

SHP2 Inhibition as a Promising Anti-cancer Therapy: Function in Tumor Cell Signaling and Immune Modulation

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Abstract

The protein tyrosine phosphatase SHP2, encoded by *PTPN11*, functions as a critical signal transduction regulator and interacts with key signaling molecules in both RAS/ERK and PD-1/PD-L1/ BTLA (B- and T-lymphocyte attenuator) pathways. Targeting SHP2 pharmacologically, therefore, may be a promising therapeutic strategy for many RAS-driven cancers. Multiple small molecule inhibitors of SHP2 (SHP2i) are currently in clinical development, both alone and in combinations. SHP2i combination therapies, including those with inhibitors of EGFR, KRAS^{G12C}, BRAF^{V600E}, MEK, ERK, CDK4/6 and PD-1, and other combinations not yet explored, represent targeted strategies with great promise for advanced or refractory RAS-dependent solid tumor malignancies. One recent study demonstrates that combined pharmacologic inhibition of SHP2 and MEK is active in models of NF1-deficient malignant peripheral nerve sheath tumors (MPNST). This article, based on the discovery that a wide range of receptor tyrosine kinases (RTK) are upregulated through the adaptive response to MEKi in this RAS-dysregulated tumor type, adds to the growing body of literature in which SHP2 inhibitors have been combined with other targeted therapies in a range of cancer types. To date, most of these reports have focused on signaling and direct cancer cell related effects of these small molecules. Here, we discuss recent advances in the preclinical and clinical development of SHP2 inhibitors, as well as their potential role in immune signaling modulation as a promising cancer-directed strategy.

SHP2 Structure and Role in Human Diseases

The SHP2 phosphatase consists of one protein tyrosine phosphatase catalytic domain (PTP domain), two tandem Src homology 2 (SH2) domains (N-SH2 and C-SH2), and a C-terminal tail with two tyrosine phosphorylation sites (Tyr542 and Tyr580) [1] (Figure 1A). SHP2 activity is normally auto-inhibited by the binding of the N-SH2 domain with the PTP domain [2]. Upon stimulation of growth factors or cytokines, the N-SH2 domain binds to specific phospho-tyrosine residues and induces a conformational change that leads to exposure of the PTP domain and an increase in the catalytic activity [3] (Figure 1B). Phosphorylated Tyr542 interacts intramolecularly with the N-SH2 domain to relieve steady-state inhibition of the phosphatase, whereas phosphorylated Tyr580

stimulates the phosphatase activity by interaction with the C-SH2 domain [4].

Germline gain of function (GOF) mutations in *PTPN11* occur in about 50% of patients with Noonan syndrome [5], which is characterized by abnormal facial features, skeletal malformations, congenital heart disease, short stature and an elevated risk of leukemia and other cancers. In contrast, more than 80% of patients with LEOPARD syndrome (lentiginos, EKG abnormalities, ocular hypertelorism, pulmonary stenosis, abnormal genitalia, retardation of growth, and deafness) harbor heterozygous germline inactivating (phosphatase-defective) mutations in *PTPN11*, despite the overlapping clinical presentations between this syndrome and those with Noonan syndrome [6,7]. Both conditions are associated with an increased risk for malignancies, including leukemia and neuroblastoma

