Advances in the Treatment of Gynecologic Malignancies: BRCA and Beyond

Todd Boren, MD

Gynecologic Oncology

1/11/20

- I have no conflict of interest to disclose

BRCA historical perspective

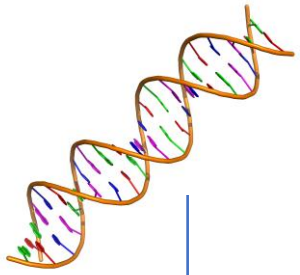
- BRCA 1/BRCA2- tumor suppressor genes that code for proteins involved in error-free homologous recombination repair (repair of double stranded DNA damage)
- Mutations in BRCA1/2 result in loss of the ability of cells to repair double stranded DNA breaks
- Which leads to homologous recombination deficiency (HDR)
  - Increased risk of Breast, Ovarian, Pancreatic, Colon, melanoma etc..

BRCA Historical Perspective

- BRCA1/2 testing has historically been used to identify patients at risk of developing BRCA associated cancers in an effort to intervene either surgically, diagnostically or pharmacologically to prevent the cancer from developing or identify cancer at an early stage
- Prophylactic mastectomy/BSO/Tamoxifen/OCPs/increased imaging surveillance etc.…

PARP inhibitors (PARPi)

- Poly-ADP-ribose polymerase (PARP)
- Repairs single strand DNA breaks
- Loss of PARP function results in double strand DNA breaks through DNA replication of the single strand breaks
- Cells with HRD (i.e. BRCA mutated cells) cannot repair these double stranded breaks and the cell dies
- Summary: **PARPi lead to persistence of double stranded DNA breaks and cell death in patients with BRCA mutations or HRD**

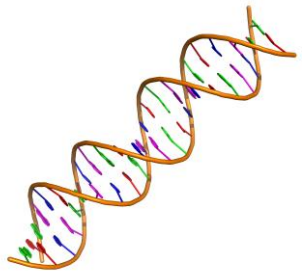


Environmental Factors etc…

Single strand DNA breaks

Single strand DNA breaks

PARP



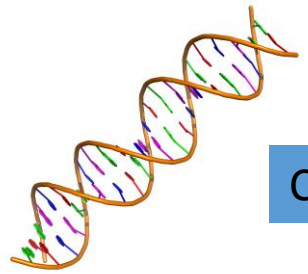
PARPi

Double stranded DNA breaks

Absent BRCA proteins or (HRD)

BRCA ½ proteins

DNA tries to replicate



Cell Survives

Cell Death

PARPi

- 2014- FDA approves Olaparib (Lynparza) for the treatment of ovarian cancer patients with $BRCA_{mut}$ after third line treatment
- ***Now we have an actionable mutation in ovarian cancer to exploit***
- 2015 NCCN guidelines recommend all women with epithelial ovarian cancer undergo BRCA testing regardless of family history

Efficacy of PARPi following therapy for recurrent epithelial ovarian cancer

Trial	PARPi	Population	PFS experimental arm	PFS Placebo	HR
NOVA	Niraparib	gBRCA+	20 .0 months	5.5 months	0.27
		non-gBRCA, HRD+	12.9 months	3.8 months	0.38
		Non-gBRCA, overall	9.3 months	3.9 months	0.45
		HRD neg	6.9 months	3.8 months	0.58
Study 19	Olaparib	ITT	8.4 months	4.8 months	0.35
		BRCAm	11.2 months	4.3 months	0.18
		BRCAwt	7.4 months	5.5 months	0.54
SOLO2	Olaparib	BRCAm	***19.1 months***	***5.5 months***	0.3
AREIL3	Rucaparib	ITT	10.8 months	5.4 months	0.36
		BRCAm	16.6 months	5.4 months	0.23
		HRD+	13.6 months	5.4 months	0.32

