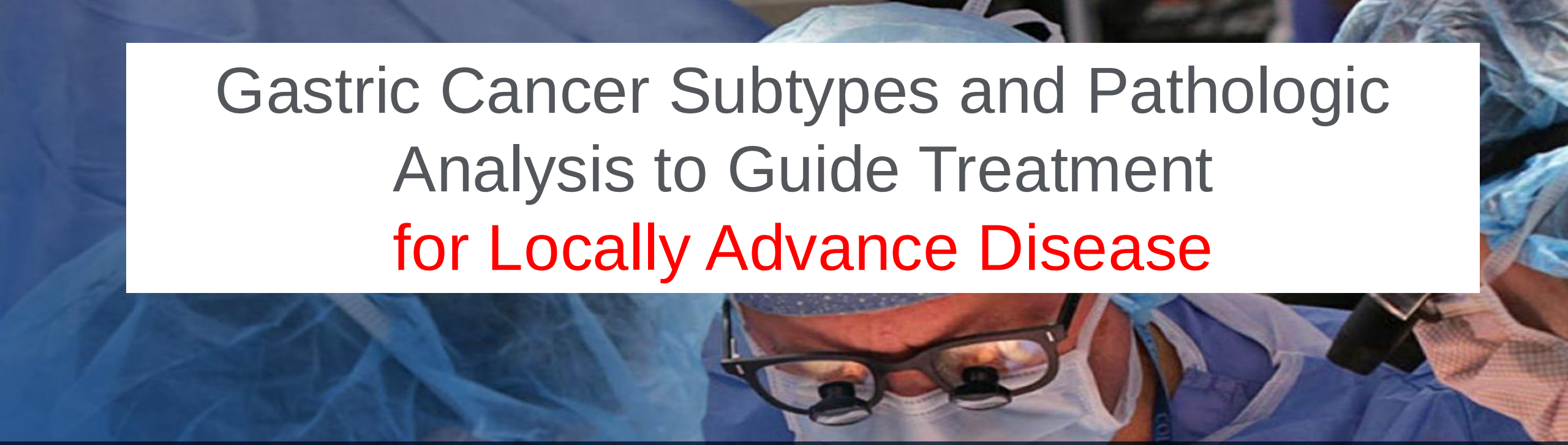


Gastric Cancer Subtypes and Pathologic Analysis to Guide Treatment for Locally Advance Disease

South Florida GI Cancer Symposium
April 11, 2025

Sam S. Yoon, M.D.
Chief, Division of Surgical Oncology
Columbia University Irving Medical Center

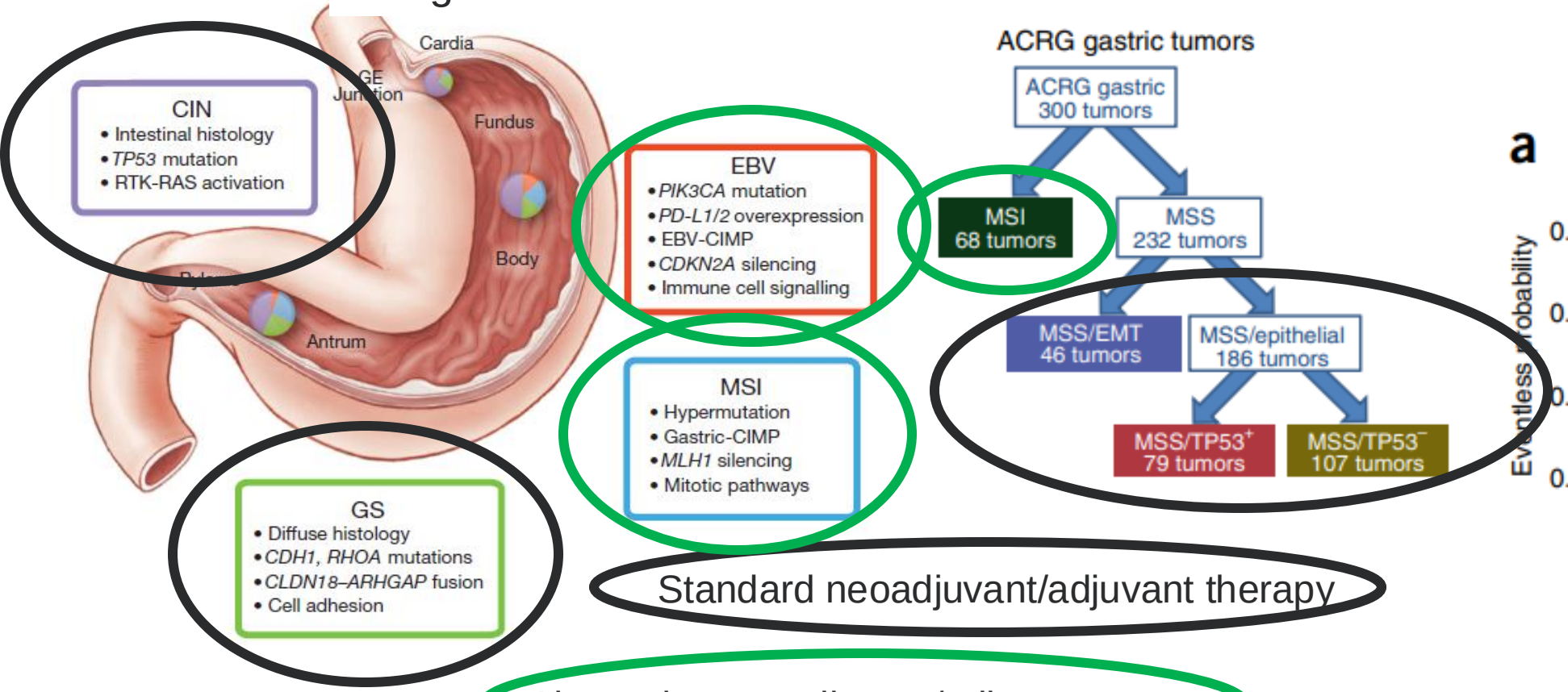
Outline

- Molecular subtypes and biomarkers
- Standard neoadjuvant/adjuvant therapy
- Immune checkpoint blockade for MSI-H tumors
- Immune checkpoint blockade plus chemo for MSS tumors
- EBV-associated tumors
- HER2 targeted therapy

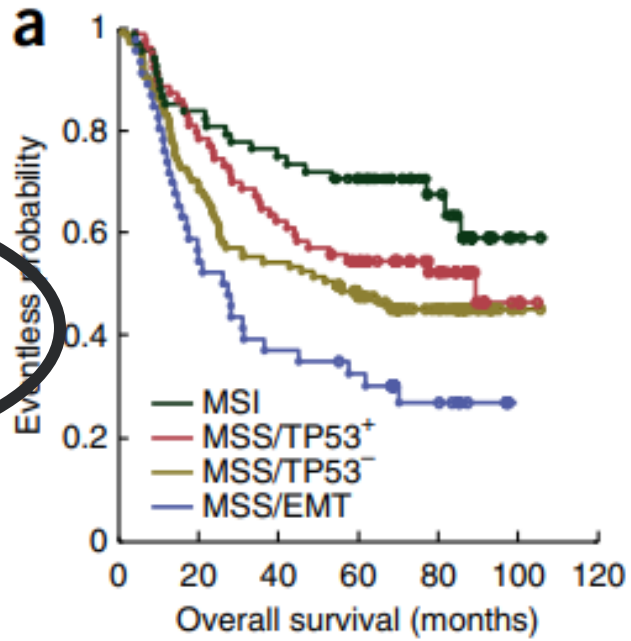
Molecular Subtypes and Biomarkers

The Cancer Genome Atlas (TCGA)

295 gastric tumors



The Asian Cancer Research Group (ACRG)



Standard neoadjuvant/adjuvant therapy

Alternative neoadjuvant/adjuvant strategy

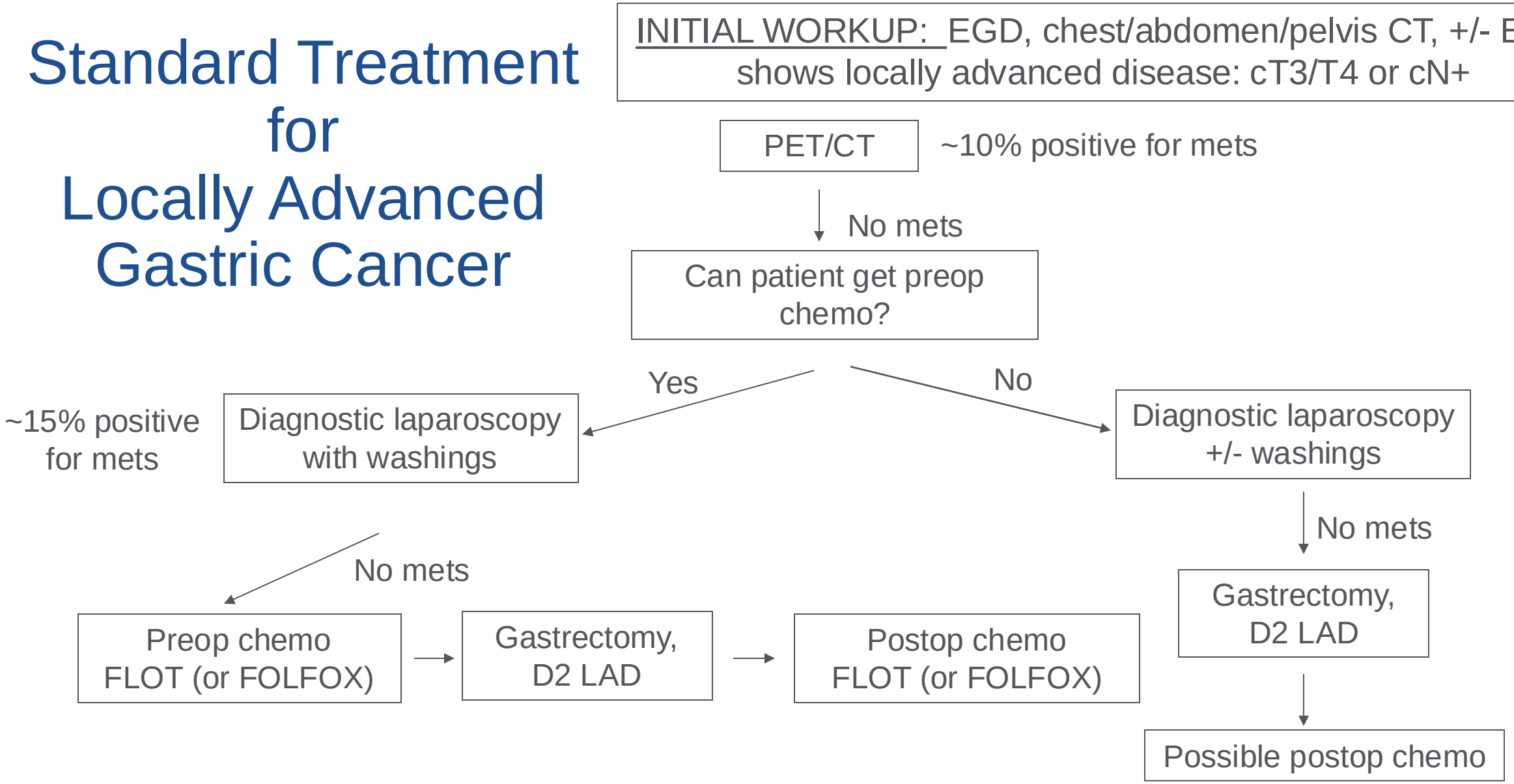
Bass A et al. Nature 2014:513:202
Cristescu R et al. Nat Med 2015:21:449

Routine Biomarkers for Newly Diagnosed GC

- Mismatch repair deficient (dMMR)/Microsatellite instability high (MSI-high)
  - Immunohistochemistry (IHC) for MMR proteins (MLH1, PMS2, MSH2, MSH6)
  - PCR-based MSI testing
- PD-L1 IHC
  - Combined Positive Score (CPS) – expression in tumor cells and immune cells
- Epstein Barr Virus (EBV)
  - EBV encoding region (EBER) in situ hybridization
- HER2 overexpression
  - HER2 IHC
    - IHC 3+
    - IHC 2+ (equivocal) and fluorescence in situ hybridization (FISH) positive
- CLDN IHC
  - 2+ or 3+ membranous staining in ≥75% of cells

