

RATIONALE FOR SITRAVATINIB IN COMBINATION WITH CHECKPOINT INHIBITOR THERAPY

Sitravatinib is a spectrum-selective receptor tyrosine kinase (RTK) inhibitor that targets several closely related RTKs including the TAM (Tyro3/Axl/MERTK) and split family receptors (Vascular endothelial growth factor receptor 2 (VEGFR2) and KIT), as well as MET (**Table 1**). Based on the function of these receptors in key immune cell types, sitravatinib and checkpoint inhibitor therapy (CIT) are predicted to have complementary roles in effectuating a tumor-directed immune response (**Figure 1**). Resistance to single-agent CIT resistance is common, as indicated by the prevalence of both refractory tumors and disease progression, therefore, there is a growing need for combinatorial strategies that improve clinical outcomes. Based on the mechanistic rationale, sitravatinib in combination with nivolumab, an anti-PD-1 (Programmed cell death protein 1) checkpoint inhibitor, was evaluated in non-small cell lung cancer (NSCLC) patients who had previously progressed following treatment with a checkpoint inhibitor, where it was found to be clinically active. These data validate the numerous genetic and pharmacological studies that revealed the therapeutic potential of targeting the TAM and split RTK families, as well as provide clinical proof-of-principle that sitravatinib can alleviate resistance to CIT.

When programmed death-ligand 1 (PD-L1) is bound to the PD-1 receptor, a negative regulator of T cell activation, anti-tumor immunity is inhibited through the suppression of T cell proliferation, migration, and tumor cell-directed cytotoxic activity. Blocking the PD-L1/PD-1 axis should alleviate this suppression, thereby bolstering tumor-killing activity. While anti-PD-1/PD-L1 antibodies produce durable responses in several major cancer types, including NSCLC, melanoma, renal cell carcinoma (RCC), urothelial and head and neck cancers [1-6], the majority of patients either do not respond to single-agent therapy from the outset or they eventually progress.

Understanding the CIT mechanism of action is an area of intense research that has yielded several predictive biomarkers that correlate with therapeutic sensitivity or resistance. PD-L1 expression by immunohistochemical analysis is one such marker. Positive/high PD-L1 expression correlates with increased response rates in multiple indications and is frequently used to inform therapeutic decision-making [1, 5, 7-9]. However, the sensitivity and specificity of this biomarker is modest, underscoring the need for additional patient selection strategies. Tumor mutational burden (TMB) has also emerged as a quantitative predictor of sensitivity to CIT. TMB can be impacted by etiological factors like smoking status or exposure to UV irradiation through chronic sun damage as well as underlying genomic alterations that result in DNA repair defects and genomic instability. Tumor cells with high TMB harbor more neoantigens, which in turn, increase T cell recruitment to the TME, initiating an anti-tumor response. High TMB correlates with response in several cancer types, distinguishing CIT responders from non-responders independent of PD-L1 expression [10-12]. Like, PD-L1, TMB is only modestly predictive of CIT activity and further underscores the need for refined patient selection strategies. Individual mutations in genes such as *β -2-microglobulin (β 2M)* and *Serine/Threonine Kinase 11 (STK11)* also impact various aspects of tumor immunity and correlate with CIT resistance [13-15].

In addition to the tumor cell-intrinsic mechanisms described above, the TME has a clear and profound role in influencing response to CIT [7, 16-19]. The TME of CIT responders often displays evidence of an inflammatory

immune response characterized by the recruitment of activated T cells and a T cell-inflamed gene expression profile [20-23]. However, tumor killing by cytotoxic T cells is ultimately blocked through the upregulation of immune checkpoint pathways, including PD-L1 expression in response to interferon- γ (IFN- γ) [24]. In contrast, the TME of CIT non-responders is often characterized by either induction of dysfunctional T cells or immunologically “cold” gene expression signatures, indicative of neoantigen-reactive T cell deficiency in tumors. Owing to the recruitment of immunosuppressive cell types to the TME, including T regulatory cells (Tregs), myeloid-derived suppressor cells (MDSCs) and M2-polarized macrophages, a pro-tumor state is maintained through the promotion of factors that constrain a T effector cell-mediated anti-tumor response. Therefore, CIT-resistant tumors may harbor a non-functional T cell population, exhibit exclusion of T cells outside of the tumor margin, or lack T cells altogether [17, 18, 25, 26]. These data provide both a framework for understanding mechanisms of resistance to CIT and a roadmap for identifying novel combination therapies with the potential to reawaken an adaptive immune response and improve response rates and the durability of responses to CIT.

