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Review

Immunomodulation by targeted anticancer agents

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SUMMARY

At odds with conventional chemotherapeutics, targeted anticancer agents are designed to inhibit precise molecular alterations that support oncogenesis or tumor progression. Despite such an elevated degree of molecular specificity, many clinically employed and experimental targeted anticancer agents also mediate immunostimulatory or immunosuppressive effects that (at least in some settings) influence therapeutic efficacy. Here, we discuss the main immunomodulatory effects of targeted anticancer agents and explore potential avenues to harness them in support of superior clinical efficacy.

INTRODUCTION

Conventional chemotherapy most often operates by damaging DNA or the mitotic apparatus, hence exhibiting at least some degree of selectivity for highly proliferating cancer cells. However, normal tissues with an elevated mitotic index (e.g., the bone marrow, hair follicles, intestinal crypts) are also sensitive to the cytotoxic effects of chemotherapy, which explains at least some of its common side effects (e.g., anemia, myelosuppression, alopecia, diarrhea) (Schirrmacher, 2019). In the late 1980s, the advent of modern molecular biology spurred a vigorous line of research aimed at the identification of molecular defects that are restricted to cancer cells, *de facto* paving the way to the development of therapeutic agents with superior specificity and (at least in principle) limited side effects (Bedard et al., 2020). The pioneer of such a new class of cancer therapeutics, imatinib, was originally approved for the treatment of patients with chronic myeloid leukemia (CML) bearing the so-called Philadelphia (Ph) chromosome in May 2001, and literally revolutionized the clinical management of the disease (Druker et al., 2001). Imatinib was rationally designed to target the oncogenic tyrosine kinase expressed by Ph^+ CML cells as a consequence of the reciprocal translocation between the long arms of chromosomes 9 and 22, which generates an in-frame juxtaposition between BCR activator of RhoGEF and GTPase (*BCR*) and ABL proto-oncogene 1, non-receptor tyrosine kinase (*ABL1*) (Druker et al., 1996).

Since only Ph^+ CML cells express the BCR-ABL1 chimera, imatinib was expected to exhibit exquisite molecular specificity. Over the years, however, it became clear that, at clinically relevant concentrations, imatinib also inhibits oncogenic tyrosine kinases other than BCR-ABL1, including KIT proto-oncogene, receptor tyrosine kinase (KIT), platelet-derived growth factor receptor alpha (PDGFRA), and platelet-derived growth factor receptor beta (PDGFRB). Consistent with this notion, imatinib has been licensed for use in patients with KIT-, PDGFRA-, or PDGFRB-associated malignancies, including (but not limited to) gastrointestinal tumors (GISTs) and some myeloproliferative neoplasms (Carlisle et al., 2020). In addition, an unexpected link between the clinical activity of imatinib and immune functions emerged (Zitvogel et al., 2016), suggesting that the actual mechanism of action of the drug may be more convoluted than initially thought.

A large amount of preclinical and clinical data indicates that imatinib and virtually all other targeted anticancer agents developed over the past three decades indeed exert

Box 1. ICD in cancer therapy

The term immunogenic cell death (ICD) refers to a specific variant of regulated cell death (RCD) that is able (in the context of an immunocompetent syngeneic host) to elicit adaptive T-cell immunity against dead cell-associated antigens (Galluzzi et al., 2020b). There are three major determinants for RCD to be productively perceived as immunogenic and initiate adaptive immune responses. First, dying cells must express antigens that are not fully covered by thymic tolerance, implying that T-cell clones potentially recognizing such antigens have not been deleted by the circulating T-cell repertoire. Second, cell death must be accompanied by the emission of adjuvant-like signals that promote the recruitment and activation of antigen-presenting cells (APCs). Third, microenvironmental conditions at sites of ongoing RCD must be permissive for APC recruitment, activation, and migration to lymph nodes or tertiary lymphoid structures for $CD8^+$ T-cell cross-priming (Galluzzi et al., 2020b). Importantly, a variety of clinically relevant anticancer interventions including conventional chemotherapeutics (Galluzzi et al., 2020a), radiation therapy (RT) (Rodriguez-Ruiz et al., 2020), and targeted anticancer agents (see main text) have been shown to elicit *bona fide* ICD and hence jumpstart the cancer-immunity cycle (Chen and Mellman, 2017) in preclinical tumor models.

Although mechanistically linking ICD with superior therapeutic responses in cancer patients remains challenging, abundant correlative data support the contention that anticancer immunity downstream of ICD is associated with improved disease outcome in a variety of oncological settings. For example, loss-of-function polymorphisms in various genes encoding immune receptors involved in the recognition of ICD-associated adjuvant-like molecules have been linked with poor disease outcome in cohorts of breast cancer patients receiving ICD-inducing anthracycline-based chemotherapy (Fucikova et al., 2015). Conversely, the ability of malignant cells to proficiently expose the endoplasmic reticulum (ER) protein calreticulin (CALR) on their surface as an adjuvant-like signal has been associated with superior disease outcome in patients with acute myeloid leukemia (Truxova et al., 2020) and ovarian carcinoma (Kasikova et al., 2019). Moreover, the expansion of a T-cell clone specific for a tumor neoantigen upregulated by radiation has been documented in the blood of a patient with non-small cell lung carcinoma experiencing a complete response to RT plus the cytotoxic T lymphocyte-associated protein 4 (CTLA4) blocker ipilimumab (Formenti et al., 2018b). Thus, ICD stands out as a prominent goal for cancer therapy, especially in the context of combinatorial treatment regimens harnessing ICD-driven anticancer immune responses with immune checkpoint inhibitors (ICIs, see Box 2) or other forms of immunotherapy.

immunostimulatory or immunosuppressive effects that can (positively or negatively) influence therapeutic efficacy. This is quite intriguing considering that the preclinical development of targeted anticancer therapy has largely (if not exclusively) hinged on human cancer cell lines maintained *in vitro* or xenografted into highly immunodeficient hosts. Moreover, it is surprising to note that most targeted anticancer agents currently approved for use in patients mediate (at least some degree of) therapeutically relevant immunostimulation, suggesting that clinical development has positively selected for molecules that support, rather than restrain, anticancer immunity (Galluzzi et al., 2015).

The immunomodulatory activity of targeted anticancer agents can originate from the interaction of the drug with cancer cells, as well as from the ability of the drug to interact with, and alter the function of, immune cells (Galluzzi et al., 2015). Both these general mechanisms of immunomodulation by targeted anticancer therapy can involve direct (i.e., an increase in a specific effect) or indirect (i.e., a decrease in an antagonistic effect) pathways. As an example, targeted anticancer agents can mediate net immunostimulatory effects by promoting the secretion of pro-inflammatory cytokines, or by limiting the release or activity of immunosuppressive factors. Finally, immunomodulation by targeted anticancer therapy can (but does not necessarily) hinge on the demise of malignant or immune cells. Thus, targeted anticancer agents can trigger a highly immunogenic variant of cancer cell death to jumpstart the so-called cancer-immunity cycle (Galluzzi et al., 2017b) (Box 1) or selectively promote the depletion of immunosuppressive cells that would otherwise favor disease progression, such as regulatory T (T_{REG}) cells (Galluzzi et al., 2018) (Figure 1).

Irrespective of these conceptual distinctions, the capacity of targeted anticancer agents to mediate immunomodulatory effects provides a strong rationale to develop combinatorial regimens involving immunotherapy. Here, we discuss recent mechanistic progress on the main immunomodulatory effects of US Food and Drug Administration (FDA)-approved and experimental targeted anticancer agents as we identify potential avenues to combine such agents with immunotherapy toward superior clinical efficacy. Although endocrine therapy technically constitutes a variant of targeted therapy, its immunomodulatory effects are not discussed in the current review.

CYCLIN-DEPENDENT KINASE INHIBITORS

Cyclin-dependent kinases (CDKs) are a family of serine/threonine kinases that regulate cell cycle progression and other cellular processes, including DNA repair, transcription, and metabolism (Hydbring et al., 2016). As deregulated CDK activity has emerged as a driver of uncontrolled proliferation in a variety of human neoplasms (Shan et al., 2020), CDKs have attracted considerable attention as potential targets for the development of novel anticancer therapeutics, recently culminating in the approval of three distinct CDK4/CDK6 inhibitors for use in patients with hormone receptor $(HR)^+$ breast cancer (Buque et al., 2020; Spring et al., 2020). Accumulating evidence suggests that CDK4/CDK6 inhibitors, as well as inhibitors of other CDKs, do not only arrest the proliferation of malignant cells, they also mediate multipronged immunomodulatory effects (Klein et al., 2018; Petroni et al., 2020) (Table 1).

In various preclinical tumor models, CDK4/CDK6 inhibition with abemaciclib mediates immunostimulatory effects by promoting the exposure of MHC class I molecules on the cancer cell surface (Goel et al., 2017; Schaer et al., 2018). Consistent with this notion, the transcriptional profile of HR^+HER2^-

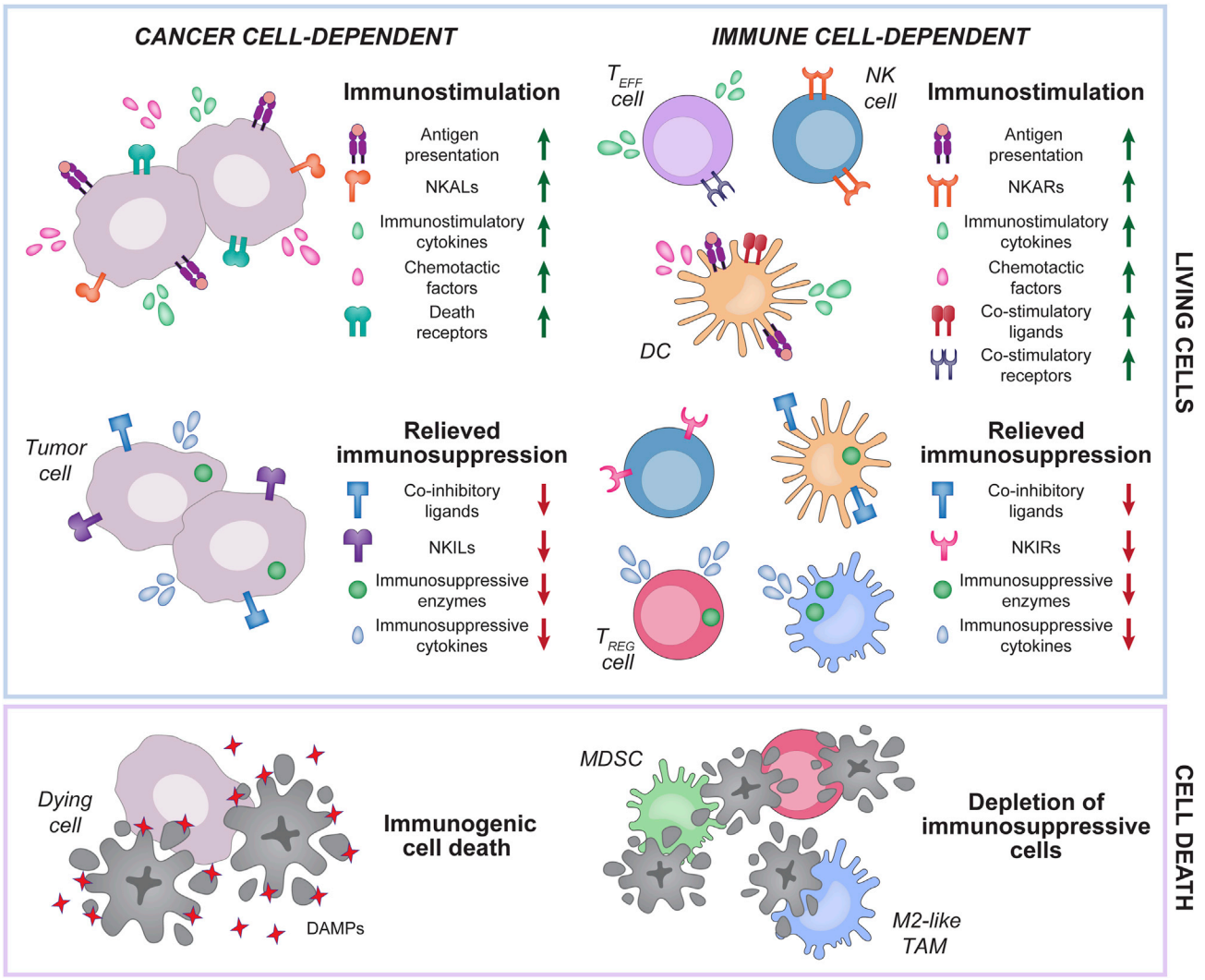

Figure 1. Principles of Immunostimulation by Targeted Anticancer Agents

Targeted anticancer agents can mediate immunostimulatory effects by interacting with malignant cells or immune cells. In both cases, the net effect can result from the enhancement of an immunostimulatory function or from the inhibition of an immunosuppressive function. Moreover, immunostimulation by targeted anticancer therapy can involve the demise of malignant or immune cells. Indeed, both the immunogenic death of malignant cells and the demise of immunosuppressive cells such as regulatory T (T_{REG}) cells and myeloid-derived suppressor cells (MDSCs) have net immunostimulatory effects. *Mutatis mutandis*, these general principles also apply to immunosuppression by targeted anticancer agents (not shown). DAMP, damage-associated molecular pattern; DC, dendritic cell; NK, natural killer; NKAL, NK-cell activating ligand; NKAR, NK-cell activating receptor; NKIL, NK-cell inhibitory ligand; NKIR, NK-cell inhibitory receptor; TAM, tumor-associated macrophage; T_{EFF}, effector T.

breast cancer biopsies from women treated with abemaciclib plus endocrine therapy exhibits signatures of antigen presentation and T-cell activation (Hurvitz et al., 2020). Along similar lines, the MHC class I peptidome of human melanoma cells exposed to the CDK4/CDK6 inhibitor palbociclib is enriched for tumor-associated antigens (TAAs) and peptides from E2F target proteins that are directly implicated in cell cycle blockage (Stopfer et al., 2020). Besides improving the antigenicity of malignant cells (i.e., their visibility to immune cells), CDK4/CDK6 inhibitors mediate immunostimulatory effects by favoring the secretion of pro-inflammatory cytokines such as type III interferon (Goel et al., 2017) and CC-chemokine ligand 5 (CCL5) (Vilgelm et al., 2016). This occurs either upon the derepression of endogenous retroviruses and consequent nucleic acid sensing (Goel et al., 2017; Vanpouille-Box et al., 2019) or following the establishment of a permanent cell cycle blockage (i.e., cellular senescence) characterized by an abundant secretory component, the so-called senescence-associated secretory phenotype (SASP) (Jerby-Arnon et al., 2018). Finally, various CDK4/CDK6 inhibitors have been shown to mediate a variety of immunostimulatory effects by directly interacting with immune cells (Petroni et al., 2020). Such effects include (1) activation of effector T (T_{EFF}) cells upon nuclear factor of activated T cells 1 (NFATC1, best known as NFAT) signaling and interleukin-2 (IL2) secretion (Deng et al., 2018), and (2) inhibition of immunosuppressive T_{REG} cells through

Table 1. Immunomodulation by CDK inhibitors.

