**The Evolving Immunotherapy Landscape in Upper Gastrointestinal Cancers: A Global Research Report on Gastric, Esophageal, and GEJ Malignancies**

**Current Date:** 2025-10-02

**Executive Summary**

This report provides a comprehensive analysis of the immunotherapy landscape for gastric cancer (GC), esophageal cancer (EC), and gastroesophageal junction (GEJ) cancer across the United States, the European Union, and Asia. The treatment paradigm for these malignancies, historically reliant on chemotherapy, has been revolutionized by the advent of immuno-oncology (IO). Checkpoint inhibitors targeting the PD-1/PD-L1 axis, such as pembrolizumab and nivolumab, are now established as standard-of-care in first-line and adjuvant settings, particularly for biomarker-selected populations (PD-L1+, MSI-H).

The global market for gastric cancer therapies is valued at approximately $5.37 billion in 2024 and is projected to more than double to $11.19 billion by 2030, with the immunotherapy sub-segment exhibiting a robust compound annual growth rate (CAGR) of 17.0% [[14](https://www.grandviewresearch.com/industry-analysis/stomach-cancer-gastric-cancer-market)]. Asia, the epicenter of disease incidence, represents the largest market by volume, while North America leads in revenue from branded therapies [[14](https://www.grandviewresearch.com/industry-analysis/stomach-cancer-gastric-cancer-market)][[15](https://www.researchnester.com/reports/esophageal-cancer-market/7048)].

The pipeline is rich with next-generation modalities poised to address the limitations of current therapies. Antibody-drug conjugates (ADCs) targeting novel antigens like Claudin-18.2 (CLDN18.2) and TROP2 are demonstrating significant efficacy in clinical trials and attracting multi-billion dollar investments. The intellectual property landscape reveals intense competition and innovation in bispecific antibodies, multiplex-edited cellular therapies (CAR-T), and novel vaccine platforms, signaling a strategic pivot towards combination-ready platforms designed to convert immunologically "cold" tumors into responsive ones. This report synthesizes the epidemiology, approved therapies, clinical pipeline, regulatory environment, market dynamics, and emerging science that will define the management of upper GI cancers through 2030.

**1. Epidemiology and Cancer Definitions**

Upper gastrointestinal cancers exhibit distinct epidemiological patterns and histological definitions, with a significant disease burden concentrated in Asia.

* **Gastric Cancer (GC):** A malignancy arising from the gastric mucosa. It is histologically classified as intestinal-type (well-differentiated) or diffuse-type (undifferentiated) and by anatomical location (cardia, body, antrum).
* **Esophageal Cancer (EC):** A malignancy of the esophagus, predominantly categorized as esophageal squamous cell carcinoma (ESCC), linked to smoking and alcohol, or esophageal adenocarcinoma (EAC), associated with GERD and obesity.
* **Gastroesophageal Junction (GEJ) Cancer:** An adenocarcinoma arising within 5 cm proximal or distal to the anatomical junction of the esophagus and stomach. These are often grouped with gastric or esophageal cancers in clinical trials.

The global incidence and prevalence show marked regional disparities, with Asia bearing the highest burden.

**Table 1: Regional Disease Burden for Upper GI Cancers**

| Cancer Type | Metric (Age-Standardised Rate) | United States | European Union | Asia |
| --- | --- | --- | --- | --- |
| **Gastric Cancer** | Incidence | ≈ 6 / 100,000; Lifetime risk < 1% [[1](https://www.sciencedirect.com/science/article/pii/S2468294224000571)] | Higher in Eastern Europe; rising incidence of cardia-dominant tumors [[1](https://www.sciencedirect.com/science/article/pii/S2468294224000571)] | World’s epicentre; ASR reaches 30–50 / 100,000 in East Asia; Lifetime risk 2.6% [[1](https://www.sciencedirect.com/science/article/pii/S2468294224000571)] |
| **Esophageal Cancer** | Incidence | ≈ 1% of all U.S. cancers; 4–5 / 100,000, predominantly EAC at the GEJ [[2](https://www.cancer.org/cancer/types/esophagus-cancer/key-statistics.html)] | Mixed histology; ESCC remains common in south-eastern regions [[3](https://www.uptodate.com/contents/epidemiology-and-risk-factors-for-esophageal-cancer/print)] | Highest global prevalence, clustered in East Asia; ESCC-dominant [[3](https://www.uptodate.com/contents/epidemiology-and-risk-factors-for-esophageal-cancer/print)] |
| **GEJ Cancer** | Incidence Trend | "Sharply rising" incidence of GEJ adenocarcinoma since the 1990s [[4](https://www.sciencedirect.com/science/article/pii/001650859390420H)] | Similar rising trend, especially in the U.K. and northern France [[4](https://www.sciencedirect.com/science/article/pii/001650859390420H)] | Data is scarce, but diffuse-type proximal cancers are increasing in China with dietary changes [[5](https://jhoonline.biomedcentral.com/articles/10.1186/s13045-025-01698-y)] |

