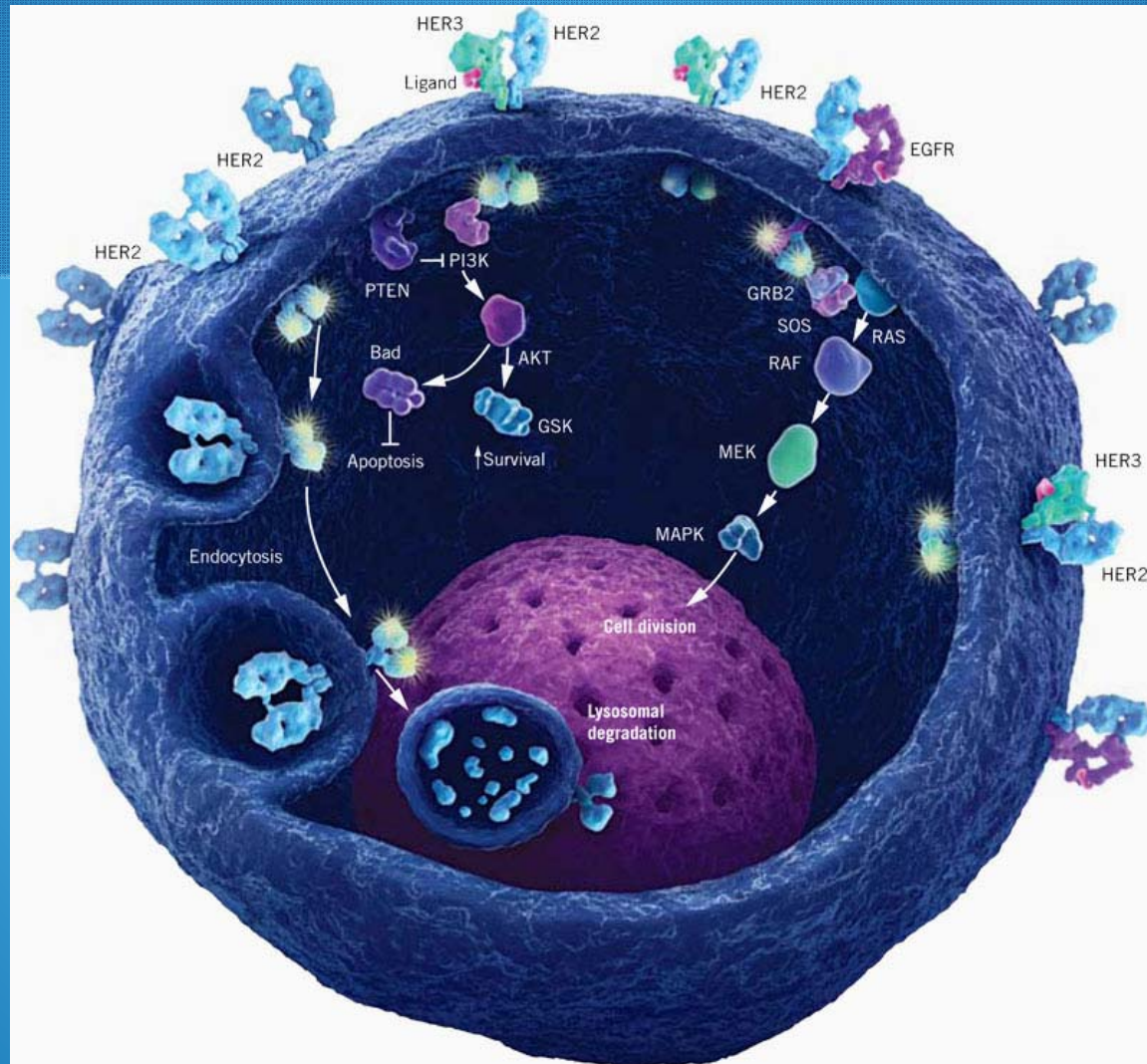


nDeath/nRisk Sunit	375	44 / 326	38 / 283	48 / 229	42 / 180	14 / 61	4 / 2
nDeath/nRisk IFN- α	375	61 / 295	46 / 242	52 / 187	25 / 149	15 / 53	1 / 1

