GBCC 2011
Symposium 8: Breast Cancer with Triple Negative Subtype

New Strategies for Treatment of Triple Negative Breast Cancer

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06 / OCT / 2011

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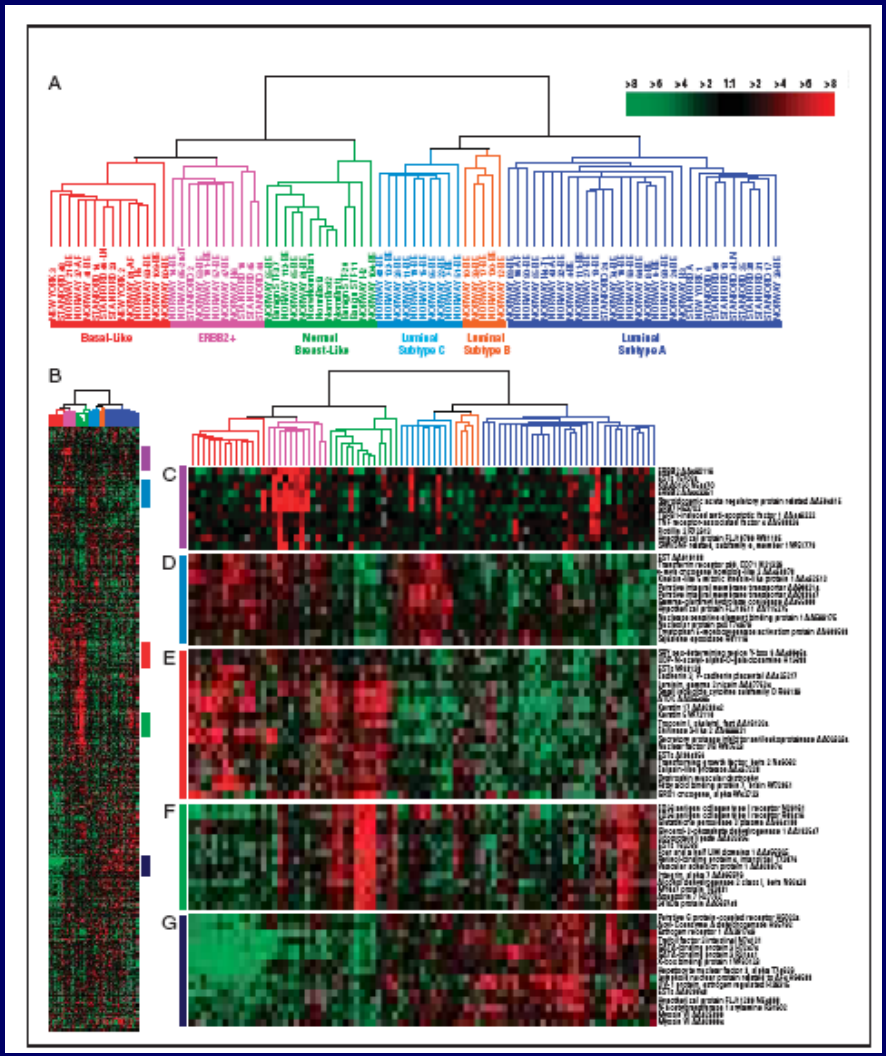
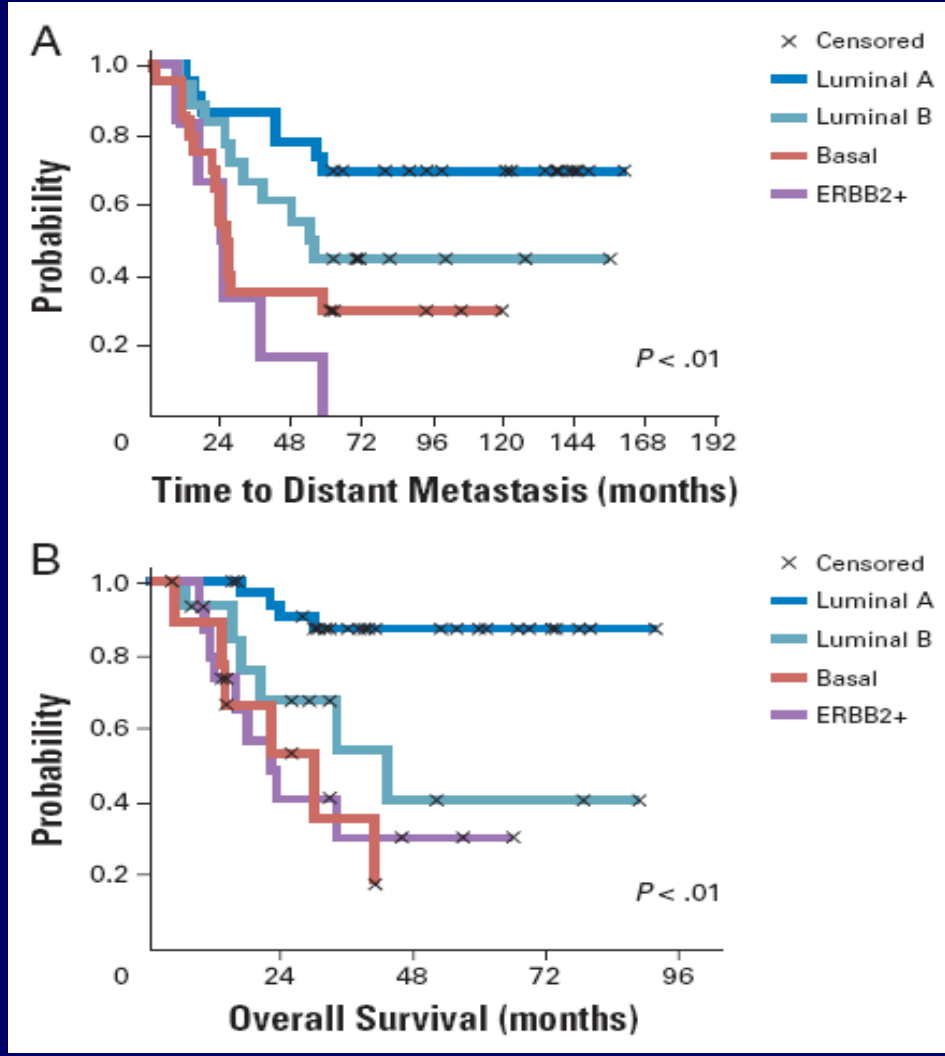
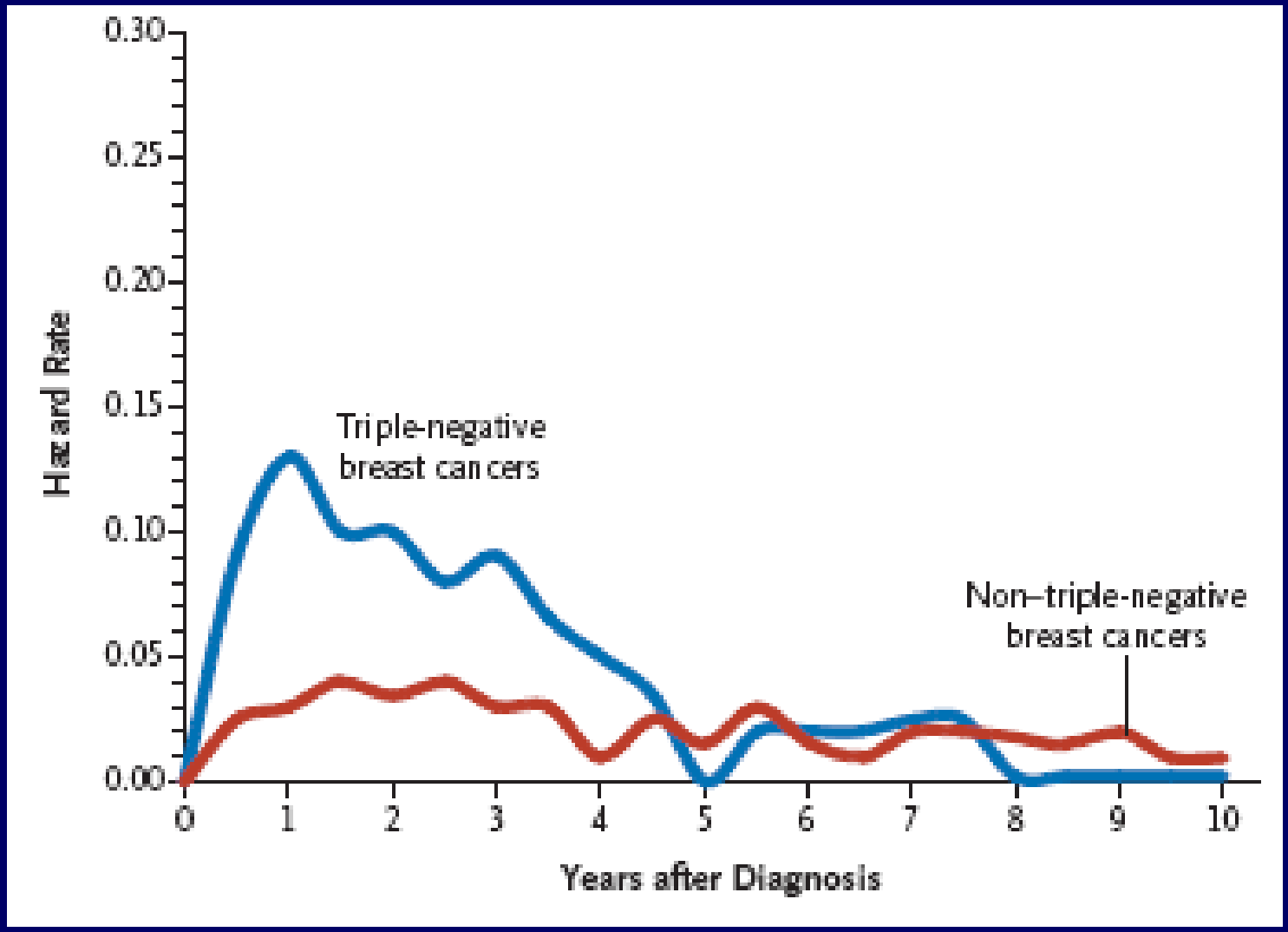
Survival difference based on molecular subtype





