International Journal of Engineering, Science and Humanities
An international peer reviewed, refereed, open access journal
Impact Factor: 8.3 www.ijesh.com ISSN: 2250 3552

AI-Driven Precision Targeting Beyond KRAS: Daraxonrasib, Pan-RAS(ON) Inhibition, and Emerging Predictive Biomarkers in RAS-Driven Cancers

Dr. Noynika Shukla

M.B.B.S., M.S. Ramaiah Medical College, Bengaluru, Karnataka, India

Abstract—The high level of therapeutic resistance, pathway activation and variation in Rat Sarcoma (RAS) mutations makes the treatment of RAS-driven cancers a significant challenge. While targeted therapy through allele-selective Kirsten Rat Sarcoma (KRAS) inhibitors has made a significant leap, the limited number of mutations covered by these inhibitors and the potential for reactivation of the pathway indicate the need for more comprehensive approaches. This review focuses on daraxonrasib (RMC-6236), an orally available, noncovalent panRAS(ON) inhibitor that targets active GTP-bound RAS through a cyclophilin A–mediated ternary complex. It is active against a wide range of RAS variants, offering a possible strategy to break through the problem of being blocked by selective inhibition of individual mutations. A review of emerging pan-RAS inhibitors, their therapeutic potential and issues of toxicity and acquired resistance are also discussed. Concurrently, the role of artificial intelligence (AI) in the precision oncology is explored, with special attention on AI for better diagnosis, prognosis, and prediction of treatment response. New predictive biomarkers such as RNA signatures or multi-omics could be used to improve patient stratification and to identify those most likely to respond to RAS intervention. The combination of pan-RAS(ON) inhibition and the discovery of biomarkers using AI may therefore contribute to the development of personalized therapy for RAS driven malignancies. In summary, these results suggest that pan-RAS(ON) inhibition, especially with the use of AI-powered biomarker strategies, is a promising approach for extending RAS targeting, better patient selection, and more targeted treatment of RAS dependent malignancies.

Keywords—Cancer Biomarkers, Daraxonrasib, Precision Medicine, Targeted Therapy, Pan RAS(ON) inhibition, Predictive biomarkers, Artificial intelligence.

Introduction

The formation and course of several human malignancies are significantly influenced by the abnormal activation of RAS proteins, which include KRAS, NRAS, and Harvey rat sarcoma virus (HRAS). RAS proteins are essential regulators of cellular proliferation, survival, and differentiation [1]. KRAS mutations have drawn a lot of therapeutic interest among these changes, however the variety of RAS mutations, isoforms, and pathway reactivation methods has brought to light significant limits of allele-selective KRAS inhibition. The limited allele coverage of mutant-specific inhibitors may restrict the number of eligible patients and allow compensatory signaling through alternative RAS isoforms or downstream pathways, despite the fact that they can offer significant therapeutic benefit. In order to achieve more thorough

International Journal of Engineering, Science and Humanities
An international peer reviewed, refereed, open access journal
Impact Factor: 8.3 www.ijesh.com ISSN: 2250 3552

and long-lasting inhibition of oncogenic signaling, these difficulties have prompted the development of more comprehensive RAS-targeting methods [2].

One significant development in this area is daraxonrasib (RMC-6236), a noncovalent pan-RAS inhibitor that is physically bioavailable and targets active, GTP-bound versions of many mutant and wild-type RAS proteins. As cyclophilin A, daraxonrasib, and GTP-bound RAS create a ternary complex, it sterically interferes with RAS's interactions with downstream effectors like RAF, which is how it acts [3]. Without relying on a chemical binding site that is specific to mutations, this unique "molecular-glue" method allows for wider RAS targeting. So, inhibiting pan-RAS(ON) might restrict adaptive pathway reactivation and treat heterogeneous RAS driven cancers [4]. Important obstacles, such as toxicity from wild-type RAS inhibition and the development of acquired resistance, persist.

Simultaneously, artificial intelligence (AI) is having a profound impact on precision oncology. This is because AI can analyze large datasets including genomics, pathology, radiology, and clinical information to better diagnose patients, predict their prognosis, and make informed decisions about their treatment. Discovering molecular signatures and predictive biomarkers that can differentiate those most likely to react to RAS-directed treatments may be made easier with the use of AI and machine-learning (ML) techniques. Patients with RAS-driven malignancies can benefit from this review's examination of the new therapeutic landscape, which goes beyond allele-selective KRAS inhibition. Topics covered include daraxonrasib, pan-RAS(ON) inhibition, and the changing role of artificial intelligence, multi-omics, and predictive biomarkers in patient stratification and individualized treatment plans.

Structure of the Paper

The review is structured into the following sections: Section II, Daraxonrasib and PanRAS(ON) Inhibition, and their limitations. Section III presents AI-Driven Precision Oncology and Biomarkers in RAS-Driven Cancers. Section IV presents a literature review and identifies current research gaps. Section V discusses the conclusion and future work.

Daraxonrasib and Pan-RAS(ON) Inhibition

Daraxonrasib (RMC-6236) is a noncovalent pan-RAS inhibitor that may be taken directly and targets the active, GTP-bound versions of several mutant and wild-type RAS proteins [5]. Table I includes a summary of the main points of pan-RAS inhibition and alleleselective RAS inhibition, such as the range of targets, possible therapeutic benefits, and significant drawbacks.

