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# 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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**equal contribution*

# Disclosure Information

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

*Denise Wolf*

**I have no financial relationships to disclose.**

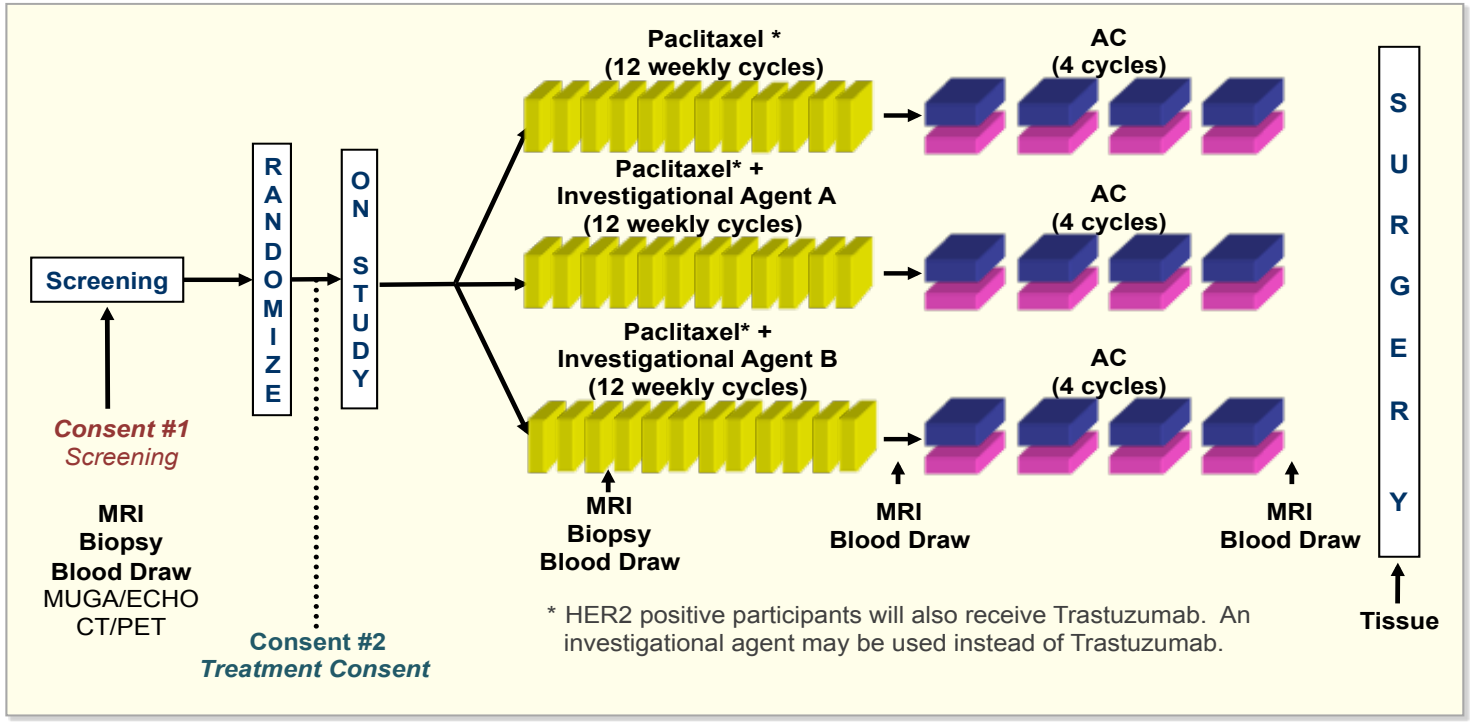
**I will not discuss off label use and/or investigational use in my presentation**

# 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

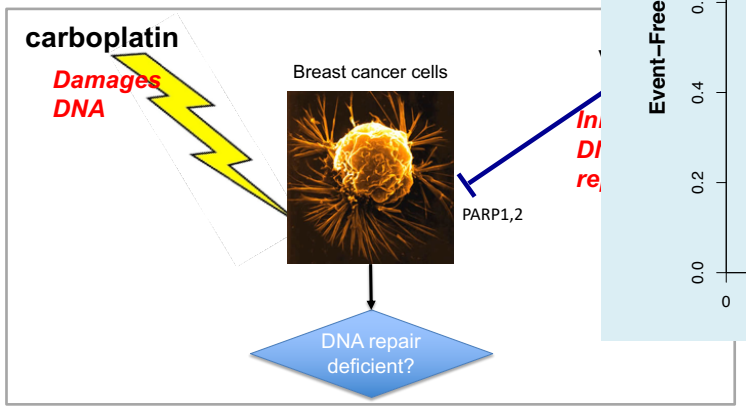
- **Phase II, adaptively-randomized neoadjuvant trial**
- **Shared control arm**
  - Standard neoadjuvant chemotherapy
  - HER2+ also gets standard of care for targeted agents
- **Simultaneous experimental arms**
  - Up to four
- **Primary endpoint**: pathologic complete response (pCR)
  - Defined as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

