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Tumour Review

The role of tumor-associated macrophages in gastric cancer development and their potential as a therapeutic target

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ABSTRACT

Gastric cancer (GC) represents the fifth cause of cancer-related death worldwide. Molecular biology has become a central area of research in GC and there are currently at least three major classifications available to elucidate the mechanisms that drive GC oncogenesis. Further, tumor microenvironment seems to play a crucial role, and tumor-associated macrophages (TAMs) are emerging as key players in GC development. TAMs are cells derived from circulating chemokine- receptor-type 2 (CCR2) inflammatory monocytes in blood and can be divided into two main types, M1 and M2 TAMs. M2 TAMs play an important role in tumor progression, promoting a pro-angiogenic and immunosuppressive signal in the tumor. The diffuse GC subtype, in particular, seems to be strongly characterized by an immuno-suppressive and pro-angiogenic phenotype. No molecular targets in this subgroup have yet been identified. There is an urgent need to understand the molecular pathways and tumor microenvironment features in the GC molecular subtypes. The role of anti-angiogenics and checkpoint inhibitors has recently been clinically validated in GC. Both ramucirumab, a fully humanized IgG1 monoclonal anti-vascular endothelial growth factor receptor 2 (VEGFR2) antibody, and checkpoint inhibitors in Epstein Bar Virus (EBV) and Microsatellite Instable (MSI) subtypes, have proved beneficial in advanced GC. Nevertheless, there is a need to identify predictive markers of response to anti-angiogenics and immunotherapy in clinical practice for a personalized treatment approach. The importance of M2 TAMs in development of solid tumors is currently gaining increasing interest. In this literature review we analyze immune microenvironment composition and signaling related to M1 and M2 TAMs in GC as well as its potential role as a therapeutic target.

The role of microenvironment in GC development and progression

Gastric cancer (GC) is characterized by high incidence and mortality and it represents the sixth most common cancer type and fifth leading cause of cancer death worldwide [1]. When diagnosed in an advanced stage, GC is characterized by very poor prognosis, with a five-year overall survival rate of about 5% [2]. Historically GC has been classified into two main subgroups, intestinal and diffuse, according to different microscopic features [3]. Several molecular classifications based on comprehensive analyses have been proposed to gain better understanding of GC biology and for a personalized medicine approach [4–6]. Findings from these classifications identified at least two phenotypes that benefit from checkpoint inhibitors including the EBV positive and MSI-H profiles. PD-L1 expression, CPS score and the presence of TILs (Tumor infiltrate lymphocytes) along several solid tumors were associated with response to checkpoint inhibitors, nevertheless, their prognostic role need to be further explored [7].

There is increasing interest in the role of the immune microenvironment in GC [8–10]. Moreover, chronic inflammation and *H. pylori* infection are the classical determinants in GC development [8].

In this scenario, the role of macrophages is fascinating. Presence and density of tumor-associated macrophages (TAMs) has been correlated with prognosis and resistance to treatment. The immunosuppressive and pro-angiogenic phenotype that TAMs promote could be of primary

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interest especially in diffuse GC and in the genomically stable subgroup, where the presence of M2 Macrophages was found to be higher and could contribute to an immunosuppressive phenotype [11 12–14]. This review aims to analyze the role of tumor-associated macrophages (TAMs) in GC to pave the way for new molecular research and therapeutic approaches.

Tumor-Associated Macrophage in solid tumors

Macrophages are players in the innate immune response and a major component of the leukocyte infiltrate present in solid tumors. TAMs play a dominant role in cancer-related inflammation and constitute important regulators of tumorigenesis. Recent evidence supports the hypothesis that these cells are characterized by a dual pro- and anti-tumor activity. Macrophages were originally found to be involved in antitumor immunity, as they are able to identify non-self cells and finally phagocytize them. Nevertheless, increasing pre-clinical and clinical evidence shows that TAMs could paradoxically also enhance tumor development and metastatic capabilities. Paradoxically, a predominant role in supporting multiple aspects of tumor progression such as immune tolerance and tumor cell activation by paracrine signaling loops has been detected [15,16] and they have also been linked to cancer treatment resistance.

