Title: Italian Position Paper (SIPMO-SICMF) on Medication-Related Osteonecrosis of the Jaw (MRONJ)

Running title: SIPMO-SICMF Position paper on MRONJ

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Appendix 1

Materials and Methods

Background

The Expert panel was appointed by the Board of Trustees of the Italian Society of Oral Pathology & Medicine (SIPMO) and the Italian Society of Maxillo-Facial Surgery (SICMF) in 2010 and comprised a multidisciplinary group of clinicians and researchers with recognized expertise in the field, who tracked the available literature and released two consecutive sets of Italian Recommendations on MRONJ in 2013 and 2020 (see full text) (Campisi, Bedogni, *et al*, 2020). The SIPMO-SICMF recommendations on MRONJ were published as a monograph in the Italian language and made available on several websites, with free access content.

Aims of the Position Paper

This 2022 Position Paper is an update of the 2020 Italian SIPMO-SICMF Recommendations on MRONJ. Patient populations at MRONJ risk were reviewed to include new groups of patients receiving novel antiresorptive medications (denosumab) and antiangiogenic agents (AAs), in addition to the established cohorts of bone metastatic cancer, Multiple Myeloma and osteoporosis patients receiving bisphosphonates (Campisi, Bedogni, *et al*, 2020; Srivastava, Nogueras Gonzalez, Geng, Won, Myers, *et al*, 2021; Kawahara *et al*, 2021). The purpose of this position paper is to point out several MRONJ debated issues and provide updates on the following aspects: epidemiology, disease definition, diagnostic pathway (including the role of imaging), staging, risk assessment, preventive strategies, and treatment algorithms. Some common practices at risk of inappropriateness in MRONJ diagnosis, prevention, and dental management of patients at increased risk of MRONJ have been evaluated elsewhere (Campisi, Mauceri, *et al*, 2020).

This Position Paper principally offers concise information for healthcare professionals who prescribe medications that increase the individual risk of MRONJ and oral health specialists.

Methods

The 2020 SIPMO-SICMF Position Paper on MRONJ was based on an extensive analysis of the available literature from January 2003 to February 2020. Overall,639 selected references were cited in the three chapters of the published monograph (Campisi, Bedogni, *et al*, 2020).

In this updated version, the literature search was conducted between March 2020 and December 2021to include all new relevant published papers with the aim of confirming or modifying the previous set of recommendations.

The computerized literature search was carried out in the PubMed database for the period 1st January 2020 – 31st December 2021using MeSH (Medical Subjects Headings) terms and free terms with the following equation “Osteonecrosis AND (Jaw OR Jaws)”, which resulted in further 689 new articles. The literature search was expanded by manual search to include some congress abstracts and papers not comprised in PubMed. Further important papers published in 2022 were proposed by single members of the board and included in the final version of this Position Paper. The references cited in the included articles were also discussed among the panel members. An integrative review approach was used to overview the knowledge base and to critically review and

re-conceptualize the most debated issues on MRONJ.

Appendix 2

Epidemiology (addendum)

The measures of disease frequency (prevalence, cumulative incidence, incidence rate) in MRONJ literature are insufficient and appear sub-optimally reported.

Prevalence is an estimate of the probability that a particular health condition exists at a particular point in time (point prevalence) or over a period of time (period prevalence). It is the proportion (not a rate) of the total number of persons who have a condition (numerator) in the total population at risk (denominator) during a specified time interval. The numerator includes cases arising before and during the time period (regardless of when the illness began). It is very helpful for quantifying disease burden (e.g., public health) and relatively easy to estimate. It is usually expressed as the number of cases per 10,000 or 100,000 people. Prevalence appears of minimal interest for MRONJ in cancer and myeloma patients, whereas it could be of higher value (if ascertainable with adequate tools) for MRONJ in osteoporotic patients.

Incidence measures new cases of a disease that develop in a defined population within a given period of time (for example, the number of new MRONJ cases in one year). Incidence of MRONJ is very often reported without specifying the period of time.

Cumulative incidence, also known as *incidence proportion* (IP) or *risk*, is an estimate of the probability that a particular health condition occurs within a given time interval (for example, the probability of MRONJ diagnosis after one, two, or three years of drug treatment) in a population at risk of getting the condition at the start of the time interval (i.e., the follow-up period). The numerator is the number of new cases of disease during a specified time interval and the denominator is the number of disease-free subjects at the start of follow-up. It is always calculated for a given period of time (e.g., annual incidence). Cumulative incidence is expressed as a proportion of the population at risk (e.g., 3.5% over 5 years) and is a measure of risk; it is the most common way to estimate risk.

The *incidence rate*, also known as *incidence density*, or *hazard rate*, describes how rapidly a health condition is occurring in a population of interest over a specific time interval; it is the rate at which new events occur in a population. The numerator is the number of new cases of disease during a specified time interval and the denominator is the total time (person-years, -months) that disease-free individuals in the study population are observed over the study period (summed person-years of observation or average population during time interval). It is usually expressed as the number of cases per time unit (e.g., patient-days, -months, or -years). The use of this measure implies the assumption that the incidence rate is constant over different periods of time. When this assumption is violated (as in the case of MRONJ after treatment of bone metastatic cancer and myeloma), it may be more useful to present incidence data in a plot of cumulative incidence (risk) over time and take into account loss to follow-up and competing risks. In survival (time-to-event) analysis, the hazard rate is the event rate at a given time t conditional on survival until time t and the Kaplan-Meier plot can show MRONJ risk. Ignoring competing risks in time-to-event analyses can lead to biased risk estimates (mostly upwards), particularly for elderly patients with multimorbidity (Abdel-Qadir *et al*, 2018). However, the Kaplan-Meier function seems to be the best tool to estimate MRONJ risk over time.

Estimates of the proportion of patients receiving bone modifying agents (BMAs) who develop MRONJ disease, and MRONJ risk estimates for future patients who will undergo the same treatments can be dependent on the following aspects:

- type of drug (generally higher risk for zoledronic acid (ZA) and denosumab (DMB) in comparison with other bisphosphonates) (Campisi *et al*, 2014; Yarom *et al*, 2019; Ruggiero *et al*, 2022; Anastasilakis *et al*, 2022);

- dose of frequency of administrations (generally higher risk after monthly doses), and cumulative dose (higher risk for higher total dose) (Ng *et al*, 2021; Fusco *et al*, 2022);

- duration of treatment and time of observation: MRONJ risk increases after prolonged and unremitting treatments, but a certain risk is also present after the conclusion of treatment, at least for ZA (Del Conte *et al*, 2010; Ng *et al*, 2021; Fusco *et al*, 2022);

- selection of patients at the denominator on the basis of specific characteristics; in most recent randomized trials, for example, only patients with sound oral health were included, so that a lower MRONJ frequency could be expected in comparison with real-life patients (Stopeck *et al*, 2010; Fusco *et al*, 2011; Saad *et al*, 2012; Raje *et al*, 2018); on the opposite, higher MRONJ figures were seen in selected patients with defective oral health (e.g., periodontal disease) and/or necessitating dental extractions (Mavrokokki *et al*, 2007; Yamazaki *et al*, 2012; Watts *et al*, 2019).

Selected examples of MRONJ estimates obtained from the pertinent and most recent literature are illustrated in:

- **Table Ia**, reporting data from clinical trials and large real-life studies on bone metastatic and Multiple Myeloma patients, mostly receiving high doses of ZA and DMB.
- **Table Ib**, reporting data from clinical trials and cohort studies on osteoporotic patients receiving low doses of BPs (including ZA) and DMB.
- **Table Ic**, reporting data from clinical studies on non-metastatic cancer patients receiving BMAs with different drugs and schedules to prevent Cancer Treatment Induced Bone Loss (CTIBL), with/without attempts to prolong time to disease recurrence as secondary endpoint.
- **Table Id**, reporting data from clinical trials on non-metastatic cancer patients receiving BMAs with different drugs and schedules aimed at improving cancer prognosis(i.e., adjuvant setting).
- **Table Ie**, reporting data from cohort studies on patients with Giant Cell Tumor of Bone (GCTB) receiving DMB treatment.