Standard neoadjuvant/adjuvant therapy

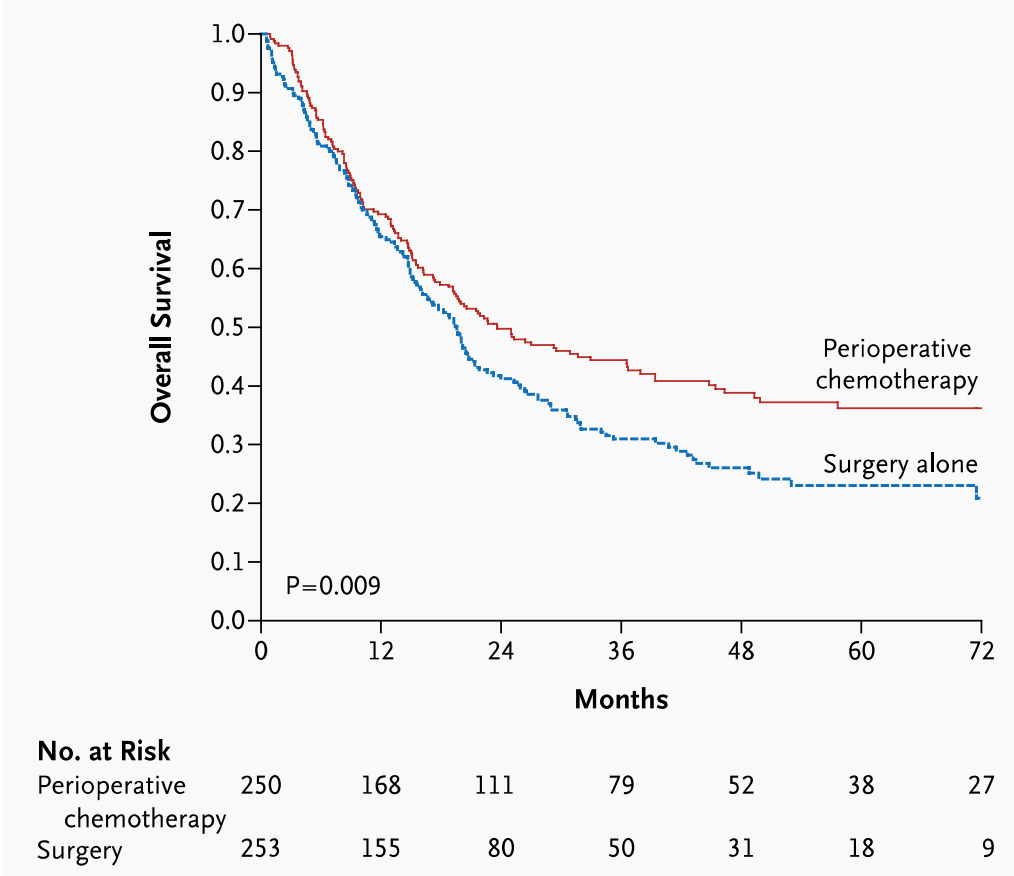
Standard Treatment for Locally Advanced Gastric Cancer



MAGIC Trial

- Patients: Resectable ≥stage II GC/GEJ/distal esophagus adenoCA
- Intervention: Periop epirubicin, cisplatin, 5-FU (ECF) plus surgery
- Control: Surgery alone

- Completion of chemo
  - 86% preop
  - 42 postop
- No significant differences in postop complications, hospital stay, and deaths



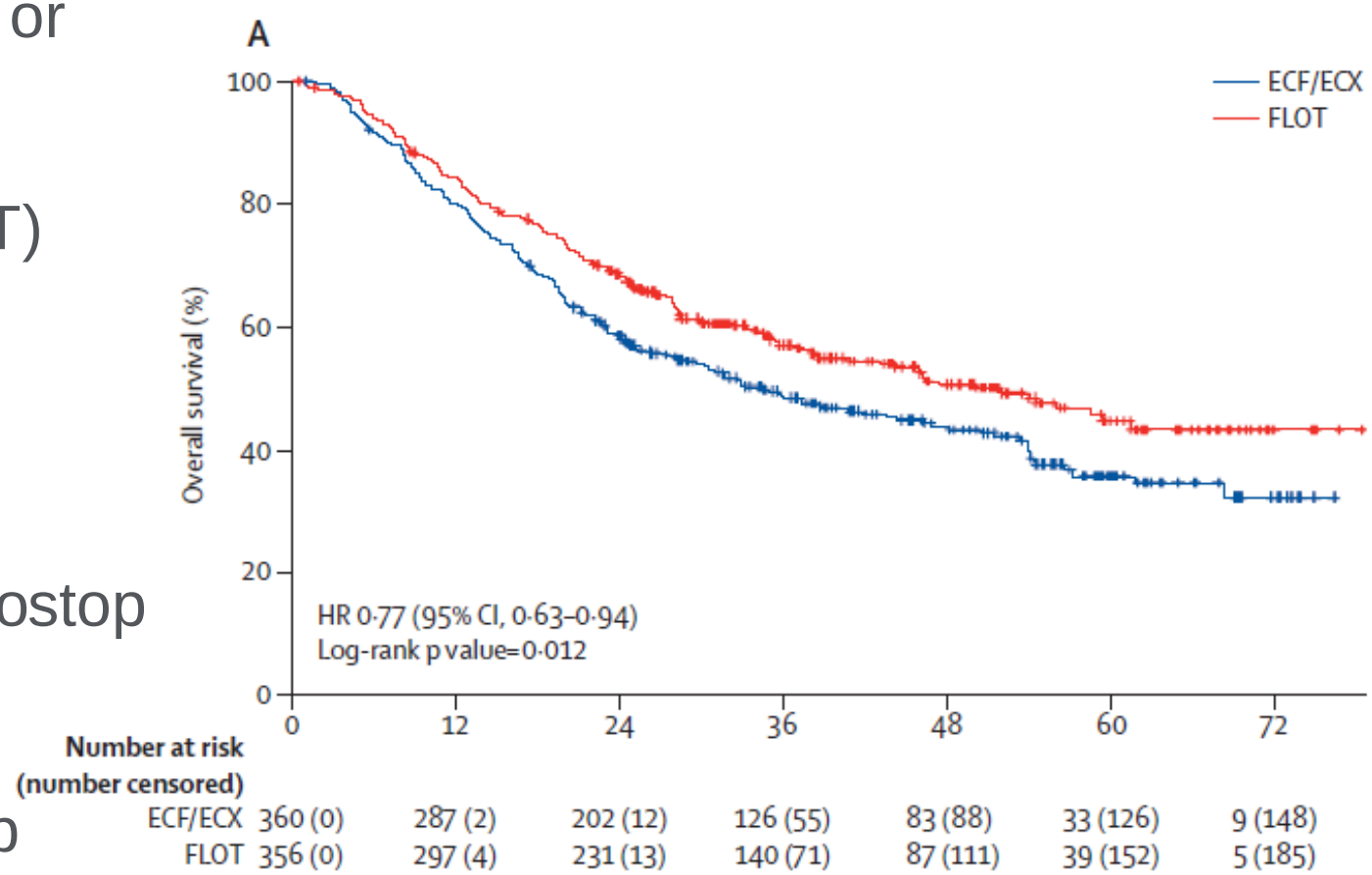
5-year OS 36% vs. 23%

Cunningham D et al. NEJM 2006:355:11

FLOT-AIO Trial

- Patients: ≥cT2 and/or cN+ gastric or GE junction adenoCA
- Intervention: Periop docetaxel, oxaliplatin, 5-FU, leucovorin (FLOT) plus surgery
- Control: Periop ECF or ECX plus surgery

- Completion of chemo preop and postop
  - 91% and 37% for ECF/ECX
  - 90% and 50% for FLOT
- No significant differences in postop complications or deaths
- pCR 16% vs 6%



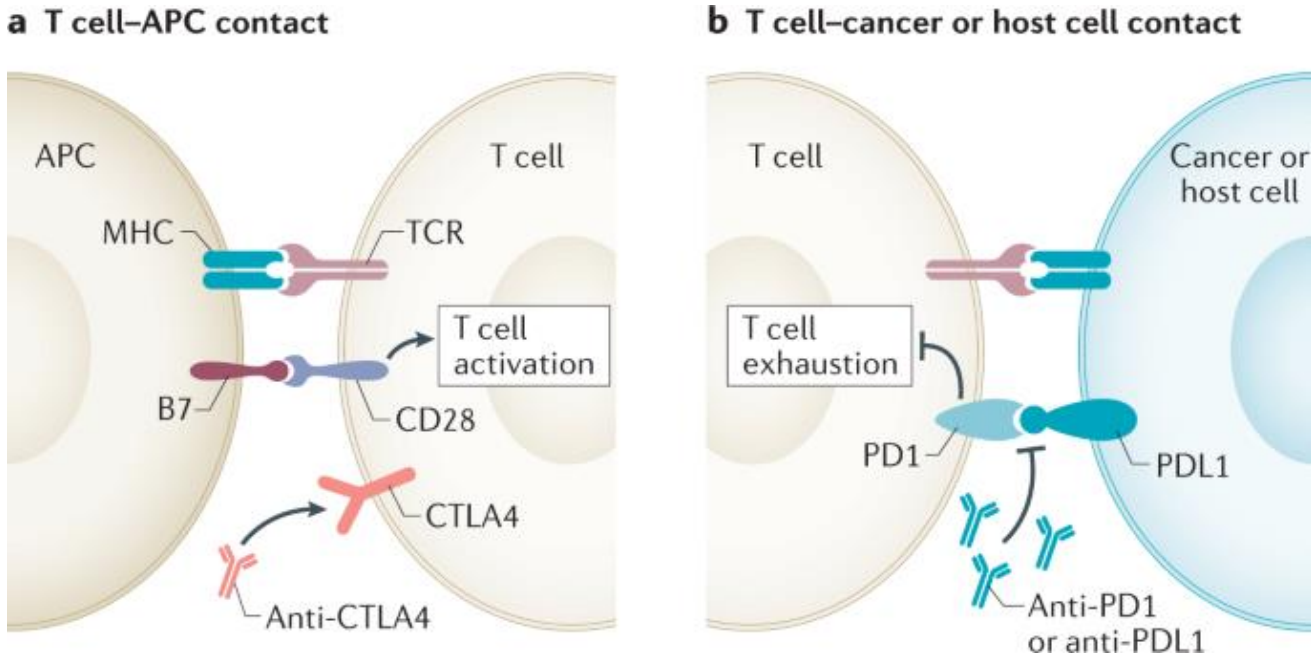
5-year OS 36% vs 45%

Al-Batran S-E et al. Lancet Oncol 2019:11:1948

Immune Checkpoint Blockade for MSI-H Tumors

Immune Checkpoint Blockade (ICB)

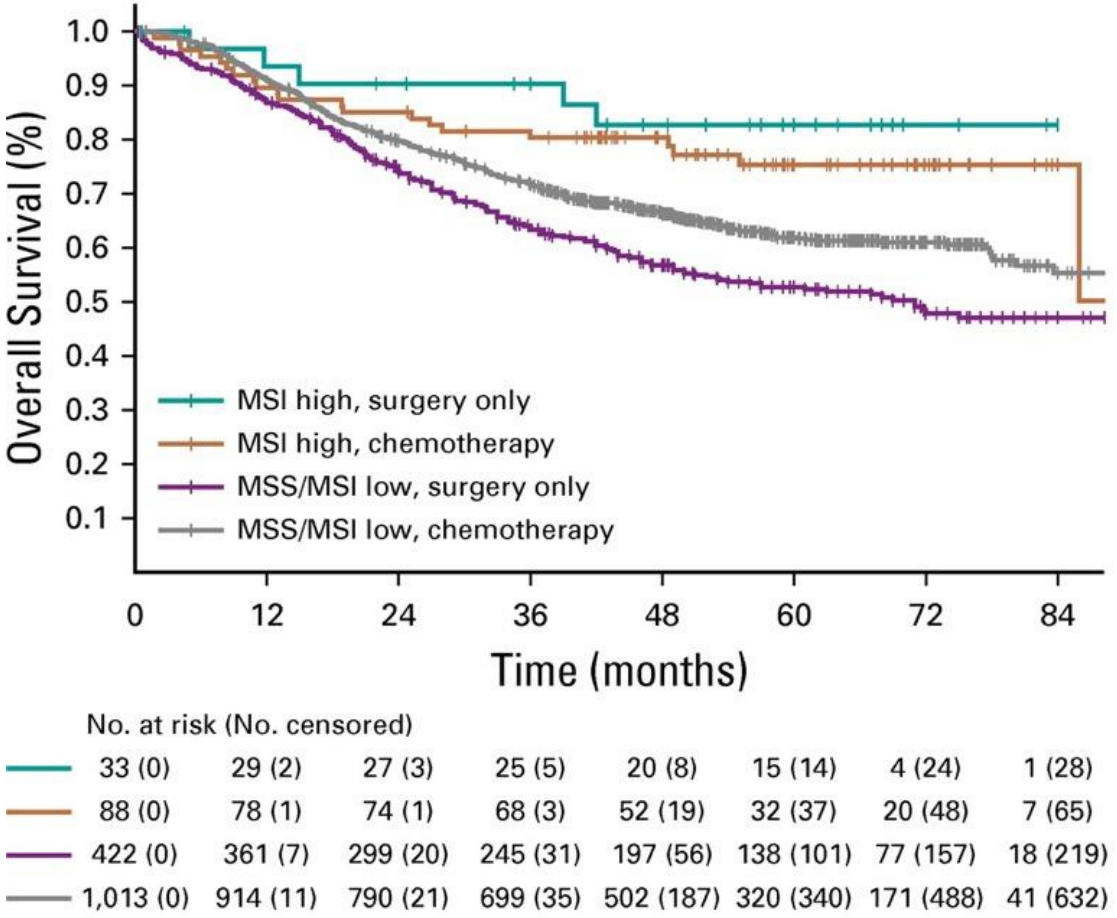
- Inhibitory communication between cancer cells, T cells, and other immune cells
- Primary pathways targeted are CTLA-4 and PD-L1/PD-1
- PD-L1 expression in tumors can correlate with response to PD-L1/PD-1 blockade



Wrigth JJ et al. Nat Rev Endocrin 2021:17:389

Chemotherapy Ineffective for MSI-H Locally Advanced Gastric Cancer (LAGC)

- Pooled meta-analysis of 4 trials (MAGIC, CLASSIC, ARTIST, ITACA-S)
- MSI-H is associated with improved prognosis
- Showed lack of benefit from periop chemo
- Consider upfront resection for MSI-H tumors
- Is there a role of neoadjuvant or adjuvant immunotherapy?



