Introduction

Osteosarcomas (OSs) are the most frequently detected bone cancers, characterized by an aggressive clinical course; they typically develop during the adolescence growth. OS is the third most common cancer type in children and in young adults.[1,2] The annual number of affected young patients is 560 in the United States.[3,4] The data from the Turkish Statistical Institute in 2015 showed that bone cancers constituted 7.7% of all pediatric-age cancers in Turkey, and OSs constituted one half of these cancers.[5] OS has different subtypes that have a different prognosis, and most of the tumors are high grade and aggressive. The knowledge and improvement of data on the treatment of OS in the past 4 decades were slow because the etiology of these aggressive tumors is still unknown.[6]

Various and conflicting cytogenetic and molecular studies investigating OS have been published in recent years. The results of these studies still provide limited information on OSs. Considering the past 20 years, however, a small development has been detected. The most significant limiting and compelling factors may be counted as the rare detection of tumors suitable for molecular studies, lack of material, complete disappearance of tumor after chemotherapy, and technical difficulties such as decalcification of the samples.[7,8]

OSs are mainly detected in the femur (42%), tibia (19%), humerus (10%), skull and jaw (8%), and pelvis (8%).[9] Metastasis is detected in 20% of patients in all age groups. Within the metastatic sites, lung
metastasis developed in 95%, bone metastasis in 33%, bone marrow and liver metastasis in 10%, and brain metastasis in 5% of patients during the course of the disease. OSs show a medium and high-grade resistance against some chemotherapeutic agents due to its aggressive biologic behavior.[2,9]

**Types of Osteosarcoma**

**Central**

a. **High Grade**
   - Conventional OS
   - Telangiectatic OS
   - Small cell OS
   - Epithelioid
   - Osteoblastoma
   - Chondroblastoma
   - Fibrohistiocytic

b. **Low Grade**
   - Low malignant central OS

**Superficial**

- Paraosteal OS (low grade)
- Periosteal OS (medium grade)
- Highly malignant superficial OS (high grade)

**Gnathic Osteosarcoma**

Extra skeletal (low and high grade) [10,11]

**Clinical Features of Osteosarcoma**

More than 90% of patients have symptoms such as pain, localized swelling, and decreased movement in the affected extremity.[1] Pathologic fractures were detected at diagnosis in a very small number of patients. Biopsy is required to make the final diagnosis and to identify the histologic OS subtype.[11]

**Treatment of Osteosarcoma**

The 5-year overall survival was reported as 20% before 1970s when the surgical resection was the primary treatment; however, the 5-year overall survival was found to range between 60% and 70% with the inclusion of chemotherapy into treatment in pediatric patients and young adults with localized disease. The current treatment of OS is organized and administered as standard neoadjuvant chemotherapy, surgical resection of the primary tumor, and adjuvant chemotherapy. Typically, high doses of the different combinations of methotrexate, doxorubicin, cisplatin, etoposide, and ifosfamide are used in chemotherapy. [1,12,13] High levels of cytokine-receptor-associated tyrosine kinase activity and/or protein expression were detected in various human cancers such as colon, breast, pancreatic, and lung, brain tumors, OSs, and Ewing sarcomas. Transcription or activation levels are generally associated with the disease stage. The inhibition of the SRC (Rous sarcoma oncogene) activation by dasatinib suppresses the tumor growth in human breast cancer cell series, human prostate cancer cell generations, head and neck, lung cancer, and OSs cell lines.[14] Dasatinib inhibits the migration and invasion in different human sarcoma cell series and triggers the apoptosis in bone sarcoma cells, which are dependent on SRC kinase.

