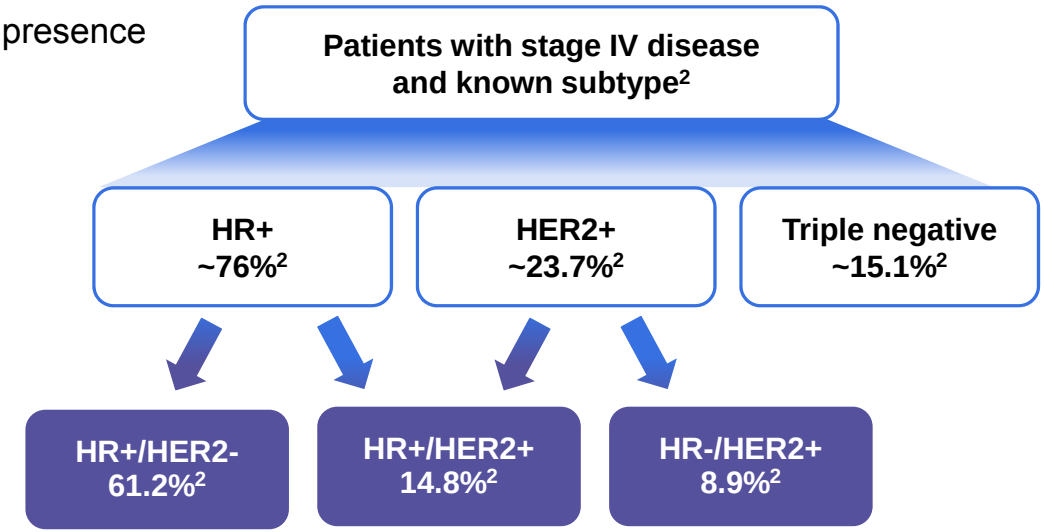
Breast Cancer Carcinogenesis: Mechanisms and Pathways in Hormone Receptor Positive Disease

Nearly Two-Thirds of Metastatic Breast Cancers Express Hormone Receptors

- Breast cancer tumors are often classified by the presence or absence of HRs* and HER2[1]

- HR+ cancers are further classified based on the presence of ER and PR[1]
  - Tumors with ≥1% of cells that are positive for ER are considered ER+[3]
  - Women with HR+ tumors may be appropriate candidates for endocrine therapy[3]

- Treatment options for metastatic disease are tailored by tumor subtype[3,4]



*HR+ includes tumors that are estrogen receptor positive and/or progesterone receptor positive.
ER=estrogen receptor; HER2=human epidermal growth factor receptor 2; HR=hormone receptor; MBC=metastatic breast cancer; PR=progesterone receptor.
1. American Cancer Society. Breast cancer. http://www.cancer.org/acs/groups/cid/documents/webcontent/003090-pdf.pdf. Accessed May 18, 2016. **2.** Howlader N, et al. *J Natl Cancer Inst.* 2014;106(5):dju055. **3.** Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Breast Cancer V.2.2016. © National Comprehensive Cancer Network, Inc. 2016. All rights reserved. Accessed May 18, 2016. To view the most recent and complete version of the guideline, go online to www.NCCN.org. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, NCCN GUIDELINES®, and all other NCCN Content are trademarks owned by the National Comprehensive Cancer Network, Inc. **4.** Brouckaert O, et al. *Int J Women's Health.* 2012;4:511-520.

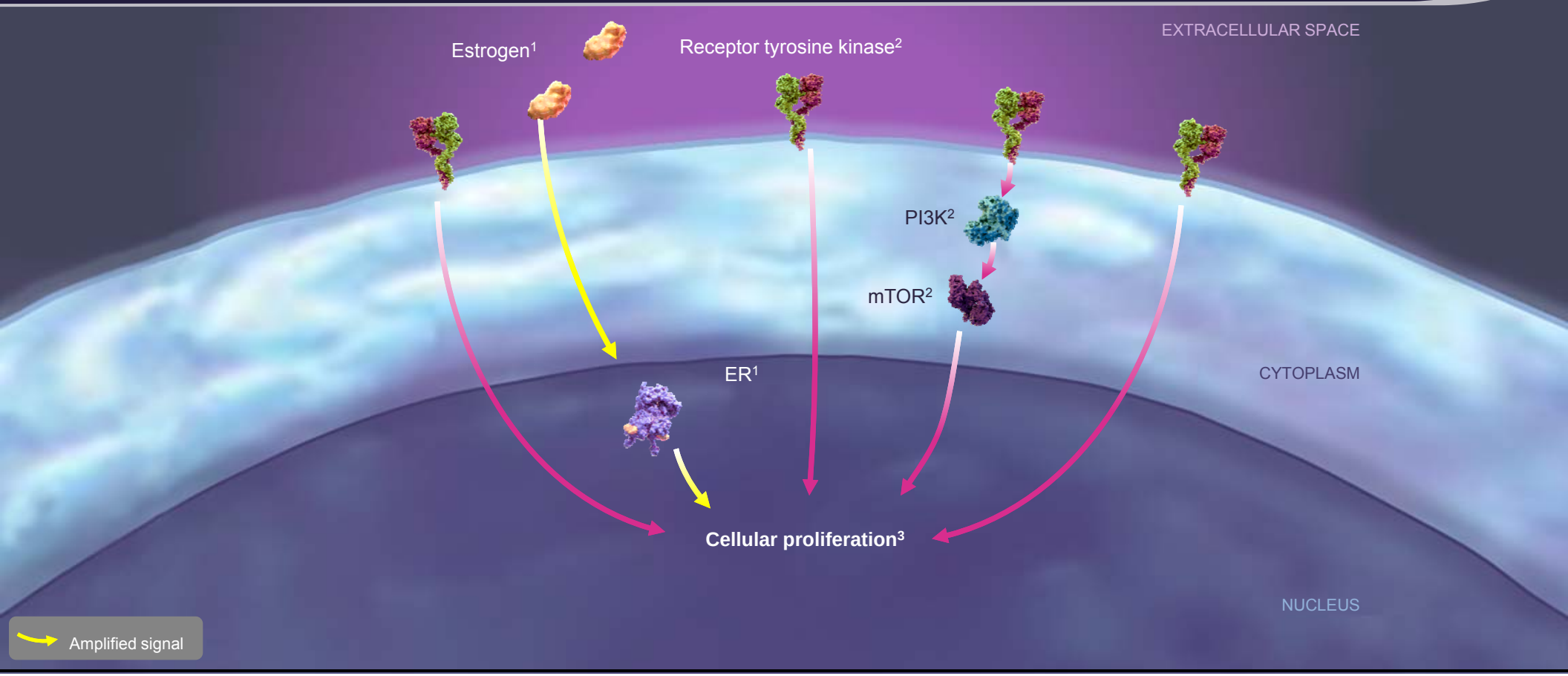
Multistep Adaptive Changes of Tumor Cells and the Tumor Microenvironment Are Required for Malignant Transformation of Normal Cells[1]

Typical Hallmarks of Cancer[1]	Breast Cancer Therapies[2]
SUSTAINED PROLIFERATIVE SIGNALING	EGFR Inhibitors Endocrine Therapy[3] • AIs, SERMs, SERDs
EVADING GROWTH SUPPRESSORS	CDK Inhibitors PI3K Inhibitors mTOR Inhibitors
GENOME INSTABILITY AND MUTATION	PARP Inhibitors
AVOIDING IMMUNE DESTRUCTION	PD-L1 Antibodies or Antagonists[4] PD1 Antibodies or Antagonists[4]
AVOIDING APOPTOSIS	HSP90 Inhibitors[5]
INHIBITING ABERRANT GENE EXPRESSION	HDAC Inhibitors[2]
ACTIVATING INVASION & METASTASIS	HGF/c-MET Inhibitors • Anti–c-MET Antibodies[2] • Multitargeted TKIs[2]
INDUCING ANGIOGENESIS	VEGF Inhibitors[3]

AI=aromatase inhibitor; CDK=cyclin-dependent kinase; c-MET=hepatocyte growth factor receptor; EGFR=epidermal growth factor receptor; HDAC=histone deacetylase; HGF=hepatocyte growth factor; HSP=heat shock protein; mTOR=mammalian targets of rapamycin; PARP=poly ADP-ribose polymerase; PD1=program cell death 1; PD-L1=programmed cell death ligand 1; PI3K=phosphoinositide 3-kinase; SERD=selective ER downregulator; SERM=selective ER modulator; TKI=tyrosine kinase inhibitor; VEGF=vascular endothelial growth factor.