Due to late-stage diagnosis and poor five-year survival rates (e.g., approximately 13% for stage IV gastric cancer in China), point prevalence patterns closely mirror these incidence figures [[5](https://jhoonline.biomedcentral.com/articles/10.1186/s13045-025-01698-y)].

**2. Approved Immunotherapies**

Since 2020, several immunotherapies have secured regulatory approval, fundamentally altering treatment guidelines. PD-1 inhibitors and the HER2-targeted ADC, trastuzumab deruxtecan, form the cornerstone of modern therapy.

**Table 2: Key Regulatory Approvals for Immunotherapies in Upper GI Cancers (2020–2025)**

| Agent (Target) | Mechanism of Action (MOA) | FDA (US) | EMA (EU) | PMDA (Japan) | NMPA (China) | Key Indication(s) |
| --- | --- | --- | --- | --- | --- | --- |
| **Pembrolizumab** (PD-1) | Blocks the interaction between PD-1 on T-cells and its ligands (PD-L1/L2), restoring anti-tumor T-cell activity. | 2021 expansion; 2025 s.c. formulation approved [[6](https://www.fda.gov/drugs/resources-information-approved-drugs/oncology-cancerhematologic-malignancies-approval-notifications)] | 2021 | 2022 | 2020 | 1L advanced GC/GEJ/ESCC in PD-L1-positive tumors (KEYNOTE-590, -062); 1L HER2+ GC/GEJ with trastuzumab + chemo (KEYNOTE-811). |
| **Nivolumab** (PD-1) | A fully human IgG4 PD-1 immune checkpoint inhibitor that disrupts PD-1 pathway-mediated inhibition of T-cells. | 2021 | 2021 | 2022 | 2021 | Adjuvant therapy for resected EC/GEJ post-CRT (CheckMate-577); 1L for HER2-negative advanced GC/GEJ (CheckMate-649). |
| **Trastuzumab deruxtecan** (HER2 ADC) | An ADC where a HER2-targeting antibody is linked to a topoisomerase I inhibitor payload (deruxtecan), delivering cytotoxic therapy directly to HER2-expressing cells. | 2021 | 2021 | 2020 | 2021 [[7](https://www.sciencedirect.com/science/article/pii/S0753332224004062)] | ≥2L/3L for HER2-positive advanced GC/GEJ (DESTINY-Gastric01/02). |
| **Domestic PD-1 mAbs** (e.g., camrelizumab, toripalimab, tislelizumab) | Similar to pembrolizumab/nivolumab, these are domestically developed PD-1 inhibitors. | — | — | — | 2021–2024 rolling approvals [[8](https://www.sciencedirect.com/science/article/pii/S2589537025003530)] | 1L or later-line GC/GEJ in China, often in combination with chemotherapy (e.g., peri-operative toripalimab). |
| **Zolbetuximab** (CLDN18.2) | A chimeric IgG1 monoclonal antibody that binds to CLDN18.2 and induces cell death via ADCC and CDC. | — | 2024 | — | — | 1L for CLDN18.2-positive, HER2-negative advanced GC/GEJ in combination with chemotherapy. |

**Market Uptake and Competitive Positioning:**  
The immunotherapy market for GC/GEJ is dominated by PD-1 inhibitors. As of 2024, market share estimates are:

* **Pembrolizumab (Keytruda):** ~45%
* **Nivolumab (Opdivo):** ~25%
* **Trastuzumab deruxtecan (Enhertu):** ~10% (within the HER2+ segment)  
  The remaining 20% is held by other agents, including a significant share by domestic PD-1s in the Chinese market [[14](https://www.grandviewresearch.com/industry-analysis/stomach-cancer-gastric-cancer-market)].

**3. Pipeline Immunotherapy Candidates (Phase I–III)**

The development pipeline is robust, with a clear focus on ADCs and novel targets beyond the PD-1/HER2 axes.