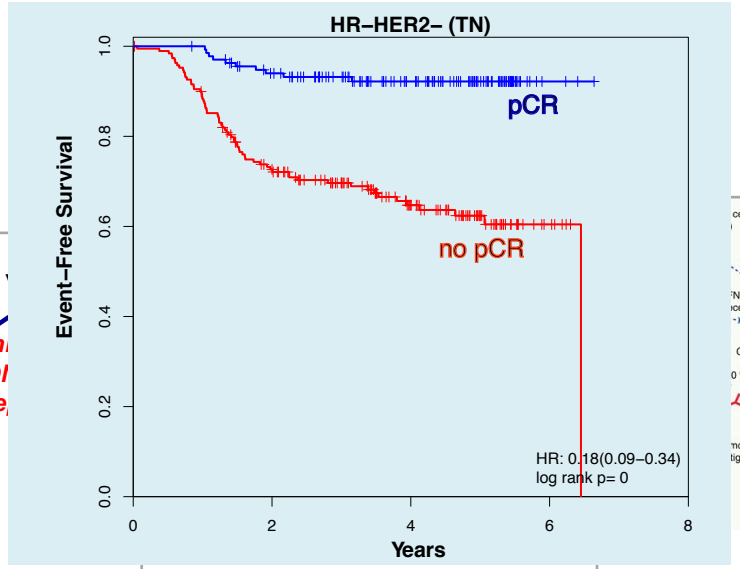



- Agents/combinations **"graduate"** for efficacy = reaching >85% predictive probability of success in a subsequent phase III trial in the most responsive patient subset

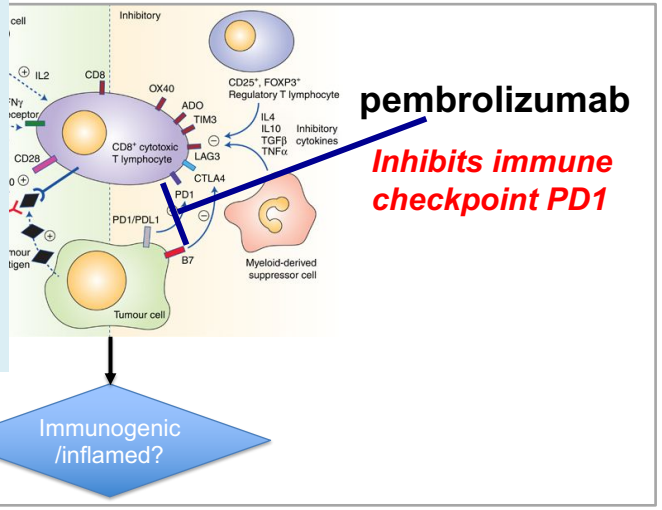
# BOTH veliparib/carboplatin (VC) combination therapy *AND* pembrolizumab (P) graduated in the triple negative (TN) subset

## Platinum-based




## Immunotherapy




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

**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?***

# I-SPY 2 is a biomarker rich trial

## Established

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

## QUALIFYING

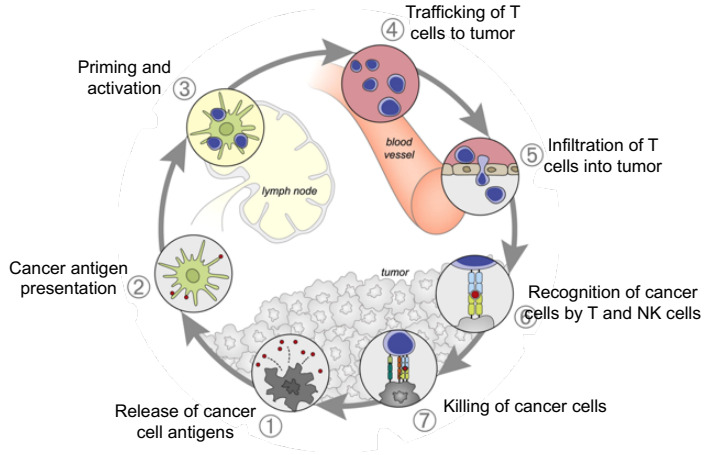
- **Level 2 evidence**
- **Have existing evidence for response prediction**
- **Evaluated in CLIA setting**
- **May be based on mechanism of action**
- **Hypothesis testing**
  - Pre-defined biomarkers
  - Pre-specified rigorous statistical framework