1. Hanahan D, et al. *Cell.* 2011;144(5):646-674. **2.** Brufsky AM. *Clin Med Insights Oncol*. 2015;9:137-147. **3.** Zhao M, et al. *World J Clin Oncol*. 2014;5(3):248-262. **4.** Moreno BH, Ribas A. *Br J Cancer.* 2015;112(9):1421-1427. **5.** Whitesell L, et al. *Proc Natl Acad Sci U S A*. 2014;111(51):18297-18302.

The ER Pathway Is the Dominant Pathway Implicated in the Development and Progression of ER+/HER2- Breast Cancer



ER=estrogen receptor; HER2=human epidermal growth factor receptor 2; mTOR=mammalian target of rapamycin; PI3K=phosphoinositide 3-kinase.

1. Osborne CK, et al. *Annu Rev Med.* 2011;62:233-247. **2.** Baselga J. *Oncologist*. 2011;16(suppl 1):12-19. **3.** Asghar U, et al. *Nat Rev Drug Discov*. 2015;14(2):130-146.

Control of Normal Cell Signaling: Role of ER

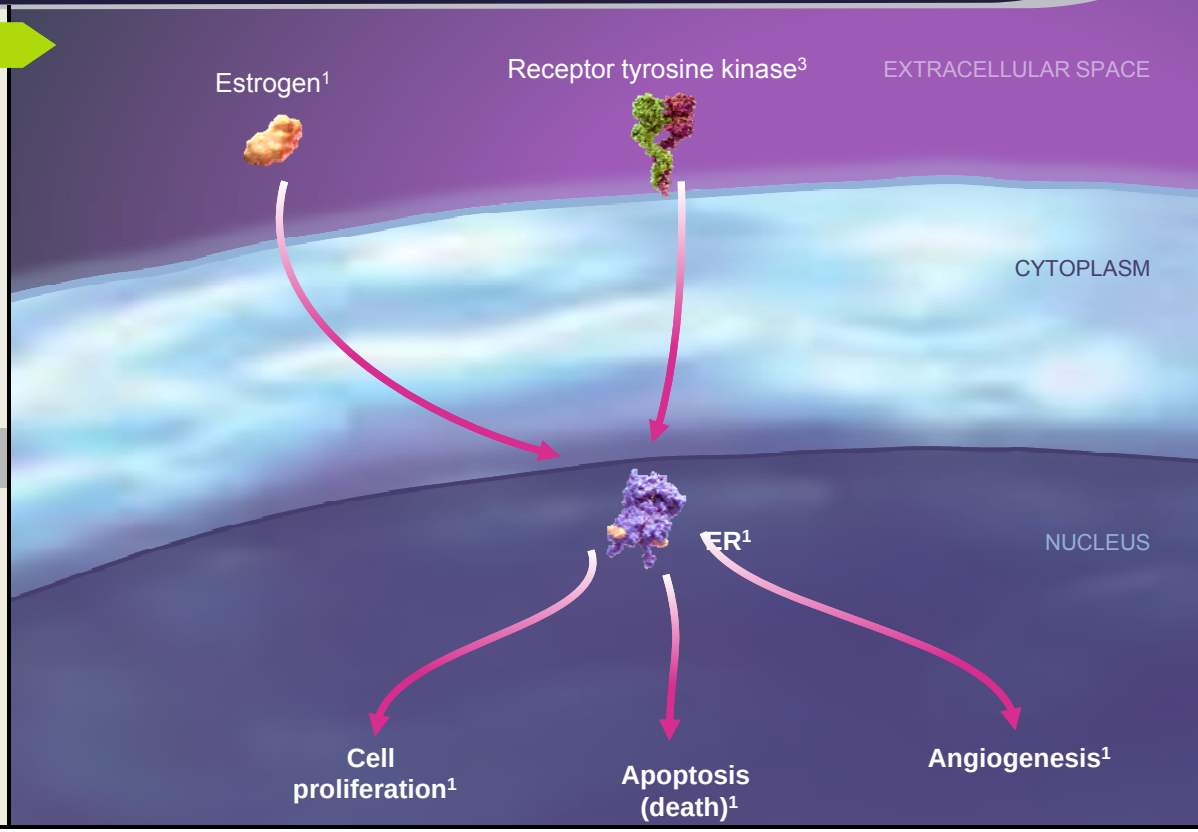
Activation

Activation of ER can occur via[1]

- Binding of its ligand, estrogen[1]
- Estrogen-independent receptor activation by RTKs including EGFR, HER2, IGF-1R, PI3K/Akt/mTOR, or MAPK[1,2]

Consequence

ER can dimerize or bind to other transcription factors and ultimately stimulate pathways involved in cell proliferation, apoptosis (death), and angiogenesis[1]



