ATLAS OF MOLECULAR ONCOLOGY

BREAST CANCER PATHWAYS

Targeting DNA repair in BRCA 1/2 and Triple Negative Breast Cancer

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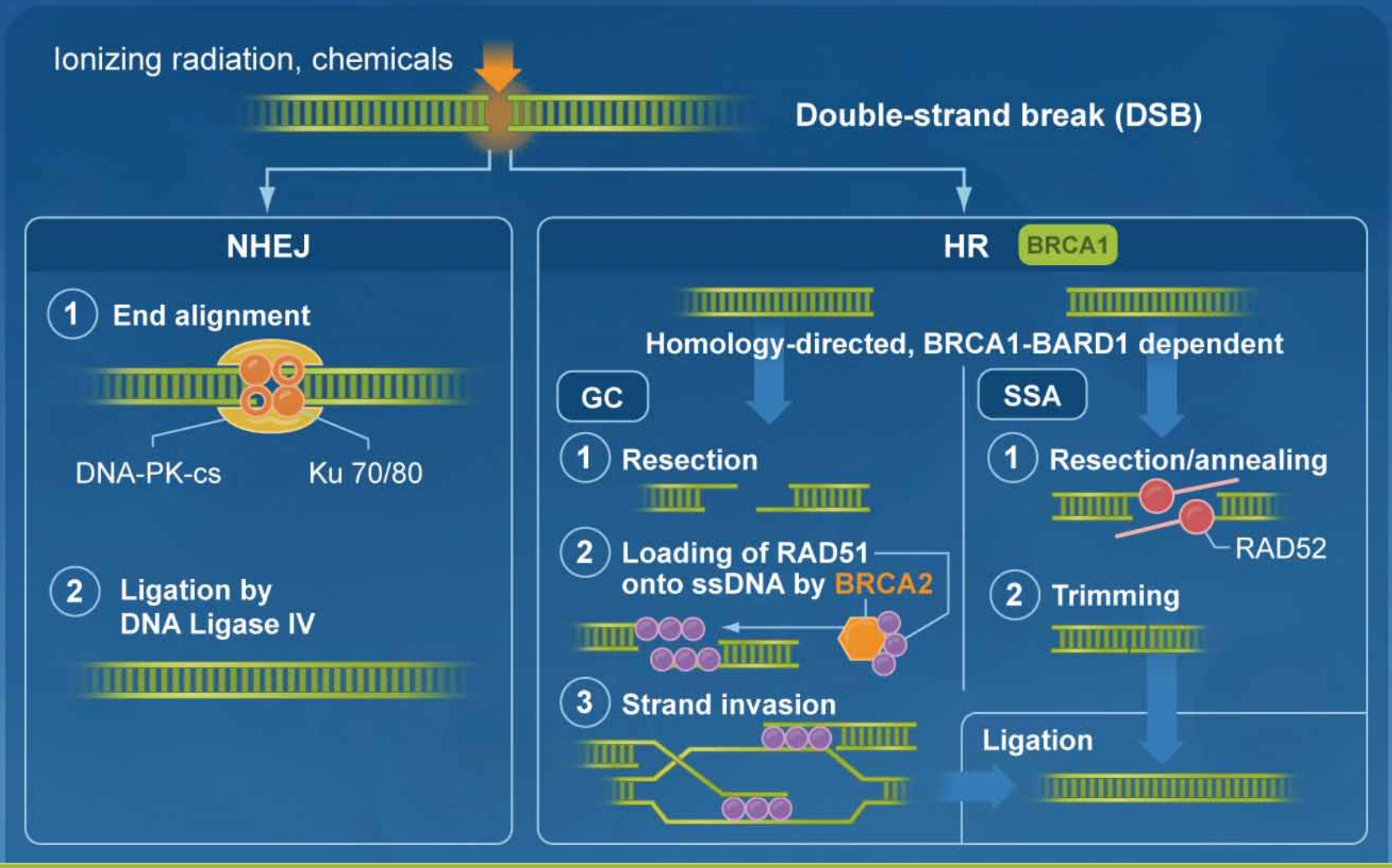
Disclosures for Andrew Tutt, MB ChB, PhD

Advisory Committee	AstraZeneca Pharmaceuticals LP, Bristol-Myers Squibb Company, Novartis Pharmaceuticals Corporation, Pfizer Inc, Sanofi-Aventis
Honoraria	AstraZeneca Pharmaceuticals LP, Sanofi-Aventis

DNA repair mechanisms in cells

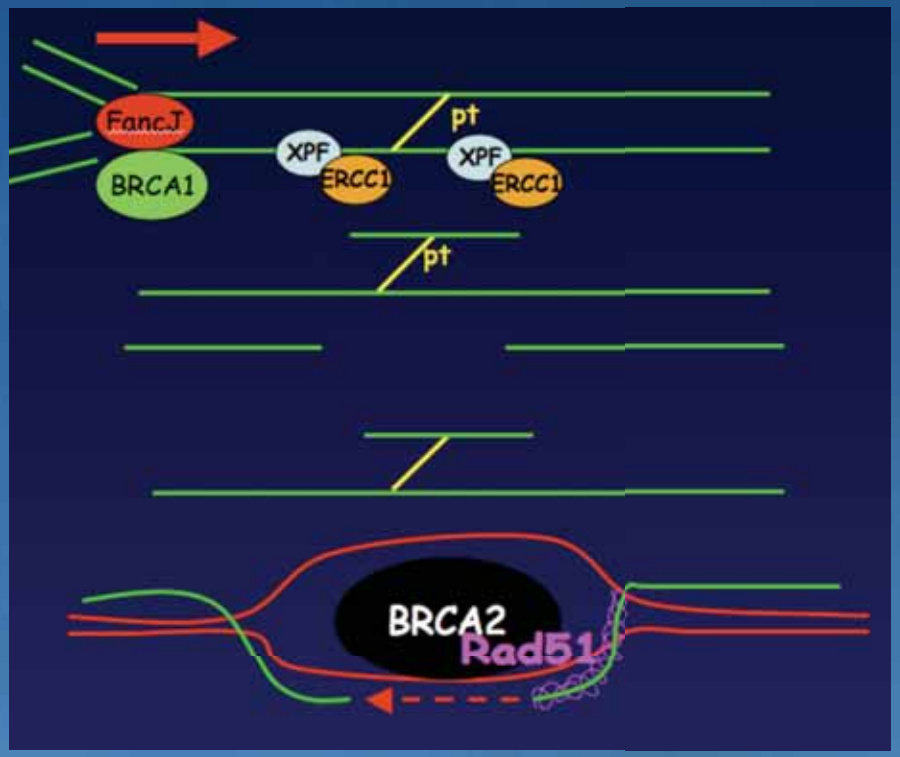
- Base-excision repair (PARP)
- Nucleotide-excision repair
- Recombinational repair (BRCA1/BRCA2)
- Mismatch repair

