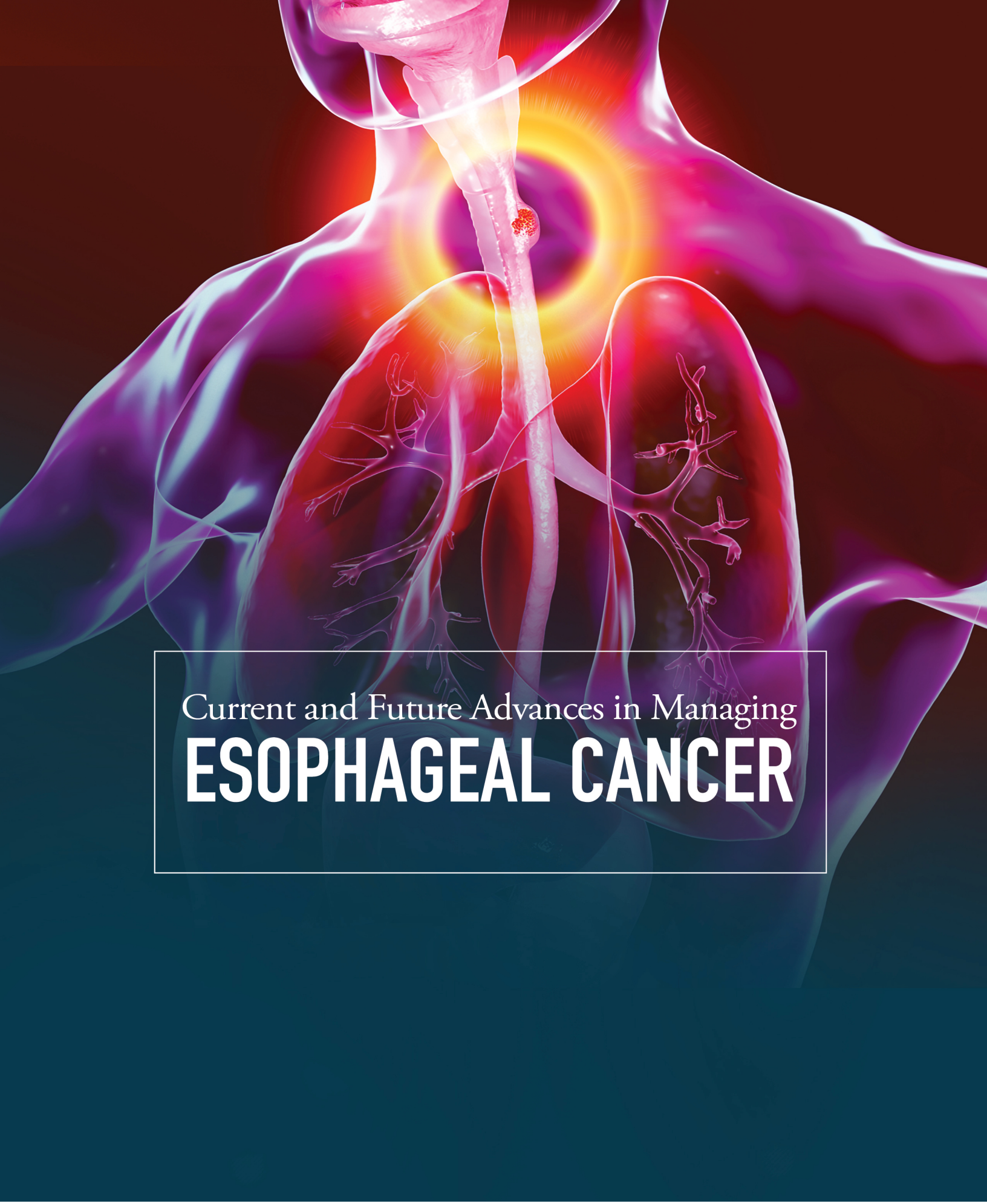

Current and Future Advances in Managing

ESOPHAGEAL CANCER

This activity is provided by Med Learning Group.
This activity is co-provided by Ultimate Medical Academy/Complete Conference Management (CCM).
This activity is supported by an educational grant from Bristol Myers Squibb.

Current and Future Advances in Managing Esophageal Cancer

PROGRAM CHAIR

Daniel Gomez, MD, MBA
Attending Physician
Director, Thoracic Radiation Oncology
Vice Chair of Clinical Operations, Department of Radiation Oncology
Memorial Sloan Kettering Cancer Center
Manhattan, NY

FACULTY PRESENTER

Henry S. Park, MD, MPH
Assistant Professor
Chief of Thoracic Radiotherapy
Yale School of Medicine
New Haven, CT

PROGRAM OVERVIEW

This live, case-based activity will explore the role of screening and surveillance for patients with esophageal cancer (EC) and review clinical trial data on the efficacy and safety of immune checkpoint inhibitors as adjuvant treatment and across lines of therapy.

TARGET AUDIENCE

This educational activity is specifically designed for U.S.-based radiation oncologists, medical oncologists and other healthcare professionals involved in the treatment of patients with EC.

EDUCATIONAL OBJECTIVES

Upon the completion of this program, attendees should be able to:

- Explain the role of radiation oncologists in EC screening and surveillance
- Discuss clinical trial data on the efficacy and safety of ICIs for the treatment of patients with advanced EC across lines of therapy
- Describe data from clinical trials on the efficacy and safety of ICIs used as adjuvant treatment for malignancies including EC

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NURSING CREDIT INFORMATION

Purpose: This program would be beneficial for nurses involved in the care of patients with EC.

CNE Credits: 1.0 ANCC Contact Hour.

CNE Accreditation Statement: Ultimate Medical Academy/Complete Conference Management (CCM) is accredited as a provider of continuing nursing education by the American Nurses Credentialing Center's Commission on Accreditation. Awarded 1.0 contact hour of continuing nursing education of RNs and APNs.

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Dr. Gomez has received consulting fees from Olympus Medical Systems; he has been contracted for research with AstraZeneca, and has received a fee for speaking/teaching a class for Varian.

Dr. Park has nothing to disclose.

CME Content Review

The content of this activity was independently peer reviewed.

The reviewer of this activity has nothing to disclose.

CNE Content Review

The content of this activity was peer reviewed by a nurse reviewer.

The reviewer of this activity has nothing to disclose.

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1. Read the CME/CNE information and faculty disclosures.
2. Participate in the live virtual activity.
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This activity is supported by an educational grant from Bristol Myers Squibb.

Program Agenda

I. Esophageal Cancer (EC): An Overview

- A. Risk factors for esophageal squamous cell carcinoma and adenocarcinoma
- ***B. Whiteboard animation: Pathophysiology of Esophageal Cancer***
- C. Screening recommendations for esophageal cancer
- D. Recommendations on surveillance of Barrett's esophagus
- E. Staging of esophageal and gastroesophageal junction tumors
- F. Depth of invasion and risk of node metastases
- G. Esophageal cancer outcomes

II. Radiation in the Management of Esophageal Cancer

- A. How to choose optimal treatment
- B. Chemoradiation vs radiation therapy alone
- C. Dose-escalation
- D. Preoperative chemoradiotherapy
- E. Principles of radiation planning for esophageal cancer

III. Immune Checkpoint Inhibitors (ICIs) for the Management of Esophageal Cancer

- A. Rationale for using ICIs for esophageal cancer
- B. Recommended immuno-oncology regimens for esophageal cancer
- ***C. Whiteboard animation: Mechanism of action of ICIs as adjuvant therapy for EC***
- D. Clinical trial data on the management of esophageal cancer
  1. ICIs for unresectable locally advanced, recurrent or metastatic disease ICIs following preoperative chemoradiation with resection and residual disease
  2. Managing HER2-positive disease

IV. Case Studies

V. Conclusions

VI. Q&A

Current and Future Advances in Managing Esophageal Cancer

Program Chair

Daniel Gomez, MD, MBA

Attending Physician

Director, Thoracic Radiation Oncology

Vice Chair of Clinical Operations, Department of Radiation Oncology

Memorial Sloan Kettering Cancer Center

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Learning Objectives

- Explain the role of radiation oncologists in esophageal cancer (EC) screening and surveillance
- Discuss clinical trial data on the efficacy and safety of immune checkpoint inhibitors (ICIs) for the treatment of patients with advanced EC across lines of therapy
- Describe data from clinical trials on the efficacy and safety of ICIs used as adjuvant treatment for malignancies including EC

Esophageal Squamous Cell Carcinoma

Epidemiology of ESCC

- Esophageal cancer is the 6th leading cause of cancer death in the world
- ESCC accounts for ~90% of EC cases worldwide
- High incidence in Eastern and Central Asia, East Africa and South America
- Incidence decreasing in the US

Risk Factors for ESCC

- Alcohol
- Tobacco

→ act synergistically

- Lower socio-economic status
- African-American ethnicity
- Lye ingestion
- Tylosis-hyperkeratosis syndrome
- Achalasia

ESCC, esophageal squamous cell carcinoma.

