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Biosketch

Cyril Konto, M.D. is an Early Clinical Development Lead, Executive Director in Immuno-Oncology (IO) at Rinat-Pfizer since March 2015. Previously he was Melanoma Program Lead at Bristol-Myers Squibb pioneering the late stage clinical development of anti-CTLA4 and anti-PD1 checkpoint inhibitors in melanoma, and supporting the early clinical development of anti-CD137 and anti-KIR in a broad range of tumors. With great clinical experience in oncology, Dr. Konto has contributed to the clinical development of several assets in breast cancer, lung cancer and melanoma. Dr. Konto is a well-experienced global drug developer and was a main leader for ipilimumab (Yervoy). As a global director of Yervoy melanoma program, he led clinical trials from early to late phase, and led BLAs and sBLAs with regulatory authorities worldwide. As an executive director of the early Immuno-oncology portfolio at Pfizer, he is now responsible for IND-enabling studies, First-in-Humans, IO combination strategy, and Proof-of-Concepts of naked monoclonal antibodies, bispecifics and allogenic CAR T cells.

He is also an Adjunct Assistant Professor in Pierre & Marie Curie University, France.

He received his MD degree and completed the clinical training of medical oncology in René Descartes University, Paris, France. Before and during his tenure at BMS Europe he was a senior consultant in La Pitie-Salpetriere academic hospital in Paris, France.

Abstract: DILI caused by checkpoint inhibitors and other anti-cancer antibodies

Checkpoint inhibitors (eg. anti-CTLA4, anti-PD1) and other immune costimulators (eg. anti-CD137) are novel immunomodulating monoclonal antibodies. Some of them have demonstrated promising efficacy in treatment of multiple cancer types. The clinical benefit from those immunotherapeutics can be hampered by immune-mediated adverse reactions (imARs) caused by dysregulation of host immune system. Liver inflammation commonly described as hepatitis is an important imAR.

Mild-to-moderate serum aminotransferase elevations are common (~10-20%) during anti-CTLA4 and anti-PD1 therapies, but are usually self-limited and resolve even with continuing cyclic therapy. Serum ALT elevations above 8 times the upper limit of normal occur in 0.5% to 3% of patients (and 15% when combining anti-CTLA4 and anti-PD1 mAb), and a proportion of these individuals develop clinically apparent liver injury that can be severe. The onset of injury occurs usually 3 to 15 weeks after initiation of treatment (sooner with anti-CTLA4 than with anti-PD1). The pattern of enzyme elevation is most frequently hepatocellular, but can be mixed, particularly at the onset of injury.

Liver histology demonstrates an acute hepatitis-like pattern with focal or confluent necrosis and prominent lymphocytic infiltrates of activated T cells, which is compatible with an immune mediated hepatic injury. Autoantibodies are usually

not present. Restarting therapy can result in recurrence of injury, although corticosteroid treatment may block recurrence.

During this presentation, we aim at describing clinicopathologic characteristics of hepatotoxicity, mechanism of liver injury, outcome and management of hepatitis diagnosed with these anti-cancer immunotherapeutics.