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Structure-Based Design of Allosteric Inhibitors Targeting Mutant KRAS in Pancreatic Cancer

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ABSTRACT

Background: Mutant KRAS drives over 90% of pancreatic ductal adenocarcinomas and was long considered undruggable because of its picomolar GTP affinity and featureless surface. Objective: This review synthesises structure-based design strategies that produced allosteric KRAS inhibitors and evaluates their relevance to pancreatic cancer. Methods: We conducted a narrative review of published structure-based drug design, X-ray crystallography, and allosteric inhibitor development studies targeting mutant KRAS, identified via PubMed, Google Scholar, Crossref, and bioRxiv. Findings: Discovery of a cryptic switch II pocket enabled covalent G12C inhibitors sotorasib and adagrasib, validated crystallographically and in clinical trials including pancreatic cohorts. Analogous switch II/switch I-adjacent pockets yielded the noncovalent G12D inhibitor MRTX1133 and related salt-bridge-forming compounds, addressing the mutation most common in pancreatic cancer. Acquired resistance mutations and adaptive feedback limit durability. Conclusions: Structure-guided targeting of allosteric pockets has transformed KRAS from undruggable to clinically tractable, with G12D-selective and pan-KRAS agents now advancing specifically for pancreatic cancer.

Keywords: *KRAS; allosteric inhibitor; pancreatic cancer; structure-based drug design; switch II pocket*

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Abstract

Background: Mutant KRAS drives over 90% of pancreatic ductal adenocarcinomas and was long considered undruggable because of its picomolar GTP affinity and featureless surface [1,2]. **Objective:** This review synthesises structure-based design strategies that produced allosteric KRAS inhibitors and evaluates their relevance to pancreatic cancer. **Methods:** We conducted a narrative review of published structure-based drug design, X-ray crystallography, and allosteric inhibitor development studies targeting mutant KRAS, identified via PubMed, Google Scholar, Crossref, and bioRxiv. **Findings:** Discovery of a cryptic switch II pocket enabled covalent G12C inhibitors sotorasib and adagrasib, validated crystallographically and in clinical trials including pancreatic cohorts [3,4,5,6,7]. Analogous switch II/switch I-adjacent pockets yielded the noncovalent G12D inhibitor MRTX1133 and related salt-bridge-forming compounds, addressing the mutation most common in pancreatic cancer [8,9,10]. Acquired resistance mutations and adaptive feedback limit durability [11,12]. **Conclusions:** Structure-guided targeting of allosteric pockets has transformed KRAS from undruggable to clinically tractable, with G12D-selective and pan-KRAS agents now advancing specifically for pancreatic cancer.

Keywords: KRAS; allosteric inhibitor; pancreatic cancer; structure-based drug design; switch II pocket

Introduction

KRAS is mutated in roughly 90% of pancreatic ductal adenocarcinomas (PDAC), most frequently at codon 12, with G12D substitutions predominating over G12V and the G12C variant common in lung and colorectal cancer [13,1]. For three decades KRAS resisted pharmacological inhibition: its GTPase domain binds GTP/GDP with picomolar affinity, precluding competitive nucleotide-site inhibitors, and its surface lacks deep, druggable hydrophobic clefts [2,14]. The 2013 discovery that a cryptic allosteric pocket beneath the switch II loop becomes accessible in the GDP-bound state of KRAS G12C reversed this paradigm, launching a structure-based design effort that has since yielded approved drugs and clinical-stage agents relevant to pancreatic cancer [3]. This review traces the structural biology underpinning allosteric KRAS inhibitor design and its translation toward pancreatic cancer therapy.

Methods

This is a narrative review of published structure-based drug design, X-ray crystallography, and allosteric inhibitor development studies targeting mutant KRAS. Literature was identified through PubMed, Google Scholar, Crossref, and bioRxiv searches combining terms for KRAS, G12C, G12D, switch II pocket, allosteric inhibitor, sotorasib, adagrasib, and pancreatic cancer. Primary discovery papers, co-crystal structure reports, and pivotal clinical trials were prioritised; each reference was individually verified against its journal record prior to inclusion. No new experimental, computational, or screening data are reported.

