Personalized Management Of Gastric Cancer In The Era Of Molecular Profiling

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ABSTRACT

This article presents a pragmatic, biomarker-centered framework for tailoring gastric cancer management in an era where molecular profiling increasingly drives everyday clinical decisions. Although stage and histopathology still define the baseline strategy, treatment selection in real practice now depends on a small group of predictive markers that inform perioperative choices, first-line therapy for metastatic disease, and the sequencing of later lines. The review concentrates on biomarkers with immediate clinical utility that routinely shape care: HER2 status, PD-L1 combined positive score, mismatch repair deficiency or microsatellite instability, and CLDN18.2 expression. It synthesizes the evidence behind key treatment "pivot points," including perioperative FLOT in resectable disease, integration of PD-1 blockade with chemotherapy for HER2-negative metastatic tumors with PD-L1 CPS guiding expectations of benefit, incorporation of pembrolizumab into trastuzumab-plus-chemotherapy backbones for HER2-positive disease, use of trastuzumab deruxtecan after failure of trastuzumab-based regimens, and first-line zolbetuximab-based combinations for CLDN18.2-positive cancers. An actionable testing-and-treatment pathway is proposed, alongside real-world challenges that can undermine implementation, such as assay-to-assay variability, intratumoral heterogeneity, and the clinical value of re-evaluation at progression in selected patients. The central conclusion is straightforward: molecular profiling has moved beyond an academic exercise and now functions as the main control mechanism guiding modern gastric cancer therapy.

Keywords: gastric cancer, molecular profiling, precision oncology, biomarkers, HER2, PD-L1 CPS, MSI-H dMMR, CLDN18.2, immunotherapy, targeted therapy.

Molekulyar profillash davrida oshqozon saratonini individuallashtirilgan davolash

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Annotatsiya. Ushbu maqolada me’da saratonini shaxsga mos davolashning bugungi strategiyasi molekulyar profilga tayangan holda yoritiladi. So‘nggi yillarda klinik qarorlar faqat TNM bosqichi va gistologiyaga tayanib qolmay, balki o‘smadagi biomarkerlar majmuasiga qarab shakllanmoqda. Amaliyotda eng ko‘p qo‘llanadigan markerlar qatoriga HER2 holati, PD-L1 CPS ko‘rsatkichi, MSI-H dMMR, shuningdek CLDN18.2 ekspressiyasi kiradi. Maqolada lokal-rezektsiya qilinadigan holatlar uchun perioperatsion yondashuv va metastatik kasallik uchun birinchi hamda keyingi liniyalar ketma-ketligi biomarkerlar bilan bog‘langan algoritm asosida bayon etiladi.
Kalit so‘zlar (UZ): me’da saratoni, molekulyar profiling, biomarkerlar, HER2, PD-L1 CPS, MSI-H dMMR, CLDN18.2, immunoterapiya, maqsadli terapiya.

ПЕРСОНАЛИЗИРОВАННОЕ ЛЕЧЕНИЕ РАКА ЖЕЛУДКА В ЭПОХУ МОЛЕКУЛЯРНОГО ПРОФИЛИРОВАНИЯ

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Аннотация. В статье представлен современный взгляд на персонализированное лечение рака желудка в эпоху молекулярного профилирования. Клиническая тактика все чаще определяется не только стадией и гистологией, но и биомаркерным портретом опухоли, который влияет на выбор периоперационной терапии, первую линию при метастатическом процессе и последовательность последующих линий. В фокусе практически значимые маркеры HER2, PD-L1 CPS, MSI-H dMMR и экспрессия CLDN18.2, а также логика их тестирования и интерпретации. Рассмотрены доказательные основы ключевых подходов: периоперационный режим FLOT при резектабельном процессе, добавление ингибитора PD-1 к химиотерапии при HER2-негативном метастатическом заболевании в зависимости от PD-L1 CPS, комбинирование пембролизумаба с трастузумабом и химиотерапией при HER2-позитивных опухолях, применение трастузумаба дерукстекана во второй и последующих линиях, а также роль анти-CLDN18.2 терапии золбетуксимабом.
Ключевые слова: рак желудка, молекулярное профилирование, биомаркеры, HER2, PD-L1 CPS, MSI-H dMMR, CLDN18.2, иммунотерапия, таргетная терапия.

