SOHC

SWISS ONCOLOGY & HEMATOLOGY CONGRESS

IKF/AIO-PHERFLOT: Perioperative Chemoimmunotherapy with Translational Biomarker Analyses in Localized HER2-Positive Esophagogastric Adenocarcinoma

category: clinical solid tumor oncology

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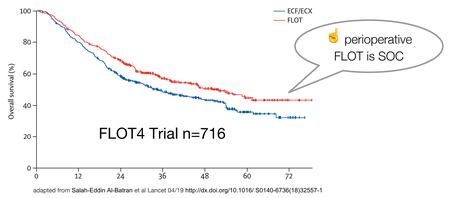
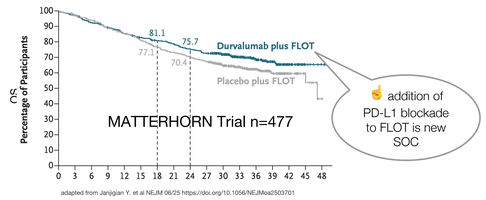
1. Localized Gastric Cancer

Localized gastric adenocarcinoma remains a high-burden disease, with **5-year overall survival of only 40–50%** despite curative-intent treatment. Perioperative chemotherapy is essential to improve long-term outcomes.

The **FLOT4** trial established FLOT as the standard perioperative regimen.



The **MATTERHORN** trial further improved outcomes by adding durvalumab, demonstrating higher major pathologic response rates and better event-free survival. This positions **FLOT + durvalumab** as the emerging **new standard of care**.

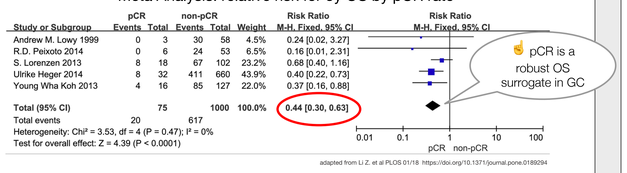


In the metastatic setting, **HER2-targeted therapy** improves survival in HER2-positive gastric cancer; however, its benefit in the **perioperative** setting **remains unproven**. This gap highlights the need for trials evaluating HER2-directed strategies in localized disease.

20-22% of gastric cancers are HER2+ 🤓 PETRARCA trial was stopped (Trastuzumab + Pertuzumab + FLOT in HER2+ GC)

Pathological complete response (pCR) has emerged as a **robust surrogate endpoint** in gastric cancer. Higher pCR rates consistently correlate with improved overall and disease-free survival, supporting the use of pCR as a valuable measure of perioperative treatment efficacy in clinical trials.

Meta Analysis: relative risk for 5y OS by pCR rate



pCR rates:

FLOT4:	16% vs 6%
DANTE:	24% vs 15%
MATTERHORN:	19% vs 7%
PETRARCA:	35% vs 12%

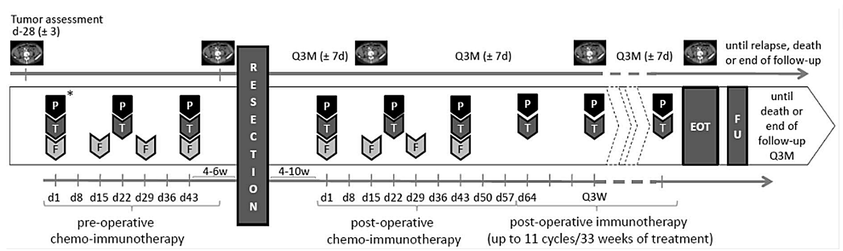
2. The IKF/AIO-PHERFLOT Trial

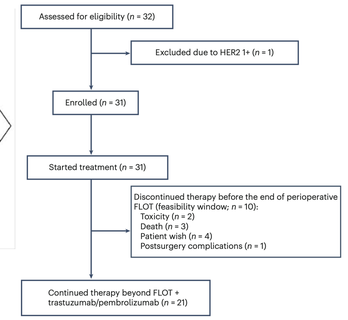
This single arm phase II trial tested the efficacy of the addition of Pembrolizumab and Trastuzumab to perioperative FLOT in patients with HER2-positive, localized esophagogastric adenocarcinoma.