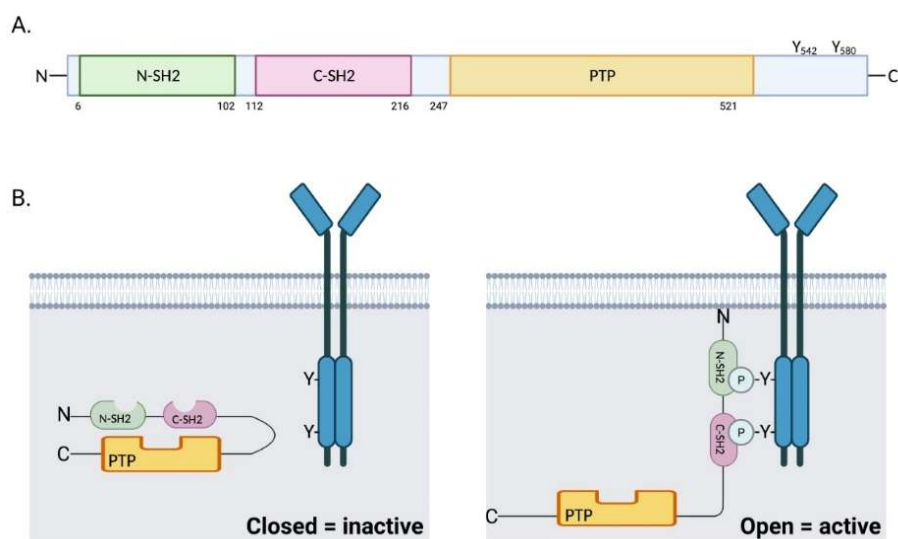


Figure 1: Structure of human SHP2. **A)** SHP2 protein domains as described, including two Src homology domains (N-SH2 and C-SH2), and a protein tyrosine phosphatase catalytic (PTP) domain. Critical tyrosine phosphorylation residues (Tyr 542 and Tyr 580) are indicated. **B)** Schematic representation of the closed (inactive) and open (active) conformations of SHP2.

[5,8], suggestive of a phosphatase-independent role of SHP2 in cancer pathogenesis. In addition, somatic GOF mutations in *PTPN11* are reported in juvenile myelomonocytic leukemia (JMML, 35%), myelodysplastic syndrome (MDS, 10%), sporadic acute myeloid leukemia (AML, 4%) [9] and solid tumors [10], making *PTPN11* the first identified proto-oncogene among tyrosine phosphatases [11].

The Role of SHP2 in Dysregulated RTK/RAS/ERK Signaling in Cancer

SHP2 has been implicated as a major contributor to regulation of RTK/RAS/ERK signaling [12,13], but how exactly the SHP2 phosphatase promotes activation of RAS/ERK signaling has been controversial. Functional studies demonstrate that SHP2 enhances RAS activation through activated protein tyrosine kinases or cytokine receptors [14]. SHP2 is required for sustained RAS/ERK signaling activation *via* multiple phosphatase-dependent and -independent mechanisms. First, SHP2 reverses negative regulators of RAS activation, including dephosphorylation and inactivation of Sprouty, as well as inhibition of RAS-GAP recruitment, both negative regulators of RAS activation [14,15]. Second, dephosphorylation of RAS at tyrosine 32, as a direct target of SHP2, increases RAS-RAF interaction and enhances downstream signaling [16]. Third, SHP2 dephosphorylates Src-regulatory proteins and leads to Src activation, which in turn promotes RAS/ERK signaling [17]. More recent evidence implicates the role of SHP2 as a scaffolding adaptor providing the major GRB2 binding site (phosphorylated Tyr542), which forms a functional signaling complex containing SHP2/GRB2/

SOS/GAB1, to promote RAS activation by its guanine exchange factor (GEF) [17-19]. However, it has been posited that the association of SHP2 with GRB2 is not sufficient for full ERK activation, and that phosphorylated Tyr580 is also required for sustained ERK signaling in response to some growth factors [20].

Considering the emerging role of SHP2 in cancer, discovery of small molecule inhibitors targeting SHP2 has recently gained significant attention. To our excitement, the first SHP2 allosteric inhibitor SHP099 was developed in 2015 [21], enabling further mechanistic studies on SHP2 function in cancer. Compared with the low selectivity/off-target effect of catalytic/active-site inhibitors targeting SHP2 among other PTP [22], the SHP2 allosteric inhibitor SHP099 potently and selectively inhibits SHP2 activity through stabilization of wild-type SHP2 in the auto-inhibited/closed conformation [23]. The earliest reports identifying novel small molecule inhibitors of SHP2 (SHP099) suggested that these compounds would be most effective in cancer cells driven by a variety of aberrantly regulated RTK (including ERBB2, FGFR2, EGFR and ALK, among others) [13]. Other studies, however, have demonstrated only modest activity of SHP2i as a single agent [24], suggesting that as a class, SHP2i may realize their full potential as cancer therapeutics when given in combination.

