"New targets for new kind of tumors"

Francesco Pantano, MD PhD
Medical Oncology Department
Campus Bio-Medico University of Rome

Breast Cancer Molecular Taxonomy

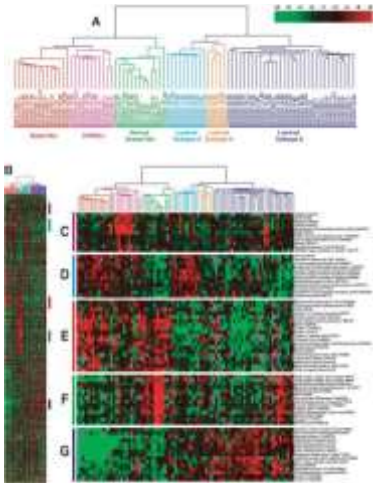
nature
International journal of science

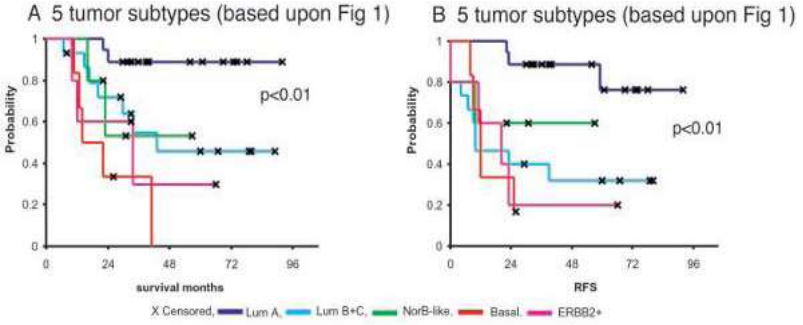
Letter | Published: 17 August 2000

Molecular portraits of human breast tumours

Charles M. Perou, Therese Sørlie, Michael B. Eisen, Matt van de Rijn, Stefanie S. Jeffrey, Christian A. Rees, Jonathan R. Pollack, Douglas T. Ross, Hilde Johnsen, Lars A. Akslen, Øystein Fluge, Alexander Pergamenschikov, Cheryl Williams, Shirley X. Zhu, Per E. Lønning, Anne-Lise Børresen-Dale, Patrick O. Brown & David Botstein

Nature **406**, 747–752 (17 August 2000) | Download Citation





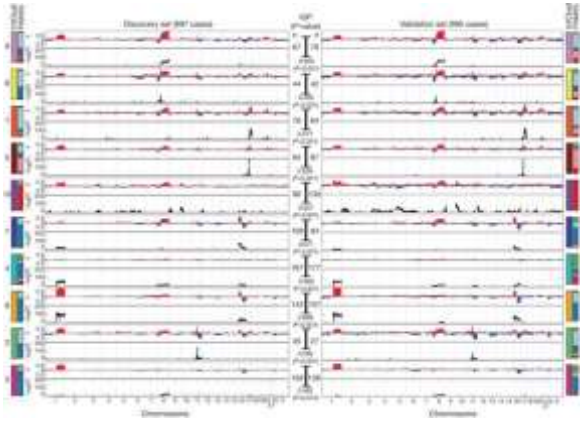
nature
International journal of science

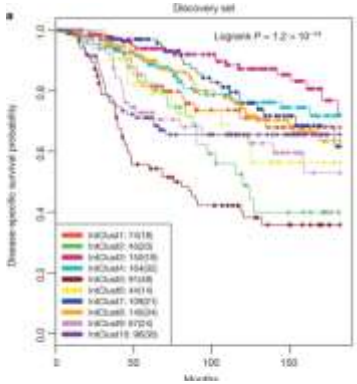
Article | Published: 18 April 2012

The genomic and transcriptomic architecture of 2,000 breast tumours reveals novel subgroups

Christina Curtis, Sohrab P. Shah [...] Samuel Aparicio

Nature **486**, 346–352 (21 June 2012) | Download Citation





Breast Cancer Molecular Taxonomy

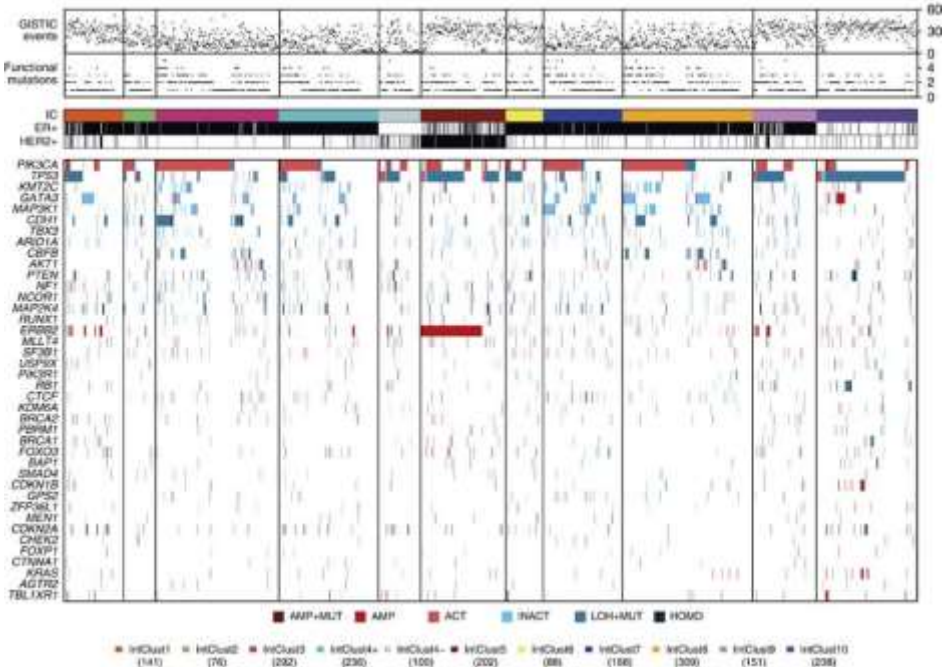
nature COMMUNICATIONS

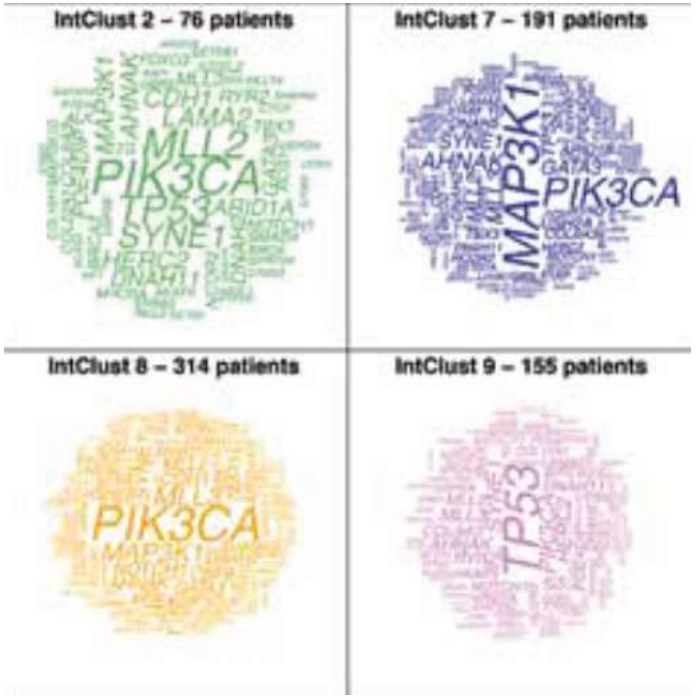
Article | OPEN | Published: 10 May 2016

The somatic mutation profiles of 2,433 breast cancers refine their genomic and transcriptomic landscapes

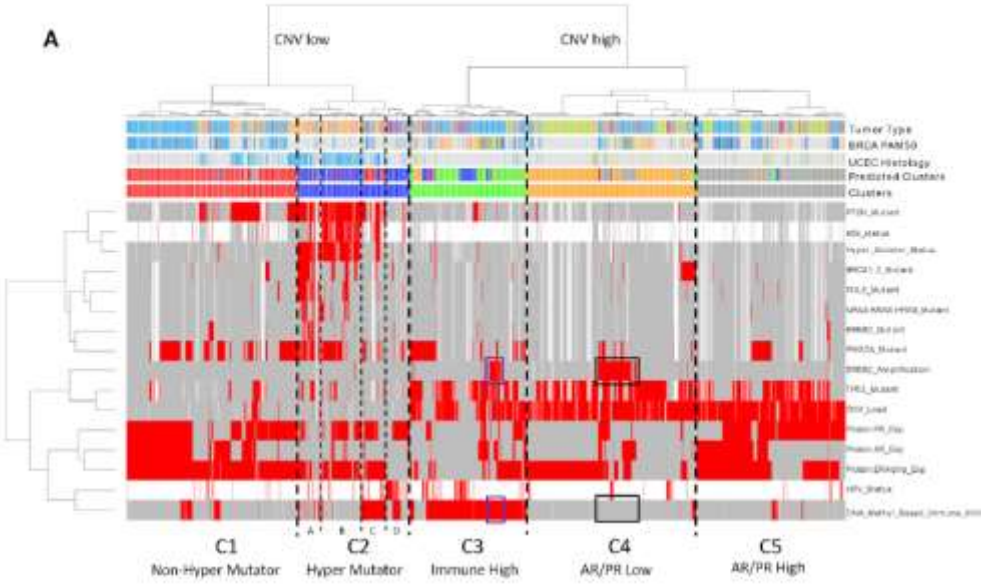
Bernard Pereira, Suet-Feung Chin [...] Carlos Caldas

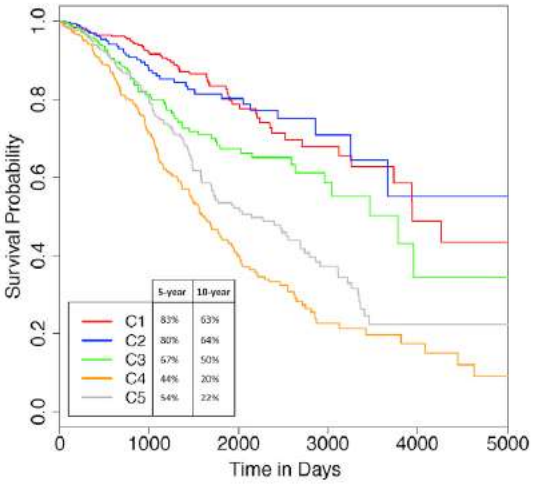
Nature Communications **7**, Article number: 11479 (2016) | Download Citation