Engel LS, et al. *J Natl Cancer Inst*. 2003;95:1404-1413. Abnet CC, et al. *Gastroenterol*. 2018;154:360-373.

Esophageal Adenocarcinoma

Incidence rates for EAC have increased dramatically in the US, with most of the increased incidence involving tumor of the GEJ and gastric cardia

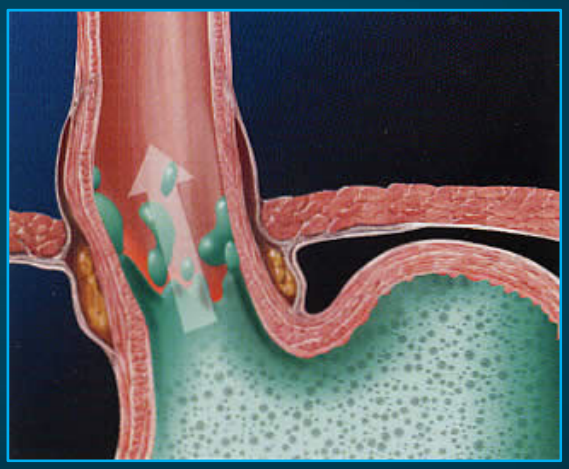
Risk Factors for EAC

1. Barrett's esophagus

2. GERD

3. Obesity

4. Tobacco (weak)



EAC, esophageal adenocarcinoma; GEJ, gastroesophageal junction; GERD, gastroesophageal reflux disease.

Engel LS, et al. *J Natl Cancer Inst*. 2003;95:1404-1413. Lagergren J, et al. *N Engl J Med*. 1999;340:825-831.

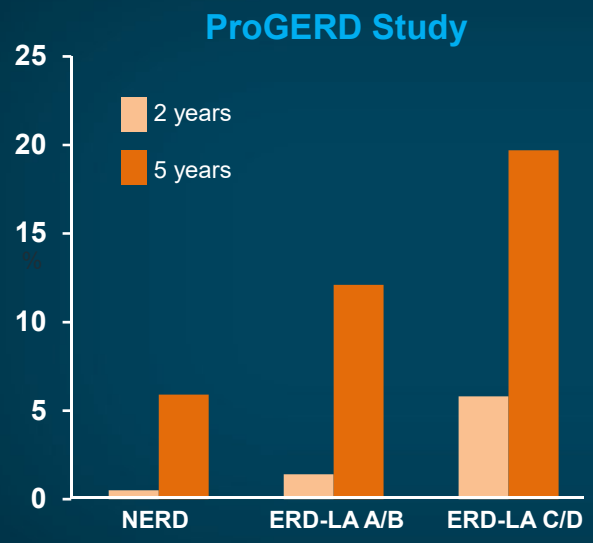
Screening Recommendation for Esophageal Cancer

Screening Recommendation for Esophageal Cancer

- Efforts at early detection of squamous cell cancer with cytological or endoscopic screening in countries with high incidence of disease have failed to demonstrate a benefit
- Although the progression from Barrett's esophagus to EAC is well recognized, there is insufficient evidence that population screening for Barrett's esophagus reduces cancer mortality

Dawsey SM, et al. *Cancer Epidemiol Biomarkers Prev*, 1997;6:121-130. Wei WQ, et al. *J Clin Oncol.* 2015;33:1951-1957. Gerson LB, et al. *Am J Med.* 2002;113:499-505.

Development of Barrett's Esophagus



- The total proportion of patients who progressed from NERD, LA grade A/B, or LA grade C/D to endoscopic or confirmed Barrett's esophagus at 5 years was 9.7% (n = 241)
- Multivariable analysis of risk factors that increase risk of progression to BE:
  - Baseline esophagitis
  - Alcohol intake
  - Regular PPI intake

NERD, nonerosive reflux disease; ERD-LA A/B, erosive reflux disease-Los Angeles grade A/B; ERD-LA C/D, erosive reflux disease-Los Angeles grade C/D; PPI, proton pump inhibitor.
Labenz J, et al. *Am J Gastroentrol*, 2006;101:2457-2462. Malfertheiner P, et al. *Aliment Pharmacol Ther*. 2012;35:154-164.

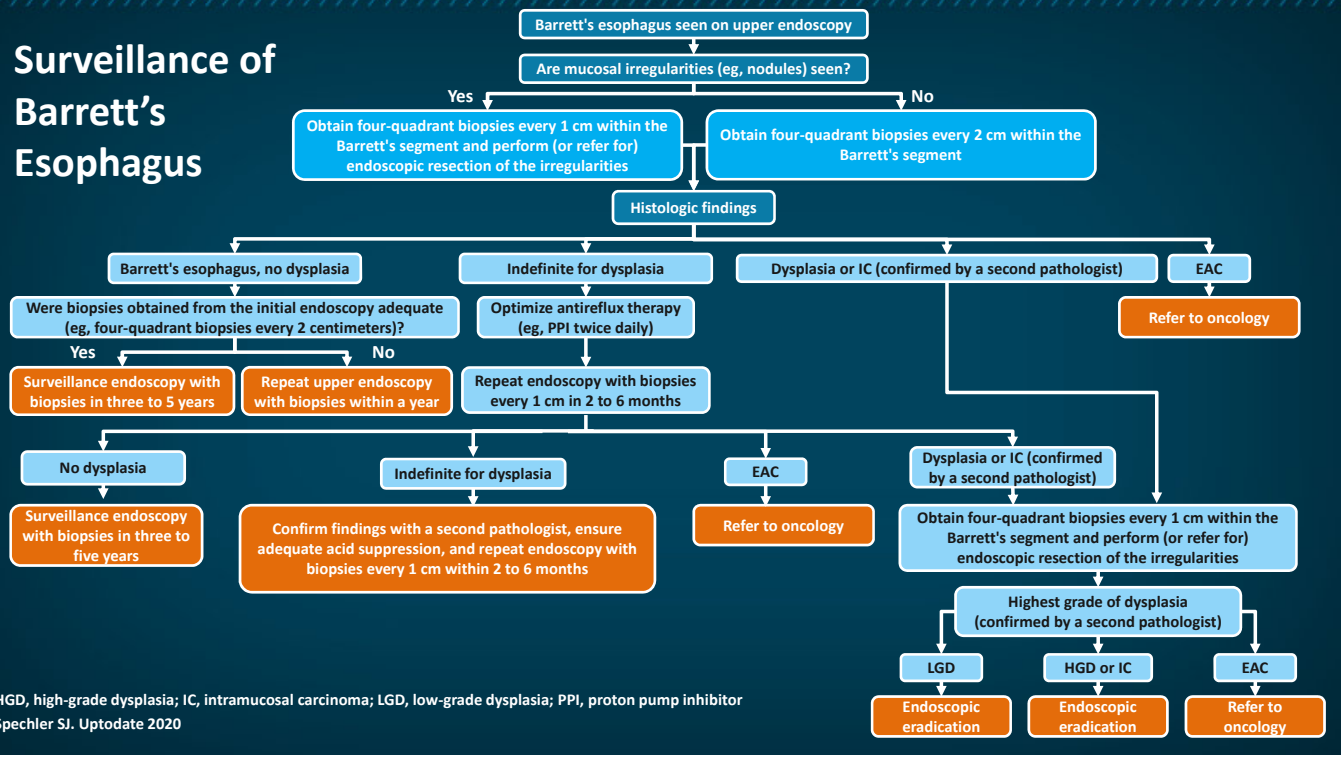
ASGE Guideline on Screening and Surveillance of BE

