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Abstract

The deregulation of a wide variety of protein kinases is associated with cancer cell initiation and tumor progression. Owing to their indispensable function in signaling pathways driving malignant cell features, protein kinases constitute major therapeutic targets in cancer. Over the past two decades, intense efforts in drug development have been dedicated to this field. The development of protein kinase inhibitors (PKIs) have been a real breakthrough in targeted cancer therapy. Despite obvious successes across patients with different types of cancer, the development of PKI resistance still prevails. Combination therapies are part of a comprehensive approach to address the problem of drug resistance. The therapeutic use of nitric oxide (NO) donors to bypass PKI resistance in cancer has never been tested in clinic yet but several arguments suggest that the combination of PKIs and NO donors may exert a potential anticancer effect. The present review summarized the current state of knowledge on common targets to both PKIs and NO. Herein, we attempt to provide the rationale underlying a potential combination of PKIs and NO donors for future directions and design of new combination therapies in cancer.

Key words: kinase, kinase inhibitor, cancer, nitric oxide, post-translational modification

The authors declare no conflicts of interest.

Introduction

Phosphorylation events are the most common and extensively studied protein post-translational modifications in mammalian systems. Coordinated by a large and diverse family of kinases, phosphorylation is a pivotal biochemical phenomenon involved in signal transduction and multiple cellular functions including cell survival, differentiation, proliferation and migration. The human kinome, which comprises approximately 535 protein kinases, controls many signaling pathways and their crosstalk that leads to virtually all fundamental biological processes [1, 2]. It is now well established that protein kinase activities disorders exert a crucial role in cancer development and progression [3]. As such, protein kinases are frequently found to be oncogenic by distinct mechanisms including somatic mutations, chromosomal translocation, amplification and also epigenetic regulation [4]. Since, many efforts have been made to develop new therapeutic strategies to restrict protein kinase activities for clinical application in oncology.

In the past two decades, a wide range of protein kinase inhibitors (PKIs) types, with various properties and mode of action *i.e* including different selectivity and modes of binding to kinases, have entered different phases of clinical development and several are currently approved by the FDA. Thus, PKIs have become a major class of cancer drugs and their therapeutic potential is still an area of increased interest. Indeed, the study of kinase biology associated with the development of PKIs is a significant component of targeted therapies. Despite encouraging clinical benefits for patients, the use of PKIs, as cancer therapeutics, remains frequently overshadowed by drug resistance mechanisms [5].

The dynamic evolution of cancer cells reflected by constant acquired mutations and genomic instability toward various protein kinases has a dramatic impact on PKI-based therapy effectiveness. The ability of cancer cells to resist to PKI therapies gives rise to a need to develop new therapeutic options. For this reason, new generation PKIs were developed and tested in an attempt to overcome resistance. Despite therapeutic benefit of PKIs to cancer patients, primary and acquired resistance still represent a major challenge in kinase-targeted drug development for cancer therapy. New combinatorial PKI-based approach that would selectively target cancer cells would open new therapeutic windows to neutralize

cancer cell evasion from targeted therapies. Basically, two possible approaches might be considered to lower cancer cell resistance to PKI. Combinatorial strategies of PKI with drugs that would target the same protein kinase or alternate signaling pathways. As a key post-translational modification, protein phosphorylation has been the foundation for signal transduction therapy for cancer. Beside phosphorylation, a number of proteins involved in signal transduction pathways are also a target of a multitude of other post-translational modifications such as glycosylation, ubiquitination, SUMOylation, acetylation or methylation among others, revealing a complex regulatory network. Such post-translation modifications modulating cellular signaling represent putative antitumor strategies that could be considered along the use of PKI.

Nitric oxide (NO)-mediated protein post-translation modifications have gained increasing consideration in the context of cancer. Studies have demonstrated that NO can regulate many classes of protein associated with signaling pathways involved either in cancer development, progression or inhibition [6-8]. Several features such as localization, concentration, cellular time exposure or the redox environment dictate the complex dichotomous action of NO in cancers : either pro-tumoral or anti-tumoral [9]. NO production is generally assumed to play a crucial role in cancer cell fate decisions. Low rate of NO can contribute to tumorigenesis and progression whereas high rate of NO can promote cancer cell death [10-12]. The insights gained into NO mode of action revealed that both S-nitrosylation (the covalent binding of NO moiety to a free cysteine of target protein), and nitration (the covalent binding of NO moiety to a tyrosine residue) are key regulatory protein post-translational modifications in cellular signaling.

As a highly selective and rapidly reversible protein post-translational modification, S-nitrosylation has probably one of the most significant biochemical impact over protein function inducing multiple changes in protein activity, conformation, localization or interaction with other protein partners [6]. Enzymes are a class of protein frequently targeted by NO. Although protein post-translational modifications induced by NO has the ability to both activate or inhibit kinases, a wide range of enzymes involved in cell survival, proliferation or cell death signaling pathways are negatively regulated by NO post-translation modifications [6].

The purpose of this review is to survey the PKIs from the perspective of how NO could have a beneficial anti-tumoral effect on PKI-based therapies. The current review will discuss the link between PKIs and NO with the aim of considering NO as potential novel combination therapies using PKIs and NO donors.

I. Background on the main PKIs

The discovery of PKIs and their clinical use have revolutionized targeted therapy in cancer. The real benefit of PKIs over conventional chemotherapy, results in less cytotoxicity for non-cancerous cells because of more selectivity and lower toxic manifestations. Despite the low toxicity, these molecules have specific toxicity profile, and the understanding of the mechanisms of action is necessary to understand this process [13, 14].