SITRAVATINIB TARGETS RTKS THAT SUPPRESS IMMUNITY IN THE TME

The TAM Receptors

The TAM RTKs, Axl and MERTK, are expressed by innate immune cell subpopulations, including macrophages, dendritic cells (DCs), and natural killer (NK) cells. TAM receptors normally function to resolve an immune response by suppressing inflammation and promoting wound healing when they encounter apoptotic cells [27, 28]. TAM receptors are activated by growth arrest-specific protein 6 (Gas6) or protein S (Pros1) proteins upon binding of these ligands to phosphatidylserines present on the plasma membranes of apoptotic cells. TAM receptor activation suppresses the pro-inflammatory M1 macrophage cytokine response, triggers clearance of apoptotic cells, and induces anti-inflammatory M2 macrophage polarization to resolve inflammation and promote wound healing after an initial immune response. In cancer, activation of this pathway results in an immunosuppressive tumor microenvironment, promotes tumor cell immune evasion, and impedes anti-PD-1 checkpoint inhibitor therapy [29, 30].

Several genetic and pharmacologic studies have elucidated the role of the TAM receptors in innate immune cell biology and cancer. The innate immune response, a first line of defense against pathological insults, is driven by DCs and macrophages. These cell types recognize diverse foreign threats and trigger an initial inflammatory response that includes cytokine secretion and antigen presentation to T cells. This initial innate pro-inflammatory attack needs to be counterbalanced by an anti-inflammatory response once the threat is resolved or else uncontrolled inflammation, as is observed in auto-immune disorders, would result. The TAM receptors are responsible for this anti-inflammatory counter-response and, often, this immunosuppressed state persists in tumors [31]. MERTK suppresses the M1 macrophage pro-inflammatory cytokine response, involving interleukin (IL)-12, IL-6, and tumor necrosis factor α (TNF- α), and enhances M2 macrophage anti-inflammatory cytokine production, involving IL-10, IL-4, transforming growth factor β (TGF β), and hepatocyte growth factor (HGF) [32, 33]. Moreover, implantation of syngeneic breast and melanoma tumors in MERTK null mice resulted in decreased tumor growth due to an enhanced innate immune environment as compared with wild-type mice [34]. Consistent with this

knockout model of MERTK, a phosphatidylserine-targeting antibody induced M1 macrophage polarization and augmented the anti-tumorigenic effect of anti-PD-1 therapy in mouse syngeneic models [35-37].

DCs play a primary role in anti-tumor immunity by processing and presenting neoantigens to T cells, one of the first steps in mounting an anti-tumor immune response. In DCs, activation of Axl functions as a mechanism to limit inflammation during the natural course of an immune response. Consistent with this observation, Axl and MERTK null mice display increased pro-inflammatory signaling and an increased ability of DCs to drive T helper 1 (Th1) responses through increased production of pro-inflammatory cytokines [38, 39]. Moreover, a small molecule Axl inhibitor reduced immunosuppressive MDSCs and M2-polarized macrophages in vivo [39, 40].

TAM receptors also regulate NK cell development and activation and are linked to the silencing of NK cell activity in cancer. NK cells are crucial effector cells of the innate immune system. The primary function of NK cells is to eliminate cells bound by IgG antibodies or cells that express stress signals and do not express major histocompatibility complex (MHC) class I molecules. MHC class I molecules are cell surface proteins expressed on all cell types that present intracellular peptides and antigens from degraded proteins to make sure cells have not been infected with a pathogen or accumulated too many mutations. If NK cells cannot detect MHC class I molecules on a cell surface, they normally eliminate that cell. Cancer cells, however, exhibit downregulation of MHC class I molecules and yet these cells persist, indicating this mechanism is disabled in cancer. TAM receptor activation has been shown to contribute to NK cell dysfunction. Gas6-mediated TAM receptor activation suppressed the proliferation and activation of NK cells, whereas a TAM receptor inhibitor impeded cancer metastasis in a mouse model through an NK-dependent mechanism [41, 42]. Collectively, these data implicate Axl and MERTK as key players in regulation of the innate immune system in the TME and indicate that inhibition of Axl and MERTK will reverse the immunosuppressive microenvironment.

