cells

MDPI

Review

Breast Cancer with Bone Metastasis: Molecular Insights and Clinical Management

Konstantinos Venetis [1,2], Roberto Piciotti [1,2], Elham Sajjadi [1,2], Marco Invernizzi [3,4], Stefania Morganti [1,5], Carmen Criscitiello [1,5,*] and Nicola Fusco [1,2,*]

1 Department of Oncology and Hemato-Oncology, University of Milan, 20141 Milan, Italy; konstantinos.venetis@unimi.it (K.V.); roberto.piciotti@unimi.it (R.P.); elham.sajjadi@unimi.it (E.S.); stefania.morganti@ieo.it (S.M.)
2 Division of Pathology, IEO, European Institute of Oncology IRCCS, 20141 Milan, Italy
3 Department of Health Sciences, University of Eastern Piedmont, 28100 Novara, Italy; marco.invernizzi@med.uniupo.it
4 Infrastruttura Ricerca Formazione Innovazione (IRFI), Azienda Ospedaliera SS. Antonio e Biagio e Cesare Arrigo, 15121 Alessandria, Italy
5 Division of Early Drug Development for Innovative Therapies, IEO, European Institute of Oncology IRCCS, 20141 Milan, Italy
* Correspondence: carmen.criscitiello@unimi.it (C.C.); nicola.fusco@unimi.it (N.F.); Tel.: +39-02-9437-2079 (N.F.)

Abstract: Despite the remarkable advances in the diagnosis and treatment of breast cancer patients, the presence or development of metastasis remains an incurable condition. Bone is one of the most frequent sites of distant dissemination and negatively impacts on patient's survival and overall frailty. The interplay between tumor cells and the bone microenvironment induces bone destruction and tumor progression. To date, the clinical management of bone metastatic breast cancer encompasses anti-tumor systemic therapies along with bone-targeting agents, aimed at slowing bone resorption to reduce the risk of skeletal-related events. However, their effect on patients' survival remains controversial. Unraveling the biology that governs the interplay between breast neoplastic cells and bone tissue would provide means for the development of new therapeutic agents. This article outlines the state-of-the art in the characterization and targeting the bone metastasis in breast cancer, focusing on the major clinical and translational studies on this clinically relevant topic.

Keywords: breast cancer; bone metastasis; therapy resistance; tumor progression; tumor-bone microenvironment; bone-targeting therapy

Citation: Venetis, K.; Piciotti, R.; Sajjadi, E.; Invernizzi, M.; Morganti, S.; Criscitiello, C.; Fusco, N. Breast Cancer with Bone Metastasis: Molecular Insights and Clinical Management. *Cells* **2021**, *10*, 1377. https://doi.org/10.3390/cells10061377

Academic Editors: Caterina Marchiò and Anna Sapino

Received: 31 March 2021
Accepted: 1 June 2021
Published: 2 June 2021

1. Introduction

Breast cancer is the most prevalent malignancy and the foremost cause of cancer-related death in women worldwide [1]. Despite the achievements in the management of this tumor, breast cancer remains an incurable disease when it is diagnosed, or it has progressed, towards advanced stages [2]. Hence, the median overall survival (OS) of patients with metastatic breast cancer (MBC) ranges from 2 to 3 years, with a 27% overall 5-year relative survival rate [3]. The most common sites of distant metastasis include bones, lungs, liver, and brain [4]. Among these, the bone is affected in more than 70% of patients with MBC [5–7].

Bone metastases not only considerably reduce the OS but also the health-related quality of life due to pain, fatigue, and skeletal-related events (SREs) [8–10]. Several therapeutic strategies to specifically target this condition (e.g., bone-modifying agents) are currently available [9,11–13]. However, their reliability and impact on patients' frailty remain a subject of debate [14]. This could be due to the lack of a complete understanding of the crosstalk between breast cancer circulating cells, tumor microenvironment, muscle tissue, and bone microenvironment [15–19]. Improved clinical management of patients

with MBC to the bone not only requires an appropriate combination of systemic and bone-targeting agents, but also the precise identification of highly responsive patients using a precision medicine approach.

In this review, we provide an overview of the biological models and the molecular heterogeneity that characterizes bone metastasis in breast cancer. Emphasis is also placed on the currently available systemic therapies and bone-modifying agents through a broad overview of the main trials involving patients with breast cancer and bone metastasis, in order to highlight the current and future therapeutic implications.

2. Biological Mechanisms of Bone Metastasis

The metastatic process is defined as the dissemination of neoplastic cells from the primary neoplasm to secondary sites [4]. Based upon a radiologic assessment that demonstrates bone destruction or deposition of new bone tissue, bone metastases are classified as osteolytic, osteoblastic, or mixed [20]. Although breast cancer bone metastases are predominantly osteolytic, 15–20% of cases have a predominant osteoblastic component [21–24]. In normal conditions, several bone modifications occur within the physiological process of bone remodeling [6,25]. When the rate of bone resorption exceeds osteogenesis, bone density decreases but remains close to normal levels [26,27]. Unbalances in this mechanism lead to an increased risk of fractures, particularly at the distal femur and proximal tibia levels [28]. This complex process is regulated by resident bone cells and other cell types of the bone microenvironment, including lymphocytes, macrophages, hematopoietic cells, and endocrine signaling molecules [29–34]. In particular, the discovery of endocrine mediators produced by the skeleton has radically changed our understanding not only of the bone biology but also of the endocrinology in general [34]. Given the intrinsic nature of the bone (i.e., hard tissue composed of a mineralized matrix), however, the invasion of cancer cells is naturally difficult in this tissue [35]. This characteristic is in apparent contradiction with the high frequency of bone metastases in breast cancer. However, there is an intricate network of pathways that enhances the potential for breast cancer metastatic clones to invade the bone (Figure 1).

In osteolytic lesions, osteoclast-mediated bone resorption is a key and early step [36]. The interaction between the receptor activator of nuclear factor-kappa B (RANK) and its ligand (RANKL) plays a consistent part in this process [21,37,38]. Specifically, increased RANKL levels lead to hyperactivation of osteoclastogenesis and bone resorption, paving the way for metastatic clones to invade the bone [39,40]. Osteoblasts and osteoclasts secrete a series of trophic factors, cytokines, and chemokines, initiating the vicious cycle that promotes bone destruction and tumor progression [41,42]. In this regard, parathyroid hormone-related peptide (PTHrP), interleukin (IL)1, IL6, IL11, prostaglandin E2 (PGE2), tumor necrosis factor (TNF), and macrophage colony-stimulating factor (M-CSF) are released in the bone microenvironment promoting differentiation of the osteoblasts [40,43–49]. Moreover, RANKL produced by both breast cancer cells and osteoblast further stimulates osteoclast differentiation and activity-binding RANK on the cell surface [50,51]. In contrast, osteoblasts secrete osteoprotegerin (OPG), a soluble decoy receptor for RANKL, which inhibits RANK/RANKL signaling negatively regulating osteoclastogenesis [52–54]. Of note, osteoclast differentiation may also be elicited by IL6, IL1, prostaglandins, and M-CSF-mediated stimulation of bone marrow macrophages [25,55,56]. Upon activation, osteoclasts reabsorb the bone by producing hydrochloric acid and metalloproteases, which dissolve the mineral in bone and cause the breakdown of the collagenous matrix, respectively [57]. Bone reabsorption causes the release of various growth factors that are stored in the bone matrix including insulin-growth factor 1 (IGF1), transforming growth factor β (TGF-β), fibroblast growth factor (FGFs) and platelet-derived growth factor (PDGF) [58–60]. Among these, IGF1 activates phosphoinositide 3-kinase (PI3K)/Akt mammalian target of rapamycin (mTOR) pathway, with subsequent breast cancer cell growth, proliferation, and migration into the bone [17,61,62]. Osteoblasts can also be regulated by metastatic tumor cell-derived factors including endothelin 1 (ET1), dickkopf 1 (DKK1), and the Wnt

signaling cascade [36,63–66]. While Wnt promotes osteoblast differentiation, its activity can be inhibited by DKK1, which is an antagonist in this cascade. ET1 downregulates the expression of DKK1, which allows the activation of Wnt inducing an osteoblastic phenotype in breast cancer bone metastases [57]. Despite these insights, further elucidation of this biological pattern is needed.