The development of imatinib, the first PKI used in cancer therapy, allows to block the kinase activity of the aberrant protein breakpoint cluster region-protein Abelson (Bcr-Abl, characterized by a chromosomic translocation between chromosome 9 and chromosome 22 in the hematological malignancy chronic myeloid leukemia (CML)), and increases overall survival (OS). Because Bcr-Abl recombination is a driver oncogenic process in CML, patients are more sensitive to PKIs-based therapies than for patients with solid tumors because of high heterogeneity and mutational rate [15]. Imatinib is not specific for Bcr-Abl kinase, and target other oncogenic kinases. Then, imatinib (STI-571) is approved by the FDA not only for the treatment of CML but also for gastrointestinal stromal tumors (GIST) harbouring c-Kit mutation [5, 16, 17] and dermatofibrosarcoma protuberans [15, 18]. Imatinib is able to block the tyrosine kinase activity because it is an ATP competitor, which can interact with the inactive catalytic site of the kinase [19, 20]. Other PKIs have the same mechanism of action, such as sorafenib, which is a multi-kinase inhibitor that blocks various kinases such as vascular endothelial growth factor receptor (VEGFR), platelet-derived growth factor receptor (PDGFR), BRAF and c-Kit [21]. Because of his multi-target activity, sorafenib is actually used for the treatment of GISTs such as imatinib [22]. Levatinib and regorafenib have the same mechanism of action. The first one principally inhibits VEGFR, and is approved for the treatment of iodine-refractory differentiated thyroid cancer and metastatic renal cell carcinoma (RCC) [23]. Regorafenib also targets VEGFR, PDGFR and BRAF and is mainly used for the treatment of advanced GIST, advanced hepatocellular carcinoma (HCC) and advanced colorectal carcinoma (CRC) [24].

Other PKIs, such as gefitinib, sunitinib and vemurafenib, are also ATP competitors [25]. Gefinitib is used to block the activation of mutated tyrosine kinase receptor EGFR (either

deleted in exon 19 or L858R point mutated within exon 21) in NSCLC resulting in permanent activation of the ATP-binding site in absence of the ligand [26]. Sunitinib is not specific to endothelial growth factor receptor (EGFR), but can also inhibit VEGFR and c-Kit and for this reason, it can be used to treat GISTs in people who do not respond to imanibib treatment [27]. More recently, FDA approves osimertinib as first-line treatment of metastatic NSCLC patients based on the FLAURA trial [28]. vemurafenib is used in patients with BRAF V600E mutated melanoma. This mutation can switch-on the serine/threonine kinase activity, with an abnormal activation of the mitogen-activated protein kinase (MAPK)/extracellular signal-regulated kinases (ERK) proliferating signaling pathway. vemurafenib block the activation of the mutated protein, stopping cancer cells proliferation. Unfortunately, this drug shows side effects on healthy cells. Indeed, vemurafenib also targets the wild type form of BRAF, causing a kinase overactivation of MAPK/ERK signaling pathway in healthy cells. Despite this side effect, vemurafenib is an established efficient therapy [29, 30].

Some PKI can block the kinase activity in an allosteric manner, by binding outside the catalytic ATP-binding site such as trametinib, a mitogen extracellular kinases (MEK) inhibitor [31, 32]. Another mechanism of action relies on the covalent bond between the PKI and the catalytic site of the kinase, as for ibrutinib, a bruton tyrosine kinase (BTK) inhibitor [33, 34].

Even though PKIs increase OS in many cancer subtypes, primary and secondary resistances are still frequently observed. Numerous potential mechanisms of resistance to PKIs have been described, requiring the use of second, third or fourth generation PKIs for patients refractory to treatment. Therefore, the development of novel combinational therapies may represent an attractive way to overcome PKI-resistant cancer cells [35].

II. Clinical use of the main PKIs in cancer

1. Bcr-Abl tyrosine kinase inhibitors

a. CML

The clinical development of imatinib has been a considerable leap in CML therapy. Indeed, in a phase II study involving 452 patients with CML who had failed to respond to

interferon α therapy, Kantarjian et al. demonstrated that imatinib treatment induced high rates of cytogenetic (60% of patients) and hematologic responses (95% of patients). Moreover, after a median follow-up of 18 months, 95% of patients were alive [36]. The last update of the ISIS study comparing interferon treatment versus imatinib (ISIS: international randomized study of interferon versus STI-571) showed an estimated OS of 83% at 10 years [37].

Imatinib resistance mechanisms were classified according to two criteria: Bcr-Abl dependent and independent mechanisms [38]. Bcr-Abl dependent mechanisms of resistance are associated with different point mutations which totally or partially impair the catalytic domain of Bcr-Abl or the imatinib-binding sites to this kinase. Almost 57 residues were identified, mostly in the ATP-binding loop (P-loop), the SH2 binding site, and the A-loop, which then dictate the efficacy of imatinib but also future therapeutic strategies to overcome imatinib-resistance [39, 40]. Because of patients refractory to imatinib treatment, more PKIs were FDA-approved for the treatment of CML such as dasatinib (inhibitor of c-KIT, PDGFR-A and B for example) [41, 42], nilotinib and bosutinib, three second generation PKIs. Another example, ponatinib, a third generation PKI is used to overcome T315I mutation (a frequent Bcr-Abl resistance mutation) not only for imatinib-resistant patients [43] but also for patients refractory to treatment with multiple PKIs [5].

The *ABL gene* deletion in 9q is another mechanism of imatinib resistance and poor prognosis in CML [44, 45]. Moreover, microRNAs (miRNAs) such as miR-199b and miR-219-2 (centromeric to the Abl gene frequently lost in CML patients) were downregulated in patients bearing 9q deletion and associated with imatinib resistance [46].

b. GIST

Imatinib has also revolutionized the medical treatment of KIT-driven GISTs. In a randomized phase III, Dematteo et al. showed that imatinib significantly improved recurrence-free survival compared with placebo (98% vs 83%) at 1 year [47]. Moreover, in another randomized phase III study including patients with KIT-positive GIST showed that,

compared with a 1-year only treatment, post-operative imatinib administered for 3 years allowed longer recurrence-free survival (RFS) (47.9 vs 65.6% respectively) and longer OS (81.7% vs 92%, respectively) [48].

Furthermore, it has been shown that mutations in KIT or PDGFRA were frequently found in GISTs patients that are primary refractory to imatinib. These mutations seem to be present within an exon that renders the protein less sensitive to imatinib, and contribute then to the development of drug resistance [49].

