CITELINE CLINICAL

White Paper

Redefining Pancreatic Ductal Adenocarcinoma Survival: How Targeted Precision Medicine Is Breaking the KRAS Barrier

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Table of Contents

The evolution of RAS-targeted therapies in PDAC 3

The burden of pancreatic cancer 4

The role and challenge of RAS in PDAC 5

The evolution of RAS-targeted therapeutics in PDAC 8
- Mutant-selective KRAS inhibitors 8
- Pan-KRAS inhibitors 9
- Pan-RAS inhibitors 10

Clinical trial landscape and the importance of combination therapies 11
- Mutant-selective KRAS inhibitor trials 11
- Pan-KRAS inhibitor trials 13
- Pan-RAS inhibitor trials 15

A new era in PDAC treatment 17

References 18

About the Author 19

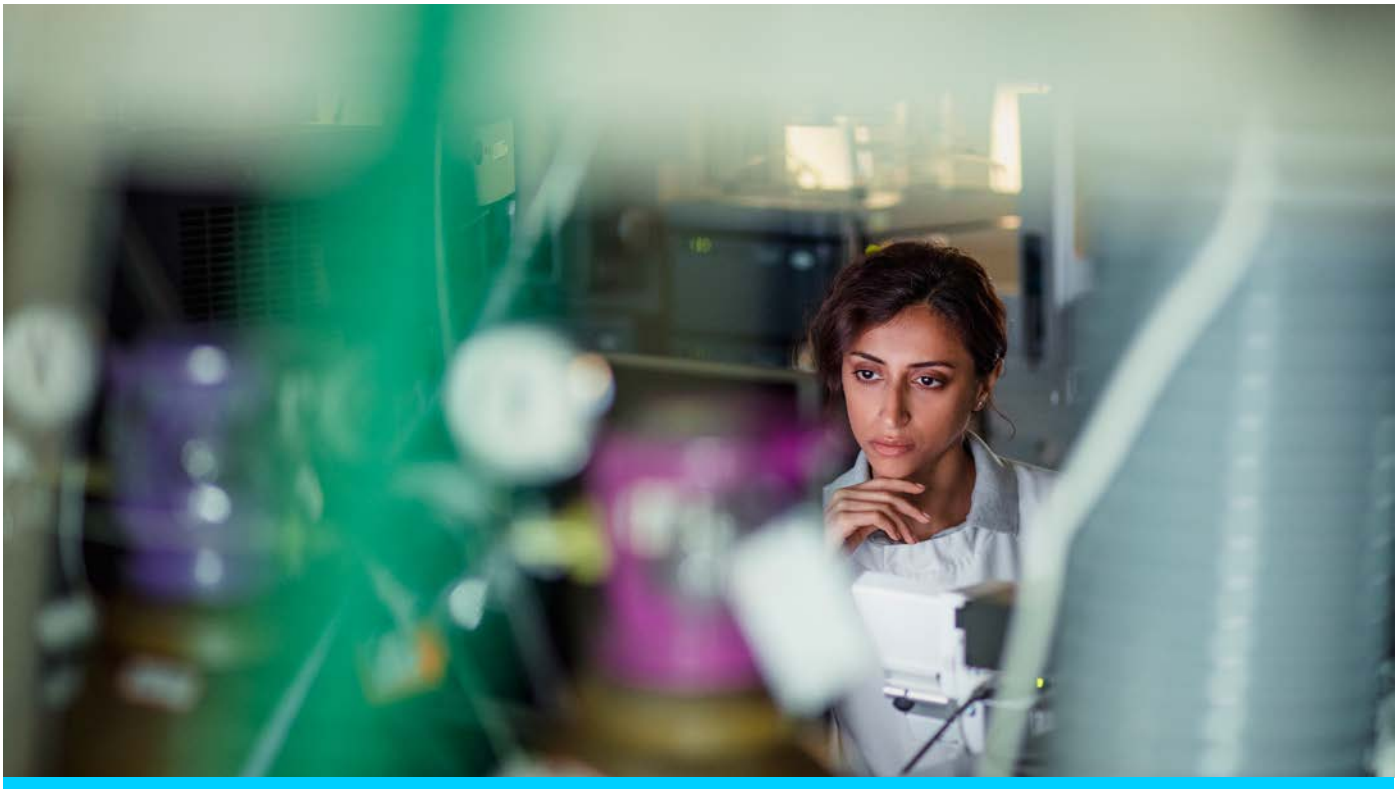
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The evolution of RAS-targeted therapies in PDAC

Pancreatic ductal adenocarcinoma (PDAC), the most prevalent histologic subtype of pancreatic cancer, remains one of the deadliest human malignancies. It is historically difficult to treat because of its aggressive nature and complex biology. PDAC is mainly driven by Kirsten rat sarcoma viral oncogene homolog (KRAS) mutations, which are present in over 90% of all cases, making it one of the most important and promising targets in PDAC research today. For decades, these mutations were deemed highly resistant to therapeutic targeting due to structural constraints, leaving clinicians with limited options and patients with poor prognoses.[1]

In recent years, the therapeutic landscape has reached a turning point, moving away from conventional chemotherapies, which have provided modest benefit,[1] toward novel mutant-specific, pan-KRAS, and pan-RAS inhibitors,[2] many of which, particularly among the pan-KRAS and pan-RAS classes, target KRAS in its active RAS(ON) state. Current drug development is now breaking through the "undruggable" barrier, opening a path toward targeted, combination-based precision medicine that could meaningfully change patient outcomes.[1]

This analysis examines the therapeutic landscape of RAS inhibitors in PDAC, covering the current drug development pipeline, landmark clinical trial data, and the future challenges these novel therapies face. PDAC represents more than 90% of pancreatic cancer cases and is most often referred to simply as "pancreatic cancer" in both clinical and research settings. Therefore, pancreatic cancer and PDAC will be used interchangeably throughout this analysis.