TABLE I. COMPARISON OF PAN-RAS AND ALLELE-SELECTIVE RAS INHIBITORS

Approach	Representative agents	Advantages	Disadvantages
Pan-RAS inhibition	RMC-6236 (daraxonrasib)	A single medication can address diverse RAS	Inhibiting wild-type RAS can reduce the therapeutic window and

International Journal of Engineering, Science and Humanities
An international peer reviewed, refereed, open access journal
Impact Factor: 8.3 www.ijesh.com ISSN: 2250 3552

		mutations; covering a wide range of alleles and isoforms enables treatment of more patients; suppressing adaptive feedback and pathway reactivation by simultaneous inhibition of mutant and wild-type RAS is possible.	harm normal tissues; resistance can be obtained via mutations at the target site, an increase in RAS abundance, or the reactivation of pathways downstream and bypass.
Alleleselective RAS inhibition	AMG 510 (sotorasib), MRTX849 (adagrasib), RMC-9805 (zoldonrasib), HRS-4642	Patients can be easily selected using biomarkers, and a treatment window that is larger due to high mutant selectivity might be created by sparing wild-type RAS.	Acquired resistance can happen due to target-site mutations, an increase in RAS abundance, or the activation of downstream and bypass pathways; the preservation of wild-type and other RAS isoforms allows adaptive feedback and pathway reactivation; and the use of separate agents for individual variants is limited by narrow allele coverage [6].

Daraxonrasib follows a unique mechanism compared to other direct RAS inhibitors, in addition to its extensive target coverage. A ternary complex consisting of cyclophilin A (CYPA), daraxonrasib, and GTP-bound RAS may be formed by daraxonrasib (Fig. 1).

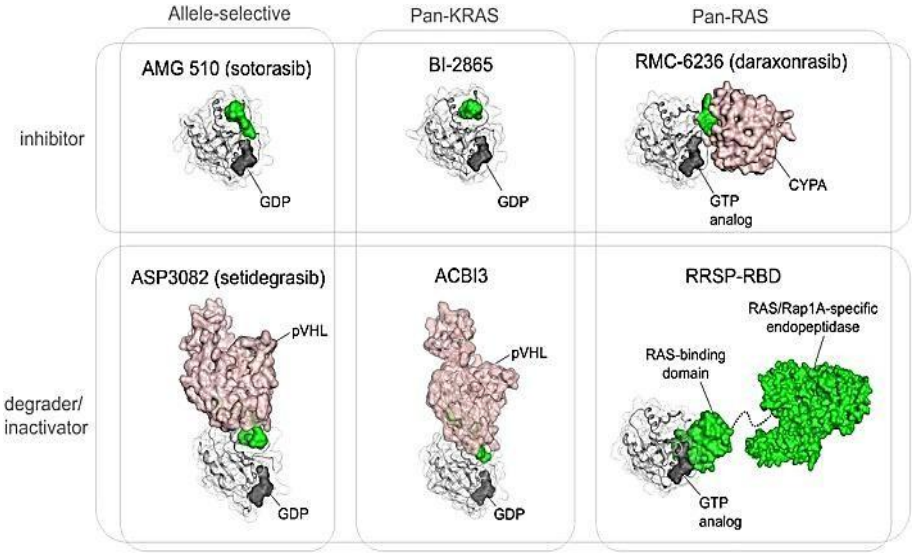

Fig. 1. Representative RAS-targeting modalities

International Journal of Engineering, Science and Humanities
An international peer reviewed, refereed, open access journal
Impact Factor: 8.3 www.ijesh.com ISSN: 2250 3552

As part of this complex, Cyclophilin (CYPA) sterically blocks the RAS surface that RAF and other effectors downstream need to interact. By using this molecular-glue technique, it is possible to suppress many RAS variations without depending on a mutation

Pan-RAS Inhibitors

Fig. 2 shows that pan-RAS inhibitors target both wild-type and mutant RAS isoforms, allowing them to exert a wide action across all three isoforms. Therefore, it is anticipated that pan-RAS inhibitors would provide long-term pathway suppression, resulting in tumor growth reduction and wider effectiveness against RAS-driven malignancies. Here, it will provide an outline of new treatment techniques that utilize pan-RAS inhibitors instead of inhibitors that target particular mutants. The emphasis will be on the preclinical and preliminary clinical data that backs up these novel approaches.

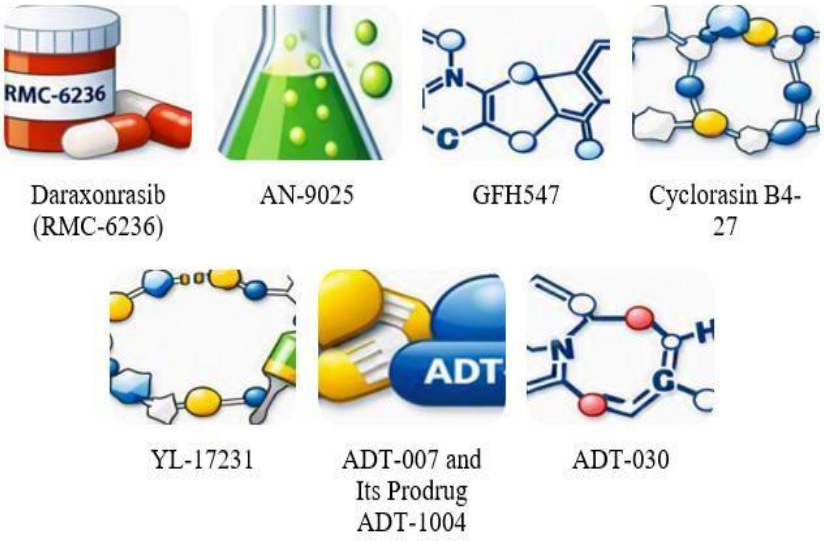

Fig. 2. Pan-RAS inhibitors

Daraxonrasib (RMC-6236)

The first pan-RAS inhibitor to reach clinical trials is daraxonrasib (RMC-6236) [7]. RMC-6236 is a member of the tri-complex inhibitor family, which consists of RAS inhibitors that all work by the same principle. A tri-complex RASMULTI (ON) inhibitor is the precise name given to RMC-6236. Direct binding to the "ON" configuration of RAS enhances inhibition of the oncogenic driver, as RAS is mainly active in the cancer "ON" state.