Double Strand Break Repair Pathways



Tutt A et al. *Cold Spring Harb Symp Quant Biol* 2005;70:139–148

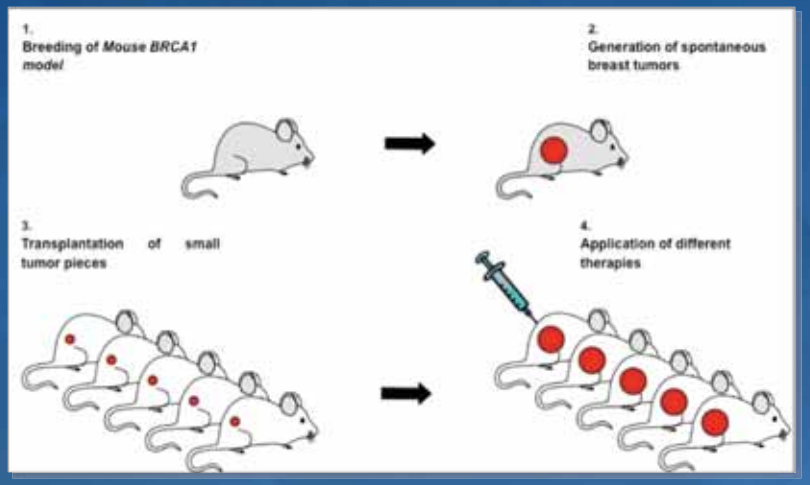
How to target loss of BRCA1 or BRCA2 function?

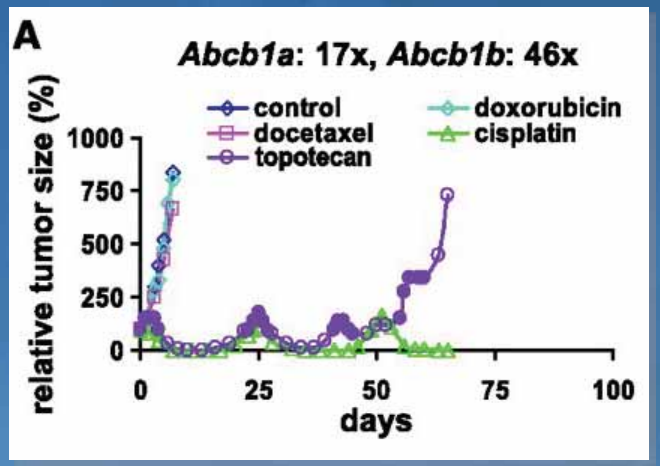


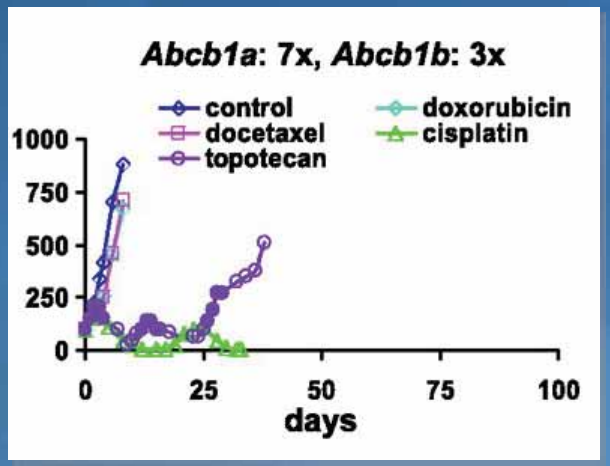
- Lesions that arrest DNA replication forks
- Loss of homologous recombination
- How could we exploit defect ?
- Platinum cross-links ?
- Topo-1 inhibitors ?
- Alkylating agents ?
- PARP inhibitors ?

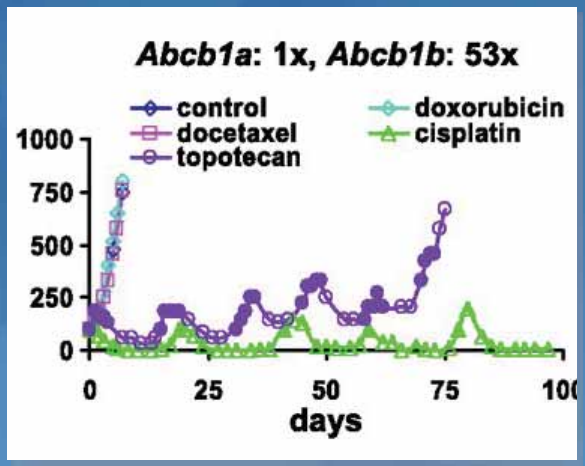
Tutt A et al. ***Cold Spring Harb Symp Quant Biol*** **2005;70:139–148**

