NCPF: Assessing Early Signals of Efficacy to Guide Clinical Development

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Gefitinib: EGFR TKI non-small cell lung cancer response

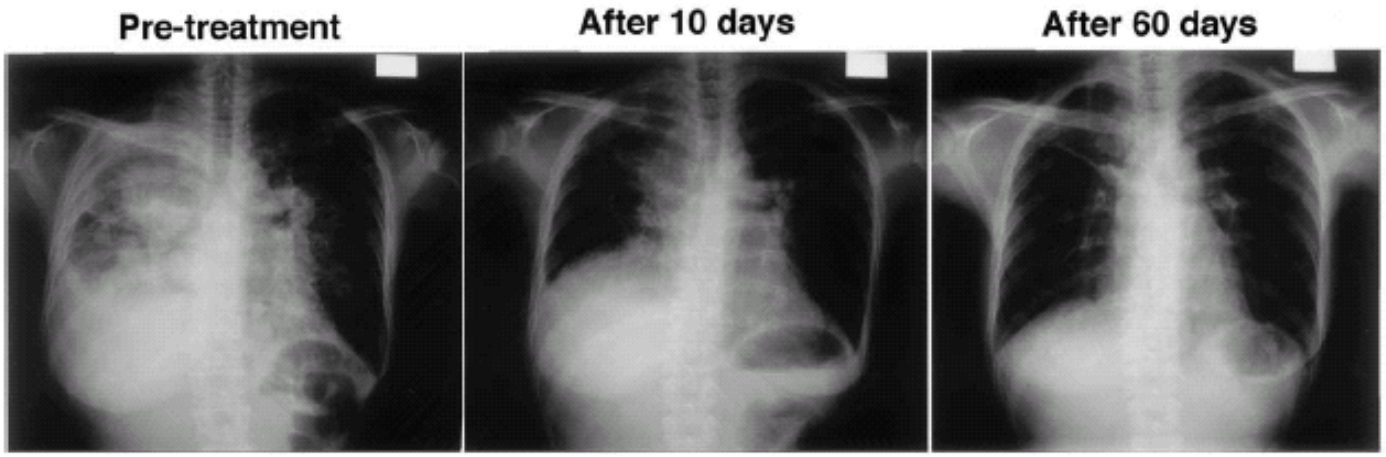
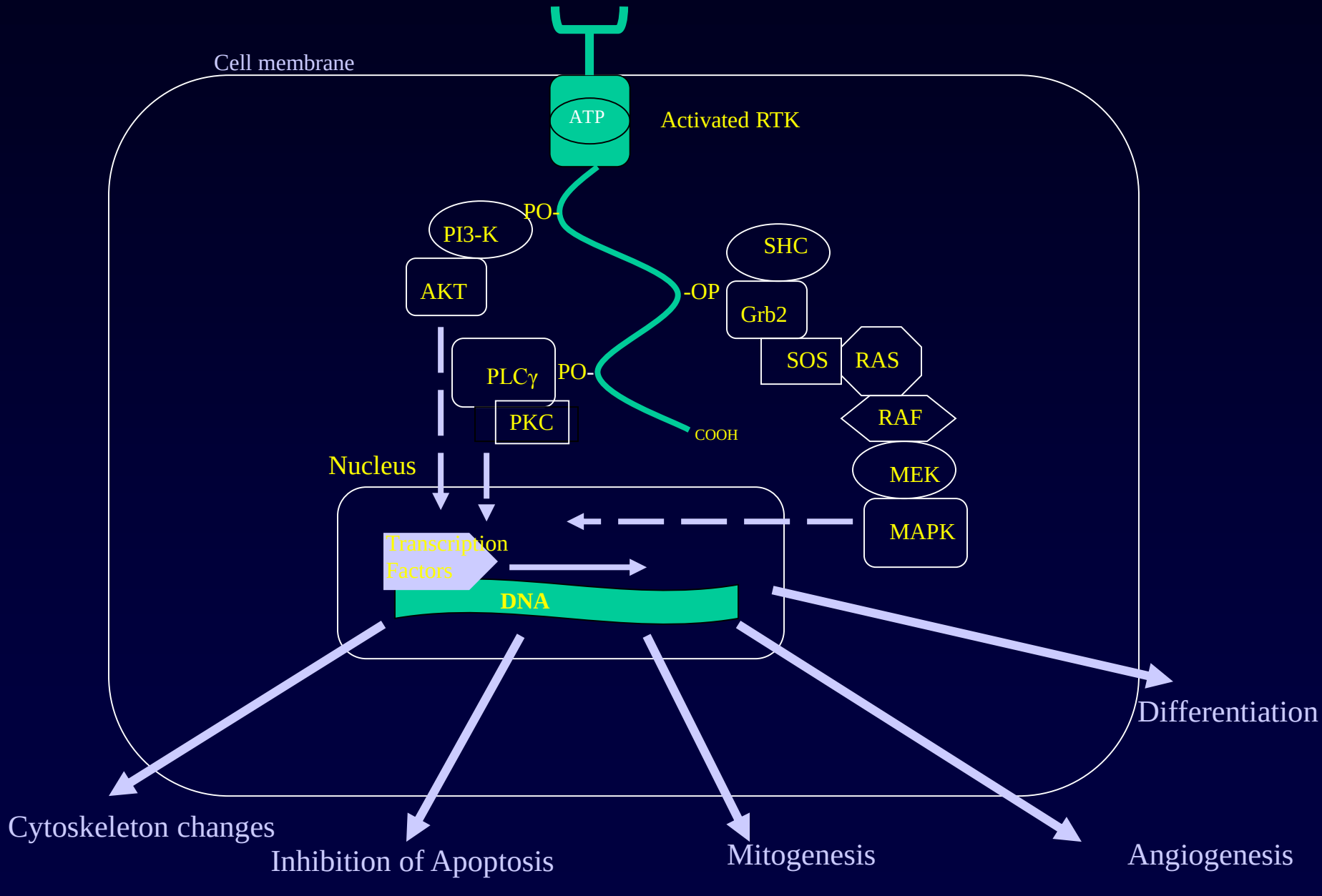
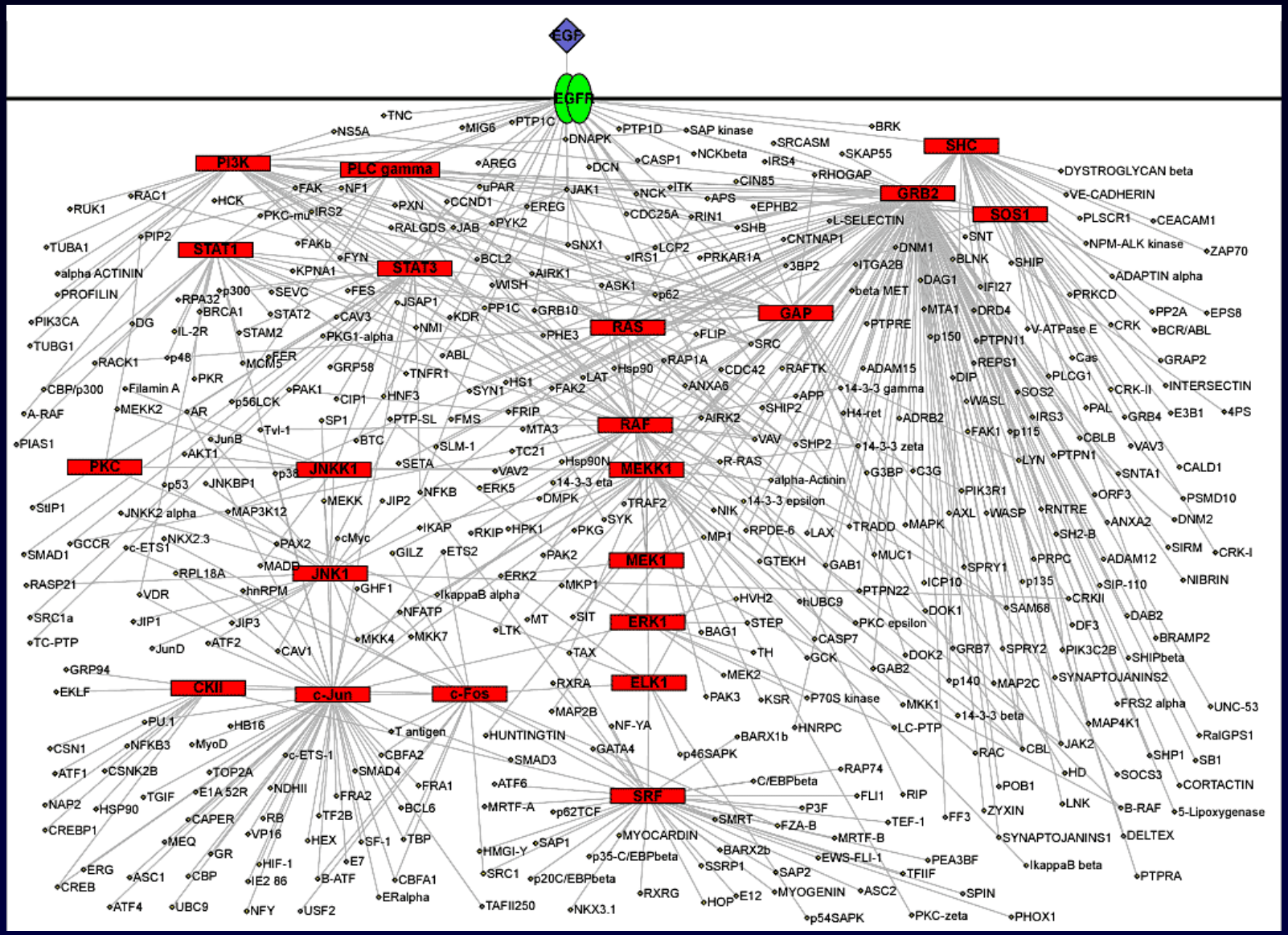


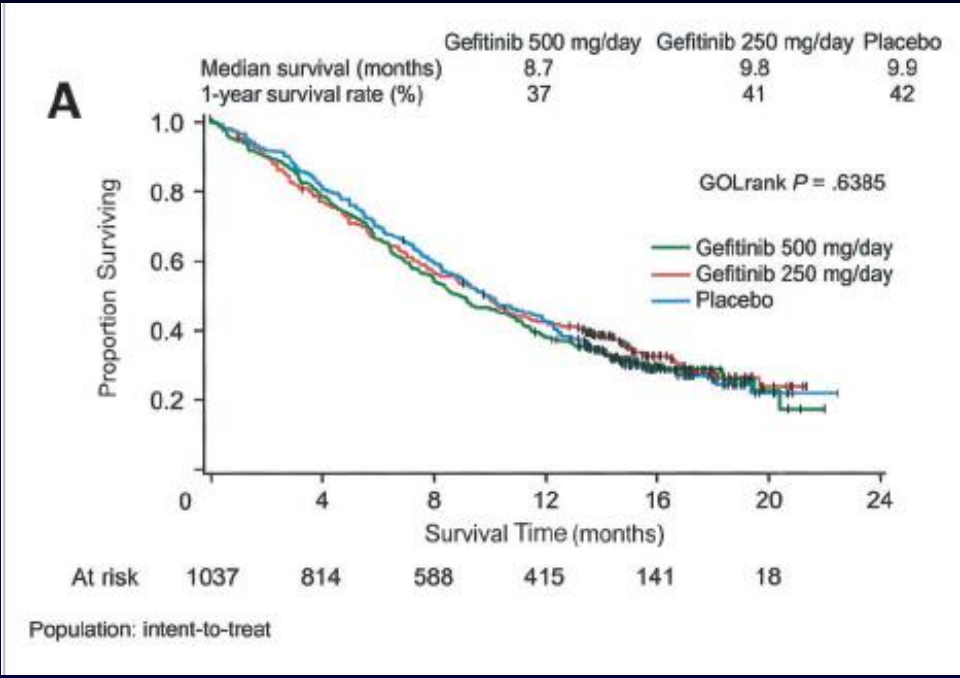
Fig. 1. Chest radiograph of a patient with adenocarcinoma of the lung, before and after treatment with ZD 1839.

