Title

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Cancer Therapy Utilizing the RAS Protein Family

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Abstract

The RAS protein family functions as binary switch proteins toggling between active (GTP-bound) and inactive (GDP-bound) states, regulating pivotal cellular pathways like PI3K, MAPK, and Ral-GEF. Dysregulation of Ras signaling, often via mutations, leads to constitutive activation of downstream pathways, driving uncontrolled cell proliferation, a hallmark of cancer. Targeting aberrant Ras signaling pathways with small molecular inhibitors represents a promising therapeutic strategy in cancer treatment. This review examines three main approaches: Farnesyltransferase inhibitors (FTIs), upstream regulation of KRAS, and kinase inhibitors targeting RAS effector pathways. FTIs: inhibiting Ras activation, exhibit cytostatic effects on cancer cells, with clinical trials demonstrating promising activity in various cancer types. Sotorasib: a KRAS p.G12C inhibitor, shows efficacy in KRAS p.G12C-mutated cancers, including pancreatic and non-small cell lung cancers, highlighting its potential as a targeted therapy. Additionally, kinase inhibitors targeting RAS effector pathways demonstrate efficacy in preclinical and clinical settings, with recent advancements in identifying direct RAS inhibitors showing promising results. Despite challenges such as drug resistance, ongoing research aims to develop more effective inhibitors, offering hope for improved cancer therapies targeting RAS-driven malignancies.

Introduction

The RAS protein family originated from experiments on Rat Sarcoma. RAS proteins are binary switch proteins, alternating from ON to OFF, the protein is also considered an auto-off switch. The OFF confirmation is an inactive guanosine diphosphate (GDP) bound state while the ON confirmation is an active guanosine triphosphate (GTP) bound state. From OFF to ON, GEF (Guanine nucleotide exchange factors) will bind to RAS to turn on the protein, and to turn off the protein GAP (GTPase-activating proteins) binds to RAS (Simanshu, 2017).

RAS plays many roles in the human body, but the main three pathways: PI3K, MAPK,

and Ral-GEF, contribute to cell transformation. Transformation may include activation of cell proliferation and division or inhibition of cell cycle arrest. These roles that RAS plays in cell development explain the connections between the RAS protein and cancer induction. Since RAS acts as an auto-OFF switch, many mutations can lead to RAS being in a constitutively ON configuration. Eventually, this leads to cell proliferation pathways to also be constitutively active.

Mutations in RAS genes can lead to the persistent activation of RAS proteins, trapping them in a perpetually "ON" state. Consequently, downstream pathways governing cell proliferation remain active, fostering uncontrolled cell growth—an established hallmark of cancer progression.

Furthermore, RAS proteins frequently engage with various pivotal signaling molecules within these pathways. For instance, in the MAPK pathway, RAS triggers the activation of RAF kinases, which subsequently catalyze the phosphorylation and activation of MEK. This cascade ultimately leads to the activation of downstream effectors such as ERK. Additionally, RAS interacts with a diverse array of proteins, including PI3K, Ral-GEFs, and downstream effectors like AKT, thereby influencing cellular processes such as survival, growth, and proliferation. Comprehending the intricate interplay between RAS proteins and their associated pathways, as well as their dysregulation in cancer, is a pivotal endeavor in developing targeted therapeutic interventions to combat malignancies propelled by aberrant RAS signaling.

Since RAS is a kinase protein, small molecular inhibitors are the main mechanism of action against cancer-inducing RAS behavior. This research paper will analyze different papers in their findings of such inhibitors, including Farnesyltransferase inhibitors, upstream regulation of KRAS, and kinase inhibitors targeting RAS effector pathways. Developing successful

treatment plans requires a thorough understanding of the complex mechanisms behind RAS signaling pathways in cancer. Sustained cell proliferation is a characteristic of cancer caused by the abnormal activation of RAS proteins caused by mutations. This instability is brought about by RAS's persistent interaction with important signaling molecules, which sustains downstream processes necessary for cell division and survival. As a result, investigating various strategies to mitigate the carcinogenic effects of RAS is imperative. The creation of tiny chemical inhibitors that specifically target RAS activity is one well-known field of study. By preventing RAS and its downstream effectors from constitutively activating, these inhibitors seek to impede the development and spread of tumors. Studies have looked into several inhibitor classes, such as kinase inhibitors that target RAS effector pathways, modulators of KRAS's upstream regulators, and Farnesyltransferases. We can improve our ability to successfully combat RAS-driven malignancies by gaining insights into the effectiveness and mechanisms of action of these inhibitors through a thorough analysis of the data from these studies.

Methods

The research question this review paper desires to address is, “How does the RAS protein affect cancer therapy?” To answer this question, this paper focuses on three commonly researched methods of cancer therapy involving the RAS protein: farnesyl transferase inhibitors, the upstream regulation of KRAS, and kinase inhibitors targeting RAS effector pathways. Previous experiments involving each method of interaction with the RAS protein and its pathways were introduced, presented, analyzed, and discussed throughout three sections, along with the treatments’ limitations.