INTRODUCTION

Gastric cancer continues to be a worldwide clinical problem not because treatment options are absent, but because the disease consistently defies any attempt to treat it as a uniform diagnosis. Two patients can present with the same TNM stage and the same “adenocarcinoma” designation, yet their tumors may be fundamentally different in oncogenic drivers, immune contexture, metastatic patterning, and responsiveness to systemic therapy. This heterogeneity helps explain why older “standard” chemotherapy approaches delivered limited and variable survival benefit

and why regional practice traditions diverged. Molecular profiling has reframed the challenge by converting diversity from an obstacle into a decision aid: when tumors are biologically distinct, management should be deliberately differentiated. The practical aim of personalization is not innovation for its own sake, but improving the likelihood that the initial strategy is the most effective one, since each non-beneficial line consumes time, erodes performance status, and narrows subsequent options. Reflecting this shift, modern guidelines increasingly position biomarker assessment as a routine component of workup and explicitly link results to recommended regimens. [1], [2]

One productive way to conceptualize the current "molecular era" is to view profiling as the interface between diagnostic pathology and rational therapy sequencing. In resectable disease, perioperative systemic therapy remains largely driven by population-level evidence, but molecular data are increasingly used for risk refinement, selection for clinical trials, and informing future escalation or de-escalation frameworks. In metastatic settings, profiling already operates as a practical triage mechanism: it determines eligibility for HER2-targeted strategies, informs whether PD-1 blockade should be incorporated into first-line treatment, and identifies patients in whom newer targets such as CLDN18.2 justify an alternative first-line route. [1], [2] The clinician's day-to-day challenge therefore becomes a sequencing exercise—not simply identifying active agents, but deciding which therapy should be prioritized up front for a given tumor biology and which options should be held in reserve for subsequent lines.

This review is designed to offer a clinically oriented synthesis of personalized gastric cancer management built around the most actionable biomarkers and the most robust supporting evidence. The emphasis is practical: selecting appropriate tests, interpreting results correctly, and translating findings into an optimized treatment pathway that accounts for disease stage and patient physiology. Landmark trial data are considered alongside guideline recommendations, while also addressing real-world limitations such as differences between assays, constraints in tissue quantity and quality, and tumor evolution under therapeutic pressure. Tumors are opportunistic rather than consistent, and biology can shift during treatment; the clinician's task is to detect meaningful change early enough to adjust strategy with clear intent.

MATERIALS AND METHODS

Personalized care starts with a common framework for defining disease groups and recognizing actionable biology. Recent guidance from leading societies increasingly aligns around two practical rules. First, biomarker assessment is a core component of baseline workup in advanced gastric cancer and must be obtained early enough to meaningfully steer first-line decisions rather than arrive after choices have already been made. [1], [2] Second, a biomarker is only valuable when it predictably changes management, which requires a test that is analytically sound, clinically interpretable, and paired with a therapy that delivers a clinically relevant benefit. In gastric cancer, this standard of "actionability" is most firmly established for HER2, PD-L1 CPS when selecting PD-1–based strategies, MSI-H or dMMR status, and CLDN18.2 expression, while additional candidates continue to emerge through trials and selected approvals.

NCCN updates distill how biomarker results translate into treatment pathways for gastric cancer and outline advanced-disease algorithms that explicitly incorporate molecular targets and immunotherapy selection principles. [1] ESMO's clinical practice guideline provides a broad European structure spanning diagnostic evaluation, staging, localized treatment, and systemic therapy for advanced disease, with biomarker integration embedded throughout therapeutic decision-making. [2] The TCGA gastric adenocarcinoma program contributed a widely cited molecular classification, grouping tumors into EBV-positive, MSI, genomically stable, and chromosomal instability categories, which has served as a conceptual scaffold for stratified research and targeted development. [3] In resectable, locally advanced disease, the randomized FLOT4 study reported superior survival with perioperative FLOT compared with older anthracycline-based triplets, shaping

