The ideas and viewpoints expressed in this commentary are those of the author and do not necessarily represent any policy, position, or program of NCCN.
In order to garner a more complete story, we need to evaluate this agent in the context of a clinical trial. Yet, what would entice a pharmaceutical company to run a clinical trial in a disease in which the actionable subset is 0.16%? This is where so-called “basket trials” become particularly pertinent, and not just because they allow for a reasonably rapid accrual of a respectable number of cancers harboring a defined genetic alteration. A basket trial also allows for separation of organ- and context-specific efficacy when distinct tumor types are treated with an identical agent, as recently shown in a trial of nonmelanoma BRAF-mutant cancers treated with vemurafenib. Within the PDAC genomic landscape, probably the most prevalent actionable subtype (currently estimated at between 5% and 10% of cases) is composed of tumors with defective DNA damage repair (“DDR-defective” PDAC), which respond to platinum agents and poly(ADP-ribose) polymerase inhibitors. Beyond DDR-defective PDAC, many other low frequency alterations (<5%, and typically <2%) now exist with available small molecule inhibitors or biologics, including mutations of BRAF and EGFR or amplifications of HER2/neu, and with the plummeting cost of NGS and availability of basket trials around the country, hunting for such actionable subsets, minor as they might be, becomes increasingly justifiable.

Third, from a biological perspective, the absence of near ubiquitous KRAS mutations in all 5 ALK-positive cases suggests that the pathogenesis of these lesions may be distinct from garden variety PDAC. For example, it was not clarified whether the pancreata contain bona fide precursor lesions, such as pancreatic intraepithelial neoplasia, which is not surprising given that resectable material was available from only 1 case. Mutant Ras signaling leads to profound immunosuppression in the tumor microenvironment, and in its absence, the theoretical possibility remains that KRAS wild-type cases might be more susceptible to immunotherapy.

Finally, as a cautionary note, in clinical oncology, common things happen commonly, and in patients who present with a pancreatic “mass” that is KRAS wild-type and ALK-mutant, the first possibility that needs to be excluded is that of a pancreatic metastasis from a lung primary. As noted earlier, the authors acknowledge this limitation, although clinical and imaging data strongly support a pancreatic primary. A robust line of communication between the oncology, radiology, and pathology teams is critical for ensuring an accurate diagnosis in such cases.

References