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ORIGINAL RESEARCH

Patterns of treatment and outcomes of patients with metastatic HER2-low breast cancer treated with CDK4/6 inhibitors and hormone therapy

Federico Sottotetti[1], Barbara Tagliaferri[1], Gianpiero Rizzo[2], Raffaella Palumbo[1], Giulia Chessa[1,3], Chiara Raso[1,3], Lorenzo Perrone[2], Alberto Malovini[4], Valentina Tibollo[4], Laura Deborah Locati[1,3], Paolo Pedrazzoli[2,3], Angioletta Lasagna[2]

[1]Medical Oncology Unit, ICS Maugeri-IRCCS SpA SB, Pavia, Italy; [2]Medical Oncology Unit, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy; [3]Department of Internal Medicine and Therapeutics, University of Pavia, Pavia, Italy; [4]Laboratory of Informatics and Systems Engineering for Clinical Research, ICS Maugeri-IRCCS SpA SB, Pavia, Italy

Abstract

Background: The 2018 American Society of Clinical Oncology/College of American Pathologists guidelines classified immunohistochemistry (IHC) 1+ or 2+, FISH-negative breast cancer as HER2-low. To date, only a few studies have investigated the role of HER2-low status in patients with hormone receptor positive/HER2$^-$ (HR$^+$/HER2$^-$) metastatic breast cancer (MBC) during CDK4/6 inhibitor (CDK4/6i) therapy.

Methods: This is a multicentre, retrospective cohort study analysing data from patients with HR$^+$/HER2-low and HR$^+$/HER2-0 MBC treated with CDK4/6i as first-line or second-line therapy at the Oncology Units of IRCCS San Matteo Hospital and ICS Maugeri IRCCS in Pavia, Italy, from January 2017 to October 2023. The aim was to assess the activity and effectiveness of CDK4/6i in a real-life setting.

Results: Of the 241 patients included, 240 (99.6%) were women. The median age at diagnosis was 57 years (IQR 48–65 years). Most patients had pM M0 (70.5%). At presentation, 112 (46.5%) had HER2-low and 129 (53.5%) had HER2-0 status. CDK4/6i were administered as first-line therapy in 89.2% of patients and as second-line therapy in 10.8% of patients, with palbociclib (61.4%) being the most common. The median progression-free survival during CDK4/6i therapy was 36.3 months (95% CI 23.6 months to not reached), while the median overall survival was 60.5 months (95% CI 54.4 months to not reached). Progression-free survival differed significantly between palbociclib and abemaciclib/ribociclib (24.4 *versus* 53.7 months; p=0.0109) and between first-line and second-line therapy (40.5 *versus* 21.2 months; p=0.0466).

Conclusion: CDK4/6i are effective in both HER2-low and HER2-0 MBC, with HER2-low potentially benefiting more from first-line therapy.

Keywords: abemaciclib, antibody–drug conjugates, HER2-low, metastatic breast cancer, palbociclib, ribociclib, therapeutic strategies.

Citation

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Introduction

HER2 expression is one of the main prognostic and predictive factors in breast cancer (BC), and its assessment requires the use of immunohistochemistry (IHC) and in situ hybridization (ISH) techniques, with results interpreted according to the 2018 American Society of Clinical Oncology/College of American Pathologists (ASCO/CAP) guidelines.[1] Recently, a new histopathological sub-group termed HER2-low, defined by an IHC score of 1+/2+ without *HER2* gene amplification, has been identified.[2]

Patients with HER2-low tumours represent approximately half of the total cases of BC, making its epidemiological relevance undoubtedly significant. Clinically and

biologically, HER2-low tumours appear to have slightly distinct features compared to HER2⁻ tumours, raising the question of whether treatment response might differ accordingly. The DESTINY-Breast04 (ref.[3]) and DESTINY-Breast06 trials have demonstrated that trastuzumab-deruxtecan can prolong progression-free survival (PFS) and overall survival (OS) in pretreated patients with unresectable or metastatic hormone receptor-positive (HR⁺)/HER2-low disease, making antibody–drug conjugates (ADCs) a highly promising treatment option following progression on first-line therapy.

CDK4/6 inhibitors (CDK4/6i) combined with endocrine therapy (ET) are the standard of care for HR⁺/HER2⁻ metastatic BC (MBC).[4] Their introduction in clinical practice significantly changed the treatment landscape of HR⁺/HER2⁻ MBC, improving PFS and OS. Several studies, mainly conducted between 2022 and 2024, have investigated the potential prognostic role of HER2 status in patients treated with CDK4/6i, but the results have been inconsistent.[5] Additionally, no ad hoc analysis was conducted in this population in the registration trials of CDK4/6i.

In a recent prospective study, Wu et al.[6] analysed the survival outcomes of two groups of HR⁺/HER2⁻ patients randomized to CDK4/6i plus ET compared to ET alone. The results suggested that HER2-low status might predict a poorer response to ET alone (with significantly worse PFS for HER2-low compared to HER2-0, the latter defined by an IHC score of 0) but not to CDK4/6i. This is likely due to the distinct genetic and biological profile of the two tumour subtypes and the fact that inhibiting the endocrine pathway alone may lead to the upregulation of alternative pathways, including HER2-dependent ones. Previous retrospective studies similarly found no significant survival differences between the two cohorts, with consensus suggesting that HER2-low status does not influence survival.[7–9]However, other studies have reported a clear survival advantage for HER2-0 over HER2-low tumours. Thus, the role of HER2 status remains controversial, and further prospective studies are needed to shed light on this issue.

This study aims to investigate, through a retrospective approach and in a real-world setting, the activity and effectiveness of CDK4/6i as first-line or second-line treatment in a HR⁺/HER2-low population compared to matched patients with HR⁺/HER2-0 disease.