Efficacy of PARPi following primary therapy for epithelial ovarian cancer

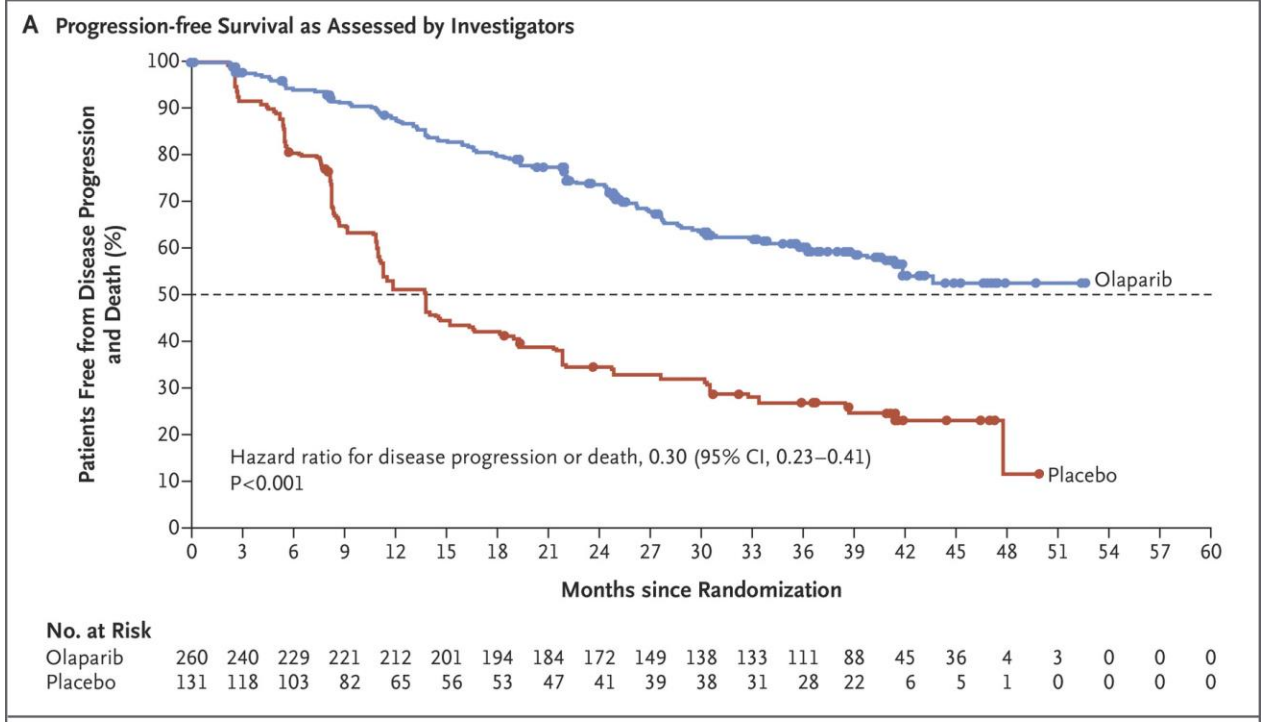
Trial	PARPi	Population	PFS experimental arm	PFS Placebo	HR
PRIMA	Niraparib	All Patients	13.8 months	8.2 months	0.62
		HRD +	21.9 months	10.4 months	0.43
		BRCAm	22.1 months	10.9 months	0.4
		HRD+, BRCAwt	19.6 months	8.2 months	0.5
		HRD neg	8.1 months	5.4 months	0.68
SOLO1	Olaparib	BRCAm (germline or somatic)	*Not reached at 60 months (36 month advantage so far)*	13.8 months	0.32
VELIA	Velaparib + CT-->velaparib maintenance	ITT	23.5 months	17.3 months	0.68
		BRCAm	37.2 months	22.0 months	0.44
		HRD +	31.9 months	20.5 months	0.57
PAOLA-1	Olaparib + Avastin	ITT	22.1 months	16.6 months	0.59
		BRCAm	37.2 months	21.7 months	0.31
		HRD+, BRCAm	37.2 months	17.7 months	0.33
		HRD+, BRCA wt	28.1 months	16.6 months	0.43
		HRD neg	16.9 months	16.0 months	0.92