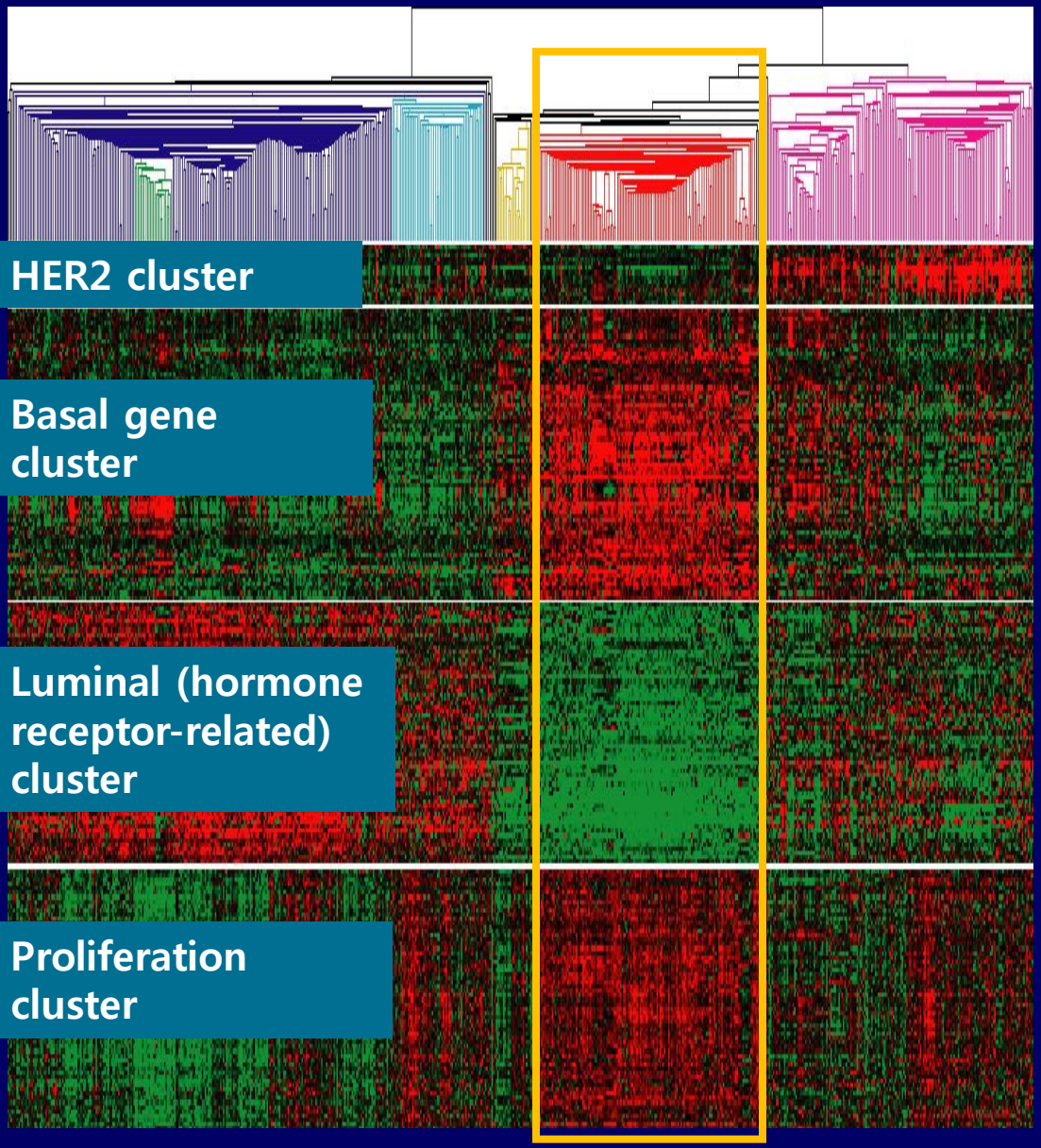
PNAS 2001
N Engl J Med 347:1999-2009, 2002

TNBC: Clinical characteristics



NEJM 2010; 363: 1938

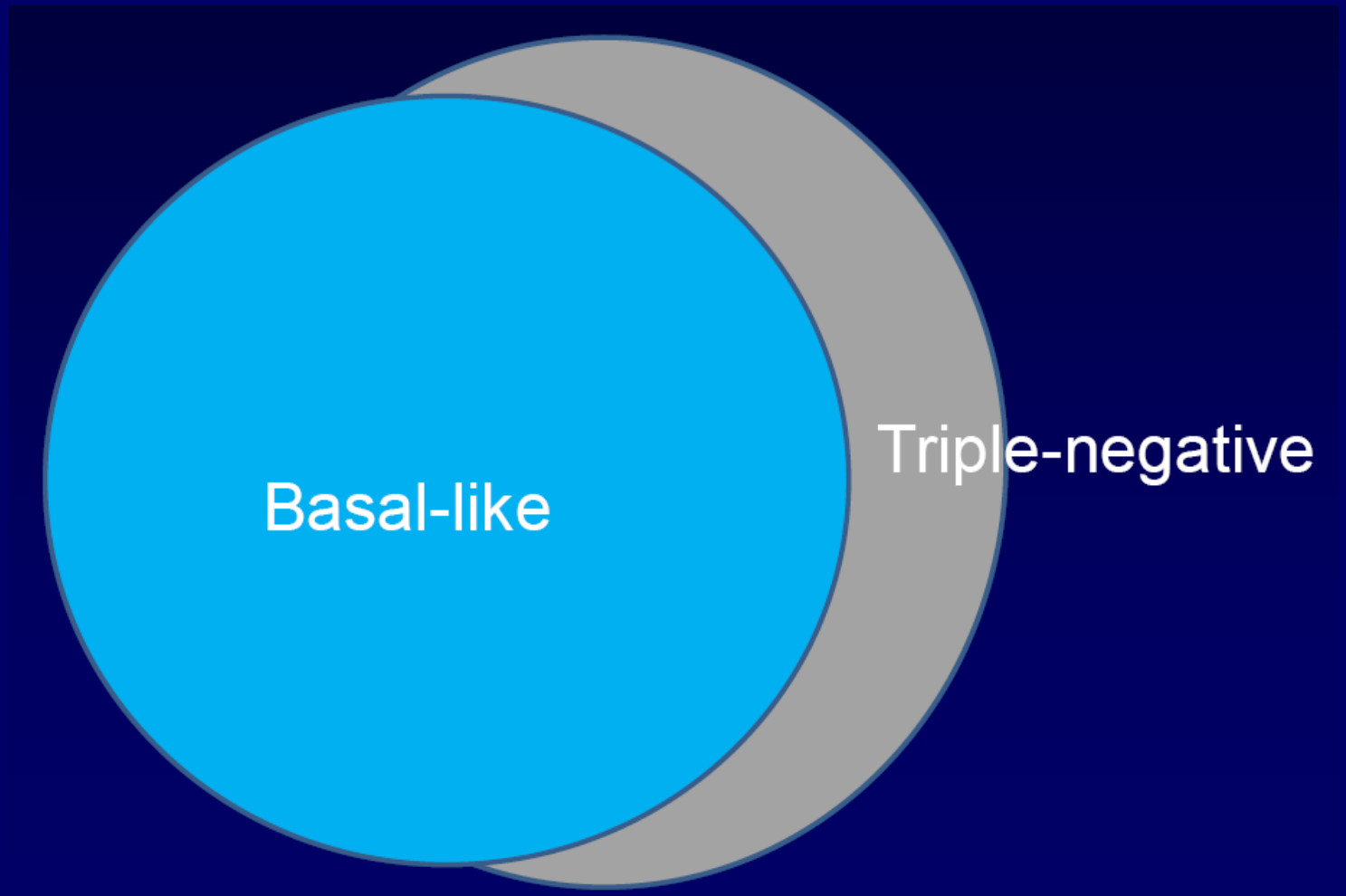
The Picture of Basal-like Breast Cancer



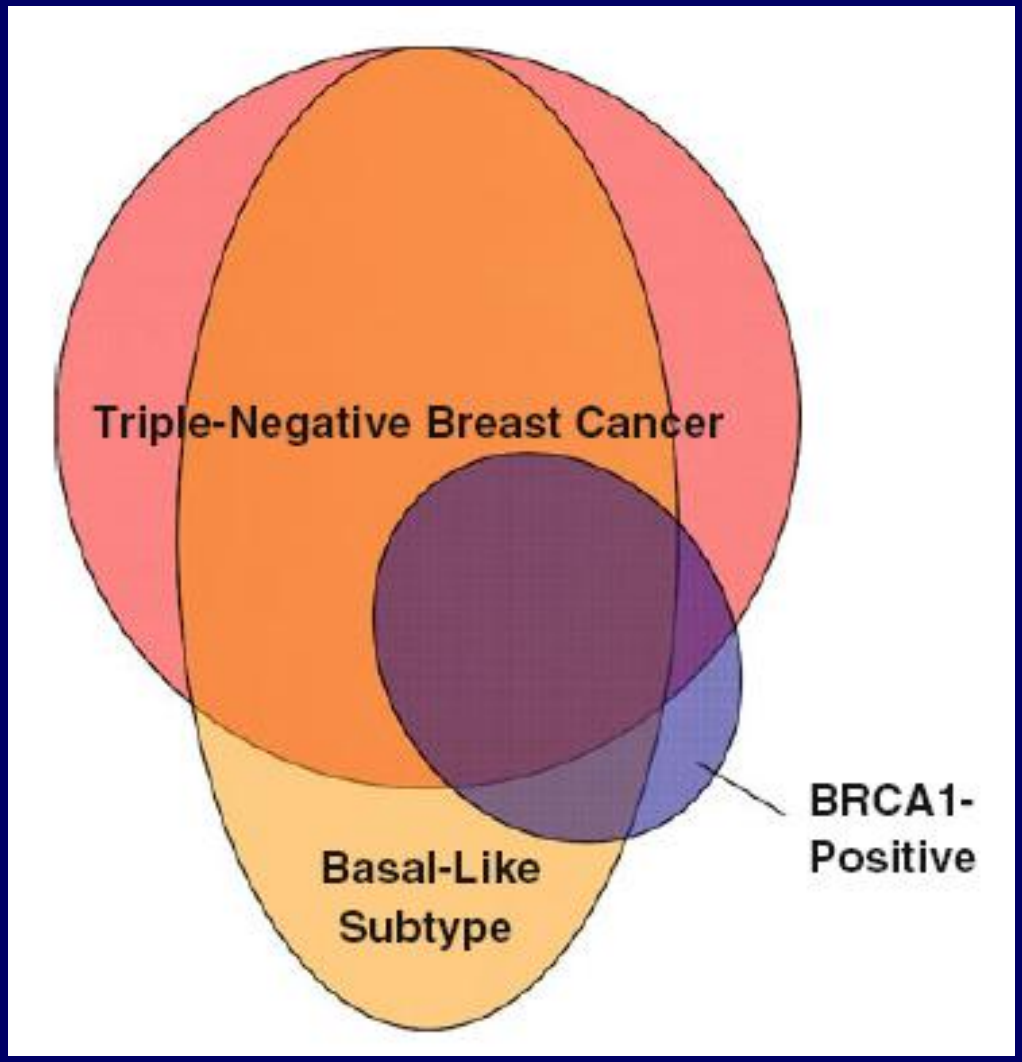
- Low ER (and related genes) expression
- Low HER2 cluster expression

  → usually “triple negative”
- High basal cluster
  - basal cytokeratins
  - EGFR
  - c-kit
  - others…
- Very proliferative
- Often p53 mutant
- Evidence of genomic instability

Triple-Negative Immunophenotype Does Not Overlap the Basal-Like Gene Expression profile



Schematic illustration of overlap among TNBC, basal-like, and BRCA1-related tumors



- Most cancers in BRCA1 mutation carriers are basal-like
- Most basal-like breast cancers are not in BRCA1 carriers.

