DNA repair deficiencies and PARP inhibitors in Triple Negative Breast Cancer

Andrew Tutt
Director
Breakthrough Breast Cancer Research Centre
London
Overview

• Evidence for targetable DNA damage defect in TNBC

• Is platinum a probe for Homologous Recombination Deficiency?

• What are the special “+ve” populations – gBRCA / “BRCAness”

• Biomarkers of Homologous Recombination Deficiency (HRD)
  Focus on Genomic Scars as biomarkers

• Potential novel combinations including targeting S-Phase Stress
Breast Cancer have variable genome complexity reflecting DNA repair competence

Risk of treatment failure?

Signatures of mutational processes in human cancer

Breast

- BRCA1
- BRCA2
- Mutation associated
- APOBEC associated

No. mutations per Mb

Alexandrov et al Nature 2013
Signatures of mutational processes in human cancer

TNBCs have highly variable Chromosome structural instability

Stable genome- low instability

Unstable genome- high instability

Alexandrov et al Nature 2013
Genomic Instability generates high tumour heterogeneity and few recurrent targetable mutations.

The mutator phenotypes that define the Baobab’s shape may be “actionable” targets.
*BRCA1* is a genome stability "caretaker" and is mutated in ≈15% of patients with TNBC.
BRCA1 and BRCA2 share function in the DNA DSB and replication fork damage response.

Roy et al Nat Rev Cancer 2012  Walsh and King Cancer Cell 2007
BRCA1 and BRCA2 share function in the DNA DSB and replication fork damage response

HR deficiency implicated in Sporadic TNBC
- Methylation
- Somatic mutation
- Other epigenetic mechanisms

Roy et al Nat Rev Cancer 2012  Walsh and King Cancer Cell 2007
When HR fails other DNA repair processes (NHEJ) take over driving a mutator phenotype
When HR fails other DNA repair processes (NHEJ) take over driving a mutator phenotype. The pattern of rearrangements across the genome may act as a diagnostic tattoo for HR failure.
BRCA1 / BRCA2 and HR are involved in repair of DNA platinum adducts

DSB at DNA crosslink

DNA crosslink unhooked by XPF/ERCC1 and RPA

Search for homologous sequence on identical sister chromatid

X-link excision and DNA resynthesis

Original sequence is restored

Models of $BRCA1$ mutated basal-like breast cancer have specific chemo-sensitivities.

Platinum for Neoadjuvant Therapy in BRCA1 Mutation Carriers

**BRCA1 Mutation Carriers with Tumors >2cm**

CISPLATIN 75mg/m2 q 3wks IV x 12 wks

- N = 25
- Median age: 46
- 28% with clinically positive lymph nodes
- 22 pts completed 4 cycles of Cisplatin

Pathological Response 72%

Gronwald et al ASCO 2009
Biomarkers of neoadjuvant cisplatin response in TNBC
Genomic scars as biomarkers of homologous recombination deficiency and drug response in breast and ovarian cancers

Johnathan A Watkins, Sheeba Irshad, Anita Grigoriadis* and Andrew NJ Tutt

Birkbak et al., Cancer Discov. 2012 Apr;2(4):366-75
Genomic scars as biomarkers of homologous recombination deficiency and drug response in breast and ovarian cancers

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Numerical and Structural Chromosomal Instability associated with BRCA1/2 inactivation and Cisplatin Sensitivity


Numerical and Structural Chromosomal Instability associated with BRCA1/2 inactivation and Cisplatin Sensitivity

Basal Like Breast Cancers & BRCA1/2 mutations

No: adjacent > 10Mb CNA

Large State Transition

High Grade Serous Ovarian Cancer

No: LoH > 15Mb

Platinum as a probe for HR deficiency in metastatic TNBC?

- Very few TNBC specific trials -> mostly subsets
- Often platinum assessed in combination
- Many cross study comparisons of subgroups
- Various “triple-negative” definitions
- *BRCA1/2* mutation rarely characterised
- Mostly no correction for differences in disease free interval

- **Randomized** data comparing platinum to standard of care chemotherapy in first or second line
Platinum in metastatic TNBC
Unselected and gBRCAm

