Synergy and toxicity in combined treatment strategies for GI-cancer

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Why combine radiotherapy with systemic therapy?

Spatial cooperation

Radiation targets locoregional disease.

Systemic therapy controls disease outside the RT field.

Biological cooperation

Systemic therapy and radiation target different cell populations.

The classic 5 R's of fractionated RT

Repair	Reoxygenation	Repopulation	Redistribution	Radiosensitivity
▼ Tumour DNA repair	▲ Oxygenation	▼ Repopulation	▲ Sensitive phase	▲ Intrinsic sensitivity
Inhibit repair of radiation-induced DNA damage between fractions	Counteract hypoxia: normalise vasculature, sensitise or kill hypoxic cells	Keep killing surviving clonogens, limiting regrowth between fractions	Arrest cells in radiosensitive G2/M, or kill radioresistant cells in S phase	Raise intrinsic sensitivity by blocking survival pathways
Examples: **Platinum, 5-FU gemcitabine, PARP-inhibitors**	Examples: **Bevacizumab, mitomycin C**	Examples: **Platinum, EGFR inhibitors**	Examples: **Taxanes, gemcitabine, 5-FU**	Examples: **EGFR inhibitors**

Concurrent drugs tilt the 5R's in favour of tumour kill, and several act on more than one "R"

Mechanisms of synergy: chemoradiation

- **5-FU / Capecitabine**
  Rectal, anal, oesophageal, gastric, pancreatic cancer
- **Gemcitabine**
  Pancreatic cancer
- **Cisplatin / Carboplatin**
  Oesophageal cancer
- **Mitomycin C**
  Anal cancer
- **Oxaliplatin**
  Investigated in rectal cancer: more toxicity, no added benefit

5-FU/capecitabine

Backbone radiosensitizer for GI radiotherapy

MECHANISM

- Thymidylate synthase inhibitor
  - Depletes thymidine triphosphate pools, impairing repair of RT-induced DNA damage
- Fraudulent nucleotides
  - Incorporated in both RNA and DNA leading to futile excision repair, causing strand breaks
- Acts in the radioresistant S phase

IN PRACTICE

5-FU

Protracted venous infusion during RT

Capecitabine

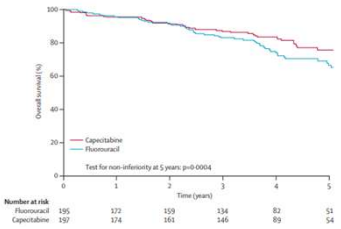
Oral prodrug, taken twice daily on RT days

5-FU vs. capecitabine

Hofheinz trial

Adjuvant: RT (50,4 Gy) + cape 1650 mg/m² vs CVI 5-FU 225 mg/m²

Neoadjuvant: RT (50,4 Gy) + cape 1650 mg/m² vs CVI 5-FU 1000 mg/m² d1–5 and d29–33



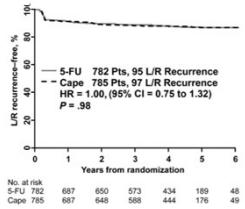
76% vs 67%
5-yr OS, non-inferior (p=0.0004)

6% vs 7%
Local recurrence (p=0.67)

19% vs 28%
Distant metastases (p=0.04)

