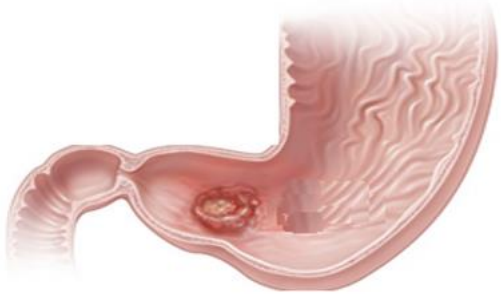
DGHO JAHRESTAGUNG 2023 13.–16. Okt. Hamburg
Jahrestagung der Deutschen, Österreichischen und Schweizerischen Gesellschaften für Hämatologie und Medizinische Onkologie
www.jahrestagung-haematologie-onkologie.com

Perioperative Therapie des Adenokarzinoms des Magens und ösophagogastralen Übergangs

15.Oktober 2023



Sylvie Lorenzen
III. Medizinische Klinik
Klinikum rechts der Isar,
Technische Universität
München

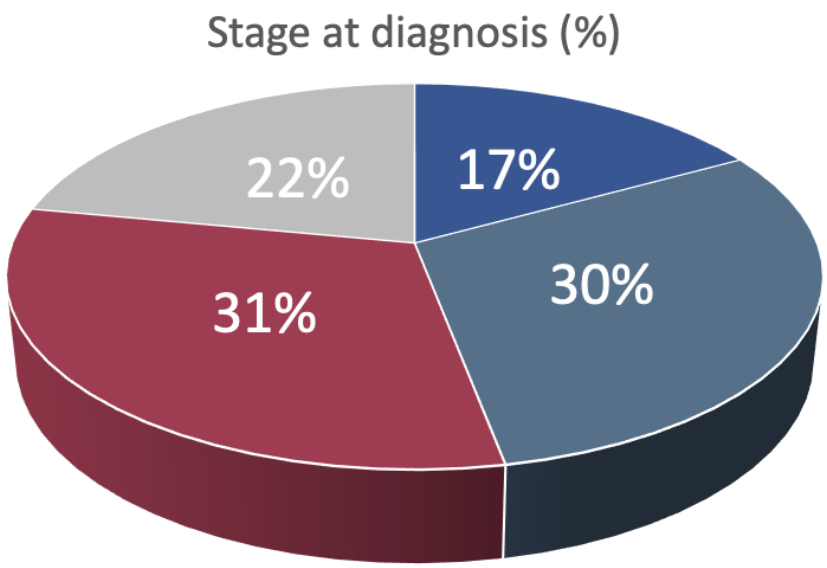
Offenlegung potentieller Interessenkonflikte

- Anstellungsverhältnis oder Führungsposition
  keine
- Beratungstätigkeit
  Eli Lilly, Roche, Servier, Merck-Serono, Sanofi-Aventis
- Aktienbesitz
  keine
- Honorare
  Eli Lilly, Roche, Amgen, Riemser, Servier
- Finanzierung wissenschaftlicher Untersuchungen
  StudienTeilfinanzierung durch Eli Lilly.
- Gutachtertätigkeit
  keine
- Andere finanzielle Beziehungen
  keine

Gastroösophageales Adenokarzinom
Stadium bei Diagnose

EUROPE

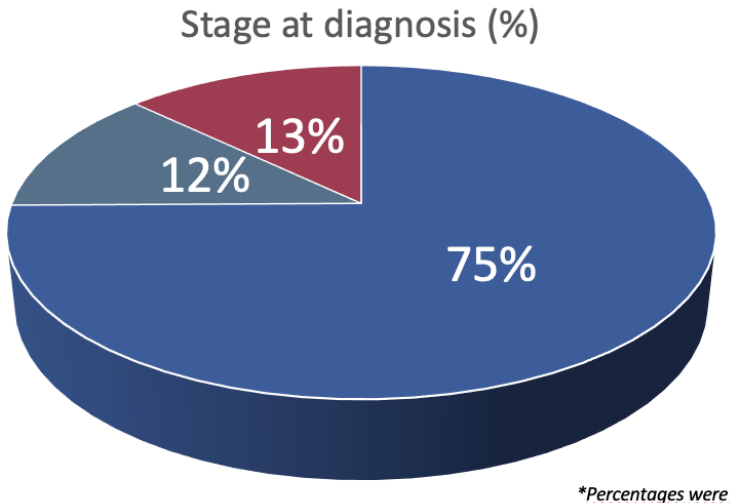
Retrospective observational study from 15 European countries



Adapted from Minicozzi P et al, 2018[1]

JAPAN

Retrospective cohort study from 2 Japanese hospitals



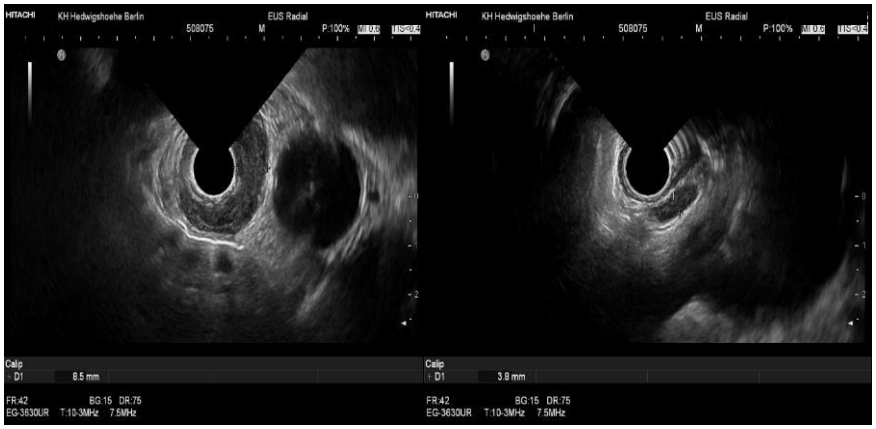
Adapted from Kuzuu K et al, 2021[2] *

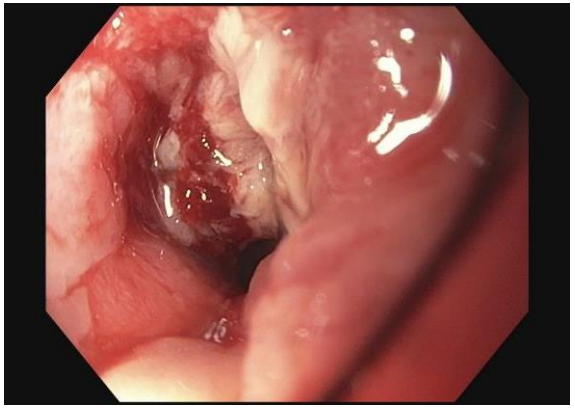
**Percentages were calculated based on the number of patients in each group and rounded to the nearest unit*

~61% in Europe vs ~25% in Japan
of all patients with newly diagnosed gastroesophageal adenocarcinoma
become **candidates for palliative chemotherapy**

1. Minicozzi P et al. *European Journal of Cancer*. 2018; 93-127-137
2. Kuzuu K et al. JAMA Netw Open. 2021;4(9):e2126334.

Lokal fortgeschrittenes Gastroösophageales Karzinom





Lokal fortgeschrittene Erkrankung – Deutsche S3 Leitlinie Perioperative Therapie Standard seit 2011

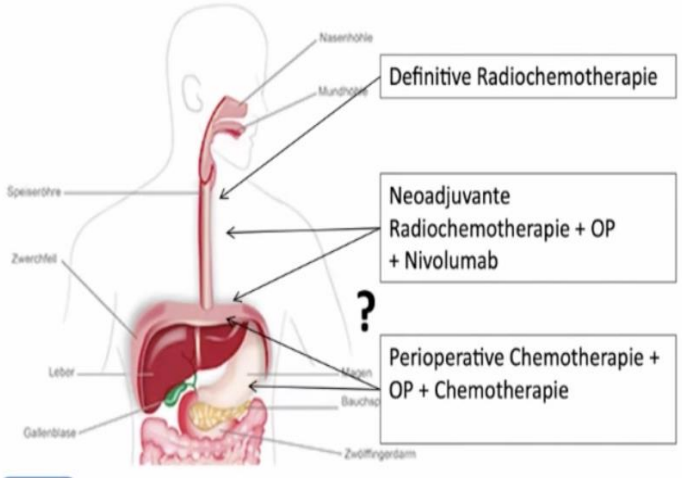
67. Empfehlung

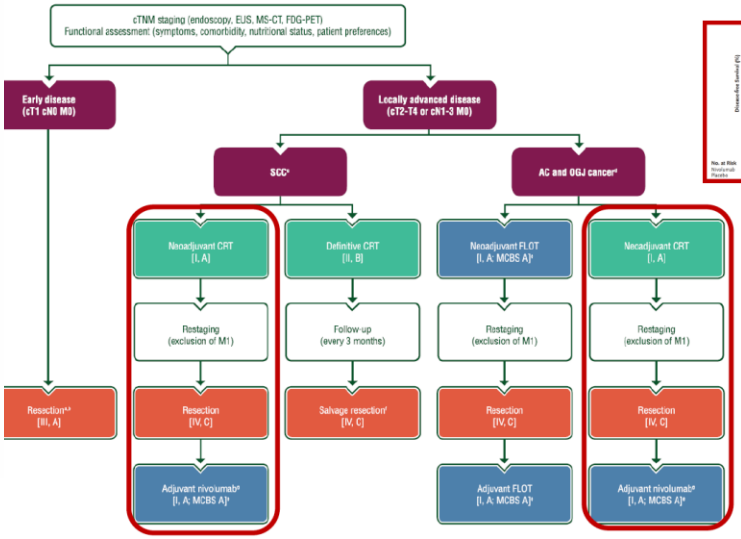
Beim lokalisierten Adenokarzinom des ösophagogastralen Übergangs der Kategorien uT3 und resektablen uT4-Tumoren soll/sollte eine perioperative Chemotherapie oder eine neoadjuvante Radiochemotherapie durchgeführt werden.

