European Institute of O

The world of mT

Nicola Fazio, M.D., Ph

The world of mTOR

- Historical notes
- Structure of mTOR
- Physiological role of mTOR
- Role of mTOR in cancer

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- **Historical notes**
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From the Easter island ……

In 1964 a Canadian researchers expedition from the Ayerst-Wyeth Pharmaceuticals traveled to Easter island to gather soil samples and plants.

In 1972 the expedition team and a microbiology team identified and isolated RAPAMYCIN from the mycobacterium Streptomyces Hygroscopicus

Rapamycin properties

Several years later Rapamycin demonstrated antifungal activity blocking the G1 to S phase of the cell cycle.

The block of G1 to S phase of the cell cycle in T-lymphocytes revealed a potent immunosuppressant activity of Rapamycin in mammalians.

The birth of the Rapalogs

Rapamycin demonstrated antiproliferative activity in vitro and in vivo in human tumor xenografts implanted into immunosuppressed mice

Rapamycin and its analogs (globally called RAPALOGS) were developed in organ transplantation and oncology, starting from the Biozentrum (Basel) and Sandoz Pharmaceuticals (now Novartis) laboratories.

The molecular target of rapamycin

Two classes of resistant yeast had mutations in genes named TOR1 and TOR2 in honor of the Spalentor, a gate of the city of Basel, where TOR was first discovered.

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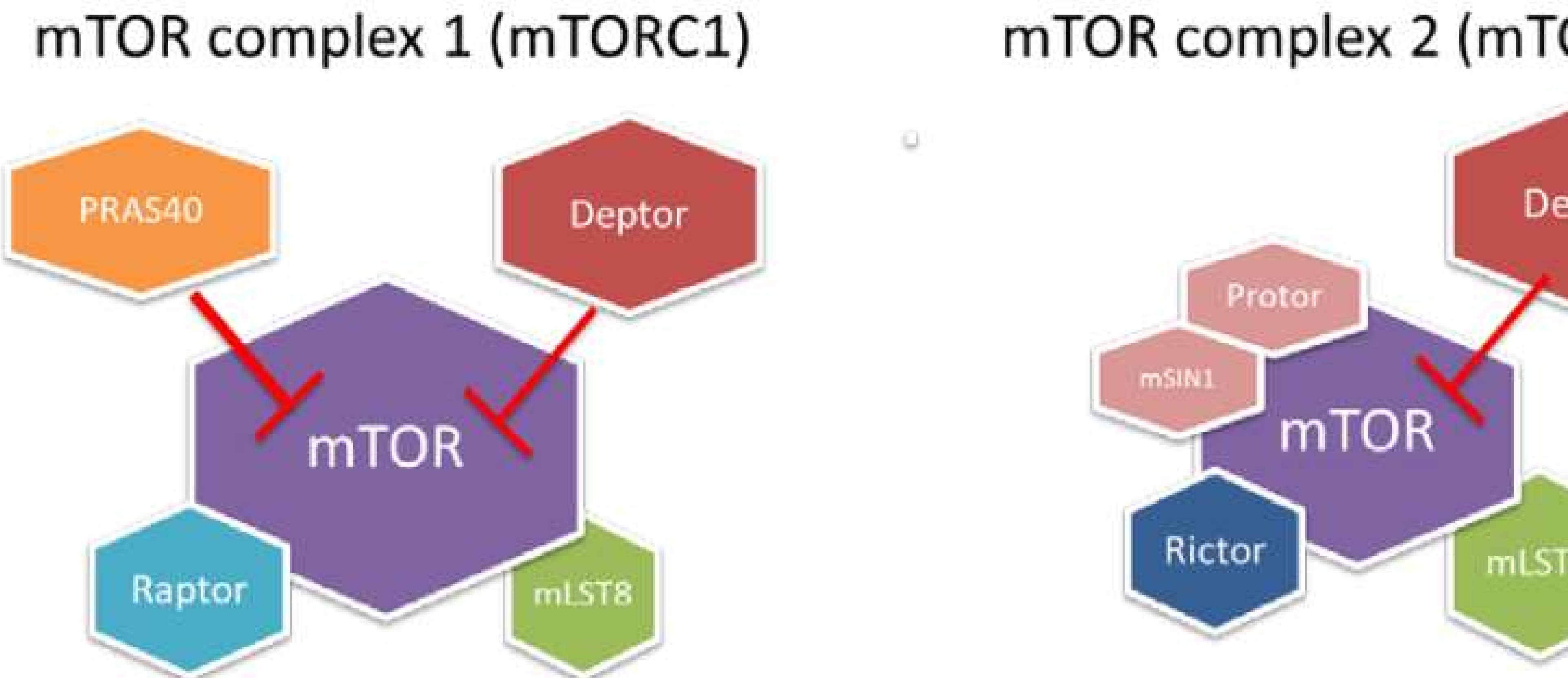
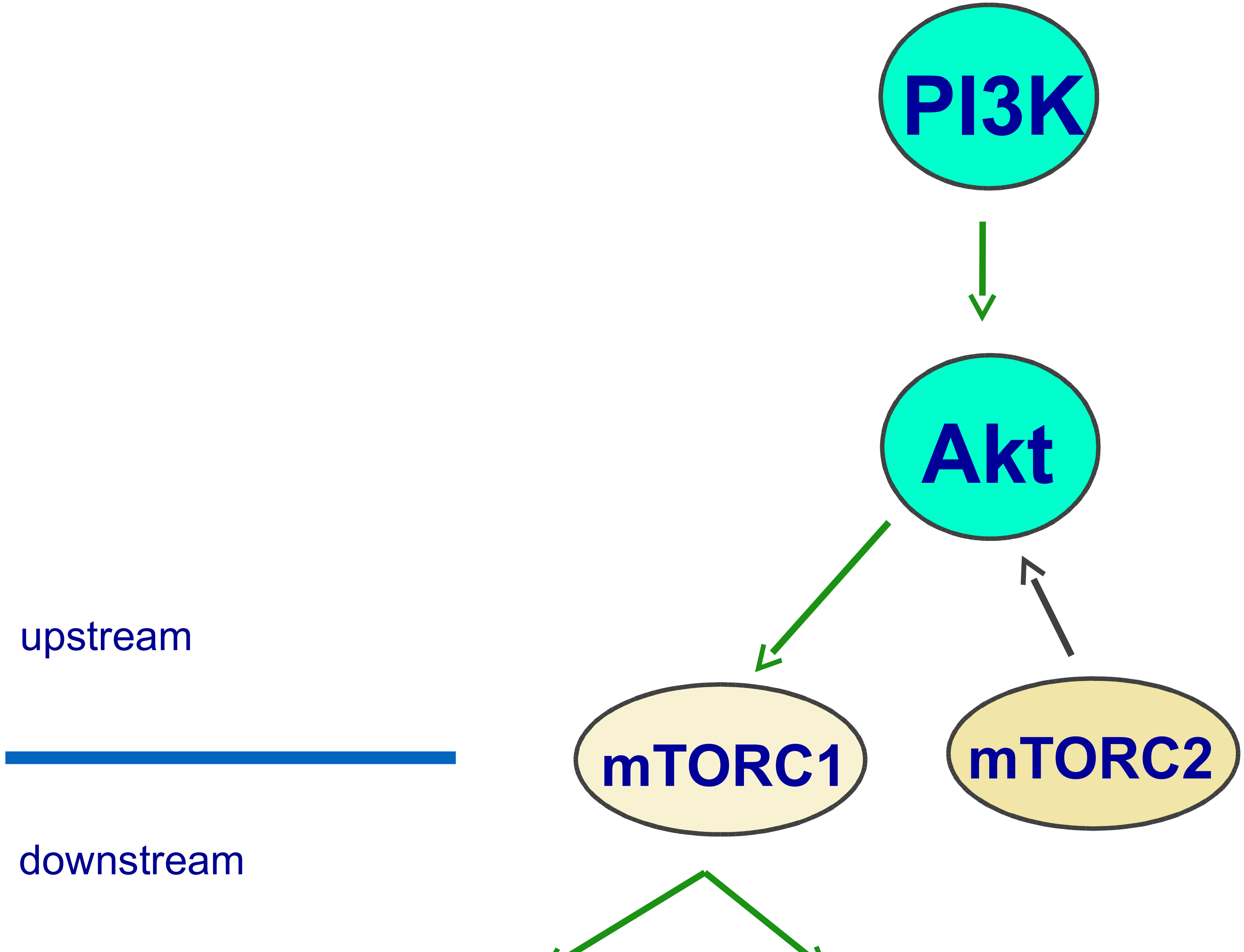


Regulatory associated protein of TOR

Rapamycin-insensitive companion of mTOR

The pathway of mTOR



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mTOR = master switch

Oxidative stress

GROWTH FACTORS
(IGF, EGF, PDGF, VEGF)

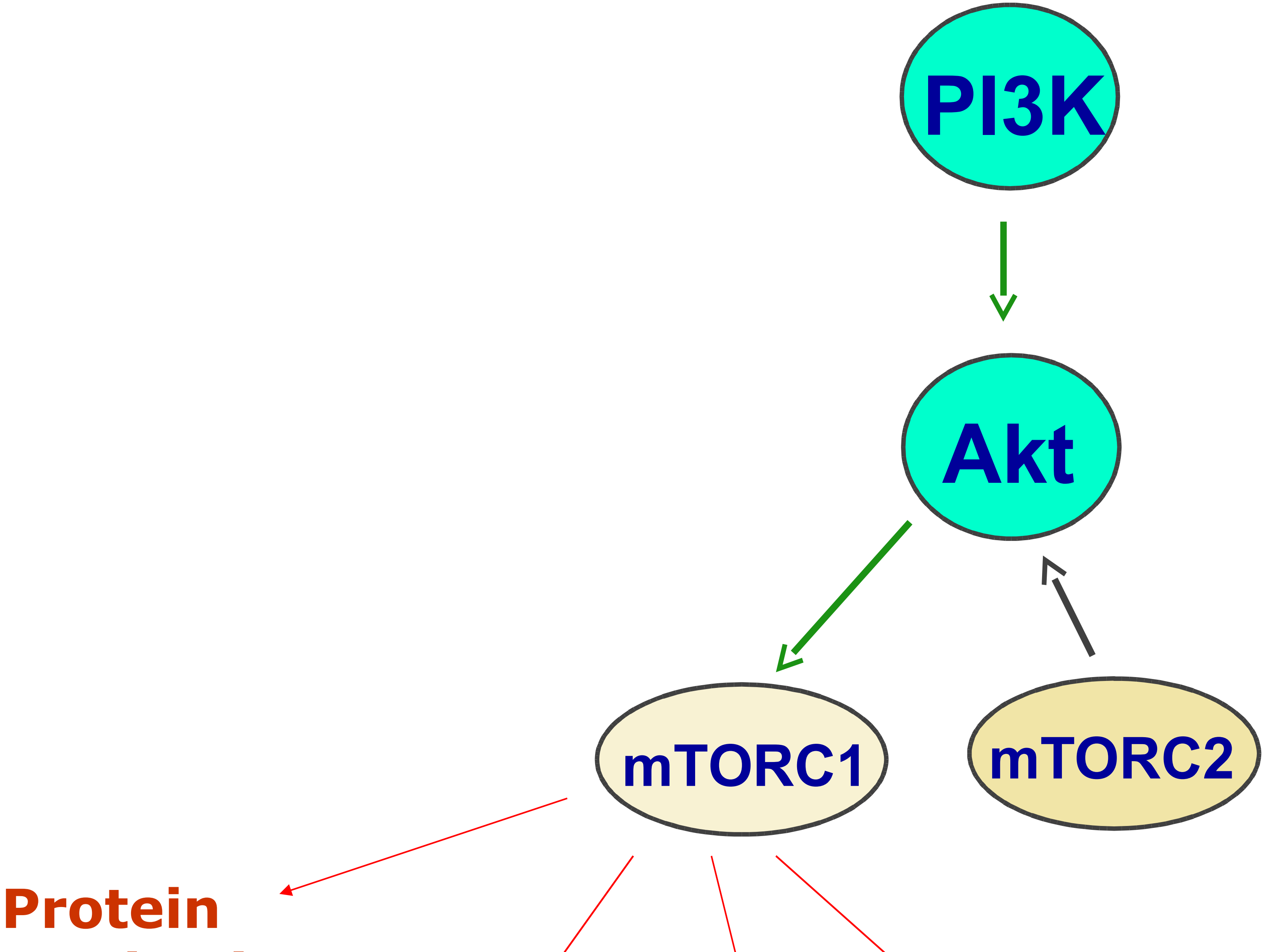
NUTRIENT
(glucose, cholesterol

Insulin

mTOR

Ami

Functions of mTORC1



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FEBS Lett. 2010 April 2; 584(7): 1287–1295. doi:10.1016/j.febslet.2010.01.017.