Target(s)	Agent(s)	Approved[a]	Cancer-Cell Dependent	Immune-Cell Dependent	Effect(s)	Notes	References
CDK4 CDK6	abemaciclib	yes	immunostimulation		improved antigen presentation by cancer cells	MHC class I and B2M upregulation in different BC and CRC models, including PDXs and $HER2^+$ transgenic models, linked to improved sensitivity to ICIs *in vivo* enhanced antigen presentation signatures in tissue specimens from $HR^+/HER2^-$ BC patients treated with abemaciclib plus an AI	Goel et al., 2017 Hurvitz et al., 2020 Schaer et al., 2018
CDK4 CDK6	abemaciclib	yes	immunostimulation		pro-inflammatory cytokine secretion by cancer cells	secretion of type III IFN upon de-repression of endogenous retroviral elements and independent of senescence in BC cells, linked to improved sensitivity to ICIs *in vivo*	Goel et al., 2017
CDK4 CDK6	abemaciclib	yes	immunostimulation		induction of senescence and secretion of SASP factors in cancer cells	upregulated SASP signatures in melanoma tumors from the TGCA, linked to improved sensitivity of mouse melanomas to ICIs	Jerby-Arnon et al., 2018
CDK4 CDK6	abemaciclib	yes		relieved immunosuppression	depletion of T_{REG} cells	reduced number of T_{REG} cells in murine CRC and BC tumors, linked to improved sensitivity to ICIs *in vivo*	Goel et al., 2017
CDK4 CDK6	palbociclib	yes	immunostimulation		improved antigen presentation by cancer cells	expression of TAAs and peptides from cell cycle regulatory proteins, linked to improved sensitivity of mouse melanomas to ICIs upregulated expression of MHC class I molecules in BC cells, potentiated by pharmacological inhibition of ER and BCL2, or cotreatment with an anti-HER2 mAb	Stopfer et al., 2020 Wang et al., 2019a Whittle et al., 2020
CDK4 CDK6	palbociclib	yes	immunostimulation		pro-inflammatory cytokine secretion by cancer cells	increased CCL5 expression in mouse melanoma cells and melanomas PDXs	Vilgelm et al., 2016
CDK4 CDK6	palbociclib	yes	immunostimulation		induction of senescence and secretion of SASP factors in cancer cells	induction of SASP signatures in *KRAS*-driven tumors, only in combination with the MEK inhibitor trametinib, linked to improved sensitivity to ICIs *in vivo*	Ruscetti et al., 2018 Ruscetti et al., 2020
CDK4 CDK6	palbociclib	yes	immunosuppression		upregulation of immunosuppressive factors in cancer cells	PD-L1 upregulation, linked to improved sensitivity to ICIs *in vivo* and potentiated by pharmacological inhibition of ER and BCL2	Jin et al., 2019b Whittle et al., 2020 Zhang et al., 2018a

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Table 1. ***Continued***

Target(s)	Agent(s)	Approved[a]	Cancer-Cell Dependent	Immune-Cell Dependent	Effect(s)	Notes	References
CDK4 CDK6	palbociclib trilaciclib	yes		immunostimulation	activation of T_{EFF} cells	increased T-cell activation and IL2 secretion via derepression of NFAT signaling, correlating with T-cell infiltration in lung tumors and improved sensitivity to ICIs	Deng et al., 2018
CDK4 CDK6	palbociclib	yes		relieved immunosuppression	depletion of T_{REG} cells	reduced number of T_{REG} cells in the spleen and lymph nodes of tumor-free mice	Goel et al., 2017
CDK4 CDK6	ribociclib	yes	immunostimulation		improved antigen presentation by cancer cells	MHC class I upregulation in BC cells, potentiated by PI3K inhibition, linked to improved sensitivity to ICIs *in vivo*	Teo et al., 2017
CDK4 CDK6	ribociclib	yes	immunosuppression		upregulation of immunosuppressive factors in cancer cells	PD-L1 upregulation in BC cells, limited by pharmacological PI3K inhibition	Teo et al., 2017
CDK7	THZ1	no	relieved immunosuppression		downregulation of immunosuppressive factors in cancer cells	PD-L1 downregulation in NSCLC, linked to improved sensitivity to ICIs *in vivo*	Wang et al., 2020b
CDK7	YKL-5-124	no	immunostimulation		T_H1 cytokine secretion by cancer cells	secretion of CXCL9 and CXCL10 upon DNA damage and micronucleation in SCLC, linked to improved sensitivity to ICIs *in vivo*	Zhang et al., 2020a
Various CDKs	dinaciclib	no	immunostimulation		ICD induction	DAMP emission by CRC cells, linked to improved sensitivity to ICIs *in vivo*	Hossain et al., 2018
Various CDKs	dinaciclib	no	immunosuppression		upregulation of immunosuppressive factors in cancer cells	PD-L1 upregulation in CRC cells, linked to improved sensitivity to ICIs *in vivo*	Hossain et al., 2018
Various CDKs	dinaciclib	no	relieved immunosuppression		downregulation of immunosuppressive factors in cancer cells	IDO1 and PD-L1 downregulation in PDACs, especially in the context of immunochemotherapy with IFNG	Huang et al., 2020b

AI, aromatase inhibitor; BC, breast cancer; CRC, colorectal carcinoma; DAMP, damage-associated molecular pattern; ER, estrogen receptor; HR, hormone receptor; ICD, immunogenic cell death; ICI, immune checkpoint inhibitor; mAb, monoclonal antibody; NSCLC, non-small cell lung carcinoma; PDAC, pancreatic ductal adenocarcinoma; PDX, patient-derived xenograft; SASP, senescence-associated secretory phenotype; SCLC, small cell lung carcinoma; T_{EFF}, effector T, T_{REG}, regulatory T; TAA, tumor-associated antigen; TGCA, The Cancer Genome Atlas.

[a]By the FDA for use in cancer patients.

the repression of DNA methyltransferase 1 (DNMT1) and consequent cell cycle blockage via CDK inhibitor 1A (CDKN1A, best known as $p21^{CIP1}$) (Deng et al., 2018; Goel et al., 2017; Schaer et al., 2018).

At least in part, the immunostimulatory activity of CDK4/CDK6 inhibitors is offset by their ability to upregulate the immunosuppressive molecule CD274 (best known as programmed death-ligand 1 [PD-L1]) via transcriptional and post-translational mechanisms (Jin et al., 2019b; Zhang et al., 2018a). Thus, immune checkpoint inhibitors (ICIs) targeting PD-L1 or its receptor programmed cell death 1 (PDCD1, best known as PD-1) stand out as promising combinatorial partners for CDK4/CDK6 inhibitors, as demonstrated by an abundant preclinical literature (Deng et al., 2018; Goel et al., 2017; Jerby-Arnon et al., 2018; Long et al., 2020; Schaer et al., 2018; Zhang et al., 2018a). Moreover, CDK4/CDK6 inhibitors have been successfully combined with other targeted anticancer agents to achieve improved immunostimulation and superior efficacy. For instance, in preclinical models of KRAS proto-oncogene, GTPase (KRAS)-driven lung and pancreatic adenocarcinoma, the mitogen-activated protein kinase kinase 1 (MAP2K1, best known as MEK1) and MEK2 inhibitor trametinib synergizes with palbociclib at inducing a SASP-dependent vascular response that enables tumor infiltration by immune effector cells (Knudsen et al., 2020; Ruscetti et al., 2018, 2020). This results in improved disease control (in the lung model, where infiltration is dominated by natural killer [NK] cells) or restored sensitivity to ICIs (in the pancreatic model, where infiltration is dominated by exhausted $CD8^+$ cytotoxic T lymphocytes [CTLs]) (Knudsen et al., 2020; Ruscetti et al., 2018, 2020). Moreover, both phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha (PIK3CA, best known as PI3Kα) and BCL2 apoptosis regulator (BCL2) blockers boost the ability of CDK4/CDK6 inhibitors to promote antigen presentation (as well as PD-L1 expression) in models of breast cancer (Teo et al., 2017; Whittle et al., 2020), correlating with (1) superior disease control *in vivo*, along with the systemic depletion of immunosuppressive cells including T_{REG} cells and myeloid-derived suppressor cells (MDSCs), as well as (2) added therapeutic benefits from ICIs (Teo et al., 2017; Whittle et al., 2020). Similar results have been obtained by combining palbociclib with a monoclonal antibody (mAb) specific for erb-b2 receptor tyrosine kinase 2 (ERBB2, best known as HER2) in a transgenic model of $HER2^+$ breast cancer ($MMTV\text{-}neu202^{Mul}$ mice) (Wang et al., 2019a). In this latter setting, however, ICIs fail to improve the efficacy of targeted anticancer agents, unless combined with the multitargeted tyrosine kinase inhibitor (TKI) cabozantinib, resulting in the establishment of a tumor microenvironment (TME) dominated by immune effector cells (rather than MDSCs) (Wang et al., 2019a).

CDKs other than CDK4 and CDK6 can also be actioned to achieve therapeutically relevant immunostimulation. Although a selective pharmacological inhibitor is still missing, deletion of *Cdk8* in NK cells results in superior effector functions coupled to robust control of syngeneic melanomas, lymphomas, and leukemias (Witalisz-Siepracka et al., 2018). Pharmacological inhibition of CDK7 in lung cancer cells promotes genomic instability linked to the secretion of T-helper 1 (T_H1) cytokines such as tumor necrosis factor (TNF), chemokine (C-X-C motif) ligand 9 (CXCL9), and CXCL10, as well as PD-L1 downregulation as a consequence of mitogen-activated protein kinase 14 (MAPK14, best known as p38) and MYCN proto-oncogene, bHLH transcription factor (MYCN) repression (Wang et al., 2020b; Zhang et al., 2020a). Consistent with this notion, CDK7 inhibition in mice bearing syngeneic lung cancers promotes tumor infiltration by immune effector cells and can be successfully combined with ICIs targeting PD-1 (Wang et al., 2020b; Zhang et al., 2020a). Finally, the multi-CDK inhibitor dinaciclib blocks the interferon gamma (IFNG)-driven upregulation of PD-L1 and the immunosuppressive enzyme indoleamine 2,3-dioxygenase 1 (IDO1) in mouse models of pancreatic adenocarcinomas, ultimately preventing adaptive immune resistance (Huang et al., 2020b). Along similar lines, dinaciclib promotes immunogenic cell death (ICD) along with robust type I IFN signaling (and despite PD-L1 upregulation in this setting) in mouse models of colorectal cancer (CRC), ultimately favoring dendritic cell (DC) activation and recruitment of $CD8^+$ T cells that can be actioned with ICIs specific for PD-1 (Hossain et al., 2018).

In summary, CDK-targeting agents, including several FDA-approved molecules, have been shown to mediate robust immunostimulatory effects that support treatment efficacy (Table 1). In some cases, such immunostimulatory activity is accompanied by at least some degree of direct or compensatory immunosuppression that generally manifests with PD-L1 upregulation. Thus, ICIs targeting the PD-1/PD-L1 axis stand out as promising candidates to improve the clinical activity of CDK inhibitors.

KRAS AND PI3K SIGNALING INHIBITORS

Several human tumors are driven by gain-of-function mutations in *KRAS*, *PI3KCA*, or B-Raf proto-oncogene, serine/threonine kinase (*BRAF*), as well as by phosphatase and tensin homolog (*PTEN*) deletions, resulting in constitutive mitogenic signaling via AKT serine/threonine kinase 1 (AKT1) and mechanistic target of rapamycin (MTOR) or MEK (Hoxhaj and Manning, 2020; Moore et al., 2020). Each of these proteins has attracted considerable attention as potential target for the development of novel anticancer therapeutics. However, while BRAF, PI3K, MTOR, and MEK inhibitors have been successfully developed into FDA-approved targeted anticancer agents, KRAS inhibitors have not yet been licensed for use in humans, and the development of AKT1 inhibitors is in its infancy (Hoxhaj and Manning, 2020; Moore et al., 2020). Interestingly, many of these agents not only limit mitogenic signaling in cancer cells but also mediate a panel of therapeutically relevant immunomodulatory effects (Table 2).

Activating *KRAS* and *BRAF* mutations in malignant cells support the establishment of an immunosuppressive microenvironment by multiple mechanisms (Spranger and Gajewski, 2018). Accordingly, both BRAF and MEK inhibitors (including the FDA-approved agents vemurafenib, dabrafenib, and trametinib) mediate various cancer-cell-dependent immunostimulatory effects, including (1) upregulation of TAAs (Boni et al., 2010; Frederick et al., 2013); (2) improved antigen presentation on MHC class I molecules (Dushyanthen et al., 2017; Kang et al., 2019; Liu et al., 2015); (3) induction of ICD (Box 1) (Erkes et al., 2020; Wang et al., 2020a); (4) secretion of T_H1 cytokines such as CXCL9 and CXCL10 (Kang et al., 2019); and (5) downregulation of immunomodulatory factors, including IL8, vascular

Table 2. Immunomodulation by KRAS and PI3K signaling inhibitors.