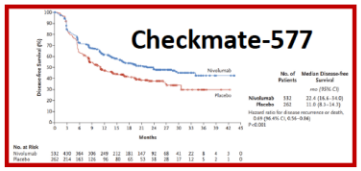
Empfehlungsgrad: A/B
Level of Evidence: 1b
perioperative Chemotherapie
de Novo: [239, 324, 327 – 329, 331, 334, 337 – 339]
Level of Evidence: 1a-LOE1b LOE1b- LOE 2b
neoadjuvante Radiochemotherapie
de Novo: [324, 326, 336, 338, 340 – 351]
Abstimmung im Plenum: Kein Konsens

S3-Leitlinienprogramm Onkologie Moehler, Al-Batran... Lorenzen, Moenig.. et al, Zeitschr f Gastroenterol 2011

Perioperative Behandlungs-Strategien: ESMO GUIDELINES Ösophagus Ca 2022





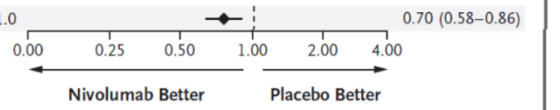


ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

Obermannová R, et al. *Ann Oncol* 2022

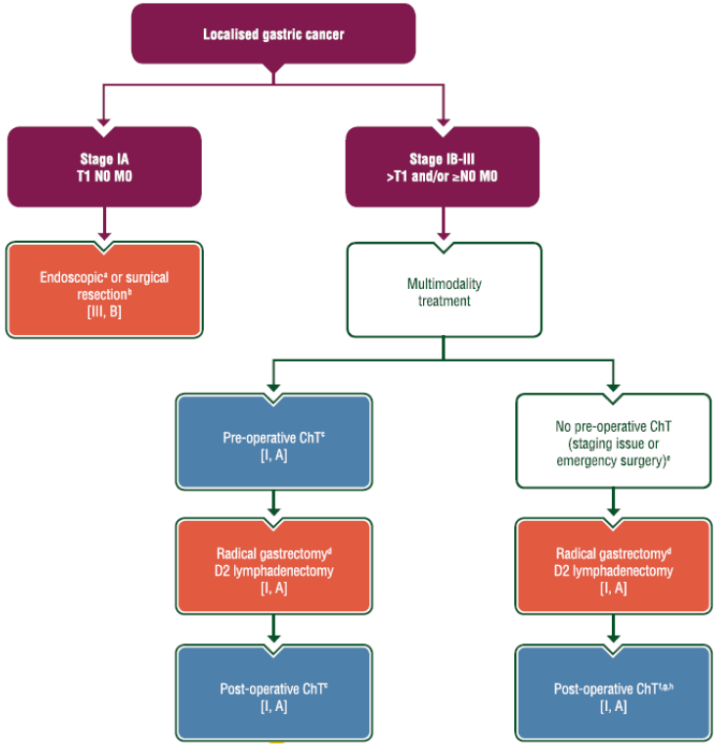
Checkmate 577-Überleben nach PD-L1 Expression

Subgroup	No. of Patients	Median Disease-free Survival (mo) Nivolumab	Median Disease-free Survival (mo) Placebo	Unstratified Hazard Ratio (95% CI)
Overall	794	22.4	11.0	0.70 (0.58–0.86)
Tumor-cell PD-L1 expression				
≥1%	129	19.7	14.1	0.75 (0.45–1.24)
<1%	570	21.3	11.1	0.73 (0.57–0.92)
Indeterminate or could not be evaluated	95	Not reached	9.5	0.54 (0.27–1.05)
PD-L1 CPS expression				
≥5 (n = 371)		29.4	10.2	0.62 (0.46–0.83)
<5 (n = 295)		16.3	11.1	0.89 (0.65–1.22)
Tumor location at initial diagnosis				
Esophagus	462	24.0	8.3	0.61 (0.47–0.78)
Gastroesophageal junction	332	22.4	20.6	0.87 (0.63–1.21)



Kelly RJ, et al. *N Engl J Med* 2021;384:1191-1203

ESMO-Guidelines Magen Ca 2022



Currently no immuno or targeted therapy

But multiple RCTs on the way, e.g.

Immuno

-	KEYNOTE-585	Pembrolizumab
-	AIO-DANTE	Atezolizumab
-	MATTERHORN	Durvalumab
-	VESTIGE	Nivolumab-Ipilimumab

HER2

-	PETRARCA	Trastuzumab-Pertuzumab
-	INNOVATION	Trastuzumab-Pertuzumab

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

Lordick F, et al. *Ann Oncol* 2022

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2023
Gastric Cancer

NCCN Guidelines Index
Table of Contents
Discussion

PRINCIPLES OF SYSTEMIC THERAPY

Perioperative Chemotherapy

Preferred Regimens
- Fluorouracil,[a] leucovorin, oxaliplatin, and docetaxel (FLOT)[c] (category 1)[1]
- Fluoropyrimidine and oxaliplatin[a,b]

Other Recommended Regimens
- Fluorouracil and cisplatin (category 1)[2]

Preoperative Chemoradiation
(Infusional fluorouracil[a] can be replaced with capecitabine)

Preferred Regimens
- None

Other Recommended Regimens
- Paclitaxel and carboplatin (category 2B)[3]
- Fluorouracil[a] and oxaliplatin (category 2B)[4,5]
- Fluorouracil and cisplatin (category 2B)[6,7]
- Fluoropyrimidine (fluorouracil or capecitabine) (category 2B)

Neoadjuvant or Perioperative Immunotherapy

Useful in Certain Circumstances
- MSI-H/dMMR tumors[c]
  - Nivolumab and ipilimumab followed by nivolumab[d,8]
  - Pembrolizumab[d,9,10]
  - Tremelimumab and durvalumab for neoadjuvant therapy only[d,11,12]

Postoperative Chemoradiation
(For patients who received less than a D2 lymph node dissection [See Principles of Surgery (GAST-C)])
- Fluoropyrimidine (infusional fluorouracil[a] or capecitabine) before and after fluoropyrimidine-based chemoradiation[13]

Postoperative Chemotherapy
(For patients who have undergone primary D2 lymph node dissection [See Principles of Surgery (GAST-C)])

Preferred Regimens
- Capecitabine and oxaliplatin[e] (category 1)[14]
- Fluorouracil[a] and oxaliplatin[e]

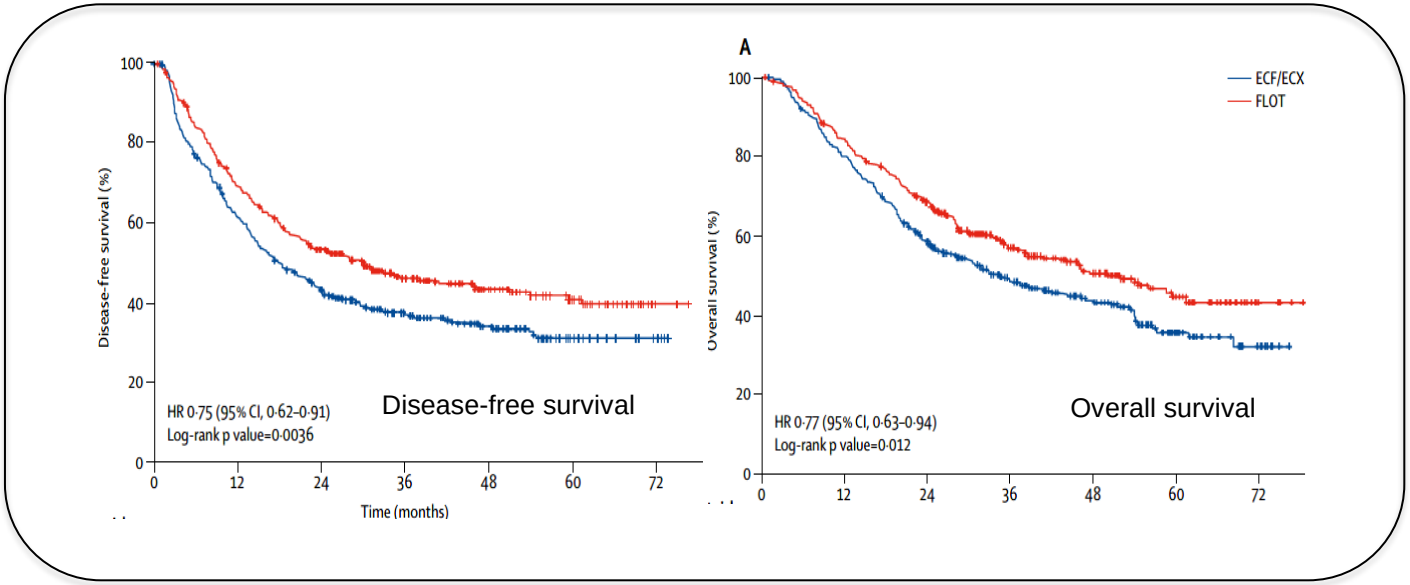
Chemoradiation for Unresectable Disease
(Infusional fluorouracil[a] can be replaced with capecitabine)

Preferred Regimens
- Fluorouracil[a] and oxaliplatin [4,5]
- Fluorouracil and cisplatin [6,7]

Other Recommended Regimens
- Fluoropyrimidine (fluorouracil or capecitabine) and paclitaxel (category 2B)[15]

Gastroösophageales Adenokarzinom: Standard – FLOT 4 Trial

Al-Batran S et al. Lancet 2019



3-Jahres Überlebensrate FLOT vs. ECF: 57% vs. 48%

Medianes Gesamtüberleben FLOT vs. ECF: 50 Monate vs. 35 Monate

Kardiakarzinom – Fall

Patient

- 65 Jahre, männlich, keine pos. Familienanamnese für Krebs, ECOG 1

Aktuelles Problem

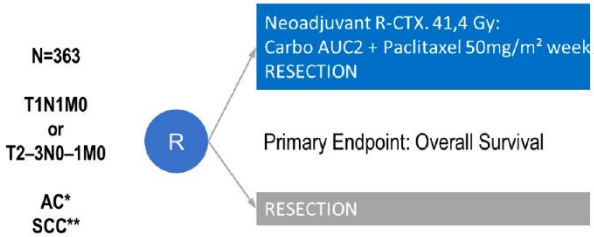
- Dysphagie, Gewichtsverlust 10 kg (ca. 10% des KG)
- **ÖGD: Teilstenosierender Tumor des ösophago-gastralen Übergangs**
- **Histologie: mäßig differenziertes intestinales Karzinom, HER2-, PD-L1 CPS 10, MSS**
- CT Thorax / Abdomen: tumorös verdickte Kardia, V.a. peritumorale Lymphknoten, keine Fernmetastasen
- Staging: **uT3 uN+ cM0**

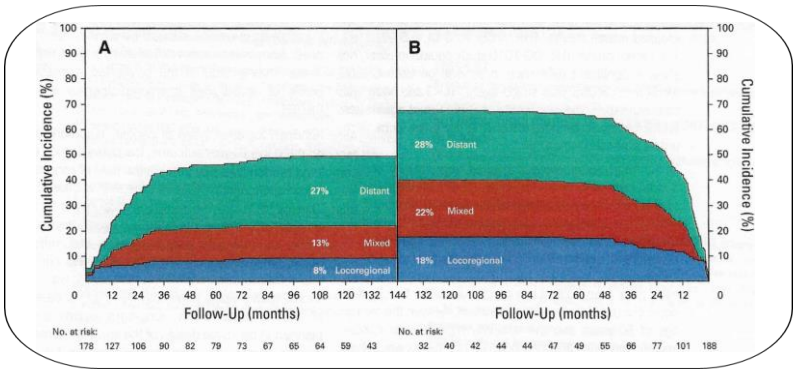
Therapieempfehlung?

