Onkologisk behandling av cancer oesophagi og cancer ventriculi

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Disclosures:

- Støtte til forskning: BMS, Ipsen
- Honoraria/foredrag på vegne av arb.giver OUS eller utenom: MSD, BMS, Pierre-Fabre, Amgen, Roche, Bayer
- Deltakelse i ekspertgruppe/ad.boards på vegne av OUS: BMS, MSD

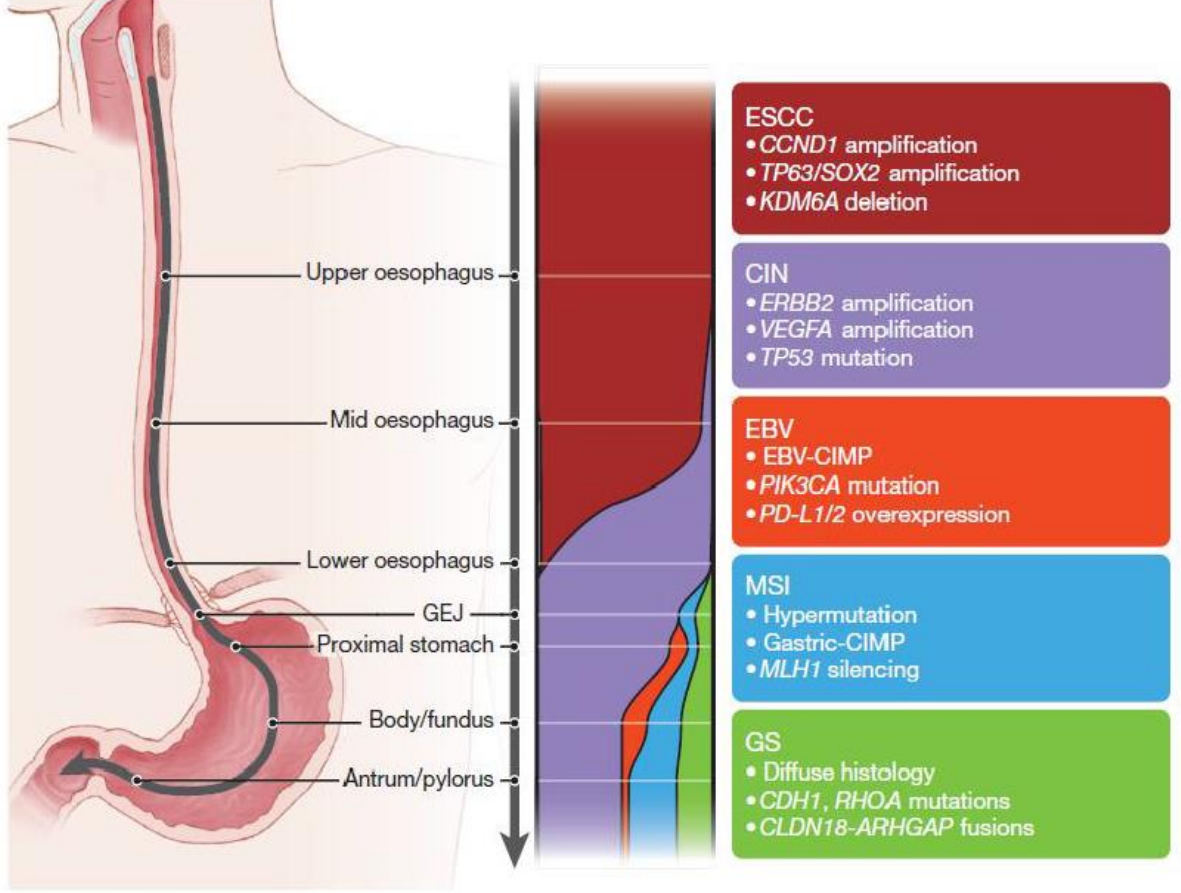
Ca oesofagi
Cancer ventriculi

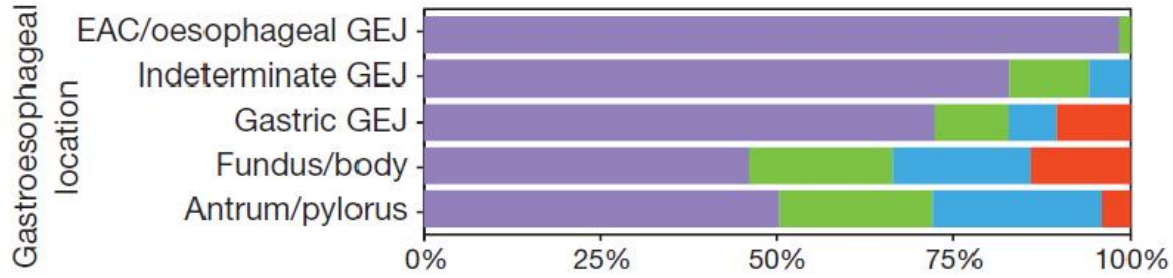
- **Spiserørskreft:** Plateepitelcarcinom eller Adenocarcinom
  - I Norge: 20% ESCC og 80% AC
- **Magekreft:** Adenocarcinom

750-800 tilfeller/år

Gradienter av typer i esofagogastrisk karsinom

- Platepitelcarcinom er forskjellig fra GEJ og GC
- HER-2 pos høyere i GEJ enn GC
- HER-2 uttrykk er ikke prognostisk



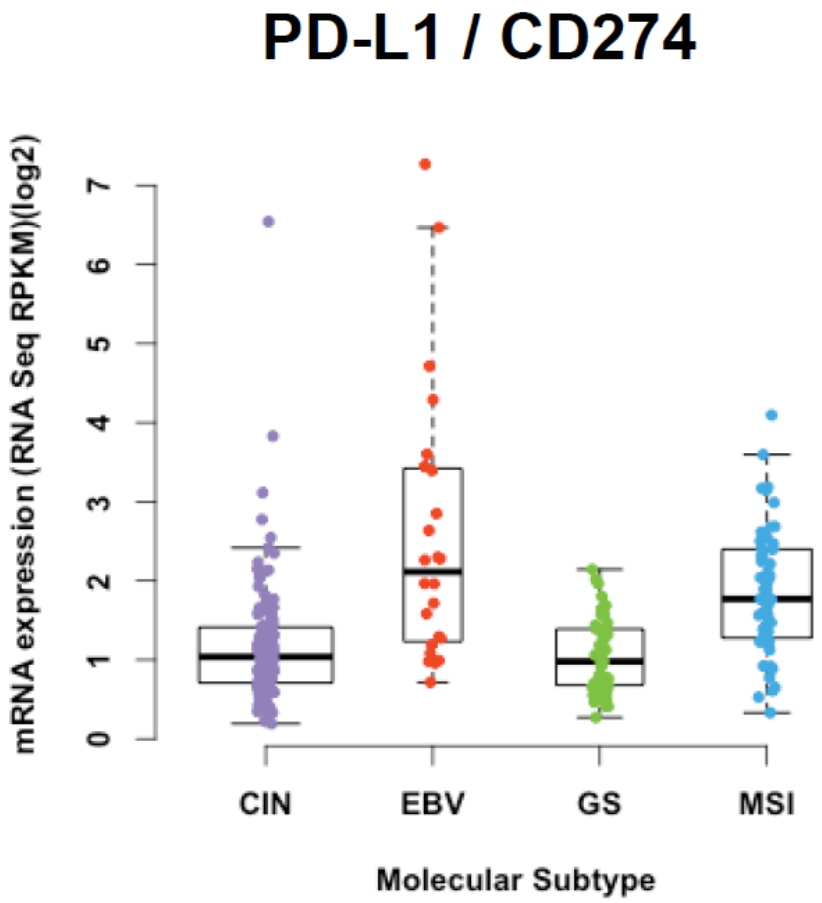


J Kim *et al. Nature* 1–9 (2017) doi:10.1038/nature20805

Aktuelle biomarkører som bør undersøkes i tumor:

- HER-2 (for adenocarcinomer)
- PDL1
- MSI (eller MMR)

PDL1 uttrykk i subgrupper



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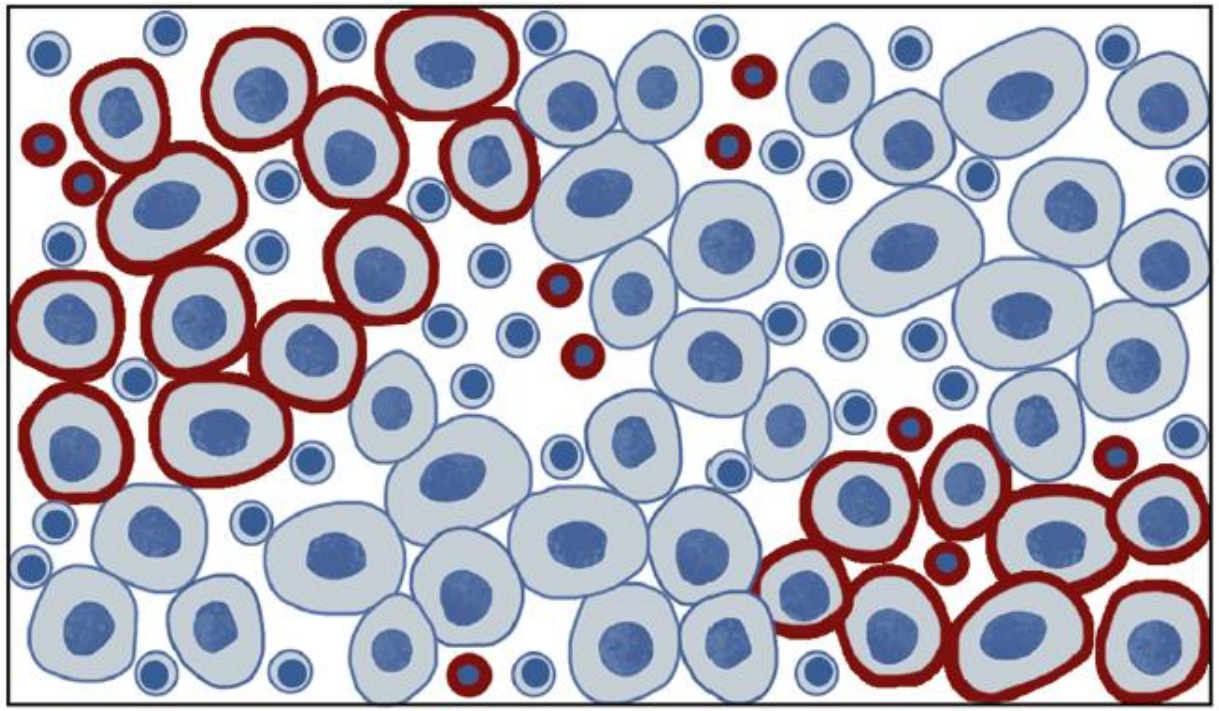
AJ Bass *et al. Nature*, 1-8 (2014) doi:10.1038/nature13480

PD-L1 scoring:



$$\text{TPS} = \frac{\text{No. PD-L1 positive tumor cells}}{\text{Total No. of viable tumor cells}} \times 100$$

$$\text{CPS} = \frac{\text{No. PD-L1 positive cells (tumor cells, lymphocytes, macrophages)}}{\text{Total No. of viable tumor cells}} \times 100$$

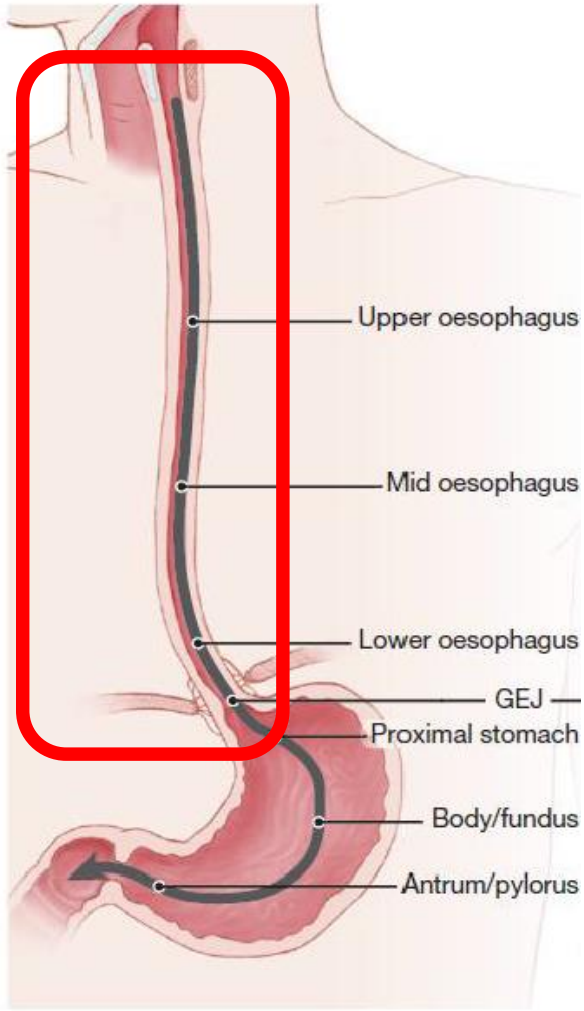
De Ruiter et al, Modern Pathol 2021

Disposisjon – onkologisk behandling:

- Behandling ved kurativ sykdom
- Behandling ved avansert/metastatisk sykdom

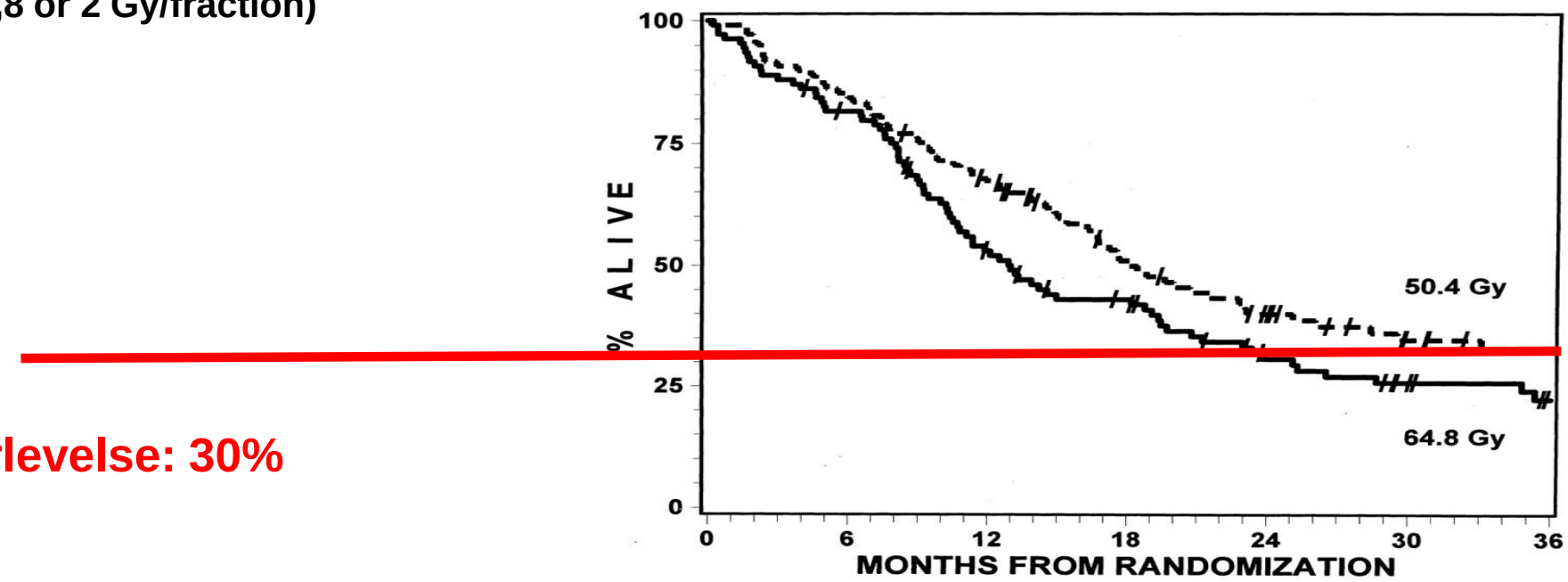
Lokalavansert inoperabel sykdom

- Aktuelt med definitiv kjemoradioterapi (dCRT)
  - Strålebehandling mot svulst og risikoområder – til 50Gy (1,8-2Gy / fx)
  - Kjemoterapi konkomitant
    - Platinum/5-FU eller Carboplatin/Paclitaxel



Lokalavansert ikke-operabel sykdom

- Definitiv radiokjemoterapi
- 4 kurer Cisplatin/5-FU over 3 mnd (uke 1,5,8 and 11)
- RT til 50Gy (1,8 or 2 Gy/fraction)

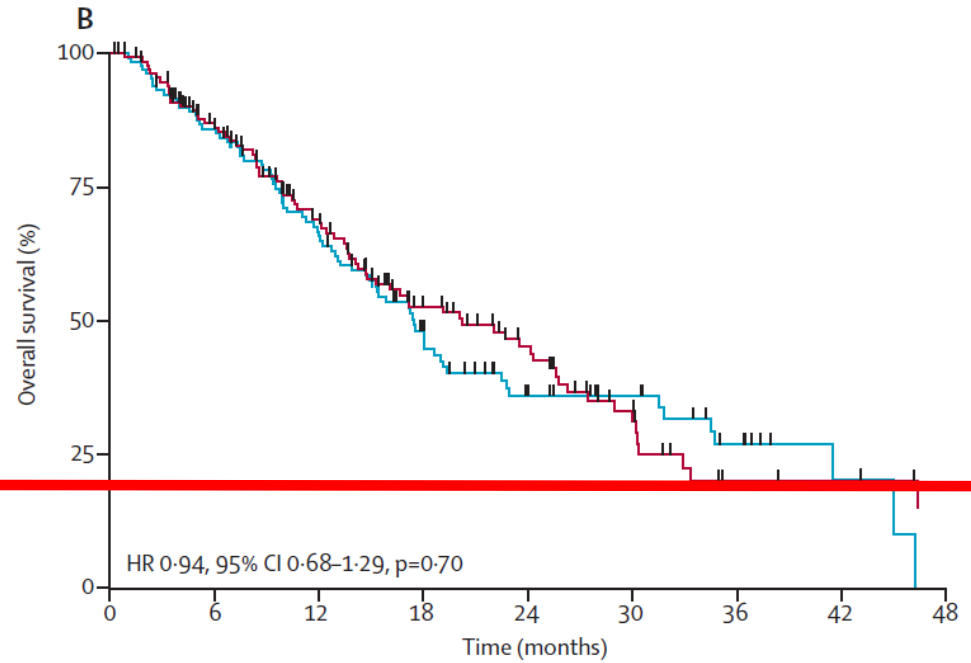


- **3-års overlevelse: 30%**

Minsky B D et al. JCO 2002;20:1167-1174

Lokalavansert ikke-operabel sykdom og definitiv radiokjemo; 50Gy med CiFu eller FOLFOX ?

- **4-års OS: ca 20%**



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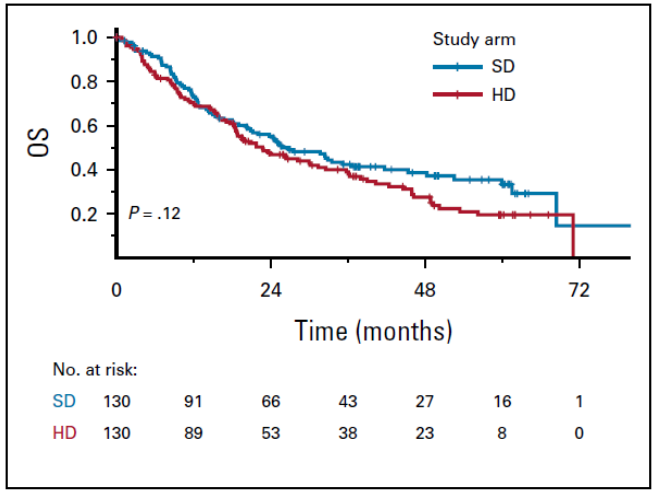
PRODIGE5/ACCORD17 trial: Thierry Conroy et al, Lancet Oncology 2014; 15:305-14

dCRT med forlenget «CROSS»-regime:

original reports

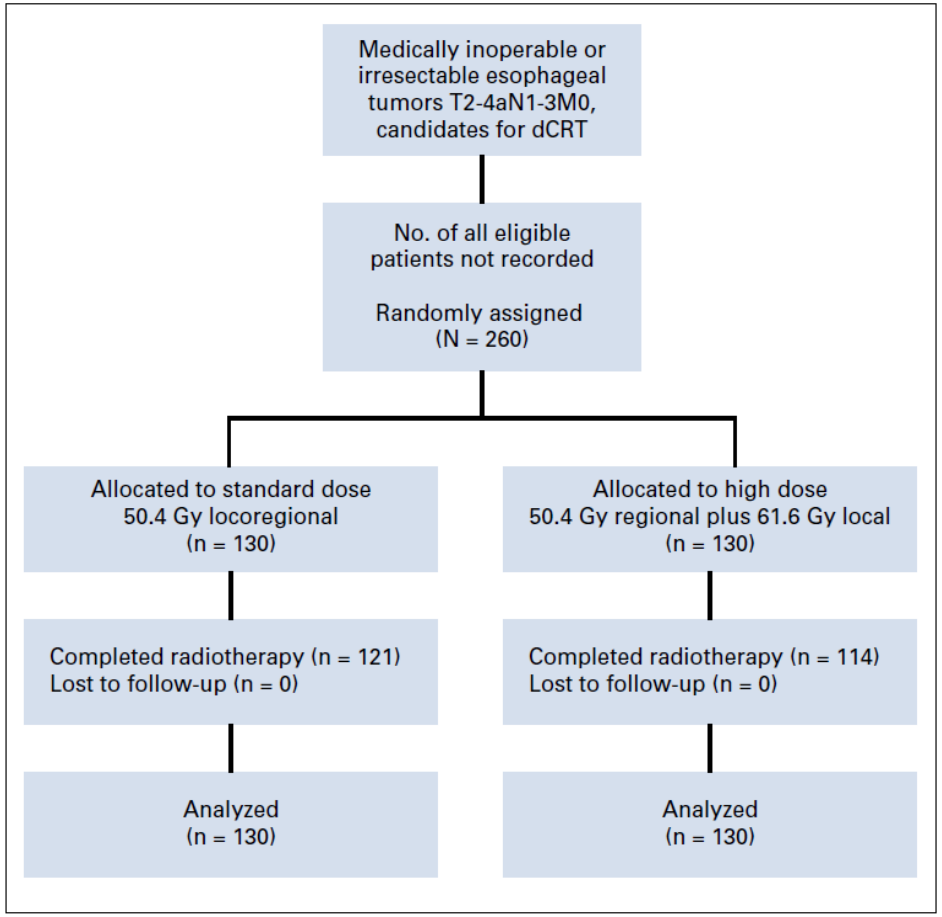
Randomized Study on Dose Escalation in Definitive Chemoradiation for Patients With Locally Advanced Esophageal Cancer (ARTDECO Study)

Maarten C. C. M. Hulshof, MD, PhD[1]; Elisabeth D. Geijsen, MD[1]; Tom Rozema, MD[2]; Vera Oppedijk, MD[3]; Jeroen Buijsen, MD, PhD[4];



Dose escalation above 50,4Gy:
Not recommended:
More toxicity
No better survival

Toxicity	Standard Dose (n = 120), %	High Dose (n = 118), %
Grade 1	3.3	0
Grade 2	25.8	14.4
Grade 3	55.0	63.6
Grade 4	12.5	14.4
Grade 5	3.3	7.6



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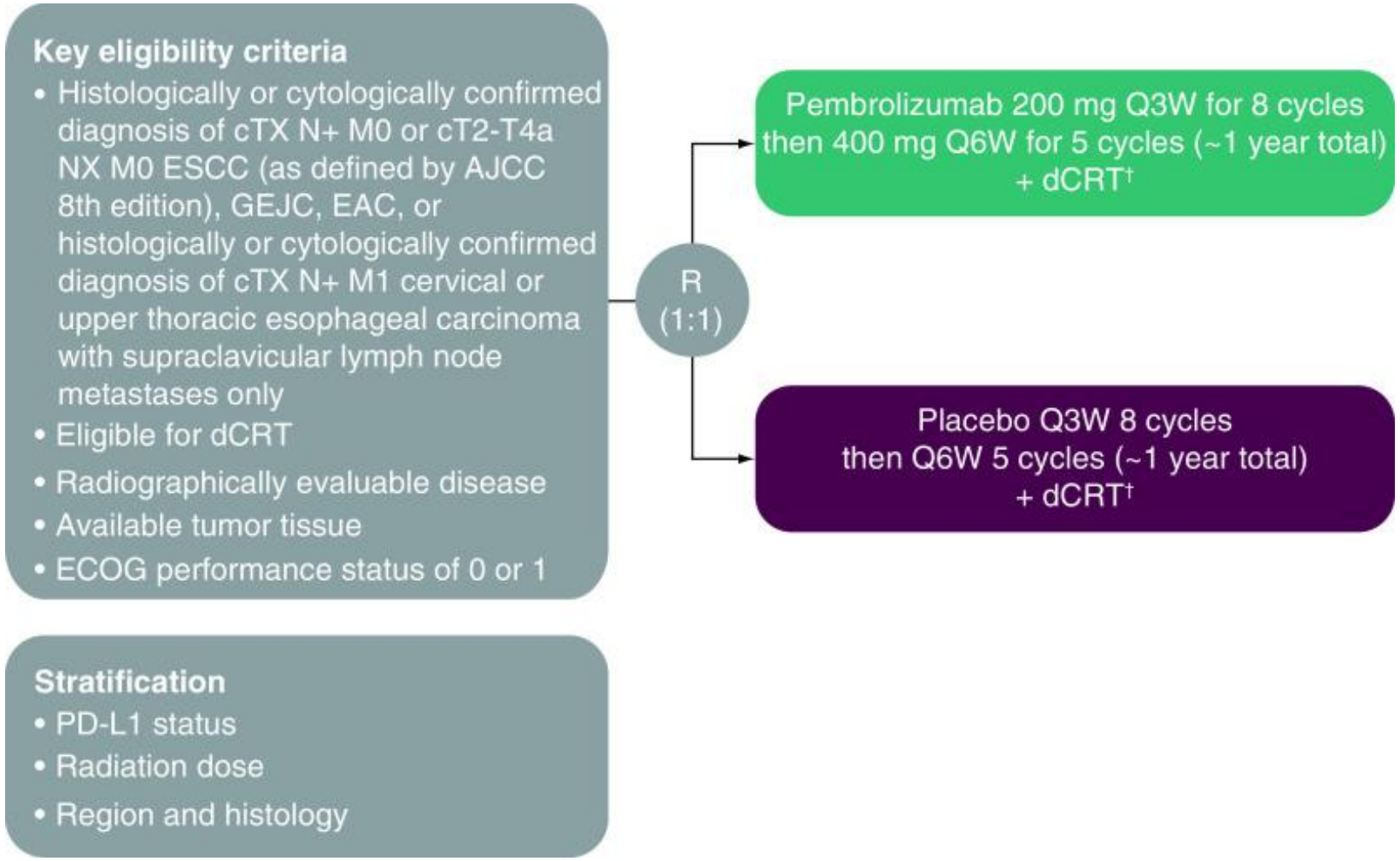
Hulshof et al, JCO 2021

Pågående studier (f.eks KEYNOTE 975):



M. Shah et al, Future Oncol, 2021 Apr;17

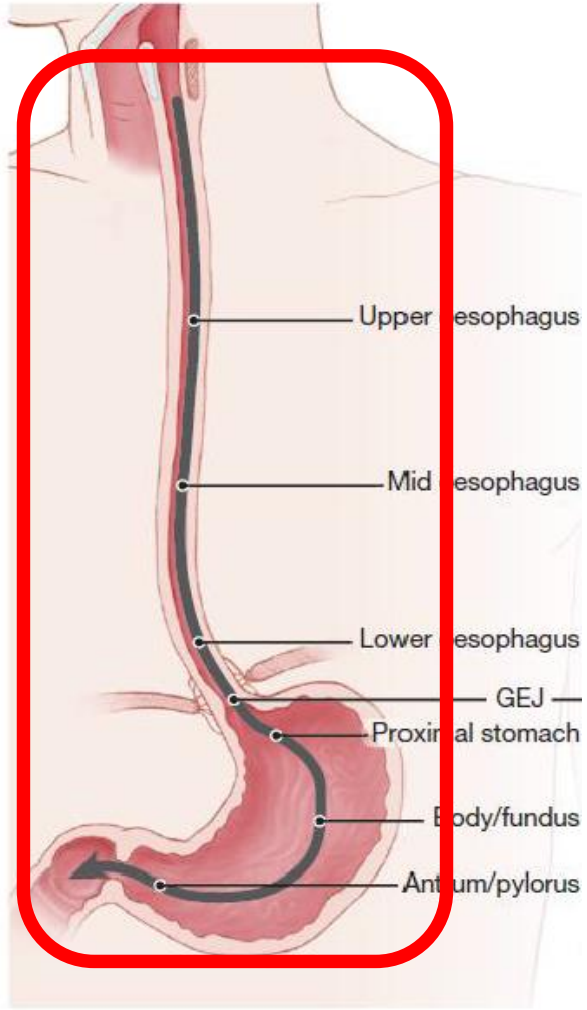
Konklusjoner hvis definitiv radiokjemoterapi:

- **Kurativ radiokjemoterapi kan vurderes:**
  - **Strålebehandling til 50Gy**
  - **4 platinum/5FU kurer eller 6 FOLFOX kurer konkomitant**

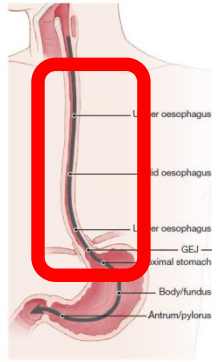
  - **Eller <u>forlenget CROSS regime</u>**
  - **Strålebeh 50,4 GY**
  - **6 Carboplatin/Paclitaxel ukeskurer**

Operabel sykdom:

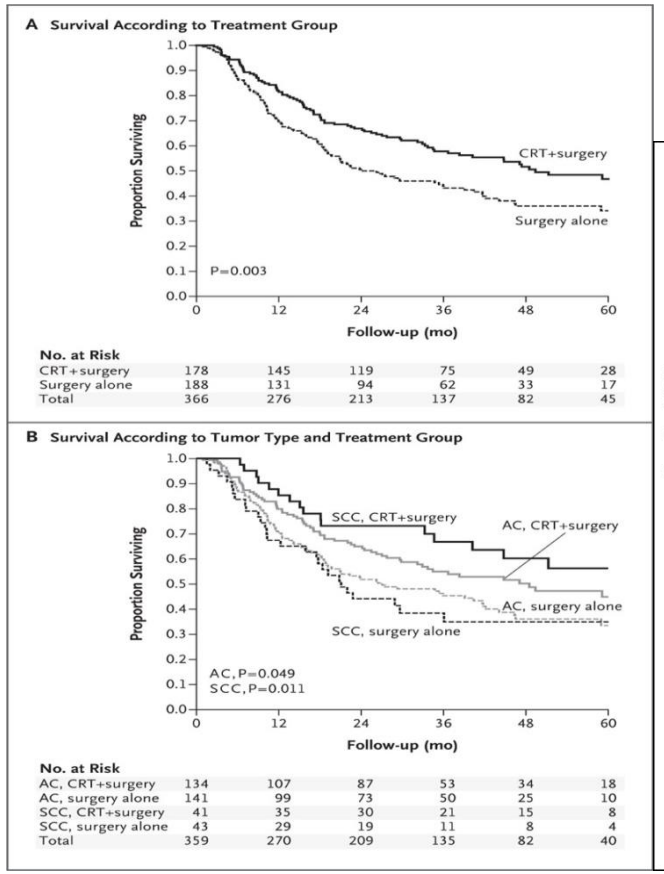
- Spiserørskreft:
  - Neoadjuvant radiokjemoterapi (CROSS)
  - Perioperativ kjemoterapi (FLOT 4+4) for adenocarcinom
- Magekreft:
  - Perioperativ kjemoterapi (FLOT 4+4)

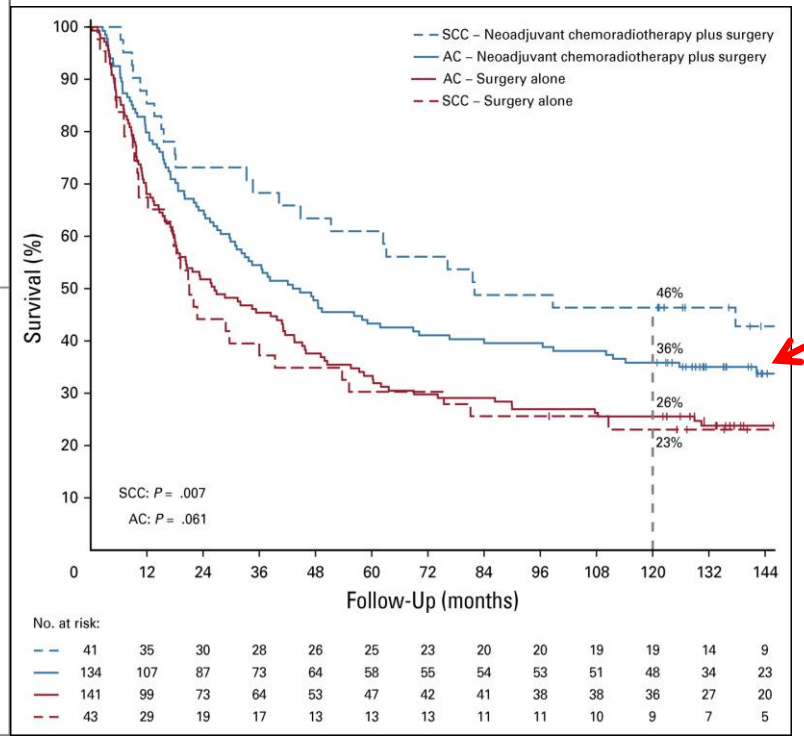


Operabel øsofagus cancer



- **CROSS studien:**
- **<u>Neoadjuvant</u> radiokjemoterapi**
- **Carboplatin/Paclitaxel (Q1W x5)**
- **1,8 Gy x23 (Total of 41,4 Gy)**
- **Kirurgi**
- **5-års overlevelse ca 50%**





van Hagen P et al. N Engl J Med 2012;366:2074-2084.
Ben M. Eyck et al. JCO 2021;39(18)1995-2004

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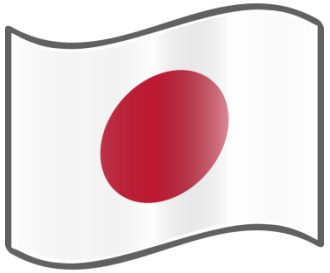
Onkologisk tilleggs-behandling magekreft ved operabel sykdom

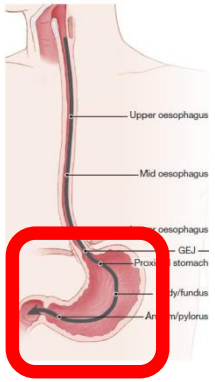
- Adjuvant kjemoradioterapi

- Perioperativ kjemoterapi



- Adjuvant kjemoterapi

Perioperativ kjemoterapi - magekreft MAGIC studien



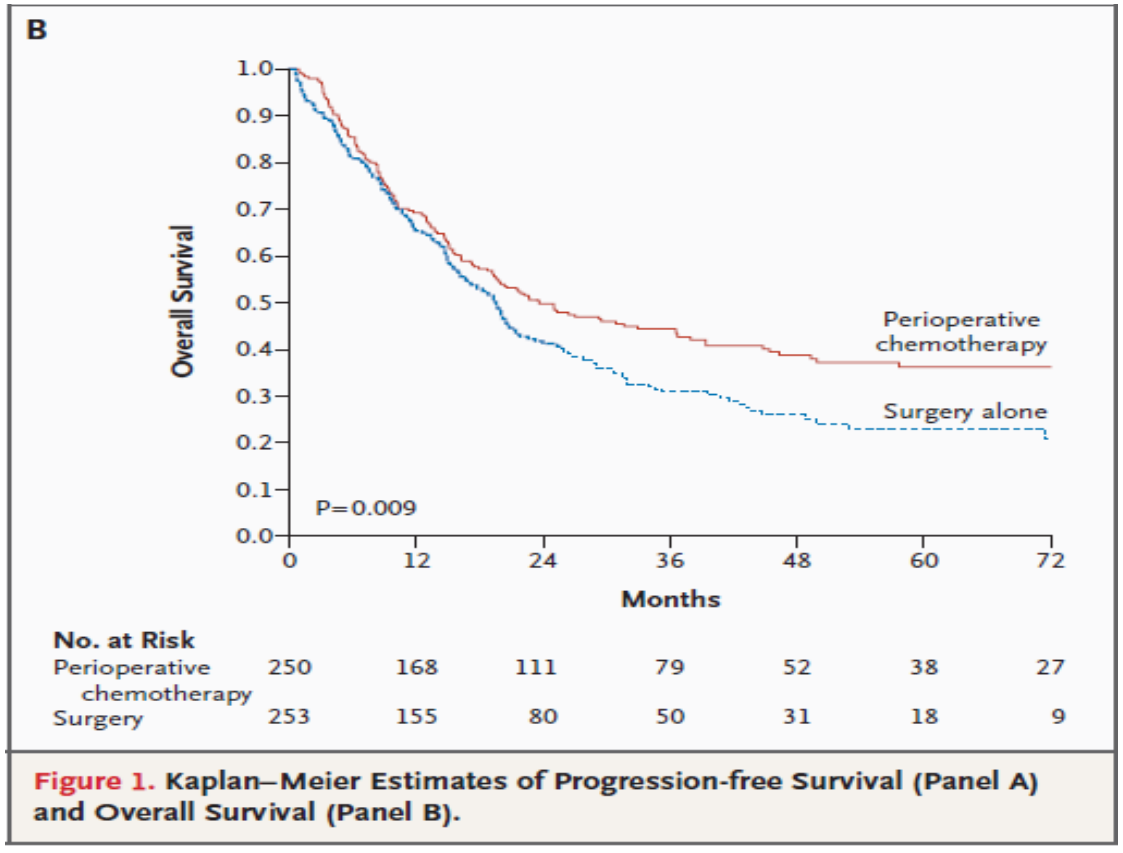
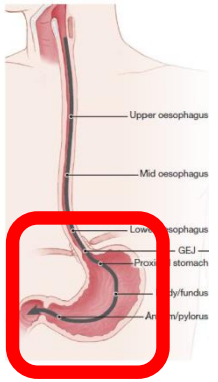


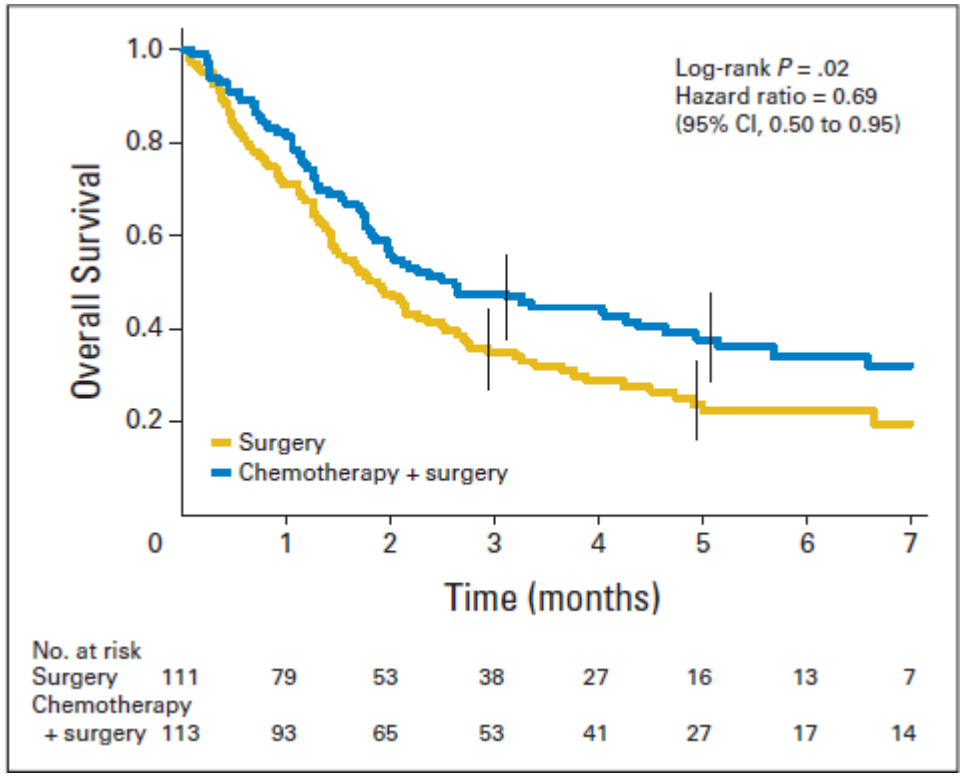
Figure 1. Kaplan–Meier Estimates of Progression-free Survival (Panel A) and Overall Survival (Panel B).

In patients with operable gastric or lower esophageal adenocarcinomas, a perioperative regimen (Epirubicin,Cisplatin, 5-FU) significantly improved progression-free and overall survival

Cunningham, D., et al. (2006) NEJM 355, 11-20

Perioperativ kjemoterapi – gastroesofageal AC





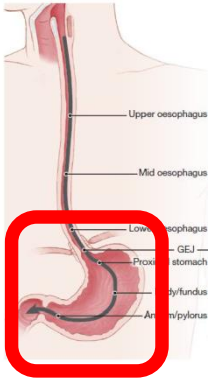
2-3 CiFu neo + 3-4 CiFu adjuvant

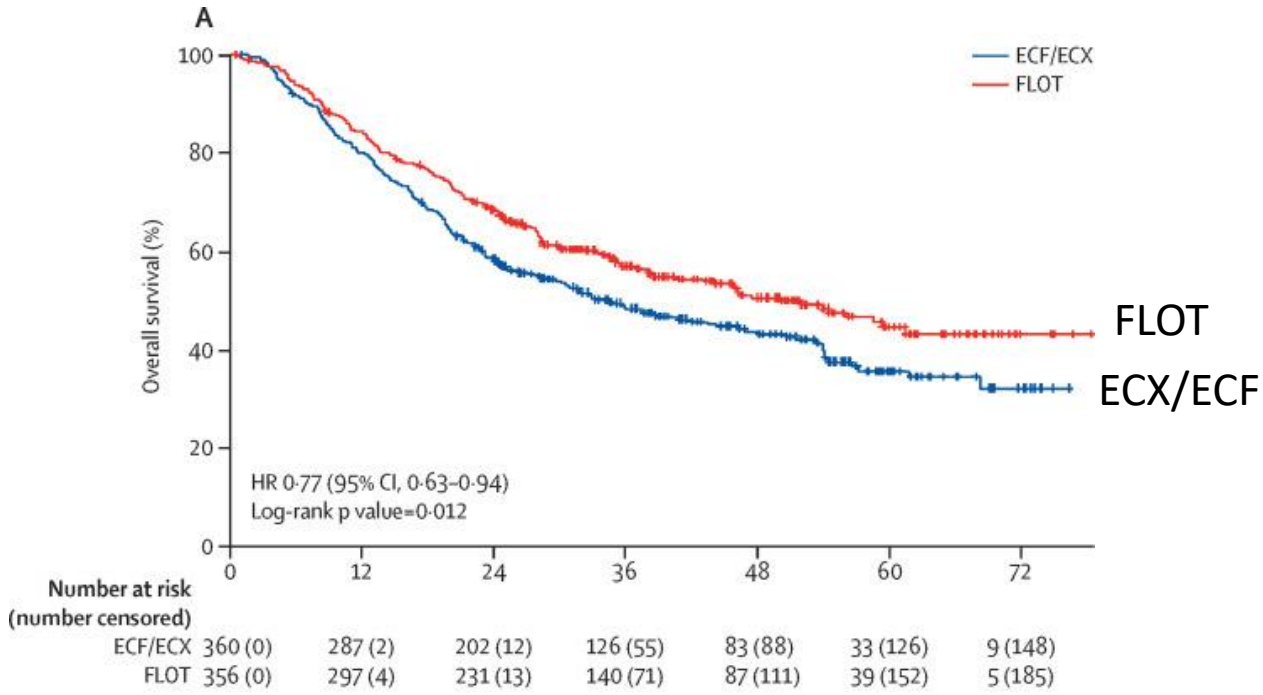
FNLCC ACCORD
07-FFCD 9703 trial

Log-rank p=0.02
HR = 0.69
(95% Cl, 0.50 to 0.95)

Ychou et al., J Clin Oncol. 2011 May 1;29(13):1715-21

Perioperativ kjemoterapi - magekreft
FLOT 4+4





FLOT

ECX/ECF

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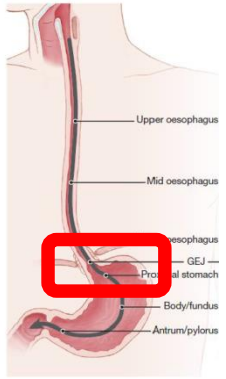
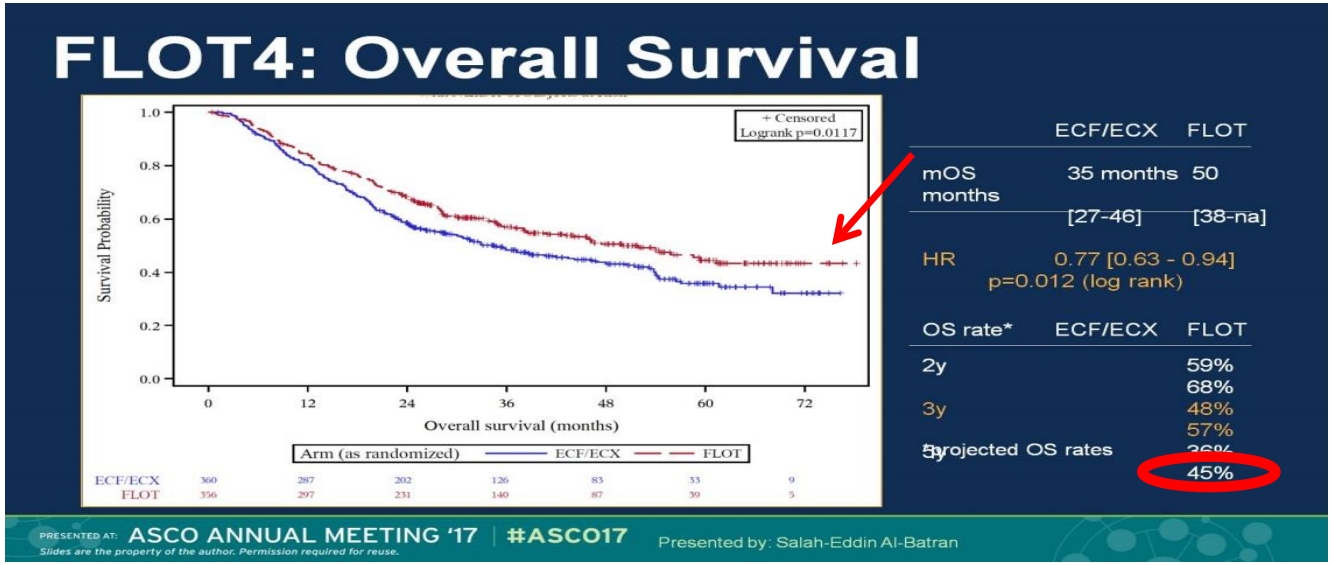
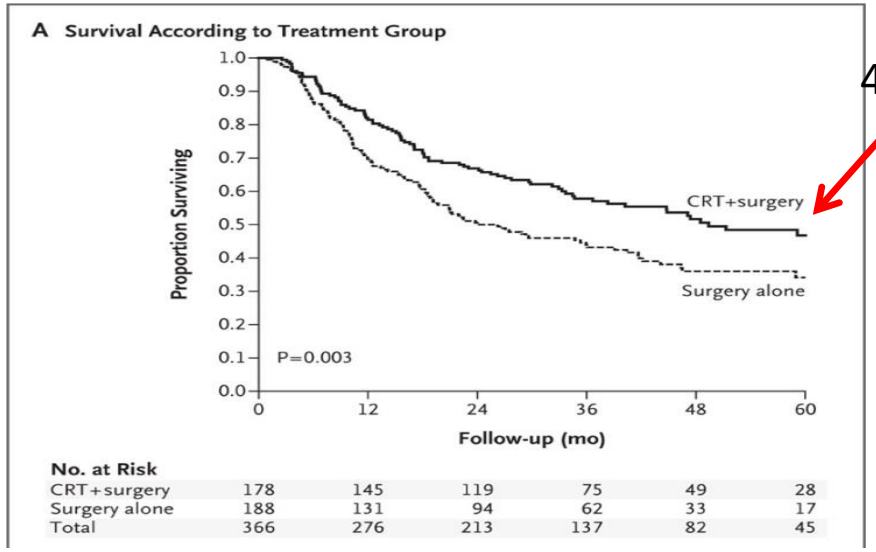
Presented By Salah-Eddin Al-Batran at 2017 ASCO Annual Meeting + Lancet 2019

Operabel GEJ adenocarcinom
2 muligheter for neo-adjuvant beh:



- **Perioperativ FLOT 4x4 *ELLER: Neoadjuvant CRT***

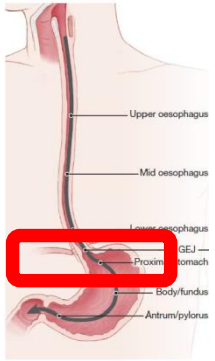




Al-Batran, ASCO 2017 / Lancet 2019

van Hagen, NEJM 2012

Neo-AEGIS
(CROSS vs MAGIC/FLOT)



377 pasienter randomiserte:

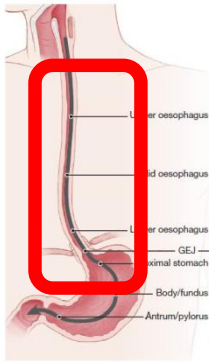
3-års OS: 56% vs 57%
HR 1,02

= ingen forskjell i OS

	Arm A (Magic/FLOT)	Arm B CROSS
R0 (negative margins)	82%	95%
ypN0	44.5%	60.1%
Tumor regression grade 1 & 2	12.1%	41.7%
Pathologic complete response	5%	16%
Neutropenia (Gr 3/4)	14.1%	2.8%
Neutropenic sepsis	2.7%	0.6%
Postoperative in-hospital deaths	3%	3%
Postoperative Pneumonia/ARDS	20%/0.6%	16%/4.3%
Anastomotic Leak	12%	11.7%
Clavien-Dindo > III<V	23.6%	22%

JV Reynolds et al, JCO 39 (suppl 15) May 2021
(Presented by J Reynolds at ASCO Annual Meeting 2021)

Adjuvant PD-1 hemmer ved spiserørskreft:



CheckMate 577 study design

- CheckMate 577 is a global, phase 3, randomized, double-blind, placebo-controlled trial[a]

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]
- Geographical regions: Europe (38%), US and Canada (32%), Asia (13%), rest of the world (16%)

Kelly RJ et al., NEJM 2021 and ESMO 2020

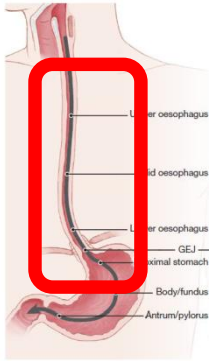
Baseline characteristics

	Nivolumab (n = 532)	Placebo (n = 262)
Median age (range), years	62.0 (26-82)	61.0 (26-86)
Male, %	84	85
Race,[a] %		
White	81	82
Asian	16	13
ECOG PS, %		
0	58	60
1	42	40
Disease stage at initial diagnosis, %		
II	34	38
III	66	62
Tumor location, %		
EC	60	59
GEJC	40	41
Histology, %		
Squamous cell carcinoma	29	29
Adenocarcinoma	71	71
Pathologic lymph node status ≥ ypN1, %	57	58
Tumor cell PD-L1 expression,[b] %		
≥ 1%	17	15
< 1%	70	75
Indeterminate/nonevaluable	13	10

[a]Other races not shown; [b]Tumor cell PD-L1 expression determined from surgical specimen by the PD-L1 IHC 28-8 pharmDx assay (Dako).

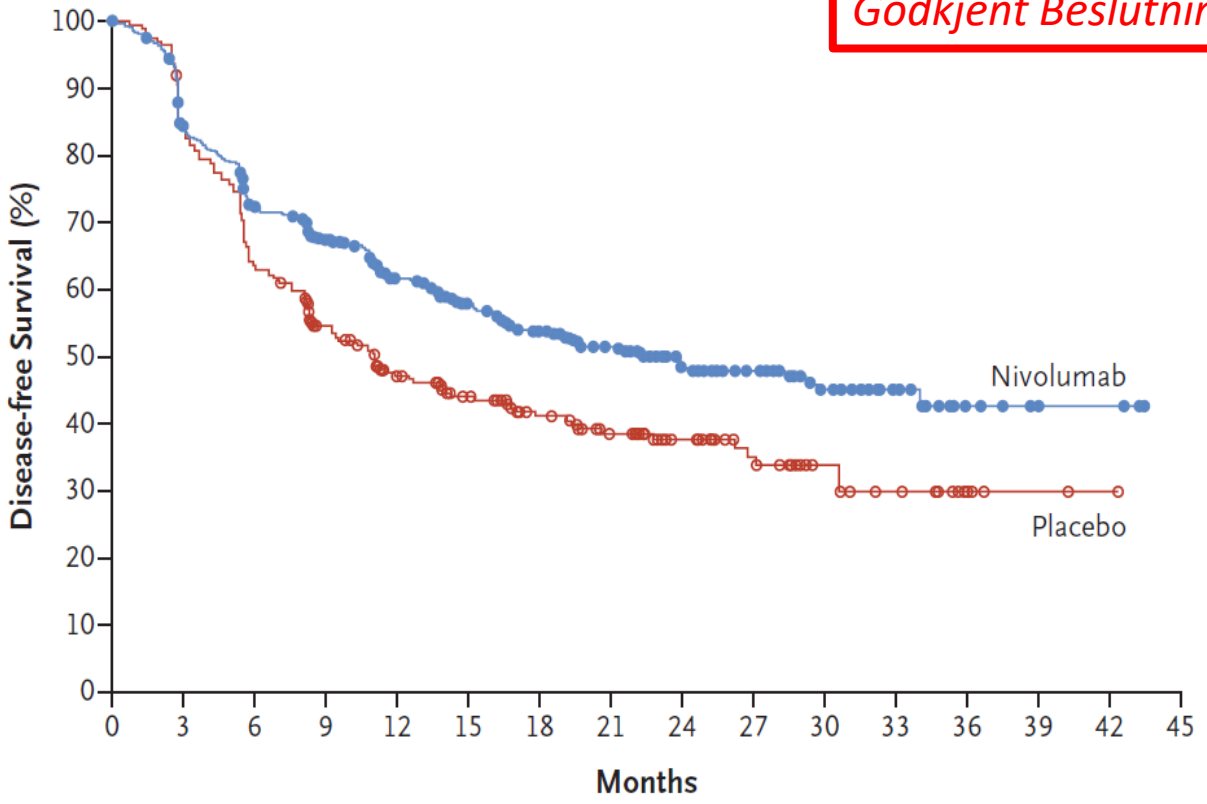
Kelly RJ et al., NEJM 2021 and ESMO 2020

Spiserørskreft - adjuvant nivolumab



Godkjent Beslutningsforum 29.08.22

A Disease-free Survival in the Overall Population



No. at Risk																
Nivolumab	532	430	364	306	249	212	181	147	92	68	41	22	8	4	3	0
Placebo	262	214	163	126	96	80	65	53	38	28	17	12	5	2	1	0

	No. of Patients	Median Disease-free Survival
		mo (95% CI)
Nivolumab	532	22.4 (16.6–34.0)
Placebo	262	11.0 (8.3–14.3)

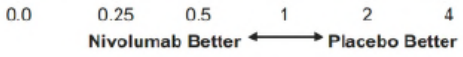
Hazard ratio for disease recurrence or death, 0.69 (96.4% CI, 0.56–0.86)
P<0.001

R Kelly et al, NEJM April 2021

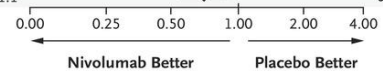
DFS – subgrupper:

Figure S2. Post Hoc Assessment of Disease-free Survival by Subgroups.