2. EGFR tyrosine kinase inhibitors

a. NSCLC

It is recognized that EGFR is overexpressed in ~80% and mutated in 20% of NSCLC [50, 51]. Phosphorylation of EGFR (e.g. Y1173; Y1068; Y1045; and Y854 residues) is required to initiate cellular signaling [52]. EGFR tyrosine kinase inhibitors (EGFR-TKIs) such as erlotinib, gefitinib and afatinib (non-exhaustive list) are widely used in cancer treatment. Erlotinib was the first EGFR-TKI assessed as first-line treatment for patients with NSCLC with EGFR mutations [5, 53]. In the EURTAC randomized phase III trial, erlotinib treatment showed beneficial results with a progression-free survival (PFS) of 9.7 months compared to standard chemotherapy with a PFS of 5.2 months [54]. Gefitinib is also a first-generation EGFR-TKIs approved by FDA in 2015 for treatment of NSCLC patients with EGFR mutations. Indeed, Douillard et al. showed in a phase IV clinical trial that gefitinib as a first line treatment was effective and well tolerated in patients with stage IIIa/B/IV EGFR mutation-positive NSCLC [55]. Afatinib is a second-generation EGFR TKI and the first irreversible oral blocker of the ErbB family. This TKI has been approved by the FDA for the treatment of locally advanced or metastatic patients with NSCLC after the two randomized phase III studies Lux-Lung3 and Lux-lung6. In these studies, afatinib improves overall survival only in patients with del19EGFR mutations (33.3 months vs 21.1 months in the chemotherapy group) [56].

Many acquired resistance mechanisms to gerfitinib, erlotinib and afatinib EGFR-TKIs have been reported and can be classified into three categories: target gene mutation, bypass

signaling pathway activation and histological transformation [57, 58]. The main mechanism of EGFR-TKIs resistance arises from the site mutation T790M in EGFR (detected in 50-60% of resistant cases), which prevents EGFR-TKIs binding [59-61]. Importantly, osimertinib has been found to prolong the survival for metastatic NSCLC patients with EGFR mutations (with or without the T790M mutation) [62].

3. VEGFR tyrosine kinase inhibitors

Several VEGFR-TKIs have been developed and used to treat different types of cancer. These PKIs include (but are not limited to) sorafenib, sunitinib, pazopanib, cabozantinib, lenvatinib, vandetanib, regorafenib, as multi-targeted TKIs, and axitinib as the only VEGFR specific inhibitor.

a. Sorafenib

As a non-specific inhibitor, sorafenib can also target PDGFRs, FLT3 receptor, BRAF, RET and c-kit [63]. Sorafenib has been the first TKI approved by the FDA for the treatment of RCC in 2005, based on the positive results of the randomized phase III TARGET trial. In this clinical trial, the sorafenib group was compared with a placebo group in a cohort of 903 patients with RCC that was resistant to standard therapy. PFS for these patients was significantly prolonged (5.5 months vs 2.8 months for placebo) [63]. This TKI is also used in HCC patients. Indeed, in a multicenter phase III trial, patients with advanced HCC receiving sorafenib had median survival, as well as time to radiologic progression nearly 3 months longer than patients receiving placebo [64].

However, multiple mechanisms that lead to sorafenib resistance have been reported including for example EGFR, Akt or c-Jun activation [65, 66]. Furthermore, cancer stem cells, Src homology 2 domain-containing phosphatase 2 (Shp2) and upregulation of fibroblast growth factor (FGF) signaling pathway may also play a role [66]. As described for imatinib drug resistance, some miRNAs such as miR-181a [67], and miR-429 [68] can also be responsible for drug resistance.

Yet, some drug combination therapies have been used successfully. Sorafenib combined with capecitabine, in advanced solid tumors, including HCC, improved anti-tumor response and survival [69]. In addition, a phase II clinical trial combining sorafenib with doxorubicine shows a synergistically inhibition of tumor cells proliferation and new blood vessels formation in tumor nodules [70]**.** Moreover, combination of sorafenib with low-dose of 5-fluorouracil (5-FU) in HCC patients showed a positive response, which could reduce adverse effects by decreasing 5-FU dose intensity [66]. Other combinatory strategies reported better curative effect with decreased side effects, as uracil-tegafur [71] or octreotide [72]. Furthermore, a clinical trial in patients with castration-resistant prostate cancer, reported that sorafenib can be combined safely with chemotherapy [73].

b. Sunitinib

Sunitinib is also a non-specific tyrosine kinase inhibitor approved by the FDA for the treatment of metastatic RCC and imatinib-resistant GIST based on the results of several randomized phase III trials [74, 75].

However, sunitinib efficacy appeared to be influenced by primary KIT gene mutations (located in exon 11) [22, 76, 77] and secondary mutations in KIT exons 17 or 18 [76, 78-80]. Furthermore, Tran et al., showed that sunitinib resistance was correlated with the upregulation of FGF1, in RCC cell line [81]. Alterations in some miRNAs expression either increased (miR-575, miR-642b-3p, miR-4430) or decreased (miR-18a-5p, miR-29b-1-5p, miR-431-3p, miR-4521) were associated with sunitinib resistance. [82].

regorafenib is another TKI with an activity against VEGFR, but also KIT, PDGFRA and BRAF used as a third line therapy for GISTs patients refractory to imatinib and sunitinib treatment that was found to increase PFS [83-86]. Tomida and collaborators, showed that the blockade of VEGFR by regorafenib, stimulates PDGFR and FGF receptor (FGFR) activation and increases cancer cells malignancy [87].

c. Lenvatinib

Lenvatinib (Lenvima®) is approved since February 2015 by the FDA for the treatment of radioiodine-refractory differentiated thyroid cancer (RR-DTC) [88]. This drug is generally a

well-tolerated treatment that offers a good alternative to sorafenib (because of its ability to stop the epithelial to mesenchymal transition (EMT) process in combination with the histone desacetylase inhibitor HNHA), another PKI currently approved in RR-DTC [89, 90]. Furthermore, most patients with diffuse thyroid diseases develop resistance to lenvatinib, with two principal mechanisms: upregulation of receptors (such as c-Met) or activation of alternative pathways (MEK and phosphoinositide-3 kinase (PI3K)/Akt/mammalian target of rapamycin (mTOR) signaling pathways) [35, 91-95].

4. BRAF-V600E

BRAF mutations are common in cancer cells, with BRAF V600E mutation being the most frequent one, particularly in melanoma (nearly 50% of patients affected) [96-98]. Even though the FDA approved vemurafenib in 2011 for the treatment of metastatic melanoma associated with BRAF V600E mutation, a short term increase in patient survival and secondary resistance quickly appears [99]. Overactivation of MAPK/ERK or PI3K/Akt/mTOR signaling pathways, either driven by upstream receptors (EGFR, FGFR and PDGFR) or by alteration of component of signal cascades confer resistance to BRAF V600E mutated tumor cells [100-104]. Jazirehi and coworkers showed also KIT proto-oncogene receptor tyrosine kinase and MET expression in resistant cell lines [105]. Of note, the association of BRAF and MEK inhibitors represent a new strategy to treat metastatic melanoma resistant to vemurafenib [106].

