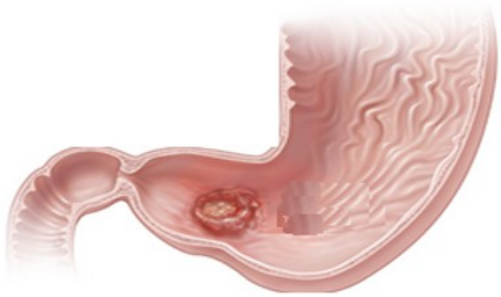
Post ASCO
Magenkarzinom & AEG

17.Juni 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

Topics

1. **Lokalisiertes AEG/Magen**

   # 4000 – ATTRACTION-5: A phase 3 study of nivolumab plus chemotherapy as postoperative adjuvant treatment for pathological stage III (pStage III) gastric or gastroesophageal junction (G/GEJ) cancer.

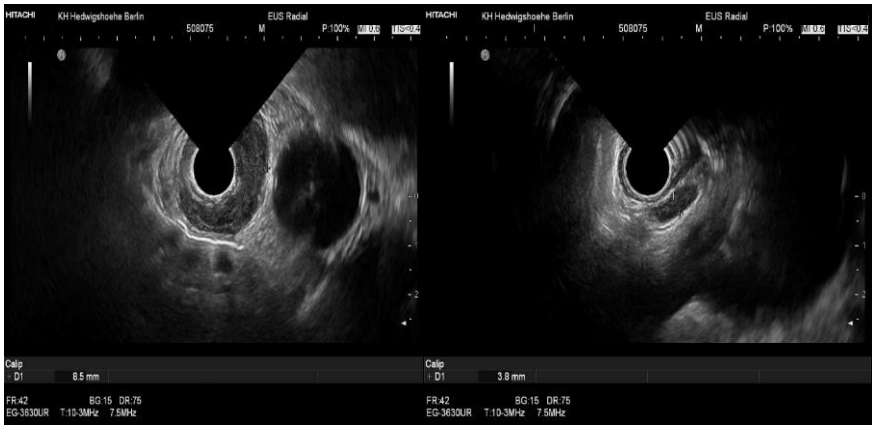
   # 4001 – Perioperative PD-1 antibody toripalimab plus SOX or XELOX chemotherapy versus SOX or XELOX alone for locally advanced gastric or gastro-oesophageal junction cancer: Results from a prospective, randomized, open-label, phase II trial.

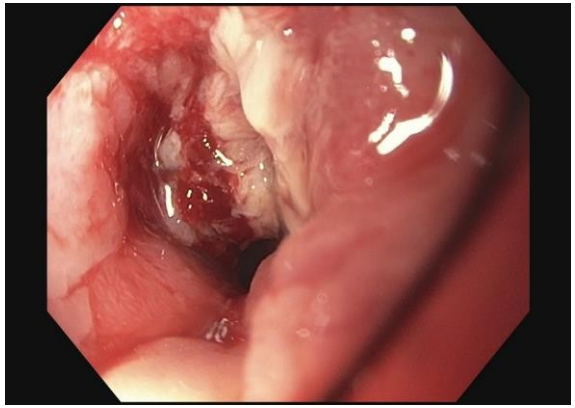
2. **Metastasiertes Magenkarzinom und AEG**

   # 4014 – KEYNOTE-859 study of pembrolizumab plus chemotherapy for advanced HER2-negative gastric or gastroesophageal junction (G/GEJ) cancer: Outcomes in the protocol-specified PD-L1–selected populations.

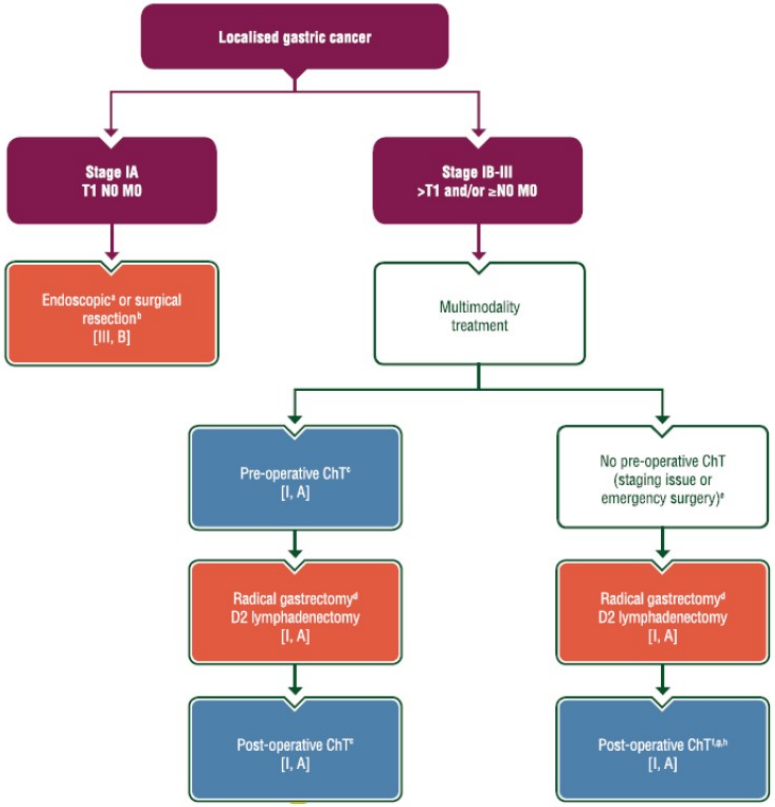
   # 4027 – A phase 2 study (DisTinGuish) of DKN-01 in combination with tislelizumab + chemotherapy as first-line (1L) therapy in patients with advanced gastric or GEJ adenocarcinoma (GEA).

Lokal fortgeschrittenes Gastroösophageales Adenokarzinom





Neue ESMO-Guidelines Magen-Ca 2022



Currently noIlmmuno 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, [online]

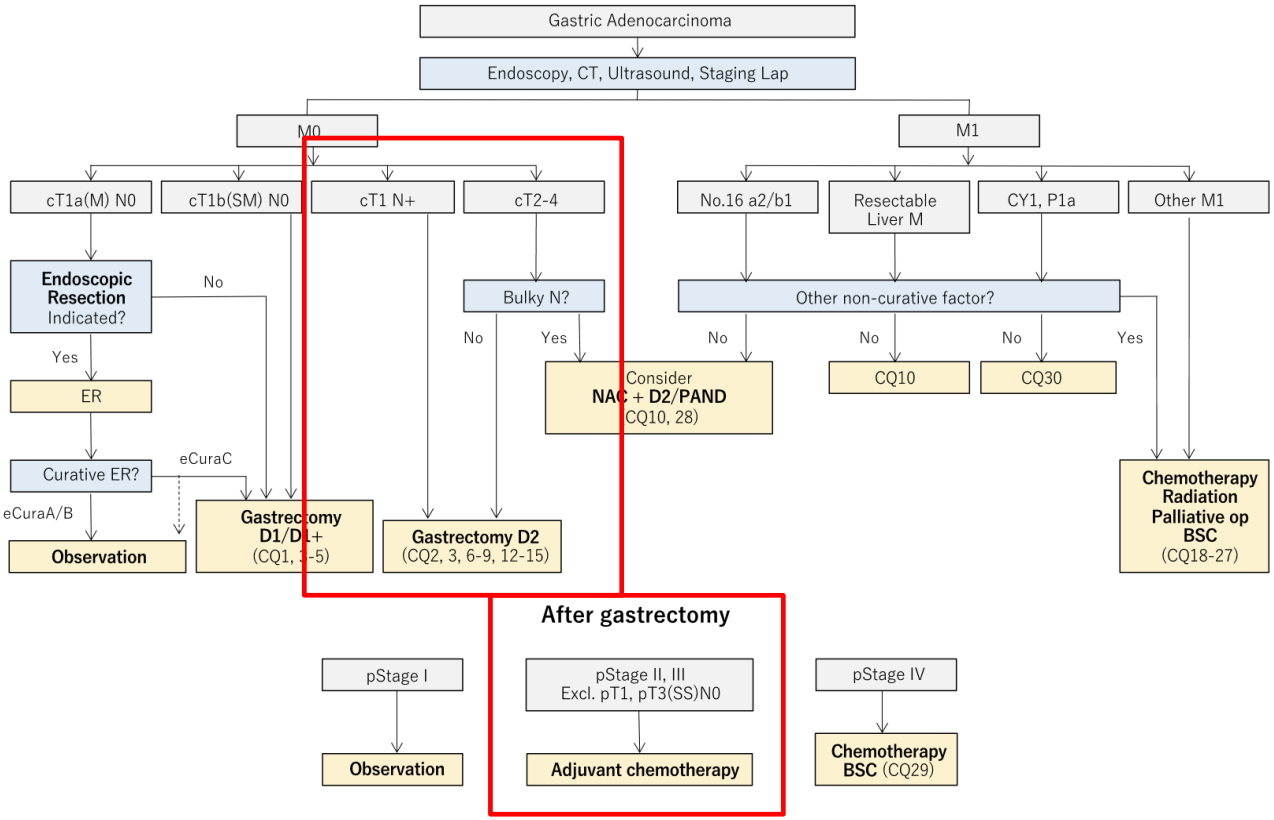
Gastric Cancer (2023) 26:1–25
https://doi.org/10.1007/s10120-022-01331-8

SPECIAL ARTICLE

Japanese Gastric Cancer Treatment Guidelines 2021 (6th edition)

Japanese Gastric Cancer Association[1]

Received: 13 July 2022 / Accepte



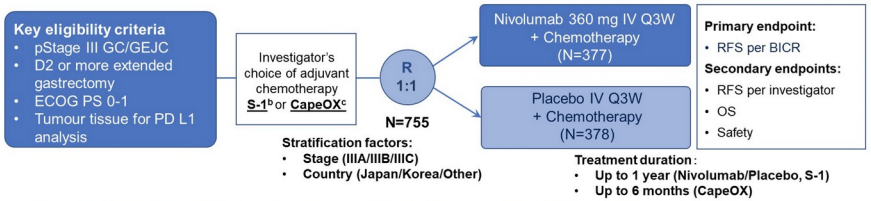
S1 plus Docetaxel (JACCRO GC-07)[1] oder Capecitabine plus Oxaliplatin (CLASSIC)[2] oder S1 plus Oxaliplatin (ARTIST II)[3] sind die empfohlenen Therapieregime in der Adjuvanz.

