TUMORZENTRUM MÜNCHEN | TZM

CCC MÜNCHEN COMPREHENSIVE CANCER CENTER

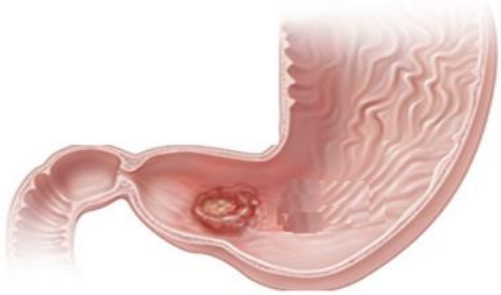
DGHO DEUTSCHE GESELLSCHAFT FÜR HÄMATOLOGIE UND MEDIZINISCHE ONKOLOGIE
ÖGHO SSMO SSOM SGMO SGKSSH

JAHRESTAGUNG
Jahrestagung der Deutschen, Österreichischen und Schweizerischen Gesellschaften für Hämatologie und Medizinische Onkologie
www.jahrestagung-haematologie-onkologie.com

2023 13.–16. Okt. Hamburg

Biomarker basierte Zweitlinientherapie des Magenkarzinoms

16.Oktober 2023



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

Offenlegung potentieller Interessenkonflikte

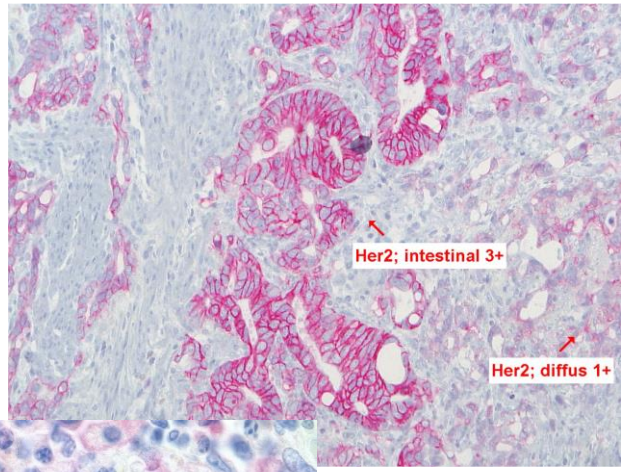
- Anstellungsverhältnis oder Führungsposition
  keine
- Beratungstätigkeit
  Eli Lilly, Roche, Servier, Merck-Serono, Sanofi-Aventis
- Aktienbesitz
  keine
- Honorare
  Eli Lilly, Roche, Amgen, Riemser, Servier
- Finanzierung wissenschaftlicher Untersuchungen
  StudienTeilfinanzierung durch Eli Lilly.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

Magenkarzinom (incl. AEG)

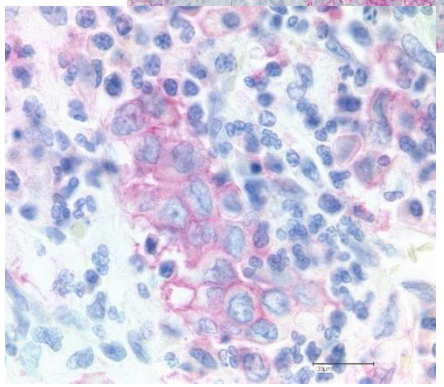
Biomarker:

- **Her2/neu**
- **PDL-1: CPS**
  Grenzwert?
- **MSI**
- ***Claudin 18.2***

FGFR2b?



HER2/neu



PDL-1

Aktualisierte ESMO-Leitlinien erweitern Empfehlungen für Biomarker-Tests bei Speiseröhrenkrebs

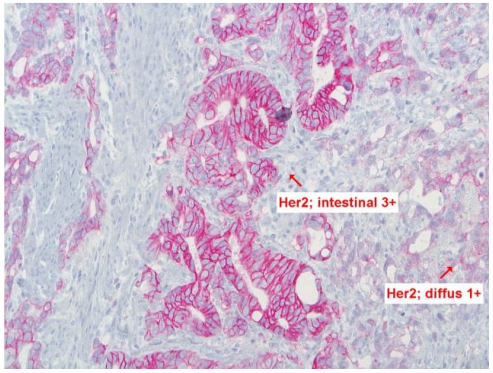
Previous ESMO Guidelines (2016)[1]

Marker	Method	Use
HER2	IHC for HER2 protein expression or ISH for *HER2* gene amplification	Select patients with metastatic disease for treatment with a trastuzumab-containing regimen

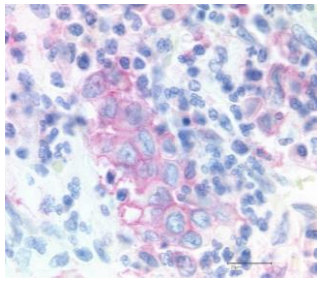
Updated ESMO Guidelines (2022)[2,3]

Marker	Method	Use	OAC	OSCC
HER2	IHC for *HER2* protein expression or ISH for *HER2* gene amplification	Select patients with metastatic disease for treatment with a trastuzumab-containing regimen	✓	✘
PD-L1	IHC for PD-L1 protein expression	Patients who are candidates for first-line treatment with a PD-1 inhibitor–containing regimen	✓ CPS	✓ CPS TPS
MSI-H/ dMMR	Not specified	Patients with locally advanced and unresectable or metastatic disease	✓	✘

HER2/neu



PDL-1



- Diagnosis should be made from multiple (5-8) endoscopic biopsies to guarantee an adequate representation of the tumour [IV, B].
- The histological diagnosis should be reported according to WHO criteria [V, B].
- HER2 expression by IHC and/or amplification by *in situ* hybridisation [I, A; ESCAT score: I-A], PD-L1 by IHC according to CPS [I, A] and MSI-H/dMMR [II, A; ESCAT score: I-B] are validated predictive biomarkers for drug therapy.

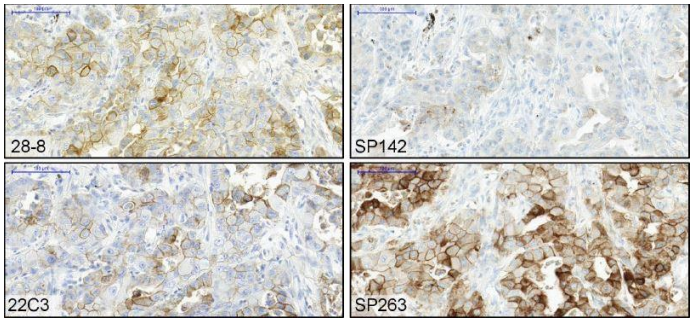
dMMR, mismatch repair deficient; ISH, in situ hybridisation.

1. Lordick F, et al. *Ann Oncol*. 2016;27(suppl 5):v50-v57; 2. Obermannová R, et al. *Ann Oncol*. Published online 29 July 2022;
2. 3. Lordick F, et al. *Ann Oncol*. Published online 29 July 2022.

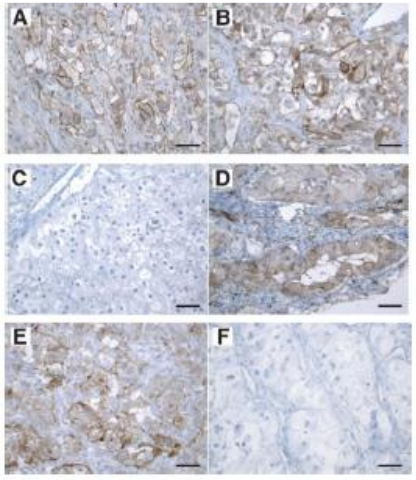
PD-L1 Expression: Kontroversen und Herausforderungen

PD- L1
Unterschiedliche Auswertescores

Score	Name	Definition	Kategorien
TPS	Tumor Proportion Score	Verhältnis PD-L1 positiver Tumorzellen zu Gesamttumorzellen	
CPS	Combined Positive Score	(Verhältnis PD-L1 positiver Tumor- **und** Immunzellen zu Gesamttumorzellen) * 100	Maximalwert 100
IC	Immune Cells	Anteil PD-L1 positiver Immunzellen zur Tumorfläche (IC 0 – 3)	IC 0: 0 -1 % IC 1: ≥ 1 % – <5 % IC 2: 5 % – < 10 % IC 3: ≥ 10 %

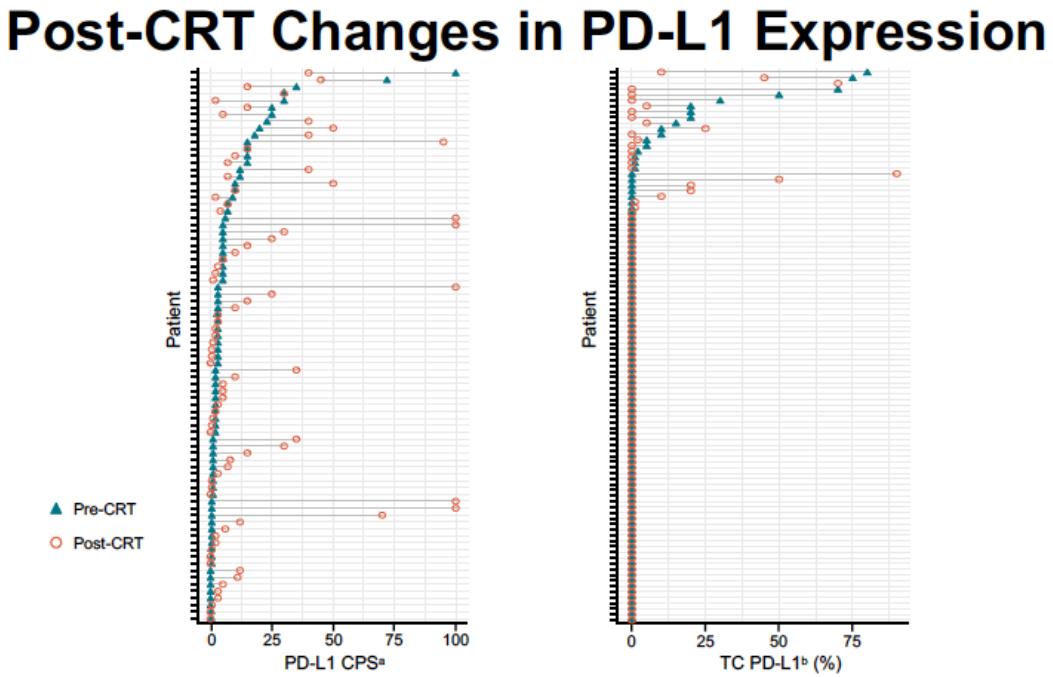


PD-L1
Unterschied: Primär-tumor/Metastase



PDL-1
Unterschiedliche Antikörper….

Idealer CPS-Bestimmungszeitpunkt?

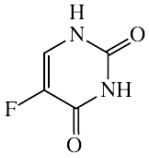
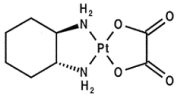
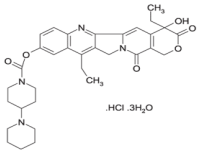
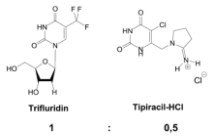
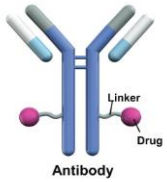
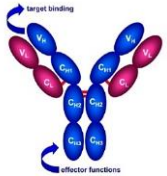


→ CPS Zunahme bei 50%!