Rough estimates of MRONJ "frequency" largely ranged between zero and more than 20% among patients at risk (Table Ia-Ie).

Recent systematic and narrative reviews generally show a higher MRONJ risk after ZA in comparison with other bisphosphonates (pamidronate, ibandronate, oral bisphosphonates), and a higher risk after DMB in comparison with ZA (Limones *et al*, 2020; Jakob *et al*, 2020; Chen *et al*, 2021; Jiang *et al*, 2021), with some exceptions (Chen and Pu, 2016; Srivastava, Nogueras Gonzalez, Geng, Won, Cabanillas, *et al*, 2021). Review results are often difficult to interpret, due to the co-presence of patient subgroups who received different drug dosages and schedules with variable treatment duration.

In populations at higher MRONJ risk (i.e., bone metastatic cancer patients and myeloma patients) as well as at lower risk (i.e., patients with osteoporosis or other non-malignant diseases) "incidence" (or "prevalence" or "frequency") data are commonly reported as simple rate (number of observed cases as numerator / total population of patients included as the denominator), without a quantified observation time.

Reported MRONJ estimates range between 1% and more than 20% in cancer and myeloma patients (Table Ia), and between 0% and 1% in osteoporotic and non-malignant patients (with some exceptions) (Table Ib).

In large randomized trials comparing DMB and ZA in cancer patients with bone metastases or multiple myeloma (BM/MM), Kaplan-Meier plots are not reported, and the estimated cumulative incidence of "adjudicated" MRONJ is reported at 1, 2 and 3 years (Stopeck *et al*, 2010; Stopeck and Warner, 2017; Raje *et al*, 2018). In contrast, Kaplan-Meier cumulative incidence estimates reported in large "real life" clinical studies show a sharp increase of MRONJ risk when monthly administrations of ZA or DMB are prolonged after 2-3 years of treatment (Manfredi *et al*, 2017; Egloff-Juras *et al*, 2018; van Cann *et al*, 2018; Loyson *et al*, 2018; Hallmer *et al*, 2020; Nakai *et al*, 2021; Ueda *et al*, 2021; Ikesue, Doi, *et al*, 2021; Ikesue *et al*, 2022; Hata *et al*, 2022).

Limited data show a reduction of MRONJ figures if ZA administrations are given on a 3-month schedule, in comparison with continuous monthly infusions (Himelstein *et al*, 2017; Fusco *et al*, 2022).

Some recent studies pointed out a higher risk of MRONJ occurrence for patients shifted from ZA to DMB (Vehmanen *et al*, 2017; Yarom *et al*, 2018; Loyson *et al*, 2018; Higuchi *et al*, 2018; Srivastava, Nogueras Gonzalez, Geng, Won, Cabanillas, *et al*, 2021; Ehrenstein *et al*, 2021; Ikesue, Doi, *et al*, 2021), similarly to the MRONJ estimates of patients who were shifted from pamidronate to ZA, which were published ten years earlier. These findings must be interpreted with caution given the observational nature of the studies and the heterogeneous populations investigated.

Patients suffering from osteoporosis (OP) and other non-malignant diseases receiving low-dose bone BMAs display a small individual MRONJ risk, generally less than 1% (Table 1b); higher MRONJ figures were reported in patients treated for many years with low-dose BMAs (in accordance with what observed in clinical practice) (Yarom *et al*, 2007; Lazarovici *et al*, 2009; Di Fede *et al*, 2016; Watts *et al*, 2019; Everts-Graber *et al*, 2022), for patients with rheumatic and autoimmune disorders(Liao *et al*, 2019; Fujieda *et al*, 2020) and for patients with defective oral health and/or necessitating dental extractions (Mavrokokki *et al*, 2007; Yamazaki *et al*, 2012; Watts *et al*, 2019). However, as the number of patients receiving low-dose BMAs is very large in the general population, the total number of MRONJ cases diagnosed in second and third-lever oral care centres is increasing, sometimes exceeding that of bone metastatic and myeloma patients (Lee *et al*, 2013; Rogers *et al*, 2015; Hallmer *et al*, 2018).

Romosozumab is a drug with both bone anabolic and antiresorptive properties that has been recently introduced for OP treatment. MRONJ has been rarely reported in OP patients treated with romosozumab, but most of them also received bisphosphonates or denosumab (Cosman *et al*, 2016; Saag *et al*, 2017; Kobayakawa *et al*, 2021; Peng *et al*, 2022). Consequently, the influence of romosozumab in promoting MRONJ remains uncertain at the moment.

Clinical studies aimed to prevent or treat CTIBL (Table Ic) in non-metastatic breast cancer patients commonly used delayed administrations of ZA (mostly every 6 months) or DMB (60 mg every 6 months) with only a few reported MRONJ cases (0%-0.5%). Nonetheless, it is likely that MRONJ estimates of real-life LD-BMA treatment to prevent or treat CTIBL will match those observed in the osteoporosis setting, after several years of treatment.

Cases of delayed jawbone alterations without frank bone exposure have been reported after zoledronic acid treatment in a single trial subpopulation (Rugani *et al*, 2014).

Some clinical trials were designed to investigate the efficacy of BPs or DMB as "adjuvant" therapy (i.e., improvement of survival or disease-free survival) in breast and prostate cancer patients with different dosages and schedules; MRONJ figures in these patient populations ranged between 0.3% and 5.4% (Table Id). Although the prescription of BMAs for this use is still limited in real-life clinical practice, oral healthcare specialists should consider non-metastatic cancer patients receiving these treatments as another subpopulation at risk.

Variable MRONJ estimates were recorded in patients with Giant Cell Tumor of Bone (GCTB) treated with prolonged administrations of DMB (Table Ie); MRONJ risk appears to increase with years of therapy (Palmerini *et al*, 2017; Chawla *et al*, 2019; Raimondi *et al*, 2020; Jiang *et al*, 2022).

MRONJ was reported in patients receiving only AAs (anticancer drugs with antiangiogenic properties, including bevacizumab, aflibercept, inhibitors of tyrosine kinase and mammalian target of rapamycin inhibitors) or other biological drugs (agents for cancer or autoimmune diseases) with no history of BMA treatment, described predominantly in case reports and case series (Fusco *et al*, 2016, 2021; Nicolatou-Galitis *et al*, 2019; Eguia *et al*, 2020; Suryani *et al*, 2022; Ruggiero *et al*, 2022).

However, data is not sound enough to completely define other subpopulations at risk of MRONJ (e.g., metastatic cancer patients receiving AAs alone without HD-BMAs; patients with rheumatic disorders receiving biological agents without LD-BMAs; etc) comparable to categories in Table Ia-Ie.

Furthermore, link between many reported drugs (see Table II) and MRONJ is questionable, due to problems inherent to interpretation of case reports as well as of data coming from adverse event reporting systems, with some realistic signals and some pseudo signals (Neha *et al*, 2020; Peng *et al*, 2022; Ellefsen *et al*, 2023; Ahdi *et al*, 2023)

Finally, MRONJ cases have been very rarely reported in patients receiving drugs different from those known to promote the disease, above all in cancer and Rheumatoid Arthritis (Aghaloo and Tetradis, 2017; Amano *et al*, 2023). These reports suggest that oral specialists should carefully address the present and past drug history of their patients, in collaboration with healthcare professionals who prescribe medications.