Target(s)	Agent(s)	Approved[a]	Cancer-Cell Dependent	Immune-Cell Dependent	Effect(s)	Notes	Reference
AKT1 AKT2	AktI-1/2 Akt inhibitor VIII	no		immunostimulation	activation of T_{EFF} cells	increased *ex vivo* priming and expansion of T cells, linked to a poorly differentiated memory phenotype	Crompton et al., 2015 van der Waart et al., 2014
AKT1 AKT2	Akt inhibitor VIII	no	immunostimulation		improved antigen presentation by cancer cells	upregulated expression of MHC class I molecules in PDAC cells	Sivaram et al., 2019
AKT1 AKT2 AKT3	MK-2206	no	relieved immunosuppression		downregulation of immunosuppressive factors in cancer cells	downregulation of PD-L1 in triple-negative BC cells	Mittendorf et al., 2014
AKT1 AKT2 AKT3	Triciribine	no		relieved immunosuppression	depletion of T_{REG} cells	decreased *ex vivo* proliferation of T_{REG} cells	Abu-Eid et al., 2014 Lim et al., 2018
$BRAF^{V600E}$	dabrafenib	yes	immunostimulation		improved antigen presentation by cancer cells	upregulated expression of MHC class I molecules in CRC cells	Liu et al., 2015
$BRAF^{V600E}$	dabrafenib	yes	relieved immunosuppression		downregulation of immunomodulatory factors in cancer cells	downregulated expression of PD-L1, IL8, and VEGFA in CRC cells	Liu et al., 2015
$BRAF^{V600E}$	PLX4720	no	immunostimulation		improved antigen presentation by cancer cells	increased TAA expression in melanoma cells	Boni et al., 2010
$BRAF^{V600E}$	PLX4720	no		immunostimulation	activation of NK cells	increased proliferation and activation of mouse and human NK cells *in vitro*, linked to increased NK-cell infiltration in $BRAF^{V600E}$-expressing melanomas	Ferrari de Andrade et al., 2014
$BRAF^{V600E}$	dabrafenib vemurafenib	yes	immunostimulation		improved antigen presentation by cancer cells	increased TAA expression in samples from metastatic melanoma patients in the context of MEK inhibition	Frederick et al., 2013
$BRAF^{V600E}$	vemurafenib	yes	inhibited immunostimulation		downregulation of immunostimulatory factors in cancer cells	decreased expression of NKALs on the surface melanoma cells, reversed by HDAC inhibition	López-Cobo et al., 2018
$BRAF^{V600E/K}$	dabrafenib	yes	immunosuppression		upregulation of immunosuppressive factors in cancer cells	PD-L2 and PD-1 upregulation in melanoma cells (in combination MEK inhibition), linked to improved sensitivity to ICIs *in vivo*	Sanlorenzo et al., 2018

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Table 2. *Continued*

Target(s)	Agent(s)	Approved[a]	Cancer-Cell Dependent	Immune-Cell Dependent	Effect(s)	Notes	Reference
$BRAF^{V600E/K}$	PLX4720	no	immunostimulation		ICD induction	DAMP emission by melanoma cells co-treated with a MEK inhibitor	Erkes et al., 2020
MEK	cobimetinib	yes		immunostimulation	activation of T_{EFF} cells	protection of CRC-infiltrating $CD8^+$ T cells from cell death, linked to improved sensitivity to ICIs *in vivo*	Ebert et al., 2016
MEK	mirdametinib	no	immunostimulation		improved antigen presentation by cancer cells	increased TAA expression by melanoma cells, enhanced by CDK4/CDK6 inhibition	Boni et al., 2010 Teh et al., 2020
MEK	mirdametinib	no	immunostimulation		ICD induction	DAMP emission by melanoma cells co-treated with a $BRAF^{V600E/K}$ inhibitor	Erkes et al., 2020
MEK	selumetinib	yes	immunostimulation		improved antigen presentation by cancer cells	upregulated expression of MHC class I molecules in CRC cells	Poon et al., 2017
MEK	selumetinib	yes		inhibited immunostimulation	impaired T_{EFF} cell function	reduced *ex vivo* proliferation of T cells, restored by cyclic MEK inhibition	Choi et al., 2019
MEK	trametinib	yes	immunostimulation		improved antigen presentation by cancer cells	MHC class I upregulation by CRC, HNSCC and BC cells, linked to improved sensitivity to ICIs *in vivo* increased TAA expression in samples from metastatic melanoma patients in the context of $BRAF^{V600E/K}$ inhibition	Dushyanthen et al., 2017 Liu et al., 2015 Loi et al., 2016 Kang et al., 2019
MEK	trametinib	yes	immunostimulation		ICD induction	DAMP emission by NSCLC cells, linked to DC activation and enhanced antitumor immunity *in vivo*	Wang et al., 2020a
MEK	trametinib	yes	immunostimulation		T_H1 cytokine secretion by cancer cells	increased CXCL9/CXCL10 secretion by HNSCC cells, linked to T-cell recruitment and improved sensitivity to ICIs *in vivo*	Kang et al., 2019
MEK	trametinib	yes	immunostimulation		induction of senescence and secretion of SASP factors in cancer cells	induction of SASP signatures in *KRAS*-driven tumors, only in combination with CDK4/CDK6 inhibition, linked to improved sensitivity to ICIs *in vivo*	Ruscetti et al., 2018 Ruscetti et al., 2020
MEK	trametinib	yes	relieved immunosuppression		downregulation of immunomodulatory factors in cancer cells	downregulated expression of PD-L1, IL8, and VEGFA in CRC cells, and OPN in BC cells	Allegrezza et al., 2016a Liu et al., 2015

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Table 2. *Continued*

Target(s)	Agent(s)	Approved[a]	Cancer-Cell Dependent	Immune-Cell Dependent	Effect(s)	Notes	Reference
MEK	trametinib	yes	immunosuppression		upregulation of immunosuppressive factors in cancer cells	PD-L1 upregulation in HNSCC and BC cells, linked to improved sensitivity to ICIs *in vivo* PD-L2 and PD-1 upregulation in melanoma cells (in combination with a $BRAF^{V600E/K}$ inhibitor), linked to improved sensitivity to ICIs *in vivo*	Loi et al., 2016 Kang et al., 2019 Sanlorenzo et al., 2018
MEK	trametinib	yes		inhibited immunostimulation	impaired T_{EFF} cell function	reduced T-cell proliferation restored by 4-1BB immunostimulatory mAbs or MEK inhibition	Choi et al., 2019 Dushyanthen et al., 2017
MEK	trametinib	yes		relieved immunosuppression	depletion of MDSCs	reduced MDSC generation from BM precursors	Allegrezza et al., 2016a
MEK	U0126	no	immunostimulation		improved antigen presentation by cancer cells	increased expression of TAAs by melanoma cells	Boni et al., 2010
MEK	U0126	no		inhibited immunostimulation	impaired T_{EFF} cell function	decreased proliferative responses and IFNG secretion in response to IL2 and melanoma cells, respectively	Boni et al., 2010
MTOR	rapamycin	yes	relieved immunosuppression		downregulation of immunosuppressive factors in cancer cells	downregulated expression of PD-L1 in triple-negative BC cells	Mittendorf et al., 2014
MTOR	rapamycin	yes		immunostimulation	activation of T_{EFF} cells	increased *ex vivo* priming and expansion of T cell, linked to a poorly differentiated memory phenotype	Araki et al., 2009
$KRAS^{G12C}$	AMG 510	no	immunostimulation		ICD induction	establishment of a pro-inflammatory TME linked to sensitivity to ICIs	Canon et al., 2019
PI3K	wortmannin	no		relieved immunosuppression	depletion of T_{REG} cells	decreased proliferation of T_{REG} cells *ex vivo*	Abu-Eid et al., 2014
PI3Kα	alpelisib	yes	immunostimulation		improved antigen presentation by cancer cells	MHC class I upregulation in BC cells along with CDK4/CDK6 inhibition	Teo et al., 2017
PI3Kα	alpelisib	yes	relieved immunosuppression		downregulation of immunosuppressive factors in cancer cells	PD-L1 downregulation by BC cells the context of CDK4/CDK6 blockage	Teo et al., 2017
PI3Kα PI3Kβ PI3Kδ	LY294002	no	immunostimulation		improved antigen presentation by cancer cells	MHC class I and II upregulation in lymphoma and melanoma cells	Marijt et al., 2019

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Table 2. ***Continued***

Target(s)	Agent(s)	Approved[a]	Cancer-Cell Dependent	Immune-Cell Dependent	Effect(s)	Notes	Reference
PI3Kα PI3Kδ	AZD8835	no		immunostimulation	activation of T_{EFF} cells	increased T-cell activation *ex vivo* via autocrine IL2 secretion	Carnevalli et al., 2018
PI3Kα PI3Kδ	pictilisib	no	immunostimulation		improved antigen presentation by cancer cells	MHC class I and II upregulation in squamous cell carcinoma cells	Chandrasekaran et al., 2019
PI3Kδ	idelalisib	yes		relieved immunosuppression	depletion of T_{REG} cells	decreased proliferation of T_{REG} cells *ex vivo*, correlating with impaired recruitment of T_{FH} and T_{REG} cells to the follicular lymphoma TME	Chellappa et al., 2019
PI3Kδ	CAL-101	no		immunostimulation	activation of T_{EFF} cells	increased T-cell activation *ex vivo* via autocrine IL2, linked to a poorly differentiated memory phenotype	Carnevalli et al., 2018 Majchrzak et al., 2017
PI3Kδ	PI-3065	no		relieved immunosuppression	depletion of T_{REG} cells	reduced abundance of peripheral T_{REG} cells in lymph nodes in mice with BC	Ali et al., 2014
PI3Kδ PI3Kγ	duvelisib		relieved immunosuppression		downregulation of immunosuppressive factors in cancer cells	downregulated PD-L1 expression in MCL cells	Harrington et al., 2019
PI3Kδ PI3Kγ	IPI-145	no		relieved immunosuppression	depletion of MDSCs	reversed splenic and tumor MDSCs suppressive capacity *ex vivo*	Davis et al., 2017
PI3K MTOR	dactolisib	no	immunostimulation		improved antigen presentation by cancer cells	MHC class I and II upregulation in squamous cell carcinoma cells	Chandrasekaran et al., 2019

BC, breast cancer; BM, bone marrow; CRC, colorectal carcinoma; DAMP, damage-associated molecular pattern; DC, dendritic cell; HNSCC, head and neck squamous cell carcinoma; ICD, immunogenic cell death; ICI, immune checkpoint inhibitor; mAb, monoclonal antibody; MCL, mantle cell lymphoma; MDSC, myeloid-derived suppressor cell; NK, natural killer; NKAL, NK cell-activating ligands; NSCLC, non-small cell lung carcinoma; PDAC, pancreatic ductal adenocarcinoma; SASP, senescence-associated secretory phenotype; TAA, tumor-associated antigen; T_{EFF}, effector T; TME, tumor microenvironment; T_{FH}, follicular helper T; T_{REG}, regulatory T.

[a]By the FDA for use in cancer patients.

endothelial growth factor A (VEGFA), and the MDSC chemoattractant secreted phosphoprotein 1 (SPP1, best known as OPN), at least in some settings (Allegrezza et al., 2016a; Liu et al., 2015). Supporting the therapeutic relevance of these mechanisms, the TME of tumors treated with BRAF or MEK inhibitors is enriched in T cells expressing IFNG and the immunostimulatory receptor CD40 ligand (CD40LG) (Ho et al., 2014) but depleted of MDSCs and immunosuppressive tumor-associated macrophages (TAMs) (Allegrezza et al., 2016a; Baumann et al., 2020; Poon et al., 2017), potentially linked to the ability of MEK inhibitors to directly limit the expansion of $CD11b^{+}CD14^{+}$ bone marrow-derived MDSCs (Allegrezza et al., 2016a). Along similar lines, the BRAF inhibitor PLX4720 reportedly mediates immunostimulatory effects on NK cells by favoring CD69 expression and boosting IFNG secretion in the context of IL2 stimulation (Ferrari de Andrade et al., 2014). Thus, various inhibitors of KRAS or its main transducers mediate immunostimulatory effects that contribute to efficacy.

Conversely, vemurafenib downregulates the expression of various NK-cell-activating ligands (NKALs) on the surface of malignant cells, hence mediating immunosuppressive effects (López-Cobo et al., 2018). Moreover, trametinib promotes PD-L1 upregulation in mouse breast cancer cells, *in vitro* and *in vivo* (Loi et al., 2016), correlating with the ability of PD-1 or PD-L1 blockers (Liu et al., 2015; Loi et al., 2016) as well as immunostimulatory antibodies targeting TNF receptor superfamily member 4 (TNFRSF4, best known as OX40) or TNFRSF9 (best known as 4-1BB) (Dushyanthen et al., 2017) to improve the therapeutic activity of MEK inhibition *in vivo*, in syngeneic immunocompetent settings. Interestingly, similar results have been obtained in melanoma models, potentially linked to the ability of BRAF and MEK co-inhibition to upregulate not only PD-L1 and PDCD1 ligand 2 (PDCD1LG2, best known as PD-L2) but also PD-1, on the surface of malignant cells (Sanlorenzo et al., 2018). Indeed, $PD\text{-}1^{+}$ melanoma cells emerging upon BRAF/MEK co-inhibition display limited proliferative potential and increased stemness features, potentially constituting the major source of chemoresistance (Sanlorenzo et al., 2018). Moreover, PD-1 blockers improve the therapeutic efficacy of the $KRAS^{G12C}$ inhibitor AMG 510 (which is currently under clinical testing) in mouse models of $KRAS^{G12C}$-driven carcinogenesis, correlating with the ability of AMG 510 to induce ICD (Canon et al., 2019).

Further supporting the therapeutic relevance of these findings, loss of antigen presentation, T_{EFF} cell exhaustion, and tumor infiltration by immunosuppressive cells have been commonly observed when tumors progress on KRAS, BRAF, or MEK inhibitors, in both preclinical (Dushyanthen et al., 2017; Liu et al., 2017b) and clinical settings (Frederick et al., 2013; Hugo et al., 2015). At least in part, this reflects the key role of MEK signaling in the expansion of naive T cells at priming, as well as in the protection of tumor-infiltrating $CD8^{+}$ CTLs from the lethal consequences of chronic TCR stimulation (Boni et al., 2010; Ebert et al., 2016). Importantly, such a potentially detrimental effect can be avoided or reversed (at least in part) with a variety of agents other than PD-1/PD-L1 blockers, including (but not limited to) (1) cytotoxic T lymphocyte-associated protein 4 (CTLA4) or hepatitis A virus cellular receptor 2 (HAVCR2, best known as TIM-3) blockers, especially in the context of cyclic MEK inhibition (Choi et al., 2019; Liu et al., 2017b); (2) immunostimulatory molecules encompassing CD40, OX40, 4-1BB, and Toll-like receptor 7 (TLR7) agonists (Baumann et al., 2020; Bellmann et al., 2020; Dushyanthen et al., 2017; Ho et al., 2014), as well as recombinant IL15 (which potently activates NK cells) (Allegrezza et al., 2016b) and the DC mitogen fms-related receptor tyrosine kinase 3 ligand (FLT3LG) (Salmon et al., 2016); (3) CDK4/CDK6 inhibitors (Teh et al., 2020); and (4) prebiotics that boost general immune tonus, such as inulin (Li et al., 2020b). Consistent with this notion, pulmonary carcinogenesis driven by *Kras* activation and *Tp53* loss has been associated with an altered microbiota linked to deranged cytokine signaling (Jin et al., 2019a). These latter finding point to the intriguing possibility of harnessing immunostimulatory prebiotics to limit clinical resistance to BRAF, MEK, and KRAS inhibitors.

Although hyperactive PI3K signaling, be it a consequence of *PI3KCA* mutations or *PTEN* deletions, also promotes the establishment of immunosuppression by developing tumors (Spranger and Gajewski, 2018), the underlying molecular mechanisms remain matter of debate. For instance, *PTEN* deletion in triple-negative breast cancer (TNBC) cell lines promotes PD-L1 upregulation, which can be reverted by AKT1 or MTOR inhibition (Mittendorf et al., 2014) as well as by PI3Kα inhibition in the context of CDK4/CDK6 blockage (Teo et al., 2017). Moreover, PTEN competence is associated with an increased incidence of $PD\text{-}L1^{-}$ cases in melanoma patients (Peng et al., 2016), but PTEN silencing in melanoma cells fails to affect PD-L1 levels (Peng et al., 2016), potentially pointing to an indirect impact of PTEN status on PD-L1 expression. Pharmacological or genetic inhibition of PI3Kα, PI3Kδ, or AKT has been proposed to boost T_{EFF} cell survival and activation by promoting autocrine IL2 signaling (Aragoneses-Fenoll et al., 2018; Carnevalli et al., 2018), or by limiting the intratumoral abundance or suppressive functions of T_{REG} cells (Abu-Eid et al., 2014; Ali et al., 2014; Chellappa et al., 2019; Lim et al., 2018), MDSCs (Davis et al., 2017), and TAMs (Kaneda et al., 2016). Similarly, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit gamma (*Pik3cg*) deletion in the host enables superior $CD8^{+}$ CTL functions and the pan-class I PI3K inhibitor buparlisib synergizes with PD-1 blockers in the control of mouse breast cancers established in immunocompetent hosts (Sai et al., 2017). Along similar lines, dual PI3Kδ/PI3Kγ inhibition with duvelisib limits PD-L1 expression by lymphoma cells (Harrington et al., 2019), correlating with a repolarization of the TAM compartment toward immunostimulation (Horwitz et al., 2018), and dual PI3Kα/PI3Kδ blockage by copanlisib has been linked to limited NF-κB signaling and hence inhibited secretion of immunomodulatory cytokines like IL6 and IL10 (Paul et al., 2017).

