Pancreatic Cancer at an Inflection Point;

An investor perspective from the BlueBox Precision Medicine Fund

Introduction: The Transformative Promise of Precision Medicine

Precision medicine — the practice of targeting the specific molecular drivers of disease rather than its symptoms — has gradually been growing in breadth of application and effectiveness. That is the underlying basis for the BlueBox Precision Medicine fund strategy and our belief that a new generation of progress is well underway in medical science.

This paper examines recent developments that we believe represent a genuine inflection point in oncology, particularly in pancreatic cancer, and it finishes with a note of reflection on the last 17 years and expectations for the future.

ASCO 2026: A Landmark Year

Each year, the Annual Meeting of the American Society of Clinical Oncology (ASCO) serves as the most significant gathering in global oncology, drawing over 30,000 clinicians, scientists, industry partners and investors to review the most consequential clinical data. The 2026 meeting will be recalled as marking a step change in what is possible in pancreatic cancer.

Among the presentations that defined the conference, none attracted more attention than the plenary data from Revolution Medicines on its RAS inhibitor programme in pancreatic cancer. The results were received with a spontaneous standing ovation: a rare occurrence at a scientific conference, and one that speaks to the profound importance of what was shown.

Revolution Medicines and the KRAS Breakthrough: RESOLUTE-302

The data presented for Revolution Medicines' RAS inhibitor, daraxonrasib (RMC-6236) in second-line pancreatic ductal adenocarcinoma (PDAC) in the phase 3 RESOLUTE-302 clinical trial was outstanding.

Pancreatic cancer has for many years been one of the most treatment-resistant malignancies in oncology. Median overall survival for previously untreated patients (first line setting) is 12 months and in the second line setting just six months, and no drug has demonstrated a transformative improvement against this benchmark.

The RESOLUTE-302 data showed approximately a doubling of median overall survival — from roughly six months to over thirteen months.

More than 90% of pancreatic cancers are driven by mutations in the RAS family of proteins — predominantly in the KRAS subtype— a protein long considered undruggable due to the absence of a suitable binding pocket. Revolution Medicines has succeeded in developing a compound that inhibits

RAS signalling sufficiently but also avoids too much toxicity in normal cells. This is the first time that a RAS inhibitor has demonstrated substantial survival benefit across an unselected population in this disease. Because the drug targets the root cause of the cancer, rather than a downstream pathway, it reaches the fundamental driver, and the clinical outcomes reflect that.

So, what for the future? Clinical trials are under way evaluating daraxonrasib in first-line PDAC, both as a single agent and in combination regimens. Given the strength of the data observed in a heavily pre-treated population, it is reasonable to expect that earlier use — in patients with less prior treatment— will yield at least equivalent benefit. It is plausible that first-line use could extend survival to two years or more. The RESOLUTE-302 results are therefore just a starting point.

Revolution Medicines also has additional RAS pathway inhibitors in development. This includes compounds targeting several specific KRAS mutations as well as a next-generation version of daraxonrasib. These may further expand the benefit, improve tolerability or increase the duration of benefit by dealing with resistance.

The Next Frontier: PRMT5 Inhibition + RAS Inhibitors

Shortly after ASCO, further data emerged that reinforces the view that the RAS inhibitor breakthrough is the beginning of a broader wave of innovation in pancreatic cancer.

Approximately 30% of pancreatic cancers carry a deletion in the MTAP gene. This deletion renders cancer cells sensitive to inhibition of a key enzyme, PRMT5. Critically, healthy cells that retain MTAP are largely unaffected by PRMT5 inhibition — a property known as synthetic lethality, and one that offers a highly targeted therapeutic window.

Phase one data recently released by Tango Therapeutics was striking. It evaluated the combination of a RAS inhibitor (Revolution Medicines' daraxonrasib) with its PRMT5 inhibitor in MTAP-deleted pancreatic cancer. The objective response rate exceeded 90%, and the six-month progression-free survival rate was also above 90%. When compared with phase one data for daraxonrasib as a single agent, the combination appeared to more than double the response rate and improve six-month progression-free survival by roughly 1.4x.

These figures must be contextualised carefully. Phase one data is preliminary, reflects small and selected patient populations, and is not yet subject to the rigorous analysis of a randomised trial. Nonetheless, results of this magnitude have not previously been observed at this stage of development in pancreatic cancer. The data warrant serious attention and close follow-up as the programme advances.