Summary of Recommendations and Quality of Evidence

Statement	Strength of Recommendation	Quality of Evidence
1. In patients with nondysplastic BE, we suggest performing surveillance endoscopy compared with no surveillance.	Conditional	Very low
2. There is insufficient evidence on the effectiveness of screening for BE. However, if screening endoscopy for BE is performed, we suggest a screening strategy that identifies an at-risk population. An at-risk population is defined as individuals with a family history of EAC or BE (high risk) or patients with GERD plus at least 1 other risk factor (moderate risk).	NA	NA
3. In patients with BE undergoing surveillance, we recommend using chromoendoscopy, including virtual chromoendoscopy and Seattle protocol biopsy sampling, compared with white-light endoscopy with Seattle protocol biopsy sampling.	Strong	Moderate
4. In patients with BE undergoing surveillance, we suggest against routine use of confocal laser endomicroscopy compared with white-light endoscopy with Seattle protocol biopsy sampling.	Conditional	Low
5. In BE patients with high-grade dysplasia/IMC or nodules, we recommend against routine use of EUS to differentiate mucosal vs submucosal disease.	Strong	Moderate
6a. In patients with known or suspected BE, we suggest using WATS-3D in addition to Seattle protocol biopsy sampling compared with white-light endoscopy with Seattle protocol biopsy sampling.	Conditional	Low
6b. In patients with BE undergoing surveillance, there is insufficient evidence to recommend for or against routine of VLE.	No recommendation	NA

ASGE, American Society for Gastrointestinal Endoscopy; BE, Barrett's esophagus; EUS, endoscopic ultrasound; NA, not applicable; IMC, intramucosal cancer; VLE, volumetric laser endomicroscopy; WATS-3D, wide-area transepithelial sampling with computer-assisted 3-dimensional analysis.
ASGE STANDARDS OF PRACTICE COMMITTEE, Qumseya B, et al. *Gastrointest Endosc*. 2019;90:335-359.e2.

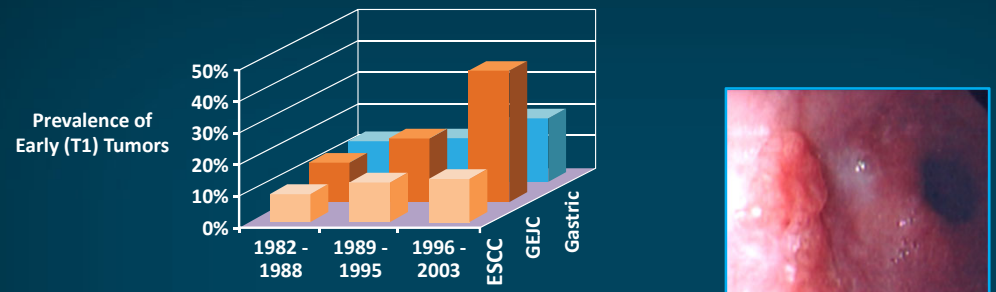
Surveillance of Barrett's Esophagus

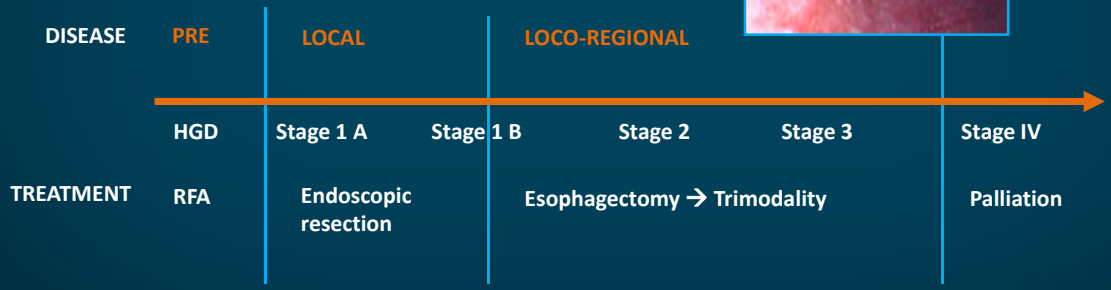


HGD, high-grade dysplasia; IC, intramucosal carcinoma; LGD, low-grade dysplasia; PPI, proton pump inhibitor

Spechler SJ. Uptodate 2020

Esophageal Cancer: A Diverse Disease

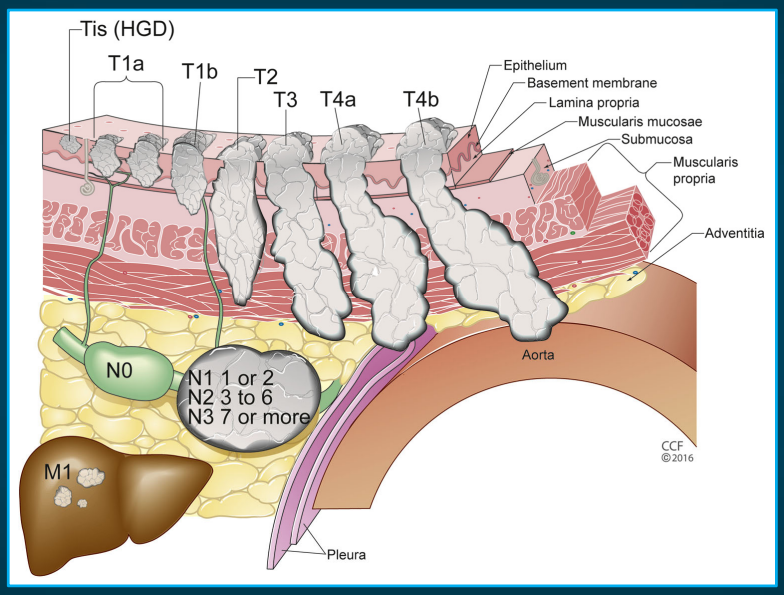




HGD, high-grade dysplasia; RFA, radiofrequency ablation.

Stein HJ, Siewert JR. *World J Surg*. 2004;28:520-525. Hoppo T, Jobe BA. *Thoracic Surg Clin*. 2013;23:471-478.

Eighth Edition Staging of Esophageal and GEJ Tumors



Rice TW, et al. *J Thorac Oncol.* 2017;12:36-42.

Eighth Edition Staging of Esophageal and GEJ Tumors (continued)

ypTNM

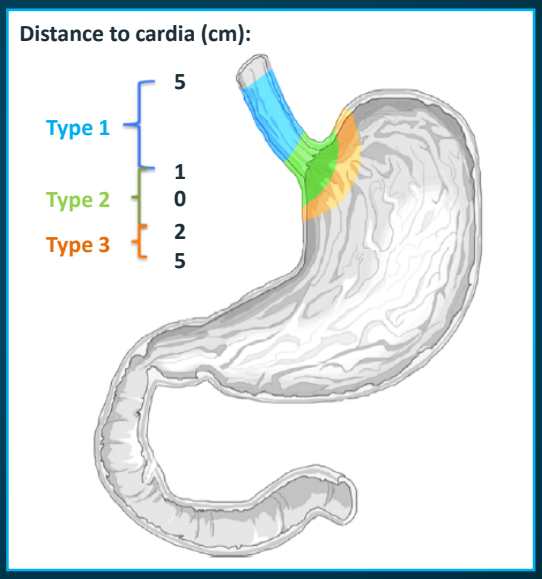
	N0	N1	N2	N3	M1
T0	I	IIIA	IIIB	IVA	IVB
Tis	I	IIIA	IIIB	IVA	IVB
T1	I	IIIA	IIIB	IVA	IVB
T2	I	IIIA	IIIB	IVA	IVB
T3	II	IIIB	IIIB	IVA	IVB
T4a	IIIB	IVA	IVA	IVA	IVB
T4b	IVA	IVA	IVA	IVA	IVB

- Added new postneoadjuvant pathologic stage groups (ypTNM)
- GEJ cancer definition changed:
  - Epicenter >2 cm distal from GEJ now considered gastric cancer
    - Former definition: any GEJ cancer with ≤5 cm gastric extension considered esophageal
- Stage IVA grouping created for very locally advanced (T4b or N2-3) tumors

Rice TW, et al. *J Thorac Oncol.* 2017;12:36-42.