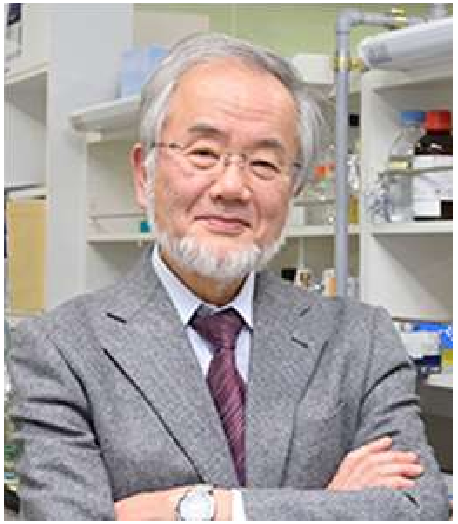
mTOR regulation of autophagy

Chang Hwa Jung, **Seung-Hyun Ro**, **Jing Cao**, **Neil Michael Otto**, and **Do-Hyung Kim**

Autophagy is a self-degradative process that is important for ba
sources of energy at critical times in development and in respo
nutrient stress.

2016 NOBEL PRIZE FOR PHYSIOLOGY OR MEDICINE TO YOSHINORI OHSUMI FOR AUTOPHAGY

Nobelförsamlingen
The Nobel Assembly at Karolinska Institutet



The Nobel Assembly at Karolinska Institutet has today decided to award

the 2016 Nobel Prize in Physiology or Medicine

to

Yoshinori Ohsumi

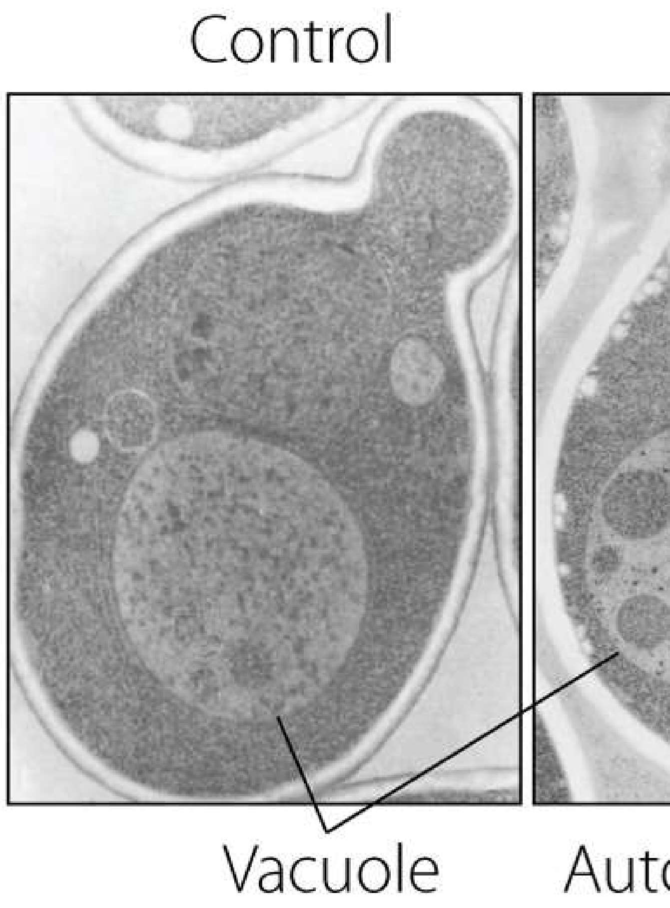
Autophagy = self eating

The cell can destroy its own components forming the lysosomes

Ohsumi identified genes involved in autophagy. Alterations in these genes can occur in cancer.

The Belgian Christian de Duve was awarded the Nobel Prize for Physiology or Medicine in 1974 for the discovery of the lysosome

“Proteasomes” represent another cellular



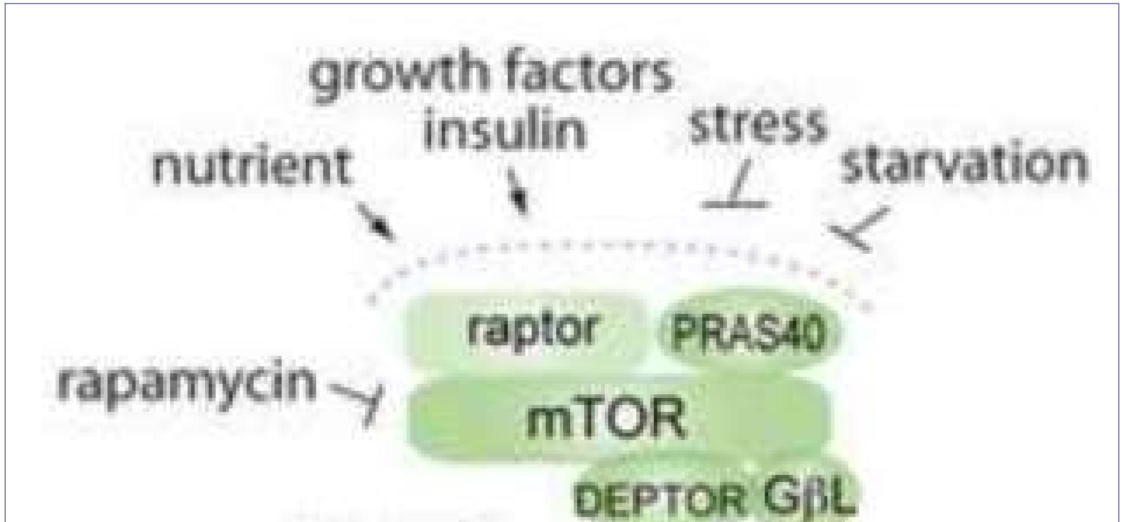
mTORC1 physiologically suppresses autophagy.

NUTRIENT STARVATION

mTOR

mTORC1
eit
pharmacolo
“nutrient c
leads to in
auto

AUTOP



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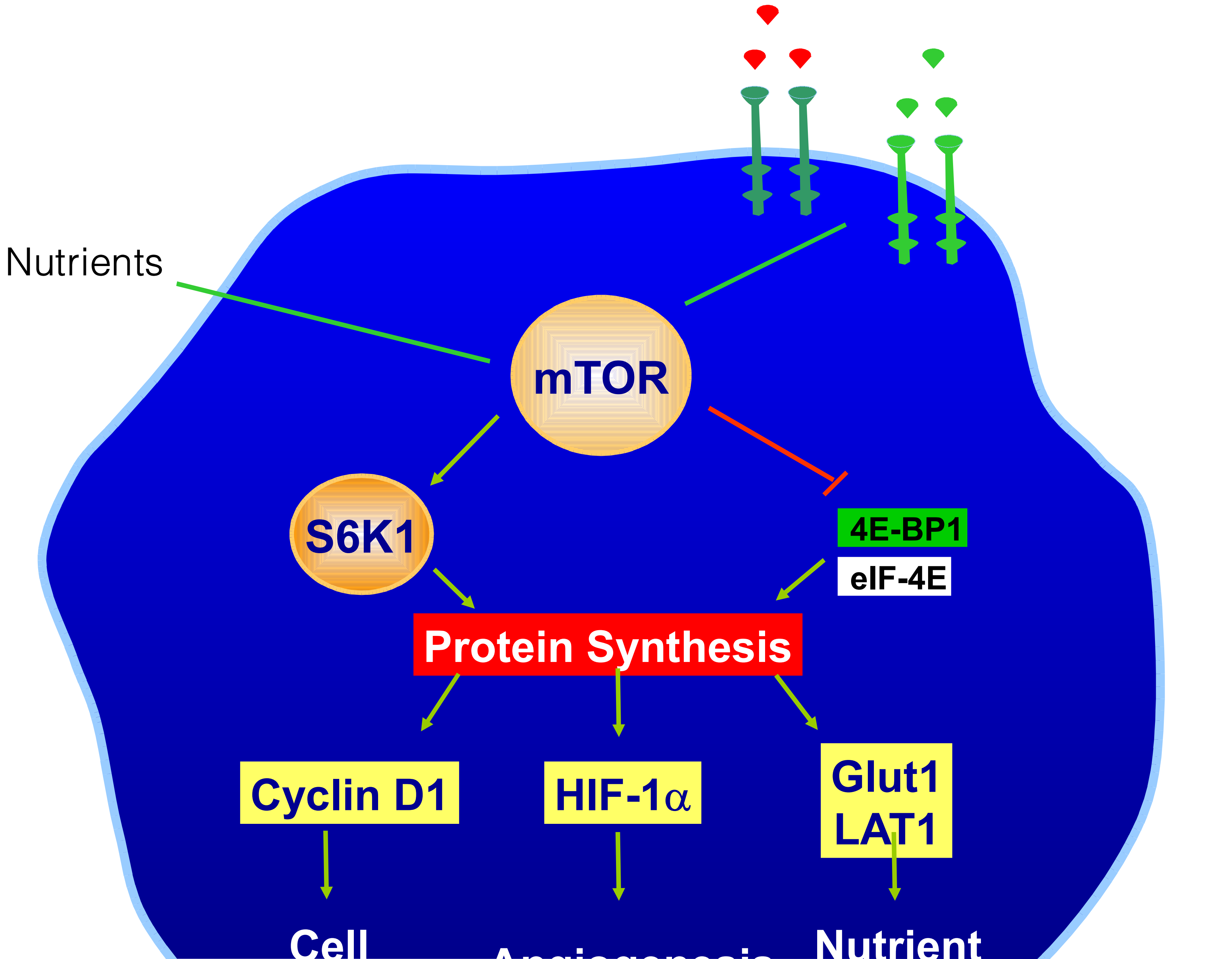
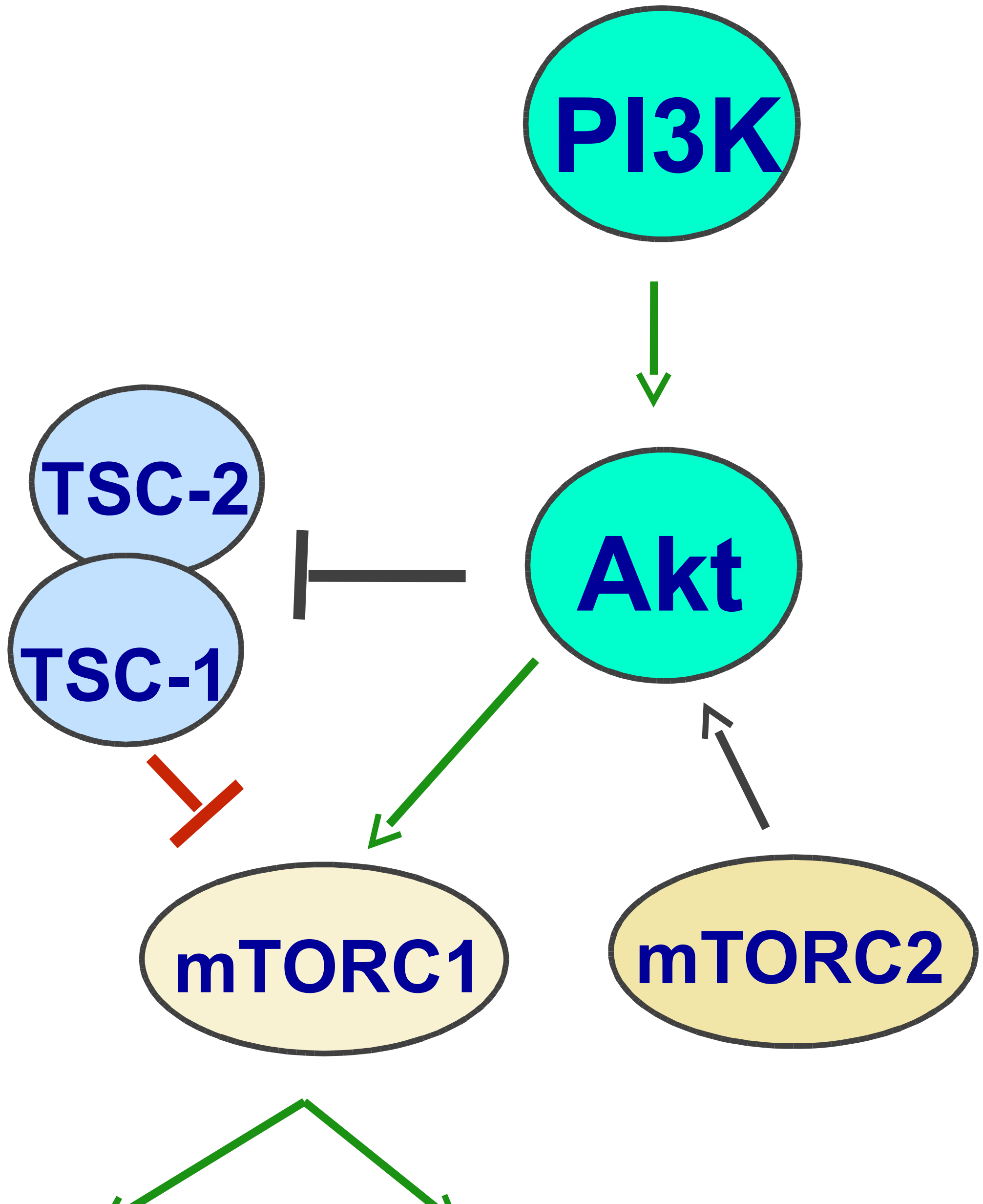
mTOR activation supports cancer cell growt