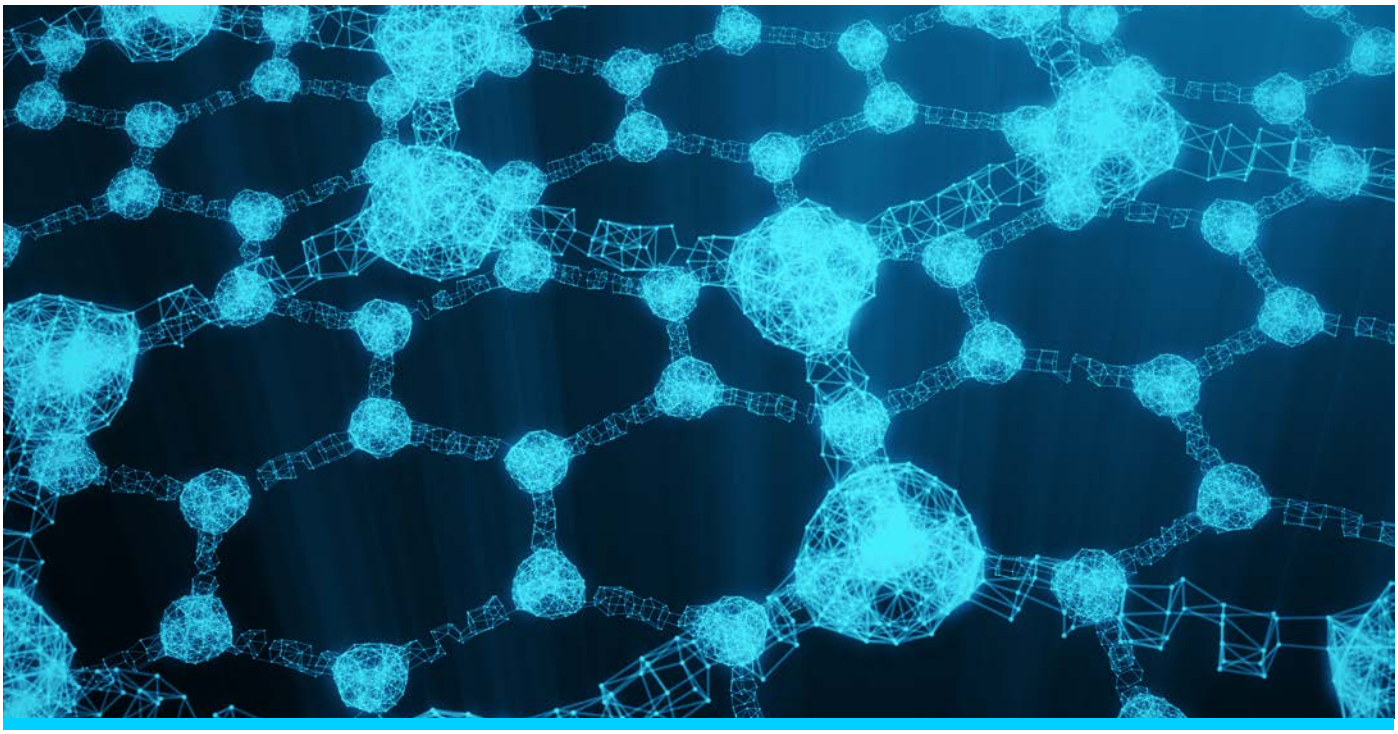


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The burden of pancreatic cancer

Pancreatic cancer is one of the deadliest malignancies in oncology, with a five-year survival rate of 13.7%.[3] This poor prognosis is primarily driven by difficulties in diagnosis, the underlying aggressive nature of this disease, and the historically sparse systemic treatment options available. In the US, pancreatic cancer ranks as the third-leading cause of cancer-related death, trailing only lung and colorectal cancers.[4] In 2026, this disease is projected to account for an estimated 67,530 new diagnoses and more than 52,740 deaths in the US.[4]

Traditionally, standard treatment options for pancreatic cancer were limited to surgical resection for a small minority of patients and broad cytotoxic systemic therapies. According to Surveillance, Epidemiology, and End Results (SEER) data, only 15% of pancreatic cancer cases are diagnosed at a localized stage, while 28% present with regional disease and 51% with distant disease, leaving curative surgical resection an option for only a small percentage of patients.[3] Consequently, the vast majority must rely solely on systemic therapies, which drastically limits the available clinical interventions. Per Citeline's Datamonitor Healthcare Disease Analysis: Pancreatic Cancer, the traditional standards of care, namely multi-agent regimens like FOLFIRINOX and gemcitabine plus nab-paclitaxel, provide modest survival benefits. These aggressive cytotoxic therapies carry severe, life-altering toxicities and typically yield a median overall survival (OS) of less than one year for metastatic disease; 11.2 months for FOLFIRINOX and 7–10 months for gemcitabine plus nab-paclitaxel. For most PDAC treatment history, there has remained an overwhelming, unmet medical need for highly precise, non-cytotoxic therapies that are capable of directly disrupting KRAS, the core oncogenic driver behind the disease's aggressive nature.

