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# Established Management Paradigms for Advanced Triple-Negative Breast Cancer (TNBC); Actionable and Other Potentially Relevant Biomarkers to Inform Decision-Making

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Sarah Cannon Research Institute
Nashville, Tennessee

# DISCLOSURES

| | |
|---|---|
| **Consulting Agreements** | AstraZeneca Pharmaceuticals LP, Black Diamond Therapeutics Inc, Boehringer Ingelheim Pharmaceuticals Inc, Daiichi Sankyo Inc, Genentech, Lilly, Mersana Therapeutics, Novartis, Pfizer Inc, Puma Biotechnology Inc, Roche Laboratories Inc, Silverback Therapeutics |
| **Contracted Research** | AbbVie Inc, Acerta Pharma — A member of the AstraZeneca Group, Aravive Inc, ArQule Inc, Arvinas, AstraZeneca Pharmaceuticals LP, BerGenBio ASA, Black Diamond Therapeutics Inc, Boehringer Ingelheim Pharmaceuticals Inc, Clovis Oncology, Curis Inc, CytomX Therapeutics, Daiichi Sankyo Inc, Deciphera Pharmaceuticals, eFFECTOR Therapeutics Inc, Eisai Inc, EMD Serono Inc, Fochon Pharmaceuticals Ltd, Fosun Orinove PharmaTech Inc, FUJIFILM Pharmaceuticals USA Inc, Genentech, H3 Biomedicine, Harpoon Therapeutics, Hutchison MediPharma, Immunomedics Inc, InventisBio, Leap Therapeutics Inc, Lilly, Lycera, MacroGenics Inc, Marker Therapeutics Inc, Medivation Inc, a Pfizer Company, Mersana Therapeutics, Merus BV, Molecular Templates, Novartis, NuCana, OncoMed Pharmaceuticals Inc, Pfizer Inc, Radius Health Inc, Regeneron Pharmaceuticals Inc, Rgenix, Roche Laboratories Inc, Seattle Genetics, Sermonix Pharmaceuticals, Silverback Therapeutics, Stemcentrx, Sutro Biopharma, Syndax Pharmaceuticals Inc, Syros Pharmaceuticals Inc, Taiho Oncology Inc, Takeda Oncology, Tesaro, A GSK Company, Torque Therapeutics, Unum Therapeutics, Verastem Inc, Zenith Epigenetics Ltd, Zymeworks |

# Case Presentation: Dr Loi

**40-year-old woman initially treated in 2016 with FEC-docetaxel and radiation therapy for T1N1 TNBC presents with newly diagnosed recurrent disease with low volume lung and sternal metastases. ECOG = 0**

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- **PD-L1 positive by SP142 assay**

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**She continues on treatment for 18 months, when her sternal metastases become symptomatic. Rest of lung disease remains in near CR.**

# Case Presentation: Dr Robson

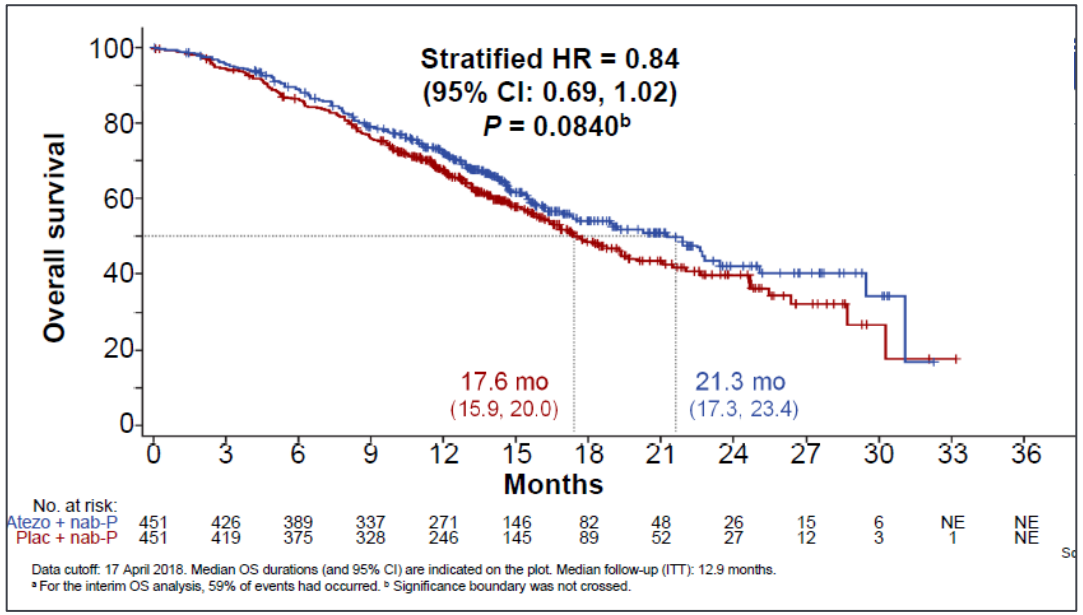
**42-year-old with cT2N1 TNBC, s/p neoadjuvant ddAC-T with ypT2N1 disease. Receives adjuvant capecitabine, XRT. Presents with bony metastasis, primary PD-L1+ (2% IC by SP142). Receives nab-paclitaxel and atezolizumab. SD on first restaging and POD on second restaging (16 weeks).**

- What is your preferred next line of therapy?
- Do you continue atezolizumab after progression?