## EXPLORATORY

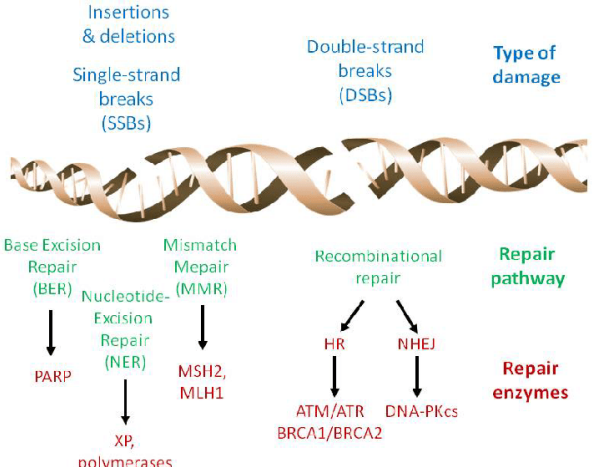
- **Biomarker discovery**
- **Hypothesis generation**

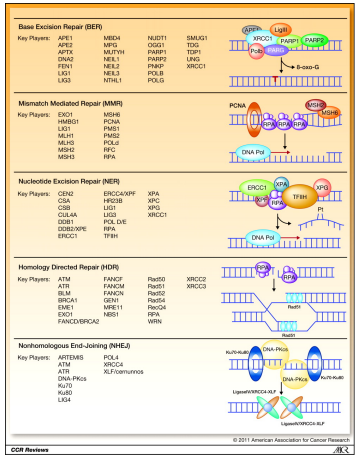
# A growing body of evidence that particular biological tumor classes are more likely to respond to a given class of agent

- **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*]