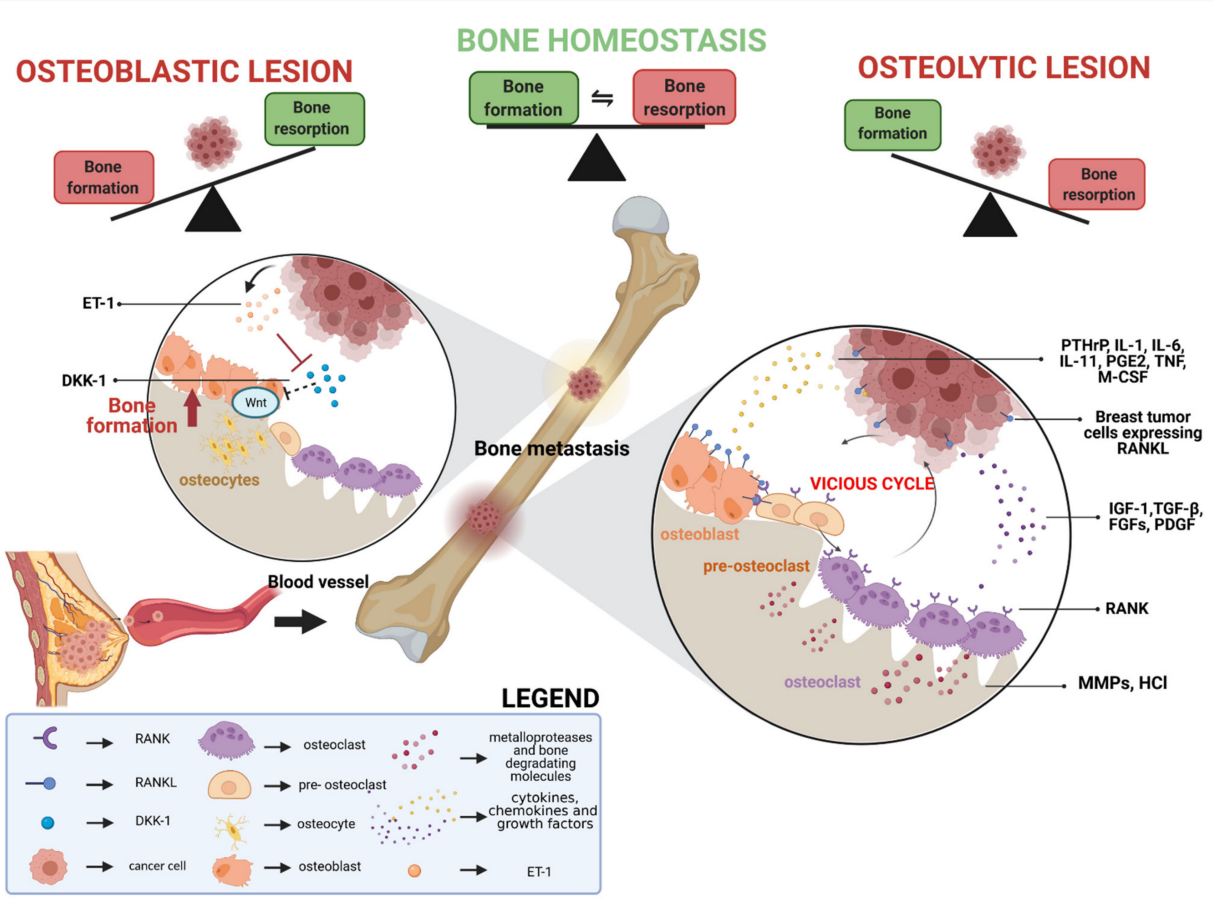

Figure 1. Schematic representation of the processes involved in breast cancer bone metastasis formation. Metastatic tumor cells migrate from the breast primary site to the bone through the bloodstream. Once they arrive in the target part of the skeleton, these neoplastic clones are able to activate a cascade of events that lead to a biological vicious cycle, ultimately leading to the dysregulation of the normal bone homeostasis. In particular, breast cancer bone metastasis can be either osteolytic or osteoblastic based on the type of mechanism that prevails in the bone disequilibrium (i.e., bone resorption or formation). When osteoclastogenic pathways are activated by the metastatic clones, several trophic factors, cytokines, and chemokines (e.g., PTHrP, IL1, IL6, IL11, PGE2, TNF and M-CSF) are secreted. These, either directly or indirectly (via osteoblasts), stimulate osteoclast differentiation and activity through a vicious cycle. Moreover, RANKL produced by both breast cancer cells and osteoblasts binds on RANK receptors, further stimulating the differentiation of the osteoclasts. These events lead to enhanced bone resorption and consequent release of metalloproteases, HCl and matrix-embedded growth factors (e.g., IGF-1, TGF-β, FGF and PDGF), which in turn cause breakdown of the collagenous matrix and promote cancer cell proliferation and tumor progression, respectively. In osteoblastic lesions, ET1 secreted by breast cancer cells inhibits the expression of DKK-1, which normally blocks Wnt signaling decreasing osteoblastic differentiation. Inhibition of DKK-1 results in an increased osteoblast activity favoring uncontrolled bone formation. Abbreviations: PTHrP, parathyroid hormone-related peptide; IL1, interleukin 1; IL6, interleukin 6; IL11, interleukin 11; PGE2, prostaglandin E2; TNF, tumor necrosis factor; M-CSF, macrophage colony-stimulating factor; HCl, hydrochloric acid; IGF1, insulin-growth factor 1; TGFβ, transforming growth factor β; FGF, fibroblast growth factor; PDGF, platelet-derived growth factor. ET1, endothelin 1; DKK1, Dickkopf 1.

3. Bone-Targeting Therapies for Breast Cancer Patients with Bone Metastasis

Patients with breast cancer metastatic to the bone require a multidisciplinary approach that should consider not only the clinical scenario but also the tumor specific biology [9,18,67–72]. Indeed, the metastatic process involves several pathways that are intimately related to breast cancer biomarkers, such as estrogen receptor, progesterone receptor, and HER2 [73]. Not surprisingly, these intrinsic characteristics govern the tailored treatment in patients with breast cancer. The currently available therapeutic strategies include a combination of the systemic therapies used in breast cancer (e.g., chemotherapy, ET, radiotherapy) and those specifically targeting the bone, known as bone-modifying agents [36]. These drugs aim at inhibiting the activity of osteoclasts, thereby decelerating the process of bone resorption [74]. Currently, bisphosphonates and RANK/RANKL inhibitors represent the foremost agents for the clinical management of patients with bone metastasis [75]. Emerging drugs include cathepsin K inhibitors, Src inhibitors, TGFβ blockers, C-X-C motif chemokine receptor type 4 (CXCR4) inhibitors, and αvβ3 integrin antagonists [39]. Current and forthcoming therapies are discussed below, and the corresponding clinical trials are summarized in Table 1.