Connection between TSC and mTORC1: the first molecular link b
mTOR and cancer



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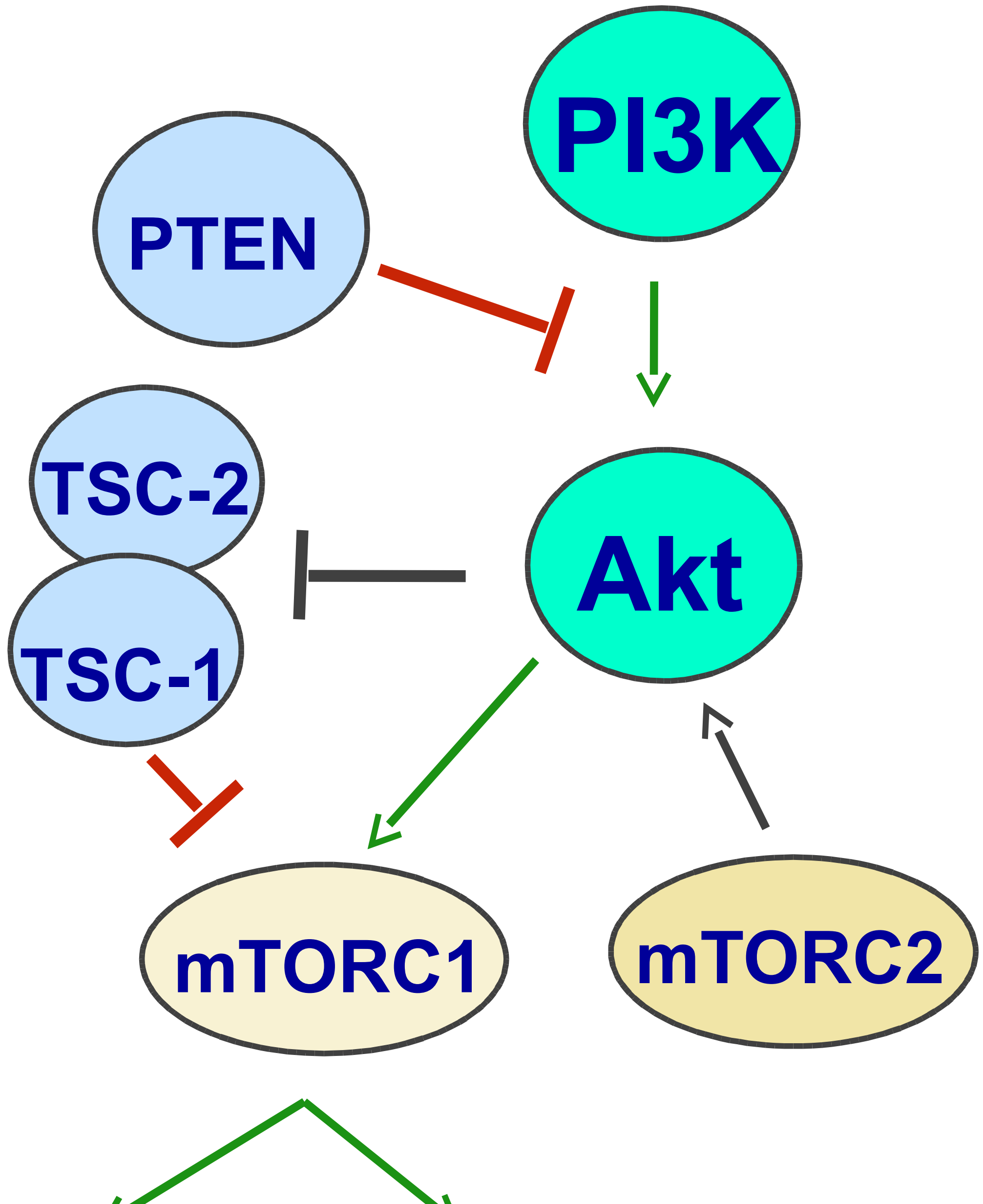
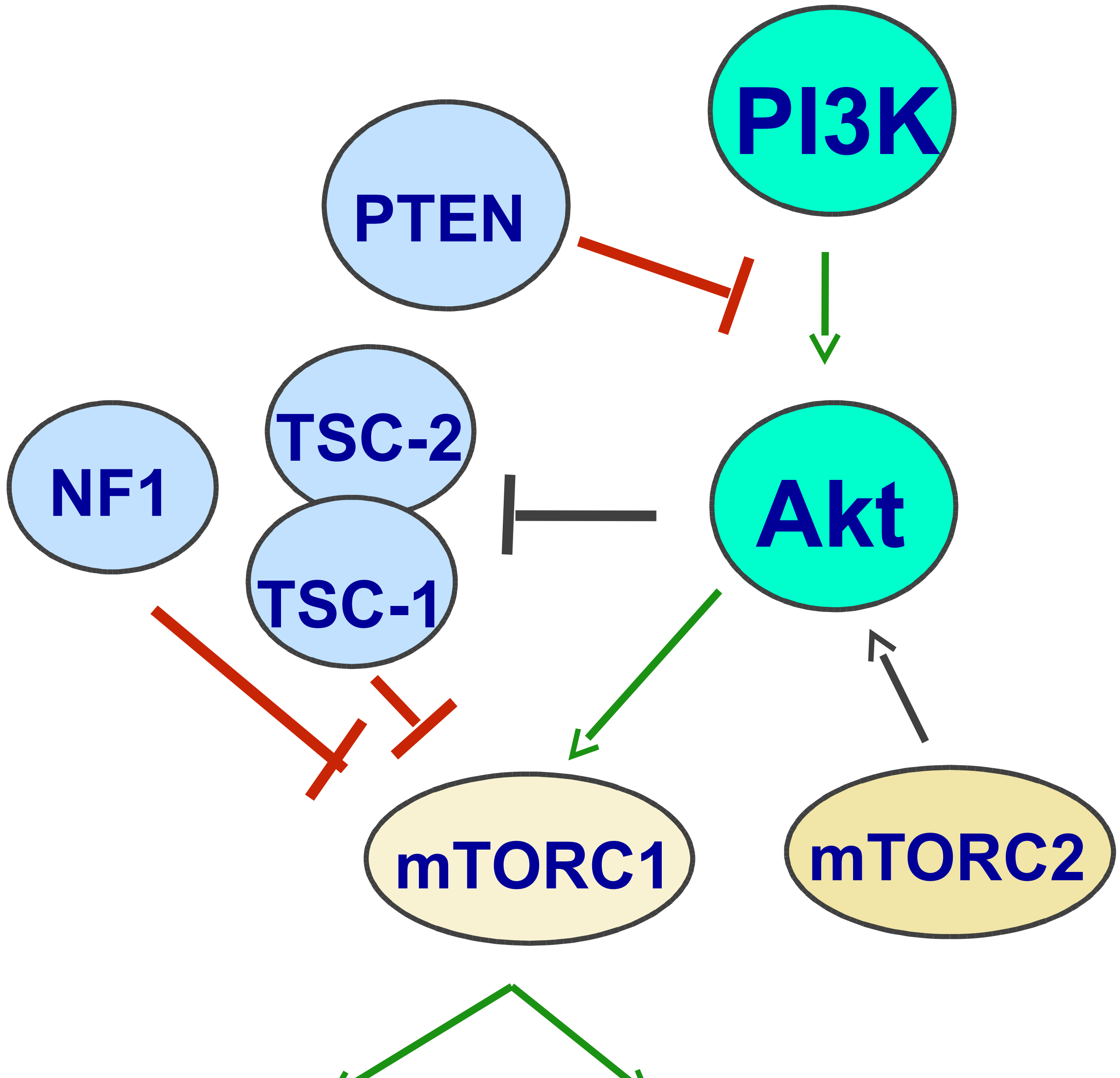
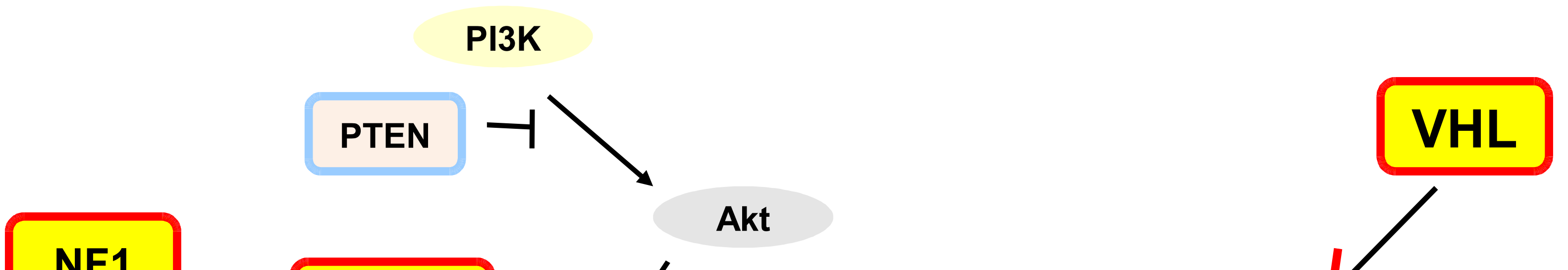


Connection between TSC and mTORC1: the first molecular link b
mTOR and cancer



mTOR pathway and NET-related inherited syndron

Syndrome	Gene	NET
Tuberous sclerosis (TS)	TSC2	pancreas
Neurofibromatosis (NF)	NF-1	Ampulla, duod mediastinu
Von Hippel Lindau (VHL)	VHL	pancreas