AN-9025

AN-9025 is an additional tri-complex inhibitor that is pan-RAS (ON). It has been found to be highly effective in preventing the growth of cancer cell lines with different RAS mutations. Similar to RMC-6236, AN-9025 forms a RAS (ON)-CypA tri-complex; however, its slower dissociation rate and 3- to 8-fold greater CypA binding affinity indicate a more stable binding complex. Analogous to this process, AN-9025 inhibited the growth of 26 RAS-mutant cancer cell lines derived from various tissues. These cell lines had sensitivity profiles similar

International Journal of Engineering, Science and Humanities
An international peer reviewed, refereed, open access journal
Impact Factor: 8.3 www.ijesh.com ISSN: 2250 3552

to RMC-6236, but AN-9025's in vitro efficacy was around 100 times higher. AN-9025 demonstrated strong anticancer effects in several xenograft models including RAS mutations, and it is orally accessible.

GFH547

GFH547 is an additional tri-complex inhibitor of pan-RAS (ON) that reportedly binds CypA to create a high-affinity complex that sterically interferes with the interaction between RAS and effectors. With a wide variety of KRAS, NRAS, and HRAS mutations represented in 29 cancer cell lines, GFH547 showed great effectiveness in preclinical models [8]. Also, GFH547 inhibited the growth of cancer cells that were driven by EGFR or FGFR2/3 amplification, mutation, or fusion, indicating that it has a wider impact when it comes to RTK activation.

Cyclorasin B4-27

The bicyclic peptide pan-RAS inhibitor cyclorasin B4-27 was developed from an earlier homolog, cyclorasin B3, which was acquired from the first-generation cyclorasin 9A5 by enlarging the monocyclic scaffold into a more rigid bicyclic design [9]. It was shown that these design improvements led to better mutant RAS selectivity, higher cell permeability, and greater RAS-binding affinity. In terms of biochemistry, the KRAS G12V-GppNHp complex (a nonhydrolyzable GTP analog) exhibits a Kd value of 21 nM, indicating that cyclorasin B4-27 binds RAS-GTP with a high affinity.

YL-17231

YL-17231 is an inhibitor of numerous oncogenic RAS mutations; it is a tiny molecule and reversible. According to preclinical research, YL-17231 decreased the proliferation of a variety of cancer cell lines that were mutant for KRAS, HRAS, and NRAS, and its IC50 was in the nanomolar range [10]. It also lowered P-ERK signaling in cancer cell lines that had the KRAS mutation. Not only did YL-17231 successfully target mutants, but it also preserved action in cells with additional KRAS mutations linked to acquired resistance and overcome resistance to sotorasib, a KRAS G12C inhibitor.

ADT-007 and Its Prodrug ADT-1004

The development of a wide range of cancer cell lines with different RAS mutations or elevated levels of activated RAS due to mutations in upstream RTKs or NF1 was recently detailed by Foote and colleagues. One such inhibitor, ADT-007, is mechanistically distinct and exhibits high potency and selectivity in inhibiting cell proliferation. Both normal tissue cells and cancer cell lines with downstream BRAF mutations showed significantly reduced sensitivity to ADT-007 therapy.

ADT-030

ADT-030, a substitute to ADT-007, inhibits phosphodiesterase 10A and consequently

International Journal of Engineering, Science and Humanities
An international peer reviewed, refereed, open access journal
Impact Factor: 8.3 www.ijesh.com ISSN: 2250 3552

both RAS driven MAPK/AKT signaling and Wnt/β-catenin transcriptional activity. The reduction of MYC transcription caused by Wnt/β-catenin was another effect of ADT-030 [64]. Therefore, ADT-030 has the potential to circumvent MYC upregulation-driven resistance to conventional RAS inhibitors [11]. At the same time as it promotes dendritic cell antigen absorption and maturation, ADT-030 triggers immunogenic cell death in cancer cells.

Pan-KRAS Inhibitors

The discovery of pan-KRAS inhibitors, as seen in Fig. 3, that target particular isoforms has also made significant strides, coinciding with the ongoing advancements in the field of panRAS inhibition. These inhibitors are effective against both wild-type and various mutant forms of KRAS. The usual HRAS and NRAS signaling is spared by these compounds, leading to a more tolerable side effect profile. Therefore, compared to pan-RAS inhibitors, KRAS isoformselective targeting might offer a safer option in terms of toxicity. There is a lack of current clinical data on the safety of KRAS-specific targeting in humans. On the other hand, resistance might emerge by compensatory signaling via wild-type NRAS or HRAS isoforms if precise KRAS targeting is allowed. It is uncertain if pan-KRAS inhibitors will be able to evade resistance, as is the case with pan-RAS inhibitors, but as a class, they have shown wide efficacy across a variety of tumors with KRAS mutations, and several have progressed into clinical trials.

