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A Prognostic Index for Advanced Biliary Tract Cancer Treated With Cisplatin, Gemcitabine and Durvalumab: The MAGIC-D Index

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ABSTRACT

Background: Over the years, prognostic indexes have been developed to help clinicians stratify patients with biliary tract cancers (BTC) into risk groups. This study aims to identify a new prognostic index for patients with BTC treated with cisplatin, gemcitabine and durvalumab (CGD) in the first-line setting.

Patients and Methods: The study population consisted of patients with BTC from 11 Eastern and Western Countries. Using multivariate analysis for overall survival (OS), we identified 5 baseline statistically significant variables: stage, carcinoembryonic antigen (CEA) levels, albumin levels, gamma glutamyl transferase (GGT) levels, neutrophil-to-lymphocyte ratio (NLR). Metastatic disease is a prognostic factor with a superior weight considering the HR of 3.62, while all the others can be considered prognostic factors with equivalent weight as the HRs are quite similar (HRs between 1.55 and 1.92). Based on these reasons, we developed a prognostic model called the MAGIC-D index by assigning a score of 2 for metastatic disease, and a score of 1 for CEA increased levels, albumin decreased levels, GGT increased levels, NLR ≥ 3. Patients were stratified into three risk groups as follows: low-risk group (Score from 0 to 2), intermediate-risk group (Score from 3 to 4) and high-risk group (Score from 5 to 6). At the

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For affiliations refer to page 11.

first data cutoff (April 2024), these data were available for 319 patients that composed the training cohort used for the analysis. At the second data cutoff (May 2025), 79 patients were further enrolled and composed the validation cohort.

Results: Median progression-free survival was 11.7 months in low-risk group (20.7%), 8.7 months in intermediate-risk group (46.4%) and 5.4 months in high-risk group (32.9%) [low-risk hazard ratio (HR): 0.27, intermediate-risk HR: 0.55, high-risk HR: 1, $p < 0.0001$]. Median OS was 18.4 months in low-risk group,15.9 months in intermediate-risk group and 7.8 months in high-risk group (low-risk HR: 0.17, intermediate-risk HR: 0.43, high-risk HR: 1, $p < 0.0001$). There was no difference in overall response rate (low-risk: 31.8%, intermediate-risk: 36.5% and high-risk: 25.7%; $p = 0.0718$), while disease control rate was significantly different across the three risk groups (low-risk: 83.3%, intermediate-risk: 70.9% and high-risk: 60.9%; $p < 0.0001$) as well as the rate of patients receiving a second-line therapy (low-risk: 54.5%, intermediate-risk: 48.6% and high-risk: 25.7%; $p = 0.0061$). Finally, the prognostic role in terms of OS and PFS of the MAGIC-D index was confirmed in a validation cohort of 79 patients.

Conclusion: The MAGIC-D index is an easy-to-use tool able to stratify patients with BTC with different prognoses undergoing first-line therapy with CGD.

1 | Introduction

Biliary tract cancers (BTC) are counted among rare tumours, but their incidence has been increasing in recent years. Based on their site of origin from the biliary tract, BTC are classified as intrahepatic cholangiocarcinoma (CCA), extrahepatic (including perihilar and distal) CCA and gallbladder carcinoma [1]. In more than 60% of cases, the diagnosis occurs when radical surgery is no longer feasible [2], and therefore the initial treatment strategy is systemic therapy based on a combination of chemotherapy, cisplatin and gemcitabine and immunotherapy, with the programmed cell death ligand 1 (PD-L1) inhibitor durvalumab or the PD-1 inhibitor pembrolizumab. These combinations represent the standard of care for the treatment of BTC in the first-line setting based on the results of the phase III TOPAZ-1 and KEYNOTE-966 trials [3–8]. Recently, the molecular characterisation of these tumours has allowed the study and approval of targeted therapies that have expanded the therapeutic armamentarium available in the second-line setting for patients carrying specific gene alterations [9–19].

In the literature, there are numerous analyses demonstrating the prognostic value of some parameters, such as albumin, carcinoembryonic antigen (CEA), carbohydrate antigen 19–9 (CA 19–9) and neutrophil-to-lymphocyte ratio (NLR), in patients with BTC undergoing radical surgery or first-line therapy with cisplatin and gemcitabine in the pre-immunotherapy era [20–32]. Over the years, prognostic indices have also been developed to help clinicians stratify patients with BTC into risk groups with the aim of identifying who can benefit the most from a specific treatment [33–39]. However, studies evaluating new prognostic indexes to be used in the first-line setting with the combination of cisplatin, gemcitabine and durvalumab (CGD) are still absent. The aim of this real-world retrospective study is to evaluate and validate a new prognostic index for stratifying patients in this treatment setting in a large population from Western and Eastern countries.

2 | Materials and Methods

The study population consisted of patients treated with CGD for locally advanced or metastatic BTC at 39 clinical institutions across 11 countries (Italy, Germany, Austria, Spain, Portugal, United Kingdom, United States of America, Republic of Korea, China, Hong Kong Special Administrative Region of China, and Japan) between September 2022 and May 2025. At the first data cutoff (1 April 2024), the population consisted of 618 patients from which the training cohort was derived. At the second data cutoff (1 May 2025), 79 patients were further enrolled and composed the validation cohort. Patients were included in the study if they had histologically confirmed BTC and if they had not received prior systemic treatments for locally advanced or metastatic disease. All patients were treated with 1500 mg durvalumab intravenously every 3 weeks (on Day 1 of the cycle) in combination with 1000 mg/m^2 gemcitabine and 25 mg/m^2 cisplatin intravenously on Day 1 and 8 every 3 weeks for up to eight cycles. Thereafter, patients received durvalumab (1500 mg) monotherapy intravenously every 4 weeks until disease progression or unacceptable toxicity as determined by the TOPAZ-1 trial [3–5]. Treatment interruptions and/or dose reductions were allowed to manage adverse events (AEs) according to local clinical practice at each centre. AEs were graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 5.0.

2.1 | Statistical Analysis

Results of the haematological blood tests and clinical parameters were collected before starting treatment with CGD.

Univariate analyses were estimated using the product-limit method of Kaplan–Meier. Unadjusted and adjusted hazard ratios (HRs) by baseline characteristics were calculated using the Cox proportional hazards model. A p-value < 0.05 was considered statistically significant.

Categorical variables were compared with Chi-square test. Overall survival (OS) was defined as the time from the start date of the studied treatment to the date of death. OS was reported as median values expressed in months, with 95% confidence interval (CI). Progression-free survival (PFS) was defined as the time interval from the first day of treatment to the progression of the disease or the day of death for any cause.