BCRT 2011; 125: 627

TNBC Shares Clinical and Pathologic Features With BRCA-Related BC: **"BRCAness"**

Characteristics	Hereditary *BRCA-1*	Triple Negative
ER/PgR/HER2 status	Negative	Negative
BRCA-1 status	**Mutational inactivation***	**Diminished expression***
Gene-expression pattern	Basal-like	Basal-like
Tumor histology	Poorly differentiated (high grade)	Poorly differentiated (high grade)
Chemosensitivity to DNA-damaging agents	Highly sensitive	Highly sensitive

*BRCA dysfunction due to germline mutations, promoter methylation, or overexpression of high-mobility group proteins of the type 1 or inhibitor of differentiation

Lisa A. Carey et al. CCR 2010, Oct

Strategies for subtypes: Highlights of the St Gallen 2011

Systemic treatment recommendations for subtypes

'Subtype'	Type of therapy
'Luminal A'	Endocrine therapy alone
'Luminal B (HER2 negative)'	Endocrine ± cytotoxic therapy
'Luminal B (HER2 positive)'	Cytotoxics + anti-HER2 + endocrine therapy
'HER2 positive (non luminal)'	Cytotoxics + anti-HER2
'Triple negative (ductal)'	Cytotoxics
'Special histological types'*	
A. Endocrine responsive	Endocrine therapy
B. Endocrine nonresponsive	Cytotoxics

Goldhirsch A et al. Ann Oncol 2011; 22: 1736

TNBC Responds to Conventional Chemotherapy

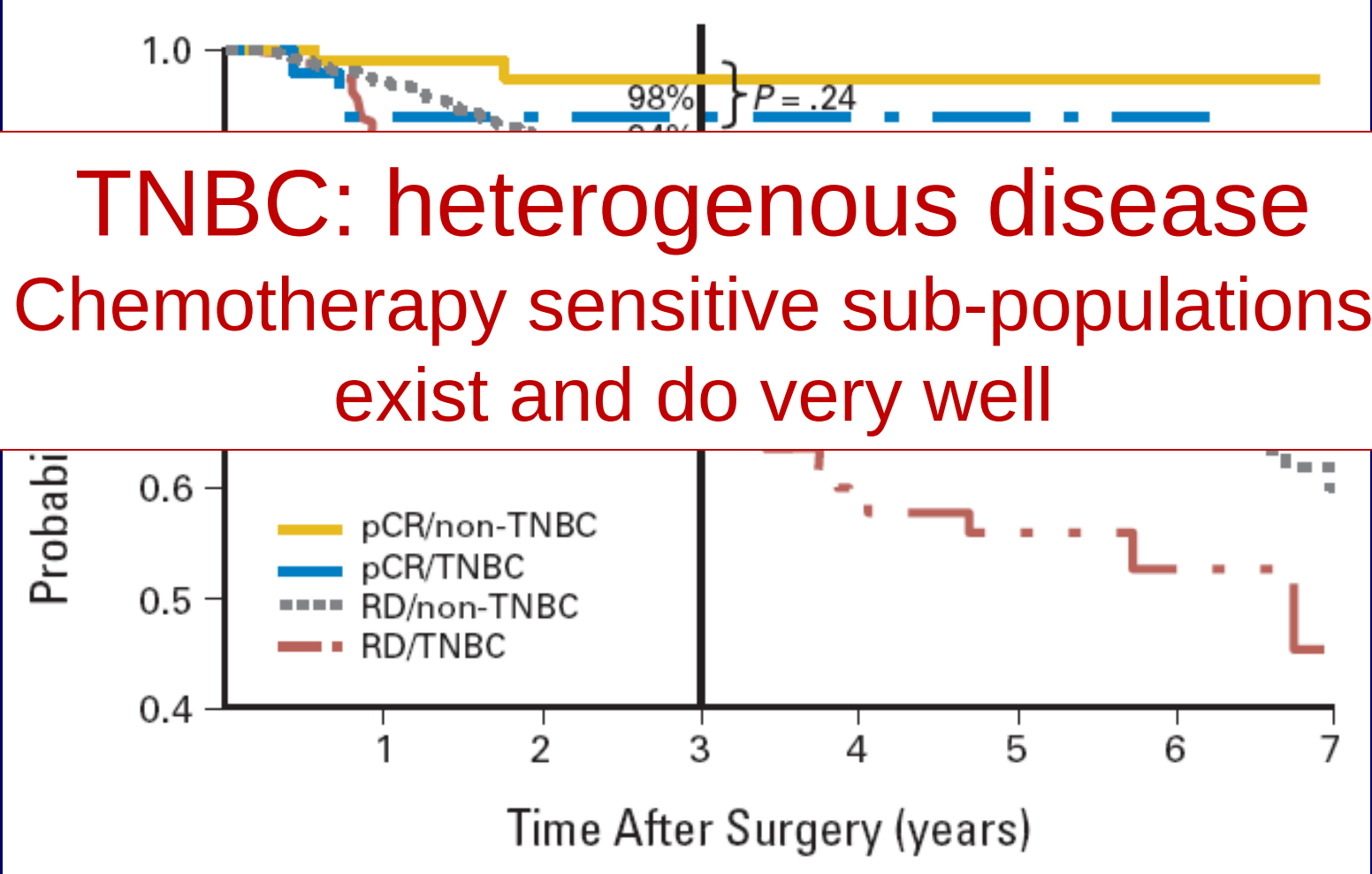
Pathologic complete response:

Molecular class	**T-FAC (n=82)**	**AC –T (n=107)**
Luminal A/B	7%	7%
Normal-like	0%	NA
HER2+/ER-	45%	36%
Basal-like/ Triple-negative	45%	26%

- Basal-like / TNBC responds to primary chemotherapy
- ? Explanation of higher response but worse outcome?

Rouzier, et al. Clin Can Res 2005, Carey, et al. Clin Canc Res 2007

TNBC: ‘Triple Negative Paradox’



TNBC: heterogenous disease

Chemotherapy sensitive sub-populations exist and do very well

Carey L et al. Clin Cancer Res 2007; 13: 2329

Treatment of TNBC

Treatment of Triple-Negative Breast Cancer

- No standard therapies

  - Treatment should be selected as it is for other cancer subtypes.

- A subset of TNBC is highly resistant to chemotherapy, changing cytotoxic provides only a small benefit.
- BRCA-1 dysfunction may be a therapeutic target
  - DNA cross-link: Platinum
  - DNA repair: PARP-1 inhibitor
- About 90 ongoing clinical trials for TNBC (http://clinicaltrials.gov)

Susan Cleator et al. Lancet Oncology 2007; 8: 235

Platinum

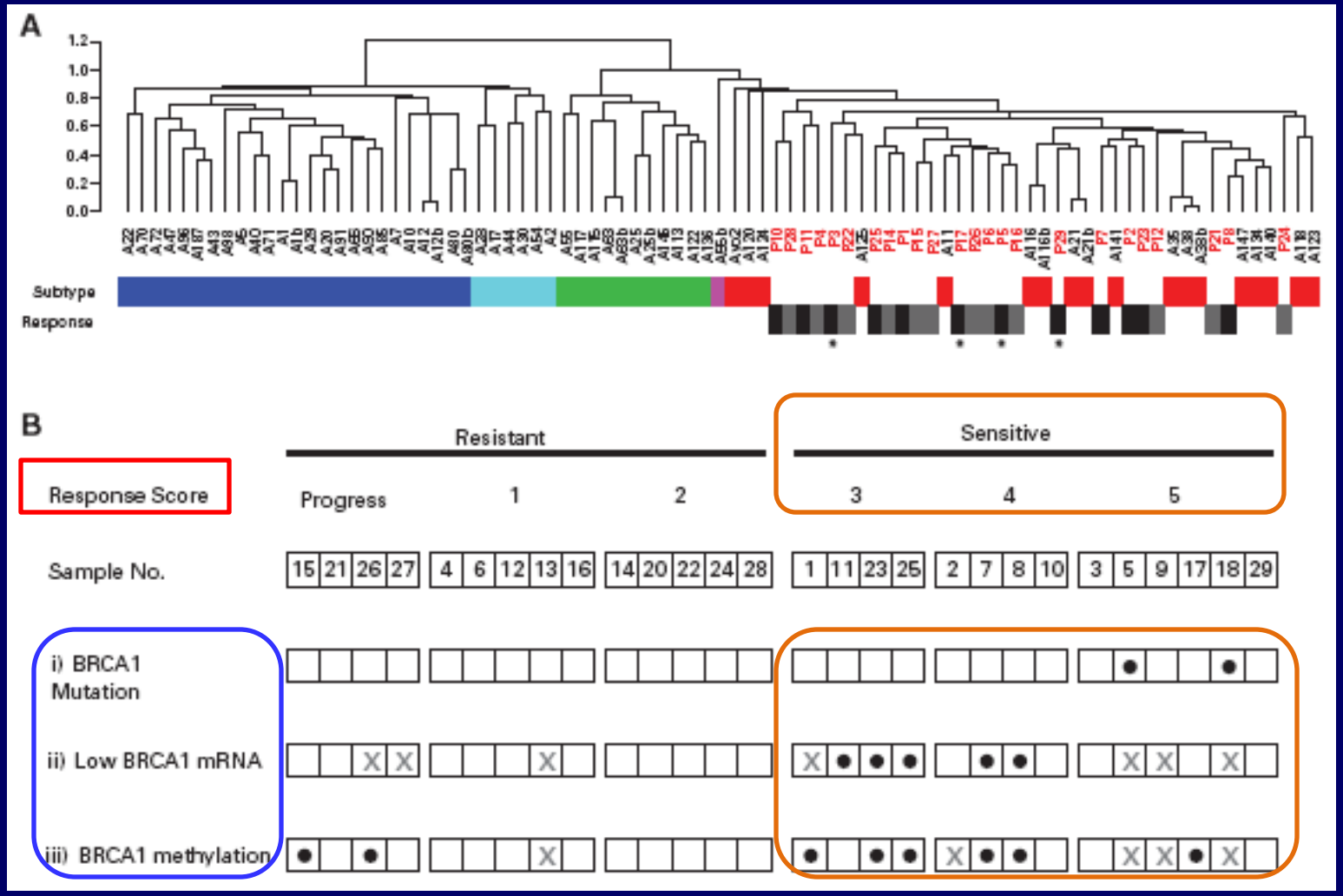
Platinum

- BRCA1: Tumor suppressor gene
  - DNA repair / Transcriptional regulation
  - Maintenance of chromosomal stability
- TNBC with BRCA1 mutations and dysfunctional DNA repair may indicate an increased sensitivity toward DNA-damaging agents.
- Only small studies exist, but are supportive of this approach, including a neoadjuvant trial of cisplatin.

Neoadjuvant Chemotherapy with Platinum Compounds: Phase II Trials in TNBC

Patients	No.	Regimen	Efficacy pCR rate
Monotherapy			
Proven BRCA1 (+)	25	4 x cisplatin q 3w	**72%**
Any TNBC	28	4 x cisplatin q 3w	22%
Combination			
TNBC with LABC	30	4 x epirubicin/cisplatin/5-FU →3 x paclitaxel q1w	40%
TNBC with LABC	55	4 x cisplatin/bevacizumab q 3w	36%
TNBC with LABC	74	8 x cisplatin/epirubicin/paclitaxel q1w + G-CSF	62%
TNBC with LABC	10	4 x taxotere/carboplatin q3w	50%
TNBC with LABC	125	4 x taxotere/carboplatin or cisplatin with 4 x AC q3w	40%

