Drug Design

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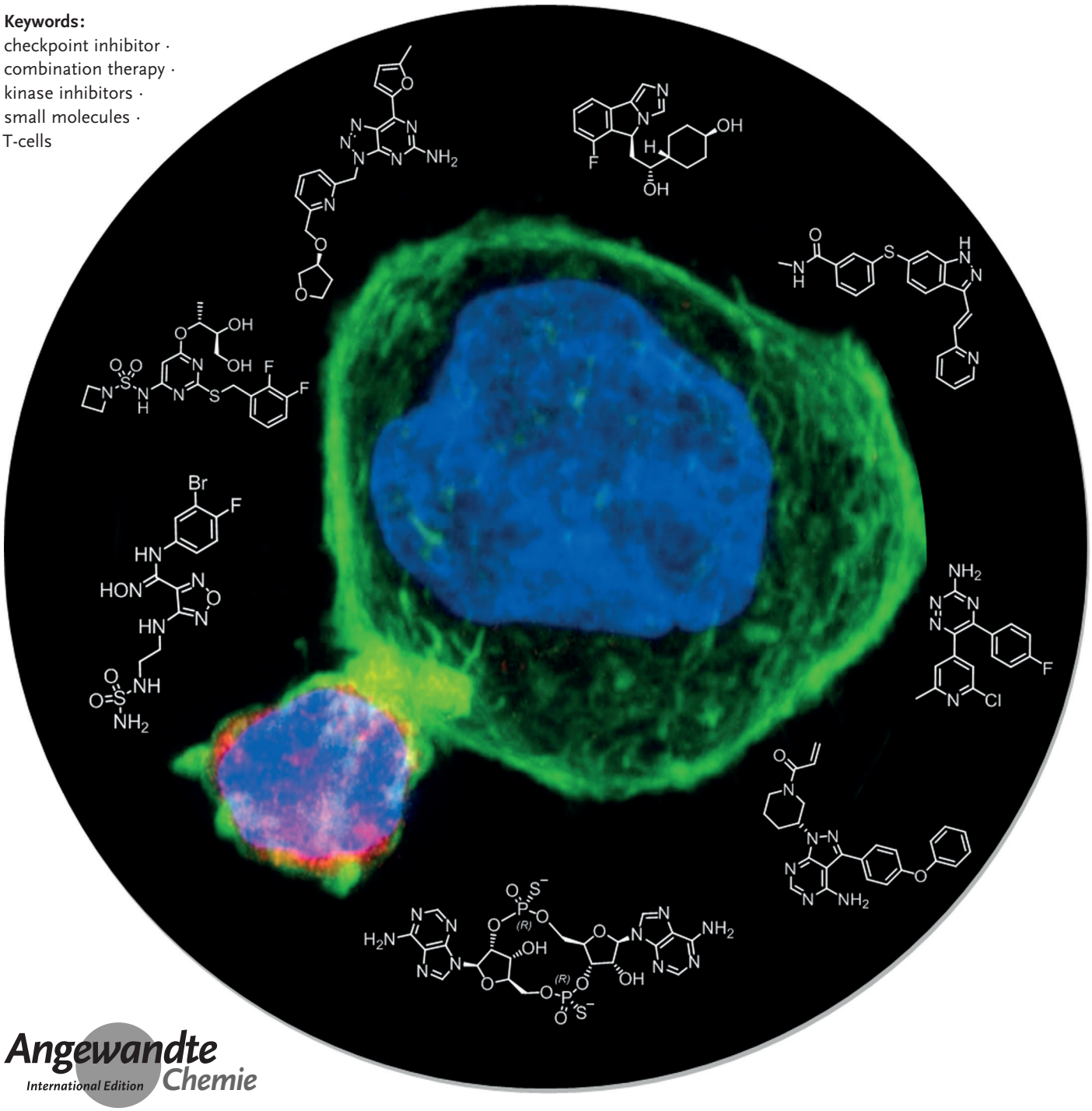
Small Molecules Drive Big Improvements in Immuno-Oncology Therapies

*Bayard R. Huck, Lisa Kötzner, and Klaus Urbahns**

Keywords:
checkpoint inhibitor · combination therapy · kinase inhibitors · small molecules · T-cells



Immuno-oncology therapies have the potential to revolutionize the armamentarium of available cancer treatments. To further improve clinical response rates, researchers are looking for novel combination regimens, with checkpoint blockade being used as a backbone of the treatment. This Review highlights the significance of small molecules in this approach, which holds promise to provide increased benefit to cancer patients.

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1. A New Era in Oncology

In the last decade, there has been remarkable success in applying targeted molecular therapies to the treatment of cancer. These approaches are typically based on modulating aberrant signal transduction pathways within the cancer cells. However, cancer remains one of the leading causes of morbidity and mortality worldwide, with approximately 14 million new cases and 8.8 million cancer-related deaths every year. Furthermore, the benefits of these targeted therapies can often be short lived, as tumor resistance is often observed. As such, new oncology treatments are needed to provide improved and more sustained benefit to patients.[1]

In the quest to expand and improve the scope of oncology treatments, researchers have attempted to harness the immune system of the body as a novel approach to fight cancer. In 1863, Rudolf Virchow detected the presence of leukocytes in tumors and suggested a causative relationship.[2] Today, we know that cytotoxic CD8+ T-cells recognize cancer cells through the T-cell receptor/MHC system. Before the cancer cell is killed, T-cells need to receive a second confirmatory signal to become activated. This signal is mediated by a variety of co-stimulatory and inhibitory receptors, which are also referred to as checkpoints. In the final step of immune-mediated tumor-cell eradication, cytotoxic T-cells inject a poisonous cocktail composed of various granzymes, granulysin, and perforin to induce programmed cell death in the cancer cell (Figure 1). Under physiological conditions, the role of checkpoint proteins is to maintain self-tolerance and prevent autoimmunity. Cancer cells, however, deregulate the expression of checkpoint proteins and are thereby capable of "hijacking" self-tolerance-enabling mechanisms within the tumor microenvironment (Figure 2). The most prominent checkpoint receptors are programmed cell death protein 1 (PD-1, CD279), cytotoxic T-lymphocyte associated protein 4 (CTLA-4, CD152), and programmed death ligand 1 (PDL-1, CD274). PD-1 and CTLA-4 are mostly found on T-cells and play a role in dampening the immune response. PD-L1, a ligand of PD-1, is mainly expressed on cancer cells and induces tolerance. Together with a multitude of other proteins, these checkpoint receptors

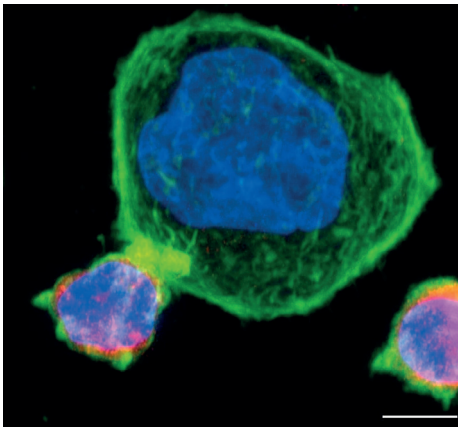

Figure 1. Kiss of death: A cytotoxic T-cell (lower left) attacking a cancer cell (upper right). Green: actin (immunofluorescence), blue: nuclei (stained with DAPI), red: T-cells (labeled with CellTracker Orange CMRA). Microscope: Zeiss LSM 880 with AiryScan, 63×/1.4 oil. Scale bar (white, lower right): 5 μm.

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Table 1: Approved and marketed antibody checkpoint inhibitors.