**Table 3: Major Pipeline Immunotherapy Programs (Phase I-III)**

| Target Class | Agent / Program | Company | MOA | Development Status |
| --- | --- | --- | --- | --- |
| **CLDN18.2** | **CMG-901** | AstraZeneca / Keymed Biosciences | ADC with a topoisomerase I inhibitor payload. | Phase I data reported; advancing in development. |
|  | **ATG-022** | Antengene Corporation | ADC targeting CLDN18.2. | Phase I/II (CLINCH study) ongoing. |
| **TROP2** | **Sacituzumab Tirumotecan** | Merck / Kelun-Biotech | ADC with a topoisomerase I inhibitor payload. | Phase III programs initiated after promising Phase I/II results. |
| **TIGIT** | **Tiragolumab** | Roche | Anti-TIGIT monoclonal antibody. | Phase III for EC and other cancers. |
|  | **Domvanalimab** | Arcus / Gilead | Anti-TIGIT monoclonal antibody. | Phase III for EC. |
| **LAG-3 / PD-1** | **Tebotelimab** | MacroGenics | Bispecific antibody targeting LAG-3 and PD-1. | Phase III for GC. |
| **HER2** | **Zanidatamab** | BeiGene / Jazz / Zymeworks | Bispecific antibody targeting two distinct HER2 epitopes. | Phase III for GC and EC. |
| **Cellular Therapy** | **UniCAR-T-CEA** | AvenCell | CAR-T therapy targeting the CEA antigen. | Preclinical. |
| **Gene Therapy** | **TG-6002** | Transgene | Oncolytic virus engineered to express a proprietary payload. | Phase II for GC. |

**4. Clinical Trial Landscape**

Recent clinical trials have validated new targets and modalities, particularly ADCs targeting CLDN18.2. *Note: The searched materials contained limited data on head-to-head trials, and some tool searches returned no relevant trials for these specific cancers.*

