TRIPLE NEGATIVE BREAST CANCER

S.I.S. INTERNACIONAL SCHOOL OF SENOLOGIE
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Founded in 1976 in Strasbourg, France

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TRIPLE NEGATIVE BREAST CANCER

- **Particular subtype of Breast Cancer, Biologicaly distinct and Molecularly defined.**

- **GENE EXPRESSION PROFILE OF BREAST CA.:**

  + LUMINAL A.
  + LUMINAL B.
  + erbB2 POSITIVE.
  + BASAL SUBTYPE.
  + NORMAL BREAST LIKE SUBTYPE.

TRIPLE NEGATIVE BREAST CANCER

ER - PR- HER 2 -

CYCLIN D1 - ; CK 5, 6, 17 + ; EGFR + ; VIMENTIN +; NESTIN +

GENE EXPRESSION ARRAY: BASAL TYPE

10% - 20% OF TRIPLE NEGATIVE ARE NOT BASAL LIKE

> 5 MOLECULAR SUBTYPES OF TU. WITHIN TN GROUP

TRIPLE NEGATIVE PHENOTYPE SUB-DIVISION

- ER - PR - HER 2 -

CK 5 or CK 5/6 +
or EGFR +

CORE BASAL PHENOTYPE (CBP)

TRIPLE NEGATIVE

- ER - PR - HER 2 -

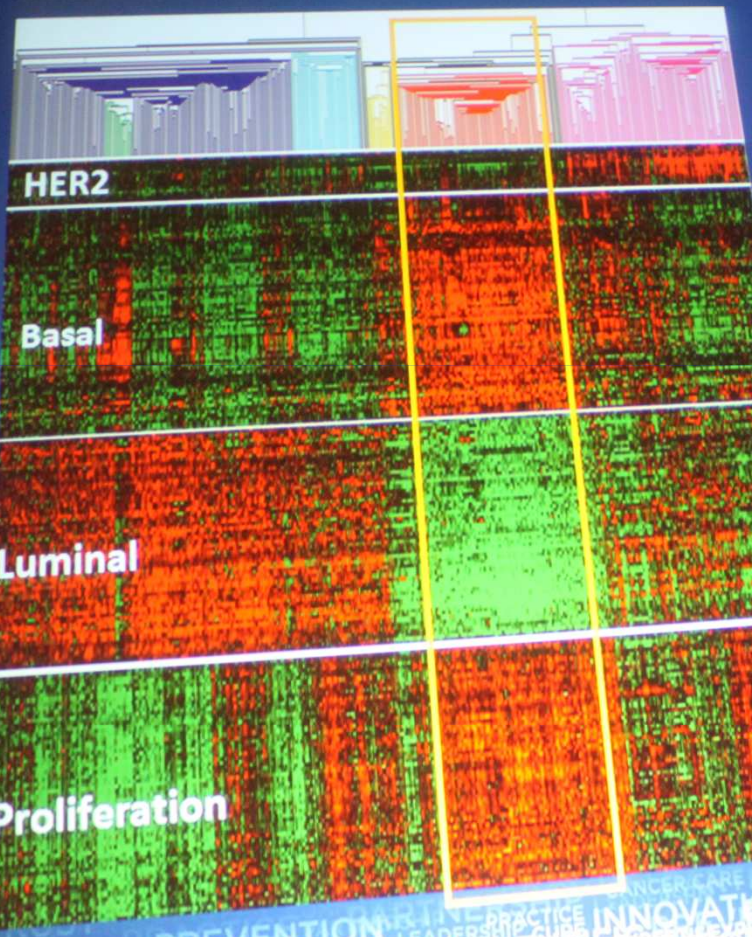
CK 5 or CK 5/6 -
or EGFR -

5 NEGATIVE PHENOTYPE

PHENOTYPE

Blows et al. PLoS Medicine

Basal-like Breast Cancer



- Low ER-related cluster
- Low HER2 cluster
- High basal cluster
  - basal cytokeratins
  - EGFR
  - c-kit
  - others…
- Very proliferative
- Evidence of genetic instability

PRESENTED AT: ASCO Annual '11 Meeting

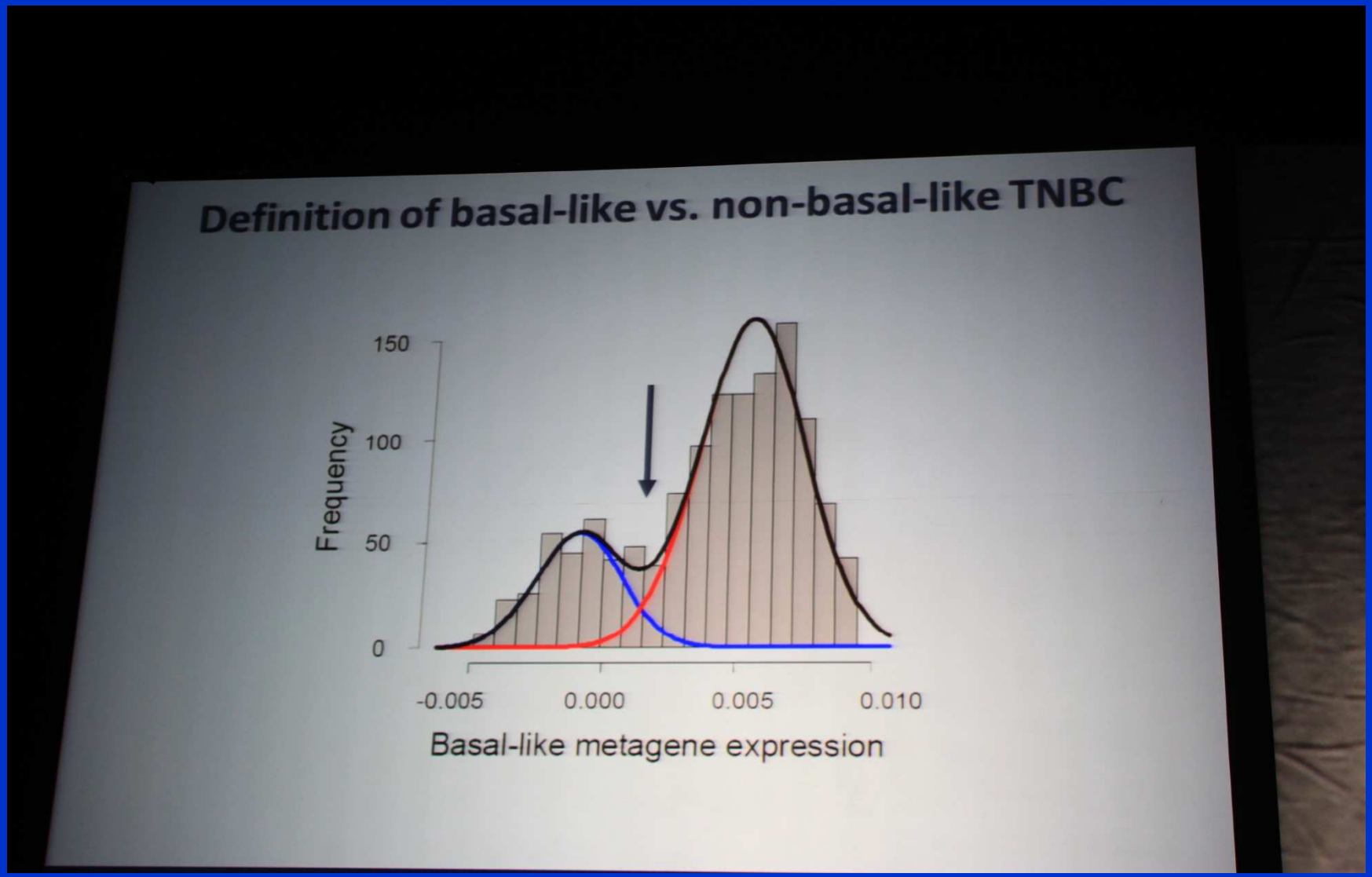
CLINICALLY RELEVANT GENE SIGNATURE IN TN AND BASAL LIKE BR. CA.

