VHIO
VALL D'HEBRON
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New Fields: Emerging Novel Targeted Treatments for ER-Positive Breast Cancer

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Treatment Guidelines for HR$^+$, HER2$^-$ Advanced Breast Cancer: Focusing on Endocrine Therapy

ESMO Treatment Guidelines for HR$^+$, HER2$^-$ ABC[1]

- ***In HR$^+$, HER2$^-$ disease, ET is the treatment of first choice independent of metastatic site,*** **unless rapid response is needed. Limited visceral metastases are not a contraindication for ET**

ABC2 Treatment Guidelines for HR$^+$, HER2$^-$ ABC[2]

- ***ET is the preferred option for HR$^+$ disease,*** **even in the presence of visceral disease, unless there is concern or proof of endocrine resistance or rapidly progressive disease needing a fast response**

AGO Treatment Guidelines for HR$^+$, HER2$^-$ ABC[3]

- ***Endocrine therapy represents the first choice for HR$^+$ metastatic breast cancer except for acute, life-threatening disease***

ABC, advanced breast cancer; AGO, Association of Gynecological Oncology; AI, aromatase inhibitor; ESMO, European Society for Medical Oncology; ET, endocrine therapy; HR hormone receptor; HER2, human epidermal growth factor receptor 2

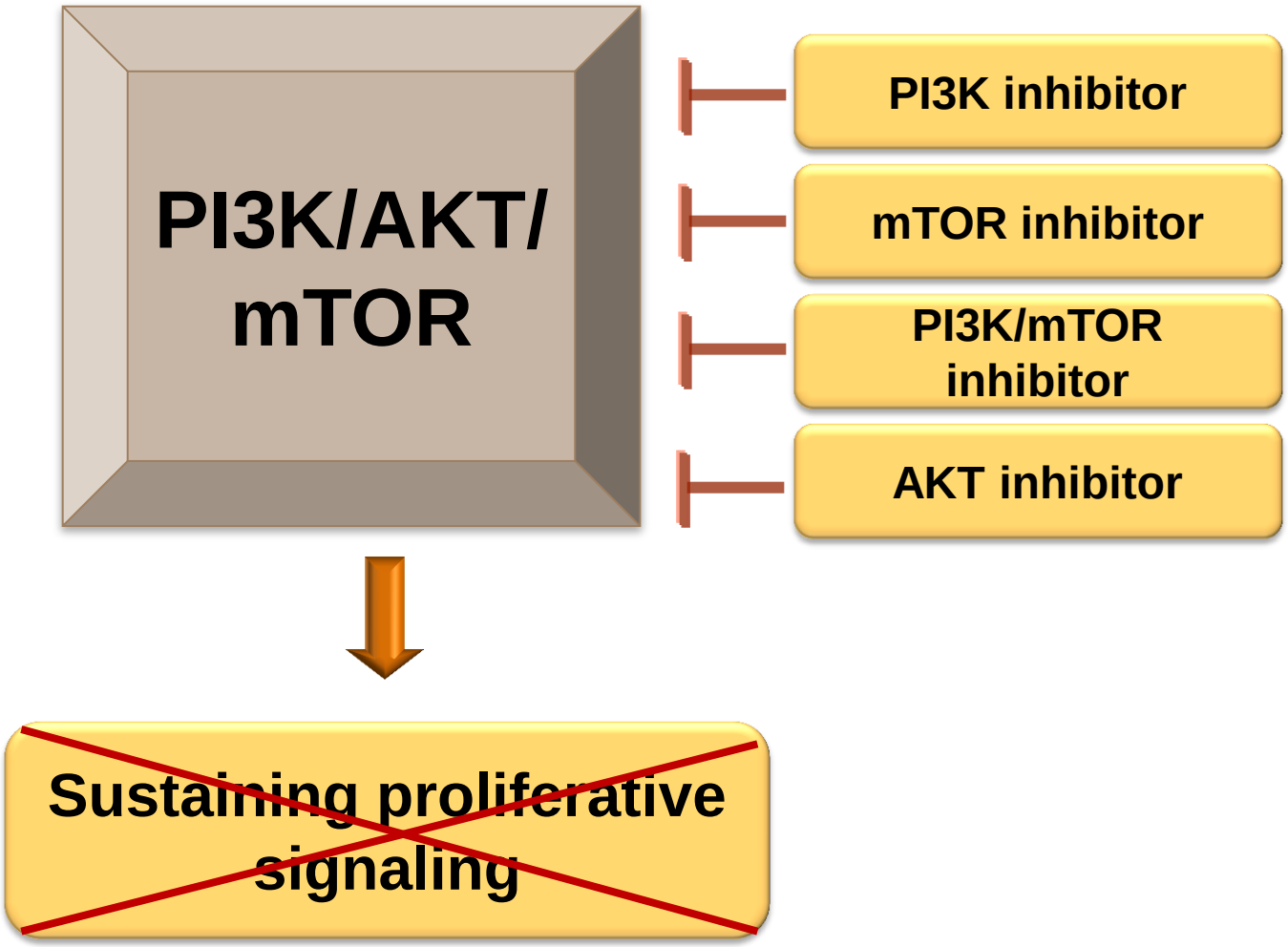
1. Cardoso F, et al. *Ann Oncol*. 2012;23(suppl 7):vii11-vii19. 2. Cardoso F, et al. *Ann Oncol*. 2014;25(10):1871-1888.
3. AGO Breast Committee. *Diagnosis and Treatment of Patients with Primary and Metastatic Breast Cancer. Recommendations 2014.* Available at http://www.ago-online.de.

Endocrine and Targeted Therapies

The Present Future…

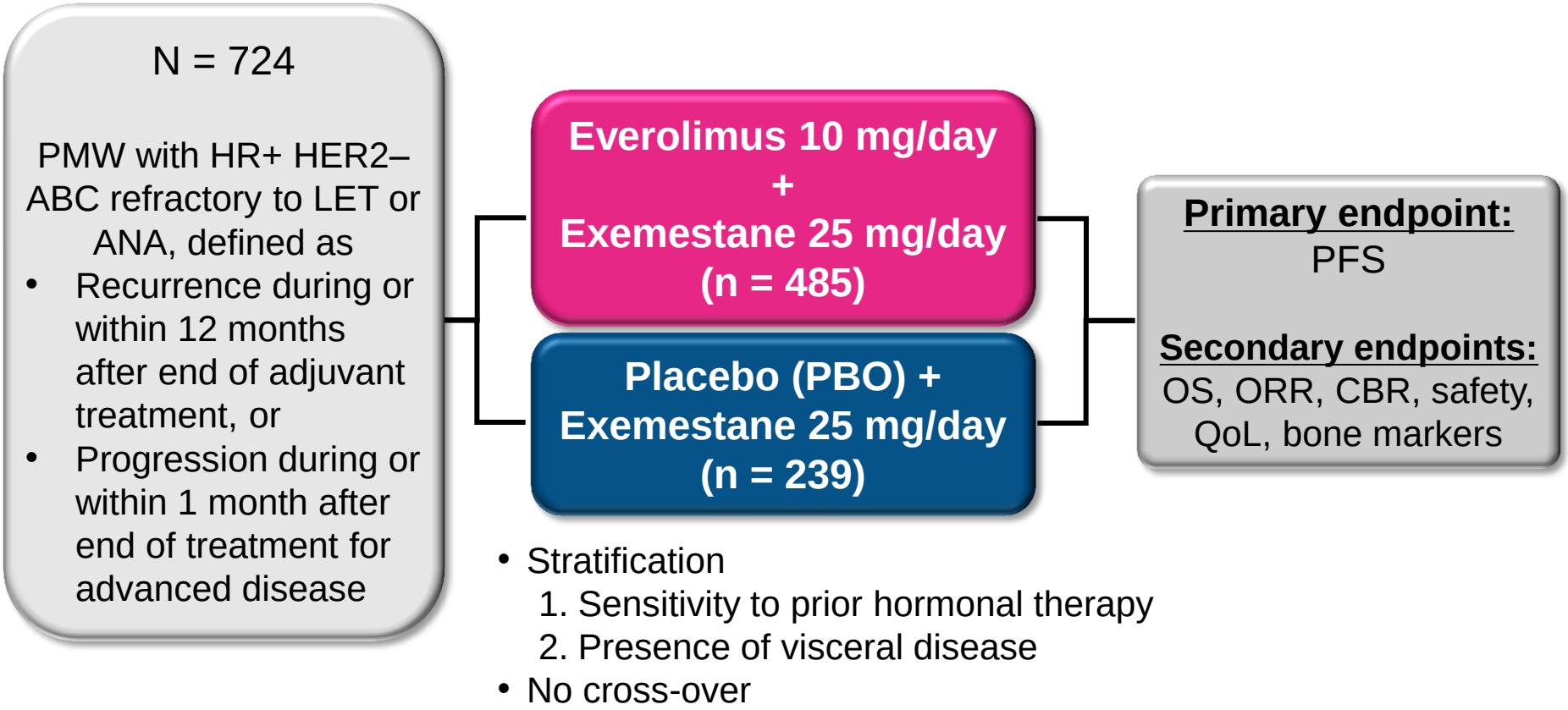
Why does hormonal resistance occur?

Novel Target Agents



mTOR, mammalian target of rapamycin; PI3K, phosphatidylinositol 3-kinase.

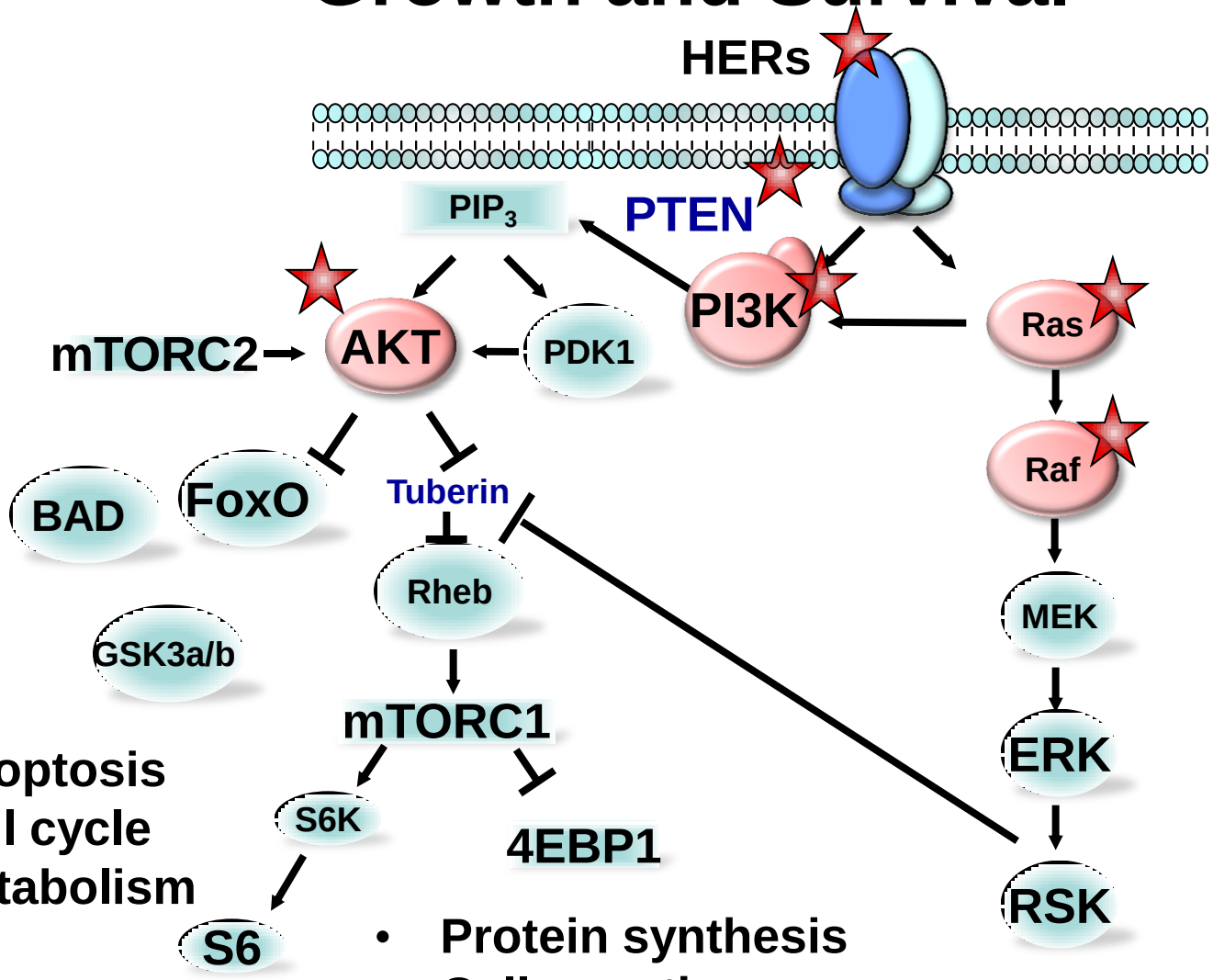
Pivotal BOLERO-2 Study: Exemestane (EXE) ± Everolimus (EVE) in ABC Progressing After NSAI: Non Steroidal Aromatase Inhibitors, NSAIs



