Therapiesequenz bei metastasierten Adenokarzinomen des Magens und gastroösophagealen Übergangs

Alexander Stein

hope

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Ein Kompetenznetzwerk des UKE

ISRAELITISCHES KRANKENHAUS HAMBURG
AKADEMISCHES LEHRKRANKENHAUS DER UNIVERSITÄT HAMBURG
GEGRÜNDET 1839

Interessenkonflikte

Forschungsunterstützung (institutionell):

- BMS, GBA Innovationsfond, Deutsche Krebshilfe, MerckKgA, MSD, Roche, Sanofi, Servier

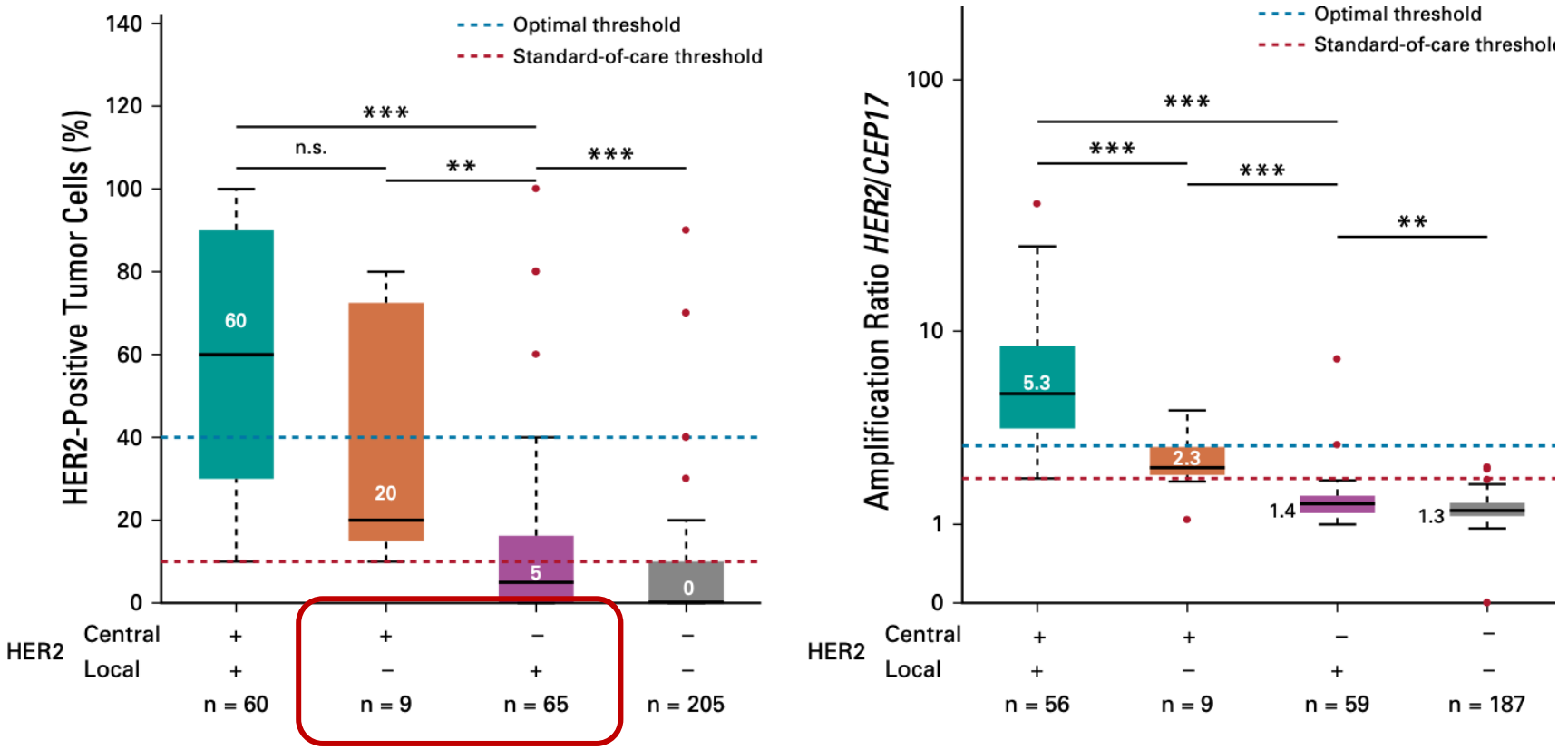
Beratung und Vortragstätigkeiten (institutionell):

- Amgen, Astra Zeneca, BMS, Daiichi Sankyo, Merck, MSD, Roche, Sanofi, Seagen, Servier, Taiho

Diagnostik – Welche Marker brauchen wir?

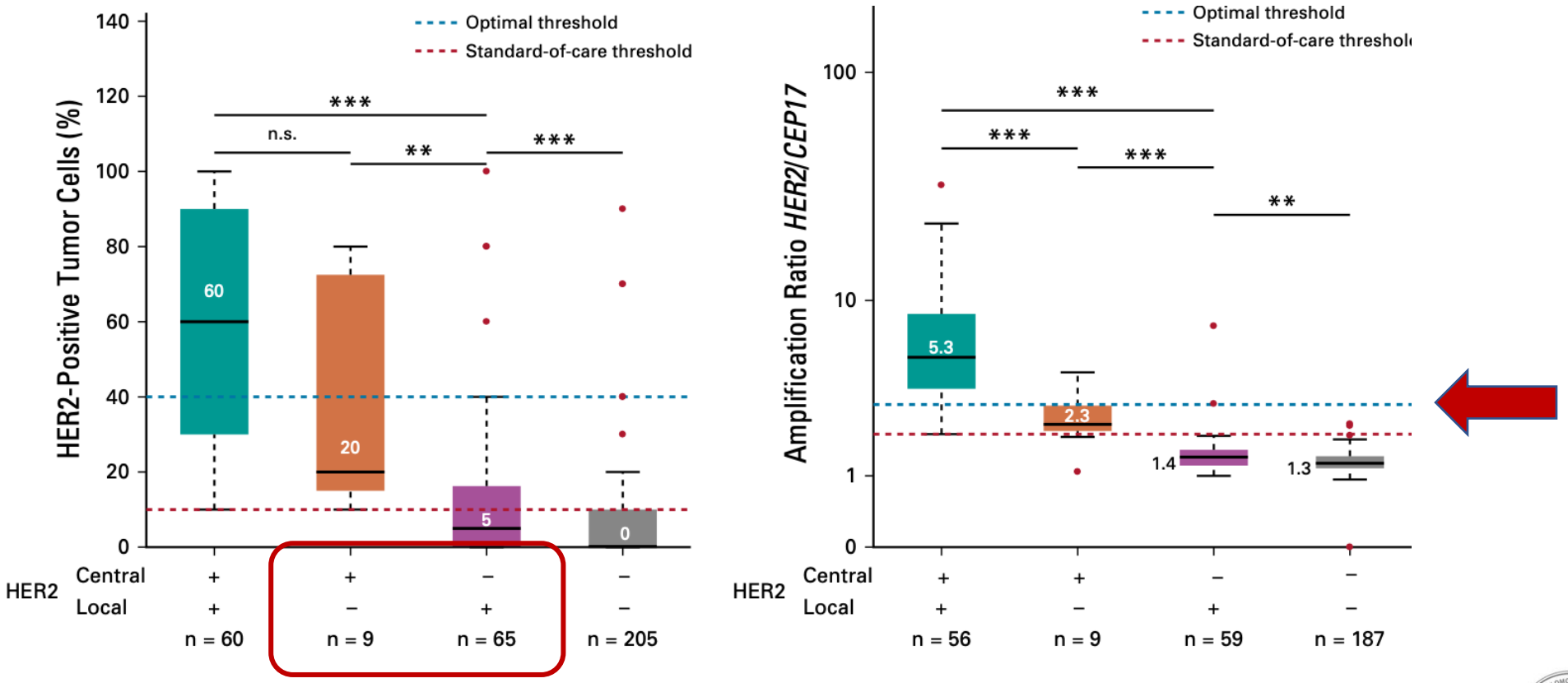
- Erstlinie
  - HER2
  - PD-L1 (CPS)
  - MSI
  - *Claudin 18.2*
- Zweit-/Drittlinie
  - NGS

Diskordanz des HER2 Status



Haffner et al JCO 2021

Diskordanz des HER2 Status



Haffner et al JCO 2021

Erstlinientherapie CTx+Trast+Pembro

Trastuzumab/Chemo +/- Pembro

ORR and DCR, % (95% CI)	Pembro Arm (N = 133)	Placebo Arm (N = 131)
ORR	74.4% (66.2-81.6)	51.9% (43.0-60.7)
ORR difference[b]	22.7% (11.2-33.7) *P* = 0.00006	
DCR	96.2% (91.4-98.8)	89.3% (82.7-94.0)

