Evaluation of BRCA1/2 and homologous recombination defects in ovarian cancer and impact on clinical outcomes

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Learning Objectives

- Describe germline or tumor aberrations in BRCA1/2 and other homologous recombination (HR) defects for ovarian cancer patients and explore implications for PARP inhibitor therapy
- Compare clinical outcomes for patients with BRCA1/2 or HR-related defects versus no HR defects
  - Neoadjuvant chemotherapy (NACT)
  - Upfront surgical debulking

BRCA1/2 and HR Defects: PARP

- Our study focused on subgroups (BRCA and HR defects) and clinical outcomes
- BRCA1/2 and HR defects are associated with better response to PARP inhibitors
- Characterization provides further insight on spectrum of defects and testing considerations for potential PARP candidates

Study Overview

- Previously untreated ovarian cancer patients were prospectively enrolled (2010-2013) under an IRB protocol approved by University of Texas MD Anderson Cancer Center
- Non-mucinous ovarian cancer patients were eligible to enroll following informed consent
- Screening for germline mutations in BRCA1/2 and other HR genes was conducted, as well as tumor characterization (when available)
- Clinical data were abstracted from the medical record

Ovarian Cancer Patients Enrolled in Study

Patients with non-mucinous ovarian cancer undergoing primary treatment at MD Anderson in 2010-2013 (n = 345)

Excluded (n = 39)
- Refused to participate (n = 6)
- Unable to reach patient to obtain consent (n = 33)

Enrolled in study (n = 306)

Excluded (n = 7)
- Insufficient clinical data available

Patients included in analysis (n=299)
- All patients with available blood sample received germline testing.

Ovarian Cancer Cases with Additional Molecular Testing

Patients included in analysis (n=299)
- All patients with available blood sample received germline testing.

Neoadjuvant (NACT) (n = 170)
- Focused on germline testing for BRCA1/2 and other HR genes

Upfront surgical debulking (n = 129)
- Germline testing for BRCA1/2 and other HR genes
- Tumor BRCA1/2 testing and HR Deficiency assay

Tumor testing:
- BRCA1/2 somatic mutations
- BRCA1 methylation
- HR Deficiency (HRD) Score

Methods- Types of Molecular Testing

- Germline mutation screening was performed on DNA from blood (BRCA1/2, ATM, BARD1, BRIP1, CHEK1, CHEK2, NBN, PALB2, RAD51C, RAD51D)
- BRCA1/2 somatic mutation screening was performed on DNA from FFPE tumor samples using custom hybridization enrichment and next generation sequencing
- BRCA1 methylation measured with DNA Methylation PCR Arrays
- HR Deficiency (HRD) Score[1] is a measure of genomic instability based on LOH, telomeric allelic imbalance, and large-scale state transitions. High HRD Score (≥ 42) indicates HR defect.

[1]Telli M et al, Clin Cancer Res 2016.

Ovarian Cancer Patient Characteristics

Histology	N	%
Serous	251	84.0
Mixed	27	9.0
Clear Cell	10	3.3
Endometrioid	7	2.3
Other, not specified	4	1.3
Grade	**N**	**%**
High	265	88.6
Low	28	9.4
Unknown	6	2.0

Primary treatment	N	%
Neoadjuvant chemotherapy	170	56.9
Upfront surgical debulking	129	43.1

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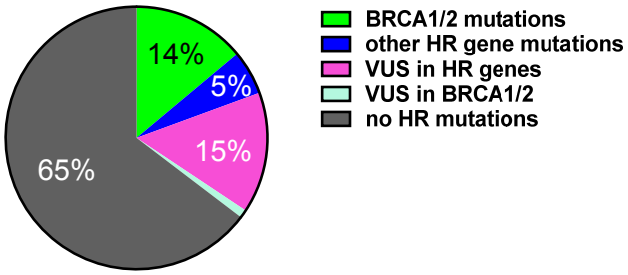
Germline Testing Characteristics