III. Regulatory relationships between protein kinases, PKIs and NO in cancer

It is worthy to note that there is little knowledge available with regard to the relationship between protein kinases, their inhibitors and NO. Nevertheless, some arguments are in favor of a complex regulatory network in which PKIs may exert an influence on endogenous production of NO, and on the other way round, NO (from other sources, mainly NO donors) may have an impact on protein kinases. We reviewed the role of NO as a negative and positive regulator of protein kinases to evaluate whether NO could provide

added value to the action of PKIs in cancer to ultimately overcome PKIs-mediated resistance (Figure 1).

1. Involvement of NO in PKIs-mediated antitumor potential

It was reported that mTOR inhibitors such as rapamycin and RAD001 increased inductible nitric oxide synthase (iNOS) expression and NO production in glioma-activated microglia cells (involved in central nervous system (CNS) cancers) to express a macrophage 1 (M1) phenotype (antitumoral). In parallel, rapamycin and RAD001 prevented the acquisition of a M2 phenotype (protumoral) by reducing both arginase and *interleukin (IL)-10 gene* expression, possibly resulting in antitumor action [107]. Another study reported that ibrutinib, an inhibitor of BTK and IL-2-inducible T-cell kinase, clinically used for the treatment of B-cell malignancies, modulates myeloid-derived suppressor cells (MDSC) function and generation. This inhibitory function is associated with ibrutinib-impaired iNOS and arginase 1 expression in MDSC cells (a hallmark for MDSC exhaustion) while indoleamine 2,3-dioxygenase 1 (IDO1) trended towards increased expression, revealing a potential strategy for enhancing immune-bases therapy in cancer [108]. Similarly, axitinib, a selective inhibitor of VEGFR tyrosine kinases, indicated in the treatment of patients with advanced renal cell carcinoma after failure of previous treatment with sunitinib or cytokine, induced the same effect as ibrutinib. Indeed, axitinib suppressed the lung metastasis of melanoma cells, prolonged survival of tumor-bearing mice and reduced the proportion of MDSC. Furthermore, axitinib inhibited the expression of iNOS in MDSC cells affecting their immunosuppressive function [109]. A translational study determined the NO levels in CML patients after imatinib therapy, one of the most effective treatment for Bcr-Abl^{+} CML patients. In this study, the authors showed that the imatinib decreased the plasma level of NO by three times (41.48 to 14.26 µmol/L). The authors concluded that NO levels might be used as a prognostic indicator in CML patients treated with imatinib [110].

While cancer treatment with the kinase inhibitors listed above decreases the NO level, other kinase inhibitors have the opposite effect, exemplified by vemurafenib and sorafenib. On the one hand, Yu et al. reported that vemurafenib initiates apoptosis and

growth inhibition of BRAF V600E mutant human melanoma cell line A375, which is correlated with vemurafenib-inducing production of intracellular NO [111]. Such effect was abolished with NG-monomethyl-L-arginine monoacetate (L-NMMA), an iNOS inhibitor [111]. Caraglia et al. showed that in patients with advanced HCC, sorafenib induced an increase of 40% of serum NO levels [112]. This effect was observed only in sensitive patients to the treatment [112]. Thereby, the determination of the NO status in patient's serum could have high value in the prediction of response to sorafenib therapy in HCC patients.

2. NO favours PKIs toxicity

It is a proven fact that the use of PKIs, as well as antibodies directed against tumor-inducing signaling pathways, has shown very beneficial effects in several types of cancer. However, this benefit is associated with some toxicities. We will focus on those involving NO, known to regulate blood pressure. Indeed, whether many PKIs induced hypertension some others do the opposite. It is well documented that bevacizumab treatment (targeting VEGF pathway) of patients with a variety of solid tumors [113] was associated with a significant increased risk of developing raised blood pressure (grade 1-2, 25%; grade 3-4, 10%) [114, 115]. The results also suggest that significant rise in blood pressure was associated with bevacizumab was dose-dependent. Indeed, high-dose of bevacizumab caused high blood pressure. In addition, increased blood pressure with high dose of bevacizumab was observed in patients with RCC and breast cancer, but not in patients with NSCLC, CRC and pancreatic cancer [115]. Although in this later work the involvement of NO in the raise of blood pressure was not investigated, other kinase inhibitors of the VEGF signaling pathway have also shown a NO-dependent increase in blood pressure. It is the case of pazopanib and sunitinib in the treatment of advanced RCC in which it was shown that pazopanib-treatment was associated with hypertension and decreased urine and plasma nitrite/nitrate, the stable NO-metabolites [116]. Similarly, the urine nitrate concentration was lower in sunitinib-treated patients that developed hypertension [117]. It is also the case of lenvatinib and regorafenib, targeting the VEGF signaling pathway, which showed an increase in blood

pressure that it was associated with a decrease of NO in sera of differentiated thyroid carcinoma [118] and in GISTs [119].

3. Regulatory impact of NO on protein kinases

a. NO as a protein kinase activator

Several reports have demonstrated that the intracellular production of NO by NOS is required for the phosphorylation of subsequent activation of EGFR signaling pathways.

It is well known that overexpression of iNOS is significantly associated with tumor growth and angiogenesis, in breast cancer among other cancer types [120, 121]. Indeed, high iNOS expression significantly correlates with EGFR phosphorylation, its activation and poor survival in various breast cancer subtypes [122, 123]. Accordingly, in response to ionizing radiation, endothelial nitric oxide synthase (eNOS) increases NO production and EGFR phosphorylation and activation [124]. Another study has showed that eNOS-induced NO can promote EGFR S-nitrosylation and tyrosine residues phosphorylation. Donnini *et al.*, demonstrating that the activation of iNOS/guanylate cyclase (CG) and MAPK-ERK1/2 are required to promote squamous cell carcinoma invasion and growth. This was mediated by EGFR transactivation via prostaglandin E receptor 2 (EP2)/protein kinase A (PKA) and c-Src signaling pathways [125]. Interestingly, EGFR, in the nucleus, can function as a transcription factor. Indeed the transcriptional activation of *iNOS gene* can result from the interaction of nuclear EGFR with signal transducer and activator of transcription 3 (STAT3) [126]. Together, these data indicate a possible feedback loop for the regulation of the EGFR signaling pathways.