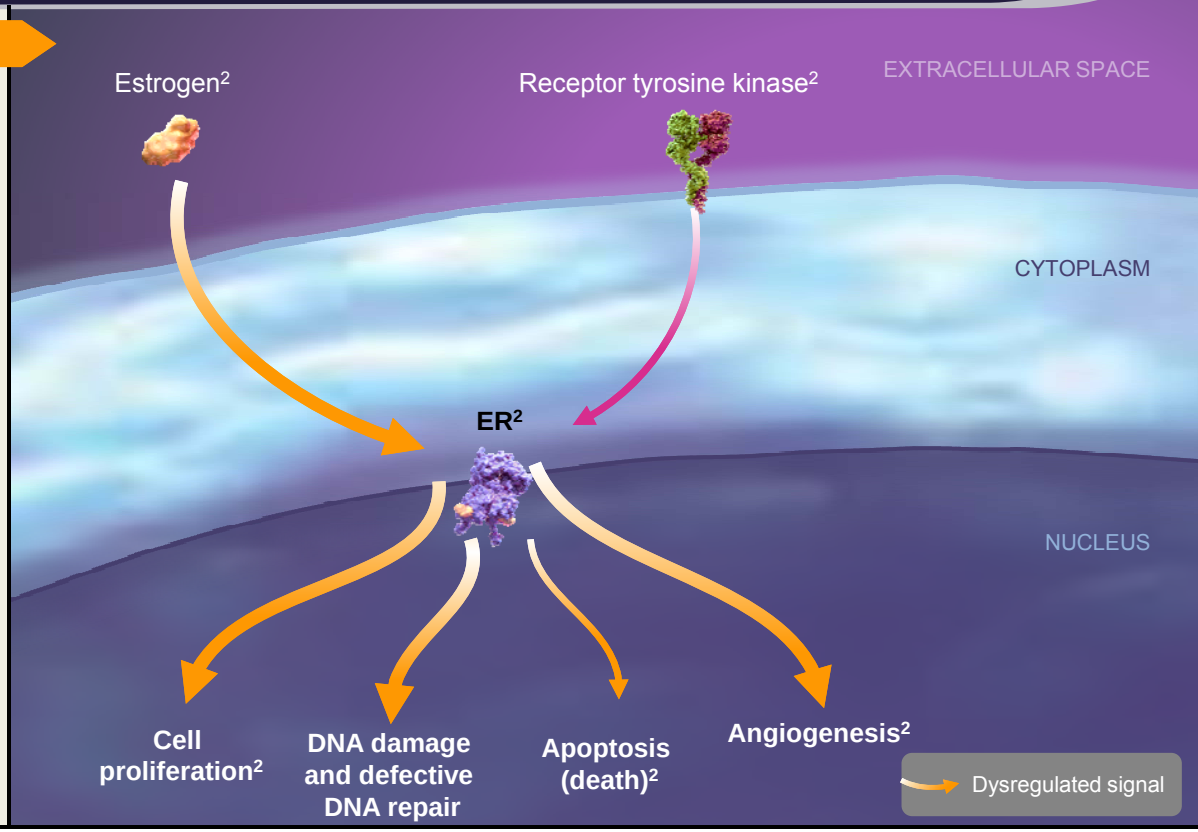
Akt=v-akt murine thymoma viral oncogene homolog 1; EGFR=epidermal growth factor receptor; ER=estrogen receptor; HER2=human epidermal growth factor receptor 2; IGF-1R=insulin-like growth factor 1 receptor; MAPK=mitogen-activated protein kinase; mTOR=mammalian target of rapamycin; PI3K=phosphoinositide 3-kinase; RTK=receptor tyrosine kinase.

1. Osborne CK, et al. *Annu Rev Med.* 2011;62:233-247. **2.** Tokunaga E, et al. *Cancer Sci*. 2014;105(11):1377-1383. **3.** Baselga J. *Oncologist*. 2011;16(suppl 1):12-19.

Dysregulation of Normal Cell Signaling Can Drive Breast Cancer: Focus on Estrogen and ER

Dysregulation

- Hyperactivation of cell proliferation with induction of DNA damage[1]
- Altered DDR in ER+ breast cancer[1]
  - Suppress effective DNA repair and apoptosis in favor of proliferation[1]
- When DDR goes awry in cancer, ER promotes the proliferation of “damaged” cells[1]

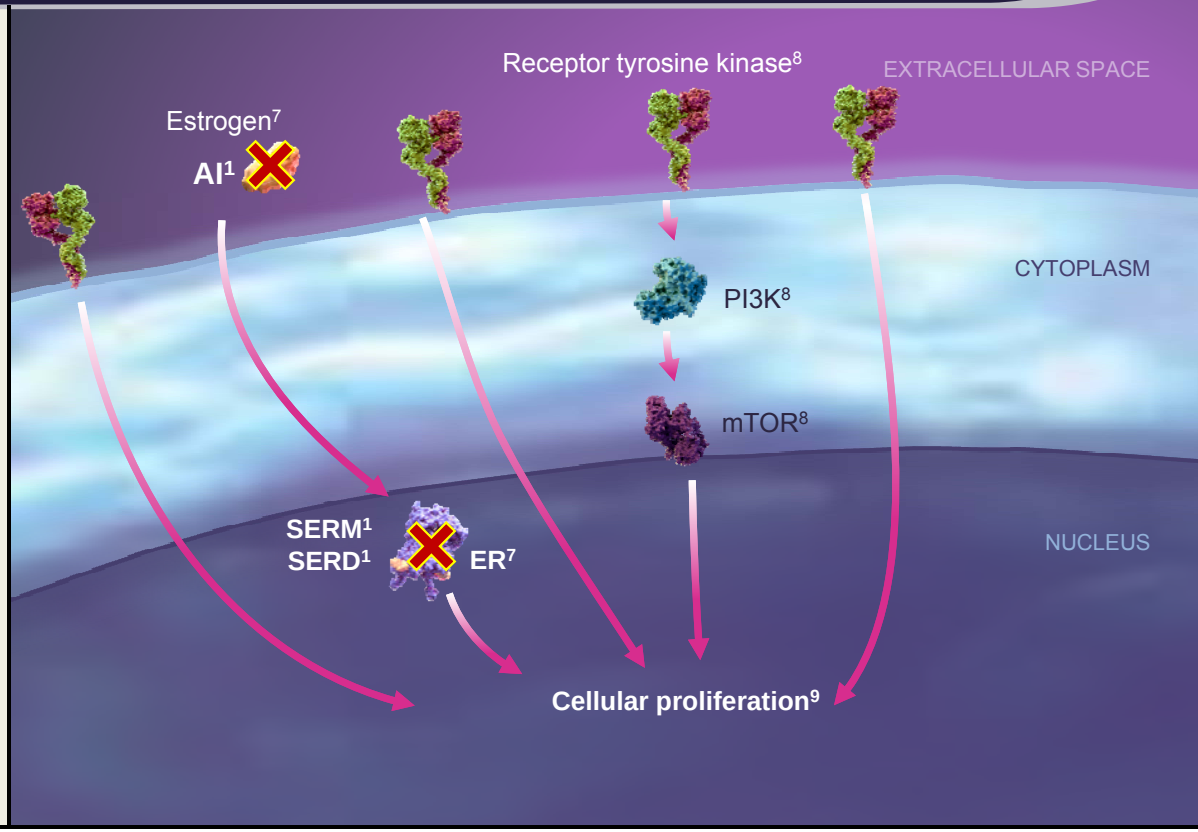


CDK=cyclin-dependent kinase; DDR=DNA damage response; DNA=deoxyribonucleic acid; ER=estrogen receptor.

1. Caldon CE. *Front Oncol.* 2014;4:106. **2.** Osborne CK, et al. *Annu Rev Med.* 2011;62:233-247.

Given the Dominant Role of the ER Pathway in ER+ Breast Cancer, Endocrine Therapy Is the Mainstay Treatment

- Endocrine therapy can target estrogen production or ER directly[1]
  - AIs inhibit aromatase, the enzyme that produces estrogen[1]
  - SERMs disrupt binding of estrogen to ER, which in time induces antiproliferative and proapoptotic effects[1]
  - SERDs bind to the ER and induce its degradation[1]
- Next-generation therapies include combination of endocrine therapy and other inhibitors involved in cellular proliferation, including PI3K, mTOR, and CDK[2-6] inhibitors



