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REVIEW

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Trial Watch: combination of tyrosine kinase inhibitors (TKIs) and immunotherapy

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ABSTRACT

The past decades witnessed the clinical employment of targeted therapies including but not limited to tyrosine kinase inhibitors (TKIs) that restrain a broad variety of pro-tumorigenic signals. TKIs can be categorized into (i) agents that directly target cancer cells, (ii) normalize angiogenesis or (iii) affect cells of the hematologic lineage. However, a clear distinction of TKIs based on this definition is limited by the fact that many TKIs designed to inhibit cancer cells have also effects on immune cells that are being discovered. Additionally, TKIs originally designed to target hematological cancers exhibit bioactivities on healthy cells of the same hematological lineage. TKIs have been described to improve immune recognition and cancer immunosurveillance, providing the scientific basis to combine TKIs with immunotherapy. Indeed, combination of TKIs with immunotherapy showed synergistic effects in preclinical models and clinical trials and some combinations of TKIs normalizing angiogenesis with immune checkpoint blocking antibodies have already been approved by the FDA for cancer therapy. However, the identification of appropriate drug combinations as well as optimal dosing and scheduling needs to be improved in order to obtain tangible progress in cancer care. This Trial Watch summarizes active clinical trials combining TKIs with various immunotherapeutic strategies to treat cancer patients.

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Introduction

Despite the caveat of major clinical side effects and mostly modest long-term therapeutic efficacy, chemotherapy with systemically active cytotoxicants (such as DNA-intercalating agents or microtubular poisons), that affect both malignant and healthy cells, is still the most frequently employed treatment for many types of cancer.[1–24] The last two decades have witnessed the development of novel antineoplastic therapies including targeted anticancer agents, which held the promise to limit nonspecific toxicity while increasing treatment efficacy.[25–27] The most commonly used compounds in precision medicine are signal transduction inhibitors that target oncogenic serine/threonine and tyrosine kinases.[28] Here, we focus on *bona fide* tyrosine kinase inhibitors (TKIs)[29–32] that have been approved by the FDA since the turn of the millennium and have meanwhile entered into clinical practice.[33,34]

TKIs target receptor tyrosine kinases as well as non-receptor tyrosine kinases.[35–37] Receptor tyrosine kinase inhibitors include, in chronological order of approval, gefitinib[38] targeting epidermal growth factor receptor (EGFR), approved for non-small cell lung cancer (NSCLC) in 2003;[39] erlotinib[40] targeting EGFR approved for NSCLC and pancreatic cancer (PC) in 2004;[41] sorafenib targeting vascular endothelial growth factor receptor (VEGFR), platelet-derived growth factor receptor (PDGFR), KIT and fms like tyrosine kinase (FLT) 3, approved for renal cell carcinoma (RCC) and hepatocellular carcinoma (HCC) in 2005;[42] sunitinib[43] targeting VEGFR, KIT, PDGFR, rearranged during transfection (RET), colony stimulating factor 1 receptor (CSF1R) and FLT3, approved for RCC and gastrointestinal stromal tumor (GIST) in 2006;[44] lapatinib[45] targeting EGFR and human epidermal growth factor receptor (HER) 2, approved for breast cancer (BC) in 2007;[46] pazopanib[47] targeting VEGFR, PDGFR and KIT, approved for RCC in 2009; vandetanib targeting RET, VEGFR, fibroblast growth factor receptor (FGFR) 3 and EGFR approved for thyroid carcinoma (TC) in 2011; crizotinib[48] targeting anaplastic lymphoma kinase (ALK) and MET, approved for NSCLC in 2011;[49] axitinib targeting VEGFR, PDGFR, KIT, RET, CSF1R and FLT3 approved for RCC in 2012; cabozantinib targeting VEGFR, PDGFR, KIT and FLT3 approved for TC in 2012; regorafenib targeting VEGFR-1, −2, −3 and TIE2, approved for colorectal cancer (CRC), GIST in 2012 and hepatocellular carcinoma in 2017; afatinib targeting EGFR, approved for NSCLC in 2013;[50] ceritinib targeting ALK, approved for NSCLC in 2014;[51] alectinib targeting ALK, approved for NSCLC in 2015;[52] lenvatinib targeting VEGFR, approved for TC, RCC in 2015;[53] osimertinib targeting EGFR, approved for NSCLC in 2015;[54] neratinib targeting EGFR, approved for BC in 2017;[55] brigatinib targeting ALK, EGFR, approved for NSCLC in 2017;[56] tivozanib targeting

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VEGFR, approved for RCC in 2021;[57] dacomitinib targeting EGFR, approved for NSCLC in 2018;[58] lorlatinib targeting ALK, approved for NSCLC in 2018;[59] larotrectinib targeting tropomyosin receptor kinases (TRKs), approved for solid tumors in 2018;[60] gilteritinib targeting FLT3 approved for acute myeloid leukemia (AML) in 2018;[61] erdafitinib targeting FGFR, approved for transitional cell carcinoma (TCC) in 2019;[62] pexidartinib targeting CSF1R, KIT, FLT3, approved for tenosynovial giant cell tumor in 2019;[63] entrectinib targeting neurotrophic tyrosine receptor kinase (NTRK) 1/2/3, ROS1, ALK, approved for NSCLC in 2019;[64,65] avapritinib targeting KIT, PDGFR, approved for GIST in 2020; tucatinib targeting HER2, approved for BC in 2020; pemigatinib targeting FGFR, approved for cholangiocarcinoma in 2020;[66] capmatinib targeting MET, approved for NSCLC in 2020;[67] selpercatinib targeting RET, approved for TC and NCSLC in 2020;[68] ripretinib targeting KIT, PDGFR, approved for GIST in 2020;[69] pralsetinib targeting RET, approved for NSCLC, TC in 2020;[70] and finally tepotinib targeting MET, approved for NSCLC in 2021.[71]

Inhibitors of non-receptor tyrosine kinases encompass imatinib,[31] targeting ABL1, KIT and PDGFR, approved for chronic myelogenous leukemia (CML), B cell acute lymphoblastic leukemia (ALL)and GIST in 2001;[30,72] dasatinib[73] targeting ABL1, PDGFR, KIT, SRC, approved for CML and ALL in 2006; nilotinib targeting ABL1, PDGFR, KIT, approved for CML in 2007; ruxolitinib[74] targeting janus kinase (JAK) 2, approved for myelofibrosis in 2011;[75] bosutinib targeting ABL1, approved for CML in 2012; ponatinib targeting ABL1, approved for CML in 2012; ibrutinib targeting Bruton's tyrosine kinase (BTK), approved for mantle cell lymphoma (MCL) in 2013;[76] acalabrutinib targeting BTK, approved for MCL and chronic lymphoblastic leukemia (CLL) in 2017; fostamatinib targeting spleen tyrosine kinase (SYK), approved for autoimmune thrombocytopenia in 2018; fedratinib targeting JAK3 and FLT3, approved for myelofibrosis in 2019; and zanubrutinib targeting BTK, approved for MCL in 2019, respectively.

Of note, a strictly target-based distinction of TKIs is hampered by the fact that most TKIs target multiple kinases with varying efficacy.

Many of the above listed TKIs have been successfully introduced into the clinical management of cancer, resulting in a significantly increased overall survival (OS). For instance, imatinib, that among other kinases inhibits BCR-ABL, converted the otherwise rapidly fatal CML into a manageable condition with a five-year progression-free survival (PFS) of 82–90%.[77–80] Imatinib also inhibits c-KIT and PDGFR and induced significant clinical responses leading to 69–74% OS at 2 year follow-up as first-line treatment of advanced GIST.[81,82] Dasatinib, a second-generation TKI that is more potent than imatinib and active against several forms of imatinib-resistant CML carrying BCR-ABL mutations, achieves similar response rates with a 5 year PFS of 86%.[83] The imatinib derivative nilotinib, a second-generation BCR-ABL inhibitor with improved specificity and affinity, was initially approved for imatinib-resistant CML and has more recently become available as first-line treatment for CML.[78] In some cases, nilotinib achieved deep and long-lasting molecular remissions, thus allowing for discontinuation of the treatment.[84,85] Ponatinib, another potent BCR-ABL inhibitor, outperformed dasatinib and nilotinib and triggered a sustained cytogenetic response in CML or ALL patients who experienced resistance to, or unacceptable side effects from, dasatinib or nilotinib. Moreover, no mutation-conferring resistance arose over a 15-months median follow-up period.[86,87]

Gefitinib is a selective inhibitor of EGFR, approved as first-line treatment of NSCLCs that bear sensitizing EGFR mutations,[88] that exerted a beneficial effect on PFS, notably in patients with EGFR mutation, and an objective response rate of 71.2% versus 47.3% for the chemotherapy treated group. However, no significant difference in OS was detectable.[89] Similarly, the EGFR inhibitors erlotinib and afatinib depicted limited efficacy on OS in patients with EGFR mutated NSCLC.[90,91] Osimertinib, a third-generation EGFR inhibitor, outperformed gefitinib and erlotinib in previously untreated advanced NSCLC with EGFR mutation. [92,93] Treatment with osimertinib significantly prolonged OS when compared to gefitinib and erlotinib (38.6 months versus 31.8 months). Moreover, the safety profiles were similar, although osimertinib was administered for 20.7 months *versus* 11.5 months of gefitinib and erlotinib exposure.[94]

Ruxolitinib, an inhibitor of JAK 1 and 2, is efficacious in treating myelofibrosis.[95,96] It achieved a significant reduction of spleen volume in 41.9% of patients and 67% of responding patients had long-lasting responses (48 weeks or more).[97] Ruxolitinib demonstrated a superior clinical efficacy when compared to the best available therapy. Accordingly, ruxolitinib-treated patients experienced a substantial amelioration of spleen size, disease-related symptoms and quality of life.[98]

Crizotinib, ceritinib and lorlatinib are first, second and third-generation ALK inhibitors, respectively.[99] Ceritinib demonstrated a higher selectivity for ALK and an increased potency of inhibition than crizotinib. In fact, the FDA approved crizotinib to treat ROS-1 and ALK-positive NSCLC, whereas ceritinib was approved to treat only ALK-positive NSCLC. Lorlatinib was designed to better penetrate the blood–brain barrier and treat NSCLC patients with brain metastases. Accordingly, a phase II trial reported a meaningful intracranial response after lorlatinib administration both in treatment naïve patients and in those who progressed after treatment with up to three different ALK inhibitors.[100,101]

Lapatinib reversibly inhibits HER2 and EGFR and is approved in combination with capecitabine for the treatment of HER2-positive advanced breast cancer, offering an effect on PFS as compared to monochemotherapy.[102,103] Neratinib is a pan-HER inhibitor that irreversibly binds to its target. It is approved for second-line combinations with capecitabine in HER2-positive advanced breast cancer that progressed after HER2 directed therapy. Neratinib cotreatment with capecitabine increased OS as compared to lapatinib continuation.[104] Tucatinib, yet another HER2 inhibitor, has recently been approved in combination with trastuzumab and capecitabine, for advanced unresectable or metastatic HER2 positive breast

cancer. Tucatinib increased the median PFS to 7.8 months as compared to 5.6 months in patients that received only trastuzumab and capecitabine.

