Current scenario of first-line treatment of ER+ ABC with CDK4/6 inhibitors

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Disclosures

- Research funding: AstraZeneca
- Speaker honoraria: AstraZeneca, Pfizer, Novartis

- Heterogeneity → resistance → evolution
- The ER pathway→ where we are
- Targeting mechanisms of resistance → where we are going
- Clinical trials of CDK4/6 inhibitors in first-line treatment of ABC
- Challenges and unanswered questions
- Take-home messages

Dr George Beatson

another thirty years it would then have entirely disappeared. The first great drop in its rate took place in the decade 1840-50, about the time that serious attention began to be given to sanitary reforms and especially to land drainage. It then remained scarcely reduced for about seventeen years; but from 1867 to 1894 it has been steadily on the decline. It is in this period that most of the great sanitary works have been carried out in this country. Can we doubt that it is to them that we owe so substantial a diminution of the disease? And need we despair of carrying it on to its fitting close? Let it be remembered that this improvement has taken place in spite of the increasing aggregation of the population in towns and without any special measures of repression

ON THE TREATMENT OF INOPERABLE CASES OF CARCINOMA OF THE MAMMA: SUGGESTIONS FOR A NEW METHOD OF TREATMENT, WITH ILLUSTRATIVE CASES.[1]

BY GEORGE THOMAS BEATSON, M.D. EDIN.,

SURGEON TO THE GLASGOW CANCER HOSPITAL; ASSISTANT SURGEON, GLASGOW WESTERN INFIRMARY; AND EXAMINER IN SURGERY TO THE UNIVERSITY OF EDINBURGH.

Beatson GW. Lancet 1896

Advanced breast cancer -➔ Heterogeneity, resistance and evolution

AN ANALYSIS OF NINETY-NINE CASES OF INOPERABLE CARCINOMA OF THE BREAST TREATED BY OOPHORECTOMY

BY

HUGH LETT, M.B.Vict., F.R.C.S.,
ASSISTANT SURGEON BELGRAVE HOSPITAL FOR CHILDREN; LATE SURGICAL REGISTRAR LONDON HOSPITAL, ETC.

Received December 6th, 1904—Read January 24th, 1905

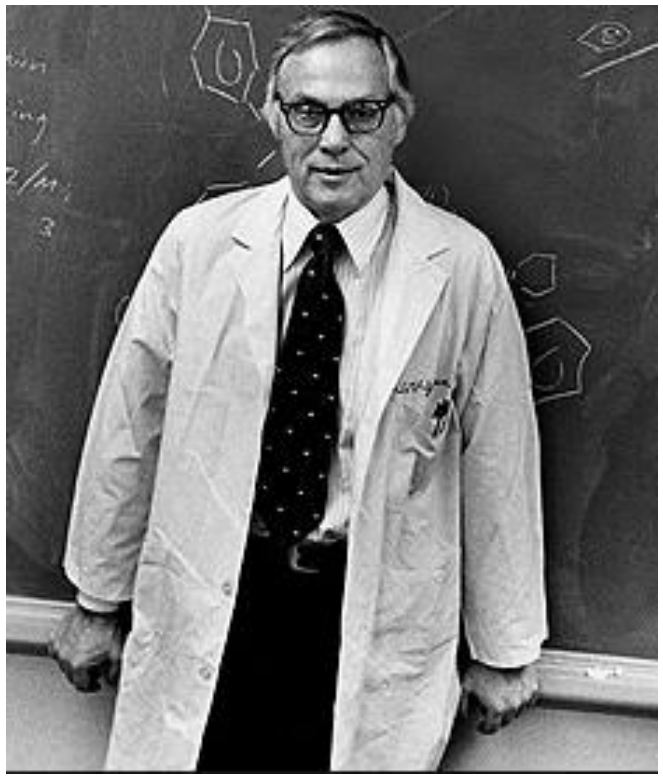
In six months most of nodules disappeared	17 months	Local recurrence. Growths in viscera. Died July, 1898.
Rapid disappearance of recurrence. Marked gain in strength and weight	14 months	Relapse of growth. Cancer of liver. Died October, 1901.
Ulcer healed, and there was no distinct lump in the left breast three months after operation. Ten months after operation had gained 2 st. 7½ lbs.	29 months	Recurrence of ulceration 18 months after operation. Died December, 1900.
Relief of pain	12 months	Died 1896; secondary growths in liver.
Very slight	5 months	Died October, 1897; growths in lung and liver.
None	5 weeks	Died September, 1899.
December 2nd, 1903: two or three small glands in left axilla; very small hard gland in left supra-clavicular region, no pain, and no recurrence in scar. September 28th, 1904: small nodule in the scar; considerable increase in size in the gland in left supra-clavicular region	40 months, still alive	—

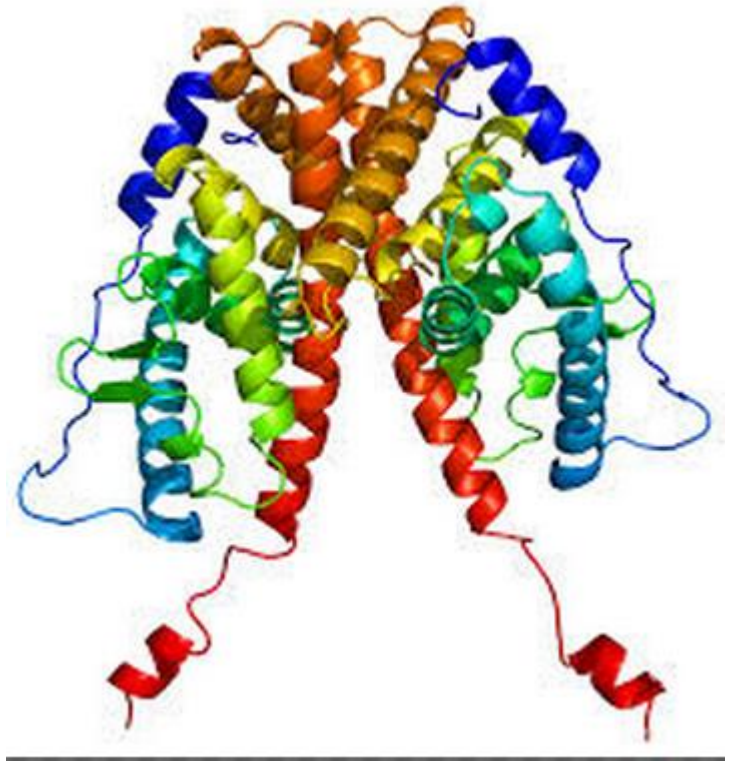
Lett H et al. BMJ 1905

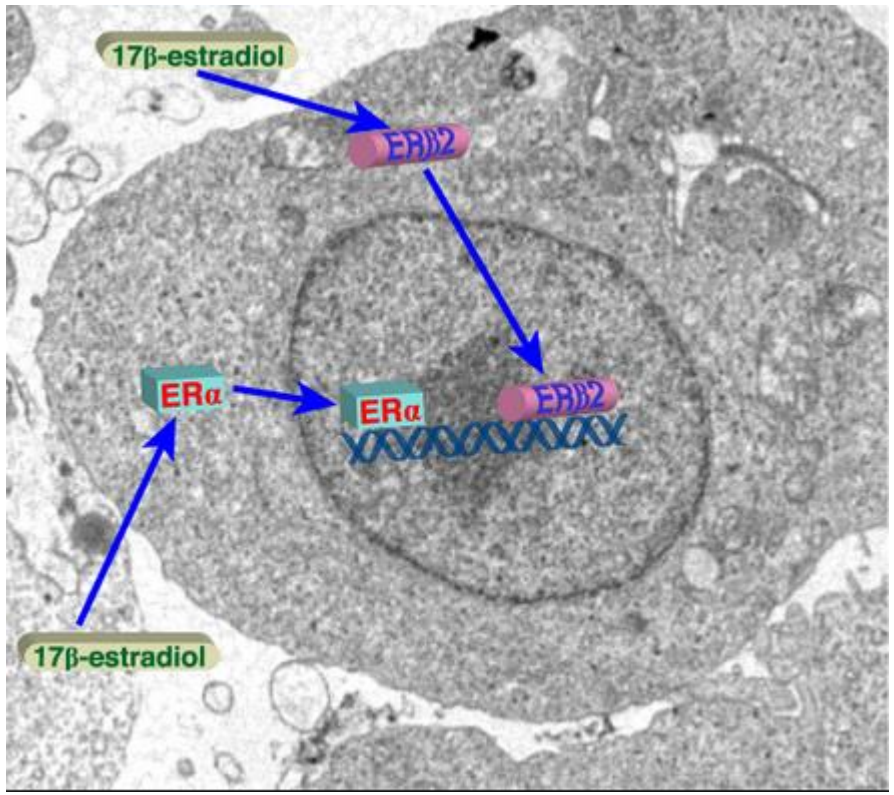
Estrogen Receptors in Human Breast Cancer