Biological comp.	Key Markers.	Reference
Basal Like Phenotype:	KRT 5, 6, 14, 17; SOX 17; SRFP1; ELF5; EPHB3;	Perou et al 2000.
Molecular Apocrine:	AR, FOXA1.	Farmer et al 2005
Immune System:		Rody et al. 2005.
+ B Cell:	IgG.	
+ T Cell:	TCR, LCK, ITK.	
+ MHC Class II:	HLA-DR, DM, DP, DQ.	
+ MHC Class I:	HLA-A, B, C, E, F, G.	
+ IFN Response:	CAS1; CAS2; CAS3; MX1.	
Stroma:	Decorin, Osteonectin, Fibronectin, COLSA1.	Farmer et al. 2009.
Claudin CD24 sig:	CLDN3; CLDN4; CD 24; ELF3.	Hennessy al 2009.
Proliferation:	BUB1; CDC2; STK6; BIRC5; TOP2A.	Wirapati et al 2008.
Blood:	HBA1; HBA2; HBB.	Whitney et al 2003.
Adypocites:	FABP4; PLIN; ADIPOQ; ADH1B.	Perou et al 2000.
Angiogenesis:	VEGF; Adrenomedulin; ANGPTL4.	Desmedt al 2008.
Inflammation:	IL-8; CXCL1; CXCL2.	Waugh et al 2008
HOXA gene cls:	HOXA-4, -5; -7, -9, -10, -11.	
Histone gene cls:	Histones H2A; h2B.	

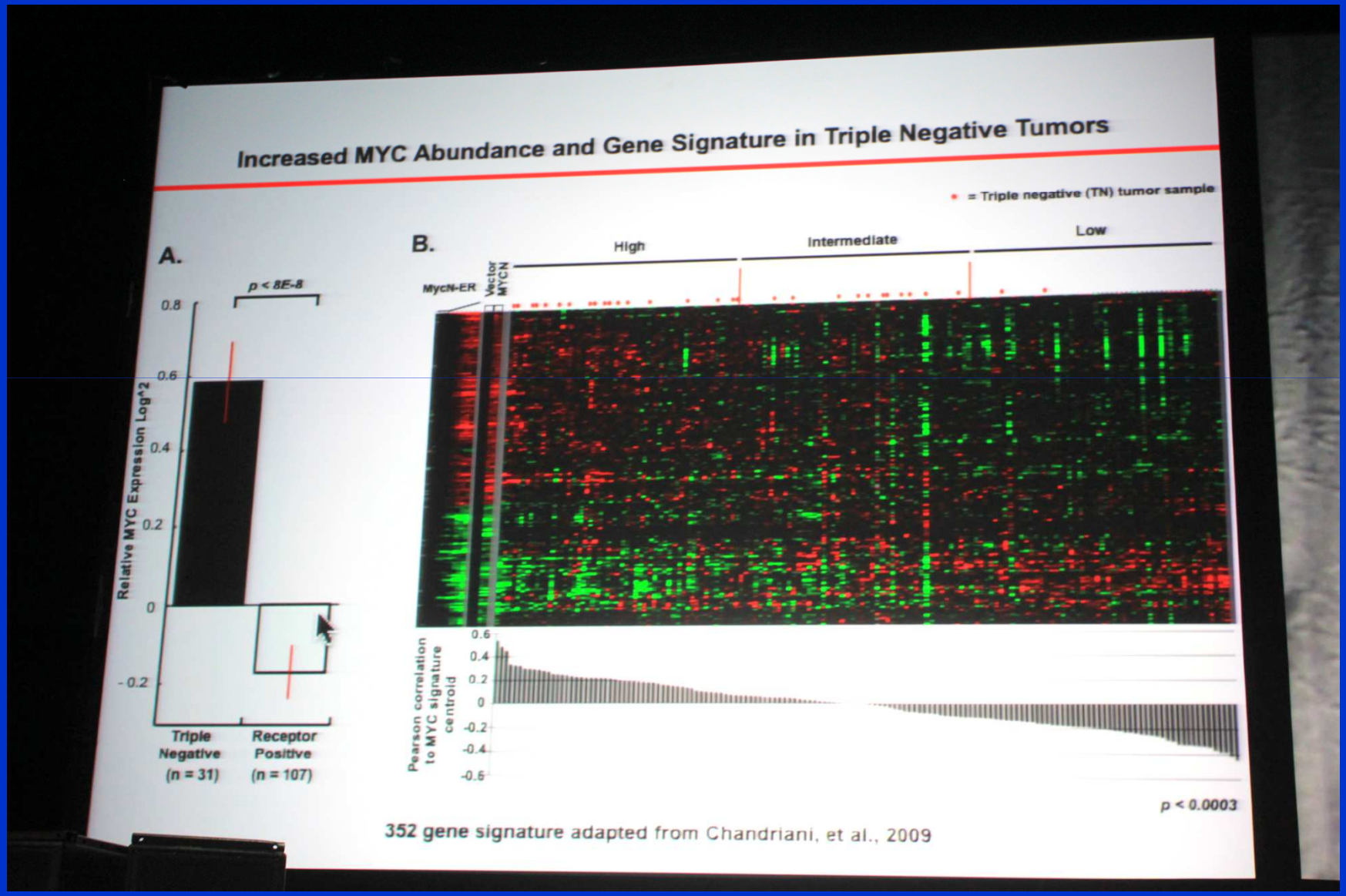
A. Rody et al. San Antonio Br. Ca. Symposium. 2010 (55-5)

METAGENE EXPRESSION: BASAL LIKE VS NON BASAL LIKE TN BR. CA.