contemporary perioperative standards. [4] In metastatic HER2-negative disease, CheckMate 649 demonstrated improved outcomes when nivolumab was added to chemotherapy and helped consolidate PD-1 blockade plus chemotherapy as a first-line option, particularly within biomarker-defined subsets. [5] For metastatic HER2-positive tumors, KEYNOTE-811 assessed pembrolizumab combined with trastuzumab and chemotherapy and showed clinically meaningful progression-free survival improvement, with ongoing overall survival evaluation and subgroup considerations linked to PD-L1 CPS. [6] After progression on trastuzumab-based therapy in later-line HER2-positive disease, DESTINY-Gastric01 reported higher response and improved survival with trastuzumab deruxtecan versus physician's choice chemotherapy, while underscoring interstitial lung disease as a toxicity requiring vigilant monitoring. [7] In CLDN18.2-positive, HER2-negative disease, the SPOTLIGHT trial demonstrated benefit from adding zolbetuximab to first-line chemotherapy, strengthening CLDN18.2 as a clinically useful stratifier for first-line planning. [8]

RESULTS AND DISCUSSION

Molecular profiling is often misread as an ever-expanding catalogue of mutations; in routine care it functions more like a disciplined sorting system that groups tumors by biology in ways that anticipate therapeutic vulnerability. The TCGA model remains influential because it connects gastric cancer subtypes to recurring pathway patterns and, importantly, offers mechanistic clues for why some tumors may be more immunologically responsive while others are dominated by receptor tyrosine kinase amplification programs. [3] EBV-associated tumors, for example, commonly show immune-enriched features and in some cases amplification of PD-L1 or PD-L2, which provides a biologic argument for sensitivity to immune checkpoint strategies. MSI tumors typically carry high mutational load and increased immunogenicity. Chromosomal instability tumors frequently harbor receptor tyrosine kinase amplifications, conceptually aligning with HER2 amplification and related targeted approaches. By contrast, genomically stable tumors often overlap with diffuse-type biology, where canonical targets are less prevalent and infiltrative growth patterns complicate both local control and systemic efficacy. TCGA is not a prescribing algorithm, but it helps explain the logic behind current "actionable" testing: the biomarkers used in clinic are not arbitrary—they cluster within coherent biological subtypes.

Clinical care, however, cannot wait for an ideal taxonomy to mature. As a result, personalization begins with a lean, high-yield biomarker set that can be delivered rapidly and reproducibly. Timing is decisive: when results arrive only after therapy has already started, personalization becomes a retrospective narrative rather than a prospective strategy. NCCN emphasizes biomarker testing within advanced-disease pathways and continues to update these recommendations, reflecting that treatment choice is now structurally tied to molecular results rather than loosely informed by them. [1] ESMO similarly anchors systemic therapy selection to biomarker-defined indications and stresses multidisciplinary, evidence-based sequencing as a core operational principle. [2]

In resectable, locally advanced gastric or gastroesophageal junction adenocarcinoma, perioperative chemotherapy remains a central standard across many settings, with FLOT widely treated as a reference regimen supported by randomized evidence. [4] The FLOT4 trial reported improved overall survival compared with older triplet approaches, reinforcing perioperative systemic therapy as the default strategy for physiologically fit patients with stage-appropriate disease. Although profiling is not yet routinely used to choose perioperative chemotherapy outside trials, it increasingly shapes clinical nuance: it identifies MSI-H or dMMR tumors that may carry distinct prognostic features and potentially different chemotherapy responsiveness, documents HER2 status that can become immediately relevant at recurrence, and enables enrollment into biomarker-stratified perioperative studies. ESMO provides structured guidance for localized management

and emphasizes multidisciplinary staging and evidence-based perioperative planning. [2]

Within localized disease, a personalized approach therefore operates along two axes. The first is physiologic tailoring—adjusting perioperative intensity to what a patient can realistically tolerate so that treatment does not jeopardize surgical candidacy or generate avoidable toxicity. The second is biologic anticipation—using profiling to forecast likely relapse behavior and to plan surveillance and future systemic options with fewer surprises. Even when molecular results do not alter the perioperative backbone today, they can materially change preparedness for tomorrow, and in oncology that often separates an orderly transition from an emergency pivot.

Therapeutic resistance is more common than durable sensitivity, and the molecular era offers a more rational response than simply rotating chemotherapy. In previously treated HER2-positive gastric or gastroesophageal junction cancer, DESTINY-Gastric01 compared trastuzumab deruxtecan with physician's choice chemotherapy and showed superior response and overall survival, while also underscoring distinct toxicities such as myelosuppression and clinically important interstitial lung disease or pneumonitis. [7] The personalization message is substantial: HER2 can remain actionable beyond trastuzumab, but the treatment class shifts and the safety framework must shift with it. For clinicians, this means profiling is not a one-time entry ticket—it functions as ongoing eligibility, provided HER2 expression is still sufficient and the patient can be monitored and managed safely.