WILLIAM L. MCGUIRE

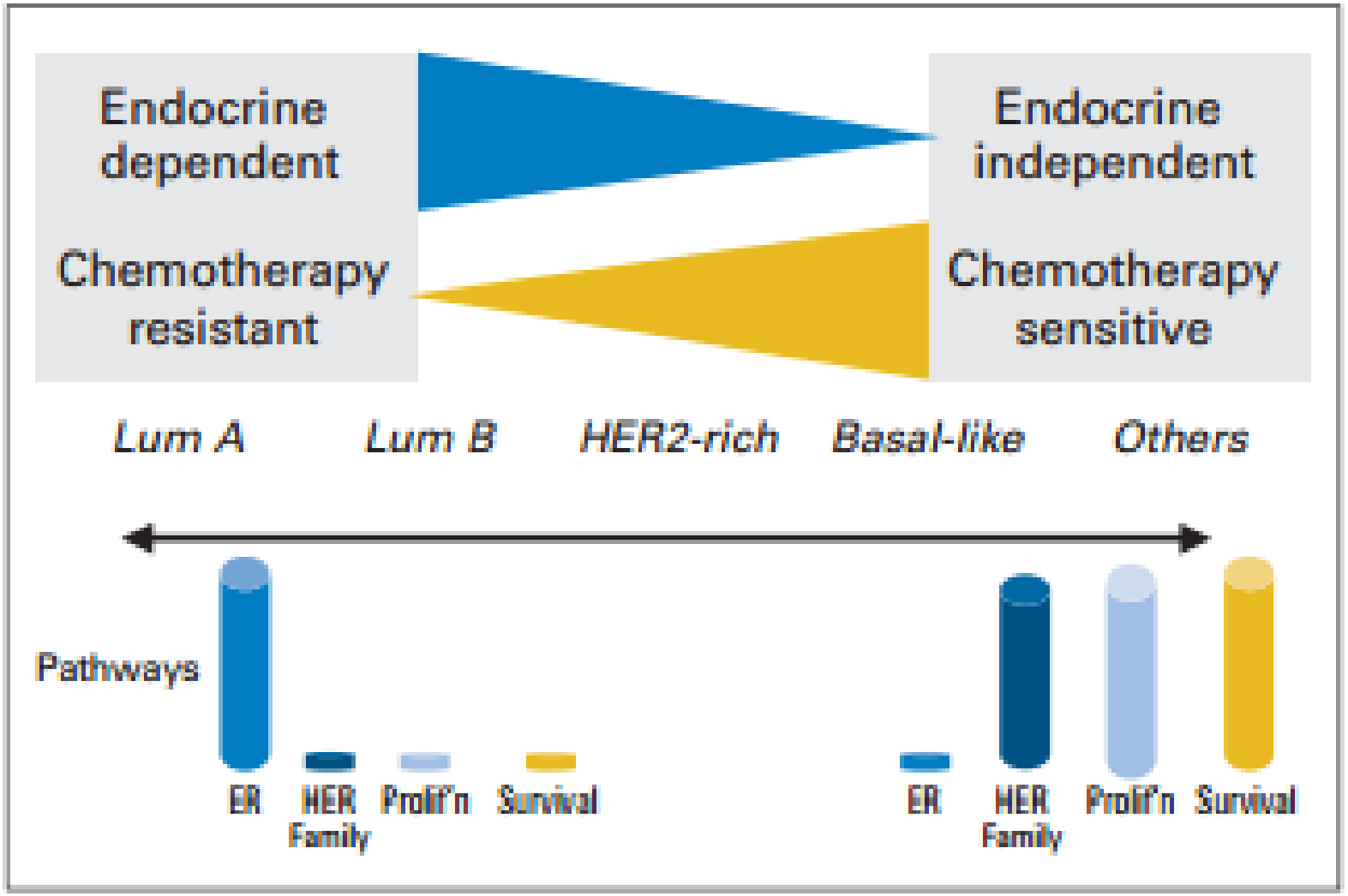
From the Department of Physiology and Medicine, University of Texas Medical School at San Antonio, San Antonio, Texas 78229







McGuire. J Clin Invest 1973

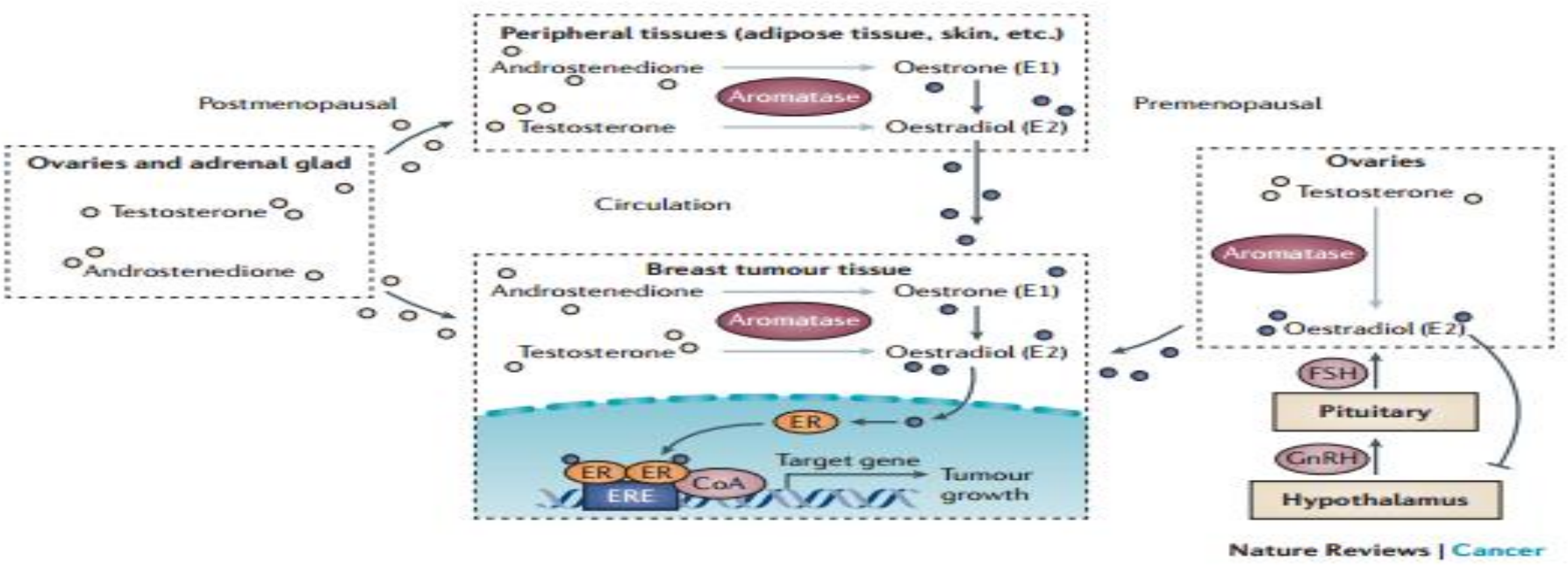


Ades F et al. J Clin Oncol 2014

Endocrine therapy mechanism of action

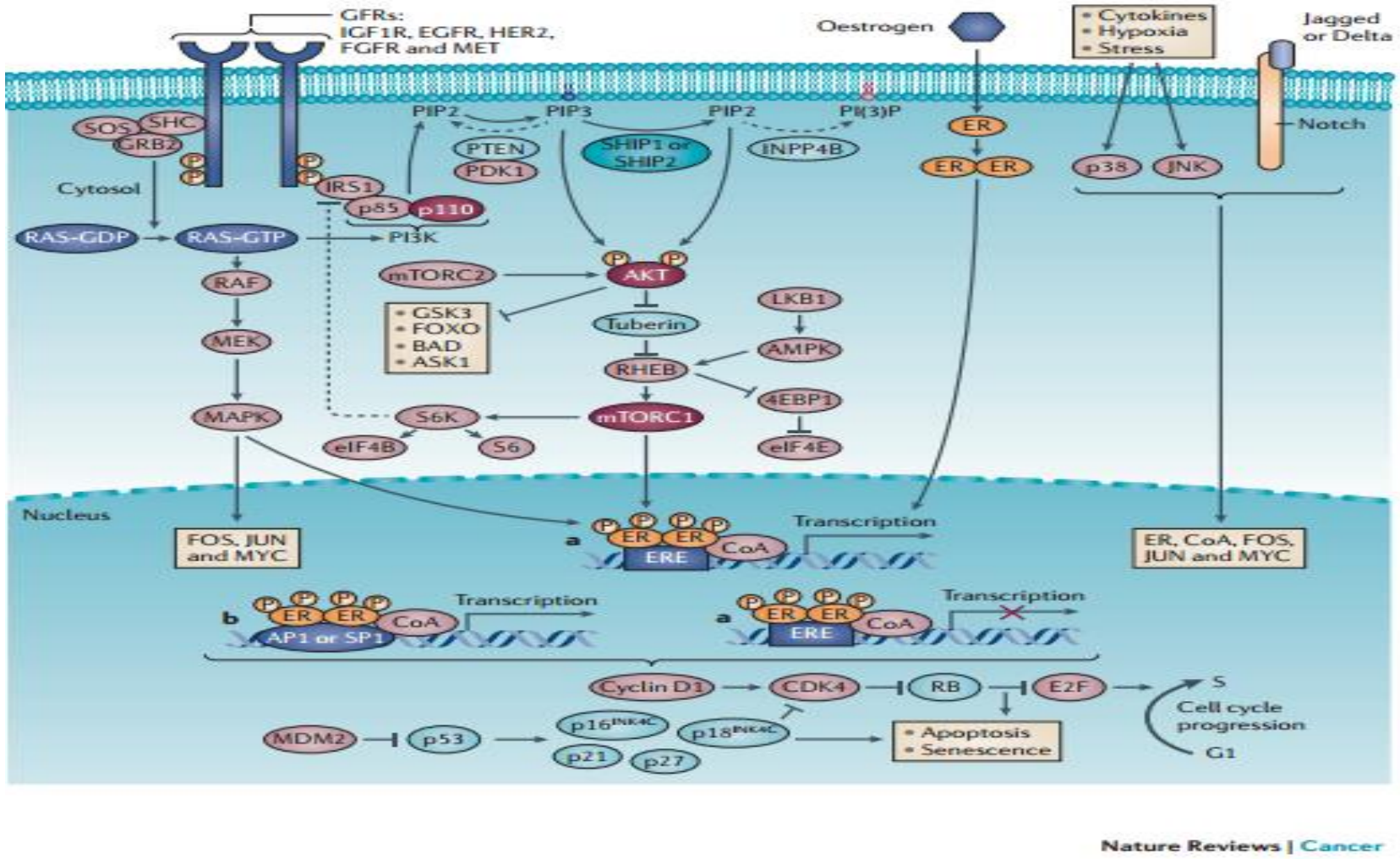
Targeting the estrogen receptor (ER) pathway

- Estrogen deprivation ➔ Aromatase inhibitors (anastrozole, letrozole and exemestane)
- Selective ER modulation/downregulation (SERMs/SERDs) ➔ tamoxifen and fulvestrant



