Polo-like kinase 4 (PLK4) Safety Review – distilling the risks with a rapid augmented intelligence approach

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Polo-like kinase 4 (PLK4) is a unique member of the Polo-like family of kinases with an essential role in centriole duplication. PLK4 turn-over must be strictly controlled to prevent centriole amplification. PLK4 inhibitors have potential in cancer treatment; rendering cells unstable and more sensitive to chemotherapy.

Using automated data mining techniques, together with expert curation and interpretation, which are the backbone of the technology-enabled KnowledgeScanTM Target Safety Assessment framework, we reviewed the safety risks associated with PLK4. PLK4 synonyms were used to create a corpus, from which we analysed 538 literature records and 45 expression profiles, together with data from sources such as Ensembl. Finally, PLK4-relevant information and risks associated with PLK4 modulation were grouped by organ/organ-system.

Consistent with the broad expression of PLK4, the evidence suggested potential risks in most organ systems (excluding haematopoietic and urinary systems). For several risks, it is possible to identify underlying mechanistic processes (like cell proliferation and ciliogenesis) which may play a key role in their pathogenesis.

Augmentation of PLK4 function suggests a risk of carcinogenesis. Supported by evidence of impacting DNA damage responses and hyperplasia in the pancreas, skin, and hair. Given the development activities on this target in the oncology space, this is unsurprising.

Attenuation of PLK4 function was associated with potential risks of neutropenia, inflammation, reproductive impacts and impaired liver regeneration. Human PLK4 mutations (e.g. loss-of-function) have been associated with microcephaly, chorioretinopathy and growth failure.

The risks associated with modulating PLK4 are diverse. The KnowledgeScan platform quickly and concisely distilled the key biological risks, together with the intelligence surrounding known PLK4 inhibitors and therapies. We logically presented this information in a PLK4 dossier.