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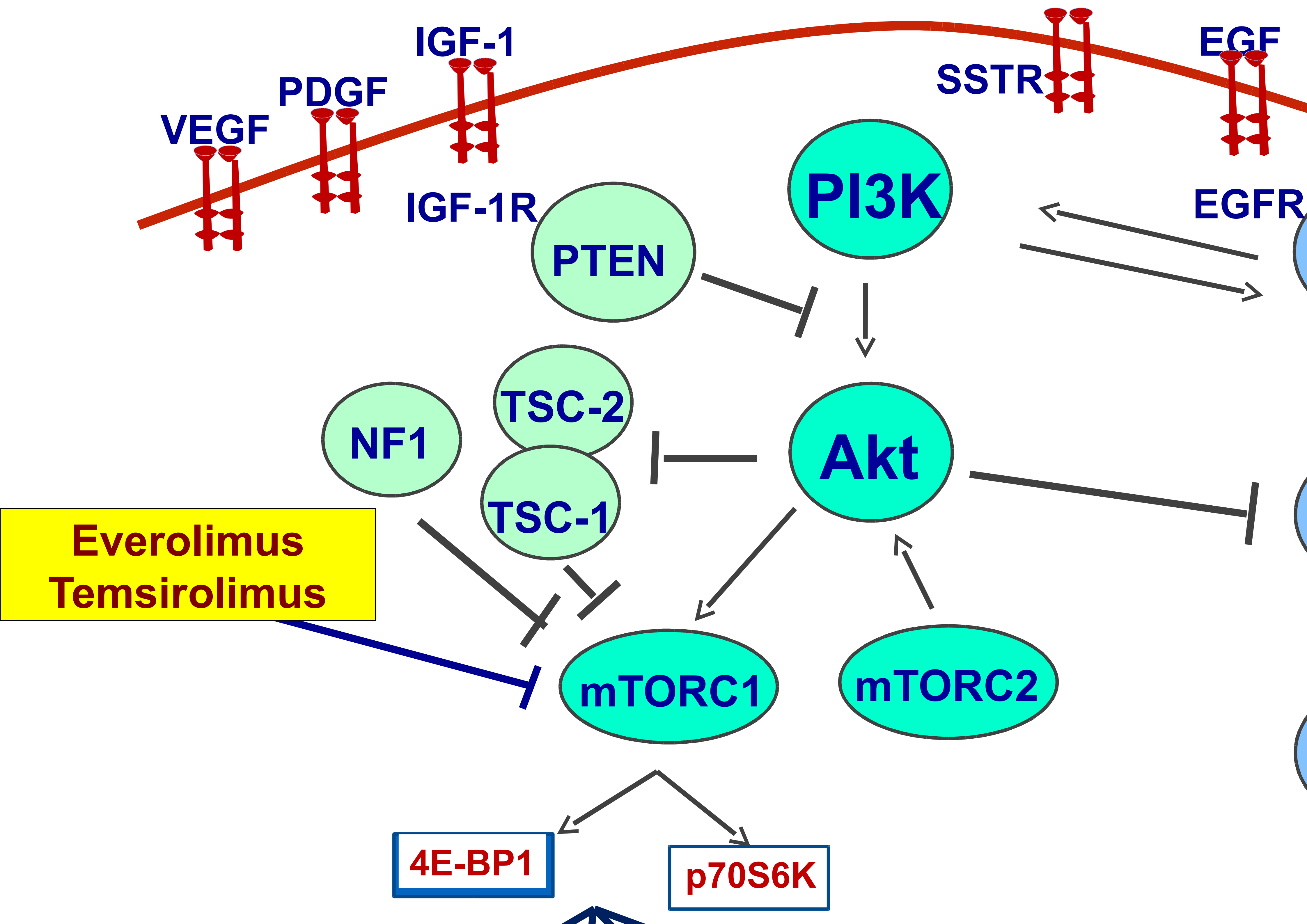
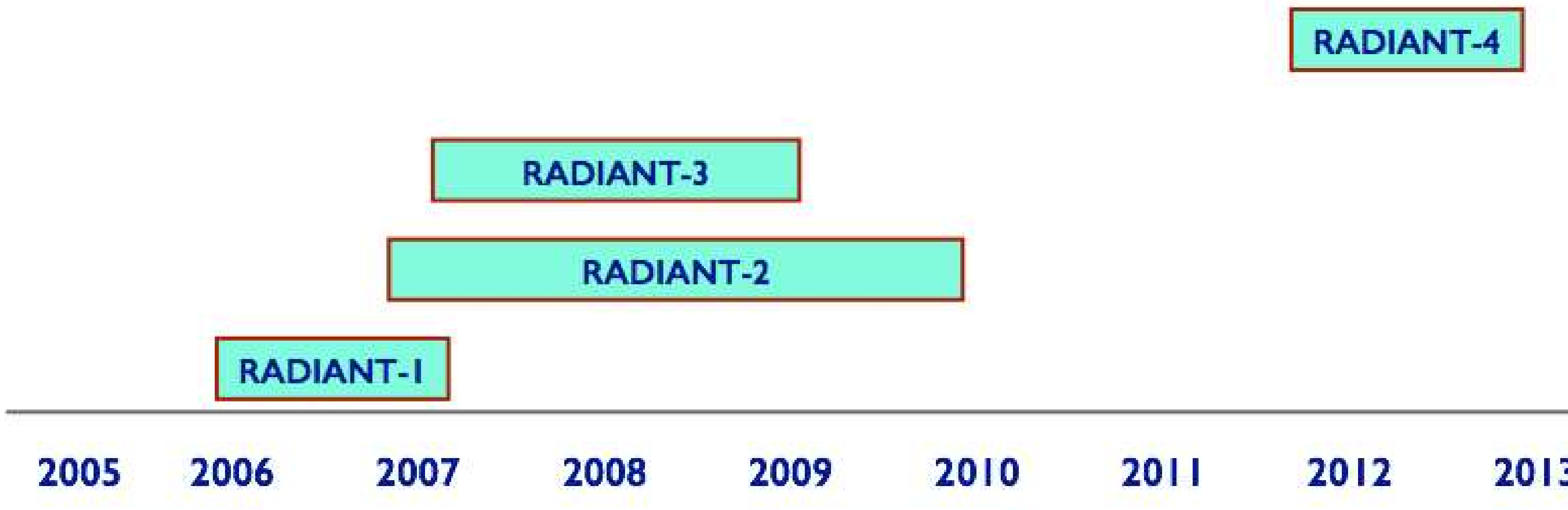
mTOR inhibitors

	Sirolimus	Everolimus	Temsirolimus	Rida (Def
Brand name	Rapamune®	Certican® Afinitor®	Torisel®	Ta
Formulation	oral	oral	I.V.	
Indication	Prevent renal rejection	Prevent renal/heart rejection, NET, RCC, Breast cancer, SEGA, renal angiomyolipomas associated with TS	RCC, MLC	S s


IGF-1
PDGF
VEGF
SSTR
EGF
IGF-1R
PI3K
EGFR
PTEN
TSC-2
NF1
Akt
TSC-1
Everolimus
Temsirolimus
mTORC1
mTORC2
4E-BP1
p70S6K

Everolimus investigation in NETs

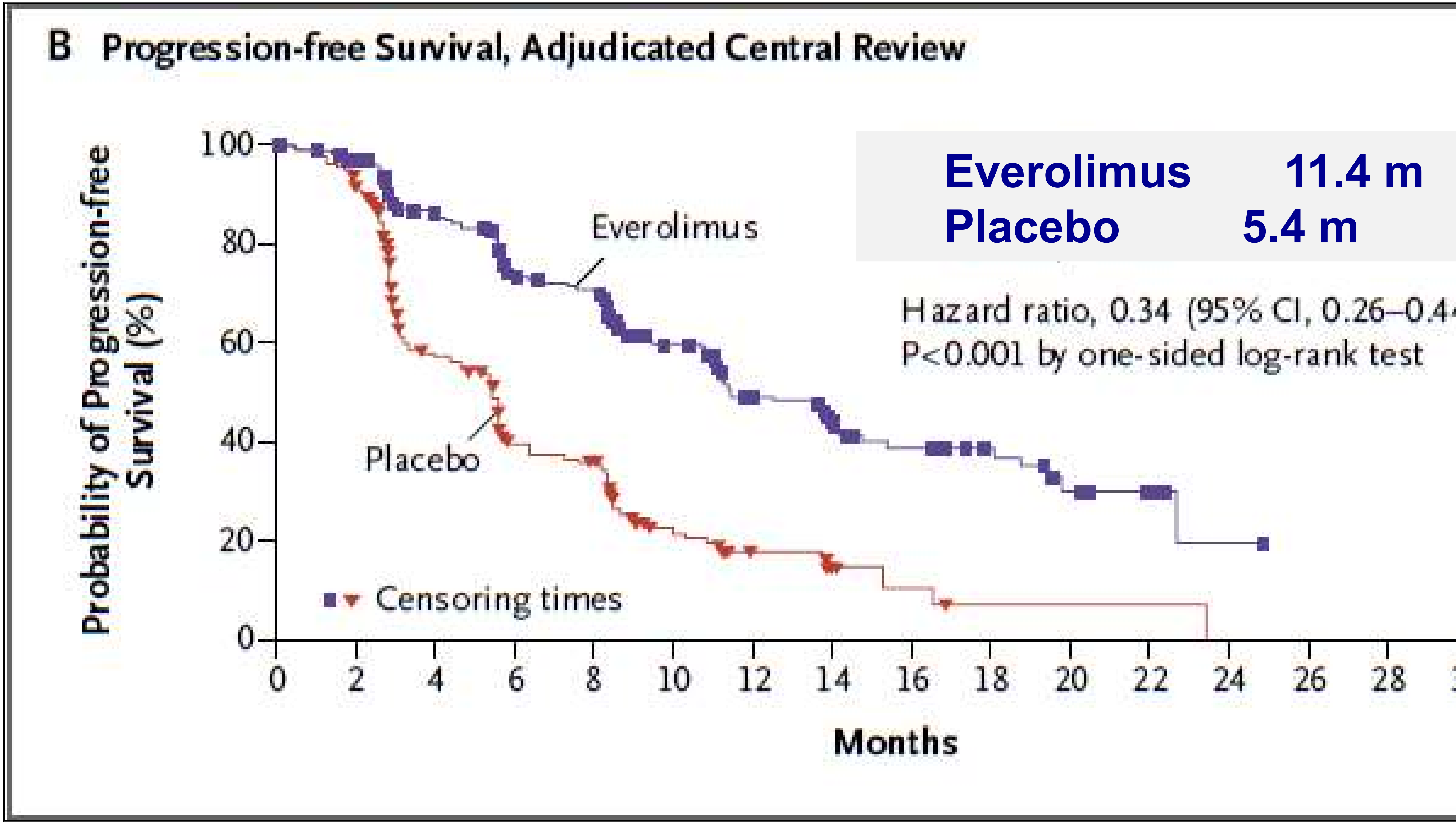


Randomised phase III trials with Everolimus in N

RADIANT (RAD001 in Advanced Neuroendocr Tumors)

Trial	N. pts	Popul.	Therapy	Approval
RADIANT-2	**429**	**carcinoid syndrome NET**		**Not approved for carci syndrome-related NE**
Arm A	216		**EVE + OCT**	
Arm B	213		**PLB + OCT**	
RADIANT-3	**410**	**Pancreatic well /moderately differentiated NET**		**Approved for well/mode differentiated, advanced, pa NET**
Arm A	207		**EVE**	
Arm B	203		**PLB**	