Bisphosphonates have a dual role in decreasing bone resorption by exerting an apoptotic effect on osteoclasts and increasing mineralization by inhibiting osteoclast activity [76]. First-generation non-nitrogen-containing bisphosphonates (e.g., etidronate and clodronate) are metabolized intracellularly to analogs of ATP. These metabolites prevent bone resorption by inducing osteoclast apoptosis through the inhibition of ATP-dependent enzymes [77]. Conversely, next generation nitrogen-containing bisphosphonates (e.g., alendronate, ibandronate, pamidronate, risedronate and zoledronic acid) promote osteoclast apoptosis by inhibiting farnesyl pyrophosphate synthase (FPPS) and are considered more potent osteoclast inhibitors [78]. The administration of these agents may reduce the risk of SREs and skeletal morbidity rate. The phase III ZOOM trial (NCT00375427) evaluated the efficacy and safety of a reduced dosing frequency of zoledronic acid in 425 patients with breast cancer who had one or more bone metastases, and showed that the drug maintains its therapeutic effects [79]. Accordingly, the skeletal morbidity rate was 0.26 (95% confidence index [CI] 0.15–0.37) in patients treated with zoledronic acid every 12 weeks, versus 0.22 (0.14–0.29) in those treated once every 4 weeks [79]. Moreover, a randomized phase III trial including 855 patients with bone MBC found no increased risk of skeletal events over 2 years in patients who received zoledronic acid every 12 weeks compared with the standard dosing interval of every 4 weeks, suggesting that this longer interval may be an acceptable treatment option (NCT00869206) [80]. A recent meta-analysis that included 44 randomized trials involving 37,302 women with breast cancer at different disease stages assessed the effects of bisphosphonates on anti-cancer treatment [81]. Regarding breast cancer patients with bone metastasis, either intravenous or oral administration of bisphosphonates significantly reduced the absolute risk of SREs by 14% (RR 0.86, 95% CI 0.78–0.95) when compared with placebo [81]. Of note, bisphosphonates delayed the median time to an SRE and reduced bone pain in comparison with placebo or no bisphosphonate; however, no significant effect was observed in terms of overall survival.

Table 1. Bone-modifying agents and corresponding clinical trials in patients with breast cancer metastatic to the bone. Abbreviations: C, completed; T, terminated; W, withdrawn; SMR, skeletal morbidity rate; SRE, skeletal-related events; PIS, pain intensity score; CTC, circulating tumor cells; PFS, progression-free survival; EMT, epithelial-mesenchymal transition; AEs, adverse events; u-NTx, urinary *n*-telopeptide of type I collagen; u-DPD, urinary deoxypyridinoline; MTD, maximum tolerated dose; DFS, disease-free survival; RR, response rate; Information has been obtained from clinicaltrials.gov and clinicaltrialsregister.eu.

Drug Class	Drug Name	Phase	Status	Patients	Basket Trial	Primary Outcome	Secondary Outcome	Trial Number
Bisphosphonates	Zoledronic acid	III	C	425	No	SMR	Incidence and proportion of SRE, Safety	NCT00375427
	Zoledronic acid	III	C	1822	Yes	SRE	PIS, Osteonecrosis of the jaw, renal dysfunction, SMR	NCT00869206
Monoclonal antibody	Denosumab vs. Zoledronic acid	III	C	2049	No	SRE	SRE	NCT00321464
	Denosumab	II	T (Low accrual)	1	No	Patients with reduced CTCs	Change in CTC, PFS	NCT03070002
	Denosumab	II	T	7	No	Effect in reducing CTCs	Changes of EMT in CTCs	NCT01952054
Cathepsin inhibitor	Odanacatib	II	C	43	No	Change in u-NTx, AEs	Change in u-DPD	NCT00399802
Src inhibitor	Dasatinib + Zoledronic acid	I/II	C	31	No	MTD	RR	NCT00566618
	Dasatinib	II	C	85	No	PFS	RR, MUC-1 Antigen Response, CTC RR	NCT00410813

The RANK/RANKL interaction significantly affects the progression of the deleterious vicious cycle between circulating breast cancer cells and the bone microenvironment. Therapeutic approaches targeting these molecules mainly rely on denosumab, a fully human monoclonal anti-RANKL antibody. This drug inhibits the RANKL/RANK signaling-mediated bone resorption, suppressing bone turnover and leading to the reduction of SRE risk [82,83]. Clinical trials that directly compared denosumab with zoledronic acid, demonstrated that the former was superior in terms of reducing bone turnover and pain as well as preventing SREs (NCT00321464) [84,85]. However, no significant differences were observed in overall survival and disease progression. Regrettably, some trials that assessed the effect of denosumab in bone metastatic breast cancer patients have been terminated without providing any essential insights (NCT03070002, NCT01952054) Notably, a novel orally available small-molecule RANKL inhibitor, AS2676293 has been found to markedly inhibit bone metastasis of human breast cancer cells in mouse models, possibly providing a more efficacious and affordable solution [86].

Additional therapeutic targets with potential clinical utility in the treatment of bone MBC are still under investigation. In this regard, odanacatib is an antagonist of cathepsin K, a protease produced by osteoclasts directly involved in bone resorption [87]. Although a phase II clinical trial carried out in bone MBC patients correlated odanacatib with reduced bone turnover and good toleration scores (i.e., if treatment-related dose-limiting toxicity was observed in $\leq$10 of 30 patients, odanacatib 5 mg was considered well-tolerated) (NCT00399802) [88], a phase III trial using odanacatib was withdrawn before subject enrolment (NCT00692458). Nevertheless, it has been recently reported that treatment with this agent is associated with an increased risk of stroke [89]. Moreover, dasatinib is an inhibitor of Src, a member of the nonreceptor tyrosine kinase family, which is overexpressed in breast cancer tissue positively regulating osteoclasts and negatively regulating osteoblasts [90]. A recently concluded phase I/II study showed that a combination of dasatinib with zoledronic acid presented clinical efficacy in treating breast cancer patients with bone metastasis (NCT00566618) [91]. Conversely, in a bone MBC population unselected by molecular markers, dasatinib did not improve the progression-free survival (PFS), stressing the need for implementation of molecularly-defined patient cohorts (NCT00410813) [92]. Finally, TGFβ, CXCR4, and αvβ3 integrin are key mediators of breast cancer metastasis to bone (Table 2) [93–96]. Antagonists of these proteins are under investigation in preclinical models of metastatic breast cancer, showing accumulating positive data [97–108]. Assessment of their safety and efficacy in phase I clinical trials is expected.

Table 2. Antagonists of breast cancer bone metastasis mediators investigated in preclinical models.

