Relationship between tumorigenesis, metastasis, immune evasion, and chemoresistance in osteosarcoma therapy

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ABSTRACT

There has been no significant efficacy in treating osteosarcoma (OS) metastasis after nearly four decades of trials. This motivates us to elucidate OS therapies using their four bidirectional mutation stages. The historical developments and clinical advancements are briefly described to refresh the OS therapy status quo. However, the main issue of metastasis remains unresolved, accounting for 90% of pulmonary metastasis deaths. Thus, this metastasis problem is related to immune evasion and chemoresistance induced after long-term treatment by immunotherapy for tumorigenesis. Therefore, it is rational to discuss the relationship cycles of mutation stages, including tumorigenesis, metastasis, immune evasion, and chemoresistance. Even though many combinational and targeted therapies have been developed to intensify these mutation treatments, successful clinical translations with higher cure rates are still rare. Through this review, an in-depth understanding of the bidirectional relationship between the four OS mutation stages and their respective therapies is provided. Herein, we summarise the medicines for treating tumorigenesis, including Collagen beta (1-O) galactosyl transferase 2 inhibitors, transformer 2β, and ArfGAP with GTPase domain 1, miR-148a and miR-21-5p exosomal vesicles, and the long non-coding RNA leukemia inhibitory factor antisense RNA1. Following the medicines for treating metastasis are AXL receptor tyrosine kinase, miR-135a-5p, messenger RNA B-cell lymphoma-6, transforming growth factor beta 1, T-cell immunoglobulin, and mucin-domain containing protein-3, suppressor of cytokine signalling-5, cancer susceptibility 15, Krüppel-like factor 3 antisense RNA 1, programmed cell death 4, autophagy-related gene 5, and Rab22a-NeoF1. Then the medicines for treating immune evasion are N-cadherin, ubiquitin-specific peptidase 12 inhibitors, latency-associated peptide domain inhibitors, anti-Wnt2 mAb, anti-αvβ8 integrin, hexokinase-2-mediated i-kappa-b-alpha, indoleamine 2,3-dioxygenase inhibitor with NO, and TGF-βRII with anti-IgG1. Finally, the medicines for treating chemoresistance are Dihydrofolate reductase, folylpoly-γ-glutamate synthetase, heat shock protein-90AA1, XCT-790, anlotinib tyrosine kinase inhibitor, and insulin-like growth factors 1.

As a result, this contribution is expected to serve as a reference and guide for scientists and clinicians.
causes a mortality rate of more than 90% [10]. As a result, only about 20%–30% of such cases live for a prolonged period, compared with 65%–70% of localized cases [11].

Over nearly four decades, scientists and clinicians have attempted to solve the 30% ineffectiveness problem [12] for the standard treatments [13,14], such as chemotherapy [15], immunotherapy [16], inhibitory therapy [17], and surgery [18], resulting in progression to malignant tumors [19]. Even after numerous trials, there has been no significant improvement. This is due to the immunotherapy on tumorigenesis [20], which develops severe immunosuppression and chemoresistance after long-term treatments [21–23]. Furthermore, the innate and acquired nature of chemoresistance in the tumor microenvironment (TME) eventually causes the therapy’s progression to stall [24]. Thus, this primary barrier needs to be encountered by intensifying more efficacious therapies with higher cure rates [25]. However, not much research provides an in-depth understanding of the relationship between tumorigenesis, metastasis, immune evasion, and chemoresistance. As a result, the efforts in designing an efficacious, long-term use [26], and personalized precision medicine [27] for combinational and targeted therapy [28–30] remain inadequate [31].

Because the four stages are intertwined and complex [32], this review focuses on clarifying their relationship and encounter therapies. First of all, the status quo of OS therapies is presented, along with their historical development and clinical advancements. A comprehensive timeline is drawn to demonstrate significant discoveries and advancements in OS studies. Besides, the summary of completed years of sarcoma clinical trials is tabulated to highlight the seminal discoveries and major clinical triumphs. In the content, the bi-directional relationship between these four OS mutation stages—tumorigenesis, metastasis, immune evasion, and chemoresistance—is clearly described. Further, short and precise definitions are given to each of them to reach a common understanding. Hereafter, their intertwined therapies could be discussed individually. Herein, it is notable that many clinically relevant therapies nowadays are combinational and multifunctional in order to cure the complex OS stages. Notably, intertwined therapy is a fact that should not be overlooked; however, it is prudent to discuss them by reconstructing them to elaborate precisely. Through this review, the stages and therapies of OS are precisely defined and clearly elucidated, which are expected to serve as guidance for scientists and clinicians.

**STATUS QUO OF OS THERAPIES**

**Historical development**

The significant discoveries and advancements in OS studies are shown as a timeline in Figure 1. The first in vivo test was the characteristic investigation of the fresh anterior lobe effects in 1922 by Evans and Long [33]. After 42 years, the first gene for human growth hormone (HGH) was cloned by Li and Liu [34]. In 1978, the first high-dose methotrexate (Mtx) for OS treatment was introduced by Jaffe et al. [35]. Later in 1982, the compliance issue of high dosage for preoperative adjuvant chemotherapy was addressed by Rosen et al. [36]. After 2 years, the biological and immunological properties of OS were investigated by Zapf et al. [37] using insulin-like growth factors (IGF). However, the first in vitro test was done in 1987 by Stashenko et al. [38] who investigated a bone inhibitor using Interleukin (IL)-1β. Six years later, the first recombinant technology for HGH was successfully developed by Bengtsson et al. [39]. In 1997, the first common childhood use of combined chemotherapy with etoposide and ifosfamide (EnI) was developed by Gentet et al. [40]. McGary et al. [41] were the first to use the Tyrosine Kinase Inhibitor STI571 in 2002 for targeted OS therapy. Further works by Nardin et al. [42]...
used liposomal muramyl tripeptide phosphatidylethanolamine in immunotherapy to target and activate macrophages. Nevertheless, Tang et al. [43] introduced the stem cell with a salinomycin inhibitor in 2011. Finally, the first preliminary efficacy and safety drug carrier with a nab-sirolimus was introduced in 2019 by Gordon et al. [44].