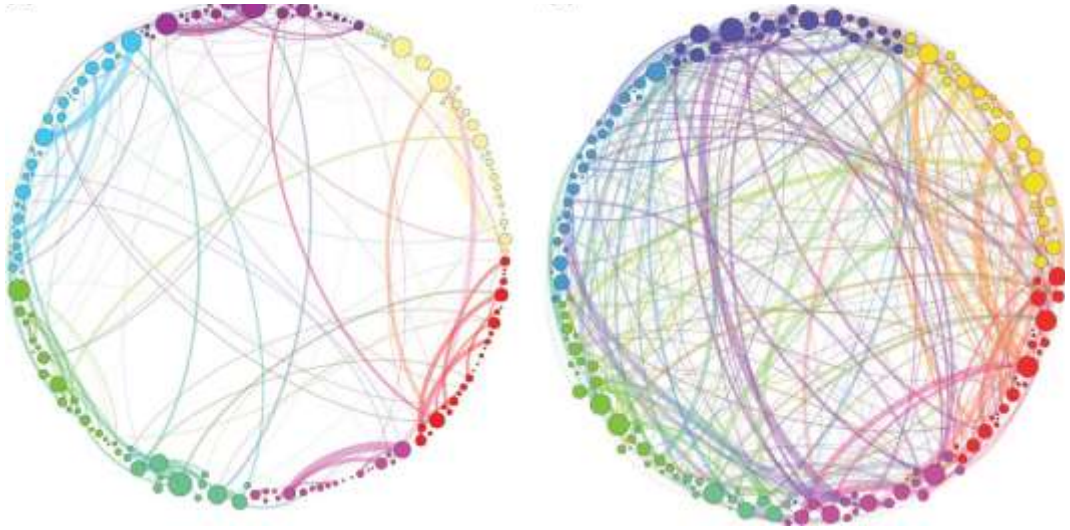


Breast Cancer Molecular Taxonomy





Breast Cancer Molecular Taxonomy..... Problem

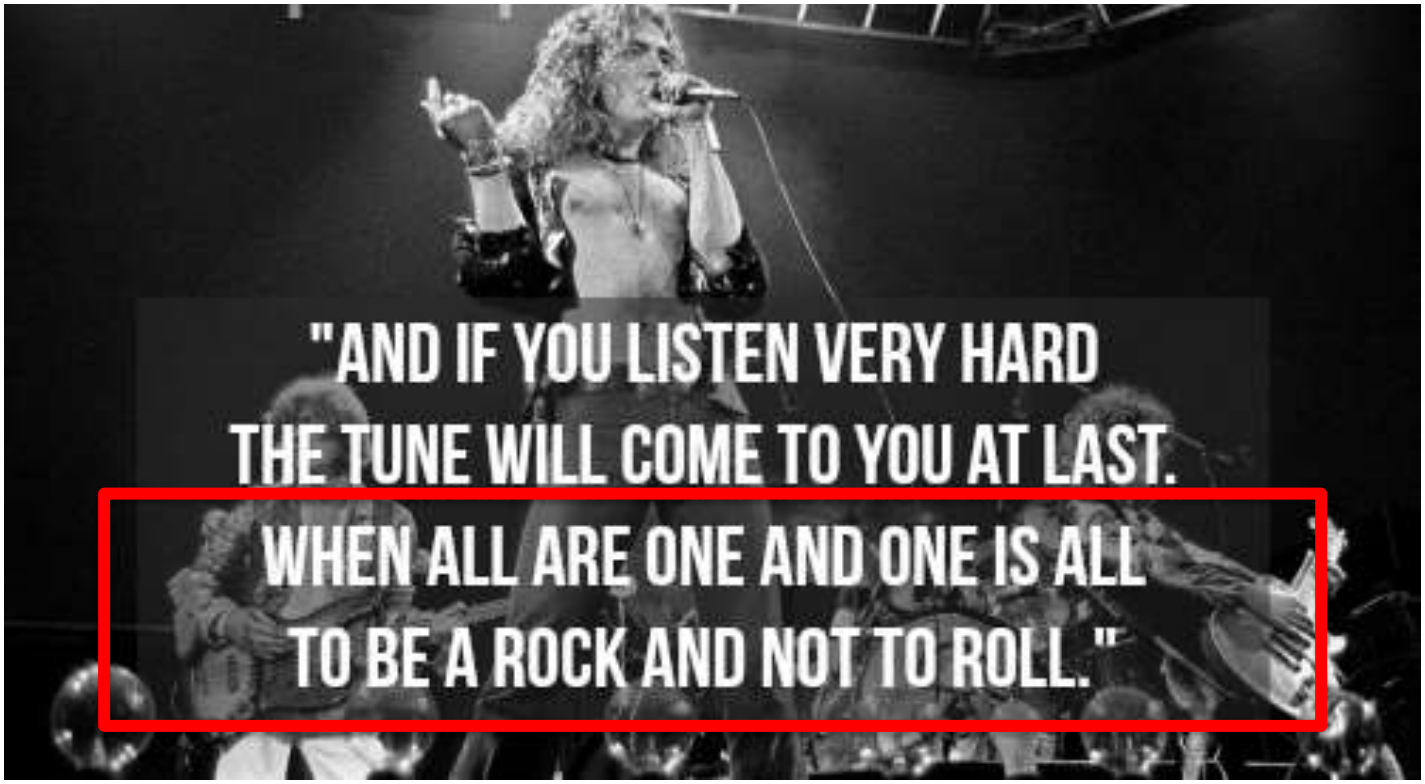


Single tumor may belong to different biological classifications
Different biological discriminants may be present within the same tumor

Breast cancer Molecular taxonomy..... Problem

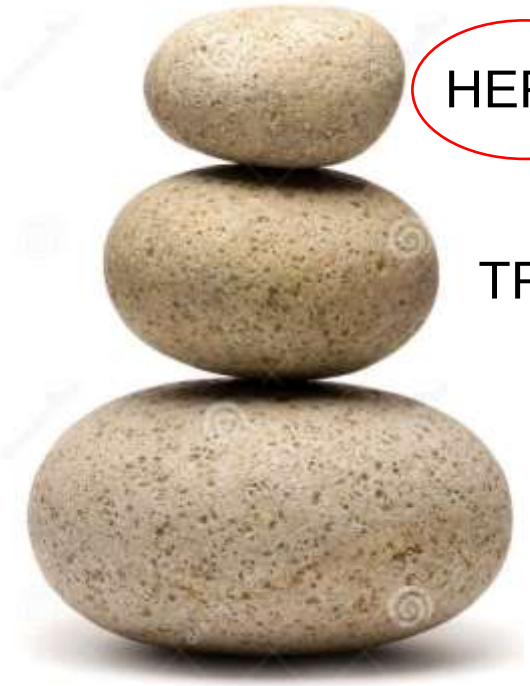
M.C. Escher, Relativity, 1953

Breast cancer Molecular taxonomy..... Problem



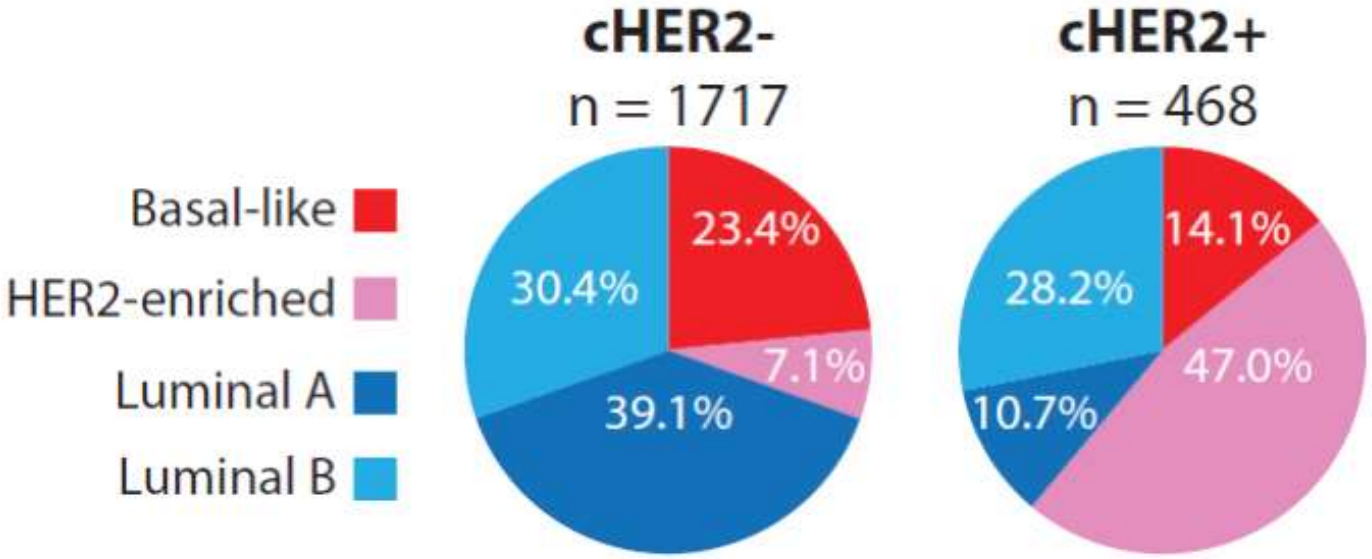
Led Zeppelin, Stairway To Heaven, 1971

Attempting to simplify the complexity



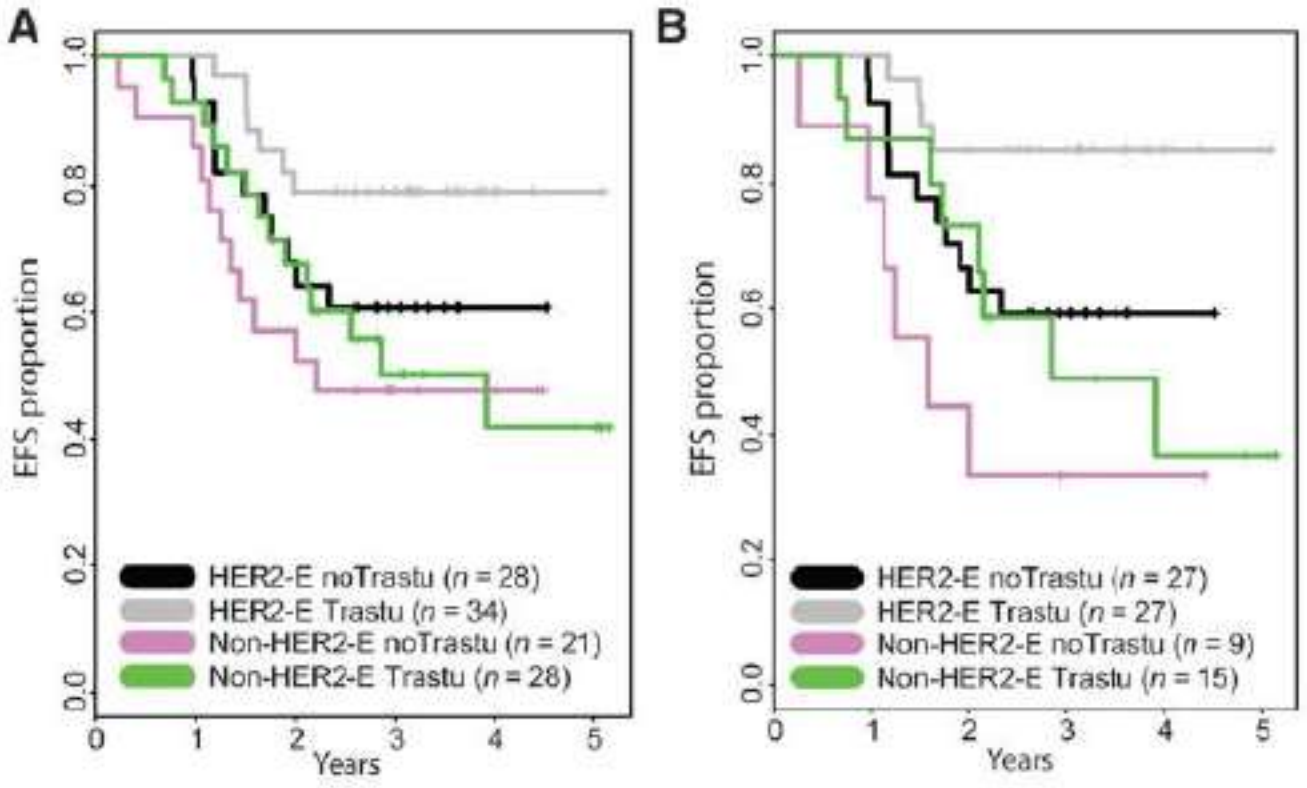
Heterogeneity of HER2+ tumors

- Heterogeneity within HER2 positive disease, largely driven by ER status
- Clinically HER2 + and – tumours within each intrinsic subtype differ only in expression of genes in or near the HER2 amplicon on 17q
- Highest levels of HER2 pathway activation in cHER2+ HER2 enriched tumours



