

Overcoming PARP Inhibitor Resistance in Cancers

Therapy designed to reinvigorate the effectiveness of
PARP inhibitors

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Team



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- Experimental Cancer Therapeutics and Drug Discovery

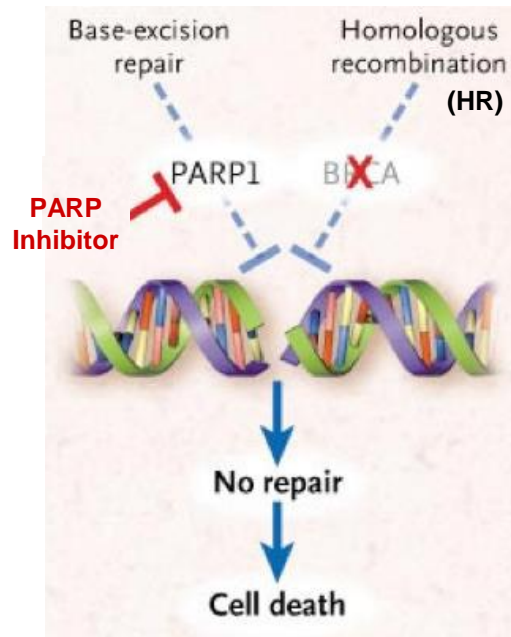


Elena Ratner, MD

- Associate Professor and Co-Chief, Division of Gynecologic Oncology
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- Cytoreductive Surgery and Treatment of Ovarian and Gynecologic Cancers

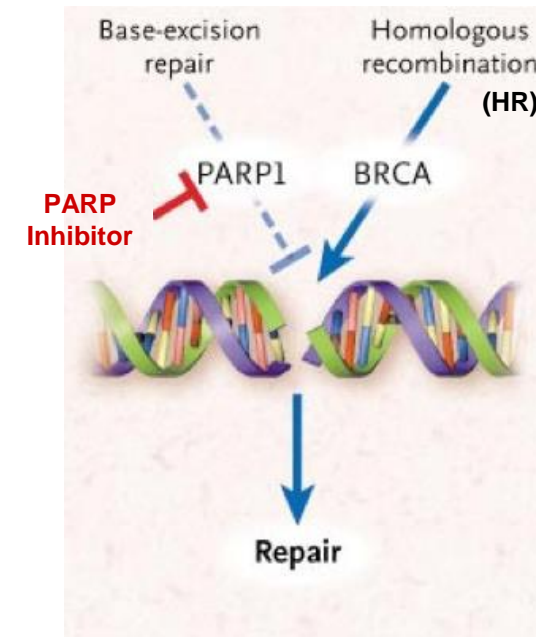
70% of ovarian cancer patients will have recurrence & develop therapeutics-resistant disease

Cancers with BRCA mutation (defective HR repair) are sensitive to PARP inhibitors