Impaired BRCA1 and neoadjuvant cisplatin response in TNBC



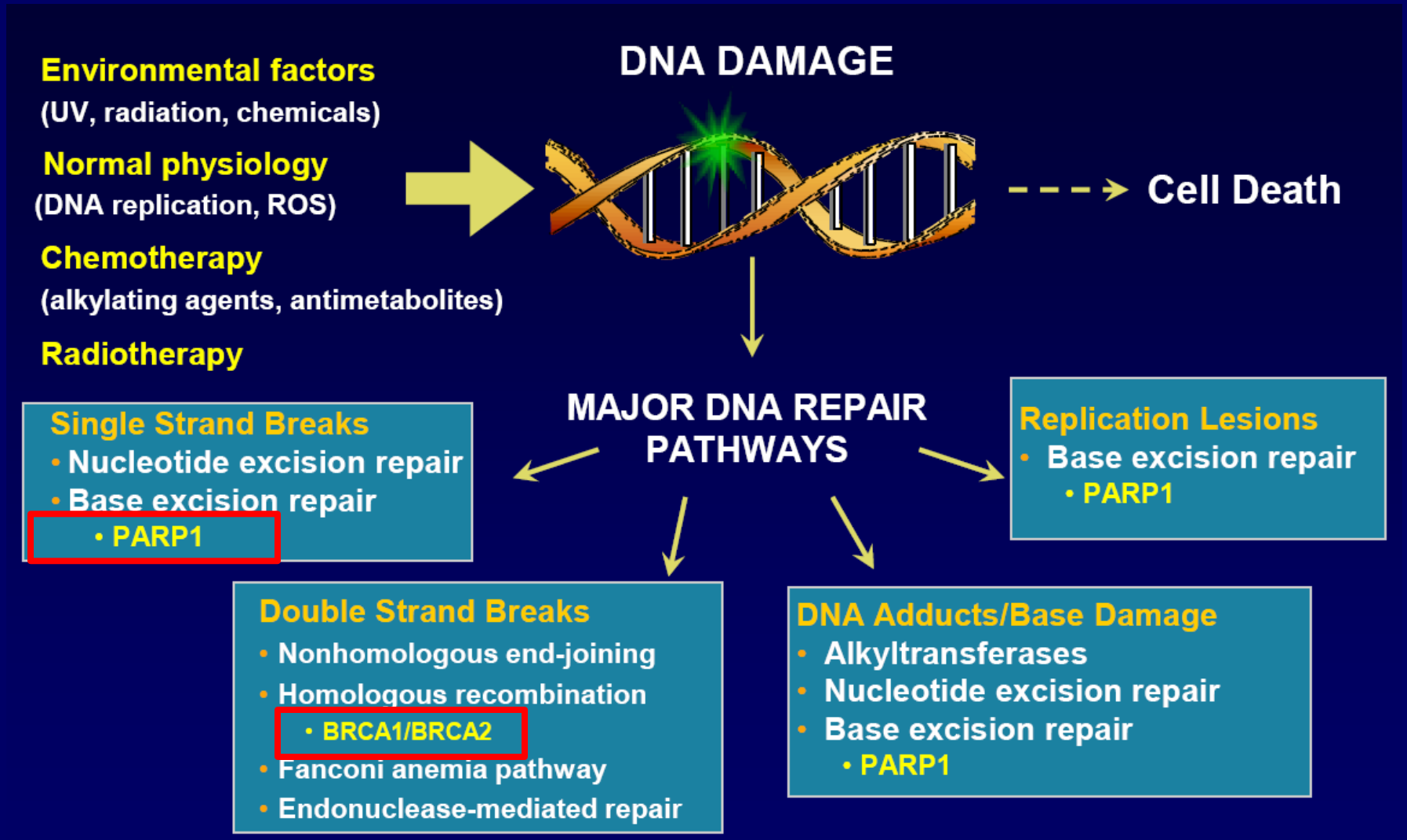
Silver DP, et al. JCO 2010; 28: 1145

Current status of platinum in TNBC

- There is no clear answer in the **unselected TNBC** population as to whether or not the platinums represent a special agent.
- Additional efforts are needed to discover biomarkers predictive of platinum response.
- There are many ongoing studies incorporating platinum agents for the treatment of TNBC patients.

PARP Inhibitor

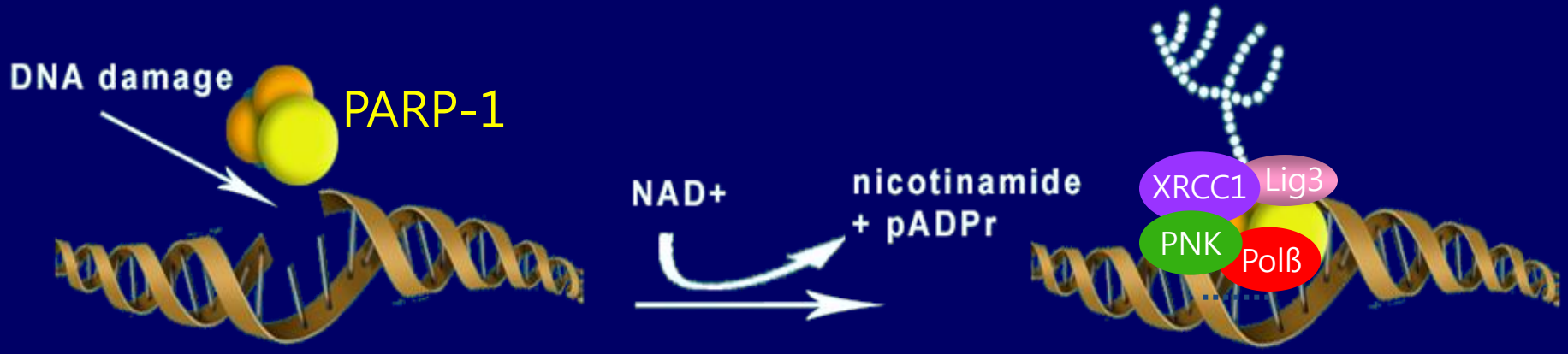
Mechanisms of DNA repair

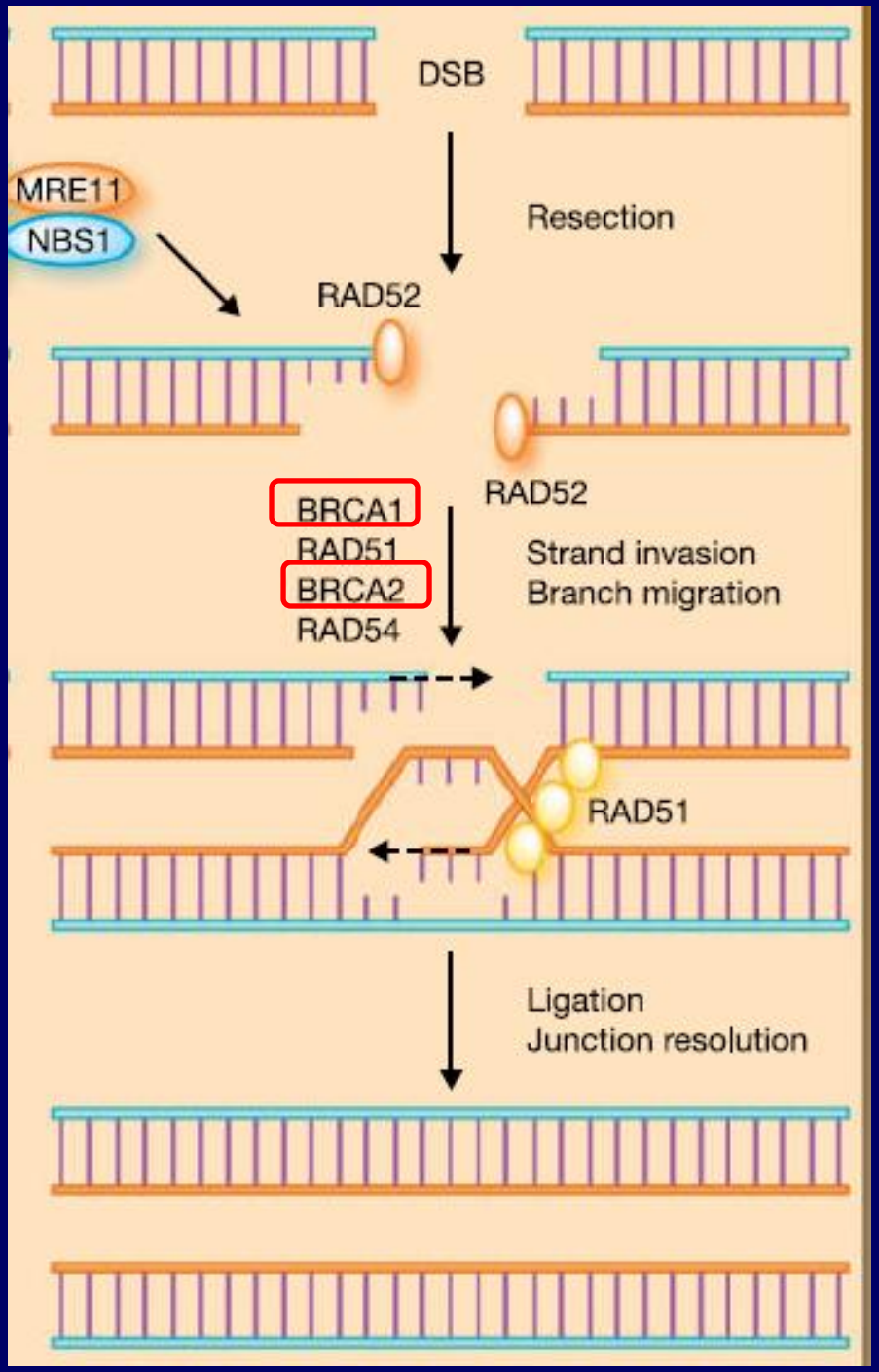


Helleday et al. Nat Rev Cancer 2008; 8: 193-204

PARP-1

- A key role in the repair of DNA single-strand breaks (base excision repair pathway)
- Binds directly to sites of DNA damage
- Recruits other DNA repair enzymes