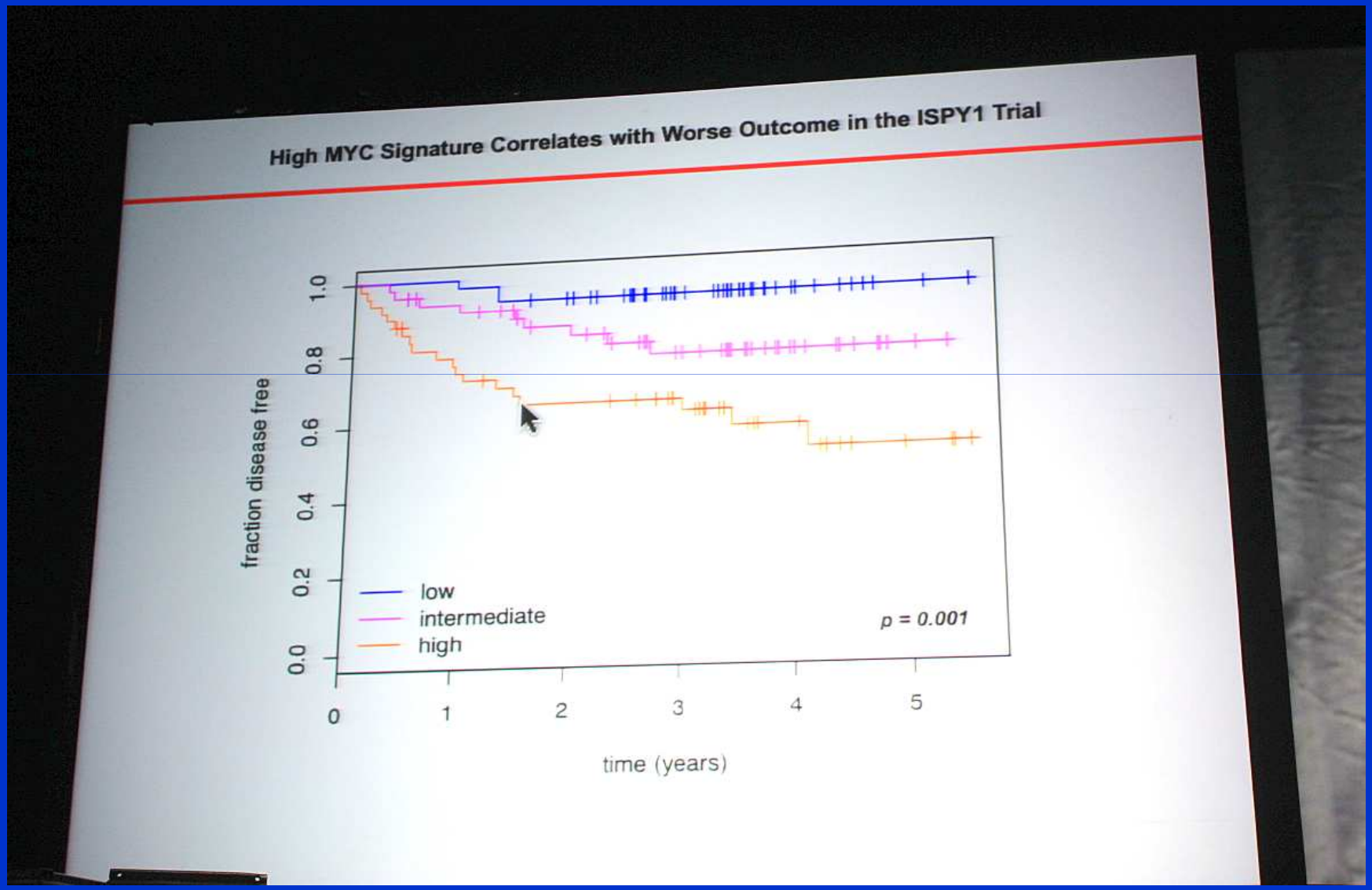
Rody A et al. San Antonio Breast Cancer Symposium 2010 (55-5)



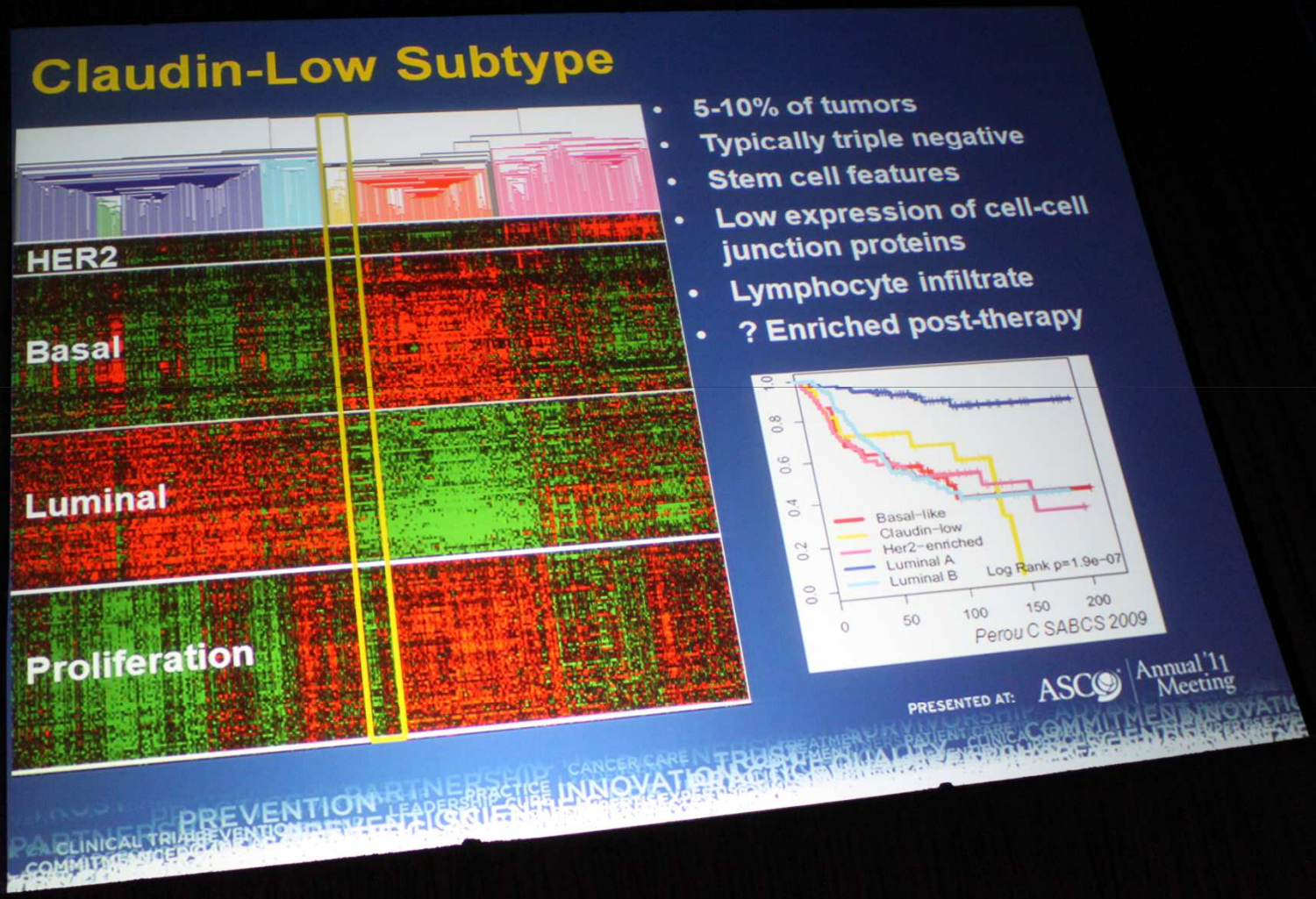
INCREASED MYC EXPRESSION IN TN TUMORS



TN HIGH MYC = WORSE OUTCOME



TNBC CLAUDIN LOW SUB-TYPE



TRIPLE NEGATIVE BREAST CANCER

- **NATURAL HISTORY:**

+ Rapid increase in the risk of recurrence after diagnosis

*** Peak risk of recurrence at 1 – 3 years**

*** Increased risk of brain metastases and, also, visceral metastasis.**

+ Rapid progression from distant recurrence to death.

+ Prevalence in Pre Menopausal woman and BRCA1 mutation carriers.

Triple negative breast cancer.
Some clinical characteristics.

- Few women experienced a local recurrence before a distant recurrence.
- Relative larger tumors: 2/3 had > 2 cm. tumours.
- High rate of Nodal metastasis: 54 %.
- Small tumours – 1cm. or less – had 55% of at least 1 positive node.