KRAS Mutant Biology and the Undruggable Challenge

KRAS cycles between active GTP-bound and inactive GDP-bound states, regulated by GEFs and GAPs; oncogenic G12 mutations impair intrinsic and GAP-stimulated GTP hydrolysis, locking KRAS in its signalling-competent conformation [14]. In PDAC, KRAS activation is typically the initiating oncogenic event, driving RAF-MEK-ERK and PI3K-AKT signalling and sustaining tumour growth, metabolism, and immune evasion [1]. Early drug-discovery campaigns targeting nucleotide-competitive inhibition or farnesyltransferase-mediated membrane localisation failed clinically, reinforcing KRAS's reputation as undruggable [2]. This impasse redirected efforts toward fragment-based and covalent tethering approaches capable of exploiting transient, mutation-specific surface pockets rather than the orthosteric nucleotide site.

Switch II Pocket and Allosteric Binding Site Discovery

Ostrem and colleagues used disulfide-tethering fragment screening and X-ray crystallography to show that electrophilic fragments could covalently engage the mutant cysteine of KRAS G12C within a pocket formed by switch II (the S-IIP), locking KRAS in an inactive, effector-disengaged state and reducing nucleotide affinity [3]. Independently, biophysical and crystallographic work demonstrated that small molecules could also engage a distinct pocket beneath switch I/II to disrupt the KRAS-SOS1 nucleotide-exchange interface without requiring a reactive cysteine, exemplified by pocket-binding compounds validated by co-crystal structures [15]. The bivalent binder BI-2852 was shown crystallographically to induce a nonfunctional KRAS dimer by simultaneously occupying the switch I/II and adjacent pockets, further expanding the structural toolkit of allosteric engagement [16]. Collectively these structures defined druggable, mutation-adjacent allosteric sites exploitable for rational inhibitor design [17].

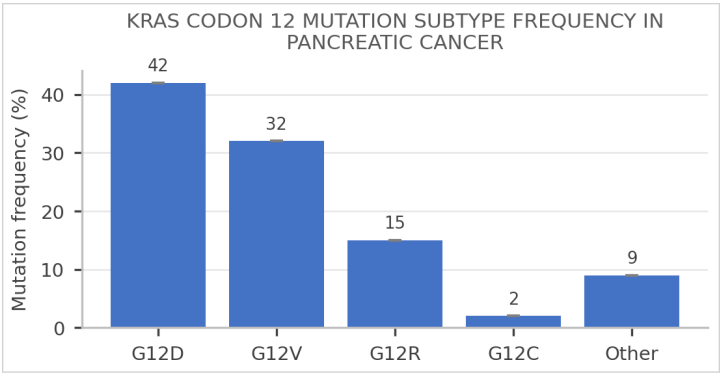
Structure-Based Design of Covalent and Non-Covalent Inhibitors

Iterative structure-based optimisation of switch II pocket binders produced the clinical candidates sotorasib (AMG 510) and adagrasib (MRTX849), both covalent, mutation-selective KRAS G12C inhibitors validated by extensive co-crystallography and cellular pharmacology [4,18,19]. Sotorasib demonstrated tumour regression and immune-permissive remodelling in preclinical models and produced objective responses in the CodeBreaK-100 phase I/II trial [4,5]. Adagrasib showed durable efficacy in the KRYSTAL-1 trial of KRAS G12C-mutant non-small-cell lung cancer [6]. Because G12D, not G12C, predominates in PDAC, parallel structure-based campaigns targeted the analogous pocket in KRAS G12D. Structure-guided design exploiting a salt bridge between inhibitor and the mutant aspartate side chain yielded MRTX1133, a noncovalent, subnanomolar, highly selective G12D inhibitor validated by co-crystal structures and shown to regress pancreatic tumours in immunocompetent mouse models [8,9,10]. Mechanistic profiling of earlier switch II binders using mass-spectrometry-based occupancy assays confirmed selective inhibition of oncogenic KRAS output at the biochemical level, informing subsequent medicinal chemistry [20,21]. Next-generation noncovalent G12C agents such as divarasib further illustrate the generalisability of switch II pocket targeting beyond first-generation covalent chemotypes [22], and emerging G12D-directed chemotypes are reviewed elsewhere as a rapidly expanding structural class [23].

Table 1: Selected structure-based allosteric KRAS inhibitors and their design features.