Gastroesophageal Junction: Treat Like Gastric or Esophageal Cancer?

- Siewert classification
  - I: >1 cm above GEJ
  - II: 1 cm above to 2 cm below GEJ
  - III: 2-5 cm below GEJ
- Gastric cancers are more typically treated with surgery and chemotherapy alone

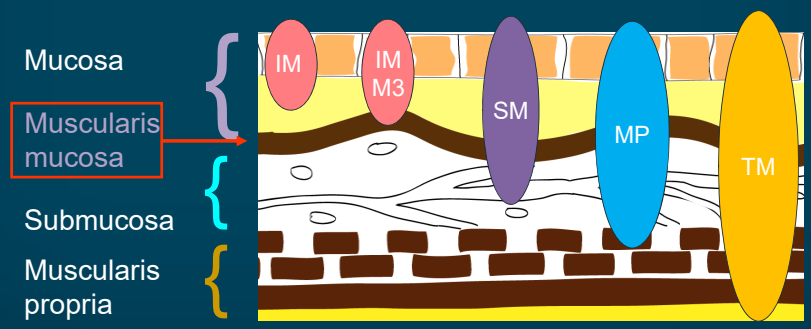


Rishi A, et al. *Gastrointestinal Malignancies.* 2017;21-50.

Depth of Invasion and Risk of Node Metastases

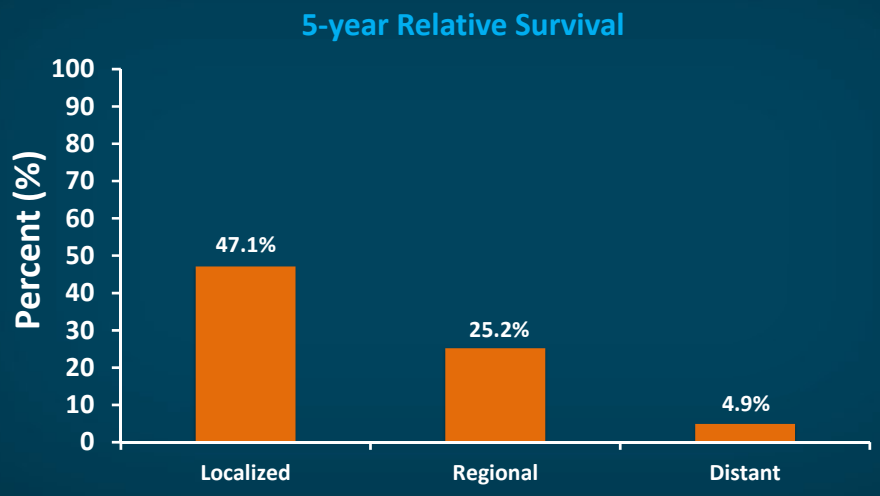
Frequency of Lymph Node Metastases with Esophageal Cancer

	T1a	T1M	T1b	T2	T3
Adenocarcinoma	0-2%	1-2%	21%	75%	85%
Squamous cell	0-2%	12-15%	30%	70-80%	>80%



Shimada H, et al. *Am J Surg.* 2006;191:250-4. Kodama M, et al. *Surgery.* 1998;123:432-9.

Outcomes of Esophageal Cancer Remain Poor



SEER. Cancer Stat Facts: Esophageal Cancer. https://seer.cancer.gov/statfacts/html/esoph.html

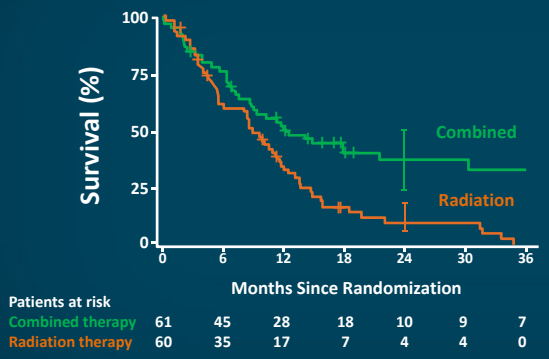
How to Choose Optimal Treatment?

- Adenocarcinoma: trimodality therapy often preferred
- Squamous: surgery deferred if complete response to CRT
- No level 1 evidence directly comparing surgery vs RT as definitive treatment
  - So esophageal literature broadly falls into 2 categories:
    1) Defining the optimal treatment without surgery
    2) Defining the optimal treatment with surgery

CRT, chemoradiation therapy; RT, radiation therapy.

Chemoradiation Is Superior to Radiation Therapy Alone

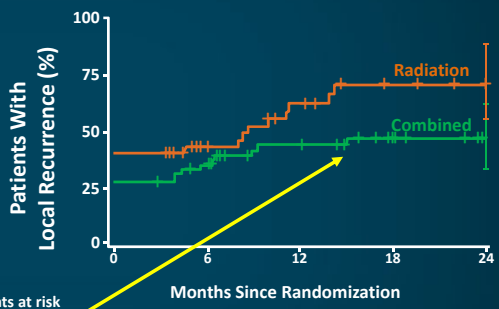
- Median survival: 12.5 mo vs 8.9 mo
- 5-year OS: 26% vs 0%



Patients at risk

Combined therapy	61	45	28	18	10	9	7
Radiation therapy	60	35	17	7	4	4	0

Time to Local Recurrence



Patients at risk

Combined therapy	55	34	24	16	10
Radiation therapy	50	20	11	5	3

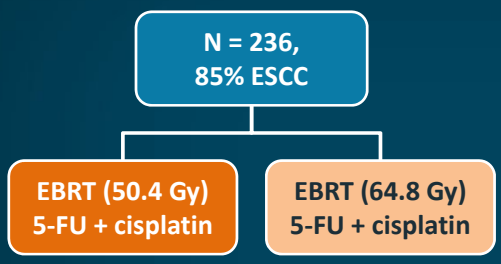
- However, local failure still high (44%) with CRT
  - Higher than distant metastasis rate

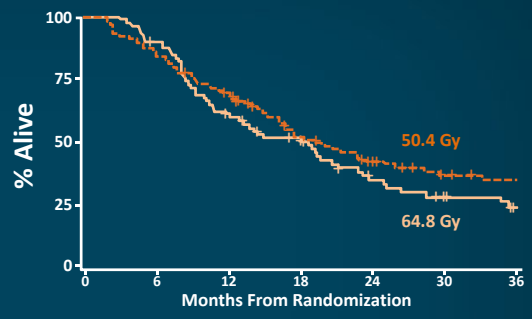
OS, overall survival.

Herskovic A, et al. *N Engl J Med*. 1992;326:1593-1598. Cooper JS, et al. *JAMA*. 1999;281:1623-7.

Dose-Escalation: INT 0123

Randomized phase 3 trial of combined-modality therapy for esophageal cancer[1]





- No difference in OS or local/regional control
  - 11 treatment-related deaths in high-dose arm vs 2 in standard-dose arm
  - 8/11 deaths occurred ≤50.4 Gy
- Analysis by delivered dose: still no benefit
- No benefit with brachytherapy either (Radiation Therapy Oncology Group Study 9207)[2]

5-FU, 5-fluorouracil; EBRT, external beam RT.

