Colon and Esophageal Cancer Updates

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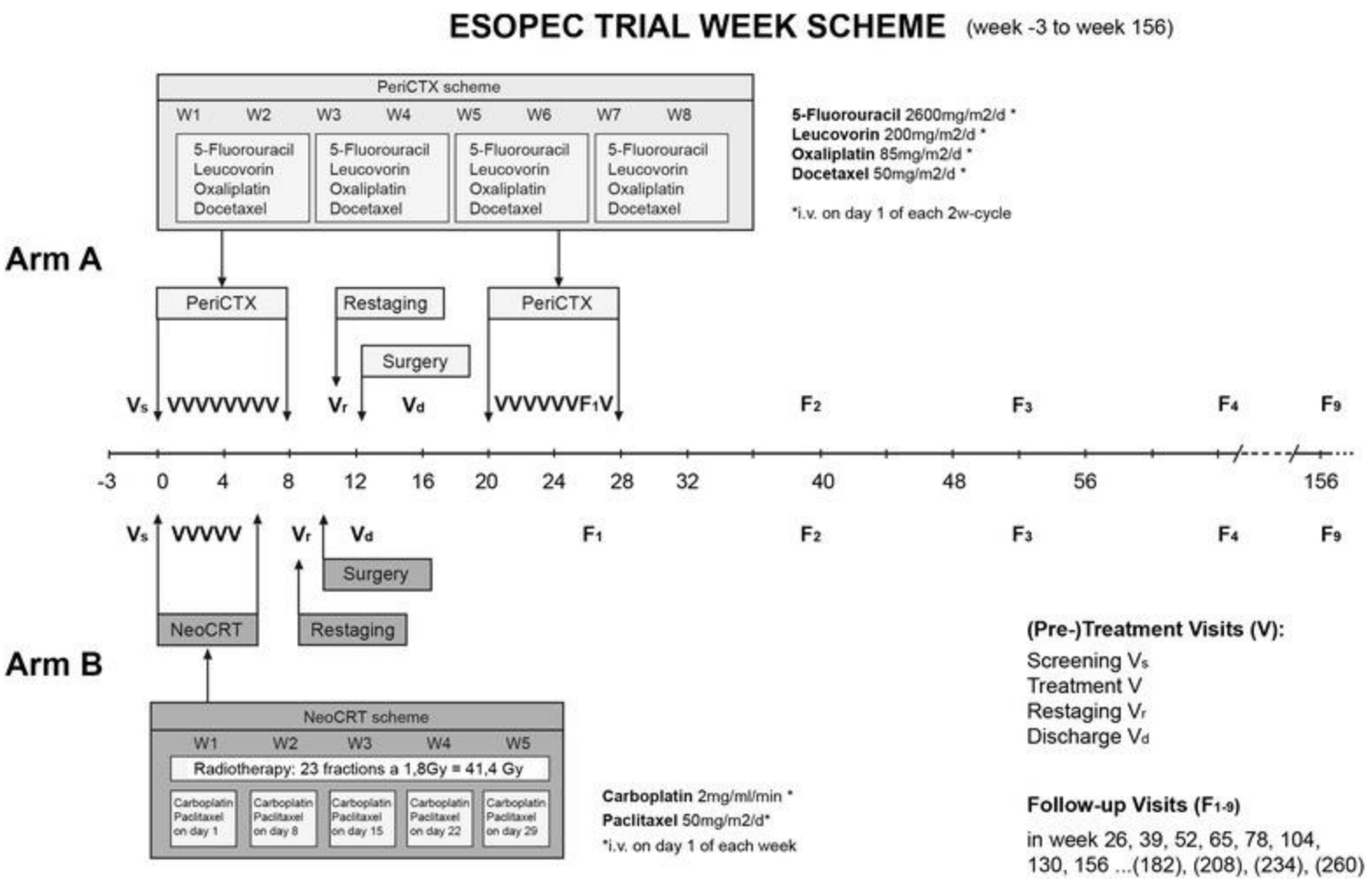
Outline

1. **Esophageal/gastroesophageal cancer updates**

2. Colorectal cancer updates

ESOPEC (ASCO 2024)



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Randomized phase III study (1:1) → 4 cycles FLOT → 4-6 wks → surgery → 4-6 wks → 4 cycles FLOT vs. CROSS → 4-6 wks → surgery

Esophageal adenocarcinoma
- cT1N+ or cT2-4a, cN0/+, cM0
- Tumor epicenter within 5 cm of the GEJ junction and also extending into the esophagus

Primary endpoint: OS

Hoeppner J, et al. BMC Cancer. 2016 Jul:16:503
Hoeppner J, et al. J Clin Oncol. 2024 Jun:42:LBA1

ESOPEC

Characteristics of ESOPEC Trial Patients

	FLOT Group	CROSS Group
N	221	217
Age mean (SD) in years	63.1 (8.6)	62.6 (9.8)
Sex male	89.1 %	89.4 %
ECOG		
> 0	26.7%	28.1%
Clinical T-stage		
cT1-2	19.5%	17.1%
cT3-4	79.1%	81.9%
Clinical N-stage		
cN0	22.2%	18.4%
cN+	77.8%	81.6%

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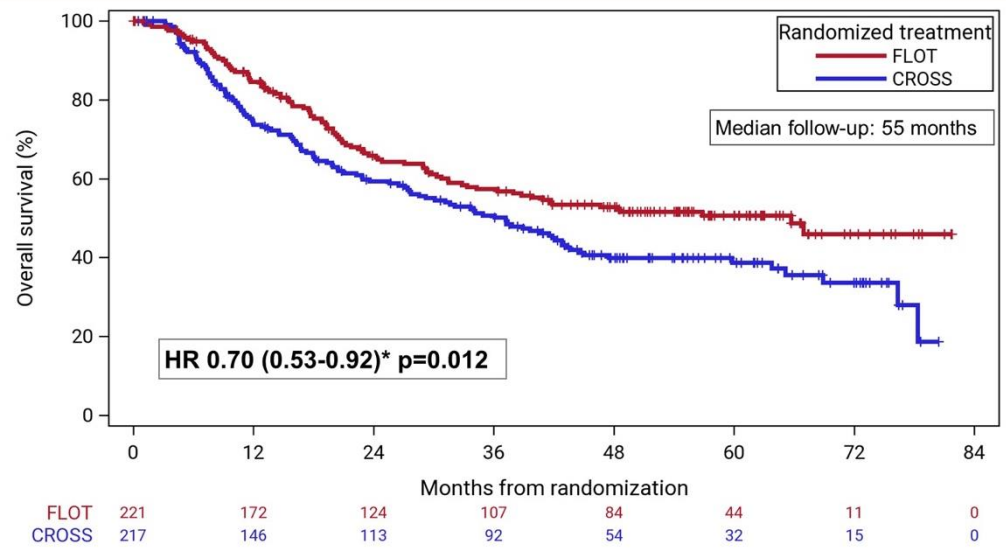
Hoeppner J, et al. J Clin Oncol. 2024 Jun:42:LBA1

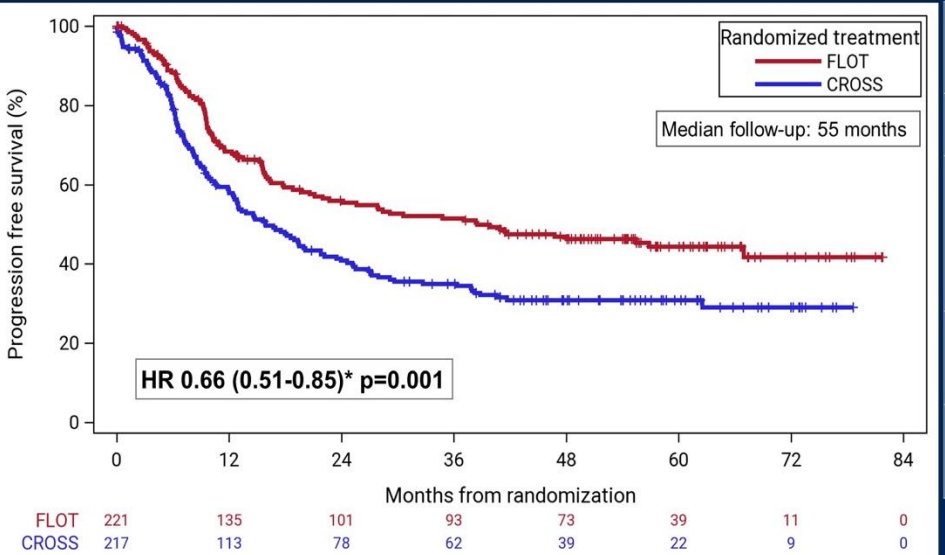
ESOPEC

Overall Survival - ITT Population



	FLOT	CROSS
Events	97	121
Median OS time (months)	66 95% CI 36 – n.e	37 95% CI 28 – 43
3-year OS rate	57.4%	50.7%
5-year OS rate	50.6%	38.7%

Progression Free Survival – ITT Population



	FLOT	CROSS
Events	107	137
Median PFS time (months)	38 95% CI 21 – n.e.	16 95% CI 12 – 22
3-year PFS rate	51.6%	35.0%
5-year PFS rate	44.4%	30.9%

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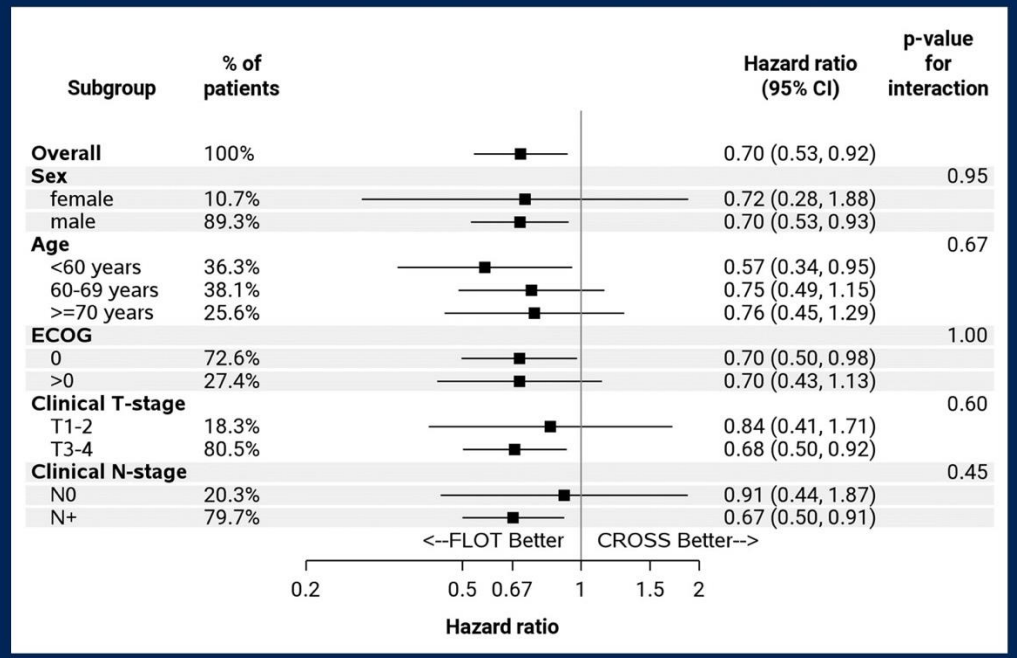
Hoeppner J, et al. J Clin Oncol. 2024 Jun:42:LBA1

ESOPEC

Overall Survival in Exploratory Subgroups



Treatment Exposure

	FLOT Group	CROSS Group
N	221	217
Started neoadjuvant treatment (PP population*)	**93.7 %**	**90.3 %**
Completed neoadjuvant treatment	**87.3 %**	**67.7 %#**
Received neoadjuvant treatment plus surgery	**86.0 %**	**82.9 %**
Received adjuvant treatment	**63.3 %**	
Completed adjuvant treatment	**52.5 %**	

*Per protocol population according to Clinical Trial Protocol and Statistical Analysis Plan

#Completion rate (41.4Gy) of radiotherapy **98%**

91% completed chemoRT in CROSS

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Hoeppner J, et al. J Clin Oncol. 2024 Jun:42:LBA1
van Hagen P, et al. N Engl J Med. 2012 May;366:2074-84

ESOPEC

Pathology Results – Surgery Population

	FLOT Group	CROSS Group
N	191	180
Resection status		
No resection	0.5%	1.1%
R0	94.2%	95.0%
R1	5.2%	3.9%
Postoperative N-Stage		
ypN-	50.8%	54.4%
ypN+	48.7%	44.4%
Pathological complete remission		
ypT0 ypN0	16.8%	10.0%
Tumor regression grade (Becker[1])		
Complete regression	18.3%	13.3%
Near complete regression (<10% vital tumor)	25.1%	39.4%

per local pathology assessment

29% pCR rate w/chemoRT in CROSS

Postoperative Complications – Surgery Population [19]

	FLOT Group	CROSS Group
N	191	180
Postoperative morbidity		
Clavien Dindo I	20.9%	20.0%
Clavien Dindo II	13.6%	15.0%
Clavien Dindo III	23.0%	23.3%
Clavien Dindo IV	6.8%	4.4%
Postoperative mortality		
30-days	1.0%	1.7%
90-days	3.2%	5.6%

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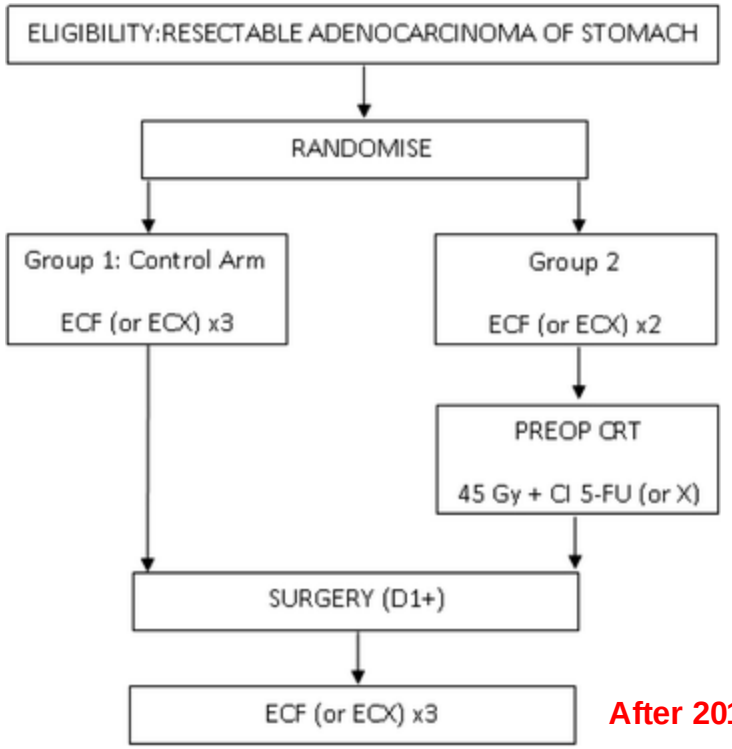
Hoeppner J, et al. J Clin Oncol. 2024 Jun:42:LBA1
van Hagen P, et al. N Engl J Med. 2012 May;366:2074-84