[1]Yoshida K et al, JCO 2019
[2]Bang YJ, et al. Lancet 2012
[3]Park SH et al, Ann Oncol 2021

ATTRACTION-5: A phase 3 study of nivolumab plus chemotherapy as postoperative adjuvant treatment for pathological stage III (pStage III) gastric or gastroesophageal junction (G/GEJ) cancer.

Studiendesign

- Phase 3, double-blind, placebo-controlled study of Asian patients (Japan, Korea, Taiwan, China)[a]



- Planned sample size: 700 patients (assuming HR=0.67; 3-year RFS, 71% vs 60%)
- Patients were randomized from February 2017 to August 2019
- All data are based on a clinical data cutoff of August 2022, at which point the minimum follow-up after the last patient randomized was 36 months

[a]ClinicalTrials.gov number, NCT03006705; [b]**S-1 therapy:** S-1 40 mg/m²/dose orally twice daily (day1-28) , Q6W; [c]**CapeOX therapy:** Oxaliplatin 130 mg/m² IV once daily (day1), and Capecitabine 1000 mg/m²/dose orally twice daily (day1-14), Q3W.

Abbreviations: BICR, blinded independent central review; CapeOX, capecitabine/oxaliplatin; GC, gastric cancer; GEJC, gastroesophageal junction cancer; IV, intravenous; Q3W, every 3 weeks; Q6W, every 6 weeks; S-1, tegafur/gimeracil/oteracil; BICR, blinded independent central review

Patienten- und Tumorcharakteristika

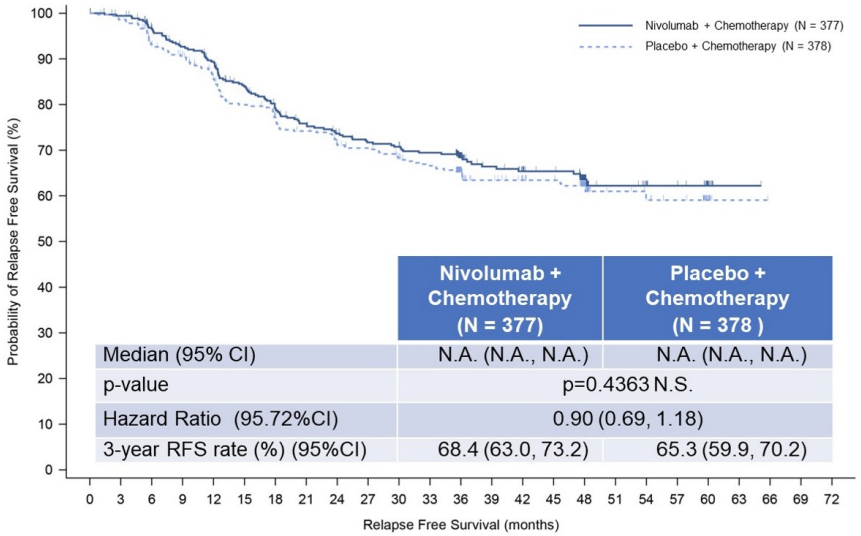
		Nivolumab + Chemotherapy (N=377)	Placebo + Chemotherapy (N=378)
Age (years), n (%)	<65	212 (56.2)	222 (58.7)
	≥65	165 (43.8)	156 (41.3)
Sex, n (%)	Female	110 (29.2)	115 (30.4)
	Male	267 (70.8)	263 (69.6)
Country, n (%)	Japan	182 (48.3)	183 (48.4)
	Korea	157 (41.6)	155 (41.0)
	Taiwan	23 (6.1)	24 (6.3)
	China	15 (4.0)	16 (4.2)
ECOG PS, n (%)	0	299 (79.3)	294 (77.8)
	1	78 (20.7)	84 (22.2)
Primary sites, n (%)	GEJ	21 (5.6)	31 (8.2)
	Gastric fundus	26 (6.9)	25 (6.6)
	Gastric corpus	161 (42.7)	154 (40.7)
	Gastric antrum and pylorus	169 (44.8)	168 (44.4)
Pathological stage, n (%)	IIIA	110 (29.2)	111 (29.4)
	IIIB	127 (33.7)	129 (34.1)
	IIIC	140 (37.1)	138 (36.5)
Type of surgery, n (%)	Total Gastrectomy	164 (43.5)	164 (43.4)
	Distal Gastrectomy	204 (54.1)	199 (52.6)
	Others	9 (2.4)	15 (4.0)
Histology, n (%)	Intestinal type	134 (35.5)	140 (37.0)
	Diffuse type	213 (56.5)	209 (55.3)
	Others	30 (8.0)	26 (6.9)
Tumor cell PD-L1 expression[a], n (%)	≥ 1%	52 (13.8)	34 (9.0)
	< 1%	309 (82.0)	333 (88.1)
Chemotherapy regimen, n (%)	S-1	132 (35.0)	135 (35.7)
	CapeOX	245 (65.0)	243 (64.3)

[a]Tumor cell PD-L1 expression determined from surgical specimen by the PD-L1 IHC 28-8 pharmDx assay (Dako).

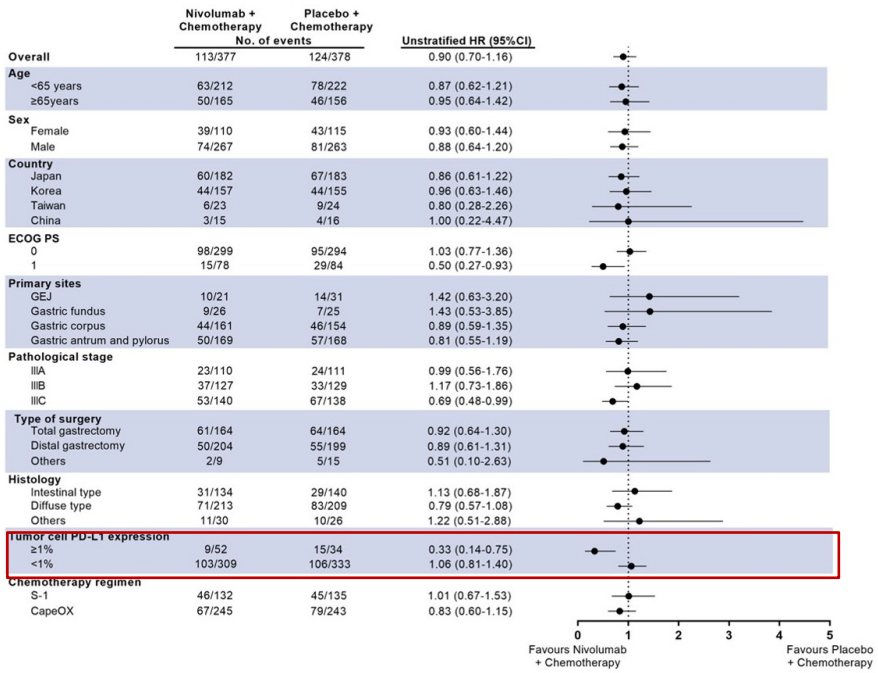
	Both	Nivolumab	Chemotherapy	Both	Placebo	Chemotherapy
Completed, n (%)	228 (61.5)	243 (65.5)	281 (75.7)	267 (71.4)	282 (75.4)	306 (81.8)
Discontinued, n (%)	75 (20.2)	128 (34.5)	90 (24.3)	53 (14.2)	92 (24.6)	68 (18.2)

Masanori Terashima, et al, Journal of Clinical Oncology 2023 41:16_suppl, 4000-4000 .

Primärer Endpunkt: RFS nach BICR



	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)

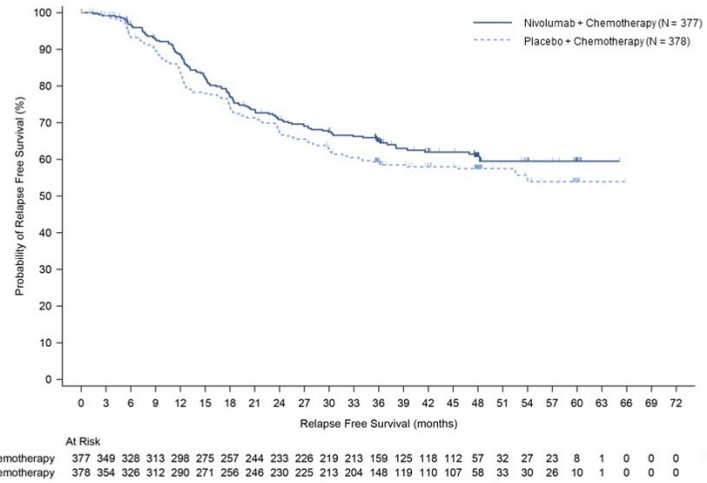


TPS ≥ 1= 14%
Wahrscheinlich 60-80 CPS positiv

Masanori Terashima, et al, Journal of Clinical Oncology 2023 41:16_suppl, 4000-4000 .