**Epidemiology of Osteosarcoma and Associated Risk Factors**

The annual OS incidence for all ages is 3.1/1.000.000. The prevalence is higher in tall individuals compared to shorter individuals. Although more prevalent in men, the disease is detected in both genders. The development of disease in OSs is generally detected at the beginning of the adolescence (between the ages 10 and 14 in girls and between 15 and 19 years in boys). The risk of OSs is higher in individuals with higher birth weight and in the bones with rapid growth.[1]

**Metastasis in Osteosarcoma**

The Insulin Growth Factor 1 receptor (IGF1R) is known as an important prognostic factor in the OSs metastasis. The IGF1R expression in OSs is highly correlated with the ABCG2 expression, which is known as the cancer stem cell producer associated with drug resistance. The correlation of the IGF1R expression with the ABCG2 and CD44 expression in OS was reported to be associated with the OS conventional prognostic factors.[15]

A SNP (single nucleotide polymorphism) located at the 9q24.1 chromosome has been demonstrated to be significantly associated with the presence of metastasis in a study that included patients with OS who were found to have metastatic disease at the first diagnosis. This SNP is the SNP that is located in the gene intron that encodes the nuclear factor IB(NFIB) into the transcription factor and is associated with the increased NFIB expression that resulted in the excessive migration, proliferation, and colonization of the cells in OS.[16]

**Cytogenetics and DNA Analysis in Osteosarcoma**

The first DNA studies on OSs suggested that these tumors had aneuploidic characteristics. They are detected as a characteristic in high-grade lesions. Bauer et al. detected aneuploidy in 92 out of 96 high-grade tumors (96%) in their study, and the studied four low-grade paraosteal OSs were reported as diploid. Re-
searchers showed that the prevalence of aneuploidy was higher in the poor responding tumors and that the survival period was worse.[6] The diploid tumor term emphasizes the healthy cells in some sections of cancer cells in the tumor tissue, and the tumors involving the same number of chromosome cells (23 pairs of chromosomes in each). The growth of such tumors highly involving these cells was slow, and they were predisposed to being less aggressive.[17] Aneuploidic tumors characterize the tumor tissues that involve a significant or small number of chromosomes in cancer cells in the tumor tissues. These cancer cells divide rapidly, and errors develop in the development of the chromosomes, resulting in the very high chromosome carrying in some cells, and a lower number of chromosome carrying in the others, and genomic instability. An aneuploidic tumor is more aggressive compared to a diploidic tumor.

Conventional cytogenetic research of OSs showed that tumor cells had cariotypic changes substantial in number and diversity. Boehm et al. (2000) compared the cytogenetic profile of 36 patients and previously published studies.[18] Chromosomal anomalies varying from diploid to tetraploid tumors were demonstrated in 25 out of 36 patients (69%). The most frequently detected chromosomal anomalies were reported as the chromosome 1 duplication, and the deletions at chromosomes 9, 10, 13, and 17.[13] The most common structural rearrangements were demonstrated to develop in the chromosome regions at 1p11, 1q11, 1q21, 15p11, 17p, and 19q13.[6] The translocation of the chromosomes 11 and 22 was demonstrated in small-cell OSs. However, the conventional cytogenetics remains limited to evaluate the different anomalies detected in OS. In recent years, compared genomic hybridization (CGH) and fluorescence in situ hybridization (FISH) have been used in the investigation of chromosomal anomalies in OSs, and new data were obtained.

It was demonstrated that an increase in the copy number of DNA series in OSs was associated with the 1q21, 3q26, 6p, 8q, 12q12-13, 14q24qter, 17p11-12, Xp11.2-21, and Xq12 chromosome regions, and the DNA series loss was common at the regions 2q, 6q, 8p, and 10p. The patients with the copy increase at 8q (particularly at 8q21.3-22 and 8cen-q13) were found to have a poor overall survival, and the patients with an increase in the copy number at 1q21 showed a tendency of short overall survival.[19]

The comparative genomic hybridization method showed that the DNA-amplification-associated chromosome region was located at 12q13-15 in the ring chromosomes developed in paraosteal OS, and the oncogenes such as CDK4, MDM2, and SAS were included in this region.[6] The amplification of CDK4 alone or with the MDM2 was demonstrated in aggressive OSs. FISH with the CCND2, ETV6, KRAS, and MDM2 genes were demonstrated to amplify at different rates in low-grade OSs.[11]