When gathering academic journals or papers to use in this review paper, search terms such as “cancer treatment and RAS protein,” “effectiveness of RAS protein in cancer treatment”

“RAS proteins and farnesyl transferase inhibitors in cancer therapy,” “KRAS upstream regulation,” and “RAS effector pathways and kinase inhibitors” were pertinent to the paper. In addition, keywords such as “the RAS protein,” “cancer treatment,” “farnesyl transferase inhibitors,” “KRAS,” “kinase inhibitors,” and “possibilities of RAS protein cancer treatment” were used multiple times throughout the research process.

Moving on, various inclusion and exclusion criteria were implemented to enhance the relevance and accuracy of the review paper. For example, the main inclusion factor of a source was its relevance to the topic. As the review paper is divided into three sections of specific treatment options related to the RAS protein, the source must contain significant information about the specific treatment option or the RAS protein itself. Another inclusion criterion was if a paper was published by a reliable or peer-reviewed source. This was done to strengthen the review paper’s credibility. However, because there were a limited number of studies on specific methods used to target cancer through the RAS protein or its pathway, the choices of research papers, in terms of their date of publication, were considerably flexible. While most experimental studies that are included in the review paper were published within the last ten years, some papers are within 20 years of publication.

Farnesyltransferase Inhibitors

Introduction

Farnesyltransferase inhibitors (FTIs) are a class of small-molecule cancer drugs that inhibit the proper functioning of the Ras protein which is an essential protein that regulates the cellular pathways responsible for proliferation and survival. Ras proteins are protein-oncogenes that are frequently mutated in human cancers. The exact mechanism of action for this class of agents is currently unknown, however, there are theories as to how it plays a role as a therapeutic

agent for cancer. It is thought that these agents block Ras activation through inhibition of the enzyme farnesyltransferase, ultimately resulting in cell growth arrest. By this inhibition, a blockade of the signal transduction pathway is accomplished with cessation of cell growth which is thought to have anti-cancer properties. FTIs have significant effects on cancer cells; these effects can be categorized into four types: inhibition of anchorage-independent growth, changes in cell cycle progression, induction of apoptosis in cancer cells, and changes in cell morphology. This section will explore the effects FTIs have on the cell cycle and tumor growth, and it will review clinical trials that test the efficacy of FTIs on cancer.

Results/Data

One of the major effects of FTIs consistently observed in several cancer cell lines is the alteration of the cell cycle. The cell cycle effects of the FTIs depend on the cell lines used. Some cells respond to FTIs by inducing the accumulation of G0/G1 phase cells with a concomitant decrease in S-phase cells. Other cell lines show accumulation of G2/M phase cells by the treatment with FTIs. The cell cycle profile of some cell lines is unaffected by FTIs. See Table 1 for the summarized results.

Table 1.

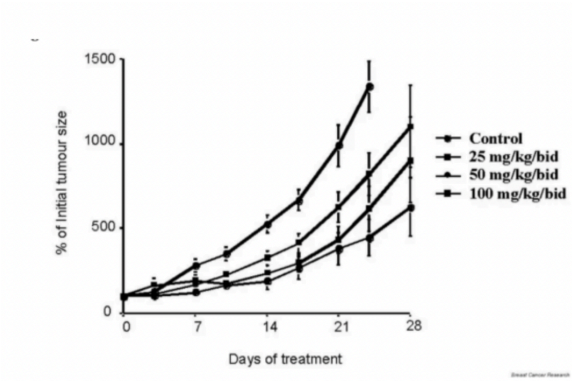
Table 1. Cell cycle effects of FTI.

	% age of cells in G0/G1		% age of cells in G2/M		% age of cells in S	
		+ FTI		+ FTI		+ FTI
Exp. 1 (SCH56582)						
LNCaP	57	91	10	3	33	6
MDA-MB468	50	70	14	20	36	10
PA1	54	74	15	9	31	17
HeLa	62	72	11	15	27	13
HL60	34	41	51	50	15	9
Exp. 2 (SCH66336)						
NIH3T3/H-ras	60	80	5	5	35	15
T24	75	90	7	2	18	8
HCT116	49	29	12	36	39	35
NCI-H460	49	43	11	25	40	32
MCF-7	36	32	26	36	38	32
MIA Pa Ca-2	52	34	13	34	35	32
T47-D	47	49	16	17	37	34
Exp. 3 (FTI-277)						
T24	37	63	26	20	37	17
HT1080	32	78	24	18	44	4
Calu-1	53	34	16	42	31	24
Colo-357	51	43	15	28	34	29
SKBr3	59	52	13	22	28	26
A-253	59	52	13	22	28	26
MDA-MB231	55	60	17	16	28	24
Panc-1	55	46	21	24	24	30

Percentage of cells in G0/G1, G2/M or S phase are shown for FTI treated (+FTI) and untreated cells. Exp. 1 is from Tamanoi, unpublished results. Exp. 2 is from [35]. Exp. 3 is from [39].

Another significant observation was that many of the cellular effects of FTIs on breast cancer appeared to be cytostatic rather than cytotoxic and that, after removal of FTI from the culture medium, cells reverted to their transformed phenotype. In hormone-sensitive, estrogen receptor (ER)-positive MCF-7 breast cancer xenografts, the FTI r115777 appeared cytostatic on tumor growth in vivo. Still, analysis of FTI-treated xenografts revealed a significant fall in cell proliferation index (Ki-67) and induction of the CDK inhibitor, together with a twofold rise in apoptotic scores as seen in Figure 1.