VEGFR2 and KIT

Preclinical and clinical data support the immune stimulatory mechanism of action of VEGFR2. Inhibition of VEGFR2 and KIT depletes Tregs and MDSCs, two key immunosuppressive cell types in the TME. Tregs are a subpopulation of T cells that suppress immune responses through inhibition of T effector cell proliferation and cytokine production, thereby maintaining homeostasis and self-tolerance. MDSCs are a heterogeneous population of diverse cells of immature myeloid origin that can be abundant in the TME where they potently suppress T cell responses. These cell types have each been associated with resistance to checkpoint inhibitors and targeting them has emerged as an attractive therapeutic strategy to overcoming CIT resistance.

Tregs express VEGFR2, the inhibition of which, utilizing a VEGFR2-specific antibody antagonist or VEGFA-neutralizing antibody, hinders Treg proliferation in vitro, and patient peripheral blood. The inhibition of the VEGF/VEGFR2 pathway utilizing VEGFA-neutralizing antibodies or VEGFR2 small molecule inhibitors also reduces intratumoral Tregs in a syngeneic mouse cancer model [43]. The depletion of Tregs in both peripheral blood and tumor tissue has been observed in several mouse models and in clinical trials with VEGFR inhibitors, including sunitinib and sorafenib [43-47].

RCC is particularly relevant as it is a tumor type that is highly responsive to VEGF pathway inhibitors, as well as immunotherapeutic agents, including checkpoint inhibitors and IL-2. Several groups have documented both the increase in MDSCs in RCC patients as well as MDSC depletion following VEGFR2 inhibition [48-51]. MDSC depletion led to a concomitant increase in tumor-infiltrating T cells. These data served, in part, as rationale for testing VEGF/VEGFR2 inhibitors in combination with CIT in RCC. Positive data has been reported from studies in metastatic RCC, including pembrolizumab or avelumab in combination with axitinib [52, 53], and phase III trials testing VEGF-targeting agents with CIT in treatment-naïve patients are underway [16, 54-56]. Likewise, several studies investigating compounds that inhibit VEGF/VEGFR2 signaling when combined with CIT are ongoing in NSCLC.

Non-clinical studies have also demonstrated that KIT inhibition through the use of small molecules or antibodies also decreases immunosuppressive cell populations. An anti-KIT antibody enhanced the anti-tumor activity of CTLA-4 and PD-1 antibodies by reducing MDSCs and restoring CD8+ and CD4+ cell populations [57]. Blocking KIT also prevented the development of Tregs and reversed MDSC-induced immune tolerance [58, 59].

MET

Based on its roles in mediating an immunosuppressive TME, as well as its role in regulating antigen-presenting cell (APC) function, MET has also been implicated in the modification of the tumor immune response. MET is expressed by immature CD14+ monocytes and can be induced to acquire an immunosuppressive phenotype when activated by HGF ligand secreted by tumor stroma and mesenchymal stem cells (MSCs) [60]. Depletion of CD14+ monocytes or neutralization of HGF secretion by MSCs reverses the suppression of T effector proliferation and triggers a shift back toward a Th1-activated T cell phenotype. MSCs were also implicated in the expansion of immunosuppressive MDSCs, which was also dependent on the secretion of HGF [61]. APCs (i.e., dendritic cells) express MET, and activation of MET by HGF resulted in suppression of APC function, including both its antigen-presenting capacity and its antigen-dependent T cell responses, both in vitro and in vivo [62-64]. HGF neutralization or MET blockade resulted in increased APC antigen-presenting capacity and triggered an antigen-mediated and T cell-directed immune response in vivo, utilizing selected mouse models of inflammatory response.

DRUGS WITH OVERLAPPING TARGET PROFILES

RTK inhibitors and biologics in clinical development have target profiles that overlap with sitravatinib have confirmed that inhibition of these RTKs can decrease immunosuppressive cell populations, including Tregs and MDSCs, and stimulate an anti-tumor immune response. Several of these drugs are being tested in combination with checkpoint inhibitors in several cancer types.