BRCA1/2 Status	N (N=299)	%
BRCA1/2 negative	227	75.9
BRCA1/2 positive	44	14.4
BRCA1+	27 (9.0%)	
BRCA2+	17 (5.4%)	
Unknown	28	9.4

Other HR genes with deleterious or suspected deleterious mutations	N (N=201 total)	%
BRIP1	5	2.5
RAD51C	2	1.0
ATM	1	0.5
BARD1	1	0.5
NBN	1	0.5
PALB2	1	0.5

Germline Testing- Variants of Uncertain Significance



- High rate of variants with unknown significance for other HR genes (15%)

Overall Survival for Entire Cohort

	N (deaths)	Median (months)	P-value	HR (multiv)	95% CI
Initial treatment					
Surgery	129 (34)	65.8		Ref	
NACT	170 (85)	45.2	**0.0032**	2.07	1.28-3.36
Debulking- residual disease					
Suboptimal	27 (15)	34.0		Ref	
≤ 1 cm	47 (28)	36.7	0.8242	0.93	0.48-1.80
R0	160 (49)	NR	**0.0226**	0.49	0.27-0.91
Germline BRCA1/2 mutation status					
Negative	227 (97)	46.1		Ref	
BRCA1/2 positive	44 (11)	65.3	**0.0331**	0.43	0.20-0.93

Event-Free Survival for Entire Cohort

	N (events)	Median (months)	P-value	HR (multiv)	95% CI
Initial treatment					
Surgery	129 (78)	24.8		Ref	
NACT	170 (139)	15.6	**0.0003**	1.93	1.35-2.76
Stage					
≤ IIIB	35 (13)	NR		Ref	
IIIC	145 (109)	17.5	**0.0025**	2.60	1.40-4.81
IV	73 (57)	15.1	**0.0253**	2.18	1.10-4.29
Germline BRCA1/2 mutation status					
Negative	227 (171)	16.4		Ref	
BRCA1/2 positive	44 (26)	27.0	**0.0050**	0.53	0.34-0.82

Specific Subgroups of Interest Analyzed

- High grade serous cancers (HGSC) only- NACT or Surgery
- Molecular subsets:

"Any germline HR mutation"

Germline mutations
BRCA1
BRCA2

Germline mutations
Other HR genes (panel)

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- Molecular subsets:

BRCA tumor testing
BRCA1 somatic
BRCA2 somatic
BRCA1 methylation

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Other tumor testing
HR Defect Score ≥ 42

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"Any HR Aberration"

Germline mutations
BRCA1
BRCA2

Germline mutations
Other HR genes (panel)

BRCA tumor testing
BRCA1 somatic
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Overall Survival- HGSC NACT

	N (deaths)	Median (months)	P-value	HR	95% CI
Any germline HR mutations (BRCA1/2, ATM, BARD1, BRIP1, NBN, PALB2, RAD51C)					
No	104 (58)	36.7		Ref	
Yes	35 (14)	50.2	**0.0236**	0.49	0.27-0.91
Germline BRCA1/2 mutation status					
Negative	113 (64)	38.1		Ref	
BRCA1/2 positive	28 (10)	65.3	**0.0162**	0.44	0.22-0.86

Only the statistically significant comparisons are included here

Event-Free Survival- HGSC NACT

	N (events)	Median (months)	P-value	HR	95% CI
Any germline HR mutations (BRCA1/2, ATM, BARD1, BRIP1, NBN, PALB2, RAD51C)					
No	104 (92)	13.9		Ref	
Yes	35 (26)	20.4	**0.0019**	0.47	0.29-0.75
Germline BRCA1/2 mutation status					
Negative	113 (100)	14.5		Ref	
BRCA1 positive	17 (13)	20.1	**0.0341**	0.53	0.30-0.95
BRCA2 positive	11 (7)	35.6	**0.0058**	0.34	0.16-0.73

