

Addressing CPI resistance in NSCLC: targeting TAM receptors to modulate the tumor microenvironment and future prospects

Solange Peters,¹ Luis Paz-Ares,² Roy S Herbst,³ Martin Reck⁴

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ABSTRACT

Lung cancer remains a leading cause of cancer death worldwide, with non-small-cell lung cancer (NSCLC) accounting for the majority of cases. Immune checkpoint inhibitors (CPIs), including those targeting programmed cell death protein-1 and its ligand (PD-1/PD-L1), have revolutionized the treatment landscape for various cancers. Notably, PD-1/PD-L1 inhibitor-based regimens now form the standard first-line therapy for metastatic NSCLC, substantially improving patients' overall survival. Despite the progress made using CPI-based therapies in advanced NSCLC, most patients experience disease progression after an initial response due to resistance. Given the currently limited therapeutic options available for second-line and beyond settings in NSCLC, new treatment approaches are needed to improve long-term survival in these patients. Thus, CPI resistance is an emerging concept in cancer treatment and an active area of clinical research.

Among the key mechanisms of CPI resistance is the immunosuppressive tumor microenvironment (TME). Effective CPI therapy is based on shifting immune responses against cancer cells, therefore, manipulating the immunosuppressive TME comprises an important strategy to combat CPI resistance. Several aspects of the TME can contribute to treatment resistance in NSCLC, including through the activation of Tyro3, Axl, MerTK (TAM) receptors which are essential pleiotropic regulators of immune homeostasis. Their roles include negatively modulating the immune response, therefore ectopic expression of TAM receptors in the context of cancer can contribute to the immunosuppressive, protumorigenic TME. Furthermore, TAM receptors represent important candidates to simultaneously target both tumor cells and immune cells in the TME. Clinical development of TAM receptor inhibitors (TAM RIs) is increasingly focused on their ability to rescue the antitumor immune response, thereby shifting the immunosuppressive TME to an immunostimulatory TME. There is a strong biological rationale for combining TAM RIs with a CPI to overcome resistance and improve long-term clinical responses in NSCLC. Combinatorial clinical trials of TAM RIs with CPIs are underway with encouraging preliminary results. This review outlines the key mechanisms of CPI resistance, including the role of the immunosuppressive TME, and discusses the rationale for targeting TAM receptors as a novel, promising therapeutic strategy to overcome CPI resistance in NSCLC.

INTRODUCTION

The development of immune checkpoint inhibitors (CPIs) has revolutionized the treatment landscape for various cancers, including melanoma, renal cell carcinoma (RCC), and non-small-cell lung cancer (NSCLC).¹ Two immune checkpoints, programmed cell death protein-1 (PD-1) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), are common inhibitory pathways that tumor cells co-opt to escape host immune surveillance.^{2,3} PD-1 is a negative costimulatory receptor expressed predominantly on the surface of activated T cells that regulates the balance among T-cell activation, tolerance, and immunopathology.⁴ After binding to one of its ligands, programmed cell death-ligand 1 (PD-L1) or 2, PD-1 suppresses cytotoxic T lymphocyte (CTL) activation, allowing tumor cells to escape immune system surveillance.⁵ Binding of PD-1/PD-L1 functions as a brake to limit overreactive T cells and autoimmunity.⁶ Monoclonal antibodies directed against PD-1/PD-L1 block the engagement of PD-1 with its ligands, effectively removing the brake on PD-1/PD-L1-mediated immunosuppression; this, in turn, leads to enhanced tumor recognition by CTLs.⁶ CTLA-4 (CD152) is a B7/CD28 family member expressed by regulatory T cells and other activated T-cell subsets with an inhibitory role in T-cell function, thereby mediating immunosuppression.^{7,8} CTLA-4 signaling has been shown to dampen immune responses against infections and tumor cells. Overall, interruption of these inhibitory pathways with antibody-targeted drugs promotes host immune response against tumor cells.

Following the regulatory approval of PD-1 or PD-L1 inhibitors for NSCLC, overall survival (OS) for patients with metastatic disease improved substantially; currently, most patients receive PD-1/PD-L1 inhibitors as part



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¹Medical Oncology, Lausanne University Hospital, Lausanne, Switzerland

²Medical Oncology Department, Hospital Universitario 12 de Octubre and CNI-O-H120 Lung Cancer Unit, Universidad Complutense and Ciberonc, Madrid, Spain

³Yale Cancer Center, Yale School of Medicine, New Haven, Connecticut, USA

⁴Lung Clinic Grosshansdorf, Airway Research Center North, Center for Lung Research, Grosshansdorf, Germany

