Cracking the "undruggable": Landmark trial sparks hope for fighting "King of Cancers"

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An experimental targeted therapy has delivered a historic breakthrough against the "King of Cancers," doubling median survival and reducing the risk of death by 60% with significantly fewer side effects than conventional chemotherapy.

The results were announced to a packed room at the American Society of Clinical Oncology (ASCO) annual meeting in Chicago, Illinois, on 31 May. As the final survival figures flashed onto the massive screens, thousands of oncologists, researchers, and industry physicians rose to their feet. The

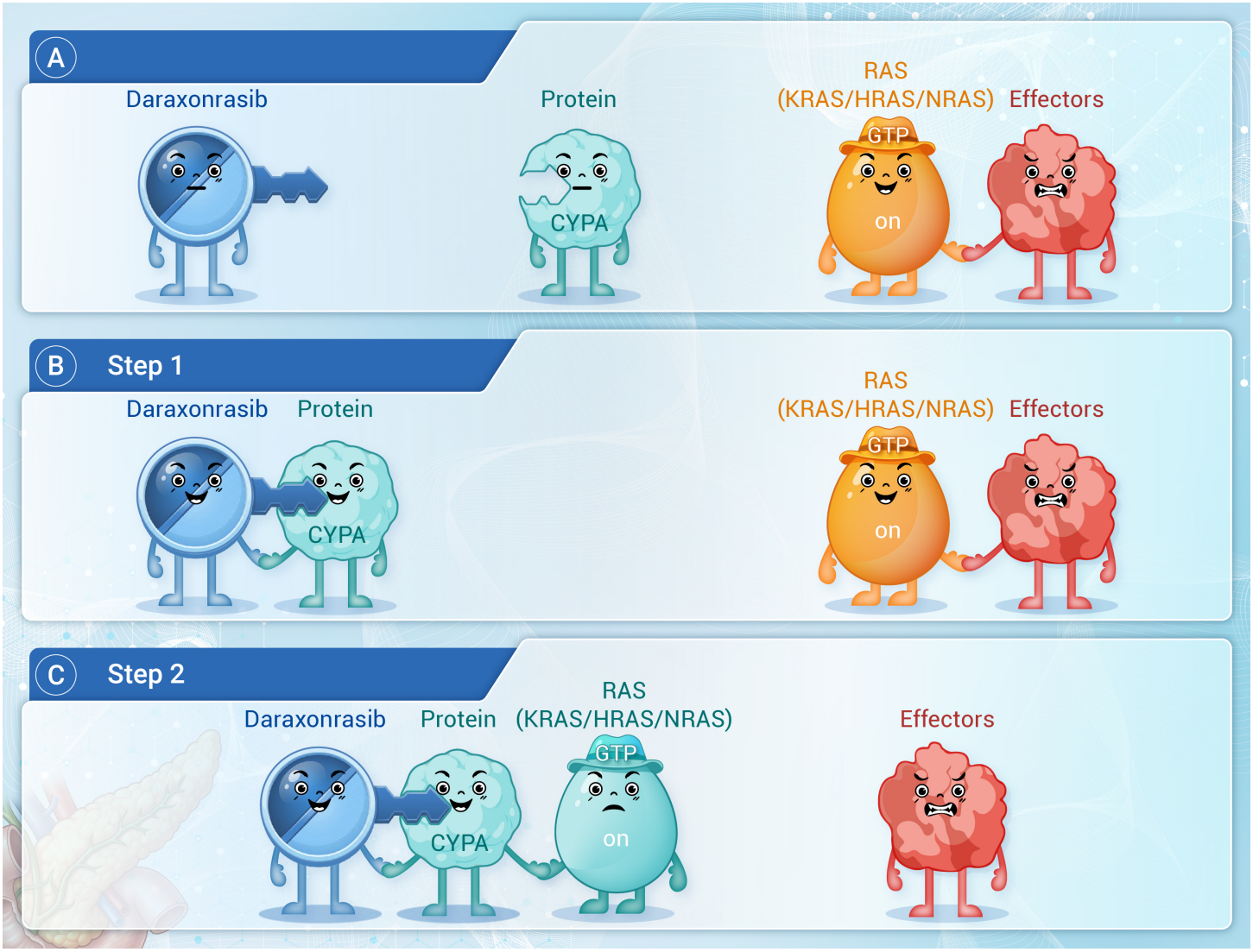

Figure 1. The mechanism of daraxonrasib: Disabling the cancer driver.

standing ovation was immediate, accompanied by a wave of cheers that cascaded through the auditorium for more than 40 seconds. It was only the second time in his career, one attending oncologist remarked, that he had witnessed an entire ASCO audience rise to its feet for a clinical study.

The source of this rare collective euphoria is an experimental oral drug called daraxonrasib. Developed by Revolution Medicines based in Redwood City, California, the small molecule has achieved what many in the field long deemed impossible: successfully breaching the defenses of a tumor driver once branded categorically "undruggable."

In a newly published phase 3 clinical trial, the results of which simultaneously topped the *New England Journal of Medicine*,[1] daraxonrasib precisely doubled the median overall survival of patients with previously treated, metastatic pancreatic ductal adenocarcinoma (mPDAC) compared to standard chemotherapy, charting an unprecedented 13.2 months of survival.

The breakthrough has sent shockwaves far beyond the clinic. On Wall Street, the market reacted with unbridled enthusiasm, sending Revolution Medicines' stock soaring by nearly 500% over the course of a single year—comfortably outperforming even the highly hyped artificial intelligence sector. For a biopharmaceutical enterprise that has yet to achieve large-scale commercial profitability, such a stratospheric valuation highlights a simple calculation known well by investors: conquering the "King of Cancers" unlocks a global therapeutic market worth hundreds of billions of dollars.