Conversely, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit delta (*Pik3cd*) deletion appears to render T_{EFF} cells less susceptible to the immunostimulatory effects of ICIs, suggesting that the main therapeutic component of systemic PI3Kδ inhibition may originate from T_{REG} cell depletion (Lim et al., 2018). Consistent with this notion, the PI3Kδ blocker idelalisib limits the recruitment of immunosuppressive follicular helper T (T_{FH}) and T_{REG} cells to the TME of follicular lymphoma (Serrat et al., 2020), and mice bearing an inactivating mutation in *Pik3cd* exhibit superior resistance to chronic lymphocytic leukemia (CLL) in the context of impaired T_{REG} cell expansion (Dong et al., 2019; Hanna et al., 2019). That said, T cells treated

ex vivo with PI3Kδ, AKT, and MTOR inhibitors appear to preserve a poorly differentiated memory phenotype coupled to enhanced proliferative capacities, resulting in improved persistence and superior effector functions upon adoptive transfer to tumor-bearing mice (Araki et al., 2009; Crompton et al., 2015; Majchrzak et al., 2017; van der Waart et al., 2014), which may also contribute to efficacy in standard therapeutic settings.

Of note, while PI3K and AKT1 inhibitors have also been shown to boost IFNG-driven class I and class II antigen presentation as a mechanism of cancer-cell-dependent immunostimulation (Chandrasekaran et al., 2019; Marijt et al., 2019; Sivaram et al., 2019), MTOR inhibitors are not expected to mediate a similar activity, largely reflecting the notions that these agents potently activate autophagy (Galluzzi et al., 2017a) and that autophagy limits MHC class I levels on the surface of malignant cells (Yamamoto et al., 2020). Moreover, autophagy is a potent inhibitor of type I IFN secretion by breast cancer cells responding to radiation (Rodriguez-Ruiz et al., 2019; Yamazaki et al., 2020), implying that caution should be taken when combining MTOR inhibitors with radiotherapy. That said, autophagy activation in cancer cells succumbing to chemotherapy is critical for cell death to be perceived as immunogenic (Box 1) (Michaud et al., 2011). Moreover, autophagy supports the development and function of various immune effector cells, including DCs, macrophages, as well as $CD4^+$, $CD8^+$, and NK cells (Clarke and Simon, 2019). Thus, autophagy activation by MTOR inhibitors mediates immunomodulatory effects with an elevated degree of context dependency, complicating the development of pharmacological autophagy modulators for cancer therapy (Galluzzi et al., 2017a).

In summary, deregulated KRAS and PI3K signaling mediates robust oncogenic effects while favoring immunoevasion. Consistent with this notion, inhibitors of KRAS and PI3K signaling generally exert robust and therapeutically relevant immunostimulation (Table 2), although in specific settings T-cell exhaustion emerges as a mechanism of resistance that can be overcome by a variety of immunotherapeutics beyond ICIs.

DDR- AND APOPTOSIS-TARGETING AGENTS

Multiple human neoplasms emerge in the context of (epi)genetic defects that limit the ability of (pre)malignant cells to repair DNA damage, such as loss-of-function mutations in BRCA1 DNA repair associated (*BRCA1*), or prevent the apoptotic demise of cells accumulating DNA damage, such as alterations in the tumor protein p53 (TP53, best known as p53) system (Pilié et al., 2019) or upregulation of the antiapoptotic protein BCL2 (Singh et al., 2019). At least in some instances, however, malignant cells bearing these defects exhibit an exquisite dependency on cDNA damage repair (DDR) mechanisms or robust antiapoptotic signaling, which has been harnessed for the development of targeted anticancer agents based on the principle of synthetic lethality (Huang et al., 2020a). Today, multiple poly(ADP)-ribose polymerase 1 (PARP1) inhibitors are licensed for the treatment of cancers bearing DDR defects, such as breast and ovarian tumors bearing *BRCA1* or *BRCA2* mutations (Pilié et al., 2019). Along similar lines, the BCL2 inhibitor venetoclax has been approved by regulatory agencies for use in patients with CLL or small lymphocytic lymphoma (SLL) (Ashkenazi et al., 2017). Conversely, pharmacological inhibitors of ATM serine/threonine kinase (ATM), ATR serine/threonine kinase (ATR), and checkpoint kinase 1 (CHEK1, best known as CHK1), as well as drugs that can (at least in some cases) recover p53 functions, have not yet entered clinical practice (Khoo et al., 2014; Pilié et al., 2019). Irrespective of this discrepancy, all these DDR-targeting agents have been shown to mediate immunomodulatory effects of therapeutic relevance (Table 3).

Both genomic stress and DDR defects favor the cytosolic accumulation of single-stranded DNA (ssDNA) in support of various oncosuppressive processes, including a cancer-cell-dependent immunostimulatory response driven by cyclic GMP-AMP synthase (CGAS) and stimulator of interferon response cGAMP interactor 1 (STING1; best known as STING) (Vanpouille-Box et al., 2018). Consistent with this notion, various FDA-approved and experimental PARP inhibitors have been shown to drive robust type I IFN secretion downstream of increased cytosolic availability of ssDNA or micronuclei (DNA-containing structures generally formed by faulty mitoses) in a variety of tumors, including (but not limited to) BRCA1- and BRCA2-deficient neoplasms (Chabanon et al., 2019; Ding et al., 2018; Pantelidou et al., 2019; Reisländer et al., 2019; Shen et al., 2019; Wang et al., 2019b). In some settings, this was accompanied by the release of T-cell chemoattractants, including CXCL10, as well as by paracrine STING activation in DCs, ultimately leading to upregulation of MHC class II molecules and co-stimulatory ligands in support of T-cell priming (Ding et al., 2018; Pantelidou et al., 2019). Of note, the ability of PARP inhibitors to drive type I IFN synthesis appears to be linked to PARP1 trapping on DNA, as it cannot be recapitulated by PARP1 degradation (Kim et al., 2020). Moreover, pharmacological inhibition of PARP1 by veliparib or olaparib reportedly mediates immunostimulatory effects by favoring the CGAS-independent upregulation of NKALs and death receptors on the surface of malignant cells, ultimately increasing their sensitivity to NK-cell cytotoxicity (Fenerty et al., 2018; Paczulla et al., 2019).

Importantly, the administration of PARP inhibitors has been associated with PD-L1 upregulation in various cancer cells regardless of *BRCA1/2* status, presumably as a consequence of type I IFN or IFNG signaling (Chabanon et al., 2019; Jiao et al., 2017; Sen et al., 2019; Shen et al., 2019). Indeed, various ICIs have been successfully harnessed to enhance the therapeutic activity of PARP inhibitors in preclinical tumor models (Ding et al., 2018; Jiao et al., 2017; Sen et al., 2019; Shen et al., 2019; Wang et al., 2019b). Moreover, increased circulating levels of type I IFN- and IFNG-related cytokines as well as PD-L1 expression in malignant cells have been associated with favorable disease outcome in patients with platinum-resistant ovarian cancer receiving PARP inhibitors plus ICIs (Färkkilä et al., 2020; Lampert et al., 2020). Interestingly, immunocompetent mice lacking both (but not either) *Parp1* and *Parp2* in T cells are more permissive for the growth of syngeneic tumors than their littermates (Moreno-Lama et al., 2020), pointing to an unrecognized role for PARPs in T-cell-dependent anticancer immunity. These latter findings call for the attentive evaluation of T-cell activity in cancer patients receiving PARP inhibitors.

ATM has been shown to cooperate with PARP1 in the activation of a non-canonical STING-dependent program converging on the NF-κB-driven secretion of type I IFN and IL6 (at least in immortalized human keratinocytes) (Dunphy et al., 2018). Along

Table 3. Immunomodulation by DDR- and apoptosis-targeting agents.

Target(s)	Agent(s)	Approved[a]	Cancer-Cell Dependent	Immune-Cell Dependent	Effect(s)	Notes	References
ATM	AZD0156	no	relieved immunosuppression		downregulation of immunosuppressive factors in cancer cells	PD-L1 downregulation and inhibited secretion of immunosuppressive factors by PDAC cells, only in combination with WEE1 inhibitors	Jin et al., 2020
AURKA	alisertib	no	immunostimulation		induction of senescence and secretion of SASP factors in cancer cells	secretion of pro-inflammatory SASP components in the context of p53 reactivation by nutlin 3a	Vilgelm et al., 2015
AURKA	alisertib	no	immunostimulation		pro-inflammatory cytokine secretion by cancer cells	non-canonical IL10 secretion by CRC cells *ex vivo*	Han et al., 2020b
AURKA	alisertib	no		relieved immunosuppression	depletion of MDSCs	apoptosis induction in MDSCs from murine mammary carcinomas	Yin et al., 2019
ATR	ceralasertib	no	immunostimulation		improved antigen presentation by cancer cells	MHC class I upregulation in lung cancer cells, in the context of RT	Dillon et al., 2019
ATR	ceralasertib	no	immunostimulation		pro-inflammatory cytokine secretion by cancer cells	potentiated RT-induced driven type I IFN secretion in BC, hepatocellular carcinoma and lung cancer cells, linked to improved sensitivity to ICIs *in vivo*	Feng et al., 2020 Dillon et al., 2019 Sheng et al., 2020
ATR	ceralasertib	no	relieved immunosuppression		downregulation of immunosuppressive factors in cancer cells	downregulated PD-L1 expression in CRC tumors co-exposed to RT	Vendetti et al., 2018
ATR	VE-821	no	immunostimulation		pro-inflammatory cytokine secretion by cancer cells	increased olaparib-induced micronuclei formation in *BRCA2*-deficient cancer cells, coupled to CCL5 secretion	Schoonen et al., 2019
BCL2	venetoclax	yes	immunostimulation		improved antigen presentation by cancer cells	MHC class I upregulation in BC cells in the context of ER and CDK4/CDK6 inhibition, linked to improved sensitivity to ICIs *in vivo*	Whittle et al., 2020
BCL2	venetoclax	yes	immunosuppression		upregulation of immunosuppressive factors in cancer cells	PD-L1 upregulation in BC cells in the context of ER and CDK4/CDK6 inhibition, linked to improved sensitivity to ICIs *in vivo*	Whittle et al., 2020
BCL2	venetoclax	yes		immunostimulation	activation of T_{EFF} cells	enhanced T-cell survival upon BCL-X_L upregulation, linked to improved sensitivity to ICIs *in vivo*	Kohlhapp et al., 2020
BCL2 BCL-X_L	ABT-737	no	immunostimulation		pro-inflammatory cytokine secretion by cancer cells	type I IFN secretion in the context of genetic or pharmacological caspase inhibition	Giampazolias et al., 2017 Rongvaux et al., 2014 Saito et al., 2019 White et al., 2014

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Table 3. ***Continued***

Target(s)	Agent(s)	Approved[a]	Cancer-Cell Dependent	Immune-Cell Dependent	Effect(s)	Notes	References
BCL2 BCL-X_L	ABT-737	no		relieved immunosuppression	depletion of MDSCs	increased sensitivity of MDSCs to FAS-driven apoptosis *in vitro*	Hu et al., 2013
BCL2 BCL-X_L	ABT-737	no		immunosuppression	enrichment of T_{REG} cells	increased resistance of T_{REG} cells isolated from murine splenocytes	Gabriel et al., 2016
CHK1	prexaserib	no	immunosuppression		upregulation of immunosuppressive factors in cancer cells	upregulated expression of PD-L1 in SCLC cells, linked to improved sensitivity to ICIs *in vivo*	Sen et al., 2019
MDM2	AMG-232	no	relieved immunosuppression		downregulation of immunomodulatory factors in cancer cells	IL6 downregulation by ovarian cancer cells upon reactivation of p53	Sahin et al., 2020
MDM2	APG-115	no	immunosuppression		upregulation of immunosuppressive factors in cancer cells	PD-L1 upregulation by hepatoma and CRC cells, linked to improved sensitivity to ICIs *in vivo*	Fang et al., 2019
MDM2	APG-115	no		relieved immunosuppression	depletion of M2-like TAMs	suppression of M2 polarization *in vitro*, correlating with increased M1-like TAMs in the spleen of tumor-free mice	Fang et al., 2019
MDM2	nutlin 3a	no	immunostimulation		ICD induction	DAMP emission by melanoma cells	Guo et al., 2017
MDM2	nutlin 3a	no	immunostimulation		induction of senescence and secretion of SASP factors in cancer cells	secretion of pro-inflammatory SASP components by melanoma cells, in the context of AURKA inhibition	Vilgelm et al., 2015
MDM2	nutlin 3a	no	immunosuppression		upregulation of immunosuppressive factors in cancer cells	upregulated expression of PD-L1 in melanoma and lung carcinoma cells	Li et al., 2020a
PARP1 PARP2	niraparib	yes	immunostimulation		pro-inflammatory cytokine secretion by cancer cells	type I IFN secretion by BC cells, linked to improved sensitivity to ICIs *in vivo*	Wang et al., 2019b
PARP1 PARP2	niraparib	yes	immunosuppression		upregulation of immunosuppressive factors in cancer cells	upregulated expression of PD-L1 in BC and NSCLC cells	Chabanon et al., 2019
PARP1 PARP2	olaparib	yes	immunostimulation		pro-inflammatory and T_H1 cytokine secretion by cancer cells	activation of CGAS-STING signaling and type I IFN secretion by various cancer cells, linked to CXCL10 secretion and paracrine STING activation in DCs and improved sensitivity to ICIs *in vivo*	Chabanon et al., 2019 Ding et al., 2018 Reisländer et al., 2019 Pantelidou et al., 2019 Schoonen et al., 2019
PARP1 PARP2	olaparib	yes	immunosuppression		upregulation of immunosuppressive factors in cancer cells	PD-L1 upregulation by SCLC, BC and ovarian cancer cells, linked to improved sensitivity to ICIs *in vivo*	Ding et al., 2018 Jiao et al., 2017 Sen et al., 2019

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Table 3. *Continued*

Target(s)	Agent(s)	Approved[a]	Cancer-Cell Dependent	Immune-Cell Dependent	Effect(s)	Notes	References
PARP1 PARP2	olaparib	yes	immunostimulation		upregulation of immune effector targets in cancer cells	upregulated expression of death receptors in PDAC cells	Fenerty et al., 2018
PARP1 PARP2	talazoparib	yes	immunostimulation		pro-inflammatory cytokine secretion by cancer cells	activation of CGAS-STING signaling and type I IFN secretion, linked to improved sensitivity to ICIs *in vivo*	Chabanon et al., 2019 Shen et al., 2019
PARP1 PARP2	talazoparib	yes	immunosuppression		upregulation of immunosuppressive factors in cancer cells	PD-L1 upregulation by several cancer cells, linked to improved sensitivity to ICIs *in vivo*	Chabanon et al., 2019 Shen et al., 2019
PARP1 PARP2	veliparib	no	immunostimulation		upregulation of immunostimulatory factors in cancer cells	upregulated expression of NKALs on the surface of AML cells	Paczulla et al., 2019
PARP1 PARP2 PARP3	rucaparib	yes	immunostimulation		pro-inflammatory cytokine secretion by cancer cells	activation of CGAS-STING signaling and type I IFN secretion by NSCLC cells	Chabanon et al., 2019
PARP1 PARP2 PARP3	rucaparib	yes	immunosuppression		upregulation of immunosuppressive factors in cancer cells	upregulated expression of PD-L1 in NSCLC cells	Chabanon et al., 2019
WEE1	AZD1775	no	relieved immunosuppression		downregulation of immunosuppressive factors in cancer cells	PD-L1 downregulation and inhibited secretion of immunosuppressive factors by PDAC cells, only in the context of pharmacological ATM inhibition	Jin et al., 2020

AML, acute myeloid leukemia; BC, breast cancer; CRC, colorectal carcinoma; DC, dendritic cell; ER, estrogen receptor; ICI, immune checkpoint inhibitor; MDSC, myeloid-derived suppressor cell; NKAL, NK cell-activating ligand; NSCLC, non-small cell lung carcinoma; PDAC, pancreatic ductal adenocarcinoma cancer; RT, radiation therapy; SASP, senescence-associated secretory phenotype; SCLC, small cell lung carcinoma; T_{REG}, regulatory T.