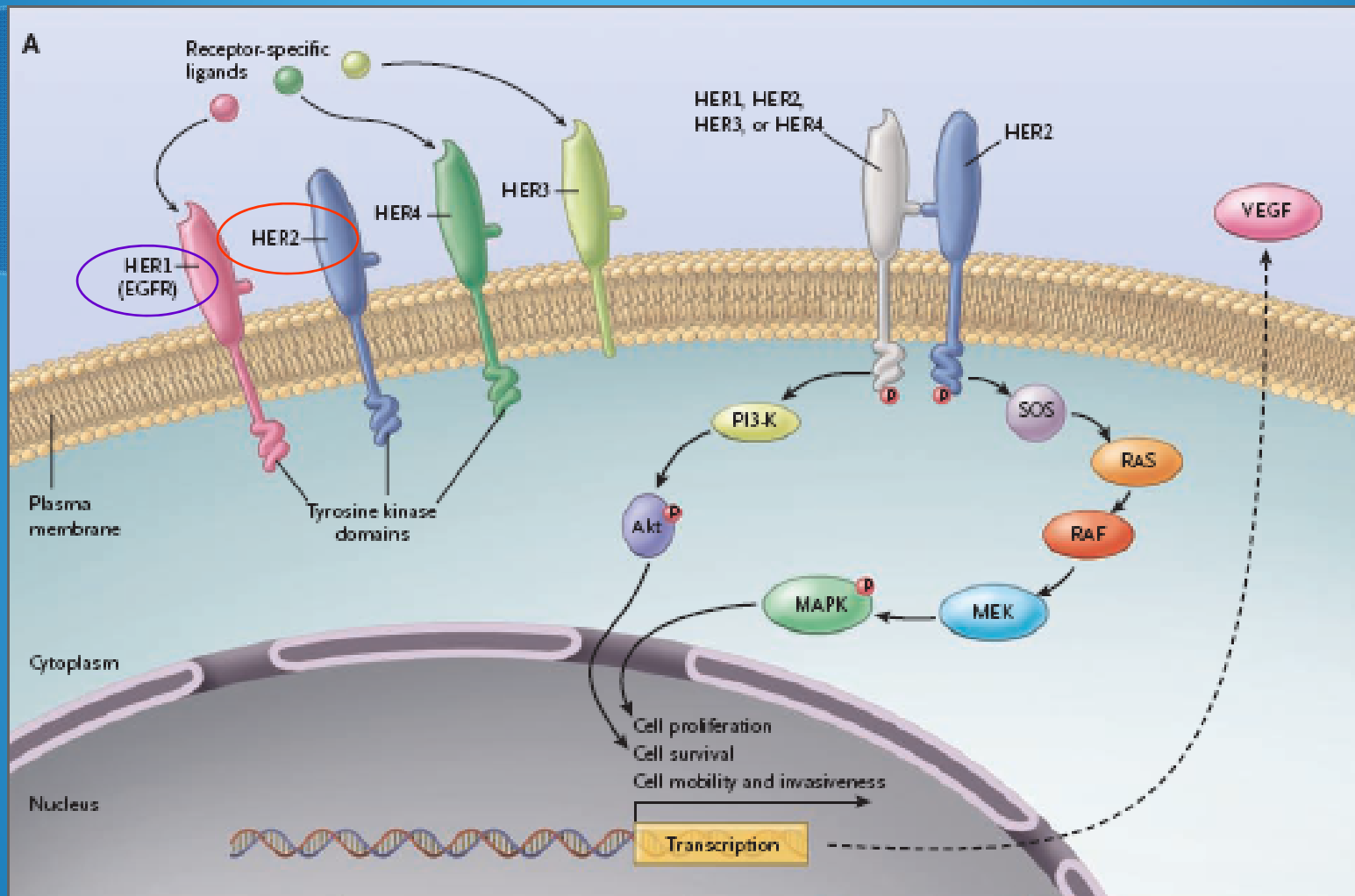


Anti EGFR & HER2

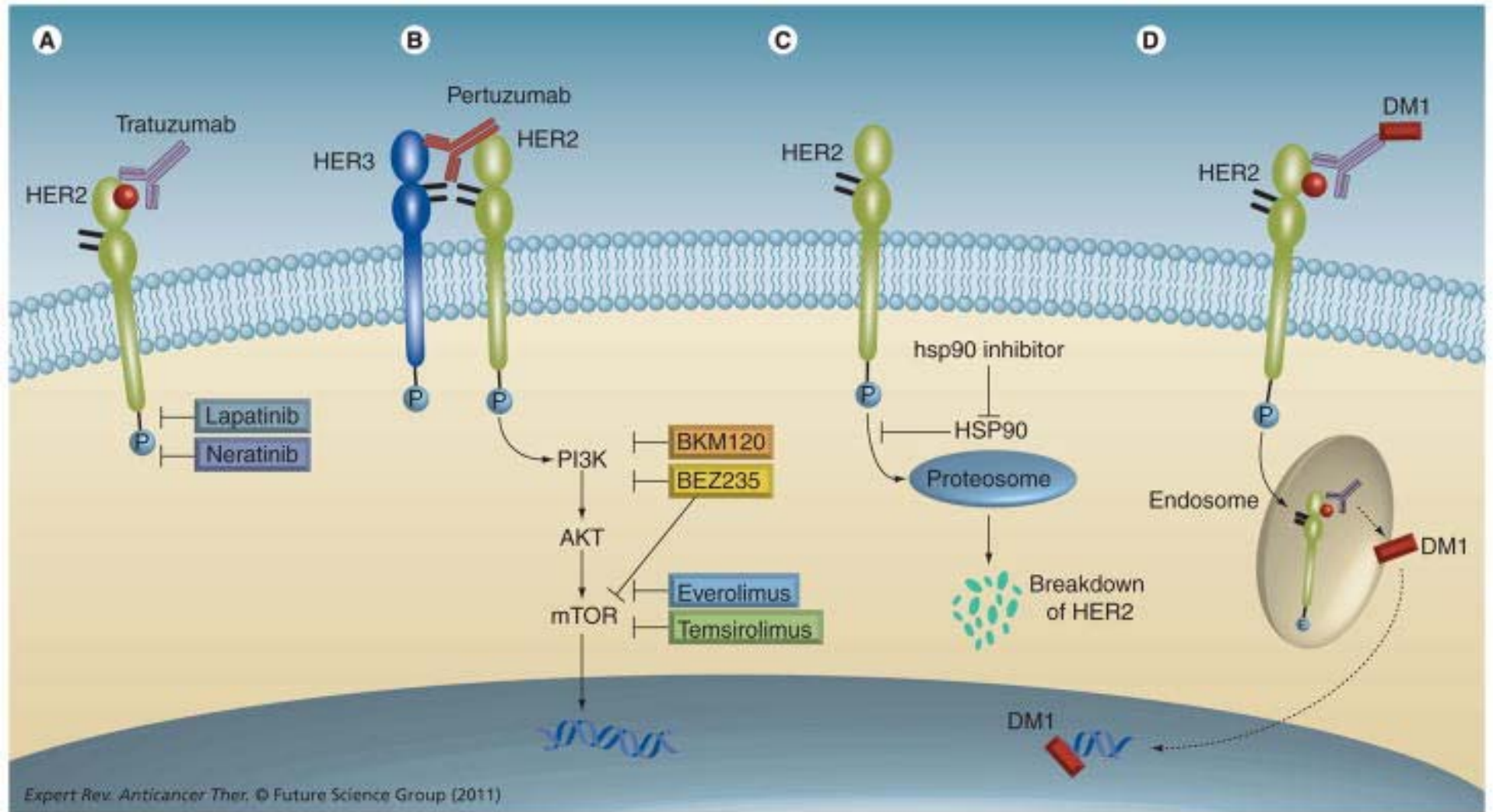
Her-2/neu overexpression



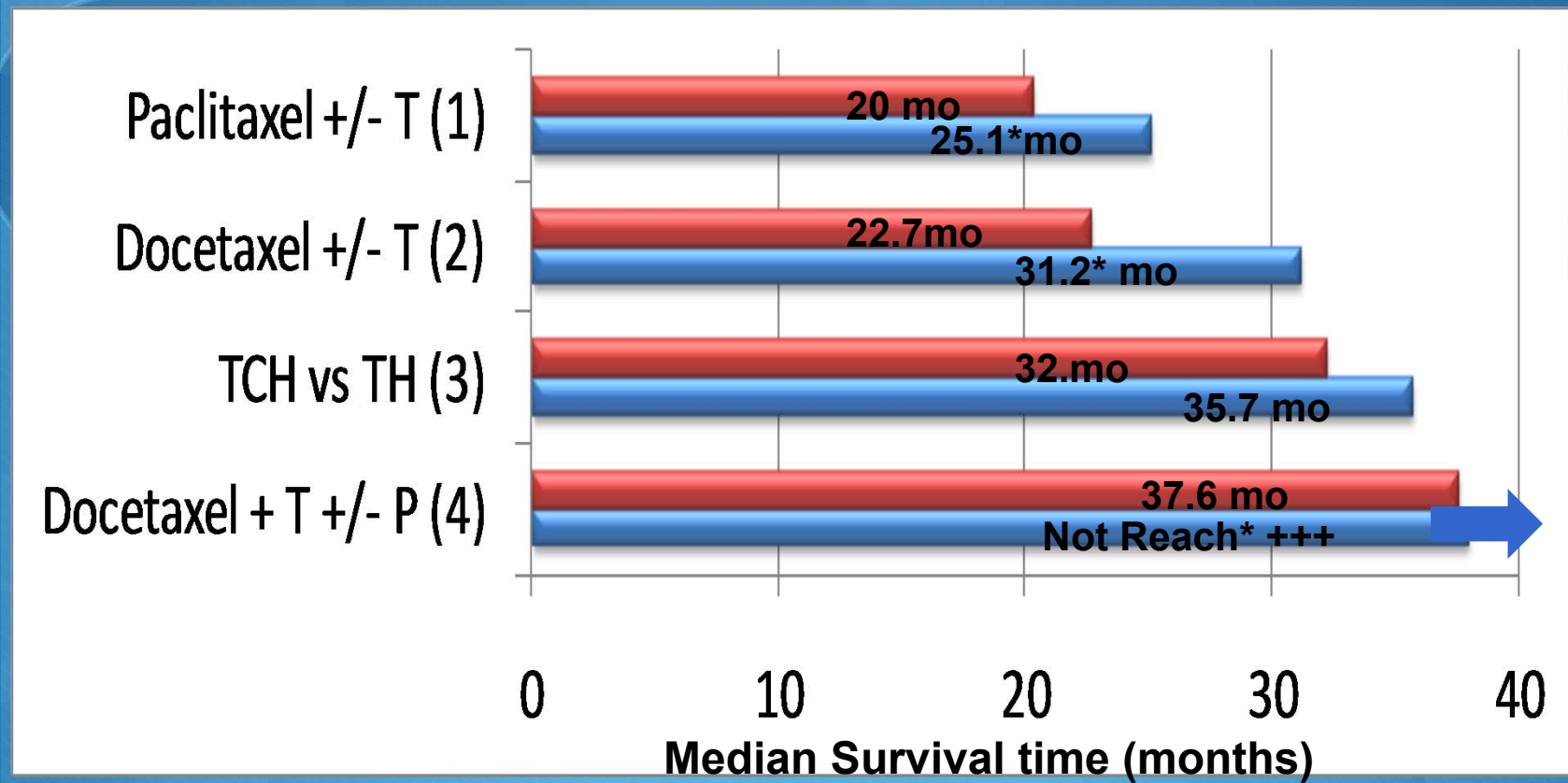
Human Epidermal Growth Factor (HER) receptors



Sites of action of novel agents for HER2-amplified breast cancer



Adding anti-HER2 with 1st line palliative chemotherapy improved overall survival in HER2 +ve metastatic Breast Cancer (2001 -2012)

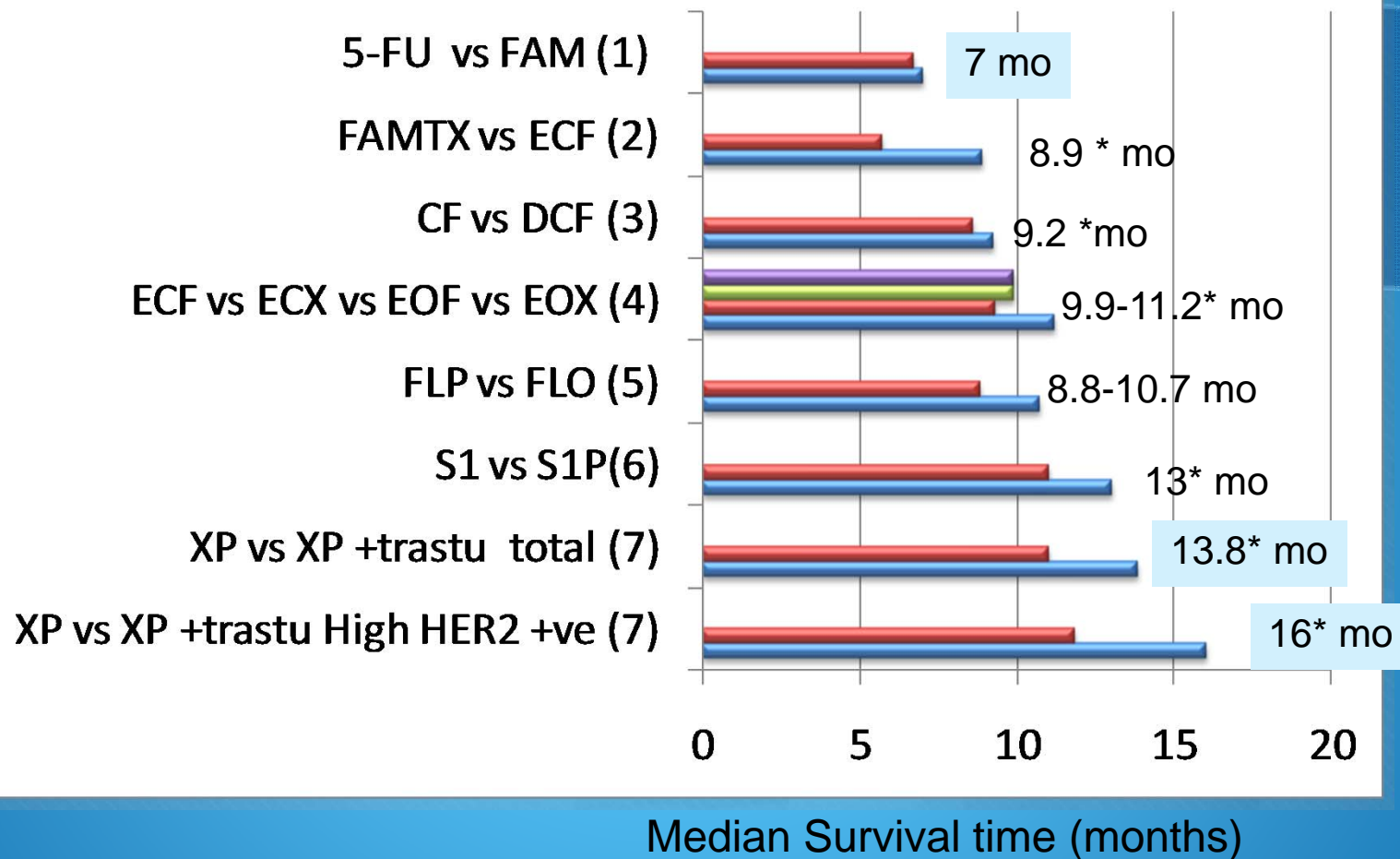


T, trastuzumab; P, pertuzumab; TCH: paclitaxel/carboplatin/trastuzumab;
 TH: paclitaxel/trastuzumab

1. Slamon DJ, et al. N Engl J Med. 2001;344:783-792. 2. Marty M, et al. J Clin Oncol. 2005;23:4265-4274. 3. Robert N, et al. J Clin Oncol. 2006;24:2786-2792. 4. Baselga J, et al. N Engl J Med. 2012;366:109-119.

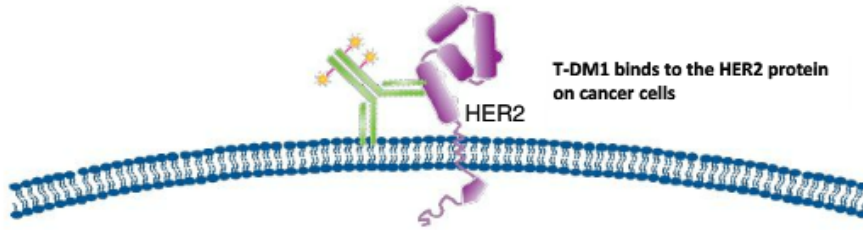
Improved Overall Survival with First line Palliative chemotherapy in

Metastatic Gastric Cancer (1980s -2012)

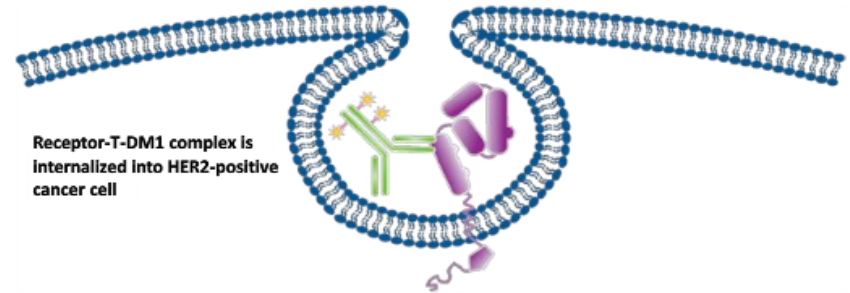


1. Kim NK et al. Cancer 1993;71:3813–18 ,2Webb A et al. J Clin Oncol 1997;15:261–7, 3.Van Cutsem, et al. J Clin Oncol 2006 , 4. Cunningham, et al. NEJM2008, 5 . Al-Batran, et al. J ClinOncol 2008 , 6.Koizumi et al. Lancet Oncol 2008, 7.Van Cutsem, et al. 2009 ASCO, Bang, et al. Lancet 2010

T-DM1 selectively delivers DM1 to HER2-positive tumor cells

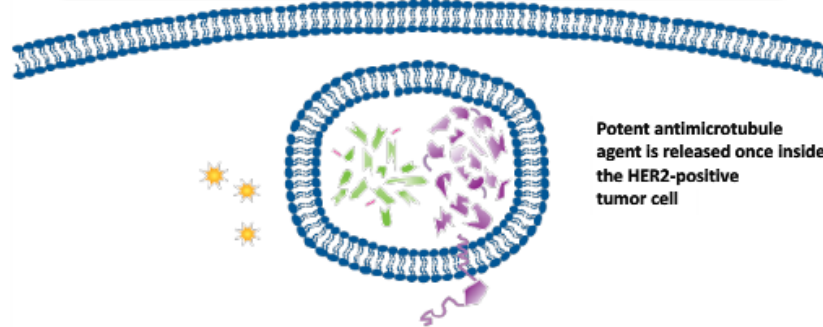


T-DM1 selectively delivers DM1 to HER2-positive tumor cells



T-DM1 selectively delivers DM1 to HER2-positive tumor cells

- Targeted intracellular delivery of a potent antimicrotubule agent, DM1
- Spares normal tissue from toxicity of free DM1
- Trastuzumab-like activity by binding to HER2