Correspondence to
Dr Solange Peters;
solange.peters@chuv.ch

of standard treatment, optimally administered as front-line therapy.^{9,10} CPI plus chemotherapy is the standard first-line therapy for patients with non-oncogenic driven metastatic NSCLC, irrespective of PD-L1 expression.^{10–12} CPI monotherapy is also a standard-of-care (SOC) option for patients with high ($\geq 50\%$) PD-L1 expression.^{10,13–15} CPI combinations that inhibit PD-1 and CTLA-4 simultaneously with or without chemotherapy represent alternative treatment options.^{10,16,17} Long-term survival benefits of first-line CPI monotherapy vs chemotherapy in NSCLC have been reported in the KEYNOTE-024, IMpower-110, and EMPOWER-Lung 1 trials for tumors with high PD-L1 expression and a tumor proportion score of $\geq 50\%$, with 1-year OS rates of 65%–70%^{14,18,19} and 5-year OS rates up to 32%.¹³ In addition, long-term survival benefits of first-line CPI plus chemotherapy have been observed in the KEYNOTE-189 and KEYNOTE-407 trials; in these trials, 3-year OS was 31% for pembrolizumab plus chemotherapy in nonsquamous NSCLC and 2-year OS was 37.5% for pembrolizumab plus chemotherapy in squamous NSCLC.^{11,12} Furthermore, long-term survival benefits of first-line immunotherapy combinations with or without chemotherapy have been reported in the CheckMate 227 and CheckMate 9LA trials, with 4-year OS of 29% for nivolumab plus ipilimumab and 2-year OS of 38% for nivolumab plus ipilimumab and chemotherapy.^{16,17}

Despite the successful use of CPIs in patients with NSCLC over the past decade, lung cancer remains one of the leading causes of cancer mortality worldwide.²⁰ The majority of patients with NSCLC experience disease progression and death after CPI plus chemotherapy, due to primary (intrinsic) or secondary (acquired) CPI resistance,^{1,21} and treatment options for these patients are limited. Thus, novel treatment options are needed to improve or extend long-term survival in patients with NSCLC, as both an initial strategy and upon development of resistance to CPI-based therapy. Primary resistance is used to denote patients who do not respond to

CPI treatment at all and progress reasonably quickly; acquired resistance refers to patients who have a period of initial response to or disease control with CPI therapy, followed by clinical or radiologic evidence of disease progression.^{1,21,22} Although distinct mechanisms of resistance have been identified, in some cases related or overlapping mechanisms allow tumors to escape antitumor immune responses either de novo or after initial response to CPI therapy.

This review discusses the immunosuppressive tumor microenvironment (TME) as a key mechanism of resistance and the role of Tyro3, Axl, and MerTK (TAM) receptors as a potential therapeutic target in overcoming CPI resistance, and explores the new treatment approaches currently in development to address CPI-refractory NSCLC.

MECHANISMS OF CPI RESISTANCE

Although current PD-1/PD-L1 inhibitors have had success in treating NSCLC, the PD-1 pathway remains a key mechanism of immune escape by tumor cells in some patients with NSCLC who respond initially but not indefinitely.²³ To optimize the development of rational CPI-combination therapies and extend the benefit of these therapies to more patients, it is necessary to understand why tumors in some patients develop immune escape mechanisms.²³ The mechanisms of primary and acquired resistance to CPI therapy are complex and multifactorial; the mechanisms most often implicated in acquired resistance to CPIs in NSCLC can be broadly divided into the following four categories^{24,25}: (1) inhibitory or other immune checkpoints; (2) defects in antigen presentation and neoantigen loss; (3) oncogenic signaling pathways; and (4) immunosuppressive TME (figure 1). However, the lack of adequate immune preclinical models in which antitumor activity is induced by CPIs and the insufficient clinical data available (due to the difficulty of performing

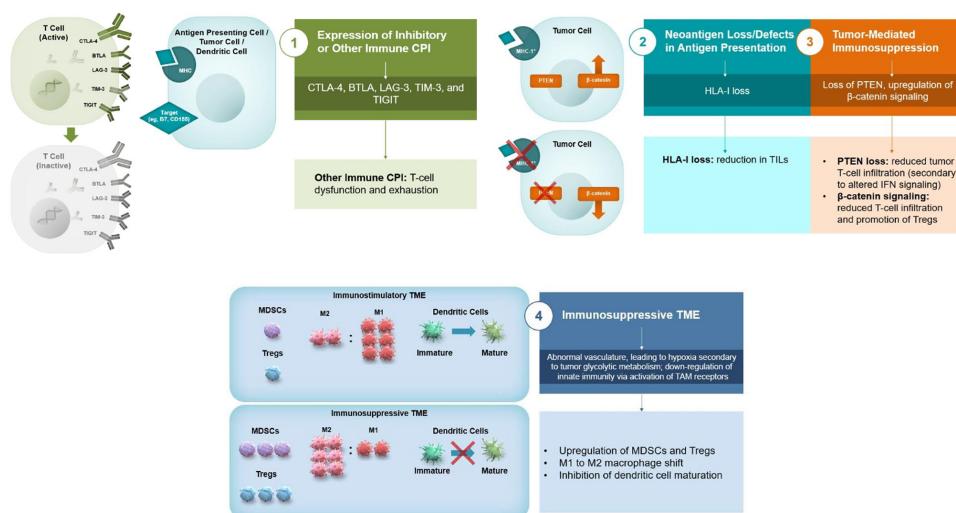


Figure 1 CPI resistance in NSCLC: the role of the tumor microenvironment (TME). CPI, checkpoint inhibitor; MDSCs, myeloid-derived suppressor cells; NSCLC, non-small-cell lung cancer; TIGIT, tyrosine-based inhibition motif domain.

rebiopsy and the lack of sufficient tissue to perform testing) limits our current understanding of the definitive mechanisms involved.^{26 27}