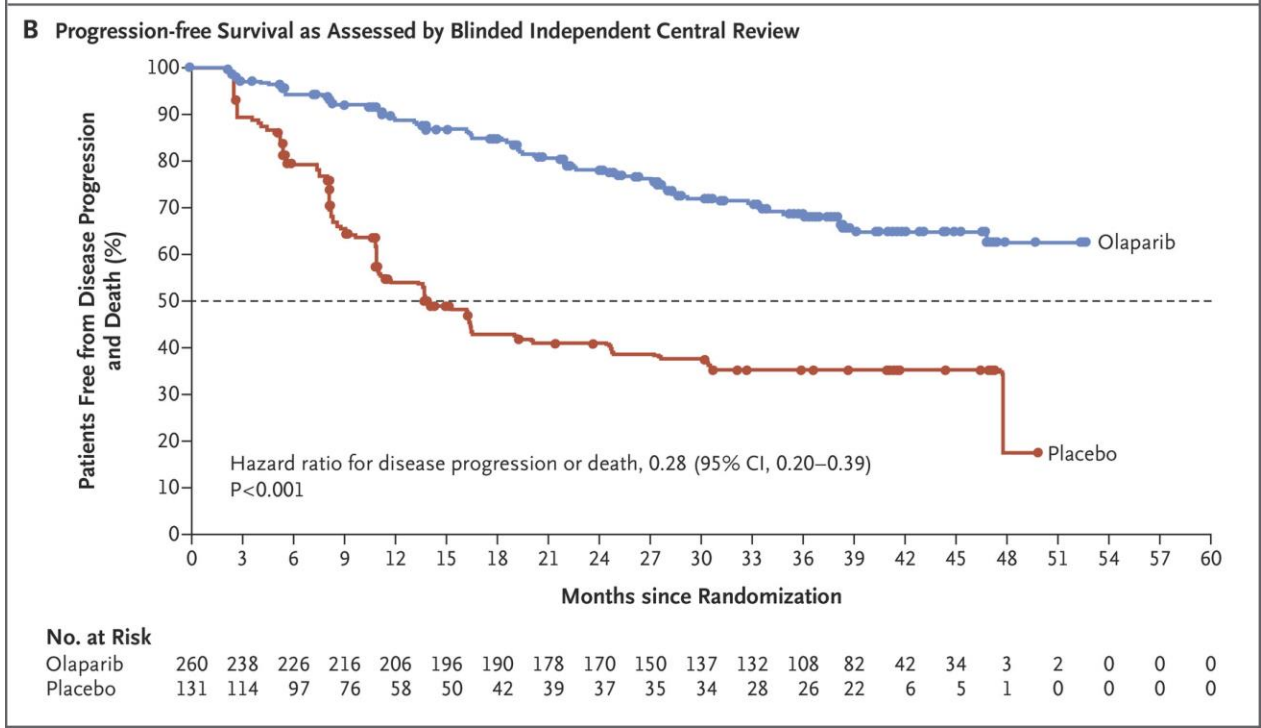
SOLO1 Trial

-Patients with newly diagnosed Ovarian Cancer

-$BRCA_{mut}$ germline or somatic

-Randomized to maintenance Olaparib vs Placebo





Types of genetic testing

- Germline testing
  - Blood test, done in office
  - Mutations you are born with
- Somatic testing
  - Tests the tumor tissue (need surgery/biopsy)
  - Acquired mutations within the tumor itself
  - Looking for ”actionable” mutations
- Possible to have a somatic BRCA mutation without a germline BRCA mutation
- HRD testing

HRD Testing

- Need tumor tissue
- Genes associated with HRD
BRCA 1/2	PALB2	BARD1	BRIP1	RAD51B	RAD51C	RAD51D
ATM	FAAP20	CHEK2	FAN1	FANCE	FANCM	POLQ

Assay looks for a “genomic scar” signature left by a build up of unrepaired double stranded DNA breaks

Riaz N, Blecua P, Lim RS, et al. Pan-cancer analysis of bi-allelic alterations in homologous recombination DNA repair genes. Nat Commun. 2017;8(1):857.

