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Original research

Denosumab is associated with longer real-world progression-free survival in BRCA1/2-mutated HR+ /HER2 - breast cancer patients with bone metastases receiving CDK4/6 inhibitors: A multicenter Italian study

Roberta Scafetta [a], Raffaella Troiano [a], Carla Gullotta [a], Alessandra Guarino [a], Cristina Fiore [b], Luisana Sisca [a], Elena Speziale [a], Marco Donato [c], Simone Foderaro [d], Fabio Venuti [a], Francesco Antonio Vilardi [a], Valentina Ricozzi [d], Michele Iuliani [a,*], Sonia Simonetti [a], Silvia Cavaliere [a], Alessio Cortellini [a,d], Annalisa La Cesa [a], Andrea Botticelli [e], Simone Scagnoli [e], Simona Pisegna [f,g], Carmen Criscitiello [h], Rebecca Pedersini [i], Caterina Sposetti [h,j,k], Elisa Tiberi [l], Giuliana D'Auria [m], Matteo Vergati [m], Marco Mazzotta [m], Roberta Caputo [n], Annarita Verrazzo [n], Ornella Garrone [o], Federica Domati [p], Claudia Piombino [p], Francesca Sofia Di Lisa [q], Lorena Filomeno [q], Teresa Arcuri [q], Federica Puce [r], Federica Riva [s], Michela Palleschi [t], Marianna Sirico [t], Marta Piras [u], Luigia Stefania Stucci [v], Delia De Lisi [w], Paolo Orsaria [x], Antonella Grasso [x], Edy Ippolito [y,z], Sara Ramella [y,z], Luca Visani [aa], Lorenzo Livi [aa,ab], Stefania Gori [ac], Luigi Rossi [ad], Icro Meattini [aa,ab,ae], Barbara Tagliaferri [r], Orazio Caffo [w,af], Maria Vittoria Bonomo [ag], Ilaria Portarena [ag], Azzurra Irelli [ah], Elisabetta Cretella [ai], Camillo Porta [v], Giampaolo Bianchini [u,aj], Maria Agnese Fabbri [b], Ugo De Giorgi [ak], Patrizia Vici [q], Angela Toss [p,al], Fiorella Ruatta [o], Michelino De Laurentiis [n], Federica Villa [am], Rossana Berardi [l], Mauro Minelli [an], Vittorio Altomare [x], Claudio Vernieri [h,k], Giuseppe Curigliano [h,ao], Alessandra Chirco [ap], Sara D'Alessandro [ap], Bruno Vincenzi [a,d], Giuseppe Tonini [a,d], Daniele Santini [aq], Francesco Pantano [a,d]

[a] *Medical Oncology, Fondazione Policlinico Universitario Campus Bio-Medico, Via Alvaro del Portillo 200, Roma 00128, Italy*
[b] *Medical Oncology Unit, Santa Rosa Hospital, Department of Oncology and Hematology, Strada Sammartinese snc, Viterbo 01100, Italy*
[c] *Division of Medical Oncology, "G.Martino" University Hospital, Via Consolare Valeria 1, Messina 98124, Italy*
[d] *Department of Medicine and Surgery, Università Campus Bio-Medico di Roma, Via Alvaro del Portillo 21, Roma 00128, Italy*
[e] *Department of Radiological, Oncological and Pathological Science, "Sapienza" University of Rome, Rome, Italy*
[f] *Department of Experimental Medicine Sapienza University, Rome, Italy*
[g] *Medical Oncology Unit, Azienda Ospedaliero Universitaria Sant'Andrea, Via Di Grottaross, Rome 1035-1039, Italy*
[h] *Department of Oncology and Hemato-Oncology, University of Milan, Milano, Italy*
[i] *Medical Oncology Department, ASST Spedali Civili of Brescia, Brescia, Italy*
[j] *Dana-Farber/Partners CancerCare, Boston, MA, USA*
[k] *Department of Medical Oncology, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy*
[l] *Department of Medical Oncology, Università Politecnica delle Marche, AOU delle Marche, Ancona, Italy*
[m] *Department of Medical Oncology, Medical Oncology Unit, Sandro Pertini Hospital, Rome, Italy*
[n] *Department of Breast and Thoracic Oncology, Division of Breast Medical Oncology, Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS) Pascale, Naples, Italy*
[o] *Medical Oncology Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan 20122, Italy*
[p] *Department of Oncology and Hematology, Azienda Ospedaliero-Universitaria di Modena, Modena, Italy*
[q] *UOSD Sperimentazioni di fase IV - IRCCS Istituto Nazionale Tumori Regina Elena, Via Elio Chianesi 53, Roma 00144, Italy*
[r] *Medical Oncology Unit, ICS Maugeri IRCCS, Pavia, Italy*
[s] *Department of Clinical and Molecular Medicine, "La Sapienza" University of Rome, Policlinico Umberto I, Viale Regina Elena 324, Rome 00161, Italy*
[t] *Medical Oncology, Breast & GYN Unit, IRCCS Istituto Romagnolo per lo Studio dei Tumori (IRST) "Dino Amadori", Meldola, Italy*
[u] *Department of Medical Oncology, IRCCS San Raffaele Scientific Institute, Milan, Italy*

* Correspondence to: Fondazione Policlinico Universitario Campus Bio-Medico, Via Alvaro del Portillo 200, Rome 00128, Italy.
E-mail address: m.iuliani@policlinicocampus.it (M. Iuliani).