ANA, anastrozole; CBR, clinical benefit rate; LET, letrozole; NSAI, nonsteroidal aromatase inhibitor; ORR; overall response rate; OS, overall survival; PFS, progression-free survival; PMW, postmenopausal women; QoL, quality of life

Baselga J, et al. *N Engl J Med*. 2012;366(6):520-529.

The PI3K Cascade Regulates Cell Growth and Survival



- Apoptosis
- Cell cycle
- Metabolism

- Protein synthesis
- Cell growth
- Cell proliferation

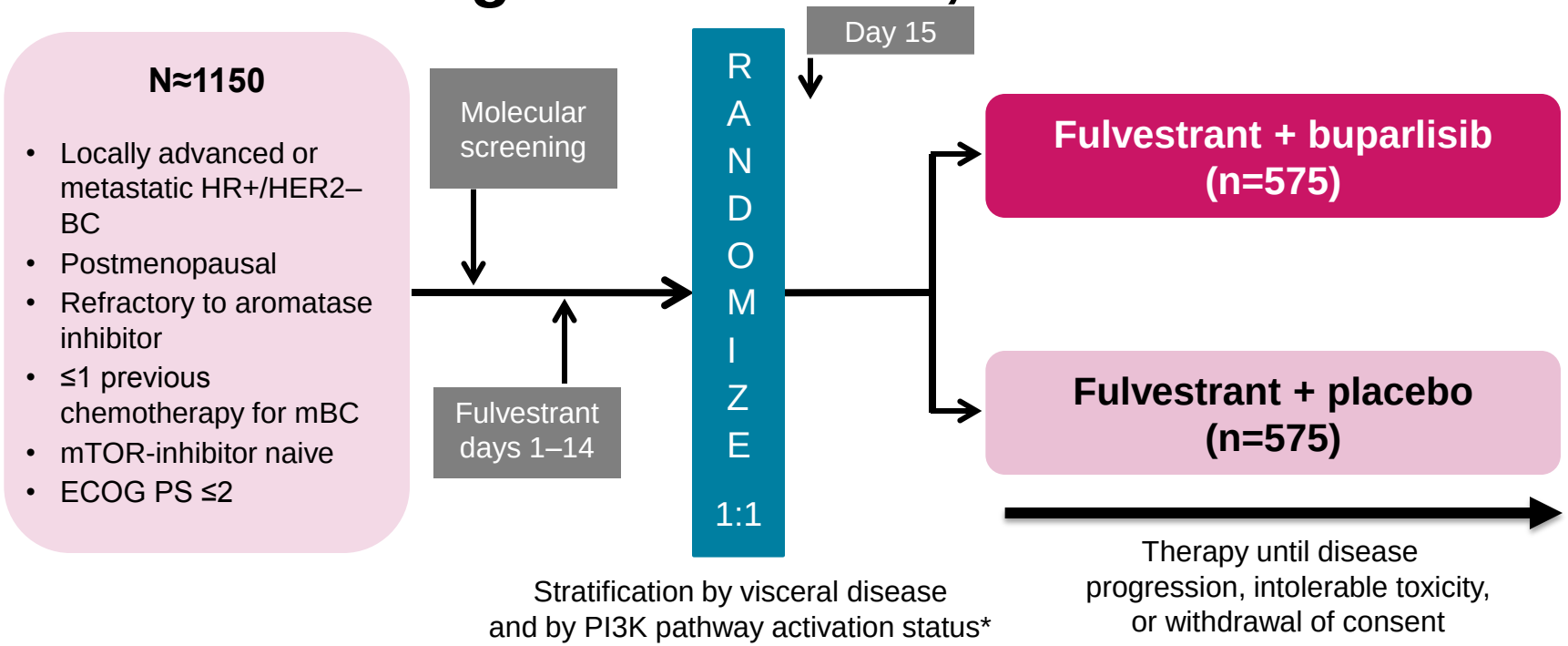
Frequent molecular alterations that activate the PI3K pathway

Clinical Activity of the First PI3K Inhibitors Monotherapy

		BEZ235	BKM120	GDC0980 QD	GDC0941	PF-4691502	SF-1126	XL-147	XL-765¥	Σ
Breast	PR	1	1		2					4
	SD	4	1 a 3			1		1	1	8 - 10
	C								1†	1
NSCLC	PR	1						1		2
	SD					1		3	1	5
Mesothelioma	PR			*						0*
	SD			3					1	4
	actividad	1‡								1
Cervical ADK	PR				1					1

† Response in skin lesions
* 29% reduction
‡ <30% reduction (NOS)

BELLE2: Hormone Receptor–Positive HER2-Negative Disease, mTORi Naïve



Study objectives:

Co-primary: PFS (local assessment)‡

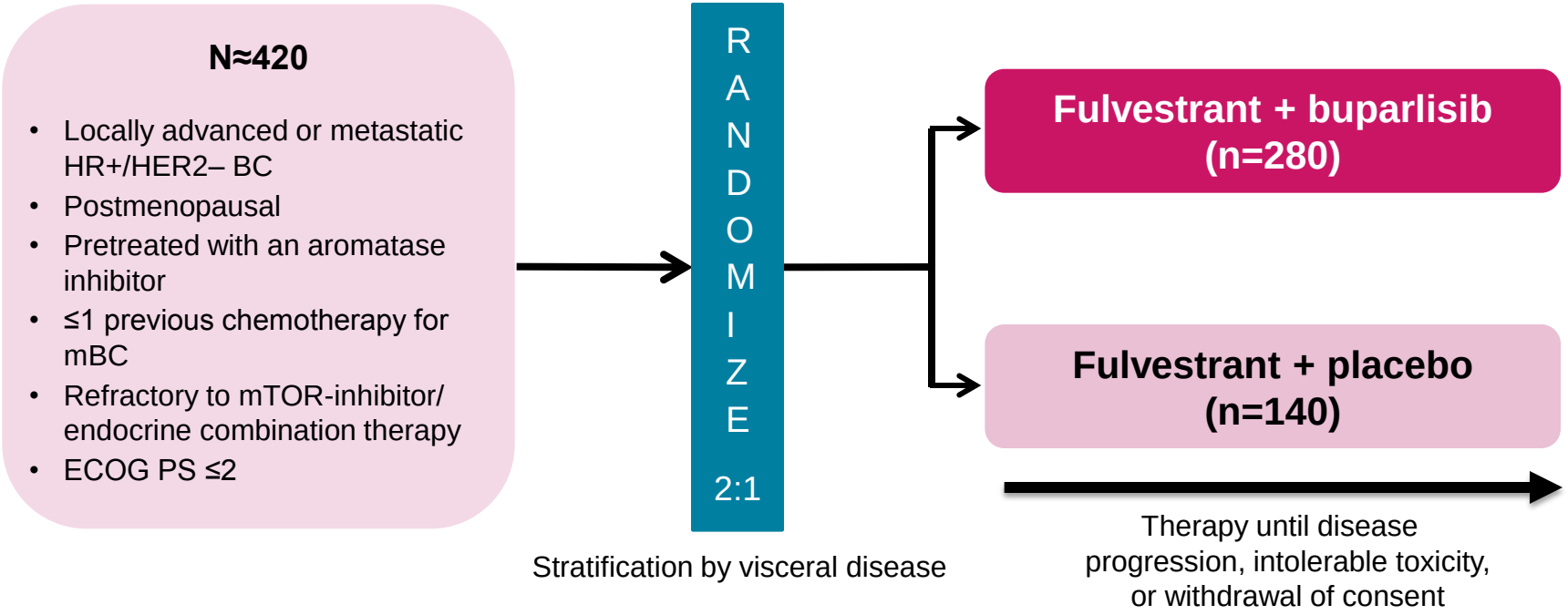
Co-key secondary: OS‡

Secondary: Efficacy (ORR,‡§ CBR,‡§ PFS,§ OS§), safetyǁ, PK¶, patient-reported outcomes‡, ECOG PS‡§

*PI3K pathway activation is defined as mutation in the *PIK3CA* gene and/or loss of PTEN expression by immunohistochemistry;
‡Tested in the main (known status) and/or full (all patients) or PI3K activated populations.
§Tested in the PI3K nonactivated and PI3K status unknown populations.
ǁTested in the main and full populations only.
¶Tested in all patients only.

National Institutes of Health, Available at: http:// clinicaltrials.gov/ct2/NCT01610284. Accessed: December 6, 2014.

BELLE-3: Hormone Receptor–Positive HER2-Negative Disease, mTORi Pretreated Study Design CBKM120F2303



Study objectives:

Co-primary: PFS (local assessment)
Co-key secondary: OS
Secondary: Efficacy (ORR, CBR), safety, PK, patient-reported outcomes, time to ECOG PS deterioration

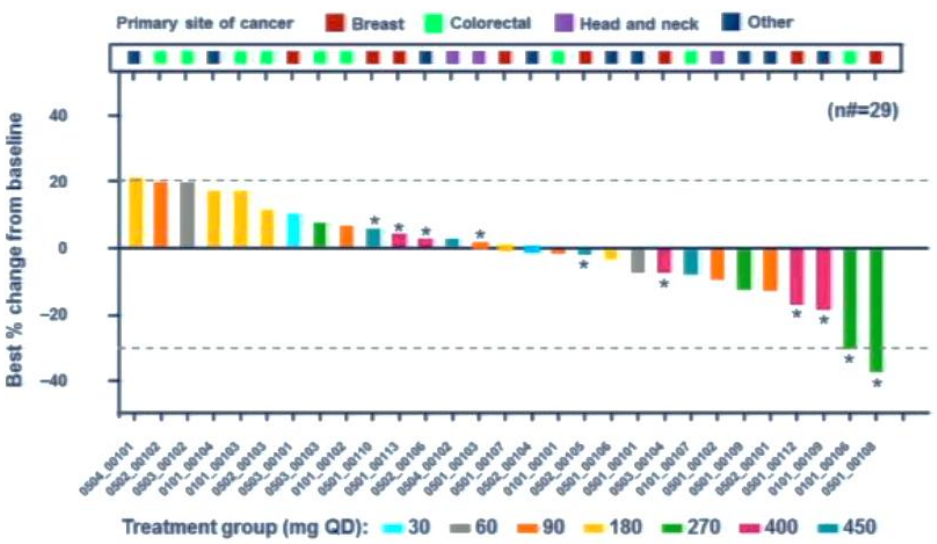
National Institutes of Health, Available at: http:// clinicaltrials.gov/ct2/NCT01610284. Accessed: December 6, 2014.

