

The image features a light gray background with several thick, wavy, brownish-tan lines that create a sense of movement. In the center, there is a hand-drawn rectangular box with a black outline. Inside this box, the text "PARP" is written in a large, black, sans-serif font. Below it, the word "Inhibitors" is written in a smaller, black, cursive script font.

PARP
Inhibitors

PARP inhibitors

- PARP - poly ADP Ribose polymerase inhibitors.

- Mechanism of action:

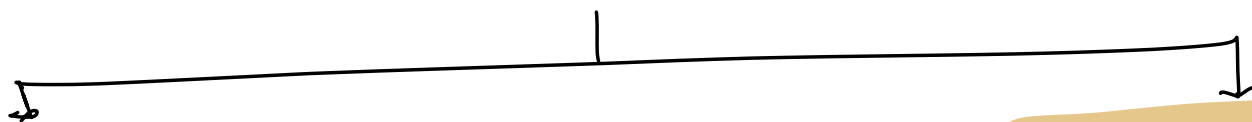
- Concept of **SYNTHETIC LETHALITY**

Mutation in either of 2 genes is not lethal individually, but combining the mutations leads to cell death.

Normal circumstance



DNA damage of
2 types



Single strand
breaks (SSB)



Easy to repair coz the other
strand acts as a complementary
template for repair.



Repaired by Base excision repair
mechanism

* mediated by PARP.

Double strand
breaks (DSB)



Difficult to repair as there
is not complementary
strand available



Repair by Homologous
recombination (HR) and

Non homologous end joining
pathway (NHEJ)



Mediated by BRCA 1/2



Mechanism of Synthetic Lethality.

In tumor cells



PARP inhibitors stop the repair of SSB

But not the repair of DSB



Persistent SSB will make the DNA fork collapse
or formation of DSB



BRCA 1/2 mutated cell cannot accomplish this $\ominus$ → DSB can be repaired effectively by BRCA 1/2 mediated pathway.

↓
Accumulation of
DSB
↓
apoptosis &
cell death.

* How PARP inhibitors work in
BRCA proficient tumors?

- many tumors exhibit features similar to
BRCA mutated tumors due to epigenetic
mutation or mutation in other components
of BRCA related pathways



"BRCAness of tumor"

eg: TNBC

Basal like breast cancer.

Grade A BRCA testing criteria.

