ASSISTANCE PUBLIQUE HÔPITAUX DE PARIS

Medical Innovations for Breast Cancer and Regulatory Handling

Review of Major Recent Data

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Availability of New drugs

Not so Frequent

Availability (MA) of new drugs in Oncology (EMA)

- Full approval:
  - Significant difference on a predefined time related endpoint
  - Acceptable comparator (active and similar to the practice)
  - Acceptable safety profile
- Conditional approval in the absence of comprenesive data in situation without alternative options
- Registration under exceptional circumstances

EU Marketing authorization for breast cancer (Centralized procedure) (From EMA website)

Name	Active substance	Date of authorisation	Orphan	Exceptional circumstances	safety alert
Abraxane	paclitaxel	11/01/2008			
Avastin	bevacizumab	12/01/2005			X
	Aromatase Inhib.	Mutual recognition			
Bondronat	ibandronic acid	25/06/1996			
Caelyx	Lip doxorubicin hydrochloride	21/06/1996			
Fareston	toremifene	14/02/1996			
Faslodex	fulvestrant	10/03/2004			
Herceptin	trastuzumab	28/08/2000			
Myocet	Lip doxorubicin hydrochloride	13/07/2000			
Taxotere	docetaxel	27/11/1995			
Tyverb	lapatinib	10/06/2008			
Xeloda	capecitabine	02/02/2001			
Halaven	Eribuline Mesylate	20.01.2011			

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FDA MA for Breast Cancer

- Same +
  - Ixempra (Ixabepilone)

Eribulin in Heavily Pretreated Metastatic Breast Cancer

Patients (N = 762)

- Locally recurrent or MBC
- 2-5 prior chemotherapies
  - ≥2 for advanced disease
  - Prior anthracycline and taxane
- Progression ≤6 months of last chemotherapy
- Neuropathy ≤ grade 2
- ECOG ≤2

Eribulin mesylate
1.4 mg/m^2, 2-5 min IV
Day 1, 8 q21 days

Randomization 2:1

Treatment of Physician's Choice (TPC)
Any monotherapy (chemotherapy, hormonal, biological) or supportive care only

Primary endpoint
- Overall survival

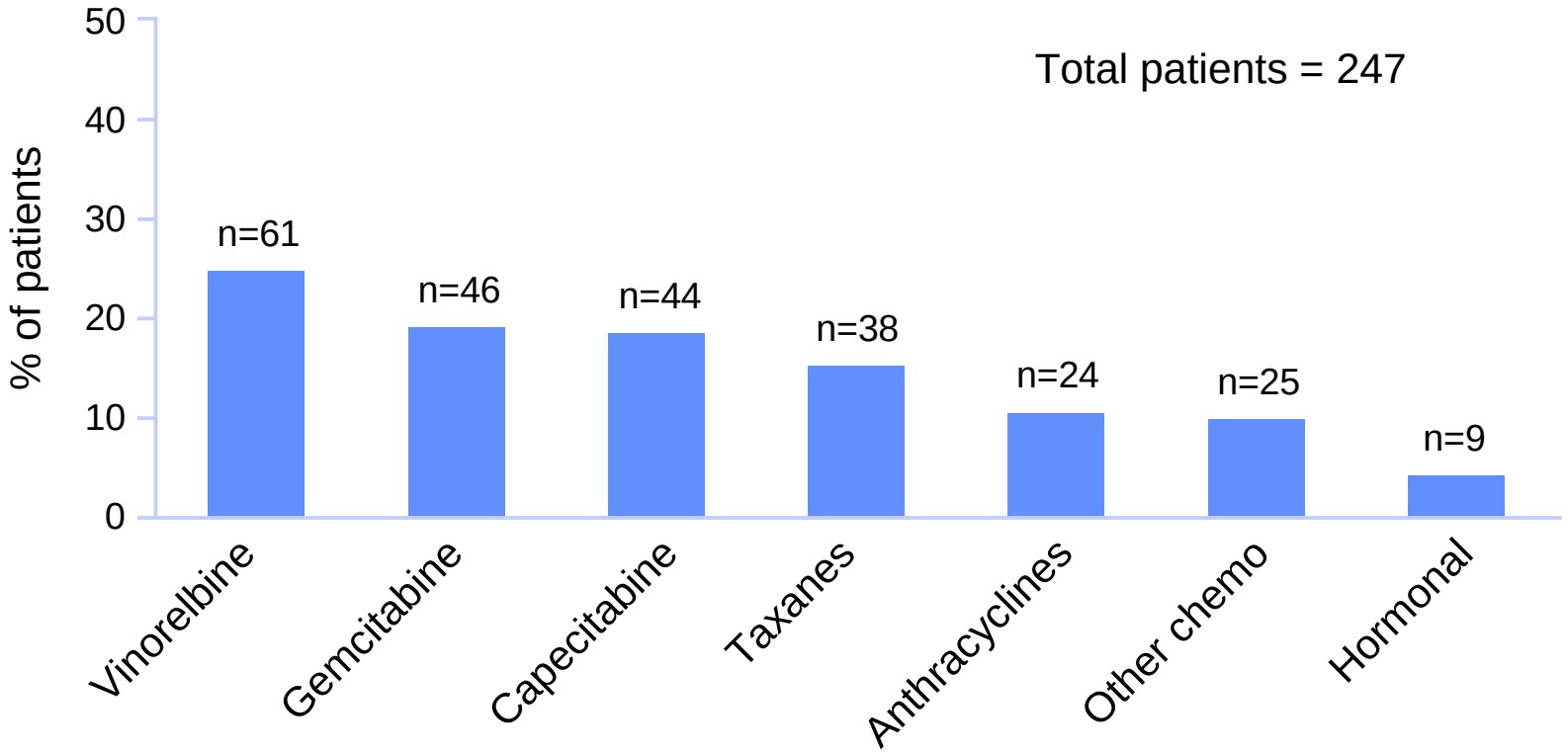
Secondary endpoints
- PFS
- ORR
- Safety

