REVIEW

Prognostic and therapeutic implications of Ki-67, BCL-2, HER2, and PD-L1 in signet ring cell carcinoma: A narrative review

ANAR TULYAYEVA[1], MARZHAN AITMAGAMBETOVA[1], NURGUL KEREYEVA[1], ARIP KOISHYBAEV[1], SAULE AKHMETOVA[2] AND NURGUL ABLAKIMOVA[3,4]

[1]Department of Oncology, West Kazakhstan Marat Ospanov Medical University, Aktobe, Kazakhstan; [2]Department of Pathological Anatomy and Forensic Medicine, West Kazakhstan Marat Ospanov Medical University, Aktobe, Kazakhstan; [3]Department of Pharmacology, Clinical Pharmacology, West Kazakhstan Marat Ospanov Medical University, Aktobe, Kazakhstan; [4]Department of Hospital Pharmacy, Regional Perinatal Center, Aktobe, Kazakhstan

ABSTRACT

Background and aim: Signet ring cell carcinoma (SRCC) is a biologically aggressive subtype of adenocarcinoma characterized by diffuse growth, early dissemination, and limited response to conventional therapies. Despite its clinical relevance, SRCC remains underrepresented in biomarker-focused research. This narrative review summarizes and critically appraises current evidence on the expression and clinical significance of key molecular biomarkers in SRCC across different anatomical sites.

Methods: A comprehensive narrative literature review was conducted using major biomedical databases, including Scopus and Web of Science. Studies evaluating the prognostic and therapeutic implications of Ki-67 antigen (Ki-67), B-cell lymphoma 2 (BCL-2), human epidermal growth factor receptor 2 (HER2), and programmed death-ligand 1 (PD-L1) in SRCC of gastric, colorectal, breast, and other origins were identified, screened, and qualitatively synthesized.

Results: Available evidence indicates that elevated Ki-67 expression is generally associated with aggressive tumor behavior and poorer outcomes, although pronounced intratumoral heterogeneity limits the use of uniform cut-off values. BCL-2 expression demonstrates marked site- and context-dependent variability and is frequently absent in gastric SRCC, reducing its value as an isolated prognostic marker. HER2 amplification is rare in SRCC, restricting the applicability of HER2-targeted therapies to molecularly confirmed exceptional cases.

Received: 13 December 2025 | Accepted: 13 January 2026

Correspondence: Saule Akhmetova, MD, Candidate of Medical Sciences
Department of Pathological Anatomy and Forensic Medicine, West Kazakhstan Marat Ospanov Medical University
Maresyev 68030000, Aktobe, Kazakhstan / E-mail: saule_7018@mail.ru
ORCID: 0000-0001-6508-7790

In contrast, PD-L1 expression, particularly when integrated with immune microenvironment features or circulating biomarkers such as exosomal PD-L1, may identify subsets of patients with potential sensitivity to immune checkpoint inhibition.

Conclusions: Individual biomarkers in SRCC should not be interpreted in isolation. An integrated, context-aware evaluation of proliferative, apoptotic, oncogenic, and immune markers more accurately reflects SRCC biology and may improve prognostic stratification and therapeutic decision-making. (www.actabiomedica.it)

Key words: carcinoma, signet ring cell, Ki-67 antigen, proto-oncogene proteins c-bcl-2, receptor, ErbB-2, programmed cell death 1 ligand 1 protein

Introduction

Signet ring cell carcinoma (SRCC) is a distinct histological subtype of adenocarcinoma characterized by the presence of tumor cells containing abundant intracytoplasmic mucin that displaces the nucleus to the periphery, creating a signet ring appearance (1). SRCC most commonly arises in the stomach but can also occur in other organs such as the colon, breast, and bladder (2, 3). Notably, over 96% of SRCC cases originate in the stomach (4). More recent studies indicate that SRCC accounts for approximately 16.8% of all gastric cancer cases (5). This carcinoma type is often associated with an aggressive clinical course, late-stage diagnosis, and poor prognosis, largely due to its diffuse growth pattern and frequent early metastatic spread (6). This upward trend contrasts with the overall declining incidence of gastric cancer, suggesting unique etiological factors and highlighting the need for focused research on SRCC. The biological behavior of SRCC differs significantly from that of conventional adenocarcinomas. SRCC is typically less cohesive, promoting early invasion and dissemination. In many cases, it demonstrates resistance to standard chemotherapy, making clinical management challenging (7). Furthermore, its molecular profile tends to differ, with a lower incidence of traditional actionable targets such as human epidermal growth factor receptor 2 (HER2) overexpression, complicating the development of effective targeted therapies (8). In the era of precision oncology, the identification and characterization of molecular biomarkers have become crucial for improving diagnostic accuracy, prognostic stratification, and the development of personalized therapeutic strategies. Biomarkers such as Ki-67 antigen (Ki-67), B-cell lymphoma 2 (BCL-2), HER2, and programmed death-ligand 1 (PD-L1) have emerged as important factors in various malignancies, offering insights into tumor proliferation, apoptosis regulation, oncogenic signaling, and immune evasion (9, 10). Understanding their expression patterns and clinical significance in SRCC could provide new opportunities for prognosis assessment and treatment optimization. The aim of this review is to summarize current knowledge on the expression and clinical significance of Ki-67, BCL-2, HER2, and PD-L1 in SRCC, highlighting their potential roles in prognosis prediction, therapeutic decision-making, and the development of novel targeted treatment strategies. Ki-67, BCL-2, HER2, and PD-L1 were selected as the focus of this review because they collectively represent core biological processes relevant to SRCC and are routinely assessable in clinical practice. Together, these biomarkers provide complementary information on tumor proliferation, regulation of apoptosis, oncogenic signaling, and immune evasion, thereby offering clinically translatable insights beyond diagnostic classification alone.

Methods

This study is a narrative review aimed at synthesizing and integrating current literature on the prognostic and therapeutic significance of Ki-67, BCL-2, HER2,

and PD-L1 expression in SRCC. A narrative review methodology was chosen to accommodate the inherently heterogeneous and multidisciplinary nature of the topic, which spans pathology, medical oncology, molecular biology, and immuno-oncology. Unlike systematic reviews, which apply strict inclusion criteria and quantitative synthesis, narrative reviews allow a broader and more flexible exploration of complex themes, facilitating the integration of diverse study designs and mechanistic insights in the context of a rare malignancy. A comprehensive literature search was conducted in the Scopus and Web of Science databases. The search covered all records from database inception through December 2025. The following combination of free-text terms and Boolean operators was used: "signet ring cell carcinoma" AND ("Ki-67" OR "Ki67" OR "MKI67" OR "BCL-2" OR "Bcl2" OR "HER2" OR "ErbB-2" OR "ERBB2" OR "PD-L1" OR "programmed death-ligand 1" OR "CD274" OR "biomarkers" OR "molecular markers" OR "immunohistochemistry" OR "prognosis"). No restrictions were applied regarding publication year, language, or study design to maximize sensitivity for this rare histologic subtype. Studies were considered eligible if they (1) reported SRCC originating from any anatomical site (e.g., stomach, colorectum, breast, pancreas, urinary tract, or esophagogastric junction), and (2) provided data on expression patterns, prognostic relevance, or therapeutic implications of at least one of the four biomarkers (Ki-67, BCL-2, HER2, PD-L1). Eligible publication types included full-text original research articles, clinical trials, retrospective cohort studies, case series, case reports with detailed immunohistochemical profiling, and review articles with explicit data on SRCC. Conference abstracts without full text, purely preclinical in vitro or animal studies without clear translational relevance to SRCC, and papers on non-epithelial neoplasms with signet-ring–like morphology were excluded from the core analysis but could be considered separately for illustrating diagnostic pitfalls. After removal of duplicates, titles and abstracts were screened for relevance to SRCC and to at least one of the four biomarkers. Full-text articles meeting inclusion criteria were then assessed for methodological quality and clinical relevance. Methodological quality and clinical relevance were assessed qualitatively as part of a narrative synthesis, with attention to study design, clarity of SRCC definition, biomarker assessment methods, and linkage to clinically meaningful outcomes. Studies with notable methodological limitations were not excluded but were interpreted with caution in the context of the overall evidence base. Data from selected studies were extracted and organized thematically according to biomarker (Ki-67, BCL-2, HER2, PD-L1), anatomical site, assessment methods (immunohistochemistry, in situ hybridization, molecular assays, liquid biopsy), cut-off definitions, and reported associations with clinicopathologic features, prognosis, or treatment response. Given the marked heterogeneity in study design, biomarker assessment, and outcome measures, no formal quantitative synthesis or meta-analysis was performed; instead, findings were qualitatively appraised and summarized narratively, with emphasis on convergent and divergent results across studies. To enhance methodological rigor and transparency, the review was prepared in accordance with the SANRA (Scale for the Assessment of Narrative Review Articles) criteria (11), addressing justification of the review's relevance, transparency of the search strategy, scientific reasoning, adequacy of referencing, and the strength and usefulness of conclusions.