CPS≥1 84%

Jangjigian et al 2021, SmPC 2023

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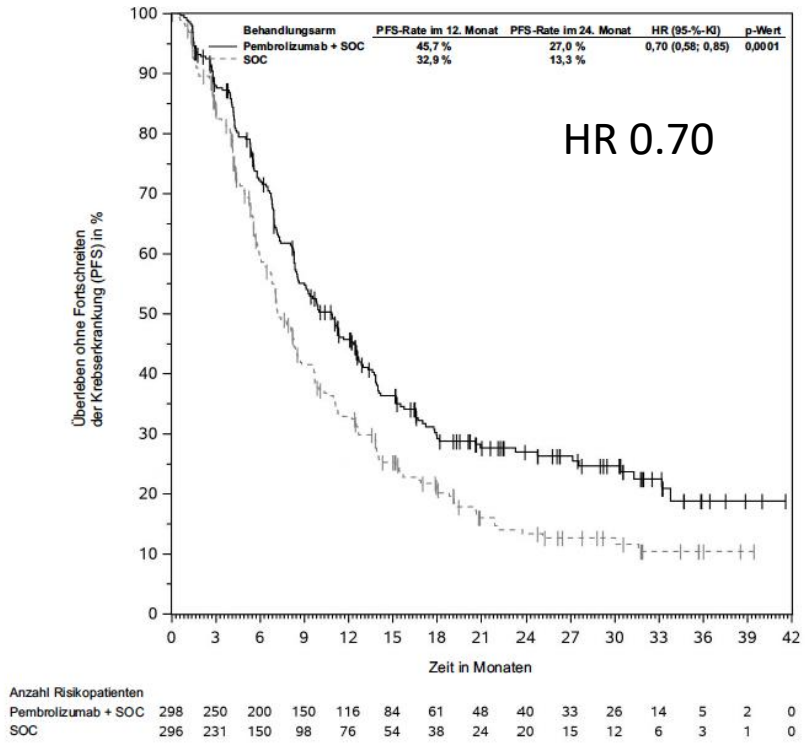
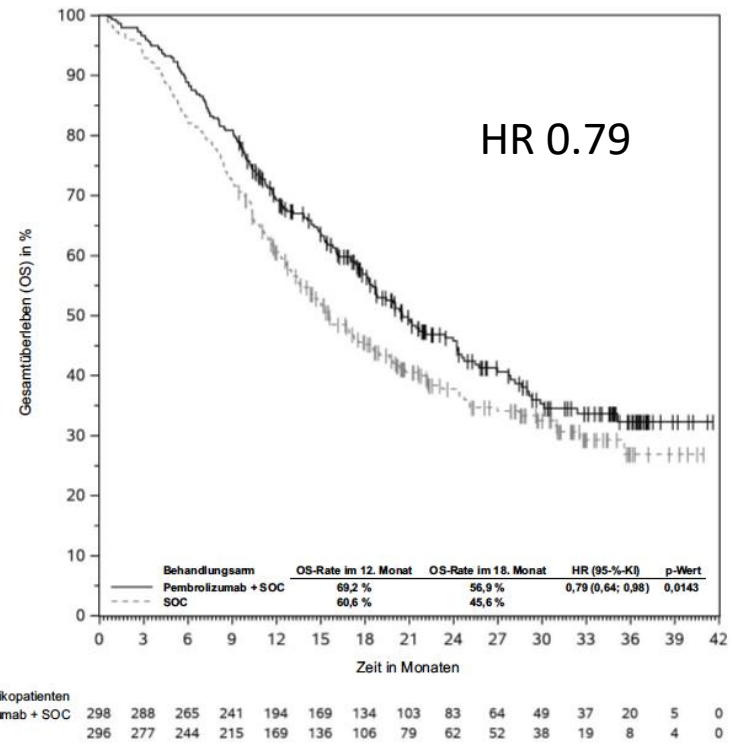
PFS in CPS≥1



OS in CPS≥1



Jangjigian et al 2021, SmPC 2023

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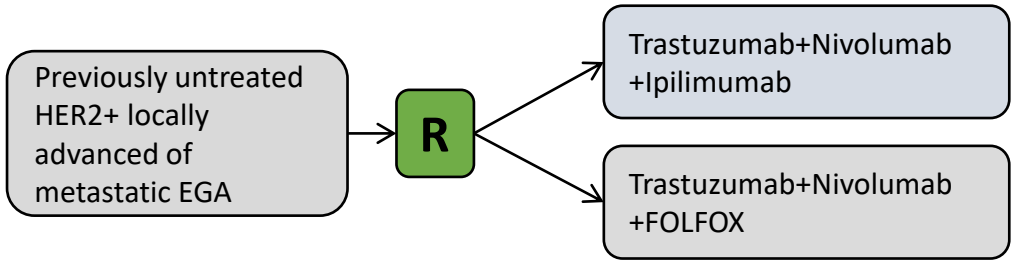
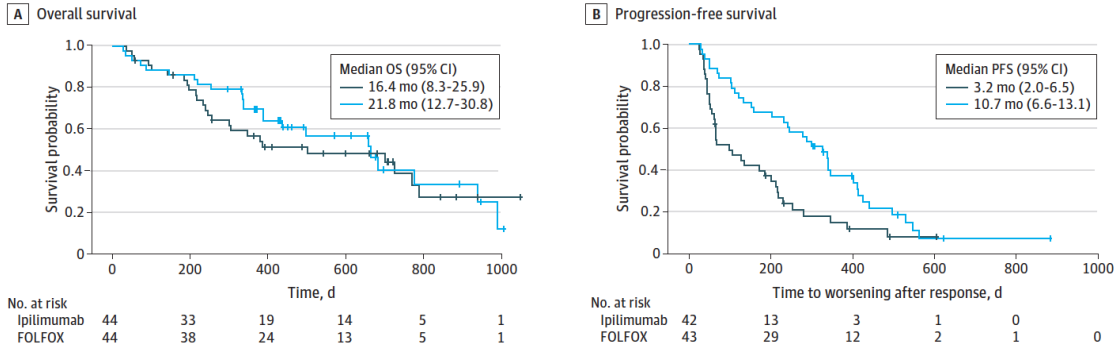
Ausblick - Chemotherapie für alle Patienten?





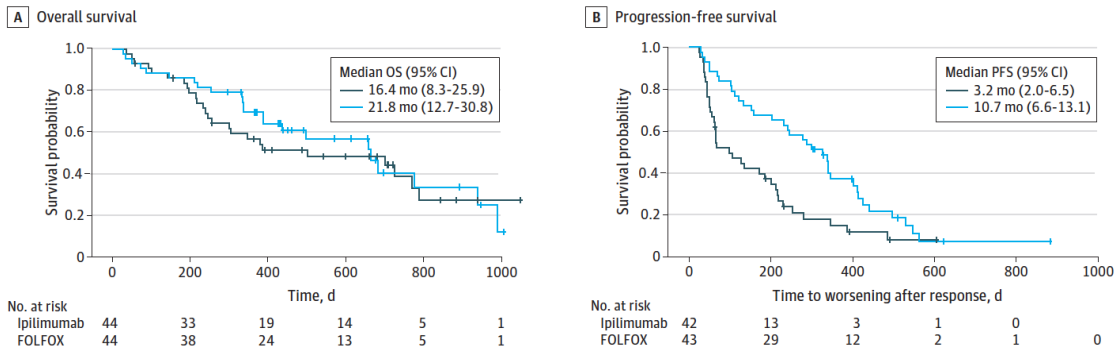
Stein et al JAMA Oncol 2022, Tintelnot et al ASCO 2023

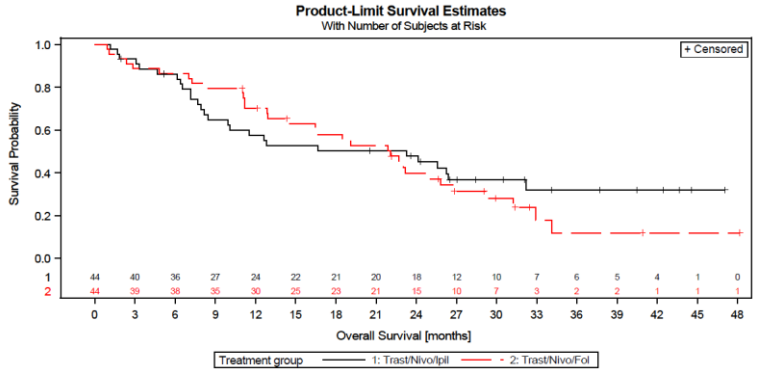
Ausblick - Chemotherapie für alle Patienten?

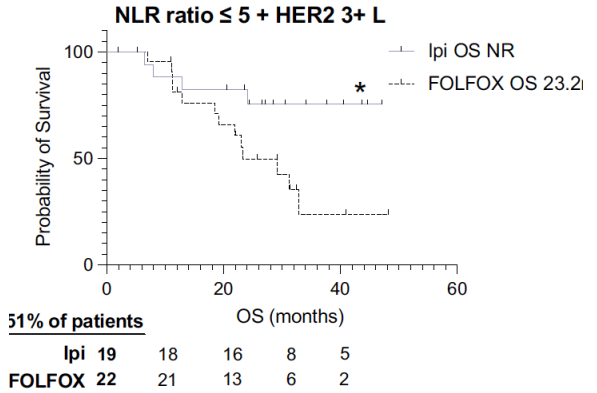
Previously untreated HER2+ locally advanced of metastatic EGA

R

- Trastuzumab+Nivolumab +Ipilimumab
- Trastuzumab+Nivolumab +FOLFOX







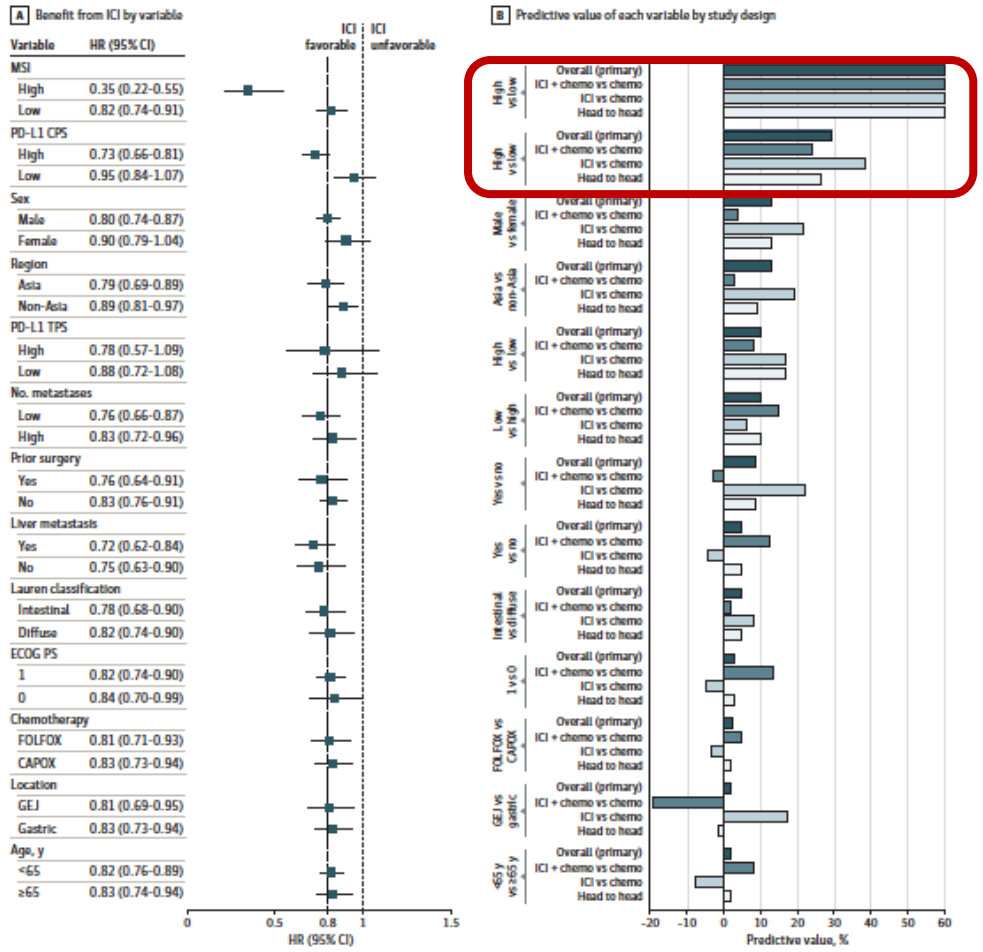
Stein et al JAMA Oncol 2022, Tintelnot et al ASCO 2023