Only the statistically significant comparisons are included here

Overall Survival- HGSC Surgery

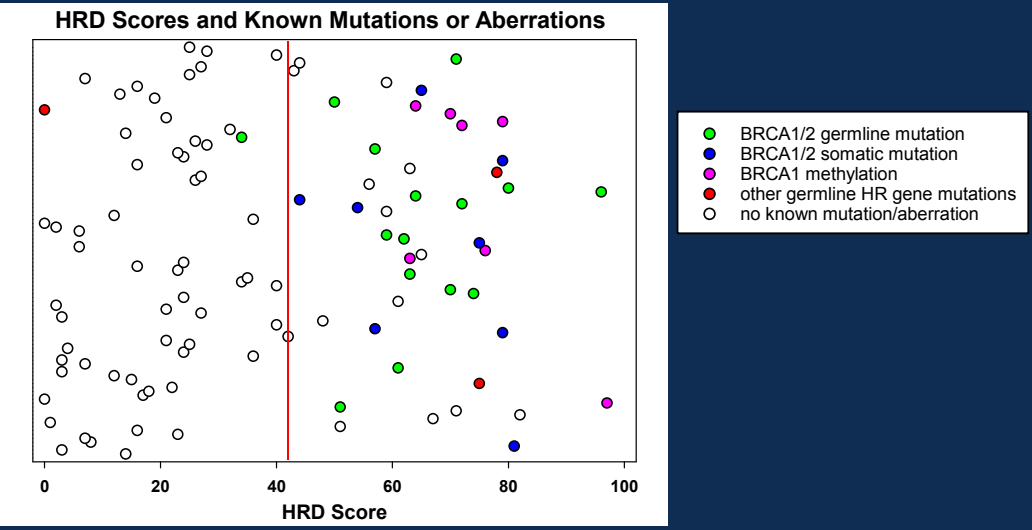
	N (deaths)	Median (months)	P-value	HR	95% CI
Debulking- residual disease					
Suboptimal	7 (5)	31.9		Ref	
≤ 1 cm	14 (8)	36.7	0.8237	0.87	0.26-2.91
R0	54 (12)	NR	**0.0462**	0.31	0.10-0.98
Germline BRCA1/2 mutation status					
Negative	70 (24)	54.4		Ref	
BRCA1/2 positive	15 (1)	NR	0.0818	0.17	0.02-1.25
HRD Score					
< 42	37 (17)	41.0		Ref	
≥ 42	40 (9)	NR	**0.0277**	0.40	0.18-0.91

Event-Free Survival- HGSC Surgery

	N (events)	Median (months)	P-value	HR	95% CI
Germline BRCA1/2 mutation status					
Negative	70 (51)	16.3		Ref	
BRCA1/2 positive	15 (6)	45.8	**0.0153**	0.35	0.15-0.82
Somatic BRCA1/2 mutations					
No	34 (28)	14.2		Ref	
Yes	9 (4)	38.1	**0.0266**	0.42	0.20-0.90
HRD Score					
< 42	37 (29)	15.9		Ref	
≥ 42	40 (24)	28.2	**0.0488**	0.58	0.34-0.99

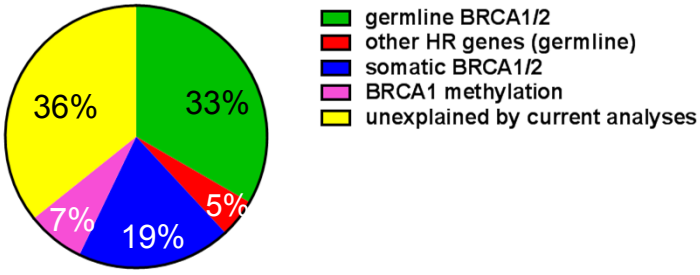
Significant changes based on stage and debulking are not included.