TOPGEAR (ESMO 2024)



After 2017, FLOT4 findings → amended to enroll periop FLOT

5-FU 200 mg/m^2 daily X7 days per week or capecitabine 825 mg/m^2 BID on days 1-5 weekly

After 2017, adjuvant FLOT X4

Randomized phase III trial (1:1)

Gastric adenocarcinoma or GEJ adenocarcinoma (Siewert II ≤2 cm of esophageal involvement or Siewert III) that was T3 or T4 and deemed resectable

Primary endpoint: OS

Leong T, et al. BMC Cancer. 2015 Jul:15:532
Leong T, et al. N Engl J Med. 2024 Sep. doi:10.1056/NEJMoa2405195

TOPGEAR

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Preoperative Chemoradiotherapy (N=286)	Perioperative Chemotherapy Alone (N=288)
Age		
Mean — yr	61±11	60±11
Distribution — no. (%)		
<50 yr	45 (16)	46 (16)
50–70 yr	180 (63)	181 (63)
>70 yr	61 (21)	61 (21)
Sex — no. (%)		
Male	208 (73)	210 (73)
Female	78 (27)	78 (27)
ECOG performance-status score of 0 — no. (%)†	200 (70)	202 (70)
Primary tumor site — no. (%)		
Gastroesophageal junction	98 (34)	101 (35)
Upper or middle third of the stomach	80 (28)	89 (31)
Multiple sites	36 (13)	28 (10)
Lower third of the stomach	72 (25)	70 (24)
Clinical tumor stage — no. (%)		
T1 or T2	33 (12)	31 (11)
T3 or T4	252 (88)	254 (88)
TX	1 (<1)	3 (1)
Clinical nodal stage — no. (%)		
Node-negative	110 (38)	111 (39)
Node-positive or unknown	176 (62)	177 (61)
Histopathological grade — no. (%)		
G1	17 (6)	17 (6)
G2	68 (24)	72 (25)
G3 or G4	122 (43)	128 (44)
Not reported	79 (28)	71 (25)
Chemotherapy regimen — no. (%)		
ECF or ECX	192 (67)	194 (67)
FLOT	94 (33)	94 (33)

* Plus–minus values are means ±SD. Clinical tumor and nodal stage and histopathological grade were determined with the use of the International Union against Cancer TNM (Tumor–Node–Metastasis) Classification of Malignant Tumors. A clinical tumor stage of TX indicates that there was no information about the primary tumor or it could not be measured. Percentages may not total 100 because of rounding. ECF denotes epirubicin, cisplatin, and fluorouracil; ECX epirubicin, cisplatin, and capecitabine; and FLOT fluorouracil, leucovorin, oxaliplatin, and docetaxel.

† Eastern Cooperative Oncology Group (ECOG) performance-status scores are assessed on a 5-point scale, with higher scores indicating greater disability. Patients were required to have a score of 0 (indicating that the patient is fully active and asymptomatic) or 1 (indicating that the patient is restricted in activity but is ambulatory and capable of light work).

Leong T, et al. N Engl J Med. 2024 Sep. doi:10.1056/NEJMoa2405195

TOPGEAR

Table 2. Surgical and Pathological Results.*

Variable	Preoperative Chemoradiotherapy (N=286)	Perioperative Chemotherapy Alone (N=288)	Difference (95% CI)†
Proceeded to surgery — no. (%)	241 (84)	256 (89)	
Operation performed — no. (%)‡	231 (81)	247 (86)	
Esophagogastrectomy — no./total no. (%)	49/230 (21)	57/247 (23)	
Total gastrectomy — no./total no. (%)	117/230 (51)	117/247 (47)	
Subtotal gastrectomy — no./total no. (%)	64/230 (28)	73/247 (30)	
Attempt abandoned — no./total no. (%)	10/241 (4)	9/256 (4)	
Missing data — no./total no. (%)	1/241 (<1)	0/256	
Lymph-node resection — no./total no. (%)§			
<D1+	37/225 (16)	45/237 (19)	
D1+	90/225 (40)	92/237 (39)	
D2	98/225 (44)	100/237 (42)	
Not specified or assessed	6/231 (3)	10/247 (4)	
Multiple-organ removal	14/229 (6)	23/242 (10)	
Pathological results: resection margin			
R0			
No. of patients/total no.	208/225	206/235	
Percent (95% CI)	92 (89–96)	88 (83–92)	
R1 — no./total no. (%)	15/225 (7)	29/235 (12)	
R2 — no./total no. (%)	2/225 (1)	0/235	
Not assessed or recorded — no./total no. (%)	6/231 (3)	12/247 (5)	
ypTNM stage — no./total no. (%)			
Not recorded	0/231	1/247 (<1)	
ypTX	1/231 (<1)	1/246 (<1)	
ypT0	34/231 (15)	17/246 (7)	
ypTis	3/231 (1)	0/246	
ypT1 or ypT2	73/231 (32)	62/246 (25)	
ypT3 or ypT4	120/231 (52)	166/246 (67)	
ypNode-negative¶	125/231 (54)	104/246 (42)	12 (3 to 21)
ypNode-positive	106/231 (46)	142/246 (58)	
ypM1	8/225 (4)	10/240 (4)	
No. of lymph nodes examined	21±10	26±14	−5 (−7 to −3)
Pathological response — no./total no. (%)			
Grade 1a: 0% residual tumor‖	36/214 (17)	18/225 (8)	9 (2 to 15)
Grade 1b: <10% residual tumor	70/214 (33)	48/225 (21)	11 (3 to 20)
Grade 2: 10–50% residual tumor	61/214 (29)	69/225 (31)	
Grade 3: >50% residual tumor	47/214 (22)	90/225 (40)	−18 (−27 to −9)
Not recorded or unknown**	17/231 (7)	22/247 (9)	
Median time to discharge (range) — days	11 (0 to 131)	10 (2 to 144)	

Received all neoadjuvant chemo:
94% CRT vs. 91% periop chemo alone

Received all adjuvant chemo (after surgery):
48% CRT vs. 59% periop chemo alone

92% completed the full protocol dose of 45 Gy in CRT group

* Plus–minus values are means ±SD. Clinical tumor and nodal stage were determined with the use of the International Union against Cancer TNM Classification of Malignant Tumors. The ypTNM classification describes the extent of cancer after preoperative therapy (chemotherapy or chemoradiotherapy). The term "is" denotes in situ and indicates that abnormal cancer cells are present but have not spread to nearby tissue. For each major variable (operation performed, lymph-node resection, pathological findings, ypTNM stage, and pathological response), the denominator was derived from the number of patients who had an operation performed (231 in the preoperative-chemoradiotherapy group and 247 in the perioperative-chemotherapy group) minus the number of patients for whom data were not recorded.

† Differences in percentage points are shown for outcomes for which the confidence interval did not include zero. For the number of lymph nodes, the difference between the counts is shown.

‡ The intent of resection was palliative in three patients in the preoperative-chemoradiotherapy group and in two patients in the perioperative-chemotherapy group.

§ D2 dissection indicates extended removal of regional lymph nodes, and D1+ dissection indicates a more limited removal of regional lymph nodes. Any lymphadenectomy at a level below D1+ indicates minimal and inadequate removal of regional lymph nodes.

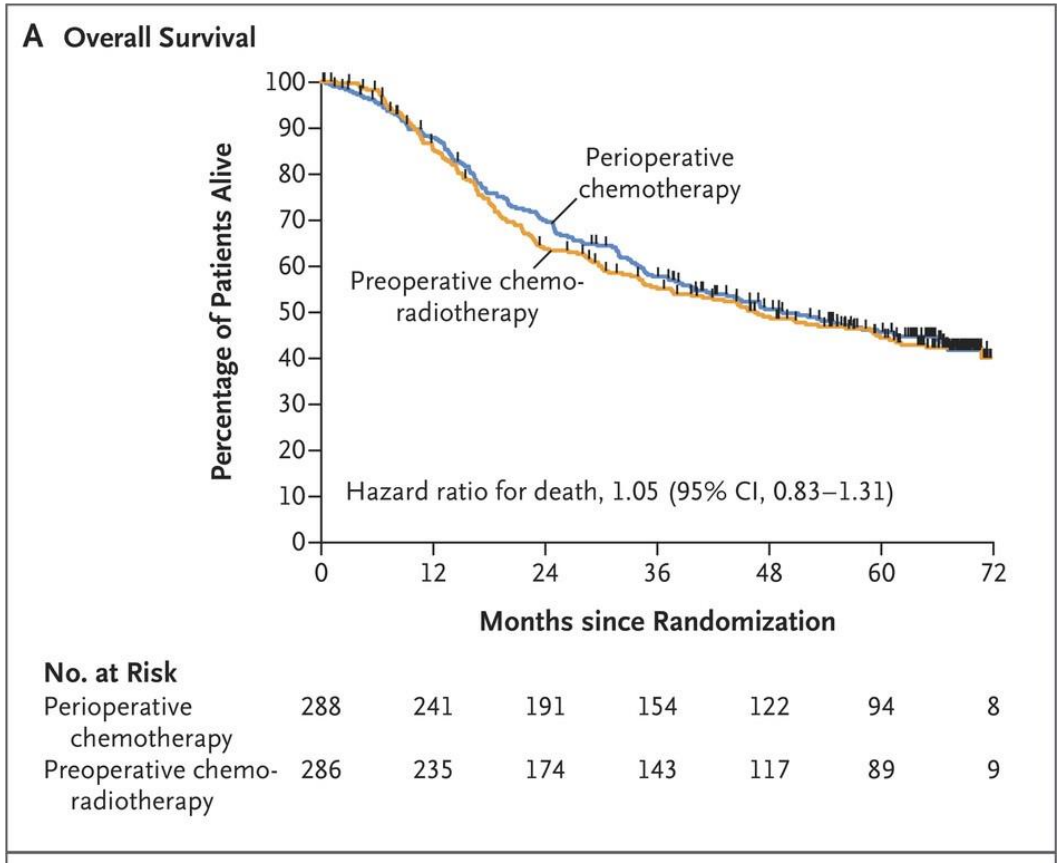
¶ One patient in the perioperative-chemotherapy group had ypNX findings.

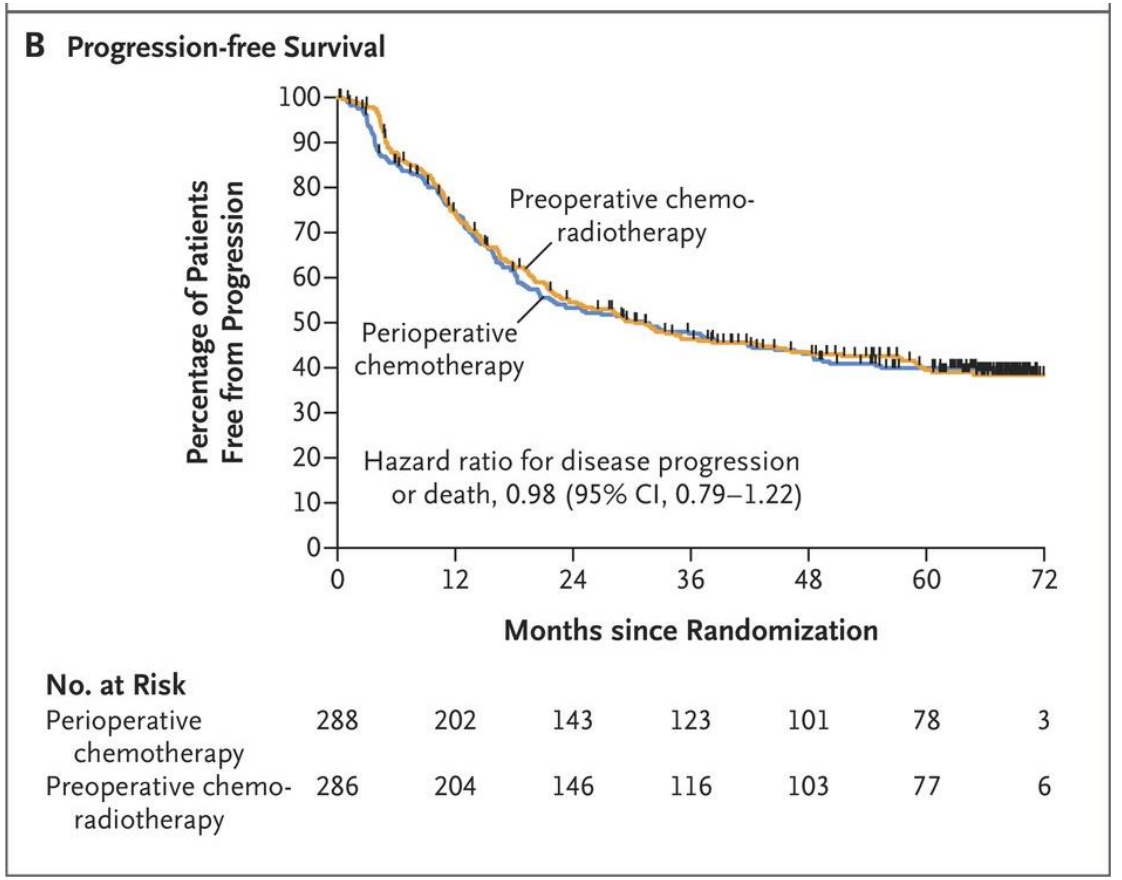
‖ In the preoperative-chemoradiotherapy group, one patient had ypTX and one had ypTis findings. One patient in the perioperative chemotherapy group had ypTX findings.

** Two patients in the preoperative-chemoradiotherapy group and one patient in the perioperative-chemotherapy group had tumor present, but it was not graded.