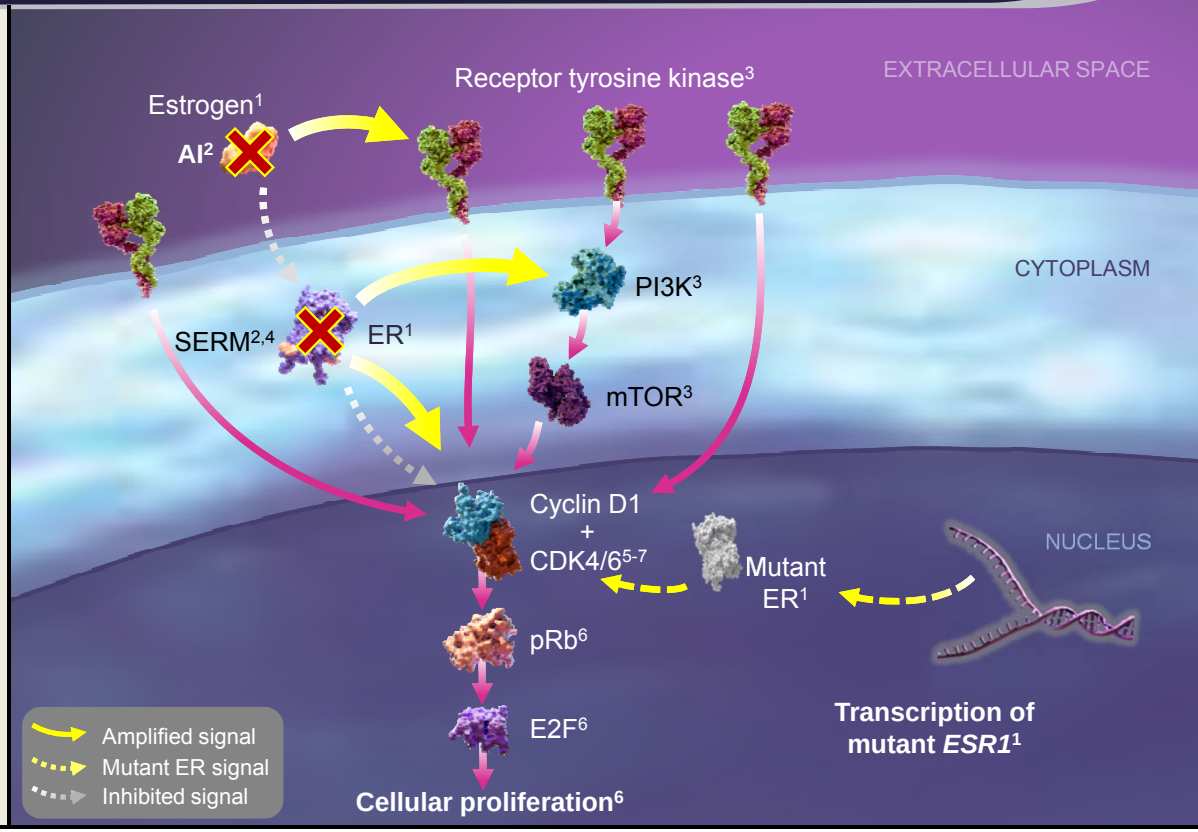
AI=aromatase inhibitor; CDK=cyclin-dependent kinase; ER=estrogen receptor; mTOR=mammalian target of rapamycin; PI3K=phosphoinositide 3-kinase; SERD=selective estrogen receptor downregulator; SERM=selective estrogen receptor modulator.

1. Milani A, et al. *World J Clin Oncol*. 2014;5(5):990-1001. **2.** Verma S, et al. *Oncologist*. 2016;21:1-11 [published ahead of print]. **3.** Cristofanilli M, et al. *Lancet Oncol*. 2016;17:425-39. **4.** Murphy CG, et al. *Oncologist*. 2015;20:483-90. **5.** Baselga J, et al. *N Engl J Med*. 2012;366(6):520-529. **6.** Lee JJX, Loh K, Yap YS. *Cancer Biol Med*. 2015;12:342-354. **7.** Osborne CK, et al. *Annu Rev Med.* 2011;62:233-247. **8.** Baselga J. *Oncologist*. 2011;16(suppl 1):12-19. **9.** VanArsdale T, et al. *Clin Cancer Res*. 2015;21(13):2905-2910.

Pathways Implicated in Endocrine Resistance

Resistance to Estrogen Therapy Can Occur Through a Variety of Mechanisms

- Resistance can occur via[1]
  - Loss of estrogen dependence either due to loss of ER or despite presence of ER
  - When there is an escape pathway from a specific therapy, although tumor is still estrogen dependent
- Resistance to endocrine therapy can be promoted via pathway activation downstream of therapeutic targets afforded by pathway crosstalk or activating mutations[2,3]
- Alternative signaling pathways to the ER may decrease long-term efficacy of hormone therapy and may increase the risk for recurrence and/or disease progression[1]



AI=aromatase inhibitor; CDK=cyclin-dependent kinase; E2F=E2 transcription factor; ER=estrogen receptor; *ESR1*=estrogen receptor 1 gene; mTOR=mammalian target of rapamycin; PI3K=phosphoinositide 3-kinase; pRb=phosphorylated retinoblastoma protein; SERM=selective estrogen receptor modulator.

1. Osborne CK, et al. *Annu Rev Med*. 2011;62:233-247. **2.** Milani A, et al. *World J Clin Oncol*. 2014;5(5):990-1001. **3.** Baselga J. *Oncologist*. 2011;16(suppl 1):12-19. **4.** Wardell SE, et al. *Clin Cancer Res*. 2015;21(22):5121-5130. **5.** Lange CA, et al. *Endocr Relat Cancer*. 2011;18(4):C19-C24. **6.** Asghar U, et al. *Nat Rev Drug Discov*. 2015;14(2):130-146. **7.** VanArsdale T, et al. *Clin Cancer Res*. 2015;21(13):2905-2910.

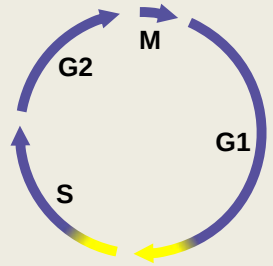
Drivers of Breast Cancer Promote Aberrant Cell Signaling: Focus on Cyclin D1 and CDK4/6