Sorafenib targets VEGFR, PDGFR, KIT, FLT3 and was approved for RCC and HCC in 2005. Sorafenib, which inhibits both cancer cell proliferation and angiogenesis, improved progression-free survival of RCC patients resistant to conventional therapies from 2.8 months to 5.5 months. However, adverse events were more common in the sorafenib-treated group than in placebo-treated controls.[105] Similar results were achieved in advanced hepatocellular carcinoma patients, who showed a 3-month improvement in median survival and time to radiologic progression compared to the placebo group.[106] These results led to its approval for the treatment of advanced RCC and unresectable HCC in 2005 and 2007, respectively.[107]

Sunitinib is a multikinase inhibitor that targets amongst other kinases c-KIT and PDGFR and is effective against imatinib-resistant GIST with a median PFS of about 6 months.[108] Furthermore, due to its ability to inhibit VEGF, sunitinib is employed as first-line treatment of advanced RCC achieving a progression-free survival of 11.1 months.[109,110]

Axitinib, yet another multikinase inhibitor, targets VEGFR, PDGFR, KIT, RET, CSF1R and FLT3. It was approved for RCC in 2012 for its increased PFS of 6.7 months compared to 4.7 months with a standard sorafenib treatment.[111,112]

Cabozantinib targeting VEGFR, PDGFR, KIT and FLT3 improved PFS in patients with medullary thyroid cancer from 4 to 11.2 months. While prolonged PFS was independent of the tumor mutational status, cabozantinib extended overall survival only in those patients harboring a specific mutation in the RET gene. Patients who harbored RET M918T mutation and were treated with cabozantinib exhibited a median OS of 44.3 months compared to 18.9 months for the placebo group.[113,114] Cabozantinib also extended PFS of radioiodine-refractory differentiated thyroid cancer patients previously treated with VEGFR-targeted therapy, leading to its approval by the FDA in September 2021.[115–118] Cabozantinib was approved in intermediate and poor-risk previously untreated advanced kidney cancer patients in December 2017 following a phase 2 trial (NCT01835158). Median progression-free survival for patients taking cabozantinib was 8.6 months compared with 5.3 months for patients taking sunitinib.

Regorafenib dually inhibits VEGFR and TIE2 and is approved for the third-line therapy of advanced GIST. Treatment with regorafenib provides benefit for patients with resistance to both imatinib and sunitinib with a median PFS of 4.8 months.[119]

Lenvatinib, VEGFR inhibitor, is a therapeutic choice for locally recurrent or metastatic thyroid cancer, advanced renal cell carcinoma (in combination with everolimus) after one antiangiogenic therapy and unresectable hepatocellular carcinoma. OS of unresectable hepatocellular carcinoma patients treated with lenvatinib was 13.6 months as compared to 12.3 months of sorafenib-treated patients.[120,121]In patients with metastatic clear cell renal cell carcinoma, lenvatinib, alone or in combination with everolimus, significantly prolonged PFS compared to everolimus treatment.[122] In thyroid cancer patients, the response rate after lenvatinib treatment was 64.8% vs 1.5% of the placebo group.[123,124]

Ibrutinib irreversibly inhibits BTK, which plays a key role in B-cell receptor signaling, and is approved for the treatment of mantel cell lymphoma (MCL) as well as CLL depicting a significant increase in PFS as compared with standard chemoimmunotherapy.[125] Acalabrutinib, a second-generation BTK-inhibitor, was approved for MCL, and more recently for CLL and SLL with increased efficacy and durability of the response.[126] Zanubrutinib, yet another second-generation BTK inhibitor, is approved for MCL and further extended PFS to 21.1 months in patients with relapsed or refractory disease.[127,128]

Despite the clinical success against some cancers, continuous treatment with TKI often results in acquired resistance, rendering TKI-mediated cytostatic effects mostly transitory.[129–131] Second and third generation TKI with higher response rates have been developed to remedy such downfall. However, combination regimens of TKIs and therapies targeting separate pro-tumoral pathways may represent another solution.

During the past decade immunotherapies have been introduced into clinical routine, demonstrating promising results in many cancer types.[132–141] Combinatorial strategies employing targeted agents together with immunotherapy may overcome TKI resistance.

This Trial Watch summarizes all active (not yet recruiting, recruiting, active not recruiting) clinical trials (as of October 2021) combining already FDA approved TKIs with various immunotherapeutic strategies. The clinical trials are presented in three tables corresponding to (i) TKIs with cytotoxic or cytostatic effects on cancer cells (Table 1); (ii) TKIs normalizing angiogenesis (Table 2); and (iii) TKIs initially conceived to treat hematological cancers which target cells of the hematologic lineage (Table 3). However, this classification is problematic in thus far that many of the TKIs falling into group 1 have also effects on immune cells, such as dendritic cells, and TKIs normalizing angiogenesis (as exemplified by cabozantinib) also have cytotoxic and cytostatic effects on cancer cells.[142]

Many lines of evidence indicate that TKIs mediate non-cell autonomous mechanisms of action including the immune-dependent elimination of tumor cells, laying the foundation for the potential synergy of TKIs and immunotherapy.[143] Here, we will discuss preclinical evidence in favor of such combination therapies and then describe the most promising combinations that are currently being evaluated in clinical trials.

Preclinical evidence for immunostimulatory effects of TKIs targeting cancer cells

TKIs listed in Table 1 halt tumor cell proliferation and survival, thus mediating a cytotoxic or cytostatic effect on cancer cells.[144] In addition, they shape the tumor environment and may switch it from immunosuppressive or tumor-permissive to immune-stimulating and tumor-intolerant.[7,145–147]

For instance, imatinib can act on DCs to inhibit endogenous c-KIT and to stimulate their capacity to activate NK cells with tumoricidal activity,[148,149] a finding that has been validated in patients with GIST.[150,151] Imatinib reduced the burden of c-KIT-positive GISTs in mice by inhibiting tumor cell

Table 1. Active clinical trials combining TKIs with cytotoxic or cytostatic effects on cancer cells and immunotherapies (source: ClinicalTrial.gov).

Target	TKI	Therapeutic indication	Immunotherapy combination	Trial number
Abl Src	Bosutinib	CML	Atezolizumab (anti-PD-L1)	Phase I–II NCT04793399
		CML	Ro-PEG-Interferon α2b	Phase II NCT03831776
Abl PDGFR FGFR1 Src	Ponatinib	ALL CML	Blinatumomab (anti-CD3/CD19)	Phase II NCT03263572 (+ chemo); Phase II NCT04688983; Phase III NCT04530565 (+ chemo, steroid); Phase III NCT04722848
		ALL AML CML	Blinatumomab (anti-CD3/CD19) & Filgrastim (G-CSF)	Phase II NCT03147612 (+ chemo, rituximab)
ALK	Alectinib	NSCLC	DC vaccination	Phase I NCT05195619 (+ CTX)
ALK InsR IGF1R	Ceritinib	Neuroblastoma	Followed by Dinutuximab (anti-GD2)/GM-CSF/IL-2/ isotretinoin/DFMO	Phase II NCT02559778
		NSCLC	Nivolumab (anti-PD-1)	Phase I NCT02393625
BCR-Abl	Nilotinib	ALL	G-CSF (Sargramostim)	Phase III NCT02611492 (+ imatinib, SCT, chemo)
		CML	PEG-IFNα2b	Phase III NCT01657604
		CML	Pembrolizumab (anti-PD-1)	Phase II NCT03516279
c-MET	Capmatinib	NSCLC	Pembrolizumab (anti-PD-1)	Phase II NCT04139317
		Esophageal cancer Gastric cancer Melanoma NSCLC	Spartalizumab (anti-PD-1)	Phase II NCT03484923; Phase II NCT04323436; Phase II NCT05135845
		TNBC	Spartalizumab (anti-PD-1) & anti-LAG3	Phase I NCT03742349
ErbB2	Tucatinib	Breast cancer Cholangiocarcinoma CRC Gallbladder cancer Gastric cancer	Pembrolizumab (anti-PD-1)	Phase I–II NCT04430738 (+ trastuzumab, ± chemo); Phase II NCT04789096 (+ trastuzumab, ± chemo)
		Breast cancer CRC Gastric cancer NSCLC	SBT6050 (TLR8 agonist)	Phase I–II NCT05091528 (+ trastuzumab, ± chemo)
EGFR ErbB4 ErbB2	Afatinib	Esophageal cancer	Toripalimab (anti-PD-1)	Phase II NCT04880811
		Head and neck cancer	Pembrolizumab (anti-PD-1)	Phase II NCT03695510
EGFR	Erlotinib	RCC	Atezolizumab (anti-PD-L1)	Phase II NCT04981509 (+ bevacizumab)
EGFR	Osimertinib	NSCLC	DC vaccination	Phase I NCT05195619 (+ CTX)
		NSCLC	Durvalumab (anti-PD-L1)	Phase I NCT02143466; Phase III NCT02454933

(*Continued*)

Table 1. (Continued).