Ösophagus- Cardia Karzinom: Ein Standard – CROSS Trial- update 2021

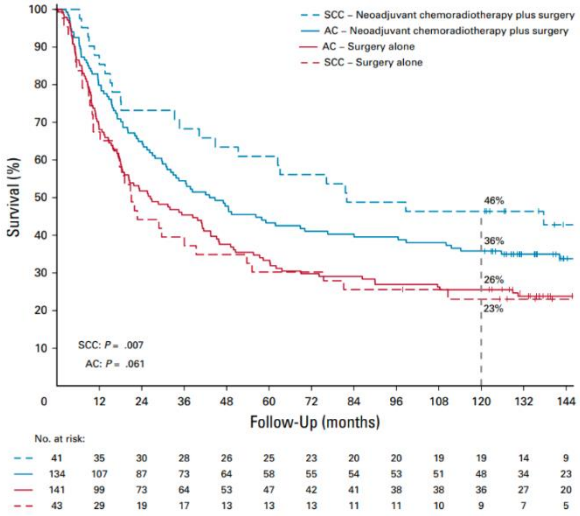
Eyck B J et al. J Clin Oncol 2021

CROSS - Longtime-Follow-up





CROSS Effekt besonders lokal

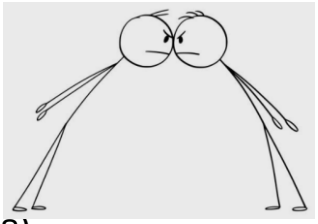


Survival SCC @ 10 years
46% vs 23%
P = 0,007

Survival Adeno @ 10 years
36% vs. 26%
P = 0,061

ASCO 2022 #4015 PROTECT Studie: Welche Backbone-CTX zur RCTX??

Preoperative chemoradiation (CRT) with carboplatin (CBP)/paclitaxel (PCL) (CP) or with 5-fluorouracil (FU)/oxaliplatin (OX) (Fx) for esophageal or junctional cancer: A randomized phase 2 trial.
***Antoine Adenis et al,* Montpellier, France**

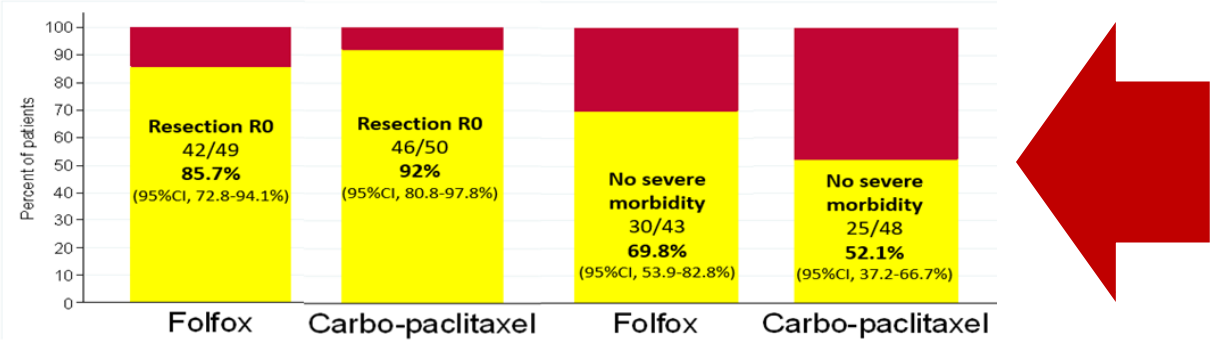


Randomized phase II, n=100

PACLITAXEL/ CARBOPLATIN versus FOLFOX

Co-primary Endpoints: R0 Resection and severe (Dindo ≥ 3 complications)

Result:



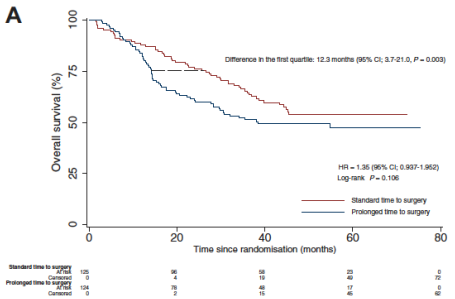
Intervall zur Resektion nach RCTX: Standard (4-6 Wochen) vs. Prolonged Time (10-12 Wochen) bei AEG I/II? NeoRes Phase II Studie

Table 1. Baseline characteristics

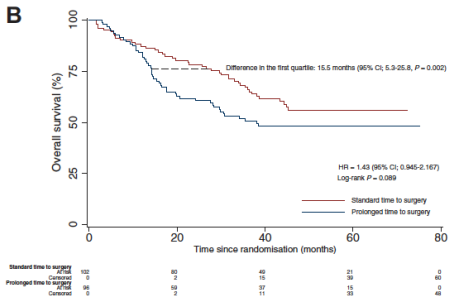
	Standard time to surgery 4-6 weeks	Prolonged time to surgery 10-12 weeks
Total, *n* (%)	125 (100)	124 (100)
Withdrawn consent, *n* (%)	2 (2)	3 (2)
Time to surgery, days/weeks		
Mean	40.2/5.7	75.8/10.8
Median	39.5/5.6	75/10.7
Range, days	26-102	42-109
Interquartile range, days	34-42	69-82
Age, mean years (range)	65 (34-78)	64 (42-79)
Sex, *n* (%)		
Female	22 (18)	18 (15)
Male	103 (83)	106 (86)
Smoking, *n* (%)		
Smoker	36 (29)	37 (30)
Previous smoker[a]	54 (43)	48 (39)
Nonsmoker	32 (26)	36 (29)
Missing data	3 (2)	3 (2)
Alcohol consumption, *n* (%)		
Overconsumption	5 (4)	6 (5)
Previous overconsumption[b]	4 (3)	2 (2)
No known overconsumption	116 (93)	116 (94)
Comorbidity, *n* (%)		
Diabetes mellitus	16 (13)	20 (16)
Cardiovascular disease	46 (37)	37 (30)
Chronic pulmonary disease	13 (10)	8 (7)
ECOG performance status, *n* (%)		
0	98 (78)	98 (79)
1	25 (20)	25 (20)
Missing data	2 (2)	1 (1)
Tumour location, *n* (%)		
Oesophagus or junctional type I	93 (74)	87 (70)
Junctional type II	32 (26)	36 (29)
Missing data	0 (0)	1 (1)
Histology, *n* (%)		
Adenocarcinoma	102 (82)	96 (77)
Squamous cell carcinoma	23 (18)	28 (23)
Clinical T-stage, *n* (%)		
T1	2 (2)	1 (1)
T2	31 (25)	29 (23)
T3	78 (62)	81 (65)
T4a	14 (11)	13 (11)
Clinical N-stage, *n* (%)		
N0	60 (48)	47 (38)
N1	48 (38)	57 (46)
N2	15 (12)	16 (13)
N3	2 (2)	4 (3)
Surgical approach, *n* (%)		
Minimally invasive	53 (42)	50 (40)
Hybrid minimally invasive	43 (34)	38 (31)
Open	21 (17)	18 (15)
No resection	6 (5)	15 (12)

Gesamtüberleben

Alle Patienten



Adeno Ca



Adenocarcinoma			
Surgical resection, *n* (%)	97 (95)	82 (87)	0.051
Chirieac tumour regression grade, *n* (%)			0.179
1: No tumour cells[a]	20 (21)	21 (26)	0.429
2: 1%-10% tumour cells	36 (37)	18 (22)	
3: >10%-50% tumour cells	23 (24)	23 (28)	
4: >50% tumour cells	18 (19)	20 (24)	
Resection margins (<1 mm), *n* (%)			0.662
Free (R0)	95 (98)	79 (96)	
Involved (R1)	2 (2)	3 (4)	
Resected lymph nodes, median (IQR)	20 (14-28)	25 (16-33)	0.053
Lymph node metastasis, *n* (%)			0.924
ypN0	61 (63)	51 (62)	
ypN1-3	36 (37)	31 (38)	
Number of lymph node metastases, median (IQR)	0 (0-2)	0 (0-1)	0.937

Kein Unterschied in pCR Rate (21% standard vs 26% prolonged) und anderen path. Kriterien aber schlechteres OS (26 vs 14 Monate) mit verlängerter Zeit bis zur Resektion

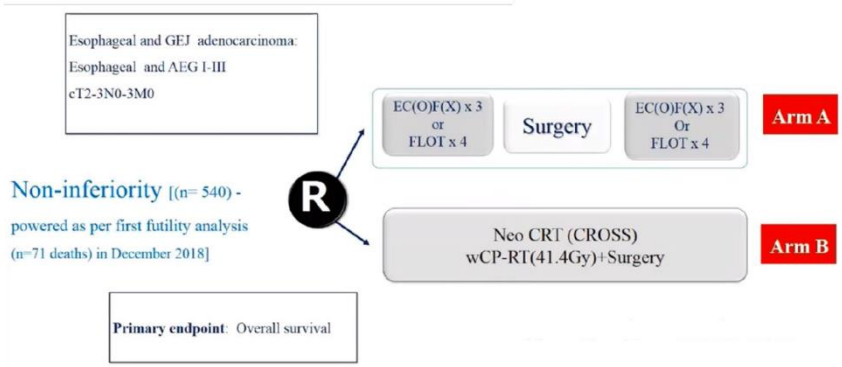
Nielsson et al, Ann Oncol 2023

Perioperative Chemotherapie versus RChT bei gastroösophagealen Übergangskarzinomen

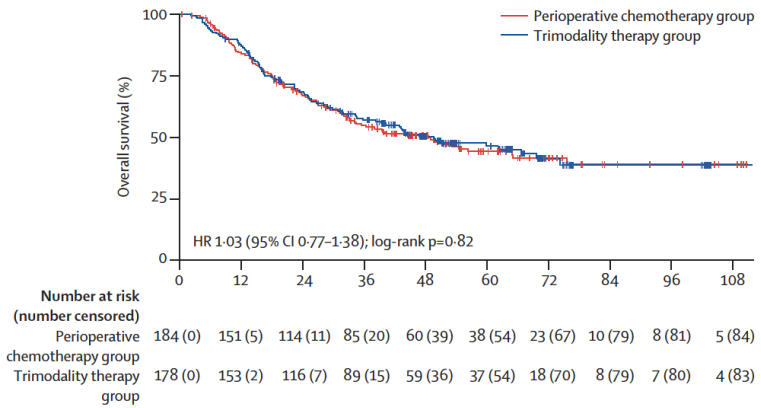
Trial	N	Key Eligibility Criteria	Treatment	Primary Endpoint
ESOPEC NCT02509286 Germany	438	adenocarcinoma of the esophagus or GEJ	**CROSS vs. FLOT** PC/RTX → surgery versus FLOTx4 → surgery → FLOTx4	OS
NEO-AEGIS NCT01726452 Ireland	540	adenocarcinoma of the esophagus or GEJ	**CROSS vs. MAGIC** PC/RTX → surgery versus ECFx3 or FLOTx4 → surgery → ECFx3 or FLOTx4	OS
RACE Germany	340	adenocarcinoma of the esophagus or GEJ T3 or T4	FLOTx2 + FU/Oxa/RTX → surgery → FLOTx4 versus FLOTx4 → surgery → FLOTx4	PFS
TOP GEAR NCT01924819 Australia/New Zealand/Europe/ Canada	570	adenocarcinoma of the stomach or GEJ Siewert type II and III	ECFx2 or FLOT x3+ 5-FU/RTX → surgery → ECFx3 versus ECFx3 or FLOTx4→ surgery → ECFx3 or FLOTx4	OS

Ösophagus/AEG Tumore: NeoAegis Studie: CTX vs. RCTX?