Ma CX, Reinert T, Ellis MJ. Nature Rev Cancer 2015

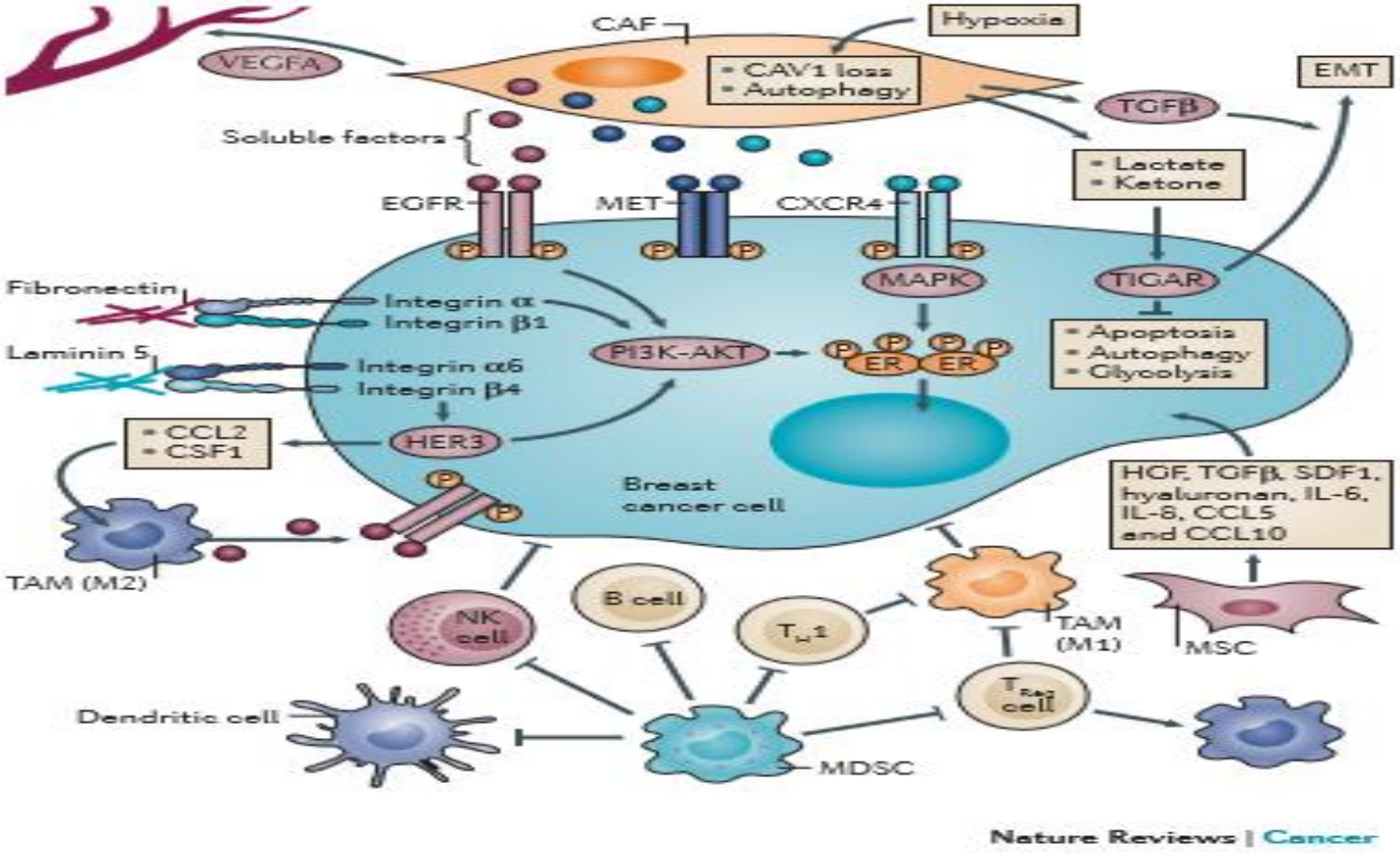
Mechanisms of resistance to endocrine therapy



Nature Reviews | Cancer

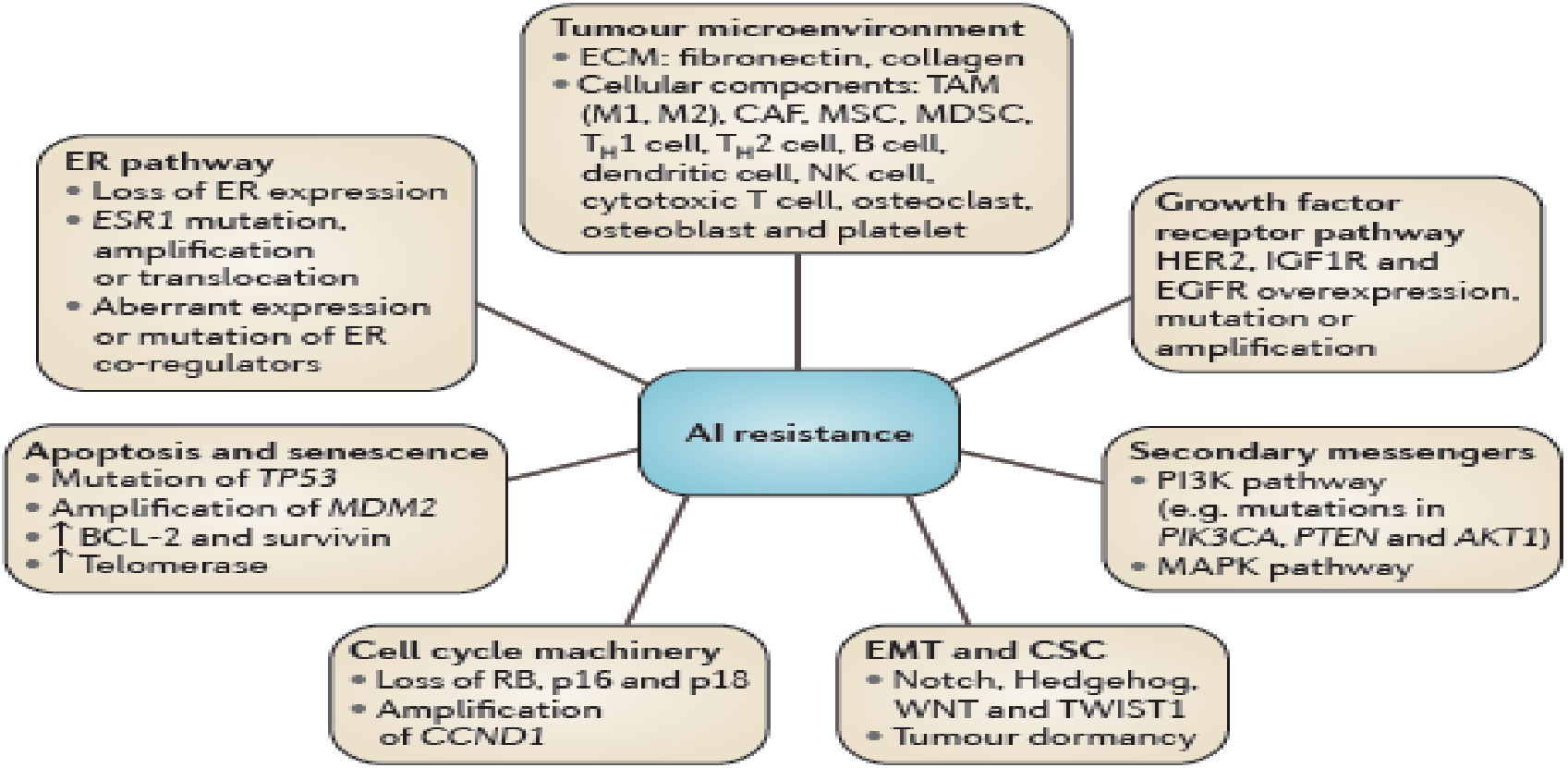
Ma CX, Reinert T, Ellis MJ. Nature Rev Cancer 2015

Mechanisms of resistance to endocrine therapy



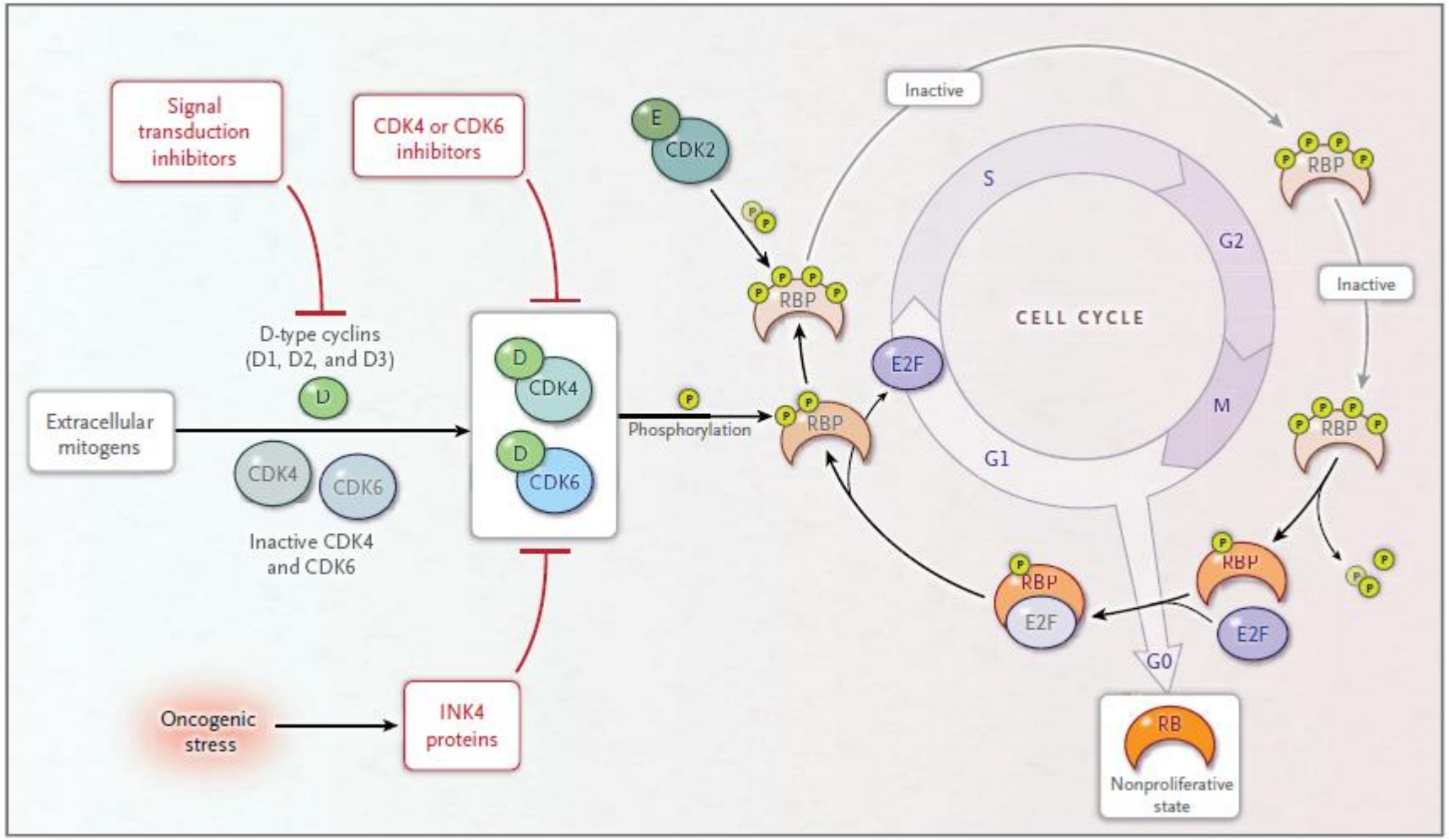
Ma CX, Reinert T, Ellis MJ. Nature Rev Cancer 2015