EMILIA 2nd/3rd line

T-DM1 vs Capecitabine + Lapatinib

- HER2-positive locally advanced BC or MBC
- Previously received trastuzumab-based therapy (N=980)

1:1

T-DM1 (3.6 mg/kg) q3w

Lapatinib (1250 mg/day, Days 1–21)
+ capecitabine (1000 mg/m², Days 1–14) q3w

- **Primary end points**

- PFS by IRF
- OS
- 1-year and 2-year survival rates
- Safety

- **Secondary end points**

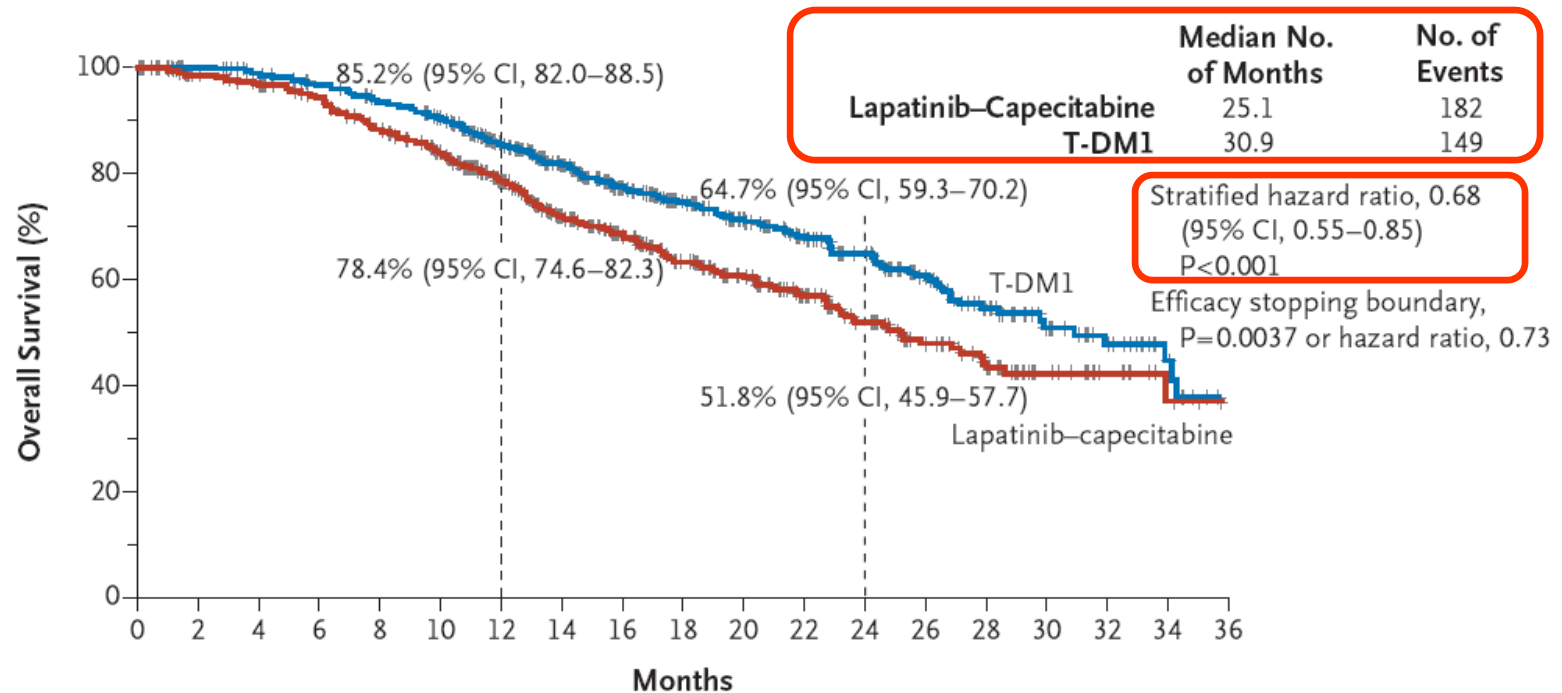
- PFS by INV, ORR, CBR, duration of response, quality of life (QOL), TTF

N Engl J Med 2012;367:1783-91.



TDM4370g

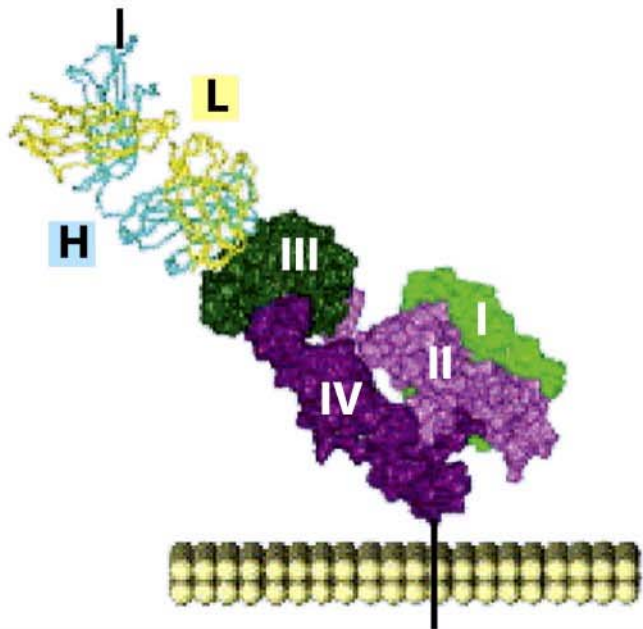
HER2-positive advanced breast cancer, who had previously been treated with trastuzumab and a taxane, to T-DM1 or lapatinib plus capecitabine



No. at Risk

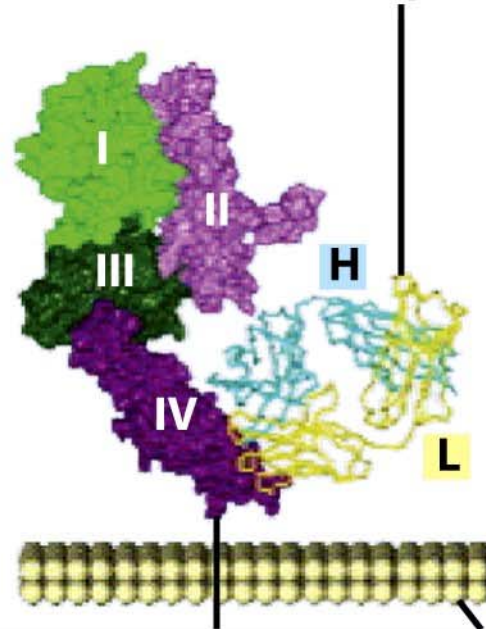
Lapatinib–capecitabine	496	471	453	435	403	368	297	240	204	159	133	110	86	63	45	27	17	7	4
T-DM1	495	485	474	457	439	418	349	293	242	197	164	136	111	86	62	38	28	13	5

cetuximab



**HER1
(EGF-R)**

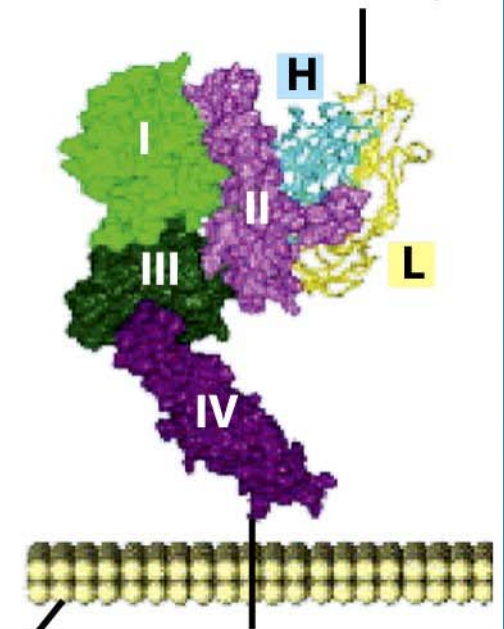
trastuzumab



HER2/Neu

**plasma
membrane**

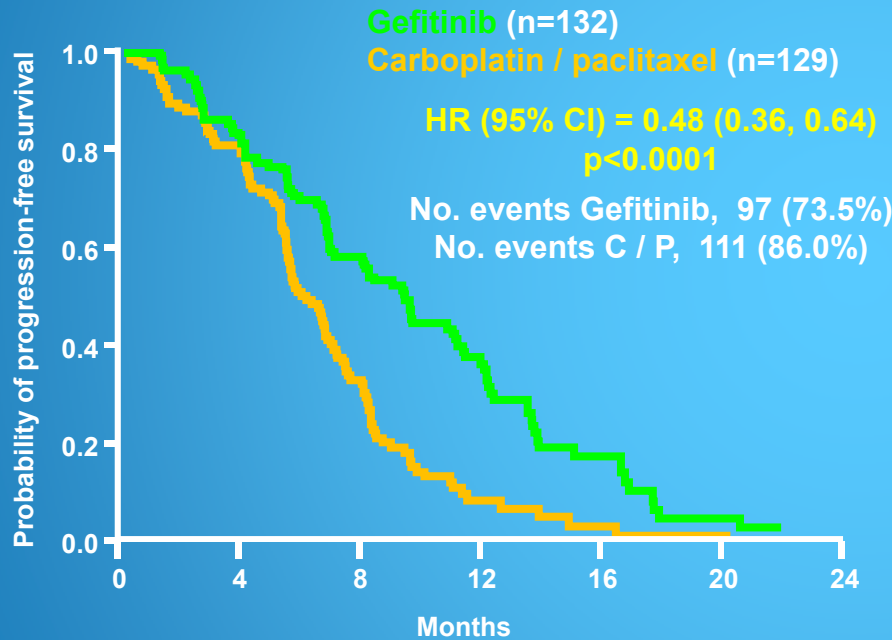
pertuzumab



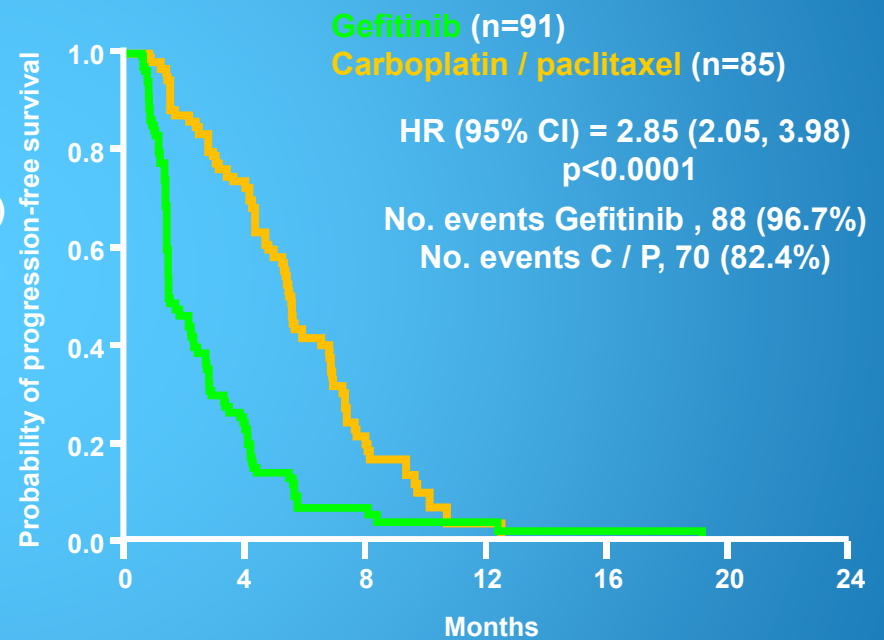
HER2/Neu

Progression-free survival in EGFR mutation positive and negative patients

EGFR mutation positive



EGFR mutation negative



At risk :