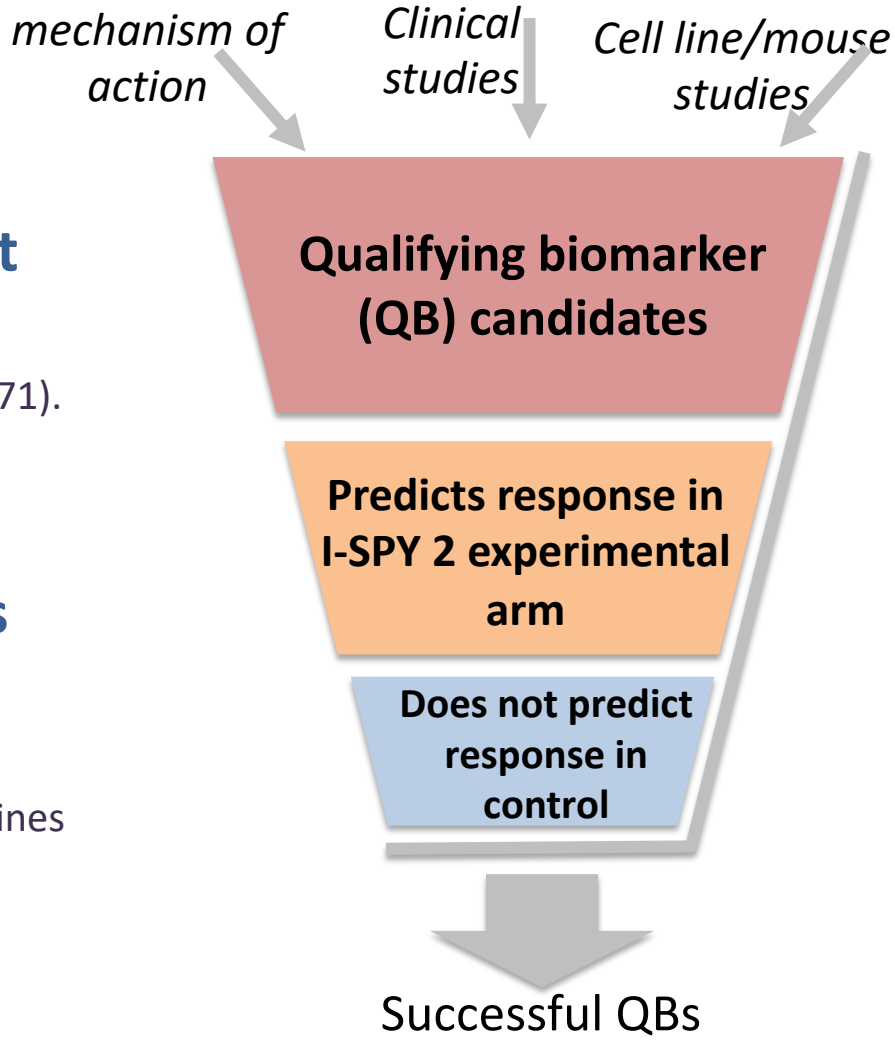

- **For platinum drugs +/- PARP inhibitors, DNA repair deficiency associated with response.**
  - **Example biomarkers**: BRCA1/2 germline mutation status, HRD in ovarian/breast cancers,..



# 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)**
  - 3 gene dendritic cell signature: CCL13, CD209, HSD11B1 (PMID: 28239471). Predicts pCR in I-SPY 2 patients in P arm relative to control (SABCS 2018)

- **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
**DNA repair biomarker:** Daemen et.al., Breast Cancer Res Treat. 2012 (PMID:22875744) ; Wolf, Yau, et.al., NPJ Breast Cancer. 2017 (PMID: 28948212)

# Hypothesis: overlap between Immune and DRD predictive biomarkers can be used to identify subgroups more likely to respond to immunotherapy vs. platinum-based therapy

| | Immune- | Immune+ |
|---|---|---|
| DRD- | -/-<br>*?* | -/+<br>***anti-PD/L1*** |
| DRD+ | +/-<br>***platinum*** | +/+<br>***anti-PD/L1 or platinum*** |

*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

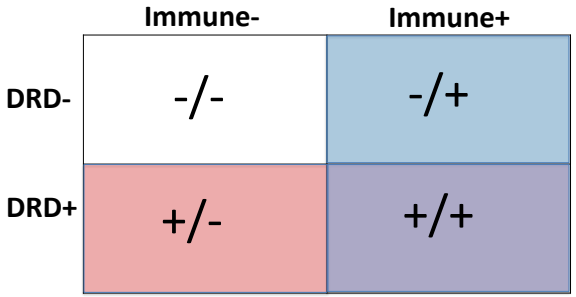
**153 TNBC patients** available for analysis in (Control: 85; VC: 39; Pembro:29)

**Step 1:**
Score continuous DRD and immune signatures as published

Using Agilent 44K data from pre-treatment biopsies, calculate:
1) DRD: PARPi7 score
2) Immune: Dendritic score

**Step 2:**
Optimally dichotomize signatures into high/low

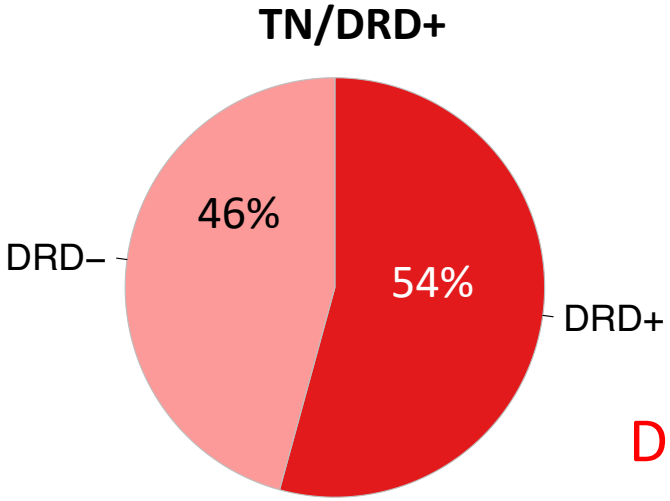
To Identify optimal dichotomizing thresholds, 2-fold cross-validation was repeated 500 times.
1. Use VC response data to dichotomize DRD signature
2. Use Pembro response data to dichotomize Immune signature