Figure 1.



Dose-related effects of the farnesyltransferase inhibitor tipifranib on the growth of oestrogen receptor-positive MCF-7 breast cancer xenografts. Reproduced with permission from Kelland and coworkers 19.

FTIs reduce the reversion of morphological changes induced by Ras, block anchorage-independent growth, and induce apoptosis in vitro. FTIs were also shown to reduce the expression of vascular endothelial growth factor (VEGF) in malignant cell lines and consequently, angiogenesis was decreased in mice bearing human tumors. Over 70% of the cancer cell lines investigated are sensitive to FTIs. In vivo experimental studies revealed that FTIs block growth in both solid and non-solid tumors with little toxicity which suggests potential usefulness in treating cancer in which clinical trials have been performed.

The results of eight phase I trials with SCH66336 and R115777 are reviewed in Table 2.

Toxicity depends on dose and administration. While the optimal dose and schedule remain undetermined, early indications of clinical efficacy are encouraging.

Table 2.

	% age of cells in G0/G1	+ FTI	% age of cells in G2/M	+ FTI	% age of cells in S	+ FTI
Exp. 1 (SCH56582)						
LNCaP	57	91	10	3	33	6
MDA-MB468	50	70	14	20	36	10
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T24	37	63	26	20	37	17
HT1080	32	78	24	18	44	4
Calu-1	53	34	16	42	31	24
Colo-357	51	43	15	28	34	29
SKBr3	59	52	13	22	28	26
A-253	59	52	13	22	28	26
MDA-MB231	55	60	17	16	28	24
Panc-1	55	46	21	24	24	30

Percentage of cells in G0/G1, G2/M or S phase are shown for FTI treated (+FTI) and untreated cells. Exp. 1 is from Tamanoi, unpublished results. Exp. 2 is from [35]. Exp. 3 is from [39].

Three FTIs undergoing clinical testing as monotherapy are listed in Table 3. These FTIs are Zarnestra, SCH66336, BMS-214662. Study types, tumor types, schedule/MTD, toxicities, and responses are all listed to determine the viability of FTIs in cancer treatments. The preliminary results highlighted in the table showcase much variability with some tumor types displaying more favorable responses to treatment. The viability of FTIs ultimately depends on the balance between therapeutic benefits and associated toxicities. Further investigations considering optimal dosing and combination therapies could increase the utility of FTIs in cancer treatment in the future.

Table 3.

Results of FTI in clinical trials

Study type (phase)	Tumour type	Schedule/MTD	Toxicities (DLTs are in italics)	Responses	Ref.
R115777					
Mono (I)	Solid	Oral 50–500 BID, continuous; MTD—300 BID	*Neutropenia, thrombocytopenia, neurosensory/motor,* skin hypersensitivity, leucopenia	1/18:PR in NSCLC 3/18: evidence of activity in CRC, pancreatic.	[12]
Mono (I)	Solid	Oral solution 25–850 mg BID or cap 500–1300 mg BID 5d q14d; MTD—500 mg BID	*Neuropathy, fatigue*, nausea, vomiting, headache, anaemia, and hypotension	1/27: SD in CRC	[63]
Mono (I)	Solid	Oral 100–400 mg BID×21d q28d; MTD—300 mg BID	*Neutropenia/leucopenia,* fatigue, fever, anorexia, nausea, vomiting, and increasing alkaline phosphatase	–	[64]
Mono (I)	Solid	Oral 200–300 mg BID×28d q35–42 d; MT—D-300 mg BID	Myelosuppression	-	[65]
Mono (I) Paediatric	Solid and plexiform neurofibromas	Oral 150–375 mg/m^2 BID×21d q28d; MTD—200 mg/m^2 BID	*Neutropenia, thrombocytopenia, rash, hypofibrinogenemia, vomiting, diarrhoea,* abdominal pain, headache, fatigue, anaemia, nausea	-	[66]
Mono (I)	Leukaemia	Oral 100–1200 mg BID; MTD-1200 mg BID×21 days	*Neurotoxicity —ataxia, confusion, and dysarthria,* nausea, renal insufficiency, paresthesia, polydipsia, myelosuppression	2/34: CR 8/34: PR	[9,13]
Combo with gemcitabine (I)	Solid	FTI—oral 100–300 mg BID and gemcitabine—i.v. 1000 mg/m^2 days 1, 8 and 15 q28d; MTD—200 mg BID	*Neutropenia,* thrombocytopenia, nausea, vomiting, fatigue	None	[67]
Combo with topotecan (I)	Solid	FTI—oral 200–300 BID×21d q28d and topotecan 1.0–1.25 mg/m^2 qd×5d q28d; MTD—200/1.0	*Neutropenia, thrombocytopenia,* fatigue, nausea, diarrhoea	–	[68]
Combo with docetaxel (I)	Solid	FTI—oral 200–300 mg BID continuous, ×7 and ×14d and docetaxel 75 mg/ m^2×3d q21d; MTD—not reached	Asthenia, diarrhoea, myalgia, mucositis, neurotoxicity	1/24: CR in breast; 4/24; PR in breast, NSCLC, unknown primary, 6/24: SD	[11]
Combo with capecitabine (I)	Solid	FTI—oral 100–300 mg BID×14d q21d and capecitabine oral 2000–2500 mg/m^2 qd×14d q21d; MTD—300/2250	*Diarrhoea, hand–foot syndrome*, nausea, mucositis, neutropenia, thrombocytopenia	3/27: PR in colon, GB, breast, head/neck; 9/27: SD	[14]
Combo with irinotecan (I)	Mostly Colorectal	FTI—Oral 200–300 mg BID continuous, ×14d q21d and Irinotecan 200–350 mg/ m^2 q21d; MTD—350 mg/m^2 for irinotecan, for FTI—not reached	*Neutropenia, thrombocytopenia,* nausea, vomiting, rash, diarrhoea	–	[69]
Combo with trastuzumab (Herceptin) (I)	Solid (4/7 breast)	FTI—oral 200–400 mg BID×14d q21d and trastuzumab i.v. 4 mg/kg day 1, then 2 mg/kg q7d; MTD—400 mg BID	*Neutropenia, thrombocytopenia,* nausea, vomiting, headache, fatigue	–	[70]
Combo with 5-FU/LV (I)	CRC, pancreas	FTI—oral 200–500 BID×21d q28d or continuous, 5FU-IV 400 mg/m^2 bolus + 600 mg/m^2 22 h infusion q14d and LV-i.v. 200 mg/m^2 q14d; MTD—200 BID intermittent	*Neutropenia, fatigue, paresthesia,* nausea, vomiting, anorexia, diarrhoea	–	[71]