What this combination illustrates, more broadly, is the way in which one foundational innovation can unlock a cascade of subsequent advances. The successful targeting of KRAS creates the basis for rational combination strategies, each addressing a defined molecular subgroup. This is the mechanism by which precision medicine generates compounding clinical progress — and, over time, compounding value for investors. It is also possible that, within a relatively near horizon, chemotherapy-free treatment regimens for subgroups of pancreatic cancer patients could be within reach — an advance that would have been considered implausible only a few years ago.

Broadening KRAS benefit: Colorectal and Lung Cancer

KRAS mutations are also present in 25-30% of lung cancer and in 40% of colorectal cancer. KRAS inhibitors specific to certain mutations have already been approved in these areas e.g. Amgen's *Lumakras* and Bristol Myers Squibb's *Krazati*. However, these are constrained by toxicity which limits combinations and relatively short-lived benefit due to resistance.

We have already seen some data with Revolution Medicine's agents in these tumour types and daraxonrasib is in a phase 3 study for second line non-small cell lung cancer, with data due in 2027/28. However, we are eagerly awaiting more data, including as combinations, which are critical in both tumours. We expect updates on development plans for both by the end of 2026.

The Broader Landscape: Seventeen Years of Progress

This year's ASCO prompted us to reflect on the state of the field when members of our team first attended the conference, approximately seventeen years ago. The clinical results we followed then were barely positive, and the clinical benefit to patients was, in most cases, marginal. The transformation that has occurred since then, due to the combined advance of targeted precision medicines and immunotherapy across multiple cancer types and stages of disease has been substantial.

Improvements have been recorded across a wide range of tumour types. Diseases that were once managed primarily with broadly cytotoxic chemotherapy are now treated with agents designed around their specific genomic or immunological characteristics. Outcomes in melanoma, lung cancer, certain haematological malignancies, and a growing number of solid tumours have improved measurably. The RAS breakthrough in pancreatic cancer represents the most recent, and in some respects the most significant, addition to that record, because it has been so resistant to prior innovation and its poor natural course.

We continue to anticipate meaningful progress both in disease areas where precision medicine has already established itself and in areas where effective targeted options remain limited. Next-generation precision medicines — compounds that are more selective, more potent, or capable of overcoming resistance to earlier agents — have already and will continue to supersede the first and second generations that established the paradigm.

Improving Cancer Detection: Liquid Biopsy and Early Diagnosis

Progress in treatment is only one dimension of the oncology landscape. Detection is equally consequential: a drug that is highly effective against early-stage disease offers limited benefit if the cancer is not identified until it has progressed to an advanced stage.

Liquid biopsy — the analysis of circulating tumour DNA (ctDNA) and other tumour-derived material from a standard blood sample — is a rapidly developing field with the potential to materially change the stage at which cancers are diagnosed. Blood-based screening tests for colorectal cancer, including approved products such as Guardant Health's Shield, are already commercially available and

demonstrate reasonable clinical sensitivity, though not without limitations. The technology is being extended to a wider range of tumour types, and early multi-cancer early detection studies have shown promising, if not yet definitive, results.

We expect that, over the coming years, improvements in testing sensitivity, specificity, and the informatics required to interpret ctDNA signals will expand the clinical utility of blood-based screening. If cancer can be identified more reliably at earlier stages, the downstream benefit in terms of patient outcomes could represent another step change in survival statistics at the population level. This remains an area of active investment interest for the fund.

Our Investment Conviction

The BlueBox Precision Medicine Fund invests in companies developing and enabling precision medicines, with a focus on identifying meaningful innovations at relatively early stages and following them through to commercialisation i.e. sustainable value creation. Revolution Medicines is a textbook example of this, where we first invested at c.$25/sh and following these successful results it now trades at c.$150/sh. We do not actively develop drugs or diagnostics, but we consider our role in supporting those that do to be a privilege, and we look forward to backing more of these innovations for the Fund's and our clients' benefit.

Our conviction in this space has strengthened over the course of the past several years. We have seen meaningful growth in the drug developers and enablers, and we expect plenty of future growth. Precision medicine is expanding into new disease areas and advancing deeper into existing ones and the emergence of next-generation compounds that improve on first-generation agents extends the investment opportunity.

The data presented at ASCO 2026, and the subsequent Tango Therapeutics combination results, illustrate a key dynamic: when the molecular biology of a disease is genuinely understood, and when a drug can reach and inhibit its core driver, outcomes change in ways that were previously not achievable.

Seventeen years of attending ASCO has afforded our team a particular vantage point on the pace and character of progress in oncology. The science moves unevenly with periods of incremental advancement punctuated by results that genuinely redefine what is possible. The data presented at ASCO 2026, and the early combination signals that followed it, belong in that second category.

The BlueBox Precision Medicine Fund is committed to remaining at the forefront of that opportunity.