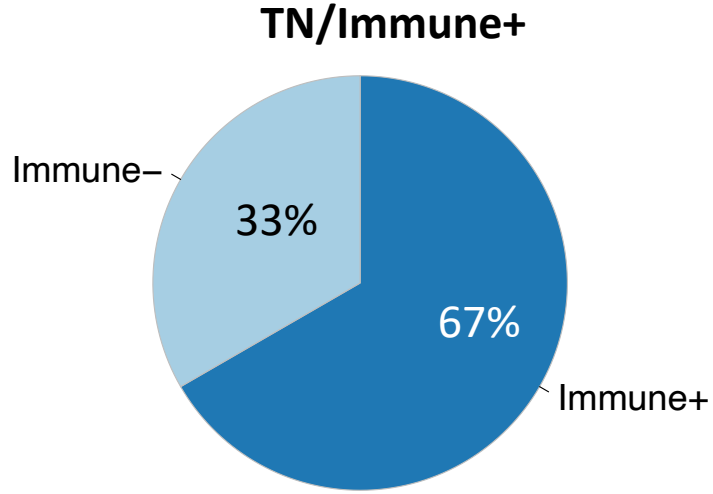



**Step 3:**
Bayesian modeling of estimated pCR rates

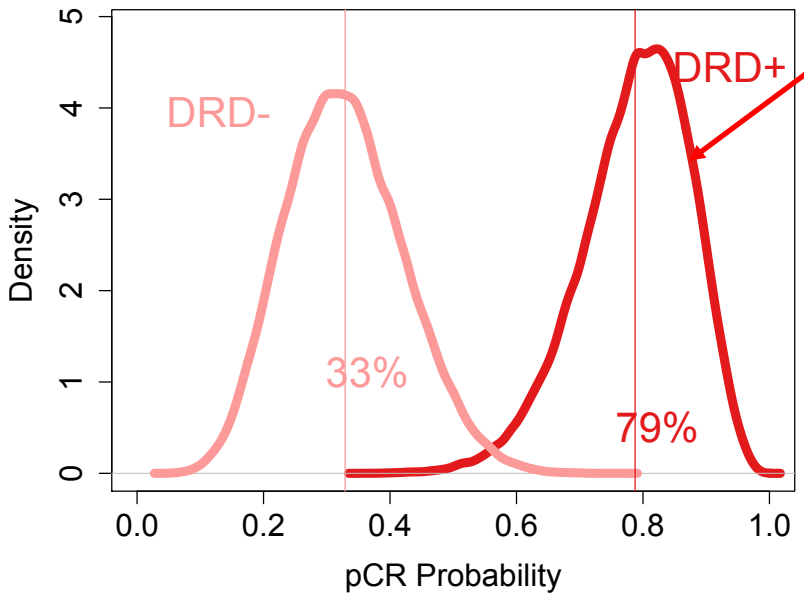
Within each patient subset defined by biomarker combinations:
1) What is the estimated pCR rates in the VC, Pembro and control arms?

# Immune and DRD biomarkers, viewed individually

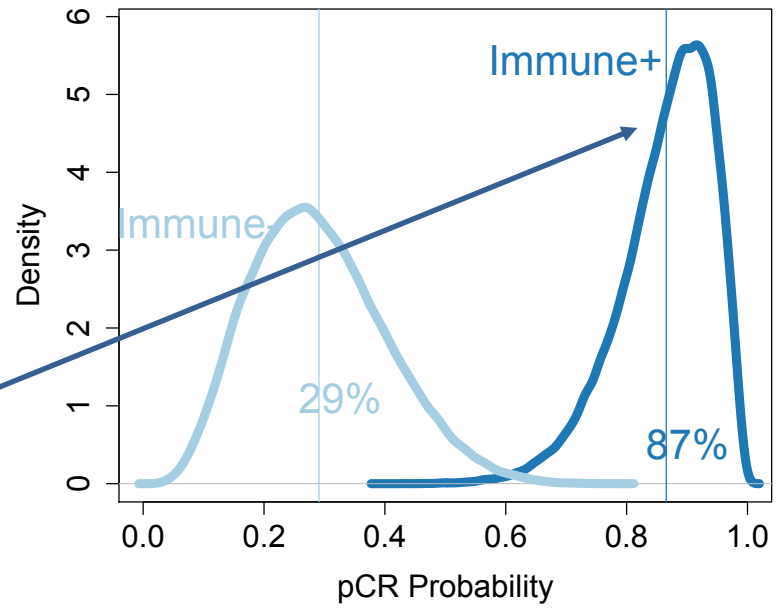



DRD+ patients have a high estimated pCR rate to VC (79%)



