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Das Leitlinienportal

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DGHO
DEUTSCHE GESELLSCHAFT FÜR HÄMATOLOGIE UND MEDIZINISCHE ONKOLOGIE

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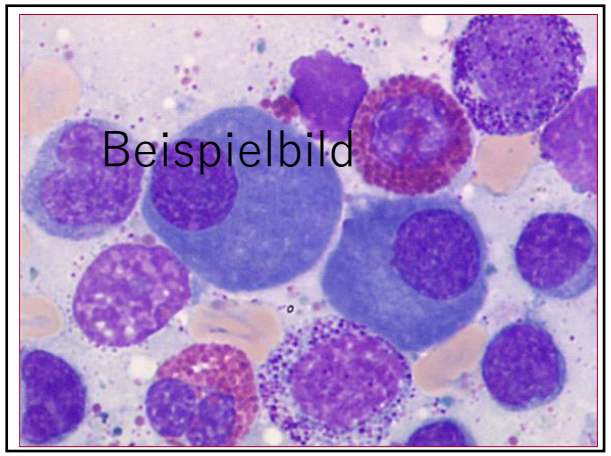
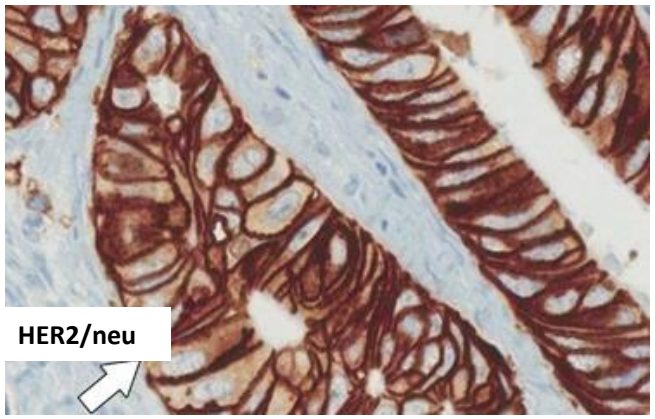
Ösophagusleitlinie

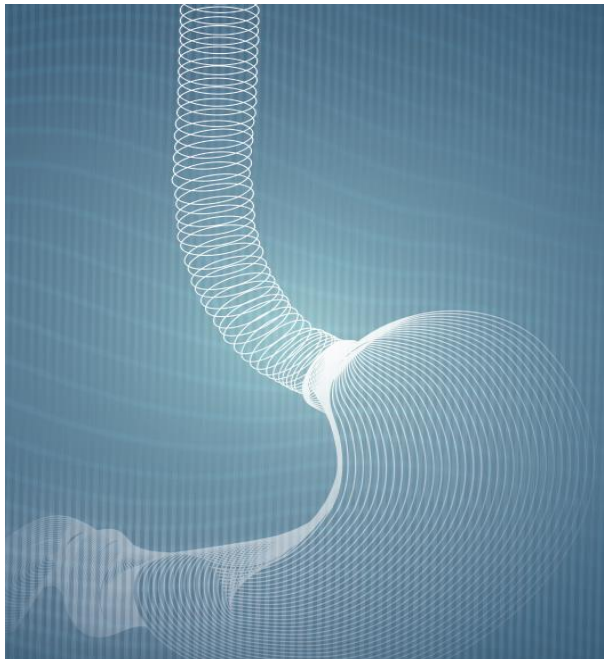
Prof. Sylvie Lorenzen

ONKOPEDIA – Online-Seminar

21.02.2025



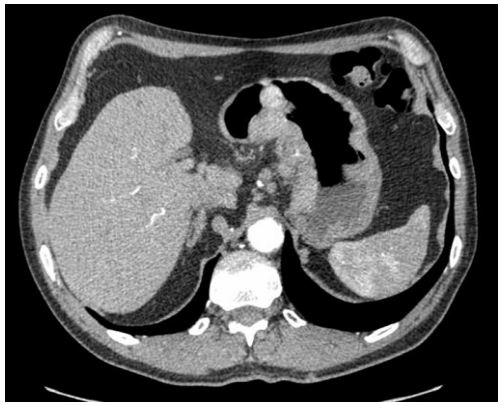


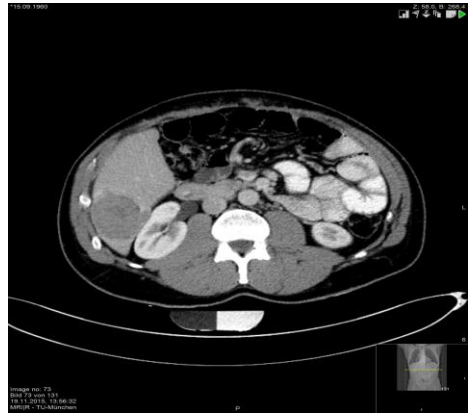


Fallbeispiel

Leitlinie

S. T., weiblich, Jahrgang 1965





Anamnese: seit 3 Monaten Dysphagie
und 4 kg Gewichtsabnahme
ÖGD: Tumor am gastro-ösophagealen Übergang
CT: keine Fernmetastasen
Klinische Klassifikation: Stadium uT3, uN+, cM0
Perioperative Therapie mit FLOT bis 4/23; ypT3, ypN0, M0, G2, R0 ; gute klinische und histopathologische Regression (II nach Becker)

10/24:neue singuläre Lebermetastase:
M1(hep), Her2-, MSS, CPS 4, CLDN 18.2 +
PNP Grad 2 nach 8xFLOT perioperativ

Kasuistik: Oktober 2024!
Wie würden Sie entscheiden:
6 Monate nach Abschluss FLOT adjuvant

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A Re-Exposition mit systemischer CTX mit FLOT

B Systemische CTX mit Folfox

C Systemische CTX mit Folfox + IO

D Systemische CTX mit Folfox + Zolbetuximab

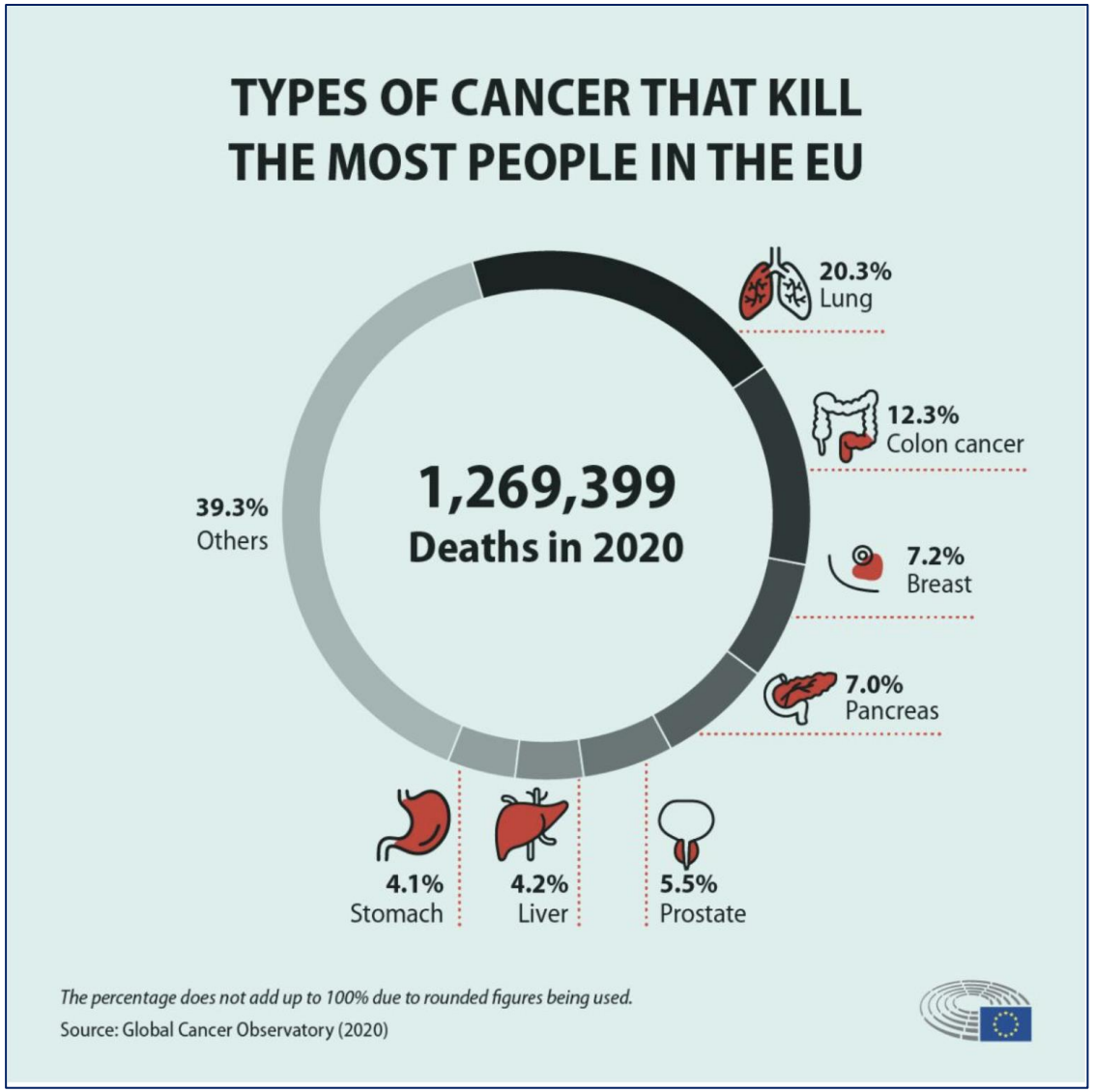
E FOLFIRI

F Ramucirumab + Paclitaxel

Entwicklung in der Krebsmedizin

- Krebs führende Todesursache in 2030
- Gastrointestinale Tumoren größte Gruppe
- Technische Entwicklungen rasant (omics, KI)
- Therapien immer individueller

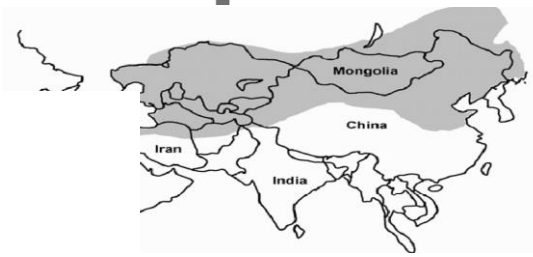
Epidemiologie – Krebs bedingte Todesursachen Europa 2020



Gastrointestinale Tumoren Nr. 1

Epidemiologie

SCC vs AC



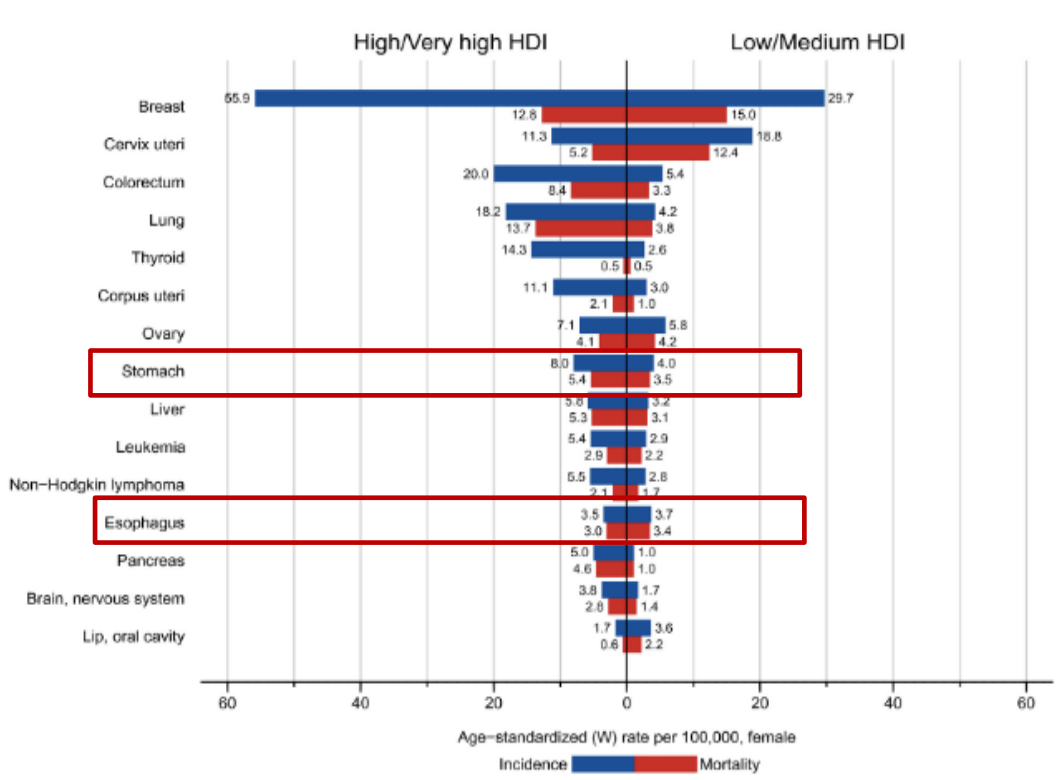
esophageal cancer belt

Plattenepithel Karzinom (SCC)
- zentral Asien, Südost Asien
- Rauchen & ETOH
- prox. Lokalisation
- 50% PD-L1 Expression (zB TPS 1+)

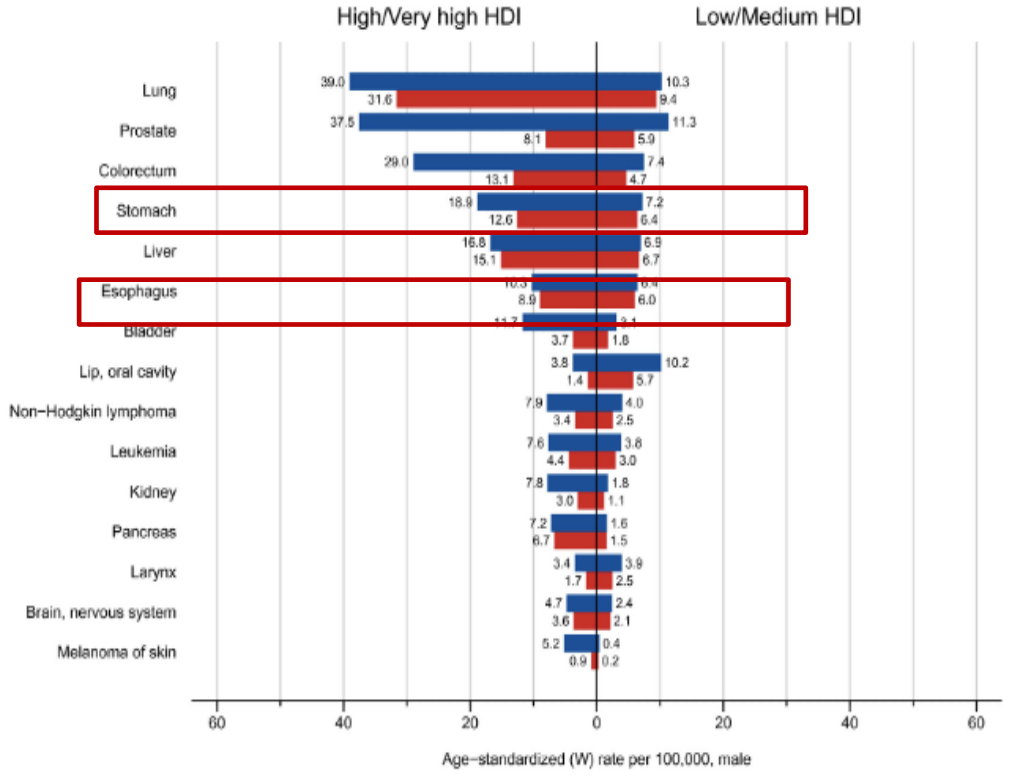
Adeno Karzinom (AC)
- Westen
- Reflux & Übergewicht
- distaler Ösophagus
- ca. 15%TPS 1+ [1,8-12]

1. Salem et al. 2018. *The Oncologist*. 2. ORIENT-15. 3. ESCORT _1st. 4. ESCORT_2L 5. CM648. 6. ATTRACTION-03. 7. CM648. 8. ATTRACTION-02. 9. CM649. 10. JAV-300. 11. ATTRACTION-04. 12. JAV100 maintenance

Global Cancer Statistics 2020: GLOBOCAN Inzidenz und Mortalität weltweit für 36 Tumore in 185 Ländern



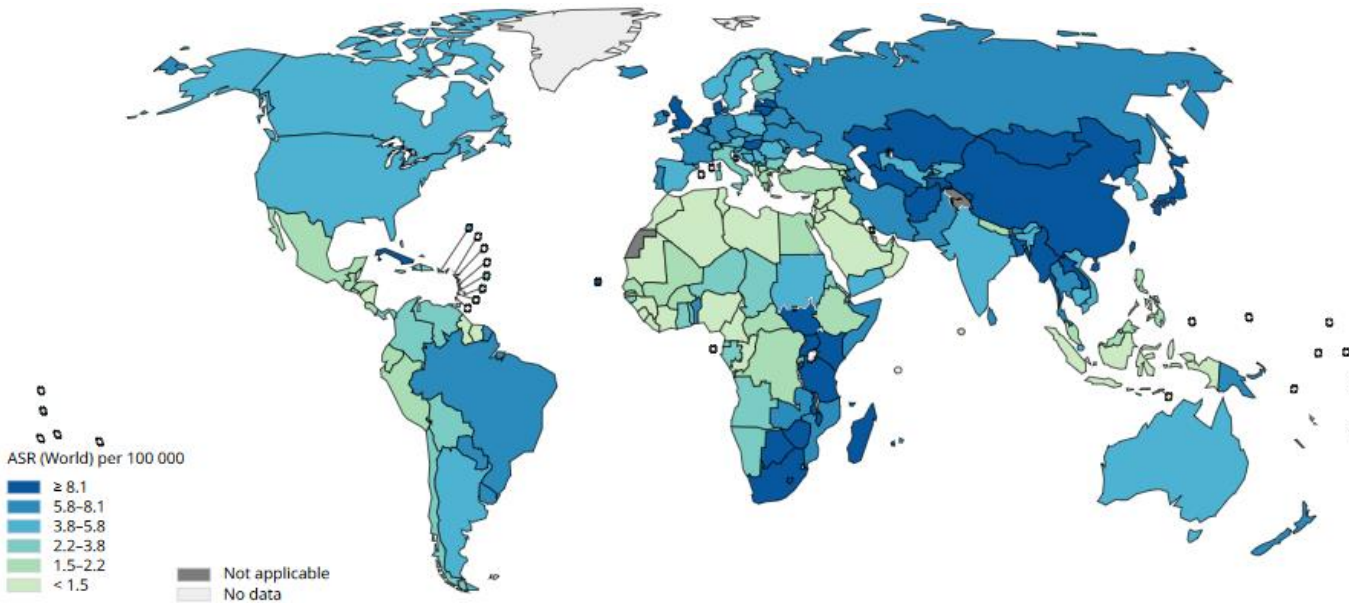
Frauen

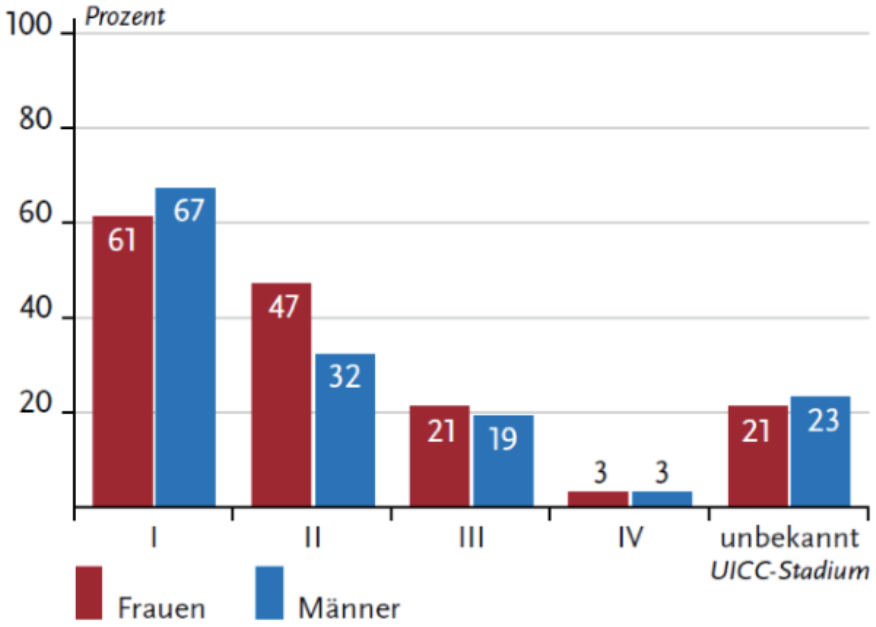


Männer

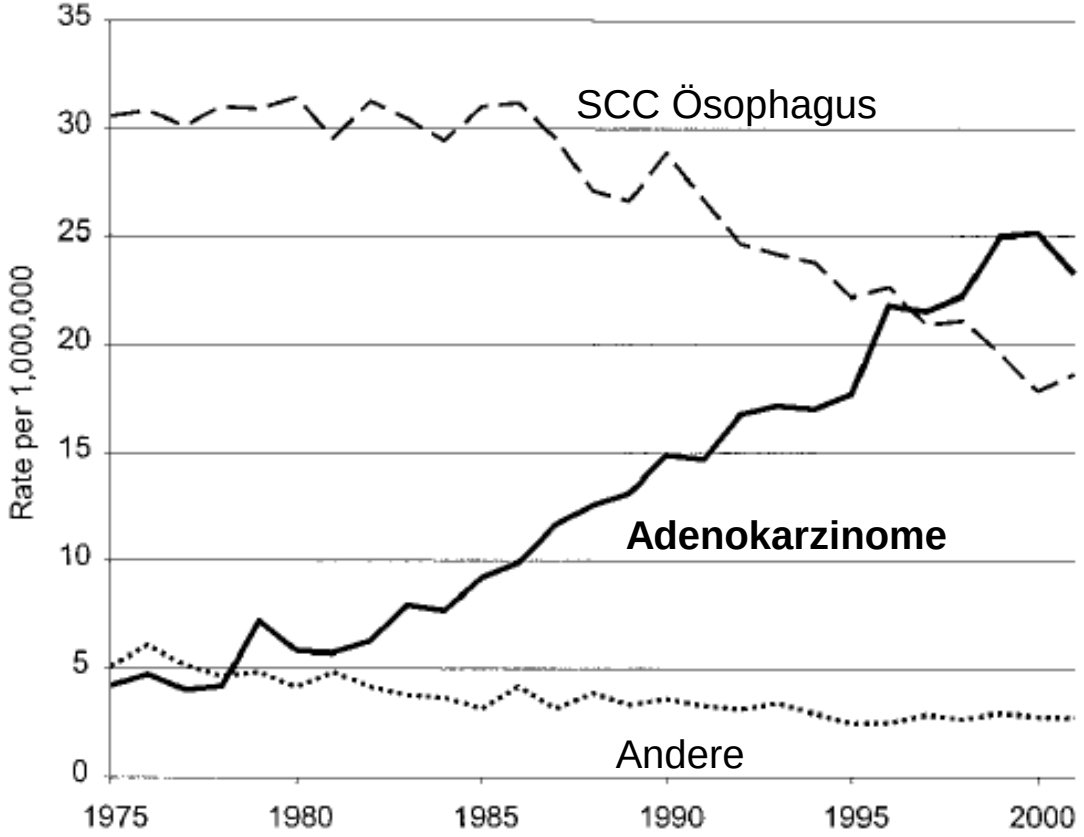
CA A Cancer J Clinicians, Volume: 71, Issue: 3, Pages: 209-249, First published: 04 February 2021, DOI: (10.3322/caac.21660)

Plattenepithelkarzinom des Ösophagus: Inzidenz und Prognose

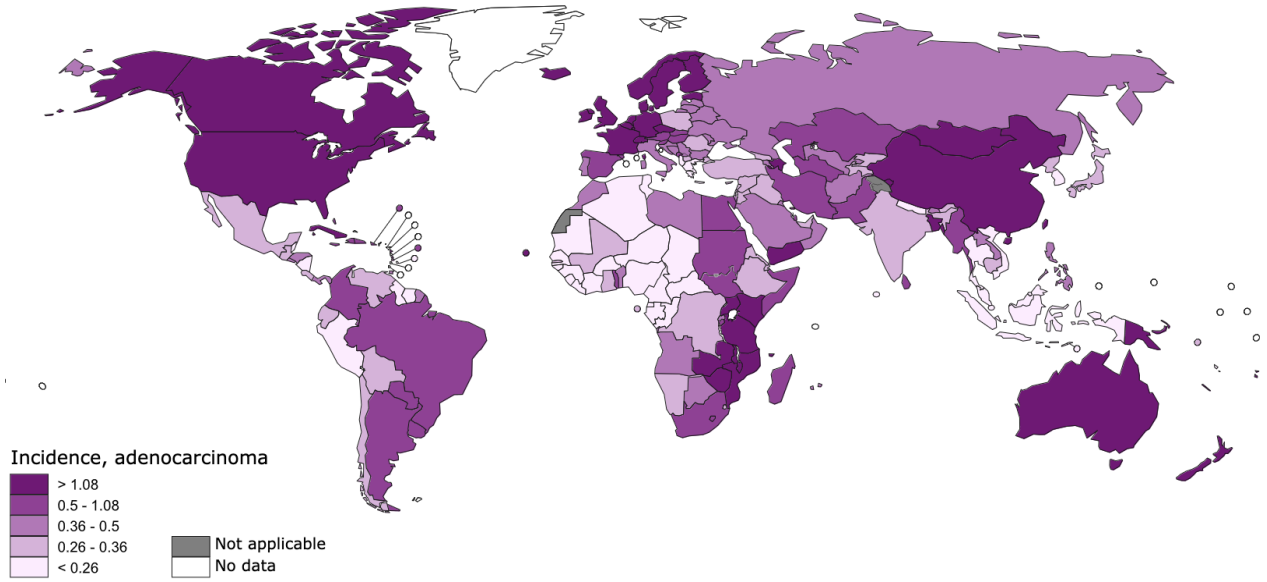




Adenokarzinome am ösophagogastralen Übergang nehmen stark zu !