Epidermal Growth Factor Receptor (EGFR)





450 genes Human Protein Reference Database (www.hprd.org)



Herbst RS, et al. JCO 2004

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MAY 20, 2004 VOL. 350 NO. 21

Activating Mutations in the Epidermal Growth Factor Receptor Underlying Responsiveness of Non–Small-Cell Lung Cancer to Gefitinib

Thomas J. Lynch, M.D., Daphne W. Bell, Ph.D., Raffaella Sordella, Ph.D., Sarada Gurubhagavatula, M.D., Ross A. Okimoto, B.S., Brian W. Brannigan, B.A., Patricia L. Harris, M.S., Sara M. Haserlat, B.A., Jeffrey G. Supko, Ph.D., Frank G. Haluska, M.D., Ph.D., David N. Louis, M.D., David C. Christiani, M.D., Jeff Settleman, Ph.D., and Daniel A. Haber, M.D., Ph.D.

Sciencexpress Report

EGFR Mutations in Lung Cancer: Correlation with Clinical Response to Gefitinib Therapy

J. Guillermo Paez,[1,2*] Pasi A. Jänne,[1,2*] Jeffrey C. Lee,[1,3*] Sean Tracy,[1] Heidi Greulich,[1,2] Stacey Gabriel,[4] Paula Herman,[1] Frederic J. Kaye,[5] Neal Lindeman,[6] Titus J. Boggon,[1,3] Katsuhiko Naoki,[1] Hidefumi Sasaki,[7] Yoshitaka Fujii,[7] Michael J. Eck,[1,3] William R. Sellers,[1,2,4†] Bruce E. Johnson,[1,2†] Matthew Meyerson[1,3,4†]

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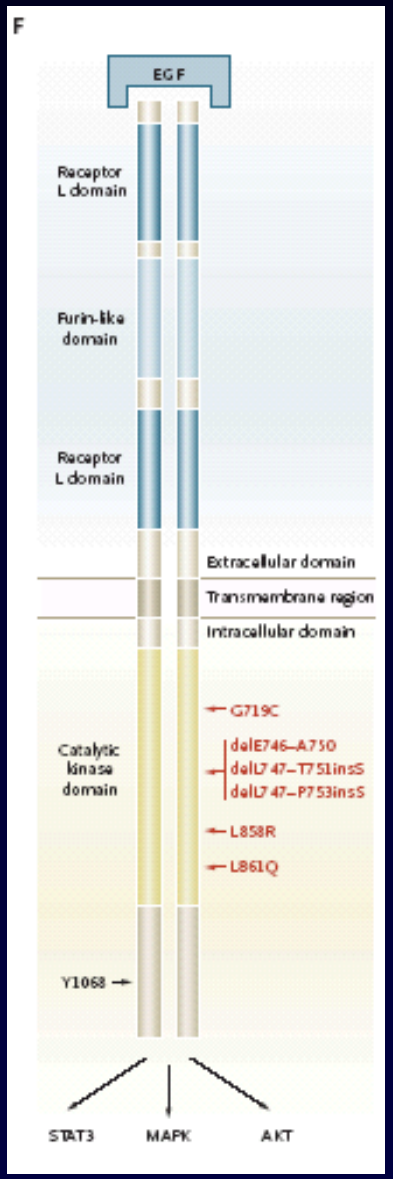
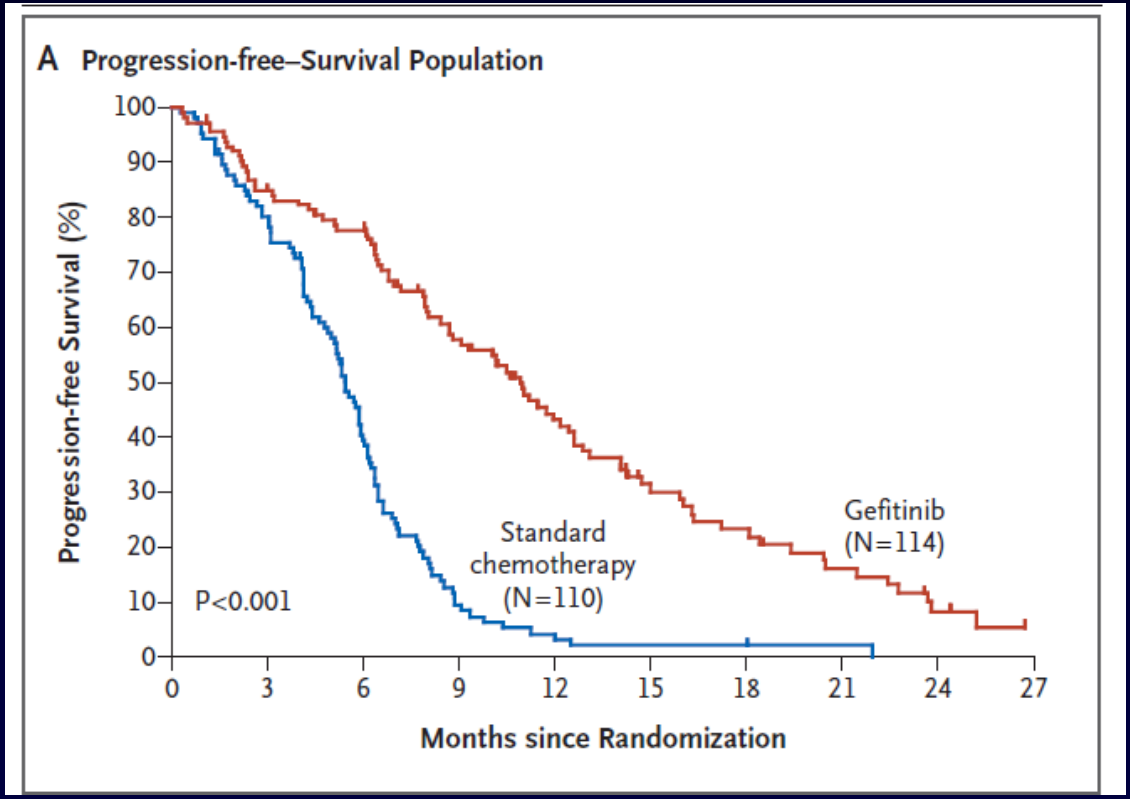