Table 3 (continued).

Study type (phase)	Tumour type	Schedule/MTD	Toxicities (DLTs are in italics)	Responses	Ref.
Mono (II)	Breast	Oral 300–400 mg BID	*Myelosuppression*, paresthesia, diarrhoea, rash, fatigue	3/26: PR; 9/26: SD	[8]
SCH66336					
Mono (I)	Solid	Oral 25–400 mg BID; MTD—350 mg BID×7d q21d	*Nausea, vomiting, diarrhoea, fatigue*, renal insufficiency, anorexia	1/20: PR in NSCLC 8/20: SD	[15]
Mono (I)	Solid	Oral 25–400 mg BID, MTD—300 mg BID continuous	*Myelosuppression, neurocortical toxicity, nausea, vomiting, diarrhoea, renal insufficiency, anorexia*	2/24: SD in pseudomyxoma peritonei and thyroid CA	[79]
Mono (IB)	SCC of head/neck	Randomised to oral 100–300 mg BID×8–14 d or no therapy prior to surgery; MTD—not reached	Nausea, diarrhoea, dehydration, anorexia	3/17 treated: PR	[10]
Combo with gemcitabine (I)	Solid	FTI—oral 100–200 mg BID continuous and gemcitabine—600–1000 mg/m^2 d1, 8, 15 q28d; MTD—100–150 mg FTI and 1000 mg/m^2 gemcitabine	*Nausea, vomiting, diarrhoea, myelosuppression*	2/25: PR in pancreas; 2/25: MR in pancreas, mesothelioma; 11/25: SD	[16]
Combo with paclitaxel (Taxol) (I)	Solid	FTI—oral 100–150 BID, paclitaxel 135–175 mg/m^2; MTD—100 BID/175 mg/m^2	Dehydration, hyperbilirubinaemia, neutropenia with fever, myelosuppression, diarrhoea	8/21: PR in NSCLC, salivary gland; 7/21: SD	[17,18]
Mono (II)	Transitional cell	Oral 200 mg BID continuous (dose escalation q28d)	*Anaemia, neutropenia, thrombocytopenia*, fatigue, anorexia, nausea, vomiting, confusion, dyspnoea, dehydration	1/14: SD, 6/14: PROG	[81]
Mono (II)	Pancreas	Randomised to FTI—oral 200 mg BID or gemcitabine 1000 mg/m^2 q7d×7, then a week off	Nausea, vomiting, diarrhoea, neutropenia, thrombocytopenia (Gem only)	FTI- 2/33 PR, 6/33 SD; Gem—1/30 PR, 11/30 SD	[80]
BMS-214662					
Mono (I)	Solid	i.v. 36–225 mg/m^2 over 1 h q21d and single oral 36–168 mg/m^2 at course 2; MTD—not reached	Nausea, vomiting, diarrhoea, transaminase elevation, somnolence, fatigue, anorexia	1/38: MR in NSCLC, disease reduction in breast, CRC, 'several' pts with SD	[85]
Mono (I)	Solid	i.v. 28–102 mg/m^2 qweek ×4 q6weeks; MTD—not reached	No grade 3 or 4 toxicities	2/12: SD, 6/12: PROG	[86]
Mono (I)	Solid	i.v. 50 mg 1 week prior to oral 50–150/d on qd or BID dosing×14d q21d; MTD—50 mg BID	*Nausea, diarrhoea*, vomiting, abdominal cramping, anorexia, fatigue and fever	1/23: SD; others PROG	[84]
Mono (I)	Solid	i.v. 56–278 mg/m^2 weekly, MTD—278 mg/m^2	*Vomiting, diarrhoea, renal insufficiency*, hypotension, transaminase elevation, neutropenia	1/30: MR in breast	[87,88]
Combo with paclitaxel (I)	Solid	FTI – i.v. 80–120 mg/m^2 over 1 h qweek and paclitaxel 80 mg/m^2 over 1 h qweek; MTD—not reached	Neutropenia, nausea	2/6: ';response' in laryngeal and prostate	[83]
Combo with cisplatin (I)	Solid	FTI—i.v. 126–225 mg/m^2 over 1 h q3 weeks and cisplatin i.v. 75–100 mg/m^2 over 1 or 4 h q3 weeks; MTD—not reached	*Transaminase elevation*, nausea, vomiting, stomatitis, lethargy, neutropenia	2/10: SD	[89]