Compound (Brand name)	Target	Originator	Approval
ipilimumab (Yervoy)	CTLA-4	Bristol-Myers Squibb	2011
pembrolizumab (Keytruda)	PD-1	Merck & Co. Inc., Kenilworth, NJ, US	2014
nivolumab (Opdivo)	PD-1	Bristol-Myers Squibb	2014
atezolizumab (Tecentriq)	PD-L1	Roche/Genentech	2016
avelumab (Bavencio)	PD-L1	Merck KGaA, Darmstadt, Germany/Pfizer	2017
durvalumab (Imfinzi)	PD-L1	AstraZeneca	2017

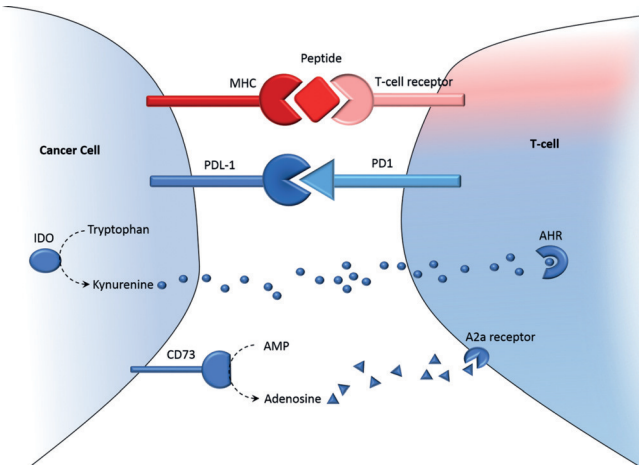

Figure 2. Cooling down the attack: A T-cell is activated through recognizing a peptide/MHC complex on a tumor cell. The tumor escapes immunity by expressing the checkpoint molecule PDL1 and by producing kynurenine through IDO or adenosine via CD73. Both molecules have immune-dampening effects mediated through the aryl-hydrocarbon receptor and the A2a adenosine receptor, respectively.

constitute molecular elements of the immunological synapse.[3]

Antibodies that target these checkpoint receptors have proven efficacious as cancer treatments. Indeed, six compounds have been approved by the regulatory agency within the last six years as a result of their effectiveness in a host of oncology indications including, skin, and lung cancer (Table 1).[4]

From a clinical perspective, results of immuno-oncology checkpoint inhibitors differ from previous standards of care in that they induce a significant subset of long-term survivors (Figure 3). These observed "cures" have sparked enthusiasm among oncologists and the general public.[4,5]

However, not all patients benefit from checkpoint inhibitors and, in addition, immune-based adverse effects are frequently observed. Thus, there is a renewed focus on identifying novel oncology treatments that increase the percentage of patients who benefit, while limiting adverse events. To achieve this goal, the combination of anti-checkpoint agents with supportive therapies is actively being explored.[6]

2. The Advantage of Small Molecules as Combination Partners in Immuno-Oncology

Combination therapies are widely regarded as the future of modern oncology. For many cancer types, we are likely to see a checkpoint inhibitor as a backbone therapy that could be combined with adjunct therapies. Although this strategy is advantageous from an efficacy point of view, researchers are also mindful of the possible clinical safety implications. One drawback of antibodies is their long half-life, which results in a duration of multiple weeks. Thus, side effects cannot be easily combated once injected into the body. The case of

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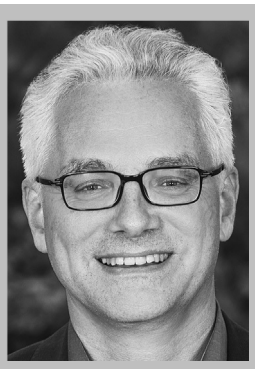

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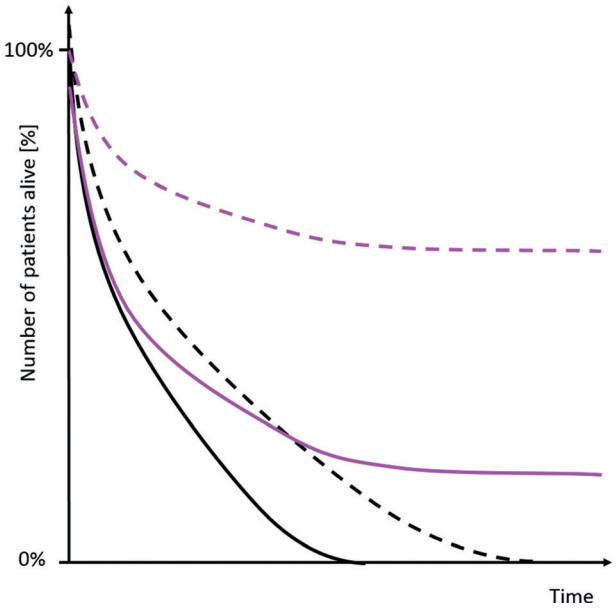


Figure 3. Lifting the tail: The difference between targeted and immuno-oncology cancer treatments as illustrated in a schematic Kaplan–Meier diagram. Targeted therapy (– – –) provides benefit to patients compared to the standard of care (——), but responses are rarely durable. Immune therapy (——, purple) provides a similar benefit, but with a "long tail", as a significant portion of the patients are cured. The aspiration in the oncology field is to enlarge this fraction of cures through combinations of targeted and immune therapy treatments (– – –, purple).

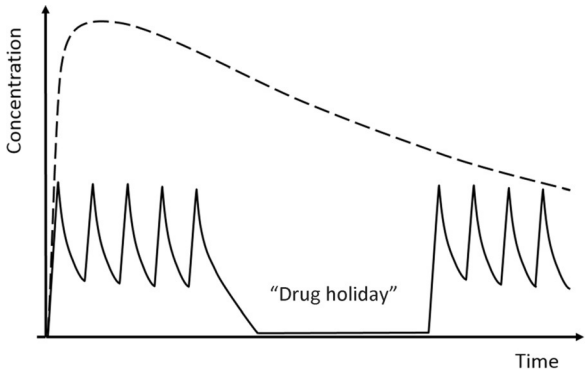


Figure 4. A schematic concentration/time diagram comparing qualitatively the pharmacokinetics of an antibody (– – –) and a small molecule (——). In contrast to antibodies, small molecules have shorter half-lives and their dosing regimen can be adapted to clinical needs in a flexible manner.

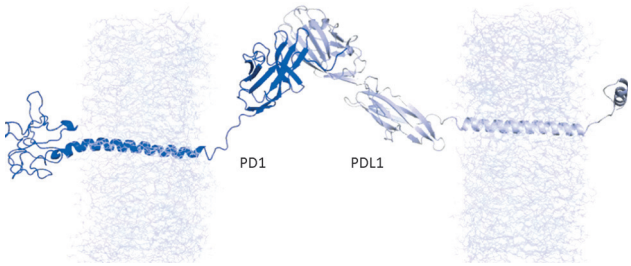


Figure 5. A molecular model of the PD-1/PD-L1 interaction. Currently, 765 clinical combination studies are being conducted to interrogate the relevance of this mechanism for human disease. 194 combination trials involve small molecules.

TGN1412, a CD28 superagonist that created disastrous cytokine storms in healthy volunteers upon injection of a single intravenous dose, was a painful reminder of the possibly dramatic nature of these side effects.[7]

Although small molecules have dominated anticancer therapies for decades, this therapeutic modality is so far missing from the reservoir of commercially available immuno-oncology agents.[4] Small molecules benefit from their ability to cross cellular membranes and other barriers, thereby reaching intracellular targets. Furthermore, small molecules typically have half-lives of less than 24 hours, and their ability to achieve efficacy after a more convenient oral administration allows for more flexibility within the treatment regimen. Thus, researchers and clinicians can use intermittent dosing and "drug holidays" to balance the risk of side effects in combination trials (Figure 4).

The area of immuno-oncology is advancing rapidly, with many investigators omitting clinical phases to register and bring medicines to cancer patients more quickly. The number of clinical combination studies involving anti PD-1/PD-L1 agents (Figure 5) has risen dramatically within the last 18 months from 215 (November 2015) to 765 (May 2017). The authors are unaware of any other molecular mechanism that is being studied clinically with this intensity. Of relevance to this Review, approximately one quarter of immuno-oncology clinical studies involve small molecules as combination partners for checkpoint inhibitors.[6b]

This Review summarizes current highlights in the field of small-molecule approaches in immuno-oncology, with an emphasis on compounds which are currently in clinical combination trials with checkpoint inhibitors (Table 2).[8] Given the huge number of drug candidates, we focus on the most advanced compounds in each category.

3. Small-Molecule Checkpoint Inhibitors

3.1. Small-Molecule PD-1/PD-L1 Inhibitors

The development of small-molecule modulators of the PD-1/PD-L1 interaction have lagged behind the development of PD-1 and PD-L1 antibodies. The crystal structure of the murine PD-1/human PD-L1 interaction revealed the overall binding mode of the PD-1/PD-L1 interaction, and provided hope for the rationally guided structure-based design of inhibitors of the PD-1/PD-L1 complex.[9] Unfortunately, sequence homology between murine PD-1 and human PD-1 is low, which precluded drug design. Recently, the crystal structure of the human PD-1/human PD-L1 complex was solved, which revealed key interactions between the two proteins and identified "hot spots" that can be mimicked with substances other than antibodies.[10]

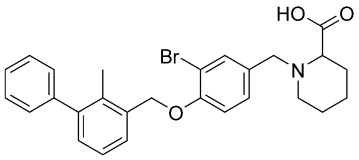
Efforts to identify non-antibody inhibitors of the PD-1/PD-L1 complex were initially undertaken with peptide mimetics[11] and macrocyclic peptides.[12] Certain molecules

Table 2: Small molecules currently in immuno-oncology clinical combination trials.