<table>
<thead>
<tr>
<th>Regimen</th>
<th>N</th>
<th>ORR (%)</th>
<th>PFS (mths)</th>
<th>Prior Adj Chemo (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iniparib Trials</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gem / Carbo(^1)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1(^{st}) line</td>
<td>258</td>
<td>30%</td>
<td>4.1</td>
<td>90%</td>
</tr>
<tr>
<td>2(^{nd}/3(^{rd}) line</td>
<td>148</td>
<td></td>
<td>4.6</td>
<td></td>
</tr>
<tr>
<td></td>
<td>110</td>
<td></td>
<td>2.9</td>
<td></td>
</tr>
<tr>
<td>Ph II gBRCA1m(^2)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1(^{st}) line</td>
<td>20</td>
<td>80%</td>
<td>(TTP)</td>
<td>65%</td>
</tr>
<tr>
<td>2(^{nd}) line</td>
<td>11</td>
<td></td>
<td>12</td>
<td></td>
</tr>
<tr>
<td></td>
<td>9</td>
<td></td>
<td></td>
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<tr>
<td>TBCRC009</td>
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<td></td>
<td></td>
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</tr>
<tr>
<td>Carbo / Cis(^3)</td>
<td>86</td>
<td>26%</td>
<td>2.9</td>
<td>86%</td>
</tr>
<tr>
<td></td>
<td>11</td>
<td></td>
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</tbody>
</table>

TBCRC 009 Tested Two HRD deficiency “scar” Fingerprints in tumour DNA

Basal Like Breast Cancers & BRCA1/2 mutations

No: adjacent > 10Mb CNA

Large State Transition

Developed in HGSOC Tested in PrECOG 0105

No: LoH > 15Mb

BRCA1/2 mutant
BRCA1/2 intact


Telli et al. ASCO 2013
Platinum sensitivity is associated with higher HRD scores

- 27 BRCA1/2 WT tumors available
  - 5 responders, 22 non-responders

Presented at the 2014 ASCO Annual Meeting.
**TNT Trial design**

ER-, PgR-/unknown & HER2- or known **BRCA1/2**
Metastatic or recurrent locally advanced

Exclusions include:
- Adjuvant taxane in ≤12 months
- Previous platinum treatment
- Non-anthracyclines for MBC

*A Priori* subgroup analyses:
- BRCA1/2 mutation
- Basal-like subgroups (PAM50 and IHC)
- Biomarkers of HRD

On progression, crossover if appropriate

**Docetaxel (D)**
100mg/m² q3w, 6 cycles

**Carboplatin (C)**
AUC 6 q3w, 6 cycles
Objective response

Randomised treatment - all patients (N=376)

<table>
<thead>
<tr>
<th>Drug</th>
<th>% with OR at cycle 3 or 6 (95% CI)</th>
<th>Absolute difference (C-D)</th>
<th>Exact p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carboplatin</td>
<td>59/188 (31.4%)</td>
<td>-4.2% (95% CI -13.7 to 5.3)</td>
<td>0.44</td>
</tr>
<tr>
<td>Docetaxel</td>
<td>67/188 (35.6%)</td>
<td></td>
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</tbody>
</table>

Crossover treatment - all patients (N=182)

<table>
<thead>
<tr>
<th>Drug</th>
<th>% with OR at cycle 3 or 6 (95% CI)</th>
<th>Absolute difference (D-C)</th>
<th>Exact p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carboplatin (Crossover=Docetaxel)</td>
<td>21/92* (22.8%)</td>
<td>-2.8% (95% CI -15.2 to 9.6)</td>
<td>0.73</td>
</tr>
<tr>
<td>Docetaxel  (Crossover=Carboplatin)</td>
<td>23/90* (25.6%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Denominator excludes those with no first progression and those not starting crossover treatment
Objective response – BRCA 1/2 status

Germline BRCA 1/2 Mutation (n=43)

Carboplatin

17/25 (68.0%)

Docetaxel

6/18 (33.3%)

Absolute difference (C-D) 34.7% (95% CI 6.3 to 63.1)

Exact p = 0.03

No Germline BRCA 1/2 Mutation (n=273)

Carboplatin

36/128 (28.1%)

Docetaxel

53/145 (36.6%)

Absolute difference (C-D) -8.5% (95% CI -19.6 to 2.6)

Exact p = 0.16

Interaction: randomised treatment & BRCA 1/2 status: p = 0.01
MYRIAD Composite HRD biomarker analysis

Bimodality
Breast & Ovarian Ca
BRCA1/2 mutation
BRCA1 methylation

Score ≥ 42 HRD High

MYRIAD Composite HRD biomarker analysis

376 patients recruited

Blood
288 patients

Negative LN
112 patients

Primary tumour
309 patients

Positive LN
143 patients

Recurrent tumour
102 patients

Bimodality
Breast & Ovarian Ca
BRCA1/2 mutation
BRCA1 methylation

HRD score
Tested: 220

Test failed: 25*

HRD high (≥42): 81
HRD low (<42): 114

*excluded from analyses
HRD score by *BRCA 1/2* mutation

- **High HRD Score ≥ 42**
- **Low HRD Score < 42**

**Myriad cut-point**

- Germline BRCA1
- Germline BRCA2
- No Mutation
- Somatic
- Tumour mutation (germline unknown)