RADIANT-3 trial
(410 pancreatic NET patients randomized 1:1

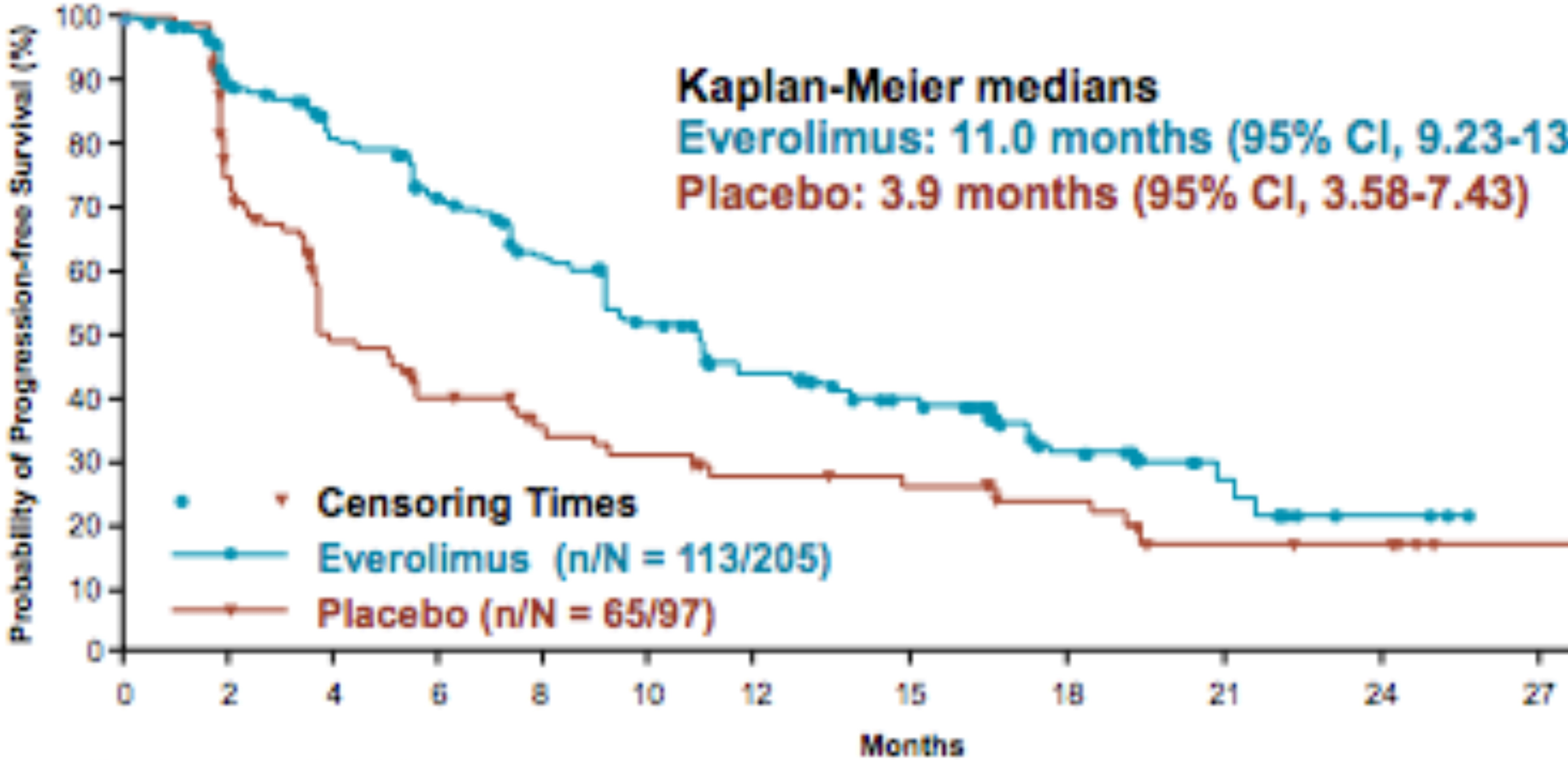


RADIANT-4 trial
(302 patients with GI and lung NET randomized

Primary Endpoint: PFS by Central Rev

52% reduction in the relative risk of progression or death with everolimus vs placebo

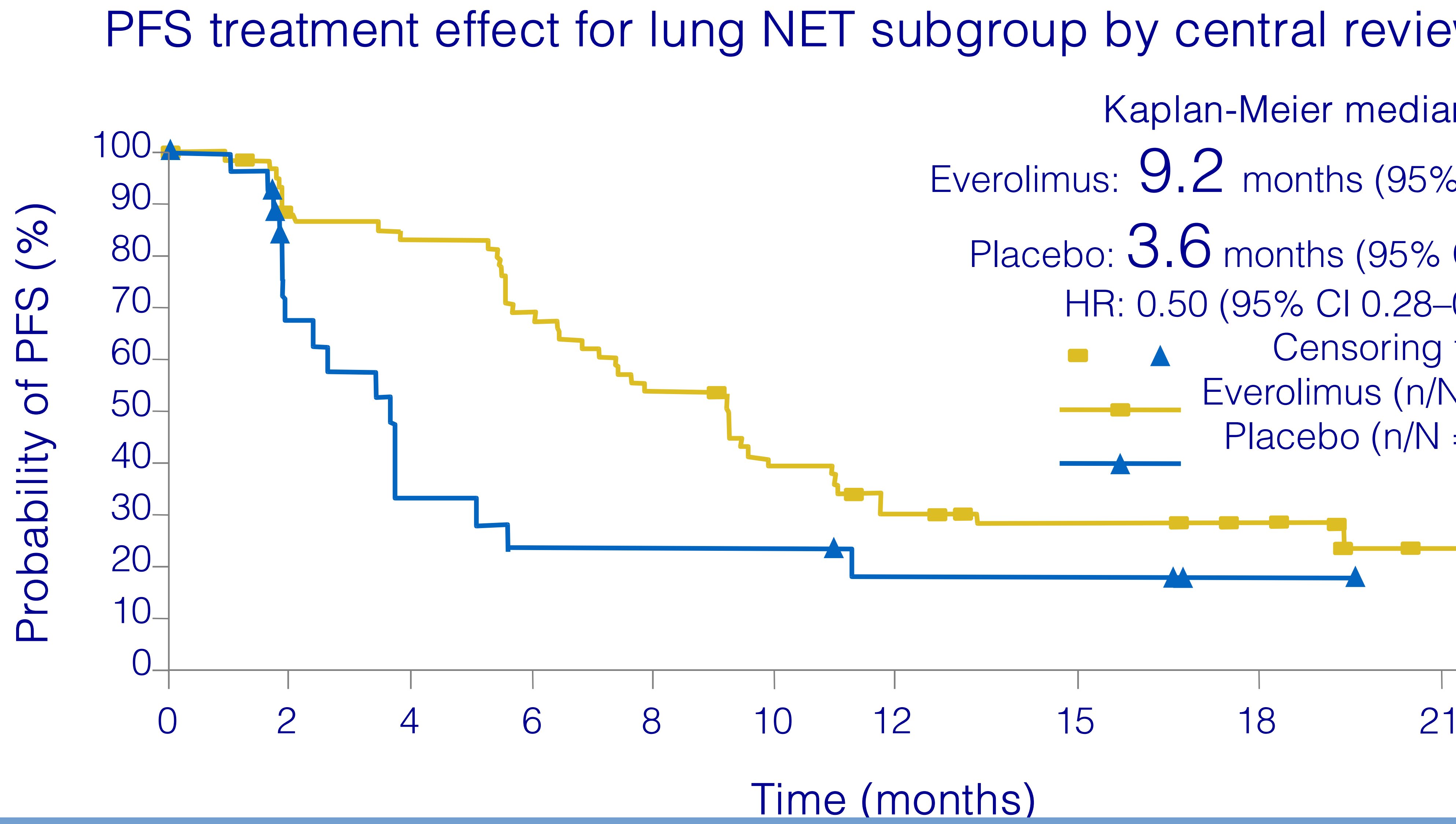
HR = 0.48 (95% CI, 0.35-0.67); *P* < 0.00001



Trials with Everolimus in lung carcinoids

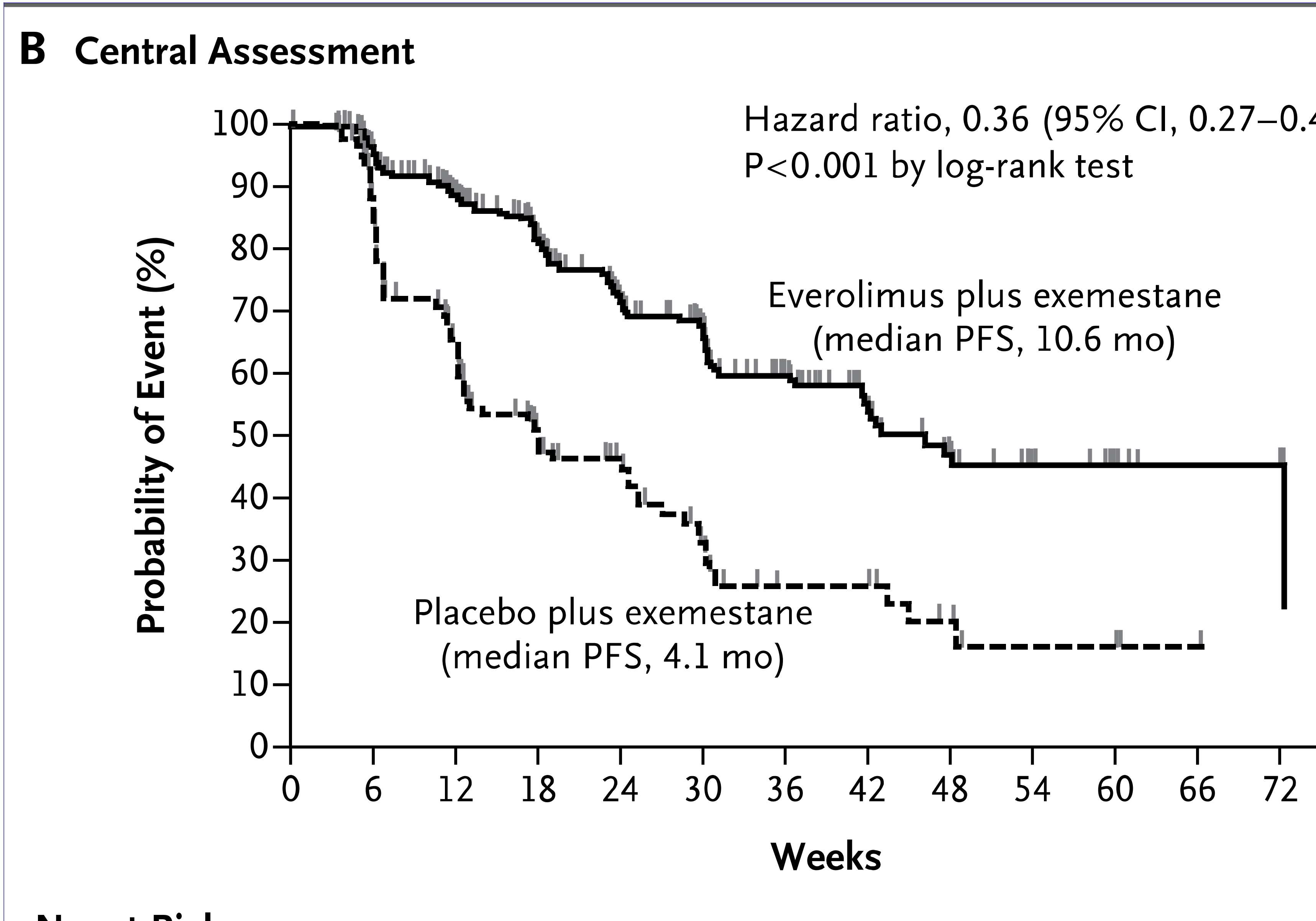
Trial	Experimental arm	Control arm	Type of study	Lung subgroup	Number of lung patients
RAMSETE	EVE	Placebo	Phase II	Non-functioning	22/73
RADIANT-2	EVE + Oct LAR	Oct LAR + Placebo	Phase III	Carcinoid syndrome	44/429
RADIANT-4	Everolimus	Placebo	Phase III	Non-functioning	90/302
LUNA	Pasireotide vs. EVE vs. Pasireotide/EVE	no	Phase II	Functioning and non-functioning	121/121