BRCA1 mutation basal-like breast cancer mouse model





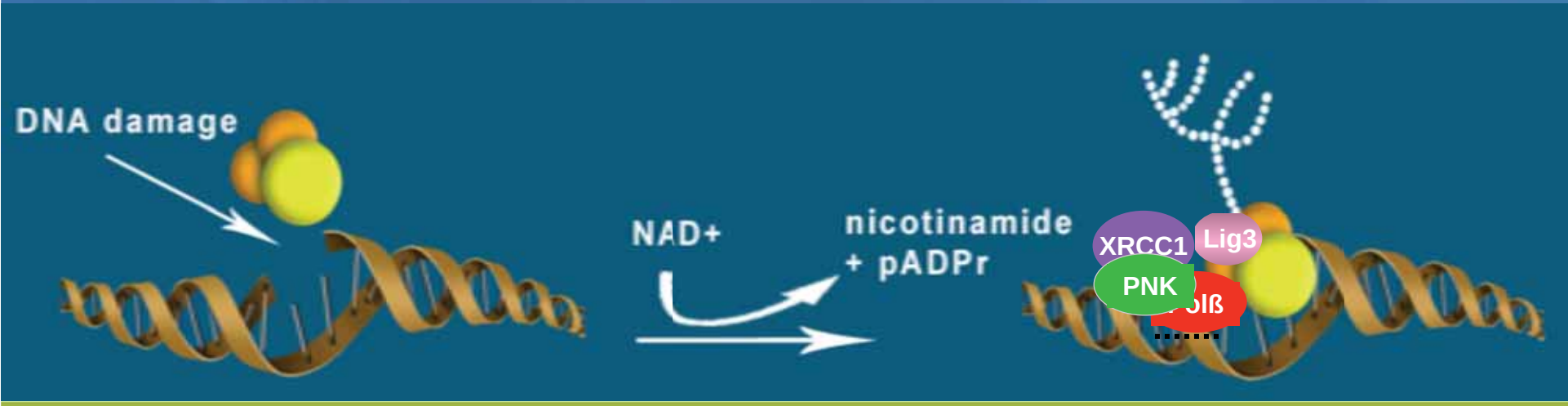




Reprinted with permission from Zander SA et al. *Cancer Res* 2010;7a0:1700-1710, figure 3.

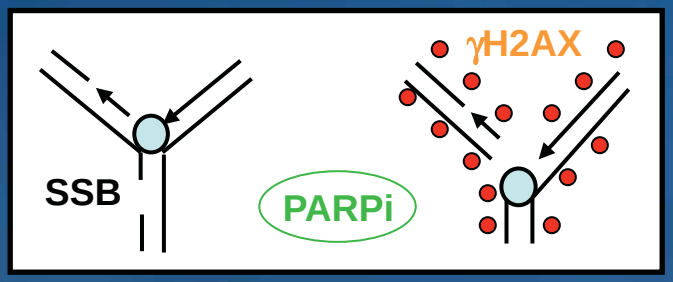
Poly (ADP-ribose) polymerase (PARP)

- A key regulator of DNA damage repair processes
- Involved in DNA base-excision repair (BER)
- Binds directly to DNA damage
- Produces large branched chains of poly (ADP-ribose)
- Attracts and assists BER repair effectors



Tutt A on behalf of ICEBERG investigators.
ASCO 2009;Abstract CRA501

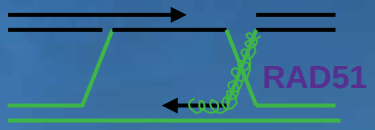
PARP inhibition and tumor selective synthetic lethality