NSABP R-04

RT (50,4–55,8 Gy) + CVI 5-FU 225 mg/m² vs capecitabine 825 mg/m² bid



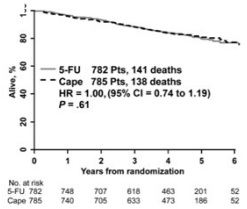


Table 2. Comparison of FU With CAPE: NSABP R-04

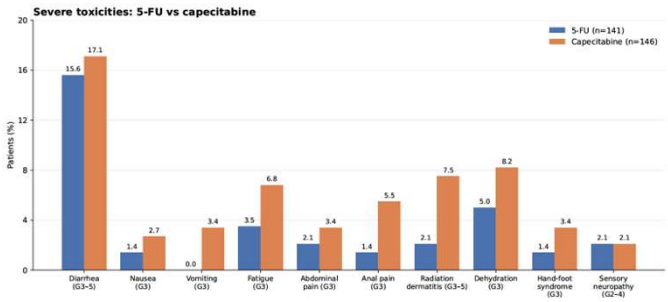
End Point	FU (± OX) No. of Patients	%	95% CI (%)	CAPE (± OX) No. of Patients	%	95% CI (%)	P
pCR	138 of 777	17.8	15.1 to 20.6	161 of 779	20.7	17.9 to 23.7	.14
SSS	463 of 780	59.4	55.8 to 62.8	462 of 779	59.3	55.8 to 62.8	.98
SD	43 of 202	21.3	15.9 to 27.6	44 of 209	21.1	15.7 to 27.2	.95
Grade 3-5 diarrhea*	75 of 639	11.7	9.3 to 14.5	75 of 641	11.7†	9.3 to 14.4	1.0

Capecitabine can replace 5-FU in CRT for LARC

Hofheinz et al, Lancet Oncol 2012; Allegra et al, JNCI 2015; O'Connell et al, JCO 2014

5-FU vs. capecitabine

Toxicity in the NSABP-R04



Capecitabine
Hand-foot syndrome,
fatigue, proctitis

5-FU
Leukopenia,
central line risks (thrombosis, infection)

! Fluoropyrimidine cardiotoxicity
Coronary vasospasm (~1–5%), more with infusional 5-FU:
stop drug, ECG/troponin

! DPYD genotyping before the first dose
- DPD inactivates ~80% of 5-FU; 3–8% carry a variant
- Carriers risk severe or fatal neutropenia, mucositis, diarrhoea
- Partial deficiency: start at 50% dose; complete: avoid

Allegra et al, JNCI 2015

5-FU chemoradiotherapy

TUMOUR	CHEMORADIATION AND KEY FINDING	KEY TRIALS
Rectum	**Preoperative CRT: 5-FU or capecitabine** ↑ Local control and pCR, not OS. Adding concurrent oxaliplatin: more toxicity, no gain	EORTC 22921 · FFCD 9203 STAR-01 · ACCORD 12 · NSABP R-04
Anal canal	**Definitive CRT: 5-FU + mitomycin C** Replaced surgery with sphincter-preserving cure	Nigro · ACT I · ACT II
Oesophagus	**Definitive CRT: 5-FU + cisplatin** Preoperatively: carboplatin/paclitaxel (CROSS) now common	RTOG 85-01
Stomach & pancreas	**Adjuvant or locally advanced CRT** Role narrowed by more effective systemic therapy	INT-0116

Bosset et al (EORTC 22921), NEJM 2006; Gérard et al (FFCD 9203), JCO 2006; Aschele et al (STAR-01), JCO 2011; Gérard et al (ACCORD 12), JCO 2010; Allegra et al (NSABP R-04), JNCI 2015; Nigro et al, Dis Colon Rectum 1974; UKCCCR (ACT I), Lancet 1996; James et al (ACT II), Lancet Oncol 2013; Herskovic et al (RTOG 85-01), NEJM 1992; van Hagen et al (CROSS), NEJM 2012; Macdonald et al (INT-0116), NEJM 2001

Gemcitabine

Potent radiosensitiser with a narrow therapeutic window

MECHANISM

- Deoxycytidine analogue
  Antimetabolite (nucleoside) that blocks DNA synthesis
- S-phase specific
  Kills cells that are copying their DNA
- Very potent radiosensitiser
  Even at non-cytotoxic doses; also sensitises normal tissue

IN PRACTICE

IV infusion over 30 minutes, 300-1000mg/m² usually weekly

Toxicity

Myelosuppression, flu-like symptoms, nausea and vomiting, raised liver enzymes

HUS, pneumonitis (rare)

+ RT: GI mucosal toxicity

Gemcitabine or 5-FU in LAPC?