One such example is cabozantinib, which targets VEGFR2, in addition to other RTKs, and is approved for the treatment of RCC and metastatic thyroid cancer. Cabozantinib is being explored in combination with immune checkpoint inhibitors in several indications, including RCC, urothelial carcinoma, and NSCLC, based, in part, on this mechanism of action. In preclinical tumor models, cabozantinib reduced splenic MDSCs and Tregs, disrupting the

latter's suppression of CD4+ T cell proliferation, an indication that the normal regulatory function of these cells had been eliminated [65]. Clinically, a reduction in Tregs has been observed with cabozantinib treatment [Apolo, AB, et al, J Clin Oncol. 2014; 32s: abstr 4501.], while in a separate study, a decrease in circulating CD14+ monocytes and an increase in CD3+ and CD8+ T cells was observed following cabozantinib treatment [66]. Moreover, results from clinical trials have demonstrated that the combination of cabozantinib plus nivolumab demonstrated promising anti-tumor activity in bladder cancer and other genitourinary cancers [Nadal, R.M., et al, J Clin Oncol. 2018; 36,6 sup 515.].

Another example is lenvatinib, a VEGFR and Fibroblast Growth Factor Receptor (FGFR) family RTK inhibitor approved for the treatment of RCC, hepatocellular carcinoma (HCC) and thyroid cancer. Lenvatinib is currently being explored in combination with checkpoint inhibitors in RCC, head and neck cancer, endometrial cancer and hepatocellular carcinoma. Pre-clinical studies confirmed CIT combination treatment reduced immunosuppressive tumor-associated macrophages and immunosuppressive signal receptors, and inhibited tumor growth [<https://www.eisai.com/news/pdf/enews201715pdf.pdf>]. Encouraging response rates were reported at ASCO 2018 in clinical updates from all four ongoing CIT combination trials [ASCO Abst #4076, 6016, 4560, 5596, and 5597].

Axitinib, a more selective VEGFR family inhibitor, has been approved for the treatment of RCC and currently being explored in combination with multiple checkpoint inhibitors in RCC. Early reports highlighting the combination of axitinib with either pembrolizumab or avelumab in independent clinical trials indicated a high durable objective response rates in treatment-naïve metastatic RCC [54, 67]. The combination of axitinib and pembrolizumab improved progression-free survival and overall survival in first line metastatic RCC [53], while a phase III trial combining axitinib and avelumab met its primary endpoint of a statistically significant improvement in progression-free survival, for which the FDA granted breakthrough therapy designation for treatment-naïve patients with advanced RCC [4].

In contrast to the majority of biologic or multi-RTK-targeting small molecule inhibitors described above, sitravatinib exhibits a unique and enhanced spectrum of target blockade centering on key immune-relevant targets including TAM, VEGFR, KIT, and MET RTKs and is, therefore, anticipated to be an ideal CIT combination partner. In addition, sitravatinib has demonstrated a favorable safety profile as a single agent and in combination compared to agents like cabozantinib.

SITRAVATINIB ANTI-PD-1 COMBINATION DATA

Non-clinical

Sitratavinib was tested alone or in combination with anti-PD-1 in the CT26 syngeneic mouse model. Alone, sitratavinib increased expression of PD-L1 on tumor cells, in vitro and in vivo; increased the fraction of systemic CD4+ and CD8+ T cells; and reduced the number of systemic MDSCs in vivo. The combination of sitratavinib and CIT demonstrated increased anti-tumor activity compared to single-agent alone.

In preclinical studies, sitravatinib inhibited the expression of IL-4-stimulated Arginase 1 (Arg1), a marker of M2 polarization, in bone marrow-derived macrophages (BMDM) [68]. Sitravatinib also inhibited the expression of the M2 markers Arg1, YM-1, and Fizz-1, upon stimulation with conditioned media from murine cancer cells, a source of TAM receptor ligands. These effects were lost in BMDM from *MERTK* $-/-$ mice, as these cells lose their ability to be effectively polarized to an M2 state, illustrating the importance of targeting MERTK to maximize immune response. Furthermore, sitravatinib reduced immunosuppressive cell populations in vivo, including monocytic MDSCs and M2-polarized macrophages, increased intratumoral and circulating CD4+ and CD8+ populations, and augmented the effect of anti-PD-1 therapy. A subset of combination-treated mice had a complete response and when these animals were re-implanted with tumor cell inoculum, no tumors formed in contrast to normal tumor implantation in naïve mice. These data provide compelling evidence that animals developed an effective adaptive immune response following sitravatinib plus anti-PD-1 therapy.