SHP2 inhibition offers a promising therapeutic strategy as a means to prevent RTK-driven adaptive and acquired resistance to targeted therapy. SHP2 inhibition enhances the efficacy of tyrosine kinase inhibitors (TKI), such as ALK/EGFR/FGFR inhibitors, in drug-resistant NSCLC

and metastatic breast cancer, in which distinct RTK activation mediates adaptive and acquired resistance [25-28]. In addition, SHP2 inhibition (or depletion) also restores sensitivity to ERK signaling inhibition and has additive/synergistic anti-tumor effects when combined with KRAS^{G12C}/RAF/MEK inhibitors in multiple models of cancers driven by hyperactivated RAS, including KRAS-mutant pancreatic, lung and colorectal cancers, KRAS^{WT}-amplified gastroesophageal cancer, RAS^{WT} triple negative breast cancer (TNBC) and ovarian cancers, NRAS-mutant neuroblastoma, NF1-deficient MPNST, and BRAF-mutant colon and thyroid cancers, among others, through blocking signal transduction from most RTK that are reactivated through loss of negative feedback following ERK pathway inhibition [19,24,26,29-38].

The Role of SHP2 in Modulating Immune Signaling Pathways

Included in the diverse roles of SHP2 is that of modulating

immune signaling responses through interactions with PD-1/PD-L1 receptor/ligand signaling. SHP2 is considered a central molecule downstream of inhibitory immune receptors. Inhibitory receptors are expressed by immune cells and regulate their function in diverse contexts. Upon binding of PD-L1, PD-1 becomes phosphorylated at its immunoreceptor tyrosine-based inhibitory motif (ITIM) and immune receptor tyrosine-based switch motif (ITSM), and then ITSM binds C-SH2, recruiting SHP2 to PD-1; while ITIM binds N-SH2, displacing it from the catalytic pocket and activating SHP2 [39]. Extensive investigation has been carried out to identify the mechanistic contribution of PD-1/PD-L1/SHP2 to T-cell inactivation. One recent study demonstrated that the costimulatory receptor CD28 is preferentially dephosphorylated and inactivated by SHP2 in the PD-1/PD-L1/SHP2 micro-cluster, thereby leading to T-cell inactivation mediated by PD-1 [40] and promoting immune escape by cancer cells (Figure 2). However, the role of SHP2 in PD-1 signaling was challenged by another study, which found that SHP2