Leong T, et al. N Engl J Med. 2024 Sep. doi:10.1056/NEJMoa2405195

TOPGEAR





Median OS 46 mos CRT vs. 49 mos periop chemo alone

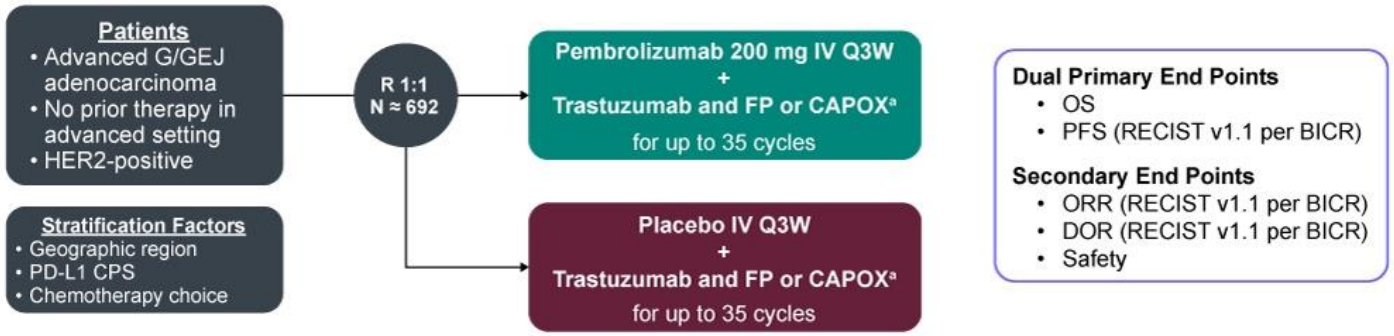
Median PFS 31 mos CRT vs. 32 mos periop chemo alone

perioperative FLOT vs. ECF in the FLOT4-AIO trial (median OS 50 mos for FLOT)

Al-Batran S, et al. Lancet. 2019 May;393(10184):1948-1957
Leong T, et al. N Engl J Med. 2024 Sep. doi:10.1056/NEJMoa2405195

KN-811 (ESMO)

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)



Dual Primary End Points
- OS
- PFS (RECIST v1.1 per BICR)

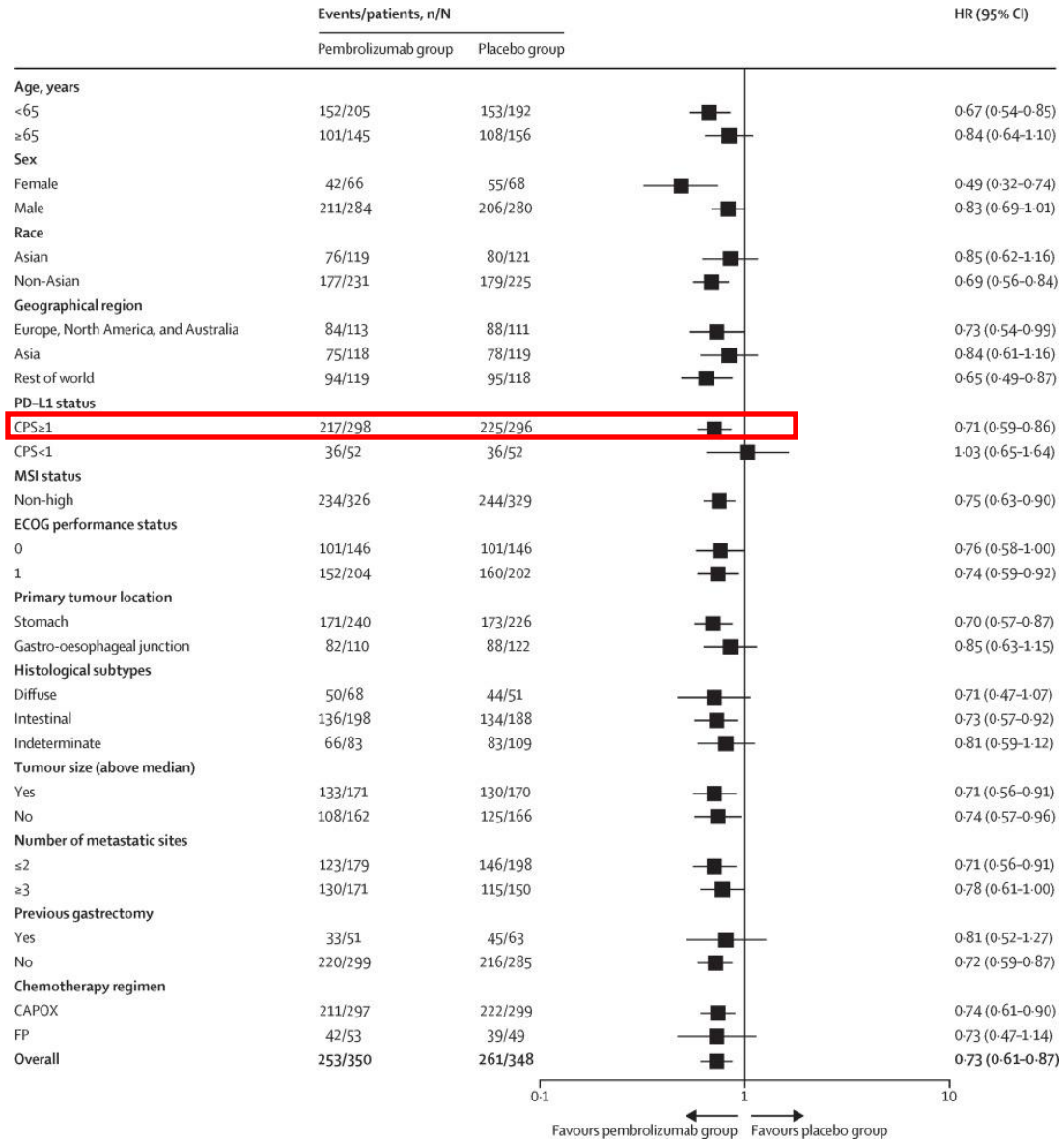
Secondary End Points
- ORR (RECIST v1.1 per BICR)
- DOR (RECIST v1.1 per BICR)
- Safety

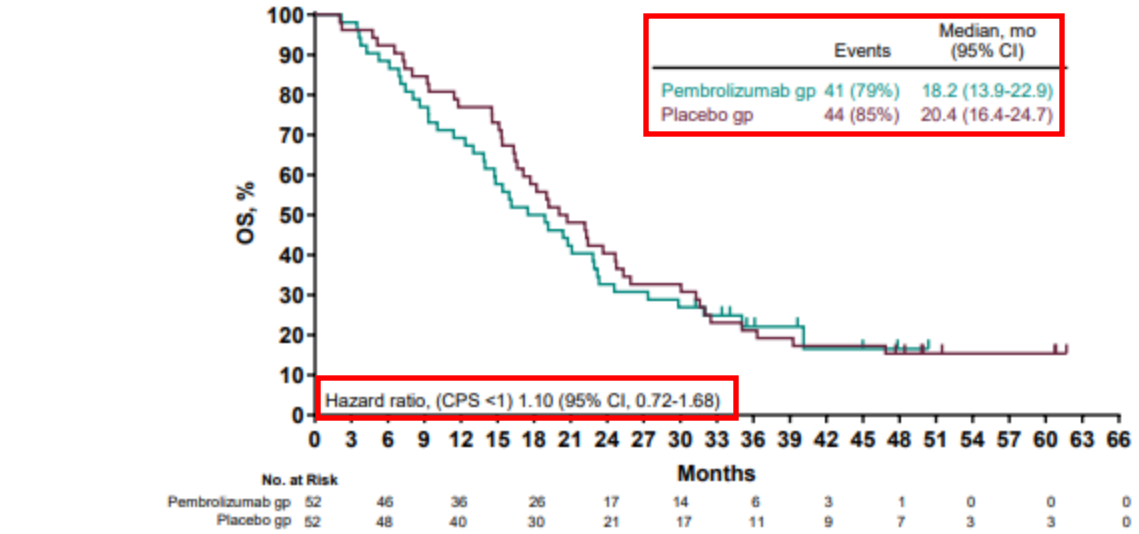
[a]Trastuzumab dose: 6 mg/kg IV Q3W following an 8 mg/kg loading dose. FP dose: 5-fluorouracil 800 mg/m^2 IV on D1-5 Q3W + cisplatin 80 mg/m^2 IV Q3W. CAPOX dose: capecitabine 1000 mg/m^2 BID on D1-14 Q3W + oxaliplatin 130 mg/m^2 IV Q3W.
BICR, blinded independent central review; CPS, combined positive score (number of PD-L1–staining cells [tumor cells, lymphocytes, macrophages] divided by the total number of viable tumor cells, multiplied by 100).

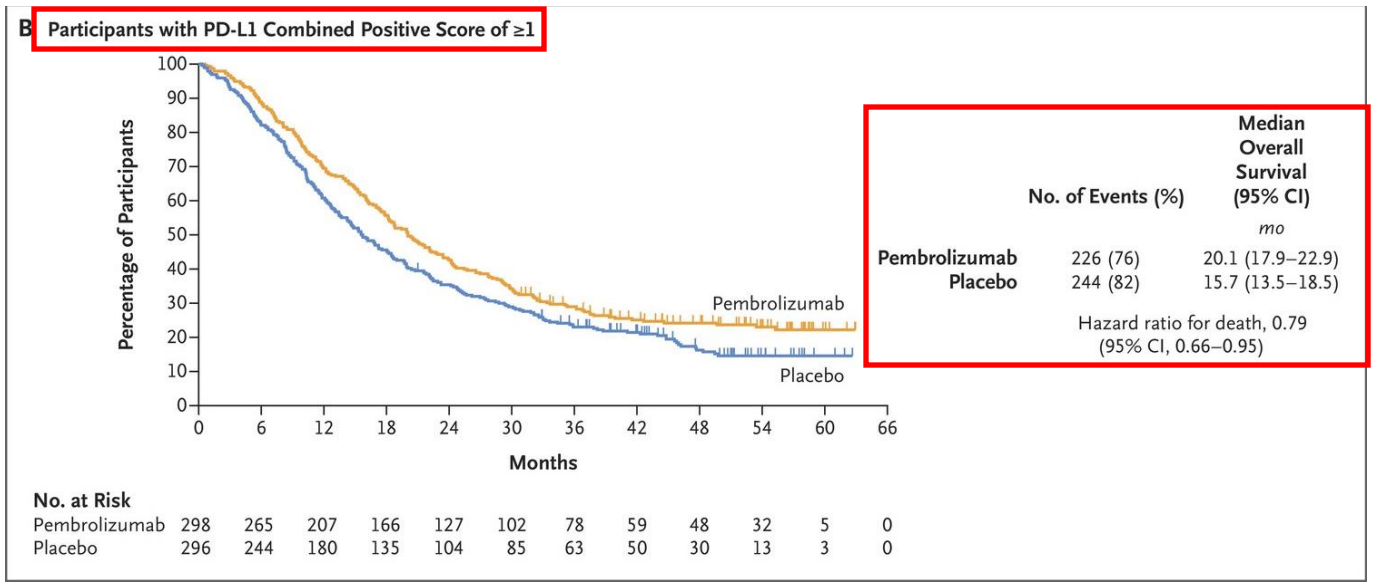
Characteristic	Pembrolizumab Group (N = 350)	Placebo Group (N = 348)
Histologic subtype, n (%)		
Diffuse	68 (19)	51 (15)
Intestinal	198 (57)	188 (54)
Indeterminate	83 (24)	109 (31)
Unknown	1 (<1)	0
Primary gastrectomy or esophagectomy, n (%)		
Yes	51 (15)	63 (18)
No	299 (85)	285 (82)
PD-L1 status, n (%)[j]		
CPS ≥1	298 (85)	296 (85)
CPS <1	52 (15)	52 (15)
HER2 status, n (%)[k]		
IHC 1+	1 (<1)	1 (<1)
IHC 2+ ISH equivocal	0	1 (<1)
IHC 2+ ISH negative	1 (<1)	1 (<1)
IHC 2+ ISH positive	62 (18)	84 (24)
IHC 3+	286 (82)	261 (75)
MSI-H status, n (%)[l]		
MSI-high	6 (2)	2 (1)
Non-MSI-high	326 (93)	329 (94)
Unknown	18 (5)	17 (5)
Tumor burden, n (%)		
<Median	162 (46)	166 (48)
≥Median	171 (49)	170 (49)
Missing	17 (5)	12 (3)
Chemotherapy regimen, n (%)		
Capecitabine and oxaliplatin (CAPOX)	297 (85)	299 (86)
5-fluorouracil and cisplatin (FP)	53 (15)	49 (14)

Janjigian YY, et al. Lancet. 2023 Dec;402(10418):2197-2208
Janjigian YY, et al. 2024 Sep. doi:10.1056/NEJMc2408121

KN-811







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

Janjigian YY, et al. 2024 Sep. doi:10.1056/NEJMc2408121

KN-811

FDA amends pembrolizumab's gastric cancer indication

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On November 7, 2023, the Food and Drug Administration revised the existing indication of pembrolizumab with trastuzumab, fluoropyrimidine, and platinum-containing chemotherapy for the first-line treatment of patients with locally advanced unresectable or metastatic HER2-positive gastric or gastroesophageal junction (GEJ) adenocarcinoma. **This updated indication, which remains approved under accelerated approval regulations, restricts its use to patients whose tumors express PD-L1 (CPS ≥ 1) as determined by an FDA-approved test.**

FDA label revised to limit to HER2+ metastatic GC/GEJ cancer with PD-L1 CPS ≥1

PRINCIPLES OF SYSTEMIC THERAPY

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

First-Line Therapy
- **Oxaliplatin is preferred over cisplatin due to lower toxicity.**

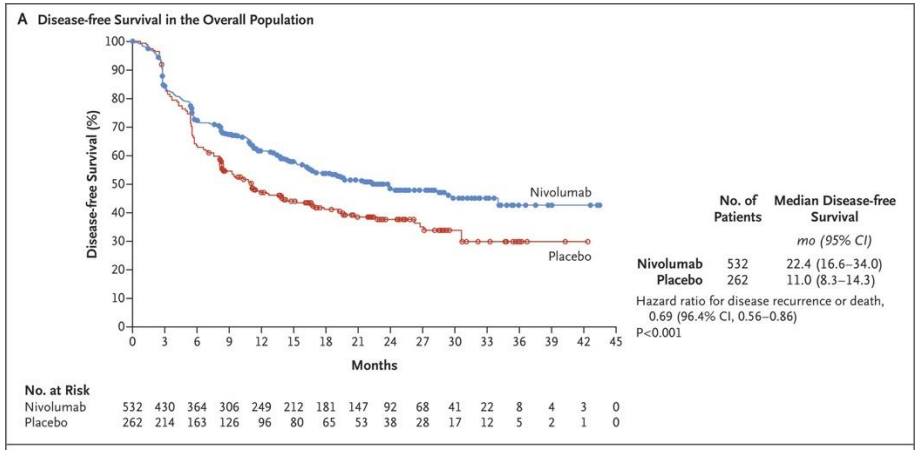
Preferred Regimens
- **HER2 overexpression positive[c]**
  - **Fluoropyrimidine (fluorouracil[a] or capecitabine), oxaliplatin and trastuzumab[f]**
  - **Fluoropyrimidine (fluorouracil[a] or capecitabine), oxaliplatin, trastuzumab[f] and pembrolizumab for PD-L1 CPS ≥1 (category 1)[g,h,17-18]**
  - **Fluoropyrimidine (fluorouracil[a] or capecitabine), cisplatin and trastuzumab (category 1)[f,19]**
  - **Fluoropyrimidine (fluorouracil[a] or capecitabine), cisplatin, trastuzumab[f] and pembrolizumab for PD-L1 CPS ≥1 (category 1)[g,h,17-18]**
- **HER2 overexpression negative[c]**
  - **Fluoropyrimidine (fluorouracil[a] or capecitabine), oxaliplatin, and nivolumab (PD-L1 CPS ≥5) (category 1)[g,h,20]**
  - **Fluoropyrimidine (fluorouracil[a] or capecitabine), oxaliplatin, and pembrolizumab for PD-L1 CPS ≥1[g,h,21] (category 1 for PD-L1 CPS ≥ 10; category 2B for PD-L1 CPS 1 to <10)**
  - **Fluoropyrimidine (fluorouracil[a] or capecitabine) and oxaliplatin[22-24]**
  - **Fluoropyrimidine (fluorouracil[a] or capecitabine), cisplatin, and pembrolizumab for PD-L1 CPS ≥1[g,h,21] (category 1 for PD-L1 CPS ≥ 10; category 2B for PD-L1 CPS 1 to <10)**
  - **Fluoropyrimidine (fluorouracil[a] or capecitabine) and cisplatin[22,25-27]**