Rothmund–Thomson, Rapadilino, Werner, and Bloom syndrome may be included among the OS-associated syndromes. The syndromes related to osteosarcoma are shown in Table 1. They emerge as the autosomal recessive disorders caused by the germline mutations in the genes RECQL4, WRN, and BLM, which encode the DNA helicase enzymes. The risk of the OS development is different for each syndrome. The development of OS was reported in approximately 30% of patients diagnosed with Rothmund–Thomson syndrome, and 10% of patients diagnosed with Werner or Bloom syndrome.[1] The molecular disorders affecting the tumor-suppressive genes are one of the important steps in the formation of sarcomas. [20] Molecular analyses showed that the inactivation of the tumor-suppressive genes TP53 and RB1, and the overexpression of the oncogenes such as MDM2, were important in cancer development. The germine mutations of the RB1 gene cause a malignant cancer of hereditary retinoblastoma. OSs are the most frequently detected secondary tumors in patients diagnosed with hereditary retinoblastoma. OSs are the most frequently detected secondary tumors in patients diagnosed with hereditary retinoblastoma. The incidence of OSs is approximately 500-fold higher in these patients compared with the normal population.[21] OSs are also the second most common malignities detected in Li–Fraumeni syndrome, which is associated with multiple and various cancers. Pathogenic variants were detected in approximately 70% of a tumor-suppressing gene of TP53 in these families.[2,6]

The cumulative OS incidence in individuals who had pathogenic variants in the TP53 gene at the germline level was reported to range between 5% and

### Table 1

<table>
<thead>
<tr>
<th>Osteosarcoma Associated Syndromes [1]</th>
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<tr>
<td>17p13.1 (TP53)</td>
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<tr>
<td>13q14.2 (RB1)</td>
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<tr>
<td>8q24.3 (REQ4)</td>
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<tr>
<td>8p12 (WRN)</td>
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<tr>
<td>15q26.1 (BLM)</td>
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<tr>
<td>Mutipe loci (RPS19, RPL5, RPL11, RPL35A, RPS24, RPS17, RPS7, RPS10, RPS26)</td>
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11% in a study conducted in 2016.[22] All the exome sequencing of 39 patients with OSs was conducted, pathogenic gene mutation occurred at the germline level, and cancer associated with this mutation was demonstrated in 7 (17.9%) of these patients. A mutation in the TP53 gene in 3 patients, and a mutation in RB1, APC, MSH2, or PALB2 genes was detected in other 4 patients. Similarly, germline gene mutation was investigated in a patient group of which 11% were diagnosed with OS, and a mutation was reported in one of the genes TP53, BRCA1, ATM, ATR, or ERCC2 in more than 50% of these patients. Single nucleotide polymorphisms that may be effective in the OS etiology were evaluated and SNPs that may be significant were identified in different loci in many studies.[23] IGF2R, which is important in the growth and development; FGFR3, which encodes fibroblast growth factor receptor 3; MDM2, which organizes the p53 function, and TGFBR1, which encodes the transforming growth factor having a role in the regulation of cellular proliferation, are the significant candidate genes in the development of OS.[1,21,24] Single nucleotide polymorphisms in the CTLA4 gene, which has a significant role in the tumor immunity, encodes the antigen 4 that has overexpression in tumor cells, and is associated with cytotoxic T-lymphocyte, is associated with the high OS risk.

The GRM4 gene located at 6p21.3 has a role in the intracellular signal transduction and in the inhibition of the cyclic AMP (cAMP) signal cascade, and it is detected in OS. Although the glutamate signal pathway is very well-described in the central nervous system, this pathway is also effective in the stimulation of the gonadotropin-releasing neurons. In addition, this pathway was reported to be effective in the bone.[25]

The GRM4 receptor is expressed in the bone osteoblast and osteoclast cells, which demonstrated that the glutamate signal pathway played a role in the cellular differentiation and regulation in the bone formation and resorption. Researchers in a study conducted in 2013 detected two regions at the chromosome loci 2p25.2, and 6p21.3, which are sensitive to OSs. Although GRM4 is expressed in the human OSs tumor cells, it is associated with a poor prognosis in colorectal cancer, pediatric CNS tumors, rhabdomyosarcoma, and multiple myeloma. The detailed investigation of these loci, identification of the association with OS, and the revealing of the biologic mechanisms are highly important.[26]

