From the Editor

It is quite likely that in the next decade, a majority of approved cancer drugs will fall into the biological as opposed to cytotoxic category—this has already been the trend in the last few years. In this issue of *AJHO*, a review of best initial treatments for *EGFR*-mutation-related non–small cell lung cancer (NSCLC) by Barber and Reckamp

Debu Tripathy, MD
Editor-in-Chief

highlights several important paradigms of targeted cancer therapies. First, many carcinomas exhibit hallmarks of cancer that may be due to drivers, ie, aberrations related to the intrinsic characteristics of the cell type affected.[1] *EGFR* is an important growth factor for epithelial cells—particularly those deriving from skin, gastrointestinal, and respiratory tract, such that its dysregulation via activating mutation can serve as a key target for both initial (as is the case in *EGFR*-mutant breast cancer), or subsequent therapy (as is the case in HER2+ breast cancer, with HER2-directed therapy recommended in both initial and later lines). Additionally, it is critical to have a reliable assay to ensure the optimal treatment is used at the right time. In the case of *EGFR* mutations, those that specifically activate *EGFR* and sensitize cells to *EGFR* tyrosine kinase inhibitors (TKIs) are of interest.

Second, the microenvironment can also be important initially. While this is not the focus of the review article, several cancer types including lung, melanoma, and renal cell cancers may yield the best treatment benefit-to-risk ratio in upfront immunotherapy. Third, bypass pathways are likely to emerge—more so in cell types that have numerous genomic aberrations and may already possess the seeds of resistance. In fact, pre-existing T790M resistance mutations were initially reported to be detectable as a minor subclone in untreated lung cancer more than 10 years ago.[2] While osimertinib is now approved for T790M-bearing resistant NSCLC, the upfront use of this TKI to subvert resistance in the first place is now being investigated, along with other combinations such as bevacizumab and dual *EGFR*-targeted therapy with cetuximab and afatinib. A big question is whether the very expensive and more toxicity-prone initial combination approach will really be better in terms of long-term outcomes. Staying ahead of the "mutation curve" may be challenging, as newer mutations mediating resistance to osimertinib have now been described.[3]

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