Janjigian YY, et al. 2024 Sep. doi:10.1056/NEJMc2408121
NCCN Guidelines. Gastric Cancer. Version 4.2024. August 12, 2024

Take-away points for today's clinic

- **Addition of pembrolizumab to trastuzumab and platinum-based chemotherapy is first-line standard in HER2+ advanced gastric/GEJ adenocarcinoma with PD-L1 CPS ≥1 (amended FDA label)**

- **Combined findings of ESOPEC and TOPGEAR support that perioperative FLOT is standard for resectable gastric/GEJ/esophageal adenocarcinoma**
  - **There is still a role for chemoRT in esophageal SCC**
  - **?role of chemoRT in those unfit for FLOT**



- **ESOPEC did not include adjuvant nivo per CM-577 following surgery and chemoRT in stage II-II esophageal/GEJ adenoca/SCC**

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

Outline

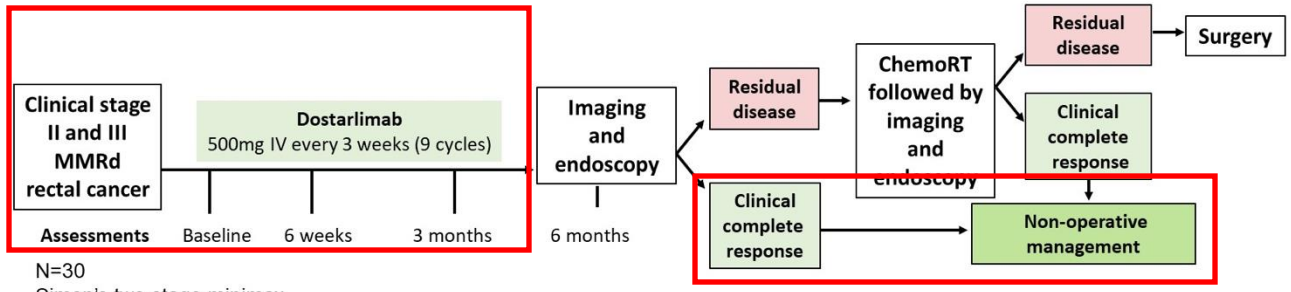
1. Esophageal/gastroesophageal cancer updates

2. Colorectal cancer updates

MSI-H rectal cancer (ASCO 2024)

Neoadjuvant PD-1 blockade for stage II/III MMRd rectal cancer

NCT 04165772



N=30
Simon's two stage minimax

Summary of patient responses

ID	Stage T	Stage N	Completed anti-PD-1 Treatment	DFS (months)	Endoscopic Best Response	Radiographic Best Response	Overall Response
1	T4	N+	Y	20.9	CR	CR	**cCR**
2	T3	N+	Y	21.7	CR	CR	**cCR**
3	T1/2	N+	Y	22.9	CR	CR	**cCR**
4	T4	N+	Y	22.4	CR	CR	**cCR**
5	T1/2	N+	Y	10.8	CR	CR	**cCR**
6	T1/2	N+	Y	10.3	CR	CR	**cCR**
7	T1/2	N+	Y	10.5	CR	CR	**cCR**
8	T3	N+	Y	6.3	CR	CR	**cCR**
9	T3	N+	Y	6.1	CR	CR	**cCR**
10	T3	N-	Y	6.4	CR	CR	**cCR**
11	T3	N+	Y	6.1	CR	CR	**cCR**
12	T3	N+	N	2.8	nCR	PR	**NE**
13	T3	N+	N	2.8	CR	CR	**NE**

NE = not evaluated
cCR = clinical complete response
nCR = near complete response

cCR rate 100% (11/11 patients)

ASCO24 update: 41 pts who completed treatment achieved a clinical complete response

- No patients required any additional therapy
- No patients experienced local or distant disease recurrence

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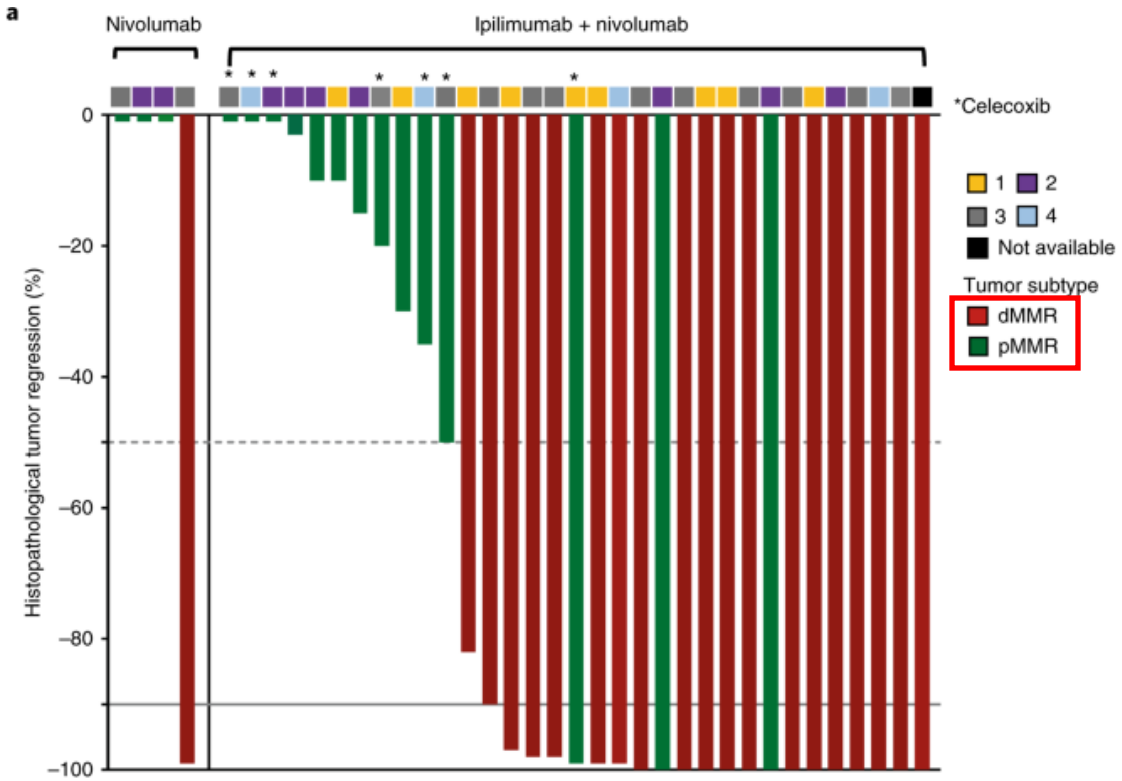
Cercek A, et al. JCO. 2024;42(17 suppl):LBA3512
Lumish M, et al. JCO. 2022;40(4 suppl):16

MSI-H colon cancer

NICHE: n=40 pts with stage I-III resectable colon cancer dMMR or pMMR tumors → ipilimumab X1 + 2 doses nivolumab before surgery



100% pathological response rate in 20/20 (95% CI: 86–100%)

Chalabi M, et al. N Engl J Med. 2024;390(21):1949-1958
Chalabi M, et al. Nat Med. 2020;26(4):566-576.

MSI-H colon cancer (ESMO 2024)

- Original NICHE, n=32 pts dMMR stage I-III colon cancer
  - Primary endpoint: safety
- NICHE-2, n=83 pts dMMR stage II-III colon cancer
  - Primary endpoint: 3-year DFS

NICHE-2: Ph II stage II-III dMMR colon cancer

First cycle (day1)
Nivolumab 3 mg/kg + ipilimumab 1 mg/kg

→

Second cycle (day 15)
Nivolumab 3 mg/kg

→

Surgery within 6 weeks of study enrollment

Table 1. Demographic and Disease Characteristics of the Patients.

Characteristic	Patients (N=115)
Female sex — no. (%)	67 (58)
Median age (range) — yr	60 (20–82)
WHO performance-status score — no. (%)*	
0	100 (87)
1	15 (13)
Race or ethnic group — no. (%)†	
White	97 (84)
Asian	6 (5)
Black	5 (4)
Other	7 (6)
Tumor stage — no. (%)‡	
cT2	17 (15)
cT3 or cT3–T4a	24 (21)
cT4a	41 (36)
cT4b	33 (29)
Nodal status — no. (%)§	
cN–	38 (33)
cN+	77 (67)
Primary tumor location — no. (%)	
Right	78 (68)
Transverse	17 (15)
Left	20 (17)
Lynch syndrome — no. (%)	37 (32)
Unexplained dMMR — no. (%)¶	2 (2)
Non–Lynch syndrome dMMR — no. (%)	76 (66)

* The World Health Organization (WHO) performance-status score ranges from 0 to 5, with higher scores indicating greater disability.
† Race or ethnic group was reported by the patients or inferred on the basis of the country of birth if patient-reported data were unavailable. The category "Other" includes patients of Hispanic, Middle Eastern, and North African descent.
‡ Tumor stage was classified according to the American Joint Committee on Cancer staging system, version 8, with higher numbers indicating a more advanced tumor.
§ Nodal status indicates the presence (cN+) or absence (cN–) of cancer cells in the lymph nodes.
¶ Unexplained mismatch repair deficiency (dMMR) was specified as dMMR that could not be explained by characteristic germline alterations, biallelic somatic inactivation of the MMR protein, or *MLH1* promoter hypermethylation.

Chalabi M, et al. N Engl J Med. 2024;390(21):1949-1958

MSI-H colon cancer (ESMO 2024)

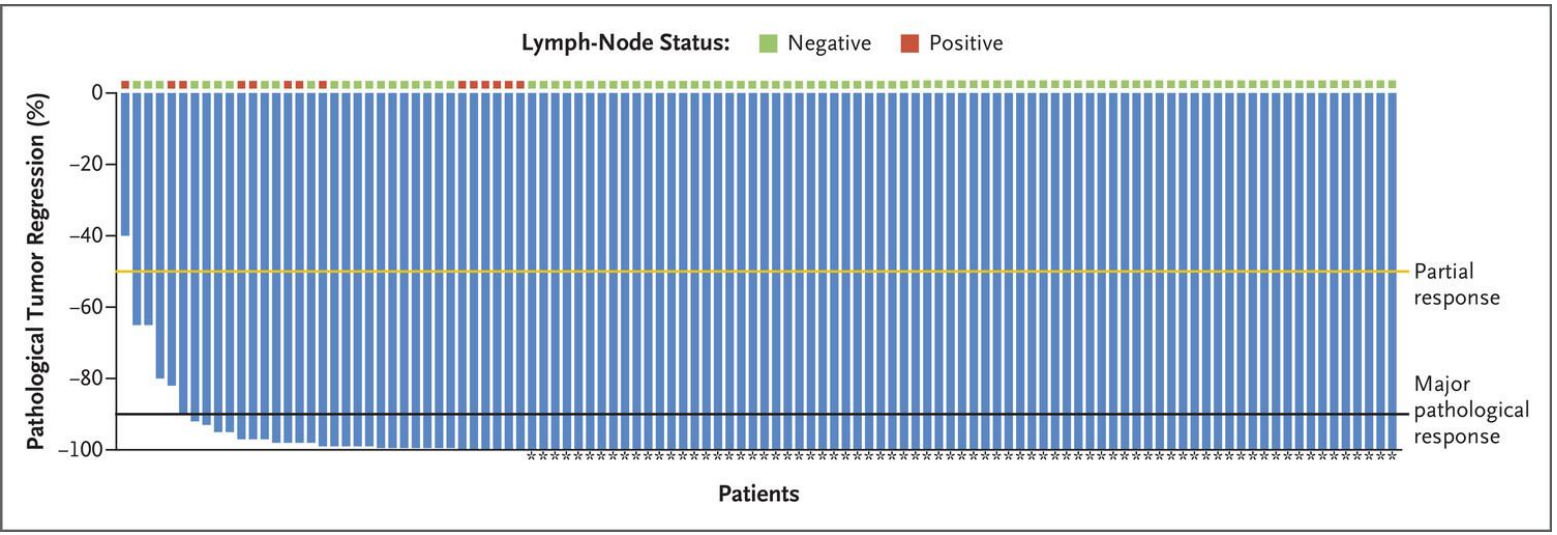


Table 2. Pathological Responses among Patients in the Efficacy Analysis.*

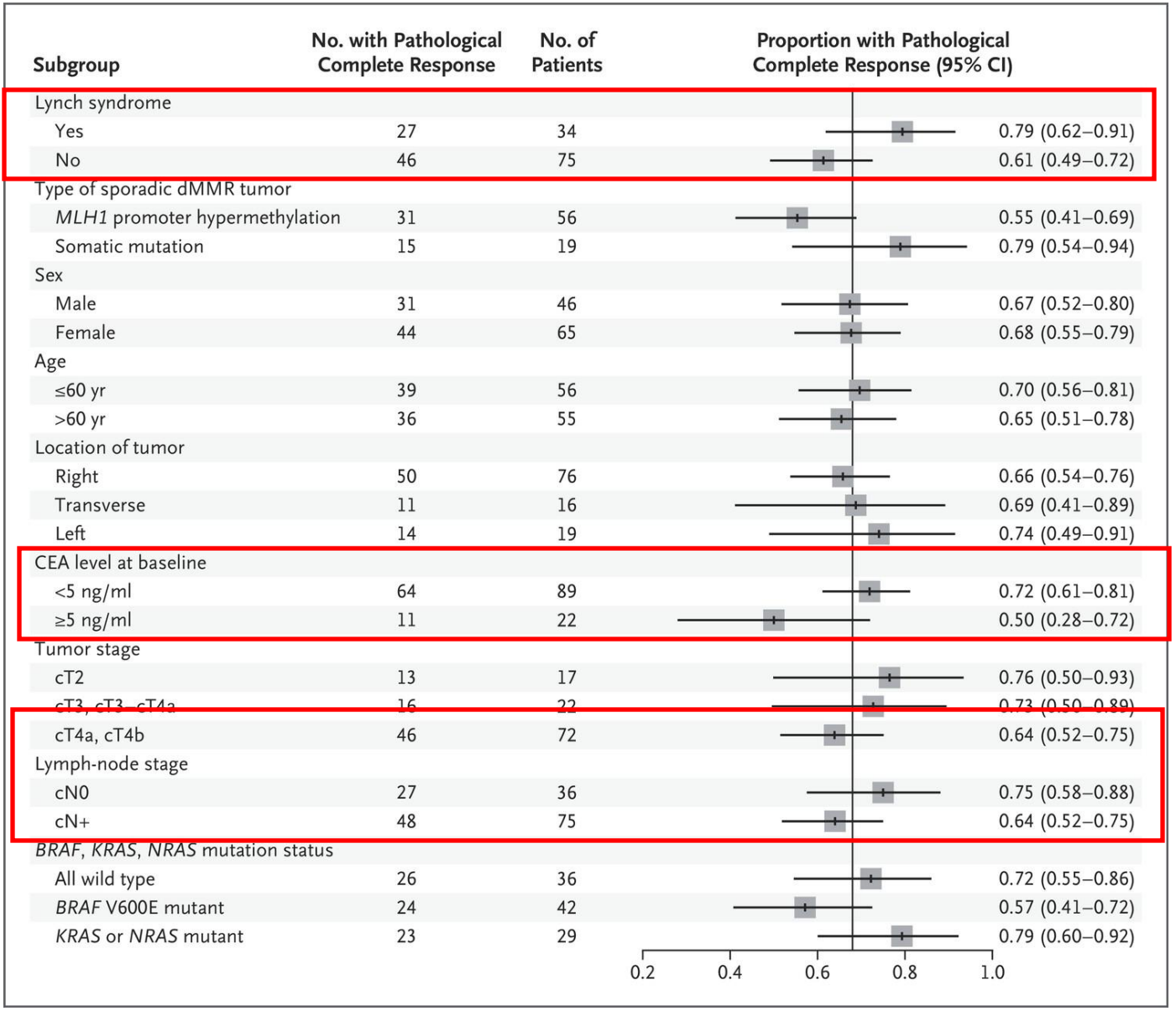
Residual Viable Tumor	Patients (N = 111)
	no. (%)
≤50% Residual viable tumor	109 (98)
≤10% Residual viable tumor: major pathological response	105 (95)
0% Residual viable tumor: complete pathological response	75 (68)
11–49% Residual viable tumor: partial pathological response	4 (4)
≥50% Residual viable tumor, indicating lack of pathological response	1 (1)
Unable to be evaluated†	1 (1)

* For patients with a synchronous second tumor in the colon, the response observed in the tumor with the highest baseline stage is shown.