Lynch etal NEJM 2004

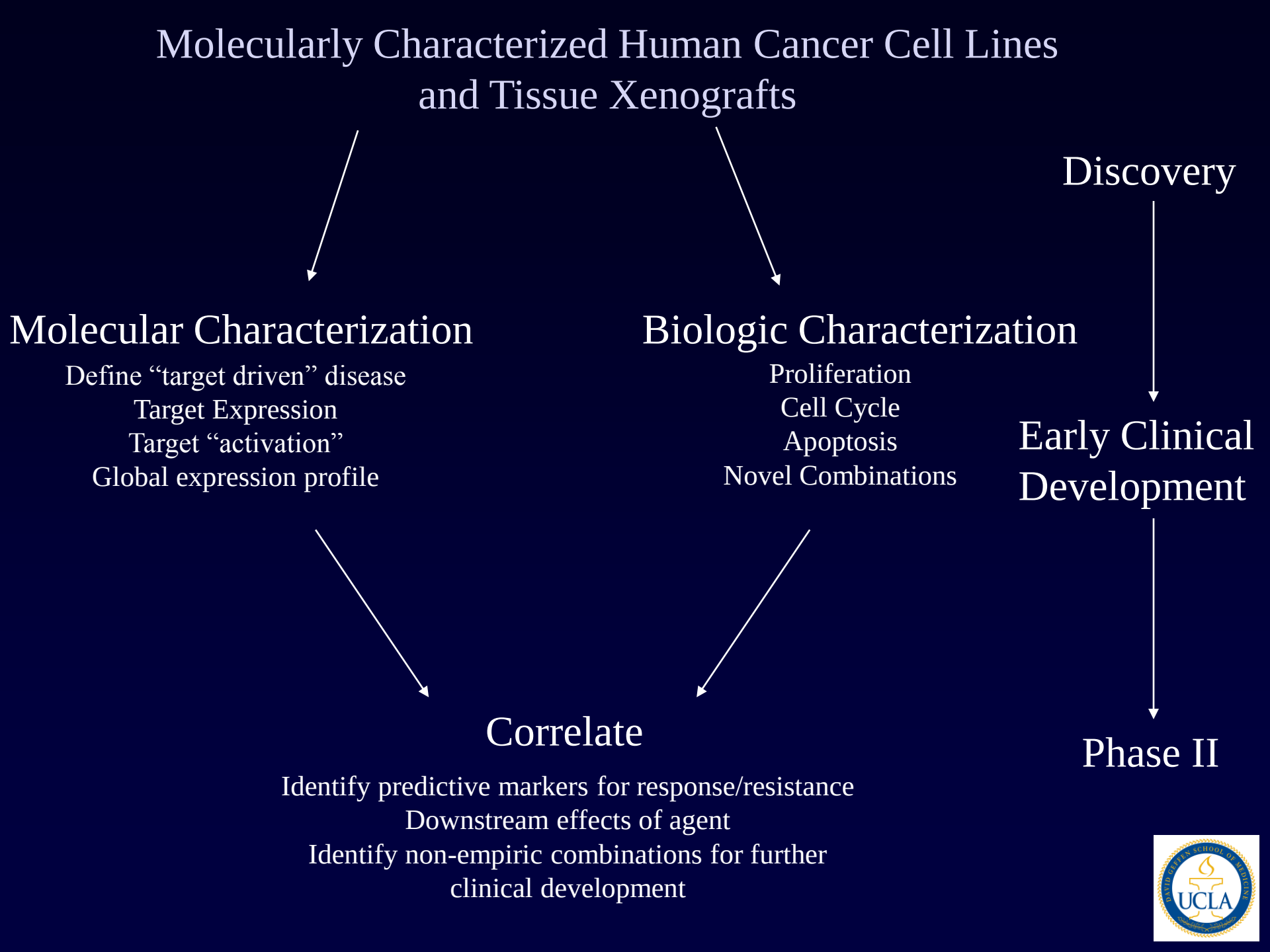
The NEW ENGLAND JOURNAL of MEDICINE

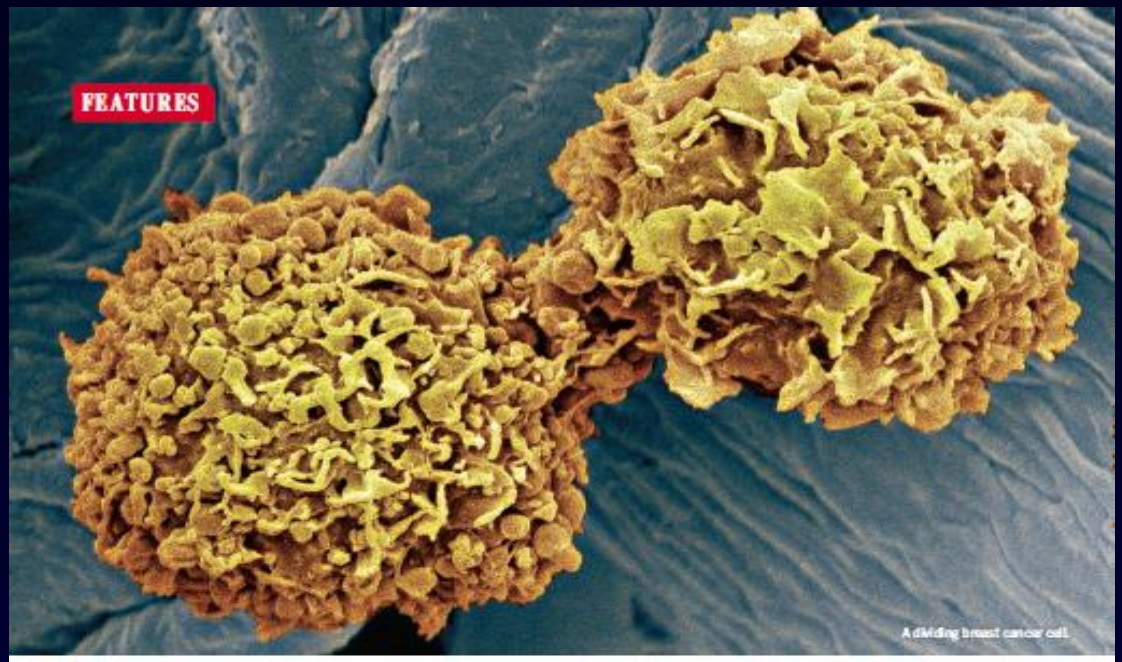
ORIGINAL ARTICLE

Gefitinib or Chemotherapy for Non–Small-Cell Lung Cancer with Mutated EGFR



Maemondo NEJM 2010


Molecularly Characterized Human Cancer Cell Lines and Tissue Xenografts
Discovery
Molecular Characterization
Define "target driven" disease
Target Expression
Target "activation"
Global expression profile
Biologic Characterization
Proliferation
Cell Cycle
Apoptosis
Novel Combinations
Early Clinical Development
Correlate
Identify predictive markers for response/resistance
Downstream effects of agent
Identify non-empiric combinations for further clinical development
Phase II



The cancer drug that almost wasn't

After years in drug development limbo, a compound that interrupts cell division has revitalized a troubled area of cancer research

By **Ken Garber**

Progress in cancer treatment can be frustratingly incremental. A new therapy often does no more than stall the disease by a few extra weeks. At a cancer meeting in San Diego, California, in April, however, University of California, Los Angeles (UCLA), oncologist Richard Finn reported that adding a drug called palbociclib to standard therapy doubled the time that women with metastatic breast cancer experienced no new tumor growth, from a median of 10 months to 20. "No study, despite efforts, has shown this dramatic improvement in progression-free survival, with the addition of a novel agent," Finn told the audience.

The results won't dispel all doubts about the drug—or the new treatment strategy it represents. The phase II trial Finn discussed enrolled just 165 women, and it is too early to know whether those taking the drug combination live significantly longer than women on standard therapy. But palbociclib, which is under development by pharmaceutical giant Pfizer, has captivated the cancer field nonetheless. "The ... buzz is that these are extremely impressive data that are really way beyond what anybody had expected," says Frank McCormick, a veteran cancer researcher at UC San Francisco, who played an early role in the drug's discovery.

Palbociclib has traveled a long and tortuous road. The product of a project started in 1995 by researchers at Parke-Davis, a now-vanished drug company, the compound blocks key enzymes driving the cell cycle, the ordered set of processes by which a cell divides. Mounting scientific evidence suggested its potential in breast cancer. Yet Pfizer, where the compound was ultimately synthesized by the Parke-Davis

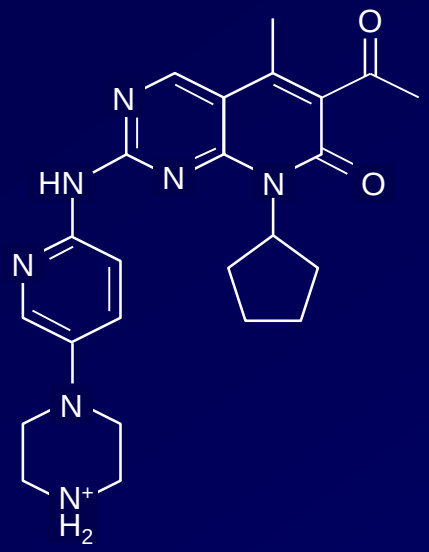
PHOTO: STEVE GSCHMEISSNER/SCIENCE SOURCE

Published by AAAS

Science 2014

Palbociclib: an Oral Selective CDK 4/6 Kinase Inhibitor

- **Inhibits cell proliferation and cellular DNA synthesis by preventing cell-cycle progression from G1 to S phase**
- ***In vitro* activity in retinoblastoma-positive tumor cell lines and primary tumors**
- **Low nanomolar concentrations block Rb phosphorylation, inducing G1 arrest in sensitive cell lines**
- **Specific cell cycle arrest in G1 phase**

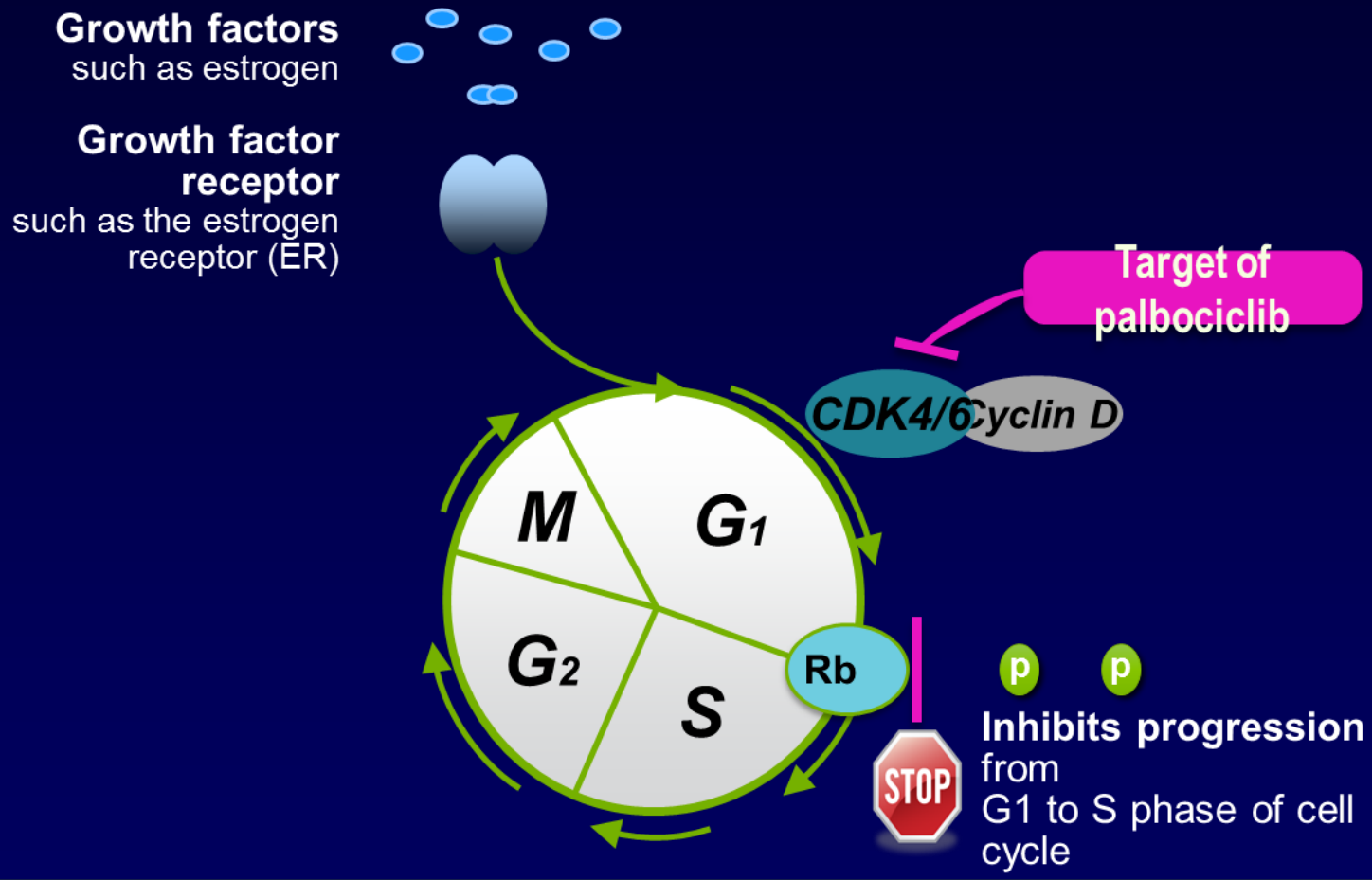


Palbociclib (PD-0332991)