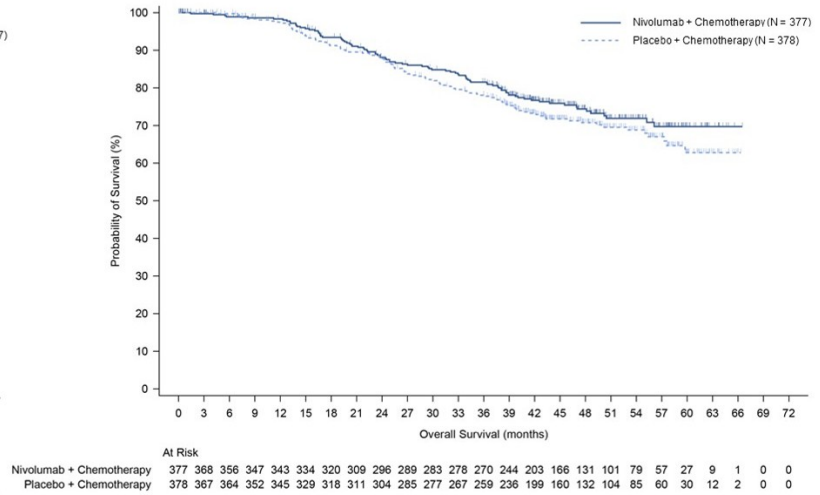
Sekundärer Endpunkt: RFS nach Investigator und OS

RFS per investigator



	Nivolumab + Chemotherapy (N = 377)	Placebo + Chemotherapy (N= 378)
Median (95% CI)	N.A. (N.A., N.A.)	N.A. (52.53, N.A.)
p-value	–	
Hazard ratio (95%CI)	0.87 (0.69, 1.11)	
3-year RFS rate (%) (95%CI)	64.9 (59.5, 69.8)	59.3 (54.0, 64.3)

OS



	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	–	
Hazard ratio (95%CI)	0.88 (0.66, 1.17)	
3-year OS rate (%) (95%CI)	81.5 (77.0, 85.3)	78.0 (73.3, 82.1)

Fazit: keine Verbesserung im RFS/OS durch die Hinzunahme von Nivolumab
Vorteil bei Subgruppe der TPS+
Outcome nach CPS und bei MSI high abzuwarten

Masanori Terashima, et al, Journal of Clinical Oncology 2023 41:16_suppl, 4000-4000 .

Perioperative PD-1 antibody toripalimab plus SOX or XELOX chemotherapy versus SOX or XELOX alone for locally advanced gastric or gastro-oesophageal junction cancer: results from a prospective, randomized, open-label, phase II trial

Shuqiang Yuan, Run-Cong Nie, Ying Jin, Cheng-cai Liang, Rui Jian, Yuan-fang Li, Haibo Qiu, Wei Wang, Shi Chen, Dong-sheng Zhang, Chun-yu Huang, Yi-hong Ling, Qiu-xia Yang, Zi-Xian Wang, Wen-long Guan, Ying-bo Chen, Xiao-wei Sun, Zhi-wei Zhou, Feng Wang, Rui-Hua Xu

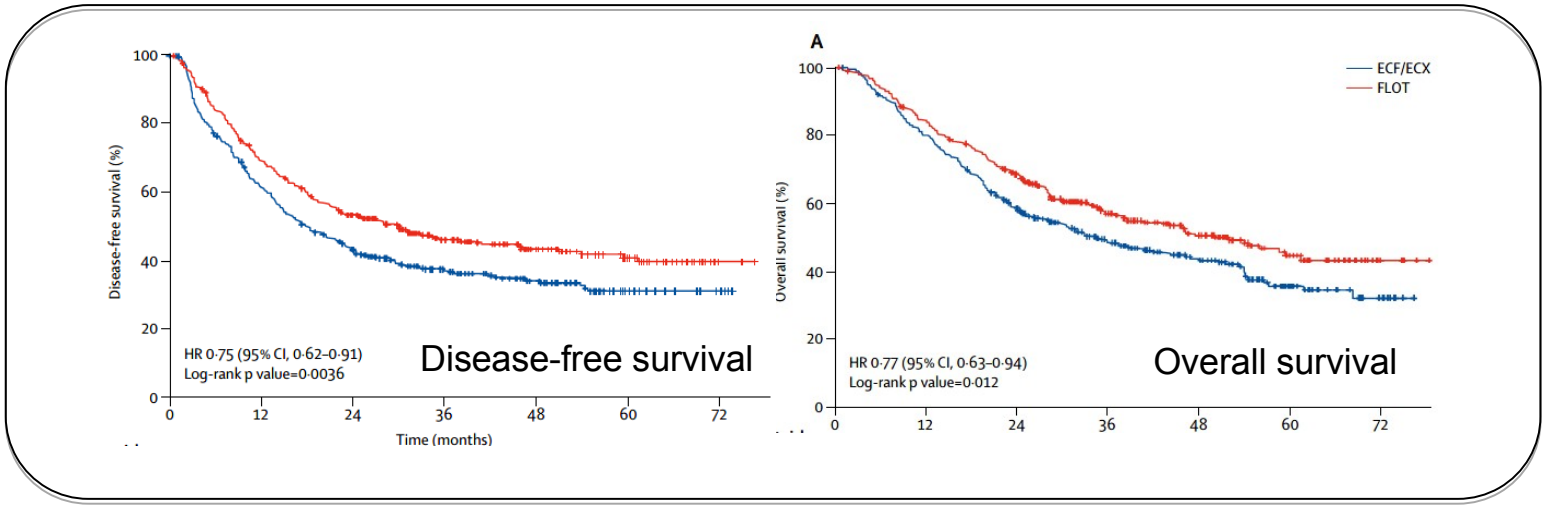
Presented by **Shuqiang Yuan, M.D., Ph.D.**

Sun Yat-sen University Cancer Center, State Key Laboratory of Oncology in South China

Yuan S et al . Journal of Clinical Oncology 2023 41:16_suppl, 4001-4001

Magenkarzinom: Der Standard – FLOT 4 Studie

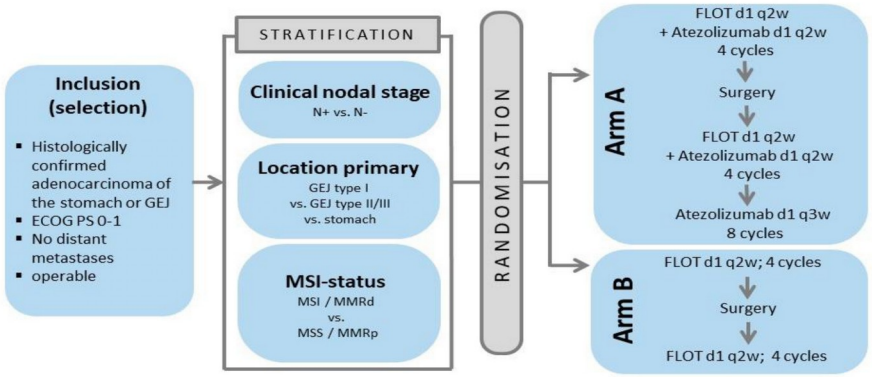
Al-Batran S et al. Lancet 2019



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

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

ASCO 2022: Phase II AIO-DANTE-Studie FLOT +/- Atezolizumab*



Biomarker / Score Subgroup	PD-L1 Score				MMR Status	
	CPS < 1	CPS ≥1	CPS ≥5	CPS ≥10	pMMR (MSS)	dMMR (MSI)
	N = 199				N = 295	
All patients	80 (40%)	119 (60%)	57 (29%)	39 (20%)	272 (92%)	23 (8%)
	N = 78				N = 114	
GC subgroup	37 (47%)	41 (53%)	16 (21%)	10 (13%)	102 (89%)	12 (11%)
	N = 121				N = 181	
GEJ subgroup	43 (36%)	78 (64%)	41 (34%)	29 (24%)	170 (94%)	11 (6%)
	N = 18*					
dMMR subgroup	6 (33%)	12 (67%)	7 (39%)	6 (33%)		