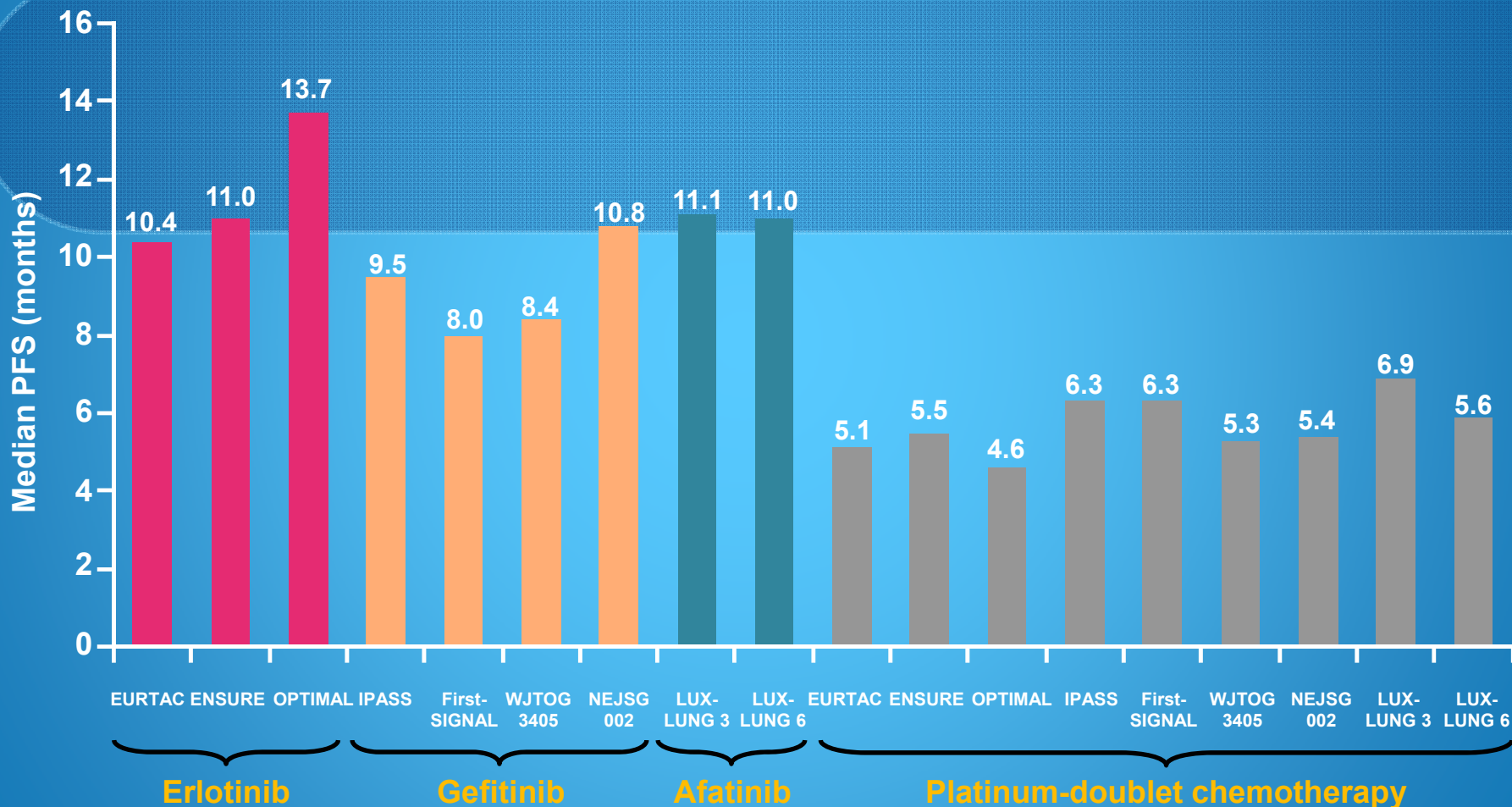
Gefitinib	132	108	71	31	11	3	0
C / P	129	103	37	7	2	1	0

Gefitinib	91	21	4	2	1	0	0
C / P	85	58	14	1	0	0	0

Treatment by subgroup interaction test, p<0.0001

ITT population
 Cox analysis with covariates

Median PFS in first-line phase III *EGFR* Mut+ studies

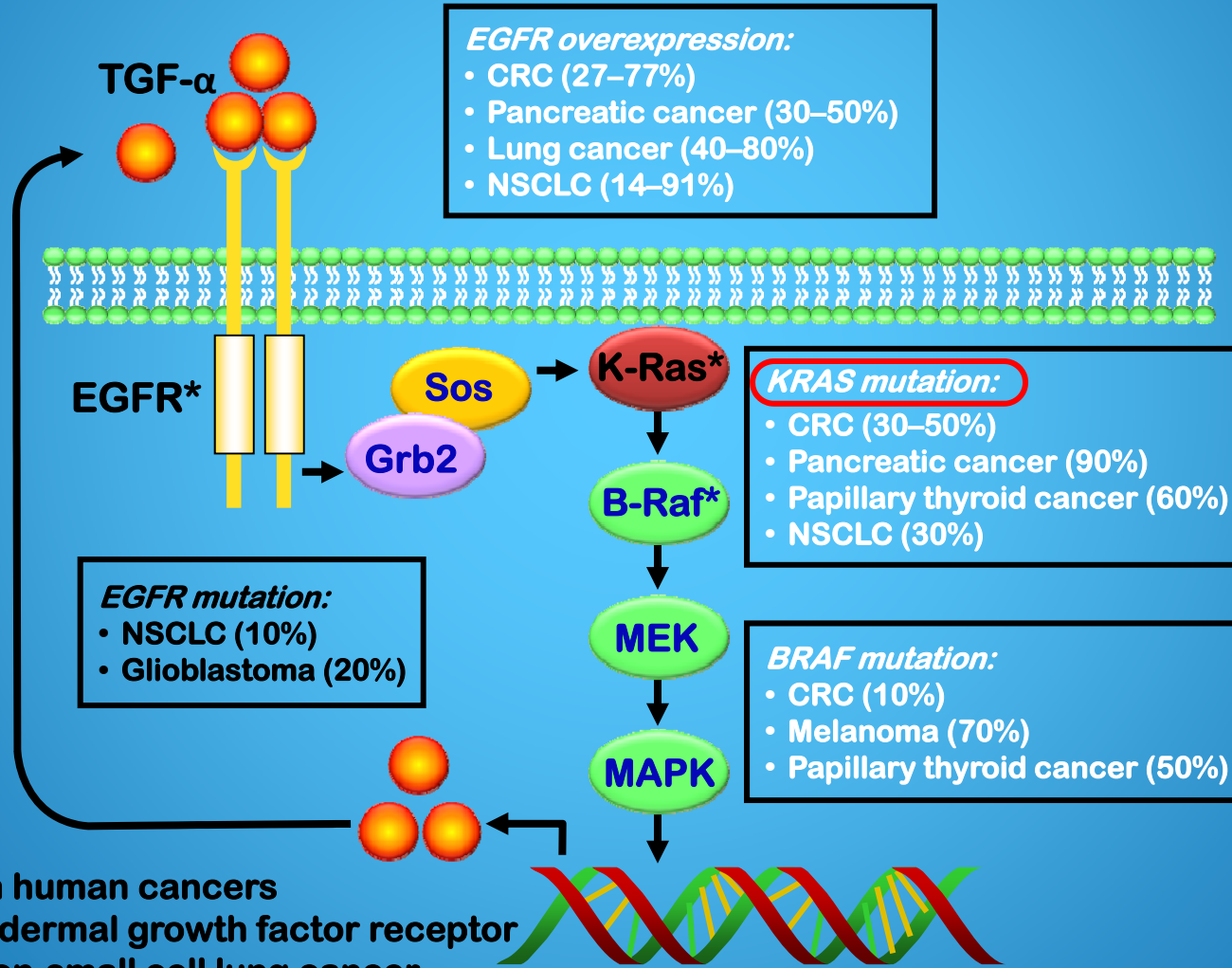


Rosell, et al. ESMO 2012; Wu, et al. WCLC 2013; Chen, et al. Ann Oncol 2013; Gefitinib SmPC 2010; Han, et al. J Clin Oncol 2012; Mitsudomi, et al. Lancet Oncol 2010; Maemondo, et al. N Engl J Med 2010; Sequist, et al. J Clin Oncol 2013; Wu, et al. ASCO 2013

A stylized graphic design featuring a large orange circle on the left side, partially overlapping a blue background. The blue background contains several overlapping, rounded rectangular shapes in various shades of blue. The word "KRAS" is written in white, bold, uppercase letters on one of the darker blue shapes. The overall aesthetic is modern and abstract.

KRAS

Targeting the EGFR pathway: *KRAS* mutations



*Mutated in human cancers
 EGFR = epidermal growth factor receptor
 NSCLC = non-small cell lung cancer
 TGF = transforming growth factor

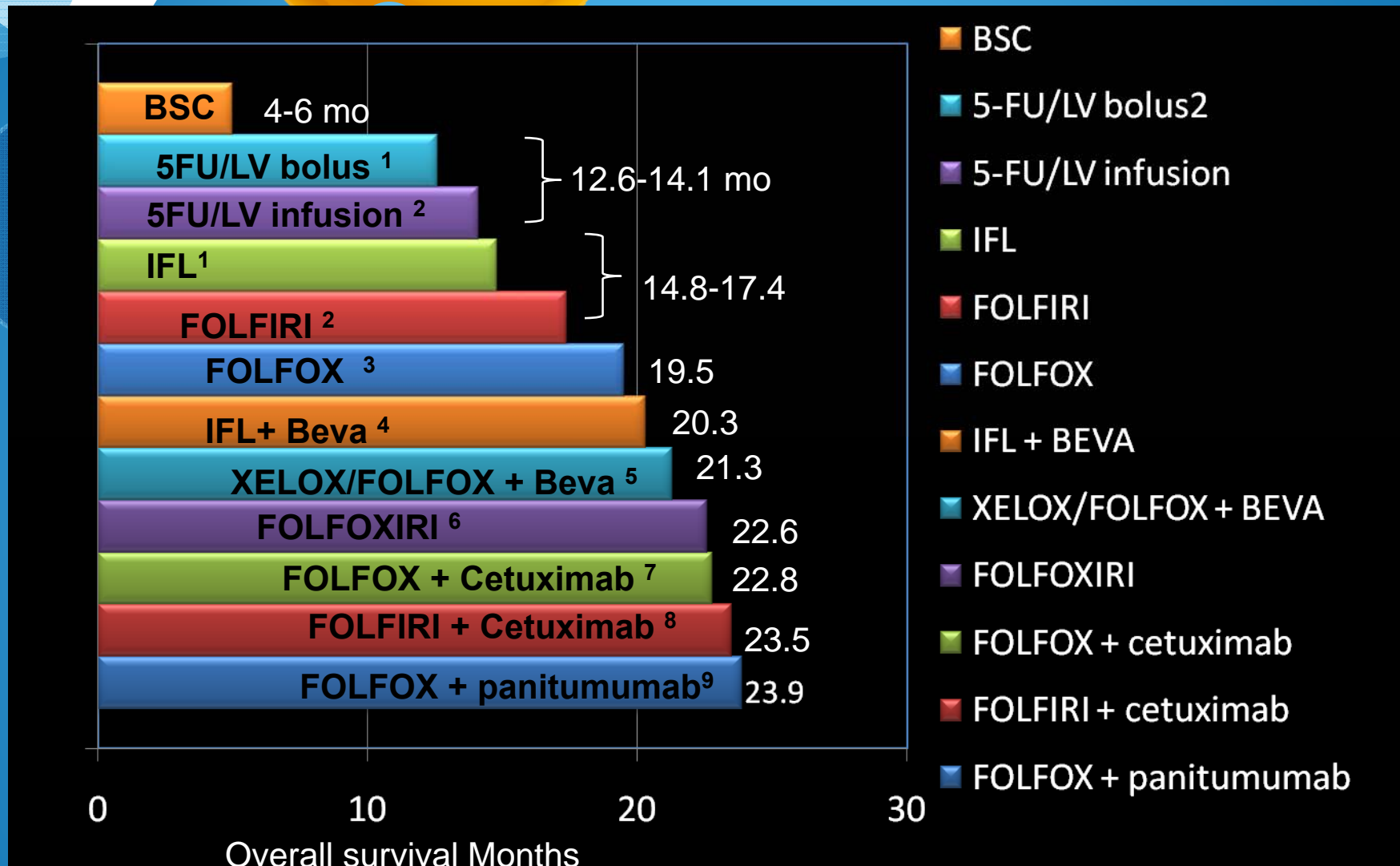
Adapted from Roberts and Der. *Oncogene* 2007