NeoAegis



	ARM A (Chemo) N = 184	ARM B (CROSS) N = 178
Median (range) age	64 (35-83)	64 (45-81)
Male	91.8%	88.8%
MAGIC/FLOT	157 (85%)/27 (15%)	-
cT3	84%	84%
cN 1-3	60.3%	56 %
Radical en bloc Transthoracic Esophagectomy	75%	80 %
Transhiatal	1.2%	4.3%



Nur 15% erhieltenFLOT

Reynolds et al. ASCO 2021; #4004
Lowery M. et al; #295 ASCO GI 2023
Reynolds et al, Lancet Gastroenterol Hepatol 2023 Sep 18:S2468-1253(23)00243-1

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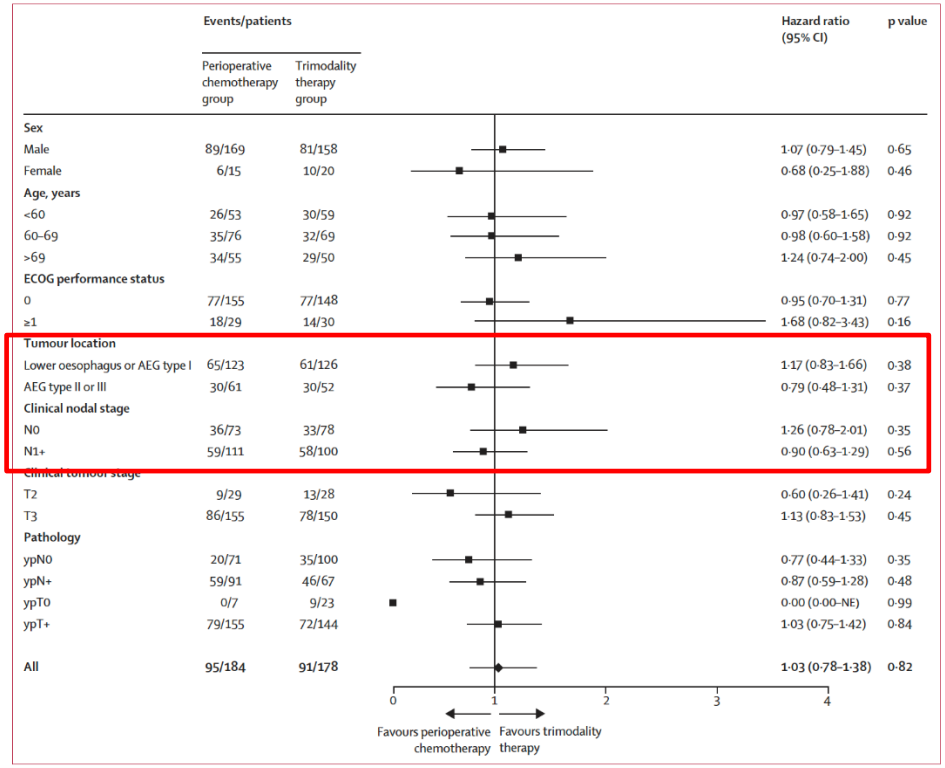
Ösophagus Adeno Ca: NeoAegis Studie CTX vs. RCTX? Finale Ergebnisse: Ansprechen und Überleben

	ARM A (Chemo)	ARM B (CROSS)
ypN0	43.8%	60%
ypT3	59.6%	52%
R0	82%	95%
pCR	5.1%	17.3%
TRG1	5.1%	17.3%
TRG 2	7.0%	24.7%
Major Path Response	12.1%	42%
TRG 3	23.4%	32.1%
TRG 4	41.6%	22.4%
TRG 5	22.8%	3.8%

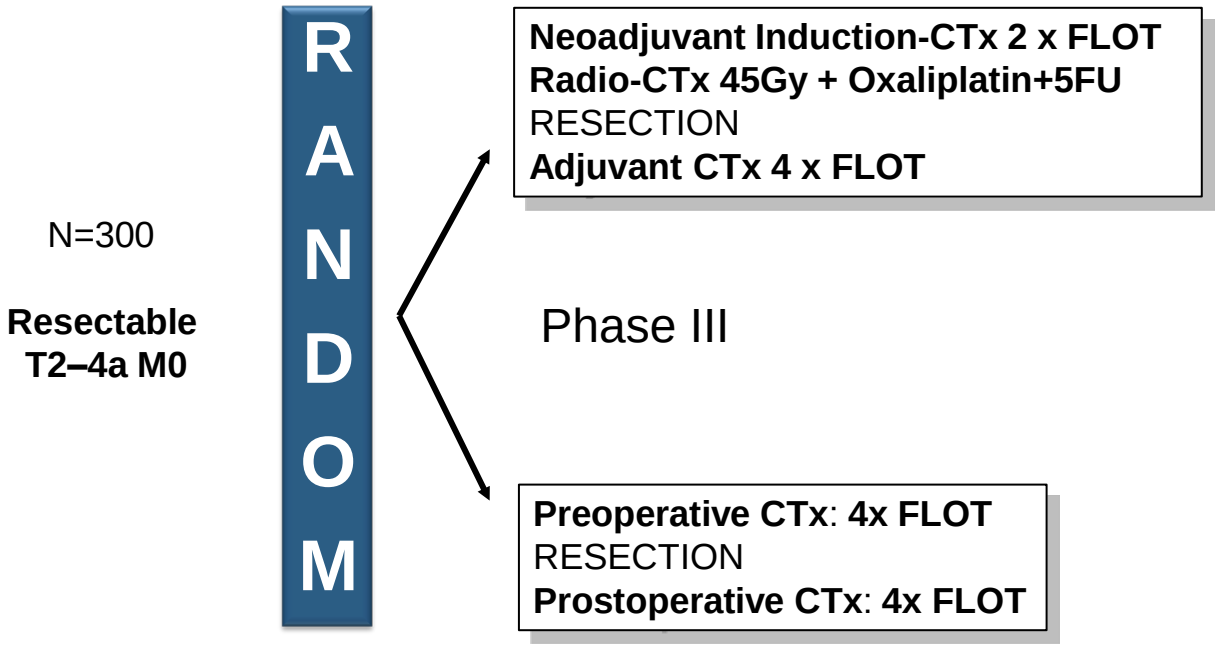
ypN0 (p=0.004)
pCR (p=0.001)
R0 (p< 0.001)
TRG (p< 0.001)

	Perioperative chemotherapy group (n=162)	Trimodality therapy group (n=167)	p value
Site of treatment failure (multiple sites possible per patient)			
Systemic	49/184 (27%)	58/178 (33%)	..
Liver	11/184 (6%)	22/178 (12%)	0·035
Lung	13/184 (7%)	24/178 (13%)	0·044
Bone	12/184 (7%)	17/178 (10%)	..
Multiple sites	22/184 (12%)	26/178 (15%)	..
Nodal non-regional	14/184 (8%)	20/178 (11%)	..
Locoregional	27/184 (15%)	34/178 (19%)	..
Anastomosis and oesophageal	17/184 (9%)	21/178 (12%)	..
Stomach	6/184 (3%)	2/178 (1%)	..
Regional nodes	15/184 (8%)	17/178 (10%)	..
Missing	1/184 (1%)	1/178 (1%)	..



Kein Gewinner!
3-Jahres Überleben 55% (CTX) vs 57% (RCTX)
Bessere lokal Kontrolle mit RCTX (pCR, R0, nodales Downstaging)
Keine Unterschiede in der Komplikationsrate und post. OP
-> Kein Unterschied in Rezidivrate- und Lokalisation

Laufende Studien- AIO-RACE



Lorenzen, Hofheinz et al, BMC Cancer. 2020 Sep 15;20(1):886

Laufende Studie: ESOPEC

ESOPEC Rekrutierungsziel erreicht

N=438

T1N1M0
oder
T2–4aN0–1M0

RANDOM

Perioperative CTX: FLOT* 4 x prä und post
RESEKTION
*FLOT = 5-FU Leucovorin, Oxaliplatin, Docetaxel

Primärer Endpunkt: Überleben
Annahme: 3-Jahres-OS-Rate
55% CROSS vs. 68% FLOT)

Neoadjuvante Radio-CTX – CROSS Regime
RESEKTION

Hoeppner J, Lordick F. et al. *BMC Cancer* 2016; 16: 503

Rolle der IO-Therapie in der adjuvanten/neoadjuvanten Behandlung des lokal fortgeschrittenen gastroösophagealen Adenokarzinoms

Adjuvanz:
- CM577
- Vestige
- ATTRACTION 5

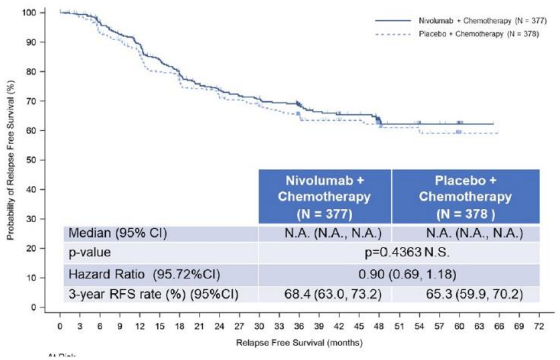
Neoadjuvanz/Adjuvanz:
- DANTE
- KEYNOTE 585
- MATTERHORN

Rolle der IO-Therapie in der adjuvanten/neoadjuvanten Behandlung des lokal fortgeschrittenen gastroösophagealen Adenokarzinoms

Adjuvant:
- CM577
- Vestige
- ATTRACTION 5

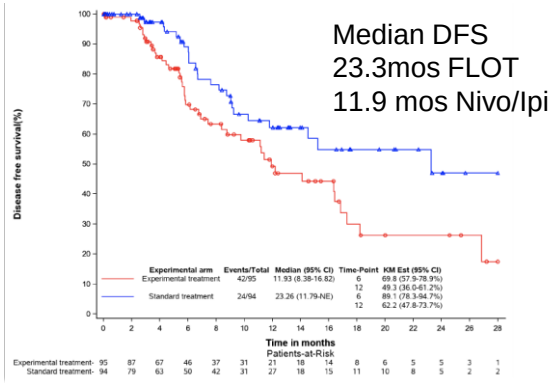
Studien in der Adjuvanz: Verbessert Immuntherapie das Überleben

ATTRACTION 5
Terashima et al ASCO 2023



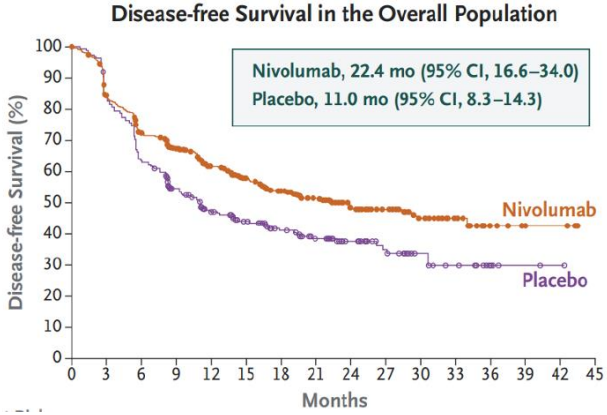
	Nivolumab + Chemotherapy (N = 377)	Placebo + Chemotherapy (N = 378)
Median (95% CI)	N.A. (N.A., N.A.)	N.A. (N.A., N.A.)
p-value	p=0.4363 N.S.	
Hazard Ratio (95.72%CI)	0.90 (0.69, 1.18)	
3-year RFS rate (%) (95%CI)	68.4 (63.0, 73.2)	65.3 (59.9, 70.2)