SCALOP PHASE II TRIAL DESIGN

114 patients
LAPC, 28 UK centres

→

Induction GEMCAP
3 cycles over 12 weeks

→

Randomised (n=74)
if stable or responding; then 1 more GEMCAP cycle

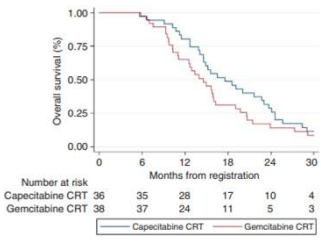
→ **Capecitabine** 830 mg/m² bid on RT days (n=36)

→ **Gemcitabine** 300 mg/m² weekly (n=38)

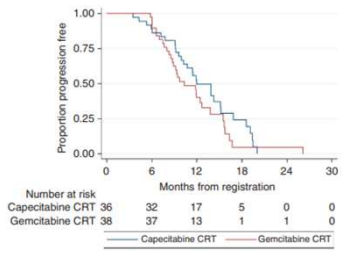
Both arms: 50.4 Gy in 28 fractions

SURVIVAL

Overall survival



Progression-free survival



KEY RESULTS

Capecitabine vs **gemcitabine**

17.6 vs **14.6** months
Median OS (long-term) · HR 0.68, p = 0.19

12.0 vs **10.4** months
Median PFS · HR 0.60, p = 0.12

12% vs **37%**
Any grade 3–4 toxicity during CRT

0% vs **18%**
Grade 3–4 haematological toxicity

Mukherjee et al, Lancet Oncol 2013; Hurt et al, BJC 2017

Gemcitabine or 5-FU in LAPC?

COMMONLY USED REGIMENS

Radiosensitiser	Typical dose
Capecitabine	825 mg/m² twice daily on RT days (Mon–Fri); SCALOP used 830 mg/m²
Infusional 5-FU	200–250 mg/m²/day continuous infusion (often 225), 5–7 days/week throughout RT
Low-dose gemcitabine	300 mg/m² weekly (SCALOP) or up to 600 mg/m² weekly (ECOG E4201)

HOW TO CHOOSE

Capecitabine or 5-FU: preferred

- Less toxic
- Allows full-dose RT with standard target volumes

Gemcitabine: alternative

- E.g. after gemcitabine-based induction, or if a fluoropyrimidine is unsuitable
- Needs a low dose, or fields limited to the gross tumour

Choice depends on the induction regimen and the patient's tolerance

Capecitabine or 5-FU is the preferred radiosensitizer, gemcitabine as an alternative

Cisplatin/Carboplatin

Platinum-based doublets in E/GEJ cancer

MECHANISM

- Platinum-DNA adducts and crosslinks
  Blocks repair of radiation-induced DNA strand breaks
- Cytotoxicity largely oxygen-independent
  Modest radiosensitisation of hypoxic cells

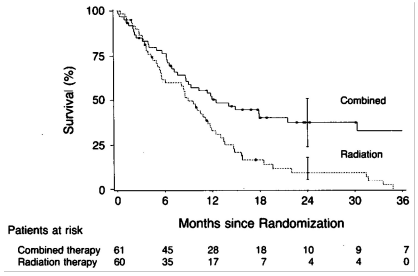
IN PRACTICE

IV infusion
Paired with a complementary drug
RTOG 85-01: 5-FU kills cells in S-phase
CROSS: paclitaxel arrests cells in G2/M
CRT mainly used for SCC and definitive CRT
Adenocarcinoma: FLOT better OS than CROSS (ESOPEC)

RTOG 85-01

Cis-5FU + RT vs RT alone

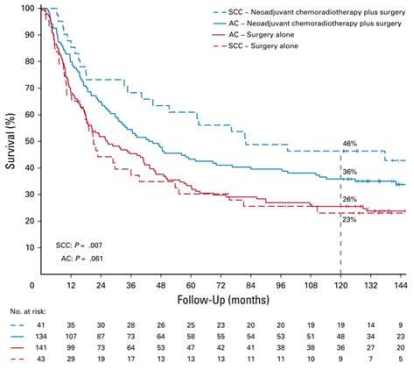
5-yr OS 26% vs 0%



CROSS

Carbo-paclitaxel RT + surgery vs surgery alone

10-yr OS 38% vs 25%



Cooper et al, JAMA 1999; Eyck et al, JCO 2021; Hoeppner et al, NEJM 2025

Platinum-based CRT

DRUG-SPECIFIC TOXICITY

Cisplatin
Nephrotoxicity, ototoxicity, emesis, PNP, needs IV hydration

Carboplatin
Mainly myelosuppression (thrombocytopenia)