Prevalence and patterns of KRAS mutation in Thai patients

- 117 colorectal cancer patients' medical records treated in medical oncology unit between April 1999 - June 2009 were reviewed and their paraffin-embedded tumor specimens from primary tumor were tested for KRAS genotyping.

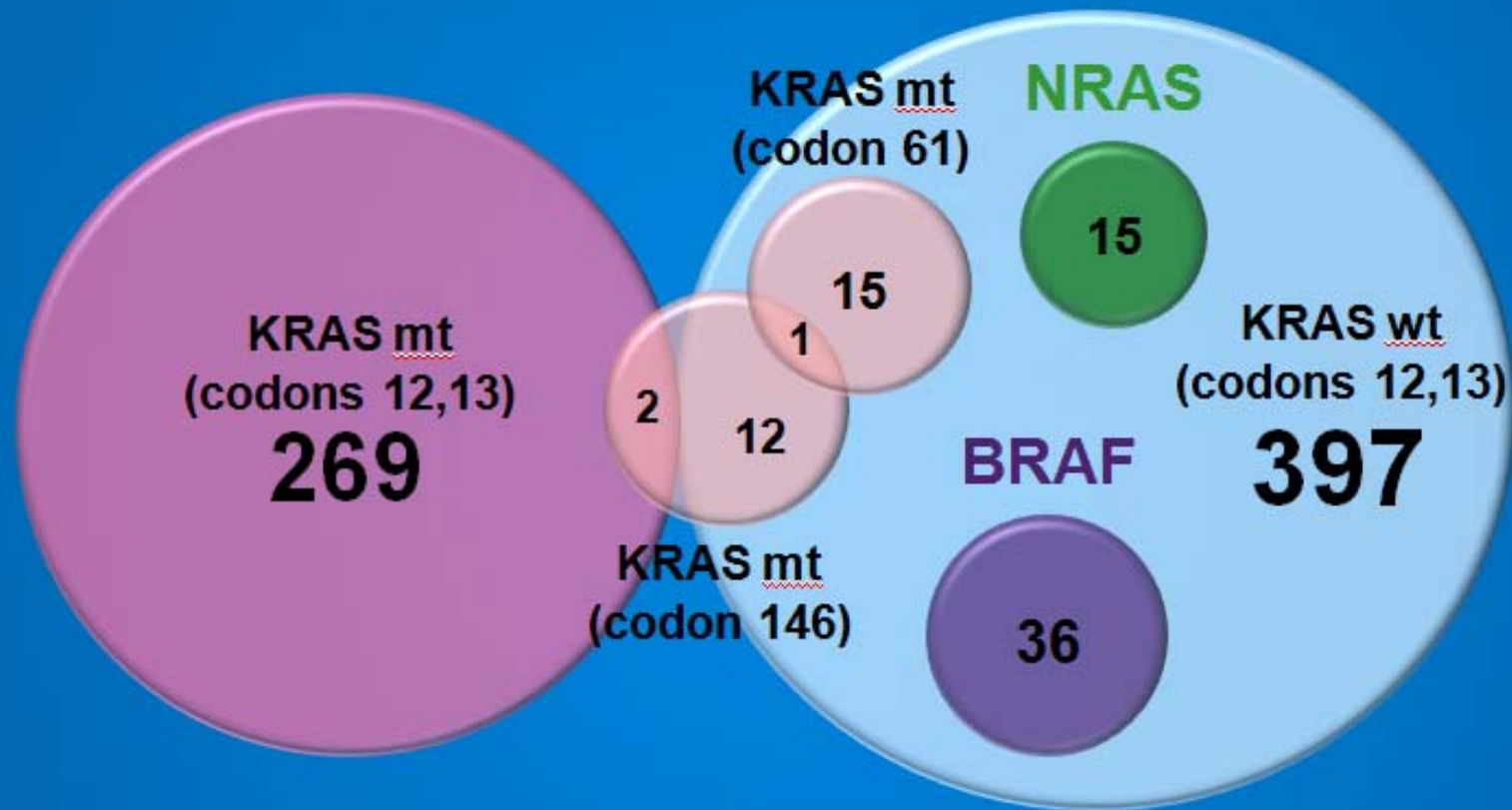
Mutation	Base change	n	Percent	Others
Negative mutation	No base change	83	70.9%	65%
Positive mutation		34	29.1%	35%
Gly12Asp	GGT → GAT at codon 12	14	41.2%	35.1-37%
Gly12Val	GGT → GTT at codon 12	8	23.5%	21.6%
Gly12Ala	GGT → GCT at codon 12	3	8.8%	5.4%
Gly12Cys	GGT → TGT at codon 12	2	5.9%	9.6%
Gly12Ser	GGT → AGT at codon 12	2	5.9%	5.6%
Gly13Asp	GGC → GAC at codon 13	5	14.7%	15-20.6%

Overall Survival from Metastatic CRC (First Line)



1. N Engl J Med 2000;343:905-14; 2. Lancet 2000;355:1041-7; 3. J Clin Oncol 2004;22:2330-3; 4. N Engl J Med 2004;350:2335-42; 5. J Clin Oncol 2008;26:2013-9; 6. J Clin Oncol 2007;25:1670-6; 7. Ann Oncol 2011;22:1535-46; 8. J Clin Oncol 2011;29:2011-9; 9. J Clin Oncol 2011;29(Suppl):3510(oral).

What we know about mutations in the EGFR pathway



Total n=747; triple wt n=397

BRIM3: Vemurafenib vs Dacarbazine in *BRAF* V600E–Positive Melanoma

Patients with untreated, unresectable stage IIIc/IV melanoma and confirmed *BRAF* V600E mutation

(N = 675)

Vemurafenib 960 mg PO BID
(n = 337)

Dacarbazine 1000 mg/m² q3w
(n = 338)

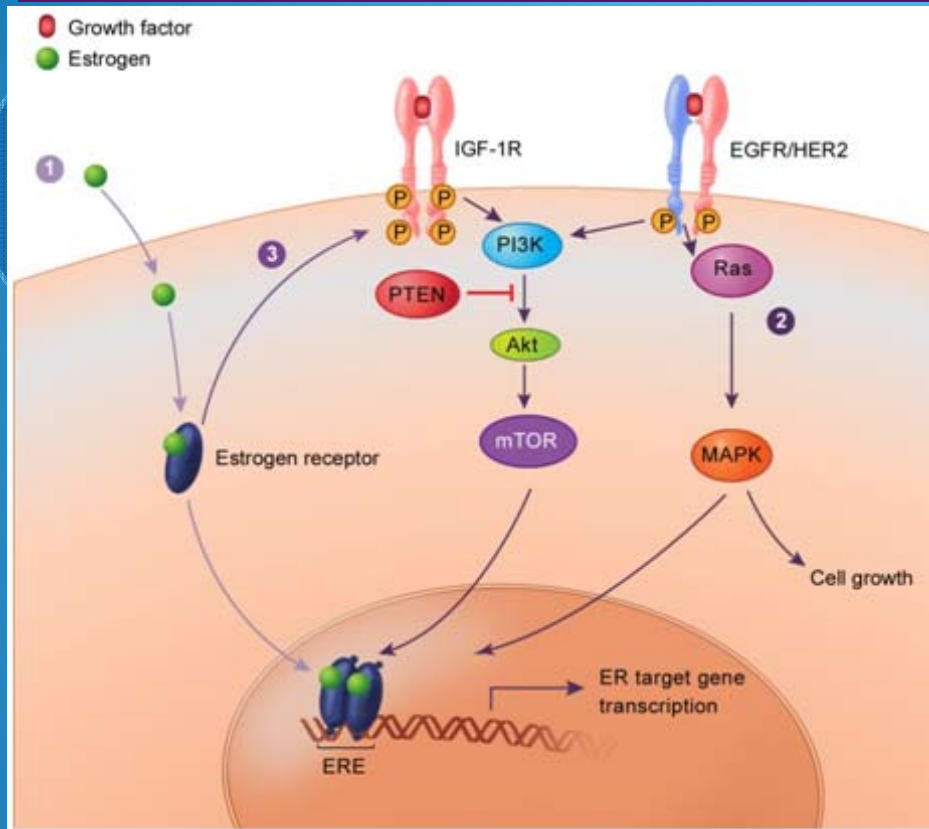
- Randomized, nonblinded phase III trial
- OS, PFS improved in all prespecified subgroups (age, sex, stage, PS, LDH)

Outcome	Vemurafenib (n = 336)	Dacarbazine (n = 336)	HR (95% CI)	P Value
Estimated 6-mo OS, %	84	64	0.37 (0.26-0.55)	< .0001
Median PFS, mos	5.3	1.6	0.26 (0.20-0.33)	< .0001
ORR, %	48.4	5.5		
▪ CR	0.9	0		
▪ PR	47.5	5.5		



mTOR inhibitor

Crosstalk Between ER and PI3K/AKT/mTOR Signaling: Rationale for Dual Inhibition



Adapted from Johnson SR. *Clin Breast Cancer*. 2009;9(suppl 1):S28-S36.

- mTORC1 activates ER in a ligand-independent fashion¹
- Estradiol suppresses the apoptosis induced by PI3K/AKT/mTOR blockade²
- **Hyperactivation of the PI3K/AKT/mTOR pathway is observed in endocrine-resistant breast cancer cells³**
- mTOR is a rational target to enhance the efficacy of endocrine therapy

Abbreviations: AKT, protein kinase B; EGFR, epidermal growth factor receptor; ER, endocrine receptor; ERE, endocrine response element; HER2, human epidermal growth factor receptor-2; IGF-1R, insulin-like growth factor-1 receptor; MAPK, mitogen-activated protein kinase; mTOR, mammalian target of rapamycin; mTORC1, mTOR complex 1; PI3K, phosphatidylinositol-3-kinase; PTEN, phosphatase and tensin.

1. Yamnik RL, et al. *J Biol Chem*. 2009;284(10):6361-6369;
2. Crowder RJ, et al. *Cancer Res*. 2009;69(9):3955-3962;
3. Miller TW, et al. *J Clin Invest*. 2010;120(7):2406-2413.