† In one patient, the tumor bed could not be determined, and therefore, the percentage of residual viable tumor could not be calculated.

Chalabi M, et al. N Engl J Med. 2024;390(21):1949-1958

MSI-H colon cancer (ESMO 2024)



Subgroup	No. with Pathological Complete Response	No. of Patients	Proportion with Pathological Complete Response (95% CI)
Lynch syndrome			
Yes	27	34	0.79 (0.62–0.91)
No	46	75	0.61 (0.49–0.72)
Type of sporadic dMMR tumor			
MLH1 promoter hypermethylation	31	56	0.55 (0.41–0.69)
Somatic mutation	15	19	0.79 (0.54–0.94)
Sex			
Male	31	46	0.67 (0.52–0.80)
Female	44	65	0.68 (0.55–0.79)
Age			
≤60 yr	39	56	0.70 (0.56–0.81)
>60 yr	36	55	0.65 (0.51–0.78)
Location of tumor			
Right	50	76	0.66 (0.54–0.76)
Transverse	11	16	0.69 (0.41–0.89)
Left	14	19	0.74 (0.49–0.91)
CEA level at baseline			
<5 ng/ml	64	89	0.72 (0.61–0.81)
≥5 ng/ml	11	22	0.50 (0.28–0.72)
Tumor stage			
cT2	13	17	0.76 (0.50–0.93)
cT3, cT3–cT4a	16	22	0.73 (0.50–0.89)
cT4a, cT4b	46	72	0.64 (0.52–0.75)
Lymph-node stage			
cN0	27	36	0.75 (0.58–0.88)
cN+	48	75	0.64 (0.52–0.75)
BRAF, *KRAS*, *NRAS* mutation status			
All wild type	26	36	0.72 (0.55–0.86)
BRAF V600E mutant	24	42	0.57 (0.41–0.72)
KRAS or *NRAS* mutant	23	29	0.79 (0.60–0.92)

Median follow-up after surgery of 36.5 mos (range 7.8-83.4)

- n=111, 3-yr DFS 100%

Chalabi M, et al. Ann Oncol. 2024;35(2 suppl):S1217-S1218
Chalabi M, et al. N Engl J Med. 2024;390(21):1949-1958

MSI-H colon cancer (ESMO 2024)

NICHE-3: Ph II non-randomized, open-label trial stage II-III dMMR colon cancer

- Locally advanced (≥T3 and/or N+) dMMR resectable colon adenocarcinoma with no signs of distant metastases
- Treatment-naïve

→ **First cycle (day 1)**
Nivolumab 480 mg + relatlimab (anti-LAG-3) 480 mg

→ **Second cycle (day 29)**
Nivolumab 480 mg + relatlimab 480 mg

→ Surgery within 6-8 weeks of study enrollment
Primary endpoint: pathologic response

Table 1 | Baseline patient characteristics

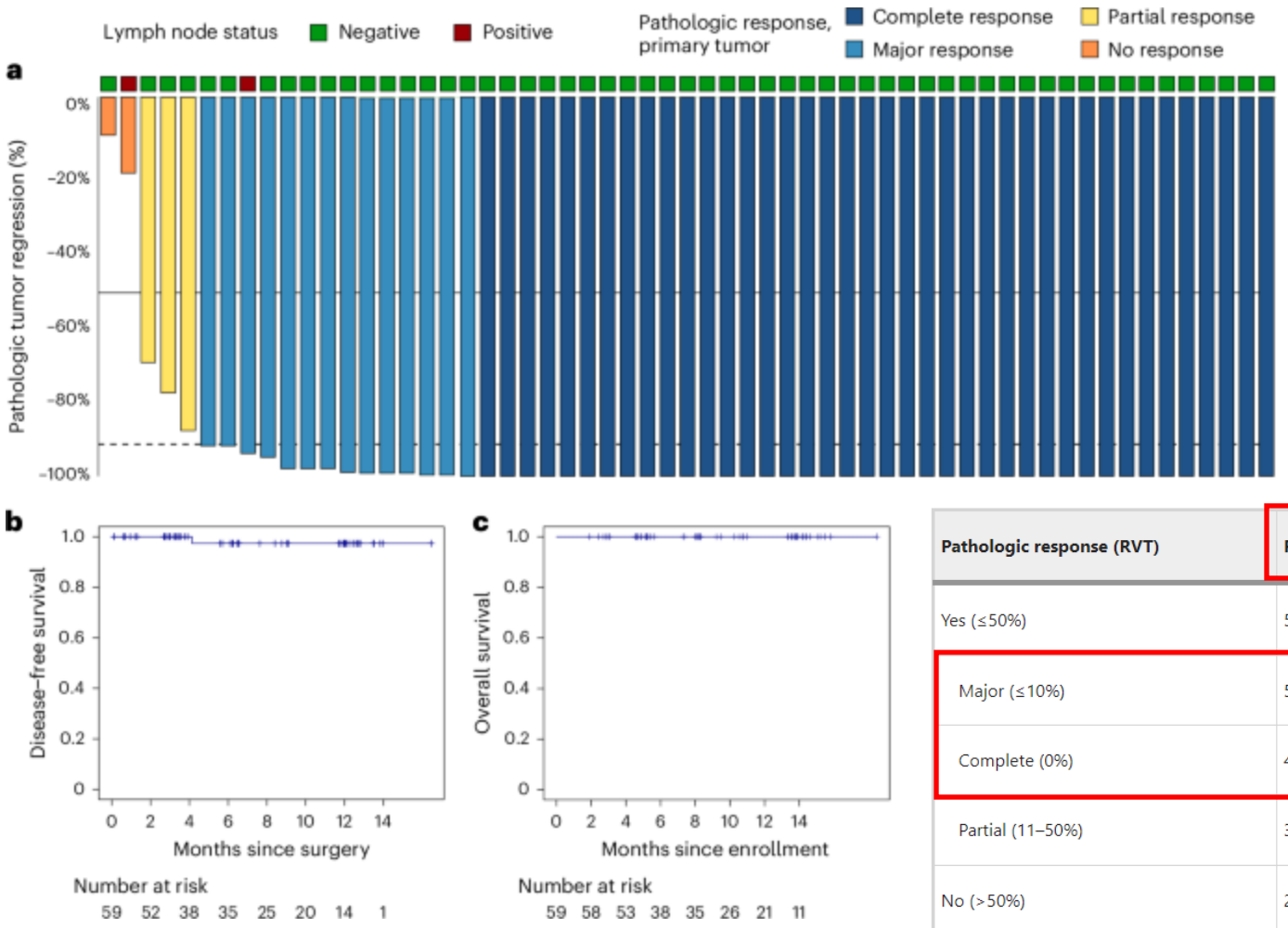
Characteristics	Patients (*n*=59)
Age at enrollment (years)	
Median (range)	65 (21–85)
Sex (%)	
Female	32 (54%)
Male	27 (46%)
Race or ethnicity[a] (%)	
White	51 (86%)
Black	3 (5%)
Asian	1 (2%)
Other	4 (7%)
WHO performance status (%)	
0	42 (71%)
1	17 (29%)
Tumor stage[b] (%)	
cT2	1 (2%)
cT3 or cT3–4a	18 (31%)
cT4a	26 (44%)
cT4b	14 (24%)
Lymph node stage[c] (%)	
cN0	22 (37%)
cN+	37 (63%)
Primary tumor location (%)	
Right	48 (81%)
Transverse	6 (10%)
Left	5 (8%)
Lynch status (%)	
Lynch syndrome	11 (19%)
Sporadic MMR deficiency[d]	48 (81%)

[a]Other includes patients of Middle Eastern or North African descent and Hispanic or Mixed heritage. [b]As assessed by CT scan, staged according to the American Joint Committee on Cancer Staging Manual, 8th edition[38]. [c]Numbers may not add up to 100% due to rounding. [d]Sporadic MMR deficiency was defined as dMMR due to *MLH1*-promoter hypermethylation or due to somatic MMR mutations.

de Gooyeri, et al. Nat Med. 2024 Sep. doi:10.1038/s41591-024-03250-w

MSI-H colon cancer (ESMO 2024)

NICHE-3: Ph II non-randomized, open-label trial stage II-III dMMR colon cancer



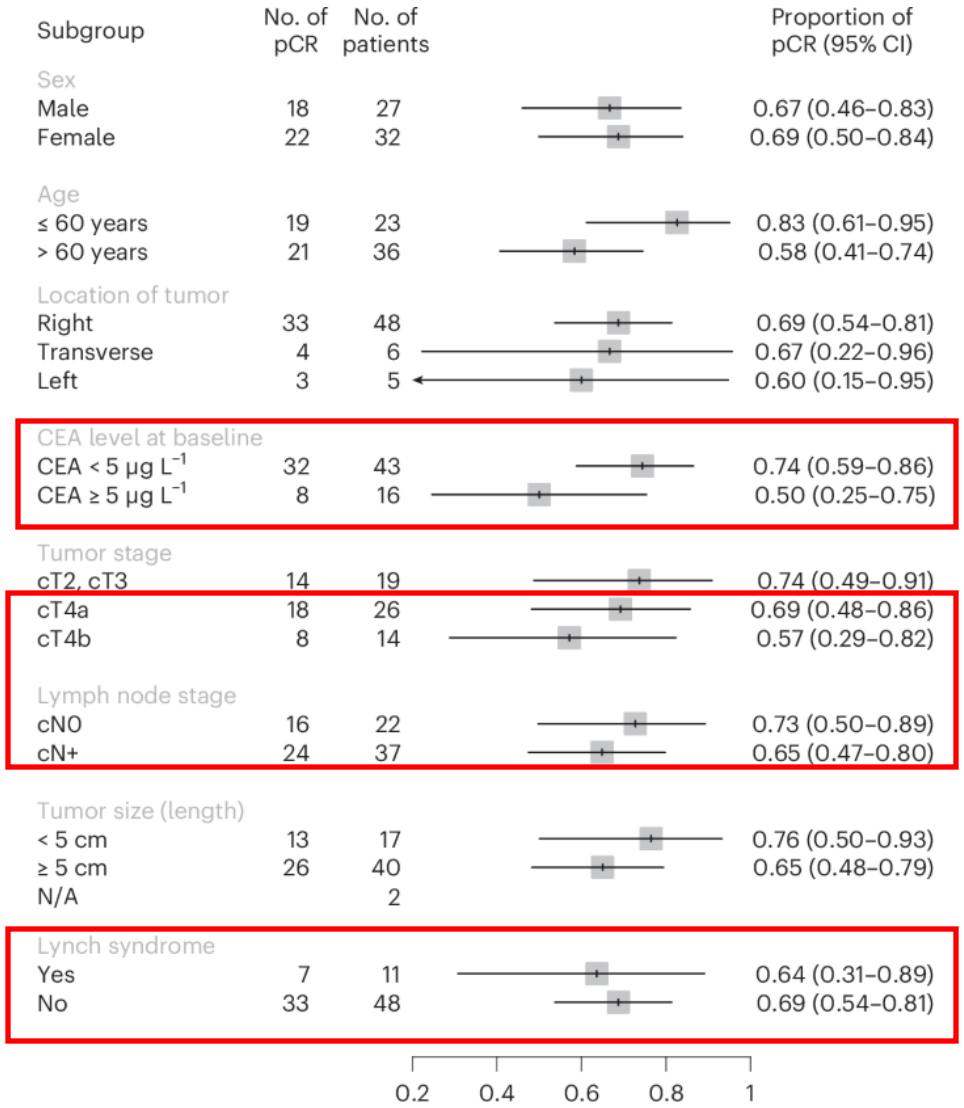
Pathologic response (RVT)	Full cohort *n* = 59	cT2–3 *n* = 19	cT4a *n* = 26	cT4b *n* = 14	cN0 *n* = 22	cN+ *n* = 37
Yes (≤50%)	57 (97%)	19 (100%)	25 (96%)	13 (93%)	22 (100%)	35 (95%)
Major (≤10%)	54 (92%)	17 (89%)	25 (96%)	12 (86%)	20 (91%)	34 (92%)[a]
Complete (0%)	40 (68%)	14 (74%)	18 (69%)	8 (57%)	16 (73%)	24 (65%)
Partial (11–50%)	3 (5%)	2 (11%)	0	1 (7%)	2 (9%)	1 (3%)
No (>50%)	2 (3%)	0	1 (4%)	1 (7%)	0	2 (5%)[a]

[a]One patient had lymph node metastases in the resection specimen.

de Gooyeri, et al. Nat Med. 2024 Sep. doi:10.1038/s41591-024-03250-w

MSI-H colon cancer (ESMO 2024)

NICHE-3: Ph II non-randomized, open-label trial stage II-III dMMR colon cancer



de Gooyeri, et al. Nat Med. 2024 Sep. doi:10.1038/s41591-024-03250-w

MSI-H colon cancer (ESMO 2024)

Study	Study drug	Duration of pre-op	Post-op IO	Primary endpoint
IMHOTEP (n=89)	Pembrolizumab	6-12 weeks	☑	pCR rate
NICHE 3 (n=59)	Nivolumab + Relatlimab	4 weeks	No	Path response (<50% RVT)
NICHE 2 (n=115)	Nivolimab + Ipilimumab	4 weeks	No	Safety & 3 yr DFS

Consistent with previous studies

Study	Design	R0 resection	pCR rate in *eligible* pts *	mPR	3 year DFS
IMHOTEP (n=77)	Peri-op pembrolizumab	100%	52.8%		-
NICHE 3 (n=59)	Pre-op Nivolumab + Relatlimab	100%	68%	92%	-
NICHE 2 (n=113)	Pre-op Nivolimab + Ipilimumab	100%	68%	95%	100%

No difference in efficacy

17% of patients over 80 – frailer patient population than recruited in other trials

Study	Design	Median age	PS >0	%cT4	% N+	% Lynch
IMHOTEP (n=89)	Peri-op pembrolizumab	66	41.9%	31.5%	78.7%	20.7%
NICHE 3 (n=59)	Pre-op Nivolumab + Relatlimab	65	29%	68%	63%	19%
NICHE 2 (n=113)	Pre-op Nivolimab + Ipilimumab	60	13%	65%	67%	31%

High proportion of high risk patients

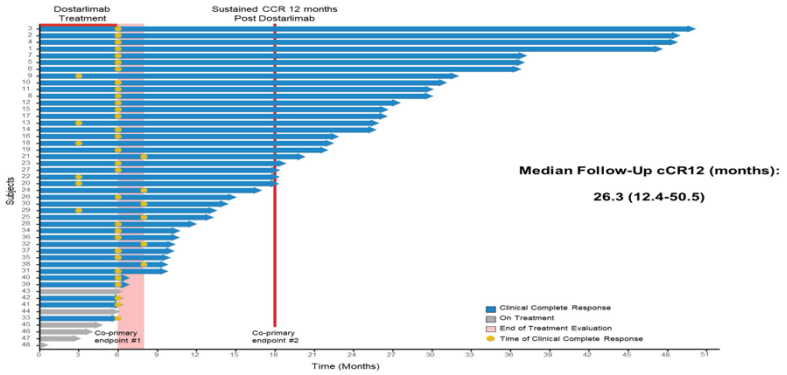
Seligman J. ESMO Congress 2024. 2024 Sep 15. Invited Discussant LBA24, 503O and 504O

MSI-H colon cancer (ESMO 2024)

What is the optimal duration for pre-operative anti-PD-1?