1. Minsky BD, et al. *J Clin Oncol*. 2002;20:1167-1174. 2. Gaspar LE, et al. *Cancer*. 2000;88:988-995.

3 New Trials With Dose Escalation Data Did Not Demonstrate Clear Benefit

Trial	Study Design	Outcomes
Xu Y, et al[1]	305 patients with ESCC randomized to 50 Gy or 60 Gy with cisplatin and docetaxel	No differences in LRPFS, PFS, OS, or toxicity between 50 Gy and 60 Gy groups
ARTDECO[2]	260 patients randomized to 50.4 Gy or 61.6 Gy with carboplatin/paclitaxel	No difference in local PFS or OS; 3-year LRPFS was 53% and 63% for the 50.4 Gy and 61.6 Gy arms (*P*= .08)
CONCORDE[3]	160 patients randomized to 50 Gy or 66 Gy combined with FOLFOX-4	Ongoing

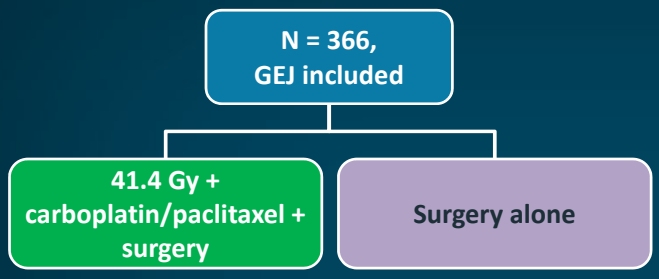
FOLFOX-4, oxaliplatin plus leucovorin and 5-FU; LRPFS, locoregional PFS; PFS, progression-free survival.

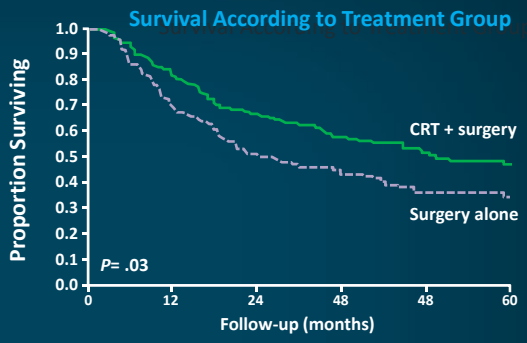
1. Xu Y, et al. ASCO 2018. Abstract 4013. 2. Hulshof MCCM, et al. GI ASCO 2020. Abstract 281. 3. Crehange G, et al. ASCO 2017. Abstract 4037.

Nonoperative Therapy: Conclusions

- Long-term survival in 1 of 4 patients treated with CRT alone
- CRT clearly superior to RT alone
- Local failure rates remain high (nearly 50%)
- Dose escalation has not clearly improved outcomes
- Surgery for distal ESCC is a gray area

CROSS Trial: Solidifying Benefit of Preoperative CRT





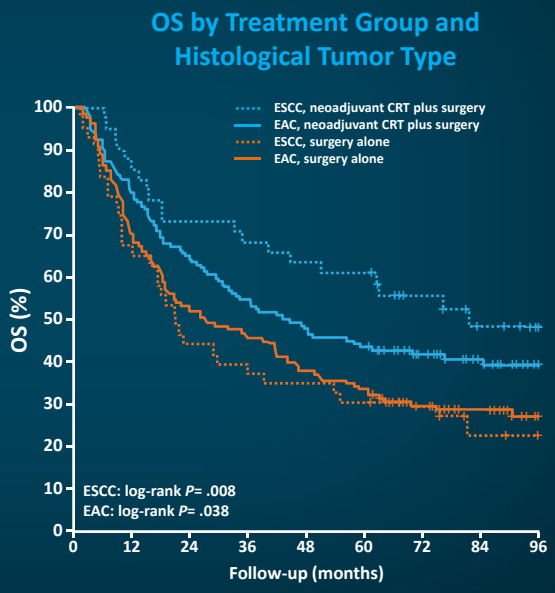
- Largest-ever RCT of preoperative CRT
- 5-year OS: 47% with CRT vs 34% with surgery alone
- Median OS: 49.4 mo with CRT vs 24.0 mo with surgery
- Complete resection (R0) achieved in 92% of CRT patients vs 69% in the surgery group (*P*< .001)
- Pathological complete response achieved in 29% of patients who underwent resection after CRT (*P*< .008)
  - 49% ESCC vs 23% EAC)
- Postoperative mortality unchanged (4%)

RCT, randomized controlled trial.

Van Hagen P, et al. *N Engl J Med.* 2012;366:2074-2084.

CROSS Trial: Long-term Results

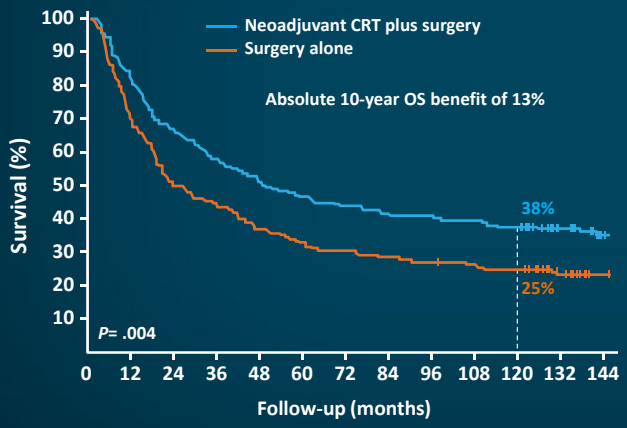
- Median 84 months of follow-up of surviving patients from CROSS trial
- Trial confirmed benefit of neoadjuvant CRT plus surgery compared with surgery alone:
  - 5-year OS: 47% vs 33%
- Significant benefit for both ESCC and EAC

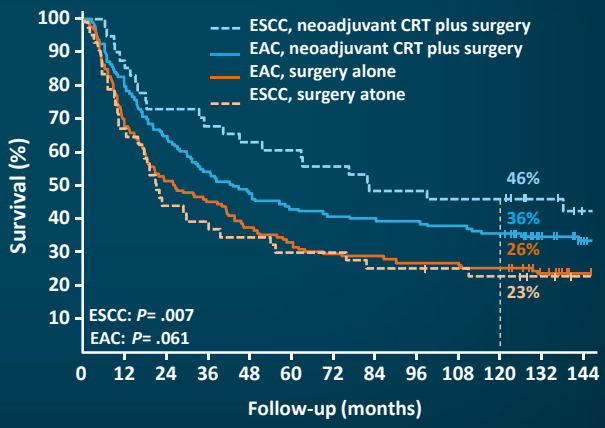


Shapiro J, et al. *Lancet Oncol*. 2015;16:1090-1098.

CROSS Trial: 10-Year Outcomes of Neoadjuvant CRT Plus Surgery

- Patients receiving neoadjuvant CRT had greater OS (HR, 0.70) and reduced risk of death from esophageal cancer (HR, 0.60)





HR, hazard ratio.

Eyck BM, et al. *J Clin Oncol.* 2021;JCO2003614. doi:10.1200/JCO.20.03614

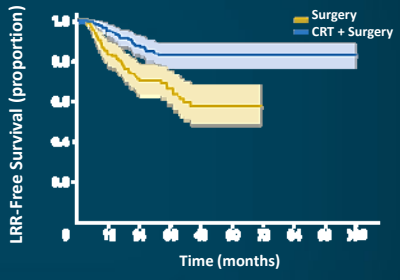
Why Does Preoperative Chemoradiation Work?