DNA replication fork arrest and collapse

Normal BRCA1/ BRCA2

BRCA1/BRCA2 failure



HR-based repair

Impaired HR repair

Alternative error prone repair

Chromosome Stability

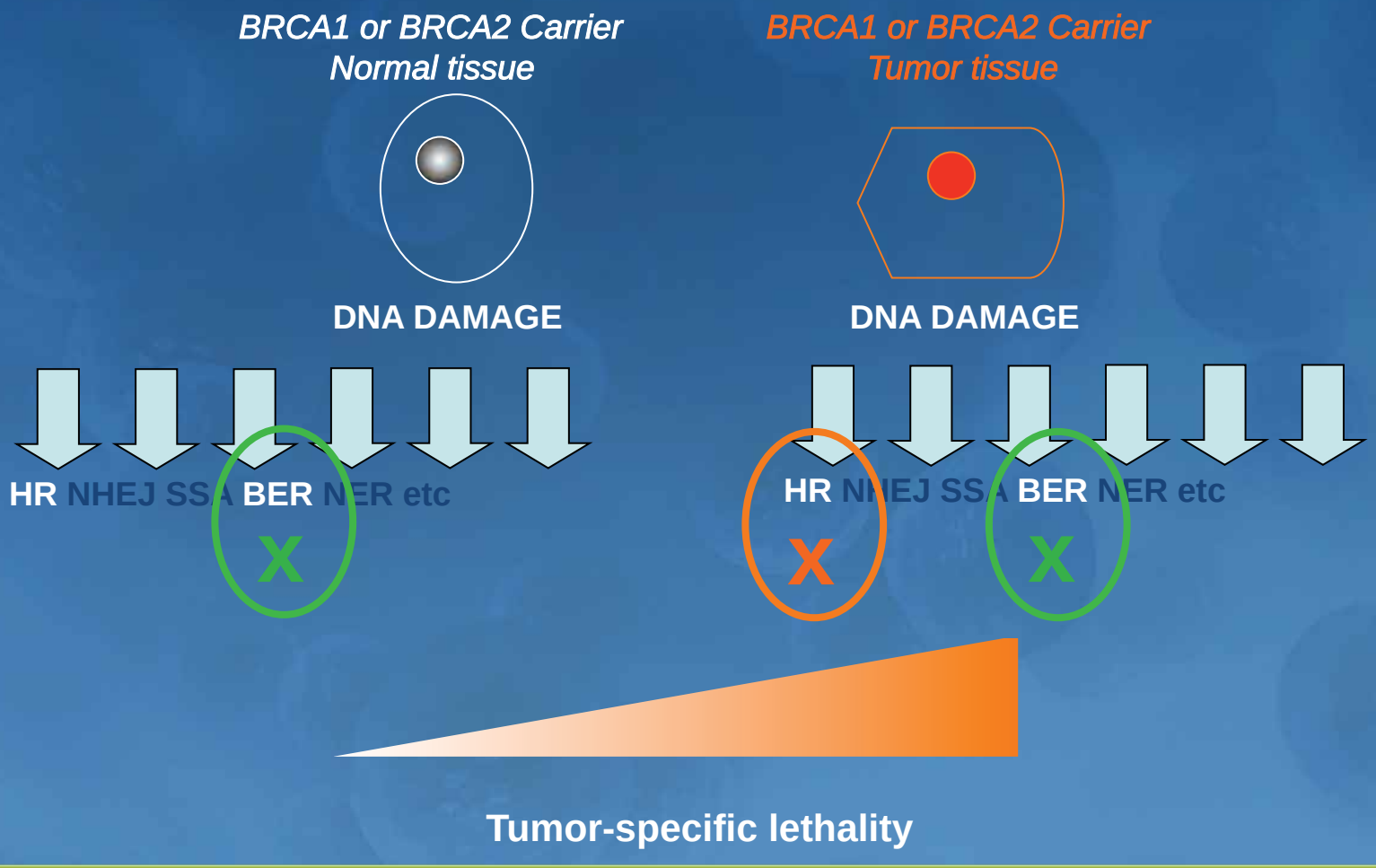
Cell Survival

Chromosomal Instability

Cell Death

Farmer H et al. *Nature* 2005;434:917–921; Bryant HE et al. *Nature* 2005;434:913–917

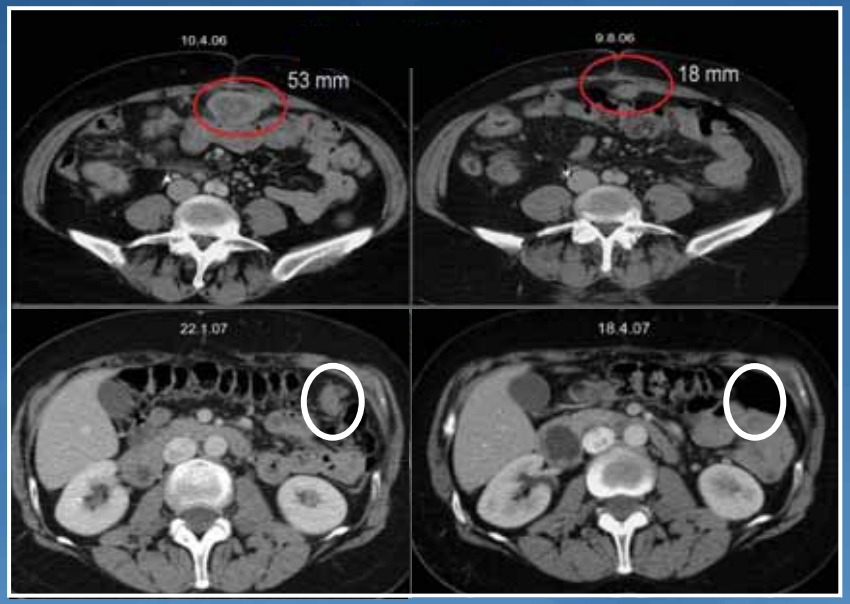
Targeting BRCA for tumor selective killing



Tutt A et al. *Cold Spring Harb Symp Quant Biol* 2005;70:139–148;
McCabe N et al. *Cancer Res* 2006;66:8109–8115

Olaparib: A novel, orally active PARP inhibitor

- A phase I trial identified olaparib (AZD2281; KU-0059436) 400 mg bid as the maximum tolerated dose[1] with a 28% (13/46 pts) response rate (RECIST) in BRCA-mutated ovarian cancer[2]
- Most common toxicities: CTCAE Grade 1 and 2 nausea and fatigue
- Significant PARP inhibition and tumor response at olaparib doses 100–400 mg bid



1. Yap T et al. *J Clin Oncol* 2007;25(18S):abst 3529
2. Fong PC et al. *N Engl J Med* 2009;361(2):123-34.

Phase II Trial of the Oral PARP Inhibitor Olaparib in BRCA-Deficient Advanced Breast Cancer

Andrew Tutt[1], Mark Robson[2], Judy E Garber[3], Susan Domchek[4], M William Audeh[5], Jeffrey N Weitzel[6], Michael Friedlander[7], James Carmichael[8]

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[2]Memorial Sloan-Kettering Cancer Center, New York, NY, USA

[3]Dana-Farber Cancer Institute, Boston, MA, USA

[4]University of Pennsylvania, Philadelphia, PA, USA

[5]Cedars-Sinai Cancer Center, Los Angeles, CA, USA

[6]City of Hope Comprehensive Cancer Center, Duarte, CA, USA

[7]Prince of Wales Cancer Centre, Randwick, Sydney, New South Wales, Australia

[8]AstraZeneca, Macclesfield, UK

Study no: D0810C00008; KU36-44

Study design and eligibility

- To assess the efficacy and tolerability of oral olaparib in *BRCA1/ BRCA2* mutation carriers with breast cancer
- Proof-of-concept phase II study, single-arm sequential cohort design

Confirmed BRCA1 or BRCA2 mutation
Advanced refractory breast cancer (stage IIIB/IIIC/IV) after failure of ≥1 prior chemotherapy for advanced disease

Cohort 1 (enrolled first)	Cohort 2
Olaparib 400 mg po bid (MTD) 28-day cycles; n = 27	Olaparib 100 mg po bid 28-day cycles; n = 27