- Global, randomized, open-label Phase III trial (Study 305, EMBRACE)
- Final analysis after 422 deaths
  - Median age 55.2 yrs, 16% HER2+, 19% TNBC, median 4 prior agents

Twelves C, et al. J Clin Oncol 28:7s, 2010 (suppl; abstr CRA1004^)

EMBRACE: Treatments of Physician's Choice

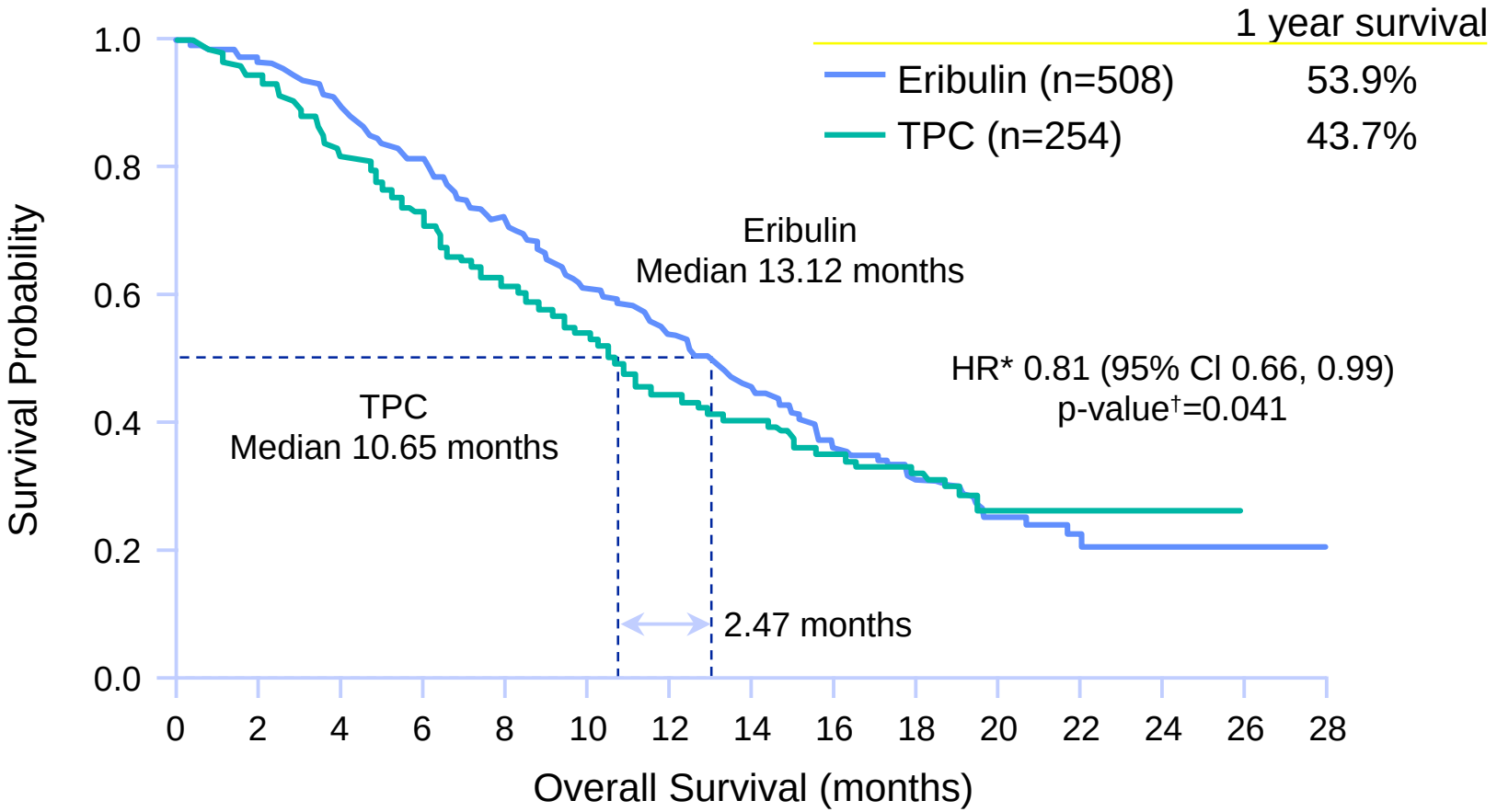
96% of patients treated with chemotherapy



No patient received best supportive care or "biological" therapies only

Twelves C, et al. J Clin Oncol 28:7s, 2010 (suppl; abstr CRA1004^)