Table 3 (continued).

Study type (phase)	Tumour type	Schedule/MTD	Toxicities (DLTs are in italics)	Responses	Ref.
L-778,123					
Mono (I)	Solid	i.v. continuous for 2 weeks at 140–840 or 4 weeks at 560 mg/m^2/day followed by 1 week off; MTD—840 mg/m^2/day on 2-week schedule	*Prolonged QTc, neutropenia*	None	[90]
Combo with XRT (I)	Solid	i.v. 280–560 mg/m^2/d week 1,2,4 and 5 of 7-week radiotherapy regimen; MTD—not reached	None reported	2/13: CR in head/neck; 2/13: PR in NSCLC	[92]
Combo with paclitaxel (I)	Solid	FTI—i.v. continuous 280 mg/m^2/d×7d and paclitaxel i.v. 175 mg/m^2 bolus	Hypersomnolence, tachycardia, hypotension, sensory neuropathy, dyspnoea, neutropenia with sepsis, mild abnormalities in the electroretinogram, increases in QTc	None	[91]

CA, cancer; combo, combined with; 5-FU, 5-fluorouracil; LV, leucovorin; SCC, squamous cell carcinoma; pts, patients; PROG, progressed; XRT, radiotherapy; CR complete response; PR, partial response; MR, minimal response, i.v., intravenous; MTD, maximum tolerated dose; DLT, dose-limiting toxicity; BID, twice daily; NSCLC, non-small cell lung carcinoma?; CRC, colorectal carcinoma; SD stable disease; d, day; qd, daily; GB, gall bladder; QTc, corrected QT interval on electrocardiogram; FTI, farnesyl transferase inhibitor.

Discussion

Though the exact mechanisms of action for FTIs are currently unknown and require further research, these classes of agents do demonstrate the capability of an anticancer agent. FTIs have demonstrated alterations in the cell cycle which leads to a cessation of cell growth, ultimately suggesting anticancer capabilities. It is cytostatic on breast cancer cells and has been tested in clinical trials, however, its efficacy as a monotherapy does not seem promising. It seems that several observations of FTIs in monotherapy do not prove clinically significant antitumor responses. Monotherapy FTIs are not sufficient, but there are promising observations from integrating FTIs with other combinations of anticancer therapies. FTIs, the mechanisms involved, and their synergistic effects with other therapies have yet to be further understood as promising anticancer agents. Potential areas of further research surrounding FTIs include understanding FTIs and the mechanisms involved, but most importantly additional clinical trials assessing its efficacy in combination therapy utilizing different inhibitors, immunotherapies, and traditional methods of cancer treatment such as chemotherapy and radiation.