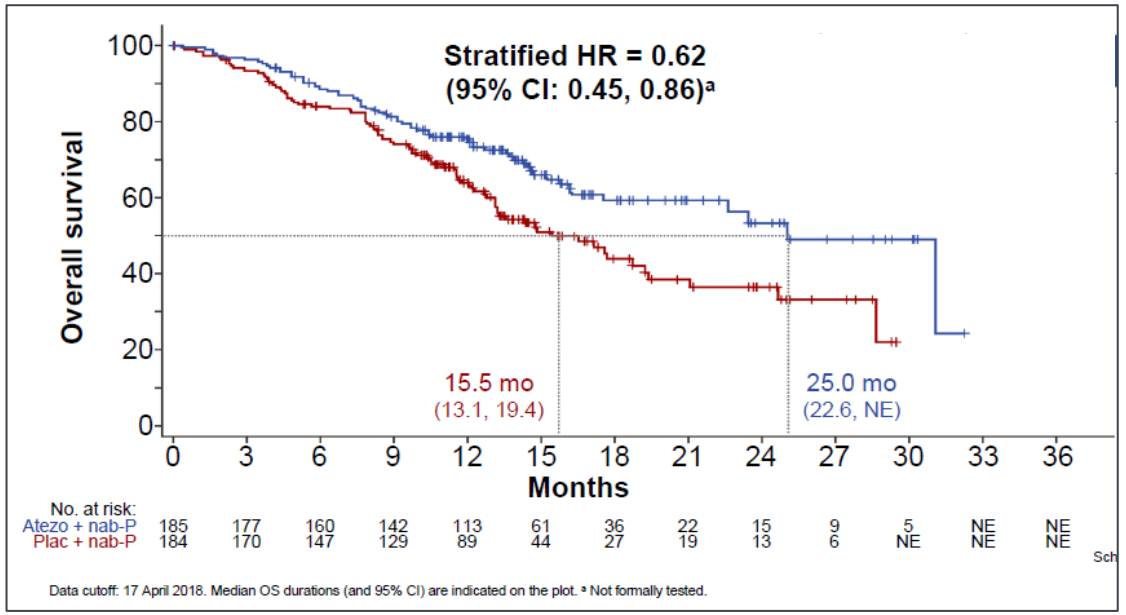
# ATEZOLIZUMAB + *NAB*-PACLITAXEL: SOC FOR PD-L1+ 1ST LINE mTNBC

## IMpassion130: Interim Overall Survival Analysis

### ITT Population




### PD-L1 IC+§ Subgroup




- The survival benefit was driven by PD-L1 IC+ patients only
- Atezolizumab + *nab*-paclitaxel received accelerated approval by FDA for PD-L1+ 1st line mTNBC in March 2019

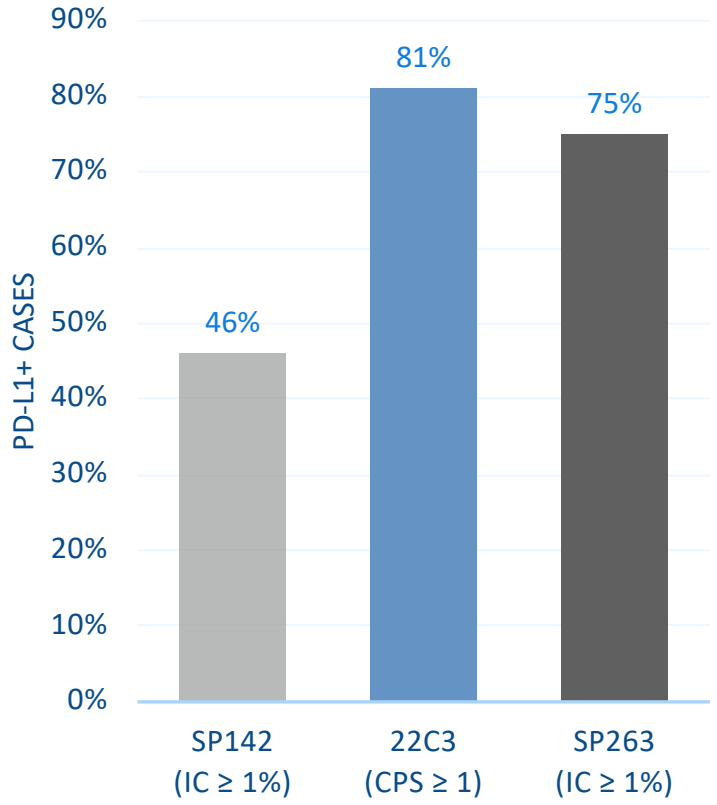
§ PD-L1 expression on IC was evaluated using the VENTANA PD-L1 SP142 IHC assay with a ≥ 1% cutoff
IC= immune cells