The molecular mechanism of GRM4 was investigated in a study of OS conducted in 2018. The GRM4 gene expression level in human OS hFOB1.19 cell line was investigated using real-time quantitative PCR(RT-qPCR) in this study. The RT-qPCR and GRM4 expression were also demonstrated to increase in the MG-63, U2OS, HOS, and Saos-2 OS cell strains in addition to human hFOB1.19 cell strains. The GRM4 expression level was detected to have the highest level in the cell strains of U2OS. The lentivirus-mediated silencing of the GRM4 gene through siRNA in U2OS cell strains showed that the GRM4 mRNA level significantly decreased.[27] The transcription factors EGR1 and CTCF generally play a role in cellular differentiation, embryonic development, and the regulation of proliferation and apoptosis. The EGR1 expression was demonstrated to be downregulated in some tumor cells, and the expression of the EGR1 gene was reported to inhibit the migration and invasion however suppressed the growth in OS cells. As a tumor suppressing candidate gene, the CTCF may directly or indirectly contribute to carcinogenesis. EGR1 and CTCF were demonstrated to play a role in the transcriptional regulation of the gene GRM4, which contributes to the development of OS by interacting with chemokines and their receptors.[26,27]

Kovac et al. investigated the complete exome sequencing of 31 OS tumors and reported that more than 80% of the tumors were associated with the BRCA1/2 deficiency phenotype.[28] Some changes in the gene ATRX were observed as the repetitive changes in both OS and brain tumors in a study conducted in 2017. The ATR-X syndrome, which is an alpha-thalassemia X-associated intellectual disability (X-associated mental retardation), is characterized by severe mental disability, slight hemoglobin H disease, genital anomalies, and skeletal anomalies. Germline mutations in the ATRX gene were detected in these patients.[29]

Signal Pathways and Other Important Genes Associated With Osteosarcoma

Wnt Signal Pathway: This pathway is an important regulator of the bone formation and remodeling. [30] Signal transmission is important for the cellular growth, normal bone development, and carcinogenesis. Wnt proteins cause the osteoblast proliferation and differentiation in this pathway. They were demonstrated to be highly upgraded in human OS cell series and OS tumors.[31] In addition, Dikkopf 3 (DKK3), an inhibitor of the Wnt pathway, was down-regulated in OS cell series, the tumor size was smaller,
and pulmonary metastasis was rarely detected in DKK3-transfected rats compared with the controls. Wnt proteins bind to Frizzled receptors in this pathway, which enables the transfer of the beta-catenin into the cell nucleus. Beta-catenin exchanged the transcriptional suppressors with activators, thus causing the osteoblast proliferation and differentiation.[1] A Wnt antagonist, sFRP3, which is also called the Frizzled-associated protein, is secreted by the osteocytes, and it plays the role of a tumor suppressor in other cancers, mainly in OS.[32,33]

**Notch Signal Pathway:** Notch has been described as an oncogene in this signal pathway; however, all members of this complex signal pathway have numerous functions. It is difficult to describe the notch as a simple oncogene or a tumor suppressor in malignant cells, and in the nonmalignant components of tumors.[34]

Notch protein family is the regulated transmembrane receptors group that shows high signaling through ligand-receptor interactions. Notch proteins are important in angiogenesis, in addition to normal bone development and homeostasis.[35]

Various notch pathway genes, including HEY1, HES1, and NOTCH2, are overexpressed in rat, canine, and human OSs compared to the expression in normal bone cells. The comparison of OS cell lines with the metastasis ability with human osteoblasts and non-metastatic OS cell lines showed that OS cell lines with metastasis ability had higher Notch 1, Notch 2, Notch ligand DLL1, and Notch-associated gene HES1 expression levels.[36]

**Runx2 Molecule:** Runx2 is a transcription factor required for osteoblast differentiation, and the overexpression of RUNX2 was reported in OS tumor cells.[37]