BIOLOGICAL CHARACTERISTICS AND TREATMENT RESPONSE.

- ER - : worse outcome; no hormone responsiveness; higher recurrences rates; inferior survival. Unfavourable histological characteristics; poor differentiation; higher histological grade.

. erbB2 negativity: lack of responsiveness to targeted agents –Trastuzumab- .

. CONSEQUENCE: LIMITED THERAPEUTIC OPTIONS IN A DISEASE WITH INTRINSIC AGRESSIVE CLINICAL BEHAVIOR.

TRIPLE NEGATIVE – BRCA 1 PATHWAY

- BRCA1 Pathway may be impaired in TN Br. Ca.
- BRCA 1 functions in DNA repair of cytotoxic agents that cause interstrand breaks (platinum) and double strand breaks.
- There is increasing evidence that BRCA1 related Br.Ca. and BLBC arise from luminal progenitor cells.
- May or not be associated with family history of Breast and/or Ovarian carcinoma.
- Account < 5% of Br.Ca. and > 10 % of Br.Cr. Ashkenazi J.
- Patients with ER - and erbB2 – N + tumours responded to taxanes significantly. (Hayes et al NEJM 2007)

SURVIVAL IN BRCA 1 COMPARED TO BASAL LIKE B.C

- **SIMILARITIES.**

- **Poor survival in first 3 – 5 years.**
- **Good survival after 10 years.**
- **Less clear relationships between tumour size, nodal status, and outcome than for other subtypes.**
- **Initial response to chemotherapy is generally good. Which CT ?**

- **DIFFERENCES.**

- **Responses to therapies that specifically target DNA repair may be more effective in BRCA 1 than in BLBC.**

Foulkes W. ASCO Educational Book 2011

CLINICO-PATHOLOGICAL FEATURES OF BRCA 1 RELATED BR. CA. COMPARED WITH NON-HEREDITARY BR. CA.

Younger age at onset.
Invasive ductal, rarely lobular.
Medullary / atypical
Medullary / pushing margins.
Central necrosis.
DCIS uncommon.
Histological grade 3.
ER / PR negative.
ERB-B2 (HER 2) negative.

All variables reported to be associated with BRCA 1 status in more than 1 study.

CK 5 / 6 positive.
EGFR positive.
Vimentin positive.
Osteonectin positive.
Caveolin-1 positive.
CDH3 (P-Cadherin) positive.
TP 53 mutations present.
MYC amplified.
CCNE 1 (Cyclin E) positive.
KIP1 (p27) negative.
BCL-2 negative.

Foulkes W. ASCO 2011.

BRCA DOWNREGULATION

- HIGH HISTOLOGIC GRADE.
- MEDULLAR HISTOLOGIC TYPE.
- BASAL LIKE AND TN IMMUNOPHENOTYPE.
- BRCA 1 SOMATIC MUTATIONS ARE VERY RARE.

- BRCA 1 INACTIVATION INDUCES LOSS OF ER AND ACQUISITION OF A BASAL – LIKE PHENOTYPE.

- BRCA 1 RECONSTITUTION INDUCES RE - EXPRESSION OF ER AND REDUCTION OF BASAL – MARKERS.

Foulkes W. ASCO 2011.

TRIPLE NEGATIVE BR.CA. - EGFR +

- Overexpression of EGFR occurs in TN Br.Ca.
- EGFR targeted therapy could be an option.
- Be aware that 73% of basal like tumours are EGFR negative, but data should be confirmed. Still a research topic.
- Occasional responses had been reported with Cetuximab and clinical trials are ongoing.

TREATMENT CONSIDERATIONS

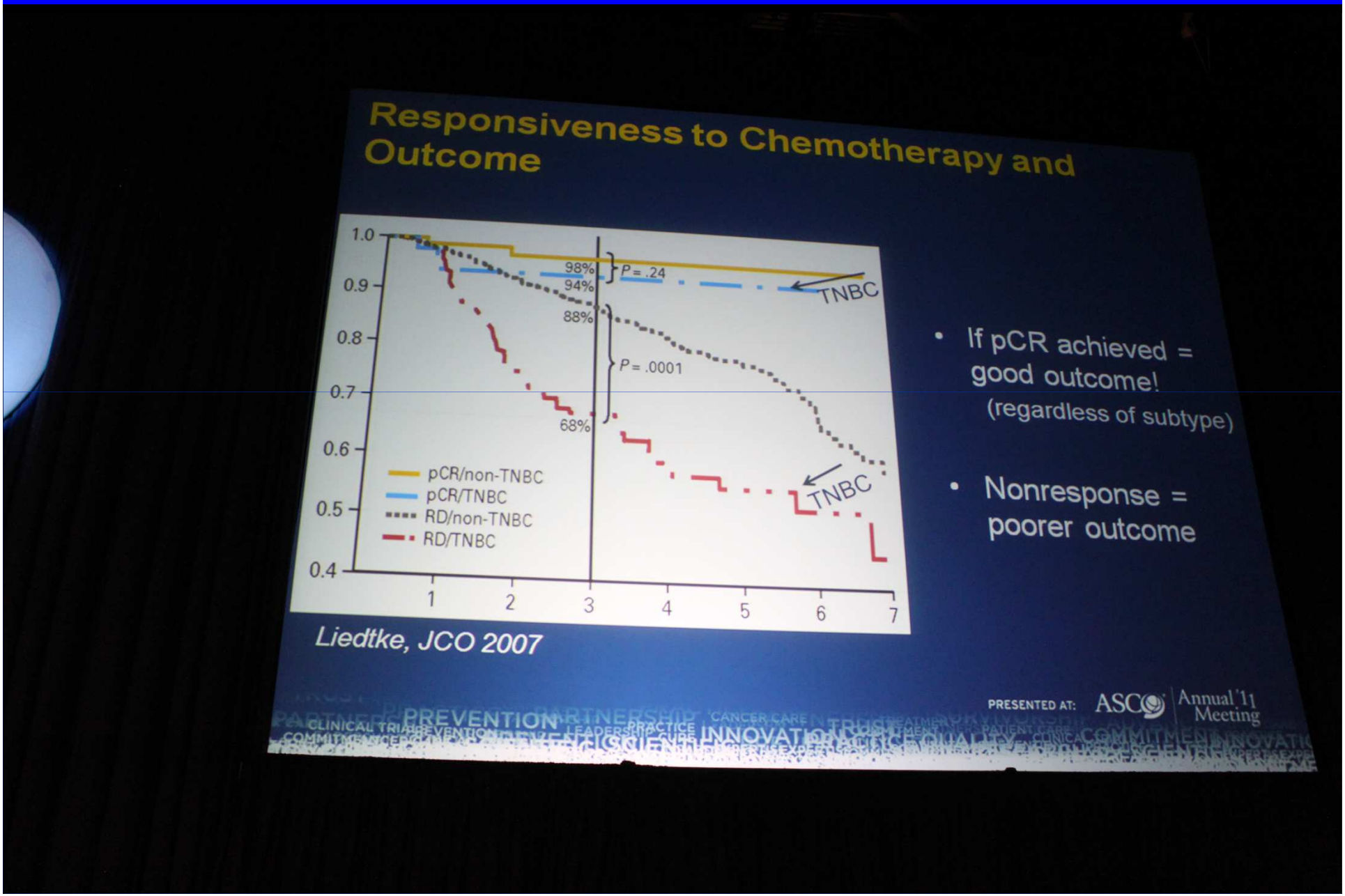
- There are no specific recommendations for the chemotherapy regimen to be used and no firm data to base any election.
- Data suggests that TN Br.Ca. is CT responsive due, perhaps, to ER negativity and high Ki 67 expression.
- Data on what agent should be used is less clear. Recomended CT: anthracyclines and taxanes.
- Bevacizumab plus Taxanes could be an option.

