A Retrospective Analysis of Real-World Tumor *BRCA* (t*BRCA*) Testing Trends in Ovarian Cancer (OC) Before and After PARP Inhibitor Approvals

Leslie M. Randall,[1] Ebru Aydin,[2] Melinda Louie-Gao,[2] Sebastien Hazard,[2] Shannon N. Westin[3]

[1]University of California Irvine, Irvine, CA, USA; [2]TESARO, Inc., Waltham, MA, USA; [3]University of Texas MD Anderson Cancer Center, Houston, TX, USA

BACKGROUND

- Approximately 50% of ovarian cancers (OCs) harbor germline or somatic homologous recombination deficiencies (HRD),[1] half of which are in the *BRCA*1/2 genes.[2]
- Poly (ADP-ribose) polymerase inhibitors (PARPi) cause irreparable double-strand DNA breaks, genomic instability, and cell death. PARPi demonstrate synthetic lethality in tumors with HRD (eg, *BRCA*1/2 mutations).[3]
- Currently, there are 3 PARPi approved by the US Food and Drug Administration (FDA) for treating recurrent OC: olaparib (approved in 2014); rucaparib (approved in 2016); and niraparib (approved in 2017).[4]
- National Comprehensive Cancer Network (NCCN) guidelines recommend tumor molecular testing for patients with recurrent OC, fallopian tube, or primary peritoneal cancer prior to initiation of therapy for persistent/recurrent disease.[5]
  - Molecular testing includes *BRCA*1/2 mutations, homologous recombination pathway genes, and microsatellite instability or DNA mismatch repair.

OBJECTIVE

- The objective of this analysis was to assess real-world *BRCA* and HRD testing trends as well as utilization of PARPi by biomarker status in OC.

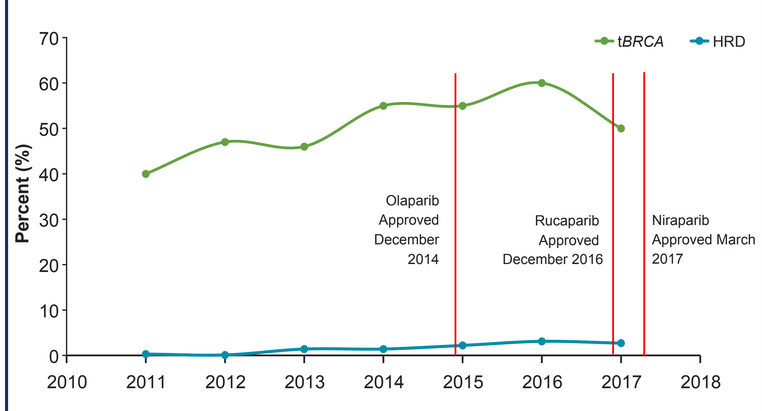
METHODS

- We performed a retrospective analysis of the Flatiron database, which is a longitudinal, demographically and geographically diverse database derived from electronic health records (EHR) from over 265 cancer clinics and more than 2 million active US cancer patients.
- Eligibility criteria included cases of ovarian, tubal, or peritoneal cancer diagnosed between January 2011 and May 2018.
- Real-world tumor *BRCA* (t*BRCA*) testing, which includes germline (g), somatic (s), and test type unknown (u) and HRD testing trends prior to initiation of therapy were analyzed.
- Patients who received PARPi therapy (niraparib: n=132, olaparib: n=49, and rucaparib: n=37) between April 2017 and April 2018 (the time interval spanning the approval of all 3 drugs) were included in this study.

RESULTS

- The database included 4950 OC patients.
- There were >12 different test types used to identify the *BRCA* status. The most common test types were Myriad BRACAnalysis®, Myriad myRisk®, and Ambry Genetics *BRCA*1/2.
- Between 2011–2016, t*BRCA* testing rates increased, while HRD testing was infrequent (**Figure 1; Table 1**)

Figure 1. Percent t*BRCA* and HRD Tested by OC Diagnosis (January 2011–May 2018)



t*BRCA*=tumor *BRCA*; HRD=homologous repair deficiency.

