Regulatory Strategy Brief — EAC dual-arm program

Regulatory pathway analysis. Precedents anchored to retrieved Drugs@FDA approvals and the ClinicalTrials.gov landscape. Forward-looking pathway choices are ASSUMPTIONS requiring regulatory-affairs and FDA-interaction validation — flagged inline.

1. Regulatory precedent in EAC (retrieved, factual)

The approved EAC/GEJ landscape establishes the regulatory template for the **treatment arm**:

- **Trastuzumab** (HER2+, Genentech/Amgen) — antibody precedent in gastric/GEJ adenocarcinoma.
- **Pembrolizumab / nivolumab** (PD-1, Merck / BMS) — checkpoint approvals, incl. adjuvant (CheckMate 577) and 1L combinations.
- **Ramucirumab** (VEGFR2, Lilly), **trastuzumab deruxtecan** (HER2 ADC, Daiichi Sankyo), **zolbetuximab** (Claudin-18.2, Astellas, 2024), **tucatinib** (HER2, Seagen).

These confirm FDA acceptance of biomarker-selected antibody/ADC modalities in this indication, and OS/PFS as registrational endpoints. All are treatment-setting; there is **no molecular-interception (chemoprevention) drug approval** in Barrett's — today's standard is endoscopic surveillance + ablation. That absence is the interception arm's whitespace *and* its regulatory risk.

2. Treatment arm (GUCY2C T-cell engager) — pathway

- **Setting/sequence:** enter in advanced/metastatic EAC after standard therapy (clearest unmet need + fastest endpoint), then move earlier (peri-operative/adjuvant, mirroring the nivolumab adjuvant precedent).
- **Designations to pursue:** Fast Track (serious disease, unmet need); Orphan Drug (EAC incidence supports it); Breakthrough Therapy if early efficacy is strong. *(assumption — eligibility needs confirmation)*
- **Endpoints:** ORR/PFS for accelerated approval in later lines; OS for full approval. Patient-priority endpoints (dysphagia-free interval, swallowing function, QoL) as key secondaries — supported by the Stage-2 PFDD rationale.
- **Biomarker strategy:** GUCY2C-positivity companion diagnostic co-developed (PMA-track CDx alongside the therapeutic).
- **Key regulatory risk:** on-target/off-tumor GI toxicity of a T-cell engager against an antigen also on normal enterocytes — FDA will scrutinize the therapeutic window; step-up dosing + CRS management plan required.

3. Interception arm (DKK1 trap) — pathway

- **The hard problem:** intervening in Barrett's/dysplasia is a **cancer-interception / chemoprevention** setting — a largely pre-malignant population, so the safety bar is very high and trials are long (progression is the event).
- **Endpoint strategy:** histologic dysplasia regression / rate of progression to HGD or EAC as the primary; requires FDA alignment on an accepted surrogate. *(assumption — surrogate acceptance is not established; this is O-4 from the science plan.)*
- **Enrichment:** target the highest-risk Barrett's (HGD, long-segment, p53-aberrant) to shorten trials and improve benefit/risk — an enrichment strategy FDA has encouraged in prevention.
- **Designations:** Orphan (HGD Barrett's is a defined smaller population); potential for an interception-focused engagement given FDA's stated interest in cancer prevention.
- **Precedent gap:** no direct approval template — model on Barrett's ablation-device trials + oncology-prevention guidance; expect an FDA meeting early to de-risk the endpoint.

4. Cross-program regulatory assumptions (flagged)

- A-1: Accelerated approval available on ORR/PFS in later-line EAC (treatment arm). *Likely but confirm current EAC guidance.*
- A-2: A histologic/molecular surrogate is negotiable for the interception arm. **High uncertainty — the central regulatory risk.**
- A-3: Both assets qualify for Orphan Drug designation. *Needs incidence confirmation for the specific setting.*
- A-4: CDx co-development timeline aligns with therapeutic (treatment arm).

5. Recommended first regulatory interactions

1. Pre-IND meeting (treatment arm) — align on later-line accelerated-approval endpoints + CDx.

2. Early FDA interception/prevention meeting (DKK1 arm) — the surrogate-endpoint question must be settled before committing to the long prevention trial.