**Carboplatin**

**Docetaxel**
Objective response – HRD score

High HRD score (n=81)

- Carboplatin: 13/34 (38.2%)
- Docetaxel: 20/47 (42.6%)

Absolute difference (C-D): -4.4% (95% CI -26.0 to 17.2)
Exact p = 0.82

Low HRD score (n=114)

- Carboplatin: 19/65 (29.2%)
- Docetaxel: 17/49 (34.7%)

Absolute difference (C-D): -5.4% (95% CI -22.7 to 11.9)
Exact p = 0.55

Interaction: randomised treatment & dichotomised HRD score: p = 0.91
HR repair can be regained by the evolutionary pressure of chemotherapy

Reversion of BRCA1 mutations

Loss of 53BP1

Tumours may regain HR repair “fitness” to survive chemotherapy S-phase stress

Adapted from Nik-Zainal et al Cell 2012
Tumours may regain HR repair “fitness” to survive chemotherapy S-phase stress

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Adapted from Nik-Zainal et al Cell 2012
Tumours may regain HR repair “fitness” to survive chemotherapy S-phase stress.

Is an old HRD “tattoo” a good marker of current repair competence?

A biker can become a Priest but can’t lose his old “Hells Angel” tattoos.

Adapted from Nik-Zainal et al Cell 2012
Tumours may regain HR repair “fitness” to survive chemotherapy S-phase stress

Is an old HRD “tattoo” a good marker of current repair competence?

A biker can become a Priest but can’t lose his old “Hells Angel” tattoos

HRD = Diagnostic filter for Early HRD

May need measures of current repair capability for metastatic clones

Adapted from Nik-Zainal et al Cell 2012
Perhaps the HRD Scar biomarker is not sophisticated enough

- Have minimum and maximum size thresholds
- Take account of CNP and regions of LOH in the germline
- Exclude effect of very localised Chromothripsis events
- Allow better differentiation of genome instability mechanisms

Allelic Imbalanced Copy Number Aberration (SAiCNA)  
Copy Neutral Loss of Heterozygosity (SCnLOH)  
Allelic Balanced Copy Number Aberration (SABCNA)  
NHEJ / SSA  
Non-Conservative HR by GC  
Genome duplication
Scores of Chromosome Instability Scarring (SCINS)

![Graph showing scores of SCINS]

KCL TNBCs

Anita Grigioradis
Johnathan Watkins
Scores of Chromosome Instability Scarring (SCINS)

- $S_{\text{AbCNA}}$
- $S_{\text{iCNA}}$
- $S_{\text{CnLOH}}$
- no scar

KCL TNBCs
Suggestions for PARPi from gBRCA+ platinum data

• A $BRCA1$ or $BRCA2$ mutation is associated with high pathological response to platinums in early disease

• This $gBRCA^+$ effect persists in advanced disease and is specific to platinum rather than taxane chemotherapy

• Suggests metastatic clones of $gBRCA^+$ BC remaining after adjuvant chemotherapy retain HR repair defect and might gain specific benefit from PARP inhibitors in advanced disease or adjuvant context

• Suggests that BRCA mutation testing of blood and possibly tumour be considered in an oncology as well as a genetics clinic in many with TNBC
Suggestions for PARPi from gBRCA+ platinum data

- Raises Q of what standard of care comparitor regimen for PARP inhibitors should be in gBRCA+ advanced breast cancer trials

- Raises need to further assess design of trials of combination platinum and PARP inhibitor strategies particularly in gBRCA+ breast cancer

- Raises questions of trials of maintenance PARP inhibitors after platinum response in gBRCA+ mBC and platinum responsive mTNBC

- Supports trial designs of adjuvant PARP inhibitors in women with BRCA1 or BRCA2 mutations with breast cancer at high metastatic risk
Suggestions from the non gBRCA+ TNBC platinum data

• HR Deficiency or BRCAAness present in early breast cancer but not associated with BRCA1 or BRCA2 mutation appears to exist

• ... but this form of HR deficiency may have more reversible biological drivers such as methylation of BRCA1 that are no longer present in the metastatic clones surviving adjuvant chemotherapy

• These non-mutated HRD scar +ve tumours might be considered to be the “Biker Priests”

• in women with TNBC and no BRCA1 or BRCA2 mutation diagnostics for targetable BRCAAness or HR Deficiency require further work especially in advanced recurrent breast cancer
PARP inhibitors in gBRCA mutated cancer

Oral poly(ADP-ribose) polymerase inhibitor olaparib in patients with BRCA1 or BRCA2 mutations and advanced breast cancer: a proof-of-concept trial

Andrew Tutt, Mark Robson, Judy E Garber, Susan M Domchek, M William Audeh, Jeffrey N Weitzel, Michael Friedlander, Banu Arun, Nicholas Loman, Rita E Schmutzler, Andrew Wordley, Gillian Mitchell, Helena Earl, Mark Wickens, James Cornish.