Results and discussion

Molecular biomarkers in signet ring cell carcinoma: Biological context and methodological considerations

Molecular markers, also known as biomarkers, have revolutionized the field of oncology by offering critical insights into tumor biology, prognosis, and therapeutic strategies. These markers are molecules – such as proteins, genes, or specific mutations – found in tumor tissue, blood, or other body fluids, that can help detect cancer, predict its behavior, and guide treatment choices. Cancer development is a multistep process characterized by genetic alterations that affect cellular proliferation, apoptosis, invasion, and metastasis. Molecular markers reflect these alterations, serving as measurable indicators of specific biological processes or responses to therapy. Molecular markers in SRCC can be broadly classified into several categories based on their clinical utility (Table 1).

Table 1. Categories of Molecular Markers in Cancer and Their Clinical Utility in Signet Ring Cell Carcinoma.

Category	Definition	Representative Markers	Clinical Utility in SRCC	References
Diagnostic markers	Identify cancer presence and assist in distinguishing histological subtypes	Cytokeratins (CK7, CK20), CDX2, E-cadherin	Differentiate SRCC from poorly differentiated adenocarcinomas; E-cadherin loss is a hallmark of SRCC, aiding diagnosis.	(12-14)
Prognostic markers	Indicate likely disease course independent of treatment	Ki-67, BCL-2, p53	High Ki-67 labeling index correlates with poor prognosis; BCL-2 overexpression may indicate apoptotic resistance and worse outcome.	(15-18)
Predictive markers	Predict response to specific therapeutic interventions	HER2, PD-L1, MSI, EGFR	HER2 amplification may predict benefit from trastuzumab; PD-L1 expression suggests potential response to immune checkpoint inhibitors (e.g., pembrolizumab).	(2, 19-21)
Therapeutic targets	Molecules that can be targeted with specific agents	HER2, PD-L1, VEGF	Enables personalized therapy; HER2-targeted agents (trastuzumab) and PD-1/PD-L1 inhibitors (nivolumab) are under clinical evaluation in gastric SRCC.	(22, 23)
Proliferation markers	Reflect tumor growth rate and mitotic activity	Ki-67, MCM2	Ki-67 proliferation index is associated with SRCC aggressiveness and metastatic potential, particularly in gastric and colorectal origin.	(12, 24)
Apoptosis regulators	Regulate programmed cell death, influencing tumor survival and chemoresistance	BCL-2, BAX, survivin	Dysregulated apoptosis contributes to resistance; BCL-2 overexpression may reduce chemosensitivity in SRCC and other diffuse-type carcinomas.	(17, 25)
Immune checkpoint markers	Inhibit anti-tumor immunity via T-cell regulation	PD-L1, CTLA-4	High PD-L1 expression in tumor cells or immune infiltrates may support use of checkpoint blockade; important in microsatellite-stable (MSS) SRCC as well.	(26, 27)
MMR/MSI markers	Reflect defects in DNA mismatch repair mechanisms, often with therapeutic implications	MLH1, MSH2, MSH6, PMS2 (MSI-H status)	MSI-H status may be rare in SRCC, but when present, it predicts favorable response to immunotherapy and suggests a distinct tumor biology.	(28, 29)

Abbreviations: SRCC – signet ring cell carcinoma, CK7/CK20 - cytokeratin 7 / cytokeratin 20, CDX2 – caudal type homeobox 2, MSI – microsatellite Instability, MMR – mismatch repair, MSI-H – microsatellite instability-high, HER2 – human epidermal growth factor receptor 2, PD-L1 – programmed death-ligand 1, PD-1 – programmed death-1, CTLA-4 – cytotoxic t-lymphocyte associated protein 4, EGFR – epidermal growth factor receptor, VEGF – vascular endothelial growth factor, Ki-67 – marker of proliferation Kiel 67, p53 – tumor protein 53, BCL-2 - B-cell lymphoma 2, BAX – BCL-2 associated X protein, MCM2 – minichromosome maintenance complex component 2, MLH1/MSH2/MSH6/PMS2 – MutL homolog 1 / MutS homolog 2 / MutS homolog 6 / postmeiotic segregation increased 2

Some of the most important molecular markers include proliferation markers like Ki-67, anti-apoptotic proteins like BCL-2, oncogenes such as HER2, and immune regulatory proteins like PD-L1 (Figure 1). These markers not only deepen our understanding of tumor aggressiveness and potential for metastasis but also identify patients who are more likely to benefit from targeted therapies or immunotherapies.

Advancements in molecular techniques such as immunohistochemistry, next-generation sequencing, and liquid biopsy have enhanced the detection and analysis of these markers, making them an integral part of modern oncology practice. Incorporating molecular marker assessment into routine clinical workflows enables oncologists to offer more accurate diagnoses, predict outcomes more reliably, and choose treatments tailored to individual tumor profiles. Across anatomical sites, SRCC comprises biologically heterogeneous entities. Biomarker expression is influenced by histologic composition (pure SRC vs mixed tumors with non–signet-ring components), molecular context (e.g., CDH1 alterations, MSI status, immune microenvironment), and tumor stage and sampling (biopsy vs resection, intratumoral heterogeneity). Therefore, cross-study comparisons require careful attention to detection methods, scoring systems, and cut-off thresholds, which remain non-uniform across SRCC-focused literature (Table 2).

As research continues, the list of actionable molecular markers in SRCC is rapidly expanding, paving the way for more effective, less toxic, and more personalized cancer care. The following sections therefore examine Ki-67, BCL-2, HER2, and PD-L1 individually, with particular emphasis on SRCC-specific biology, methodological variability, and their prognostic and therapeutic implications.

