The "Risk" in Pediatric Low-Grade Glioma

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In this issue of *Cancer Cell*, Ryall et al. report on the largest clinically and molecularly characterized cohort of pediatric low-grade gliomas (pLGGs) published to date. They provide new insight into the pLGG molecular landscape and a novel risk stratification system with the potential to revolutionize prognostication and impact treatment.

The last decade has generated a wealth of new molecular and genetic insights into the pathogenesis of many cancers, heralding clinical optimism. This is particularly true for pediatric low-grade gliomas (pLGGs), the most common childhood central nervous system (CNS) tumor, which frequently harbor genetic alterations that activate mitogen-activated protein kinase (MAPK) and/or mTOR signaling (Jones et al., 2013; Zhang et al., 2013). The availability of small molecule inhibitors that target these pathways have facilitated their rapid translation into the clinic, with pLGGs leading the way for precision medicine approaches among childhood cancers (Garcia et al., 2016).

Despite the promise of these approaches, pLGGs are associated with specific diagnostic and therapeutic challenges. While most patients will survive their disease, they are often left with a lifetime of devastating morbidity, including vision loss, epilepsy, endocrine dysfunction, motor disability, neurocognitive dysfunction, and decreased quality of life (Bandopadhayay et al., 2014; Packer et al., 2017). Moreover, pLGGs encompass a heterogeneous group of tumors, both genetically, with respect to their driver alterations, and clinically, arising in various locations throughout the CNS while afflicting children of all ages. To date, there has not been an effective strategy to identify poor-risk groups other than basic characteristics such as age and tumor location.

In the current issue of *Cancer Cell*, Ryall et al. present the largest cohort of clinically annotated and molecularly characterized pLGGs reported to date. These data are leveraged to address the issue of prognosticating pLGGs and developing a novel, molecularly informed risk algorithm (Ryall et al., 2020). In doing so, the manuscript not only verifies some of the well-accepted paradigms of pLGGs but also begins to address some unanswered questions. First, the authors confirm that pLGGs are by and large a disease of aberrant MAPK and/or mTOR activation, with confirmation that some pLGGs harbor non-canonical driver alterations (for example, MYB family rearrangements) that also activate MAPK and/or mTOR signaling. This suggests that MAPK blocking agents may even be therapeutically effective in patients without identifiable MAPK alterations. However, further preclinical validation is required, including clearer characterization of the mechanisms through which such signaling occurs, to minimize the risk of paradoxical MAPK pathway activation and associated tumor growth as was observed in children with *BRAF*-rearranged pLGG treated with the multi-kinase inhibitor sorafenib (Karajannis et al., 2014).

One of the most impactful aspects of the manuscript was the development of a molecular-based risk stratification system which begins to provide a tool to prognosticate and anticipate the clinical course of individual patients with a specific histologic and molecular signature. The manuscript reassuringly confirms that the majority of children with pLGGs are unlikely to succumb to their disease, with the reported deaths seen later in life often attributable to other factors that increase the risk of transformation or secondary malignancy such as radiation treatment. The presence of *H3.3* p.K27M mutations (as seen in high-grade gliomas) was a notable exception, with all children eventually succumbing to their disease. Also highlighted is the fact that many children with pLGGs are faced with inferior progression-free survival rates and associated morbidities that result from tumor progression and treatments. This risk stratification system can provide clinicians with the tools to better anticipate these more aggressive tumors and consider alternative therapies sooner, with the potential to better preserve patient function and quality of life. However, it is also important to recognize that these analyses were performed on a retrospective cohort of children who were treated with heterogeneous regimens in an era that largely predated targeted agents. Thus, the proposed risk stratification system requires prospective validation that must include children treated with small-molecule inhibitors.

The authors nominate specific individual assays and approaches to identify driver alterations. While these approaches will vary across institutions, the underlying goal of systematically identifying pLGG-relevant single nucleotide variants (SNVs) and rearrangements using assays optimized for low-input samples remains the same. pLGG alterations are distinct from adult gliomas and frequently occur in non-coding regions of the genome. It is therefore imperative that diagnostic testing is

performed by teams with specific expertise in pLGGs and these techniques.

Another noteworthy finding is the stratification of neurofibromatosis-type 1 (NF1)-associated pLGGs into differing risk groups. The far majority of patients with NF1-associated pLGGs will have a favorable outcome, but we have long recognized that there is a small subgroup of patients with a more aggressive clinical course despite appearing the same on imaging and histologic review. Ryall et al. found that NF1-associated pLGGs located outside the optic pathway had a worse prognosis. Moreover, among the high-risk NF1 tumors with multiple recurrences, 20% of those biopsied harbored additional alterations other than the classic NF1 mutation, representing potential secondary driver events (Ryall et al., 2020). This preliminary data may begin to shape how clinicians view NF1-associated pLGGs at the outset while providing more realistic expectations for patients and families based upon molecular profiling. Obtaining tumor tissue in NF1-associated pLGG is becoming a more accepted paradigm in an effort to better understand the tumor's molecular characteristics, and these current data further support this unmet need to comprehensively characterize the somatic landscape of NF1-associated pLGGs and identify prognostic biomarkers (Packer et al., 2020).

These analyses also shed interesting insights into potential associations between the types of genetic alterations and clinical outcomes. The authors report that pLGGs defined by SNV driver events had worse progression-free and overall survival rates as compared to those tumors with structural variants (Ryall et al., 2020). This observation has been reported previously in both newly diagnosed patients treated with classic chemotherapy and recurrent patients treated with the MEK-inhibitor selumetinib (Fangusaro et al., 2019; Lassaletta et al., 2017). However, this finding may also reflect the underlying processes that result from the mechanisms that determine whether a pLGG is more likely to harbor a SNV or a structural variant. For example, cell of origin, presence of co-occurring mutations that may shape mutational and rearrangement signatures, the presence of underlying germline predisposition syndromes, and clinical factors such as patient age, tumor location, and extent of resection may all interplay to determine the overall genomic landscape and outcomes of specific pLGGs. It will be important to verify these findings in larger cohorts of patients using multivariate analyses, particularly in prospective studies utilizing molecularly targeted therapies.

Ryall et al. provide an eloquent evaluation of the largest clinically and molecularly annotated cohort of pLGGs published. The manuscript harnesses our current understanding of the pLGG landscape and provides new insight into tumor biology and associated clinical behavior. These data have the ability to shape a new era of prognostication and clinical trials based upon this risk stratification, with a hope of choosing the most effective treatment strategies for each patient with pLGG based on the tumor's histologic and molecular profile as well as patient and tumor characteristics. However, many questions remain. Future prospective testing of this newly proposed stratification as we treat with specific targeted agents will be essential to verify and possibly modify risk groups when necessary. Finally, it is important to acknowledge our limited understanding of the effects of novel targeted therapies on normal growth and development. It is imperative that clinical trials evaluating the efficacy of these agents also include systematic evaluation of both immediate and late toxicities while incorporating functional outcomes (such as visual acuity and motor abilities), quality of life, and neuro-psychological assessments.

DECLARATION OF INTERESTS

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