Commercial & Financing Brief — EAC dual-arm program

Market and financing analysis. Epidemiology anchored to cited public sources; commercial projections are ASSUMPTIONS/scenarios, not forecasts. Not investment advice.

1. Epidemiology & addressable population

- **EAC incidence:** ~22,370 new US esophageal cancer cases and ~16,130 deaths projected for 2024; EAC is now the predominant US subtype and the only one still rising (AAPC +1.6%/yr 1992–2019). Age-standardized EAC incidence roughly doubled (1.7 → 3.6 per 100,000, 1988–2020). *(SEER/CA Cancer J Clin analyses.)*
- **Barrett's esophagus (interception TAM):** estimated to affect up to ~5.6% of US adults; commonly cited at ~3 million US adults; ~6–7% prevalence in GERD populations. High-risk enrichable subsets: long-segment BE, and HGD (the highest-progression group).
- **Trajectory framing:** the treatment arm addresses a ~22k/yr incident, high-mortality cancer; the interception arm addresses a multi-million pre-malignant pool that must be **risk-enriched** (HGD/long-segment/p53-aberrant) to be a tractable, payable population.

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

- **Positioning:** biomarker-selected (GUCY2C+) immunotherapy for advanced EAC, entering post-standard-of-care then moving to peri-operative. Differentiated from the crowded HER2/PD-1/VEGF field (novelty steer) and from the emerging B7-H3/TROP2 ADC wave by mechanism (T-cell redirection) and by GUCY2C's GI-restriction.
- **Comparables:** the EAC/GEJ biologic market is validated and competitive — trastuzumab, pembrolizumab, nivolumab, ramucirumab, T-DXd, zolbetuximab are all approved (Drugs@FDA). Pricing/uptake templates exist; oncology biologics in this setting command high per-patient revenue.
- **Value driver:** if the GUCY2C therapeutic window holds, a redirected T-cell engager could deliver deep responses where checkpoint/ADC leave gaps. **Commercial make-or-break = the same as the science make-or-break: GI safety window.**

3. Interception arm (DKK1 trap) — commercial thesis

- **Positioning:** first molecular interception agent for high-risk Barrett's — a category that today has **no drug**, only surveillance + ablation. Large latent population, strong patient-priority fit (avoid/defer esophagectomy; well-tolerated).
- **Commercial risk:** prevention economics are hard — long trials, pricing pressure for a pre-malignant indication, and reimbursement tied to demonstrating progression reduction. Value hinges on the surrogate-endpoint outcome (regulatory A-2) and on enrichment to a payable high-risk subset.
- **Upside:** a validated interception drug would define a new market and pair naturally with the diagnostic/surveillance ecosystem (Cytosponge, ctDNA).

4. Financing strategy (staged, milestone-gated)

- **Seed/Series A:** fund the CMC + IND-enabling package for the **treatment arm first** (clearer regulatory path, faster value inflection); carry DKK1 as a fast-follow.
- **Value inflections that unlock the next round:** (i) developability + affinity data on the leads (G1/G2); (ii) in-vivo PoC in EAC models (G4); (iii) first-in-human safety establishing the GUCY2C window (the key de-risking event).

- **Interception arm financing:** best advanced after an early FDA meeting settles the surrogate endpoint — until then it is option value, not a fundable trial.
- **Partnering:** the treatment arm fits pharma EAC/GI-oncology portfolios (multiple active players from the landscape); the interception arm may suit a prevention-focused or GI-specialty partner + diagnostics co-development.

5. Commercial assumptions (flagged)

- C-1: GUCY2C+ prevalence in EAC is high enough to support a biomarker-selected launch — **needs IHC prevalence data (not yet measured).**
- C-2: T-cell-engager GI safety is manageable at efficacious doses (mirrors regulatory O-3).
- C-3: A high-risk Barrett's subset is large and identifiable enough to make interception economics work.
- C-4: Payers will reimburse a pre-malignant interception drug — unproven; depends on progression-reduction evidence.

6. One-line commercial verdict

A **de-risked-by-precedent treatment asset** (GUCY2C, crowded-market-avoidant, gated on a GI window) paired with a **high-upside/high-uncertainty first-in-class interception asset** (DKK1, gated on a regulatory surrogate) — fund the treatment arm to first-in-human, hold the interception arm as milestone-gated option value.