Session PO.ET06.05 - Novel Antitumor Agents 3

Add To My Itinerary

4799 / 13 - Inhibition of STAT3 in pancreatic ductal adenocarcinoma and immunotherapeutic implications

April 3, 2019, 8:00 AM - 12:00 PM | Section 13

Presenter/Authors

Rafal Zielinski[1], Izabela Fokt[1], Stanislaw Skora[1], Edward Felix[1], Krzysztof Grela[1], Jayakumar Arumugam[1], Radj Venugopal[1], Midan Ai[2], Genevieve Hartley[1], Michael Curran[1], Waldemar Priebe[1]. [1]UT MD Anderson Cancer Center, Houston, TX; [2]Carolina BioOncology Institute, Houston, TX

Disclosures

R. Zielinski: None. **I. Fokt:** None. **S. Skora:** None. **E. Felix:** None. **K. Grela:** ; Moleculin Biotech, Inc. **J. Arumugam:** None. **R. Venugopal:** None. **M. Ai:** None. **G. Hartley:** None. **M. Curran:** None. **W. Priebe:** ; Moleculin Biotech, Inc.

Abstract

Introduction: Signal Transducer and Activators of Transcription 3 (STAT3) plays a pivotal role in carcinogenesis, chemo- and radio-sensitivity, metastasis and immune evasion in multiple malignances including Pancreatic Ductal Adenocarcinoma (PDAC). Our drug discovery program focused on modulators of transcriptional activity led us to identify small molecules that potently inhibits tyrosine 705 phosphorylated STAT3 (p-STAT3). Compound WP1066, currently being evaluated in a Phase I clinical trial (NCT01904123) as orally administered agent and its novel, analog WP1732 suitable for IV administration, were selected as promising, potent p-STAT3 inhibitors with drug-like properties for further development as lead compounds. The purpose of these study is to perform a preclinical evaluation of WP1066 and WP1732 aiming at their future application for treatment of PDAC.

Materials and Methods: The chemical synthesis of WP1066 and WP1732 and their characterization was performed at UT MD Anderson Cancer Center. In vitro efficacy of both inhibitors was assessed using proliferation and apoptosis induction assays in a panel of patient-derived and commercially-available PDAC cell lines. Inhibition of p-STAT3 was investigated using western blot (WB) and immunofluorescence. Acute and multiple dose toxicity of WP1732 was tested in CD-1 mice. Pharmacokinetic parameters of WP1732 after intravenous administration was evaluated in naïve CD-1 mice using Mass Spectrometry LC/MS/MS or rats by liquid scintillation counting (LSC) using radio-labeled agent. Efficacy of both agents alone or in combination with immune checkpoints inhibitors was tested in PDAC tumor models.

Results: Both WP1066 and WP1732 were shown to induce apoptosis and inhibit p-STAT3 and its nuclear localization in all tested PDAC cell lines. Observed IC50 values ranged from 0.5 to 2 μM. WP1732 was well tolerated by mice (LD50 85 mg/kg given IV). Pharmacokinetic and biodistribution studies indicate high plasma levels of the drug and significant accumulation of WP1732 in the pancreas of mice and rats after a single bolus injection of the drug. Importantly, both agents show

in vivo efficacy in preliminary experiments when tested alone or in combination with T cell immune checkpoint inhibitors.

Conclusion: WP1066 and WP1732 are inhibitors of p-STAT3 with demonstrated in vitro and in vivo activity against PDAC tumor models. Our preliminary data warrant the further pre-clinical and clinical evaluation of these oncology agents alone and in combination with immunotherapy as a promising new therapeutics for pancreatic cancer.