Overall response rate (ORR) was assessed by the investigator and defined as the proportion of patients who achieved complete response (CR) or partial response (PR); disease control rate (DCR) was defined as the proportion of patients who achieved ORR or stable disease (SD). Treatment response was

Summary

- The MAGIC-D index is a prognostic index able to stratify patients with locally advanced or metastatic biliary tract cancer undergoing first-line chemoimmunotherapy with cisplatin, gemcitabine and durvalumab.
- This index comprises of factors widely used in clinical practice: disease stage, carcinoembryonic antigen, albumin levels, gamma glutamyl transferase levels and neutrophil-to-lymphocyte ratio.

evaluated by computed tomography and categorised as CR, PR, SD, or progressive disease by local review according to Response Evaluation Criteria in Solid Tumours (RECIST) 1.1.

To build a prognostic model using baseline clinical and laboratory characteristics, we performed univariate and multivariate analyses to identify variables with prognostic value for OS. We then stratified patients into risk groups by assigning scores to each significant variable, weighted by its HR.

Patients were stratified into three risk groups based on their score: low-risk group (score 0–2); intermediate-risk group (score 3–4); high-risk group (score 5–6).

MedCalc package (MedCalc version 16.8.4) was employed for statistical analysis.

3 | Results

Overall, 618 patients with locally advanced unresectable or metastatic BTC were enrolled.

With a median duration of follow-up (FU) of 8.5 months (95% CI: 7.9–9.5 months) at the data cutoff (1 April 2024), 327 (52.9%) patients discontinued treatment due to disease progression, and 188 (30.4%) patients died. In the whole population, the median OS was 15.1 months (95% CI: 13.4–17.9 months) and the median PFS was 8.1 months (95% CI: 7.5–8.8 months). This population was included in the univariate and multivariate analysis. Patient characteristics are listed in Table 1.

3.1 | Training Cohort

When assessed by univariate analysis, intrahepatic site, metastatic disease, no previous surgery, ECOG performance status ≥1, NLR ≥3, albumin, bilirubin, CA 19–9, CEA, aspartate transaminase, alanine transaminase, or gamma glutamyl transferase (GGT) levels outside of normal ranges were significantly associated with shorter OS. At multivariate analysis, the following variables retained statistical significance as poor prognostic factors: disease stage, CEA, albumin, GGT levels and NLR. Noteworthy, metastatic disease is a prognostic factor with a superior weight considering the HR of 3.62, while all the others can be considered prognostic factors with equivalent weight as the HRs are quite

TABLE 1 | Baseline characteristics of the overall population.

Characteristics	No. (%)
Gender	
Male	328 (53.1%)
Female	290 (46.9%)
Age	
≤70 years	355 (57.4%)
>70 years	247 (40.0%)
ECOG PS	
0	302 (48.9%)
≥1	316 (51.1%)
Primary site	
Intrahepatic CCA	330 (53.4%)
Other primary sites	288 (46.6%)
Stage	
Locally advanced	142 (23.0%)
Metastatic	476 (77.0%)
Surgery	
Yes	168 (27.2%)
No	450 (72.8%)
Biliary drainage	
Yes	163 (26.4%)
No	455 (73.6%)
Albumin	
NV	312 (50.5%)
DV	124 (20.1%)
Bilirubin	
NV	468 (75.7%)
IV	121 (19.6%)
AST	
NV	316 (51.1%)
IV	232 (37.5%)
ALT	
NV	474 (76.7%)
IV	112 (18.1%)
GGT	
NV	132 (21.3%)
IV	359 (58.1%)
CA 19.9	
NV	189 (30.6%)
IV	395 (63.9%)

(Continues)

TABLE 1 | (Continued)

Characteristics	No. (%)
CEA	
NV	314 (50.8%)
IV	244 (39.5%)
NLR	
< 3	238 (38.5%)
≥ 3	298 (48.2%)

Abbreviations: ALT, alanine transaminase; AST, aspartate transaminase; CCA, cholangiocarcinoma; CEA, carcinoembryonic antigen; DV, decreased value; GGT, gamma glutamyl transferase; IV, increased value; NLR, neutrophil-lymphocyte ratio; NV, normal value; ECOG PS, performance status.

similar (HRs between 1.55 and 1.92). Based on these reasons, we developed a prognostic model by assigning a score of 2 for metastatic disease, and a score of 1for CEA increased levels, albumin decreased levels, GGT increased levels, NLR ≥ 3 (Table 2). These data were available for 319 patients that composed the population cohort included in the analysis, with a median FU of 7.9 months (95% CI: 7.4–9.0 months). Patient characteristics of the study cohort are listed in Table S1. According to the assigned weight, patients were stratified into three risk groups: the low-risk group (score from 0 to 2), the intermediate-risk group (score from 3 to 4) and the high-risk group (score from 5 to 6) (Table 3). We have denominated this model the Multicenter study Assessing GGT, albumin, CEA, NLR, and stage in patients receiving cisplatin, gemcitabine, and Durvalumab index 'MAGIC-D index'

TABLE 2 | Univariate and multivariate analyses for OS.

	Univariate analysis for OS		Multivariate analysis for OS	
Characteristics	**HR (95% CI)**	***p***	**HR (95% CI)**	***p***
Gender				
Female	1.05 (0.79–1.40)	0.7472		
Male	1			
Age				
≤ 70 years	1.18 (0.88–1.59)	0.2652		
> 70 years	1			
ECOG PS				
0	1	**< 0.0001**	1	0.1055
≥ 1	1.92 (1.44–2.56)		1.40 (0.93–2.10)	
Primary site				
Intrahepatic CCA	1.42 (1.07–1.90)	**0.0163**	1.17 (0.78–1.75)	0.4532
Other primary sites	1		1	
Stage				
Locally advanced	1	**< 0.0001**	1	**0.0001**
Metastatic	2.13 (1.55–2.93)		3.62 (1.98–6.62)	
Surgery				
Yes	1	**0.0017**	1	0.6265
No	1.64 (1.20–2.24)		1.22 (0.79–1.90)	
Biliary drainage				
Yes	1	0.8757		
No	1.03 (0.73–1.43)			
Albumin				
NV	1	**< 0.0001**	1	**0.0162**
DV	3.11 (2.08–4.64)		1.63 (1.09–2.42)	
Bilirubin				
NV	1	**0.0010**	1	0.2206
IV	1.90 (1.30–2.79)		1.33 (0.84–2.08)	
AST				

(Continues)

TABLE 2 | (Continued)

Characteristics	Univariate analysis for OS		Multivariate analysis for OS	
	HR (95% CI)	*p*	HR (95% CI)	*p*
NV	1	**0.0018**	1	0.4676
IV	1.64 (1.20–2.24)		1.17 (0.76–1.82)	
ALT				
NV	1	**0.0075**	1	0.2512
IV	1.68 (1.15–2.47)		1.56 (0.88–2.16)	
GGT				
NV	1	**0.0006**	1	**0.0185**
IV	1.82 (1.29–2.57)		1.92 (1.20–2.34)	
CA 19.9				
NV	1	**0.0482**	1	0.1176
IV	1.37 (1.00–1.86)		1.58 (0.95–2.08)	
CEA				
NV	1	**0.0001**	1	**0.0043**
IV	1.85 (1.36–2.50)		1.73 (1.19–2.51)	
NLR				
< 3	1	**< 0.0001**	1	**0.0242**
≥ 3	2.14 (1.59–2.88)		1.55 (1.03–2.32)	

Note: Bold values indicate statistically significant.
Abbreviations: ALT, alanine transaminase; AST, aspartate transaminase; CCA, cholangiocarcinoma; CEA, carcinoembryonic antigen; CI, confidence interval; DV, decreased value; GGT, gamma glutamyl transferase; HR, hazard ratio; IV, increased value; NLR, neutrophil-lymphocyte ratio; NV, normal value; OS, overall survival; ECOG PS, performance status.