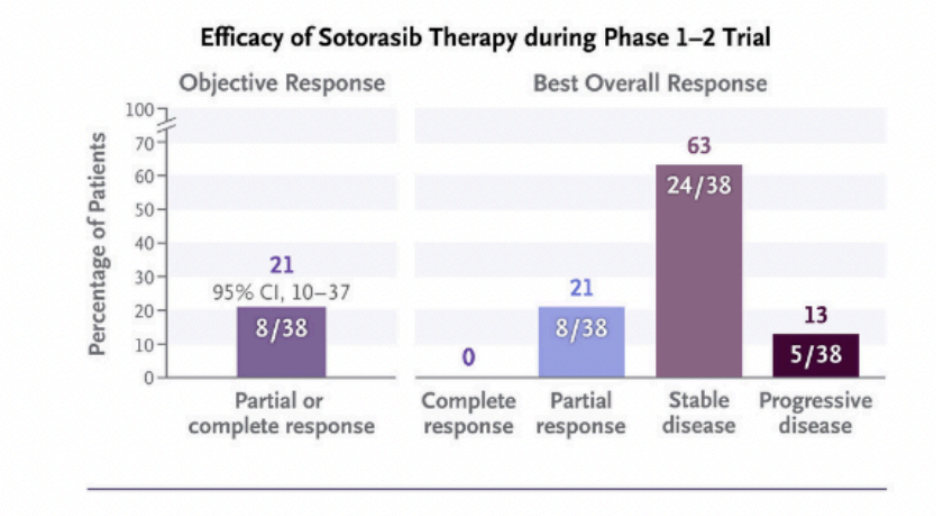
KRAS

Introduction

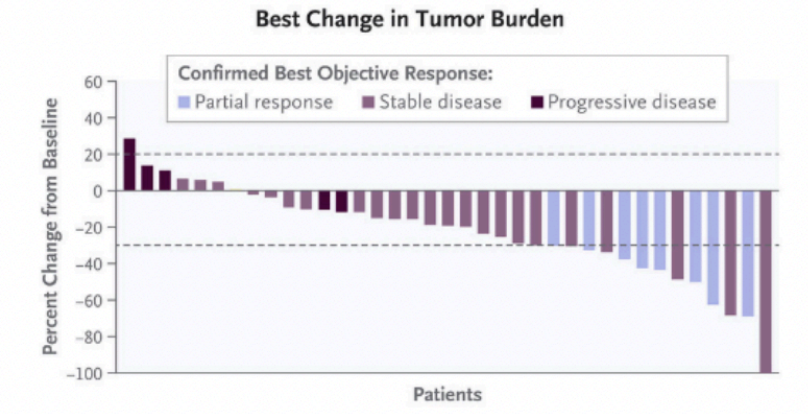
The RAS oncogene is the most frequently mutated oncogene in human cancer with the KRAS isoform being the most frequently mutated, showing up in a large portion of pancreatic, colorectal, lung cancers, and more. Efforts have been made to inhibit KRAS. However, the lack of a binding pocket has made it difficult to develop a direct KRAS inhibitor, until the Shokat lab was able to discover a switch II pocket that can be used to inhibit KRAS. Further advancements based on Shokat's findings led to the creation of Sotorasib, the first therapy to target the KRAS

oncoprotein in KRAS-mutant cancers. Sotorasib has been tested against pancreatic and lung cancer by administering a daily dose of Sotorasib to previously treated cancer patients. In this section, we will present the results of the effectiveness of Sotorasib and discuss its viability as a cancer therapy.

Results/Data



The graph depicts the response of patients with KRAS p. G12C-mutated cancer.



The graph depicts the percent change in tumor burden in patients with KRAS p. G12C-mutated pancreatic cancer.

The graph depicts the response and percent change in tumor burden in patients with KRAS p.G12C-NSCLC

The graph depicts the progression-free survival of patients with KRAS p.G12C-NSCLC The first experiment was a phase 1-2 trial to evaluate the safety and efficacy of Sotorasib in patients with KRAS p.G12C-mutated pancreatic cancer. The objective of Phase 1 was to evaluate the safety and side-effect profile of Sotorasib and identify a recommended dose for Phase 2. In contrast, in Phase 2, the efficacy of that dose was evaluated. Tumor response was assessed by a blinded independent central review according to the Response Evaluation Criteria in Solid Tumors.

Patients who are 18 years or older and are pathologically documented with metastatic cancer and treatment of at least one therapy were included in this study. Exclusion criteria were being positive for HIV, having surgery done in the past 28 days, being pregnant, and having any active brain metastases from non-brain tumors. Each of these additional exclusion

criteria was chosen to maintain patient safety, minimize confounding variables, and enhance the validity of the study. Magnetic resonance imaging or contrast-enhanced computed tomography was used for tumor assessments every six weeks for the first eight assessments and every twelve weeks until the disease progressed or the treatment stopped, whichever occurred later.

The experiment had a total of 38 patients, with 12 patients in phase 1 and 26 patients in phase 2. All patients received a dose of 960 mg daily, and the median duration of the treatment was 18 weeks. Eight patients had a partial response to the treatment with zero patients having a complete response. The median time to a response was 1.5 months and the duration was 5.7 months. Tumor shrinkage of any magnitude was observed in 30 patients. Disease control was observed in 84% of patients. The median progression-free survival was 4.0 months, and the overall survival was 4 months. Adverse events of any grade were observed in all patients with the most common adverse events being abdominal pain, diarrhea, nausea, vomiting, and pyrexia. Adverse events in 16 patients were considered to be connected to the treatment. 14 patients had fatal events, which were evaluated to not be related to the treatment.

The second experiment was a phase 2 trial to evaluate the efficacy and safety of Sotorasib in treating patients with KRAS p.G12C-mutated NSCLC. The inclusion and exclusion criteria are similar to those of the previous experiment. 960 mg doses of Sotorasib were administered daily. Magnetic resonance imaging was used for tumor imaging, and tumor response was assessed by independent central review according to RECIST. The experiment consisted of 126 patients. The median duration of the treatment was 5.5 months. 4 had a complete response and 42 had a partial response. Disease control occurred in 100 patients. Tumor shrinkage was observed in 102 patients, of which the median percentage decrease was 60%. Of the 46 patients that had an

objective response, the median time to respond was 1.4 months, and the duration was 11.1 months. The median progression-free survival was 6.8 months.