Target	TKI	Therapeutic indication	Immunotherapy combination	Trial number
		NSCLC	Ipilimumab (anti-CTLA-4)	Phase I NCT04141644
		Solid tumors	ONC-392 (anti-CTLA-4)	Phase I NCT04140526
FGFRs	Pemigatinib	Advances malignancies	Pembrolizumab (anti-PD-1)	Phase II NCT04949191
		Advances malignancies Endometrial cancer	Retifanlimab (anti-PD-1)	Phase II NCT04463771; Phase II NCT04949191
		NSCLC	Sintilimab (anti-PD-1)	Phase II NCT05004974
FLT3 RTKs	Gilteritinib	AML	Sargramostim (G-CSF)	Phase I–II NCT04240002 (+ chemo)
JAK1/2	Ruxolitinib	ALCL AML Angioimmunoblastic T-cell lymphoma Endometrial cancer Mycosis fungoides Myelodysplastic syndrome NHL PTCL-NOS Plasma cell myeloma Uterine corpus cancer	VSV-IFNβ VSV- IFNβ-NIS	Phase I NCT03017820 (± CTX); Phase I NCT03120624
		ALL LLy	Blinatumomab (anti-CD3/CD19)	Phase II–III NCT03117751 (+ steroid, chemo)
		ALL LLy	CAR T cells	Phase II–III NCT03117751 (+ steroid, chemo)
		Bone metastasis Breast cancer	Pembrolizumab (anti-PD-1)	Phase I NCT03012230
		HL	Nivolumab (anti-PD-1)	Phase I–II NCT03681561
		Myelofibrosis	G-CSF (Sargramostim)	Phase II NCT04370301 (+ chemo, tacrolimus, TBI, SCT)
		Myelofibrosis	PEG-IFNα2	Phase I–II NCT02742324
JAK3 FLT3 BRD4	Fedratinib	Myelofibrosis	Sargramostim (G-CSF)	Phase II NCT04370301 (+ chemo, tacrolimus, TBI, SCT)
Multiple tyrosine kinase	Dasatinib	ALL LLy	Blinatumomab (anti-CD3/CD19)	Phase I–II NCT05192889 (+ steroid, chemo, Bcl-2 inhibitors); Phase II NCT02143414 (+ steroid); Phase II NCT04329325 (+ steroid, chemo); Phase II–III NCT03117751 (+ steroid, chemo); Phase III NCT04530565 (+ steroid, chemo)
		ALL LLy	CAR T cells	Phase II–III NCT03117751 (+ steroid, chemo)
		ALL MM NHL	CD19/BCMA CAR T cell	Early phase I NCT04603872
		ALL	G-CSF (Filgrastim)	Phase II NCT00792948 (+ steroid, chemo, sirolimus, tacrolimus ± SCT, TBI); Phase II NCT01256398 (+ alemtuzumab, steroid, chemo, SCT, tacrolimus)
		CML	Pembrolizumab (anti-PD-1)	Phase II NCT03516279

(*Continued*)

Table 1. (Continued).

Target	TKI	Therapeutic indication	Immunotherapy combination	Trial number
		Neuroblastoma	Followed by Dinutuximab (anti-GD2)/GM-CSF /IL-2/isotretinoin/DFMO	Phase II NCT02559778
PDGFR c-KIT Abl	Imatinib	ALL	G-CSF (Filgrastim)	Phase III NCT03007147 (+ chemo, steroid, ± SCT)
		CML Melanoma	Pembrolizumab (anti-PD-1)	Phase I–II NCT04546074; Phase II NCT03516279
		GIST	Atezolizumab (anti-PD-L1)	Phase II NCT05152472
		GIST	Spartalizumab (anti-PD-1)	Phase I–II NCT03609424
		Melanoma	Toripalimab (anti-PD-1)	Phase II NCT05274438
		Solid tumors	Ipilimumab (anti-CTLA-4)	Phase I NCT01738139
ROS ALK LTK	Lorlatinib	NSCLC Solid tumors	Avelumab (anti-PD-L1)	Phase I–II NCT02584634; Phase III NCT05059522
		NSCLC	DC vaccine	Phase I NCT05195619 (+ CTX)
ROS MET ALK	Crizotinib	Neuroblastoma	Sargramostim (G-CSF)	Phase III NCT03126916 (+ dinutuximab, radiation, chemo, surgery, SCT)
		NSCLC	Avelumab (anti-PD-L1)	Phase I–II NCT02584634
		NSCLC	DC vaccination	Phase I NCT05195619 (+ CTX)

Anaplastic large cell lymphoma, ALCL; acute lymphoblastic leukemia, ALL; acute myeloid leukemia, AML; chronic myeloid leukemia, CML; colorectal cancer, CRC; cyclophosphamide, CTX; granulocyte colony-stimulating factor, G-CSF; gastrointestinal stromal tumor, GIST; Hodgkin lymphoma, HL; lymphoblastic lymphoma, LLy; non-Hodgkin lymphoma, NHL; multiple myeloma, MM; non-small cell lung cancer, NSCLC; peripheral T-cell lymphoma not other specified (PTCL-NOS); renal cell cancer, RCC, stem cell transplantation, SCT; total-body irradiation, TBI; triple negative breast cancer, TNBC.

Table 2. Active clinical trials combining TKIs normalizing angiogenesis and immunotherapies (source: ClinicalTrial.gov).

Target	TKI	Therapeutic indication	Immunotherapy combination	Trial number
Multiple tyrosine kinase	Regorafenib	Biliary tract cancer HCC	Durvalumab (anti-PD-L1)	Phase I–II NCT04781192; Phase II NCT05194293
		CRC	Atezolizumab (anti-PD-L1)	Phase I–II NCT03555149 (± AB928)
		CRC	Avelumab (anti-PD-L1) & Adenoviral vaccination & IL15	Phase I–II NCT03563157 (+ chemo, radiation, cetuximab)
		CRC	Toripalimab (anti-PD-1)	Phase I NCT04819516 (+ ultrasound therapy); Phase I–II NCT03946917; Phase II NCT04483219
		CRC HCC	anti-PD-1	NCT05233358 (+ HAIC or TACE); Phase I–II NCT04110093; Phase II NCT05048017
		CRC HCC	Camrelizumab (anti-PD-1)	Phase I–II NCT04446091 (± irinotecan); Phase II NCT04806243; Phase II NCT05135364 (+ HAIC)
		CRC HCC	Pembrolizumab (anti-PD-1)	Phase I NCT03347292; Phase I–II NCT03657641; Phase II NCT04696055
		CRC Gastroesophageal cancer HCC Hepatoma Osteosarcoma Rectal cancer Solid tumors	Nivolumab (anti-PD-1)	Phase I NCT03712943; Phase I–II NCT04170556; Phase II NCT04126733; Phase II NCT04310709; Phase II NCT04503694 (+ radiotherapy, surgery); Phase II NCT04704154; Phase II NCT04757363 (+ chemo); Phase II NCT04803877; Phase III NCT04777851; Phase III NCT04879368
		CRC HCC Liver metastasis	Sintilimab (anti-PD-1)	Phase II NCT04718909; Phase II NCT04745130 (± cetuximab); Phase II NCT05057052 (+ cryoablation)
		CRC Colon cancer Rectal cancer	Nivolumab (anti-PD-1) & Ipilimumab (anti-CTLA-4)	Phase I NCT04362839
		HCC	Tislelizumab (anti-PD-1)	Phase II NCT04183088
		Solid tumors	Avelumab (anti-PD-L1)	Phase I–II NCT03475953
Multiple tyrosine kinase	Sorafenib	ABL AML Myelodysplastic syndrome Myeloproliferative neoplasm	Filgrastim (G-CSF)	Phase I–II NCT02728050 (+ chemo); Phase I–II NCT03247088 (+ chemo, tacrolimus, SCT); Phase II NCT03164057 (+ chemo, ± SCT)
		Digestive system cancer HCC Liver cancer	Anti-PD-1	Phase II NCT04518852 (+ TACE)
		HCC	Atezolizumab (anti-PD-L1)	Phase III NCT04770896
		HCC	DC vaccine	Phase II NCT04317248 (+ CTX)
		HCC	H101 (recombinant human adenovirus type 5)	Phase IV NCT05113290

(*Continued*)

Table 2. (Continued).

Target	TKI	Therapeutic indication	Immunotherapy combination	Trial number
		HCC	Nivolumab (anti-PD-1)	Phase II NCT03439891
		HCC	Pembrolizumab (anti-PD-1)	Phase I–II NCT03211416
		HCC	Tislelizumab (anti-PD-1)	Phase II NCT04599777 (+ TACE); Phase II NCT04992143 (+ TACE)
		HCC	Toripalimab (anti-PD-1)	Phase I–II NCT04926532
		Neuroblastoma	Followed by Dinutuximab (anti-GD2) /GM-CSF/IL-2/isotretinoin/DFMO	Phase II NCT02559778
Multiple tyrosine kinase	Sunitinib	Bone sarcoma Soft tissue sarcoma	Nivolumab (anti-PD-1)	Phase I–II NCT03277924 (+ chemo)
		RCC	Nivolumab (anti-PD-1) & Ipilimumab (anti-CTLA-4)	Phase III NCT02231749
		Thymic carcinoma	Pembrolizumab (anti-PD-1)	Phase II NCT03463460
VEGFR2 MET Kit	Cabozantinib	Adenocarcinoma Anaplastic thyroid cancer Bladder cancer Esophageal cancer Glioblastoma HCC Neuroendocrine tumors NSCLC Pancreatic cancer Paraganglioma Pheochromocytoma Prostate cancer Osteosarcoma RCC Solid tumors	Atezolizumab (anti-PD-L1)	Phase I–II NCT03170960; Phase I–II NCT05039281; Phase II NCT04289779 (+ surgery); Phase II NCT04400474; Phase II NCT04820179; Phase II NCT05007613; Phase II NCT05019703; Phase II NCT05168163; Phase II NCT05168618; Phase III NCT03755791; Phase III NCT04338269; Phase III NCT04446117; Phase III NCT04471428;

(*Continued*)

Table 2. (Continued).