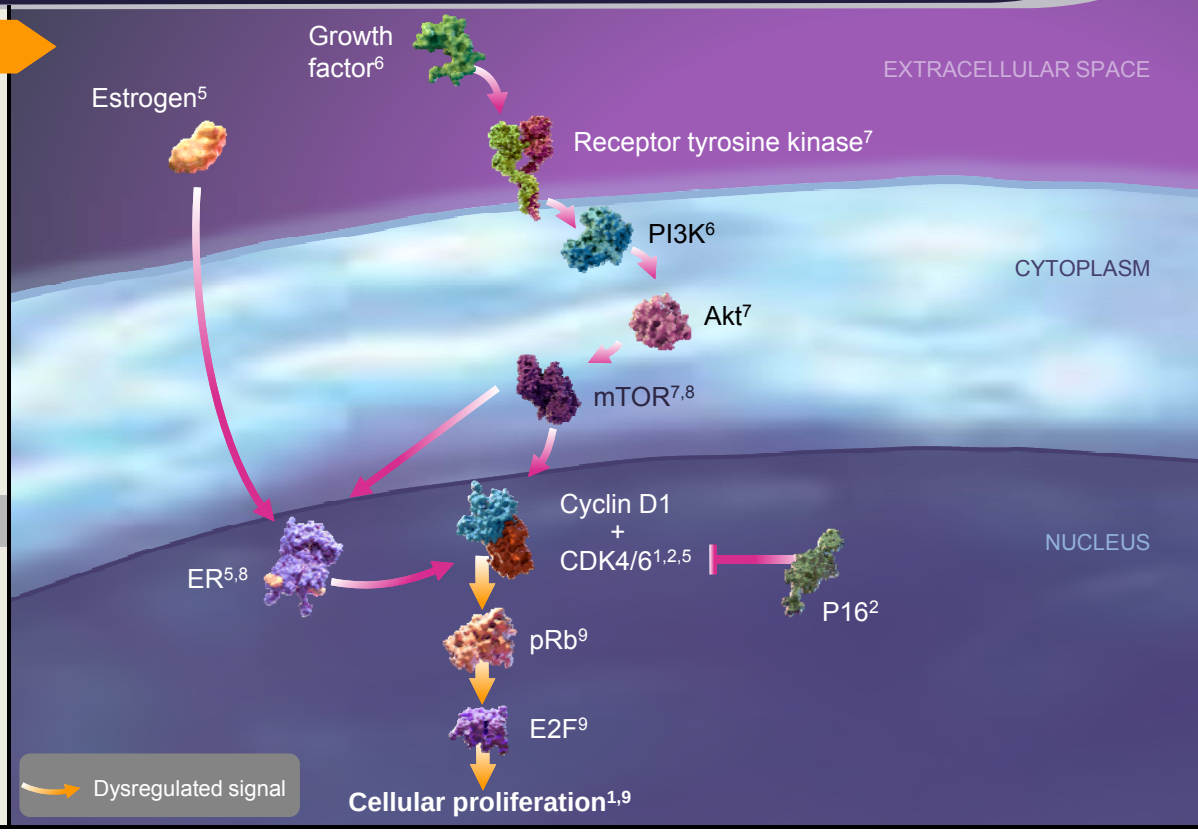
Potential Dysregulation Mechanisms

- Gene amplification of *CCND1* increases cyclin D1 and is observed in 15% of breast cancers[1]
  - mRNA and protein levels of cyclin D1 are overexpressed in 50% of breast cancers, primarily ER+ tumors[1]
- Amplification of the cyclin D1 gene or loss of its inhibitor, p16, facilitates the formation of an active cyclin D1–CDK4/6 complex[2]

Consequence

- Increased activity of CDK4/6[3,4]
  - Initiation of the transition from G1 to the S phase of the cell cycle, which can lead to a loss of proliferative control



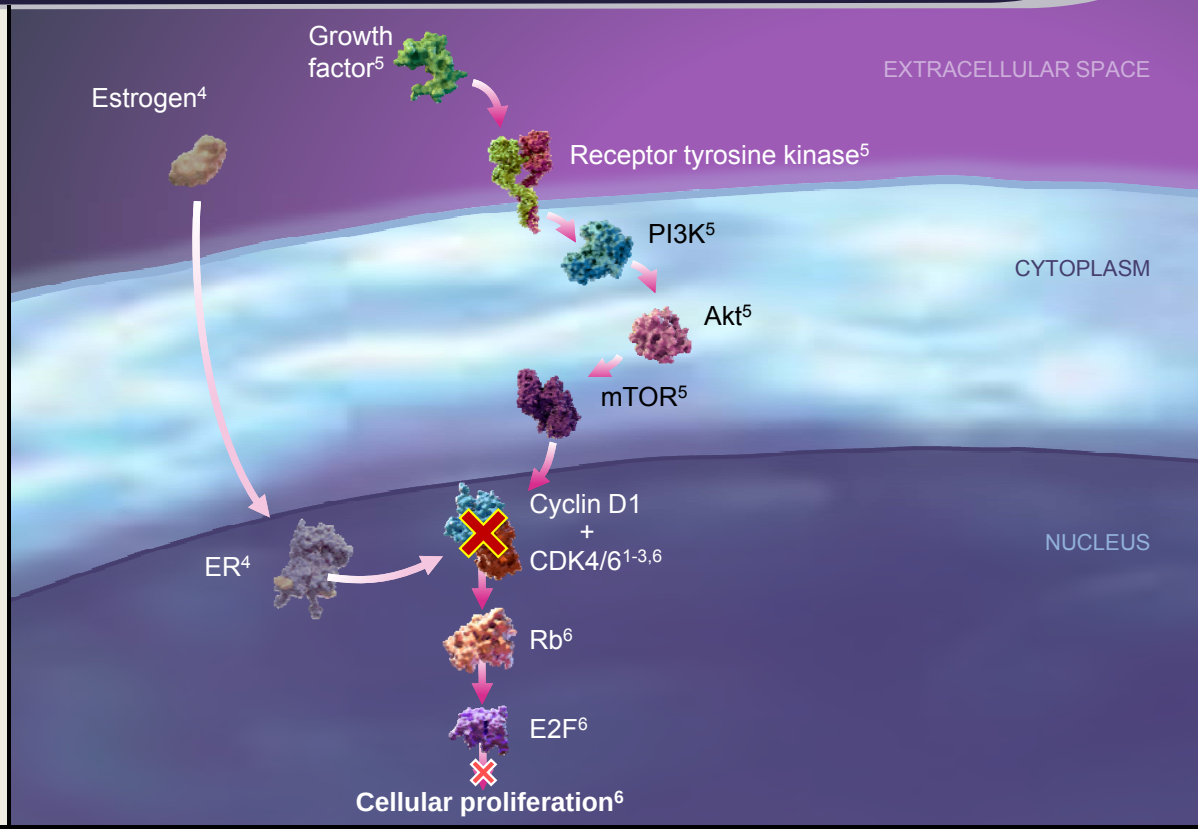


Akt=v-akt murine thymoma viral oncogene homolog 1; *CCND1*=cyclin D1 gene; CDK=cyclin-dependent kinase; E2F=E2 transcription factor; ER=estrogen receptor; G1=growth 1; G2=growth 2; M=mitosis; mRNA=messenger ribonucleic acid; mTOR=mammalian target of rapamycin; PI3K=phosphoinositide 3-kinase; pRb=phosphorylated retinoblastoma protein; S=synthesis.

1. Taneja P, et al. *Clin Med Insights*. 2010;4:15-34. **2.** VanArsdale T, et al. *Clin Cancer Res*. 2015;21(13):2905-2910. **3.** Prall OW, et al. *J Biol Chem*. 1997;272(16):10882-10894. **4.** Weinberg RA. *The Biology of Cancer*. 2nd ed. New York, NY: Garland Science, Taylor & Francis Group; 2014. **5.** Osborne CK, et al. *Annu Rev Med*. 2011;62:233-247. **6.** Vicier C, et al. *Breast Cancer Res*. 2014;16(1):203. **7.** Baselga J. *Oncologist*. 2011;16(suppl 1):12-19. **8.** Lange CA, et al. *Endocr Relat Cancer*. 2011;18(4):C19-C24. **9.** Asghar U, et al. *Nat Rev Drug Discov*. 2015;14(2):130-146.

Targeting CDK4/6 Is a Relevant Approach in Hormone-Resistant Breast Cancer Because Aberrant Signaling Pathways Rely on the Cyclin D1–CDK4/6 Complex for Cell Proliferation

- Phosphorylation of the Rb protein and subsequent E2F activation are mediated by CDK4/6 in both hormone-independent and ER-independent growth of ER+ cells[1,2]
- Inhibition of CDK4/6 results in the arrest of cellular proliferation during the G1 phase in cells expressing a functional Rb protein[3]



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1. Miller TW, et al. *Cancer Discov*. 2011;1(4):338-351. **2.** Thangavel C, et al. *Endocr Relat Cancer*. 2011;18(3):333-345. **3.** VanArsdale T, et al. *Clin Cancer Res*. 2015;21(13):2905-2910. **4.** Osborne CK, et al. *Annu Rev Med*. 2011;62:233-247. **5.** Baselga J. *Oncologist*. 2011;16(suppl 1):12-19. **6.** Asghar U, et al. *Nat Rev Drug Discov*. 2015;14(2):130-146.