The dual role of TAMs: M2 macrophages and cancer development and progression

This dual role of macrophages in cancer has been justified by their functional plasticity, that may explain their differing behavior: “classically-activated” M1 macrophages produce type I proinflammatory cytokines such as IL-1β, IL-1α, IL-12, TNF-α, and GFAP [17,18]. Conversely, “alternatively-activated” M2 macrophages produce type II cytokines, such as IL-4, IL-6, IL-10 promoting anti-inflammatory responses, and have pro-tumorigenic functions [18,14,19–23].

During the transition from M1 to M2, the microenvironment appears to be dominated by cytokines and growth factors, such as IL-4 synthesized by CD4 + T cells and/or tumor cells [24,25], growth factors such as CSF-1 [26] and Granulocyte-macrophage colony-stimulating factor (GM-CSF) [27]. This environment (Th2) is enriched in transforming growth factor-β1 (TGF-β1) and Arginase 1, as well as an increased number of CD4 + T cells [28]. All these factors cause a switch in the polarization of macrophages from TAM-M1 to an alternatively immunoregulatory TAM-M2 (Fig. 1) [29]. Certain extracellular matrix (ECM) molecules and their proteolytic fragments including elastin fragments, denatured and fragmented collagen I or soluble biglycan have been shown to act as inflammatory stimuli for recruitment of macrophages [30]. Tumor-derived hyaluronic acid (HA) fragments have also been shown to promote development of immunosuppressive M2 macrophages by triggering a transient early activation of monocytes [31]. Moreover, transcriptomic profiling of fluorescence-activated cell sorting (FACS)-isolated TAMs revealed a distinct ECM-catabolic signature, characterized by high expression of ECM-degrading enzymes and low expression of ECM proteins [32,33]. In general, metabolism differs depending on TAM phenotype: M1 TAMs are characterized by exhibit enhanced glycolysis, pentose phosphate pathway (PPP) and Fatty acid (FA) synthesis, with a truncated tricarboxylic acid cycle leading to accumulation of succinate and citrate. In contrast, M2 TAM-activated macrophage metabolism is characterized by oxidative phosphorylation, decreased glycolysis and PPP, and FA oxidation [34,35]. Emerging evidence reveals that macrophage metabolic features are closely associated with their immune functions.

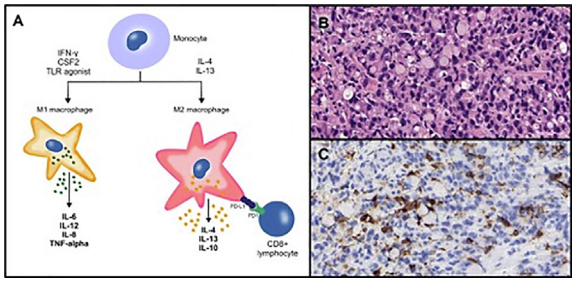

Fig. 1. A. Monocyte differentiation into M1 and M2 macrophages phenotypes. Proinflammatory M1 or “activated macrophages” promotes type I T helper (Th1) antitumoral immune response by producing IL-6, IL-12, IL-8 and TNFα. In contrast, alternatively activated M2 macrophages are involved in Th2 immune responses including humoral immunity and wound healing. In solid tumors, M2 macrophages, promotes tumor progression and invasion by inducing angiogenesis and suppressing the host immune response. B. Histopathological section of a diffuse-type gastric tumor with signet ring cells (HE, 200×). C. CD163 immunostaining highlights the presence of numerous M2 macrophages between tumor cells (CD163, 200×).