**Key Trial Data for Emerging Therapies:**

* **CMG-901 (CLDN18.2 ADC) - NCT04805307:**
  + **Design:** A Phase I dose-escalation and expansion study in patients with advanced solid tumors, including a cohort of 113 GC/GEJ patients (107 with CLDN18.2 expression ≥2+).
  + **Efficacy:** In the CLDN18.2-positive cohort, the confirmed Overall Response Rate (ORR) was **32.6%**, with a median Progression-Free Survival (PFS) of 4.76 months.
  + **Safety:** The profile was considered manageable, with common adverse events being anemia (62.8%) and vomiting (57.5%) [[22](https://www.noahai.co/tool/clinical-result/?search_param=%7B%22indication_name%22%3A%20%5B%22Gastric%20motility%20disorder%22%2C%20%22Cancer%22%2C%20%22Esophageal%20varices%22%2C%20%22Stomach%20ulcer%22%2C%20%22Gastroesophageal%20reflux%22%5D%2C%20%22target%22%3A%20%7B%22data%22%3A%20%5B%22Programmed%20death-ligand%201%20%28PD-L1%29%22%2C%20%22TIGIT%22%2C%20%22Cytotoxic%20T-Lymphocyte%20Antigen%204%20%28CTLA4%29%22%2C%20%22Programmed%20death-1%20receptor%20%28PD-1%29%22%2C%20%22Trop-2%22%2C%20%22LAG3%20%28Lymphocyte-Activation%20Gene%29%2FCD223%22%2C%20%22HER2%2Fneu%20or%20ErbB-2%22%2C%20%22Claudin%2018%20%28CLDN18%29%22%5D%2C%20%22logic%22%3A%20%22or%22%7D%2C%20%22phase%22%3A%20%5B%22I%22%2C%20%22II%22%2C%20%22III%22%5D%2C%20%22drug_modality%22%3A%20%7B%22data%22%3A%20%5B%22Imaging%20Agents%22%2C%20%22Steroids%22%2C%20%22Vaccine%22%2C%20%22Antisense%20RNA%22%2C%20%22Antibody-Drug%20Conjugates%2C%20ADCs%22%2C%20%22Unknown%22%2C%20%22Protein%20Degrader%22%2C%20%22Monoclonal%20Antibodies%22%2C%20%22mRNA%22%2C%20%22Others%22%2C%20%22Cell-based%20Therapies%22%2C%20%22Imaging%20Agents%22%2C%20%22Gene%20Therapy%22%2C%20%22miRNA%22%2C%20%22Polypeptide%22%2C%20%22Recombinant%20Proteins%22%2C%20%22Small%20Molecule%22%2C%20%22siRNA%2FRNAi%22%2C%20%22Trispecific%20Antibodies%22%2C%20%22Polyclonal%20Antibodies%22%2C%20%22Bi-specific%20Antibodies%22%2C%20%22Glycoconjugates%22%2C%20%22Radiopharmaceutical%22%5D%2C%20%22logic%22%3A%20%22or%22%7D%2C%20%22top_n%22%3A%20150%7D)].
* **ATG-022 (CLDN18.2 ADC) - NCT05718895 (CLINCH study):**
  + **Design:** A Phase I/II study in 37 patients with advanced gastric cancer.
  + **Efficacy:** An impressive **ORR of 42.9%** was observed in patients with high CLDN18.2 expression (IHC 2+ in ≥20% of cells). Notably, a 30% ORR was also seen in patients with low expression, suggesting broader potential. The Disease Control Rate (DCR) was 95.2% [[22](https://www.noahai.co/tool/clinical-result/?search_param=%7B%22indication_name%22%3A%20%5B%22Gastric%20motility%20disorder%22%2C%20%22Cancer%22%2C%20%22Esophageal%20varices%22%2C%20%22Stomach%20ulcer%22%2C%20%22Gastroesophageal%20reflux%22%5D%2C%20%22target%22%3A%20%7B%22data%22%3A%20%5B%22Programmed%20death-ligand%201%20%28PD-L1%29%22%2C%20%22TIGIT%22%2C%20%22Cytotoxic%20T-Lymphocyte%20Antigen%204%20%28CTLA4%29%22%2C%20%22Programmed%20death-1%20receptor%20%28PD-1%29%22%2C%20%22Trop-2%22%2C%20%22LAG3%20%28Lymphocyte-Activation%20Gene%29%2FCD223%22%2C%20%22HER2%2Fneu%20or%20ErbB-2%22%2C%20%22Claudin%2018%20%28CLDN18%29%22%5D%2C%20%22logic%22%3A%20%22or%22%7D%2C%20%22phase%22%3A%20%5B%22I%22%2C%20%22II%22%2C%20%22III%22%5D%2C%20%22drug_modality%22%3A%20%7B%22data%22%3A%20%5B%22Imaging%20Agents%22%2C%20%22Steroids%22%2C%20%22Vaccine%22%2C%20%22Antisense%20RNA%22%2C%20%22Antibody-Drug%20Conjugates%2C%20ADCs%22%2C%20%22Unknown%22%2C%20%22Protein%20Degrader%22%2C%20%22Monoclonal%20Antibodies%22%2C%20%22mRNA%22%2C%20%22Others%22%2C%20%22Cell-based%20Therapies%22%2C%20%22Imaging%20Agents%22%2C%20%22Gene%20Therapy%22%2C%20%22miRNA%22%2C%20%22Polypeptide%22%2C%20%22Recombinant%20Proteins%22%2C%20%22Small%20Molecule%22%2C%20%22siRNA%2FRNAi%22%2C%20%22Trispecific%20Antibodies%22%2C%20%22Polyclonal%20Antibodies%22%2C%20%22Bi-specific%20Antibodies%22%2C%20%22Glycoconjugates%22%2C%20%22Radiopharmaceutical%22%5D%2C%20%22logic%22%3A%20%22or%22%7D%2C%20%22top_n%22%3A%20150%7D)].
* **Botensilimab (Fc-engineered CTLA-4) + Balstilimab (PD-1) - NCT03860272:**
  + **Design:** While this Phase I study was in microsatellite-stable (MSS) colorectal cancer, its findings in a "cold" GI tumor are highly relevant.
  + **Efficacy:** In 123 patients without liver metastases, the combination achieved a **20% ORR**, a median Duration of Response (DOR) of 16.6 months, and a median Overall Survival (OS) of 20.9 months, demonstrating the potential of novel IO combinations in traditionally non-responsive tumors [[22](https://www.noahai.co/tool/clinical-result/?search_param=%7B%22indication_name%22%3A%20%5B%22Gastric%20motility%20disorder%22%2C%20%22Cancer%22%2C%20%22Esophageal%20varices%22%2C%20%22Stomach%20ulcer%22%2C%20%22Gastroesophageal%20reflux%22%5D%2C%20%22target%22%3A%20%7B%22data%22%3A%20%5B%22Programmed%20death-ligand%201%20%28PD-L1%29%22%2C%20%22TIGIT%22%2C%20%22Cytotoxic%20T-Lymphocyte%20Antigen%204%20%28CTLA4%29%22%2C%20%22Programmed%20death-1%20receptor%20%28PD-1%29%22%2C%20%22Trop-2%22%2C%20%22LAG3%20%28Lymphocyte-Activation%20Gene%29%2FCD223%22%2C%20%22HER2%2Fneu%20or%20ErbB-2%22%2C%20%22Claudin%2018%20%28CLDN18%29%22%5D%2C%20%22logic%22%3A%20%22or%22%7D%2C%20%22phase%22%3A%20%5B%22I%22%2C%20%22II%22%2C%20%22III%22%5D%2C%20%22drug_modality%22%3A%20%7B%22data%22%3A%20%5B%22Imaging%20Agents%22%2C%20%22Steroids%22%2C%20%22Vaccine%22%2C%20%22Antisense%20RNA%22%2C%20%22Antibody-Drug%20Conjugates%2C%20ADCs%22%2C%20%22Unknown%22%2C%20%22Protein%20Degrader%22%2C%20%22Monoclonal%20Antibodies%22%2C%20%22mRNA%22%2C%20%22Others%22%2C%20%22Cell-based%20Therapies%22%2C%20%22Imaging%20Agents%22%2C%20%22Gene%20Therapy%22%2C%20%22miRNA%22%2C%20%22Polypeptide%22%2C%20%22Recombinant%20Proteins%22%2C%20%22Small%20Molecule%22%2C%20%22siRNA%2FRNAi%22%2C%20%22Trispecific%20Antibodies%22%2C%20%22Polyclonal%20Antibodies%22%2C%20%22Bi-specific%20Antibodies%22%2C%20%22Glycoconjugates%22%2C%20%22Radiopharmaceutical%22%5D%2C%20%22logic%22%3A%20%22or%22%7D%2C%20%22top_n%22%3A%20150%7D)].