Target	TKI	Therapeutic indication	Immunotherapy combination	Trial number
		Advanced cancer (HIV infection) Angiosarcoma Carcinoid tumors Colon cancer CRC Endometrial cancer Genitourinary tumors HCC Head and neck caner Hormone refractory prostate cancer Kidney cancer Liver cancer Lung cancer Melanoma Neuroendocrine tumor NSCLC Oral cavity cancer Rectal cancer RCC Uterine corpus cancer	Nivolumab (anti-PD-1)	Phase I NCT02496208; Phase I NCT03299946; Phase I NCT04477512 (+ abiraterone acetate, steroid); Phase I NCT04514484; Phase I NCT05122546 (+ CBM 588 probiotic); Phase I–II NCT01658878; Phase I–II NCT04540705; Phase II NCT03367741; Phase II NCT03468985; Phase II NCT03635892; Phase II NCT04197310; Phase II NCT04310007 (± chemo, ramucirumab); Phase II NCT04322955 (+ surgery); Phase II NCT04339738; Phase II NCT04963283; Phase II NCT05039736; Phase II NCT05111574; Phase II NCT05136196; Phase III NCT03141177
		Bladder cancer Cancer of the oral cavity Cervical cancer Gastro and gastroesophageal cancer Head and neck cancer HCC Melanoma Pancreatic cancer RCC Sarcoma Urothelial cancer	Pembrolizumab (anti-PD-1)	Phase I–II NCT03149822; Phase I–II NCT03957551; Phase II NCT03468218; Phase II NCT03534804; Phase II NCT04164979; Phase II NCT04230954; Phase II NCT04442581; Phase II NCT05052723; Phase II NCT05182164
		Brain metastasis Genitourinary tumors HCC Melanoma Neuroendocrine tumors NSCLC RCC Soft tissue sarcoma	Nivolumab (anti-PD-1) & Ipilimumab (anti-CTLA-4)	Early Phase I NCT05188118; Phase I NCT02496208; Phase I–II NCT01658878; Phase II NCT03468985; Phase II NCT03866382; Phase II NCT04079712; Phase II NCT04091750; Phase II NCT04413123; Phase II NCT04472767 (+ TACE); Phase II NCT04551430; Phase II NCT05048212; Phase II NCT05200143; Phase III NCT03793166; Phase III NCT03937219
		Bladder cancer CRC Esophageal tumors Gastric tumors HCC	Durvalumab (anti-PD-L1)	Phase I–II NCT03539822; Phase II NCT03824691
		CRC Esophageal cancer Gastric cancer HCC	Durvalumab (anti-PD-L1) & Tremelimumab (anti-CTLA-4)	Phase I–II NCT03539822

(*Continued*)

Table 2. (Continued).

Target	TKI	Therapeutic indication	Immunotherapy combination	Trial number
		Neuroendocrine cancer	Avelumab (anti-PD-L1)	Phase II NCT05289856; Phase III NCT05092958
		Urothelial cancer		
		RCC	DC vaccine	Phase II NCT05127824
		RCC	Nivolumab (anti-PD-1) & Bempegaldesleukin (PEG-IL2)	Phase I–II NCT04540705
		Sarcoma	Filgrastim (G-CSF)	Phase I NCT04661852 (+ CTX, topotecan)
VEGFRs PDGFRs c-KIT	Axitinib	Adenoid cystic carcinoma	Avelumab (anti-PD-L1)	Proof-of-concept NCT03826589; Phase I–II NCT03386929 (+ palbociclib); Phase II NCT02912572; Phase II NCT03341845; Phase II NCT03472560; Phase II NCT03990571; Phase II NCT04258956; Phase II NCT04562441; Phase II NCT04698213; Phase II NCT05176288 (+ palbociclib); Phase II NCT05249569 (+ bavituximab); Phase III NCT02684006; Phase III NCT04510597 (± surgery); Phase III NCT05059522
		Cervical cancer		
		Endometrial cancer		
		GIST		
		HCC		
		Nasopharyngeal cancer		
		NSCLC		
		Ovarian cancer		
		RCC		
		Solid tumors		
		Urothelial cancer		
		Alveolar soft part sarcoma	Pembrolizumab (anti-PD-1)	Phase II NCT02636725; Phase II NCT04370509 (+ surgery); Phase II NCT04995016; Phase II NCT05096390; Phase II NCT05263609; Phase III NCT02853331; Phase III NCT04510597 (± surgery)
		RCC		
		Soft tissue sarcoma		
		Biliary tract cancer	Toripalimab (anti-PD-1)	Phase I NCT03086174; Phase II NCT03941795; Phase II NCT04010071; Phase II NCT04118855; Phase II NCT04180995; Phase II NCT04385654; Phase II NCT04459663; Phase III NCT04394975
		Hepatobiliary cancer		
		Kidney cancer		
		Liver cancer		
		Melanoma		
		Mucosal melanoma		
		NSCLC		
		RCC		
		Melanoma	Anti-PD-1 & rHSV2 (oncolytic virus)	Phase I NCT05070221
		Melanoma	Ipilimumab (anti-CTLA-4)	Phase II NCT04996823
		Melanoma	Toripalimab (anti-PD-1) & LBL-007 (anti-LAG-3)	Phase I NCT04640545
		Melanoma	Nivolumab (anti-PD-1)	Phase I–II NCT03172754; Phase II NCT04493203
		RCC		
		RCC	anti-OX40	Phase II NCT03092856
		RCC	Nivolumab (anti-PD-1) & Bempegaldesleukin (PEG-IL2)	Phase I–II NCT04540705
		RCC	Sintilimab (anti-PD-1)	Phase II NCT04387500; Phase II NCT04958473
		RCC	Tislelizumab (anti-PD-1)	Phase II NCT05172440
VEGFRs PDGFR c-KIT	Pazopanib	Sarcoma	Durvalumab (anti-PD-L1)	Phase II NCT03798106

(*Continued*)

Table 2. (Continued).

Target	TKI	Therapeutic indication	Immunotherapy combination	Trial number
		Solid tumors	Pegilodecakin (PEG-IL10)	Phase I NCT02009449
		Solid tumors	Spartalizumab (anti-PD-1)	Phase I–II NCT05210413
VEGFRs FGFRs PDGFRs	Lenvatinib	Adenoid cystic carcinoma Adrenocortical carcinoma Biliary tract cancers Brain metastasis Breast cancer Cervical cancer Cholangiocarcinoma CRC EGFR, ALK, ROS1 positive cancer Endometrial cancer Esophageal cancer Fallopian tube cancer Gastric cancer Gastroesophageal cancer Glioblastoma Head and neck cancer HCC Kidney cancer Leptomeningeal metastasis Liver cancer Melanoma Merkel cell carcinoma Neuroendocrine tumors NSCLC Ovarian cancer Pancreatic cancer Peritoneal cancer Pleural mesothelioma Prostate cancer RCC Salivary gland cancer Sarcoma SCLC Serous adenocarcinoma Solid tumors Thyroid cancer TNBC Trabecular carcinoma of the skin Urothelial cancer Uterine carcinosarcoma Uveal melanoma	Pembrolizumab (anti-PD-1)	NCT04425226; Early phase I NCT05041153; Early phase I NCT05273554; Phase I NCT03006926; Phase I NCT04427293; Phase I NCT05030506 (+ belzutifan); Phase I–II NCT02501096; Phase I–II NCT02861573; Phase I–II NCT04626479 (± belzutifan); Phase I–II NCT04626518; Phase I–II NCT04700072; Phase I–II NCT05286320 (+ SBRT); Phase II NCT02973997; Phase II NCT03321630; Phase II NCT03516981; Phase II NCT03776136; Phase II NCT03797326; Phase II NCT03895970; Phase II NCT04171622; Phase II NCT04207086; Phase II NCT04209660; Phase II NCT04267120; Phase II NCT04287829; Phase II NCT04393350; Phase II NCT04428151; Phase II NCT04519151; Phase II NCT04550624; Phase II NCT04622566; Phase II NCT04729348; Phase II NCT04745988; Phase II NCT04781088 (+ chemo); Phase II NCT04784247; Phase II NCT04848337; Phase II NCT04865887; Phase II NCT04869137; Phase II NCT04875585 (+ surgery); Phase II NCT04887805; Phase II NCT04924101 (+ chemo); Phase II NCT04929392 (+ chemo, radiation, surgery); Phase II NCT04955743; Phase II NCT04976634 (+ belzutifan); Phase II NCT04989322 (+ chemo); Phase II NCT05036434; Phase II NCT05064280; Phase II NCT05078931; Phase II NCT05101629; Phase II NCT05106127 (+ EG-007); Phase II NCT05114421; Phase II NCT05147558; Phase II NCT05185739; Phase II NCT05258279 (+ chemo); Phase II NCT05263492; Phase II NCT05282901; Phase II NCT05286437 (+ letrozole); Phase II NCT05296512; Phase III NCT02811861; Phase III NCT03517449; Phase III NCT03713593; Phase III NCT03820986; Phase III NCT03829319 (+ chemo); Phase III NCT03829332; Phase III NCT03884101; Phase III NCT03898180; Phase III NCT03976375; Phase III NCT04199104; Phase III NCT04246177 (+ TACE); Phase III NCT04662710 (+ chemo); Phase III NCT04676412; Phase III NCT04716933 (+ chemo); Phase III NCT04736706 (± belzutifan); Phase III NCT04776148; Phase III NCT04865289; Phase III NCT04889118; Phase III NCT04949256 (+ chemo); Phase III NCT05077215 (± EG-007)

(*Continued*)

Table 2. (Continued).

