Üçlü Negatif Metastatik Meme Kanserinde Tedavi Sıralaması Nasıl Olmalı?

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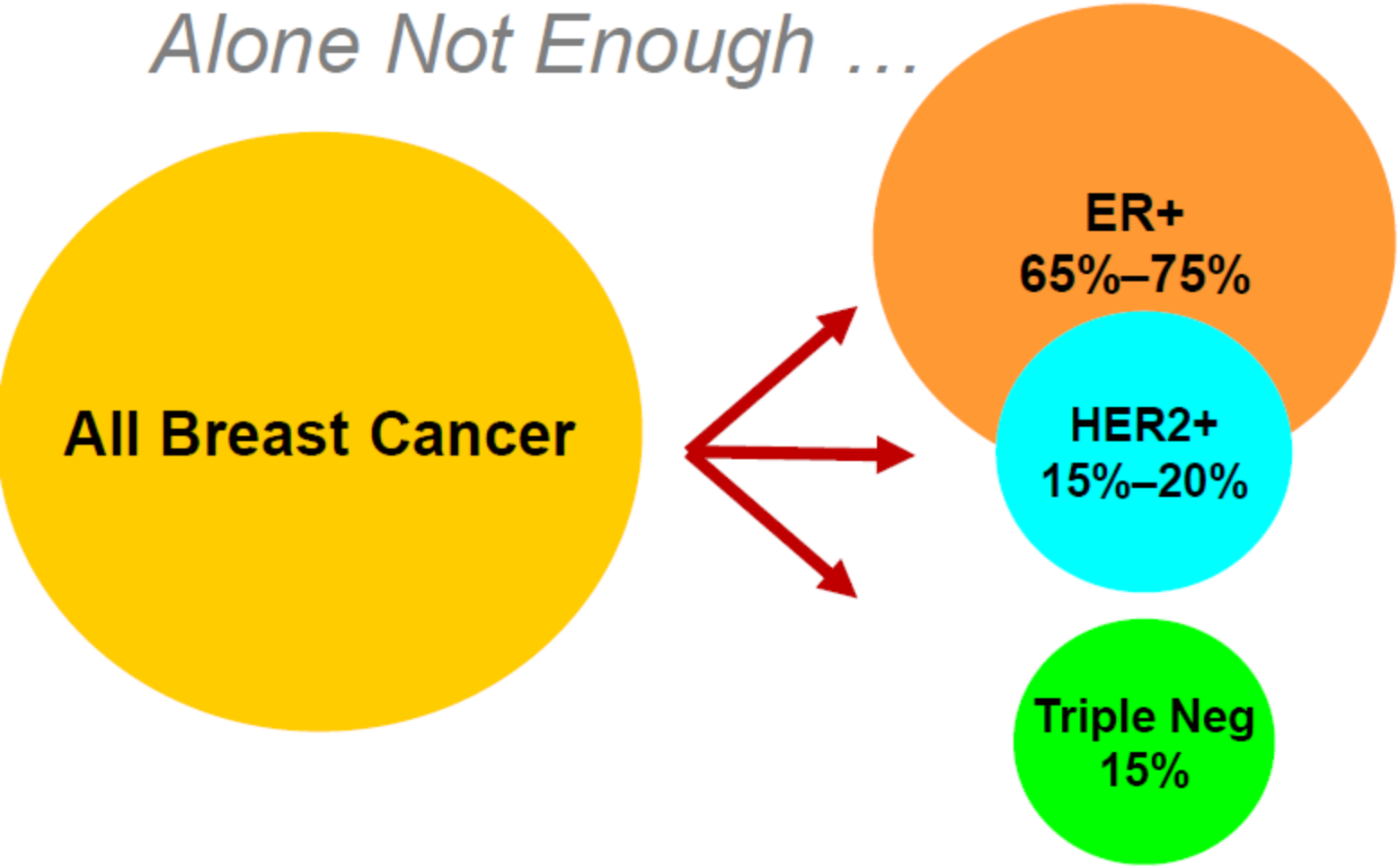
Breast Cancer Phenotypes

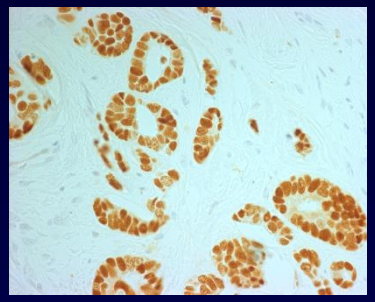
Alone Not Enough …



- *Accurate predictive biomarker testing is critical as current phenotypes determine <u>what</u> type of therapy to give (strong NPV)*
- *However, they do not tell us <u>who</u> will benefit (modest PPV)*
- *Nor do they alone tell us in absolute terms <u>whether</u> to give it (modest prognostic utility)*

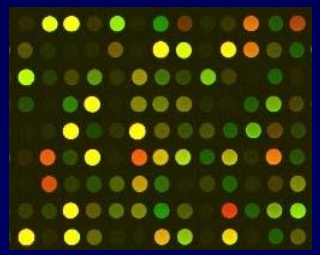
“Üçlü Negatif” ≅ “Basal-like”

“Üçlü negatif”
İmmünohistokimyasal profil



ER-, PR-, HER2-
(cyclin D1-, CK5/6/17+, EGFR+, vimentin+, nestin+…)

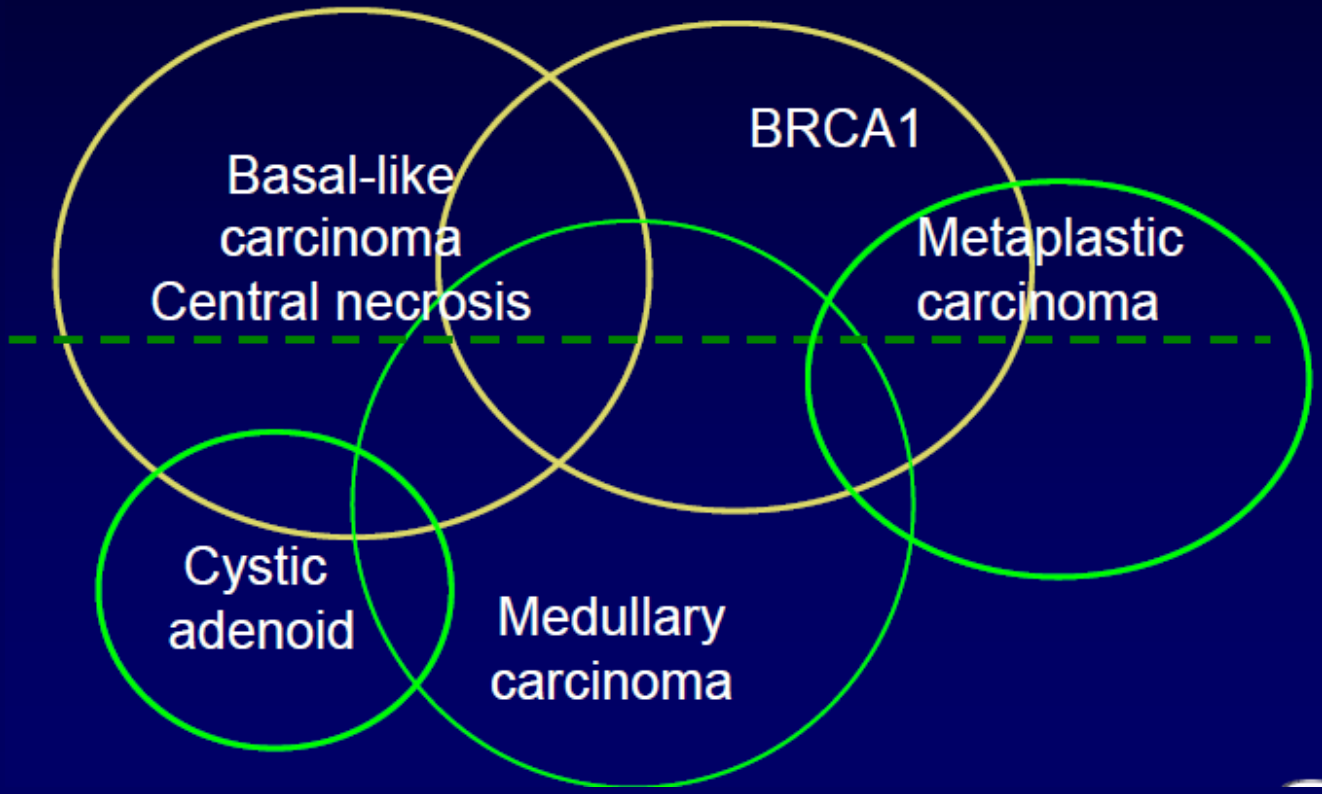
Gen Ekspresyon Profili



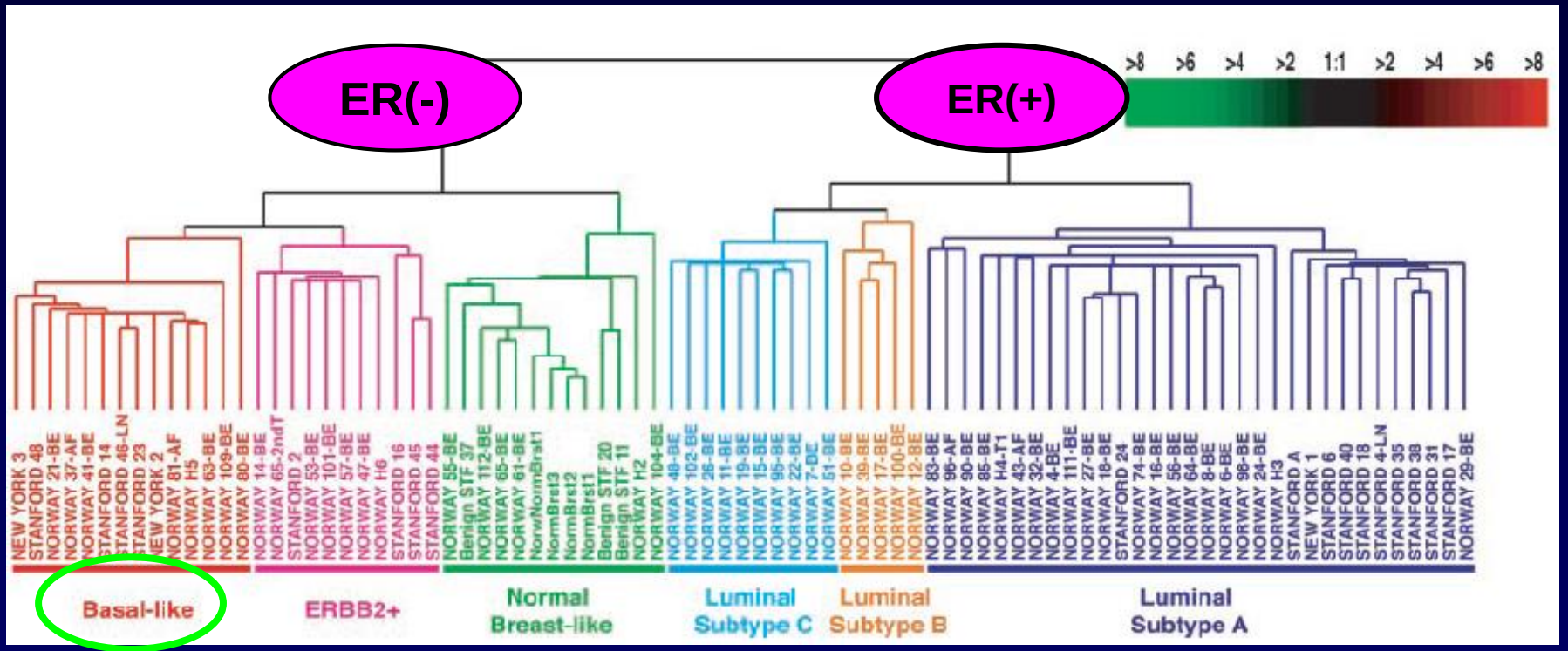
Üçlü negatif meme kanserlerinin~ % 15-50 si bazal değildir….
?