Methods

This is a multicentre, retrospective cohort study. Every patient with HR⁺/HER2⁻ MBC treated with CDK4/6i in first-line or second-line therapy at the Oncology Units of IRCCS Policlinico San Matteo and IRCCS ICS Maugeri in Pavia, Italy, from January 2017 to October 2023, was enrolled. Oestrogen receptor and progesterone receptor were detected by IHC and were considered positive if ≥10%, whilst HER2 negativity was defined as IHC 0, +1 or +2 with negative ISH, as recommended by the ASCO/CAP guidelines, and were then divided into two groups: HER2-0 and HER2-low.[10] HER2-0 was defined as IHC 0, and HER2-low was defined as IHC 1+ or IHC 2+/ISH negative. The study was conducted according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement for reporting observational studies.[11]

The study was approved by the Institutional Review Board from the enrolling institutions (approval code 2604). All retrospectively collected data were pseudo-anonymized. All patients signed, before the initiation of treatment, an informed consent provided by the Fondazione IRCCS Policlinico San Matteo and ICS Maugeri IRCCS at the time of hospitalization.

Data were collected from the hospital's electronic patient records, including sociodemographic data (age at the diagnosis, sex) and comorbidities, menopausal status, tumour histology and differentiation, HR and HER2 expression status, Ki67 index, TNM stage, de novo metastatic/recurrent disease status, site of metastases, neo/adjuvant treatment, progression date, and death.

The inclusion criteria were (1) patients aged 18 and older, regardless of sex; (2) having metastatic hormone-positive BC confirmed radiologically and (3) having received treatment with CDK4/6i (either ribociclib or palbociclib or abemaciclib according to physician's choice) in combination with ET in the first-line or second-line setting. Patients with a follow-up duration of less than 3 months, incomplete pathological data or inadequate evaluation of treatment response were excluded from the study.

Patients received treatment with CDK4/6i until disease progression, death or unacceptable toxicity. Response was assessed using the revised RECIST criteria (version 1.1) in the case of CT evaluation[12] or using PERCIST criteria[13] in the case of PET-CT imaging according to the physician's choice.

Endpoints and objectives

The primary objective was the evaluation of clinical and biological characteristics of patients with HR⁺/HER2⁻ MBC and the assessment of efficacy and activity of CDK4/6i in a real-life setting. Accordingly, the primary endpoints were PFS and OS to assess efficacy and best response to assess activity.

Secondary objectives were identified as (1) investigating the association between HER2 status (low *versus* 0)

and PFS; (2) investigating the association between HER2 status (low *versus* 0) and OS; and (3) investigating post-progression treatment patterns.

Statistical methods

Statistical analyses were performed using the R software v4.2.2 (www.r-project.org). Quantitative variables distribution is expressed in terms of median, 25th and 75th percentiles due to deviations from the normal distribution; minimum and maximum values are also reported. The categorical variables distribution is expressed in terms of absolute and relative frequency (%). The Pearson χ^2 test with 100,000 Monte Carlo simulations was applied to test for association between categorical variables. The log-rank test was applied to compare survival profiles between sub-groups. Multivariable Cox regression was applied to compare the risk of progression and death between groups with stratification by hospital centre (coxph function "strata"). The following variables were included in multivariable Cox proportional hazard regressions: HER2 status (HER2-low, HER2$^-$), CDK4/6i type (palbociclib, abemaciclib/ribociclib), CDK4/6i therapy line (first, second), metastasis (synchronous, metachronous), visceral metastases (yes, no), bones metastases (yes, no), other metastases (yes, no), age at diagnosis (≤65 years old, >65 years old), and number of therapy lines after CDK4/6i therapy line (quantitative, included only in overall survival analyses). The "emmeans" function implemented in the emmeans package was used to estimate hazard ratios and corresponding 95% CIs by sub-groups after fitting a multivariate Cox proportional hazard regression model including interaction terms on the whole sample. The significance level α was set to 0.05.

Results

Sample characteristics

A total of 125 (51.9%) patients were enrolled at ICS Maugeri IRCSS and 116 (48.1%) at IRCCS San Matteo Hospital Foundation. Both hospitals are tertiary referral centres and academic hospitals. Of the 241 patients included in the analysis, 240 (99.6%) were women. The median age at diagnosis and at CDK4/6i start was 57 years (IQR 48–65 years) and 64 years (IQR 55–71 years), respectively. Most patients were characterized by pM M0 (70.5%) at diagnosis; 71 (29.5%) patients had synchronous metastases, whilst 170 (70.5%) had metachronous metastases. A previous adjuvant treatment was reported in 70.1% of patients, with median treatment duration of 48.0 months (IQR 5.5–60.2 months).

A total of 112 (46.5%) and 129 (53.5%) patients were characterized by HER2-low and HER2-0 status at disease presentation (primary tumour), respectively. Amongst patients with metachronous metastatic disease, 88 (51.7%) patients underwent metastatic tissue biopsy. The analysis of metastatic tissue revealed a switch from HER2-low to HER2-0 in 38.7%, and a switch from HER2-0 to HER2-low in 36.8% of cases, respectively. In the remaining cases (24.5%), the tissue rebiopsy confirmed the stability of HER2 status. Thus, according to the most recent histological characterization available at the start of CDK4/6i therapy, the total number of HER2-low patients was 121 (50.2%), whilst the remaining 120 (49.8%) were classified as HER2-0. HER2-low status was observed in 47.6% and 56.3% of patients with metachronous and synchronous metastases, respectively (p=0.2636). The frequency of HER2 status at disease presentation and at biopsy of metastatic tissue is reported in Supplementary Table 1 (available at: https://www.drugsincontext.com/wp-content/uploads/2025/03/dic.2024-12-1-Suppl.pdf).

CDK4/6i were administered as first-line therapy in 89.2% of patients and as second-line therapy in the remaining 10.8% of cases. Palbociclib was the most commonly administered drug (61.4%), followed by ribociclib (26.1%) and abemaciclib (12.5%). Aromatase inhibitors were administered as the sole hormonal treatment companion in 52.7% of patients whilst in combination with a luteinizing hormone-releasing hormone analogue in 5.8% of cases. Fulvestrant was administered in the remaining 41.5% of patients.

The baseline characteristics of the analysed sample and the distribution of biopsy sites are summarized in Table 1.

Disease progression and PFS in the whole sample

The median disease PFS time during CDK4/6i therapy was 36.3 months (95% CI 23.6 months to not reached (NR)), with a total of 101 (41.9%) patients experiencing disease progression during CDK4/6i therapy (Figure 1). Most of these patients (63.4%) were characterized by both numeric (development of new metastases) and dimensional progression (enlargement of existing metastases), whilst purely numeric and dimensional progression events were observed in the remaining 32.7% and 4.0% of cases, respectively.