EMBRACE: Significant Improvement in OS with Eribulin vs Physicians' Choice



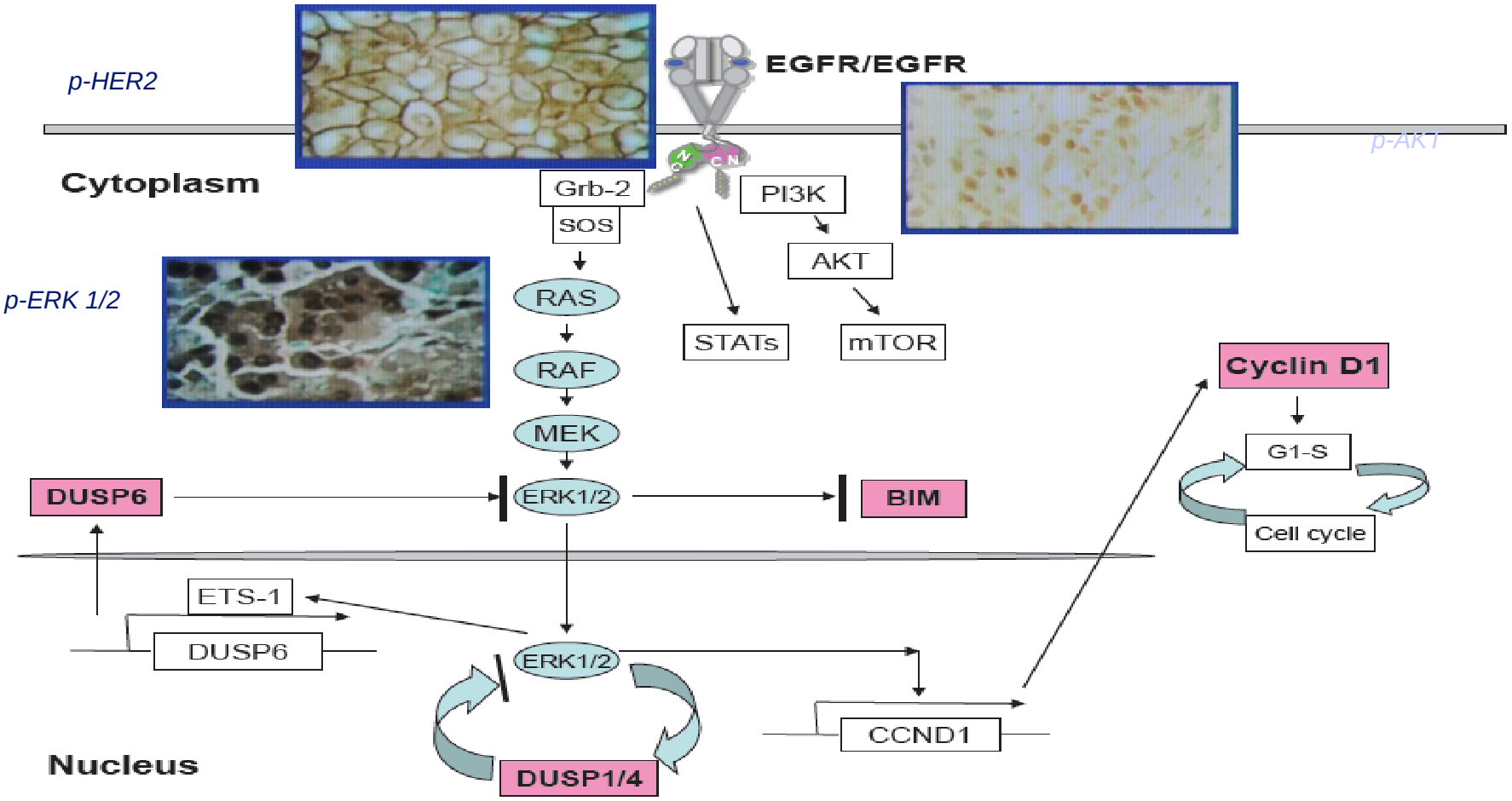
ITT population, *HR Cox model including geographic region, HER2/*neu* status, and prior capecitabine therapy as strata
† p value from stratified log-rank test (pre-defined primary analysis); TPC, treatment of physicians' choice, HR, hazard ratio; CI, confidence intervals

Twelves C, et al. J Clin Oncol 28:7s, 2010 (suppl; abstr CRA1004^)

What is changing

- Biomarker-based classification and adaptative design if validated during POC study
- Hierarchy of primary endpoints
  - DFS/PFS in adjuvant and early metastatic progression
  - OS in late stages without further options
- Number of pivotal studies ? (1)
- Introduction of Health Technology Assessment approaches in registration trials