VESTIGE
Smith et al ESMO GI 2023



Median DFS
23.3mos FLOT
11.9 mos Nivo/Ipi

KN577
Kelly et al NEJM 2022

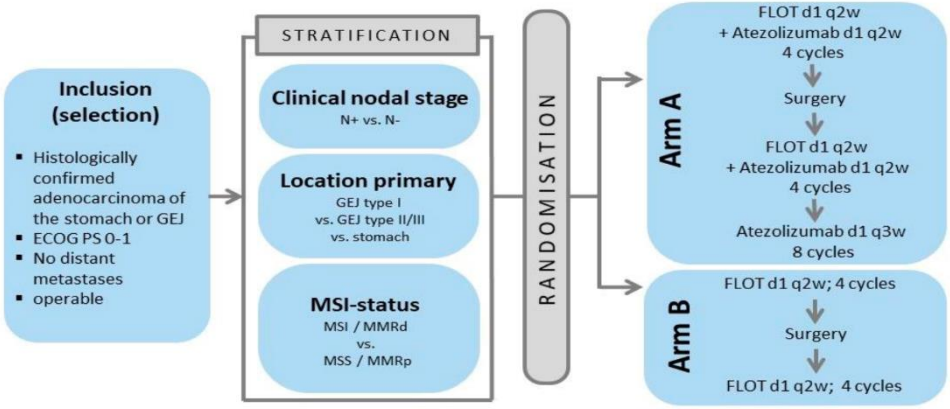


Kein Vorteil der IO Therapie bei unselektierten Patienten mit Hoch-Risiko Tumoren (N+)

Rolle der IO-Therapie in der adjuvanten/neoadjuvanten Behandlung des lokal fortgeschrittenen gastroösophagealen Adenokarzinoms

Neoadjuvant/Adjuvant:
- DANTE
- KEYNOTE 585
- MATTERHORN

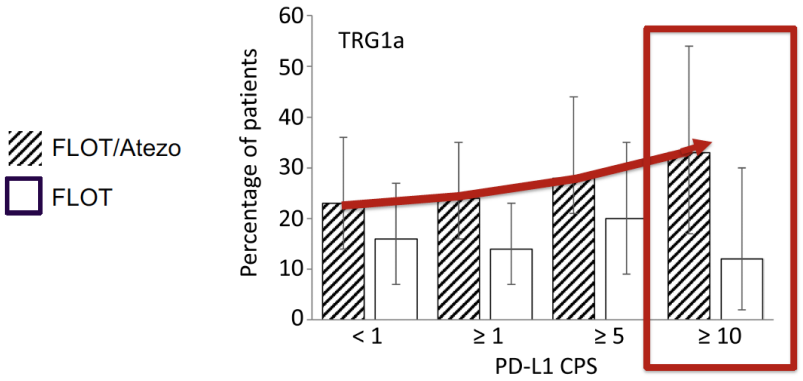
Perioperativ DANTE IKFs633 Studie: FLOT+/-Atezolizumab



Pathological Regression FLOT + Atezolizumab (arm A) vs. FLOT (arm B)	Becker Classification			
	TRG1a[1]		TRG1a/b[2]	
	A	B	A	B
All patients (N= 295; 146|149)	35 (24%)	23 (15%)	71 (49%)	58 (39%)
PD-L1 CPS ≥1 (N=170; 82|88)	20 (24%)	13 (15%)	42 (51%)	40 (46%)
PD-L1 CPS ≥5 (N=81; 40|41)	11 (28%)	8 (20%)	22 (55%)	18 (44%)
PD-L1 CPS ≥10 (N=53; 27|26)	9 (33%)	3 (12%)	18 (67%)	10 (39%)
MSI high (N=23; 8|15)	5 (63%)	4 (27%)	6 (75%)	7 (47%)

	FLOT + Atezolizumab (N=146)		FLOT (N=149)	
pT0-stage	34	23%	22	15%
pN0-stage	100	69%	81	54%
pT0/N0	34	23%	21	14%
pT-stage				
≤T1	62	43%	55	37%
T2	27	19%	16	11%
T3	47	32%	61	41%
T4	4	3%	10	7%
pT0-T2	89	61%	71	48%
pT3-T4	51	35%	71	48%
pM1-stage	2	1%	4	3%

pCR nachPD-L1 CPS Expression



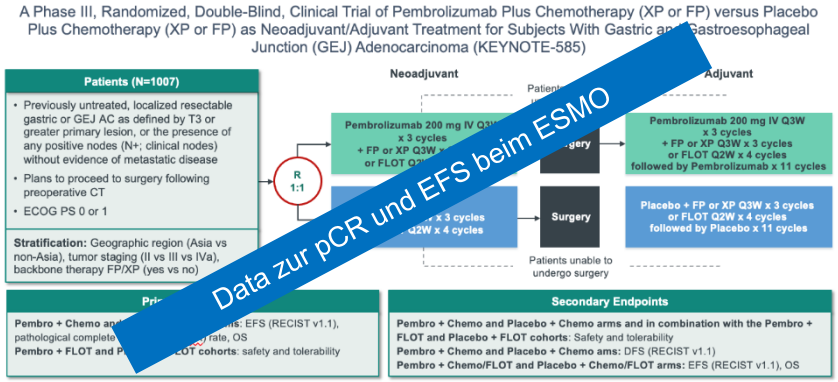
Kopp et al., ESMO 2021 1430P
Al-Batran et al., *J Clin Oncol 40*, 2022 (suppl 16; abstr 4003)
Lorenzen et al JCO 2023 accepted

Laufende Phase III Studien zu Checkpoint Inhibitoren als perioperative Therapie in gastroösophagealen Adenokarzinomen

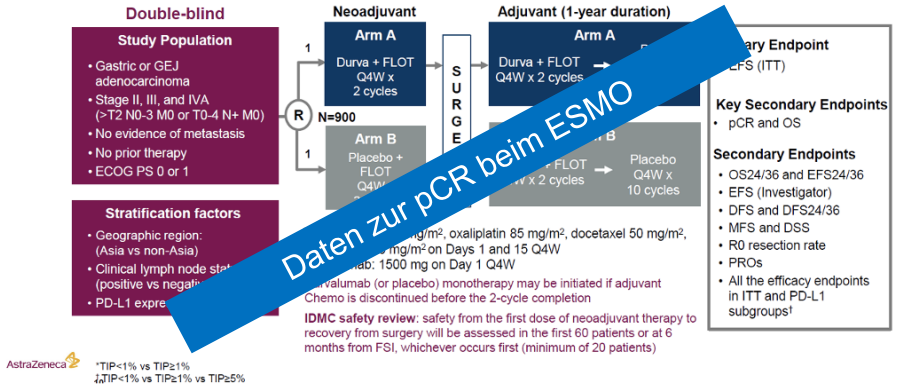
Trial	N	Key eligibility criteria	Treatment	Primary endpoint
DANTE/FLOT8 **Phase 2/3** NCT03421288 IKF-s633	295/556	≥T2 or N+ gastric and GEJ cancer, (phase3, PD-L1 >1)	Perioperative FLOT +/- atezolizumab	Phase 2: pCR/ pTNM pCR and pTN improved
KEYNOTE 585 **Phase 3** NCT03221426 MSD	1007[3]	>T3 or N+ gastric and GEJ cancer	Perioperative FP/XP (or FLOT) +/- pembrolizumab	pCR, EFS, OS pCR improved, EFS not
MATTERHORN **Phase 3** D910GC00001 AstraZeneca	900	T3–4 or N+ gastric and GEJ cancer	Perioperative FLOT +/- durvalumab	EFS pCR improved

CPI, check-point inhibitor, EFS, event-free survival; FLOT, fluorouracil plus leucovorin, oxaliplatin, and docetaxel; FP, fluorouracil and cisplatin; GEJ, gastroesophageal junction; N, node; OS, overall survival;
pCR, pathologic complete response; PFS, progression-free survival; T, tumor; XP, capecitabine and cisplatin.

Phase III Studien KEYNOTE 585 und MATTERHORN



Data zur pCR und EFS beim ESMO



Daten zur pCR beim ESMO

RAHWAY, N.J., June 20, 2023--(BUSINESS WIRE)--Merck (NYSE: MRK), known as MSD outside of the United States and Canada, today announced topline results from the Phase 3 KEYNOTE-585 trial, investigating KEYTRUDA, Merck's anti-PD-1 therapy, in combination with chemotherapy as neoadjuvant treatment, followed by adjuvant treatment with KEYTRUDA plus chemotherapy, then KEYTRUDA monotherapy in patients with locally advanced resectable gastric and gastroesophageal junction (GEJ) adenocarcinoma. At a pre-specified interim analysis conducted by an independent Data Monitoring Committee, the study met one of its primary endpoints of pathological complete response (pCR) rate and demonstrated a statistically significant improvement in pCR rates compared with chemotherapy alone. For the primary endpoint of event-free survival (EFS), there was an improvement in the KEYTRUDA arm; however, results did not meet statistical significance per the pre-specified statistical analysis plan. The endpoint of overall survival (OS) was not formally tested since superiority was not reached for EFS. The safety profile of KEYTRUDA in this trial was consistent with that observed in previously reported studies. Results will be presented at an upcoming medical meeting.

MATTERHORN
AZ IO TRIALS

AstraZeneca

02 Jun 2023

Dear Investigators,

We are delighted to inform you of the positive high-level results from a planned interim analysis of the MATTERHORN Phase III trial that showed treatment with durvalumab added to standard-of-care FLOT chemotherapy before surgery demonstrated a statistically significant improvement in the secondary endpoint of pathologic complete response (pCR) versus neoadjuvant chemotherapy alone for patients with resectable, early-stage and locally advanced (Stages II, III, IVA) gastric and gastroesophageal junction cancers.
The safety and tolerability of adding durvalumab to neoadjuvant FLOT chemotherapy was consistent with the known profile of this combination and no new safety signals were observed.
The trial will continue as planned to assess the primary endpoint of event-free survival (EFS) to which the study team, investigators, and participants remain blinded.
The data from the MATTERHORN Study will be presented at a forthcoming conference.
Thank you for your belief and dedication to this important trial.

