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ISSUE 2

Plenary Lecture 2: Advances in Understanding Whole-Genome Sequenced Tumors

Serena Nik-Zainal, MD, PhD
The Wellcome Trust Sanger Institute • Cambridge, United Kingdom
HALL 3

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.

ISSUE AT A GLANCE

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SYMPOSIUM UPDATES

THURSDAY, DECEMBER 7

WITHDRAWN

POSTER SESSION 2

- P2-02-20
- P2-04-01
- P2-12-13

POSTER SESSION 3

- P3-06-11
- P3-07-11
- P3-09-04

ABSTRACT CORRECTION

9:45 AM

GS3-02. Invasive disease-free survival and gene expression signatures in CALGB (Alliance) 40601, a randomized phase III neoadjuvant trial of dual HER2-targeting with lapatinib added to chemotherapy plus trastuzumab.

Krop IE, Hillman D, Polley M-Y, Tanioka M, Parker J, Huebner L, Henry NL, Tolaney SM, Dang C, Harris L, Berry DA, Perou CM, Partridge A, Winer EP, Carey LA. Dana-Farber Cancer Institute, Boston, MA; Alliance Statistics and Data Center, Mayo Clinic, Rochester, MN; University Of North Carolina, Chapel Hill, NC; University Of Michigan, Ann Arbor, MI; Memorial Sloan Kettering Cancer Center, New York, NY; National Cancer Institute, Bethesda, MD; MD Anderson Cancer Center, Houston, TX.

*AT PRESS TIME

Tenth Annual AACR Distinguished Lectureship in Breast Cancer Research

THURSDAY, DECEMBER 7, 11:30 AM, HALL 3

Leveraging Preclinical Models of Breast Cancer

Jeffrey M. Rosen, PhD
Baylor College of Medicine, Houston, TX

The AACR Distinguished Lectureship in Breast Cancer Research has been established to recognize outstanding science that has inspired or has the potential to inspire new perspectives on the etiology, diagnosis, treatment, or prevention of breast cancer.

Dr. Jeffrey M. Rosen is recognized for his outstanding leadership in breast cancer research.

AACR honors his seminal contributions to the understanding of normal mammary gland biology and alterations that occur in breast cancer.

Dr. Rosen studied chemistry at Williams College where he received a BA degree in 1966. His Ph.D. research at the Roswell Park Cancer Institute helped elucidate the mechanisms for glucocorticoid resistance in lymphomas. His postdoctoral studies at Vanderbilt University School of Medicine under the supervision of Dr. Bert W. O'Malley were concerned with the mechanism of action of estrogen in the chick oviduct. His postdoctoral studies involved the isolation of ovalbumin mRNA and the first demonstration of steroid hormone induction of a specific mRNA. He joined the faculty of Baylor College of Medicine in 1973, and was a founder member of the first Department of Cell Biology in the USA. In 1987-88 he spent a sabbatical leave in the laboratories of Drs. George Stark and Ian Kerr at the Imperial Cancer Research Laboratories funded by an American Cancer Society Scholar Grant, where he participated in early studies to elucidate the mechanisms of interferon action that helped lead to the discovery of the Jak/Stat pathway.

Dr. Rosen is currently a Distinguished Service Professor, the Vice-Chair and the C.C. Bell Professor of Molecular & Cellular Biology and Medicine at Baylor College of Medicine. He was the recipient of two MERIT awards from the National Cancer Institute on a grant entitled, "Hormonal Regulation of Breast Cancer" currently in its forty-first year of consecutive funding.

His laboratory has authored 287 publications and book chapters. He is the PI on the CPRIT BCM Comprehensive Cancer Training Program. Previously he served as the co-director and director of the BCM Medical Scientist Training Program. Dr. Rosen has trained 33 graduate students and 45 postdoctoral fellows many of whom are now faculty at major academic institutions in the USA and abroad.

Dr. Rosen has received the Marc Dresden Excellence in Graduate Education Award, the Barbara & Corbin J. Robertson, Jr. Presidential Award for Excellence in Education at BCM, the Endocrine Society Edwin B. Astwood Lecture Award, the Michael E. DeBakey, M.D., Excellence in Research Award, the Susan G. Komen for the Cure Brinker Basic Science Award, and the AACR Distinguished Lectureship in Breast Cancer Research. He was recently designated as an AAAS Fellow. Dr. Rosen is a Susan G. Komen Scholar, and the co-leader of Breast Program of the Dan. L. Duncan NCI-designated Comprehensive Cancer Center.

Hot Topic: Dose-Intense Chemotherapy Regimens in Early Breast Cancer

On Wednesday morning, Richard Gray, MSc, from the University of Oxford in the United Kingdom, presented findings on behalf of the Early Breast Cancer Trialists' Collaborative Group (EBCTCG). According to data from an EBCTCG meta-analysis, increasing dose intensity (ie, amount of drug delivered per unit time) of anthracycline- and taxane-based chemotherapy by shortening the interval between treatment cycles, or by giving drugs sequentially rather than concurrently, reduces breast cancer recurrence and breast cancer mortality, compared to standard regimens.

First, Gray presented findings from a "dose-dense" chemotherapy analysis of 7 trials looking at ≈10,000 women who received chemotherapy agents every 2 weeks. Compared to women who received the same treatment every 3 weeks, patients on the 2-weekly regimen had statistically significant reductions in breast cancer recurrence rate (24% vs 28.3%) and 10-year breast cancer mortality rate (16.8% vs 19.6%).