TAMs and immune response

One of the most critical roles TAMs play in tumor initiation and progression is their ability to induce immune tolerance. This is a highly complex process in which T lymphocytes, macrophages and other cells may have a primary role [36–39]. Ligand expression of programmed cell death protein 1 (PD-1) and cytotoxic T-lymphocyte antigen 4 (CTLA-4) inhibitory receptors could also contribute to this. These inhibitory ligands are normally upregulated in activated immune effector cells such as T cells, B cells, and NK T cells, as part of a safety mechanism that controls the intensity of the immune response the Blockade of PD-1 and CTLA-4 by their ligands (PD-L1, PD-L2, and B7-1 [D80], B7-1 [CD86], respectively) directly inhibits T-Cell Receptor and B-Cell Receptor signaling. This activation also inhibits cytotoxic T cell function, regulating their cell cycles. PD-L1 and PD-L2 are differentially expressed, with PD-L1 constitutively expressed by immune cells including T cells, B cells, macrophages, DCs, non-hematopoietic cells and cancer cells. In contrast, PD-L2 expression is limited to antigen-presenting cells (APCs) and its expression induced in monocytes and macrophages by CSF-1, IL-4, and interferon- α (INF-α) [40]. Both PD-L1 and L2 are regulated in TAMs and myeloid-derived suppressor cells [40–42], PD-L1 and PD-L2 are up-regulated in macrophages as dynamic response to cytokines. PD-L1 is highly expressed on inflammatory Macrophages. In contrast, PD-L2 is not expressed on inflammatory macrophages but can be induced by alternative activation via IL-4 suggesting that PD-L1 and PD-L2 might have different functions in regulating type 1 and type 2 responses [40–42].

TME alteration also enables development of immunoediting, a dynamic process during which cancer cells able to immune surveillance [43,44]. Immunoediting can be promoted by tumor cells secreting cytokines and chemokines to recruit MDSCs, regulatory T cells (Tregs), and TAMs.

Another important factor in tumor initiation is neo-angiogenesis [45]. It has been suggested that environmental conditions such as tumor hypoxia may mediate this phenomenon. Indeed, TAMs accumulate in regions of hypoxia in growing tumors [46] mediated by an upregulation of macrophage chemo-attractants including endothelin-2 and vascular endothelial growth factor (VEGF). Of note, TAM accumulation in these regions correlates with the subsequent acquisition of an invasive phenotype [46], causing a switch in macrophage polarization [47]. Several anti VEGF and VGFR inhibitors have been tested in GC; nevertheless, only ramucirumab, a selective VRGFR2 monoclonal antibody, was able to improve clinical outcomes in advanced disease. Ramucirumab was also observed to act against TAMs and its inhibition of VEGFR2 could cause the decrease in TAM immune infiltration, cytokine and chemokine release, that reduces tumor growth and proliferation [48]. This potential role against TAM could be one of the cornerstones of ramucirumab activity across the different GC subtypes.

In addition, it was recently shown that TAMs in hypoxic tumor

regions upregulate PD-L1 expression as a consequence of hypoxia-induced factor-1 α (HIF-1α) signaling [49]. CSF-1-regulating macrophages have been recognized as playing a pivotal role in tumor neoangiogenesis through VEGF production [50]. Several experiments in solid tumor models have confirmed that macrophage-synthesized WNT7B targets vascular endothelial cells, stimulating their VEGF production, resulting in neo-angiogenic development. These angiogenic TAMs express Tie2, a tyrosine-protein kinase that acts as a cell-surface receptor for angiopoietins, which regulate angiogenesis, endothelial cell survival, proliferation, migration, adhesion and cell spreading. Inhibition of this population ultimately blocks the neo-angiogenesis process in several cancer models [51–55], Interestingly, CSF-1 upregulates Tie2 in TAMs [55] indicating a link between CSF-1, Tie2 + macrophages and neo-angiogenesis induction. Moreover, Tie2 + macrophages aligned along the vessels also could promote tumor cell intravasation into the circulation [15], leading to metastasis. In fact, macrophage infiltration correlates significantly with tumor vascularity in human GC and promotes directional tumor cell migration and invasion via a paracrine loop consisting of tumor-cell-synthesized CSF-1, which induces epidermal growth factor (EGF) expression by macrophages, creating a positive feedback loop [15,16,56,57].