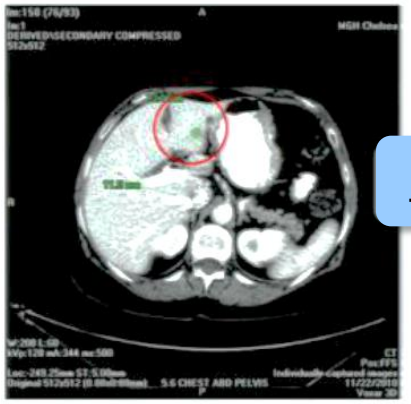
Selective Targeting of PI3K Alpha (*PIK3CA*)

Two leading selective inhibitors

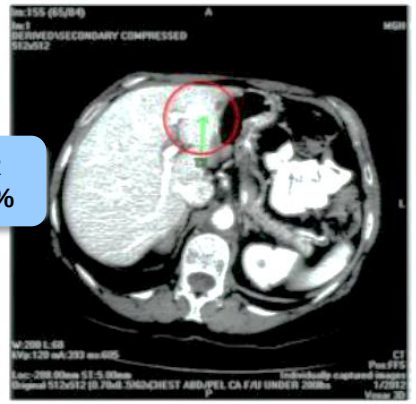
Inhibit alpha >> beta	**alpelisib**	**(alpha selective)**
	taselisib	**(beta sparing)**

Clinical responses with alpelisib (BYL719) in *PIK3CA* mutant cancer





PR
-52%



Baseline **End cycle 8**

Juric D, et al. *Cancer Res*. 2012.*72:* Abstract CT-01.

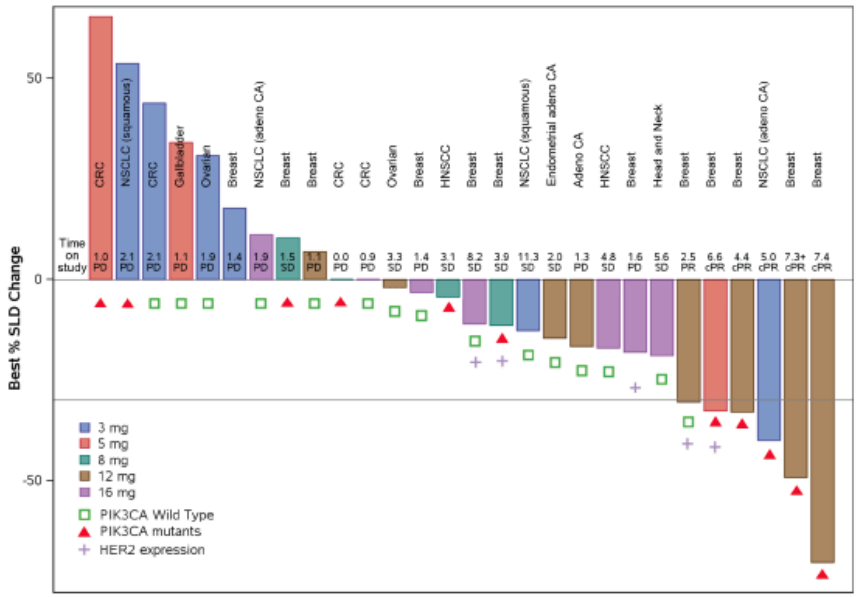
Selective Targeting of PI3K Alpha (*PIK3CA*)

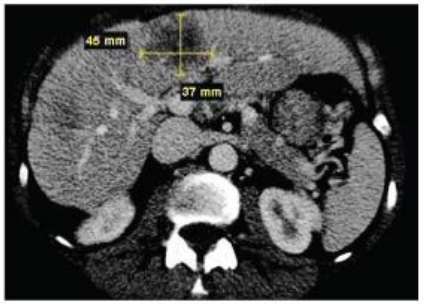
Two leading selective inhibitors

Inhibit alpha > beta	**alpelisib**	**(alpha selective)**
	taselisib	**(beta sparing)**

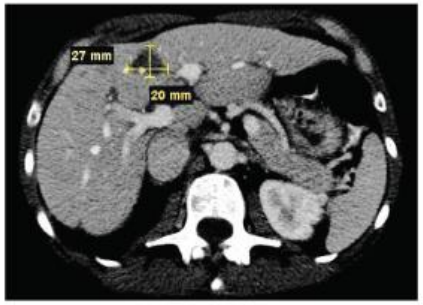
Clinical responses with GDC0032 in *PIK3CA* mutant cancer

Dose escalation patients





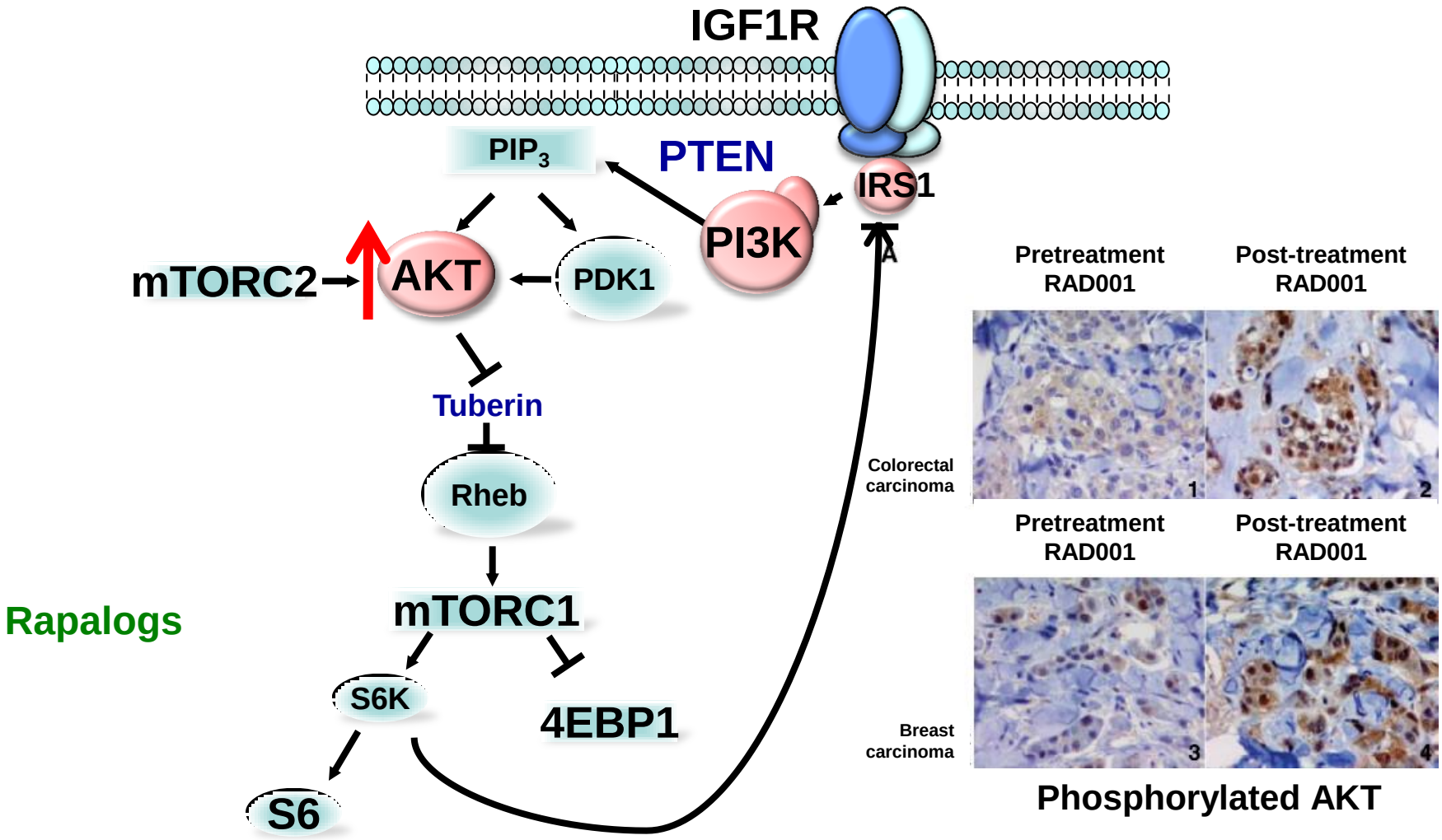
Baseline



End cycle 8

Juric D, et al. *Eur J Cancer.* 2013;49(Suppl 3): Abstract P017.

Rapalogs Disturb a Negative Feedback Activating AKT

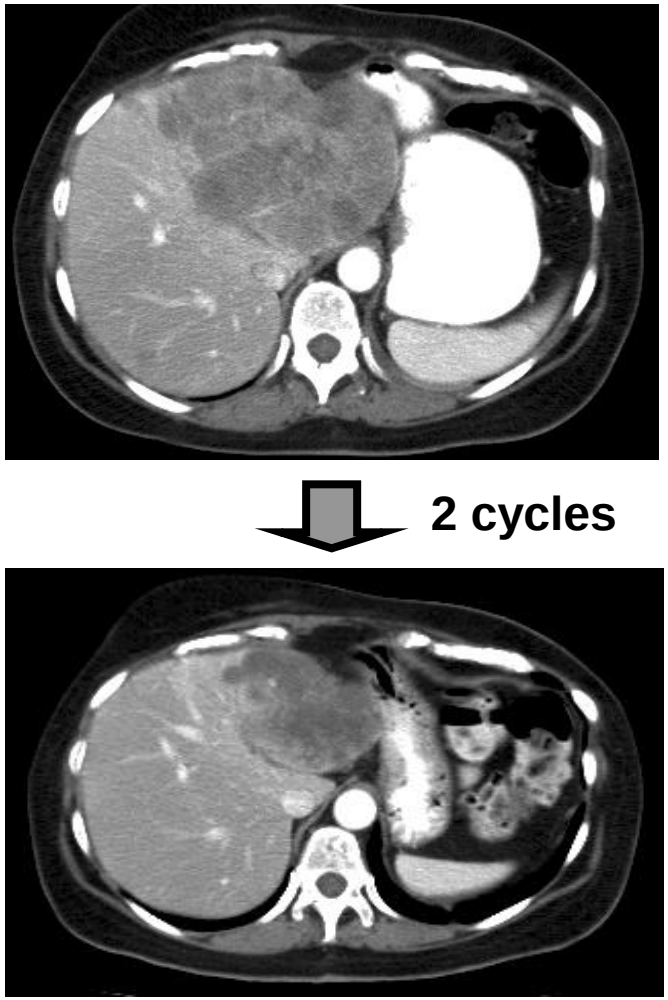


O'Reilly KE, et al. *Cancer Res*. 2006;66(3):1500-1508. Tabernero J, et al. *J Clin Oncol*. 2008;26(10):1603-1610.