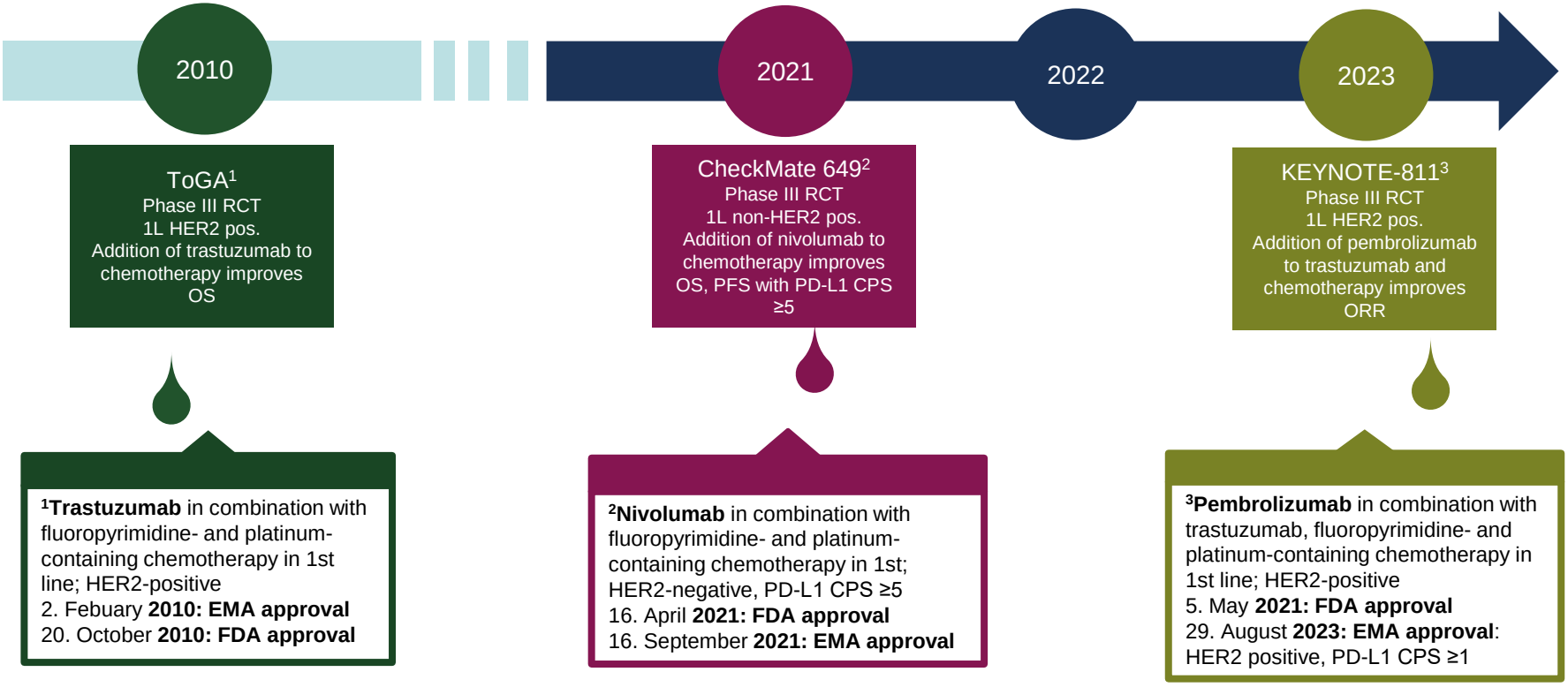
→ PD-L1 Expressionsänderungen vorrangig in Immunzellen (Lymphozyten, Makrophagen)

Kelly et al ESMO GI 2023

Metastasiertes Magen Ca/AEG – EMA zugelassene Substanzen 2023

5-Fluorouracil & Derivate	Oxaliplatin	Irinotecan	FTD/TPI 102	T-DXd Trastuzumab Deruxtecan (seit 12/2022)	Trastuzumab Ramucirumab Pembrolizumab Nivolumab
					

Zulassung zielgerichteter Therapien in der Erstlinie



[1]Bang et al., *Lancet*. 2010, [2]Janjigian et al., *Lancet.* 2021, [3]Janjigian et al., *Nature.* 2021

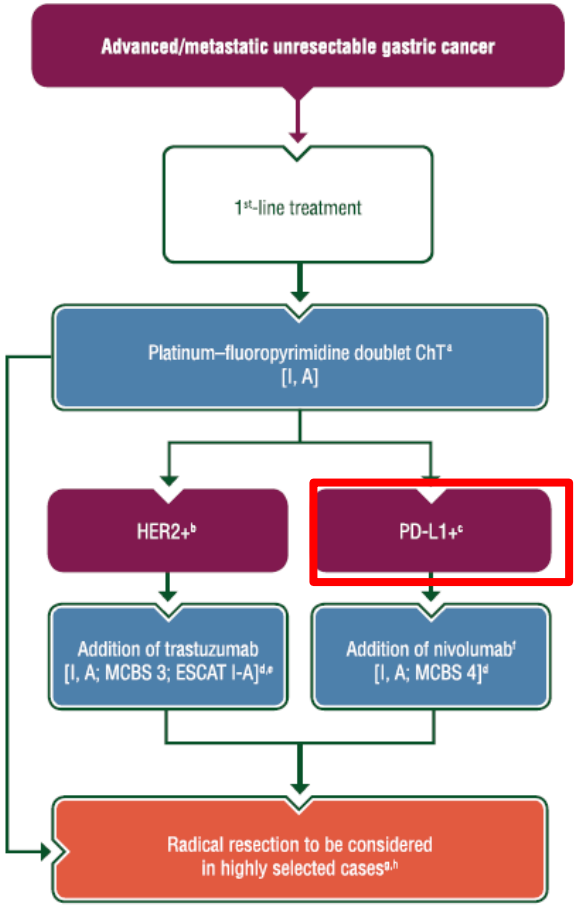
ESMO GUIDELINES 2022: 1ST-LINE – HER2 NEGATIV

October 13, 2023 7:45 am ET

Opinion granted based on positive overall survival results from the Phase 3 KEYNOTE-859 trial

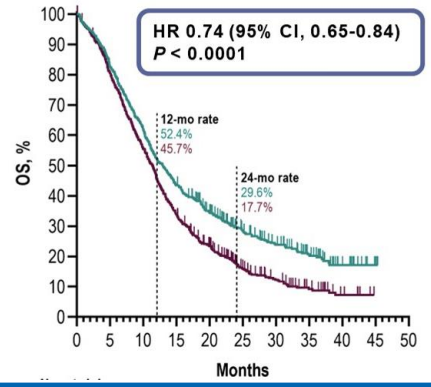
If approved, a KEYTRUDA combination would become an option in the EU for the treatment of both HER2-negative and HER2-positive advanced gastric or GEJ adenocarcinoma in tumors expressing PD-L1 (CPS ≥1)

RAHWAY, N.J.--(BUSINESS WIRE)-- Merck (NYSE: MRK), known as MSD outside of the United States and Canada, today announced that the European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion recommending approval of KEYTRUDA, Merck's anti-PD-1 therapy, in combination with fluoropyrimidine- and platinum-containing chemotherapy, for the first-line treatment of locally advanced unresectable or metastatic HER2-negative gastric or gastroesophageal junction (GEJ) adenocarcinoma in adults whose tumors express PD-L1 (Combined Positive Score [CPS] ≥1).

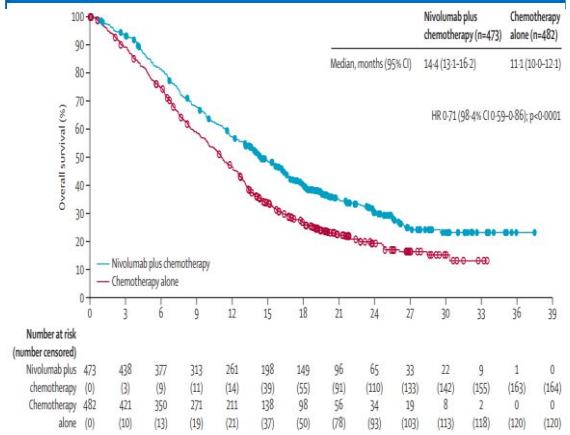


Lordick et al Ann Oncol 2022

KN 859, PD-L1 CPS ≥ 1

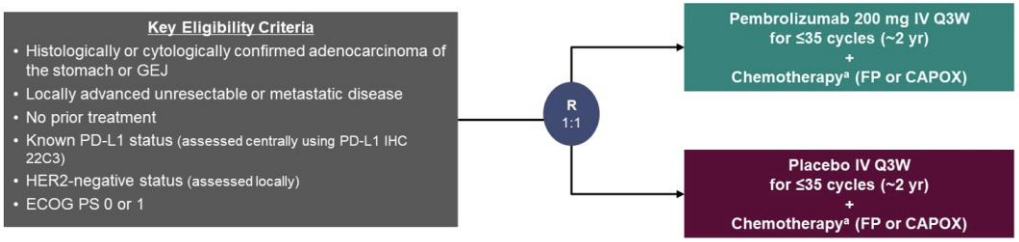


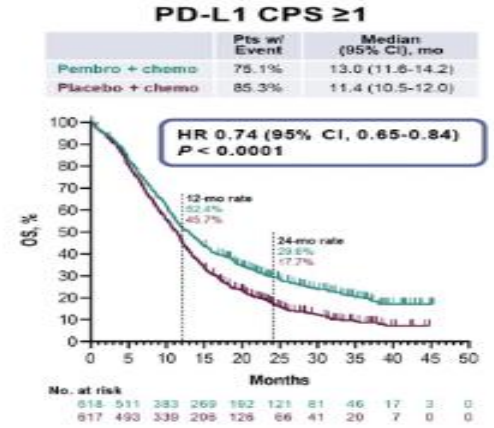
CHECKMATE-649, PD-L1 CPS ≥ 5



Janjigian Y, et al. Lancet. 2021 Jul 3;398(10294):27-40
Rha SY et al. Ann Oncol 2023; 34:319-320

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





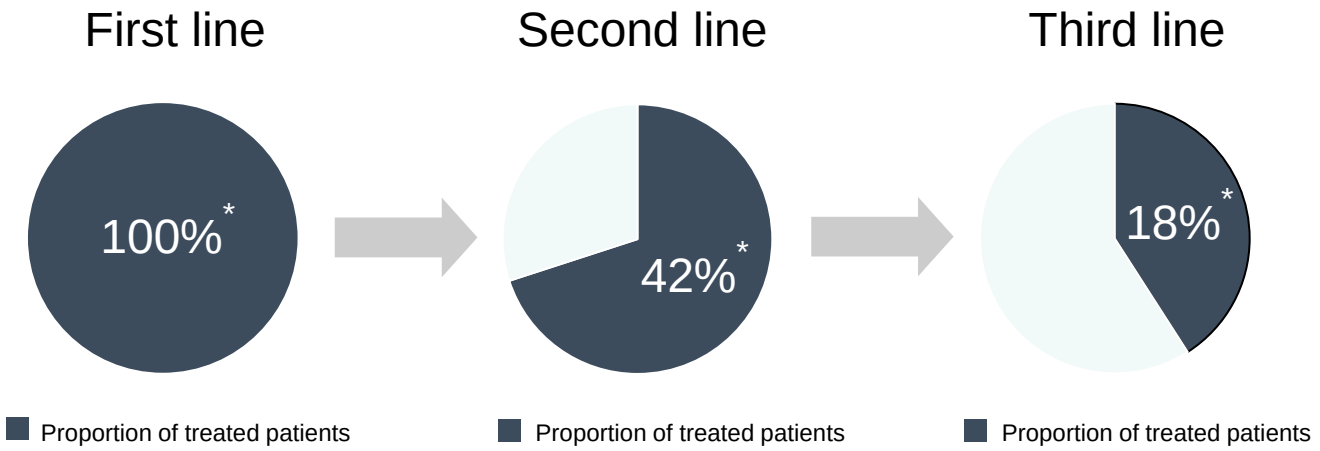
78% der Patienten mit gastroösophagealem Adeno Ca profitieren (CPS ≥ 1):
Medianes OS: 12.9 vs 11.5 Monate (HR 0.78)
Medianes PFS: 6.9 vs 5.6 Monate (HR 0.72)
ORR: 52.1% vs 42.6% (p=0.0004)
DOR: 8.3 vs 5.6 Monate

Merck Receives Positive EU CHMP Opinion for KEYTRUDA® (pembrolizumab) Plus Chemotherapy as First-Line Treatment for HER2-Negative Advanced Gastric or Gastroesophageal Junction (GEJ) Adenocarcinoma Expressing PD-L1 (CPS ≥1)

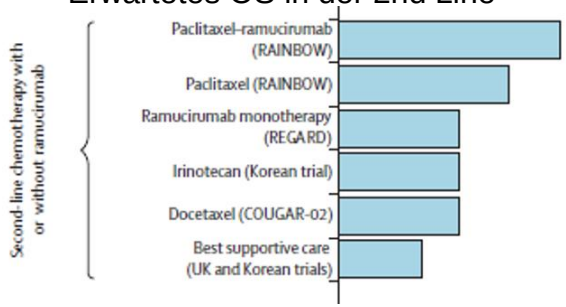
Zweitlinientherapie Her-2 negatives Magen Ca

Was tun bei Progress? Rezidiv?

Folgetherapien beim metastasierten Magen Ca (2004–2012 US)



Erwartetes OS in der 2nd Line



40-50% der Patienten sind in der Lage, eine Zweitlinienbehandlung zu erhalten[2]

2L Behandlung verlängert das Überleben[1]

*N=1982 patients with gastric cancer and EMR data who received chemotherapy between January 2004 and January 2012 in oncology practices subscribing to the US-wide IMS Health Oncology Database.

EMR, electronic medical record; mGC, metastatic gastric cancer.

Hess LM, et al. Gastric Cancer. 2016;19:607–15.

Smyth E. et al. Lancet 2020;398:635–48.