Schmid P et al NEJM 2018

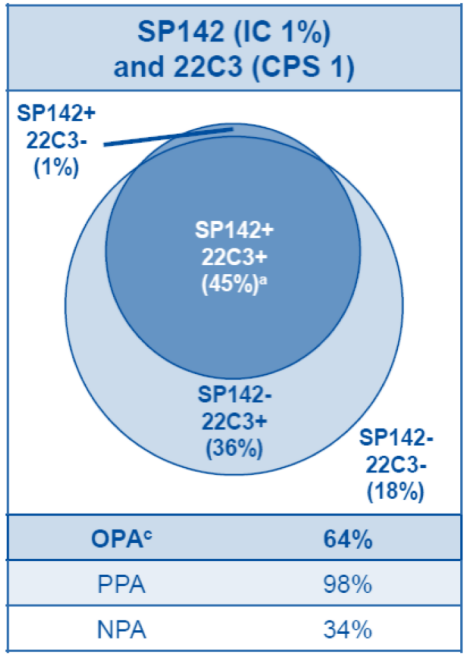
# ALL PD-L1 IHC TESTS ARE NOT EQUAL

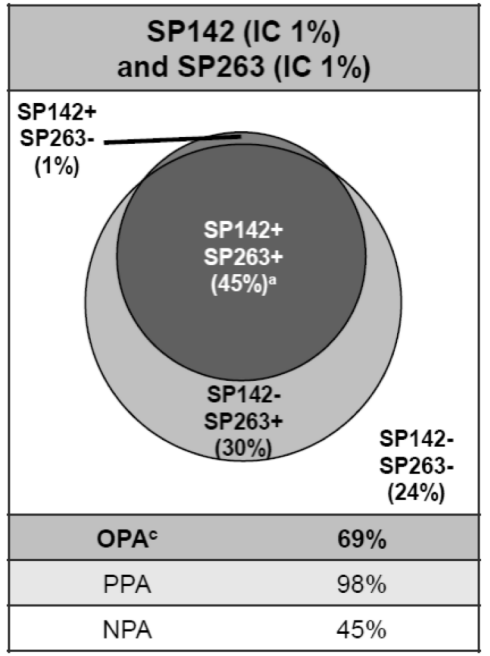
**Different PD-L1 assays were analyzed in a post-hoc analysis of IMpassion130**

## PD-L1+ Prevalence




## Analytical Concordance

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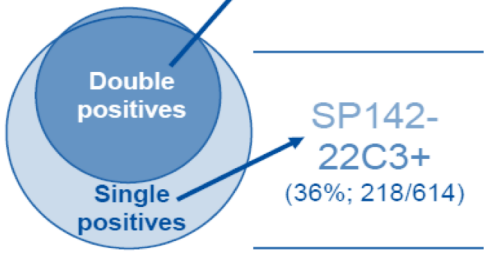
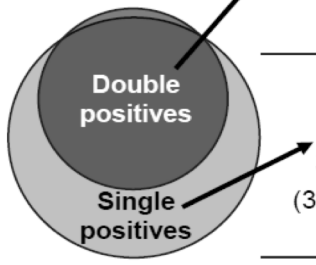
Rugo H et al ESMO 2019

# IMpasssion130: CLINICAL OUTCOMES BY PD-L1 TEST TYPE

## Analysis conducted in 614 patients (biomarker evaluable population)




| Population | Median OS, months | | | HR (95% CI) |
|---|---|---|---|---|
| | A+nP | P+nP | Δ | |
| SP142+ 22C3+ (45%; 279/614) | 27.3 | 18 | 9.3 | 0.71 (0.52, 0.98) |
| SP142- 22C3+ (36%; 218/614) | 21.3 | 21.8 | -0.5 | 0.92 (0.64, 1.31) |
| SP142- 22C3- (18%, 111/614) | 14.7 | 19.6 | -4.9 | 1.08 (0.67, 1.76) |




| Population | Median OS, months | | | HR (95% CI) |
|---|---|---|---|---|
| | A+nP | P+nP | Δ | |
| SP142+ SP263+ (45%; 278/614) | 27.3 | 17.9 | 9.4 | 0.71 (0.52, 0.97) |
| SP142- SP263+ (30%; 182/614) | 21.4 | 21.0 | 0.4 | 0.87 (0.58, 1.29) |
| SP142- SP263- (24%; 147/614) | 17.9 | 20.5 | -2.6 | 1.10 (0.72, 1.68) |

**Clinical benefit in 22C3+ and SP263+ subgroups driven by the SP142+ subgroup**

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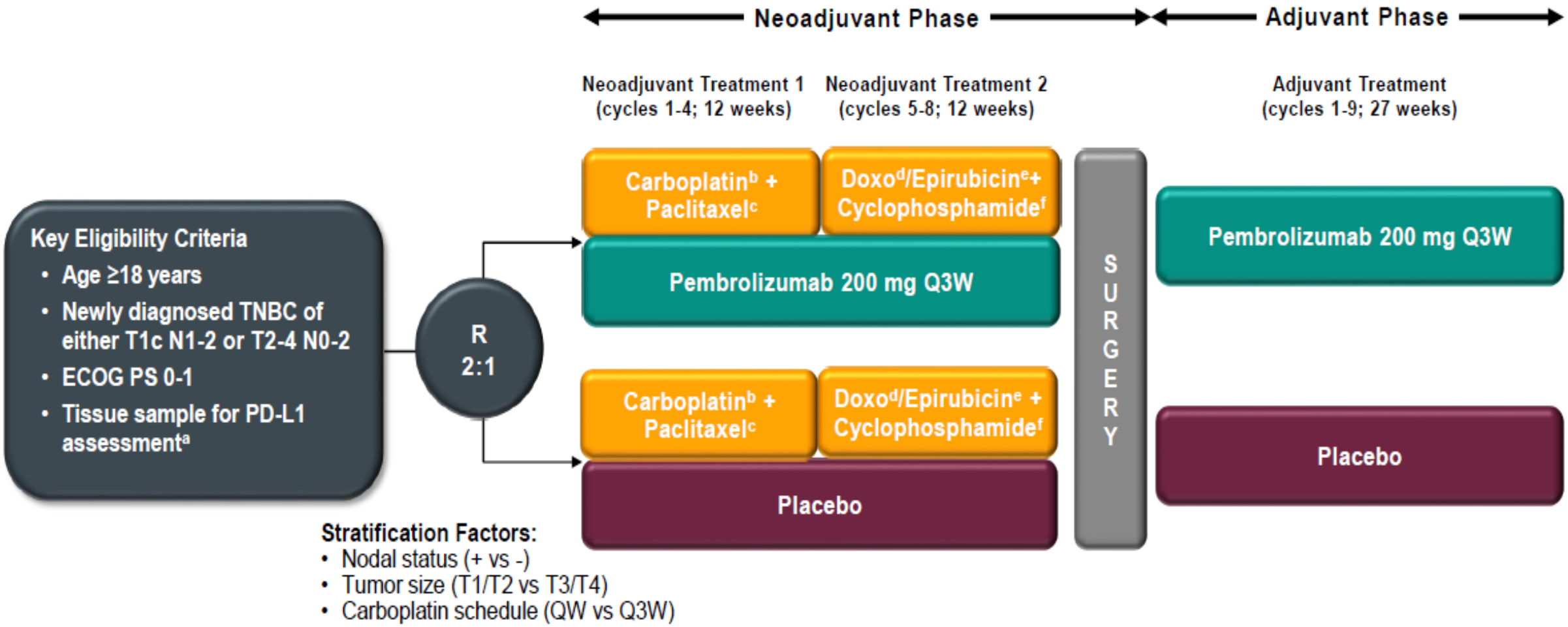
Rugo H et al ESMO 2019