Appendix 3

SIPMO-SICMF stage-related surgical algorithm.

The SIPMO-SICMF stage-related surgical algorithm has been originally developed in 2013 to specifically address increasing levels of surgical intensity based on the extent of BRONJ and the primary disease of affected patients (Campisi et al, 2014). This algorithm has been recently upgraded to include a separate treatment protocol for DMB-ONJ (Campisi, Bedogni, et al, 2020). The SIPMO-SICMF stage-related surgical algorithm describes the combination of medical therapies and surgical techniques to be adopted in BRONJ and DMB-ONJ; it also describes the non-surgical treatment of MRONJ (see full text, Table 8a, Table 8b, and Table 8c).

A detailed description of the SIPMO-SICMF stage-related surgical algorithm, including jawbone reconstructive options, see Table IIIa and Table IIIb.

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Tables:

Table Ia – MRONJ following administration of zoledronic acid (monthly and/or q3months) and/or monthly denosumab in Multiple Myeloma or bone metastatic cancer patients – selected papers

Disease (Number of patients)	**Authors (Year of publication)**	**Treatment (Schedule)**	**MRONJ frequency**	**Notes (*potential strengths/weaknesses*)**
Solid cancers (5723)	Saad (2012), Raje (2019) (European Medicines Agency; Saad *et al*, 2012; Raje *et al*, 2019)	ZA, DMB (q4wks)	ZA 1.3% DMB 1.8% Per 100 patient-year: 1.1% in the first year, 3.7% in the second year; 4.6% per year thereafter	• Randomized trials (data merged from 3 trials) • Strict inclusion criteria (sound oral health) • Very short observation time (median on-study time 12.1 months). • 89 (1.5%) "adjudicated" MRONJ cases out of 287 (4.8%) "potential" MRONJ cases • Lack of Kaplan-Meier plots
Breast/prostate cancer (917)	Stopeck (2016), Fusco (2017), Stopeck (2017) (Open-label extension study) (Stopeck *et al*, 2016; Fusco *et al*, 2017; Stopeck and Warner, 2017)	ZA, DMB, ZA→ DMB (q4wks)	5.4% - 8.2% in different subgroups(Stopeck *et al*, 2016)	• Randomized trial. • Selected patients (good oral health). • Longer observation time(extension study). • 140 "adjudicated" MRONJ cases out of 341 "potential" MRONJ cases. • Lack of Kaplan-Meier plots.
Myeloma (1718)	Raje (2018), Fusco (2018), Raje (2019) (Myeloma denosumab registration trial) (Raje *et al*, 2018, 2019; Fusco *et al*, 2018)	ZA, DMB (q4wks)	ZA 2.8% DMB 4.1% Per 100 patient-year: 2.0% in the first year, 5.0% in the second year; 4.5% per year thereafter	• Randomized trial. • Selected patients (good oral health). • Short observation time (median on-study time 17.6 months). • Reported 59 (3.4%) "adjudicated" MRONJ cases out of 158 (9.2%) "potential" cases. • Lack of Kaplan-Meier plots.
Myeloma (1960)	Jackson (2014) (MRC Myeloma IX trial) (Jackson *et al*, 2014)	ZA (q4wks) CLO oral	ZA 3.7% CLO 0.5%	• Randomized trial. • Accrual 2002-2006; evaluation 2009, with median follow-up of 3.7 years. • Lack of Kaplan-Meier plot.
Myeloma (119)	Catania (2016) (Catania *et al*, 2016)	ZA/PAM	4.2%	• Single-centre experience 2005-2014. • Lack of Kaplan-Meier plot.

Myeloma (120)	Then (2012) (Then *et al*, 2012)	ZA/PAM/ IBAN	19.2%	• MRONJ cases in myeloma patients undergoing stem cell transplant. Cumulative incidence illustrated.
Breast cancer (425)	Amadori (2013) (ZOOM trial) (Amadori *et al*, 2013)	ZA (q4wks vs q12wks)	1.3% / 1.9%	• Randomized trial. • Short follow-up.
Breast/prostate cancer and myeloma (1822)	Himelstein (2017) (Himelstein *et al*, 2017)	ZA (q4wks vs q12wks)	1.0% / 2.0%	• Randomized trial. • Only 795 out of 1822 patients completed the study at 2 years. • Short follow-up.
Breast cancer (416)	Hortobagyi (2017) (OPTIMIZE-2 trial) (Hortobagyi *et al*, 2017)	ZA (q4wks vs q12wks)	0.0%/ 1.0%	• Randomized trial. • Short treatment and short follow-up.
Solid cancer (155)	Kajizono (2015) (Kajizono *et al*, 2015)	ZA DMB (q4wks)	8.4% (breast cancer subgroup 15.3%)	• Cancer patients receiving ZA or DMB in 2010-2013.
Solid cancer (156)	Manfredi (2017) (Manfredi *et al*, 2017)	ZA (q4wks)	10.9%	• Unselected (real-life) patients. Long observation. Kaplan-Meier plots reported.
Solid cancers (649)	Loyson (2018) (Loyson *et al*, 2018)	ZA, DMB, ZA→DEN (q4wks)	ZA 6.7%, DMB10% ZA→DMB15.5%	• Unselected (real-life) patients. Median follow-up 17.5-36 months in different subgroups. • Kaplan-Meier evaluation reported.
Solid cancers (90+533)	Van Cann (2018) (van Cann *et al*, 2018)	ZA or DMB(q4wks w/ or w/oAAs)	11.1% w/ AAs 10.9% w/o AAs	• Unselected (real-life) patients. Median observation: 24 months. • Kaplan-Meier estimates.
Solid cancer (161)	Higuchi (2018) (Higuchi *et al*, 2018)	ZA→ DMB(q4wks)	10.6%	• High risk for patients receiving denosumab after zoledronic acid.
Prostate cancer (254)	Vehmanen (2017) (Vehmanen *et al*, 2017)	ZA DMB, ZA→ DMB (q4wks)	Total 11.4%	• Higher risk for patients receiving denosumab or denosumab after zoledronic acid.
Solid cancer (141)	Egloff-Juras (2018) (Egloff-Juras *et al*, 2018)	DMB	7.1%	• Single-centre experience 2010-2015; median follow-up: 25 months. MRONJ: 3% at 1 year, 7% at 2 years, and 8% from 30 months on.
Thyroid cancer (23)	Wassermann (2019) (Wassermann *et al*, 2019)	DMB	26.1%	• 3 MRONJ out of 15 patients receiving TKIs and DMB • 3 MRONJ out of 8 patients not receiving TKIs
Breast cancer (242)	Hallmer (2020) (Hallmer *et al*, 2020)	ZA DMB (q4wks)	ZA 4.1% DMB 13.6%	• Regional experience 2012-2015. • Kaplan-Meier estimates reported.
Solid cancers (374)	Ikesue (2021) (Ikesue, Mouri, *et al*, 2021)	ZA DMB (q4wks)	Total 9.1% DMB 12.6% ZA 4.4%	• Unselected (real-life) patients, undergoing risk-reducing pre-treatment measures. Short observation (median 15.5 months). Maximum risk for prostate cancer patients (26.3%