Compounds	Mechanism of Action	References
LY2109761	TGFβ I and II dual inhibitor	[98–101]
AMD3465, AMD3100, AMD070	CXCR4 antagonists	[102–105]
ProAgio	integrin alphavbeta3 inhibitor	[106–108]

4. Concluding Remarks

An improved understanding of the mechanisms that drive the metastatic dissemination of breast cancer to the bone and the development of therapy resistance are essential to concretely establish the most suitable clinical management strategies for these patients. Pathways leading to bone remodeling represent the ideal target for future translational and clinical research studies. These discoveries would lead to a possible improvement in the precision medicine approach in the treatment of breast cancer with bone metastasis, not only for patients' survival but also for their health-related quality of life. Novel agents including bisphosphonates and denosumab may now be administered along with the traditional therapeutic regimens. Despite the positive results of these drugs in reducing the risk of SREs, no significant effect has been observed in terms of OS. Future research should

focus on a deeper understanding of metastatic heterogeneity as well as on identifying key regulators of molecular signaling pathways, which might be potential therapeutic targets.

Author Contributions: Conceptualization, M.I. and N.F.; methodology, C.C. and N.F.; writing—original draft preparation, K.V., E.S. and R.P.; writing—review and editing, M.I., S.M., C.C. and N.F.; visualization, R.P.; supervision, N.F.; All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

Acknowledgments: Not applicable.

Conflicts of Interest: M.I. received consultation honoraria from Errekappa Euroterapici S.p.a. C.C. received honoraria for consulting/advisory role/speaker fees from Novartis, Eli-Lilly, Pfizer, and Roche. N.F. has received honoraria for consulting, advisory role, and/or speaker fees from Merck Sharp & Dohme (MSD), Boehringer Ingelheim, and Novartis. These companies had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript, and/or in the decision to publish the results. All other authors declare no potential conflicts of interest.

References

1. Sung, H.; Ferlay, J.; Siegel, R.L.; Laversanne, M.; Soerjomataram, I.; Jemal, A.; Bray, F. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J. Clin.* **2021**. [CrossRef] [PubMed]
2. Westphal, T.; Gampenrieder, S.P.; Rinnerthaler, G.; Greil, R. Cure in metastatic breast cancer. *Memo Mag. Eur. Medical Oncol.* **2018**, *11*, 172–179. [CrossRef] [PubMed]
3. Wang, R.; Zhu, Y.; Liu, X.; Liao, X.; He, J.; Niu, L. The Clinicopathological features and survival outcomes of patients with different metastatic sites in stage IV breast cancer. *BMC Cancer* **2019**, *19*, 1091. [CrossRef] [PubMed]
4. Riggio, A.I.; Varley, K.E.; Welm, A.L. The lingering mysteries of metastatic recurrence in breast cancer. *Br. J. Cancer* **2021**, *124*, 13–26. [CrossRef]
5. Monteran, L.; Ershaid, N.; Sabah, I.; Fahoum, I.; Zait, Y.; Shani, O.; Cohen, N.; Eldar-Boock, A.; Satchi-Fainaro, R.; Erez, N. Bone metastasis is associated with acquisition of mesenchymal phenotype and immune suppression in a model of spontaneous breast cancer metastasis. *Sci. Rep.* **2020**, *10*, 13838. [CrossRef]
6. Xiong, Z.; Deng, G.; Huang, X.; Li, X.; Xie, X.; Wang, J.; Shuang, Z.; Wang, X. Bone metastasis pattern in initial metastatic breast cancer: A population-based study. *Cancer Manag. Res.* **2018**, *10*, 287–295. [CrossRef]
7. Kuchuk, I.; Hutton, B.; Moretto, P.; Ng, T.; Addison, C.L.; Clemons, M. Incidence, consequences and treatment of bone metastases in breast cancer patients—Experience from a single cancer centre. *J. Bone Oncol.* **2013**, *2*, 137–144. [CrossRef]
8. Thanopoulou, E.; Khader, L.; Caira, M.; Wardley, A.; Ettl, J.; Miglietta, F.; Neven, P.; Guarneri, V. Therapeutic strategies for the management of hormone receptor-positive, human epidermal growth factor receptor 2-Positive (HR+/HER2+) breast cancer: A review of the current literature. *Cancers* **2020**, *12*, 3317. [CrossRef]
9. Invernizzi, M.; Kim, J.; Fusco, N. Editorial: Quality of life in breast cancer patients and survivors. *Front. Oncol.* **2020**, *10*. [CrossRef]
10. Baek, Y.-H.; Jeon, H.-L.; Oh, I.-S.; Yang, H.; Park, J.; Shin, J.-Y. Incidence of skeletal-related events in patients with breast or prostate cancer-induced bone metastasis or multiple myeloma: A 12-year longitudinal nationwide healthcare database study. *Cancer Epidemiol.* **2019**, *61*, 104–110. [CrossRef]
11. Hong, S.; Youk, T.; Lee, S.J.; Kim, K.M.; Vajdic, C.M. Bone metastasis and skeletal-related events in patients with solid cancer: A Korean nationwide health insurance database study. *PLoS ONE* **2020**, *15*, e0234927. [CrossRef]
12. Nardin, S.; Mora, E.; Varughese, F.M.; D'Avanzo, F.; Vachanaram, A.R.; Rossi, V.; Saggia, C.; Rubinelli, S.; Gennari, A. Breast cancer survivorship, quality of life, and late toxicities. *Front. Oncol.* **2020**, *10*, 864. [CrossRef]
13. Jeong, H.; Jeong, J.H.; Kim, J.E.; Ahn, J.H.; Jung, K.H.; Koh, S.J.; Cheon, J.; Sohn, J.; Kim, G.M.; Lee, K.S.; et al. Final results of the randomized phase 2 LEO trial and bone protective effects of everolimus for premenopausal hormone receptor-positive, HER2-negative metastatic breast cancer. *Int. J. Cancer* **2021**. [CrossRef]
14. D'Oronzo, S.; Wood, S.; Brown, J.E. The use of bisphosphonates to treat skeletal complications in solid tumours. *Bone* **2021**, *147*, 115907. [CrossRef]
15. Guise, T.A. Breast cancer bone metastases: It's all about the neighborhood. *Cell* **2013**, *154*, 957–959. [CrossRef]
16. Rani, A.; Stebbing, J.; Giamas, G.; Murphy, J. Endocrine resistance in hormone receptor positive breast cancer-from mechanism to therapy. *Front. Endocrinol.* **2019**, *10*, 245. [CrossRef]