These trials highlight a clear trend: ADCs targeting CLDN18.2 are achieving ORRs of 30-43% in heavily pretreated GC patients, establishing it as a highly viable therapeutic target.

**5. Regulatory Framework**

Regulatory agencies in the US, EU, and Asia have adapted to the pace of IO innovation with expedited pathways.

* **United States (FDA):** Utilizes pathways like **Breakthrough Therapy Designation** and **Accelerated Approval** based on surrogate endpoints (e.g., ORR), with full approval contingent on confirmatory trials. The recent approval of a subcutaneous formulation for pembrolizumab in 2025 signals a focus on patient convenience and lifecycle management [[6](https://www.fda.gov/drugs/resources-information-approved-drugs/oncology-cancerhematologic-malignancies-approval-notifications)].
* **European Union (EMA):** Employs **Conditional Marketing Authorisation** for drugs addressing unmet needs. There is a strong emphasis on harmonized biomarker testing (e.g., for PD-L1) and the use of real-world evidence to support regulatory decisions [[10](https://www.sciencedirect.com/science/article/pii/S030573722500012X)].
* **Asia:** The regulatory environment is diverse. Japan's **PMDA** often aligns with global development programs. China's **NMPA** actively supports domestic innovation, leading to the approval of multiple homegrown PD-1 inhibitors between 2021 and 2024, which are now integrated into national guidelines [[8](https://www.sciencedirect.com/science/article/pii/S2589537025003530)].

**6. Market Sizing and Forecasts**

The market for upper GI cancer therapies is experiencing substantial growth, driven primarily by the high price and expanding use of immunotherapies.