BMN 673
Breast

Niraparib

Ramanathan et al Abst 29LBA ECCO 2013

Michie et al Abst 2513 ASCO 2013
PARPi monotherapy in sporadic TNBC

Best % change from baseline

-100 -80 -60 -40 -20 0 20 40 60 80 100 120

TNBC BRCA
TNBC non-BRCA
Non-TNBC BRCA

BRCAness sufficient for synthetic lethality uncommon in advanced non-BRCA TNBC?

BRCA1 methylation present in 20% TNBC
Timms et al Breast Cancer Res 2014, 16:475

23 treated patients with target lesions identified at baseline
22 had at least one follow-up assessment
1 patient had no follow-up tumour size assessment
-1 due to missing / incomplete post-baseline assessments

K Gelmon et al Lancet Oncology 2011
PARP inhibition focused on gBRCA companion diagnostic group including those with TNBC

- gBRCA1 / BRCA2 Carriers
  - Advanced anthracycline taxane resistant breast cancer

Primary endpoint PFS

Potent PARP inhibitor at MTD as continuous exposure

- Physician Choice within SOC options
  - Capecitabine
  - Vinorelbine
  - Eribulin
  - Gemcitabine

Niraparib – EORTC / BIG BRAVO Trial
BMN 673 – EMBRACA - NCT01945775
OLYMPIAD – Olaparib - NCT02000622
Can we combine platinums with potent PARP inhibitors?

- Balmana et al tested 75mg/m² cis with continuous olaparib
- Not tolerable but reduction of Cisplatin to 60mg/m² with olaparib at 50mg BD D1-5 tolerable.

Can we combine platinum drugs with potent PARP inhibitors?

- Another Phase I study found Carboplatin dose of AUC 5 Q21 could be delivered with Olaparib at 400mg BD for 14 days\(^1\)

- Combination of carboplatin with paclitaxel (175 mg/m\(^2\)) required lowering the doses of carboplatin (AUC 4) and olaparib (200 mg bid, days 1–10) but was then tolerable\(^2\)

- Combinations with paclitaxel and carboplatin and veliparib have been achieved in early\(^3\) and advanced\(^4\) breast cancer

- Differences in drug mechanisms of action on PARP trapping may be relevant

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1. Lee et al J Clin Oncol 31, 2013 (suppl; abstr 2514)
2. Oza A et al J Clin Oncol 30, 2012 (suppl abstr 5001)
3. Rugo et al SABCS 2013 abst S5-02
4. Somlo et al ASCO 2014 (Abstr 1021)
Can veliparib sensitized chemotherapy improve on a platinum directed chemotherapy approach?

**Abbott Clinical Trial M12-895**

**Overall Study Design**

**Patient Population**
- Men and women ≥ 18 years of age
- Measurable or non-measurable (but radiologically evaluable) metastatic breast cancer
- Documented BRCA1 or BRCA2 deleterious germline mutation

**Endpoints**

**Primary Endpoint**
Progression Free Survival

**Secondary Endpoints**
- Overall Survival
- Clinical Benefit Rate
- Objective Response Rate
- Peripheral Neuropathy
- Safety and Tolerability

**Randomization 1:1:1**

- Veliparib BID + Temozolomide
- Placebo + Carboplatin/Paclitaxel
- Veliparib BID + Carboplatin/Paclitaxel

[Link to Clinical Trials.gov](http://www.clinicaltrials.gov/ct2/show/NCT01506609)
If combinations are challenging perhaps platinums followed by PARP as maintenance?