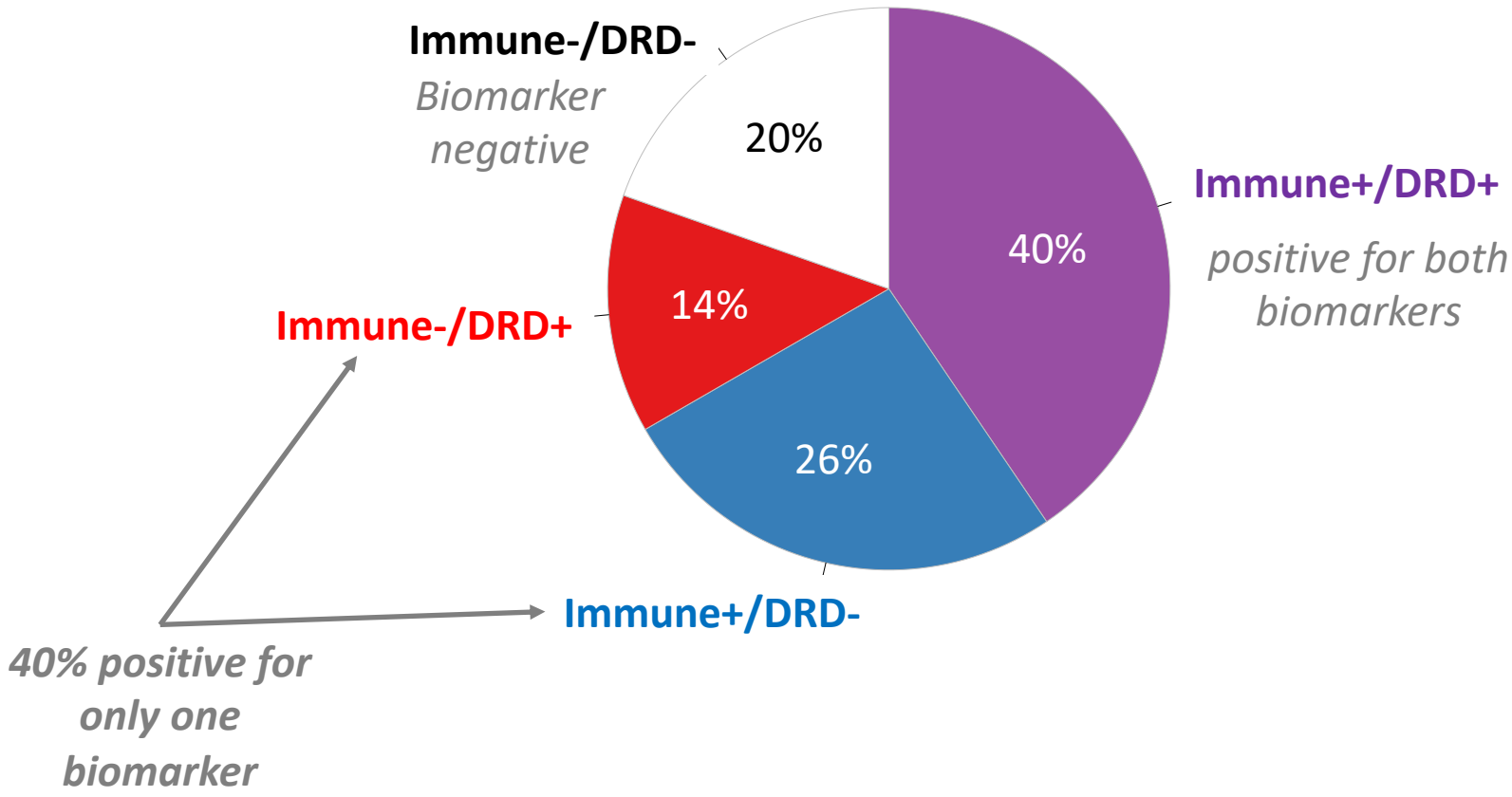

Immune+ patients have a high estimated pCR rate to Pembro (87%).