Interrupt crosstalk pathway between ER and other signaling pathways with "mTOR inhibitor"

BOLERO-2: Exemestane ± Everolimus in Non-Steroidal Aromatase Inhibitor-Refractory Advanced Breast Cancer

**Phase 3 study;
N = 724**

Postmenopausal women with ER⁺ HER2⁻ advanced breast cancer refractory to letrozole or anastrozole

Recurrence during or within 12 mo after end of adjuvant treatment or progression during or within 1 mo after end of treatment for advanced disease

**Everolimus 10 mg/d +
Exemestane 25 mg/d
(n = 485)**

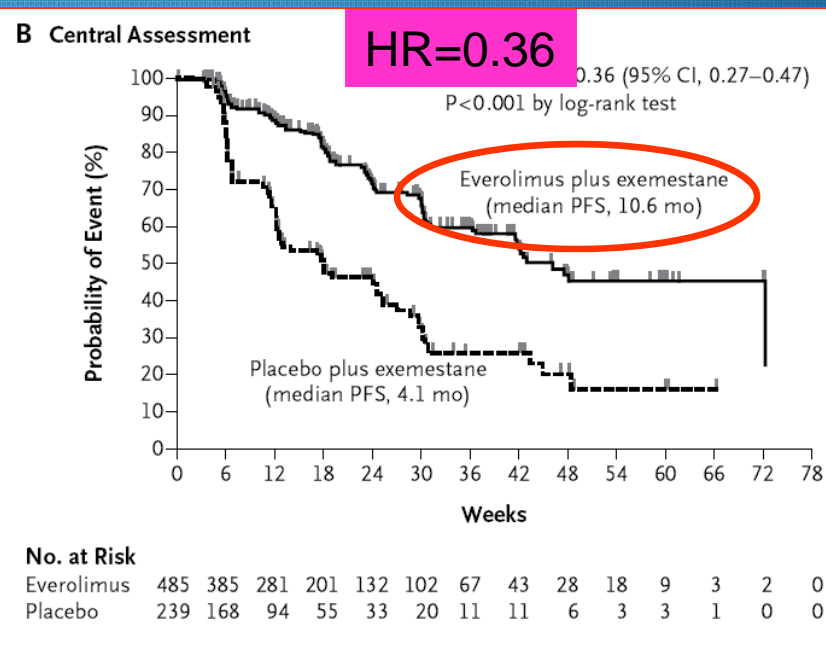
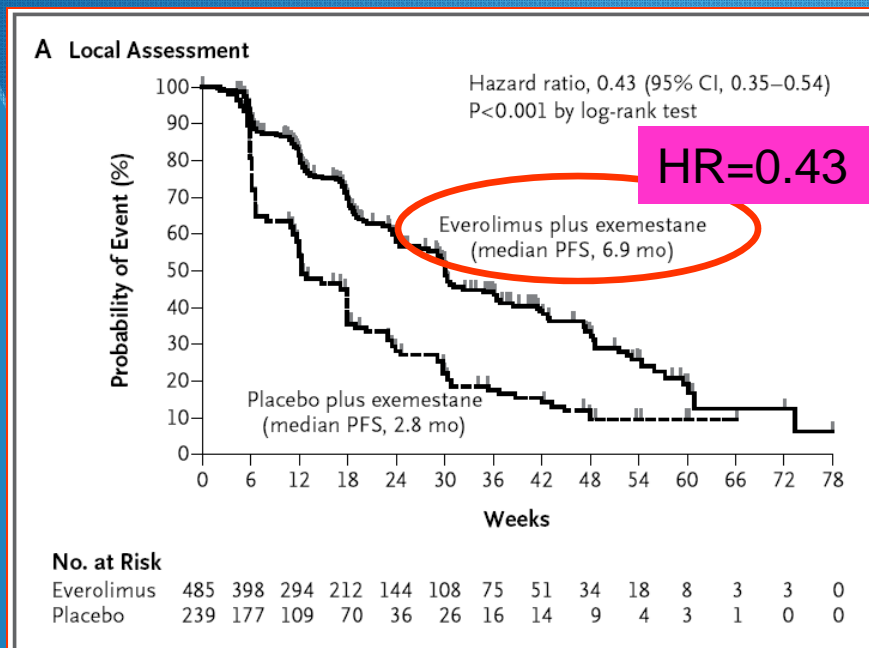
**Placebo +
Exemestane 25 mg/d
(n = 239)**

**Primary endpoint:
PFS**

**Secondary endpoints:
OS, ORR, CBR, safety, QoL, bone markers**

Everolimus in Postmenopausal Hormone-Receptor-Positive Advanced Breast Cancer

José Baselga, M.D., Ph.D., Mario Campone, M.D., Ph.D.,



- Median PFS was 6.9 months with everolimus plus exemestane and 2.8 months with placebo plus exemestane, according to assessments by local investigators (HR for progression or death, 0.43; 95% CI, 0.35 to 0.54; P<0.001).
- Median PFS was 10.6 mo and 4.1 mo, HR 0.36; 95% CI, 0.27 to 0.47; P<0.001 central assessment

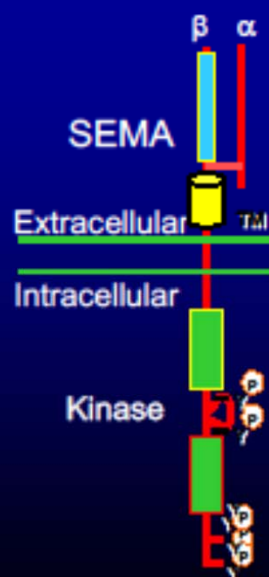


ALK inhibitor

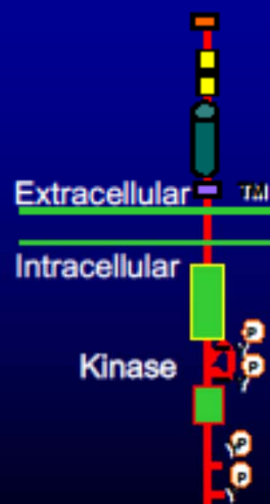
Crizotinib, PF-02341066

Potent & selective ATP competitive oral inhibitor of MET and ALK kinases and their oncogenic variants

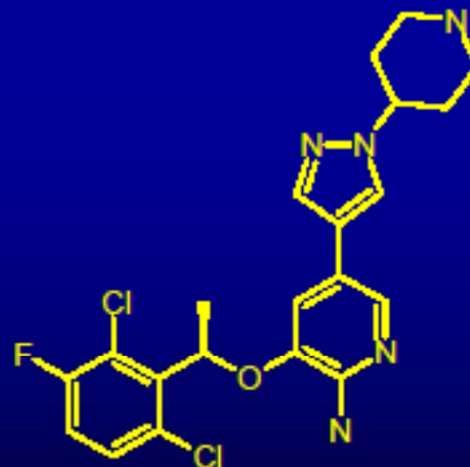
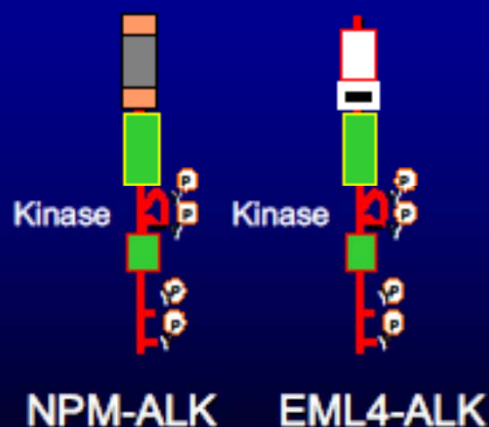
MET



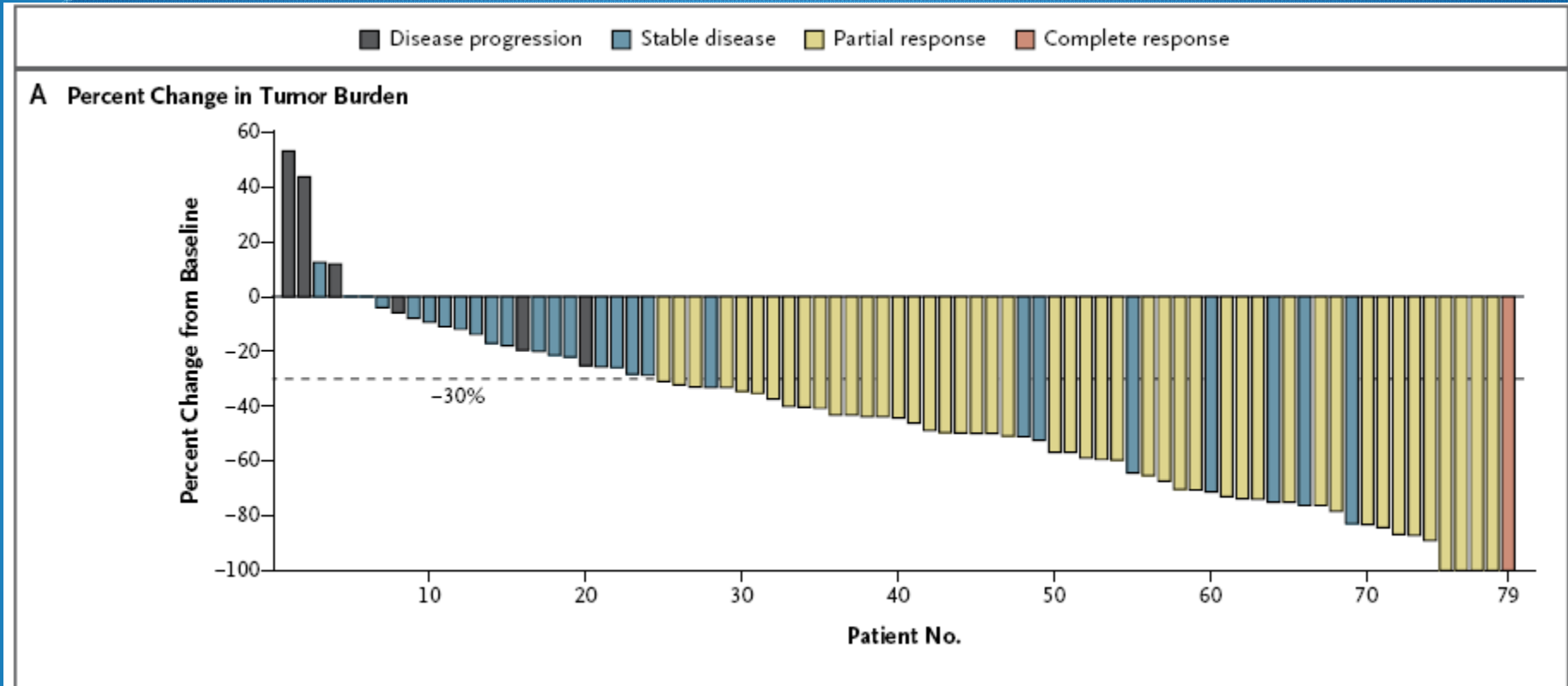
ALK



Cytoplasmic Fusion Variants of ALK



Tumor Responses to Crizotinib (PF-02341066) for Patients With ALK-positive NSCLC



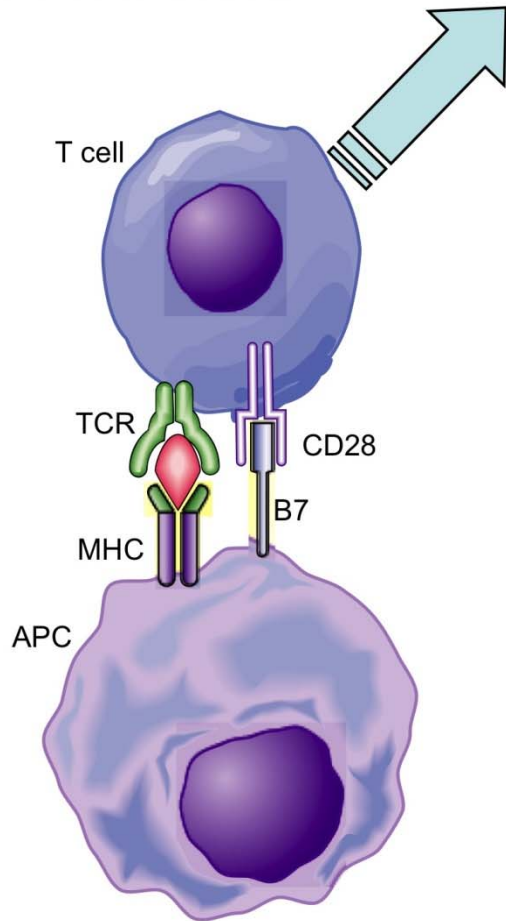
- **ORR: 57%**
- **DCR at 8 weeks: 87%**

A stylized graphic design featuring a large orange sun in the top left corner, several light blue thought bubbles of varying sizes, and a dark blue pen nib pointing towards the center. The background is a solid blue color. The word "Immunotherapy" is written in white, bold, sans-serif font on a dark blue, rounded rectangular banner that is part of the pen nib graphic.