Inhibitory or other immune checkpoints

Upregulation of inhibitory or other immune checkpoints, including CTLA-4, B- and T-lymphocyte attenuator, lymphocyte-activation gene 3 (LAG-3), T-cell immunoglobulin and mucin domain-3 protein (TIM-3), and T-cell immunoreceptor tyrosine-based inhibition motif domain (TIGIT), has been observed in patients exhibiting secondary resistance to CPIs.^{24 28–31} It has been hypothesized that inhibition of LAG-3 may restore T-effector cell activity and reduce the activity of regulatory T cells (Tregs), thereby enhancing the antitumor activity of PD-L1 inhibition.³² Furthermore, a study in immunocompetent mouse models of lung adenocarcinoma found significant upregulation of TIM-3 in PD-1 antibody-bound T cells, and demonstrated a survival advantage with addition of a TIM-3 blocking antibody following failure of PD-1 blockade.²⁹ Although it remains uncertain whether there is a causal relationship between the upregulation of other checkpoints and CPI resistance, aside from the possible functional redundancy of these co-inhibitory receptor pathways, another model proposes a two-tiered system with PD-1 and CTLA-4 representing the first tier primarily responsible for self-tolerance, and the second tier represented by LAG-3, TIM-3, and TIGIT having distinct and specific roles in regulating immune responses (with some functional overlap).³² Finally, recent data also suggest that these other checkpoints may be associated with T-cell dysfunction and exhaustion.³³

Defects in antigen presentation and neoantigen loss

Defects in tumor antigen presentation, including neoantigen loss and alterations in antigen presentation pathways, may also contribute to CPI resistance.³⁴ Disruption in antigen presentation pathways can be associated with class I human leucocyte antigen (HLA-I) loss, which causes a reduction in tumor-infiltrating lymphocytes (TILs), or β2-microglobulin dysfunction.³⁵ Furthermore, tumor cells may escape immune elimination by expressing nonclassic HLA-I antigens, such as HLA-G and HLA-E, which bind to inhibitory receptors on T cells and other immune cell types.^{36 37} A recent study reported that loss of heterozygosity (LOH) at HLA-I in patients with advanced solid tumors treated with CPI therapy was associated with poor survival outcomes; these clinical findings suggest that HLA-I genes may influence survival in patients treated with CPIs³⁸ and that additional studies are needed to further characterize the relationship between HLA-I and outcomes in patients treated with CPIs.³⁹

Secondary resistance in NSCLC has been associated with the removal of mutation-associated neoantigens, which occurs through the deletion of truncal chromosomal regions or abolition of tumor subclones.³⁹ Recent data suggest that homologous recombination deficiency and human leucocyte antigen-LOH (HLA-LOH) can

impact response to CPI therapy. Although additional studies are needed to further characterize these observations, HLA-LOH may have predictive and prognostic value for response to CPIs.⁴⁰ Novel strategies to improve tumor antigenicity include combining a CPI with another treatment modality, such as conventional chemotherapy, radiotherapy, vascular endothelial growth factor (VEGF) inhibitors, epigenetic therapies, oncolytic viruses, and cancer vaccines. However, a more detailed discussion of these novel strategies is outside the scope of this review.

Oncogenic signaling pathways

Loss of the tumor suppressor phosphatase and tensin homolog (PTEN), a negative regulator of the phosphoinositide 3-kinase, protein kinase B, mechanistic target of rapamycin (PI3K/Akt/mTOR) pathway, has been associated with reduced tumor T-cell infiltration (secondary to altered interferon (IFN) signaling) and resistance to PD-L1 inhibitor therapy in clinical studies.^{41 42} IFN-induced upregulation of antigen-processing machinery (APM) components improves antitumor-specific CTL responses.⁴³ However, some tumors remain insensitive to IFN therapy, despite the absence of structural alterations in APM components; this finding suggests that impaired IFN signaling may play a role in reducing CD8+ T cell responses.⁴³ Similar to PTEN loss, upregulation of β-catenin signaling has been associated with reduced T-cell infiltration and promotion of Tregs, resulting in resistance to CPIs.^{44 45} Recent data suggest that combining a wingless-related integration site/β-catenin pathway inhibitor with a CPI may be an effective therapeutic strategy to overcome CPI resistance; however, additional studies are needed to further characterize the role of β-catenin signaling in NSCLC.⁴⁶

Immunosuppressive TME

The TME is a highly heterogeneous milieu consisting of cancer cells, stromal tissue, the extracellular matrix, and immune cells whose collective molecular signals influence disease outcome by altering the balance of suppressive vs cytotoxic responses in the vicinity of the tumor.^{47 48} The immune system is an important determinant of the TME, with complex interplay between tumor cells and the host immune response, involving multiple components including tumor parenchymal cells, fibroblasts, mesenchymal cells, blood, lymph vessels, TILs, chemokines, and cytokines.^{47 48} Therefore, the TME has a decisive role in tumor differentiation, epigenetics, dissemination, and immune evasion. Once tumor cells evade immune surveillance and progress, tumor-released molecules shape the TME with increasing immunosuppression that debilitate robust anti-tumor immune responses.⁴⁸ Shifting immune responses is key for effective CPI therapy, and manipulation of the TME is an important strategy to combat resistance (figure 1).⁴⁹ Several factors, including the mechanisms described above, may induce changes within the TME that contribute to CPI resistance.