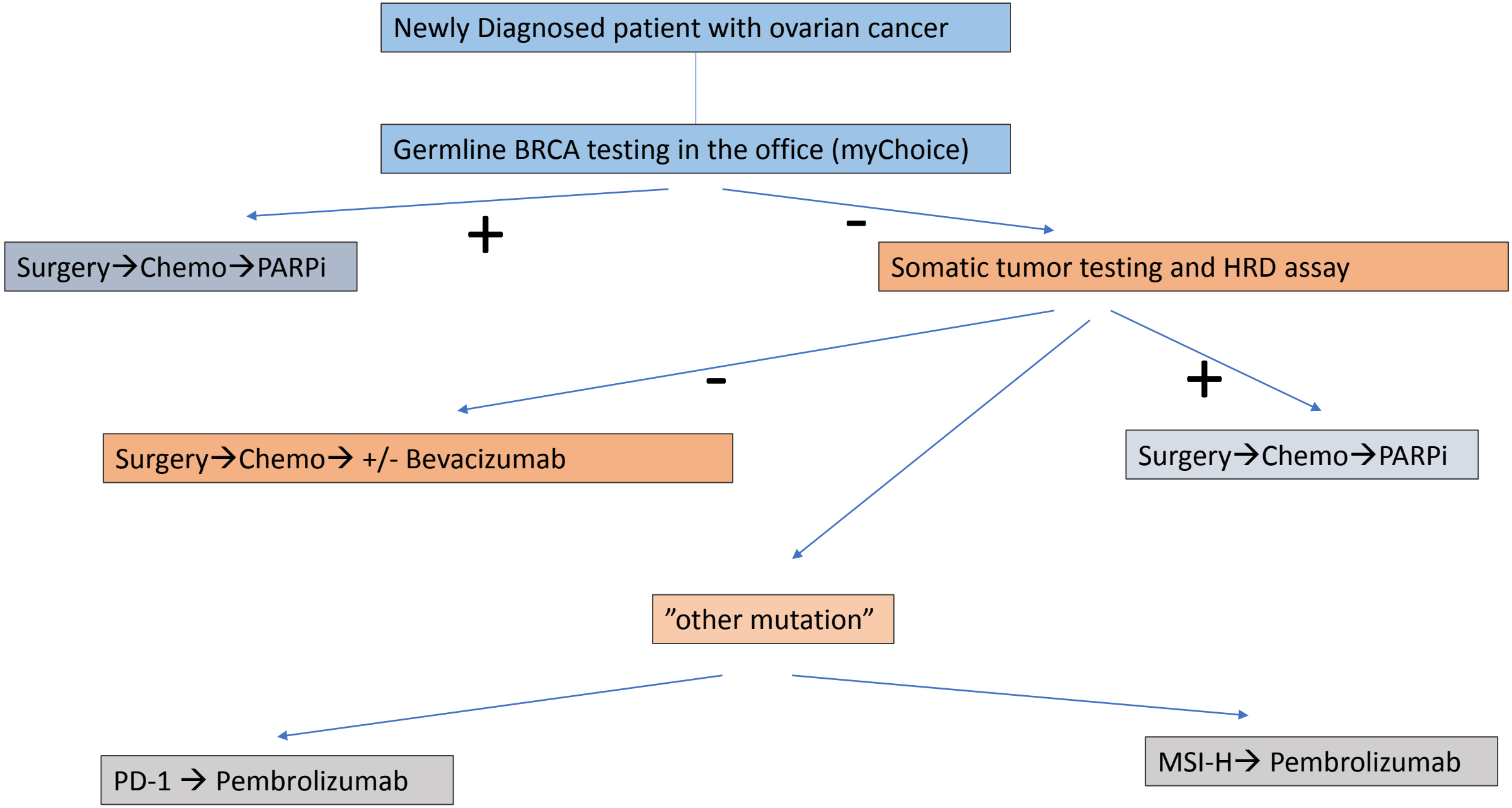
Cancer Genome Atlas Research Network. Integrated genomic analyses of ovarian carcinoma. Nature. 2011;474(7353):609–615.

