Integration of DNA repair deficiency and immune biomarkers to predict which early stage triple negative breast cancer patients are likely to respond to platinum containing regimens vs. immunotherapy: the neoadjuvant I-SPY 2 TRIAL

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Disclosure Information

AACR, 4/1/2019, mini-symposium #

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I have no financial relationships to disclose.

I will not discuss off label use and/or investigational use in my presentation.
A changing treatment landscape for triple negative breast cancer

- **HR-HER2- (triple negative TN)**
  - Aggressive breast cancer subtype negative for estrogen receptor and HER2 amplification

- **Historically few treatment options**
  - Standard chemotherapy (anthracycline + taxane)
  - No targeted treatments

- **Multiple recent trials showing increased efficacy!**
  - *Platinum*-containing regimens (with and without PARP-inhibition)
    - GeparSixto, CALGB 40603, BrighTNess, **I-SPY 2**
  - *Immunotherapy*-containing regimens
    - **I-SPY 2**; IMpassion130,.. FDA approval - stage IV (atezolizumab); in progress: NeoTRIPaPDL1, KEYNOTE-522
The I-SPY 2 TRIAL Standing Platform for High Risk Early Stage Breast Cancer

- Phase II, adaptively-randomized neoadjuvant trial
- Shared control arm
  - Standard neoadjuvant chemotherapy
  - HER2+ also gets standard of care for targeted agents
- Simultaneous experimental arms
  - Up to four
- Primary endpoint: pathologic complete response (pCR)
  - Defined as no residual invasive cancer in the breast or lymph nodes

- Agents/combinations "graduate" for efficacy = reaching >85% predictive probability of success in a subsequent phase III trial in the most responsive patient subset
BOTH veliparib/carboplatin (VC) combination therapy AND pembrolizumab (P) graduated in the triple negative (TN) subset.

Platinum-based

- **carboplatin**
- **Damages DNA**
- **Breast cancer cells**
- **DNA repair deficient?**

51% estimated pCR rate in VC in TN (vs 26% in control)

Immunotherapy

- **pembrolizumab**
- **Inhibits immune checkpoint PD1**
- **Immunogenic/inflamed?**

60% estimated pCR rate in P in TN (vs 22% in control)

• **Who should get what and can we prioritize based on biomarkers to improve outcome?**

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I-SPY 2 is a biomarker rich trial

Established
- Level 1 evidence
- FDA cleared or approved or IDE filed
- Used in clinical decision

QUALIFYING
- Level 2 evidence
- Have existing evidence for response prediction
- Evaluated in CLIA setting
- May be based on mechanism of action
- Hypothesis testing
  - Pre-defined biomarkers
  - Pre-specified rigorous statistical framework

EXPLORATORY
- Biomarker discovery
- Hypothesis generation
A growing body of evidence that particular biological tumor classes are more likely to respond to a given class of agent:

- For pembrolizumab and other immune checkpoint inhibitors, immune infiltrate/inflamed phenotype is associated with response.
  - Example biomarkers: TILs, CD8+ T cells, PDL1/PD1 staining, immune expression signatures across cancer types,.. [LOTS of evidence]

- For platinum drugs +/- PARP inhibitors, DNA repair deficiency associated with response.
  - Example biomarkers: BRCA1/2 germline mutation status, HRD in ovarian/breast cancers,..
Example mechanism-of-action qualifying expression signatures predicting response to pembrolizumab and carboplatin/veliparib

Previously we showed..

- Immune signatures, including for dendritic cells, predict response to pembrolizumab (P)

- DNA repair deficiency (DRD) biomarker PARPi7 predicts response to platinum/PARPi (VC)
  - 7 gene DNA-repair deficiency signature PARPi-7: BRCA1, CHEK2, MAPKAPK2, MRE11A, NBN, TDG, XPA. Predicts olaparib-sensitivity in cell lines (PMID:22875744) and pCR in I-SPY 2 patients in the VC arm relative to control (PMID: 28948212)

Immune biomarkers: Danaher et. al., J Immunother Cancer. 2017 (PMID: 28239471); Yau et. al., SABCS 2018
Hypothesis: overlap between Immune and DRD predictive biomarkers can be used to identify subgroups more likely to respond to immunotherapy vs. platinum-based therapy

To test this hypothesis, we used the example qualifying biomarkers: PARPi7 as our DRD biomarker (DRD+/-) and the dendritic signature as our Immune biomarker (Immune+/-)
Patients and methods

153 TNBC patients available for analysis in (Control: 85; VC: 39; Pembro: 29)

Step 1: Score continuous DRD and immune signatures as published

Step 2: Optimally dichotomize signatures into high/low

To identify optimal dichotomizing thresholds, 2-fold cross-validation was repeated 500 times.
1. Use VC response data to dichotomize DRD signature
2. Use Pemb roast response data to dichotomize Immune signature

Step 3: Bayesian modeling of estimated pCR rates

Within each patient subset defined by biomarker combinations:
1) What is the estimated pCR rates in the VC, Pembro and control arms?
Immune and DRD biomarkers, viewed individually

**DRD+ patients have a high estimated pCR rate to VC (79%).**

**Immune+ patients have a high estimated pCR rate to Pembro (87%).**
Are these the same patients?

(What is the overlap between Immune+ and DRD+?)
Overlap between immune and DRD predictive biomarkers in TNBC

- 40% positive for only one biomarker
- 14% Immune-/DRD+
- 26% Immune+/DRD-
- 20% Immune-/DRD-
- 40% Immune+/DRD+

Biomarker negative
Estimated pCR distributions within biomarker subgroups

- **Immune+/DRD+**: high pCR in Pembro (84%) and VC (83%)
- **Immune+/DRD-**
  - higher pCR in VC (64%)
- **Immune-+/DRD-**: low pCR in all arms
- **Immune-DRD-**
  - red line

- **Immune-DRD+**
  - highest pCR in Pembro (90%)
Which drug should be prioritized for whom?

- **TNBC**
  - Biomarker negative (Immune-/DRD-): ?
  - 1 biomarker positive
    - Immune+/DRD-: Pembro
    - Immune-/DRD+: VC
  - Both biomarkers positive (Immune+/DRD+): Pembro OR VC

*Pembro OR VC*
Summary

• TNBC is experiencing a period of optimism, with trials showing increased efficacy for platinum and immunotherapy containing regimens

• **Question:** are patients likely to respond to one treatment also likely to respond to the other, or is there specificity: *for what percentage does treatment selection matter? How to prioritize?*

• In I-SPY 2, carboplatin/veliparib and pembrolizumab both graduated in the TN subset

• Previously we showed: DRD signatures (e.g. PARPi7) predict response to VC; and immune signatures (e.g., dendritic cell score) predict response to Pembro

• One can use the overlap between Immune and DRD biomarkers to identify patient subgroups more likely to respond to immunotherapy vs. platinum-based therapy

• 40% high in both biomarkers (Immune+/DRD+) => high pCR in both arms (*either treatment good!*)

• 40% high in just one biomarker => highest pCR in Pembro if Immune+/DRD-; highest pCR in platinum if Immune-/DRD+ (*treatment choice matters! Basis for prioritizing?*)

• 20% low in both (Immune-/DRD-). Low pCR rate in both arms. *Alternative approach?*

• Caveat: numbers are small. Validation required.
I-SPY 2 Platform Trial Study Team

Working Group Chairs

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Thank you to the remarkable patients and families, and all of the investigators, staff, our DSMB and advocates for supporting the trial
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