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A1

Predictive and prognostic biomarker panel for targeted application of radioembolisation improving individual outcomes in hepatocellular carcinoma

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Keywords: Liver tumour, Hepatocellular carcinoma, Radioembolisation, Radiosensitivity, Patient stratification, Individual patient profiles, Biomarker panel, Multilevel diagnostics, Multi-omics, Predictive preventive personalized medicine

Liver cancer is the fifth most common form of cancer worldwide [1], with an incidence rate almost equals the mortality rate and ranks 3rd among causes of cancer related death [2]. The coexistence of two life threatening conditions, cancer and liver cirrhosis makes the staging challenging. However, there are some staging systems, e.g. the Barcelona staging system for Hepatocellular carcinoma (HCC) [3], that suggest treatment options and management. Whereas diagnosis in early stages gives hope for a curative outcome, the treatment regime for around 80 % [2] of the patients classified as severe stages only gears towards palliation [4]. An intra-arterial radiation approach, radioembolisation (RE) is ubiquitously applied as one of palliative approaches. Although, in general RE shows promising results in intermediate and advanced stage HCC [5], individual treatment outcomes are currently unpredictable. Corresponding stratification criteria are still unclear.

We hypothesised that individual radioresistance/radiosensitivity may play a crucial role in treatment response towards RE strongly influencing individual outcomes. Further, HCC represents a highly heterogeneous group of patients which requires patient stratification according to clear criteria for treatment algorithms to be applied individually. Multilevel diagnostic approach (MLDA) is considered helpful to set-up optimal predictive and prognostic biomarker panel for individualised application of radioembolisation. Besides comprehensive medical imaging, our MLDA includes non-invasive multi-omics and sub-cellular imaging. Individual patient profiles are expected to give a clue to targeting shifted molecular pathways, individual RE susceptibility, treatment response. Hence, a dysregulation of the detoxification pathway (SOD2/Catalase) might indicate possible adverse effects of RE, and highly increased systemic activities of matrix metalloproteinases indicate an enhanced tumour aggressiveness and provide insights into molecular mechanisms/targets. Consequently, an optimal set-up of predictive and prognostic biomarker panels may lead to the changed treatment paradigm from untargeted "treat and wait" to the cost-effective predictive, preventive and personalised approach, improving the life quality and life expectancy of HCC patients.

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A2

Integrated market access approach amplifying value of "Rx-CDx"

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Keywords: Market access, Value, Strategy, Companion diagnostics, Cost-effectiveness, Reimbursement, Health technology assessment, Economic models, Predictive preventive personalized medicine

Achieving and sustaining seamless "drug – companion diagnostic" market access requires a sound strategy throughout a product life cycle, which enables timely creation, substantiation and communication of value to key stakeholders [1, 2]. The study aims at understanding the root cause of market access inefficiencies of companies by gazing at the "Rx-CDx" co-development process through the prism of "value", and developing a perfect co-development scenario based on the literature review and discussions with the subject matter experts. The presenter suggests that an integrated market access approach is the need of the hour, and it should cover the entire "Rx-CDx" value chain – from early-stage pre-clinical (Rx) and feasibility (CDx) studies to post-launch considerations of a co-labeled product [3]. Such approach can leverage patient selection strategies to reduce clinical study size, increase chances to achieve earlier regulatory submission and launches, contribute to better upside for drug developers, simplify value justification, fit with the emerging "value-based" healthcare delivery practices, enable risk sharing, and facilitate funding of the biomarker research [1, 3, 4].

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Flammer Syndrome and potential formation of pre-metastatic niches: A multi-centred study on phenotyping, patient stratification, prediction and potential prevention of aggressive breast cancer and metastatic disease

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Keywords: Predictive preventive personalised medicine, Cancer advancement, Breast cancer, Pre-metastatic niches, Metastatic disease, Flammer Syndrome, Hypoxic effect, Phenotyping, Patient stratification, Multi-centred study

Detailed autopsy findings demonstrate that the absolute majority of people are carriers of hardly detectable micro and asymptomatic tumour lesions which, however, not necessarily may progress into clinically manifested disease. Further, in case of manifested oncologic diseases, less than 1 % of all disseminated and circulated tumour cells have a potential to form secondary and distanced tumours (metastatic diseases) – the phenomenon known as the "metastatic inefficiency" [1]. In this context, the key question puzzling modern predictive preventive and personalised medicine is how to discriminate between those carriers who are predisposed to a disease manifestation / progression and "silent" carriers.

By evidence, both initial tumours and secondary metastases need a "fertile" microenvironment effectively supporting their growth and progression [2]. What are the mechanisms "fertilising" the microenvironment for a particularly effective cancer advancement? In general, these are local and systemic effects at molecular, cellular and tissue levels which create hospitable conditions for tumour and metastatic colonisation. Amongst pronounced risk factors hypoxia is recognised as a strong driver of aggressive cancer types and active metastatic disease, e.g. triple negative breast cancer. Systemic hypoxic effects have been demonstrated as forming pre-metastatic niches in distant organs [2,3].

Regarding specific phenotypes particularly predisposed to local and systemic hypoxic effects, individuals with Flammer Syndrome (FS) phenotype create prominent cohorts of healthy individuals in sub-optimal health condition [4] as well as patients suffering from severe diseases such as eye disorders [5,6]. In the above introduced context, FS individuals are of particular interest, due to

- clearly defined phenotype [4]
- onset of symptoms early in life (puberty)
- more frequent in young women
- systemic hypoxic/ischaemic effects
- involvement of systemic molecular events (altered stress response, multi-drug resistance and energy metabolism; shifted regulation of transcription, apoptosis and adhesion; deficits in DNA-repair efficacy; blood-brain-barrier-breakdown; extensive tissue remodelling accompanied by highly increased activity of the core of metalloproteinase) into pathogenesis of severe disorders in patients with FS phenotype [7, 8]. All these pathways are considered as evidently involved into effective cancer advancement [9].

Our multi-centred study has been designed to respond to the following questions:

1. Are women with FS phenotype more predisposed to cancer onset and progression compared to the general population?
2. Are women with FS phenotype more predisposed to breast cancer?
3. Which types of breast cancer are more frequent in women with FS phenotype?
4. Has FS phenotype a power to predict pre-metastatic niches in cancer patients?
5. Is patients' stratification in cancer and metastatic disease possible by phenotyping with FS symptoms?
6. Is cancer prediction and prevention possible by FS phenotyping in predisposed individuals?

Our multi-centred consortium will, further, report on the results coming from this exciting study. A series of research articles is currently in preparation by the EPMA nominated working group.

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A26

Innovative tools for prenatal diagnostics and monitoring: improving individual pregnancy outcomes and health-economy in EU

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Keywords: Prenatal diagnostics, Healthcare system, Economical burden, Predictive preventive personalised medicine

EU birth rates in the global context

In the world ranking for annual birth rates (from place 1 for Nigel till place 224 for Monaco with 46.12 *versus* 6.72 annual births, respectively), all the EU countries are positioned very low beginning with the highest rank 132 for Ireland (15.18 births/1000) and going deep into the lowest rank for 219 for Germany – position 6th from the last place [1].

Improving healthcare for and increasing life quality of pregnant women in EU

From the above statistical data it is evident that the birth rates in the EU belong to the lowest ones worldwide. This fact motivates European Union for improving the healthcare for and increasing life quality of pregnant women, advancing the level of professional monitoring of