TABLE 3 | Scoring system of the MAGIC-D index.

Stage	
Locally advanced	0
Metastatic	+2
CEA	
NV	0
IV	+1
Albumin	
NV	0
DV	+1
GGT	
NV	0
IV	+1
NLR	
< 3	0
≥ 3	+1
Score	0–2 ➔ Low-risk group 3–4 ➔ Intermediate-risk group 5–6 ➔ High-risk group

Abbreviations: CEA, carcinoembryonic antigen; DV, decreased value; GGT, gamma glutamyl transferase; IV, increased value; NLR, neutrophil-lymphocyte ratio; NV, normal value.

Overall, 66 (20.7%) patients were categorised as low-risk-group, 148 (46.4%) patients as intermediate-risk group and 105 (32.9%) as high-risk group.

Median PFS was 11.7 months (95% CI: 10.5–15.3 months) in the low-risk group, 8.7 months (95% CI: 7.1–9.6 months) in the intermediate-risk group and 5.4 months (95% CI: 3.9–6.6 months) in the high-risk group [low-risk HR: 0.27 (95% CI: 0.17–0.41), intermediate-risk HR: 0.55 (95% CI: 0.38–0.80), high-risk HR: 1 (reference group), $p < 0.0001$] (Figure 1).

Median OS was 18.4 months (95% CI: 15.3–23.4 months) in the low-risk group,15.9 months (95% CI: 11.2–19.1 months) in the intermediate-risk group and 7.8 months (95% CI: 6.6–10.2 months) in the high-risk group [low-risk HR: 0.17 (95% CI: 0.10–0.28), intermediate-risk HR: 0.43 (95% CI: 0.27–0.68), high-risk HR: 1 (reference group), $p < 0.0001$] (Figure 2). Receiver operating characteristic curve analysis displayed an area under the curve of 0.71 (95% CI: 0.64–0.77; $p < 0.0001$).

There was no difference in ORR [low-risk: 21 (31.8%), intermediate-risk: 54 (36.5%) and high-risk: 27 (25.7%); $p = 0.0718$], while the DCR was significantly different across the three risk groups [low-risk: 55 (83.3%), intermediate-risk: 105 (70.9%) and high-risk: 64 (60.9%); $p < 0.0001$], as well as the rate of patients receiving a second-line therapy [low-risk: 12 (54.5%), intermediate-risk: 36 (48.6%) and high-risk: 18 (25.7%); $p = 0.00061$].

Median OS for subsequent anticancer treatments from the start of second-line therapy was 6.7 months (95% CI: 2.2–10.1 months)

in the low-risk group, 10.0 months (95% CI: 3.7–10.8 months) in the intermediate-risk group and 5.5 months (95% CI: 2.6–8.6 months) in the high-risk group [low-risk HR: 0.48 (95% CI: 0.16–1.43), intermediate-risk HR: 0.61 (95% CI: 0.24–1.56), high-risk HR: 1 (reference group), $p = 0.3095$] (Figure 3).

The safety profile was similar in the three risk groups, except for neutropenia (low-risk: 54.5%, intermediate-risk: 52.0%, high-risk: 27.6%; $p = 0.0001$) and nausea (low-risk: 36.4%, intermediate-risk: 41.9%, high-risk: 26.7%; $p = 0.0447$) (Table 4).

3.2 | Validation Cohort

The validation cohort consisted of 79 patients with BTC treated with CGD in the first-line setting. At the data cutoff (May 2025, 1), with a median FU of 12.0 months (95% CI: 10.2–15.8 months), the median OS was 20.7 months (95% CI: 12.2–21.9 months) and the median PFS was 8.4 months (95% CI: 6.2–11.0 months). Patients' characteristics are listed in Table S2.

In the validation cohort, 23 (29.1%) patients were categorised as low-risk group, 38 (48.1%) patients as intermediate-risk group and 18 (22.8%) as high-risk group.

Median PFS was 12.8 months (95% CI: 7.0–12.8 months) in the low-risk group, 8.5 months (95% CI: 5.9–11.0 months) in the intermediate-risk group and 5.0 months (95% CI: 2.2–10.5 months) in the high-risk group [low-risk HR: 0.23 (95% CI: 0.08–0.66), intermediate-risk HR: 0.42 (95% CI: 0.15–1.13), high-risk HR: 1 (reference group), $p = 0.0026$] (Figure 4).

Median OS was not reached in the low-risk group,19.6 months (95% CI: 10.0–20.7 months) in the intermediate-risk group and 12.2 months (95% CI: 2.9–21.9 months) in the high-risk group [low-risk HR: 0.13 (95% CI: 0.04–0.42), intermediate-risk HR: 0.63 (95% CI: 0.21–1.85), high-risk HR: 1 (reference group), $p = 0.0154$] (Figure 5).

4 | Discussion

This is the first real-world study to propose and validate a prognostic index, named the MAGIC-D index, for stratifying patients with BTC who are candidate for first-line therapy with CGD. The MAGIC-D index allows for the stratification of patients into three risk groups with different survival outcomes.

Patients with a score from 0 to 2, in the low-risk group, presented a maximum of two of the parameters used to construct the MAGIC-D index, including patients with metastatic or locally advanced disease and preserved liver function. These patients achieved an OS of 18.4 months and a PFS of 11.7 months, which are longer than those reported in the pivotal phase III