TRIPLE NEGATIVE BREAST CANCER

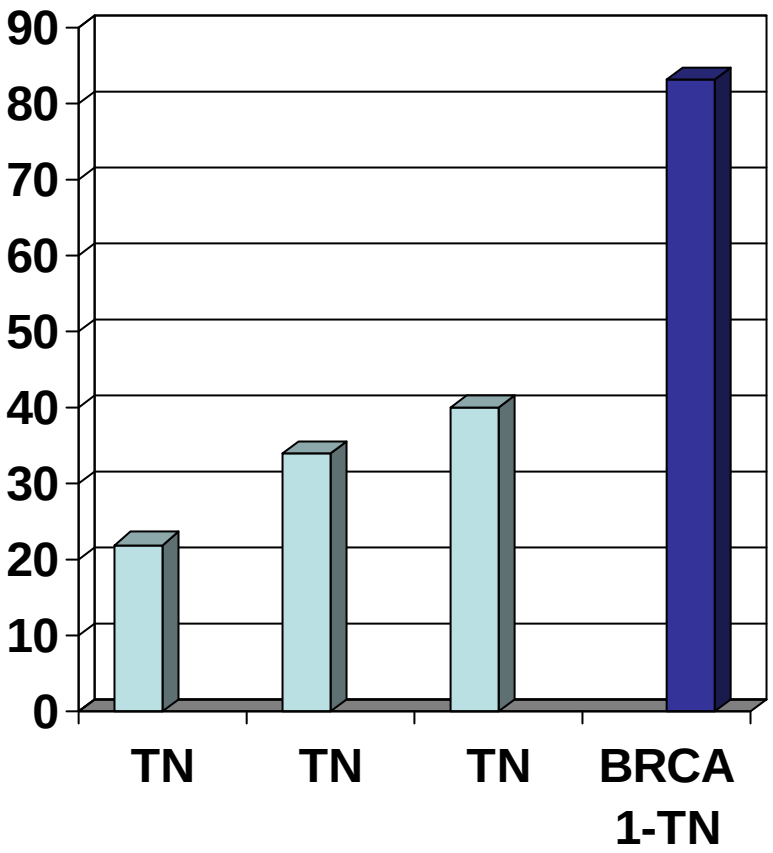
- NEO-ADJUVANT CHEMOTHERAPY

TRIALS

TNBC: NEO-ADJUVANT CHEMOTHERAPY RESPONSE



NEO-ADJ CT WITH PLATINUM SALTS. PHASE II



1) CARBO – S. N: 28.- SILVER 2010.

2) DDP + DX + AC – S. N: 125. LEONE 2009.

3) ECF + DDP + S. N: 30. TORRISI 2008

4) CARBO – S. N: 12. BYRSKI 2010

% pCR

PARP1 I – INIPARIB / NEO-BIG NEPTUNE TRIAL

	1. NO CT	DOCET. X 4	SURGERY	
R	2. INIPARIB	DOCET + INIP X4	pCR	ADJ CT
	3. INIPARIB	GEM/CARBO + INIP X 4	Primary endpoint	RT

Tutt A. St. Gallen 2011

RESPONSE TO NEO - ADJ "A – T" BY SUBTYPE.

pCR RESPONSE DATA

	T – FAC n 82	AC – T n 107
LUMINAL A / B	7 %	7 %
HER 2 + / ER -	45 %	36 %
TRIPLE NEGATIVE	45 %	26 %

Perez E. ASCO 2010

TNBC – NEOADJUVANT TRIALS.

CT	TNBC	NON TNBC	REFERENCE
A –T	255: pCR 22 %	863: pCR 11 %	
IXABEPI			
LONE	11: pCR 26 %	All group 28: pCR 18 %	Baselga JCO 2009; 27, 526.
GEICAM	EC+DOC. vs EC+DOC/CARB	Ongoing	A. Anton.
PACLITAXEL R 1) CARBO vs none versus 2) SAME + BEVACIZUMAB			Sikov, W.
CIBOMA	NEO AD/AD. L-REG TREAT. +/- CAPECITABINE MAINTAINANCE.		Barrios C. Lluch A.

TRIPLE NEGATIVE BREAST CANCER

- ADJUVANT CHEMOTHERAPY

TRIALS

T N Br.Ca. ONGOING TRIALS.

- **PARP1 Inhibitors.**
- **C-KIT Tyrosine Kinase inhibitors: Imatinib.**
- **Multikinase Inhibitors: Lapatinib; Pertuzumab.**
- **Downstream messenger inhibition: Ras farnesylation, Raf, MEK, mTOR, Src, HSP90.**

- **There is no concrete evidence of activity to date.**

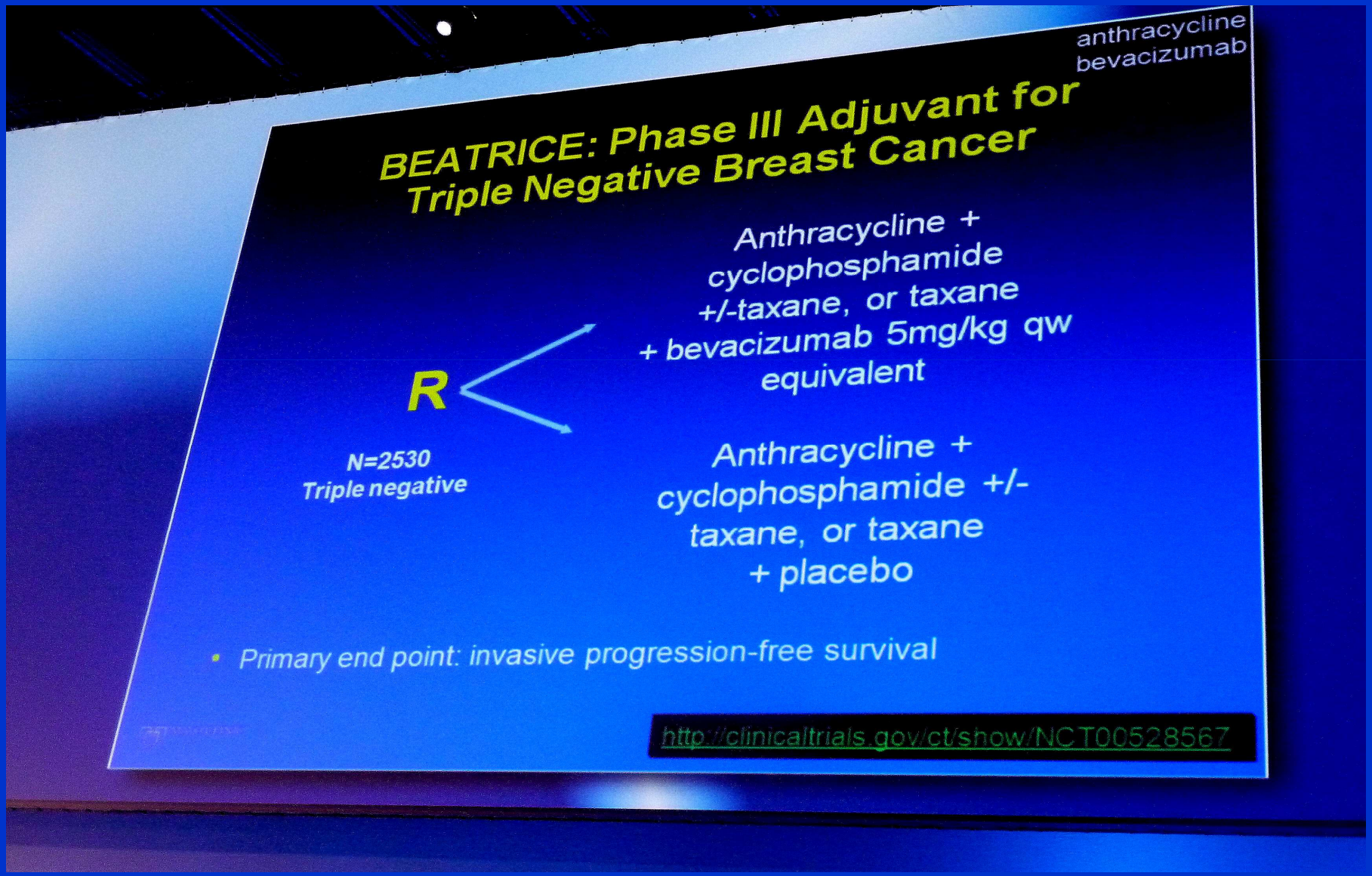
- **HDCh.: had been suggested to be evaluated in clinical trials with adequate patient identification.**