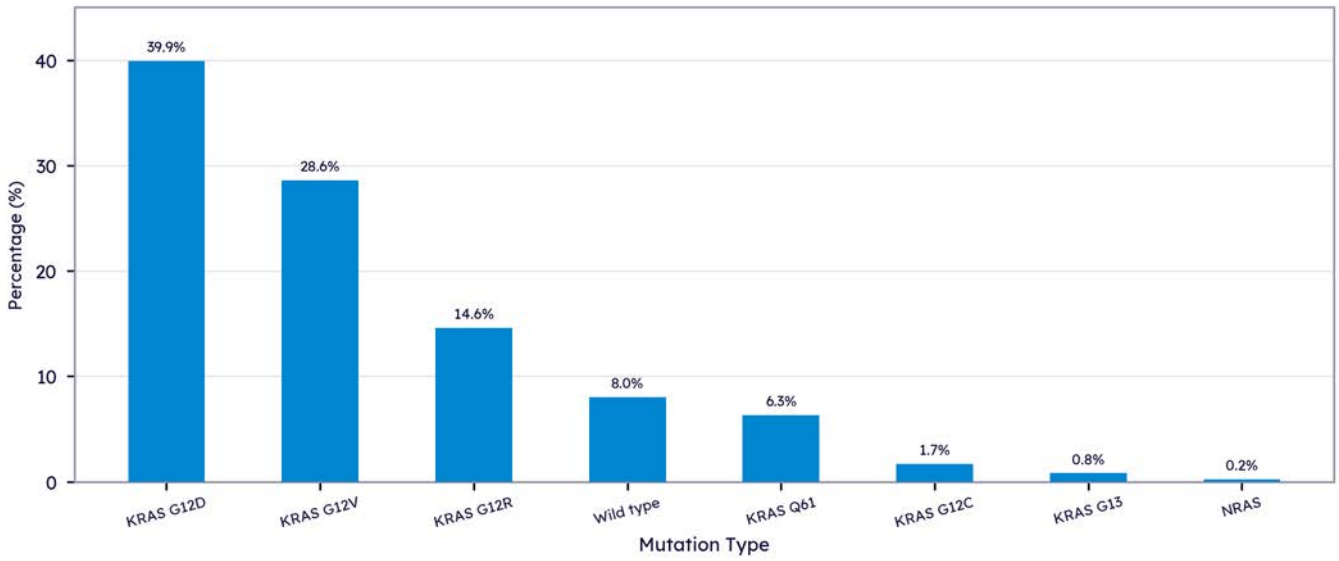


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The role and challenge of RAS in PDAC

The rat sarcoma virus (RAS) oncogene, specifically the KRAS viral oncogene homolog, is the primary driver of PDAC, playing an essential role in its development, progression, and survival. This mutation is present in more than 90% of PDAC cases, with the most common KRAS mutation occurring at the G12 position (~86%).[5,6] The KRAS mutation spectrum in PDAC is spread across different single-nucleotide variants. As shown in Figure 1, the G12D variant is the most dominant, accounting for ~40% of tumors, followed by G12V (~29%) and G12R (~15%).

Figure 1: Prevalence of KRAS mutation subtypes in PDAC



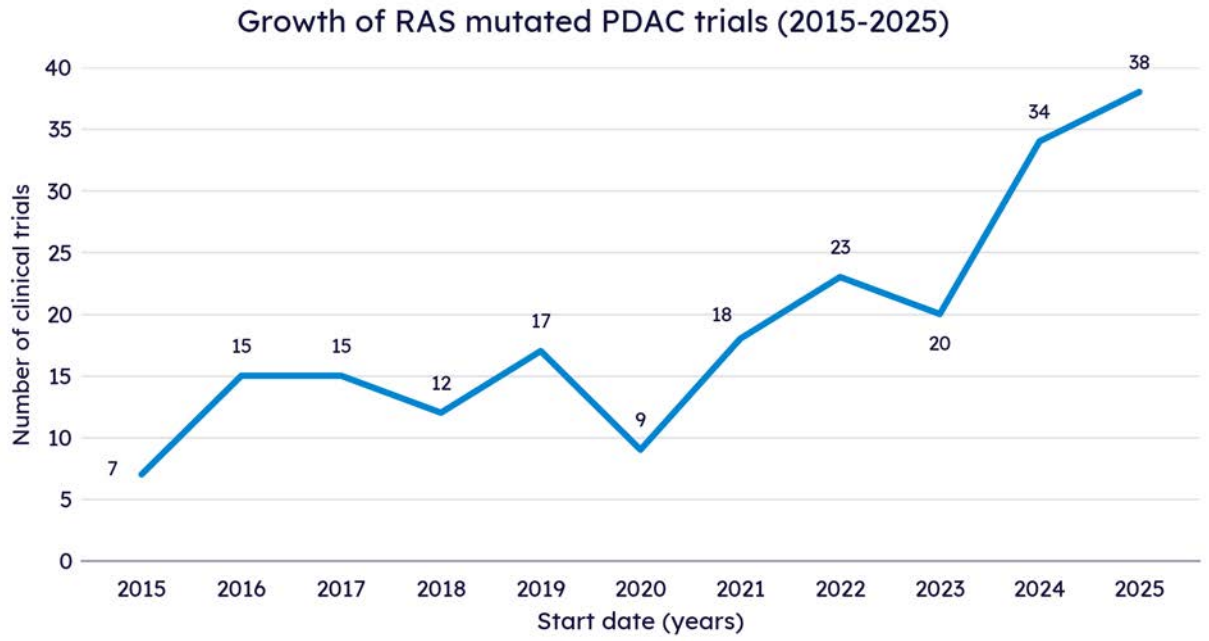
Source: Revolution Medicines[5]

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KRAS proteins are essentially molecular on/off switches that help control cell growth and division. When KRAS is mutated, it can get stuck in the "on" position, constantly signaling cells to grow. Effectively targeting this switch requires a drug that binds tightly to a pocket on the protein's surface — but the challenge is that the surface of KRAS proteins is unusually smooth and shallow, lacking such accessible binding pockets. Inhibitors that bind to RAS in its active, guanosine triphosphate (GTP)-bound state and block downstream signaling needed for tumor growth are referred to as RAS(ON) inhibitors. RAS(OFF) inhibitors, by contrast, work by locking on RAS while it's in its inactive, guanosine diphosphate (GDP)-bound state and holding it there, preventing it from flipping back to its active "on" state.[1]

For decades, RAS-mutant PDAC was viewed as an "undruggable" target with no approved mutation-targeted therapies. Because RAS drives PDAC growth, it has represented a long-sought target for novel therapeutics, offering an extraordinary opportunity to address a devastating unmet need. This clinical focus is evident in the overall increase in the number of RAS-mutant PDAC clinical trials from 2015 to 2025 (Fig. 2). There has also been a surge in RAS inhibitors under active development across a broad spectrum of indications over the last several years (Fig. 3). As of September 2026, there were 206 RAS inhibitors in active development, with 67 being developed for pancreatic cancer (Pharmaprojects, September 2026). As a result, this surge in research has set the stage for a new era, shifting the clinical focus toward rapidly evolving RAS-targeted therapies for PDAC.