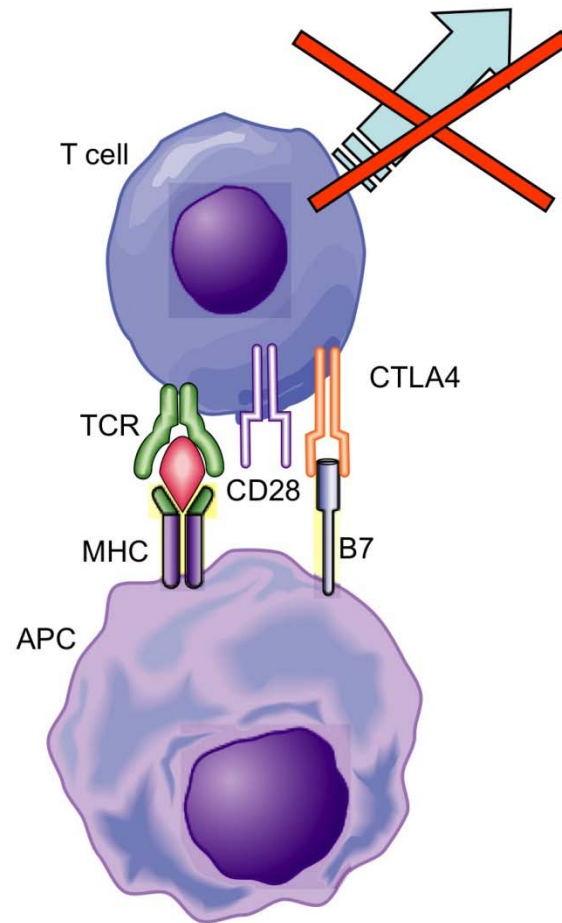
Immunotherapy

Ipilimumab Blocks Negative Signaling From CTLA-4

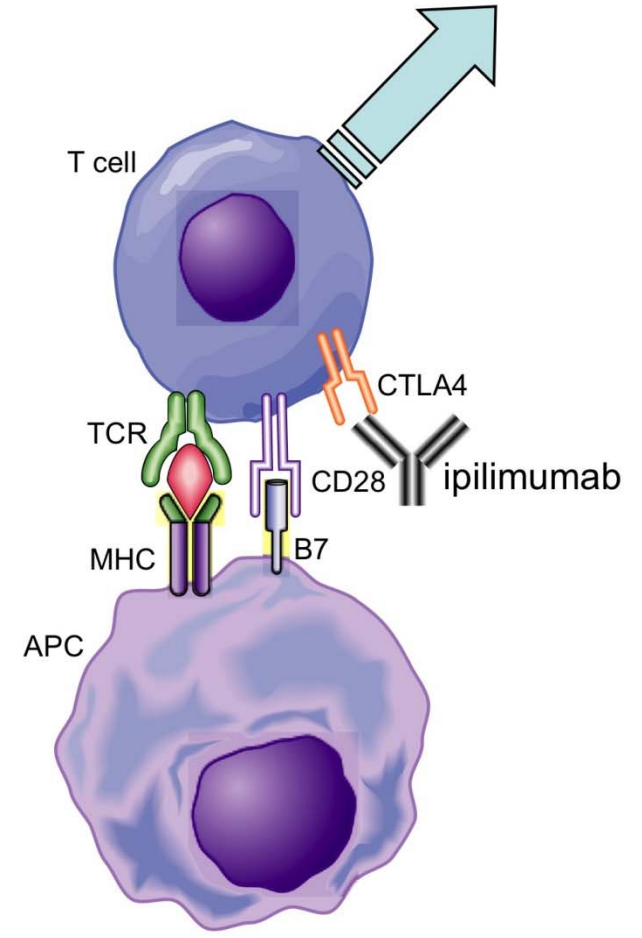
Co-stimulation via CD28:
T-cell activation



CTLA-4 blocks co-stimulation:
No T-cell activation



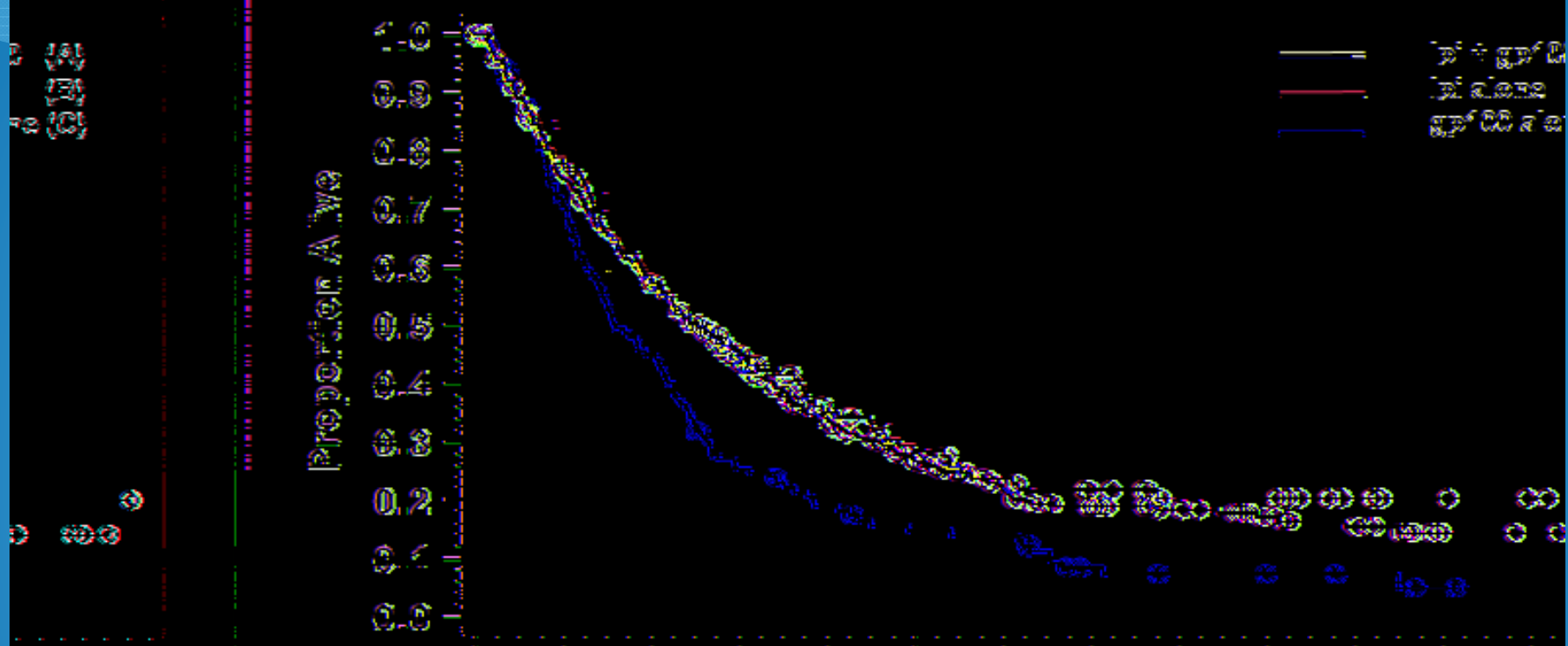
Ipilimumab blocks CTLA-4:
T-cell activation



Adapted from Lebbé et al. ESMO 2008

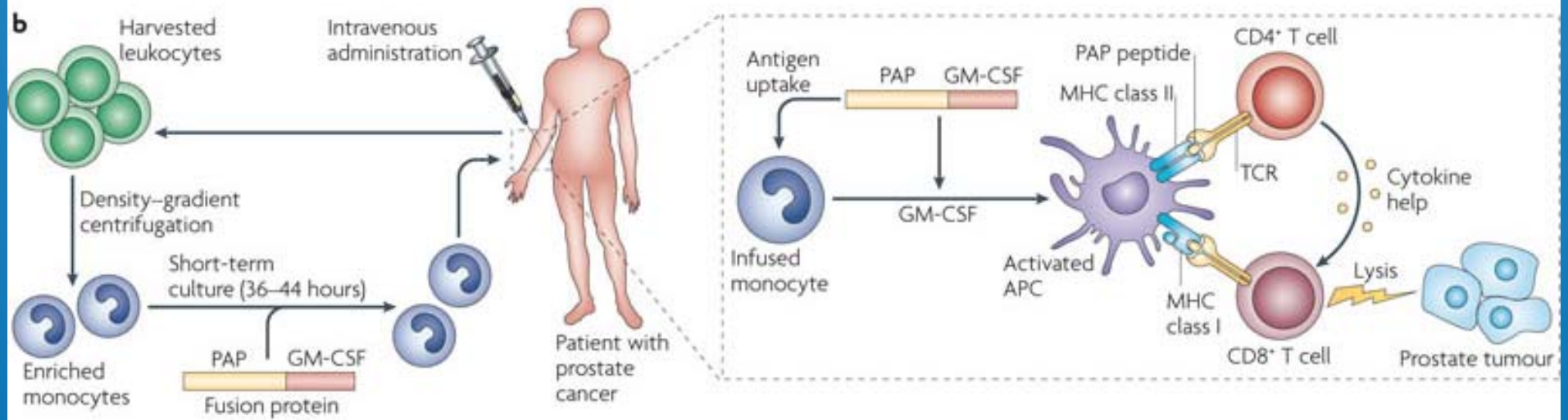
APC, antigen-presenting cell; CTLA-4, cytotoxic T-lymphocyte antigen-4; MHC, major histocompatibility complex; TCR, T-cell receptor.