Cleator S et al.: Lancet Oncol 2007;8: 235-244

Rodenhius S et al: Ann. Oncol 2006;17: 588-596.

Tan S, Wolff A: Diseases of the Breast. 2010.p 888.

BEATRICE: TNBC ADJUVANT P III
AC +/- TAXANE OR +/- TAXANE - BEVACIZUMAB



TNBC: PHASE III IXABEPILONE ADJUVANT TRIALS

- **PACS 08**

  ER +/-, PR -, HER2 –

  N 2500

  PRIMARY END POINT

  5 YEARS DFS

  Campone,Tan,Perez

  FEC X 3

  * IXABEPILONE 40 mg/m2 Q 3 w x 3

  * DOCETAXEL 100 mg/m2 Q 3 w x 3

- **TITAN**

  ER- ,PR- ,HER2-

  N 1800

  PRIMARY ENDPOINT

  5 YEARS DFS

  Yadley

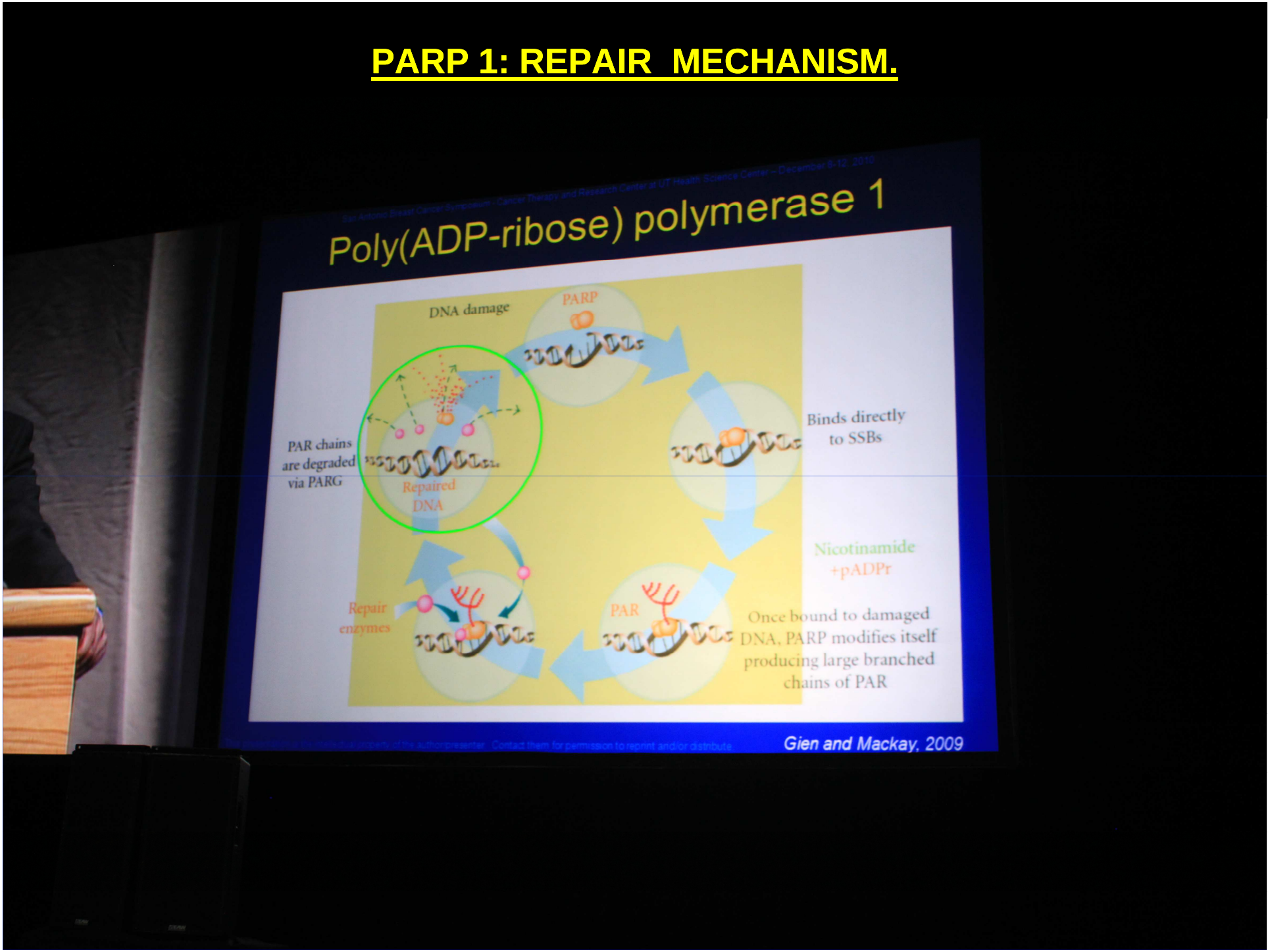
  AC x 4

  * IXABEPILONE 40 mg/m2 Q 3 w x 3

  * PACLITAXEL 80 mg/m2 w x 12

NCT identifier numbers: NCT 00630032 (PAC S08), NCT 00789681 (TITAN)

PARP 1: REPAIR MECHANISM.