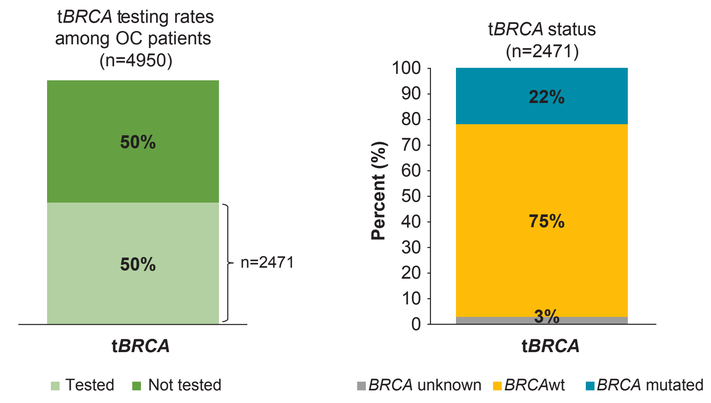
Table 1. t*BRCA* and HRD Testing by Year of Diagnosis

Year	2011	2012	2013	2014	2015	2016	2017	2018
Diagnosed (n)	629	716	714	722	687	738	599	145
t*BRCA* tested (n)	250	337	330	396	375	441	297	45
t*BRCA* tested (%)	40	47	46	55	55	60	50	31
HRD tested (n)	2	1	10	10	15	23	16	2
HRD tested (%)	0.3	0.1	1.4	1.4	2.2	3.1	2.7	1.4

t*BRCA*=tumor *BRCA*; HRD=homologous repair deficiency.

- Of the 4950 patients diagnosed with OC between January 2011 and May 2018, 2471 (≈50%) underwent t*BRCA* testing (**Figure 2**).
  - Of these patients, 539 (22%) harbored mutations (t*BRCA*mut), 1853 (75%) were t*BRCA* wildtype (t*BRCA*wt), and 79 (3%) were deemed *BRCA* unknown (t*BRCA* unknown).

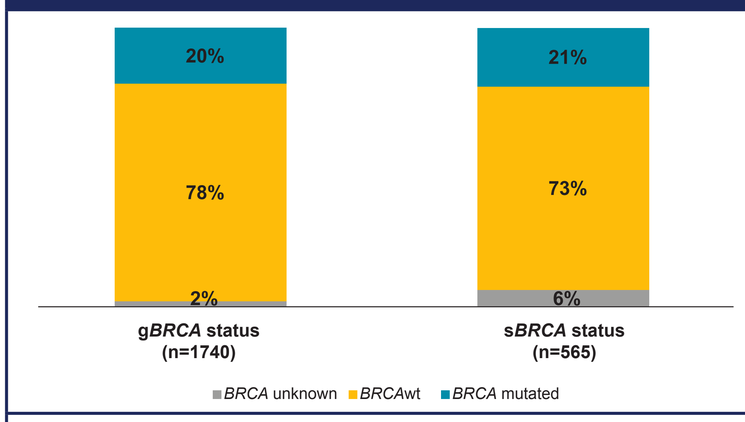
Figure 2. t*BRCA* (g*BRCA* + s*BRCA* + u*BRCA*) Testing Rates and Test Status in the OC Cohort (January 2011–May 2018)



g*BRCA*=*BRCA* germline mutation; s*BRCA*=*BRCA* somatic mutation; u*BRCA*=test type unknown.

- Of the 2471 patients who underwent t*BRCA* testing, 1740 (70%) had g*BRCA* testing and 565 (23%) had s*BRCA* testing, (**Figure 3**). t*BRCA* testing type was undetermined in 493 patients (20%).
  - Of the 1740 patients who underwent g*BRCA* testing, 342 (20%) were g*BRCA* mutated, 1363 (78%) were g*BRCA*wt, and 35 (2%) were g*BRCA* unknown.
  - Of the 565 patients who underwent s*BRCA* testing, 120 (21%) were s*BRCA* mutated, 413 (73%) were s*BRCA*wt, and 32 (6%) were s*BRCA* unknown.

Figure 3. g*BRCA* and s*BRCA* Status*



*Some patients received both g*BRCA* and s*BRCA* testing.
g*BRCA*=*BRCA* germline mutation; s*BRCA*=*BRCA* somatic mutation.

- From April 2017 to April 2018, 212 patients were treated with PARPi (niraparib, olaparib, and rucaparib). Of these patients, 70 (33%) were t*BRCA*mut, 102 (48%) were t*BRCA*wt, 9 (4%) were t*BRCA* unknown, and 31 (15%) did not undergo t*BRCA* testing.
- Among the 212 PARPi-treated patients, 132 (62%) received niraparib, 49 (23%) received olaparib, and 37 (17%) received rucaparib.
  - Of the PARPi-treated patients, 70 (33%) had t*BRCA* mutations. Of these patients, 29 (41%) were treated with niraparib, 21 (30%) received olaparib, and 23 (33%) received rucaparib (**Table 2**).
  - Of the 102 (48%) PARPi-treated patients with t*BRCA*wt status, 76 (75%) received niraparib, 18 (18%) received olaparib, and 11 (11%) received rucaparib.
  - Nine (4%) of the PARPi-treated patients were t*BRCA* unknown and 7 of these patients (78%) received niraparib, 1 patient (11%) received olaparib, and 1 patient (11%) received rucaparib.
  - t*BRCA* testing was not undertaken in 31 (15%) PARPi-treated patients. Of these, 20 (65%) received niraparib, 9 (29%) received olaparib, and 2 (6%) received rucaparib.