Recurrent cancers without BRCA mutation are resistant to PARP inhibitors

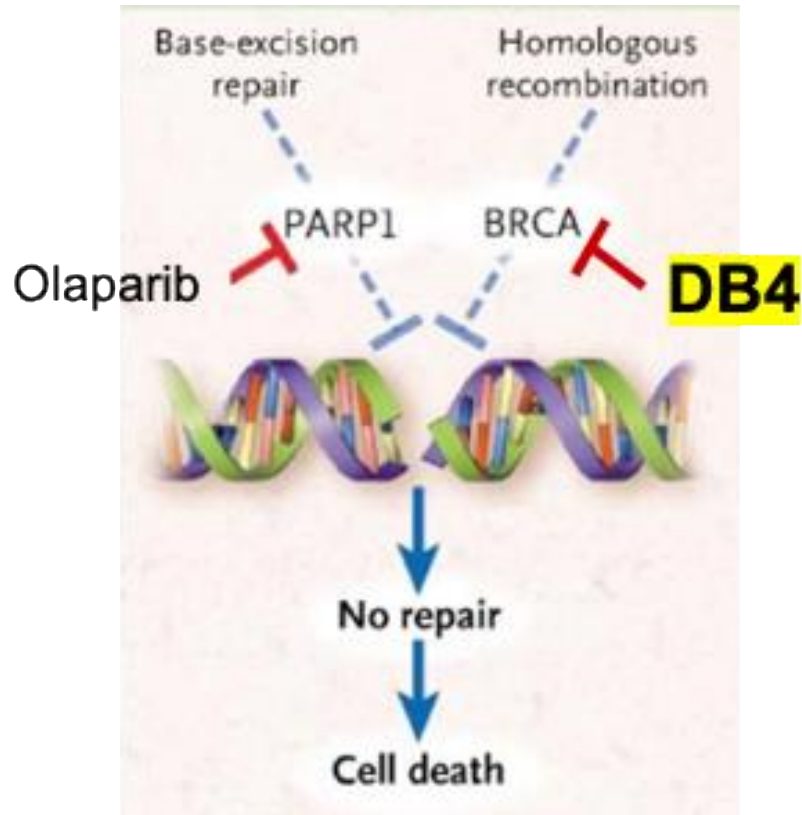
Reversion of BRCA mutation to restore HR repair



Adapted from Iglehart JD, Silver DP. N Engl J Med 2009;361:189-191.

As PARP Inhibitors become widely used, there will be an increase in patients who develop PARP inhibitor resistant cancers§

Our team has developed DB4, a small molecule drug that inhibits HR repair. **DB4 + Olaparib[¶] combo provides effective therapy for cancers without BRCA mutation**

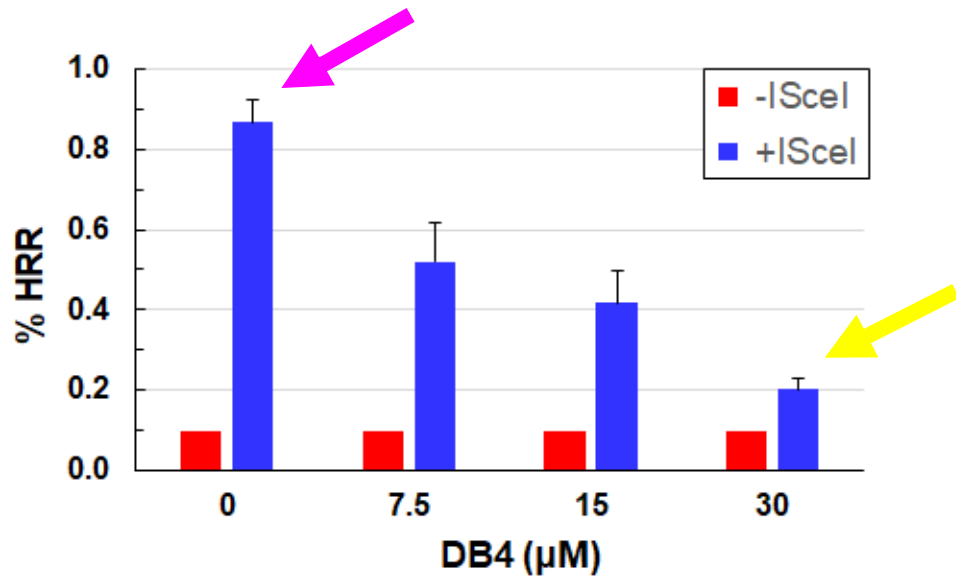


- PARP inhibitors are used for the treatment of ovarian, breast, prostate, and pancreatic cancers.
- The 2017 US PARP inhibitor market for ovarian cancer: \$305.5 million. The 2023 market for ovarian, breast, prostate, and pancreatic cancers: \$2.2 billion.[#]