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[v] Interdisciplinary Department of Medicine, University of Bari "A. Moro" and Division of Medical Oncology, A.O.U. Consorziale Policlinico di Bari, Bari, Italy
[w] Medical Oncology Unit, Santa Chiara Hospital, APSS Trento, Italy
[x] Department of Breast Surgery, Fondazione Policlinico Universitario Campus Bio-Medico, Rome, Italy
[y] Department of Radiation Oncology (Medicine and Surgery), Università Campus Bio-Medico di Roma, Rome, Italy
[z] Radiation Oncology, Fondazione Policlinico Universitario Campus Bio-Medico, Rome, Italy
[aa] Radiation Oncology Unit & Breast Unit, Azienda Ospedaliero-Universitaria Careggi, University of Florence, Florence, Italy
[ab] Department of Experimental and Clinical Biomedical Sciences "M. Serio", University of Florence, Florence, Italy
[ac] Medical Oncology, IRCCS Ospedale Sacro Cuore Don Calabria, Negrar di Valpolicella (VR), Italy
[ad] UOC of Oncology - ASL Latina - Distretto 1, University of Rome "Sapienza", Formia, Italy
[ae] Department of Radiation Oncology (MAASTRO), GROW Research Institute for Oncology and Developmental Biology, Maastricht University Medical Centre, Maastricht, the Netherlands
[af] Center of Medical Science – University of Trento, Italy
[ag] Medical Oncology Unit, Policlinico Universitario Tor Vergata, Rome, Italy
[ah] Medical Oncology Unit, Department of Oncology, "Giuseppe Mazzini" Hospital, AUSL 04 Teramo, Teramo 64100, Italy
[ai] Medical Oncology Unit, Ospedale di Bolzano, Bolzano, Italy
[aj] Università Vita-Salute San Raffaele, Milano, Italy
[ak] Department of Experimental Medicine, University of Salento, Lecce, Italy
[al] Department of Medical and Surgical Sciences, University of Modena and Reggio Emilia, Italy
[am] Medical Oncology, Oncology Department ASST Lecco, Lecco 23900, Italy
[an] UOC Oncologia Azienda Ospedaliera San Giovanni Addolorata, Rome, Italy
[ao] European Institute of Oncology, IRCCS, Milano, Italy
[ap] ASST Papa Giovanni XXIII-SC Oncologia, Bergamo 24127, Italy
[aq] Dip. Scienze e Biotecnologie Medico-chirurgiche, Policlinico Umberto I, "Sapienza" University of Rome, Rome, Italy

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ABSTRACT

Background: Preclinical evidence suggests that BRCA1/2-mutated tumors may rely on RANKL signaling for survival and proliferation. RANKL inhibition with denosumab could disrupt tumor–bone microenvironment crosstalk and potentially limit metastatic progression. We evaluated the association between denosumab and real-world progression-free survival (rwPFS) in germline BRCA1/2-mutated hormone receptor–positive/HER2-negative (HR+/HER2−) metastatic breast cancer (mBC) with bone metastases.
Methods: We performed a retrospective, multicenter study across 24 Italian hospitals including HR+/HER2− bone mBC patients treated in first- or second-line with a CDK4/6 inhibitor plus endocrine therapy. rwPFS was estimated by Kaplan–Meier and compared with log-rank tests. Center-stratified multivariable Cox models adjusted for clinically relevant covariates were used to assess the association between denosumab exposure and rwPFS. Effect modification by BRCA status was evaluated using a denosumab×BRCA1/2 mutation status.
Results: Among 1399 patients, 46 harbored germline BRCA1/2 mutations (13 BRCA1, 33 BRCA2), and 21 of these patients received denosumab. Among patients not receiving denosumab, BRCA1/2-wild-type/unknown patients had better rwPFS than BRCA1/2-mutated patients (median 28 vs 13 months; hazard ratio (HR) 0.48, 95% CI 0.32–0.73; p = 0.001). Among BRCA1/2-wild-type/unknown patients, denosumab use did not affect rwPFS (HR 0.98, 95% CI 0.85–1.12). Conversely, denosumab use was associated with longer rwPFS among patients with BRCA1/2 mutations (median 35 months, 95% CI 24–NR vs 13 months, 95% CI 9–27; HR 0.34, 95% CI 0.16–0.74; p = 0.006), with no significant difference between BRCA1 and BRCA2-mutated subgroups. Multivariable analysis confirmed the rwPFS benefit of denosumab in BRCA1/2-mutated patients (adjusted HR 0.45, 95% CI 0.21–0.99; p = 0.048).
Conclusion: In this real-world cohort, denosumab use was associated with longer rwPFS in germline BRCA1/2-mutated HR+/HER2− mBC with bone metastases.