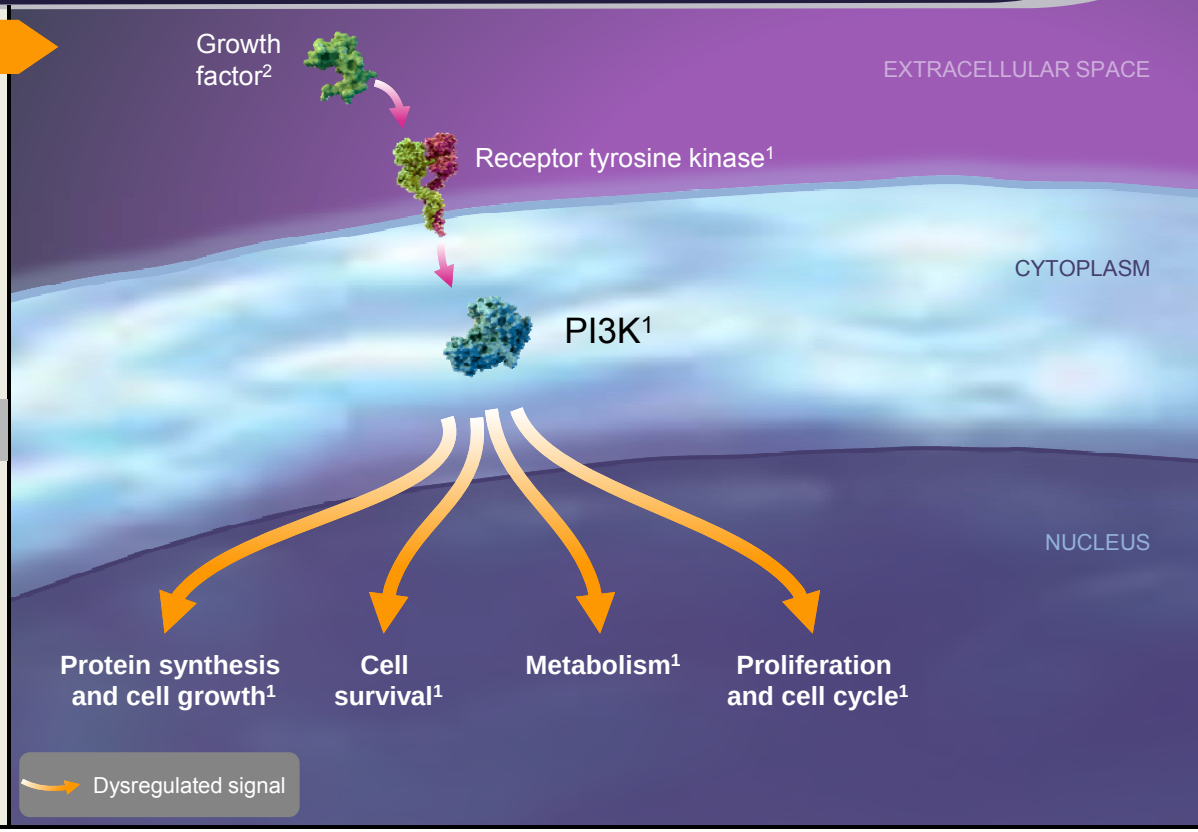
Drivers of Breast Cancer Promote Aberrant Cell Signaling: Focus on PI3K[1]

Dysregulation

- PI3K can be aberrantly activated in breast cancer
- PI3K mutations occur in 20%–25% of breast tumors (>30% of ER+ patients)

Consequence

- Increased enzymatic function
- Enhanced downstream signaling elements such as Akt, which can activate mTOR
- Promotion of oncogenic transformation

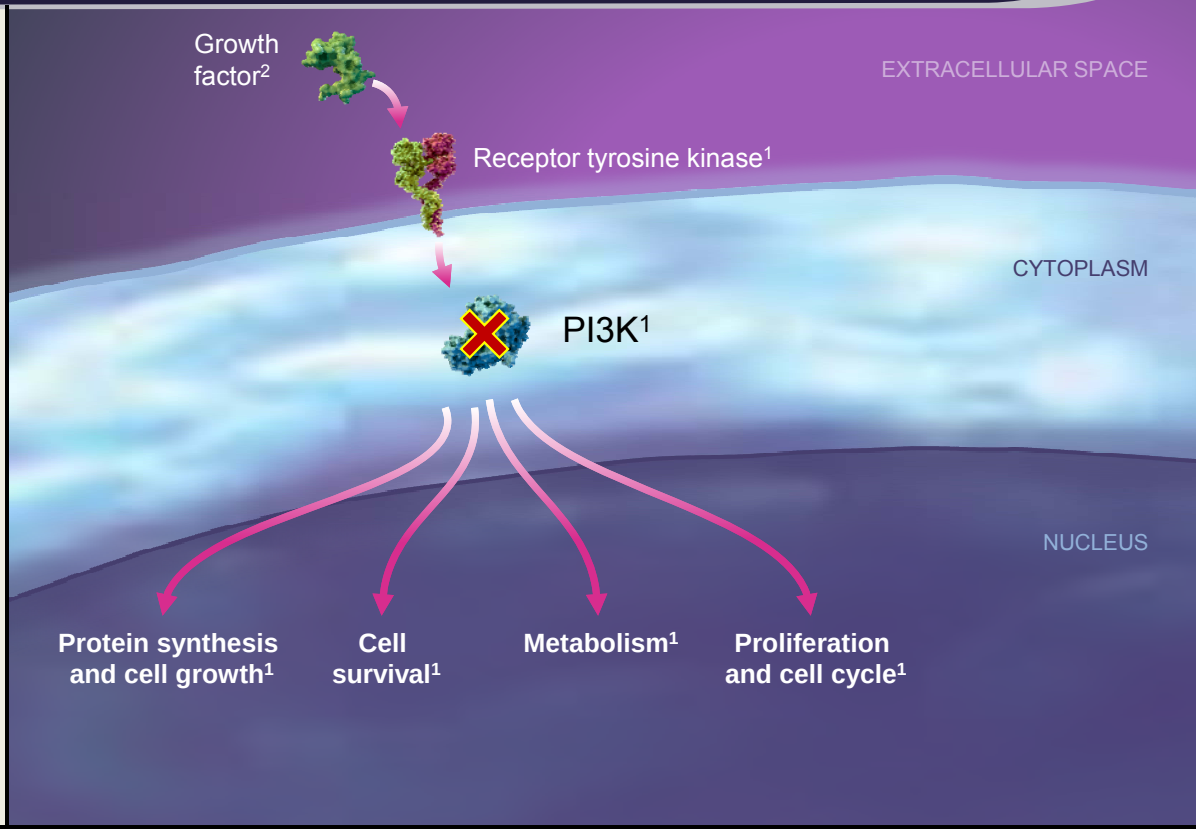


Akt=v-akt murine thymoma viral oncogene homolog 1; ER=estrogen receptor; mTOR=mammalian target of rapamycin; PI3K=phosphoinositide 3-kinase.

1. Baselga J. *Oncologist.* 2011;16(suppl 1):12-19. **2.** Vicier C, et al. *Breast Cancer Res*. 2014;16(1):203.

Targeting PI3K May Curtail Endocrine Resistance and Resistance to Targeting mTOR in Breast Cancer[1]

- PI3K mutations play a role in resistance to therapies that block RTKs
- PI3K can induce estrogen resistance through direct induction of ER transcription
- PI3K activation mediates resistance to downstream mTOR inhibition
  - Inhibition of mTOR causes a negative feedback loop, which increases PI3K signaling



ER=estrogen receptor; mTOR=mammalian target of rapamycin; PI3K=phosphoinositide 3-kinase; RTK=receptor tyrosine kinase.