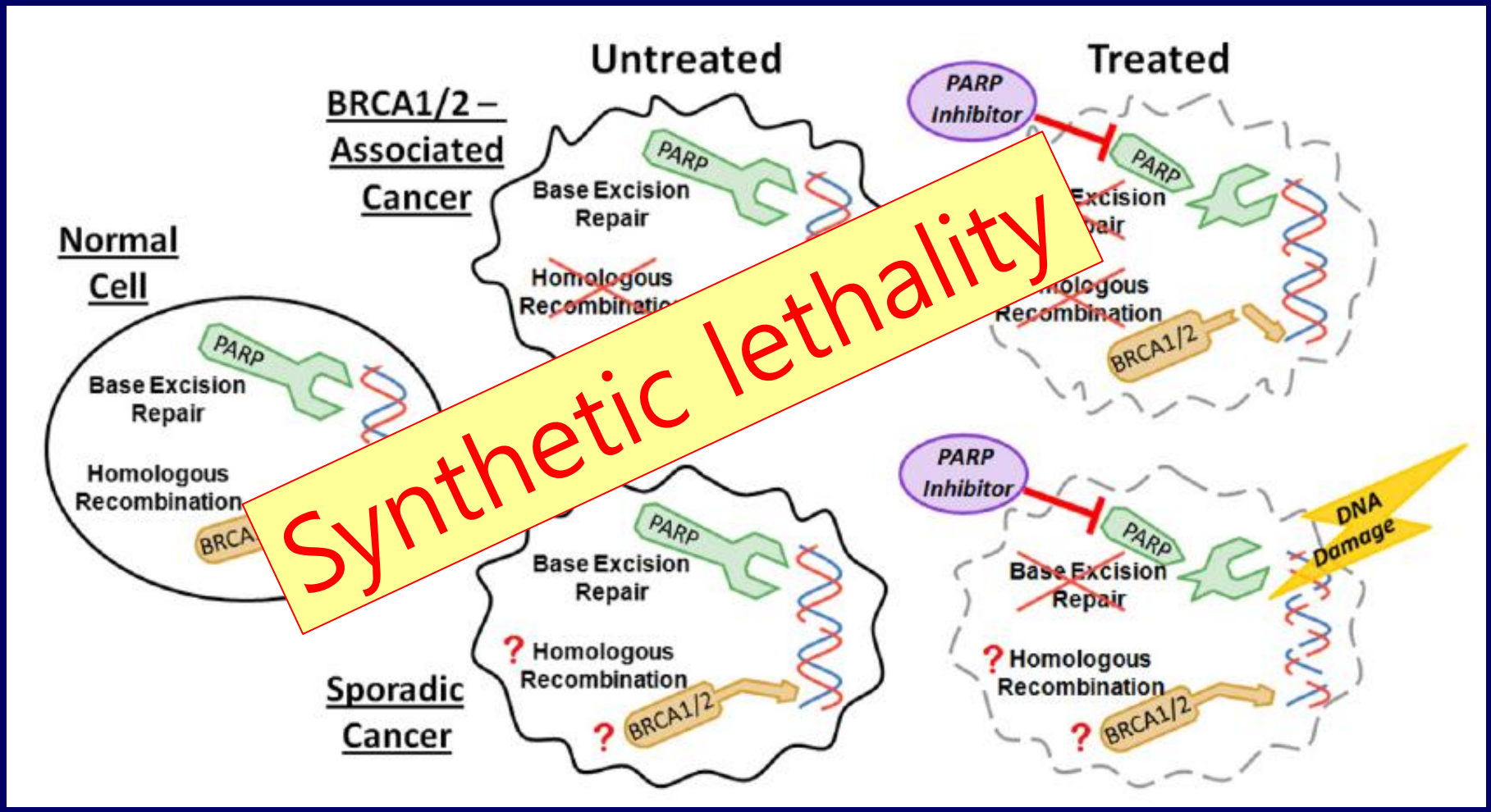


BRCA1/2

Homologous recombination

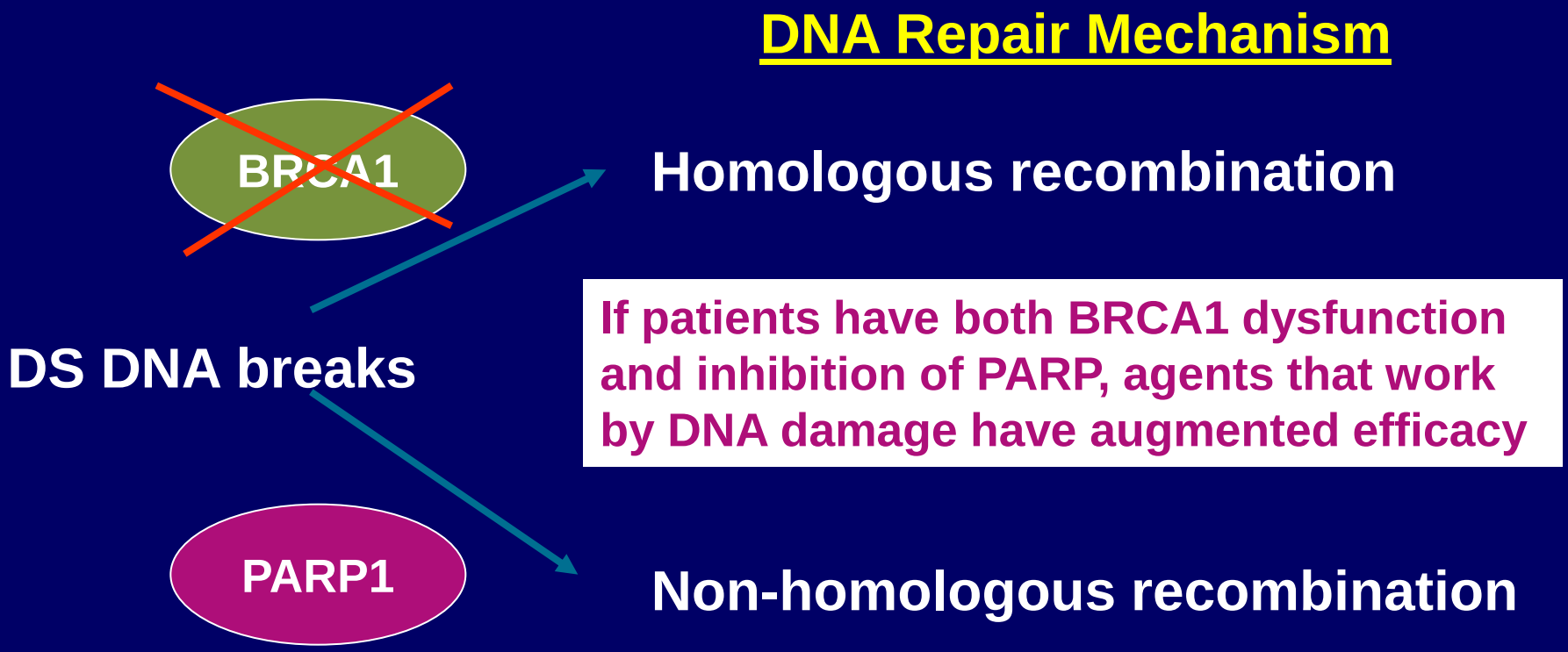
Lisa A. Carey et al. CCR 2010, Oct

PARP Inhibitor Treatment of BRCA1/2-Associated and Sporadic Cancers



Ellisen LW. Cancer Cell 2011, Feb

BRCA dysfunction in TNBC



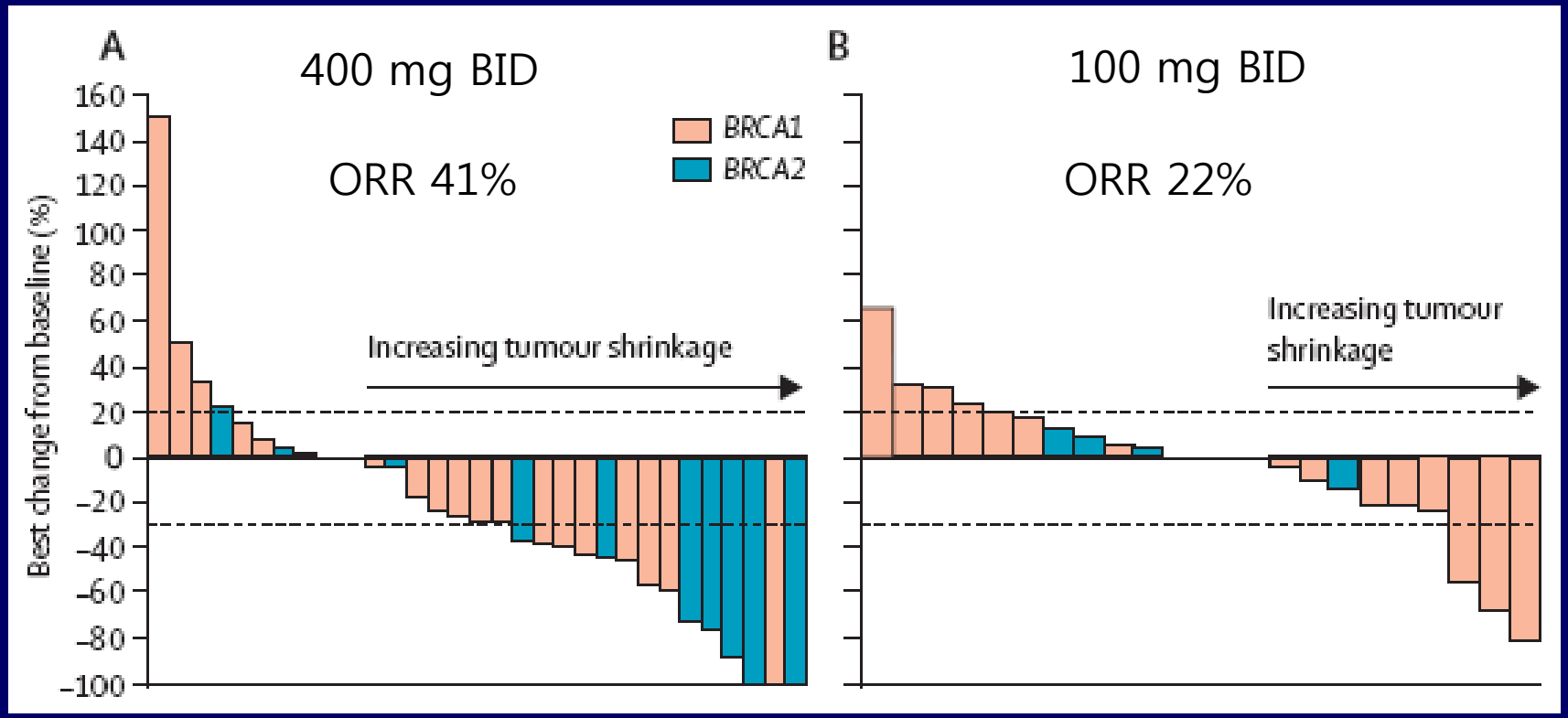
PARP inhibitors are in clinical trials* for both BRCA1 and Triple Negative

PARP inhibitors in development

Agent	Route	Clinical status	company
Olaparib (AZD2281)	Oral	Phase I and II	AstraZeneca
Iniparib (BSI-201)	IV	Phase II and III	Sanofi-Aventis
AGO14699	IV (oral)	Phase I and II	Pfizer
Veliparib (ABT888)	Oral	Phase I and II	Abbott
INO-1001	IV	Phase I	Inotek
CEP-9722	Oral	Phase I	Cephalon
MK4827	Oral	Phase I	Merck & Co

Proof of concept trial in BRCA1/2 breast cancer

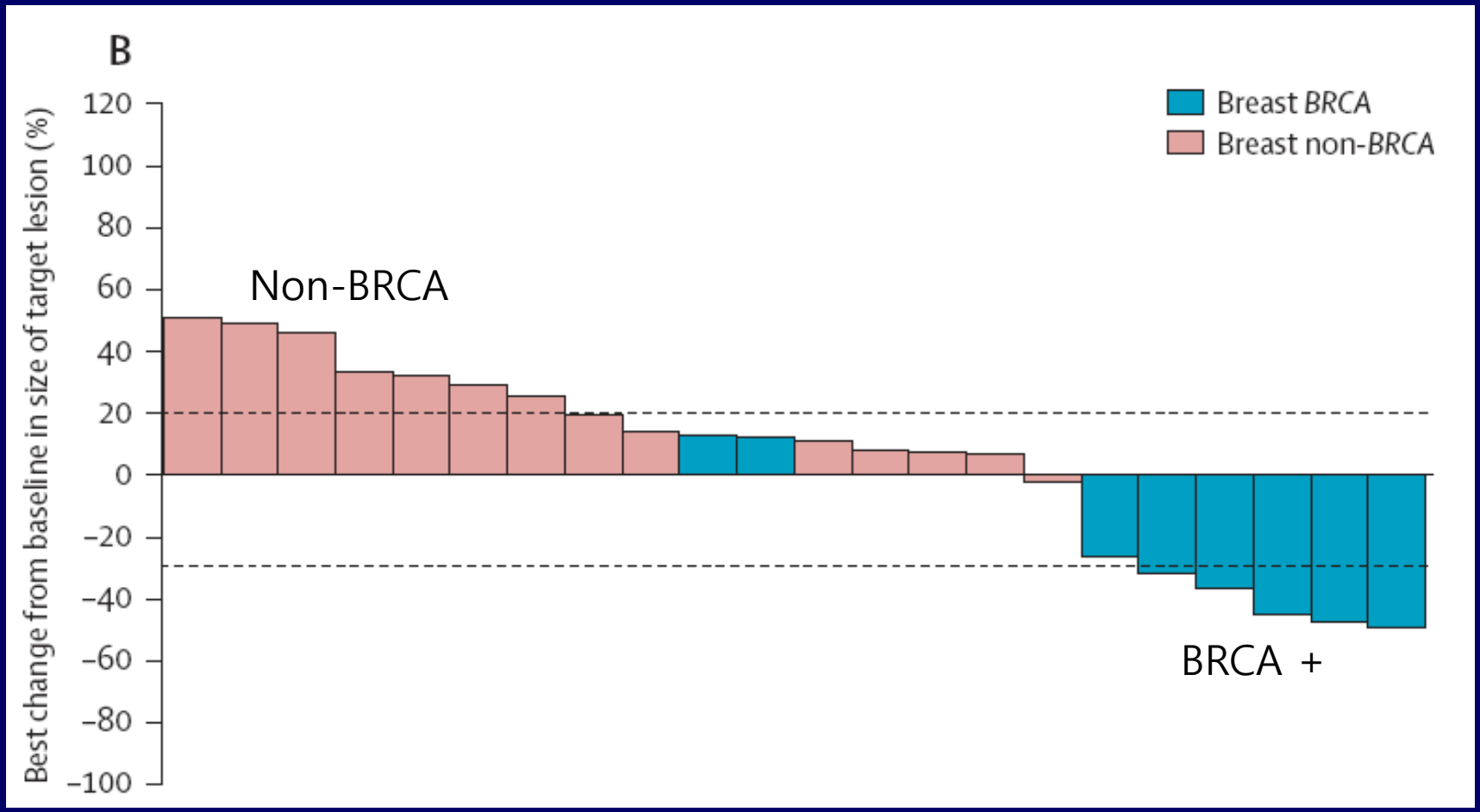
Olaparib in 54 patients with BRCA1 or BRCA2 mutations and advanced breast cancer