**Osterix Molecule:** Osterix (transcription factor SP7) is an important transcription factor in osteoblast differentiation. Osteoclasts are suggested to mediate in the cortical bone destruction in OS. Although the mechanism of osterix action is unknown, researchers showed that the osterix expression decreased in the osteoblast differentiation and that it increased the osteoclast activity.[1]

**Ezrin Molecule:** Differentiations in the ezrin expression were demonstrated in various cancer types, including ovarian cancer, colon cancer, soft tissue sarcoma, and breast cancer. Han et al. emphasized that the ezrin expression was higher in many cancer types; however, Jörgen et al. showed that the ezrin expression had no effect on the overall expression in the overall survival of the patients diagnosed with rectal cancer.[38,39,40] Ezrin, is a member of the protein family that normally binds the cellular skeleton ERM (ezrin, radixin, and moesin).[41] Ezrin occurs mainly in the inactive form in the cytoplasm, and it transforms to a special active form after the activation with treonin and tirosin phosphorylation. The main biologic function of ezrin is to bind the transmembrane proteins to actin cell skeleton. In addition, the metastasis-associated oncogene ezrin regulates various cellular processes, such as the microvillus formation, preservation of the cell type, cell–cell adhesion, cell motility, and invasion.[38] The ezrin expression is associated with the diagnosis of aggressive OS tumors and with a poor overall survival.[34] A higher expression of the ezrin gene in the circulation of peripheral blood in OS is associated with the distant metastasis. Bullet et al. reported that the lung metastasis ability of OS cells significantly decreased with ezrin inhibition. Therefore, the ezrin expression plays a significant role in the lung metastasis of the OS cells.[41,42]

**Receptor Tyrosine Kinases:** Ewing sarcoma is a malignant tumor and a member of the round-cell tumors group that is commonly detected between the age of 5 and 25 years and is located in the diaphysis region of the long bones. Ewing sarcoma is the second most commonly detected sarcoma after OS and is detected in the out-of-bone soft tissue location. A t(11; 22)(q24; q12) anomaly is detected in 90% and t(21; 22) (q2; q12) anomaly in 5%-10% of patients. When the RTKs bind to the ligands, a signaling cascade starts, which initiates with the autophosphorylation and ends with the regulation of the physiologic function, such as cellular proliferation and apoptosis. The RTKs that are activated in the OS cell series include AXL, EPHB2 (Ephrin type-B receptor 2), FGFR2, IGF1R, and RET175. A more detailed identification of the association of OS information and RTKs will enable the use of RTKs in the clinical treatment.[1]

**miRNA, circRNA, and IncRNA in Osteosarcoma**

There is a wide miRNA spectrum (miR-21, miR-29a, miR-34a, miR-107, miR-143, miR-148a, miR-195a, miR-199a-3p, miR-382) associated with the specific MRAs effect on OSs. KCNH1, and UBAP2 are the host genes that are effective in OSs.[43] microRNA-145-3p suppresses proliferation and supports the apoptosis and autophagy of OSs by targeting the HDAC4. miRNAs that play a role in osteosarcoma
are shown in Table 2. Studies showed that miR-145-3p functioned as a tumor suppressor and was associated with the tumor growth and metastasis. The overexpression of miR-145-3p was reported to significantly decrease the proliferation and induce the apoptosis and autophagy of the OS cells.[44] These results suggest that miR-145-3p may play a role as a tumor suppressor in OSs.[45,46]

Circular RNAs (circRNAs) have a circular structure and represent a common class of the unencoded RNAs. Many circRNAs have been reported to play a significant role in cancer development and to have the potential to serve as a new bioindicator class for clinical diagnosis. circRNAs may widely regulate the gene expression at different levels by interacting with DNA, miRNA, lncRNA, or protein to play a role in the regulation of the physiologic and pathologic processes of the cell.[13] The increase of circUBAP2 may stimulate the OSs development and may inhibit the in vitro and in vivo apoptosis. Mechanically, circUBAP2 was demonstrated to inhibit the expression of miR-143, thereby enhancing the expression and function of anti-apoptotic Bcl-2, a direct target of miR-143. Studies have demonstrated the role of circUBAP2 in the development of OS, and it plays a significant role in the prognosis prediction and cancer treatment.[45,47]