				after denosumab). • Kaplan-Meier estimates reported (cumulative MRONJ incidence after denosumab: at 2 years next to 15%; at 3 years next to 25%).
Solid cancers (795)	Ikesue (2021) (Ikesue, Doi, *et al*, 2021)	ZA DMB ZA→DMB(q4 wks)	Total 8.2% ZA 5.4% DMB 9.7% ZA→DMB 16.3%	• Higher risk for patients receiving denosumab after zoledronic acid. • Kaplan-Meier estimates reported (at 3 years: 10% after ZA, >30% after DMB).
Solid cancers (218)	Sakai (2021) (Sakai *et al*, 2021)	ZA DMB (q4wks)	Total 23% (22% prostate, 25% kidney cancer)	• Multicentre study in urological patients only
Prostate cancer (191)	Nakai (2021) (Nakai *et al*, 2021)	ZA DMB (q4wks)	ZA 12.9% DMB 15.6%	• Hormone-sensitive and castration-resistant prostate cancer patient. Observation time: median 23 months, (range 1-130). • Kaplan-Meier estimates reported (MRONJ risk at 5 years: 22.7% for ZA, 41.0% for DMB)
Prostate cancer (113)	Yasui (2021) (Yasui *et al*, 2021)	ZA DMB (q4wks)	ZA 30.3% DMB 22.5%	• Single-centre experience 2012-2020; longer treatment duration and observation for ZA subgroup. • No Kaplan-Meier evaluation.
Solid cancer (398), including prostate cancer (79)	Ueda (2021) (Ueda *et al*, 2021)	ZA DMB (q4wks)	Total 10.6% (prostate cancer 32.9%)	• Single centre experience 2007-2018. • Kaplan-Meier estimates reported (MRONJ: 4.5%, 12.9%, 17%, and 21.6% at 1, 2, 3, and 4 years, respectively).
Solid cancer (2877)	Ehrenstein (2021) (Ehrenstein *et al*, 2021)	ZA DMB ZA→DMB (q4wks)	ZA 1.4% DMB 5.7% ZA→ DMB 6.6%	• Cohort study in Denmark, Norway, and Sweden in 2011-2018.
Solid cancers (799)	Ikesue (2022) (Ikesue *et al*, 2022)	ZA DMB (q4wks)	Total 7.3% ZA 4.8% DMB 9.6%	• Propensity score-matched analysis on a large patient population. • Kaplan-Meier estimates reported before and after propensity score matching.
Solid cancers or myeloma (862)	Hata (2022) (Hata *et al*, 2022)	ZA (q4wks)	MRONJ cumulative incidence: 4.7%, 18.1%, and 32.1% at 2, 5, and 8 years	• Long-term observation. The cumulative incidence of MRONJ was related to the frequency of anti-resorptive drug use and the increased risk over time in breast cancer, prostate cancer, and multiple myeloma; it increased early in renal cancer. • Kaplan-Meier estimates reported.
Unspecified cancer types	Soutome (2022) (Soutome *et al*, 2022)	High-dose BMAs	13.3%	• Patients with dental diseases but that did not undergo tooth

(92)				extraction

Abbreviations: ZA = zoledronic acid; DMB = denosumab; pla = placebo; BPs = bisphosphonates; CLO = clodronate; ALE= Alendronate; IBA = ibandronate; PAM = pamidronate; q4wks = every 4 weeks; q3-4wks = every 3-4 weeks; q12wks = every 12 weeks; q3mo = every 3 months; q6mo = every 6 months; q12mo = every 12 months

Table Ib – MRONJ after administration of bisphosphonates (oral or intravenous) and/or denosumab (60 mg q 6 months) in osteoporosis patients – selected papers

Disease (Number of patients)i	**Authors (Year of publication)**	**Treatment (Schedule)**	**MRONJ frequency**	**Notes (*potential strengths*/*weaknesses*)**
Osteoporosis (304900)	Mavrokokki (2007) (Mavrokokki *et al*, 2007)	Oral BPs	0.01% to 0.04%	• 0.09% to 0.34%, after dental extractions. • Denominator estimated on drug prescriptions.
Osteoporosis (208)	Sedghizadeh (2009) (Sedghizadeh *et al*, 2009)	Oral BPs	4.3%	• Selection bias.
Osteoporosis (12752)	Hong (2010) (Hong *et al*, 2010)	Oral BPs	0.1%	• 7 MRONJ in OP patients followed in one hospital between 2000-2008 (but 24 cases observed in dental care centre).
Osteoporosis (1541)	Lo (2011) (Lo *et al*, 2011)	Oral BPs	0.6%	• Kaiser patients, in 2006-2008.
Osteoporosis (76)	Villa (2011) (Villa *et al*, 2011)	Oral BPs	9.2%	• Selection bias.
Osteoporosis (99)	Yamazaki (2012) (Yamazaki *et al*, 2012)	Oral BPs	1%	• MRONJ after tooth extractions in patients receiving BPs - osteoporosis subgroup.
Osteoporosis (4129)	Yamazaki (2013) (Yamazaki *et al*, 2013)	Oral BPs	1%	• ONJ/OMJ (osteomyelitis) in osteoporosis patients receiving oral BPs.
Osteoporosis (1284)	Kwok (2016) (Kwok *et al*, 2016)	Oral BPs	0.3%	• 103 suspected, 4 confirmed MRONJ cases.
Osteoporosis (2047)	Saag (2017) (Saag *et al*, 2017)	ALE	0.05%	• Short observation (24 months).
Osteoporosis (not specified)	Hallmer (2018) (Hallmer *et al*, 2018)	Oral BPs	0.043%	• Prospective cohort study: all patients diagnosed with MRONJ in a Swedish region (estimation on hypothetic treated population).
Osteoporosis (222477)	Veszelyne Kotan (2019) (Veszelyne Kotan *et al*, 2019)	BPs	0.1%	• Non-cancer patients receiving BPs in Hungarian national service data; ICD codes.
Sjogren's syndrome (11944+1454)	Liao (2019) (Liao *et al*, 2019)	BPs	0.1% / 0.3%	• MRONJ in patients with Sjögren's syndrome in Taiwan (cohort study). • Two groups: w/ and w/o tooth extraction.
Osteoporosis and other diseases (232)	Fujieda (2020) (Fujieda *et al*, 2020)	BPs	4.3%	• MRONJ after tooth extraction in non-cancer patients (0.9% in osteoporosis, 7.2% in autoimmune disease subgroup, 13% in RA patients).

Osteoporosis (5903)	Grbic (2008), Grbic (2010) (Grbic *et al*, 2008, 2010)	ZA (5mgq12mo)	0.02%	• Several studies with yearly ZA.
Osteoporosis (3591)	Watts (2019) (FREEDOM Extension study) (Watts *et al*, 2019)	DMB (60mg/q6mo)	0.05%-0.68%	• Randomized trial. • Long-term observation. • The exposure-adjusted ONJ rate in FREEDOM Extension was 5.2 per 10,000 person-years. • ONJ incidence was higher in those reporting an oral procedure or event (0.68%) than not (0.05%).
Osteoporosis (3068)	Everts-Graber (2022) (Everts-Graber *et al*, 2022)	BPs (oral/iv) DMB (60mg/q6mo) or sequence	0.55%	• The risk of ONJ was higher in patients receiving denosumab therapy compared with BPs. • Nine of 12 patients who developed ONJ during DMB treatment had been pre-treated with BPs, but none of the 5 patients with BP-ONJ had previously received denosumab.

