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FOREWORD

Rare cancers, the continued agenda for progress – editor's special foreword

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Rare cancers affect one in five new patients with cancer and this second special edition highlights some of the continued activity in the field (first special edition[1]). Of note since the first special edition, the Joint Action on Rare Cancers (JARC) published in 2019 ten recommendations and this special edition reflects some of the ambitions of the rare cancer agenda 2030 [2]. These JARC recommendations are important and are replicated below in this editorial, helping to frame the subsequent papers.

1. RARE CANCER AGENDA 2030: *ten recommendations from the EU joint action on rare cancers*

(1) Rare cancers are the rare diseases of oncology
(2) Rare cancers should be monitored
(3) Health systems should exploit networking
(4) Medical education should exploit and serve healthcare networking
(5) Research should be fostered by networking and should take into account an expected higher degree of uncertainty
(6) Patient-physician shared clinical decision-making should be especially valued
(7) Appropriate state-of-the-art instruments should be developed in rare cancer
(8) Regulation on rare cancers should tolerate a higher degree of uncertainty
(9) Policy strategies on rare cancers and sustainability of interventions should be based on networking
(10) Rare cancer patients should be engaged

Cholangiocarcinoma (CCA) is the second most common primary liver tumor and Bagante et al. review the evolving approaches to genetic markers and the era of innovative imaging [3]. They describe the distinct molecular profiles of CCA and how radiomics and radiogenomics may improve clinical outcomes. They reflect however that future studies are needed to better define the molecular features of CCA as well as combine genetic markers with novel imaging approaches, increasing therapeutic options and improving outcomes for CCA patients.

Uterine serous carcinoma (USC) is an aggressive subtype of endometrial cancer, accounting for a disproportionate number of uterine cancer-related deaths. Najjar et al. provide a comprehensive and detailed overview of the diagnostic approaches and management of USC, including pre-operative diagnostic and prognostic tools, surgical staging and pathology, pathogenesis and tumor markers, adjuvant, early, late and recurrent stage disease management [4]. They describe the significant advances that have been made in characterizing the molecular landscape and the potential for a number of different targeted therapies. Despite these advances, clinical trials are needed to establish the safety and clinical efficacy of these promising targeted therapies if improved survival outcomes are to be realized.

Soft tissue sarcomas (STS) are a heterogeneous group of cancers and epithelioid sarcoma is an aggressive subtype. Weiss & Agulnik present a therapeutic overview of tazemetostat, a selective, oral EZH2 inhibitor [5]. Tazemetostat received US orphan drug designation in 2017 and earlier this year was the first FDA approval for the treatment of advanced epithelioid sarcomas. The authors conclude that tazemetostat is a step forward in the field of sarcomas and as an oral agent allows for the opportunity for patients to be treated at home.

Chronic lymphocytic leukemia (CLL) is the most frequent leukemia in Western countries and a heterogeneous disease, both biologically and clinically. In a detailed review, Moia et al. describe the considerable body of evidence from genomic studies which have helped to bring more clarity around the pathogenesis of CLL, allowing for the identification of prognostic and predictive biomarkers [6]. Currently two molecular predictors are routinely used in clinical practice for treatment decision (mutational status of immunoglobulin heavy chain variable (IGHV) genes and abnormalities of the TP53 tumor suppressor gene). However, this is set to change with recent studies identifying novel molecular features with potential for precision medicine application. These include BIRC3, NOTCH1, Bcl-2, BTK and PLCγ2 mutations, and Minimal Residual Disease assessment. The authors propose that new molecular predictors may further increase the effectiveness of treatment, allowing for longer survival and improved patient outcomes.

Multiple endocrine neoplasia type 1 (MEN1) is an autosomal dominant tumor syndrome requiring lifelong surveillance. It is caused by heterozygote inactivating mutation of the

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MEN1 tumor suppressor gene. Marini et al. comprehensively review the current diagnostic and treatment approaches for this complex multiple tumor syndrome, providing up-to-date insight (clinical practice guidelines were published in 2012) [7]. The authors note that one of the main challenges for clinicians is to reach a compromise between the risk of exposure to repeated doses of ionizing radiation and the benefit of tumor diagnosis at an early stage. However, molecular targeted therapies and RNA-based therapies, interfering with menin-regulated pathways, could be the future of MEN1 treatment.

Langerhans cell histiocytosis (LCH) is an inflammatory myeloid neoplasia characterized by accumulation of bone marrow-derived immature dendritic cells harboring oncogenic mutations in mitogen-activated protein kinase (MAPK) pathway genes. Morimoto & Kudo describe disease classification, treatment, clinical course and outcomes with a focus on hematopoietic stem cell transplantation [8]. The authors make a number of recommendations in the pediatric population but reflect that in adults there are few prospective interventional clinical trials and currently little evidence for HSCT.

A clear theme running through these papers is the advances in the molecular understanding of these different tumor types and how this information is driving opportunities to improve diagnostic capabilities and development of new or repurposed therapies. However, there is the need for further clinical studies to confirm the benefits and define the safety profiles of a number of exciting emerging therapeutic options.

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