Long noncoding RNAs (lncRNAs) are a subclass of a transcriptional RNA molecules longer than 200 nucleotides that function as the regulatory factors in various human disease. IncRNA-ATB may be a potential therapeutic target for OSs. Long noncoding RNAs (lncRNAs) function as the regulatory factors in various human diseases. Studies showed that lncRNAs have roles in various cellular processes, including reproduction, apoptosis, migration, and invasion. Recent evidence showed that IncRNA-ATB was nonfunctional in various cancers, such as hepato-cellular, gastrointestinal, colorectal, breast cancer, prostate cancer, renal cell cancer, nonsmall cell lung cancer, pancreatic cancer, OSs, and glioma. The overexpression of IncRNA-ATB affects the tumor proliferation, migration, and invasion. IncRNA-ATB induces the epithelial-mesenchymal transmission by competitively binding to miRNAs, thus supporting the tumor development. In the light of these data, IncRNA-ATB was concluded to be a possible new bioindicator in cancer diagnosis and prognosis.[48]

### Osteosarcoma and Pharmacokinetics

Many of the pharmacokinetic studies provided data on common genetic variants in OSs with drug interaction and toxicity.[49]

The pharmacogenomics studies conducted with methotrexate, doxorubicin, and cisplatin were found to be associated with overall survival and treatment-associated toxicity. The overexpression of a new bioindicator circPVT1 contributes to the doxorubicin and cisplatin resistance of OSs cells by regulating ABCB1. CircPVT1 is located in the long noncoding RNA region in the oncogene PVT1 locus on the cancer sensitivity locus of chromosome 8q24. The ABCB1 (MDR1) gene is known to be highly expressed in the drug-resistant cell series and supported the chemoresistance by P-glycoprotein (P-gp) protein to pump out the intracellular drugs.[50] Many noncoding RNAs, such as miRNA and IncRNA, were identified to be included in the drug resistance process of the cancer cells by regulating the ABCB1 expression. These results suggest a new perspective with regard to the role of circPVT1 as a biological indicator for the diagnostic and treatment target of OSs.[13]

### Results and Recommendations

Significant research has been conducted to identify the anomalies that may have possible prognostic and

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<tr>
<th>Gene</th>
<th>Associated miRNA</th>
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<tr>
<td>IGF-1R</td>
<td>miR-16</td>
<td>AKT pathway</td>
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<td>miR-194</td>
<td>MAPK pathway</td>
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<td>EGFR</td>
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<td>miR-143</td>
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<td>miR-199a-3p</td>
<td>STAT3 pathway</td>
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<td>c.MET</td>
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<td>miR-369-3p</td>
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<td>PTEN</td>
<td>miR-225</td>
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therapeutic effects on the OS treatment. The OS genetics will contribute significantly to the treatment methods. Although there were a small number of specific molecular bioindicators for OSs in the past, the number of the bioindicators has recently increased. Many significant cytogenetic results were associated with chromosomes, and chromosome regions enabled the description of disease-associated genes. In recent period, studies particularly on OS-associated signal pathway genes, and on miRNA, circRNA, and IncRNA, became important.

Bulut et al. found that the higher expression of the ezrin gene in the peripheral blood circulating tumor cells was associated with distant metastasis in approximately 95% of lung metastases detected in patients with OSs.[38] Ezrin inhibition significantly reduced the lung metastasis ability of OSs cells.[42] Conducting of more detailed genetic studies, particularly on OS and metastasis, will provide more data on OS and on the prevention of metastasis in OS.

Cytogenetic studies, microarray analyses, comparative genome hybridization, and new generation sequencing methods are promising for new inventions. Many biological indicators in OS will help to extend and facilitate the biomedical research areas that will improve the OS treatment and diagnosis.

Peer-review: Externally peer-reviewed.

Conflict of Interest: I have no conflict of interest.

Financial Support: I have no financial support.

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