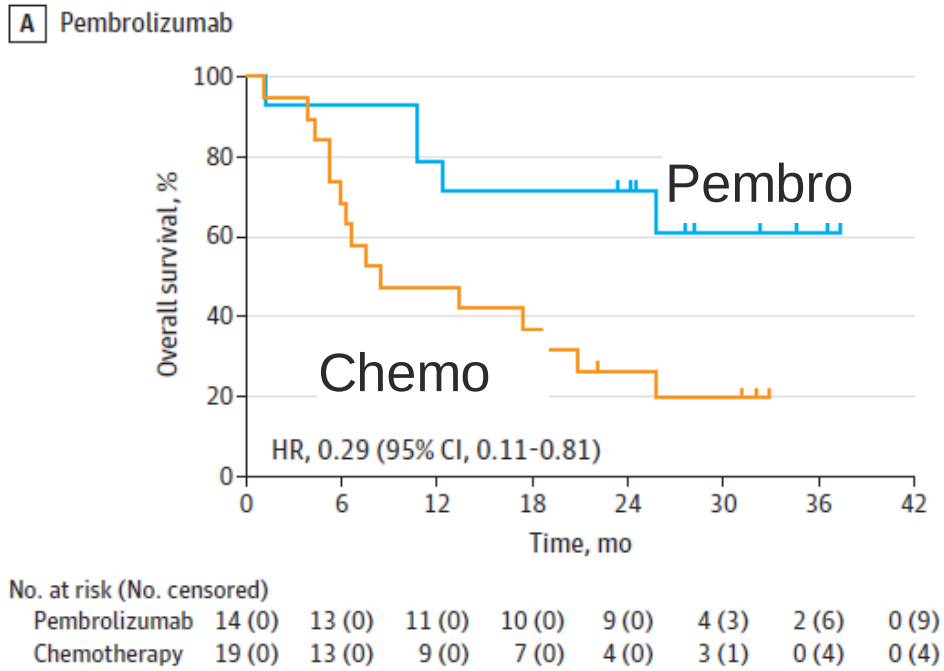
Pietrantonio et al. J Clin Oncol 2019:37:3392

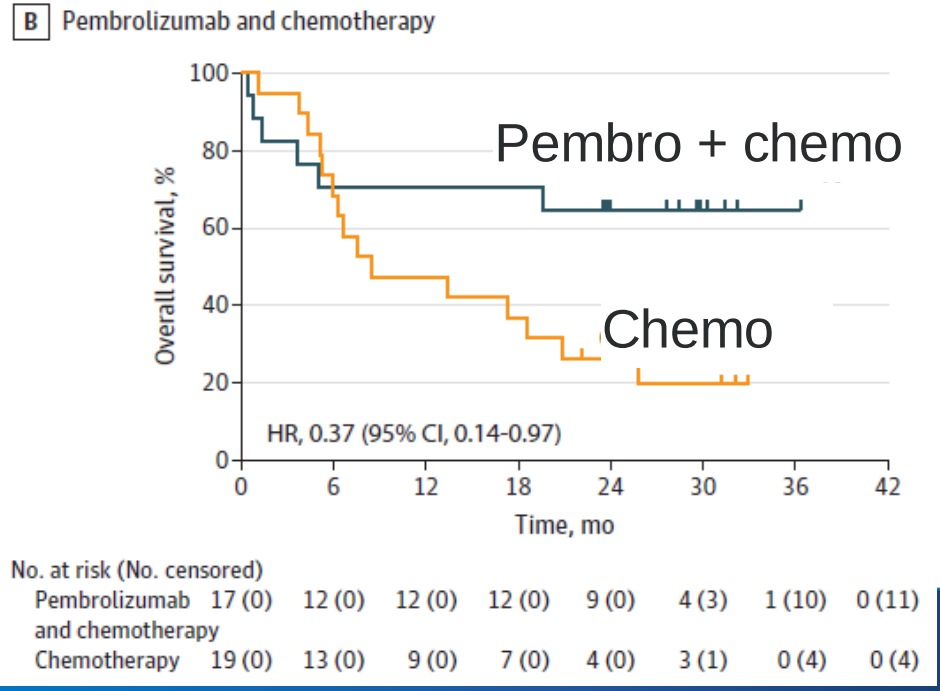
First-line ICB for MSI-H Advanced Gastric Cancer

KEYNOTE-062 Phase III

- Patients: Advanced GC/GEJC adenoCA
- Intervention: Pembrolizumab alone or pembro plus chemo (5-FU + cisplatin)
- Control: Placebo plus chemo

Shitara K et al. JAMA Oncol 2020:6:1571

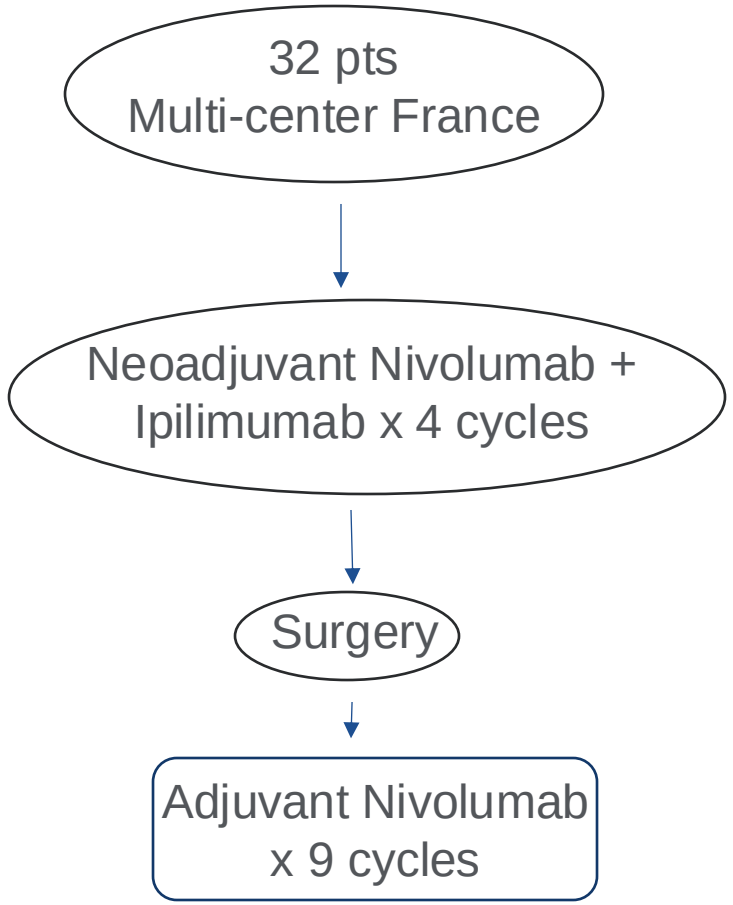




ICB for MSI-H LAGC

GERCOR NEONIPIGA Phase II

- Patients: cT2-T4/NX/M0 resectable GC/GEJC adenoCA dMMR/MSI-H
- Intervention: Nivolumab + Ipilimumab; Surgery; Nivolumab
- Control: Historical



Andre T et al. J Clin Oncol 2023:41:255

ICB for MSI-H LAGC

GERCOR NEONIPIGA

TRG Becker	
TRG 1a: complete tumor regression without residual tumor	17 (59)
TRG 1b: < 10% residual tumor per tumor bed	4 (14)[a]
TGR 2: 10% to 50% residual tumor	2 (7)
TRG 3: > 50% residual tumor cells	6 (21)

73%

At last FU, no recurrences and no deaths

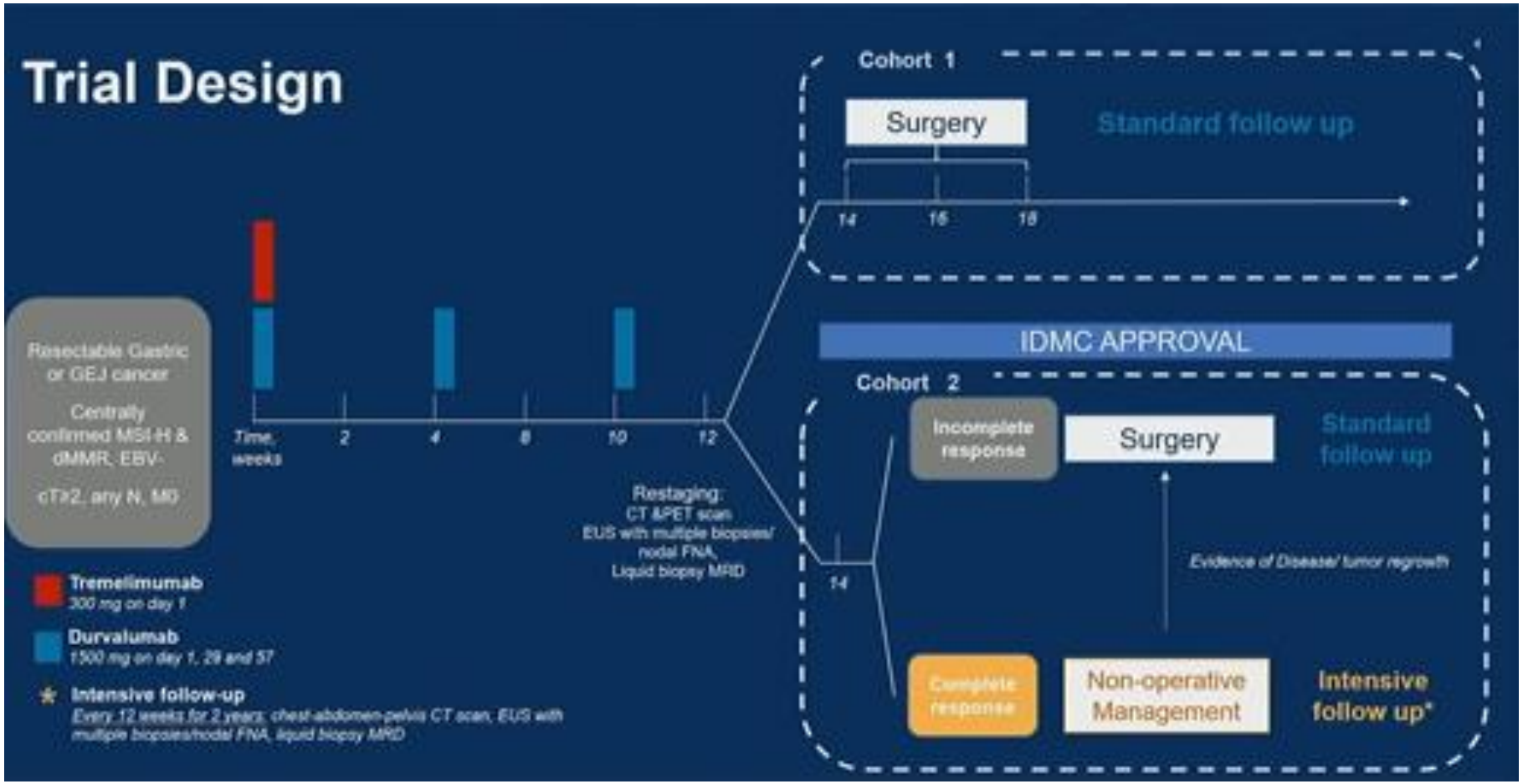
- Outcome: "Nivolumab and ipilimumab-based neoadjuvant therapy is feasible and associated with no unexpected toxicity and a high pCR rate in patients with dMMR/MSI-H resectable gastric/GEJ adenocarcinoma."