Ki-67 in signet ring cell carcinoma

Ki-67 is a nuclear protein encoded by the *MKI67* gene, commonly used as a marker for cellular proliferation. It is expressed during all active phases of the cell cycle (G1, S, G2, and mitosis), but is absent in resting cells (G0), making it a valuable tool in

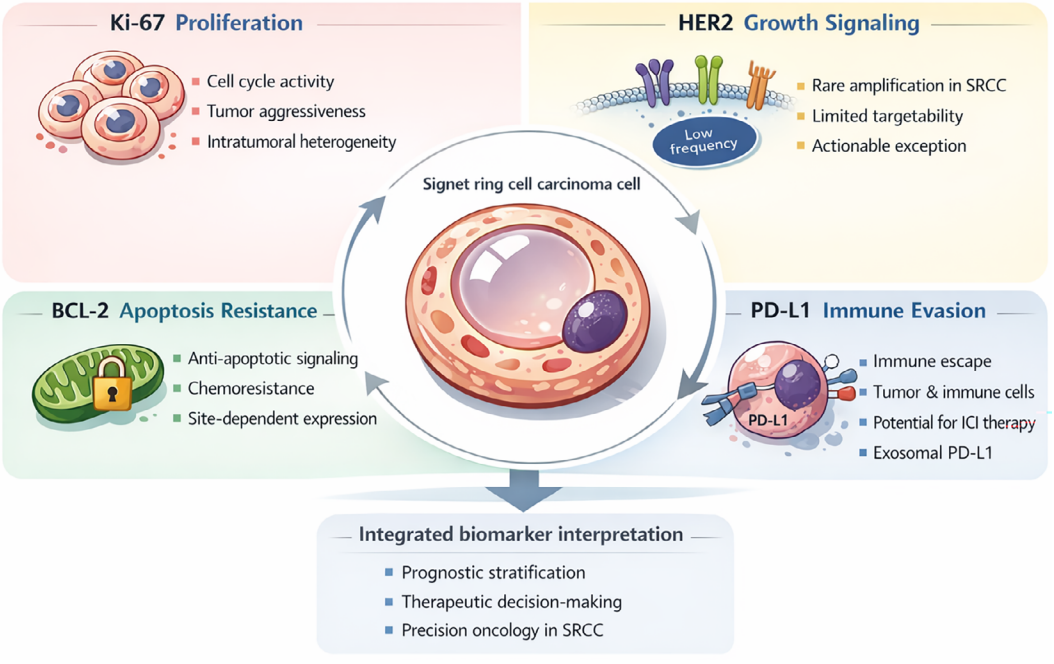

Figure 1. Biological roles and clinical implications of Ki-67, BCL-2, HER2, and PD-L1 in signet ring cell carcinoma. Figure created with AI-assisted illustration tools (ChatGPT, OpenAI; GPT-5.2), followed by author editing.

Table 2. Methodological heterogeneity across SRCC biomarker studies

Biomarker	Main assay(s) reported	Common scoring system	Typical cut-offs used in cited SRCC studies (range)	Key pitfalls in SRCC	Practical interpretive note
Ki-67	IHC (MIB-1)	IHC (22C3, 28-8, SP263 depending on study/trial)	Heterogeneous across studies; commonly dichotomized using study-specific thresholds (often around ~10–50% LI) rather than a single validated cut-off in SRCC	Intratumoral heterogeneity (hotspots), biopsy vs resection sampling, mixed histology (pure SRC vs mixed), stage-related biology; non-standardized counting fields and cut-points	Report Ki-67 as continuous LI when possible; if categorizing, explicitly state method (hotspots/fields) and justify threshold; interpret primarily as context marker (proliferation) rather than SRCC-specific actionable target
BCL-2	IHC (cytoplasmic)	% positive tumor cells ± intensity (semiquantitative); "positive" frequently defined by % threshold	Non-uniform, typically low thresholds (e.g., ≥5–10% positive tumor cells) in many solid tumor studies; SRCC-specific cut-offs are inconsistent and often extrapolated	SRCC often shows low/absent BCL-2 (site-dependent); mixing non-SRCC adenocarcinoma cohorts inflates perceived prevalence; cut-offs and antibodies vary; interpretive drift between "tumor-cell" vs stromal/immune signal	Avoid overstating "targetability": treat BCL-2 as supportive/apoptosis-context marker; emphasize that SRCC-specific evidence is limited and heterogeneous and clinical targeting is not validated in SRCC
HER2	IHC ± ISH/FISH (reflex)	Gastric/GEA HER2 IHC 0/1+/2+/3+ algorithm; 2+ = equivocal → reflex ISH	Clinically aligned with GEA algorithms: IHC 3+ = positive; IHC 2+ requires ISH; SRCC: true HER2 positivity is uncommon; equivocal/atypical patterns may require reflex testing beyond routine	Highest risk of misclassification in SRCC due to mucin-rich cytology and incomplete/artifactual membranous staining; heterogeneity; biopsy limitations; mixed tumors where non-SRC component drives positivity	In SRCC, treat HER2 positivity as an "actionable exception": confirm equivocal/atypical staining by ISH/FISH to prevent overtreatment; document histologic component scored (pure vs mixed)
PD-L1	IHC (22C3, 28-8, SP263 depending on study/trial)	CPS (combined positive score), sometimes TPS/IC; CPS includes tumor + immune cells in numerator	Cut-offs are trial/regulatory driven (commonly CPS ≥1, ≥5, ≥10 in gastric/GEJ contexts); SRCC-only thresholds are not harmonized	SRCC pitfalls: immune-rich microenvironment → CPS heavily influenced by immune cells; inter-reader variability at "borderline" CPS (esp. around 5); assay interchangeability not perfect; sampling (biopsy) may under/overestimate immune infiltrate	Use CPS definition and trial-relevant cut-offs with explicit assay; highlight that PD-L1 in SRCC is predictive-contextual, not a standalone biological classifier; recommend standardized reporting (assay + scoring + cut-off)

Abbreviations: SRCC – signet ring cell carcinoma, IHC – immunohistochemistry, ISH – in situ hybridization, FISH – fluorescence in situ hybridization, MIB-1 – monoclonal antibody against Ki-67 antigen, LI – labeling index, SRC – signet ring cell, GEA – gastroesophageal adenocarcinoma, CPS – combined positive score, TPS – tumor proportion score, IC – immune cell score, HER2 – human epidermal growth factor receptor 2, PD-L1 – programmed death-ligand 1.

ACTA BIOMED 2026; VOL. 97, N. 3: 18427 DOI: 10.23750/ABM.2026.18427

oncology for assessing tumor growth and aggressiveness (30). Functionally, Ki-67 is associated with the organization of the perichromosomal layer during mitosis and has been implicated in chromatin structure maintenance, although its precise mechanistic roles are still being elucidated (31). In the context of SRCC, a histologically distinct and often aggressive variant of adenocarcinoma characterized by mucin-producing cells with peripherally displaced nuclei, Ki-67 plays a critical role in evaluating tumor biology. These tumors typically exhibit a diffuse growth pattern, complicating early detection and contributing to a generally poor prognosis (1). Numerous studies have demonstrated the prognostic significance of Ki-67 in SRCC. Higher Ki-67 labeling indices (LI) are frequently associated with increased tumor proliferation, higher histologic grade, deeper invasion, and poorer overall survival (32, 33). In gastric SRCC, for instance, elevated Ki-67 expression correlates with lymphovascular invasion and advanced tumor stage, highlighting its potential utility in stratifying patient risk and guiding treatment decisions (34). Notably, a study analyzing gastric SRCC found that patients with a Ki-67 LI greater than 25% exhibited significantly higher rates of lymph node metastasis (70.1% vs. 45.0%, P = 0.025), larger tumor diameters (69.2% vs. 40.0%, P = 0.020), deeper wall invasion (92.3% vs. 72.5%, P = 0.048), and more advanced TNM stages (69.2% vs. 40.0%, P = 0.020) compared to those with Ki-67 LI at or below 25%. Furthermore, a Ki-67 LI exceeding 25% was associated with a markedly poorer 3-year survival rate (31.82% vs. 68.75%, P = 0.0146), reinforcing its role as a powerful prognostic indicator (35). Similarly, in colorectal SRCC, increased Ki-67 expression has been linked with greater tumor infiltration, higher rates of lymph node metastasis, and more frequent vascular invasion. These pathological features contribute collectively to a worse prognosis (9). The findings suggest that Ki-67 not only reflects tumor proliferative activity but may also play a role in enhancing the invasive and metastatic potential of SRCC, ultimately leading to diminished survival outcomes. However, the role of Ki-67 in SRCC is not entirely uniform across all studies. For example, a comparative analysis of 42 primary SRCC cases in the stomach and colorectum revealed universal Ki-67 expression, with a mean LI of 36% ± 23% in gastric SRCC and 47% ± 26% in colorectal SRCC, but without a direct link to patient outcomes (36). Additionally, another study on colorectal carcinomas noted a significantly lower Ki-67 index in SRCC (11%) compared to conventional adenocarcinoma (38.2%) and mucinous adenocarcinoma (28.3%), suggesting that SRCC may, in some contexts, exhibit lower proliferative activity (37). Moreover, a meta-analysis of 34 studies encompassing over 6,000 colorectal cancer patients concluded that high Ki-67 expression is generally associated with worse overall and disease-free survival. Nonetheless, the prognostic value varied by tumor subtype and cut-off thresholds, indicating that Ki-67's utility as a prognostic marker may depend on broader clinicopathological context (38). Mechanistically, Ki-67 is linked to pathways that drive tumor progression, including epithelial-to-mesenchymal transition (EMT), PI3K/Akt signaling, and suppression of apoptosis – all of which are relevant to SRCC's pathogenesis. EMT contributes to the invasive and metastatic capabilities of SRCC cells, often in association with loss of E-cadherin, a hallmark feature in these tumors (39). Ki-67 overexpression may indirectly reflect increased activation of these oncogenic pathways, serving as a surrogate marker of molecular aggressiveness. Practically, this means Ki-67 should be interpreted as a "context marker": its prognostic meaning is strongest when reported together with (i) depth of invasion/stage, (ii) tumor cellularity (mucin-rich vs. non-mucinous areas), and (iii) sampling strategy (biopsy vs resection), because SRCC often shows patchy proliferative hotspots rather than uniform labeling (36). Ki-67 is a critical marker for evaluating proliferative activity in SRCC. Its expression correlates with tumor aggressiveness and clinical outcomes, offering potential utility in patient stratification and therapeutic planning. Further studies exploring Ki-67-targeted interventions or its integration into multimodal biomarker panels may enhance the clinical management of this challenging carcinoma.