Clinical advancement

OS research is extremely hard and remains a global challenge. Despite the fact that many clinical trials had begun, the majority of them could not be completed. For the past 20 years, only ten clinical trials with United States federal government clinical trial identifiers (GCTI) have been successfully completed. Thus, the sarcoma types completed their clinical trials in years with active pharmaceutical ingredients (API) and primary tests, as shown in Table 1. For all these trials, there are only two main types of OS: soft and solid, as observed in the table. The following API are appropriate for OS: topotecan (Tpt) [45], pazopanib (Pzp) [46], placebo (Plb) [47], gemcitabine (Gct) [48], M6620 [49,50], regorafenib (Rgf) [51,52], glembatumumab vedotin (GV) [53,54], lenvatinib [55], Enl [56], nab-rapamycin (Rpm) [57,58], cyclophosphamide (Cfa) [59], simvastatin (Sim) [60], myeloid growth factor (MGF) [61], nab-paclitaxel [62,63], Mtx [64], and doxorubicin (Dox) [65]. Lastly, only two types of primary tests were successfully conducted, such as laboratory biomarker analyses [66] and dose escalation studies [67].

OS BIDIRECTIONAL MUTATION STAGES

In all kinds of OS or human carcinoma, the TP53 gene is mutated (somatic mutations) in more than 50% of cases. The DNA-binding domain is principally mutated. Other than this site, 20% of cases mutated [68,69]. Thereby, TP53 gene mutations have remained prospective diagnostic components, which can, to a greater extent, increase the precision of forecasting continuity of life and cancer-free longevity among patients with carcinoma [69,70]. The carcinogenic activity of mutant TP53 is almost indistinguishable in sarcoma and multiple other neoplastic diseases [71]. Multiple appraisal techniques were applied among OS cases, revealing that the TP53 gene was lost in the presence of two different alleles. Consequently, there is frequent demand for an up-grade in chemoresistance to achieve chemotherapeutic efficacy [72].

OS therapies are difficult because they progress and reverse through four mutation stages and are intertwined, including TME, metastasis, immune evasion, and chemotherapeutic resistance, as shown in Figure 2. The bidirectional complexity of progression and reversion in OS mutation stages is influenced by the exosomes of a tumor, stem, mesenchymal, immune, fibroblast, and endothelial cells [73]. There is mounting evidence that signal molecules such as neurotransmitters, enzymes, hormones, and nucleic acids [74] are involved in the angiogenesis, growth, migration, metastasis, and apoptosis of the above-mentioned cells, involving intercellular cell communication, body regulation, and immune responses [75]. In this cellular communication, extracellular vesicles (EV) play a key role [76], which could be derived from various cells such as OS cells, mesenchymal stem cells (MSC), adipose-derived MSC (ADMSC), cancer-associated stromal fibroblasts (CAF), and macrophages [77]. These EVs regulate the activity of recipient cells, including angiogenesis, proliferation, invasion, migration, metastasis, chemotherapeutic resistance, and apoptosis, by using their cargoes of proteins, DNA, and RNA [78]. These three cargoes have distinct metabolic dynamics [79] including a connection with the EV components’ biogenesis machinery, a cellular homeostasis regulator with cytoplasmic DNA sensor activation, and parental cell function efficiency at different states [80]. The creation of biomarker vehicles [81] that employ the aforementioned protumorigenic components and signaling pathways to circulate immune responses from OS cancer diseases remains a significant clinical trial challenge [82].

Tumorigenesis

TME is composed of EV secretion cells, MSC, and tumor cells. The EV cells are secreted by MSC and immune cells

Table 1. Summary of completed years for sarcoma clinical trials with their types, API, and primary tests.

<table>
<thead>
<tr>
<th>No</th>
<th>Completed year</th>
<th>GCTI</th>
<th>Sarcoma type</th>
<th>API</th>
<th>Primary test</th>
<th>Refs.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2022</td>
<td>NCT02357810</td>
<td>SSM</td>
<td>Tpt and Pzp</td>
<td>Laboratory biomarker analysis</td>
<td>[45,46]</td>
</tr>
<tr>
<td>2</td>
<td>2021</td>
<td>NCT01532687</td>
<td>Refractory soft</td>
<td>Pzp, Plb, and Gct</td>
<td>Laboratory biomarker analysis</td>
<td>[47,48,146]</td>
</tr>
<tr>
<td>3</td>
<td>2022</td>
<td>NCT03718091</td>
<td>Advanced solid</td>
<td>M6620 (VX-970)</td>
<td>Laboratory biomarker analysis</td>
<td>[49,50]</td>
</tr>
<tr>
<td>4</td>
<td>2022</td>
<td>NCT02048371</td>
<td>Selected subtypes</td>
<td>Plb and Rgf</td>
<td>Laboratory biomarker analysis</td>
<td>[51,52]</td>
</tr>
<tr>
<td>5</td>
<td>2022</td>
<td>NCT02487979</td>
<td>RRS</td>
<td>GV in GPNMB carrier</td>
<td>Laboratory biomarker analysis</td>
<td>[53,54]</td>
</tr>
<tr>
<td>6</td>
<td>2022</td>
<td>NCT02432274</td>
<td>RRS malignancies</td>
<td>Lenvatinib, Enl</td>
<td>Dose escalation study</td>
<td>[55,56]</td>
</tr>
<tr>
<td>7</td>
<td>2021</td>
<td>NCT03190174</td>
<td>Advanced</td>
<td>Nab-Rpm in Nvl carrier</td>
<td>Dose escalation study</td>
<td>[57,58]</td>
</tr>
<tr>
<td>8</td>
<td>2020</td>
<td>NCT02390843</td>
<td>RRS</td>
<td>Cfa, Sim, Tpt, and MGF</td>
<td>Dose escalation study</td>
<td>[59,60]</td>
</tr>
<tr>
<td>9</td>
<td>2019</td>
<td>NCT01962103</td>
<td>RRS</td>
<td>Nab-paclitaxel</td>
<td>Dose escalation study</td>
<td>[61–63]</td>
</tr>
<tr>
<td>10</td>
<td>2005</td>
<td>NCT00180908</td>
<td>Solid</td>
<td>Enl, Mtx, and Dox</td>
<td>Laboratory biomarker analysis</td>
<td>[64,65]</td>
</tr>
</tbody>
</table>

Abbreviations: SSM, soft and solid metastatic; RRS, refractory and relapsed solid; Pzp, pazopanib; Tpt, topotecan; Gct, gemcitabine; Plb, placebo; Rgf, regorafenib; GV, glembatumumab vedotin; GPNMB, Glycoprotein non-metastatic melanoma protein B; Enl, etoposide and ifosfamide; Rpm, Rapamycin; Nvl, Nivolumab; Sim, simvastatin; Cfa, cyclophosphamide; MGF, myeloid growth factor; Mtx, methotrexate; Dox, doxorubicin.