Tutt A on behalf of ICEBERG investigators.
ASCO 2009;Abstract CRA501

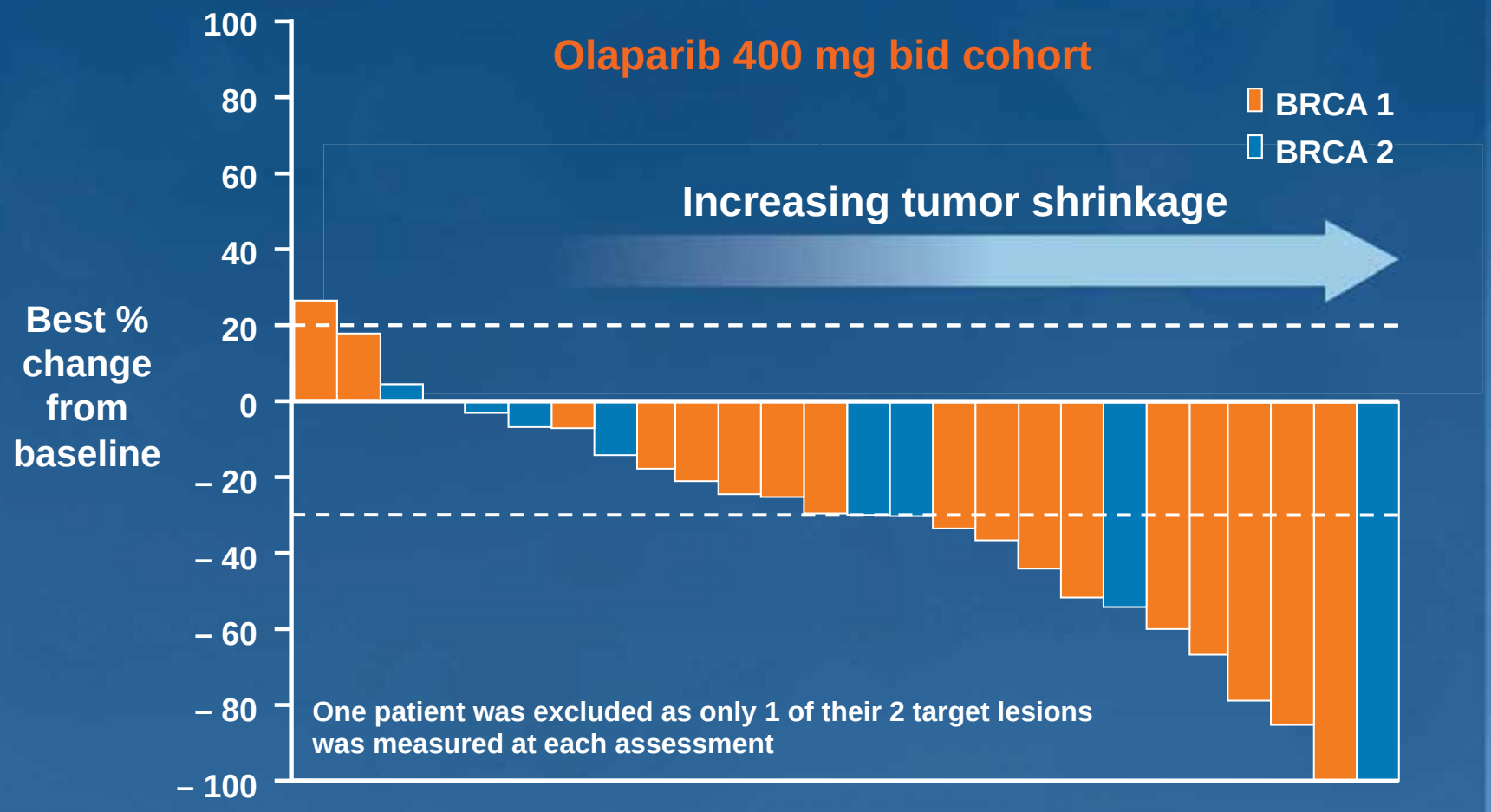
Efficacy

ITT cohort	Olaparib 400 mg bid (n = 27)	Olaparib 100 mg bid (n = 27)
Overall Response Rate, n (%)	11 (41)*	6 (22)*
Complete Response, n (%)	1 (4)	0
Partial Response, n (%)	10 (37)	6 (22)

*An additional 1 patient in the 400 mg cohort and 3 patients in the 100 mg cohort had unconfirmed responses

Tutt A on behalf of ICEBERG investigators.
ASCO 2009;Abstract CRA501

Best percent change from baseline in target lesions by genotype



Tutt A on behalf of ICEBERG investigators.
ASCO 2009;Abstract CRA501

BRCA1 downregulation

Int. J. Cancer: **116**, 340–350 (2005)

FAST TRACK

High-throughput protein expression analysis using tissue microarray technology of a large well-characterised series identifies biologically distinct classes of breast cancer confirming recent cDNA expression analyses

Dalia M. Abd El-Rehim[1], Graham Ball[2], Sarah E. Pinder[1], Emad Rakha[1], Claire Paish[1], John F.R. Robertson[3], Douglas Macmillan[3], Roger W. Blamey[1] and Ian O. Ellis[1]*

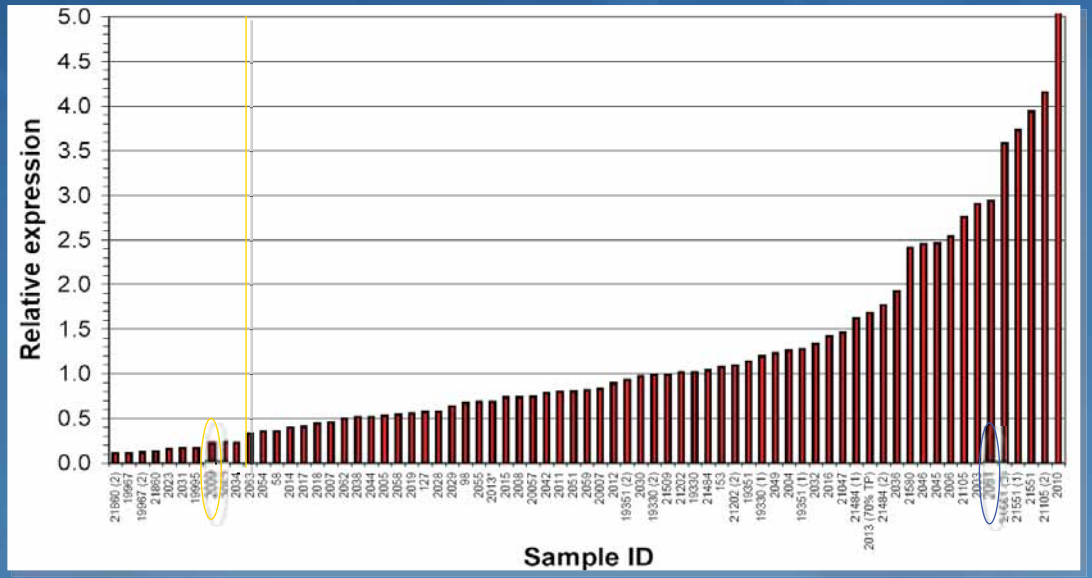
Journal of Pathology
J Pathol 2003; **200**: 207–213.
Published online 17 March 2003 in Wiley InterScience (www.interscience.wiley.com). **DOI:** 10.1002/path.1348