Primary end point: pathological complete response **(pCR)**

Summary Inclusion Criteria:

- cT2–4, any N, M0, or any T, N+ or M0
- HER2-positive, defined as IHC 3+ or IHC 2+ with ISH+
- Laparoscopy was required in T3, T4 or diffuse histology
- no more than 10mg Prednisolon/day

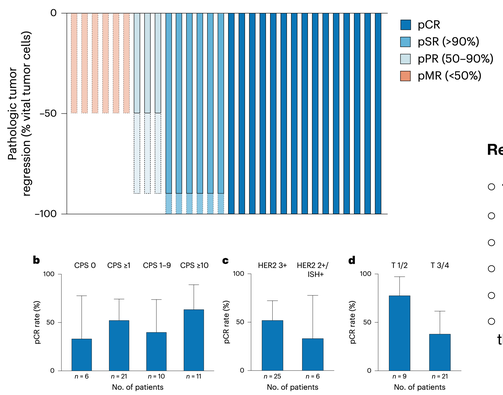




➢ **31 patients** were enrolled across 11 centers between 03/23 and 05/24

3. Clinical Trial Results

Pathological response in operated patients and in molecular and clinical subgroups.



Pathological response in the ITT population

	pCR	pSR	pPR	pMR	pNR	NA
ITT, n=31	n = 15, 48.4% (30–67)	n = 6, 19.4% (8–38)	n = 3, 9.7% (2–26)	n = 5, 16.1% (6–34)	n = 1, 3.2% (0–17)	n = 1, 3.2%

Results:

- **~50% pCR rate** 🤯
- ~70% with a major pathological response
- highest pCR rate in: T1/2, HER3+, CPS≥10, dMMR (3/3)
- 100% R0 resection rate
- deep responses also in CPS0 patients
- SAEs≥ G3: ~50% - in line with FLOT and anit HER2 therapy

Might organ preservation be possible? 🤔

4. Translational Trial Results

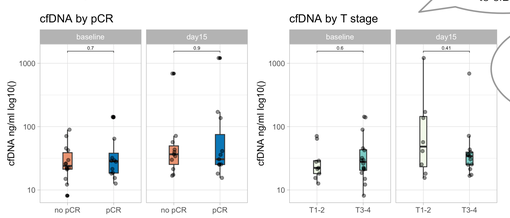
Q: Are there blood biomarkers to predict pCR for potential organ preservation? 🤔

Methods:

- Serial blood samples from 27 patients; 23 paired baseline and day 15 samples.
- T cell receptor β-chain variable region (TRBV) repertoires profiled from PBMCs.
- Diversity and clonality indices calculated at baseline and day 15.
- cfDNA isolation: QIAamp Circulating Nucleic Acid Kit, quantified with Qubit dsDNA HS.
- Leukocyte gDNA isolated from STRECK BCT tubes for TRBV repertoire amplification.
- TRBV libraries sequenced on Illumina MiSeq, ~30.000 reads/sample.
- Alignment performed with MiXCR; downstream analyses done in R with Immunarch.
- Statistical analyses: Wilcoxon signed-rank test; p<0.05.

cfDNA = cell free DNA

cfDNA analysis:

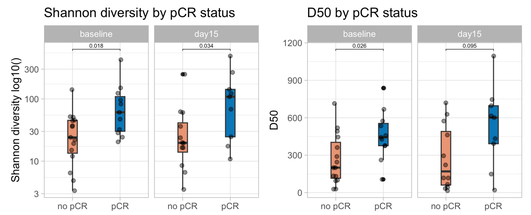


➢ day 15 levels no correlation with pCR rate

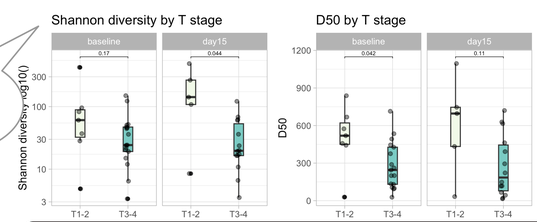
➢ higher levels in stage T3/T4 tumors at baseline but not significant

T cell immunerepertoire analysis (TRBV):

D50 measures diversity and clonality. High: many different T cells



➢ Serial immune profiling revealed that patients achieving pCR had higher TRBV diversity and richness both at baseline and after cycle 1 compared to non-pCR cases.



➢ Similarly, patients with lower tumor stage (T1/T2) exhibited higher repertoire diversity than those with T3/T4 tumors. These findings suggest that preserved T cell repertoire diversity may support more effective tumor clearance under chemoimmunotherapy.

Conclusions:

1. Pembrolizumab + Trastuzumab + FLOT was feasible and yielded an unusually high pCR rate (~50%) in localized HER2⁺ gastric cancer.
2. Patients with higher TRBV diversity/richness and lower tumor stage were more likely to achieve pCR, suggesting a role for preserved immune repertoire competence in treatment response.
3. cfDNA monitoring was feasible but did not predict pCR in this cohort. …further analysis are ongoing… 🛠️

clinical results paper:
Stein A. et al. Nat Med 10/25
https://doi.org/10.1038/s41591-025-03979-y

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