INTERVIEW

Professor Alan Ashworth, FRS

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Tracks 1-6

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Tracks 3-4

DR LOVE: Would you outline the development of PARP inhibitors and the concept of synthetic lethality?

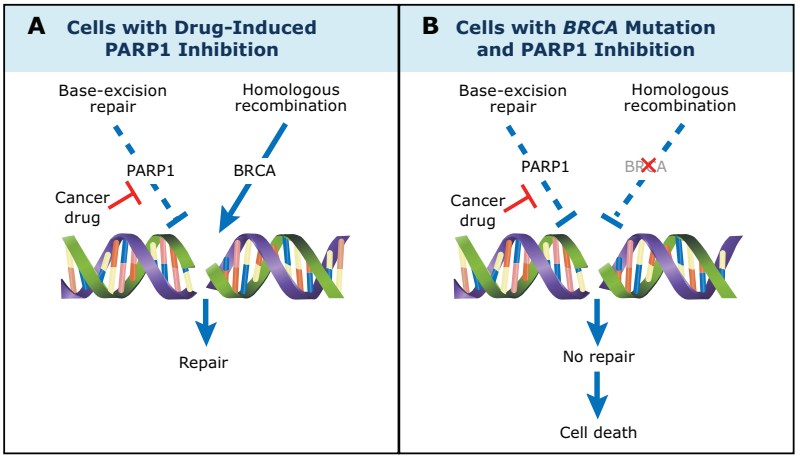
PROF ASHWORTH: The PARP enzyme was discovered in the early 1960s, and PARP inhibitors have been around for approximately 20 years. The early PARP inhibitors were not potent or specific. However, the recent agents in this class have proven to be active in inhibiting the PARP enzyme.

The idea of using PARP inhibitors is to induce synthetic lethality in BRCA-mutant cells by damaging the DNA with chemotherapy and then inhibiting the PARP to prevent repair (Iglehart 2009; [2.1]).

Imagine two separate defects in biochemical pathways not having any ostensible effects by themselves, but if the two defects are put together, then we have a combination or "synthesis" of lethalities. The two pathways act in a semiredundant fashion, and one takes over when the other has a malfunction. If both pathways are inhibited, then the system collapses.

The Phase I and II clinical trials of olaparib established the proof of concept of synthetic lethality in vivo (Tutt 2010). The other clinically evaluated PARP inhibitor, iniparib, has distinct properties and appears promising in combination with chemotherapy (O'Shaughnessy 2011; [2.2]).

2.1 **Mechanism of Cell Death from Synthetic Lethality Induced by PARP Inhibition**



In normal cells, both base-excision repair (BER) and homologous recombination (HR) are available for the repair of damaged DNA. In cells that have lost BER function because of PARP1 inhibition but retain at least one functioning copy of BRCA1 and BRCA2, HR is intact and can repair DNA damage, including damage left unrepaired because of the loss of BER (A). In the cancer cells of mutation carriers, all BRCA1 or BRCA2 function is absent, and when PARP1 is inhibited, cancer cells are unable to repair DNA damage by HR or BER, and cell death results (B).

DR LOVE: Do you believe PARP inhibitors should be combined with chemotherapy, used alone, or are both options feasible?

PROF ASHWORTH: I believe it depends on the genetic background of the tumor. Tumors with a hard defect in homologous recombination DNA repair — such as those with BRCA mutations — will benefit from a single-agent PARP inhibitor. In contrast, tumors such as triple-negative breast cancer (TNBC), which might be considered to have a soft or minor defect in DNA repair, might benefit the most with additional DNA damage from chemotherapy.

Track 5

DR LOVE: Would you discuss the concept of BRCAness, particularly as related to triple-negative breast cancer, and whether predictive biomarkers exist for PARP inhibitors?

PROF ASHWORTH: BRCAness is a clinical situation in which a defect is present in the pathway of homologous recombination — not caused by BRCA mutations — and the tumors phenotypically resemble those with BRCA1 or BRCA2 mutations. An example is TNBC, which appears similar to tumors

2.2

Gemcitabine/Carboplatin with or without Iniparib (BSI-201) in Metastatic Triple-Negative Breast Cancer

	Gemcitabine/ carboplatin (n = 62)	Gemcitabine/ carboplatin + BSI-201 (n = 61)	Hazard ratio	*p*-value
ORR	32%	52%	—	0.02
PFS	3.6 months	5.9 months	0.59	0.01
OS	7.7 months	12.3 months	0.57	0.01

"The addition of iniparib to chemotherapy improved the clinical benefit and survival of patients with metastatic triple-negative breast cancer without significantly increased toxic effects. On the basis of these results, a Phase III trial adequately powered to evaluate overall survival and progression-free survival is being conducted."

ORR = overall response rate; PFS = progression-free survival; OS = overall survival

O'Shaughnessy J et al. *N Engl J Med* 2011;364(3):205-14.

with BRCA1 mutations. We are still at a stage at which BRCAness is useful as a concept for discussing issues rather than being predictive for clinical benefit. However, one can imagine that in the future we may have assays for BRCAness that could involve measuring DNA repair processes in tumors and may eventually predict response to a PARP inhibitor.

One of the key proteins involved in DNA repair is RAD1, and it is switched on in response to DNA damage as a marker of homologous recombination. RAD1 binds to BRCA1 and BRCA2, which carry out the repair of double-strand breaks. Breast tumors not expressing RAD1 tend to resemble the BRCAness phenotype and appear similar to triple-negative tumors. If we could implement RAD1 in a prospective trial and validate it, then it might be used for patient selection.

DR LOVE: What are your thoughts on assays for PARP?

PROF ASHWORTH: One school of thought proposes that levels of PARP influence response to a PARP inhibitor. This is a traditional way of considering drug targets, and in my view this does not address the concept of synthetic lethality. However, PARP is activated by DNA damage, and it is possible that higher PARP levels are a surrogate of DNA repair defects. All the data are preliminary, and we would like to see, with proper studies conducted in a powered fashion, if PARP levels are related to response to treatment. ■

SELECT PUBLICATIONS

Iglehart JD et al. **Synthetic lethality — A new direction in cancer drug development.** *N Engl J Med* 2009;361(2):123-34.

O'Shaughnessy J et al. **Iniparib plus chemotherapy in metastatic triple-negative breast cancer.** *N Engl J Med* 2011;364(3):205-14.

Tutt A et al. **Oral poly(ADP-ribose) polymerase inhibitor olaparib in patients with BRCA1 or BRCA2 mutations and advanced breast cancer: A proof of concept trial.** *Lancet* 2010;376(9737):245-51.