Andre T et al. J Clin Oncol 2023:41:255

ICB for MSI-H LAGC

INFINITY Phase II

- P: MSI-H, c≥T2, any N, M) GC/GEJC adenoCA
- I: Tremelimumab (anti-CTLA-4) and durvalumab (anti-PD-L1) followed by surgery
- C: Historical



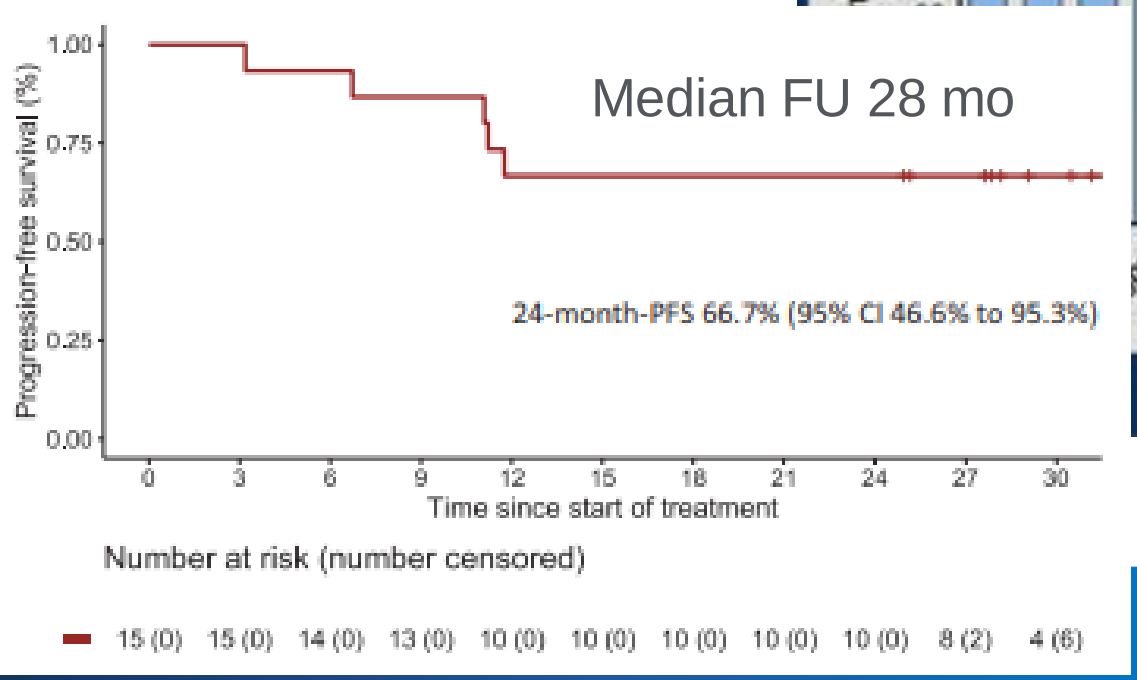
Pietrantonio F et al. ASCO GI 2023 abstract 358

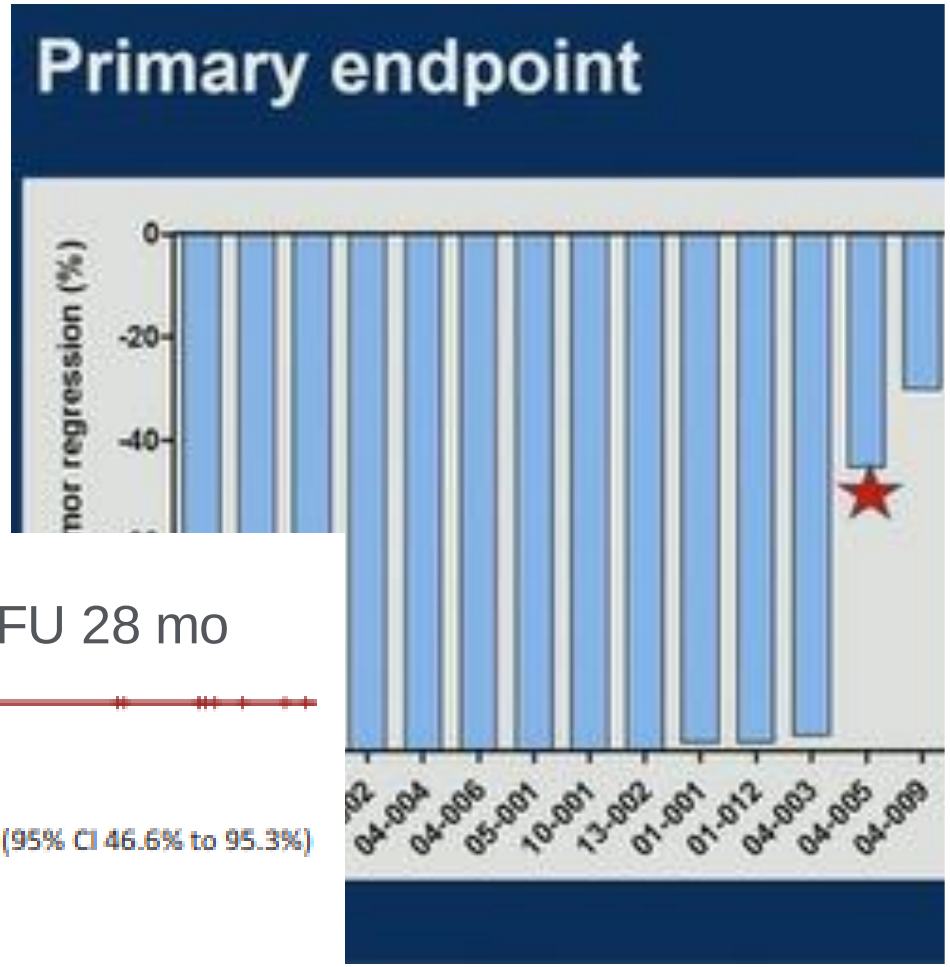
INFINITY

ICB for MSI-H LAGC

Cohort 1

- 18 enrolled pts
  - 1 pt withdrew
  - 2 pts had cCR and refused surgery
- 15 evaluable pts





Cohort 1

- 9/15 (60%): pCR
- 12/15 (80%): <10% viable tumor
- pCR for T4 tumors 1/7 (17%)

Raimondi A et al. Ann Oncol 2025:36:285

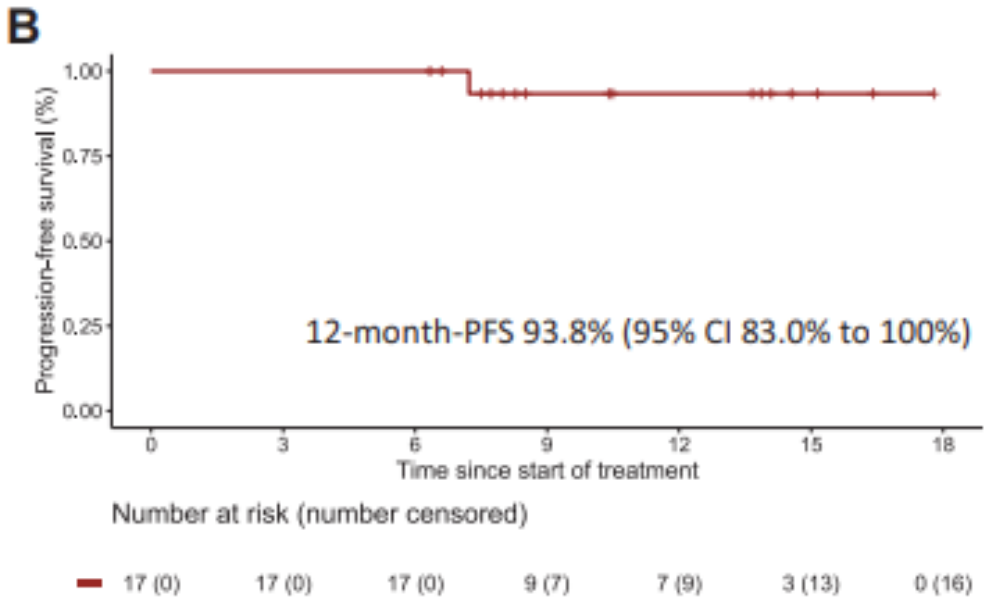
ICB for MSI-H LAGC

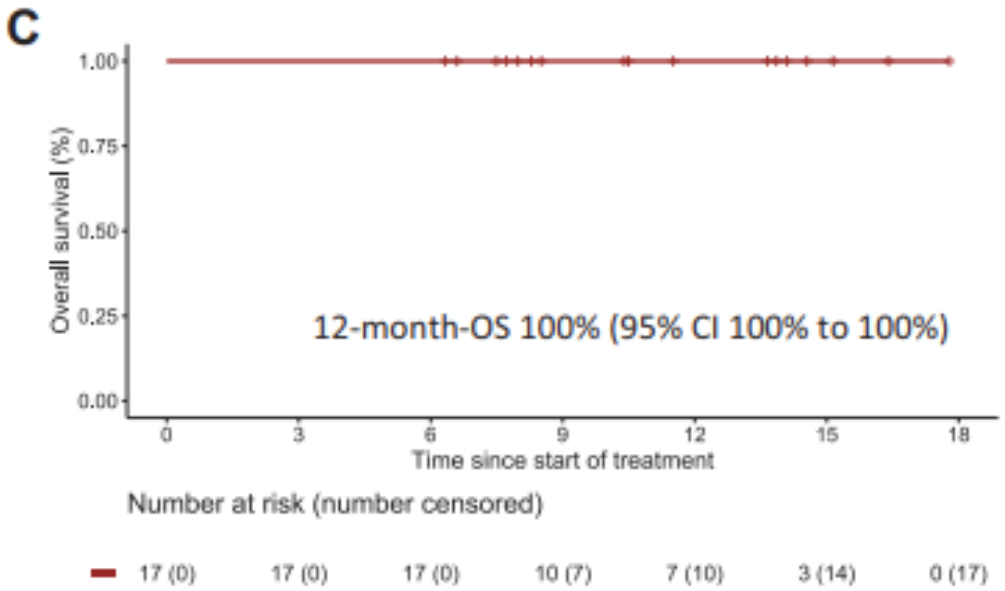
INFINITY

Cohort 2

- T4 tumors excluded
- 18 enrolled pts
  - 1 pt withdrew
- 17 evaluable pts

- 13/17 (76%): cCR and followed
  - Other 4 patients underwent surgery
- At 11.5 mo median FU
  - 1 pt with local regrowth and had salvage surgery





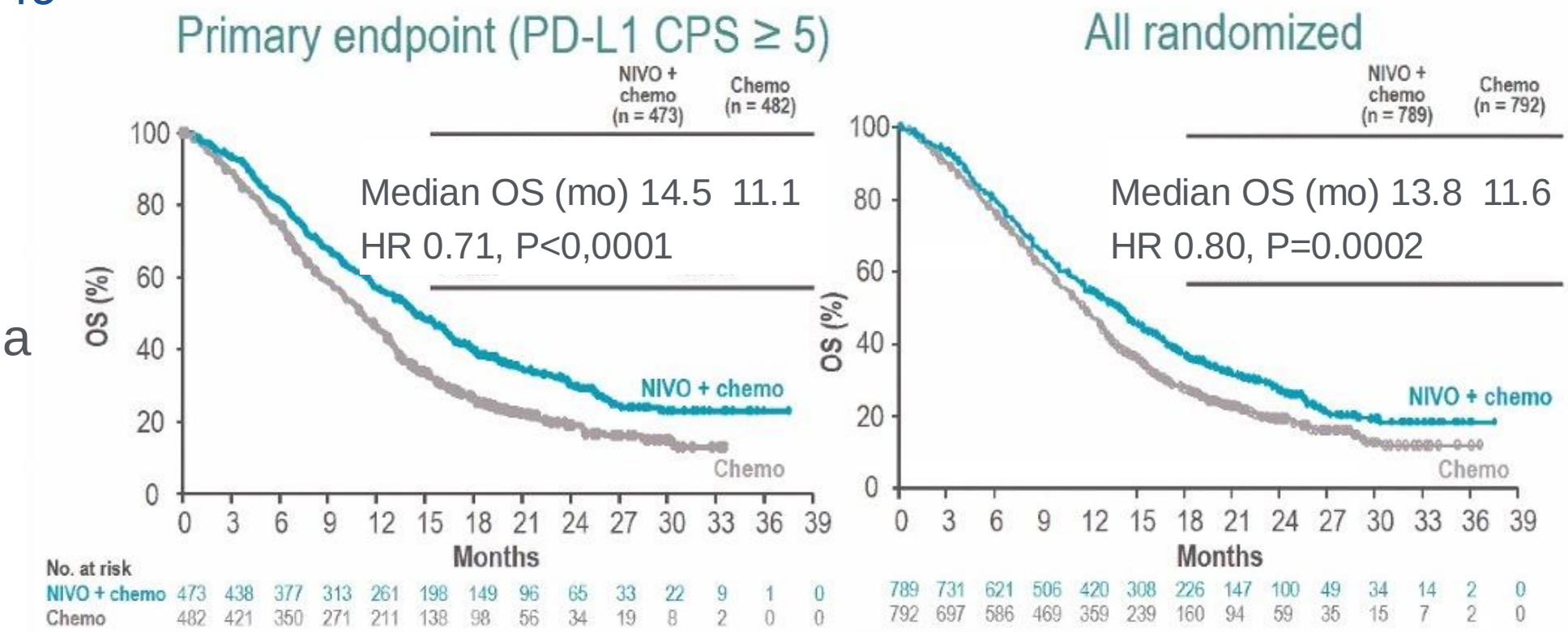
Raimondi A et al. Ann Oncol 2025:36:285

Immune checkpoint blockade plus chemo for MSS tumors

Chemotherapy and ICB for Advanced Disease

CHECKMATE- 649
Phase III

- P: Untreated advanced GC/GEJC/EC adenocarcinoma (regardless of PD-L1 status)
- I: Nivolumab plus chemo
- C: CAPOX or FOLFOX



