

PARP inhibitors create buzz at ASCO

Posted At : June 8, 2009 4:45 PM | Posted By : Debu Tripathy

Related Categories: Treatment

What happens when a preliminary study that was not designed for drug approval ends up showing dramatic results? A study in patients with advanced "triple negative" breast cancer (defined as being negative for estrogen, progesterone, and HER2 receptors) compared chemotherapy (Gemzar and carboplatin) with or without BSI-201, a poly ADP-ribose polymerase (PARP) inhibitor. PARP inhibitors have been shown to work exceptionally well in the laboratory against cancers that have defects in DNA repair – this is an abnormality that is prominent in cancers that derive from patients who have inherited mutations in the breast and ovarian cancer predisposing genes BRCA1 and 2. It turns out that BRCA1-associated tumors tend to be triple negative (although not all triple negative tumors have abnormalities of the BRCA pathways). This was a preliminary phase II study, so even though it was randomized, it did not have enough patients to qualify as an FDA-approval trial. But it nevertheless showed unprecedented effects on inducing tumor responses, delaying time to progression, and improving survival – even greater than hormonal therapy and Herceptin have. We all know that smaller studies can sometimes be irreproducible and overestimate real benefits, but given the paucity of therapies and the aggressive nature of refractory triple negative advanced breast cancer, we might see some unusual developments as a result of this study – such as the establishment of a compassionate trial that is made widely available while more definitive trials are being pursued. These results have created quite a buzz among my colleagues in the breast cancer research arena. Many of us wonder whether it would even be possible to randomize patients with this type of cancer to a non-PARP containing arm in a clinical trial. At the same time, these results must be confirmed in a larger and more reliable study. A trial design that allows patients to cross over to the active drug if they progress on the placebo arm is a strategy that might address some of the concerns, but this trial design tends to obscure survival benefits. The trials will also need to be able to explore different biological subsets to pin down exactly what type of patient benefits most. Still, we prefer to have all these dilemmas to address when a potentially new important drug can be added to our armamentarium.