RADIANT-4 trial: lung subgroup, 90 pts



Patients at risk, n

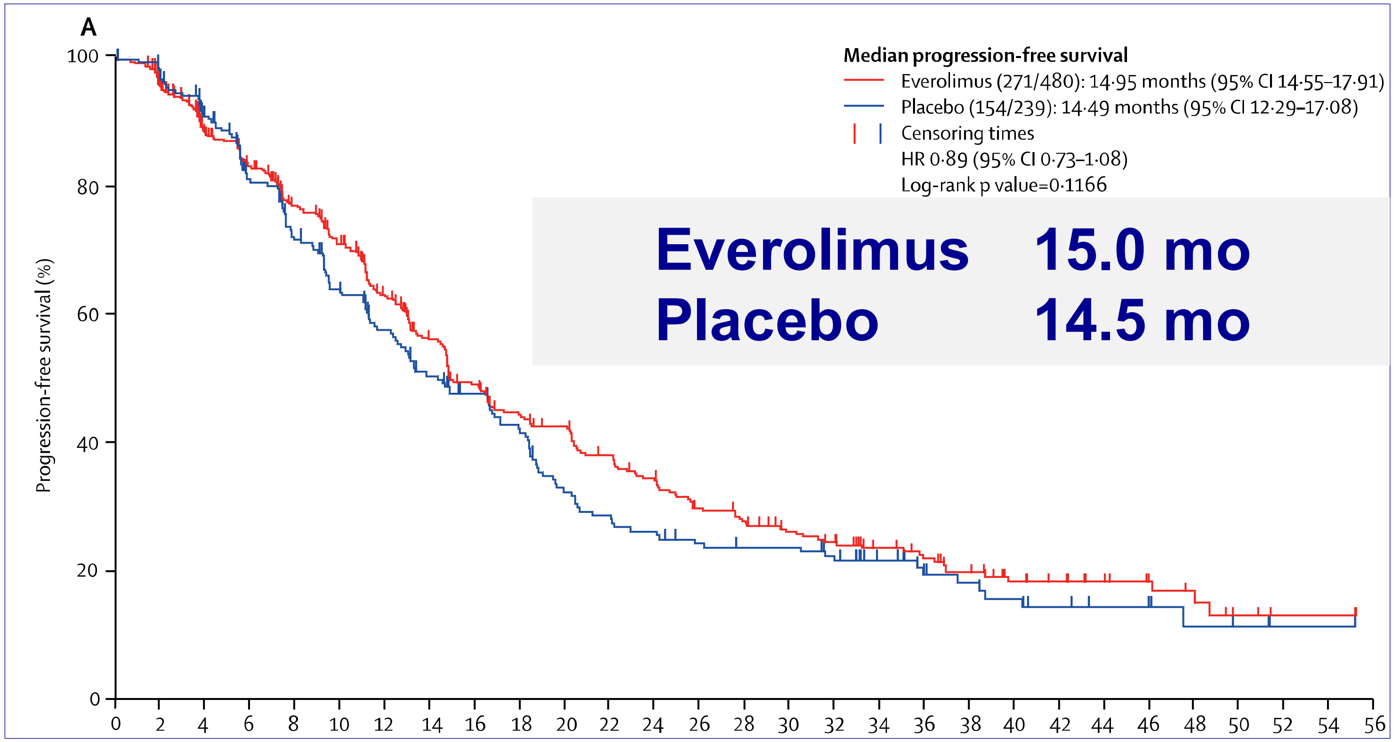
BOLERO-2 trial: 724 pts with HR+, HER-2 neg, a
breast cancer, progressing on letrozole or ana



Resistance to trastuzumab has been attributed to aberran
of PI3K pathway (loss or disregulation of PTEN

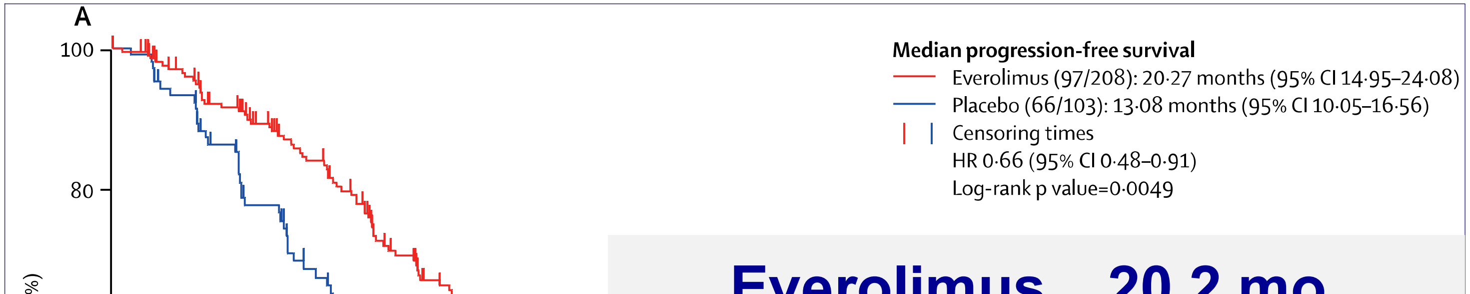
BOLERO-1 trial: 719 pts with HER-2+ advan
breast cancer

PFS in global population

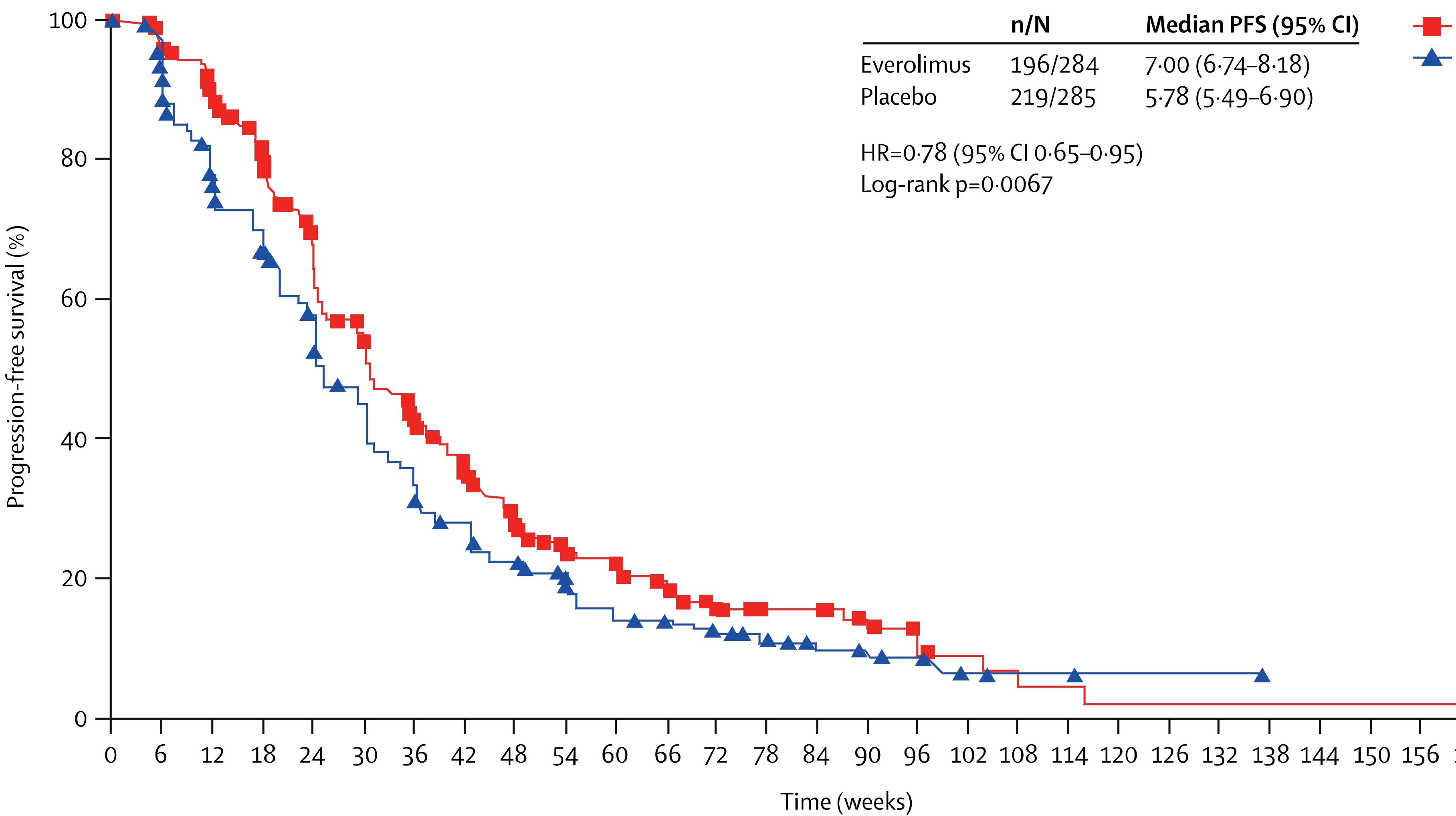


The p value did no
prespecified criter
significance by a sma

PFS in HR- sub-population



BOLERO-3 trial: 569 pts with HER-2+, trastuzumab-
advanced breast cancer

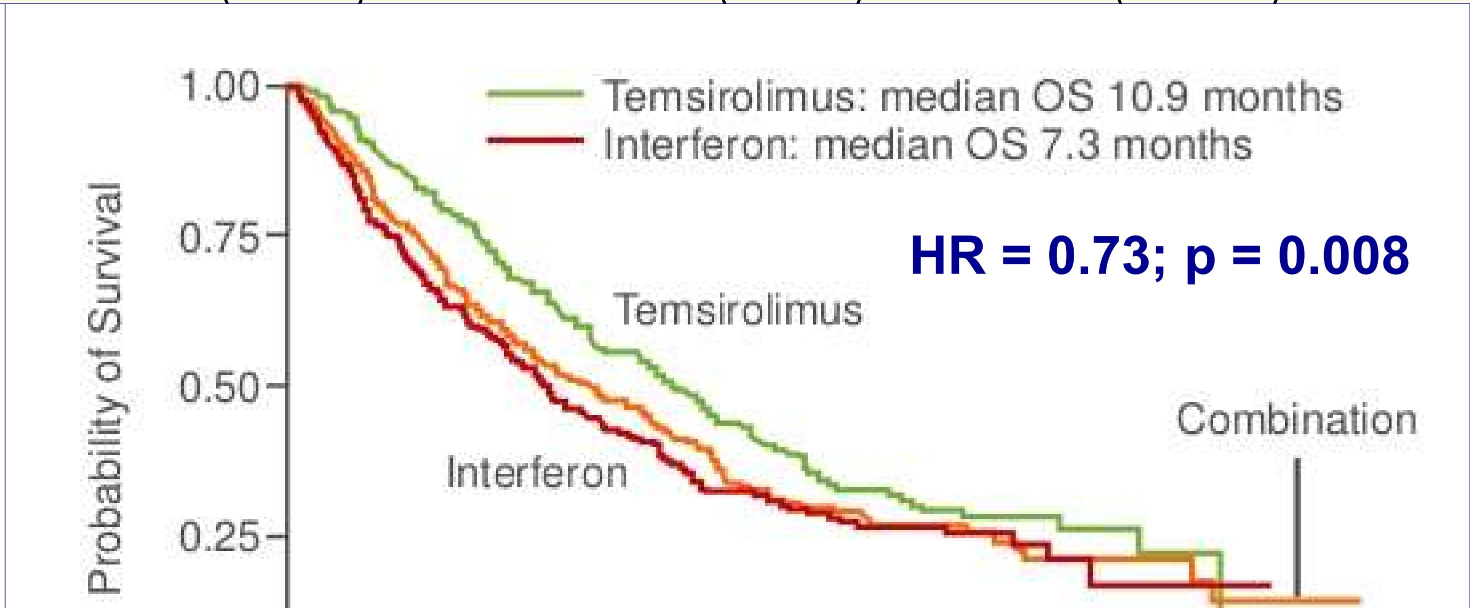


Randomised phase III trials with Everolimus in breas
BOLERO (Breast Cancer Trial of Oral Everolin