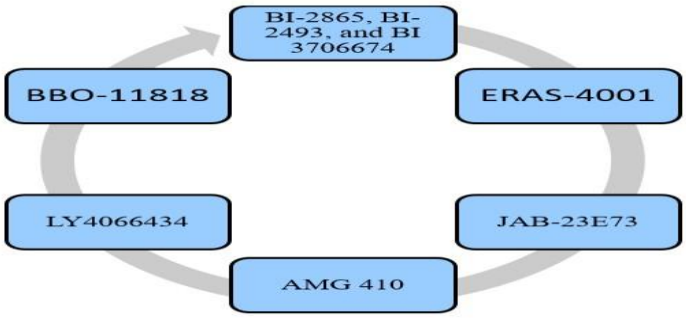

Fig. 3. Pan-KRAS inhibitors

BI-2865, BI-2493, and BI 3706674

The pan-KRAS inhibitor BI-2865 binds to RAS in its GDP-bound inactive form and reversibly targets various KRAS mutations, including as G12C, G12D, G12V, and G13D. Chemical experiments show that BI-2865 strongly inhibits RAS, with IC50 values in the nanomolar range; it selectively inhibits cancer cell growth with mutant KRAS but not with HRAS or NRAS mutations. Although BI-2865 had modest effects on MAPK signaling in WT KRAS cancer cell lines, it markedly reduced ERK phosphorylation in KRAS-mutant cancer cell lines, suggesting that it repressed downstream MAPK signaling.

ERAS-4001

An innovative pan-KRAS inhibitor, ERAS-4001 binds to wild-type KRAS as well as

International Journal of Engineering, Science and Humanities
An international peer reviewed, refereed, open access journal
Impact Factor: 8.3 www.ijesh.com ISSN: 2250 3552

many KRAS G12X mutants, inhibiting downstream RAF protein interaction in both the GTP and GDP-loaded states with nanomolar efficacy in the single digits. When compared to HRAS and NRAS, biochemical investigations reveal that KRAS is quite selective. Nanomolar IC50 values were observed for ERAS-4001 in cellular experiments, where it inhibited ERK phosphorylation and decreased proliferation across NSCLC, PDAC, and CRC cell lines amplified by wild-type and mutant KRAS.

JAB-23E73

One other pan-KRAS inhibitor that works against both GDP- and GTP-bound KRAS is JAB-23E73. According to research, JAB-23E73 has nanomolar IC50 values and suppresses ERK phosphorylation, which in turn reduces the growth of cancer cell lines that carry mutant KRAS or amplified wild-type KRAS. The medication's ability to decrease ERK phosphorylation in tumors from mice treated with JAB-23E73 was shown to be correlated with tissue and plasma levels of the drug.

AMG 410

One reversible pan-KRAS inhibitor, AMG 410, binds to the same allosteric region as another, sotorasib, which is an inhibitor of KRAS G12C. AMG 410 showed strong antiproliferative effects in cell lines with a KRAS mutation and a selectivity for KRAS that was 100 times higher than that of HRAS and NRAS.

LY4066434

LY4066434 is a small-molecule pan-KRAS inhibitor that is highly selective for NRAS and HRAS; it is taken orally. In mice models of gastric, colorectal, non-small cell lung, and prostate cancers (NCL), the chemical showed strong anticancer effects. Even in orthotopic NSCLC animal models, LY4066434 stifled the development of metastatic brain tumors mutated in KRAS.

BBO-11818

BBO-11818 is a pan-KRAS inhibitor that may be taken orally and binds to mutant KRAS in both its active and inactive forms without forming a covalent bond. By keeping KRAS in its inefficient "dark" state 1 conformation and preventing GTP-bound KRAS from associating with RAF1, this pan-KRAS inhibitor inhibits RAS-RAF signaling. BBO-11818 inhibited MAPK signaling and the growth of KRAS-mutant cells with low nanomolar potency, according to cell-based tests. In mice tumor xenograft models for NSCLC, PDAC, and CRC CDX, BBO-11818 showed promising PK/PD and anticancer efficacy.

Limitations of Daraxonrasib and Next-Generation RAS-Targeting Strategies

Suppression of RAS-dependent mitogenic signaling and tissue homeostasis in normal epithelial compartments might explain the frequent incidence of rash, diarrhea, and stomatitis or mucositis. In the ternary complex, KRAS Y64 alterations reduce daraxonrasib binding, whereas KRAS Y71 mutations boost natural RAS-RAF binding, which promotes signaling via

International Journal of Engineering, Science and Humanities
An international peer reviewed, refereed, open access journal
Impact Factor: 8.3 www.ijesh.com ISSN: 2250 3552

drug-resistant effector complexes. Table II and the following discussion outline potential methods that might augment or prolong pan-RAS inhibition.

TABLE II. EMERGING RAS-TARGETING STRATEGIES

Strategy	Concept and examples	Advantages	Disadvantages
Pan-KRAS inhibition [12]	Inhibits multiple mutant and wildtype KRAS proteins while sparing NRAS and HRAS; BI 3706674	Broad KRAS coverage; potential safety advantage over panRAS inhibition; oral small-molecule development	Potential toxicity from wild-type KRAS inhibition; potential compensation by NRAS or HRAS
RAS degradation [13]	E3 ligase-mediated elimination of RAS; setidegrasib, ASP5834	Deep and potentially prolonged target suppression; removal of the entire protein	High molecular weight and limited oral exposure; current clinical RAS degraders require intravenous administration; dependence on E3 ligase activity and target resynthesis
Protein-based RAS inactivation	Competitive or catalytic RAS inactivation; PencRaf-v1, RRSP-RBD	Broad RAS coverage; modular protein engineering; catalytic and irreversible RAS cleavage by RRSPRBD	Intracellular delivery, clearance, and immunogenicity
Tumor-selective delivery [14][15][16]	DACs, masked biologics, aptamer or nanoparticle systems	May reduce normaltissue toxicity and widen the therapeutic window	Antigen heterogeneity or loss; inefficient internalization and endosomal escape; manufacturing complexity