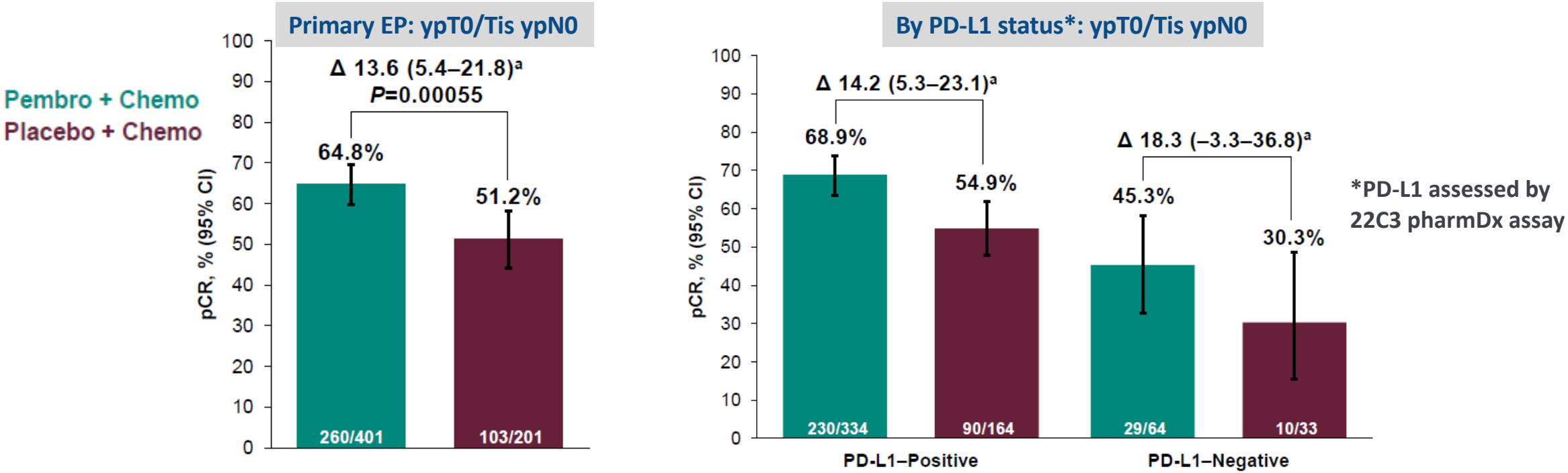
# KEYNOTE 522: NEOADJUVANT CHEMO + PEMBROLIZUMAB IN TNBC




Schmid P et al ESMO 2019

# KEYNOTE 522: NEOADJUVANT CHEMO + PEMBROLIZUMAB IN TNBC

- Addition of pembrolizumab to neoadjuvant chemo led to statistically significant improvement in pCR of 13.6%
- Benefit with pembrolizumab was independent of PD-L1 status