1. Introduction

Germline mutations in BRCA1 and BRCA2 genes disrupt homologous recombination, fostering genomic instability and elevating lifetime cancer risk for breast cancer and other malignancies. The resulting homologous recombination deficiency also shapes tumor biology and therapeutic vulnerabilities in the metastatic setting [1]. Beyond DNA repair, the RANK/RANKL axis, initially involved in bone remodeling, plays a pivotal role in mammary gland development and hormone-driven epithelial proliferation [2,3]. Preclinical studies established RANKL as a key mediator of progestin-driven mammary tumorigenesis by showing that progesterone-induced RANKL signaling expands the mammary epithelium and promotes cancer development. [2,3]. More recently, translational data linked aberrant RANK signaling to BRCA1 mutated–driven tumorigenesis. RANK positive (RANK+) luminal progenitors in breast tissue from BRCA1 mutation carriers display high proliferative capacity and DNA repair defects. Short-window exposure to denosumab, a monoclonal antibody against RANKL, reduced epithelial proliferation in these women, while RANKL blockade delayed tumor onset in BRCA1-deficient models [4].

In patients with bone metastases from solid tumors, denosumab was more effective than zoledronic acid in preventing skeletal-related events (SREs) without affecting overall survival or treatment toxicities [5]. In early-stage BC, data on the antitumor effects of RANKL inhibition are inconsistent: the ABCSG-18 trial reported improved disease-free outcomes with adjuvant denosumab in postmenopausal, hormone receptor–positive patients receiving aromatase inhibitors, but the large phase III D-CARE trial showed no clinical benefit in patients with high-risk, early-stage disease [6,7].

In the context of metastatic HR+/HER2− BC, endocrine therapy in combination with the CDK4/6i palbociclib, ribociclib or abemaciclib is now the standard-of-care therapy for almost all patients [8–10]. Bone is the most common single site of metastasis in patients with HR+/HER2− mBC, underscoring the clinical relevance of optimizing bone-targeted strategies alongside systemic therapy [11]. However, whether pharmacological RANKL inhibition confers therapeutic benefit when combined with endocrine therapy plus CDK4/6 inhibition, particularly in BRCA-mutated HR+/HER2− metastatic disease, remains insufficiently defined, providing the rationale for the present study.

2. Patients and methods

2.1. Study design and participants

We retrospectively analyzed data from HR+/HER2− bone mBC patients who received a CDK4/6i in combination with endocrine therapy (ET) as first- or second-line treatment. Eligible patients had bone metastases at or before initiation of CDK4/6i+ET, an Eastern Cooperative Oncology Group (ECOG) Performance Status of 0–1, and at least 12 months of potential follow-up unless real-world progression-free survival (rwPFS) events (progression/death) occurred earlier.

The study period extended from January 2019 to December 2023. The coordinating center's ethics committee (Fondazione Policlinico Universitario Campus Bio-Medico, PAR 30.22 OSS) granted ethical approval. The study was conducted in accordance with the Declaration of Helsinki. Informed consent was obtained from patients alive at the time of data analysis, while the Data Protection Officers of the participating institutions authorized data collection from deceased patients.

Patients were identified through systematic review of medical records in each participating center. Patients were enrolled if they had HR+/HER2− mBC with radiologically or clinically documented bone metastases, and if they received ET plus a CDK4/6i as first- or second line of therapy. Germline BRCA1/2 status - mutated, wild type, or unknown - was systematically recorded from patient charts.

Patients were considered denosumab-exposed only if denosumab was initiated before the first response assessment, which was typically scheduled at 8–12 weeks after CDK4/6i initiation; to mitigate immortal-time bias, a landmark analysis at 12 weeks was performed excluding patients with progression or death before the landmark date. In addition to the prespecified 12-week landmark, we conducted additional landmark analyses at 2, 3, 4, 6, and 9 months as sensitivity analyses.

Subsequent radiologic assessments were performed according to routine local practice and/or clinical indications. Exact imaging data were not systematically captured in the database; therefore, we could not reconstruct patient-level imaging intervals. To mitigate potential detection bias and between-center heterogeneity, we stratified Cox models by center and performed leave-one-center-out analyses (Supplementary Table 2; Supplementary Figure S4).

The pre-specified primary endpoint was rwPFS, operationalized as the interval from the start of CDK4/6i+ ET to the earliest occurrence of documented disease progression, based on clinical assessment and/or imaging, per local practice, or patient death from any cause. Patients without an event were censored at the date of last known follow-up.

Table 1
Patients' characteristics.