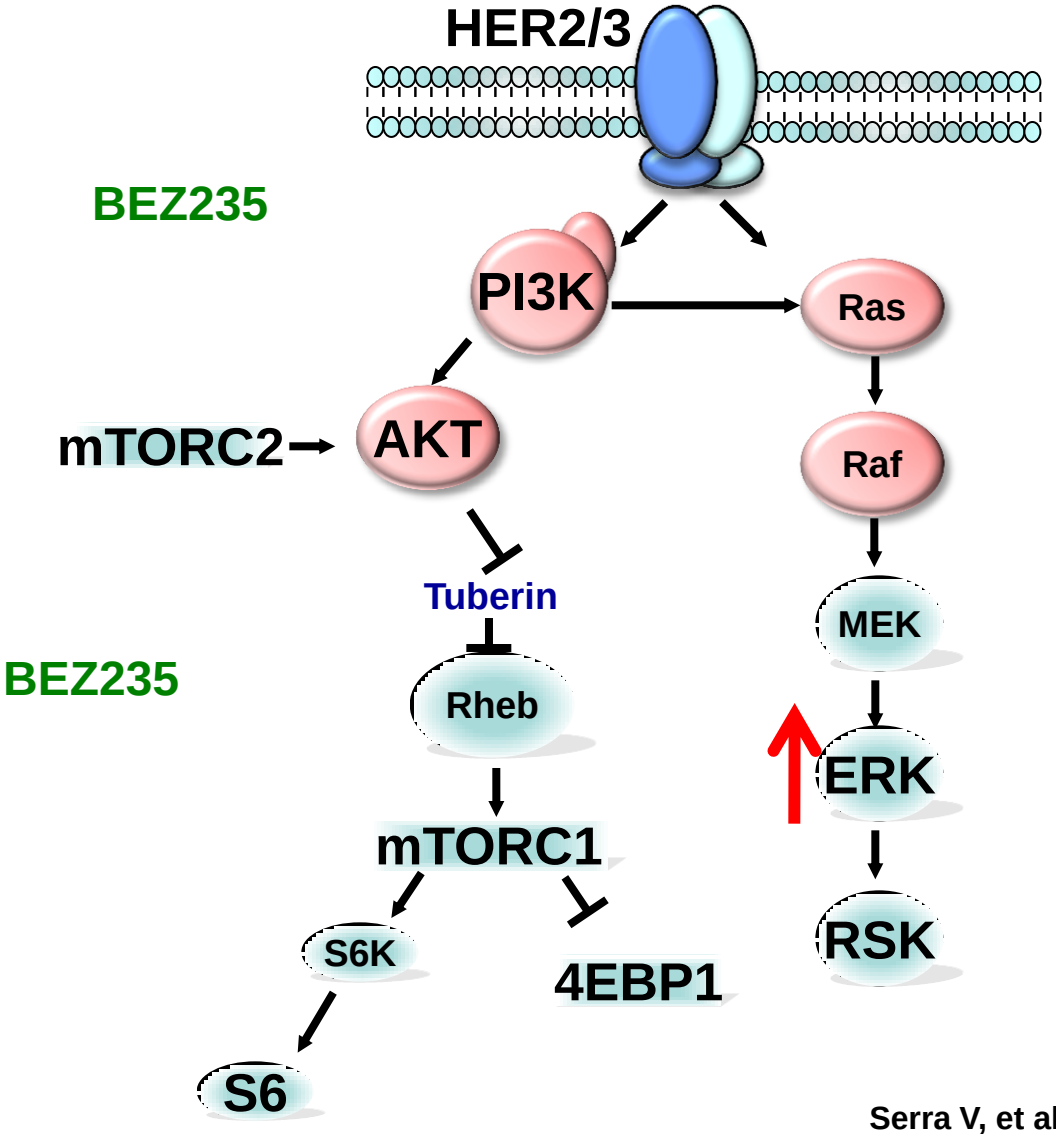
Example of a Partial Response to Ridaforolimus + Dalotuzumab

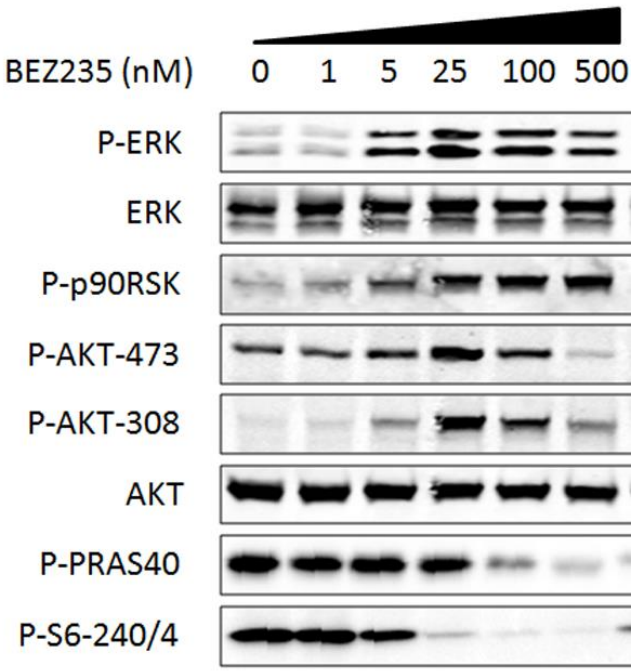
History

- **56 year-old female**
  - **Stage IV breast cancer**
- **ER+/PR+/HER2 neg, Ki67 20%**
- **Adjuvant chemotherapy**
  4 prior chemotherapy regimens
  3 prior hormone therapies
- **Patient remained on study treatment for 9 months before progression**



PI3K/mTORC Inhibition in HER2 Overexpressing Cells Activates MAPK (and Is HER2 Dependant)

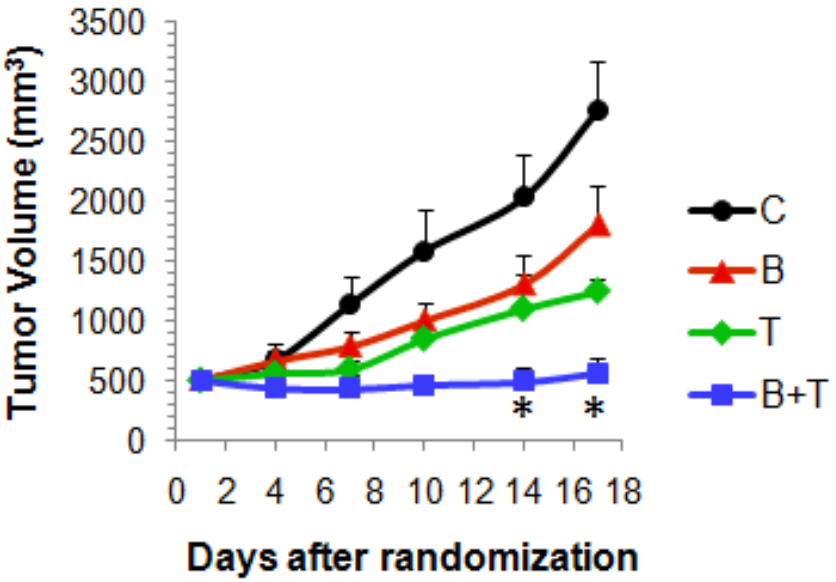




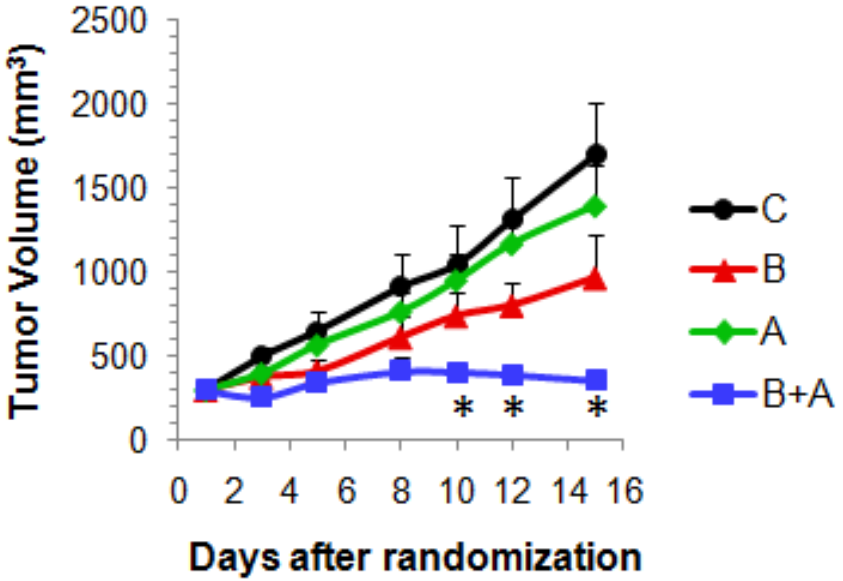
Serra V, et al. *Oncogene*. 2011;30(22):2547-2557.

Combination of PI3K/mTOR and HER2 Inhibition or MEK Inhibition Shows Enhanced Anticancer Activity

BEZ235 + trastuzumab



BEZ235 (PI3K/mTOR) + AZD6244 (MEK)

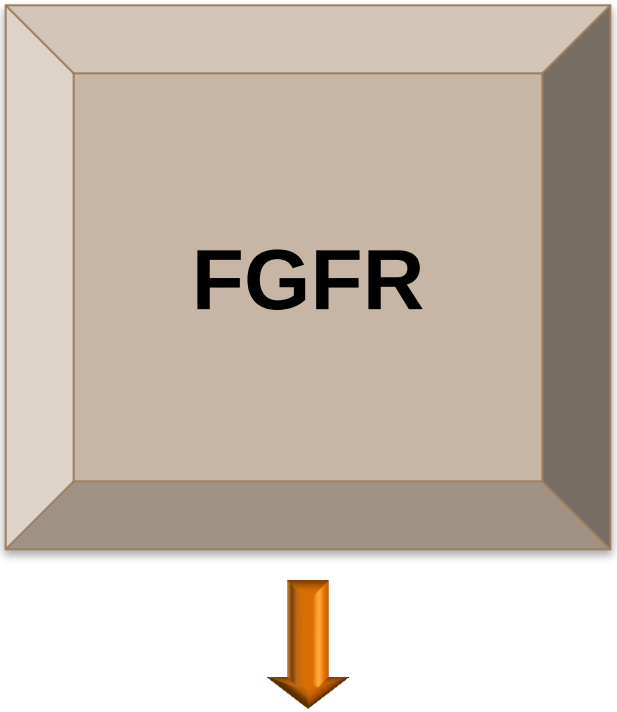


BT474-Tr xenografts

B- BEZ235 (20 mg/Kg QD); T- Trastuzumab (10mg/Kg, BIW)
B-BEZ235 (25 mg/Kg QD); A- AZD6244 (8mg/Kg QD)

Serra V, et al. *Oncogene*. 2011;30(22):2547-2557.