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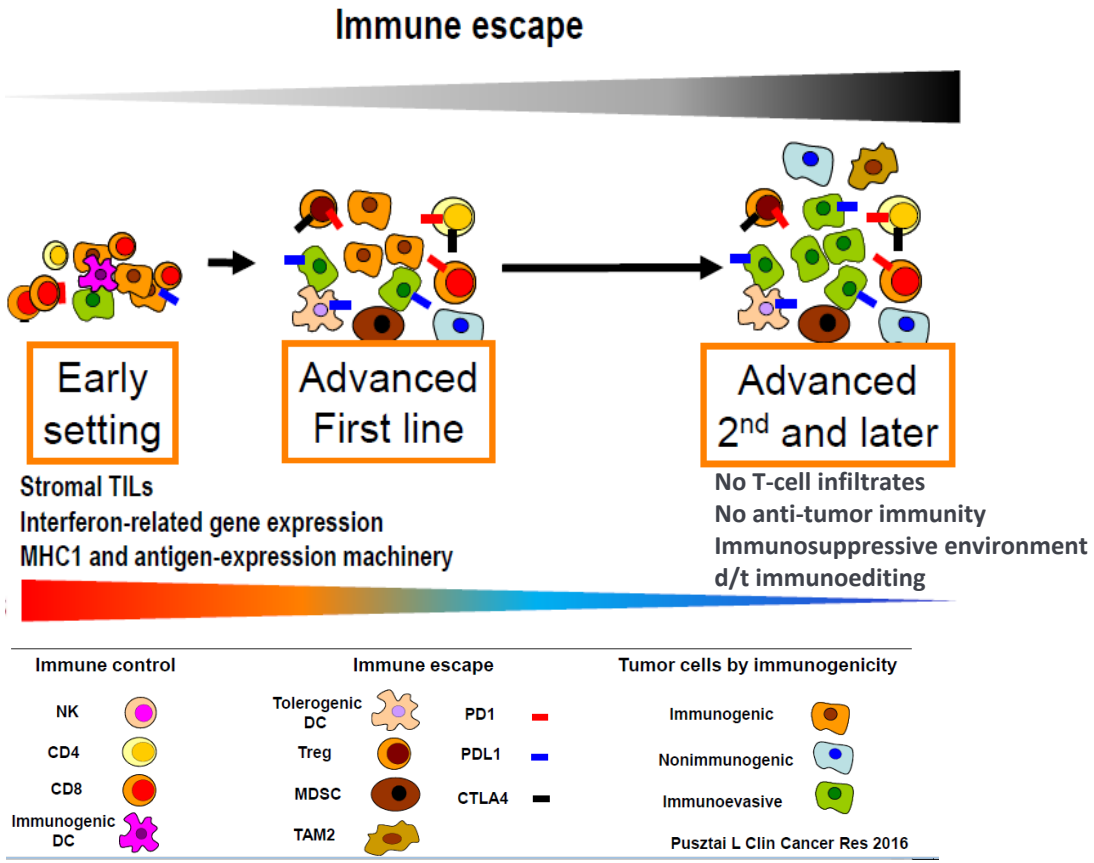
# HIGHER IMMUNOGENICITY IN PRIMARY TUMORS COMPARED TO METASTATIC

## Tumor/immune co-evolution leads to an increasing immunoediting and immune subversion




## Potential Biomarkers of Immune Response

- PD-L1 IC or TC
- CD8+ T cells
- Stromal TILs
- Stromal Granzyme B expression
- Interferon-related gene expression
- MHC-1 and antigen expression machinery
- Cytokines
- MDSCs
- Tumor mutational burden
- Immune gene signatures
- Microsatellite instability
- Gut microbiome

Bianchini G et al 2017; Szekely B et al 2018
Tarantino P & Curigliano G 2019

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# THE MSI TESTING STORY

**Histology agnostic approval of pembrolizumab[1] in all dMMR and/or MSI-H tumors was based on:**

- 39.6% ORR among 149 pts with 15 different tumor types and
- Durable responses: ≥6 months in 78% of responders

↓

**Endometrial cancer is associated with dMMR in ~20-33% of cases[2,3] and MSI testing is standard for endometrial cancer**

↓

**However, MSI-H is rare in breast cancer (<2%)[2,3] and hence most often is tested as part of a broad NGS profiling test**

↓

**TNBC patients who test positive for dMMR/MSI-H can be treated with pembrolizumab**

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1. https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm560167.htm
2. Bonneville R et al 2017
3. Dudley JC et al 2016

# gBRCA ALTERATIONS AND IMPACT ON BREAST CANCER

## Prevalence of *BRCA* mutations

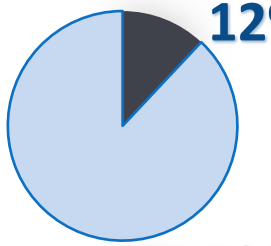
*BRCA1* **1 in 300**

*BRCA2* **1 in 800**

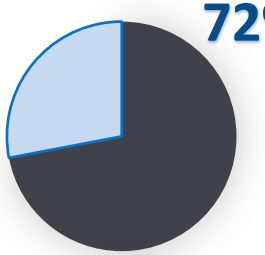
*Certain ethnic groups have higher prevalence:*

*Ashkenazi Jews* **1 in 40**

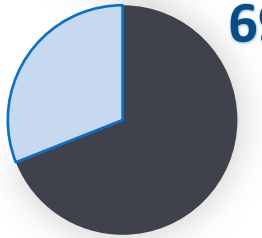
## Development of breast cancer in women