AI-Driven Precision Oncology and Emerging Predictive Biomarkers in RAS-Driven Cancers

With the advent of precision oncology, cancer treatment has undergone a sea change, moving away from standard chemotherapy and toward more focused and individualized approaches. Although conventional chemotherapy is good at lowering tumor burden, it is not very targeted and can cause systemic toxicity and other negative side effects [17]. Targeted treatments selectively impede oncogenic pathways with minimal damage to normal tissues [18]

International Journal of Engineering, Science and Humanities
An international peer reviewed, refereed, open access journal
Impact Factor: 8.3 www.ijesh.com ISSN: 2250 3552

thanks to advances in cancer genomics and molecular biology that have allowed the discovery of tumor-specific genetic alterations. Precision oncology has been revolutionized by AI, which uses advanced computer approaches to improve cancer detection, prognostic prediction, and treatment decision-making. Algorithms trained on massive datasets of genetic profiles, radiological scans, and histological pictures can detect minor patterns linked to cancer development and response to therapy [19].

AI in Cancer Diagnostics and Prognostics

Research and clinical applications of AI are quickly altering cancer detection, characterization, and clinical evaluation methods. Traditional diagnostic and prognostic approaches may not be able to handle the increasing complexity and amount of imaging, pathology, genomic, and clinical data, despite their reliability and long history of use [20]. By combining large and multidimensional datasets, AI improves diagnostic accuracy and efficiency in radiology, digital pathology, and molecular testing. Simultaneously, recurrence risk, treatment efficacy, and survival rates are becoming more and more predicted using machine learning algorithms, which allows for more individualized patient care. Artificial intelligence is playing an increasingly important role in risk stratification frameworks, which help with therapy selection and clinical decision-making, as these capabilities come together.

Radiology and Image-Based Diagnostics

Artificial intelligence (AI) has the potential to revolutionize radiological imaging, a key area of cancer care. Pattern recognition works well with the comprehensive, high-dimensional data produced by modalities including mammography, CT, MRI, and PET. Artificial intelligence algorithms, and deep learning models in particular, can locate and describe tumors with remarkable precision, frequently picking up on minor characteristics that humans may overlook. **Digital Pathology**

In cancer research, histopathology provides valuable visual data in addition to radiological imaging. With the advent of whole-slide imaging, the door has been opened to robust AI applications in histopathology, the diagnostic gold standard in cancer [21]. Helping pathologists with tasks like tumor grading, mitosis detection, and subtype categorization, deep learning algorithms can examine cellular shape, tissue architecture, and biomarker expression with amazing precision.

Molecular and Genomics-Based Diagnostics

Modern molecular profiling tools, including as next-generation sequencing, have generated massive datasets that are crucial for precision oncology but difficult to manually analyze [22]. To aid in the identification of driver mutations, the classification of tumor subtypes, and the detection of actionable biomarkers, AI allows the fast and scalable analysis of expression patterns, multi-omics signatures, genomic changes, and driver mutations.

International Journal of Engineering, Science and Humanities
An international peer reviewed, refereed, open access journal
Impact Factor: 8.3 www.ijesh.com ISSN: 2250 3552

Risk Assessment and AI-Guided Prevention

Cancer diagnosis and early risk assessment using artificial intelligence are two areas that are seeing significant growth in recent years. Artificial intelligence may identify nuanced, multivariate patterns linked to cancer risk by sifting through large datasets that include medical records, family histories, lifestyle variables, imaging tests, and genetic profiles.

Literature Review

Recent studies have improved patient selection and treatment methods for KRA Smutant malignancies through the use of RAS-pathway targeting, biomarkers, KRAS inhibitors, and AI-based techniques.

Josh Wheeler *et. al.* (2024) provide updates on the development of Responder ID™ KRAS, an innovative RNA-based biomarker that can use RNA sequencing data to stratify the response of lung cancer patients to the KRAS G12C inhibitor. With training on hundreds of lung cancer samples, their biomarker predicts treatment response by combining the two primary KRAS biologic axes, activation and dependence, to find individuals with the best chance of responding. Up to this point, Responder ID™ KRAS's performance features have been assessed using a real-world dataset consisting of patients with lung cancer who have been treated with Sotorasib. Clinical trial design, therapeutic effectiveness selection, rational combination strategy identification, and expedited approvals across therapeutic settings are all aided by Responder ID™ KRAS, an independent biomarker [23].

Yue Zhou *et. al.* (2024) elucidate the most recent developments in biomarker-based anticancer therapies, which are gaining momentum as prospective cancer therapeutic strategies and breakthroughs. Additionally, they address the field's limitations and concerns, offering insights and viewpoints on how to transform obstacles into possibilities. This study highlights the potential benefits of discovering and using various tumor biomarkers. These biomarkers have the potential to improve precision medicine and open up new avenues for future research [24].

Xuan Wu *et. al.* (2023) review the current state of small-molecule inhibitors that are being tested in clinical trials to enhance the prognosis of tumors mutated in RAS, including those that directly inhibit KRAS, those that pan-RAS, those that inhibit RAS effector signaling, and those that work in combination with RAS inhibitors or immune checkpoint inhibitors [25].

