Ralph R. Weichselbaum, MD, the Daniel K. Ludwig Distinguished Service Professor of Radiation and Cellular Oncology and Chair of the Department of Radiation and Cellular Oncology of the University of Chicago, will discuss the emerging understanding of oligometastasis and potential new therapies for its treatment in his plenary lecture, “The Role of Radiotherapy Combined with Immunotherapy in Oligometastatic Cancer.” Dr. Weichselbaum will present at the Symposium on Wednesday morning.

In 1995, Dr. Weichselbaum and his colleague Samuel Hellman advanced the hypothesis that many cancers represent a spectrum of disease from purely localized to widespread; within that spectrum, they highlighted a disease state they termed ‘oligometastasis,’ an intermediary state between localized and widespread disease. They further proposed that this particular group of cancers were amenable to cure by a specific set of metastasis-directed therapies.

More than a decade ago, Dr. Weichselbaum’s group noted that large radiation doses used in stereotactic radiotherapy of oligometastatic tumors induced immunogenic cell death. This, in turn, led them to investigate the potential interaction between radiotherapy and immunotherapy. In his lecture, Dr. Weichselbaum will present data to support the basis and classification of oligometastatic disease, and discuss the results of clinical trials that inform us regarding future clinical strategies. He will also explore the concept of “oligoprocessor,” tumor clones that escape systemic therapies, and how they might be targets for ablation by focal treatments.

“Oligo isn’t just a number,” Dr. Weichselbaum said. “It’s a biology.” He proposes that oligo- and poly- metastasis are distinct entities at the clinical and molecular level. The mechanism behind the fairly slow rate of progress is this classification is still under investigation. “This may relate to the immune status of the host or the growth characterizers of the tumor,” Dr. Weichselbaum said. Regardless of the mechanism, however, many patients who initially present with oligometastases progress to polymetastases, and predictors of progression could improve patient selection for metastasis-directed therapy. In the plenary lecture, he will present basic and clinical data from investigations into combined radio-immunotherapy treatment and suggest how these investigations might improve treatment of patients.

The degree to which these metastasis-directed treatments will be relevant to breast cancer treatments remains to be seen. “We’re not sure the extent to which this applies to breast cancer,” he said. “I think one of the complicating factors with breast cancer is that it’s such a heterogenous disease, and it might be difficult to identify which groups would benefit most. But there are clinical trials underway to see who might benefit.” In the lecture, he will discuss the trials that are exploring the potential benefits to breast cancer patients, as well as similar investigations into prostate and colorectal cancer treatment.

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AACR OUTSTANDING INVESTIGATOR AWARD FOR BREAST CANCER RESEARCH

supported by the Breast Cancer Research Foundation

Novel non-canonical Functions of EZH2 in Triple Negative Breast Cancer

Friday, December 13, 11:30 AM – Hall 3

RECIPIENT:
Celina Kleer, MD
University of Michigan Medical School
Ann Arbor, MI

The AACR Outstanding Investigator Award for Breast Cancer Research, supported by the Breast Cancer Research Foundation, will be presented to Celina Kleer, MD, a physician scientist, whose laboratory has pioneered studies on the function and mechanism by which EZH2, a regulator of cellular transcriptional memory and cell type identity, promotes breast cancer invasion and metastasis, and has demonstrated that EZH2 overexpression in human breast cancer samples is an independent indicator of survival. Her hypothesis-driven research and pathology expertise resulted in a major breakthrough: conditional, mammary epithelial cell-specific Cre+ colony knockout mice developed mammary carcinomas that closely recapitulate human metastatic carcinomas. This research has far reaching implications, as it may enable a better understanding of the molecular determinants of this aggressive form of breast cancer and provide a model to test new and existing treatments for metastatic carcinomas.

AACR OUTSTANDING INVESTIGATOR AWARD FOR BREAST CANCER RESEARCH

Essential Genes and Cistromes in Breast Cancer

Thursday, December 12, 11:30 AM – Hall 3

RECIPIENT:
Myles Brown, MD
Dana-Farber Cancer Institute
Boston, MA

The AACR Outstanding Lectureship in Breast Cancer Research will be presented to Myles Brown, MD whose research laboratory focuses on elucidating the epigenetic factors underlying the action of steroid hormones. He is recognized for three seminal discoveries. His lab opened the steroid receptor coregulator field, illuminated the dynamic nature of receptor and coregulator interaction with the genome and elucidated the importance of epigenetically determined distant cis-regulatory steroid receptor binding sites. His contributions have uniquely reformulated the understanding of steroid hormone action in normal physiology and in hormone-dependent cancer.