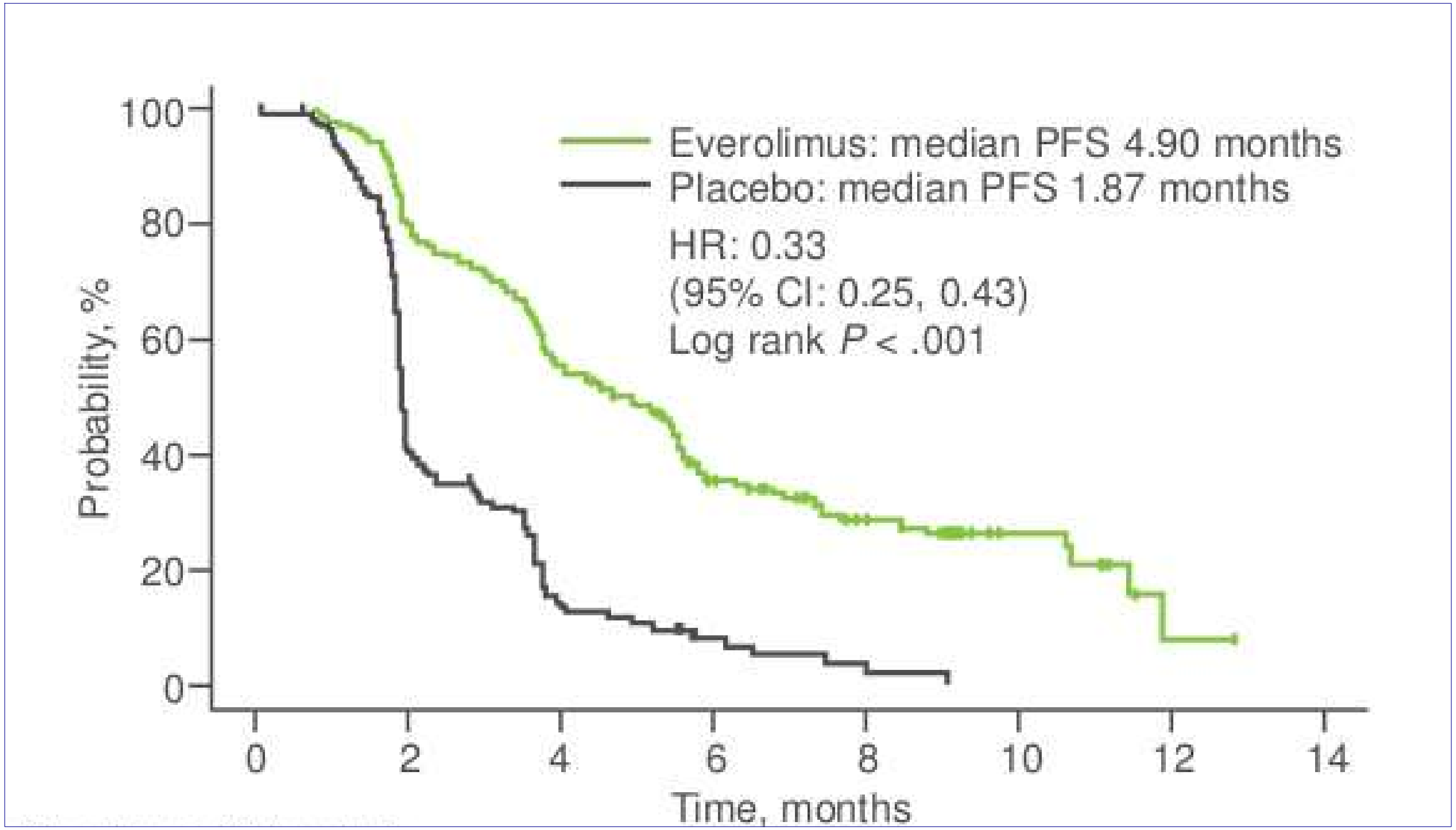
Trial	N. pts	Popul.	Therapy	Approval		
BOLERO-1	**719**	**HER-2+ BC**		Not approved for first-li advanced BC		
Arm A	480		**Paclitaxel/Trastuzumab/EVE**			
Arm B	239		**Paclitaxel/Trastuzumab/PLB**			
BOLERO-2	**724**	**HR+ HER-2- BC progressive on letrozole/anastrozole**		Approved for HR+ HER-2- a progressing on letrozole o		
Arm A	485		**EVE + EXE**			
Arm B	239		**PLB + EXE**			
BOLERO-3	**569**	**HER-2+ BC progressing**		Not approved for HER-2+		
Arm A	284		**EVE/Trastuz**			

Temsirolimus, IFN-alpha or both for advanced ren carcinoma: a phase III trial

End Point	Interferon (N=207)	Temsirolimus (N=209)	Interferon p Temsirolin (N=210
Median overall survival — mo (95% CI)	7.3 (6.1–8.8)	10.9 (8.6–12.7)	8.4 (6.6–1(



RECORD-1 trial: 416 pts with pre-treated meta renal cell carcinoma



Positive results for cabozantinib and nivolumab co with everolimus in pre-treated patients with adva renal cell carcinoma

The NEW ENGLAND JOURNAL *of* MEDICINE

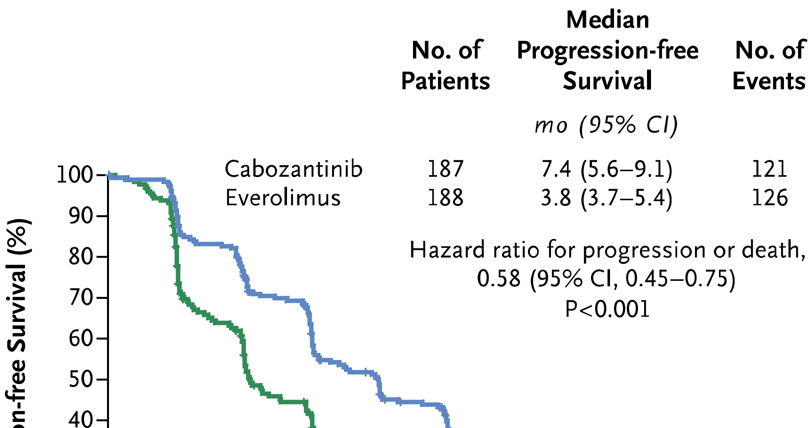
September 2015

The NEW ENGLAND JOURNAL *of* ME

ORIGINAL ARTICLE

Cabozantinib versus Everolimus in Advanced Renal-Cell Carcinoma

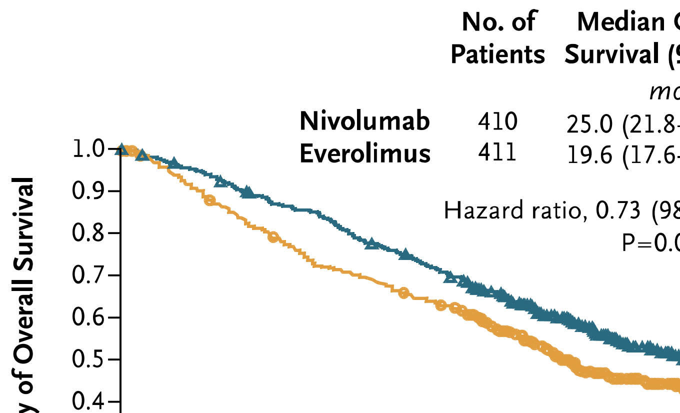
T.K. Choueiri, B. Escudier, T. Powles, P.N. Mainwaring, B.I. Rini, F. Donskov, H. Hammers, T.E. Hutson, J.-L. Lee, K. Peltola, B.J. Roth, G.A. Bjarnason, L. Géczi, B. Keam, P. Maroto, D.Y.C. Heng, M. Schmidinger, P.W. Kantoff, A. Borgman-Hagey, C. Hessel, C. Scheffold, G.M. Schwab, N.M. Tannir, and R.J. Motzer, for the METEOR Investigators*



ORIGINAL ARTICLE

Nivolumab versus Everolimus Renal-Cell Carcinor

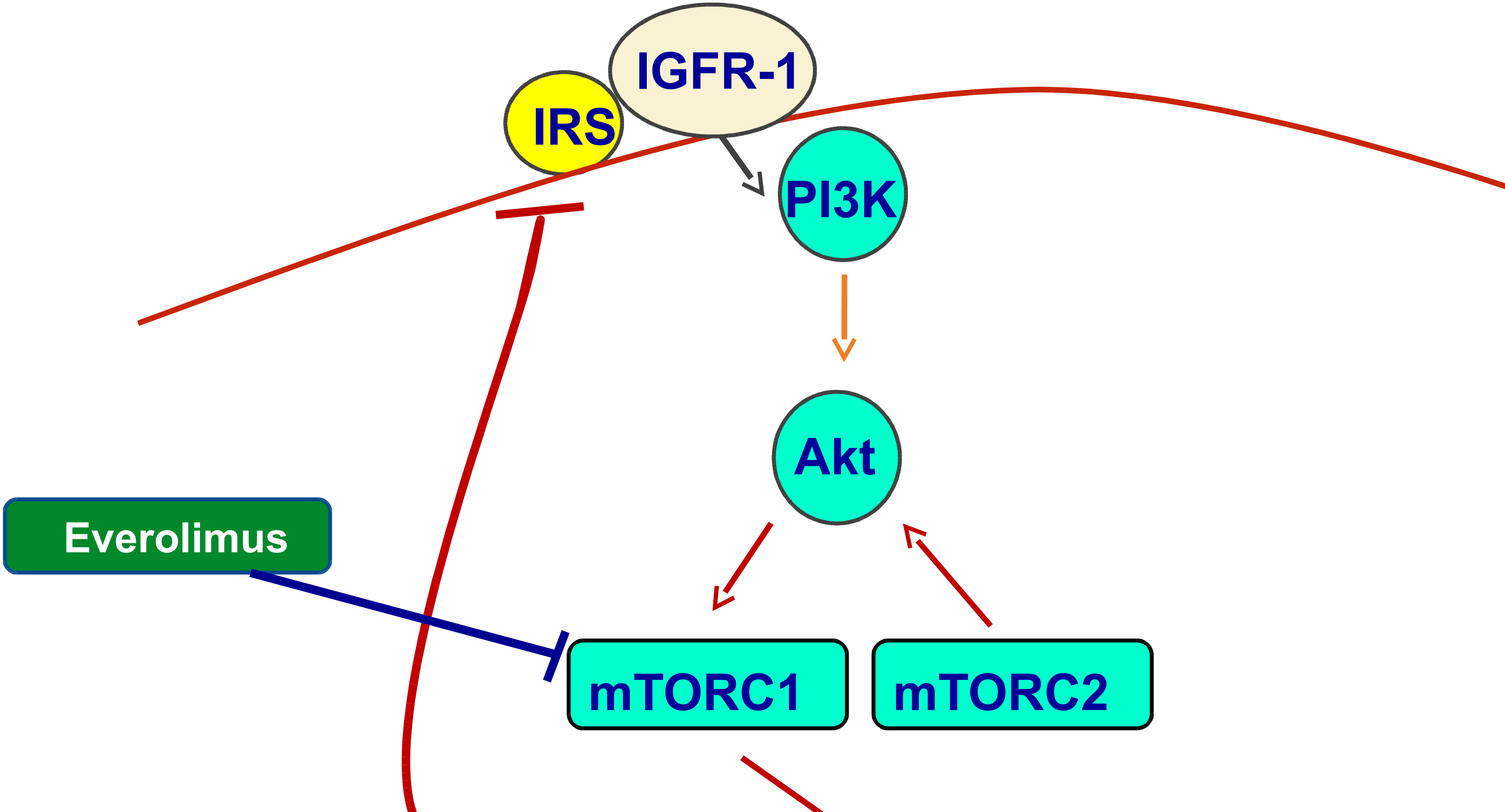
R.J. Motzer, B. Escudier, D.F. McDermott, S. George, H. S.S. Tykodi, J.A. Sosman, G. Procopio, E.R. Plimack, D. C H. Gurney, F. Donskov, P. Bono, J. Wagstaff, T.C. Gaul F.A. Schutz, C. Kollmannsberger, J. Larkin, A. Ravaud I.M. Waxman, and P. Sharma, for the CheckMate