17. Fusco, N.; Malapelle, U.; Fassan, M.; Marchiò, C.; Buglioni, S.; Zupo, S.; Criscitiello, C.; Vigneri, P.; Dei Tos, A.P.; Maiorano, E. PIK3CA mutations as a molecular target for hormone receptor-positive, HER2-negative metastatic breast cancer. *Front. Oncol.* **2021**, *11*, 562. [CrossRef]
18. Invernizzi, M.; de Sire, A.; Fusco, N. Rethinking the clinical management of volumetric muscle loss in patients with spinal cord injury: Synergy among nutritional supplementation, pharmacotherapy, and rehabilitation. *Curr. Opin. Pharmacol.* **2021**, *57*, 132–139. [CrossRef]
19. Invernizzi, M.; Venetis, K.; Sajjadi, E.; Piciotti, R.; de Sire, A.; Fusco, N. Understanding the biology of volumetric muscle loss for an individualized exercise rehabilitation approach in breast cancer patients. *Curr. Opin. Pharmacol.* **2021**, *58*, 27–34. [CrossRef]
20. Ortiz, A.; Lin, S.H. Osteolytic and osteoblastic bone metastases: Two extremes of the same spectrum? *Recent. Results Cancer Res.* **2012**, *192*, 225–233. [CrossRef]
21. Wu, X.; Li, F.; Dang, L.; Liang, C.; Lu, A.; Zhang, G. RANKL/RANK system-based mechanism for breast cancer bone metastasis and related therapeutic strategies. *Front. Cell Dev. Biol.* **2020**, *8*, 76. [CrossRef] [PubMed]
22. Hiraga, T. Bone metastasis: Interaction between cancer cells and bone microenvironment. *J. Oral. Biosci.* **2019**, *61*, 95–98. [CrossRef] [PubMed]
23. Lee, J.H.; Kim, B.; Jin, W.J.; Kim, J.W.; Kim, H.H.; Ha, H.; Lee, Z.H. Trolox inhibits osteolytic bone metastasis of breast cancer through both PGE2-dependent and independent mechanisms. *Biochem. Pharmacol.* **2014**, *91*, 51–60. [CrossRef] [PubMed]
24. Kolb, A.D.; Shupp, A.B.; Mukhopadhyay, D.; Marini, F.C.; Bussard, K.M. Osteoblasts are "educated" by crosstalk with metastatic breast cancer cells in the bone tumor microenvironment. *Breast Cancer Res. BCR* **2019**, *21*, 31. [CrossRef]
25. Kim, J.M.; Lin, C.; Stavre, Z.; Greenblatt, M.B.; Shim, J.H. Osteoblast-osteoclast communication and bone homeostasis. *Cells* **2020**, *9*, 73. [CrossRef]
26. Xiong, G.; Yang, Y.; Guo, M. Effect of resveratrol on abnormal bone remodeling and angiogenesis of subchondral bone in osteoarthritis. *Int. J. Clin. Exp. Pathol.* **2021**, *14*, 417–425.
27. Morimoto, A.; Kikuta, J.; Nishikawa, K.; Sudo, T.; Uenaka, M.; Furuya, M.; Hasegawa, T.; Hashimoto, K.; Tsukazaki, H.; Seno, S.; et al. SLPI is a critical mediator that controls PTH-induced bone formation. *Nat. Commun.* **2021**, *12*, 2136. [CrossRef]
28. Hirano, F.; Okuma, K.F.; Zenke, Y.; Menuki, K.; Ohnishi, H.; Fukuda, F.; Sakai, A.; Yamamoto, N.; Shimakura, T.; Sano, H.; et al. Disturbance of osteonal bone remodeling and high tensile stresses on the lateral cortex in atypical femoral fracture after long-term treatment with Risedronate and Alfacalcidol for osteoporosis. *Bone Rep.* **2021**, *14*, 101091. [CrossRef]
29. Sajjadi, E.; Venetis, K.; Piciotti, R.; Invernizzi, M.; Guerini-Rocco, E.; Haricharan, S.; Fusco, N. Mismatch repair-deficient hormone receptor-positive breast cancers: Biology and pathological characterization. *Cancer Cell Int.* **2021**, *21*, 266. [CrossRef]
30. Sajjadi, E.; Venetis, K.; Scatena, C.; Fusco, N. Biomarkers for precision immunotherapy in the metastatic setting: Hope or reality? *Ecancermedicalscience* **2020**, *14*, 1150. [CrossRef]
31. Burckhardt, P.; Faouzi, M.; Buclin, T.; Lamy, O. Fractures after denosumab discontinuation: A retrospective study of 797 cases. *J. Bone Miner. Res.* **2021**. [CrossRef]
32. Fusco, N.; Bonometti, A.; Augello, C.; Fabris, S.; Boiocchi, L.; Fiori, S.; Morotti, D.; Fracchiolla, N.; Berti, E.; Gianelli, U. Clonal reticulohistiocytosis of the skin and bone marrow associated with systemic mastocytosis and acute myeloid leukaemia. *Histopathology* **2017**, *70*, 1000–1008. [CrossRef]
33. Kijima, Y.; Kondo, N.; Okumura, G.; Endo, N. Bone histomorphometry of femoral head cancellous bone in patients who underwent total hip arthroplasties due to destructive hip in rheumatoid arthritis. *Acta Med. Okayama* **2021**, *75*, 125–131. [CrossRef]
34. Jaschke, N.; Sipos, W.; Hofbauer, L.C.; Rachner, T.D.; Rauner, M. Skeletal endocrinology: Where evolutionary advantage meets disease. *Bone Res.* **2021**, *9*, 28. [CrossRef]
35. Katsimbri, P. The biology of normal bone remodelling. *Eur. J. Cancer Care* **2017**, *26*. [CrossRef]
36. Tahara, R.K.; Brewer, T.M.; Theriault, R.L.; Ueno, N.T. Bone metastasis of breast cancer. *Adv. Exp. Med. Biol.* **2019**, *1152*, 105–129. [CrossRef]
37. Kim, B.; Kim, H.; Jung, S.; Moon, A.; Noh, D.Y.; Lee, Z.H.; Kim, H.J.; Kim, H.H. A CTGF-RUNX2-RANKL axis in breast and prostate cancer cells promotes tumor progression in bone. *J. Bone Miner. Res.* **2020**, *35*, 155–166. [CrossRef]
38. Asano, T.; Okamoto, K.; Nakai, Y.; Tsutsumi, M.; Muro, R.; Suematsu, A.; Hashimoto, K.; Okamura, T.; Ehata, S.; Nitta, T.; et al. Soluble RANKL is physiologically dispensable but accelerates tumour metastasis to bone. *Nat. Metab* **2019**, *1*, 868–875. [CrossRef]
39. Brook, N.; Brook, E.; Dharmarajan, A.; Dass, C.R.; Chan, A. Breast cancer bone metastases: Pathogenesis and therapeutic targets. *Int. J. Biochem. Cell Biol.* **2018**, *96*, 63–78. [CrossRef]
40. Liang, M.; Ma, Q.; Ding, N.; Luo, F.; Bai, Y.; Kang, F.; Gong, X.; Dong, R.; Dai, J.; Dai, Q.; et al. IL-11 is essential in promoting osteolysis in breast cancer bone metastasis via RANKL-independent activation of osteoclastogenesis. *Cell Death Dis.* **2019**, *10*, 353. [CrossRef]
41. Chen, Y.-C.; Sosnoski, D.M.; Mastro, A.M. Breast cancer metastasis to the bone: Mechanisms of bone loss. *Breast Cancer Res.* **2010**, *12*, 215. [CrossRef]
42. Liang, Y.; Zhang, H.; Song, X.; Yang, Q. Metastatic heterogeneity of breast cancer: Molecular mechanism and potential therapeutic targets. *Semin Cancer Biol.* **2020**, *60*, 14–27. [CrossRef]
43. Shupp, A.B.; Kolb, A.D.; Mukhopadhyay, D.; Bussard, K.M. Cancer metastases to bone: Concepts, mechanisms, and interactions with bone osteoblasts. *Cancers* **2018**, *10*, 182. [CrossRef]