NO derived from NO donors can also positively regulate the EGFR signaling pathways. Upon exposure of triple negative breast cancer cell lines (MDA-MB-468 and HCC1806) to the NO donor DETA/NO an increase in EGFR tyrosine phosphorylation (Y1173 in MDA-MB-468 and Y1173, Y1068 and Y1045 in HCC1806 cells) and subsequent activation were found involved in tumor cell migration and invasion [127].

Another very important tyrosine kinase receptor is VEGFR, which upon binding to its ligand VEGF leads to vasculogenesis and angiogenesis [128]. VEGF is known to be upregulated by cancer cells generating NO, which contributes to increased neovascularization and tumor metastasis [129]. Furthermore, Nakamura, Y. *et al.*, showed that treatment of breast cancer cells MDA-MB6231 with the NO donor DETA/NONOate, induced an increase in VEGF-C expression and nitrite/nitrate production. All of these changes were correlated with lymph node metastasis [130].

NO can also positively regulate non-receptor tyrosine kinases as Src and KRAS. Indeed, NO donors such as DETANO triggered c-Src S-nitrosylation leading to tyrosine kinase activation attested by its phosphorylation at Tyr419 and increased Akt Ser473 and STAT3 Tyr705 phosphorylation [123]. Similarly, the NO donor SNP causes S-nitrosylation of c-Src at cysteine 498 to stimulate its kinase activity in fibroblasts. Similar effect was found in breast cancer cells treated with beta-estradiol via iNOS activation [131]. However iNOS can be targeted by Src. Actually Src induces Tyr1055 iNOS residue phosphorylation [132]. It is well documented that KRAS is also oncogenic. Its mutation in cancer maintained it in its activated status. KRAS activation could occur through other mechanisms. Studies showed that eNOS induces the S-nitrosylation of cysteine at position 118 and activation of wild-type Ras protein leading to the stimulation of PI3K/Akt signaling, thus promoting tumor growth [133]. The same year, Oliveira *et al.,* found that, in rabbit aortic endothelial cells, low concentrations of S-Nitrosothiols/NO (RSNO/NO) induced Ras S-nitrosylation and consequently Ras-ERK1/2 MAP kinase signaling pathway activation [134]. Lopez-Carera *et al.,* investigated the impact of iNOS overexpression observed in melanoma and others cancer cells. They found that iNOS induced mTOR pathway activation in melanoma cells. Mechanistically, the authors showed that iNOS triggered S-nitrosylation of tuberous sclerosis complex (TSC) 2, a driver for the inhibition of dimerization of TSC2 with its inhibitory partner TSC1, increased GTPase activity of its target Ras homolog enriched in brain (Rheb), a key activator of mTOR signaling pathway [135]. NO could also activate the mTOR signaling pathway indirectly. Indeed, Zhu *et al.,* showed that neuronal NOS (nNOS) S-nitrosylates the phosphatase and tensin homolog

(PTEN) protein resulting to Akt/mTOR signaling activation, reducing autophagy and promoting the survival of nasopharyngeal carcinoma cells [136].

b. NO as a protein kinase inhibitor

In agreement with the well-documented ambivalent role of NO in cancer, various studies have reported a negative regulatory effect of NO on protein kinases. Indeed, NO can inhibit pathways involved in the proliferation and survival of cancer cells via its potential to downregulate the activity of several protein kinases. Some of these protein kinases are the target of selective PKIs currently undergoing clinical trials.

The S-nitrosylation of EGFR cysteine residues at position 166 and 305 leads to its inactivation in fibroblast and neuroblastoma cells, respectively [137, 138]. Ruano *et al.*, also demonstrated that NO-mediated inhibition of human epidermoid carcinoma cells was correlated with the inhibition of EGFR tyrosine phosphorylation and the induction of a tyrosine phosphorylation of a nitric oxide-induced 58-kDa phosphoprotein (NOIPP-58), only in the presence of EGF [139]. Accordingly, but in another context, tyrosine nitration of EGFR, caused by NO derived from iNOS, induces a decrease in tyrosine phosphorylation and an inhibition of neural stem cell proliferation [140].

In addition, the MEK family proteins ERK1/2 that are targeted by tramatenib and cobimetinib in the treatment of *BRAF* mutated metastatic melanoma, are S-nitrosylated by NO. Indeed, NO donors SNP or GSNO led to increase in ERK1/2 S-nitrosylation at cysteine residue 183, and a reduction of ERK1/2 phosphorylation that can trigger cell growth inhibition and apoptosis of cancer cells [141, 142]. Similarly, S-nitrosylated Akt (cysteine residue 224) [143] and nitrated Janus kinase-2 (JAK2) (tyrosine residues 1007 and 1008) [144] can negatively control both oncogenic PI3K/Akt and JAK2/STAT signaling pathways. These oncogenic pathways in various types of cancer are targeted by selective inhibitory molecules. Idelalisib and copenlalisip (PI3K inhibitors) in the treatment of chronic lymphoid

leukemia (CLL), non-Hodgkin lymphoma (NHL), follicular lymphoma (FL) and ruxolitinib (JAK2 inhibitor) in the treatment of myelofibrosis [145]. Several other protein kinases including STAT3, JNK and IKKβ involved in growth factors or cytokine-mediated signaling pathways are also targeted by NO. STAT3, a key partner of JAK2 in IL-6 mediated signaling pathways, was inhibited by S-nitrosylation at cysteine residue 259 by the NO donor (GSNO) or through iNOS activation. This was associated with decreased cancer cell proliferation and increased apoptosis [146, 147]. Also, JNK proteins (JNK1, 2, 3) are S-nitrosylated upon NO generation via interferon gamma (IFNγ)-induced iNOS or the NO-donor SNAP in murine microglial cells thus suppressing their interaction and kinase activity [148]. Finally, the IKKβ kinase activity was also repressed by S-nitrosylation (Cysteine 179). Such effect caused inhibition of the enzymatic activity of this kinase preventing the activation of an essential cell survival pathway, the classical NF-kB pathway [149, 150].

c. Effect of NO on PKIs-mediated cell death

In addition to the different relationships between NO and kinase inhibitors mentioned above, NO can synergize with certain kinase inhibitors to induce death or inhibit the proliferation of cancer cells. Studies have shown that two EGFR signaling pathway inhibitors erlotinib and ZD1839 synergized with NO donors, NO-aspirin and SNP, to induced antiproliferative effect or cell death in several lung and prostatic cancer cell lines, respectively [151, 152].