Target	TKI	Therapeutic indication	Immunotherapy combination	Trial number
		CNS tumors	Avelumab (anti-PD-L1)	Phase I NCT05081180
		Endometrial cancer HCC Liver cancer	Durvalumab (anti-PD-L1)	NCT04443322; NCT04444193; Phase II NCT04961918 (+ HAIC)
		HCC	Atezolizumab (anti-PD-L1)	Phase II NCT05168163; Phase III NCT04770896
		HCC	Camrelizumab (anti-PD-1)	Phase I–II NCT04443309; Phase I–II NCT05042336 (+ TACE); Phase II NCT05003700 (+ HAIC); Phase II NCT05135364 (+ HAIC); Phase II NCT05166239 (± HAIC); Phase II–III NCT04909866 (+ TACE);
		HCC	DC vaccine	Phase II NCT04317248 (+ CTX)
		HCC	Nivolumab (anti-PD-1)	Phase I NCT03418922; Phase II NCT03841201
		HCC Intrahepatic cholangiocarcinoma Liver cancer Liver metastases Portal vein tumor	Sintilimab (anti-PD-1)	NCT05277675 (+ RFA); NCT04618367 (+ HAIC); Phase I NCT05225116 (+ radiotherapy); Phase II NCT04042805; Phase II NCT04599790 (+TACE); Phase II NCT04769908 (+ chemo); Phase II NCT04814043 (+ TACE-HAIC, chemo); Phase II NCT05010668 (+ cryoablation); Phase II NCT05010681; Phase II NCT05098847 (+ cryoablation); Phase II–III NCT05250843 (+ TACE-HAIC or chemo, followed by surgery)
		Biliary system tumors HCC Solid tumors	Tislelizumab (anti-PD-1)	NCT05277675 (+ RFA); Early phase I NCT05131698 (+ TACE); Phase II NCT04401800; Phase II NCT04615143; Phase II NCT04834986; Phase II NCT05014828; Phase II NCT05036798 (+ chemo); Phase II NCT05057845 (+ cryoablation); Phase II NCT05156788 (+ chemo); Phase II NCT05254847 (+ chemo); Phase II NCT05291052 (+ chemo)
		Biliary tract cancer Cholangiocarcinoma HCC Intrahepatic cholangiocarcinoma	Toripalimab (anti-PD-1)	NCT05162898 (+ RFA); NCT05215665 (± chemo); Phase I–II NCT03867370; Phase II NCT03951597 (+ chemo); Phase II NCT04170179 (+ chemo); Phase II NCT04211168; Phase II NCT04361331; Phase II NCT04368078; Phase II NCT04506281 (+ chemo); Phase II NCT04627363 (+ bevacizumab, HAIC) Phase II–III NCT04669496 (+ chemo); Phase III NCT04523493
		Endometrial cancer HCC	Pembrolizumab (anti-PD-1) & Vibostolimab (anti-TIGIT)	Phase II NCT05007106
		HCC	Durvalumab (anti-PD-L1) & Tremelimumab (anti-CTLA-4)	Phase III NCT05301842 (+ TACE)
		HCC Melanoma RCC SCLC	Pembrolizumab (anti-PD-1) & Quavonlimab (anti-CTLA-4)	Phase I–II NCT04305041; Phase I–II NCT04305054; Phase I–II NCT04626479; Phase I–II NCT04700072; Phase II NCT04740307; Phase I–II NCT04938817; Phase III NCT04736706
		Pancreatic cancer	Tislelizumab (anti-PD-1) & H101 (oncolytic virus)	Phase I NCT05303090
		RCC	Autologous DC & Nivolumab (anti-PD-1) & Ipilimumab (anti-CTLA-4)	Phase II NCT04203901 (+ everolimus)

(*Continued*)

Table 2. (Continued).

Target	TKI	Therapeutic indication	Immunotherapy combination	Trial number
		RCC	Pembrolizumab (anti-PD-1) & anti-ILT-4	Phase I NCT03564691
		RCC Solid tumors	Pembrolizumab (anti-PD-1) & Favezelimab (anti-LAG-3)	Phase I NCT02720068; Phase I–II NCT04626479
		RCC	Nivolumab (anti-PD-1) & Ipilimumab (anti-CTLA-4)	Phase II NCT04203901 (+ everolimus)
		SCLC	AK-112 (anti-PD -1/VEGF bispecific)	Phase II NCT05296603
		Solid tumors	GI-101 (CD80-IgG4Fc-IL2v)	Phase I–II NCT04977453
	Nintedanib	Lung adenocarcinoma	Nivolumab (anti-PD-1)	Phase I–II NCT04046614
		NSCLC	Nivolumab (anti-PD-1) & Ipilimumab (anti-CTLA-4)	Phase I–II NCT03377023
		Solid tumors	Pembrolizumab (anti-PD-1)	Phase I NCT02856425
VEGFRs	Catequentinib	Lung cancer Soft tissue sarcoma	Nivolumab (anti-PD-1)	Phase I–II NCT04165330
VEGFRs	Tivozanib	Bile duct cancer Breast cancer Gall bladder cancer Neuroendocrine tumors Ovarian cancer Pancreatic cancer Prostate cancer Soft tissue sarcoma Vulvar cancer	Atezolizumab (anti-PD-L1)	Phase I–II NCT05000294
		HCC	Durvalumab (anti-PD-L1)	Phase I–II NCT03970616
		RCC	Nivolumab (anti-PD-1)	Phase III NCT04987203

Acute biphenotypic leukemia, ABL; acute myeloid leukemia, AML; cyclophosphamide, CTX; dendritic cell, DC; granulocyte colony stimulating factor, G-CSF; hepatic arterial infusion chemotherapy, HAIC; human immunodeficiency virus, HCC; renal cell carcinoma, HIV; renal cell carcinoma, RCC; radiofrequency ablation, RFA; small cell lung cancer, SCLC; stem cell transplant, SCT; transarterial chemoembolization, TACE; triple-negative breast cancer, TNBC

Table 3. Active clinical trials combining TKIs originally developed to target hematological cancers and immunotherapies (source: ClinicalTrial.gov).

Target	TKI	Therapeutic indication	Immunotherapy combination	Trial number
BTK	Ibrutinib	AIDS-Related lymphoma DLBCL CNS lymphoma	Filgrastim (G-CSF)	Phase I NCT03220022 (+ chemo, steroid, rituximab); Phase I–II NCT02315326 (+ rituximab, chemo)
		ALL BCR-ABL^{+}	Blinatumomab (anti-CD3/CD19)	Phase II NCT02997761
		ALL CLL DLBCL SLL	YTB323 (CD19 CAR-T cells)	Phase I NCT03960840
		CLL	Personalized multi-peptidevaccine & XS15 (TLR1/2 ligand)	Phase I NCT04688385
		CLL CNS lymphoma Colon cancer CRC DLBCL Follicular lymphoma Hematologic malignancies Mantle cell lymphoma Melanoma SLL Richter syndrome	Pembrolizumab (anti-PD-1)	Phase I–II NCT03153202; Phase I–II NCT03332498; Phase I–II NCT04421560 (+ rituximab); Phase II NCT02332980 (+ idelalisib); Phase II NCT03021460; Phase II NCT03204188 (+ fludarabine); Phase II NCT03514017
		CLL CNS lymphoma DLBCL DLBCL of the CNS Follicular lymphoma Head and neck cancer HL Metastatic solid tumors Richter syndrome SLL	Nivolumab (anti-PD-1)	Phase I NCT03525925; Phase I NCT05211336 (+ obinutuzumab, steroid, lenalidomide, venetoclax); Phase I–II NCT02329847; Phase II NCT02940301; Phase II NCT03646461; Phase II NCT03770416
		CLL DLBCL Follicular lymphoma NHL SLL	Lisocabtagene maraleucel (CD19 CAR-T)	Phase I–II NCT03310619; Phase I–II NCT03331198
		CLL Lymphoma	Durvalumab (anti-PD-L1)	Phase I–II NCT02733042
		CLL Macroglobulinemia SLL	Daratumumab (anti-CD38)	Phase I NCT03447808; Phase II NCT03679624; Phase II NCT03734198; Phase II NCT04230304
		CLL SLL	Pneumococcal 13-valent conjugate vaccine, trivalent influenza vaccine DTaP vaccine	Phase II NCT02518555
		CLL SLL Richter Syndrome	Ipilimumab (anti-CTLA4)	Phase I NCT04781855

(*Continued*)

Table 3. (Continued).

Target	TKI	Therapeutic indication	Immunotherapy combination	Trial number
		CLL SLL Richter syndrome	Ipilimumab (anti-CTLA4) & Nivolumab (anti-PD-1)	Phase I NCT04781855
		DLBCL Mantle cell Lymphoma	Avelumab (anti PD-L1) & Utomilumab (anti-CD137)	Phase I NCT03440567 (+ rituximab)
		Follicular lymphoma Mantle cell lymphoma Marginal zone lymphoma	SD-101 (TLR9 agonist)	Phase I–II NCT02927964 (+ radiation)
		Mantle cell lymphoma	Tisagenlecleucel (CD19 CAR-T cells)	Phase II NCT04234061
BTK	Acalabrutinib	B cell lymphoma	Axicabtagene Ciloleucel (CD19 CAR T cells)	Phase I–II NCT04257578
		CNS lymphoma	Durvalumab (anti-PD-L1)	Phase I NCT04462328; Phase I NCT04688151 (+ rituximab)
		Hematologic malignancies	Pembrolizumab (anti-PD-1)	Phase I–II NCT02362035
		Mantle cell lymphoma	CD19 CAR T cells	Phase II NCT04484012
BTK	Zanubrutinib	B cell lymphoma	CAR T cells	Phase II NCT05202782
		EBV^+ DLBCL Primary mediastinal large B cell lymphoma Richter transformation	Tislelizumab (anti-PD-1)	Phase II NCT04271956; Phase II NCT04705129

Acute lymphocytic leukemia, ALL; chimeric T cell receptor, CAR; chronic lymphocytic leukemia, CLL; central nervous system, CNS; diffuse large B-cell lymphoma, DLBCL; diphtheria, tetanus & pertussis, DTaP; Epstein-Barr virus, EBV; granulocyte colony stimulating factor, G-CSF; non-Hodgkin lymphoma, NHL; small lymphocytic lymphoma, SLL.