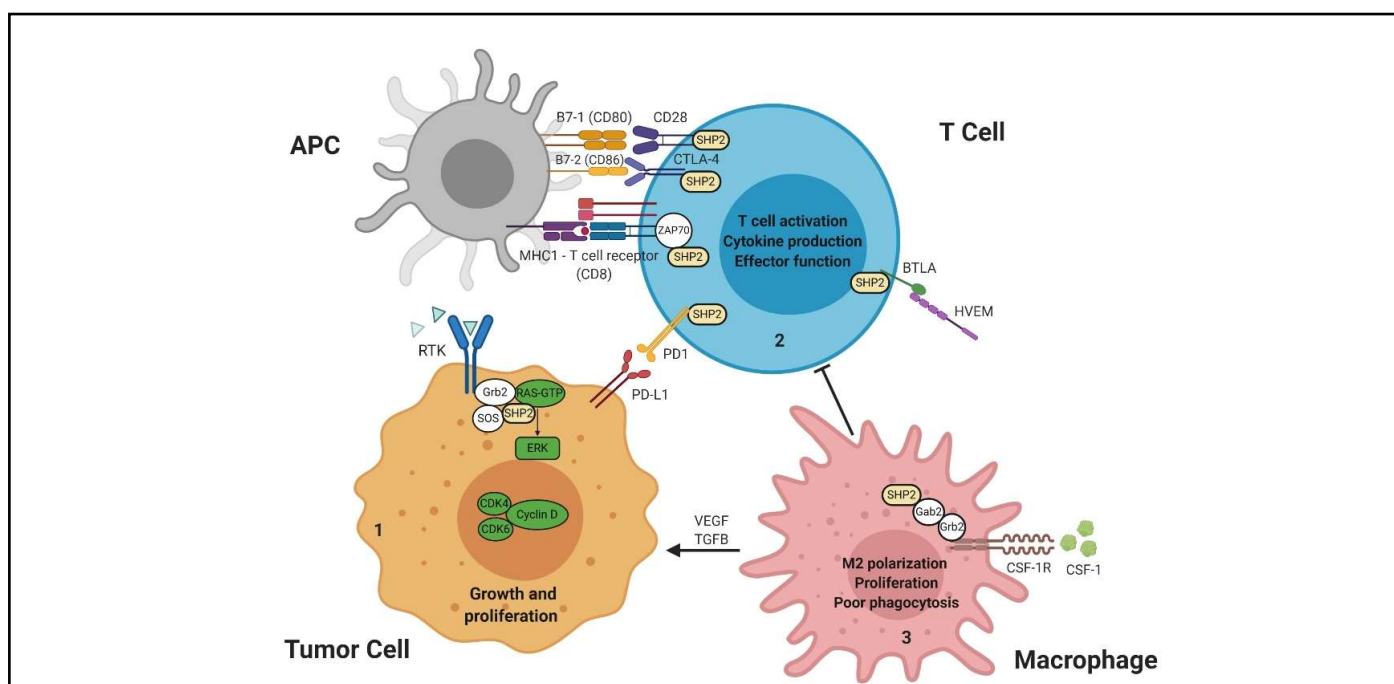


Figure 2: This figure depicts main cancer cell and immune cell signaling pathways regulated by SHP2. 1. SHP2 is a critical regulator of the RAS-ERK pathway leading to rapid cell proliferation and cancer growth. 2. SHP2 is an integral downstream effector for the T cell receptor, the CD28/B7 and the PD-1/PD-L1 pathways resulting in deactivation and exhaustion of T cells. 3. SHP2 is a pivotal effector for the CSF-1/CSF-1R axis culminating in macrophage immunosuppressive polarization and poor phagocytosis. SHP2 inhibition is as a promising anti-cancer therapy given its multiple roles in the function/fate of tumor cells and its immune modulatory properties.

RTK: Receptor Tyrosine Kinase; SHP2: Src Homology region 2 domain-containing Phosphatase-2; Grb2: Growth factor receptor-bound protein 2; Gab2: Grb2 associated binding protein 2; SOS: Son of sevenless, RAS guanine nucleotide exchange factor; GTP: Guanosine-5'-triphosphate; ERK: Extracellular signal-regulated kinase; CDK4/6: Cyclin-dependent kinase 4/6; PD-1: Programmed cell Death-1; PD-L1: Programmed cell Death Ligand 1; APC: Antigen Presenting Cell; MHC1: Major Histocompatibility Complex 1; B7-1/2: Peripheral membrane proteins 1 and 2; CD28: Cluster of Differentiation 28; CTLA-4: Cytotoxic T-lymphocyte-associated protein 4; ZAP70: Zeta chain of T cell receptor Associated Protein kinase 70; BTLA: B- and T-lymphocyte-associated protein; HVEM: Herpes Virus Entry Mediator; CSF-1: Colony Stimulating Factor 1; CSF-1R: Colony Stimulating Factor 1 Receptor.

is dispensable for establishing T-cell exhaustion as well as for PD-1 signaling *in vivo*, supported by the evidence that specific SHP2 depletion in CD8+ T lymphocytes only moderately improves their proliferation and results in decreased polyfunctionality and compromised cytotoxic-related cytokine production upon chronic infection. Mice with SHP2-deficient T-cells showed no significant improvement in controlling immunogenic tumors and demonstrated responses to α -PD-1 treatment similar to controls, suggesting the existence of redundant or alternative mechanisms complementing SHP2/PD-1 signaling [41]. Furthermore, another report provides evidence supporting the existence of compensatory mechanisms by which 1) PD-1 selectively recruits SHP2; and 2) BTLA preferentially recruits SHP1, and both suppress T cell signaling. Intriguingly, PD-1 and BTLA potently inhibit T-cell proliferation and cytokine production in SHP1/2 double-deficient primary T-cells, suggesting that PD-1 and BTLA suppress T-cell signaling only partially through SHP1/2 [42], and SHP2 depletion or inhibition limits the durability of PD-1 signaling. Further studies are needed to investigate the bypass mechanisms and design combinatorial strategies to target T-cell exhaustion. SHP2 has also been implicated in the response to IL-2 and IL-15 [43-48]. IL-2 is essential for regulatory, effector CD4+, and effector CD8+ T-cells. IL-15 is critical to the survival of memory CD8+ T-cells and for development, survival, and activation of NK cells, two cytotoxic immune cell subsets which are central to immunity against intracellular pathogens and cancers.

