Plenary Lecture 2: 
Advances in Understanding Whole-Genome Sequenced Tumors
Serena Nik-Zainal, MD, PhD
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On Thursday morning, Serena Nik-Zainal, MD, PhD, from the Wellcome Trust Sanger Institute in Cambridge, United Kingdom, discusses advances in the understanding of whole-genome sequenced breast cancer tumors. Characteristics of tumors vary from patient to patient, and whole-genome sequencing helps identify individual tumor abnormalities that would have otherwise been missed by standard care approaches. Dr. Nik-Zainal highlights the advantages of taking a whole-genome sequencing approach to better understand a patient’s tumor and inform treatment decisions.

Mismatch repair deficiency is relatively rare in breast cancer tumors. It is a deficiency found in DNA repair pathways and is more commonly evaluated in tumors of patients with other forms of cancer, such as colon or uterine cancer. However, as Dr. Nik-Zainal explains, a specific whole-genome approach can be taken in breast cancer studies.

Whole-genome sequencing is used to look at mutational signatures, or patterns of mutations or damage to DNA that arise when mismatch repair goes awry. These particular mutational signatures clearly identify mismatch repair deficiency, which is found to occur in ≈2% of tumors. Patients who have been identified as having a mismatch repair-deficient breast cancer tumor could potentially benefit from treatments that have been shown to work more effectively for this abnormality. Potential treatment options include immune checkpoint inhibitors and programmed death (PD)-1/PD-ligand 1 inhibitors.

Another advancement highlighted by Dr. Nik-Zainal is the use of whole-genome sequencing to identify BRCA1 and BRCA2 deficiency in breast tumors. While looking at mutational signatures in whole-genome sequences, Dr. Nik-Zainal and her team have discovered that BRCA1 and BRCA2 deficiency is far more common than previously thought. Rather than the previously reported number of 1% to 5% of inherited BRCA1 deficiency, her group is finding that many more women are acquiring the deficiency, estimating that 20% of breast cancers are BRCA1 and BRCA2 deficient. Since poly ADP ribose polymerase (PARP) inhibitors have been used to selectively target BRCA-deficient cells, this finding identifies a larger patient population that could potentially benefit from more targeted and/or more tolerable treatment strategies.

Dr. Nik-Zainal points out that whole-genome sequencing is still a research-based strategy. Currently, many clinics focus on using only a targeted gene approach or whole-exome sequencing approach, where only a portion of the genome is sequenced. But whole-genome sequencing trials are under way, and as the process becomes less expensive, it is likely to become more widely available to patients. “It can be difficult to analyze and interpret the data, but findings can inform treatment, so it’s important to start thinking about how whole-genome sequencing can be used,” says Dr. Nik-Zainal.
ABSTRACT

Correlation

4:15 PM

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Women aged ≤70 years with node-negative, HER2-positive metastatic breast cancer are candidates for neoadjuvant chemotherapy. Neoadjuvant chemotherapy with 3 cycles of paclitaxel and 3 cycles of carboplatin has been a standard of care for these patients. However, there is increasing interest in using 4 cycles of carboplatin and weekly paclitaxel for this patient group. The recent results from the phase III ATAC trial showed comparable results for both regimens. The aim of this study was to evaluate the use of 4 cycles of carboplatin and weekly paclitaxel in patients with HER2-positive metastatic breast cancer.

METHODS

We conducted a single-arm, multicentre phase II trial of neoadjuvant chemotherapy with 4 cycles of carboplatin and weekly paclitaxel for women aged ≤70 years with node-negative, HER2-positive metastatic breast cancer. The primary end point was the pathologic complete response rate at the time of surgery. Secondary end points included toxicities, response to treatment, disease control, and progression-free survival.

RESULTS

A total of 114 eligible patients with node-negative, HER2-positive metastatic breast cancer were enrolled and were treated with 4 cycles of carboplatin and weekly paclitaxel. The pathologic complete response rate was 41.9% (95% CI, 32.5% to 51.3%). Of the 46 patients who underwent surgery, pathologically complete response was achieved in 18 (39.1%). The overall response rate was 74.5% (95% CI, 64.3% to 82.9%). The most common grade 3 and 4 toxicities were neutropenia (77.1%), anemia (33.9%), and thrombocytopenia (14.3%). The median progression-free survival was 8.8 months (95% CI, 6.6 to 11.0). The median overall survival has not been reached.