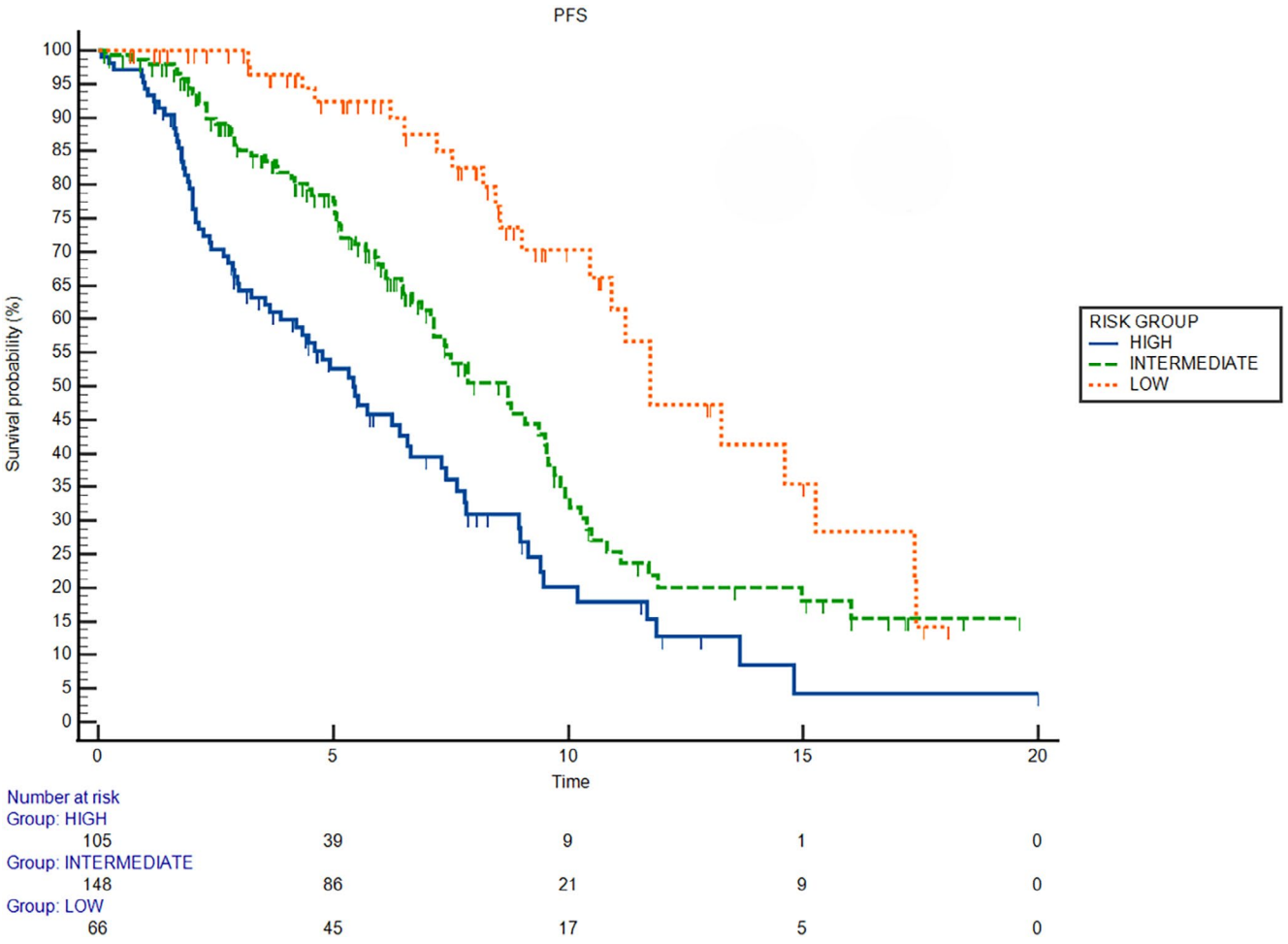

FIGURE 1 | Progression-free survival of risk groups in accordance with MAGIC-D index in the training cohort.

TOPAZ-1 trial [3] and in the currently available real-world analyses [40–46].

In contrast, high-risk group patients achieved a median OS of 7.8 months and a median PFS of 5.4 months, figures that are lower than the median OS of approximately 1 year reported in both real-world studies and in the TOPAZ-1 trial. All high-risk group patients presented distant metastases or other negative prognostic factors, including a reduction in liver function (albumin decreased levels and GGT increased levels) as well as a high disease burden (elevated CEA levels) at the time of starting first-line therapy. The negative prognostic role of these parameters has already been extensively investigated in several studies involving patients with BTC undergoing surgical resection or first-line therapy with cisplatin and gemcitabine [20–32].

In recent years, there has been an increasing number of studies highlighting the correlation between immune system activity, carcinogenesis and the effectiveness of anticancer treatments. NLR is representative of the state of activation of the immune system [30, 47–52]. An elevated NLR can result from lymphopenia or neutrophilia. Lymphopenia can lead to an ineffective immune system response to tumour cells [53], while neutrophilia is associated with the high release of cytokines by macrophages recruited to the tumour microenvironment, contributing to a chronic inflammatory state where the perpetually active immune system undergoes functional exhaustion [54]. Several studies have demonstrated the prognostic role of NLR in patients with BTC treated with first-line cisplatin and gemcitabine or undergoing surgical resection [20, 22, 25, 27–29]. This finding was confirmed by our previous works, which demonstrated that NLR is a prognostic factor for patients treated with first-line chemoimmunotherapy [40, 42, 43].

There was no difference in ORR, while the DCR was significantly different among the three risk groups. These results are consistent with the three-year survival analysis of the phase III TOPAZ-1 trial that showed that the DCR, not the response rate, was correlated with prognosis [4]. Another interesting finding highlighted by our analysis is that a lower percentage of high-risk group patients accessed second-line therapy, probably due to their worse clinical conditions, not allowing the use of subsequent anticancer treatments. However, there was no significant difference in terms of OS for subsequent anticancer treatments across the three risk groups. This suggests that the outcome obtained with first-line therapy determines the observed difference in OS across the three risk groups, regardless of second-line therapy. Indeed, second-line therapy for patients with BTC without targetable gene alterations still represents an unmet clinical need, offering only modest results as shown by a recent analysis published by our research group, which reported a median OS