Paclitaxel
Neuropathy, alopecia, hypersensitivity, myalgia, arthralgia

TOXICITY OF COMBINED CHEMORADIOTHERAPY

ACUTE · during CRT

- **Oesophagitis & dysphagia:** odynophagia, weight loss, feeding tube
- **Fatigue**
- **Nausea**
- **Anorexia**
- **Neutropenia,** risk of neutropenic fever

SUBACUTE · 1–6 months

- **Radiation pneumonitis:** risk rises with V5, V20 and MLD
- **Pericardial effusion:** related to V30 and MHD

LATE · months–years

- **Stricture & fistula:** dilatation, stent
- **Cardiac disease:** coronary disease, heart failure
- **Lung fibrosis**
- **Hypothyroidism**

Nutrition in the neoadjuvant setting: nasogastric tube or jejunostomy rather than PEG, to preserve the stomach for reconstruction

Mitomycin C

Bioreductive alkylator that complements 5-FU in anal cancer

MECHANISM

- Alkylating DNA crosslinker
- Preferentially kills hypoxic radioresistant cells
- Complementary to 5-FU
  - 5-FU sensitises oxic S-phase cells; MMC adds the hypoxic fraction

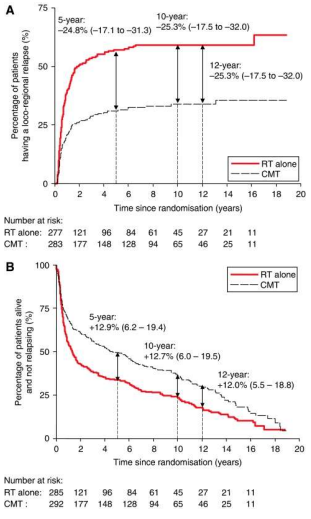
IN PRACTICE

IV bolus
10 mg/m² d1 + d29 (RTOG 98-11) or 12 mg/m² d1 (ACT II)

5-FU or capecitabine
5-FU (1000mg/m²) d1–4 + d29–32, or capecitabine (825mg/m²) bid on RT days

Importance of OTT: delays in RT can impact LC

ACT I



UKCCCR, Lancet 1996; Northover BJC 2010

Mitomycin C

TOXICITY

	ACUTE during CRT and the first weeks after	LATE months to years
Skin	Radiodermatitis (grade 3 moist desquamation)	Fibrosis (ulceration, necrosis rare)
Bowel / anorectum	Radioenteritis (diarrhoea, urgency, frequency)	Faecal incontinence, urgency Anal stenosis, chronic proctitis
Urogenital / sexual	Dysuria / cystitis Vaginal mucositis	Vaginal stenosis, dyspareunia, erectile dysfunction Ovarian insufficiency
Bone / lymphatics	—	Pelvic insufficiency fractures Lymphoedema
Systemic / drug	Fatigue; myelosuppression **(MMC, nadir ~4 wk)** HUS **(MMC, rare)**; HFS, mucositis **(5-FU)**	—

! Vaginal dilators, fertility counselling, HRT, bone health

Mechanisms of synergy: targeted therapies

TARGETED AGENT	MECHANISM WITH RT	GI SITES
Anti-angiogenic therapy bevacizumab	Transient vascular normalisation reduces hypoxia, improves drug delivery	**Rectum:** encouraging pCR in phase II vs historical controls, wound and bowel complications **Pancreas:** no gain vs historical controls (RTOG 0411) ! Risk: GI ulceration, perforation, fistula
EGFR inhibitors cetuximab, panitumumab	Blocks RT-induced survival signalling	**Rectum:** no consistent gain in pCR, added skin and GI toxicity **Oesophagus:** more toxicity, worse survival (SCOPE1, RTOG 0436)
PARP inhibitors veliparib	Block single-strand break repair	**All GI sites:** still investigational
Multikinase TKI sorafenib	Reduced RT-induced survival signalling (RAF) Anti-angiogenic (VEGFR)	**HCC:** concurrent use toxic SBRT *followed* by sorafenib improved OS, PFS (RTOG 1112)
HER2 inhibitors trastuzumab	Blocks HER2 pro-survival signalling in HER2+ tumours	**Oesophagus / GEJ:** no gain in pCR and DFS, no added toxicity (RTOG 1010)