Variables associated with PFS and disease progression risk in the whole sample

No statistically significant difference in terms of PFS was observed between HER2-low and HER2$^-$ patients (median PFS 27.2 *versus* 40.5 months; log-rank p=0.4329) (Table 2 and Supplementary Figure 1). Patients over 65 years old were characterized by a significantly prolonged PFS compared to younger patients (median PFS 60.6 *versus* 27.2 months; log-rank p=0.0334) (Table 2 and Supplementary Figure 1). Patients with synchronous

Table 1. Patient characteristics.

Variable	N	Overall	Min:Max
Centre	241		
ICSM		125 (51.87%)	
OSM		116 (48.13%)	
Sex	241		
Female		240 (99.59%)	
Male		1 (0.41%)	
Age_diagn (years)	241	57 (48:65)	25:89
Age_diagn_ above_65	241		
no		186 (77.18%)	
yes		55 (22.82%)	
age_CDK4.6_years	241	64 (55:71)	26:89
age_CDK4.6_ above_65	241		
no		129 (53.53%)	
yes		112 (46.47%)	
Surgery	241		
No		53 (21.99%)	
Si		188 (78.01%)	
Histology	241		
IDC		189 (78.42%)	
ILC		48 (19.92%)	
other		4 (1.66%)	
ki_67_ prim _tum	240	15 (10:20)	2:70
er _prim_tum	240	90 (80:95)	30:100
pgr_value	240	70 (30:90)	0:100
pgr_positive _prim_ tum	240		
No		14 (5.83%)	
Yes		226 (94.17%)	
her2 _prim_tum	241		
0		128 (53.11%)	
1+		81 (33.61%)	
2+		32 (13.28%)	
pt	240		
T1a		5 (2.08%)	
T1b		11 (4.58%)	
T1c		82 (34.17%)	
T2		101 (42.08%)	
T3		22 (9.17%)	
T4		19 (7.92%)	
pn	240		
N0		75 (31.25%)	
N1		67 (27.92%)	
N2		60 (25%)	
N3		38 (15.83%)	
pm _prim_tum	241		
M0		170 (70.54%)	
M1		71 (29.46%)	
grading	241		
G1		5 (2.07%)	
G2		164 (68.05%)	
G3		72 (29.88%)	
Adiuvant_treatment	241		
No		72 (29.88%)	
Yes		169 (70.12%)	
Metastasis type	241		
Metachronous		170 (70.54%)	
Synchronous		71 (29.46%)	
Metastasis site	241		
Kidney		0 (0%)	
Lymph nodes		87 (36.1%)	
Lungs		45 (18.67%)	
Brain		6 (2.49%)	
Liver		42 (17.43%)	
Bone		151 (62.66%)	
Pancreas		1 (0.41%)	
Soft tissues		16 (6.64%)	
Thyroid		0 (0%)	
Pleura		20 (8.3%)	
Peritoneum		5 (2.07%)	
Skin		7 (2.9%)	
Other		2 (0.83%)	
Visceral		113 (46.89%)	
Other		89 (36.93%)	
biopsy_met	240		
No		141 (58.75%)	

(*Continued*)

(*Continued*)

Table 1. (Continued)

Variable	N	Overall	Min:Max
Yes		99 (41.25%)	
site_of_biopsy	99		
Brain		1 (1.01%)	
Liver		22 (22.22%)	
Lymph nodes		22 (22.22%)	
Breast		1 (1.01%)	
Omentum		1 (1.01%)	
Bone		20 (20.2%)	
Skin		1 (1.01%)	
Peritoneum		1 (1.01%)	
Pleura		3 (3.03%)	
Lungs		18 (18.18%)	
Soft tissues		9 (9.09%)	
line_number	241		
1		215 (89.21%)	
2		26 (10.79%)	
cdk_4_6_inhibitor	241		
Abemaciclib		30 (12.45%)	
Palbociclib		148 (61.41%)	
Ribociclib		63 (26.14%)	

Quantitative variable distributions are described by median (25th, 75th percentiles), minimum and maximum values; categorical and ordinal variable distributions are described by absolute and relative (%) frequency. ICSM, Istituti Clinici Scientifici Maugeri IRCCS; OSM, Ospedale San Matteo IRCCS; IDC, invasive ductal carcinoma; ILC, invasive luminal carcinoma.

metastases had significantly longer PFS compared to those with metachronous metastases (median PFS NR *versus* 26.5 months; log-rank p=0.0358) (Table 2 and Supplementary Figure 1). An additional statistically significant difference in terms of PFS was observed between patients treated by palbociclib compared to those treated by abemaciclib/ribociclib (median PFS 24.4 *versus* 53.7 months; log-rank p=0.0109) (Table 2 and Supplementary Figure 1) as well as between patients who underwent CDK4/6i therapy as first-line compared to second-line therapy (median PFS 40.5 *versus* 21.2 months; log-rank p=0.0466) (Table 2 and Supplementary Figure 1). Metastasis sites were not informative with respect to PFS (log-rank p>0.05) (Table 2). In a multivariable Cox proportional hazard regression, CDK4/6i type and age showed evidence of statistical association with the risk of disease progression. In particular, being treated by palbociclib was associated with a higher risk whilst being over 65 years was associated with a lower risk of progression (HR 1.82, p=0.0139 and HR 0.53, p=0.0444) (Table 3).

CDK4/6i type: association with PFS and disease progression risk by HER2 status

Sub-group analyses (Table 4) showed that, amongst HER2$^-$ patients, those treated by palbociclib were characterized by significantly lower PFS compared to those treated by abemaciclib/ribociclib (median PFS 22.4 *versus* 53.7 months; log-rank p=0.0078) (Figure 2). No statistically significant difference in terms of PFS was observed between palbociclib and abemaciclib/ribociclib treatments amongst HER2-low patients (median PFS 26.5 *versus* 27.6 months; log-rank p=0.4087) (Figure 2). Multivariable Cox proportional hazard regression (Table 4) confirmed that the risk of progression in patients treated by palbociclib with respect to those treated by abemaciclib/ribociclib was higher amongst HER2$^-$ compared to HER-low patients (HER2-low: HR 1.41, p=0.2824; HER2$^-$: HR 2.42, p=0.0134), although there was no significant difference between the two groups (CDK4/6i type x HER2 status interaction p=0.2576).

