Third, the exact role of all these molecular alterations in the pathogenesis and development of KIT/PDGFRA WT GIST should be better defined to understand whether they could have a therapeutic relevance as novel targets. It has already been suggested that the loss of SDH complex induces a pseudohypoxic status leading to the activation of several nuclear genes involved in angiogenesis, erythropoiesis and apoptosis. Therefore, SDH-deficient KIT/PDGFRA WT GIST could be reasonably considered a metabolic disease, and antiangiogenetic treatments in this subset of patients may represent a valid strategy. Moreover, the functional relationship between SDH loss of function and overexpression of IGF1R should be clarified to understand whether IGF1R could be considered a true target in these patients. Similarly, the biological significance and potential pathological role of the V600E BRAF mutation, even if much more rare, also should be investigated to support the development of clinical trials that evaluate the activity of BRAF inhibitors. Finally, the biological background of the small subgroup of KIT/PDGFRA WT GIST that lacks a SDH loss of function remains uncertain. The lack of known driver alterations could be overcome by mapping the whole genome with next-generation sequencing platforms that are now the most detailed approach for detection of cancer-related DNA or RNA alterations. Therefore, the main effort of research in this area should be directed toward the collection of a large series of...