General Population



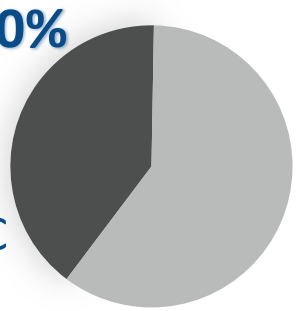

*BRCA1* Mutation



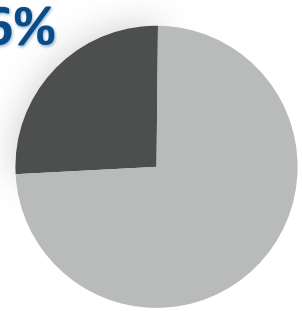

*BRCA2* Mutation

## 20 years after the 1st breast cancer diagnosis

Women with *BRCA1* mutation that will have contralateral BC




Women with *BRCA2* mutation that will have contralateral BC

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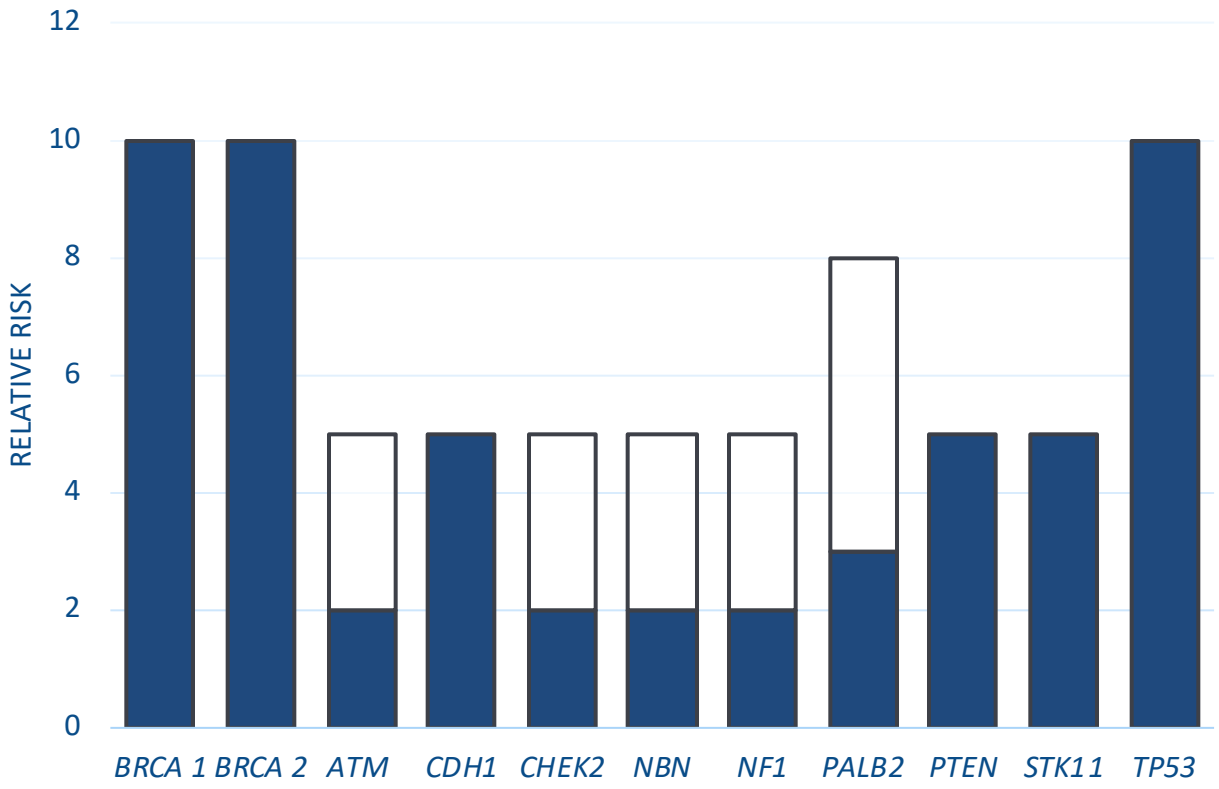
# OTHER GENES ASSOCIATED WITH HIGHER RISK OF BREAST CANCER

**Table 1. Estimated cancer risks and guidelines for breast cancer-associated genes on multigene germline panels**

| Gene | Breast cancer relative risk | Other cancer risks and syndromes | Clinical practice guidelines | References |
|---|---|---|---|---|
| *ATM* | Two to three-fold (c.7271T>G missense mutation with estimated 60% risk of breast cancer by age 80) | Ataxia telangiectasia syndrome in homozygotes; colon, pancreas, prostate (possibly family history dependent) | National Comprehensive Cancer Network (NCCN): Screening with breast MRI; consider RRM based on family history | [13, 35, 37] |
| *BRCA1* | 10-fold | Ovarian | American Cancer Society (ACS) and NCCN: Screening with breast MRI, recommend RRBSO, discuss RRM | [8, 13, 18, 35, 38] |
| *BRCA2* | 10-fold | Ovarian, pancreatic, prostate, melanoma | NCCN: Screening breast MRI, recommend RRBSO, discuss RRM | [8, 13, 18, 35, 38] |
| *CDH1* | Fivefold (particular association with lobular breast carcinoma) | Gastric | NCCN: Screening breast MRI; consider RRM based on family history | [13, 35, 39–41] |
| *CHEK2* | Two to threefold (threefold risk with truncating mutation 1100delC) | Possible link with colorectal, thyroid, lung (possibly family history dependent) | NCCN: Screening breast MRI, Patient with first-degree relative with colorectal cancer, consider colonoscopy every 5 years at 40, or 10 years prior to age of cancer diagnosis. Patient with no first-degree relative with colorectal cancer, consider colonoscopy every 5 years beginning at age 40 | [13, 35, 42, 43] |
| *NBN* | Two to threefold | Nijmegen breakage syndrome in homozygotes; possibly ovarian | Consider screening breast MRI | [35, 44, 45] |
| *NF1* | Two to threefold | Central nervous system, peripheral nerve sheath | Consider screening breast MRI | [35, 46] |
| *PALB2* | Three to fivefold | Pancreas; possibly ovarian | NCCN: Screening breast MRI, discuss RRM | [13, 35, 47] |
| *PTEN* | At least fivefold | Thyroid, endometrial | NCCN: Screening breast MRI, discuss RRM | [13, 35, 48, 49] |
| *STK11* | At least fivefold | Pancreas, colon, ovarian sex cord-stromal | NCCN: Screening breast MRI | [13, 35, 50] |
| *TP53* | At least 10-fold | Multiple sites including adrenocortical, brain, leukemia, sarcoma | NCCN: Screening breast MRI, discuss RRM; whole-body MRI, colonoscopy, complete blood count, and other tests | [13, 35, 51] |

*RRBSO* bilateral risk-reducing salpingo-oophorectomy, *RRM* risk-reducing mastectomy

## ESTIMATED CANCER RISK FOR ASSOCIATED GENES

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Afghahi A & AW Kurian, Curr. Treat. Options in Oncol. 2017

# BRCA TESTING PRIOR TO 2018 WAS COMPLICATED

Genetic testing for BRCA mutations was contingent on meeting one of a complicated set of criteria:

