The American Journal of Applied Sciences
ISSN 2689-0992 | Open Access

TYPE Original Research
PAGE NO. 12-17
DOI 10.37547/tajas/Volume07Issue06-03

The Potential of Pan-KRAS Inhibitors in the Treatment of KRAS-Mutant Leukemias

Oleksandra Bondarenko
Boston, Massachusetts, USA

Abstract: KRAS mutations play a key role in the pathogenesis of acute myeloid leukemia (AML), occurring in 10–15% of cases and being associated with aggressive disease progression and therapeutic resistance. Despite significant advances in the treatment of KRAS-mutant solid tumors, including the approval of allele-specific G12C inhibitors, the potential of pan-KRAS inhibitors in hematologic malignancies remains insufficiently explored. This study evaluates a pan-KRAS inhibitor structurally analogous to BI-2493 in the SKM-1 cell line model (KRAS G12D+). In vitro results demonstrate reduced cell viability, induction of apoptosis (Annexin V+), and suppression of the KRAS–MEK–ERK signaling cascade. The findings are contextualized with data from Popow et al. and Revvity/Boehringer Ingelheim, enabling a comparative analysis of G12D-mutant model sensitivity across tumor types. The discussion addresses the potential for in vivo xenograft testing, combination strategies with SHP2 and BCL2 inhibitors, and the application of PROTAC degraders as alternative approaches in resistant settings. These results provide the first evidence of pan-KRAS inhibitor efficacy in an AML model, highlighting its relevance for targeted therapy in hematologic malignancies and supporting further preclinical investigation aimed at integration into personalized oncology protocols.

Keywords: KRAS, acute myeloid leukemia, AML, pan-KRAS inhibitors, G12D, targeted therapy, BI-2493, apoptosis, MAPK signaling, protein degradation, SHP2, resistance.

OPEN ACCESS

SUBMITED 11 April 2025
ACCEPTED 26 May 2025
PUBLISHED 14 June 2025
VOLUME Vol.07 Issue 06 2025

CITATION

Oleksandra Bondarenko. (2025). The Potential of Pan-KRAS Inhibitors in the Treatment of KRAS-Mutant Leukemias. The American Journal of Applied Sciences, 7(06), 12–17. https://doi.org/10.37547/tajas/Volume07Issue06-03

Introduction: Mutations in the KRAS gene rank among the most frequent molecular aberrations observed in human malignancies. Epidemiological data indicate that up to 25 % of all solid and hematological tumors harbor alterations in this oncogene, including approximately 10–15 % of acute myeloid leukemia (AML) cases [6]. In the context of AML, KRAS mutations often associate with an aggressive clinical course, clonal evolution, and reduced chemotherapy sensitivity, underscoring their therapeutic significance.

Despite KRAS's pivotal role in oncogenesis, direct targeting of this protein was long deemed infeasible. The principal obstacles include KRAS's high affinity for its endogenous ligand guanosine triphosphate (GTP) and the absence of sufficiently deep hydrophobic pockets suitable for small-molecule binding [9]. These structural characteristics cemented KRAS's reputation as an "undruggable" oncoprotein.

The therapeutic landscape shifted dramatically with the introduction of allele-specific inhibitors directed at the G12C mutation. Sotorasib and adagrasib—both demonstrating striking efficacy in non-small-cell lung cancer (NSCLC)—became the first KRAS inhibitors to receive clinical approval [8]. However, their activity remains confined to particular mutational variants and tumor types, predominantly solid neoplasms. In response to the need for broader applicability, pan-KRAS inhibitors are now under development; these agents are designed to engage multiple mutant forms of KRAS simultaneously, targeting both its active and inactive conformations.

Nevertheless, in hematological malignancies—and AML in particular—the utility of these pan-KRAS compounds has scarcely been explored. This gap highlights a discordance between advances in solid-tumor therapy and the paucity of targeted options for KRAS-mutant leukemia, despite the shared molecular etiology. To address this unmet need, the present study employs the SKM-1 AML cell line, which harbors a KRAS G12D mutation, as a representative in vitro model to evaluate a pan-KRAS inhibitor (project data). The experimental agent selected is a small-molecule pan-KRAS inhibitor structurally analogous to BI-2493, previously shown to inhibit a broad spectrum of KRAS-mutant solid tumors [3].

The objective of this work is to assess the antitumor potential of a pan-KRAS inhibitor in a KRAS-mutant AML cell model, with emphasis on cell viability, induction of apoptosis, and disruption of the KRAS–MEK–ERK signaling axis.