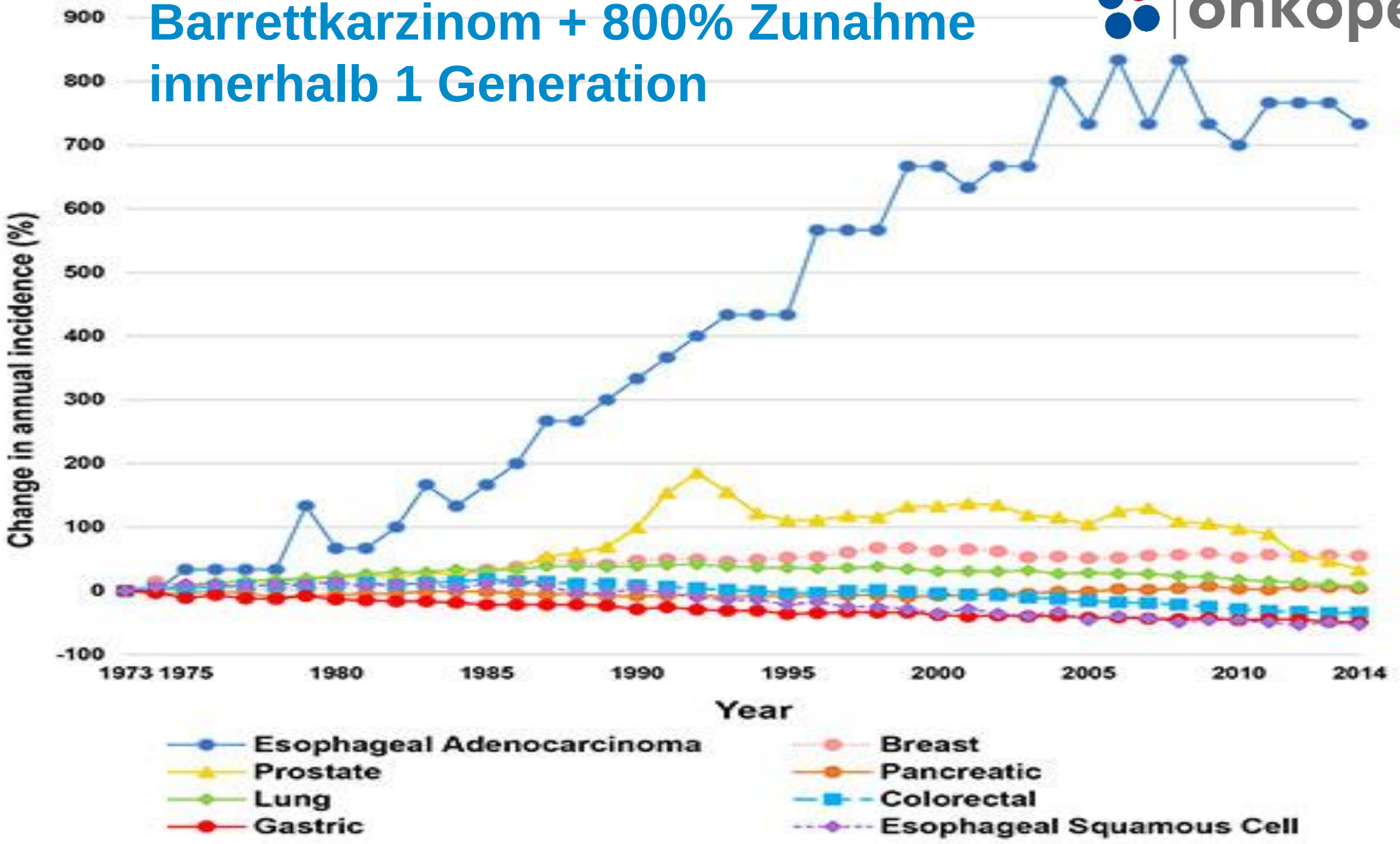
Pohl & Welch. *J Natl Canc Inst* 2005



Morgan et al, Gastroenterology 2022;163:649–658

Barrettkarzinom + 800% Zunahme innerhalb 1 Generation

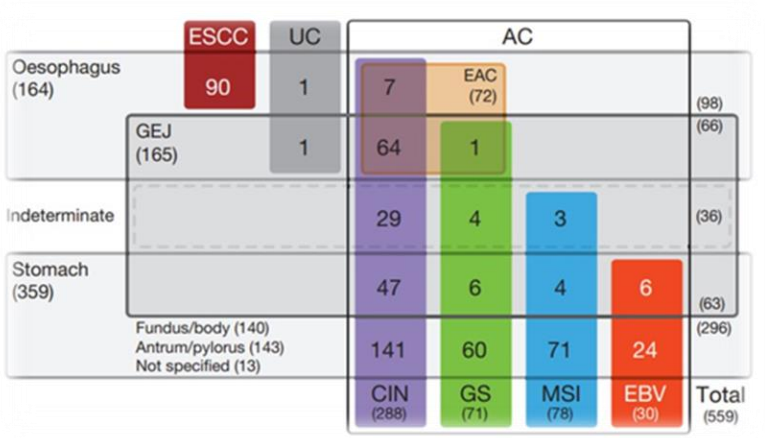
onkopedia

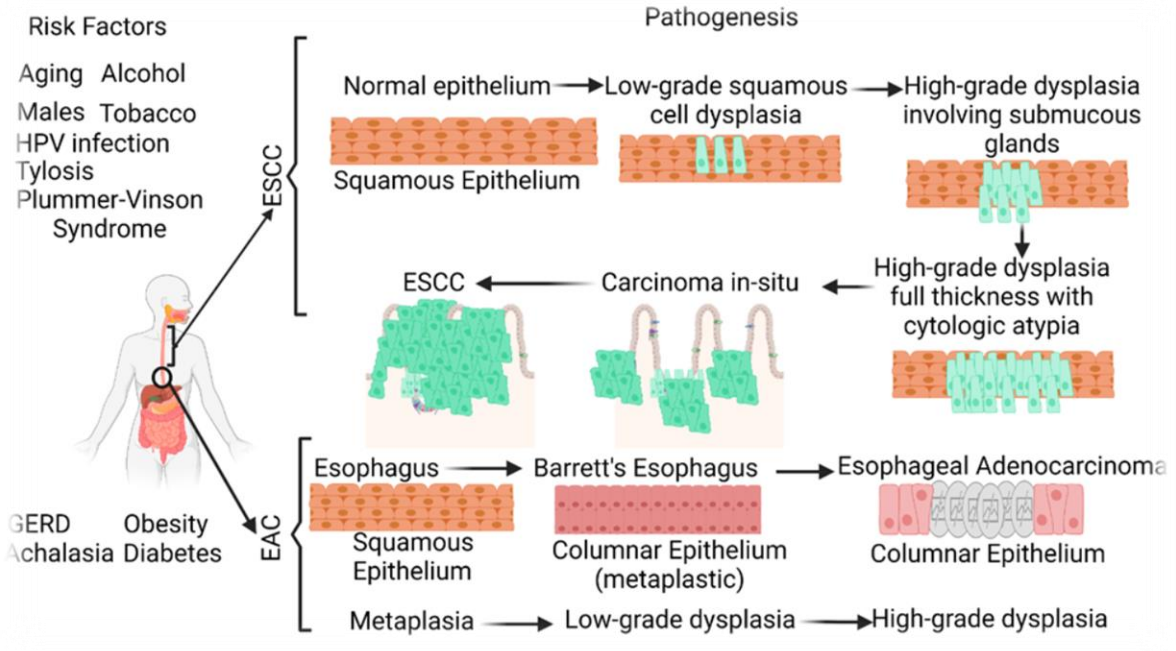


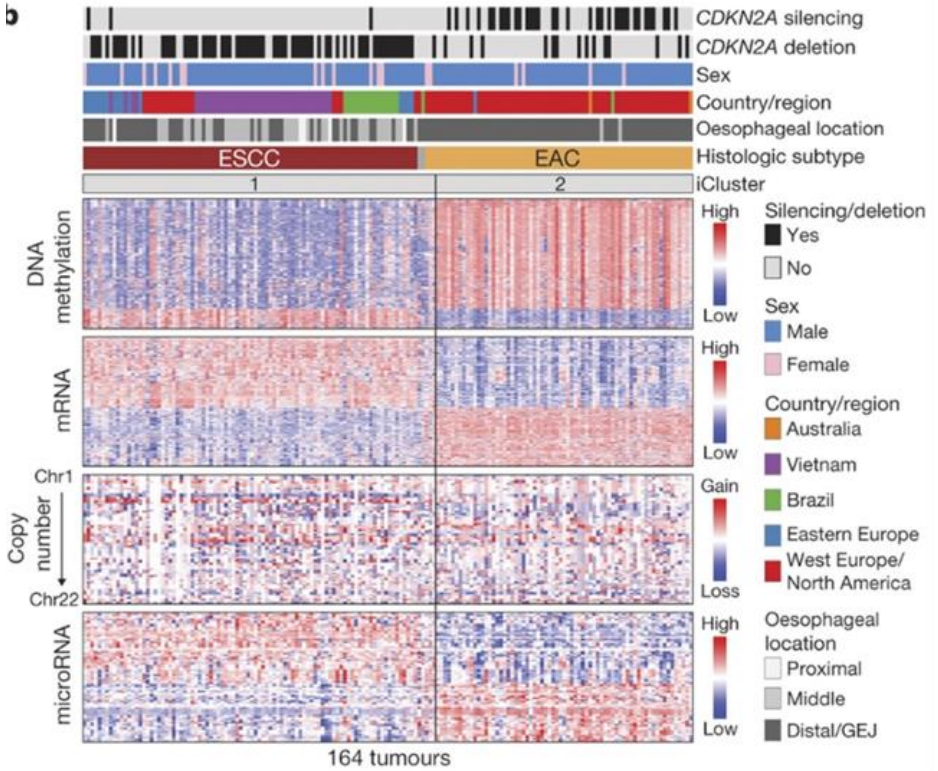
POHL & WELCH. J NATL CANCER INST. 2005 JAN 19;97(2):142-6

Biologie

Adeno vs. Platte= Genomisch Genese komplett unterschiedlich

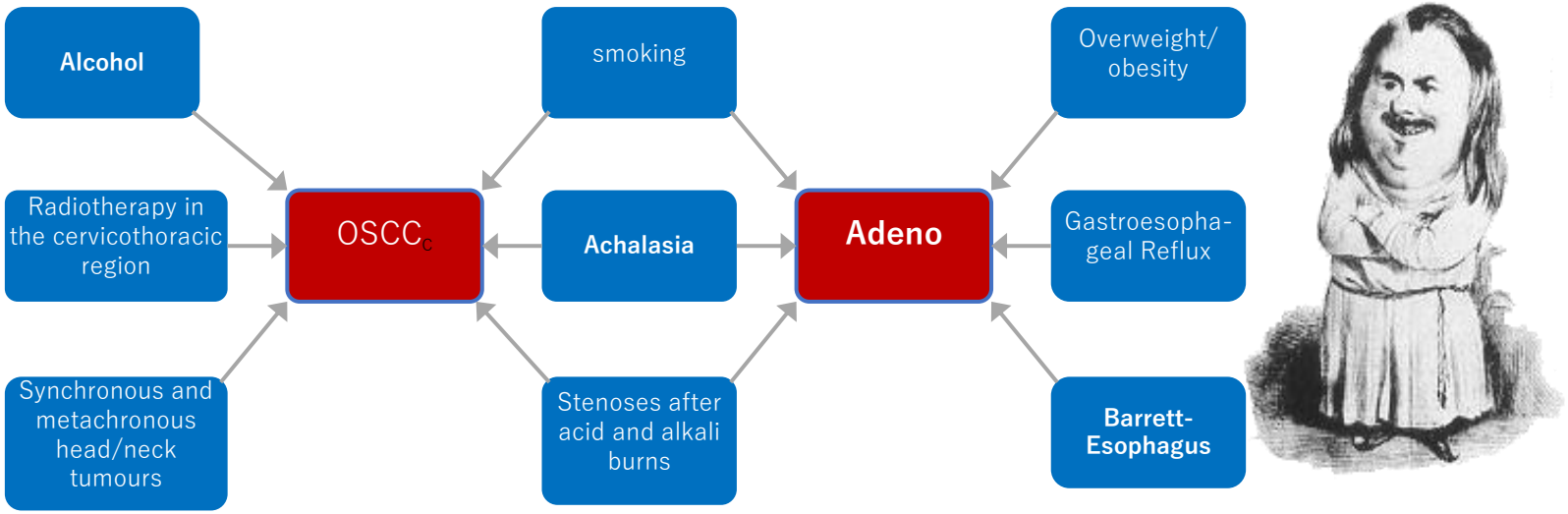






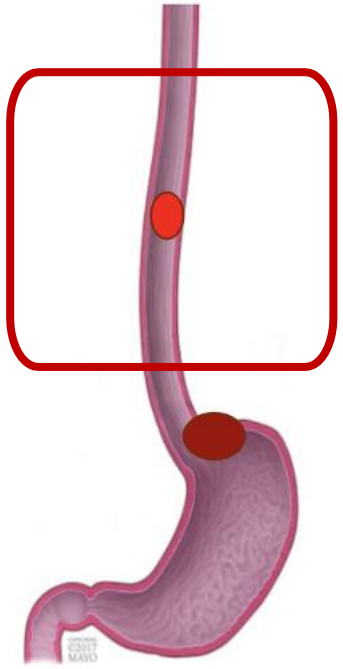
Nature 2017 Jan 12;541(7636) 169-175
Rai V et al. ; Int. J. Mol. Sci. 2023, 24, 3316

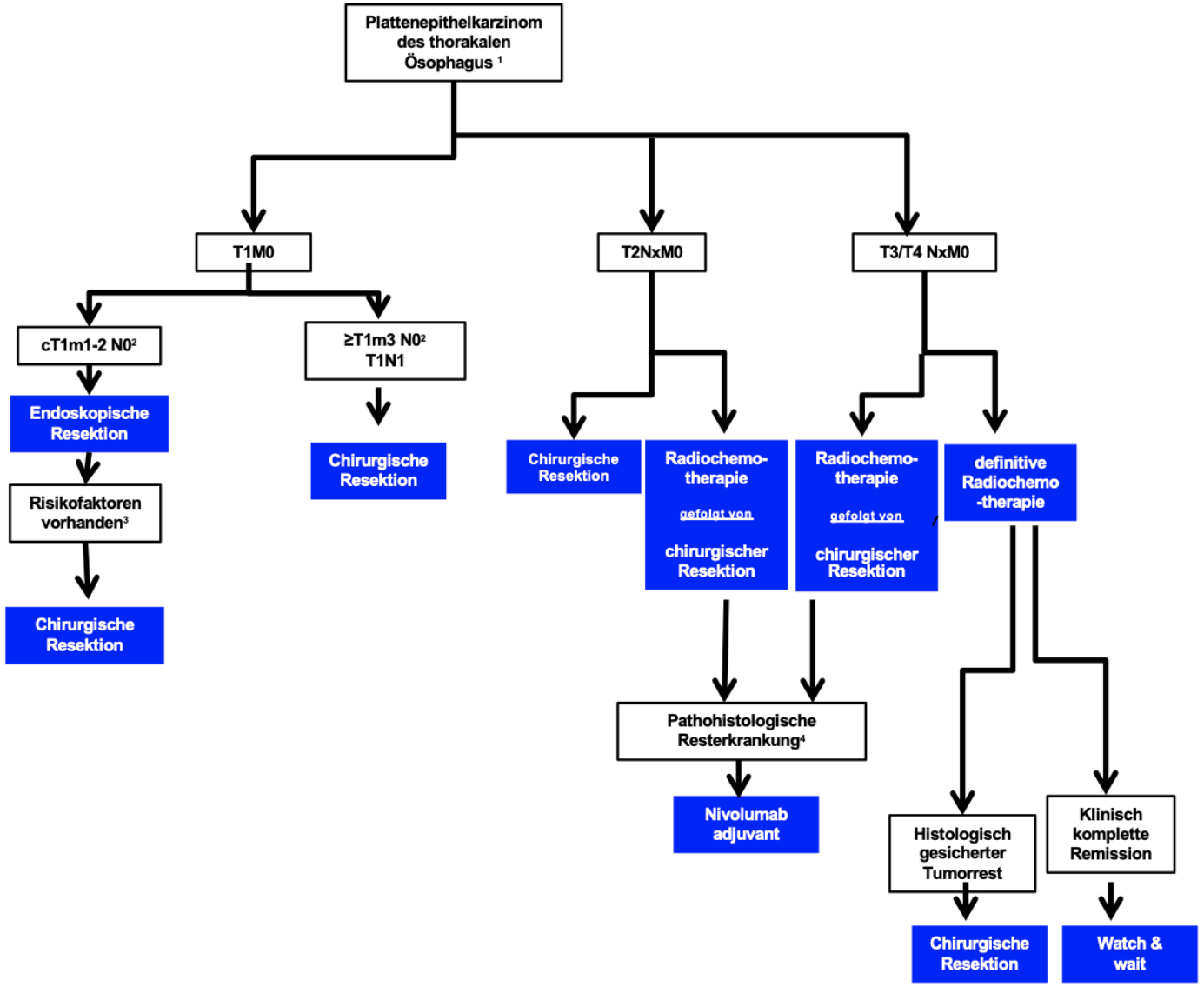
Risikofaktoren für die Entstehung



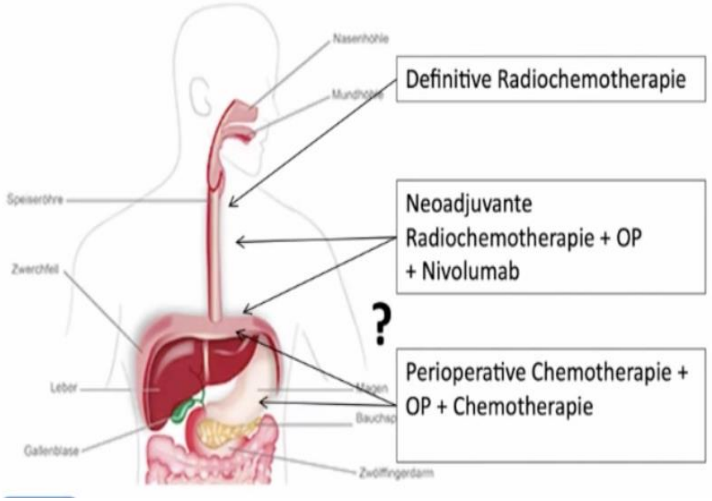
Therapie

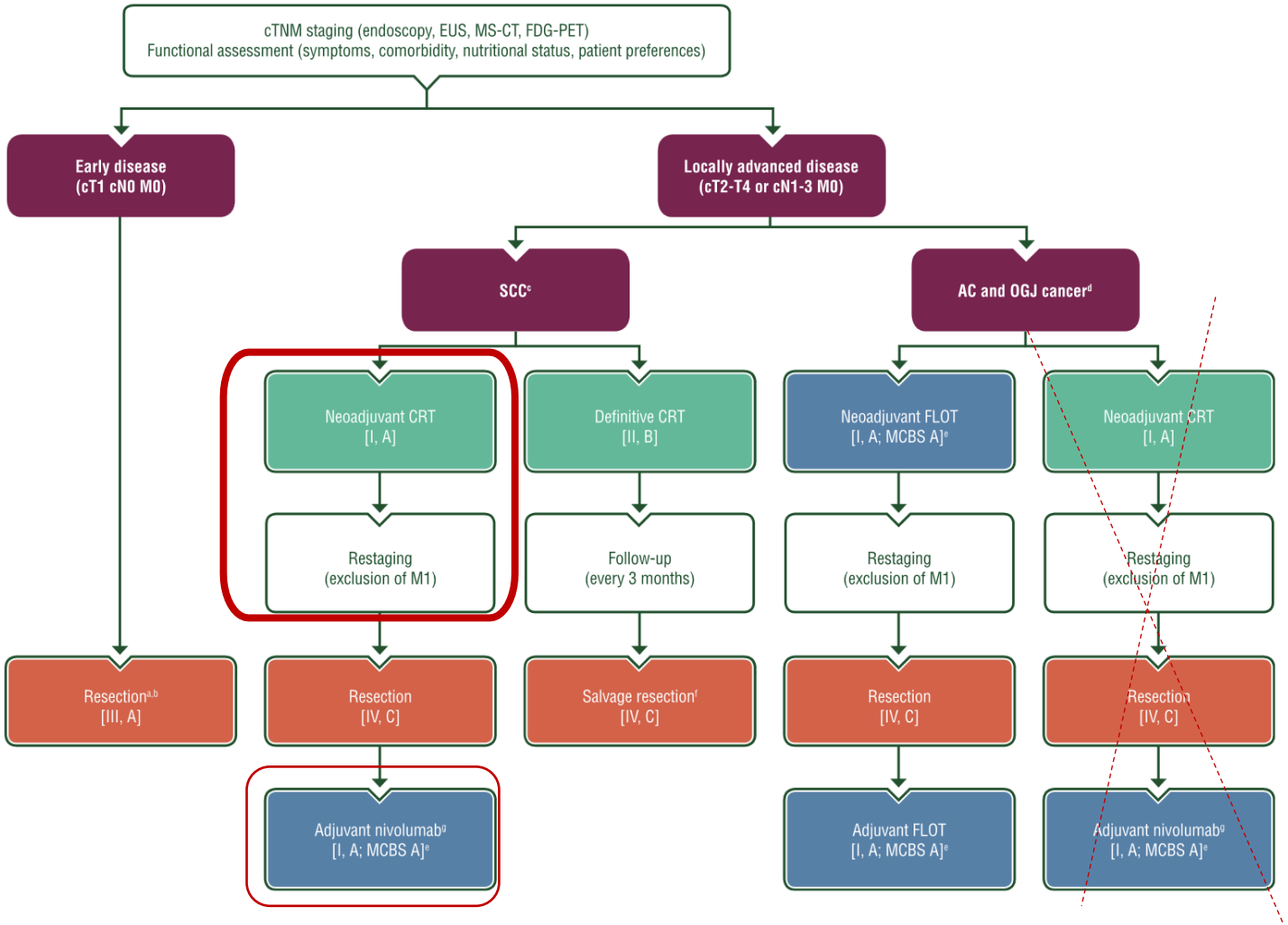
Onkopedia Algorithmus –Primärtherapie beim Plattenepithelkarzinom (update 10/2024)





ESMO Leitlinien Ösophagus Ca 2022

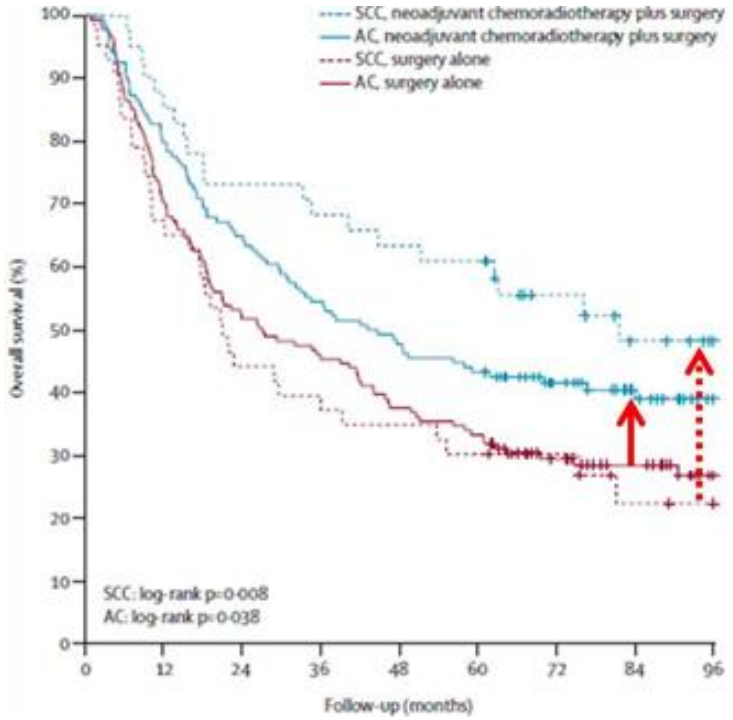




Obermannova et al. Ann Oncol 2022

CROSS- Trial: Adeno vs. SCC

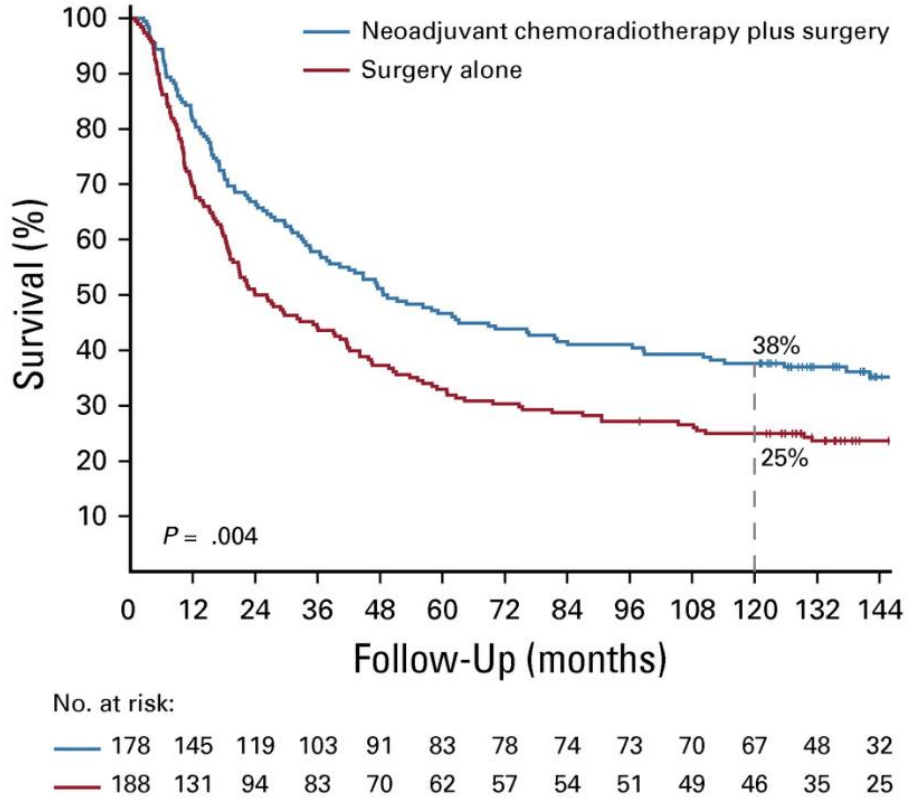
	Neoadjuvant chemoradiotherapy plus surgery (n=178)	Surgery alone (n=188)
Age, years	60 (55–67)	60 (53–66)
Sex		
Women	44 (25%)	36 (19%)
Men	134 (75%)	152 (81%)
Tumour histology		
Squamous cell carcinoma	41 (23%)	43 (23%)
Adenocarcinoma	134 (75%)	141 (75%)
Could not be established	3 (2%)	4 (2%)
Tumour length, cm	4 (3–6)	4 (3–6)
Tumour location		
Proximal third oesophagus	4 (2%)	4 (2%)
Middle third oesophagus	25 (14%)	24 (13%)
Distal third oesophagus	104 (58%)	107 (57%)
Oesophagogastric junction	39 (22%)	49 (26%)
Missing data	6 (3%)	4 (2%)

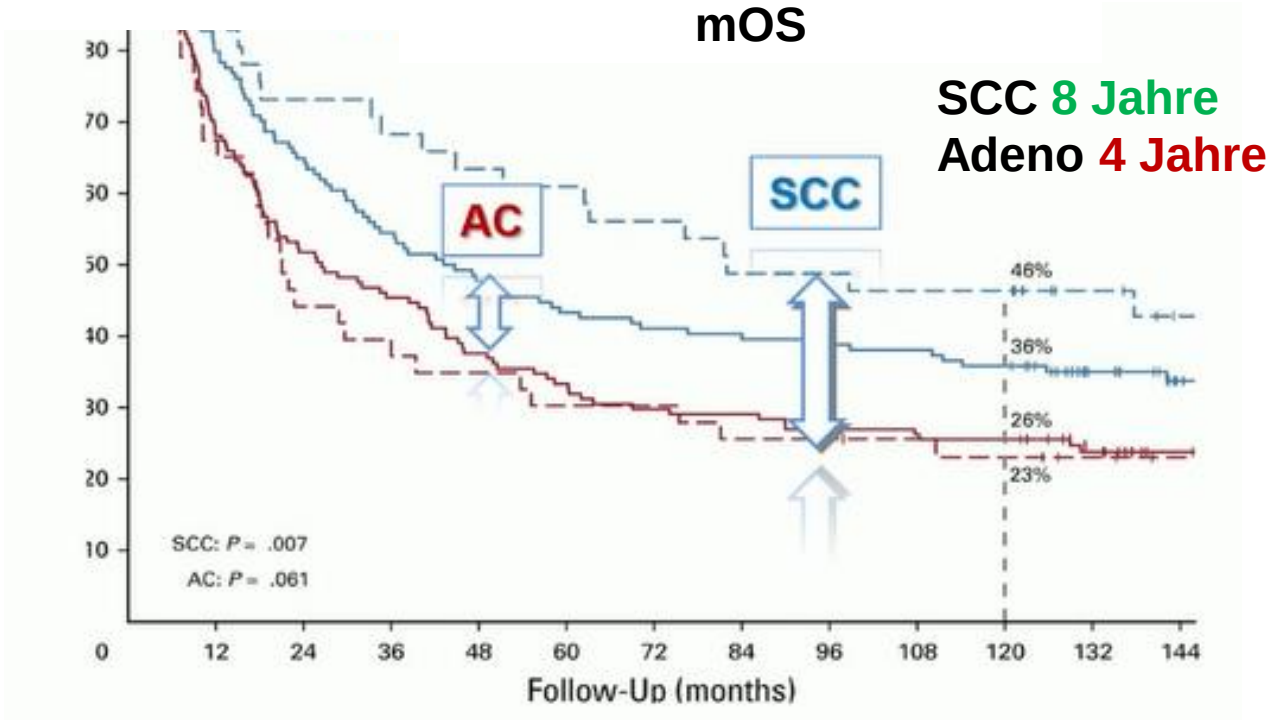


group. A pathological complete response was observed in 28 of 121 patients with adenocarcinoma (23%) versus 18 of 37 with squamous-cell carcinoma (49%) (P=0.008). A median of 15 lymph

Shapiro J, et al Lancet Oncol. 2015 Sep;16(9):1090-8

10-Jahres Update CROSS Trial - Neoadj RCht Ösophagus Ca (SCC/Adeno)





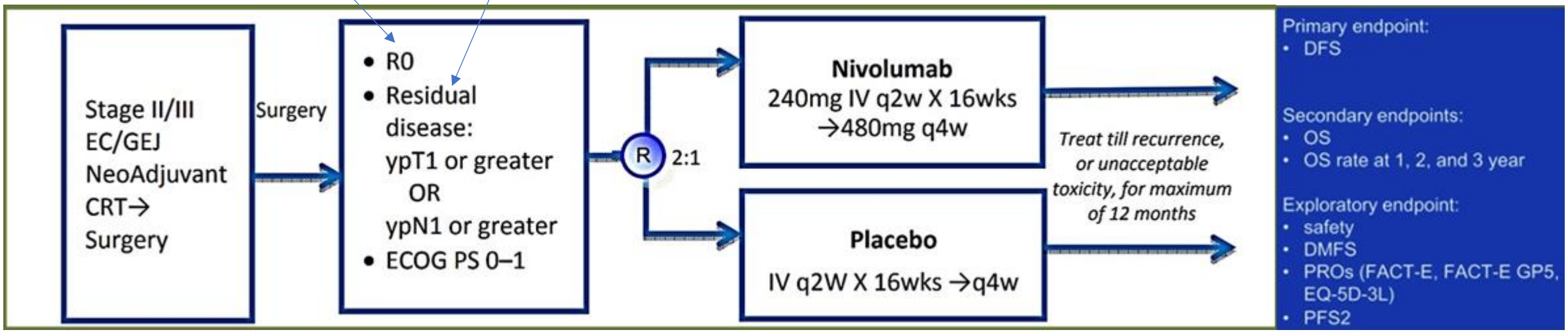
Überleben SCC @ 10 Jahren 46% vs. 23%; P = 0,007

Eyck BM; J Clin Oncol 2021 Jun 20;39(18):1995-2004

CM- 577 - Adjuvant Nivolumab für AC & ESCC

The NEW ENGLAND JOURNAL of MEDICINE
ESTABLISHED IN 1812 APRIL 1, 2021 VOL. 384 NO. 13

Adjuvant Nivolumab in Resected Esophageal or Gastroesophageal Junction Cancer



Median FU: ***24.4 mo (range 6.2- 44.9)***

Gebiete ***Europa (38%); Kanada & USA (32%), Asien (13%), andere (16%)***

Kelly et al. N Engl J Med 2021 Apr 1;384(13):1191-1203

Checkmate 577- DFS nach PD-L1 Expression

Key eligibility criteria
- Stage II/III EC/GEJC
- Adenocarcinoma or squamous cell carcinoma
- Neoadjuvant CRT + surgical resection (R0,[b] performed within 4-16 weeks prior to randomization)
- Residual pathologic disease
  - ≥ ypT1 or ≥ ypN1
- ECOG PS 0-1

Stratification factors
- Histology (squamous vs adenocarcinoma)
- Pathologic lymph node status (≥ ypN1 vs ypN0)
- Tumor cell PD-L1 expression (≥ 1% vs < 1%[c])

N = 794 → R 2:1
- n = 532 → **Nivolumab** 240 mg Q2W × 16 weeks then 480 mg Q4W
- n = 262 → **Placebo** Q2W × 16 weeks then Q4W

Total treatment duration of up to 1 year[d]