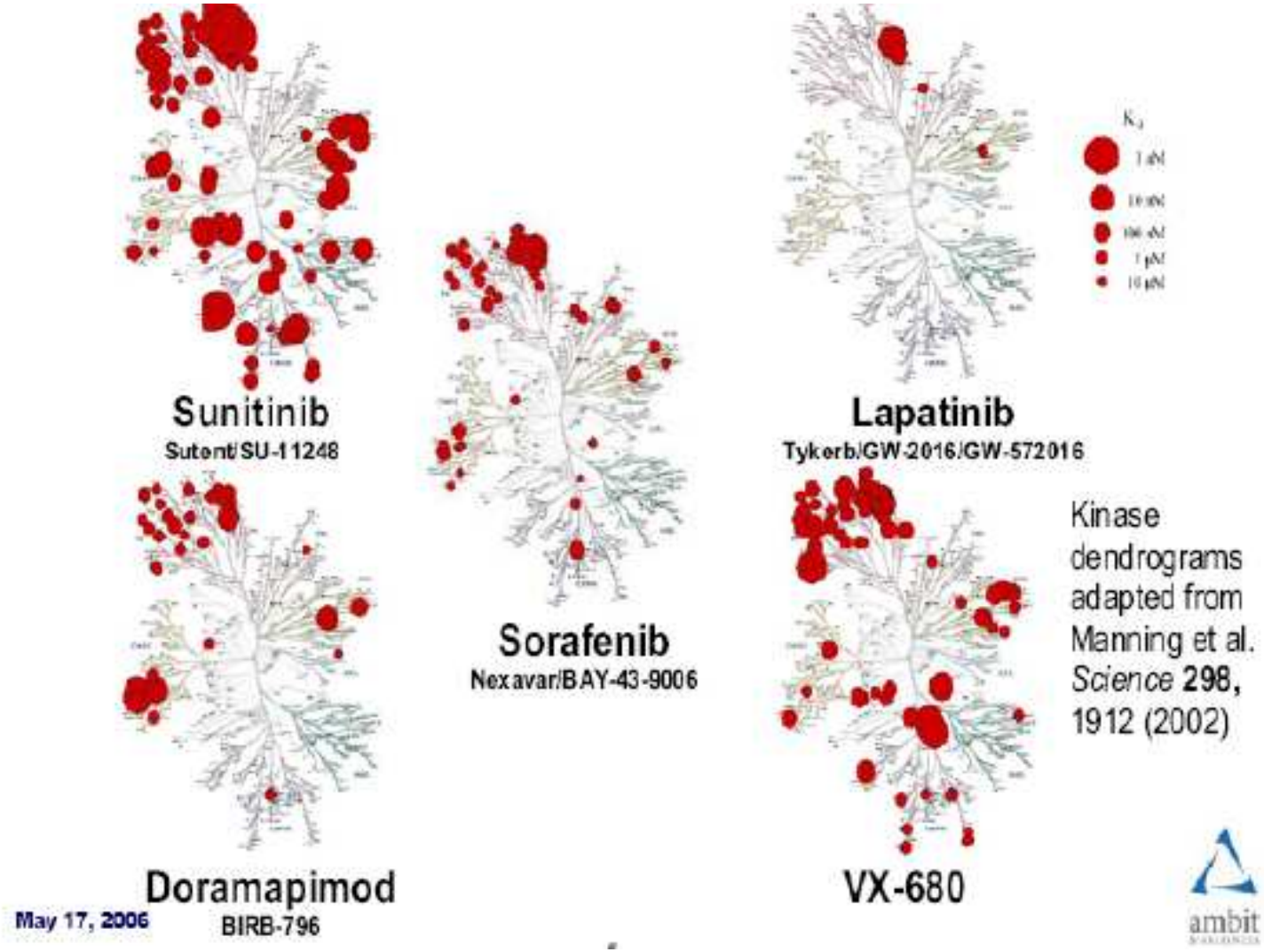
Selection of pts on biomarkers: HR, HER2, EGFR, bRAF, PI3Km



Some of the Known Issues In Assessing ANA (EMA)

- Definition of different ANA (cytotoxics, targeted-few targets, targeted multitargets, immunomodulators…)
- PD from preclinical models to clinical trials
- Less stringent definition of phases (0.I.II.III, IV→POC and demonstration studies)
- New endpoints : functional imaging, CTC…at least in the early part of trials
- Endpoints (PFS/DFS and OS)
- Non inferiority vs superiority
- Agents which will be studied only in combination

Some (Multi)-Receptor-kinase inhibitors



Some of the Known Issues

- Definition of different ANA (cytotoxics, targeted-few targets, targeted multitargets, immunomodulators…)
- Pharmacodynamics in clinical trials
- Less stringent definition of phases (0.I.II.III, IV→POC and demonstration studies)
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PD endpoints using CTC?

FDA U.S. Food and Drug Administration

When is it used?

The CellSearch? ™ Epithelial Cell Kit / CellSpotter?™ Analyzer are used for patients undergoing treatment for breast cancer. The presence of CTC in the blood is associated with decreased survival in patients treated for spreading (metastatic) breast cancer.

What will it accomplish?

The CellSearch™ Epithelial Cell Kit / CellSpotter™ Analyzer monitors breast cancer treatment **and indicates its effectiveness.**

Would CTC become a surrogate marker?

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POC study: NEOSPHERE : should help selecting the best scheme

HER2+ve BC not considered for primary surgery N=417)