Hallmarks of endocrine therapy resistance



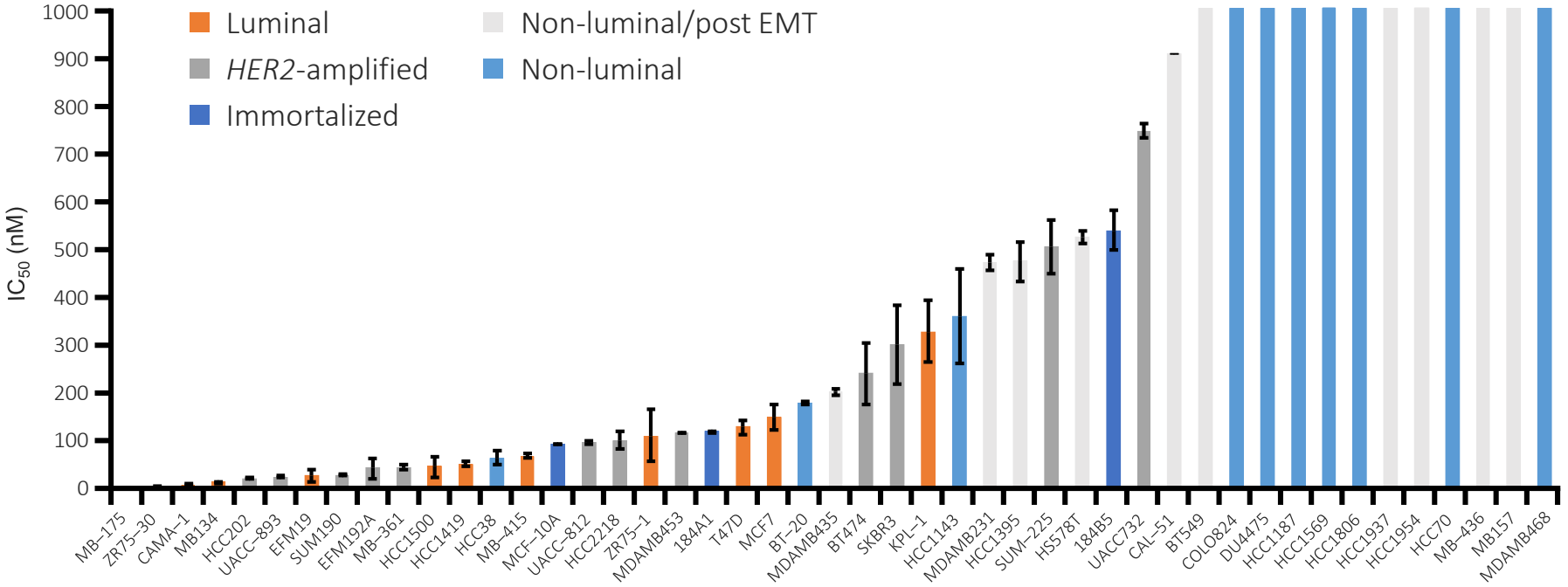
Ma CX, Reinert T, Ellis MJ. Nature Rev Cancer 2015

The cyclinD/CDK/pRB pathway



Sherr CJ, NEJM 2016

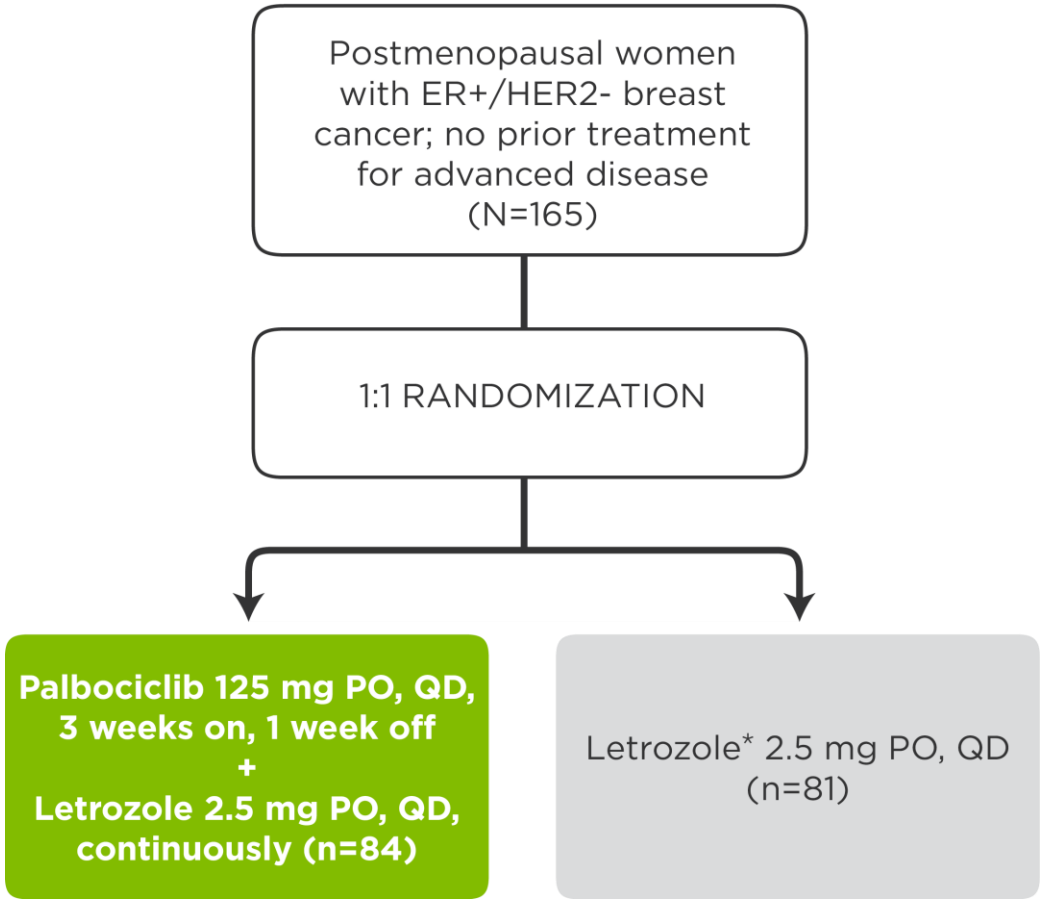
Palbociclib Preferentially Inhibits Proliferation of Luminal ER+ Human Breast Cancer Cell Lines In Vitro



- Luminal, ER+ or *HER2*-amplified breast cancer cell lines most sensitive to CDK4/6 inhibition of proliferation (non-luminal resistant)
- Synergistic growth inhibitory activity between palbociclib and tamoxifen (ER+) or trastuzumab (HER2+)
- Palbociclib activity seen in acquired tamoxifen resistance

Finn R et al, Breast Cancer Res Treat 2008

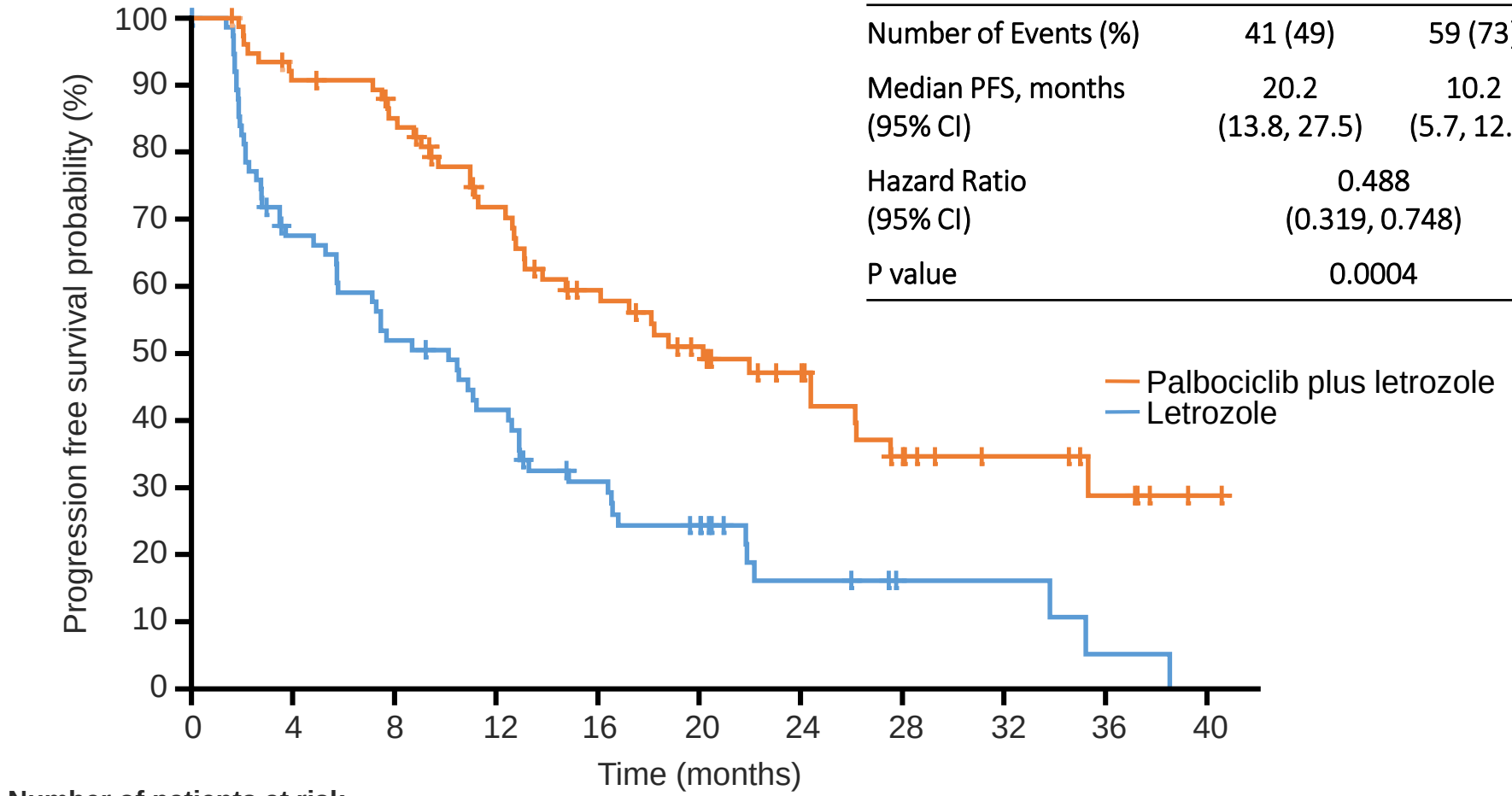
PALOMA 1/TRIO 18: Phase II Study Design in Patients with ER+, HER2– Locally Recurrent or Metastatic Breast Cancer