Hao Wang *et. al.* (2023) analyzed publications published in 2022 regarding the development of KRAS inhibitors that may be used to treat cancer. In order to facilitate the development of more powerful inhibitors targeting different mutated-KRAS with desirable drug-like characteristics, the following aspects were emphasized: design strategies, discovery processes, structure-activity relationship (SAR) studies, cocrystal structure analysis, and in vitro and in vivo activity [26].

International Journal of Engineering, Science and Humanities
An international peer reviewed, refereed, open access journal
Impact Factor: 8.3 www.ijesh.com ISSN: 2250 3552

Cen Liu *et. al.* (2023) provide a concise overview and comparison of the biochemical and structural characteristics of various RAS mutations. In addition, clinical data are used to compile the pathological features and treatment outcomes of various malignancies that possess RAS mutations. There is also a synopsis of the research and development of RAS inhibitors that aim at the downstream components of the RAS pathway. With optimism, this study will increase their understanding of RAS-targeting techniques and encourage more research into the potential of novel RAS allele-specific inhibitors [27].

Da Zhao *et. al.* (2022) examined 33 different types of tumor tissues for differences in KRAS expression. Furthermore, they investigated the correlation between KRAS expression levels and clinicopathological characteristics, tumor immunity, diagnostic and prognostic values, and more. The PPI network was built by carefully selecting KRAS genes, immunological checkpoint genes, and interacting genes. For this association analysis, they used 79 immune checkpoint genes and their relevant interaction genes. To identify the KRAS and other cancer-related co-expressed genes, they used genome set enrichment analysis (GSEA) on 33 tumor expression datasets. There is hope that KRAS may be incorporated into cancertargeted medications and that it is a valid predictive biomarker for cancer patients [28].

Sophia J. Wagner *et. al.* (2022) establish a novel transformer-based pipeline that integrates a pre-trained transformer encoder with a transformer network for patch aggregation to provide end-to-end biomarker prediction from pathology slides. In comparison to state-ofthe-art algorithms, their transformer-based method greatly enhances performance, generalizability, data efficiency, and interpretability. A sensitivity of 0.99 and a negative predictive value of over 0.99 for the prediction of microsatellite instability (MSI) on surgical resection specimens were achieved after training and evaluation on a large multicenter cohort of more than 13,000 patients from 16 colorectal cancer cohorts [29].

Salman R. Punekar *et. al.* (2022) offer summary of the RAS pathway and examine the history, present state, and future prospects of therapeutic approaches aimed at inhibiting oncogenic RAS, with the hope that they may enhance prognoses for patients afflicted with RAS-mutant cancers. Afterward, go over the difficulties caused by resistance mechanisms and possible solutions to these problems [30].

TABLE III. SUMMARY OF RECENT STUDIES ON KRAS-TARGETED THERAPY AND BIOMARKER DEVELOPMENT

Author & Year	Focus	Benefits	Contributions	Recommendation
Josh Wheeler et al. (2024)	Development of ResponderID™ KRAS, an	Enables identification of patients most likely to respond to KRAS	Created a biomarker that takes KRAS activity and dependence into account; tested it in actual lung	Prior to routinely use ResponderIDTM KRAS in clinical practice, it is

International Journal of Engineering, Science and Humanities
An international peer reviewed, refereed, open access journal
Impact Factor: 8.3 www.ijesh.com ISSN: 2250 3552

	RNA-based biomarker for predicting KRAS G12C inhibitor response in lung cancer	G12C inhibitors and may improve treatment selection	cancer patients who had received sotorasib.	recommended to conduct further validation trials with varied patient groups.
Yue Zhou et al. (2024)	Biomarker-based anticancer targeted therapies	Supports precision medicine and molecular classification of cancer patients	Identified areas for further study after reviewing the successes, failures, and obstacles of biomarker-based targeted medicines	Improve biomarker validation, standardization, and clinical integration to enable more precise treatment decisions
Xuan Wu et al. (2023)	Small-molecule inhibitors and combination strategies for RAS-mutant cancers	Provides multiple therapeutic strategies for cancers driven by RAS mutations and may help overcome treatment limitations	Analyzed immune checkpoint inhibitors, individual RAS inhibitors, pan-RAS inhibitors, combo treatments, and direct KRAS inhibitors	Prioritize development of effective RAS-targeted combinations and investigate strategies for overcoming resistance
Hao Wang et al. (2023)	Research and development of KRAS inhibitors	Facilitates development of more potent and selective KRAS-targeted drugs with improved drug-like properties	Summarized inhibitor design, discovery, SAR studies, co-crystal structures, and in vitro/in vivo activities	Keep working on improving KRAS inhibitors through structure-guided drug design for various KRAS mutations
Cen Liu et al. (2023)	Structural, biochemical, and therapeutic characteristics of RAS mutations	Improves understanding of mutation-specific biology and potential therapeutic vulnerabilities	Compared different RAS mutations, cancer characteristics, treatment responses, and direct/indirect RAS-targeting approaches	Develop allele-specific RAS inhibitors and conduct more studies on mutation-specific therapeutic strategies
Da Zhao et	KRAS expression, prognosis, and	May improve cancer diagnosis, prognosis	Investigated the correlation between KRAS expression and 33 different tumor	Validate KRAS as a prognostic and therapeutic biomarker