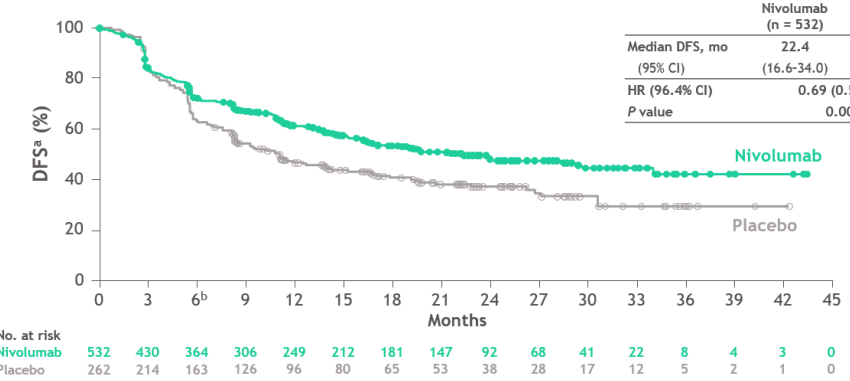
Primary endpoint:
- DFS[e]

Secondary endpoints:
- OS[f]
- OS rate at 1, 2, and 3 years

- Median follow-up was 24.4 months (range, 6.2-44.9)[g]

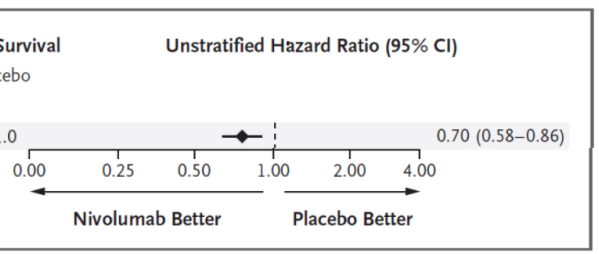
71% AC, 85% nicht-asiatische Patienten

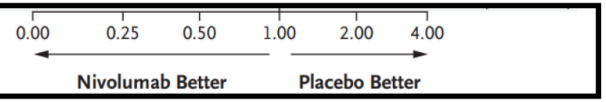
Disease-free survival (DFS)



	Nivolumab (n = 532)	Placebo (n = 262)
Median DFS, mo	22.4	11.0
(95% CI)	(16.6-34.0)	(8.3-14.3)
HR (96.4% CI)	0.69 (0.56-0.86)	
P value	0.0003[c]	

Subgroup	No. of Patients	Median Disease-free Survival (mo) Nivolumab	Placebo	Unstratified Hazard Ratio (95% CI)
Overall	794	22.4	11.0	0.70 (0.58–0.86)
Tumor-cell PD-L1 expression				
≥1%	129	19.7	14.1	0.75 (0.45–1.24)
<1%	570	21.3	11.1	0.73 (0.57–0.92)
Indeterminate or could not be evaluated	95	Not reached	9.5	0.54 (0.27–1.05)

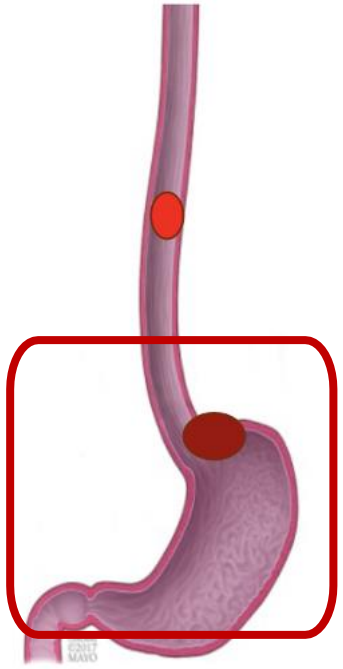


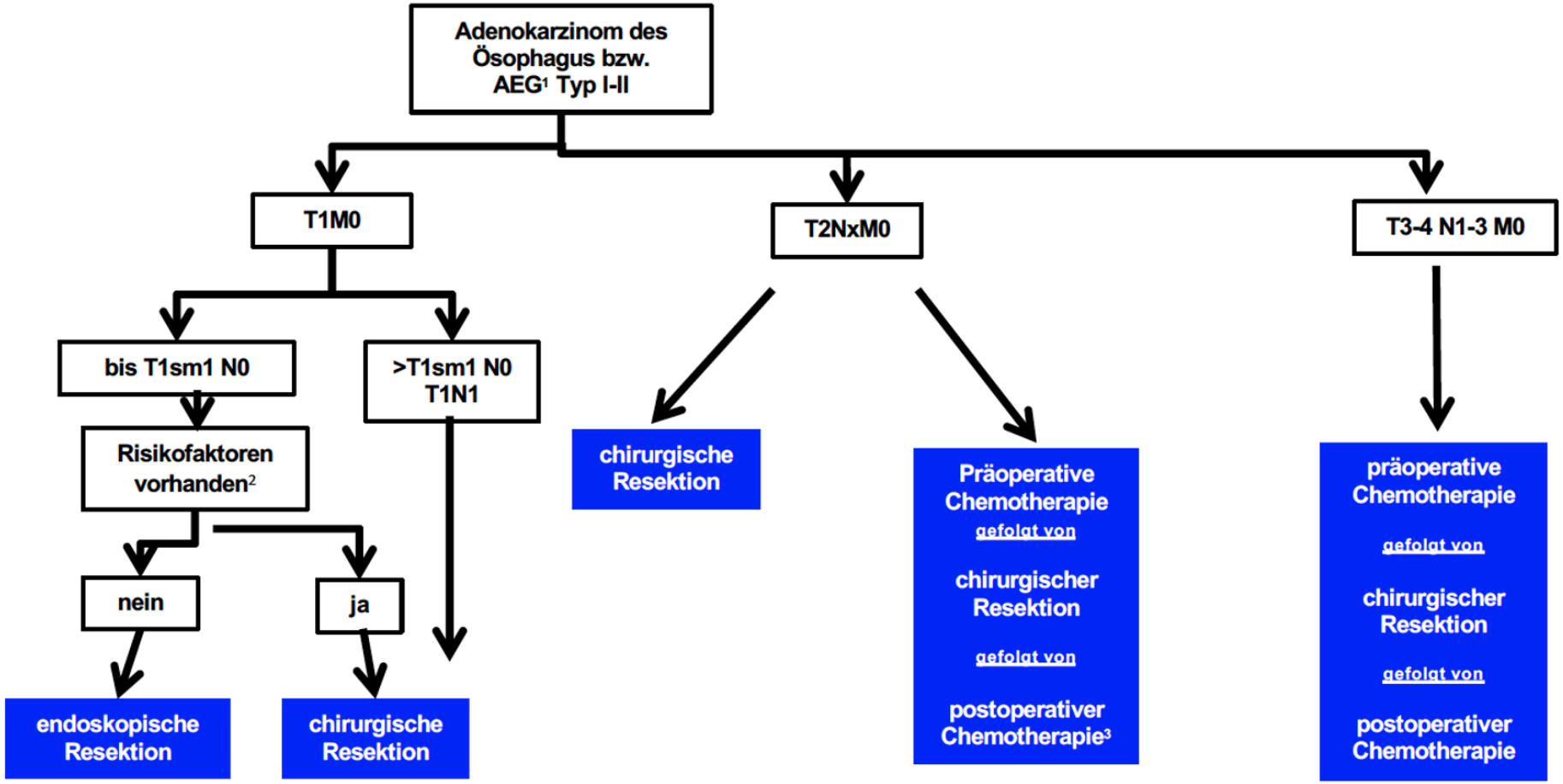


Subgroup	Median Disease-free Survival, months Nivolumab	Placebo	Unstratified Hazard Ratio (95% CI)
PD-L1 CPS expression			
≥5 (n = 371)	29.4	10.2	0.62 (0.46–0.83)
<5 (n = 295)	16.3	11.1	0.89 (0.65–1.22)
Tumor location at initial diagnosis			
Esophagus	462	24.0	8.3	0.61 (0.47–0.78)
Gastroesophageal junction	332	22.4	20.6	0.87 (0.63–1.21)

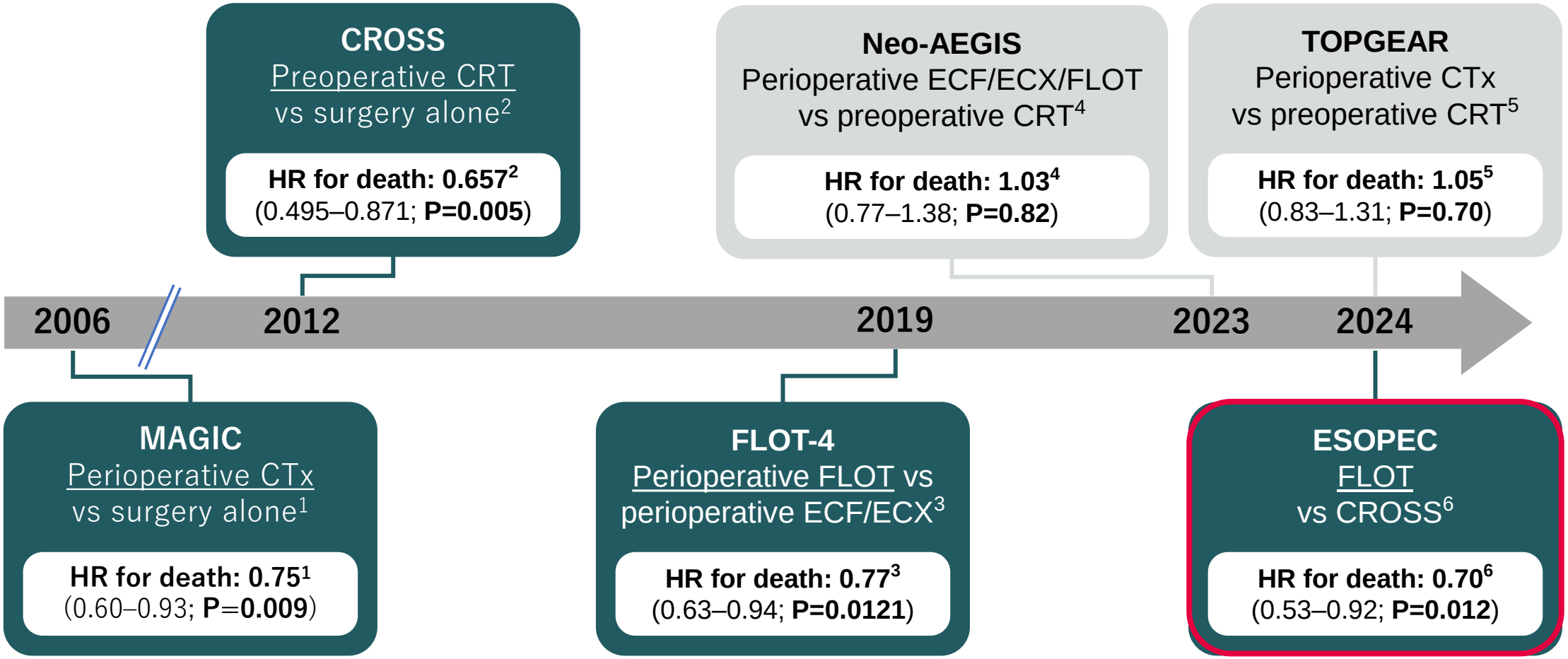
Kelly et al. N Engl J Med 2021 Apr 1;384(13):1191-1203

Onkopedia Algorithmus –Primärtherapie beim Adenokarzinom (update 10/2024)



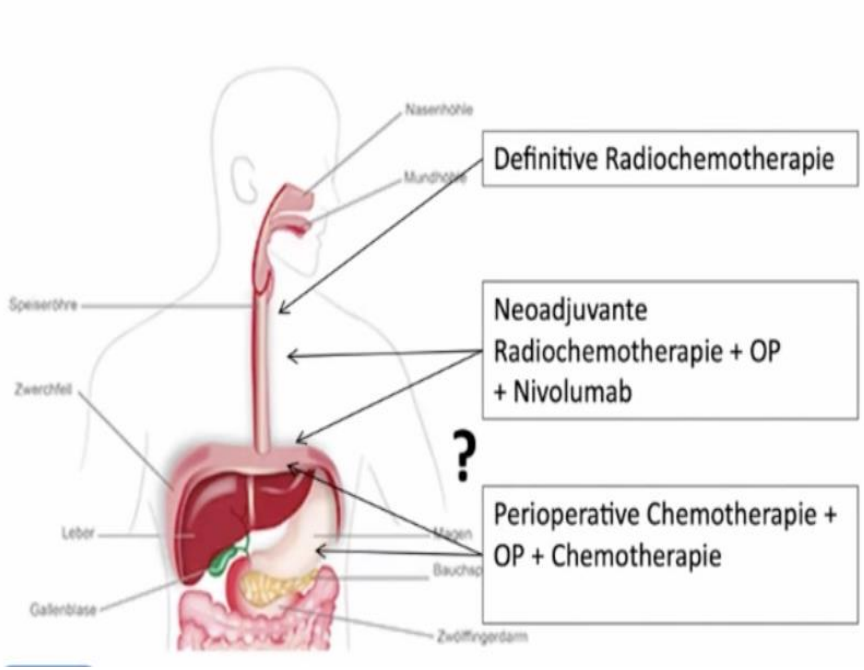


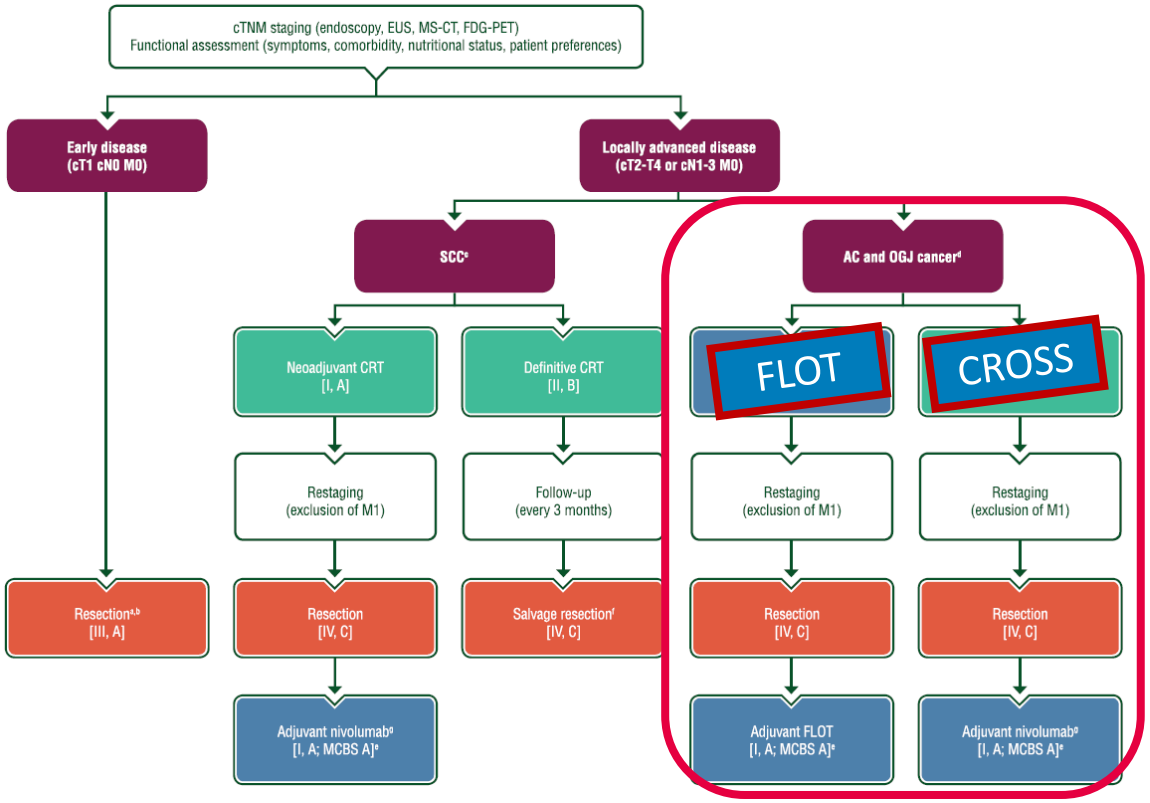
Neoadjuvante Studien in GEA



- HRs are shown with their 95% CIs
- CI, confidence interval; CRT, chemoradiotherapy; CTx, chemotherapy; ECF, epirubicin, cisplatin, and 5-fluorouracil; ECX, epirubicin, cisplatin, and capecitabine; FLOT, fluorouracil, leucovorin, oxaliplatin, and docetaxel; HR, hazard ratio1. Cunningham D, et al. N Eng J Med 2006;355:11–20; 2. van Hagen P, et al. N Engl J Med 2012;366:2074–2084; 3. Al-Batran SE, et al. Lancet 2019;393:1948–1957; 4. Reynolds JV, et al. Lancet Gastroenterol Hepatol 2023;8:1015–1027; 5. Leong T, et al. N Engl J Med 2024;doi: 10.1056/NEJMoa2405195: Sep 14 [Epub ahead of print]; 6. Hoeppner J, et al. J Clin Oncol 2024;42(Suppl. 17) (Abstract LBA1)

ESMO Leitlinien ÖsophagusADENO Ca 2022





Obermannova et al. Ann Oncol 2022

ASCO 2024 LBA1: ESOPEC: CROSS vs. FLOT.....oder

Jens Hoeppner et al. ASCO 2024 Plenary session; NEJM accepted

ESOPEC

N=438

T1N1M0
oder
T2–4aN0–1M0

RANDOM

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

Primary Enpoint: Survival
Assumption:3-years-OS Rate
(55% CROSS vs 68% FLOT)

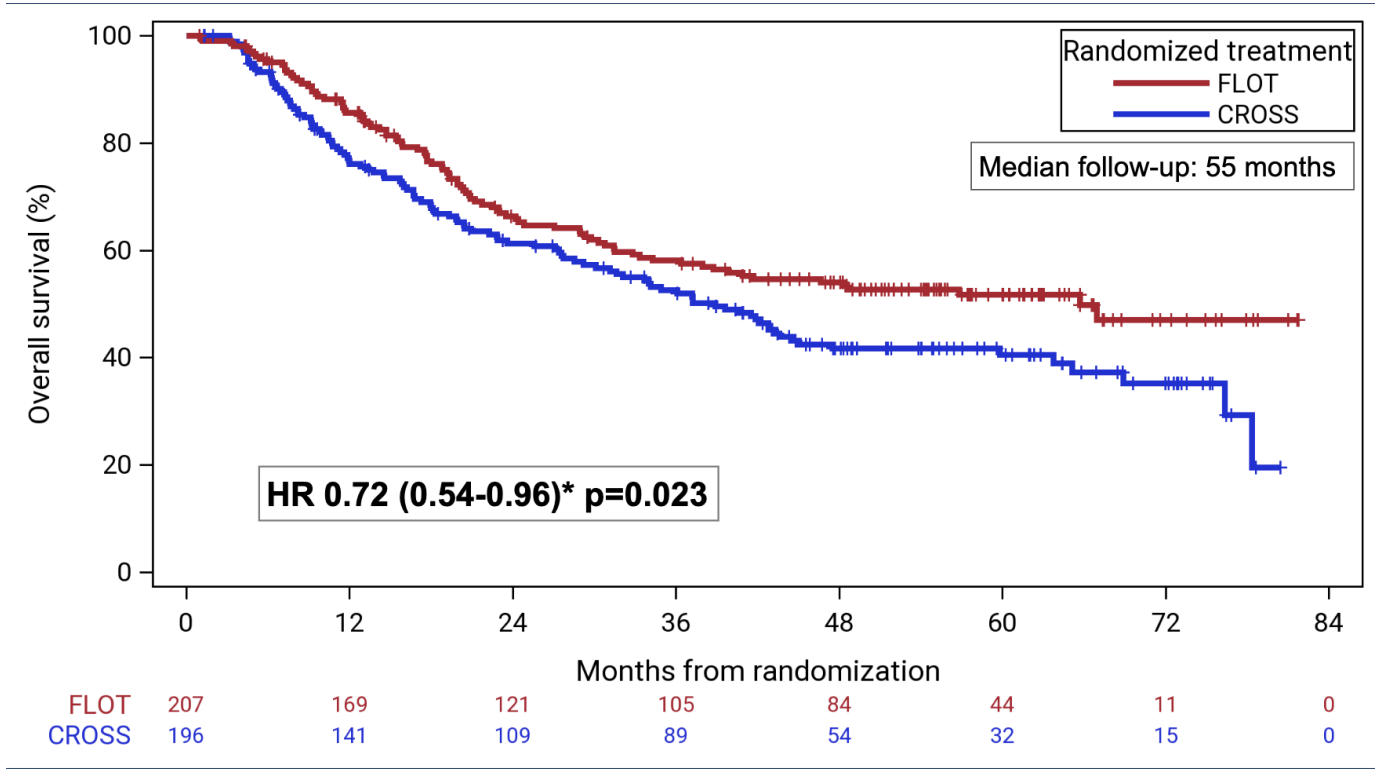
VS.

Neoadjuvante Radio-CTX – CROSS Regime
RESEKTION

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

ESOPEC: Neoadjuvante Therapie beim AEG - FLOT vs CROSS - OS

Primärer Endpunkt: Overall survival (PP)



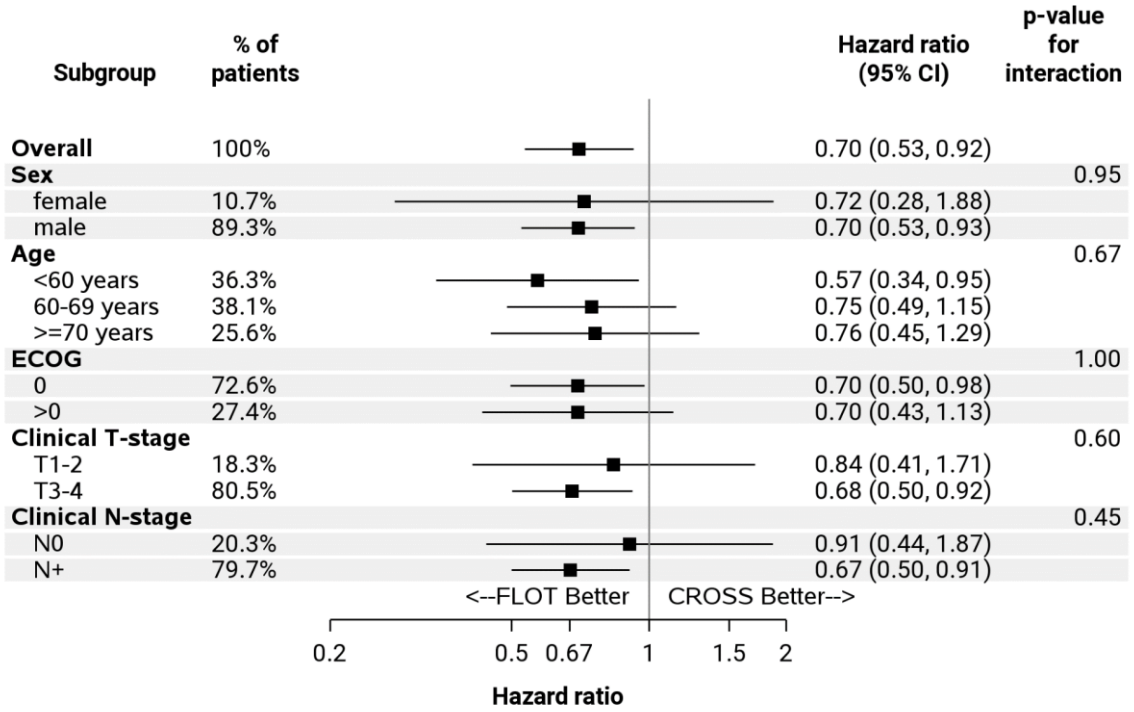
	FLOT Group	CROSS Group
Completed **pre-op** treatment	87.3%	**67.7%**
Completed **post-op** treatment	52.5%	
pCR	16.8%	**10%**
Median OS	66 mos	**39 mos**
3-year OS	57.4%	50.7%

FLOT4, 57%!

Hoeppner J et al. N Engl J Med. 2025 Jan 23;392(4):323-335

ESOPEC: Neoadjuvante Therapie beim AEG

Gesamtüberleben- Subgruppenanalyse

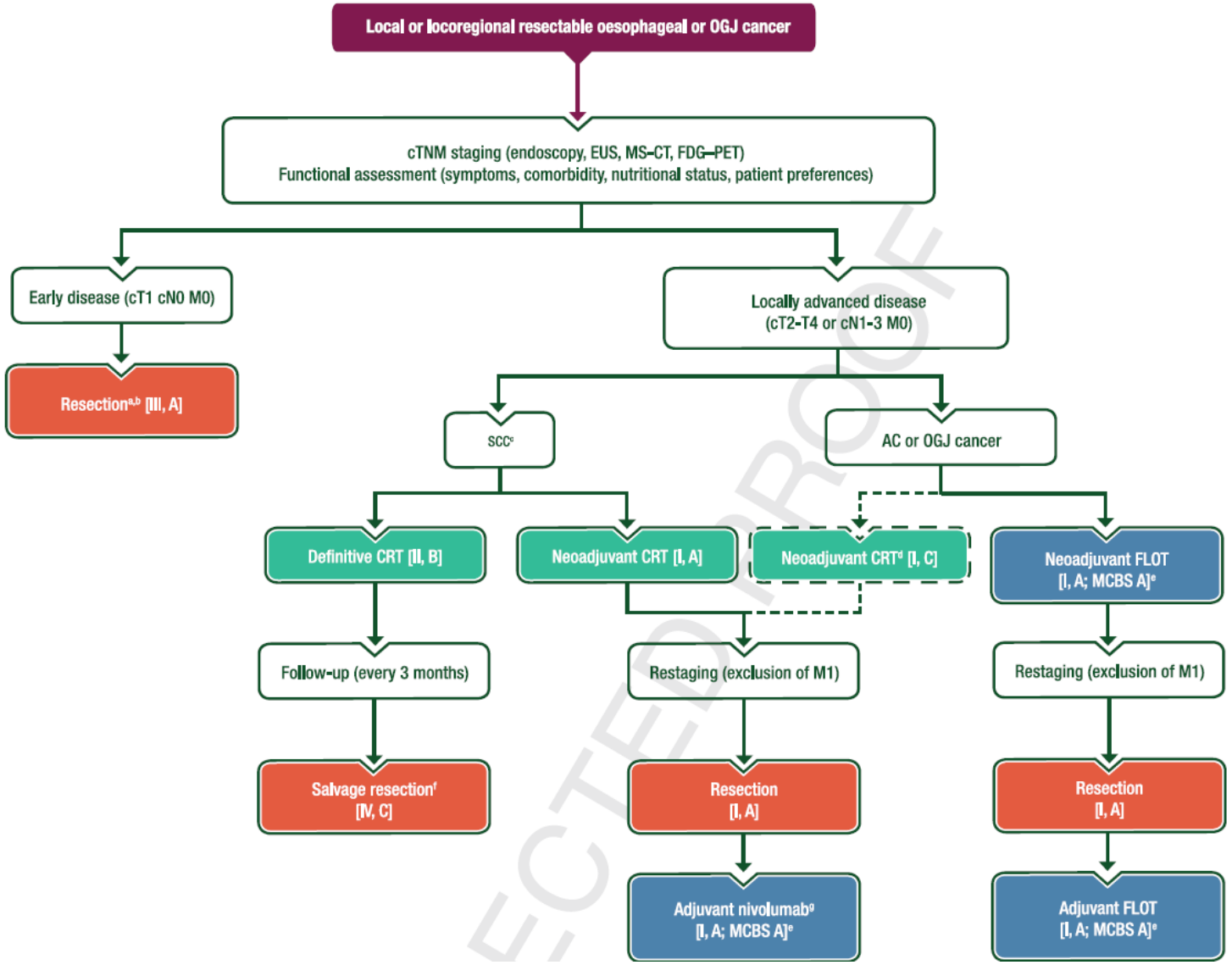


Rezidivlokalisation IIT Population

	FLOT (N=221)	CROSS (N=217)
Rezidiv Lokalisation		
Rezidiv	89	118
isoliert lokoregional	17	9
Isoliert distant	**46**	**80**
lokoregional and distant	26	29
Kein Rezidiv	132	99

Hoeppner J et al. N Engl J Med. 2025 Jan 23;392(4):323-335

ESMO Guidelines nach ESOPEC- e-Update 2025



Derzeit keine Immun- oder biologisch zielgerichtete Therapie

Trotz zahlreicher laufender Studien

Immun-Checkpoint-Inhibition

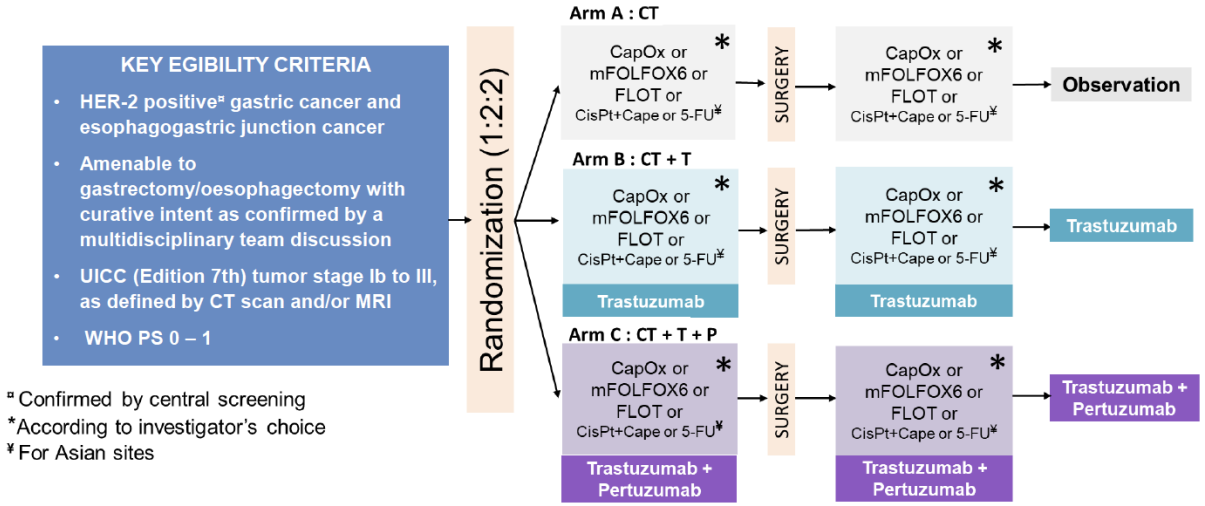
-	**ATTRACTION-5**	Nivolumab
-	**VESTIGE**	Nivolumab-Ipilimumab
-	**DANTE**	Atezolizumab
-	**MATTERHORN**	Durvalumab
-	**KEYNOTE-585**	Pembrolizumab

