In the three decades since Dr. Lesley Fallowfield began her research on cancer outcomes, extraordinary advances have been made in breast cancer diagnosis and management. Although these improvements have undoubtedly led to better survival rates, they have not been accompanied by comparable improvements in patients' psychosocial, functional, and sexual well-being. In her plenary lecture, Dr. Fallowfield addresses issues related to patient-provider communication, the early identification and management of adverse effects of therapy, and the efficient allocation of resources devoted to psychosocial support.

When speaking about breast cancer diagnosis, Dr. Fallowfield is quick to point out that it "is not a medical emergency; it is an emotional emergency,"— and one which elicits a broad range of responses in different patients. Although initiating appropriate therapy in a timely manner is important, major decisions about management should not be rushed, as these decisions have consequences beyond those pertaining to survivorship. The pacing and tone of management discussions are largely set by the treating clinicians, and care must be taken to ensure good concordance of information provided by various members of the management team.

Once therapy has been initiated, adverse effects can be substantial, affecting not only quality of life but also the patient's ability to function and return to work, which in turn may have serious psychological and financial effects. While the litany of adverse effects associated with surgery, chemotherapy, radiotherapy, and hormonal therapy is well known, management rarely is adequate.

Numerous studies have demonstrated that insufficient management of adverse effects is associated with poor adherence, but many of these effects can be mitigated by appropriate interventions. For example, therapy with tamoxifen or aromatase inhibitors commonly results in vasomotor symptoms, arthralgia, and sexual dysfunction, but effective pharmacologic and nonpharmacologic interventions can help mitigate these problems.

Another concern expressed by Dr. Fallowfield is that the conversation about breast cancer management is dominated by issues related to early-stage cancer. She urges that additional attention be
paid to patients with metastatic disease. Her vision of the future: “I want to see the day when the patient shows up at clinic, goes for her blood work, CT scan or [other tests] then completes a quality-of-life survey and symptom checklist using a touchscreen device. This then is made available, along with the latest lab results, for the [treating clinicians]. It would allow people to channel resources and to refer patients to the kinds of supportive services that may help them.”

Lesley Fallowfield is Professor of Psycho-oncology at Brighton & Sussex Medical School, University of Sussex, where she is Director of the Sussex Health Outcomes Research & Education in Cancer (SHORE-C) group.

Friday, December 13th - 9:00 a.m.
Exhibit Hall D

Funded by Susan G. Komen®, the AACR Outstanding Investigator Award for Breast Cancer Research is presented to an investigator no more than 50 years of age whose novel and significant work has had, or may have, a far-reaching impact on the etiology, detection, diagnosis, treatment, or prevention of breast cancer.

Understanding estrogen receptor transcription in breast cancer
Jason S. Carroll, PhD

Dr. Jason Carroll, of Cancer Research UK of the Cambridge Institute at the University of Cambridge, will be the recipient of the 6th Annual Outstanding Investigator Award for Breast Cancer Research. He is widely recognized for his work on estrogen receptor (ER) biology in breast cancer that has led to the identification of how the ER interacts with DNA, what proteins are used, and what occurs during drug resistance. Dr. Carroll’s work has been applicable to both breast cancer and prostate cancer as his discoveries have had an impact in understanding the mechanisms of action of ER and the androgen receptor (AR). Furthermore, this work redefined the paradigms of nuclear receptors in cancer and provided the first genome-wide map of ER binding and transcriptional activity. It provided insight into the global ER interactions with the DNA in breast cancer cell populations, revealing additional proteins that ER utilizes to interact with chromatin. His laboratory was also the first to implicate FoxA1 in nuclear receptor pathways, which provided the motivation for development of FoxA1 inhibitors for therapeutic intervention in patients with drug resistant breast cancer.

Dr. Carroll obtained his B.Sc (1st Hons) at University of Melbourne, Australia, and then carried out his PhD studies with Prof Rob Sutherland at the Garvan Institute of Medical Research and University of New South Wales, Sydney, Australia. In 2002, Dr. Carroll began his postdoctoral work in the laboratory of Professor Myles Brown at Dana-Farber Cancer Institute and Harvard Medical School. As an independent investigator, Dr. Carroll set up his own research group at the Cancer Research UK, University of Cambridge in 2006 and in 2010 was promoted from junior to senior group leader. He is currently a senior group leader at Cancer Research UK, University of Cambridge and a fellow of Clare College, University of Cambridge. He is the recipient of the British Association for Cancer Research: Frank Rose Young Scientist of the Year Award (2009); EMBO Young Investigator Award (2010) and Cancer Research UK Future Leaders Award (2012).
Aromatase Inhibitors: Benefits in Primary and Secondary Prevention

The nonsteroidal aromatase inhibitor (AI) anastrozole, approved for the management of breast cancer (BC), may also prevent the development of primary BC, as suggested by data from the IBIS-II trial, presented yesterday by Dr. Jack Cuzick. At a median follow-up of 5 years, the risk of developing BC was 53% lower in the anastrozole group. Interestingly, anastrozole therapy was associated with a lower risk for other cancers as well.

However, many studies have shown that, when it comes to primary prevention of disease, the adverse effects associated with therapy can have a profound impact on adherence. Such has been the case with selective estrogen-receptor modulators (SERMs), which are associated with potentially serious adverse effects, such as thromboembolic disorders and, in the case of tamoxifen, uterine cancer. These adverse effects represent a major concern, given that long-term use is required—and when used for prevention, the positive effects of the agents are relatively intangible.