First-line chemotherapy plus nivolumab approved by US FDA in April 2021

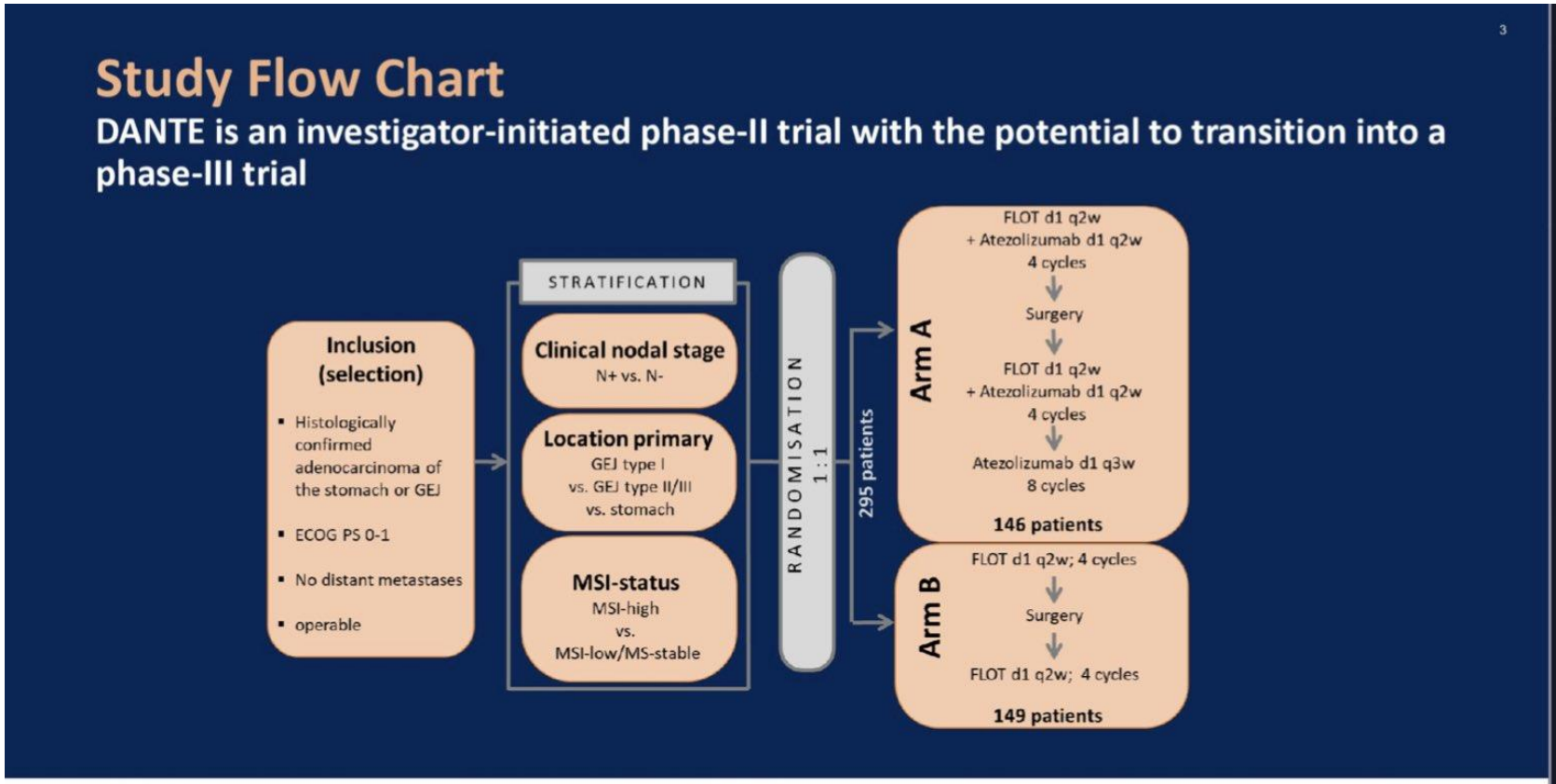
Janjigian YY et al, Lancet 2021:398:27

Chemotherapy and ICB for LAGC

DANTE

- P: ≥cT2 or N+ GC/GEJC adenocarcinoma (regardless of PD-L1 status)
- I: Atezolizumab plus FLOT
- C: FLOT
- O: pT0: 23% vs. 15%
  pN0: 68% vs. 54%

Complete regression (pCR+TRG1a): 24% vs. 15%



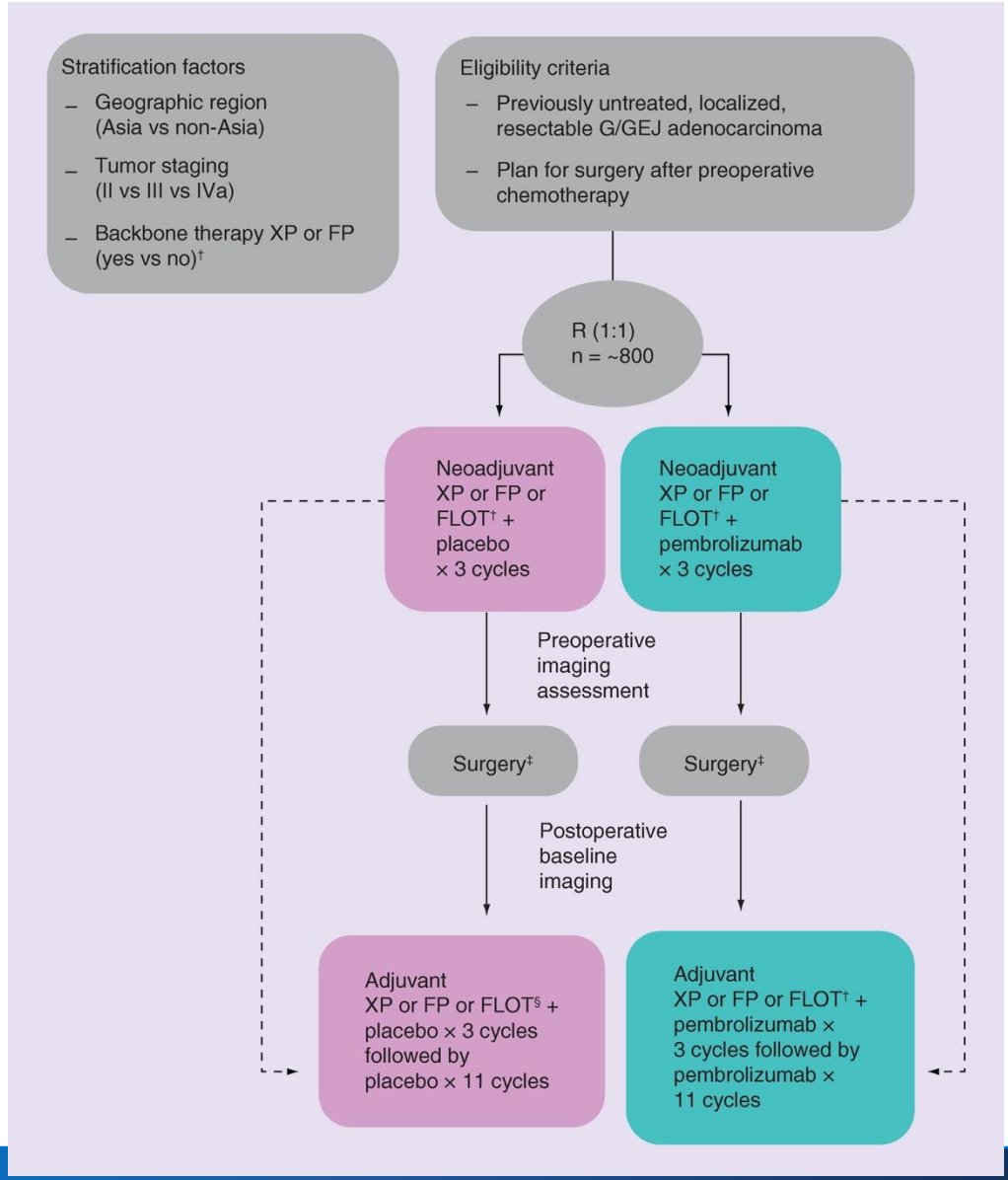
Lorenzen S et al. J. Clin Oncol 2023:42:410

Chemotherapy and ICB for LAGC

KEYNOTE-585

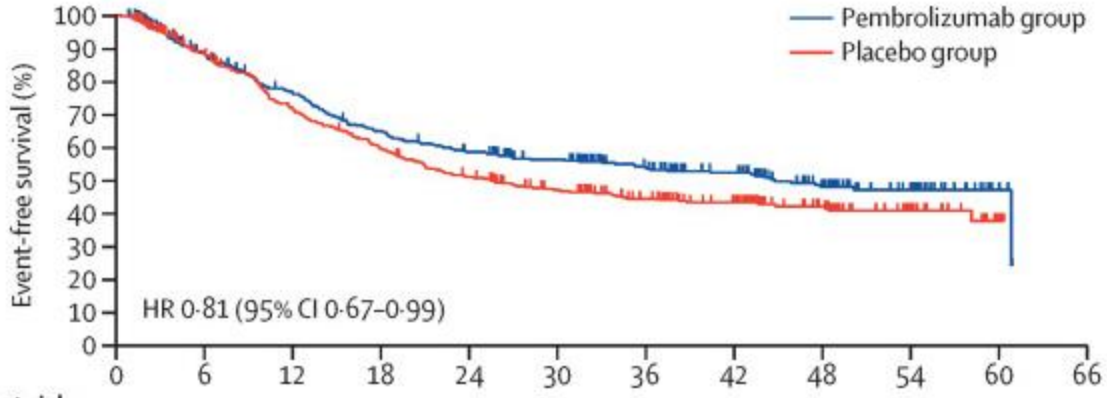
- P: Resectable stage II-IVa GC/GEJC adenoCA (regardless of PD-L1 status); 47.5% Asia, 25% Western Europe, 4.5% USA, 26.5% Other
- I: Pembrolizumab plus periop chemo
- C: XP or FP or FLOT
- O:

-- Pathologic complete response 12.9% vs 2.0% (P<.00001)
-- No significant difference in event-free survival or overall survival



Shitara K et al. Lancet Oncol 2024:25:212

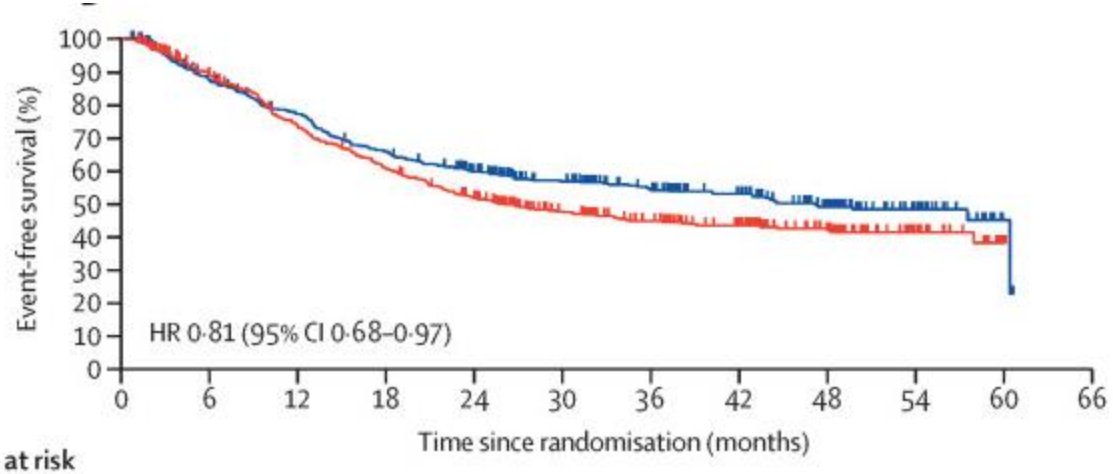
KEYNOTE-585



Number at risk (number censored)												
Pembrolizumab group	402	326	276	233	207	182	147	118	77	36	3	0
	(0)	(33)	(38)	(39)	(42)	(59)	(87)	(112)	(145)	(185)	(217)	(219)
Placebo group	402	332	265	217	183	154	126	105	63	25	3	0
	(0)	(28)	(32)	(33)	(36)	(51)	(71)	(89)	(129)	(165)	(186)	(189)

Event-free survival – Main cohort

Event-free survival – Main plus FLOT cohort



Number at risk (number censored)												
Pembrolizumab group	502	410	353	300	261	204	162	132	88	37	3	0
	(0)	(39)	(45)	(46)	(56)	(101)	(136)	(161)	(197)	(247)	(280)	(282)
Placebo group	505	423	345	282	235	176	142	120	77	26	3	0
	(0)	(35)	(40)	(41)	(46)	(87)	(111)	(129)	(170)	(219)	(241)	(244)