One hallmark of solid tumors is an abnormal vasculature, and the TME plays critical roles in tumor growth, angiogenesis, and metastasis, with the microvasculature comprising a major component of the TME.^{48–51} Tumor cells alter the TME by high production of VEGF which is crucial in promoting tumor angiogenesis.^{50–51} VEGF may also contribute to an immunosuppressive TME and resistance to CPIs by increasing myeloid-derived suppressor cells (MDSCs) and Tregs, reducing T-cell tumor infiltration, and inhibiting dendritic cell (DC) maturation.^{52–54} VEGF receptors (VEGFRs) stimulate production of immunosuppressive cells, promote T-cell exhaustion, and inhibit T-cell infiltration into tumors.⁵⁵ Thus, the most common approach to normalizing the vasculature of the TME is blockade of the VEGF pathway or its receptors with anti-VEGF agents.⁵⁶

The occurrence of hypoxia secondary to tumor glycolytic metabolism and acidosis also plays a pivotal role in the TME by inducing the upregulation of VEGF.^{48–50} Hypoxia, in turn, has an immunosuppressive effect on the TME, leading to upregulation of MDSCs and Tregs, reduction in CTL activity, T-cell exhaustion, production of immunosuppressive cytokines, and a transition of macrophages from an inflammatory M1 phenotype to an immunosuppressive M2 phenotype.^{56–59} Preclinical studies in lung cancer models have reported hypoxia-induced resistance to CTL-mediated lysis; most recently, tumor-associated macrophages were shown to improve tumor hypoxia and modulate the activity of CPIs in NSCLC.^{60–61}

TAM RECEPTORS: A POTENTIAL NEW TARGET FOR OVERCOMING CPI RESISTANCE

Altogether, several aspects of the TME may contribute to resistance to CPI therapy in NSCLC, including through the activation of TAM receptors.^{62–63} The TAM family of receptor tyrosine kinases (RTKs) includes Tyro3, Axl, and MerTK receptors which together are essential regulators of immune homeostasis with pleiotropic effects on the immune response.^{62–63} TAM receptors are broadly expressed by a variety of cells and tissues of the body, but notably on antigen-presenting cells as well as natural killer (NK) cells.^{63–64} Their most prominent roles as immune modulators include the negative regulation of inflammation and the phagocytosis of cellular debris and apoptotic cells, a process known as efferocytosis.^{63–64} Notably, an important feature of macrophages ingesting apoptotic cells is their subsequent propensity to downregulate the generation of proinflammatory cytokines and upregulate factors associated with immunosuppression.⁶⁴ Besides their primary role as efferocytosis receptors, downstream signaling of TAM receptors also has independent immunomodulatory effects, including the negative modulation of the innate immune response (ie, dampening activation of innate cells), their role as integrators of innate and adaptive immunity, and their implication in restoring vascular integrity.^{62–64–67} TAM receptor activation controls inflammatory cytokines, such as type I IFN, tumor necrosis

factor-alpha (TNF- α), interleukin (IL)-1 β , and IL-6, and the inhibitory effects of TAM receptors on cytokines help limit the prolonged activation of macrophages.^{68–71} TAM kinases can be considered innate immune checkpoints that may contribute to the immune-resistant nature of different tumors.⁶⁴

How TAM receptors modulate the TME

TAM receptors have been found to be overexpressed or ectopically activated across many types of human cancer including lung, breast, colon, renal, skin, liver, brain, ovarian, prostate, thyroid, and hematological malignancies.^{64–72–75} In the setting of cancer, TAM receptors appear to have a dual regulatory role, controlling the initiation and progression of tumor development and the associated antitumor responses of diverse immune cells, including macrophages, NK cells, DCs, and T cells.⁶³ TAM receptors may also have a negative effect on cell death and apoptotic signaling, as demonstrated on inhibition of Axl and MerTK.⁷⁶ They have also been linked to the phenomenon of apoptotic mimicry, in which cancer cells can express both TAM receptors and their ligands as a means to dampen the anticancer immune responses.⁷² Furthermore, TAM receptor activation and downstream signaling have been associated with driving several hallmarks of oncogenesis, such as cytoskeleton rearrangement, which can promote migration and invasion, as well as angiogenesis;⁷⁶ upregulation of Axl has been shown to be a marker for epithelial-to-mesenchymal transition.^{76–78}

In addition to these cell-specific effects, the activation of TAM receptors is thought to contribute to an immunosuppressive TME through a number of mechanisms, via subversion of their normal roles in suppressing the innate immune inflammatory response and/or their pro-angiogenic effects.^{73–75} Immune suppression in the TME is protumorigenic and propagated by the major immune cell components of the TME, tumor-associated macrophages, and MDSCs, which mainly express TAM receptors.