Target	Compound	Checkpoint inhibitor
PD-1/VISTA	CA170	none
PI3Kδ	idelalisib	pembrolizumab
PI3Kγ	IPI-549	nivolumab
TGFβ	galunisertib	durvalumab
		nivolumab
BTK	ibrutinib	pembrolizumab
		nivolumab
		durvalumab
	acalabrutinib	pembrolizumab
VEGF	axitinib	pembrolizumab
		avelumab
	lenvatinib	pembrolizumab
	sorafenib	PDR001
	sunitinib	avelumab
	pazopanib	pembrolizumab
FAK	defactinib	pembrolizumab
		avelumab
MEK+BRAF	trametinib dabrafenib	pembrolizumab
		nivolumab
		durvalumab
		PDR001
	binimetinib encorafenib	pembrolizumab
	cobimetinib +/- vemurafenib	atezolizumab
IDO	epacadostat	pembrolizumab
		atezolizumab
	GDC-0919	atezolizumab
	indoximod	nivolumab
A2a	PBF-509	PDR001
	CPI-444	atezolizumab
	AZD4635	durvalumab
	preladenant	pembrolizumab
CXCR4	BL-8040	pembrolizumab
		atezolizumab
	X4P-001	pembrolizumab
		nivolumab
	LY2510924	durvalumab
CCR5	BMS-813160	nivolumab
HDAC	vorinostat	pembrolizumab
HDAC	entinostat	avelumab
		pembrolizumab
		atezolizumab
		nivolumab
	mocetinostat	nivolumab
		durvalumab
	chidamid	nivolumab
TLR7/8	MEDI9197	durvalumab
STING	ADU-S100	PDR001
	MK-1454	pembrolizumab

have been identified that mimic the binding motif of PD-1 and indeed inhibit the PD-1/PD-L1 interaction. Preclinical studies also reveal antitumor activity of these molecules. Nonetheless, there has been no clinical evaluation of these peptide-related molecules.

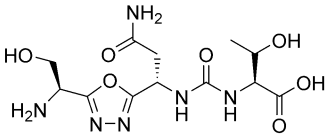
The evolution from peptide-related molecules to small-molecule PDL1 inhibitors has recently been reported. The initial small-molecule inhibitors of the PD-1/PD-L1 interaction were identified by researchers at Bristol Myers Squibb (BMS).[13] A homogeneous time-resolved fluorescence (HTRF) binding assay has shown that compound **1** directly binds PD-L1 (Figure 6). An X-ray structure analysis revealed that this molecule binds to PD-L1 in the PD-1 binding pocket. Its mechanism of action seems to involve the induction of PD-L1 dimerization, thereby occluding the PD1 interaction surface.[14]



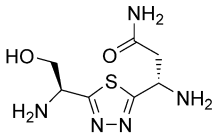
1
WO2015/034820, Example 8

Figure 6. A small-molecule inhibitor of the PD-1/PD-L1 complex.

A second reported example of small molecules that disrupt the PD-1/PD-L1 interaction comes from researchers at Aurigene. In a recent patent application, the inventors highlight 1,3,4-oxadiazoles **2** and 1,3,4-thiadiazoles **3** (Figure 7).[15] There is speculation that these or related derivatives have been the subject of a reported license agreement with Curis.



2
WO2015/033301, Example 2



3
WO2015/033301, Example 3

Figure 7. Small-molecule inhibitors of the PD-1/PD-L1 complex.

Recently, Curis provided details on two small molecules, CA-170 and CA-327, which can disrupt the PD-1/PD-L1 complex. CA-170 is a dual PD-L1 and VISTA antagonist with activities of 17 nM and 37 nM, respectively. The compound potently and selectively rescues human T-cell activation.[16] In a dose-dependent manner, CA-170 activates T-cells inhibited by exogenous PD ligands or VISTA, with a similar depth of response as observed for anti-PD-1 or anti-VISTA antibodies. Interestingly, there was no rescue of T-cells of other immune checkpoints, namely, CTLA-4, TIM3, or LAG3. CA-170 is orally bioavailable and displays dose-proportional exposure up to 1000 mg kg^{-1}. Antitumor activity was observed in vivo in immunocompetent mice, with an efficacy similar to that of

an anti-PD-1 antibody. Interestingly, there was no efficacy observed in immune-deficient mice. CA-170 is currently under evaluation in a first phase I clinical study in humans.[17] Clinical results for CA-170 will shape the evaluation of whether small molecules offer improvements over the approved PD-1 and PD-L1 antibodies.

CA-327 selectively and potently inhibits PD-L1 and TIM3.[18] In a dose-dependent manner, CA-327 activates T-cells inhibited by exogenous PD ligands or TIM3, with a similar depth of response as observed for anti-PD-1 or anti-TIM3 antibodies. CA-327 is orally bioavailable across multiple preclinical species and inhibits tumor growth in immunocompetent mice. The structures of CA-170 and CA-327 have not been disclosed.

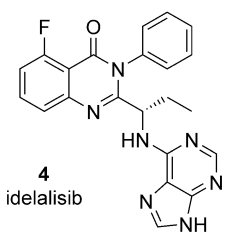
4. Kinase Inhibitors

4.1. PI3K Pathway—PI3Kδ and PI3Kγ

The phosphoinositide-3-kinases (PI3K) are a family of lipid kinases which catalyze the phosphorylation of the 3′-hydroxy group of phosphatidylinositol.[19] This transformation mediates receptor signaling, contributes to cell growth and development, and is implicated in cell survival. The PI3K family can be categorized into three classes, with the best studied being the class I PI3Ks. Class Ia PI3Ks include PI3Kα, PI3Kβ, and PI3Kδ, which are activated by receptor tyrosine kinases, G-protein coupled receptors (GPCRs), and certain oncogenes. Class Ib PI3Ks include PI3Kγ, which is activated by GPCRs. PI3Kδ and PI3Kγ are expressed strictly in immune and hematopoietic cells and are, therefore, of interest for the treatment of cancer.[20] PI3K inhibitors have been studied for many years, but their clinical use seems to be limited by side effects. The opportunity to combine these agents with checkpoint inhibitors offers new possibilities for these compounds, raising hope that therapeutic windows can be enhanced.

4.1.1. PI3Kδ Inhibitors

PI3Kδ plays a role in B-cell proliferation and differentiation, and is often overexpressed in B-cell malignancies. As such, PI3Kδ is viewed as an interesting oncology target. Indeed, multiple PI3Kδ inhibitors are under evaluation in clinical studies for the treatment of B-cell malignancies. An important example is idelalisib (**4**, Calistoga/Gilead, Figure 8) which was approved by the FDA for the treatment of several B-cell malignancies, including chronic lymphocytic leukemia (CLL), follicular lymphoma (FL), and small lymphocytic lymphoma (SLL).



4
idelalisib

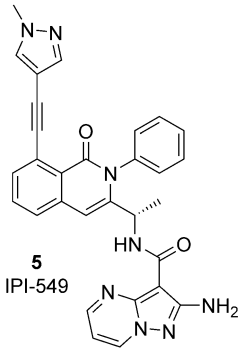
Figure 8. The PI3Kδ inhibitor idelalisib (**4**).

Recent preclinical data suggest that inhibition of PI3Kδ may play a role in immuno-oncology, as PI3Kδ is required for the immunosuppressive function of regulatory T-cells. Inhibition of PI3Kδ in T-reg cells leads to enhanced cytotoxic T-cell function and restricts tumor growth.[21] Currently, idelalisib is being evaluated in combination with pembrolizumab in indications where idelalisib is already approved, including CLL and B-cell lymphomas.[22]

4.1.2. PI3Kγ Inhibitors

PI3Kγ plays an important role in the function and migration of immune cells, as well as supporting the function of myeloid cells in the tumor microenvironment.[23] In tumors, PI3Kγ is activated to promote myeloid cell recruitment and tumor progression.[24] In models with inactivated PI3Kγ, reduction in tumor growth is observed due to abrogation of myeloid cells. Thus, pharmacological inhibition of PI3Kγ may suppress inflammation, growth, and metastasis of tumors.

IPI-549 (**5**, Infinity) is an orally available, selective PI3Kγ inhibitor (Figure 9).[25] Preclinical data in solid tumor models reveal that IPI-549 targets immune cells and alters the immune-suppressive microenvironment, thereby promoting an antitumor immune response that leads to inhibition of tumor growth. Additionally, in preclinical models, IPI-549 combined with an anti-PD-1 agent leads to enhanced inhibition of tumor growth.[26]



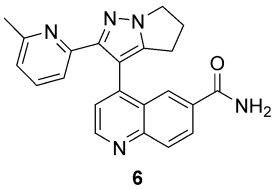
5
IPI-549

Figure 9. The PI3Kγ inhibitor IPI-549 (**5**).