Macrophages recruitment is also an important step for pre-metastatic niche formation. LOX, a copper-dependent amine oxidase secreted from tumor cells, forms the cross-links of collagen IV in the basement membranes at the pre-metastatic sites where TAMs then adhere to the cross-linked collagen IV and produce MMP-2. This positive feed-forward loop eventually increases extracellular matrix remodelling and contributes to forming the pre-metastatic niche [58]. The potential impact of TAMs on cancer cell metastases has also been linked to epithelial mesenchymal transition (EMT) promotion. This phenomenon is mediated by TAM production of osteonectin (SPARC), cathepsin proteases and TGF-β, fundamental for cancer cell migration and invasion [47,59-61]. All these factors support tumor-associated angiogenesis, promotion of tumor cell invasion, migration, and intravasation and suppression of antitumor immune responses [16,23,62].

Inflammation, microenvironment and TAMs in GC development

Inflammation is one of the hallmarks of cancer [63] and many types of solid tumors are preceded by a chronic inflammatory process, mostly initiated by infections or exposure to environmental factors. One characteristic of the tumor microenvironment (TME) in GC is chronic inflammation derived from infection, such as *H. pylori*, which cause the upregulation of pathways that promote cell survival, activate stem cells and epithelial proliferation [4,64]. *H. pylori* and other pathogens impair M1 macrophage responses inducing an M2-like state, and increase the rate of ROS-induced macrophage apoptosis, enhancing the risk of disease progression [65].

TME alteration also enables development of immunoediting, the process by which the immune system can either block or promote cancer development, supporting the increase of tumor cells with reduced immunogenicity [43,44]. Immunoediting can be promoted by tumor cells secreting cytokines and chemokines to recruit MDSCs, regulatory T cells (Tregs), and TAMs. High density of M2 TAM macrophages has been associated with worse overall survival in several malignancies, including GC [66–68]. TAM infiltration differs essentially when tumor tissue and normal tissue are compared, with worse survival in cases with high abundance of M2 TAMs [69]. When the microenvironment was better characterized, it was possible to observe that the co-existence of TAMs and TGF-β was associated with aggressive cancer features, leading to poor prognosis, and could therefore be used as an independent prognostic factor in GC [70–72]. M2 TAMs were also correlated to worse OS in resected GC patients with lymph node metastases. Moreover, research suggests that a higher number of CD204-positive macrophages (a M2-polarized macrophage receptor) in stroma could be related to GC carcinogenesis. Another interesting observation warranting further investigation is the relationship between TAMs and tumor-infiltrating lymphocytes (TILs) as a potential prognostic biomarker [66,73]. PD-1 overexpression in TAMs has also been demonstrated as a mechanism associated with reduction in the phagocytic capacity of macrophages and tumor progression and impaired NK response through TGF-β activation [74,75].

M2 macrophages level was descripted to be lower in signet ring cell carcinoma and mucinous adenocarcinoma but ample in poor-differentiated adenocarcinoma [76]. A meta-analysis showed that the number of infiltrating M2 macrophages and total TAMs could be negative prognostic factors for GC patients, while M1 macrophage infiltration may be associated with a favorable survival rate [72]. In a recent investigation, the PDL1 expression and TAMs were analyzed according the different molecular subtypes of GC. Among the PDL1-high patients analyzed in this cohort, the CD68 + macrophages were predominant in the GS and diffuse subtypes, whereas the CD68 + CD206 + + (M1) macrophages were enriched in the MSI and intestinal subtype. In addition, TAMs in the GS and diffuse cancer subtypes had significantly lower median PDL1 expression. Nevertheless, no prognostic differences were identified [77].

To better characterize [78] TME infiltration patterns, in a recent study analyzing 1,524 gastric cancer patients, three TME phenotypes were identified using principal component analysis algorithms. The high TME score subtype exhibited immune activation and response to virus and IFN-α, while activation of TGF-β, EMT angiogenesis, TGFb signaling and hypoxia pathways were observed in the low TME score subtype, which are considered T-cell suppressive and may be responsible for significantly worse prognosis in GC.

In another study mRNA expression of GC was evaluated, and in the diffuse subtype there was notable high expression of ECM, angiogenesis, intracellular and cytoskeleton and collagen related genes. Moreover, ECM-related modules showed inverse correlation with immune response gene expression and this was identified as the key factor associated with the aggressive features of diffuse gastric tumours, which indicates tumour progression involving mechanisms to evade immune surveillance in diffuse tumours [79]. Furthermore, at single-cell gene expression level, a recent study had shown impressive cellular changes in GC tumor samples compared to matched normal mucosa, with increased stromal cells and cytotoxic T cells in tumor samples with heterogenous profiles of exhaustion and expression of multiple immune checkpoint and costimulatory molecules as well as an heterogenous population of macrophages not confined to M1/M2 stages [80].