CONCLUSIONS

Our results suggest that 4 cycles of carboplatin and weekly paclitaxel is feasible and safe in patients with HER2-positive metastatic breast cancer. The pathologic complete response rate of 41.9% is comparable to that reported in the ATAC trial. Further studies are needed to confirm these findings and to evaluate the role of adjuvant systemic therapy in patients who achieve a pathologic complete response.
GS2-07: MANTA - A randomized phase II study of fulvestrant in combination with the dual mTOR inhibitor AZD2014 or everolimus or fulvestrant alone in estrogen receptor-positive advanced or metastatic breast cancer.

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BACKGROUND: Resistance to endocrine therapy remains a major clinical challenge with aberrant PI3K/mTOR pathway activation being one of the main drivers. Randomised clinical trials have demonstrated a substantial benefit of adding everolimus to endocrine therapy. Vistusertib (AZD2014), a dual inhibitor of mTORC1 and mTORC2, has shown a broader range of activity in preclinical ER+ breast cancer models, showing superior activity to everolimus (EVE) both in hormone-sensitive and resistant models. The MANTA trial was designed to evaluate the safety and efficacy of vistusertib (VIS) in combination with fulvestrant (FULV) relative to FULV alone or FULV + EVE. In addition to a continuous (cont) daily schedule of VIS, the study also explored an intermittent (int) schedule to assess the potential of short-term, maximum target inhibition.

METHODS: MANTA is an investigator-led, randomised, open-label phase II trial. Postmenopausal women with estrogen-receptor (ER)-positive breast cancer were eligible if they had disease recurrence while on or within 12 months of end of adjuvant treatment with an aromatase inhibitor (AI), or progression while on or within one month of end of AI treatment for locally advanced or metastatic breast cancer. Patients were randomly assigned (2:3:3:2) to receive either FULV (500 mg intramuscular injection on day 1, followed by 500 mg doses on days 15 and 29, and then every 28 days); FULV + daily VIS (50mg BD), FULV + intermittent VIS (2 days on, 5 days off; 125mg BD); or FULV + EVE (10mg OD). Treatment was given until disease progression (RECIST 1.1) or intolerable toxicity. Patients were stratified by disease measurability and response to prior endocrine therapy. The primary endpoint was investigator-assessed progression-free survival (PFS). Secondary objectives included objective response, clinical benefit rate, duration of response and clinical benefit, overall survival and safety.

Results: Between 04/2014 and 10/2016, a total of 333 patients were randomised at 88 sites in 9 countries. 66 patients were assigned to receive FULV; 101 to FULV+VIS (cont), 95 to FULV+VIS (int); and 64 to FULV+EVE. Median PFS was 4.6 months (95% CI 3.4–6.9) in patients assigned to FULV; 7.5 months (95% CI 5.6–9.4) in those assigned to FULV+VIS (cont); 7.6 months (95% CI 5.5–9.6) in those assigned to FULV+VIS (int); and 12.2 months (95% CI 7.5–14.3) in those assigned to FULV+EVE. No significant difference was recorded between the patients assigned to FULV+VIS (cont) and FULV (hazard ratio 0.87, 95% CI 0.62–1.23; log-rank p=0.42); FULV+VIS (int) and FULV (HR 0.78, 95% CI 0.55-112; log-rank p=0.16); and FULV+VIS (cont) and FULV+EVE (int) (HR 1.11, 95% CI 0.81-1.52; log-rank p=0.32). FFS was significantly longer in patients assigned to FULV+EVE compared to FULV+VIS (cont) (HR 0.64, 95% CI 0.45-0.91; log-rank p=0.01) and FULV+EVE compared to FULV (HR 0.64, 95% CI 0.43-0.94; log-rank p=0.02).

CONCLUSION: The trial failed to demonstrate a benefit of adding the TORC1/2 inhibitor vistusertib (AZD2014) to FULV. The combination FULV+EVE demonstrated significantly longer PFS compared to FULV+VIS or FULV.