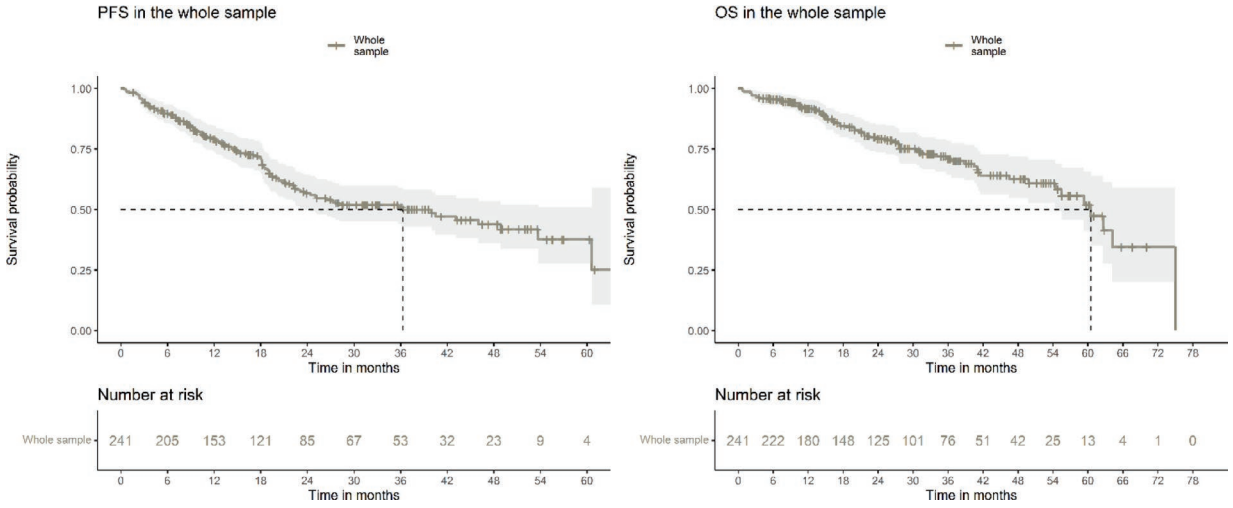
HER2 status: association with PFS and disease progression risk by CDK4/6i line of therapy

Sub-group analyses (Table 4) showed that, amongst patients who underwent CDK4/6i therapy as second-line therapy, HER2-low patients were at significantly higher risk of progression compared to HER2$^-$ patients (median PFS 11.3 *versus* 46 months; log-rank p=0.0397) (Figure 3). No evidence of statistically significant difference in terms of PFS was observed between HER2-low and HER2$^-$ patients who underwent CDK4/6i therapy as first-line therapy (median PFS 43.1 *versus* 40.5 months; log-rank p=0.8602) (Figure 3). Multivariable Cox proportional hazard regression (Table 4) confirmed that the risk of progression was significantly higher in patients with HER2-low status than in those with HER2$^-$ status amongst patients receiving CDK4/6i therapy as second-line therapy (HR 3.17; p=0.0223) but not amongst those receiving the treatment as first-line therapy (HR 0.99; p=0.9787). The risk of progression was significantly different between the two groups (interaction p=0.0366).

OS in the whole sample

The median OS time was 60.5 months (95% CI 54.4 months to NR), with a total number of 67 (27.8%) patients who died between CDK4/6i therapy start and the end of follow-up (Figure 1).

Figure 1. Progression-free and overall survival profiles.



Kaplan–Meier curves describing progression-free survival (PFS) and overall survival (OS) profiles in the whole sample. The numbers reported in the table below each plot describe the number of patients at risk at different time points. Time is expressed in months.

Variables associated to OS in the whole sample

No statistically significant difference in terms of OS was observed between HER2-low and HER2⁻ patients (median OS 62.6 *versus* 60.5 months; log-rank p=0.6473) (Table 2 and Supplementary Figure 1). Similarly, no other variable showed evidence of association with OS either in univariable statistical tests (log-rank p>0.05) (Table 2) or in multivariable regression models (Cox proportional hazard regression p>0.05) (Table 3).

CDK4/6i type: association with OS by HER2 status

No statistically significant difference in terms of OS was observed between patients treated with palbociclib compared to those treated with abemaciclib/ribociclib either amongst HER2-low (median OS 62.6 *versus* 41.5 months; log-rank p=0.6945) (Table 4 and Figure 2) or amongst HER2⁻ patients (median OS 55.5 months *versus* NR; log-rank p=0.0724) (Table 4 and Figure 2). Multivariable Cox proportional hazard regression confirmed that the risk of death in patients treated with palbociclib was not significantly different with respect to those treated with abemaciclib/ribociclib either amongst HER-low patients (HR 0.84, p=0.6736) (Table 4) or amongst HER2⁻ patients (HR 2.33, p=0.0516) (Table 4). Further, the difference in terms of death risk as a function of CDK4/6i type was not significantly different between the two groups (CDK4/6i type x HER2 status interaction p=0.0808).

HER2 status: association with OS by CDK4/6i line of therapy

No statistically significant difference in terms of OS was observed between HER2-low and HER2⁻ patients, either amongst those in first CDK4/6i line of therapy (median OS 62.6 *versus* 55.5 months; log-rank p=0.3657) (Table 4 and Figure 3) or amongst those in second-line therapy (median OS 27.6 *versus* 60.5 months; log-rank p=0.1720) (Table 4 and Figure 3). Multivariable Cox proportional hazard regression (Table 4) confirmed that the risk of death in HER2-low patients was not significantly different with respect to HER2⁻ patients either amongst those taking CDK4/6i as first-line therapy (HR 0.74; p=0.3170) or amongst those receiving them as second-line therapy (HR 2.44; p=0.1371). Further, the difference in terms of death risk as a function of HER2 status was not significantly different between the two groups (CDK4/6i line of therapy x HER2 status interaction p=0.0731).

Resistance type: association with PFS, disease progression risk and OS

Primary endocrine resistance, defined as progressive disease within the first 6 months of first-line ET, was observed in 26.9% of HER2-low and 23.8% of HER2-0 patients. No statistically significant difference in terms of incidence of primary endocrine resistance was observed between the two populations; likewise, no significant difference in PFS or OS was observed between patients with primary resistance and those with secondary resistance

Table 2. Progression-free survival and overall survival estimates in the whole sample.