Characteristics		BRCA1/2mut-Denosumab	BRCA1/2mut-No Denosumab	BRCA1/2wt/unk-Denosumab	BRCA1/2wt/unk-No Denosumab	Total
Total N (%)		21 (1.5)	25 (1.8)	664 (47.5)	689 (49.2)	1399
Premenopausal State	No	6 (28.6)	19 (76.0)	509 (76.7)	566 (82.1)	1100 (78.6)
	Yes	15 (71.4)	6 (24.0)	155 (23.3)	123 (17.9)	299 (21.4)
Age	Mean (SD)	45.7 (8.8)	59.5 (14.0)	60.5 (12.6)	62.3 (12.4)	61.1 (12.6)
Performance Status	0	21 (100.0)	20 (80.0)	598 (90.1)	556 (80.7)	1195 (85.4)
	1	0 (0.0)	5 (20.0)	66 (9.9)	133 (19.3)	204 (14.6)
Histology	Ductal	17 (81.0)	18 (72.0)	480 (72.3)	496 (72.0)	1011 (72.3)
	Lobular	3 (14.3)	3 (12.0)	144 (21.7)	154 (22.4)	304 (21.7)
	Other	1 (4.8)	4 (16.0)	40 (6.0)	39 (5.7)	84 (6.0)
Ki67	Mean (SD)	28.4 (13.8)	32.0 (19.5)	23.8 (13.9)	24.7 (16.1)	24.5 (15.2)
Grading	G1/G2	13 (61.9)	21 (84.0)	463 (69.7)	454 (65.9)	951 (68.0)
	G3	8 (38.1)	4 (16.0)	201 (30.3)	235 (34.1)	448 (32.0)
Estrogen Receptor	Mean (SD)	87.6 (10.2)	88.9 (10.5)	86.6 (15.8)	86.9 (15.2)	86.8 (15.4)
Progesterone Receptor	Mean (SD)	51.3 (35.4)	38.9 (34.9)	46.9 (35.5)	51.5 (34.2)	49.1 (34.9)
HER2	0	11 (52.4)	13 (52.0)	441 (66.4)	432 (62.7)	897 (64.1)
	1	6 (28.6)	8 (32.0)	154 (23.2)	164 (23.8)	332 (23.7)
	2	4 (19.0)	4 (16.0)	69 (10.4)	93 (13.5)	170 (12.2)
Neoadjuvant Chemotherapy	No	17 (81.0)	20 (80.0)	609 (91.7)	612 (88.8)	1258 (89.9)
	Yes	4 (19.0)	5 (20.0)	55 (8.3)	77 (11.2)	141 (10.1)
Adjuvant Chemotherapy	No	16 (76.2)	7 (28.0)	391 (58.9)	450 (65.3)	864 (61.8)
	Yes	5 (23.8)	18 (72.0)	273 (41.1)	239 (34.7)	535 (38.2)
Adjuvant Endocrine Therapy	No	8 (38.1)	3 (12.0)	240 (36.1)	242 (35.1)	493 (35.2)
	Yes	13 (61.9)	22 (88.0)	424 (63.9)	447 (64.9)	906 (64.8)
Bone Only Disease	No	10 (47.6)	9 (36.0)	342 (51.5)	346 (50.2)	707 (50.5)
	Yes	11 (52.4)	16 (64.0)	322 (48.5)	343 (49.8)	692 (49.5)
CDK-Inhibitor	Abemaciclib	3 (14.3)	3 (12.0)	104 (15.7)	109 (15.8)	219 (15.7)
	Palbociclib	8 (38.1)	16 (64.0)	355 (53.5)	407 (59.1)	786 (56.2)
	Ribociclib	10 (47.6)	6 (24.0)	205 (30.9)	173 (25.1)	394 (28.2)
Line of Treatment	First	20 (95.2)	22 (88.0)	559 (84.2)	541 (78.5)	1142 (81.6)
	Second	1 (4.8)	3 (12.0)	105 (15.8)	148 (21.5)	257 (18.4)
Setting	Endocrine Resistant	9 (42.9)	15 (60.0)	263 (39.6)	312 (45.3)	599 (42.8)
	Endocrine Sensitive	12 (57.1)	10 (40.0)	401 (60.4)	377 (54.7)	800 (57.2)

3. Statistical analysis

We estimated rwPFS using Kaplan–Meier and compared groups with log-rank tests. To address confounding, we fitted multivariable Cox proportional-hazards models to quantify the association between denosumab exposure and rwPFS within BRCA1/2-mutated patients, reporting HRs and 95% CIs. Cox models were stratified by center to account for between-center heterogeneity and support the interpretability of the results. Pre-specified covariates included menopausal status, age, ECOG performance status, histology, tumor grade, Ki67, ER and PR expression, (neo)adjuvant chemotherapy, adjuvant endocrine therapy, bone-only disease, metastatic setting (de novo vs recurrent), line of treatment, type of CDK4/6 inhibitor, and endocrine therapy partner, as available across centers (see Table 1 and Supplementary Table 1).

To evaluate effect modification by BRCA status, we fitted a center-stratified Cox model in the full cohort including a denosumab×BRCA1/2 status interaction term. Pre-specified sensitivity analyses were performed to assess robustness of the association and mitigate potential biases related to treatment timing and inter-center heterogeneity: an active-comparator analysis among BRCA1/2-mutated patients receiving any bone-targeted agent (denosumab vs zoledronic acid); landmark analyses at 2, 3, 4, 6, and 9 months; restricted mean survival time (RMST) comparisons up to 24 months with bootstrap confidence intervals; nonparametric bootstrap resampling of the BRCA1/2-mutated subgroup; and leave-one-center-out analyses. Detailed results are provided in Supplementary Table 2 and Supplementary Figures S1–S5.

For covariate-adjusted visualization, we generated adjusted survival curves from the Cox model using the average-covariate (direct-adjusted) method and plotted the trajectories over time. All tests were two-sided with $\alpha = 0.05$.