No targeted agent has become standard with RT in GI cancer

Mechanisms of synergy: immunotherapy

6th R: Radio-immunomodulation

CHECKMATE 577 Phase III · n = 794 · oesophageal/GEJ cancer with residual disease after neoadjuvant CRT + R0 resection · nivolumab vs placebo (2:1), 1 year

KEY RESULTS · *final analysis, median FU 78 mo*

DISEASE-FREE SURVIVAL (PRIMARY)

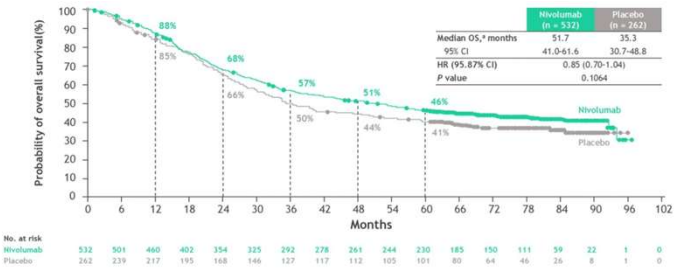
21.8 vs 10.8 mo HR 0.76 (0.63–0.91), p < 0.001

OVERALL SURVIVAL

51.7 vs 35.3 mo HR 0.85 (0.70–1.04), not significant

OS BY PD-L1

CPS ≥1: HR 0.79 vs CPS <1: HR 1.40



More promising than targeted agents: proven after CRT, concurrent use still investigational

Kelly et al, NEJM 2021; Kelly et al, JCO 2025 (ASCO)

Conclusions

CHEMORADIATION

- Fluoropyrimidines are the backbone
  Capecitabine can replace infusional 5-FU
  DPYD testing before the first dose
- Platinum used as doublet
- Mitomycin C complements 5-FU
- Gemcitabine potent but narrow window

TOXICITY

- Radiosensitisers also sensitise normal tissue
  - Conformal RT techniques
  - Avoid treatment breaks
  - Drug-specific monitoring and survivorship care

NEW AGENTS

- No targeted agent is standard with RT
- Immunotherapy: proven after CRT, concurrent still investigational

PREOPANC: long-term results

Neoadjuvant gemcitabine-based chemoradiotherapy vs upfront surgery in resectable and borderline resectable pancreatic cancer

Design Phase III · 16 Dutch centres · 2013–2017 · n = 246



Long-term results median follow-up 59 months · intention-to-treat

20.5% vs 6.5%
5-year overall survival (CRT vs surgery)

HR 0.73
Overall survival, p = 0.025

15.7 vs 14.3 mo
Median overall survival (CRT vs surgery)

Gem = gemcitabine 1000 mg/m² days 1, 8, 15. Small gain in median survival, but substantially more long-term survivors with neoadjuvant CRT.

Versteijne E, et al. J Clin Oncol 2022;40:1220–1230.

Mitomycin C in anal cancer

Adding mitomycin C: better local control, more myelosuppression

Trial	Comparison	Local control / CR	Survival	Toxicity
ACT I	RT vs RT + 5-FU/MMC	**LRF 59 vs 36%**	OS NS	Early morbidity ↑
EORTC 22861	RT vs RT + 5-FU/MMC	**CR 54 vs 80%**	OS NS	Severe: similar
RTOG 87-04	5-FU vs 5-FU + MMC	**Colostomy 22 vs 9%**	**DFS 51 vs 73%**	**G4–5: 7 vs 23%**
RTOG 98-11	Cisplatin* vs MMC	**Colostomy 19 vs 10%**	**OS 70.7 vs 78.3%**	**Haem G3–4: 42 vs 61%**
ACT II	Cisplatin vs MMC	CR 89.6 vs 90.5%	PFS similar	**Haem G3–4: 16 vs 26%**

Without vs with MMC. * RTOG 98-11: cisplatin arm also received induction 5-FU/cisplatin.
Late toxicity similar in ACT I; IMRT lowers acute skin, GI and haematological toxicity (RTOG 0529, phase II).