Immuntherapieeffektivität beim EGA

→ MSI

→ CPS

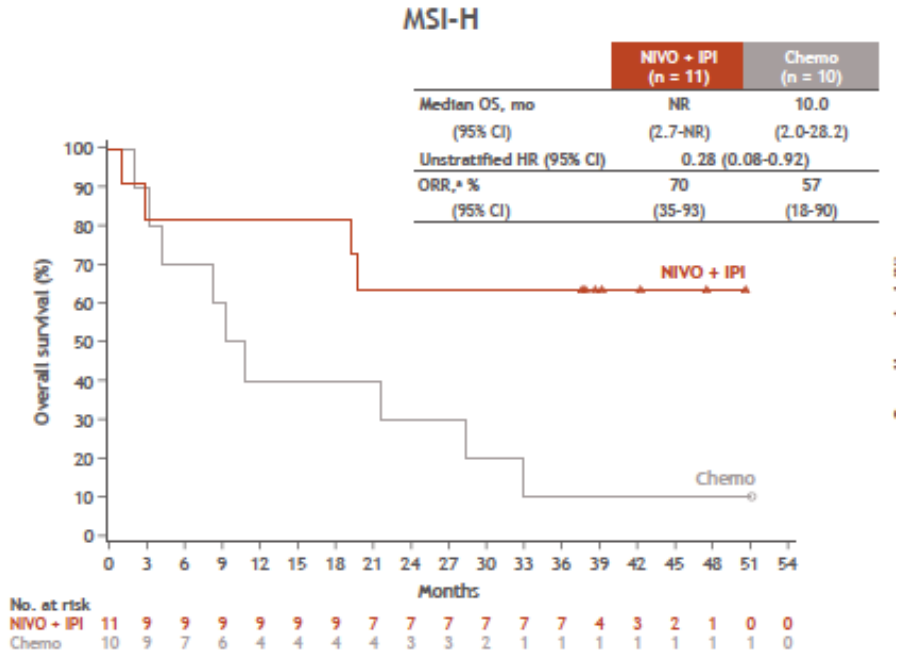
→ TPS



Yoon et al., JAMA Oncol 2022

MSI-H/dMMR – prädiktiv für anti PD-1/L1

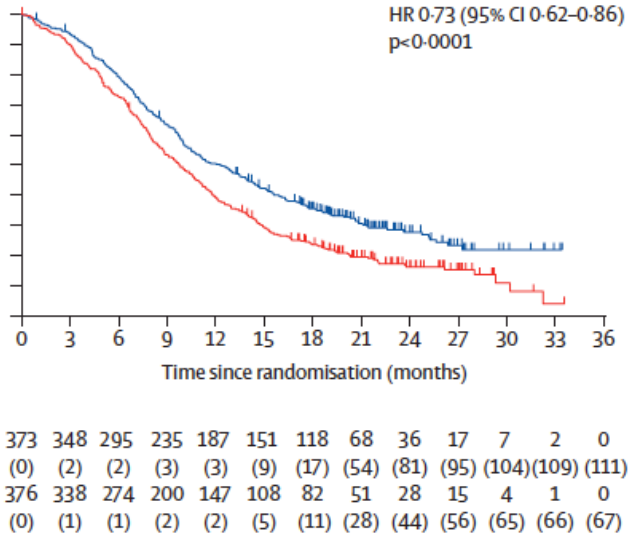
CPS>1			OS Rate 12	OS Rate 24	OS median	HR (OS) vs Chemo
MSI-H	chemo	19	47%	26%	8.5	
	PD-1i	14	79%	71%	NR	0.29
	chemo+ PD1i	17	71%	65%	NR	0.37
MSS	chemo	231	46%	19%	11.5	



Shitara et al., ESMO 2019, Janjigian et al., ESMO 2021

Immuntherapie 1st line EGA – CPS≥10 (HER2-)

F5FU/Cisplatin +/- Pembrolizumab

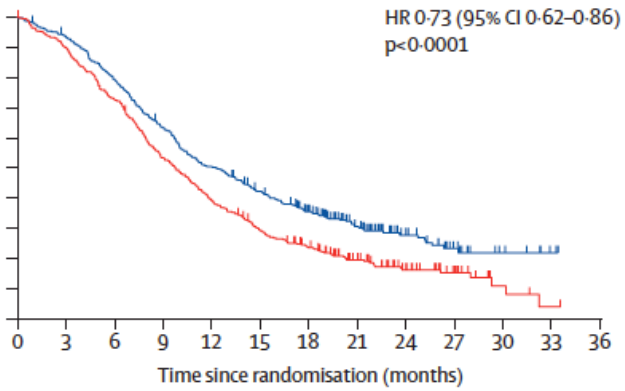


→ **Pembrolizumab + Chemo in CPS≥10**

Sun et al., Lancet Oncol 2021

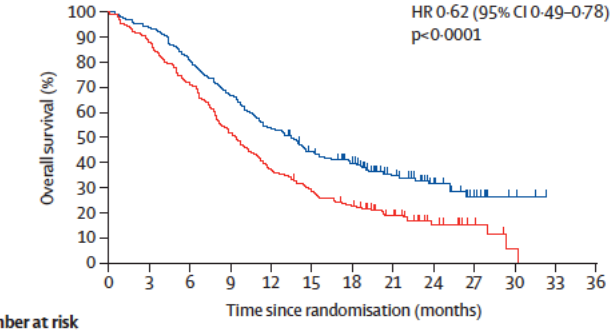
Immuntherapie 1st line EGA – CPS≥10 (HER2-)

F5FU/Cisplatin +/- Pembrolizumab



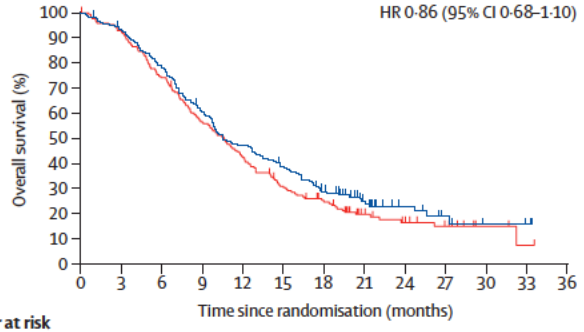
373	348	295	235	187	151	118	68	36	17	7	2	0
(0)	(2)	(2)	(3)	(3)	(9)	(17)	(54)	(81)	(95)	(104)	(109)	(111)
376	338	274	200	147	108	82	51	28	15	4	1	0
(0)	(1)	(1)	(2)	(2)	(5)	(11)	(28)	(44)	(56)	(65)	(66)	(67)

CPS≥10

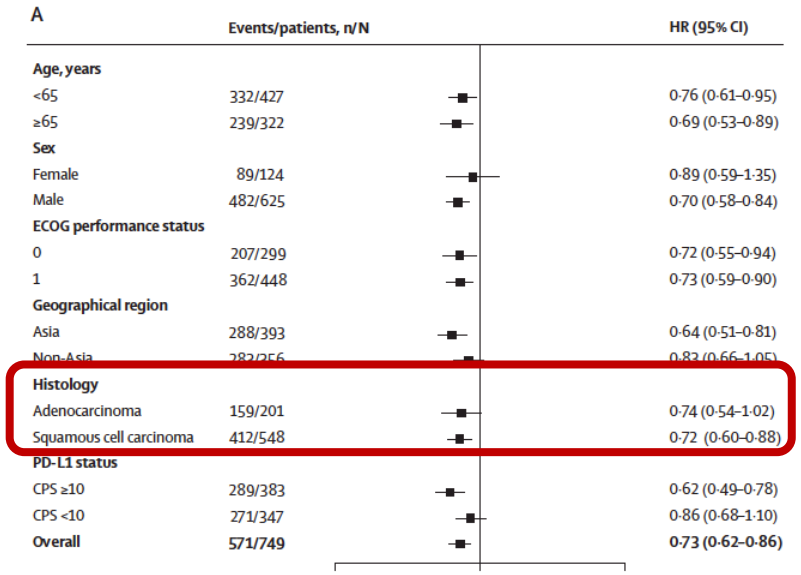


Number at risk (number censored)													
Pembrolizumab plus	186	175	151	125	100	79	66	40	23	10	4	0	0
chemotherapy group	(0)	(0)	(0)	(0)	(0)	(4)	(9)	(28)	(42)	(52)	(58)	(58)	(58)
Placebo plus	197	174	142	102	73	55	42	28	13	6	1	0	0
chemotherapy group	(0)	(0)	(0)	(0)	(0)	(1)	(3)	(11)	(22)	(29)	(32)	(32)	(32)

CPS<10



Number at risk (number censored)													
Pembrolizumab plus	175	162	135	104	81	66	47	26	12	6	3	2	0
chemotherapy group	(0)	(2)	(2)	(3)	(3)	(5)	(7)	(22)	(34)	(38)	(40)	(41)	(41)
Placebo plus	172	159	127	96	72	51	38	21	14	9	3	1	0
chemotherapy group	(0)	(1)	(1)	(2)	(2)	(4)	(8)	(17)	(21)	(25)	(31)	(32)	(32)