Clinical: Phase II Trial of Sitravatinib + Nivolumab in Checkpoint Refractory NSCLC (MRTX500)

MRTX500 is a phase II trial evaluating the efficacy and safety of sitravatinib in combination with nivolumab, an anti-PD-1 immune checkpoint inhibitor, in patients with NSCLC who have experienced documented disease progression following prior treatment with an immune checkpoint inhibitor. Data presented at the European Society for Medical Oncology (ESMO) Congress in October 2018 demonstrated that the combination was clinical active. In this checkpoint refractory population, retreatment with a checkpoint inhibitor alone would not be expected to provide meaningful clinical benefit.

As of the cut-off date of August 27, 2018, 56 patients from this ongoing trial were evaluable. The rate of confirmed objective response (ORR) was 20% (11/56), with tumor regressions observed in 80% (45/56) of patients and tumor reductions of greater than 30% observed in 32% (18/56) of patients. The clinical benefit rate (stable disease + partial response + complete response) was 75% (42/56). Preliminary Kaplan-Meier estimates of median duration of response (DOR, 9.2 months), progression free survival (PFS, 6.8 months) and overall survival (OS, 15.1) were encouraging when compared with the historical performance of docetaxel, the standard of care in this setting. The combination of sitravatinib plus nivolumab was well-tolerated with manageable side effects. Sitravatinib-related AEs (>10% of pts; all grades) included diarrhea, nausea, vomiting, decreased appetite, fatigue, mucosal inflammation, dysphonia, AST/ALT increase, weight decrease, hypertension, and palmar-plantar erythrodysesthesia syndrome.

Additional biomarker studies were performed on tissue and blood-based patient samples from this trial in an effort to understand the mechanism of action of the combination. Preliminary biomarker analyses revealed a trend towards increased clinical benefit in patients with high PD-L1 expression (<https://www.mirati.com/mgcd516/>). This trend was not significant and clinical benefit, including partial responses, was also observed in patients with low PD-L1. An increase in the fold change of circulating T effector cells between C1D15 and C1D1 was observed in patients with partial responses and patients with clinical benefit versus the rest of the cohort. Total mutation burden was also evaluated from cell-free DNA in baseline plasma samples and no correlation with clinical benefit was observed. These data support the proposed mechanism of action that sitravatinib in combination with nivolumab is able to stimulate an immune cell-mediated anti-tumor response in patients who previously progressed on CIT therapy. It should be noted, while this trial design specifically tests the combination of sitravatinib and nivolumab in

patients who were resistant to single agent CIT, the resistance mechanisms are predicted to be the same in the CIT naïve setting. Therefore, sitravatinib in combination with CIT may demonstrate improved activity relative to single agent CIT in CIT-naïve patients as well.

Clinical: Phase III Trial of Sitravatinib + Nivolumab in Checkpoint Refractory NSCLC

Based on the promising data from the MRTX500 phase II trial, a phase III randomized trial compares sitravatinib in combination with nivolumab versus docetaxel in the treatment of patients with NSCLC who have progressed following treatment with the combination of an immune checkpoint inhibitor and platinum-based chemotherapy. In this second line setting, salvage chemotherapies like docetaxel are utilized but with limited clinical benefit and adverse toxicities. The primary endpoint for the phase III trial is overall survival (OS), with an interim analysis of objective response rate (ORR) as a surrogate endpoint that may serve as the basis for a potential Subpart H accelerated approval.