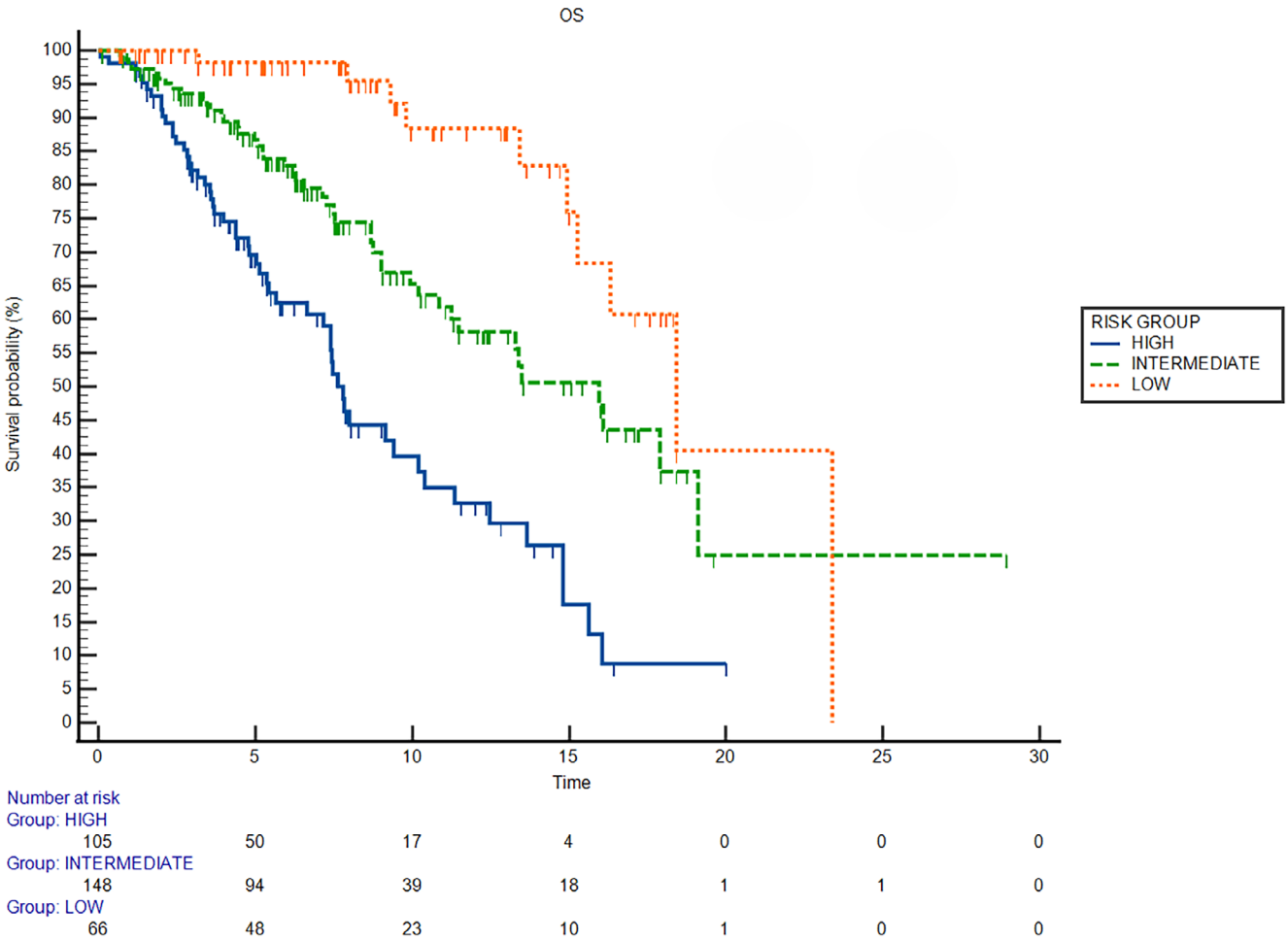

FIGURE 2 | Overall survival of risk groups in accordance with MAGIC-D index in the training cohort.

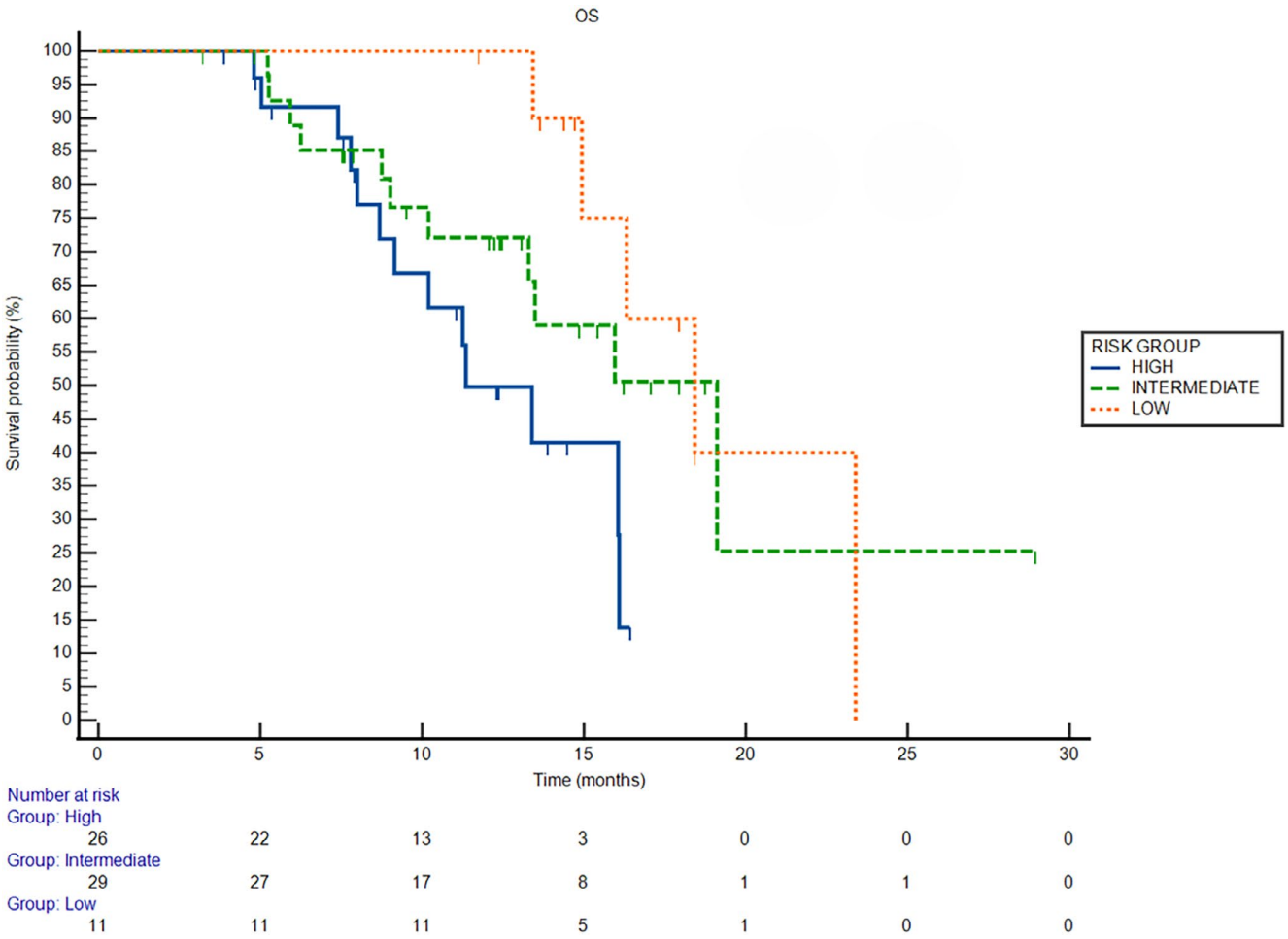

FIGURE 3 | Overall survival for subsequent anticancer treatments of risk groups in accordance with MAGIC-D index in the training cohort.

TABLE 4 | Safety profiles of the three risk groups.