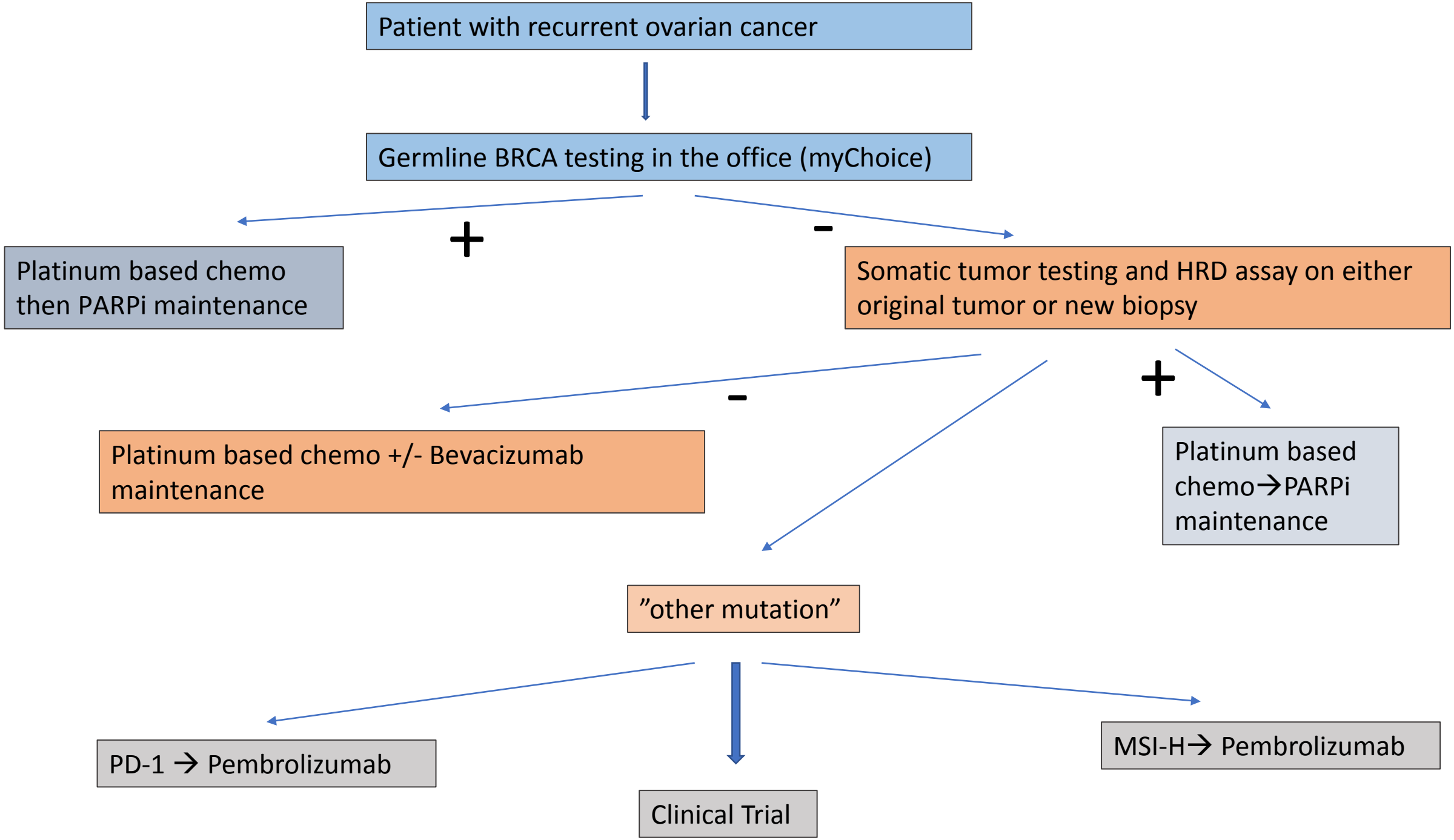
HRD Testing

- Approximately ***15%*** of Ovarian Cancer patients have a ***germline BRCA*** mutation
- ***22%*** of ovarian cancer patients have a ***somatic BRCA mutation*** (able to find an additional 7% of patients who may respond to PARPi)
- Approximately ***50%*** of ovarian cancer patients will be ***HRD positive***
- ***We would miss about 50% of patients who would benefit from a PARPi without HRD testing.***
- ***Currently <50% of patients with ovarian cancer undergo any type of genetic testing***

- Cancer Genome Atlas Research N. Integrated genomic analyses of ovarian carcinoma. Nature. 2011;474:609–15.
- Meyer LA, Anderson ME, Lacour RA, Suri A, Daniels MS, Urbauer DL, et al. Evaluating women with ovarian cancer for BRCA1 and BRCA2 mutations: missed opportunities. Obstet Gynecol. 2010;115:945–52.

What does all this mean clinically? 🤷‍♂️


Newly Diagnosed patient with ovarian cancer
Germline BRCA testing in the office (myChoice)
+
-
Surgery→Chemo→PARPi
Somatic tumor testing and HRD assay
-
+
Surgery→Chemo→ +/- Bevacizumab
Surgery→Chemo→PARPi
”other mutation”
PD-1 → Pembrolizumab
MSI-H→ Pembrolizumab


Patient with recurrent ovarian cancer
Germline BRCA testing in the office (myChoice)
+
-
Platinum based chemo then PARPi maintenance
Somatic tumor testing and HRD assay on either original tumor or new biopsy