New Receptors…

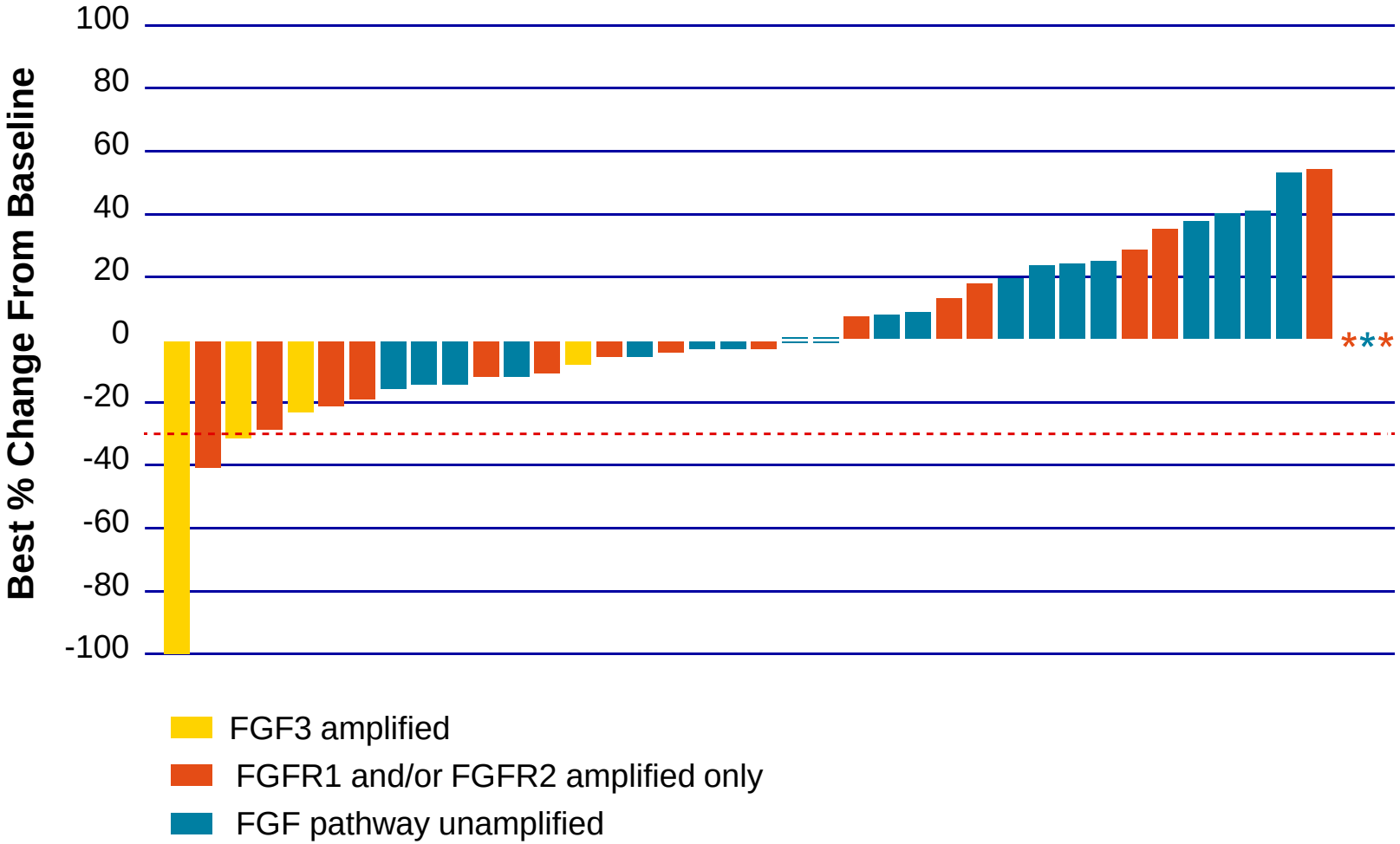


FGFR, fibroblast growth factor receptor

Turner N, et al. *Cancer Res*. 2010;70(5):2085-2094. Roidl A, et al. *Clin Cancer Res*. 2009;15(6):2058-2066.

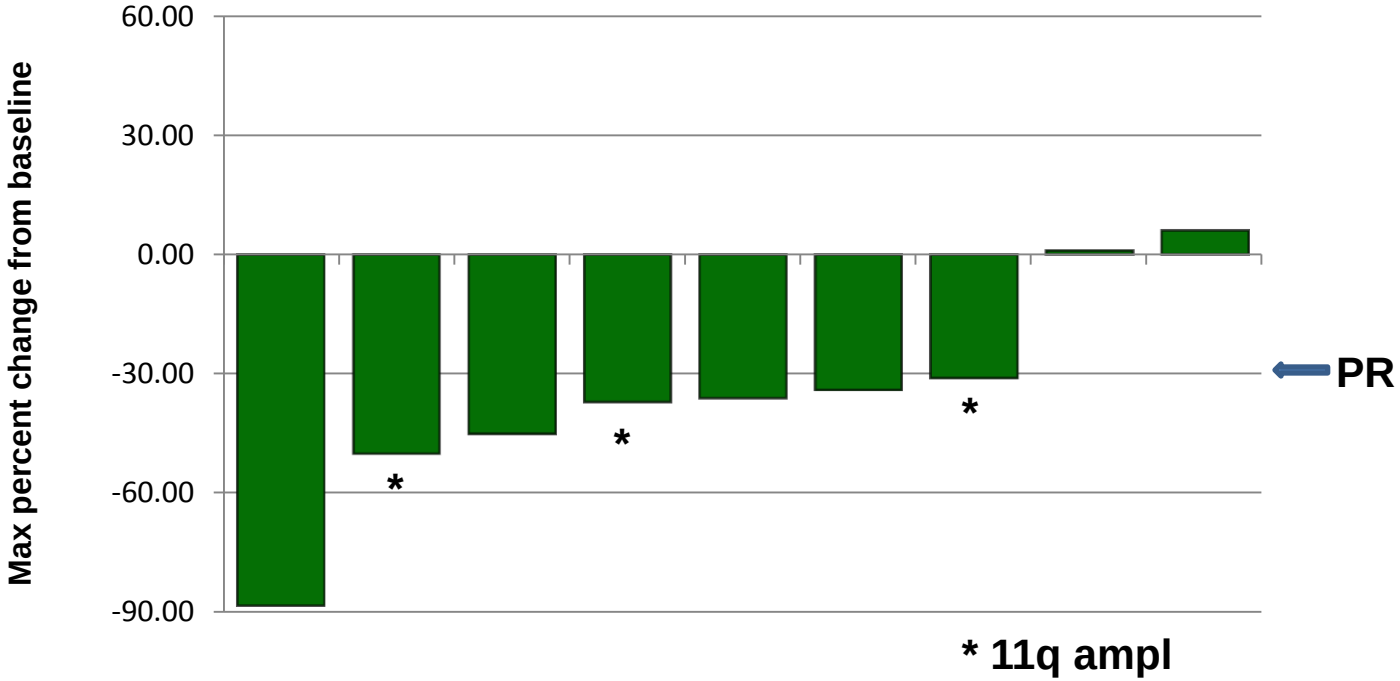
Dovitinib (TKI258) in Breast Cancer

A multicenter, open-label phase II trial of dovitinib, an FGFR1 inhibitor, in FGFR1-amplified and -nonamplified metastatic breast cancer



Andre F, et al. *J Clin Oncol.* 2012;30(15S): Abstract 508.

E3810: FGF+ Breast Cancer Patients With Measurable Disease

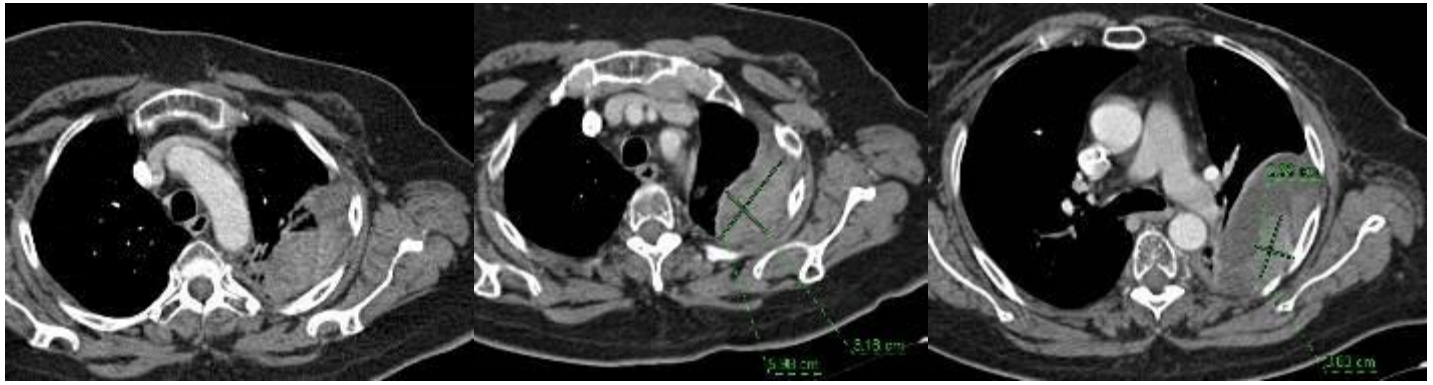


One patient with non-measurable target lesions and off study for PD not shown

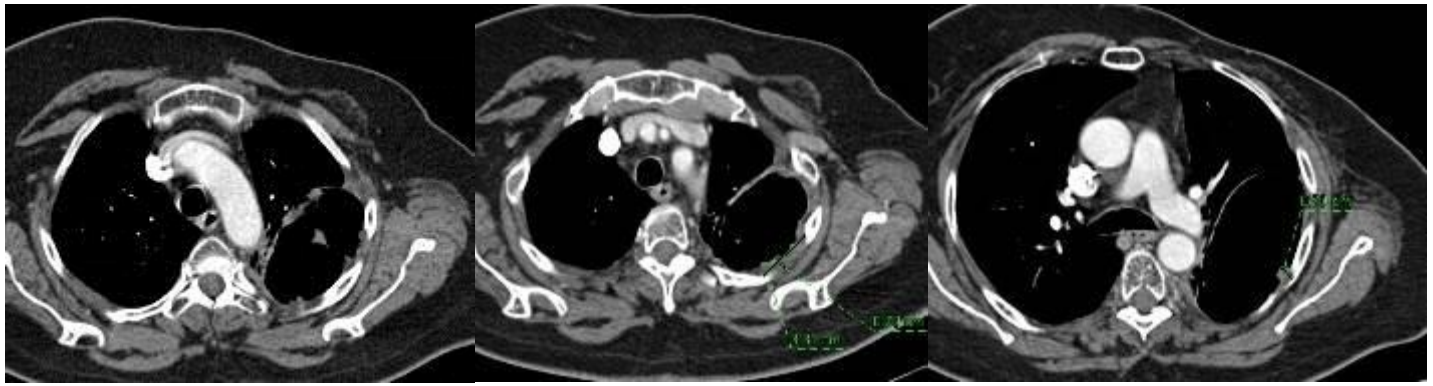
Dienstmann R, et al. *Ann Oncol*. 2012;23(Suppl 9): Abstract 2115.

Patient 18032 (VHIO)

Baseline
Sept. 20, 2011



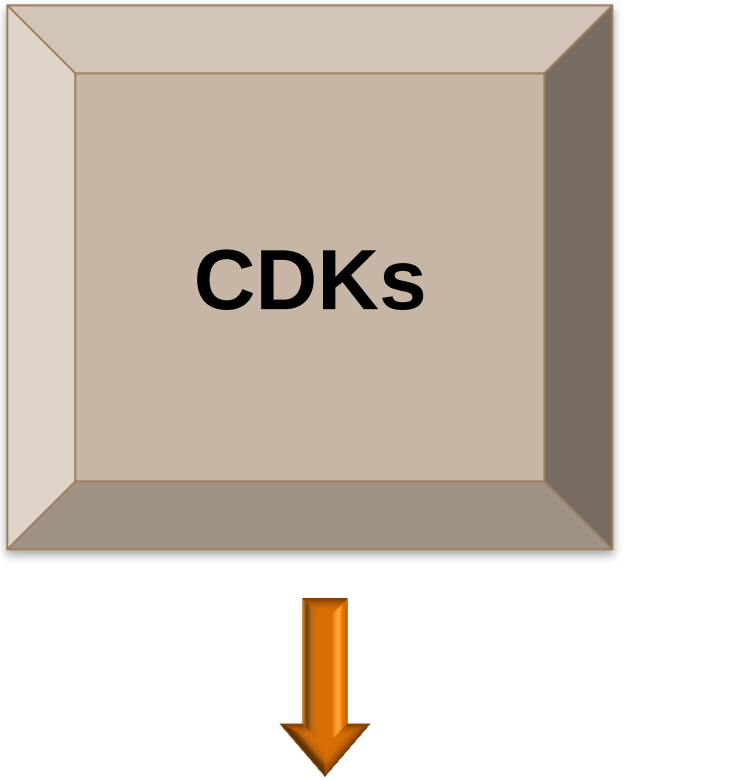
C3D1
Nov. 18, 2011



- **HR+/HER2-, *FGFR1* ampl (ratio 2.21) and CGH**
- Bone, lung and pleura metastases
- 14 prior treatment lines, including 5 Phase 1 trials
- E-3810 at 20 mg/day

Dienstmann R, et al. *Ann Oncol*. 2012;23(Suppl 9): Abstract 2115.