- Randomized phase II open-label trial at 50 centers in 12 countries (NCT00721409)
- Key eligibility criteria: inoperable 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 PS ≤1, adequate bone marrow and renal function

PALOMA 1/TRIO 18: Progression-Free Survival (ITTP)

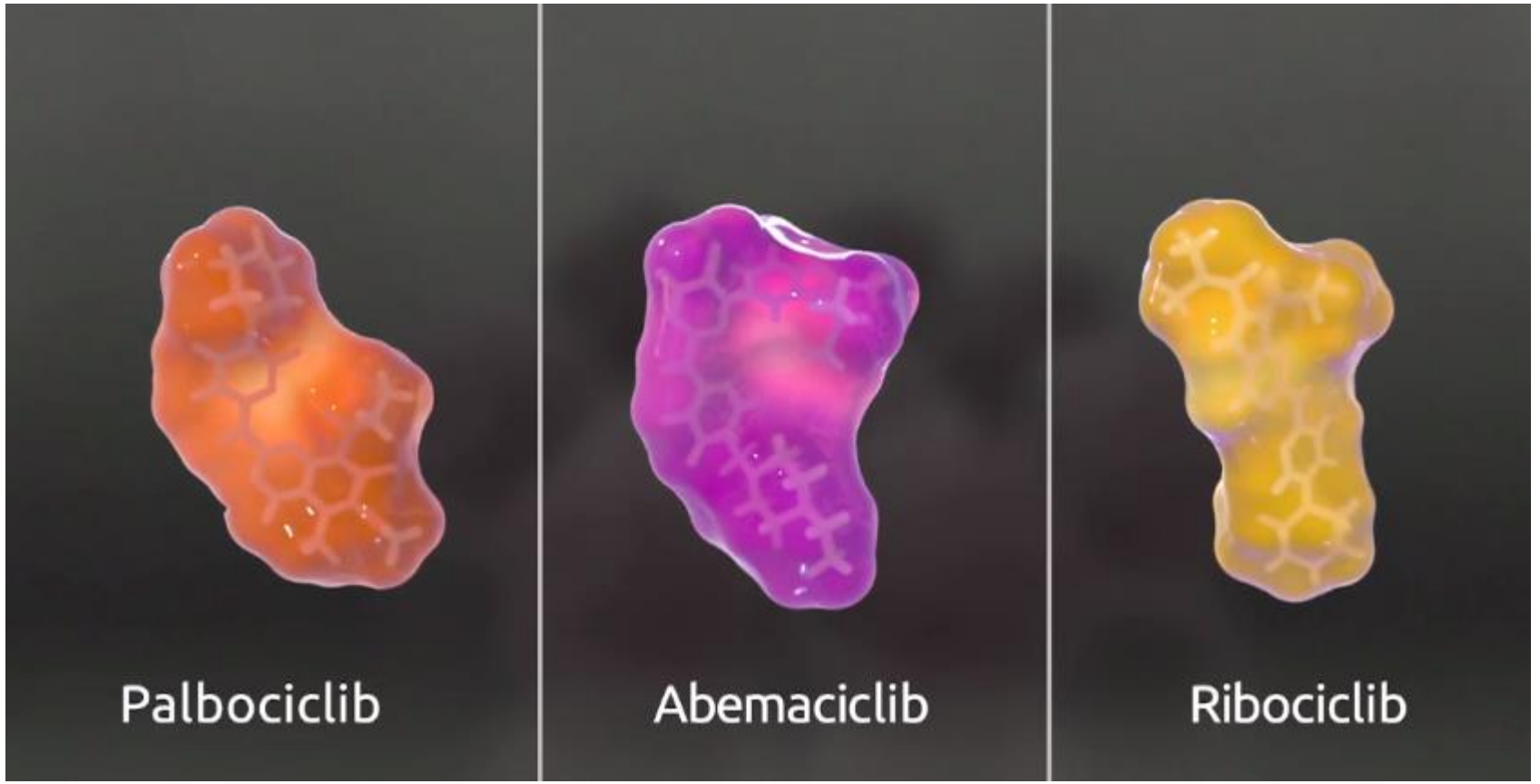
	PAL + LET (N=84)	LET (N=81)
Number of Events (%)	41 (49)	59 (73)
Median PFS, months (95% CI)	20.2 (13.8, 27.5)	10.2 (5.7, 12.6)
Hazard Ratio (95% CI)	0.488 (0.319, 0.748)	
P value	0.0004	



Number of patients at risk

PAL + LET	84	67	60	47	36	28	21	13	8	5	1
LET	81	48	36	28	19	14	6	3	3	1	

Finn R, NEJM 2016


Palbociclib
Abemaciclib
Ribociclib

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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.

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

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

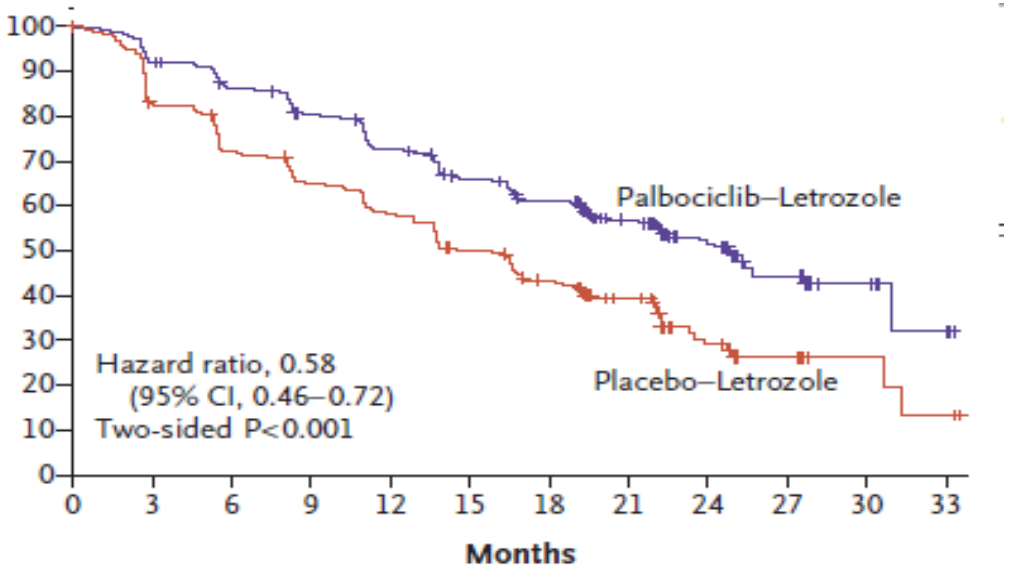
MONARCH 3: Abemaciclib As Initial Therapy for Advanced Breast Cancer

Matthew P. Goetz, Masakazu Toi, Mario Campone, Joohyuk Sohn, Shani Paluch-Shimon, Jens Huober, In Hae Park, Olivier Trédan, Shin-Cheh Chen, Luis Manso, Orit C. Freedman, Georgina Garnica Jaliffe, Tammy Forrester, Martin Frenzel, Susana Barriga, Ian C. Smith, Nawel Bourayou, and Angelo Di Leo

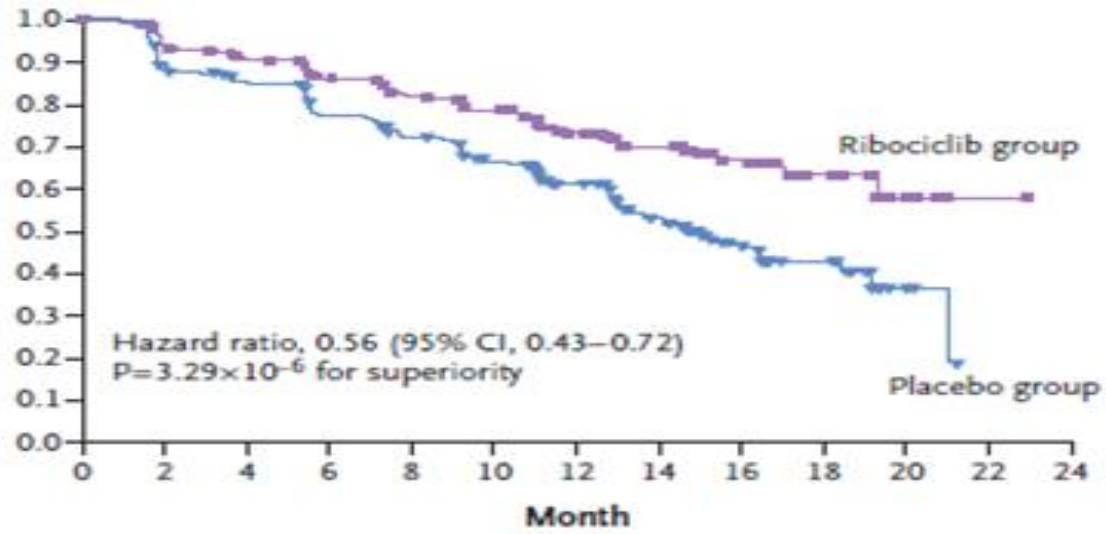
First-line ribociclib or placebo combined with goserelin and tamoxifen or a non-steroidal aromatase inhibitor in premenopausal women with hormone receptor-positive, HER2-negative advanced breast cancer: Results from the randomized Phase III MONALEESA-7 trial