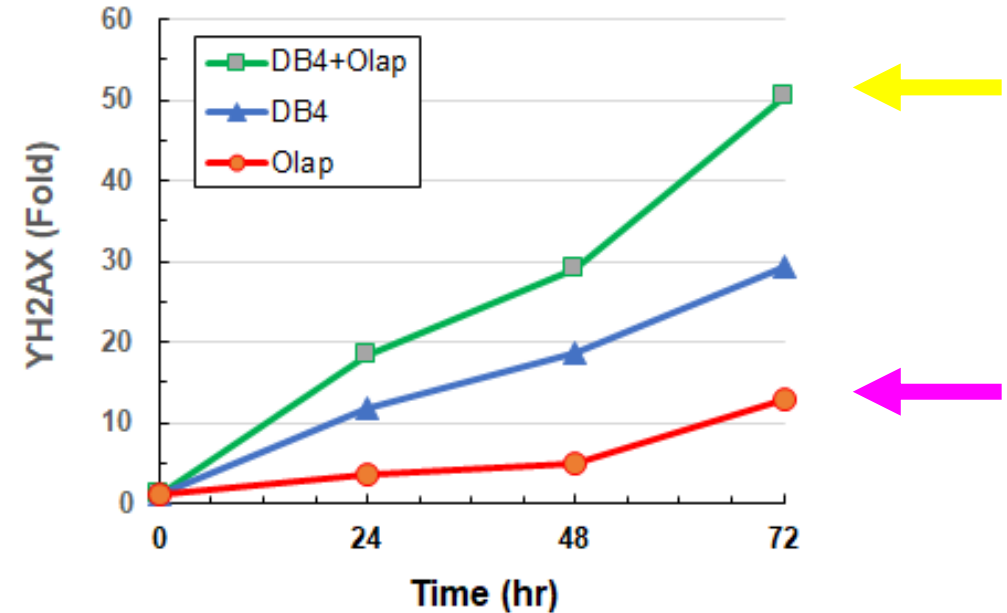
¶ Trade name: Lynparza[®]. It is an FDA-approved PARP inhibitor for the treatment of BRCA-mutated advanced ovarian cancer

<https://decisionresourcesgroup.com/downloads/parp-inhibitor-cheat-sheet-for-oncology-strategists/>

DB4 demonstrates effectiveness to inhibit HR repair and increase DNA damage in cancers without BRCA mutation