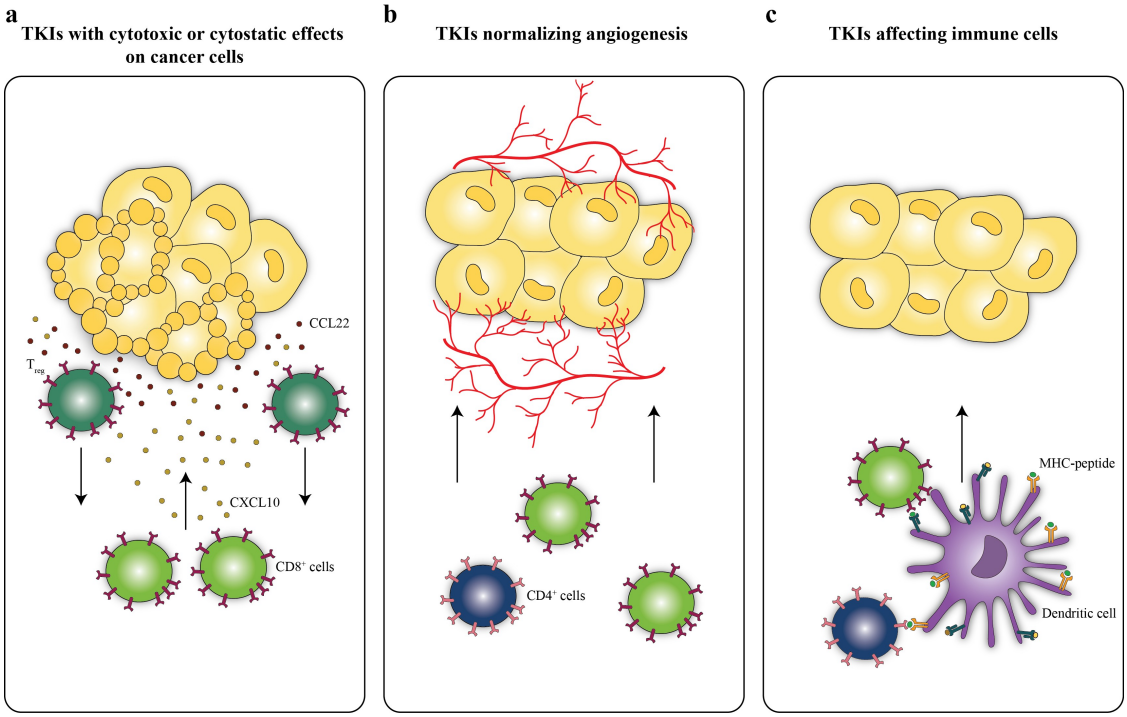

Figure 1. Functional TKI categories. Tyrosine kinase inhibitors (TKIs) can be functionally categorized into agents with cytotoxic or cytostatic effects on cancer cells leading to the establishment of chemokine gradients and improving the elimination of tumors by $CD8^+$ cytotoxic T lymphocytes (CTLs) (A). TKIs from the second category are endowed with angiogenesis normalizing effects and favor immune cell migration toward tumors (B). The third category of TKIs encompasses inhibitors originally developed to target hematological cancers that have been found to also activate immune cells such as dendritic cells and CTLs (C).

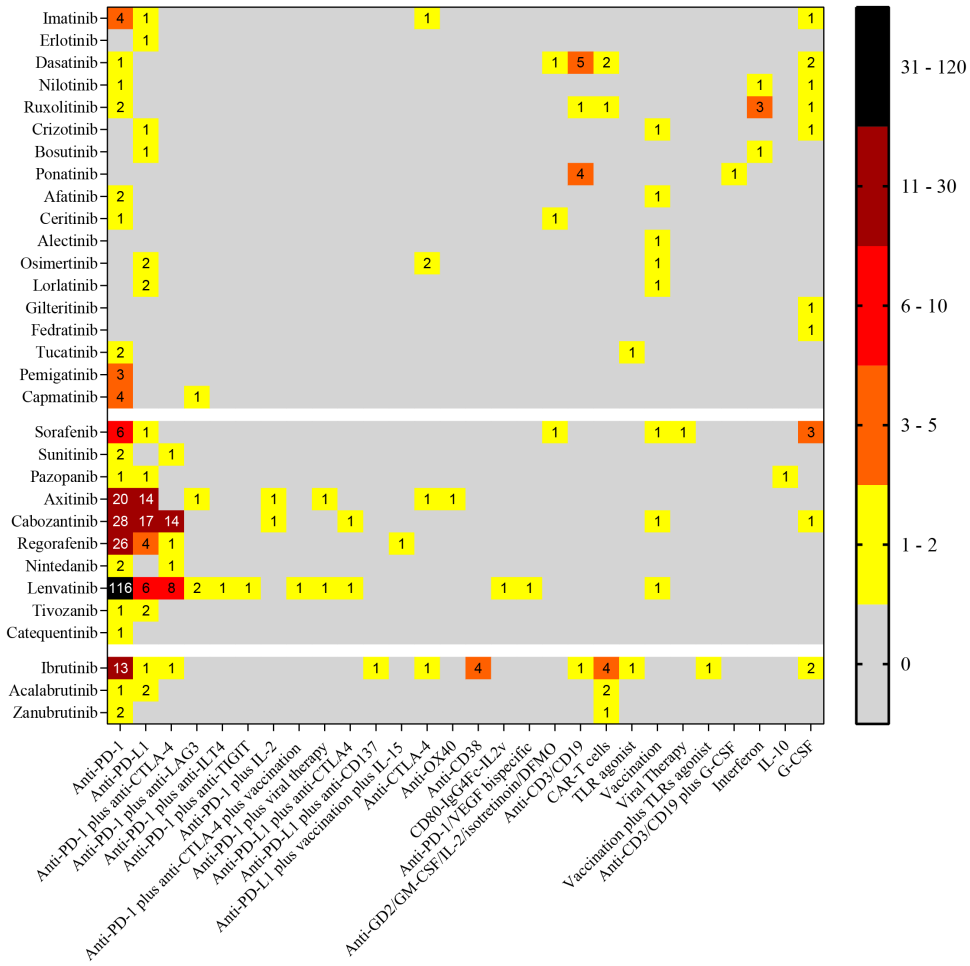

Figure 2. Heatmap of TKI combination with immunotherapy.The heatmap shows the number of clinical trials combining FDA-approved tyrosine kinase inhibitors (TKIs) with immunotherapies grouped according to their mechanism of action.

proliferation, but also by reducing tryptophan-derived immunosuppressive metabolites through the inhibition of indoleamine-2,3-dioxygenase (IDO) expression. Therefore, imatinib boosted intratumoral $CD8^+$ T cell activation and proliferation, thus promoting tumor cell killing by cytotoxic lymphocytes.[152] Combination of imatinib with anti-cytotoxic T lymphocyte antigen 4 (CTLA-4) blocking antibody significantly decreased tumor size compared to single treatments, as a result of the increased interferon (IFN)-γ production by intratumoral $CD8^+$ T cells.[153] Of note, Seifert and colleagues showed that intratumoral $CD8^+$ T cells displayed surface programmed cell death protein 1 (PD-1), and GIST cells as well as tumor infiltrating leukocytes expressed programmed cell death protein 1 (PD-L1) . Therefore, the authors investigated the therapeutic efficacy of concurrent administration of imatinib and anti-PD-1 or anti-PD-L1. Importantly, the efficacy of imatinib plus anti-PD-1 was visible as early as 1 week after treatment and persisted for 3 months.[154–156]

Inhibition of EGFR by erlotinib or osimertinib increased secretion of C-X-C motif chemokine ligand (CXCL) 10 (notoriously attracting $CD8^+$ T cells) and reduced C-C motif chemokine ligand (CCL) 22 (which is a chemoattractant for T regulatory cells (Tregs)).[157] Accordingly, EGFR inhibitors reprogram the immune environment and increase $CD8^+$ T cell-mediated killing of lung adenocarcinoma cells.[157] Erlotinib showed impressive preclinical success when combined with anti-PD-1 blockade therapy. Sugiyama and colleagues treated tumors derived from murine lung adenocarcinoma cell lines engineered to express human mutant EGFR and implanted them subcutaneously or intravenously into immunocompetent mice. Erlotinib plus anti-PD-1 showed superior therapeutic efficacy compared to single treatments.[145,157] However, despite the fact that the oncogenic signaling may induce PD-L1 upregulation in NSCLC, the superiority of immune checkpoint inhibitors in advanced EGFR-mutant NSCLC is only moderate in patients. Indeed, multiple mechanisms, including dynamic immune TME, PD-L1 expression levels and low tumor mutational burden, may account for the conflicting results regarding associations between the EGFR mutation status and response rates with PD-L1/PD-1 inhibitors.[158]