As the only selective PI3K-γ inhibitor in clinical development, IPI-549 has the potential to offer a unique approach to the field of immuno-oncology therapies. IPI-549 is being evaluated in a phase I clinical study, in which the combination of IPI-549 with nivolumab is being investigated in a variety of cancer indications.[26,27]

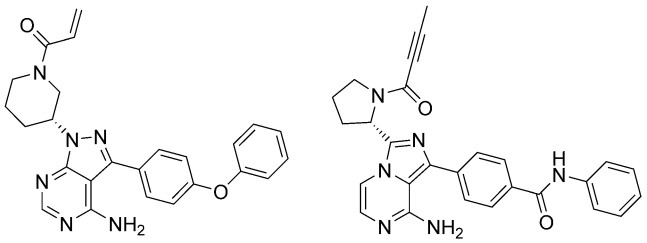
4.2. TGFβ Kinase Inhibitors

The transforming growth factor β (TGFβ) signaling pathway is complex and results in either tumor-suppressor or tumor-promoting activity depending on the cellular context. The tumor-suppressor function of TGFβ is lost during cancer progression, which leads to proliferation of tumor cells.[28] Preclinical studies reveal the utility of TGFβ inhibition for the treatment of cancer.[29] Indeed, the small-molecule TGFβ inhibitor galunisertib (**6**, Eli Lilly) is currently in phase II clinical studies in hepatocellular carcinoma (Figure 10).



6
galunisertib

Figure 10. The TGFβ inhibitor galunisertib (**6**).



7
ibrutinib

8
acalabrutinib

Figure 11. The BTK inhibitors ibrutinib (**7**) and acalabrutinib (**8**).

In the context of the immune system, TGFβ exerts systemic immune suppression and inhibits immune surveillance. Furthermore, in the tumor microenvironment, TGFβ regulates the infiltration of immune cells and cancer-associated fibroblasts. In preclinical models, pharmacological inhibition of TGFβ drives immune activation, including synergy with other immunotherapeutic agents.[30] Galunisertib is being investigated in clinical studies with checkpoint inhibitors, that is, durvalumab for pancreatic cancer and nivolumab for hepatocellular carcinoma and NSCLC.[31]

4.3. Bruton's Tyrosine Kinase (BTK) and Interleukin-2-Inducible Kinase (ITK) Inhibitors

Bruton's tyrosine kinase (BTK) and interleukin-2-inducible kinase (ITK) are members of the TEC family of kinases, which also includes TEC, BMX, and RLK. Members of the TEC family of kinases are primarily expressed in the hematopoietic system and are involved in signaling of the antigen receptor. BTK is an integral component of the B-cell receptor signal transduction pathway and is responsible for the regulation of B-cell proliferation and survival.[32] BTK propagates B-cell signaling and is crucial for the maintenance of humoral immunity and myeloid cell function. Dysregulation of BTK is linked to B-cell malignancies. ITK is the T-cell-dominant member of the TEC family of kinases, and is responsible for driving proximal T-cell receptor signaling.[33] Ablation of ITK subverts Th2 immunity, thereby potentiating Th1-based immune responses. ITK is crucial for regulating T-cell differentiation, and inhibition of ITK leads to the generation of T_H1 cells. Inhibition of ITK may shift the balance between Th1 and Th2 T-cells and lead to an enhancement in antitumor immune responses. Given their biological relevance, both BTK and ITK have drawn attention as oncology targets.

As a consequence of the influence of BTK and ITK on hematopoietic malignancies, inhibitors of these kinases are under intense evaluation in clinical settings. The most developed examples of these molecules include ibrutinib (**7**, Pharmacyclics/Janssen) and acalabrutinib (**8**, Acerta, Figure 11). Ibrutinib is an irreversible inhibitor of BTK and ITK, as well as other kinases, and has been approved for use against leukemia, mantle cell lymphoma, and Waldenstrom macroglobulinaemia. Acalabrutinib is reported to be a selective BTK inhibitor and is currently in phase III clinical studies. As an ITK-sparing molecule, acalabrutinib may provide some clarity on the therapeutic impact of ITK inhibition.

Preclinical data reveal that the combination of ibrutinib with an anti-PD-L1 antibody provides improved benefit compared to either molecule alone.[34] Interestingly, the combination benefit was not only observed in lymphomas, but in solid tumors (breast cancer and colon cancer) where monotherapy treatment of ibrutinib is not effective, thus indicating that the combination may significantly increase the indication reach.

Both BTK inhibitors are being evaluated in clinical studies with checkpoint inhibitors. Ibrutinib is being evaluated together with nivolumab against CLL and NHL, and with durvalumab against lymphoma,[35] while acalabrutinib is under evaluation with pembrolizumab against NSCLC, H&NC, bladder cancer, pancreatic cancer, and ovarian cancer.[36]

4.4. VEGF Inhibitors

Vascular endothelial growth factor (VEGF) is a signal protein that stimulates angiogenesis, that is, the formation of new blood vessels. Cancers that express VEGF are able to grow and metastasize. Not surprisingly, this is a highly sought after drug target.[37] A host of small-molecule VEGF inhibitors have been identified and approved for renal cell cancer and a small subset of other indications: sunitinib (**11**, Sugen/Pfizer), sorafenib (**10**, Bayer), axitinib (**9**, Pfizer), lenvatinib (**12**, Eisai), and pazopanib (**13**, Glaxo SmithKline) (Figure 12).

Inhibitors of VEGF may also find utility in combination with immuno-oncology agents, as antiangiogenic therapies are associated with positive immunological changes because of their ability to normalize aberrant tumor vasculature. Specifically, VEGF inhibitors increase the number of intratumoral effector T-cells and reduce the accumulation of immunosuppressive regulatory T-cells.[38] Not surprisingly, multiple clinical studies are underway that evaluate VEGF inhibitors in combination with either anti-PD-1 or anti-PD-L1 agents. Positive combination benefits have been observed with several of the combination partners in advanced clinical studies.[39]

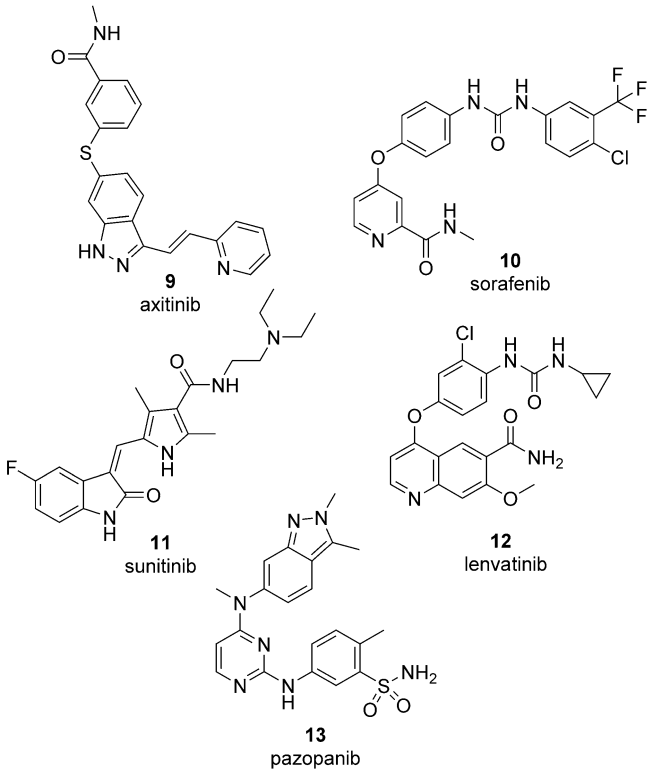


Figure 12. The VEGF inhibitors axitinib (**9**), sorafenib (**10**), sunitinib (**11**), lenvatinib (**12**), and pazopanib (**13**).

4.5. FAK Inhibitors

Focal adhesion kinase (FAK) is overexpressed in many tumors, especially those with a high degree of metastasis. The role of FAK is implicated in cell motility, invasion, and survival. Furthermore, FAK has been shown to be an important regulator of the immunosuppressive tumor microenvironment, which has been shown to limit the clinical benefit of immunotherapy.

Defactinib (**14**, Pfizer) is a well-studied FAK inhibitor (Figure 13). It is currently in clinical evaluation for a number of indications, including mesothelioma. Although defactinib may not have much utility in a monotherapy setting, preclinical studies reveal defactinib to improve immune imbalance in the tumor microenvironment and improve efficacy when combined with checkpoint inhibitors.[40]

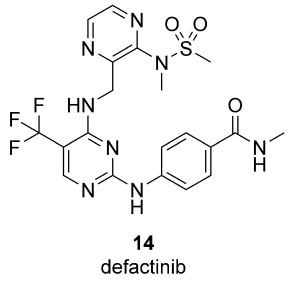


Figure 13. The FAK inhibitor defactinib (**14**).