More translational studies are necessary to elucidate the complex relationship of the immune microenvironment with GC in order to apply a more rational and personalized therapeutic approach that could improve outcomes across different phenotypes.

Limitations of the current evidence on TAMs

Despite the attractive role of TAMs and their implication in the immune response, their role and therapeutic implication need to be further validated. Moreover, TAMs evaluation in different subgroups of GC, should be further clarified to provide theoretical for GC immunotherapy.

TAMs as a potential target for cancer treatment

In the era of immunotherapy, there is an increasing need to identify new treatment strategies for a personalized treatment approach and to overcome resistance to check-point inhibition. Moreover, the potential role of macrophages in tumor development has driven the development of new anti-cancer treatments. Indeed, several strategies have been proposed to deplete TAM or to reconvert TAM M2 into TAM M1. In some preclinical models, the reversion of TAMs back to a M1 phenotype was associated with tumor regression by disrupting NFkB signaling or interacting with TNF-α [81,82]. The nuclear factor κB (NF-κB) signaling

pathway is important in cancer-related inflammation and malignant progression. Recent preclinical studies in mouse models of colon and liver cancer have defined an important role for NF-κB activation in driving cancer-associated inflammation. Cytokines of the TNF family trigger a variety of NF-κB-dependent responses that can be specific to both cell type and signaling pathway. The cytokine tumor necrosis factor (TNF) initiates tissue inflammation, a process mediated by the NF-κB transcription factor. In response to TNF, latent cytoplasmic NF-κB is activated, enters the nucleus, and induces expression of inflammatory and anti-apoptotic gene expression programs. Recently it has been shown that NF-κB displays two distinct activation modes, monophasic and oscillatory, depending on stimulus duration [83].

Another interesting strategy was reported, demonstrating the inhibition of intratumoral macrophage M2 polarization through endostatin (an antiangiogenic) gene therapy in renal cell carcinoma [84].

Direct inhibition of TAM

The most important pathway associated with TAM recruitment and proliferation is (CSF-1)/CSF-1 receptor (CSF-1R) signaling, essential for macrophage survival and for the transition from TAM M1 into TAM M2type. The CSF-1R belongs to the platelet-derived growth factor family. It is characterized by a highly glycosylated extracellular region comprised of five immunoglobulin domains, a transmembrane domain, and an intracellular domain comprised of a juxtamembrane domain and an intracellular tyrosine kinase domain. The known ligands for the CSF-1R are CSF-1 and IL-34. CSF-1R signaling promotes myeloid differentiation, monocytic commitment, and the survival, proliferation, and chemotaxis of macrophages [85].

Several monoclonal antibodies and tyrosine kinase inhibitors targeting CSF-1/CSF-1R are under development in clinical trials and being tested as single agents or in combination (Table 1).

Emactuzumab is a humanized monoclonal antibody directed againstCSF-1R. It was studied as a single agent in a phase I trial enrolling patients with tenosynovial giant cell tumors, in which it showed no significant toxicity at the optimal immunomodulatory dose of 1000 mg every two weeks. In the dose-expansion phase, 24 (86%) of the 28 patients tested showed an objective response, and 2 (7%) achieved a complete response [86].

The same pathway was also inhibited by using Tyrosine kinase inhibitors (TKis) (Table 1). Results from phase I and phase II trials indicated that pexidartinib (PLX3397) was well tolerated; however, when it was tested in a phase II trial enrolling patients with recurrent glioblastoma, pexidartinib did not improve six-month progression-free survival rates compared with standard radiotherapy and temozolomide [87]. Nevertheless, another TKi, BLZ945 [88], showed promising results in glioma when used in combination with inhibitors of insulin-like growth factor 1 receptor (IGF1R) and phosphoinositide 3 kinase (PI3K) [89], and is currently under assessment in a trial in advanced-stage solid tumors as a single agent and in combination with the anti-PD1 antibody PDR001 (NCT02829723).