Parker J, et al. JCO 2009, Rakha EA, et al. Breast Cancer Res Treat 2009

Triple Negative Breast Cancers
Basal-Like Carcinomas



Meme Kanser Gen Profili

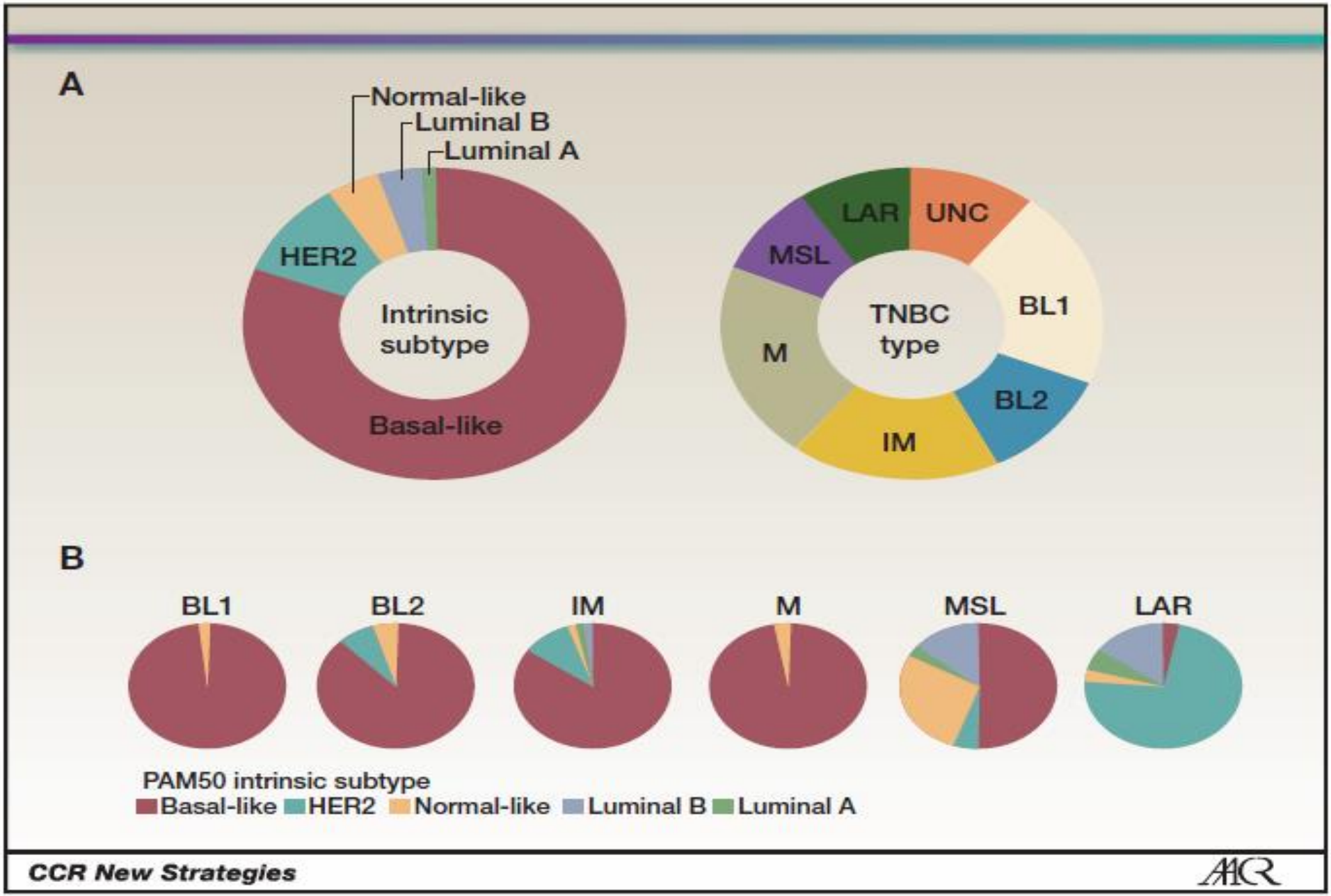


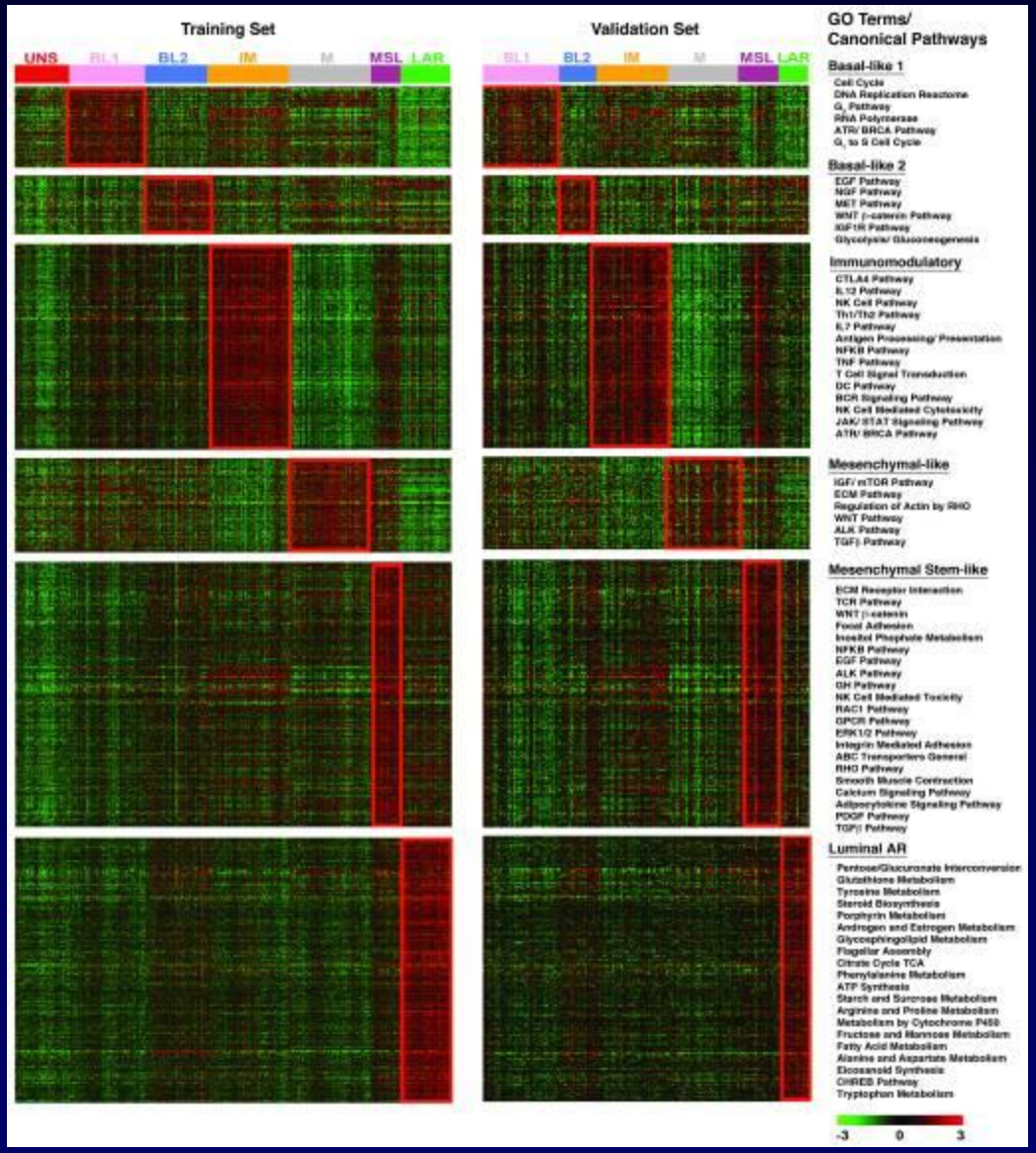
Sorlie et al. PNAS 2001; 98:10869-10874

Intrinsic Molecular Classification of Breast Cancer

Intrinsic Subtypes	IHC markers	Proliferation & Grade	Rx Implications
Basal-like	Mostly triple-negative (not always!)	High Ki67, high grade	Worse natural history, quite responsive to chemo (eg, preop chemo & pCR)
Luminal A	Mostly ER+	Low Ki67, low grade	Indolent, responsive to endocrine Rx
Luminal B	Mostly ER+	Often high Ki67, high grade	Less/unresponsive to endocrine Rx, more responsive to chemo
HER2+	HER2 over expressed	High Ki67	Worse natural history, quite sensitive to anti-HER2 Rx

Üçlü Negatif Meme Kanseri İntrinsik Alttipleri





Lehmann et al JCI 2011

Basal-like 1: cell cycle, DNA repair and proliferation genes

Basal-like 2: Growth factor signaling (EGFR, MET, Wnt, IGF1R)

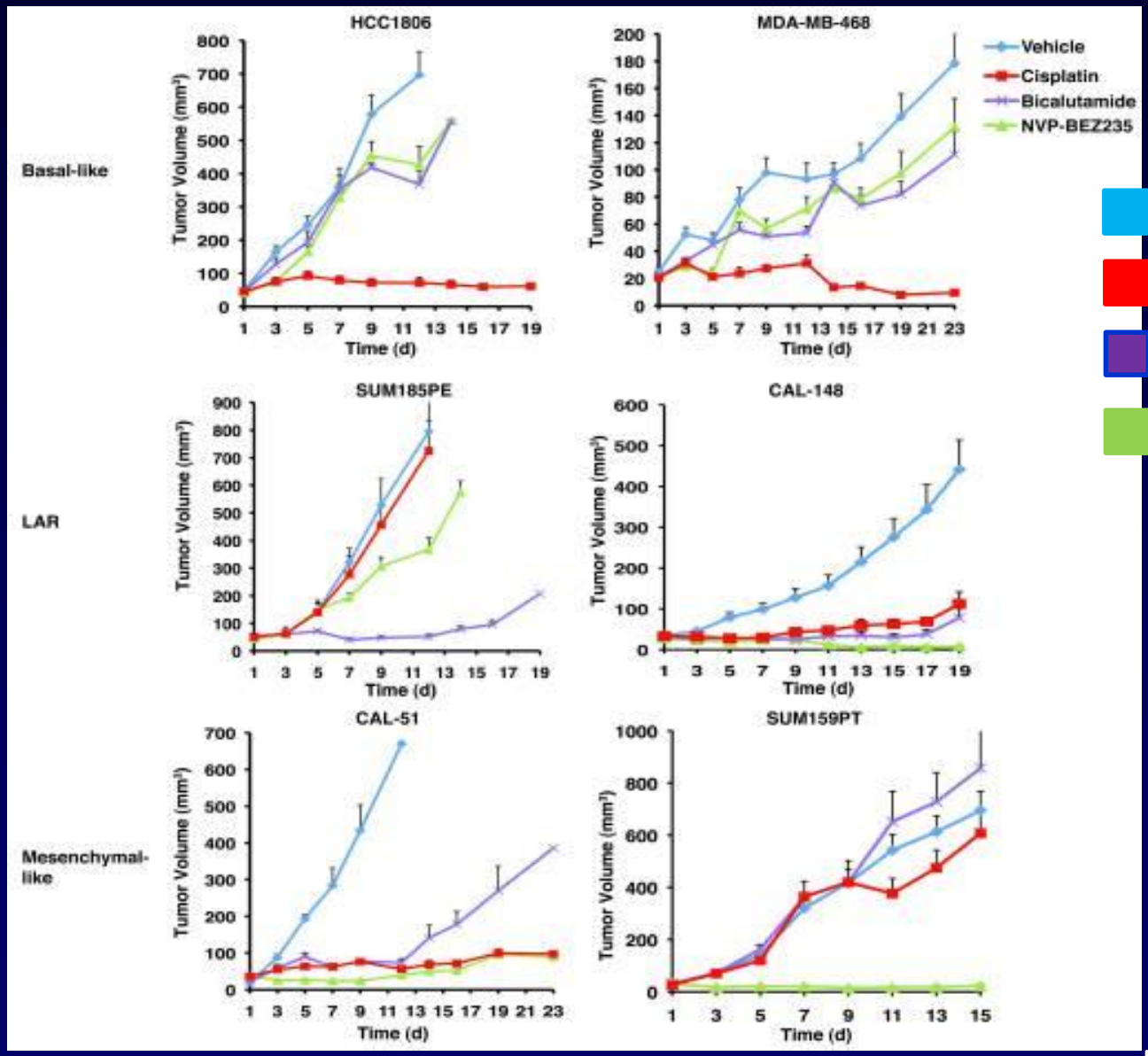
IM: immune cell processes (medullary breast cancer)

M: Cell motility and differentiation, EMT processes

MSL: similar to M but growth factor signaling, low levels of proliferation genes (metaplastic cancers)

LAR: Androgen receptor and downstream genes, luminal features

Sub-types demonstrate differential response to therapies *in vivo*



Vehicle

Cisplatin

Anti-androgen

P13K/mTOR inhibitor

Lehmann et al JCI 2011

Üçlü Negatif Meme Kanseri Altiplerinin Sağkalım Analizleri

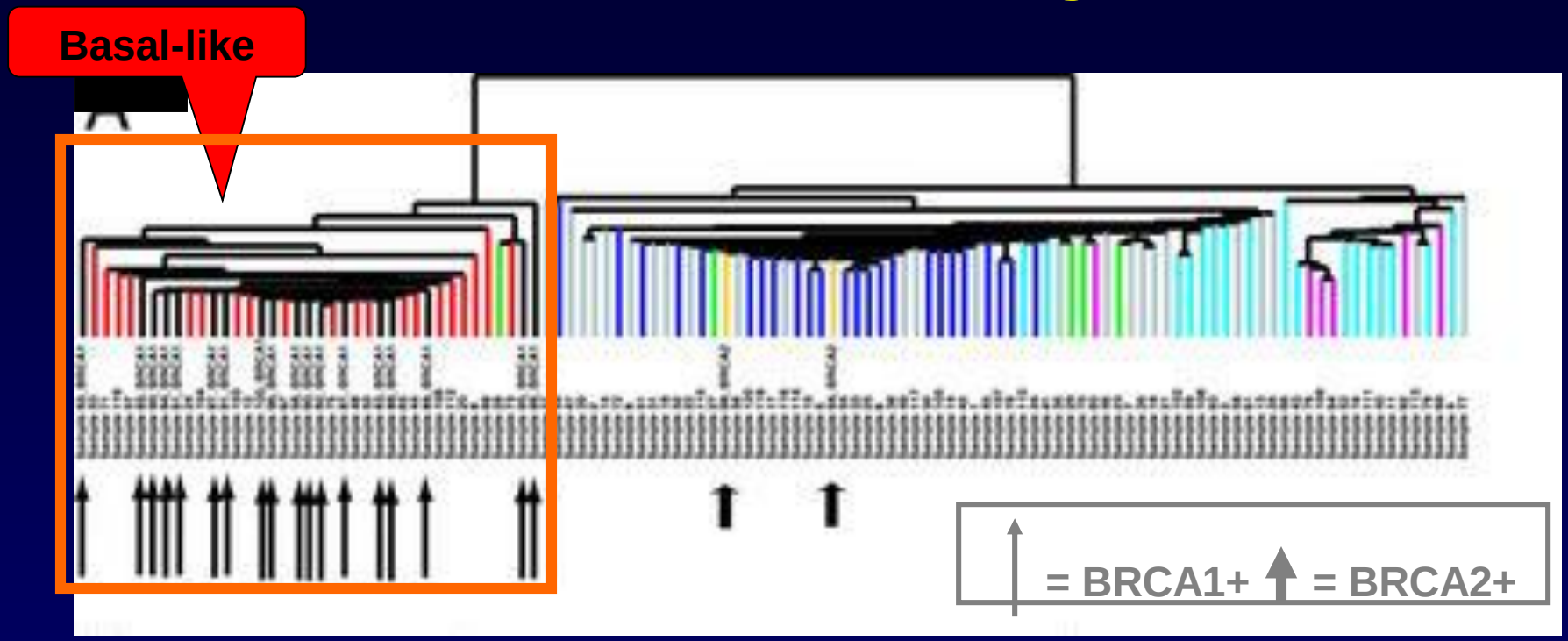
Table 1. TNBC subtyping predictions for TCGA primary breast tumors