Discussion

The data demonstrates that Sotorasib, a KRAS p.G12C inhibitor, is a promising option for KRAS p.G12C-mutated pancreatic cancer and KRAS p.G12C-NSCLC therapy. 21% of patients with KRAS p.G12C-mutated pancreatic cancer exhibited an objective response to Sotorasib therapy, while 37.1% of patients with KRAS p.G12C-NSCLC exhibited an objective response to Sotorasib therapy. The reason behind the variation of percent objective response in patients between types of cancers is unknown, and further studies need to be conducted on the sensitivity of different tumor types to Sotorasib. In addition, around 84% of patients with KRAS p.G12C-mutated pancreatic cancer and around 90% of patients with KRAS p.G12C-NSCLC showed tumor shrinkage. Although the data supports the efficacy of Sotorasib therapy as a monotherapy, additional studies need to be done to evaluate the efficacy of Sotorasib as a part of combination therapy.

Kinase Inhibitors

Introduction

Kinase inhibitors targeting RAS effector pathways represent a promising area of research in cancer treatment. RAS proteins, pivotal in cellular signaling, are frequently mutated in cancers. The RAF-MEK-ERK and PI3K-AKT-mTOR pathways, downstream effectors of RAS, drive cell proliferation, survival, and differentiation. Notably, mutations in RAS can lead to constitutive activation of these pathways, contributing to tumorigenesis.

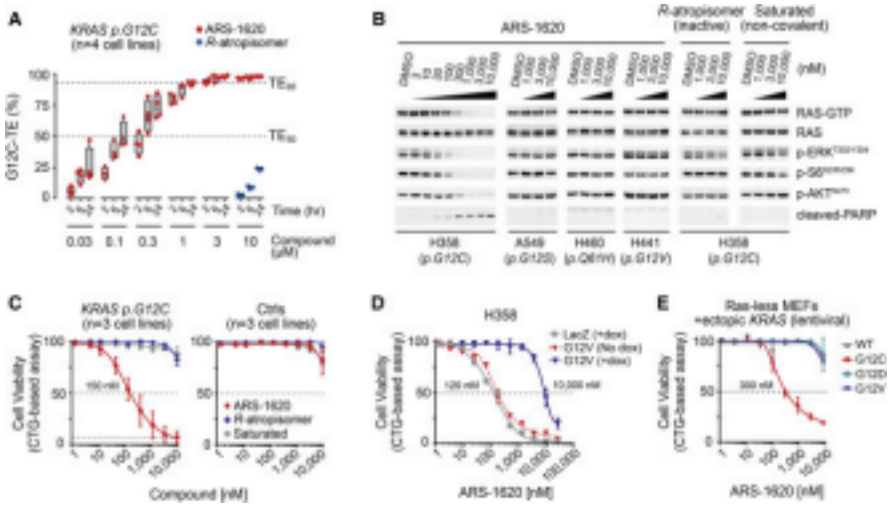
To counteract this, researchers have developed kinase inhibitors tailored to disrupt these signaling cascades. For instance, small molecule inhibitors like vemurafenib and trametinib

target BRAF, a downstream effector of RAS, in melanoma treatment. Similarly, antibodies such as cetuximab and panitumumab inhibit EGFR, a receptor upstream of RAS, in colorectal cancer therapy.

In preclinical and clinical settings, these inhibitors show promise. For example, in a clinical trial, vemurafenib demonstrated significant improvements in progression-free survival in patients with BRAF-mutant melanoma. However, challenges persist, including the development of resistance mechanisms. Further investigations aim to address these hurdles, offering hope for more effective and targeted cancer therapies in the future. This section will delve into the therapeutic potential of kinase inhibitors, highlighting their successes and ongoing challenges in treating RAS-mutant cancers.

Results/Data

Recent work identified the most recent version of the SII-P G12C inhibitor, ARS-1620. This inhibitor exhibits pharmacokinetic and pharmacodynamic properties that are necessary to drive KRAS(G12C) into the GDP-bound state that causes selective inhibition of KRAS(G12C) mutant cells and tumors (Janes et al., 2018).



This figure showcases the validation of ARS-1620 Allele-Specific Inhibition of KRAS G12 in