RAS: LOCKED INTO OVERDRIVE

To appreciate the magnitude of daraxonrasib's triumph, one must look at the brutal landscape of pancreatic cancer. Long carrying the ominous moniker "King of Cancers," pancreatic malignancies are notoriously stealthy. Over 80% of patients are diagnosed only after the disease has reached an advanced, metastatic stage. Worse still, these tumors have proven aggressively recalcitrant to conventional chemotherapy and radiotherapy. Historically, once first-line chemotherapy fails, advanced patients face a bleak prognosis, surviving an average of just six to seven months, while the overall five-year survival rate has stubbornly plateaued around 10% for three decades.

At the heart of this lethality is a family of molecular on–off switches known as RAS proteins, which normally control cell growth and division. In more than 90% of pancreatic cancer cases, specific genetic mutations lock these switches permanently in the "on" position, driving malignant cells into uninhibited, wild proliferation.

For decades, resolving this bottleneck was the ultimate holy grail for oncology chemists, yet RAS earned a reputation as a molecular fortress. Unlike typical drug targets, which feature deep, accommodating pockets where small-molecule inhibitors can nestle and disrupt activity, the surface of a RAS protein is unhelpfully, deceptively smooth—often described by researchers as resembling a polished egg. Unable to find a structural foothold, the world's premier drug design teams routinely hit a brick wall.[2]

While the US Food and Drug Administration approved the very first anti-RAS drug in 2021, that agent was a highly specialized tool tailored to a single, specific mutation (G12C) in just one member of the protein family, called KRAS. This narrow utility meant it benefited only a sliver of cancer patients, and even then, targeted tumors rapidly developed resistance, bypassing the block.

Daraxonrasib,[2] however, deploys a radically different strategic blueprint. Rather than trying to squeeze into a non-existent pocket on its own, the drug utilizes a multi-selective "RAS(ON)" inhibitor mechanism (Figure 1). It essentially recruits an abundant cellular chaperone protein to form a tri-complex, locking all three major members of the RAS family (KRAS, NRAS, and HRAS) in their active, GTP-bound states. By shutting down the entire family simultaneously, the drug forces the rogue, stuck-in-on switches to go dark.

SHIFTING THE SURVIVAL CURVE

The clinical dividend of this structural ingenuity became clear in the phase 3 data reported at ASCO. Among patients with previously treated mPDAC, the survival curves shifted dramatically. Patients treated with daraxonrasib achieved a median overall survival of 13.2 months, a profound leap from the 6.6-month median survival seen in historical cohorts relegated to standard chemotherapy. The hazard ratio for death was an astonishing 0.40, representing a 60% reduction in the risk of death. Furthermore, nearly a third of the advanced patients experienced a substantial, measurable shrinkage of their tumors.

Beyond giving patients more time, the targeted agent also delivered a vastly superior quality of life compared to the harrowing toll of cytotoxic regimens. Traditional chemotherapy is synonymous with systemic misery—severe nausea, vomiting, debilitating fatigue, hair loss, and peripheral nerve damage. Because daraxonrasib is an oral, once-daily medication, it bypasses the grueling routine of infusion chairs.

The study noted that while treatment-related adverse events occurred in most patients, they were predominantly manageable, lower-grade side effects like skin rashes and mouth inflammation. Grade 3 or higher adverse events occurred in 30% of the participants. Stripped of the systemic toxicity of chemotherapy, many trial participants reported a striking reduction in cancer-related pain and a renewed vitality. Clinical coordinators noted that several advanced patients felt well enough to resume long-distance travel, return to hobbies, and re-establish normal daily routines with their families.

EXPANDING THE PRECISION FRONTIER

Despite the justified jubilation, researchers are maintaining a sober outlook: 13.2 months is a monumental milestone, but it is not a cure. Advanced pancreatic cancer remains a lethal adversary. However, what daraxonrasib has fundamentally achieved is transforming a near-hopeless death sentence into a medically manageable condition. The drug is currently under expedited regulatory review by the FDA, having secured the coveted Breakthrough Therapy Designation, with commercial approval anticipated as early as this year.

For the wider field of oncology, the smashing of the RAS barrier acts as a powerful proof of concept. RAS mutations are not unique to pancreatic tumors; they drive approximately 40% of colorectal cancers and a massive subset of non-small-cell lung cancers. Clinicians are already actively expanding trials to test daraxonrasib against these targets.

Furthermore, the path to unlocking the drug's full therapeutic potential lies in combination strategies. "Sometimes the very first molecule just shows that it's possible," says Kevan Shokat, a pioneer in chemical biology at the University of California, San Francisco. Shokat points out that pairing daraxonrasib with single-mutation inhibitors, immunotherapies, cancer vaccines, or specialized antibody-drug conjugates could prevent the onset of drug resistance and yield even more durable, long-lasting remissions.

Meanwhile, this success has injected fresh momentum into the hunt for other historically "undruggable" oncology targets, including MYC, p53, and β-catenin. Early-stage clinical candidates—such as the MYC-blocking mini-protein OMO-103, the p53-restabilizing agent rezatapopt, and the β-catenin-selective peptide zolucatetide—have shown initial biological activity and tolerability in small cohorts. Although these data are preliminary, they offer a glimpse that rational targeting of these long-intractable nodes may eventually become feasible.

The ultimate takeaway from daraxonrasib's breakthrough is a profound psychological and technical shift. Over the next decade, the frontier of precision medicine will not merely expand by adding derivative iterations of existing therapies. Instead, the real revolution will be the systematic, one-by-one dismantling of cancer's most untouchable fortresses, bringing the once "undruggable" dark matter of oncology fully into the light.

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DECLARATION OF INTERESTS

The author declares no competing interests.