	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%

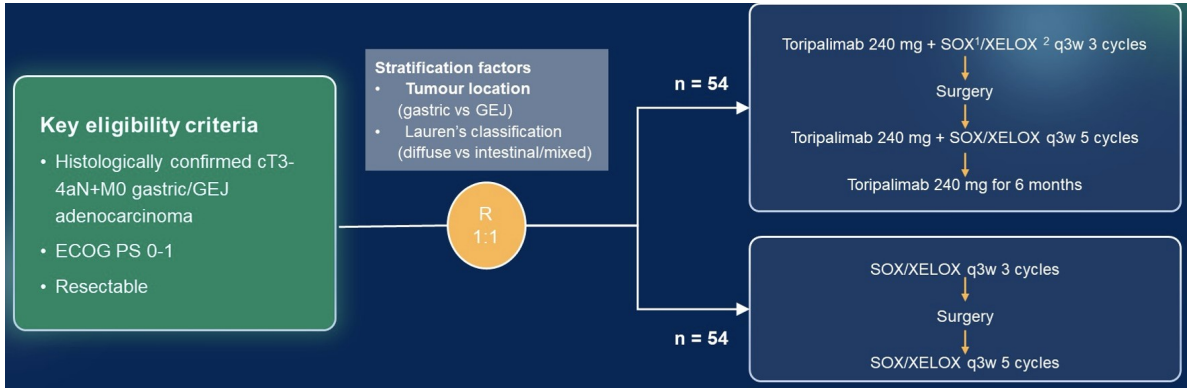
Pathological Regression FLOT + Atezolizumab (arm A) vs. FLOT (arm B)	Becker Classification			
	TRG1a[1]		TRG1a/b[2]	
	A	B	A	B
All patients (N= 295; 146|149)	35 (24%)	23 (15%)	71 (49%)	58 (39%)
PD-L1 CPS ≥1 (N=170; 82|88)	20 (24%)	13 (15%)	42 (51%)	40 (46%)
PD-L1 CPS ≥5 (N=81; 40|41)	11 (28%)	8 (20%)	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%)

*keine zugelassene Therapie
Kopp et al., ESMO 2021 1430P
Al-Batran et al., *J Clin Oncol 40*, 2022 (suppl 16; abstr 4003)

ASCO 2022: Histopathologische Regression in Abhängigkeit von der PD-L1-Expression

	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%)

Perioperative PD-1 antibody toripalimab plus SOX or XELOX chemotherapy versus SOX or XELOX alone for locally advanced gastric or gastro-oesophageal junction cancer: Results from a prospective, randomized, open-label, phase II trial.



Primary endpoint

TRG 0/1: rates of pathological complete response (TRG 0) or near complete response (TRG 1), according to NCCN guideline

Tumor Regression Grade (TRG)	Microscopic findings
0 (complete regression)	No residual tumor cells
1 (near complete response)	Only single cells or small groups of residual tumor cells
2 (minor regression)	Presence of residual tumor cells but less than fibrotic stroma
3 (no regression)	Extensive residual tumor with no or a small amount of tumor cell necrosis

Main secondary endpoints

- Pathological complete response of primary tumour, ypT0
- R0 resection
- RFS, EFS, and OS
- Treatment safety

Yuan S et al . Journal of Clinical Oncology 2023 41:16_suppl, 4001-4001

Phase II Perioperative PD-1 antibody toripalimab plus SOX or XELOX chemotherapy versus SOX or XELOX alone

Alle N+

	Toripalimab + chemotherapy (n = 54)	Chemotherapy (n = 54)
Signet-ring cell composition		
No	43 (80%)	40 (74%)
Yes	11 (20%)	14 (26%)
Clinical tumour stage		
cT3	21 (39%)	17 (31%)
cT4a	33 (61%)	37 (69%)
Clinical node stage		
cN1	24 (44%)	22 (41%)
cN2	18 (33%)	26 (48%)
cN3	12 (22%)	6 (11%)
Diagnostic laparoscopy		
Yes	54 (100%)	53 (96%)
No	0	1 (4%)
Chemotherapy regimen		
SOX	33 (61%)	25 (46%)
XELOX	21 (39%)	29 (54%)

Yuan S et al . Journal of Clinical Oncology 2023 41:16_suppl, 4001-4001

Primärer Endpunkt: TRG 0/1

24% Dante

49% Dante

	Toripalimab + chemotherapy (n = 54)	Chemotherapy (n = 54)	P value
TRG			
TRG 0 (ypT0N0M0)	**12 (22%)**	**4 (7%)**	0.03
TRG 1	12 (22%)	7 (13%)	
TRG 2	16 (30%)	29 (54%)	
TRG 3	11 (20%)	12 (22%)	
Combined TRG 0-1	**24 (44%)**	**11 (20%)**	0.01
No surgery	3 (6%)	2 (4%)	

Primary endpoint

TRG 0/1 stratifiziert nach Tumorlokalisation und histopathologischem Subtyp

	Toripalimab + chemotherapy (n = 54)	Chemotherapy (n = 54)
Tumor location		
Gastric	18/38 (49%)	9/34 (27%)
Gastro-oesophageal junction	6/17 (35%)	2/20 (10%)
Lauren's classification		
Diffuse	4/18 (22%)	3/20 (15%)
Intestinal/Mixed	20/36 (56%)	8/34 (24%)

Yuan S et al . Journal of Clinical Oncology 2023 41:16_suppl, 4001-4001

Sekundärer Endpunkt: ypTNM Downstaging

23% Dante

69% Dante

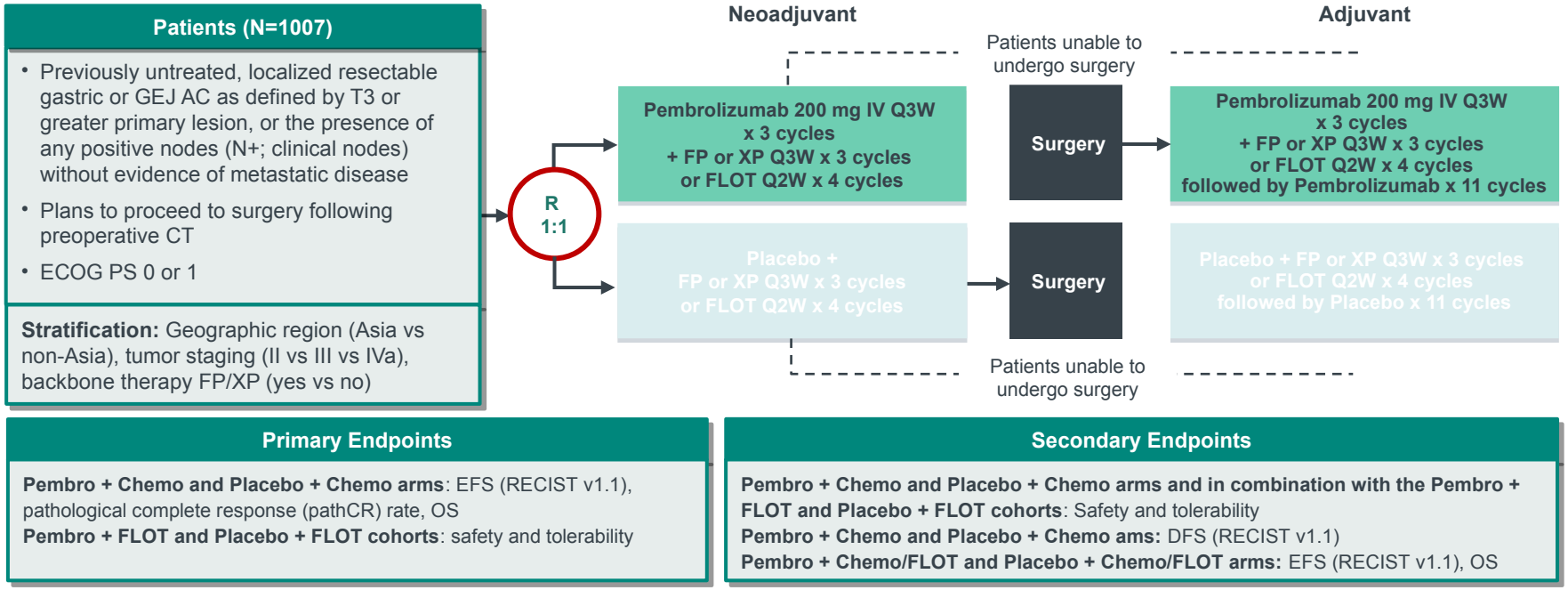
	Toripalimab + chemotherapy (n = 54)	Chemotherapy (n = 54)
Pathological tumour stage (ypT)		
ypT0 (pCR of primary tumour)	13 (24%)	5 (9%)
ypT1	7 (13%)	5 (9%)
ypT2	5 (9%)	2 (4%)
ypT3	20 (37%)	28 (52%)
ypT4	6 (11%)	12 (22%)
Combined ypT0-2	25 (46%)	12 (22%)
Combined ypT3-4	26 (48%)	40 (74%)
Pathological node stage (ypN)		
ypN0	22 (41%)	21 (39%)
ypN1	9 (17%)	11 (20%)
ypN2	11 (20%)	9 (17%)
ypN3	9 (17%)	11 (20%)
Combined ypN0-1	31 (57%)	32 (59%)
Combined ypN2-3	20 (37%)	20 (37%)

Fazit: **IO plus preop. CTX verbessert pCR und TRG 0/1**
Keine Daten zu MSI, CPS Status
Dante: MSI high: 8% mit besten Ergebnissen (pCR 63%)
Sollen MSI Pat aus IO -CTX Studien ausgeschlossen werden?
EFS/OS ausstehend

Yuan S et al . Journal of Clinical Oncology 2023 41:16_suppl, 4001-4001

KEYNOTE-585: Study Design[1,2]

A Phase III, Randomized, Double-Blind, Clinical Trial of Pembrolizumab Plus Chemotherapy (XP or FP) versus Placebo Plus Chemotherapy (XP or FP) as Neoadjuvant/Adjuvant Treatment for Subjects With Gastric and Gastroesophageal Junction (GEJ) Adenocarcinoma (KEYNOTE-585)