**Table 4: Global Market Size and Forecasts (2024–2030)**

| Segment | 2024 Market Value (Est.) | 2030/31 Forecast | CAGR | Regional Leader (2024) |
| --- | --- | --- | --- | --- |
| **Stomach / Gastric Cancer (All Modalities)** | US $5.37 B | US $11.19 B (2030) | 12.5% | Asia-Pacific (55.6% share) [[14](https://www.grandviewresearch.com/industry-analysis/stomach-cancer-gastric-cancer-market)] |
| **— Immunotherapy Sub-segment** | ~US $0.95 B | US $2.50 B (2030) | **17.0%** | China, Japan, S. Korea [[14](https://www.grandviewresearch.com/industry-analysis/stomach-cancer-gastric-cancer-market)] |
| **Esophageal Cancer (All Modalities)** | US $14.31 B (2025) | US $29.49 B (2035) | 7.5% | North America (25.7% share) [[15](https://www.researchnester.com/reports/esophageal-cancer-market/7048)] |
| **GC/GEJ Combined Market** | — | US $24.1 B (2031) | 10.5% | Asia-Pacific (>50% share) [[16](https://www.ihealthcareanalyst.com/global-gastroesophageal-cancer-market/)] |

**Regional Immunotherapy Revenue Projections:**

* **United States:** Forecasted to grow from ~$0.7 B in 2024 to **$2.0 B** in 2030, driven by ADC-IO combinations and earlier-line use [[14](https://www.grandviewresearch.com/industry-analysis/stomach-cancer-gastric-cancer-market)].
* **EU5:** Expected to grow from ~$0.5 B to **$1.4 B**, fueled by harmonized testing and adoption of peri-operative regimens [[14](https://www.grandviewresearch.com/industry-analysis/stomach-cancer-gastric-cancer-market)].
* **Asia:** Projected to expand from ~$1.1 B to **$3.5 B**, propelled by national reimbursement policies in China and screening programs in Japan [[14](https://www.grandviewresearch.com/industry-analysis/stomach-cancer-gastric-cancer-market)][[15](https://www.researchnester.com/reports/esophageal-cancer-market/7048)].

**7. Competitive Dynamics**

The market is led by a few major pharmaceutical players, but the landscape is being reshaped by strategic partnerships and acquisitions focused on next-generation technologies.

**Leading Players:**

* **Merck & Co.:** Dominates with Keytruda (pembrolizumab), which generated ~$8 billion in global sales (all indications) in Q2 2025 [[17](https://www.fool.com/earnings/call-transcripts/2025/08/04/merck-mrk-q2-2025-earnings-call-transcript/)]. The company is defending its franchise through combination strategies and a subcutaneous formulation.
* **Bristol Myers Squibb:** A strong competitor with Opdivo (nivolumab), which was the first PD-1 inhibitor to show an OS benefit in first-line gastric cancer (CheckMate-649).
* **AstraZeneca / Daiichi Sankyo:** This partnership has successfully launched Enhertu (trastuzumab deruxtecan), the fastest-growing ADC, and is expanding into earlier lines of therapy and IO combinations [[18](https://www.biochempeg.com/article/447.html)].

**Strategic Mergers & Acquisitions (M&A):**  
Big Pharma is aggressively acquiring ADC and bispecific antibody technologies to complement their existing IO portfolios.

**Table 5: Key Strategic Transactions Shaping the Landscape**

| Date | Deal | Value | Rationale |
| --- | --- | --- | --- |
| Mar-23 | **Pfizer acquires Seagen** | US $43 B | To gain a leading ADC platform and pipeline [[21](https://www.pharmaceutical-technology.com/data-insights/ma-activity-immuno-oncology-pharmaceutical-industry/)]. |
| Nov-23 | **AbbVie buys ImmunoGen** | US $10.1 B | To access next-generation ADC technology [[21](https://www.pharmaceutical-technology.com/data-insights/ma-activity-immuno-oncology-pharmaceutical-industry/)]. |
| Apr-24 | **Vertex acquires Alpine Immune Sciences** | US $4.9 B | To diversify into PD-1/ICOS bispecifics [[21](https://www.pharmaceutical-technology.com/data-insights/ma-activity-immuno-oncology-pharmaceutical-industry/)]. |
| Ongoing | **Daiichi Sankyo + AstraZeneca** | Up to US $6.9 B | Global co-development and profit-sharing for Enhertu [[18](https://www.biochempeg.com/article/447.html)]. |

**8. Emerging Targets and Next-Generation Approaches**

The patent landscape from 2020-2025 reveals a clear trajectory toward highly specific, multi-pronged attacks on cancer cells, moving far beyond simple checkpoint blockade.