Adverse event	Low-risk group no. (%)	Intermediate-risk group no. (%)	High-risk group no. (%)	*p*
Any toxicity	58 (87.9%)	132 (89.2%)	95 (90.5%)	0.8634
Any toxicity G > 2	33 (50.0%)	63 (42.6%)	47 (44.8%)	0.6006
Decreased appetite	12 (18.2%)	39 (26.3%)	31 (29.5%)	0.2478
Fatigue	33 (50.0%)	84 (56.7%)	56 (53.3%)	0.6407
Fever	12 (18.2%)	29 (19.6%)	30 (28.6%)	0.1605
Neuropathy	8 (12.1%)	14 (9.4%)	6 (5.7%)	0.3266
Nausea	24 (36.4%)	62 (41.9%)	28 (26.7%)	**0.0447**
Vomiting	10 (15.1%)	22 (14.9%)	11 (10.5%)	0.5450
Diarrhoea	11 (16.7%)	27 (18.2%)	11 (10.5%)	0.2277
Constipation	12 (18.2%)	39 (26.3%)	22 (20.9%)	0.3575
Anaemia	34 (51.5%)	67 (45.3%)	51 (48.6%)	0.6815
Leukopenia	20 (30.3%)	45 (30.4%)	19 (18.1%)	0.0586
Neutropenia	36 (54.5%)	77 (52.0%)	29 (27.6%)	**0.0001**
Thrombocytopenia	26 (39.4%)	47 (31.7%)	48 (45.7%)	0.0758

(Continues)

TABLE 4 | (Continued)

Adverse event	Low-risk group no. (%)	Intermediate-risk group no. (%)	High-risk group no. (%)	*p*
Thrombocytosis	3 (4.5%)	11 (7.4%)	7 (6.7%)	0.7333
Alt IV	11 (16.7%)	33 (22.3%)	29 (27.6%)	0.2455
Immunotoxicity	13 (19.7%)	37 (25.0%)	24 (22.8%)	0.6940
Hypothyroidism	2 (3.0%)	11 (7.4%)	7 (6.7%)	0.4613
Hyperthyroidism	0 (0%)	2 (1.3%)	1 (0.9%)	0.6392
Rash	5 (7.6%)	18 (12.2%)	7 (6.7%)	0.2860
Itching	7 (10.6%)	22 (14.9%)	8 (7.6%)	0.1994
Colitis	1 (1.5%)	4 (2.7%)	0 (0%)	0.2335
Other immunotoxicity	8 (12.1%)	10 (6.7%)	7 (6.7%)	0.3473
Other toxicity	6 (9.1%)	20 (13.5%)	17 (16.2%)	0.4165

Note: Bold values indicate statistically significant.
Abbreviations: ALT, alanine transaminase; G, grade; IV, increased value; NV, normal value.

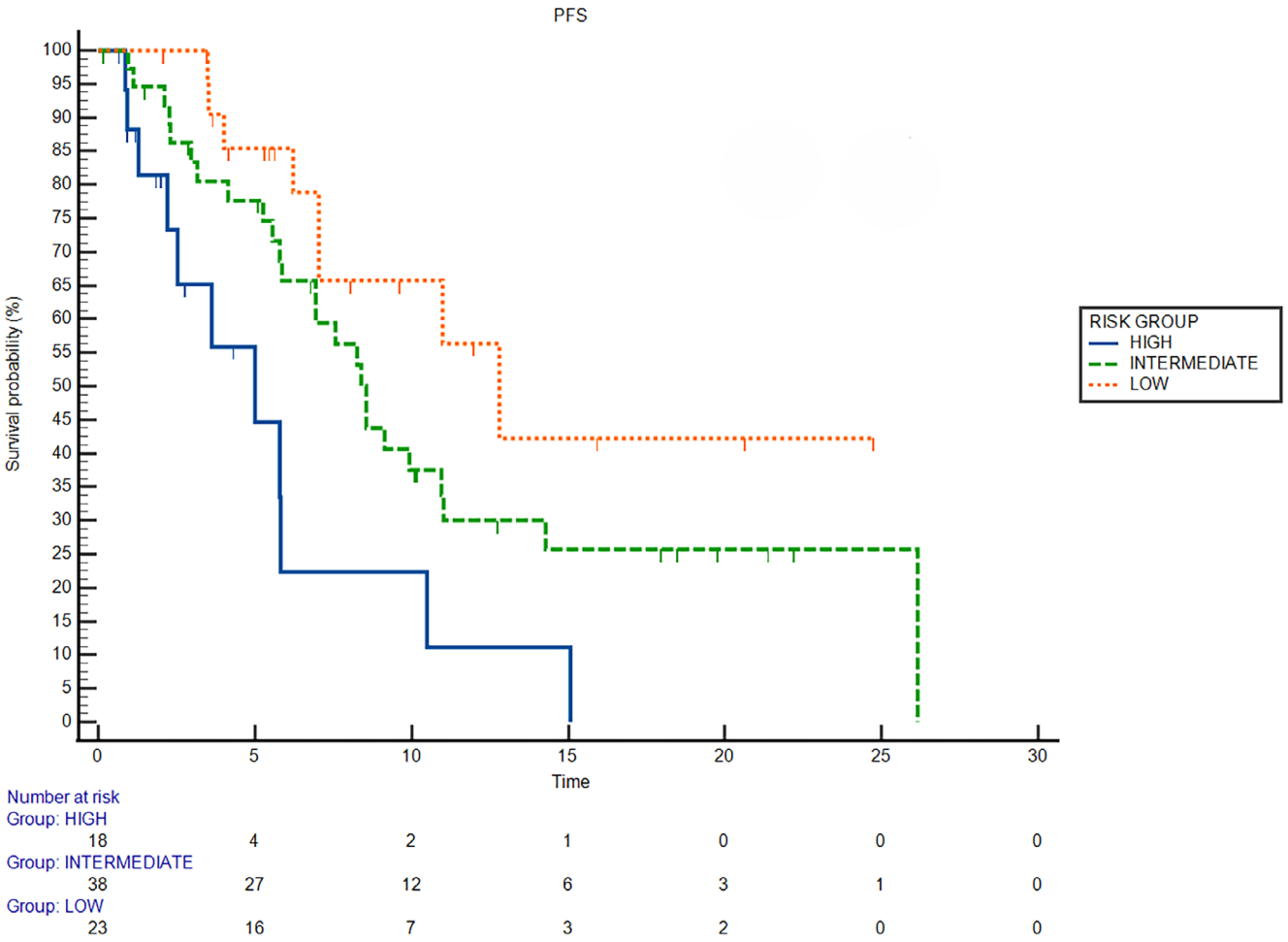

FIGURE 4 | Progression-free survival of risk groups in accordance with MAGIC-D index in the validation cohort.

of 6.2 months in patients treated with second-line chemotherapy after progression to CGD [43].