Understanding HR Defect Scores

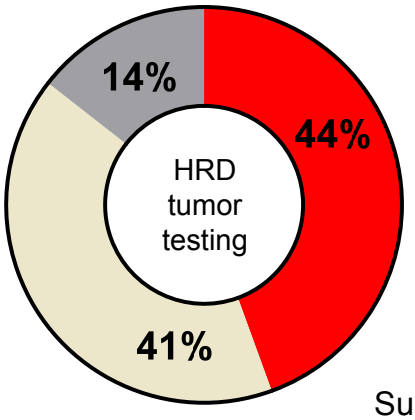


Cases with High HRD Scores

- Standard of care germline testing should identify 33-38% of these patients
- Somatic tumor BRCA1/2 testing identifies an additional 26%
- 36% with HR defects not explained by current analysis



HRD Assay- Tumor Analysis



High HRD Score
Low HRD Score
testing failed

Subset: HGSC undergoing upfront surgery

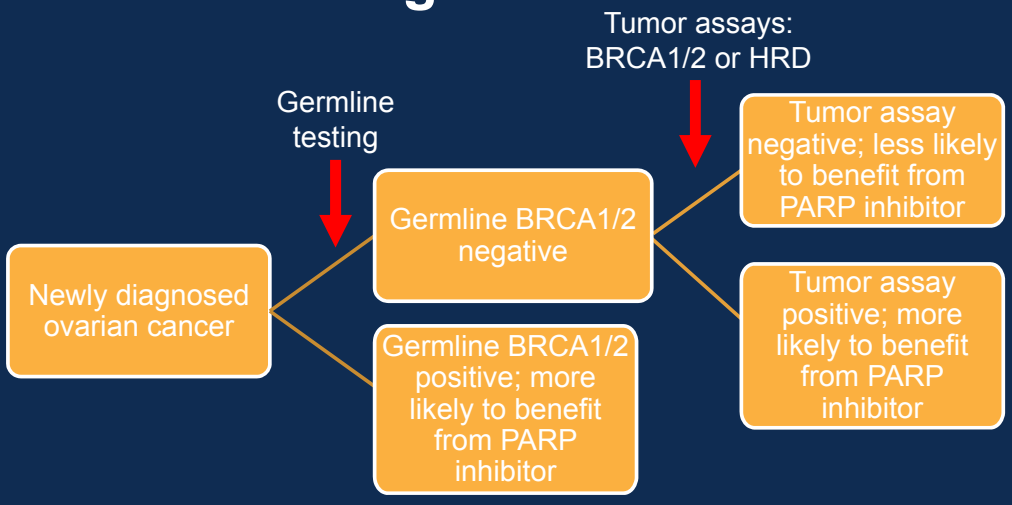
HR Defect Assay Limitations

- FFPE tumor samples were used for analysis, with 14% failure rate for samples with sufficient DNA yield
- Failure based on noise to signal ratio metric (non-tumor DNA and DNA quality)
- Core biopsies from NACT patients (pre-treatment) were also screened for the assay, but insufficient tumor cells were present

PARP: Germline, Somatic, or HRD Testing?

- HRD assay identifies larger group than germline and somatic tumor BRCA1/2 analyses
- The benefit of BRCA1/2 germline testing is identification of deleterious mutations that allows for “cascade” genetic testing for relatives
- When caring for an ovarian cancer patient, when should germline or HRD testing be performed?

MD Anderson Proposed Flow for Germline and Tumor Testing



Summary

- Ovarian cancer patients with germline mutations of BRCA1/2 or other HR genes have improved clinical outcomes
- Ovarian cancer patients receiving upfront surgery with somatic BRCA1/2 mutations or a high HRD Score also have improved clinical outcomes
- Germline screening, tumor profiling for BRCA1/2 defects, or HRD analysis identifies patients that might benefit from PARP inhibitors
- We propose initial germline testing followed by tumor profiling for germline negative patients

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