- Individuals with family history of known deleterious BRCA 1/2 mutation
- Personal history of:
  - diagnosed with breast cancer at ≤ 50 years
  - or TNBC ≤ 60 years
  - any ovarian cancer
- Strong family history via genetic pedigree
- Ashkenazi Jewish ancestry

However, this changed in 2018 after new clinical trial data

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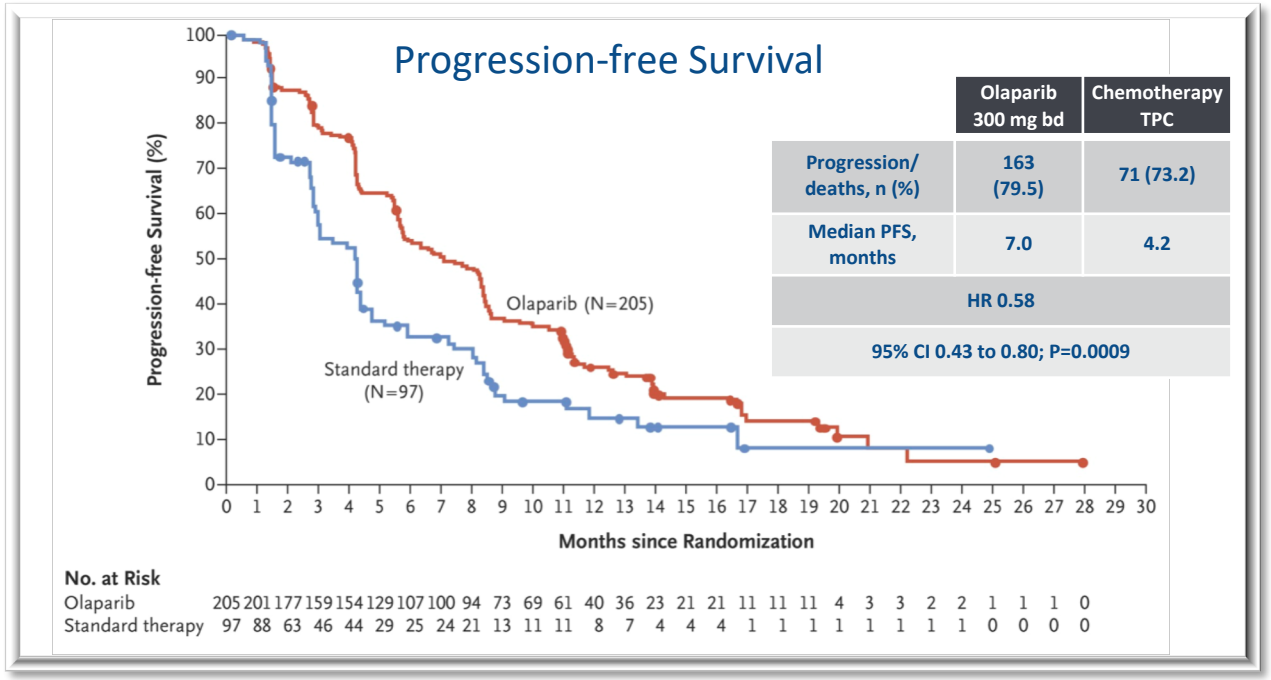
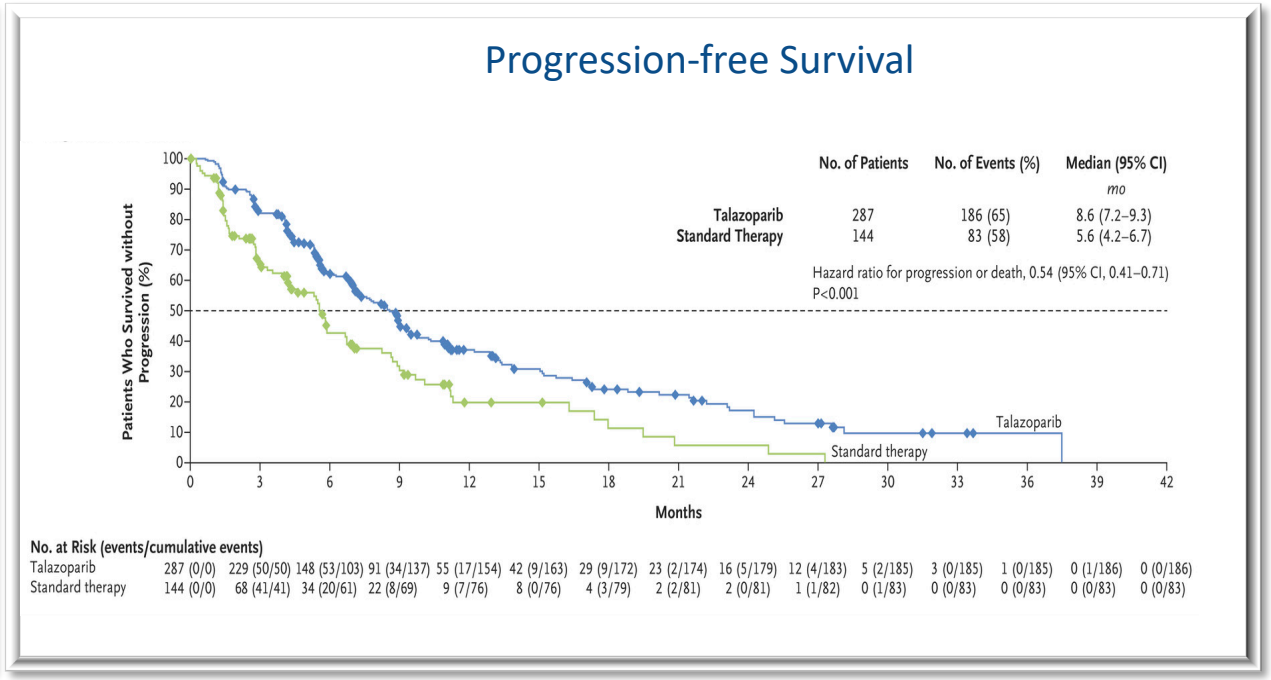
# PARP INHIBITORS FOR TREATMENT OF gBRCA MUTANT HER2- MBC