TNBC subtype[a]	# Samples (percentage)	Median DFS (mo)[b]	Median OS (mo)[b]
BL1	27 (17%)	20.1	21.1
BL2	12 (7%)	12.5	8.4
IM	30 (18%)	22.7	24.8
M	39 (24%)	9.1	9.5
MSL	10 (6%)	13.9	20.9
LAR	14 (9%)	4.4	5.7
UNC	31 (19%)	22.0	24.9
All TNBC	163 (100%)	11.8	15.2

Alttip	pCR
BL1	%52
BL2	%0
LAR	%10
MSL	% 23

Lehmann 2011, JCI

Basal Hücre Benzeri Meme Kanseri ve BRCA1 Mutasyonu

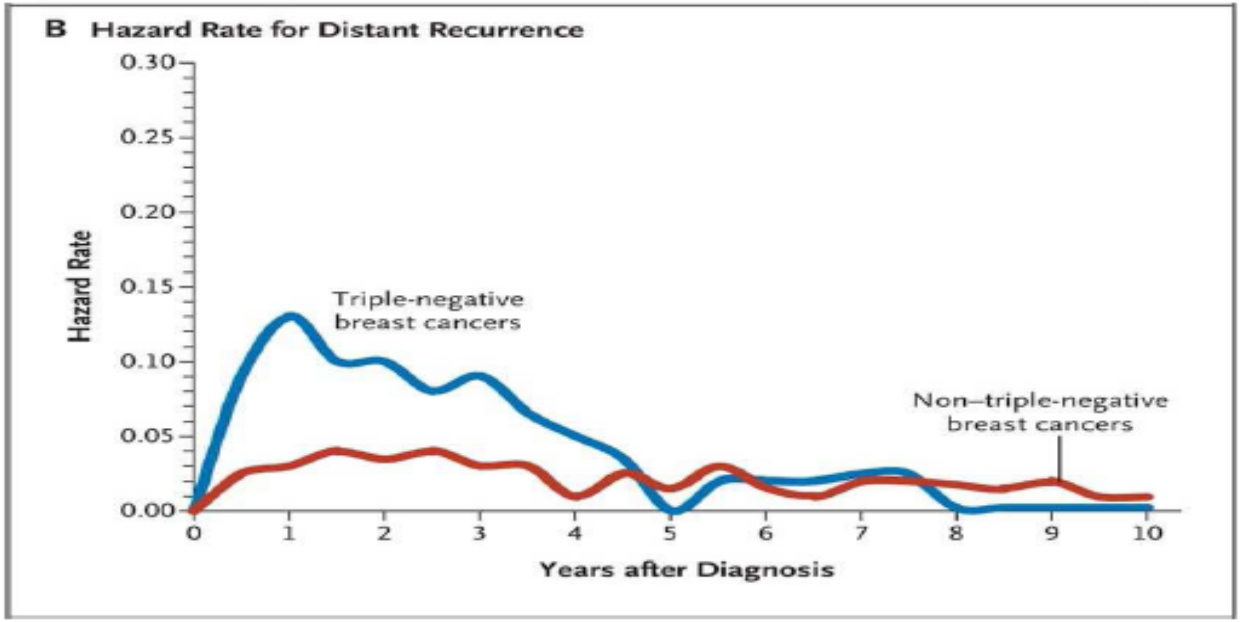


- BRCA1 mutasyonu gösteren kanserlerin çoğu basal-like ve ÜNMK
- BLBC lerinin bir kısmında BRCA1 mutasyonu var. Diğer BLBC de mutasyon olmaksızın BRCA1 gen promoter bölgelerinde metilasyon → İnaktif BRCA1

Sorlie T et al. PNAS 2003

Üçlü-Negatif ve Diğer Meme Kanserlerinde Uzak Metastaz Oranları

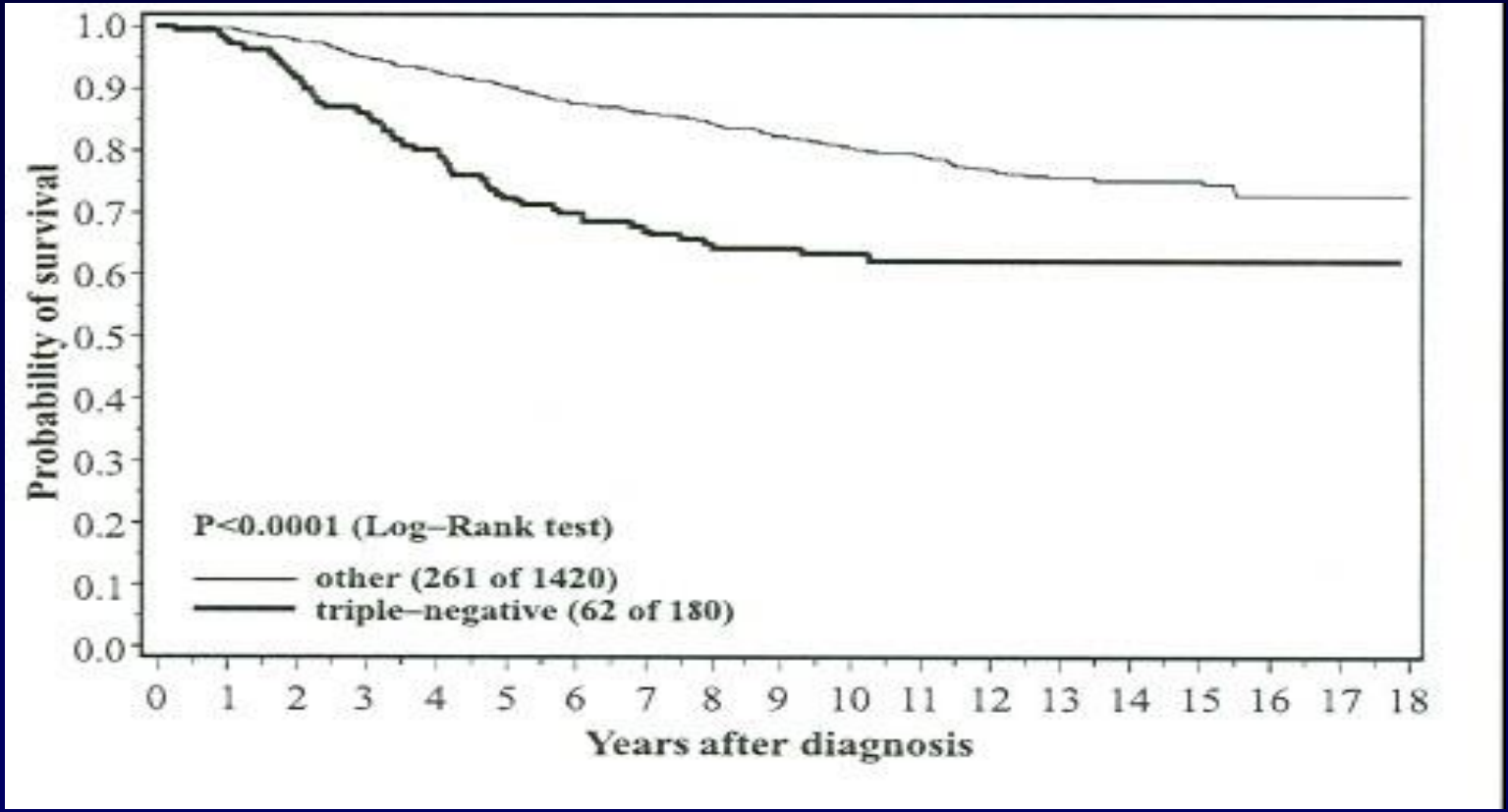
Early risk of recurrence



Foulkes WD et al. N Engl J Med 2010;363:1938-1948

The NEW ENGLAND JOURNAL of MEDICINE

Meme Kanseri Spesifik Sağkalım
ÜN vs Non-ÜN



Dent R, et al. Clin Cancer Res 2007;13: 4429-4434

Üçlü Negatif Meme Kanseri

- **Doğal Seyir**
  - Tarama mamografilerinde atlanabiliyor (İnterval kanserler)
  - Tümör boyutu ile nodal durum arasında ilişki zayıf
  - Tanı sonrası rekürrens riski yüksek
    - Özellikle ilk 1-3 yılda
    - Artmış viseral ve beyin metastazı riski
  - Uzak metastaz sonrası ölüm riski yüksek

Dent R, et al. Clin Cancer Res 2007; Hines S, et al. Annals Oncol 2008; Liedtke C, et al. J Clin Oncol 2008

Üçlü Negatif Meme Kanserleri

- Yüksek gradeli-agresif tümörler ve uzak metastaz riski çok fazla

- Kötü prognoz multi-faktoryel
  - Kemo-direnç (Ancak üçte biri kemoterapiye duyarlı)
  - Moleküler hedefe yönelik standard tedavi yok

Treatment Considerations

- Currently cytotoxic-based
  - Anthracyclines
  - Taxanes
  - DNA-damaging agents
  - Anti-metabolites
  - Other
- Single agents or in combination
- More sensitive to cytotoxics compared to ER+ tumors, however, inferior survival outcomes

Therapeutic Targets

- DNA damaging agents
- Tyrosine kinase inhibitors
- Anti-angiogenic agents
- Androgen receptor antagonists
- Epigenetic modulators
- Mesenchymal stem like
- Immune modulation

Altgruplara Göre Neoadjuvan Tedavilerle Elde Edilen pCR Oranları

Rejim Altgrup	T-FAC[1] (N=82)	AC-T[2] (n=107)
Luminal A/B	2/30 (%7)	4/62 (%7)
Normal	0/10 (0)	NA
HER2+/ER-	9/20 (%45)	4/11 (%36)
Bazal hücre benzeri	10/22 (%45)	9/34 (%26)
	P<0.001	P=0.003

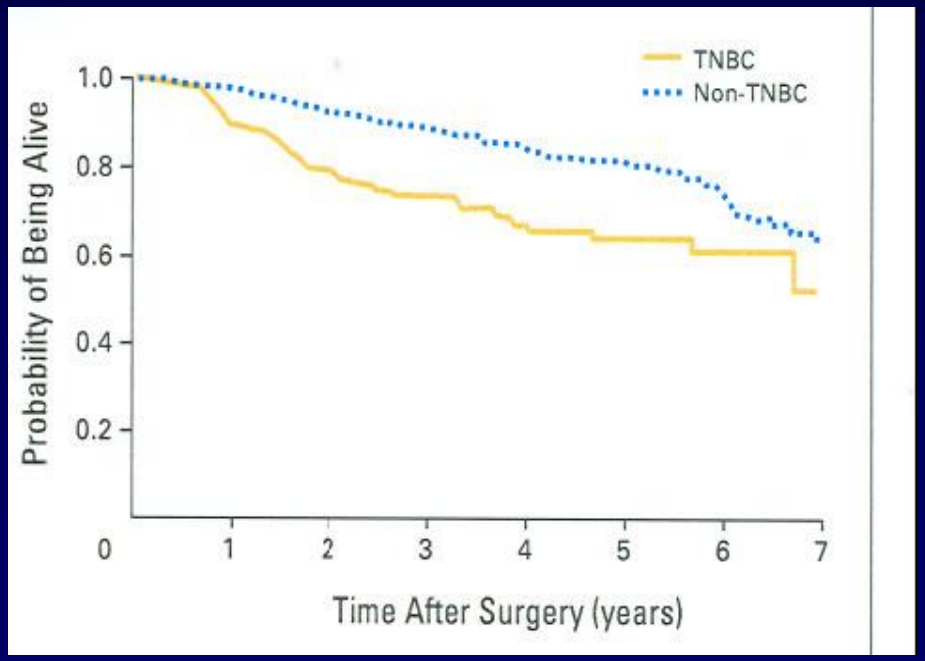
1 Rouzier et al, Clin Cancer Res 2005;
2 Carey LA et al, SABCS 2004

ÜN vs Non-ÜN Meme Kanseri ve Neo-adjuvant Kemoterapiye Cevap

- 1118 hasta- T-FAC neo-adjuvan kemoterapi rejimi almış
  - 255 (%23) ÜN
    - pCR = % 22
  - 863 (%77) non-ÜN
    - pCR = % 11