This later-line setting also illustrates a broader principle of precision therapy: as targeting becomes sharper, toxicity becomes more specific. With antibody–drug conjugates, respiratory symptoms demand a lower threshold for evaluation, imaging triggers may need to be more proactive, and coordination with pulmonology becomes part of standard oncology workflow. Precision oncology, in other words, expands not only the set of available drugs, but also the clinical monitoring discipline required to use them responsibly.

Table 1.

Actionable biomarkers and therapy implications in contemporary gastric cancer care

Biomarker and typical assay	**Clinical setting where it most often changes management**	**Typical treatment implication in a biomarker-driven pathway**	**Evidence anchor**
HER2 by IHC with confirmatory ISH when indicated	Advanced or metastatic disease, also informative at baseline in many patients	Enables trastuzumab-based first line and informs later HER2-directed sequencing	KEYNOTE-811 supports pembrolizumab addition to trastuzumab plus chemotherapy in HER2-positive disease [6]
PD-L1 combined positive score by IHC	Primarily advanced or metastatic disease, especially HER2-negative, also refines HER2-positive strategy	Supports integrating PD-1 inhibitor with chemotherapy in appropriate CPS-defined groups; refines benefit expectations	CheckMate 649 shows nivolumab plus chemotherapy benefit and uses CPS stratification logic [5]
MSI-H dMMR by IHC and or molecular methods	Advanced disease and trial stratification; prognostic and predictive considerations	Signals an immunogenic phenotype and influences immunotherapy expectations; supports enrollment and individualized choices	Conceptual and guideline integration in major frameworks [1], [2], with molecular rationale linked to MSI subtype biology [3]

CLDN18.2 by IHC with threshold aligned to pivotal trials	Advanced HER2-negative gastric or GEJ adenocarcinoma	Opens first-line zolbetuximab plus chemotherapy pathway in eligible tumors	SPOTLIGHT established benefit in CLDN18.2-positive disease [8]
HER2 positivity after progression on trastuzumab-based therapy, confirmed appropriately	Second line or later in HER2-positive disease	Enables trastuzumab deruxtecan with specific toxicity monitoring	DESTINY-Gastric01 demonstrated benefit with ILD risk considerations [7]

This table summarizes the "minimum actionable set" used in many contemporary pathways. NCCN and ESMO emphasize biomarker testing as a driver of treatment selection in advanced disease [1], [2]. The evidence anchors highlight how biomarkers translate into therapy choices: nivolumab plus chemotherapy in CheckMate 649 [5], pembrolizumab addition in KEYNOTE-811 [6], trastuzumab deruxtecan benefit in DESTINY-Gastric01 [7], and zolbetuximab benefit in SPOTLIGHT [8].

Personalization fails when it assumes stability. Gastric cancer often exhibits spatial heterogeneity, meaning different metastatic sites can carry different biomarker expression levels, and temporal heterogeneity, meaning treatment pressure can select clones that escape the targeted mechanism. This is why guidelines discuss biomarker testing as an evolving clinical asset rather than a static checkbox [1].

Conclusion

Personalized gastric cancer care has moved beyond being a research catchphrase and now functions as a practical requirement in routine oncology. A useful way to frame current practice is as a biomarker-guided branching algorithm, anchored in high-level trial evidence and implemented through guideline-consistent staging, multidisciplinary review, and sequencing discipline. In resectable, locally advanced disease, perioperative FLOT remains a central evidence-based backbone for physiologically fit patients, offering a population-derived standard while molecular profiling increasingly adds value by refining future risk thinking and facilitating enrollment into biomarker-stratified perioperative trials.

In unresectable or metastatic settings, molecular results become immediately determinant. HER2 status separates patients into a distinct targeted pathway that can be further optimized with immunotherapy integration based on the KEYNOTE-811 framework, and HER2 expression remains clinically actionable even after progression on trastuzumab-based therapy through antibody–drug conjugates such as trastuzumab deruxtecan, provided monitoring culture adapts to therapy-specific toxicities and pulmonary vigilance is treated as non-negotiable.

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