Subgroup	Median Disease-free Survival, months		Unstratified Hazard Ratio (95% CI)
	Nivolumab	Placebo	
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)
Radiotherapy dosage			
<41.4 Gray (n = 92*)	19.7	13.8	0.69 (0.38–1.23)
41.4–50.4 Gray (n = 504)	24.0	11.1	0.73 (0.57–0.95)
>50.4 Gray (n = 152)	21.4	8.3	0.72 (0.46–1.13)
Not reported (n = 41)	14.4	6.1	0.41 (0.16–1.07)



Subgroup	No. of Patients	Median Disease-free Survival (mo)		Unstratified Hazard Ratio (95% CI)
		Nivolumab	Placebo	
Overall	794	22.4	11.0	0.70 (0.58–0.86)
Age				
<65 yr	507	24.4	10.8	0.65 (0.51–0.84)
≥65 yr	287	17.0	13.9	0.80 (0.57–1.12)
Sex				
Male	671	21.4	11.1	0.73 (0.59–0.91)
Female	123	Not reached	11.0	0.59 (0.35–1.00)
Race				
White	648	21.3	10.9	0.71 (0.57–0.88)
Asian	117	24.0	10.2	0.70 (0.41–1.22)
Black	9	14.4	8.3	0.43 (0.06–3.06)
Other	20	Not reached	14.1	0.48 (0.11–2.02)
Region				
Asia	106	24.0	14.3	0.78 (0.43–1.41)
Other	688	21.4	11.0	0.69 (0.56–0.86)
ECOG performance-status score				
0	464	29.4	11.1	0.73 (0.56–0.96)
1	330	17.0	10.9	0.66 (0.48–0.89)
Disease stage at initial diagnosis				
II	278	34.0	13.9	0.72 (0.51–1.02)
III	514	19.4	8.5	0.68 (0.53–0.88)
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)
Histologic type				
Adenocarcinoma	563	19.4	11.1	0.75 (0.59–0.96)
Squamous-cell carcinoma	230	29.7	11.0	0.61 (0.42–0.88)
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)
Pathological lymph-node status				
ypN0	336	Not reached	27.0	0.74 (0.51–1.06)
≥ypN1	457	14.8	7.6	0.67 (0.53–0.86)
Pathological tumor status				
ypT0	47	34.0	5.2	0.35 (0.15–0.82)
ypT1 or ypT2	308	28.3	9.3	0.60 (0.44–0.83)
ypT3 or ypT4	436	18.9	14.1	0.84 (0.64–1.11)
Histologic grade				
1 or 2	438	29.4	13.9	0.68 (0.51–0.91)
3 or 4	253	14.1	9.2	0.73 (0.52–1.02)
Not assessed	101	Not reached	11.1	0.65 (0.37–1.16)
Time from complete resection to randomization				
<10 wk	256	24.0	14.1	0.84 (0.57–1.22)
≥10 wk	538	21.4	10.8	0.66 (0.52–0.84)
HER2 status				
Positive	63	19.6	7.6	0.78 (0.40–1.55)
Negative	207	21.4	9.4	0.69 (0.46–1.03)
Not reported	522	24.0	11.1	0.70 (0.55–0.90)



R Kelly et al, NEJM April 2021

Safety summary

Patients, n (%)	Nivolumab[a] n = 532		Placebo[a] n = 260	
	Any grade	Grade 3-4	Any grade	Grade 3-4
Any AEs[b]	510 (96)	183 (34)	243 (93)	84 (32)
Serious AEs	158 (30)	107 (20)	78 (30)	53 (20)
AEs leading to discontinuation	68 (13)	38 (7)	20 (8)	16 (6)
Any TRAEs[b,c]	376 (71)	71 (13)	119 (46)	15 (6)
Serious TRAEs[c]	40 (8)	29 (5)	7 (3)	3 (1)
TRAEs leading to discontinuation[c]	48 (9)	26 (5)	8 (3)	7 (3)
TRAEs in ≥10% of treated patients in either arm[b]				
Fatigue	90 (17)	6 (1)	29 (11)	1 (< 1)
Diarrhea	88 (17)	2 (< 1)	39 (15)	2 (< 1)
Pruritus	53 (10)	2 (< 1)	9 (3)	0
Rash	52 (10)	4 (< 1)	10 (4)	1 (< 1)

- Nivolumab was well tolerated and the majority of TRAEs were grade 1 or 2

[a]Patients who received ≥1 dose of study treatment; [b]Events reported between first dose and 30 days after last dose of study drug; [c]Only 1 grade 5 TRAE was recorded in either arm (cardiac arrest in the nivolumab arm that was reported as not treatment related after database lock).

Oslo universitetssykehus

Kelly RJ et al., NEJM 2021 and ESMO 2020

Treatment-related adverse events with potential immunologic etiology

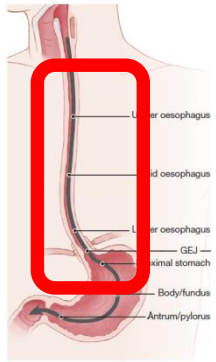
Select TRAEs,[b,c] n (%)	Nivolumab[a] n = 532		Placebo[a] n = 260	
	Any grade	Grade 3-4	Any grade	Grade 3-4
Endocrine	93 (17)	5 (< 1)	6 (2)	0
Gastrointestinal	91 (17)	4 (< 1)	40 (15)	3 (1)
Hepatic	49 (9)	6 (1)	18 (7)	4 (2)
Pulmonary	23 (4)	6 (1)	4 (2)	1 (< 1)
Renal	7 (1)	1 (< 1)	2 (< 1)	0
Skin	130 (24)	7 (1)	28 (11)	1 (< 1)

- The majority of select TRAEs were grade 1 or 2
- Grade 3-4 select TRAEs occurred in ≤ 1% of patients in the nivolumab arm and there were no grade 5 select TRAEs
- The most common grade 3-4 select TRAEs in the nivolumab arm were pneumonitis (n = 4) and rash (n = 4) (0.8% each); in the placebo arm, these events occurred in 1 patient each (0.4%)

[a]Patients who received ≥ 1 dose of study treatment; [b]Select TRAEs are those with potential immunologic etiology that require frequent monitoring/intervention; [c]Events reported between first dose and 30 days after last dose of study drug.

Oslo universitetssykehus

Kelly RJ et al., NEJM 2021 and ESMO 2020



ESMO Guidelines – lokalisert spiserørskreft

cTNM staging (endoscopy, EUS, MS-CT, FDG-PET)
Functional assessment (symptoms, comorbidity, nutritional status, patient preferences)

Early disease (cT1 cN0 M0)

- Resection[a,b] [III, A]

Locally advanced disease (cT2-T4 or cN1-3 M0)

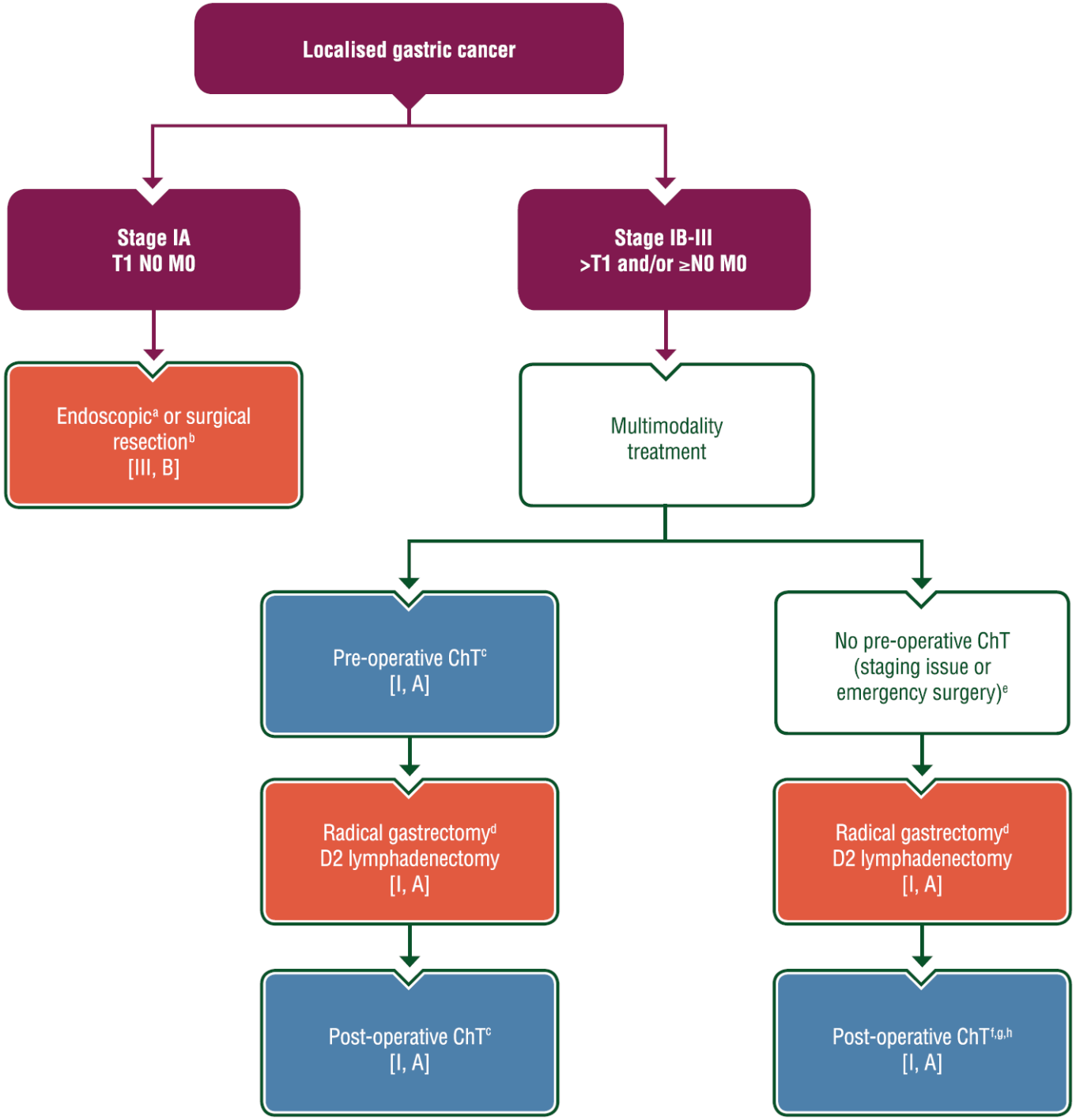
SCC[c]

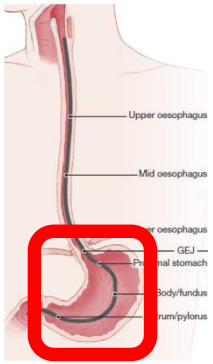
- Neoadjuvant CRT [I, A]
  - Restaging (exclusion of M1)
    - Resection [IV, C]
      - Adjuvant nivolumab[g] [I, A; MCBS A][e]
- Definitive CRT [II, B]
  - Follow-up (every 3 months)
    - Salvage resection[f] [IV, C]

AC and OGJ cancer[d]

- Neoadjuvant FLOT [I, A; MCBS A][e]
  - Restaging (exclusion of M1)
    - Resection [IV, C]
      - Adjuvant FLOT [I, A; MCBS A][e]
- Neoadjuvant CRT [I, A]
  - Restaging (exclusion of M1)
    - Resection [IV, C]
      - Adjuvant nivolumab[g] [I, A; MCBS A][e]

Obermannova et al, Ann Oncol 2022

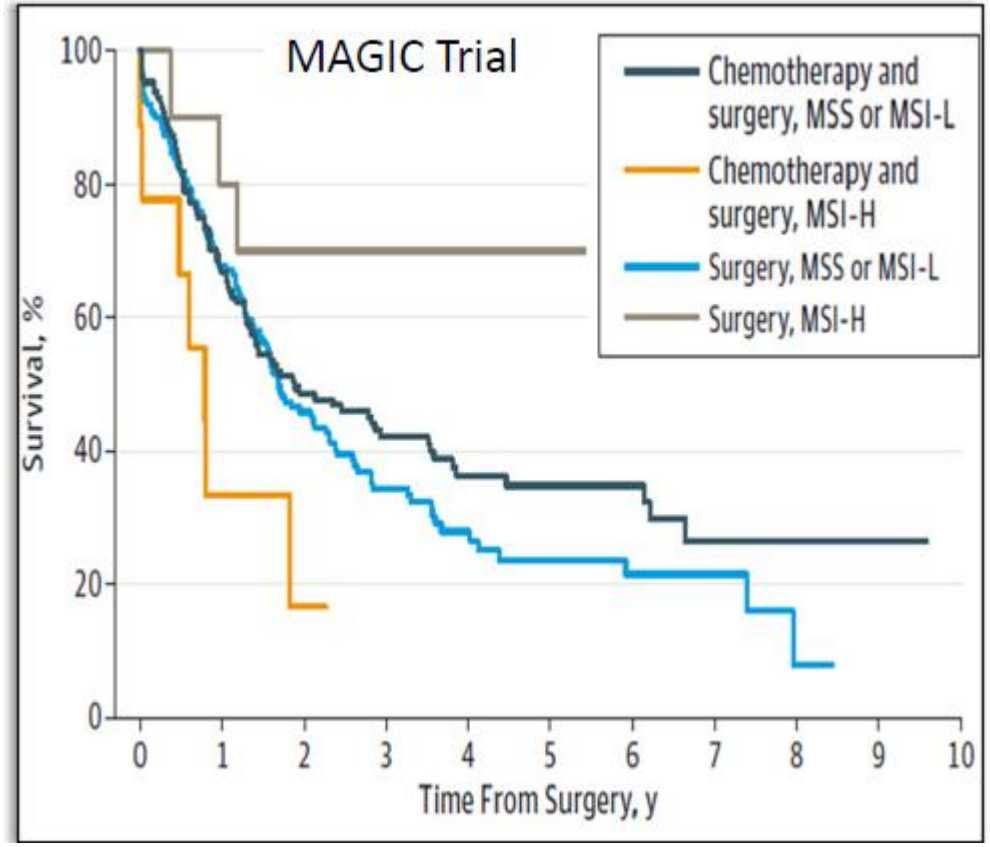




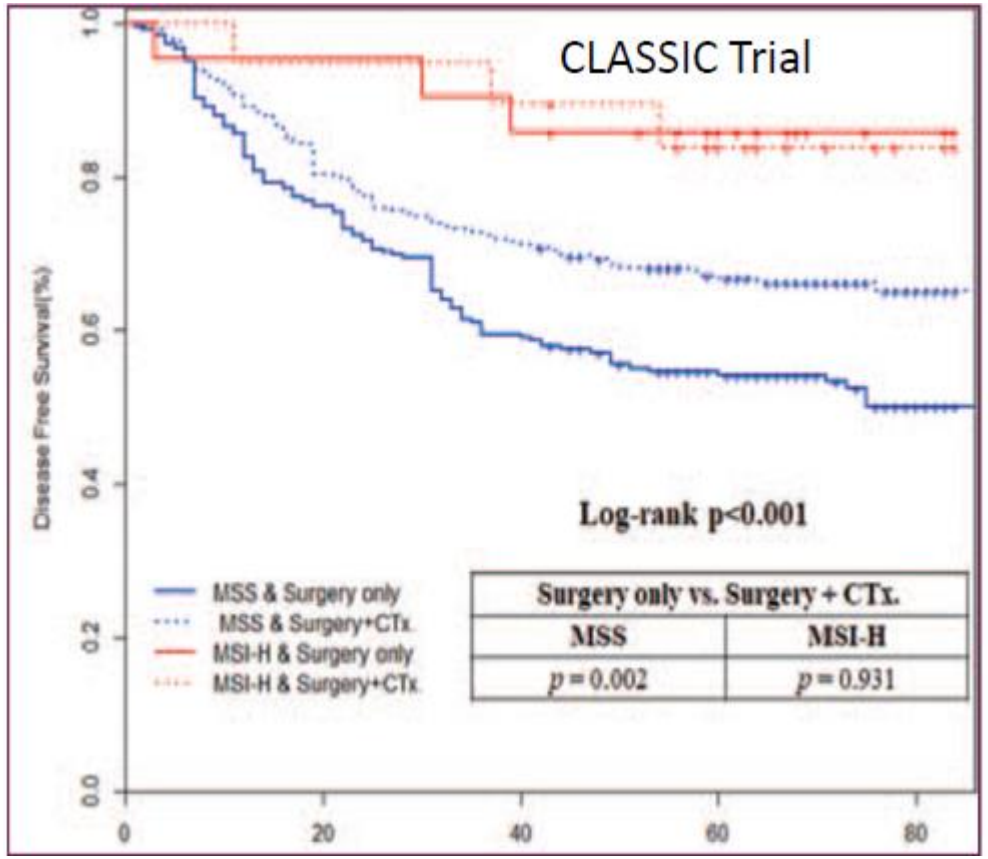
ESMO Guidelines – lokalisert magekreft

Lordick et al, Ann Oncol 2022

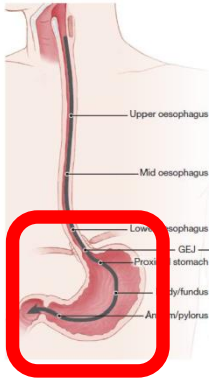
MSI post hoc analyser MAGIC og CLASSIC



-Ingen gevinst av perioperativ kjemoterapi hos MSI-H, mulig negativ effekt (NB små tall)



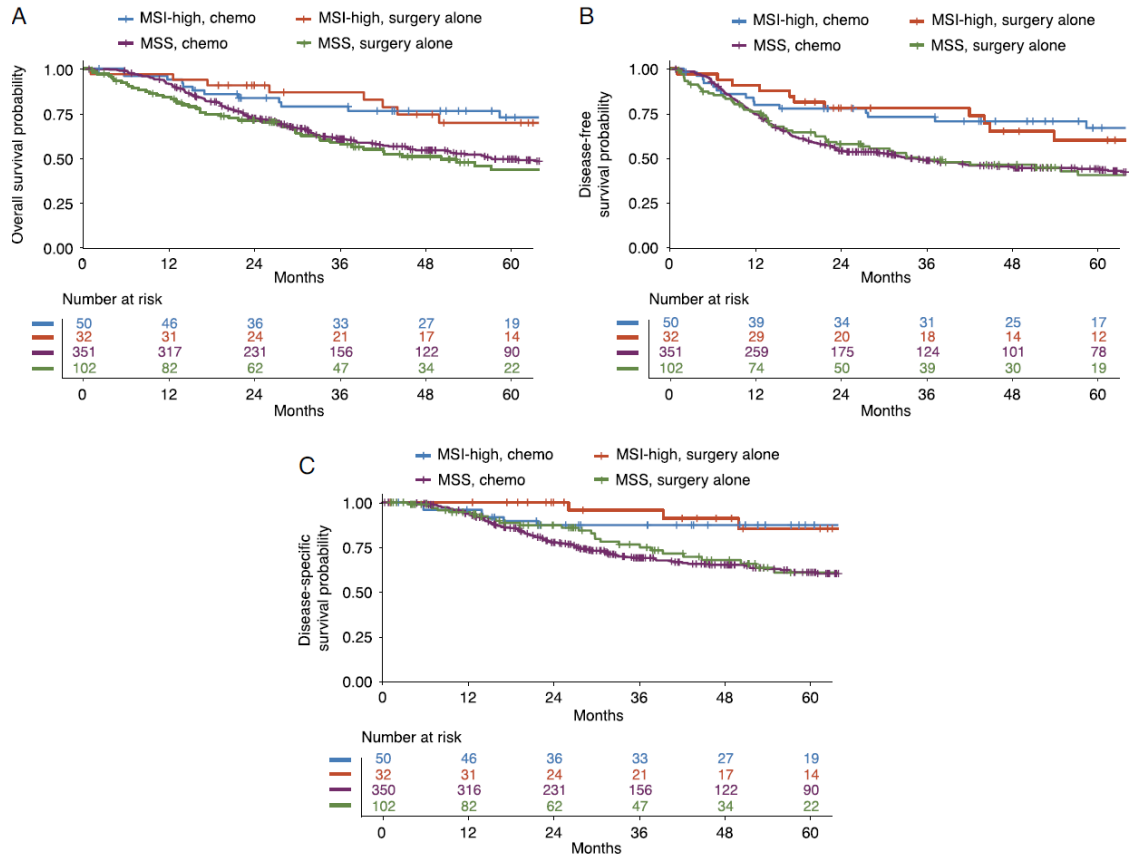
-Ingen gevinst i adjuvant kjemoterapi hos MSI-H
-MSI-H gir god prognose

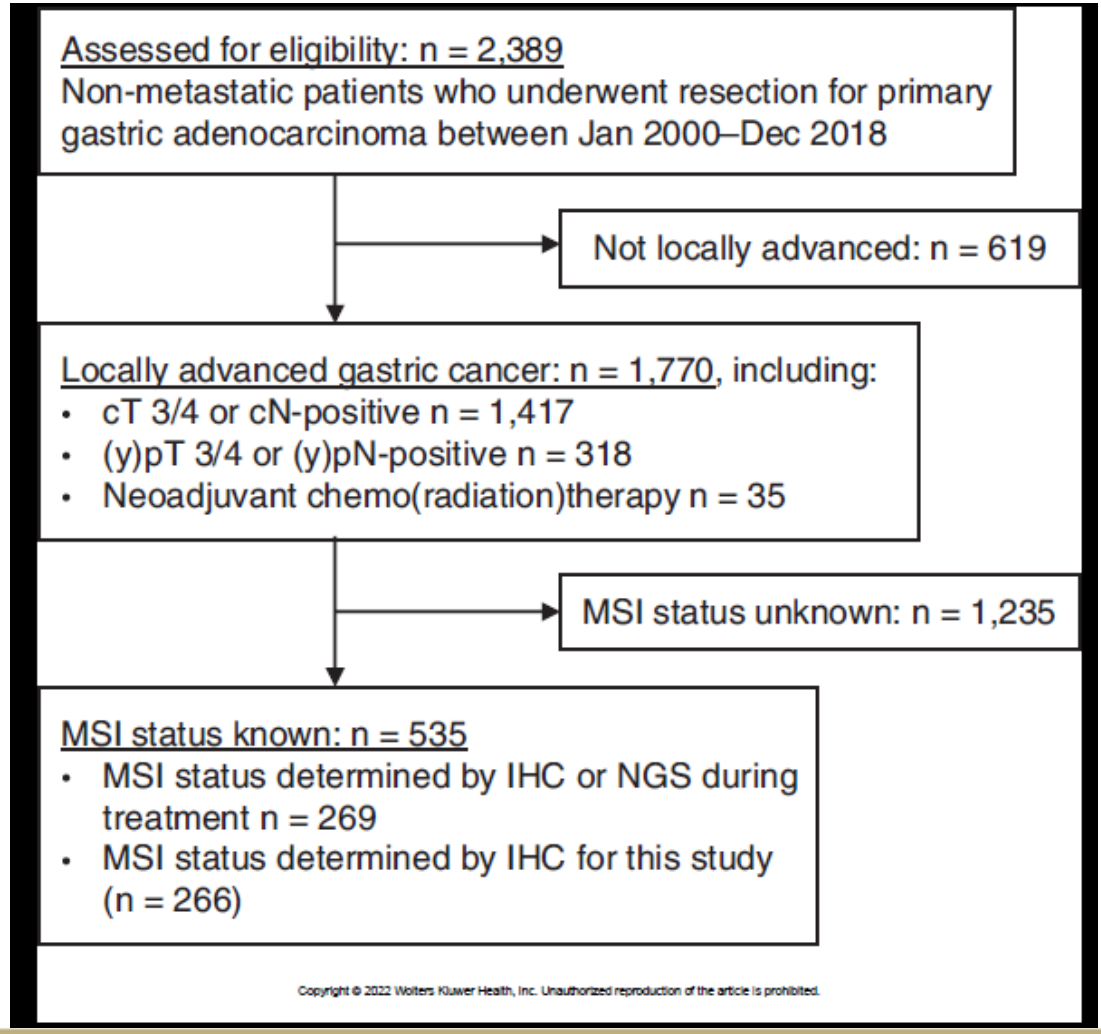


NB – POST HOC analyser

Smyth et al, JAMA Oncol, 2017
Choi et al, Ann Surg 2018

MSI-H operabel ventrikkelcancer: (15% var MSI-H)





Elvira Vos et al, Ann Surg, 2022

Oslo universitetssykehus

NEONIPIGA studien (fase II): -MSI-H/dMMR operabel ventrikkelcancer

- Ipilimumab x2 Q6W og Nivolumab x 6 Q2W før kirurgi, deretter adjuvant Nivolumab Q4W i 9 mnd.

- pCR 59%

TABLE 4. Pathologic Characteristics of Patients Who Underwent Surgery (the mITT population)

Characteristic	Patients (n = 29), No. (%)
ypT stage	
ypT0	19 (65)[a]
ypT1a	1 (3)
ypT1b	2 (7)
ypT2	2 (7)
ypT3	5 (17)
ypN stage	
ypN0	23 (79)
ypN1	6 (21)
TRG Mandard	
TRG 1: complete regression/fibrosis without tumor cells	17 (59)
TRG 2: fibrosis with scattered tumor cells	4 (14)[a]
TRG 3: fibrosis and tumor cells with a dominance of fibrosis	2 (7)
TRG 4: fibrosis and tumor cells with dominance of tumor cells	4 (14)
TRG 5: tumor without evidence of regression	2 (7)
TRG Becker	
TRG 1a: complete tumor regression without residual tumor	17 (59)
TRG 1b: < 10% residual tumor per tumor bed	4 (14)[a]
TGR 2: 10% to 50% residual tumor	2 (7)
TRG 3: > 50% residual tumor cells	6 (21)

J Clin Oncol. 2023 Jan 10; 41(2): 255–265.

Konklusjoner kurativ onkologisk behandling:

- *For gastroøsofageal cancer-pasienter som er aktuelle for neo- eller adjuvant behandling, kan vurderes:*

- **Neoadjuvant radiokjemoterapi for plateepitelcarcinomer**

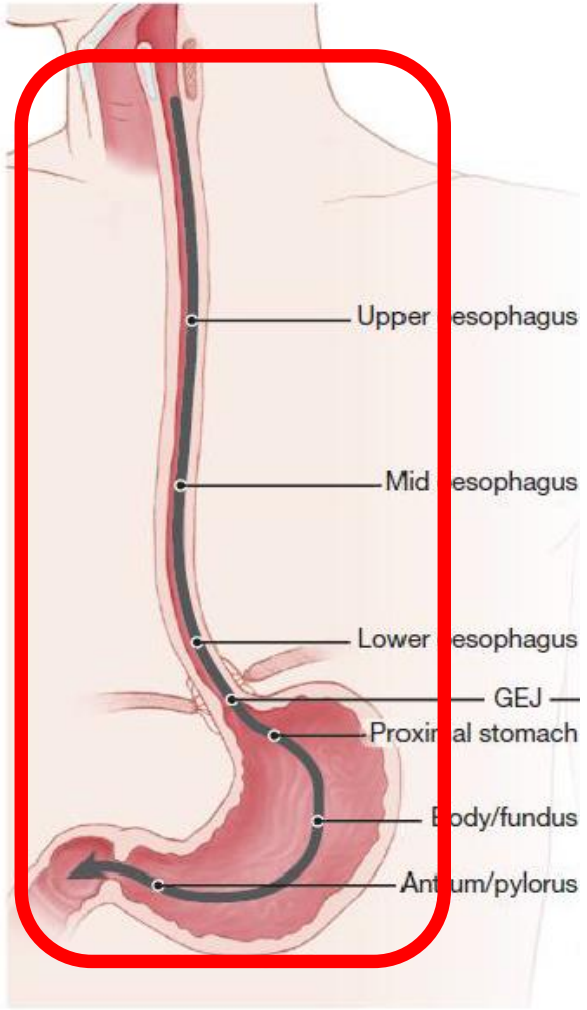
- ***ENTEN* perioperativ FLOT 4+4 *ELLER* neoadjuvant radiokjemoterapi for adenocarcinom i GEJ**

- **Perioperativ FLOT 4+4 kjemoterapi for adenocarcinom i ventrikkel**

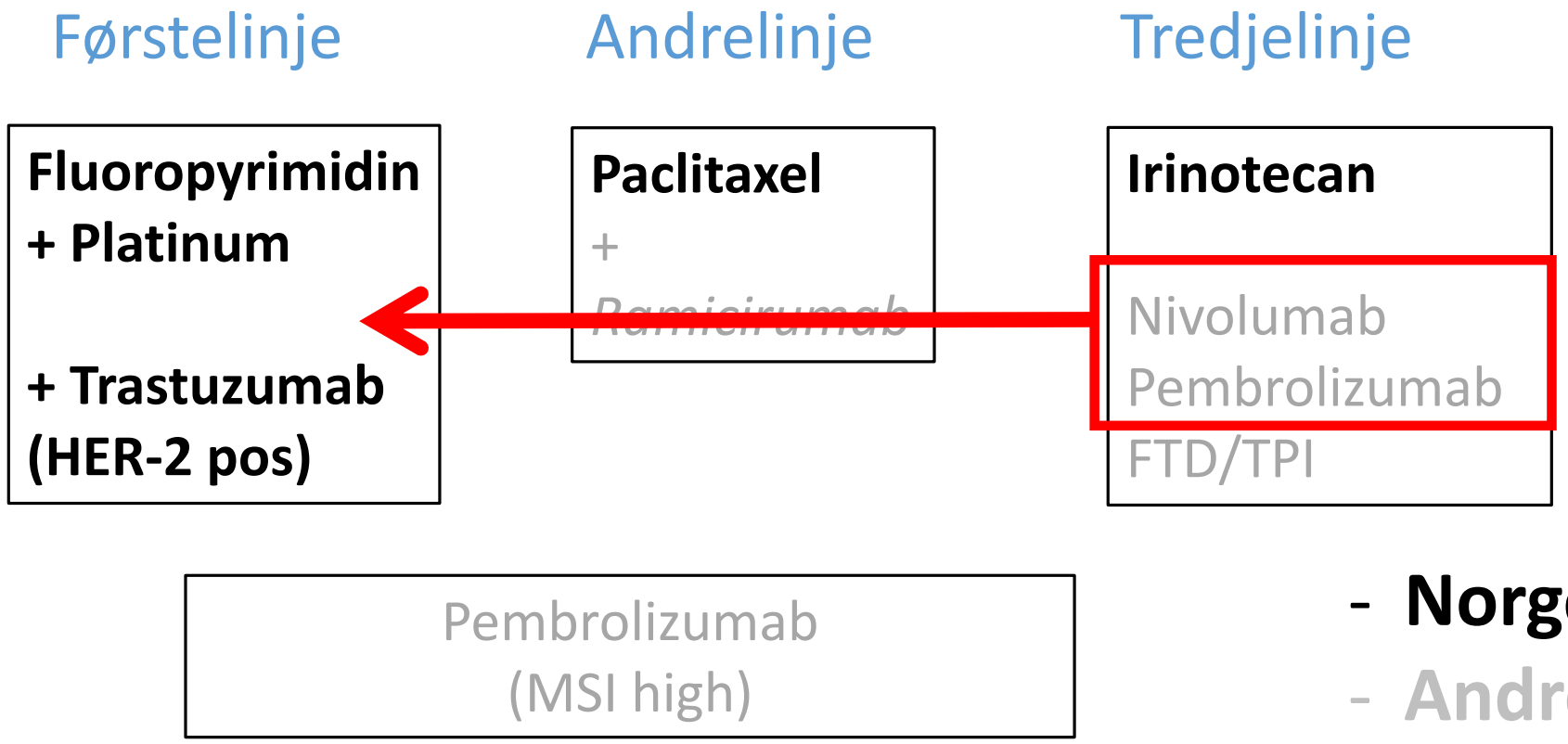
- **Adjuvant nivolumab for pasienter som har gjennomgått neoadjuvant radiokjemoterapi (unntatt ypT0N0)**