Primary Endpoints

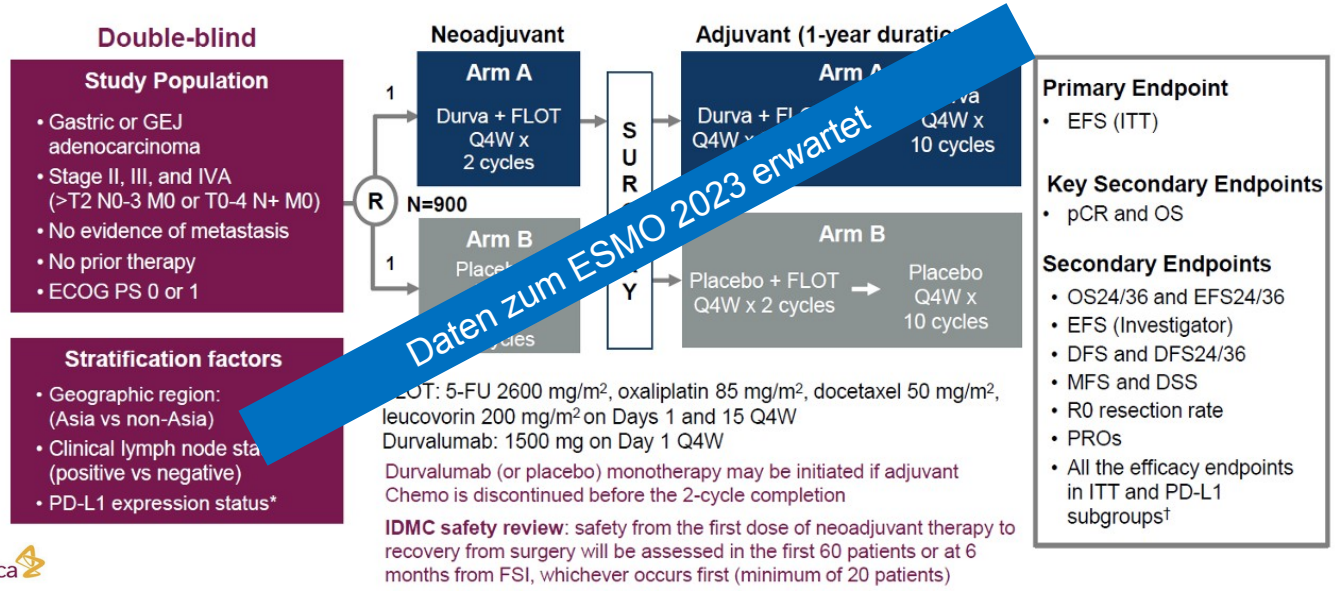
Pembro + Chemo and Placebo + Chemo arms: EFS (RECIST v1.1), pathological complete response (pathCR) rate, OS
Pembro + FLOT and Placebo + FLOT cohorts: safety and tolerability

Secondary Endpoints

Pembro + Chemo and Placebo + Chemo arms and in combination with the Pembro + FLOT and Placebo + FLOT cohorts: Safety and tolerability
Pembro + Chemo and Placebo + Chemo ams: DFS (RECIST v1.1)
Pembro + Chemo/FLOT and Placebo + Chemo/FLOT arms: EFS (RECIST v1.1), OS

1. ClinicalTrials.gov. https://www.clinicaltrials.gov/ct2/show/NCT03221426. Accessed March 6, 2023. 2. Bang YJ et al. *Future Oncol.* 2019;15(9):943–952

MATTERHORN: neoadj/adj FLOT +/- Durvalumab in resectable gastroesophageal cancer



Daten zum ESMO 2023 erwartet

MATTERHORN
AZ IO TRIALS

AstraZeneca

P<1% vs TIP≥1%
P<1% vs TIP≥1% vs TIP≥5%

02 Jun 2023

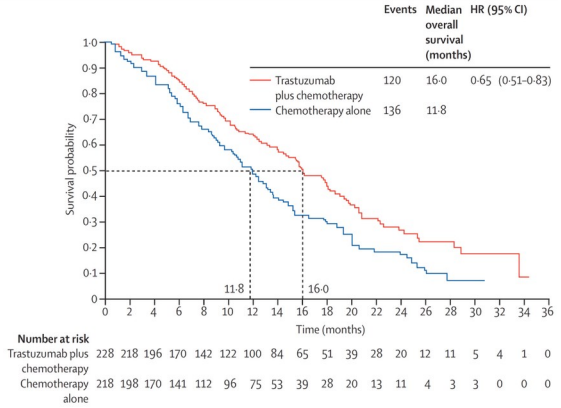
Dear Investigators,

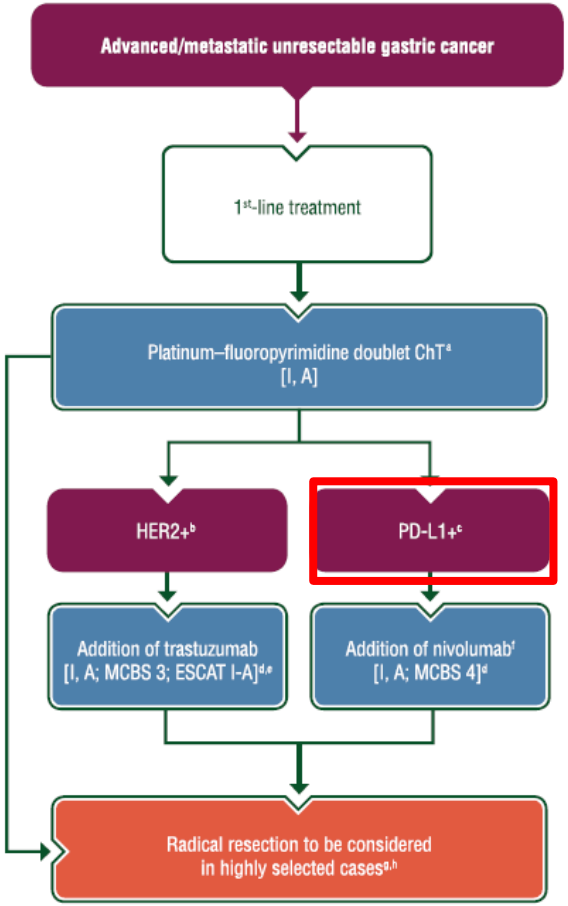
We are delighted to inform you of the positive high-level results from a planned interim analysis of the MATTERHORN Phase III trial that showed treatment with durvalumab added to standard-of-care FLOT chemotherapy before surgery demonstrated a statistically significant improvement in the secondary endpoint 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.

Metastastiertes gastroösophageales Adenokarzinom

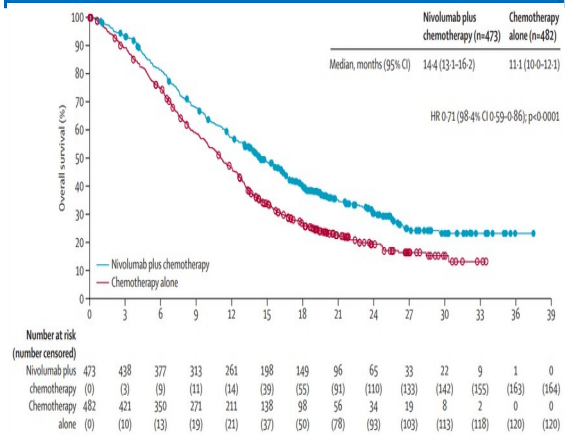
METASTASIERTES MAGENKARZINOM 1ST-LINE – ESMO GUIDELINES 2022

TOGA, Trastuzumab+Chemo, HER2-positiv





CHECKMATE-649, PD-L1 CPS ≥ 5



Lordick F, et al. *Ann Oncol* 2022

Janjigian Y, et al. *Lancet.* 2021 Jul 3;398(10294):27-40

PD-L1 Expression: Magen- und Ösophaguskarzinom

- **Keynote 590 Ösophagus:** CPS ≥ 10 in **50%** SCC (283/548) and AC (100/203)
  22C3 (Agilent Techmologies) Sun JM et al. Lancet 2021; 398:759-71

- **Checkmate-648 Ösophagus:** TPS ≥ 1% in **49%** SCC (283/548)
  22C3 (Agilent Techmologies) Chau I et al. ASCO 2021: abstract 4001

- **Checkmate-649 Gastric/GEJ:** CPS ≥ 1 **82%,** CPS ≥ 5 **60%** (955/1581)
  28-8 pharmDx(Dako)C3 Janjigian YY et al. Lancet 2021: 398:27-40

- **Keynote-062 Gastric/GEJ:** CPS ≥ 10 **37%** (281/763)
  22C3 (Agilent Techmologies) 2020;6:1571-1580 Shitara K et al. Jama Oncol.

- **Keynote-811 Gastric/GEJ:** CPS ≥ 1 **84%** (364/434)
  22C3 (Agilent Techmologies)

  Janjigian YY et al. Nature. 2021; 600:727-730

- **RATIONALE- 305 Gastric/GEJ:** CPS ≥ 5 13.5% (41/311)
  Dako PD-L1 IHC 28-8 pharmDx assay Möhler M. et al; #286 ASCO GI 2023

- **KEYNOTE - 859** **Gastric/GE:** CPS ≥ 1 78% (1235/1479) Rha S et al; ESMO virtual plenary 2023
  PD-L1 IHC 22C3

KEYNOTE-859 study of pembrolizumab plus chemotherapy for advanced HER2-negative gastric or gastroesophageal junction (G/GEJ) cancer:

Outcomes in the protocol-specified PD-L1–selected populations.