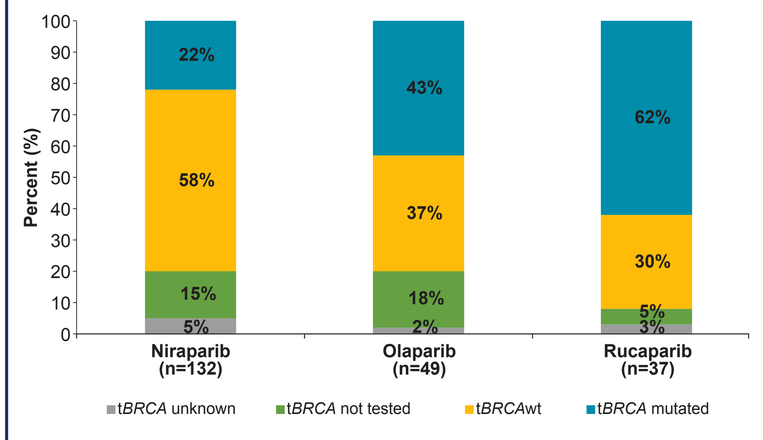
Table 2. PARPi % Among t*BRCA* Mutated, Wildtype, or Unknown (April 2017–April 2018)

	t*BRCA*mut n (%)	t*BRCA*wt n (%)	t*BRCA* unknown n (%)	t*BRCA* not tested n (%)
PARPi*	70 (100)	102 (100)	9 (100)	31 (100)
Niraparib	29 (41)	76 (75)	7 (78)	20 (65)
Olaparib	21 (30)	18 (18)	1 (11)	9 (29)
Rucaparib	23 (33)	11 (11)	1 (11)	2 (6)

*Some patients received multiple PARPi. t*BRCA*= tumor *BRCA*.

- t*BRCA* mutation rates for patients receiving niraparib, olaparib, and rucaparib were 22%, 43%, and 62%, respectively. t*BRCA*wt rates were 58%, 37%, and 30%, and t*BRCA* not tested rates were 15%, 18%, and 5% (**Figure 4**).

Figure 4. PARPi by t*BRCA* Mutation Status (April 2017–April 2018)



t*BRCA*=tumor *BRCA*.

CONCLUSIONS

- This real-world analysis suggests that despite strong societal recommendations[6] only 50% of OC patients are tested for t*BRCA* mutations.
- The t*BRCA*mut rate (≈22%) observed from real-world data is comparable with t*BRCA*mut rates reported in the literature (≈25%).[3]
- HRD testing rates remained infrequent and unchanged since 2014.
  - Infrequent HRD testing may be attributed to PARPi efficacy regardless of *BRCA* or HRD status.
- Niraparib was the most frequently used PARPi in OC patients, across all t*BRCA* subtypes.
- After an initial increase in the testing rates following PARPi approvals in 2014, a decrease in the testing rates was noted in 2017, possibly due to the broadening of PARPi labels to all-comers.

REFERENCES

1. Ledermann JA et al. *Eur J Cancer*. 2016;60(suppl C):49-58.
2. Alsop K et al. *J Clin Oncol*. 2012;30:2654-2663.
3. Liu JF, Konstantinopoulos PA, Matulonis UA. *Gynecol Oncol*. 2014;133:362-369.
4. FDA Centerwatch. https://www.centerwatch.com/drug-information/fda-approved-drugs/medical-conditions/O. Accessed August 15, 2018.
5. National Comprehensive Cancer Network (NCCN) Clinical Guidelines for Ovarian Cancer. https://www.nccn.org/professionals/physician_gls/pdf/ovarian.pdf. Accessed August 15, 2018.
6. Randall LM et al. *Gynecol Oncol*. 2017;146:217-224.

ACKNOWLEDGEMENTS

Editorial and graphics support, funded by TESARO, Inc. (Waltham, MA), and coordinated by Ashujit Tagde, PhD, were provided by Ashfield Healthcare Communications (Middletown, CT).