A synergistic effect, between PKIs and NO in promoting cancer cell death, has been also observed with other PKIs currently undergoing preclinical studies. Indeed, H89 (N-[2-bromocinnamylamino)ethyl]-5-isoquinolinesulfonammide) is a small molecule that has always been known as PKA inhibitor [153]. Although Davies and collaborators showed that H89 is able to inhibit at least 8 other kinases, such as MSK1, S6K1, ROCK II, AMPK, CHK1, KBα, MAPKAP-K1b and SGK [13]. H89 structure is similar to ATP, so this small molecule is able to inhibit kinases activity competitively with ATP [154]. Some studies used H89 to assess the role of PKA in different tissues *in vitro*, such as heart muscle, liver, smooth muscle, epithelial cells and neuronal tissue [155-159]. Moreover, H89 also has an activity *in vivo* as

an anti-inflammatory strategy to treat inflammation in mice [160]. Unfortunately, the role of H89 in cancer is not well established. Recent studies have shown that H89 is able to enhance tetrandrine (a bisbenzylisoquinoline alkaloid) and HA22 (moxetumomab pasudotox) effect on human cancer cells *in vit*ro and *in vivo* [161, 162]. Recently, Li and coworkers showed that H89 is able to improve the activity of the oncolytic virus M1 to induce tumor regression in various cancer cells [163]. The relationship between H89 and NO is not clearly understood. The anti-tumor effect of the NO-donor nitroglycerin (NTG) is well established in various cancer types. Some studies have shown that the combination of H89 and NTG enhances cell death in colon cancer cells. Indeed, H89 induces reactive oxygen species (ROS) production which combined with NO, triggers apoptotic cell death by caspase activation [164]. Even if H89 is primarily known for kinases inhibition, Boina-Ali and coworkers showed that the molecule induces an unexpected Akt activation. In fact, Akt activation induced by H89 sensitizes colon cancer cells to death induced by NTG and triciribine (an Akt inhibitor) [165].

IV. PKIs and NO donors: towards potential combinatory treatments?

Over the last two decades, the clinical development and approval of a growing number of novel PKIs have tremendously improved the landscape of targeted therapies to treat cancer. Despite significant clinical benefits (improvement in OS and PFS) observed for some patients, persistent tumor intrinsic resistance or acquired resistance to PKIs are still a limitation of treatment. How to make the best use of PKIs to treat cancer patients remains an open question. To this end, better knowledge of the molecular mechanisms of resistance currently represents an intensive area of research to achieve durable efficacy.

As a hallmark of cancer cell development, novel mutations mediating resistance to PKIs occurs inevitably and rapidly with the emergence of resistant tumor clones. A first strategy consisted in developing the so called “next-generation” PKIs in order to improve over and over again their potency and selectivity toward specific newly mutated kinases. Indeed, the difficulty to circumvent protein kinase mutational resistance is well exemplified by EAI045, a fourth-generation EGFR PKI under current preclinical investigation [166]. Although EAI045 seems to unveil encouraging results in terms of overcoming resistance to

the third-generation EGFR PKI in advanced NSCLC models, clinical trials with EAI045 have not been conducted yet. In the era of precision medicine, the design and development of novel generation of PKIs is a perpetual challenge in an attempt to maximize clinical benefit.

The second approach consists in combining PKIs with chemotherapeutic agents. Major success on combination therapies has been realized in cancer but the design of more personalized treatment is needed PKIs are signaling therapeutic agents designed to mainly target some of the fundamental hallmarks of cancer *i.e.* cell proliferation, cell survival and tumor angiogenesis. Various clinical trials studying combinatorial strategies of such cytostatic agents with cytotoxic agents like chemotherapeutic drugs (soliciting other hallmarks of cancer) have been focused on NSCLC patients. Many clinical trials have demonstrated the clinical benefit of certain VEGFR-PKIs when combined with chemotherapy in NSCLC patients [167]. However, whether the combinations of either VEGFR-PKIs or EGFR-PKIs with various chemotherapeutic agents present higher efficiency than with PKIs alone in advanced NSCLC remain controversial [168-170]. From a molecular perspective, one possible explanation may in part account for p53 mutational status. *TP53* tumor suppressor gene is the most frequently mutated genes in cancers. It is well documented that p53 is associated with resistance to many chemotherapeutic agents [171]. Because of high frequency p53 mutations in tumors, the activation of alternative cell death pathways in a p53-independent manner, such as apoptosis promoted by cytokines of the Tumor Necrosis Factor (TNF) family, should be considered. A growing number of studies have demonstrated sensitizing effect of NO to tumor-necrosis-factor related apoptosis inducing ligand (TRAIL) [172], Fas Ligand (FasL) [173], and TNFα [174] mediated apoptosis in cancer cells. A limited number of proteins modified by either S-nitrosylation or nitration processes are known to drive cell death pathways (for review [6]).

Interestingly, a substantial body of evidences indicates that NO-based treatment (particularly via NO donors) could potentially contribute to overcome resistance to PKIs in cancer patients.

It is now well recognized that NO-mediated post-translational modifications influence cell signaling in a similar extent as for phosphorylation or other major post-translation modification such as ubiquitination [175]. S-nitrosylation is a critical regulator of

phosphorylation, ubiquitination or acetylation for example. S-nitrosylation is also an important regulatory mechanism of several protein kinases and subsequent post-translational modification by phosphorylation. Even though protein post-translation modification by S-nitrosylation can either activate or inhibit enzymatic activities, S-nitrosylated protein kinases are most likely inhibited [175]. NO can alter protein kinase activity not only by S-nitrosylation of the cysteine residue in its catalytic domain, but also by preventing the binding to its downstream target. Consistently, tyrosine nitration can also change the function of key proteins involved in cellular signaling events. Phosphorylation and nitration can occur within the same tyrosine residue. Since tyrosine nitration rather inhibits than activate the function of proteins, tyrosine nitration may cooperate with PKIs to efficiently prevent phosphorylation events and downstream signaling pathways that control cancer cell growth. Thus, NO have the added benefit to act not only as a multi-targeted kinase inhibitor but also as inhibitor of numerous protein substrates which is of particular interest to overcome PKI resistance-mediated activation of redundant and alternative signaling pathways.