SAPHIR Registerplattformstudie

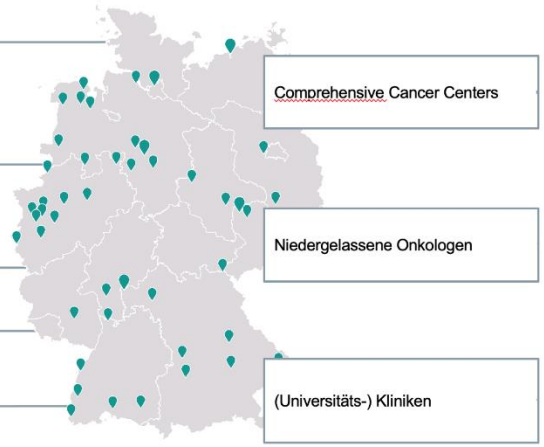
Metastasiertes Ösophagus- oder Magenkarzinom oder Karzinom des gastroösophagealen Übergangs

900 Patient*innen
- 250 ESCC
- 150 EAC
- 250 AEG
- 250 GAC

Prospektive Dokumentation

Bis zu 150 Zentren deutschlandweit

Projektdauer:
3 Jahre Rekrutierung +
2 Jahre Nachbeobachtung



Comprehensive Cancer Centers

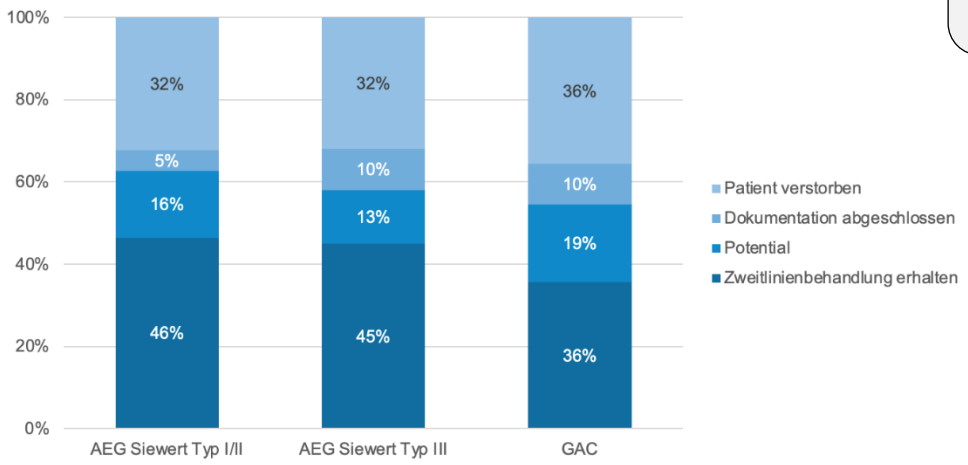
Niedergelassene Onkologen

(Universitäts-) Kliniken

Patientencharakteristika

	AEG Siewert Typ I/II	AEG Siewert Typ III	GAC
Patient*innen (N)	**142**	**66**	**234**
Geschlecht			
Männlich n (%)	127 (89.4%)	55 (83.3%)	137 (58.5%)
Alter bei Diagnose (Jahre)			
Median (25-75% Quantile)	65.8 (59.9 - 72.8)	64.4 (58.5 - 72.9)	67.0 (57.9 - 75.3)
Mind. 1 Begleiterkrankung bei Therapiestart			
Ja n (%)	119 (83.8%)	51 (77.3%)	193 (82.5%)
Charlson Comorbidity Index bei Therapiestart			
CCI 0	92 (64.8%)	52 (78.8%)	175 (74.8%)
Metastasierung bei Erstdiagnose			
M1 n (%)	105 (73.9%)	57 (86.4%)	163 (69.7%)
ECOG Performance Status bei Therapiestart			
0 n (%)	40 (28.2%)	18 (27.3%)	58 (24.8%)
1 n (%)	64 (45.1%)	22 (33.3%)	117 (50.0%)

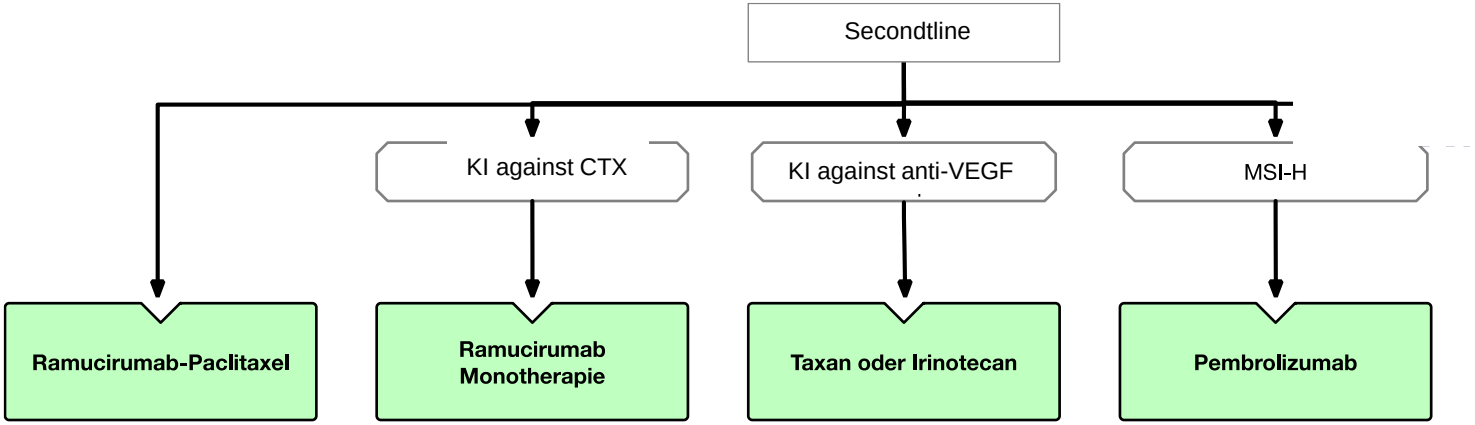
Anzahl Patienten mit einer Zweitlinientherapie



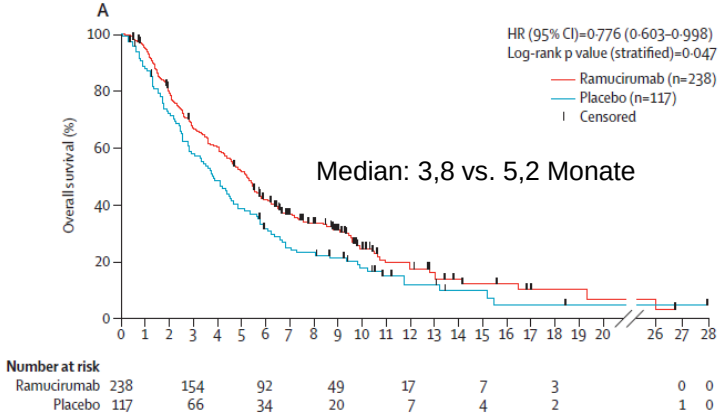
Ca. 1/3 der Patienten sind vor Beginn einer Zweitlinientherapie bereits verstorben.

Lorenzen et al DGHO 2022

Zweitlinientherapie Magen Ca

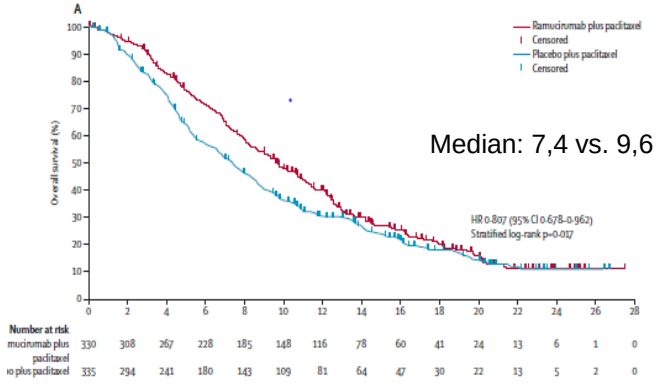


Ramucirumab versus BSC



Charles S. Fuchs et al. Lancet 2014;383(9911):31-39.

Paclitaxel + /- Ramucirumab



Hansjochen Wilke et al. Lancet Oncol. 2014; 15(11): 1224-35.

NCCN 2nd Line Behandlungsempfehlungen update 2023

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2023
Gastric Cancer

NCCN Guidelines Index
Table of Contents
Discussion

PRINCIPLES OF SYSTEMIC THERAPY

Systemic Therapy for Unresectable Locally Advanced, Recurrent or Metastatic Disease (where local therapy is not indicated)

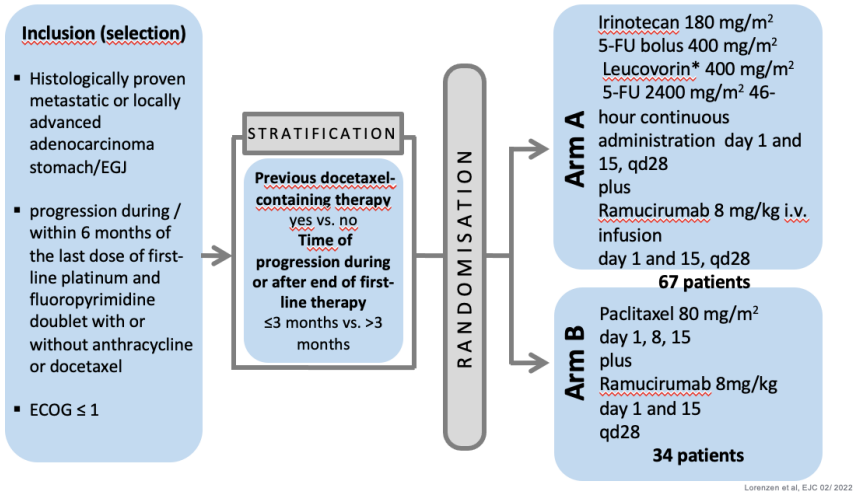
Second-Line or Subsequent Therapy
- Dependent on prior therapy and PS

Preferred Regimens
- Ramucirumab and paclitaxel (category 1)[43]
- Fam-trastuzumab deruxtecan-nxki for HER2 overexpression positive adenocarcinoma[44]
- Docetaxel (category 1)[37,38]
- Paclitaxel (category 1)[33,34,45]
- Irinotecan (category 1)[45-48]
- Fluorouracil[a,i] and irinotecan[46,49,50]
- Trifluridine and tipiracil for third-line or subsequent therapy (category 1)[51]

Other Recommended Regimens
- Ramucirumab (category 1)[52]
- Irinotecan and cisplatin[20,53]
- Fluorouracil and irinotecan + ramucirumab[a,i,54]
- Irinotecan and ramucirumab[55]
- Docetaxel and irinotecan (category 2B)[56]

Useful in Certain Circumstances
- Entrectinib or larotrectinib for *NTRK* gene fusion-positive tumors[57,58]
- Pembrolizumab[g,h] for MSI-H/dMMR tumors[59-61]
- Nivolumab and ipilimumab[g,h,18] for MSI-H/dMMR tumors
- Pembrolizumab[g,h] for TMB high (≥10 mutations/megabase) tumors[62]
- Dostarlimab-gxly[g,h,k] for MSI-H/dMMR tumors[28]
- Dabrafenib and trametinib for *BRAF* V600E mutated tumors[63]
- Selpercatinib for *RET* gene fusion-positive tumors[64]

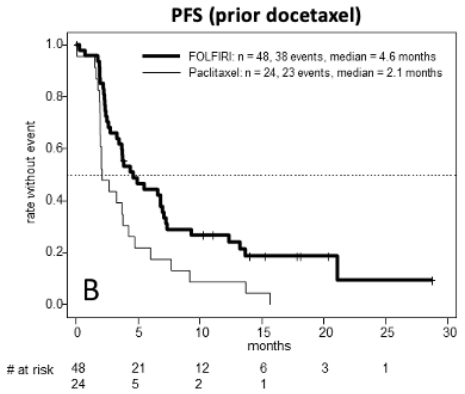
RAMIRIS Phase II



Original Research

FOLFIRI plus ramucirumab versus paclitaxel plus ramucirumab as second-line therapy for patients with advanced or metastatic gastroesophageal adenocarcinoma with or without prior docetaxel – results from the phase II RAMIRIS Study of the German Gastric Cancer Study Group at AIO

Sylvie Lorenzen [a,*], Peter Thuss-Patience [b], Claudia Pauligk [c], Eray Gökkurt [d], Thomas Ettrich [e], Florian Lordick [f], Michael Stahl [g], Peter Reichardt [h], Martin Sökler [i], Daniel Pink [j,k], Stefan Probst [l], Axel Hinke [m], Thorsten O. Goetze [c,n,1], Salah E. Al-Batran [c,n,1]