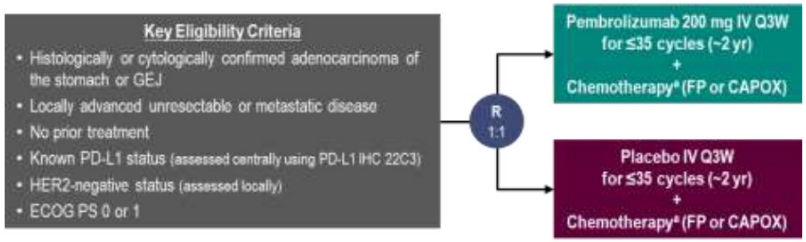
Sun Young Rha, et al. Journal of Clinical Oncology 2023 41:16_suppl, 4014-4014

KEYNOTE-859: Erstlinientherapie des metastasierten HER2-negativen gastroösophagealen Adenokarzinoms

ESMO virtual Penary 2023

KEYNOTE-859

Design and baseline characteristics



- Large, well powered clinical trial with global reach
- Majority gastric cancer but GEJ represented
- Most tumours not highly immune activated (CPS <10 65%)
- Chemotherapy use represents changing patterns globally

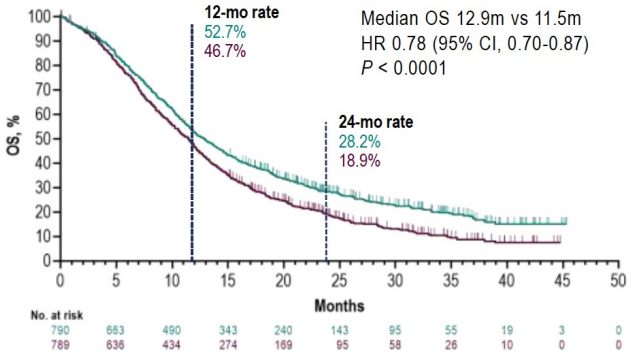
Key Baseline Characteristics	Pembro + Chemo (N = 790)	Placebo + Chemo (N = 789)
Age, median (range)	61 y (23-86)	62 y (21-85)
Male	527 (66.7%)	544 (68.9%)
Geographic region		
Asia	263 (33.3%)	262 (33.2%)
Primary tumor location		
Adenocarcinoma of the stomach	640 (81.0%)	603 (76.4%)
MSI-high status	39 (5.0%)	35 (4.4%)
PD-L1 CPS ≥1 at baseline	618 (78.2%)	617 (78.2%)
PD-L1 CPS ≥10 at baseline	279 (35.3%)	272 (34.5%)
Chemotherapy		
CAPOX	682 (86.3%)	681 (86.3%)
FP	108 (13.7%)	108 (13.7%)

Rha S et al.; ESMO virtual plenary 2023

KEYNOTE-859: Erstlinientherapie des metastasierten HER2-negativen gastroösophagealen Adenokarzinoms

KEYNOTE-859

Overall survival in ITT population (all levels PD-L1)



- Long term benefits are meaningful
- At 2 years
  - 9.3% absolute benefit,
  - ~50% relative improvement

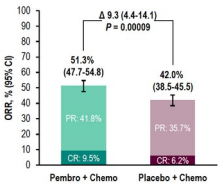
- 1/3 patients are alive at 2 years
  - How do we identify these patients?

KEYNOTE-859 toxicity results

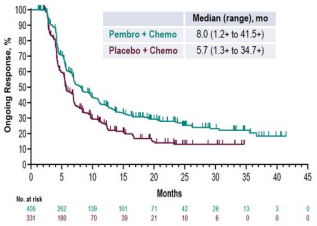
All Immune-Mediated AEs	Pembro + Chemo (N = 785)	Placebo + Chemo (N = 787)
Any grade	213 (27.1%)	73 (9.3%)
Grade 3-5	62 (7.9%)	13 (1.7%)
Led to death	1 (0.1%)[a]	1 (0.1%)[a]

Significant anti-PD-1 toxicities are not very common, but not rare
QoL data not shown

ORR



DOR



Rha S et al.; ESMO virtual plenary 2023

Pembrolizumab Plus Chemotherapy as First-Line Therapy for Advanced HER2-Negative Gastric or Gastroesophageal Junction Cancer: Phase 3 KEYNOTE-859 Study

Baseline Characteristics, ITT Population

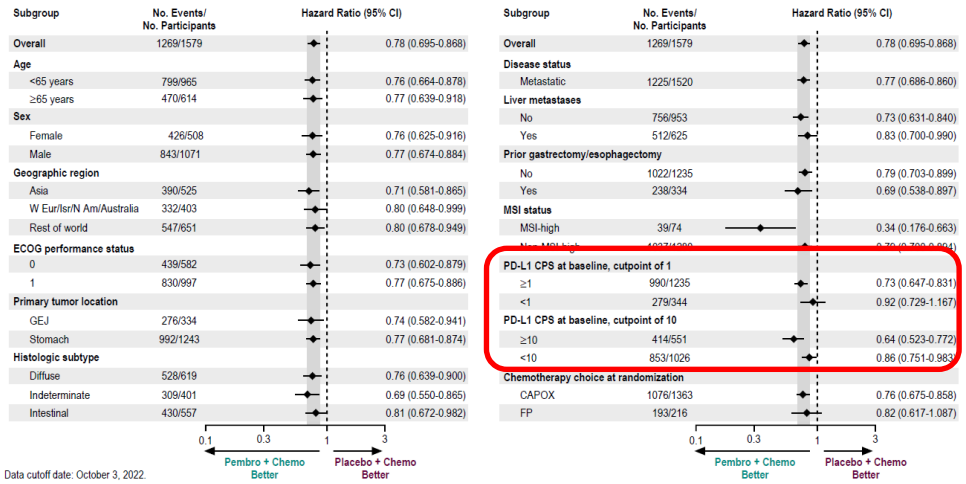
	Pembro + Chemo (N = 790)	Placebo + Chemo (N = 789)
Age, median (range)	61 y (23-86)	62 y (21-85)
≥65 y	304 (38.5%)	310 (39.3%)
Male	527 (66.7%)	544 (68.9%)
Geographic region		
Asia	263 (33.3%)	262 (33.2%)
W Europe/Israel/N America/Australia	201 (25.4%)	202 (25.6%)
Rest of world	326 (41.3%)	325 (41.2%)
ECOG PS 1	509 (64.4%)	488 (61.9%)
Primary tumor location[a]		
Adenocarcinoma of the GEJ	149 (18.9%)	185 (23.4%)
Adenocarcinoma of the stomach	640 (81.0%)	603 (76.4%)
Disease status[b]		
Locally advanced	28 (3.5%)	30 (3.8%)
Metastatic	761 (96.3%)	759 (96.2%)

	Pembro + Chemo (N = 790)	Placebo + Chemo (N = 789)
Histologic subtype[c]		
Diffuse	318 (40.3%)	301 (38.1%)
Indeterminate	186 (23.5%)	215 (27.2%)
Intestinal	284 (35.9%)	273 (34.6%)
Liver metastases present[d]	314 (39.7%)	311 (39.4%)
Prior gastrectomy/esophagectomy[e]	172 (21.8%)	162 (20.5%)
HER2-negative status	790 (100%)	789 (100%)
MSI-high status[f]	39 (5.0%)	35 (4.4%)
PD-L1 CPS ≥1 at baseline	618 (78.2%)	617 (78.2%)
PD-L1 CPS ≥10 at baseline[g]	279 (35.3%)	272 (34.5%)
Combination chemotherapy at randomization		
CAPOX	682 (86.3%)	681 (86.3%)
FP	108 (13.7%)	108 (13.7%)

[a] Other in 1 (0.1%) patient in the placebo + chemo group and missing in 1 (0.1%) in the pembro + chemo group. [b] Missing in 1 (0.1%) patient in the pembro + chemo group. [c] Unknown in 1 (0.1%) patient in the pembro + chemo group and missing in 1 (0.1%) patient in the pembro + chemo group. [d] Missing in 1 (0.1%) patient in the pembro + chemo group. [e] Missing in 5 (0.6%) patients in each group. [f] Missing in 106 (13.5%) patients in the pembro + chemo group and 112 (14.2%) in the placebo + chemo group. [g] Missing in 2 (0.3%) patients in the pembro + chemo group.

Data cutoff date: October 3, 2022.