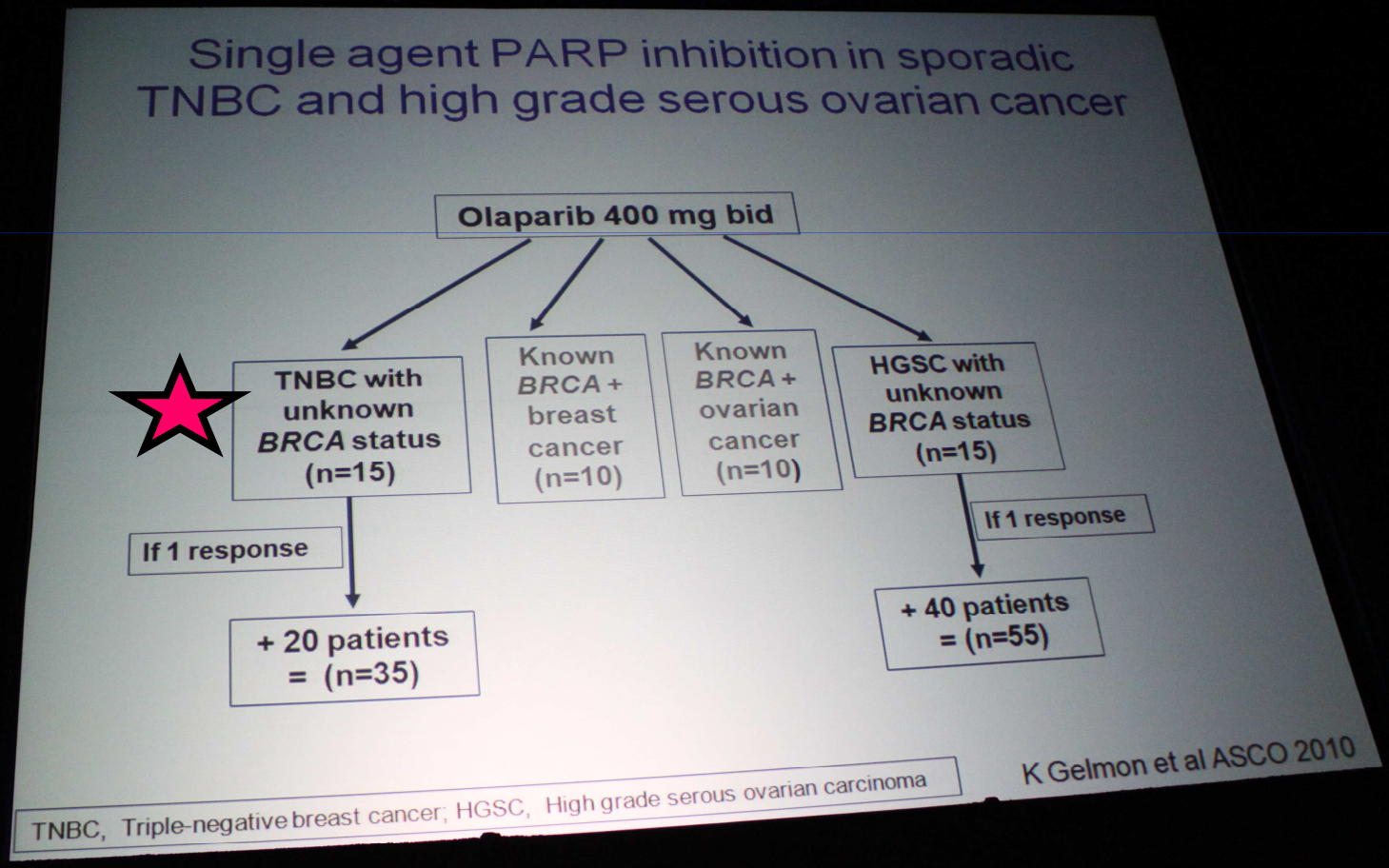


PARP 1 INHIBITORS IN DEVELOPMENT

AGENT	COMPANY	PHASE- ROUTE	SINERGY in vitro
OLAPARIB	ASTRA Z.	I-II oral	Platins, Tmz, IR
VELIPARIB	ABBOTT	I-II oral	DDP, Tmz, CTX, Topo I inh
INIPARIB	S. AVENTIS	I-III i/v	Gem/Carb, Top, Oxali, Irinot.
AGO14699	Pfizer	I-II i/v	Tmz, Topo, Irt.
MK-4827	Merck	I oral	
CEP 9722	Cephalon	I oral	Tmz, Topo I, Plt
INO-1001	Inotek	i/v	
E7016	Eisai	oral	

TRIALS IN METASTATIC TRIPLE NEGATIVE BREAST CANCER

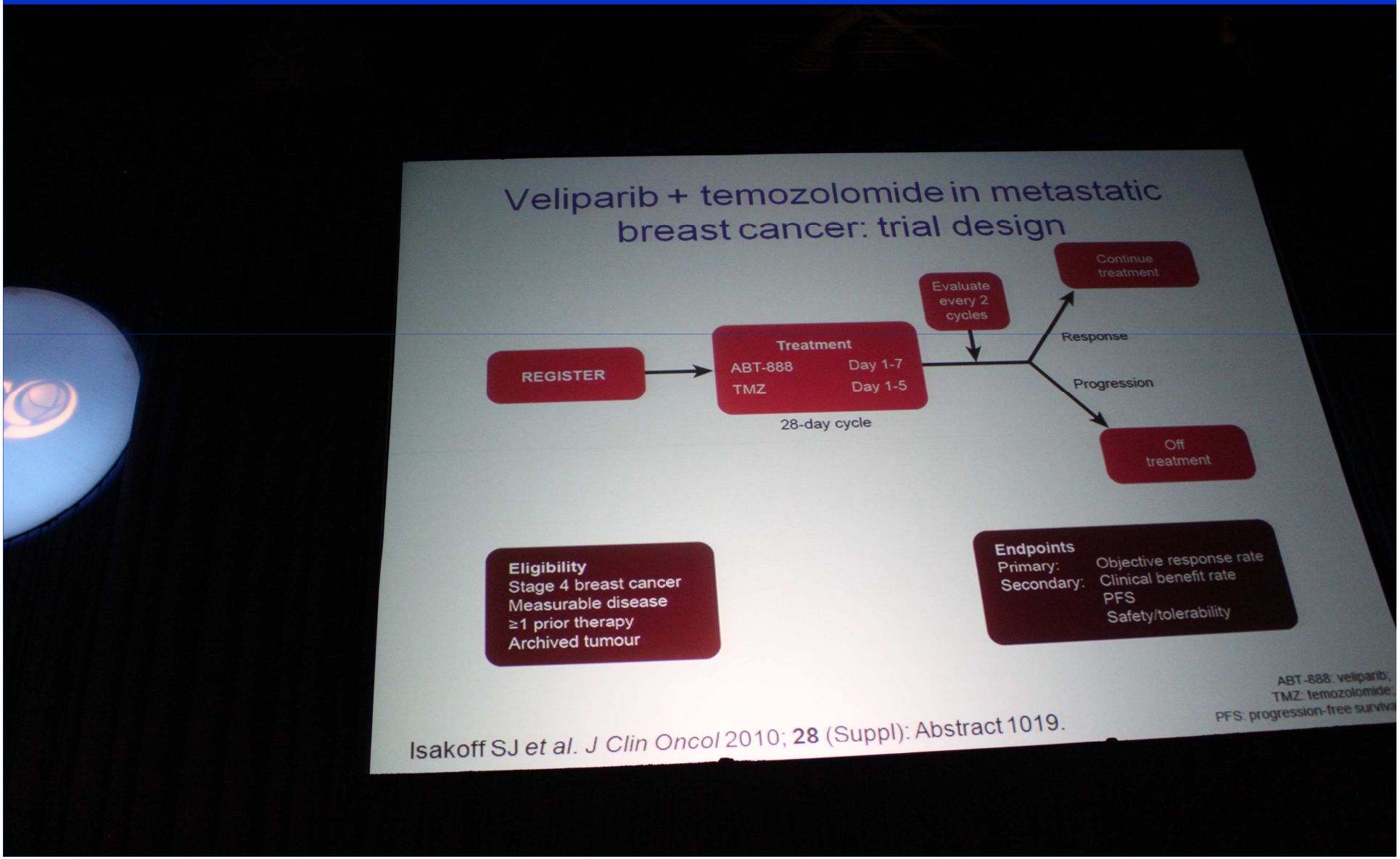
PARP 1 INH. OLAPARIB IN TNBC AND HIGH GRADE SEROUS OVARIAN CANCER



VELAPARIB + TEMOZOLAMIDE IN MBC.