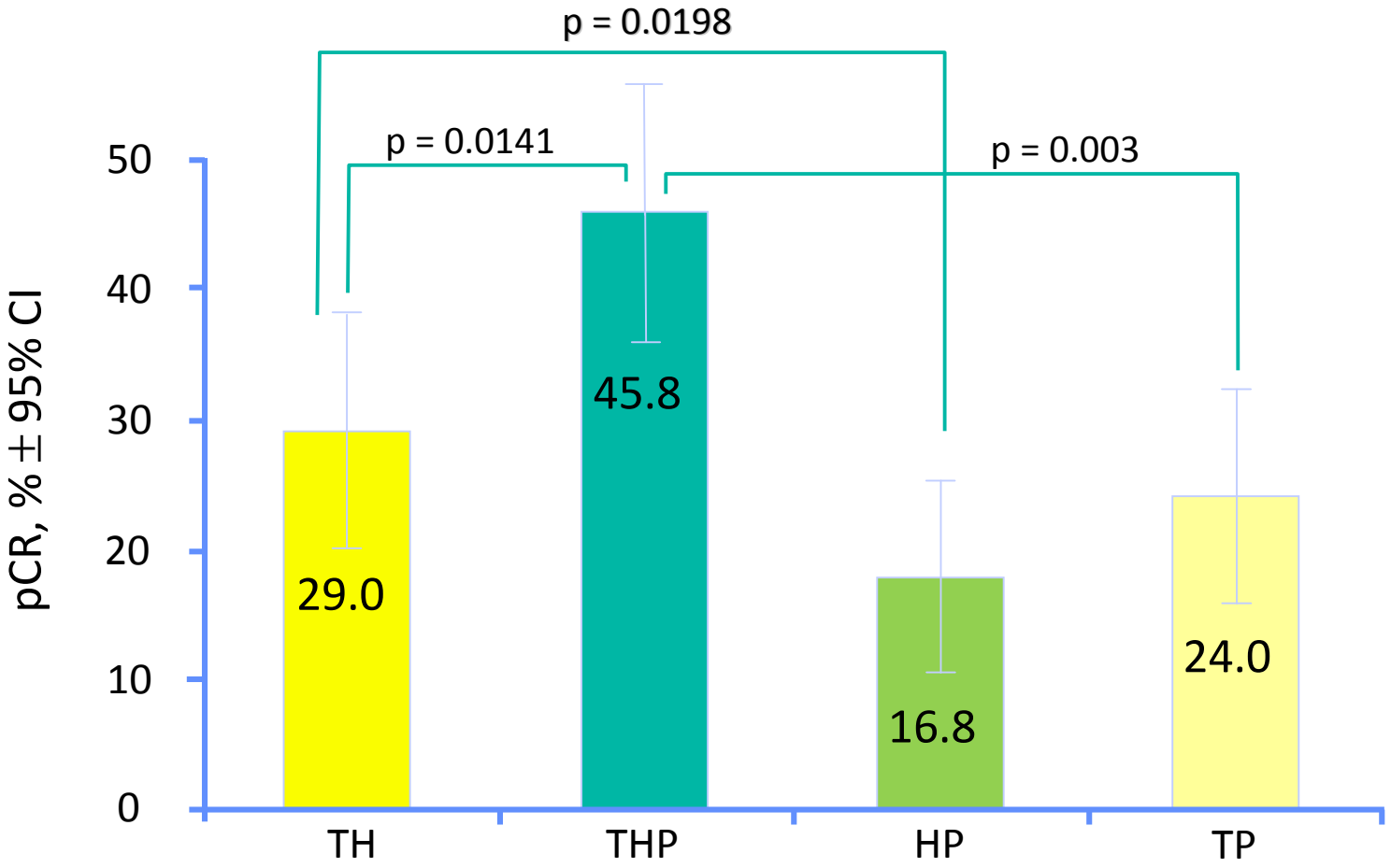
TH (n=107) docetaxel + trastuzumab	SURGERY	FEC /3 sem x 3 trastuzumab /3 sem cycles 5–17
THP (n=107) docetaxel + trastuzumab + pertuzumab		FEC /3 sem x 3 trastuzumab /3 sem cycles 5–17
HP (n=107) trastuzumab + pertuzumab		Docetaxel 3 sem x 4→FEC /3 sem x 3 Trastuzumab /3 sem cycles 5–17
TP (n=96) docetaxel + pertuzumab		FEC /3 sem x 3 trastuzumab /3 sem cycles 5–21

3 sem x 4

T: Docetaxel 75→100 mg/m^2; H: Trastuzumab (8→6 mg/kg) ; P: Pertuzumab (840→420 mg)

Gianni L *et al*. SABCS 2010. Abs S3.2

NEOSPHERE : pCR (ITT)



H, trastuzumab; P, pertuzumab; T, docetaxel

Gianni L *et al*. SABCS 2010. Abs S3.2

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Non Inferiority: different scenarii

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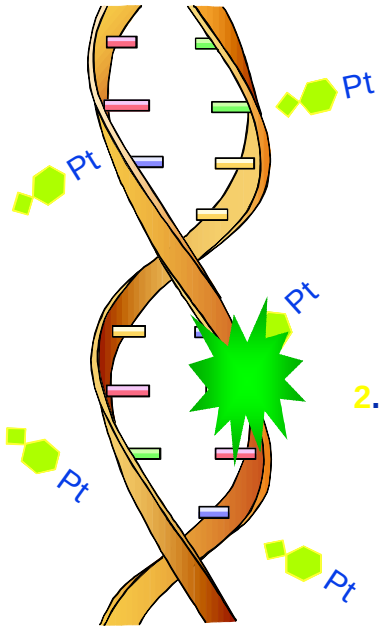
PARP Inhibitor Mechanism of Action

1. DNA BINDING CHEMOTHERAPY

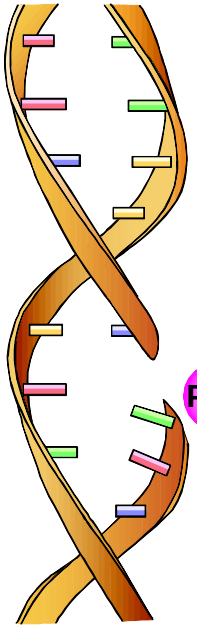
DNA damage via adducts and DNA crosslinking