Tutt A, et al. Lancet 2010; 376: 235

Olaparib in TNBC

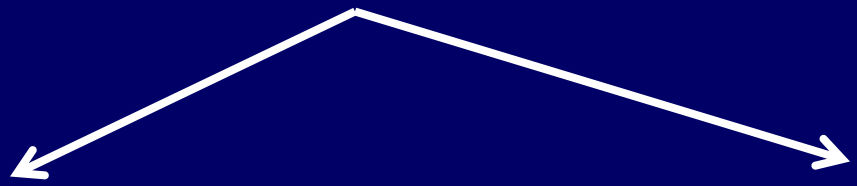
Both BRCA (n=10) and non-BRCA (n=16)



Gelmon KA et al. Lancet 2011; 12: 852

Randomized Phase II chemotherapy + Iniparib in TNBC

Metastatic triple negative
123 patients
No more than 2 prior chemo regimens
(except gemcitabine, platinum)



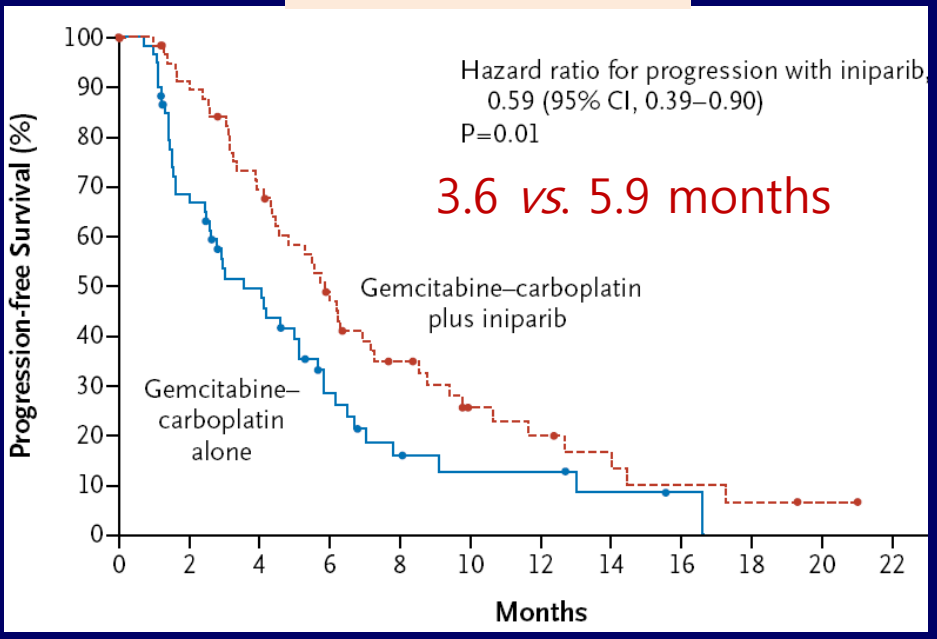
Gemcitabine + Carboplatin	**Iniparib +** Gemcitabine + Carboplatin

- Primary goals: clinical benefit rate, toxicity
- Secondary goals: response, PFS, OS

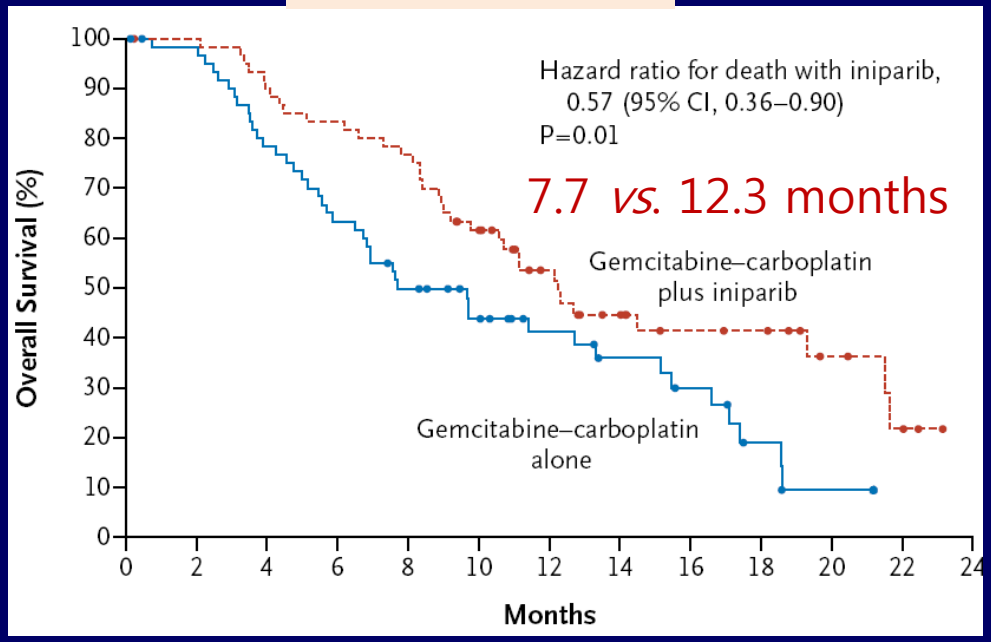
O'Shaughnessy J et al. NEJM 2011

Randomized Phase II chemotherapy + Iniparib in TNBC: Results

HR 0.59 for PFS



HR 0.59 for OS



	GC (n=62)	GC + I (n=61)	*P-value*
Response	32%	52%	0.02
Clinical benefit	34%	56%	0.01

No difference in toxicity

O'Shaughnessy J et al. NEJM 2011

PARP1 inhibitor in TNBC

- PARP1 inhibitor is one of the most promising “targeted therapies” for TNBC.
- Future directions
  - More precisely defining the patients population most likely to respond to the PARP inhibition
  - Discovering and validating candidate biomarkers to predict responders
  - Determining the optimal chemotherapy backbone to combine with PARP inhibitors

Anti-angiogenic agent : Bevacizumab

Phase III study of Bevacizumab (BV) and the First-Line Chemotherapy in Metastatic Breast Cancer

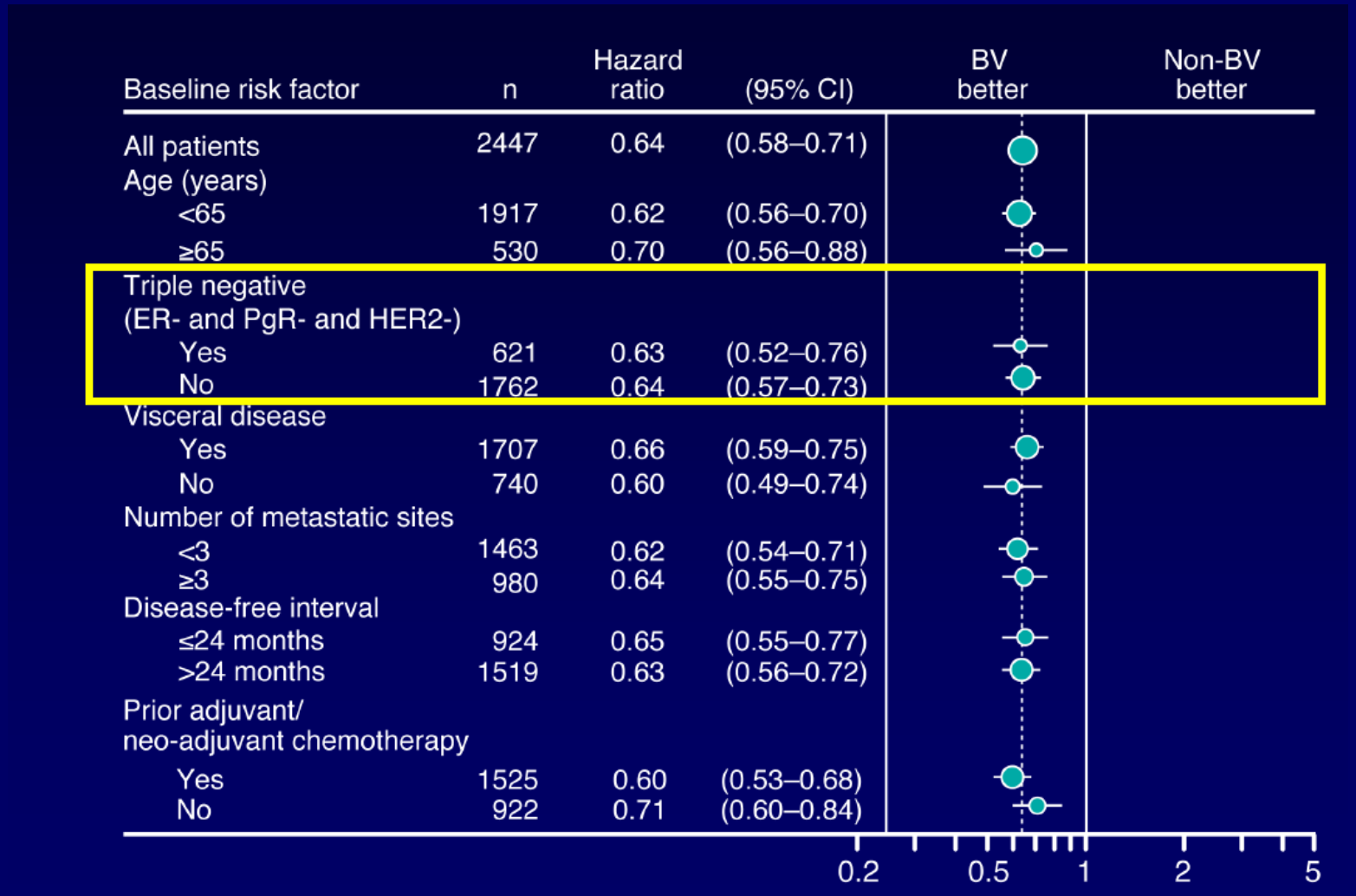
	E2100		AVADO		RIBBON-1 (Cape)		RIBBON-1 (Tax/Anthra)	
	Non-BV	BV	Non-BV	BV	Non-BV	BV	Non-BV	BV
Median PFS, mo	5.8	11.3	7.9	8.8	5.7	8.6	8.0	9.2
Stratified HR (95% CI)	0.48 (0.39-0.81)		0.62 (0.48-0.79)		0.69 (0.58-0.84)		0.64 (0.52-0.80)	
***P* values**	<.0001		.0003		.0002		.0001	