44. Watters, R.J.; Verdelis, K.; Lucas, P.C.; Jiang, S.; Chen, Y.; Lu, F.; Martin, B.M.; Lukashova, L.; Pecar, G.; Morales-Restrepo, A.; et al. A novel mouse model for SNP in Steroid Receptor Co-activator-1 reveals role in bone density and breast cancer metastasis. *Endocrinology* **2021**. [CrossRef]
45. Shepherd, A.J.; Mickle, A.D.; Kadunganattil, S.; Hu, H.; Mohapatra, D.P. Parathyroid hormone-related peptide elicits peripheral TRPV1-dependent mechanical hypersensitivity. *Front. Cell Neurosci.* **2018**, *12*, 38. [CrossRef]
46. Holen, I.; Lefley, D.V.; Francis, S.E.; Rennicks, S.; Bradbury, S.; Coleman, R.E.; Ottewell, P. IL-1 drives breast cancer growth and bone metastasis in vivo. *Oncotarget* **2016**, *7*, 75571–75584. [CrossRef]
47. Filipenko, I.; Schwalm, S.; Reali, L.; Pfeilschifter, J.; Fabbro, D.; Huwiler, A.; Zangemeister-Wittke, U. Upregulation of the S1P(3) receptor in metastatic breast cancer cells increases migration and invasion by induction of PGE(2) and EP(2)/EP(4) activation. *Biochim. Biophys. Acta* **2016**, *1861*, 1840–1851. [CrossRef]
48. Guo, J.; Duan, Z.; Zhang, C.; Wang, W.; He, H.; Liu, Y.; Wu, P.; Wang, S.; Song, M.; Chen, H.; et al. Mouse 4T1 Breast Cancer Cell-Derived Exosomes Induce Proinflammatory Cytokine Production in Macrophages via miR-183. *J. Immunol.* **2020**, *205*, 2916–2925. [CrossRef]
49. Kang, J.; Choi, Y.J.; Seo, B.Y.; Jo, U.; Park, S.I.; Kim, Y.H.; Park, K.H. A Selective FGFR inhibitor AZD4547 suppresses RANKL/M-CSF/OPG-dependent ostoclastogenesis and breast cancer growth in the metastatic bone microenvironment. *Sci. Rep.* **2019**, *9*, 8726. [CrossRef]
50. Honma, M.; Ikebuchi, Y.; Suzuki, H. Mechanisms of RANKL delivery to the osteoclast precursor cell surface. *J. Bone Miner. Metab.* **2021**, *39*, 27–33. [CrossRef] [PubMed]
51. Liu, Y.; Zhang, R.X.; Yuan, W.; Chen, H.Q.; Tian, D.D.; Li, H.; Jiang, X.; Deng, Z.L.; Wang, Y. Knockdown of bone morphogenetic proteins Type 1a Receptor (BMPR1a) in breast cancer cells protects bone from breast cancer-induced osteolysis by suppressing RANKL expression. *Cell Physiol. Biochem.* **2018**, *45*, 1759–1771. [CrossRef] [PubMed]
52. Udagawa, N.; Koide, M.; Nakamura, M.; Nakamichi, Y.; Yamashita, T.; Uehara, S.; Kobayashi, Y.; Furuya, Y.; Yasuda, H.; Fukuda, C.; et al. Osteoclast differentiation by RANKL and OPG signaling pathways. *J. Bone Miner. Metab.* **2021**, *39*, 19–26. [CrossRef] [PubMed]
53. Segaliny, A.I.; Cheng, J.L.; Farhoodi, H.P.; Toledano, M.; Yu, C.C.; Tierra, B.; Hildebrand, L.; Liu, L.; Liao, M.J.; Cho, J.; et al. Combinatorial targeting of cancer bone metastasis using mRNA engineered stem cells. *EBioMedicine* **2019**, *45*, 39–57. [CrossRef] [PubMed]
54. Elfar, G.A.; Ebrahim, M.A.; Elsherbiny, N.M.; Eissa, L.A. Validity of osteoprotegerin and receptor activator of NF-κB ligand for the detection of bone metastasis in breast cancer. *Oncol. Res.* **2017**, *25*, 641–650. [CrossRef]
55. Liang, M.; Yin, X.; Zhang, S.; Ai, H.; Luo, F.; Xu, J.; Dou, C.; Dong, S.; Ma, Q. Osteoclast-derived small extracellular vesicles induce osteogenic differentiation via inhibiting ARHGAP1. *Mol. Ther. Nucleic Acids* **2021**, *23*, 1191–1203. [CrossRef]
56. Kao, Y.F.; Tu, M.C.; Chai, H.J.; Lin, Y.L.; Chen, Y.C. Suppressive effects of an apoptotic mimicry prepared from jumbo-flying squid-skin phospholipids on the osteoclastogenesis in receptor activator of nuclear factor kappa B ligand/macrophage colony-stimulating factor-induced RAW 264.7 cells. *J. Chin. Med. Assoc.* **2021**, *84*, 51–60. [CrossRef]
57. Boyce, B.F.; Li, J.; Xing, L.; Yao, Z. Bone remodeling and the role of TRAF3 in osteoclastic bone resorption. *Front. Immunol.* **2018**, *9*, 2263. [CrossRef]
58. Jann, J.; Gascon, S.; Roux, S.; Faucheux, N. Influence of the TGF-β superfamily on osteoclasts/osteoblasts balance in physiological and pathological bone conditions. *Int. J. Mol. Sci.* **2020**, *21*, 7597. [CrossRef]
59. Feger, M.; Hase, P.; Zhang, B.; Hirche, F.; Glosse, P.; Lang, F.; Föller, M. The production of fibroblast growth factor 23 is controlled by TGF-β2. *Sci. Rep.* **2017**, *7*, 4982. [CrossRef]
60. Brzęczek, M.; Hyla-Klekot, L.; Kokot, F.; Synder, M. Contribution of Bone tissue to regulation of calcium and phosphate metabolism. role of FGF23 and klotho protein. *Ortop. Traumatol. Rehabil.* **2020**, *22*, 69–76. [CrossRef]
61. Rieunier, G.; Wu, X.; Macaulay, V.M.; Lee, A.V.; Weyer-Czernilofsky, U.; Bogenrieder, T. Bad to the bone: The role of the insulin-like growth factor axis in osseous metastasis. *Clin. Cancer Res.* **2019**, *25*, 3479. [CrossRef]
62. Aleksic, T.; Browning, L.; Woodward, M.; Phillips, R.; Page, S.; Henderson, S.; Athanasou, N.; Ansorge, O.; Whitwell, D.; Pratap, S.; et al. Durable response of spinal chordoma to combined inhibition of IGF-1R and EGFR. *Front. Oncol.* **2016**, *6*, 98. [CrossRef]
63. Moon, H.H.; Clines, K.L.; Cooks, M.A.; Cialek, C.A.; Esvelt, M.A.; Clines, G.A. Castration determines the efficacy of ETAR blockade in a mouse model of prostate cancer bone metastasis. *Endocrinology* **2019**, *160*, 1786–1796. [CrossRef]
64. Park, K.R.; Kim, S.; Cho, M.; Yun, H.M. Limonoid triterpene, obacunone increases runt-related transcription factor 2 to promote osteoblast differentiation and function. *Int. J. Mol. Sci.* **2021**, *22*, 2483. [CrossRef]
65. Lehmann, J.; Thiele, S.; Baschant, U.; Rachner, T.D.; Niehrs, C.; Hofbauer, L.C.; Rauner, M. Mice lacking DKK1 in T cells exhibit high bone mass and are protected from estrogen-deficiency-induced bone loss. *iScience* **2021**, *24*, 102224. [CrossRef]
66. Bhandari, D.; Elshaarrawi, A.; Katula, K.S. The human WNT5A isoforms display similar patterns of expression but distinct and overlapping activities in normal human osteoblasts. *J. Cell Biochem.* **2021**. [CrossRef]
67. Alečković, M.; McAllister, S.S.; Polyak, K. Metastasis as a systemic disease: Molecular insights and clinical implications. *Biochim. et Biophys. Acta BBA Rev. Cancer* **2019**, *1872*, 89–102. [CrossRef]
68. Invernizzi, M.; de Sire, A.; Renò, F.; Cisari, C.; Runza, L.; Baricich, A.; Carda, S.; Fusco, N. Spinal cord injury as a model of bone-muscle interactions: Therapeutic implications from in vitro and in vivo studies. *Front. Endocrinol.* **2020**, *11*, 204. [CrossRef]