The activation of TAM receptors by their ligands (eg, protein S (PROS1)) in the TME inhibits the expression of pro-inflammatory cytokines and promotes the production of immunosuppressive cytokines.⁷⁹ Furthermore, TAM receptors on MDSCs contribute to the formation of a suppressive TME.⁸⁰ MerTK has more recently been directly implicated in the regulation of myeloid cell-mediated immunosuppression, with MerTK-positive cells found to be quite common in the TME.⁶⁶ Collectively, findings support the idea that MerTK-dependent phagocytosis of apoptotic tumor cells leads to a signaling cascade that favors tumor-promoting polarization of macrophages, and these pro-tumorigenic programs increase production of immunosuppressive cytokines that aid tumor growth.⁶⁴ In recent studies, activated CD4+ and CD8+ T cells have been shown to act as part of an autocostimulatory axis through the expression of MerTK and PROS1.^{79–81} In the TME (and other possible environments, such as the lymph nodes), the expression

of TAM by cancer cells may cause these cells to compete with other TAM+ cells for PROS1. This competitive effect has been shown to starve T cells in the TME, particularly CD8+ cells, of PROS1, inhibiting T cell activation by cancer cells.⁷² Further research is required to assess the effects of new and potent MerTK-specific inhibitors and their implications in the clinical setting. Finally, TAM receptor ligands (such as Gas6) are also expressed by tumor cells and stromal and myeloid cells in the TME, enabling crosstalk between the different cell populations and contributing to an immunosuppressive TME.^{66 75}

Targeting TAM receptors to address CPI resistance via TME modulation

An increasing body of evidence strongly suggests that TAM receptors play major roles in resistance to cancer therapies (both conventional and targeted) through multiple mechanisms.⁷⁵ This supports the notion that targeting of TAM receptors represents a novel, promising strategy for overcoming CPI resistance by shifting the immunosuppressive TME to an immunostimulatory TME.^{64 82} The immunosuppressive TME inhibits the function of the main player involved in antitumor immunity, namely CD8+ T cells, resulting in CPI resistance.⁸² TAM receptors represent important candidates to simultaneously target the tumor cells and the immune cells in the TME.^{72 73 75 83} The immunosuppressive effects within the TME may be reversed through inhibition of TAM receptors, resulting in an increased number of M1-polarized versus M2-polarized macrophages and release of IL-12, IL-6, and TNF- α , which enhance CD8+ T cell activation, as well as increased Toll-like receptor-dependent inflammatory response in DCs.^{69 73 84} Preclinical data suggest that Axl inhibition reduces MDSCs and M2 type tumor-associated macrophages, as well as levels of C-C motif chemokine ligand 11 and other inflammatory TILs.⁸⁵ Inhibition of TAM receptors may also result in higher NK cell activity by releasing the negative feedback regulatory mechanism and may complement PD-1/PD-L1 checkpoint inhibition to augment anticancer immune responses.⁸⁶ Therefore, targeting TAM receptors could remove TME barriers that contribute to CPI resistance through a variety of mechanisms. Given the contribution of these receptors to the TME, together with the effects of tumor hypoxia, novel therapies that target TAM receptors and multiple split-TK domain-containing receptors may help combat resistance to CPIs by reinvigorating immune responses, thereby increasing the number of patients who are responsive to CPI therapy.^{60 61 87}

NEW THERAPEUTIC APPROACHES TO ADDRESS CPI RESISTANCE USING TAM RECEPTOR INHIBITORS

There is a strong biological rationale for combining a TAM tyrosine kinase inhibitor (TKI) with a CPI to overcome resistance and improve clinical responses of patients with NSCLC.^{80 88-92} Despite inducing an inflammatory TME, TAM inhibition leads to an adaptive resistance to

immune cell killing by upregulating molecules of the PD-1/PD-L1 axis, therefore combining TAM inhibition with anti-PD-1 blockade seems necessary and has proven efficacious in both preclinical models and early clinical data.⁷² In a breast cancer model, Axl inhibition induced an antitumor response including tumor-associated effecrocytosis with a synergistic response in combination with PD-1 blockade.⁹² In another preclinical study, Axl inhibition was shown to induce antitumor responses in murine ovarian and breast cancer models by reprogramming the TME, and enhancing the activation and function of tumor-infiltrating CD4+ and CD8+ T cells, an effect which was further potentiated by PD-1 blockade.⁹⁰ Moreover, a recent study using leukemia models, demonstrated that Axl inhibition (specifically in macrophages) triggers durable anti-leukemic immunity and elicits susceptibility to PD-1 blockade; interestingly this efficacy was also observed in Axl negative tumors, which has the potential to extend the clinical benefit of Axl inhibition to a wider population of cancer patients.⁹³

Data from murine lung cancer models indicate that Axl inhibition, when combined with a CPI, promotes infiltration of CTLs and NK cells into the TME, which augments antitumor activity.⁸⁸ Other preclinical studies combining TAM receptor inhibition with anti-PD-L1 therapy in murine models have corroborated the resulting enhanced efficacy of PD-1 blockade.^{87 89 91} Some small-molecule therapies inhibit one or more TAM receptors (Tyro3, Axl, and/or MerTK), and may also provide varying potency of VEGFR family inhibition. Several early-phase to late-phase clinical trials of such combinations are ongoing (table 1).