Cape, capecitabine;Tax/Anthra, taxane/anthracycline
*15 mg/kg cohort

O'Shaughnessy J et al. J Clin Oncol 2010; 28 (7s): Abstract 1005

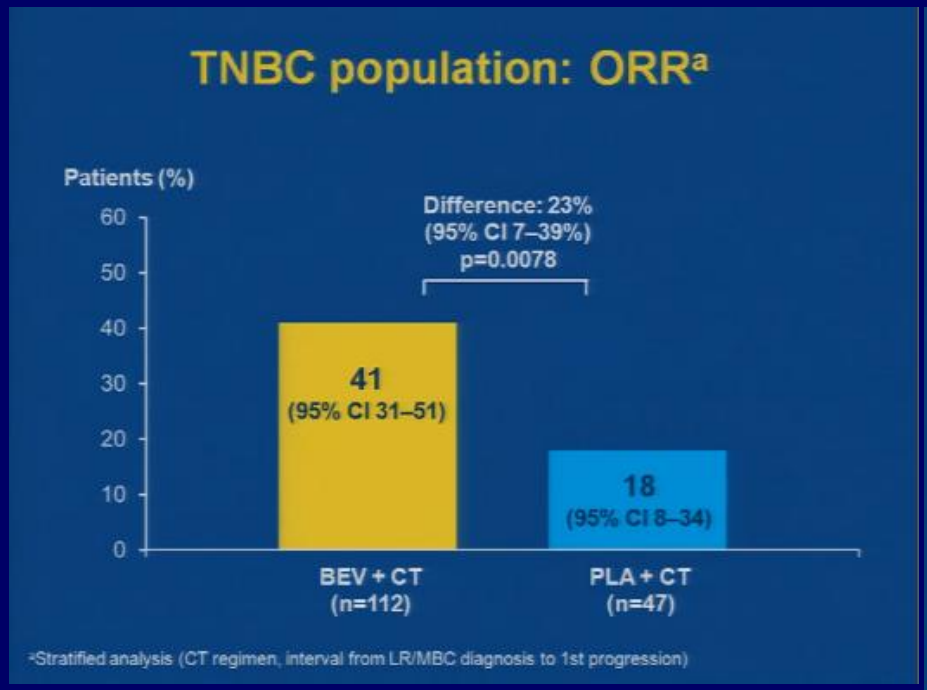
TNBC: Bevacizumab

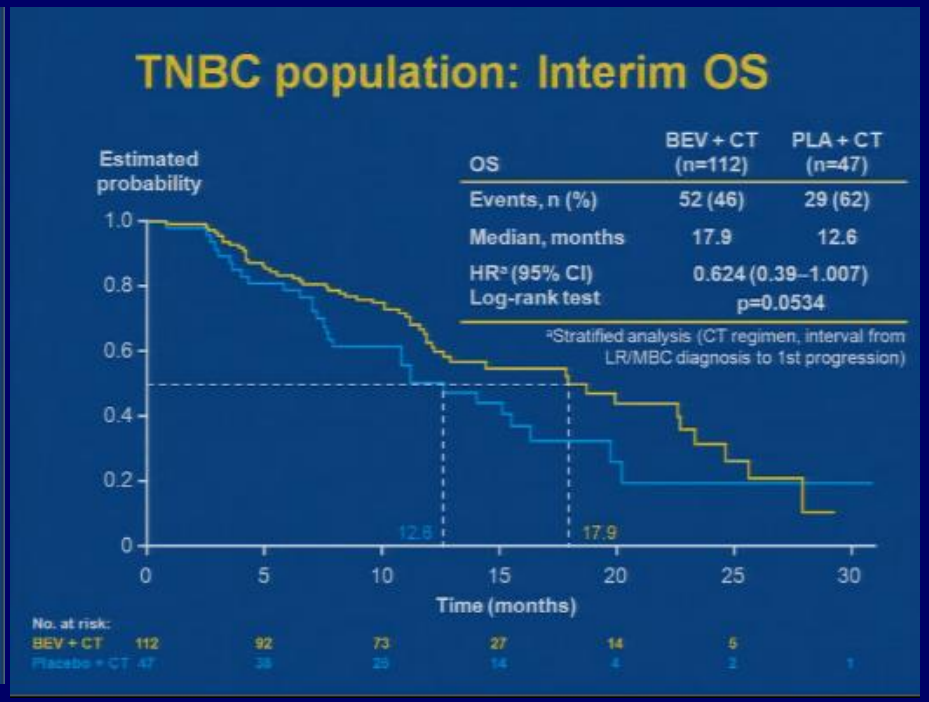
Analysis of PFS by Subgroups in meta-analysis



O'Shaughnessy J et al. J Clin Oncol 2010; 28 (7s): Abstract 1005

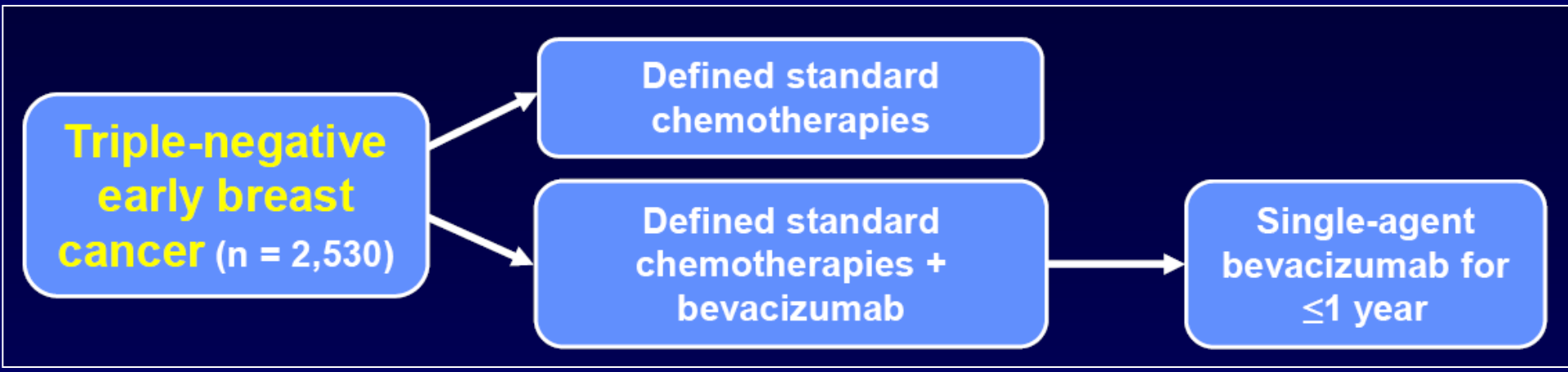
Subgroup analysis of RIBBON-2 study





ASCO 2011

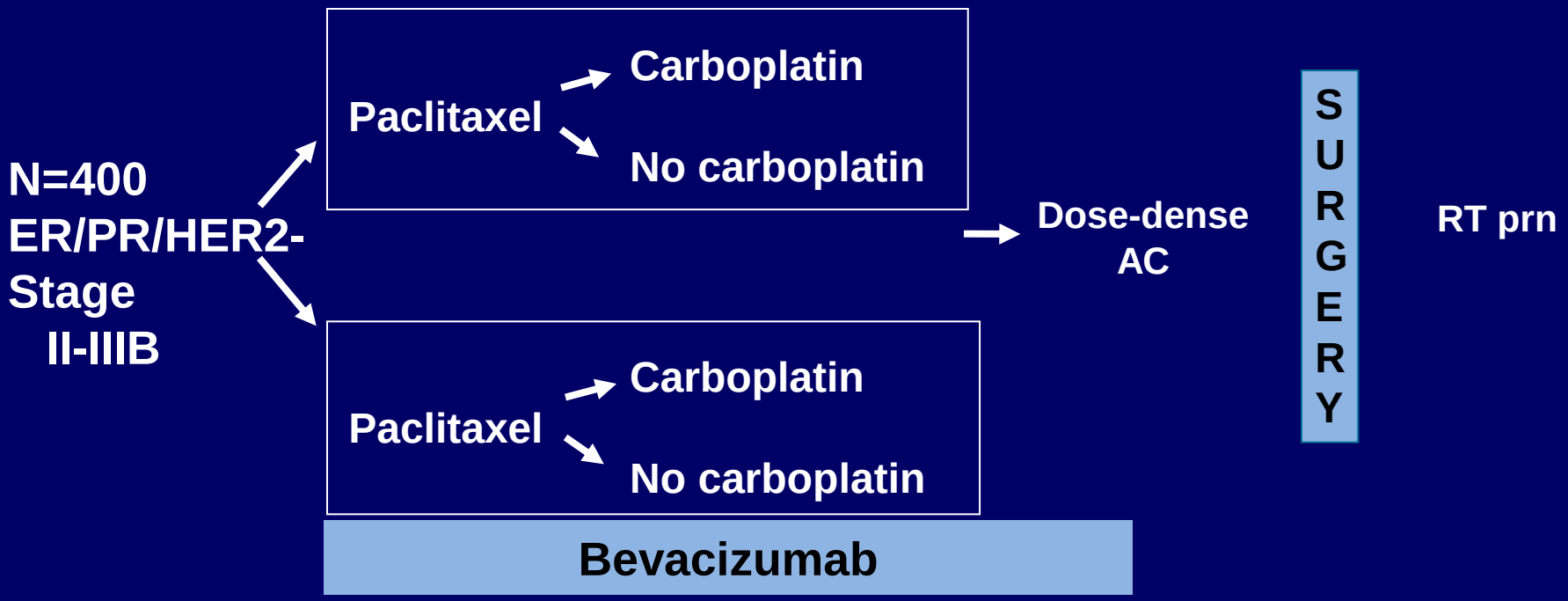
Phase III Trial of Adjuvant Bevacizumab Plus Chemotherapy in Early TNBC (BEATRICE)



- Primary endpoint: invasive DFS
- Secondary endpoints:

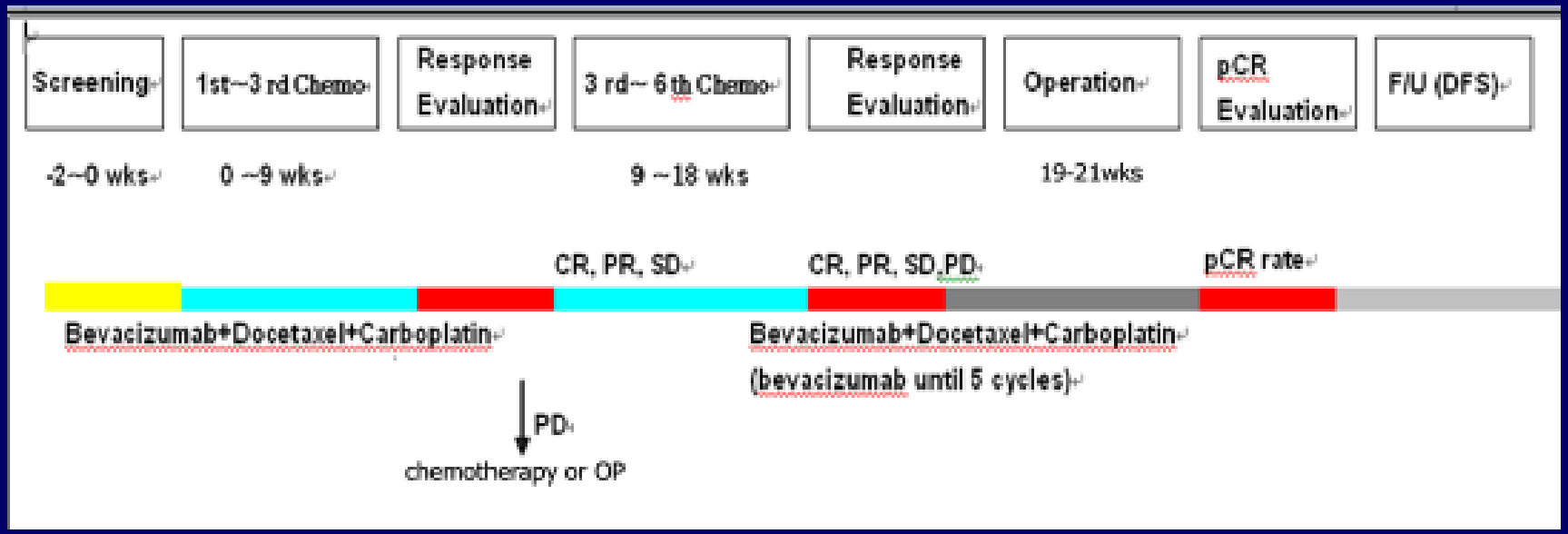
  OS, DFS, distant DFS, tolerability and safety