PARP1

2. PARP1 UPREGULATION

→BER



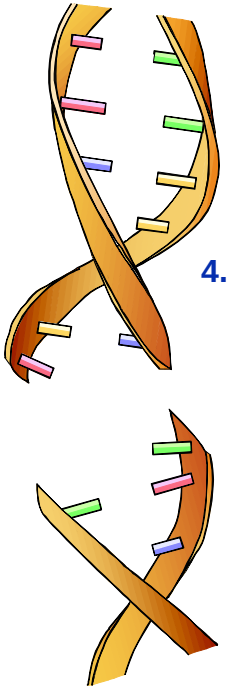
PARP1

3. INHIBITION OF PARP1

Disables DNA base-excision repair

PARP1

BSI-201



4. REPLICATION FORK COLLAPSE

Double strand DNA break

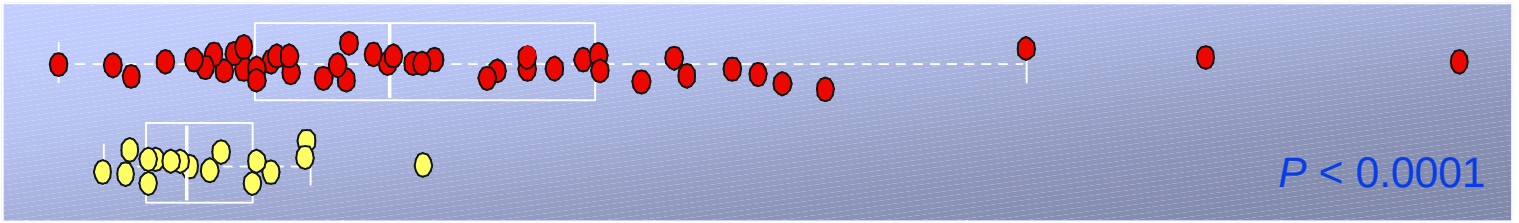
BRCA1
BRCA2

CELL SURVIVAL

CELL DEATH

PARP1 is Upregulated in TNBC

Gene expression profiling showed that *PARP1* was significantly upregulated in the majority of triple negative breast cancers (n = 50)



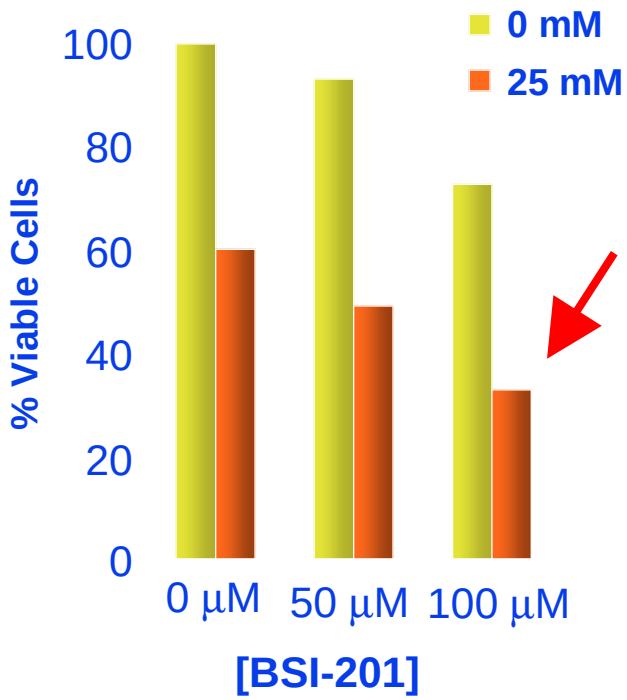
***PARP1* mRNA**

(Red Fluorescence Units Normalized to β-Glucoronidase)

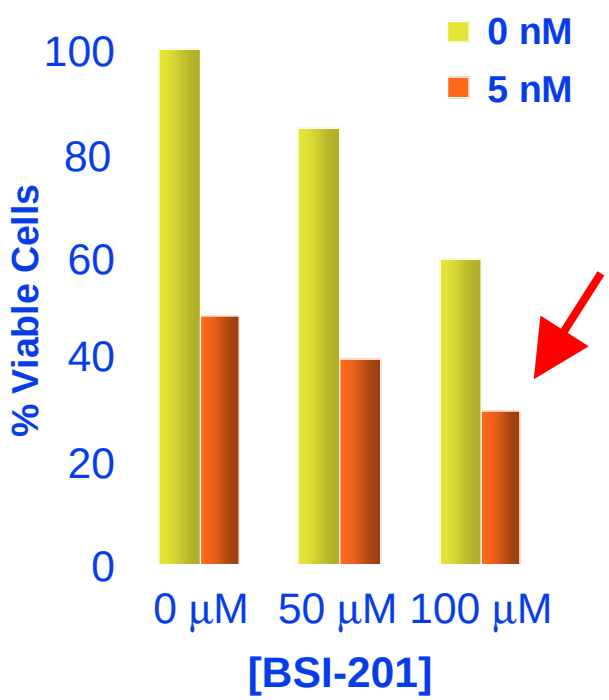
Preclinical Evidence for Synergy:
Combination of BSI-201 with Carboplatin or Gemcitabine

BSI-201 potentiated antitumor effects of carboplatin and gemcitabine in the MDA-MB-468 triple negative breast cancer cell line

Carboplatin



Gemcitabine



BiPar Sciences, data on file

Phase II TNBC Study: Treatment Schema

Metastatic TNBC
N = 120
0-2 prior CTX

RANDOMIZE

Gemcitabine (1000 mg/m², IV, d 1, 8)
Carboplatin (AUC 2, IV, d 1, 8)

21-Day Cycle

BSI-201 (5.6 mg/kg, IV, d 1, 4, 8, 11)
Gemcitabine (1000 mg/m2, IV, d 1, 8)
Carboplatin (AUC 2, IV, d 1, 8)