HER2

-	**PETRARCA**	Trastuzumab-Pertuzumab
-	**INNOVATION**	Trastuzumab
		Trastuzumab-Pertuzumab

Obermannová R et al. ESMO Open 2025

Anti-Her 2 plus Chemotherapie: Phase II INNOVATION Studie: primärer Endpunkt mpCR



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

Ca. 45% FLOT

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

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

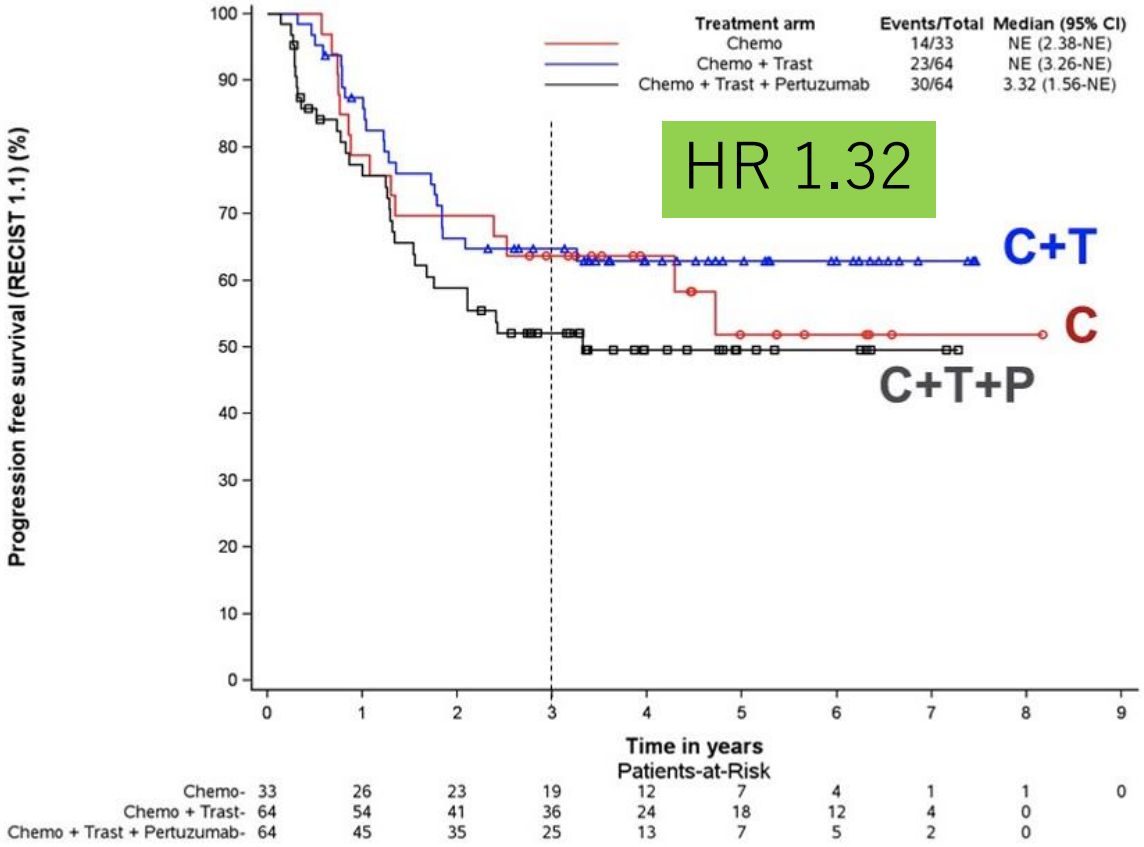
	CT + T	CT + T + P
Difference in mpRR between each experimental arm and CT arm [asymptotic two-sided 80% CI]	13.7% [0.7%, 26.7%]	3.1% [-9.5%, 15.7%]

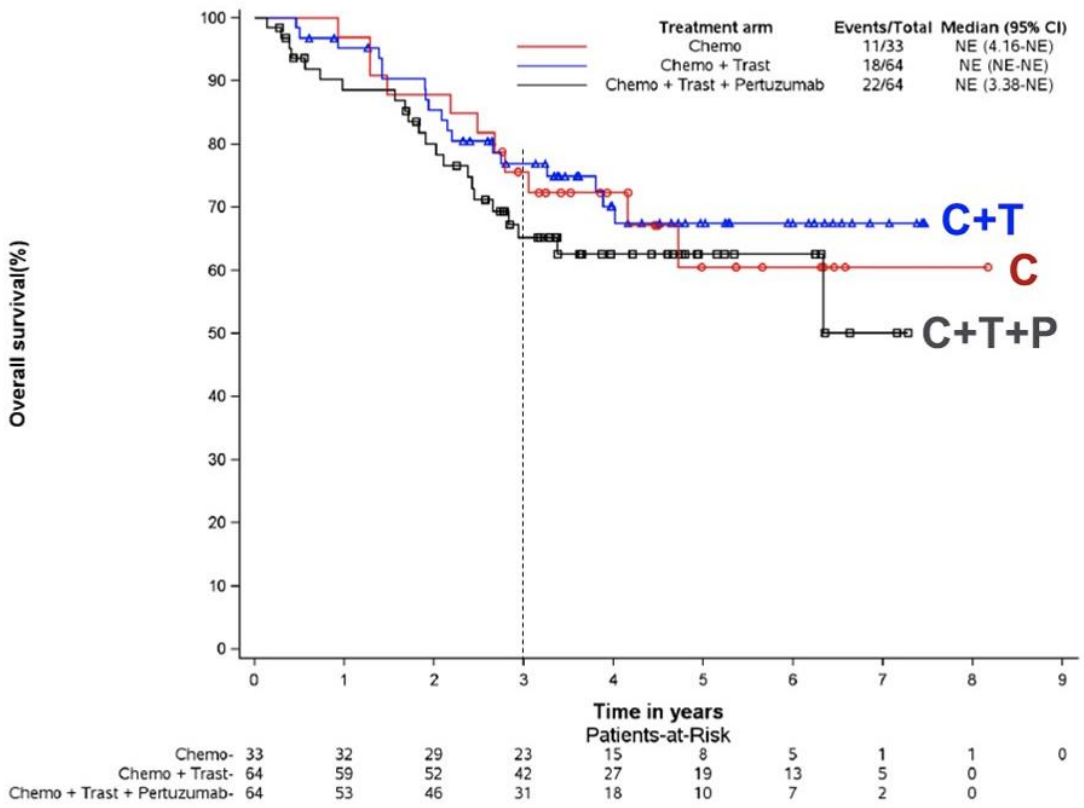
➢ **pCR verbessert um 14% (37% + tras vs 23% ctx alleine)**

Anna Dorothea Wagner, et al. ASCO GI 2025

NEU: ASCO GI 2025: Sekundärer Endpunkt PFS & OS in Gesamtpopulation

Medianes Follow-up: 4.5 Jahre

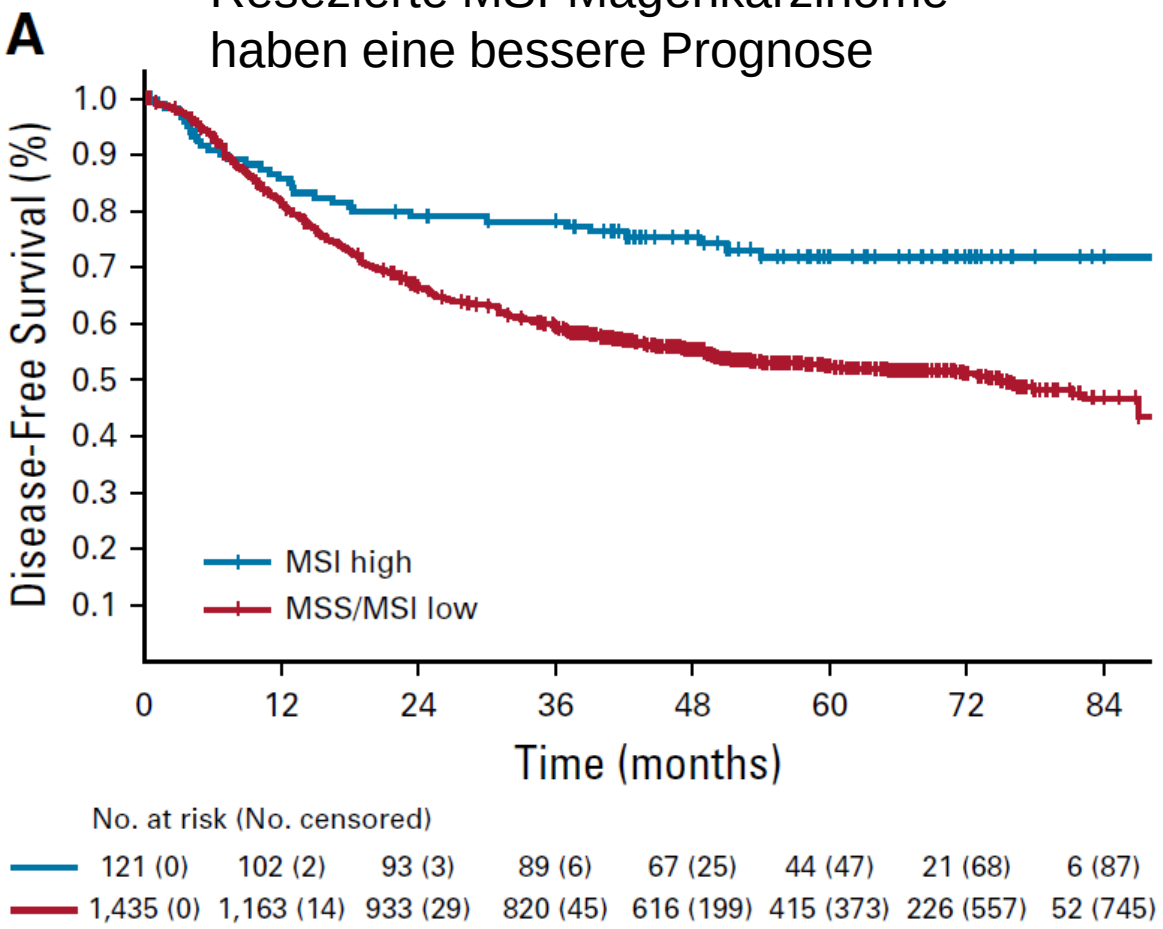




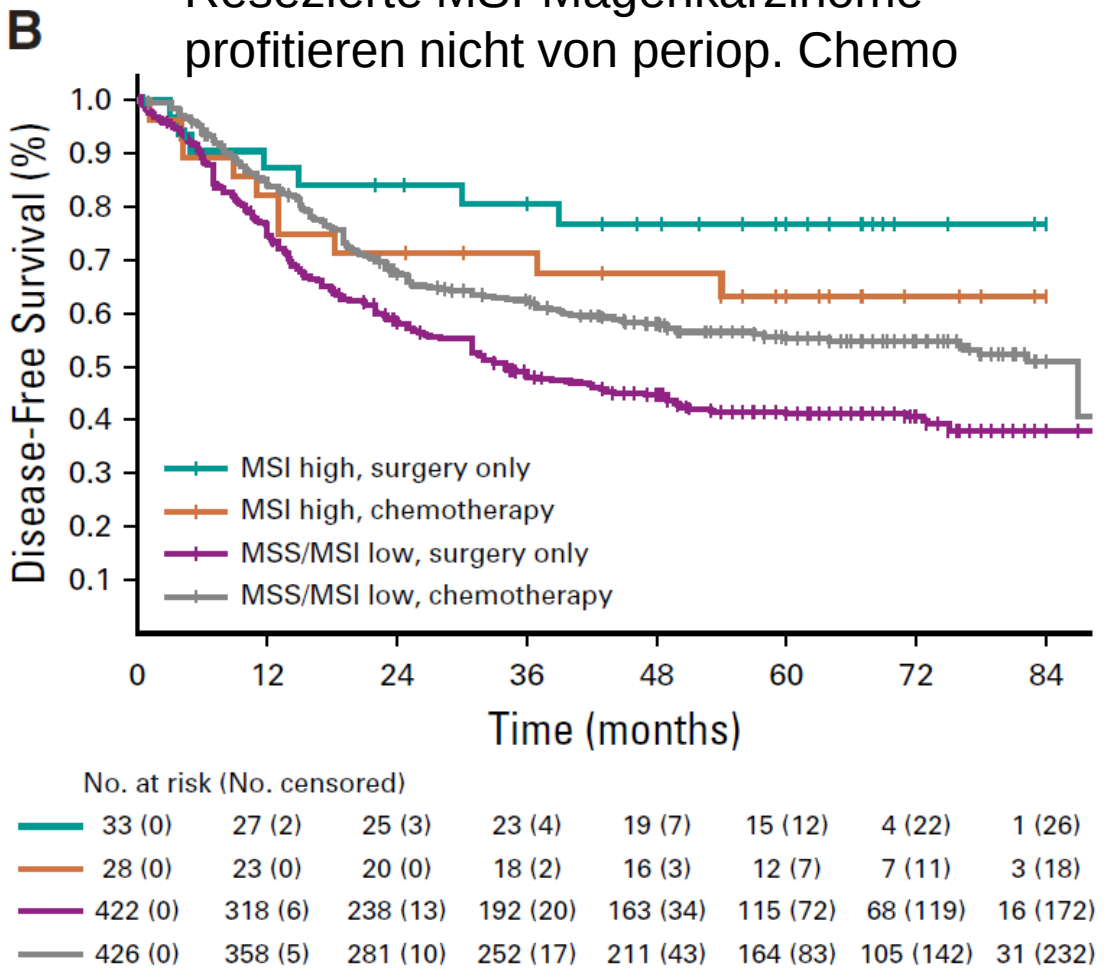
Anna Dorothea Wagner, et al. ASCO GI 2025

dMMR / MSI-High-Magenkarzinom

Resezierte MSI-Magenkarzinome haben eine bessere Prognose



Resezierte MSI-Magenkarzinome profitieren nicht von periop. Chemo

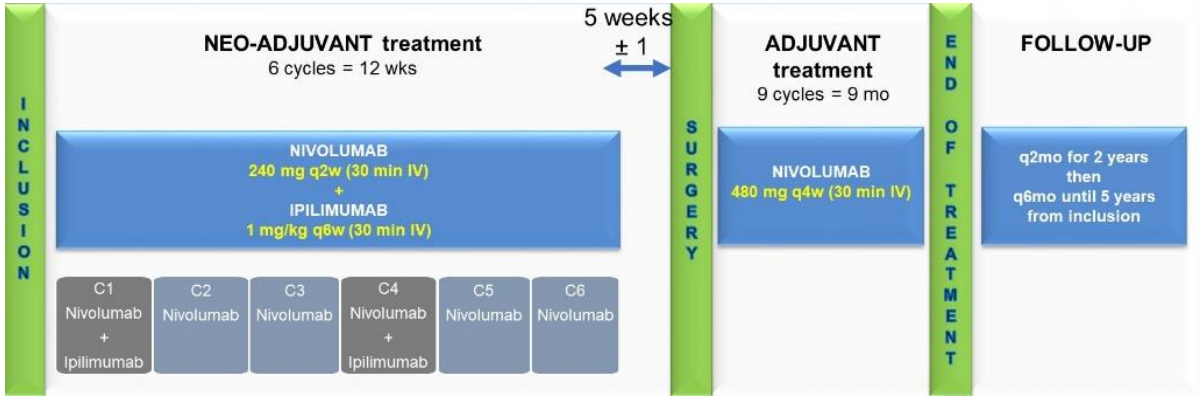


Pietrantonio F et al. J Clin Oncol. 2019 Dec 10;37(35):3392-3400

dMMR / MSI-High-Magenkarzinom

NEONIPIGA

Hohe pCR-Rate (58,6%) bei lokal begrenztem MSI-H Magenkarzinom nach12 Wochen Nivolumab-Ipilimumab



Type of surgery (N=29)	N	%
R0	29	100
Total oesogastrectomy	1	3,5
Total gastrectomy	7	24
4/5 gastrectomy	9	31
Lewis-Santy procedure	11	38
Pancreaticoduodenectomy	1	3,5

ypT stage (N=32)	
ypT0*	19
ypT1a	1
ypT1b	2
ypT2	2
ypT3	5
unknown**	3
ypN stage (N=32)	
ypN0	23
ypN1	6
unknown*	3

TRG Mandard (N=29)	N	%
TRG 1: complete regression/fibrosis with no tumor cells	17	58.6
TRG 2: fibrosis with scattered tumor cells	4	13.8
TRG 3: fibrosis and tumor cells with a dominance of fibrosis	2	6.9
TRG 4: fibrosis & tumor cells with dominance of tumor cells	4	13.8
TRG 5: tumor without evidence of regression	2	6.9
TRG Becker (N=29)		
TRG 1a: complete tumor regression without residual tumor	17	58.6
TRG 1b: < 10% residual tumor per tumor bed	4	13.8
TGR 2: 10% to 50% residual tumor	2	6.9
TRG 3: > 50% residual tumor cells	6	21.7

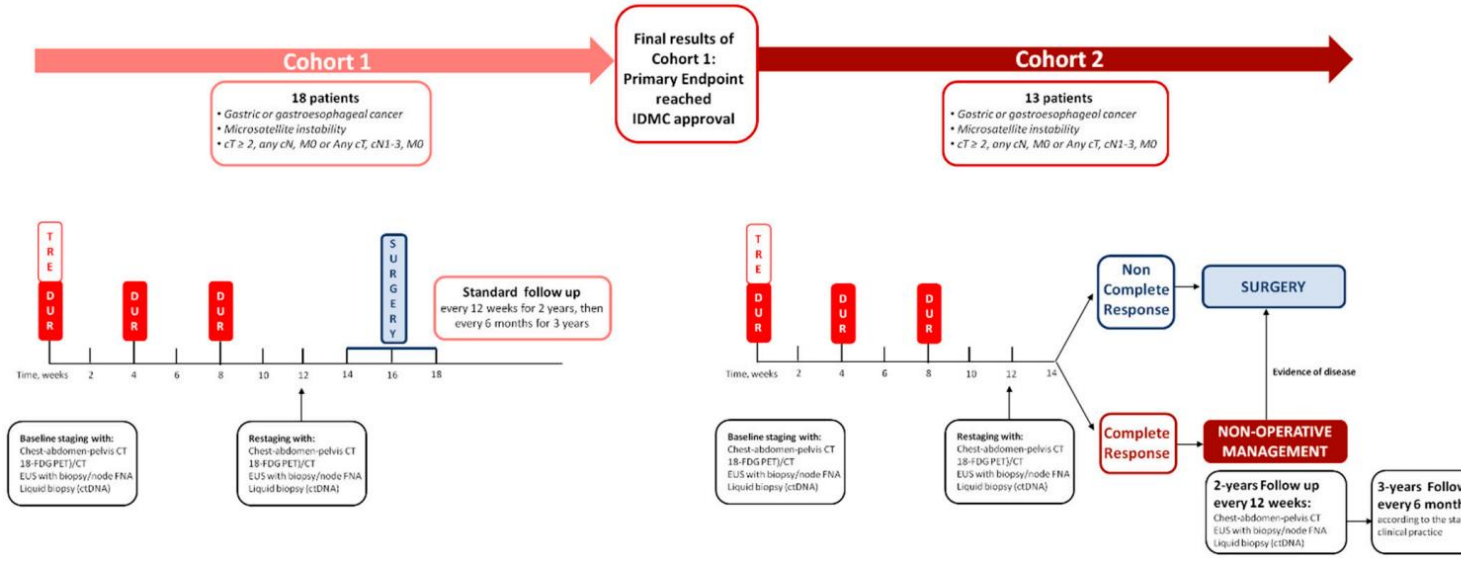
- * 2 patients ypT0 and ypN1 (residual tumoral cells < 10% in only one node)
- ** 3 patients without surgery, 1 in metastatic PD and 2 in complete response in endoscopy with no tumoral cell on biopsy

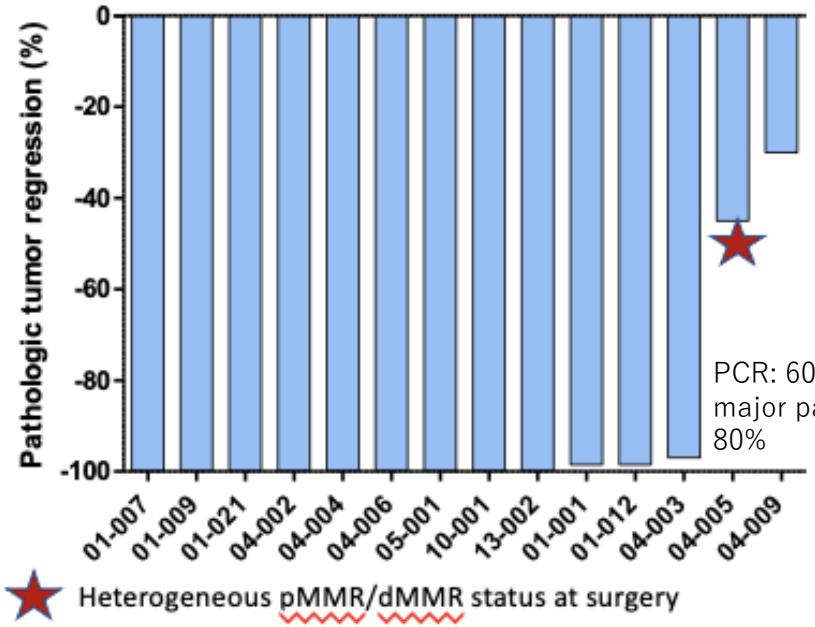
André T et al. J Clin Oncol. 2023 Jan 10;41(2):255-265.

dMMR / MSI-High-Magenkarzinom

INFINITY

Hohe pCR-Rate (60%) bei lokal begrenztem MSI-H Magenkarzinom nach12 Wochen Durvalumab-Tremelimumab

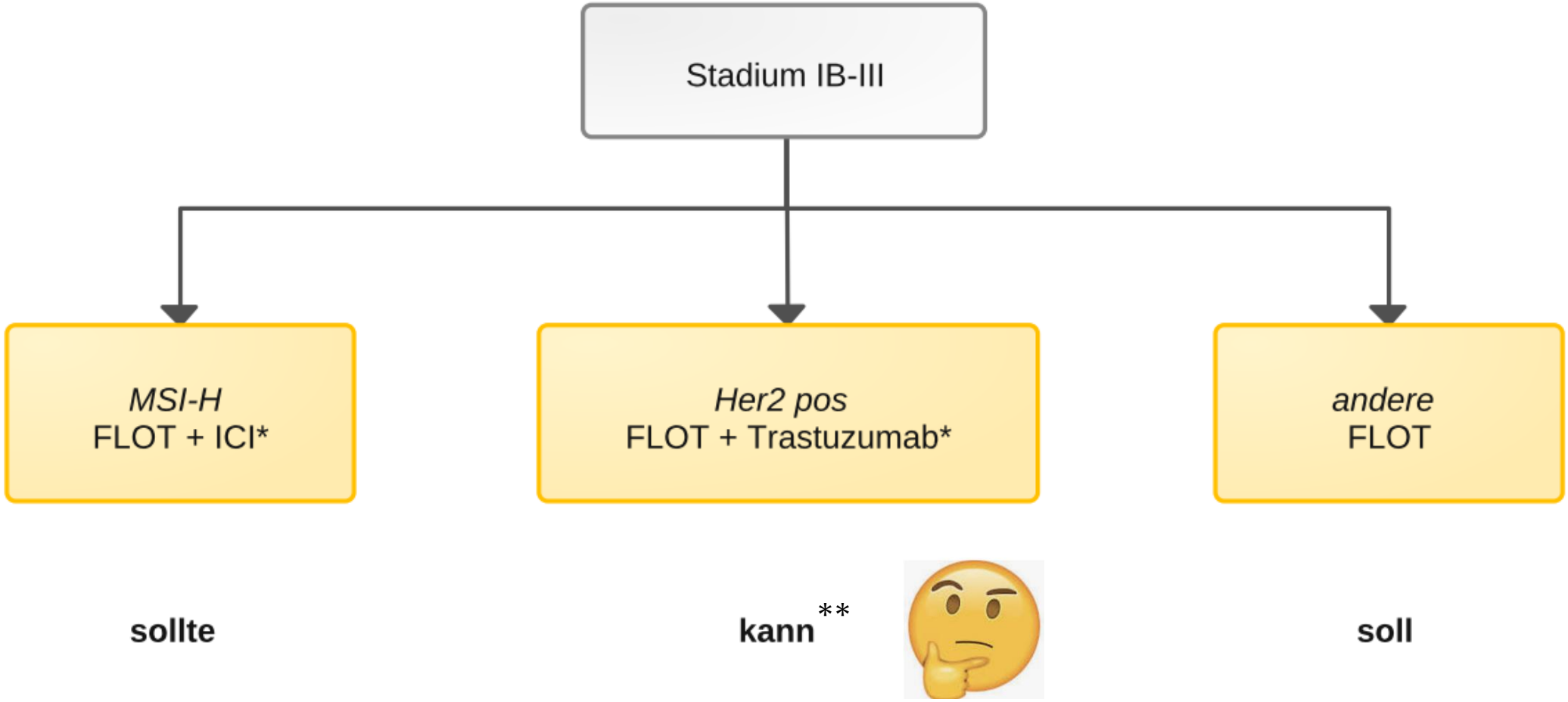




PCR: 60%;
major path. Remission: 80%

Pietrantonio F et al., ESMO GI 2023; abstract 358,
Raimondi et al, Ann Oncol. 2024

Onkopedia 2024 – Lokal fortgeschrittene Magen/AEG Tumore

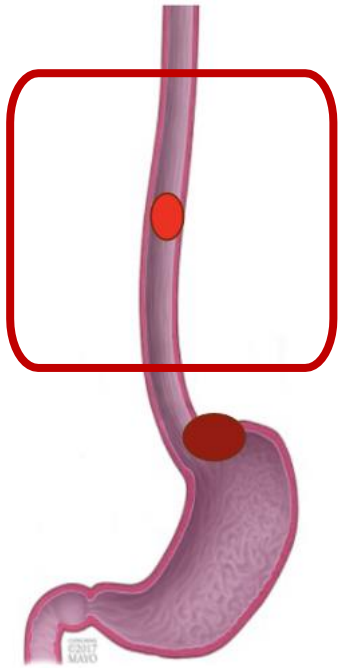


**off-label, vorherige Abklärung mit Kostenträger zu empfehlen*

***zu empfehlen bei grenzwertig resektablen oder lokal irresektabler lokaler Tumorausbreitung im Sinne einer Konversionstherapie; (Update Onkopedia LLMagen Ca in progress)*

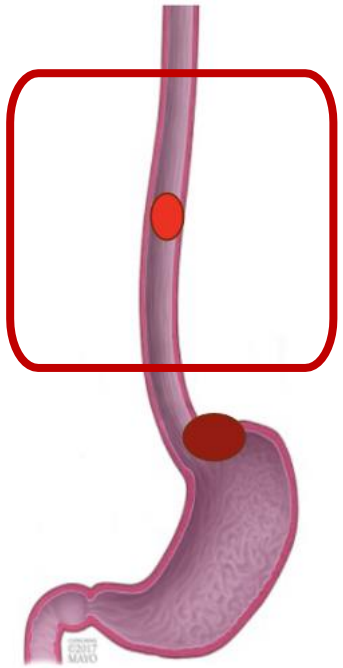
FAZIT: Lokal fortgeschrittenes Ösophagus Ca

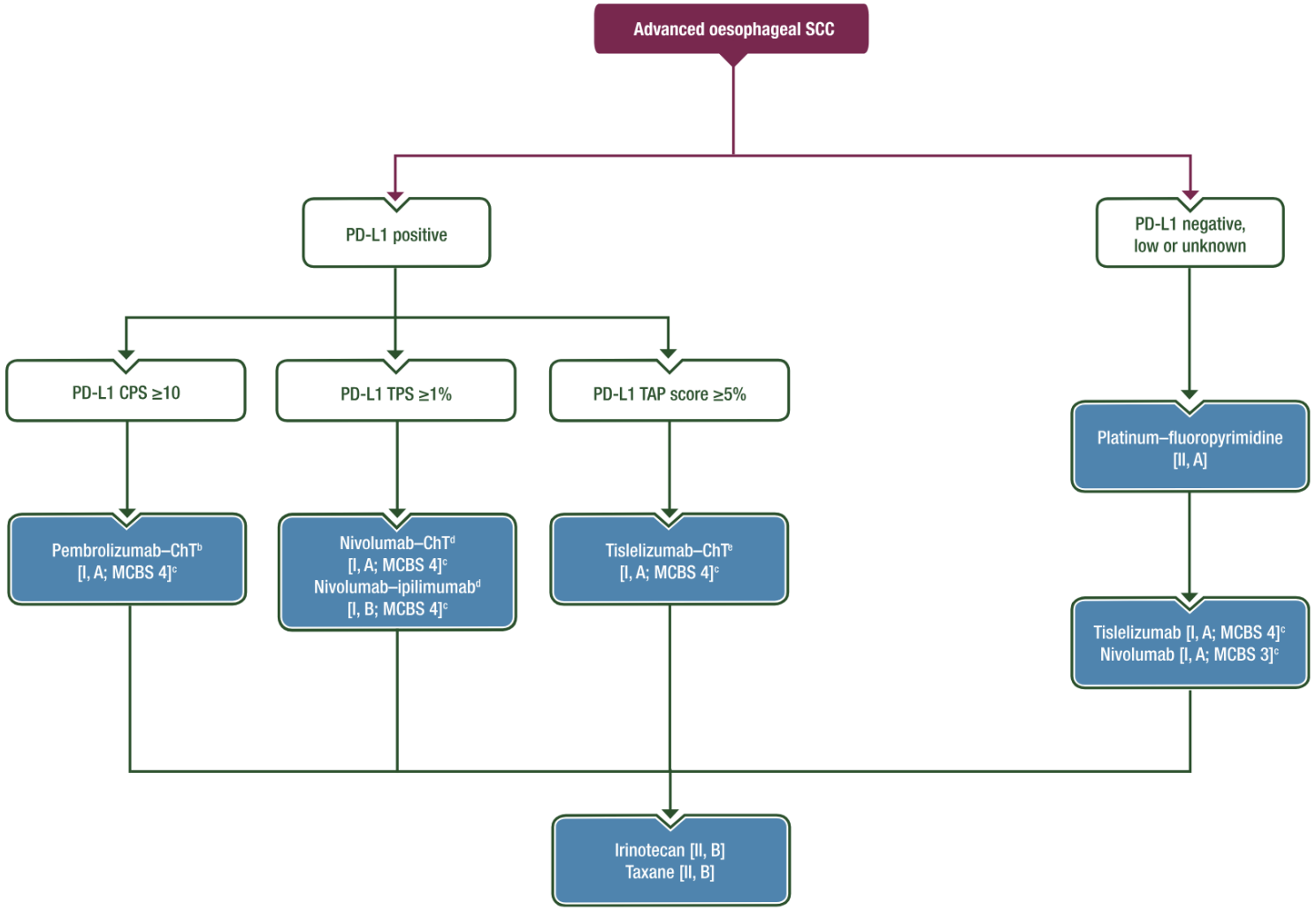
- Die **perioperative FLOT-Chemotherapie** ist jetzt Standard für alle lokal fortgeschrittenen Adenokarzinome des Magens / gastroösophagealen Übergangs
- Die Rolle der **präoperativen Strahlentherapie** ist **Standard beim SCC** und beim **AC sehr begrenzt**
- **Adjuvante Immuntherapie** – keine Evidenz außerhalb des CM-577-Studiensettings- nach neoadj. RCTX: SCC!
- **Prä-/perioperative Immuntherapie bei MSS-**Magen-/Ösophagus-Krebs – in klinischer Prüfung
- **MSI-high-Magen-/Ösophagus-Karzinom**
  - Fragwürdiger Nutzen der perioperativen Chemotherapie
  - Primäre Operation ist eine Option (wenn eindeutig resezierbar)
  - Zugang zu Immuntherapie ermöglichen, wann immer möglich (Studien, Off-Label-Use, …)