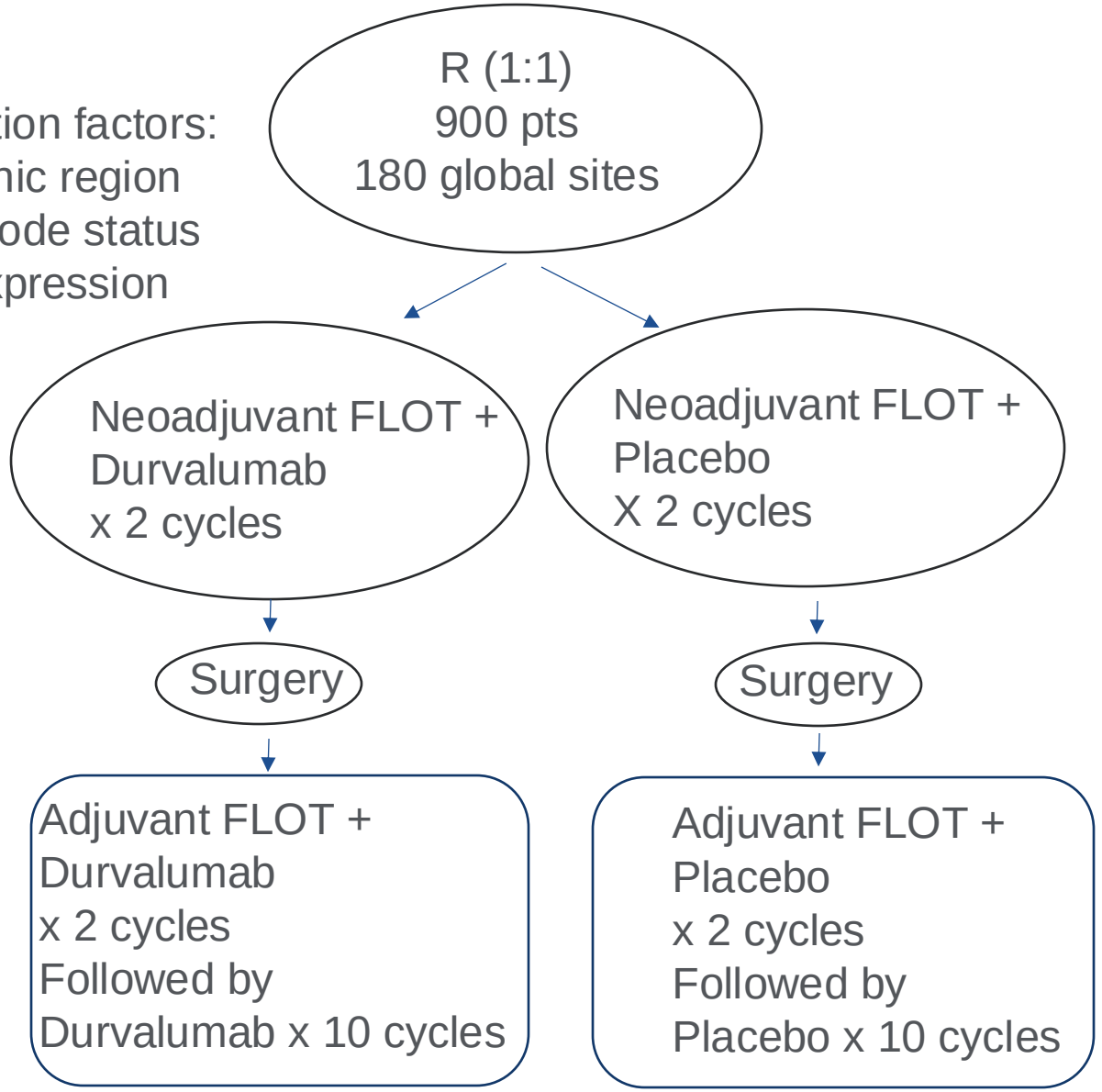
Shitara K et al. Lancet Oncol 2024:25:212

Chemotherapy and ICB for LAGC

MATTERHORN

- P: Resectable ≥stage II GC/GEJC adenoCA (regardless of PD-L1 status)
- I: Durvalumab plus FLOT
- C: FLOT

Stratification factors:
Geographic region
Clinical node status
PD-L1 expression



Janjigian YY et al. Future Oncol 2022:18:2465

Matterhorn

- Geographic region
  - 53% Europe, 19% Asia, 19% South America, 9% North America
- Pathologic complete response 19% vs. 7% (OR 3.09, P<.00001)
  - Pathologic complete or near complete response 27% vs. 14% (OR 2.19, P<0.00001)
- “Superior event-free survival”

2024 ASCO GI Cancer Symposium Abstract LBA 246
AstraZeneca press release 3/7/2025

EBV-associated tumors

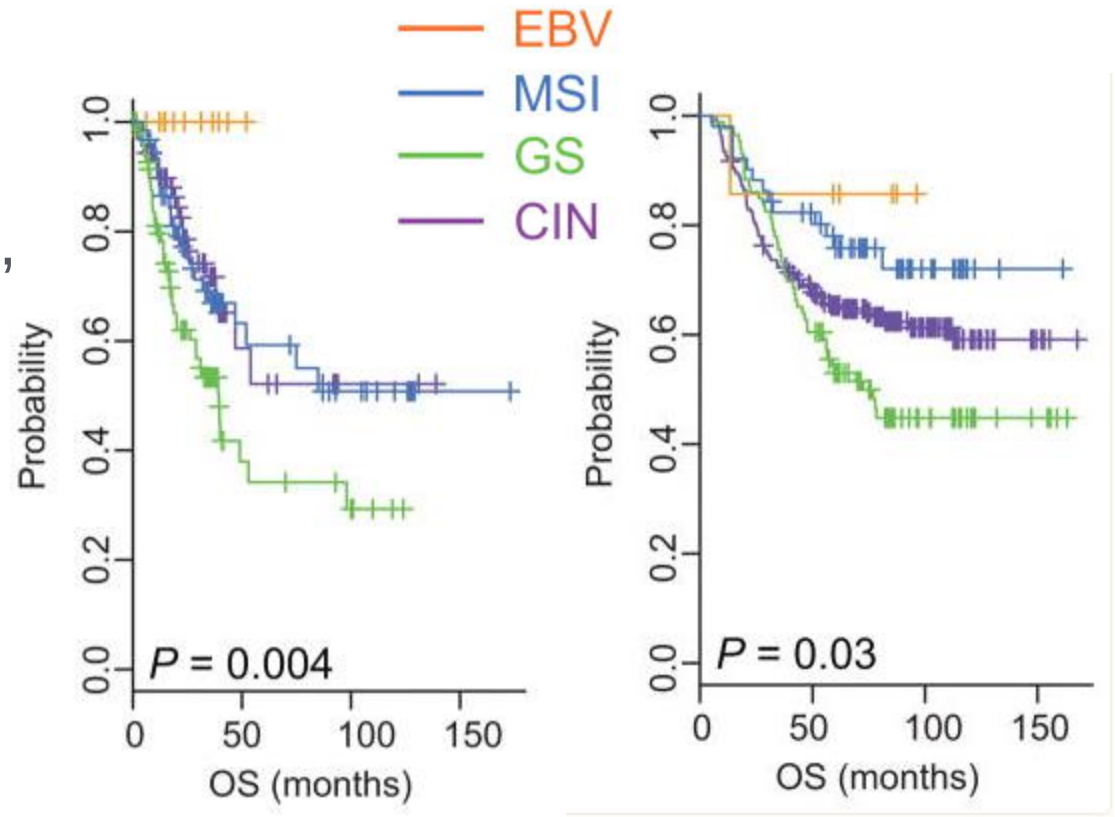
EBV-Associated Gastric Cancer

- About 8% of GCs
  - More common in pts early stage disease compared to metastatic disease
- Genetics
  - Common mutations in PIK3CA (80%), ARID1A (55%)
  - Hypermethylation
- Epidemiology
  - More common in men and younger individuals
- May have better prognosis
- Chemosensitivity unclear
- May be more responsive to immunotherapy

Sohn BH et al. Clin Cancer Res 2017:23:4441
Kohlruss M et al J Pathol Clin Res 2019:5:227
Roh CK et al. Yonsei Med 2019:60:132

EBV-Associated Gastric Cancer

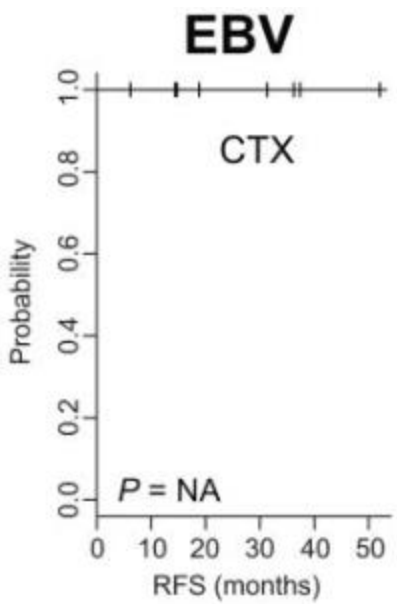
- P: Resected GC adenoCA, 2 cohorts (retrospective)
- I: Molecular analysis
- C: None



MDACC

SMC

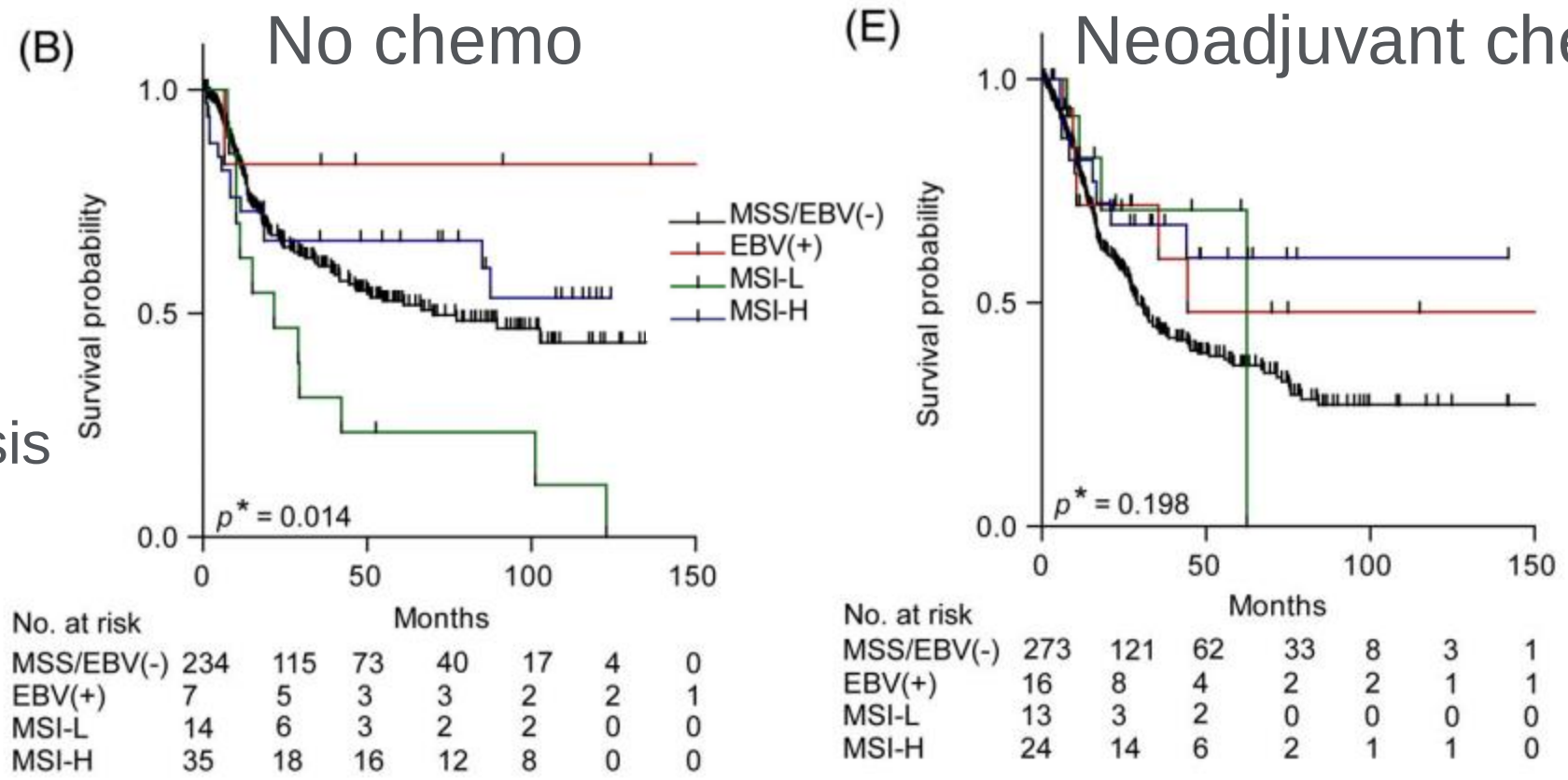
MDACC



Sohn BH et al. Clin Cancer Res 2017:23:4441

EBV-Associated Gastric Cancer

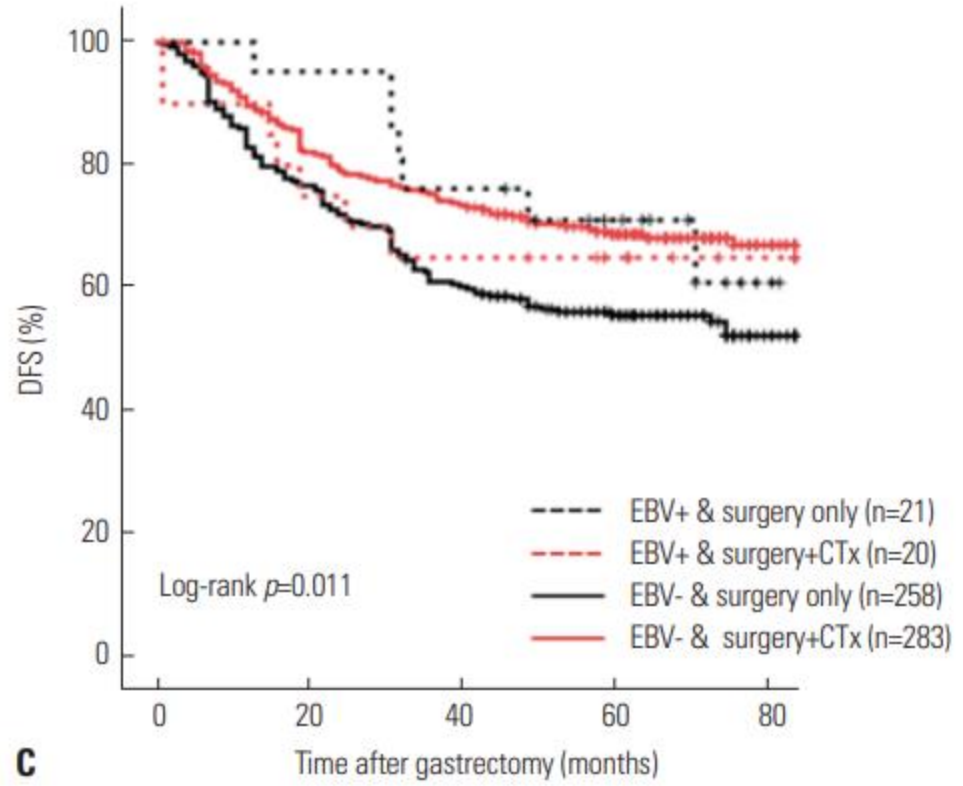
- P: 760 resected GC/GEJ adenoCA
- I: Molecular analysis
- (retrospective)
- C: None