BCL-2 expression in signet ring cell carcinoma

BCL-2 is a key regulator of apoptosis, primarily functioning to inhibit programmed cell death and

promote cell survival. As an anti-apoptotic member of the BCL-2 protein family, it preserves mitochondrial membrane integrity by preventing the release of cytochrome c and the subsequent activation of caspases (40). Dysregulation of BCL-2 expression is frequently observed in various malignancies and has been implicated in cancer cell resistance to therapy, tumor progression, and poor clinical outcomes. In gastric SRCC, available data consistently demonstrate low or absent BCL-2 expression, highlighting a clear distinction from intestinal-type gastric adenocarcinoma. In a large cohort of 413 curatively resected gastric carcinomas, BCL-2 expression was detected in only 11.4% of cases, with 95% of BCL-2–positive tumors belonging to the intestinal type; notably, diffuse-type tumors, including signet ring cell carcinoma, were uniformly BCL-2–negative (41). Other studies have reported higher BCL-2 expression rates in gastric cancers. For instance, one study found BCL-2 expression in 55.7% of gastric cancer patients, with a significant correlation to the intestinal type according to Lauren's classification (42). Another study reported BCL-2 protein expression in 82% of gastric carcinoma cases, predominantly associated with intestinal-type tumors (43). These findings underscore that apparent discrepancies in reported BCL-2 expression largely reflect histologic composition and cohort heterogeneity, rather than true overexpression in gastric SRCC. In colorectal SRCC, BCL-2 expression appears to be variable. A study investigating colorectal carcinoma associated with schistosomiasis in Egypt found that 58.3% of cases with schistosomiasis were BCL-2 positive, compared to 33.3% of cases without schistosomiasis (44). Another study reported BCL-2 protein expression in 19 out of 22 colorectal adenocarcinomas and 12 out of 13 adenomas, suggesting a role for BCL-2 in promoting cell survival in colorectal tumors (45). However, specific data on BCL-2 expression in colorectal SRCC remain limited. In breast cancer, BCL-2 expression varies among molecular subtypes. A study analyzing 1,304 patients with breast cancer found BCL-2 expression in 54.4% of cases. By subtype, BCL-2 was expressed in 74% of hormone receptor-positive and HER2-negative cases, 10.7% of hormone receptor-positive and HER2-positive cases, 2.8% of hormone receptor-negative and HER2-positive cases, and 12.5% of triple-negative breast cancer cases. High BCL-2 expression was associated with favorable prognosis in luminal A breast cancer but did not show a prognostic relationship in other subtypes (46). Specific data on BCL-2 expression in breast SRCC are scarce, necessitating further investigation. Targeting BCL-2 in SRCC represents a theoretical or hypothesis-generating strategy extrapolated from other malignancies. B-cell lymphoma 2 Homology 3 (BH3) mimetics, such as venetoclax, are designed to inhibit BCL-2 and restore apoptotic sensitivity. In small-cell lung cancer (SCLC), venetoclax has demonstrated efficacy in tumors with high BCL-2 expression, inducing apoptosis and tumor regression in preclinical models (47). However, resistance to venetoclax can occur due to factors like Myeloid Cell Leukemia-1 (MCL-1) overexpression and low BCL2 associated X (BAX) levels. Combining BCL-2 and MCL-1 inhibitors has shown synergistic anti-tumor activity in resistant SCLC models (48). While these findings are encouraging, clinical evidence of venetoclax efficacy in SRCC remains limited, underscoring the need for further studies. For SRCC specifically, the most clinically “safe” way to use BCL-2 is as a supportive (not standalone) marker: gastric SRCC is often BCL-2–negative (so positivity should trigger re-check of subtype and panels), and strong BCL-2 positivity can be a red flag for mimickers (particularly lymphoid neoplasms with signet-ring–like vacuoles) rather than true epithelial SRCC, so parallel cytokeratins/CD45 should be considered when morphology is equivocal (28). Overall, while BCL-2 plays a critical role in apoptotic regulation across cancers, its expression in SRCC is site-dependent, often absent in gastric primaries, and insufficiently characterized in colorectal and breast SRCC. Current evidence supports its use as an adjunctive interpretive marker rather than a validated therapeutic target in SRCC, highlighting the need for SRCC-focused molecular and clinical studies.

HER2 in signet ring cell carcinoma

HER2 is a transmembrane tyrosine kinase receptor involved in cell proliferation and differentiation (49). HER2 overexpression or gene amplification has been identified as a therapeutic target in various cancers, notably breast and gastric carcinomas (50).

Methodologically, HER2 is one of the "highest-risk" markers for SRCC misclassification because mucin-rich signet-ring cells can generate incomplete or artifactual membranous patterns on IHC; therefore, any equivocal pattern should be reflex-tested by ISH/FISH to avoid overtreatment with anti-HER2 therapy (51). In addition, recent SRCC-focused literature continues to emphasize that HER2-positive SRCC is uncommon and should be considered an "actionable exception": when ERBB2 amplification is confirmed, it may open a therapeutic window, but the baseline probability remains low compared with intestinal-type gastric adenocarcinoma (52). In gastric cancer, HER2 overexpression is observed in approximately 10–20% of cases, predominantly in the intestinal-type adenocarcinomas. In contrast, diffuse-type gastric cancers, including SRCC, typically exhibit low HER2 expression. A study reported that HER2 overexpression was present in about 5% of diffuse-type tumors, with signet ring type tumors being typically negative for HER2 (53). Another study found that HER2 expression detected by immunohistochemistry (IHC) was susceptible to misinterpretation in signet ring cells, and the true HER2 positivity rate was only 1.9% in 155 gastric SRCCs (51). These findings suggest that HER2-targeted therapies may have limited applicability in gastric SRCC. A study by Zheng et al. analyzing five cases of primary breast carcinoma with signet ring cell differentiation found consistent strong ER positivity and uniformly negative HER2 expression, with variable progesterone receptor (PR) and Ki67 levels ranging from 10–30% (12). This suggests that HER2-targeted therapies may not be effective for breast SRCC. However, due to the rarity of this subtype, further studies are needed to confirm these findings. In colorectal cancer, HER2 overexpression is less common compared to breast and gastric cancers. A study reported that among mucinous carcinoma cases, five showed no expression and three showed 1+ expression of HER2/neu out of a total of eight cases. Both cases of SRCC showed 1+ expression, indicating low HER2 expression in colorectal SRCC. These findings suggest that HER2-targeted therapies may have limited efficacy in colorectal SRCC. HER2 expression in SRCC varies depending on the tumor's anatomical origin. Gastric and colorectal SRCCs generally exhibit low HER2 expression, limiting the applicability of HER2-targeted therapies. Breast SRCC also appears to lack HER2 overexpression, although data are limited. These findings underscore the importance of accurate HER2 assessment in SRCC and suggest that alternative therapeutic targets should be explored for this aggressive carcinoma subtype.