1. For all

2. In this cellular communication, extracellular vesicles (EV) play a key role [76], which could be derived from various cells such as OS cells, mesenchymal stem cells (MSC), adipose-derived MSC (ADMSC), cancer-associated stromal fibroblasts (CAF), and macrophages [77]. These EVs regulate the activity of recipient cells, including angiogenesis, proliferation, invasion, migration, metastasis, chemotherapeutic resistance, and apoptosis, by using their cargoes of proteins, DNA, and RNA [78]. These three cargoes have distinct metabolic dynamics [79] including a connection with the EV components’ biogenesis machinery, a cellular homeostasis regulator with cytoplasmic DNA sensor activation, and parental cell function efficiency at different states [80]. The creation of biomarker vehicles [81] that employ the aforementioned protumorigenic components and signaling pathways to circulate immune responses from OS cancer diseases remains a significant clinical trial challenge [82].

Tumorigenesis

TME is composed of EV secretion cells, MSC, and tumor cells. The EV cells are secreted by MSC and immune cells
to alter macrophage phenotype-2 (M2) \([83]\) and regulate tumor progression via the Wnt signaling pathway \([84]\). Furthermore, the EV cells are the paracrine factors secreted by human bone marrow MSC (BMSC), such as osteoclasts, osteoblasts, and endothelial cells, to regulate tumor cells via communication with the Hedgehog signaling pathway \([85]\). As a result, the M2 and tumor cells regulate TME by EV secretions in order to promote angiogenesis, growth, and metastasis \([86, 87]\). Tumorigenesis research in TME is concerned with how coexisting cells interact and communicate with one another.

### Metastasis

The metastasis potential is affected by the communication between the stressed MSC and the micro RNA (miRNA) content of EV. Tumor cells metastasize in three ways: by secreting EV, by influencing TME, and by mediating the transformation of distant MSC. Direct EV secretion by osteoblasts and CAF can improve migrability. The induction of metastasis can be influenced by regulating tumor and MSC oncogenic phenotypes in TME. The pro-angiogenic factors from endothelial cells can mediate EV transformation to modulate cell invasiveness and promote metastasis. Metastasis could be activated either by modulating tumor-associated macrophage (TAM) cellular signaling to promote the M2 or by producing transforming growth factor beta (TGFβ)-2 to create an immunosuppressive and pro-TME \([88]\). As a result, the tumor cells could be metastasized by inducing a pro-metastatic and tumorigenic phenotype and mediating transformation into local or distant cells.

### Immune evasion

The immune system is divided into innate and adaptive immunizations, which are always related to the bone microenvironment \([89]\). The immune evasion occurred because the inefficient immune cells allowed the tumors to evade the immune surveillance systems or the host immune checkpoint through multiple mechanisms \([24]\). This inefficiency induced a tolerance for the T-cell receptor (TCR), resulting in a dormant response to tumor recognition \([90]\). Therefore, the tumor cancer cells in TME escaped immunotherapy. However, this peripheral tolerance of host-cell immune responses is protected by regulating T regulatory cells (Treg) to prevent autoimmune disorders \([91]\). In fact, two major mechanisms induce immune tolerance \([92]\); T-cell-mediated inflammation suppression and no tumor signals received by the major histocompatibility complex antigen presentation \([93]\). Traditionally, the plasma protease thrombin cleaves glycoprotein A repetitions predominant in tumor immune evasion to release active TGFβ \([94]\). TGFβ is the main coordinator and mediator between both mechanisms mentioned in immune evasion \([95]\). TGFβ increased programmed cell death protein (PD) ligand-1 expression on TAM \([96]\) to bind with PD-1 (CD279) for cytotoxic T lymphocyte-associated anti-gen (CTLA)-4 inhibition. CTLA4 (CD152) is a membrane glycoprotein of immunosuppressive Treg that binds to costimulatory molecules CD80 and CD86 to inhibit early T cell (CD8+ and CD4+) activation \([97]\). These T cells are anti-tumor cells that respond to CAF for immune evasion regulation \([98]\).

### Chemoresistance

Chemoresistance is chemotherapeutic resistance, resulting in a chemotherapeutic efficacy deficit \([99]\). It always results in cytotoxic agents being minimally delivered or severely off-target, destroying therapeutic compliance effects \([100]\). Chemoresistance in cancer cells can be either inherent or acquired, with the latter increasing proportionally with the duration of the therapy \([101]\). Chemoresistance is commonly known as multidrug resistance (MDR), which is drug resistance to
Mtx, Dox, and cis-diaminedichloroplatinum (II) (CDDP) drugs \cite{102}. Drug accumulation in clones and stem cells altered TME, leading to mutation and decreased drug sensitivity \cite{103}. For instance, chemoresistance decreased Dox sensitivity, resulting in M2 induction, which caused tumor cells to spread without responsiveness to Dox \cite{104}. However, the sensitivity of drugs can be induced by the transfer of specific bioactive molecules, such as non-coding RNA and proteomic signatures \cite{105}.

**RECENT OS THERAPIES**

Because there have been numerous OS therapies over the last four decades, only the five most recent years are considered below. Although many OS therapies have been developed, their individual and combinational mechanisms are dispersed \cite{106}. Therefore, a schematic is drawn to elucidate their recent medicines and therapy mechanisms in OS, as shown in Figure 3. Medicines are used to inhibit and suppress tumorigenesis, metastasis, immune evasion, and chemoresistance via communication mediums \cite{107}. Targeted therapies can be developed to intensify the therapies and achieve higher cure rates by thoroughly understanding the roles of genes in communication axes and signaling pathways \cite{108}.