A noteworthy aspect for daily clinical practice is that no differences in terms of immune-related AEs were observed across the three groups, confirming the good safety profile of chemoimmunotherapy, even in high-risk group patients. The only differences reported concerned AEs typically related to chemotherapy, neutropenia, and nausea, which were less frequent in the high-risk group. This is probably due to the shorter treatment duration and

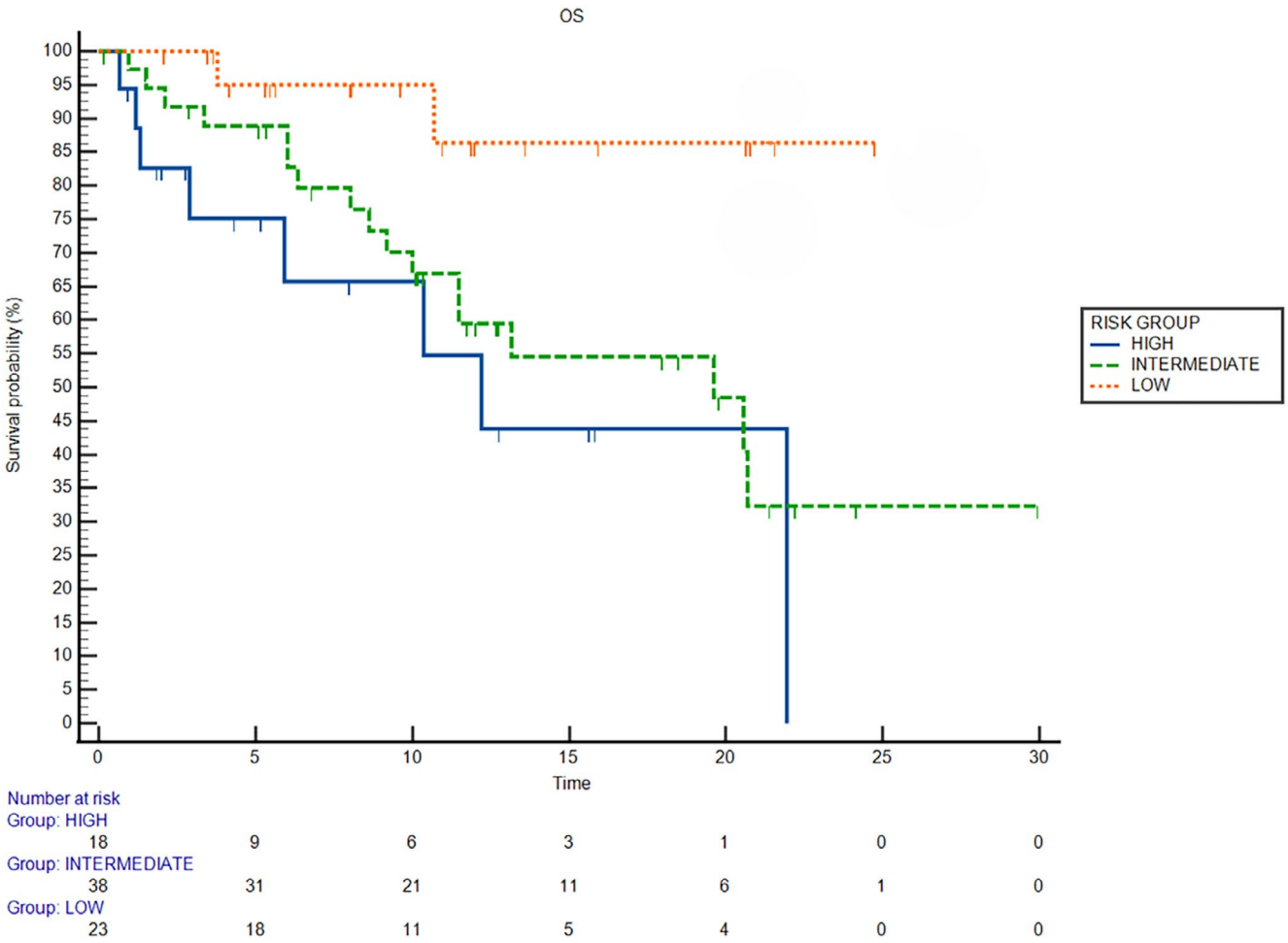

FIGURE 5 | Overall survival of risk groups in accordance with MAGIC-D index in the validation cohort.

the reduction in chemotherapy dose implemented during the treatment of these patients.

The MAGIC-D index is not the first prognostic index developed for patients with BTC treated with chemoimmunotherapy. In fact, in 2023, Zhang et al. published a retrospective analysis on 229 Chinese patients, developing and validating a prognostic nomogram based on NLR, monocyte-to-lymphocyte ratio, platelet-to-lymphocyte ratio, systemic inflammatory index and controlling nutritional status scores. In contrast to our study, the population included was made up exclusively of Chinese patients and was extremely heterogeneous from a therapeutic perspective, including patients treated with different chemoimmunotherapy combinations [39].

An interesting aspect of our analysis is the evidence of a worse OS for patients with intrahepatic CCA compared to those with extrahepatic origin. This result contrasts with previous literature suggesting a better prognosis in patients with intrahepatic CCA treated with cisplatin and gemcitabine [55–57]. However, this is not an entirely surprising result, as it has also been observed in a phase I/II trial of patients with BTC treated with oxaliplatin, gemcitabine and nab-paclitaxel [58].

The survival outcomes reported in the overall cohort of our study are superior to those observed in the phase III TOPAZ-1 trial. Randomised clinical trials often apply very strict inclusion criteria, leading to the hyper-selection of patients in good clinical conditions, typically with no significant comorbidities. This could lead us to expect worse outcomes when treating less-selected patients in real-world settings. However, the opposite is often observed, with the same treatment performing better in patients treated outside the stringent setting of a randomised clinical trial. One possible explanation for this phenomenon is that, in the absence of effective second-line therapeutic options for patients without targetable genetic alterations, those treated outside of randomised clinical trials may receive additional locoregional procedures in the event of oligoprogression or an excellent response to first-line therapy, with the aim of extending the benefits deriving from first-line chemoimmunotherapy. Additionally, the learning curve associated with the management of novel therapeutic combinations in patients with BTC, such as first-line chemoimmunotherapy, should also be considered. As clinicians gain experience, they become increasingly skilled in managing AEs, allowing for the use of supportive therapies that can prevent the permanent discontinuation of potentially highly effective treatments.

Our study has several limitations. First, its retrospective nature may introduce selection bias. Additionally, as a multicenter study, response evaluation and the timing of assessment were performed at the discretion of individual physicians, leading to variability

that may have impacted PFS, DCR and ORR estimates and to a missing data rate in the overall population included in the multivariate analysis. The median FU is quite short, 8.5 months, much shorter than the median OS achieved. This is a known strong limitation when building a prognostic model. Another limitation of the study is that there is currently no established consensus on the optimal cutoff value for NLR in clinical practice. However, much of the available literature on patients with BTC treated with first-line therapy has identified an NLR cutoff value of 3 as a significant prognostic factor [20, 27, 28, 40, 42, 43].

