Trial Watch

SYNTHETIC LETHAL SUCCESS

In preclinical studies inhibition of poly(ADP-ribose) polymerase (PARP) has been shown to specifically kill cancer cells that have defects in their ability to repair DNA damage by the homologous recombination pathway — as is the case for patients with mutations in *BRCA1* or *BRCA2* — through a synthetic lethal effect. Phase I data on the PARP inhibitor olaparib in patients with mutations in *BRCA1* or *BRCA2* have now been published in the *New England Journal of Medicine*.

The trial enrolled 60 patients with advanced solid tumours, 22 of whom were known *BRCA1* or *BRCA2* mutation carriers and 1 of whom had a suspected mutation but declined testing. The adverse effect profile of olaparib was acceptable. PARP inhibition was confirmed in pharmacodynamic studies using peripheral-blood mononuclear cells and plucked eyebrow hair follicles. Of the 23 patients with known or suspected *BRCA1* or *BRCA2* mutations, responses could be evaluated in 21. Of these, 19 had ovarian, breast or prostate cancer; clinical benefit was seen in 12 (63%).

Interim analyses of data from two Phase II trials of olaparib in breast and ovarian cancer were presented at the 2009 American Society of Clinical Oncology meeting. These studies seem to support the Phase I data that show efficacy of this agent in carriers of *BRCA1* or *BRCA2* mutations, and full results are eagerly awaited.

ORIGINAL RESEARCH PAPER Fong, P. C. *et al.* Inhibition of poly(ADP-ribose) polymerase in tumors from *BRCA* mutation carriers. *N. Engl. J. Med.* 24 Jun 2009 (doi:10.1056/NEJMoa0900212)
FURTHER READING Audeh, M. W. *et al.* Phase II trial of the oral PARP inhibitor olaparib (AZD2281) in BRCA-deficient advanced ovarian cancer. *J. Clin. Oncol. Abstr.* **27**, 5500 (2009) | Tutt, A. *et al.* Phase II trial of the oral PARP inhibitor olaparib in BRCA-deficient advanced breast cancer. *J. Clin. Oncol. Abstr.* **27**, CRA501 (2009)

ANTI-VEGF ALTERNATIVE

Although vascular endothelial growth factor (VEGF) pathway inhibitors have been approved for treating various tumour types, safety issues and acquired resistance are matters of concern. Interfering with other angiogenic pathways, such as the angiopoietin–TIE2 (also known as TEK) pathway, may improve anti-tumour efficacy. Phase I data on AMG 386, a peptide–Fc fusion protein (peptibody) that blocks the interaction of angiopoietins 1 and 2 with their receptor, TIE2, seem promising.

The trial enrolled 32 patients with relapsed and refractory advanced solid tumours. AMG 386 was well tolerated, and most toxicities were distinct from those resulting from VEGF inhibition. Dynamic contrast-enhanced magnetic resonance imaging suggested that AMG 386 reduced tumour vascularity, but further studies must be conducted. Of 29 patients whose tumour response could be evaluated, 1 with ovarian cancer had a partial response, and 4 with other tumour types had stable disease for ≥16 weeks.

ORIGINAL RESEARCH PAPER Herbst, R. S. *et al.* Safety, pharmacokinetics, and antitumor activity of AMG 386, a selective angiopoietin inhibitor, in adult patients with advanced solid tumors. *J. Clin. Oncol.* 22 Jun 2009 (doi:10.1200/JCO.2008.19.6683)