In an analysis of 6 trials (≈11,000 patients) comparing sequential and concurrent therapy (both given 3-weekly), Gray and his group saw statistically significant reductions in breast cancer recurrence (≈13%) and breast cancer death (slightly >10%) with sequential dosing. Gray acknowledged that the dose intensification achieved with sequential 3-weekly dosing was slightly lower than that achieved by giving a 2-weekly regimen, so a slightly smaller treatment effect was expected.

In the analysis comparing sequential (2-weekly) regimens to concurrent (3-weekly) dosing, Gray and colleagues looked at 6 trials (≈6500 women). Gray reported a 10-year recurrence rate of 30% with sequential dosing, compared to 34.9% in the concurrent dosing group. 10-year breast cancer mortality in the sequential group was 22%, compared to 26% in the concurrent group.

Finally, Gray presented data from a pooled analysis of all 25 dose-dense and sequential trials (≈34,000 women), reporting a 15% reduction in breast cancer recurrence and 13% reduction in breast cancer mortality. Gray noted that though a 13% reduction in mortality "seems grossly modest, it is important to identify these step-by-step improvements because these incremental gains when together are what have resulted in reducing breast cancer deaths by one-half over the last 30 years."

Gray concluded by stating that these highly significant benefits (eg, 15% reductions in recurrence) were seen in both ER-negative and ER-positive breast cancers, and did not differ significantly by any other tumor or patient characteristics. Also, there were no increases in mortality without recurrence in those who received dose-intense treatment.

No Benefit from Trastuzumab in Low HER2-Receptor Status Breast Cancer

Some earlier reports hinted that adjuvant trastuzumab might benefit even some patients with low HER2-receptor status. However, data from NSABP B-47 reported by Louis Fehrenbacher, MD, of Kaiser Permanente Northern California, showed no benefit in either the primary endpoint — 5-yr overall invasive disease-free survival rate (89.2% in women treated with chemotherapy alone vs 89.6% in women who received chemotherapy with trastuzumab) — or in any secondary endpoints.

Safety and Efficacy of Pembrolizumab with Trastuzumab

Dr. Sherene Loi presented the results from a Phase Ib/II study evaluating the safety and efficacy of pembrolizumab with trastuzumab in patients with trastuzumab-resistant HER2-positive (HER2+) metastatic breast cancer.

PANACEA is a single-arm study conducted in two cohorts: PD-L1+ and PD-L1-. In Phase Ib, two doses of pembrolizumab (2mg/kg and 10mg/kg IV) were evaluated in combination with a standard dose of trastuzumab Q3W. Phase II evaluated a 200mg dose of pembrolizumab with trastuzumab. In Phase II of the PD-L1+ cohort, the primary endpoint was the objective response rate (ORR) by RECIST 1.1. In the PD-L1- cohort, the single-stage design simply asked if further investigation was warranted.

Out of the 146 patients screened, 58 were enrolled. At the time of reporting, 84% had discontinued participation due to progressive disease. The median time from diagnosis of metastatic disease to enrollment was 40 months. With regards to immune-related adverse events, the frequencies were consistent with what has been observed to date with pembrolizumab monotherapy.

In the primary efficacy analysis, in Phase II of the PD-L1+ cohort, ORR: 15.2% and disease control rate (DCR): 24%. In the PD-L1- cohort, there were no responses observed. The PD-L1+ patients who achieved objective response or stable disease experienced a medical duration of disease control of 11.1 months. Five patients continued with no progression at the time of reporting. The effects were proven to be quite striking for

Continued to Page 4

the progression-free survival and overall survival (OS) differences of the two cohorts. The 12-month OS of PD-L1+ was 65% (52% to 76%) while PD-L1- was 12% (1% to 36%). However, follow-up is lacking, which calls for further validation.

Regarding the explorative endpoint, the sTILs median in metastatic lesions was 1%, which is 20 times less than what was observed in primary lesions. However, a higher sTIL level was observed in the PD-L1+ cohort as expected. It was also observed that patients with sTILs ≥5% made up 41% of the PD-L1+ cohort with an ORR: 39% and DCR: 47%. This highlights sTILs ≥5% as a potential predictive marker.

In conclusion, the PANACEA study met its primary endpoint in the PD-L1+ cohort (ORR 15%, DCR 25%). For responders, the combination offered durable control without chemotherapy. Metastatic HER2+ disease in the heavily pretreated setting was found to be poorly immunogenic. Dr. Loi suggested that future studies in metastatic HER2+ trials should focus on combinations with effective anti-HER2 therapy, especially in low sTIL patients.

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.

Peter Schmid, Matthias Zaiss, Catherine Harper-Wynne, Marta Ferreira, Sidharth Dubey, Stephen Chan, Andreas Makris, Gia Nemsadze, Adrian Murray Brunt, Sherko Kuemmel, Isabel Ruiz, Antonia Perelló, Anne Kendall, Janet Brown, Hartmut Kristeleit, John Conibear, Cristina Saura, Julien Grenier, Károly Máhr, Michael Schenker, Sohn Joo Hyuk, Lee Keun Seok, Shah-Jalal Sarker, Aaron Prendergast, Carike Coetzee, Kelly Mousa, Javier Cortes

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 desgined 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 0.55-1.12; log-rank p=0.16); and FULV+VIS (cont) and FULV+VIS (int) (HR 1.11, 95% CI 0.81-1.52; log-rank p=0.52). PFS 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.