Metastasiertes, irresektables Plattenepithelkarzinom des Ösophagus
Palliative Therapie: Status quo 2025

ESMO Stadium IV Plattenepithel Ca Ösophagus

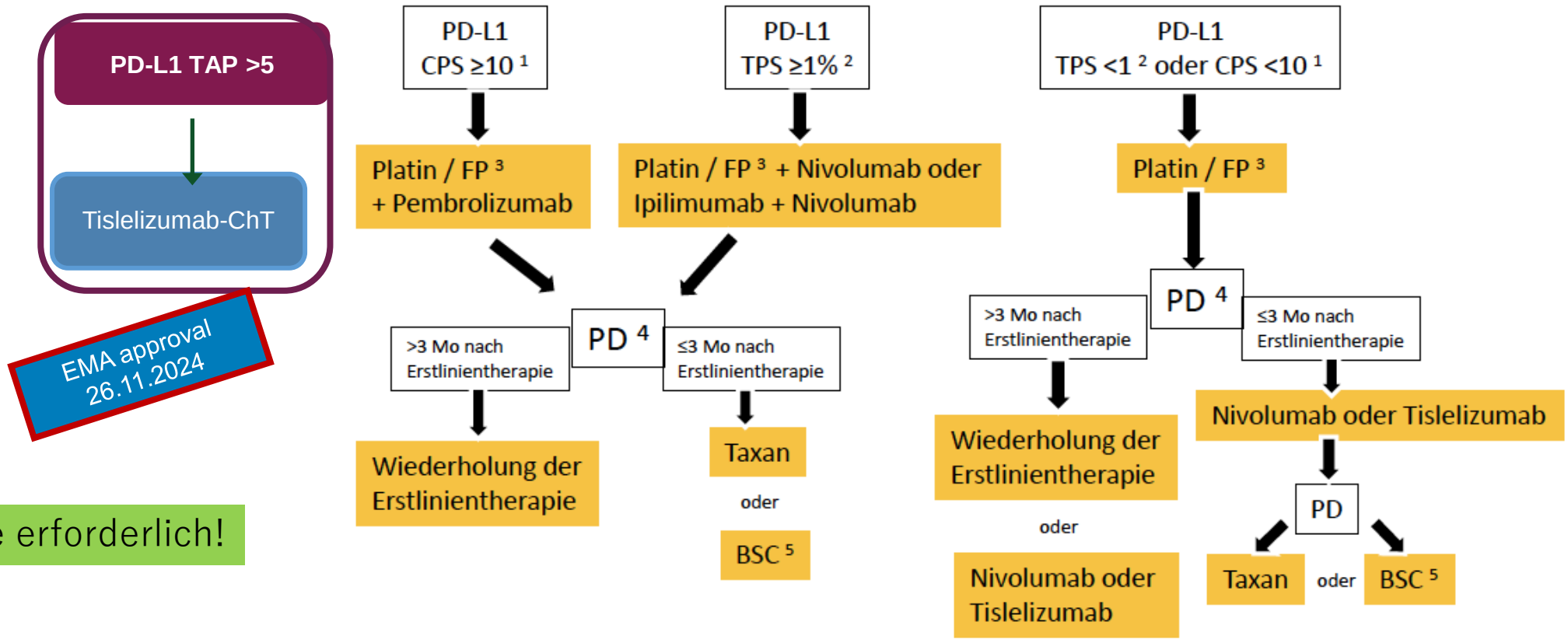




Obermannová R et al ESMO Open 2025

Algorithmus für die Therapie des Plattenepithelkarzinoms des Ösophagus im Stadium IV

Lorenzen update Onkopedia LL Okt 2024



Update erforderlich!

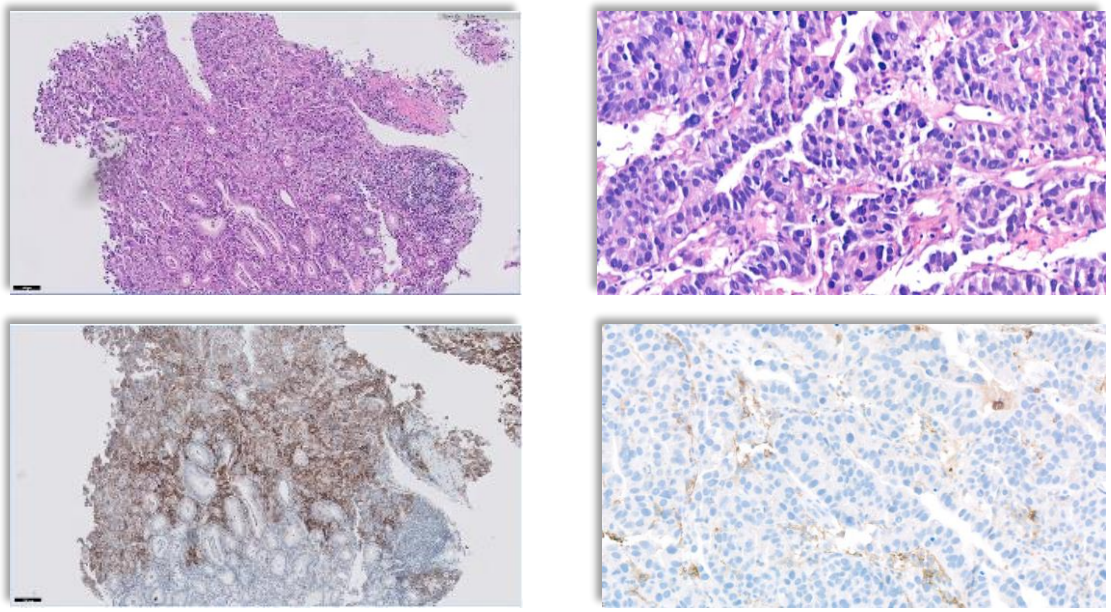
PD-L1

- Adenocarcinomas:
  - CPS ≥ 5

$$\text{CPS} = \frac{\text{Number of PD-L1 positive cells (tumor cells, lymphocytes, macrophages)}}{\text{Total number of tumor cells}} \times 100$$

- Squamous cell carcinomas:
  - TPS ≥ 1 %
  - CPS ≥ 10

$$\text{TPS} = \frac{\text{Number of PD-L1 positive tumor cells}}{\text{Total number of tumor cells}} \times 100$$



PD-L1 CPS: 100

PD-L1 CPS: 3

	TAP Score (%)	CPS
Score Formula	$\frac{\text{Area occupied by PD-L1 staining tumour cells and immune cells}}{\text{Tumour area}} \times 100\%$	$\frac{\text{\# PD-L1 staining tumour cells and immune cells}}{\text{Total \# viable tumour cells}} \times 100$
Cell Types Included in PD-L1 Score	• Tumour cells • Immune cells (including lymphocytes, macrophages, histiocytes, reticular dendritic cells, plasma cells, and neutrophils)	• Tumour cells • Immune cells (including lymphocytes and macrophages)
Scoring Method	• Visual-based estimation on tumour area	• Cell count (time consuming)

[a] Off-label for the VENTANA PD-L1 (SP263) assay.
Abbreviations: CPS, combined positive score; PD-L1, programmed death-ligand 1; TAP, Tumor Area Positivity.

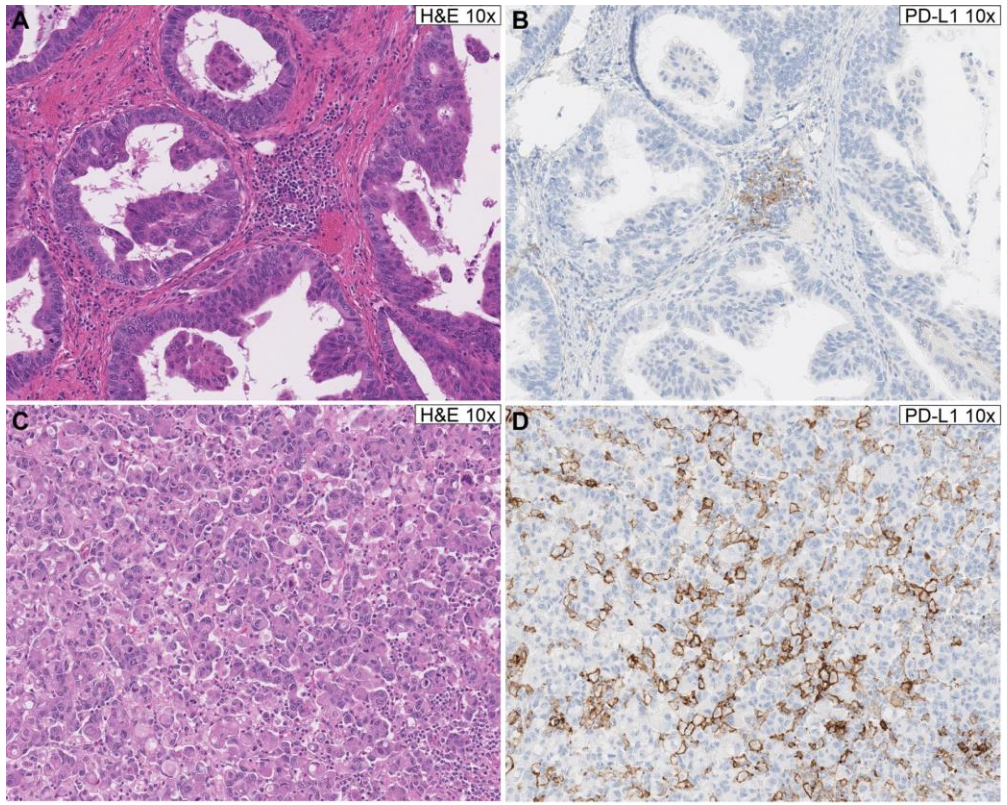
PD-L1 TAP score

- TAP = Tumor Area Positivity

$$TAP = \frac{\text{\% PD-L1 positive tumor cells and immune cells}}{\text{Tumor area}}$$

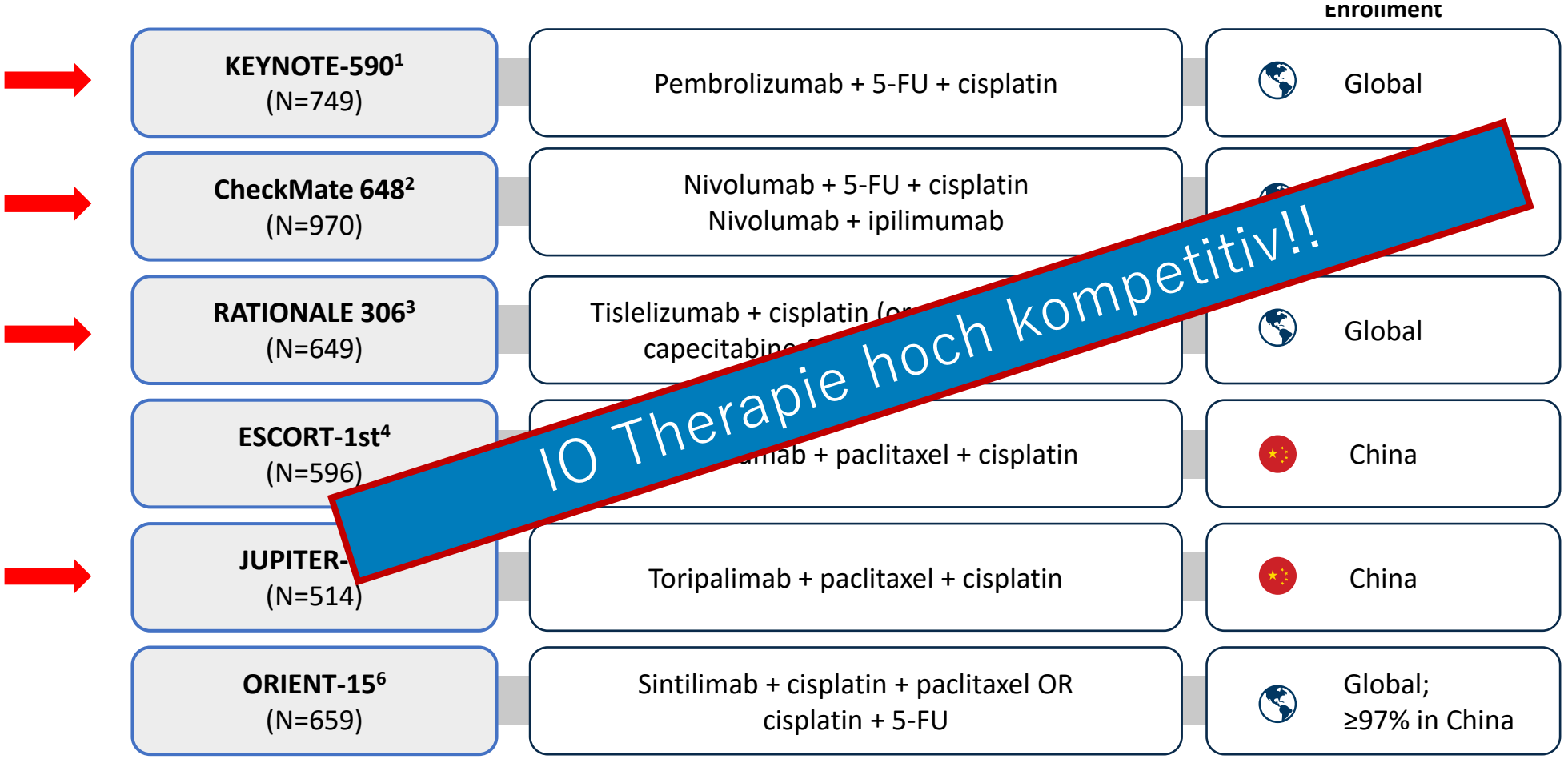
- Mucin pools are included in tumor area
- Tumor in lymphovascular spaces are included

➢ PD-L1 TAP ≥ 5 is used as cutoff for tislelizumab



Liu *et al*. Diagn Pathol. 2023

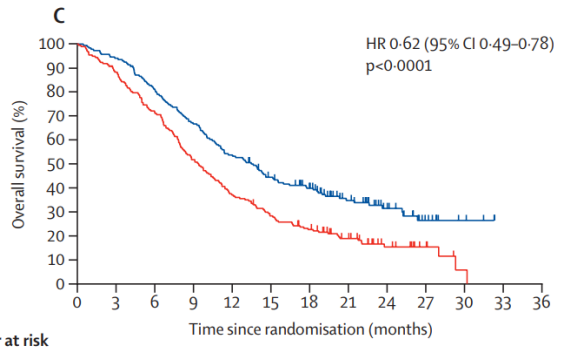
Übersicht über die wichtigsten Erstlinienstudien beim Plattenepithel Karzinom mit Immuntherapie



1. Sun JM, et al. *Lancet*. 2021;398:759-771; 2. Doki Y, et al. *N Engl J Med*. 2022;386:449-462; 3. Xu J, et al. ASCO 2019. Abstract TPS2656.; 4. Luo H, et al. *JAMA*. 2021;326:916-925; 5. Wang ZX, et al. *Cancer Cell*. 2022;40(3):277-288; 6. Lu Z, et al. *BMJ*. 2022;377:e068714.

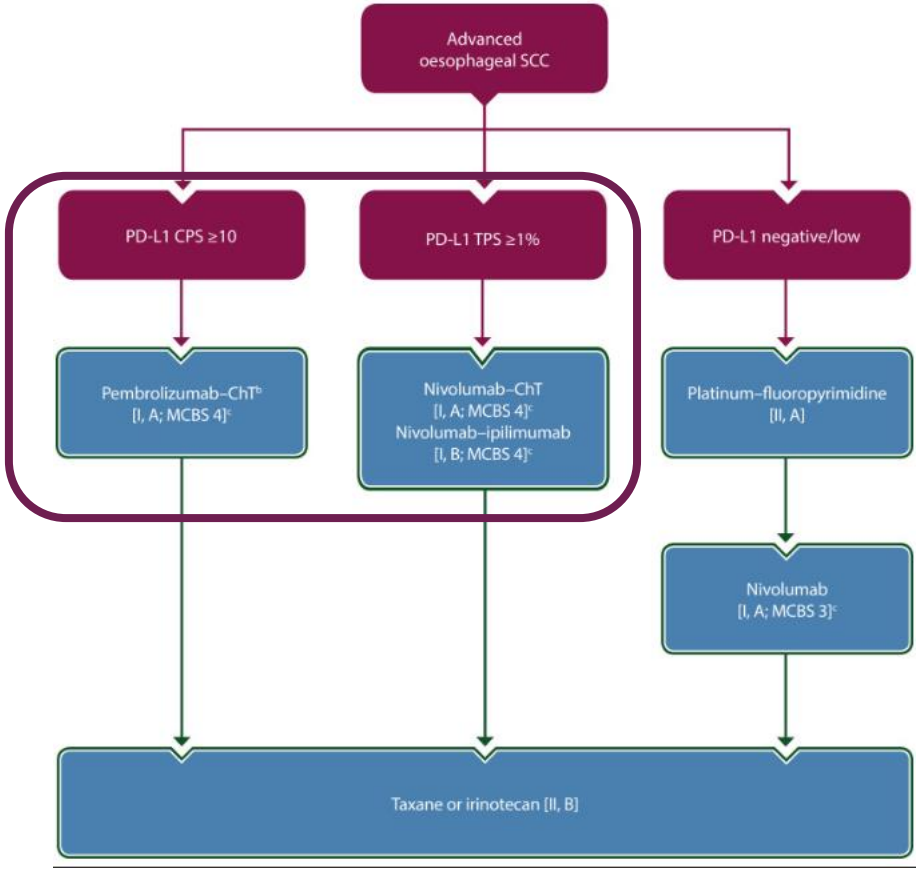
ESMO LEITLINIEN FORTGESCHRITTENES SCC 2022

KN 590, PD-L1 CPS ≥ 10



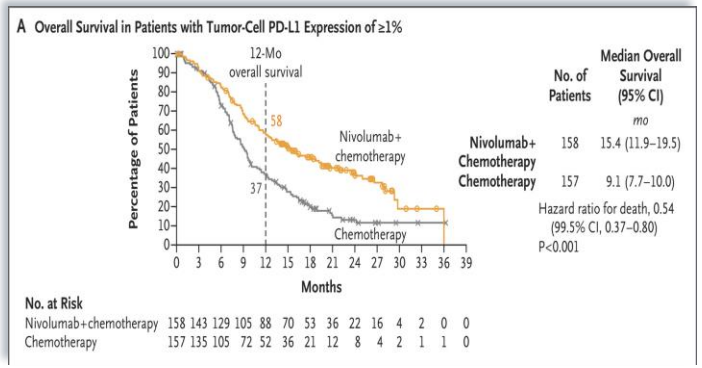
Number at risk (number censored)													
Pembrolizumab plus chemotherapy group	186 (0)	175 (0)	151 (0)	125 (0)	100 (0)	79 (4)	66 (9)	40 (28)	23 (42)	10 (52)	4 (58)	0 (58)	0 (58)
Placebo plus chemotherapy group	197 (0)	174 (0)	142 (0)	102 (0)	73 (0)	55 (1)	42 (3)	28 (11)	13 (22)	6 (29)	1 (32)	0 (32)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

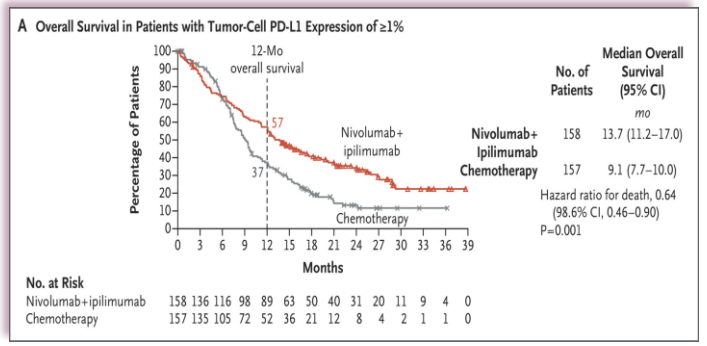
Sun JM et al Lancet. 2021 Aug 28;398(10302):759-771



Obermannová, R. et al. Annals of Oncol 2022. 33(10), 992-1004

CM648, PD-L1 TPS ≥ 1





Doki Y N Engl J Med 2022; 386:449-462

Erstlinientherapie Plattenepithel Ca– RATIONALE-306 STUDIE

Key eligibility criteria

- Unresectable locally advanced or metastatic ESCC
- No prior systemic treatment for advanced disease
- ECOG PS 0 or 1
- Measurable or evaluable disease per RECIST v1.1

R 1:1 DB

N=649

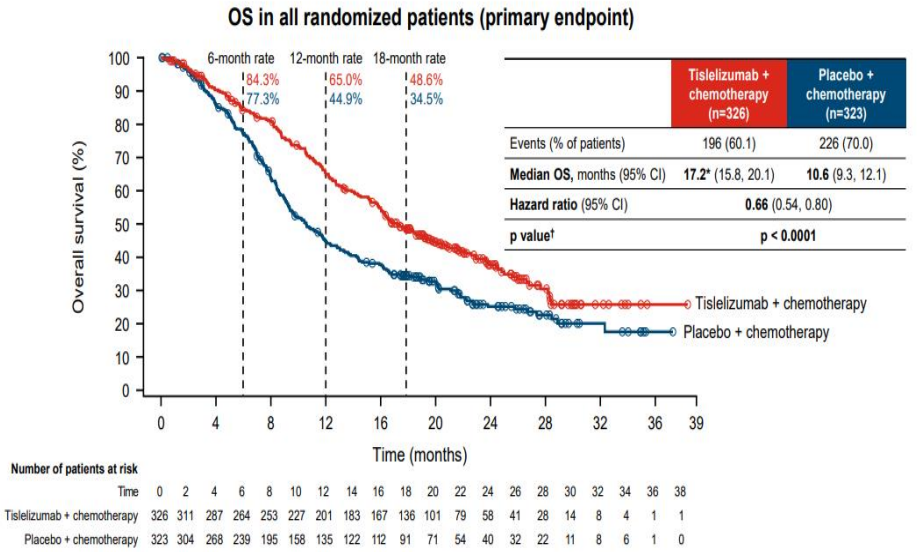
Tislelizumab 200 mg IV Q3W + investigator-chosen chemotherapy

Treatment until disease progression, intolerable toxicity, or withdrawal for other reasons

Matching placebo IV Q3W + investigator-chosen chemotherapy

Investigator-chosen chemotherapy:

- **Option A: Platinum + fluoropyrimidine**
  Cisplatin or oxaliplatin* + fluoropyrimidine†
- **Option B: Platinum + paclitaxel**
  Cisplatin or oxaliplatin* + paclitaxel‡



Primärer Endpunkt: OS

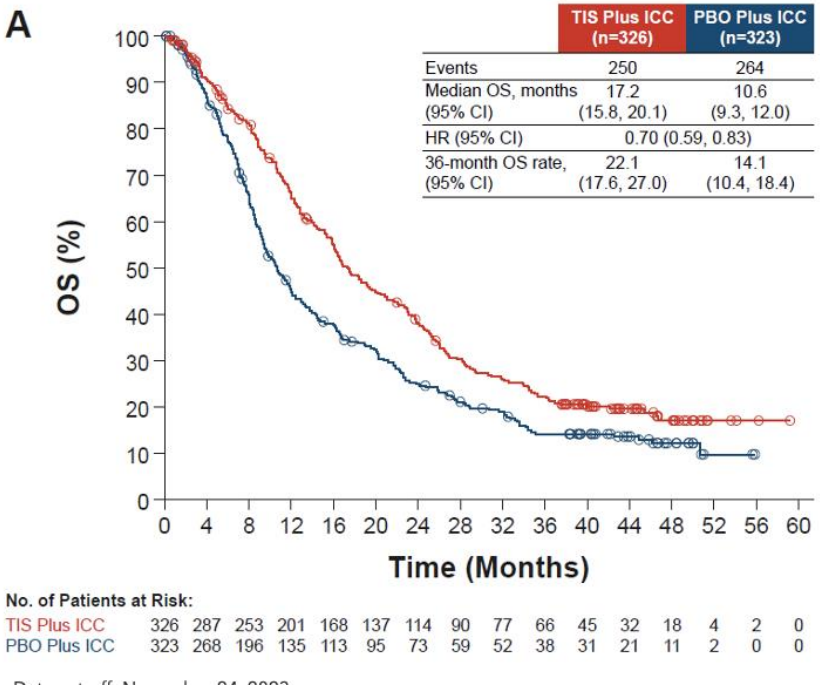
Stratification factors

- Geographic region (Asia [excluding Japan] vs Japan vs Rest of World)
- Prior definitive therapy (yes vs no)
- Investigator-chosen chemotherapy (platinum/fluoropyrimidine vs platinum/paclitaxel)

Yoon H, et al. RATIONALE-306: 2022 ESMO World Congress on Gastrointestinal Cancer; LBA1
Xu et al; Lancet Oncol. 2023 May;24(5):483-495..