Kohlruss M et al. J Pathol Clin Res 2019:5:227

EBV-Associated Gastric Cancer

- P: stage II and III resected GC adenoCA
- I: Adjuvant capecitabine and oxaliplatin (retrospective)
- C: No adjuvant therapy



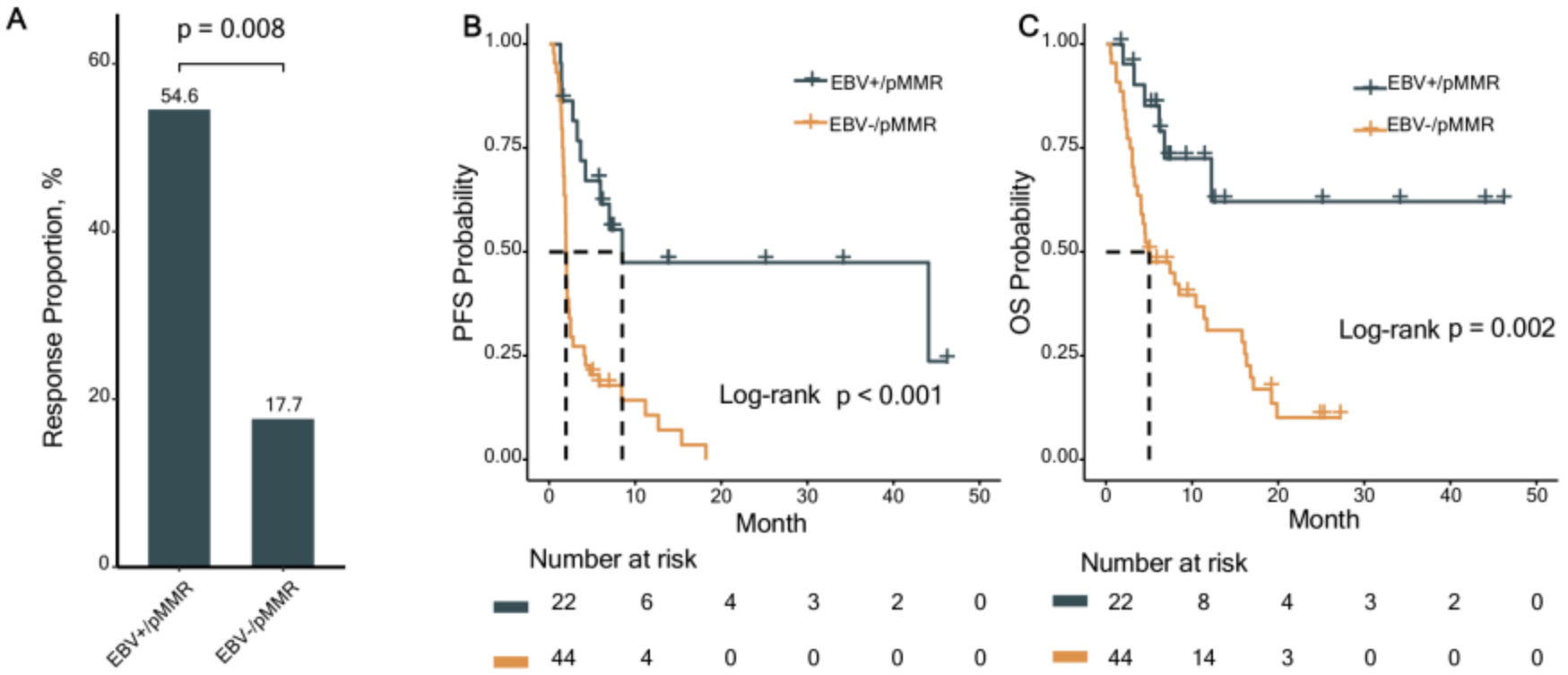
Roh CK et al. Yonsei Med 2019:60:132

EBV-Associated Gastric Cancer

- P: Advanced or metastatic GC stratified by EBV and MMR status

EBV+/pMMR 22
EBV-/pMMR 44
EBV-/dMMR 29
(retrospective)

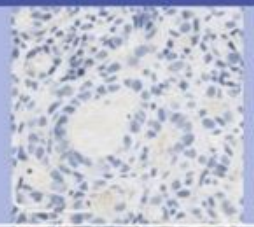
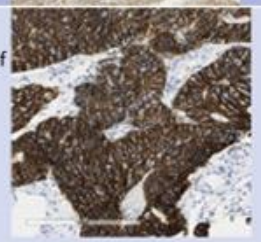
- I: Immunotherapy
- C: None

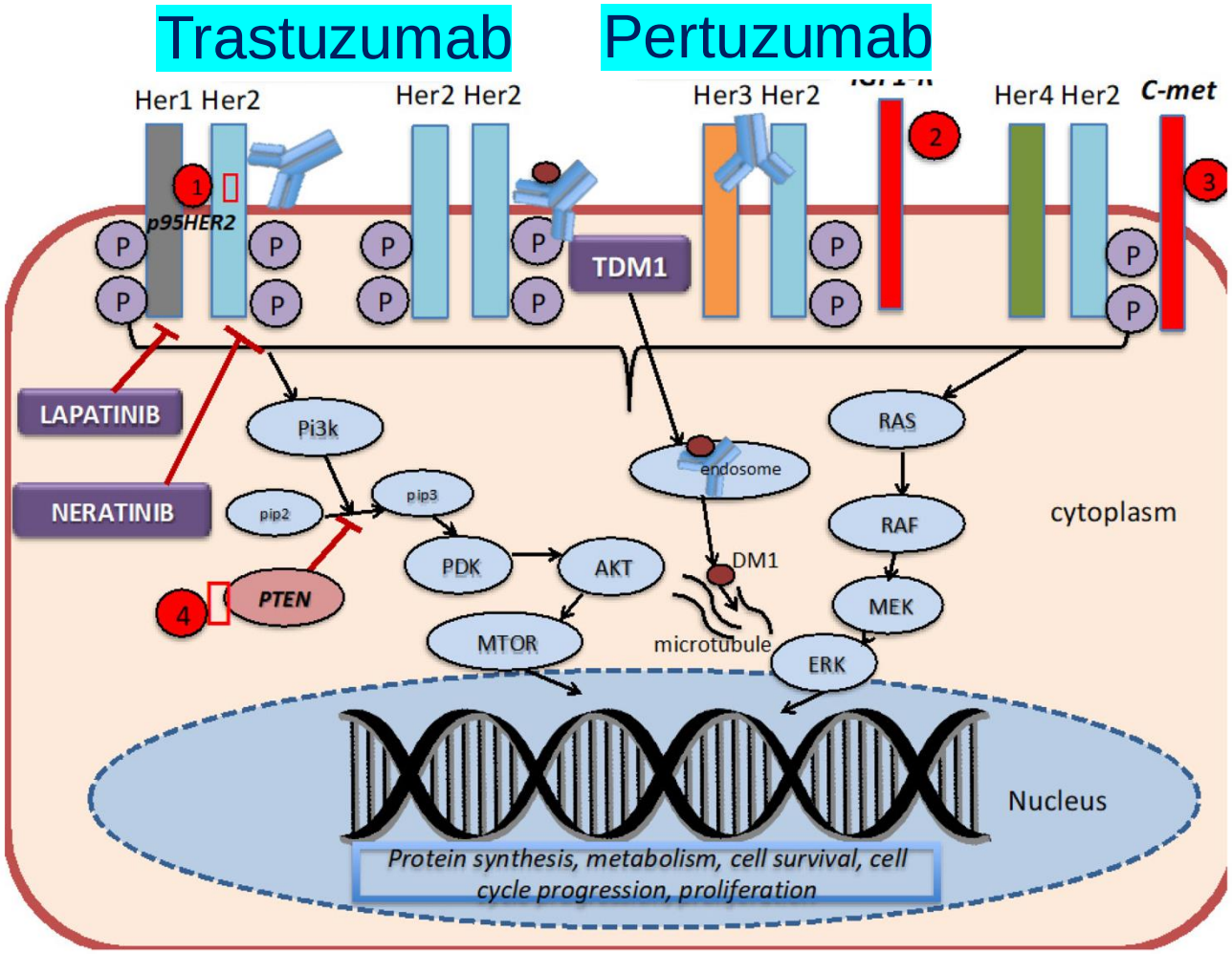


Bai Y et al. J Immunother Cancer 2022:10:e004080

HER2 targeted therapy

HER2 in Gastric Cancer

HER2 IHC Score	Gastric biopsy	Resections	Figure
0	No membranous staining or staining only in rare cells (less than 5 cohesive cells)	No membranous staining or staining of < 10% of the tumor cells	
+1	Staining is weak or detected in only one part of the membrane of at least 5 cohesive cells	Staining is weak or detected in only one part of the membrane in ≥ 10% of the cells	
+2	Moderate/weak complete or basolateral membranous staining of at least 5 cohesive cells	Moderate/weak complete or basolateral membranous staining in ≥ 10% of the cells	
+3	Strong complete or basolateral membranous staining of at least 5 cohesive cells	Strong complete or basolateral membranous staining in ≥ 10% of the neoplastic cells	



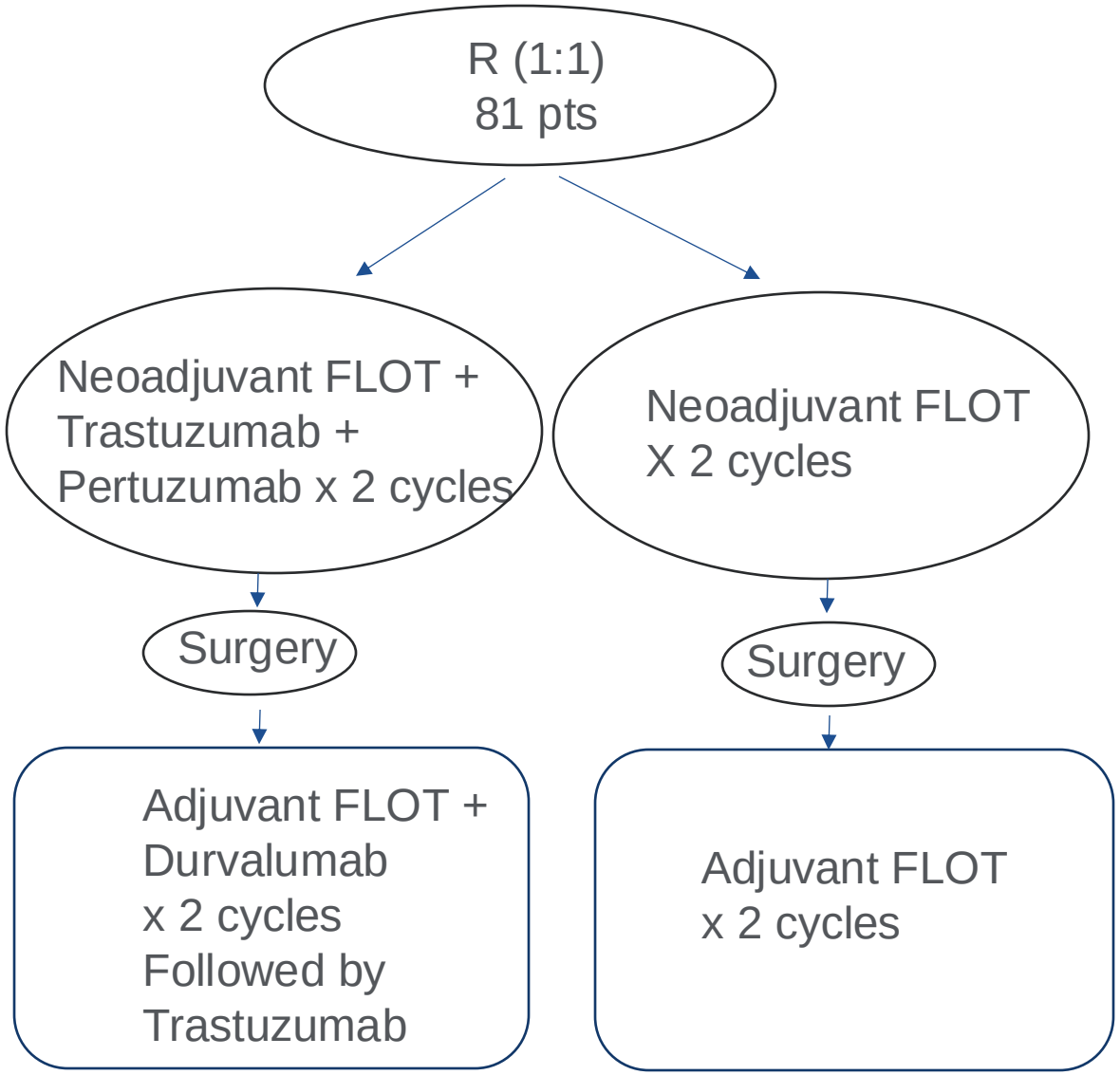
HER2 is amplified in ~15-20% GC/GEJC adenoCA