Weighted Average Analysis

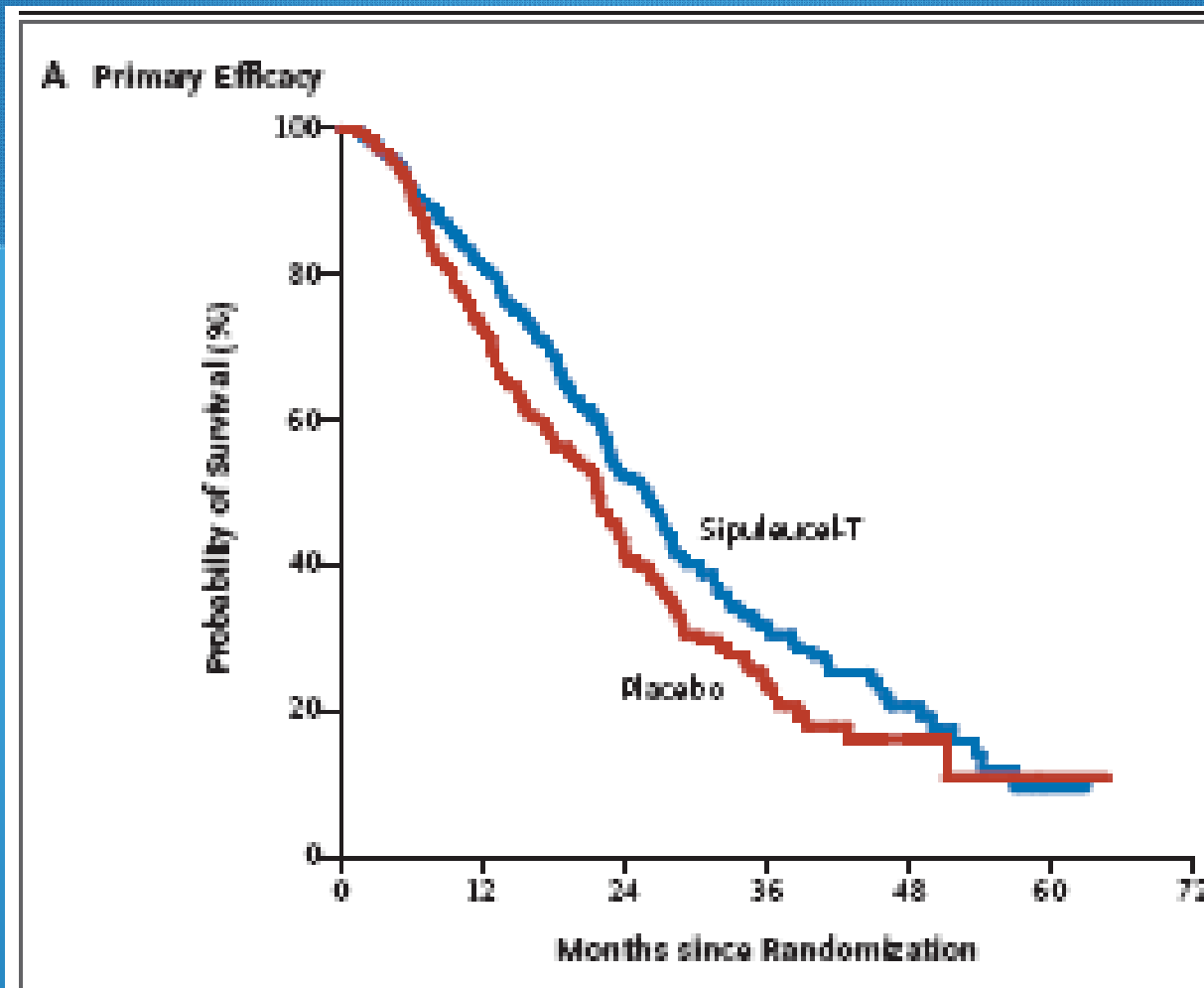


		1	2	3	4
n = 300	Survival Rate	n = 300	n = 300	n = 300	n = 300
		N = 453	N = 37	N = 6	N = 6
%	1 year	44%	43%	25%	25%
%	2 year	22%	24%	14%	14%

Sipuleucel-T



Sipuleucel-T Immunotherapy for Castration-Resistant Prostate Cancer



The background features a large orange sun in the top left corner, several light blue thought bubbles of varying sizes, and a stylized blue microscope on the left side. The main title is centered in a dark blue, rounded rectangular box.

Pharmacogenomics in cancer treatment

A Multigene Assay to Predict Recurrence of Tamoxifen-Treated, Node-Negative, HR positive, HER2 negative Breast Cancer

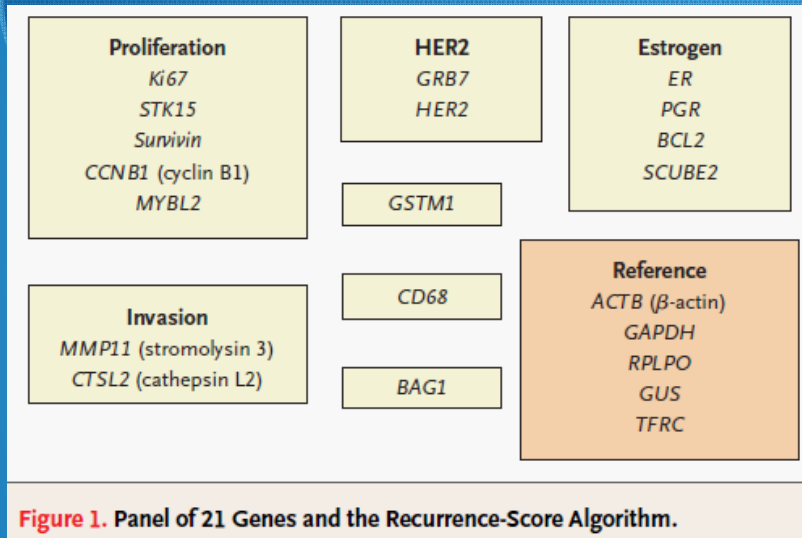
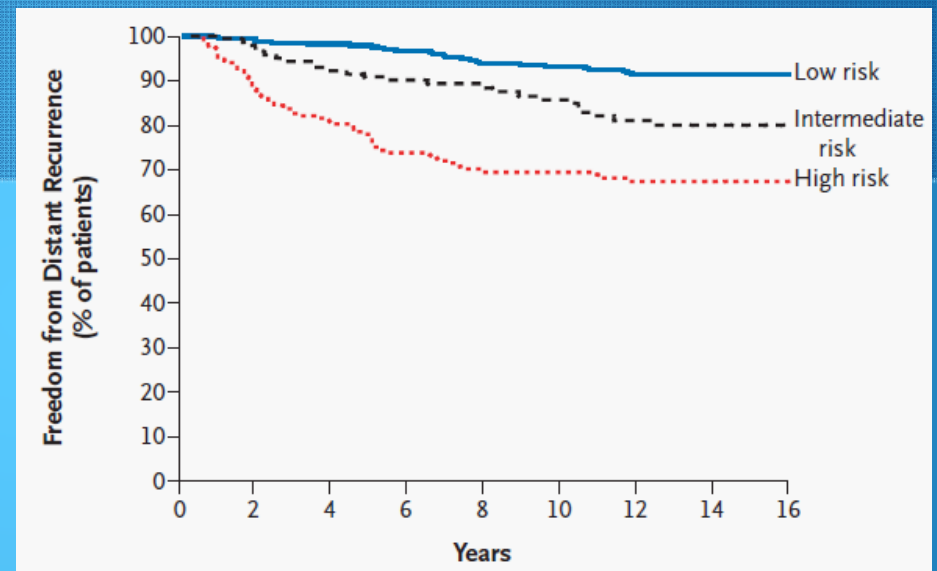
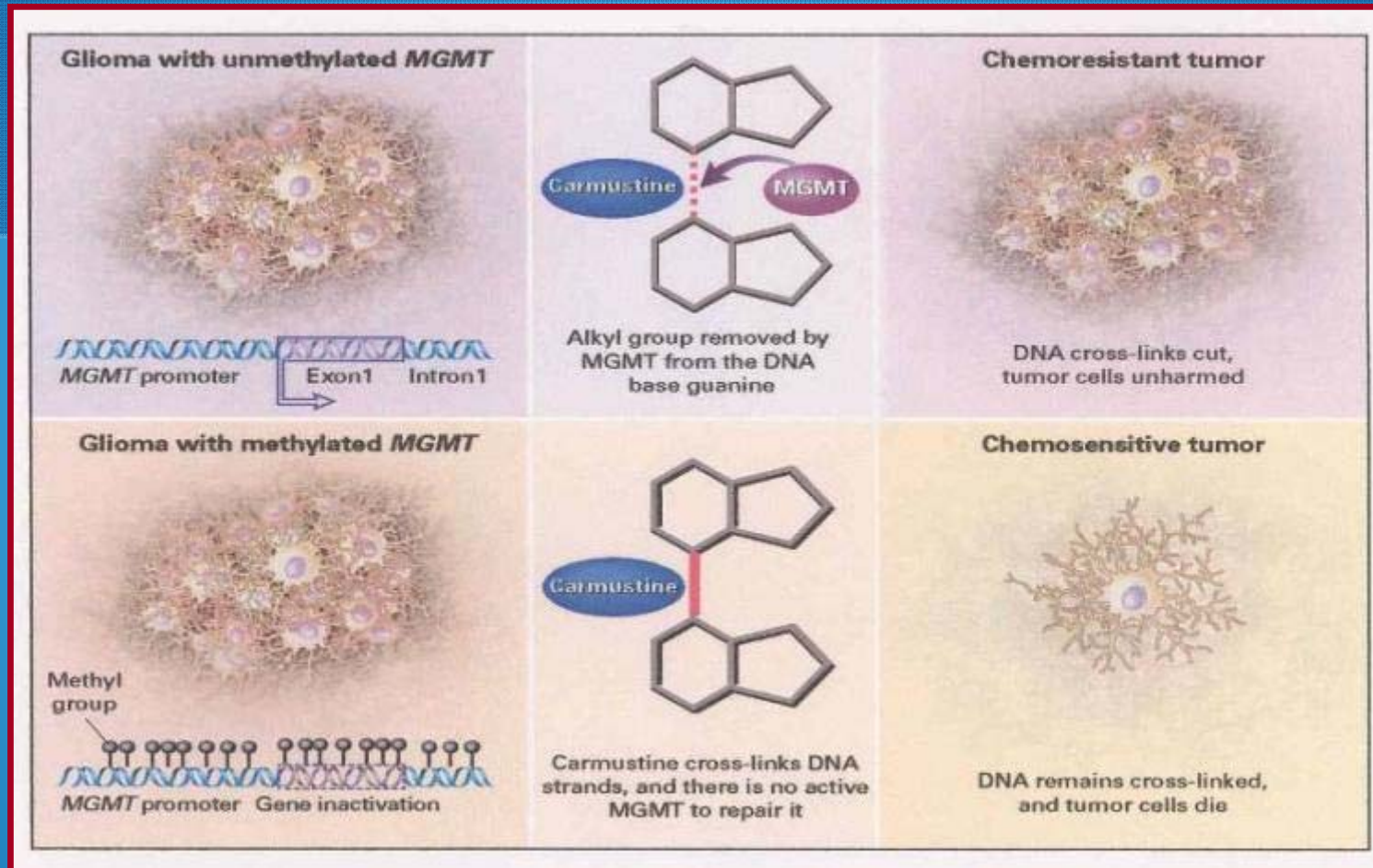


Figure 1. Panel of 21 Genes and the Recurrence-Score Algorithm.



Paik, et al. N Engl J Med 2004;351:2817-26.

MGMT and Glioblastoma



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Esteller M, et al. N Engl J Med. 2000;343:1350-1354.

Effect of MGMT Promoter Methylation Status on Survival Following TMZ Plus RT

Outcome	Methylated MGMT Promoter (↓ MGMT) (n = 46)	Unmethylated MGMT Promoter (↑ MGMT) (n = 60)
PFS		
▪ Median duration, mos	10.3	5.3
▪ Median 6 mos, %	68.9	40.0
OS		
▪ Median duration, mos	21.7	12.7
▪ Median 2 yrs, %	46.0	13.8

The Promise of Pharmacogenomic Testing Personalized treatment