→ **Pembrolizumab + Chemo in CPS≥10**

Sun et al., Lancet Oncol 2021

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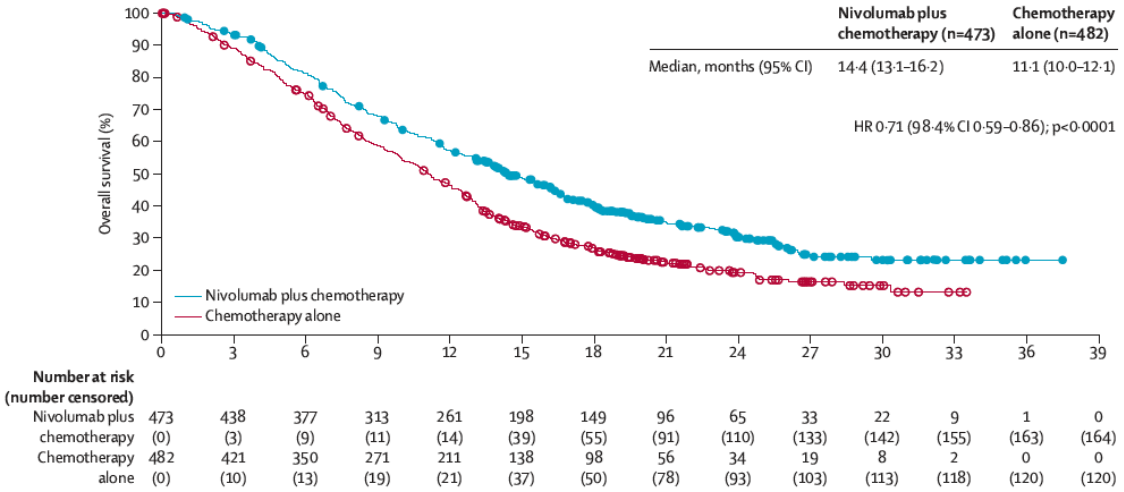
Immuntherapie 1st line EGA – CPS≥5 (HER2-)

FOLFOX/CAPOX +/- Nivolumab



	Nivolumab plus chemotherapy (n=473)	Chemotherapy alone (n=482)
Median, months (95% CI)	14·4 (13·1–16·2)	11·1 (10·0–12·1)

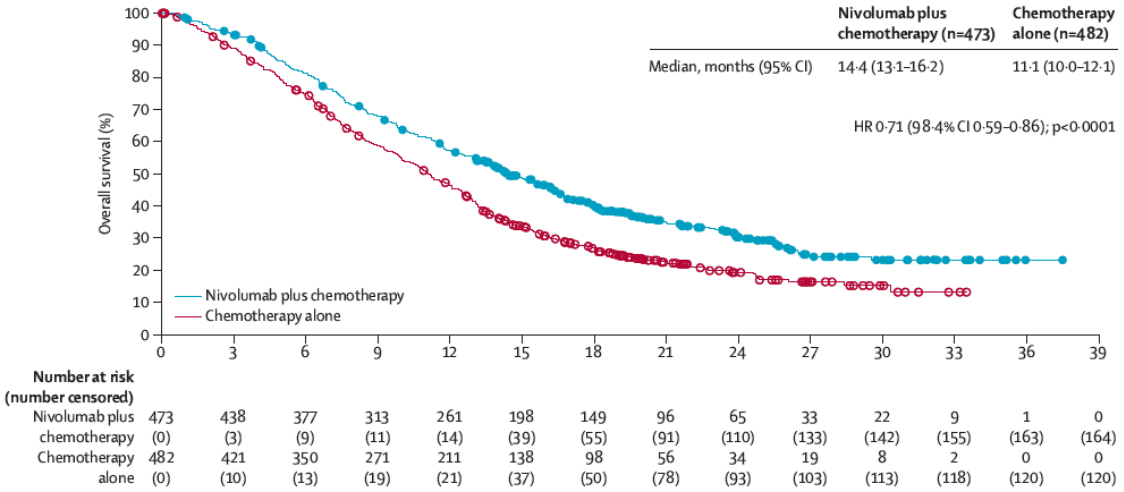
HR 0·71 (98·4% CI 0·59–0·86); p<0·0001

Number at risk (number censored)														
Nivolumab plus chemotherapy	473 (0)	438 (3)	377 (9)	313 (11)	261 (14)	198 (39)	149 (55)	96 (91)	65 (110)	33 (133)	22 (142)	9 (155)	1 (163)	0 (164)
Chemotherapy alone	482 (0)	421 (10)	350 (13)	271 (19)	211 (21)	138 (37)	98 (50)	56 (78)	34 (93)	19 (103)	8 (113)	2 (118)	0 (120)	0 (120)

Janjigian et al Lancet Oncol 2021

Immuntherapie 1st line EGA – CPS≥5 (HER2-)

FOLFOX/CAPOX +/- Nivolumab



Population*	Median overall survival, months		Unstratified hazard ratio for death (95% CI)	Interaction test p value
	Nivolumab plus chemotherapy	Chemotherapy alone		
Overall (N=1581)	13·8	11·6	0·79 (0·70–0·89)	
PD-L1 CPS <1 (n=265)	13·1	12·5	0·92 (0·70–1·23)	
PD-L1 CPS ≥1 (n=1296)	14·0	11·3	0·76 (0·67–0·87)	0·2041
PD-L1 CPS <5 (n=606)	12·4	12·3	0·94 (0·78–1·13)	
PD-L1 CPS ≥5 (n=955)	14·4	11·1	0·70 (0·60–0·81)	0·0107†

0·5 1 2 4
Nivolumab plus chemotherapy better ↔ Chemotherapy alone better

→ Nivolumab + Chemo in CPS≥5

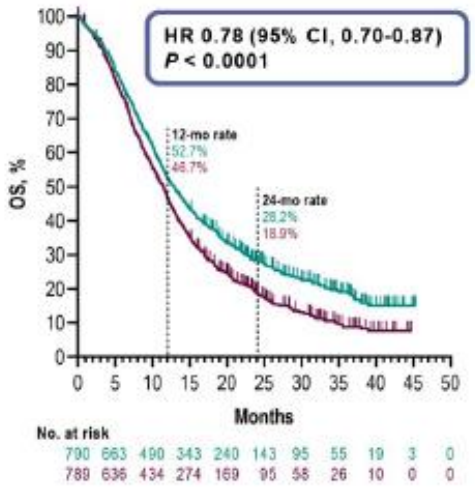
Janjigian et al Lancet Oncol 2021

Immuntherapie 1st line EGA – CPS≥1 (HER2-)

FP/CAPOX +/- Pembrolizumab

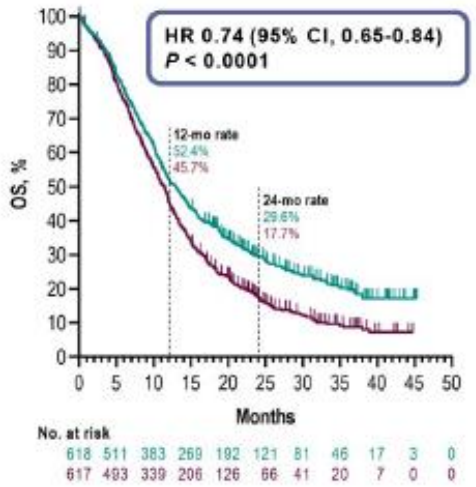
Overall[1]

	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)



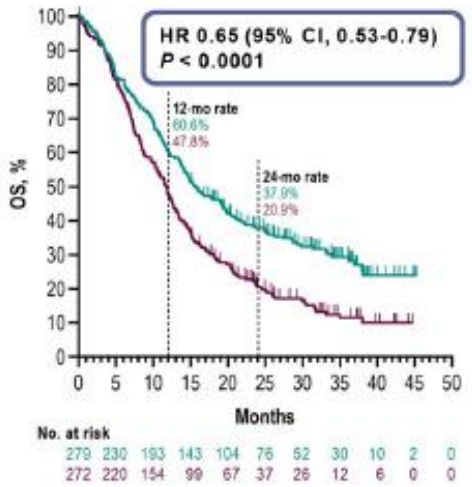
PD-L1 CPS ≥1

	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)



→ Pembrolizumab + Chemo in CPS≥1 (CHMP 13.10.2023)

Rha et al ASCO 2023

Idealer CPS Cut Off?

	Pembro (KN 062)	Pembro (KN 590)	Nivo (CM 649)	Pembro (KN 859)
all	0.74 (n=201)	0.74 (n=201)		0.78 (n=1579)
CPS<1			0.92 (n=265)	0.92 (n=344)
CPS≥1	0.85 (n=507)		0.76 (n=1296)	0.74 (n=1235)
CPS<5			0.94 (n=606)	
CPS≥5			0.70 (n=955)	
CPS 1-9				0.83 (n=682)
CPS<10		0.66 (n=100)	0.91 (n=794)	0.86 (n=1026)
CPS≥10	0.85 (n=189)	0.83 (n=97)	0.66 (n=768)	0.65 (n=551)

Shitara et al 2020, Sun et al 2021,
Janjigian et al 2021/2023, Rha et al 2023

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→ ideal HR 0.66

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Shitara et al 2020, Sun et al 2021,
Janjigian et al 2021/2023, Rha et al 2023

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CPS<5			0.94 (n=606)		
CPS≥5			**0.70 (n=955)**		→ akzeptabel HR 0.7
CPS 1-9				0.83 (n=682)	
CPS<10		0.66 (n=100)	0.91 (n=794)	0.86 (n=1026)	
CPS≥10	0.85 (n=189)	0.83 (n=97)	**0.66 (n=768)**	**0.65 (n=551)**	→ ideal HR 0.66

Shitara et al 2020, Sun et al 2021,
Janjigian et al 2021/2023, Rha et al 2023

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CPS≥5			**0.70 (n=955)**		→ akzeptabel HR 0.7
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→ HR 0.74/76

→ akzeptabel HR 0.7

→ ideal HR 0.66

→ CPS 1-4 HR?