Figure 2: Growth of RAS-mutated PDAC trials by initiation date, 2015–2025

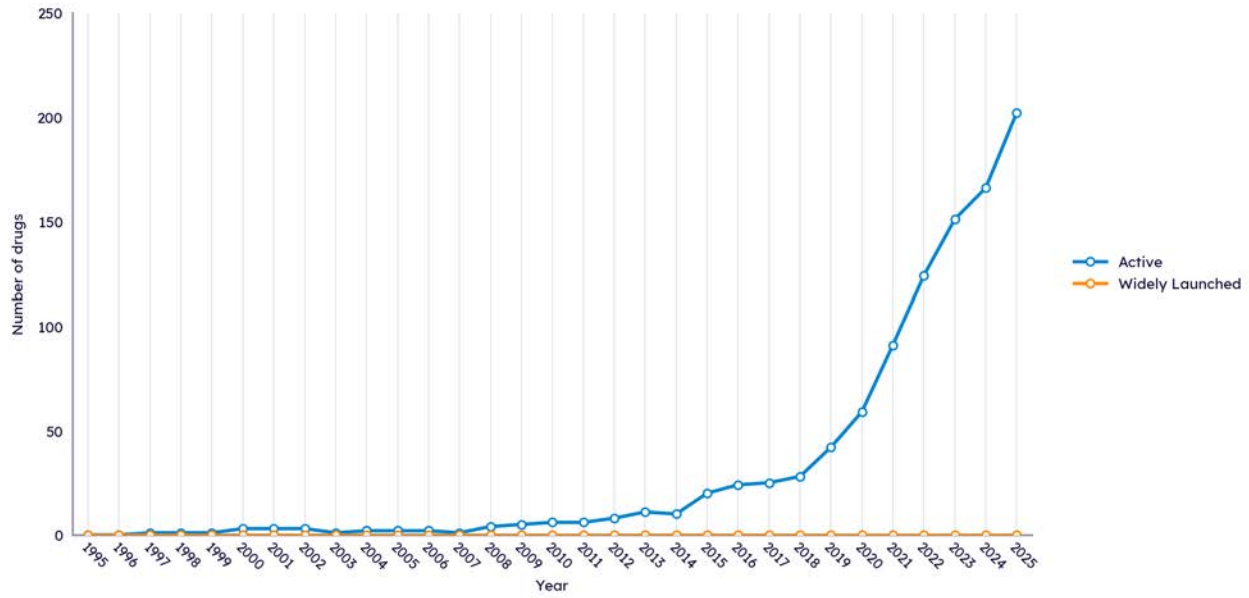


Note: Trial years are based on trial initiation start dates. Trials without a disclosed start date are excluded.

Source: Trialtrove, September 2026

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Figure 3: Global development trends of RAS inhibitors, across indications



Source: Pharmaprojects, September 2026



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The evolution of RAS-targeted therapeutics in PDAC

Targeted therapy is a type of cancer treatment that acts on specific molecular features, alterations, mutations, or substances present in or on cancer cells and typically does not damage normal healthy cells, unlike traditional cytotoxic chemotherapy.[7] Historically, KRAS has been considered "undruggable" due to its nearly spherical and flat surface structure and the inability of drugs to compete with GTP, which strongly binds to KRAS, keeping it continuously in the "on" position.[1] Direct therapeutic targeting of KRAS has transitioned from a long-standing challenge into a clinical reality.

In 2013, researchers discovered a small molecule that engaged the inactive, GDP-bound state of KRAS G12C by targeting a shallow, previously unrecognized surface groove: the switch II pocket.[8] Then, in 2018, the first KRAS G12C-targeted therapies entered clinical development. In May 2021, the FDA granted accelerated approval to the first of these therapies, sotorasib, for previously treated KRAS G12C-mutant advanced or metastatic non-small cell lung cancer (NSCLC), and, roughly a year and a half later, the second KRAS G12C-specific covalent inhibitor, adagrasib, was granted its own accelerated approval.[8] The discovery of these inhibitors expanded the possibilities for targeting KRAS and laid the groundwork for a broader class of investigational agents now being evaluated in KRAS-mutated PDAC. These novel KRAS inhibitors can be widely grouped into three classes based on target selectivity: mutant-selective inhibitors, pan-KRAS inhibitors, and pan-RAS inhibitors.[2]

Mutant-selective KRAS inhibitors

Mutant-specific KRAS inhibitors act on a single KRAS mutation, such as KRAS G12C or G12D, while largely sparing wild-type RAS isoforms, which limits off-target toxicities.[2] While the approval of mutant-specific KRAS G12C inhibitors (RAS(OFF)) was a landmark achievement in oncology,[8] these inhibitors carry two major limitations in PDAC: allele instability that drives rapid drug resistance,[1] and a narrow addressable population, as only ~1.7% of PDAC tumors harbor the KRAS G12C mutation.[5] KRAS G12D and G12V, the most common G12 variants in PDAC, currently have 21 mutant-selective drugs in PDAC clinical trials: 20 KRAS G12D and one KRAS G12V inhibitor (Pharmaprojects, September 2026). The majority of KRAS G12D inhibitors are currently in early phase trials, but six assets are in late-stage trials (Table 1). The one KRAS G12V inhibitor, RMC-5127 being developed by Revolution Medicines, is in a Phase I trial in the US.

Table 1: Mutant-specific KRAS G12D inhibitors in Phase III PDAC trials

Drug name	Most advanced status in PDAC	Trial location	Trial sponsor
DN-022150	Phase III	China	Jiangxi Qingfeng Pharmaceutical/Jiangxi Kvvit Pharmaceutical
GFH375	Phase III	China	GenFleet Therapeutics
HRS-4642	Phase III	China	Jiangsu Hengrui Pharmaceuticals
INCB161734	Phase III	Global	Incyte Corporation
setidegrasib	Phase III	Global	Astellas Pharma
zoldonrasib	Phase III	Global	Revolution Medicines
	Phase III	USA	

Source: Pharmaprojects and Trialtrove, September 2026

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Pan-KRAS inhibitors

Pan-KRAS, or isoform-selective, inhibitors act on multiple KRAS variants and target wild-type KRAS but show negligible activity against NRAS and HRAS isoforms.[2] Because KRAS mutations drive over 90% of PDAC tumors,[1,6] these isoform-selective drugs hold therapeutic potential for the majority of PDAC patients. Currently, 14 pan-KRAS inhibitors are undergoing clinical trials in PDAC to evaluate their safety and efficacy (Pharmaprojects, September 2026). The majority of these drugs are in Phase I or II trials, but there are two in late-stage studies, as shown in Table 2.