### Tumorigenesis therapies

The tumorigenesis therapies are generally medicated in connection with suppressive, regulative, and inhibitive treatment mechanisms \cite{109}. There is a summary of five recent studies that have addressed tumorigenesis with medicines for their treatment mechanisms, as shown in Table 2. For instance, three studies used suppressive mechanism treatments to halt tumorigenesis’ proliferation, migration, and invasion. Collagen beta (1-O) galactosyl transferase 2 (COLGALT2) inhibitor \cite{110,111}, transformer 2β (Tra2B) \cite{112,113}, and ArfGAP with GTPase domain 1 (AGAP1) \cite{114,115} were used as the medicines to suppress ADMSC exosomes, miR-206, and miR-1307, respectively. In studies of chondrogenesis like osteoclast differentiation and bone resorption activity, the miR-148a and miR-21-5p EVs were used to increase their genes to mimic umbilical vein endothelial cell (UVEC) formation in TME \cite{86,116}. Furthermore, long non-coding RNA (lncRNA) leukemia inhibitory factor receptor antisense RNA1 (LIFR-AS1) inhibitor was used to inhibit miR-29a in the nuclear factor IA (NFIA) axis to suppress human peripheral-blood monocytes-induced macrophage-derived exosomes \cite{115,117}. All 10 studies are related to exosomal-derived genes, and these could be used as diagnosis and prognosis markers in OS progression \cite{118}.

**Interfere communication mediators’ therapies**

Metastasis is stimulated and controlled by intercellular communication in endothelial cells \cite{119}. Both stages can be inhibited by interfering with their direct and indirect communication mediators against endothelial changes \cite{120}. There is a summary of 20 recent studies that have addressed metastasis with medicines that interfere with communication mediators in signaling pathways, as shown in Table 3. For instance, 12 studies interfered with communication mediators

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**Table 2. Treatment mechanisms for tumorigenesis**

<table>
<thead>
<tr>
<th>Inhibitors</th>
<th>Suppressors</th>
<th>Signalling Pathway and Communication Mediums</th>
</tr>
</thead>
<tbody>
<tr>
<td>COLGALT2</td>
<td>miR-148a</td>
<td>ADMSC exosomes, miR-206, miR-1307</td>
</tr>
<tr>
<td>Tra2B</td>
<td>miR-21-5p</td>
<td>NFKB axis</td>
</tr>
<tr>
<td>AGAP1</td>
<td>LIFR-AS1</td>
<td></td>
</tr>
</tbody>
</table>

**Table 3. Treatment mechanisms for metastasis and immune evasion**

<table>
<thead>
<tr>
<th>Interfere</th>
<th>USP12</th>
<th>USP12</th>
<th>PD-L1</th>
<th>PD-L1</th>
</tr>
</thead>
<tbody>
<tr>
<td>N-cadherin</td>
<td>HK2 with</td>
<td>PD-1</td>
<td>M-MDSC</td>
<td>JAK2</td>
</tr>
<tr>
<td>TGFβ</td>
<td>Anti-αvβ3</td>
<td>TGFβRII</td>
<td>Anti-Wnt2</td>
<td>JARID2</td>
</tr>
<tr>
<td>TGFβ1</td>
<td>LAP</td>
<td>TGFβRII</td>
<td>Anti-Wnt2</td>
<td>JARID2</td>
</tr>
<tr>
<td>PD-L1</td>
<td>IDO with</td>
<td>PD-1</td>
<td>M-MDSC</td>
<td>JAK2</td>
</tr>
<tr>
<td>PD-L1</td>
<td>NO synthase</td>
<td>PD-1</td>
<td>M-MDSC</td>
<td>JAK2</td>
</tr>
</tbody>
</table>

**Figure 3.** Schematic of recent OS medicines and their therapy mechanisms for tumorigenesis, metastasis, immune evasion, and chemoresistance.
using inhibitors, including AXL receptor tyrosine kinase (AXL) [121,122], miR-135a-5p [123,124], messenger RNA (mRNA) B-cell lymphoma 6 (BCL6) [125,126], TGFβ1 [127,128], T-cell immunoglobulin and mucin-domain containing protein-3 (Tim-3) [129,130], and suppressor of cytokine signaling-5 (SOCS5) [131,132]. These inhibitors interfered with miR-29a-3p, BMSC-derived exosomal lymphocyte cytosolic protein-1 (LCPI), miR-101 EV, CRISPR-associated protein-9 (Cas9), M2 mediation, and signal transducers and activators of transcription (STAT)-1 mediation by suppressing long intergenic non-protein coding RNA (linc)-00852 in the jumonji and AT-rich interaction domain containing 2 (JARID2) axis; neutregulin receptor degradation protein-1 (NRDP1) in the Janus kinase-2 (JAK2)/STAT3 signaling path-way; ADMSC-derived miR-101; CAF and α-smooth muscle actin expression and fibronectin (ASMAFN) differentiation; IL-10, TGFβ, and vascular endothelial growth factor (VEGF) secretions; and collagen type VI alpha 1 (COL6A1) from histone3 lysine27 acetylation (H3K27ac) activated in CAF conversion with IL-6 and IL-8 secretions; respectively.

The other eight studies interfered with communication mediators using other medicines, such as cancer susceptibility 15 (CASC15) or Krüppel-like factor 3 antisense RNA 1 (KLF3-AS1) [133,134], programmed cell death 4 (PDCD4) [135,136], autophagy-related gene 5 (ATG5) [137,138], and Rab22a-NeoF1 fusion protein [139,140]. Other medicines interfered with Ras-associated binding 14 (RAB14), extracellular signal-regulated kinase-1/2 (ERK1/2) signaling pathway, oncogenic autophagy, and M2 with Arginylglycylaspartic acid (RGD) peptide internalization in STAT3 by suppressing miR-338-3p; miR-208a EV; BMSC-derived EV; and protein tyrosine kinase-2 (PYK2) and Ras homolog family member A (RhoA); respectively. All of the medicines used in the 20 studies interfered with communication mediators related to EV secretions or protein expression.

**Immune evasion therapies**

The suppression and communication barriers of immune cells allow immune evasion [141]. Tumour cells escape being destroyed by the immune system because the immune cells, such as neutrophils, monocytes, macrophages, dendritic cells, natural killer cells, and B and T lymphocytes, are suppressed [142]. Besides, tumor’s immune responses are barred from immune checkpoint activations, thereby causing immune evasion [143]. Therefore, immune evasion is eliminated by suppressing and inhibiting both mechanisms. There is a summary of 20 recent studies with medicines and prevention mechanisms for immune evasion, as shown in Table 4. For instance, eight studies used medicines to suppress immune evasion mechanisms, such as mRNA N-cadherin [144,145], ubiquitin-specific peptidase 12 (USP12) inhibitor [146,147], latency-associated peptide domain (LAP) inhibitor [148,149], and anti-Wnt2 mAb [98,150]. These medicines suppressed PD-L1, PD-1, monocyctic myeloid-derived suppressor cells (M-MDSC), NO synthase, and CAF in order to activate CD8+ T cells and TCR. The remaining eight studies used medicines to inhibit immune evasion mechanisms, such as anti-αvβ8 integrin [151,152], hexokinase-2 (HK2)-mediated phosphorylation of i-kappa-b-alpha (IκBα) [153,154], indoleamine 2,3-dioxygenase (IDO) inhibitor with NO [155,156], and TGFβ receptor II (TGFβRII) with anti-IgG1 (also known as bintrafusp alfa) [157,158]. These medicines inhibited the expression of TGFβ, TGFβ1, PD-L1, and glycolysis in order to activate CD8+ T cells.