[a]By the FDA for use in cancer patients.

similar lines, ATM reportedly drives IL8 secretion by breast cancer cells independently of its role in the DDR, ultimately favoring disease progression via autocrine or paracrine mechanisms (Chen et al., 2015). Accordingly, co-inhibition of ATM and WEE1 G2 checkpoint kinase (WEE1, another component of the DDR machinery) in human $KRAS^{G12C}$-driven pancreatic ductal adenocarcinoma cancer (PDAC) cells results in decreased secretion of IL8 and other factors supporting local invasion, as well as in reduced PD-L1 expression (Jin et al., 2020). Thus, the ATM→NF-κB signaling axis stands out as a promising target not only to achieve local immunostimulation but also to counteract cancer-cell-intrinsic pathways to disease progression.

Yet another DDR-relevant kinase, ATR, has been shown to mediate robust immunosuppressive effects, especially in the context of radiation therapy (RT)-driven DNA damage and consequent arrest in the G_2/M phase of the cell cycle (Rodriguez-Ruiz et al., 2020). Thus, pharmacological ATR inhibitors not only boost CGAS signaling and consequent type I IFN responses (involving CCL5 and CXCL10) driven by RT (Dillon et al., 2019; Feng et al., 2020) but also enhance antigen presentation on MHC class I molecules, ultimately favoring tumor infiltration by DCs, repolarization of the TAM compartment toward an immunostimulatory profile, and T-cell-dependent anticancer immunity (Dillon et al., 2019; Sheng et al., 2020). Moreover, ATR inhibitors appear to offset the ability of RT to drive PD-L1 upregulation (Vendetti et al., 2018) and hence synergize with RT and ICIs in the control of mouse hepatocellular carcinomas established in immunocompetent hosts (Sheng et al., 2020). Interestingly, the immunosuppressive effects of RT-driven G_2/M cell cycle blockage can also be offset by genetic (loss of the mouse p53-coding gene) and pharmacological (CHEK1 inhibition) interference with the G_1 checkpoint, ultimately resulting in accrued accumulation of micronuclei, superior type I IFN signaling, and initiation of potent anticancer immunity with systemic outreach (Chen et al., 2020). Similar results have been obtained by actioning extranuclear sources of CGAS-activatory DNA such as permeabilized mitochondria (by autophagy or BCL2 inhibition) (Yamazaki et al., 2020), as well as by delaying the terminal breakdown of cancer cells undergoing caspase-dependent apoptosis upon mitochondrial permeabilization (Bqué et al., 2019; Han et al., 2020a; Rodriguez-Ruiz et al., 2019). Moreover, ATR inhibition reportedly potentiates olaparib-driven micronuclei formation and consequent CGAS signaling in *BRCA2*-deficient cancer cells (Schoonen et al., 2019).

While the possibility to delay apoptosis with caspase blockers in support of immunostimulation has been poorly explored and autophagy modulators present various issues, including poor specificity (Galluzzi et al., 2017a), BCL2 inhibitors stand out as promising targeted agents to boost anticancer immunity. Venetoclax and navitoclax (an experimental inhibitor of various BCL2 family members) are particularly toxic for senescent cells, which (at least in some settings) produce immunomodulatory cytokines, including IL6 and VEGFA (Gorgoulis et al., 2019). In line with such a "senolytic" activity, venetoclax effectively eliminates HR^+ breast cancer cells undergoing senescence in response to CDK4/CDK6 inhibitors, culminating in increased levels of both MHC class I molecules and PD-L1 (Whittle et al., 2020). PD-L1 upregulation has also been documented in a small cohort of CLL patients who developed resistance to BCL2 inhibition (Herling et al., 2018), suggesting the existence of a clinically actionable axis for treatment resistance. Of note, venetoclax limits several features of CLL-associated immunosuppression in patients, including CTL exhaustion and NK-cell dysfunction (de Weerdt et al., 2019) and does not reduce the number of peripheral T cells in patients with HR^+BCL2^+ metastatic breast cancer (Lok et al., 2019). Along similar lines, BCL2 inhibition by venetoclax does not impair T_{EFF} cell responsiveness to antigenic stimuli *in vitro*, but rather promotes the compensatory upregulation of BCL2-like 1 (BCL2L1, best known as BCL-X_L) and hence supports T-cell survival, *de facto* synergizing with ICIs in immunocompetent mouse models of colorectal carcinoma (Kohlhapp et al., 2020). Interestingly, increased tumor infiltration by exhausted $PD\text{-}1^+CD8^+$ CTLs has been associated with the relapse of MYCN-driven mammary carcinomas upon withdrawal of BCL2/BCL-X_L inhibitors, which also appears to be therapeutically actionable with PD-1 blockers (Haikala et al., 2019). Finally, ABT-737 (an experimental inhibitor of multiple BCL2 family members) is known for its ability to drive robust type I IFN secretion by cancer cells downstream of mtDNA-driven CGAS activation, especially in the context of caspases inhibition (Rongvaux et al., 2014; White et al., 2014). *In vivo*, this has been associated with increased tumor infiltration by MHC class II-expressing tumoricidal macrophages and CTLs (Giampazolias et al., 2017; Saito et al., 2019). Moreover, ABT-737 increases the sensitivity of MDSCs to FAS-driven apoptosis *in vitro* and suppresses MDSC accumulation in murine mammary carcinomas (Hu et al., 2013), even though its administration has been related to depletion of T_{EFF} cells and enrichment of T_{REG} cells in tumor-free mice (Gabriel et al., 2016). Although the clinical development of ABT-737 has been discontinued owing to on-target thrombocytopenia (Mason et al., 2007), these findings lend strong support to the notion that inhibition of antiapoptotic BCL2 proteins mediates robust immunostimulatory effects of therapeutic relevance.

One of the main actors in DDR-driven BCL2-inhibitable apoptosis, p53, is genetically or functionally lost in a variety of malignancies (Pilié et al., 2019), correlating with signs of local immunosuppression (Cui and Guo, 2016). Accordingly, p53 reactivation by nutlin 3a, a pharmacological inhibitor of the p53-degrading enzyme MDM2 proto-oncogene (MDM2), elicits ICD in B16 melanomas, correlating with DC activation, expansion of tumor-infiltrating $CD8^+$ CTLs, and depletion of immunosuppressive MDSCs (Guo et al., 2017). Additional immunostimulatory effects linked to pharmacological p53 reactivation in cancer cells include (but are not limited to) (1) downregulation of immunomodulatory cytokines linked to tumor progression, such as IL6 (Sahin et al., 2020); (2) upregulation of NKALs (Textor et al., 2011); and (3) establishment of cellular senescence linked to an immunostimulatory SASP that favors the recruitment and activation of NK cells, T_{EFF} cells, and tumoricidal macrophages (Iannello et al., 2013; Lujambio et al., 2013; Xue et al., 2007; Kang et al., 2011, 2208947). Most likely reflecting such a robust immunostimulation, MDM2 inhibitors reportedly favor PD-L1 upregulation *in vivo* (Fang et al., 2019; Li et al., 2020a; Thiem et al., 2019), pointing to a potential value for combinatorial regimens involving ICIs. Moreover, the MDM2 inhibitor APG-115 appears to mediate immunostimulatory effects by directly promoting

the repolarization of immunosuppressive M2-like macrophages into their M1-like counterparts (Fang et al., 2019). Finally, inhibition of the mitotic kinase aurora kinase a (AURKA) appears to synergize with an MDM2 antagonist in inducing senescence coupled to immunological disease control in p53-competent melanomas (Vilgelm et al., 2015). Consistent with this notion, the AURKA inhibitor alisertib appears to promote tumor infiltration of $CD8^+$ T cells via a non-canonical pathway involving IL10 secretion (Han et al., 2020b) and to directly deplete the MDSC compartment of mouse mammary tumors, ultimately mediating an immunotherapeutic effect that can be enhanced by ICIs (Yin et al., 2019).

Altogether, these observations exemplify therapeutically relevant immunomodulation by various agents targeting the molecular pathways that emanate from DNA damage.

HER2, EGFR, VEGFA, AND TGF-β INHIBITORS

HER2, epidermal growth factor receptor (EGFR), VEGFA, and transforming growth factor β (TGF-β) were among the first proteins to attract interest as potentially druggable targets for cancer therapy, reflecting their key role in cancer-cell-intrinsic or environmental aspects of oncogenesis. Indeed, while *ERBB2* gene amplifications and gain-of-function *EGFR* mutations support the proliferation of various cancer cell types (Oh and Bang, 2020; Pao and Chmielecki, 2010), VEGFA is critical for tumor-driven neoangiogenesis (Apte et al., 2019) and TGF-β promotes the establishment of a fibrotic microenvironment that is poorly permissive to access by therapeutics (Derynck et al., 2020). Over the past two decades, a number of mAbs and TKIs have been developed to target these proteins or their binding partners, and some of these molecules, including HER2-, EGFR-, and VEGFA-specific agents, have been licensed for use in a variety of oncological indications (Apte et al., 2019; Oh and Bang, 2020; Pao and Chmielecki, 2010). Conversely, TGF-β blockers have not yet entered the clinical routine (Derynck et al., 2020), although both TGF-β traps and TGF-β receptor 1 (TGFBR1) inhibitors continue to be scrutinized for safety and efficacy in phase I–II clinical trials (source https://clinicaltrials.gov/). All these agents have been shown to mediate immunomodulatory effects of therapeutic relevance (Table 4).

The therapeutic efficacy of multiple mAbs targeting plasma membrane receptors involved in oncogenesis stems (at least in part) from their ability to bridge malignant cells and immune effector cells expressing Fc gamma receptors (FcγRs), culminating in antibody-dependent cellular cytotoxicity (ADCC) (Ferris et al., 2010). This applies to the humanized HER2-specific mAbs trastuzumab and pertuzumab (Misumi et al., 2018; Park et al., 2010; Stagg et al., 2011). Accordingly, the therapeutic activity of these mAbs correlates with the abundance of NK cells, is influenced by genetic polymorphisms affecting FcγR functions, and can be boosted (at least preclinically) by immunotherapeutic interventions preventing NK dysfunction (e.g., IL2 or IL12 administration) (Gennari et al., 2004; Jaime-Ramirez et al., 2011; Klein et al., 2017; Kono et al., 2002; Musolino et al., 2008). HER2-targeted mAbs also appear to engage some degree of $CD8^+$ and $CD4^+$ T-cell-dependent HER2-specific immune responses (Mittal et al., 2016; Mortenson et al., 2013; Park et al., 2010; Taylor et al., 2007), at least in part reflecting improved antigen presentation on MHC class I and II molecules (Kono et al., 2004; Triulzi et al., 2018), as well as MYD88 innate immune signal transduction adaptor (MYD88)-dependent immunostimulation (Stagg et al., 2011), culminating in increased antigen processing and presentation by DCs (Gall et al., 2017). In line with this notion, the progressive loss of HER2-targeting $CD4^+$ T_H1 cells reportedly facilitates HER2-driven mammary carcinogenesis (Datta et al., 2015a), and multiple immunotherapeutic agents, including DC-based vaccines (Datta et al., 2015b; Linch et al., 2016), TLR2 agonists (Lu et al., 2011), recombinant IL21 (Roda et al., 2006), and PD-L1 blockers (Mittal et al., 2019), can be exploited to magnify the efficacy of HER2-targeting mAbs along with the elicitation of robust anticancer immunity. A similar therapeutic benefit linked to signs of immune activation has also been documented (in preclinical tumor models) upon combining HER2-specific mAbs with other targeted anticancer agents that mediate immunomodulatory properties, including pan-PI3K inhibitors (Choi et al., 2018) and EGFR-specific mAbs (Roda et al., 2007).

HER2-targeting mAbs also elicit antibody-dependent cellular phagocytosis (ADCP), involving the clearance of antibody-bound tumor cells by macrophages (Shi et al., 2015), a phenomenon that may be accompanied by macrophage polarization toward an M2-like immunosuppressive phenotype (Su et al., 2018). This process appears to rely on the sensing of DNA from phagocytosed tumor cells by absent in melanoma 2 (AIM2), resulting in CGAS cleavage coupled to PD-L1 and IDO1 upregulation via an inflammasome-dependent mechanism (Su et al., 2018). Consistent with this, PD-L1 and IDO1 blockade improves the therapeutic activity of HER2-targeting mAbs in mouse models of $HER2^+$ breast cancer (Su et al., 2018). Moreover, the abundance of $PD\text{-}L1^+IDO1^+$ TAMs has been negatively correlated with the intratumoral abundance of NK cells and sensitivity to trastuzumab in a cohort of patients with $HER2^+$ breast cancer (Su et al., 2018), and the local delivery of IL21 promotes the therapeutic activity of HER2-targeting mAbs in preclinical models of the disease as it favors TAM repolarization toward an immunostimulatory phenotype (Xu et al., 2015).

Not only EGFR-specific mAbs (Roberti et al., 2011) but also EGFR-targeting TKIs such as erlotinib (in the presence of a tumor-targeting mAb) (Cavazzoni et al., 2012; Mallmann-Gottschalk et al., 2019) promote ADCC by NK cells, which, in the case of TKIs, originates from the upregulation of the mAb target (e.g., EGFR, HER2) by malignant cells (Cavazzoni et al., 2012; Mallmann-Gottschalk et al., 2019). In addition, various EGFR-targeting agents improve MHC class I antigen presentation by cancer cells (Lizotte et al., 2018; Pollack et al., 2011) and favor the uptake of tumor material by DCs (Banerjee et al., 2008; Nigro et al., 2019) as well as their ability to prime T cells and promote NK-cell activation in the absence of additional immunostimulatory signals (Banerjee et al., 2008; Lee et al., 2011; Venugopalan et al., 2016). At least in part, this reflects the ability of EGFR-targeted agents to induce ICD (Garrido et al., 2011; Pozzi et al., 2016) (Box 1) and the consequent exposure of the "eat-me" signal calreticulin (CALR) coupled to the downregulation of the "don't eat me" signal CD47 on the surface of malignant cells (Nigro et al., 2019).