Clinical: Other Trials with Sitravatinib in Combination with CIT

The utility of sitravatinib in combination with CIT is also being explored in other tumor types and clinical settings. Sitravatinib plus nivolumab is being explored in a phase II trial in urothelial carcinoma patients previously treated with CIT. As described earlier, RCC and hepatocellular cancer (HCC) are likely to be sensitive to the combination of an RTK inhibitor with the profile of sitravatinib in combination with immunotherapeutic agents. The combination of sitravatinib plus tislelizumab (a PD-1 inhibitor) is being evaluated as a treatment for CIT naïve and refractory patients with RCC or HCC as part of multi-cohort phase II trials in China. Also included in these trials are cohorts of patients CIT naïve and refractory ovarian cancer, gastric cancer and NSCLC.

The combination of sitravatinib and nivolumab is also being evaluated in neo-adjuvant RCC and neo-adjuvant head and neck squamous cell cancers. These ‘window of opportunity’ presurgical settings allow pre- and post-treatment biopsies, followed by tumor resection, which will support an in-depth characterization of sitravatinib’s effect on the TME. Such data are expected to provide additional insight into sitravatinib’s mechanism of action in combination with CIT as well as initial data in the neoadjuvant setting.

SUMMARY

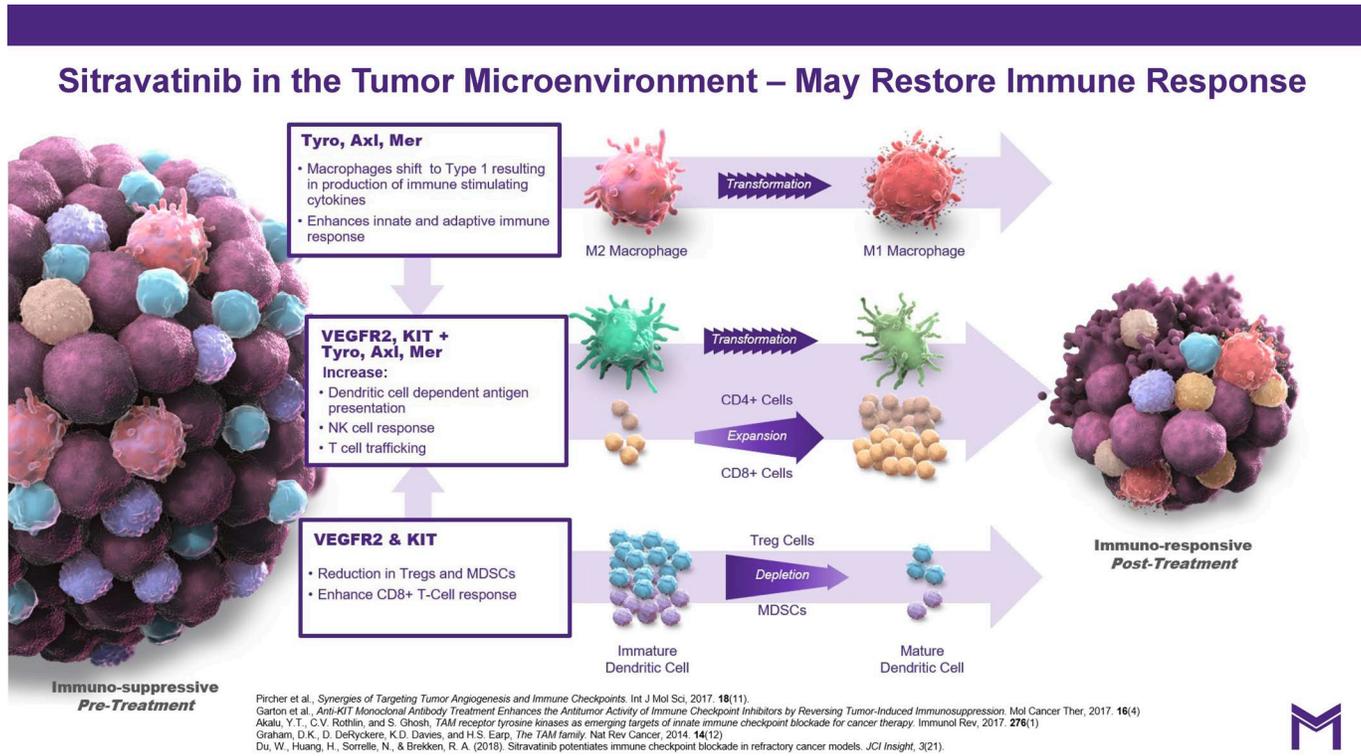
Primary and secondary resistance to CIT is common and significantly limits the therapeutic success of immunotherapy. Several mechanisms underlying intrinsic and acquired resistance to CIT have been elucidated. These mechanisms appear to be mediated, in part, through activation of the TAM and split family receptors, as well as MET activation, which work together to suppress anti-tumor immunity at several nodes and stages of the cancer-immunity cycle [5, 7, 17-19, 69]. The demonstration that inhibition of these RTKs with sitravatinib can reverse CIT resistance in NSCLC patients distinguishes this regimen as one of the first effective CIT combination therapies and provides a much-needed therapeutic option for patients who have disease progression on CIT.