Prat et al., JNCI 2014;106(8)

Heterogeneity of HER2+ tumors



Prat et al., Clini Cancer Res 2014;120(2):511-21

- Retrospective analysis of NOAH study looking at PAM50 subtypes

  Only 55% of HER2+ tumours HER2-E subtype; 21% luminal, 7% basal-like, 18% normal-like

  Better pCR rates in HER2-E vs luminal HER2+ tumours (53% v 29%) with larger improvement in EFS with addition of Trastuzumab

Heterogeneity of HER2+ tumors

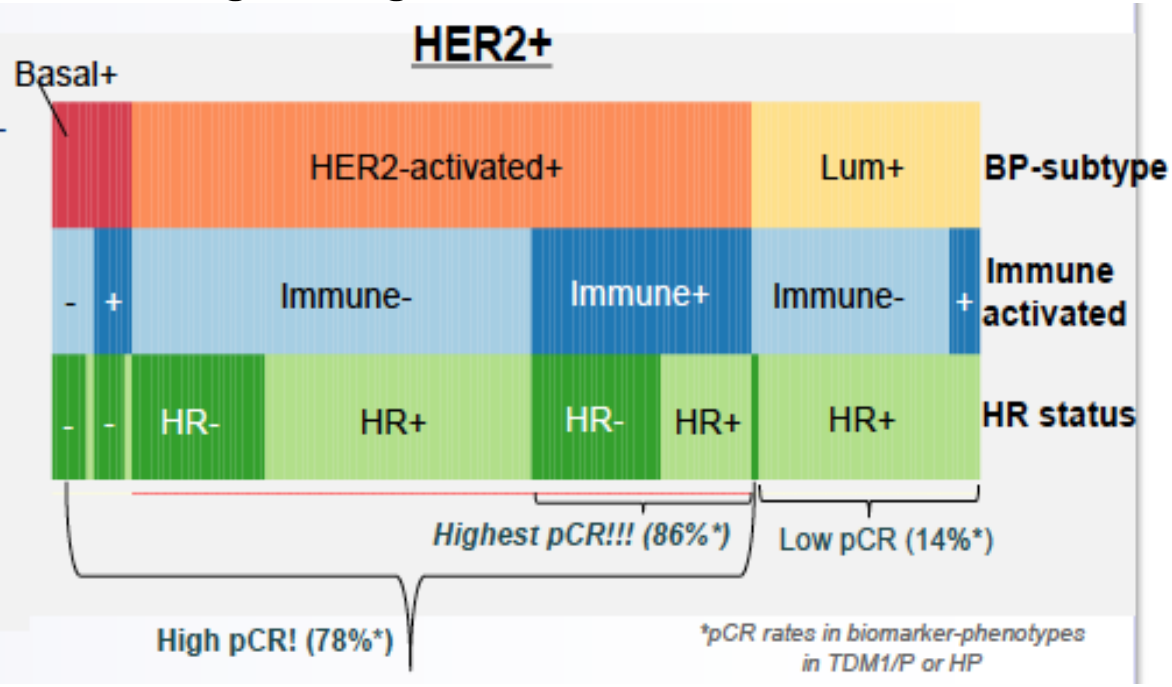
Identifying breast cancer molecular phenotypes to predict response in a modern treatment landscape: lessons from ~1000 patients across 10 arms of the I-SPY 2 TRIAL

Denise M Wolf[1*], Christina Yau[1*], Julia Wulfkhule[2], Chip Petricoin[2], Lamorna Brown-Swigart[1], Smita Asare[3], Gillian Hirst[1], Zelos Zhu[1], Evelyn Pei Rong Lee[1], Amy Delson[1], I-SPY 2 Investigators[3], Nola Hylton[1], Minetta Liu[4], Paula Pohlmann[5], Fraser Symmans[6], Angela DeMichele[7], Doug Yee[8], Don Berry[9], Laura Esserman[1], Laura van 't Veer[1]

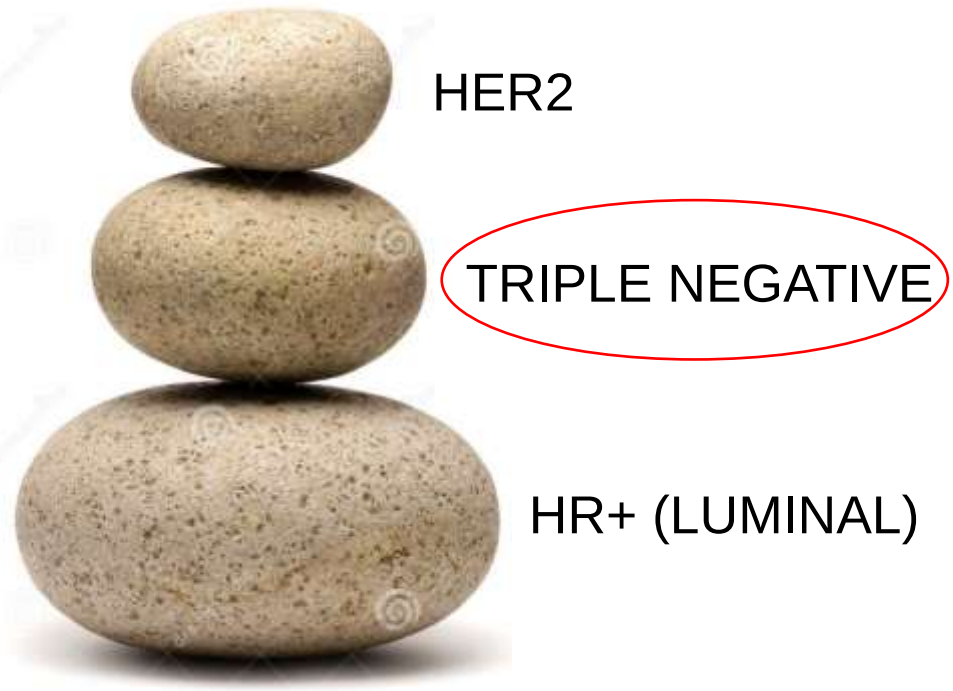
[1]University of California San Francisco, [2]George Mason University, [3]Quantum Leap Healthcare Collaborative, [4]Mayo Clinic, Rochester, [5]Georgetown University, [6]University of Texas, MD Anderson, [7]University of Pennsylvania, [8]University of Minnesota, [9]Berry Consultants, LLC, [*]Equal contribution

Biomarker phenotypes predict differential response to HER2-targeted agents

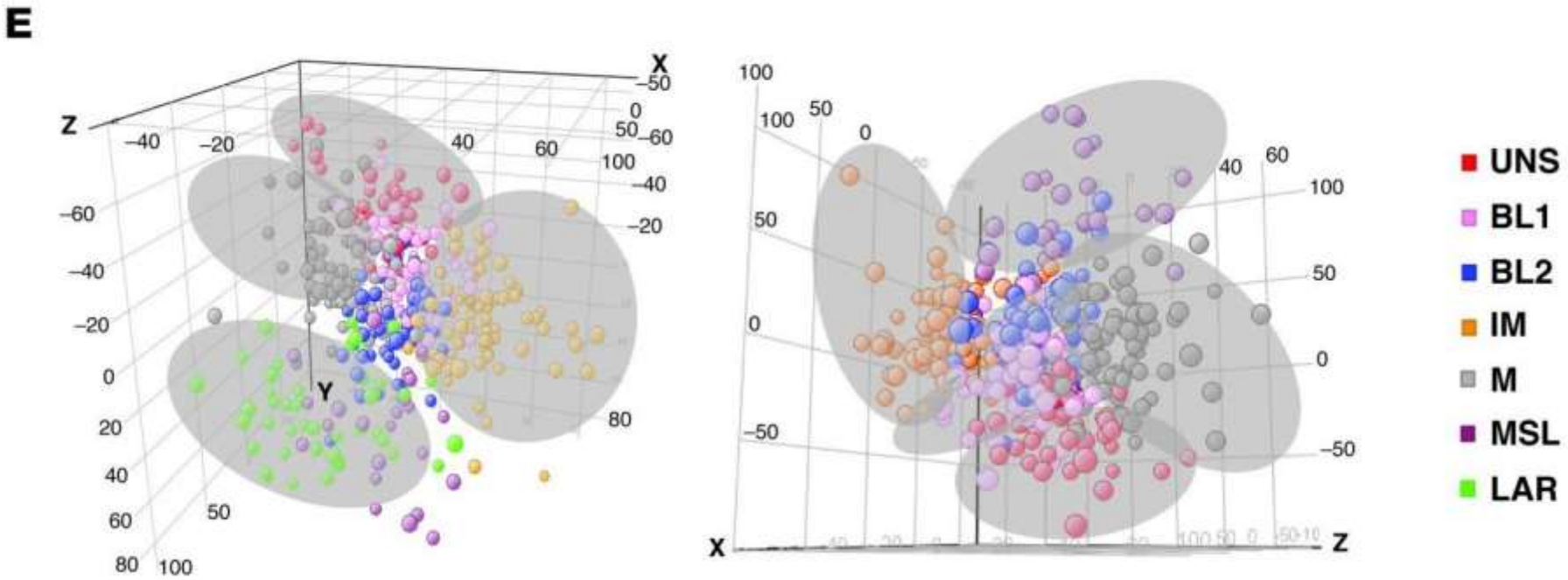
- For the HER2+ subset, 67% are HER2-activated+, and 25% Lum+
- HER2-activated+ patients are more likely to be Immune+ (44%), vs 23% in lum+.
- HER2-activated+/Immune+ patients have higher predicted sensitivity to HER2-targeted agents than lum+ or Immune- patients.