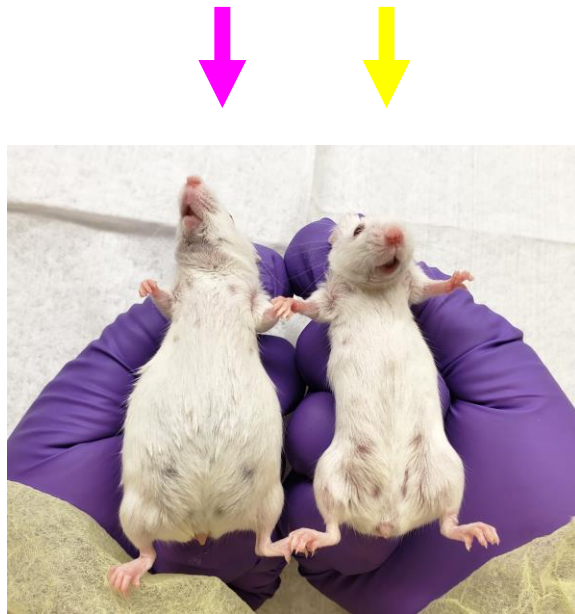


DB4 inhibits HR repair (HRR) in ovarian cancer cells

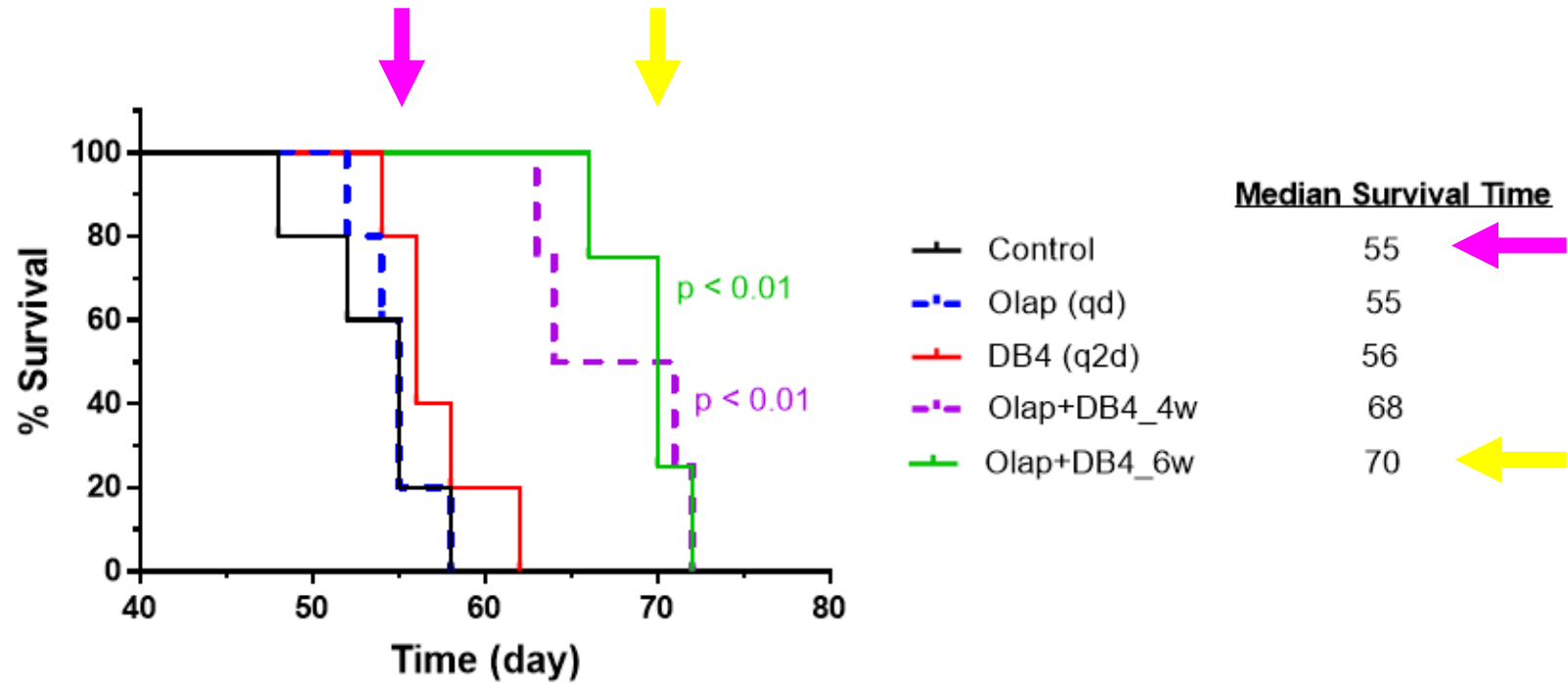


DB4 + Olaparib combo increases DNA damage (γH2AX) in ovarian cancer cells

DB4 + Olaparib combo inhibits ovarian cancer progression and increases the survival time of CDX tumor-bearing mice



Control DB4+Olap



DB4 + Olaparib combo reduces ascitic/abdominal distension

DB4 + Olaparib combo prolongs the survival time of mice

Competitive Landscape for PARPi vs. PARPi + DB4 for Treatment of Various Cancer Types

Cancer Type	PARPi	PARPi+DB4
BRCA mutation	Yes	Yes
No BRCA mutation	No	Yes
PARP inhibitor-resistant	No	Yes
Recurrent	Yes to No [¶]	Yes

The estimated market opportunity for DB4: \$0.5-1 billion

¶ Likelihood of YES reduces with each cancer recurrence following treatment

Next Steps: Milestones & Cost for Development of DB4