Sitravatinib

Sitravatinib is a spectrum-selective RTK inhibitor that targets several closely related RTKs, including the TAM receptors and split-family receptors (ie, VEGFR2 and platelet-derived growth factor receptor) (figure 2).⁸⁷ These receptors regulate several immunosuppressive cell types in the TME, including M2-polarized macrophages, MDSCs, and Tregs.⁹⁴ Preclinical data have demonstrated that sitravatinib potentiates immune checkpoint inhibition by causing innate and adaptive immune cell changes within the TME, and by increasing immunostimulatory M1 and decreasing immunosuppressive M2 macrophages; both mechanisms augment the efficacy of PD-L1 blockade.⁸⁷ In a phase 1 window-of-opportunity study evaluating neoadjuvant sitravatinib plus nivolumab in oral cavity cancer (NCT03575598), sitravatinib alone shifted tumor macrophage polarization toward an immunostimulatory state, leading to a reduction in intratumoral MDSCs and an increase in the ratio of M1:M2 macrophages within the TME.⁹⁵

In a phase 2 study of sitravatinib plus nivolumab in patients with NSCLC who had progressed following prior CPI therapy (NCT02954991), the combination was clinically active. After a 28-month median follow-up, median OS was 15 months (1-year and 2-year OS rates were

**Table 1** Selected studies of TAM receptor inhibitors combined with CPI therapies in CPI-resistant NSCLC

Treatment/targets	Sponsor	ClinicalTrials.gov identifier	Phase	PCD	n	Treatment regimen and latest results
Sitravatinib Tyro3, Axl, MerTK, VEGFR2, PDGFR, KIT, FLT3, MET, RET	Mirati Therapeutics, Inc.	NCT02954991	2	05/2021	206*	Sitravatinib + nivolumab arm After a median follow-up of 28 mo, among 68 pts with prior clinical benefit from CPI: ⁹⁶ ► ORR: 16% (including 2 CRs) ► mOS: 15 mo (95% CI 9.3 to 21.1) ► 1-year and 2-year OS rates: 56% and 32%, respectively ► mPFS: 6 months
	Mirati Therapeutics, Inc. and Bristol-Myers Squibb	NCT03906071	3	09/2022	532†	SAPPHIRE: ⁹⁷ Sitravatinib + nivolumab versus docetaxel
	BeiGene	NCT04921358	3	06/2024	420†	Sitravatinib + tislelizumab versus docetaxel
Cabozantinib Tyro3, Axl, MerTK, VEGFR2, KIT, FLT3, MET, RET	Exelixis	NCT03170960	1–2	12/2021	1732†	COSMIC-021: Cabozantinib + atezolizumab ⁸⁸ After a median follow-up of 8.9 months (n=30): ► ORR: 23% (all PRs including three pts refractory to prior CPI) ► DCR: 83%
	Roche/Exelixis	NCT04471428	3	09/2022	366*	CONTACT-01: Cabozantinib + atezolizumab vs docetaxel
Bemcentinib Axl	BerGenBio/ Merck Sharp & Dohme	NCT03184571	2	09/2022	106†	Bemcentinib + pembrolizumab ¹⁰⁶ ¹¹⁴ After a median treatment duration of 8.9 weeks, among CPI-refractory pts (Cohort B) with cAxl-positive tumors (n=7): ► ORR: 14% (1 pt with PR) ► CBR: 86% (6 pts) ► mPFS: 4.73 mo (HR 0.22; 95% CI 0.04 to 1.26; p=0.066)
BA3011 Axl	BioAlta	NCT04681131	2	12/2022	240†	BA3011 monotherapy BA3011 + PD-1 inhibitor
INCB081776 Axl, MerTK	Incyte Corporation	NCT03522142	1	09/2022	140†	INCB081776 + retifanlimab (INCMGA00012) ⁸⁹
PF-07265807/ ARRAY-067 Axl, MerTK	Pfizer	NCT04458259	1	01/2024	115†	PF-07265807 + sasanlimab arm ¹⁰⁹

*Actual enrolment.

†Estimated enrolment.

CBR, clinical benefit rate; CPI, checkpoint inhibitor; CR, complete response; DCR, disease control rate; FLT3, FMS-like tyrosine kinase; KIT, KIT proto-oncogene RTK; MET, hepatocyte growth factor receptor; mOS, median overall survival; mPFS, median progression-free survival; NSCLC, non-small-cell lung cancer; ORR, objective response rate; OS, overall survival; PCD, primary completion date; PDGFR, platelet-derived growth factor receptor; PR, partial response; pts, patients; RET, rearranged during transfection; TAM, Tyro3, Axl, MerTK; VEGFR2, vascular endothelial growth factor receptor 2.

56% and 32%, respectively); median progression-free survival was 6 months, and overall response rate (ORR) was 16% (11/68, including 2 complete responses), with a median duration of response (DOR) of 13 months.⁹⁶ Based on these results, the phase 3 SAPPHIRE trial was

initiated to compare the combination of sitravatinib and nivolumab versus docetaxel alone in patients with advanced nonsquamous NSCLC who had progressed during or after platinum-based chemotherapy in combination with CPI treatment (NCT03906071); this trial is

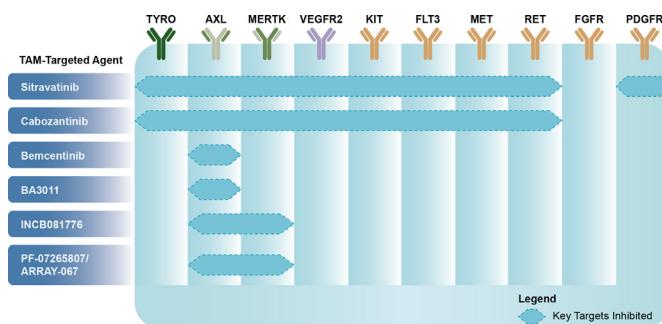


Figure 2 Key immunomodulatory pathways within the TME targeted by TAM-targeted RTKs (including TAM TKI sitravatinib).⁸⁷ RTK, receptor tyrosine kinase; TAM, Tyro3, Axl, MerTK; TKI, tyrosine kinase inhibitor; TME, tumor microenvironment.

currently ongoing.⁹⁷ Sitravatinib is also being investigated in a phase 3 trial in combination with another CPI, anti-PD-1 therapy tislelizumab, vs docetaxel alone in patients with advanced/metastatic NSCLC who have disease progression following platinum-based chemotherapy with CPI treatment (NCT04921358); this trial is currently recruiting.