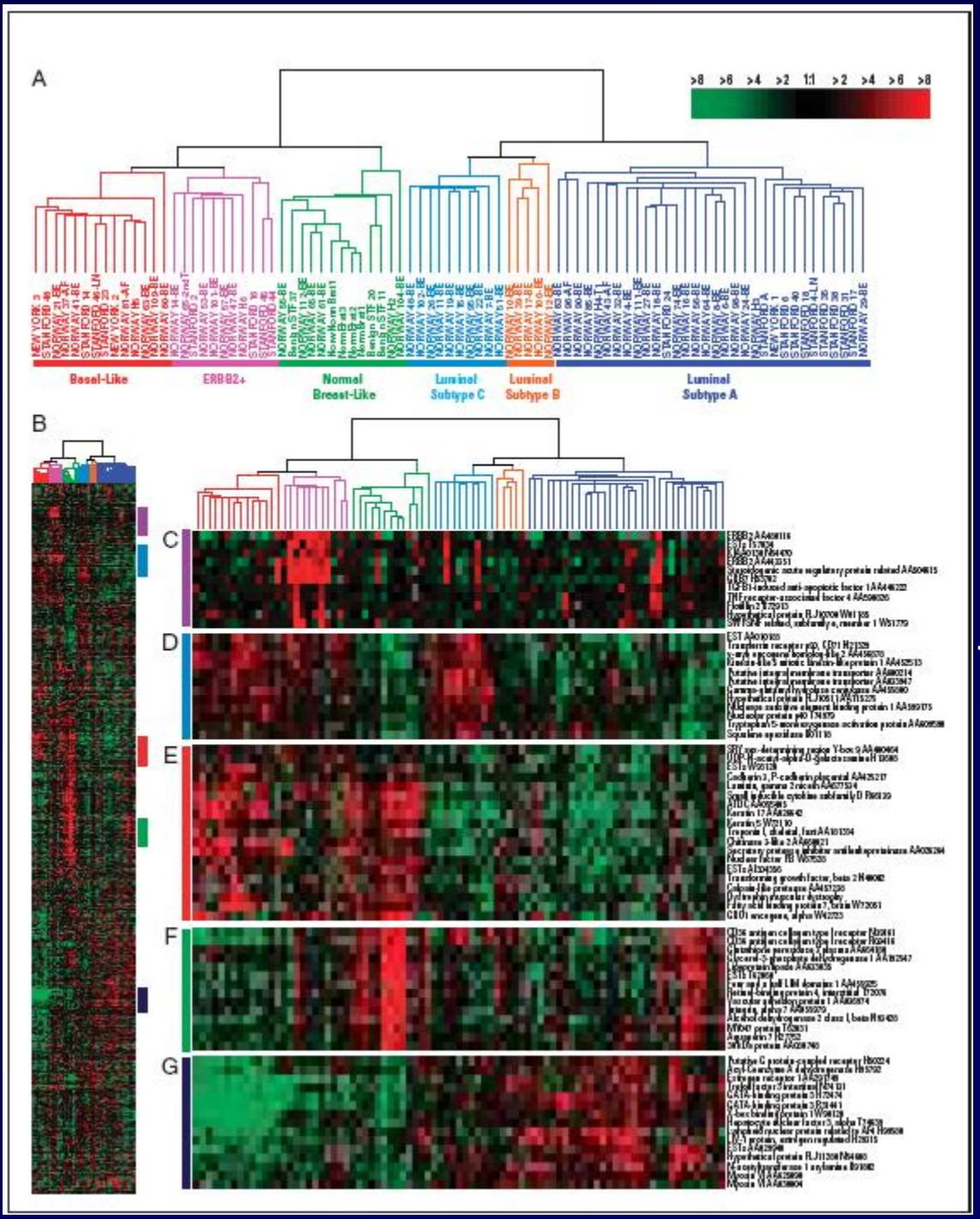
CDK (partner)	IC_{50} (mM)
CDK4 (cyclin D1)	0.011
CDK4 (cyclin D3)	0.009
CDK6 (cyclin D2)	0.015
CDK2 (cyclin A)	>10
CDK1 (cyclin B)	>10
CDK5 (p25)	>10

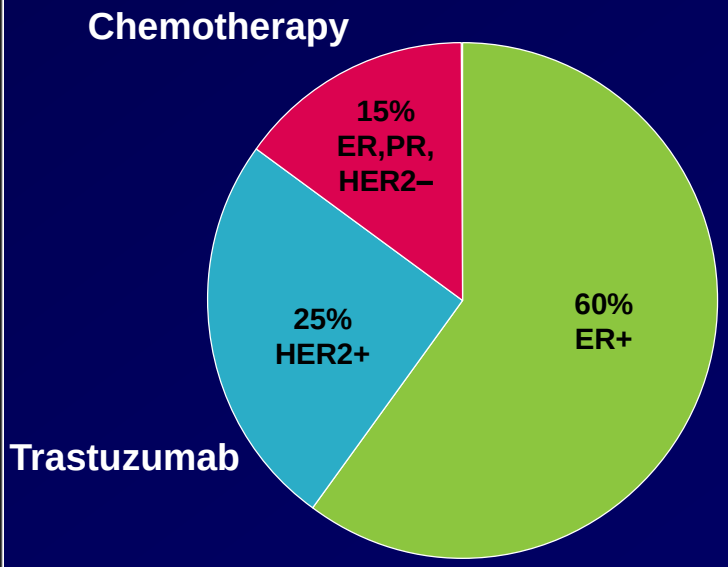
Fry DW, et al. *Mol Cancer Ther* 2004;3:1427-38
Menu E, et al. *Cancer Res* 2008;68:5519-23
Sutherland RL, Musgrove EA. *Breast Cancer Res* 2009;11:112

Palbociclib Mechanism of Action: *Inhibition of the Cell Cycle*



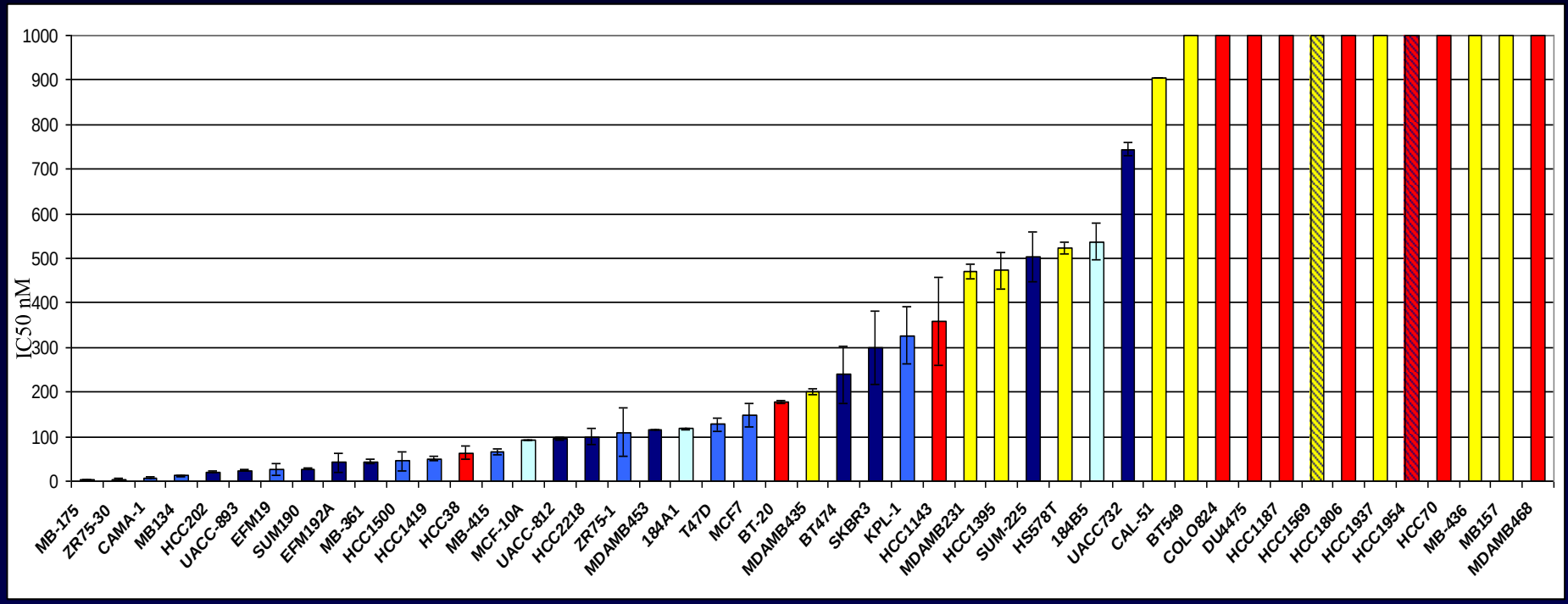
Palbociclib arrests the cell cycle at G_1 by selective inhibition of CDK4/6





Sörlie T, et al. *PNAS*. 2001;98:10869-74

Palbociclib: CDK 4/6 Inhibitor – Breast Panel

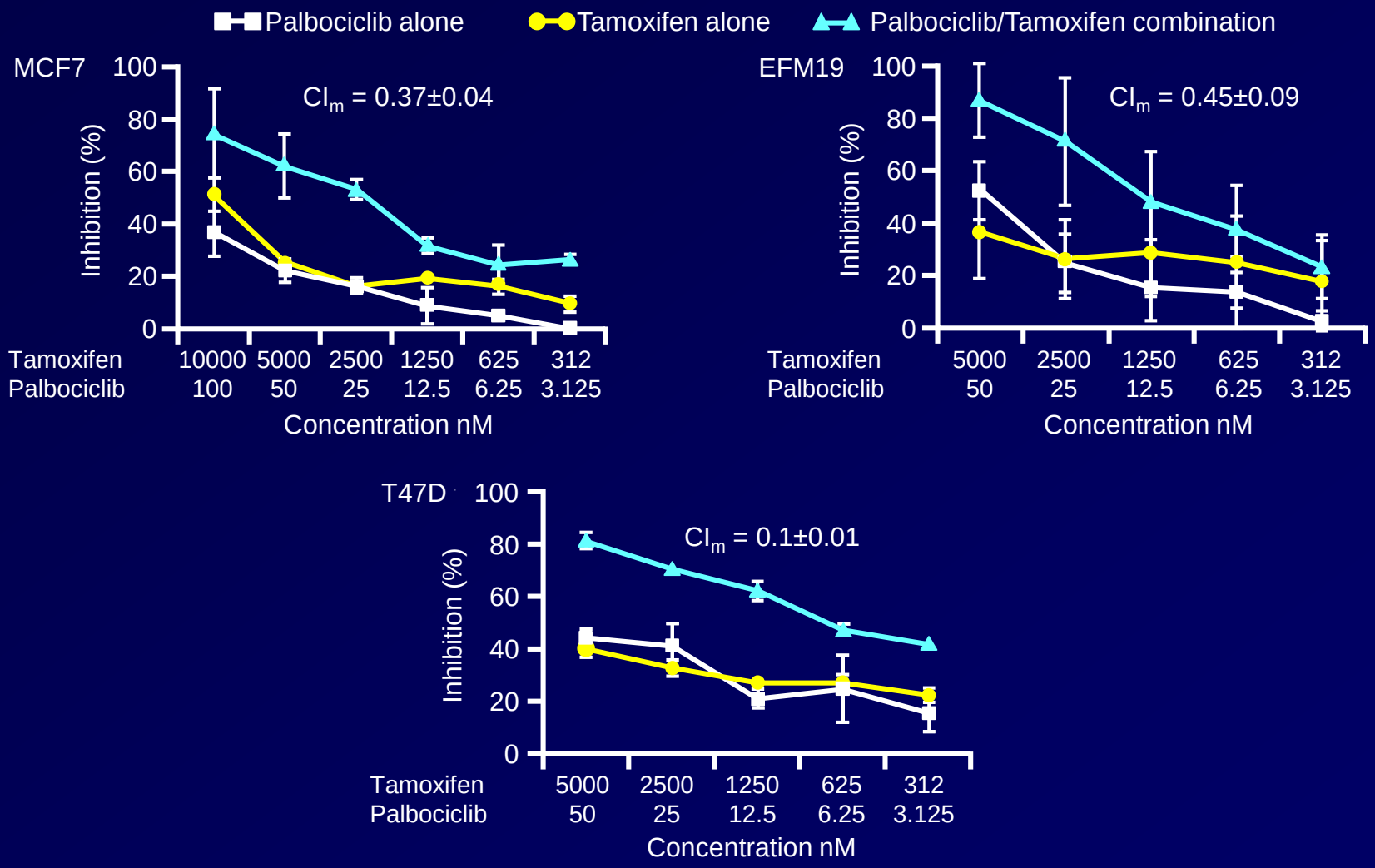


Subtype

- Luminal
- HER2 amplified
- Immortalized
- Non-luminal/post EMT
- Non-luminal

Finn RS, et al. *Breast Cancer Res.* 2009;11(5):R77.