Patel A et al. Cancers 2020:12:2081

Chemotherapy and HER2 Blockade for HER2+ LAGC

AIO EGA Study Group Randomized Phase II Trial

- P: cT2-4 and/or N+ GC/GEJC adenocarcinoma with HER2 overexpression
- I: Periop Trastuzumab plus Pertuzumab plus FLOT
- C: Periop FLOT

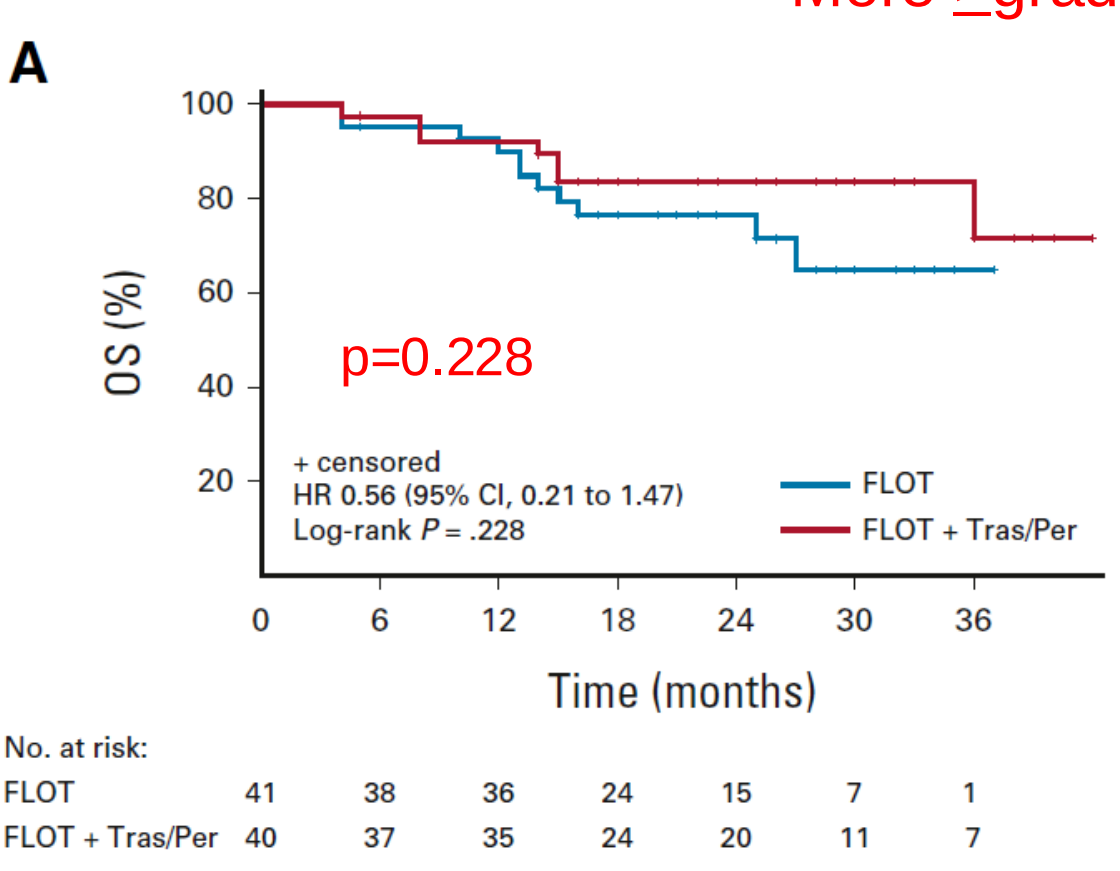


Hofheinz R-D et al, J Clin Oncol. 2022;40(32):3750

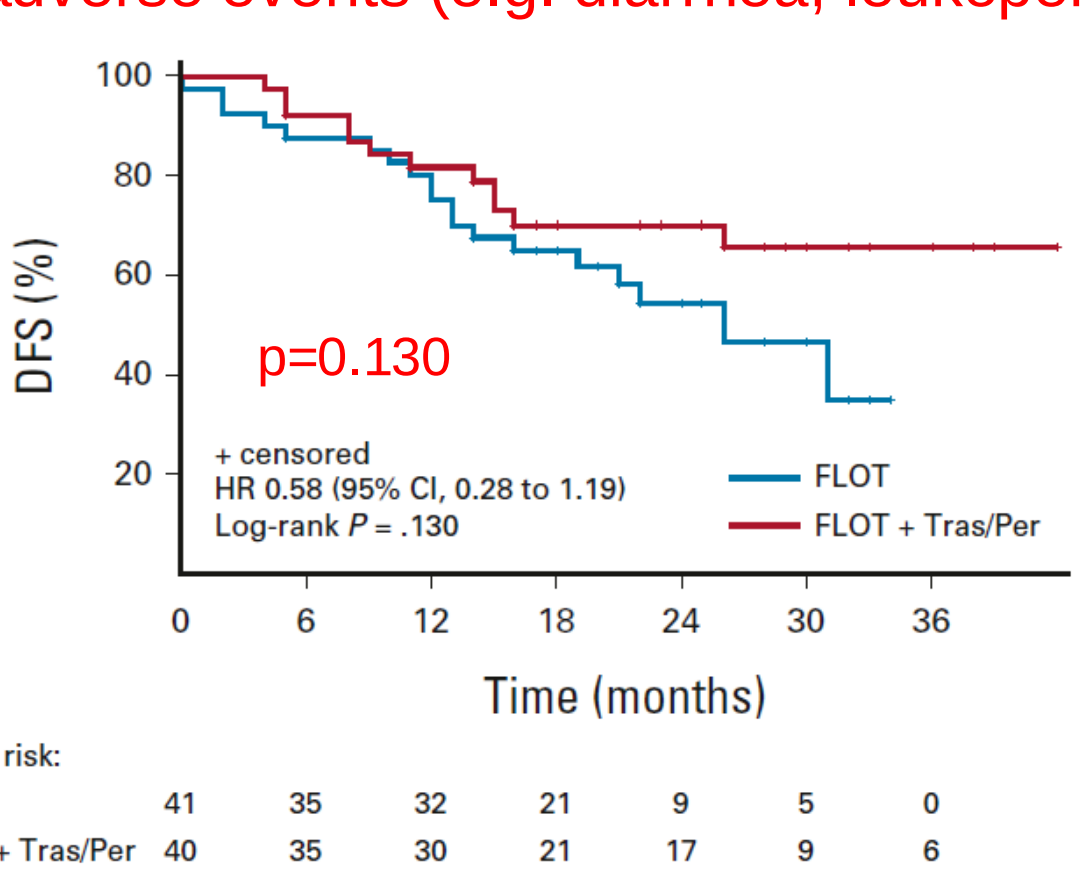
Chemotherapy and HER2 Blockade for HER2+ LAGC

AIO EGA Study Group Randomized Phase II Trial

- Path CR 35% vs 12%
- Node negative 68% vs. 39%
- More ≥grade 3 adverse events (e.g. diarrhea, leukopenia)



No. at risk:							
FLOT	41	38	36	24	15	7	1
FLOT + Tras/Per	40	37	35	24	20	11	7



No. at risk:							
FLOT	41	35	32	21	9	5	0
FLOT + Tras/Per	40	35	30	21	17	9	6

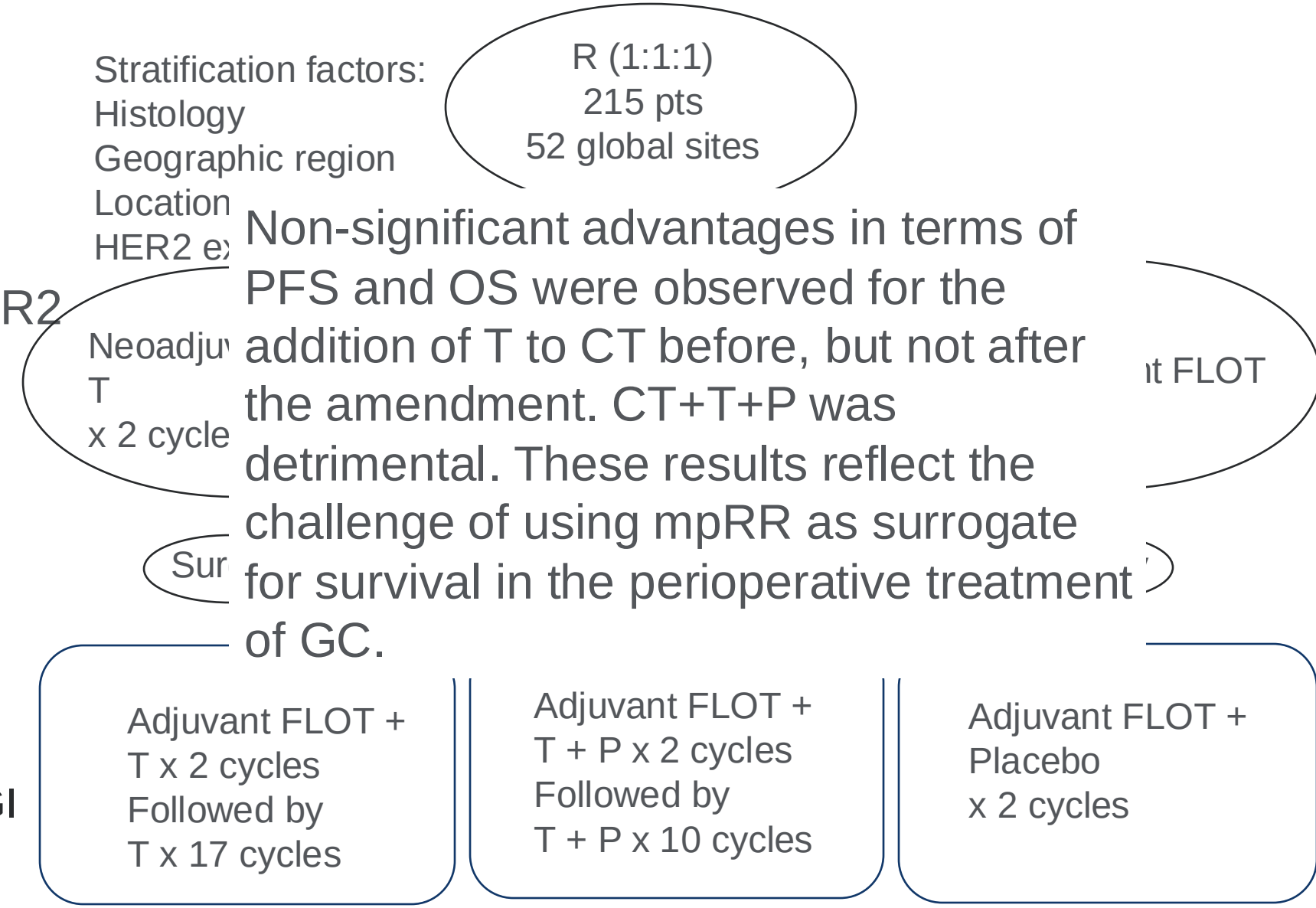
Hofheinz R-D et al, J Clin Oncol. 2022;40(32):3750

Chemotherapy and HER2 Blockade for HER2+ LAGC

INNOVATION

- P: Resectable GC adenocarcinoma with HER2 overexpression
- I: Periop Trastuzumab or Trastuzumab and Pertuzumab plus FLOT
- C: Periop FLOT

Wagner AD et al, BMC Cancer. 2019:19:494
Wagner AD et al. 2025 ASCO GI LBA 331



Summary - 1

- Molecular subtypes and biomarkers
  - Dividing gastric adenoCA into an increasing number of subtypes based on molecular profiling and targetable pathways
- Standard periop therapy is FLOT +/- immunotherapy
- dMMR/MSI-H tumors
  - Better prognosis
  - Less sensitive to chemotherapy, more sensitive to immunotherapy
  - Consider skipping preop therapy
  - Immunotherapy and avoiding surgery in cT1-3 tumors with cCR controversial

Summary - 2

- EBV-associated tumors
  - May have better prognosis
  - May be less responsive to chemotherapy, more responsive to immunotherapy
  - Correct periop therapy unclear
- HER2 targeted therapy for HER2+ tumors
  - Addition of trastuzumab and/or pertuzumab NOT shown to improve survival
  - Give standard periop therapy


Thank You