69. De Sire, A.; Baricich, A.; Renò, F.; Cisari, C.; Fusco, N.; Invernizzi, M. Myostatin as a potential biomarker to monitor sarcopenia in hip fracture patients undergoing a multidisciplinary rehabilitation and nutritional treatment: A preliminary study. *Aging Clin. Exp. Res.* **2020**, *32*, 959–962. [CrossRef]
70. Cisternino, A.; Asa'ad, F.; Fusco, N.; Ferrero, S.; Rasperini, G. Role of multidisciplinary approach in a case of Langerhans cell histiocytosis with initial periodontal manifestations. *Int. J. Clin. Exp. Pathol.* **2015**, *8*, 13539–13545.
71. Pagni, F.; Guerini-Rocco, E.; Schultheis, A.M.; Grazia, G.; Rijavec, E.; Ghidini, M.; Lopez, G.; Venetis, K.; Croci, G.A.; Malapelle, U.; et al. Targeting immune-related biological processes in solid tumors: We do need biomarkers. *Int. J. Mol. Sci.* **2019**, *20*, 5452. [CrossRef]
72. Invernizzi, M.; Michelotti, A.; Noale, M.; Lopez, G.; Runza, L.; Giroda, M.; Despini, L.; Blundo, C.; Maggi, S.; Gambini, D.; et al. Breast cancer systemic treatments and upper limb lymphedema: A risk-assessment platform encompassing tumor-specific pathological features reveals the potential role of trastuzumab. *J. Clin. Med.* **2019**, *8*, 138. [CrossRef]
73. Lopez, G.; Costanza, J.; Colleoni, M.; Fontana, L.; Ferrero, S.; Miozzo, M.; Fusco, N. Molecular insights into the classification of luminal breast cancers: The genomic heterogeneity of progesterone-negative tumors. *Int. J. Mol. Sci.* **2019**, *20*, 510. [CrossRef]
74. Marazzi, F.; Orlandi, A.; Manfrida, S.; Masiello, V.; Di Leone, A.; Massaccesi, M.; Moschella, F.; Franceschini, G.; Bria, E.; Gambacorta, M.A.; et al. Diagnosis and treatment of bone metastases in breast cancer: Radiotherapy, local approach and systemic therapy in a guide for clinicians. *Cancers* **2020**, *12*, 2390. [CrossRef]
75. Wu, Z.; Lu, J. Advances in treatment of metastatic breast cancer with bone metastasis. *Chin. Clin. Oncol.* **2018**, *7*, 31. [CrossRef]
76. Goldvaser, H.; Amir, E. Role of bisphosphonates in breast cancer therapy. *Curr. Treat. Options Oncol.* **2019**, *20*, 26. [CrossRef]
77. Drake, M.T.; Clarke, B.L.; Khosla, S. Bisphosphonates: Mechanism of action and role in clinical practice. *Mayo Clin. Proc.* **2008**, *83*, 1032–1045. [CrossRef]
78. Wang, L.; Fang, D.; Xu, J.; Luo, R. Various pathways of zoledronic acid against osteoclasts and bone cancer metastasis: A brief review. *BMC Cancer* **2020**, *20*, 1059. [CrossRef] [PubMed]
79. Amadori, D.; Aglietta, M.; Alessi, B.; Gianni, L.; Ibrahim, T.; Farina, G.; Gaion, F.; Bertoldo, F.; Santini, D.; Rondena, R.; et al. Efficacy and safety of 12-weekly versus 4-weekly zoledronic acid for prolonged treatment of patients with bone metastases from breast cancer (ZOOM): A phase 3, open-label, randomised, non-inferiority trial. *Lancet Oncol.* **2013**, *14*, 663–670. [CrossRef]
80. Himelstein, A.L.; Foster, J.C.; Khatcheressian, J.L.; Roberts, J.D.; Seisler, D.K.; Novotny, P.J.; Qin, R.; Go, R.S.; Grubbs, S.S.; O'Connor, T.; et al. Effect of longer-interval vs standard dosing of zoledronic acid on skeletal events in patients with bone metastases: A randomized clinical trial. *JAMA* **2017**, *317*, 48–58. [CrossRef] [PubMed]
81. O'Carrigan, B.; Wong, M.H.; Willson, M.L.; Stockler, M.R.; Pavlakis, N.; Goodwin, A. Bisphosphonates and other bone agents for breast cancer. *Cochrane Database Syst. Rev.* **2017**, *10*, Cd003474. [CrossRef]
82. Diel, I.; Ansorge, S.; Hohmann, D.; Giannopoulou, C.; Niepel, D.; Intorcia, M. Real-world use of denosumab and bisphosphonates in patients with solid tumours and bone metastases in Germany. *Supportive Care Cancer* **2020**, *28*, 5223–5233. [CrossRef]
83. Kiesel, L.; Kohl, A. Role of the RANK/RANKL pathway in breast cancer. *Maturitas* **2016**, *86*, 10–16. [CrossRef]
84. Fizazi, K.; Lipton, A.; Mariette, X.; Body, J.J.; Rahim, Y.; Gralow, J.R.; Gao, G.; Wu, L.; Sohn, W.; Jun, S. Randomized phase II trial of denosumab in patients with bone metastases from prostate cancer, breast cancer, or other neoplasms after intravenous bisphosphonates. *J. Clin. Oncol.* **2009**, *27*, 1564–1571. [CrossRef]
85. Stopeck, A.T.; Lipton, A.; Body, J.J.; Steger, G.G.; Tonkin, K.; de Boer, R.H.; Lichinitser, M.; Fujiwara, Y.; Yardley, D.A.; Viniegra, M.; et al. Denosumab compared with zoledronic acid for the treatment of bone metastases in patients with advanced breast cancer: A randomized, double-blind study. *J. Clin. Oncol.* **2010**, *28*, 5132–5139. [CrossRef]
86. Nakai, Y.; Okamoto, K.; Terashima, A.; Ehata, S.; Nishida, J.; Imamura, T.; Ono, T.; Takayanagi, H. Efficacy of an orally active small-molecule inhibitor of RANKL in bone metastasis. *Bone Res.* **2019**, *7*, 1. [CrossRef]
87. Dai, R.; Wu, Z.; Chu, H.Y.; Lu, J.; Lyu, A.; Liu, J.; Zhang, G. Cathepsin K: The action in and beyond bone. *Front. Cell Dev. Biol.* **2020**, *8*, 433. [CrossRef]
88. Jensen, A.B.; Wynne, C.; Ramirez, G.; He, W.; Song, Y.; Berd, Y.; Wang, H.; Mehta, A.; Lombardi, A. The cathepsin K inhibitor odanacatib suppresses bone resorption in women with breast cancer and established bone metastases: Results of a 4-week, double-blind, randomized, controlled trial. *Clin. Breast Cancer* **2010**, *10*, 452–458. [CrossRef]
89. McClung, M.R.; O'Donoghue, M.L.; Papapoulos, S.E.; Bone, H.; Langdahl, B.; Saag, K.G.; Reid, I.R.; Kiel, D.P.; Cavallari, I.; Bonaca, M.P.; et al. Odanacatib for the treatment of postmenopausal osteoporosis: Results of the LOFT multicentre, randomised, double-blind, placebo-controlled trial and LOFT Extension study. *Lancet Diabetes Endocrinol.* **2019**, *7*, 899–911. [CrossRef]
90. Győri, D.S.; Mócsai, A. Osteoclast signal transduction during bone metastasis formation. *Front. Cell Dev. Biol* **2020**, *8*, 507. [CrossRef]
91. Mitri, Z.; Nanda, R.; Blackwell, K.; Costelloe, C.M.; Hood, I.; Wei, C.; Brewster, A.M.; Ibrahim, N.K.; Koenig, K.B.; Hortobagyi, G.N.; et al. TBCRC-010: Phase I/II Study of Dasatinib in Combination with Zoledronic Acid for the Treatment of Breast Cancer Bone Metastasis. *Clin. Cancer Res.* **2016**, *22*, 5706–5712. [CrossRef] [PubMed]
92. Schott, A.F.; Barlow, W.E.; Van Poznak, C.H.; Hayes, D.F.; Moinpour, C.M.; Lew, D.L.; Dy, P.A.; Keller, E.T.; Keller, J.M.; Hortobagyi, G.N. Phase II studies of two different schedules of dasatinib in bone metastasis predominant metastatic breast cancer: SWOG S0622. *Breast Cancer Res. Treat.* **2016**, *159*, 87–95. [CrossRef] [PubMed]
93. Hao, Y.; Baker, D.; Ten Dijke, P. TGF-β-mediated epithelial-mesenchymal transition and cancer metastasis. *Int. J. Mol. Sci.* **2019**, *20*, 2767. [CrossRef] [PubMed]