1. Baselga J. *Oncologist.* 2011;16(suppl 1):12-19. **2.** Vicier C, et al. *Breast Cancer Res*. 2014;16(1):203.

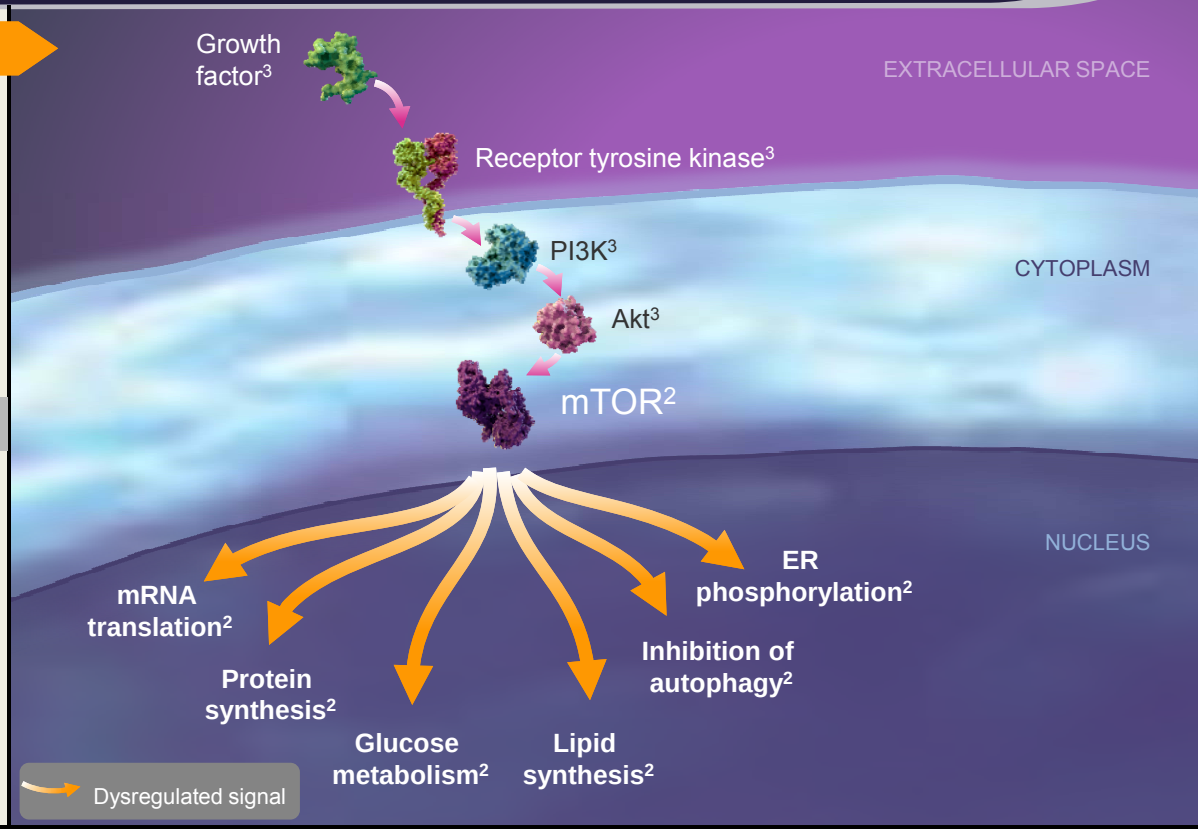
Drivers of Breast Cancer Promote Aberrant Cell Signaling: Focus on mTOR

Dysregulation

- Hyperactivation of mTOR occurs as a downstream effect of Akt hyperactivation[1,2]

Consequence

- Hyperactivation contributes to constitutive activity and, thereby, promotion of downstream events[1,2]

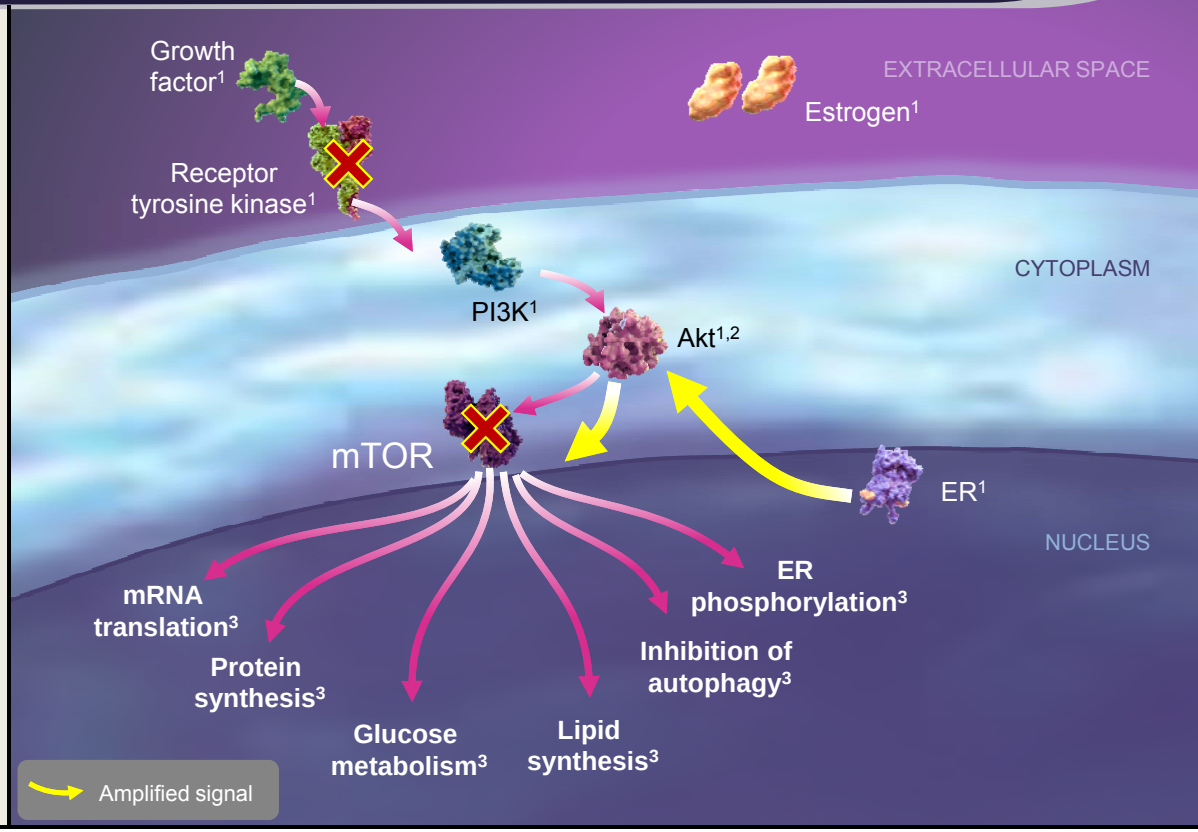


Akt=v-akt murine thymoma viral oncogene homolog 1; ER=estrogen receptor; mTOR=mammalian target of rapamycin; mRNA=messenger ribonucleic acid; PI3K=phosphoinositide 3-kinase.