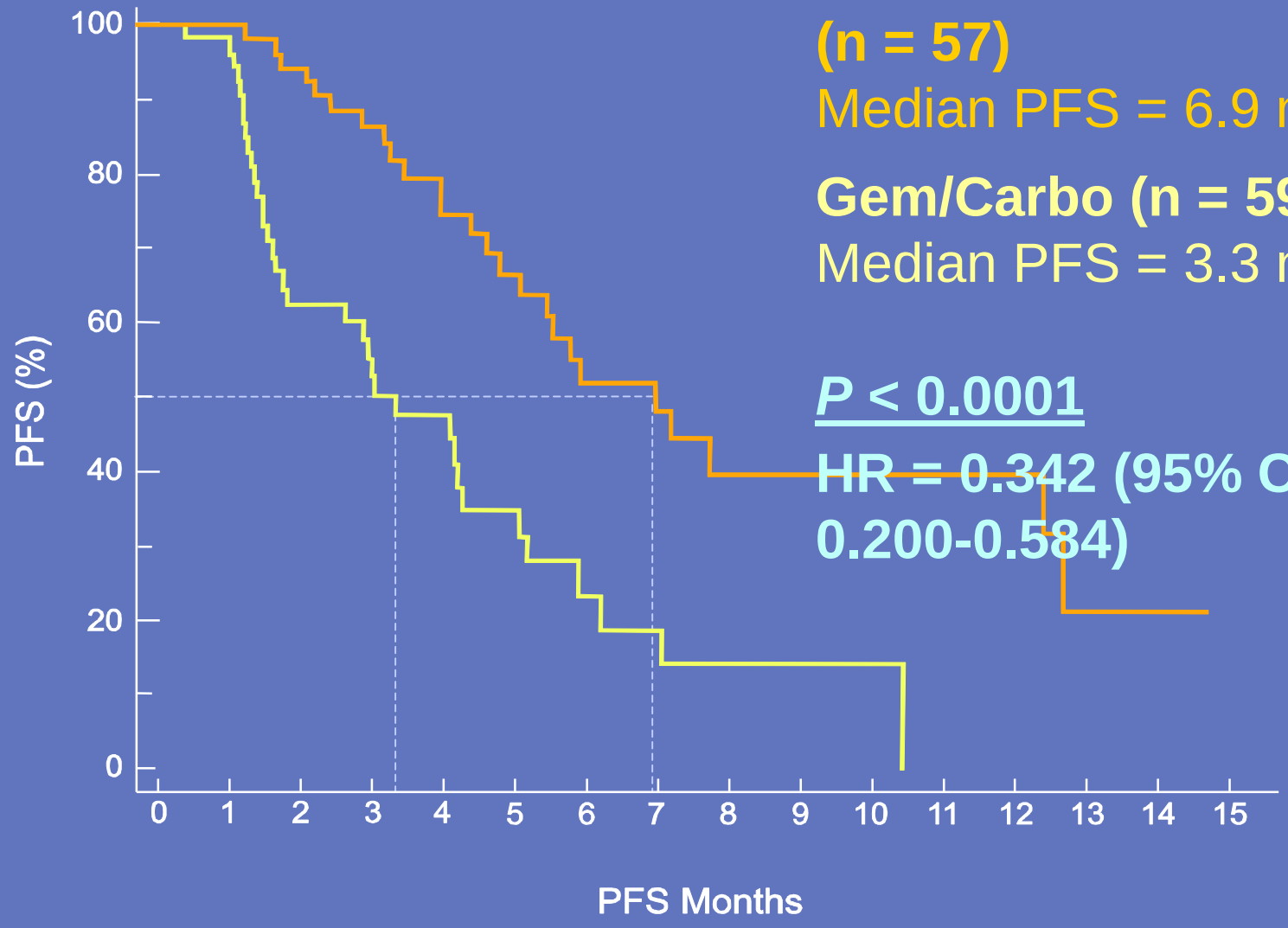
RESTAGING
Every 2 Cycles

* Patients randomized to gem/carbo alone could crossover to receive gem/carbo + BSI-201 at disease progression

Preliminary Efficacy Results*

	Gem/Carbo (n = 44)	BSI-201 + Gem/Carbo (n = 42)	*P*-value
Objective Response Rate n (%)	7 (16%)	20 (48%)	0.002
****Clinical Benefit Rate n (%)**	9 (21%)	26 (62%)	0.0002