Defactinib is currently in clinical evaluation with multiple checkpoint inhibitors, including pembrolizumab and avelumab.[41]

4.6. MAPK Pathway—MEK and B-Raf Inhibitors

The kinases MEK and B-Raf are both members of the mitogen-activated protein kinase (MAPK) pathway. As a result of the role of MAPK signaling and its impact on tumorigenesis, the pathway has been heavily evaluated in the search for inhibitors of nodes of the pathway, which may have an impact on tumor growth. Inhibition of the MAPK signaling pathway by MEK inhibition, B-Raf inhibition, or a combination of both has been an effective strategy for the treatment of metastatic tumors bearing BRAF mutations.[42] Several MEK inhibitors have been approved, including trametinib (**15**, GSK) and cobimetinib (**17**, Exelixis/Roche), while binimetinib (**19**, Array) is currently under evaluation in several phase III clinical studies (Figure 14). In addition, multiple B-Raf inhibitors have been approved including, dabrafenib (**16**, GSK) and vemurafenib (**18**, Plexxikon/Roche), while encorafenib (**20**, Novartis/Array) is currently in multiple phase III studies. Furthermore, the combination of a MEK inhibitor and a B-Raf inhibitor has superior efficacy than either agent alone. Indeed, the combination of trametinib with dabrafenib, as well as the combination of cobimetinib with vemurafenib, have been approved for treating BRAF-mutated metastatic melanoma.

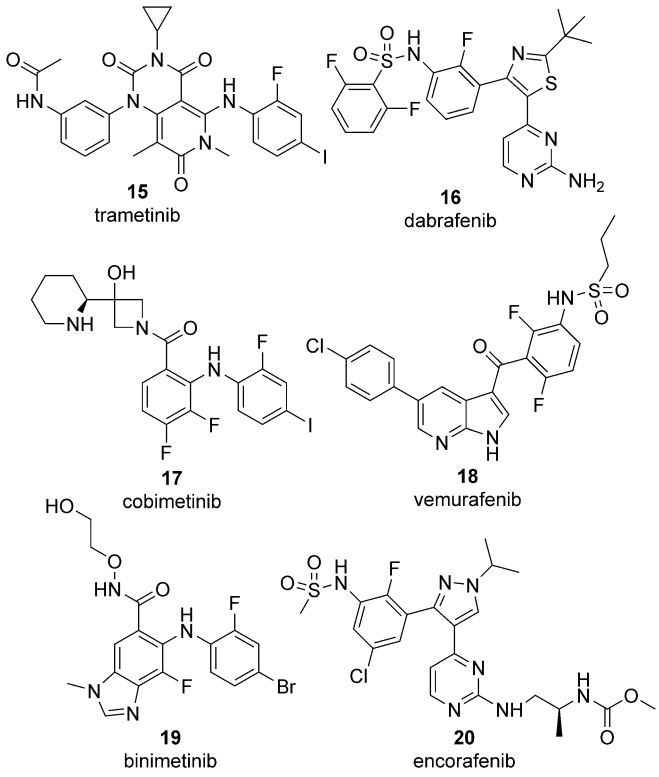


Figure 14. The MEK inhibitors trametinib (**15**), cobimetinib (**17**), and binimetinib (**19**); the B-Raf inhibitors dabrafenib (**16**), vemurafenib (**18**), and encorafenib (**20**).

The MAPK pathway is also involved in T-cell-receptor signaling. Inhibition of the MAPK pathway leads to enhanced T-cell activation. MEK inhibitors potentiate antitumor immunity by inducing expansion of antigen-specific CD8+ T-cells, which leads to an enhanced antitumor effector T-cell response.[43] In vivo preclinical studies reveal a combination benefit with trametinib and an anti-PD-1 agent. Interestingly, the initial administration of the MEK inhibitor alone followed by a combination of the MEK inhibitor and an anti-PD-1 agent was superior to the initial administration of the anti-PD-1 agent. As a result of the positive preclinical outcomes, multiple clinical studies are underway that are evaluating MAPK pathway inhibitors in combination with a checkpoint inhibitor. Initial results of the combination of cobimetinib and atezolizumab reveal that the combination is well-tolerated and active in patients with colorectal cancer.[44] The surprising immune-potentiating effects of MEK inhibitors offer the opportunity to combine them with checkpoint inhibitors and thereby broaden their therapeutic utility towards cancer types beyond melanoma.

5. IDO and A2a Inhibitors

5.1. IDO

The depletion of tryptophan and indoleamine results in immunosuppressive effects in the tumor microenvironment. Indoleamine-2,3-dioxygenase 1 (IDO-1), a porphyrin-containing oxidoreductase, catalyzes the degradation of L-tryptophan to *N*-formylkynurenine and, therefore, controls a major pathway of tryptophan catabolism. As IDO is overexpressed in tumors, the inhibition of IDO so as to restore tryptophan levels could be a principle target in immuno-oncology.[45]

Given the potential clinical impact of this pathway, almost any company active in the immuno-oncology field will try to develop an IDO inhibitor as part of its immuno-oncology portfolio. The recent acquisition of Flexus pharmaceuticals by BMS illustrates the excitement in this area: BMS paid 800 million US$ upfront and 470 million US$ in milestones, mainly to purchase the company's preclinical IDO asset, F001287. BMS-986205 (**24**) is an IDO inhibitor with single-digit nanomolar cellular potency and is in phase I/II clinical trials.[46]

Currently, there are multiple IDO inhibitors in clinical development. Epacadostat (**21**, Incyte) is the most advanced molecule and is in numerous clinical combination trials with anti-PD1 agents such as pembrolizumab and atezolizumab (Figure 15).[47] In 2016, "orphan drug" designation was assigned to the compound in the USA for the treatment of stage IIB–IV melanoma.[48] With 17 clinical trials identifiable in the NIH database, epacadostat is the most investigated small-molecule drug in the immuno-oncology space.[49]

The tricyclic IDO inhibitor navoximod (**23a**, NewLink Genetics) is from a structurally unrelated class of molecules and is in phase I clinical trials.[50] NewLink Genetics is also investigating indoximod (**23b**), which is a direct inhibitor of neither IDO nor TDO at relevant pharmaceutical concentrations. Indoximod is believed to merely inhibit downstream tryptophan catabolism, thereby relieving the autophagic response induced by tryptophan deprivation.[51] A final example of a clinically relevant IDO inhibitor is EOS-200271 (**22**, PF-06840003, Pfizer/iTeos). This agent is in phase I clinical trials for the treatment of patients with grade IV glioblastoma or grade III anaplastic glioma.[52]

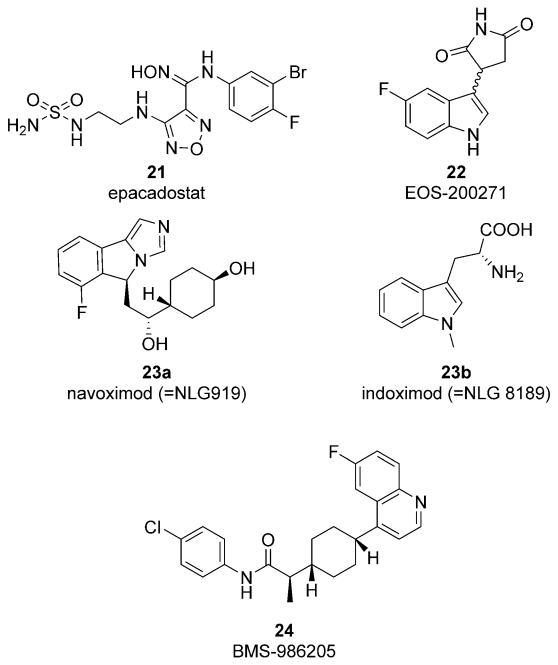


Figure 15. The IDO inhibitors epacadostat (**21**), EOS-200271 (**22**), navoximod (**23a**) and indoximod (**23b**), and BMS-986205 (**24**).