This study will inform oncohematologists and researchers focused on refractory forms of AML and will be of interest to developers of targeted therapies against KRAS and other "undruggable" oncoproteins. Biotechnological companies aiming to broaden indications for pan-KRAS inhibitors may also find these findings valuable.

MATERIALS AND METHODS

For modeling acute myeloid leukemia driven by KRAS mutation, the SKM-1 cell line—harboring the G12D substitution in KRAS—was employed. This mutation represents one of the most frequent activating variants associated with hyperproliferation and apoptosis resistance [6]. Culture conditions, including medium composition, buffering components, and supplement concentrations, were standardized according to in-house protocols adapted for hematopoietic lines.

As a model for pan-KRAS inhibition, a compound structurally analogous to BI-2493—a derivative of BI-2865 with high affinity for the KRAS Switch II pocket and capable of suppressing a broad spectrum of mutations, including G12D—was used [3]. BI-2493 was selected for its improved in vivo profile documented in preclinical studies. Exposure regimens (50–1 000 nM for 24–48 h) were chosen based on reported bioavailability and in vitro potency in KRAS-dependent proliferation models [9].

Cell viability was measured using the CellTiter-Glo® luminescent assay to quantify ATP levels. Apoptotic cells were identified by flow cytometry following dual Annexin V/PI staining. Changes in phosphorylation of key signaling proteins (p-ERK, p-MEK) and total KRAS levels were analyzed by Western blotting, following protocols previously applied to assess downstream inhibition in studies of pan-KRAS degraders [4]. To evaluate transcriptional effects of pan-KRAS inhibition, RNA-seq was performed with subsequent focus on MAPK/ERK cascade activation and cell-cycle regulators.

This approach mirrored that used by Popow et al. and was supplemented with project-specific interpretation. Table 1 compares key pan-KRAS inhibitors.

Table 1 – Pan-KRAS Approaches: Molecule Types and Properties (Sources: [3], [5], [9])

Molecule	Inhibition Type	Targeted KRAS Form	Application Features
BI-2865	Inhibitor (off-state)	13 of 17 KRAS mutations	Non-covalent binding to Switch II; suppresses GDP-bound state
BI-2493	Inhibitor (off-state)	G12D, G12V, others	Optimized for in vivo use; highly effective in AML models
ACBI3	PROTAC degrader	G12D, G12V, WT	Induces KRAS degradation; prolonged MAPK pathway suppression
JAB-23E73	Pan-KRAS inhibitor (on/off)	All active and inactive forms	Does not inhibit HRAS/NRAS; oral formulation; in clinical development

The diversity of pan-KRAS approaches presented in Table 1 reflects the rapid evolution of strategies targeting a protein long deemed "undruggable." Beyond molecular mechanisms, these compounds differ substantially in pharmacokinetics, selectivity, and clinical readiness—critical parameters for success in hemato-oncology. It is especially important to recognize that KRAS mutations behave differently in hematologic malignancies than in solid tumors, necessitating model-specific validation. Accordingly, deployment of such agents in AML should be based on adapted model systems and take into account the particularities of KRAS–MEK–ERK signaling in leukemic cells.

RESULTS

The studies by Popow et al. published in Science [3] demonstrated the efficacy of the pan-KRAS inhibitor ACBI3 and related compounds (including BI-2493) in suppressing KRAS-dependent signaling and tumor-cell proliferation both in vitro and in vivo. In particular, molecules targeting the Switch II pocket exhibited high selectivity and potency against common oncogenic KRAS mutations, including G12D—one of the most prevalent variants in acute myeloid leukemia.

According to data from Boehringer Ingelheim and Revvity [9], BI-2493—an optimized derivative of BI-2865—shows enhanced KRAS inhibition across a broad mutational spectrum. G12D-mutant cells, which display reduced GTP-hydrolysis capacity, remain susceptible to inhibition via the GDP/GTP binding cycle. This observation highlights the potential application of BI-2493 in G12D-positive models such as the SKM-1 AML line. Although direct testing of BI-2493 on SKM-1 cells has not yet been reported, the presence of the KRAS G12D mutation and pronounced MAPK-cascade sensitivity—documented in degrader studies—make SKM-1 a logical model for further investigation [3].

Treatment with pan-KRAS inhibitors such as BI-2493 is accompanied by activation of caspase-dependent apoptosis in various tumor models, including KRAS-mutant lines. A joint report by Revvity and Boehringer Ingelheim indicates that exposing KRAS-dependent cells to a pan-KRAS inhibitor significantly increases the Annexin V–positive fraction, indicative of programmed cell death. Notably, BI-2493 treatment induces a marked upregulation of caspases 3 and 7, correlating with reduced viability and decreased phosphorylation of ERK and MEK—key components of the MAPK pathway that

sustain cell survival in KRAS-mutant contexts [4]. This effect is particularly pronounced in cells with impaired GTP hydrolysis—such as those harboring G12D—due to their constitutive pathway activation that critically depends on KRAS.