	Event type: disease progression				Event type: death		
Variable	**Events[a]**	**Median PFS (95% CI)[b]**	**Log-rank, *p* value[c]**		**Events[a]**	**Median OS (95% CI)[b]**	**Log-rank, *p* value[c]**
Age at diagnosis			0.0334	*			0.9992
≤65 years old	88/186	27.2 (22.4–46.0)			55/186	59.3 (49.8–NA)	
>65 years old	13/55	60.6 (48.9–NA)			12/55	62.6 (NA–NA)	
HER2 status			0.4329				0.6473
Negative	50/120	40.5 (23.1–NA)			37/120	60.5 (49.8–NA)	
Low	51/121	27.2 (21.2–NA)			30/121	62.6 (41.5–NA)	
CDK4/6 inhibitor type			0.0109	*			0.2710
Abemaciclib/ribociclib	26/93	53.7 (40.0–NA)			17/93	NA (41.5–NA)	
Palbociclib	75/148	24.4 (19.3–46.0)			50/148	60.5 (54.4–NA)	
CDK4/6 inhibitor therapy line			0.0466	*			0.1356
First	84/215	40.5 (25.0–NA)			55/215	62.6 (54.4–NA)	
Second	17/26	21.2 (9.3–NA)			12/26	60.5 (17.4–NA)	
Metastasis type			0.0358	*			0.1312
Metachronous	82/170	26.5 (21.2–48.9)			57/170	59.3 (46.5–NA)	
Synchronous	19/71	NA (35.7–NA)			10/71	NA (NA–NA)	
Visceral metastases			0.1794				0.3004
No	49/128	46.0 (25.0–NA)			33/128	62.6 (60.5–NA)	
Yes	52/113	27.6 (20.0–NA)			34/113	54.4 (41.2–NA)	
Bone metastases			0.6050				0.9359
No	33/90	40.0 (23.6–NA)			23/90	59.3 (41.5–NA)	
Yes	68/151	35.7 (22.1–NA)			44/151	62.6 (55.5–NA)	
Other metastases			0.7097				0.4791
No	67/152	40.0 (23.1–NA)			47/152	59.3 (49.8–NA)	
Yes	34/89	28.1 (21.2–NA)			20/89	64.2 (54.4–NA)	

[a]Number of disease progression and death events/total number of available observations by variable level. [b]Median survival (95% CI), median disease progression-free survival and overall survival estimates in months and corresponding 95% CI.
[c]*p* value from the log-rank test.
*$p<0.05$. NA, not available.

(median PFS 21.2 *versus* 28.1 months; log-rank $p=0.3535$; median OS 62.6 *versus* 64.2 months; log-rank $p=0.1200$) (Supplementary Figure 2).

Best response

Partial response was recorded as best response during CDK4/6i therapy in 47.3% of patients followed by stable disease (24.5%), complete response (11.2%) and progressive disease (8.7%). The best response was not recorded during the follow-up period for the remaining 8.3% of patients. No evidence of statistical association was observed between HER2 status and best response type during CDK4/6i therapy ($p>0.05$) (Supplementary Table 2).

Therapy lines after disease progression

No further line of therapy was recorded after disease progression for 21.8% of patients, whilst 33.7% and 44.6%

Table 3. Results from multivariable Cox proportional hazard regression for disease progression and death events.

	Event type: progression			Event type: death	
Variable	**HR (95% CI)**	***p* value**		**HR (95% CI)**	***p* value**
Age at diagnosis: >65 years old	0.53 (0.29–0.98)	0.0444	*	1.21 (0.60–2.45)	0.5935
HER2 status: HER2-low	1.21 (0.79–1.85)	0.3781		0.92 (0.54–1.58)	0.7682
CDK4/6 inhibitor type: palbociclib	1.82 (1.13–2.94)	0.0139	*	1.45 (0.78–2.69)	0.2395
CDK4/6 inhibitor therapy line: second	1.58 (0.92–2.72)	0.0990		1.34 (0.69–2.61)	0.3855
Metastasis: synchronous	0.76 (0.45–1.28)	0.2965		0.56 (0.27–1.15)	0.1134
Visceral metastases: yes	1.29 (0.80–2.05)	0.2932		1.37 (0.75–2.49)	0.3045
Bone metastases: yes	1.20 (0.74–1.95)	0.4571		1.27 (0.68–2.38)	0.4555
Other metastases: yes	0.86 (0.55–1.35)	0.5084		0.98 (0.55–1.76)	0.9416
Number of therapy lines after CDK4/6 inhibitor	NT			1.03 (0.89–1.20)	0.6668

*$p<0.05$; NT, not tested.

of patients underwent a single line of therapy and more than one line of therapy, respectively. A maximum number of eight lines of therapy following disease progression were recorded during follow-up. For patients whose disease progressed following treatment with CDK4/6i, the most common choice for the subsequent therapy line was chemotherapy, followed by mTOR inhibitors and ET alone (Table 5).