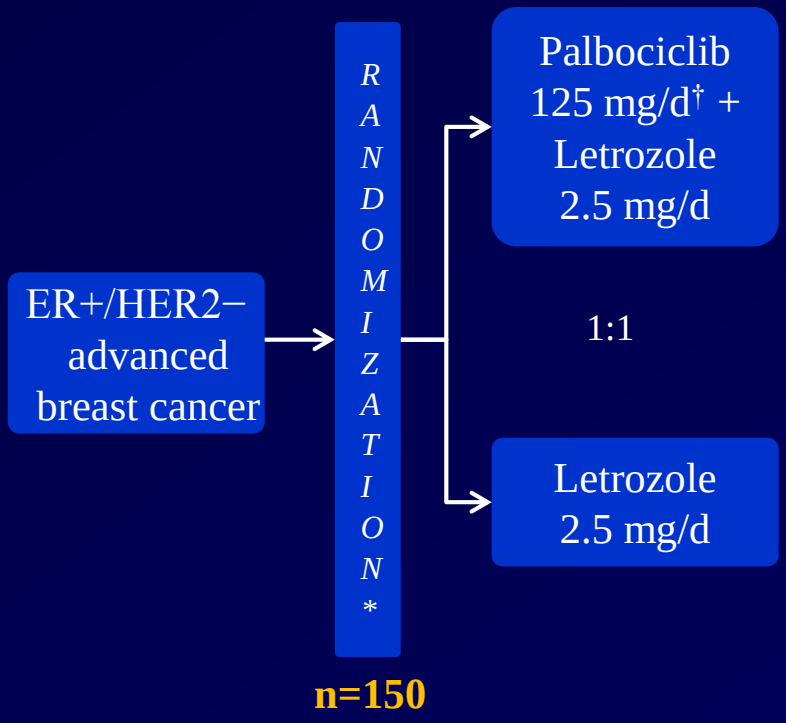
Palbociclib Acts Synergistically with Tamoxifen in ER+ Breast Cancer Cell Lines



- **Mean combination index (CI_m) <1 indicates synergy for the combinations**

Finn RS, et al. *Breast Cancer Res.* 2009;11(5):R77

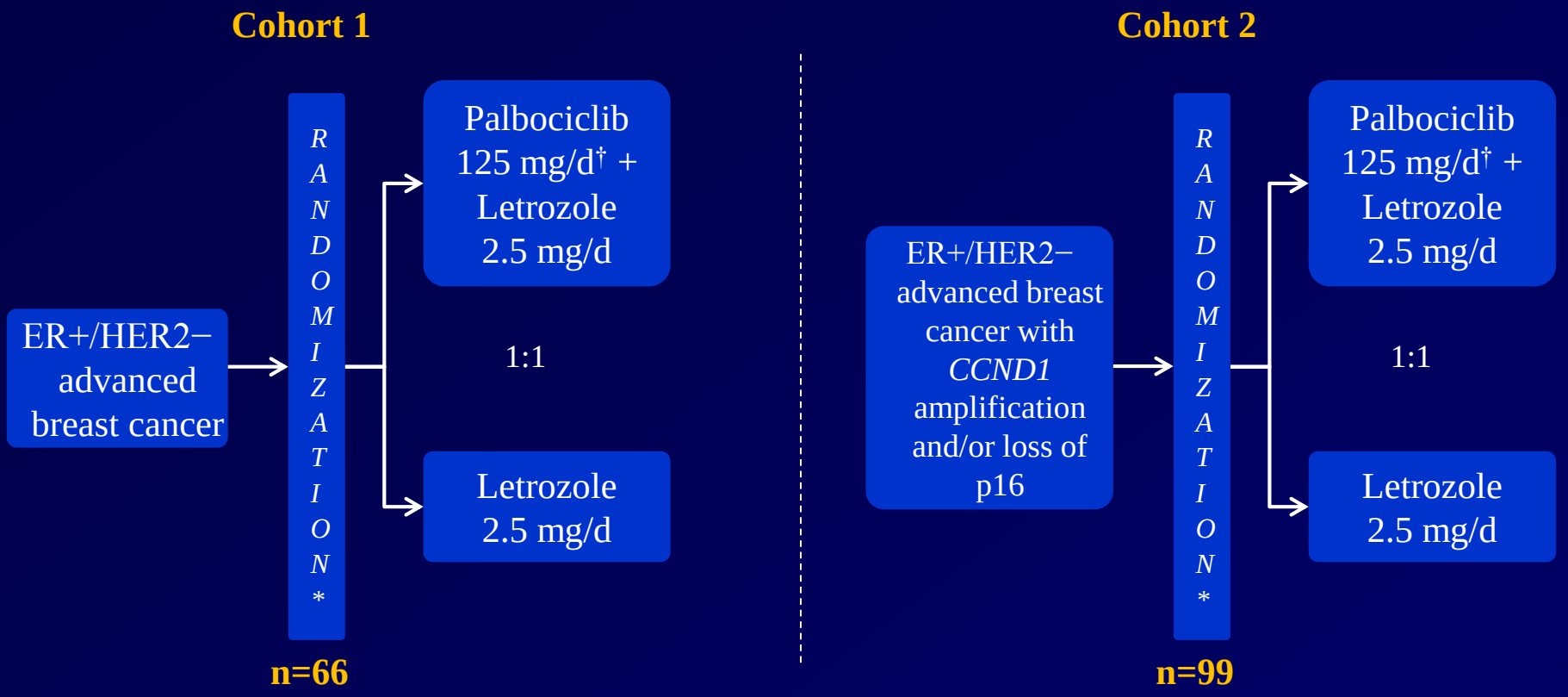
PALOMA-1/TRIO-18 Study Design (NCT00721409)



- Randomized phase II open-label trial involving 50 centers in 12 countries
- Key eligibility criteria: inoperable ER+/HER2– locally recurrent disease, postmenopausal status, no prior therapy for advanced breast cancer, no prior CDK inhibitors, no letrozole within 12 months, no prior/current brain metastases, measurable disease (RECIST 1.0) or bone-only disease, ECOG performance status ≤1, adequate bone marrow and renal function

*Randomization stratified by disease site and disease-free interval.
† Palbociclib schedule 3/1 (28-day cycles).
Finn RS, et al. *Lancet Oncol*. 2015;16(1):25-35.

PALOMA-1/TRIO-18 Study Design (NCT00721409)



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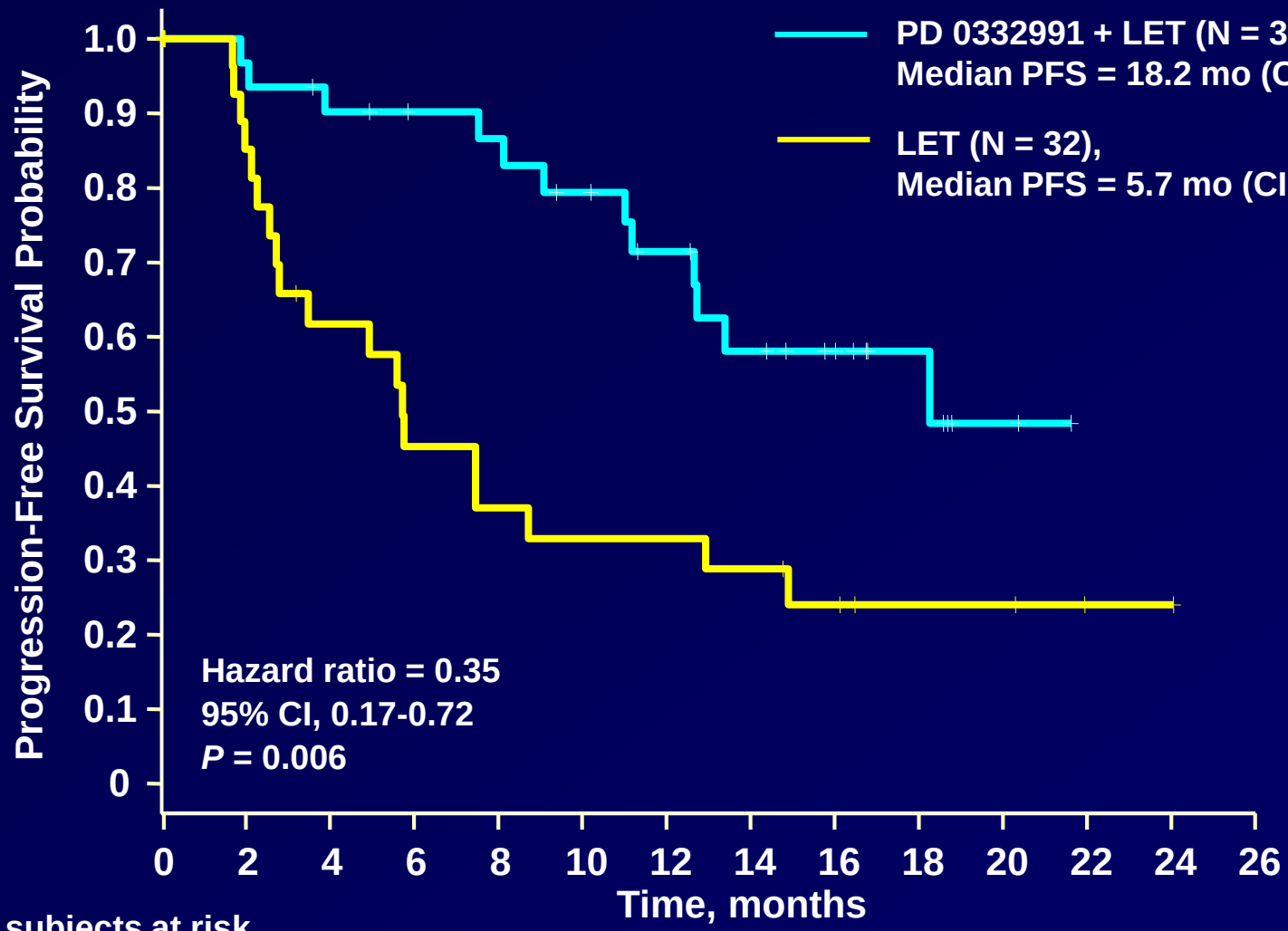
*Randomization stratified by disease site and disease-free interval.
† Palbociclib schedule 3/1 (28-day cycles).
Finn RS, et al. *Lancet Oncol*. 2015;16(1):25-35.