5.2. Adenosine Receptor Inhibitors

Extracellular adenosine reaches micromolar levels in the tumor microenvironment and results in tumor-promoting effects. Adenosine blocks the activation of immune cells and increases the number of regulatory T-cells through activation of the A2a and also the low-affinity A2b adenosine receptor.[53] The A2a receptor has been investigated for many years in the area of Parkinson's disease; however, no clinical asset has reached the market. Meanwhile, high expression levels of both A2a and A2b receptors in the tumor microenvironment have sparked the interest of oncologists and medicinal chemists alike (Figure 16).[54] Although caffeine (**25**) is a weak and unspecific antagonist of all adenosine receptor subtypes, modern agents have significantly different structures and specificities to caffeine.[55] Some companies decided to in-license A2a receptor antagonists such as vipadenant (**27**, Juno/Vernalis) and repurpose them for immuno-oncology.[56] Preladenant (**29**, SCH 420815, MK3814, MSD) has also taken on a second life as a cancer compound after its discontinuation in the treatment of Parkinson's disease. The compound is now in early combination trials with pembrolizumab.[57]

Recent discovery efforts have yielded a new wave of A2a inhibitors. CPI-444 (**28**, Corvus) is an isoform-selective A2a

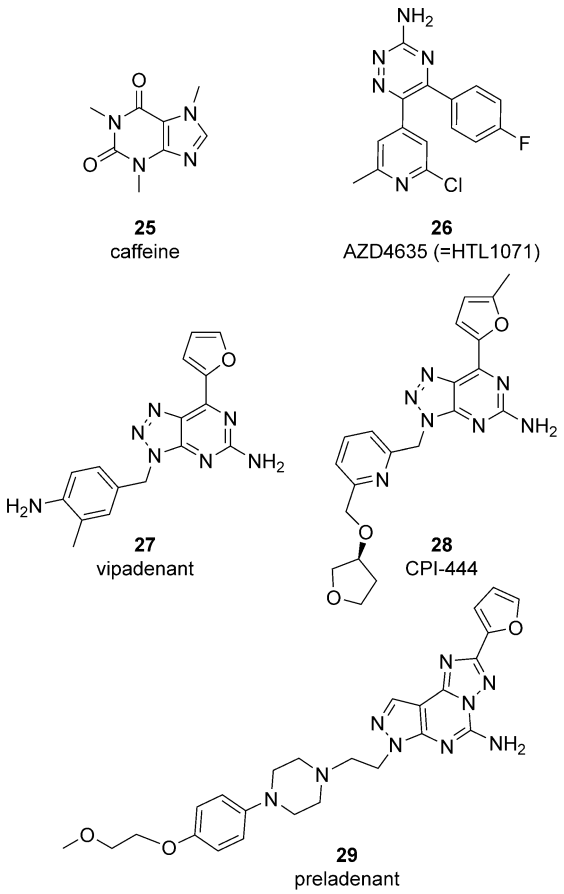


Figure 16. The A2a inhibitors AZD4635 (**26**), vipadenant (**27**), CPI-444 (**28**), preladenant (**29**), and caffeine (**25**).

inhibitor that demonstrates 55-fold selectivity over A1 and 400-fold selectivity against the A2b and A3 receptors. Initial clinical data for CPI-444 have recently been disclosed and reveal that the molecule is well-tolerated at a clinical dose of 100 mg, with clinical activity as a single agent and in combination with atezolizumab in multiple tumor types.[58] PBF 509 (Novartis/Palobiofarma; structure not disclosed)[59] and AZD4635 (**26**, HTL 1071, AstraZeneca/Heptares)[60] are additional A2a antagonists under clinical investigation. AZD4635 is a relatively selective A2a inhibitor with at least 30-fold selectivity to other adenosine receptors. The agent led to tumor regression in syngeneic mouse models. AZD4635 is in clinical trials against solid tumors and is being investigated as a single agent and in combination with the PD-L1 blocker durvalumab.[61]

6. Phoenix from the Ashes: Chemokine Receptor Antagonists

Chemokines are chemotactic cytokines which control the migratory patterns of immune cells. They play a major role in the mediation of acute inflammation as well as in the induction of primary and secondary adaptive immune responses. Moreover, they are involved in the priming of naive T-cells and in regulatory T-cell function.[62] Chemokine receptors can be expressed on immune cells, endothelial cells, as well as tumor cells and belong to the class of G-protein-coupled receptors.[8] So far, about 20 chemokine receptors and 50 ligands have been reported.[8,63] Initially appreciated as essential mediators of immune-cell migration, chemokines are now known to also be involved in non-immune cell processes which are important for tumor growth and progression, such as the induction of proliferation or prevention of apoptosis in cancer cells. Moreover, they can induce the movement of tumor cells, which is necessary for metastasis. Chemokines also affect tumor stromal cells and are involved in the release of growth and angiogenic factors from cells in the tumor microenvironment, thus having an indirect effect on tumor growth.[62b] The inhibition of chemokine receptors can prevent infiltration of macrophages or spread of metastasis and can induce the arrest of tumor growth or apoptosis. However, despite all efforts in the investigation of chemokine inhibitors in cancer research, there is currently no small molecule approved by regulatory agencies for the treatment of cancer. As a consequence of the large number of different chemokine receptors and ligands (CXC, CC, XC, and CX3C subfamilies), the following section will highlight only some selected examples in the context of immune-oncology.

6.1. CXCR2 Inhibitors

The CXC chemokine receptor CXCR2 is upregulated in a variety of different tumor cell types and involved in the proliferation and progression of tumor cells. It is located in the tumor microenvironment and regulates the movement of immune cells. It was recently reported that genetic ablation or inhibition of CXCR2 led to reduced metastasis and decreased tumorigenesis. It was also shown that CXCR2 signaling can promote pancreatic tumorigenesis and plays an essential role in the metastasis of pancreatic cancer, thus rendering CXCR2 a promising cancer target.[64]

Moreover, CXCR2 inhibition is believed to enhance the sensitivity to immunotherapies by preventing the attraction of myeloid-derived suppressor cells (MDSCs) to tumors.[65] AZD5069 (**30**, AstraZeneca),[66] an antagonist of CXCR2, is currently being investigated in phase Ib/II studies in combination with the PD-L1 antibody durvalumab for patients with advanced solid malignancies as well as metastatic pancreatic ductal adenocarcinoma (Figure 17). Currently, there are also plans for a phase I study of the dual CXCR1/2 antagonist SX-682 (**31**, Syntrix Biosystems)[67] in combination with pembrolizumab for the treatment of metastatic melanoma.[68]

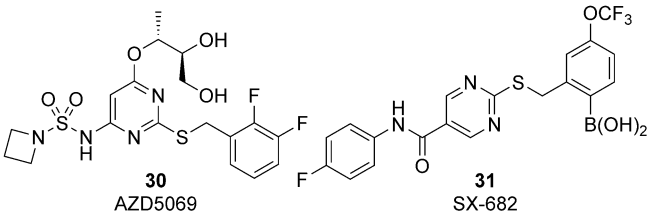


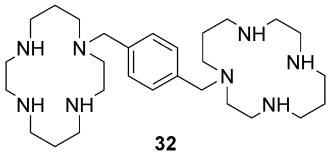
Figure 17. The CXCR2 antagonist AZD5069 (**30**) and dual CXCR1/2 antagonist SX-682 (**31**).

6.2. CXCR4 Inhibitors

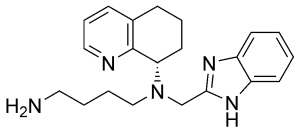
The chemokine receptor CXCR4 is often upregulated in tumor cells and known to be involved in the metastasis of various cancer types. Binding of the corresponding ligand CXCL12 (stromal-derived factor-1, SDF-1), leads to stimulation of cell proliferation and survival processes, thereby promoting tumor growth. The inhibition of CXCR4 diminishes the proliferation and migration of tumor cells overexpressing CXCR4. Moreover, it prevents the recruitment of regulatory T-cells and MDSCs to the tumor.[69]

A plethora of CXCR4 inhibitors have been described;[70] the following will focus on compounds which are clinically the most progressed.

The CXCR4 inhibitor plerixafor (**32**, AMD3100, AnorMED/Genzyme) has already been approved by the FDA for the treatment of non-Hodgkin lymphoma and multiple myeloma (Figure 18). A phase I study for the treatment of chronic lymphocytic leukemia or small lymphocytic lymphoma investigated its possible synergistic effects in combination with rituximab.[71] However, so far, no combination trial with a checkpoint inhibitor has been reported for plerixafor.



32
plerixafor
(AMD3100)



33
X4P-001

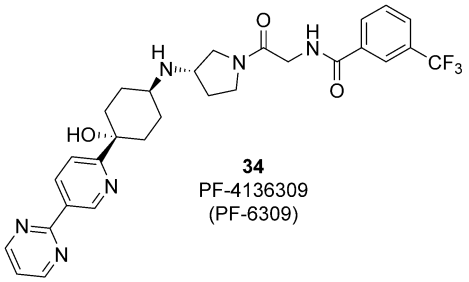
Figure 18. The CXCR4 antagonists plerixafor (**32**) and X4P-001 (**33**).