Inoperabel avansert/metastatisk sykdom

- Medikamentell behandling
- Palliativ strålebehandling
  - Øsofagus /magesekk
    - Dysfagi
    - Blødninger
  - Metastaser
    - Smerter
    - CNS/nerverotspåvirkning
- Stent i øsofagus
  - Dysfagi



Standardbehandling avansert/metastatisk Øsofagus & Ventrikkelkreft



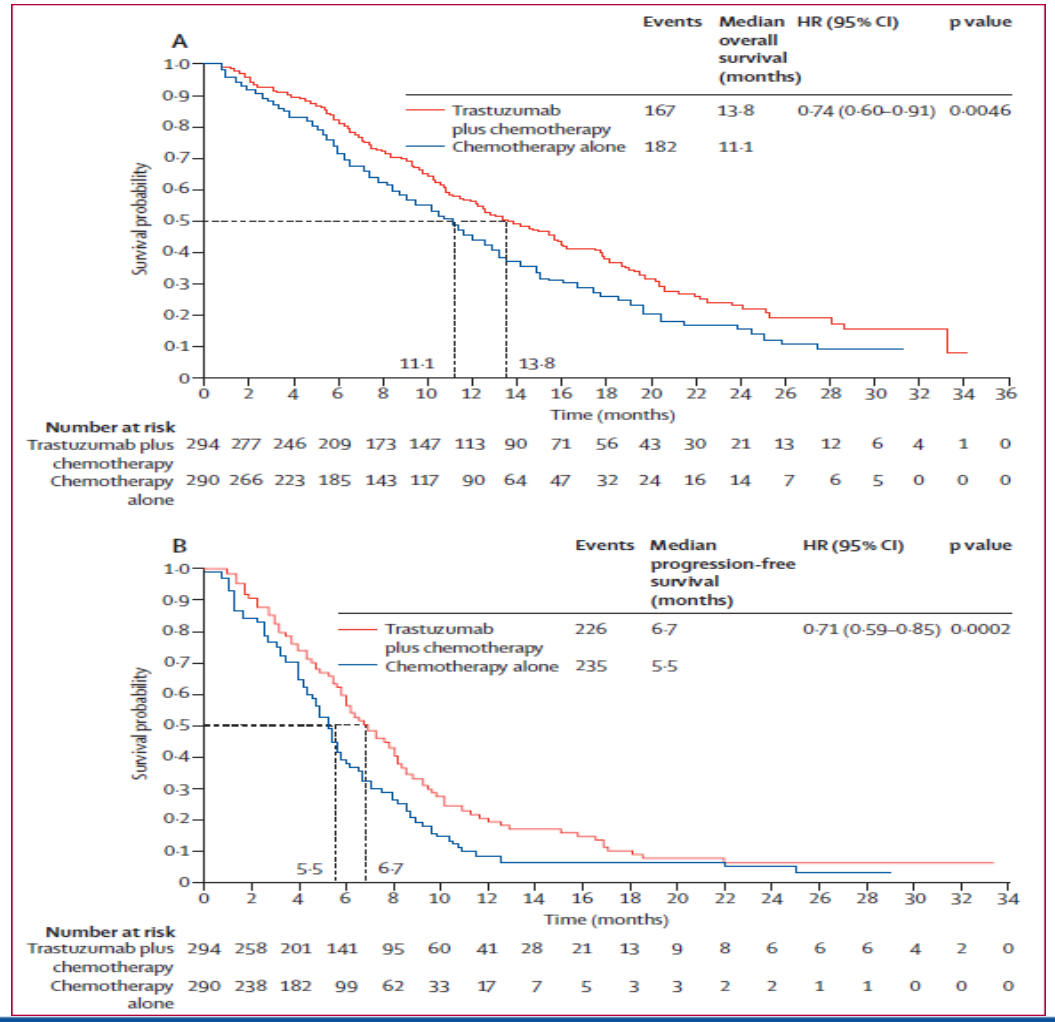
- **Norge**
- **Andre land**

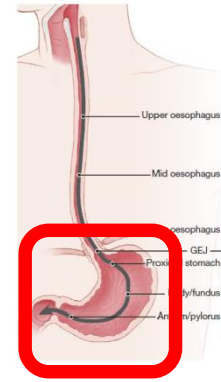
Standardbehandling avansert/metastatisk Øsofagus & Ventrikkelkreft

Førstelinje	Andrelinje	Tredjelinje
Fluoropyrimidin + Platinum +Nivolumab /Pembrolizumab + Trastuzumab (HER-2 pos)	**Paclitaxel** + *Ramicirumab*	**Irinotecan** FTD/TPI
Pembrolizumab (MSI high)		

- **Norge**
- **Andre land**

Anti-HER-2 + kjemoterapi -ToGA studien:





Gastroesophageale adenocarcinomer

6.1% to 22.6% of pts with gastric cancer are HER-2 positive (*)

In advanced gastric cancer, trastuzumab + standard chemotherapy improved PFS, OS & RR

*M. A. Gordon Ann Oncol. 2013 Jul;24(7):1754-61
*Hsu, J. T., et al., 2011 The oncologist 16, 706-1713
*Bang, Y.J., Van Cutsem, E., et al., 2010 Lancet 376, 687-697

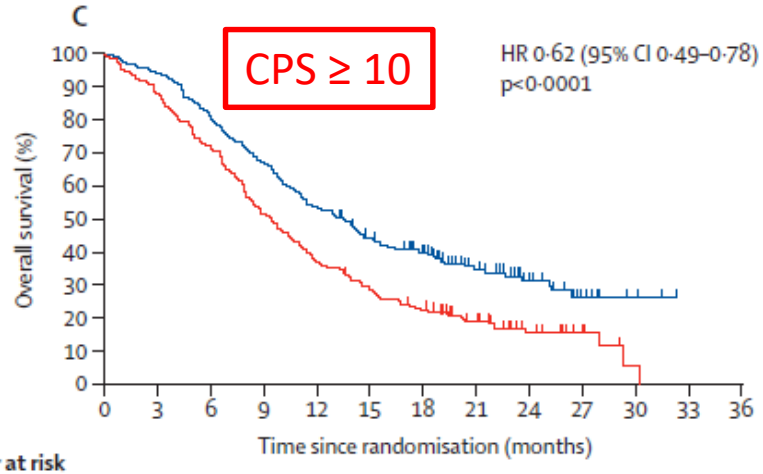
Oslo universitetssykehus

Immun sjekk-punkt hemmere i øvre GI kreft -aktuelle studier i førstelinjes behandling:

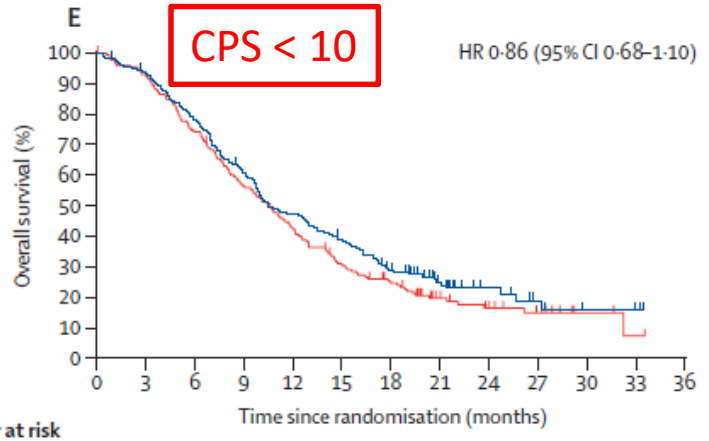
- **Keynote 590**
- **CheckMate 649**
- **CheckMate 648**

Pembrolizumab plus chemotherapy versus chemotherapy alone for first-line treatment of advanced oesophageal cancer (KEYNOTE-590): a randomised, placebo-controlled, phase 3 study

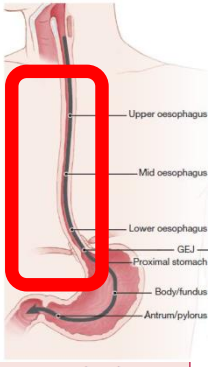
Jong-Mu Sun, Lin Shen, Manish A Shah, Peter Enzinger, Antoine Adenis, Toshihiko Doi, Takashi Kojima, Jean-Philippe Metges, Zhigang Li,



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)



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

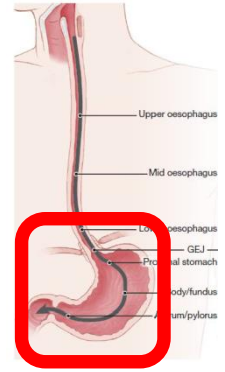


	Pembrolizumab plus chemoth group (n=373	
Age, years		
Median (range)	64 (28–94)	
≥65	172 (46%)	
Sex		
Female	67 (18%)	
Male	306 (82%)	
Asia region*	196 (53%)	197 (52%)
Race		
Asian	201 (54%)	199 (53%)
White	139 (37%)	139 (37%)
Missing	14 (4%)	15 (4%)
Native American	9 (2%)	12 (3%)
African American	5 (1%)	2 (1%)
Other†	5 (1%)	9 (2%)
ECOG performance status		
0	149 (40%)	150 (40%)
1	223 (60%)	225 (60%)
2	1 (<1%)	1 (<1%)
Oesophageal squamous cell carcinoma	274 (73%)	274 (73%)
Adenocarcinoma	99 (27%)	102 (27%)
Oesophageal adenocarcinoma	58 (16%)	52 (14%)
Siewert type 1 gastro-oesophageal junction adenocarcinoma‡	41 (11%)	50 (13%)
Disease status		
Metastatic	344 (92%)	339 (90%)
Unresectable locally advanced	29 (8%)	37 (10%)
PD-L1 CPS ≥10	186 (50%)	197 (52%)
Oesophageal squamous cell carcinoma	143 (38%)	143 (38%)
Adenocarcinoma	43 (12%)	54 (14%)
PD-L1 CPS <10	175 (47%)	172 (46%)
Oesophageal squamous cell carcinoma	121 (32%)	126 (34%)
Adenocarcinoma	54 (14%)	46 (12%)
PD-L1 status not evaluable or missing	12 (3%)	7 (2%)

VIRTUAL 2020 ESMO congress

Nivolumab plus chemotherapy versus chemotherapy as first-line treatment for advanced gastric cancer/gastroesophageal junction cancer/esophageal adenocarcinoma: first results of the CheckMate 649 study

Markus Moehler,[1] Kohei Shitara,[2] Marcelo Garrido,[3] Pamela Salman,[4] Lin Shen,[5] Lucjan Wyrwicz,[6] Kensei Yamaguchi,[7] Tomasz Skoczylas,[8] Arinilda Campos Bragagnoli,[9] Tianshu Liu,[10] Michael Schenker,[11] Patricio Yanez,[12] Mustapha Tehfe,[13] Valerie Poulart,[14] Dana Cullen,[14] Ming Lei,[14] Kaoru Kondo,[14] Mingshun Li,[14] Jaffer A. Ajani.[15] Yelena Y. Janjigian[16]



Articles

THE LANCET

First-line nivolumab plus chemotherapy versus chemotherapy alone for advanced gastric, gastro-oesophageal junction, and oesophageal adenocarcinoma (CheckMate 649): a randomised, open-label, phase 3 trial

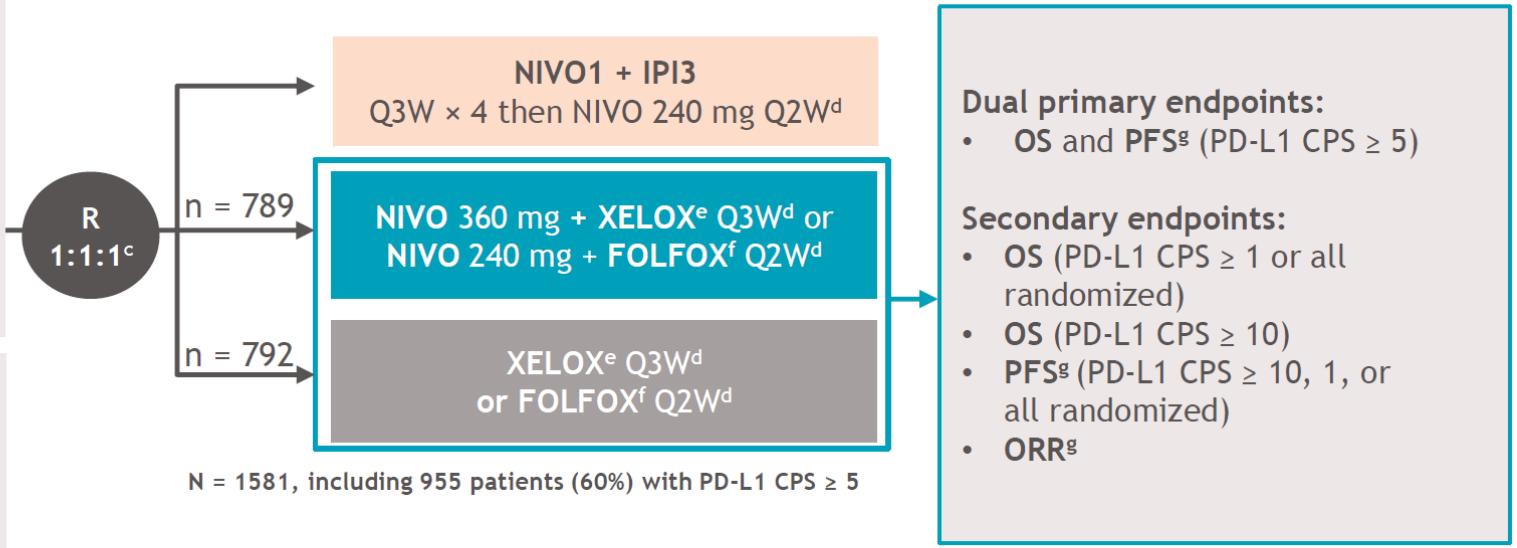
Yelena Y Janjigian, Kohei Shitara*, Markus Moehler, Marcelo Garrido, Pamela Salman, Lin Shen, Lucjan Wyrwicz, Kensei Yamaguchi, Tomasz Skoczylas, Arinilda Campos Bragagnoli, Tianshu Liu, Michael Schenker, Patricio Yanez, Mustapha Tehfe, Ruben Kowalyszyn, Michalis V Karamouzis, Ricardo Bruges, Thomas Zander, Roberto Pazo-Cid, Erika Hitre, Kynan Feeney, James M Cleary, Valerie Poulart, Dana Cullen, Ming Lei, Hong Xiao, Kaoru Kondo, Mingshun Li, Jaffer A Ajani*

CheckMate 649 study design

- CheckMate 649 is a randomized, open-label, phase 3 study[a]

Key eligibility criteria
- Previously untreated, unresectable, advanced or metastatic gastric/GEJ/ esophageal adenocarcinoma
- No known HER2-positive status
- ECOG PS 0-1

Stratification factors
- Tumor cell PD-L1 expression (≥ 1% vs < 1%[b])
- Region (Asia vs United States/Canada vs ROW)
- ECOG PS (0 vs 1)
- Chemo (XELOX vs FOLFOX)

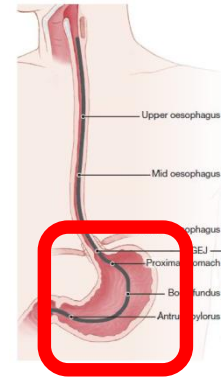


- At data cutoff (May 27, 2020), the minimum follow-up was 12.1 months[h]

[a]ClinicalTrials.gov number, NCT02872116; [b]< 1% includes indeterminate tumor cell PD-L1 expression; determined by PD-L1 IHC 28-8 pharmDx assay (Dako); [c]After NIVO + chemo arm was added and before new patient enrollment in the NIVO1+IPI3 group was closed; [d]Until documented disease progression (unless consented to treatment beyond progression for NIVO + chemo), discontinuation due to toxicity, withdrawal of consent, or study end. NIVO is given for a maximum of 2 years; [e]Oxaliplatin 130 mg/m^2 IV (day 1) and capecitabine 1000 mg/m^2 orally twice daily (days 1-14); [f]Oxaliplatin 85 mg/m^2, leucovorin 400 mg/m^2, and FU 400 mg/m^2 IV (day 1) and FU 1200 mg/m^2 IV daily (days 1-2); [g]BICR assessed; [h]Time from concurrent randomization of the last patient to NIVO + chemo vs chemo to data cutoff.

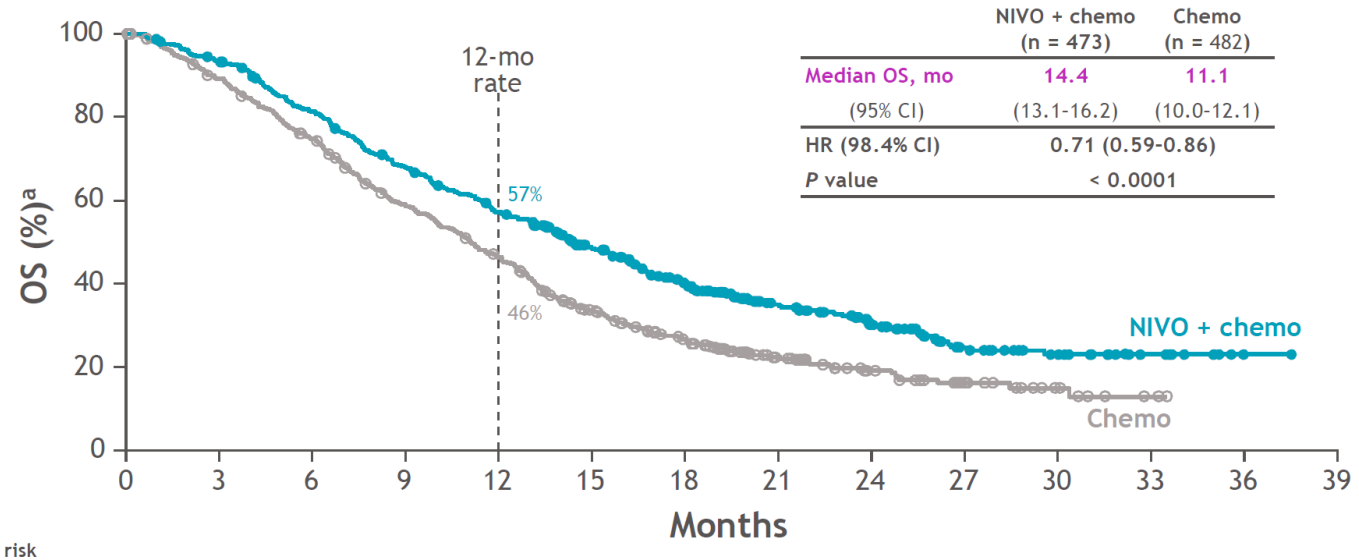
Moehler M et al., Lancet Onc 2021 and ESMO 2020

Checkmate 649 – Total overlevelse (Gastric/GEJ, CPS≥5):



Overall survival

Primary endpoint (PD-L1 CPS ≥ 5)



	NIVO + chemo (n = 473)	Chemo (n = 482)
Median OS, mo	14.4	11.1
(95% CI)	(13.1-16.2)	(10.0-12.1)
HR (98.4% CI)	0.71 (0.59-0.86)	
P value	< 0.0001	

No. at risk														
NIVO + chemo	473	438	377	313	261	198	149	96	65	33	22	9	1	0
Chemo	482	421	350	271	211	138	98	56	34	19	8	2	0	0

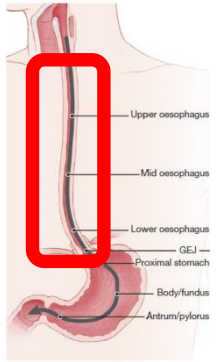
- Superior OS, 29% reduction in the risk of death, and a 3.3-month improvement in median OS with NIVO + chemo versus chemo in patients whose tumors expressed PD-L1 CPS ≥ 5

[a]Minimum follow-up 12.1 months.

Oslo universitetssykehus

Moehler M et al., Lancet Onc 2021 and ESMO 2020

Checkmate 648 (Plateepitelcarcinom i spiserøret)



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Nivolumab Combination Therapy in Advanced Esophageal Squamous-Cell Carcinoma

Y. Doki, J.A. Ajani, K. Kato, J. Xu, L. Wyrwicz, S. Motoyama, T. Ogata, H. Kawakami, C.-H. Hsu, A. Adenis, F. El Hajbi, M. Di Bartolomeo, M.I. Braghiroli, E. Holtved, S.A. Ostoich, H.R. Kim, M. Ueno, W. Mansoor, W.-C. Yang, T. Liu, J. Bridgewater, T. Makino, I. Xynos, X. Liu, M. Lei, K. Kondo, A. Patel, J. Gricar, I. Chau, and Y. Kitagawa, for the CheckMate 648 Trial Investigators*

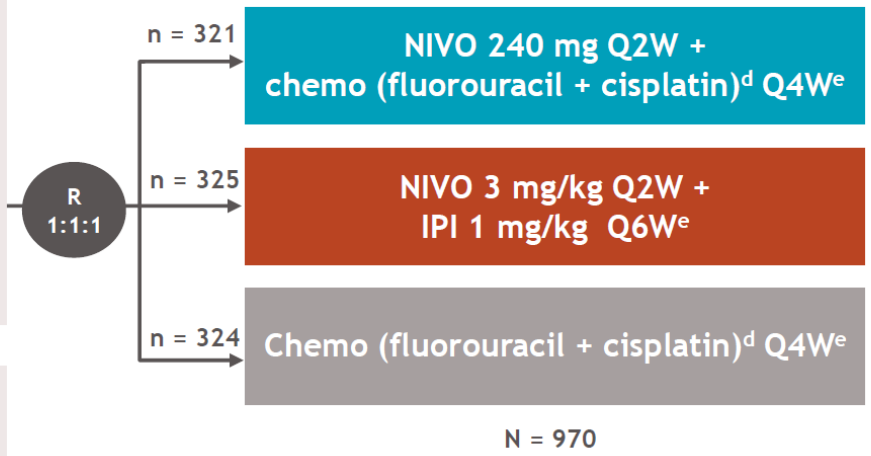
Doki Y et al., NEJM 2022 and ASCO 2021

CheckMate 648 study design

- CheckMate 648 is a global, randomized, open-label phase 3 study[a]

Key eligibility criteria
- Unresectable advanced, recurrent or metastatic ESCC
- ECOG PS 0-1
- No prior systemic treatment for advanced disease
- Measurable disease

Stratification factors
- Tumor cell PD-L1 expression (≥ 1% vs < 1%[b])
- Region (East Asia[c] vs rest of Asia vs ROW)
- ECOG PS (0 vs 1)
- Number of organs with metastases (≤ 1 vs ≥ 2)



Primary endpoints:
- OS and PFS[f] (tumor cell PD-L1 ≥ 1%)

Secondary endpoints:
- OS and PFS[f] (all randomized)
- ORR[f] (tumor cell PD-L1 ≥ 1% and all randomized)

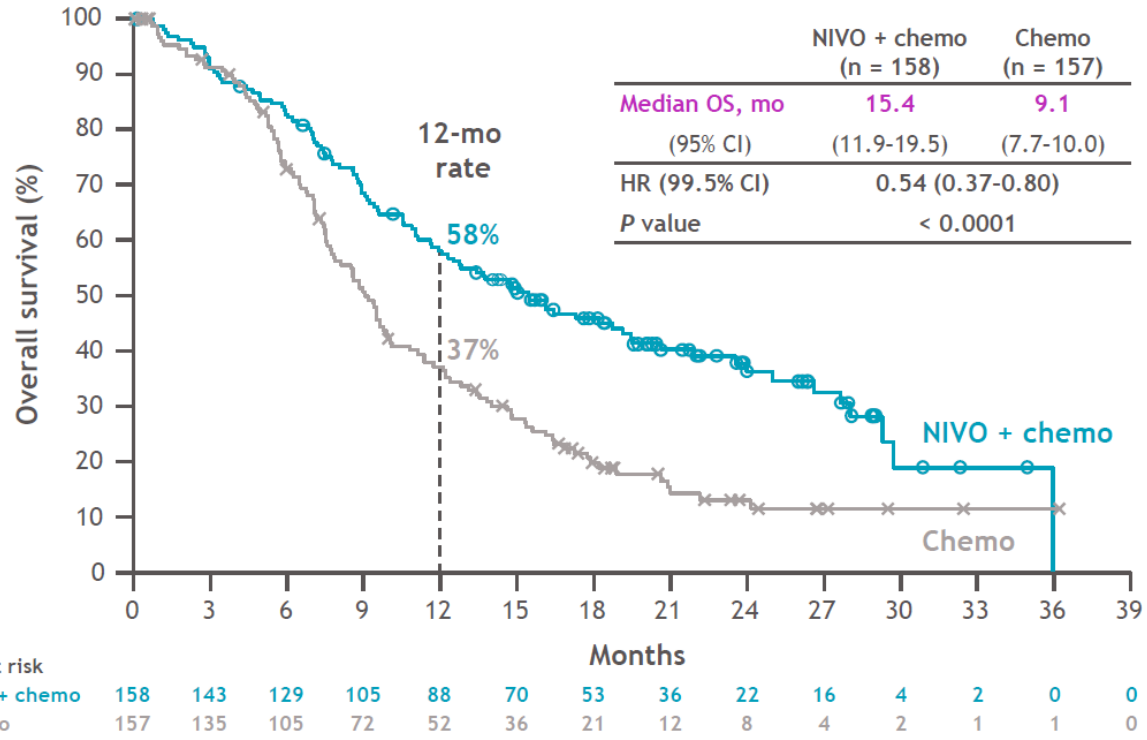
- At data cutoff (January 18, 2021), the minimum follow-up was 12.9 months[g]

[a]ClinicalTrials.gov. NCT03143153; [b]< 1% includes indeterminate tumor cell PD-L1 expression; determined by PD-L1 IHC 28-8 pharmDx assay (Dako); [c]East Asia includes patients from Japan, Korea, and Taiwan; [d]Fluorouracil 800 mg/m^2 IV daily (days 1-5) and cisplatin 80 mg/m^2 IV (day 1); [e]Until documented disease progression (unless consented to treatment beyond progression for NIVO + IPI or NIVO + chemo), discontinuation due to toxicity, withdrawal of consent, or study end. NIVO is given alone or in combination with IPI for a maximum of 2 years; [f]Per blinded independent central review (BICR); [g]Time from last patient randomized to clinical data cutoff.