Study	Design	pCR rate
Xu et al	Sintilimab **4 weeks**	47.7%
IMHOTEP	Pembrolizumab **6 weeks**	46.0%
NEOPRISM (n=32)	Pembrolizumab **9 weeks**	53%
PICC (n=34)	Toripalimab +/- celecoxib **12 weeks**	76.5%
IMHOTEP	Pembrolizumab **12 weeks**	68.2%
Ludford (n=27)	Pembrolizumab **24 weeks**	79%

Duration to cCR with Dostarlimab in MSI-H rectal cancer



All reached cCR by 6 months

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Seligman J. ESMO Congress 2024. 2024 Sep 15. Invited Discussant LBA24, 503O and 504O

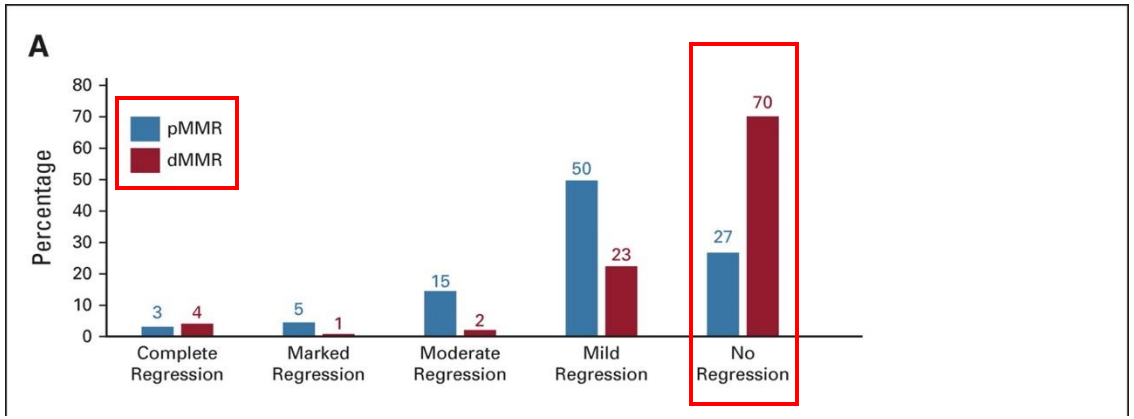
MSI-H colon cancer (ESMO 2024)

- Over shorter treatment duration combination appears superior
- Lesser difference in pCR if longer treatment of anti-PD1 delivered
- Heterogeneity in study designs limit definitive conclusions

Study	Design	pCR rate
PICC	Toripalimab +/- celecoxib (12 weeks)	76.5%
Ludford	Pembrolizumab (24 weeks)	79%
NEOPRISM	Pembrolizumab (9 weeks)	53%
IMHOTEP	Pembrolizumab (**6 weeks)**	46.0%
IMHOTEP	Pembrolizumab (**12 weeks)**	68.2%
Xu et al	Sintilimab (4 weeks)	47.7%
NICHE 2	Nivolimab + ipilimumab (4 weeks)	68.0%
NICHE 3	Nivolumab +. Retalimab (4 weeks)	68.0%
Xu et al	IBI310 + Sintilimab (4 weeks)	80%
Kasi et al	Botensilimab + bastilimab (4 weeks)	100%

Seligman J. ESMO Congress 2024. 2024 Sep 15. Invited Discussant LBA24, 503O and 504O

MSI-H: Localized/locally advanced colorectal cancer



FOxTROT (T3-4, N0-2, M0 colon cancer) 2:1 randomization to 6 wks FOLFOX (NAC) -> 18 wks adjuvant FOLFOX vs. surgery -> adjuvant FOLFOX 24 wks

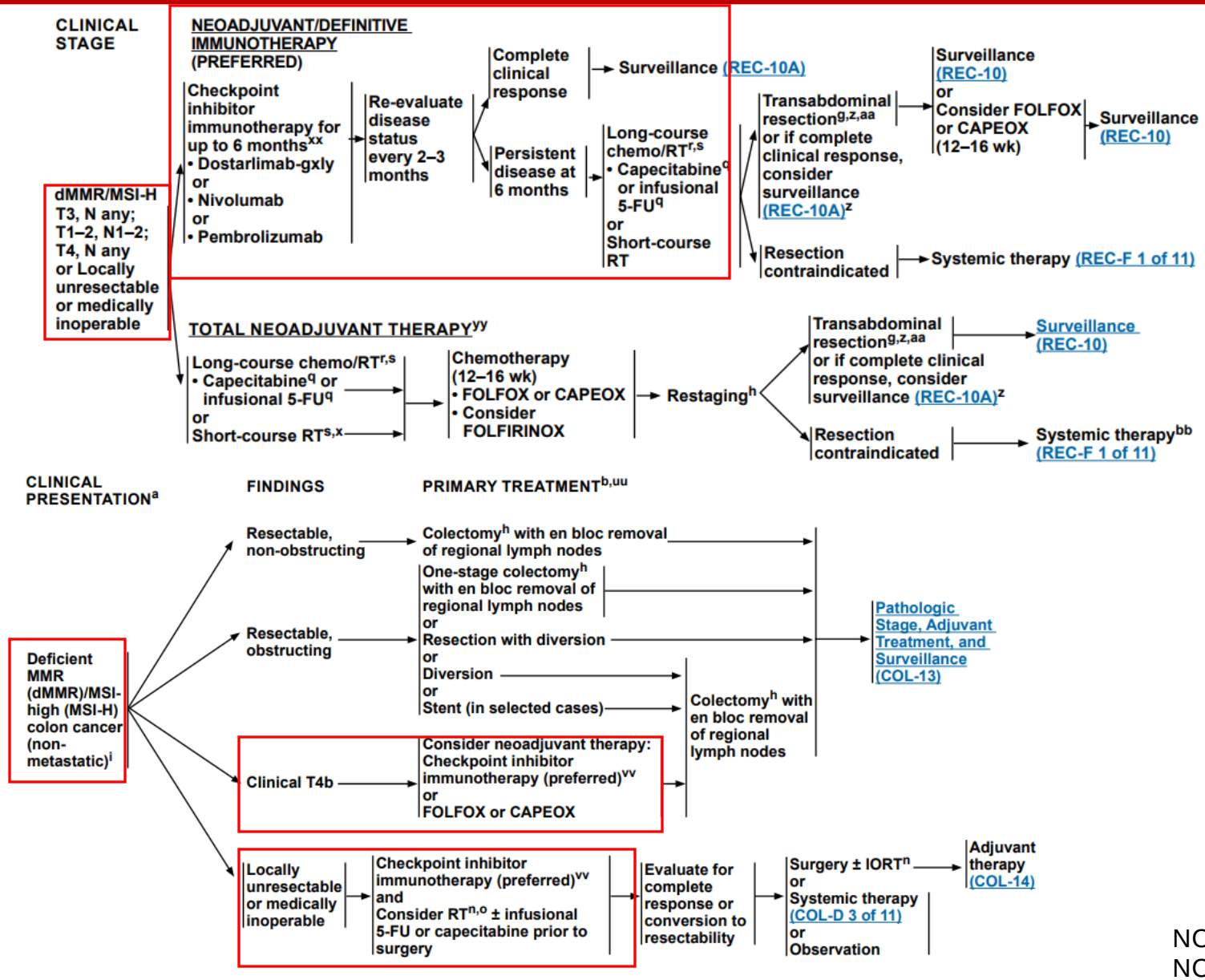
Table 4. Overall response rate.

	Exploratory cohort				Validation cohort			
	pMMR		dMMR		pMMR		dMMR	
	No. of patients	%	No. of patients	%	No. of patients	%	No. of patients	%
Complete response	26	17.6	0	–	24	16.4	0	–
Partial response	103	69.6	3	25	101	69.2	4	33.4
Stable disease	19	12.8	8	66.7	21	14.4	6	50
Progressive disease	0	–	1	8.3	0	–	2	16.6
ORR	129	87.2	3	25	125	85.6	4	33.4
	$p = 0.0114$				$p = 0.035$			

Retrospective series, dMMR locally advanced rectal cancer, unlike pMMR subjects, had poor or no response to neoadjuvant chemoradiation

Morton D, et al. J Clin Oncol. 2023;41(8):1541-1552
Pretta A, et al. Br J Cancer. 2023;129(10):1619-1624.

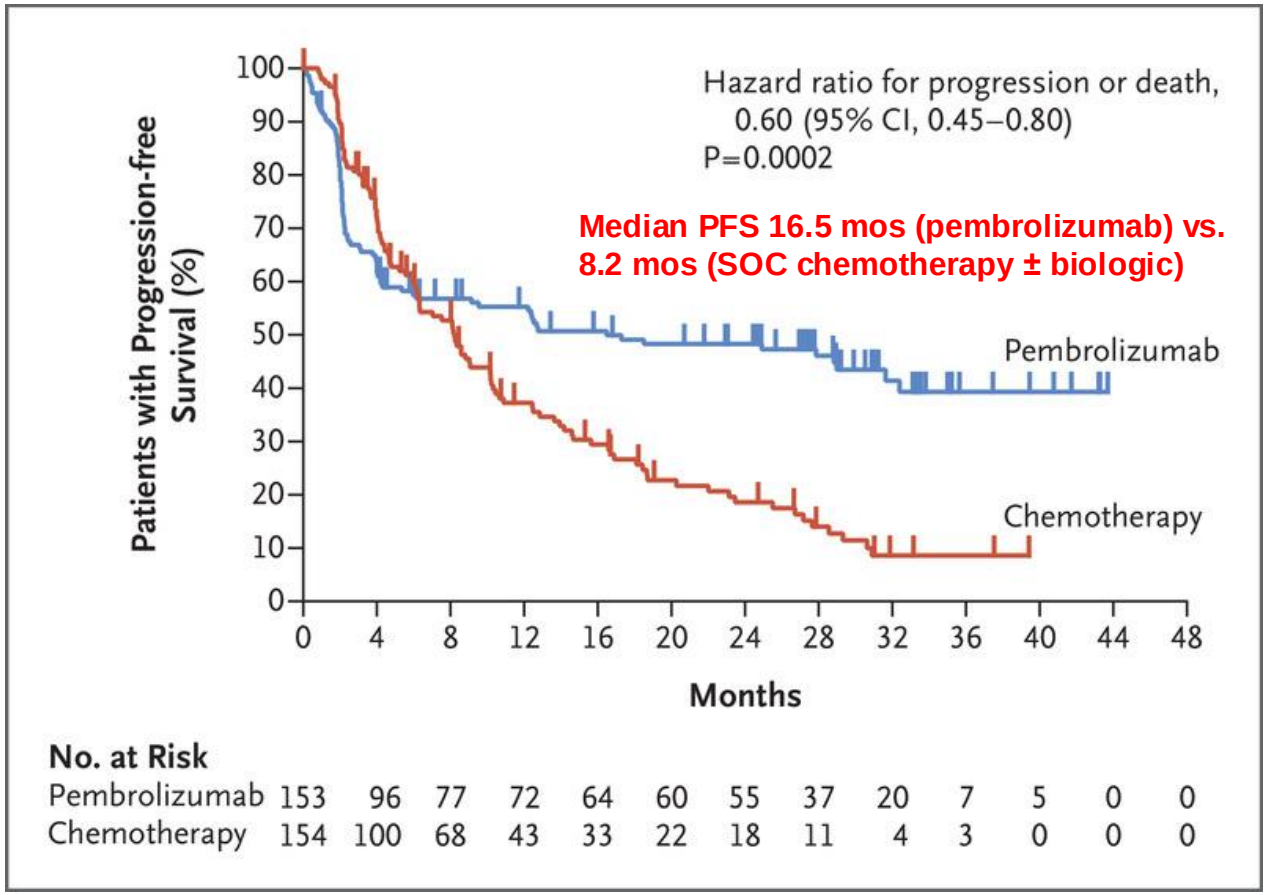
MSI-H: Localized/locally advanced colorectal cancer



NCCN Guidelines. Colon Cancer. Version 5.2024. August 22, 2024
NCCN Guidelines. Rectal Cancer. Version 4.2024. August 22, 2024

First-Line MSI-H/dMMR

ORR 44% vs. 33%
CR 11.1% vs.4%



FDA approves pembrolizumab for first-line treatment of MSI-H/dMMR colorectal cancer

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On June 29, 2020, the Food and Drug Administration approved pembrolizumab for the first-line treatment of patients with unresectable or metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) colorectal cancer.