Attempting to simplify the complexity



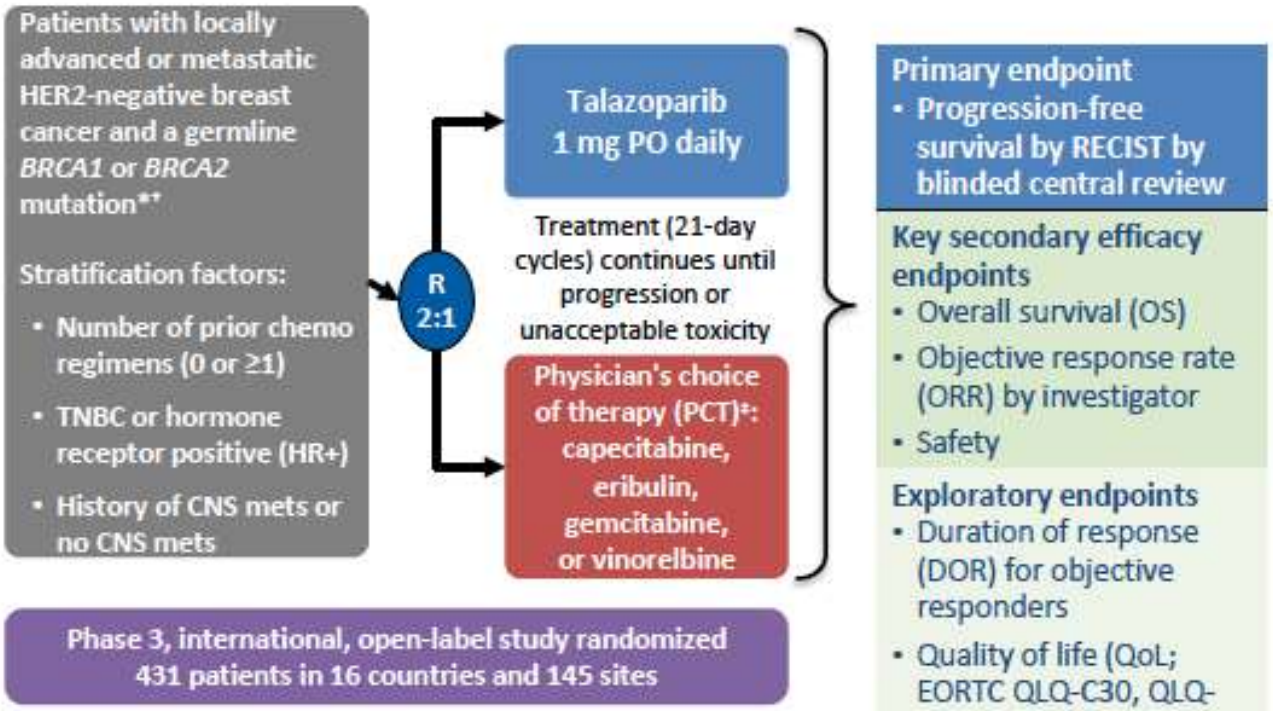
Heterogeneity of triple negative tumors



Subtype	Gene expression profile	Clinical
Basal-like 1	high Ki-67; DNA damage response GF pathways	BRCA-associated Higher pCR
Basal-like 2 Immunomodulatory	Immune genes	
Mesenchymal	Cell motility	Lower DDFS
Mesenchymal stem-like	Cell motility; claudin-low	
Luminal androgen receptor	Steroid pathways	Apocrine features, higher LRF;

Lehman BD, et al. J Clin Invest 2011; 121:2750-67

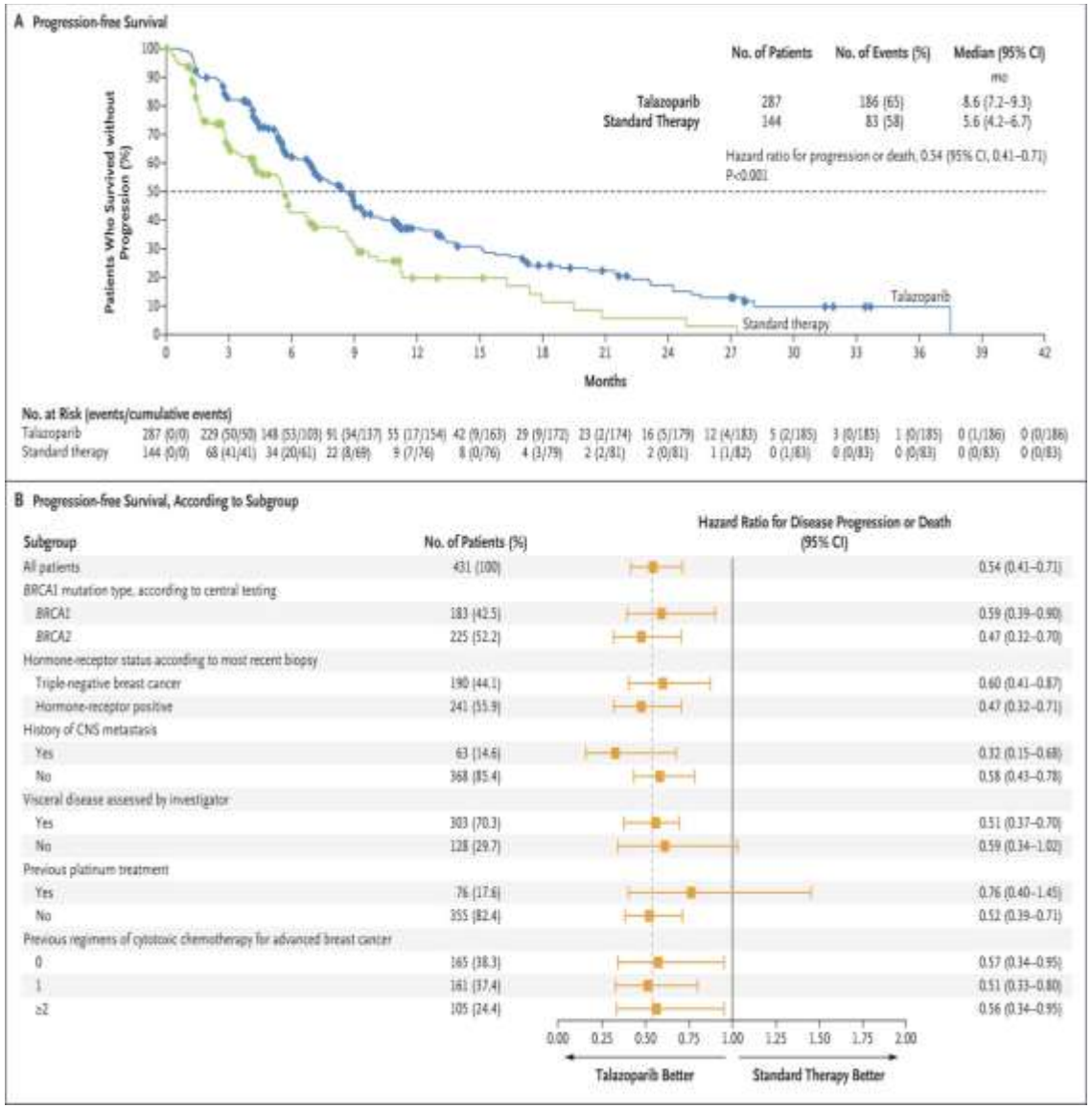
EMBRACA: Study Design



*Additional inclusion criteria included: no more than 3 prior cytotoxic chemotherapy regimens for locally advanced or metastatic disease;
prior treatment with a taxane and/or anthracycline unless medically contraindicated.
†HER2-positive disease is excluded.
‡Physician's choice of therapy must be determined prior to randomization.
CNS=central nervous system; EORTC=European Organisation for Research and Treatment of Cancer; HER2=human epidermal growth factor receptor 2; mets=metastases; PO= by mouth; QLQ-BR23=Quality of Life Questionnaire breast cancer module; QLQ-C30=Quality of Life Questionnaire Core 30; R=randomized; RECIST=Response Evaluation Criteria In Solid Tumors version 1.1;
TNBC=triple-negative breast cancer.

Litton J, et al. N Engl J Med 2018; 379:753-763.

Progression free survival



Litton J, et al. N Engl J Med 2018; 379:753-763.

Response rate

Table 2. Secondary and Exploratory Efficacy End Points.

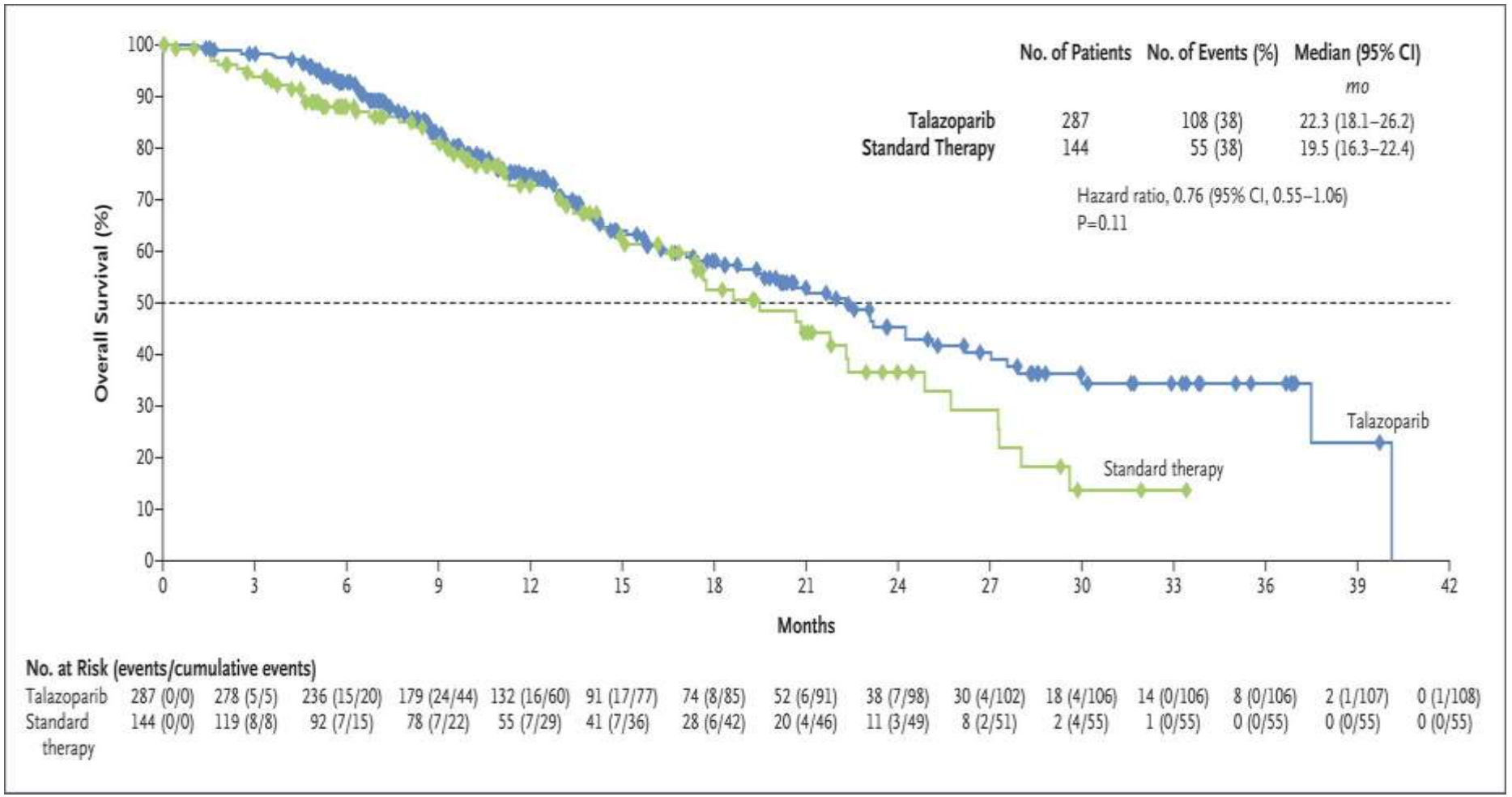
Variable	Talazoparib Group (N=219)	Standard-Therapy Group (N=114)	Odds Ratio (95% CI)	P Value*
	number (percent)			
Best overall response among patients with measurable disease — no. (%)†				
Complete response	12 (5.5)	0	—	—
Partial response	125 (57.1)	31 (27.2)	—	—
Stable disease	46 (21.0)	36 (31.6)	—	—
Could not be evaluated	4 (1.8)	19 (16.7)	—	—
Investigator-assessed overall objective response among patients with measurable disease — % of patients (95% CI)†	62.6 (55.8–69.0)	27.2 (19.3–36.3)	5.0 (2.9–8.8)	<0.001
Clinical benefit rate at 24 wk in intention-to-treat population				
Patients with clinical benefit — no./total no.	197/287	52/144	—	—
Percent of patients (95% CI)	68.6 (62.9–74.0)	36.1 (28.3–44.5)	4.3 (2.7–6.8)	<0.001
Investigator-assessed response in subgroup of patients with objective response				
No. with response	137	31	—	—
Median duration of response — mo	5.4	3.1	—	—
Interquartile range	2.8–11.2	2.4–6.7	—	—

