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The late phase of drug development: A bioanalytical dealing with the health authorities

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Background: Bioanalytics are necessary and crucial during the drug's development, especially in the most advanced phase when approaching the health authorities' requests. At this phase, bioanalytics are not only involved in the preparation of regulatory dossiers, but also in a series of additional investigations to meet the demands from health authority (HA) itself. The present report summarizes some of the investigations related to the biological activity evaluation, upon approval request from HAs. As case report, the successful example of the just approved Bavencio (Avelumab) has been chosen. The biological activity is monitored, according to the regulatory dossiers, in terms of cell binding activity and ADCC (Antibody Dependent Cell Cytotoxicity) of Avelumab (Anti PDL-1 therapeutic antibody) as result of physicochemical modifications. Anti-PDL-1 is a fully human IgG1 monoclonal antibody direct against the PDL-1, a receptor highly expressed in a variety of human cancer cells. The Anti-PDL-1 binds PD-L1 blocking the interaction between PD-L1 and the PD-1 expressed on activated immune cells, thereby releasing cells from immunosuppression and strongly enhancing anti-tumor immunity. Beside this major MoA, Anti-PDL-1 is also able to mediate an ADCC.

Analytical Approach/Methods: Upon HA requirement, for a complete biological characterization of the product, physicochemical modifications have been evaluated starting from a highly modified form of the Anti PDL-1 in term of aggregation (HMW) fragmentation (LMW) and fucosylation level to identify a correlation between different percentage of each modified form and its biological activity. The biological effect of each modifications on both Fab and Fc portions of the molecule have been verified applying both ADCC assay and cell binding assays.

Results: Each physicochemical modification have highlighted a biological impact. Regarding the fucosylation level, a clear correlation between the ADCC activity and the level of fucose in Anti PDL1 has been shown, confirming that the removal of fucose residues greatly enhances therapeutic MAb ADCC activity. Significant biological results have been proven also by the effect of aggregation (HMW) and fragmentation (LMW) on Anti PDL-1. Upon each HA requirement, it has been demonstrated the complete knowledge of the molecule from the physicochemical and biological point of view. The critical quality attributes are monitored by a dedicated analytical panel and the possible modifications are under control, ensuring to satisfy the expectations of HAs, the market and the patients.

Conclusions: These studies contributed the submission to the FDA of a biological license application for Anti PDL-1 (Bavencio) as the first metastatic carcinoma of Merkel cells (mMCC). Subsequently, a second US FDA approval for urothelial or advanced metastatic carcinoma (UC), commonly diagnosed as a metastatic bladder tumor has been obtained.

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