PD-L1 expression in signet ring cell carcinoma

PD-L1 is an immune checkpoint protein that plays a crucial role in tumor immune evasion. Its expression in SRCC, varies depending on the tumor's anatomical origin. In gastric SRCC, PD-L1 expression has been observed in a significant subset of cases. A study involving 89 patients with advanced gastric SRCC reported PD-L1 positivity in 40.4% of tumors (54). This expression correlated with increased CD3+ T-cell infiltration and microsatellite instability (MSI), suggesting an active tumor immune microenvironment. Furthermore, PD-L1 expression was associated with peritoneal recurrence in advanced gastric SRCC. Patients with peritoneal metastases exhibited higher PD-L1 positivity (35.5%) compared to those without peritoneal recurrence (12.5%) (55). These findings imply that PD-L1 expression may serve as a biomarker for identifying gastric SRCC patients who could benefit from immune checkpoint inhibitors. In metastatic esophagogastric SRCC, PD-L1 expression has also been evaluated as a predictive biomarker for immunotherapy response. A study assessing HER2-negative patients receiving first-line PD-1 blockade plus chemotherapy found that exosomal PD-L1 levels correlated with treatment efficacy. Patients with higher exosomal PD-L1 levels demonstrated better objective response rates and progression-free survival. This suggests that non-invasive biomarkers like exosomal PD-L1 could aid in selecting patients for immunotherapy (26). Data on PD-L1 expression in colorectal SRCC are limited. However, a case report described a patient with right-sided colorectal SRCC exhibiting microsatellite stability (MSS) and negative PD-L1 expression, who did not respond to first-line chemotherapy (56). This highlights the aggressive nature of colorectal SRCC and the need for alternative therapeutic

strategies. A key "upgrade" from the newest evidence is that tissue PD-L1 alone may be insufficient for selecting metastatic esophagogastric SRCC patients for PD-1 blockade: in a prospective exploratory cohort of HER2-negative metastatic esophagogastric SRCC treated with PD-1 inhibitor plus XELOX, objective response rate (ORR) was 51.5% and median PFS was 6.63 months, yet PD-L1 in tumor tissue did not define a subgroup with significantly better ORR/PFS, whereas low exosomal PD-L1 and low exosomal lactate before treatment were associated with markedly higher ORR and longer PFS (26). In that same study, a combined predictor of exosomal PD-L1 and lactate below a reported threshold was associated with ORR 82.1% vs 30.0% and median PFS 13.83 vs 5.50 months, supporting liquid-biopsy "immune-metabolic" stratification specifically for SRCC. Mechanistically, exosomal PD-L1 was correlated with CD8+ T-cell frequency, and high exosomal PD-L1 after therapy was linked with more PD-1+ Treg cells, suggesting that circulating vesicle markers may capture immunosuppressive dynamics that are not visible on a single tissue PD-L1 snapshot. PD-L1 expression in SRCC varies across different anatomical sites, with notable expression in gastric and esophagogastric tumors. Its presence correlates with specific clinical features, such as peritoneal recurrence in gastric SRCC, and may predict responsiveness to immune checkpoint inhibitors. Further research is warranted to standardize PD-L1 assessment and to explore its role in guiding immunotherapy for SRCC patients.

Conceptual integrated framework and proposed clinically oriented stratification

The integration of Ki-67, BCL-2, HER2, and PD-L1 expression profiles offers a more nuanced approach to understanding the clinical behavior and therapeutic vulnerabilities of SRCC. While each marker individually provides insight into proliferation, apoptosis resistance, receptor signaling, or immune evasion, their combined interpretation can better reflect tumor biology and guide clinical decisions. For example, tumors with high Ki-67 and positive BCL-2 expression may exhibit both rapid proliferation and evasion of apoptosis, contributing to aggressive growth and potential chemoresistance. In contrast, low Ki-67 with BCL-2 negativity might represent a less proliferative but equally evasive tumor phenotype, requiring alternative therapeutic strategies. The absence of HER2 expression in most SRCCs limits options for HER2-targeted therapy, but this negativity – when paired with positive PD-L1 expression – may indicate potential benefit from immune checkpoint blockade. On the other hand, PD-L1-negative, HER2-negative tumors lacking actionable targets may fall into an immunologically "cold" category with limited current therapeutic options, emphasizing the need for novel approaches. An integrated biomarker assessment can also help stratify patients into prognostic subgroups (Table 3).

Importantly, this proposed stratification should be interpreted as a conceptual, hypothesis-generating framework rather than a clinically validated model specific to SRCC. Robust validation will require prospective, SRCC-focused cohorts with standardized biomarker assessment, harmonized scoring systems and cut-off thresholds, and analyses stratified by tumor stage. In addition, future studies should explicitly distinguish pure SRCC from mixed tumors with non–signet-ring components, given their distinct biological behavior and potential impact on biomarker expression and clinical relevance.

Diagnostic pitfalls and morphologic mimics in signet ring cell carcinoma

SRCC presents significant diagnostic complexity because its characteristic cytoplasmic mucin accumulation and eccentrically displaced nuclei may closely resemble several unrelated neoplasms. This morphologic overlap complicates both initial tumor classification and the interpretation of molecular biomarkers that guide prognosis and therapy. A number of tumors can reproduce signet-ring–like morphology, including cutaneous squamous cell carcinoma with intracellular vacuoles mimicking mucin (14), invasive lobular breast carcinoma which frequently demonstrates intracytoplasmic mucin droplets and can be mistaken for metastatic gastrointestinal SRCC when relying solely on morphology (12), and rare prostatic carcinomas with signet-ring–like cells, which may present with variable

Table 3. Proposed Biomarker-Based Subgroups in Signet Ring Cell Carcinoma

Subtype	Ki-67	BCL-2	HER2	PD-L1	Clinical Implication
Proliferative and Apoptosis-Resistant	High	Variable (site- and context-dependent)	Negative	Variable (tumor- vs immune-cell expression)	Aggressive biological behavior driven by high proliferative activity; possible apoptotic resistance in selected contexts; may require intensified or alternative therapeutic strategies.
Low Proliferation, Apoptosis-Prone	Low	Negative	Negative	Variable (often low or focal)	Less aggressive biology, particularly in early or intramucosal disease; may respond to standard therapies; careful longitudinal monitoring is recommended.
Immune-Responsive	Variable (reflecting heterogeneity)	Variable	Negative	Positive (tumor and/or immune cells)	Potential candidates for immune checkpoint inhibition, particularly when supported by immune-cell infiltration or complementary immune biomarkers.
Triple-Negative SRCC	Variable	Variable	Negative	Negative	Limited targeted options; consider clinical trials and novel therapeutic approaches.

"Variable" indicates context-dependent expression influenced by tumor location, histologic composition, intratumoral heterogeneity, and technical factors related to immunohistochemical assessment. In SRCC, biomarker expression may differ between classic signet-ring cells and adjacent non-mucinous tumor components, as well as between tumor cells and immune infiltrates. *Abbreviations:* Ki-67 – marker of proliferation Kiel 67, BCL-2 - B-cell lymphoma 2, HER2 – human epidermal growth factor receptor 2, PDL-1 – programmed death-ligand 1.