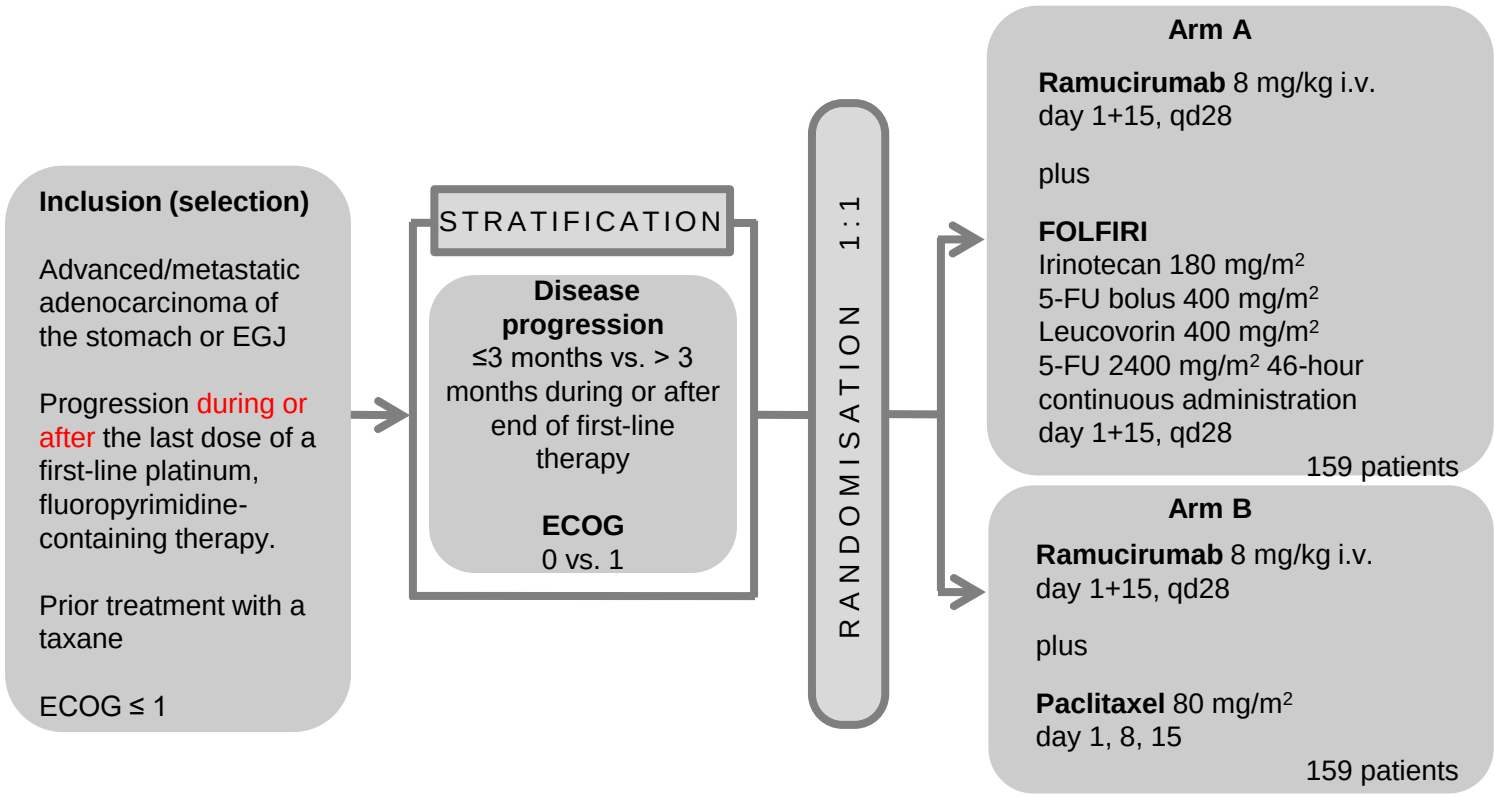
Tab. 1 ***Progression-free survival (total population), Kaplan-Meier estimation***

Type	Arm A	Arm B
n	72	38
PFS events	58	34
Median PFS (months)	4.4	3.6
95% confidence interval	3.3 – 6.8	2.1 – 5.5
PFS rate at 6 months	40%	25%
95% confidence interval	30 – 54%	14 – 44%
p (logrank, 2sided)	0.12	
Hazard ratio (arm B as standard)	0.72	
95% confidence interval	0.47 – 1.10	

Lorenzen S et. al. European Journal of Cancer 2022; 165: 48-57

IKF RAMIRIS

RAMIRIS: Phase III Trial- Design



Aktueller Rekrutierungsstatus 10/23: 238/318

Ändert sich der Therapiestandard durch IO Therapie in der Erstlinientherapie?

Retrospektive Analyse aus Japan (Shitara et al.)

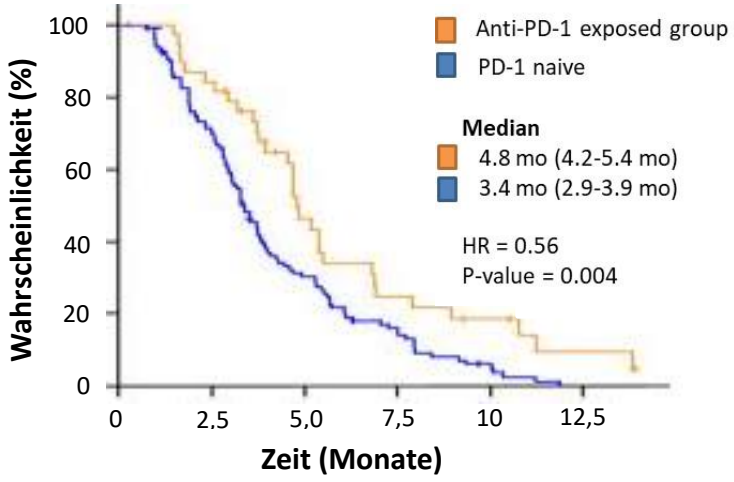
ESMO Open Cancer Horizons
Check for updates

Improved efficacy of taxanes and ramucirumab combination chemotherapy after exposure to anti-PD-1 therapy in advanced gastric cancer

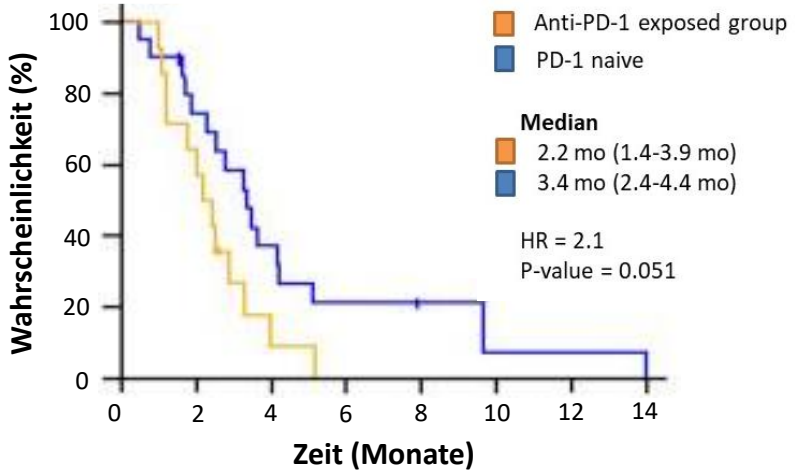
Akinori Sasaki,[1,2] Akihito Kawazoe,[1] Testuya Eto,[1] Mashiro Okunaka,[3] Saori Mishima ,[1] Kentaro Sawada,[1] Yoshiaki Nakamura,[1,4] Daisuke Kotani ,[1] Yasutoshi Kuboki,[1] Hiroya Taniguchi,[1] Takashi Kojima,[1] Toshihiko Doi,[1] Takayuki Yoshino ,[1] Tetsuo Akimoto,[2] Kohei Shitara [1]

Progression-free survival

Ramucirumab + Taxan



Taxan Monotherapie

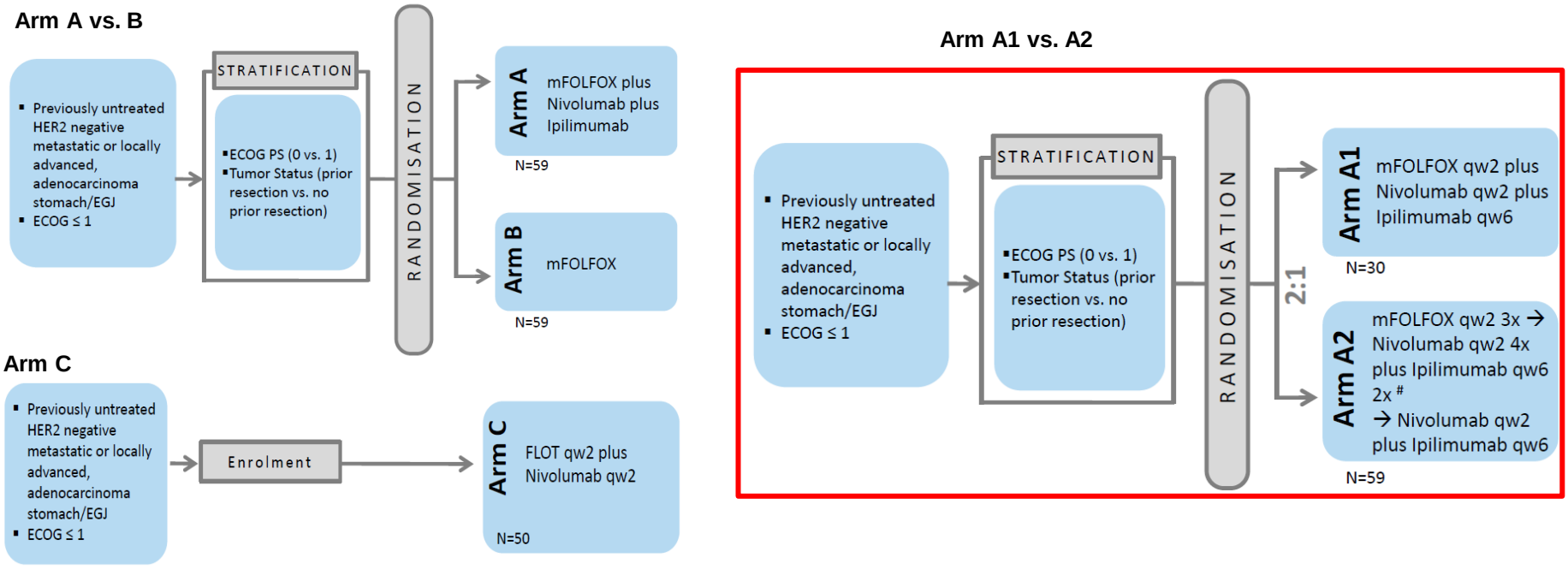


Ramucirumab plus Paclitaxel after Check-point Inhibition meaningful sequence!

Sasaki A, 2020. *ESMO Open*; 4: e000775

AIO-STO-0417 Studien Design

The AIO-STO-0417 trial (Moonlight) is a four-arm investigator-initiated phase II trial



Supported with a Grant from BMS

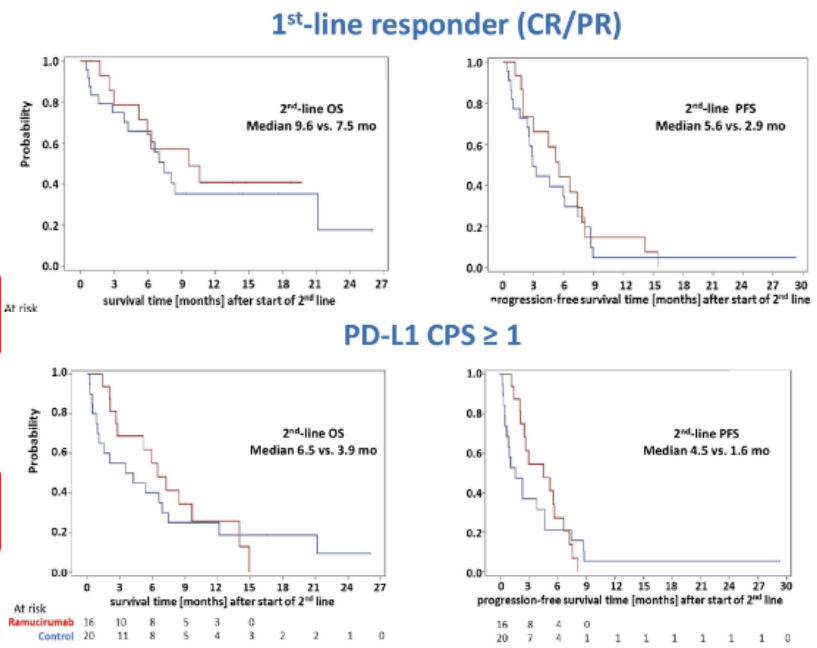
Rolle der Angiogeneseinhibition in der Zweitlinientherapie nach vorangegangener IO Therapie?

Sylvie Lorenzen, et al. Journal of Clinical Oncology 2023 #4045

Sekundäranalyse der prospektiven AIO-STO-0417 (Moonlight) für Patienten mit nachfolgender 2nd line Therapie aus Ramucirumab plus Chemotherapie

	RAM group	Control group
Overall population	n=38	n=45
Median 2nd-line OS in months [95%CI]	6.5 [3.0,10.6]	6.6 [2.9,8.4]
Median 2nd-line PFS in months [95%CI]	4.5 [2.6,6.0]	2.9 [1.6,4.6]
ORR	16%	13%
DCR	40%	31%
1st-line responder (achieved CR or PR)	n=15	n=24
Median 2nd-line OS in months [95%CI]	9.6 [3.0,-]	7.5 [3.9,21.2]
Median 2nd-line PFS in months [95%CI]	5.6 [1.9,7.9]	2.9 [1.6,6.1]
ORR	20%	17%
DCR	53%	29%
PD-L1 CPS ≥ 1	n=16	n=20
Median 2nd-line OS in months [95%CI]	6.5 [2.7,9.6]	3.9 [0.9,7.5]
Median 2nd-line PFS in months [95%CI]	4.5 [2.1,6.6]	1.6 [0.5,4.6]
ORR	25%	10%
DCR	44%	30%

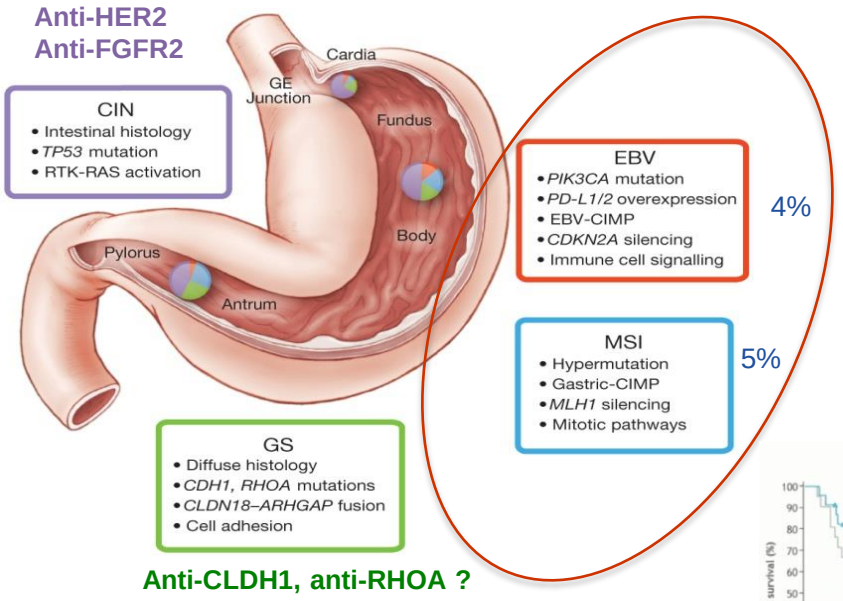
Abbreviations: OS, overall survival; PFS, progression-free survival; 95% CI, 95% confidence interval; ORR, overall response rate; DCR, disease control rate; CR/PR, complete/partial response; CPS, combined positive score.