Cell Cycle



CDK, cyclin-dependent kinase

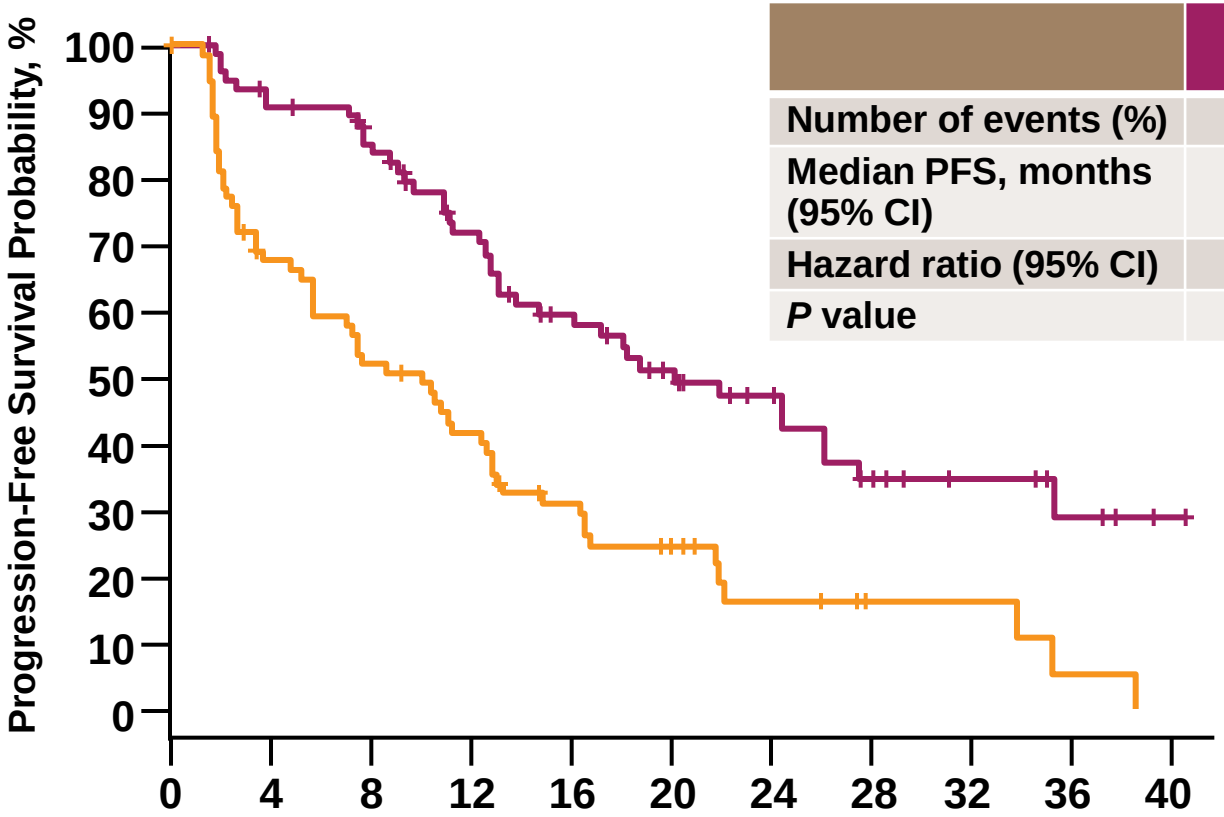
Summary of Ongoing Clinical Trials of CDK4/6 Inhibitors in ER+ ABC

Agent	Phase	Regimen	Patients (planned enrollment, N)
Palbociclib (PD0332991)	Phase III (PALOMA-2) (NCT01740427)	Palbociclib+LET vs LET+PBO	ER^+, $HER2^-$ ABC, no prior systemic therapy for ABC (450)
	Phase III (PALOMA-3) (NCT01942135)	Palbociclib+FUL vs FUL+PBO	ER^+, $HER2^-$ MBC or LABC after progression on endocrine therapy (417)
	Phase I/II (TRIO-18/PALOMA-1) (NCT00721409)	PD0332991+LET vs LET	Untreated ER^+, $HER2^-$ ABC, no prior therapy for ABC (177)
Ribociclib (LEE011)	Phase III (MONALEESA-2) (NCT01958021)	Ribociclib+LET vs LET+PBO	ER^+, $HER2^-$ ABC, no prior systemic therapy for ABC (500)
	Phase I/II (NCT01857193)	Ribociclib+EVE+EXE	ER^+, $HER2^-$ MBC or LABC resistant to LET or ANA (185)
	Phase I/II (NCT01872260)	Ribociclib+alpelisib+LET	ER^+ MBC or LABC (130)
Abemaciclib (LY2835219)	Phase III (MONARCH-2) NCT02107703	Abemaciclib+FUL vs FUL	ER^+, $HER2^-$ MBC (no prior endocrine therapy OR progression on prior AI/antiestrogen) (550)

Palbociclib is being evaluated as a breakthrough therapy by the FDA

National Institutes of Health, Available at: http:// clinicaltrials.gov. Accessed: December 6, 2014.

PALOMA-1/TRIO-18: Progression-Free Survival



	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	.0004	

Number of patients at risk

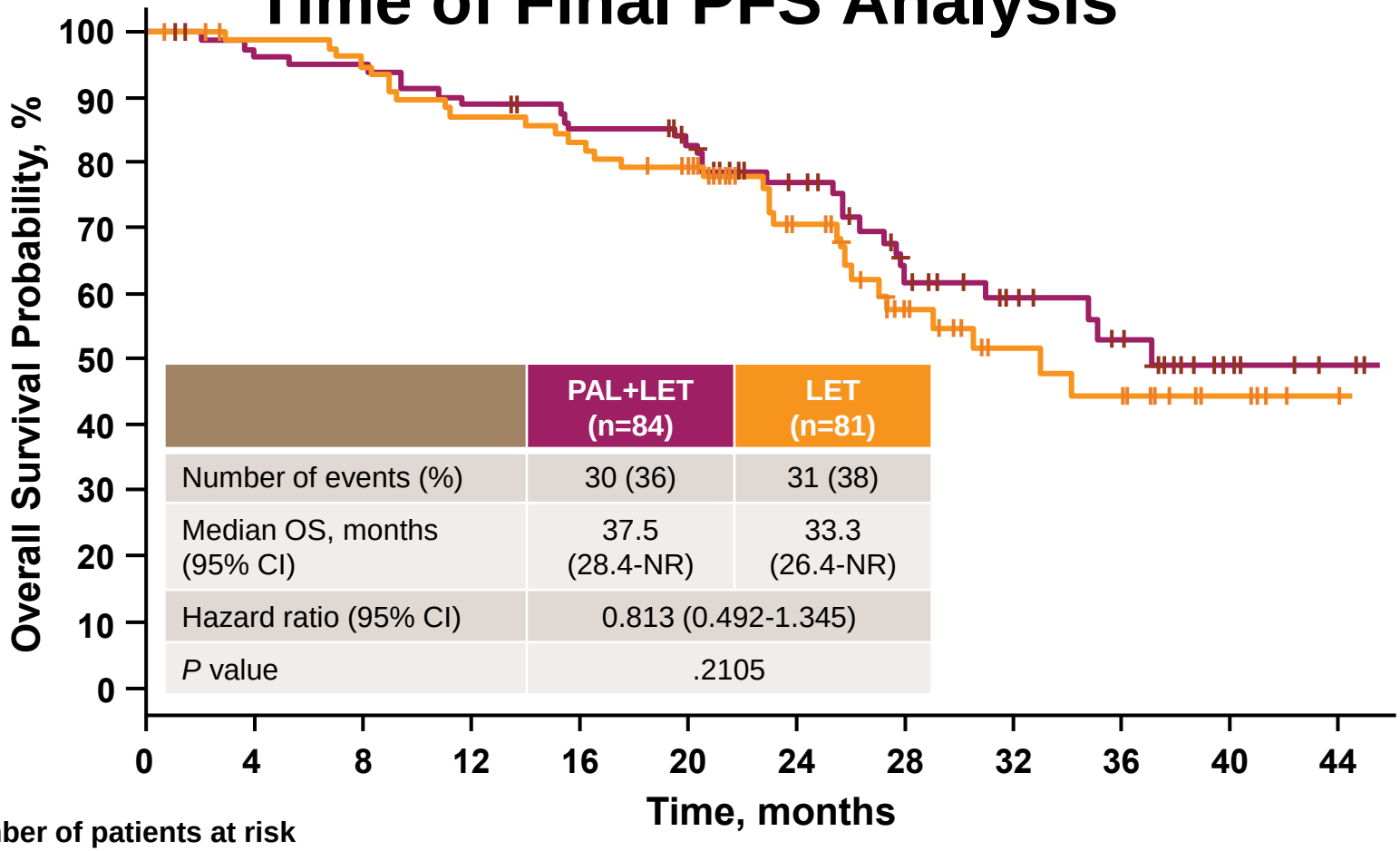
PAL + LET	84	67	60	47	36	28	21	13	8	5	1
LET	81	48	36	28	19	14	6	3	3	1	

PAL, palbociclib

Finn RS, et al. Presented at: American Association of Cancer Research Annual Meeting 2014; April 5-9, 2014; San Diego. Abstract #CT101.

PALOMA-1/TRIO-18: OS (Intent-to-Treat)

Positive Trend in Favor of Palbociclib Arm at Time of Final PFS Analysis



	PAL+LET (n=84)	LET (n=81)
Number of events (%)	30 (36)	31 (38)
Median OS, months (95% CI)	37.5 (28.4-NR)	33.3 (26.4-NR)
Hazard ratio (95% CI)	0.813 (0.492-1.345)	
P value	.2105	

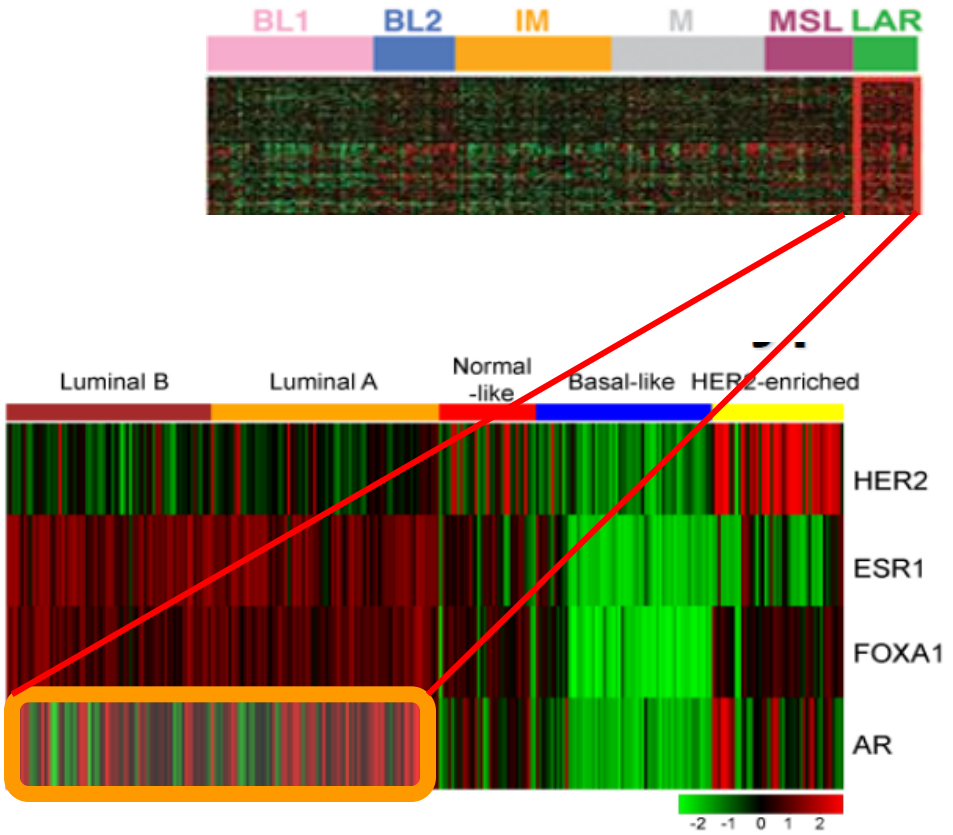
Number of patients at risk

PAL+LET	84	80	78	73	68	65	47	35	22	17	7	2
LET	81	76	74	67	64	59	37	23	14	12	5	1

Finn RS, et al. Presented at: American Association of Cancer Research Annual Meeting 2014; April 5-9, 2014; San Diego. Abstract #CT101.