Mitomycin C + 5-FU + RT remains the standard in anal SCC

20

UKCCCR Lancet 1996; Northover BJC 2010; Bartelink JCO 1997; Flam JCO 1996; Ajani JAMA 2008; Gunderson JCO 2012; James Lancet Oncol 2013; Kachnic IJROBP 2013

Oxaliplatin

Adding oxaliplatin to chemoradiation: more toxicity, no benefit

Trial	Regimen	pCR (%)	Grade 3–4 toxicity (%)	DFS (%)
STAR-01	5-FU CI ± oxaliplatin	16 vs 16	**8 vs 24**	Not reported
ACCORD 12	Cape 45 Gy vs capox 50 Gy	13.9 vs 19.2	**11 vs 25**	3-yr: 67.9 vs 72.7
NSABP R-04	5-FU or cape ± oxaliplatin	17.8 vs 19.5	**28 vs 40**	5-yr: 64.2 vs 69.2
PETACC-6	Cape ± oxaliplatin (+ adjuvant)	11.6 vs 14.0	**14.5 vs 37.2**	5-yr: 71.3 vs 70.5
CAO/ARO/AIO-04*	5-FU ± oxaliplatin (+ adjuvant)	**13 vs 17**	20 vs 23	**3-yr: 71.2 vs 75.9**

* Only trial with a DFS benefit, but oxaliplatin was also given as adjuvant FOLFOX and the control arm used a different 5-FU schedule; no OS benefit. ACCORD 12 also compared 50 vs 45 Gy.

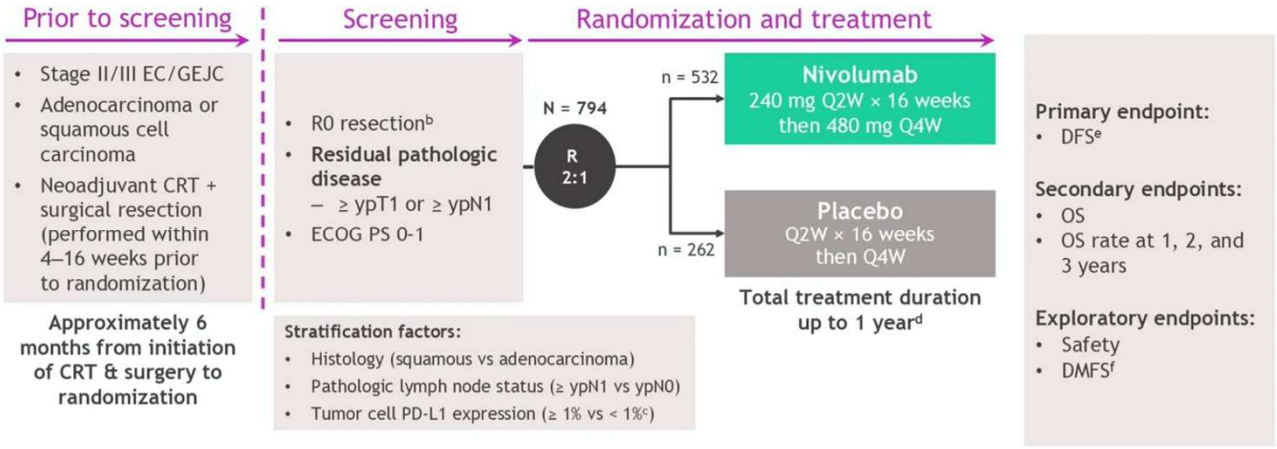
Oxaliplatin is not recommended in the concomitant LARC setting

Aschele et al, JCO 2011; Gérard et al, JCO 2010 & 2012; O'Connell et al, JCO 2014; Allegra et al, JNCI 2015; Rödel et al, Lancet Oncol 2012 & 2015; Schmoll et al, JCO 2021