Progression-Free Survival



Number of subjects at risk

PD 0332991 + LET	34	30	27	25	24	21	17	13	10	6	2		
LET	32	22	15	11	9	8	8	7	5	3	3	1	1

Finn RS et al IMPAKT 2012

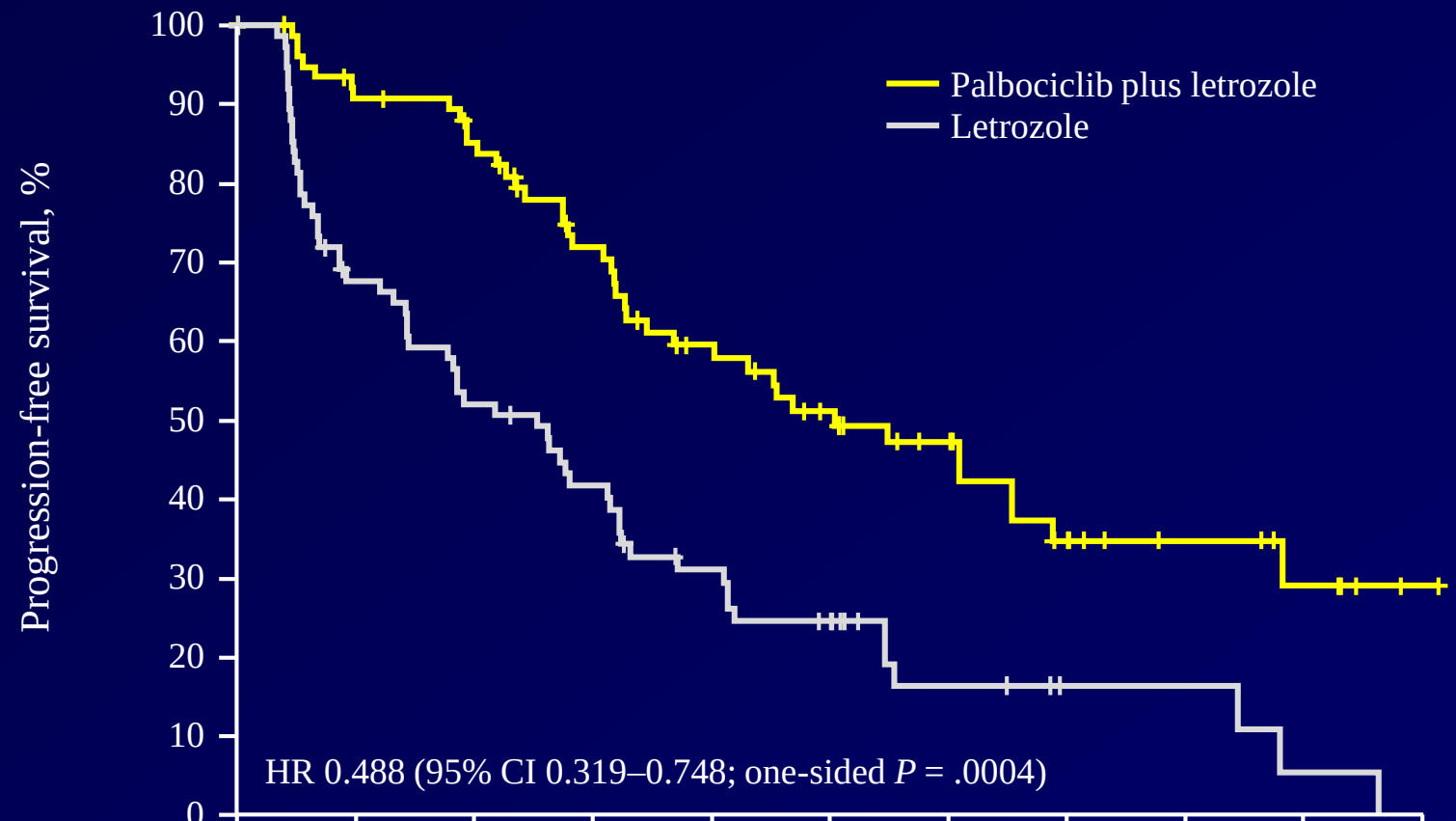
Progression-Free Survival by Biomarker Status*

Population	Comparison	Number of Patients	HR (95% CI) / P value
Biomarker Positive	*PD 0332991 + Letrozole vs. Letrozole*	12 9	0.37 (0.10, 1.40) / 0.13
Biomarker Negative	*PD 0332991 + Letrozole vs. Letrozole*	10 15	0.19 (0.05, 0.67) / <0.01
Biomarker Status Unknown	*PD 0332991 + Letrozole vs. Letrozole*	12 8	0.59 (0.11, 3.08) / 0.53
PD 0332991 + Letrozole	*Biomarker Positive vs. Biomarker Negative*	12 10	1.42 (0.31, 6.43) / 0.65
Letrozole	*Biomarker Positive vs. Biomarker Negative*	9 15	0.68 (0.24, 1.94) / 0.47

* CCND1 amplification and/or loss of p16.

Finn RS et al IMPAKT 2012

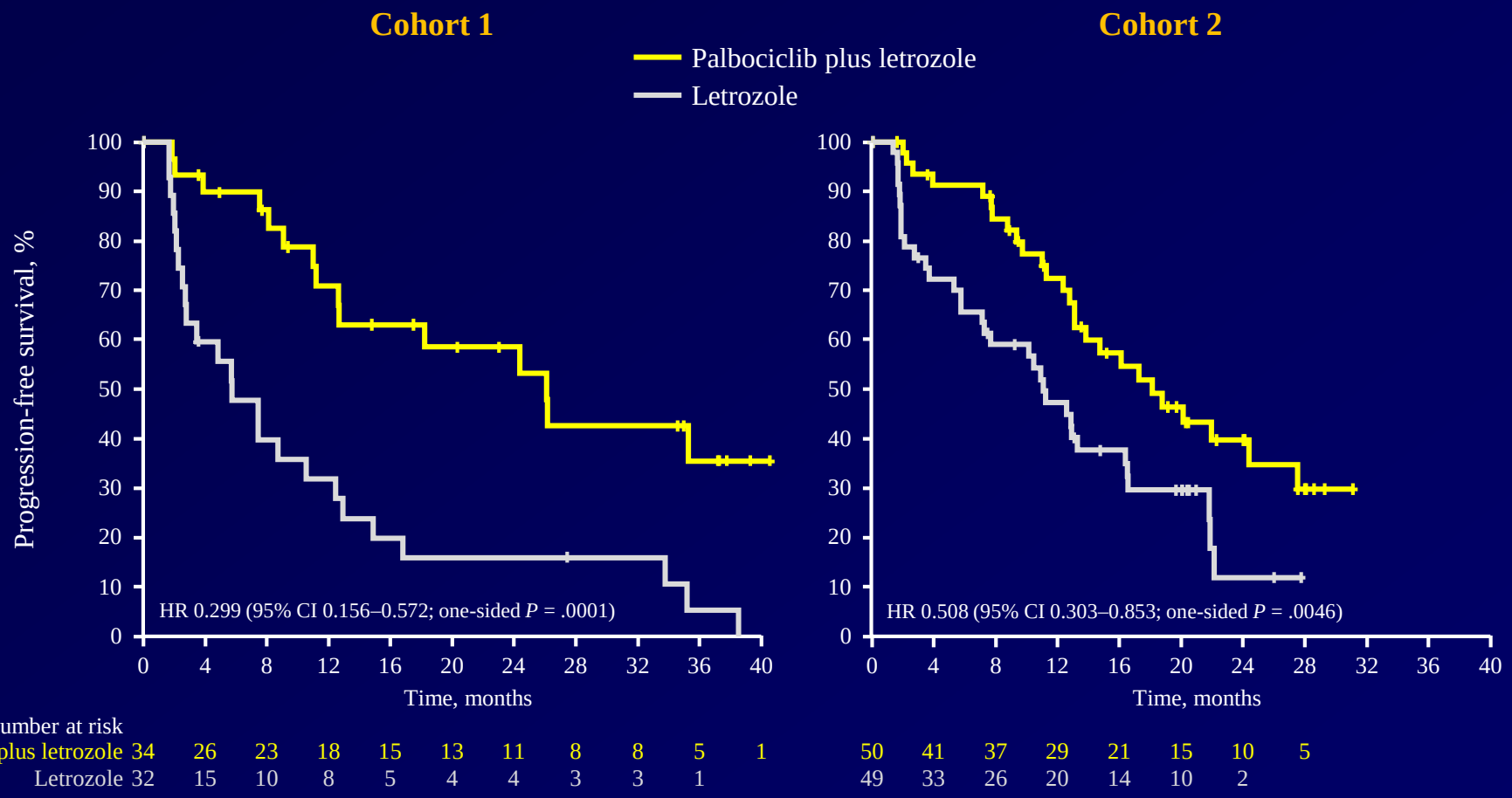
PALOMA-1/TRIO-18: PFS (ITT Population)



Number at risk											
Palbociclib plus letrozole	84	67	60	47	36	28	21	13	8	5	1
Letrozole	81	48	36	28	19	14	6	3	3	1	

Finn RS, et al. *Lancet Oncol*. 2015;16(1):25-35.

PALOMA-1/TRIO-18: PFS (Cohorts)



Finn RS, et al. *Lancet Oncol*. 2015;16(1):25-35.