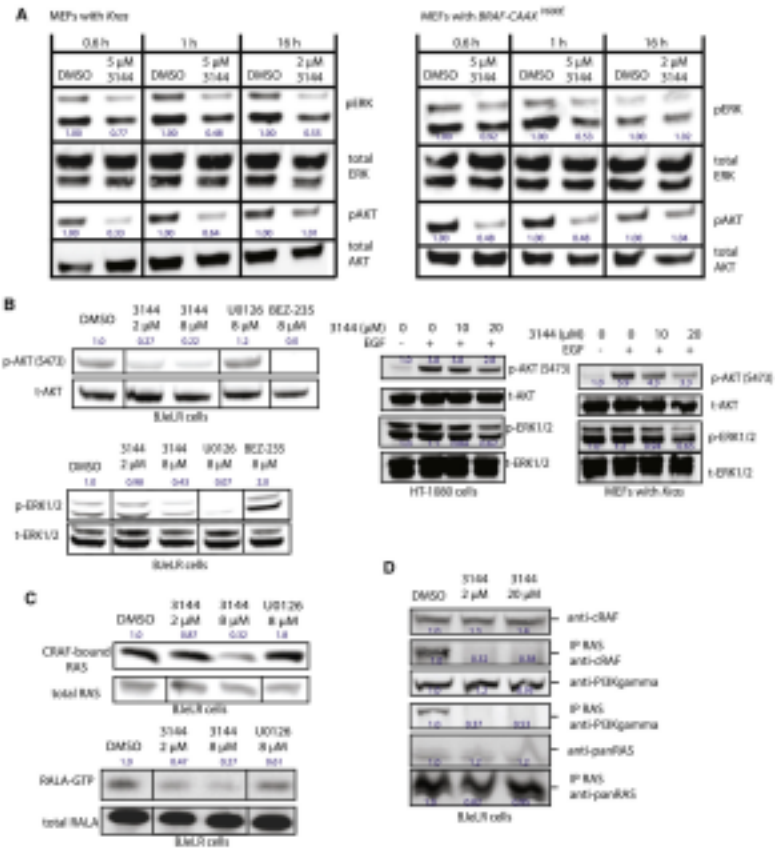
Cells

A. Is a graph of the time course and dose-response of ARS-1620 and R-atropisomer cellular engagement of KRAS G12C (G12C-TE). The dotted lines represent concentrations needed to achieve half-maximal (TE50) or 95% (TE95) G12C target engagement.

B. This is a RAS-GTP pull-down and immunoblot analysis of KRAS mutant lung cancer cells following a 24-hour treatment with DMSO or ARS-1620, R-atropisomer, or an analog of ARS-1620 containing saturated acrylamide.

C. This shows the anti-proliferative effects of ARS-1620 analogs on KRAS p.G12C mutant cell lines (n = 3) or control cell lines lacking G12C (n = 3) following 5 days of treatment.
D. The rescue of ARS-1620 anti-proliferative effects in H358 cells by inducible overexpression of FLAG-KRAS G12V (n = 2 technical replicates).

E. The anti-proliferative effect of ARS-1620 on Ras-less MEFs ectopically expressing human WT, G12C, G12D, or G12V KRAS (n = 2 technical replicates).



This figure showcases the wells of Inhibitor 3144 inhibiting RAS-Dependent Signaling in Cells Welsch et al, Computational docking screen identified by Welsch et al. (2017) found a pan-RAS inhibitor 3144 that targeted three sites in RAS around SW1 and the nucleotide-binding pocket. This inhibition disrupts the RAS effector interactions and reduces RAS-driven tumors in genetically engineered mouse models.

250,000 cells/well of the indicated MEFs were seeded in six-well dishes in medium with 10% FBS. The medium was then changed to serum-free medium and incubated for 24 hr. The cells were stimulated for 15 min with 10 ng/mL human EGF, washed with cold PBS, and analyzed by western blotting. The effects on the abundance of phospho-ERK, total ERK, phospho-AKT, and total AKT were measured. The normalized relative abundance of pERK and pAKT is indicated next to these bands.

Discussion

The resurgence in the identification of direct RAS inhibitors has given rise to encouraging results. The work done by Janes et al. (2018) shows a significant step toward the development of a direct RAS(G12C) inhibitor that could be introduced to clinics. The computational drug discovery done by Welsch et al. (2017) has helped identify several promising lead RAS inhibitory compounds for further development. Janes et al. work is the most promising so far. SII-P inhibitors that target KRAS(G12C) mutants can be made into efficient drug treatments for cancer, especially lung cancer, which is where this KRAS mutation is most represented. As more treatments are being made for Ras-dependent cancers, resistance to these drugs may arise, therefore it is vital to continue developing new and more effective inhibitors of critical signaling pathways driving cancer, such as the RAS pathway. With the data mentioned in this section, the future seems promising for the eventual development of direct RAS inhibitors to treat cancer.

Conclusion

The intricate role of RAS proteins in cellular signaling pathways and their dysregulation in cancer underscores the importance of understanding and targeting these proteins for therapeutic interventions. This research paper has delved into various strategies aimed at inhibiting RAS-mediated oncogenesis, focusing on farnesyl transferase inhibitors (FTIs), upstream regulation of KRAS, and kinase inhibitors targeting RAS effector pathways.

FTIs, by disrupting Ras activation through farnesyltransferase inhibition, have shown promise in preclinical and clinical settings. While exhibiting cytostatic effects on various cancer cell lines, their efficacy as monotherapy seems limited, emphasizing the need for further exploration

of combination therapies. Similarly, efforts to inhibit KRAS, particularly the G12C mutation, have led to the development of Sotorasib, showing encouraging results in clinical trials for pancreatic and non-small cell lung cancers.

Moreover, kinase inhibitors targeting RAS effector pathways present a promising avenue in cancer therapy. Recent advancements in identifying direct RAS inhibitors, such as SII-P and pan-RAS inhibitors, offer hope for more effective treatments. These inhibitors disrupt critical signaling cascades, inhibiting RAS-driven tumors in preclinical models and paving the way for potential clinical applications.

However, challenges persist, including the development of resistance mechanisms and the need for further understanding of the complex RAS signaling network. Continued research and development efforts are crucial to overcome these challenges and optimize therapeutic strategies for RAS-driven malignancies.

In conclusion, while the journey toward effective RAS-targeted therapies may be complex, the progress made thus far underscores the potential for significant advancements in cancer treatment. By unraveling the intricacies of RAS signaling and leveraging innovative therapeutic approaches, we strive towards improving patient outcomes and ultimately combating cancer more effectively.

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