Abbreviations: ZA = zoledronic acid; DMB = denosumab; pla = placebo; BPs = bisphosphonates; CLO = clodronate; ALE= Alendronate; IBA = ibandronate; PAM = pamidronate; q4wks = every 4 weeks; q3-4wks = every 3-4 weeks; q12wks = every 12 weeks; q3mo = every 3 months; q6mo = every 6 months; q12mo = every 12 months

Table Ic– MRONJ after administration of zoledronic acid and/or denosumab to prevent CTIBL (Cancer Treatment Induced Bone Loss), with/without attempts to prolong time to disease recurrence as secondary endpoint, with different schedules – selected papers

Disease (Number of patients)	**Authors (Year of publication)**	**Treatment (Schedule)**	**MRONJ frequency**	**Notes (*potential strengths/weaknesses*)**
Breast cancer (50 ZA treated; 53 placebo)	Hershman (2008) (Hershman *et al*, 2008)	ZA (4mg/q12wks, for 1 year)	0%	• Short treatment duration • Short follow-up.
Breast cancer (900 ZA treated out of 1803)	Gnant (2009) (ABCSG-12 trial) (Gnant *et al*, 2009)	ZA (4mg/q6mo, for 3 yrs.)	0%	• No "adjudicated"cases of MRONJ at 62-month follow-up, but 5/48 "stage 0" cases in a subpopulation study. (Rugani *et al*, 2014)
Breastcancer (439)	Shapiro (2011) (CALGB 79809 trial) (Shapiro *et al*, 2011)	ZA (4mg/q12wks) for 2 yrs.)	0%	• ZA started within 1-3 months following randomization (arm A) or 1 year after randomization (arm B, controls).
Breast cancer (301 upfront, 301 delayed ZA treatment)	Brufsky (2012) (Z-FAST trial) (Brufsky *et al*, 2012)	ZA (4mg/q6mo, for 5 yrs.)	0%	• Long-term observation (61 months).
Breast cancer (263 upfront, 264 delayed ZA treatment)	Llombart (2012) (EZO- FAST trial) (Llombart *et al*, 2012)	ZA (4mg/q6mo, for 5 yrs.)	0%	• Short observation (only 12 months?).
Breast cancer (532 upfront, 533 delayed ZA treatment)	Coleman (2013) (ZO- FAST trial) (Coleman *et al*, 2013)	ZA (4mg/q6mo, for 5 yrs.)	0.5%	• Long-term observation (60 months). • MRONJ: 3 "adjudicated" and 2 "suspected" cases, out of 9 potential events.
Breast cancer (48 ZA treated; 52 control patients)	Rugani (2014) (Rugani *et al*, 2014)	ZA (4mg/q6mo, for 3 yrs.)	10.4%	• Clinical subpopulation study on patients of trial ABCSG-12. Very long-term observation, after ZA treatment cessation. Five "stage 0" MRONJ cases (fistulas / radiological signs of MRONJ), out of 48 examined patients.
Breast cancer (1711 DMB treated out of 3425 recruited)	Gnant (2019) (ABCSG-18 trial) (Gnant *et al*, 2019)	DMB (60 mg/q6mo, for 5 yrs.)	0%	• Long-term observation (median 73 months). No "adjudicated" MRONJ cases (out of 31 suspected cases).

Abbreviations: ZA = zoledronic acid; DMB = denosumab; q4wks = every 4 weeks; q3-4wks = every 3-4 weeks; q12wks = every 12 weeks; q3mo = every 3 months; q6mo = every 6 months; q12mo = every 12 months

Table Id– MRONJ data from trials on "adjuvant" treatment of non-metastatic cancer (studies aimed to attempt to improve prognosis) – selected papers

Disease (Number of patients)	**Authors (Year of publication)**	**Treatment (Schedule)**	**MRONJ frequency**	**Notes (*potential strengths*/*weaknesses*)**
Prostate cancer (716 DMB treated/ 716 pla)	Smith (2012) (Smith *et al*, 2012)	DMB (120 mg/q4wks)	5%	• Yearly cumulative incidence of "adjudicated" MRONJ for DMBwas: 1%, 3%, 4% in years 1, 2, 3, respectively; overall, less than 5% (n=33).
Breast cancer (1681ZA treated out of 3360)	Rathbone (2013) (AZURE trial) (Rathbone *et al*, 2013)	ZA 4 mg (19 courses for 5 yrs; 6 doses monthly →8 doses q3mo →5 doses q6mo)	2.1%	• Long-term observation (median 73.9 months). • Twenty-six "confirmed" MRONJ cases out of 33 "suspected" cases.
Breast cancer (355 ZA treated out of 1065)	Perrone (2019) (HOBOE trial) (Perrone *et al*, 2019)	ZA (4 mg q6mo, for 5 yrs.)	1.1%	• Long-term observation (median 64 months). • Four MRONJ cases (after 24, 30, 48, 60 months) out of 340 patients.
Breast cancer (2256 DMB treated out of 4509)	Coleman (2020), Fusco (2020), Coleman (2020) (D-CARE trial) (Coleman, Finkelstein, *et al*, 2020; Coleman, Zhou, *et al*, 2020; de Boissieu *et al*, 2020)	DMB (120 mg q4wks for 6 months, then q3mo, for 5 yrs.)	5.4%	• Selected patients (sound oral health). • Long observation (median follow-up: 67 months) • MRONJ:122 (5.4%) "adjudicated" cases out of 362 (16.2%) "suspected" cases among DMB-treated patients; 4(0.2%) out of 202 (9.1%) among symptomatic patients receiving placebo. • Lack of Kaplan-Meier plot.
Breast cancer (6097)	Gralow (2020), Kizub (2021) (SWOG S0307trial) (Gralow *et al*, 2020; Kizub *et al*, 2021)	ZA (4 mg q4wks→ q12wks) Oral daily CLO Oral daily IBA	ZA 1.2%, CLO 0.3%, IBA 0.7%	• Adequate follow-up.
Breast cancer (565)	Vliek (2022) (TEAM-IIB trial) (Vliek *et al*, 2022)	Oral IBA (50mg/day, for 3 yrs.)	1.9%	• Long follow-up (8.5 years).

Abbreviations: ZA = zoledronic acid; DMB = denosumab; pla = placebo; CLO = clodronate; IBA = ibandronate; q4wks = every 4 weeks; q3-4wks = every 3-4 weeks; q12wks = every 12 weeks; q3mo = every 3 months; q6mo = every 6 months; q12mo = every 12 months

Table Ie – MRONJ data from cohort studies on denosumab treatment of patients with Giant Cell Tumor of Bone, GCTB – selected papers

Disease **(Number of patients)**	**Authors** **(Year of publication)**	**Treatment (Schedule)**	**MRONJ frequency**	**Notes (*potential strengths/weaknesses*)**
GCTB (97)	Palmerini (2017) (Palmerini *et al*, 2017)	DMB (120 mg)	6.1%	• Cumulative risk of all patients: 5% at 5 years.
GCTB unresectable (54)	Palmerini (2017) (Palmerini *et al*, 2017)	DMB (120 mg)	9.2%	• Cumulative risk of unresectable patients: 8% at 5 years.
GCTB unresectable (532)	Chawla (2019) (Chawla *et al*, 2019)	DMB (120 mg)	Total 5.2% (8% in cohort 1 / 2.8% in cohort 2 / 0% in cohort 3)	• 28 investigator-reported and adjudicated cases (21 in cohort 1, 7 in cohort 2, none in cohort 3). • Cumulative incidence in single years is reported in the paper.
GCTB (29)	Raimondi(2020) (Raimondi *et al*, 2020)	DMB (120 mg)	13.8%	• At a median follow-up of 70months (range 1–125), 4 (13.8%) patients experienced MRONJ while on treatment, after 125, 119, 85 and 41 months of DMB, respectively.
GCTB (37)	Jiang (2022) (Jiang *et al*, 2022)	DMB (120 mg)	13.5%	• The median cumulative dose of DMB received was 43 (range 15-139 doses). • Recorded 5 sites of ONJ plus 2 sites of non-healing dental wound.

Abbreviations: DMB= denosumab.