Debu Tripathy,[1] Joohyuk Sohn,[2] Seock-Ah Im,[3] Marco Colleoni,[4] Fabio Franke,[5] Aditya Bardia,[6] Nadia Harbeck,[7] Sara Hurvitz,[8] Louis Chow,[9] Keun Seok Lee,[10] Saul Campos-Gomez,[11] Rafael Villanueva Vazquez,[12] Kyung Hae Jung,[13] Gary Carlson,[14] Gareth Hughes,[15] Ivan Diaz-Padilla,[15] Caroline Germa,[14] Samit Hirawat,[14] Yen-Shen Lu[16]

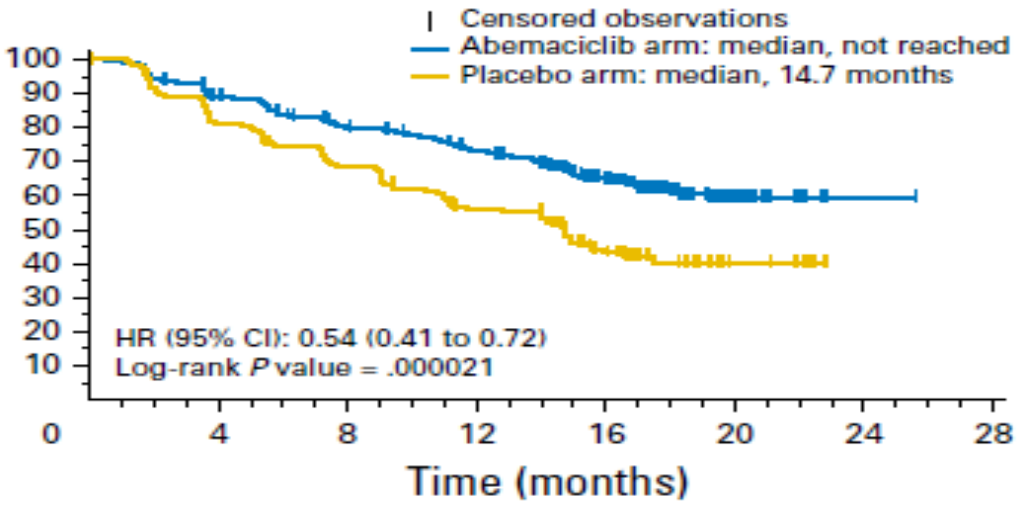
PALOMA- 2



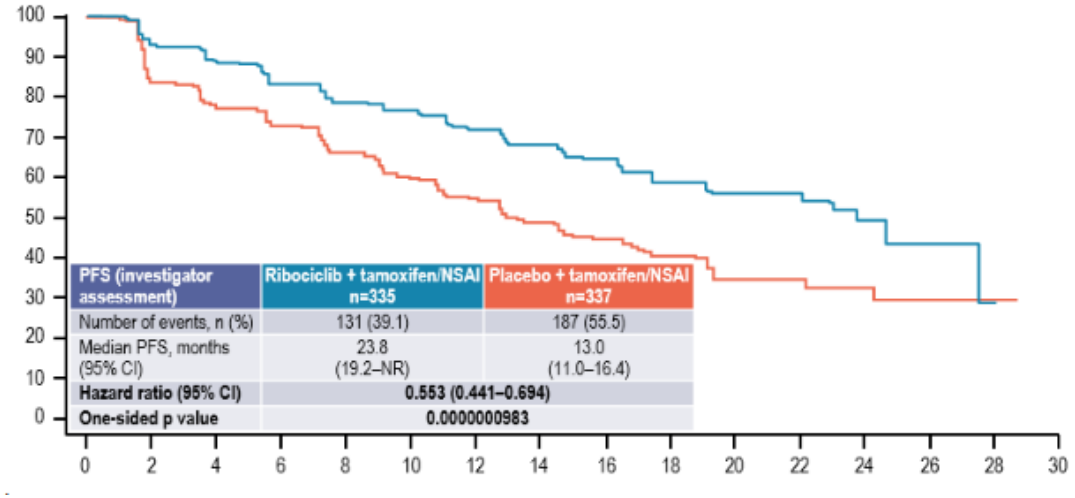
MONALEESA- 2



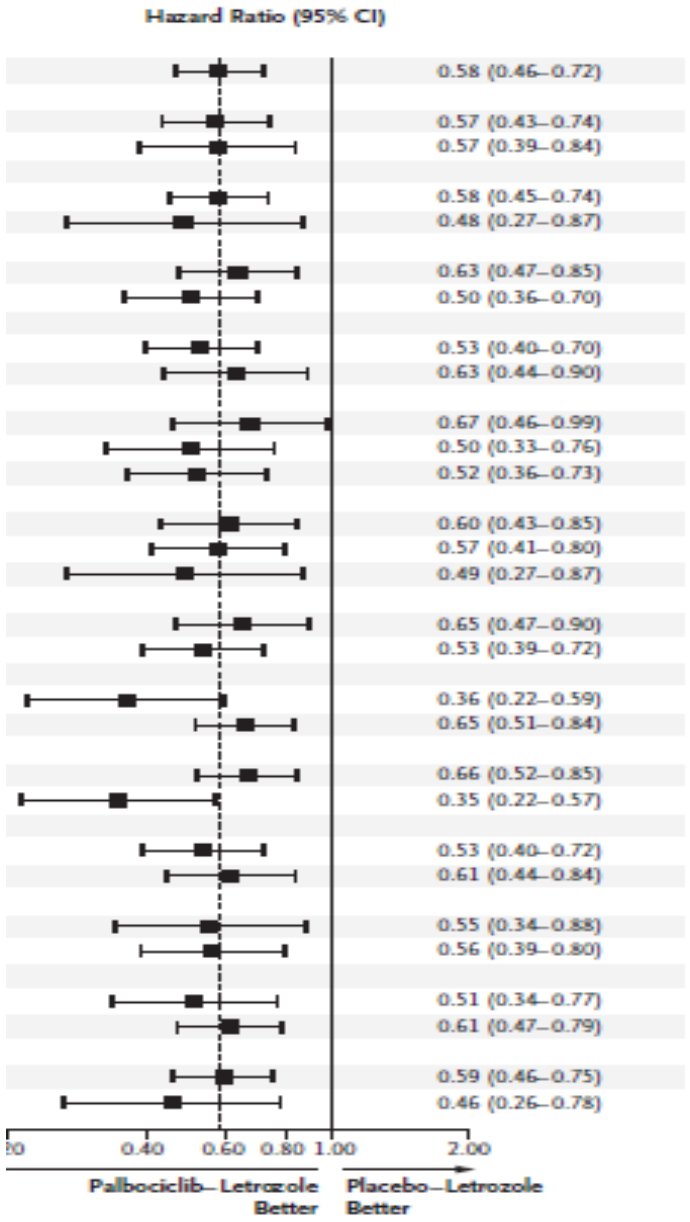
MONARCH-3



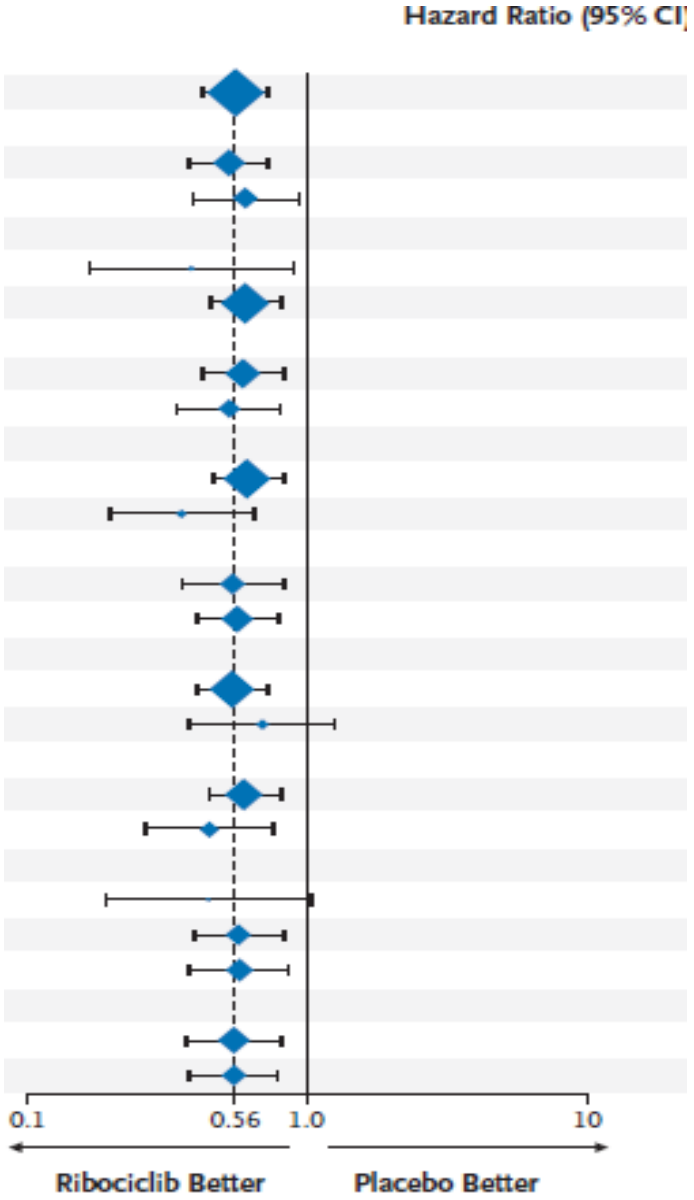
MONALEESA-7



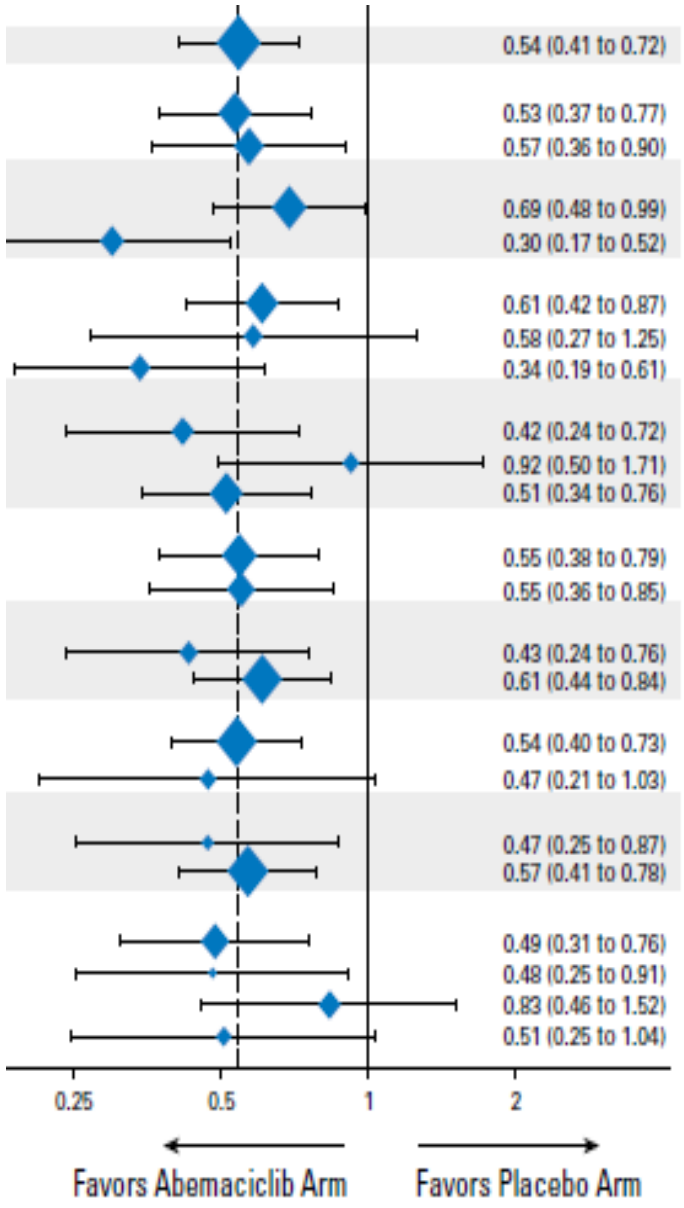
PALOMA- 2



MONALEESA-2



MONARCH-3



Consistent Clinical Benefit Seen Across First-Line CDK4/6 Studies

	PALOMA-2	MONALEESA-2	MONARCH-3
Design	Phase 3 Placebo control	Phase 3 Placebo control	Phase 3 Placebo control
Endocrine partner	Letrozole	Letrozole	Letrozole or anastrozole
Patients on study, N	n=666	n=668	N=493
Efficacy (CDK4/6 vs control arm)			
Primary endpoint: PFS			
HR	0.58	0.56	0.54
Median PFS, mo	24.8 vs 14.5	NR vs 14.7	NR vs 14.7
Secondary endpoints, %			
ORR (ITT)	42 vs 35,	40 vs 27	48 vs 34
CBR (ITT)	85 vs 70	79 vs 72	79 vs 69

Consistent Clinical Benefit Seen Across First-Line CDK4/6 Studies

- Increase in PFS (HR 0.54-0.58)
- Consistent PFS benefits across all subgroups
- Increase in ORR (↑7-14%) and CBR (↑7-15%)
- Manageable toxicities profile

Challenges and unanswered questions

- Lack of predictive biomarkers
- Patient selection
- Optimal sequencing strategies are unclear
- Mechanisms of resistance to CDK4/6 inhibitors
- Are we likely to see OS benefit with CDK4/6 targeted agents?
- Financial toxicity

Lack of predictive biomarkers

Benefit across all subgroupos:

- Age
- Menopausal status
- Bone-only vs Visceral metastasis
- Relapse vs *de novo*
- Exposure to previous treatment

- Genomics
- Transcriptomics
- Proteomics

Challenges and unanswered questions

- Lack of predictive biomarkers
- Patient selection
- Optimal sequencing strategies are unclear
- Mechanisms of resistance to CDK4/6 inhibitors
- Are we likely to see OS benefit with CDK4/6 targeted agents?
- Financial toxicity

Factors to consider when selecting endocrine therapy for patients with HR+ advanced breast cancer

- Patient
  - Age, menopausal status, PS, comorbidities, adherence
- Tumor
  - Histological subtype, HR expression, HER2 amplification, intrinsic subtype
- Disease
  - Previous ET, DFI on adjuvant ET, response to previous line, tumor burden, visceral metastasis
- Agent
  - Mechanism of action, toxicities, cost, availability
- Other issues
  - Availability of clinical research, financial hardship, existing guidelines

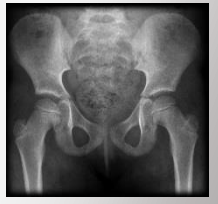
Reinert T, Barrios CH. Ther Adv Med Onc 2015

Câncer de Mama Avançado, ER+, HER2-, pós-menopausa

Perfil A

Doença Lenta

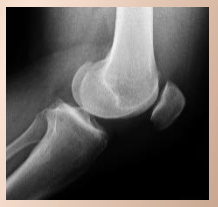
- Progressão Lenta
- Mínimas metátases ósseas / Baixo risco para metastases de tecidos moles (ex. pele/ nódulos linfáticos)
- Assintomáticas



Perfil B

Alta carga Tumoral Óssea

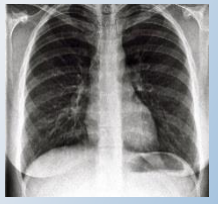
- **Progressão de doença lenta a moderada**
- **Poucos sintomas**



Perfil C

Baixa Carga visceral

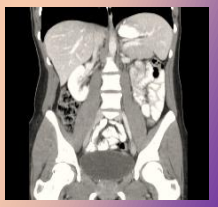
- **Progressão de doença lenta a moderada**