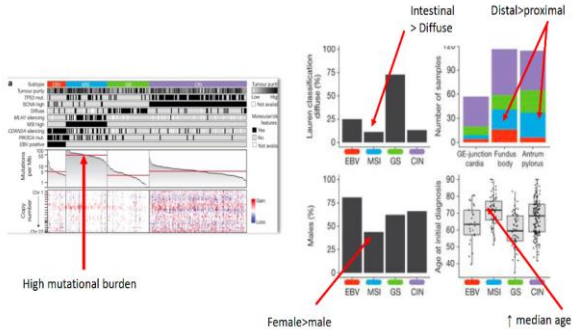


Ramucirumab ist wirksam als Zweitlinientherapie nach Progress unter 1st Linie FOLFOX plus duale Checkpoint Inhibition, besonders bei Patienten die ansprechen und mit positiver PD-L1 Expression.

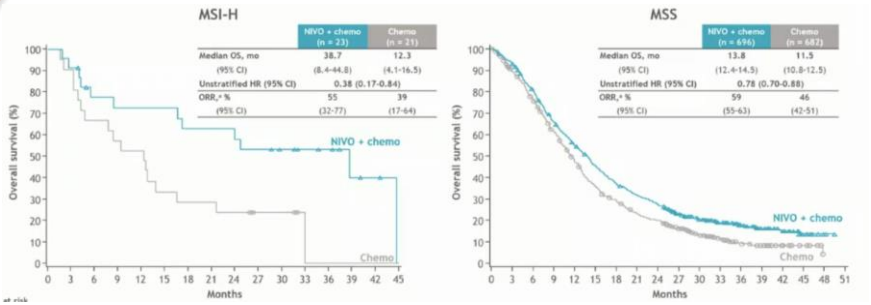
Zweitlinientherapie MSI-high Magen Ca

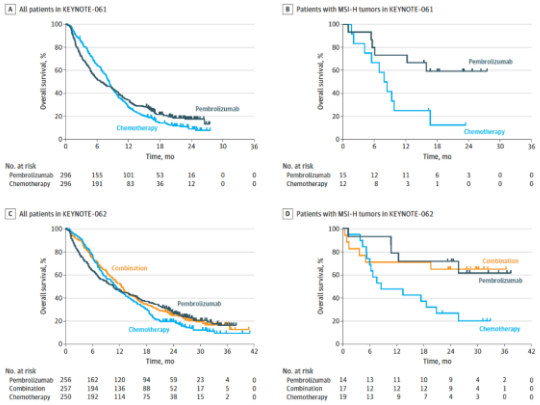
Magenkarzinom: MSI Subgruppe





Nivo + Chemo





Der MSI-H Status sollte standardmäßig beim fortgeschrittenen gastroösophagealen Adenokarzinom erhoben werden. Wirksamkeit der IO Therapie unabhängig von der Therapielinie!

The Cancer Genome Atlas Research Network; Bass et al Nature 2014
Smyth. Lancet 2020; 398: 635-8
Chao J et al. Jama Oncol 2021; 7(6): 895-902

MSI-H Agnostische Zulassung

Pembrolizumab in MSI-H Tumoren

- Kolorektalkarzinom (nach FU basierter Therapie)
- Dünndarmkarzinom (nach Therapie)
- **Magenkarzinom (nach Therapie)**
- Biliäre Tumore (nach Therapie)
- *Endometriumkarzinom*

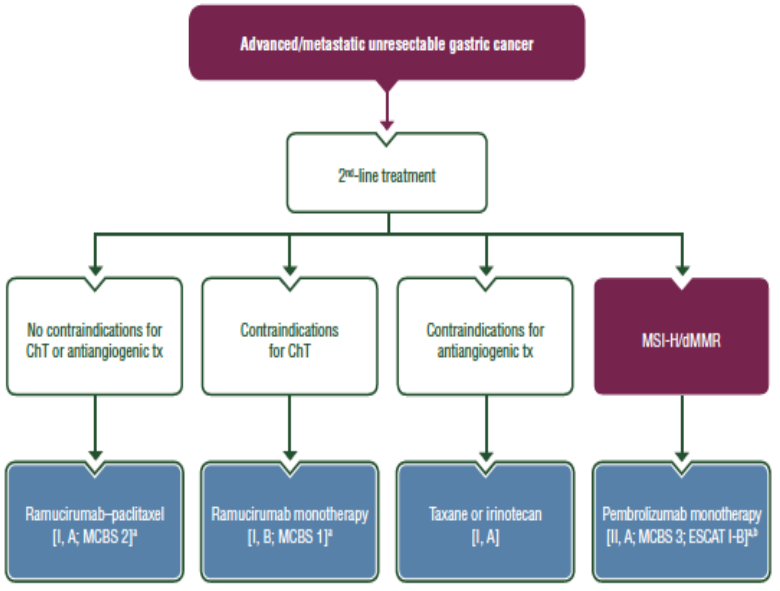
TABLE 3. Antitumor Activity for Tumor Types With Greatest Enrollment

Tumor Type	No.	CR, No.	PR, No.	ORR, % (95% CI)	Median PFS, Months (95% CI)	Median OS, Months (95% CI)	Median DOR, Months (range)
Endometrial	49	8	20	57.1 (42.2 to 71.2)	25.7 (4.9 to NR)	NR (27.2 to NR)	NR (2.9 to 27.0+)
Gastric	24	4	7	45.8 (25.6 to 67.2)	11.0 (2.1 to NR)	NR (7.2 to NR)	NR (6.3 to 28.4+)
Cholangiocarcinoma	22	2	7	40.9 (20.7 to 63.6)	4.2 (2.1 to NR)	24.3 (6.5 to NR)	NR (4.1+ to 24.9+)
Pancreatic	22	1	3	18.2 (5.2 to 40.3)	2.1 (1.9 to 3.4)	4.0 (2.1 to 9.8)	13.4 (8.1 to 16.0+)
Small intestine	19	3	5	42.1 (20.3 to 66.5)	9.2 (2.3 to NR)	NR (10.6 to NR)	NR (4.3+ to 31.3+)
Ovarian	15	3	2	33.3 (11.8 to 61.6)	2.3 (1.9 to 6.2)	NR (3.8 to NR)	NR (4.2 to 20.7+)
Brain	13	0	0	0.0 (0.0 to 24.7)	1.1 (0.7 to 2.1)	5.6 (1.5 to 16.2)	–

NOTE. Efficacy analyses included all patients who received at least one dose of pembrolizumab. Only confirmed responses are included. Response was assessed per RECIST version 1.1 by independent central radiologic review.

Abbreviations: +, no progressive disease by the time of last disease assessment; CR, complete response; DOR, duration of response; NR, not reached; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PR, partial response.

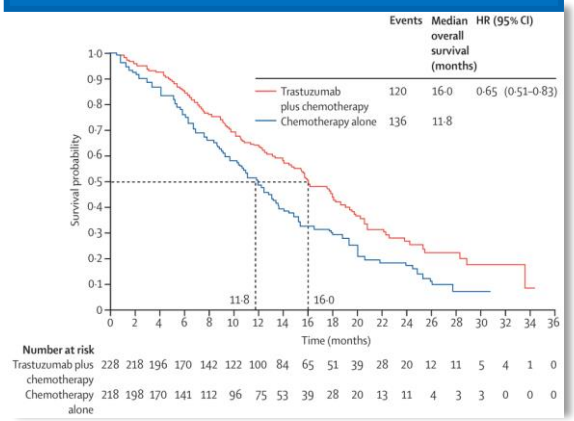
Marabelle et al, J Clin Oncol. 2020 Jan 1;38(1):1-10

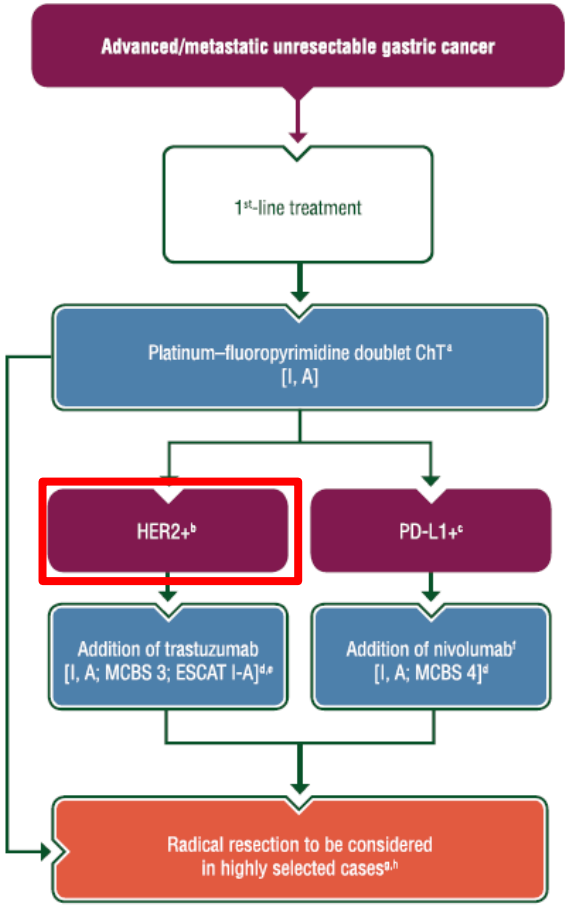


Lordick F , et al. Ann Oncol. 2022;

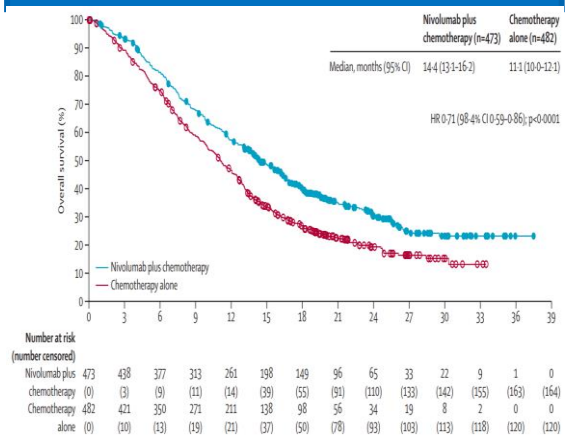
ESMO GUIDELINES 2022: 1ST-LINE – HER2 POSITIV