Table 2: Pan-KRAS inhibitors in late-stage PDAC trials

Drug name	Most advanced status in PDAC	Trial location	Trial sponsor
JAB-23E73	Phase III	China	Jacobio Pharmaceuticals
SIL-204	Phase II/III	Global	Silexion Therapeutics
BLU-924	Phase I/II	Spain, USA	Sanofi/Blueprints Medicines
HBW-012462	Phase I/II	China	Chengdu Hyperway Pharmaceutical
ABSK-211	Phase I	China, USA	Abbisko Therapeutics
ALTA-3263	Phase I	USA	Alterome Therapeutics
AMG-410	Phase I	Global	Amgen
AN-9025	Phase I	China, USA	Adlai Nortye
ASP-5834	Phase I	Global	Astellas Pharma
BBO-11818	Phase I	Global	BridgeBio Oncology Therapeutics
ERAS-4001*	Phase I	USA	Erasca
KST-6051	Phase I	USA	Kestrel Therapeutics
LY4066434	Phase I	Global	Eli Lilly
PT-0511	Phase I	South Korea, USA	PAQ Therapeutics

*ERAS-4001 is under development and in a Phase 1 first-in-human (FIH) trial for KRAS mutant solid tumors. PDAC is not listed as a specific indication in this trial, but we are including it in this list as preclinical data suggests development in PDAC.

Source: Pharmaprojects and Trialtrove, September 2026

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Pan-RAS inhibitors

The final strategy for targeting RAS proteins is the use of multi-specific or pan-RAS inhibitors. These inhibitors offer the broadest coverage by simultaneously inhibiting mutant and wild-type forms of all RAS family members (KRAS, NRAS, and HRAS).[1,2] There are presently eight assets in PDAC clinical trials, one being the recently approved drug, daraxonrasib (marketed as Rasonque), as reflected in Table 3.

Table 3: Pan-RAS inhibitors in PDAC clinical trials

Drug name	Most advanced status in PDAC	Trial location	Trial sponsor
daraxonrasib (Rasonque)	Registered*	Global**	Revolution Medicines
GFH276	Phase II	China	GenFleet Therapeutics
ERAS-0015	Phase I/II	China	Guangzhou Joyo Pharma***
AN4035	Phase I	Australia, China, USA	Adlai Nortye
HZ-V055	Phase I	China	Hangzhou Hezheng Pharmaceutical
RO-7673396	Phase I	Global	Roche
SIM0532	Phase I	China	Simcere Pharmaceutical Group
TEB-17231	Phase I	China	Shanghai Yingli Pharmaceutical
	Phase I	USA	

*In USA

**Pivotal RASolute 302 trial

***Erasca has licensed worldwide rights for ERAS-0015, but Guangzhou Joyo is the sponsor of this trial

Source: Pharmaprojects and Trialtrove, September 2026

Daraxonrasib is the clear frontrunner in this space, serving as the first-in-class, multi-specific oral RAS(ON) inhibitor with a tri-complex mechanism of action. Inside the cell, this drug binds to cyclophilin A to form a binary complex, which then selectively locks onto the active RAS(ON) state, preventing their interaction with downstream effectors and inhibiting RAS signaling, causing the pancreatic cancer cells to slow down or stop growing. Although this drug targets PDAC in a way never done before and represents a groundbreaking leap forward in PDAC treatment, direct RAS inhibition still contends with resistance mechanisms that persist even in its broadest, pan-RAS form.[9]

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Clinical trial landscape and the importance of combination therapies

Clinical trials targeting KRAS mutations in PDAC are gaining momentum as new targeted inhibitors turn once historically difficult-to-treat cancer cells into active treatment targets. This growing landscape is currently defined by three distinct approaches, as explained in the previous section: mutant-selective KRAS inhibitors, pan-KRAS inhibitors, and pan-RAS inhibitors. However, turning these targeted approaches into durable clinical benefit faces a recurring obstacle: resistance to single-agent treatment.[9] Pancreatic tumors are especially skilled at getting around monotherapy, whether through rapid feedback reactivation of the MAPK pathway, the development of secondary RAS mutations, or metabolic rewiring that restores tumor growth.[6,9]

Consequently, the current clinical trial landscape reflects a major shift from broad chemotherapy toward highly personalized, combination-based precision medicine, pairing these novel inhibitors with other therapies, including standard chemotherapies, other targeted agents, or immunotherapies, to address distinct resistance mechanisms and achieve deeper, longer-lasting responses.

Mutant-selective KRAS inhibitor trials

Allele-specific strategies designed to optimize target engagement and safety are emerging. The KRAS G12D mutation is the most common KRAS alteration in PDAC, making it a central focus of ongoing therapeutic development.[5,6] This is evidenced by the steady increase in the number of trials targeting KRAS G12D mutated PDAC patients over the last five years (Fig. 4). There are currently more than 50 ongoing trials in this patient population (Trialtrove, September 2026).

Two important ongoing early phase trials are evaluating the drug zoldonrasib (RMC-9805), a key allele-specific KRAS G12D inhibitor, with updated data reported in July 2026 that highlight strong efficacy across two distinct trial settings. In the refractory Phase I RMC-9805-001 trial, zoldonrasib is paired with the pan-RAS inhibitor daraxonrasib in 60 previously treated patients, yielding a 50% overall response rate (ORR) in the second line and a 47% ORR in the third line or later, with disease control rates (DCR) reaching 90% or higher. This all-oral doublet was also well-tolerated. Meanwhile, in the treatment-naive front-line setting, the Phase I/II RMC-GI-102 trial, combining zoldonrasib with standard chemotherapies in 81 patients, demonstrated exceptional early tumor shrinkage: an 82% ORR with modified FOLFIRINOX (mFOLFIRINOX) and a 61% ORR with gemcitabine plus nab-paclitaxel. The chemotherapy combinations showed a manageable safety profile. In September 2026, the FDA granted Breakthrough Therapy Designation to daraxonrasib plus gemcitabine and nab-paclitaxel in first-line metastatic PDAC and this was supported by the data from the RMC-GI-102 trial. These strong early outcomes have led to the immediate advancement of zoldonrasib into global Phase III registrational trials: RASolute 305 and RASolute 309 (Trialtrove, September 2026).