- **Possiveis Metástases ósseas**
- **Baixo volume de metástases viscerais (ou tecidos moles)**
- **Metástases de baixo risco de complicação**
- **Ausência de ou sintomas moderados**



Perfil D

Carga visceral moderada

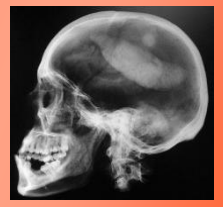
- **Progressão Moderada**
- **Metástases Viscerais**
- **Grande volume de doença**
- **Crise médica iminente**
- **Sintomas requerendo tratamento**



Perfil E

Crise Médica

- **Progressão rápida**
- **Doença agressiva**
- **Metástases em locais de alto risco e requerendo intervenção médica**
- **Altamente sintomáticas e requerendo intervenções**
- **Ameaça de morte**



Dados Clínicos

(Drivers do tratamento: Presença de Metástase(s) ex.óssea, visceral, cerebral), Sintomas (ex. dor, impacto em orgãos funcionais, etc), Caracteristicas Tumourais (ex. Tamanho, nrs, dispersçao, ects). Taxa de Progressão / Taxa de Recorrência)

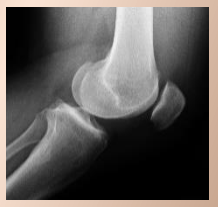
Paciente (inclui *performance status*, idade, escolhas, motivação, co-morbidades, condição financeiraa, etc)

Câncer de Mama Avançado, ER+, HER2-, pós-menopausa

Perfil B

Alta carga Tumoral Óssea

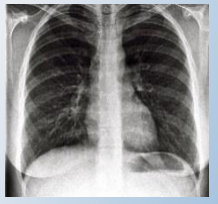
- **Progressão de doença lenta a moderada**
- **Poucos sintomas**



Perfil C

Baixa Carga visceral

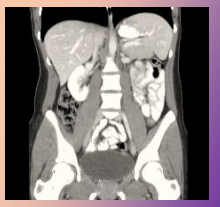
- **Progressão de doença lenta a moderada**
- **Possiveis Metástases ósseas**
- **Baixo volume de metástases viscerais (ou tecidos moles)**
- **Metástases de baixo risco de complicação**
- **Ausência de ou sintomas moderados**



Perfil D

Carga visceral moderada

- **Progressão Moderada**
- **Metástases Viscerais**
- **Grande volume de doença**
- **Crise médica iminente**
- **Sintomas requerendo tratamento**



Dados Clínicos

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Paciente (inclui *performance status*, idade, escolhas, motivação, co-morbidades, condição financeiraa, etc)

Challenges and unanswered questions

- Lack of predictive biomarkers
- Patient selection
- Optimal sequencing strategies are unclear
- Mechanisms of resistance to CDK4/6 inhibitors
- Are we likely to see OS benefit with CDK4/6 targeted agents?
- Financial toxicity

Optimal sequencing strategies are unclear

- Upfront CDk4/6 inhibition
- Upfront ET → Second-line CDK4/6 inhibition
- Role of mTOR inhibitors
- Role of PI3K inhibitors
- Timing of chemotherapy

Challenges and unanswered questions

- Lack of predictive biomarkers
- Patient selection
- Optimal sequencing strategies are unclear
- Mechanisms of resistance to CDK4/6 inhibitors
- Are we likely to see OS benefit with CDK4/6 targeted agents?
- Financial toxicity

VANDERBILT UNIVERSITY MEDICAL CENTER

SAN ANTONIO BREAST CANCER SYMPOSIUM
December 5-9, 2017

Gain-of-function kinase library screen identifies FGFR1 amplification as a mechanism of resistance to antiestrogens and CDK4/6 inhibitors in ER+ breast cancer

Luigi Formisano, Yao Lu, Valerie M. Jansen, Joshua A. Bauer, Ariella Hanker, Paula Gonzalez Ericsson, Kyung-min Lee, Mellissa J. Nixon, Angel L. Guerrero-Zotano, Luis J. Schwarz, Melinda E. Sanders, Dhivya Sudhan, Teresa C. Dugger, Marcelo Rocha Cruz, Amir Behdad, Massimo Cristofanilli, Aditya Bardia, Joyce O'Shaughnessy, Ingrid A. Mayer, Justin M. Balko, Carlos L. Arteaga