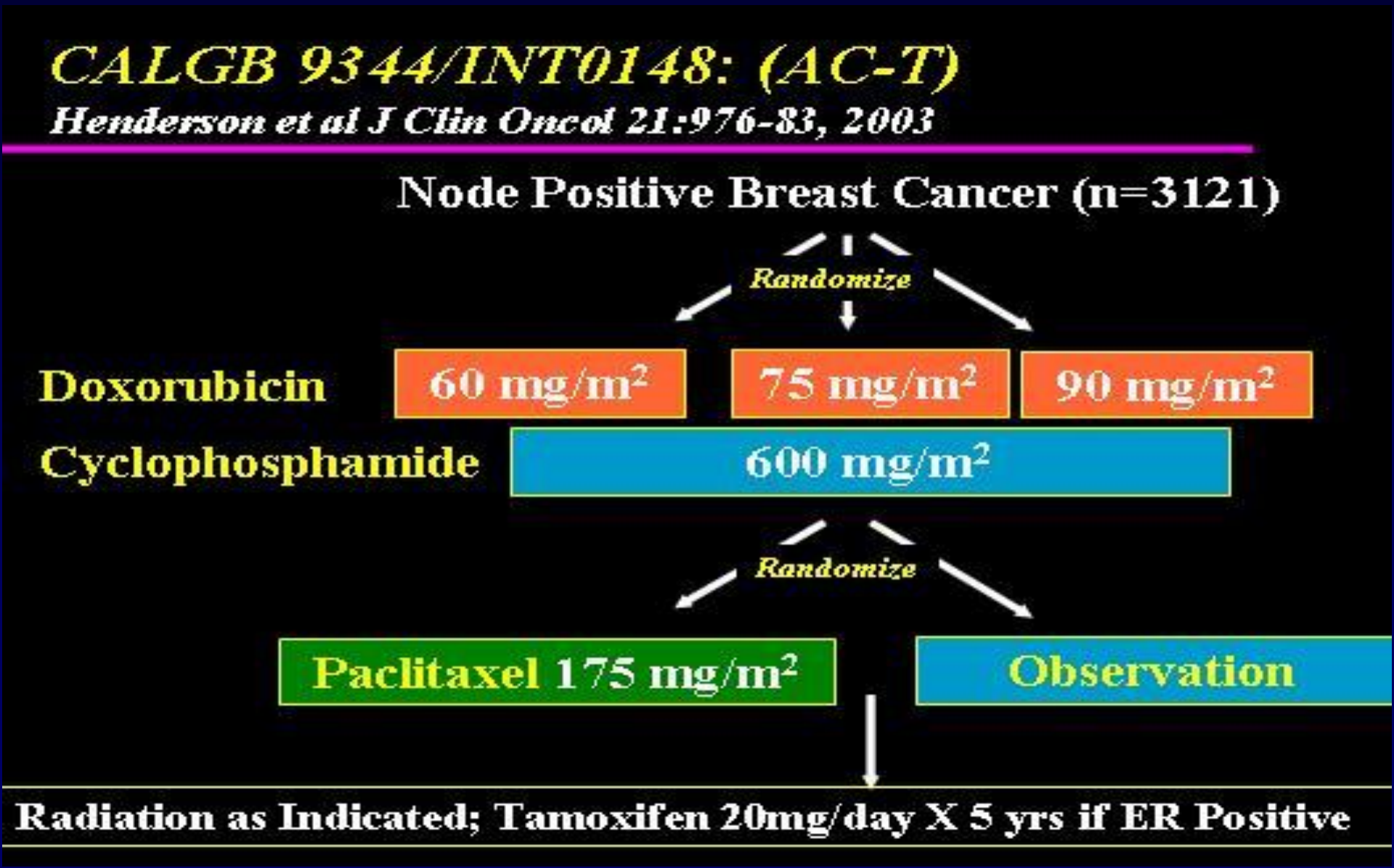
•Paradox…çok iyi cevap ama daha kötü sağkalım?

Genel Sağkalım



Liedtke C, et al. J Clin Oncol 2008;26:1275-1281

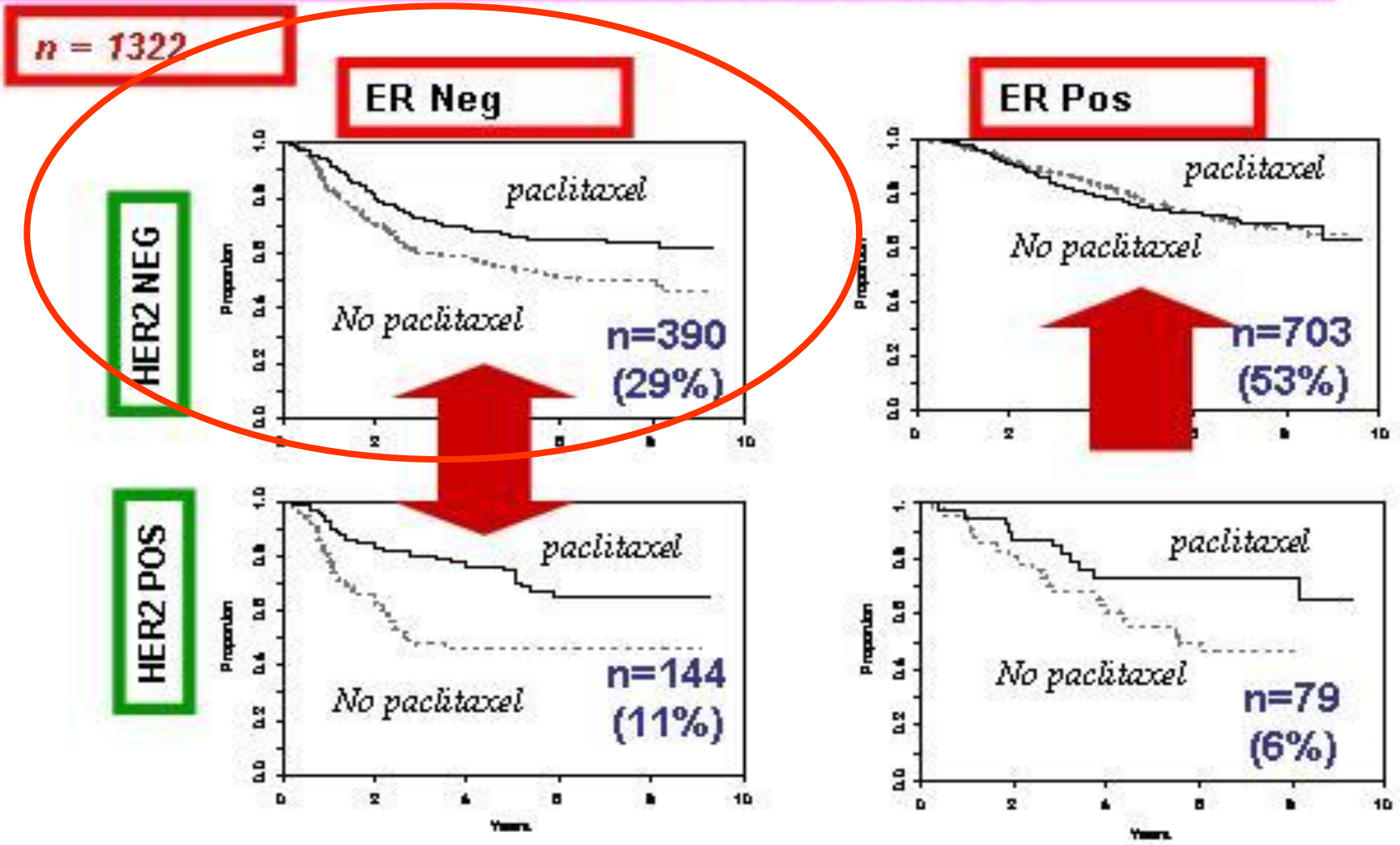
CALGB 9344 Adjuvan AC ve Paklitaksel çalışması



HER2 is Predictive of Paclitaxel Benefit By Estrogen Receptor

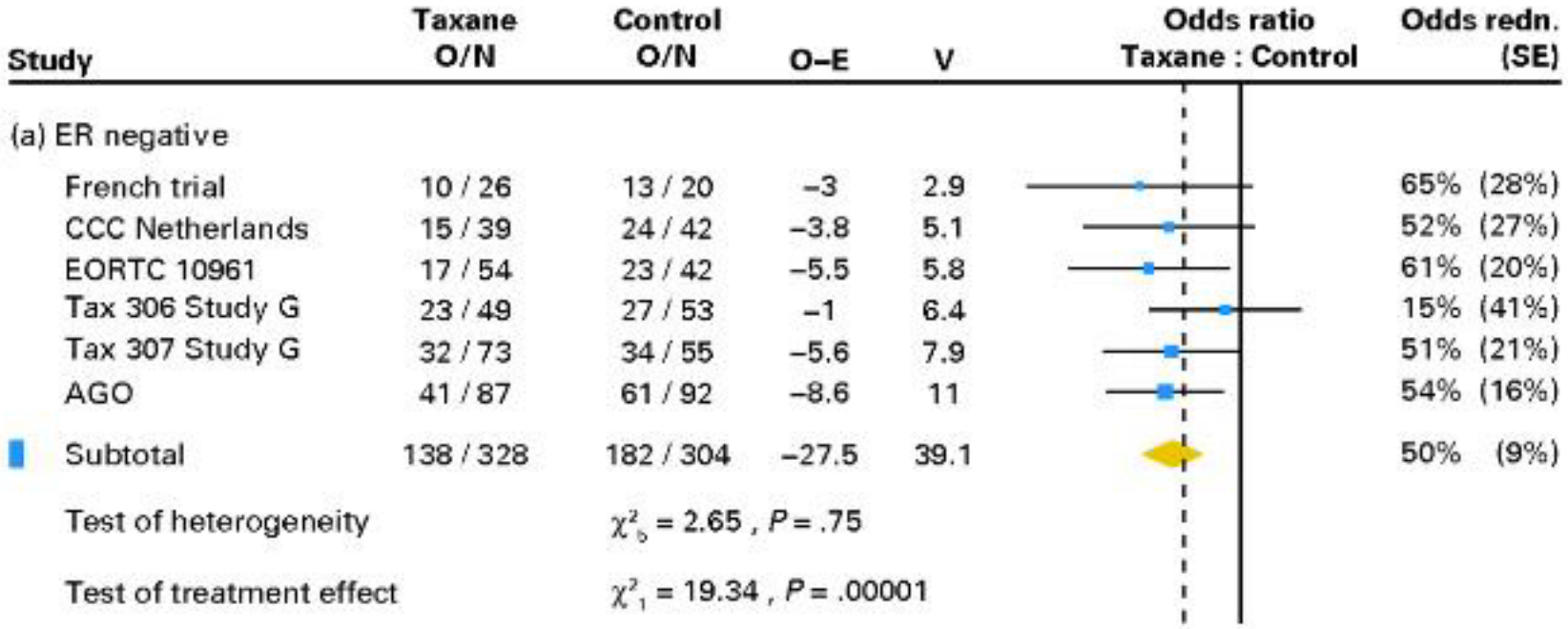
Disease Free Survival

n = 1322



Hayes et al. ASCO 2006

Is TNBC Taxane-Resistant?



Study	Taxane O/N	Control O/N	O–E	V	Odds ratio Taxane : Control	Odds redn. (SE)
(a) ER negative						
French trial	10 / 26	13 / 20	–3	2.9		65% (28%)
CCC Netherlands	15 / 39	24 / 42	–3.8	5.1		52% (27%)
EORTC 10961	17 / 54	23 / 42	–5.5	5.8		61% (20%)
Tax 306 Study G	23 / 49	27 / 53	–1	6.4		15% (41%)
Tax 307 Study G	32 / 73	34 / 55	–5.6	7.9		51% (21%)
AGO	41 / 87	61 / 92	–8.6	11		54% (16%)
Subtotal	138 / 328	182 / 304	–27.5	39.1		50% (9%)
Test of heterogeneity		$\chi^2_5 = 2.65$, $P = .75$				
Test of treatment effect		$\chi^2_1 = 19.34$, $P = .00001$				

- Meta-analysis, stage IV, first-line trials
- Taxane-based vs anthracycline-based
- Results: Taxane better, ER-negative ~ ER-positive
  - HER2 not evaluated, but bias likely in other direction

Piccart-Gebhart et al, JCO 2008

Later Lines of Therapy?