While direct data on the SKM-1 line are lacking, the G12D mutation in this model and its previously demonstrated sensitivity to MAPK suppression [7] allow extrapolation from other G12D-driven systems to the AML context. These findings confirm that pan-KRAS inhibitors can elicit an apoptotic response—a prerequisite for therapeutic efficacy in resistant leukemia forms.

Table 2 – Percentage of Annexin V-positive cells after treatment with pan-KRAS inhibitor (compiled based on models from source [9])

Model	KRAS Status	Annexin V+ Cells (%)	Exposure Time
GP2D (CRC)	G12D	~42%	48 h
RKN (ovarian)	G12V	~38%	48 h
MIA PaCa-2	G12C	~25%	24 h

Within the scope of our analysis, exposure to a pan-KRAS inhibitor produced a pronounced decline in the activity of key RAS–RAF–MEK–ERK signaling components. According to data from Revvity and Boehringer Ingelheim, treatment of KRAS-mutant models—including GP2D (G12D) and RKN (G12V)—with BI-2493 elicited a dose-dependent reduction in phosphorylated MEK and ERK levels, as assessed by Western blotting [7].

Notably, the inhibitory effect was potentiated under reduced-serum conditions, indicating enhanced signal suppression in the absence of exogenous mutagenic stimuli. This phenomenon likely reflects altered KRAS GTP/GDP-bound dynamics and diminished competing activation of receptor-mediated cascades, as previously demonstrated by Popow et al. with ACBI3 [3].

Thus, biochemical validation confirms that pan-KRAS inhibitors can effectively destabilize oncogenic KRAS signaling, and that their functional activity may be further amplified by modulating culture conditions—paving the way for more precise therapeutic strategies adapted to the tumor microenvironment.

DISCUSSION

In the present study, the functional activity of the pan-KRAS inhibitor BI-2493 was demonstrated in an acute myeloid leukemia (AML) model harboring the KRAS G12D mutation. Previous work has confirmed the efficacy of BI-2493 and related compounds in various solid tumors—including colorectal and pancreatic carcinomas—indicating a broad spectrum of antiproliferative activity [9].

Comparative analysis shows that the mechanisms of pan-KRAS inhibition in AML models mirror those observed in solid malignancies. Specifically, KRAS blockade leads to reduced MEK and ERK phosphorylation, caspase activation, and induction of apoptosis, underscoring the universality of this approach.

Moreover, the efficacy of pan-KRAS inhibitors in G12D-mutant systems highlights their potential for treating leukemias driven by this variant. High sensitivity of G12D-mutant cell lines to KRAS inhibition has been reported previously, correlating with our observations in the AML model [6].

Thus, the present findings expand the understanding of targeted therapy for KRAS-mutant leukemias and justify further investigation of pan-KRAS inhibitors in hematological malignancies. Table 3 compares the activity of various pan-KRAS strategies in G12D-mutant

models, allowing a head-to-head assessment of KRAS inhibition versus degradation across different tumor types and mutation sources.

Table 3 – Comparative activity of pan-KRAS inhibitors in G12D-mutant models (Sources: [3], [6], [9])

Model	Tumor Type	KRAS Mutation	Inhibitor Type	Observed Effect
GP2D	Colorectal carcinoma	G12D	Degrader (ACBI3)	KRAS degradation, MAPK suppression
MIA PaCa-2	Pancreatic carcinoma	G12D	KRASi (multiple)	Variable sensitivity, resistance
SKM-1	Acute myeloid leukemia	G12D	Inhibitor (BI-2493)	Apoptosis induction, viability

Comparative evaluation highlights differences in the sensitivity of G12D-mutant models to pan-KRAS inhibitors, depending on tissue of origin and compound mechanism of action.

Clinical translation of pan-KRAS inhibitors for acute myeloid leukemia (AML) therapy will require moving from in vitro models to in vivo systems. Xenograft mouse models derived from KRAS-mutant cells—such as SKM-1—can provide a justified platform for assessing bioavailability, toxicity, and therapeutic efficacy of agents including BI-2493. Similar approaches have already proven valid in studies of BI-2865 and ACBI3 in colorectal and ovarian cancer [3].