Two additional KRAS G12D assets are advancing close behind. GFH375 (VS-7375), an oral KRAS G12D (ON/OFF) inhibitor developed by GenFleet and Verastem, produced a 40.7% ORR and a 96.7% DCR in a Phase I/II monotherapy trial of 59 evaluable, previously treated PDAC patients in China, with a manageable safety profile. This data supported FDA Fast Track Designation in July 2025 and the initiation of GFH375X1301, an open-label Phase III registrational trial comparing GFH375 monotherapy to

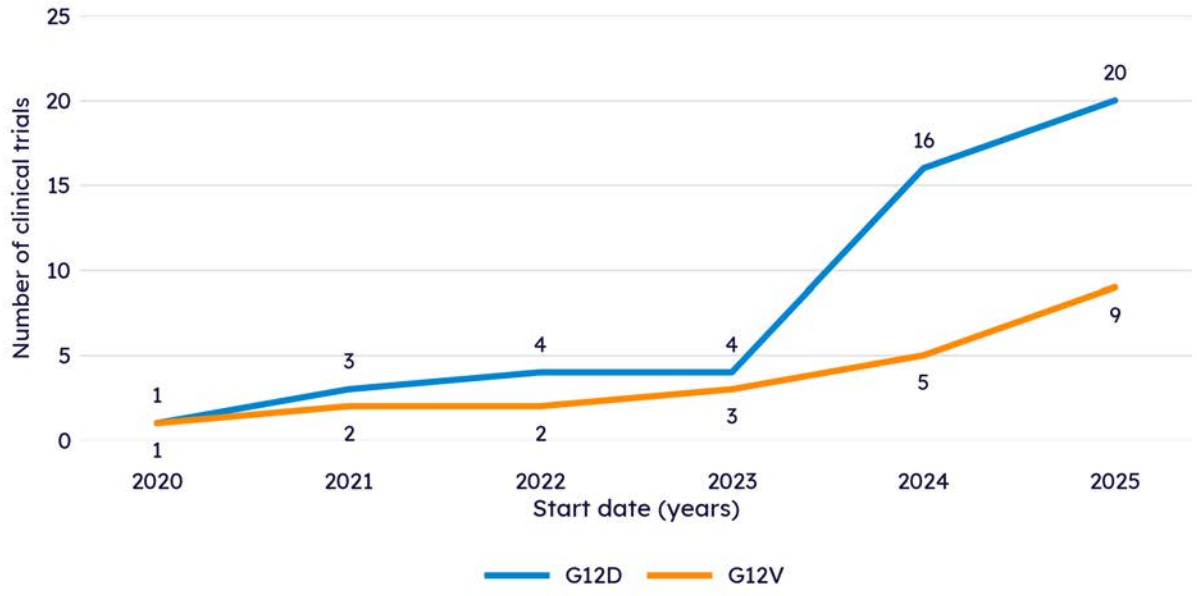
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chemotherapy in roughly 320 second-line-plus PDAC patients, the first-in-world registrational study of an oral KRAS G12D inhibitor in PDAC (Trialtrove, September 2026).

Another key trial to watch is the global registrational Phase III, randomized, double-blind DAWN-303 study, evaluating INCB161734 in previously untreated, KRAS G12D-mutated metastatic PDAC patients, combining investigator-choice of mFOLFIRINOX or gemcitabine plus nab-paclitaxel plus either INCB161734 or placebo across an estimated 588 patients. This pivotal trial builds on an earlier Phase I study (INCB161734-101), in which INCB161734 resulted in a 37% ORR and 78% DCR among 41 patients at the confirmed recommended Phase II dose of 1200mg. It is also important to note that no dermatologic rash or stomatitis was reported, which are primary toxicities associated with pan-RAS inhibition (Trialtrove, September 2026).

Development of KRAS G12V inhibitors has lagged behind G12D, with only one drug currently in an early phase clinical trial. However, there has still been an increase in the number of trials conducted in this population since 2020 (Fig. 4), with over 20 studies currently ongoing. Revolution Medicines is developing RMC-5127 and has announced initial trial data from its ongoing first-in-human RMC-5127-001 study, which is evaluating this investigational drug alone and in combination with either daraxonrasib or cetuximab in patients with KRAS G12V-mutant solid tumors, including PDAC. These results demonstrate that this drug has been well tolerated across all dose levels evaluated to date, with no dose-limiting toxicities reported as of July 20, 2026. Additionally, encouraging preliminary anti-tumor activity was observed across multiple tumor types, including objective responses beginning at the lowest dose level tested (Trialtrove, September 2026).

Figure 4: Trend of PDAC trials in KRAS G12D and G12V mutations (2020–2025)



Note: Trial years are based on trial initiation start dates. Trials without a disclosed start date are excluded. These numbers represent ongoing, terminated, or completed trials that started between 2020 and 2025.

Source: Trialtrove, September 2026

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Pan-KRAS inhibitor trials

Clinical trials evaluating selective pan-KRAS inhibitors represent a strategic shift in the therapeutic management of PDAC. This class of inhibitors addresses the vast majority of PDAC patients whose tumors are primarily driven by the highly prevalent KRAS mutation. Ongoing clinical investigations are comprehensively evaluating both monotherapy and combinatory efficacy of these agents (Table 4). Notably, the KONQUER-101 trial investigating the dual-state inhibitor BBO-11818, alongside ongoing trials for LY4066434, JAB-23E73, SIL-204, and the fast-tracked KST-6051, serve as critical testing grounds for both single-agent efficacy and multi-targeted regimens designed to block adaptive resistance mechanisms (Trialtrove, September 2026).

Table 4: Overview of key ongoing pan-KRAS inhibitor trials in PDAC

Trial Identifier	Drug name	Trial Sponsor	Trial Phase/ Status	Monotherapy/ Combination Therapy	Key Trial Details
SIL204SL-P001	SIL-204	Silexion Therapeutics	II/III Open	Combination (standard of care chemotherapy)	Pivotal trial in locally advanced PDAC harboring KRAS mutation; dual-route administration strategy combining intratumoral delivery to target primary tumors with systemic administration to address metastatic disease
JAB-23E73-2001	JAB-23E73	Jacobio Pharmaceuticals	Ib/III Open	Combination (gemcitabine plus nab-paclitaxel)	Pivotal trial in 1L KRAS-altered metastatic PDAC; initiation of this study is supported by encouraging preliminary data from the ongoing Phase I JAB-23E73-1001 trial
JAB-23E73-1001	JAB-23E73	Jacobio Pharmaceuticals	I/II Open	Monotherapy	Dose escalation and dose expansion study in advanced solid tumors harboring KRAS gene alteration. Interim results reported among the 13 PDAC patients (2-2L and 11- 3L+) within the predicted effective dose range, the ORR was 38.5%, and the DCR was 84.6%.