Discussion

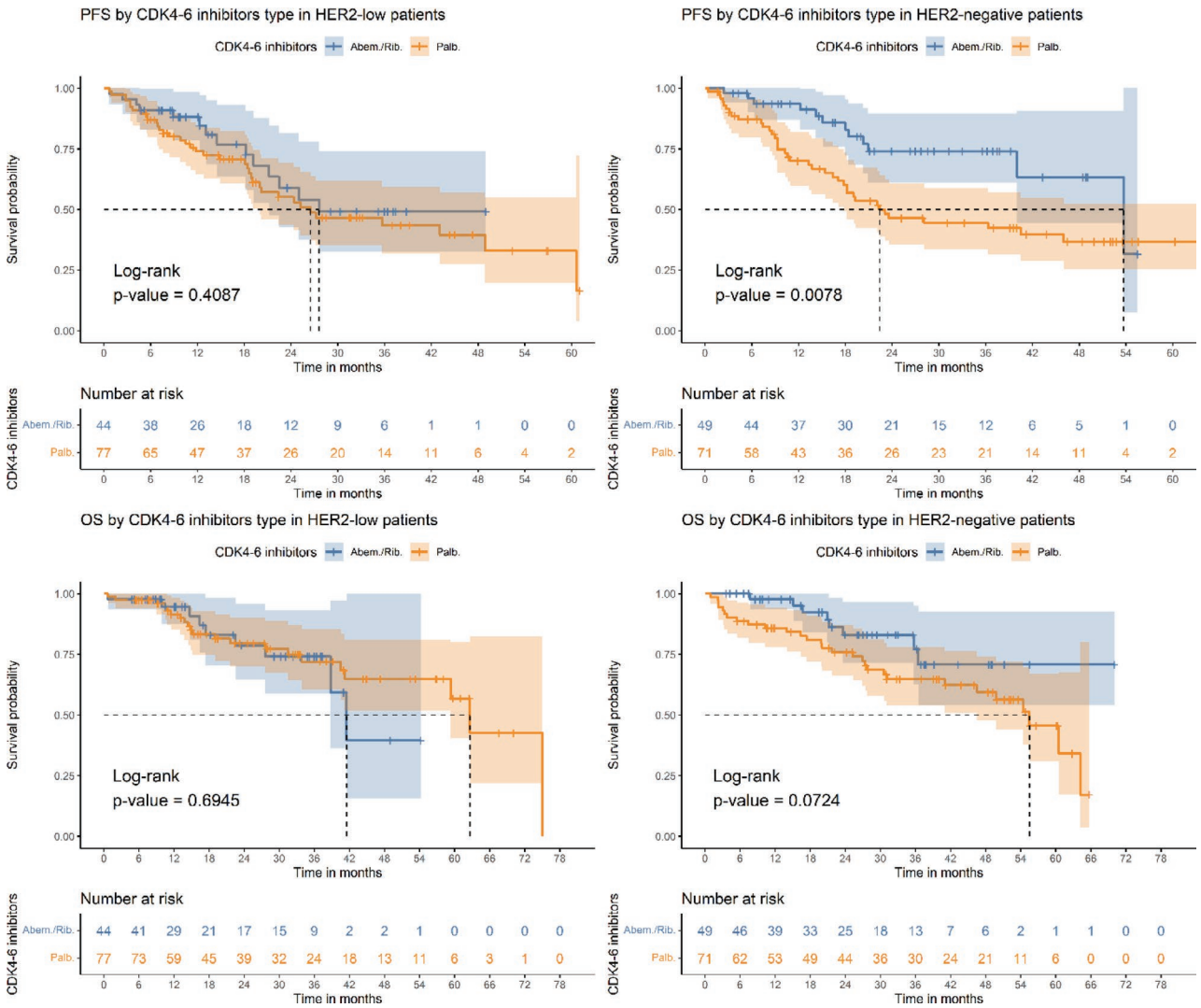
We have herein reported data from a large and well-characterized series of patients with BC enrolled in two tertiary referral oncology centres. We have evaluated the activity of CDK4/6i in both first-line and second-line therapy within a HR$^+$/HER2$^-$ and HR$^+$/HER2-low MBC cohort in a real-world setting, reflecting daily clinical practice. Our data confirm the well-established activity and effectiveness of CDK4/6i in HER2$^-$ patients, regardless of HER2 expression levels, but also provides some novel insights such as the decreased efficacy of CDK4/6i as second-line therapy in a HER2-low population.

Indeed, in registration trials, the efficacy of CDK 4/6i has been widely reported with different outcomes. First, the PALOMA-2 trial[14] demonstrated significantly longer PFS in patients with HR$^+$/HER2$^-$ advanced BC treated with palbociclib in combination with standard ET than in those receiving ET, whilst the PALOMA-3 trial[15] showed a longer OS, that did not achieve significance, amongst patients with HR$^+$/HER2$^-$ advanced BC treated with palbociclib-fulvestrant compared to those receiving placebo-fulvestrant. Second, in the MONARCH 2 trial,[16] abemaciclib plus fulvestrant was effective, and significantly improved PFS and overall response rate in patients with HR$^+$/HER2$^-$ advanced BC. Third, the MONALEESA-3 and MONALEESA-7 trials[17,18] finally showed significantly longer OS with ribociclib in addition to ET than with ET alone amongst patients with HR$^+$/HER2$^-$ advanced BC.

Our results confirm the cumulated evidence available as of today, showing a significant clinical benefit in metastatic HER2-low and HER2-0 patients treated with CDK4/6i, especially in first-line therapy. Recently, it has been recognized that HER2 expression is a continuous variable, ranging from HER2$^+$ to HER2-0 disease, encompassing a broad spectrum of low HER2 status (1+ and 2+, FISH negative). The HER2-low and ultra-low categories include distinct disease entities in which HER2 expression varies spatially and temporally. However, methods to identify such heterogeneity amongst lesions remain lacking.

Until now, patients with HER2-low tumours have been treated according to guidelines for HR$^+$/HER2$^-$ disease. Recent evidence has demonstrated the high efficacy of ADCs in both HER2 low and ultra-low disease as well as in HER2$^+$ disease. According to the most recent results from DESTINY-Breast 06 presented at San Antonio Breast Cancer Symposium 2024, T-DXd outperforms second-line chemotherapy in patients who underwent progression after a first-line treatment with CDK4/6i + ET (median PFS 13 months *versus* 8 months), both in HER2-low and ultra-low sub-groups. This advantage was significant regardless of PFS on first-line treatment (>6 months or <6 months). Currently, researchers are developing new AI models that integrate clinical and genomic information

Figure 2. Progression-free and overall survival profiles as a function of CDK4/6 inhibitor type by HER2 status.



Kaplan–Meier curves describing progression-free survival (PFS) and overall survival (OS) profiles as a function of CDK4/6 inhibitor type by HER2 status. The numbers reported in the table below each plot describe the number of patients at risk at different time points by strata. Time is expressed in months. *p* value is derived from the log-rank test.