A Phase III, Open-Label, Randomized, Multicenter Study Of Eribulin Mesylate Versus Capecitabine In Patients With Locally Advanced Or Metastatic Breast Cancer Previously Treated With Anthracyclines And Taxanes

Patients (N=1102)

Locally advanced or MBC

- ≤3 prior chemotherapy regimens (≤2 for advanced disease)
- Prior anthracycline and taxane in (neo)adjuvant setting or for locally advanced or MBC

Randomization 1:1

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

Capecitabine
1250 mg/m^2 BID orally
Days 1-14, q21 days

Co-primary endpoint

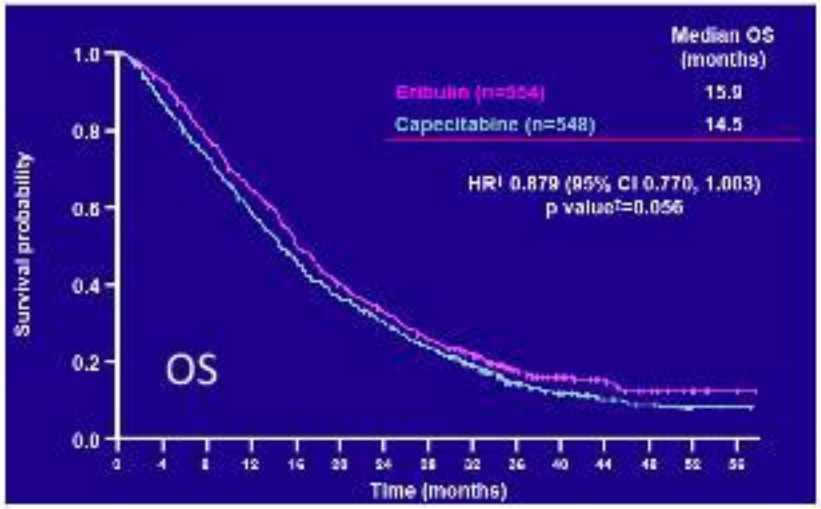
- OS and PFS

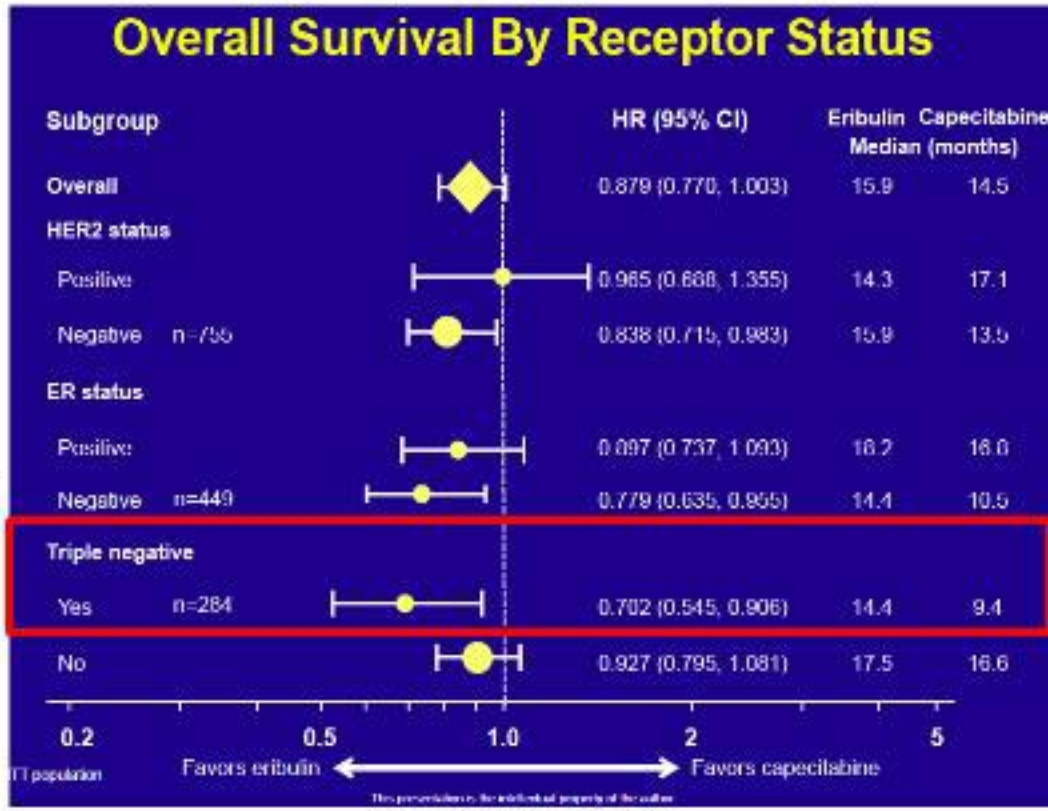
Secondary endpoints

- Quality of life
- ORR
- Duration of response
- 1-, 2- and 3-year survival
- Tumor-related symptom assessments
- Safety parameters
- Population PK (eribulin arm only)

Kaufmann P et al, SABCS 2012

Eribulin Vs. Capecitabine



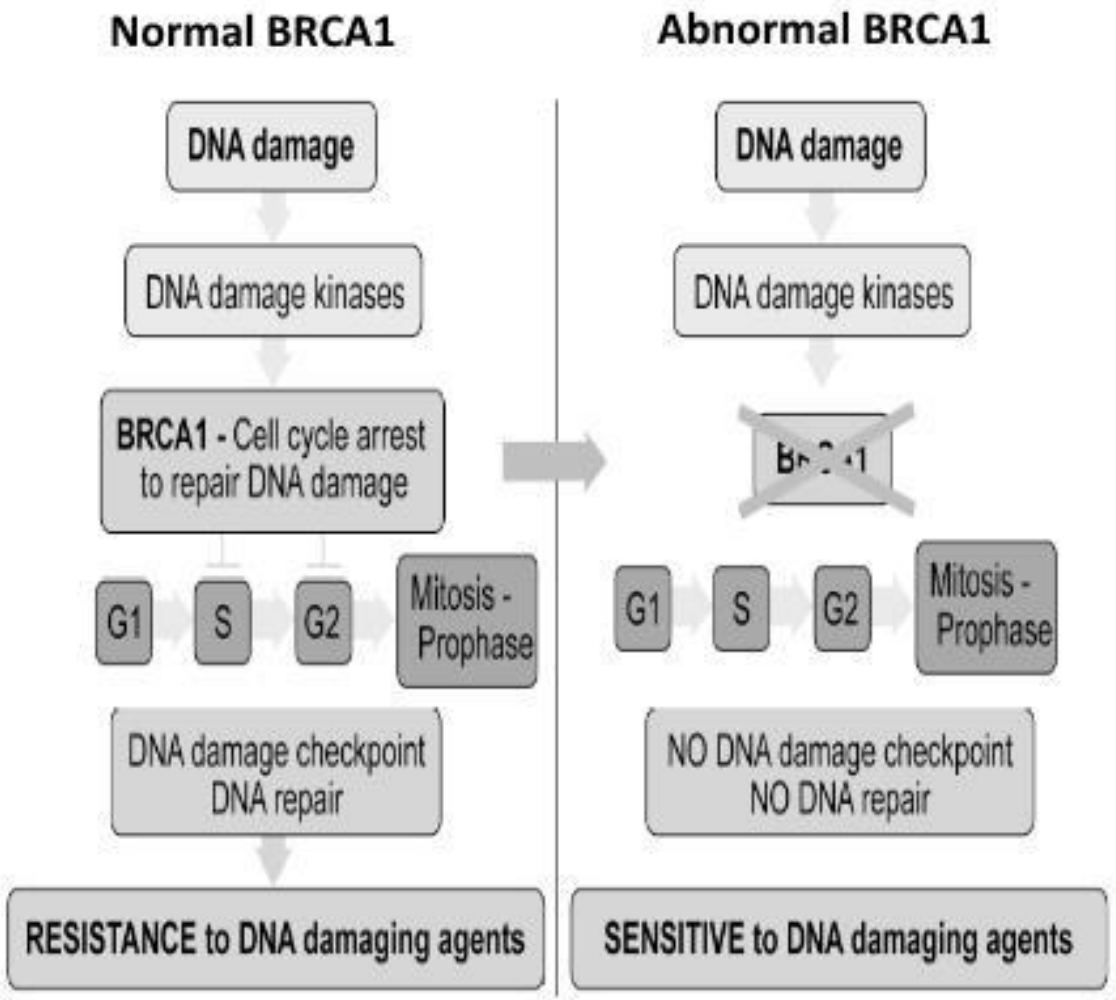


- Eribulin = capecitabine in 2nd+ line therapy
- Very different toxicity profiles:
  - Eribulin: neutropenia, alopecia, neuropathy
  - Capecitabine: HFS, diarrhea

Kaufmann P et al, SABCS 2012

“BRCAness” = Characteristic of BRCA+

- High grade
- ER- and HER2-negative
- C-myc amplified
- Medullary
- Pushing margins
- DCIS less common
- Lymphocytic infiltrate
- TP53 mutations
- Basal phenotype
- EGFR expression
- X-chromosome inactivation pattern
- Sensitivity to DNA damage
- Aneuploidy



Platinum Responsiveness in TNBC (Neoadjuvant)

Trial	Type	n	Drugs	Population	pCR
DFCI1	Single arm Ph 2	21	CDDP x 4	TNBC	21%
DFCI2	Single arm Ph 2	51	CDDP+bev	TNBC	15%
Polish	Retrospective	13	CDDP x 4	BRCA+	83%
GEICAM	Randomized Ph 2	94	EC-D EC-D+carbo	Basal-like (IHC)	30% 30%
GeparSixto	Randomized Ph 3	165	PM/bev PMCb/bev	TNBC (subset)	38% 59%
PreCOG0105	Single arm Ph 2	80	G/Carbo/iniparib	TNBC	36%
CALGB 40603	Randomized Ph 2	455	T-AC(bev) T/carbo-AC(bev)	TNBC	?? ??

Silver et al, JCO'12; Ryan et al, ASCO'09; Byrski et al, JCO'10; Alba et al, BCRT'12; von Minckwitz et al, ASCO'13 ; Telli et al, ASCO'13; Sikov et al, SABCS'13