**Table 2. Summary of medicines for tumorigenesis with treatment mechanisms.**

<table>
<thead>
<tr>
<th>Medicine</th>
<th>Tumorigenesis</th>
<th>Treatment mechanisms</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>COLGALT2 inhibitor</td>
<td>Proliferation, migration, and invasion</td>
<td>Suppress ADMSC exosome-mediated</td>
<td>[110,111]</td>
</tr>
<tr>
<td>Tra2B</td>
<td></td>
<td>Suppress BMSC-derived exosomal miR-206</td>
<td>[112,113]</td>
</tr>
<tr>
<td>AGAPI</td>
<td></td>
<td>Suppress OS cel-derived exosomal miR-130</td>
<td>[114,115]</td>
</tr>
<tr>
<td>miR-148a and miR-21-5p EVs</td>
<td>Chondrogenesis</td>
<td>Increase genes to mimic UVEC formation in TME</td>
<td>[86,116]</td>
</tr>
<tr>
<td>LIFR-AS1 inhibitor</td>
<td>Progression</td>
<td>Inhibit miR-29a in the NFIA axis</td>
<td>[115,117]</td>
</tr>
</tbody>
</table>

**Table 3. Summary of medicines that interfere communication mediators’ therapies.**

<table>
<thead>
<tr>
<th>Medicine</th>
<th>Interfere communication mediator in signalling pathway</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>AXL inhibitor</td>
<td>Interfere miR-29a-3p by suppressing linc00852 in JARID2 axis</td>
<td>[126,120]</td>
</tr>
<tr>
<td>miR-135a-5p inhibitor</td>
<td>Interfere BMSC-derived exosomal LCP1 by suppressing Nrdp1 in JAK2/STAT3 signalling pathway</td>
<td>[127,121]</td>
</tr>
<tr>
<td>BCL6 inhibitor</td>
<td>Interfere miR-101 EV by suppressing ADMSC-derived miR-101</td>
<td>[128,129]</td>
</tr>
<tr>
<td>TGFβ1 inhibitor</td>
<td>Interfere CRISPR-Cas9 by suppressing CAF and ASMAFN differentiation</td>
<td>[130,131]</td>
</tr>
<tr>
<td>Tim-3 inhibitor</td>
<td>Interfere the M2 mediation by suppressing IL-10, TGFβ, and VEGF secretions</td>
<td>[132,133]</td>
</tr>
<tr>
<td>SOCS5 inhibitor</td>
<td>Interfere STAT1 mediation by suppressing COL6A1 from H3K27ac activated in CAF conversion with IL-6 and IL-8 secretions</td>
<td>[134,135]</td>
</tr>
<tr>
<td>CASC15 or KLF3-AS1</td>
<td>Interfere RAB14 trafficking by suppressing miR-338-3p</td>
<td>[136,137]</td>
</tr>
<tr>
<td>PDCD4</td>
<td>Interfere ERK1/2 signalling pathway by suppressing miR-208a EV</td>
<td>[138,139]</td>
</tr>
<tr>
<td>ATG5</td>
<td>Interfere oncogenic autophagy by suppressing BMSC-derived EV</td>
<td>[140,141]</td>
</tr>
<tr>
<td>Rab22a-NeoF1</td>
<td>Interfere M2 with RGD peptide internalisation in STAT3 by suppressing PYK2 and RhoA</td>
<td>[142,143]</td>
</tr>
</tbody>
</table>
and Treg cells. In all 20 studies, ignoring the immune evasion due to innate and adaptive immunizations, the medical therapies focus on activating immune cells, such as CD8+ T cells, TCR, and Treg cells. As a result, immune evasion is prevented by checkpoint blockade therapy [159], such as PD-L1, PD-1, IL-4, IL-10, M-MDSC, NO synthase, CAF, TGFβ, and TGFβ1 [160].

Chemoresistance therapies

Chemoresistance therapies are always accompanied by treatments for severe off-target effects to restore therapeutic compliance [161]. The acquired nature of chemoresistance in cancer cells will minimize the cytotoxic agent’s delivery proportionally to the chemotherapeutic treatment duration [162]. Hence, this becomes a primary challenge for therapeutic agents and cellular lesions in OS therapy [8]. Drug accumulation in cells, intracellular detoxification, apoptosis, DNA repair, signal transduction disruption, and tumor stem cell immunity all contribute to chemoresistance [163]. Most therapeutic approaches involve inhibition of the onco-gene’s expression to interfere with or mute the communication pathways or axis [164]. Some use drug carriers to avoid rapid drug clearance and prolong release [165,166]. As a result, chemoresistance therapies should focus on oncogene inhibition, drug influx and efflux, and drug carriers [167].

Chemoresistance therapies are divided into two types: inhibitor therapies and gene knockdown therapies. There is a summary of ten recent studies that used inhibitor therapies for different types of drug resistance and their chemoresistance prevention in OS cells, as shown in Table 5. For instance, there are four studies focused on reducing folate receptors for Mtx and Dox drug resistance. Dihydrofolate reductase (DHFR) [168,169] and folylpoly-γ-glutamate synthetase (FPGS) [170,171] inhibitors were used to induce cancer cell apoptosis and inhibit the interaction of spindle and kinetochore associated complex subunit 1 (SKA1) and RNA polymerase II subunit 3 (RPB3), respectively. DHFR reduced the affinity of Mtx resistance by converting dihydrofolate to tetrahydrofolate in order to inhibit purine and thymidine synthesis, resulting in a deficit in DNA replication and apoptosis. Another two studies of (CDDP or cisplatin) drug resistance used the heat shock protein (HSP)-90AA1 gene inhibitor [85,172] to deactivate autophagy activating kinase 1 (ULK1) in FUN14 domain-containing protein 1 (FUNDC1) mediation for mitophagy activation to induce apoptosis. Mitophagy is mitochondrial removal through autophagy, which allows tumor cells to survive cellular stress by clearing damaged organelles and proteins. Two studies of P-glycoprotein (PGP) were inhibited by the inverse agonist XCT-790 or the anlotinib tyrosine kinase (ATK) inhibitor [173,174] for mRNA ATP-binding cassette subfamily B member 1 (ABCB1) in the estrogen-related receptor alpha (ERRα) axis. Another two studies of ABCB1 in the ERRα axis were inhibited by IGF-1 [175,176] in order to reverse metabolic disorders. As a result, folate receptors, FUNDC1-mediated Ulk1, and ABCB1 in the ERRα axis are the key targets in chemoresistance therapies.