Table II. Non-antiresorptive drugs reported as associated with MRONJ

Class of agents and drugs	Route of administration	Main indications
VEGF inhibitors		
- Bevacizumab	IV	Cancers (colon, breast, ovary, renal, etc); ocular diseases
- Aflibercept	IV	Colon cancer
- Ramucirumab	IV	Gastric cancer
Tyrosine kinase inhibitors and drugs with antiVEGF properties		
- Sunitinib	OS	Cancers (renal, GIST, neuroendocrine, etc.)
- Sorafenib	OS	Cancers (renal, liver, etc)
- Pazopanib	OS	Renal cancer; sarcomas
- Axitinib	OS	Renal cancer
- Cabozantinib	OS	Cancers (renal, thyroid, liver, etc)
- Regorafenib	OS	Colon cancer; liver cancer
- Lenvatinib	OS	Thyroid cancer; liver cancer
- Imatinib	OS	GIST; CML
mTOR inhibitors		
- Everolimus	OS	Breast cancer, renal cancer
- Temsirolimus	IV	Renal cancer, lymphomas
Immune checkpoint inhibitors		
- Ipilimumab	IV	Cancers (lung, melanoma, renal, etc)
- Pembrolizumab	IV	Cancers (lung, melanoma, renal, etc)
- Nivolumab	IV	Cancers (lung, melanoma, renal, etc)
Other drugs with sporadic reports or only suspected role		
- Adalimumab	IV	Autoimmune and inflammatory disorders
- Aromatase inhibitors	OS	Breast cancer
- Arsenic trioxide	IV	Leukemias
- Azacitidine	SC	Leukemias
- Bemcetinib	OS	LMC
- Bosutinib	OS	LMC; haematological disorders
- Corticosteroids	OS/IV/IM	Cancer; myeloma; non malignant diseases
- Dabrafenib / trametinib	OS	Melanoma
- Dasatinib	OS	LMC
- Epacadostat	OS	Melanoma
- Erlotinib	OS	Lung cancer; pancreatic cancer
- Etanercept	OS	Autoimmune and inflammatory disorders
- Infliximab	SC	Autoimmune and inflammatory disorders
- Lenalidomide	IV	Myeloma
- Methotrexate	OS / IM /IV	Autoimmune and inflammatory disorders; cancer
- Palbociclib	OS	Breast cancer
- Pomalidomide	OS	Myeloma
- Radium 223	IV	Prostate cancer
- Raloxifene	OS	Osteoporosis
- Ranibizumab	Intravitreal	Macular degenerations
- Rituximab	IV	Lymphomas; CML; autoimmune and inflammatory disorders
- Romosozumab	SC	Osteoporosis
- Simvastatin	OS	Hypercholesterolemia
- Tocilizumab	IV	Rheumatoid Arthritis; autoimmune and inflammatory

		disorders

Legend – VEGF = Vascular Endothelial Growth Factor ; IV = intravenous; SC = subcutaneously; OS =oral; IM = intramuscular; GIST = Gastrointestinal Stromal Tumors; CML = Chronic Myeloid Leukemia; mTOR = mammalian target of rapamycin

Table IIIa. SIPMO-SICMF stage-related surgical algorithm of BRONJ (including jawbone reconstructive options)

SIPMO-SICMF staging system	*Surgical algorithm of BRONJ*
Stage 1 (Focal BRONJ)	○ ***Dentoalveolar surgery*** ○ Oral mouth rinses ○ Systemic broad-spectrum antibiotics ○ Pain control ○ Temporary BP withdrawal *Details of Dentoalveolar surgery:* ▪ **bone curettage and sequestrectomy** (local anaesthesia w/ or w/o nerve blockage): extraction of the involved teeth, removal of bone sequestra, debridement of necrotic bone up to clinically vital bone, bone smoothing and tension-free soft tissue closure with muco-periosteal flaps. No need for bone reconstruction. Indication: LD-BP patients. ▪ **Marginal (Rim) resection**, (general anaesthesia): bone resection of the dentoalveolar process of the diseased mandible and/or maxilla (without entering the maxillary sinus), up to clinically vital bone; bone smoothing and tension-free soft tissue closure with muco-periosteal flaps (double-layer soft-tissue closure may be achieved in mandible rim resection with a mylohyoid muscle flap. No need for bone reconstruction. Indication: HD-BP patients; failure of sequestrectomy in LD-BP patients. Preoperative assessment of the resection margins: CT-based imaging techniques. Adjunctive treatment options: use of piezoelectric or laser-assisted surgery to minimize ischemic damage to the bone. *Details of perioperative antiseptic mouth rinses:* ▪ **Stage 1a** *(no suppuration):* Perioperative mouth rinses with chlorhexidine 0.2% antiseptic formulation (10ml x30', twice-day), starting the day before surgery. and lasting until bone healing has been achieved. ▪ **Stage 1b** *(suppuration):* Perioperative mouth rinses with chlorhexidine 0.2% antiseptic formulation (10ml x30', twice-day), starting 1 week before surgery and lasting until bone healing has been achieved. *Details of perioperative antibiotic treatment:* **Stage 1a** *(no suppuration)* ○ **amoxicillin + clavulanic**[1] **acid**[1] [1gr x 3/ day] or **ampicillin/sulbactam** [750mg x3/day]. Combination therapy with **metronidazole**[2] [500mgx 3/day] in selected cases. In patients with penicillin allergy: **erythromycin, clindamycin, or ciprofloxacin.** ○ *Route of administration***: oral** ○ *Duration:* start the day of surgery and last for 7-10 days (or until soft-tissue healing has been achieved). **Stage 1b** *(suppuration)* ○ **amoxicillin + clavulanic**[1] **acid**[1] [1gr x 3/ day] or **ampicillin/sulbactam** [750mg x3/day], combined with **metronidazole**[2] [500mgx 3/day]. In patients with penicillin allergy: **erythromycin, clindamycin, or ciprofloxacin.** ○ *Route of administration***: oral** ○ *Duration:* start the week before surgery and last for 7-10 days (or until soft-tissue healing has been achieved). *Details of temporary BP withdrawal* ▪ One week before surgery until wound healing has been achieved (4-6 weeks after surgery). ▪ *Post-operative follow-up*: clinical recall visits at 1, 3, 6 and 12 months. CT-based imaging at 6 and 12 months after surgery.
Stage 2 (Diffuse ONJ)	○ ***Surgical resection*** ○ Oral mouth rinses ○ Systemic broad-spectrum antibiotics

- Pain control
- Temporary BP withdrawal

Details of surgical resection:

- **Marginal (Rim) resection**, (general anaesthesia): bone resection of the dentoalveolar process of the diseased mandible and/or maxilla (without entering the maxillary sinus), up to clinically vital bone; bone smoothing and tension-free soft tissue closure with muco-periosteal flaps (double-layer soft-tissue closure may be achieved in mandible rim resection with a mylohyoid muscle flap. No need for bone reconstruction. Indication: *LD-BP patients.*
- **Segmental resection** (general anesthesia): full-thickness resection and discontinuation of the bone (i.e., mandibulectomy or maxillectomy). Indication: HD-BP patients; failure of sequestrectomy in LD-BP patients.
    a. Upper jaw: partial maxillectomy is the standard treatment. Soft tissue sparing resection of the diseased bone is obtained via intraoral approach, entering the sinus to remove the infected tissue. Removal of the palatal bone is not required in most cases. Bone smoothing and tension-free double-layer soft tissue closure is achieved with buccal fat pad flap transposition and muco-periosteal flaps (Gallego *et al*, 2012; Rotaru *et al*, 2015; Aljohani *et al*, 2019). Reconstruction with vascularised bone flaps is required for bilateral maxillectomy defects only. Free fibula flap is the standard of care in such cases (negligible risk of metastatic fibula involvement in cancer patients as compared with other donor sites - iliac bone and scapula) (Mundy, 2002). Temporalis muscle or microsurgical soft tissue flap repair is unnecessary, except for defects encompassing the palate.
    b. Lower jaw: Segmental mandibulectomy is the standard treatment. Soft tissue sparing resection of the diseased bone usually requires a combined intraoral/extraoral approach. Mandible reconstruction is always necessary: Standard reconstruction plates, CAD-CAM titanium prosthesis or vascularized bone flaps can be safely used depending on the extent of the defect (Nocini *et al*, 2009; Bedogni *et al*, 2011, 2014, 2021; Hanasono *et al*, 2013; Mücke *et al*, 2016; Sacco *et al*, 2018, 2020; Ricotta *et al*, 2020; Zhou *et al*, 2020). Reconstruction with vascularised bone flaps is indicated for subtotal mandibulectomy defects only. Free fibula flap is the standard of care in such cases (negligible risk of metastatic fibula involvement in cancer patients as compared with other donor sites - iliac bone and scapula) (Mundy, 2002). Bone smoothing and tension-free soft tissue closure with muco-periosteal flaps is required. Facial artery musculomucosal (FAMM) flap can be rarely used to cover large areas of exposed bone. Microsurgical soft tissue flap repair is hardly necessary.