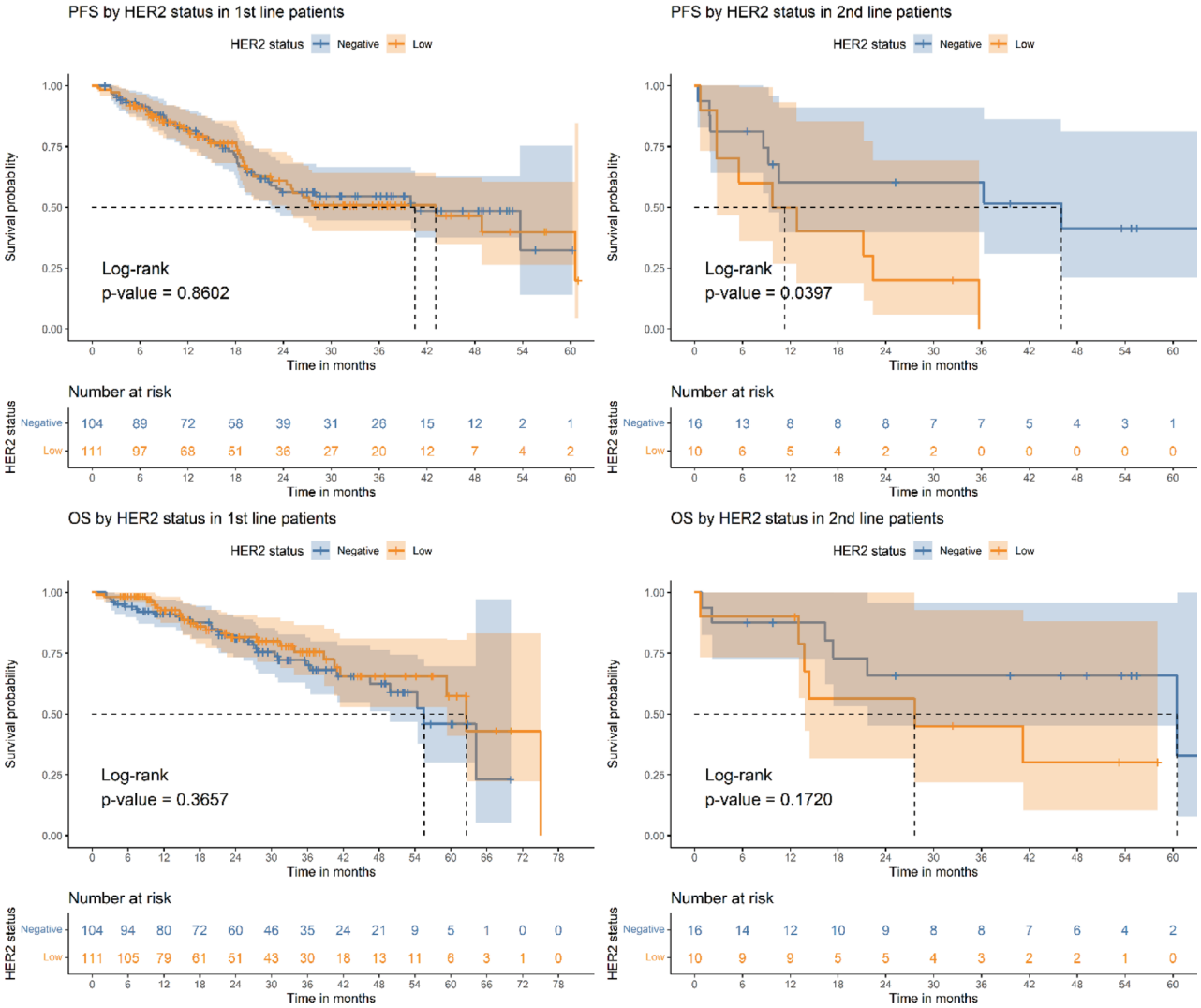
to predict response to CDK4/6i in patients with metastatic HR$^+$/HER2$^-$ BC.[19] Therefore, we can anticipate that, in the future, trastuzumab-deruxtecan (T-DXd) may become the treatment of choice for patients with an estimated poor response to CDK4/6i.

Furthermore, we analysed the clinical and biological characteristics of our cohort, and we found that some patients underwent a switch in HER2 status, possibly due to reasons that include both the intratumoural heterogeneity, which complicates the precise determination of HER2 status on biopsy samples, and the intrinsically dynamic nature of HER2 status itself.[20] Indeed, HER2 expression can be influenced by pharmacological pressure or spontaneous acquisition of new mutations. However, our cohorts remained numerically well balanced, with approximately half of patients classified as HER2-low; this aligns with the epidemiological data reported in the literature.[21]

The analysis also uncovered a distinctive distribution in the prescription patterns of the three drugs within the study population with the vast majority of patients receiving palbociclib. This disparity in usage reflects the realities of clinical practice, where the later approval of ribociclib and abemaciclib, combined with clinicians' greater familiarity with palbociclib due to prior experience, has influenced these prescribing trends.

Our data showed that the HER2-low status did not have a statistically significant impact on PFS and OS in patients with HR$^+$/HER2$^-$ MBC undergoing CDK4/6i and ET treatment.

Figure 3. Progression-free and overall survival profiles as a function of HER2 status by CDK4/6 inhibitor line of therapy.



Kaplan–Meier curves describing progression-free survival (PFS) and overall survival (OS) profiles as a function of HER2 status by CDK4/6 inhibitor line of therapy. The numbers reported in the table below each plot describe the number of patients at risk at different time points by strata. Time is expressed in months. *p* value is derived from the log-rank test.

Our results, in terms of OS and PFS, align with data from high-quality prospective phase III trials comparing CDK4/6i combined with standard ET versus ET alone in patients with $HR^+/HER2^-$ MBC.

Our results are corroborated by other studies. For example, Yildirim et al.[7] found no significant impact of HER2-low status on survival in a multicentre retrospective cohort of 204 patients with MBC. Likewise, Shao et al.[22] described no statistically significant differences in terms of PFS and OS between 24 HER2-0 and 21 HER2-low patients treated with palbociclib plus ET. Finally, Douganiotis et al.[8] confirmed the absence of statistically significant differences between the two groups in a retrospective multicentre study in Greece.

In our cohort, the median PFS in the HER2-low group was remarkably inferior to that of the HER2-0 group but the difference was not statistically significant. In the HER2-0 sub-group, patients treated with palbociclib showed worse outcomes in terms of median PFS compared to those treated with ribociclib and abemaciclib. These clinical data are similar to those reported by Önder et al.[9] Recently, Zattarin et al.[23] confirmed the association between HER2-low status and worse patient PFS results in a larger cohort of patients (*n*=28).