In contrast to studies on T cell-specific SHP2 depletion, however, an abundance of evidence points to additional roles of SHP2 in immunomodulation beyond PD-1 checkpoint signaling in T-lymphocytes. Preclinical studies support the role of SHP2 inhibition in adaptive and innate immunity. SHP2 inhibition provokes increases in intratumoral CD8+ T-lymphocytes and tumor-associated B-lymphocytes, augmenting anti-tumor immunity [38,49]. Recent findings have emerged regarding the role of SHP2 in modulating the myeloid compartment as well [26,38,50]. Myeloid cells are the most abundant white blood cells in the human body and they are present practically in all tissues. They are key regulators of tissue homeostasis and tumor microenvironments [51]. Tumor-associated macrophages (TAM- M2 macrophages) that infiltrate tumor tissues are driven by cancer-derived cytokines to acquire a polarized immunosuppressive phenotype, which in turn de-activates the T cell compartment [52-54]. The salient feature of these cells is their ability to inhibit T cell function and their high density in the tumor microenvironment (TME) is associated with poor prognosis and survival across multiple cancer types [51,55,56]. Moreover, tumor-associated myeloid cell infiltration is associated with clinical resistance to immunotherapy [57]. M2 macrophages exhibit potent T-cell suppressive phenotypes

in vitro and *in vivo* [52,58,59]. SHP2 inhibition in RAS-driven cancers results in depletion of immunosuppressive M2 macrophages through attenuation of CSF1R signaling [26,50], which is essential for T-cell suppression by immunosuppressive TAM [60] within the TME. These findings raise the possibility that SHP2 inhibition relieves T cell suppression largely through reduction of M2 macrophages *via* CSF1R signaling, and partially through PD-1 signaling, where SHP2 appears dispensable due to functionally redundant mechanisms. Interestingly, despite modest effect of PD-1 blockade on M2 TAM, further reduction of M2 macrophages is elicited with combined SHP2i and PD-1 blockade through an undefined mechanism [26,50], which may be the potential basis for additive anti-tumor activity of combined SHP2i and anti-PD-1. Furthermore, combined SHP2i and anti-PD-1 treatment also demonstrates synergistic effects on colon cancer models that are sensitive to checkpoint blockade [49,50]. In models of pancreatic ductal adenocarcinoma (PDAC), a cancer type with limited response to checkpoint blockade, the antitumor immunity and efficacy of SHP2 and KRAS^{G12C} inhibition can be enhanced by anti-PD-1 [38,61], implicating a combination benefit of immune checkpoint inhibitors (ICI) in PDAC treatment. A growing understanding of the mechanism of action of SHP2 in these immune regulating cascades is therefore relevant and timely. Overall, the effects of SHP2i on the TME remain to be clarified and could certainly have implications for the development of synergistic combinations in antitumor therapy.

The Effects of RAS Pathway Inhibition on Immune Modulation

RAS/ERK signaling activation is associated with significantly reduced levels of tumor-infiltrating lymphocytes (TIL), thereby potentially facilitating immune evasion by the tumor cells [62]. ERK signaling inhibition therefore alleviates a local immunosuppressive phenotype, and promotes TIL homing to the tumor [63]. Distinct effects on immune cell modulation in the TME due to inhibition of different nodes in the RAS/ERK signaling pathway have been observed. Similar to the modulatory effect of SHP2i on TME, KRAS^{G12C}i also improves anti-tumor immunity in KRAS-mutant cancers through an increase in CD8+ T-cells and cytokine production [38,64], and decrease in immunosuppressive CD4+ T-cells and CD11b+ myeloid cells [38]. Likewise, BRAFi induces a favorable TME through multiple mechanisms, enhancing T-cell specific recognition of BRAF^{V600}-mutant melanoma *in vitro* and in patients, with no obvious effects on lymphocyte function [65-69]. MEKi can also improve tumor immunogenicity *via* enhancement of MHC-1 expression [70]. However, in contrast to selective mutation-specific inhibitors that exclusively suppress RAS/ERK pathway in tumor cells, the effects of broad ERK signaling inhibition using MEKi