GeparSixto Trial: Chemotherapy regimen

N=595

centrally confirmed TNBC or Her2-positive breast cancer

R

PM

PMCb

Surgery

Paclitaxel 80 mg/m² q1w

Non-pegylated liposomal doxorubicin 20 mg/m² q1w

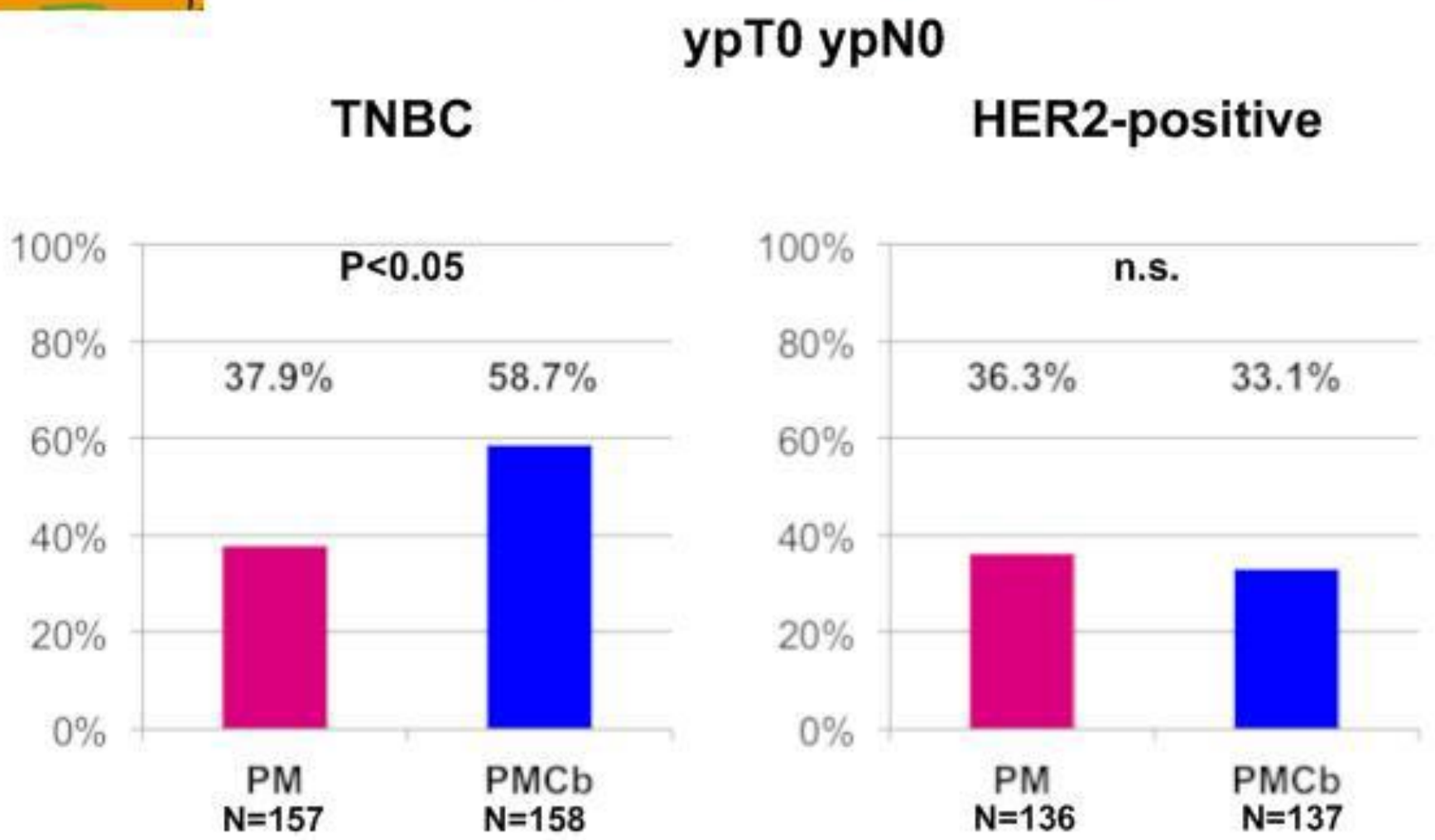
Carboplatin AUC 1.5* q1w

*reduced from AUC 2 at amendment 1 after enrolment of 330 patients

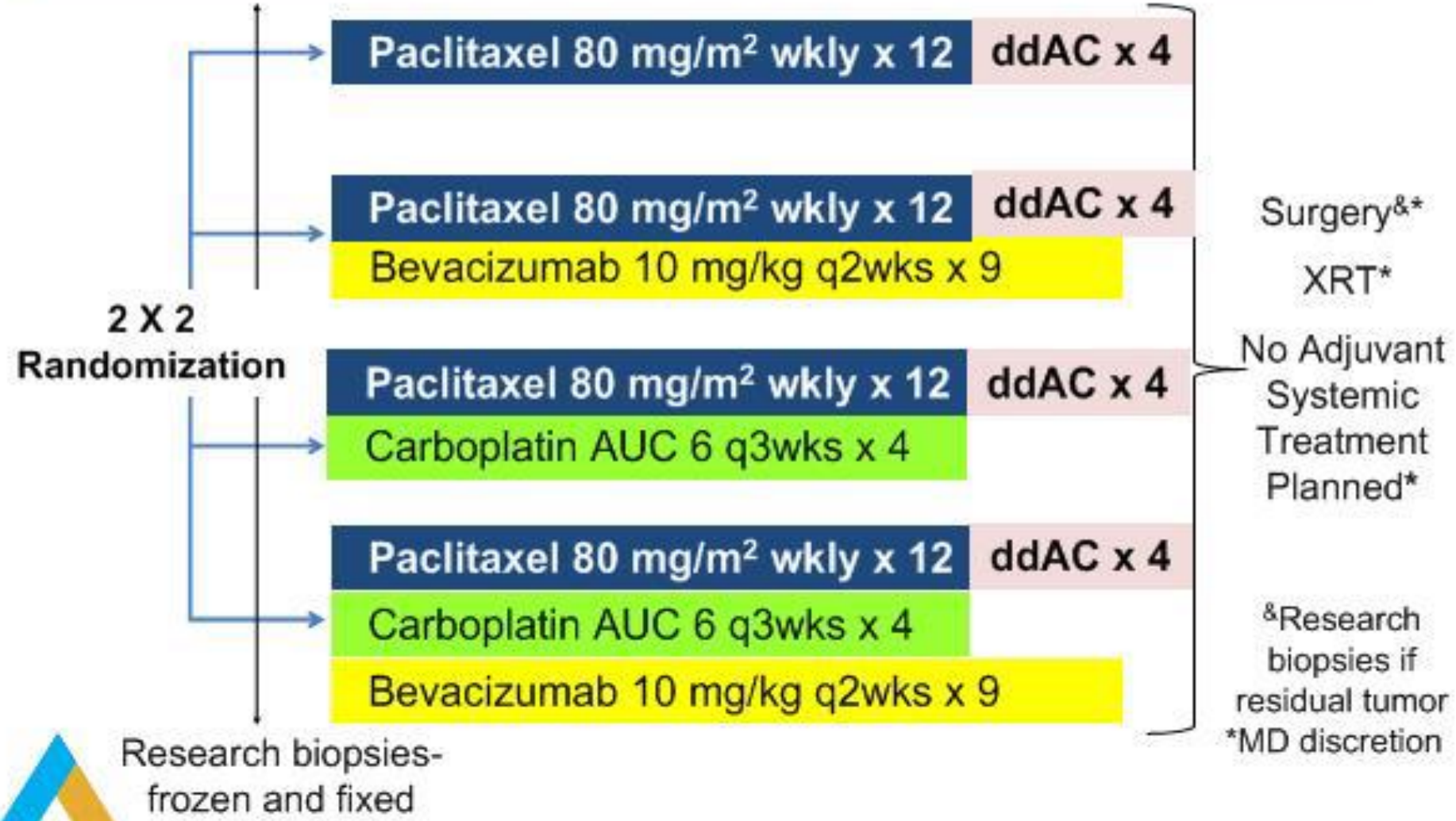
AGO-B BREAST STUDY GROUP

GBG GERMAN BREAST GROUP

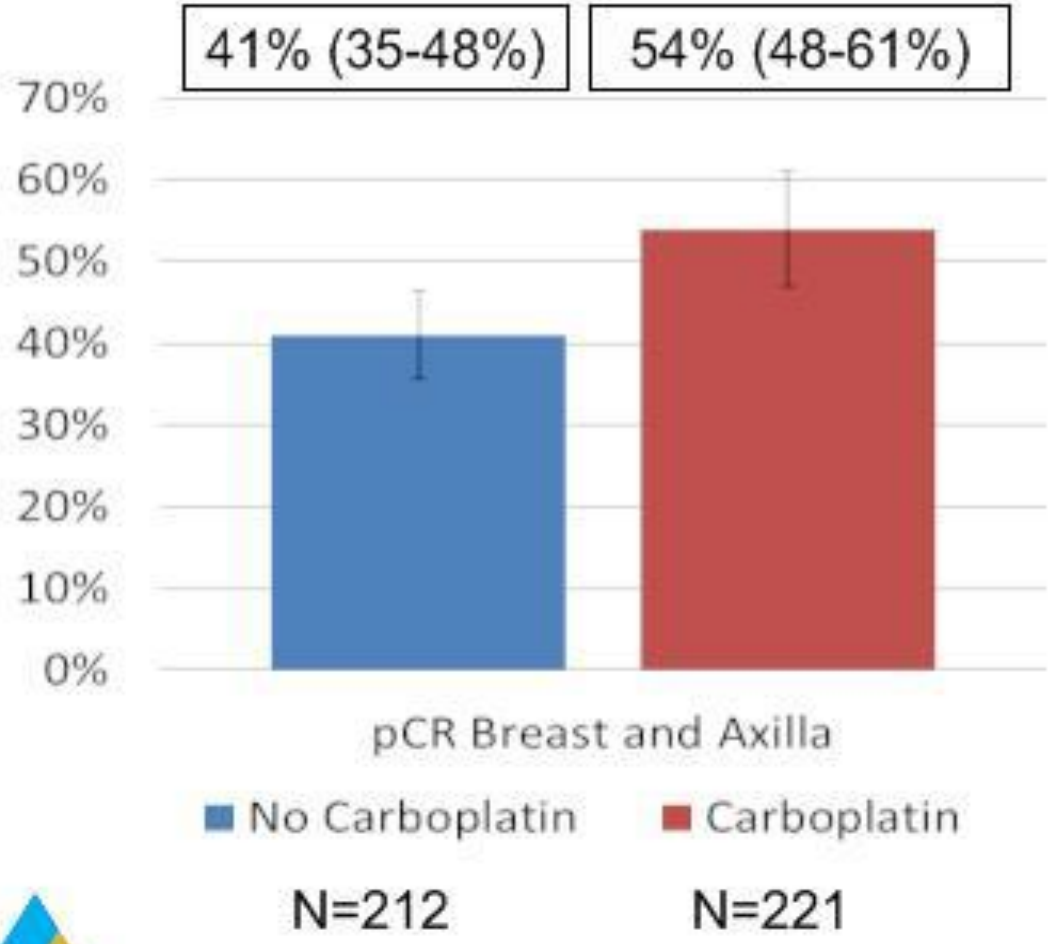
pCR Rates by Subtype



CALGB 40603: Schema – Randomized Phase II



pCR Breast/Axilla (ypT0/is N0) + / - Carboplatin



Odds ratio: 1.71
p = 0.0029

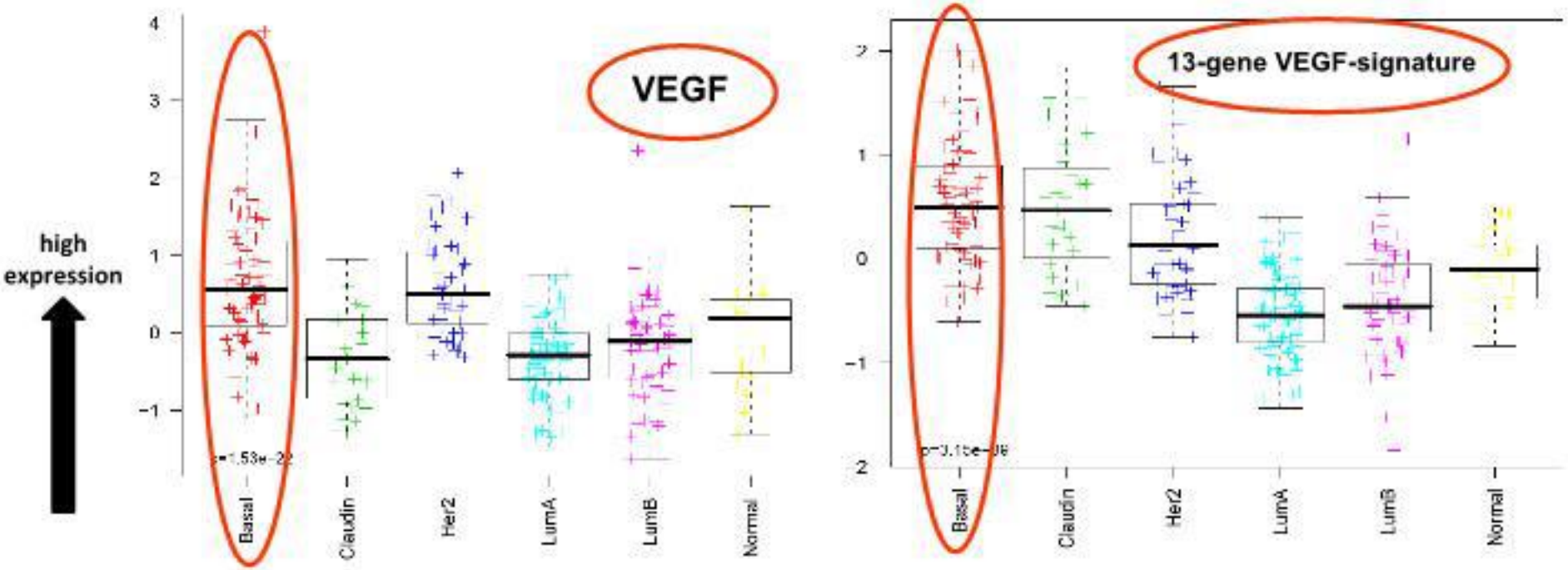
Tailoring Chemotherapy

- Insufficient evidence that subtype matters.
- Polydrug regimens for symptomatic, rapid progression.
- Palliative, choose by efficacy/toxicity/preference.
  - Taxanes, anthracyclines
  - Eribulin, capecitabine, platinums
  - Gemcitabine, vinorelbine, others

Anjiogenez İnhibitörleri

Rationale for Antiangiogenic Drugs in TNBC

Preclinical data suggests that TNBC may be particularly susceptible to antiangiogenic approaches …



Hu et al, BMC Medicine 2009

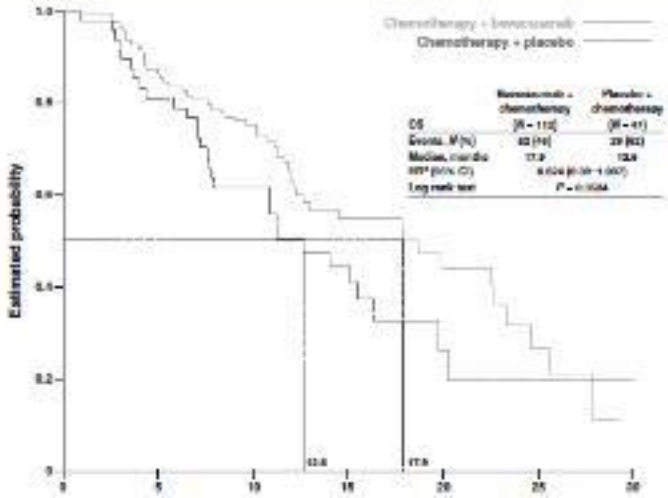
Bevacizumab in Triple Negative: Stage IV Setting

First-line randomized phase III trials:

Stage IV Trial	Regimen	DFS HR (95% CI)
ECOG 2100	Weekly paclitaxel ± bevacizumab	0.53 (0.41-0.70)
AVADO	Docetaxel ± bevacizumab	0.68 (NR~1.00)
RIBBON-1	Chemotherapy ± bevacizumab	0.72 (0.49-1.06
However....		OS HR (95% CI)
Meta-analysis 3 first-line studies chemo ± bevacizumab		0.96 (0.79-1.16)

RIBBON-2 randomized phase III trial, pretreated:

TNBC subset	HR (95% CI)
chemo ± bevacizumab	PFS 0.494 (0.33–0.74)
* exploratory	OS 0.624 (0.39–1.007)



O'Shaughnessy J et al, ASCO 2011; Brufsky BCRT 2012

Bevacizumab and Response in HER2-Negative

Trial	Regimen	RR Bev arm	RR placebo
Initial Ph 3	Capecitabine ± B	20%*	9%
E2100	Paclitaxel ± B	37%*	21%
AVADO	Docetaxel ± B	64%*	46%
RIBBON-1	Chemotherapy ± B	35%*	24%
RIBBON-2 (TNBC subset)	Chemotherapy ± B	41%*	18%

*statistically significant

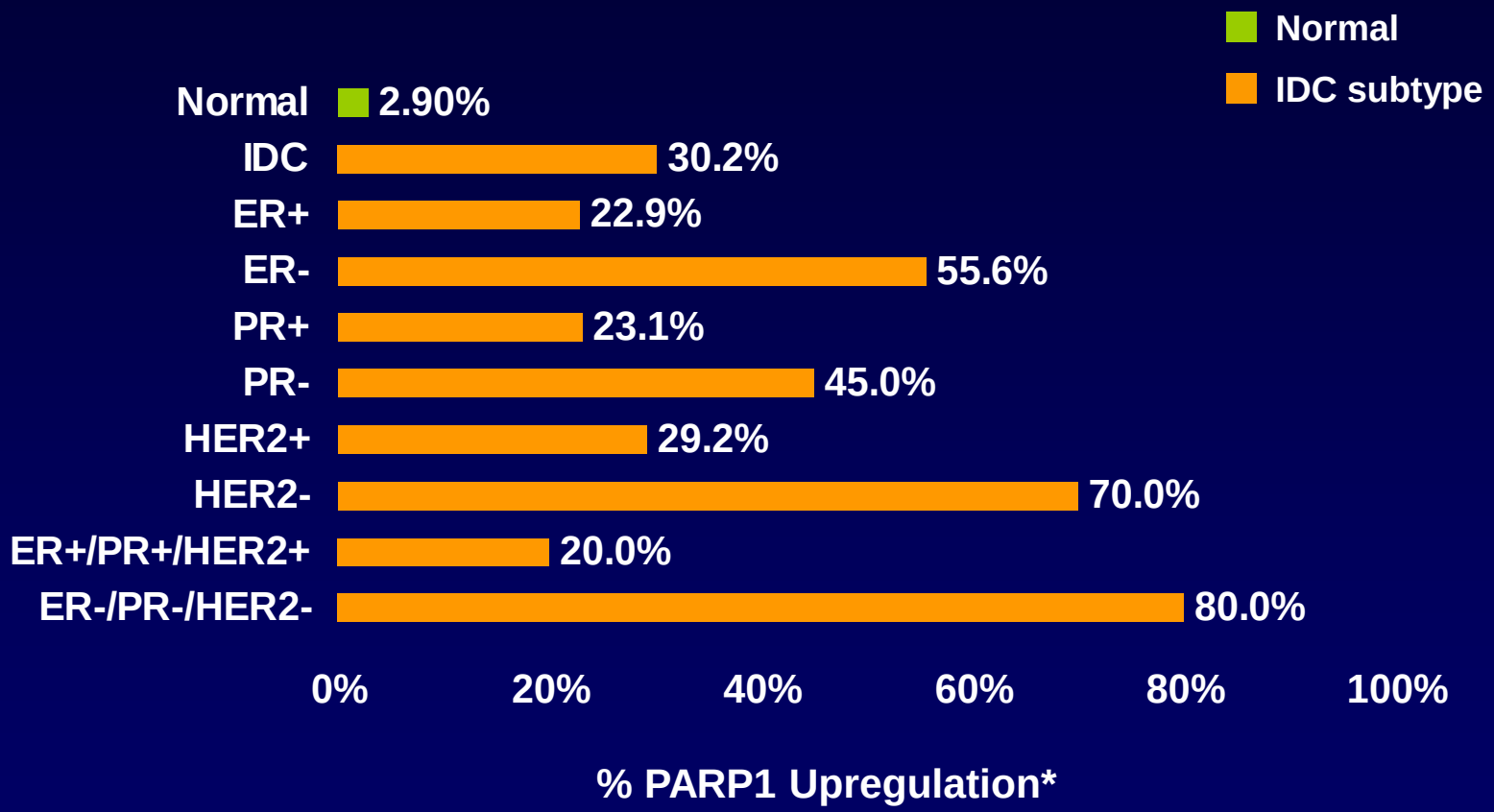
Miller et al, JCO'05; Miller et al, NEJM'07; Miles et al, JCO'10; Robert et al, JCO'11 Brufsky et al, BCRT'12