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CheckMate 577 study design

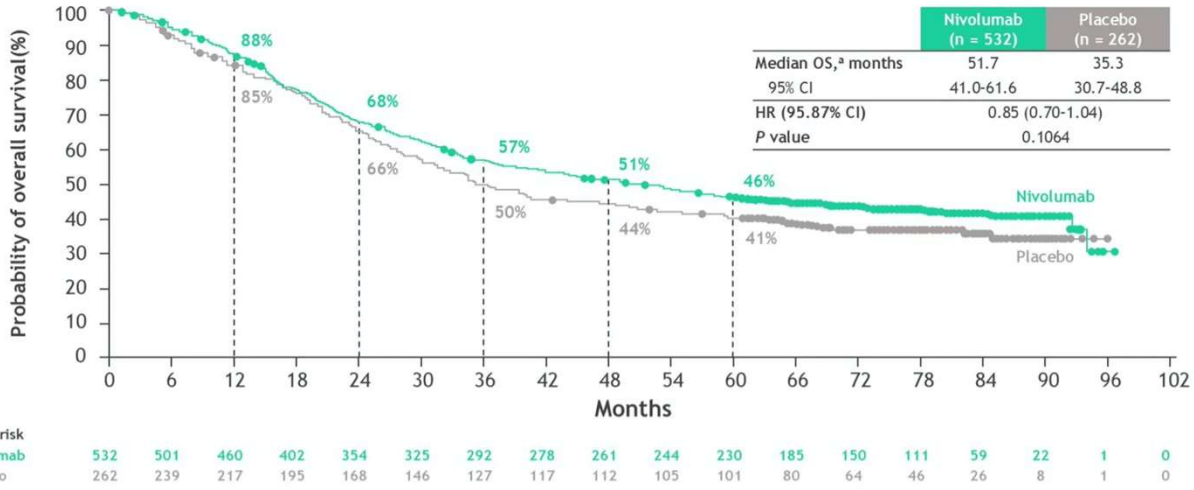
- CheckMate 577 is a global, phase 3, randomized, double-blind, placebo-controlled trial[a]



- At the data cutoff (November 7, 2024), the median follow-up was 78.3 months (range, 60.1-96.6)[g]

[a]ClinicalTrials.gov. NCT02743494. [b]Patients must have been surgically rendered free of disease with negative margins on resected specimens, defined as no vital tumor present within 1 mm of the proximal, distal, or circumferential resection margins. [c]< 1% includes indeterminate/nonevaluable tumor cell PD-L1 expression. [d]Until disease recurrence, unacceptable toxicity, or withdrawal of consent. [e]Assessed by investigator. [f]DMFS is defined as the time between randomization and the first distant recurrence or death, whichever occurs first. [g]Time from randomization date to clinical data cutoff.

Overall survival



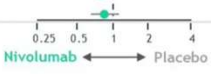
	Nivolumab (n = 532)	Placebo (n = 262)
Median OS,[a] months	51.7	35.3
95% CI	41.0-61.6	30.7-48.8
HR (95.87% CI)	0.85 (0.70-1.04)	
P value	0.1064	

- Median OS was 16.4 months longer and the 5-year OS rate was higher with nivolumab vs placebo, suggesting clinically meaningful improvement in OS, although statistical significance was not met

[a]Median (range) follow-up, 78.3 (60.1-96.6) months.

Overall survival subgroup analysis

Category	Subgroup	Median OS, mo		Unstratified HR (95% CI)
		Nivolumab	Placebo	
Overall	N = 794	51.7	35.3	0.85 (0.70-1.03)
Age, years	< 65 (n = 507)	56.4	36.6	0.83 (0.65-1.06)
	≥ 65 (n = 287)	39.3	35.2	0.87 (0.64-1.19)
Sex	Male (n = 671)	45.5	34.7	0.88 (0.72-1.08)
	Female (n = 123)	NR	48.0	0.70 (0.41-1.19)
Race[a]	White (n = 648)	49.5	34.8	0.84 (0.68-1.03)
	Asian (n = 117)	61.5	NR	1.10 (0.63-1.93)
ECOG PS	0 (n = 464)	60.5	40.3	0.85 (0.66-1.10)
	1 (n = 330)	37.2	32.1	0.84 (0.63-1.12)
Disease stage at initial diagnosis[b]	II (n = 278)	58.2	44.1	0.86 (0.62-1.19)
	III (n = 516)	49.3	32.8	0.84 (0.66-1.06)
Tumor location at trial entry	Esophagus (n = 467)	49.5	31.4	0.69 (0.54-0.88)
	Gastroesophageal junction (n = 327)	54.9	64.2	1.14 (0.83-1.56)
Histologic type[c,d]	Adenocarcinoma (n = 563)	51.7	40.2	0.92 (0.73-1.15)
	Squamous cell carcinoma (n = 230)	50.7	31.4	0.72 (0.51-1.03)
Tumor cell PD-L1 expression[e]	≥ 1% (n = 128)	60.0	51.2	0.88 (0.54-1.43)
	< 1% (n = 571)	47.7	34.6	0.82 (0.66-1.02)
PD-L1 CPS[f]	≥ 1 (n = 585)	45.5	33.5	0.79 (0.64-0.99)
	< 1 (n = 81)	39.2	52.8	1.40 (0.77-2.56)
Pathologic lymph node status[d,g]	ypN0 (n = 333)	92.8	68.5	0.81 (0.58-1.14)
	≥ ypN1 (n = 459)	33.6	28.0	0.86 (0.68-1.10)