4. Results

4.1. Patient characteristics

Between January 2019 and December 2023, we identified 1399 HR+ /HER2 − mBC patients with bone metastases, and treated with CDK4/6i+ ET across 24 Italian hospitals. Forty-six patients carried a germline *BRCA1/2* mutation (BRCA1 =13; BRCA2 =33), of whom 21 received denosumab. Most patients were postmenopausal (78.6%), while 21.4% were premenopausal. Mean age in the overall cohort was 61.1 years (SD 12.6), with lower mean age in the BRCA1/2mut denosumab group (45.7 ± 8.8) compared with the other groups. ECOG performance status was 0 in 85.4%. The predominant histology was ductal carcinoma (72.3%), followed by lobular (21.7%) and other histologies (6.0%). Bone-only disease was present in 49.5% of cases. Regarding CDK4/6 inhibitors, palbociclib was most frequently used (56.2%), followed by ribociclib (28.2%) and abemaciclib (15.7%). All baseline clinicopathologic features are summarized in Table 1. Median follow-up was 39 months (95% CI, 37–40). The flow chart (Fig. 1) details screening, exclusions, and analytic subgroups by BRCA status and denosumab exposure.

4.2. rwPFS analysis

Among patients who did not receive denosumab, patients with *BRCA1/2*-wild-type/unknown status had longer rwPFS when compared to patients who were carriers of germline *BRCA1/2* mutations (median 28 months, 95% CI 26–32 vs 13 months, 95% CI 9–27; HR 0.48, 95% CI 0.32–0.73; p = 0.001). Among *BRCA1/2*-wild-type/unknown patients, denosumab use was not associated with rwPFS (HR 0.98, 95% CI 0.85–1.12). Conversely, within the BRCA1/2-mutated subgroup (n = 46), rwPFS events occurred in 9/21 denosumab-exposed versus 23/25 non-exposed patients, and denosumab was associated with longer rwPFS (median 35 months, 95% CI 24–NR vs 13 months, 95% CI 9–27; unadjusted HR 0.34, 95% CI 0.16–0.74; p = 0.006), with no significant differences between BRCA1 and BRCA2 carriers (Fig. 2**A**). Effect modification by BRCA status was assessed in a center-stratified Cox model including a denosumab×BRCA term; the interaction was significant (Pinteraction=0.005), while no association was observed in confirmed BRCA1/2 wild-type patients (HR 1.05; 95% CI 0.86–1.29; p = 0.636).

Multivariable Cox regression models confirmed the results of unadjusted analyses (Fig. 2**B**). Among patients with *BRCA1*/2-mutated tumors, those treated with denosumab had longer rwPFS when compared to patients not receiving denosumab (adjusted HR 0.45, 95% CI 0.21–0.99; p = 0.048). Among patients not receiving denosumab, *BRCA1/2*-wild-type/unknown patients had longer adjusted rwPFS when compared to BRCA1/2-mutated patients (Fig. 2**B**). Variables independently associated with rwPFS in the multivariable Cox model were: ECOG performance status, tumor grade, use of neoadjuvant chemotherapy, presence of bone only disease, type of CDK4/6i used, expression of PR. Full univariate and adjusted estimates are reported in Supplementary Table 1. Active-comparator and robustness analyses were consistent. Among BRCA1/2-mutated patients receiving any bone-targeted agent (n = 34), denosumab versus zoledronic acid was associated with longer rwPFS (unadjusted HR 0.36, 95% CI 0.15–0.84; p = 0.0188; adjusted HR 0.18, 95% CI 0.06–0.61; p = 0.005). RMST up to 24 months was 21.5 months with denosumab versus 13.9 months without (difference +7.6 months; 95% bootstrap CI +3.8 to +11.1). Landmark and leave-one-center-out analyses yielded stable estimates