Shitara et al 2020, Sun et al 2021,
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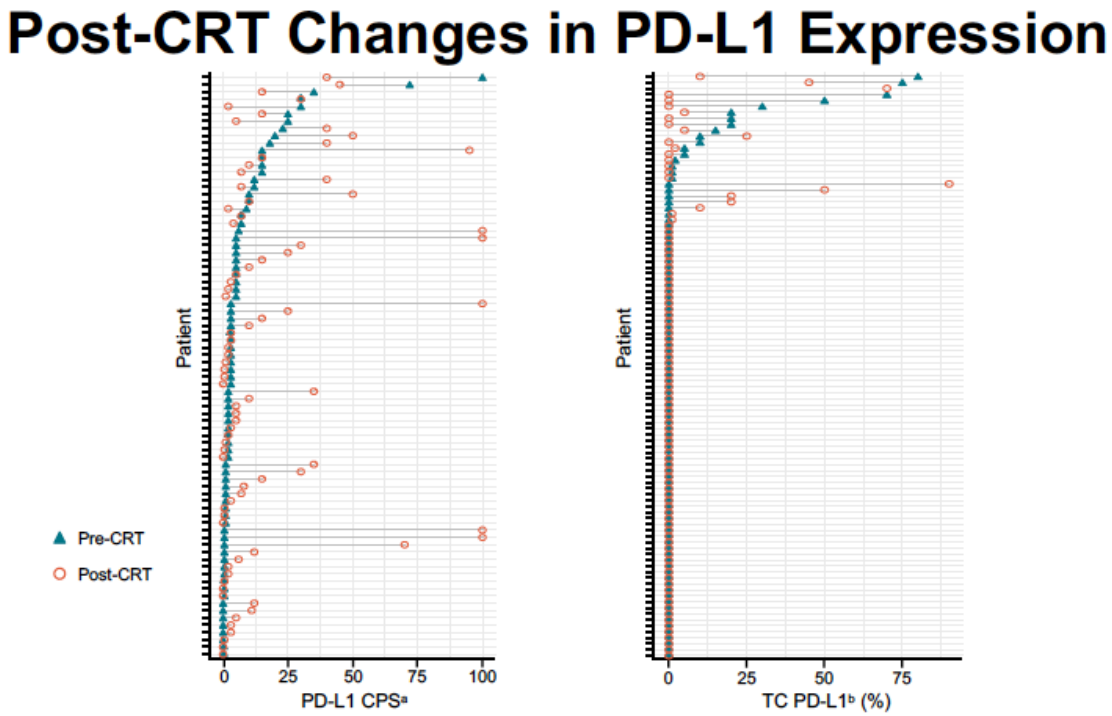
Idealer CPS-Bestimmungszeitpunkt?

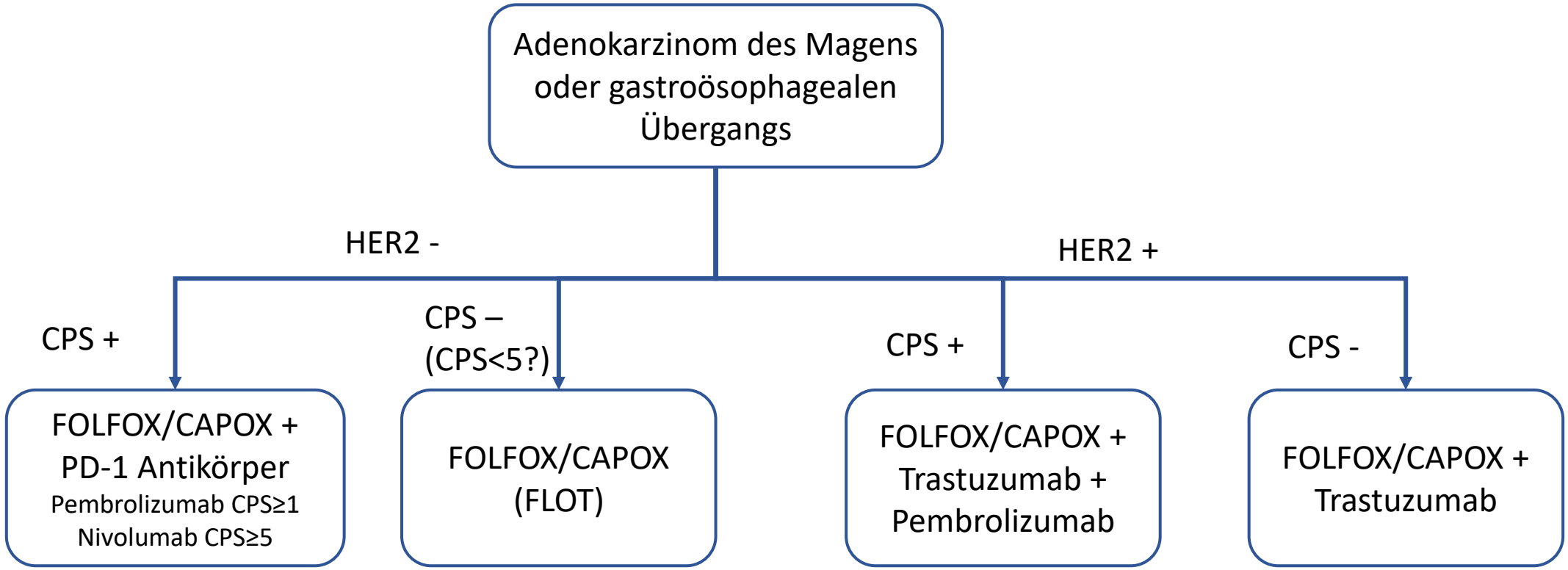


→ CPS Zunahme bei 50%!

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

Kelly et al ESMO GI 2023

Therapiealgorithmus Erstlinie



CAVE: Ösophagus (Adeno) CPS≥10

MSI-H/dMMR → frühe Chemotherapiedeeskalation

Therapiealgorithmus Erstlinie (nach periop)

Adenokarzinom des Magens oder gastroösophagealen Übergangs (<6-12 Monate nach periop FLOT)

Rebiopsie (HER2, CPS, MSI)

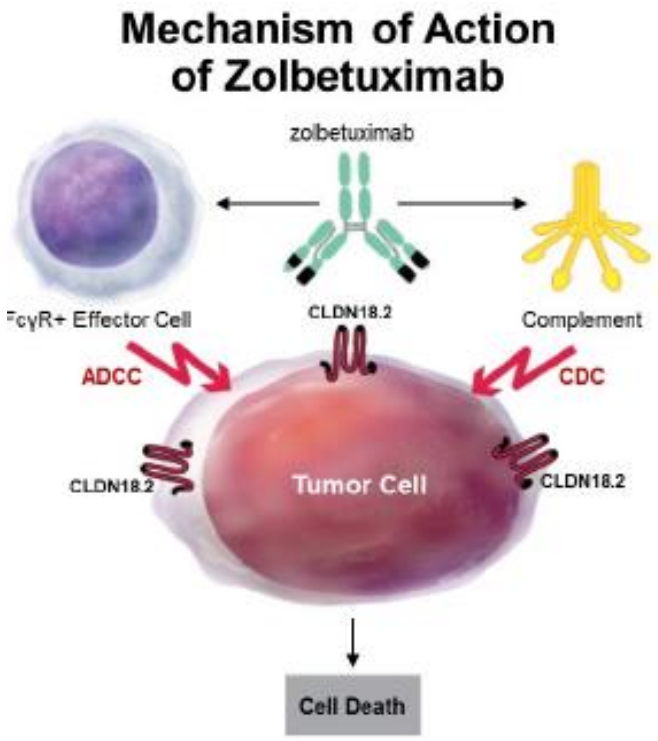
HER2+ und/oder CPS+

→ 5FU/(Cis)Platin +/- anti-PD-1 +/- Trastuzumab
Pembrolizumab CPS≥1, Nivolumab CPS≥5

HER2- und CPS-

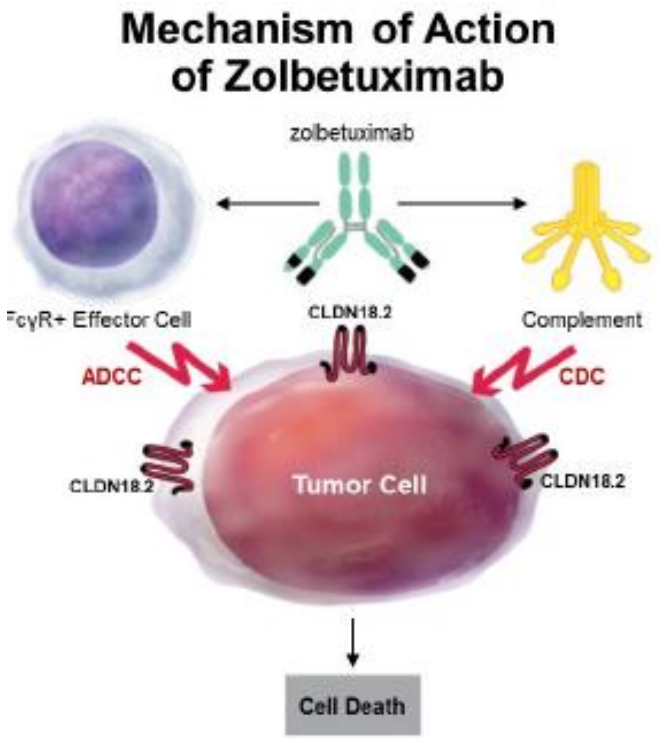
→
1. RAMIRIS Studie (Pacli-Ram vs. FOLFIRI Ram)
2. FOLFIRI (bevorzugt bei ausgeprägter PNP)
3. Paclitaxel+Ramucirumab
4. bei >6 Monaten ggf. nochmal FU/Platin

Zolbetuximab+FP+OX in Claudin 18.2+ EGA



Shitara et al LBA 292 ASCO GI, Xu et al ASCO Plenary 2023

Zolbetuximab+FP+OX in Claudin 18.2+ EGA



	FOLFOX +Zol	FOLFOX +Pla	HR	CAPOX+ Zol	CAPOX+ Pla	HR
ORR	60.7	62.1		54%	49%	
PFS	10.6	8.7	0.75	8.2	6.8	0.69
OS	18.2	15.5	0.75	14.4	12.1	0.77

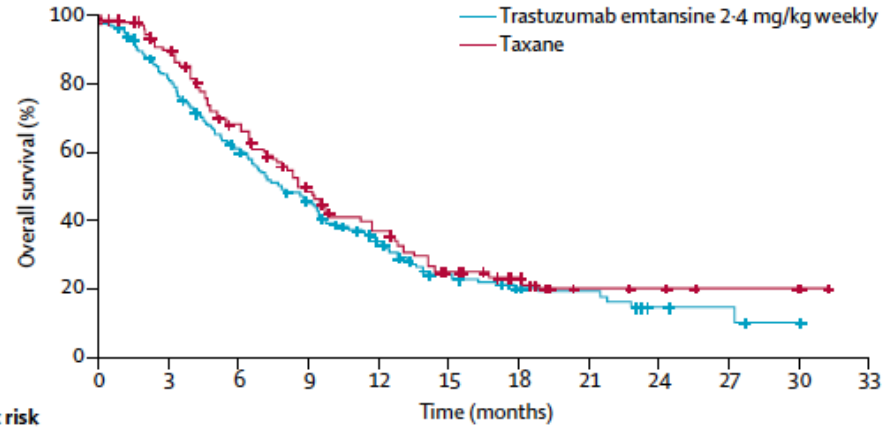
ca. 20% CPS≥5 (1?)