Doki Y et al., NEJM 2022 and ASCO 2021

Overall survival: NIVO + chemo vs chemo

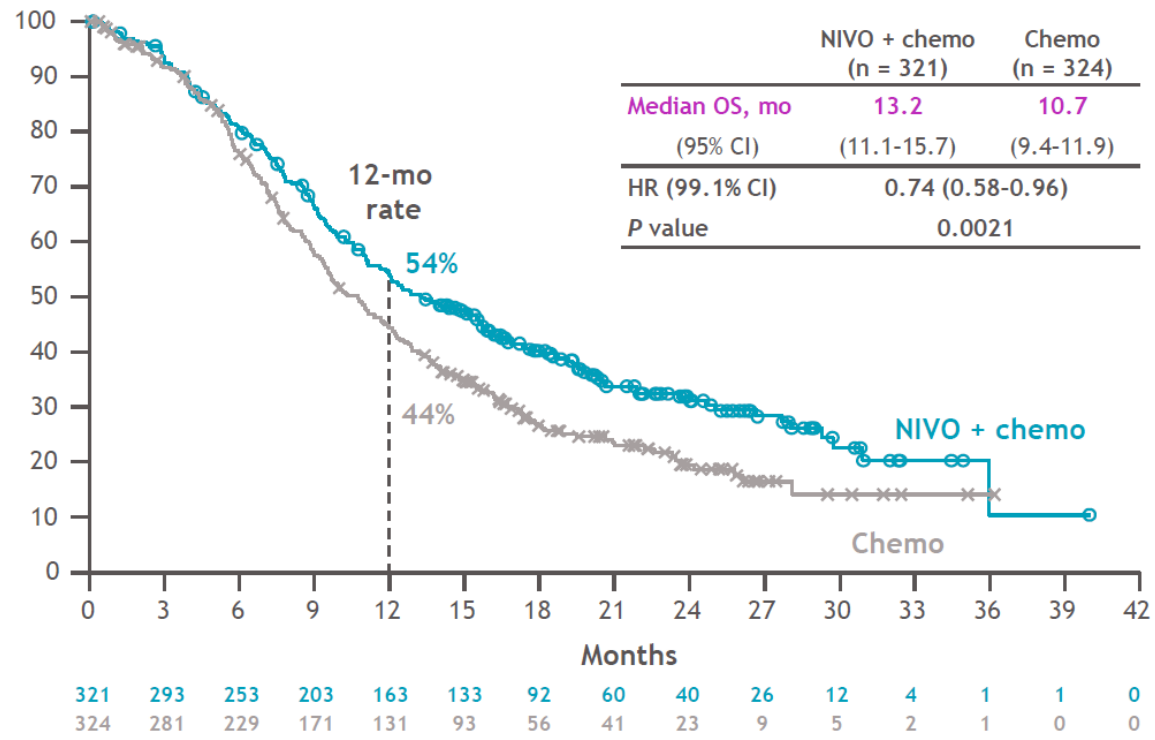
Primary endpoint (tumor cell PD-L1 ≥ 1%)[a]



	NIVO + chemo (n = 158)	Chemo (n = 157)
Median OS, mo	15.4	9.1
(95% CI)	(11.9-19.5)	(7.7-10.0)
HR (99.5% CI)	0.54 (0.37-0.80)	
P value	< 0.0001	

lo. at risk														
IIVO + chemo	158	143	129	105	88	70	53	36	22	16	4	2	0	0
:hemo	157	135	105	72	52	36	21	12	8	4	2	1	1	0

All randomized[a]



	NIVO + chemo (n = 321)	Chemo (n = 324)
Median OS, mo	13.2	10.7
(95% CI)	(11.1-15.7)	(9.4-11.9)
HR (99.1% CI)	0.74 (0.58-0.96)	
P value	0.0021	

NIVO + chemo	321	293	253	203	163	133	92	60	40	26	12	4	1	1	0
Chemo	324	281	229	171	131	93	56	41	23	9	5	2	1	0	0

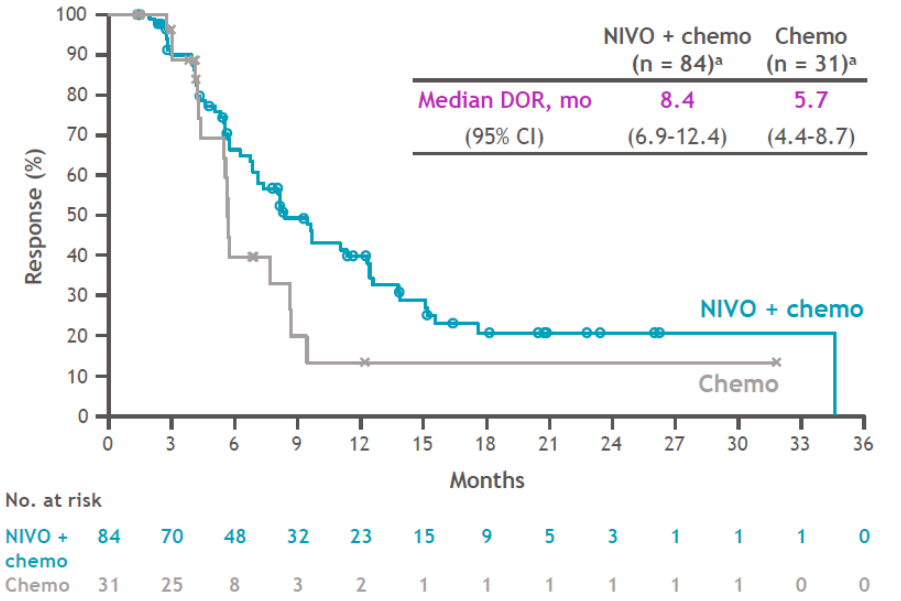
- Superior OS with NIVO + chemo vs chemo in tumor cell PD-L1 ≥ 1% and all randomized populations
  - Tumor cell PD-L1 ≥ 1%: 46% reduction in the risk of death and a 6.3-month improvement in median OS
  - All randomized: 26% reduction in the risk of death and a 2.5-month improvement in median OS

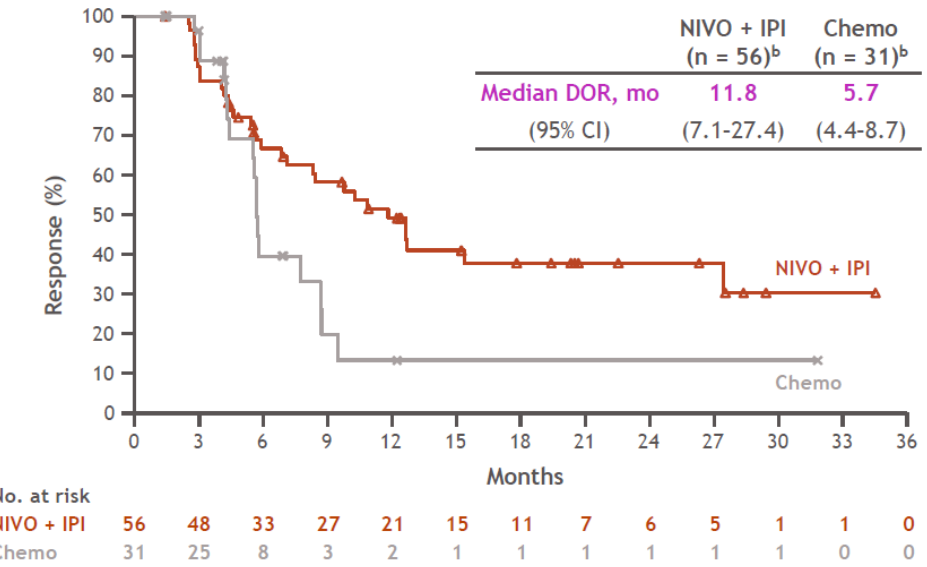
[a]Minimum follow-up 12.9 months.

Oslo universitetssykehus

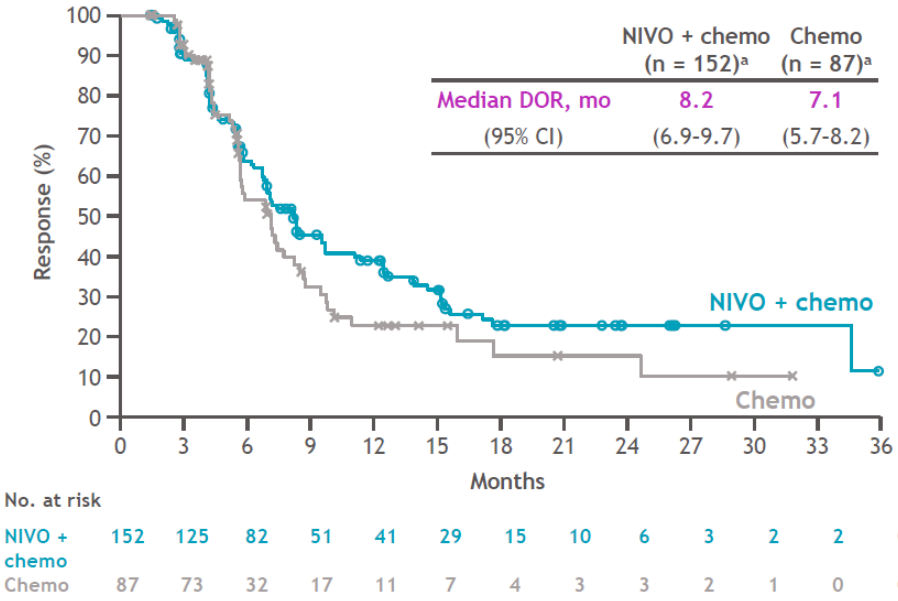
Doki Y et al., NEJM 2022 and ASCO 2021

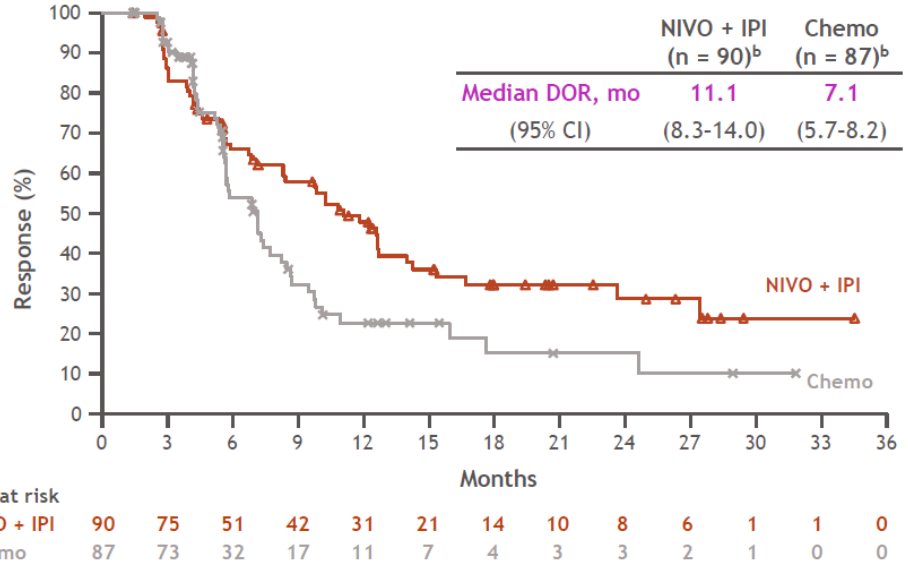
PD-L1 TPS ≥ 1%





All randomized





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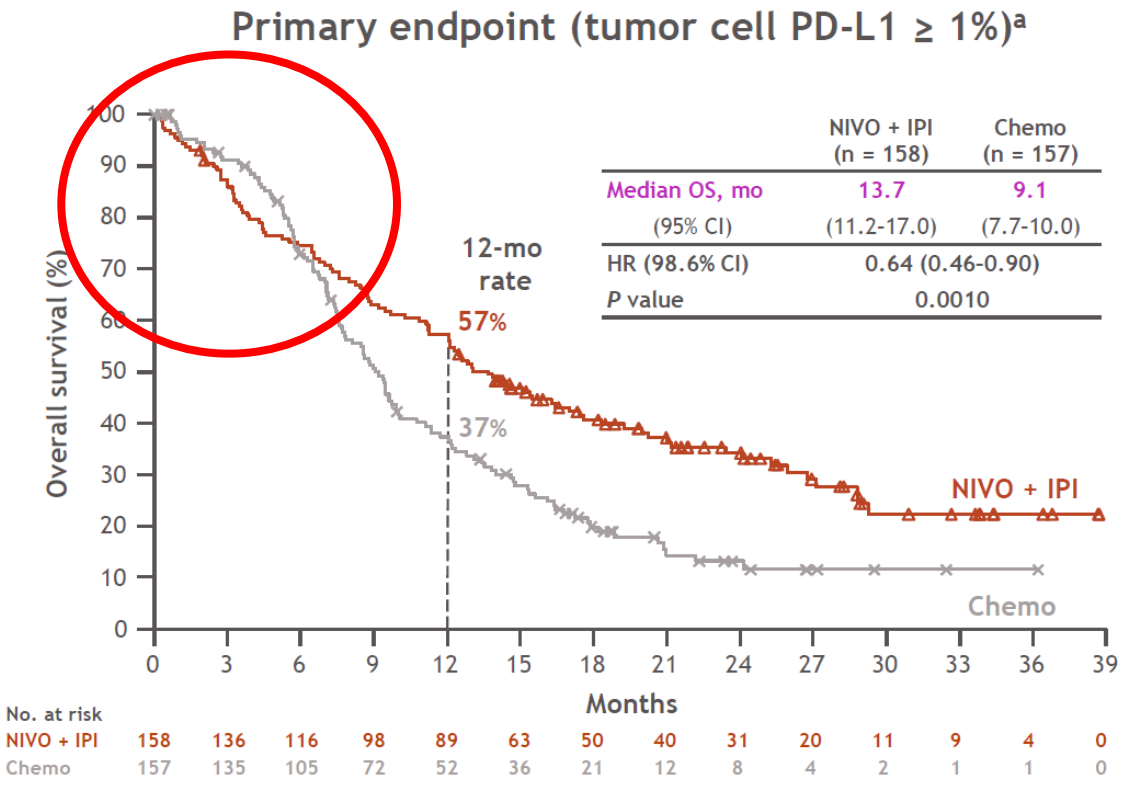
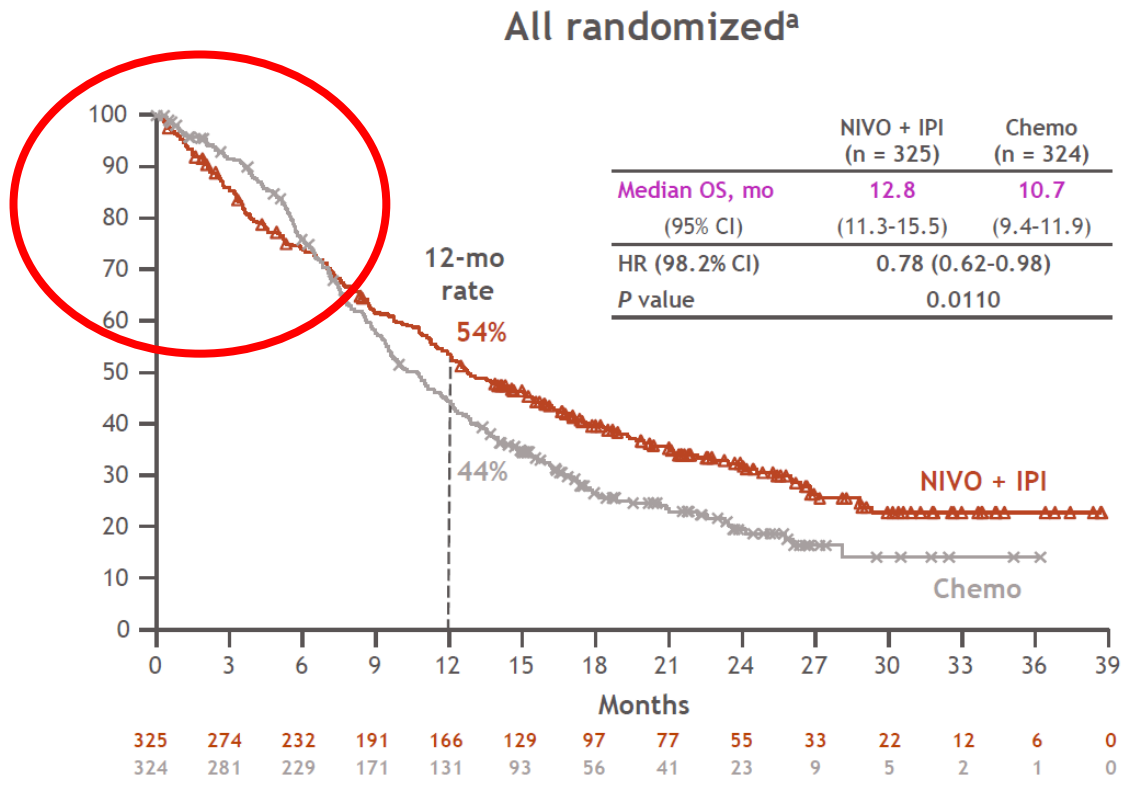
Doki Y et al., NEJM 2022 and ASCO 2021

Overall survival: NIVO + IPI vs chemo



	NIVO + IPI (n = 158)	Chemo (n = 157)
Median OS, mo	13.7	9.1
(95% CI)	(11.2-17.0)	(7.7-10.0)
HR (98.6% CI)	0.64 (0.46-0.90)	
P value	0.0010	



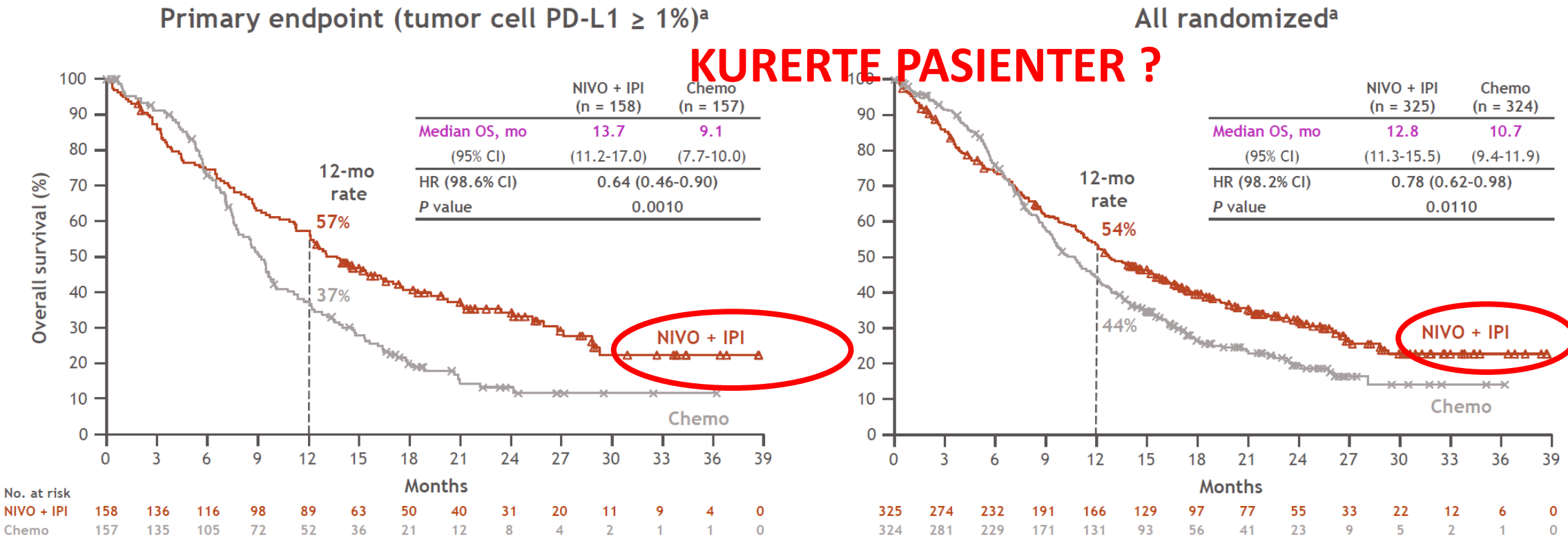
	NIVO + IPI (n = 325)	Chemo (n = 324)
Median OS, mo	12.8	10.7
(95% CI)	(11.3-15.5)	(9.4-11.9)
HR (98.2% CI)	0.78 (0.62-0.98)	
P value	0.0110	

- Superior OS with NIVO + IPI vs chemo in tumor cell PD-L1 ≥ 1% and all randomized populations
  - Tumor cell PD-L1 ≥ 1%: 36% reduction in the risk of death and a 4.6-month improvement in median OS
  - All randomized: 22% reduction in the risk of death and a 2.1-month improvement in median OS

Doki Y et al., NEJM 2022 and ASCO 2021

Overall survival: NIVO + IPI vs chemo

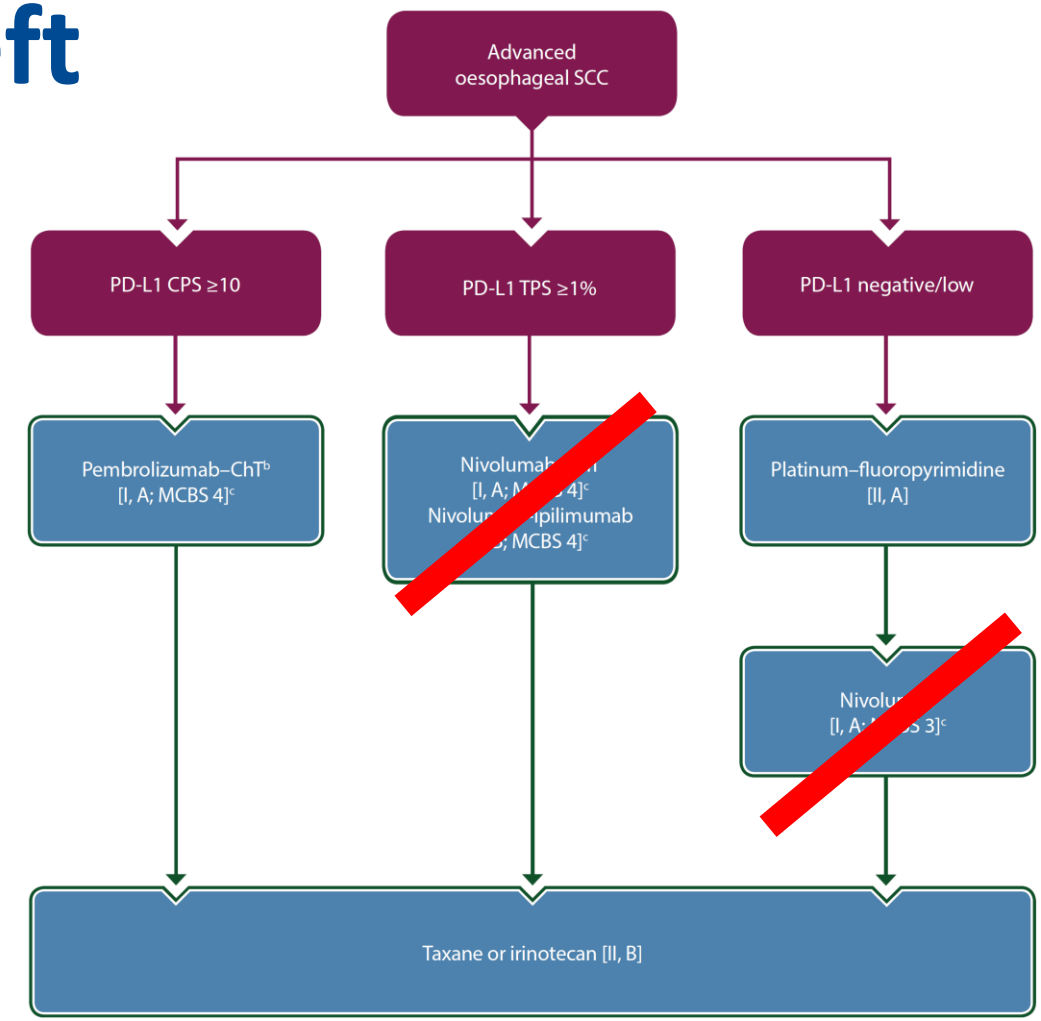
KURERTE PASIENTER ?



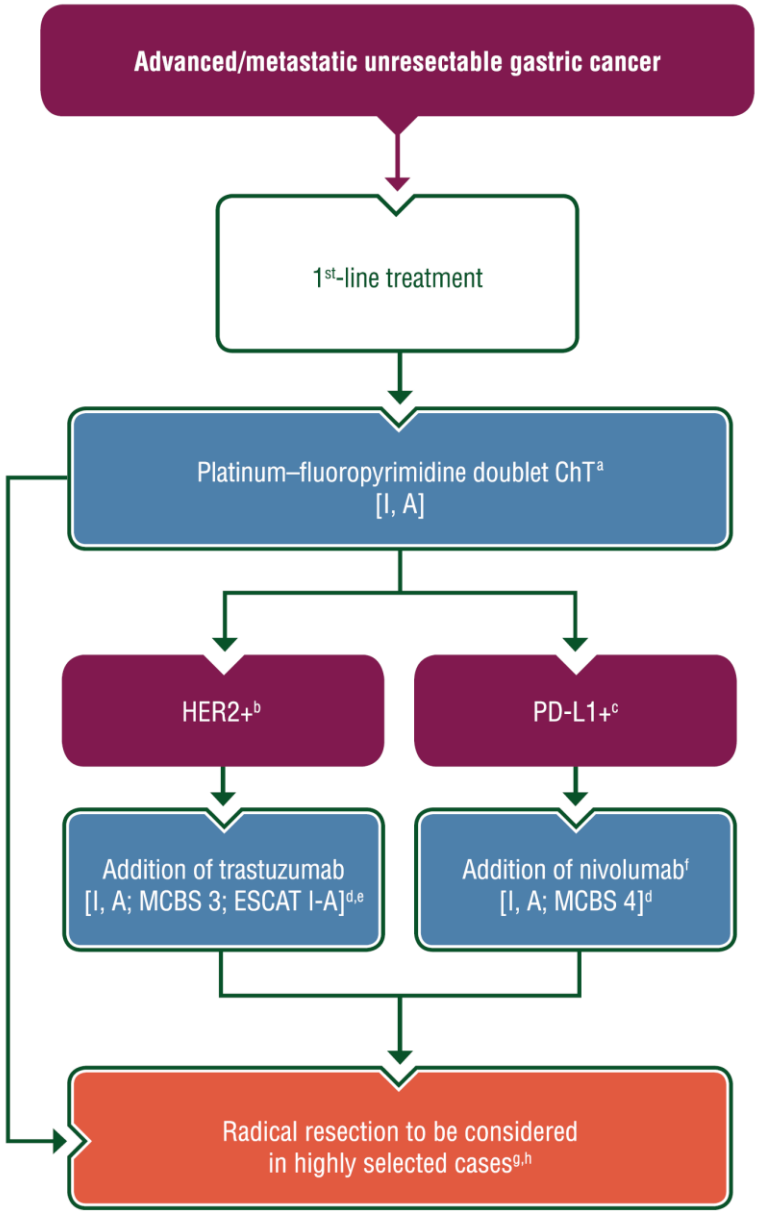
- Superior OS with NIVO + IPI vs chemo in tumor cell PD-L1 ≥ 1% and all randomized populations
  - Tumor cell PD-L1 ≥ 1%: 36% reduction in the risk of death and a 4.6-month improvement in median OS
  - All randomized: 22% reduction in the risk of death and a 2.1-month improvement in median OS

Doki Y et al., NEJM 2022 and ASCO 2021

ESMO Guidelines avansert GØ kreft



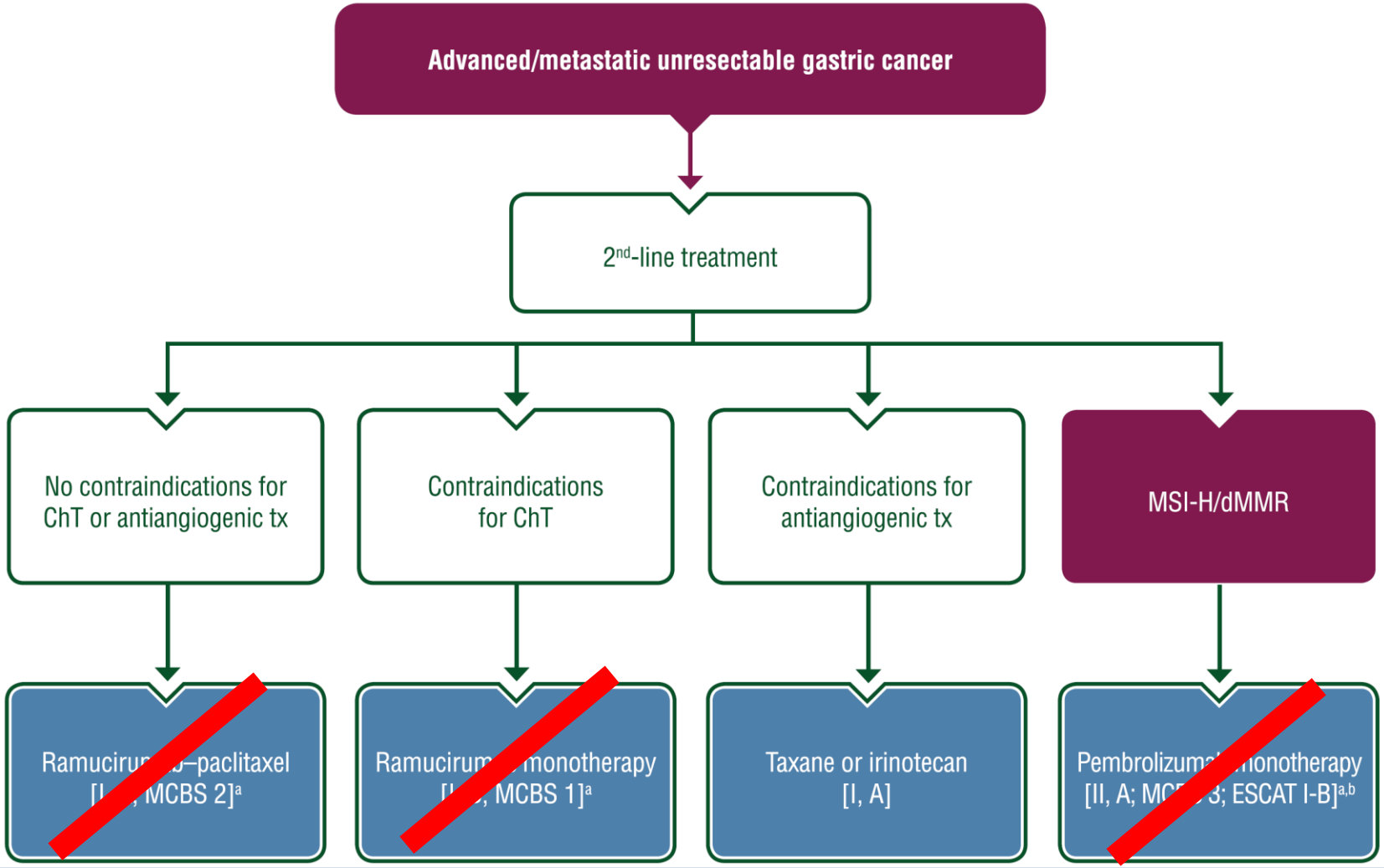
NORGE



Oslo universitetssykehus

Obermannova et al, Ann Oncol 2022
Lordick et al, Ann Oncol, 2022

ESMO Guidelines, magekreft – 2. linjes beh



NORGE

Lordick et al, Ann Oncol, 2022

Godkjenninger nivolumab/pembrolizumab gastroøsofageal kreft Sve, Dan, Eng og Nor:

Indikasjoner	EMEA godkjenning	Sverige (NT rådet)	Danmark (Medicinrådet)	England (NICE)	Norge (Beslutningsforum)
Nivolumab + kjemoterapi (1-linje - gastroøsofageal EAC+GC) CPS≥5	16.09.2021	19.11.2021	26.10.2022	24.11.2022	23.01.2023
Nivolumab + Ipi eller kjemoterapi (1-linje - ESCC) TPS≥1	(25.02.2022)	27.04.2022	15.06.2022	-	-
Pembrolizumab + kjemoterapi (1-linje - gastroøsofageal karsinom) CPS≥10	20.05.2021	30.08.2021	26.01.2022	20.10.2021	29.08.2022
Adjuvant nivolumab spiserørskreft	30.07.2021	25.02.2022	15.06.2022	17.11.2021	29.08.2022

Hvorfor kommer de norske godkjenningene så sent ?