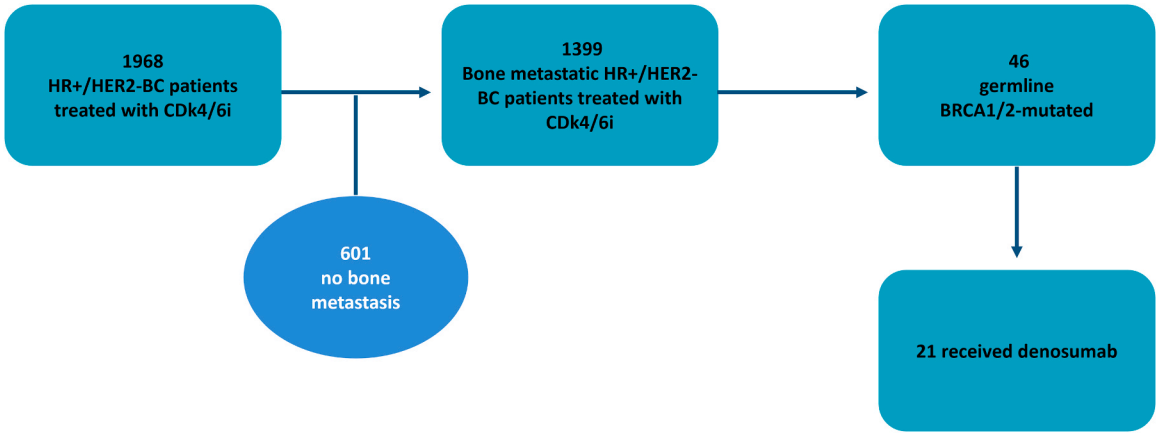
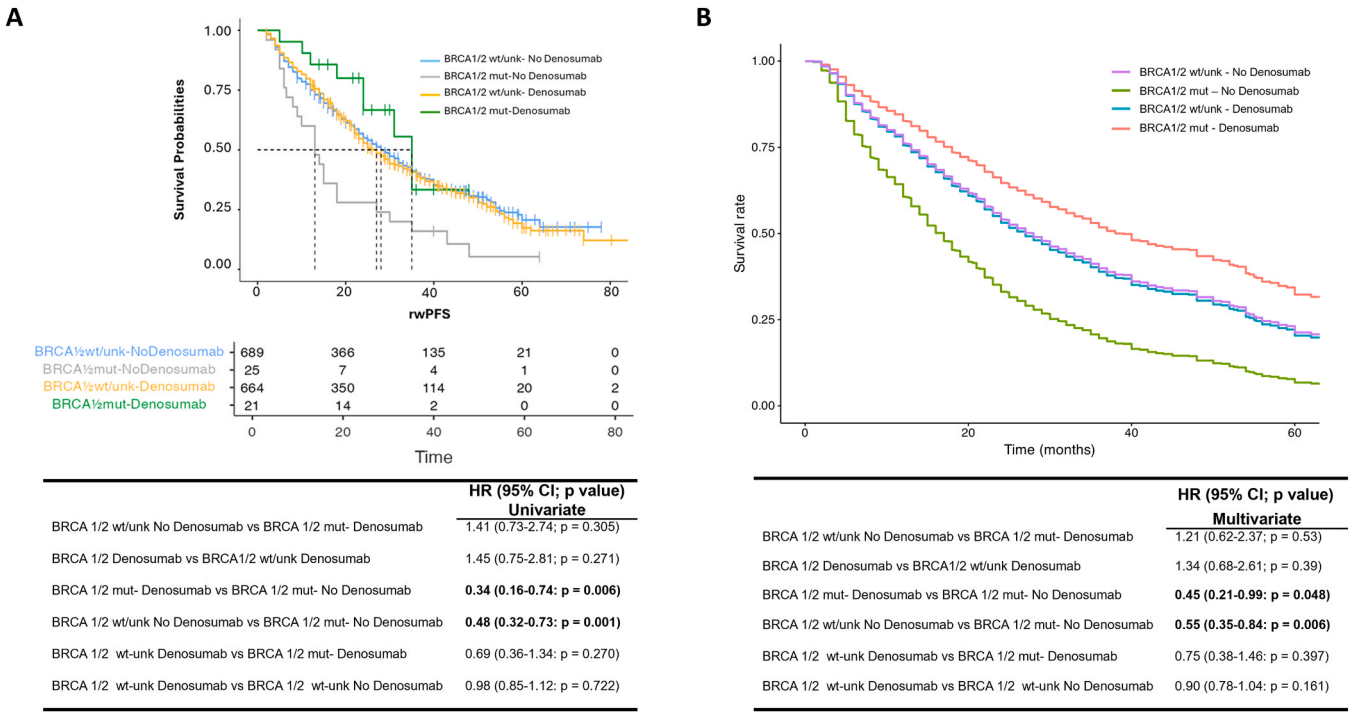


Fig. 1. Flow diagram of patient identification and selection across 24 Italian hospitals (January 2019–December 2023). Abbreviations: BC, breast cancer; ET, endocrine therapy; CDK4/6i, CDK4/6 inhibitor.



	HR (95% CI; p value) Univariate
BRCA 1/2 wt/unk No Denosumab vs BRCA 1/2 mut- Denosumab	1.41 (0.73-2.74; p = 0.305)
BRCA 1/2 Denosumab vs BRCA1/2 wt/unk Denosumab	1.45 (0.75-2.81; p = 0.271)
BRCA 1/2 mut- Denosumab vs BRCA 1/2 mut- No Denosumab	**0.34 (0.16-0.74: p = 0.006)**
BRCA 1/2 wt/unk No Denosumab vs BRCA 1/2 mut- No Denosumab	**0.48 (0.32-0.73: p = 0.001)**
BRCA 1/2 wt-unk Denosumab vs BRCA 1/2 mut- Denosumab	0.69 (0.36-1.34: p = 0.270)
BRCA 1/2 wt-unk Denosumab vs BRCA 1/2 wt-unk No Denosumab	0.98 (0.85-1.12: p = 0.722)

	HR (95% CI; p value) Multivariate
BRCA 1/2 wt/unk No Denosumab vs BRCA 1/2 mut- Denosumab	1.21 (0.62-2.37; p = 0.53)
BRCA 1/2 Denosumab vs BRCA1/2 wt/unk Denosumab	1.34 (0.68-2.61; p = 0.39)
BRCA 1/2 mut- Denosumab vs BRCA 1/2 mut- No Denosumab	**0.45 (0.21-0.99: p = 0.048)**
BRCA 1/2 wt/unk No Denosumab vs BRCA 1/2 mut- No Denosumab	**0.55 (0.35-0.84: p = 0.006)**
BRCA 1/2 wt-unk Denosumab vs BRCA 1/2 mut- Denosumab	0.75 (0.38-1.46: p = 0.397)
BRCA 1/2 wt-unk Denosumab vs BRCA 1/2 wt-unk No Denosumab	0.90 (0.78-1.04: p = 0.161)

Fig. 2. (A) Kaplan–Meier curves of rwPFS according to BRCA1/2 status and denosumab exposure. (B) Direct-adjusted rwPFS curves from the multivariable Cox model, showing covariate-adjusted survival estimates for the four groups (BRCA1/2-mutated vs BRCA1/2-wild-type/unknown; denosumab users vs non-users).