Resistance to mTOR inhibitors

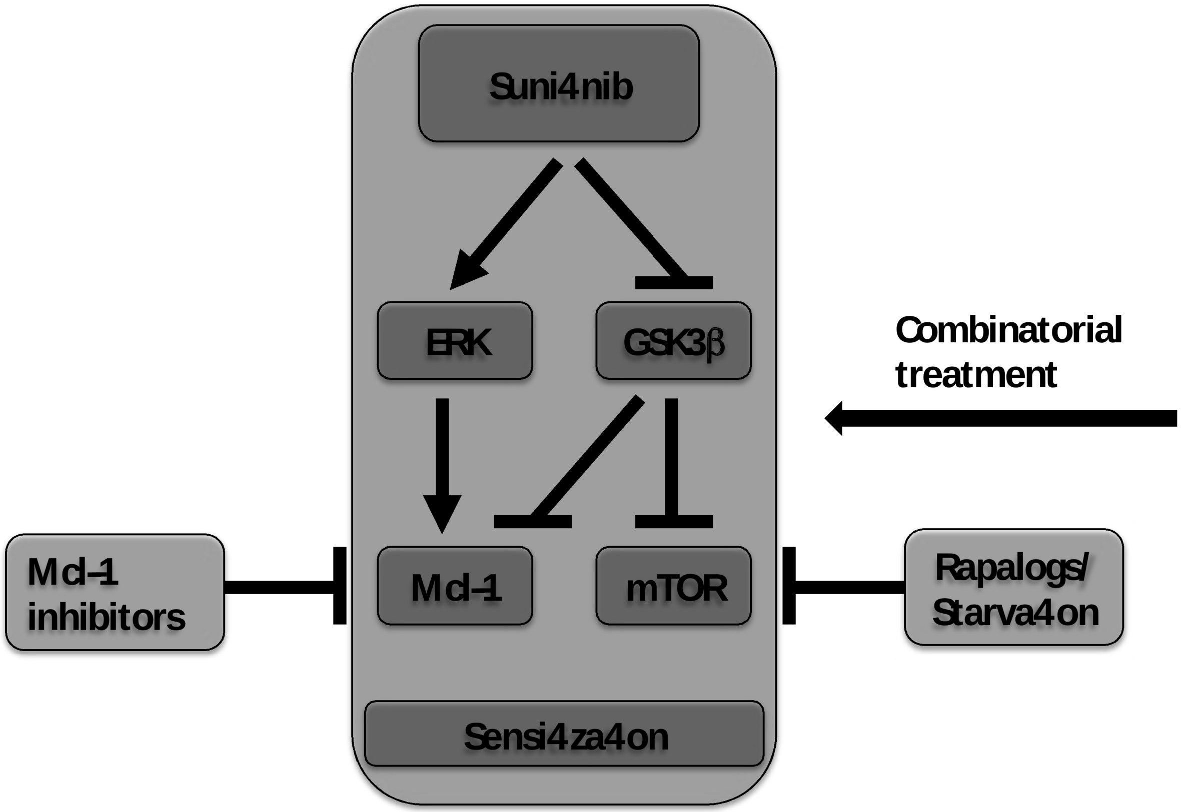
Deconstructing feedback-signaling networks to improve anticancer therapy with mTORC1 inhibitors

Arkaitz Carracedo[1], Jose Baselga[2], and Pier Paolo Pandolfi[1] *Cell Cycle*. 2008



Dual modulation of Mcl-1 and mTOR by sunitinib determines t response of cancer cells

Comparison of patient samples prior and post sunitinib treatment suggests that increasing Mcl-1 levels and mTORC1 activity correlat with resistance to sunitinib in patients



Toxicity of mTOR inhibitors

Toxicity of everolimus: data from phase III tr

Table 1. Incidence of key class-effect toxicities from phase III studies of everolimus in advanced solid tumors

	Metastatic renal cell carcinoma [8]		Neuroendocrine tumors of pancreatic origin [6]		Advanced bre
	Everolimus + best supportive care ($n = 274$), %		Everolimus ($n = 204$), %		Everolimus + ($n = 482$), %
	All Grades	Grade 3/grade 4	All grades	Grade 3/4[a]	All grades
Stomatitis	44	4/<1	64	7	59
Rash	29	1/0	49	<1	39
Noninfectious pneumonitis	14	4/0	17	2	16
Hyperglycemia	57[b]	15/<1[b]	13	5	14[c]
Infections[d]	37	7/3	23	2	50[e]

[a]Breakdown by grade 3 and 4 not reported.
[b]Based on laboratory values.
[c]Based on investigator-reported adverse events.
[d]Incidence based on system organ class (SOC); includes all infections.
[e]Data from Afinitor prescribing information [2].

The adverse event profile of everolimus is broadly similar across various approved indicati

Outcomes in Patients With Metastatic Renal Cell Carcinoma Who Develop Everolimus-Related Hyperglycemia and Hypercholesterolemia: Combined Subgroup Analyses of the RECORD-1 and REACT Trials

Petri Bono,[1] Stephane Oudard,[2] Istvan Bodrogi,[3] Thomas E. Hutson,[4] Bernard Escudier,[5] Jean-Pascal Machiels,[6] John A. Thompson,[7] Robert A. Figlin,[8] Alain Ravaud,[9] Mert Basaran,[10] Camillo Porta,[11] Sergio Bracarda,[12] Thomas Brechenmacher,[13] Chinjune Lin,[14] Maurizio Voi,[14] Viktor Grunwald,[15] Robert J. Motzer[16]

Clinical Genitourinary Cance

Hyperglycemia and hypercholesterolemia were observed in low numbers of patients, and although these events might be associated with improved response to everolimus, the differences were not statistically significant.

Lung toxicity of mTOR inhibitors: a meta-analysi
published trials

Patients treated with mTOR inhibitors have an increas
of pulmonary toxicity.
The high grade is a rare event but one in 10 patients
experience grade G1-2 toxicity with a worsening of qu
of life and interruption of therapy.

Predictive factors to everolimus

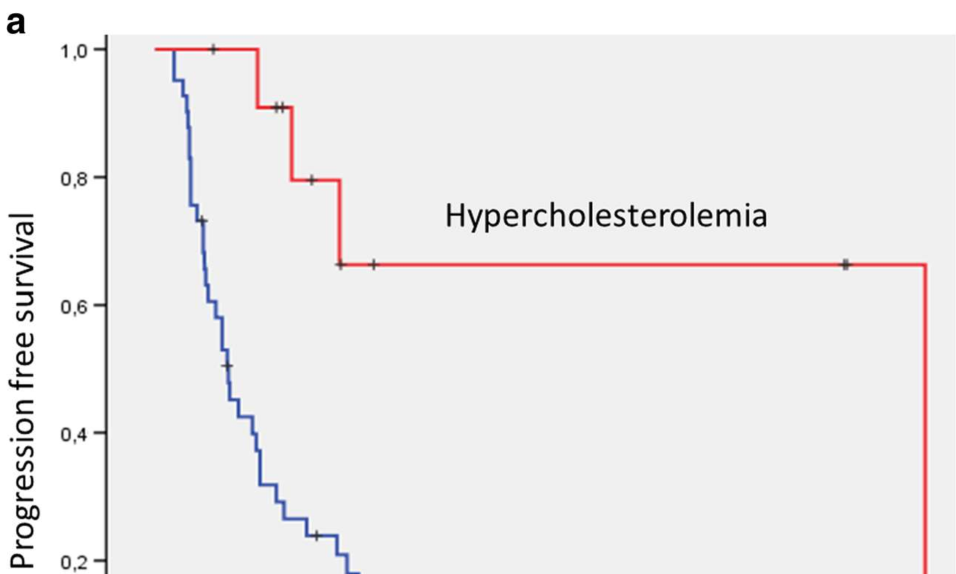
Invest New Drugs
DOI 10.1007/s10637-016-0363-6

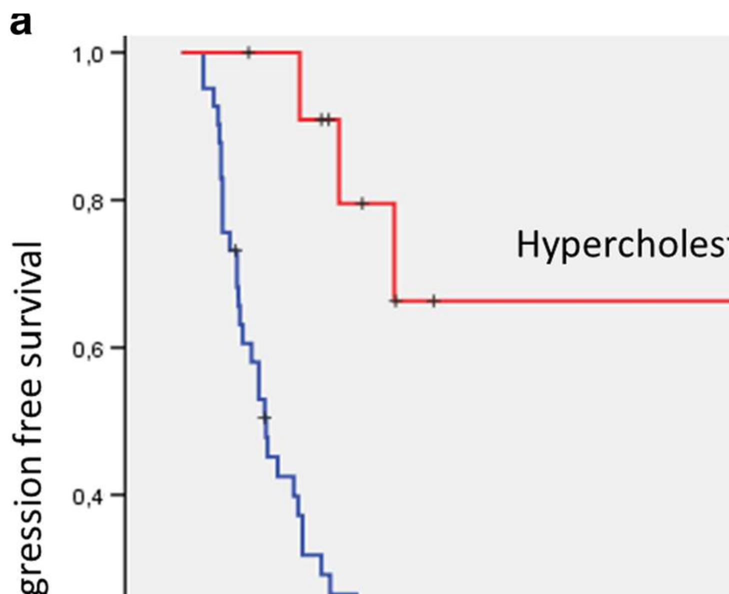
SHORT REPORT

Published online: 26 May 2016

Prediction of response to everolimus in neuroendocrine tumors: evaluation of clinical, biological and histological factors

Noura Benslama[1,2,3] & Julien Bollard[2] & Cécile Vercherat[2] & Patrick Massoma[2] & Colette Roche[2] & Valérie Hervieu[2,3,4] & Julien Peron[5] & Catherine Lombard-Bohas[1] & Jean-Yves Scoazec[2] & Thomas Walter[1,2,3]



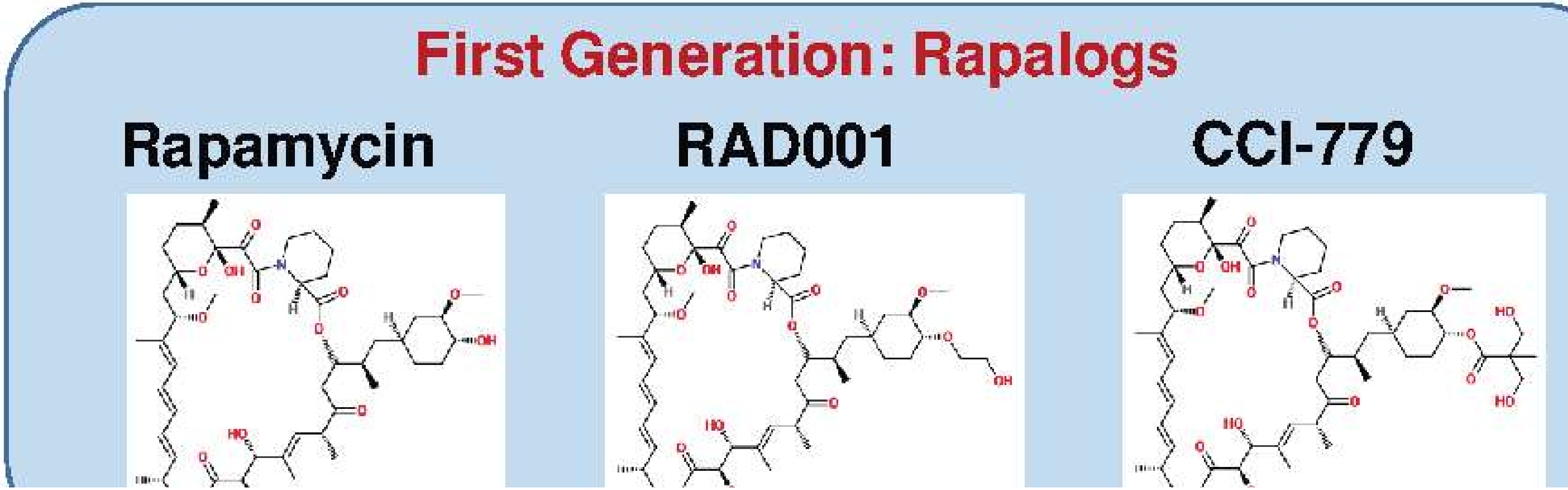


mTOR inhibitors response and mTOR pathway in pancreatic neuroendocrine tumors

Primary cultures

*IHC characterization of **p-AKT** might help in identifying human p-NET who can benefit from Everolimus treatment*

mTORC1 + mTORC2 inhibitors



2nd	AZD8055	Phase I/II (5)	AstraZeneca	Advanced solid t
2nd	INK128/MLN0128	Phase I/II (25)	Intellikine	Advanced solid tu myeloma/Walden macroglobulinem
2nd	OSI027	Phase I/II (1)	OSI Pharmaceuticals	Advanced solid t

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Inhibition of PI3K/Akt/mTOR Signaling by Natural Products

Shile Huang[*]
Department of Biochemistry and Molecular Biology, Feist-Weiller Cancer Center, Louisiana State University Health Sciences Center, 1501 Kings Highway, Shreveport, LA 71130-3932, USA

Nutraceuticals
Apigenin (flavonoid) (fruits, vegetables and beverages)
Cryptotanshinone (roots of the plant Salvia miltiorr[illegible] also called red sage)
C[illegible]
Fi[illegible]
[illegible]ssels sprouts)
[illegible]es (soybeans)
[illegible]uercetin (tea, red grapes, onions)
Resveratrol (red grapes)
Tocotrienols (vit. E)

Thanks !

Red sage