Criteria

Individual (BC) Age ≤ 40

Age ≤ 50 : bilateral[£], founder effect^{\$}

Age ≤ 60 triple negative

Male

Family history BC with BC in two FDR*

BC with any of individual above criteria in a FDR**

Any relative of a known BRCA mutation carrier

Theragnostic Epithelial ovarian cancer***

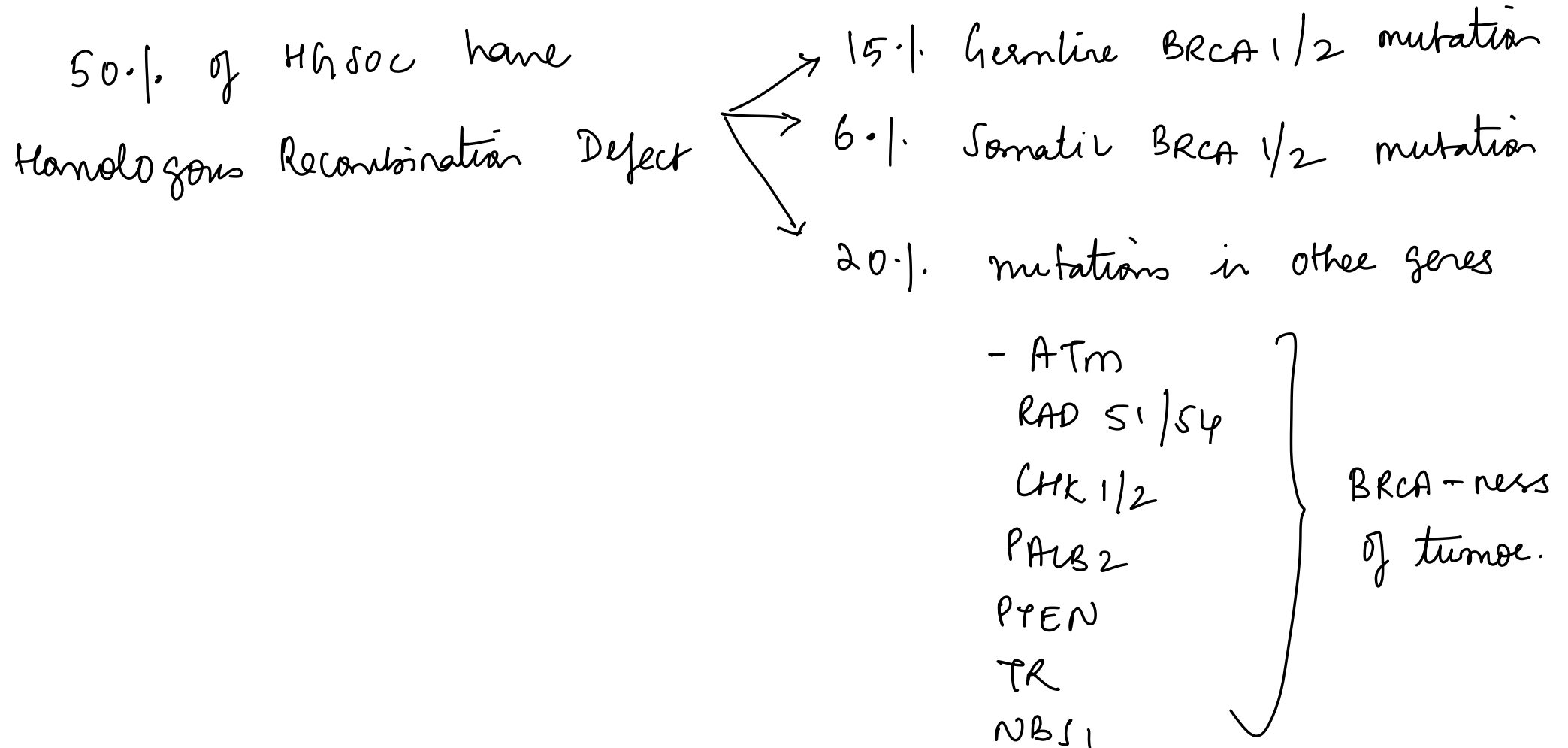
Metastatic HR and TN BC

Metastatic HR prostate cancer

Metastatic platinum-sensitive pancreatic cancer

BC, breast cancer; FDR, first-degree relative; HR, hormone resistant; £bilateral BC with one ≤ 50 years; \$ Ashkenazi Jewish or Icelandic heritages; * within maternal or paternal side; ** anytime possible the affected relative would be the most relevant to test first; *** also fulfil individual preventive grade A criteria; non-mucinous, including primary peritoneal and fallopian tube; TN, triple negative.

→ Principles of BRCA & HRD testing:



Germline mutation → Blood Sample

Somatic mutation → Tumour tissue Sample

→ levels of testing :

Germline BRCA 1 & 2 testing

Positive for mutation
in either BRCA 1 or 2

Follow guidelines

Negative for mutation
in both BRCA 1 & 2

Proceed to HRD testing

3 types

Homologous Recombination
Repair gene level
test

Identifies methylation of
Promoters of all
genes involved in
Homologous Recombination

Genomic Scars &
Signature

measures loss of
Heterozygosity (LOH)

2 tests
available

① Foundation One CDx test

[LOH high (HR Deficient)
LOH low (HR Proficient)

Cut off - 15%.

② Mychoice CDx test

Genomic Instability Score

GIS high - HR Deficient

GIS low - HR Proficient

cut off - 42

Functional assays

Provide real time

HRD / HRP status of a
tumor (Dynamic
testing)

Research ongoing.

→ clinical trials approved for PARP inhibitors:

TABLE 14.1

PARP Inhibitors That Have Received U.S. Food and Drug Administration (FDA) Regulatory Approval for Clinical Use

Agent	Company	FDA Approval
Olaparib	AstraZeneca (formerly KuDOS)	Treatment and maintenance therapy of BRCA-mutant ovarian cancer. Treatment of BRCA-mutant breast cancer. Maintenance therapy of BRCA-mutant pancreatic cancer. Treatment of prostate cancer with BRCAness.
Rucaparib	Clovis (formerly Agouron, Warner Lambert, Pfizer)	Treatment of BRCA-mutant ovarian cancer. Treatment of BRCA-mutant ovarian cancer Treatment of BRCA-mutant prostate cancer.
Niraparib	GSK (formerly Tesaro, Merck)	Maintenance therapy of BRCA-mutant ovarian cancer (also Pt sensitive non-BRCA).
Talazoparib	Pfizer (formerly Lead, Biomarin, Medivation).	Treatment of BRCA-mutant breast cancer.

→ SOHO - 1 trial

→ OLYMPIA trial - MBC
OLYMPIA trial → EBC

→ POLO trial.

→ TRITON, PROfound trials

→ ARIEL-2 trial

→ EMBRACA trial

→ Future of PARP therapy:

- combination of PARP inhibitors with ICI
- Target residual repair pathways beyond PARP and BRCA pathways by understanding synthetic lethality.