Progression-Free Survival



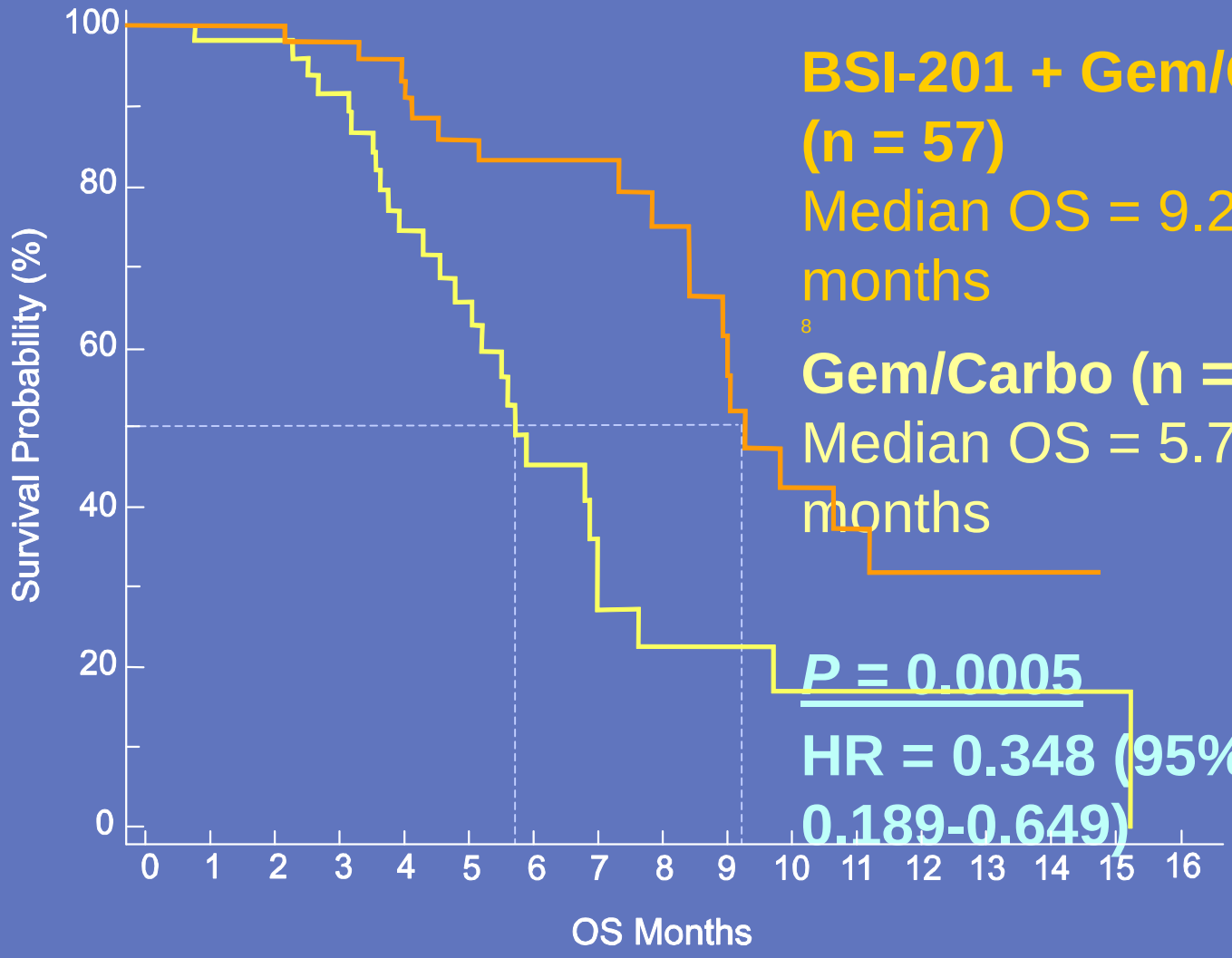
BSI-201 + Gem/Carbo (n = 57)
Median PFS = 6.9 mo

Gem/Carbo (n = 59)
Median PFS = 3.3 mo

***P* < 0.0001**

HR = 0.342 (95% CI, 0.200-0.584)

Overall Survival



BSI-201 + Gem/Carbo (n = 57)
Median OS = 9.2 months

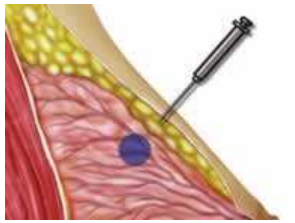
[8]

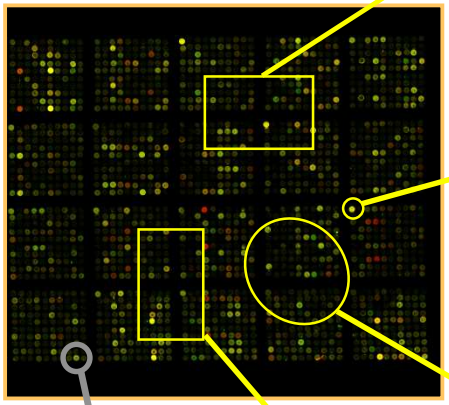
Gem/Carbo (n = 59)
Median OS = 5.7 months

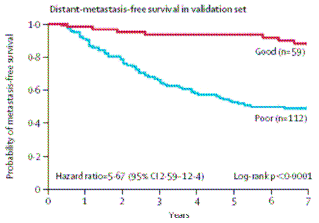
***P* = 0.0005**

HR = 0.348 (95% CI, 0.189-0.649)

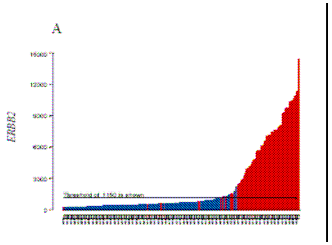
The Way to the Future: all in one?



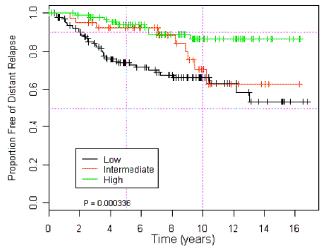




Estimate prognosis



Measure ER and HER2



Predict endocrine sensitivity if ER+

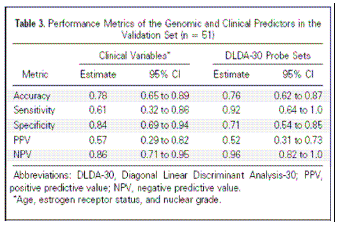


Table 3. Performance Metrics of the Genomic and Clinical Predictors in the Validation Set (n = 61)

	Clinical Variables*		DLDA-30 Probe Sets	
Metric	Estimate	95% CI	Estimate	95% CI
Accuracy	0.78	0.65 to 0.89	0.76	0.62 to 0.87
Sensitivity	0.61	0.32 to 0.86	0.92	0.64 to 1.0
Specificity	0.84	0.69 to 0.94	0.71	0.54 to 0.85
PPV	0.57	0.29 to 0.82	0.52	0.31 to 0.73
NPV	0.86	0.71 to 0.95	0.96	0.82 to 1.0

Abbreviations: DLDA-30, Diagonal Linear Discriminant Analysis-30; PPV, positive predictive value; NPV, negative predictive value.
*Age, estrogen receptor status, and nuclear grade.

Predict Taxol / FAC sensitivity

Therapeutic target "X"