International Journal of Engineering, Science and Humanities
An international peer reviewed, refereed, open access journal
Impact Factor: 8.3 www.ijesh.com ISSN: 2250 3552

al. (2022)	tumor immunity across cancers	assessment, and identification of potential therapeutic targets	types, as well as prognosis, clinicopathological features, immunological checkpoints, and gene pathways.	through experimental and clinical studies
Sophia J. Wagner et al. (2022)	Transformer-based biomarker prediction from pathology slides	Provides highly sensitive and generalizable biomarker prediction while reducing reliance on conventional testing	Created a pipeline based on transformers and proved good at predicting MSI in over 13,000 colorectal cancer patients from 16 different cohorts.	Continue to prospectively verify AI-based pathology biomarkers and evaluate their therapeutic utility for a variety of other cancers.
Salman R. Punekar et al. (2022)	RAS pathway and therapeutic strategies for oncogenic RAS	Provides an overview of current treatment approaches and potential methods to overcome resistance	Reviewed RAS biology, therapeutic strategies, resistance mechanisms, and approaches for overcoming treatment resistance	Develop rational combination therapies and investigate resistance mechanisms to improve outcomes in RAS-mutant cancers

Research gaps

There are a number of issues that still need to be addressed, but there is also significant progress. Numerous biomarker methods have yet to be validated in prospective and external clinical studies before they can be used routinely in the clinic. The variability of KRAS mutations and between cancer types also make current biomarkers and therapeutics less broadly applicable. The high rate of resistance to KRAS targeted treatment drugs is a major hurdle and there is a need for rational combination strategies. In addition, multi-omics data integration, AI-driven biomarkers, and clinically validated molecular signatures are not fully developed. Further studies are thus warranted to focus on prospective validation, mutation specific biomarker, mechanisms of resistance, and integrated biomarker-guided treatment strategies. These research gaps are summarized in Table III.

Conclusion and Future Work

The therapeutic paradigm of RAS-driven cancers is transitioning from single KRAS mutations to targeting oncogenic RAS signaling. A significant step in this process is the discovery of Daraxonrasib, which has been shown to target multiple RAS proteins at once, instead of targeting a specific mutant allele. Current evidence that is presented in this paper suggests this more comprehensive strategy might be especially applicable to those tumors with heterogeneous RAS alterations and activated adaptive pathways. The therapeutic value of RAS

inhibition is greater, but it needs to be tempered by the biological relevance of RAS signaling in normal tissue and the development of resistance mechanisms.

AI and multi-omics approaches may improve patient selection and prediction of response to RAS-targeted therapies. Yet, there is a need to further validate current biomarkers for better clinical utility, and the performance of AI can be influenced by the quality and diversity of the data sets. Alteration of the target and reactivation of the pathways can also result in wild type RAS related toxicity and resistance upon pan-RAS inhibition. Future studies are therefore warranted to validate predictive biomarkers, combine multi-omics-based approaches, and develop rational combination therapy to enhance personalized RAS-mediated cancer treatment.

References

[1] K. Chen, Y. Zhang, L. Qian, and P. Wang, "Emerging strategies to target RAS signaling in human cancer therapy," *J. Hematol. Oncol.*, vol. 14, no. 1, p. 116, Dec. 2021, doi: 10.1186/s13045-021-01127-w.

[2] A. Q. Khan *et al.*, "RAS-mediated oncogenic signaling pathways in human malignancies," *Semin. Cancer Biol.*, vol. 54, pp. 1–13, Feb. 2019, doi: 10.1016/j.semcancer.2018.03.001.

[3] A. Kaushik, H. Kest, M. Sood, B. Steussy, C. Thieman, and S. Gupta, "Biofilm Producing Methicillin-Resistant Staphylococcus aureus (MRSA) Infections in Humans: Clinical Implications and Management," *Pathogens*, vol. 13, no. 1, p. 76, Jan. 2024, doi: 10.3390/pathogens13010076.

[4] M. Buyanova *et al.*, "Discovery of a Bicyclic Peptidyl Pan-Ras Inhibitor," *J. Med. Chem.*, vol. 64, no. 17, pp. 13038–13053, Sep. 2021, doi: 10.1021/acs.jmedchem.1c01130.

[5] J. Jiang *et al.*, "Translational and Therapeutic Evaluation of RAS-GTP Inhibition by RMC6236 in RAS-Driven Cancers," *Cancer Discov.*, vol. 14, no. 6, pp. 994–1017, Jun. 2024, doi: 10.1158/2159-8290.CD-24-0027.

[6] J. Desai *et al.*, "Divarasib plus cetuximab in KRAS G12C-positive colorectal cancer: a phase 1b trial," *Nat. Med.*, vol. 30, no. 1, pp. 271–278, Jan. 2024, doi: 10.1038/s41591-023-02696-8.

[7] N. T. Ihle *et al.*, "Effect of KRAS Oncogene Substitutions on Protein Behavior: Implications for Signaling and Clinical Outcome," *JNCI J. Natl. Cancer Inst.*, vol. 104, no. 3, pp. 228–239, Feb. 2012, doi: 10.1093/jnci/djr523.

[8] F. Yan *et al.*, "Abstract LB165: GFH547: An orally bioavailable, cyclophilin A-hijacking panRAS(on) inhibitor with broad spectrum anti-tumor activities," *Cancer Res.*, vol. 84, no. 7_Supplement, pp. LB165–LB165, Apr. 2024, doi: 10.1158/1538-7445.AM2024-LB165.

[9] P. Upadhyaya *et al.*, "Inhibition of Ras Signaling by Blocking Ras–Effector Interactions with Cyclic Peptides," *Angew. Chemie Int. Ed.*, vol. 54, no. 26, pp. 7602–7606, Jun. 2015, doi: 10.1002/anie.201502763.

[10] Z. Xu, D. T. Weaver, R. Drakas, and Y. Lou, "Abstract 2627: The small molecule KRAS inhibitor, TEB-17231, blocks tumor progression and overcomes KRASG12C inhibitor mediated resistance," *Cancer Res.*, vol. 83, no. 7_Supplement, pp. 2627–2627, Apr. 2023, doi: 10.1158/1538-7445.AM2023-2627.