PD-L1 expression and mismatch repair abnormalities and thereby further mimic metastatic SRCC (28). In addition, certain lymphoid malignancies may accumulate immunoglobulin-rich cytoplasmic vacuoles that resemble signet-ring cells but demonstrate strong BCL-2 and CD45 expression rather than epithelial differentiation. These mimics underscore that morphology alone is insufficient for reliably diagnosing SRCC and necessitate careful use of immunohistochemical panels including cytokeratins, E-cadherin, CDX2, ER/PR, PSA, and lymphoid markers to avoid misclassification. Beyond morphologic traps, interpretation of key biomarkers used in SRCC poses additional challenges. Ki-67, a marker of cellular proliferation, is subject to considerable intratumoral heterogeneity in SRCC. Classic signet-ring cells filled with mucin often show low Ki-67 labeling, while adjacent non-mucinous or poorly cohesive tumor regions may exhibit markedly higher proliferative activity, meaning that limited sampling can substantially underestimate the true proliferative capacity of the tumor (36). Some early intramucosal SRCCs, particularly those arising in Helicobacter pylori–negative stomachs with germline or somatic CDH1 alterations, may also display very low and stable Ki-67 activity for years, creating a misleading impression of indolence despite underlying molecular instability (13). These features emphasize the need for assessing Ki-67 expression across multiple tumor regions rather than relying on a single field. Evaluation of BCL-2 expression may likewise be misleading in SRCC. Gastric SRCCs generally lack BCL-2 positivity, in contrast with intestinal-type gastric cancers,

in which BCL-2 expression is more common (41). This absence of BCL-2 can be diagnostically useful, but BCL-2 positivity – when present – should prompt caution and consideration of mimickers such as certain lymphomas or breast carcinomas, which characteristically retain strong BCL-2 expression. Thus, BCL-2 should be interpreted within a broader immunophenotypic context rather than viewed in isolation. HER2 testing in SRCC is particularly prone to technical pitfalls. The cytoplasmic mucin vacuole compresses and distorts the cell membrane, often creating incomplete, basolateral, or artifactual membranous staining patterns that mimic HER2 immunohistochemistry (IHC) scores of 2+ without true ERBB2 amplification (51). Because diffuse-type gastric cancers, including SRCC, display substantial intratumoral heterogeneity, focal HER2 expression may also be missed or erroneously overinterpreted depending on the biopsy site. HER2 IHC in SRCC therefore requires especially cautious interpretation, and equivocal staining should be confirmed by ISH/FISH to prevent inappropriate trastuzumab use. PD-L1 evaluation in SRCC presents additional diagnostic difficulties. The abundant mucin within signet-ring cells can obscure or dilute membrane staining, contributing to false-negative PD-L1 assessments (54). In many cases, PD-L1 expression is localized predominantly to tumor-infiltrating immune cells rather than to the tumor cells themselves, complicating TPS and CPS scoring and sometimes leading to underestimation of immunologic activation. Recent evidence suggests that exosomal PD-L1 may correlate more reliably with immunotherapy response in metastatic esophagogastric SRCC than tissue PD-L1 staining, indicating that liquid biopsy biomarkers could help overcome some of the histologic limitations of conventional PD-L1 assessment (26). Collectively, these diagnostic and biomarker-related pitfalls demonstrate that SRCC requires an especially meticulous diagnostic approach. Signet-ring morphology alone is insufficient to establish the diagnosis, and molecular marker interpretation–particularly for Ki-67, BCL-2, HER2, and PD-L1–is vulnerable to sampling bias, mucin-associated artifacts, and biologic heterogeneity. Accurate characterization of SRCC depends on integrating morphology with a broad immunohistochemical panel and, when appropriate, molecular testing. Awareness of these traps is essential for avoiding misdiagnosis, guiding appropriate therapy, and improving the precision of biomarker-driven decision-making in this aggressive and heterogeneous carcinoma.

Future directions and perspectives

Despite advances in the characterization of SRCC, significant challenges remain in translating molecular biomarker data into routine clinical practice. The heterogeneous expression patterns of Ki-67, BCL-2, HER2, and PD-L1 highlight the need for a more standardized and integrated approach to biomarker evaluation. Current studies are often limited by small cohort sizes, retrospective design, and lack of molecular subtyping across anatomical sites. Future research should prioritize integrative analyses using genomics, transcriptomics, proteomics, and immunoprofiling to classify SRCC into molecular subtypes (56). This may uncover new therapeutic targets and reveal combinations of biomarkers that better predict response to therapy. Non-invasive approaches such as circulating tumor DNA (ctDNA), exosomes, and circulating tumor cells could provide real-time insight into tumor evolution and biomarker dynamics, particularly in metastatic or unresectable SRCCs (26). Beyond expression levels, the functional activity of BCL-2 and PD-L1 pathways in SRCC remains poorly understood. Preclinical studies using patient-derived xenografts or organoid models are necessary to explore the biological role of these markers and evaluate responses to targeted therapies such as BH3 mimetics or immune checkpoint inhibitors. Given the limited and inconsistent expression of PD-L1 in SRCC, future trials should incorporate additional immune biomarkers (e.g., tumor mutational burden, T-cell infiltration, microsatellite instability) to refine patient selection for immunotherapy (57). Combinatorial strategies that include chemotherapy, targeted agents, or epigenetic modulators may enhance efficacy. As SRCC occurs in diverse anatomical locations (stomach, colon, breast, bladder), comparative studies examining biomarker expression and clinical outcomes across sites will be critical for understanding site-specific biology versus shared SRCC features. Most biomarker-driven clinical trials exclude or underrepresent SRCC patients. Dedicated trials or stratified analyses within existing studies

are needed to determine the true predictive and prognostic value of key biomarkers in this unique subtype. In summary, future research in SRCC should move toward a systems biology approach that integrates molecular, histologic, and clinical data. Such efforts may pave the way for personalized therapy and improved outcomes for patients with this aggressive and poorly understood carcinoma.

Conclusion

SRCC is a clinically and biologically distinct malignancy rather than a mere histological variant of adenocarcinoma. Its molecular profile is characterised by aggressive proliferative activity (Ki-67), selective resistance to apoptosis (BCL-2), a predominantly HER2-negative signalling landscape, and variable immune-evasive phenotypes mediated through PD-L1. These markers individually carry prognostic and therapeutic relevance, yet their true value emerges only when interpreted collectively. An integrated biomarker perspective provides a more accurate reflection of SRCC biology and allows identification of clinically meaningful subgroups that may benefit from tailored therapeutic strategies. The current translation of biomarker data into clinical practice remains limited by non-standardised scoring, heterogeneous cut-off thresholds, and insufficient evidence from SRCC-specific cohorts. To advance precision oncology in this setting, future research should prioritise SRCC-focused clinical investigations, multi-omics profiling, and harmonised evaluation frameworks for biomarker interpretation. Ultimately, progress in SRCC management will depend not on extrapolating treatment principles from conventional adenocarcinoma, but on developing biomarker-driven, SRCC-specific therapeutic pathways.

Conflict of Interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

Authors Contribution: A.B. and S.A. contributed to the conception and design of the study. M.A., N.K., and A.K. were involved in data acquisition, analysis, and interpretation. N.A. drafted the manuscript. A.B., S.A., and A.K. critically revised the manuscript for important intellectual content. All authors (A.B., M.A., N.K., A.K., S.A. and N.A.) approved the final version of the manuscript to be published and agree to be accountable for all aspects of the work, ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Declaration on the use of AI: An AI-based chatbot (ChatGPT, OpenAI) was used exclusively to assist in the creation of a schematic illustration. No AI tools were used for data analysis, interpretation of results, or manuscript text generation.