**Key Trends from Patent Filings:**

1. **Dominance of CLDN18.2:** This target is the subject of intense competition, with at least six independent patent families filed since 2020 by companies like Bolt Biotherapeutics, Harbour BioMed, and Henlius. Innovations focus on novel antibody scaffolds, unique epitopes, and advanced ADC payloads, such as TLR7/8 agonists that add innate immune activation [[26](https://patents.google.com/patent/WO2024173387A1/en)][[27](https://patents.google.com/patent/WO2021063336A1/en)][[28](https://patents.google.com/patent/WO2021058000A1/en)][[29](https://patents.google.com/patent/WO2021032157A1/en)].
2. **Evolution of TROP2-Targeted ADCs:** Following the success of sacituzumab govitecan, new patents from Daiichi Sankyo and Biosion focus on second-generation ADCs with refined linkers and smaller binding domains (nanobodies) for deeper tumor penetration [[30](https://patents.google.com/patent/WO2020240467A1/en)][[31](https://patents.google.com/patent/WO2022095851A1/en)].
3. **Multiplex Checkpoint Inhibition:** Innovation is shifting from single targets to multi-faceted approaches. Patents from Fate Therapeutics describe iPSC-derived CAR-T/NK cells with CRISPR-mediated knockouts of multiple checkpoints (PD-1, LAG-3, TIGIT) to create "off-the-shelf" allogeneic products resistant to exhaustion [[25](https://patents.google.com/patent/WO2021011919A1/en)].
4. **Novel Therapeutic Modalities:**
   * **Antibody-Immune-Agonist Conjugates (AIACs):** Patents from Genequantum Healthcare describe platforms that link a tumor-targeting antibody (e.g., anti-CLDN18.2) to a STING or TLR agonist, designed to convert "cold" tumors into inflamed, IO-responsive ones [[32](https://patents.google.com/patent/WO2022188740A1/en)].
   * **Circular RNA (circRNA) Vaccines:** Orna Therapeutics has filed patents on a self-amplifying circRNA platform that can encode tumor antigens like CLDN18.2 or neoantigens from EBV-positive gastric cancer, creating a potential off-the-shelf therapeutic vaccine [[35](https://patents.google.com/patent/WO2022261490A2/en)].
   * **Multi-Targeting CARs:** Patents cover dual/triple-CAR constructs targeting a menu of antigens (CLDN18.2, TROP2, EpCAM) to address tumor heterogeneity and prevent antigen escape [[33](https://patents.google.com/patent/WO2021062281A2/en)].

**Table 6: Representative Patent Filings for Next-Generation Immunotherapies (2020-2025)**

| Modality | Patent No. / Status | Applicant | Core Invention |
| --- | --- | --- | --- |
| **TIGIT mAb** | WO 2021247591 A1 | Arcus Biosciences | Fully-human anti-TIGIT IgG1 panel optimized for ADCC [[24](https://patents.google.com/patent/WO2021247591A1/en)]. |
| **CLDN18.2 ADC** | WO 2024173387 A1 | Bolt Biotherapeutics | ADC with a novel TLR7/8-agonist payload [[26](https://patents.google.com/patent/WO2024173387A1/en)]. |
| **Multiplex-Edited iPSC-CAR** | WO 2021011919 A1 | Fate Therapeutics | iPSC-derived CAR-T/NK cells with PD-1, LAG-3, and TIGIT knockouts [[25](https://patents.google.com/patent/WO2021011919A1/en)]. |
| **TROP2 Nanobody** | WO 2022095851 A1 | Biosion Inc. | Camelid-derived single-domain antibodies for ADC/BiTE/CAR formats [[31](https://patents.google.com/patent/WO2022095851A1/en)]. |
| **circRNA Vaccine** | WO 2022261490 A2 | Orna Therapeutics | Self-amplifying circRNA platform for encoding tumor antigens [[35](https://patents.google.com/patent/WO2022261490A2/en)]. |

**Conclusion**

The therapeutic landscape for gastric, esophageal, and GEJ cancers is in a period of rapid and profound transformation. PD-1/PD-L1 inhibitors have established a new standard of care, but their efficacy is largely confined to biomarker-positive subgroups. The next wave of innovation, driven by a deeper understanding of tumor biology, is already underway. Antibody-drug conjugates targeting CLDN18.2 and TROP2 are poised to deliver significant clinical benefits and capture substantial market share. The intense R&D and M&A activity surrounding ADCs, bispecifics, and cellular therapies underscores a collective strategic pivot toward combination-ready platforms that can overcome immune resistance. With a market projected to grow at a double-digit CAGR through 2030, the successful development and commercialization of these next-generation immunotherapies will be critical for improving patient outcomes and will define the competitive dynamics in this challenging but highly promising field of oncology.