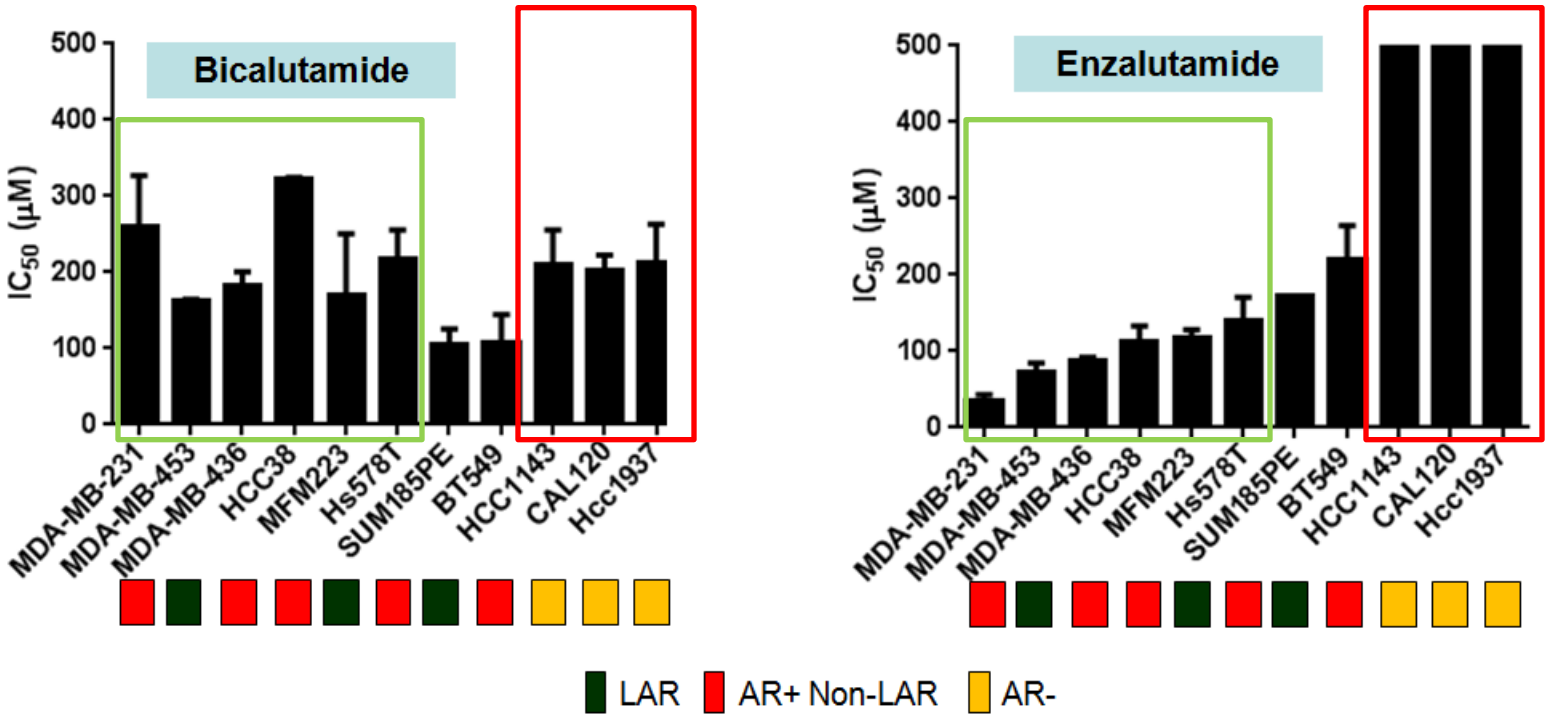
Luminal Androgen Receptor Subtype

- Triple negative breast cancer is comprised of 6 molecularly distinct subtypes
  - 10% are “Luminal AR” (LAR)
  - LAR express higher levels of AR mRNA vs other TNBC subtypes
  - LAR breast cancers are heavily enriched in hormonally-regulated pathways
  - Luminal AR is more closely related to hormone receptor positive breast cancer (Luminal A and B) than to other subtypes



B, basal like; IM, immunomodulatory; ML, mesenchymal like; MS, mesenchymal stem like

Luminal Androgen Receptor Subtype Sensitivity to Bicalutamide and Enzalutamide



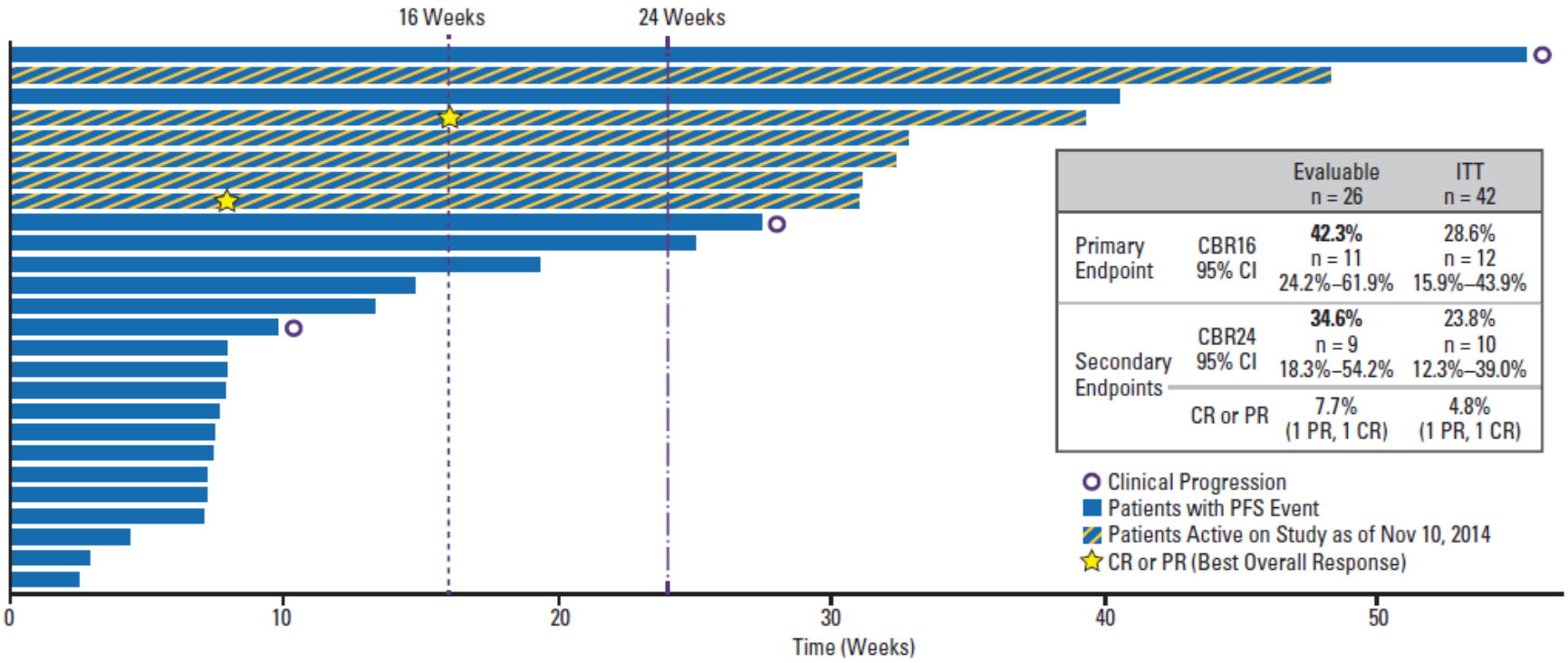
Denne L, et al. Presented at: 36th Annual San Antonio Breast Cancer Symposium; December 10-14, 2013; San Antonio, Texas. Abstract P2-09-05.

Phase II Trial of Bicalutamide in Androgen Receptor Positive, Estrogen Receptor Negative Metastatic Breast Cancer

Pts with clinical benefit on bicalutamide	AR%	ER%	PgR%	HER2	Site of Testing	Site of Mets	Prior Therapy LABC/ MBC	DOR on Prior Therapy (weeks)	DOR on bicalutamide (weeks)
1	10-20	1	0	Neg	1^{o}	LN	0	NA	231+
#2	>80	3	0	Neg	Met	GI	0	NA	54
#3	>80	0	0	-/+	1^{o}	Breast LN	1	NR	25
#4	>90	0	0	Neg	1^{o}	LN Bone	1	158	35
#5	>50	0	0	Neg	1^{o}	LN Bone	1	15	43+

Gucalp A, et al. *Clin Cancer Res.* 2013;19(19):5505-5512.

Stage I Phase II Trial of Enzalutamide in Androgen Receptor Positive, Triple Negative Metastatic Breast Cancer



		Evaluable n = 26	ITT n = 42
Primary Endpoint	CBR16 95% CI	**42.3%** n = 11 24.2%–61.9%	28.6% n = 12 15.9%–43.9%
Secondary Endpoints	CBR24 95% CI	**34.6%** n = 9 18.3%–54.2%	23.8% n = 10 12.3%–39.0%
	CR or PR	7.7% (1 PR, 1 CR)	4.8% (1 PR, 1 CR)

Traina T, et al. . Presented at: 2014 San Antonio Breast Cancer Symposium; December 9-13, 2014; San Antonio, Texas. Abstract P5-15-09.

Beyond Kinases: Other Targets in Clinical Development (1/2)

Target	Select agents	Stage of development in BC
Histone deacetylases	Vorinostat[1] MS-275 (entinostat)[2] PDX1011 (belinostat)[3] LBH789 (panobinostat)[4]	Phase II, metastatic/recurrent BC Phase II, HR+ BC Phase I, solid tumors Phase I, metastatic HER2+ BC
IAPs	GEM640 (AEG35156)[5] LCL161[6] HGS1029 (AEG40826)[7]	Phase I/II, mBC Phase I, solid tumors Phase I, solid tumors
Microtubules	Sagopilone (ZK-EPO)[8]	Phase II, mBC
HSP90	AUY922[9] Ganetespib (STA-9090)[10]	Phase II, solid tumors
PARP	AZD2281[11] Rucaparib[12, 13]	Phase II, TNBC Phase II, locally advanced or mBC; TNBC

IAP, inhibitor of apoptosis

National Institutes of Health. Available at: http:// clinicaltrials.gov. Accessed: December 6, 2014: 1. NCT01153672; 2. NCT01349959; 3. NCT00413075; 4. NCT00788931. 5. NCT00558545; 6. NCT01098838; 7. NCT00708006; 8. NCT00313248; 9. NCT00526045; 10. NCT00687934; 11. NCT00707707; 12. NCT00664781; 13. NCT01074970.