OS in Key Subgroups, ITT Population

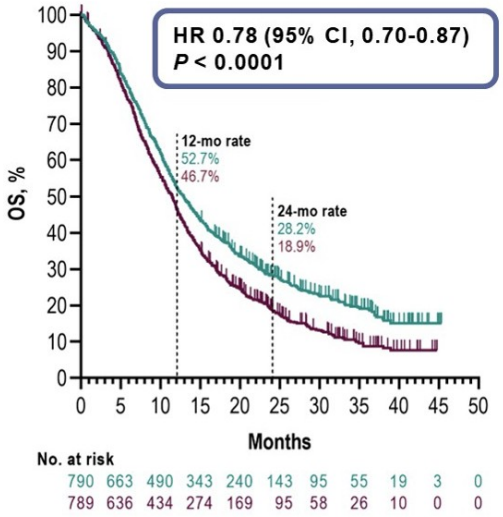


S.Y. Rha et al. ESMO virtual plenary 2023

ASCO 2023: KEYNOTE-859:
Outcomes in the protocol-specified PD-L1–selected populations
Primärer Endpunkt: OS

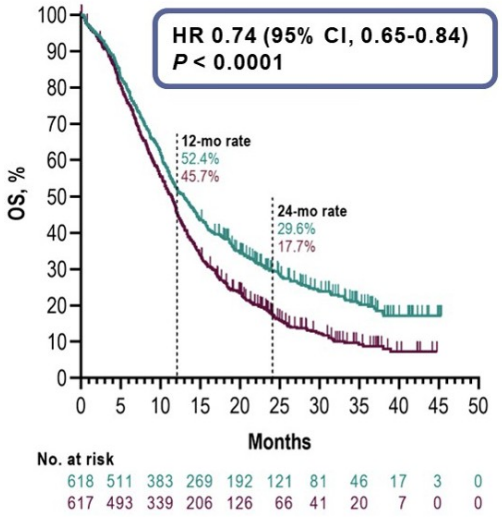
Overall[1]

	Pts w/ Event	Median (95% CI), mo
Pembro + chemo	76.3%	12.9 (11.9-14.0)
Placebo + chemo	84.4%	11.5 (10.6-12.1)



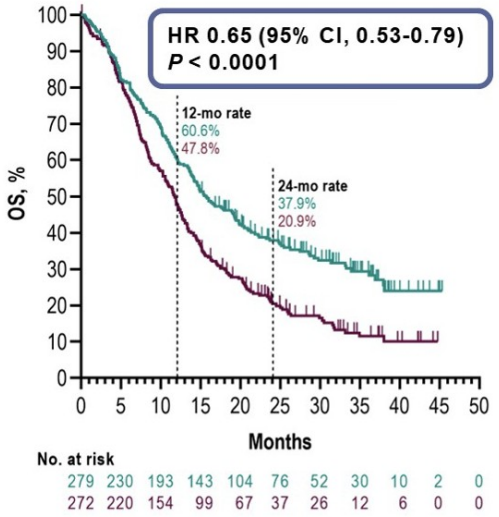
PD-L1 CPS ≥1

	Pts w/ Event	Median (95% CI), mo
Pembro + chemo	75.1%	13.0 (11.6-14.2)
Placebo + chemo	85.3%	11.4 (10.5-12.0)



PD-L1 CPS ≥10

	Pts w/ Event	Median (95% CI), mo
Pembro + chemo	67.4%	15.7 (13.8-19.3)
Placebo + chemo	83.1%	11.8 (10.3-12.7)

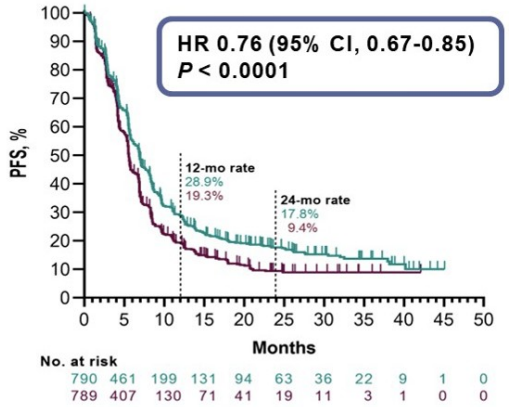


Sun Young Rha, et al. Journal of Clinical Oncology 2023 41:16_suppl, 4014-4014

ASCO 2023 KEYNOTE-859: Outcomes in the protocol-specified PD-L1–selected populations. Sekundäre Endpunkte: PFS, ORR, DOR

Overall[1]

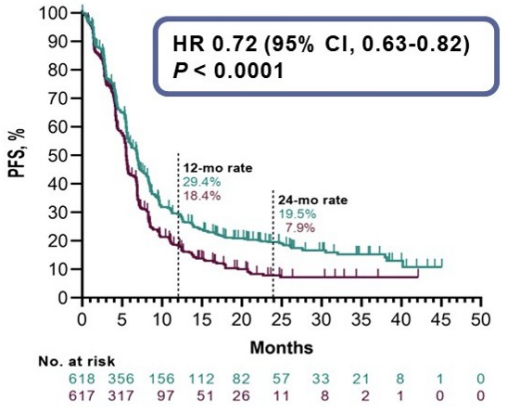
	Pts w/ Event	Median PFS (95% CI), mo
Pembro + chemo	72.4%	6.9 (6.3-7.2)
Placebo + chemo	77.1%	5.6 (5.5-5.7)



	Pembro + Chemo	Placebo + Chemo
ORR, % (95% CI)	51.3% (47.7-54.8)	42.0% (38.5-45.5)
Δ (95% CI)	9.3 (4.4-14.1); P = 0.00009	
mDOR (range)	8.0 mo (1.2+ - 41.5+)	5.7 mo (1.3+ - 34.7+)

PD-L1 CPS ≥1

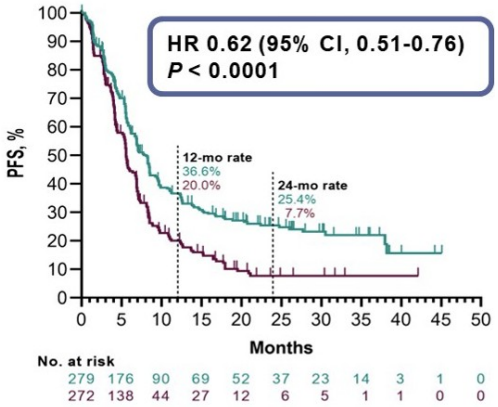
	Pts w/ Event	Median PFS (95% CI), mo
Pembro + chemo	71.7%	6.9 (6.0-7.2)
Placebo + chemo	78.3%	5.6 (5.4-5.7)



	Pembro + Chemo	Placebo + Chemo
ORR, % (95% CI)	52.1% (48.1-56.1)	42.6% (38.7-46.6)
Δ (95% CI)	9.5 (3.9-15.0); P = 0.00041	
mDOR (range)	8.3 mo (1.2+ - 41.5+)	5.6 mo (1.3+ - 34.2+)

PD-L1 CPS ≥10

	Pts w/ Event	Median PFS (95% CI), mo
Pembro + chemo	68.1%	8.1 (6.8-8.5)
Placebo + chemo	77.2%	5.6 (5.4-6.7)

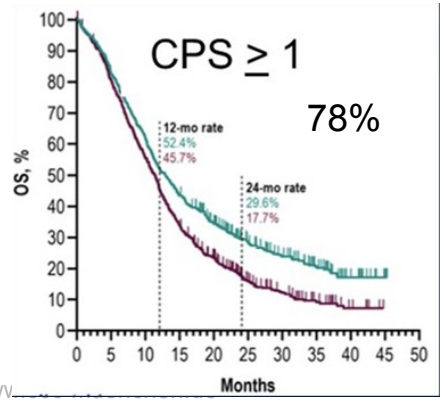


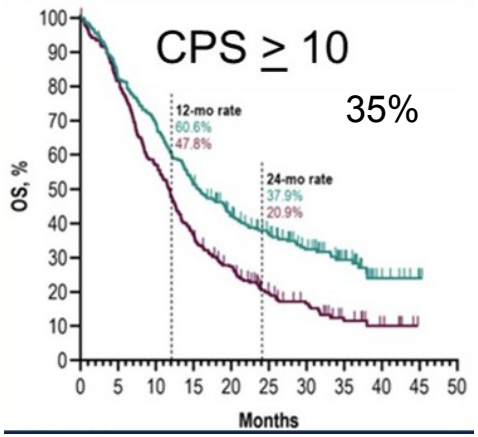
	Pembro + Chemo	Placebo + Chemo
ORR, % (95% CI)	60.6% (54.6-66.3)	43.0% (37.1-49.1)
Δ (95% CI)	17.5 (9.3-23.5); P = 0.00002	
mDOR (range)	10.9 mo (1.2+ - 41.5+)	5.8 mo (1.4+ - 31.2+)

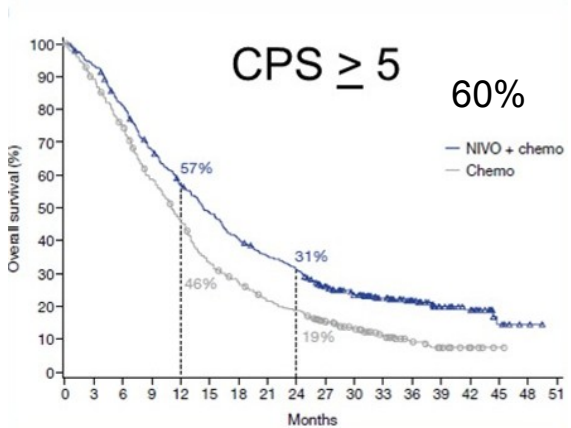
Sun Young Rha, et al. Journal of Clinical Oncology 2023 41:16_suppl, 4014-4014

KEYNOTE-859 vs CM 649

	Keynote 859	Checkmate 649
	n=1579 double-blind, pembrolizumab vs. placebo + chemo	n= 1581 open-label, nivolumab vs. placebo + chemo
Inclusion criteria	▪ Known PD-L1-status (centrally determined IHC 22C3)	▪ Regardless PD-L1-status (Dako IHC 28-8 pharm Dx assay)
Endpoints	Primary: OS Secondary: PFS/ ORR both in CPS ≥ 10 and CPS ≥ 1	Dual primary: OS and PFS in CPS ≥ 5
Results Overall survival	All pts: HR 0.78 (95% CI 0.70-0.87), *P* < 0.0001	All pts: HR 0.80 (99.3% CI 0.68-0.94) P = 0.0002 Janjigian, Y, Lancet, 2021; Rha, SY Ann Oncol 2023; 34:319