on T-cell function have been perplexing and somewhat contradictory, as T-cell immune response is at least partially dependent on RAS/ERK signaling downstream of the TCR. Two early reports revealed that MEKi impairs peripheral blood derived T-cell function through reduction in proliferation and cytokine secretion [65,71]. Nevertheless, this notion was supplemented with follow-up studies demonstrating that MEKi promotes recruitment of TIL and increases antigen specific CD8+ T cells within the tumor; whereas markedly inhibits naïve CD8+ T-cell priming which rebounds after the early onset of the suppression, in tumor-draining lymph nodes [72,73]. A recent study extended these observations and further explored the mechanistic basis of the immunomodulatory effects of MEKi on TME. MEKi treatment reprograms naïve CD8+ T-cells into stem cell-like memory T-cells with potent antitumor activity, through cell cycle inhibition and metabolic enhancement [74]. Additionally, given the potential inhibitory effect of MEKi on T cell function, an alternative regimen with intermittent, rather than continuous, exposure to MEKi was found to induce T-cell activation and anti-tumor immunity [75]. Despite this apparent paradox, MEKi still further enhances anti-PD-1/PD-L1/CTLA4 immunotherapy through enhanced T-cell activation [62,63,72,75,76]. Based on the effects of SHP2i and the equivocal impact of MEKi on innate and adaptive immunity, consequently, additional studies are needed to further explore the effectiveness and toxicity of combined MEK and SHP2 inhibition, either alone or in combination with immunotherapy. These studies will need to be carefully optimized, using immune-competent syngeneic and/or genetically engineered mouse models, careful study of dose and treatment schedules to achieve optimal efficacy and minimize toxicity, and ultimately select combinations and regimens that hold the most promise for achieving superior anti-tumor responses.

The Combination Partner SHP2 as a Promising Co-Target in MPNST and Other Cancers

NF1 and *CDKN2A* tumor suppressor losses are genomic hallmarks found in the majority of human MPNST (90%, and 60-80%, respectively) [77]. As loss of *NF1* is a major driver of RAS-ERK signaling in many cancers, MEK inhibition seems a logical focus for the design of combination strategies in MPNST and other tumors with loss of *NF1*. MEKi alone, however, has limited anti-tumor activity, leading to the notion that combinations that target the adaptively upregulated molecules that emerge upon loss of ERK-induced negative feedback should be effective. Our data suggested that a number of tyrosine and serine/threonine kinases become adaptively upregulated in response to MEKi, leading to challenges in the design of MEKi plus TKI combination strategies, as genomic or other predictive biomarkers to identify the adaptively

changed RTK are not readily discernible [24,32]. In order to overcome this challenge, we posited that inhibition of the central node of convergence between the RTK and RAS recruitment to the membrane and activation – SHP2 – would serve as a viable strategy. Indeed, *in vitro* and *in vivo* analysis of the MEKi/ SHP2i combination demonstrated more profound and durable inhibition of ERK signaling, improved anti-proliferative effects and synergy *in vivo* [24]. The success of this combination in patients with MPNST remains to be seen.

In addition to *CDKN2A* deletion, hyperactivation/ and/or upregulation of cyclin dependent kinases (CDK) and D-type cyclins, leading to inactivation of the RB1 tumor suppressor, occurs in the majority of MPNST, and suggests that small-molecule inhibitors of CDK4/6 (CDK4/6i) may be an additional therapeutic strategy [78]. However, CDK4/6i elicits a primarily cytostatic phenotype and has limited efficacy as a single agent, due to early adaptive upregulation of cyclin D1 and subsequent CDK2 hyperactivation, and other bypass mechanisms such as *E2F* amplification [79-83]. The CDK4/6i ribociclib improves the efficacy of SHP2 inhibition in RTK-driven and a subset of *KRAS*-mutant NSCLC and colorectal cancer models, and is equally efficacious as the combination of MEKi and SHP2i [26]. Despite similar anti-tumor activity, combined SHP2i and CDK4i may be a better tolerated regimen, with a wider therapeutic index, given the preliminary toxicity data reported for MEKi and SHP2i combinations [84]. According to our understanding, combined SHP2i and CDK4/6i may provide a viable therapeutic approach not yet tested in immunocompetent models of MPNST.

Macrophage infiltrates are abundant in neurofibromas and MPNST, accounting for nearly half of the cells within a tumor [85]. The tumor promoting and immunosuppressive M2 macrophages are dependent on CSF1R signal and CSF1R+ TAM correlate with poor survival in many tumor types, making this receptor an attractive target to decrease these cells [86]. A previous study reported a marked depletion of TAM and a shift from M2 to M1 TAM upon CSF1R inhibition, and demonstrated the combination benefit of co-targeting CSF1R and mTOR using PLX3397 and rapamycin in an MPNST xenograft model [87], which provided a translational basis for the MPNST-specific prospective phase 2 clinical trial (NCT02584647). Preliminary data from this trial reported objective responses and durable stable disease in MPNST patients treated with PLX3397 and sirolimus [88]. Furthermore, combined SHP2i and CSF1Ri demonstrated additive anti-tumor activity in CT26 colon syngeneic mice, a model known to express high levels of TIL [50]. As such, combined SHP2i and CSF1Ri may hold promise as a potential treatment strategy for MPNST.