Stellenwert der IO Therapie in der Adjuvanz/Neoadjuvanz bei lokal fortgeschrittenen Magenkarzinomen und AEG

Adjuvanz:
- CM577 DFS ✓
- Vestige DFS ✗
- ATTRACTION 5 RFS ✗

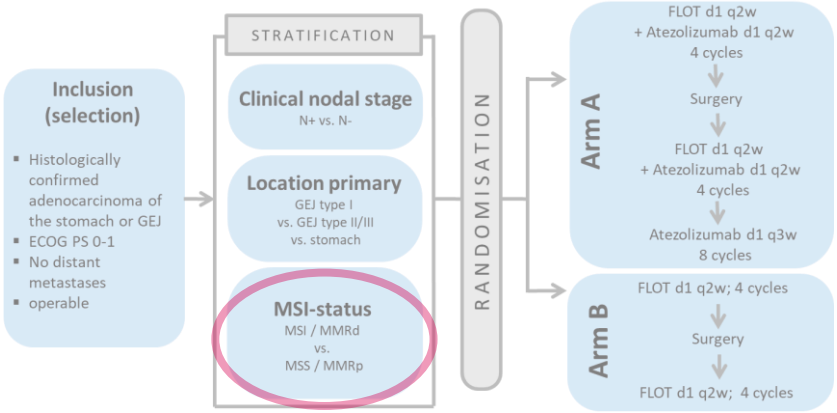
Neoadjuvanz/Adjuvanz:
- DANTE pCR/pTNM ✓
- KEYNOTE 585 pCR ✓
- MATTERHORN pCR ✓ EFS ✗

No trial showed an improvement in survival yet

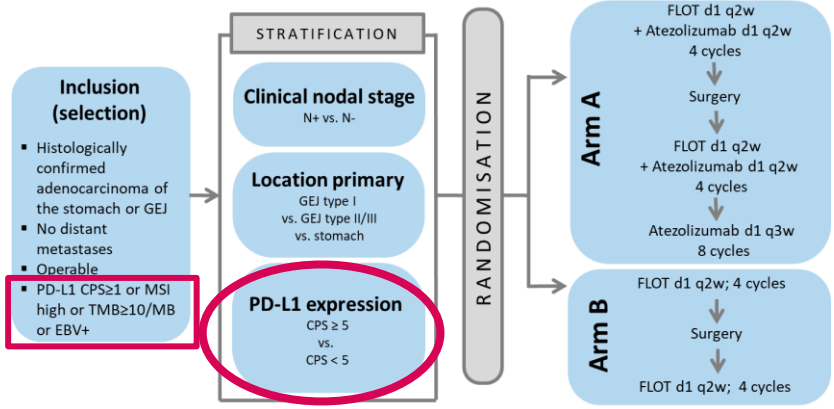
DANTE Studien Design

DANTE

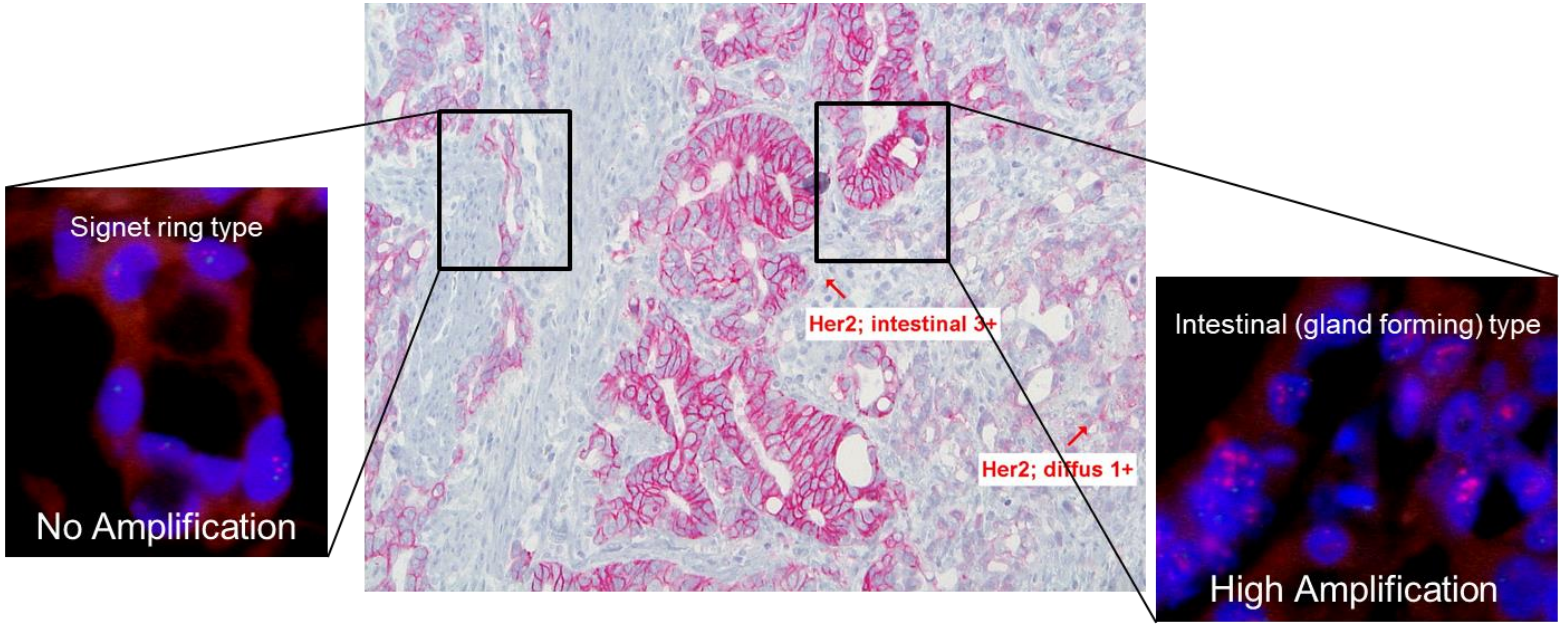
Phase II



Phase III



Das lokal fortgeschrittene Her-2 positive gastroösophageale Adenokarzinom



Lordick F, Janjigian YY. *Nat Rev Clin Oncol.* 2016 Jun;13(6):348-60

Kardiakarzinom – Fall

Patient

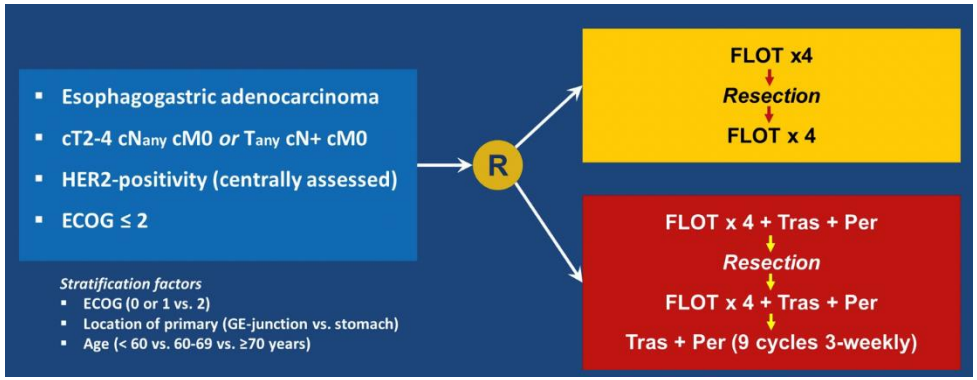
- 65 Jahre, männlich, keine pos. Familienanamnese für Krebs, ECOG 1

Aktuelles Problem

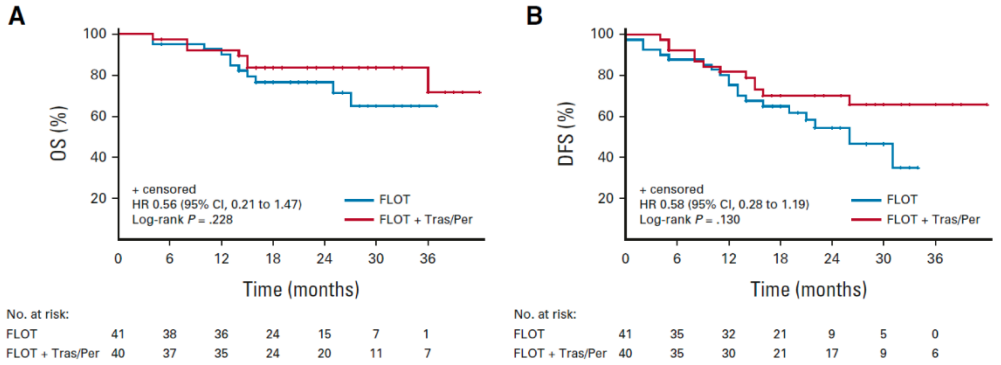
- Dysphagie, Gewichtsverlust 10 kg (ca. 10% des KG)
- **ÖGD: Teilstenosierender Tumor des ösophago-gastralen Übergangs**
- **Histologie: mäßig differenziertes intestinales Karzinom, HER2 + PD-L1 CPS 10, MSS**
- CT Thorax / Abdomen: tumorös verdickte Kardia, V.a. peritumorale Lymphknoten, keine Fernmetastasen
- Staging: **uT3 uN+ cM0**

Therapieempfehlung?

Anti-Her 2 plus Chemotherapie: AIO PETRARCA Studie



ypT-stage	FLOT N = 41	FLOT + Tras / Per N = 40	P-value
≤T1	11 (27%)	17 (43%)	
T2	9 (22%)	8 (20%)	
T3	17 (41%)	14 (35%)	
T4	3 (7%)	0 (0%)	
N0	16 (39%)	27 (68%)	
pCR	5 (12%)	14 (35%)	p = 0.02



Hofheinz et al; JCO 2022

Die Zugabe von Trastuzumab und Pertuzumab zu FLOT verbessert signifikant die pathologische Remission und die Rate nodal negativer Patienten bei resezierbarem HER2+ EGA
Vermehrt Rate and >/= Grad 3 Diarrhö (41%) und Leukopenie (23%) unter Zugabe von Trastuzumab+Pertuzumab

2023 ASCO ANNUAL MEETING

EORTC European Organisation for Research and Treatment of Cancer
The future of cancer therapy
KCSG DUCG

Integration of trastuzumab (T), with or without pertuzumab (P), into perioperative chemotherapy (CT) of HER-2 positive gastric (GC) and esophagogastric junction cancer (EGJC)

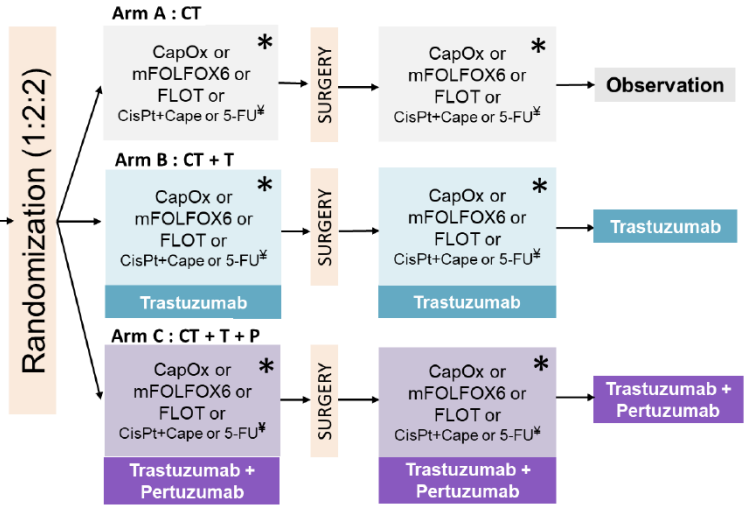
First results of the EORTC 1203 "INNOVATION" Study, in collaboration with the Korean Cancer Study Group (KCSG) and the Dutch Upper GI Cancer Group (DUCG)

A.D. Wagner, H.I. Grabsch, M.E. Mauer, R.U. Fumagalli, Y.-K Kang, O. Bouche, S. Lorenzen, M. Moehler, P. Thuss-Patience, A. Elme, G. Folprecht, U.M. Martens, D. Smith, M.d C. Galan Guzman, M. Ducreux, M. Diez Garcia, G. Piessen, S.Y. Rha, M. Collienne, F. Lordick