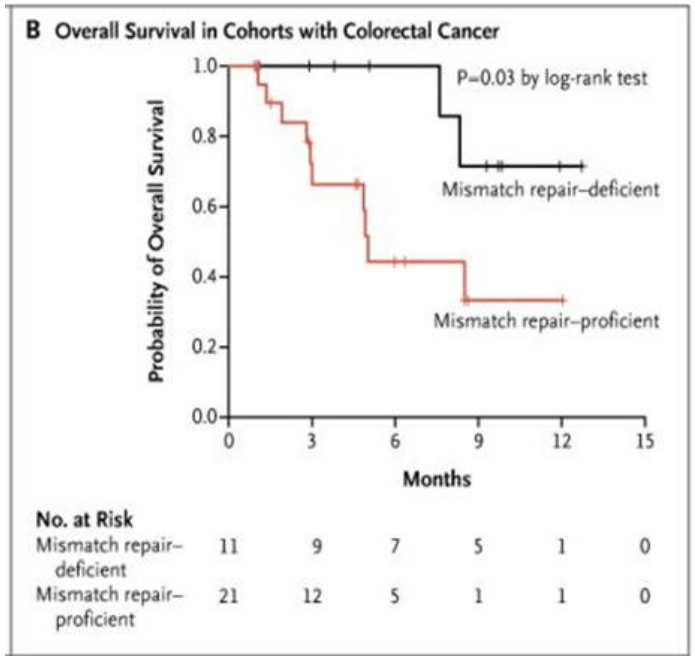
Approval was based on KEYNOTE-177 (NCT02563002), a multicenter, international, open-label, active-controlled, randomized trial that enrolled 307 patients with previously untreated unresectable or metastatic MSI-H or dMMR colorectal cancer. Determination of MSI or MMR tumor status was made locally using polymerase chain reaction (PCR) or immunohistochemistry (IHC), respectively. Patients were randomized (1:1) to receive pembrolizumab 200 mg intravenously every 3 weeks or investigator's choice of mFOLFOX6/FOLFIRI ± bevacizumab or cetuximab given intravenously every 2 weeks. Patients randomized to chemotherapy were offered pembrolizumab at the time of disease progression.

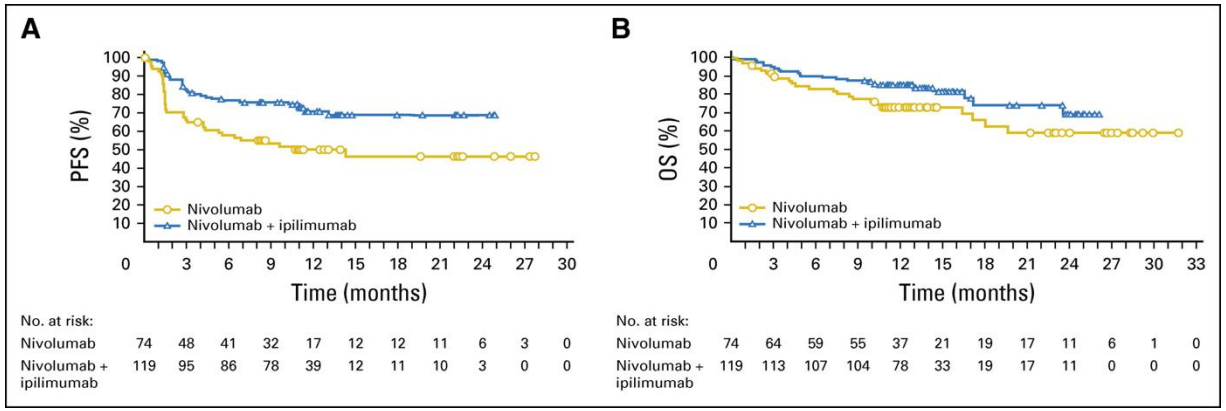
The main efficacy outcome measures were progression-free survival (PFS) and overall survival (OS). Median PFS was 16.5 months (95% Confidence Interval [CI]: 5.4, 32.4) in the pembrolizumab arm and 8.2 months (95% CI: 6.1, 10.2) in the chemotherapy arm (HR 0.60, 95% CI 0.45, 0.80; two-sided p-value=0.0004). At the time of the PFS analysis, the OS data were not mature.

The most common adverse reactions reported in ≥20% of patients receiving

André T, et al. N Engl J Med. 2020;383(23):2207-2218

Second-Line and Beyond: MSI-H





FDA grants accelerated approval to dostarlimab-gxly for dMMR advanced solid tumors

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On August 17, 2021, the Food and Drug Administration granted accelerated approval to dostarlimab-gxly for adult patients with mismatch repair deficient (dMMR) recurrent or advanced solid tumors, as determined by an FDA-approved test, that have progressed on or following prior treatment and who have no satisfactory alternative treatment options.

Today, the FDA also approved the VENTANA MMR RxDx Panel as a companion diagnostic device to select patients with dMMR solid tumors for treatment with dostarlimab-gxly.

FDA approvals:
Pembrolizumab
Nivolumab
Nivolumab and ipilimumab

Antoniotti C, et al. Cancer Treat Rev. 2021;92:102135.
Gong J, et al. J Immunother Cancer. 2018;6(1):8.
Le DT, et al. N Engl J Med. 2015;372:2509-20
Overman MJ, et al. JCO. 2018;36:773-779

First-Line: MSI-H mCRC (ASCO 2024)

CheckMate 8HW study design

- CheckMate 8HW is a randomized, multicenter, open-label phase 3 study[a]

Key eligibility criteria:
- Histologically confirmed unresectable or metastatic CRC
- MSI-H/dMMR status by local testing
- ECOG PS 0 or 1

Stratification factors:
- Prior lines of treatment (0 vs 1 vs ≥ 2)
- Primary tumor location (right vs left)

R 2:2:1

1L setting: n = 202
- NIVO 240 mg Q2W for 6 doses, followed by NIVO 480 mg Q4W[b]
- NIVO 240 mg + IPI 1 mg/kg Q3W for 4 doses, followed by NIVO 480 mg Q4W[b]

1L setting: n = 101
- Investigator's choice chemo[c] (mFOLFOX6 or FOLFIRI ± bevacizumab or cetuximab)

Treatment until disease progression, unacceptable toxicity, withdrawal of consent (all arms), or a maximum treatment duration of 2 years (NIVO and NIVO + IPI arms only)

Dual primary endpoints in patients with centrally confirmed MSI-H/dMMR status[d]:
- PFS by BICR[e] (NIVO + IPI vs chemo in the 1L setting)
- PFS by BICR[e] (NIVO + IPI vs NIVO across all lines)

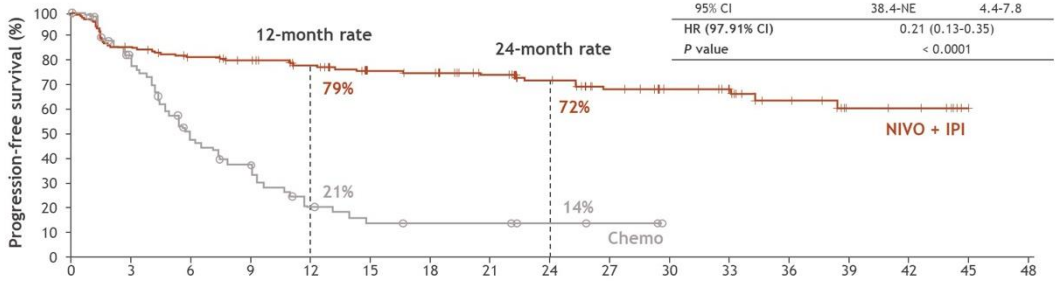
Other select endpoints:
- Safety
- OS; PFS2 by investigator[e]; ORR by BICR[e]; PROs

- At data cutoff (October 12, 2023), the median follow-up[f] was 31.5 months (range, 6.1-48.4)

[a]ClinicalTrials.gov. NCT04008030. [b]Patients with ≥ 2 prior lines are randomized only to the NIVO or NIVO + IPI arms. [c]Patients receiving investigator's choice of chemotherapy are eligible to receive NIVO + IPI upon progression (crossover treatment). [d]Confirmed using either immunohistochemistry and/or polymerase chain reaction-based tests. [e]Evaluated using RECIST v1.1. [f]Time between randomization and data cutoff.

Progression-free survival

1L centrally confirmed MSI-H/dMMR	NIVO + IPI (n = 171)	Chemo (n = 84)
Median PFS,[a,b] mo	NR	5.9
95% CI	38.4-NE	4.4-7.8
HR (97.91% CI)	0.21 (0.13-0.35)	
P value	< 0.0001	



No. at risk																	
NIVO + IPI	171	144	132	122	108	95	92	77	64	53	42	37	22	10	9	1	0
Chemo	84	53	29	20	10	6	5	5	3	2	0	0	0	0	0	0	0

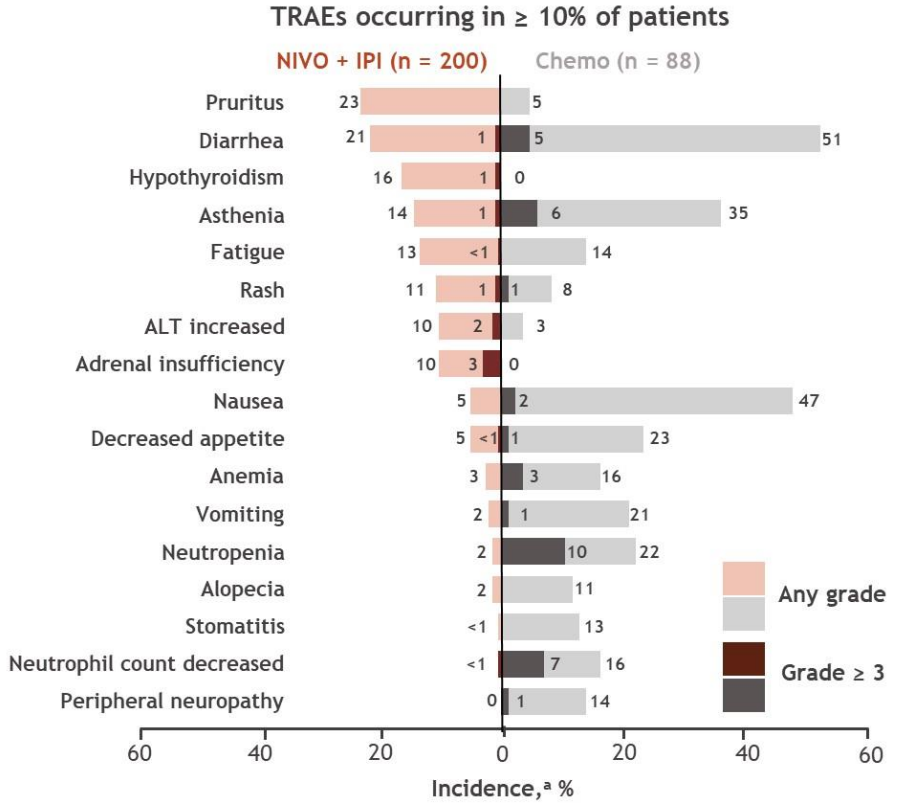
- PFS benefit with NIVO + IPI vs chemo was robust and consistent across the sensitivity and supportive analyses, including PFS by BICR in 1L all randomized patients (HR, 0.32; 95% CI, 0.23-0.46)

[a]Per BICR. [b]Median follow-up in patients with centrally confirmed MSI-H/dMMR, 31.6 months.

Lenz HJ, et al. JCO. 2024;42(16 suppl):3503

First-Line: MSI-H mCRC (ASCO 2024)

Treatment-related adverse events



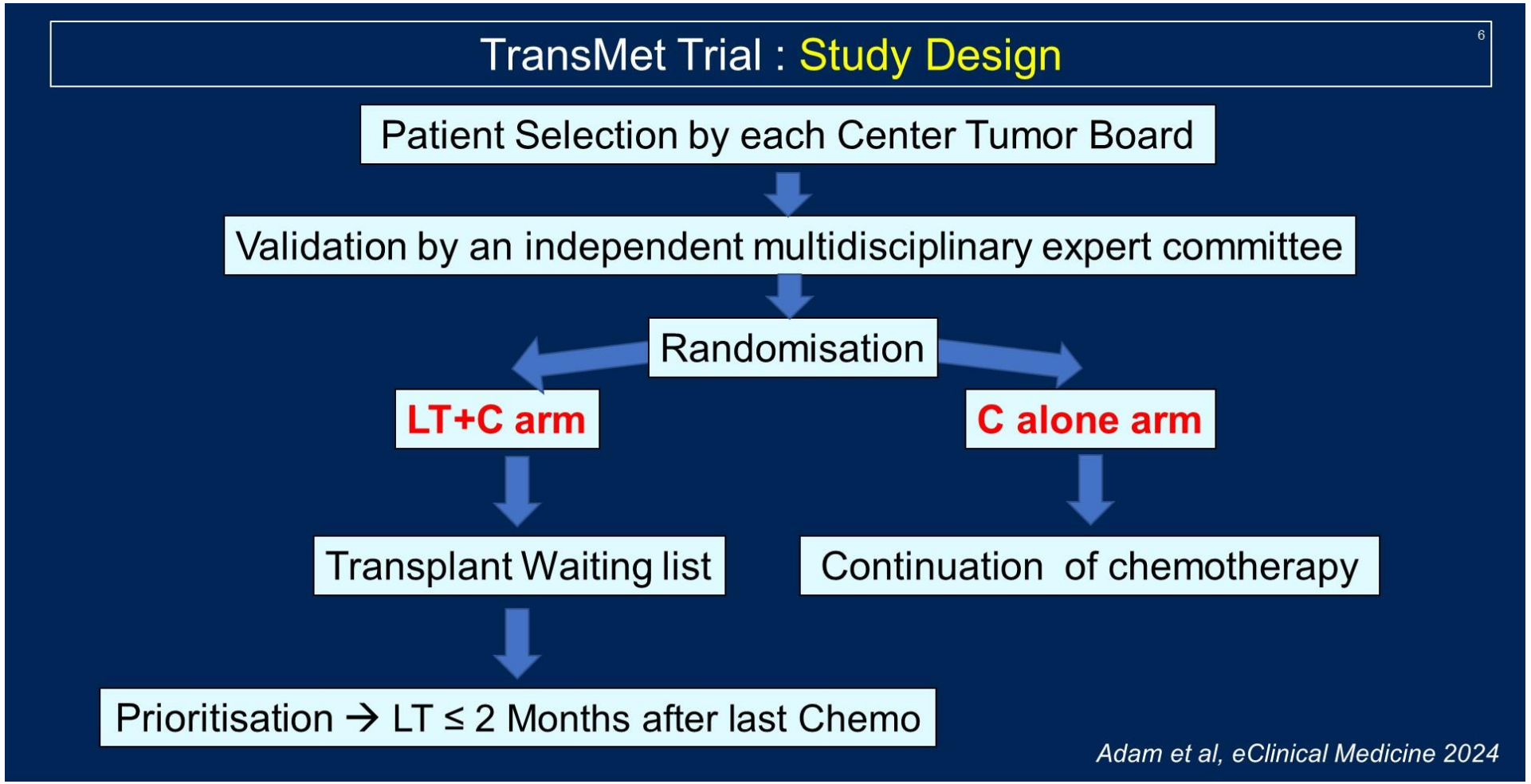
1L all treated patients	NIVO + IPI (n = 200) Any grade	NIVO + IPI (n = 200) Grade 3/4	Chemo (n = 88) Any grade	Chemo (n = 88) Grade 3/4
TRAEs,[a] n (%)				
Any TRAEs	160 (80)	46 (23)	83 (94)	42 (48)
Serious TRAEs	38 (19)	32 (16)	17 (19)	14 (16)
TRAEs leading to discontinuation	33 (17)	23 (12)	28 (32)	9 (10)
Treatment-related deaths, n (%)	2 (1)[b]		0 (0)[c]	

- Any-grade and grade 3/4 TRAEs were less frequent in the NIVO + IPI arm than in chemo arm
- The most common any-grade TRAEs occurring in ≥ 10% of patients were:
  - NIVO + IPI: pruritis (23%), diarrhea (21%), and hypothyroidism (16%)
  - Chemo: diarrhea (51%), nausea (47%), and asthenia (35%)

[a]Includes events reported between first dose and 30 days after last dose of study therapy. [b]Includes 1 event each of myocarditis and pneumonitis. [c]One death (acute myocarditis) was related to crossover treatment.