N 41. mixed population. Few evaluable patients. Neut. G 4. Pt G4.

ORR 7 %



GEM-CARBO +/- INIPARIB PHASE III MET. TN BR. CA.

O´Shaughnessy. Proc. ASCO 2011. Abst. 1007

- Gemcitabine 1.000 mg/m2, i/v, D 1, 8 every 21 d.
- Carboplatin AUC 2, i/v, D 1, 8 every 21 d.

+ / -

- Iniparib 5,6 mg/hg, i/v, D 1, 4, 8 and 11 every 21 d.

……

N: 519. Previous CT for E IV, 1 to 3 combinations.

Main Toxicity: Haematological G 3 – 4.

……

	GC	GCI	HR	
	258	261	95% CI	p value
Median OS m.	11.1	11.8	0.876 (0.687-1.118)	0.284
Median PFS m.	4.1	5.1	0.794 (0.646-0.976)	0.027

NO THERAPEUTIC BENEFIT.-

Tumor Histology – Immunohistochemically-defined subtypes

TYPE	TOTAL (%) 8801	LUM. A 2629 (29%)	LUM. B 4858 (55%)	HER 2 + 533 (6%)	TRIPLE Neg 782 (8.8%)
Ductal	6899 (78 %)	1683	4024	499	693
Lobular	875 (9 %)	433	418	6	18
Ductal-Lob.	341 (3 %)	126	212	1	2
Cribiforme	251 (2 %)	191	59		1
Mucinous	147 (1 %)	73	70	3	1
Tubular	84 (1 %)	81	2		1
Apocrine	72 (1 %)	6	16	21	29
Papillary	45 (0.5 %)	11	24	1	9
Medullary	13 (0.3 %)		3		10
Metaplastic	11 (0.1 %)		1		10

MAPK and PI3K / AKT Pathways Co-activating events in Metastatic TNBC.
O´Shaughnessy J et al. SABCS 2011

Whole Genome (WGS) and Transcriptome sequencing performed in TNBC to identify mutations that could be therapeutically targeted –Phase I/II.-

TRIPLE NEGATIVE BREAST CANCER.

- A Subset of Dominant Mutations can Drive Metastatic TNBC.-

+ RAS / RAF / MEK and PI3K / AKT / mTOR Pathways, mutations and possible Co-activation by multiple mechanisms are common in Metastatic TNBC.-

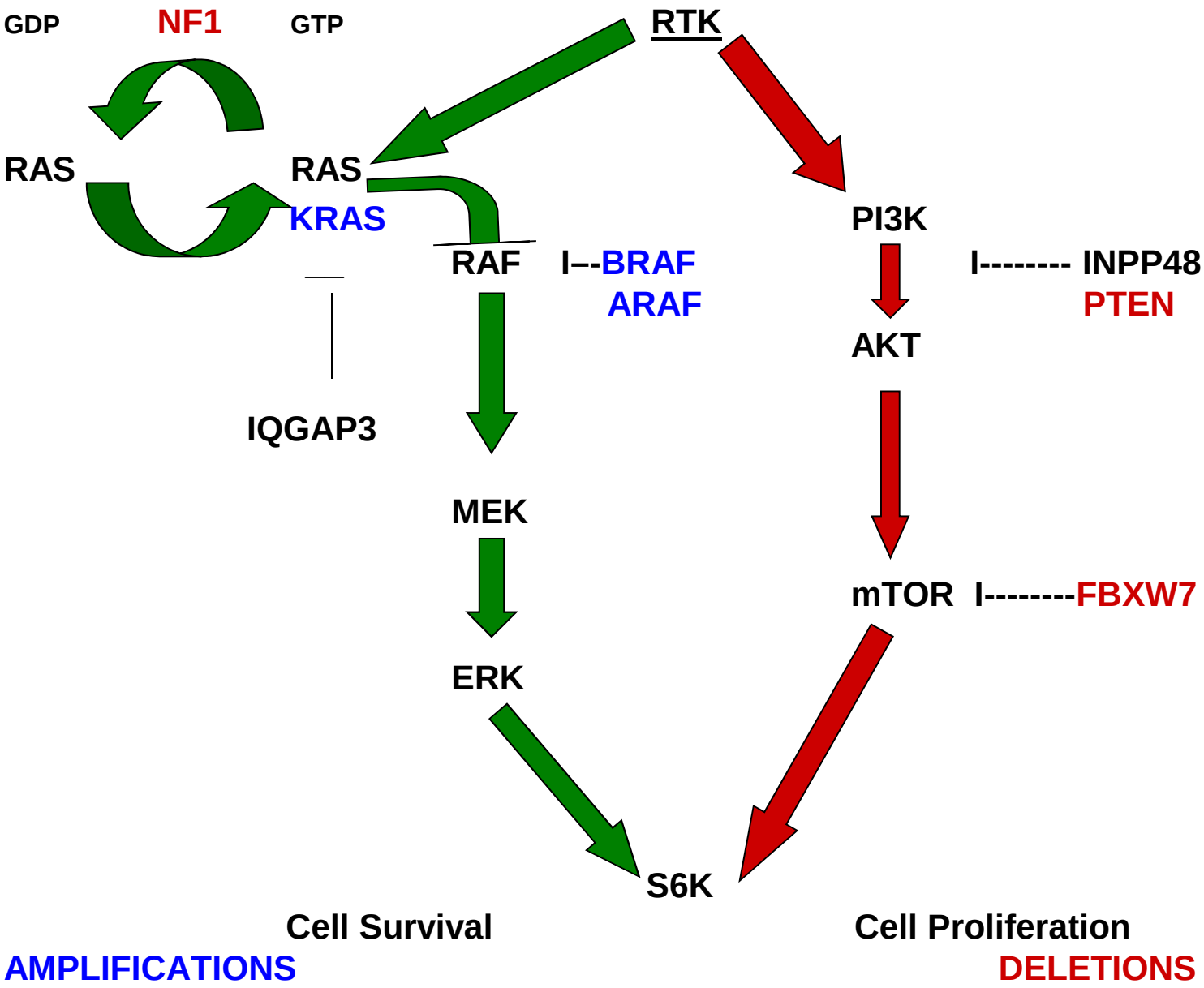
+ SUSPECTED DOMINANT MUTATIONS:

  * BRAF, ARAF, KRAS AMPLIFICATIONS.

  * NF1, PTEN, FBZW7 DELETIONS.

  May predict for MEK / AKT Inhibitor efficacy.-

+ Somatic alterations or loss of expression of ERBB4 are common in TNBC.-


GDP
NF1
GTP
RTK
RAS
RAS
KRAS
RAF
I–-BRAF
ARAF
PI3K
I-------- INPP48
PTEN
AKT
IQGAP3
MEK
mTOR I--------FBXW7
ERK
S6K
Cell Survival
Cell Proliferation
AMPLIFICATIONS
DELETIONS

PHASE I ONGOING STUDY

- COMBINED CHEMOTRHERAPY:

- + AKT INHIBITOR: 2110183.

- + MEK INHIBITOR: TRAMETINIB.

Based on the frequency of this genomic content.