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Trial Identifier	Drug name	Trial Sponsor	Trial Phase/ Status	Monotherapy/ Combination Therapy	Key Trial Details
FALCON	KST-6051	Kestrel Therapeutics	I Open	Monotherapy	FIH dose-escalation study in 2L advanced or metastatic KRAS-mutant solid tumors; granted FDA Fast Track Designation in September 2026 for advanced or metastatic solid tumors harboring KRAS mutations
KONQUER-101	BBO-11818	BridgeBio Oncology Therapeutics	I Open	Monotherapy & Combination (pembrolizumab, pembrolizumab + cisplatin/ carboplatin + pemetrexed, cetuximab, cetuximab ± mFOLFOX6, BBO-10203 + mFOLFOX6, BBO-10203 + cetuximab, mFOLFIRINOX, gemcitabine + nab-paclitaxel, or BBO-10203	FIH study in advanced KRAS mutant cancers; received FDA Fast Track Designation in April 2026 for advanced KRAS-mutant PDAC; early monotherapy data reported a partial response (PR) with a 56% tumor reduction in a PDAC patient
J5Q-OX-JRDA	LY4066434	Eli Lilly	I Closed	Monotherapy & Combination (PDAC cohort: gemcitabine plus nab-paclitaxel; mFOLFIRINOX)	FIH, dose escalation & dose optimization study enrolling ~750 patients with locally advanced or metastatic KRAS-mutant solid tumors; ≥1 prior systemic therapy (Part B1) and treatment naive (Part B2 and B3) enrolling in PDAC cohort

Source: Trialtrove, September 2026

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Pan-RAS inhibitor trials

Pan-RAS inhibition is now the most clinically advanced of the three strategies to target RAS in PDAC, anchored by a randomized Phase III readout. The RASolute program, Revolution Medicines' trial backbone, is where that evidence originates.

RASolute 302 enrolled approximately 500 patients with metastatic PDAC that had progressed on one prior line of chemotherapy, randomizing them to daraxonrasib monotherapy (300mg orally once daily) versus investigator's choice of chemotherapy. All primary and secondary study endpoints were successfully met in the RAS G12 mutant subgroup and in the broader intent-to-treat population, regardless of RAS mutation status. In the RAS G12-mutated population, the median OS was 13.2 months on daraxonrasib versus 6.7 months on chemotherapy, roughly a 60% reduction in the risk of death. On the strength of this data, daraxonrasib received FDA approval in August 2026 for previously treated metastatic PDAC, following breakthrough therapy designation in 2025 and review under the FDA's Commissioner's National Priority Voucher program, a fast track for the pancreatic cancer indication (Pharmaprojects and Trialtrove, September 2026). Per Evaluate's Rasonque Product Report, the forecasted worldwide revenue in 2031 is $6.1b, with $4.2b being from the US.

Revolution Medicines is also testing whether this benefit extends earlier in the disease course and after resection. RASolute 303 is a Phase III trial in first-line metastatic PDAC, comparing daraxonrasib alone and in combination with gemcitabine plus nab-paclitaxel, against chemotherapy alone; it began enrolling in March 2026 and has not yet reported efficacy data. The Phase III RASolute 304 trial is testing daraxonrasib as adjuvant therapy after surgical resection versus observation, targeting fewer than 20% of patients who present with resectable disease (Datamonitor Healthcare and Trialtrove, September 2026).

While the clinical efficacy of daraxonrasib is encouraging, resistance can still occur. Resistance mechanisms were observed in patients treated with daraxonrasib, including acquired mutations in RAS, such as Y64, which interfere with the drug's binding, and through mutations in CYPA (Ppia) or MAP2K1 that circumvent its tri-complex mechanism altogether. These acquired resistance mechanisms reflect the importance of combination strategies.[9]

Beyond this single-company program, Erasca's ERAS-0015 is generating Phase I dose-escalation data in the same mechanistic class. The Phase I AURORAS-1 trial is running in the US and is evaluating monotherapy as well as various combination therapies, including pembrolizumab and panitumumab. There is also the Phase I/II JYP0015M101 trial running in parallel in China. ERAS-0015 in second-line KRAS G12X PDAC has shown early, dose-dependent activity: a 57% unconfirmed response rate at the 32mg recommended expansion dose as of the May 2026 cutoff, with most responders still on therapy and a favorable tolerability profile. Although it is small, uncontrolled Phase I data, it was strong enough to earn FDA Fast Track Designation, with the company now planning to move directly into a first-line Phase III pivotal trial in 2027. Beyond Erasca's program, a broader wave of pan-RAS assets is in early stage trials in PDAC, summarized in Table 5 (Trialtrove, September 2026).

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Table 5: Overview of key ongoing pan-RAS inhibitor PDAC trials

Trial Identifier	Drug name	Trial Sponsor	Trial Phase/ Status	Monotherapy/ Combination Therapy	Key Trial Details
GFH276X1101	GFH276	GenFleet Therapeutics	I/II Open	Monotherapy	Multicenter China trial in RAS-mutant advanced solid tumors; dose escalation/RP2D-finding ongoing; GenFleet's third candidate in its RAS-targeted profile to enter clinical research
SIM0532-101	SIM0532	Simcere Pharmaceutical Group	I Closed	Monotherapy	FIH, dose escalation, dose expansion, multicenter China trial enrolling ~346 patients
AN4035S0101	AN4035	Adlai Nortye Biopharma Co., Ltd.	I Open	Monotherapy & Combination (cetuximab)	FIH, dose escalation and dose expansion study in advanced or metastatic RAS mutated solid tumors, including PDAC, with high CEACAM5 expression; ADC delivery strategy rather than small molecule; initial clinical readout is expected in H2 2027
YO45758	RO-7673396	Hoffmann-La Roche	I Open	Monotherapy & Combination (anti-cancer agents)	Dose escalation and dose expansion study in RAS mutated advanced solid tumors; major pharma entrant into the pan-RAS space
QIANKUN-1	HZ-V055	Hangzhou Hezheng Pharmaceutical	I Open	Monotherapy	Multicenter China trial in RAS-mutant advanced solid tumors, including PDAC; first patient enrolled in August 2026
YL-17231-001 YL-17231-002	TEB-17231	Shanghai Yingli Pharmaceutical Co.	I Open	Monotherapy	US and China trials running in parallel in patients with advanced RAS-mutant (US) and KRAS-mutant (China) solid tumors