However, despite the fact that the oncogenic signaling may induce PD-L1 upregulation in NSCLC, the superiority of immune checkpoint inhibitors in advanced EGFR-mutant NSCLC is only moderate in patients. Indeed, multiple mechanisms including dynamic immune TME, PD-L1 expression levels and low tumor mutational burden, may account for the conflicting results regarding associations between the EGFR mutation status and response rates with PD-L1/PD-1 inhibitors.[158] Dasatinib also sensitized resistant tumors to anti-PD1 effect. Tu and collaborators identified discoidin domain-containing receptor 2 (DDR2) kinase, one of the dasatinib targets, as responsible for anti-PD1 resistance. Thus, its inhibition in combination with PD-1 blockade reduced growth and induced regression of subcutaneous prostate, colon and sarcoma tumors. The increased number of $CD8^+$ T cells among tumor infiltrating lymphocytes (TILs) suggested the recognition of specific tumor antigens occurring only in mice treated with dasatinib and anti-PD1.[159]

Crizotinib, an inhibitor of ALK, MET and ROS kinases,[160,161] stopped tumor cell proliferation and induced immunogenic cell death,[12] which alerts the immune system to the presence of the tumor and triggers a specific response.[162–164] Thus, immunotherapy with an anti-PD1 antibody administered after crizotinib cured almost 90% of mice bearing orthotropic NSCLCs.[145,165,166]

Ruxolitinib reduced tumor cell proliferation by inhibiting the signaling cascade involving JAK and signal transducer and activator of transcription (STAT).[167] Moreover, it suppressed the production of immunosuppressive cytokines (such as interleukin (IL)-6, IL-10 and granulocyte-macrophage colony-stimulating factor (GM-CSF)) by pancreatic tumor cells through STAT3 inhibition.[168] Treatment of orthotopic pancreatic tumors with ruxolitinib switched the tumor environment to immunostimulation and increased the number of infiltrating $CD8^+$ T cells as well as the expression of IL-21 and IL-17A. Combination with anti-PD-1 showed a synergistic activity.[169] Moreover, ruxolitinib has been successfully combined with oncolytic viral therapy. This effect may be explained by a ruxolitinib-mediated inhibition of the type-I-IFN antiviral response, thus sensitizing tumor cells to the lytic effect of the virus.[170–172]

Preclinical evidence for immunostimulatory effects of TKIs targeting angiogenesis

Tumor-induced angiogenesis interferes with immunosurveillance. For instance, newly formed blood vessels within tumors are frequently malformed, dysfunctional and leaky, thus representing a physical barrier for immune cell infiltration.[173] In addition, endothelial cells may express immunosuppressive molecules,[174] such as PD-L1 or Fas ligand (FasL) and cause T cell inactivation or death before they ever reach tumor cells.[175] Moreover, abnormal tumor blood vessels fail to deliver sufficient oxygen to the malignant tissue, which is frequently hypoxic. Hypoxia triggers secretion of chemokines attracting suppressive immune populations, such as myeloid-derived suppressor cells (MDSCs), tumor associated macrophages (TAM) of the M2 subtype or Tregs.[176–179] Accordingly, inhibition or normalization of intratumoral angiogenesis reverses the state of immunosuppression of the tumor environment and improves immunosurveillance.[180,181] Notably, inhibitors of VEGFR interfere with angiogenesis and serve as immune modulators.

Sunitinib, a TKI targeting multiple pathways, reduced newly formed blood vessels within adenocarcinomas and breast tumors. Addition of sunitinib or sorafenib to a vaccine against a tumor-derived antigen improved $CD4^+$ and $CD8^+$ T cell infiltration into tumors and increased the frequency of antigen-specific T cells.[182] As a consequence, vaccination coupled to angiogenesis inhibition significantly reduced tumor burden, achieving complete remissions in 20% of tumor-bearing mice.[182] Sorafenib, another TKI targeting multiple kinases, was tested together with vaccination to treat breast tumors. Thus, a dendritic cell (DC)-based, GM-CSF-secreting, HER2

targeted cellular vaccine increased $CD4^+$ and $CD8^+$ T cell infiltration into tumors and reduced tumor burden in a particularly efficient fashion when the vaccine was combined with sorafenib.[183,184]

Axitinib is a specific VEGFR inhibitor, the therapeutic efficacy of which relies on functional T cells.[185] Accordingly, immunotherapeutic strategies boosting T cell function greatly improved axitinib therapeutic success. In particular, addition of anti-PD-1 and antibody-mediated blockade of T cell immunoglobulin and mucin-domain containing (TIM)-3 plus an anti-CD137 agonistic antibody to axitinib induced complete regression of more than 90% of lung and colon carcinomas.[185] Similarly, lenvatinib-mediated tumor growth control relied on the presence of functional $CD8^+$ T cells and synergized with PD-1 blockade.[185]

Preclinical evidence for the use of ibrutinib and next-generation BTK inhibitors

Ibrutinib and BTK next generation inhibitors[186–192] were originally developed to target hematological cancers. However, they also target immune cells of the hematologic lineage.[193,194] Ibrutinib influences the phenotype and function of both innate and adaptive immune cells. For instance, ibrutinib improves DC maturation,[195] enhancing their capacity to prime T cells. In addition, it suppresses Th2 differentiation *in vitro, in vivo* and in CLL patients.[196] Mechanistically, ibrutinib reduces the expression of immunosuppressive molecules, such as PD-1 or CTLA-4, on the T cell surface.[197,198] As a consequence, T cells of ibrutinib-treated patients effectively kill tumor cells. Such direct immunological consequences of ibrutinib might be explained by inhibition of interleukin-2-inducible T-cell kinase (ITK) as an off-target effect.[199] Next-generation BTK inhibitors are more specific. However, BTK expression has recently been described in T cells, suggesting that even highly selective BTK inhibitors may act on immune cells to improve their anticancer function.[200]

BTK inhibitor effects on T cells have been exploited to improve the engraftment of chimeric antigen receptor-T (CAR-T) cells and CAR-T-mediated tumor clearance. As a matter of fact, CD19-directed CAR-T cells generated from ibrutinib-treated patients showed improved engraftment in blood and bone marrow after reinfusion into the patients.[201] Accordingly, concurrent treatment of xenograft models of ALL or CLL with human CAR-T cells and ibrutinib reduced tumor burden and greatly increased mouse survival, compared to single treatments. The efficacy of the combinatorial treatment could be attributed to an increased expansion of CAR-T cells after engraftment as well as improved effector functions, due to the downregulation of PD-1.[201] A similar synergism was described in a model of MCL. Combination of CD19-directed CAR-T cells and ibrutinib yielded long-term disease control in 80–100% of the mice.[202]

One preclinical study explored the combination of acalabrutinib and CAR-T cells targeting $CD19^+$ tumor cells. Combination of acalabrutinib and CD19-specific CAR-T cells was tested in a xenogeneic tumor model where luciferase-expressing B-ALL precursor cells were injected into NOD SCID gamma (NGS) mice.[203] The combinatorial treatment elicited superior cytotoxic effects compared to single agents, resulting in increased mouse survival and reduced tumor burden. Improved efficacy resulted from simultaneous inhibition of BTK in tumor cells by acalabrutinib, which enhanced their CAR-T cell-mediated lysis. However, acalabrutinib also improved CAR-T cell-mediated killing of $CD19^+$ tumor cells *in vitro* and increased cytokine release by CAR-T cells. Accordingly, in vivo injection of acalabrutinib increased the frequency of CAR-T cells in the blood and skewed their phenotype toward that of memory T cells.[203]

TKIs and modulation of gut dysbiosis

TKIs are often causing adverse effects in the digestive tract, including diarrhea.[204] In fact, fecal microbiota transplantation (FMT) from healthy donors has been randomized against placebo to treat TKI–induced diarrhea in patients with metastatic renal cell carcinoma (NCT04040712). The primary outcome was the resolution of diarrhea at four weeks. Healthy donor FMT was more effective than placebo in treating TKI-induced diarrhea, when a successful engraftment of allogeneic feces was obtained.[205]

Moreover, the impact of the baseline taxonomic composition of the stools before TKI-based therapy has been recently studied in randomized trials testing the effects of yogurt products in advanced kidney cancer patients. Among those 20 evaluable for response, 15 patients achieved objective responses that were correlated with the fecal overrepresentation of immunogenic metagenomic species (such as *Akkermansia muciniphila* and *Barnesiella intestinihominis*).[206,207] Moreover, Derosa et al. confirmed in preclinical studies that TKIs exert a direct effect on the composition of the gut commensals in naïve animals orally given three different types of TKIs daily for 3 weeks.[205] All three TKIs markedly induced significant changes in the alpha- and beta-diversity of the microbiota over time, in both BALB/c and C57BL/6 mice, with a common dominant deviation of the microbiota composition. Sunitinib and cabozantinib favored a higher abundance of immunostimulatory *Alistipes senegalensis*, as observed in humans. In C57BL/6 intestines, there was an over-representation of the immunostimulatory *Eubacterium siraeum*, among other species shared by all three TKIs (such as *Akkermansia muciniphila*, especially for cabozantinib). Altogether, we concluded that TKIs induced a significant and prototypic microbiota shift including immunostimulatory commensals that could be harnessed to improve the efficacy of ICIs in RCC patients.

Ongoing clinical trials

Driven by the aforementioned preclinical experimentation, the potential synergism between TKIs and immunotherapies is being evaluated in cancer patients. In March 2022, the website https://www.clinicaltrials.gov listed 408 combinations of TKIs and immunotherapy (Table 1, 2 and 3). Thirty-one FDA approved TKIs are being combined with immunotherapy for several therapeutic indications. With the only exception of ponatinib, alectinib, gilteritinib and fedratinib all TKIs are being tested in combination with PD-1 or PD-L1 blockade therapies.