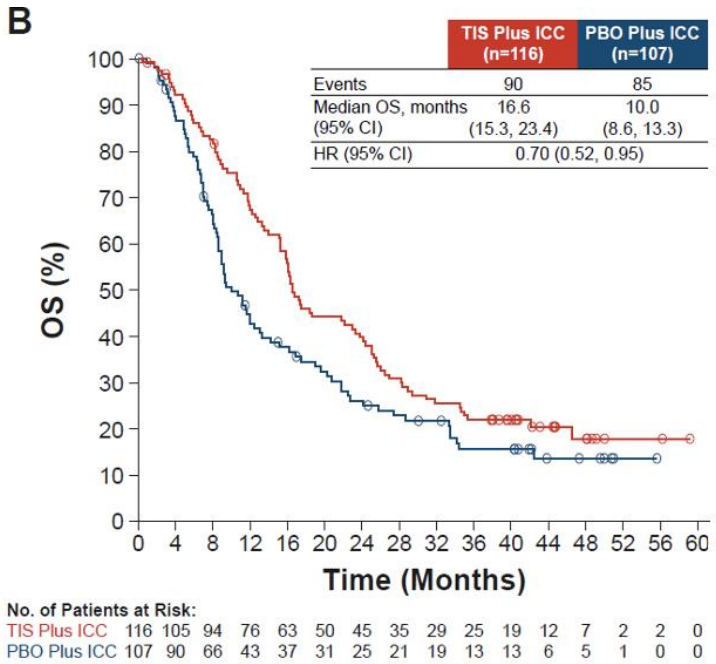
Erstlinientherapie Plattenepithel Ca– RATIONALE-306 STUDIE- 3 Jahres Follow-up

ITT



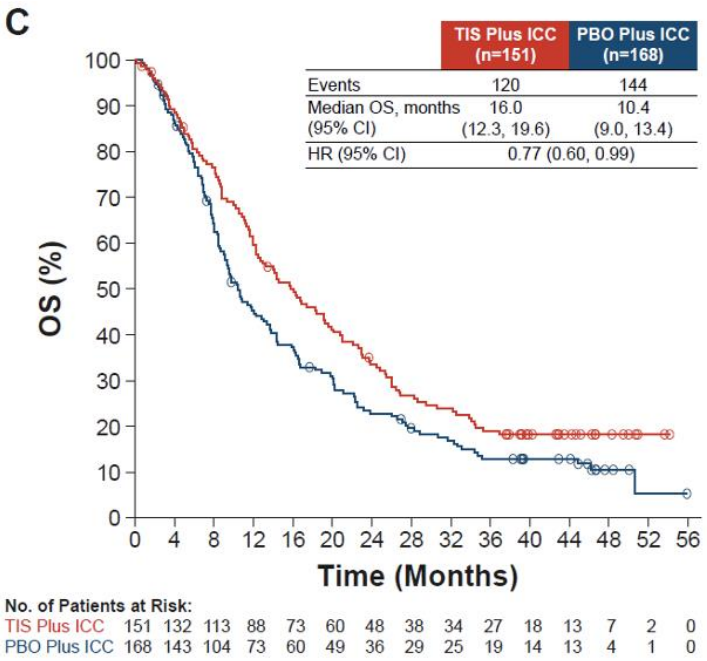
+6.6 Monate

TAP ≥ 10



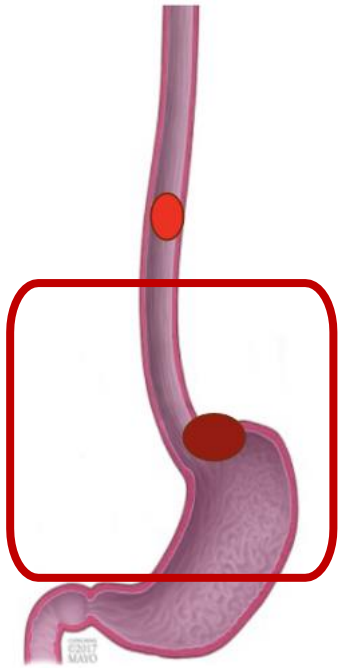
+6.6 Monate

TAP <10



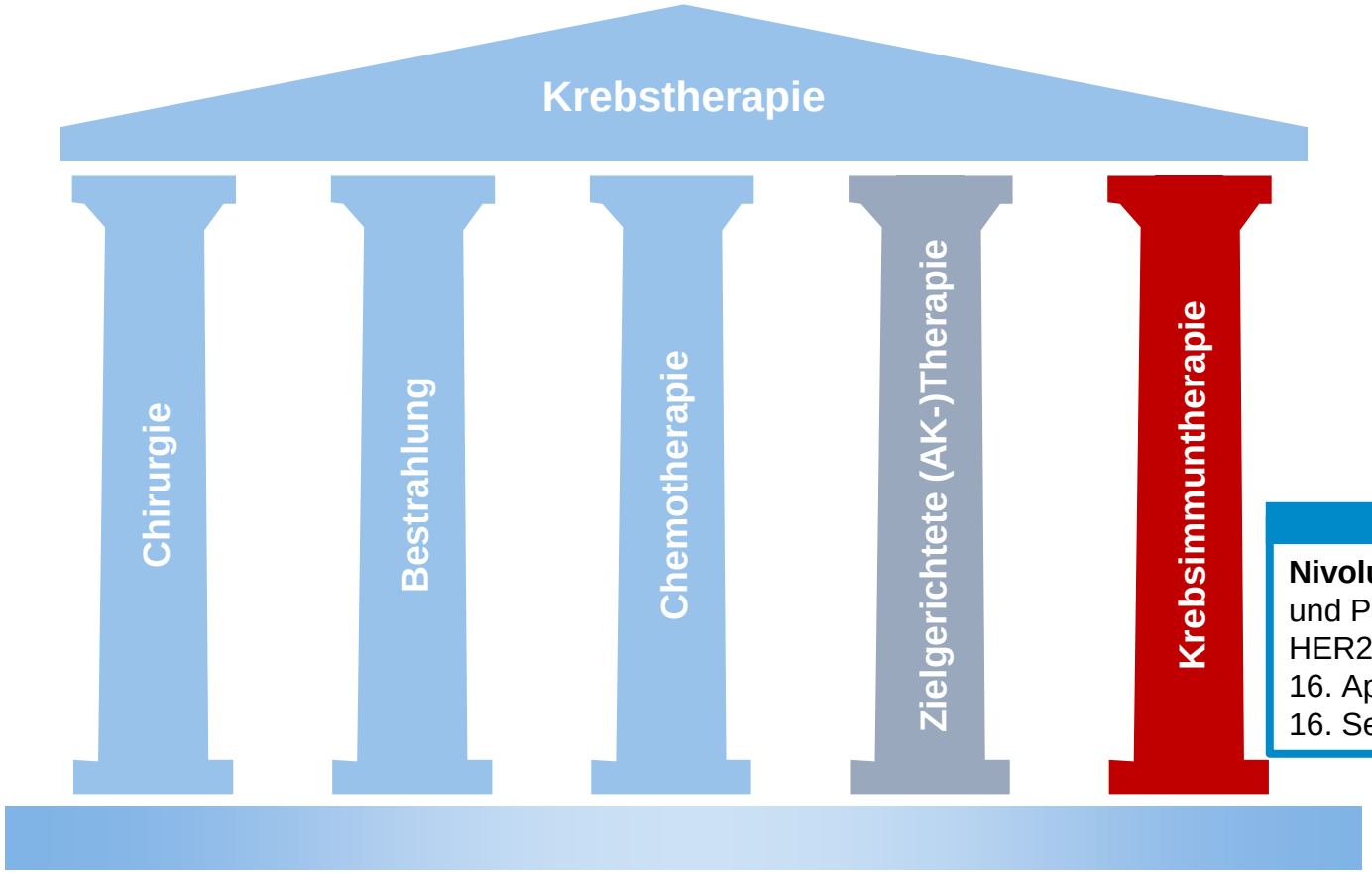
+5.6 Monate

Yoon HH, et al. Poster Presentation at ASCO 2024;abstract 4032

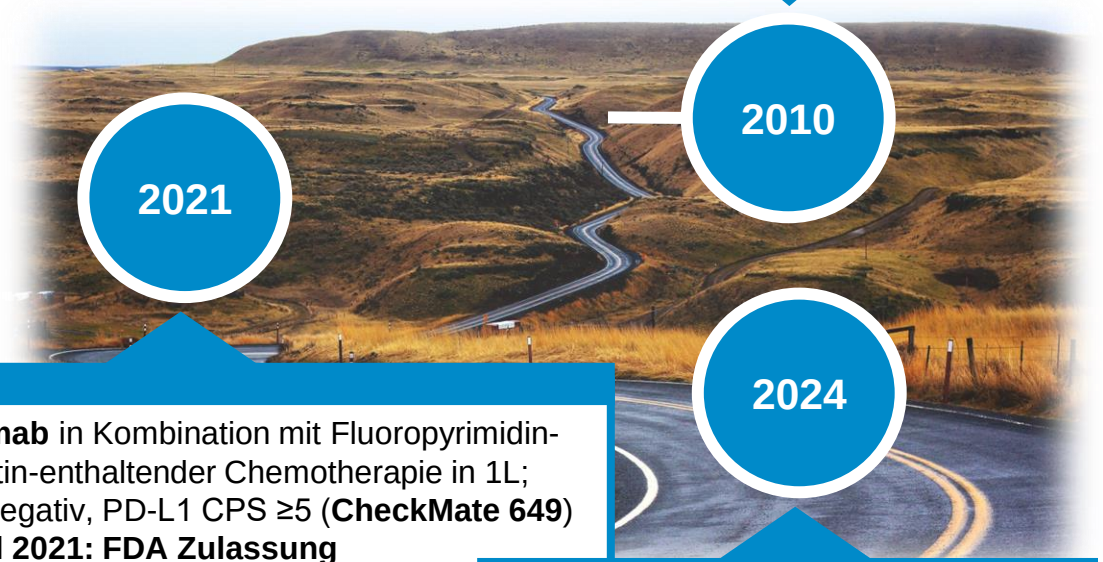


Metastasiertes, irresektables Adenokarzinom des Ösophagus
Palliative Therapie: Status quo 2025

Individualisierte Therapie als tragende Säulen beim Adenokarzinom des Magens und gastroösophagealen Übergangs



Trastuzumab in Kombination mit Fluoropyrimidin- und Platin-enthaltender Chemotherapie in Erstlinie; HER2-positiv (**ToGA**)
2. Februar **2010: EMA Zulassung**
20. Oktober **2010: FDA Zulassung**



Nivolumab in Kombination mit Fluoropyrimidin- und Platin-enthaltender Chemotherapie in 1L; HER2-negativ, PD-L1 CPS ≥5 (**CheckMate 649**)
16. April **2021: FDA Zulassung**
16. September **2021: EMA Zulassung**

Zolbetuximab in Kombination mit Fluoropyrimidin- und Platin-enthaltender Chemotherapie in 1L; CLDH18.2 + **(SPOTLIGHT**)
19. September **2024 EMA Zulassung**

Bang YJ, et al. Lancet. 2010;376(9742):687–97; Shitara et al., Nature Medicine volume 29, pages 2133–2141 (2023); Janjigian YY, et al. Lancet. 2021;398(10294):27–4; Shitara et al., Nature Medicine 2023

1st-Linien -Therapien 2024/25

ToGA[1]
Phase III RCT
1L HER2 pos.
Addition of trastuzumab to chemotherapy improved OS

CheckMate 649[2]
Phase III RCT
1L non-HER2 pos.
Addition of nivolumab to chemotherapy improved OS, PFS in PD-L1 CPS ≥5

KEYNOTE-811[3]
Phase III RCT
1L HER2 pos.
Addition of pembrolizumab to trastuzumab and chemotherapy improved ORR in PD-L1 CPS ≥1

KEYNOTE-859[4]
Phase III RCT
1L HER2 neg.
Addition of pembrolizumab to chemotherapy improved OS, PFS, ORR, DOR in PD-L1 CPS ≥1

GLOW[5]**/SPOTLIGHT**[6]
Phase III RCTs
1L HER2 neg.
CLDN18.2 positive
Addition of zolbetuximab to CAPOX/mFolfox6 improved PFS, OS in

RATIONALE-305[7]
Phase III RCT
1L HER2 neg.
In PD-L1 TAP score ≥5% addition of tislelizumab to CAPOX or FP improved PFS, OS

[1]**Trastuzumab** in combination with fluoropyrimidine- and platinum-containing chemotherapy in 1st line; HER2-positive
2. Febuary **2010: EMA approval** 20. October **2010: FDA approval**

[2]**Nivolumab** in combination with fluoropyrimidine- and platinum-containing chemotherapy in 1st line; HER2-negative, PD-L1 CPS ≥5
16. April **2021: FDA approval**
16. September **2021: EMA approval**

[3]**Pembrolizumab** in combination with trastuzumab, fluoropyrimidine- and platinum-containing chemotherapy in 1st line; HER2-positive, PD-L1 CPS ≥1
5. May **2021: FDA approval**
29. August **2023: EMA approval**

[4]**Pembrolizumab** in combination with fluoropyrimidine- and platinum-containing chemotherapy in 1st line; HER2-negative, PD-L1 CPS ≥1
2023: FDA approval
13. October **2023: EMA approval**

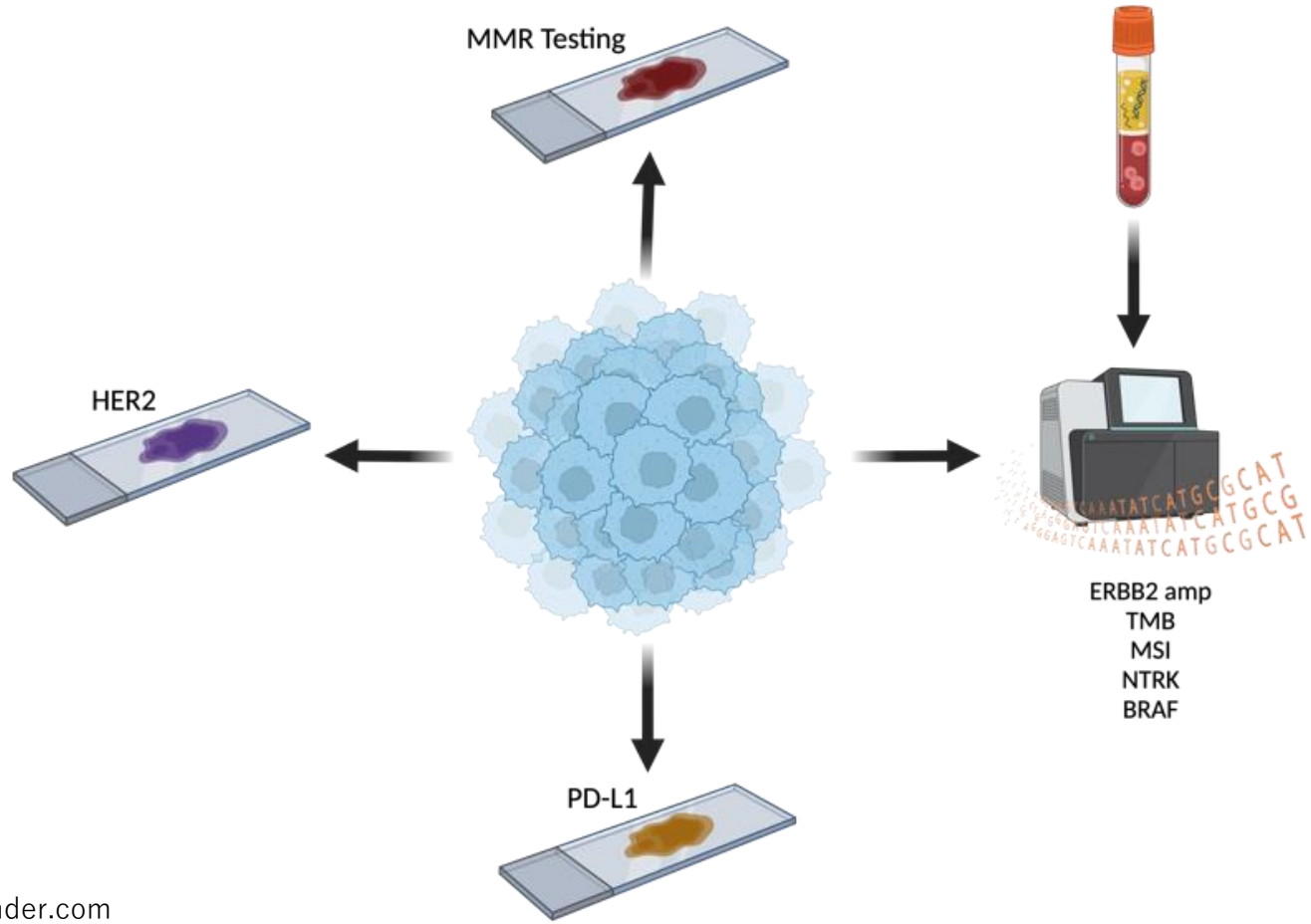
[5, 6]**Zolbetuximab** in combination with [5]CAPOX or [6]mFOLFOX6 in 1st line; HER2-negative, CLDN18.2 positive (moderate-to-high) mGEA

[7]**Tislelizumab** in combination with CAPOX (or FP) in 1st line; HER2-negative, PD-L1 positive (TAP score ≥5%) mGEA

FDA approval pending, **EMA approval 26.11.2024**

1Bang et al., Lancet. 2010; 2Janjigian et al., Lancet. 2021; 3Janjigian et al., Lancet. 2023; 4Rha et al., Lancet Oncology. 2023
5Shah et al., Nat. Med. 2023; 6Shitara et al., Lancet. 2023; 7Moehler et al., 2023 ASCO GI Cancers Symposium (Abstract 286). 2023

Zweimal messen, einmal schneiden: Biomarker-Tests



Made on Biorender.com

ALLE PATIENTEN brauchen BIOMARKER TESTUNG

MMR/MSI
HER2
PD-L1
CLDN18.2

Andere sind Bonus

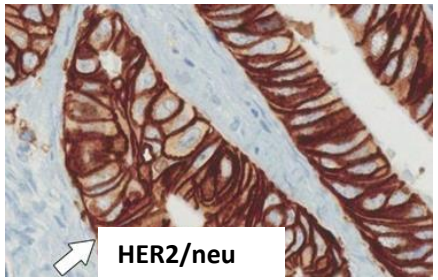
Zunehmende Anzahl Biomarker-stratifizierter Behandlungen

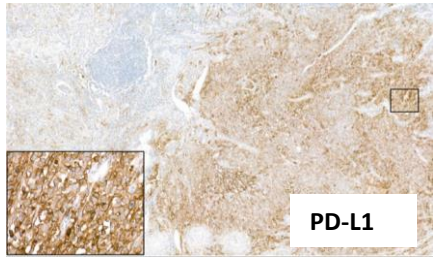
Etablierte Biomarker

HER2
10-20%

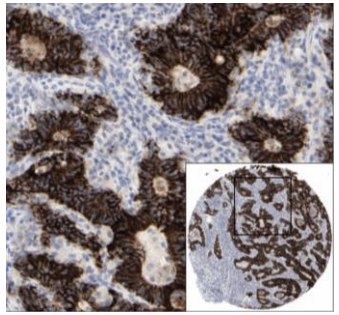
MSI/MMR IHC
5-10%

PD-L1
40-60%





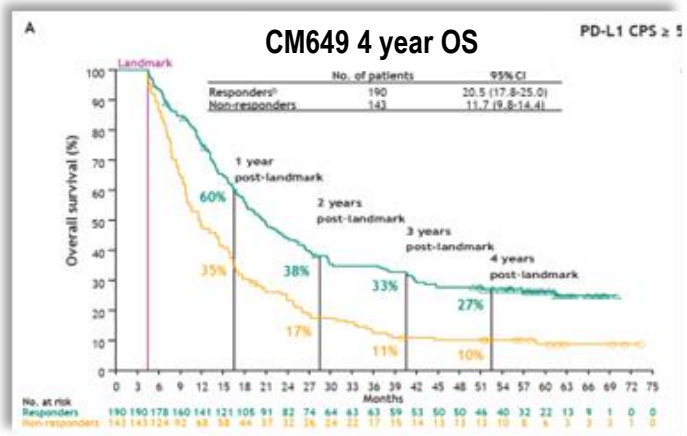
Claudin 18.2
30-40%

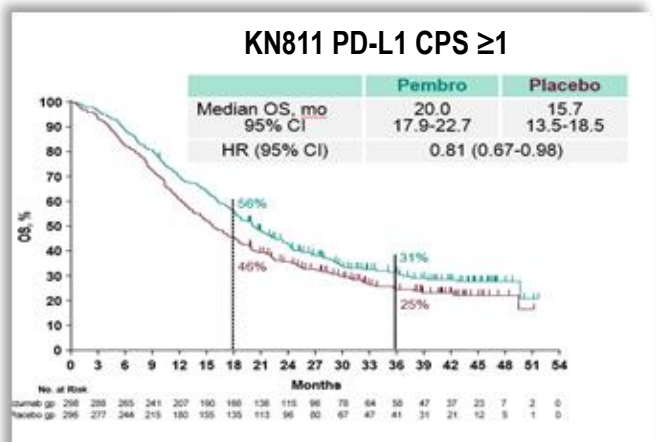


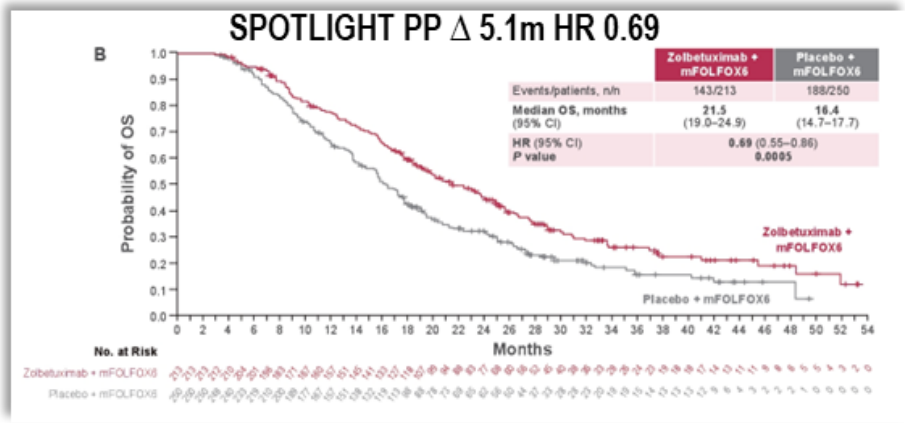
First-Line Systemic Treatment	Biomarker	mOS
Nivolumab + Chemotherapy Checkmate 649	PDL1 CPS ≥ 5	**14.4 mo**
Pembrolizumab + Chemotherapy KEYNOTE 859	PDL1 CPS ≥ 1	**13 mo**
Pembrolizumab + Chemotherapy + Trastuzumab KEYNOTE 811	PDL1 CPS ≥ 1 HER2 +	**20 mo**
Zolbetuximab + Chemotherapy SPOTLIGHT	CLDN 18.2	**19.2 mo**
Bemarituzumab + Chemotherapy FIGHT	FGFR2b	**18.2 mo**

Erstlinientherapie Magen CA & AEG 2025

Zielgerichtete Therapie in nach Biomarkern selektionierten Patienten



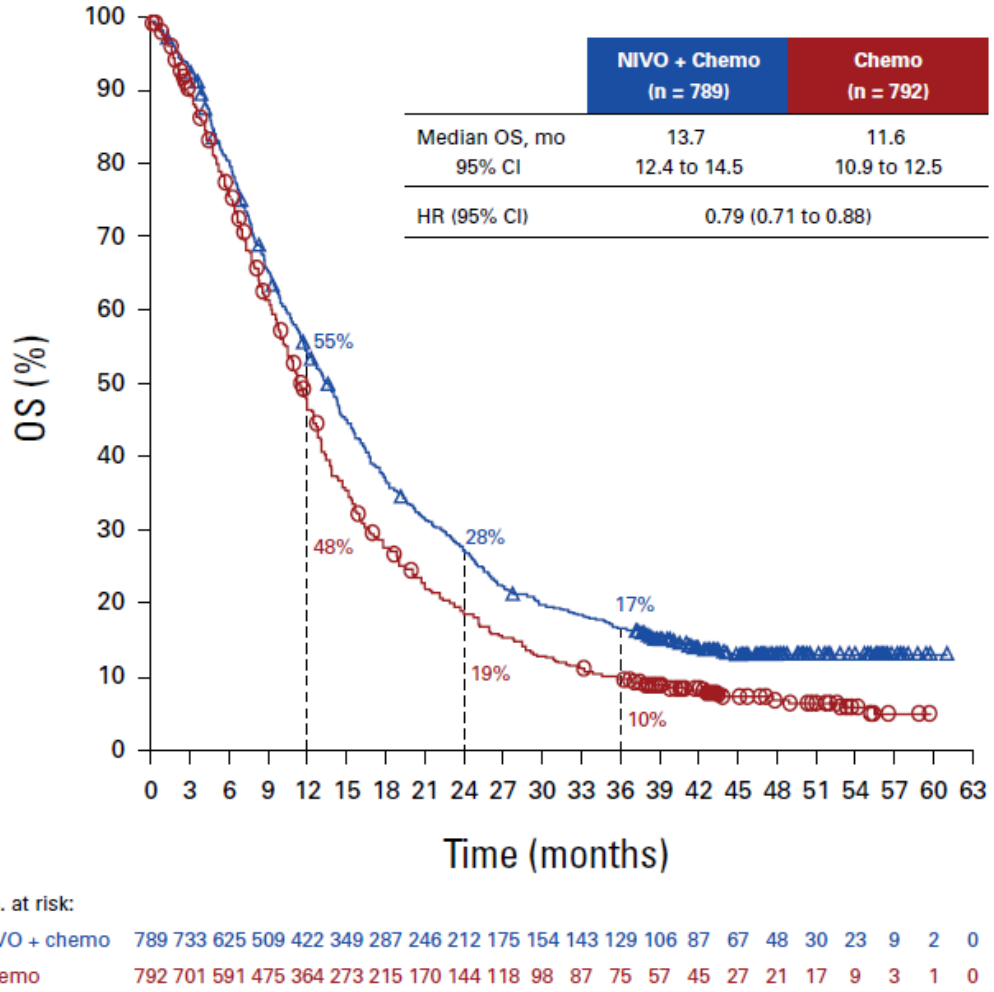




Trial	mAb	Cohort	Median OS
CM649	Nivolumab	CPS ≥ 5 responding patients	20.5m
KN811	Trastuzumab + pembrolizumab	HER2+ PD-L1 CPS≥1	20.0m
SPOTLIGHT	Zolbetuximab	CLD 18.2+ PP analysis	21.5m

Janjigian et al, ASCO GI 2024
Jangigian et al, Lancet 2023
Shitara et al, ASCO 2024

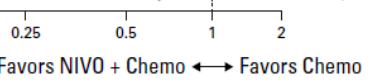
Checkpoint-Inhibitor Nivolumab – Langzeiteffekte in CM-649



	NIVO + Chemo (n = 789)	Chemo (n = 792)
Median OS, mo	13.7	11.6
95% CI	12.4 to 14.5	10.9 to 12.5
HR (95% CI)	0.79 (0.71 to 0.88)	

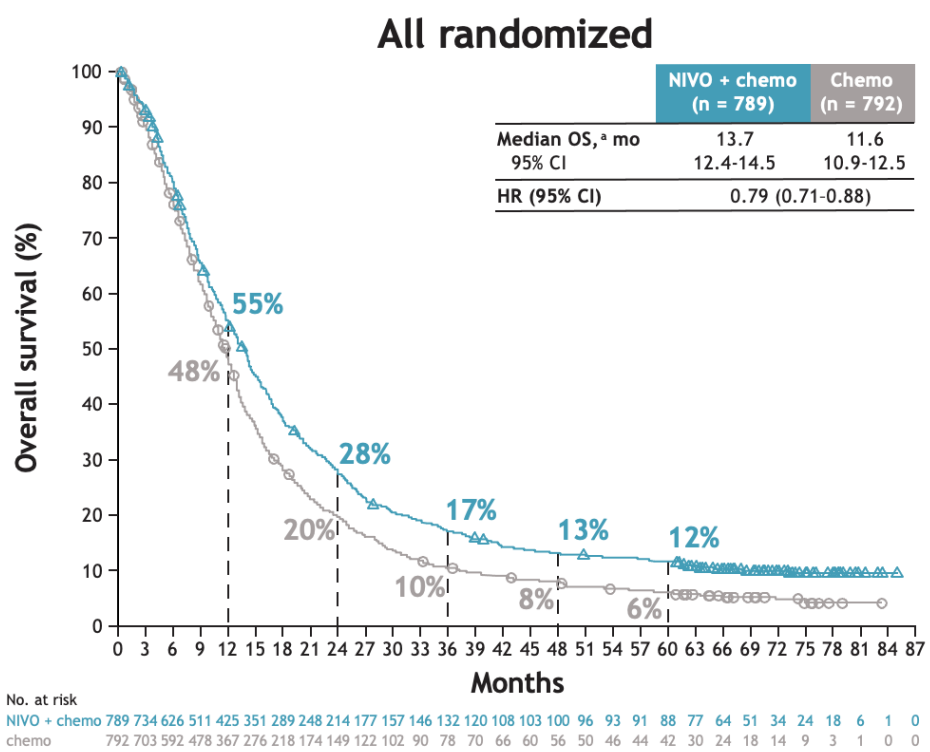
A

Category (PD-L1 CPS ≥5)	Subgroup	Median OS, Months NIVO + Chemo	Median OS, Months Chemo	Unstratified HR for Death (95% CI)
Overall (N = 955)		14.4	11.1	0.69 (0.60 to 0.79)
Age, years	<65 (n = 552)	14.4	11.1	0.69 (0.57 to 0.83)
	≥65 (n = 403)	14.3	11.2	0.69 (0.56 to 0.85)
Sex	Male (n = 680)	14.4	10.8	0.66 (0.56 to 0.78)
	Female (n = 275)	14.3	12.1	0.77 (0.60 to 0.99)
Region	Asia (n = 228)	16.1	11.8	0.61 (0.46 to 0.82)
	United States/Canada (n = 137)	18.2	12.6	0.65 (0.44 to 0.94)
	ROW (n = 590)	13.1	10.4	0.74 (0.62 to 0.88)
ECOG PS	0 (n = 397)	17.8	13.8	0.74 (0.59 to 0.92)
	1 (n = 558)	12.6	8.5	0.64 (0.54 to 0.77)
Primary tumor location	GC (n = 667)	15.0	10.5	0.64 (0.54 to 0.76)
	GEJC (n = 170)	13.4	13.1	0.81 (0.58 to 1.12)
	EAC (n = 118)	11.2	11.3	0.80 (0.54 to 1.19)
Signet ring cell carcinoma	Yes (n = 141)	12.1	10.1	0.67 (0.47 to 0.96)
	No (n = 814)	15.0	11.3	0.69 (0.59 to 0.80)
Liver metastases[a]	Yes (n = 407)	13.1	9.8	0.64 (0.52 to 0.79)
	No (n = 519)	15.5	11.6	0.73 (0.60 to 0.88)
Tumor cell PD-L1 expression[b]	<1% (n = 724)	14.2	11.6	0.75 (0.64 to 0.87)
	≥1% (n = 230)	16.2	8.8	0.54 (0.40 to 0.72)
MSI status[c]	MSS (n = 847)	14.3	11.1	0.71 (0.62 to 0.83)
	MSI-H (n = 34)	44.8	8.8	0.29 (0.12 to 0.71)
Chemotherapy regimen	FOLFOX (n = 479)	14.3	11.3	0.68 (0.56 to 0.83)
	XELOX (n = 454)	15.0	11.0	0.69 (0.57 to 0.85)