- Patterns of recurrence after CRT + surgery or surgery alone in the CROSS trials

Tumor Recurrences in Relation to Radiation Target Volumes in Patients Undergoing CRT Plus Surgery (n = 213)

Recurrence	Infield	Outfield	Borderline	Unknown	Total
LRR only	2	2	2	1	7
Distant only	0	43	0	1	44
LRR plus distant	9	11	3	0	23
Total	11	56	5	2	74

LRR-Free Survival

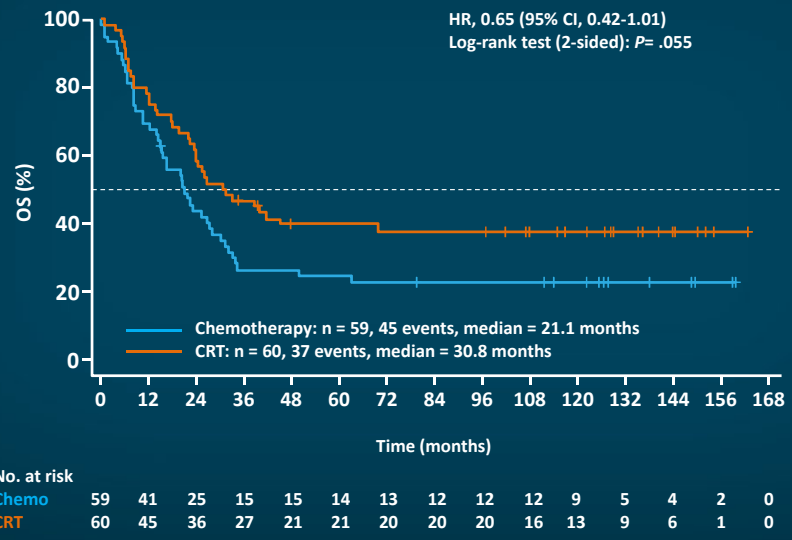


- Recurrence within the radiation target volume occurred in only 5% of patients
- Preoperative CRT reduced LRR from 34% to 14% (*P*< .001)
- Peritoneal carcinomatosis reduced from 14% to 4% with CRT (*P*< .001)

LRR, locoregional recurrence.

Oppendijk V, et al. *J Clin Oncol.* 2014;32:385-391.

POET Study: CRT + Surgery Improves Survival vs Chemo + Surgery



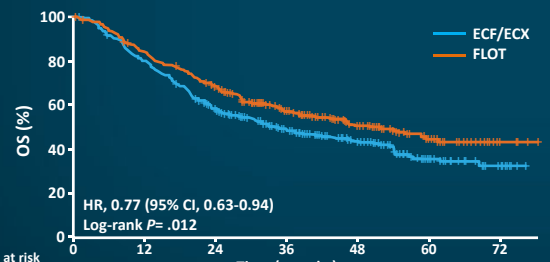
No. at risk														
Chemo	59	41	25	15	15	14	13	12	12	12	9	5	4	2	0
CRT	60	45	36	27	21	21	20	20	20	16	13	9	6	1	0

Stahl M, et al. *Eur J Cancer.* 2017;81:183-190.

FLOT4: Perioperative Chemotherapy Without RT

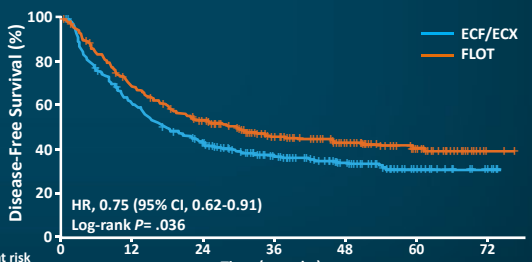
- 716 patients with locally advanced, resectable gastric/GEJ adenocarcinoma randomized to perioperative ECF/ECX (epirubicin/cisplatin/5-FU or capecitabine) or FLOT (docetaxel/oxaliplatin/leucovorin/5-FU)
- Median OS was increased in the FLOT group compared with ECF (50 mo vs 35 mo; HR, 0.77; 95% CI, 0.63-0.94)

Overall Survival



No. at risk (no. censored)							
ECF/ECX	360 (0)	287 (2)	202 (12)	126 (55)	83 (88)	33 (126)	9 (148)
FLOT	356 (0)	297 (4)	231 (13)	140 (71)	87 (111)	39 (152)	5 (185)

Disease-Free Survival

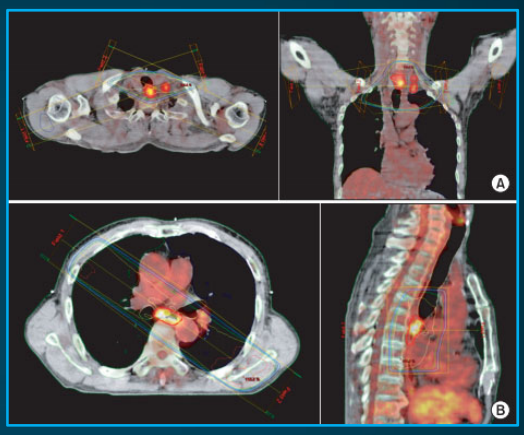


No. at risk (no. censored)							
ECF/ECX	360 (0)	215 (7)	145 (16)	90 (50)	56 (78)	24 (106)	6 (124)
FLOT	356 (0)	241 (6)	175 (17)	102 (70)	66 (101)	35 (129)	3 (160)

Al-Batran SE, et al. *Lancet.* 2019;393:1948-1957.

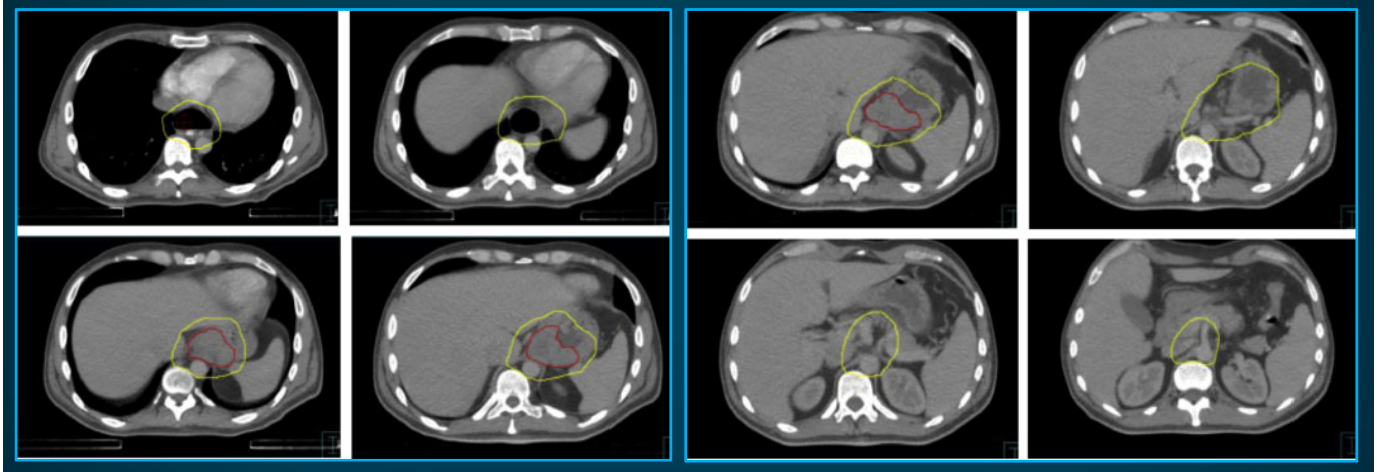
Principles of Radiation Planning for Esophageal Cancer

- General simulation guidelines
  - Arms up in alpha cradle (cervical with mask)
  - IV and oral contrast
  - 4DCT ± gating
  - No large meals 3 hours before simulation
- Target volume guidelines
  - Gross tumor volume (GTV): use EGD and PET
  - Clinical target volume (CTV)
    - Typically 3- to 4-cm proximal and distal mucosal margin
    - 1-cm radial margin
  - Tumors above carina: SCV nodes treated
  - Distal esophagus/GEJ tumors: celiac nodes treated



4DCT, 4-dimensional computed tomography; EGD, esophagogastroduodenoscopy; IV, intravenous; PET, positron emission tomography; SCV, supraclavicular.
Seol KH, Le EJ. *Radiat Oncol J*. 2014;32:31-42.

Contouring Guidelines for Radiation Oncologists



Consensus contours with GTV in red.
Wu AJ, et al. *Int J Radiat Oncol Biol Phys*. 2015;92:911-920.

Is There a Role for Radiation Therapy or Surgery in Stage IV Disease?