February 3rd 2015

- U.S. Food and Drug Administration (FDA) granted accelerated approval of palbociclib (IBRANCE®)

- Indicated in combination with letrozole, for the treatment of postmenopausal women with ER+/ HER2- advanced breast cancer as initial endocrine-based therapy

- This indication is approved under accelerated approval based on progression-free survival (PFS). Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial (PALOMA-2)

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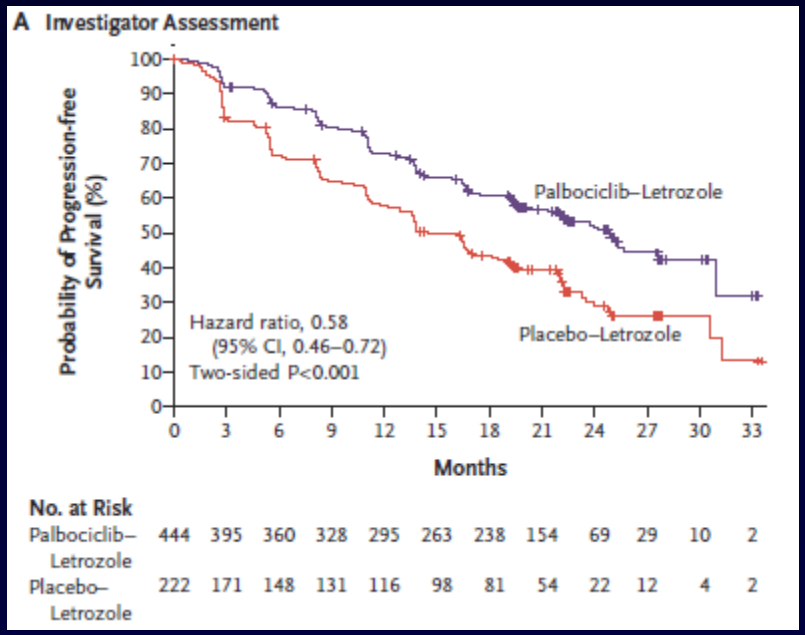
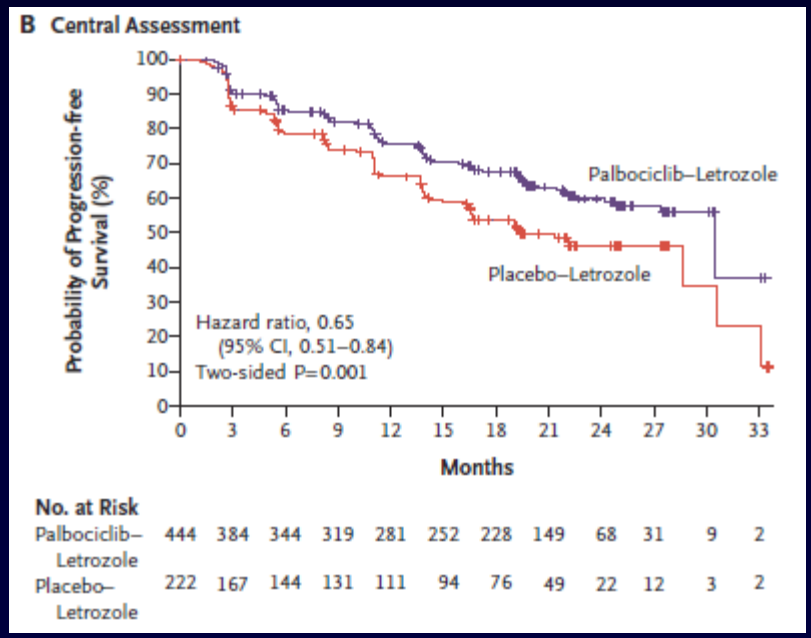
Palbociclib and Letrozole in Advanced Breast Cancer

Richard S. Finn, M.D., Miguel Martin, M.D., Hope S. Rugo, M.D., Stephen Jones, M.D., Seock-Ah Im, M.D., Ph.D., Karen Gelmon, M.D., Nadia Harbeck, M.D., Ph.D., Oleg N. Lipatov, M.D., Janice M. Walshe, M.D., Stacy Moulder, M.D., Eric Gauthier, Pharm.D., Ph.D., Dongrui R. Lu, M.Sc., Sophia Randolph, M.D., Ph.D., Véronique Diéras, M.D., and Dennis J. Slamon, M.D., Ph.D.





August 2007: in lab

Development of Palbociclib:
First Approved CDK 4/6 Inhibitor

Nov 2007: data shared

September 2008: Phase I open

November 2009: Phase II open

FDA Approved February 2015

Global Approval 2016

The NEW ENGLAND JOURNAL of MEDICINE

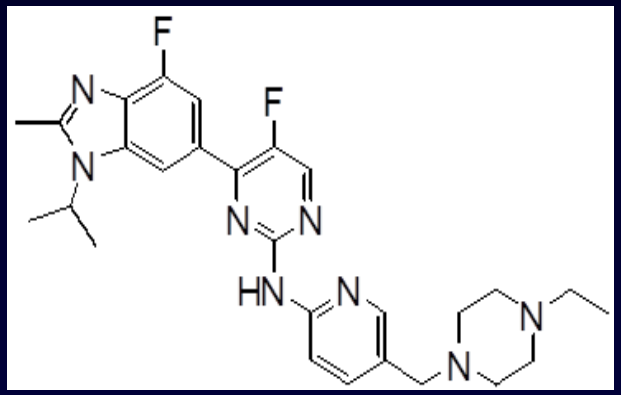
ORIGINAL ARTICLE

Ribociclib as First-Line Therapy for HR-Positive, Advanced Breast Cancer

G.N. Hortobagyi, S.M. Stemmer, H.A. Burris, Y.-S. Yap, G.S. Sonke, S. Paluch-Shimon, M. Campone, K.L. Blackwell, F. André, E.P. Winer, W. Janni, S. Verma, P. Conte, C.L. Arteaga, D.A. Cameron, K. Petrakova, L.L. Hart, C. Villanueva, A. Chan, E. Jakobsen, A. Nusch, O. Burdaeva, E.-M. Grischke, E. Alba, E. Wist, N. Marschner, A.M. Favret, D. Yardley, T. Bachelot, L.-M. Tseng, S. Blau, F. Xuan, F. Souami, M. Miller, C. Germa, S. Hirawat, and J. O'Shaughnessy

http://www.nejm.org/doi/pdf/10.1056/NEJMoa1609709
DOI: 10.1056/NEJMoa1609709

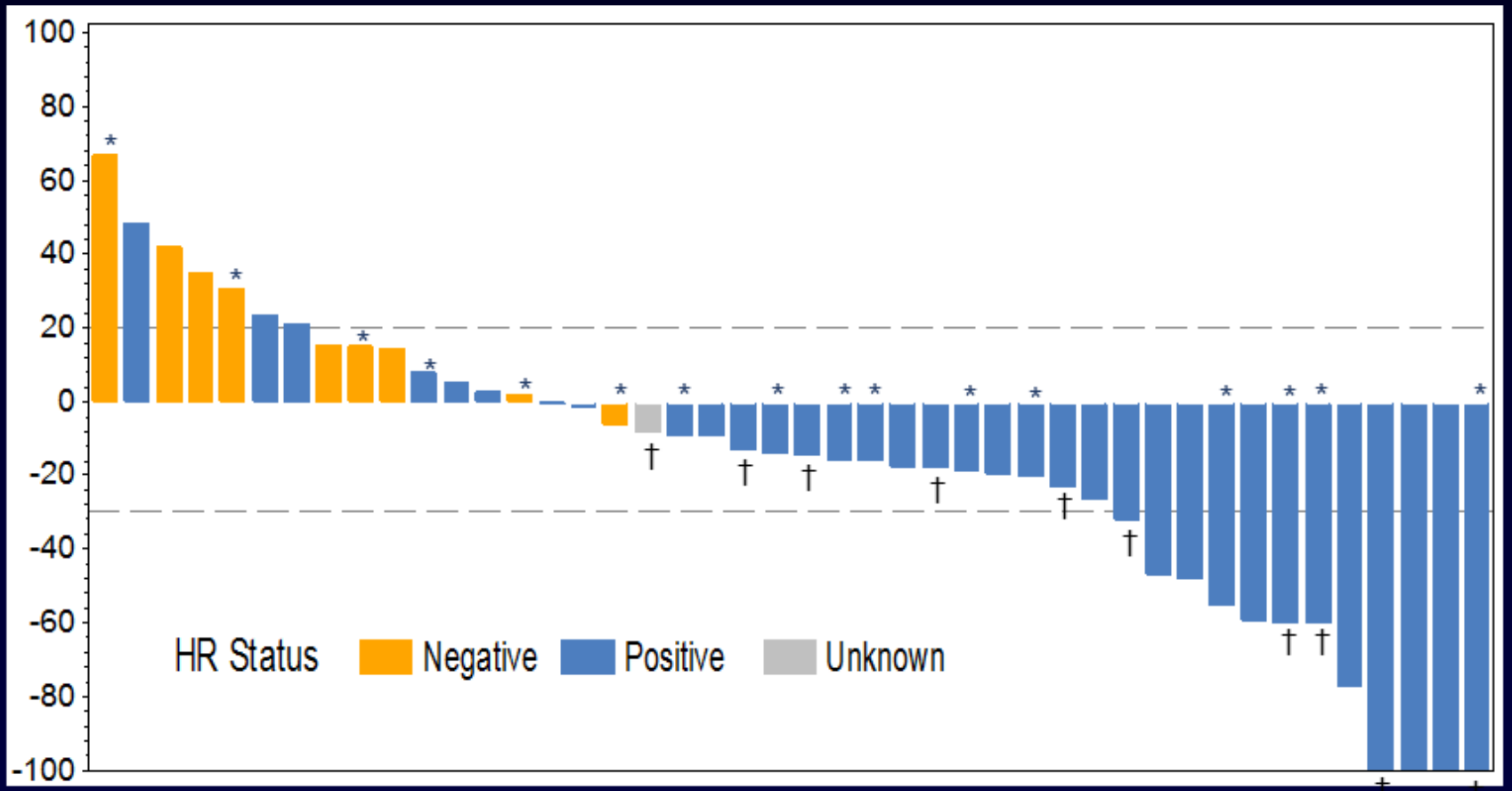
Abemaciclib (LY2835219)



Kinase	IC50 (nM)*
hCDK4 / cyclinD1	2.0
hCDK6 / cyclinD1	9.9
hCDK1 / cyclinB1	1627.0
hCDK9 / cyclinT1	57.0
hPIM1	50.0

**Abemaciclib mesylate*

Change in Tumor Size (Part D, Abemaciclib)



[a]3 non-evaluable patients are not shown. All patients in Part D were required to have measurable disease.