TOGA, Trastuzumab+Chemo, HER2-positiv





CHECKMATE-649, PD-L1 CPS ≥ 5



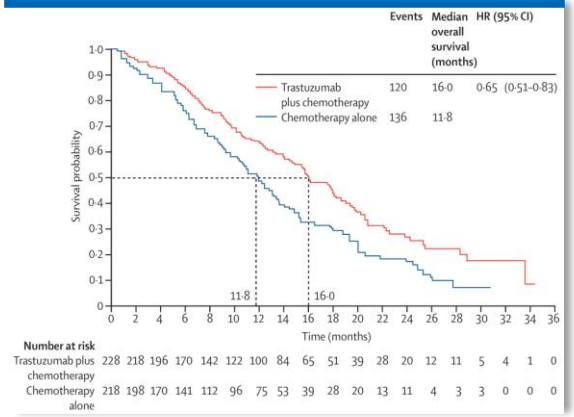
Lordick F, et al. *Ann Oncol* 2022

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

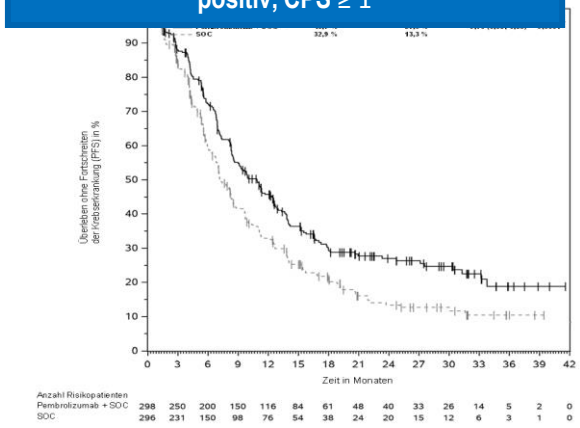
Lordick et al Ann Oncol 2022

METASTASIERTES MAGENKARZINOM 1ST-LINE – ESMO GUIDELINES 2022

TOGA, Trastuzumab+Chemo, HER2-positiv



KN811, Trastuzumab+Pembro + Chemo, HER2-positiv, CPS ≥ 1



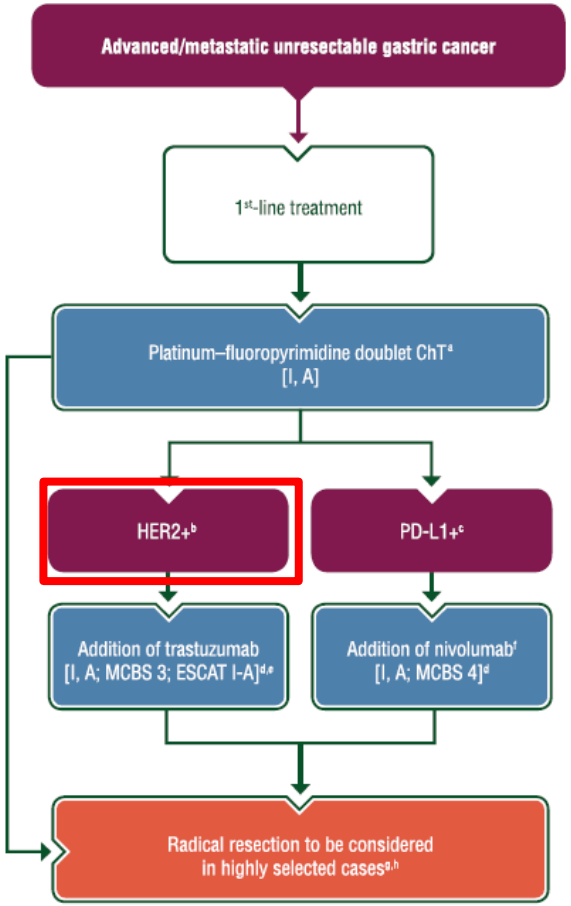
August 29, 2023 6:50 am ET

Approval based on progression-free survival benefit demonstrated in Phase 3 KEYNOTE-811 trial

KEYTRUDA is the first immunotherapy approved in the EU for the first-line treatment of this patient population

RAHWAY, N.J.--(BUSINESS WIRE)-- Merck (NYSE: MRK), known as MSD outside of the United States and Canada, today announced that the European Commission (EC) has approved KEYTRUDA, Merck's anti-PD-1 therapy, in combination with trastuzumab, fluoropyrimidine- and platinum-containing chemotherapy, for the first-line treatment of locally advanced unresectable or metastatic human epidermal growth factor receptor 2 (HER2)-positive gastric or gastroesophageal junction (GEJ) adenocarcinoma in adults whose tumors express PD-L1 (Combined Positive Score [CPS] ≥1).

This approval by the EC follows the positive recommendation from the Committee for Medicinal Products for Human Use received in July 2023 and was based on results from the Phase 3 KEYNOTE-811 trial. In the study, KEYTRUDA plus trastuzumab and chemotherapy significantly improved progression-free survival (PFS), and objective response rate (ORR), compared to trastuzumab and chemotherapy alone in this patient population. In the study, more than 80% of patients had tumors that were PD-L1 positive.

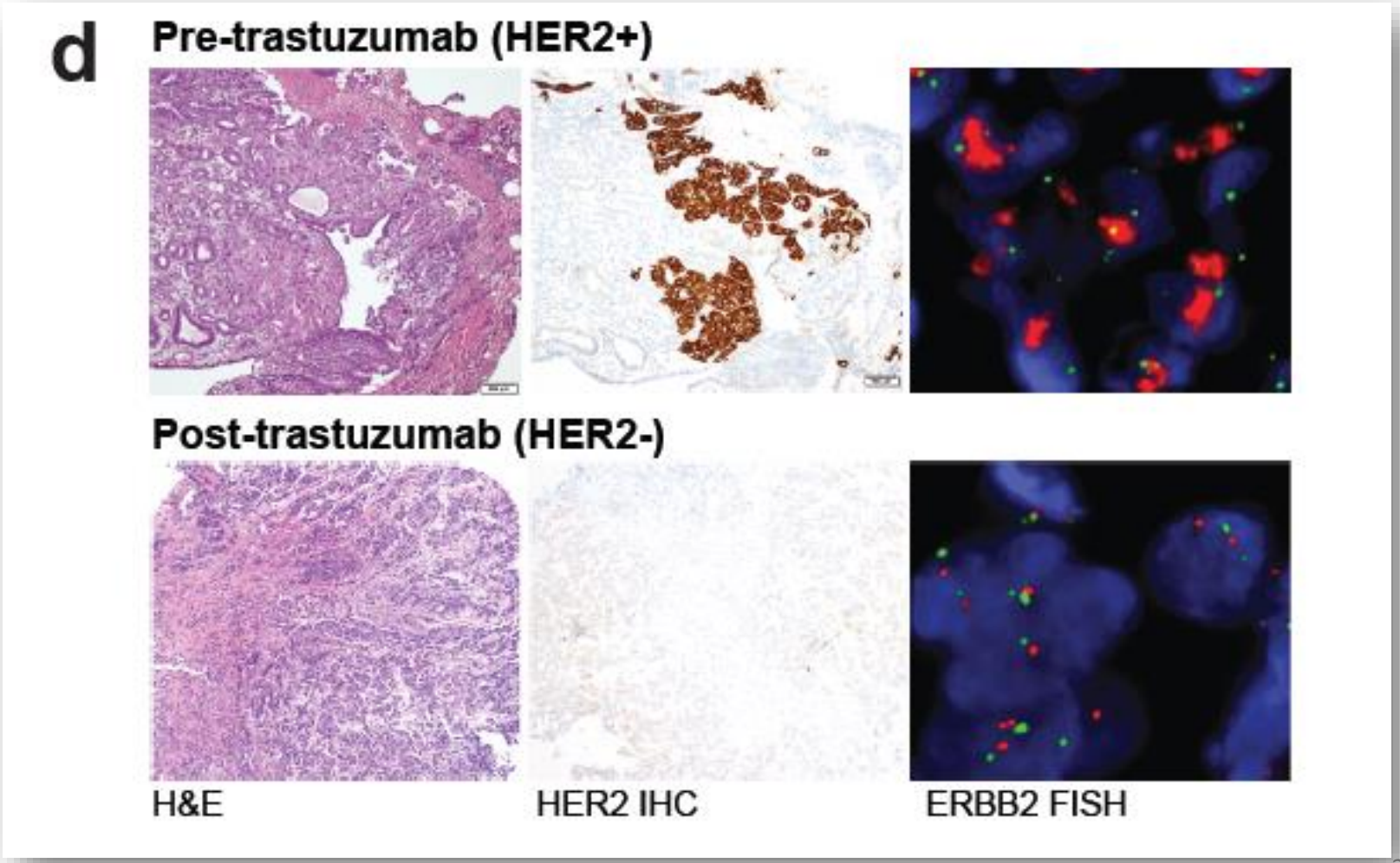


Lordick et al Ann Oncol 2022

Zweitlinientherapie Her-2 positives Magen Ca

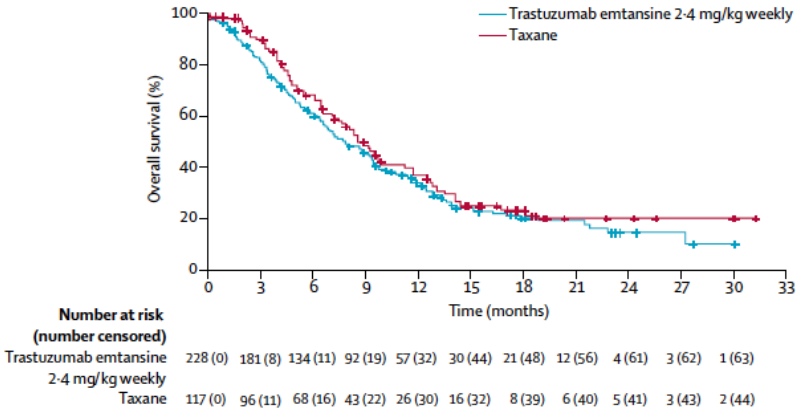
Was tun bei Progress? Rezidiv?

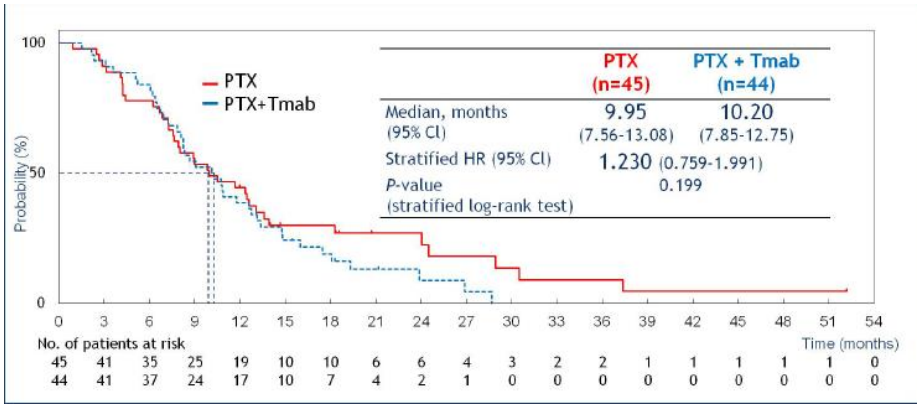
Intratumorale Heterogenität und klonale Evolution

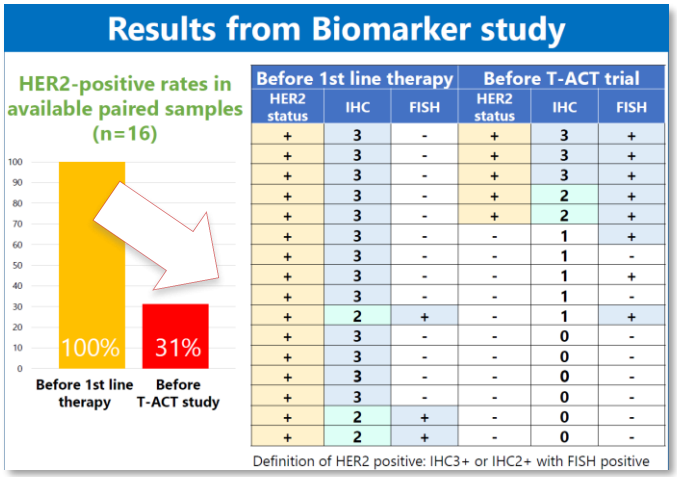


Janjigian YY et al., Cancer Discov. 2017 Nov 9. pii: CD-17-0787

Zweitlinientherapie HER2+







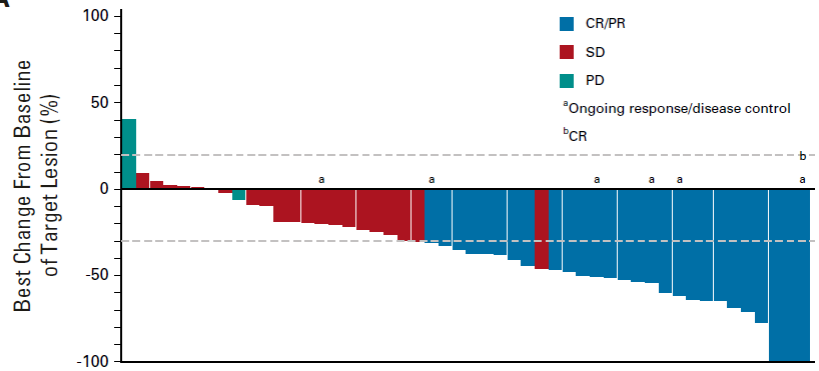
→ kein Nutzen für T-DM1 oder Trastuzumab nach Trastuzumabversagen

Thuss-Patience et al 2017, Sukawa et al 2018

Makiyama et al, J Clin Oncol. 2020 Jun 10;38(17):1919-1927

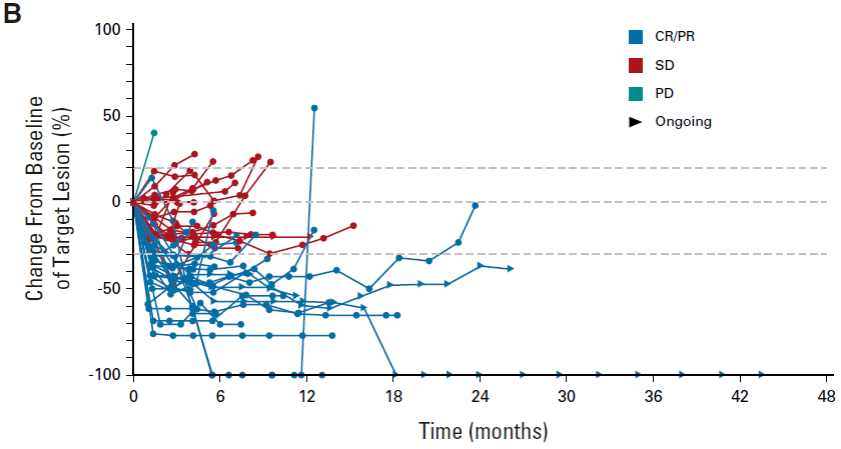
Trastuzumab plus Ramucirumab-Paclitaxel in Her2+ mGC: Einarmige Phase II 2nd Line HER-RAM-Studie aus Korea