Resembling their HER2-targeting counterparts, EGFR-specific mAbs efficiently drive ADCP by macrophages (Boross

Table 4. Immunomodulation by HER2, EGFR, VEGF, and TGF-β inhibitors.

Target	Agent(s)	Approved[a]	Cancer-Cell Dependent	Immune-Cell Dependent	Effect(s)	Notes	References
EGFR	cetuximab	yes	immunostimulation		improved antigen presentation by cancer cells	MHC class I upregulation in primary and malignant human keratinocytes	Pollack et al., 2011
EGFR	cetuximab	yes		immunostimulation	activation of NK cells	induction of NK-cell-mediated ADCC of cancer cells with mutated *KRAS*	Roberti et al., 2011
EGFR	cetuximab	yes	immunostimulation		ICD induction	DAMP emission by rectal carcinoma cells, enhanced by chemotherapy and linked to phagocytosis of tumor cells by DCs	Pozzi et al., 2016
EGFR	cetuximab	yes		immunostimulation	activation of DCs	enhanced uptake of tumor material and cross-presentation by DCs, followed by priming of T cells and activation of NK cells	Banerjee et al., 2008 Lee et al., 2011
EGFR	cetuximab	yes		immunosuppression	M2-like TAM polarization	PD-L1 upregulation in macrophages upon ADCP *in vitro*	Pander et al., 2011
EGFR	IgA2 EGFR	no		immunostimulation	activation of macrophages	induction of ADCP of epidermal carcinoma cells *in vivo*	Boross et al., 2013
EGFR	7A7 mAb	no	immunostimulation		ICD induction	DAMP emission by lung cancer cells, linked to DC maturation *in vitro*	Garrido et al., 2011
EGFR	afatinib erlotinib gefitinib	yes	immunostimulation		improved antigen presentation by cancer cells	MHC class I and II upregulation by ovarian carcinoma cells	Lizotte et al., 2018
EGFR	erlotinib	yes		immunostimulation	activation of NK cells	induction of NK-cell-mediated ADCC of ovarian cancer and NSCLC cells	Cavazzoni et al., 2012 Mallmann-Gottschalk et al., 2019
EGFR	erlotinib	yes		immunostimulation	improved antigen presentation by immune cells	MHC class II upregulation by DCs and macrophages	Venugopalan et al., 2016
EGFR	gefitinib	yes	relieved immunosuppression		downregulation of immunosuppressive factors in cancer cells	PD-L1 downregulation in NSCLC cells bearing *EGFR* mutations *in vitro* and *in vivo*	Lin et al., 2015 Zhang et al., 2016
EGFR	gefitinib	yes	immunostimulation		upregulation of immunostimulatory factors in cancer cells	NKAL upregulation by NSCLC cells, linked to enhanced NK-mediated ADCC	He et al., 2013 Kim et al., 2011
EGFR	gefitinib	yes	inhibited immunostimulation		downregulation of immunostimulatory factors in cancer cells	NKAL downregulation in NSCLC cells, linked to reduced NK-mediated ADCC	Okita et al., 2015
EGFR	gefitinib	yes		immunostimulation	activation of DCs	enhanced uptake of tumor material by DCs independent of ICD	Nigro et al., 2019
EGFR	PD168393	no	immunostimulation		improved antigen presentation by cancer cells	MHC class I upregulation in primary and malignant human keratinocytes	Pollack et al., 2011

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Table 4. *Continued*

Target	Agent(s)	Approved[a]	Cancer-Cell Dependent	Immune-Cell Dependent	Effect(s)	Notes	References
EGFR	gefitinib osimertinib	yes		immunomodulation	functional alteration of the immunological TME	temporary DC and $CD8^+$ T_{EFF} accumulation coupled to T_{REG} cell and M2 TAM depletion, rapidly followed by MDSC-driven immunosuppression *in vivo*	Jia et al., 2019
HER2	trastuzumab	yes	immunostimulation		improved antigen presentation by cancer cells	MHC class I and II upregulation in different HER2-overexpressing cancer cells and $HER2^+$ BC biopsies	Kono et al., 2004 Triulzi et al., 2018
HER2	trastuzumab	yes		immunostimulation	activation of DCs	enhanced uptake and cross-presentation of HER2 by DCs followed by T-cell priming	Gall et al., 2017
HER2	trastuzumab pertuzumab	yes		immunostimulation	activation of NK cells	induction of NK-cell-mediated ADCC of HER2-expressing cancer cells	Misumi et al., 2018
HER2	trastuzumab	yes		immunostimulation	activation of macrophages	induction of ADCP of HER2-expressing cancer cells	Shi et al., 2015
HER2	trastuzumab	yes		immunosuppression	M2-like TAM polarization	PD-L1 and IDO1 upregulation by TAMs upon ADCP, linked to improved sensitivity to ICIs in mouse models of $HER2^+$ BC	Su et al., 2018
TGFβ1 TGFβ2	anti-TGFβ1,2 IgG2a	no	immunostimulation		improved antigen presentation by cancer cells	MHC class I upregulation by squamous cell carcinoma cells	Tauriello et al., 2018
TGFβR	galunisertib	no	immunostimulation		improved antigen presentation by cancer cells	MHC class I upregulation by hepatic tumor organoid, linked to boosted T_{EFF} cell responses and improved sensitivity to ICIs *in vivo*	Dodagatta-Marri et al., 2019
TGFβR1	vactosertib	no	relieved immunosuppression		downregulation of immunosuppressive factors in cancer cells	PD-L1 downregulation by melanoma *in vivo*, in the context of delayed TGFβ inhibition	Zhao et al., 2018
VEGFA	bevacizumab	yes	relieved immunosuppression		downregulation of immunosuppressive factors in cancer cells	PD-L1 downregulation in biopsies from patients with glioblastoma	Tamura et al., 2019
VEGFA	A2V	no		relieved immunosuppression	vascular remodeling	T_{EFF} cell extravasation upon expression of adhesion molecules and pro-inflammatory cytokines by ECs in mammary tumors	Schmittnaegel et al., 2017
VEGFA	A2V	no	immunosuppression		upregulation of immunosuppressive factors in cancer cells	PD-L1 upregulation in cancer and ECs of mammary tumors, linked to improved sensitivity to ICIs *in vivo*	Schmittnaegel et al., 2017
VEGFRs	apatinib sunitinib	yes	relieved immunosuppression		downregulation of immunosuppressive factors in cancer cells	PD-L1 downregulation in osteosarcoma cells upon inactivation of STAT3	Duan et al., 2020 Zheng et al., 2018

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Table 4. *Continued*

Target	Agent(s)	Approved[a]	Cancer-Cell Dependent	Immune-Cell Dependent	Effect(s)	Notes	References
VEGFRs	sunitinib	yes		relieved immunosuppression	depletion of T_{REG} cells	inhibition of T_{REG} cell activity *in vitro*, linked to reduced frequency of T_{REG} cells and secretion of immunosuppressive cytokines in various tumor-bearing mice	Liu et al., 2017a Ozao-Choy et al., 2009
VEGFRs	sunitinib	yes		relieved immunosuppression	depletion of MDCSs	inhibition of MDSC suppressive activity *in vitro*, linked to reduced frequency of MDSCs in CRC-bearing mice	Ozao-Choy et al., 2009

ADCC, antibody-dependent cellular cytotoxicity; ADCP, antibody-dependent cellular phagocytosis; BC, breast cancer; CRC, colorectal carcinoma; DAMP, damage-associated molecular pattern; DC, dendritic cell; EC, endothelial cell; ICD, immunogenic cell death; ICI, immune checkpoint inhibitor; MDSC, myeloid-derived suppressor cell; NK, natural killer; NKAL, NK cell activating ligand; NSCLC, non-small cell lung carcinoma; TAM, tumor-associated macrophage; TEFF, effector T; TREG, regulatory T.
[a]By the FDA for use in cancer patients.

et al., 2013), which (at least in some settings) is coupled to the accumulation of immunosuppressive M2-like TAMs expressing high PD-L1 levels and secreting IL10 and VEGFA (Pander et al., 2011). The latter effect has been correlated with poor responses to cetuximab in patients with locally advanced neck squamous cell carcinoma (Li et al., 2015). Of note, while the EGFR-targeting TKI gefitinib has been suggested to upregulate the expression of NKALs by non-small lung carcinoma (NSCLC) cells (He et al., 2013; Kim et al., 2011), similar findings have not been reproduced by independent investigators, potentially reflecting a cell-type-dependent mechanism linked to *EGFR* mutational status and/or the concentration of the drug employed in this context (Okita et al., 2015). Irrespective of this apparent discrepancy, multiple EGFR-targeting TKIs efficiently decrease PD-L1 expression by NSCLC cells, reflecting their ability to interrupt NF-κB and IL6 signaling (Lin et al., 2015; Zhang et al., 2016). Consistent with this immunomodulatory profile, the TME of NSCLC exposed to EGFR-targeting agents exhibits increased abundance of DCs and $CD8^+$ T_{EFF} cells exhibiting limited signs of exhaustion coupled to the depletion of T_{REG} cells and M2 TAMs, although such an effect appeared to be temporary and rapidly followed by MDSC-driven immunosuppression (Jia et al., 2019). Intriguingly, EGFR inhibitors have also been shown to promote the resolution of neutrophilic inflammation (Rahman et al., 2019), but the impact of this effect on anticancer immunity remains obscure.

VEGFA-neutralizing mAbs as well as agents targeting VEGFA receptors (VEGFRs) mediate immunostimulatory effects independent of ADCC and ADCP, largely reflecting the key role of VEGFA in the establishment of cancer-related immunosuppression (Yang et al., 2018). For instance, VEGFA signaling is directly involved in T_{REG} cell expansion (Terme et al., 2013) and expression of co-inhibitory receptors, including PD-1 by $CD8^+$ CTLs (Voron et al., 2015). Consistent with this notion, the FDA-approved VEGFA blocker bevacizumab (alone or combined with chemotherapy or radiation) and other agents that suppress VEGFA signaling, such as the multi-TKI sunitinib (which, among other kinases, inhibits VEGFRs), have been associated with increased tumor infiltration by activated T_{EFF} cells coupled to T_{REG} (and TAM) depletion (Liu et al., 2017a; Napoletano et al., 2019; Ozao-Choy et al., 2009), improved DC maturation (Osada et al., 2008), as well as PD-L1 downregulation by malignant and myeloid cells (Duan et al., 2020; Tamura et al., 2019; Zheng et al., 2018), in preclinical cancer models. Similar findings have been documented in blood or tumor samples from patients with renal cell carcinoma receiving sunitinib (Finke et al., 2008) as well as patients with NSCLC and mammary carcinoma exposed to bevacizumab (de Goeje et al., 2019; von der Lippe Gythfeldt et al., 2020). In addition, transcriptomic analyses revealed an inverse correlation between *VEGFA* levels and signatures of $CD8^+$ CTL infiltration in biopsies from breast cancer patients as well as in preclinical models of mammary and colorectal carcinoma (Palazon et al., 2017; Wang et al., 2020c). Finally, the accumulation of immunosuppressive cells, including TAMs, has been linked with resistance to VEGFA-targeting antibodies in mouse models of ovarian cancer (Dalton et al., 2017). Consistent with this notion, kinase insert domain receptor (KDR, best known as VEGFR2) inhibition with apatinib reverses immunosuppression and sensitizes VEGFA-overexpressing mammary and colorectal mouse

tumors to immunotherapy with PD-1 blockers (Wang et al., 2020c). However, *VEGFA* deletion in T cells facilitates the growth of mouse B16 melanomas (Palazon et al., 2017), not only pointing to an immunosuppressive mechanism that may offset the therapeutic activity of VEGFA-targeting agents but also suggesting that T-cell recruitment and activation downstream of VEGFA inhibition likely stems from non-lymphoid TME components. Endothelial cells (ECs), which express abundant VEGF levels, stand out as major candidates for this role, as ECs exposed to various VEGFA inhibitors have been shown to express increased levels of adhesion molecules involved in T-cell extravasation, PD-L1, and pro-inflammatory cytokines (Dirkx et al., 2006; Schmittnaegel et al., 2017). These findings suggest that the superior therapeutic response achieved with VEGFA-targeting agents plus PD-L1 inhibitors may involve an unsuspected vascular component (Allen et al., 2017).

Although, in specific settings, TGF-β reportedly supports anticancer immune responses, this cytokine is best known for its ability to upregulate PD-L1 on malignant and myeloid TME compartments, promote PD-1 expression by T cells, and favor the expansion of T_{REG} cells and MDSCs, culminating in local and systemic immunosuppression (Batlle and Massagué, 2019). Moreover, TGF-β is intimately involved in the establishment of immunological exclusion, an active process through which cancer cells co-opt cancer-associated fibroblasts to prevent tumor infiltration by immune effector cells (Galluzzi et al., 2018). Consistent with this notion, genetic signatures linked to TGF-β signaling and stromal remodeling are associated with poor disease outcome and immunotherapy failure across multiple human cancers (Chakravarthy et al., 2018). Moreover, pharmacological inhibition of TGF-β or its receptors resolves immunological exclusion and improves antigen presentation by malignant cells, culminating in potent anticancer immune responses that can be actioned with ICIs toward disease eradication and establishment of protective immunological memory, at least in mouse models of melanoma (Ravi et al., 2018), as well as colorectal (Mariathasan et al., 2018; Tauriello et al., 2018), breast (Holmgaard et al., 2018), and squamous cell carcinoma (Dodagatta-Marri et al., 2019). Along similar lines, TGF-β inhibition has been shown to potently boost focal RT-driven immunostimulation in preclinical mouse models of breast carcinoma, especially when combined with systemic ICIs (Vanpouille-Box et al., 2015). Consistent with this notion, patients with metastatic breast cancer receiving fresolimumab, a TGF-β-targeting mAb, in the context of hypofractionated RT exhibited an expanded $CD8^+$ memory T-cell pool in the periphery (Formenti et al., 2018a). Nonetheless, clinical responses in this study were limited, most likely as a consequence of PD-1-dependent functional defects of the T-cell compartment at baseline (Formenti et al., 2019). Thus, while TGF-β plays a central role in the establishment of cancer-associated immunosuppression, combinatorial regimens involving one or multiple ICIs may be required to fully harness the potential of TGF-β inhibitors in the clinic. In this context, treatment sequencing may be a key determinant for success. Indeed, upfront TGF-β inhibition appears to promote at least some degree of resistance to PD-1 blockers by favoring matrix metallopeptidase 9 (MMP9)-driven PD-L1 cleavage (Zhao et al., 2018). Conversely, the administration of TGF-β inhibitors once acquired PD-1 resistance has emerged mediates robust therapeutic effects (Zhao et al., 2018).

Taken together, these observations highlight the multipronged immunostimulatory effects of HER2, EGFR, VEGFA, and TGF-β inhibitors, with emphasis on the added therapeutic possibilities offered by combinatorial regimens involving ICIs and other immunomodulatory drugs that should be administered according to optimal, yet-to-be-established schedules.