Despite the above key targets in chemoresistance therapies, the expression of siRNA oncogenes has been popularly used recently to interfere with or mute the communication pathways or axis [177]. There is a summary of 20 recent studies that used siRNA gene knockdown therapies for different types of drug resistance and their chemoresistance prevention in OS cells, as shown in Table 6. Transmitting circular RNA (circRNA) is used to prevent the Mtx, Dox, and CDDP drug resistance in the 4, 10, and 6 studies, respectively. For Mtx instances, the circ_0000073 [178,179] and circ_0081001 [180,181] gene knockdowns inhibited the N-Ras pathway by sponging miR-145-5p and miR-151-3p and the transglutaminase-2 (TGM2) axis by miR-494-3p, respectively. For Dox instances, the gene knockdowns of circ_0004674 [182,183], circ_0001721 [184,185], circ_SAMD4A(sterilealphamotifdomain)[186,187],

<table>
<thead>
<tr>
<th>Medicine</th>
<th>Prevention mechanisms</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>mRNA N-cadherin</td>
<td>Suppress PD-L1 to reduce immunosuppression and tumorigenesis</td>
<td>[147,148]</td>
</tr>
<tr>
<td>USP12 inhibitor</td>
<td>Suppress M-MDSC, NO synthase, and PD-L1 to activate CD8+ T cells to stabilize p65</td>
<td>[149,123]</td>
</tr>
<tr>
<td>LAP inhibitor</td>
<td>Suppress PD-1 to activate CD8+ T cells with effector molecule phenotypes</td>
<td>[150,151]</td>
</tr>
<tr>
<td>Anti-Wnt2 mAb</td>
<td>Suppress CAF and PD-1 to activate DC-mediated anti-tumour TCR</td>
<td>[98,152]</td>
</tr>
<tr>
<td>Anti-αvβ8 integrin</td>
<td>Inhibit TGFβ or TGFβ1 immunosuppression to activate TCR or Treg cells</td>
<td>[153,154]</td>
</tr>
<tr>
<td>HK2 with 1xBu</td>
<td>Inhibit PD-L1 expression and activate CD8+ T-cell</td>
<td>[155,124]</td>
</tr>
<tr>
<td>IDO inhibitor with NO</td>
<td>Inhibit glycolysis to increase the functions of CD8+ T-cells and Treg cells</td>
<td>[156,157]</td>
</tr>
<tr>
<td>TGFβRII with anti-IgG1</td>
<td>Inhibit TGFβ and PD-L1</td>
<td>[158,159]</td>
</tr>
</tbody>
</table>

**Table 4. Summary of immune evasion medicines with their prevention mechanisms.**

<table>
<thead>
<tr>
<th>Inhibitor</th>
<th>Resistance</th>
<th>Chemoresistance prevention</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>DHFR</td>
<td>Mtx and Dox</td>
<td>Reduce folate receptors to induce apoptosis in cancer cells</td>
<td>[170,171]</td>
</tr>
<tr>
<td>FPGS</td>
<td>Mtx</td>
<td>Reduce folate receptors by inhibiting the interaction of SKA1 and RPB3</td>
<td>[172,175]</td>
</tr>
<tr>
<td>HSP90</td>
<td>CDP</td>
<td>Inhibit Ulk1 in FUNDC1 mediation for mitophagy activation</td>
<td>[85,173]</td>
</tr>
<tr>
<td>XCT-790</td>
<td>Dox</td>
<td>Inhibit PGP for ABCB1 in the ERRα axis</td>
<td>[174,175]</td>
</tr>
<tr>
<td>IGF1</td>
<td>Dox</td>
<td>Inhibit ABCB1 in the ERRα axis to reverse metabolic disorder</td>
<td>[176,177]</td>
</tr>
</tbody>
</table>

**Table 5. Summary of inhibitors, drug resistance, and their chemoresistance prevention in OS cells.**
Resistance

<table>
<thead>
<tr>
<th>Gene Knockdown</th>
<th>Resistance</th>
<th>Chemoresistance prevention</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>circ_0000073</td>
<td>Mtx</td>
<td>Inhibit N-Ras pathway by sponging miR-145-5p and miR-151-3p</td>
<td>[179,180]</td>
</tr>
<tr>
<td>circ_0081001</td>
<td>Mtx</td>
<td>Inhibit TGM2 axis by sponging miR-494-3p</td>
<td>[105,181]</td>
</tr>
<tr>
<td>circ_0004674</td>
<td>Dox</td>
<td>Inhibit fibrillin-1 axis by sponging miR-342-3p</td>
<td>[182,183]</td>
</tr>
<tr>
<td>circ_0001721</td>
<td>Dox</td>
<td>Inhibit TCF4 axis by sponging miR-758</td>
<td>[184,185]</td>
</tr>
<tr>
<td>circ_SAMD4A</td>
<td>Dox</td>
<td>Inhibit KLF8 axis by sponging miR-218-5p</td>
<td>[186,187]</td>
</tr>
<tr>
<td>circ_0002060</td>
<td>Dox</td>
<td>Inhibit ABCB1 axis by sponging miR-198</td>
<td>[188,189]</td>
</tr>
<tr>
<td>circ_0003496</td>
<td>Dox</td>
<td>Inhibit KLF12 axis by sponging miR-370</td>
<td>[190,191]</td>
</tr>
<tr>
<td>circ_CH13L1.2 or OPI5-AS1</td>
<td>CDDP</td>
<td>Inhibit LPAATβ axis by sponging miR-340-5p</td>
<td>[192,193]</td>
</tr>
<tr>
<td>circ_TADA2A</td>
<td>CDDP</td>
<td>Inhibit TRPS1 and YAP1 axis by sponging miR-129-5p</td>
<td>[194,195]</td>
</tr>
<tr>
<td>circ_103801</td>
<td>CDDP</td>
<td>Inhibit MDR-associated protein 1 and PGP</td>
<td>[196,197]</td>
</tr>
</tbody>
</table>