Funding: This work was supported by the Science Committee of the Ministry of Science and Higher Education of the Republic of Kazakhstan under grant No. AP23490776 'Prognostic value of gastric cancer biomarkers in relation to the Lauren classification'.

References

1. Pernot S, Voron T, Perkins G, Lagorce-Pages C, Berger A, Taieb J. Signet-ring cell carcinoma of the stomach: impact on prognosis and specific therapeutic challenge. World J Gastroenterol. 2015;21(40):11428-38. doi: 10.3748/wjg.v21.i40.11428
2. Nuytens F, Drubay V, Eveno C, Renaud F, Piessen G. Systematic review of risk factors, prognosis, and management of colorectal signet-ring cell carcinoma. World J Gastrointest Oncol. 2024;16(5):2141-58. doi: 10.4251/wjgo.v16.i5.2141
3. Jin X, Tang H, Chen H, Chen G. Case report: metastatic signet-ring-cell carcinoma of the bladder from breast invasive lobular carcinoma detected by computed tomography. Front Oncol. 2022;12:835487. doi: 10.3389/fonc.2022.835487
4. Nie D, Lan Q, Huang Y, Fang C, Cao Y, Chen Y. Epidemiology and prognostic analysis of patients with pancreatic signet ring cell carcinoma: a population-based study. BMC Gastroenterol. 2022;22(1):458. doi: 10.1186/s12876-022-02543-z
5. Benesch MGK, Mathieson A. Epidemiology of signet ring cell adenocarcinomas. Cancers (Basel). 2020;12(6):1544. doi: 10.3390/cancers12061544
6. Yan J, Liu Y, Liu T, Zhu Q. A predictive and prognostic model for metastasis risk and prognostic factors in gastrointestinal signet ring cell carcinoma. Eur J Med Res. 2024;29(1):545. doi: 10.1186/s40001-024-02135-5
7. Zhao S, Lv L, Zheng K, Tian Y, Zheng JC, Jiang CG. Prognosis and biological behavior of gastric signet-ring cell carcinoma better or worse: a meta-analysis. Front Oncol. 2021;11:603070. doi: 10.3389/fonc.2021.603070

8. Tewari M, Kumar A, Mishra RR, Kumar M, Shukla HS. HER2 expression in gastric and gastroesophageal cancer: report from a tertiary care hospital in North India. Indian J Surg. 2015;77(Suppl 2):447-51. doi: 10.1007/s12262-013-0871-y
9. Yuan C, Huang J, Wang Y, Xiao H. Exploration and validation of the Ki67, HER2, and mutant p53 protein-based risk model, nomogram and lymph node metastasis model for predicting colorectal cancer progression and prognosis. Front Oncol. 2023;13:1236441. doi: 10.3389/fonc.2023.1236441
10. Hong W, Hu Q, Tan Y, et al. Gastrointestinal signet ring cell malignancy: current advancement and future prospects. Invest New Drugs. 2023;41(6):861-9. doi: 10.1007/s10637-023-01403-1
11. Baethge C, Goldbeck-Wood S, Mertens S. SANRA-a scale for the quality assessment of narrative review articles. Res Integr Peer Rev. 2019;4(1):5. doi: 10.1186/s41073-019-0064-8
12. Zheng J, Liu J, Yang W, Yao J, Guo J, Liu C. The clinicopathological and immunohistochemical features of breast carcinomas with signet-ring-cell differentiation. World J Surg Oncol. 2023;21(1):181. doi: 10.1186/s12957-023-03074-x
13. Nikaido M, Miyamoto S, Minato Y, Muto M. Intramucosal signet-ring cell carcinoma with reduced expression of E-cadherin in a Helicobacter pylori-uninfected stomach remained unchanged for 8 years. Clin J Gastroenterol. 2022;15(1):268-9. doi: 10.1007/s12328-021-01545-w
14. Zada S, Tao J, Estopinal MDV. Cutaneous squamous cell carcinoma with signet-ring cell component and CDX2 expression in a patient treated with PD-1 inhibitor: a case report of a common tumor with unusual differentiation. Case Rep Pathol. 2023;2023:3378044. doi: 10.1155/2023/3378044
15. Zhang ZS, Deng WY, Huang SL, et al. Clinicopathological characteristics of signet-ring cell carcinoma derived from gastric fovelar epithelium. J Dig Dis. 2022;23(7):396-403. doi: 10.1111/1751-2980.13120
16. Razmi M, Tajik F, Hashemi F, Yazdanpanah A, Hashemi-Niasari F, Divsalar A. The prognostic importance of Ki-67 in gastrointestinal carcinomas: a meta-analysis and multi-omics approach. J Gastrointest Cancer. 2024;55(2):599-624. doi: 10.1007/s12029-024-01022-w
17. Tao S, Gu J, Wang Q, Zheng L. Translational control of Bcl-2 promotes apoptosis of gastric carcinoma cells. BMC Cancer. 2021;21(1):12. doi: 10.1186/s12885-020-07711-6
18. Anjorin AO, Olaofe OO, Anjorin AO, Omoniyi-Esan GO, Komolafe AO. P53 marker expression in epithelial ovarian tumours in a centre in Nigeria-a descriptive study. BMC Womens Health. 2024;24(1):639. doi: 10.1186/s12905-024-03487-0
19. Shilai Z, Shaozhou M, Linlin W, et al. Predictive significance of 18F-FDG PET/CT metabolic parameters for the expression level of HER2 in gastric cancer. Front Oncol. 2025;15:1580166. doi: 10.3389/fonc.2025.1580166
20. Albrecht T, Brinkmann F, Albrecht M, et al. Programmed death ligand-1 (PD-L1) is an independent negative prognosticator in Western-world gallbladder cancer. Cancers (Basel). 2021;13(7):1682. doi: 10.3390/cancers13071682
21. Yatabe Y. Molecular pathology of non-small cell carcinoma. Histopathology. 2024;84(1):50-66. doi: 10.1111/his.15080
22. Yamaguchi K, Yoshihiro T, Ariyama H, et al. Potential therapeutic targets discovery by transcriptome analysis of an in vitro human gastric signet ring carcinoma model. Gastric Cancer. 2022;25(5):862-78. doi: 10.1007/s10120-022-01307-8
23. Weng MT, Chao KH, Tung CC, et al. Characteristics of primary signet ring cell carcinoma of colon and rectum: a case control study. BMC Gastroenterol. 2022;22(1):173. doi: 10.1186/s12876-022-02258-1
24. Pranjali C, Sulatha K, Mysorekar VV. CDX2 and Ki-67 expression in gastric carcinoma and its association with clinicopathological parameters. Asian Pac J Cancer Biol. 2022;7(3):255-63. doi: 10.31557/APJCB.2022.7.3.255-263
25. Zheng HC, Xue H, Zhang CY. REG4 promotes the proliferation and anti-apoptosis of cancer. Front Cell Dev Biol. 2022;10:1012193. doi: 10.3389/fcell.2022.1012193
26. Tian Y, Shi W, Wang J, et al. Exosomal PD-L1 and lactate versus tissue PD-L1 as biomarkers for clinical outcomes of PD-1 blockade plus chemotherapy in metastatic esophagogastric signet ring cell carcinoma. Exp Hematol Oncol. 2025;14(1):34. doi: 10.1186/s40164-025-00615-w
27. Wojtukiewicz MZ, Rek MM, Karpowicz K, et al. Inhibitors of immune checkpoints-PD-1, PD-L1, CTLA-4-new opportunities for cancer patients and a new challenge for internists and general practitioners. Cancer Metastasis Rev. 2021;40(3):949-82. doi: 10.1007/s10555-021-09976-0
28. Koufopoulos N, Ieronimaki AI, Zacharatou A, et al. A case of prostatic signet-ring cell-like carcinoma with pagetoid spread and intraductal carcinoma and long-term survival: PD-L1 and mismatch repair system proteins (MMR) immunohistochemical evaluation with systematic literature review. J Pers Med. 2023;13(6):1016. doi: 10.3390/jpm13061016
29. Shash LS, Elgohary SA, Ibrahim RA. FOXM1 and MMR genes immunohistochemical expression in colorectal cancer: promising prognostic insights and candidate therapeutic targets. Egypt J Pathol. 2023;43(1):75-85. doi: 10.4103/egjp.egjp_6_23
30. Scholzen T, Gerdes J. The Ki-67 protein: from the known and the unknown. J Cell Physiol. 2000;182(3):311-22. doi: 10.1002/(SICI)1097-4652(200003)182:3<311::AID-JCP1>3.0.CO;2-9
31. Sun X, Kaufman PD. Ki-67: more than a proliferation marker. Chromosoma. 2018;127(2):175-86. doi: 10.1007/s00412-018-0659-8
32. Sandilya U, K M. Expression of Ki-67 in invasive breast carcinoma and its correlation with different clinicopathological features. Cureus. 2024;16(9):e69820. doi: 10.7759/cureus.69820
33. Ko GH, Go SI, Lee WS, et al. Prognostic impact of Ki-67 in patients with gastric cancer-the importance of depth of