- Common strategy in several types of cancer
- No guidelines concerning treatment of synchronous or metachronous distant metastases of esophageal cancer
- Often patients are treated with palliative chemotherapy

Current guidelines for oligometastasic disease in different cancers

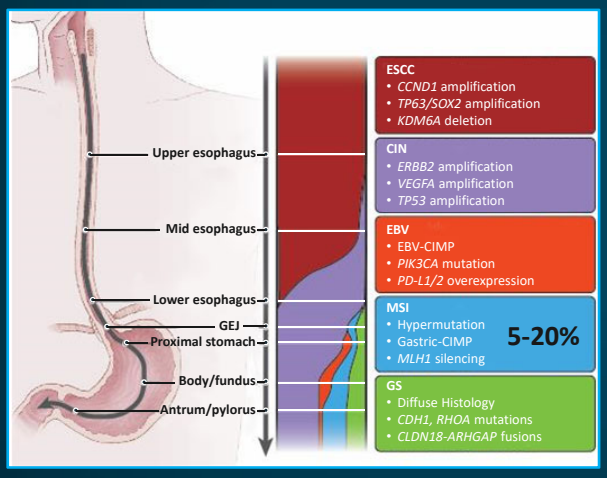
Year, cancer	Guidelines	Oligometastatic disease definition	Recommendation
2018, breast	4th ESO—ESMO International Consensus Guidelines for Advanced Breast Cancer	Low volume metastatic disease with limited number and size of metastatic lesions (up to 5 and not necessarily in the same organ), potentially amenable for local treatment, aimed at achieving a complete remission status	A multimodal approach, including locoregional treatments with curative intent, should be considered for these selected patients
2019, NSCLC	Pan-Asian adapted Clinical Practice Guidelines for the management of patients with metastatic non-small-cell lung cancer: a CSCO—ESMO initiative endorsed by JSMO, KSMO, MOS, SSO and TOS	Synchronous or metachronous metastases with one to five metastases	Discussed within a multidisciplinary tumor board and inclusion in clinical trials is preferred. Surgery in oligometastatic disease is limited, and the relative contribution of surgery versus RT as local treatment modality has not been established yet
2017, colorectal	Pan-Asian adapted ESMO consensus guidelines for the management of patients with metastatic colorectal cancer: a JSMO—ESMO initiative endorsed by CSCO, KACO, MOS, SSO and TOS	Characterized by the existence of metastases at up to 2 or occasionally 3 sites and 5 or sometimes more lesions, confined to a single organ (most frequently the liver), or a few organs	Systemic therapy is the standard of care and should be considered as the initial part of every treatment strategy. Locally ablative treatment strategies could be selected accordingly

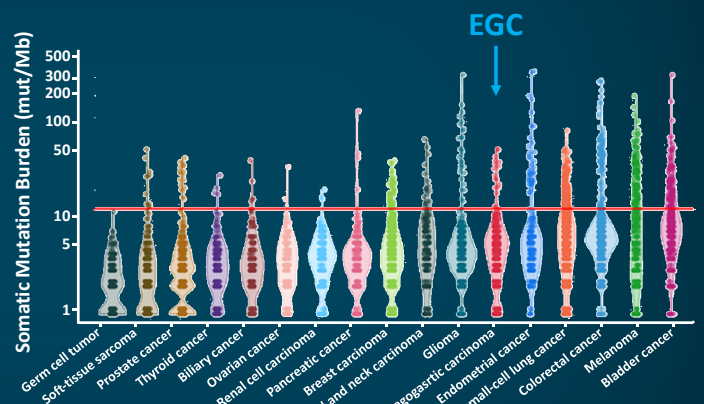
Jin P, et al. *Clin Res Hepatol Gastroenterol.* 2020;44:638-645.

ICIs for the Management of Esophageal Cancer

Why Use IO for Esophageal Cancer?

- MSI-H and high TMB are known biomarkers for immunotherapy response





CIN, gastroesophageal adenocarcinomas with chromosomal instability; EBV, gastric adenocarcinomas with EBV infection; IO, immuno-oncology; MSI, gastric adenocarcinomas with microsatellite instability; GS, gastric adenocarcinomas with genomic stability; mut/Mb, mutations per megabase; MSI-H, microsatellite instability-high; TMB, tumor mutational burden.

TCGA Research Network. *Nature*. 2017;541:169-175. Zehir et al. *Nat Med*. 2017;23:703-713.

Recommended IO Regimens in Esophageal Cancer

Postoperative Therapy
Preferred Regimens • Nivolumab only after preoperative chemoradiation with R0 resection and residual disease (category 1)
Other Recommended Regimens • Capecitabine and oxaliplatin • Fluorouracil and oxaliplatin

→ CheckMate 577

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

First-Line Therapy
• Oxaliplatin is generally preferred over cisplatin due to lower toxicity
• HER2 overexpression negative ► Fluoropyrimidine (fluorouracil or capecitabine), oxaliplatin, and nivolumab (PD-L1 CPS ≥5) for adenocarcinoma only (category 1) ► Fluoropyrimidine (fluorouracil or capecitabine), oxaliplatin, and pembrolizumab (PD-L1 CPS ≥10) ► Fluoropyrimidine (fluorouracil or capecitabine), cisplatin, and pembrolizumab (PD-L1 CPS ≥10) (category 4) ► Fluoropyrimidine (fluorouracil or capecitabine) and oxaliplatin ► Fluoropyrimidine (fluorouracil or capecitabine) and cisplatin

→ CheckMate 649

→ KEYNOTE-590

CPS, combined positive score.

NCCN Guidelines. Version 1.2021. Available at: https://www.nccn.org/professionals/physician_gls/PDF/esophageal.pdf

Immunotherapy in Esophageal & Gastric Cancers

Adenocarcinoma

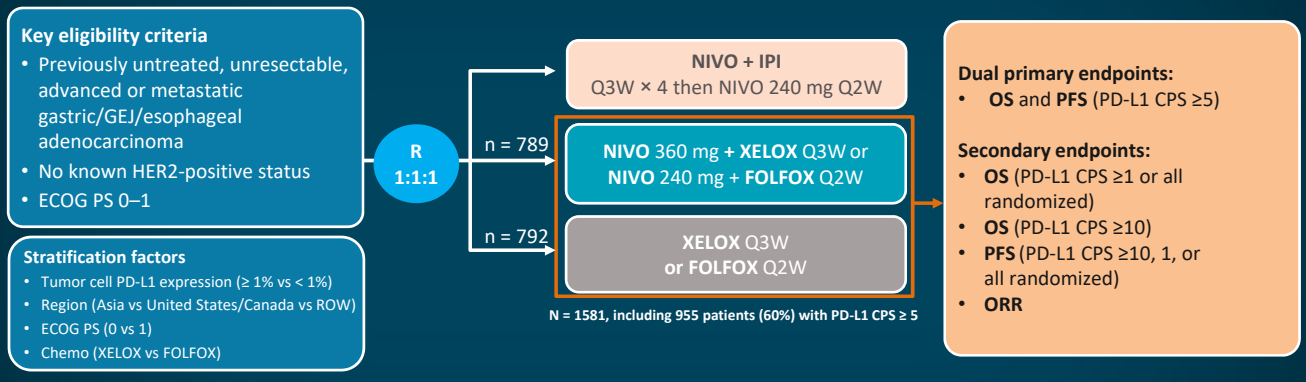
- Nivolumab approved for patients with advanced or metastatic gastric cancer, gastroesophageal junction cancer, or esophageal adenocarcinoma in combination with fluoropyrimidine- and platinum-containing chemotherapy, regardless of PD-L1 expression status
- Pembrolizumab approved in ≥3rd line in the US for PD-L1 CPS ≥1, TMB ≥10 or MSI-H tumors
- Minimal benefit in PD-L1 CPS <1 patients

Squamous cell cancer

- Nivolumab approved ≥2nd-line irrespective of PD-L1 status
- Pembrolizumab approved in PD-L1 CPS ≥10