In conclusion, despite these limitations and considering the large population on which it was analysed the MAGIC-D index is a potentially useful tool comprised of factors widely used in clinical practice. It can better stratify patients with BTC who are candidates for combination therapy with CGD from a prognostic standpoint. However, its predictive role should be investigated by applying it to patients treated with other available first-line therapies.

Author Contributions

Conception and design: Mara Persano, Andrea Casadei-Gardini, Margherita Rimini, Lorenza Rimassa, Lorenzo Fornaro. Acquisition of data (acquired and managed patients): All authors. Analysis and interpretation of data: Mara Persano, Andrea Casadei-Gardini, Margherita Rimini, Lorenza Rimassa, Lorenzo Fornaro. Writing, review and/or revision of the manuscript: Mara Persano, Andrea Casadei-Gardini, Margherita Rimini, Lorenza Rimassa, Lorenzo Fornaro. Final approval of manuscript: All authors.

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Disclosure

Institutional Review Board Statement: The Ethical Review Board of each Institutional Hospital approved the present study. This study was performed in line with the principles of the Declaration of Helsinki.

Ethics Statement

The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Ethics Committee of each institution involved in the project. Under the condition of retrospective archival tissue collection and patients' data anonymisation, our study was exempted from the acquisition of informed consent from patients by the institutional review board.

Consent

Written informed consent for treatment was obtained for all patients.

Conflicts of Interest

L.R. received consulting fees from AbbVie, AstraZeneca, Basilea, Bayer, BMS, Eisai, Elevar Therapeutics, Exelixis, Genenta, Hengrui, Incyte, Ipsen, IQVIA, Jazz Pharmaceuticals, MSD, Nerviano Medical Sciences, Roche, Servier, Taiho Oncology, Zymeworks; lecture fees from AstraZeneca, Bayer, BMS, Guerbet, Incyte, Ipsen, Roche, Servier; travel expenses from AstraZeneca and Servier; research grants (to Institution) from AbbVie, Agios, AstraZeneca, BeiGene, Eisai, Exelixis, Fibrogen, Incyte, Ipsen, Jazz Pharmaceuticals, Lilly, MSD, Nerviano Medical Sciences, Roche, Servier, Taiho Oncology, TransThera Sciences, Zymeworks. A.C.-G. reports consulting fees from AstraZeneca, Bayer, BMS, Eisai, Incyte, Ipsen, IQVIA, MSD, Roche, Servier; lecture fees from AstraZeneca, Bayer, BMS, Eisai, Incyte, Ipsen, Roche, Servier; travel expenses from AstraZeneca; research grants (to Institution) from AstraZeneca, Eisai. S.L.C. serves an advisory member for AstraZeneca, MSD, Eisai, BMS, Ipsen and Hengrui, received research funds from MSD, Eisai, Ipsen, SIRTEX, and Zailab, and honoraria from AstraZeneca, Eisai, Roche, Ipsen and MSD. T.P. received consulting fees from Bayer, Ipsen and AstraZeneca; institutional research funding from Roche, Bayer and AstraZeneca; travel expenses from Roche. C.B. received honoraria as speaker (Astrazeneca, Incyte, Servier) and consultant (Incyte, Servier, Boehringer Ingelheim, Astrazeneca, Tahio, Jazz), received research funds (Avacta, Medannex, Servier) and her spouse is an employee of Astrazeneca. M.I. reports honoraria from AstraZeneca, Chugai Pharma, Eisai, Incyte, Lilly Japan, MSD, Novartis, Ono Pharmaceutical, Takeda, Teijin Pharma, Nihon Servier, Taiho and research funding from AstraZeneca, Bayer, Bristol-Myers Squibb, Chiome Bioscience, Chugai, Eisai, Eli Lilly Japan, Delta-Fly Pharma, Invitae, J-Pharma, Merck biopharma, Merus N.V., MSD, Novartis, Nihon Servier, Ono, Syneos Health and Rakuten Medical. G.W.P. reports advisories and/or speaker fees for Servier, Bayer, Roche Amgen, Merck, MSD, BMS, Sanofi, Lilly, Astra Zeneca, Astellas, Pierre-Fabre, Incyte, Arcus, CECOG. F.F. has received travel support from Ipsen, Abbvie, Astrazeneca and speaker's fees from AbbVie, MSD, Ipsen, Astrazeneca. L.P. reports advisory role for AstraZeneca, Servier, Travel expenses: AstraZeneca, Ipsen. G.G. reports consulting fees for Astra Zeneca, MSD, Servier, Seagen, Bayer, Amgen, Novartis, Ipsen, BMS; Travel Expenses: Astra Zeneca, Servier, Bayer, Novartis. S.L. reports personal honoraria as an invited speaker from Amgen, Astra Zeneca, Bristol-Myers Squibb, Incyte, GSK, Lilly, Merck Serono, MSD, Pierre-Fabre, Roche, Servier; participation in an advisory board for Amgen, Astellas, Astra Zeneca, Bayer, Bristol-Myers Squibb, Daiichi-Sankyo, GSK, Incyte, Lilly, Merck Serono, MSD, Servier, Takeda, Rottapharm, Beigene, Fosun Pharma, Nimbus Therapeutics. J.D. received consulting fees and/or speaker honoraria from Amgen, AstraZeneca, Bayer, BMS, Eisai, Need Inc., Ipsen, Lilly, MediMix, Merck, MSD, Novartis, Roche and Servier. J.A. received consulting fees from AstraZeneca, Jazz Pharmaceuticals, MSD, Roche, Servier, Taiho Oncology, Zymeworks; lecture fees from AstraZeneca, Roche, Servier; travel expenses from AstraZeneca, Roche, Servier. N.C. received consulting fees and/or speaker honoraria from AstraZeneca, Novartis, Roche and Servier. A.P. received consulting fees from AstraZeneca, Amgen and MSD; travel expenses from Merck, Daiichi-Sankio and Accord. S.C. reports consulting fees and/or speaker honoraria from Amgen, AstraZeneca, Merck Serono and Daiichi-Sankyo; travel expenses from AstraZeneca, Incyte, MSD, Roche, Viatris. G.T. received speaker honoraria from AstraZeneca and is supported by a Short Term Scientific Mission grant from the Precision-BTC-Network (COST Action 22125). G.P.S. reports consulting fees and/or speaker honoraria from BMS, Janssen, Novartis, Roche, Bayer. M.N. reports travel expenses from AstraZeneca, speaker honoraria from Accademia della Medicina, Incyte and Servier; honoraria from Sandoz, Medpoint SRL, Incyte, AstraZeneca and Servier for editorial collaboration; consulting honoraria from EMD Serono, Basilea Pharmaceutica, Incyte, MSD Italia, Servier, Astrazeneca and Taiho. All remaining authors declare no conflicts of interest.

Data Availability Statement

Data available on request from the authors.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.