Little is known about the potential roles of immune modulating clinical therapeutics in *NF1*-deficient MPNST.

Characterization of TME on a series of MPNST revealed overall low PD-L1 expression but significant CD8+ TIL presence [89,90]. Given the genomic heterogeneity of this tumor type, in several cases, *PD-L1* copy number gain/amplification were also reported [91,92]. There have been three single-patient case reports describing anti-tumor response to immune checkpoint inhibition in patients with MPNST: 1) a patient with metastatic NF1-MPNST harboring *PD-L1* genomic amplification had a partial response to nivolumab [92]; 2) a patient with metastatic MPNST, with PD-L1 positivity in the tumor, achieved a complete metabolic response to pembrolizumab [93]; and 3) a patient with MPNST with significant PD-L1 expression (tumor proportion score of 90%) had a complete tumor response to pembrolizumab and procarbazine [94], suggestive of a potential clinical benefit to immune checkpoint blockade in a molecularly-defined subset of MPNST. Three phase 1/2 clinical trials are ongoing using immune checkpoint inhibitors (anti-PD-1 and anti-CTLA4) in patients with MPNST, including the use of pembrolizumab (NCT02691026), or the combination of nivolumab and

ipilimumab (NCT02834013 and NCT04465643). Given the preclinical additive combination benefits of SHP2i/ KRAS^{G12C}i plus anti-PD-1 in *KRAS*-mutant PDAC [38] and SHP2i plus anti-PD-1/anti-CTLA-4 in immunocompetent CT26 colon mouse model [50], additional investigation into SHP2i plus anti-PD-1/anti-CTLA-4 in MPNST is also of significant interest and an area of current pre-clinical investigation in MPNST.

SHP2 Inhibitor-based Therapeutics in Clinical Development

At the time of this manuscript preparation, seven type II SHP2 allosteric inhibitors, based on the structure of SHP099, are currently under clinical assessment for adult advanced/metastatic solid tumors, including: TNO155 (NCT03114319, NCT04000529, NCT04330664, NCT04699188, NCT04294160; Novartis) [26,95], RMC-4630 (NCT03634982, NCT03989115, NCT04185883, NCT04418661; Revolution Medicines/ Sanofi) [18,50,84], JAB-3068 (NCT03565003 and NCT03518554) and JAB-

SHP2 inhibitor	Combination partner (target)	Phase	Identifier	Condition	Sponsor
TNO155	single agent; nazartinib [EGFR]	1	NCT03114319	Advanced EGFR-mutant or KRAS G12-mutant NSCLC, Esophageal SCC, HNSCC, Melanoma	Novartis
	spartalizumab [PD-1]; ribociclib [CDK4/6]	1b	NCT04000529	NSCLC, HNSCC, Esophageal SCC, GIST, CRC	Novartis
	MRTX849 [KRAS G12C]	1/2	NCT04330664	Advanced solid tumors with KRAS G12C mutation	Mirati Therapeutics; Novartis
	JDQ443 [KRAS G12C]; spartalizumab [PD-1] plus JDQ443 [KRAS G12C]	1/2	NCT04699188	Advanced solid tumors with KRAS G12C mutation	Novartis
	dabrafenib [BRAF V600E] plus LTT462 [ERK1/2]	1	NCT04294160	Advanced or metastatic BRAF V600 CRC	Novartis
RMC-4630	single agent	1	NCT03634982	Advanced relapsed or refractory solid tumors	Revolution Medicines/Sanofi
	cobimetinib [MEK]; osimertinib [EGFR]	1b/2	NCT03989115	Relapsed/refractory solid tumors; advanced or metastatic EGFR-mutant NSCLC	Revolution Medicines/Sanofi
	sotorasib [KRAS G12C]	1	NCT04185883	Advanced solid tumors with KRAS G12C mutation	Amgen
	pembrolizumab [PD-1]	1	NCT04418661	Advanced or metastatic solid tumors with KRAS mutations and amplifications, BRAF class 3 mutations, or NF1 LOF mutations	Sanofi/Revolution Medicines