Advanced
1. gBRCA1 / BRCA2
2. TNBC

Responding to Platinum Regimen after 3 or 6 cycles

R

Potent PARP inhibitor at MTD as continuous maintenance

Continue chemotherapy while tolerable
Maintenance therapy after platinum response early in ovarian cancer management

- Statistically significant PFS improvement (HR 0.35, \( P<0.00001 \))
- In gBRCA carriers (HR=0.18 95% \( P<0.00001 \))

To avoid late resistance can we bring novel PARP inhibitor approaches in earlier in High Risk TNBC

New Diagnosis

Neoadjuvant Rx

Post-Rx residual disease

Second Adjuvant Investigational Drug Rx

Definitive Surgery

Relapse

Vs

No Relapse
Cisplatin with or without rucaparib after preoperative chemotherapy in patients with triple-negative breast cancer (TNBC): Hoosier Cancer Research Network BRE09-146

Abstract 1019

Sujaata Dwadasi, Yan Tong, Tom Walsh, Michael A. Danso, Cynthia X. Ma, Paula Silverman, Mary-Claire King, Susan M. Perkins, Sunil S. Badve, Kathy Miller

Presented by: Steven Isakoff - Discussant

Eligibility

- TNBC (or BRCA+)
- Residual disease (RCB 2/3, M-P 0-2, node +)
- No prior cisplatin (carbo allowed)

- 128 patients
  - 65 cisplatin
  - 63 cis/rucaparib

Median RCB 2.6 v 2.7

1 Year DFS
C 83% v C/R 83%

22/128 patients BRCA mutation

DFS C 85% v C/R 100%

Rucaparib 100mg PO q wk X 24 weeks
**OlympiA**

Olaparib in Adjuvant BRCAm breast cancer

**Randomise 1:1**
Double blind

N=1320

IDFS

Distant DFS; OS

**Post neoadjuvant gBRCA**
TNBC,
Non-PathCR pts

**Restricted to Germline Mutation carriers**

**Post adjuvant gBRCA**
TNBC
T2 or N+

**Olaparib**
300 mg bd
12 month duration

**Placebo**
12 month duration

**IDFS**

**Distant DFS; OS**

Restricted to Germline Mutation carriers
PIK3CA pathway and PARPi synergy

PIK3CA Mutation / PTEN or INPP4 loss

PIK3CA blockade of overactive pathway

Activation of ERK

Suppression of BRCA1/2 and reduced HR

Susceptibility to a PARP inhibitor


Matulonis et al Abstract 2510 ASCO 2014
Targeting Mutant TP53 with Platinum and ATR inhibition

DNA Damage

- p53
- ATM

- Cdk1
- Cyclin B

- G1
- S
- G2
- M
Targeting Mutant TP53 with Platinum and ATR inhibition

- Replication stress (c-MYC)
- Platinum adducts Replication Inhibitors PARPi?
- Stalled DNA replication forks
- DNA Damage
- ATR
- Chk-1
- Wee1
- Cdk1
- Cyclin B
- G1, S, G2, M
Targeting Mutant TP53 with Platinum and ATR inhibition

Replication stress (c-MYC)
Platinum adducts Replication Inhibitors PARPi?

Stalled DNA replication forks

DNA Damage

ATR

Chk-1
Wee1

Cdk1 Cyclin B

G1 S G2 M

Normal Mitosis
Targeting Mutant TP53 with Platinum and ATR inhibition

- Replication stress (c-MYC)
- Platinum adducts
- Replication Inhibitors
- PARPi?
- Stalled DNA replication forks

DNA Damage

- Wee1
- Cdk1
- Cyclin B

Cell cycle phases: G1, S, G2, M

Normal Mitosis
Targeting Mutant TP53 with Platinum and ATR inhibition

- Replication stress (c-MYC)
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DNA Damage

G1 S G2 M

Cdk1 Cyclin B

Normal Mitosis
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DNA Damage

- G1
- S
- G2
- M

Normal Mitosis
Cdk1, Cyclin B
Targeting Mutant TP53 with Platinum and ATR inhibition

- Replication stress (c-MYC)
- Platinum adducts Replication Inhibitors PARPi?
- Stalled DNA replication forks
- DNA Damage
- Forced Early Mitotic Entry
- Premature Chromatin Condensation
- Normal Mitosis

Cdk1
Cyclin
Blk1
G1
S
G2
M
Targeting p53 loss with ATR inhibition in combination with platinum therapy

Reaper Nat. Chem. Biol. 2011
Conclusions

• Significant evidence *BRCA1* and *BRCA2* mutation carriers have systemic therapy clinical trial and standard of care options distinct from others

• Identification of *BRCA1/2* mutation is currently the clearest diagnostic of an HRD defect that is targeted by platinum chemotherapies and PARP inhibitors

• *BRCA1* and *BRCA2* mutation in germline and tumour should be reported in trials testing these agents and new HRD diagnostics

• The development of tumour based diagnostics for DNA repair deficiencies to inform choice of treatment for metastatic sites of disease outside the context of *BRCA1/2* mutation remains a work in progress

• Trials specific to women with uncommon but important genetic forms of DNA repair deficient BC are possible and should be conducted
Acknowledgments

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