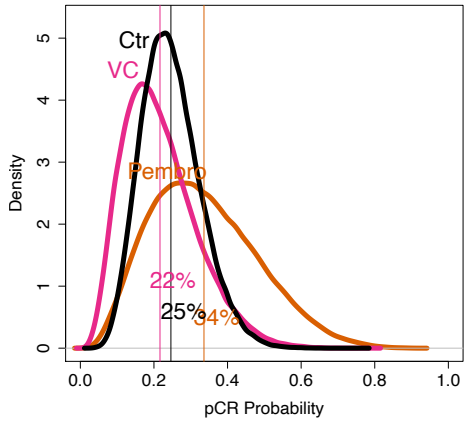
# Are these the same patients?

(*What is the overlap between Immune+ and DRD+?)*

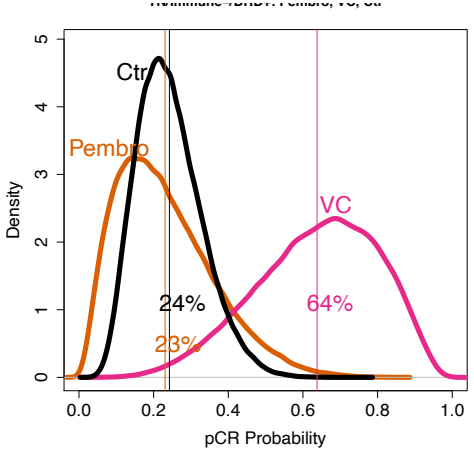
# Overlap between immune and DRD predictive biomarkers in TNBC



# Estimated pCR distributions within biomarker subgroups

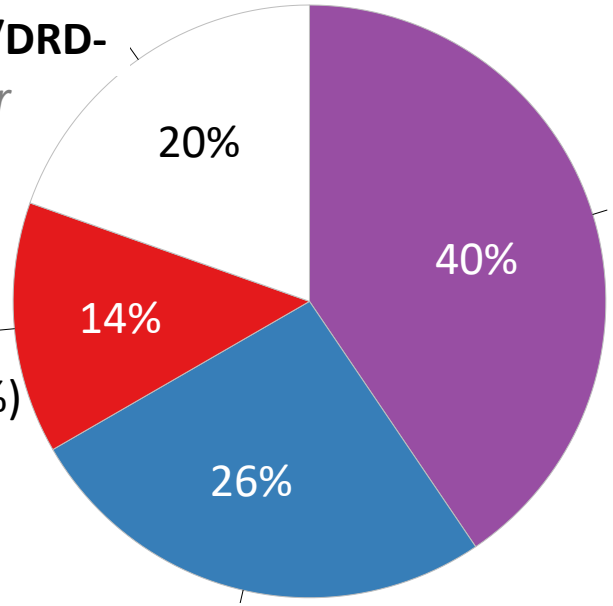


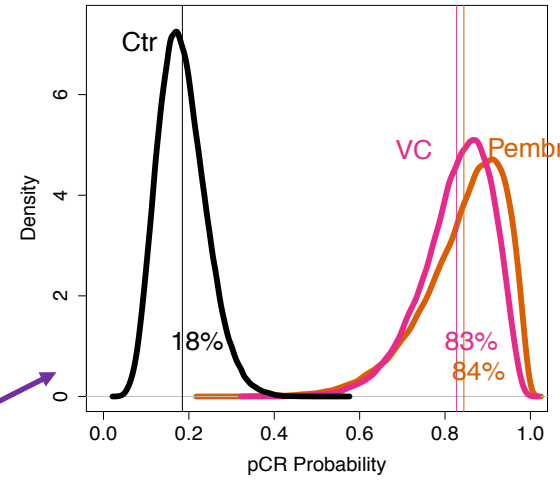

Low pCR in all arms




**Immune-/DRD-**

*Biomarker negative*



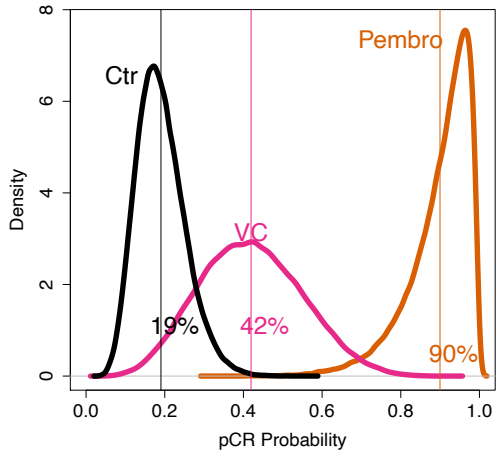

**Immune+/DRD+**

*positive for both biomarkers*

high pCR in Pembro (84%) ***and*** VC (83%)