Both monoclonal antibodies and TKis seem to be well tolerated with a favorable safety profile. Frequently reported adverse events (AEs) include fatigue, elevated liver enzymes, facial and peripheral edema, asthenia, pruritus, rash, nausea/vomiting, headache and dry skin [90–98].

Asymptomatic increases in liver enzymes seen in CSF-1R-targeting treatment are most likely caused by a decrease in physiologic clearance through partial depletion of sessile liver macrophages (CSF-1R + Kupffer cells) [99].

Potentially immune-related AEs have been described for monoclonal antibodies (mAbs), but serious liver injuries have not been reported. In contrast, pexidartinib caused serious non-fatal liver toxicity [100]. In line with the generally favorable safety profile of CSF-1R inhibitors, combination treatment studies have been initiated for both chemotherapies and targeted therapies or immunotherapies.

Another way to inhibit macrophages is through the CCL2–CCR2 axis. CCL2 is a potent chemoattractant for monocytes, T cells and NK cells [101–105]. CCL2 released by tumor cells recruits classical monocytes that express the receptor CCR2 to the tumor sites, and its inhibition reduced tumor burden and metastasis in experimental models. High CCL2 levels in serum and in the tumor were associated with poor prognosis in different types of tumors [106,107]. For these reasons, several CCL2-neutralizing antibodies are now being tested in clinical trials (NCT00992186).

Indirect inhibition of TAM

Use of bisphosphonates has been related to inhibited proliferation, migration and invasion of macrophages, which share the same lineage with osteoclasts, causing apoptosis [108–111]. Zoledronic acid reduced tumor progression in mouse models of bone metastases from breast cancer [112] and modulated the TME by reducing the number of TAMs and their polarization status [113]. It has also been demonstrated that treatment with zoledronic acid impairs macrophage polarization, reduces macrophage-induced angiogenesis and decreases tumor invasion in prostate cancer [114].

An important observation is that the efficacy of some chemotherapeutic agents such as trabectedin may be also related to their ability to kill TAMs. In preclinical experiments, it was shown that trabectedin maintained anticancer activity when resistant cells were transplanted in immunocompetent mice[115]. The drug activity was probably associated with the capability in decreasing of TAM density.

Radiotherapy was also found to influence TAM: Low-dose irradiation of mouse pancreatic and colorectal cancers functionally reprogrammed TAMs to an antitumor phenotype, characterized by a NOS2-dependent increase in their T cell stimulatory properties [116]. The changes in microenvironment observed with both chemotherapy and radiotherapy and their therapeutic impact on cancer confirm the importance of inhibiting TAM in solid malignancy.

A summary of the different clinical trials targeting TAMs are described in Table 1.

Conclusion

This review summarizes the role of macrophages in solid tumors and in GC, in particular in the diffuse subtype where no targeted molecular alterations have been detected so far. In several translational studies the role of TAM2 was found to be predominant in this subgroup according to FACs evaluations and transcriptomic analyses. The prognostic value of TAMs seems to suggest a more aggressive phenotype, nevertheless perspective studies and further evaluations are needed to better clarify their role in resistance to chemotherapy and in the development of an immunosuppressive phenotype. As immunotherapy represents a relevant part of the treatment of many solid tumors where predictive markers such as PD-L1 expression, TILs and Tumor mutation border could help in identifying those patients who will benefit from this approach, the role of TME needs to be further understood. In particular when TAMs are significantly represented it would be necessary to investigate about their role and possibly acting by the use of specific inhibitors actually under development. Nevertheless, the impact of this treatment in GC should be further evaluated.

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Table 1
Clinical trials targeting tumor-associated macrophages in solid tumors.