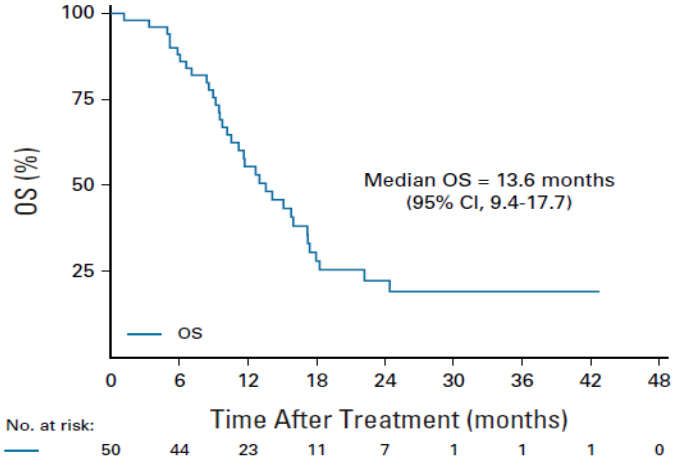
A



Category	Frequency (N = 50)
Best response, No. (%)	
CR	1 (2)
PR	26 (52)
SD	21 (42)
PD	2 (4)
ORR, % (95% CI)[a]	54 (39.3 to 68.2)
DCR, % (95% CI)[b]	96 (86.3 to 99.5)

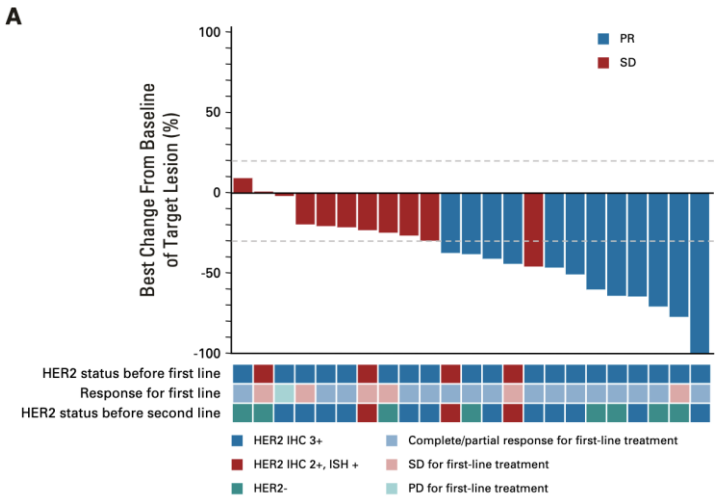
B



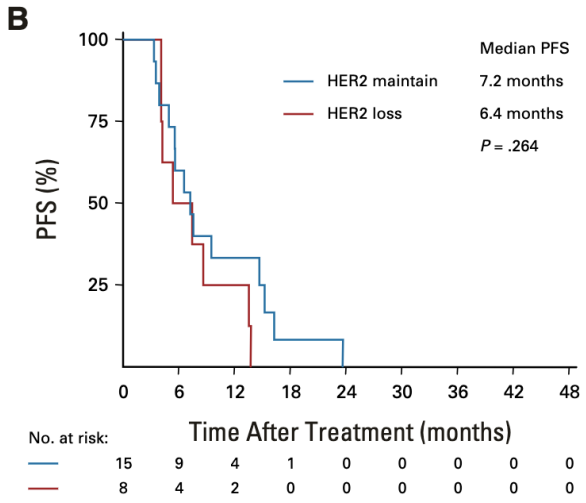


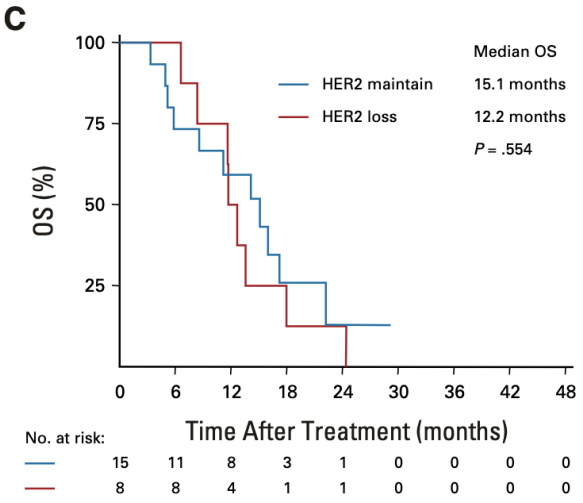
Kim CG et al. J Clin Oncol. 2023;41:4394-4405

Einfluss der Her-2 Expression auf das Überleben



Her-2 Expressionsverlust nach 1st line Trastuzumab+ Chemo: 35% (n=23; 46% Rebiopsien vor 2nd Line Therapie)





Kim CG et al. J Clin Oncol. 2023;41:4394-4405

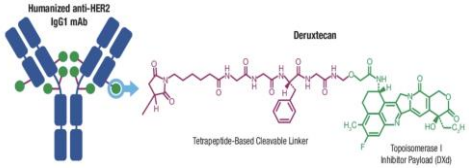
Derzeitige Standard 2nd Line Therapie: Trastuzumab Deruxtecan- DESTINY Gastric 01 und 02

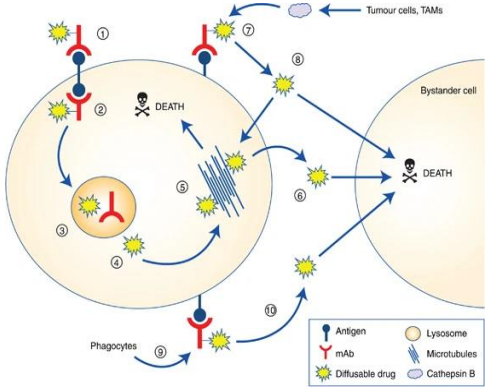
Hintergrund:

• Trastuzumab Deruxtecan (T-DXd): Kombination aus anti-HER2 und Topoisomerase-I-Inhibitor

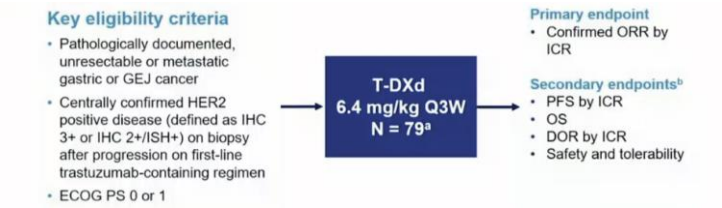
• Zulassung (FDA und EMA) für met Brustkrebs nach >2 Vortherapien und in Japan nach 1 CTX

• Phase-I-Studie: ORR 43,2% und medianes PFS 5,6 Monate mit T-Dxd bei fortgeschrittenem HER2+ GC

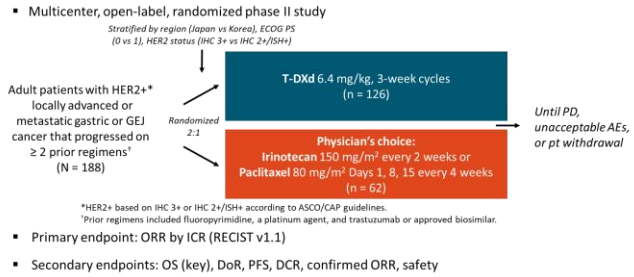




DESTINY-Gastric02: T-DXd in ≥ 2rd Line in Kaukasiern

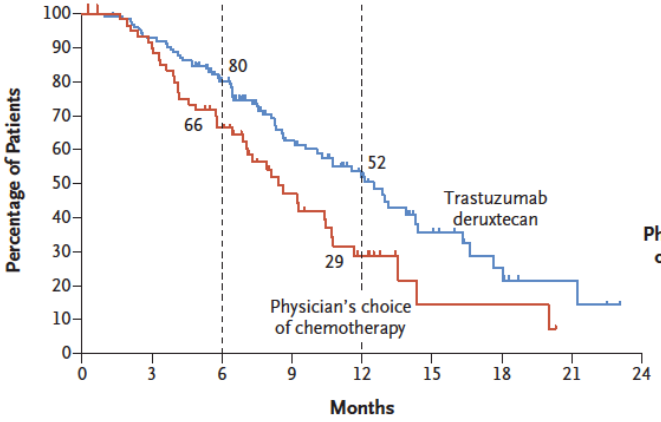


DESTINY-Gastric01: T-DXd in ≥ 3rd Line in Asien



Shitara et al, Lancet Oncol. 2019 Jun;20(6):827-836,
Shitara et al, N Engl J Med 2020 Jun 18;382(25): 2419-2430.
Ku G et al. ESMO 2022; #1205

Destiny Gastric 01: Drittlinientherapie mit T-DXd



No. at Risk

Trastuzumab deruxtecan	125	115	88	54	33	14	7	3	0
Physician's choice of chemotherapy	62	54	37	19	10	2	2	0	0

	No. of Deaths/ No. of Patients	Median Overall Survival (95% CI) *mo*
Trastuzumab Deruxtecan	62/125	12.5 (9.6–14.3)
Physician's Choice of Chemotherapy	39/62	8.4 (6.9–10.7)

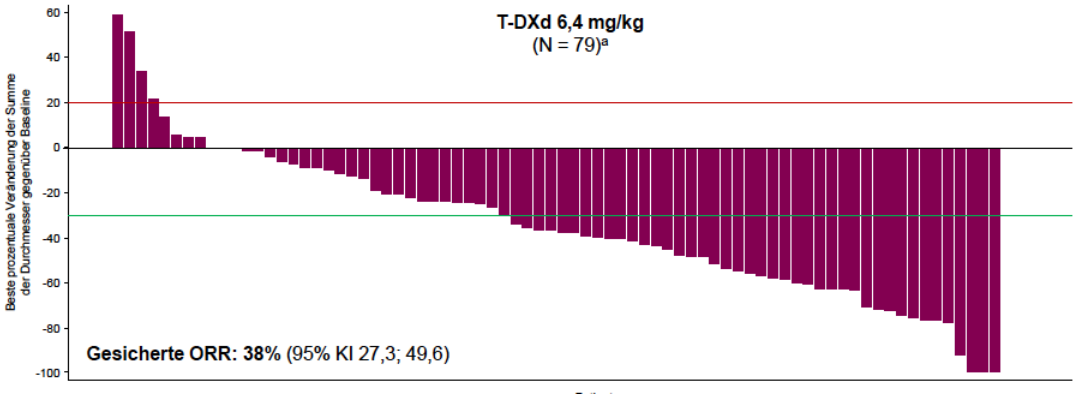
Hazard ratio for death, 0.59 (95% CI, 0.39–0.88)
P=0.01

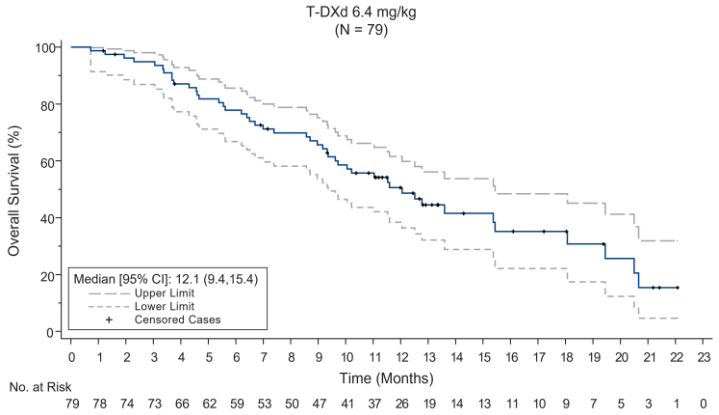
ORR 43%
mPFS 5.6 Monate
mOS 12.5 Monate

→ HER2 Positivität bei 30% Rebiopsie

Shitara et al., NEJM 2020

Fdestiny Gastric 02: Zweitlinientherapie mit T-DXd





→ HER2 Positivität bei 100% Rebiopsie

ORR 42%
mPFS 5.6 Monate
mOS 12.1 Monate

→ Zulassung nach vorheriger Trastuzumabtherapie

Van Cutsem et al Lancet Oncol 2023

DESTINY-Gastric01

TEAEs bei ≥20% der mit T-DXd behandelten Patienten*

Table 3. Adverse Events Occurring in at Least 20% of the Patients Treated with Trastuzumab Deruxtecan.*