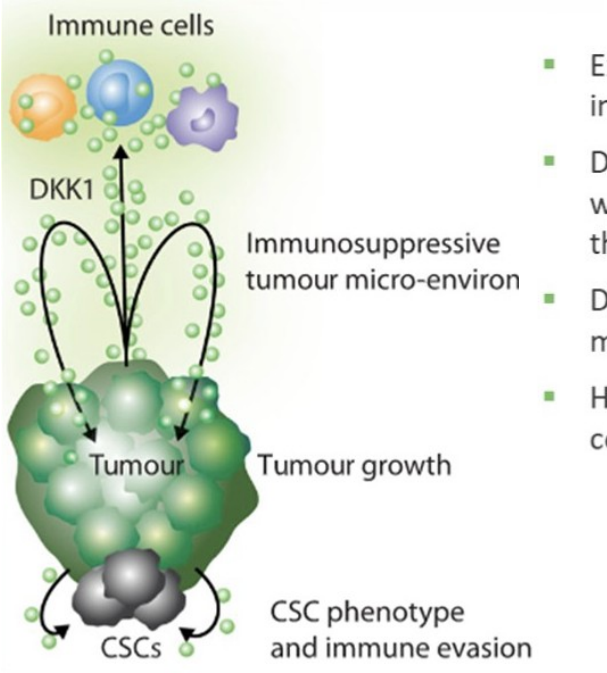






A phase 2 study (DisTinGuish) of DKN-01 in combination with tislelizumab + chemotherapy as first-line (1L) therapy in patients with advanced gastric or GEJ adenocarcinoma (GEA).

Einarmige Phase IIa Studie: 1st Linie DKN-01 300mg + Tislelizumab + CAPOX (n=25)

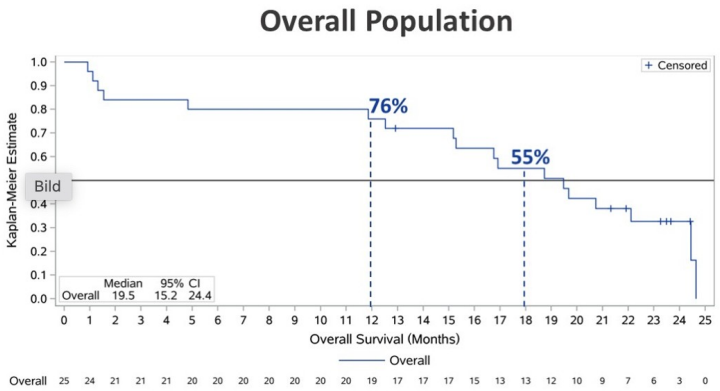


- Expression of DKK1 is associated with poor survival and resistance to chemotherapy in multiple tumor types.[6,7]
- DKN-01 is an anti-DKK1 mAb which has demonstrated anti-tumor activity in patients with advanced GEA with low tumor PD-L1 expression,[8] a subset with very limited therapeutic options.
- DKN-01 has immunomodulatory activity, stimulates a pro-inflammatory tumor microenvironment and upregulates PD-L1 levels. [9,10]
- Here we present 2-year survival data for 1L advanced GEA patients who received combination treatment with DKN-01 plus tislelizumab and CAPOX.

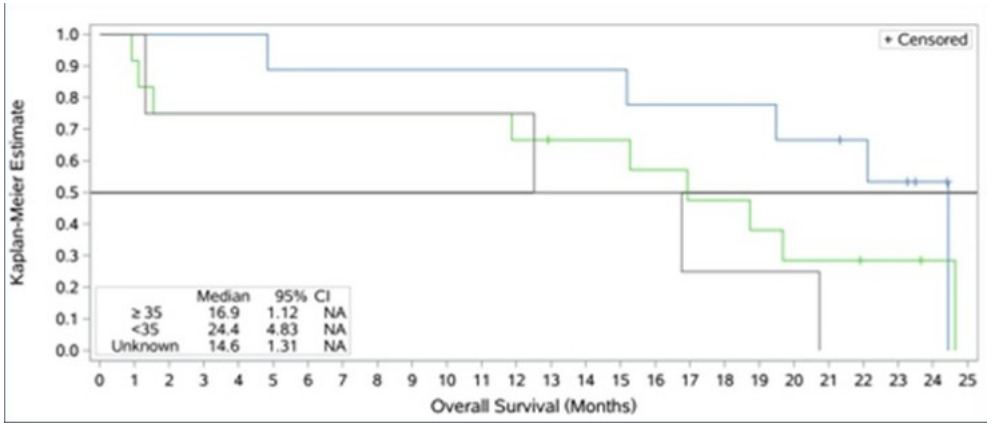
Samuel J Klempner, et al.

DisTinGuish: DKN-01 in combination with tislelizumab + chemotherapy as first-line (1L) therapy in patients with advanced gastric or GEJ adenocarcinoma (GEA).

OS (ITT n=25)



Nach DKK-1 Expression

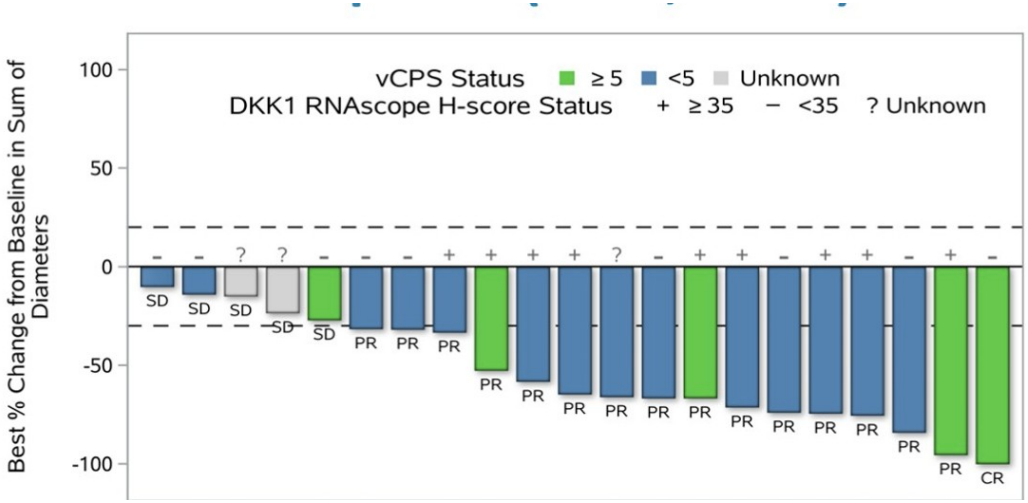


	Progression-free Survival (months)	Overall Survival (months)
	median (95% CI)	median (95% CI)
Overall (n=25)	11.3 (5.75, 12.0)	19.5 (15.2, 24.4)
vCPS < 5 (n=16)	10.7 (5.39, NA)	18.7 (11.9, NA)
vCPS ≥ 5 (n=6)	11.6 (1.12, NA)	22.0 (1.12, NA)

Samuel J Klempner, et al. J Clin Oncol 41, 2023 (suppl 16; abstr 4027)

DisTinGuish: DKN-01 in combination with tislelizumab + chemotherapy as first-line (1L) therapy in patients with advanced gastric or GEJ adenocarcinoma (GEA).

Response (mITT, n=25)



Fazit: mit 2 Jahren Follow-up: vielversprechendes OS mit DKN-01 in der ITT (19.5mos) und in PD-L1 low Gruppe (18.4mos)
anhaltendes Ansprechen in der mITT (73%) und bei PD-L1 low (10.7mos)
Random. Phase II mit DKN-1 +/- Tislelizumab und CTX rekrutiert (NCT04363801)

Samuel J Klempner, et al. J Clin Oncol 41, 2023 (suppl 16; abstr 4027)

Zusammenfassung

- **ATTRACTION-5: Keine Verbesserung im RFS/OS durch die Hinzunahme von Nivolumab zu CTX adjuvant nach D2 Resektion.** Vorteil bei Subgruppe der TPS+; Outcome nach CPS und bei MSI high abzuwarten- keine Relevanz für Europa!

- **Perioperative Therapie mit FLOT Standard! IO Therapie vielversprechend- Phase II Toripalimab Studie konfirmatorisch! DANTE Trial:** ca. 10% Verbesserung der pCR Rate mit FLOT + Atezolizumab (24% vs. 15%)- Abwarten von **Matterhorn** und **Keynote-585** Studienergebnissen

- **Wird KEYNOTE- 859 den Standard verändern** und IO Therapie zukünftig für mehr Patienten (CPS ≥ 1) verfügbar sein? CPS ≥ 1 und <10 (48%): HR nicht berichtet

Viele offene Fragen: beste backbone Chemotherapie? Lokalisation des Primarius? Verwendeter Assay/AK bei der PD-L1 Testung?

- **DisTinGuish: Erste vielversprechende Wirksamkeits und Feasibility Daten** mit DKN-01 + Tislelizumab + CTX – auch unabhängig von der PD-L1 Expression- ABER: n=21!- weitere Daten abwarten

DANKE FÜR IHRE AUFMERKSAMKEIT!