The orally bioavailable CXCR4 inhibitor X4P-001 (**33**, X4Pharma) has been evaluated in phase I/II studies in different solid tumors. In preclinical cancer models, the compound reduces tumor growth and increases overall survival. Currently, clinical trials are investigating the combination of X4P-001 with nivolumab for the treatment of renal cell carcinoma[72] and with pembrolizumab in patients with advanced melanoma.[73]

Several cyclic peptides are also in clinical evaluation as CXCR4 inhibitors in combination with checkpoint inhibitors. LY2510924 (a small cyclic peptide containing non-natural amino acids, Eli Lilly) is in a phase I clinical trial in combination with durvalumab in patients with solid tumors.[74] BL-8040 (a disulfide-bridged cyclic peptide containing non-natural amino acids, BKT140, BioLineRx), is another cyclic peptide CXCR4 inhibitor that is currently under evaluation in numerous clinical combination trials with pembrolizumab for treatment of pancreatic and gastrointestinal cancers[75] as well as with atezolizumab for treatment of acute myeloid leukemia.[76]

6.3. CCR2

The chemokine receptor CCR2 is mainly expressed on monocytes. The binding of the corresponding ligand CCL2 induces chemotaxis, which results in directed migration of monocytes and macrophages to tumor sites.[77] The CCL2-CCR2 axis is important for the recruitment of tumor-associated macrophages in pancreatic ductal adenocarcinoma and leads to an immunosuppressive tumor microenvironment. Further preclinical models also demonstrated that blockade of CCR2 can lead to recovery of antitumor immunity.[78] The orally bioavailable CCR2 inhibitor PF-4136309 (**34**, Pfizer, Figure 19) was investigated in a phase I



34
PF-4136309
(PF-6309)

Figure 19. The CCR2 antagonist PF-416309 (**34**).

study in combination with the FOLFIRINOX chemotherapy regimen in patients with borderline resectable and locally advanced pancreatic adenocarcinoma. The compound was reported to be safe, and an improvement in tumor response could be observed.[78,79] PF-413609 is also being tested in a phase Ib/II study in combination with Gemcitabine and Nab-Paclitaxel in first-line metastatic pancreatic patients.[80] Moreover, the CCR2 inhibitor CCX-872 (structure not disclosed, ChemoCentryx), has been studied in a phase I clinical trial in combination with FOLFIRINOX in patients with advanced nonresectable pancreatic cancer.[81] A further phase II study of CCX-872 in combination with an undisclosed checkpoint inhibitor for pancreatic cancer and pancreatic neoplasms is planned to be initiated in 2017.[82]

6.4. CCR5

The chemokine receptor CCR5 is expressed by metastatic tumor cells, lymphocytes, and macrophages. The corresponding ligand CCL5 is produced by T-cells at the invasive margin and induces tumor-promoting effects. Inhibition of CCR5 is hypothesized to repolarize tumor-associated macrophages and promote antitumor immunity.[83]

The CCR5-selective inhibitor maraviroc (**35**, Pfizer), which has already been approved by the FDA for the treatment of HIV, showed promising results in a phase I

study (MARACON) for the treatment of advanced colorectal cancer with hepatic liver metastases (Figure 20). CCR5 blockade led to clinical responses in colorectal cancer patients, with regression of metastases and changes in the tumor microenvironment without significant side effects.[83,84]

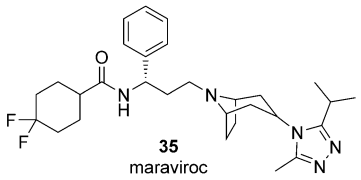


Figure 20. The CCR5 antagonist maraviroc (**35**).

Moreover, a phase I/II study of a dual CCR2/5 antagonist BMS-813160 (structure not disclosed, BMS)[85] in combination with nivolumab for patients with advanced solid tumors is envisaged to start in 2017.[86]

7. Epigenetic Modulators

Epigenetic silencing is a frequent event during the initiation and progression of cancer. Cancers carry mutations in genes encoding proteins that epigenetically regulate gene expression by modifying DNA and histones.[87] The balance between histone acetylation (HAC) and histone deacetylation (HDAC) is usually well-regulated, but an imbalance is frequently observed in tumors.[88] HDAC inhibitors play an important role in epigenetic regulation, inducing apoptosis, cell-cycle arrest, and cell death. The use of HDAC inhibitors as a therapeutic tool in oncology has been validated, with approval being granted to vorinostat (**36,** MK0683, Columbia University/MSD) for the treatment of cutaneous T-cell lymphoma, as well as of chidamide (**39**, Chenzen Chipscreen) being given approval in China for treatment of peripheral T-cell lymphoma. Additional clinical studies of other HDAC inhibitors, including, entinostat (**37**, Syndax) and mocetinostat (**38**, Mirati), are currently ongoing (Figure 21).

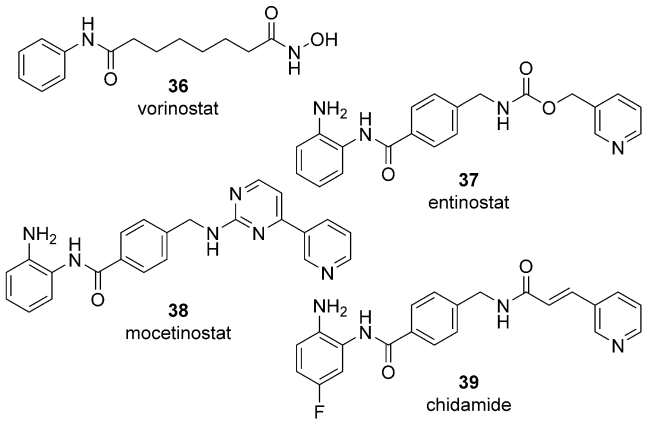


Figure 21. The HDAC inhibitors vorinostat (**36**), entinostat (**37**), mocetinostat (**38**), and chidamide (**39**).

HDAC inhibitors influence the immunogenicity of tumors by upregulating the expression of NK cell activating ligands, MHC class I and class II molecules, and proinflammatory cytokines.[89] In preclinical models, treatment with entinostat led to a decrease in the number of regulatory T-cells and suppression of MDSCs.[90] Combination with immune checkpoint blockade is expected to suppress evasion of the tumor immune system even further and activate the adaptive antitumor immune response. According to this rationale, multiple HDAC inhibitors are now in clinical evaluation with checkpoint inhibitors (Table 2).

8. TLR Modulators and STING Agonists

The activation of the innate immune system can counteract tumor-induced immunosuppression and potentially has a synergistic effect with existing cancer therapies. Toll-like receptors (TLRs) and stimulator of interferon genes (STING) are therefore promising innate immune targets in cancer immunotherapy.[91]

8.1. TLR Modulators

Toll-like receptors (TLRs) are type I transmembrane proteins and have a variety of members (TLR 1–13).[92] TLRs are expressed in antigen-presenting cells such as macrophages, B-cells, monocytes, neutrophils, or dendritic cells, but can also be found on tissues which are exposed to the external environment, such as, for example, lungs or the gastrointestinal tract.[93] As a consequence of their ability to elicit tumor-specific T-cell responses, TLR agonists are currently investigated in clinical settings.[94]

The majority of clinical trials are based on the use of TLR agonists as vaccine adjuvants or as a monotherapy, mainly investigating endosomal TLRs which bind nucleic acids such as TLR3, 7, 8, or 9. Whereas the structures of TLR3 and TLR9 agonists are mainly based on oligonucleotides, TLR7 and TLR8 can be activated by using small molecules as agonists.[95] The antitumor activity of TLR7 and TLR8 agonists is mainly based on the activation of dendritic cells and natural killer cells as well as the suppression of regulatory T-cells.[94a,c,96] TLR agonists could be applied in combination therapies with checkpoint inhibitors to trigger a synergistic effect, alternatively they could be used as therapeutic cancer vaccine adjuvants to activate dendritic cells.

