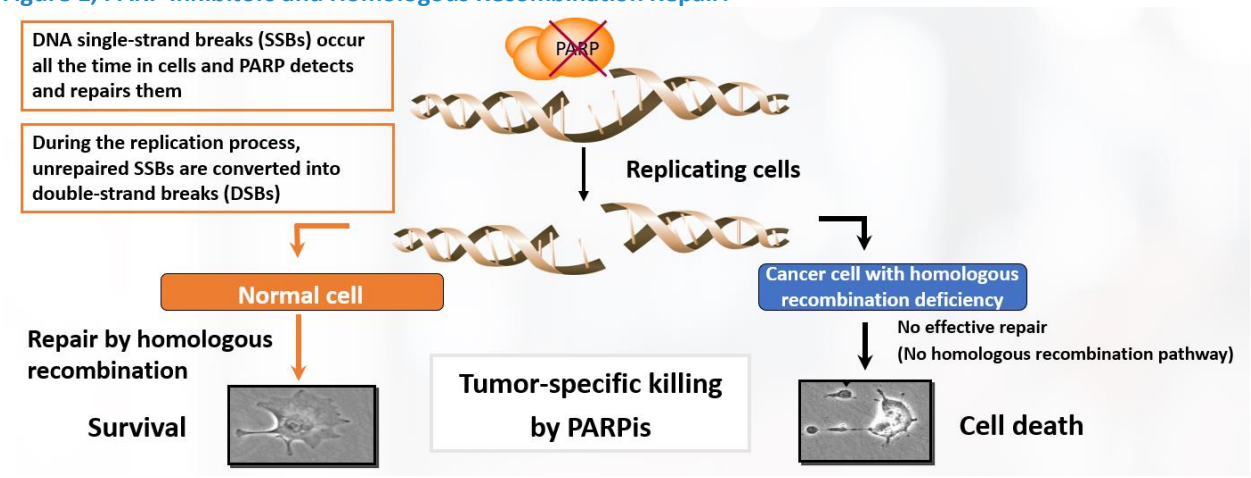
MOA of PARP Inhibitors

SUMMARY

Inhibitors of PARP interfere with the molecular events needed for DNA repair.[1] PARP inhibitors interact with the binding site of β-NAD+.[2] The interaction occurs in the catalytic domain of both PARP1 and PARP2. Data suggest that PARP inhibitors "trap" PARP on DNA, which prevents autoPARylation and PARP1 release from the damage site.**Error! Bookmark not defined.** Thus, interference of the catalytic cycle of PARP1 occurs. Progression of replication forks is impaired by the trapped PARP1/DNA nucleoprotein complexes. The hypothesis of trapping is supported by the observation of resistance to PARP inhibitors by PARP1 defective cells. Other mechanisms of PARP inhibition may exist, as both PARP1 and PARP2 have roles beyond the DNA damage response. These roles include transcription, apoptosis, and immune function.**Error! Bookmark not defined.**

A DNA damage response would normally be induced by an impeded replication fork that would be caused by trapped PARP1.**Error! Bookmark not defined.** The optimal DNA repair process is homologous recombination repair, which involves the tumor suppressor proteins *BRCA1* and *BRCA2*. However, if homologous recombination repair is absent, synthetic lethality and tumor cell death may occur with a PARP inhibitor. In short, cell death is caused by the simultaneous alteration of 2 genes or proteins. So, tumor cells with a homologous recombination repair dysfunction may be killed with a PARP inhibitor. In other words, 2 conditions that are lethal in combination but not in isolation is defined as synthetic lethality.[3] Selectivity of the PARP inhibitor for the tumor cells over normal cells may be afforded because of the genomic instability of some tumor cells.**Error! Bookmark not defined.**

Figure 1, PARP Inhibitors and Homologous Recombination Repair.



ABBREVIATIONS

β-NAD+, beta nicotinamide adenine dinucleotide positive; *BRCA,* BReast CAncer gene; DNA, deoxyribonucleic acid; DSB, double-strand breaks; PARP, poly-ADP ribose polymerase; PARPis, poly-ADP ribose polymerase inhibitors; SSB, single-strand breaks.

REFERENCES

[1] Pan Z, Xie X. BRCA mutations in the manifestation and treatment of ovarian cancer. *Oncotarget*. 2017;8(57):97657-97670.
[2] Lord CJ, Ashworth A. PARP inhibitors: Synthetic lethality in the clinic. *Science.* 2017;355(6330):1152-1158.
[3] Weil MK, Chen AP. PARP inhibitor treatment in ovarian and breast cancer. *Curr Probl Cancer.* 2011;35(1):7-50.