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Session PO.ET06.06 - PI3K/AKT/mTOR Inhibitors

666 / 13 - A novel, highly selective PI3Kδ inhibitor for the treatment of solid malignancies that express high levels of target protein as assessed by immunohistochemistry

June 22, 2020, 9:00 AM - 6:00 PM | Virtual Meeting II: E-Posters

Presenter/Authors

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Disclosures

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Abstract

The inhibition of PI3Kδ preferentially targets regulatory T cells and myeloid derived suppressor cells, breaking tumour-induced immune tolerance and restoring anti-tumour immunity. Bioinformatics and protein expression studies have shown that PIK3CD/PI3Kδ is also highly expressed in certain solid malignancies. IOA-244 is a novel, highly selective PI3Kδ inhibitor, with the unique property of being ATP non-competitive. In addition to the effects of PI3Kδ inhibition on the balance of $CD8^+$ T cells and T regulatory cells in the tumour microenvironment, we have recently demonstrated that IOA-244 effectively controls the growth of tumour cells with high levels of PI3Kδ *in vivo* in T-cell deficient hosts.

Analysis of TCGA datasets shows that certain solid tumours express high levels of PIK3CD transcript, comparable to that of diffuse large B cell lymphoma. Of these indications, cutaneous and uveal melanoma are amongst the highest expressers. To support the clinical development of IOA-244, we demonstrate that patient-derived melanoma cells with a high expression of PIK3CD are susceptible to treatment with IOA-244 in a mouse patient-derived xenograft model. Furthermore, *in vitro* explant studies using clinical biopsy material demonstrates that PI3Kδ expression can be detected in tumour tissue and that IOA-244 has an anti-proliferative function when added to these samples. Based on these and other supporting data, IOA-244 has received clinical trial approval in Europe and phase I clinical testing is underway in solid tumours with an anticipated high Treg:CD8 ratio and/or high protein expression of PI3Kδ.