

## **Pancreatic Cancer**

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### **New Strategies for Success in Pancreatic Adenocarcinoma**

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Pancreatic adenocarcinoma ranks as the most challenging of human malignancies, with overall 5-year survivorship being measured in a couple of percent. Major progress has occurred regarding the molecular underpinnings and pathogenesis of pancreatic adenocarcinoma, definition of the epidemiology and genetics of this disease, identification of individuals at risk, and now in 2008, the pending description of the pancreatic genome. However, progress in the therapeutic arena has lagged far behind, and, in frankness, the summary of clinical developments over the past decade has been modest and incremental at most. For investigators, clinicians, scientists, and most of all patients and their families, the expectations are high for the next decade with regard to meaningful therapeutic advances in this disease.

In 2008, the core drug and the backbone of treatment in all settings of this disease – adjuvant, locally advanced and metastatic – remains gemcitabine. Most of the gemcitabine data pertain to a standard 30-minute infusion and more limited data suggest minor gains from fixed-dose infusion schedules.<sup>1-3</sup> The past decade of research focused initially on combining cytotoxic therapies with gemcitabine, and more recently, on combining newer “targeted agents.” Some success has been observed by combining the platinum analogs and the fluoropyrimidines with gemcitabine in the advanced pancreatic cancer setting.<sup>4,5</sup> For many patients with a preserved performance status, such combinations represent a reasonable therapeutic option outside of a clinical trial. Three- and four-drug combinations have also been assessed, but for most such combinations there is finite data and the major trade-off becomes a toxicity-benefit equation. In relative terms, more limited incremental gains have been observed by combining erlotinib with gemcitabine,<sup>6</sup> while other randomized phase III trials of targeted agents (cetuximab,

bevacizumab, R115777) combined with gemcitabine have essentially shown no benefit.<sup>7-</sup>  
<sup>9</sup> Several of the newer-generation anti-vascular agents (VEGF-trap, Axitinib) are being evaluated in ongoing phase III trials.

Emerging points of consensus over the last few years in treating pancreatic cancer are: (1) Increasing focus on the basic science and pathogenesis of pancreatic cancer to provide new therapeutic leads. The older era of empiricism and serendipitous drug development has yielded the limited, albeit real, gains observed to date. In parallel, biomarker discovery may assist the platform of truly targeted approaches and subpopulation identification for tailoring therapeutics; (2) Recognition of the greater need for preclinical models that more reliably mimic the genetic complexity and spectrum of human pancreatic neoplasia. While the limitations of such approaches have been well elucidated, they provide a platform for validation of pathways, biomarker identification and some broad surrogacy for the in vivo setting; (3) From the clinical trial design perspective, consolidated opinion suggests moving away from a gemcitabine backbone; either larger phase II trials or more randomized phase II designs to try and overcome issues related to patient selection and the heterogeneity of the disease; segregation of locally advanced and metastatic disease patients in separate studies; firmer signals before effecting a transition from a phase II to a phase III trial.

In the short-term, expectations for advances in pancreatic adenocarcinoma therapy are reserved, with most progress likely to be made in therapy refinement and patient selection. However, it is reasonable and realistic to surmise that major progress in this disease will evolve as the fundamentals of the molecular biology of pancreatic adenocarcinoma continue to be unraveled, as the infrastructure for translational research is strengthened with new preclinical models, and with recognition of the prerequisite requirement for intensive cross-disciplinary collaboration.

## References

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