circ_0002060 [188,189], and circ_0003496 [190,191] inhibited the fibrillin-1 axis by sponging miR-342-3p, the transcription factor 4 (TCF4) axis by miR-758, the Krüppel-like factor (KLF)-8 axis by miR-218-5p, the ABCB1 axis by miR-198, and the KLF12 axis by miR-370, respectively. For CDDP instances, the gene knockdowns of circ_CH13L1.2 (chitinase 3-like 1.2) or IncRNA OPI5-AS [192,193], circ_transcriptional adaptor 2A (TADA2A) [194,195], and circ_103801 [196,197] inhibited the lysophosphatidic acid acyltransferase β (LPAATβ) axis by sponging miR-340-5p, the yes-associated protein (YAP) and trichorhinophalangeal syndrome 1 (TRPS1) axis by miR-129-5p, and the MDR-associated protein 1 and PGP, respectively. As a result, the communication pathways of chemoresistance in OS cells would be more effectively prevented by the therapies targeting oncogene expression with their knockdowns.

CONCLUSION

Despite the innate and acquired nature of OS, its progression is intertwined, including cycles of tumorigenesis, metastasis, immune evasion, and chemoresistance. Firstly, tumorigenesis is the result of M2 alterations, which are progressed via signaling pathways by the MSC- and immune cell-secreted EV. Secondly, metastasis is potentially affected by the communication between the stressed MSC and the miRNA content of EV. Thirdly, immune evasion occurred because tumor cells evaded the host immune checkpoint through the TCR tolerance mechanism, resulting in Treg in autoimmune disorders. Finally, chemoresistance causes cytotoxic agents to be delivered severely off-target, resulting in a chemotherapeutic efficacy deficit. These four stages of progression are treated by the combinational and multifunctional therapies listed below. Five tumorigenesis therapy studies have been conducted using medicines such as COLGALT2 inhibitors, Tra2B, and AGAP1, miR-148a and miR-21-5p EVs, and the IncRNA LIFR-AS1 inhibitor. The mechanisms of tumorigenesis were being suppressed, regulated, and inhibited, such as proliferation, migration, invasion, chondrogenesis, and UVEC formation. Their targets include ADMSC exosomes, miR-206, miR-1307, miR-148a, miR-21-5p, and miR-29a in the NFIA axis. Metastasis therapies are treated with medicines related to EV secretions and protein expression for intercellular communication in endothelial cells. There have been 20 therapy studies using inhibitor and disruptor medicines to inhibit protumorigenic expression and disrupt signaling pathways. AXL, miR-135a-5p, mRNA BCL6, TGFβ1, Tim-3, and SOCS5 are the inhibitor medicines. These medicines inhibit miR-29a-3p and lnc-00852 in the JARID2 axis, LCP1 and NRP1 in the JAK2/STAT3 signaling pathway, miR-101 EV, Cas9 in CAF and ASMAFN differentiation, IL-10, TGFβ, and VEGF secretions for M2, and CAF conversion with COL6A1 and H3K27ac in the STAT1 signaling pathway. CASC15, KLF3-AS1, PDCD4, ATG5, and R022a5-1e1 are the disruptor medicines. These medicines disrupt RAB14 by miR-338-3p, the ERK1/2 signaling pathway by miR-208a EV, oncogenic autophagy by BMSC-derived EV, and M2 with RGD in STAT3 by PYK2 and RhoA. Immune evasion is treated by activating CD8+ T cells and connecting TCR and Treg cells for immune checkpoint activations and communication checkpoint regulations, respectively. Sixteen therapy studies have been conducted using medicines to suppress and inhibit immune evasion mechanisms. These medicines are mRNA N-cadherin, USP12 inhibitor, LAP inhibitor, anti-Wnt2 mAb, anti-avβ8 integrin, HK2-mediated IκBα, IDO inhibitor with NO, and TGFβRII with anti-IgG1. Medical targets include PD-L1, PD-1, M-MDSC, NO synthase, CAF, TGFβ, and TGFβ1. Chemoresistance therapies use oncogene inhibition as well as drug carriers for influx and efflux to repair immune therapies and disrupt communication pathways. There are 30 studies of chemoresistance therapies focused on Mtx, Dox, and CDDP drug resistance by using inhibitor therapies and gene knockdown therapies. The inhibitors are DHFR, FPGS, HSP-90AA1, XCT-790, ATKI, and IGF1. The inhibitor targets folate receptors, FUNDC1-mediated Ulk1, and ABCB1 in the ERRα axis. Besides, the gene knockdowns are circ_0000073, circ_0081001, circ_0004674, circ_0001721, circ_SAMD4A, circ_0002060, circ_0003496, circ_CH13L1.2 or IncRNA OPI5-AS, circ_TADA2A, and circ_103801. The gene knockdown’s targets are miR-145-5p and miR-151-3p in the N-Ras pathway, miR-494-3p in the TGM2 axis, miR-342-3p in the fibrillin-1 axis, miR-758 in the TCF4 axis, miR-218-5p in the KLF-8 axis, miR-198 in the ABCB1 axis, miR-370 in the KLF12 axis, miR-340-5p in the LPAATβ axis, miR-129-5p in the YAP/TRPS1 axis, and the MDR-associated protein 1 and PGP. In conclusion, all these OS therapies are individually elucidated to treat tumorigenesis, metastasis, immune evasion, and chemoresistance.
and chemoresistance. However, their OS mutation stages are bidirectional and intertwined, resulting in their being combinational and multifunctional.

**CHALLENGES AND FUTURE**

OS is an unusual and complicated malignant tumor that necessitates an integrative and interdisciplinary therapeutic approach [198–200]. It has been reported that a multidisciplinary approach requires collaboration and cooperation between pediatric or medical cancer specialists, surgeons, pathologists, psychiatrists, radiologists, and radiotherapists [5]. Thus, several models of OS neoplasm have diverse clinical outcomes [201], making the diagnosis and treatment of OS cancer extremely challenging. Thereby, the therapeutic regimen for OS patients has not been systematized, harmonized, or standardized [202]. It has been reported that thorough surgical eradication of all sites of primary and metastatic OS is obligatory, foretelling better clinical end results and continuity of quality life [5]. However, those OS cases have several primary and metastatic OS disease locations that are not manageable for total surgical resection and result in impecunious clinical consequences. Furthermore, preoperative chemotherapies cause chemoresistance, resulting in a two-fold increase in the cisplatin capability of mutational load in OS cases [71]. As a result, chemotherapeutic regimens for recurring or replacement cases of chemotherapy resistance are constantly being improved [203].