Cabozantinib

Cabozantinib is a multitargeted TKI that inhibits VEGFR2, hepatocyte growth factor receptor (MET), rearranged during transfection, KIT proto-oncogene RTK, FLT3, Tyro3, Axl, and MerTK, all of which have been implicated in various tumor-promoting processes, including immune cell dysregulation, tumor cell proliferation, and neovascularization.^{98–100} Cabozantinib has been approved by the US Food and Drug Administration (FDA) for the treatment of patients with medullary thyroid cancer, advanced RCC, and hepatocellular carcinoma (HCC) who have been previously treated with sorafenib.¹⁰¹ The European Medicines Agency has also approved cabozantinib for use in patients with advanced RCC and HCC who have been previously treated with sorafenib.¹⁰²

Several clinical trials are currently evaluating the combination of cabozantinib and CPI therapy in various tumor types. The phase 1/2 COSMIC-021 trial is assessing the effects of cabozantinib plus atezolizumab in patients with locally advanced or metastatic solid tumors (NCT03170960). Results from a cohort of patients with NSCLC who had progressed on prior CPI treatment demonstrated that the combination was clinically active. After a median follow-up of 8.9 months, ORR was 23% (7/30, all partial responses) with a DOR of 5.6 months and disease control rate of 83%, and the safety profile was acceptable.¹⁰³ Based on these results, the phase 3 CONTACT-01 trial was initiated to compare the combination of cabozantinib and atezolizumab versus docetaxel alone in patients with NSCLC who had previously received a CPI and platinum-based chemotherapy (NCT04471428); the trial is currently ongoing.¹⁰⁴

Other TAM receptor inhibitors

Bemcentinib (BGB324) is a selective, small-molecule inhibitor that targets the intracellular catalytic kinase domain of Axl.⁸⁵ In a preclinical lung cancer model, the combination of bemcentinib and anti-PD-L1 therapy significantly reduced tumor growth versus anti-PD-L1 therapy alone; tumors treated with the combination showed altered cytokine signaling, enhanced infiltration by effector cells, and a reduction in MDSCs.¹⁰⁵ A single-arm, two-stage, multicohort phase 2 study of bemcentinib plus pembrolizumab in refractory patients with advanced NSCLC (NCT03184571) showed that this combination was well tolerated and clinically active in both the chemotherapy-naïve patients (cohort A) and the CPI-refractory patients (cohort B) with cAxl-positive tumors. In cAxl-positive postchemotherapy and post-CPI patients, the clinical benefit rate was 73% and 86%, respectively.¹⁰⁶ Bemcentinib in combination with a PD-L1 inhibitor recently received a fast track designation from the FDA for the treatment of patients with serine/threonine kinase 11 (*STK11*)-altered advanced/metastatic NSCLC without actionable mutations.¹⁰⁷

BA3011 is a humanized monoclonal antibody conjugate (CAB-AxL-ADC) that specifically binds to Axl in conditions similar to those found within the TME.¹⁰⁸ It is currently being investigated in a phase 2 study alone or in combination with a PD-1 inhibitor in patients with metastatic NSCLC who have previously progressed on a PD-1/PD-L1 inhibitor (NCT04681131).

INCB081776 is a potent and selective dual inhibitor of Axl and MerTK. Preclinical data have demonstrated that INCB081776 partially reversed M2 macrophage-mediated suppression of T-cell proliferation which was associated with increased IFN-γ production. In vivo, treatment was associated with increased proliferation of intratumoral CD4+ and CD8+ T cells and M1 macrophages, and the antitumor activity of INCB081776 was enhanced in combination with anti-PD-L1 blockade resulting in synergistic anti-tumor effects compared with either single agent.^{89 91} INCB081776 is currently being investigated in combination with anti-PD-1 antibody retifanlimab (INCMGA00012) in a phase 1 trial for patients with advanced solid tumors including NSCLC (NCT03522142).

Finally, a phase 1 trial is currently evaluating the safety, tolerability, and PK of PF-07265807/ARRAY-067, an Axl/MerTK small-molecule inhibitor, in patients with selected advanced or metastatic solid tumors (NCT04458259).¹⁰⁹ The second part of the dose-escalation will investigate its combination with anti-PD-1 therapy sasanlimab.

FUTURE APPROACHES TO ADDRESS CPI RESISTANCE IN NSCLC

TAM receptors represent an emerging target, offering the potential to overcome CPI resistance, with a robust pipeline of investigational therapies in various stages of clinical development. Nonetheless, several key questions remain unanswered: (1) Can uniform consensus



definitions of primary and secondary resistance to CPI be established? (2) Can biomarkers be used to identify, characterize, and tailor treatments for patient subsets within the CPI-resistant population? (3) How can clinical trial design and preclinical models be optimized to better investigate novel CPI-combination-based approaches and mechanisms of resistance? (4) What are the challenges associated with combining TAM receptor inhibitors and CPI?