AACR OUTSTANDING INVESTIGATOR AWARD FOR BREAST CANCER RESEARCH

Tucatinib in combination with Trastuzumab and Capecitabine reduces risk of death by one-third and reduces risk of progression or death by half in all patients

For patients with HER2-positive metastatic breast cancer who have been treated with trastuzumab, pertuzumab, and T-DXI, no single regimen is considered the standard of care. Additionally, up to half of patients with HER2-positive metastatic breast cancer may develop brain metastases, and options are needed for effective and tolerable treatment options.

Rashmi K. Murthy, MD, presented the results of the HER2CLIMB Trial, a randomized trial completed in patients with HER2+ metastatic breast cancer that included patients with untreated or previously treated progressing brain metastases that may offer some effective options in the future. Tucatinib is an investigational, oral TKI that is highly selective for the kinase domain of HER2 with minimal inhibition of EGFR.

HER2CLIMB is a randomized, double-blind, placebo-controlled, active comparator, global pivotal trial of 612 subjects, encompassing 155 sites enrolled in 11 different countries. The results suggest that tucatinib, in combination with trastuzumab and capecitabine, reduces the risk of death by one-third and reduces the risk of progression or death by half in all patients. The confirmed objective response rate nearly doubled, to 41% from 23%, and tucatinib benefit across all subgroups was consistent with the overall outcome in the primary and secondary endpoints.

“The combination therapy was also well tolerated,” Dr. Murthy said. “the majority of adverse events experienced were low-grade.” These events included reversible elevations of liver enzymes and diarrhea. “The tolerability profile and low discontinuation rate allows for continued HER2 inhibition until progression in heavily pre-treated patients.”

“Tucatinib in combination with trastuzumab and capecitabine has the potential to become a new standard of care in this patient population with and without brain metastases,” Dr. Murthy concluded.
A benefit of capecitabine for disease-free survival (DFS) and overall survival (OS) was demonstrated in patients with triple-negative breast cancer (TNBC), particularly when administered with another treatment, according to a meta-analysis presented by Marion van Mackelenbergh, MD, on Wednesday.

The meta-analysis included 15,457 patients (7983 of whom received capecitabine over the course of their treatment) enrolled in 12 randomized controlled trials. The primary objective was to determine the effect of capecitabine on DFS. Key secondary objectives included examination of the effects of capecitabine on OS and whether an interaction between capecitabine-specific toxicity and treatment effect existed. Analyses were performed on the overall data and in two predefined subsets in which capecitabine was given in addition to or instead of another therapy.

The median age of patients at initial diagnosis was 53 years. Nodal involvement was identified in 74.3% of patients, and 56.7% presented with T2 disease. Nearly 80% of trials were conducted in the adjuvant setting.

Although capecitabine did not alter DFS in the overall analysis, it improved DFS when added to another therapy (hazard ratio [HR] 0.888). However, Dr. van Mackelenbergh pointed out that only the CreateX trial reported a significant benefit for this endpoint. Capecitabine also improved OS (HR 0.892), although analysis of the predefined subsets demonstrated a benefit in OS only when capecitabine was added to other therapy (HR 0.837).

Dr. van Mackelenbergh and her colleagues further analyzed the data according to biologic subtypes of disease and demonstrated a benefit in DFS for TNBC overall (HR 0.886) and if capecitabine was added to other systemic treatment (HR 0.818). However, she pointed out that only the FinXX and CreateX trials reported a significant treatment benefit of capecitabine for DFS.

A benefit for OS was demonstrated in patients with TNBC overall (HR 0.828) and when added to other treatment (HR 0.778). However, only the CreateX trial reported a significant OS benefit of capecitabine in its results. No significant associations were reported between capecitabine-related toxicities and treatment benefit.

Dr. van Mackelenbergh concluded that the addition of capecitabine to other systemic treatment may be recommended for patients with TNBC but pointed out the need for prospective trials that assess addition of capecitabine to carboplatin or other systemic treatments in patients with TNBC.