Recent preclinical reports currently abound for the development of NO donors to overcome primary or acquired resistance to PKIs. For example, NO donor/natural product hybrids represent a promising anticancer strategy to potentiate different PKIs anti-cancer properties. Indeed, an oleanolic acid/hederagenin-NO donor hybrid has demonstrated potent cytotoxicity against gefitinib-resistant (EGFR—L858R/T790M mutations) and osimertinib-resistant (EGFR-L858R/T790M/C797S mutations) NSCLC cancer cells. This novel NO-donor hybrid represents a potent compound to overcome frequent EGFR-PKI resistance in NSCLC lung cancer [176]. The design of a dual-functional inhibitor NO donor/selective STAT3 inhibitor ((NO)-releasing quinolone-1,2,4-triazole/oxime hybrid) significantly improved the cytotoxicity of melanoma cell lines with BRAF-V600E mutant and resistant to BRAF inhibitors [177]. Interestingly, in a previous report, a series of NO donor/EGFR inhibitors (phenylsulfonyfuroxan-based anilinopyrimidines) harbouring a strong activity against EGFR T790M mutant, had yet demonstrated EGFR kinase inhibitory and antiproliferative potential against EGFR mutated NSCLC cell lines [178].

The treatment of the Bcr-Abl$^+$ CML cell line K562 with the NO donor sodium nitroprusside have shown to enhance imatinib-mediated apoptosis [179]. Moreover, NAC mediated-scavenging of ROS in Bcr-Abl$^+$ CML cell lines and primary cells from CML patients (imatinib-resistant and imatinib-sensitive cells) co-treated with imatinib are correlated with enhanced production of NO and subsequent NO-dependent cell death [179].

Vemurafenib-mediated growth inhibition of the BRAF-V600E melanoma cell line A375 has been shown to be dependent on the production of the superoxide anion $O_2^{\cdot-}$ and NO [180]. These results suggest a peroxynitrite-dependent cytotoxicity involving protein tyrosine nitration. Thus, NO appears as a key factor for PKI efficacy which sustains the rationale for the development of novel combination therapies PKI/NO donor.

Preclinical studies demonstrated that vemurafenib-mediated antitumor activities can be enhanced by abrogating nucleus translocation of NF-kB p50/p65 [180]. On the other hand, NO (either endogenously produced or released by NO donors) can inhibit the activation of the NF-kB pathway through the S-nitrosylation of IKKβ, p50, p65 and cellular inhibitor of apoptosis protein 1 (cIAP1) [149, 174, 181-183].

Concluding remarks

The mode of action of both PKIs and NO-based protein post-translational modifications revealed functional overlaps for some oncogenic targets underlying an interest in PKIs and NO donors combination in cancer therapy. In this context, the effect of NO (S-nitrosylation or nitration) could possibly overcome PKI resistance. Whether it acts through a direct or indirect way, NO may exert a regulatory control over protein kinases involved in important cancer signaling pathways as observed with PKIs.

A growing number of clinical studies have evaluated the NO donor NTG as an anticancer drug in combination with either radiotherapy or chemotherapy agents. The majority of clinical studies were conducted in patients with NSCLC. The results obtained for the first phase II trial demonstrated clinical benefit (improved overall survival) for patients treated with the combination therapy NTG/vinorelbine and cisplatin [184].

New combinatorial treatments, designed with PKIs currently approved by the FDA and NO donors (such as NTG), have never been explored yet. Studies are needed to determine whether the use of NO donors would enhance the effectiveness of PKIs in cancer treatment.

Acknowledgements

The authors acknowledge the financial support from « Région Bourgogne », « La Ligue Contre le Cancer (Conférence de coordination Interrégionale Est) » and « Qatar Foundation ».

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Figure legend

Figure 1. Impact of NO on protein kinases and PKIs activities. Summary of the ambivalent impact of NO toward PKI (either promoting or inhibiting PKI's antitumoral potential) and protein kinases function (regulated at the transcriptional or the post-translational level by NO).

Abbreviations

5-Fluorouracil: 5-FU

Akt serine/threonine kinase: AKT

Breakpoint cluster region-protein Abelson: Bcr-Abl

Bruton tyrosine kinase: BTK

Central nervous system: CNS

Cellular inhibitor of apoptosis protein 1: cIAP1

Chronic lymphoid leukemia: CLL

Chronic myeloid leukemia: CML

Colorectal carcinoma: CRC

Endothelial growth factor receptor: EGFR

Endothelial nitric oxide synthase: eNOS

Epithelial to mesenchymal transition: EMT

Extracellular signal- regulated kinases: ERK

Fas Ligand: FasL

Fibroblast growth factor: FGF

Fibroblast growth factor receptor: FGFR

Follicular lymphoma: FL

Food and Drugs Administratin: FDA

Gastrointestinal stromal tumors: GIST

Guanylate cyclase: GC

Hepatocellular carcinoma: HCC

Indoleamine 2,3-dioxygenase 1 : Ido1

Inductible nitric oxide synthase: iNOS

Interleukin: IL

Janus kinase 2: JAK2

Macrophage 1/2 phenotype: M1/M2

Mammalian target of rapamycin: mTOR

MET proto-oncogene receptor tyrosine kinase: MET

Mitogen-activated protein kinase: MAPK

Mitogen extracellular kinases: MEK

Micro RNA: miRNA

Myeloid-derived suppressor cells: MDSC

(N-[2-bromocinnamylamino)ethyl]-5-isoquinolinesulfonammide): H89

Neuronal nitric oxide synthase: nNOS

Nitric Oxide: NO

Nitroglycerin: NTG

NG-monomethyl-L-arginine monoacetate: L-NMMA

Non-Hodgkin lymphoma: NHL

Non-small-cell lung carcinoma: NSCLC

Overall survival: OS

Phosphatase and tensin homolog: PTEN

Phosphoinositide-3 kinase: PI3K

Platelet-derived growth factor receptor: PDGFR

Progression free survival: PFS

Prostaglandin E receptor 2: EP2

Protein kinase A: PKA

Protein kinase inhibitors(s): PKI(s)