Lenz HJ, et al. JCO. 2024;42(16 suppl):3503

Unresectable colorectal liver mets (ASCO 2024)



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Adam R, et al. JCO. 2024;42(16 suppl):3500
Adam R, et al. Lancet. 2024 Sep;404:1107-1118

Unresectable colorectal liver mets (ASCO 2024)

TransMet Trial : Eligibility criteria

- ≤ 65 years
- Good performance status (ECOG 0 or 1)
- Confirmed unresectability of CLM by expert surgeons
- Gold standard Resection of the primary
- No extrahepatic disease
- Partial Response or Stability with Chemo : ≥ 3 months, ≤ 3 lines
- No BRAF mutation
- CEA < 80 ng/ml or 50% decrease from baseline
- Platelets count > 80.000 and white blood cell count > 2500

absence of local recurrence on colonoscopy performed within 12 months of enrollment (unless primary tumor resection was performed within the past 12 months)

Adam R, et al. JCO. 2024;42(16 suppl):3500
Adam R, et al. Lancet. 2024 Sep;404:1107-1118

Unresectable colorectal liver mets (ASCO 2024)

TransMet Trial : Patients Demographics at Diagnosis

	LT+C group (n=47)	C alone group (n=47)
Age (years)	52·0 (47·0, 59·0)	55·0 (47·0, 59·0)
Gender, n (%)		
Male	27 (57%)	28 (60%)
Female	20 (43%)	19 (40%)
Right sided primary tumour, n (%)	**7 (15%)**	**7 (15%)**
RAS mutation, n (%)	11 (23%)	12 (26%)
No of nodules at diagnosis (Median IQR)	**20·0** (14·0, 25·0)	**20·0** (12·0, 25·0)
< 10	5 (11%)	7 (15%)
Between 10 and 20	19 (40%)	18 (38%)
> 20	23 (49%)	22 (47%)
Diameter max (mm) at diagnosis (Median IQR)	**55·0** (43·0, 76·0)	**50·0** (27·0, 83·0)
Synchronous (0-1 Mo)	**47 (100%)**	**45 (96%)**
CEA (ng/mL) at diagnosis	305·0 (32·9, 762·0)	81·0 (20·0, 530·0)
CA 19-9 (U/mL) at diagnosis	96·0 (19·7, 800·0)	193·0 (20·9, 1949·0)
Fong's clinical risk score > 2	**42 (89%)**	**42 (89%)**

Adam R, et al. JCO. 2024;42(16 suppl):3500
Adam R, et al. Lancet. 2024 Sep;404:1107-1118

Unresectable colorectal liver mets (ASCO 2024)

TransMet Trial : Patients Demographics at Randomisation

	LT+C group (n=47)	C alone group (n=47)
Type of chemotherapy		
5-FU alone	7 (15%)	1 (2%)
Oxaliplatin-based	12 (26%)	11 (23%)
Irinotecan-based	20 (43%)	27 (57%)
Triplet	8 (17%)	8 (17%)
Targeted therapy agent		
None	2 (4%)	4 (9%)
Anti-VEGF	17 (36%)	16 (34%)
Anti-EGFR	28 (60%)	27 (57%)
Total Number of lines		
1	18 (38%)	23 (49%)
2	21 (45%)	17 (36%)
3	8 (17%)	7 (15%)
Total Number of cycles (Median (IQR)	**21.0** (18.0, 29.0)	**17.0** (12.0, 24.0)
Tumour response		
Partial response	26 (55%)	21 (45%)
Stable disease	21 (45%)	26 (55%)
Delay primary resection – randomisation (Mo)	**16** (12 - 26)	**13·5** (9 - 19)
Delay randomization – LT (days)	51 (30 - 65)	-

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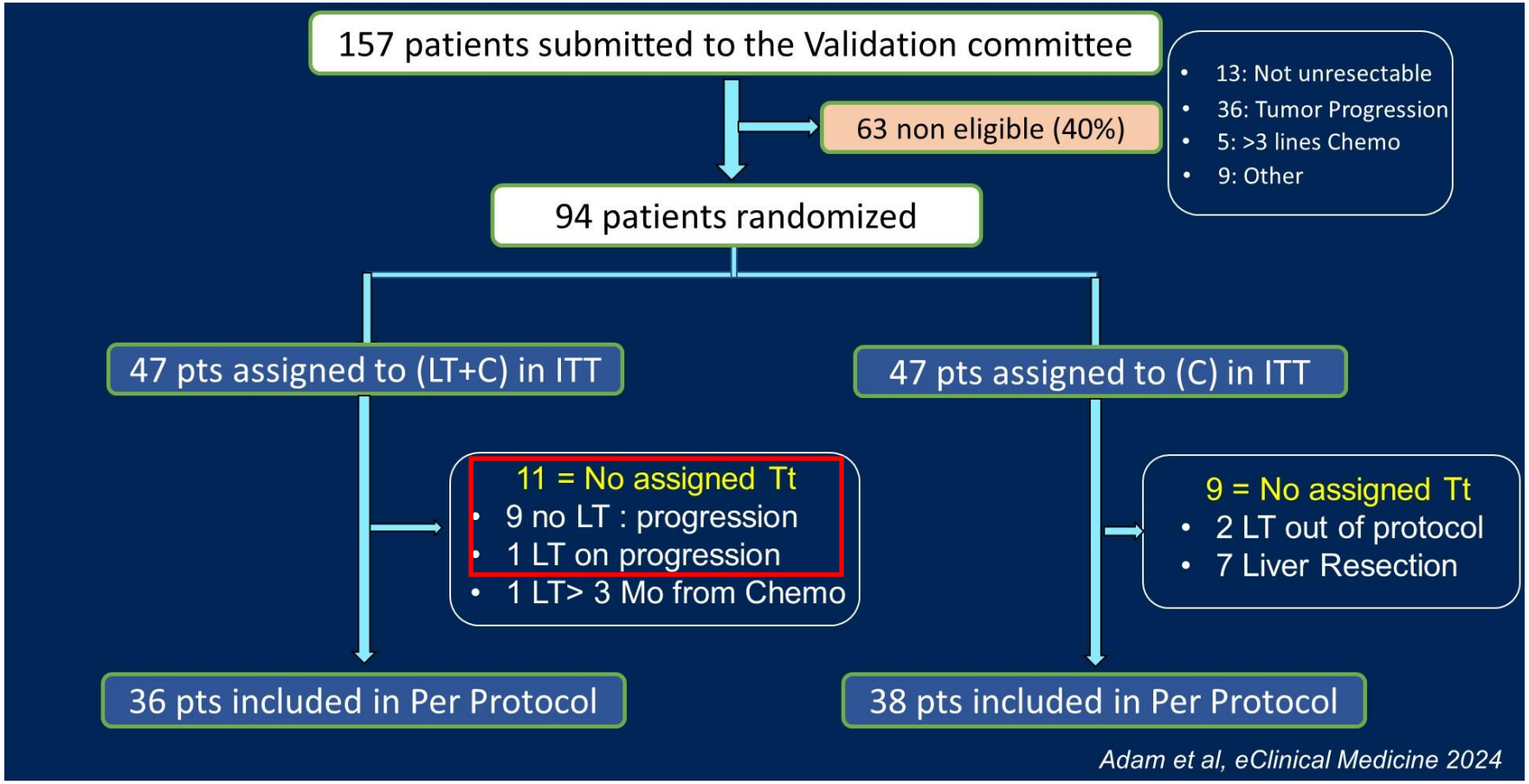
Unresectable colorectal liver mets (ASCO 2024)



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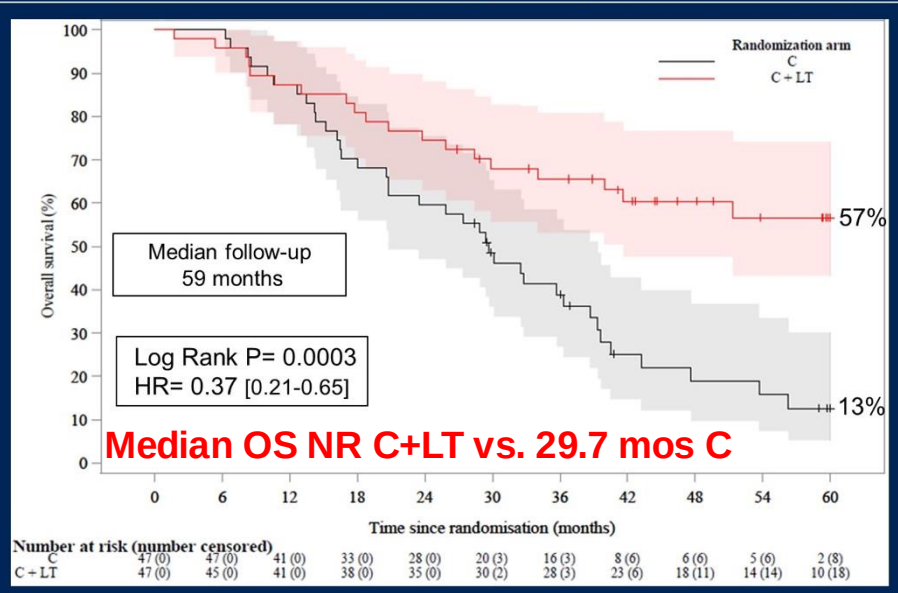
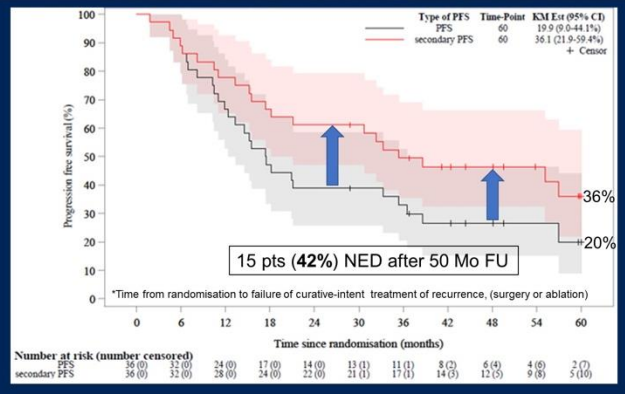
Adam R, et al. Lancet. 2024 Sep;404:1107-1118

Unresectable colorectal liver mets (ASCO 2024)

TransMet Trial : Primary Endpoint 5-Yr OS (ITT)



TransMet Trial : 5-Yr PFS* after Rescue Surgery in LT+C group



TransMet Trial : Recurrence (LT+C) or Progression (C)

Per Protocol population

- 36 Patients (LT+C)
  - 26 Recurrence (72%)
    - Liver (1)
    - Lungs (14)
    - Lymph N (3)
    - Other (5)
    - Multiple (3)
  - Surgery or Ablation : 12/26 (46%)
  - 15 Patients NED (42%)
- 38 Patients (C)
  - 37 Progression (97%)
  - New Regimen Chemotherapy
  - 1 Patient NED (3%)

Median FU: 50 Mo

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Unresectable colorectal liver mets (ASCO 2024)

Rapid access to an organ ready for transplantation →

- agreed with national organ-sharing organizations for transplant within 2 months of interruption of chemotherapy (achieved in 79% of pts, only one patient waited >3 mos after last cycle of chemotherapy

Chemotherapy alone group → primary tumor was resected if the patient was eligible for enrollment w/disease control by postoperative chemotherapy for at least 2 months was mandatory to definitively validate patient eligibility

Supplementary Table S10 (online only): Post-LT chemotherapy

	Total (n=26)
Delay in initiating post-LT chemotherapy, days:	68·0 (44·0, 109·0)
≤30	2 (8%)
31–60	10 (38%)
61–90	7 (27%)
>90	7 (27%)
Duration of post-LT chemotherapy, days	87.5 (62·0, 139·0)
Type of chemotherapy:	
5-FU alone	9 (35%)
oxaliplatin-based	3 (12%)
irinotecan-based	11 (42%)
triplet	1 (4%)
other	2 (8%)
Targeted therapy agent:	
none	19 (73%)
anti-EGFR	6 (23%)
missing	1 (4%)
Number of cycles of chemotherapy post-LT >6 or duration >3 months:	
yes	15 (58%)
no	11 (42%)

5-FU=5-fluorouracil. EGFR=epidermal growth factor receptor. LT=liver transplantation. Data are n (%) or median (interquartile range).

Supplementary Table S6 (online only): Description of patients in the C group who were excluded from the ITT population

Patient number	Allocation group	Cause of exclusion from ITT population	Resection	LT	Delay between randomisation and surgery, months	Did the patient leave the study?	Progression	Treatment	Last visit	Status	Survival time, months
#1	C	Curative intent procedure	Yes	No	12·2	Yes	Yes	Chemotherapy and surgery	M24	Dead	29·4
#2	C	Curative intent procedure	Yes	No	25·8	..	Yes	Chemotherapy and surgery	M36	Alive	36·9
#3	C	Curative intent procedure	Yes	No	NA	..	Yes	Local ablation only	M24	Alive	29·5
#4	C	Curative intent procedure	Yes	No	5·6	No	Yes	Chemotherapy only	M60	Alive	59·7
#5	C	Curative intent procedure	Yes	No	20·7	..	Yes	Surgery only	M24	Alive	28·4
#6	C	Curative intent procedure	Yes	No	28·3	..	Yes	Chemotherapy and surgery	M42	Alive	40·7
#7	C	Curative intent procedure	No	Yes	13·8	Yes	Yes	Chemotherapy only	M9	Dead	20·8
#8	C	Curative intent procedure	No	Yes	..	Yes	NA	NA	M3	Dead	40·5
#9	C	Curative intent procedure	Yes	No	22·4	Yes	Yes	Chemotherapy and surgery	M36	Dead	43·2

C=chemotherapy. ITT=intention-to-treat. LT=liver transplantation. M=month. NA=not available.

Adam R, et al. Lancet. 2024 Sep;404:1107-1118

Take-away points for today's clinic

- **Molecular profiling/NGS should be standard at diagnosis for mCRC (at minimum, MMR/MSI, HER2 IHC/ISH, extended RAS, BRAF testing)**
  - **MMR/MSI testing is mandatory in localized/locally advanced colorectal cancer in consideration for immunotherapy**

- **Liver transplantation plus chemotherapy may be a new standard option for carefully selected patients with permanently unresectable liver metastases from colorectal cancer**
  - **Eye to the future: further validation, multidisciplinary review, transplant center**

Questions?