† Patient progressing on endocrine therapy before study entry and continued on that specific therapy

* Indicates HER2+

NCT01394016

Tolaney et al. SABCS 2014

October 8th 2015

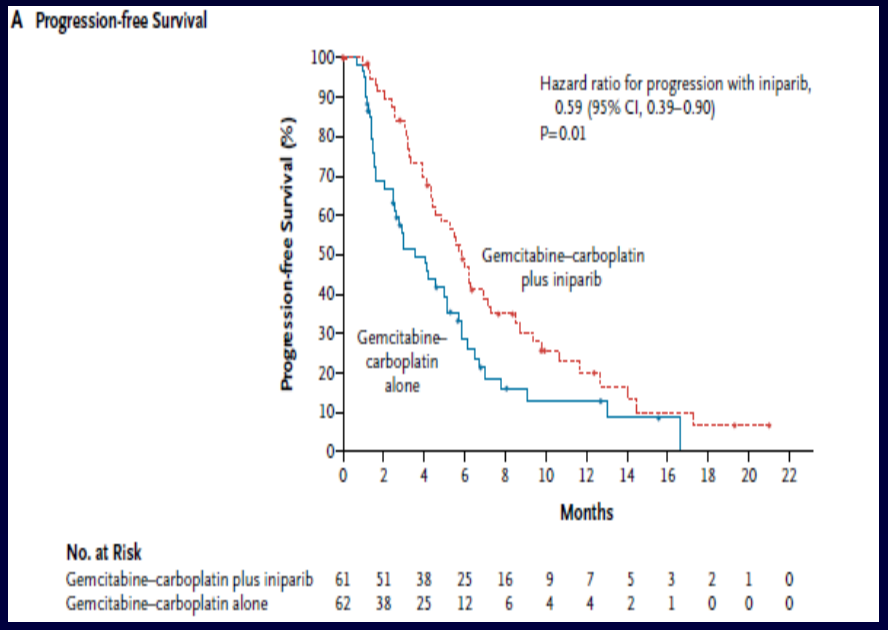
- U.S. Food and Drug Administration (FDA) granted "Breakthrough Therapy Designation" as monotherapy for heavily pre-treaetd patients with refractory hormone-receptor-positive advanced breast cancer

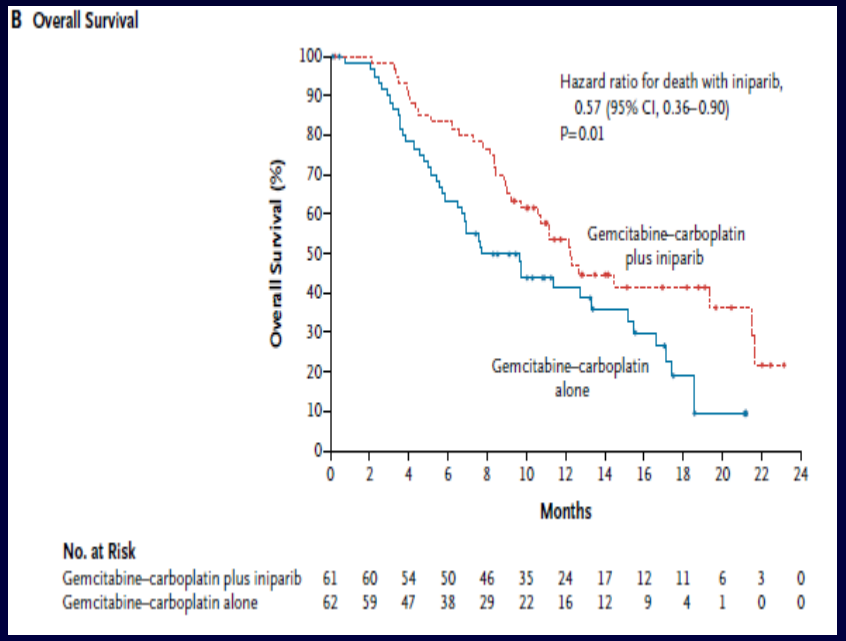
The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JANUARY 20, 2011 VOL. 364 NO. 3

Iniparib plus Chemotherapy in Metastatic Triple-Negative Breast Cancer

Joyce O'Shaughnessy, M.D., Cynthia Osborne, M.D., John E. Pippen, M.D., Mark Yoffe, M.D., Debra Patt, M.D., Christine Rocha, M.Sc., Ingrid Chou Koo, Ph.D., Barry M. Sherman, M.D., and Charles Bradley, Ph.D.*





Genomic Data by Breast Subtype

Table 1 | Highlights of genomic, clinical and proteomic features of subtypes

Subtype	Luminal A	Luminal B	Basal-like	HER2E
$ER^+/HER2^-$ (%)	87	82	10	20
$HER2^+$ (%)	7	15	2	68
TNBCs (%)	2	1	80	9
TP53 pathway	*TP53* mut (12%); gain of *MDM2* (14%)	*TP53* mut (32%); gain of *MDM2* (31%)	*TP53* mut (84%); gain of *MDM2* (14%)	*TP53* mut (75%); gain of *MDM2* (30%)
PIK3CA/PTEN pathway	*PIK3CA* mut (49%); *PTEN* mut/loss (13%); *INPP4B* loss (9%)	PIK3CA mut (32%) PTEN mut/loss (24%) INPP4B loss (16%)	PIK3CA mut (7%); PTEN mut/loss (35%); INPP4B loss (30%)	PIK3CA mut (42%); PTEN mut/loss (19%); INPP4B loss (30%)
RB1 pathway	Cyclin D1 amp (29%); *CDK4* gain (14%); low expression of *CDKN2C*; high expression of *RB1*	Cyclin D1 amp (58%); *CDK4* gain (25%)	*RB1* mut/loss (20%); cyclin E1 amp (9%); high expression of *CDKN2A*; low expression of *RB1*	Cyclin D1 amp (38%); *CDK4* gain (24%)
mRNA expression	High ER cluster; low proliferation	Lower ER cluster; high proliferation	Basal signature; high proliferation	HER2 amplicon signature; high proliferation
Copy number	Most diploid; many with quiet genomes; 1q, 8q, 8p11 gain; 8p, 16q loss; 11q13.3 amp (24%)	Most aneuploid; many with focal amp; 1q, 8q, 8p11 gain; 8p, 16q loss; 11q13.3 amp (51%); 8p11.23 amp (28%)	Most aneuploid; high genomic instability; 1q, 10p gain; 8p, 5q loss; *MYC* focal gain (40%)	Most aneuploid; high genomic instability; 1q, 8q gain; 8p loss; 17q12 focal *ERRB2* amp (71%)
DNA mutations	*PIK3CA* (49%); *TP53* (12%); *GATA3* (14%); *MAP3K1* (14%)	*TP53* (32%); *PIK3CA* (32%); *MAP3K1* (5%)	*TP53* (84%); *PIK3CA* (7%)	*TP53* (75%); *PIK3CA* (42%); *PIK3R1* (8%)
DNA methylation	–	Hypermethylated phenotype for subset	Hypomethylated	–
Protein expression	High oestrogen signalling; high MYB; RPPA reactive subtypes	Less oestrogen signalling; high FOXM1 and MYC; RPPA reactive subtypes	High expression of DNA repair proteins, PTEN and INPP4B loss signature (pAKT)	High protein and phospho-protein expression of EGFR and HER2

Percentages are based on 466 tumour overlap list. Amp, amplification; mut, mutation.

TCGA Nature 2012

Conclusions:

- The greatest advances in patient outcomes have come from integrating biology into clinical care
- Critical use of pre-clinical models can help guide this process
- Generate hypothesis driven phase 1/2 studies

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Ireland
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Russia
M Kopp, O Lipatov, S Tjulandin, V Vladimirov

Canada
P Desjardins, H Lim

South Korea
SA Im, JS Ro

US
J Blum, D Chan, R Dichmann, R Finn, E Hu, W Lawler, A Montero, R Patel, N Robert, A Thummala

Ukraine
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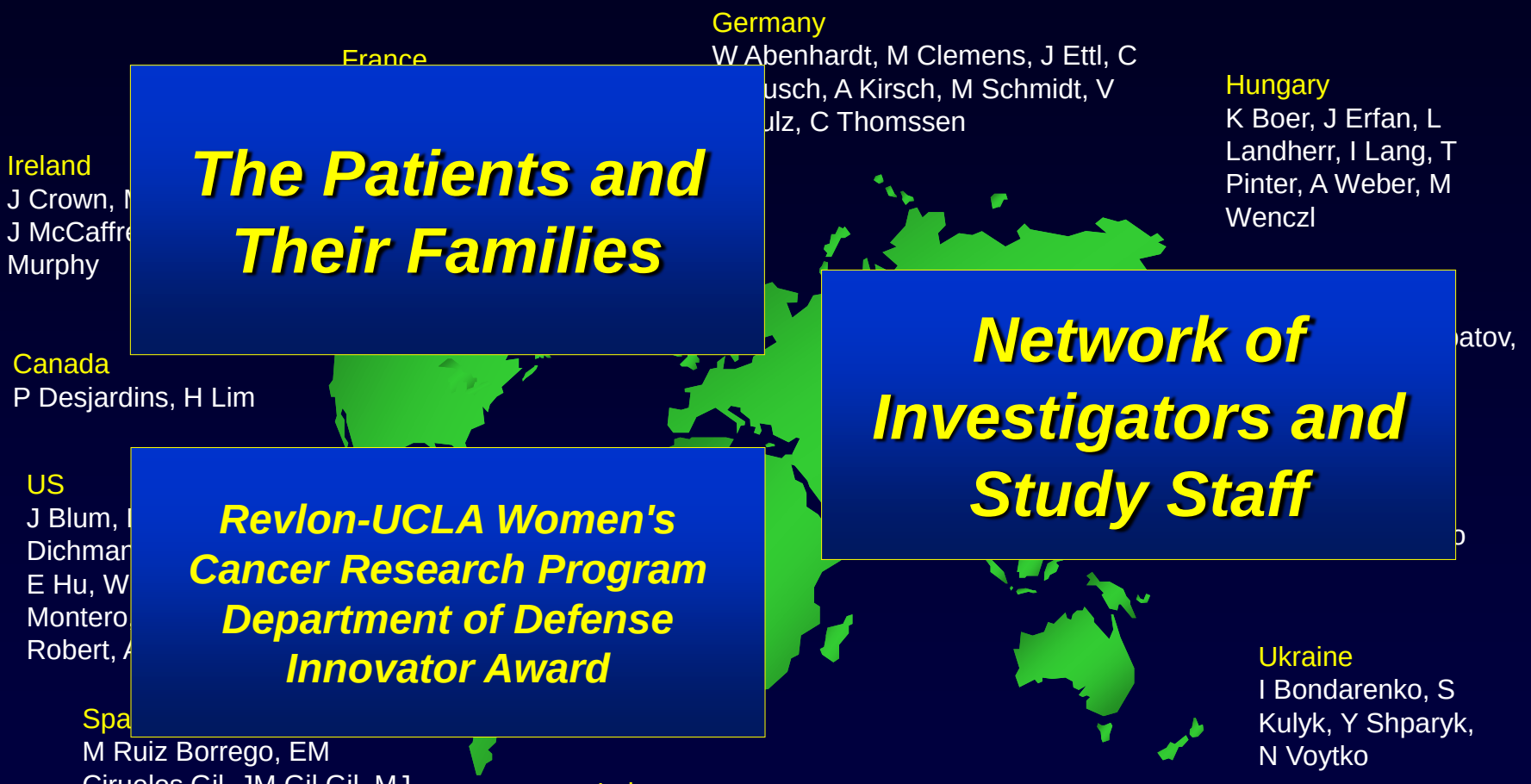

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