AACR Adaptive Biomarker-Driven Organ Preservation Trial in Gastroesophageal Adenocarcinomas (AACR-ADOPT-GEA)

Poster #CT223

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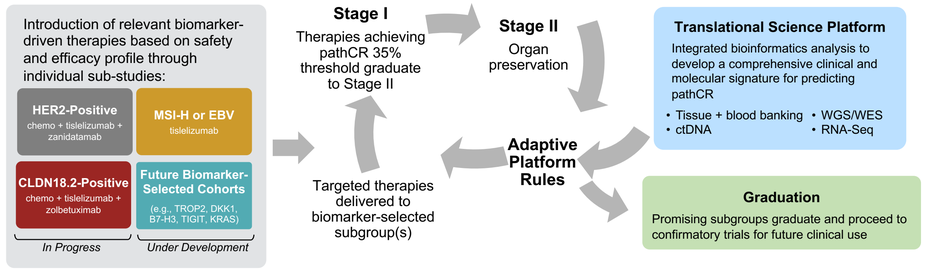
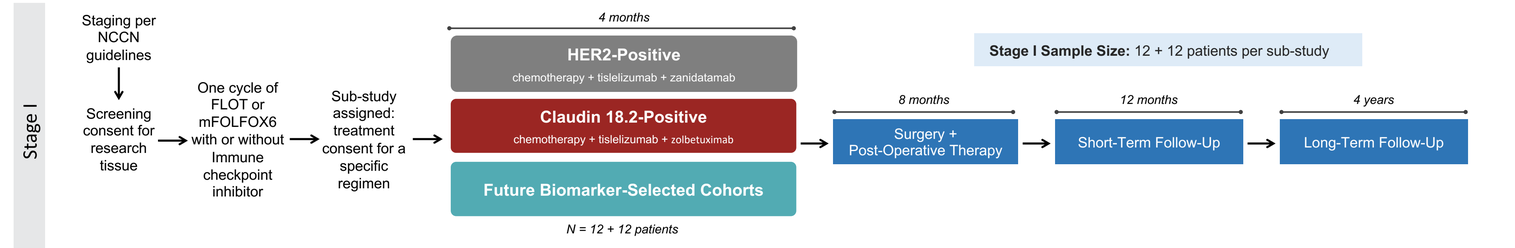
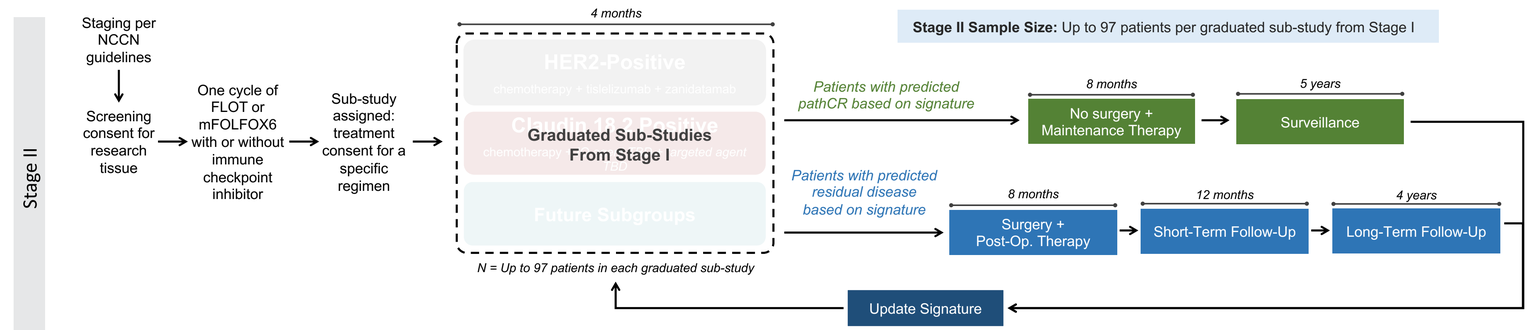
Background

- Localized gastroesophageal adenocarcinomas (GEA) are molecularly heterogeneous and often exhibit limited sensitivity to current systemic therapies[1]. The 5-year survival rate with standard perioperative chemotherapy is ~40%, and only ~15% of patients achieve a pathologic complete response (pathCR)[2,3].
- The addition of durvalumab to perioperative chemotherapy in the MATTERHORN[4] trial has begun to shift the treatment paradigm in localized GEA, with improvements observed in pathCR and survival outcomes.
- Several targetable biomarkers – HER2[5, 6], MSI[7,8], EBV[9], and CLDN18.2[10, 11] – have demonstrated therapeutic relevance in metastatic GEA.
- AACR-ADOPT-GEA (NCT07290985) was designed to investigate, for the first time in GEA, if organ preservation is achievable by delivering biomarker-matched targeted therapies to patients.
- AACR-ADOPT-GEA is a two-stage, prospective, multi-centre, adaptive, perioperative biomarker driven open-label study, consisting of a screening and testing phase.
- We hypothesize that in biomarker-selected cohorts, addition of a targeted agent to perioperative chemotherapy and immune checkpoint inhibition in locally advanced GEA can increase pathCR rates and enable 5-year organ preservation in approx. 20% of patients.



Study Design





Study Objectives

Stage I

Primary:
To identify a specific biomarker-directed perioperative systemic therapy with a target of a 35% pathological complete response in each biomarker selected subgroup to qualify to enter Stage II to implement an organ preservation approach

Secondary:
1) To demonstrate non-inferior outcomes relative to historical reference in:
   a) Event free survival (EFS)
   b) Overall survival (OS)
   c) Tumor regression grade in the surgical specimen as per NCCN guidelines
2) To evaluate the association between ctDNA levels / clearance and patient outcomes
3) To assess toxicity and tolerability of each treatment

Stage II

Primary:
To identify biomarker-driven treatments that enable organ preservation in at least 20% of patients

Secondary:
1) To evaluate the association between ctDNA levels / clearance and patient outcomes
2) To develop a predictive model for pathCR based on clinical variables and molecular parameters

Key Inclusion Criteria

- Age ≥18 years and baseline Eastern Cooperative Oncology Group (ECOG) performance status ≤1
- Histologically confirmed diagnosis of resectable adenocarcinoma of the stomach or esophagus including the GE junction; stage II or higher disease (≥T2 N0-3 M0 or T0-4a N1-3 M0)
- Tumor sample tested at a central laboratory confirming PD-L1 TAP score ≥1%
- **Zanidatamab + Tislelizumab (HER2) Sub-Protocol:** HER2-positive status (HER2 IHC3+ or IHC2+ expression with ISH-positivity)
- **Zolbetuximab + Tislelizumab (Claudin-18.2) Sub-Protocol:** CLDN18.2-positive status (≥75% of tumor cells with moderate [2+] -to-strong [3+] expression)

Key Exclusion Criteria

- Prior treatment with more than one dose of an SOC anti-PD-1, anti-PD-L1, anti-PD-L2 or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways
- **Zanidatamab + Tislelizumab (HER2) Sub-Protocol:** Prior treatment with a HER2-targeted agent, except for subjects who received HER2-targeted treatment for breast cancer >5 years prior to initial diagnosis of GEA
- **Zolbetuximab + Tislelizumab (Claudin-18.2) Sub-Protocol:** Prior treatment with a CLDN18.2-targeted agent.

Acknowledgments

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