Table 1: Sitravatinib Activity Against Immune RTKs

RTK	Biochemical IC ⁵⁰ (nM)	Cellular IC ⁵⁰ (nM)
Axl	1	0.4
MERTK	1	0.8
TYRO3	ND	5.1
VEGFR2	5	2.0
KIT	6	16
MET	20	13.2

ND – Not determined

Figure 1: Sitravatinib in the Tumor Microenvironment



GLOSSARY OF TERMS

APC – Antigen presenting cell

Arg1 – Arginase 1; Marker of immunosuppressive M2 macrophages

β 2M – β -2-microglobulin; Component of major histocompatibility complex class I (MHC I)

BMDM – Bone marrow-derived macrophages

CD4 – Cluster of differentiation 4; Co-receptor for the T cell receptor expressed on helper T cells

CD8 – Cluster of differentiation 8; Co-receptor for the T cell receptor expressed on cytotoxic T cells

CTLA-4 – Cytotoxic T-lymphocyte-associated protein 4; Immune checkpoint protein that down regulates immune responses when activated

Fizz-1 – Resisitn like beta (RETNLB); Marker of M2 alternatively activated macrophages

Gas6 – Growth arrest-specific protein 6; TAM receptor ligand

HGF – Hepatocyte growth factor

IFN- γ – Interferon- γ ; Proinflammatory cytokine

IgG – Immunoglobulin G; Class of antibody

IL-4 – Interleukin 4; Cytokine that promotes M2 alternatively activated macrophages

KIT – KIT proto-oncogene receptor tyrosine kinase

M1 macrophage – Pro-inflammatory macrophage

M2 macrophage – Alternatively activated, immunosuppressive macrophage

MDSC – Myeloid-derived suppressor cell; Heterogenous immunosuppressive myeloid cells

MET – MET proto-oncogene, receptor tyrosine kinase

MHC class I – Major histocompatibility complex class I; Cell surface protein that presents antigens to immune cells

MSC – Mesenchymal stem cells

NSCLC – Non-small cell lung cancer

PD-1 – (aka Pcd1, cluster of differentiation 279 (CD279)) – Programmed cell death protein 1; Immune checkpoint receptor expressed on immune cells that blocks T cell activation when bound by PD-L1 or PD-L2 ligand

PD-L1 – (aka cluster of differentiation 274 (CD274), B7 homolog 1 (B7-H1)) – Programmed death-ligand 1; Immune checkpoint ligand for PD-1 expressed on tumor cells and other cells in response to IFN γ which then transmits an inhibitory signal to PD-1-expressing immune cells.

Pros1 – Protein S; TAM receptor ligand

RCC – Renal cell carcinoma

RTK – Receptor tyrosine kinase

Split RTK family – Family of RTKs that have a split tyrosine kinase domain; includes VEGFRs

STK11 – (aka liver kinase B1 (LKB1)) Serine/Threonine Kinase 11

TAM – Tyro3, AXL, MERTK; Receptor tyrosine kinase family

Th1 – Subtype of helper T cells that activate cytotoxic T cells

TMB – total mutation burden

TME – Tumor microenvironment

Treg – T regulatory cell; Immunosuppressive T cell, down regulates the induction and proliferation of effector T cells

VEGF – Vascular endothelial growth factor; Stimulates blood vessel formation and immunosuppression in cancer.

VEGFR2 – Vascular endothelial growth factor-receptor 2

YM-1 – Chitinase-3-like protein 3; Marker of M2 alternatively activated macrophages

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