Very promising is the combination of ABL TKIs and blinatumomab, a bispecific CD19-directed CD3 T-cell engager indicated for the treatment of Philadelphia chromosome-negative relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL), and minimal residual disease (MRD)-positive B-cell precursor ALL. Results of a phase II trial evaluating the efficacy of dasatinib and blinatumomab in newly diagnosed ALL adult patients showed impressive results (NCT02744768). In this trial, 61 patients received dasatinib as induction therapy, followed by consolidation treatment with blinatumomab (58 patients received at least one cycle). At the end of the induction phase, 98% of patients exhibited a complete hematological response (defined as ≤5% bone marrow blasts, absence of blasts in the peripheral blood, no extramedullary involvement and full recovery of the peripheral blood count) and 29% had a molecular response (defined as ratio between BCR-ABL1 to ABL1 equal 0 as detected by qPCR from bone marrow samples). Two cycles of blinatumomab increased the molecular responses to 60%. At 18 months, the OS was 95% and disease-free survival (DFS) amounted to 88%. Interestingly, sequencing of the *ABL* gene in 15 patients experiencing an increase in minimal residual disease after dasatinib treatment revealed *ABL* mutations in 7 patients. Even more interestingly, such mutations were undetectable when dasatinib was combined with blinatumomab, arguing in favor of the hypothesis that immunotherapy might clear resistant clones arising in the context of a TKI treatment.[208] Such results encouraged a Phase III trial (NCT04722848, not yet recruiting) which will assess the efficacy of ponatinib followed by blinatumomab in patients with BCR-ABL+ ALL treatment naïve. Patients will receive ponatinib for 10 weeks and then will receive blinatumomab (minimum 2 cycles, up to a maximum of 5). The active comparator arm will be chemotherapy plus imatinib. A second Phase III trial (NCT04530565, recruiting) is evaluating the combination of dasatinib or ponatinib with blinatumomab (simultaneous administration) together with chemotherapy and steroids. Treatment scheduling is of major importance. For instance, the trial I–II NCT02574078 tested the combination of crizotinib (250 mg twice daily) and nivolumab (240 mg once every two weeks) administered simultaneously, and 38% of patients developed severe hepatic toxicities. Similarly, mice treated with crizotinib and anti-PD1 at the same time exhibited liver toxicity. However, no signs of liver toxicity were observed when PD-1 blockade was administered one week after crizotinib.[166]

The number of clinical trials testing angiogenesis inhibitors plus immunotherapies is impressive. The majority of them combine antiangiogenic TKIs with PD-1 blockade.[209] Notably, results of the phase Ib/II trial (KEYNOTE-146, NCT02501096) demonstrated robust therapeutic efficacy of lenvatinib plus pembrolizumab in six different cancer types: urothelial cancer, head and neck squamous cell carcinoma, melanoma, non-small-cell lung cancer, renal cell carcinoma and endometrial cancer.[210] In the endometrial cancer cohort, enrolling 94 patients with previously treated metastatic endometrial cancer, lenvatinib plus pembrolizumab yielded an objective response rate of 38.3% with 10 complete responses (10.6%). These results spurred accelerated FDA approval of lenvatinib plus pembrolizumab in 2019 for advanced endometrial cancer patients progressing after prior systemic therapy (not candidates for curative surgery or radiation). Moreover, these remarkable results encouraged the development of the LEAP program, which is currently evaluating the efficacy of lenvatinib and pembrolizumab in various clinical indications in nine phase III and three phase II trials.[210]

Recently, in January 2021, FDA approved the combination of nivolumab and cabozantinib as first-line treatment for patients with advanced renal cell carcinoma. A pivotal phase III trial (CHECKMATE-9ER, NCT03141177) evaluated the efficacy of nivolumab, administered intravenously every two weeks, and daily cabozantinib in treatment-naïve renal cell carcinoma patients. The active comparator was sunitinib. Patients treated with nivolumab and cabozantinib exhibited improved progression-free survival (16.6 months *vs* 8.3 months) and overall response rates (55.7% *vs* 27.1%) when compared with sunitinib-treated patients.[211]

Ibrutinib and BTK next-generation inhibitors are frequently combined with anti-PD1 monoclonal antibodies. However, efforts are being made to evaluate combinations with CAR T cells engineered to recognize CD19. Such efforts stemmed from the observation that treatment with ibrutinib prior to CAR-T cell infusion had some beneficial effects in heavily pretreated CLL patients. The phase I trial NCT00466531 investigated safety and efficacy of CD19 CAR-T cells in 16 patients, 5 of whom had received ibrutinib before leukapheresis or CAR-T cell infusion. T cells isolated from such patients showed greater expansion efficiency and had more frequently a central memory phenotype. Altogether, objective responses were observed in 12 out of 16 patients (4 out of 5 treated with ibrutinib). Moreover, three patients experienced complete responses (2 were on ibrutinib at CAR-T cell infusion).[212]

As mentioned in the introduction, the classification used throughout this Trial Watch is not flawless. Several TKIs belonging to the first category also inhibit TKs expressed by immune cells, and a few clinical trials exploit this feature. For instance, ruxolitinib suppresses JAKs-STATs pathways in tumor cells as well as in immune cells and blunts the secretion of cytokines including IL-6, IFN-γ and TNF-α. A case report described a beneficial effect of ruxolitinib in reducing cytokine release syndrome after treatment with CD19/CD22 bispecific CAR-T cells without impairing CAR-T cell anti-tumor effects. With the same rationale, the Phase II–III trial NCT03117751 evaluates this JAK inhibitor in combination with CAR-T cells.

Concluding remarks

The combination of TKIs that target tumor-promoting pathways and immunotherapy might constitute a highly promising approach to treat cancer patients owing to the facts that: (i) TKIs reduce tumor size by halting cancer cell proliferation or by starving tumor cells to death; (ii) TKIs simultaneously improve immune-mediated recognition and elimination of tumor cells; and (iii) immunotherapy

boosts immunosurveillance against mutant cancer cells that are on the verge of developing resistance to TKIs (Figure 1)), iv) TKI act on the intestinal barrier and modulate gut dysbiosis. Preclinical studies have demonstrated the efficacy of such combinations in multiple mouse models. This Trial Watch has provided an overview of active clinical trials testing TKIs and immunotherapies as oncological indications (Figure 2). The number of ongoing clinical trials is impressive, reflecting an ever-increasing interest in such a combinatorial strategy. Moreover, the diversity of cancers being treated with combination therapies suggests that such a strategy may successfully target many different types of cancer. The identification of appropriate drug combinations as well as optimal dosing and scheduling will be essential for obtaining tangible improvements in cancer care. For this, cognitive insights still will be essential. Thus, the elucidation of the immunomodulatory (immunostimulatory or immunosuppressive) side effects of each TKI will be mandatory to choose the right immunotherapeutic combination partner. Then, appropriate scheduling (simultaneous or asynchronous, TKI first or immunotherapy first, TKI provided in a continuous or intermittent fashion, etc.) will be important to obtain the best imaginable clinical benefit for cancer patients.[213]

List of abbreviations

ALCL	Anaplastic large cell lymphoma
ALK	Anaplastic lymphoma kinase
ALL	Acute lymphoblastic leukemia
AML	Acute myeloid leukemia
BC	Breast cancer
BCMA	B-cell maturation antigen
BCR-Abl	Breakpoint cluster region-Abelson
BTK	Bruton's tyrosine kinase
CAR	Chimeric antigen receptor
CCL	C-C motif chemokine ligand
CLL	Chronic lymphocytic leukemia
CML	Chronic myelogenous leukemia
CNS	Central nervous system
CRC	Colorectal cancer
CSF1R	Colony stimulating factor 1 receptor
CTLA-4	Cytotoxic T lymphocyte antigen 4
CTX	Cyclophosphamide
CXCL	C-X-C motif chemokine ligand
DC	Dendritic cell
D-CIK	Dendritic and cytokine-induced killer cell
DFMO	Difluoromethylornithine
DLBCL	Diffuse large B-cell lymphoma
EBV	Epstein–Barr virus
EGF	Epidermal growth factor
EGFR	Epidermal growth factor receptor
FGFR	Fibroblast growth factor receptor
FLT3	Fms like tyrosine kinase 3
G-CSF	Granulocyte colony-stimulating factor
GM-CSF	Granulocyte-macrophage colony-stimulating factor
GIST	Gastrointestinal stromal tumor
HAIC	Hepatic arterial infusion chemotherapy
HER	Human epidermal growth factor receptor
HCC	Hepatocellular carcinoma
HIV	Human immunodeficiency virus
HL	Hodgkin lymphoma
IDO	Indoleamine-pyrrole 2,3-dioxygenase
IGFR	Insulin-like growth factor receptor
IL	Interleukin
ILT-4	Immunoglobulin-like transcript 4
InsR	Insulin receptor
IFN	Interferon
JAK	Janus kinase
LAG-3	Lymphocyte-activation gene 3
LLy	Lymphoblastic lymphoma
LTK	Leukocyte receptor tyrosine kinase
MCL	Mantle cell lymphoma
MM	Multiple myeloma
NHL	Non-Hodgkin lymphoma
NIS	Sodium iodine symporter
NOS	Not other specified
NSCLC	Non-small-cell lung carcinoma
OS	Overall survival
PC	Pancreatic cancer
PEG	Polyethylene glycol
PD-1	Programmed cell death protein 1
PDGFR	Platelet-derived growth factor receptor
PD-L1	Programmed cell death protein 1
PFS	Progression free survival
RCC	Renal cell carcinoma
RET	Rearranged during transfection
SLL	Small lymphocytic lymphoma
STAT	Signal transducer and activator of transcription
TACE	Transarterial chemoembolization
TC	Thyroid carcinoma
TCC	Transitional cell carcinoma
TIGIT	T cell immunoreceptor with Ig and ITIM domains
TIL	Tumor infiltrating lymphocyte
TLR	Toll-like receptor
TNBC	Triple-negative breast cancer
VEGFR	Vascular endothelial growth factor receptor
VSV	Vesicular stomatitis virus

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Data availability statement

The data that support the findings of this study are openly available in clinicaltrials.gov at https://clinicaltrials.gov under the reference numbers cited in this article.

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