Preoperative assessment of the resection margins: CT-based imaging techniques.
Adjunctive treatment options: use of piezoelectric or laser-assisted surgery to minimize ischemic damage to the bone.

Details of perioperative antiseptic mouth rinses:

- **Stage 2a** *(no suppuration):* Perioperative mouth rinses with chlorhexidine 0.2% antiseptic formulation (10ml x30', twice-day), starting the day before surgery and lasting until bone healing has been achieved.
- **Stage 2b** *(suppuration):* Perioperative mouth rinses with chlorhexidine 0.2% antiseptic formulation (10ml x30', twice-day), starting 1 week before surgery and lasting until bone healing has been achieved.

Details of perioperative antibiotic treatment:

Stage 2a *(no suppuration)*

- **amoxicillin + clavulanic**[1] **acid**[1] [1gr x 3/ day] or **ampicillin/sulbactam** [750mg x3/day]. Combination therapy with **metronidazole**[2] [500mgx 3/day] in selected cases. In patients with penicillin allergy: **erythromycin, clindamycin, or ciprofloxacin.**
- *Route of administration***: oral**
- *Duration:* start the day of surgery and last for 7-10 days (or until soft-tissue healing has been achieved).

Stage 2b *(suppuration)*

- **amoxicillin + clavulanic**[1] **acid**[1] [1gr x 3/ day] or **ampicillin/sulbactam** [750mg x3/day], combined with **metronidazole**[2] [500mgx 3/day]. In patients with penicillin allergy:

erythromycin, clindamycin, or ciprofloxacin.

- *Route of administration*: **oral**
- *Duration:* start the week before surgery and last for 7-10 days (or until soft-tissue healing has been achieved).

Details of temporary BP withdrawal

- One week before surgery until wound healing has been achieved (4-6 weeks after surgery).

Post-operative follow-up: clinical recall visits at 1, 3, 6 and 12 months. CT-based imaging at 6 and 12 months after surgery.

Stage 3 (Complicated ONJ)

- ***Surgical resection***
- Oral mouth rinses
- Systemic broad-spectrum antibiotics
- Pain control
- Temporary BP withdrawal

Details of surgical resection:

- **Segmental resection** (general anesthesia): full-thickness resection and discontinuation of the bone (i.e., mandibulectomy or maxillectomy). Indication: HD-BP patients; failure of marginal resection in *LD-BP patients*.
    a. Upper jaw: partial maxillectomy is the standard treatment. Soft tissue sparing resection of the diseased bone is obtained via intraoral approach, entering the sinus to remove the infected tissue. Removal of the palatal bone is not required in most cases. Bone smoothing and tension-free double-layer soft tissue closure is achieved with buccal fat pad flap transposition and muco-periosteal flaps (Gallego *et al*, 2012; Rotaru *et al*, 2015; Aljohani *et al*, 2019). Reconstruction with vascularised bone flaps is required for bilateral maxillectomy defects only. Free fibula flap is the standard of care in such cases (negligible risk of metastatic fibula involvement in cancer patients as compared with other donor sites - iliac bone and scapula) (Mundy, 2002). Temporalis muscle or microsurgical soft tissue flap repair is unnecessary, except for defects encompassing the palate.
    b. Lower jaw: Segmental mandibulectomy is the standard treatment. Soft tissue sparing resection of the diseased bone usually requires a combined intraoral/extraoral approach. Mandible reconstruction is always necessary: Standard reconstruction plates, CAD-CAM titanium prosthesis or vascularized bone flaps can be safely used depending on the extent of the defect (Nocini *et al*, 2009; Bedogni *et al*, 2011, 2014, 2021; Hanasono *et al*, 2013; Mücke *et al*, 2016; Sacco *et al*, 2018, 2020; Ricotta *et al*, 2020; Zhou *et al*, 2020). Reconstruction with vascularised bone flaps is indicated for subtotal mandibulectomy defects only. Free fibula flap is the standard of care in such cases (negligible risk of metastatic fibula involvement in cancer patients as compared with other donor sites - iliac bone and scapula) (Mundy, 2002). Bone smoothing and tension-free soft tissue closure with muco-periosteal flaps is required. FAMM flap can be rarely used to cover large areas of exposed bone. Microsurgical soft tissue flap repair is hardly necessary

Preoperative assessment of the resection margins: CT-based imaging techniques.
Adjunctive treatment options: use of piezoelectric or laser-assisted surgery to minimize ischemic damage to the bone.

Details of perioperative antiseptic mouth rinses:

- **Stage 3a** *(no suppuration):* Perioperative mouth rinses with chlorhexidine 0.2% antiseptic formulation (10ml x30', twice-day), starting the day before surgery and lasting until bone healing has been achieved.
- **Stage 3b** *(suppuration):* Perioperative mouth rinses with chlorhexidine 0.2% antiseptic formulation (10ml x30', twice-day), starting 1 week before surgery and lasting until bone healing has been achieved.

Details of perioperative antibiotic treatment:

Stage 3a *(no suppuration)*

- **amoxicillin + clavulanic**[1] **acid**[1] [1gr x 3/ day] or **ampicillin/sulbactam** [750mg x3/day]. Combination therapy with **metronidazole**[2] [500mgx 3/day] in selected cases. In patients with penicillin allergy: **erythromycin, clindamycin, or ciprofloxacin.**
- *Route of administration***: oral**
- *Duration:* start the day of surgery and last for 7-10 days (or until soft-tissue healing has been achieved).

Stage 3b *(suppuration)*

- **amoxicillin + clavulanic**[1] **acid**[1] [1gr x 3/ day] or **ampicillin/sulbactam** [750mg x3/day], combined with **metronidazole**[2] [500mgx 3/day]. In patients with penicillin allergy: **erythromycin, clindamycin, or ciprofloxacin.**
- *Route of administration***: oral**
- *Duration:* start the week before surgery and last for 7-10 days (or until soft-tissue healing has been achieved).

Details of temporary BP withdrawal

- One week before surgery until wound healing has been achieved (4-6 weeks after surgery).

Post-operative follow-up: clinical recall visits at 1, 3, 6 and 12 months. CT-based imaging at 6 and 12 months after surgery.