## OlympiAD: Olaparib vs Chemo in gBRCA mutant HER2- MBC




| | Olaparib 300 mg bd | Chemotherapy TPC |
|---|---|---|
| Progression/ deaths, n (%) | 163 (79.5) | 71 (73.2) |
| Median PFS, months | 7.0 | 4.2 |
| HR 0.58 | | |
| 95% CI 0.43 to 0.80; P=0.0009 | | |

## EMBRACA: Talazoparib vs chemo in gBRCA mutant HER2- MBC




**Olaparib and Talazoparib received FDA approval for the treatment of gBRCA mutant HER2- MBC in January and October 2018 respectively**

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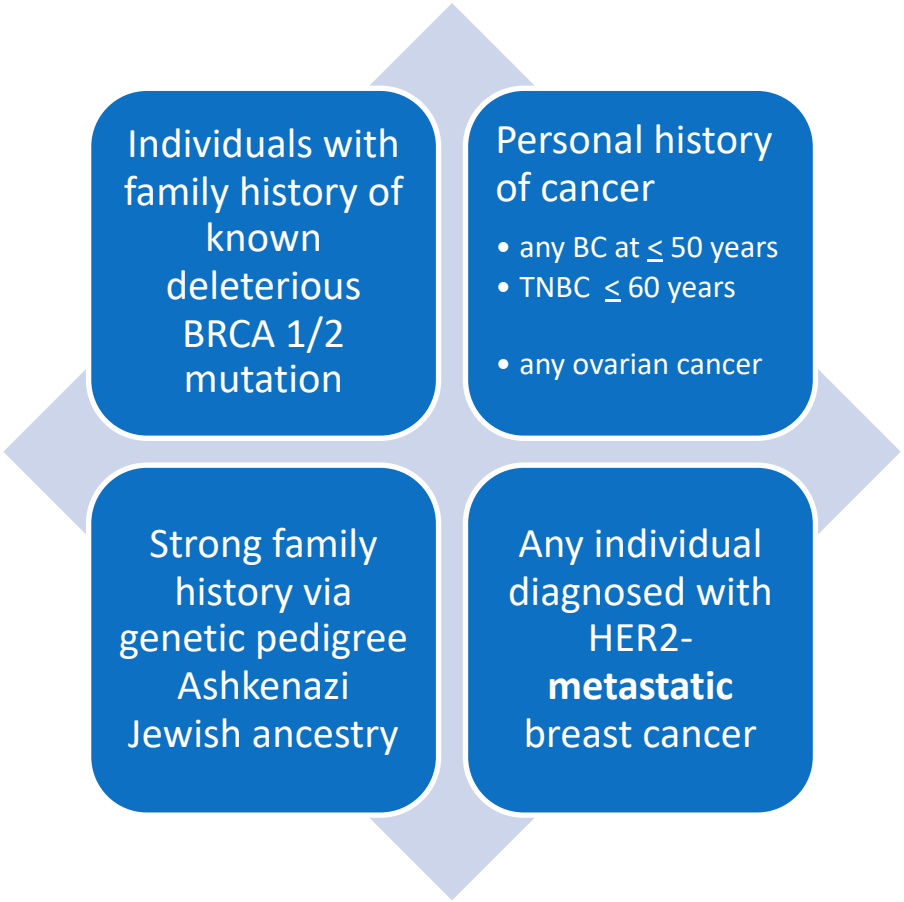
Robson M et al NEJM 2017
Litton J et al NEJM 2018

# GERMLINE BRCA TESTING IN 2019




## *Select BRCA1/2* Testing Criteria - NCCN guidelines Version 3.2019

Individual from a family with a known *BRCA1/2* pathogenic/likely pathogenic variant, including such variants found on research testing

Personal history of breast cancer + one or more of the following:

- Diagnosed ≤ 45y
- Diagnosed 46-50y with:
  - An additional breast cancer primary at any age
  - ≥1 close blood relative with breast cancer at any age
  - ≥1 close blood relative with high-grade (Gleason score ≥7) prostate cancer
  - An unknown or limited family history
- Diagnosed ≤ 60y with:
  - Triple-negative breast cancer
- Diagnosed at any age with:
  - ≥1 close blood relative with:
    - Breast cancer diagnosed ≤50y; or
    - Ovarian carcinoma; or
    - Male breast cancer; or
    - Metastatic prostate cancer; or
    - Pancreatic cancer
  - ≥2 additional diagnoses of breast cancer at any age in patient and/or in close blood relatives
- Ashkenazi Jewish ancestry

Personal history of ovarian carcinoma

Personal history of male breast cancer

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# GENETIC TESTING FOR BRCA AND OTHER GENES ASSOCIATED WITH HEREDITARY BREAST CANCER

Ambry Genetics®
A Konica Minolta Company

GeneDx
an OPKO Health Company

Blueprint Genetics

INVITAE

color

fulgent

Integrated GENETICS
LabCorp Specialty Testing Group


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GENETICS

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