(Supplementary Table 2; Supplementary Figures S2–S4).

5. Discussion

In this multicenter, real-world study including patients with HR+ / HER2 − mBC with bone metastases, denosumab use was associated with a longer rwPFS among *BRCA1/2*-mutated patients. Conversely, we found no significant difference between denosumab users vs. non-users in the *BRCA1/2*-wild-type/unknown subgroup. The impact of denosumab on treatment effectiveness according to BRCA1/2 mutational status suggests a possible effect modification by germline BRCA1/2 mutations rather than a non-specific class effect. These findings should be interpreted as hypothesis-generating and do not establish a causal effect of denosumab on tumor control. Given that imaging schedules were not fully captured, residual detection bias cannot be excluded despite center-stratified modeling and sensitivity analyses.

The lack of denosumab benefit in *BRCA1/2*-wild-type/unknown patients argues against a non-specific class effect and supports biological specificity.

Preclinical studies first positioned RANK/RANKL signaling as a driver of progestin-dependent mammary carcinogenesis: enforced RANK signaling accelerates preneoplasia and tumor formation, whereas RANKL blockade delays tumor development and reduces incidence in mouse models [2,3]. Mechanistically, progesterone-responsive luminal cells upregulate RANKL, which acts in a paracrine manner on RANK+ luminal progenitors, thereby expanding the proliferative pool and lowering the threshold for oncogenic transformation [2,3]. Translational work in *BRCA1* mutation carriers subsequently identified an expanded RANK+ luminal progenitor compartment with hyperproliferation, defective DNA repair, and basal-like transcriptional features, nominating RANKL as a targetable vulnerability in BRCA1-associated tumorigenesis; Moreover, short-window RANKL blockade dampened epithelial proliferation in ex vivo human tissues and delayed tumor onset in BRCA1-deficient models [4]. Complementary observations suggest that BRCA1 haploinsufficiency may skew the RANK/RANKL axis (e.g., increased RANKL/suppressed antagonists), providing a cell-intrinsic rationale for heightened pathway dependence and for the selective antitumor signal observed in BRCA-mutated disease [11–13]. This provides a rationale for the heightened dependence on RANKL signaling in BRCA1/2-mutant tumors and may explain the selective antitumor effect observed in BRCA-mutated patients in this study.

Within the metastatic bone niche, RANKL produced by tumor and stromal cells drives osteoclastogenesis through the RANK–TRAF6 axis with downstream activation of NF-κB and NFATc1, thereby promoting bone resorption and the release of matrix-sequestered growth factors such as TGF-β, IGF-1, and calcium. These cues, together with RANK-dependent signalling in tumor cells that engages the NF-κB, AKT, and MAPK pathways, reinforce a feed-forward vicious cycle that sustains colonization, outgrowth, and treatment resistance of bone metastases. Neutralization of RANKL with denosumab can interrupt this loop at multiple levels—attenuating osteoclast activity, limiting the liberation of pro-metastatic factors, and depriving RANK-dependent, homologous recombination deficiency clones of pro-survival signals. This multipronged disruption provides a biologically plausible explanation for the improvement in rwPFS observed exclusively in the BRCA-mutated subgroup in our study.

Beyond bone, RANK/RANKL signaling also shapes the immune microenvironment. Preclinical models and early “window-of-opportunity” studies indicate that RANK pathway inhibition can increase CD8+ T-cell infiltration, reduce immunosuppressive myeloid/Treg circuits, and enhance antigen-presenting functions, collectively suggesting both intrinsic (tumor-cell) and extrinsic (microenvironment/immune) antitumor effects of RANKL blockade [11–13]. In BRCA-mutated tumors, already burdened by genomic instability and neoantigen load, such immunologic remodeling may further contribute to disease control when RANKL is blocked, complementing the disruption of bone–tumor crosstalk and the dependency of RANK+ luminal progenitors observed in the BRCA1 setting [2–4].

In unselected patients with advanced breast cancer, the use of denosumab resulted in reduced SREs when compared to zoledronic acid, but it did not result in consistent PFS/OS advantages, underscoring that

its antitumor effects may be restricted to specific patient cohorts characterized by specific biological features [5]. In the context of early-stage disease, the ABCSG-18 trial revealed that adjuvant denosumab use reduced the incidence of fractures and improved disease-free survival in postmenopausal HR+ patients treated with aromatase inhibitors [6], whereas the large D-CARE trial, which was conducted in high-risk early breast cancer patients, did not reveal bone-metastasis-free and disease-free survival benefit [7]. Against this backdrop, our BRCA-stratified analysis is novel: no rwPFS benefit with denosumab in BRCA1/2-wild-type/unknown, but a marked rwPFS prolongation in BRCA-mutated patients, consistent with a BRCA-linked reliance on RANKL signaling that may be therapeutically exploitable.

If validated prospectively, BRCA status could help identify patients most likely to derive disease-control benefits from adding RANKL inhibition to CDK4/6i ET in bone-metastatic HR+/HER2 − mBC. Given the non-overlapping mechanisms, rational combinations, for example with PARP inhibitors in HR-deficient tumors, warrant study. Biomarker-embedded trials should integrate germline BRCA, tumor RANK/RANKL expression, bone turnover markers, and immune correlatives (e.g., tumor-infiltrating lymphocytes, CD8+ density), leveraging signals from window studies that showed immune activation after short-course denosumab [14–16].