Radioiodine-refractory differentiated thyroid cancer: RR-DTC

Ras homolog enriched in brain: Rheb

Reactive oxygen species: ROS

Recurrence-free survival: RFS

Renal cell carcinoma: RCC

Signal transducer and activator of transcription 3: STAT3

S-nitrosothiols: RSNO

Src homology 2 domain-containing phosphatase 2: Shp2

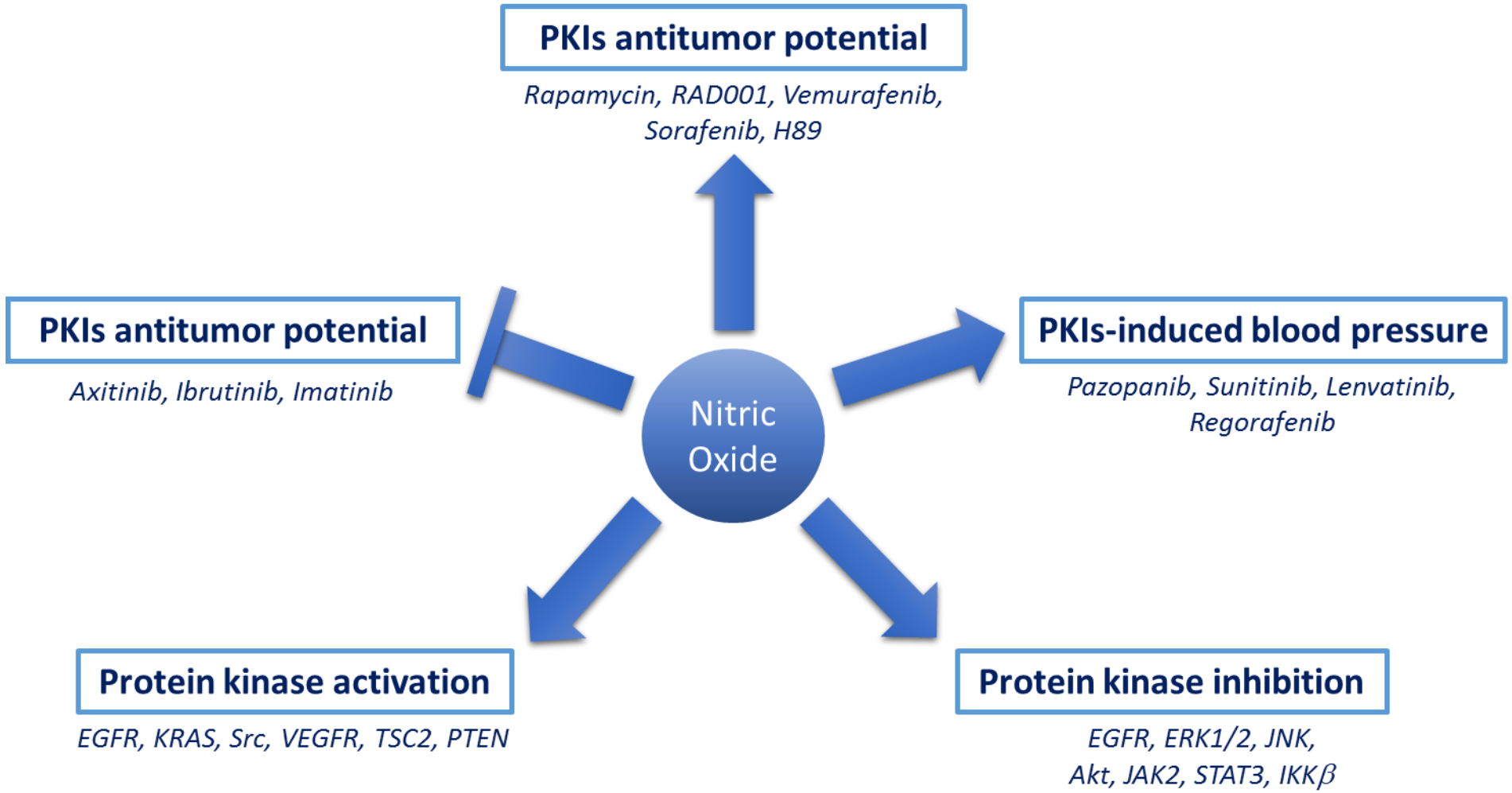
Tuberous sclerosis complex: TSC

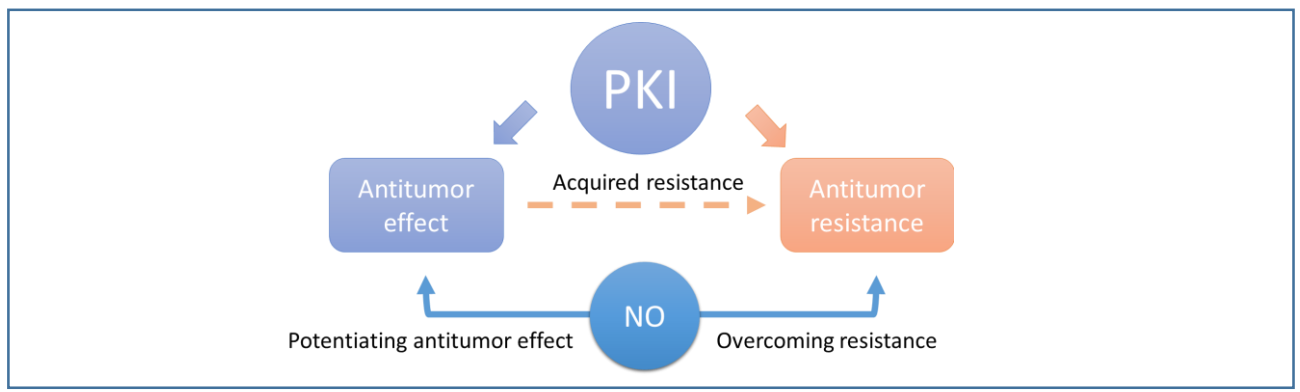
Tumor necrosis factor: TNF

Tumor-necrosis-factor related apoptosis inducing ligand: TRAIL

Tyrosine kinase inhibitor: TKI

Vascular endothelial growth factor receptor: VEGFR


PKIs antitumor potential
Rapamycin, RAD001, Vemurafenib, Sorafenib, H89
PKIs antitumor potential
Axitinib, Ibrutinib, Imatinib
Nitric Oxide
PKIs-induced blood pressure
Pazopanib, Sunitinib, Lenvatinib, Regorafenib
Protein kinase activation
EGFR, KRAS, Src, VEGFR, TSC2, PTEN
Protein kinase inhibition
EGFR, ERK1/2, JNK, Akt, JAK2, STAT3, IKKβ


PKI
Antitumor effect
Acquired resistance
Antitumor resistance
NO
Potentiating antitumor effect
Overcoming resistance