invasion and histologic differentiation. Medicine (Baltimore). 2017;96(25):e7181. doi: 10.1097/MD.0000000000007181
34. Wang Y, Li Y, Wang B, et al. Early onset, development and histological features of gastric signet-ring cell carcinoma. Front Oncol. 2023;13:1166549. doi: 10.3389/fonc.2023.1166549
35. Tian MM, Zhao AL, Li ZW, Li JY. Phenotypic classification of gastric signet ring cell carcinoma and its relationship with clinicopathologic parameters and prognosis. World J Gastroenterol. 2007;13(23):3189-98. doi: 10.3748/wjg.v13.i23.3189
36. Terada T. An immunohistochemical study of primary signet-ring cell carcinoma of the stomach and colorectum: III. Expressions of EMA, CEA, CA19-9, CDX-2, p53, Ki-67 antigen, TTF-1, vimentin, and p63 in normal mucosa and in 42 cases. Int J Clin Exp Pathol. 2013;6(4):630-8
37. Bhagyalakshmi A, Sreelekha A, Kasi Babu A, et al. Ki-67 proliferation index and clinicopathological patterns in colorectal carcinomas. J Clin Sci Res. 2015;4(2):119-28. doi: 10.15380/2277-5706.JCSR.14.039
38. Luo ZW, Zhu MG, Zhang ZQ, Ye FJ, Huang WH, Luo XZ. Increased expression of Ki-67 is a poor prognostic marker for colorectal cancer patients: a meta analysis. BMC Cancer. 2019;19(1):123. doi: 10.1186/s12885-019-5324-y
39. Lei ZN, Teng QX, Tian Q, et al. Signaling pathways and therapeutic interventions in gastric cancer. Signal Transduct Target Ther. 2022;7(1):358. doi: 10.1038/s41392-022-01190-w
40. Adams JM, Cory S. The Bcl-2 apoptotic switch in cancer development and therapy. Oncogene. 2007;26(9):1324-37. doi: 10.1038/sj.onc.1210220
41. Müller W, Schneiders A, Hommel G, Gabbert HE. Prognostic value of bcl-2 expression in gastric cancer. Anticancer Res. 1998;18(6B):4699-704
42. Gryko M, Pryczynicz A, Zareba K, Kędra B, Kemona A, Guzińskan-Ustymowicz K. The expression of Bcl-2 and BID in gastric cancer cells. J Immunol Res. 2014;2014:953203. doi: 10.1155/2014/953203
43. Liu HF, Liu WW, Fang DC, Men RP. Expression of bcl-2 protein in gastric carcinoma and its significance. World J Gastroenterol. 1998;4(3):228-30. doi: 10.3748/wjg.v4.i3.228
44. Zalata KR, Nasif WA, Ming SC, et al. P53, Bcl-2 and C-Myc expressions in colorectal carcinoma associated with schistosomiasis in Egypt. Cell Oncol. 2005;27(4):245-53
45. Hague A, Moorghen M, Hicks D, Chapman M, Paraskeva C. BCL-2 expression in human colorectal adenomas and carcinomas. Oncogene. 1994;9(11):3367-70
46. Eom YH, Kim HS, Lee A, Song BJ, Chae BJ. BCL2 as a subtype-specific prognostic marker for breast cancer. J Breast Cancer. 2016;19(3):252-60. doi: 10.4048/jbc.2016.19.3.252
47. Lochmann TL, Floros KV, Naseri M, et al. Venetoclax is effective in small-cell lung cancers with high BCL-2 expression. Clin Cancer Res. 2018;24(2):360-9. doi: 10.1158/1078-0432.CCR-17-1606
48. Valko Z, Megyesfalvi Z, Schwendenwein A, et al. Dual targeting of BCL-2 and MCL-1 in the presence of BAX breaks venetoclax resistance in human small cell lung cancer. Br J Cancer. 2023;128(10):1850-61. doi: 10.1038/s41416-023-02219-9
49. Hung MC, Lau YK. Basic science of HER-2/neu: a review. Semin Oncol. 1999;26(4 Suppl 12):51-9
50. Tolmachev V. Imaging of HER-2 overexpression in tumors for guiding therapy. Curr Pharm Des. 2008;14(28):2999-3019. doi: 10.2174/138161208786404290
51. Woo CG, Ho WJ, Park YS, et al. A potential pitfall in evaluating HER2 immunohistochemistry for gastric signet ring cell carcinomas. Pathology. 2017;49(1):38-43. doi: 10.1016/j.pathol.2016.09.064
52. Beattie A, Ma K, Li H, et al. HER2 over-expression is not involved in signet ring cell carcinoma of stomach: single institution large cohort study. Mod Pathol. 2014;27(Suppl 2):165A
53. Rüschoff J, Hanna W, Bilous M, et al. HER2 testing in gastric cancer: a practical approach. Mod Pathol. 2012 25(5):637-50. doi: 10.1038/modpathol.2011.198
54. Jin S, Xu B, Yu L, et al. The PD-1, PD-L1 expression and CD3+ T cell infiltration in relation to outcome in advanced gastric signet-ring cell carcinoma, representing a potential biomarker for immunotherapy. Oncotarget. 2017 ;8(24):38850-62. doi: 10.18632/oncotarget.16407
55. Huang KH, Chen MH, Fang WL, et al. The clinicopathological characteristics and genetic alterations of signet-ring cell carcinoma in gastric cancer. Cancers (Basel). 2020;12(8):2318. doi: 10.3390/cancers12082318
56. Park PY, Goldin T, Chang J, Markman M, Kundranda MN. Signet-ring cell carcinoma of the colon: a case report and review of the literature. Case Rep Oncol. 2015;8(3):466-71. doi: 10.1159/000441772
57. Vickram S, Infant SS, Manikandan S, Jenila Rani D, Mathan Muthu CM, Chopra H. Immune biomarkers and predictive signatures in gastric cancer: optimizing immunotherapy responses. Pathol Res Pract. 2025;265:155743. doi: 10.1016/j.prp.2024.155743

Copyright: The Author(s), 2026. Licensee Mattioli 1885, Fidenza, Italy. This is an open-access article distributed under the terms of the Creative Commons Attribution NonCommercial License (CC BY-NC-4.0).
Disclaimer/Publisher's Note: The statements, opinions and data contained in this article are solely those of the author(s) and contributor(s) and do not necessarily reflect those of their affiliated organizations, the publisher, the editors or the reviewers. The publisher and the editors disclaim any responsibility for injury to people or property resulting from any ideas, methods, instructions or products mentioned in the content. Any product that may be evaluated in this article, or claim made by its manufacturer, is not guaranteed or endorsed by the publisher.