Source: Trialtrove, September 2026

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A new era in PDAC treatment

For decades, KRAS-mutated PDAC was the clearest example of an "undruggable" cancer target: a genomic driver that oncology could identify but not target. At the same time, the disease itself remained one of the deadliest solid tumors as measured by five-year survival rates. That premise no longer holds. The progression outlined in this paper, from mutant-specific inhibitors that first proved RAS was druggable in other cancers before extending into investigational use against PDAC alleles like G12D and G12V, to pan-KRAS agents now advancing through late-phase PDAC trials, to pan-RAS inhibitors that delivered the first PDAC approval by extending coverage across KRAS, NRAS, and HRAS alike, reflects a field that has progressively expanded its coverage of the pathways tumors depend on to survive. This progress is now supported by real clinical evidence: Randomized Phase III data for pan-RAS inhibition has nearly doubled median OS in previously treated metastatic disease, and a deep, multi-sponsor trial pipeline, spanning mutant-specific, pan-KRAS, and pan-RAS mechanisms alike, is now testing whether that benefit can move earlier in the treatment sequence, extend into the adjuvant setting, and be strengthened further through combination strategies.

But this progress should be read as a turning point, not a resolution. While the clinical and survival benefits of RAS inhibitors are promising, sustaining them will depend on solving resistance. Tumors' ability to escape treatment remains the field's biggest obstacle. Even the most advanced RAS(ON) inhibitors eventually see acquired resistance emerge in treated patients, through mechanisms such as acquired RAS mutations, complete disruption of the tri-complex, and MAPK pathway rewiring that differs from prior mechanisms yet are equally capable of restoring tumor growth. No single-agent strategy, however broad its RAS coverage, has yet shown it can hold the disease in check indefinitely. The next phase of progress will be defined less by the breadth of RAS coverage and more by how intelligently these agents are combined with other anti-cancer therapies to stay ahead of resistance rather than react to it. KRAS-mutant PDAC is no longer an undruggable disease but a treatable one, with combination strategies still needed to sustain that benefit.



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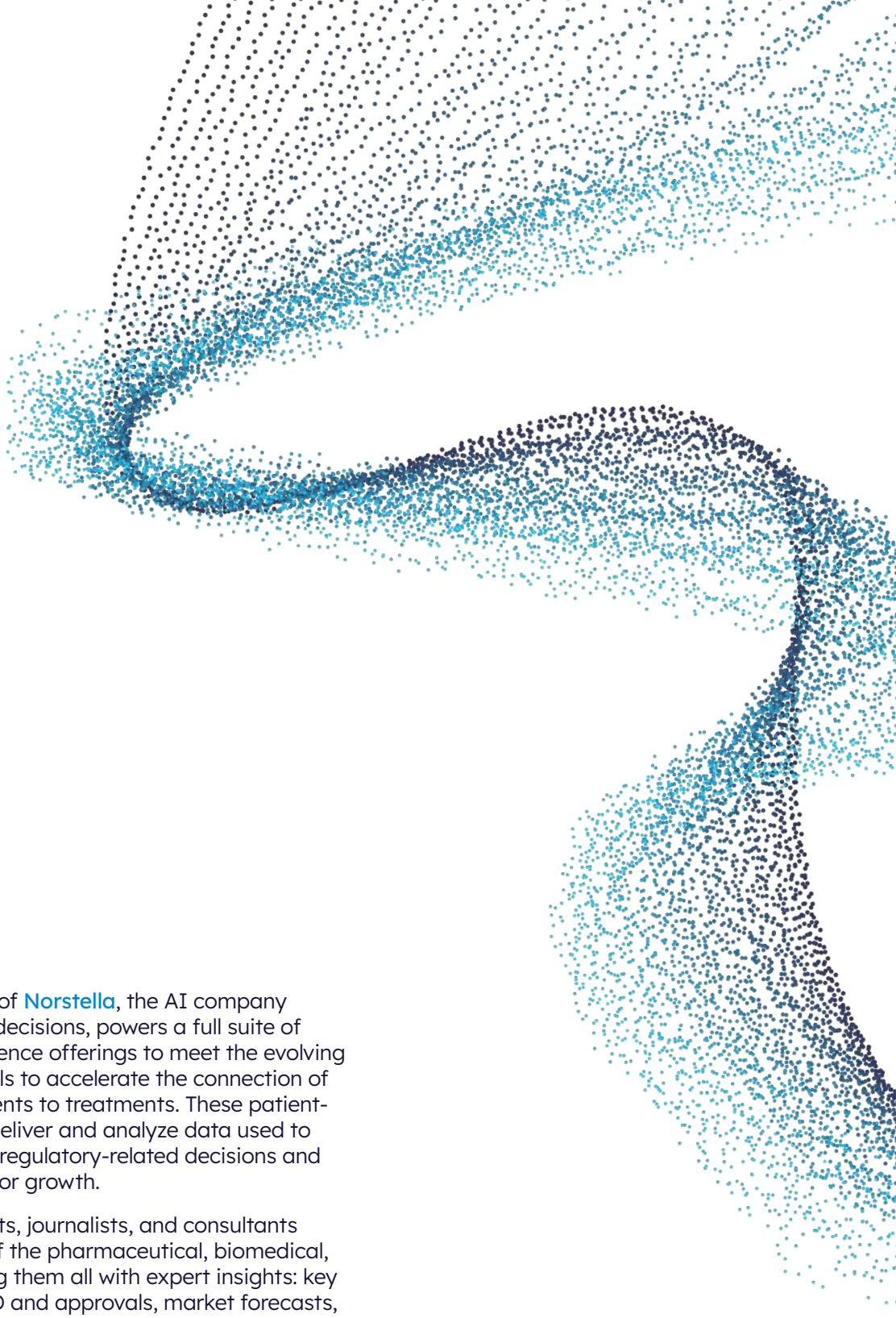
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