KEY EGIBILITY CRITERIA

- HER-2 positive[¤] gastric cancer and esophagogastric junction cancer
- Amenable to gastrectomy/oesophagectomy with curative intent as confirmed by a multidisciplinary team discussion
- UICC (Edition 7th) tumor stage Ib to III, as defined by CT scan and/or MRI
- WHO PS 0 – 1

¤ Confirmed by central screening
*According to investigator's choice
¥ For Asian sites



Ca. 45% FLOT

Statistik: Verbesserung des primären Endpunktes mpRR (<10%vitale Tumorzellen) von 25% mit CT auf 45% mit CT+T+P und CT+T

	Treatment arm (Per protocol population)		
	CT (N=33)	CT + T (N=64)	CT + T + P (N=64)
Age (years), Median (Range)	63 (32–79)	63 (36–84)	64 (42–78)
Sex, N (%)			
Male	31 (93.9)	43 (67.2)	57 (89.1)
Female	2 (6.1)	21 (32.8)	7 (10.9)
Tumor localization, N (%)			
Stomach	12 (36.4)	26 (40.6)	23 (35.9)
Esophagogastric junction	21 (63.6)	38 (59.4)	41 (64.1)
Histological subtype, N (%)			
Intestinal	25 (75.8)	45 (70.3)	46 (71.9)
Non-intestinal	8 (24.2)	19 (29.7)	18 (28.1)
Region, N (%)			
Asia	4 (12.1)	7 (10.9)	5 (7.8)
Europe	29 (87.9)	57 (89.1)	59 (92.2)
HER-2 status, N (%)			
IHC2+/FISH+	4 (12.1)	16 (25.0)	16 (25.0)
HER-2 IHC 3+	29 (87.9)	48 (75.0)	48 (75.0)

Anna Dorothea Wagner, et al. J Clin Oncol 41, 2023 (suppl 16; abstr 4057)

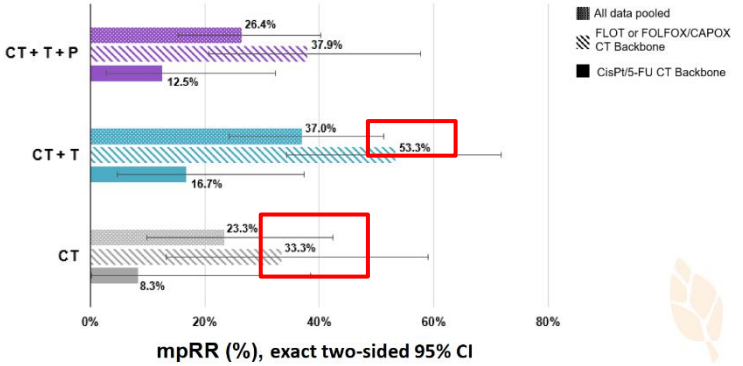
Phase II EORTC 1203 INNOVATION Studie: Primärer Endpunkt mpRR

		Per protocol population – Treatment arm		
		CT (N=33)	CT + T (N=64)	CT + T + P (N=64)
Major pathological response, N (%)		N=30	N=54	N=53
	Yes	7 (23.3)	20 (37.0)	14 (26.4)
Final Becker tumor regression grade, N (%)		N=26	N=53	N=48
	0	1 (3.8)	8 (15.1)	3 (6.3)
	1	6 (23.1)	12 (22.6)	11 (22.9)
	2	9 (34.6)	8 (15.1)	14 (29.2)
	3	10 (38.5)	25 (47.2)	20 (41.7)
Surgery performed, N (%)				
	Yes	28 (84.8)	63 (98.4)	59 (92.2)

For 24 patients operated, sample was missing or judged by the central reviewers of insufficient quality
Patients not operated (n=10) were considered as failures for mpRR

	CT + T	CT + T + P
Difference in mpRR between each experimental arm and CT arm [asymptotic two-sided 80% CI]	13.7% [0.7%, 26.7%]	3.1% [-9.5%, 15.7%]

mpRR according to CTX backbone



FLOT +/- T/P (AIO PETRARCA) 12% -> 35%

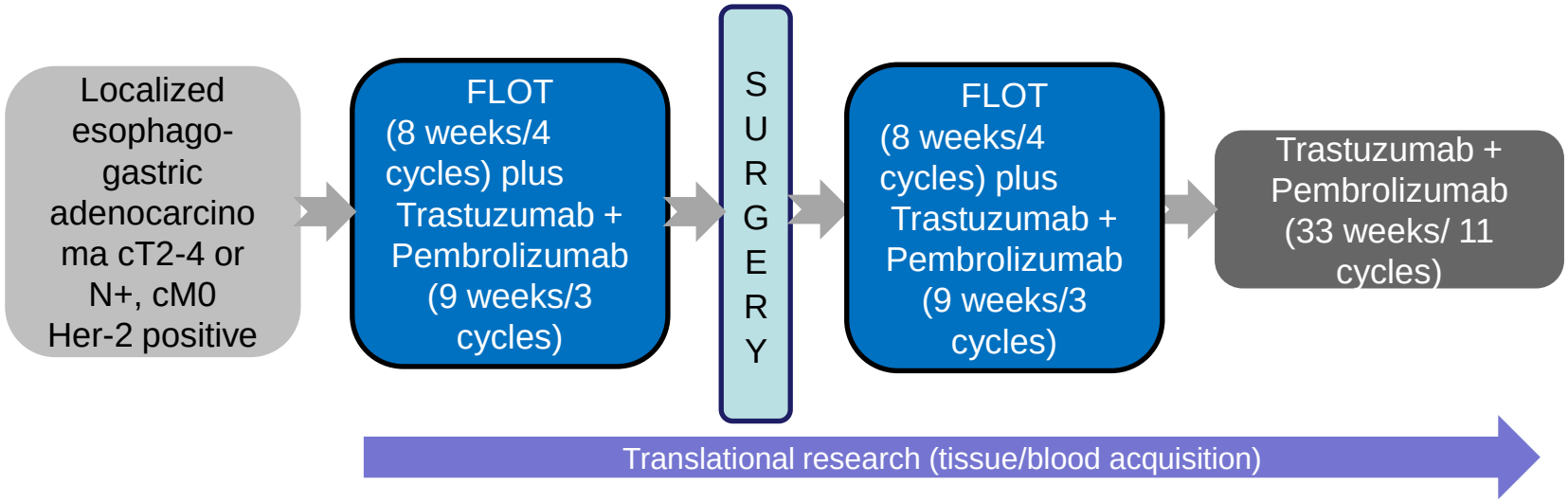
Fazit: **primärer Endpunkt nicht erreicht (mpRR von 25->45% in PPP!**
Vielversprechende Ergebnisse für FLOT plus Trastuzumab mit 20%iger Verbesserung der mpRR gegenüber CTX alleine (53% vs 33%) und verbessertes R0 Resektionsrate um 15%
Zusätzliche Gabe von Pertuzumab erhöhte die Nebenwirkungen (22% >Grad 3 Diarrhoe)
EFS/OS ausstehend

Anna Dorothea Wagner, et al. J Clin Oncol 41, 2023 (suppl 16; abstr 4057)

AIO – PHERFLOT Studie

Studiendesign

1° endpoint (co-primary): pCR/DFS rate@2y
2° endpoint: feasibility, toxicity, DFS, R0 resection, OS



Kardiakarzinom – Fall

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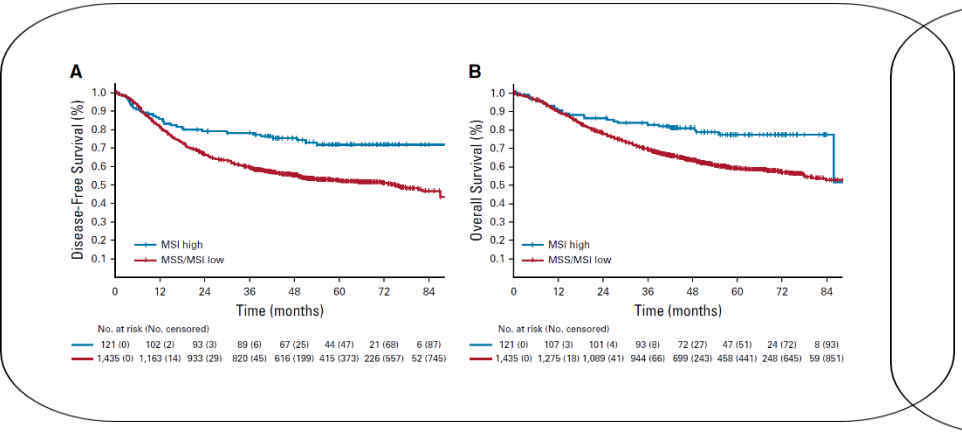
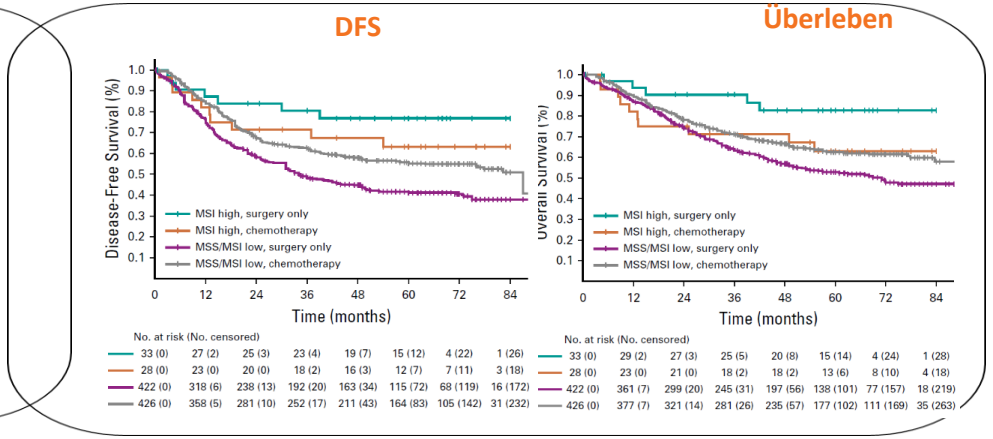
- **ÖGD: Teilstenosierender Tumor des ösophago-gastralen Übergangs**
- **Histologie: mäßig differenziertes intestinales Karzinom, HER2-**, PD-L1 CPS 10, **MSI**
- CT Thorax / Abdomen: tumorös verdickte Kardia, V.a. peritumorale Lymphknoten, keine Fernmetastasen
- Staging: **uT3 uN+ cM0**

Therapieempfehlung?

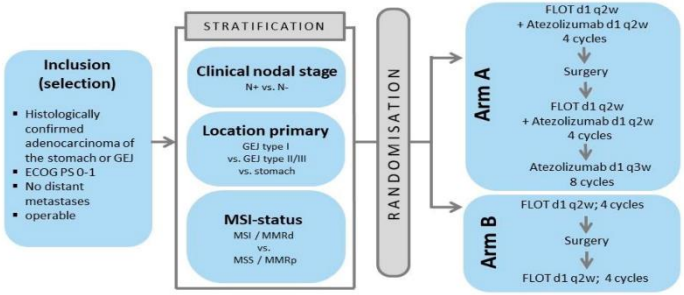
Localisiertes MSI high Adenokarzinom
Gute Prognose nach Resektion
Kein Vorteil von der Chemotherapie?