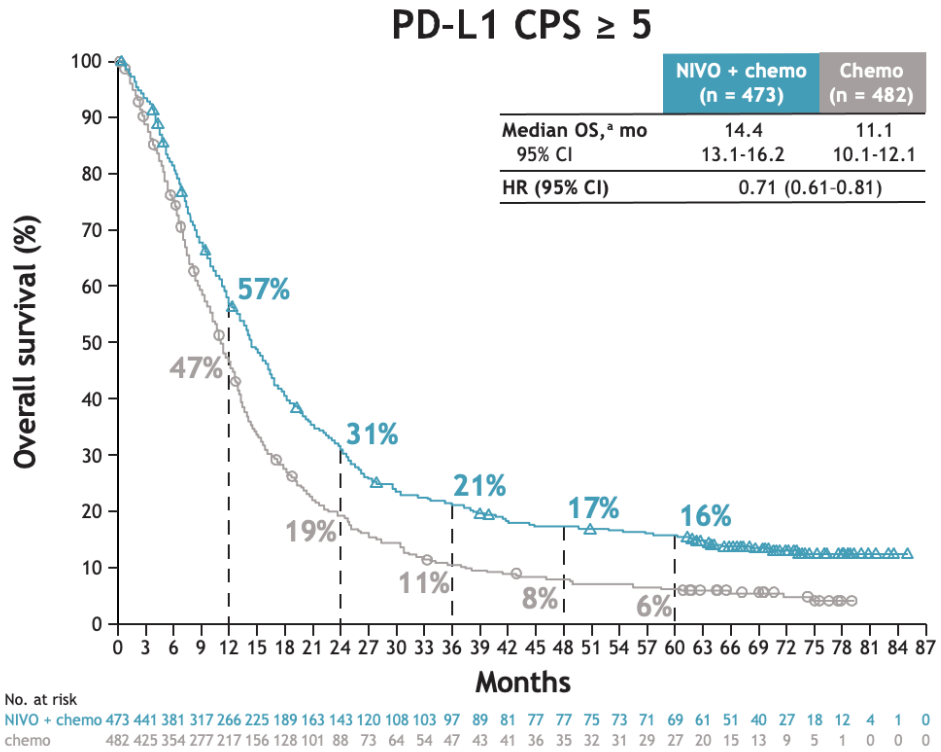


Janjigian YY et al., J Clin Oncol. 2024 Jun 10;42(17):2012-2020

Checkpoint-Inhibitor Nivolumab: 5-Jahres Überleben in CM-649



Follow-up 60,1 Monate

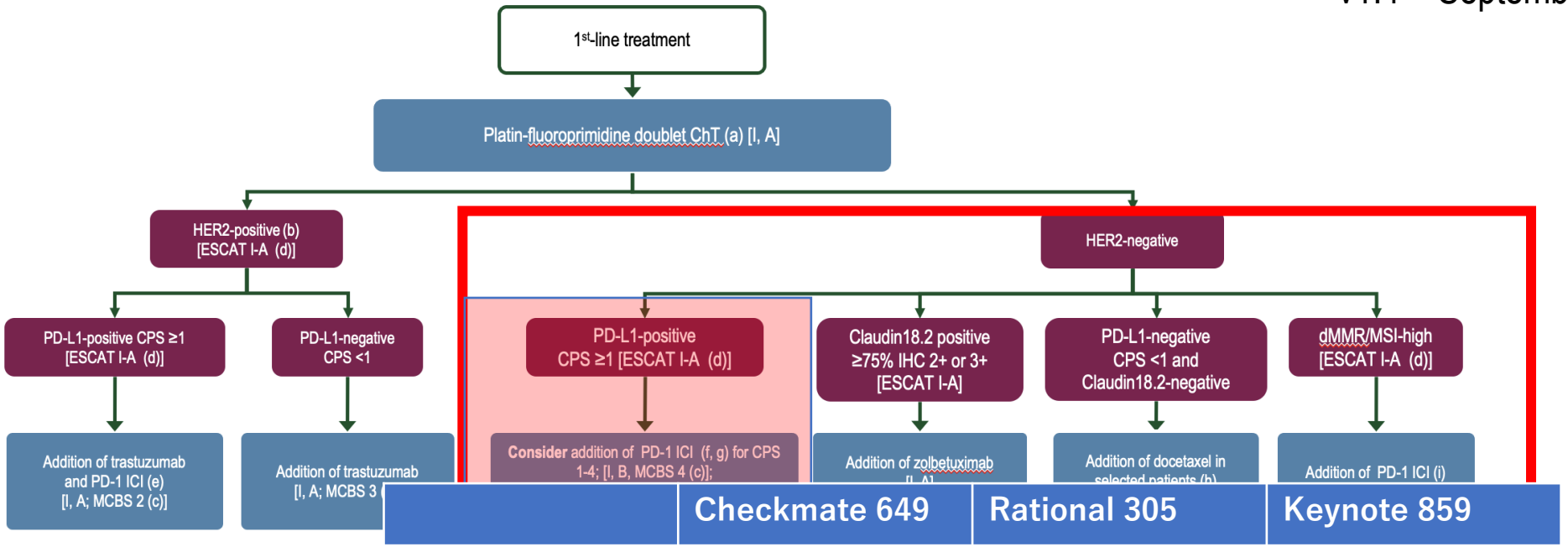


- **In CPS ≥5:**
  5-Jahres Überleben um 10% verbessert mit Nivolumab

Janjigian YY et al., ASCO GI 2025 # *398*

Erstlinientherapie HER2 - : Update ESMO Living Guideline

v1.4 – September 2024



	Checkmate 649	Rational 305	Keynote 859
Anti-PD-1	Nivolumab	Tislelizumab	Pembrolizumab
OS	All HR 0.80 CPS ≥1 HR 0.77 CPS ≥ 5 HR 0.71 CPS ≥ 10 HR 0.66	TAP ≥ 5 HR 0.74	All HR 0.78 CPS ≥1 HR 0.73 CPS ≥10 HR 0.64

Gleichwertige Anti-PD1-Antikörper in globalen klinischen Studien für Patienten mit hoher PD-L1-Expression

Checkpoint-Inhibitoren und niedrige PD-L1 Expression

PD-L1 CPS 1-9 (HR 0.84) PD-L1 CPS 1-4 (HR 0.86) PD-L1 CPS 5-9 (HR 0.86)

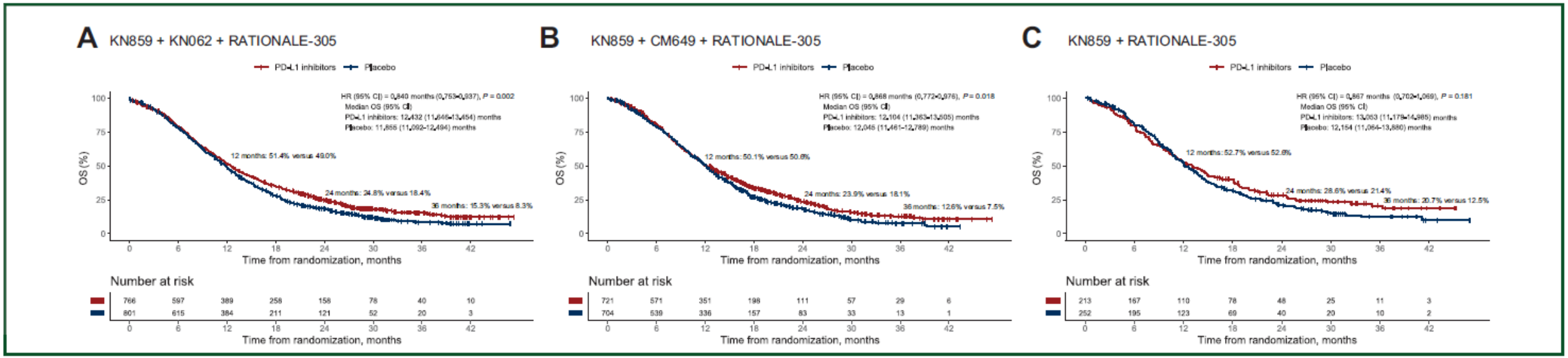


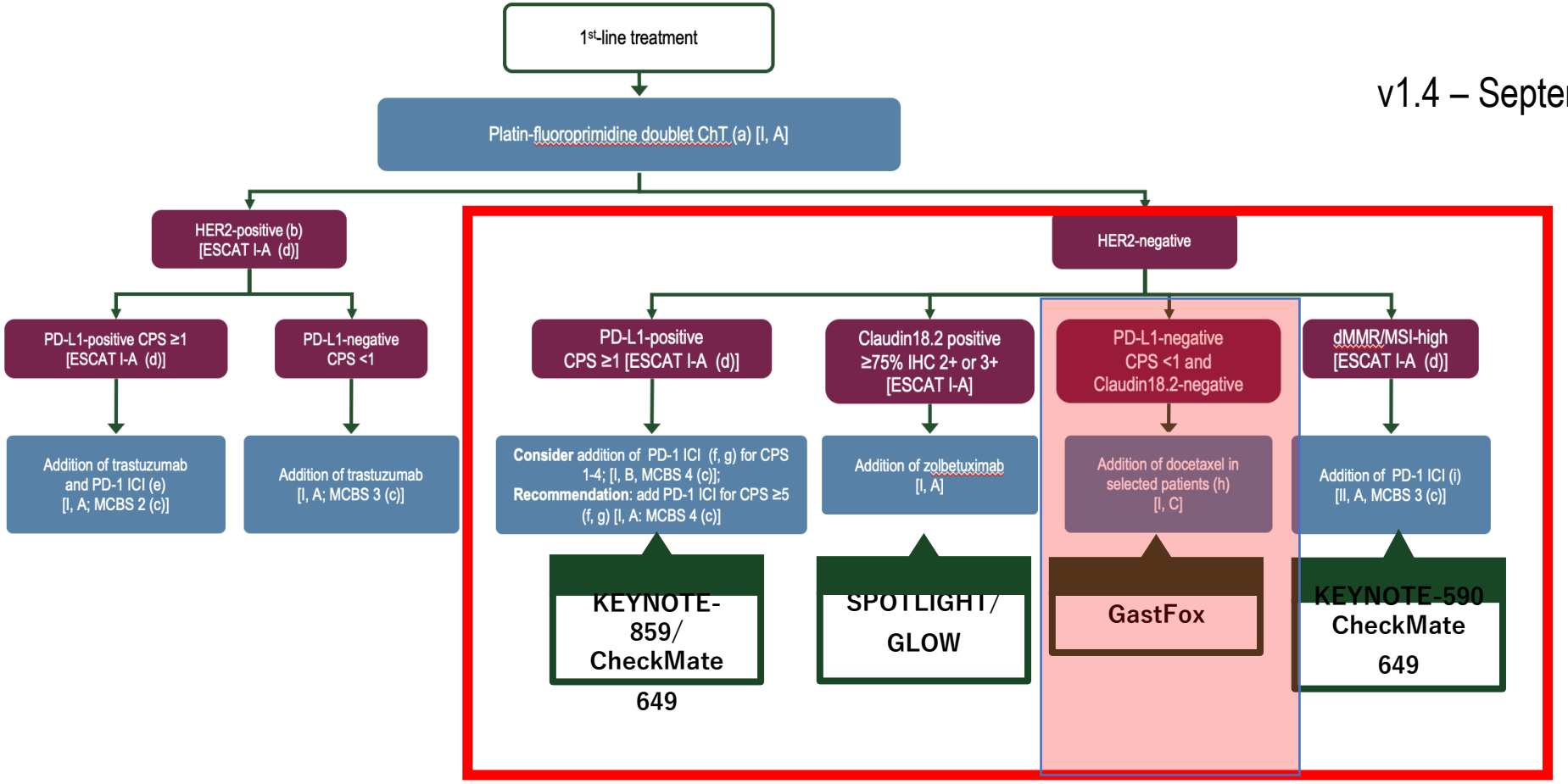
Figure 4. Pooled analysis of PD-L1$_{low}$ subgroups in human epidermal growth factor receptor 2 (HER2)-advanced GEAC. (A) OS outcomes for the PD-L1 CPS 1-9 subgroup comprising KEYNOTE-859, KEYNOTE-062, and RATIONALE-305. (B) OS outcomes for the PD-L1 CPS 1-4 subgroup comprising KEYNOTE-859, CHECKMATE-649, and RATIONALE-305. (C) OS outcomes for the PD-L1 CPS 5-9 subgroup comprising KEYNOTE-859 and RATIONALE-305.
CI, confidence interval; CPS, combined positive score; GEAC, gastroesophageal adenocarcinoma; HR, hazard ratio; OS, overall survival; PD-L1, programmed death-ligand 1.

Leone AG et al., ESMO Open. 2024 Nov;9(11):103962.

Update ESMO Living Guideline September 2024

Doublette vs Triplette 1L Therapie?

v1.4 – September 2024



Phase 3 GASTFOX Studie (FFCD-PRODIGE 51)
First-line Her-2 negativ

Key eligibility criteria
- Previously untreated, locally advanced unresectable or metastatic G/GEJ adenocarcinoma
- HER2-negative
- ECOG PS 0-1
- Docetaxel naïve

R 1:1

- mFLOT/TFOX
- FOLFOX

Maintenance treatment until unacceptable toxicity or disease progression

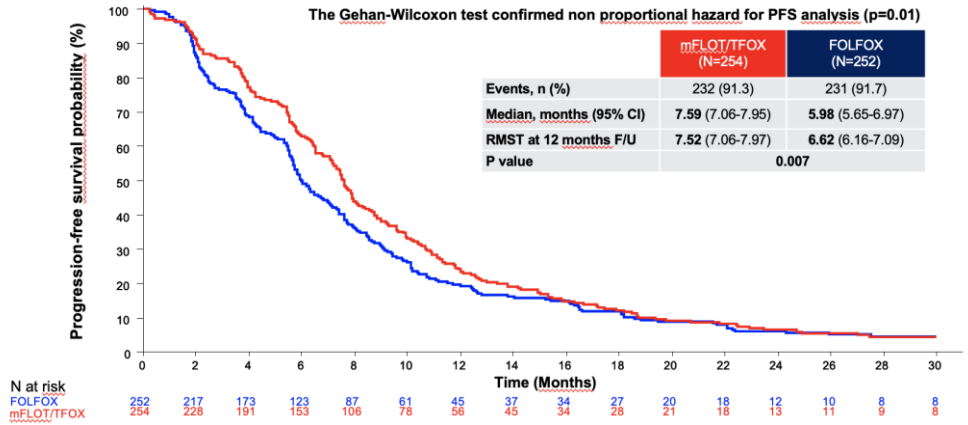
Stratification factors:

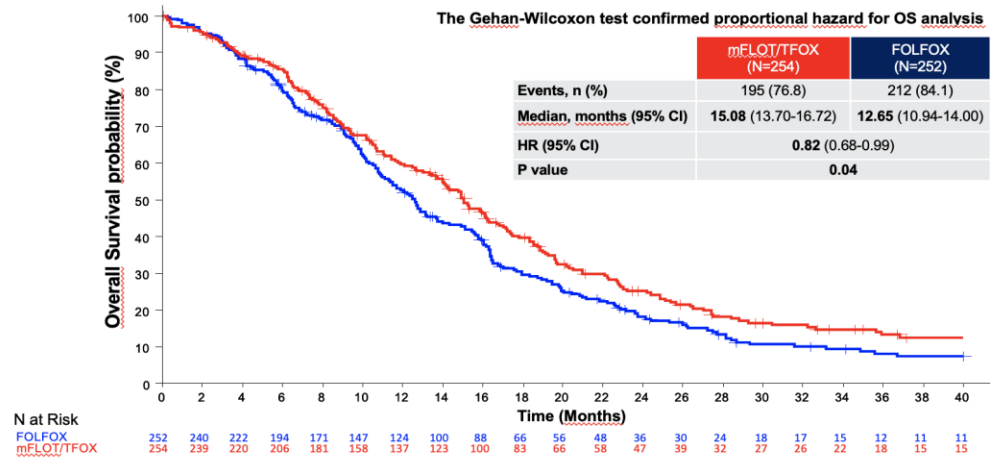
ECOG (0 vs 1),
prior (neo)adjuvant (yes vs no),
tumor stage (LA vs metastatic),
tumor location (G vs GEJ),
pathological subtype
(signet ring cell : yes vs no)

Primary endpoint: EFS (ITT) and an expected HR=0.733 in favor to mFLOT/TFOX

Q2W	FOLFOX	mFLOT/TFOX (1)	FLOT (2-3)
Docetaxel	-	50 mg/m²	50 mg/m²
Oxaliplatin	85 mg/m²	85 mg/m²	85 mg/m²
5FU bolus	400 mg/m²	-	
5FU continuous	2400 mg/m² /46h		² /24h

Nur für selektionierte Patienten: jung, fit, hoher Remissionsdruck

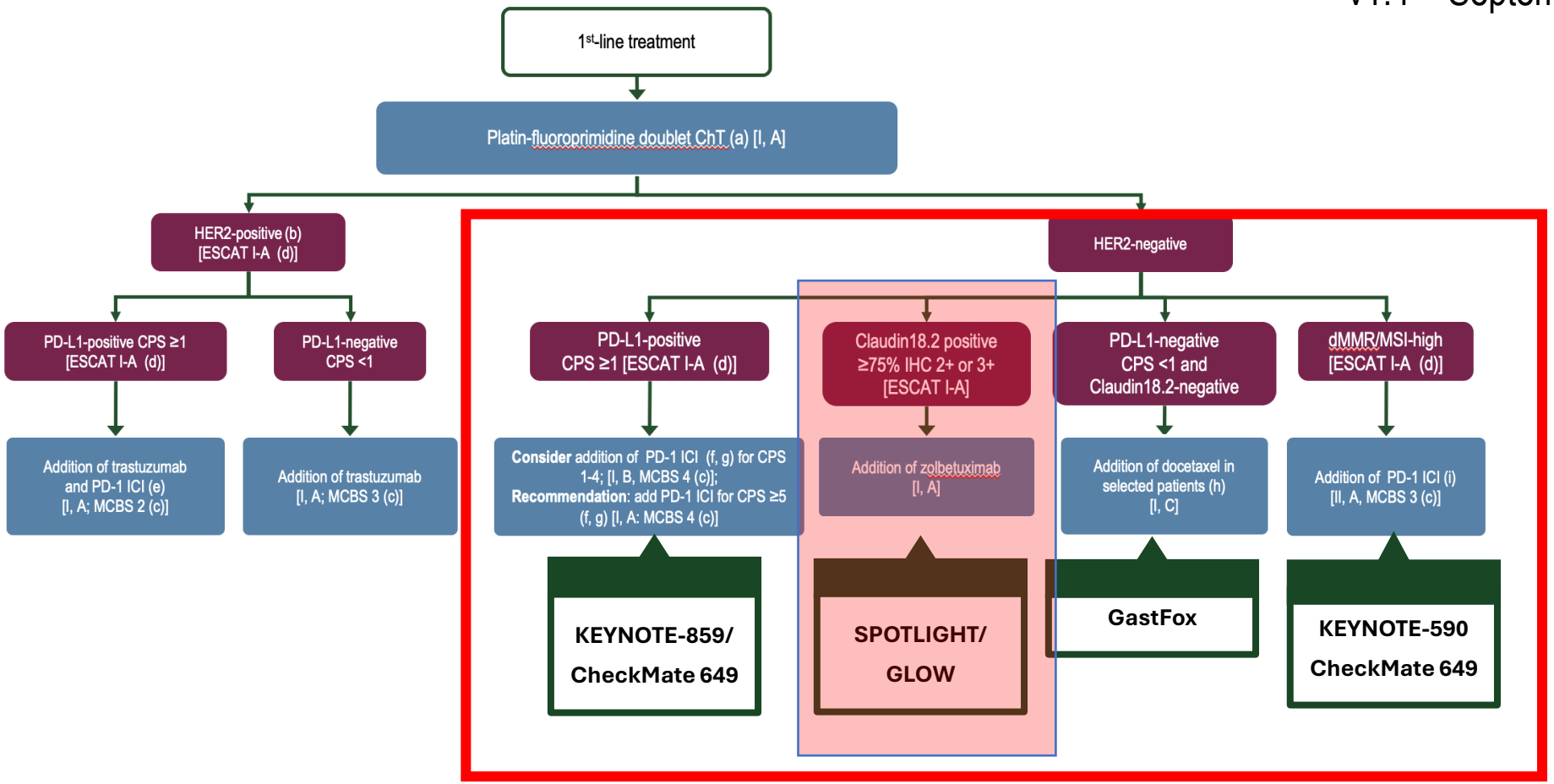




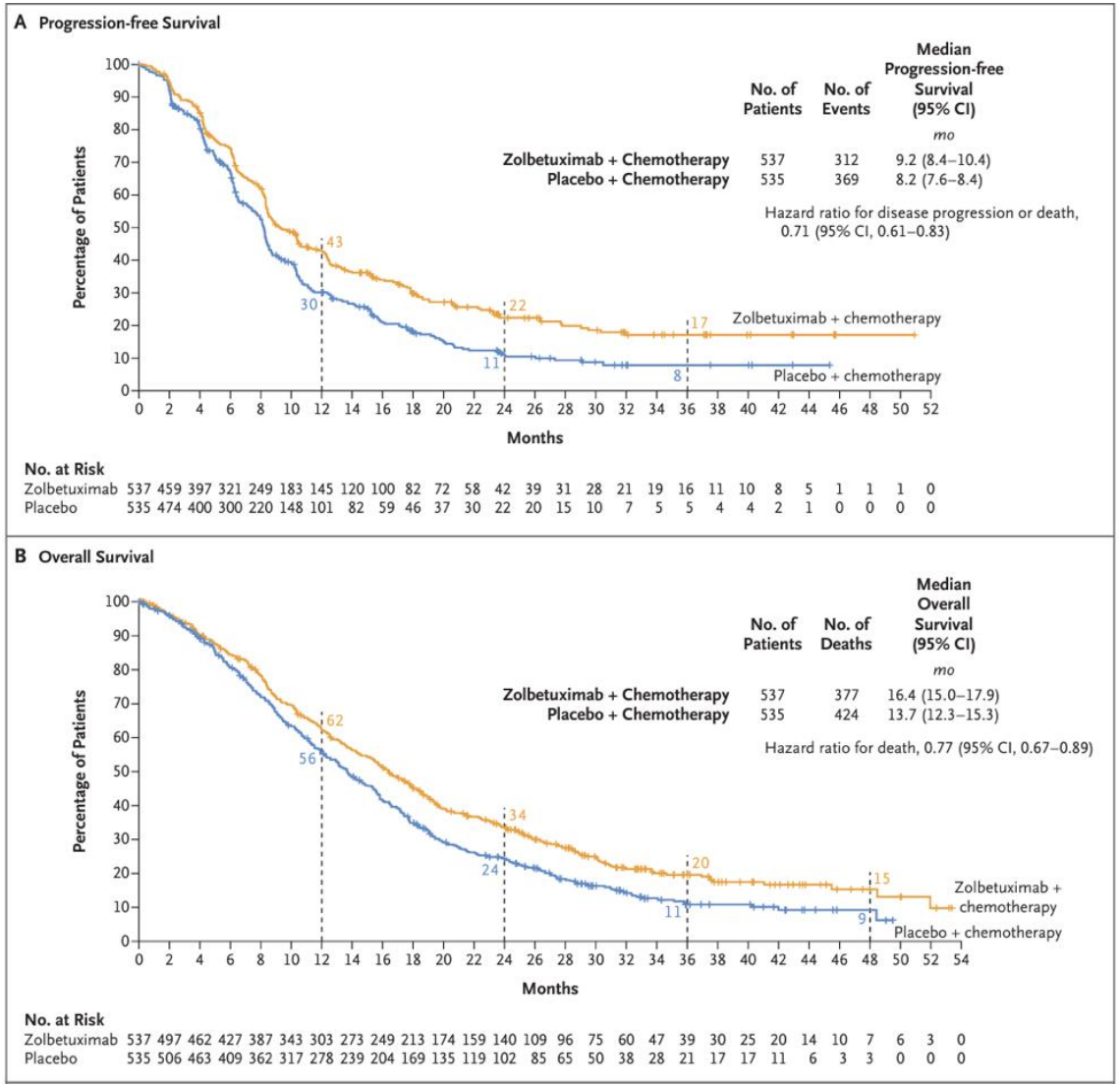
Zaanan A ESMO 2023; # 3625

Update ESMO Living Guideline September 2024

v1.4 – September 2024



Erstlinientherapie des HER2- GEA: CLDN18.2



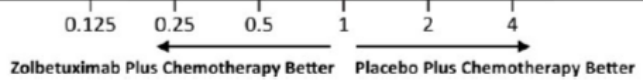
- CLDN18.2 wird in ~40% aller GEA in höherem Maße exprimiert (2+/3+ in > 75% der Tumorzellen).
- Eine auf CLDN18.2 gerichtete Therapie mit Zolbetuximab in Kombination mit 5FU/Platin verbessert das PFS und OS
- CLDN 18.2 ist ein validierter Biomarker in Verbindung mit einer Therapie.

ESMO 2024: Y.-K. Kang et al., 1438P
Shitara et al.Lancet. 2023 May 20;401(10389):1655-1668
Shah et al. Nat Med. 2023 Aug;29(8):2133-2141.

Zolbetuximab – Überleben in Subgruppen

B

Subgroup	Zolbetuximab Plus Chemotherapy (no. events/no. patients)	Placebo Plus Chemotherapy (no. events/no. patients)	Hazard Ratio (95% CI)
All patients	377/537	424/535	0.77 (0.67–0.89)
Age			
≤65 yr	241/357	284/361	0.73 (0.62–0.87)
>65 yr	136/180	140/174	0.85 (0.67–1.07)
Sex			
Male	243/335	272/331	0.78 (0.66–0.93)
Female	134/202	152/204	0.76 (0.60–0.96)
Region			
Asia	166/245	190/247	0.71 (0.58–0.88)
Non-Asia	211/292	234/288	0.83 (0.69–1.00)
Number of metastatic sites			
0–2	274/408	312/407	0.76 (0.65–0.90)
≥3	103/129	112/128	0.78 (0.59–1.02)
Prior gastrectomy			
No	276/378	303/378	0.83 (0.71–0.98)
Yes	101/159	121/157	0.65 (0.50–0.85)
Lauren classification			
Diffuse	120/169	164/217	0.82 (0.65–1.04)
Intestinal	75/106	90/107	0.65 (0.47–0.88)
Mixed/other	96/135	85/103	0.88 (0.66–1.18)
Primary site			
Stomach	301/438	331/419	0.72 (0.62–0.84)
Gastroesophageal junction	76/99	93/116	1.02 (0.76–1.39)
Race			
White	175/234	183/224	0.89 (0.72–1.09)
Asian	171/254	196/255	0.69 (0.56–0.85)



CI, confidence interval; HR, hazard ratio.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

25 July 2024
EMA/CHMP/318981/2024
Committee for Medicinal Products for Human Use (CHMP)

Summary of opinion[1] (initial authorisation)

Vyloy
zolbetuximab

On 25 July 2024, the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion, recommending the granting of a marketing authorisation for the medicinal product Vyloy[2], intended for the treatment of gastric or gastro-oesophageal junction (GEJ) adenocarcinoma.

The full indication is:

Vyloy, in combination with fluoropyrimidine- and platinum-containing chemotherapy, is indicated for the first-line treatment of adult patients with locally advanced unresectable or metastatic HER2-negative gastric or gastro-oesophageal junction (GEJ) adenocarcinoma whose tumours are Claudin (CLDN) 18.2 positive (see section 4.2).

Shitara K et al. N Engl J Med. 2024 Sep 26;391(12):1159-1162

Zolbetuximab – Unerwünschte Effekte

Table S9. Treatment-Emergent Adverse Events*,† in the Safety Analysis Set in the Combined Analysis

Event – no. (%)	Zolbetuximab + chemotherapy (n = 533)		Placebo + chemotherapy (n = 527)	
	All grade	Grade ≥3	All grade	Grade ≥3
Nausea	405 (76.0)	67 (12.6)	296 (56.2)	25 (4.7)
Vomiting	356 (66.8)	76 (14.3)	180 (34.2)	26 (4.9)
Decreased appetite	241 (45.2)	34 (6.4)	183 (34.7)	13 (2.5)
Anemia	199 (37.3)	53 (9.9)	199 (37.8)	54 (10.2)
Diarrhea	197 (37.0)	27 (5.1)	212 (40.2)	28 (5.3)
Neutrophil count decreased	167 (31.3)	95 (17.8)	150 (28.5)	93 (17.6)
Peripheral sensory neuropathy	164 (30.8)	13 (2.4)	175 (33.2)	21 (4.0)
Neutropenia	152 (28.5)	97 (18.2)	129 (24.5)	72 (13.7)
Constipation	141 (26.5)	3 (0.6)	166 (31.5)	4 (0.8)
Fatigue	118 (22.1)	25 (4.7)	136 (25.8)	24 (4.6)
Aspartate aminotransferase increased	113 (21.2)	10 (1.9)	122 (23.1)	16 (3.0)
Abdominal pain	111 (20.8)	15 (2.8)	143 (27.1)	11 (2.1)
Asthenia	108 (20.3)	28 (5.3)	96 (18.2)	10 (1.9)
Weight decreased	108 (20.3)	7 (1.3)	81 (15.4)	4 (0.8)
Hypoalbuminemia	103 (19.3)	20 (3.8)	53 (10.1)	6 (1.1)
Platelet count decreased	102 (19.1)	22 (4.1)	111 (21.1)	27 (5.1)
White blood cell count decreased	102 (19.1)	13 (2.4)	86 (16.3)	26 (4.9)
Pyrexia	95 (17.8)	2 (0.4)	73 (13.9)	1 (0.2)
Hypokalemia	88 (16.5)	30 (5.6)	80 (15.2)	27 (5.1)
Alanine aminotransferase increased	83 (15.6)	4 (0.8)	103 (19.5)	17 (3.2)

*The all-grade events reported here occurred in ≥15% of patients in either treatment group in the combined analysis.
†Preferred terms were defined according to the Medical Dictionary for Regulatory Activities terminology version 25.0.

Shitara K et al. N Engl J Med. 2024 Sep 26;391(12):1159-1162

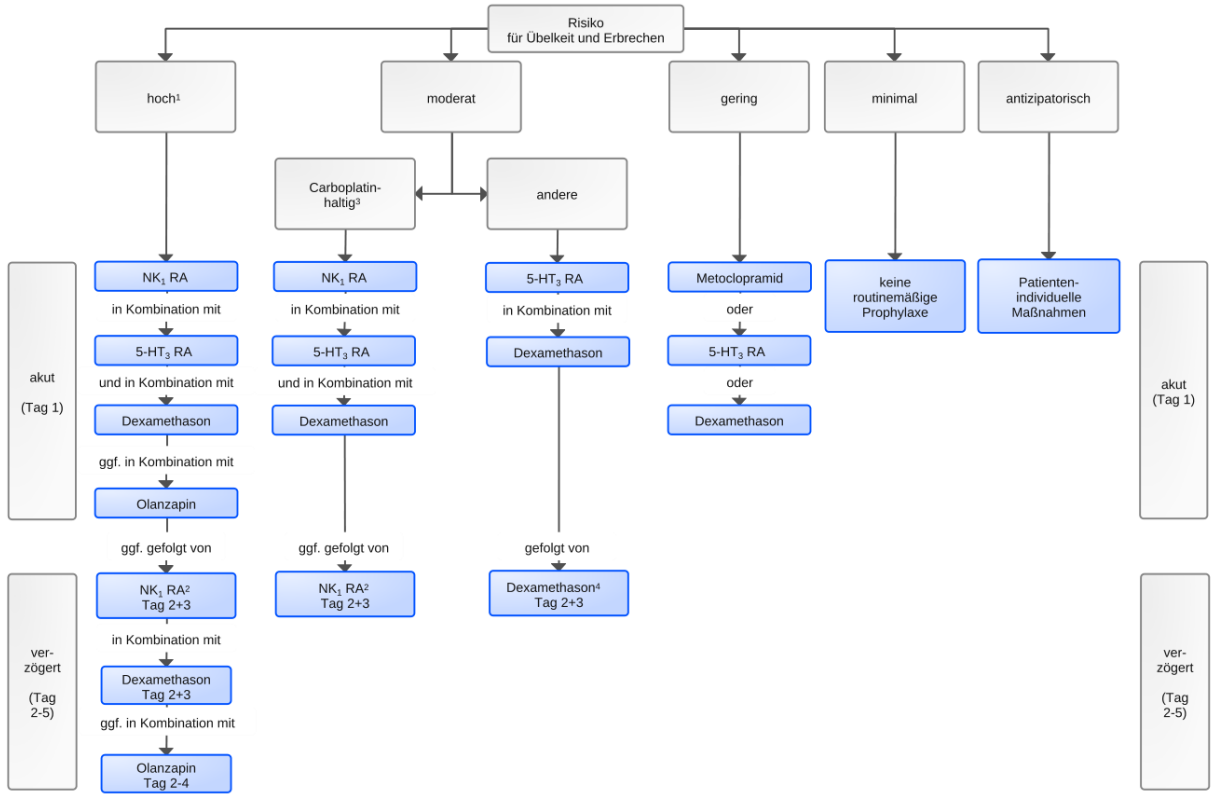
Zolbetuximab – Unerwünschte Effekte

Zolbetuximab ist hoch emetogen!