Original Paper

Prognostic significance of BRCA1 expression in sporadic breast carcinomas

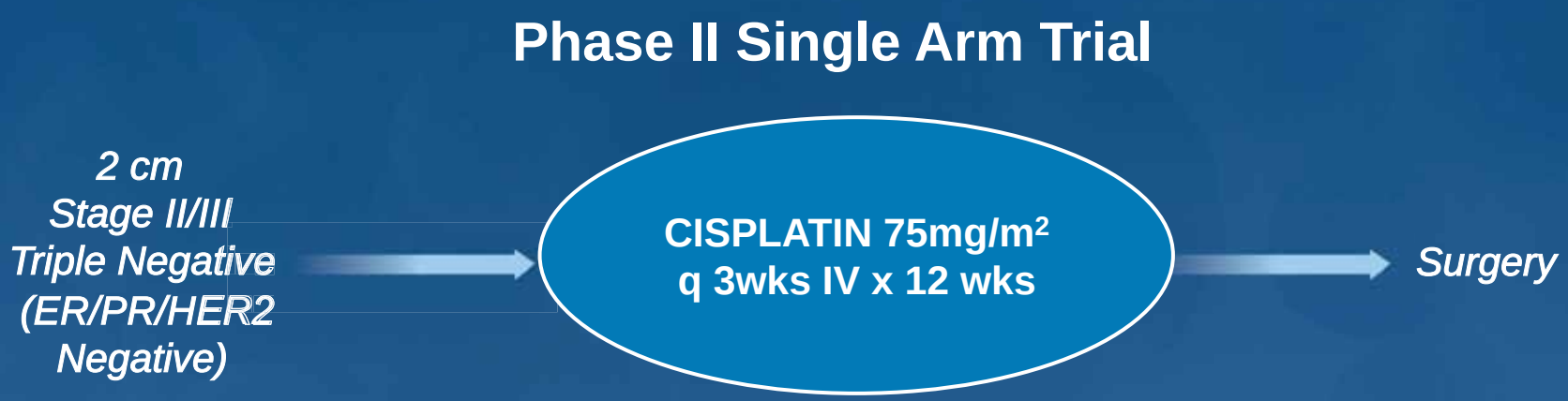
H Lambie,[1] A Miremadi,[1] SE Pinder,[1] JA Bell,[1] P Wencyk,[1] EC Paish,[1] RD Macmillan[2] and IO Ellis[1]*

- High histological grade
- Medullary histological type
- Metaplastic histological type
- Basal-like IHC phenotype



With permission from Hanneman J. EBCC-6 2008;Abstract 308; Turner et al. *Oncogene* 2007; Rakha, Reis-Filho, Ellis; *J Clin Oncol* 2008