-
+
Platinum based chemo +/- Bevacizumab maintenance
Platinum based chemo→PARPi maintenance
”other mutation”
PD-1 → Pembrolizumab
Clinical Trial
MSI-H→ Pembrolizumab

Other targeted therapies in gyn malignancies

- Germline or somatic mutations in
- PMS-2, MLH-1, MSH-2, MSH-6
  - All endometrial cancers undergo somatic testing after resection
  - 28% of all endometrioid endometrial cancers
- PD-L1
  - Included with somatic testing on all gyn tumors
  - 35% of cervical cancers

Treatment efficacy in recurrent/metastatic endometrial cancer				
Trail	Drug	Population	PFS	ORR
GOG 209	Carboplatin/paclitaxel	Metastatic/Recurrent	13.5 months	51%
Keynote 158	Pembrolizumab	MSI-H/dMMR	25.7 months	57%
Makker et al	Pembrolizumab/Lenvatinib	Non-dMMR	80%>12 months	51%

Treatment efficacy in recurrent/metastatic Cervical cancer				
Trail	Drug	Population	PFS (median)	ORR
GOG 240	Single agent +/- Bev	Metastatic/Recurrent	6-8 months	48%
Keynote 158	Pembrolizumab	PD-L1 +/ > one prior chemo	Not reached at 10 months	15%

Summary

- Test all women with epithelial ovarian cancer for germline mutations
- Send all gyn tumor tissue samples for somatic testing
- >50% of women with ovarian cancer will be candidates for PARPi and will have a significant improvement in prognosis
- ”Actionable” mutations will be found in approximately 1/3 of endometrial and cervical cancers
- ”Moving Target”