Entsprechende antiemetische Prophylaxe

Pausen und langsamere Infusionsrate bei Nausea & Emesis

Algorithmus für die antiemetische Prophylaxe bei intravenöser Tumortherapie



Legende:
*[1]Zur hoch emetogenen Risikogruppe zählen auch Patient*innen mit Mammakarzinom, die eine Anthrazyklin/Cyclophosphamid-basierte Chemotherapie erhalten.*
[2]Gabe an den Tagen 2 und 3 bei Aprepitant erforderlich; bei Fosaprepitant und Netupitant (NEPA) erfolgt die Gabe nur an Tag 1.
[3]Randomisierte Studien liegen nur für Carboplatin AUC ≥ 4 vor.
[4]Gabe von Dexamethason in der verzögerten Phase nur bei Chemotherapien mit erhöhtem Potential für verzögertes Erbrechen (z.B. Oxaliplatin, Doxorubicin, Cyclophosphamid.
Abkürzungen: NK_1-RA – Neurokinin$_1$-Rezeptorantagonist; 5-HT_3-RA – 5HT_3- Rezeptorantagonist

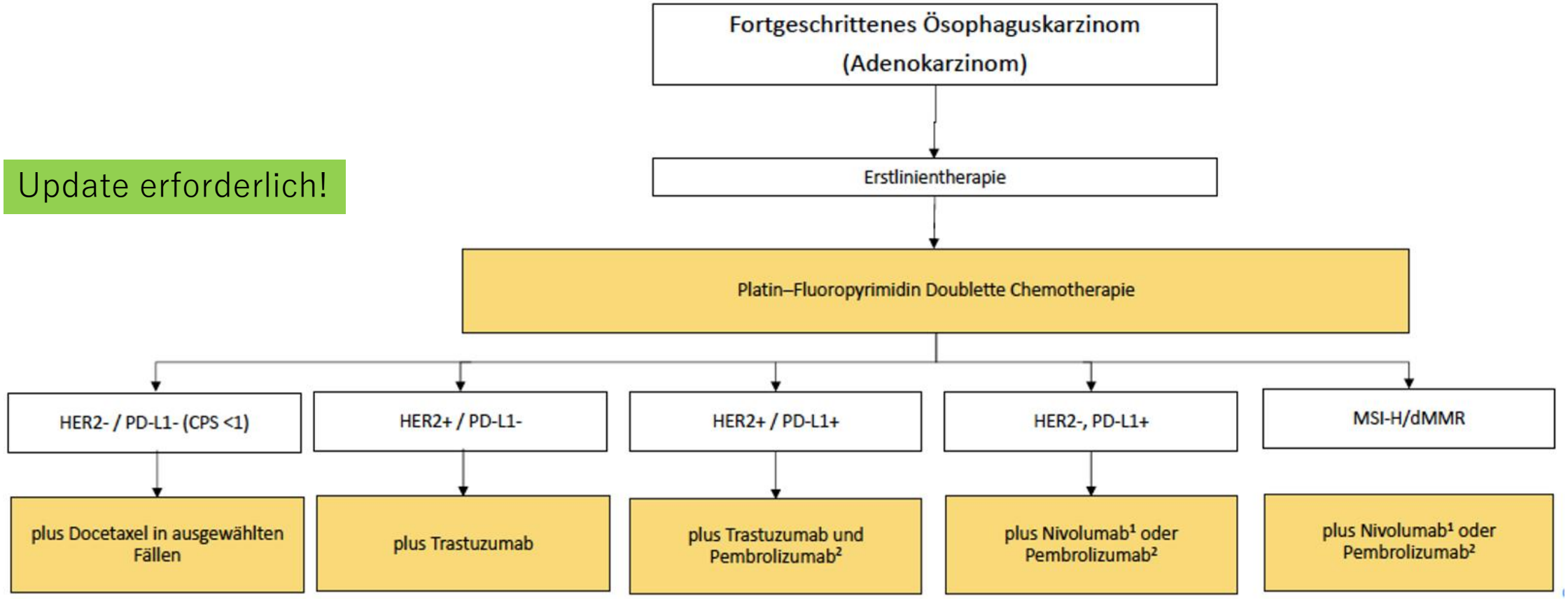
Antiemese bei medikamentöser Tumortherapie — Onkopedia

Karin Jordan et al., Onkopedia.de

Algorithmus für die Erstlinientherapie des Adenokarzinoms des Ösophagus im Stadium IV

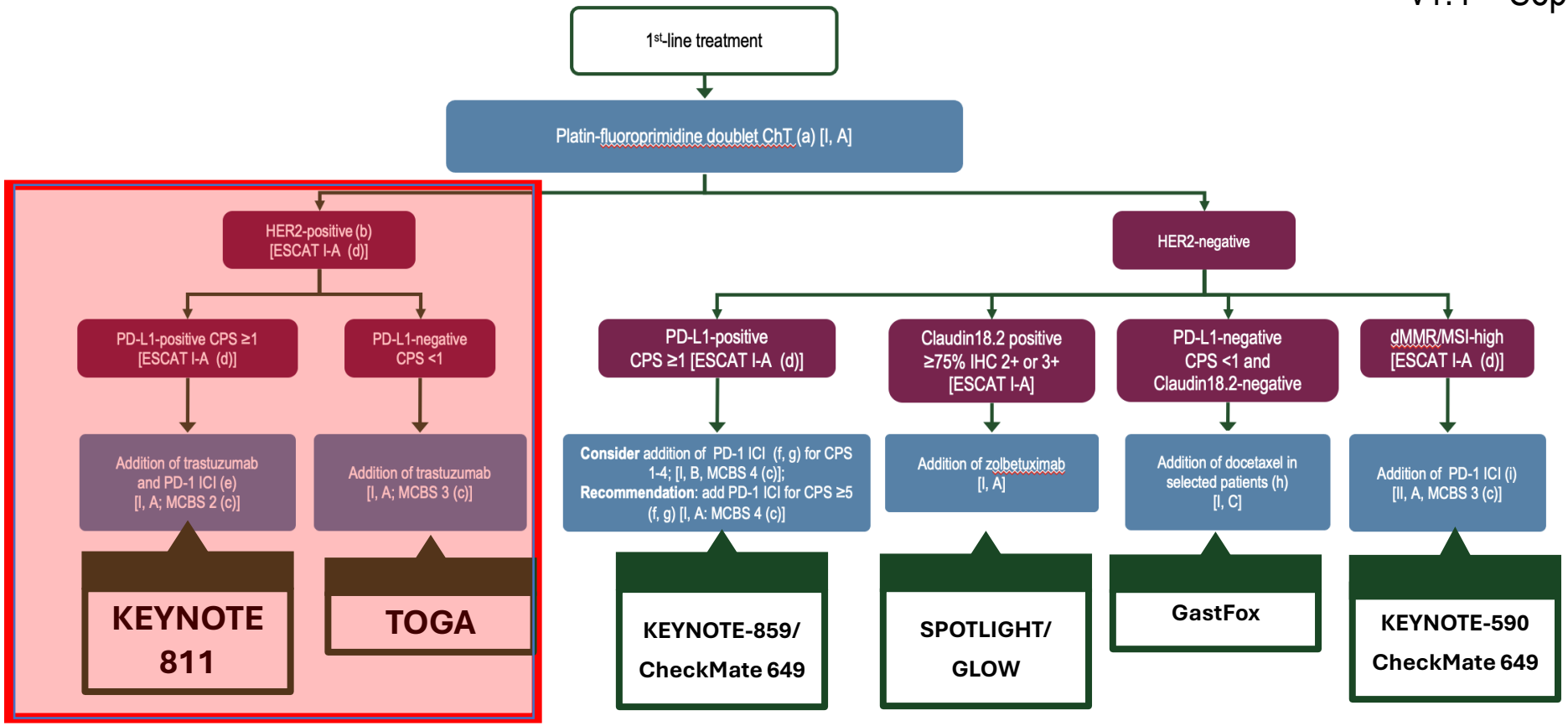
Lorenzen update Onkopedia LL Okt 2024

Update erforderlich!



Erstlinientherapie HER2 +: Update ESMO Living Guideline September 2024

v1.4 – September 2024

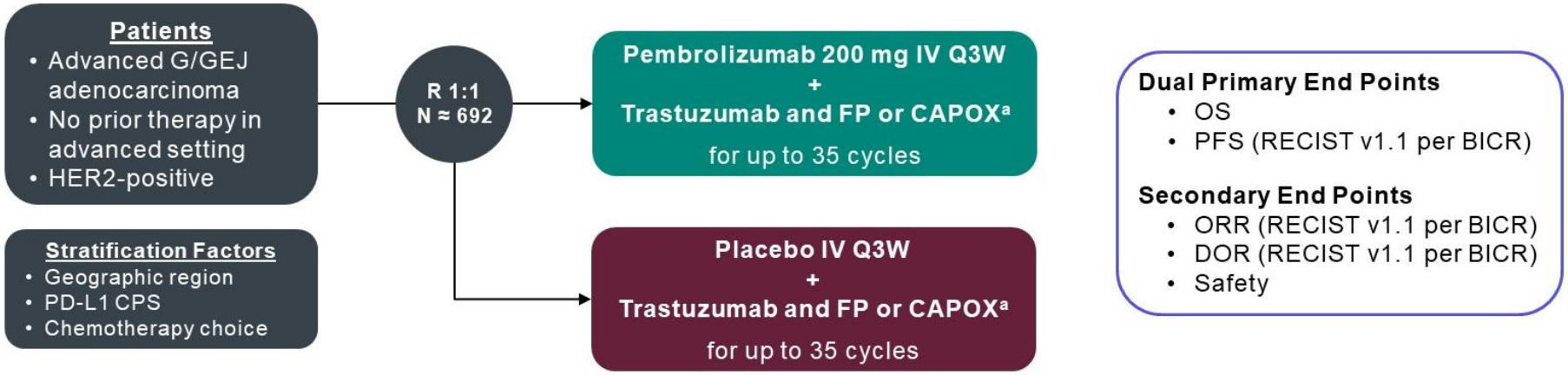


Immuntherapie 1st-line, HER2-pos.

KEYNOTE-811: Randomisierte globale Phase III

First-line fortgeschrittenes HER2-positives Magen-Ca/ AEG

Double-Blind Phase 3 Study of Pembrolizumab + Trastuzumab and Chemotherapy vs Placebo + Trastuzumab and Chemotherapy as First-Line Therapy For HER2-Positive Unresectable or Metastatic G/GEJ Cancer (NCT03615326)



[a]Trastuzumab dose: 6 mg/kg IV Q3W following an 8 mg/kg loading dose. FP dose: 5-fluorouracil 800 mg/m² IV on D1-5 Q3W + cisplatin 80 mg/m² IV Q3W. CAPOX dose: capecitabine 1000 mg/m² BID on D1-14 Q3W + oxaliplatin 130 mg/m² IV Q3W.
BICR, blinded independent central review; CPS, combined positive score (number of PD-L1–staining cells [tumor cells, lymphocytes, macrophages] divided by the total number of viable tumor cells, multiplied by 100).

Janjigian YY et al., Lancet. 2023; 402(10418):2197–2208

Erstlinientherapie des Her2+ GEA: KEYNOTE- 811

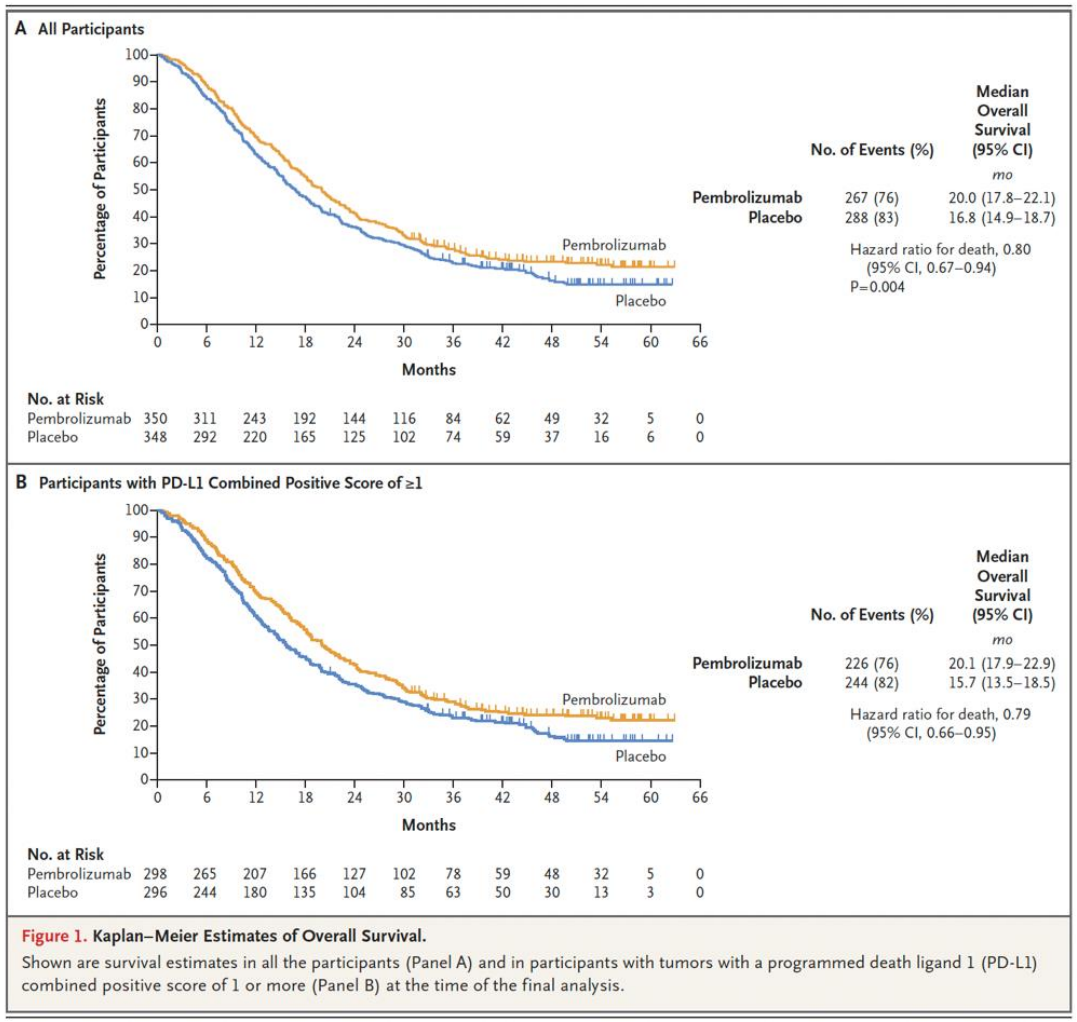


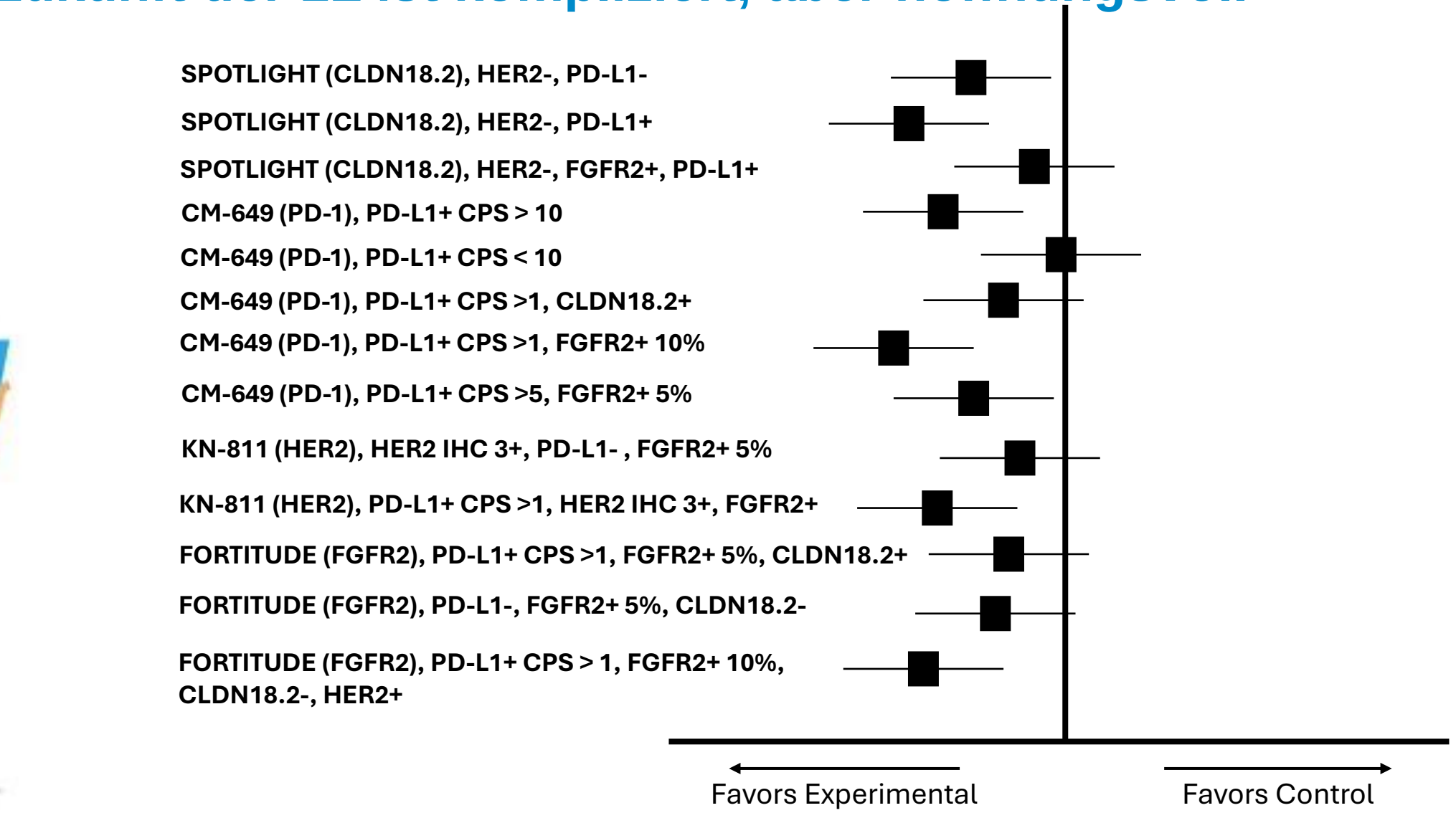
Figure 1. Kaplan–Meier Estimates of Overall Survival.
Shown are survival estimates in all the participants (Panel A) and in participants with tumors with a programmed death ligand 1 (PD-L1) combined positive score of 1 or more (Panel B) at the time of the final analysis.

1. HER2+ bei 18-30% der GEA
2. Wie PD-L1 ist auch der Grad der HER2-Expression/Amplifikation von Bedeutung
3. IO zu 5FU/Platin/Trastuzumab verbessert PFS **und OS** bei HER2+ (> bei PD-L1+)

	PD-L1 CPS ≥1		PD-L1 CPS <1	
	Pembrolizumab Group N = 298	Placebo Group N = 296	Pembrolizumab Group N = 52	Placebo Group N = 52
PFS, median	10.9	7.3	9.5	9.5
HR (95% CI)	0.72 (0.60-0.87)		0.99 (0.62-1.56)	
OS, median	20.1	15.7	18.2	20.4
HR (95% CI)	0.79 (0.66-0.95)		1.10 (0.72-1.68)	

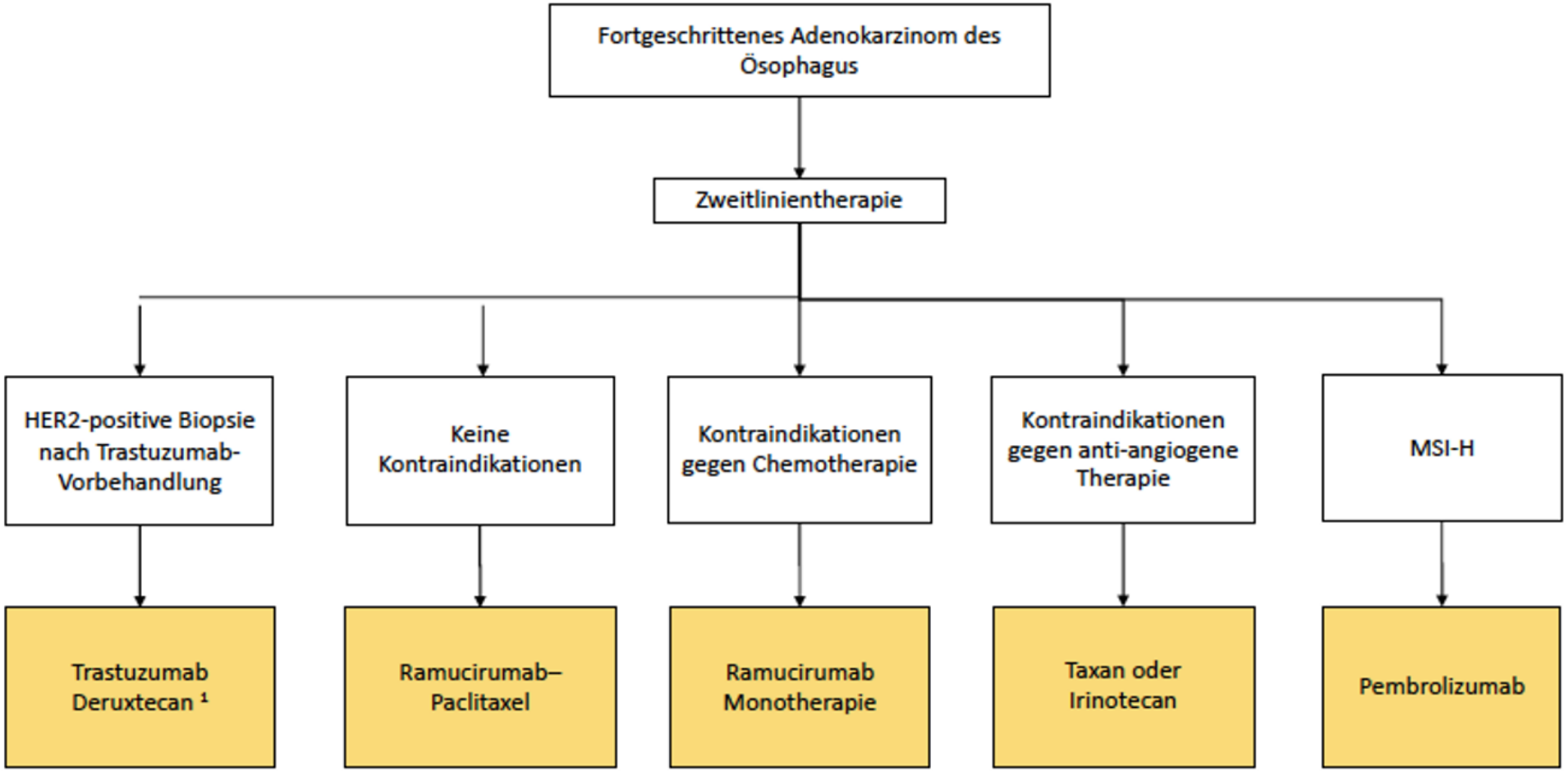
Janjigian et al, ESMO 2024, Rha et al, ESMO Asia 2024

Die Zukunft der 1L ist kompliziert, aber hoffnungsvoll



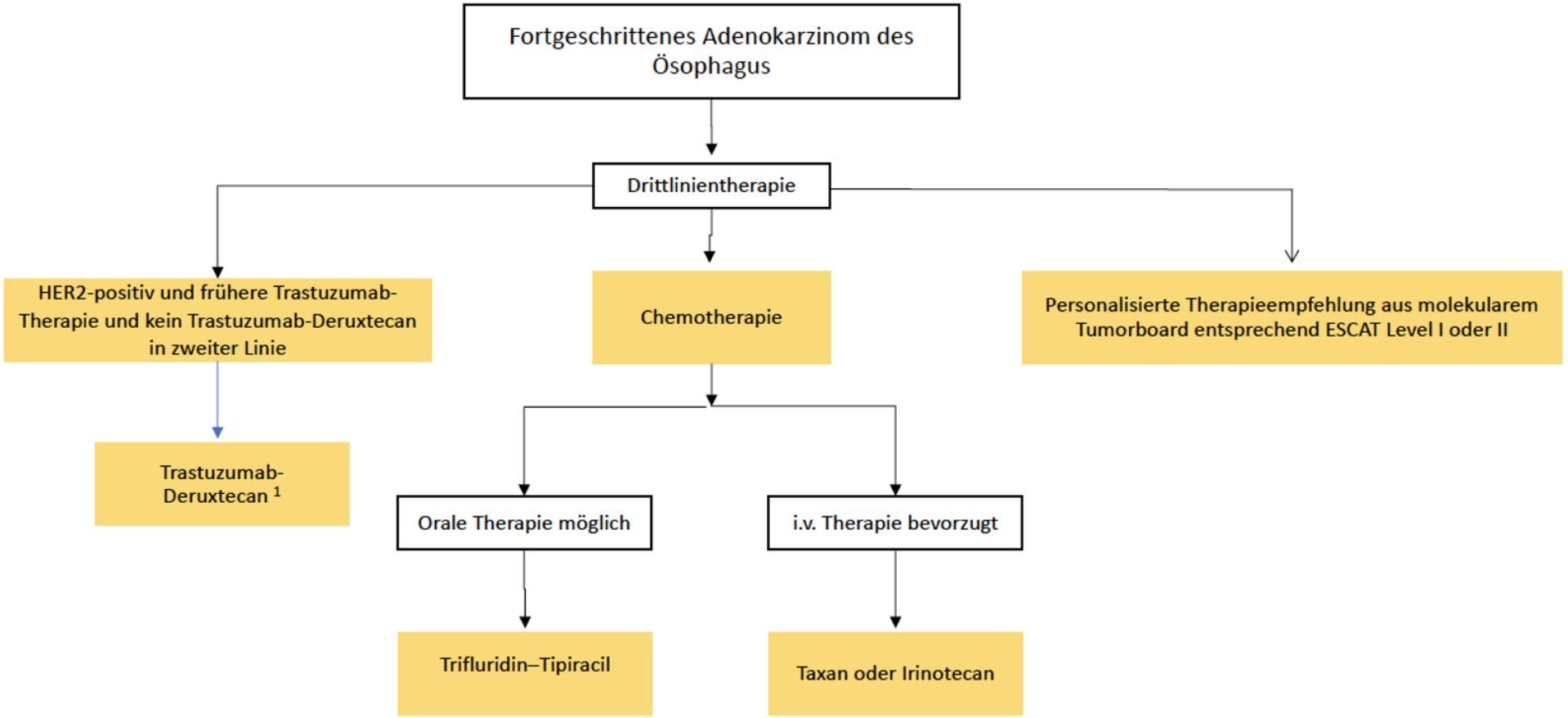
Algorithmus für die Zweitlinientherapie des Adenokarzinoms des Ösophagus im Stadium IV

Lorenzen update Onkopedia LL Okt 2024



Algorithmus für die Drittlinientherapie des Adenokarzinoms des Ösophagus im Stadium IV

Lorenzen update Onkopedia LL Okt 2024



Zusammenfassung

Leitlinie

onkopedia

Was ist neu?

- **Lokal fortgeschriittenes AEG:**
  - perioperativ FLOT nach ESOPEC Studie
  - HER2+: kein Trastuzumab zu FLOT nach INNOVATION Studie
  - dMMR/MSI high: zusätzlich Immuntherapie zu FLOT (DANTE/KN585/MATTERHORN)

- **SCC Zweitlinientherapie**: Nivolumab und Tislelizumab unabhängig von der PD-L1 Expression

- **Adeno Ca Erstlinientherapie:** Für selektionierte Patienten
  Ist eine Triplet-Chemotherapie (mFLOT/TFOX) eine Erstlinientherapie

Update erforderlich: **Tislelizumab in der Erstlinine bei SCC und Adeno Ca ab TAP >/=5 zugelassen**
Zolbetuximab bei CLDN 18.2 + Tumoren (Adeno) in der Erstlinientherapie zugelassen

Abschlussfragen

Kasuistik: Oktober 2024!
Wie würden Sie entscheiden: 6 Monate nach Abschluss FLOT adjuvant

- **A** Re-Exposition mit systemischer CTX mit FLOT
- **B** Systemische CTX mit Folfox
- **C** Systemische CTX mit Folfox + IO
- **D** Systemische CTX mit Folfox + Zolbetuximab
- **E** FOLFIRI
- **F** Ramucirumab + Paclitaxel

Alles mögliche Therapien

A/B) pro: initiales Ansprechen contra: PNP Grad II

C) +IO- pro: gute Verträglichkeit, contra: grenzwertiger CPS

D) +Zolbetuximab:- pro: gute Response wenn NW beherrscht!

CAVE: Kumulative Neuropathie mit Oxaliplatin!

E). FOLFIRI pro: NW contra: nicht Biomarker getriggert

D) Ram/Paclitaxel: pro: Standard 2nd Line; contra: Kreuzresistenz Taxan

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