Bevacizumab

- Antiangiogenic strategies outside of bevacizumab are a work in progress – participate in clinical trials!
- Bevacizumab has unusual activity profile
  - Augments PFS but has zero impact on OS
  - Augments response added to chemotherapy
- Where response is the endpoint, adding bevacizumab (where available) is an option
  - (as is polychemotherapy)
-

Poly (ADP-Ribose) Polimeraz (PARP) İnhibitörleri

PARP1 Upregulation in Breast Cancer IDC Subtypes



* Defined by percentage of samples exceeding the 95% UCL of normal tissue distribution.

O'Shaughnessy J. TNBC 101 Research To Practice Webinar, 2010.

A Randomized Phase III Study of Iniparib (BSI-201) in Combination with Gemcitabine and Carboplatin in Metastatic Triple Negative Breast Cancer (mTNBC)

Joyce O'Shaughnessy,[1,2,3] Lee Schwartzberg[4,5] Michael A. Danso,[3,6] Hope Rugo,[7] Kathy Miller,[8] Denise Yardley,[9,10] Robert W. Carlson,[11] Richard Finn,[12] Eric Charpentier,[13] Sunil Gupta,[13] Monica Freese,[13] Anne Blackwood-Chirchir,[14] and Eric P. Winer[15]

Schema

Study Design: Multi-center, randomized open-label Phase III Trial

N = 519

Study Population:

- Stage IV TNBC
- ECOG PS 0–1
- Stable CNS metastases allowed
- 0-2 prior chemotherapies for mTNBC

- **Randomization stratified by prior chemo in the metastatic setting:**
  - **1st-line (no prior therapy)**
  - **2nd/3rd-line (1-2 prior therapies)**

R

Gem/Carbo (GC)
(N= 258)

Gemcitabine 1000 mg/m^2 IV d 1, 8
Carboplatin AUC2 IV d 1, 8

21-day cycles

Crossover allowed to GCI following Disease Progression*
(central review)

Gem/Carbo + Iniparib (GCI)
(N= 261)

Gemcitabine - 1000 mg/m2 IV d 1, 8
Carboplatin - AUC2 IV d 1, 8
Iniparib - 5.6 mg/kg IV d 1,4,8,11

21-day cycles

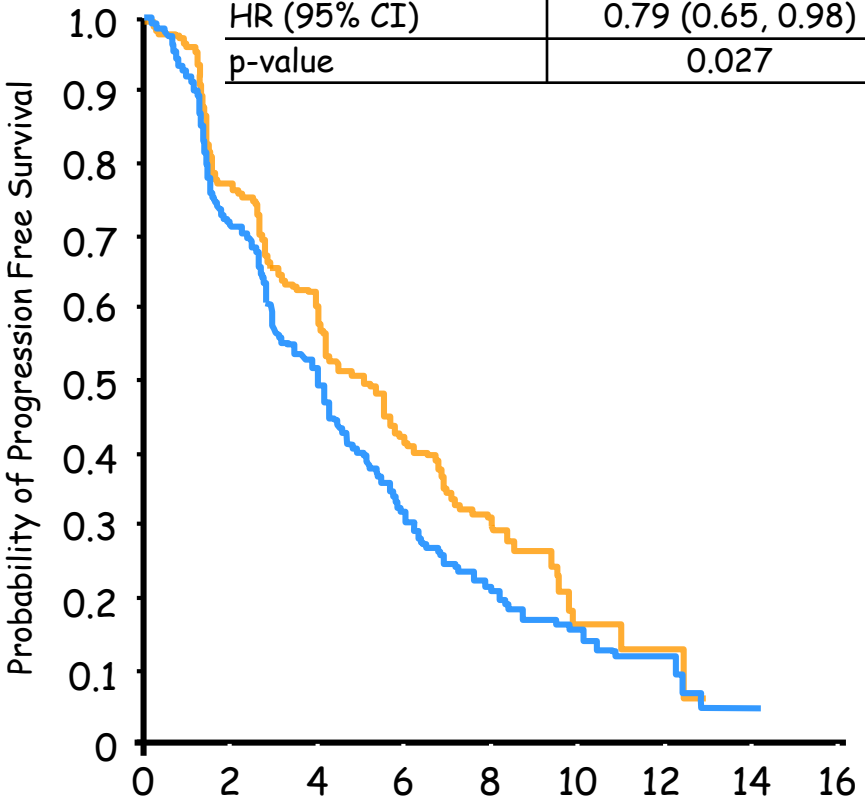
*Prospective central radiology review of progression required prior to crossover

96% (n=152) of progressing patients crossed over to GCI at time of primary analysis

NCT00938652

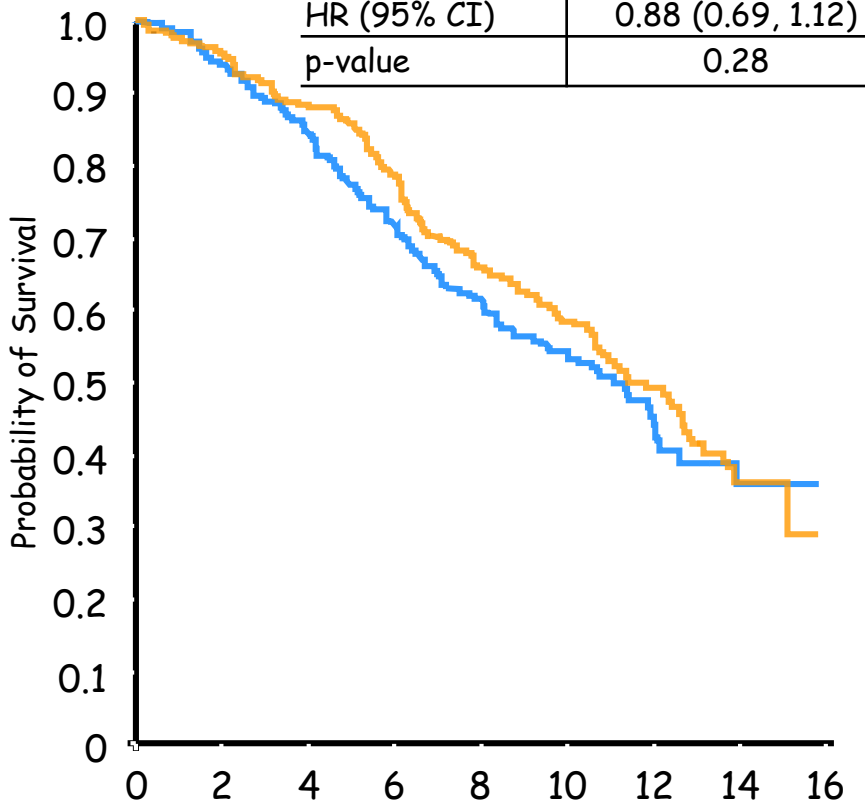
Iniparib does not improve outcome in unselected metastatic triple negative breast cancer

PFS	GC (N=258)	GCI (N=261)
Median PFS, mos (95% CI)	4.1 (3.1, 4.6)	5.1 (4.2, 5.8)
HR (95% CI)	0.79 (0.65, 0.98)	
p-value	0.027	



No. at risk									
GC	258	171	116	63	38	18	6	1	0
GCI	261	187	138	83	53	11	2	0	0

OS	GC (N=258)	GCI (N=261)
Median OS, mos (95% CI)	11.1 (9.2, 12.1)	11.8 (10.6, 12.9)
HR (95% CI)	0.88 (0.69, 1.12)	
p-value	0.28	



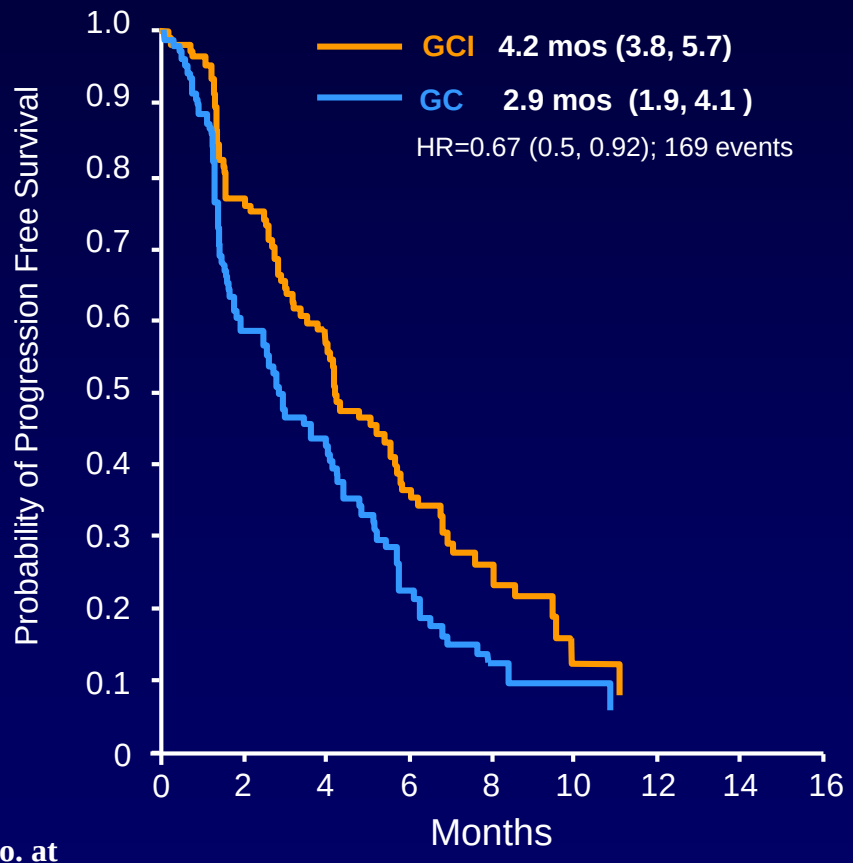
No. at risk									
GC	258	239	214	181	151	99	38	11	0
GCI	261	248	230	204	169	111	52	15	0

O' Shaughnessy PASCO 2011

Exploratory Analysis 2nd /3rd-line ITT Population

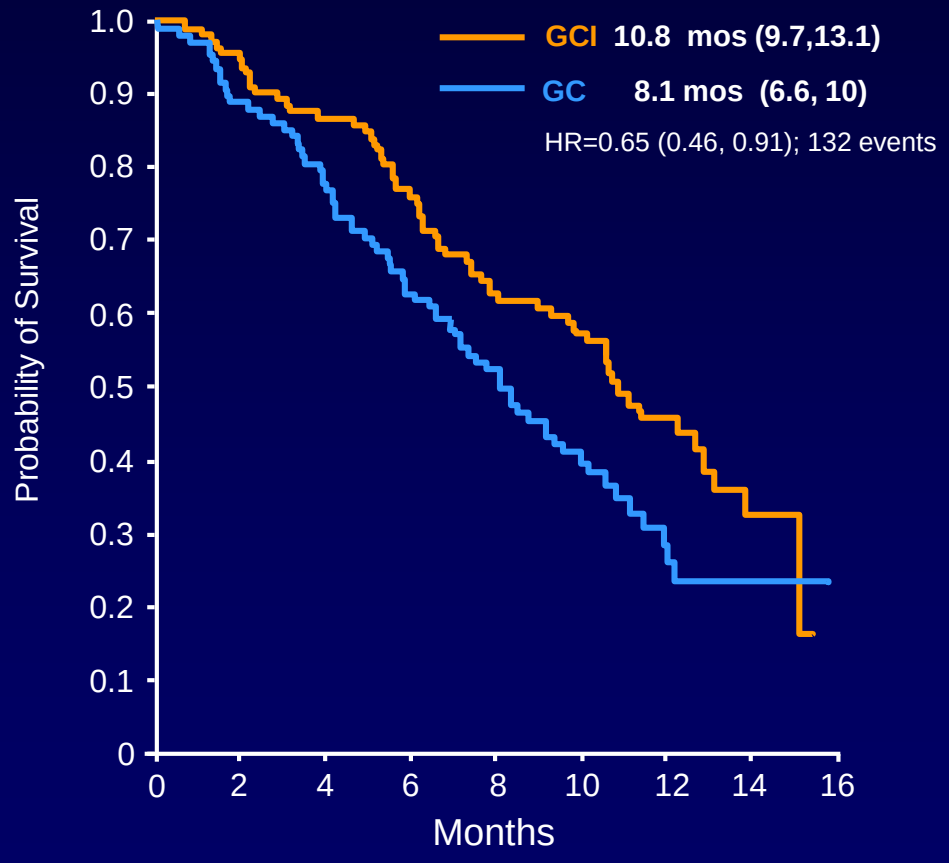
2nd / 3rd -line = 43% patients (222/519)