Oslo universitetssykehus

SPOTLIGHT studien:

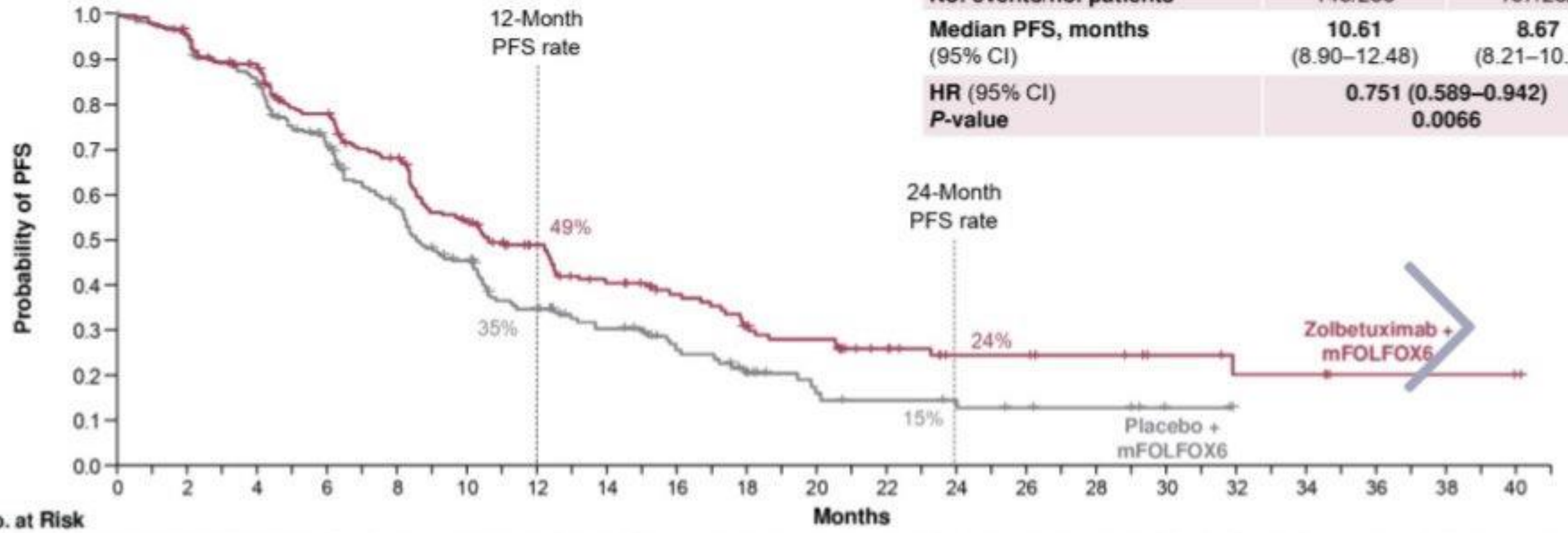
Claudin18.2 positiv ventrikkelcancer:

	Zolbetuximab + mFOLFOX6 283 patients	Placebo + mFOLFOX6 282 patients
Progression-free survival (primary endpoint)		
Events, patients (%)	146 (51.6)	167 (59.2)
Median, months (95% CI)	10.61 (8.90, 12.48)	8.67 (8.21, 10.28)
HR (95% CI), 1-sided *P* value	0.751 (0.589, 0.942), .0066	
Secondary endpoints		
Overall survival		
Deaths, patients (%)	149 (52.7)	177 (62.8)
Median, months (95% CI)	18.23 (16.43, 22.90)	15.54 (13.47, 16.53)
HR (95% CI), 1-sided *P* value	0.750 (0.601, 0.936), .0053	
Objective response rate (95% CI)	60.7 (53.72, 67.30)	62.1 (55.17, 68.66)
Best overall response		
Complete response	12 (5.7)	7 (3.3)
Partial response	116 (55.0)	124 (58.8)
Stable disease	45 (21.3)	52 (24.6)
Progressive disease	14 (6.6)	14 (6.6)
Median duration of response, months (95% CI)	8.51 (6.80, 10.25)	8.11 (6.47, 11.37)
3rd quartile	29.9 (10.41, NE)	15.5 (13.27, NE)

K. Shitara, LBA292, ASCO-GI 2023

Primary End Point: PFS by Independent Review Committee[a]

	Zolbetuximab + mFOLFOX6	Placebo + mFOLFOX6
No. events/no. patients	146/283	167/282
Median PFS, months (95% CI)	**10.61** (8.90–12.48)	**8.67** (8.21–10.28)
HR (95% CI) *P*-value	**0.751 (0.589–0.942)** **0.0066**	



No. at Risk

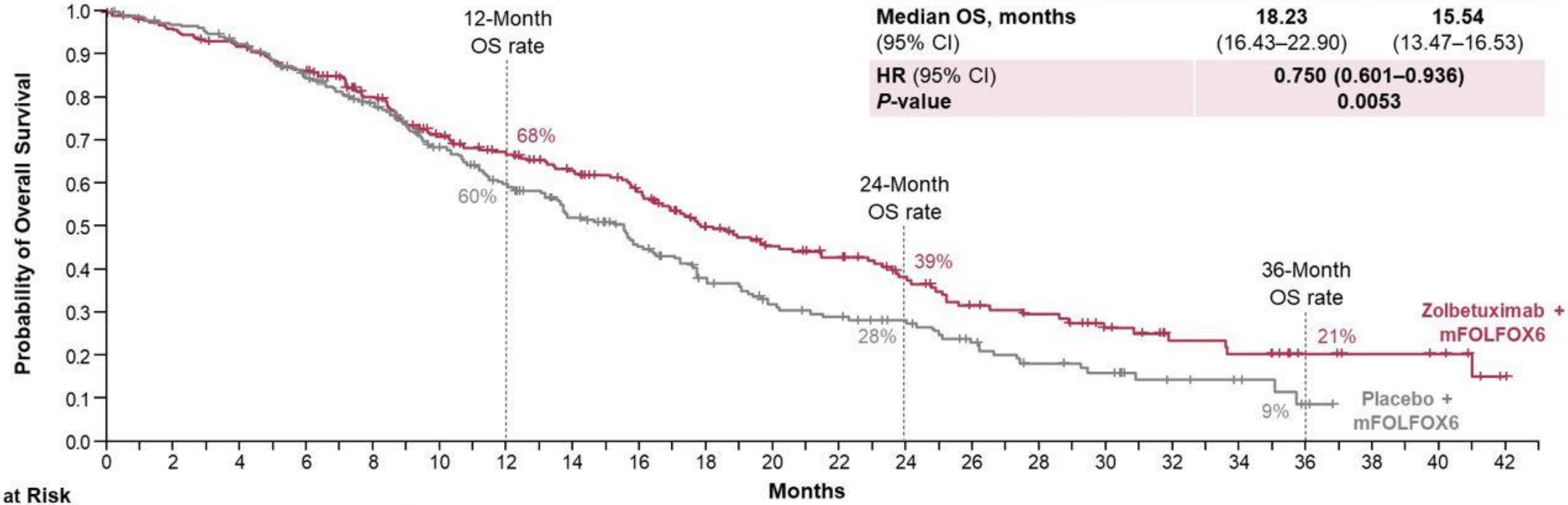
	0		2		4		6		8		10		12		14		16		18		20		22		24		26		28		30		32		34		36		38		40	
Zolbetuximab + mFOLFOX6	283	263	254	232	226	190	187	148	143	108	102	84	78	59	56	53	43	40	33	28	28	21	19	17	12	12	12	10	10	9	7	7	5	5	5	2	2	2	2	2	1	0
Placebo + mFOLFOX6	282	273	260	237	226	183	168	136	122	91	83	60	56	43	40	38	26	25	19	14	12	9	9	9	8	7	6	5	5	4	2	2	0	0	0	0	0	0	0	0	0	0

- PFS was significantly longer in patients treated with zolbetuximab + mFOLFOX6 vs placebo + mFOLFOX6

Data cutoff: September 9, 2022; Median follow-up = 12.94 months (zolbetuximab + mFOLFOX6) vs 12.65 months (placebo + mFOLFOX6).
[a]Per RECIST version 1.1.

Key Secondary End Point: OS

	Zolbetuximab + mFOLFOX6	Placebo + mFOLFOX6
No. events/no. patients	149/283	177/282
Median OS, months (95% CI)	**18.23** (16.43–22.90)	**15.54** (13.47–16.53)
HR (95% CI)	**0.750 (0.601–0.936)**	
***P*-value**	**0.0053**	



No. at Risk

Zolbetuximab + mFOLFOX6	283	270	264	255	251	241	233	217	196	178	164	152	146	135	125	117	107	93	83	75	70	67	62	58	49	42	34	32	30	27	23	20	15	15	13	13	9	8	7	7	6	4	1	0
Placebo + mFOLFOX6	282	277	271	266	253	242	224	210	197	183	164	152	139	129	108	101	85	77	64	60	49	42	40	36	34	30	25	21	18	17	15	9	8	7	6	5	2	0	0	0	0	0	0	0

- OS was significantly longer in patients treated with zolbetuximab + mFOLFOX6 vs placebo + mFOLFOX6

Data cutoff: September 9, 2022; Median follow-up = 22.14 months (zolbetuximab + mFOLFOX6) vs 20.93 months (placebo + mFOLFOX6).

2 nylig positive fase III studier for Claudin18.2 pos ventrikkel-cancer:

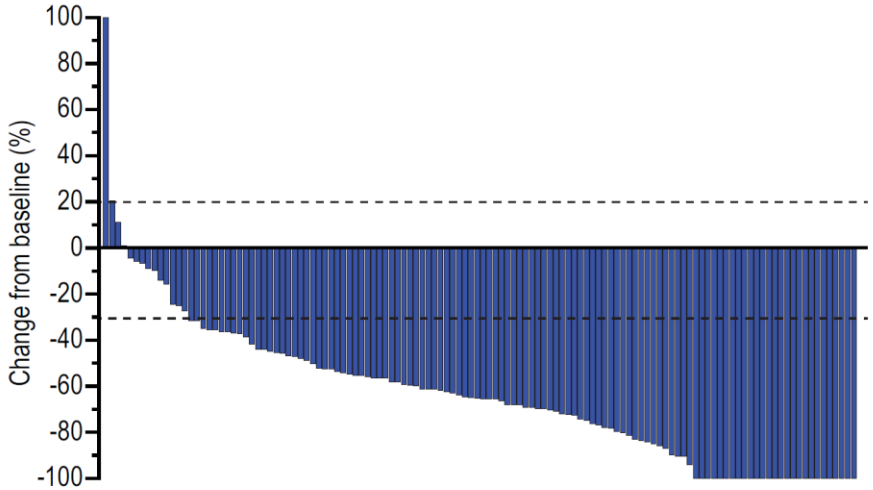
- **SPOTLIGHT**, zolbetuximab + FOLFOX
  - pos studie med sign. bedret PFS (og OS)

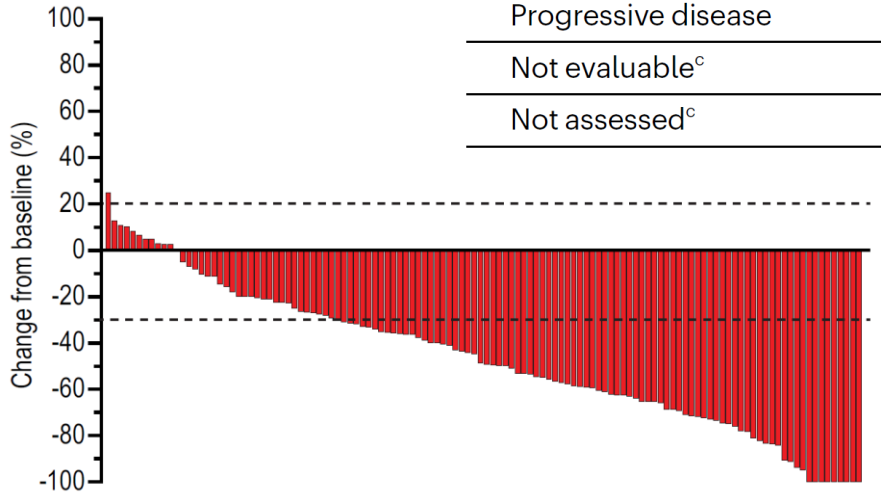
- **GLOW**, zolbetuximab + CAPOX
  - pos studie med sign. bedret PFS i følge pressemelding des-22.

KEYNOTE 811 (fase III) – interim-analyse: HER-2 pos AC: Trastuzumab +kjemo + pembrolizumab eller placebo

Article

The KEYNOTE-811 trial of dual PD-1 and HER2 blockade in HER2-positive gastric cancer



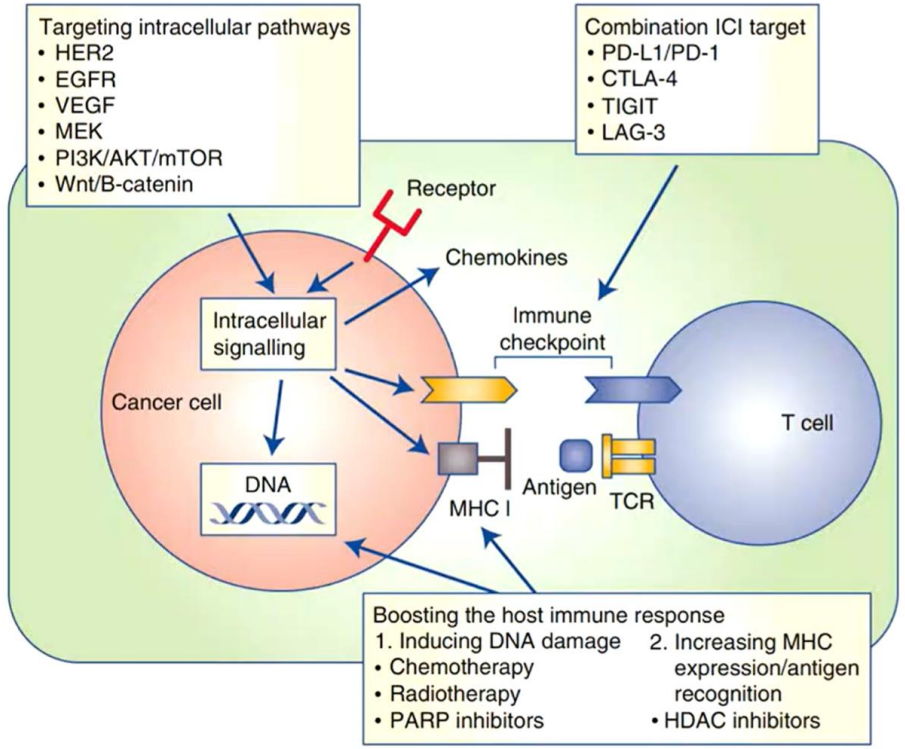


Variable	Pembrolizumab group (*n* = 133)	Placebo group (*n* = 131)
Objective response (% (95% confidence interval))[a]	74.4 (66.2–81.6)	51.9 (43.0–60.7)
Disease control (% (95% confidence interval))[b]	96.2 (91.4–98.8)	89.3 (82.7–94.0)
Best overall response (number (%))		
Complete response	15 (11.3)	4 (3.1)
Partial response	84 (63.2)	64 (48.9)
Stable disease	29 (21.8)	49 (37.4)
Progressive disease	5 (3.8)	7 (5.3)
Not evaluable[c]	0 (0.0)	2 (1.5)
Not assessed[c]	0 (0.0)	5 (3.8)

Janjigian et al, Nature, 2021

Mulige fremtidige kombinasjoner med immunterapi som undersøkes i studier :

Overcoming Resistance to PD-1 Inhibition



Mechanism to overcome ICI resistance	Proposed/currently under investigation
Boosting the host immune system	Inducing DNA damage • Chemotherapy • Radiotherapy • PARP inhibitors Increasing MHC expression/ Ag recognition • HDAC inhibitors • STING agonists
Combination ICI strategies	Targets • PD-L1 • PD-1 • CTLA-4 • TIGIT • LAG-3
Targeting intracellular pathways	Targets • HER2 • VEGF • MEK • PI3K • Wnt/8-catenin

Baxter MA...Petty RD. *British Journal of Cancer* 2021; 125:1068–1079

Baxter et al et al, Br J Cancer, 2021

Oppsummering medikamentell behandling metastatisk øvre GI kreft i første linje:

- Bedret overlevelse i førstelinjes behandling sammenliknet med kjemoterapi alene ved tillegg av:
  - Trastuzumab (HER-2 positiv adenocarcinom)
  - Pembrolizumab (CPS ≥ 10, spiserørskreft)
  - Nivolumab (CPS ≥ 5, adenocarcinom)
  - *Nivolumab+kjemoterapi eller dual immunterapi alene med nivolumab + ipilimumab (TPS ≥ 1%, plateepitelcarcinom)*

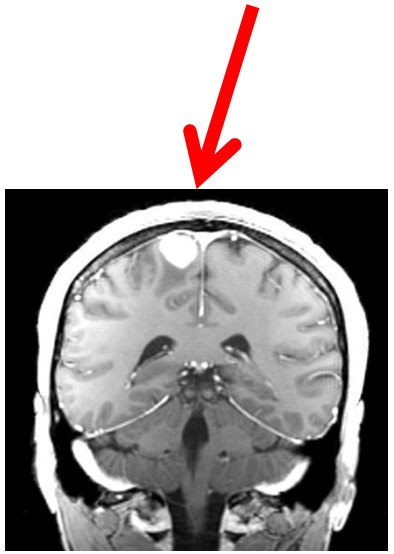
Oppsummering medikamentell behandling metastatisk øvre GI kreft i første linje:

- Bedret overlevelse i førstelinjes behandling sammenliknet med kjemoterapi alene ved tillegg av:
  - Trastuzumab (HER-2 positiv adenocarcinom)
  - Pembrolizumab (CPS ≥ 10, spiserørskreft)
  - *Nivolumab (CPS ≥ 5, adenocarcinom)*
  - *Nivolumab + kjemoterapi eller dual immunterapi alene med nivolumab + ipilimumab (TPS ≥ 1%, plateepitelcarcinom)*

Avventer avgjørelse i Beslutningsforum

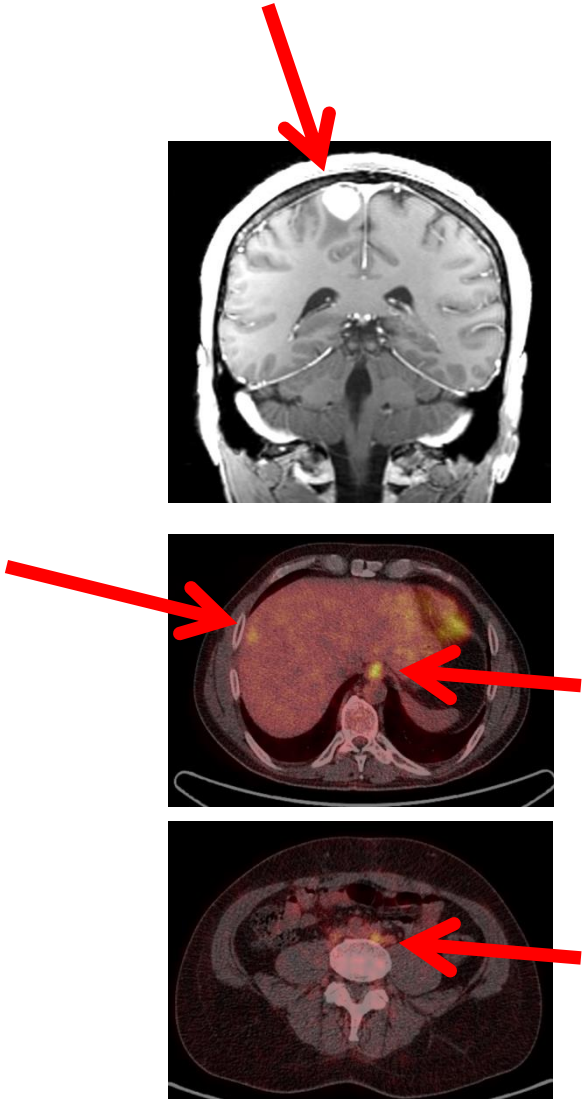
Kasuistikk

- M -42 år
- Debut-symptomer: Kraftsvikt ve arm/ben
- Biopsi (hjerne): Adenocarcinom
- Stereotaktisk strålebeh.



Videre utredning

- Ca øsofagus/cardia (adenocarcinom)
- Multiple lymfeknutemetastaser
- Levermetastase



Pasienten har samtykket til at sykehistorie og bilder kan presenteres

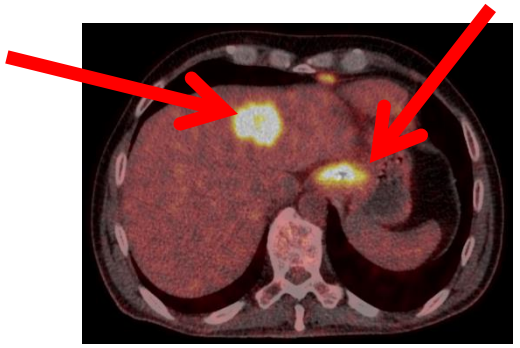
Førstelinjes kjemoterapi

- 6 CiFu kurer med respons
- Etter 4 mnd pause: Progresjon

- Ny hjernemetastase – ny stereotaktisk stråleb.
- CEA ↑

Andrelinjes behandling:

- PD-1 hemmer monoterapi i studie (pembrolizumab)
- 2 års behandling
- Beste respons: PR (↓levermetastase/primærtumor ++)
- Men progresjon mot slutten av beh.perioden
- *Bivirkninger:*
  - *Hypothyreose, artritt, hypofysesvikt*



Deretter

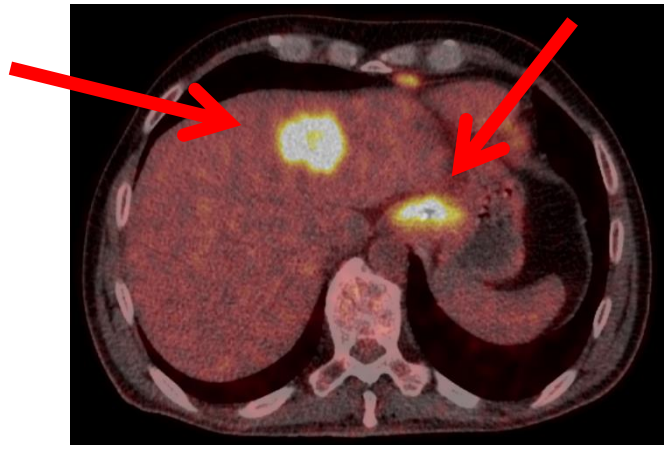
- 3. linjes kjemoterapi med FLIRI kurer beh i 10 mnd

- Leverreseksjon

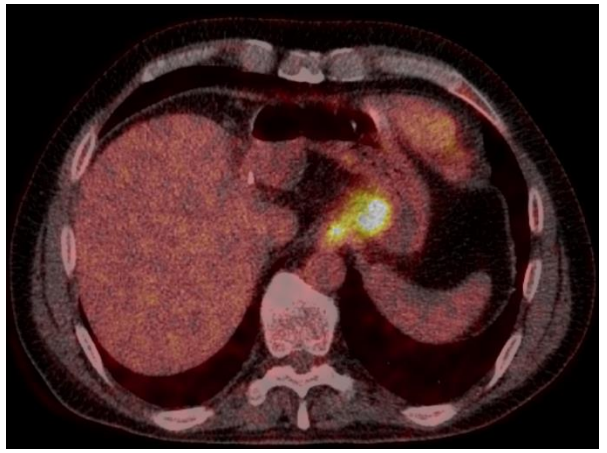
2 mnd deretter:

- Opr Øsofagus-reseksjon

(Før FLIRI kurer)



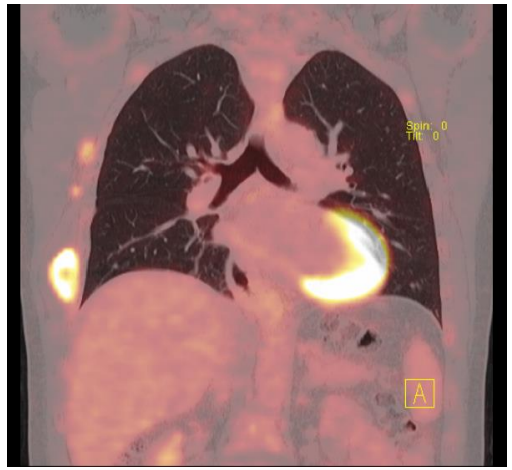
(Etter lever-reseksjon)



Pasienten har samtykket til at sykehistorie og bilder kan presenteres

1 år senere:

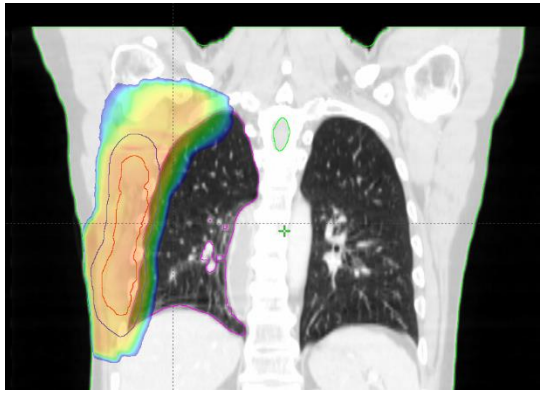
- Residivtumor hø thorax-vegg:



Definitiv radiokjemoterapi:

2,8Gy x 15

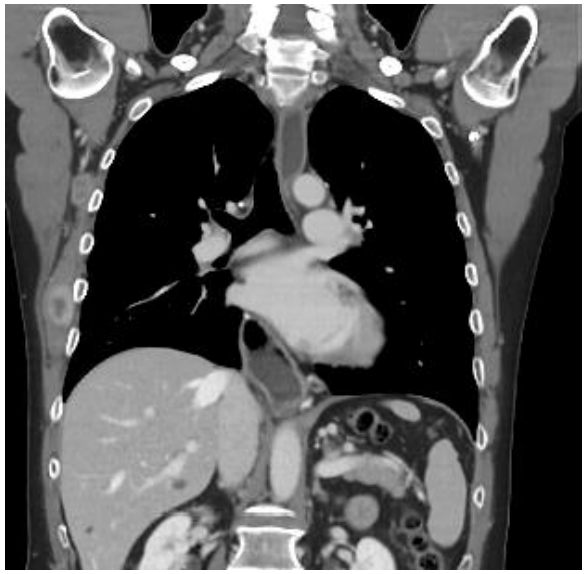
6 ukeskurer Carboplatin/Paclitaxel



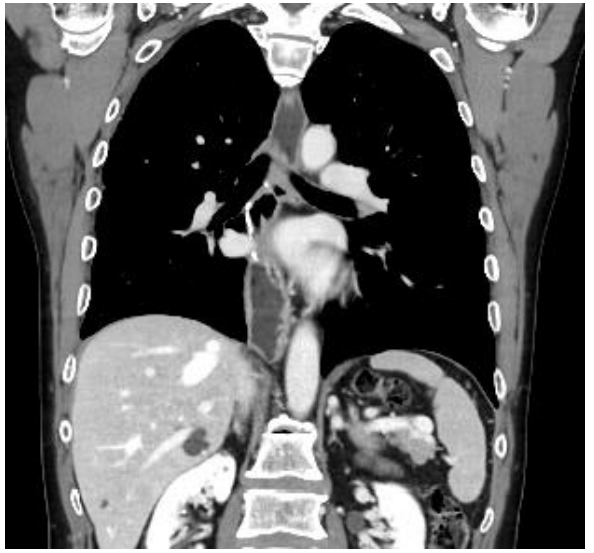
Pasienten har samtykket til at sykehistorie og bilder kan presenteres

Observasjon/oppfølging:

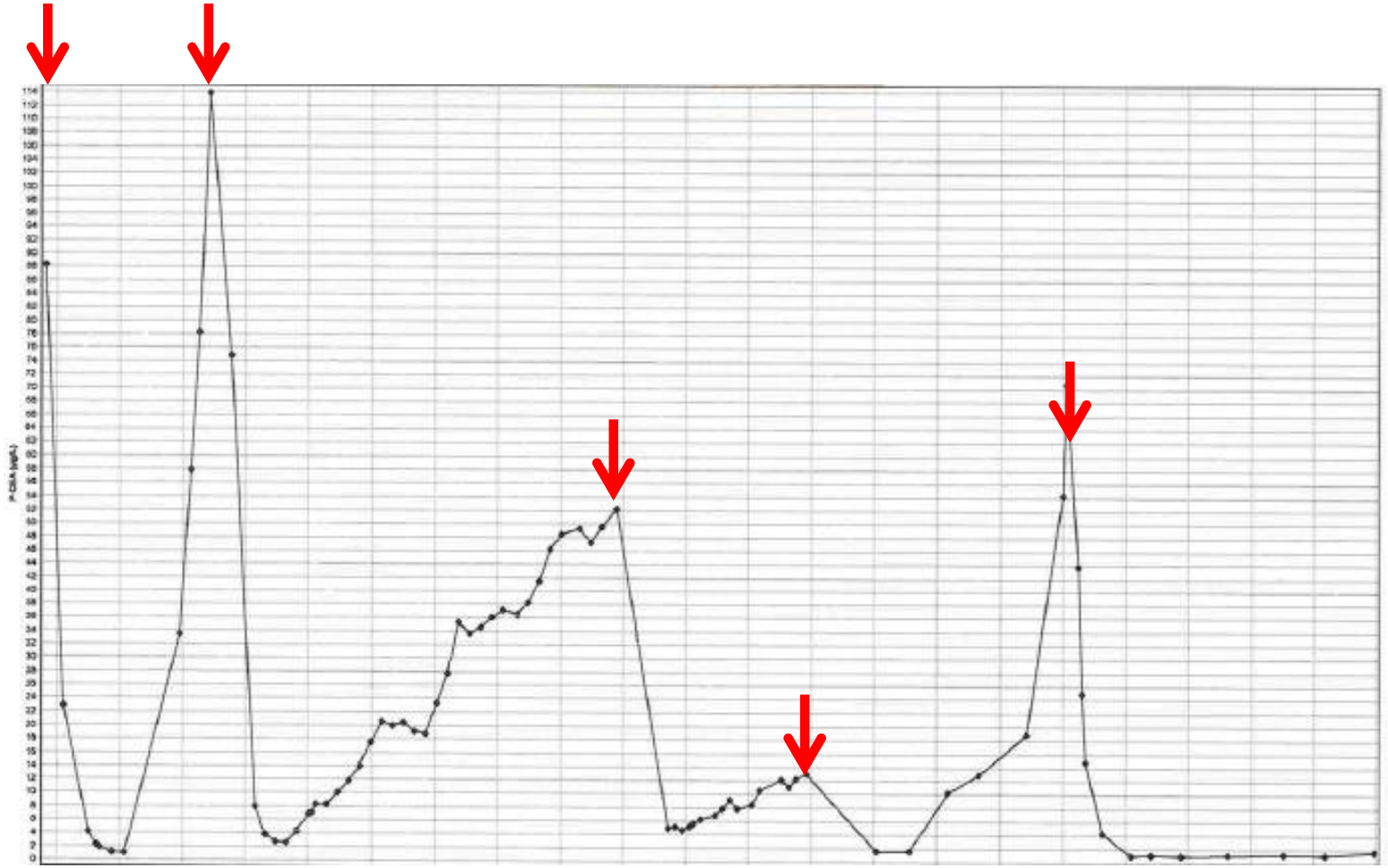
- 1,5 år etter definitiv radiokjemoterapi hø thoraxvegg:



- FDG PET: **NEG**
- CT thx/abdomen: **NEG**
  - *(ytterligere skrumpning av oppfylning hø thoraxvegg – måler nå 0,4cm)*

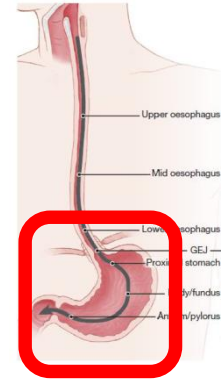


CEA historikk (8 år)



Siste måling aug-22:
CEA = 1,2

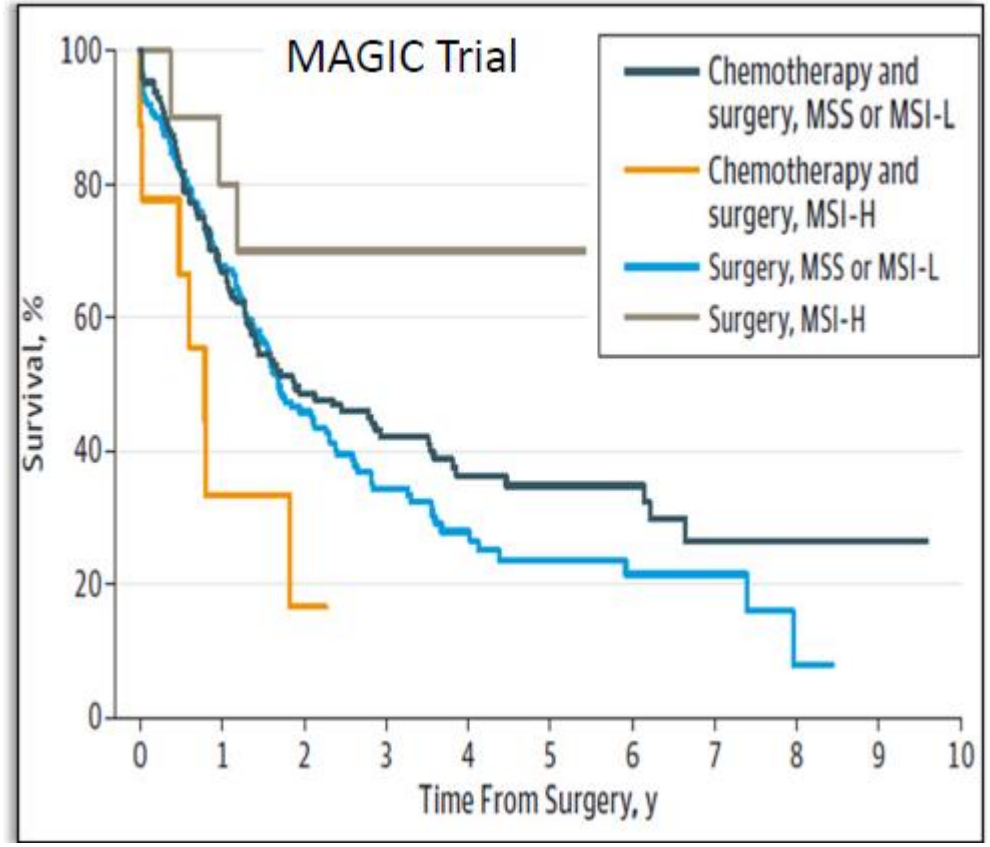
Hva med MSI-H / dMMR ?



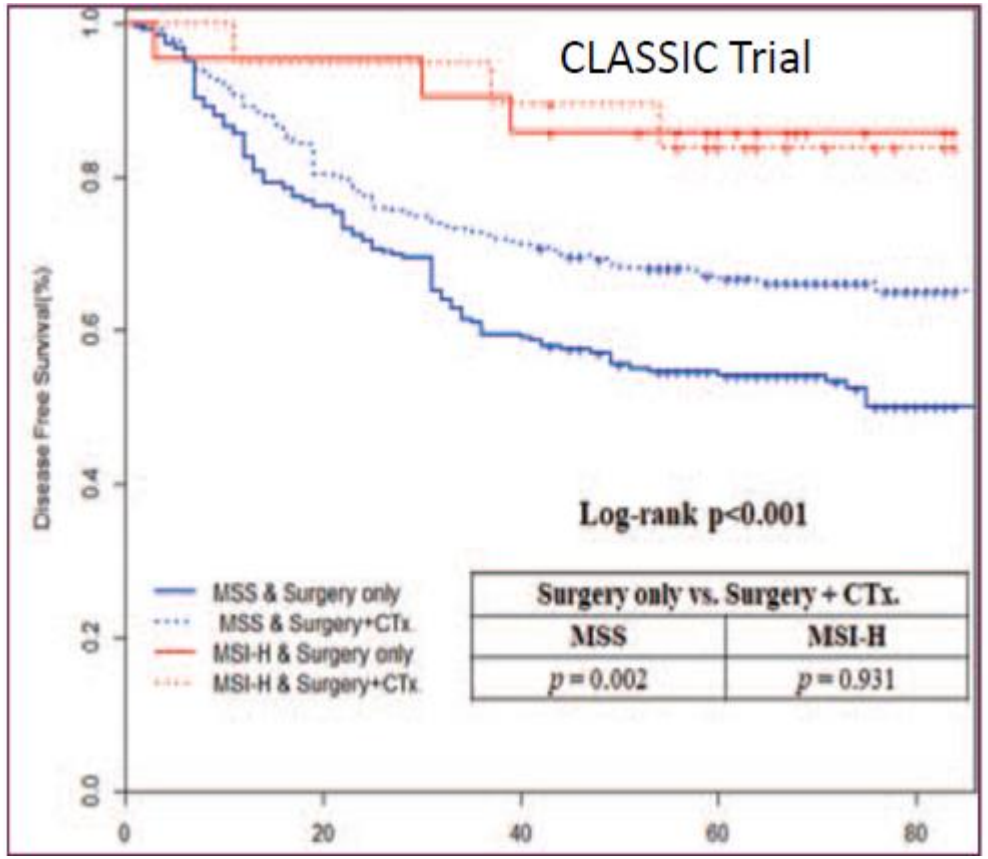
- Ca 10-15 % av pasientene i tidlig stadie
- Ca 5-10% av pasientene i metastatisk situasjon

- Tidlig fase studier har vist høye responsrater ved immun-sjekkpunkt hemmere
- Enda ikke godkjent i Norge ved øvre GI.....

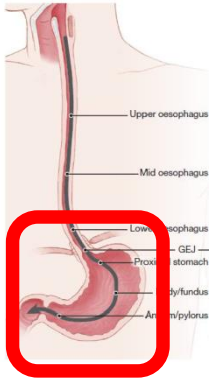
MSI post hoc analyser MAGIC og CLASSIC



-Ingen gevinst av perioperativ kjemoterapi hos MSI-H, mulig negativ effekt (NB små tall)



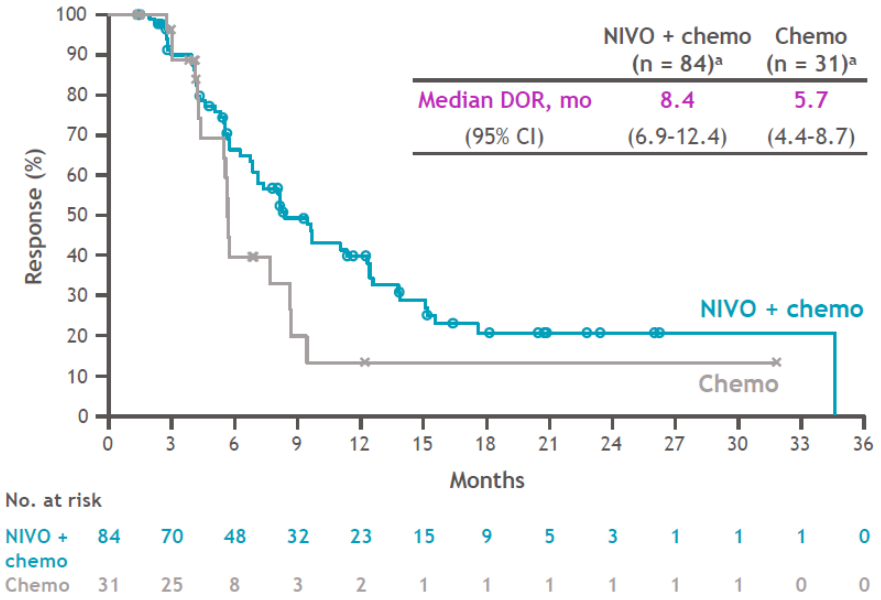
-Ingen gevinst i adjuvant kjemoterapi hos MSI-H
-MSI-H gir god prognose

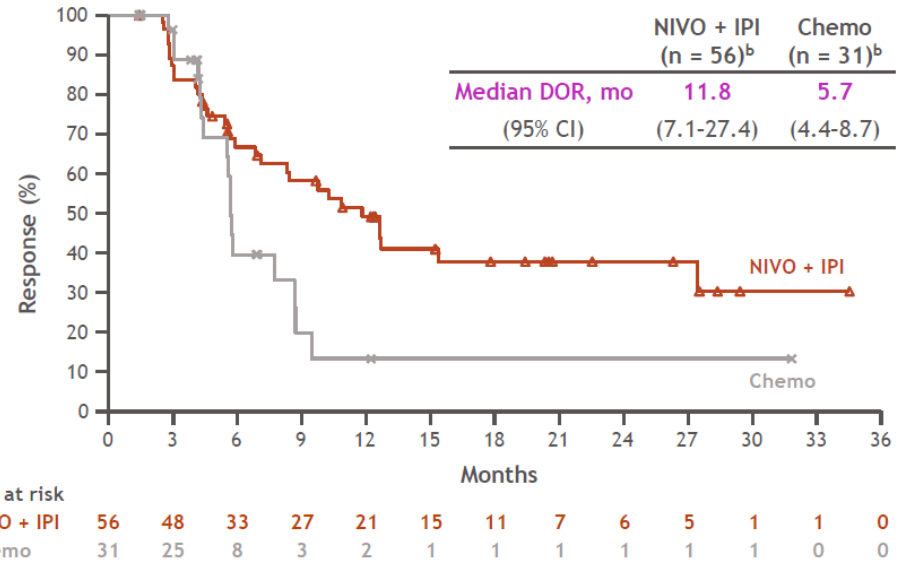


NB – POST HOC analyser

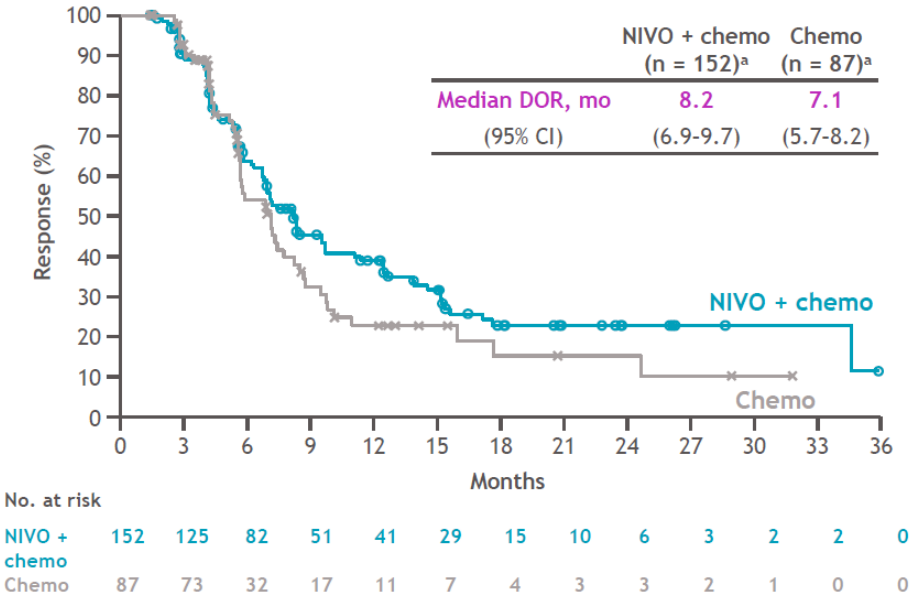
Smyth et al, JAMA Oncol, 2017
Choi et al, Ann Surg 2018

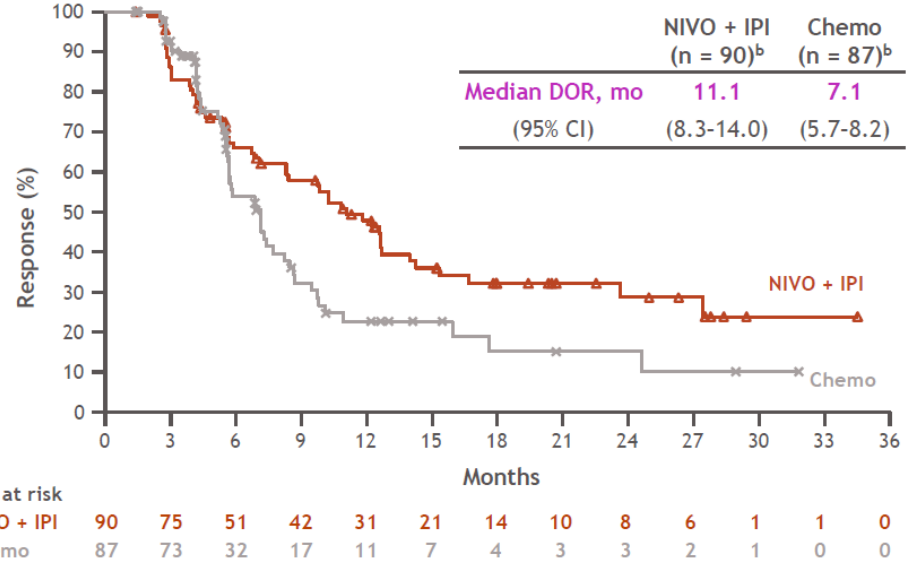
PD-L1 TPS ≥ 1%





All randomized





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Doki Y et al., NEJM 2022 and ASCO 2021

TRAEs with potential immunologic etiology

Select TRAEs[a] All treated,[b,c] n (%)	NIVO + chemo (n = 310)		NIVO + IPI (n = 322)		Chemo (n = 304)	
	Any grade	Grade 3-4[d]	Any grade	Grade 3-4[d]	Any grade	Grade 3-4
Endocrine	36 (12)	4 (1)	88 (27)	19 (6)	1 (< 1)	0
Gastrointestinal	64 (21)	7 (2)	38 (12)	5 (2)	47 (15)	7 (2)
Hepatic	32 (10)	7 (2)	42 (13)	14 (4)	12 (4)	2 (< 1)
Pulmonary	18 (6)	2 (< 1)	26 (8)	9 (3)	2 (< 1)	0
Renal	74 (24)	7 (2)	8 (2)	2 (< 1)	57 (19)	5 (2)
Skin	54 (17)	1 (< 1)	110 (34)	13 (4)	11 (4)	0

- The majority of select TRAEs were grade 1 or 2
- Grade 3-4 events occurred in ≤ 6% of patients across organ categories

[a]Select TRAEs are those with potential immunologic etiology that require frequent monitoring/intervention; [b]Patients who received ≥ 1 dose of study drug; [c]Assessed in all treated patients during treatment and for up to 30 days after the last dose of study treatment; [d]The most common grade 3-4 select TRAEs (≥ 2%) in the NIVO + IPI arm were ALT increased (n = 7), pneumonitis (n = 7), and rash (n = 7). No grade 3-4 events were reported for ≥ 2% of patients in the NIVO + chemo arm.

Doki Y et al., NEJM 2022 and ASCO 2021

Baseline characteristics

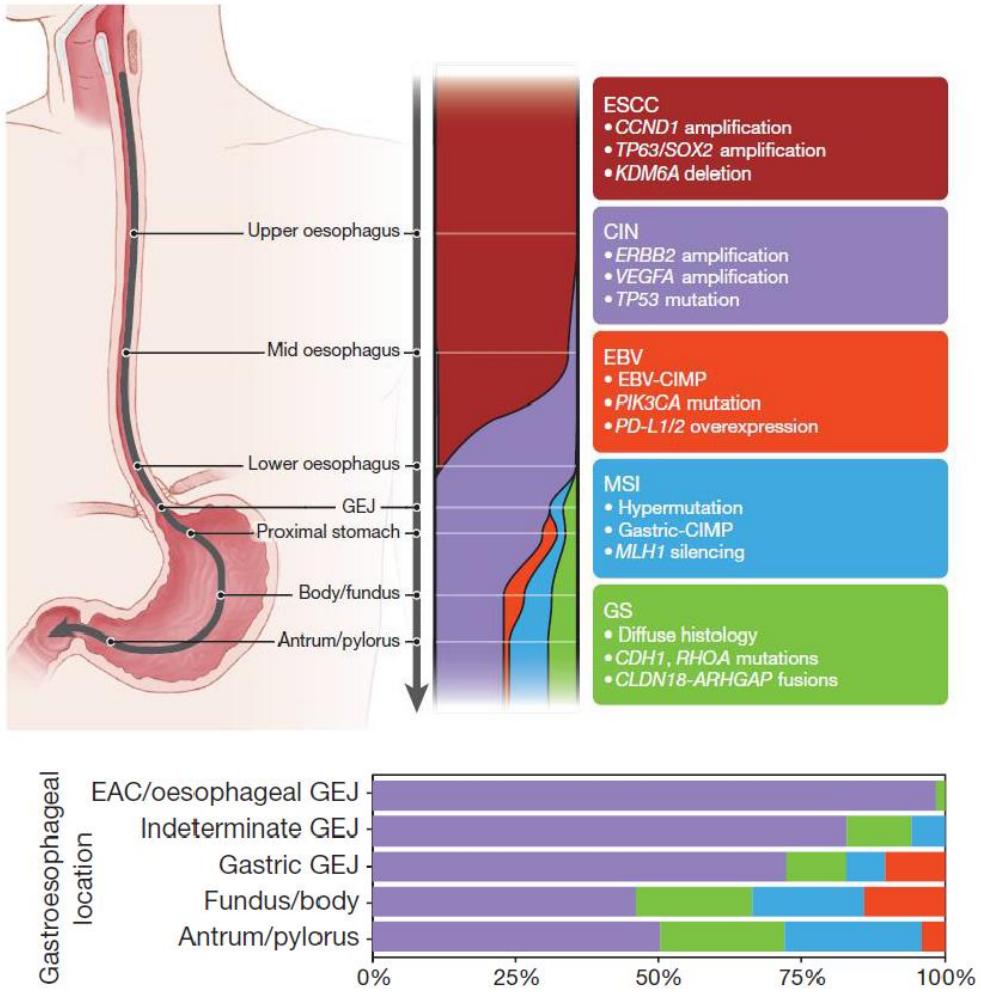
All randomized	NIVO + chemo (n = 321)	NIVO + IPI (n = 325)	Chemo (n = 324)[a]
Median age, years (range)	64 (40-90)	63 (28-81)	64 (26-81)
Male, %	79	83	85
Asian/non-Asian,[b] %	70/30	70/30	70/30
ECOG PS 1,[c] %	54	54	53
ESCC,[d] %	97	99	98
Tumor cell PD-L1 expression,[e] %			
≥ 1%	49	49	48
< 1%	51	51	52
Disease status at study entry, %			
De novo metastatic	57	60	58
Recurrent - locoregional	7	8	8
Recurrent - distant	22	22	19
Unresectable advanced	14	10	16
Number of organs with metastases[f]			
≤ 1	49	49	49
≥ 2	51	51	51
Current or former smoker, %	79	82	79

- Baseline characteristics were balanced across the 3 arms and were consistent with that of patients with tumor cell PD-L1 ≥ 1%

[a]Percentages may not add up to 100% due to rounding; [b]Refers to geographic region; [c]ECOG PS was not reported for 1 patient; [d]18 patients had adenosquamous histology, and 1 patient was classified as other; [e]Tumor cell PD-L1 was indeterminate, not evaluable, or missing in 5 patients; [f]Based on interactive response technology.