1. Azab SS. *J Biochem Pharmacol Res*. 2013;1(2):75-83. **2.** Vicier C, et al. *Breast Cancer Res*. 2014;16(1):203. **3.** Baselga J. *Oncologist*. 2011;16(suppl 1):12-19.

Targeting mTOR May Limit Endocrine Resistance in Breast Cancer[1]

- Activation of mTOR occurs downstream of the ER and can allow for an escape from ER inhibition



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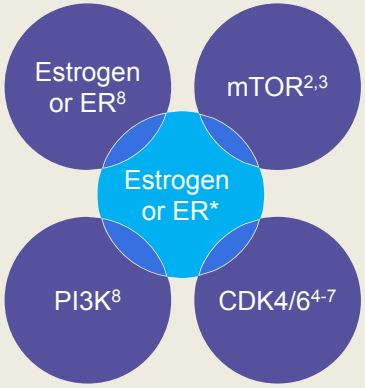
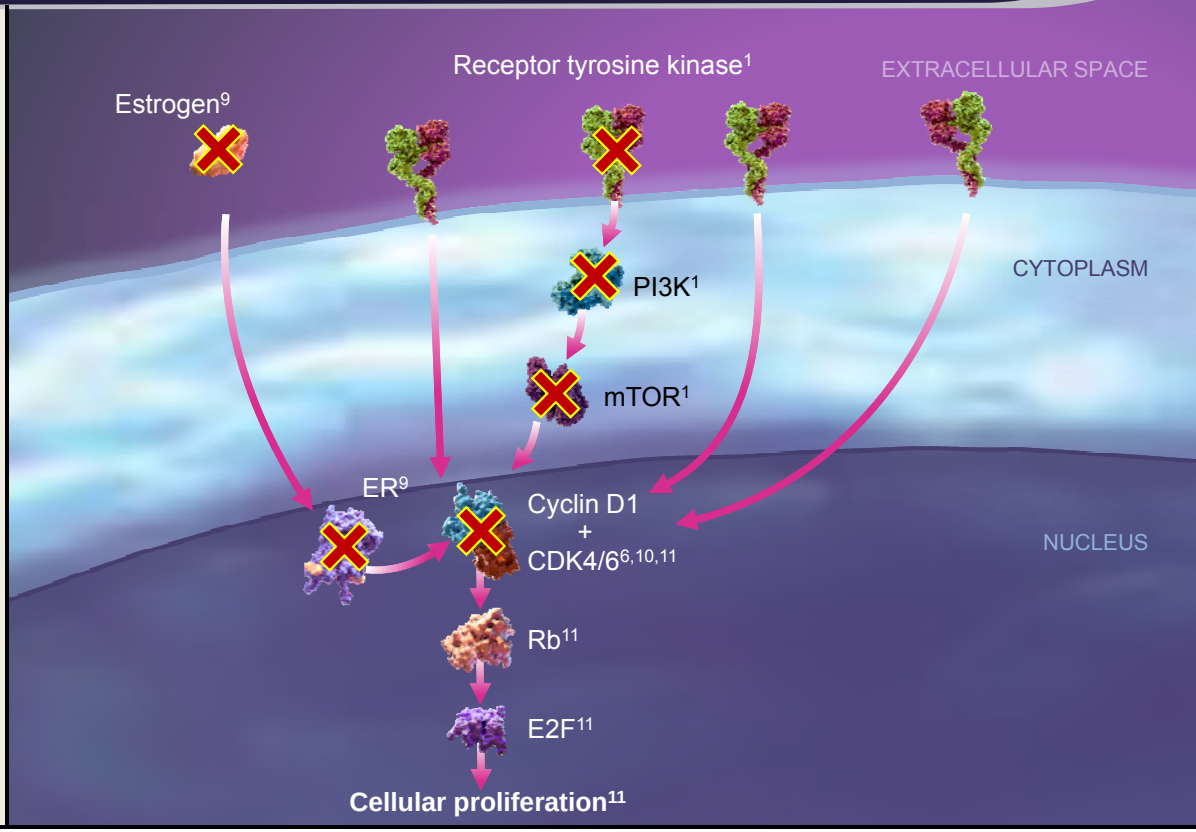
1. Baselga J. *Oncologist.* 2011;16(suppl 1):12-19. **2.** Osborne CK, et al. *Annu Rev Med*. 2011;62:233-247. **3.** Vicier C, et al. *Breast Cancer Res*. 2014;16(1):203.

Eliminating Crosstalk Between Multiple Components of Breast Cancer Signaling Pathways via Potentially Synergistic Targeting Is One Strategy Under Investigation to Circumvent Resistance

- Targeting breast cancer signaling pathways at different nodal points of signaling can eliminate molecular crosstalk and modulate response to estrogen therapy[1]
- Potential different target combinations include



These are potential target combinations and not an exhaustive list.



*Includes treatment with SERM, AI, or NSAI.
AI=aromatase inhibitor; CDK=cyclin-dependent kinase; E2F=E2 transcription factor; ER=estrogen receptor; mTOR=mammalian target of rapamycin; NSAI=nonsteroidal aromatase inhibitor; PI3K=phosphoinositide 3-kinase; Rb=retinoblastoma protein; SERM=selective estrogen receptor modulator.

1. Baselga J. *Oncologist.* 2011;16(suppl 1):12-19. **2.** deGaffenried LA, et al. *Clin Can Res*. 2004;10(23):8059-8067. **3.** Yardley DA, et al. *Adv Ther.* 2013;30(10):870-884. **4.** Finn RS, et al. *Breast Cancer Res.* 2009;11(5):R77. **5.** Finn RS, et al. *Lancet Oncol.* 2015;16(1):25-35. **6.** VanArsdale T, et al. *Clin Cancer Res*. 2015;21(13):2905-2910. **7.** Wardell SE, et al. *Clin Cancer Res.* 2015;21(22):5121-5130. **8.** Milani A, et al. *World J Clin Oncol*. 2014;5(5):990-1001. **9.** Osborne CK, et al. *Annu Rev Med.* 2011;62:233-247. **10.** Lange CA, et al. *Endocr Relat Cancer.* 2011;18(4):C19-C24. **11.** Asghar U, et al. *Nat Rev Drug Discov*. 2015;14(2):130-146.

Summary

- Developing cancers take advantage of normal cellular processes in order to grow and proliferate[1]
- Many pathways have been implicated in the development and progression of ER+/HER2- breast cancer[1,2]
- The ER pathway plays a dominant role in the pathogenesis of ER+/HER2- breast cancer[3]
- Endocrine therapy directly targets the ER pathway, and is the mainstay treatment for ER+ breast cancer[3,4]
- The complex nature of the adaptive signaling network to which ER belongs allows resistance to endocrine therapy[4]
- Targeting supportive components, such as those linked to ER function may aid in the prevention of resistance to estrogen therapy[5,6]

ER=estrogen receptor; HER2=human epidermal growth factor receptor 2.

1. Weinberg RA. *The Biology of Cancer*. 2nd ed. New York, NY: Garland Science, Taylor & Francis Group; 2014. **2.** Lange CA, et al. *Endocr Relat Cancer.* 2011;18:C19-C24. **3.** Osborne CK, et al. *Annu Rev Med.* 2011;62:233-247. **4.** Milani A, et al. *World J Clin Oncol.* 2014;5:990-1001. **5.** Hanahan D, et al. *Cell.* 2011;144:646-674. **6.** Sledge GW, et al. *J Clin Oncol.* 2014;32:1979-1986.