Can consensus definitions of CPI resistance be reached?

Although resistance to PD-1 blockade can be classified as either primary or secondary, there is no consensus in the literature on the definition of each type of resistance. The Society for Immunotherapy of Cancer (SITC) has defined primary resistance as denoting a patient who experiences disease progression after receiving at least 6 weeks of exposure to PD-L1 CPIs; this generally correlates with two complete cycles of FDA-approved PD-L1 inhibitor therapy but no more than 6 months of treatment.¹¹⁰ According to SITC, secondary resistance refers to a patient who is treated with antineoplastic therapy and has a documented, confirmed objective response or prolonged stable disease (SD) lasting longer than 6 months but experiences disease progression during ongoing treatment.¹¹⁰ A more conservative definition of acquired resistance specifically for advanced NSCLC has recently been proposed to account for tumor-specific factors, minimize confounding, and improve consistency for application in future research. In this definition, patients with NSCLC should meet the following criteria: have received treatment that includes PD-(L)1 blockade; experienced an objective response on PD-(L)1 blockade (inclusion of a subset of SD will require future investigation); have progressive disease occurring within 6 months of last anti-PD-(L)1 antibody treatment or rechallenge with anti-PD-(L)1 antibody in patients not exposed to anti-PD-(L)1 in 6 months.²²

We suggest the need for future studies in lung cancer to incorporate standardized, consensus-based definitions, ideally from a large international oncology society, whenever possible. This would allow for better classification of CPI response and long-term evaluation to predict treatment changes and mechanisms of resistance. Furthermore, in order to identify patients who have developed acquired resistance to PD-(L)1 blockade, a strict and specific documentation of response is required. In the context of PD-(L)1 monotherapy, this determination of response is straightforward; however, in the context of PD-(L)1 combination therapies, the potential confounding effect of chemotherapy needs to be considered, as the combination could induce responses via synergistic immunological effects and/or independent cumulative drug action of either agent in a heterogeneous patient population.

Potential use of biomarkers

Establishing biomarkers of CPI resistance is an emerging, rapidly evolving area of research. Other biomarkers

besides PD-L1 have been proposed to identify specific subgroups of patients with NSCLC for whom CPI therapy may be most effective; these include patients with tumor mutation burden, immune-gene expression signatures, and STK11 mutations.^{23 28 111 112} However, these potential biomarkers need to be prospectively validated in the clinic,¹¹³ and the mechanisms of resistance have remained elusive due to the complex and dynamic nature of the TME, as well as immune heterogeneity among individuals. Currently, there is interest in developing routine clinical biomarkers that can be evaluated in a minimally invasive manner, such as serum- or whole blood-derived predictive biomarkers of CPI response. Recent data suggest that peripheral blood neutrophil to lymphocyte ratio values may be predictive of survival benefit from anti-CTLA4 and anti-PD-1 treatment across a wide range of cancer types. Several components of peripheral blood have also been associated with CPI response. Although the potential utility of these biomarkers is promising, clinical implementation warrants further prospective validation.¹¹¹

In addition, specific HLA-I supertypes are associated with survival following CPI treatment. Certain patients with germline heterozygous HLA-I loci can harbor somatic LOH at the HLA-I in their tumors, which has been associated with decreased response to CPI treatment.⁴⁰ HLA-LOH may have predictive and prognostic value for response to CPIs.⁴⁰

Optimizing clinical trial design and preclinical models

The majority of ongoing trials investigating novel CPI-combination approaches lack monotherapy control arms with a CPI or novel agent; control arms are necessary to adequately compare combination therapy with either strategy alone. In addition, it may be important to consider other clinically meaningful endpoints, such as response rates, when designing clinical trials aimed at identifying new strategies, especially for patient populations with major unmet needs. In these cases, confirmatory phase 3 trials are required to further investigate the long-term efficacy and safety of a novel CPI-combination approach, using classical endpoints. Furthermore, detailed clinical descriptions of patients, comorbidities, and other parameters to pinpoint the specific type of resistance will be important components of future clinical trials. Moreover, novel immune preclinical models are needed to better elucidate the underlying mechanisms of CPI resistance and distinguish between related or overlapping resistance mechanisms. An optimal immune preclinical evaluation technique would effectively model the dynamics and heterogeneity of the TME. The production of humanized mice by engraftment with human hematopoietic stem cells may be a viable strategy to overcome current obstacles. These and other new models may help investigate the immune system's role in cancer and the efficacy of various CPI therapies.

Potential challenges of combining TAM receptor inhibitors and CPI

Challenges with this combinatorial approach include potential toxicities, for example, such an immunomodulatory strategy may be associated with immune-related toxicities which will require monitoring and management. In addition, it is difficult to quantify and directly prove that combining these treatments produces a meaningful impact on OS compared with their sequential administration.⁸⁰

CONCLUSION

The clinical development of CPI-based therapies has revolutionized the management of NSCLC in the last decade, but CPI resistance is the unfortunate consequence for most patients. A key mechanism of resistance in this context is the immunosuppressive TME, in which TAM receptor signaling plays a major immunoregulatory and protumorigenic role. Although many open questions remain, several rational therapeutic approaches, including strategies targeting TAM receptors, show promise for overcoming CPI resistance. Further collaborative research efforts are needed to help answer these questions and provide a deeper understanding of the distinct mechanisms of resistance to CPI-based treatment.

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