OTHERS

The list of targeted anticancer agents that are approved for use in cancer patients or are being developed in that sense keeps growing, largely reflecting a relentless line of investigation aimed at defining therapeutically actionable, cancer-specific molecular alterations (Bedard et al., 2020). Besides molecules mentioned here above, like imatinib, such a list includes (but is limited to) relatively selective ALK receptor tyrosine kinase (ALK); AXL receptor tyrosine kinase (AXL); Bruton tyrosine kinase (BTK); enhancer of zeste 2 polycomb repressive complex 2 subunit (EZH2); histone deacetylase (HDAC); isocitrate dehydrogenase ($NADP^+$) 1 (IDH1); Janus kinase 1 (JAK1); MET proto-oncogene; receptor tyrosine kinase (MET); ret proto-oncogene (RET); ROS proto-oncogene 1; receptor tyrosine kinase (ROS1); smoothened, frizzled class receptor (SMO), and exportin 1 (XPO1) inhibitors; mAbs (at least in some cases combined with cytotoxic drugs) specific for CD20, CD22, CD33, CD52, CD58; IL2 receptor subunit alpha (IL2RA, best known as CD25); IL3 receptor subunit alpha (IL3RA); and tumor-associated calcium signal transducer 2 (TACSTD2, best known as TROP2); as well as multitargeted TKIs (Bedard et al., 2020). Interestingly, most of these clinically employed drugs mediate at least some degree of immunomodulation, offering a rationale to design combinatorial treatment regimens involving ICIs (Table 5).

Imatinib was arguably the first targeted anticancer agent to demonstrate immunostimulatory effects that are directly linked to NK-cell activation (Borg et al., 2004; Menard et al., 2009) and T_{REG} cell depletion (Tanaka et al., 2020). In line with this notion, the clinical activity of imatinib in individuals with GIST is linked to IFNG production by the patient's NK cells (Menard et al., 2009), as well as to their NK-cell-activating receptor (NKAR) expression pattern (Delahaye et al., 2011; Rusakiewicz et al., 2017). Thus, patients with CML achieving deep molecular responses upon treatment with imatinib or other TKIs (i.e., nilotinib and dasatinib) exhibit signs of restored NK-cell activity coupled to PD-1 downregulation on T cells and contraction of the MDSC compartment (Hughes et al., 2017). A similar reversal of T-cell exhaustion coupled to a diversification of the circulating TCR repertoire has been observed in patients with CLL treated with the BTK inhibitor ibrutinib (Kondo et al., 2018; Yin et al., 2017). Moreover, ibrutinib reportedly favors the depletion of MDSCs coupled to their differentiation toward a mature DC-like phenotype associated with MHC class II upregulation and improved antigen-presentation capacity (Stiff et al., 2016; Varikuti et al., 2020), while both imatinib and nilotinib enable M2-like TAMs to repolarize toward an M1-like phenotype and activate NK cells in response to TLR stimulation (Bellora et al.,

2017; Zhang et al., 2018b). However, ibrutinib has also been suggested to limit CTL and NK-cell proliferation and effector functions in response to activating stimuli (Flinsenberg et al., 2020; Hofland et al., 2019), albeit such immunosuppressive effects may not stem from BTK inhibition (as demonstrated with the more specific second-generation BTK inhibitor zanubrutinib) (Flinsenberg et al., 2020). Along similar lines, imatinib treatment has been associated with PD-1 upregulation in T cells from patients with GIST (but with PD-L1 downregulation on mouse GIST cells), correlating with an added therapeutic effect for PD-1 blockage in the context of imatinib administration in a preclinical GIST model (Seifert et al., 2017).

The multi-TKI crizotinib has also been associated with increased markers of T-cell exhaustion and PD-L1 upregulation on malignant cells in preclinical NSCLC models, an effect that presumably reflected the ability of crizotinib to robustly drive ICD and that could be actioned therapeutically with PD-1-targeting mAb (Liu et al., 2019). Similar findings have been documented in syngeneic mouse models of melanoma subjected to epigenetic reprogramming with HDAC inhibitors (Knox et al., 2019; Woods et al., 2015), which is aligned with the observations that HDAC-targeting agents favor NKAL expression by melanoma cells (López-Cobo et al., 2018) and that an intact immune system is required for the prototypic HDAC inhibitor vorinostat to mediate therapeutic activity against hematological and solid malignancies in mice (West et al., 2013). Yet another epigenetic intervention, namely EZH2 inhibition, is associated with multipronged immunomodulatory effects, encompassing immunostimulation downstream of improved antigen presentation by cancer cells (Ennishi et al., 2019; Zhou et al., 2020), restored expression of CD58 (which is generally downregulated in lymphoma cells in support of immunoevasion) (Otsuka et al., 2020) and T_H1 cytokines (Peng et al., 2015), as well as T_{REG} reprogramming coupled to the establishment of a TME permissive for anticancer immunity (Sun et al., 2020; Wang et al., 2018; Zingg et al., 2017). That said, EZH2 inhibition with GSK126 reportedly favors MDSC expansion and immunosuppressive functions (Huang et al., 2019), and short hairpin RNAs (shRNAs) targeting EZH2 compromise the ability of $CD8^+$ CTLs to mount robust immune responses, correlating with a positive prognostic impact for tumor infiltration by $EHZ2^+CD8^+$ cells in patients with ovarian cancer (Zhao et al., 2016). Thus, while in some settings pharmacological strategies that deplete MDSCs, including 5-fluorouracil- or gemcitabine-based chemotherapy (Galluzzi et al., 2020a), stand out as promising candidates to maximize the therapeutic profile of EZH2 inhibitors, the precise impact of pharmacological EZH2 inhibition on anticancer immunity remains to be fully elucidated. Of note, epigenetic reprogramming with shRNAs targeting DNA methyltransferase 1 (DNMT1) or pan-DNMT blockers like decitabine and guadecitabine has been shown to resemble EZH2 inhibition in its capacity to promote CXCL9 and CXCL10 secretion in various models of breast, lung, and ovarian carcinoma (Lai et al., 2018; Luo et al., 2018; Peng et al., 2015; Wang et al., 2015). Moreover, various DNMT inhibitors have been consistently associated with improved MHC class I presentation (Luo et al., 2018; Natsume et al., 2008; Yu et al., 2019), upregulation of TAAs (Coral et al., 2002; Klar et al., 2015; Natsume et al., 2008), derepression of endogenous retroviral elements coupled to robust type I and type III IFN signaling (Chiappinelli et al., 2015; Liu et al., 2018; Roulois et al., 2015), and reconfiguration of the TME (Luo et al., 2018; Travers et al., 2019; Wang et al., 2015; Yu et al., 2019) in support of anticancer immunity or increased sensitivity to CTLA4-or PD-1 blockage (Chiappinelli et al., 2015; Luo et al., 2018; Wang et al., 2015; Yu et al., 2019). Potentially, such a therapeutic cooperativity reflects the ability of decitabine to promote the upregulation of multiple immunosuppressive mediators, including CTLA4, PD-1, and its ligands, as demonstrated in the $CD34^+$ compartment of patients with myelodysplastic syndromes (Yang et al., 2014).

Finally, a variety of mAbs targeting malignant cells mediate immunostimulation upon the engagement of ADCC, ADCP, or complement-dependent cytotoxicity. These agents include (but may not be limited to) CD20-targeting mAbs such as rituximab, obinutuzumab, ocaratuzumab, and ofatumumab (Dall'Ozzo et al., 2004; Herter et al., 2013; Teeling et al., 2004; VanDerMeid et al., 2018); the CD22-specific drug epratuzumab (Carnahan et al., 2007); the CD52-directed mAb alemtuzumab (Zhang et al., 2018c); as well as CD33- and CD58-targeting mAbs (Cooley et al., 1999; Vasu et al., 2016). That said, FcγR engagement on NK cells by unbound tumor-specific mAbs reportedly limits NK-cell responsiveness to stimulation (Capuano et al., 2015), potentially identifying an immunological mechanism of resistance to targeted anticancer therapies based on mAbs.

Taken together, these observations lend additional support to the notion that most, if not all, targeted anticancer agents mediate immunomodulatory effects that are highly relevant not only for therapeutic efficacy but also for the design of novel combinatorial regimens with superior clinical impact.

CONCLUDING REMARKS

Targeted anticancer agents have been developed based on a cell-autonomous vision of cancer biology (Hanahan and Weinberg, 2000), most often based on preclinical xenograft models in which human cancer cell lines were implanted into severely immunodeficient mice. However, as discussed here, the targeted agents that have entered clinical evaluation and obtained regulatory approval for use in cancer patients generally mediate immunostimulatory effects. This suggests that clinical development has positively selected such immunostimulatory agents as it negatively selected agents that instead mediate immunosuppressive effects. If this conjecture is correct, the future development of targeted anticancer drugs should include not only genetic and drug screens based on immune-cell/cancer-cell co-cultures (Lizotte et al., 2018; Zhang et al., 2020b) coupled with validation experiments in immunocompetent mouse models of cancer (Buque and Galluzzi, 2018) but also active immunomonitoring programs for patients enrolled in clinical trials (ideally starting in phase I studies to promote the early detection of desirable versus deleterious immune effects) (Hegde et al., 2016).

Targeted anticancer agents mediate robust immunomodulatory effects that may influence their clinical activity, either as they favor immune responses that support efficacy (e.g., ICD induction by EGFR inhibitors) (Pozzi et al., 2016) or as they stimulate immunosuppressive pathways that offset efficacy but may be therapeutically actionable (e.g., PD-L1 upregulation by

Table 5. Examples of immunomodulation by other targeted anticancer agents.

Target(s)	Agent(s)	Approved[a]	Cancer-Cell Dependent	Immune-Cell Dependent	Effect(s)	Notes	References
ALK MET ROS1	crizotinib	yes	immunostimulation		ICD induction	DAMP emission by NSCLC cells *in vitro* and *in vivo*, linked to improved sensitivity to ICIs *in vivo*	Liu et al., 2019
ALK MET ROS1	crizotinib	yes	immunosuppression		upregulation of immunosuppressive factors in cancer cells	PD-L1 upregulation in several cancer cells lines, linked to improved sensitivity of NSCLC to ICIs *in vivo*	Liu et al., 2019
BCR-ABL1	imatinib	yes	relieved immunosuppression		downregulation of immunosuppressive factors in cancer cells	PD-L1 downregulation in human GIST cells *in vitro* and murine GISTs *in vivo*	Seifert et al., 2017
BCR-ABL1	imatinib	yes		immunostimulation	activation of NK cells	activation of NK cells co-cultured with allogenic DCs isolated from mice or GIST patients treated with imatinib	Borg et al., 2004 Menard et al., 2009
BCR-ABL1	imatinib	yes		relieved immunosuppression	depletion of T_{REG} cells	inhibition of T_{REG} cell proliferation *in vitro*, linked to reduced frequency of T_{REG} cells in murine CRC	Tanaka et al., 2020
BCR-ABL1	imatinib nilotinib	yes		relieved immunosuppression	depletion of MDSCs	MDSCs polarization toward an M1-like phenotype, linked to NK-cell activation	Bellora et al., 2017 Zhang et al., 2018b
BTK	ibrutinib	yes		relieved immunosuppression	depletion of MDSCs	differentiation of MDSCs from tumor-free mice toward DCs with high MHC class II expression inhibition of MDSC generation *in vitro*, linked to reduced amounts of MDSCs in tumor-bearing mice	Stiff et al., 2016 Varikuti et al., 2020
BTK	ibrutinib	yes		inhibited immunostimulation	inactivation of NK cells	inhibition of NK-cell proliferation and effector functions driven by immunostimulatory cytokines *in vitro*	Flinsenberg et al., 2020 Hofland et al., 2019
CD20	obinutuzumab ocaratuzumab ofatumumab rituximab	yes no yes yes		immunostimulation	activation of NK cells	induction of NK-cell-mediated ADCC of lymphoma cells	Dall'Ozzo et al., 2004 Herter et al., 2013 VanDerMeid et al., 2018
CD20	obinutuzumab ocaratuzumab ofatumumab rituximab	yes no yes yes		immunostimulation	activation of macrophages	induction of ADCP of lymphoma cells	Dall'Ozzo et al., 2004 Herter et al., 2013 VanDerMeid et al., 2018
CD20	ofatumumab ocaratuzumab rituximab	yes no yes		immunostimulation	activation of the complement cascade	induction of complement-dependent cytotoxicity of cancer cells	Herter et al., 2013 Teeling et al., 2004 VanDerMeid et al., 2018
CD22	epratuzumab	yes		immunostimulation	activation of NK cells	induction of NK-cell-mediated ADCC of lymphoma cells	Carnahan et al., 2007

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Table 5. *Continued*

Target(s)	Agent(s)	Approved[a]	Cancer-Cell Dependent	Immune-Cell Dependent	Effect(s)	Notes	References
CD33	BI 836858	no		immunostimulation	activation of NK cells	induction of NK-cell-mediated ADCC of AML cells, linked to upregulation of NKALs expression in AML patients	Vasu et al., 2016
DNMT	decitabine	yes	immunostimulation		improved antigen presentation by cancer cells	MHC class I and/or TAA upregulation in various cancer cell lines, *in vitro*, coupled to increased sensitivity to ICIs in CRC-bearing mice	Coral et al., 2002 Klar et al., 2015 Natsume et al., 2008 Yu et al., 2019
DNMT	5-azacytidine decitabine	yes yes	immunostimulation		T_H1 cytokine secretion by cancer cells	CXCL9/CXCL10 secretion by cancer cells, coupled to TME infiltration by immune cells and superior response to ICIs in various tumor models	Lai et al., 2018 Peng et al., 2015 Wang et al., 2015 Travers et al., 2019
DNMT	5-azacytidine decitabine	yes yes	immunostimulation		pro-inflammatory cytokine secretion by cancer cells	type I and III IFN secretion by cancer cells, linked to improved response to ICIs in melanoma-bearing mice	Chiappinelli et al., 2015 Liu et al., 2018 Roulois et al., 2015
DNMT	decitabine	yes	immunosuppression		upregulation of immunosuppressive factors in cancer cells	upregulation of CTLA4, PD-1 and its ligands in AML cells and the $CD34^+$ compartment of MDS patients	Yang et al., 2014
DNMT	guadecitabine	no	immunostimulation		improved antigen presentation by cancer cells	MHC class I upregulation in mouse BC models, linked to improved response to ICIs in BC-bearing mice	Luo et al., 2018
EZH2	EPZ-6438	no	immunostimulation		improved antigen presentation by cancer cells	MHC class I upregulation in human DLBCL harboring *EZH2* mutations	Ennishi et al., 2019
EZH2	GSK126	no		immunosuppression	expansion of MDSCs	generation of MDSCs from hematopoietic progenitors *in vitro*, and MDSC infiltration in lung tumors developing in immunocompetent mice	Huang et al., 2019
EZH2	GSK126	no	immunostimulation		T_H1 cytokine secretion by cancer cells	increased CXCL9/CXCL10 secretion by cancer cells, *in vitro* and *in vivo*, in combination with decitabine	Peng et al., 2015
EZH2	GSK126 tazemetostat	no yes	immunostimulation		improved antigen presentation by cancer cells	MHC class I upregulation in HNSCC cell lines, linked to improved response to ICIs in mice with HNSCCs	Zhou et al., 2020
EZH2	GSK126 tazemetostat	no yes	immunostimulation		upregulation of immunostimulatory factors in cancer cells	CD58 upregulation in B-cell lymphoma, linked to enhanced T- and NK-cell activation in co-culture assays	Otsuka et al., 2020
EZH2	GSK503	no	relieved immunosuppression		downregulation of immunosuppressive factors in cancer cells	PD-L1 downregulation by melanomas *in vivo*, linked to improved response to ICIs in melanoma-bearing mice	Zingg et al., 2017

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Table 5. *Continued*

Target(s)	Agent(s)	Approved[a]	Cancer-Cell Dependent	Immune-Cell Dependent	Effect(s)	Notes	References
HDAC	entinostat	no	immunosuppression		upregulation of immunosuppressive factors in cancer cells	PD-L1 and PD-L2 upregulation in melanoma cells *in vitro* and *in vivo*, linked to improved response to ICIs in melanoma-bearing mice	Woods et al., 2015
	mocetinostat	no					
	panobinostat	yes					

ADCC, antibody-dependent cellular cytotoxicity; ADCP, antibody-dependent cellular phagocytosis; AML, acute myeloid leukemia; BC, breast cancer; CRC, colorectal carcinoma; DAMP, damage-associated molecular pattern; DC, dendritic cell; DLBCL, diffuse large B-cell lymphoma; GIST, gastrointestinal stromal tumor; HNSCC, head and neck squamous cell carcinoma; ICD, immunogenic cell death; ICI, immune checkpoint inhibitor; MDS, myelodysplastic syndrome; MDSC, myeloid-derived suppressor cell; NK, natural killer; NKAL, NK cell activating ligand; NSCLC, non-small cell lung carcinoma; TAA, tumor-associated antigen; T_{REG}, regulatory T.