CPS 1-9 (+anti PD1) → HR 0.83

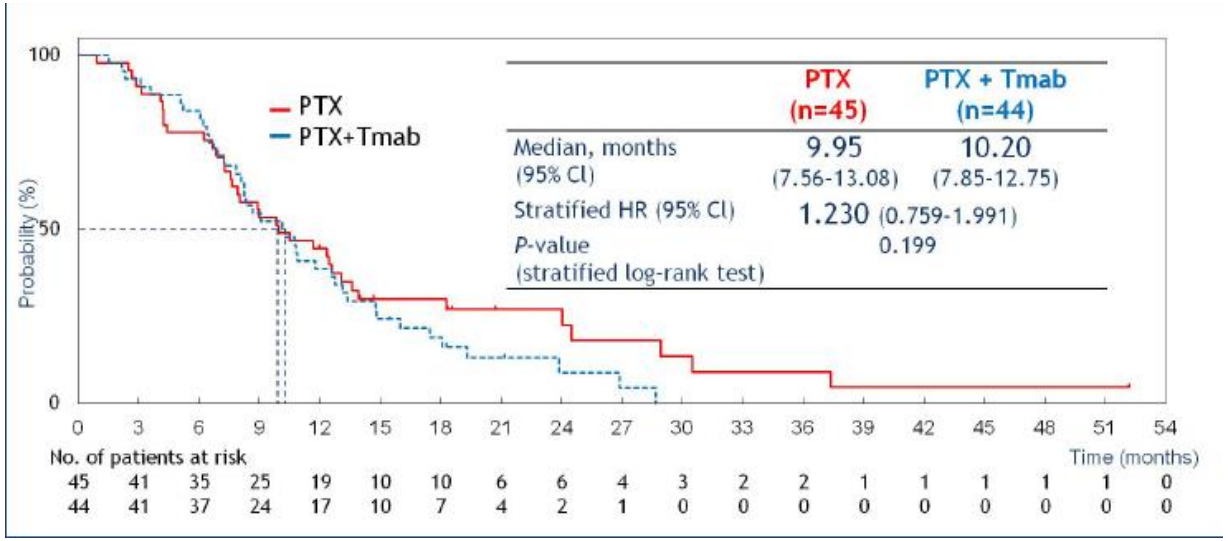
Shitara et al LBA 292 ASCO GI, Xu et al ASCO Plenary 2023

Zweitlinientherapie HER2+

	Taxane (n=117)	Trastuzumab emtansine 2·4 mg/kg weekly (n=228)
Median overall survival, months (95% CI)	8·6 (7·1–11·2)	7·9 (6·7–9·5)
Number of events	71 (60·7%)	164 (71·9%)
Unstratified hazard ratio (95% CI) weekly trastuzumab emtansine vs taxane	1·15 (0·87–1·51), p=0·86*	



Number at risk (number censored)												
Trastuzumab emtansine 2·4 mg/kg weekly	228 (0)	181 (8)	134 (11)	92 (19)	57 (32)	30 (44)	21 (48)	12 (56)	4 (61)	3 (62)	1 (63)	
Taxane	117 (0)	96 (11)	68 (16)	43 (22)	26 (30)	16 (32)	8 (39)	6 (40)	5 (41)	3 (43)	2 (44)	



	PTX (n=45)	PTX + Tmab (n=44)
Median, months (95% CI)	9.95 (7.56-13.08)	10.20 (7.85-12.75)
Stratified HR (95% CI)	1.230 (0.759-1.991)	
P-value (stratified log-rank test)	0.199	

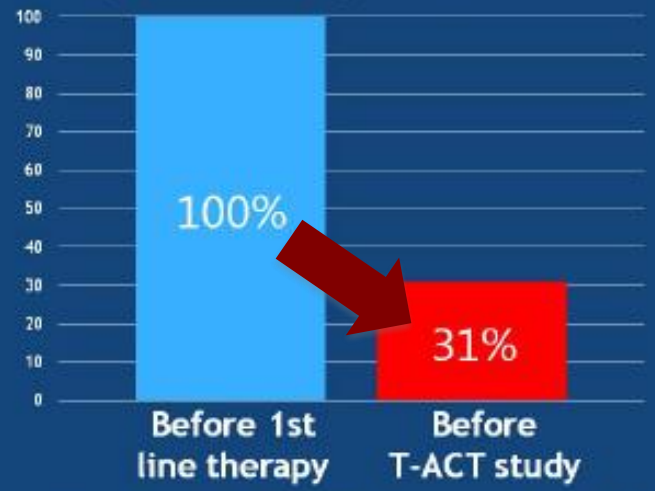
→ kein Nutzen für T-DM1 oder Trastuzumab nach Trastuzumabversagen

Thuss-Patience et al 2017, Sukawa et al 2018

HER2 Status nach anti HER2 Therapie

HER2 status after 1st line chemotherapy

HER2-positive rates in available paired samples (n=16)



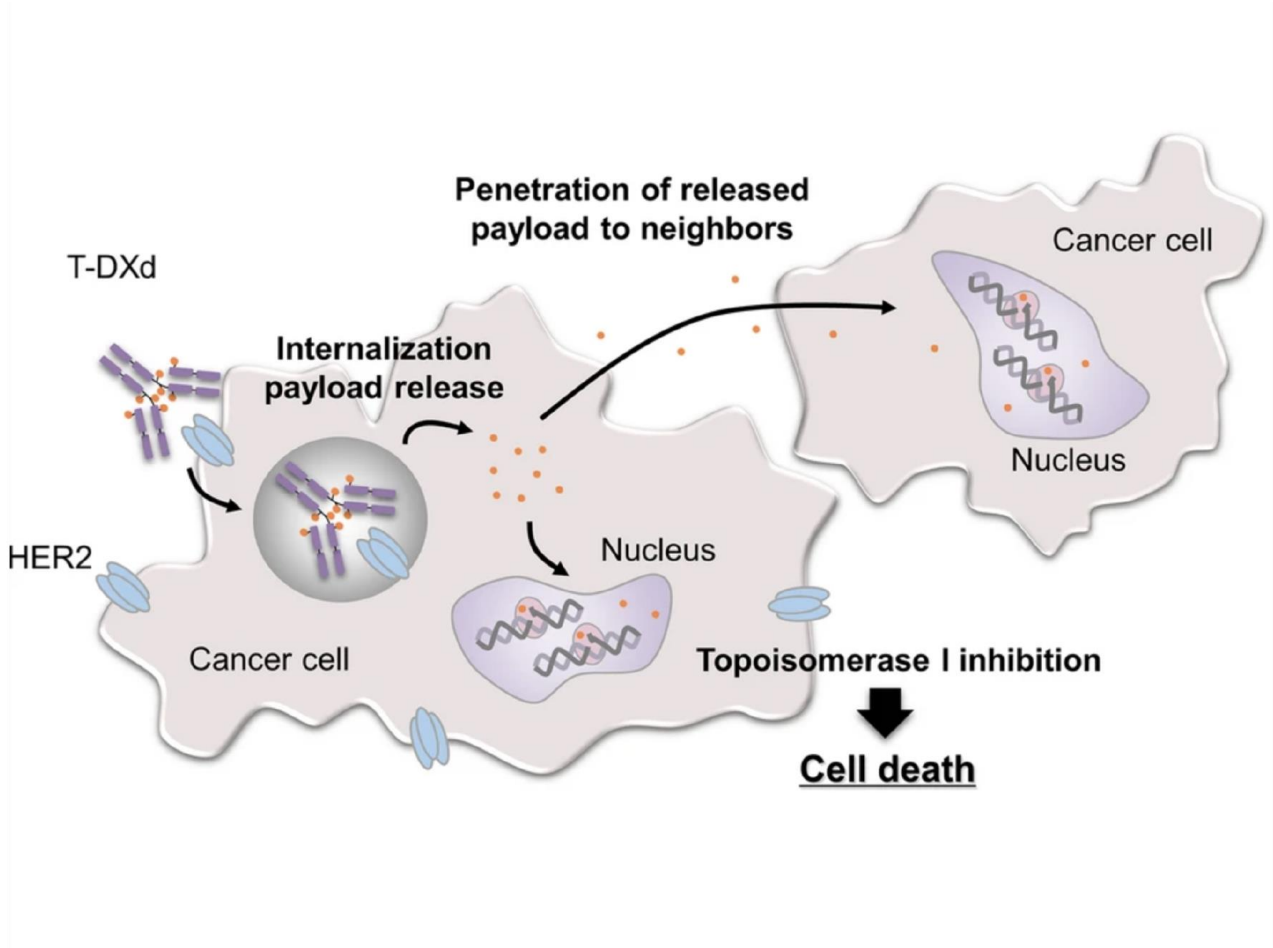
See Abstract 4029 Sukawa Y et al for more biomarker data

Before 1st line therapy			Before T-ACT trial		
HER2 status	IHC	FISH	HER2 status	IHC	FISH
+	3	-	+	3	+
+	3	-	+	3	+
+	3	-	+	3	+
+	3	-	+	2	+
+	3	-	+	2	+
+	3	-	-	1	+
+	3	-	-	1	-
+	3	-	-	1	+
+	3	-	-	1	-
+	2	+	-	1	+
+	3	-	-	0	-
+	3	-	-	0	-
+	3	-	-	0	-
+	3	-	-	0	-
+	2	+	-	0	-
+	2	+	-	0	-