94. Li, X.; Jin, L.; Tan, Y. Different roles of matrix metalloproteinase 2 in osteolysis of skeletal dysplasia and bone metastasis (review). *Mol. Med. Rep.* **2021**, *23*, 1. [CrossRef]
95. Zielińska, K.A.; Katanaev, V.L. The signaling duo CXCL12 and CXCR4: Chemokine fuel for breast cancer tumorigenesis. *Cancers* **2020**, *12*, 71. [CrossRef]
96. Kwakwa, K.A.; Sterling, J.A. Integrin αvβ3 signaling in tumor-induced bone disease. *Cancers* **2017**, *9*, 84. [CrossRef]
97. Korpal, M.; Yan, J.; Lu, X.; Xu, S.; Lerit, D.A.; Kang, Y. Imaging transforming growth factor-beta signaling dynamics and therapeutic response in breast cancer bone metastasis. *Nat. Med.* **2009**, *15*, 960–966. [CrossRef]
98. Dunn, L.K.; Mohammad, K.S.; Fournier, P.G.; McKenna, C.R.; Davis, H.W.; Niewolna, M.; Peng, X.H.; Chirgwin, J.M.; Guise, T.A. Hypoxia and TGF-beta drive breast cancer bone metastases through parallel signaling pathways in tumor cells and the bone microenvironment. *PLoS ONE* **2009**, *4*, e6896. [CrossRef]
99. Bouquet, F.; Pal, A.; Pilones, K.A.; Demaria, S.; Hann, B.; Akhurst, R.J.; Babb, J.S.; Lonning, S.M.; DeWyngaert, J.K.; Formenti, S.C.; et al. TGFβ1 inhibition increases the radiosensitivity of breast cancer cells in vitro and promotes tumor control by radiation in vivo. *Clin. Cancer Res.* **2011**, *17*, 6754–6765. [CrossRef]
100. Kim, S.; Han, J.; Jeon, M.; You, D.; Lee, J.; Kim, H.J.; Bae, S.; Nam, S.J.; Lee, J.E. Silibinin inhibits triple negative breast cancer cell motility by suppressing TGF-β2 expression. *Tumor Biol.* **2016**, *37*, 11397–11407. [CrossRef]
101. Sun, X.; He, Z.; Guo, L.; Wang, C.; Lin, C.; Ye, L.; Wang, X.; Li, Y.; Yang, M.; Liu, S.; et al. ALG3 contributes to stemness and radioresistance through regulating glycosylation of TGF-β receptor II in breast cancer. *J. Exp. Clin. Cancer Res.* **2021**, *40*, 149. [CrossRef]
102. Tilley, A.M.C.; Howard, C.M.; Sridharan, S.; Subramaniyan, B.; Bearss, N.R.; Alkhalili, S.; Raman, D. The CXCR4-dependent LASP1-Ago2 interaction in triple-negative breast cancer. *Cancers* **2020**, *12*, 2455. [CrossRef]
103. Zhou, J.; Le, K.; Xu, M.; Ming, J.; Yang, W.; Zhang, Q.; Lu, L.; Xi, Z.; Ruan, S.; Huang, T. CXCR4 antagonist AMD3100 reverses the resistance to tamoxifen in breast cancer via inhibiting AKT phosphorylation. *Mol. Ther. Oncolytics* **2020**, *18*, 161–170. [CrossRef]
104. Shen, D.; Zhu, L.; Liu, Y.; Peng, Y.; Lan, M.; Fang, K.; Guo, Y. Efficacy evaluation and mechanism study on inhibition of breast cancer cell growth by multimodal targeted nanobubbles carrying AMD070 and ICG. *Nanotechnology* **2020**, *31*, 245102. [CrossRef]
105. Peng, Y.; Zhu, L.; Wang, L.; Liu, Y.; Fang, K.; Lan, M.; Shen, D.; Liu, D.; Yu, Z.; Guo, Y. Preparation of nanobubbles modified with a small-molecule CXCR4 antagonist for targeted drug delivery to tumors and enhanced ultrasound molecular imaging. *Int. J. Nanomed.* **2019**, *14*, 9139–9157. [CrossRef]
106. Li, Y.; Drabsch, Y.; Pujuguet, P.; Ren, J.; van Laar, T.; Zhang, L.; van Dam, H.; Clément-Lacroix, P.; Ten Dijke, P. Genetic depletion and pharmacological targeting of αv integrin in breast cancer cells impairs metastasis in zebrafish and mouse xenograft models. *Breast Cancer Res.* **2015**, *17*, 28. [CrossRef]
107. Fox, G.C.; Su, X.; Davis, J.L.; Xu, Y.; Kwakwa, K.A.; Ross, M.H.; Fontana, F.; Xiang, J.; Esser, A.K.; Cordell, E.; et al. Targeted therapy to β3 integrin reduces chemoresistance in breast cancer bone metastases. *Mol. Cancer Ther.* **2021**. [CrossRef]
108. Sharma, M.; Turaga, R.C.; Yuan, Y.; Satyanarayana, G.; Mishra, F.; Bian, Z.; Liu, W.; Sun, L.; Yang, J.; Liu, Z.R. Simultaneously targeting cancer-associated fibroblasts and angiogenic vessel as a treatment for TNBC. *J. Exp. Med.* **2021**, *218*. [CrossRef]