According to a recent study, the genetic framework and oncogenesis process of OS are largely unknown, which is impeding research efforts. The immune microenvironment of OS tumors has been extensively studied. It found that OS possesses a noticeable diversity and a complicated all-around mode of process regarding malignancy continuation and metastasis [192]. Another study reported that MDSCs massively invade OS tumors and promote anti-cancer immune-suppressive activities [142,204,205]. Research studies said that preoperative chemotherapy agents, e.g., Dox, CDDP, and ifosfamide, effectively brought down tumor progression and size. Metformin also shows substantial activity in reducing polymorphonuclear MDSC; nevertheless, the MDSC count in OS cases and, after that, augmented both immune sensitivities and the overall immune system [206]. Metformin has been shown in studies to effectively reduce OS tumor progression and size. Metformin also shows substantial activity in reducing polymorphonuclear MDSC; nevertheless, no considerable variability was observed for M-MDSC [207]. Sodium-glucose cotransporter 2 (SGLT2) is a principal intercessor of epithelial glucose transport. It has been proclaimed that SGLT2 is vigorously and exaggeratedly exhibited in several malignant tumor cells, including OS [208]. Antagonizing overexpressed SGLT2 appreciably hinders cancer advancement, e.g., breast cancer, cervical cancer, hepatocellular cancer, prostate cancer, and lung cancer [209]. Although the antimalignant pharmacodynamics of SGLT2 antagonists in OS malignancy remain imprecise [208–210]. This narrative review advocates more research regarding this malignancy and safeguards our children and adults from the atrocities of this cancer.

**LIST OF ABBREVIATIONS**

ABCB1, ATP-binding cassette subfamily B member 1; ADMSC, adipose-derived MSC; AGAP1, ArfGAP with GTPase domain 1; API, active pharmaceutical ingredients; ASMAFN, α-smooth muscle actin expression and fibronectin; ATK, anotinib tyrosine kinase; ATG5, autophagy-related gene 5; AXL, AXL receptor tyrosine kinase; BCL6, B-cell lymphoma-6; BMSC, bone marrow MSC; CAF, cancer-associated stromal fibroblasts; Cas9, CRISPR-associated protein-9; CASC15, cancer susceptibility 15; CDDP, cis-diaminedichloroplatinum (II); Cfa, cyclophosphamide; CHI3L1.2, chitinase 3-like 1.2; COL6A1, collagen type VI alpha 1; circ., circular RNA; COLGALT2, Collagen beta (1-O) galactosyl transferase 2; CTLA, cytotoxic T lymphocyte-associated antigen; DHFR, Dihydrofolate reductase; Dox, doxorubicin; Enl, etoposide and ifosfamide; ERK1/2, extracellular signal-regulated kinase-1/2; ERRα, oestrogen-related receptor alpha; EV, extracellular vesicles; FPGS, folypoly-γ-glutamate synthetase; FUNDC1, FUN14 domain-containing protein 1; Gct, gemcitabine; GCTI, United States federal government clinical trial identifiers; GPNMB, Glycoprotein non-metastatic melanoma protein B; GV, glembatumumab vedotin; H3K27ac, histone3 lysine27 acetylation; HGH, human growth hormone; HK2, hexokinase-2; HSP, heat shock protein; IDO, indoleamine 2,3-dioxygenase; IGF, insulin-like growth factors; IkBα, phosphorylation of i-kappa-b-alpha; IL, Interleukin; JAK2, Janus kinase-2; JARID2, jumonji and AT-rich interaction domain containing 2; KLF, Krüppel-like factor; KLF3-AS1, Krüppel-like factor 3 antisense RNA 1; LAP, latency-associated peptide domain; LCP1, lymphocyte cytotoxic protein-1; LIFR-AS1, leukaemia inhibitory factor receptor antisense RNA1; linc, long intergenic non-protein coding RNA; IncRNA, long non-coding RNA; LPAATβ, lysophosphatidic acid acyltransferase β; M-MDSC, monocytic myeloid-derived suppressor cells; M2, macrophage phenotype-2; MDR, multidrug resistance; MGF, myeloid growth factor; miRNA, micro RNA; mRNA, messenger RNA; MSC, mesenchymal stem cells; Mtx, methotrexate; NFIA, nuclear factor Iα; NRDP1, neuregulin receptor degradation protein-1; OS, osteosarcoma; PD, programmed cell death protein; PDCD4 programmed cell death 4; PGP, P-glycoprotein; Plb, placebo; PYK2, protein tyrosine kinase-2; Pzp, pazopanib; Rgf, regorafenib; RAB14, Ras-associated binding 14; RGD, Arginylglycylaspartic acid; RhoA, Ras homolog family member A; RPB3, RNA polymerase II subunit 3; Rpn, Rapamycin; RSS, refractory and relapsed solid; SAMD4A, sterile alpha motif domain; SBSA, simvastatin; SKA1, spindle and kinetochore associated complex subunit 1; SOCS5, suppressor of cytokine signalling-5; SSM, soft and solid metastatic; STAT, signal transducers and activators of transcription; TADA2A, transcriptional adaptor 2A; TAM, tumour-associated macro-phage; TCF4, transcription factor 4; TCR, T-cell receptor; TGFβ, transforming growth factor beta; TGFβRII, TGFβ receptor II; TGM2, transglutaminase-2; Tim-3, T-cell immunoglobulin and mucin-domain containing protein-3; TME, tumour microenvironment; Tpt, topotecan; Tra2B, transformer 2β; Treg, T regulatory cells; TRPS1, trichorhinophalangeal syndrome 1; ULk1, autophagy activating kinase 1; USP12, ubiquitin-specific peptidase 12; UVEC, umbilical vein endothelial cell; VEGF, vascular endothelial growth factor; and YAP, yes-associated protein.
AUTHOR CONTRIBUTIONS
All authors made substantial contributions to the conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work. All the authors are eligible to be an author as per the international committee of medical journal editors (ICMJE) requirements/guidelines.

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ETHICAL APPROVALS
This study does not involve experiments on animals or human subjects.

DATA AVAILABILITY
All data generated and analyzed are included in this research article.

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