Curis-Sponsored 2nd Annual IRAK4 in Cancer Symposium Highlights IRAK4 as an Emerging Therapeutic Target in Hematologic Malignancies and Solid Tumors

Experts across industry and academia discussed IRAK4's role in cancers and promising developments in the therapeutic targeting of IRAK4.

Presentations highlighted the activation of IRAK4 by splicing mutations or upstream signaling as a key driver of multiple cancer types. This more active form of IRAK4 has increased sensitivity to investigational IRAK4 inhibitors such as emavusertib. Speakers discussed IRAK4 inhibition in preclinical models and emerging clinical data.

Curis, Inc. (NASDAQ: CRIS), a biotechnology company focused on the development of emavusertib, an orally available, small molecule IRAK4 inhibitor for the treatment of hematologic malignancies, hosted a successful 2nd Annual IRAK4 in Cancer Symposium, held virtually on September 22, 2023, and chaired by Drs. Guillermo Garcia-Manero and Eric Winer.

Interleukin-1 receptor-associated kinase-4 (IRAK4) is a protein kinase belonging to the tyrosine-like kinase family. IRAK4 mediates signaling from Toll-like receptor (TLR) and interleukin-1 receptor (IL1R) signaling pathways to nuclear factor kappa B (NF-κB) and mitogen-activated protein kinase (MAPK) and plays an important role in the innate immune response. Emerging evidence has identified activation of IRAK4 as a consequence of multiple oncogenic mutations, including spliceosome mutations, indicating the potential of targeting IRAK4 for therapeutic intervention.

Highlights of the 2nd Annual IRAK4 in Cancer Symposium included:

IRAK4 Pathway Biology

Dr. Amit Verma (Montefiore; Albert Einstein College of Medicine) shared research on mutations in two spliceosome components that are common in myelodysplastic syndromes (MDS) and acute myeloid leukemia (AML). These mutations drive expression of a maximally active long isoform of IRAK4 termed IRAK4-L. IRAK4-L expression confers sensitivity to the IRAK4 inhibitor emavusertib (CA-4948). Treatment with emavusertib blocked NF-κB activation in cell assays and reduced leukemic growth in patient-derived AML/MDS models.

IRAK4 Inhibition in Hematological Malignancies

Dr. Guillermo Garcia-Manero (MD Anderson Cancer Center) explored the current landscape of MDS treatment, noting a need for new therapies. He also presented encouraging clinical data of the IRAK4 inhibitor emavusertib in patients with relapsed or refractory MDS.

Dr. Omar Abdel-Wahab (Memorial Sloan Kettering Cancer Center) presented on the therapeutic potential of inhibiting two emavusertib targets, cdc-like kinase (CLK) and dual-specificity tyrosine-regulated kinase (DYRK), in myeloid malignancies. Their inhibition has demonstrated therapeutic efficacy in preclinical models of AML, including overcoming venetoclax resistance.

Dr. Eric Winer (Dana-Farber Cancer Institute) discussed the role of IRAK4 signaling as a mechanism of adaptive resistance to chemotherapy in AML and showed promising clinical data from patients with AML or MDS treated with emavusertib. He noted the synergy seen between emavusertib and both azacitidine

and venetoclax and expressed interest in seeing outcomes of these combinations from future clinical studies.

Dr. Claudio Cerchione (Istituto Scientifico Romagnolo per Io Studio e la Cura dei Tumori) presented encouraging clinical data of emavusertib monotherapy and combination therapy with ibrutinib in patients with hematological malignancies and highlighted IRAK4 as an emerging target in myeloma.

Dr. Christian Grommes (Weill Cornell Medical College, Memorial Sloan-Kettering Cancer Center) reviewed the current treatment landscape in primary central nervous system lymphoma (PCNSL), noting that optimal therapy has not been established for this malignancy. He also highlighted clinical tumor responses to emavusertib treatment in ibrutinib-resistant patients with PCNSL.

Dr. Daniel Starczynowski (Cincinnati Children's Hospital Medical Center) presented research on potential IRAK4- and inflammation-related biomarkers for MDS/AML through measurement of inflammatory markers, intracellular signaling, and predictive gene expression signatures.

IRAK4 Inhibition in Solid Tumors

Dr. Kian-Huat Lim (Washington University School of Medicine) explored the potential of IRAK4 as a therapeutic target in gastrointestinal malignancies, specifically pancreatic cancer and colorectal cancer. He showed preclinical evidence of improved tumor responses when emavusertib was combined with either chemotherapy or immunotherapy.

Dr. Bently Doonan (University of Florida College of Medicine) discussed compelling preclinical evidence for combining IRAK4 and PD-1 inhibition in the treatment of melanoma brain metastases (MBM) and introduced a clinical study testing emavusertib in combination with pembrolizumab in patients with MBM following radiotherapy.

Dr. Matthew Galsky (Icahn School of Medicine at Mount Sinai) presented data demonstrating that IRAK4 inhibition mitigates gene expression changes associated with resistance to immune checkpoint blockade. He introduced a phase 1 trial combining emavusertib with immune checkpoint inhibitors in bladder cancer that is underway.

The symposium closed with a discussion led by Dr. Richard Stone (Dana-Farber Cancer Institute) and Dr. Guillermo Garcia Manero on the mechanism of IRAK4 inhibition as an anti-cancer agent and next steps in the field.

Summary

The presentations at the IRAK4 symposium provided valuable insights into the biology of IRAK4 and the potential of its inhibition in anti-cancer therapies. IRAK4 activity has been implicated in the progression of multiple hematologic malignancies and solid tumors. Understanding the biology driving IRAK4 and the effects of IRAK4 signaling on innate immunity is key to harnessing its therapeutic potential. Notably, the IRAK4 inhibitor CA-4948 (emavusertib) has shown promise in multiple preclinical cancer models. It is currently being assessed in clinical trials as a monotherapy and combination therapy for AML, MDS, and B cell cancers.