[a]By the FDA for use in cancer patients.

CDK4/CDK6 inhibitors) (Jin et al., 2019b). Thus, ICIs and other immunotherapeutic strategies stand out as particularly promising partners for targeted anticancer agents in the context of combinatorial treatment regimens (Box 2). However, the biology underlying immunomodulation by targeted anticancer agents has just begun to emerge and several questions remain to be addressed in this respect.

First, what is the actual specificity of these drugs for their molecular targets? Imatinib, which was designed to target the kinase domain of ABL1 for inhibiting constitutive signaling from the BCR-ABL1 chimera, turned out to inhibit a variety of clinically relevant kinases (Carlisle et al., 2020). Along similar lines, abemaciclib was conceived to inhibit CDK4/CDK6 but has been shown to target other CDKs as well as CDK-unrelated kinases (Chen et al., 2016). Thus, although in some cases immunomodulation by targeted anticancer therapy clearly originates from on-target effects, in many others it stems from alternative (often uncharacterized) molecular players. Identifying such alternative targets is urgent, especially when immune cells are directly involved, as the latter generally do not express proteins that are actively involved in oncogenesis. As one of the exceptions to this principle, T_{REG} cells express CDK4/CDK6 as well as VEGF receptors (Goel et al., 2017; Terme et al., 2013) and hence are particularly sensitive to CDK4/CDK6 inhibitors and bevacizumab.

Second, when immunomodulation actually stems from the inhibition of the intended molecular target in malignant cells, what are the precise molecular mechanisms at play? No targeted anticancer agent was purposely designed to mediate immunomodulatory effects, implying that various proteins that support oncogenesis also influence the ability of neoplastic cells to deliver immunostimulatory or immunosuppressive signals. As an example, active CDK4/CDK6 signaling limits the ability of DNMT1 to drive the expression of endogenous retroviral elements that would otherwise promote type III IFN secretion, a pathway that can be actioned with clinically employed CDK4/CDK6 inhibitors (Goel et al., 2017). Precisely identifying similar pathways that are elicited by targeted anticancer agents will offer a variety of additional targets that may be harnessed to boost tumor-specific immune responses of clinical relevance. This is especially important when the immunomodulatory activity of a drug is multipronged and involves both beneficial and detrimental effects that could be differentially harnessed by targeting downstream signal transducers.

Third, what are the key factors underlying the divergent immunomodulatory effects that some targeted anticancer agents mediate in specific settings? Most of the drugs discussed herein have been associated with both immunostimulatory and immunosuppressive effects, depending on the specific experimental scenario (Tables 1, 2, 3, 4, and 5). However, while in some cases the source of such discrepancy is obvious (e.g., different experimental model, modulation of cell populations that divergently regulate tumor progression), in many others the underlying mechanisms remain obscure. In the latter cases, experimental variables such as drug concentration, precise medium composition, and time may have unsuspected effects on biological outcomes. Moreover, potentially neglected and/or hardly controllable genetic, epigenetic, or metabolic sources of heterogeneity may have a critical impact, especially *in vivo* (Hausser and Alon, 2020). Additional work is required to clarify

Box 2. ICIs for cancer therapy

Immune effector cells, especially (but not only) activated $CD4^+$ and $CD8^+$ T cells, express a panel of co-inhibitory receptors that are key for the extinguishment of ongoing immunity and the preservation of peripheral tolerance (Sharma and Allison, 2020). Consistent with this notion, monoclonal antibodies that block co-inhibitory receptors (on immune effector cells) or their ligands (on neoplastic and myeloid cells) mediate immunostimulatory effects so robust as to translate in the (re)activation of anticancer immune responses associated with clinical benefits in patients affected by an ever-growing number of malignancies (Ribas and Wolchok, 2018). Indeed, no less than seven different immune checkpoint inhibitors (ICIs) are currently approved by the FDA or equivalent agencies worldwide for use in cancer patients, cumulatively encompassing a large panel of oncological indications (Ribas and Wolchok, 2018). These agents include blockers of cytotoxic T lymphocyte-associated protein 4 (CTLA4), such as ipilimumab, as well as inhibitors of programmed cell death 1 (PDCD1, best known as PD-1), such as pembrolizumab, nivolumab, and cemiplimab, or its main ligand CD274 (best known as PD-L1), such as avelumab, atezolizumab, and durvalumab (Ribas and Wolchok, 2018). In addition, various ICIs targeting other co-inhibitory receptors are being extensively tested for efficacy in clinical trials (Tang et al., 2018; Vanpouille-Box et al., 2017). These hitherto experimental molecules encompass inhibitors of lymphocyte activating 3 (LAG3), V-set immunoregulatory receptor (VSIR, best known as VISTA), and hepatitis A virus cellular receptor 2 (HAVCR2, best known as TIM-3), as well as drugs that block the NK-cell co-inhibitory receptor killer cell lectin-like receptor C1 (KLRC1, best known as NKG2A) (Tang et al., 2018; Vanpouille-Box et al., 2017).

Importantly, ICIs employed as standalone immunotherapeutic agents have been shown to induce highly durable clinical responses, but only in a relatively small (15%–30%, depending on oncological setting) fraction of patients (Ribas and Wolchok, 2018), calling for the development of combinatorial treatment regimens. In this setting, targeted anticancer agents that mediate immunostimulatory effects including (but not limited to) the induction of immunogenic cell death (ICD, see Box 1) stand out as particularly promising partners for ICIs, as discussed in the main text.

the influence of tumor heterogeneity on the immunomodulatory effects of targeted anticancer agents.

Fourth, how can conventional chemotherapy and RT be harnessed to maximize the ability of targeted anticancer agents to drive tumor-specific immune responses of clinical relevance? It is clear that (at least some) targeted anticancer agents stand out as promising combinatorial partners for various immunotherapeutics, including ICIs. However, whether the efficacy of such combinations can be further boosted with conventional chemotherapeutics or RT (both of which can also mediate clinically relevant immunomodulatory effects) (Galluzzi et al., 2020a; Rodriguez-Ruiz et al., 2020) has not been thoroughly investigated. For instance, preclinical data suggest that TGF-β blockers may be useful not only to boost the ability of RT to initiate anticancer immune responses with systemic outreach (Vanpouille-Box et al., 2015) but also to limit the exclusion of immune cells from the TME, hence enabling (at least some) responsiveness to ICIs targeting PD-1 or PD-L1 (Mariathasan et al., 2018; Tauriello et al., 2018). However, clinical responses to RT combined with the TGF-β blocker fresolimumab were limited in a clinical trial enrolling patients with metastatic breast cancer (Formenti et al., 2018a), at least in part reflecting PD-1-dependent functional defects of the T-cell compartment at baseline (Formenti et al., 2019). Besides confirming the key role of immune effector in the therapeutic efficacy of RT and TGF-β blockers, these findings suggest the need for multimodal treatment regimens for overcoming the complex networks that underlie immune evasion in metastatic tumors. Along similar lines, CDK4/CDK6 inhibitors plus PD-1 or PD-L1 blockers stand out as promising tools to offset the ability of RT to promote the secretion of mitogens such as prostaglandin E_2 (PGE_2) from dying cells (Huang et al., 2011) and stimulate the upregulation of PD-L1 on cells from the myeloid compartment (Prima et al., 2017), which otherwise would potentially support tumor repopulation in the context of accrued immunosuppression. Similar considerations can be made for various other agents, highlighting an urgent need for preclinical and clinical work testing novel multimodal therapeutic regimens with superior immunostimulatory effects (Figure 2).

In conclusion, we surmise that gaining in-depth knowledge into the molecular pathways through which targeted anticancer agents mediate clinically relevant immunomodulation and conceiving multimodal treatment regimens that exert superior immunostimulatory activity will further expand the number of oncological indications obtaining clinical benefits from the use of targeted anticancer therapy.

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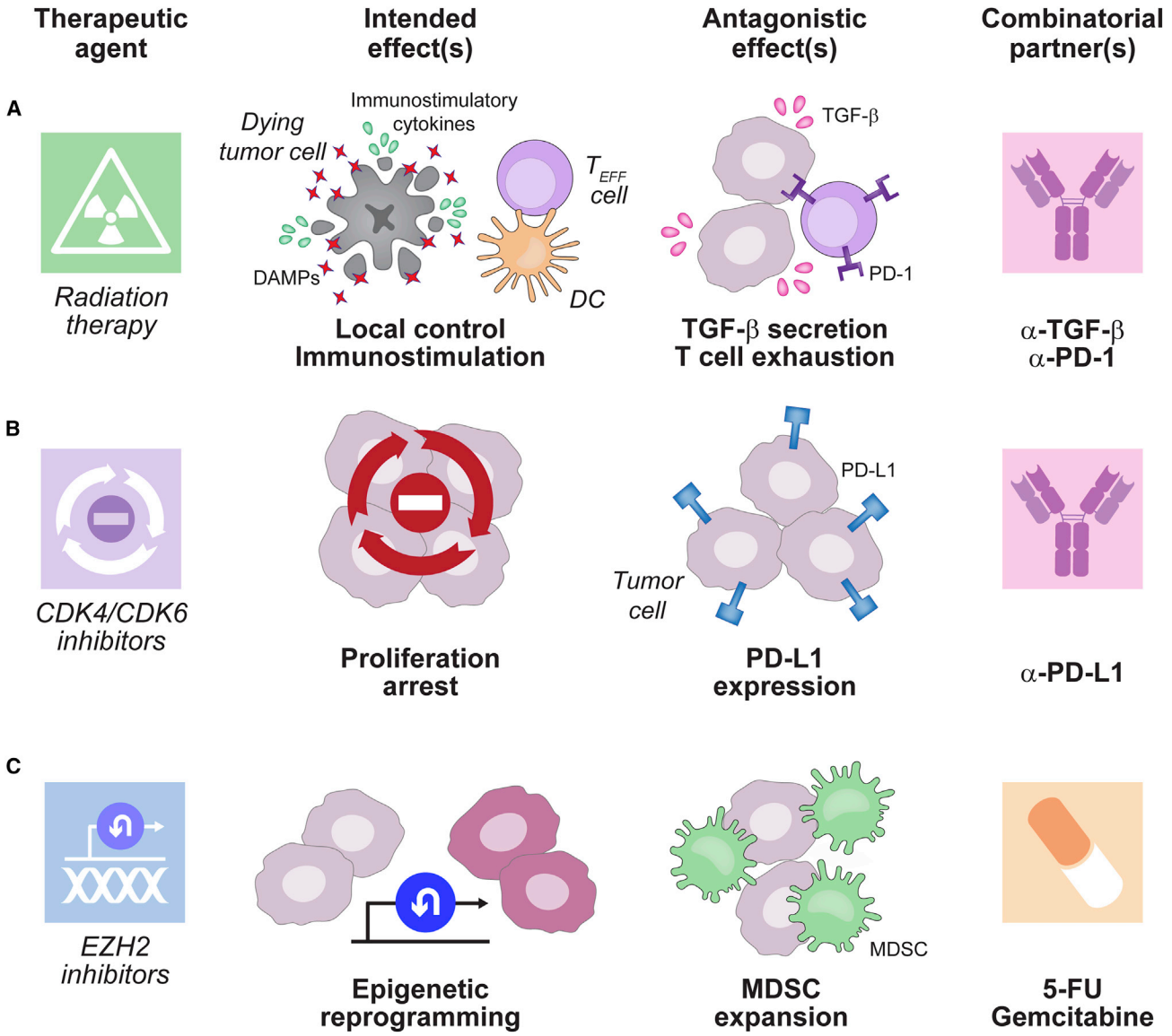

Figure 2. Examples of Multimodal Treatment Regimens that May Be Conceived to Maximize the Efficacy of Targeted Anticancer Agents with Immunotherapy, Conventional Chemotherapeutics, or Radiotherapy

(A) Immunogenic cell death induction by radiation therapy (RT) often occurs in the context of latent transforming growth factor beta (TGF-β) activation, suggesting that RT could advantageously be combined with TGF-β blockers in patients. In the context of metastatic breast cancer, however, programmed cell death 1 (PDCD1, best known as PD-1)-dependent T-cell dysfunction at baseline appears to prevent optimal efficacy, suggesting a benefit for the addition of an immune checkpoint inhibitor (ICI) specific for PD-1 or its ligand CD274 (best known as PD-L1).

(B) Cyclin-dependent kinase 4 (CDK4)/CDK6 inhibitors mediate robust cytostatic activity that is accompanied by multipronged immunostimulatory effects but also PD-L1 upregulation. Thus, ICIs targeting PD-1 or PD-L1 stand out as promising combinatorial partners for CDK4/CDK6 inhibitors to circumvent (at least partially) PD-L1-dependent immunosuppression.

(C) Pharmacological inhibition of enhancer of zeste 2 polycomb repressive complex 2 subunit (EZH2) exerts therapeutic activity linked to robust immunostimulation, but appears to be associated with myeloid-derived suppressor cell (MDSC) expansion. Thus, chemotherapeutic regimens that deplete MDSCs and/or limit their immunosuppressive functions, such as 5-fluorouracil (5-FU)- or gemcitabine-based chemotherapy, stand out as promising combinatorial partners for EZH2 inhibitors.

DAMP, damage-associated molecular patter; DC, dendritic cell; T_{EFF}, effector T.

AUTHOR CONTRIBUTIONS

G.K. and L.G. conceived the article. G.P. and A.B. wrote the first version of the manuscript under supervision by L.G. and with constructive input from L.Z. and G.K. G.P. and A.B. prepared display items under supervision from L.G. G.K. and L.G. addressed reviewers' concerns and editorial requests. All authors approve the final version of the article.

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