Table IIIb. SIPMO-SICMF stage-related surgical algorithm of DMB-ONJ (including jawbone reconstructive options)

SIPMO-SICMF staging system	*Surgical algorithm of DMB-ONJ*
Stage 1 (Focal DMB-ONJ) and Stage 2 (Diffuse DMB-ONJ)	○ ***Dentoalveolar surgery*** ○ Oral mouth rinses ○ Systemic broad-spectrum antibiotics ○ Pain control ○ DMB withdrawal/delay *Details of Dentoalveolar surgery:* ▪ **bone curettage and sequestrectomy** (local anaesthesia w/ or w/o nerve blockage): extraction of the involved teeth, removal of bone sequestra, debridement of necrotic bone up to clinically vital bone, bone smoothing and tension-free soft tissue closure with muco-periosteal flaps. No need for bone reconstruction. Indication: first occurrence of DMB-ONJ. ▪ **Marginal (Rim) resection**, (general anaesthesia): bone resection of the dentoalveolar process of the diseased mandible and/or maxilla (without entering the maxillary sinus), up to clinically vital bone; bone smoothing and tension-free soft tissue closure with muco-periosteal flaps (double-layer soft-tissue closure may be achieved in mandible rim resection with a mylohyoid muscle flap. No need for bone reconstruction. Indication: recurrence of DMB-ONJ after bone curettage and sequestrectomy. Preoperative assessment of the resection margins: CT-based imaging techniques. Adjunctive treatment options: use of piezoelectric or laser-assisted surgery to minimize ischemic damage to the bone. *Details of perioperative antiseptic mouth rinses:* ▪ **Stage 1a/2a** *(no suppuration):* Perioperative mouth rinses with chlorhexidine 0.2% antiseptic formulation (10ml x30', twice-day), starting the day before surgery. and lasting until bone healing has been achieved. ▪ **Stage 1b/2b** *(suppuration):* Perioperative mouth rinses with chlorhexidine 0.2% antiseptic formulation (10ml x30', twice-day), starting 1 week before surgery and lasting until bone healing has been achieved. *Details of perioperative antibiotic treatment:* **Stage 1a/2a** *(no suppuration)* ▪ **amoxicillin + clavulanic**[1] **acid**[1] [1gr x 3/ day] or **ampicillin/sulbactam** [750mg x3/day]. Combination therapy with **metronidazole**[2] [500mgx 3/day] in selected cases. In patients with penicillin allergy: **erythromycin, clindamycin, or ciprofloxacin.** ▪ *Route of administration***: oral** ▪ *Duration:* start the day of surgery and last for 7-10 days (or until soft-tissue healing has been achieved). **Stage 1b/2b** *(suppuration)* ▪ **amoxicillin + clavulanic**[1] **acid**[1] [1gr x 3/ day] or **ampicillin/sulbactam** [750mg x3/day], combined with **metronidazole**[2] [500mgx 3/day]. In patients with penicillin allergy: **erythromycin, clindamycin, or ciprofloxacin.** ▪ *Route of administration***: oral** ▪ *Duration:* start the week before surgery and last for 7-10 days (or until soft-tissue healing has been achieved). *Details of temporary DMB withdrawal/delay* ▪ HD-DMB patients: 6-month DMB withdrawal before surgery; DMB restart feasible once wound healing has been achieved (4-6 weeks after surgery). ▪ LD-DMB patients: surgery should be performed 5 months after the last dose, with 1-month postoperative delay of the following dose, until complete healing is achieved. *Post-operative follow-up*: clinical recall visits at 1, 3, 6 and 12 months. CT-based imaging at 6 and

12 months after surgery.

Stage 3 (DMB-ONJ)

- ***Surgical resection***
- Oral mouth rinses
- Systemic broad-spectrum antibiotics
- Pain control
- DMB withdrawal/delay

Details of surgical resection:

- **Marginal (Rim) resection**, (general anaesthesia): bone resection of the dentoalveolar process of the diseased mandible and/or maxilla (without entering the maxillary sinus), up to clinically vital bone; bone smoothing and tension-free soft tissue closure with muco-periosteal flaps (double-layer soft-tissue closure may be achieved in mandible rim resection with a mylohyoid muscle flap. No need for bone reconstruction. Indication: first occurrence of DMB-ONJ.

- **Segmental resection** (general anesthesia): full-thickness resection and discontinuation of the bone (i.e., mandibulectomy or maxillectomy). Indication: recurrence of DMB-ONJ after marginal resection.
    a. Upper jaw: partial maxillectomy is the standard treatment. Soft tissue sparing resection of the diseased bone is obtained via intraoral approach, entering the sinus to remove the infected tissue. Removal of the palatal bone is not required in most cases. Bone smoothing and tension-free double-layer soft tissue closure is achieved with buccal fat pad flap transposition and muco-periosteal flaps (Mundy, 2002). Reconstruction with vascularised bone flaps is required for bilateral maxillectomy defects only. Free fibula flap is the standard of care in such cases (negligible risk of metastatic fibula involvement in cancer patients as compared with other donor sites -iliac bone and scapula) (Mundy, 2002). Temporalis muscle or microsurgical soft tissue flap repair is unnecessary, except for defects encompassing the palate.
    b. Lower jaw: Segmental mandibulectomy is the standard treatment. Soft tissue sparing resection of the diseased bone usually requires a combined intraoral/extraoral approach. Mandible reconstruction is always necessary: Standard reconstruction plates, CAD-CAM titanium prosthesis or vascularized bone flaps can be safely used depending on the extent of the defect (Nocini *et al*, 2009; Bedogni *et al*, 2011, 2014, 2021; Hanasono *et al*, 2013; Mücke *et al*, 2016; Sacco *et al*, 2018, 2020; Ricotta *et al*, 2020; Zhou *et al*, 2020). Reconstruction with vascularised bone flaps is indicated for subtotal mandibulectomy defects only. Free fibula flap is the standard of care in such cases (negligible risk of metastatic fibula involvement in cancer patients as compared with other donor sites -iliac bone and scapula). Bone smoothing and tension-free soft tissue closure with muco-periosteal flaps is required. FAMM flap can be rarely used to cover large areas of exposed bone. Microsurgical soft tissue flap repair is hardly necessary.

Preoperative assessment of the resection margins: CT-based imaging techniques.
Adjunctive treatment options: use of piezoelectric or laser-assisted surgery to minimize ischemic damage to the bone.

Details of perioperative antiseptic mouth rinses:

- **Stage 3a** *(no suppuration):* Perioperative mouth rinses with chlorhexidine 0.2% antiseptic formulation (10ml x30', twice-day), starting the day before surgery and lasting until bone healing has been achieved.
- **Stage 3b** *(suppuration):* Perioperative mouth rinses with chlorhexidine 0.2% antiseptic formulation (10ml x30', twice-day), starting 1 week before surgery and lasting until bone healing has been achieved.

Details of perioperative antibiotic treatment:

Stage 3a *(no suppuration)*

- **amoxicillin + clavulanic**[1] **acid**[1] [1gr x 3/ day] or **ampicillin/sulbactam** [750mg x3/day].

Combination therapy with **metronidazole**[2] [500mgx 3/day] in selected cases. In patients with penicillin allergy: **erythromycin, clindamycin, or ciprofloxacin.**

- *Route of administration***: oral**
- *Duration:* start the day of surgery and last for 7-10 days (or until soft-tissue healing has been achieved).

Stage 3b *(suppuration)*

- **amoxicillin + clavulanic**[1] **acid**[1] [1gr x 3/ day] or **ampicillin/sulbactam** [750mg x3/day], combined with **metronidazole**[2] [500mgx 3/day]. In patients with penicillin allergy: **erythromycin, clindamycin, or ciprofloxacin.**
- *Route of administration***: oral**
- *Duration:* start the week before surgery and last for 7-10 days (or until soft-tissue healing has been achieved).

Details of temporary DMB withdrawal/delay

- HD-DMB patients: 6-month DMB withdrawal before surgery; DMB restart feasible once wound healing has been achieved (4-6 weeks after surgery).
- LD-DMB patients: surgery should be performed 5 months after the last dose, with 1-month postoperative delay of the following dose, until complete healing is achieved.

Post-operative follow-up: clinical recall visits at 1, 3, 6 and 12 months. CT-based imaging at 6 and 12 months after surgery.