* The P value was calculated with the use of the stratified Cochran–Mantel–Haenszel method. Stratification factors were the number of previous cytotoxic chemotherapy regimens, triple-negative status, and history of central nervous system metastases.

† According to Response Evaluation Criteria in Solid Tumors, version 1.1, confirmation of complete response or partial response was not required.

Litton J, et al. N Engl J Med 2018; 379:753-763.

Overall survival



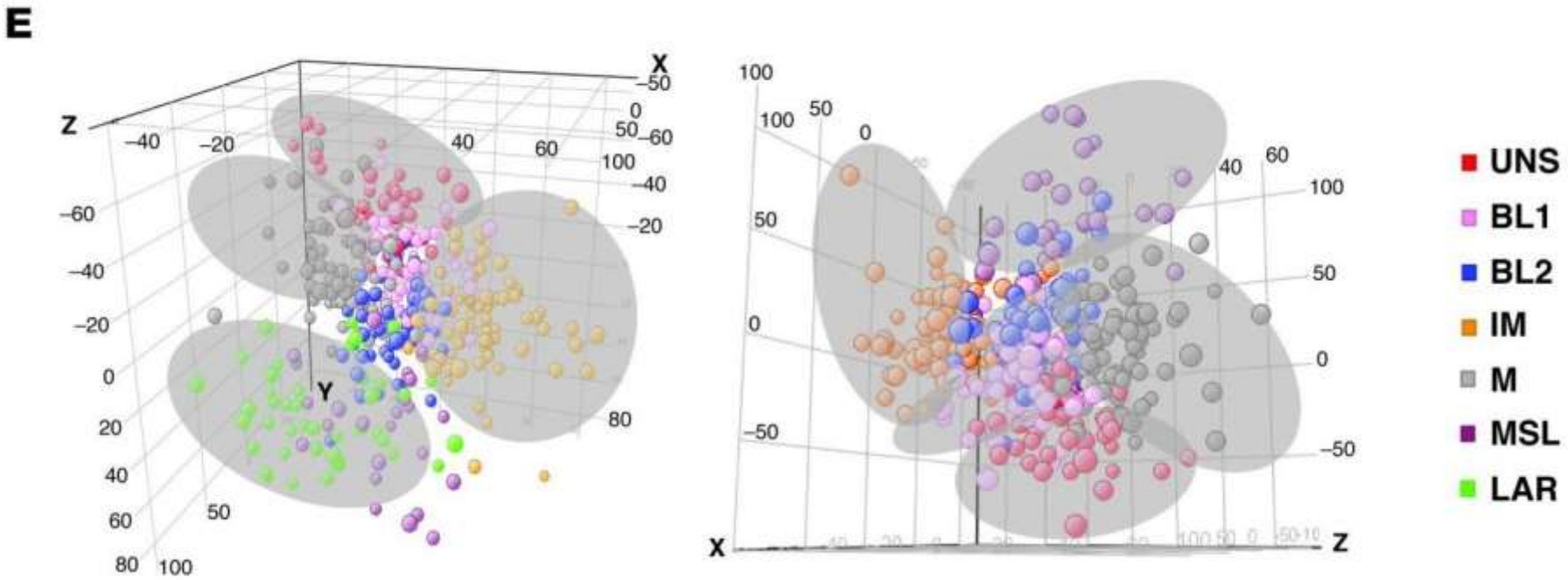
Litton J, et al. N Engl J Med 2018; 379:753-763.

Summary of efficacy data

- Talazoparib resulted in prolonged progression-free survival vs physician's choice of therapy by blinded central review HR: 0.54 (95% CI: 0.41, 0.71); P<0.0001
- Overall survival is immature (51% of projected events); HR: 0.76 (95% CI: 0.54, 1.06); P=0.105
- Global Health Status/Quality of Life showed overall improvement from baseline
- Talazoparib was generally well tolerated, with minimal nonhematologic toxicity and few adverse events resulting in treatment discontinuation

Litton J, et al. N Engl J Med 2018; 379:753-763.

Heterogeneity of triple negative tumors



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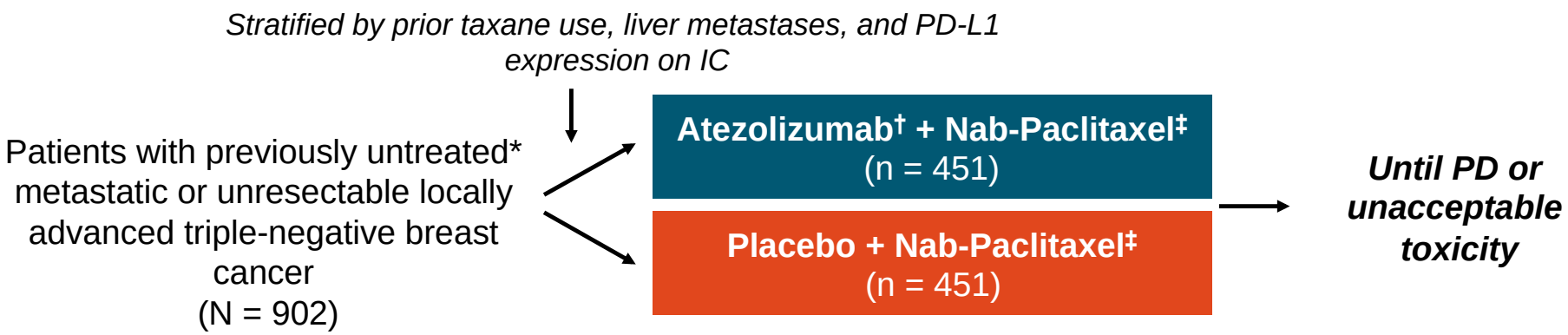
Lehman BD, et al. J Clin Incest 2011; 121:2750-67

IMpassion130

Biomarker Analysis in TNBC Patients Receiving Frontline Atezolizumab + Nab-Paclitaxel

- International, randomized, double-blind phase III study[1,2]



*Prior chemo in curative setting permitted if tx-free for ≥ 12 mos. †840 mg IV Q2W. ‡100 mg/m^2 IV on D1, 8, and 15 of 28-day cycle.

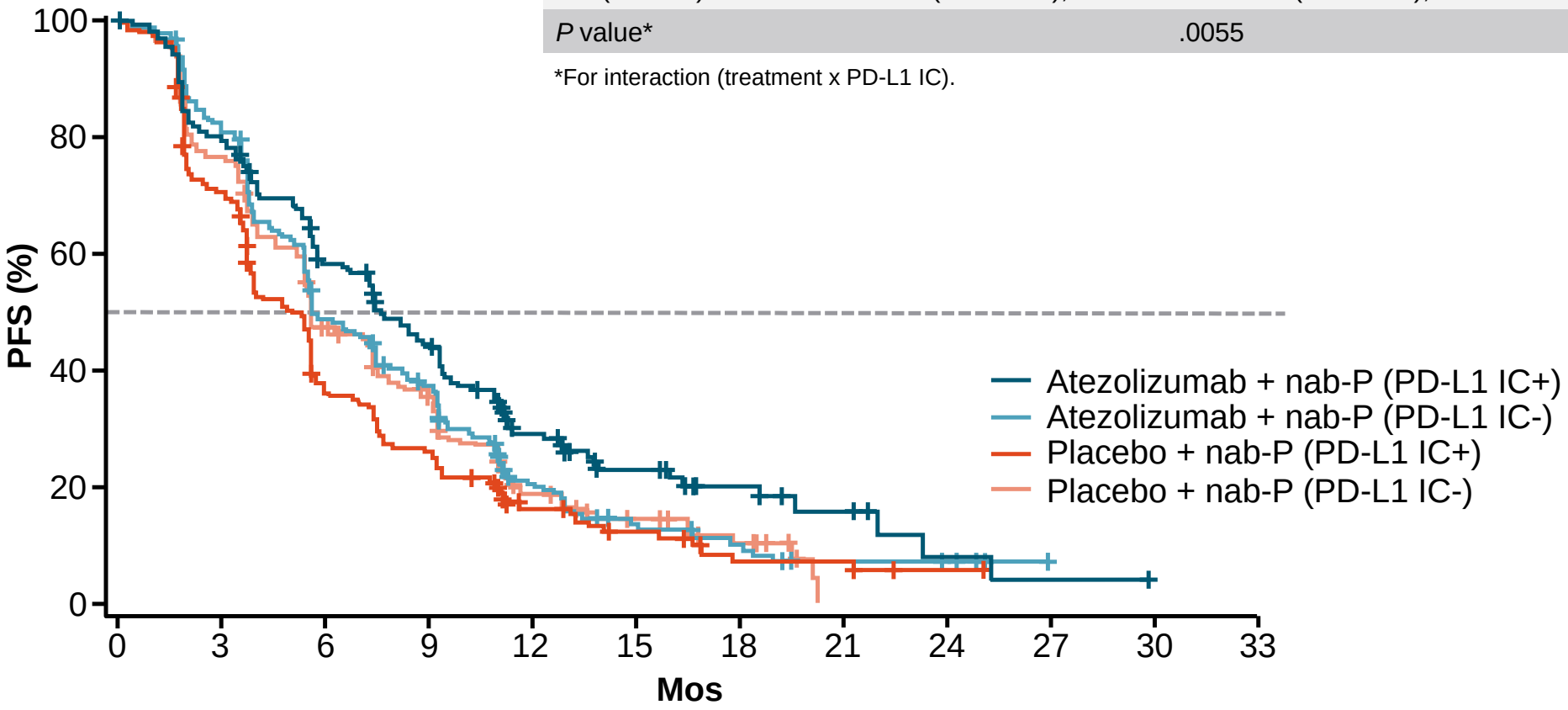
- Coprimary endpoints: PFS, OS in ITT population and PD-L1+ subgroup (≥ 1% on tumor infiltrating IC)[1]
- Exploratory analysis: efficacy by PD-L1 expression on TC, intratumoral CD8+ T-cells, sTILs, *BRCA1/2* status[2]

1.Schmid. NEJM. 2018;379:2108. 2. Emens. SABCS 2018. Abstr GS1-04.