**Immune-/DRD+**

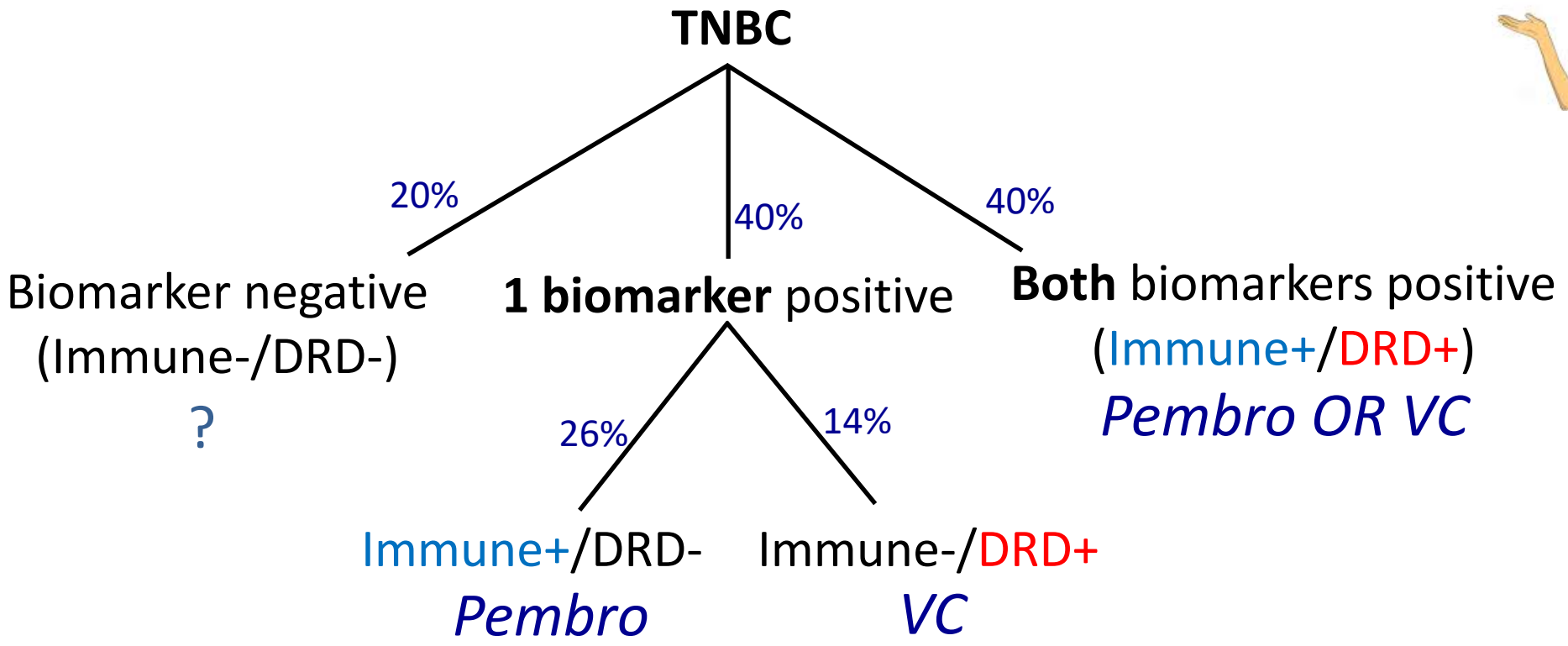
higher pCR in VC (64%)




**Immune+/DRD-**

highest pCR in Pembro (90%)

# Which drug should be prioritized for whom?



# 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

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**PI:** Don Berry
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**Agents:** Doug Yee
**Safety:** Hope Rugo
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**Biomarkers:** Laura van 't Veer
**Pathology:** Fraser Symmans
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**PRO/QOL:** Michelle Melisko

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**Business Development:**
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**Grants:**
Jeff Matthews

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**Biomarkers**: Denise Wolf, Christina Yau, Chip Petricoin, Julia Wulfkuhle, Lamorna Swigert, Gill Hirst, Mark Magbanua & Collaborators

# I-SPY 2 Participating Organizations and Funders