[11] U. N. Wasko *et al.*, "Tumour-selective activity of RAS-GTP inhibition in pancreatic cancer," *Nature*, vol. 629, no. 8013, pp. 927–936, May 2024, doi: 10.1038/s41586-024-07379z.

[12] D. Kim *et al.*, "Pan-KRAS inhibitor disables oncogenic signalling and tumour growth," *Nature*, vol. 619, no. 7968, pp. 160–166, Jul. 2023, doi: 10.1038/s41586-023-06123-3.

[13] J. Popow *et al.*, "Targeting cancer with small-molecule pan-KRAS degraders," *Science*, vol. 385, no. 6715, pp. 1338–1347, Sep. 2024, doi: 10.1126/science.adm8684.

[14] K. B. Hong and H. An, "Degrader–Antibody Conjugates: Emerging New Modality," *J. Med. Chem.*, vol. 66, no. 1, pp. 140–148, Jan. 2023, doi: 10.1021/acs.jmedchem.2c01791.

[15] J. Gao *et al.*, "Engineered bioorthogonal POLY-PROTAC nanoparticles for tumour-specific protein degradation and precise cancer therapy," *Nat. Commun.*, vol. 13, no. 1, p. 4318, Jul. 2022, doi: 10.1038/s41467-022-32050-4.

[16] S. He, F. Gao, J. Ma, H. Ma, G. Dong, and C. Sheng, "Aptamer-PROTAC Conjugates (APCs) for Tumor-Specific Targeting in Breast Cancer," *Angew. Chemie Int. Ed.*, vol. 60, no. 43, pp. 23299–23305, Oct. 2021, doi: 10.1002/anie.202107347.

[17] Z. Dlamini, F. Z. Francies, R. Hull, and R. Marima, "Artificial intelligence (AI) and big data in cancer and precision oncology," *Comput. Struct. Biotechnol. J.*, vol. 18, pp. 2300–2311, Jan. 2020, doi: 10.1016/j.csbj.2020.08.019.

[18] S. Quazi, "Artificial intelligence and machine learning in precision and genomic medicine," *Med. Oncol.*, vol. 39, no. 8, p. 120, Jun. 2022, doi: 10.1007/s12032-022-01711-1.

[19] L. Wei *et al.*, "Artificial intelligence (AI) and machine learning (ML) in precision oncology: a review on enhancing discoverability through multiomics integration," *Br. J. Radiol.*, vol. 96, no. 1150, Oct. 2023, doi: 10.1259/bjr.20230211.

[20] W. Quanyang *et al.*, "Artificial intelligence in lung cancer screening: Detection, classification, prediction, and prognosis," *Cancer Med.*, vol. 13, no. 7, Apr. 2024, doi: 10.1002/cam4.7140.

[21] D. Xiong *et al.*, "Global bibliometric mapping of the research trends in artificial intelligence-based digital pathology for lung cancer over the past two decades," *Digit. Heal.*, vol. 10, Jan. 2024, doi: 10.1177/20552076241277735.

[22] M. Darmofal *et al.*, "Deep-Learning Model for Tumor-Type Prediction Using Targeted Clinical Genomic Sequencing Data," *Cancer Discov.*, vol. 14, no. 6, pp. 1064–1081, Jun. 2024, doi: 10.1158/2159-8290.CD-23-0996.

[23] J. Wheeler *et al.*, "Abstract 6446: ResponderID™ KRAS: Biology-driven machine learning to personalize KRAS inhibitor therapeutics," *Cancer Res.*, vol. 84, no. 6_Supplement, p. 6446, 2024, doi: 10.1158/1538-7445.AM2024-6446.

[24] Y. Zhou *et al.*, "Tumor biomarkers for diagnosis, prognosis and targeted therapy," *Signal Transduct. Target. Ther.*, vol. 9, no. 1, p. 132, 2024, doi: 10.1038/s41392-024-018232.

[25] X. Wu *et al.*, "Small molecular inhibitors for KRAS-mutant cancers," *Front. Immunol.*, vol. 14, Aug. 2023, doi: 10.3389/fimmu.2023.1223433.

[26] H. Wang *et al.*, "Annual review of KRAS inhibitors in 2022," *Eur. J. Med. Chem.*, vol. 249, p. 115124, Mar. 2023, doi: 10.1016/j.ejmech.2023.115124.

[27] C. Liu *et al.*, "RAS-targeted cancer therapy: Advances in drugging specific mutations.," *MedComm*, vol. 4, no. 3, p. e285, Jun. 2023, doi: 10.1002/mco2.285.

[28] D. Zhao, L. Wang, Z. Chen, and L. Zhang, "KRAS is a prognostic biomarker associated with diagnosis and treatment in multiple cancers," vol. 4, no. October, pp. 1–13, 2022, doi: 10.3389/fgene.2022.1024920.

[29] S. J. Wagner *et al.*, "Transformer-based biomarker prediction from colorectal cancer histology: A large-scale multicentric study," *Cancer Cell*, vol. 41, no. 9, pp. 1650-1661.e4, Sep. 2023, doi: 10.1016/j.ccell.2023.08.002.

[30] S. R. Punekar, V. Velcheti, B. G. Neel, and K.-K. Wong, "The current state of the art and future trends in RAS-targeted cancer therapies," *Nat. Rev. Clin. Oncol.*, vol. 19, no. 10, pp. 637–655, 2022, doi: 10.1038/s41571-022-00671-9.