Doki Y et al., NEJM 2022 and ASCO 2021

Gradienter av typer i esofagogastrisk karsinom



- Platepitelcarcinom er forskjellig fra GEJ og GC
- HER-2 pos høyere i GEJ enn GC
- HER-2 uttrykk er ikke prognostisk

nature

J Kim *et al. Nature* 1–9 (2017) doi:10.1038/nature20805

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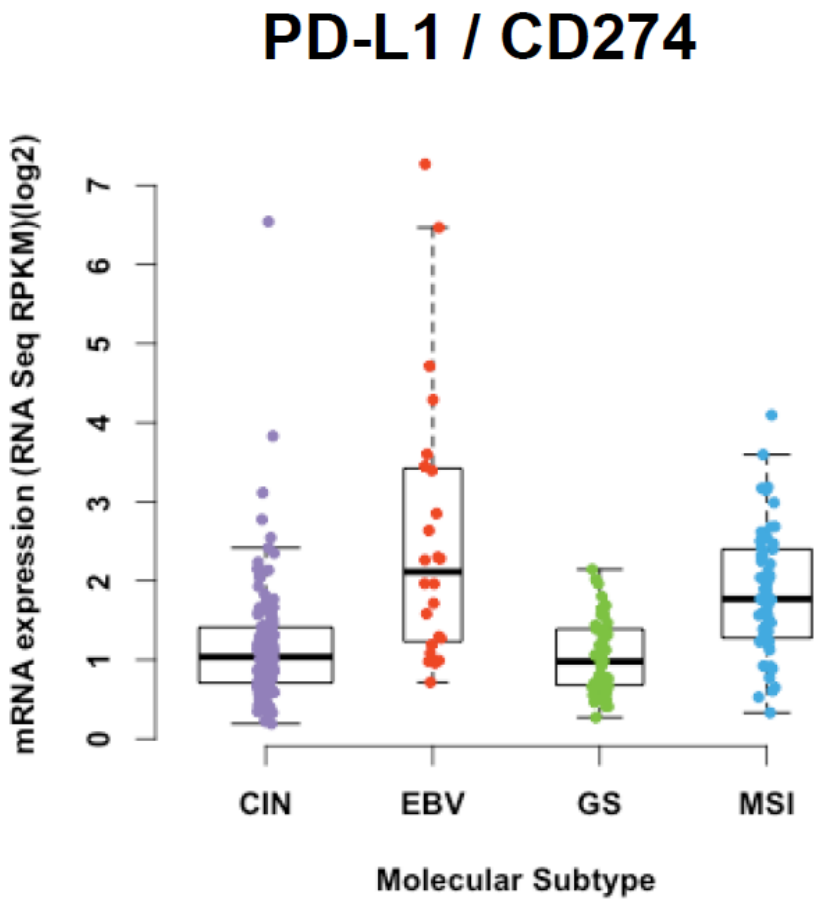
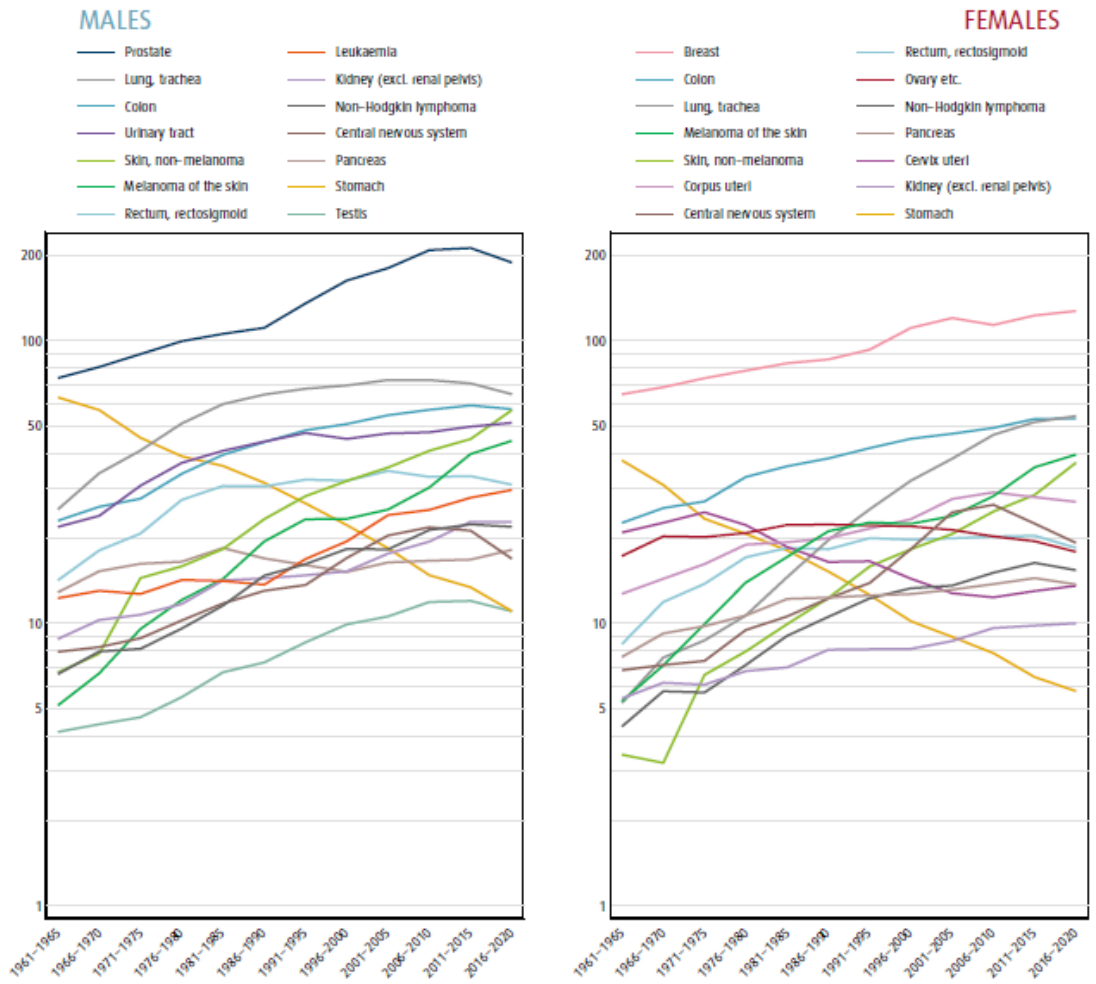
PDL1 uttrykk i subgrupper



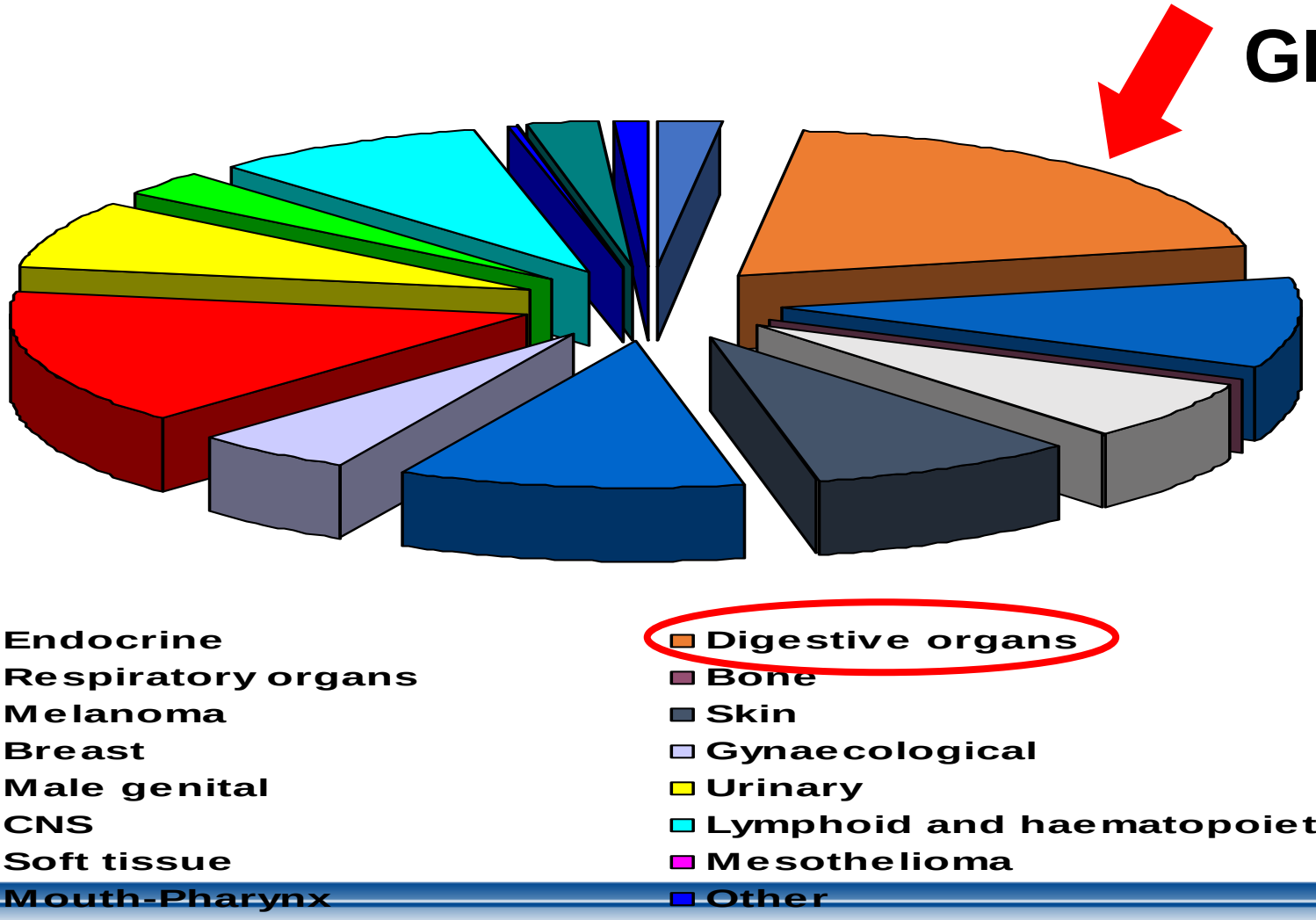
AJ Bass *et al. Nature*, 1-8 (2014) doi:10.1038/nature13480

Kreftinsidens i Norge siste 50 år



Nye kreft-tilfeller i Norge 2021

*Totalt **36998** nye tilfeller*



GI: 7328 tilfeller

Inkluderer:

-**Oesophageal** (344)

-**Gastric** (393)

-**Small intestine** (245)

-**Colon** (3204)

-**Rectum** (1346)

-**Anus** (106)

-**Hepatobiliary** (594)

-**Pancreas** (962)

-**Other GI** (134)

Adaptert fra «Cancer in Norway 2021», utgitt av Kreftregisteret

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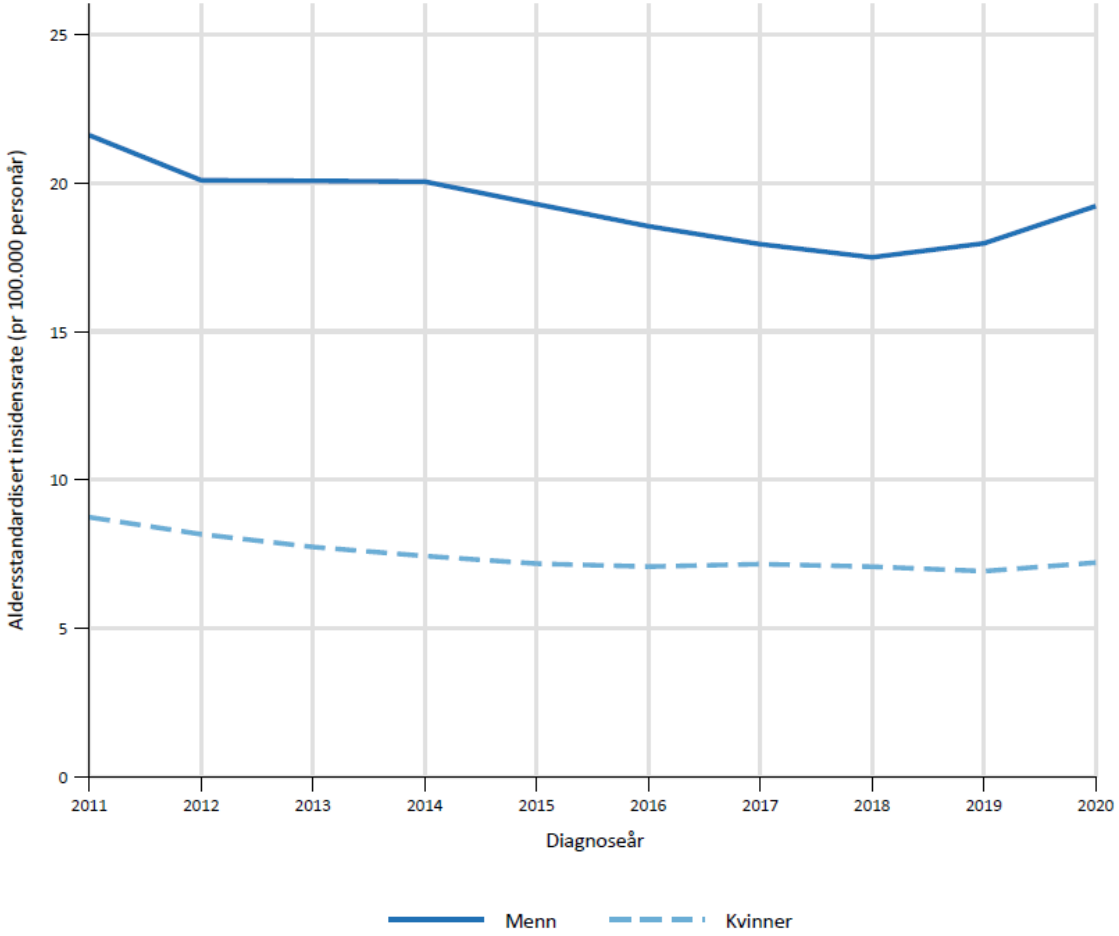
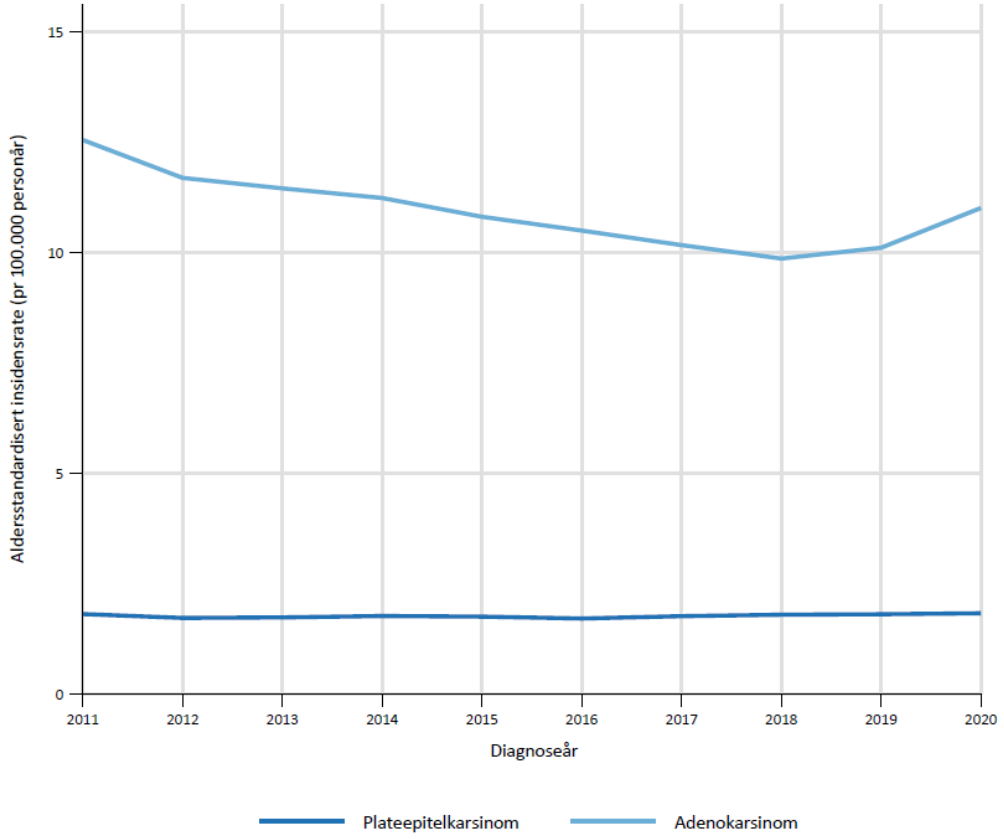
Magekreft + spiserørskreft



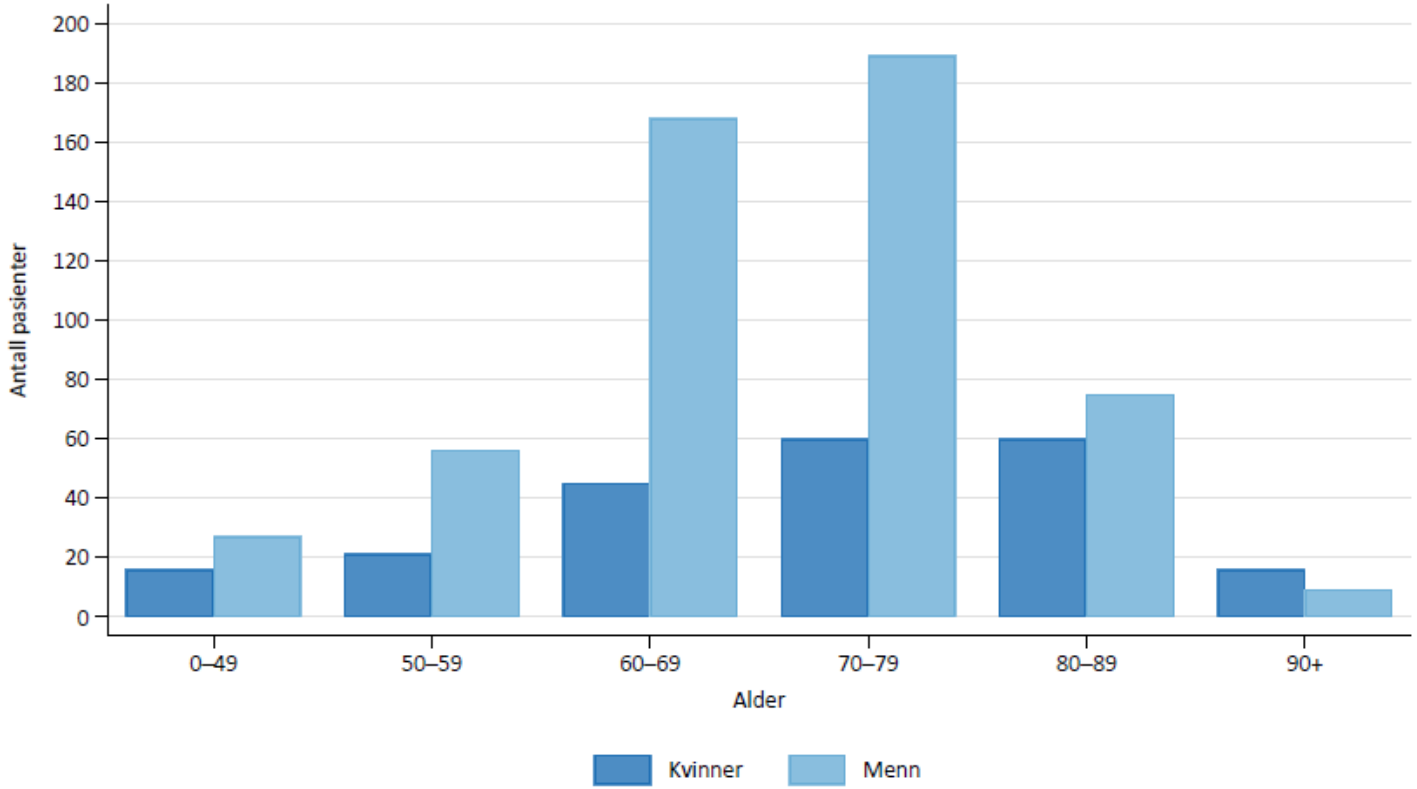
ICDO-3	Lokalisasjon	Antall
C15.3	Øvre tredel av spiserør	28
C15.4	Midtre tredel av spiserør	42
C15.5	Nedre tredel av spiserør	224
C15.8	Svulst utbredt innen C15.3-C15.5 Lokalisasjon kan ikke bestemmes	4
C15.9	Spiserør (uten nærmere spesifikasjon	61
C16.0	Cardia - inkludert spiserør-magesekkovergang (Siewert I,II og III)	127
C16.1	Fundus	12
C16.2	Corpus	80
C16.3	Antrum, canalis, angulus	58
C16.4	Pylorus (inkludert prepylort)	26
C16.5	Curvatura minor	0
C16.6	Curvatura major	1
C16.8	Svulst utbredt i magesekk (innen C16.1 - C16.6)	7
C16.9	Magesekk uten nærmere spesifikasjon	72
	Total antall pasienter	742

Magekreft + spiserørskreft

Adenokarsinom dominerer sammenliknet med plateepitelkarsinom

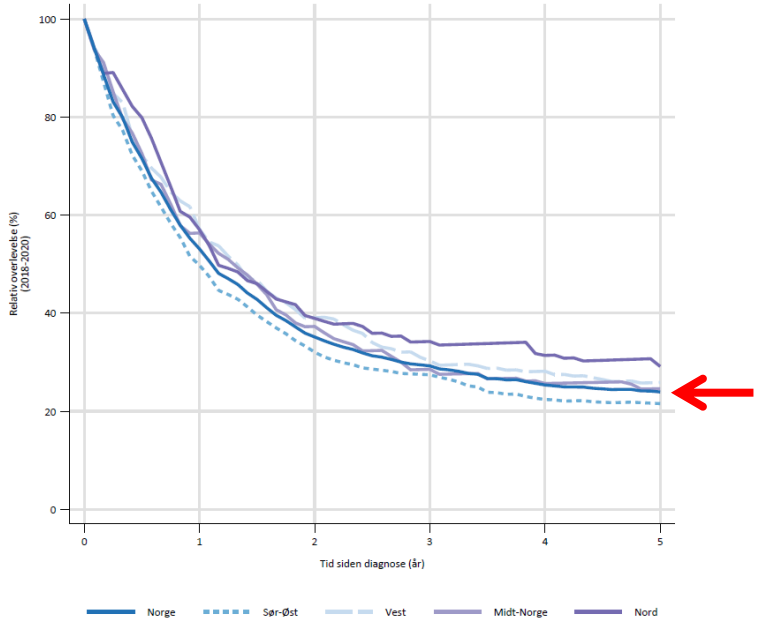


Magekreft + spiserørskreft
Aldersfordeling

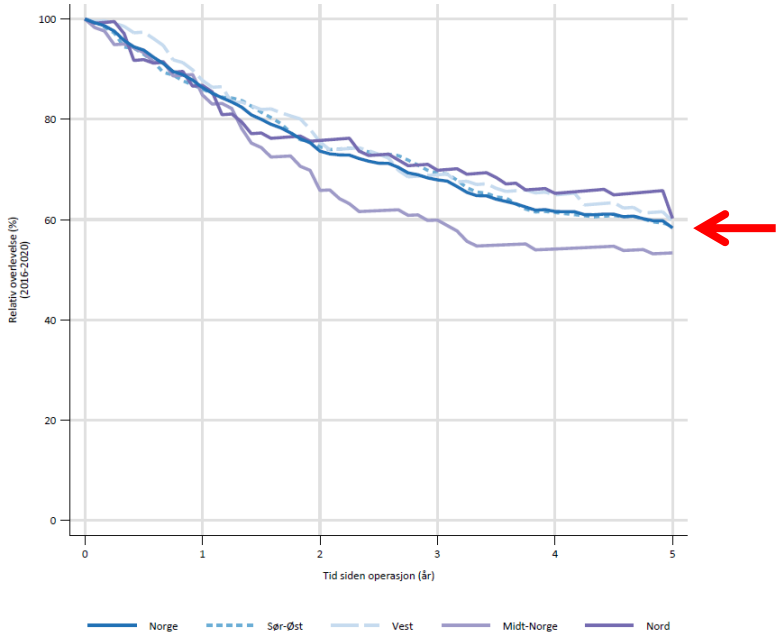


Spiserørskreft – Overlevelse i Norge

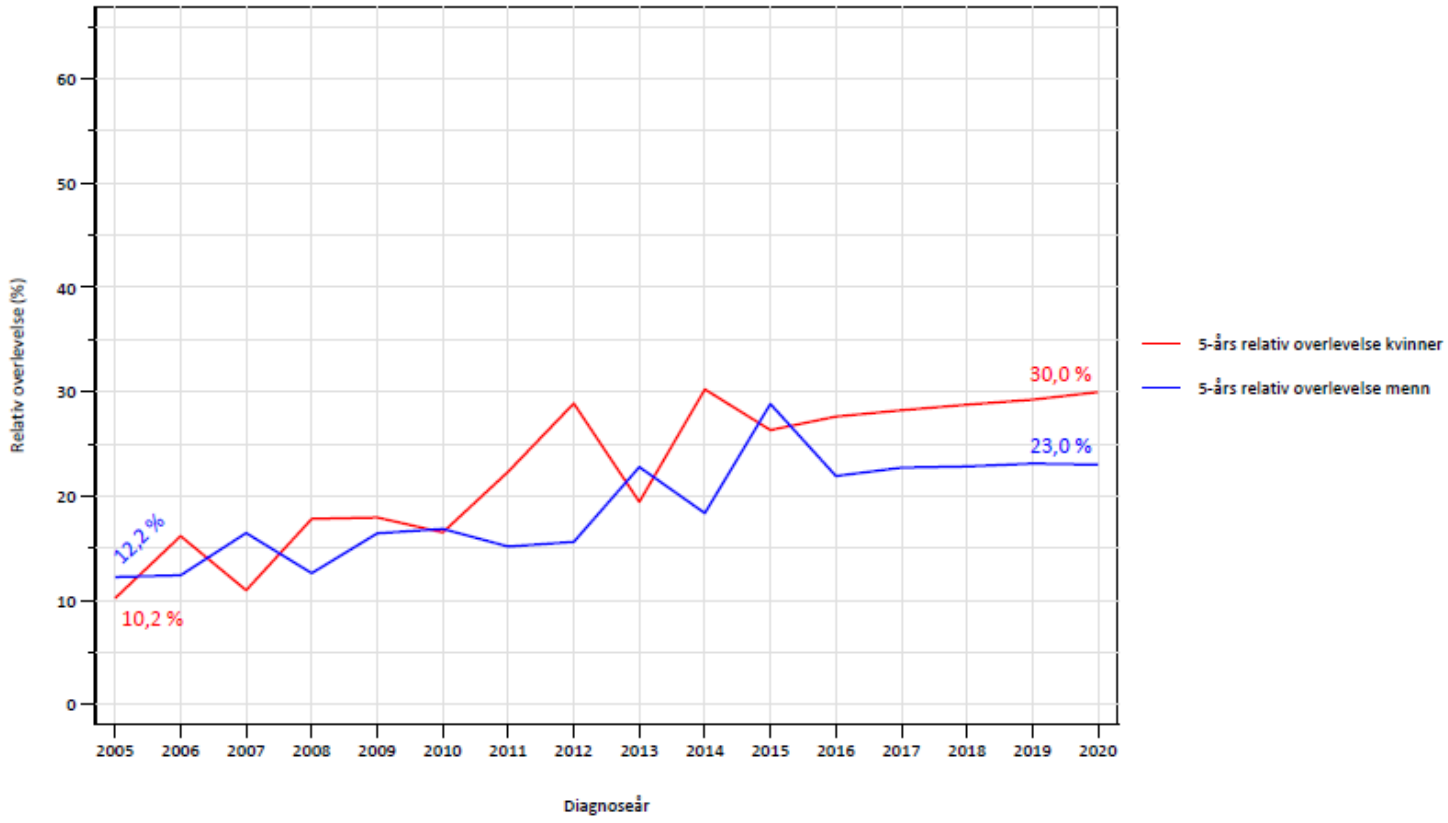
Alle pasientene 2018-2020:



Opererte pasienter 2016-2020:

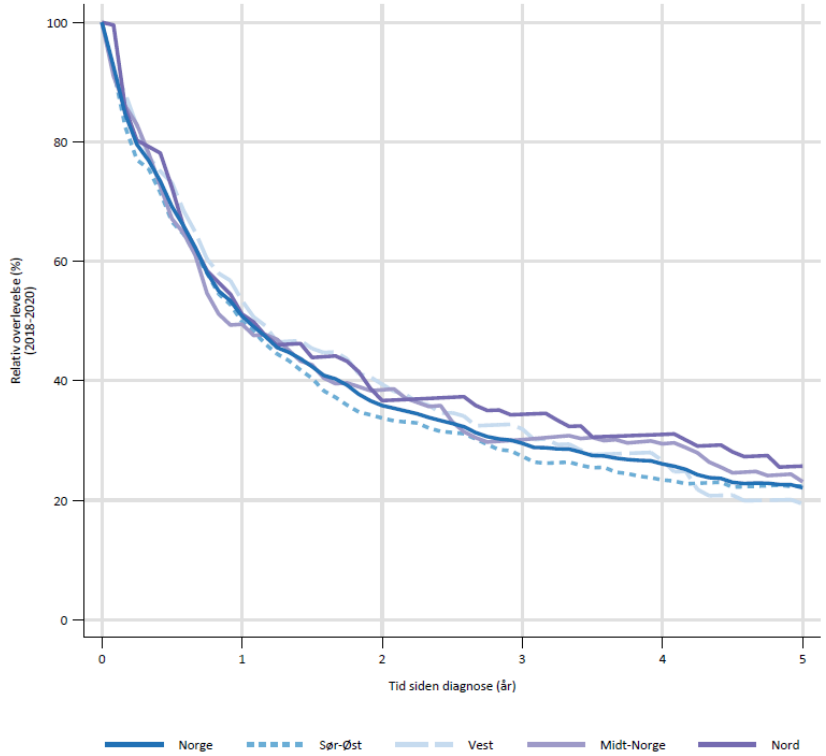


Spiserørskreft:
5-års relativ overlevelse har økt (siste 15 år)

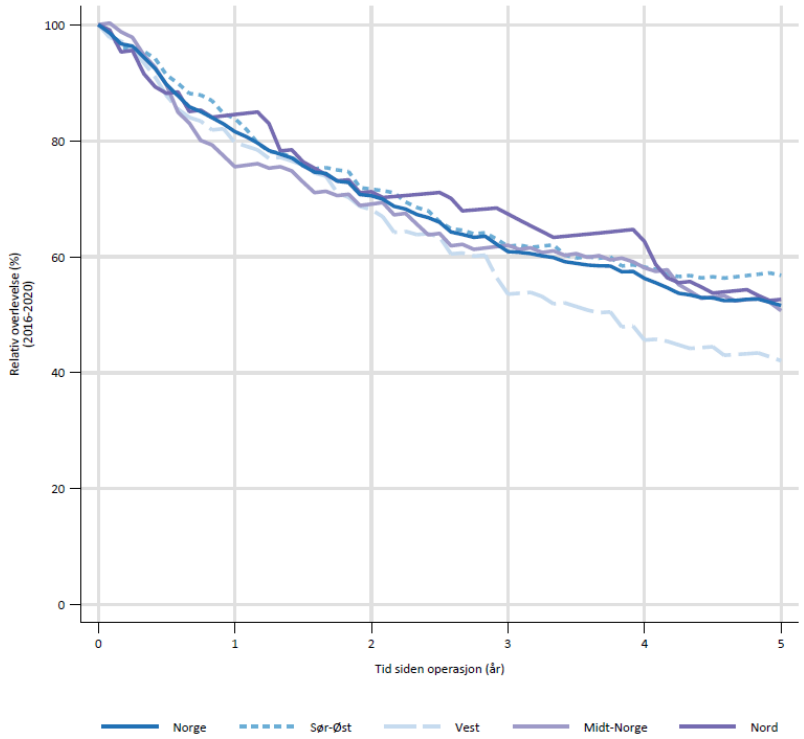


Magekreft – Overlevelse i Norge

Alle pasientene 2018-2020:



Opererte pasienter 2016-2020:



Magekreft:
5-års relativ overlevelse har også økt (noe)