[a]Other/not reported: nivolumab, n = 17; placebo, n = 12. [b]Not reported: nivolumab, n = 2. [c]Other, n = 1. [d]Per case report form. [e]Indeterminate/not evaluable/not reported: nivolumab, n = 68; placebo, n = 27. [f]Indeterminate/not evaluable/not reported: nivolumab, n = 97; placebo, n = 31. [g]Unknown, n = 2.

Adjuvant setting

CheckMate 577

SAFETY

Table 2. Adverse Events in the Safety Population.*

Event	Nivolumab (N = 532)		Placebo (N = 260)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
	number of patients with event (percent)			
Any adverse event†	510 (96)	183 (34)	243 (93)	84 (32)
Serious adverse event	158 (30)	107 (20)	78 (30)	53 (20)
Adverse event leading to discontinuation of trial regimen	68 (13)	38 (7)	20 (8)	16 (6)
Any adverse event related to nivolumab or placebo†‡	376 (71)	71 (13)	119 (46)	15 (6)
Serious adverse event related to nivolumab or placebo‡	40 (8)	29 (5)	7 (3)	3 (1)
Related adverse event leading to discontinuation of trial regimen‡	48 (9)	26 (5)	8 (3)	7 (3)
Adverse event related to nivolumab or placebo in ≥5% of patients in either group†				
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)
Hypothyroidism	50 (9)	0	4 (2)	0
Nausea	47 (9)	0	13 (5)	0
Hyperthyroidism	35 (7)	0	1 (<1)	0
Arthralgia	30 (6)	1 (<1)	4 (2)	0
Increase in AST level	29 (5)	2 (<1)	10 (4)	0
Asthenia	28 (5)	0	4 (2)	0
Decreased appetite	26 (5)	0	5 (2)	0

PROM

FACT-E =

EQ-5D-3L utility index score =

EQ-5D-3L VAS ↑ ↑

Kelly et al, NEJM 2021

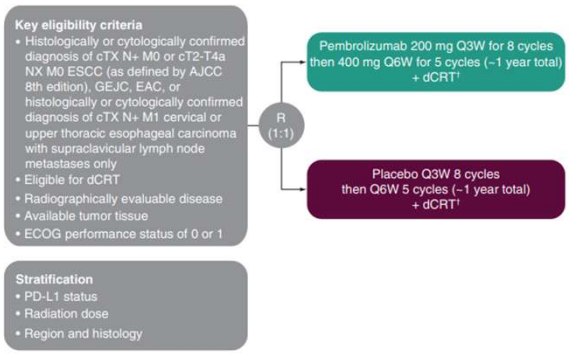


Figure 1. KEYNOTE-975 study design. Definitive chemoradiotherapy consists of definitive radiotherapy + concurrent chemotherapy.
†Patients in both treatment arms will receive a total of 50 Gy (FOLFOX) or 50 or 60 Gy (FP) radiotherapy over 5 weeks (6 weeks for 60 Gy). The choice of mandatory concurrent definitive chemoradiotherapy (FP with 50 Gy or 60 Gy or FOLFOX) will be at the discretion of the study site, but each investigational site must choose FP or FOLFOX and must use the same definitive chemoradiotherapy regimen for every patient at that site (i.e., a site will either be an 'FP 50 Gy site,' an 'FP 60 Gy site,' or a 'FOLFOX site').
EAC: Esophageal adenocarcinoma; dCRT: Definitive chemoradiotherapy; ECOG: Eastern Cooperative Oncology Group; ESCC: Esophageal squamous cell carcinoma; GEJC: Gastroesophageal junction cancer; FP: 5-Fluorouracil and cisplatin; QXW: Every 'X' weeks; R: Randomized.