Preferred Term	Trastuzumab Deruxtecan (N=125)			Physician's Choice of Chemotherapy (N=62)		
	Any Grade	Grade 3	Grade 4	Any Grade	Grade 3	Grade 4
	number of patients (percent)					
Nausea	79 (63)	6 (5)	0	29 (47)	1 (2)	0
Neutrophil count decreased†	79 (63)	48 (38)	16 (13)	22 (35)	10 (16)	5 (8)
Decreased appetite	75 (60)	21 (17)	0	28 (45)	8 (13)	0
Anemia‡	72 (58)	47 (38)	0	19 (31)	13 (21)	1 (2)
Platelet count decreased§	49 (39)	12 (10)	2 (2)	4 (6)	1 (2)	1 (2)
White-cell count decreased¶	47 (38)	26 (21)	0	22 (35)	5 (8)	2 (3)
Malaise	43 (34)	1 (1)	0	10 (16)	0	0
Diarrhea	40 (32)	3 (2)	0	20 (32)	1 (2)	0
Vomiting	33 (26)	0	0	5 (8)	0	0
Constipation	30 (24)	0	0	14 (23)	0	0
Pyrexia	30 (24)	0	0	10 (16)	0	0
Alopecia	28 (22)	0	0	9 (15)	0	0
Fatigue	27 (22)	9 (7)	0	15 (24)	2 (3)	0
Lymphocyte count decreased‖	27 (22)	8 (6)	6 (5)	2 (3)	0	1 (2)

DESTINY-Gastric 02

TRAEs bei ≥15% der Patienten

N (%)	Patienten (N=79)	
	Alle Grade	Grad ≥3
Patienten mit ≥1 TRAEs	74 (93,7)	21 (26,6)
TRAEs mit einer Inzidenz von ≥15% aller Patienten		
Übelkeit	46 (58,2)	3 (3,8)
Fatigue	29 (36,7)	3 (3,8)
Erbrechen	26 (32,9)	1 (1,3)
Diarrhö	22 (27,8)	1 (1,3)
Verminderter Appetit	18 (22,8)	1 (1,3)
Alopezie	17 (21,5)	0
Anämie	15 (19,0)	6 (7,6)
Verringerte Thrombozytenzahl	13 (16,5)	1 (1,3)
Verringerte Neutrophilenzahl	12 (15,2)	6 (7,6)

van Cutsem E et al. | Abstract #LBA55 | ESMO 2021, Virtuell

Antiemese – NCCN Guidelines 2023

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2023
Antiemesis

NCCN Guidelines Index
Table of Contents
Discussion

EMETOGENIC POTENTIAL OF PARENTERAL ANTICANCER AGENTS

LEVEL	AGENT		
High emetic risk (>90% frequency of emesis)[a]	• AC combination defined as any chemotherapy regimen that contains an anthracycline and cyclophosphamide • Carboplatin AUC ≥4 • Carmustine >250 mg/m²	• Cisplatin • Cyclophosphamide >1500 mg/m² • Dacarbazine • Doxorubicin ≥60 mg/m² • Epirubicin >90 mg/m² • Fam-trastuzumab deruxtecan-nxki	• Ifosfamide ≥2 g/m² per dose • Mechlorethamine • Melphalan ≥140 mg/m² • Sacituzumab govitecan-hziy • Streptozocin
Moderate emetic risk (>30%–90% frequency of emesis)[a]	• Aldesleukin >12–15 million IU/m² • Amifostine >300 mg/m² • Bendamustine • Busulfan • Carboplatin[b] AUC <4 • Carmustine[b] ≤250 mg/m² • Clofarabine • Cyclophosphamide[b] ≤1500 mg/m² • Cytarabine >200 mg/m² • Dactinomycin[b] • Daunorubicin[b]	• Dinutuximab • Doxorubicin[b] <60 mg/m² • Dual-drug liposomal encapsulation of cytarabine and daunorubicin • Epirubicin[b] ≤90 mg/m² • Idarubicin[b] • Ifosfamide[b] <2 g/m² per dose • Irinotecan[b] • Irinotecan (liposomal) • Lurbinectedin • Melphalan <140 mg/m²	• Methotrexate[b] ≥250 mg/m² • Naxitamab-gqgk • Oxaliplatin[b] • Romidepsin • Temozolomide • Trabectedin[b]

Adapted with permission from: Hesketh PJ, Kris MG, Grunberg SM, et al. Proposal for classifying the acute emetogenicity of cancer chemotherapy. J Clin Oncol 1997;15:103-109. Grunberg SM, Warr D, Gralla RJ, et al. Evaluation of new antiemetic agents and definition of antineoplastic agent emetogenicity--state of the art. Support Care Cancer 2011;19:S43-S47.

Interstitielle Lungenerkrankung (ILD) / Pneumonitis

DESTINY-Gastric-02: Ku G et al. ESMO 2022; #1205 – GC-02

	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Any Grade
% (n)	2.5 (2)	5.1 (4)	0	0	2.5 (2)	10.1 (8)

- Median time to onset of drug-related ILD was 80.5 days (range, 42-344 days), with a median duration of 36.0 days

DESTINY-Gastric-01: Shitara K et al. NEJM 2020;382:2419-30 – GC-01

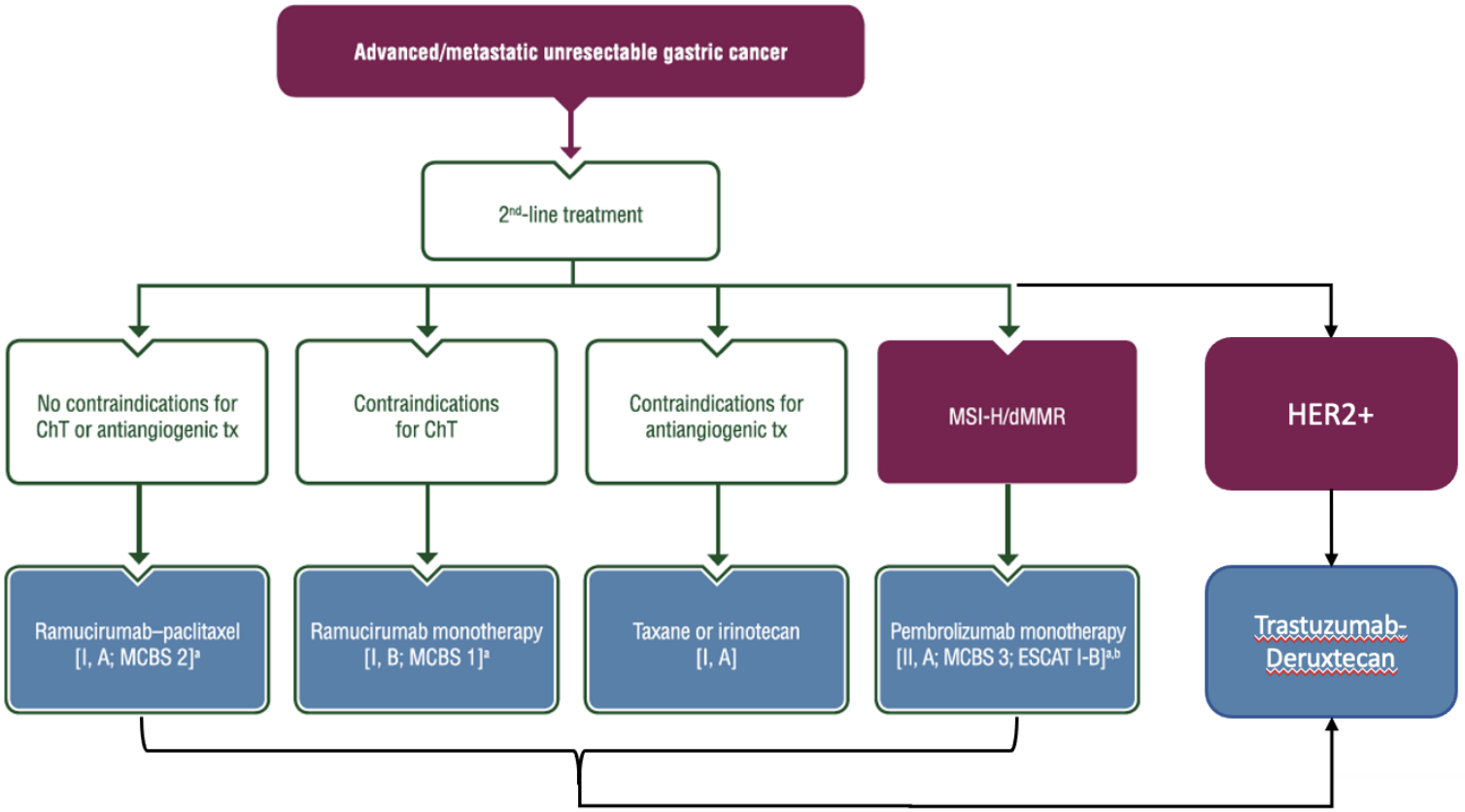
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Any Grade
% (n)	2.4 (3)	4.8 (6)	2.4 (3)	0.8 (1)	0	10.4 (13)

- Median time to onset of drug-related ILD was 84.5 days (range, 36-638 days), with a median duration of 57.0 days

FAZIT: beherrschbare NW der T-DXd Therapie als 2L bei kaukasischen Pat. mit HER2 pos. Magen/GEJ Karzinom
(10.2% ILD, CAVE 2 Todesfälle durch ILDs)
27% ≥ Grad 3 TRAEs (weniger als in Rainbow)

2nd-L Behandlungsoptionen (mGC)- Ausblick

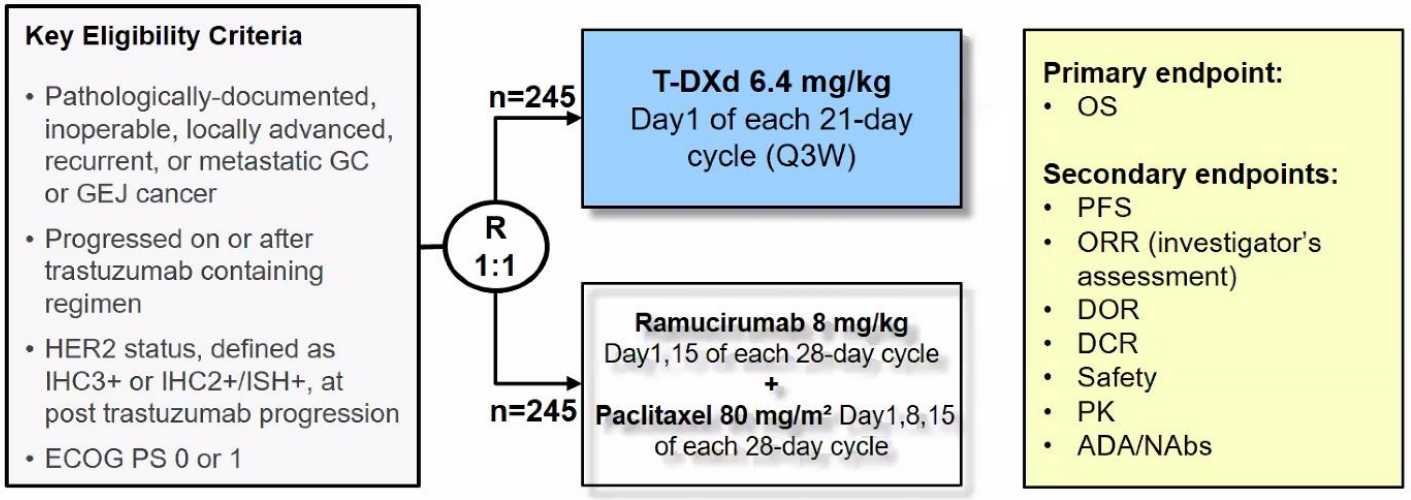
ESMO Guidelines - 2022



adapted Lordick et al 2022

DESTINY GASTRIC 04 STUDIE REKRUTIEREND

DESTINY-Gastric04 study design



Stratification factors:
- HER2 Status (IHC3+ vs IHC2+/ISH+)
- Geography (Asia [excl. mainland China] vs. US/EU vs. mainland China/ROW
- Time to progression on 1L therapy (<6 months vs. ≥6 months)

Study Duration: 36 months (Accrual: 25 m + Follow-up: 11 m)

Zusammenfassung metastasiertes gastroösophageales Karzinom

- Die **Sequenztherapie** hat sich beim metastasierten Magenkarzinom etabliert!
- Allerdings < 50% der Patienten in Studien erhalten 2.Linientherapie

  ->**Zweitlinientherapie**: **Chemo + Ramucirumab** Standard (RAINBOW) - KEIN Stellenwert der IO Therapie
- Anti-angiogene Substanzen vermitteln auch immunmodulatorische Effekte:

  ->Die **Sequenz von 1st Linien IO + CTX gefolgt von Ramucirumab** zeigte in retrospektiven Analysen Vorteile in der Wirksamkeit gegenüber historischen Daten

  -> Ramucirumab/Folfiri möglicherweise neue Zweitlinientherapie Option nach Taxan Vortherapie? Phase III **Ramiris Studie** rekrutierend!
- **Her2 positiv: T-DXd neue Zweitlinientherapie!** Konkordanz der Ergebnisse aus Destiny Gastric 01 (kaukasier) und 02 Studie (Asiaten) bzgl. ORR, OS und PFS (ESMO 2022). Cave ILD und Nausea und Vomiting! Bestimmung der Her-2 Überexpression vor Beginn empfohlen

- **MSI-high-Tumore**(~4%) hohe Sensitivität für IO Therapie- Testung ab Erstdiagnose! Brauchen wir hier die Chemotherapie?

DANKE FÜR IHRE AUFMERKSAMKEIT!