Definition of HER2 positive: IHC3+ or IHC2+ with FISH positive

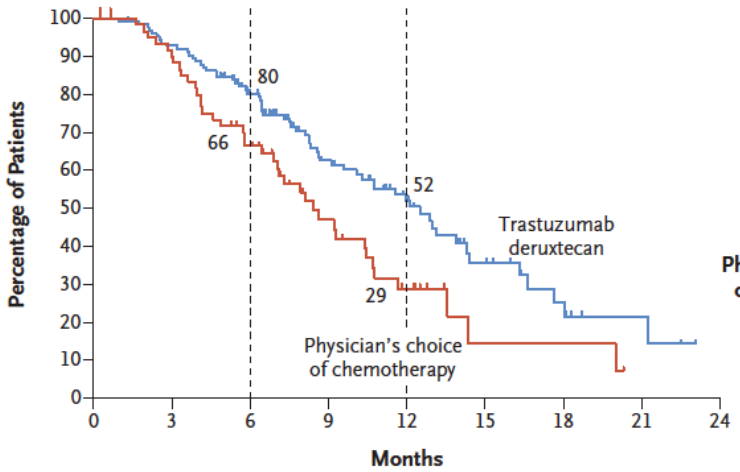
Sukawa et al., ASCO 2018

Antibody-Drug Conjugate (ADC)
Trastuzumab – Deruxtecan



Shitara et al Gastric Cancer 2021

Drittlinientherapie mit T-DXd



	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)

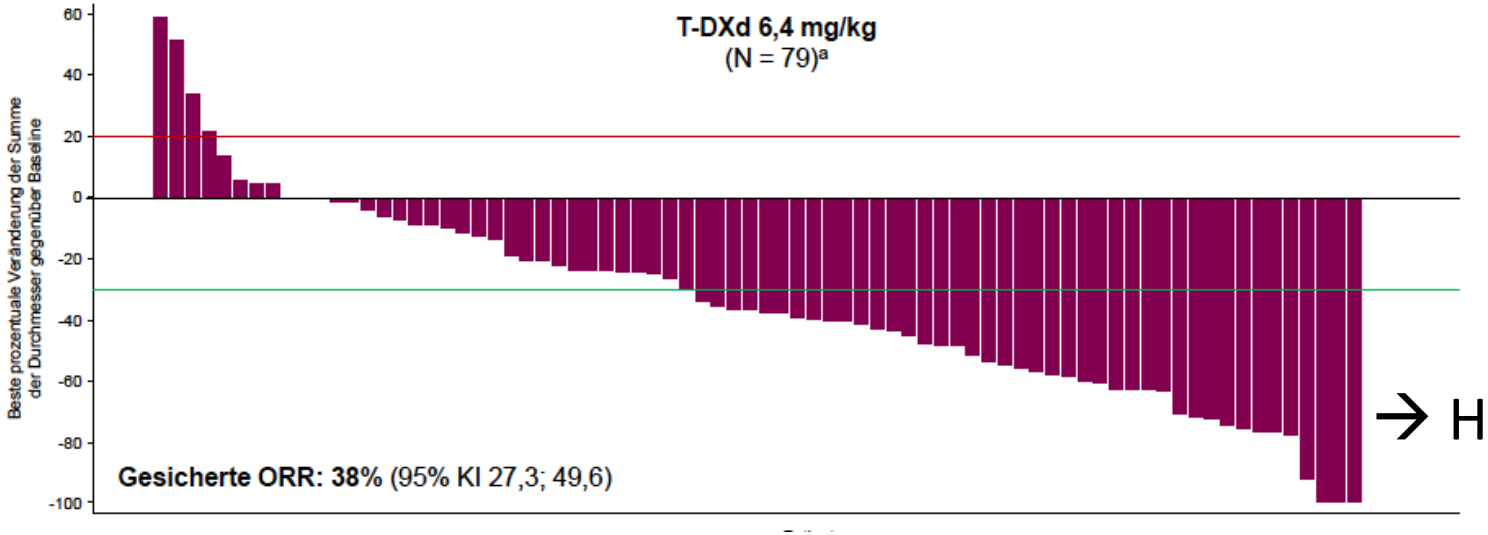
Hazard ratio for death, 0.59
(95% CI, 0.39–0.88)
P=0.01

ORR 51%
mPFS 5.6 Monate

→ HER2 Positivität bei 30% Rebiopsie

Shitara et al., NEJM 2020

Zweitlinientherapie mit T-DXd



ORR 38%
mPFS 5.5 Monate

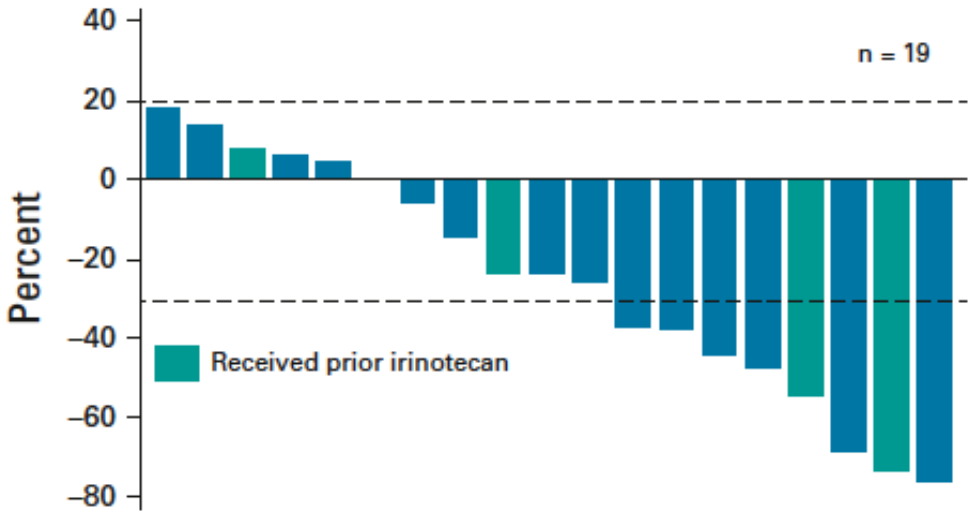
→ HER2 Positivität bei 100% Rebiopsie

→ Zulassung nach vorheriger Trastuzumabtherapie

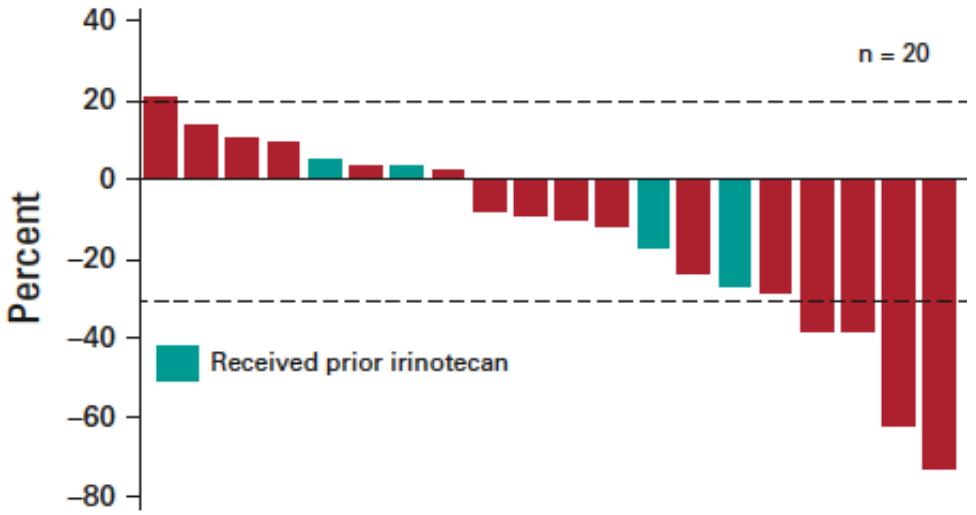
VanCutsem et al Lancet Oncol 2023

Wirksamkeit bei HER2 low?

IHC 2+/ISH-



IHC 1+



Yamaguchi et al JCO 2022

MSI-H - Agnostische Zulassung

Pembrolizumab in MSI-H Tumoren

- Kolorektalkarzinom (nach FU basierter Therapie)
- Dünndarmkarzinom (nach Therapie)
- **Magenkarzinom (nach Therapie)**
- Biliären Tumoren (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)	–

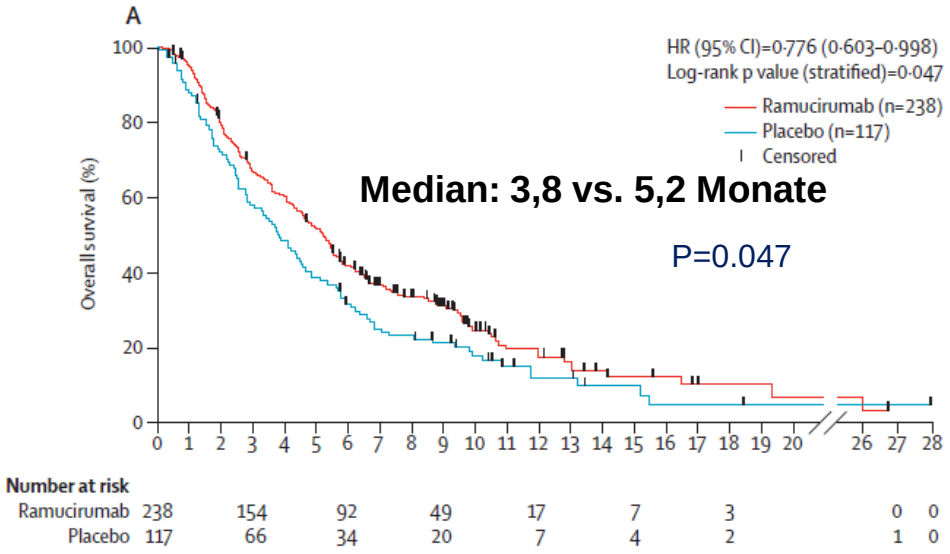
NOTE. Efficacy analyses included all patients who received at least one dose of pembrolizumab. Only confirmed responses are included. Response was assessed per RECIST version 1.1 by independent central radiologic review.

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.