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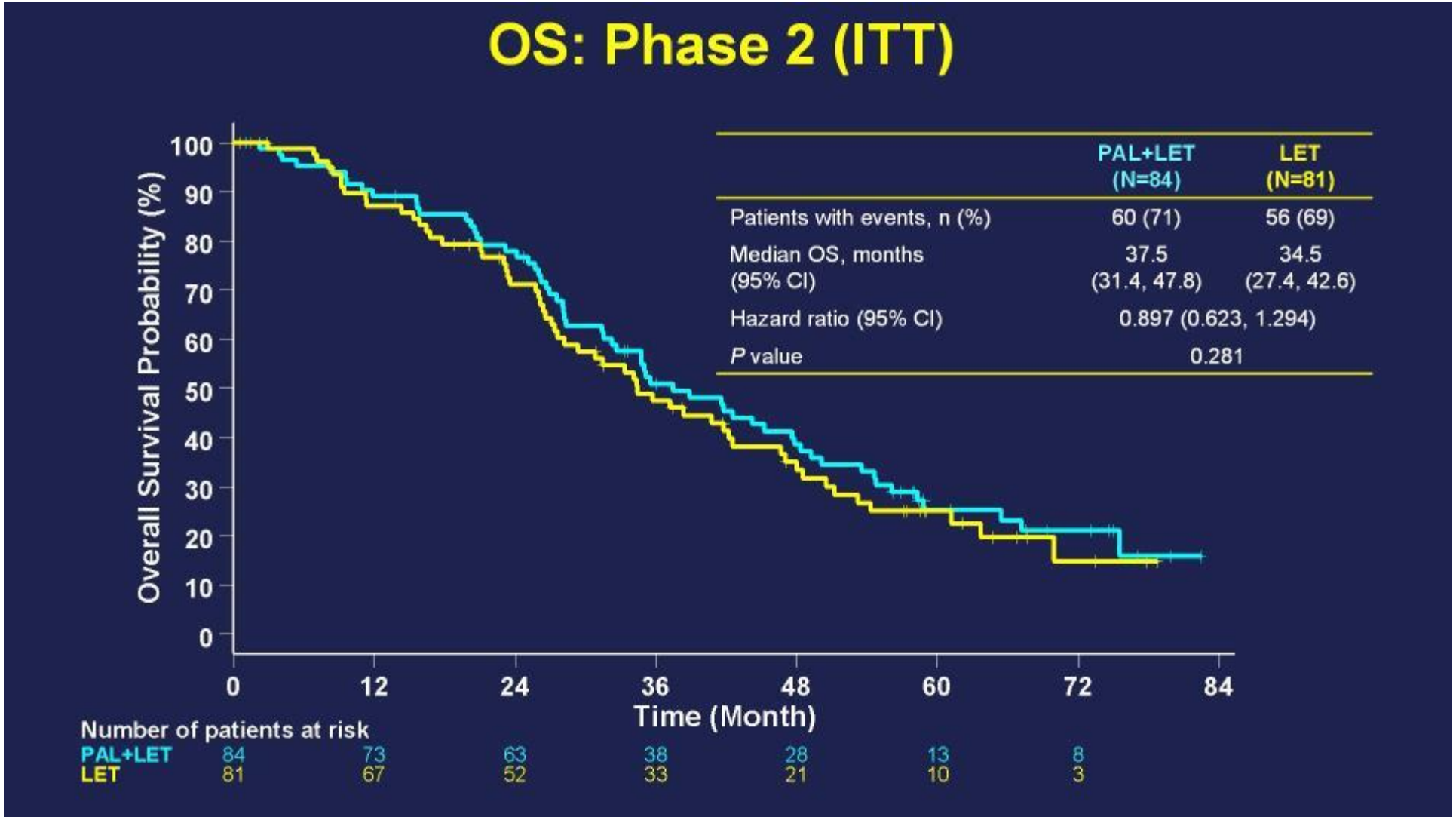
Challenges and unanswered questions

- Lack of predictive biomarkers
- Patient selection
- Optimal sequencing strategies are unclear
- Mechanisms of resistance to CDK4/6 inhibitors
- Are we likely to see OS benefit with CDK4/6 targeted agents?
- Financial toxicity

PALOMA 1 TRIAL



Presented By Richard Finn at 2017 ASCO Annual Meeting

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Research Paper

Rapid Breast Cancer Disease Progression Following Cyclin Dependent Kinase 4 and 6 Inhibitor Discontinuation

Sami I. Bashour[1], Iman Doostan[2], Khandan Keyomarsi[2], Vicente Valero[1], Naoto T. Ueno[1], Powel H. Brown[1,3], Jennifer K. Litton[1], Kimberly B. Koenig[1], Meghan Karuturi[1], Sausan Abouharb[1], Debasish Tripathy[1], Stacy L. Moulder-Thompson[1*], Nuhad K. Ibrahim[1*]✉

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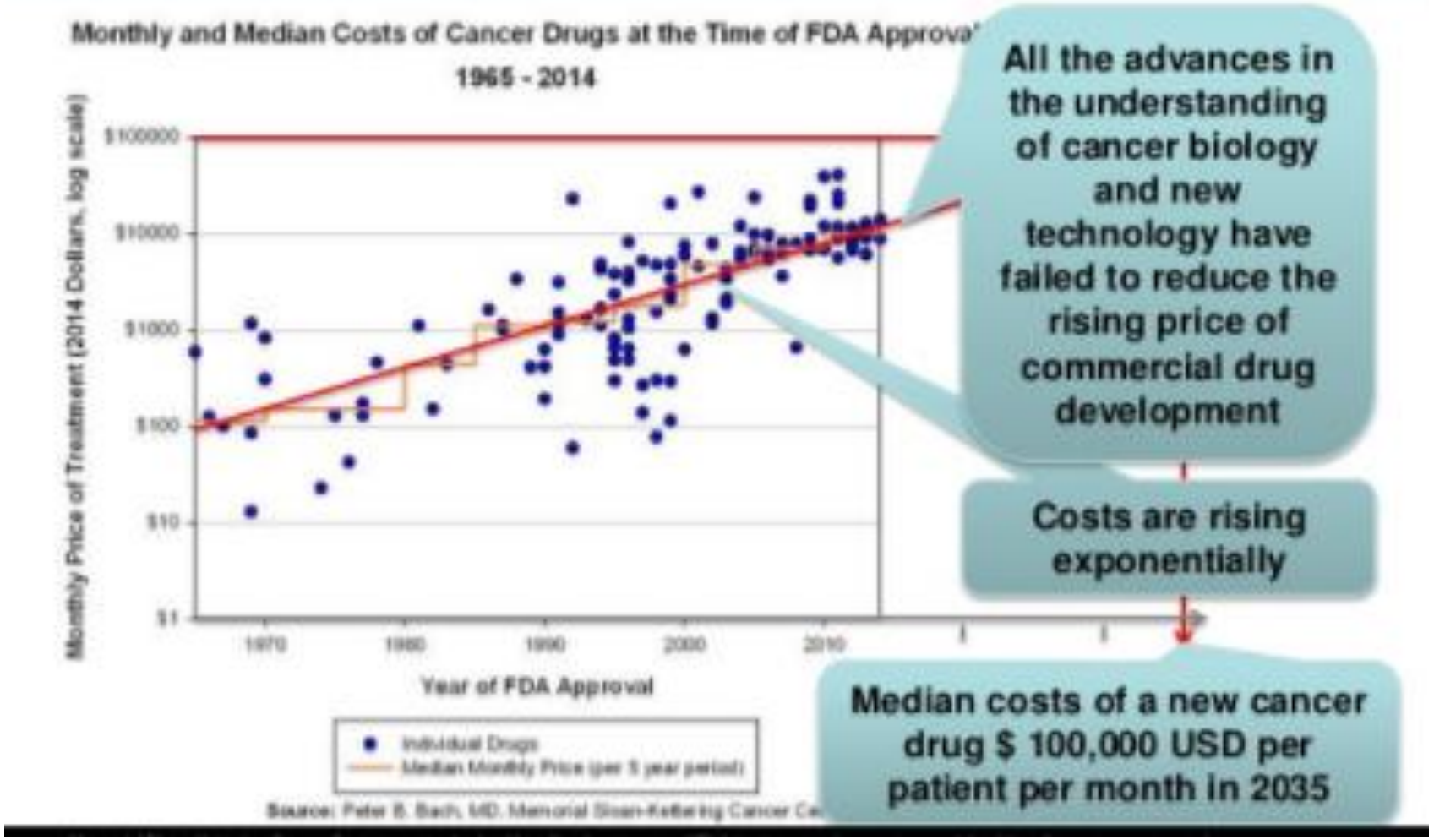
Challenges and unanswered questions

- Lack of predictive biomarkers
- Patient selection
- Optimal sequencing strategies are unclear
- Mechanisms of resistance to CDK4/6 inhibitors
- Are we likely to see OS benefit with CDK4/6 targeted agents?
- Financial toxicity

When will new cancer drug costs fall?



- Heterogeneity → resistance → evolution
- The ER pathway→ where we are
- Targeting mechanisms of resistance → where we are going
- Clinical trials of CDK4/6 inhibitors in first-line treatment of ABC
- Challenges and unanswered questions
- Take-home messages

Emerging Innovative Therapeutic Approaches Leveraging Cyclin-Dependent Kinase Inhibitors to Treat Advanced Breast Cancer

Marcelo Cruz[1], Tomás Reinert[2] and Massimo Cristofanilli[3]

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- CDK 4/6 inhibitors in combination with ET consistently improves PFS and should be **considered a first line treatment option** in patients with HR+ advanced BC
- The optimal sequencing of ET +/- CDKi therapy remains to be determined
- The toxicity profile of CDK 4/6 inhibitors is manageable
- The choice of therapy (ET vs ET/CDKi) will be driven by many factors including: tumor and disease characteristics, patient choice, compliance with monitoring, as well as access to therapy

Cruz M, Reinert T, Cristofanilli M. Clin Pharm Ther 2017

Obrigado pela atenção!

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