Triple Negative Neoadjuvant Trial

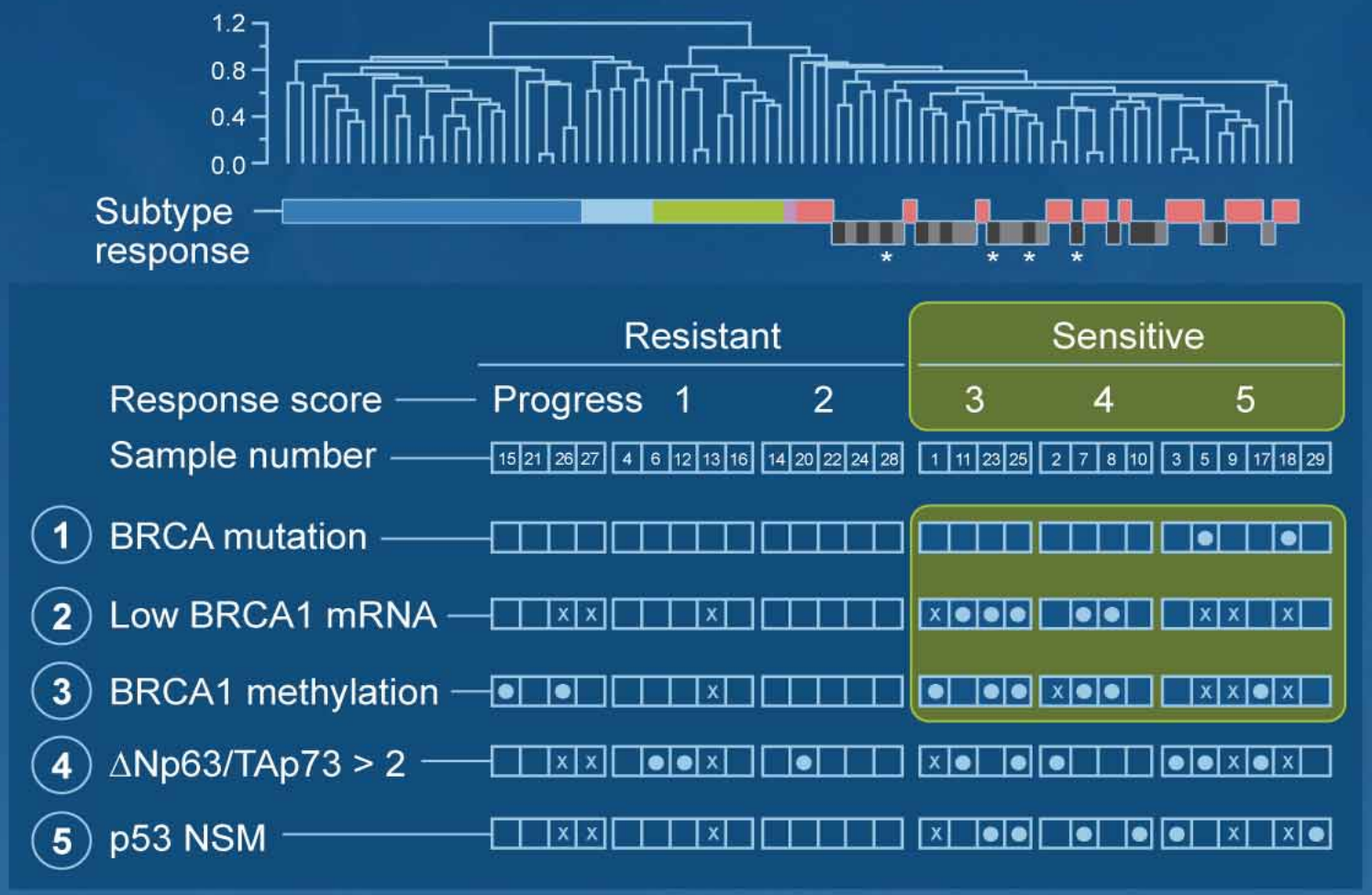


- N = 28
- median age: 50 yrs
- median tumor size = 3.0 cm (1.5 - 6.3 cm)
- 2 BRCA1 mutation carriers

- pCR – 22% - incl 2 BRCA1 carriers
- Good MP Score 3-5 – 50%
- Minor response MP 1-2 – 36%
- Progression 14%

Silver DP et al. J *Clin Oncol* 2010; 28:1145-1153

Impaired BRCA1 and neoadjuvant cisplatin response in TNBC



Silver DP et al. *J Clin Oncol* 2010;28:1145-1153.

PTEN pathway loss and loss of HR repair and PARPi sensitivity

- Essential role for nuclear PTEN in maintaining chromosomal integrity
  Shen et al Cell 128, 157–170, January 12, 2007
- PTEN pathway loss common in TN/basal-like
  (Saal LH Nat Genet. 2008;40:102–107, Marty Breast Cancer Res. 2008; 10(6), López-Knowles Int J Cancer. 2009 Aug 14)
- Loss of PTEN causes a reduction in HR repair and induces sensitivity to PARP inhibition
  (Mendes-Pereira A, EMBO Mol Med 1(6-7) 2009)

Efficacy of BSI-201, a PARP Inhibitor, in Combination with Gemcitabine/Carboplatin in Triple Negative Metastatic Breast Cancer: Results of a Phase II Study

Joyce O'Shaughnessy [1,2,4], Cynthia Osborne [1,2,4], John Pippen [1,2,4], Debra Patt [3,4], Christine Rocha[5], Valeria Ossovskaya [5], Barry M. Sherman [5], Charles Bradley [5]