Compound	Target allele	Binding mode	Key structural feature
Sotorasib (AMG 510)	G12C	Covalent, switch II pocket	Irreversible acrylamide-Cys12 adduct locks GDP state
Adagrasib (MRTX849)	G12C	Covalent, switch II pocket	Extended macrocyclic scaffold with prolonged tissue exposure
MRTX1133	G12D	Noncovalent, switch II/I-adjacent pocket	Salt bridge to mutant Asp12 side chain
BI-2852	Pan-KRAS (WT/mutant)	Noncovalent, switch I/II bridging pocket	Induces nonfunctional KRAS homodimer
Divarasib (GDC-6036)	G12C	Covalent, switch II pocket	Optimized selectivity and reduced off-target reactivity

Figure 1: Distribution of KRAS codon 12 mutation subtypes reported in pancreatic ductal adenocarcinoma, showing G12D predominance over the G12C variant targeted by first-generation covalent inhibitors.



Clinical Translation and Resistance Mechanisms

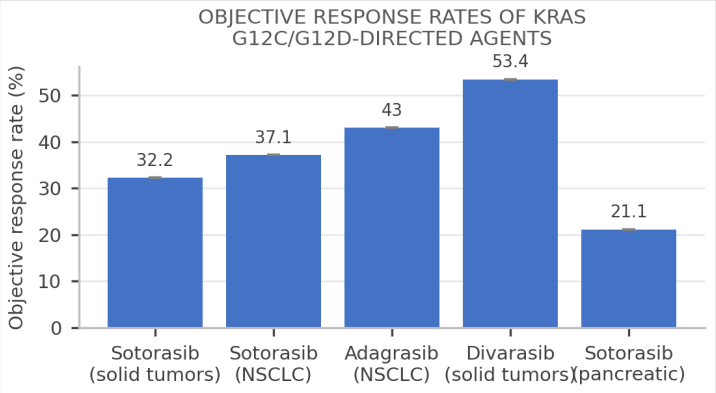
Sotorasib is approved for KRAS G12C-mutant non-small-cell lung cancer on the strength of the CodeBreaK-100 phase II trial [24] and produced measurable, albeit modest, disease control in a phase I/II cohort of pretreated KRAS G12C-mutant pancreatic cancer, the first clinical validation of direct KRAS inhibition in PDAC [7]. Adagrasib similarly extended into gastrointestinal and pancreatic cohorts within KRYSTAL-1. However, acquired

resistance emerges through secondary KRAS mutations, bypass RTK/MAPK reactivation, and epithelial-mesenchymal transition, limiting durability of covalent G12C inhibitors [11]. Broader reviews highlight combinatorial strategies-pairing KRAS inhibitors with SHP2, SOS1, EGFR, or immune checkpoint agents-as necessary to overcome adaptive feedback and heterogeneous resistance across RAS-driven cancers, including pancreatic cancer [25,26,12,27].

Table 2: Selected clinical trial outcomes of allosteric KRAS inhibitors relevant to pancreatic cancer.

Trial/Study	Agent	Tumor type	Outcome
CodeBreaK 100 (phase I)	Sotorasib	Advanced solid tumors	ORR 32.2% in NSCLC subgroup
CodeBreaK 100 (phase II)	Sotorasib	NSCLC	ORR 37.1%, median PFS 6.8 months
KRYSTAL-1	Adagrasib	NSCLC	ORR 43.0%, median PFS 6.5 months
Phase I (GDC-6036)	Divarasib	Solid tumors	ORR 53.4% in NSCLC cohort
Phase I/II	Sotorasib	Advanced pancreatic cancer	ORR 21.1%, disease control 84.2%

Figure 2: Objective response rates reported for KRAS G12C/G12D-directed allosteric inhibitors across clinical trials, including sotorasib in advanced pancreatic cancer.



Conclusion

Structure-based discovery of cryptic allosteric pockets transformed KRAS from an undruggable target into a validated drug target, first for G12C-mutant lung cancer and now extending to G12D-predominant pancreatic cancer through agents such as MRTX1133 and sotorasib in pancreatic trials. Continued crystallographic and medicinal-chemistry innovation, combined with rational combination strategies to counter resistance, will determine whether allosteric KRAS inhibition can meaningfully improve outcomes in pancreatic ductal adenocarcinoma.

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Conflict of Interest

The authors declare no conflict of interest.

Author Contributions

Vogel S conceived the review, conducted the literature search, and drafted the manuscript. Balazova Z contributed to the literature screening and technical framing and critically revised the manuscript for important intellectual content. Zarins A contributed additional context and approved the final version for submission.

Ethics Statement

Not applicable. This is a narrative review of previously published literature and did not involve new experimental data, human participants, or animal subjects.

Data Availability

No new data were generated or analyzed for this review. All sources synthesized are cited in the reference list and are available through their original publishers.

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