JAB-3068	single agent	1/2a	NCT03565003	NSCLC, HNSCC, Esophageal SCC, other metastatic solid tumors	Jacobio/AbbVie
	single agent	1	NCT03518554	NSCLC, HNSCC, Esophageal SCC, other metastatic solid tumors	Jacobio/AbbVie
JAB-3312	single agent	1	NCT04121286	Advanced solid tumors including NSCLC, CRC, PDAC, Esophageal SCC, HNSCC and breast cancer	Jacobio/AbbVie
	single agent	1	NCT04045496	Advanced solid tumors including NSCLC, CRC, PDAC, Esophageal SCC, HNSCC and breast cancer	Jacobio/AbbVie
RLY-1971	single agent	1	NCT04252339	Advanced or metastatic solid tumors	Relay Therapeutics
BBP-398	single agent	1/1b	NCT04528836	Advanced KRAS G12C or EGFR-mutant NSCLC; solid tumors with other MAPK-pathway alterations.	Navire Pharma/ BridgeBio
ERAS-601	single agent; a MEK inhibitor (MEK)	1/1b	NCT04670679	Advanced or metastatic solid tumors with specific molecular alterations	Erasca

NSCLC: Non-small Cell Lung Cancer; SCC: Squamous Cell Cancer; HNSCC: Head and Neck Squamous Cell Cancer; GIST: Gastrointestinal Stromal Tumors; CRC; Colorectal Cancer; PDAC: Pancreatic Ductal Carcinoma; LOF: Loss of Function.

Table 1: SHP2 inhibitor-based therapeutics in clinical development for cancer.

3312 (NCT04121286 and NCT04045496) (Jacobio/AbbVie), RLY-1971 (NCT04252339; Relay Therapeutics), BBP-398 (NCT04528836; Navire Pharma/ BridgeBio) [28], and ERAS-601 (NCT04670679; Erasca). Multiple clinical trials of SHP2 inhibitors as single agents, and several which combine SHP2i with inhibitors of semi-autonomous oncogenic partners, such as EGFR mutants, MEK, CDK4/6, PD-1, and KRAS^{G12C}, are ongoing (Table 1). Recently, anti-tumor activity of dual intermittent dosing of RMC-4630 (SHP2i) and cobimetinib (MEKi) in patients with KRAS mutant colorectal cancer has been studied, with acceptable tolerability based on preliminary reports. Among these, preliminary evidence revealed an unconfirmed partial response (30% reduction in tumor burden at end of cycle 2; 25% reduction at end of cycle 4; progressive disease at 6 months) in a patient with KRAS^{G12D} colorectal cancer [84]. Future studies of SHP2 combinations may ideally then focus on optimal dosing schedules and potential combinations to achieve the fine balance needed between efficacy and toxicity in patients with RAS-driven cancers.

Closing Remarks and Future Perspective

SHP2 has recently taken a well-deserved center-stage

role in cancer therapeutics, owing to its multifaceted roles directed toward growth-promoting signaling pathways within the tumor cells, as well as the surrounding immunosuppressive microenvironment. Further investigation into the various functional roles of SHP2 will be critically instructive in realizing its full potential as an anti-cancer therapy. Future studies of combinations, as well as preclinical and clinical investigation focused on the mechanisms of resistance to allosteric SHP2 inhibitors, will be critically informative as these agents advance in clinical trials. Preclinical studies demonstrate relative insensitivity to SHP2i associated with oncogenic RAS or RAF mutations; and intrinsic or feedback activation of FGFR in response to inhibition of ERK signaling [13,19,96]. FGFR signal may promote the open active conformation of SHP2, leading to resistance to allosteric SHP2 inhibitors [96]. An alternative therapeutic concept is the utilization of RAS-SOS1 interaction inhibitors, such as BI-3406, RMC-5845 and BAY-293 [97,98] to block adaptive activation of FGFR upon ERK signaling inhibition in some cellular context. Overall, biochemical and genomic exploration of the preclinical and clinical mechanisms that limit the anti-tumor efficacy of SHP2 inhibitors, promises to inform future development of novel combination strategies and new generations of allosteric SHP2 inhibitors.

Disclosure of Competing Interest

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