This retrospective, non-randomized analysis is vulnerable to selection bias and confounding by indication despite covariate adjustment. The BRCA-mutated subgroup was small, limiting precision and power, especially for BRCA1 vs BRCA2 comparisons. Denosumab exposure reflected routine practice (variable start relative to CDK4/6i, dose/interval/duration), introducing potential immortal-time and time-dependent confounding, while rwPFS was ascertained without central review and at nonuniform intervals, raising risks of detection bias and informative censoring. Pooling BRCA wild type with unknown status may have caused misclassification, and additional heterogeneity (CDK4/6i/endocrine partner, line of therapy, use of other bone-targeted agents or radiotherapy) could affect outcomes. In addition, response assessments were performed according to local practice and/or clinical indications, and exact imaging dates were not systematically recorded; we addressed this through center-stratified models, landmark analyses, and leave-one-center-out sensitivity analyses, but some heterogeneity may remain.

In HR+/HER2 − mBC with bone metastases, denosumab was associated with longer rwPFS in BRCA1/2-mutated patients, with no benefit in BRCA1/2-wild-type/unknown patients—coherent with preclinical and translational evidence of BRCA–RANKL interplay. These real-world data support prospective trials evaluating RANKL inhibition as part of tailored strategies for BRCA-mutated.

CRediT authorship contribution statement

Francesco Pantano: Supervision, Methodology, Formal analysis, Conceptualization. **Federica Domati:** Writing – review & editing. **Daniele Santini:** Writing – review & editing, Supervision. **Ornella Garrone:** Writing – review & editing, Supervision. **Giuseppe Tonini:** Supervision. **Annarita Verrazzo:** Investigation. **Bruno Vincenzi:** Supervision. **Roberta Caputo:** Investigation. **Teresa Arcuri:** Investigation. **Alessandra Chirco:** Investigation. **Lorena Filomeno:** Investigation. **Sara D′Alessandro:** Investigation. **Francesca Sofia Di Lisa:** Investigation. **Claudia Piombino:** Writing – review & editing. **Federica Puce:** Investigation. **Michela Palleschi:** Investigation. **Federica Riva:** Investigation. **Delia De Lisi:** Investigation. **Luigia Stefania Stucci:** Investigation. **Marta Piras:** Investigation. **Marianna Sirico:** Investigation. **Sara Ramella:** Writing – review & editing. **Edy Ippolito:** Writing – review & editing. **Antonella Grasso:** Writing – review & editing. **Paolo Orsaria:** Writing – review & editing. **Stefania Gori:** Writing – review & editing, Supervision. **Lorenzo Livi:** Investigation. **Luca Visani:** Investigation. **Orazio Caffo:** Supervision. **Barbara Tagliaferri:** Writing – review & editing, Supervision. **Icro Meattini:** Writing – review & editing, Supervision. **Luigi Rossi:** Writing – review & editing, Supervision. **Raffaella Troiano:** Investigation. **Azzurra Irelli:** Investigation. **Roberta Scafetta:** Writing – original draft, Investigation, Conceptualization. **Ilaria Portarena:** Investigation. **Maria Vittoria Bonomo:** Investigation. **Luisana Sisca:** Investigation. **Cristina Fiore:** Investigation. **Alessandra Guarino:** Investigation. **Carla Gullotta:** Investigation. **Maria Agnese Fabbri:** Supervision. **Giampaolo Bianchini:** Writing – review & editing, Supervision. **Camillo Porta:** Writing – review & editing. **Elisabetta Cretella:** Writing – review & editing. **Fiorella Ruatta:** Investigation. **Simona Pisegna:** Investigation. **Simone Foderaro:** Investigation. **Angela Toss:** Writing – review & editing, Supervision. **Simone Scagnoli:** Investigation. **Marco Donato:** Investigation. **Patrizia Vici:** Supervision. **Andrea Botticelli:** Investigation. **Elena Speziale:** Investigation. **Ugo De Giorgi:** Supervision. **Annalisa La Cesa:** Investigation. **Elisa Tiberi:** Investigation. **Michele Iuliani:** Writing – original draft, Visualization. **Caterina Sposetti:** Investigation. **Valentina Riccozzi:** Investigation. **Federica Villa:** Writing – review & editing. **Rebecca Pedersini:** Investigation. **Francesco Antonio Vilardi:** Investigation. **Michelino De Laurentiis:** Writing – review & editing, Supervision. **Carmen Criscitiello:** Writing – review & editing. **Fabio Venuti:** Investigation. **Alessio Cortellini:** Writing – review & editing. **Matteo Vergati:** Investigation. **Silvia Cavaliere:** Visualization. **Giuliana D′Auria:** Writing – review & editing. **Sonia Simonetti:** Writing – original draft, Visualization. **Rossana Berardi:** Writing – review & editing, Supervision. **Giuseppe Curigliano:** Writing – review & editing, Supervision. **Marco Mazzotta:** Investigation. **Claudio Vernieri:** Writing – review & editing, Supervision. **Vittorio Altomare:** Supervision. **Mauro Minelli:** Supervision.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ejca.2026.116703.

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