[1]Baylor Sammons Cancer Center

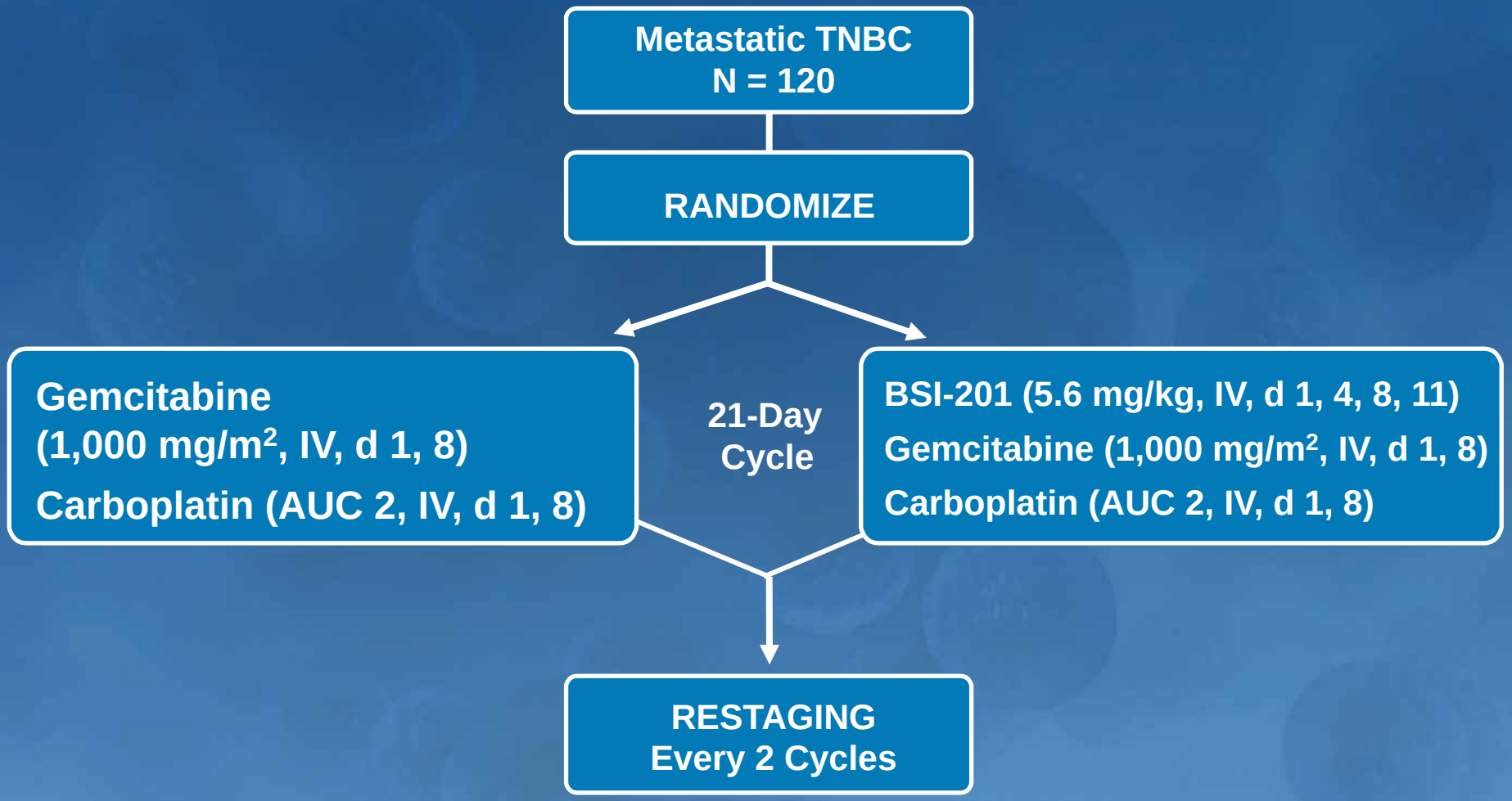
[2]Texas Oncology, Dallas, TX

[3]Texas Oncology Cancer Center, Austin, TX

[4]US Oncology, Dallas, TX

[5]BiPar Sciences, Inc., Brisbane, CA

Gem/Carbo +/- BSI-201 in unselected TNBC



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

O'Shaughnessy et al. ASCO 2009

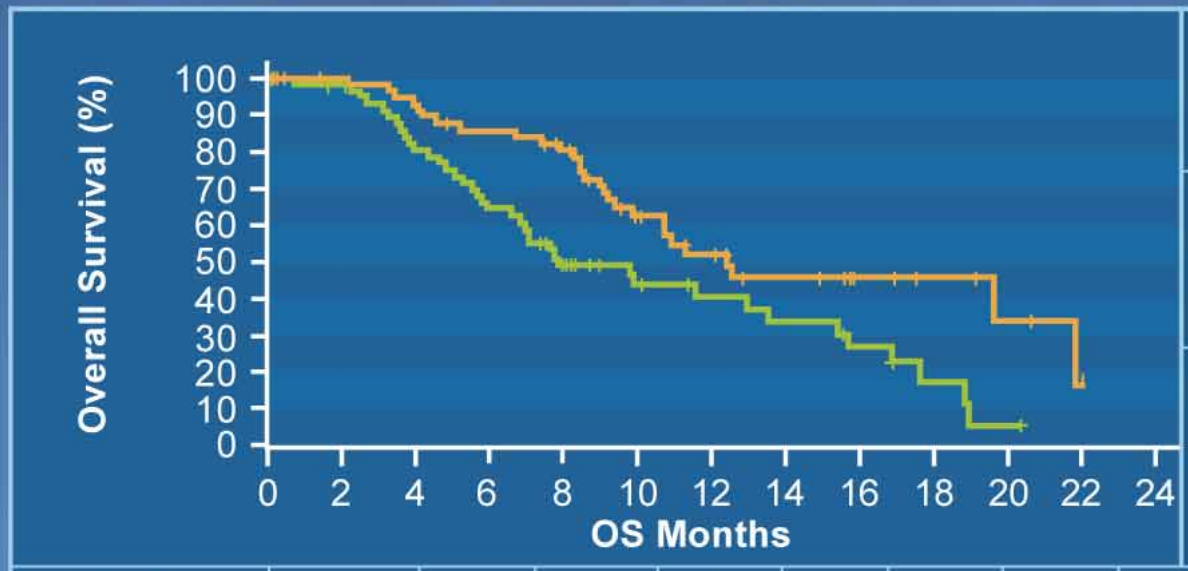
Preliminary Efficacy Results*

	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

*Includes patients enrolled before September 30, 2008 and patients who had a confirmed response or disease progression

**Clinical Benefit Rate = CR + PR + SD ≥ 6 months

Updated BSI-201 SABCS 2009



BSI-201/Gem/Carbo; median = 12.2 months

Gem/Carbo:median = 7.7 months

Hazard Ratio = 0.50
95% CI = (0.30, 0.82)
p-value = 0.005

Months	0	2	4	6	8	10	12	13	16	18	20	22
Deaths	0	0	5	8	11	20	24	26	26	26	27	28
At Risk	61	57	52	48	42	26	18	12	8	6	3	1
Deaths	0	1	11	20	28	30	31	33	35	37	39	39
At Risk	62	57	45	35	23	16	12	10	7	3	1	0

With permission from O'Shaughnessy et al. SABCS 2009 poster 3122

Conclusions

- Single agent synthetic lethality concept shown for olaparib in BRCA1 and BRCA2 mutation carriers with advanced breast and advanced ovarian cancer
- Randomised phase II data for BSI-201 very promising for PARPi combined with gemcitabine/ carboplatin in sporadic TNBC
- Phase III RCT of BSI-201 gemcitabine/carboplatin completed and results awaited
- Consideration of investigation of novel PARPi/ chemotherapy combinations in advanced disease and in early breast cancer trials in TNBC and BRCA1 and BRCA2 carriers

Acknowledgements

- Our patients and their families
- ICEBERG Investigators
- BRCA carrier advocacy community
  - FORCE
  - Susan G Komen
- ICR Breakthrough Centre
  - Alan Ashworth, Chris Lord, Hannah Farmer, Nuala McCabe
  - Nick Turner, Jorge Reis-Filho
- KCL Breakthrough Unit
- Cancer Research UK
- KuDOS/AstraZeneca
  - Stephen Jackson, Niall Graham Graeme Smith, Jim Carmichael