The discrepancies in the results may depend on the different sample sizes of the studies as well as on the lack of a centralized pathology assessment. Moreover, not all patients with MBC may have undergone a rebiopsy,

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Table 4. Progression-free survival and overall survival estimates by subgroup.

Sub-group and variable	Event type: disease progression						Event type: death				
	Events[a]	Median PFS (95% CI)[b]	Log-rank, *p* value[c]	Cox regression			Events[a]	Median OS (95% CI)[b]	Log-rank, *p* value[c]	Cox regression	
				HR (95% CI)[d]	*p* value[e]					HR (95% CI)[d]	*p* value[e]
Analysis by CDK4-6 therapy line					*0.0366*	#					*0.0731*
CDK4-6 therapy line: 1st			0.8602						0.3657		
HER2 status: HER2-negative	42/104	40.5 (22.4–NA)					31/104	55.5 (49.8–NA)			
HER2 status: HER2-low	42/111	43.1 (24.4–NA)		0.99 (0.63–1.58)	0.9787		24/111	62.6 (59.3–NA)		0.74 (0.41–1.34)	0.3170
CDK4-6 therapy line: 2nd			0.0397	*					0.1720		
HER2 status: HER2-negative	8/16	46.0 (9.3–NA)					6/16	60.5 (21.7–NA)			
HER2 status: HER2-low	9/10	11.3 (2.8–NA)		3.17 (1.18–8.52)	0.0233	*	6/10	27.6 (13.8–NA)		2.44 (0.75–7.85)	0.1371
Analysis by HER2 status					*0.2576*						*0.0808*
HER2 status: HER2-low			0.4087						0.6945		
CDK4-6 inhibitor type: abemaciclib/ribociclib	14/44	27.6 (21.2–NA)					9/44	41.5 (38.8–NA)			
CDK4-6 inhibitor type: palbociclib	37/77	26.5 (20.0–NA)		1.41 (0.75–2.66)	0.2824		21/77	62.6 (59.3–NA)		0.84 (0.37–1.92)	0.6736
HER2 status: HER2-negative			0.0078	*					0.0724		
CDK4-6 inhibitor type: abemaciclib/ribociclib	12/49	53.7 (40.0–NA)					8/49	NA (NA–NA)			
CDK4-6 inhibitor type: palbociclib	38/71	22.4 (17.8–NA)		2.42 (1.20–4.88)	0.0134	*	29/71	55.5 (46.5–NA)		2.33 (0.99–5.47)	0.0516

[a]Number of disease progression and death events/total number of available observations by sub-group and variable level. [b]Median survival (95% CI), median disease progression-free survival and overall survival estimates in months and corresponding 95% CI. [c]*p* value from the log-rank test. [d]Hazard ratio and corresponding 95% CI from multivariable Cox proportional hazard regression; [e]*p* value from multivariable Cox proportional hazard regression, where values in italic correspond to CDK4/6 inhibitor line of therapy x HER2 status and HER2 status x CDK4/6 inhibitor type interaction term *p* values.
*$p<0.05$; #interaction $p<0.05$; NA, not available.

Table 5. Distribution of the different types of therapy (limited to the subsequent line to CDK4/6 inhibitor).

Number of therapy lines	Chemotherapy	mTOR inhibitor	Hormone therapy
2	44	18	5
3	6	7	0

which may be a bias in all studies available to date, including ours.

Regarding OS, our data must be interpreted considering the length of the follow-up period. Indeed, patients received up to eight lines of therapy following CDK4/6i, reducing the measurability of the effect of a single line. Moreover, the choice of drug sequence (chemotherapy *versus* mTOR inhibitors *versus* ADCs *versus* ET alone) and treatment patterns was highly variable amongst physicians and highly dependent on the clinical context. Therefore, whilst the advantage in terms of PFS is immediately assessable, the impact of the first-line treatment on OS is buffered by the necessity to prescribe numerous subsequent therapy lines in long-term survivors. Indeed, our data allowed us to determine the type of treatment administered following progression on CDK4/6i. The results indicated that chemotherapy was the most commonly used option, especially as a second-line treatment, followed by mTOR inhibitors and ET alone. In the third-line setting, mTOR inhibitors were the most frequently chosen, followed by chemotherapy. These differences reflect the lack of a structured framework of guidelines in the post-CDK4/6i setting, in which therapeutic choices are entirely at the discretion of the clinician's judgment.

As previously mentioned, ADCs are currently acquiring a significant role in the therapeutic management of patients with HR$^+$/HER2-low disease who underwent progression during CDK4/6i therapy,[24] and their importance may increase in the future. However, due to limited evidence supporting their use and to their later approval, only two patients in our study received ADCs following progression after CDK4/6i, one of them in third-line and the other one in fifth-line therapy.

Looking at the best response, most of our patients had a partial response or stable disease, regardless of HER2 status, proving that CDK4/6i are effective at least in delaying disease progression. Hence, no significant statistical association was found between HER2 status and best response.

Some limitations of the study must be mentioned, including the retrospective and observational nature, the relatively small sample size, the lack of a centralized determination of HER2 status, and the short follow-up time. Finally, the limited sample size precluded the analysis of PFS and OS in the sub-population of patients who underwent a switch in HER2 status.

Conclusion

CDK4/6i have demonstrated comparable effectiveness in both HER2-low and HER2$^-$ MBC. Moreover, whilst CDK4/6i provide similar benefits to HER2-0 patients regardless of the line of therapy, our findings suggest that the HER2-low population may derive greater benefit from first-line therapy with CDK4/6i compared to second-line treatment.

Supplementary material available at: https://www.drugsincontext.com/wp-content/uploads/2025/03/dic.2024-12-1-Suppl.pdf

Contributions: FS, AL, BT and RP designed the study; AM and VT designed the statistical plan analysis and performed all analyses. VT, CR and GC designed the database, collected data, and clinically followed-up the patients. AL and FS interpreted data and drafted the manuscript. FS, AL, PP, LP, GR, LDL reviewed the manuscript for important intellectual contents. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

Data availability statement: The data generated in this study are available upon request from the corresponding author.

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Correspondence: Federico Sottotetti, Medical Oncology Unit, ICS Maugeri-IRCCS SpA SB, Via Maugeri, 10 27100, Pavia, Italy. Email: federico.sottotetti@icsmaugeri.it

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