Anastrozole and other AIs have long been associated with arthralgias, vasomotor symptoms, and vaginal dryness, so it was expected that these adverse effects would be reported by a substantial proportion of women randomized to the anastrozole arm of the IBIS-II trial. Far more surprising, however, were the high rates of many adverse effects reported by women in the placebo arm. A variety of symptoms, including joint pain, mood disorders, fatigue, and sleep problems, were assessed by questionnaires at baseline and regularly throughout the first year of the study. By 12 months, almost 30% of participants had discontinued therapy, and the probability of doing so was greater in participants with higher symptom scores at baseline. These findings suggest one way to identify women at high risk for discontinuing therapy. As Dr. Henry noted in her closing statement, “preemptive management of these symptoms, rather than [post hoc] treatment of AI toxicity, may improve adherence to and persistence with therapy.”

An example of such a preemptive strategy is exercise, which was evaluated in the HOPE study, presented by Dr. Melinda Irwin. The exercise intervention used in the study conformed to standard recommendations: twice weekly supervised sessions of strength training and 2.5 hours/week of moderate-intensity aerobic exercise. At 12 months, women randomized to the exercise arm had substantial improvements in pain scores. Although the benefit was strongest in those participants adhering to the exercise regimen by at least 80%, improvements in pain scores also were seen with lower rates of adherence. While the study had some important limitations, the findings reinforce the idea that the assessment and management of adverse effects can improve adherence, which ultimately affects clinical outcomes.

Symposium
UPDATES
Friday, Dec 13, 2013

Posters Withdrawn:
• P1-14-02
• PDS-4
• P3-05-12
• P4-06-07
• P4-06-08
• P4-07-06
• P4-12-05
• P4-12-13
• P4-13-03
• P4-15-11
• P4-05-13

Poster Rescheduled:
• P6-06-35 will be presented as poster P4-20-01
• P6-06-36 will be presented as poster P4-20-02
• P6-06-43 will be presented as poster P4-20-03
• P3-15-07 will be presented as poster P5-14-20

Revised Abstract:
• P4-12-17

New Abstract:
• P5-04-18

Presenter Changes:
• P4-07-18 - Dr. Filippo De Braud
• P4-12-25 – Dr. Giuseppe Gullo
• S6-05 – Dr. John W.M. Martens
ER Mutations and Resistance to Hormonal Therapy

Resistance of breast cancer to endocrine therapy may be either de novo or acquired. A lack of estrogen receptor (ER) expression is the primary cause of the former, but acquired resistance usually develops despite continued expression of ER, prompting the search for other explanatory mechanisms.

Such a search was described by Dr. Jieya Shao, who presented data from a patient-derived xenograft study of advanced endocrine resistant luminal breast tumors. This work revealed three distinct mutational mechanisms affecting the ER-encoding gene, ESR1, driving endocrine therapy resistance. The mechanisms consist of an ESR1 point mutation (Y537S), an ESR1 gene amplification, and a gene translocation causing an in-frame fusion between N-terminal ER and C-terminal Yes-associated protein 1 (YAP1)—each with different therapeutic implications.

Next, Dr. Rinath Jeselsohn presented evidence for the emergence of constitutively active estrogen receptor mutations in advanced ER+ breast cancer. Using next-generation sequencing, the investigators found that ER mutations were significantly more frequent in the metastatic samples (12%) than in samples from primary tumors (0%). In a subset of heavily pretreated patients, the frequency was 20%. All the described mutations were within the ligand binding domain of the ER; most were missense mutations in positions 537 and 538. According to Dr. Jeselsohn, “these mutations may have the potential to be important markers of endocrine resistance in ER+ metastatic breast cancer and could assist in clinical decision making as disease progresses.”

ER Mutations

The phosphatidylinositide 3-kinases (PI3Ks) are involved in a variety of cellular functions ranging from motility to cell growth, proliferation, and survival. Hyperactivation of the PI3K pathway occurs in 70% of breast cancers (BCs); approximately 30% of BCs have mutations in the PIK3CA gene. Although most of these cancers are initially sensitive to therapy with PI3K inhibitors, resistance commonly develops.

This problem of acquired resistance was discussed by Dr. Sadhna Vora. Dr. Vora and colleagues used PI3KCA mutated cell lines that were initially sensitive to PI3K inhibition. Resistance was selected by growing the cultures in increasing concentrations of PI3K inhibitor. They next performed a combinatorial drug screen, using escalating doses of targeted agents, with and without the presence of a fixed dose of PI3K inhibitor, to determine which agents synergized with PI3K inhibition in the resistant cells. One agent stood out: the CDK4/6 inhibitor LEE-011.

Using a mouse model, the researchers show that treatment with the combination of a PI3K inhibitor and LEE-011 is associated with tumor regression that is more substantial than with either agent alone. Combination treatment also was associated with delayed acquisition of treatment resistance.

In the next presentation, Dr. Yizhou Jiang discussed PIK3CA mutation status after paclitaxel-based neoadjuvant chemotherapy (NCT). Significant decreases in mutation rates (PIK3CA and TP53) occurred after NCT. Furthermore, loss of mutation was significantly associated with better pathological response, and appeared to improve survival. That NCT can result in changed gene expression profiles has been described previously, but Dr. Jiang and colleagues were the first to demonstrate its effect on somatic mutations in breast cancer.

The third presenter on this topic was Dr. Sibylle Loibl, who addressed the clinical implications of PIK3CA mutation status. Using biopsy samples from participants in GeparQuinto and GeparSixto, the PIK3CA mutation was identified in 20.8% of HER2+ tumors and in 7.4% of triple-negative tumors. Importantly, the pathologic complete response (pCR) rate was affected by PIK3CA mutation status: the mutated gene was associated with lower pCR. The difference was especially evident in patients receiving dual HER2 blockade. These findings emphasize the need for additional therapies, such as PI3K inhibitors, along with HER2 blockade.