IMpassion130: PFS by PD-L1 expression

PFS	PD-L1 IC Positive		PD-L1 IC Negative	
	Atezo + Nab-P (n = 185)	PBO + Nab-P (n = 184)	Atezo + Nab-P (n = 266)	PBO + Nab-P (n = 267)
Median, mos (95% CI)	7.5 (6.7-9.2)	5.0 (3.8-5.6)	5.6 (5.5-7.3)	5.6 (5.4-7.2)
HR (95% CI)	0.62 (0.49-0.78); *P* < .0001		0.94 (0.78-1.13); *P* = .5152	
P value*	.0055			

*For interaction (treatment x PD-L1 IC).

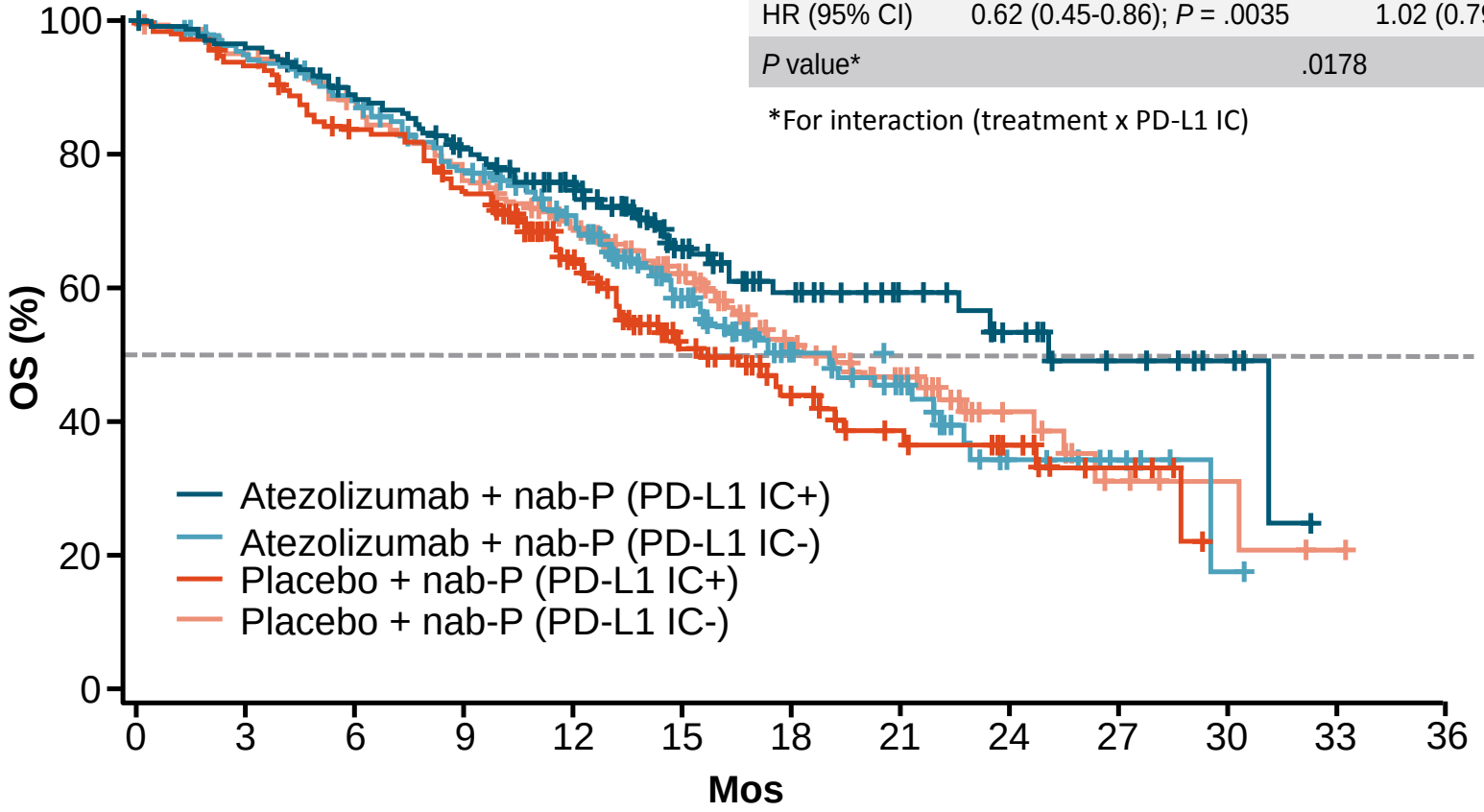


Emens. SABCS 2018. Abstr GS1-04. Reproduced with permission.

IMpassion130: OS by PD-L1 expression

OS	PD-L1 IC Positive		PD-L1 IC Negative	
	Atezo + Nab-P (n = 185)	PBO + Nab-P (n = 184)	Atezo + Nab-P (n = 266)	PBO + Nab-P (n = 267)
Median, mos (95% CI)	25.0 (22.6-NE)	15.5 (13.1-19.3)	18.9 (15.5-22.0)	18.4 (16.4-24.7)
HR (95% CI)	0.62 (0.45-0.86); *P* = .0035		1.02 (0.79-1.31); *P* = .9068	
P value*	.0178			

*For interaction (treatment x PD-L1 IC)



Emens. SABCS 2018. Abstr GS1-04. Reproduced with permission.

IMpassion130: conclusions

- In patients with untreated metastatic or unresectable locally advanced triple-negative breast cancer, PD-L1 IC positivity (≥ 1%) predicted survival benefit with atezolizumab vs placebo addition to nab-paclitaxel

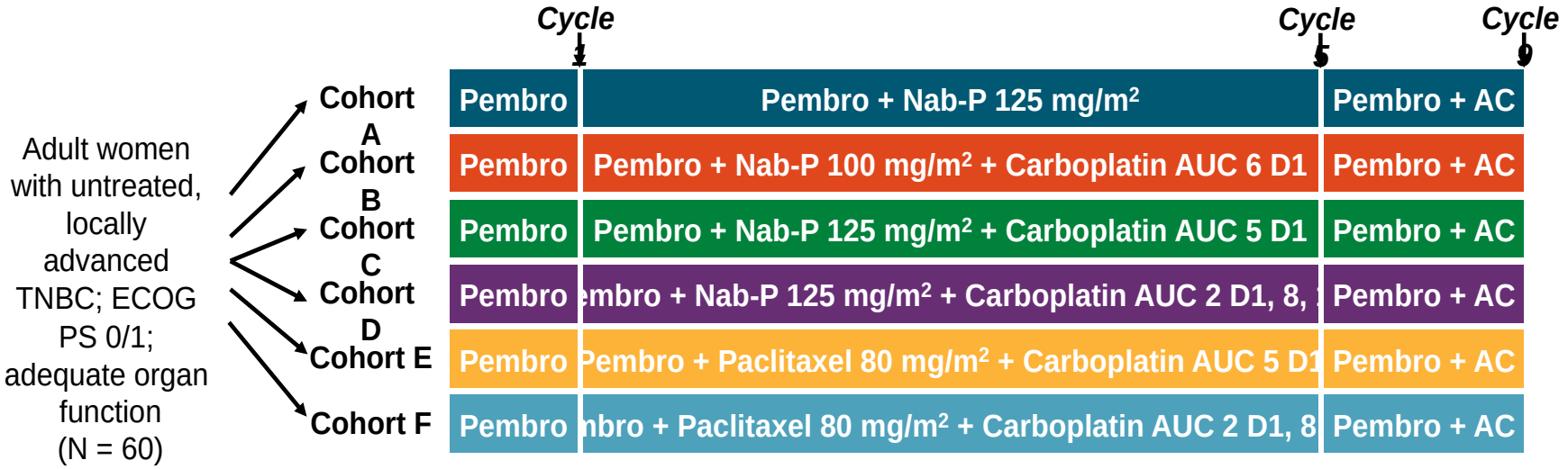
  -Subgroups positive for intratumoral CD8+ T-cells, sTILs, or *BRCA1/2* mutations demonstrated prolonged OS and/or PFS with atezolizumab only when simultaneously PD-L1 IC+

- Study investigators suggest that PD-L1 IC testing should be routine in this population to identify individuals who would most benefit from combination treatment

Emens. SABCS 2018. Abstr GS1-04.

KEYNOTE- 173: Pembrolizumab + chemoterapy as neoadjuvant therapy for TNBC

- Multicohort, open-label phase Ib study



All tx given IV. Cyclophosphamide: 600 mg/m^2 Q3W. Doxorubicin: 60 mg/m^2 Q3W. Nab-P, Pac: Days 1, 8, 15 Q3W. Pembro: 200 mg Day 1 in cycle 1, then Q3W. Definitive surgery per local standards and tissue collection for pCR 3-6 wks following completion of neoadjuvant therapy.

- Primary endpoint: safety/tolerability

- Secondary endpoints including: pCR rate, ORR, EFS, OS

Schmid. SABCS 2018. Abstr PD5-01. NCT02622074.

KEYNOTE- 173: Treatement-related AEs

- 100% of patients experienced treatment-related AEs
  - Grade ≥ 3 events reported in 90%
  - Led to pembrolizumab discontinuation in 18%
- 30% of patients experienced immune-related AEs

Treatment-Related AEs, %	All Patients (N = 60)
Any	100
Grade ≥ 3	90
▪ Neutropenia	73
▪ Febrile neutropenia	22
▪ Anemia	20
▪ Thrombocytopenia	8
Immune-related	30
▪ Hypothyroidism	8
▪ Hyperthyroidism	5

Schmid. SABCS 2018. Abstr PD5-01.

