Diffuse intrinsic pontine gliomas (DIPG) are tumors that diffusely involve the brainstem and appear almost exclusively during childhood and adolescence. This devastating cancer is the main cause of brain tumor–related death in children, with a median survival time of less than 1 year for the majority of affected patients. Because of the location, surgical resection is not an option for this disease, and diagnosis is currently based on clinical findings and radiologic appearance. The mainstay of therapy is largely palliative, and decades of clinical trials of numerous chemotherapeutic regimens have not led to an improvement in outcome for these patients. DIPGs usually histologically resemble high-grade astrocytic tumors (anaplastic astrocytoma or glioblastoma [GBM], WHO grade 3/4). Thus many pediatric clinical trials over the past several decades have been based on agents with activity in adult GBM, although they have failed to show any benefit in pediatric DIPGs. However, we are now entering an era in which molecular data specific to pediatric DIPG are becoming available, thus potentially overcoming one of the roadblocks to smarter trial design and improved patient outcome.

Although still relatively limited when compared with those from large-scale genomic studies of adult cancer, several important conclusions can be drawn from the data available for DIPGs so far that can help inform future clinical trials. First, consistent with previous data, receptor tyrosine kinases (RTKs) appear to be upregulated at the genomic or expression level (or both) in the majority of pediatric DIPGs. The most common recurrent focal gain in pediatric DIPGs encompasses PDGFRA, occurring at the genomic level in at least 30% of DIPGs, with an even larger number showing overexpression at the RNA and protein levels. Gain of EGFR does not appear to be a frequent event in pediatric DIPG. However, two other RTKs are reported by Paugh et al to frequently show gains in DIPGs: MET and IGFIR. Interestingly, most, but not all, of the DIPGs showing gain of these RTKs also show gain of PDGFRA (64% and 88% of tumors showing gain of MET or IGFIR, respectively, have a concomitant gain of PDGFRA). Using fluorescence in situ hybridization (FISH), Paugh et al were able to demonstrate that this represented both cases where the same cells showed amplification of both genes and cases where different clones within the same tumor showed amplification of either PDGFRA or MET. Further, their FISH studies uncovered cases with RTK amplification that were missed by single nucleotide polymorphism (SNP) array analysis and vice versa. This raises important questions related to use of these data for clinical trials: (1) If we are to use targeted agents, what method should be used to identify gain of the target (FISH v SNP array)? (2) Should we be looking for gain/amplification of the target at the genomic level or expression of the target at the protein level? (3) What about tumor heterogeneity? If we use biopsy samples (the only real option for real-time, biology-based stratification for clinical trials), will they be representative of the tumor as a whole? The study by Paugh et al suggests substantial tumor heterogeneity at the genomic level. Will this be the same at the protein level? How many cells within the tumor need to express the RTK before a response to a targeted inhibitor might be anticipated? Can we expect a bystander effect, or will we, as suggested by Paugh et al, simply be allowing outgrowth of tumor cells lacking that particular RTK?

In addition to open biologic questions, the availability of these data raises further clinical questions. Can this information translate into a clinical breakthrough after 30 years of unsuccessful clinical trials? Can molecular biology really help to identify the best drug out of a growing number of targeted therapeutics currently under development? Without any doubt, the collection of material from postmortem samples has generated immense hope in the neuro-oncology community, offering insight into critical pathways involved in DIPG growth. The lack of tissue material has certainly been one of the major limiting factors for the development of innovative clinical trials. However, it is unlikely that this new information alone will be sufficient to change the outcome of this deadly disease. These findings need to be linked to other recent breakthroughs in DIPG research, such as the generation of PDGF-induced brainstem glioma models and orthotopic DIPG xenograft models that can potentially be used as preclinical tools for the testing of novel molecules with or without concomitant radiation. Together, these findings will provide new insights into DIPG pathogenesis and may ultimately result in successful therapeutic avenues to treat DIPG. Some recent trials of biologic modifiers have already identified a subset of patient with...
longer than expected survival. In a phase II study of gefitinib, an EGFR inhibitor, and concomitant radiation, Pollack et al\textsuperscript{9} reported three patients who were progression free more than 36 months after diagnosis. In a European study that mandated diagnostic biopsy for patients with DIPG, Geoerger et al\textsuperscript{10} used erlotinib, another EGFR inhibitor, in combination with focal radiotherapy. Patients with high EGFR immunohistochemical expression (eight of 20 patients) had a marginally longer survival, suggesting that molecular stratification may have led to better results.

At this stage, another critical question is whether we should consider biopsy-driven clinical trials for patients with DIPG, in order to stratify treatment according to their biologic signatures. The feasibility, and particularly the safety, of DIPG biopsies in the context of multicenter cooperative trials still need to be evaluated. In addition, although potentially promising, the limitations of personalized therapy for DIPG using molecular analyses of limited tumor samples taken from a heterogeneous tumor by stereotactic biopsies remain to be seen.

As we enter the long-awaited molecular era for pediatric DIPG, clinicians involved in the treatment of these patients now face the challenge of translating these findings into clinical practice. At this point in time, studies using clinical samples from living patients are most defensible if there is a rationale for obtaining biopsy tissue that influences therapy. The work on postmortem material has identified a number of potential targets, and many of these targets can be treated with drugs. There are now opportunities to conduct studies, either based on biopsy findings or not, using small molecule inhibitors. True translational research is required, along with clinician-scientist collaboration, to choose the best potential drug. Even though true incidence studies for DIPGs are lacking, it is estimated that more than 150 patients are diagnosed annually with DIPG in North America and a similar number in European countries. It is now essential to combine bench-to-bedside efforts to tailor optimized targeted trials, and to build up a cooperative network to capitalize on these exciting findings after so many years of disappointing results.

**AUTHORS’ DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST**
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