Association pour la Recherche sur les Tumeurs de la Prostate

Session II :
Signaling & Targeted therapies for prostate cancer

Lukas Kenner (Medical University Vienna, Vienna, Austria; University of Veterinary Medicine, Vienna, Austria)

'gp130/Stat3: a tumor suppressive pathway in prostate cancer'

Prostate cancer (PCa), one of the most diagnosed cancers in men, has its progression intricately tied to the GP130 receptor and its downstream signaling. Recent insights reveal that GP130-mediated STAT3 activation plays a dual role in PCa. On one hand, cell autonomous activation of GP130 triggers active STAT3 signaling, leading to cellular senescence via the Stat3-p19ARF-p53 axis and bolstering anti-tumor immunity through cytotoxic T-cell recruitment. This mechanism suggests a tumor-suppressive role for GP130-STAT3 in PCa. On the other hand, a frequent genomic co-deletion of PTEN and STAT3 has been observed in metastatic PCa (mPCa). Loss of STAT3, alongside PTEN deletion, activates the mTOR/CREB pathway, promoting metastasis. However, constitutive STAT3 activation can counteract this, suppressing mPCa development. The therapeutic potential of this pathway is highlighted by the response to metformin, a common type 2 diabetes drug. Metformin's efficacy in PCa, marked by reduced tumor growth and mTORC1/CREB inhibition, is significantly influenced by STAT3 presence. This interplay between GP130, STAT3, and associated pathways offers a novel perspective on PCa's molecular landscape and potential therapeutic avenues.

Guilhem Roubaud (Institut Bergonié, Bordeaux)

‘Advanced prostate cancer and HRR alterations: from bench to bedside’

Homologous recombination repair (HRR) is a well conserved cellular process of mainly double-strand DNA breaks. Up to one third of patients with advanced prostate cancer exhibit germline and/or somatic deleterious alteration of genes involved in HRR. While associated with a poor prognosis, those alterations may be exploited through synthetic letality, using Poly (ADP-ribose) Polymerase inhibitors (PARPi). In this lecture we will revue the rationale for using PARP inhibitors in patients with advanced prostate cancer either alone or in combination with androgen receptor targeting agents (ARTA) and briefly describe their related clinical outcomes. Mechanism of action (i.e. catalytic activity and trapping) of different PARPIs as well as their mechanisms of resistance will be explained. Challenges regarding screening from solid and/or liquid biopsies will be highlighted. Finally, beyond BRCA alteration (mostly driving the response to PARPi) we will briefly explore other genes involved in HRR, and potential rationales for combining with other drugs such as ATR inhibitors or immune checkpoint inhibitors.

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Bram De Laere (Ghent University, Belgium & Karolinska Institutet, Stockholm, Sweden)

'Prostate Cancer Genomics :How comprehensive genomic profiling can guide precision uro-oncology'

Prostate cancer remains a significant health challenge, necessitating innovative approaches to address unmet medical needs, particularly in the realm of predictive biomarkers. This presentation delves into the comprehensive genomic profiling of prostate cancer and explores how it can serve as a guiding force in precision uro-oncology.The talk commences with a clear definition of the problem, emphasizing the critical unmet medical need for predictive biomarkers in prostate cancer. Through a systematic approach, the presentation outlines strategies to solve this problem, highlighting five key components:

1) Defining the Drug Class context,
2) Distinguishing Prognostic from Predictive Biomarkers
3) Identifying Genomic Biomarkers with Treatment-Predictive Potential
4) Embracing New Methods such as Liquid Biopsy
5) Setting Up Clinical Trials for Validation:

The presentation ends with an introduction on the Prostate Biomarkers (ProBio) trial. This academic, outcome adaptive, and biomarker-driven study randomizes patients, comparing biomarker-driven treatment selection in experimental arms against physician's choice standard-of-care in the control arm. Additionally, the trial evaluates the comparative efficacy of agents within the experimental treatment arms, offering tangible insights into the clinical utility of the identified biomarkers.

In conclusion, this presentation not only identifies the challenges posed by the lack of predictive biomarkers in prostate cancer but also provides a roadmap for leveraging comprehensive genomic profiling to address these challenges.