KEYNOTE- 173: conclusions

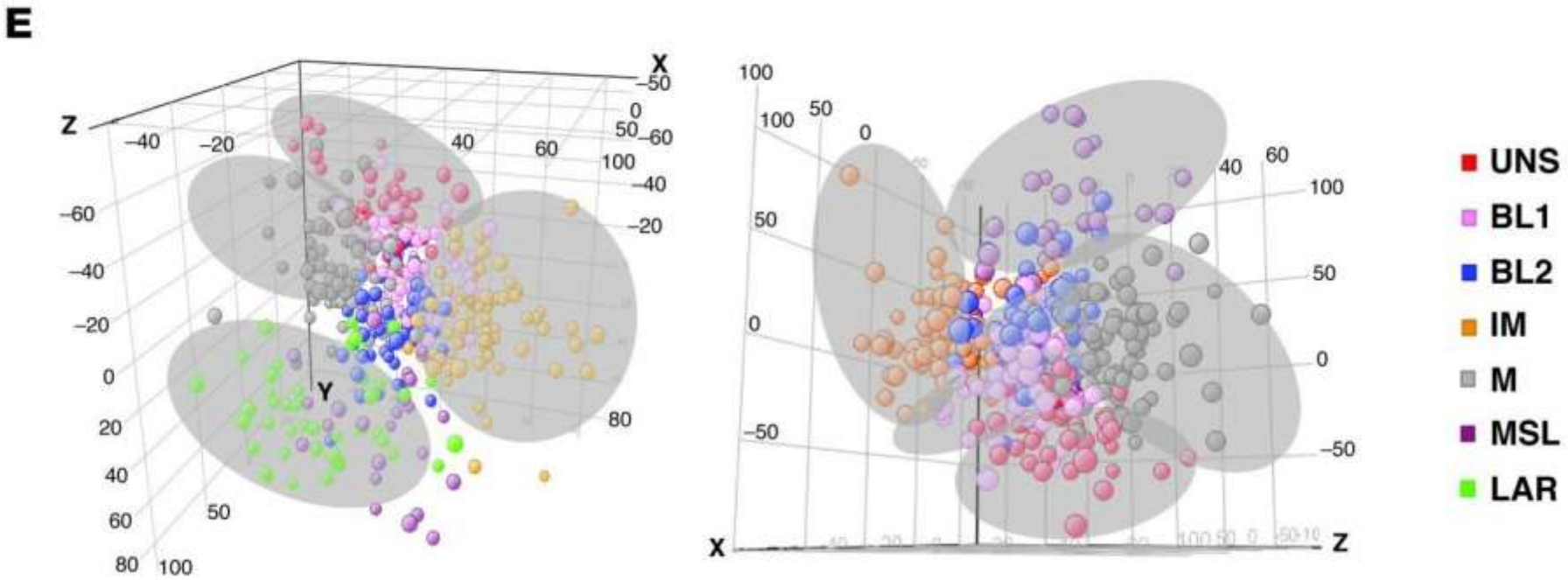
- In patients with untreated, locally advanced TNBC, preliminary data suggest promising antitumor activity and manageable toxicity with neoadjuvant pembrolizumab + chemotherapy according to investigators[1]
  - DLTs in 36.7% of patients
  - Higher pCR and extended EFS and OS in cohorts receiving carboplatin

- Exploratory analyses suggest that higher pretreatment sTIL level or PD-L1 CPS may predict higher pCR/ORR[2]

- Phase III KEYNOTE-522 examining neoadjuvant pembrolizumab + chemotherapy in patients with high-risk, early-stage TNBC ongoing[3]

1. Schmid. SABCS 2018. Abstr PD5-01. 2. Loi. SABCS 2018. Abstr P3-10-09. 3. NCT03036488.

Heterogeneity of triple negative tumors



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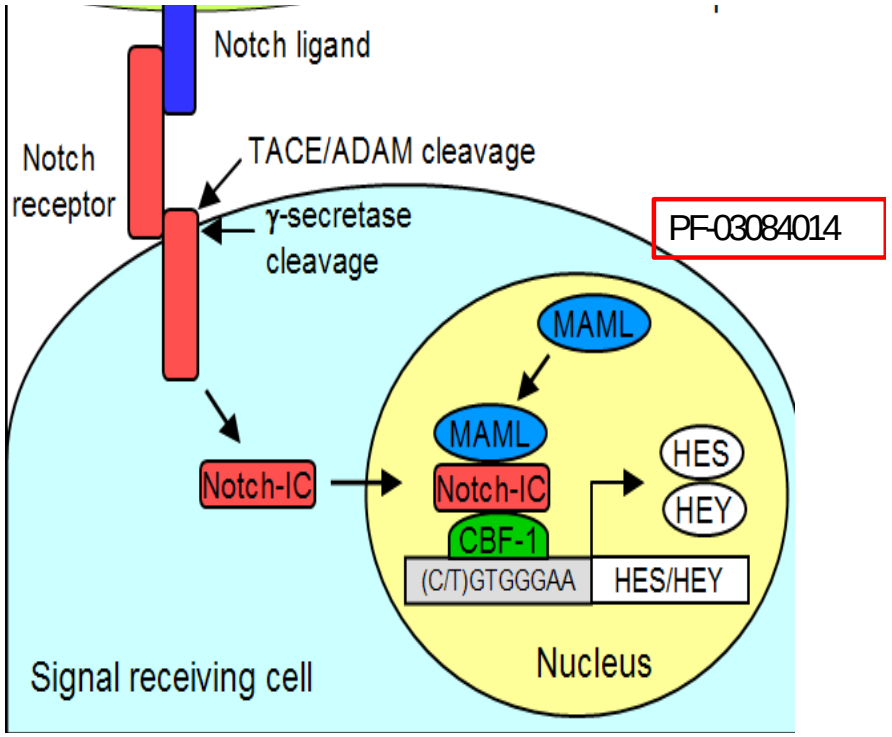
Lehman BD, et al. J Clin Incest 2011; 121:2750-67

Notch pathway

Phase 1b Study of docetaxel + PF- 03084014 in Triple-negative Breast Cancer



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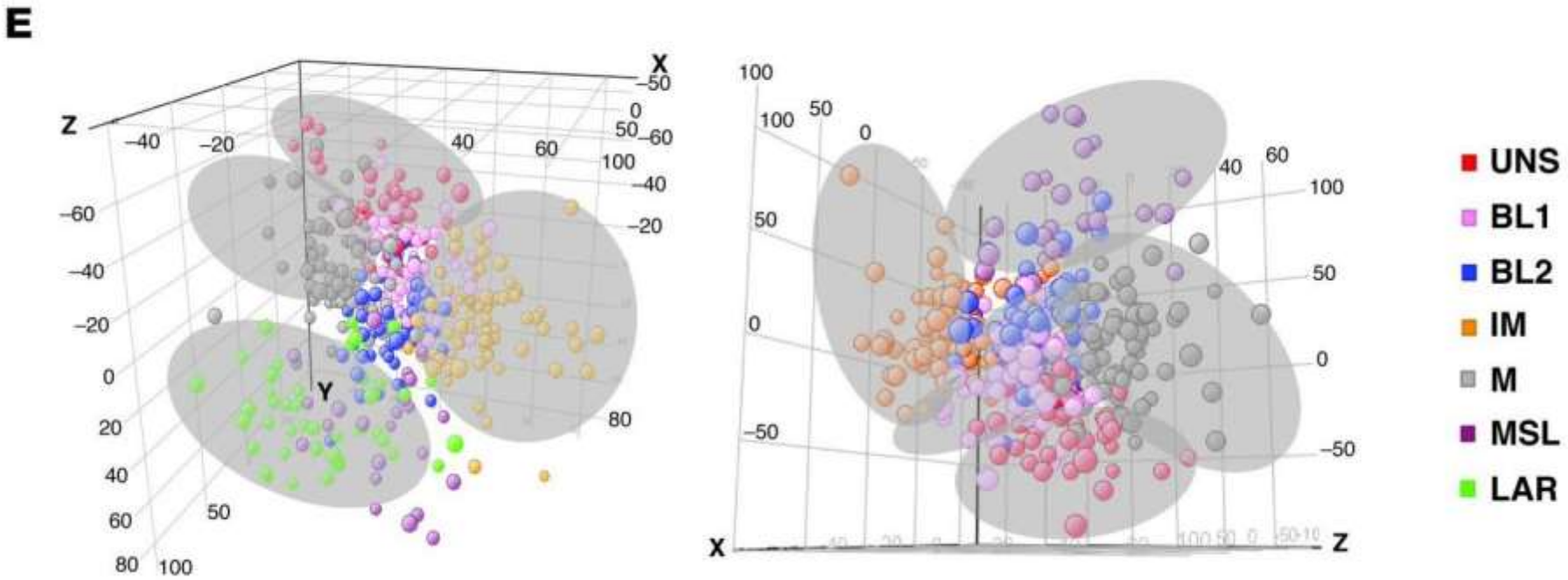

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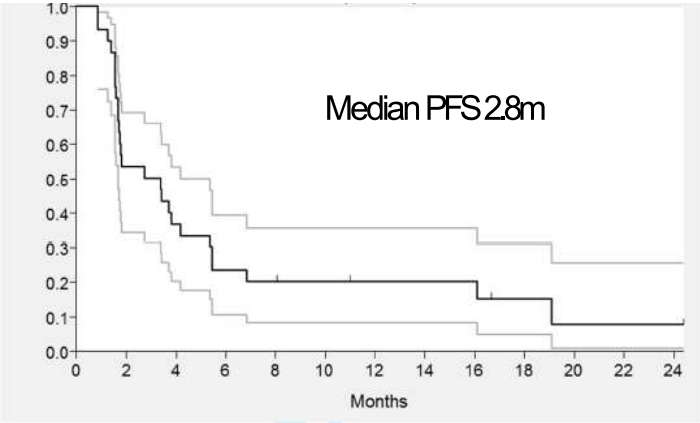
Lehman BD, et al. J Clin Incest 2011; 121:2750-67

Luminal Androgen Receptor: Abiraterone and Enzalutamide

- MBC ER/PR ≤10%
- 138 screened → 38% AR+ (≥10%)
- Primary Endpoint = CBR24
- N = 30 evaluable patients
- ~ 2.5 prior lines Rx
- ~ 50% visceral mets
- Most common, related AEs:
  - fatigue (18%)
  - HTN (12%)
  - hypokalemia (9%)
  - nausea (6%)

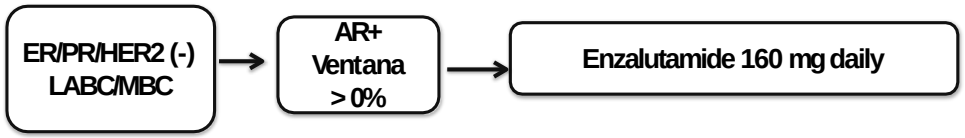


Abiraterone

CBR24 = 20% (95% CI: 8-39%)

1 confirmed CR

Enzalutamide

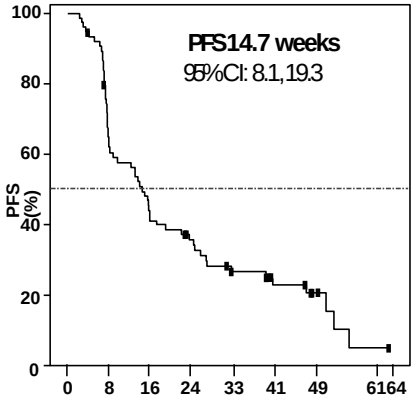


- Primary endpoint = CBR16 (CR + PR + SD > 16)