PFS



No. at risk									
GC	109	61	42	19	9	5	1	0	0
GCI	113	81	59	32	18	4	0	0	0

OS



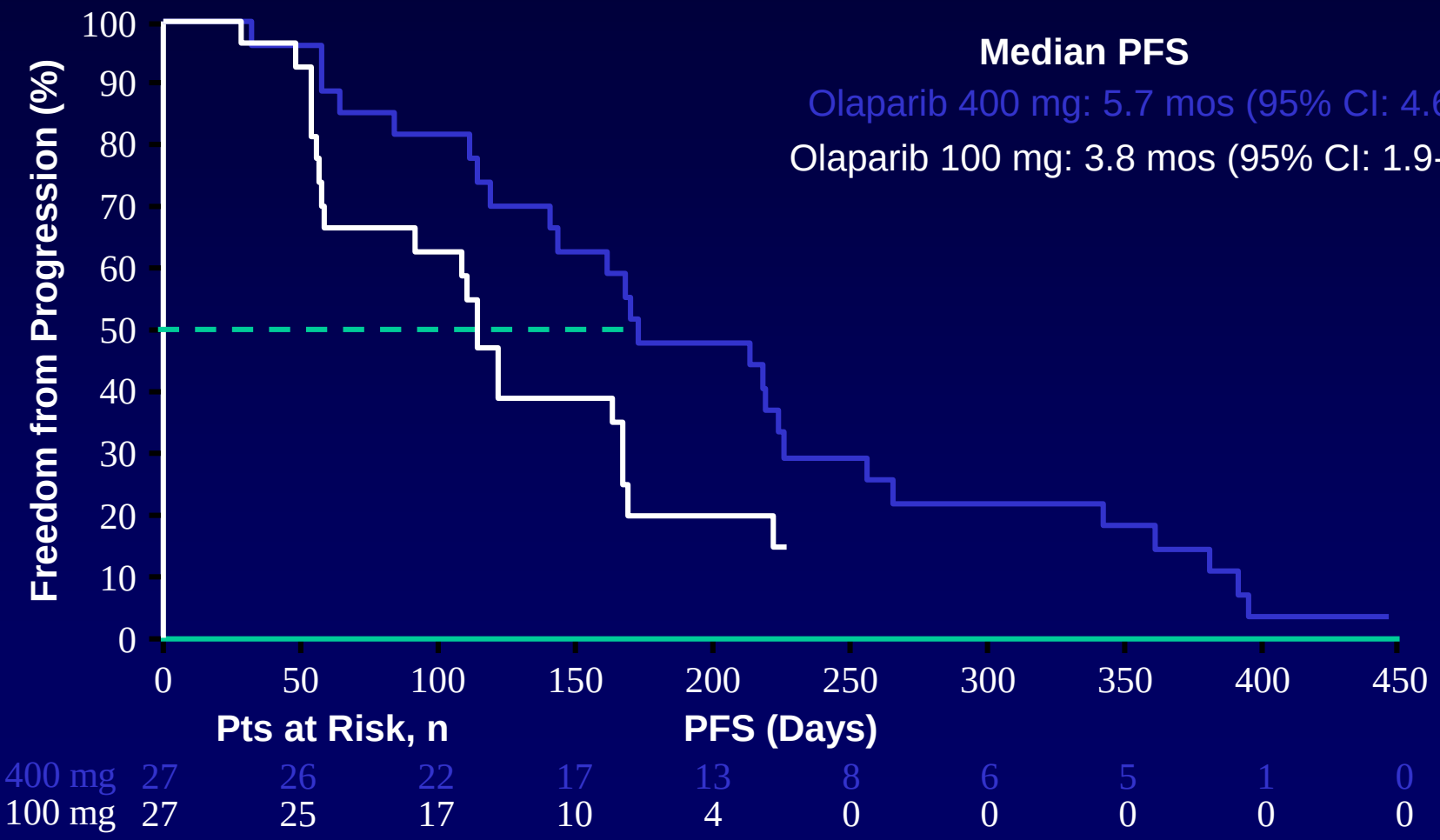
	109	96	84	68	54	29	11	2	0
	113	107	98	86	70	47	24	9	0

Oral Poly(ADP-ribose) Polymerase Inhibitor Olaparib in Patients with BRCA1 or BRCA2 Mutations and Advanced Breast Cancer: A Proof-of-Concept Trial

Tutt A et al.

Lancet 2010;376(9737):235-44.

BRCA-Mutasyonu Gösteren Metastatik Meme Kanserinde Olaparib: PFS

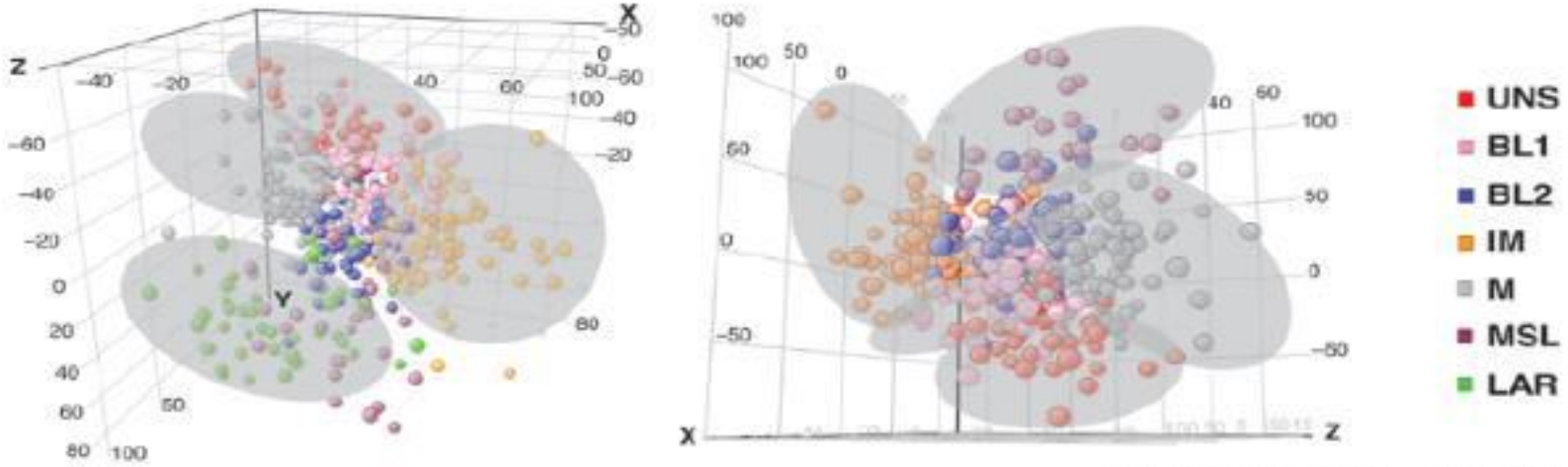


PARP Inhibitors in Development

Agent	Company	Route	Current Trials
Rucaparib	Clovis	IV/Oral	BRCA+, post-neoadjuvant TNBC +cisplatin
Olaparib	AstraZeneca	Oral	BRCA+
Veliparib	Abbott	Oral	BRCA+, TNBC + paclit/carbo
Iniparib BSI-201	BiPar/Sanofi-Aventis	IV	Dose escalation
LT673 (2011)	Biomarin	Oral	-
INO-1001	Inotek	IV	-
MK4827	Merck	Oral	-
CEP-9722	Cephalon	Oral	-
E7016	Eisai	Oral	-

Plummer R *BCR* 2011 vol. 13 (4) pp. 218. with edits

Targeting Heterogeneity of TNBC



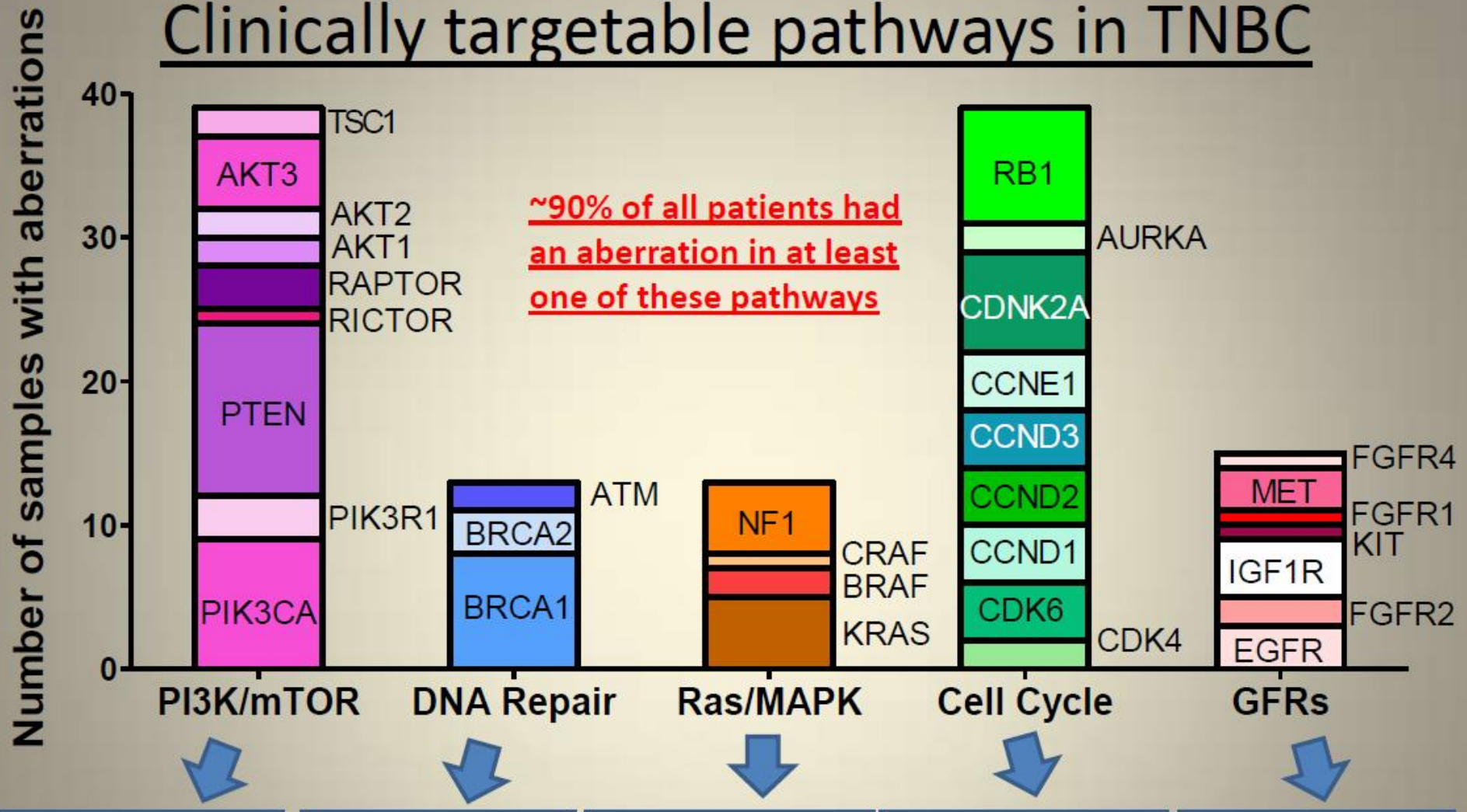
Lehmann et al, JCI 2011

Are they targetable?

- Basal-like 1 and 2 – DNA damage response genes, growth factor paths (EGFR)
- Immunomodulatory - ? Immune approaches
- Mesenchymal and mesenchymal / stem cell – PI3K/mTOR pathway
- LAR – androgen receptor signaling

UNC

Clinically targetable pathways in TNBC



~90% of all patients had an aberration in at least one of these pathways

PI3K/mTOR inhibitors	DNA-repair targeting agents	RAF/MEK inhibitors	Cell cycle/mitotic spindle inhibitors	Targeted RTK inhibitors

Published Guidelines for the Management of ÜNMK

- **NCCN: No specific algorithm**
  - NCCN Guidelines 2010, v.2
- **ESMO: No specific algorithm**
  - Cardoso F et al. *Ann Oncol* 2010;21(Suppl):v15-v19;
  - Aebi S et al. *Ann Oncol* 2010;21(Suppl):v9-v14;
  - Balmana J et al. *Ann Oncol* 2010;21(Suppl):v20-v22.
- **St Gallen: No specific algorithm**
  - Goldhirsch A et al. *Ann Oncol* 2009;20:1319-29.

Summary

What we know:

- **TNBC is heterogeneous**
- **Chemotherapy is mainstay and (at the moment) is the same as for other subtypes.**
  - **First-line taxanes appropriate**
  - **Second+ lines: add eribulin to other options**

BRCA1-associated TNBC may be different:

- **Platinums**
- **PARP inhibition**

Is Triple Negative Breast Cancer ripe for individualized therapy approaches?

Teşekkürler