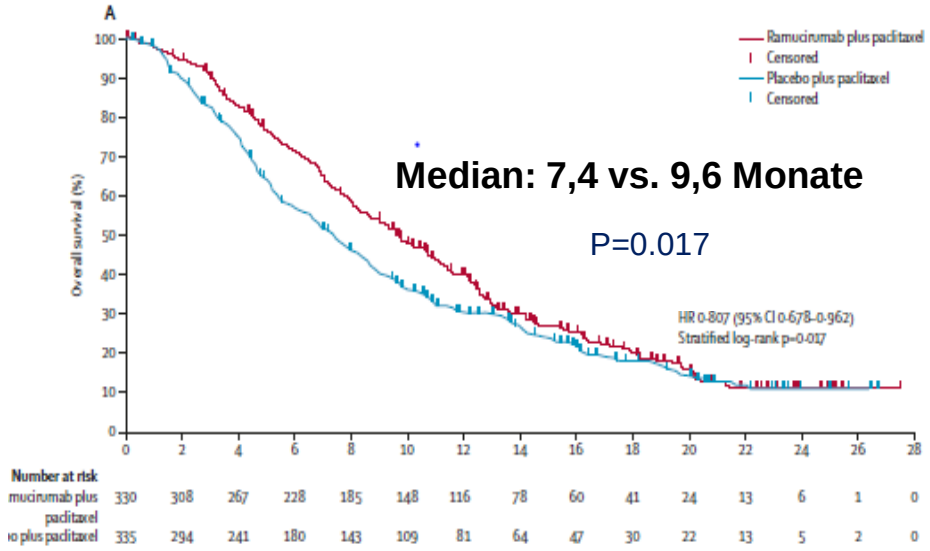
Marabelle et al., JCO 2020

Zweitlinie - Ramucirumab

Ramucirumab versus BSC



Paclitaxel + /- Ramucirumab

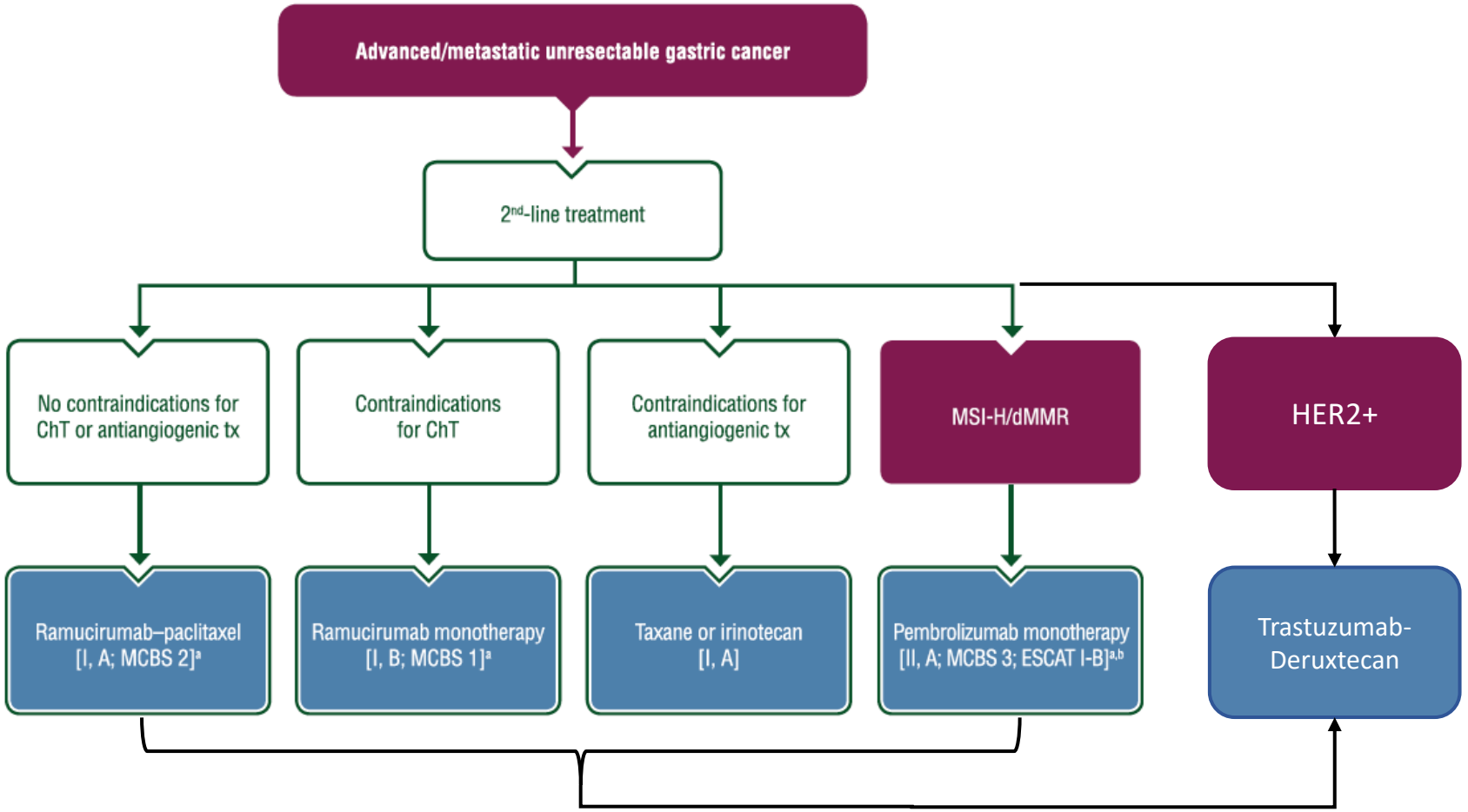


Hubertus Wald Tumorzentrum
Universitäres Cancer Center Hamburg
Ein Kompetenznetzwerk des UKE

Fuchs et al., Lancet Oncol 2014,
Wilke, Lancet Oncol 2014

ISRAELITISCHES KRANKENHAUS HAMBURG
AKADEMISCHES LEHRKRANKENHAUS DER UNIVERSITÄT HAMBURG
GEGRÜNDET 1839

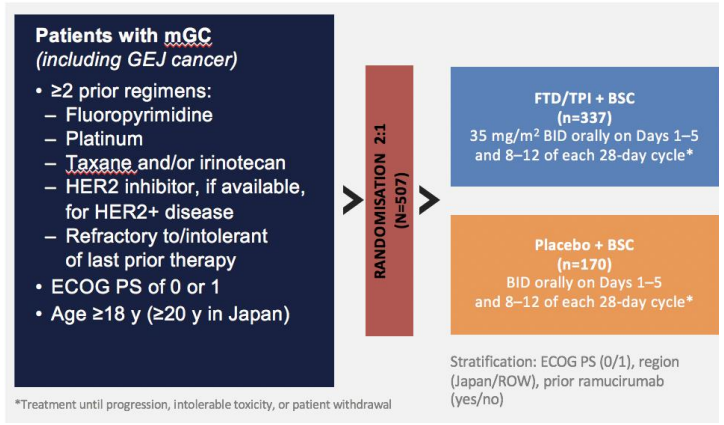
Leitlinienempfehlung Zweitlinie

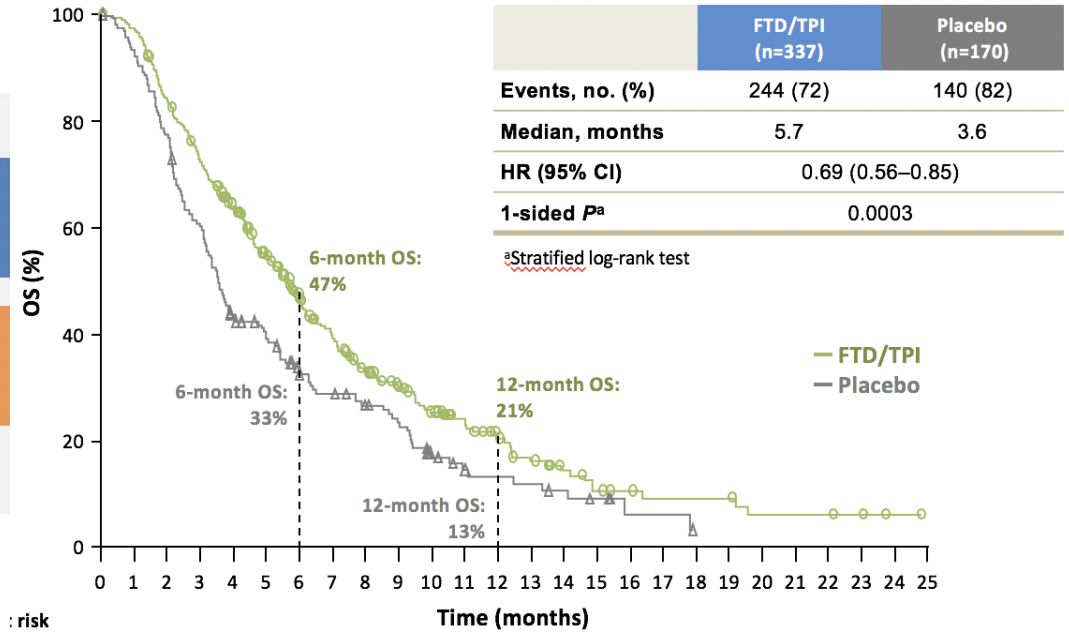


adapted Lordick et al 2022

Drittlinie-/Salvagetherapie

TAGS





	FTD/TPI (n=337)	Placebo (n=170)
Events, no. (%)	244 (72)	140 (82)
Median, months	5.7	3.6
HR (95% CI)	0.69 (0.56–0.85)	
1-sided *P*[a]	0.0003	

[a]Stratified log-rank test

Shitara et al., Lancet Oncol 2018

Biomarkerbasierte Salvagetherapien

- NTKR – Entrectinib/Larotrectinib

Off label

- HER2 low – Trastuzumab Deruxtecan
- MET Amplifikation – Crizotinib
- FGFR2 Amplifikation – Futibatinib
- BRCA/-ness – PARPi (+/- PD-1i)
  → Artzenroth et al Poster heute abend
- …..

Yamaguchi et al 2022, Aparicio et al 2021, Meric-Bernstam et al 2022

Vielen Dank für Ihre Aufmerksamkeit

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