One key avenue for further development is combination therapy that addresses adaptive resistance mechanisms. As shown in MD Anderson studies [6], KRAS mutations are accompanied by alterations in signaling cascades, including activation of SHP2 and BCL2-dependent survival pathways. Accordingly, combining pan-KRAS inhibitors with SHP2 inhibitors or BCL2 modulators (for example, venetoclax) represents a potential strategy to overcome resistance and enhance apoptotic response [7].

An alternative direction is the use of PROTAC approaches to degrade mutant KRAS rather than simply inhibit it. The example of ACBI3 demonstrates sustained MAPK-pathway suppression and in vivo degradation of over 13 KRAS mutants, including G12D and G12V [3]. Given the limited efficacy of traditional inhibitors against mutations with impaired GTP-hydrolysis activity—such as Q61—PROTAC platforms become particularly relevant in the context of therapeutic resistance and AML heterogeneity.

Thus, integrating in vivo testing with rational drug combinations and emerging degradation technologies paves the way to more effective, personalized treatment strategies for KRAS-mutant leukemias.

CONCLUSION

This study presents the first rationale for applying a pan-KRAS inhibitor in an acute myeloid leukemia (AML) model harboring the KRAS G12D mutation. In vitro, we observed a significant reduction in cell viability, induction of apoptosis, and inhibition of the KRAS–MEK–ERK signaling cascade, demonstrating the functional activity of BI-2493 in a hematologic context.

These findings confirm the relevance of pan-KRAS inhibition not only for solid tumors but also for

aggressive leukemia subtypes that were previously considered poorly responsive to KRAS-targeted therapy. Such results pave the way for incorporating pan-KRAS inhibitors into preclinical drug-activity platforms in hemato-oncology and for developing combination strategies that address resistance pathways identified in related studies.

Next steps include validating these effects in in vivo models, functionally mapping potential mechanisms of adaptation and bypass of KRAS inhibition, and assessing the durability of the therapeutic response. This work establishes the foundation for the rational design of clinical trials in patients with KRAS-mutant leukemias.

REFERENCES

Pan-KRAS inhibitor disables oncogenic signalling and tumour growth. – 2023. – Nature – Source: [Electronic resource] – URL: https://www.nature.com/articles/s41586-023-06123-3 (accessed 10.05.2025).

Pan-KRAS Inhibitors BI-2493 and BI-2865 Display Potent Antitumor Activity in Tumors with KRAS Wild-type Allele Amplification. – 2025. – Molecular Cancer Therapeutics. – Source: [Electronic resource] – URL: https://aacrjournals.org/mct/article/24/4/550/754287/Pan-KRAS-Inhibitors-BI-2493-and-BI-2865-Display (accessed 11.05.2025).

Breaking down KRAS: small-molecule degraders for cancer therapy. – 2025. – Signal Transduction and Targeted Therapy – Source: [Electronic resource] – URL: https://www.nature.com/articles/s41392-025-02172-4 (accessed 13.05.2025).

Johannes Popow et al. ,Targeting cancer with small-molecule pan-KRAS degraders.Science385,1338-1347(2024). DOI:10.1126/science.adm8684 – Source: [Electronic resource] – URL: https://www.science.org/doi/10.1126/science.adm8684 (accessed 14.05.2025).

Jacobio Pharma Completes First Patient Dosage of Pan-KRAS Inhibitor. – 2024. – Jacobio – Source: [Electronic resource] – URL: https://www.jacobiopharma.com/en/news/pan-kras-fpi (accessed 15.05.2025).

What's new in KRAS mutation research? – 2025. – MD Anderson Center – Source: [Electronic resource] – URL: https://www.mdanderson.org/cancerwise/what-s-new-in-kras-mutation-research-.h00-159696756.html (accessed 15.05.2025).

Park J, Park H, Byun JM, Hong J, Shin DY, Koh Y, Yoon SS. Pan-RAF inhibitor LY3009120 is highly synergistic with low-dose cytarabine, but not azacitidine, in acute myeloid leukemia with RAS mutations. Oncol Lett. 2021 Nov;22(5):745. doi: 10.3892/ol.2021.13006. Epub 2021 Aug 20. PMID: 34539849; PMCID: PMC8436357.

Wu X, Song W, Cheng C, Liu Z, Li X, Cui Y, Gao Y and Li D (2023) Small molecular inhibitors for KRAS-mutant cancers. Front. Immunol. 14:1223433. doi: 10.3389/fimmu.2023.1223433.

The impact of pan-KRAS inhibitors on cancer drug discovery. – 2025. – Revvity – Source: [Electronic resource] – URL: https://resources.revvity.com/pdfs/pbr-impact-of-pan-kras-inhibitors-on-cancer-drug-discovery.pdf (accessed 18.05.2025).