Class of drug	Drug	Target	Compound characteristics	Clinical trial	Tumor Type	Trial design	Treatment
Monoclonal antibodies	**Emactuzumab (RG7155)**	CSF1R	Mactuzumab binds to CSF1R expressed on macrophages and inhibits binding of colony-stimulating factor-1 (CSF-1) to CSF1R.	NCT02323191 NCT02760797 NCT02923739 NCT03369964 NCT03821246 NCT01494688 NCT03193190	Locally advanced or metastatic solid tumors	Phase I Phase I Phase II Phase I Pahse II Phase I Phase I	Single agent Single agent Paclitaxel Bevacizumab Anti CD20. Enzalutatmide + Atezolizumab. Paclitaxel. Multiple immunotherapy
	Cabiralizumab (FPA008)		Binds to CSF1R expressed on monocytes, macrophages, and osteoclasts and inhibits CSF1R ligands colony-stimulating factor-1 (CSF-1) and interleukin-34 (IL-34), from binding to CSF1R	NCT02526017 NCT03336216 NCT03768531 NCT03335540	Advanced Solid Tumors, Including But Not Limited to Lung Cancer Head and Neck Cancer Pancreatic Cancer Ovarian Cancer Renal Cell Carcinoma Malignant Glioma Biliary tract	Phase I Phase I Phase I Phase I	Nivolumab. Nivolumab ± CT. Single agent. Multiple immunotherapy
	IMC-CS4		Bactuzumab binds to CSF1R expressed on macrophages and inhibits binding of colony-stimulating factor-1 (CSF-1) to CSF1R.	NCT01346358 NCT03153410 NCT02265536	Advanced solid tumors refractory to standard therapy, Pancreatic cancer, Breast Cancer, Prostate Cancer	Phase I Phase I Phase I	Single agent CY, Pembrolizumab, GVAX Single agent
Tyrosine Kinase inhibitors	**Pexidartinib (PLX3397)**	CSF1R, cKIT, FLT3, PDGFR	Pexidartinib binds to and inhibits phosphorylation of stem cell factor receptor (KIT), colony-stimulating factor-1 receptor (CSF1R) and FMS-like tyrosine kinase 3 (FLT3	NCT02584647 NCT02071940 NCT02452424 NCT01499043 NCT01349036 NCT01596751 NCT01525602	Advanced solid tumors refractory to standard therapy, Sarcoma, Melanoma, Melanoma Non-small Cell Lung Cancer Squamous Cell Carcinoma of the Head and Neck Gastrointestinal Stromal Tumor (GIST) Ovarian Cancer	Phase I Phase I Phase I Phase I Phase II Phase Ib/II Phase I	Single agent Single Agent Combined with Pembrolizumab Single Agent Single Agent Combined with Eribulin Single Agent
	ARRY-382,	CSF-1R	A small molecule and orally available inhibitor of CSF-1	NCT01316822	Advanced solid tumors refractory to standard therapy	Phase I	Single agent
	PLX7486	CSF-1R, TRKA-B-C	The tosylate salt form of PLX7486, a selective inhibitor of the receptor tyrosine kinases colony-stimulating factor-1 receptor (CSF1R; fms) and neurotrophic tyrosine kinase receptor types 1, 2 and 3 (TrkA, TrkB, and TrkC, respectively)	NCT01804530	Advanced solid tumors refractory to standard therapy	Phase I	Single agent
	BLZ945	CSF-1R	BLZ945 selectively binds to CSF1R expressed on tumor-associated macrophages (TAMs), blocks CSF1R activity, and inhibits CSF1R-mediated signal transduction pathways.	NCT02829723	Advanced solid tumors refractory to standard therapy	Phase I/II	Combined with PDR001
	JNJ- 40,346,527	CSF-1R	A small molecule, orally available inhibitor of colony-stimulating factor-1 receptor (CSF1R; FMS) with potential antineoplastic activity. FMS tyrosine kinase inhibitor JNJ-40346527 blocks the receptor-ligand interaction between FMS and its ligand CSF1	NCT03177460 NCT01054014	Advanced solid tumors refractory to standard therapy, Prostate	Phase I Phase I	versus Daratumumab. Single agent

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Declaration of Competing Interest

AC declares institutional research funding from Genentech, Merck Serono, BMS, MSD, Roche, Beigene, Bayer, Servier, Lilly, Novartis, Takeda, Astelas and Fibrogen and advisory board or speaker fees from Merck Serono, Roche, Servier, Takeda and Astelas in the last five years. The other authors declare no potential conflicts of interest.

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