Intergroup/CALGB 40603: Triple Negative Neoadjuvant Trial



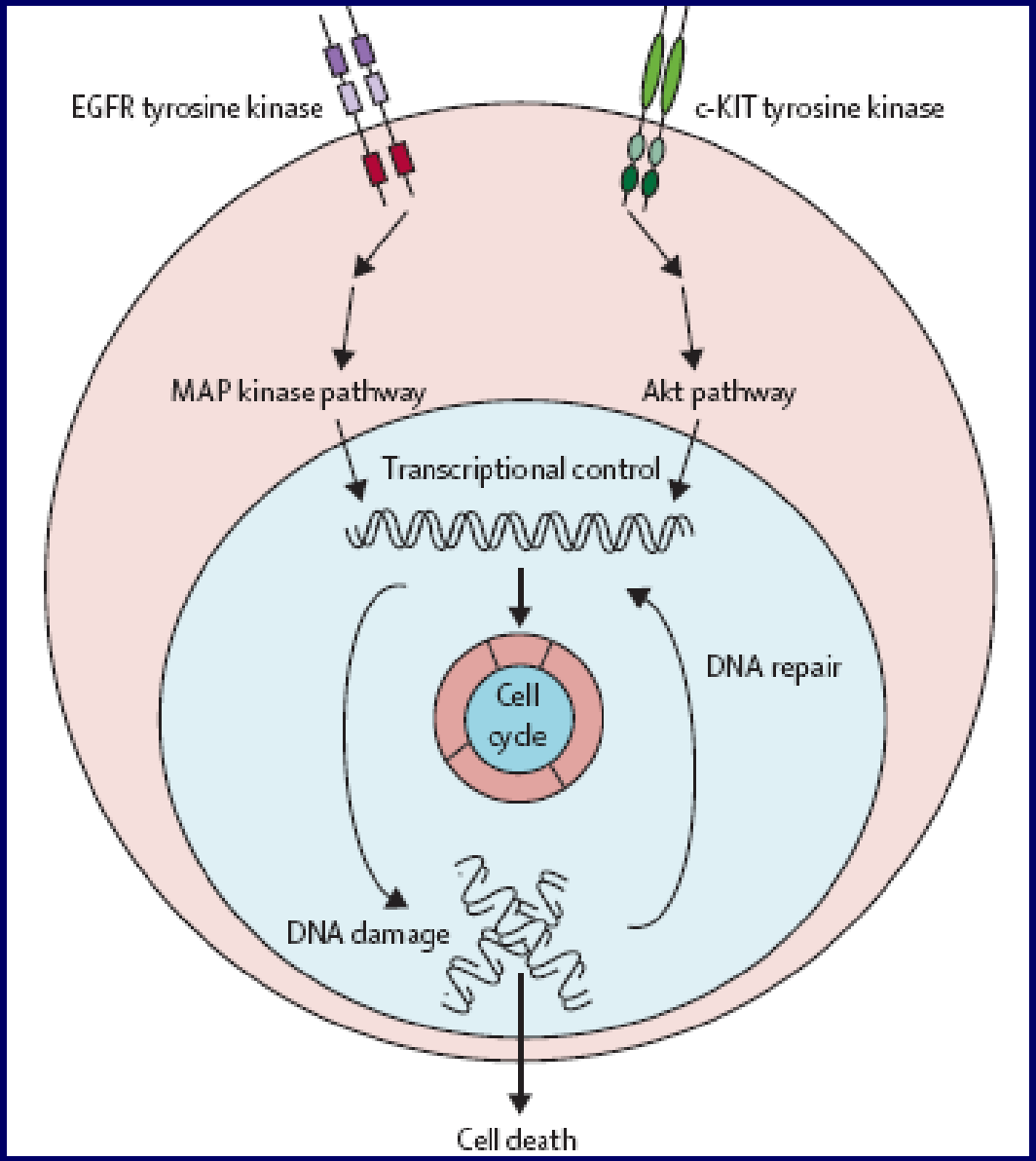
NEAT trial in Korea

- Phase II trial of NEoadjuvant bevAcizumab, docetaxel and carboplatin for Triple negative breast cancer
- Primary endpoint: pathologic CR
- Enrollment was finished in 7/2011



Others

Potential therapeutic targets in TNBC



Coombes RC et al.
Lancet Oncology 2007; 8: 235

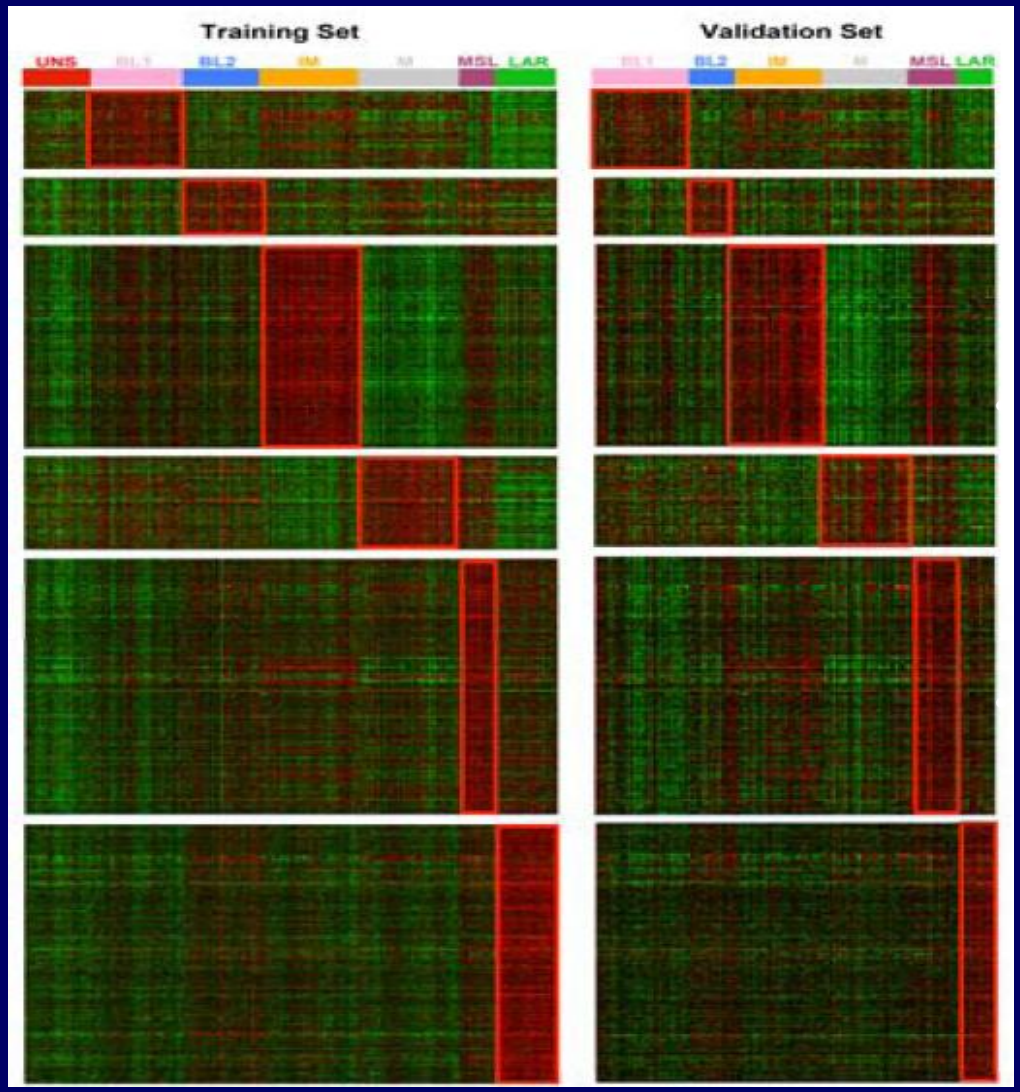
Ongoing clinical trials of targeted agents in TNBC

Agent	Mechanism	Phase	Setting	Other agents in combination	NCT registry number
Iniparib (BSI-201)	PARP inhibitory activity	III	Metastatic	Gemcitabine/carboplatin	00938654
		II	Metastatic	Gemcitabine/carboplatin	00540358, 01045304
		II	Neoadjuvant	Gemcitabine/carboplatin	00813956
Veliparib (ABT-888)		II	Metastatic	Temozolomide	NCT01009788
		I	Metastatic	Cisplatin/vinorelbine	NCT01104259
Olaparib (AZD2281)		II	Metastatic	Paclitaxel	00707707
		II	Neoadjuvant	None	0078254
PF-01367338		II	Neoadjuvant	Cisplatin	01074970
Bevacizumab	VEGF monoclonal	III	Adjuvant	None	00528567
		II	Metastatic	Nab-paclitaxel	00472693
		II	Metastatic	Paclitaxel/carboplatin	00691379
		II	Metastatic	Paclitaxel/capecitabine	01069796
		II	Metastatic	Docetaxel/carboplatin	00608972
Cetuximab	EGFR monoclonal	II	Neoadjuvant	Docetaxel	00600249
		II	Metastatic	Cisplatin	00463788
		II	Metastatic	Ixabepilone	00633464
Panitumumab		II	Metastatic	Paclitaxel/carboplatin	01009983
		II	Metastatic	Gemcitabine/carboplatin	00894504
Erlotinib	EGFR kinase inhibitor	II	Metastatic	None	00739063
		II	Neoadjuvant	Chemotherapy	00491816
Dasatinib	Src/Abl kinase inhibitor	II	Metastatic	None	00371254, 00817531
Sunitinib	Multikinase inhibitor	II	Metastatic	None	00246571
		II	Neoadjuvant	Paclitaxel/carboplatin	00887575
Everolimus	mTOR inhibitor	II	Metastatic	None	00827567
		II	Neoadjuvant	Cisplatin/paclitaxel	00930930

Transcriptome Analysis of Triple Negative Breast Cancers Identifies Six Distinct Biological Subgroups and Reveals Therapeutic Strategies

Brian D Lehmann[1], Joshua A Bauer[1], Xi Chen[2], Melinda E Sanders[3], Yu Shyr[2,4] and Jennifer A Pietenpol[1,4]

[1]Department of Biochemistry, [2]Department of Biostatistics, [3]Department of Pathology and [4]The Vanderbilt-Ingram Cancer Center, Nashville, TN, United States, 37232



- Basal-like TNBC express high levels of proliferation and DNA damage response genes and representative cell lines that are sensitive to cisplatin.
- Mesenchymal-like TNBC are enriched in growth factor and EMT genes and cell lines referentially respond to Src and PI3K/mTOR inhibitors.
- Luminal AR TNBC express high levels of the androgen receptor and cell lines are sensitive to the AR antagonist bicalutamide and Hsp90 inhibitors.

Lehmann BD, et al. SABCS 2010, J Clin Invest 2011; 121: 2750

Conclusions

- TNBC is a distinct subtype of BC and is associated with treatment challenges due to its aggressive nature
- TNBC has no specific target…. Yet
  - Molecular pathways that control tumor development could determine treatment
  - Platinum based chemotherapy is emerging as backbone of new treatments
  - Introduction of novel agents (PARP inhibitor) is showing promise
  - Results from huge amounts of research ongoing in this subtype will help determine the best treatment strategy.

Thank you for your attention !