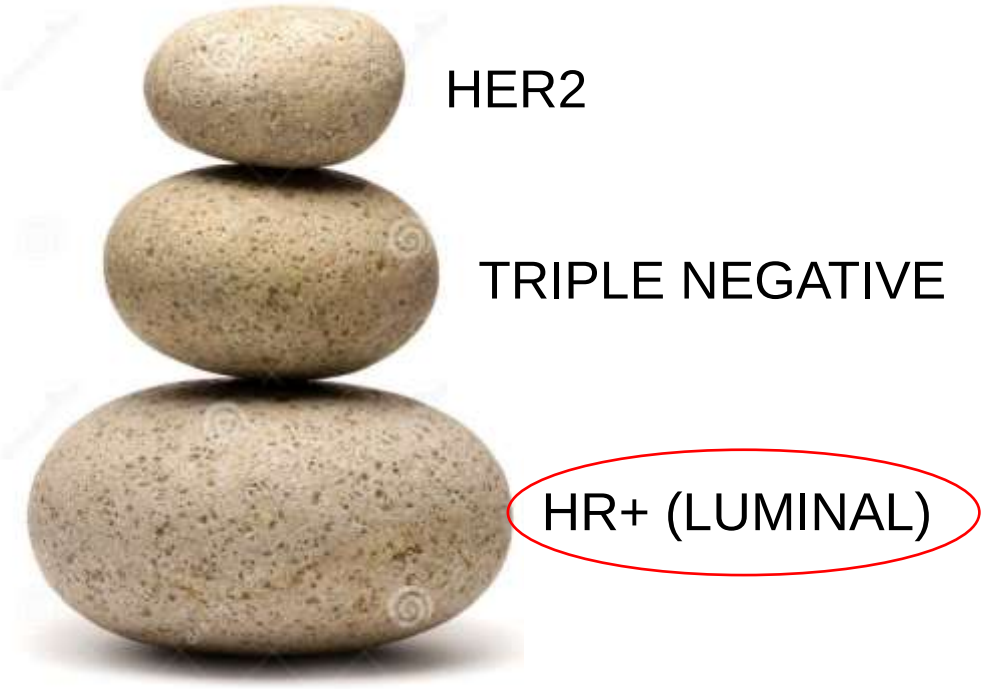
Screened patients 79% AR+ (55% by 10% cutoff)

- Median 1 prior Rx

Evaluable (n=75 AR≥10%)	
CBR16	35% (24-46%)
CBR24	29% (20-41%)
RR	8%
SAE	29%



Attempting to simplify the complexity

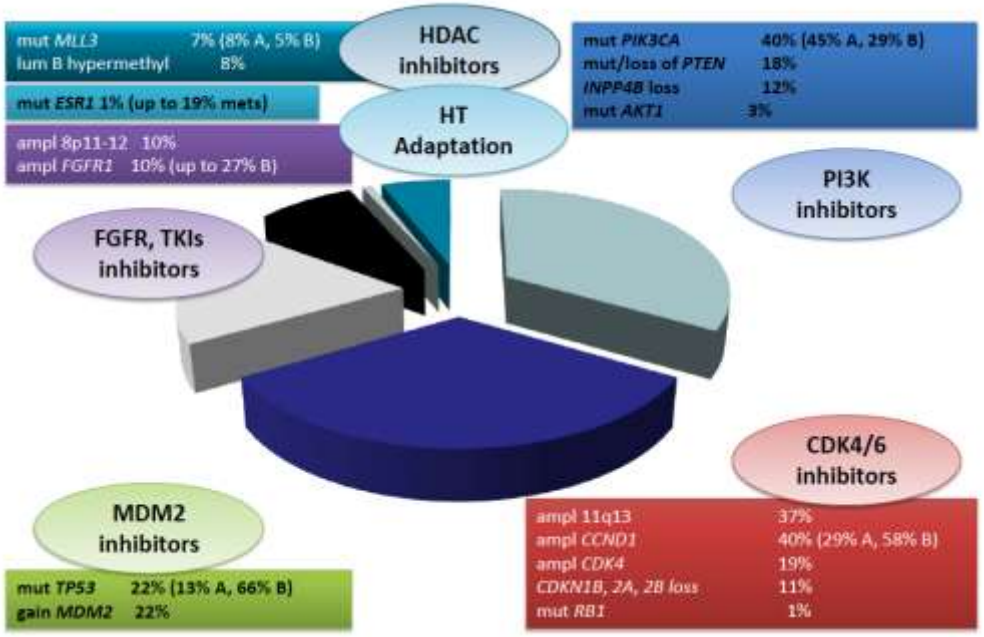


Luminal tumors – heterogeneous group

- The principal characteristic of the luminal group is the luminal expression signature, composed of *ESR1*, *GATA3*, *FOXA1*, *XBP1*, and *cMYB*
  - the most frequent mutations in the **luminal A** subtype are ***PIK3CA* (45%),** *MAP3K1* (13%), *GATA3* (13%), *TP53* (12%), and *CDH1* (9%)
  -the most frequent mutations in **luminal B** tumors are ***TP53*(29%), *PIK3CA* (29%)**,*GATA3* (13%), and *TTN* (12%)

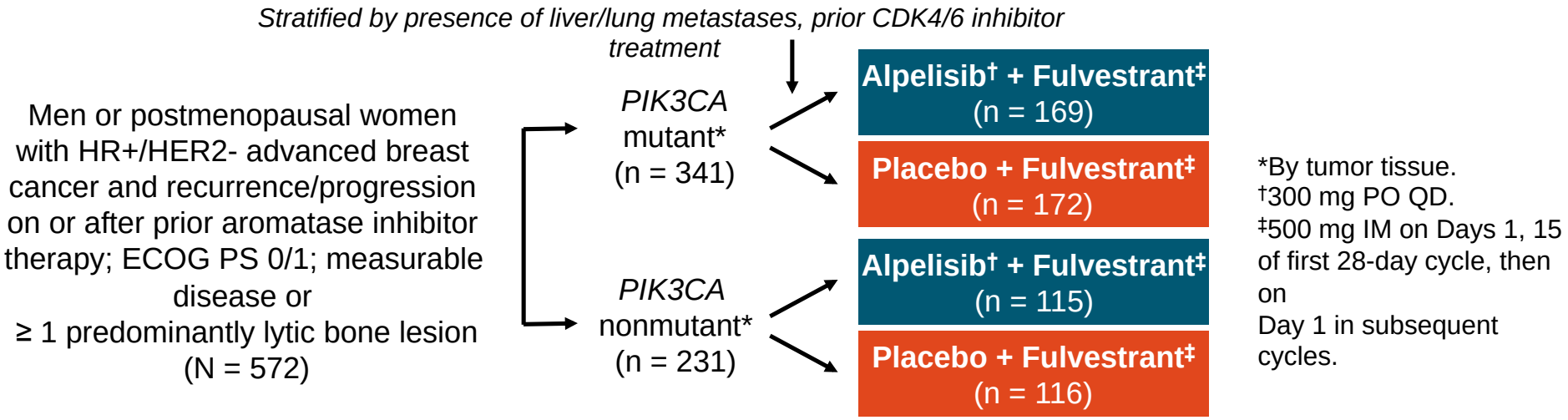
- In addition to *TP53* mutations, several other events may intervene in other steps of the same pathway, including *ATM* loss and *MDM2* amplification

- **ESR1**mutations (up to 19%) after hormonal treatment => resistance



SOLAR-1: Alpelisib + Fulvestrant for Men and Postmenopausal Women With HR-Positive ABC

- International, randomized, double-blind phase III study



- Primary endpoint: PFS in *PIK3CA*-mutant cohort (locally assessed)
- Secondary endpoints including: OS, PFS in *PIK3CA* non-mutant cohort, PFS by *PIK3CA* status as evaluated with ctDNA, ORR/CBR, safety

Juric. SABCS 2018. Abstr GS3-08.

SOLAR-1: PFS in *PIK3CA*-Mutant Cohort (Locally Assessed)

PFS	Alpelisib + Fulvestrant (n = 169)	Placebo + Fulvestrant (n = 172)
Median, mos (95% CI)	11.0 (7.5-14.5)	5.7 (3.7-7.4)
HR (95% CI)	0.65 (0.50-0.85); *P* = .00065	
Events, n (%)	103 (60.9)	129 (75.0)
▪ Progression	99 (58.6)	120 (69.8)
▪ Death	4 (2.4)	9 (5.2)
▪ Censored	66 (39.1)	43 (25.0)

- Similar PFS outcome for alpelisib + fulvestrant vs placebo + fulvestrant in retrospective analysis of *PIK3CA* mutation status via ctDNA testing
  - Median PFS: 10.9 vs 3.7 mos, respectively; HR: 0.55
- More patients with BL measurable disease experienced decreases in tumor burden with alpelisib + fulvestrant vs placebo + fulvestrant (75.9% vs 43.5%, respectively)

Juric. SABCS 2018. Abstr GS3-08. André. ESMO 2018. Abstr LBA3_PR.

SOLAR-1: PFS by Prior Therapy in *PIK3CA*-Mutant Cohort

Median PFS, Mos	Alpelisib + Fulvestrant	Placebo + Fulvestrant	HR (95% CI)
First line (n = 177)	11.0	6.8	0.71 (0.49-1.03)
▪ Endocrine sensitive* (n = 39)	22.1	19.1	0.87 (0.35-2.17)
▪ Endocrine resistant† (n = 138)	9.0	4.7	0.69 (0.46-1.05)
Second line‡ (n = 161)	10.9	3.7	0.61 (0.42-0.89)
Prior CDK4/6i therapy			
▪ Yes (n = 20)	5.5	1.8	0.48 (0.17-1.36)
▪ No (n = 321)	11.0	6.8	0.67 (0.51-0.87)

*PD > 1 yr after (neo)adjuvant ET; excluded later per protocol amendment.
†PD ≤ 1 yr after (neo)adjuvant ET.
‡PD > 1 yr after (neo)adjuvant ET and while on/after 1 line of ET for ABC *or* newly diagnosed ABC with PD on/after 1 line of ET.

Juric. SABCS 2018. Abstr GS3-08.

SOLAR-1: Interim OS in *PIK3CA*-Mutant Cohort

OS	Alpelisib + Fulvestrant (n = 169)	Placebo + Fulvestrant (n = 172)
Median, mos (95% CI)	NE (28.1-NE)	26.9 (21.9-NE)
HR (95% CI)	0.73 (0.48-1.10); *P* = .06	

- Data cutoff (June 12, 2018) included 52% of planned events for final OS analysis
- Median follow-up: 15.9 mos (range: 0.4-31.7)

Juric. SABCS 2018. Abstr GS3-08.

SOLAR-1: Hyperglycemia in Alpelisib-Containing Arm

- Glucose > 160 mg/dL typically observed by Day 15
  - Median duration: 10 days
- Fasting plasma glucose and A1C spikes highest in alpelisib recipients who were diabetic (4%) or prediabetic (56%) at BL
  - 87% with hyperglycemia received antidiabetic medication, typically metformin

Event, %	Alpelisib + Fulvestrant
Hyperglycemia serious AEs	10.6
Hyperglycemia-related AEs	
▪ Dose interruption	40.6
▪ Dose adjustment	43.9
▪ Discontinuation	6.3

Juric. SABCS 2018. Abstr GS3-08.

THANK YOU

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