The TLR7 agonist imiquimod (**40**, Aldara, Graceway Pharmaceuticals) is a small-molecule agonist based on an imidazoquinoline scaffold (Figure 22), and has been approved as a topical treatment of basal cell carcinoma.[97] Recently, the compound also showed promising results in a phase II study for the treatment of bladder cancer.[98] A structurally similar analogue, resiquimod (**41**), is a dual TLR7 and TLR8 agonist. The compound has been well-tolerated as a topical treatment of actinic keratosis and proved to be even more effective than imiquimod.[97c] Moreover, it showed promising results in the topical treatment of early stage cutaneous T-cell lymphoma.[99] The TLR7 agonist 852A (**42**)[100] and the TLR8

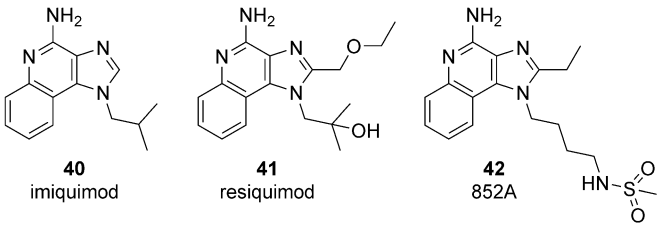


Figure 22. Imidazoquinoline-based TLR agonists.

agonist VTX-2337 (**43**; Figure 23)[101] are reported to be suitable for systemic administration, and have been investigated as single agents for the treatment of solid and hematological malignancies. The dual TLR7/8 agonist MEDI9197 (**44**, MedImmune/LLC) is currently being investigated in a phase I study as a single agent and in combination with durvalumab for treatment of solid tumors and cutaneous T-cell lymphoma (CTCL).[102]

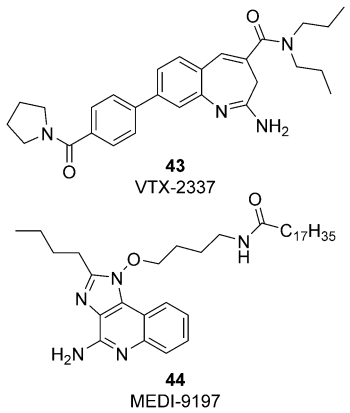


Figure 23. The TLR8 agonist VTX-2337 (**43**) and TLR7/8 agonist MEDI-9197 (**44**).

It is important to mention recent studies which have shown that TLR-induced immunity could also promote, rather than inhibit, carcinogenesis.[103] Moreover, it has been reported that chronic low-grade stimulation of TLRs can prevent tumor apoptosis through the activation of the NF-κB pathway.[96,104] This can lead to regulatory T-cell stimulation and impaired effector T-cells.[8] Additionally, several TLRs can also be expressed on specific tumor cells and thereby promote tumor survival.[94a,105] Thus, it is important to get a more detailed understanding of TLR-mediated biology in various cell types to avoid tumor-promoting effects.

8.2. STING Modulators

Stimulator of interferon genes (STING) is expressed in the endoplasmic reticulum and plays an essential role in innate immunity. It is expressed in various epithelial and endothelial cells as well as in haematopoietic cells, including T-cells, dendritic cells, and macrophages.[106] Activation of the STING signaling pathway leads to the expression of various interferons, cytokines, and T-cell recruitment factors (Figure 24).[8,107] The STING signaling pathway can be activated through the binding of small molecules such as cyclic dinucleotides (CDNs, Figure 25).[108] Whereas cyclic di-GMP (**45**) is produced by bacteria, cGAMP (**46**) is generated by an endogenous cyclic GMP-AMP synthase (cGAS). The binding of cGAMP to the STING receptor induces interferon-β expression.[8c,109]

The structurally unrelated STING activator vadimezan (**47**, University of Auckland/Novartis) showed an immune-mediated antitumor response in mice.[110] Although active in mice, the compound was found to bind to the human STING without activation and failed in a phase III clinical trial in combination with chemotherapy for the treatment of NSCLC.[111]

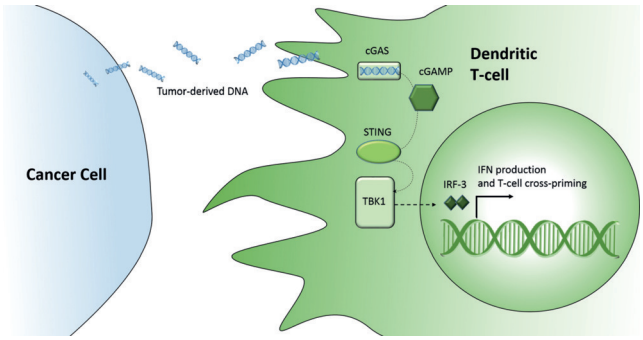


Figure 24. A dendritic cell detects tumor-derived DNA, which often stems from cancer cells undergoing necrosis. After binding to cyclic GMP AMP synthase (cGAS), cGAMP is produced which activates STING, thereby resulting in increased interferon production and T-cell-priming events in the lymph node. Researchers are trying to identify synthetic STING agonists to activate this pathway.

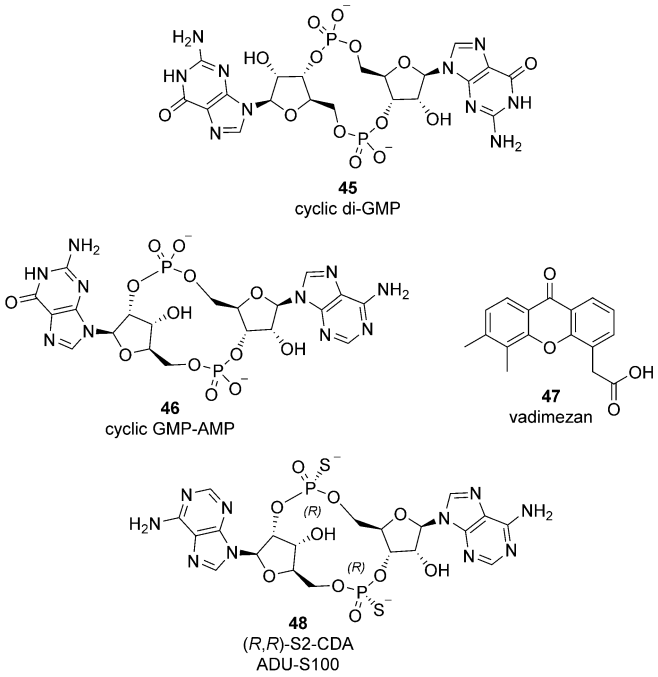


Figure 25. Small-molecule STING agonists.

Recent synthetic CDN derivatives feature a chiral phosphothioate group and show increased stability in vivo as well as enhanced activity for the human STING receptor.[108,112] Interestingly, the *R*,*R* derivative **48** showed resistance to phosphodiesterase degradation, thereby leading to an increased level of interferon-β in murine DC2.4 cells, whereas the *R*,*S* analogue was comparable to the parent CDN. Currently, the safety and efficacy of **48** ((*R*,*R*)-S2-CDA, ADU-S100, MIW815; Aduro BioTech/Novartis) is being investigated in a phase I clinical trial against advanced/metastatic solid tumors and lymphomas, administered through intratumoral injection.[113] Another study investigates the combination of ADU-S100 with the anti-PD-1 antibody PDR001.[114] The cyclic dinucleotide MK-1454 (structure undisclosed) is also being evaluated in a phase I clinical trial alone and in combination with pembrolizumab.[115]

Despite the recent success in the development of STING agonists in antitumor therapy, an intratumoral injection is necessary to activate the STING receptor efficiently, which may have an impact on the clinical development of this class of molecules. It is desirable to identify safe and systemically available STING agonists to treat tumors that are inaccessible through direct injection. Despite vadimezan's failure, it is encouraging to see that drug-like, non-nucleotide molecules such as vadimezan exist and work in mice. This bodes well for the development of future oral clinical agents with full agonistic properties.

9. Conclusion

Rather than influencing the biology of the cancer cell, immuno-oncology is aimed at harnessing the power of immune cells. The immune system has traditionally been a rich source of targets for small-molecule intervention. However, most immune-checkpoint signals involve protein–protein interactions, and finding small-molecule inhibitors with the classical armamentarium of methods has proven challenging. In many cases, medicinal chemists have reverted to stabilized peptides or nucleic acids to achieve therapeutic effects. Another pragmatic solution includes focusing on more druggable targets from the outset, such as enzymes, kinases, and GPCRs.

As the tumor microenvironment contains a whole variety of cells, the preclinical characterization of immuno-oncology agents often involves the investigation of cellular co-cultures and the elucidation of combination effects. This can be demanding given the high number of experimental parameters as well as the sensitive nature of these complex systems. In vivo, special models using immune-competent animals are required, involving transplantable, carcinogen-induced, or genetically engineered malignancies. The importance of parameters such as the effect of the ambient housing temperature of the animal on tumor growth and immune control is just one example that illustrates the high level of complexity inherent to these models.[116,117]

As a modality, small molecules have ideal, proven features for cancer therapy, such as cell-membrane penetration and oral bioavailability, thus positioning them uniquely as a compound class for the next generation of immuno-oncology treatments. Small-molecule clinical trial results will be paramount in shaping the promise of this modality in the field of immuno-oncology. Of equal importance is the identification of novel immuno-oncology-relevant targets that can be accessed through small-molecule inhibition.

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Conflict of interest

The authors declare no conflict of interest.

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