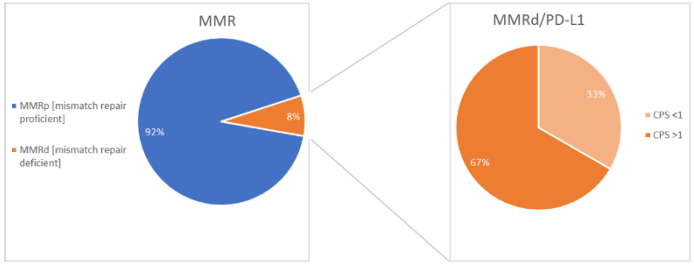
Pietrantonio F et al. J Clin Oncol 2019





Histopathologische Regression nach PD-L1-Expression



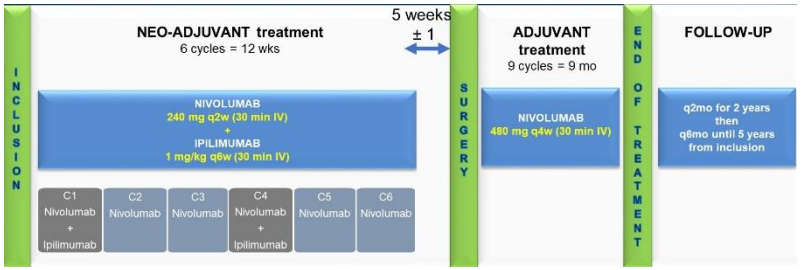


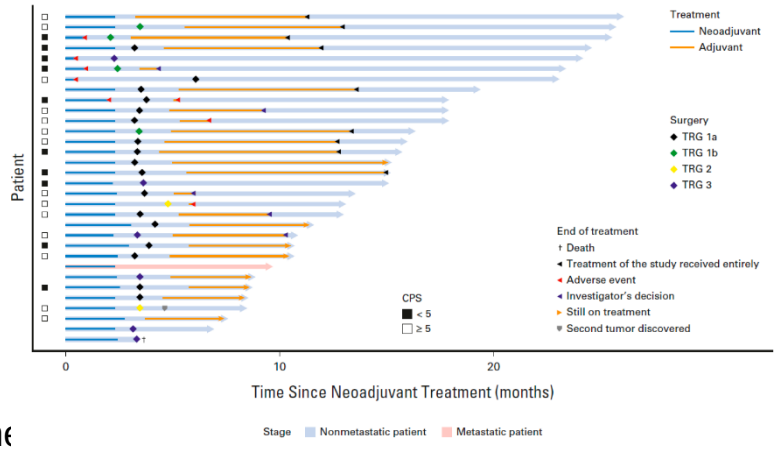
8% were dMMR-positive and 60% PD-L1-positive (CPS ≥ 1). dMMR appears to increase with age and is higher in gastric Gastric Ca and intestinal/diffuse subtype

	Arm A: FLOT + Atezolizumab (*n*=146)	**Arm B: FLOT** (*n*=149)
Regression grading according to Becker		
Complete response (no residual tumor)	35 (24%)	23 (15%)
Subtotal response (<10% residual tumor)	36 (25%)	35 (24%)
Partial response (10%-50% residual tumor)	40 (27%)	37 (25%)
Minor response (>50% residual tumor)	27 (19%)	40 (27%)
No response	2 (1%)	7 (5%)
Missing	6 (4%)	7 (5%)
Regressing grading in subgroups		
< CPS 1 (n=64/58): CR & CR/SR	15 (23%) & 29 (45%)	9 (16%) & 17 (29%)
≥ CPS 1 (n=82/88): CR & CR/SR	20 (24%) & 42 (51%)	13 (15%) & 40 (31%)
≥ CPS 5 (n=40/41): CR & CR/SR	11 (28%) & 22 (56%)	8 (20%) & 18 (44%)
≥ CPS 10 (n=27/26): CR & CR/SR	9 (33%) & 18 (67%)	3 (12%) & 10 (39%)
MSI/MMRd (n=8/15): CR & CR/SR	5 (63%) & 6 (76%)	4 (27%) & 7 (47%)

Prof. Dr. Salah-Eddin Al-Batran

NEONIPIGA: MSI-high/dMMR –Neoadjuvant Nivolumab + Ipilimumab





Tumorstadium nach neoadjuvanter Tx (n=29)

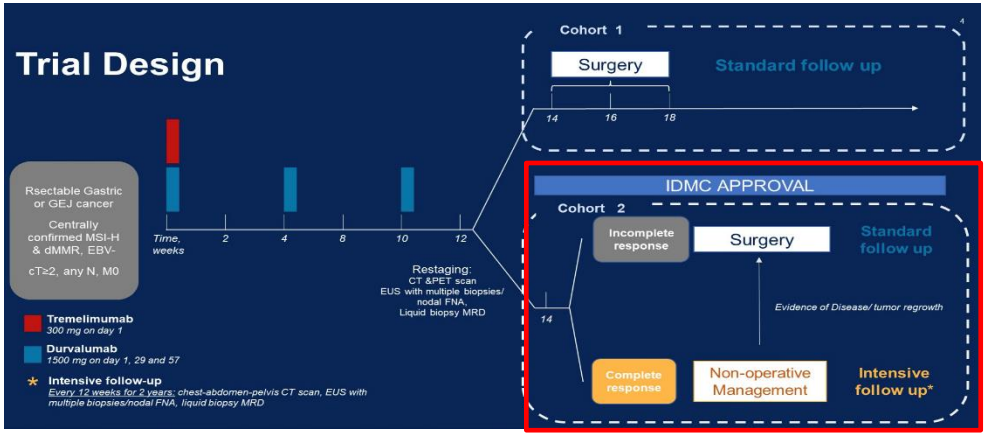
Characteristic	Patients (n = 29), No. (%)
ypT stage	
ypT0	19 (65)[a]
ypT1a	1 (3)
ypT1b	2 (7)
ypT2	2 (7)
ypT3	5 (17)
ypN stage	
ypN0	23 (79)
ypN1	6 (21)

Histologische Ansprechen Tx

TRG Mandard	
TRG 1: complete regression/fibrosis without tumor cells	17 (59)
TRG 2: fibrosis with scattered tumor cells	4 (14)[a]
TRG 3: fibrosis and tumor cells with a dominance of fibrosis	2 (7)
TRG 4: fibrosis and tumor cells with dominance of tumor cells	4 (14)
TRG 5: tumor without evidence of regression	2 (7)
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)

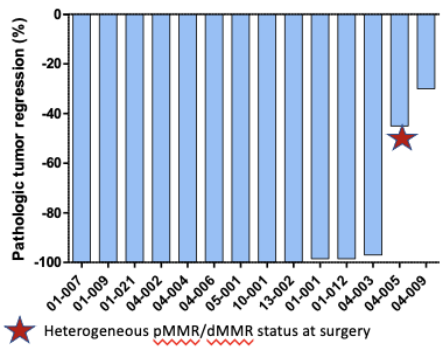
André et al ASCO GI 2022 #244
André et al. JCO 2022

Phase II INFINITY Trial GONO: Neoadjuvant Tremelilumab und Durvalumab in MSI-high lokal fortgeschrittenen gastroösophagealen Adenokarzinomen



Characteristics	N=18 (%)
Age, years: median (IQR)	71.5 (65-80)
Sex	
Male	12 (67)
Female	6 (33)
ECOG PS	
0	12 (67)
1	6 (33)
Primary site	
Gastric	14 (78)
Gastroesophageal junction	4 (22)
T stage	
T2	1 (5)
T3	10 (56)
T4	7 (39)
N stage	
N0	3 (17)
N1	6 (33)
N2	9 (50)
N bulky	
yes	4 (22)
no	14 (78)

	mITT (n, %) N=15†
TRG Becker, N (%)	
1a	9 (60)
1b	3 (20)
3	2 (13)



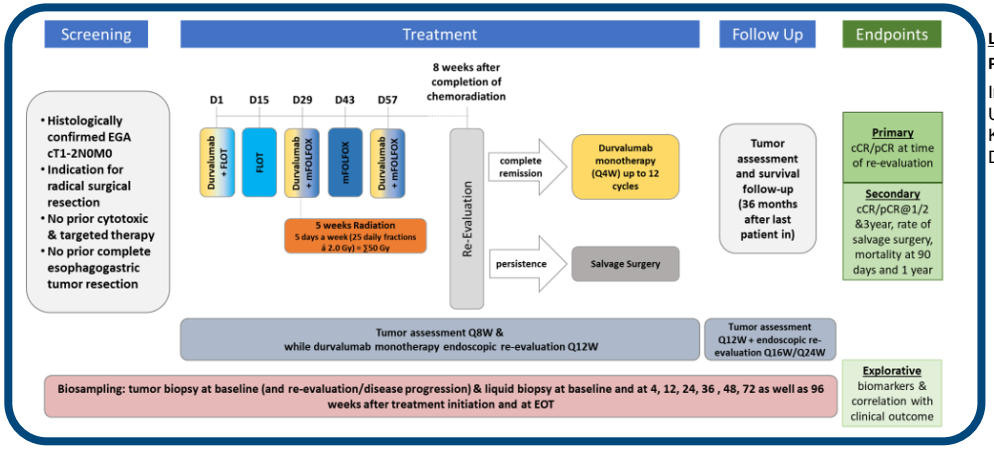
PCR: 60%; major path. Remission: 80%

Pietrantonio F et al; #358 ASCO GI 2023

PRESTO:
Organ preservation with durvalumab-based immunotherapy in combination with chemoradiation as definitive therapy for early stage, cT1 and cT2N0, esophageal adenocarcinoma (incl. gastroesophageal junction adenocarcinoma) with indication for radical surgery: A prospective, multicenter study of the FLOT-AIO Gastric Cancer Group

IKF FLOT-AIO Gastric Cancer Group

AIO



Cohort 1 will consist of participants with PD-L1 combined positive score (CPS) < 10.
Cohort 2 will consist of participants with PD-L1 CPS ≥ 10.

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Zusammenfassung

- **Neoadjuvante RCTX vs. perioperative CTX** bei gastroösophagealen Übergangskarzinomen: **Kein klarer Sieger bis 2023** (NeoAegis-Studie)! Ergebnisse der Phase-III-Studien TopGear, RACE, ESOPEC stehen noch aus

- Biomarker-Tests werden entscheidend sein!

- **Her-2 negativ**: **Perioperative Therapie mit FLOT Standard!** IO-Therapie vielversprechend - Phase II DANTE pCR Verbesserung 10%- Ergebnisse der Studien Matterhorn und KEYNOTE-585 abwarten (ESMO 2023)

- **Her-2 positiv**: Phase II PETRARCA & INNOVATION: Perioperative Therapie mit CTX und anti Her-2 vielversprechend! **Aber kein Standard!**

- IO-Therapie allein möglicherweise neue neoadjuvante Therapie für **MSI high/dMMR**? **NEONIPIGA und INFINITY Studien mit hohen pCR-und DCR Raten (60% bzw. 80%)**
- -> obwohl größere Studien erforderlich sind, werden chemofreie ICI-basierte Strategien in dieser molekularen Untergruppe bald ein Standard der Behandlung darstellen

- -> wird Organerhaltung vs. neoadjuvantes Vorgehen eine Option sein?

Danke