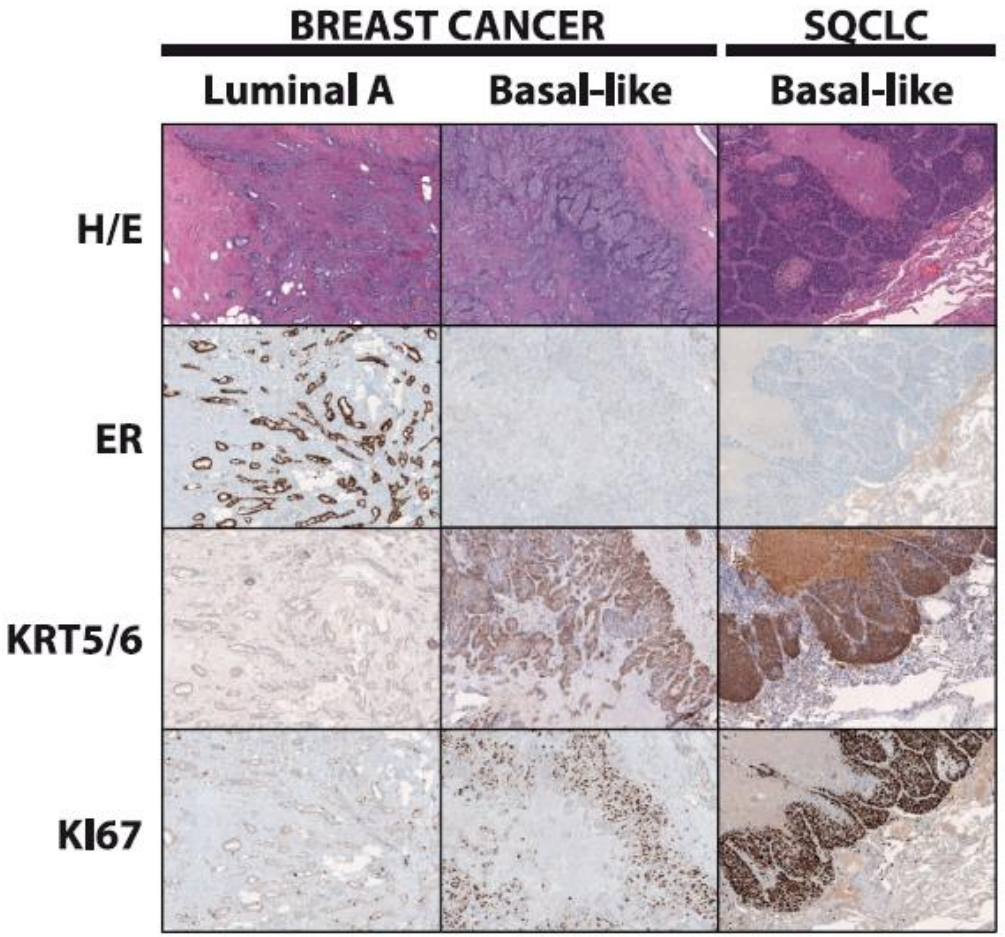
Beyond Kinases: Other Targets in Clinical Development (2/2)

Target	Select Agents	Stage of Development in BC
VEGF	Bevacizumab[1] Aflibercept[2] Ramucirumab[3]	EMA-approved (with paclitaxel) in mBC Phase II, mBC Phase III, BC
IGF1R	Ganitumumab[4]; OSI-906[5]; MEDI-573[6] BMS-754807[7]; Cixutumumab[8,9]; Dalotuzumab[10]	Phase II, HR+ ABC Phase II, HR+ ABC Phase II, HER2+ ABC
cMET	ARQ 197[11]	Phase II, TNBC
AKT	MK 2206[12]	Phase II, ABC with PIK3CA mutation and/or PTEN loss; Phase I HER2+ ABC
AP	LCL161[13]	Phase II, TNBC
Porcupine enzyme	LGK974[14]	Phase I, solid tumors dependent on WNT ligands

1. EMA 2010. From:http://www.ema.europa.eu/ema. Accessed December 2014. National Institutes of Health, Available at: http:// clinicaltrials.gov. Accessed: December 6, 2014: 2. NCT00369655; 3. NCT00703326; 4. NCT00626106; 5. NCT01205685; 6. NCT01446159; 7. NCT01225172; 8. NCT00728949; 9. NCT00684983; 10. NCT01234857; 11. NCT01542996; 12. NCT01277757; 13. NCT01617668; 14. NCT01351103.

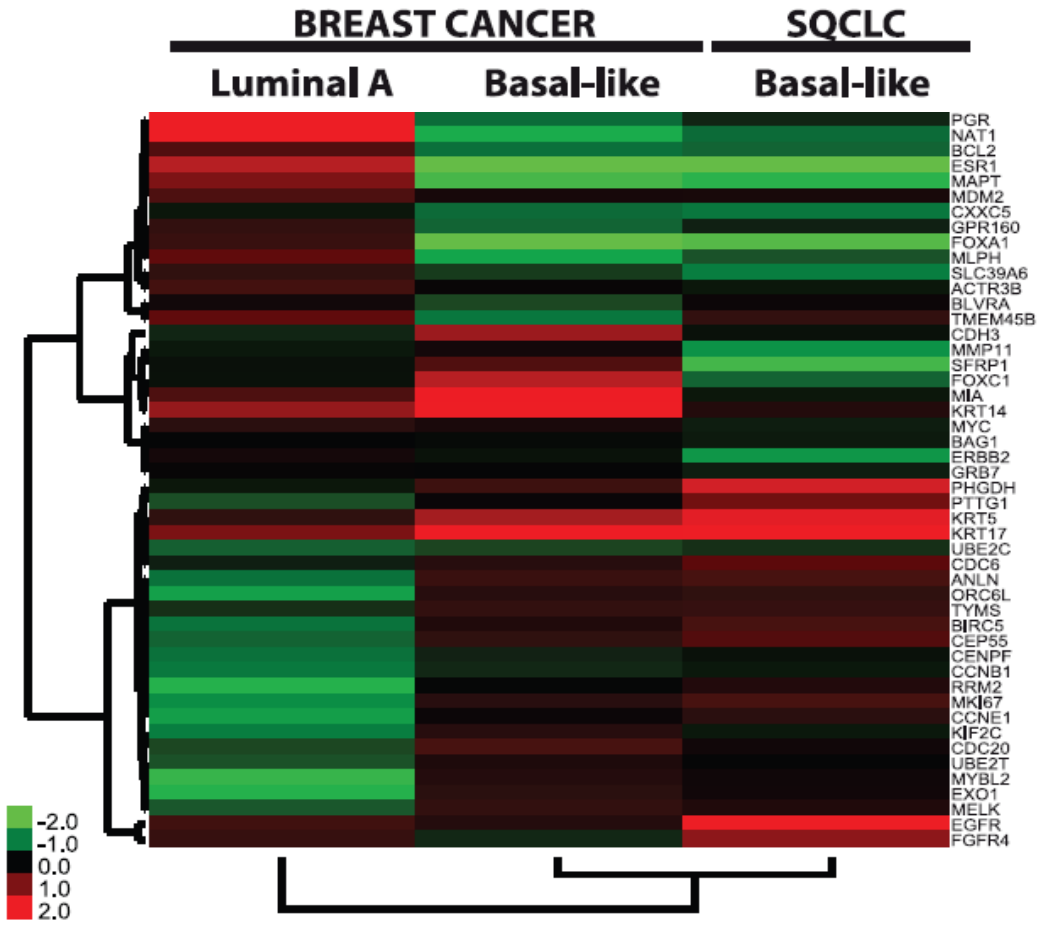
The Future…
Reality or Fiction?

IHQ and Gene Expression of a Basal Like Breast Cancer, a SQCLC With a Basal Like Profile and a Luminal A Breast Cancer



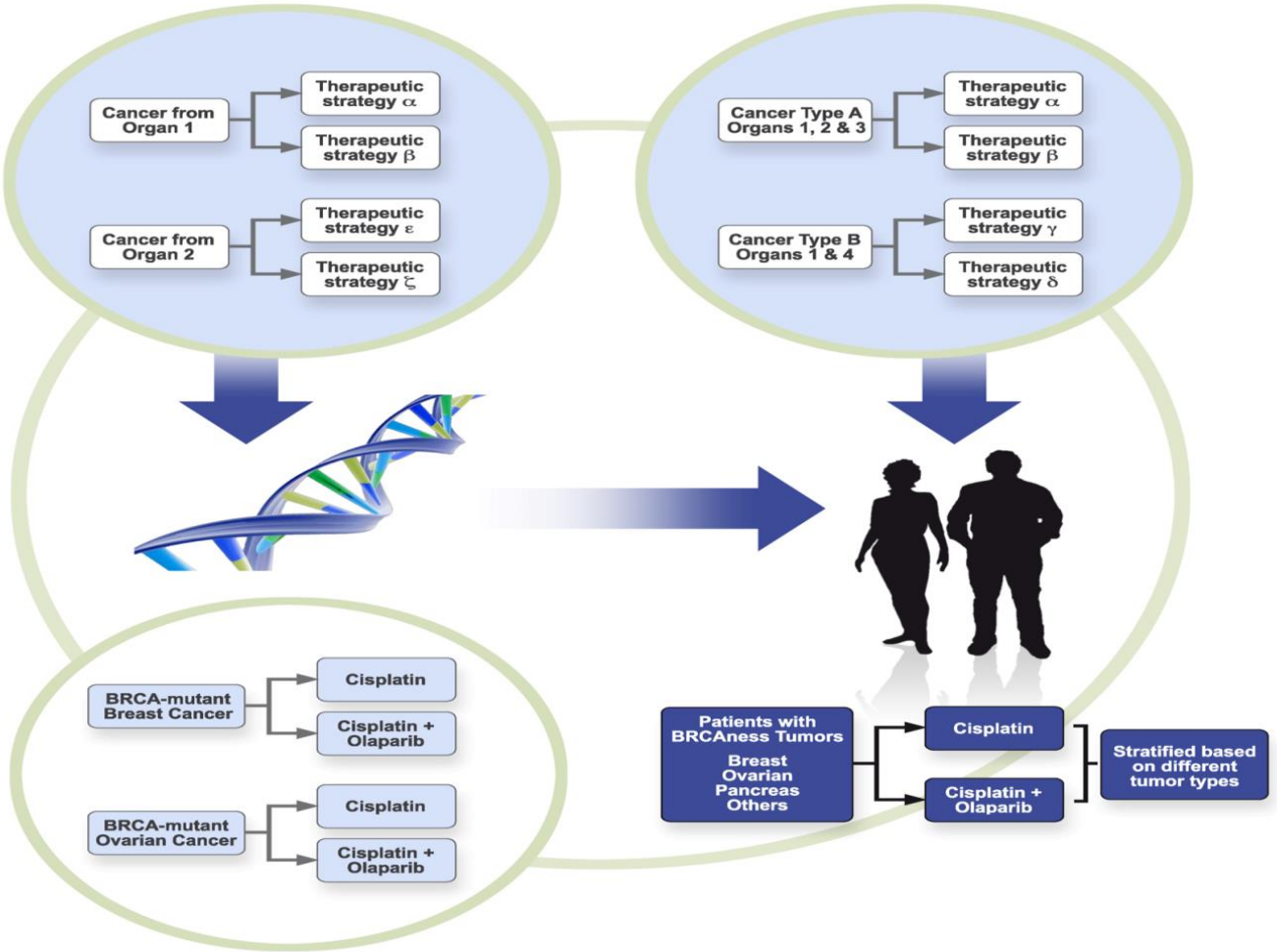
Prat A, et al. *Sci Rep*. 2013;3:3544.

IHQ and Gene Expression of a Basal Like Breast Cancer, a SQCLC With a Basal Like Profile and a Luminal A Breast Cancer



Prat A, et al. *Sci Rep*. 2013;3:3544.

Conclusion



Cortés J, et al. *CA Cancer J Clin*. 2014;64(1):70-74.

Striking Success:

The Emergence of New Targeted Treatment Strategies for Advanced Breast Cancer