CheckMate 649 Study Design

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



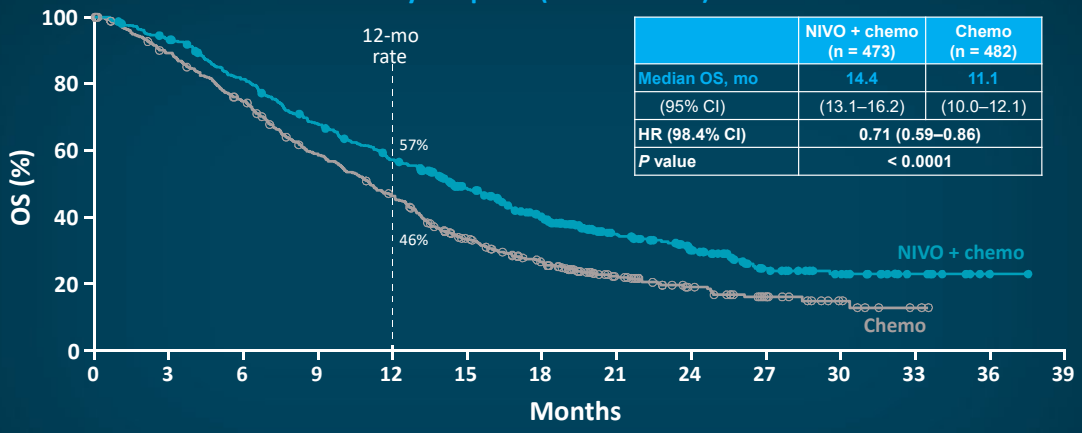
- At data cutoff (May 27, 2020), the minimum follow-up was 12.1 months

ECOG PS, Eastern Cooperative Oncology Group Performance Status; FOLFOX, 5-FU/leucovorin/oxaliplatin; IPI, ipilimumab; NIVO, nivolumab; ROW, rest of world; XELOX, capecitabine/oxaliplatin.

Moehler M, et al. ESMO 2020. Abstract LBA6_PR.

CheckMate 649: Overall Survival

Primary Endpoint (PD-L1 CPS ≥5)



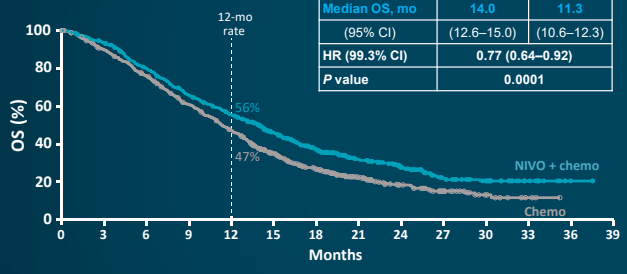
	NIVO + chemo (n = 473)	Chemo (n = 482)
Median OS, mo	14.4	11.1
(95% CI)	(13.1–16.2)	(10.0–12.1)
HR (98.4% CI)	0.71 (0.59–0.86)	
P value	< 0.0001	

- 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

Moehler M, et al. ESMO 2020. Abstract LBA6_PR.

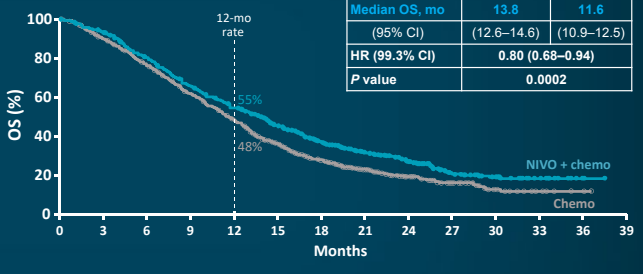
CheckMate 649: Overall Survival

PD-L1 CPS ≥ 1



	NIVO + chemo (n = 641)	Chemo (n = 655)
Median OS, mo	14.0	11.3
(95% CI)	(12.6–15.0)	(10.6–12.3)
HR (99.3% CI)	0.77 (0.64–0.92)	
P value	0.0001	

All randomized



	NIVO + chemo (n = 789)	Chemo (n = 792)
Median OS, mo	13.8	11.6
(95% CI)	(12.6–14.6)	(10.9–12.5)
HR (99.3% CI)	0.80 (0.68–0.94)	
P value	0.0002	

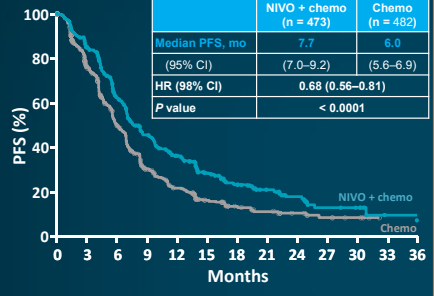
- Superior OS benefit in PD-L1 CPS ≥ 1 and all randomized patients with NIVO + chemo versus chemo

Moehler M, et al. ESMO 2020. Abstract LBA6_PR.

CheckMate 649: Progression-free Survival

Primary endpoint (PD-L1 CPS ≥5)

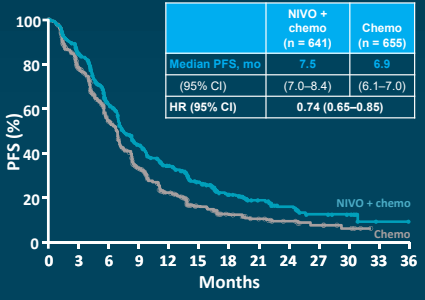
	NIVO + chemo (n = 473)	Chemo (n = 482)
Median PFS, mo	7.7	6.0
(95% CI)	(7.0–9.2)	(5.6–6.9)
HR (98% CI)	0.68 (0.56–0.81)	
P value	< 0.0001	



12-mo rate: NIVO + chemo, 36%; chemo, 22%

PD-L1 CPS ≥1

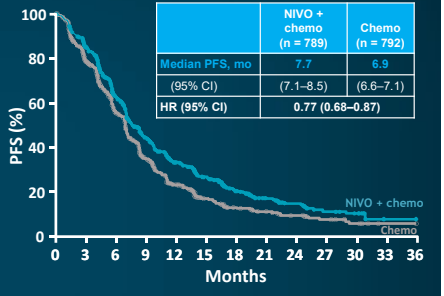
	NIVO + chemo (n = 641)	Chemo (n = 655)
Median PFS, mo	7.5	6.9
(95% CI)	(7.0–8.4)	(6.1–7.0)
HR (95% CI)	0.74 (0.65–0.85)	



NIVO + chemo, 34%; chemo, 22%

All randomized

	NIVO + chemo (n = 789)	Chemo (n = 792)
Median PFS, mo	7.7	6.9
(95% CI)	(7.1–8.5)	(6.6–7.1)
HR (95% CI)	0.77 (0.68–0.87)	



NIVO + chemo, 33%; chemo, 23%

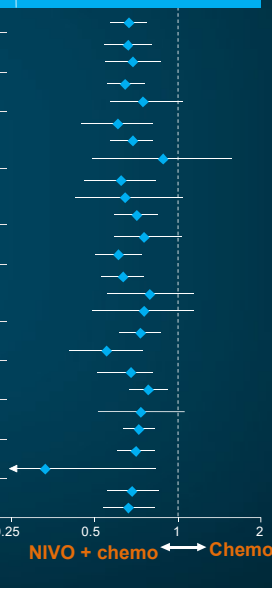
- Superior PFS, 32% reduction in the risk of progression or death with NIVO + chemo versus chemo in patients whose tumors expressed PD-L1 CPS ≥5
- PFS benefit with NIVO + chemo versus chemo in PD-L1 CPS ≥ 1 and all randomized patients

Moehler M, et al. ESMO 2020. Abstract LBA6_PR.

CheckMate 649: Overall Survival Subgroup Analysis

- OS consistently favored NIVO + chemo versus chemo across multiple pre-specified subgroups

Category (PD-L1 CPS ≥5)	Subgroup	Median OS, months		Unstratified HR for death
		NIVO + chemo	Chemo	
Overall (N = 955)		14.4	11.1	0.70
Age, years	< 65 (n = 552)	14.8	11.0	0.69
	≥ 65 (n = 403)	14.3	11.2	0.72
Sex	Male (n = 680)	14.4	10.8	0.67
	Female (n = 275)	14.4	12.1	0.78
Race	Asian (n = 236)	16.1	11.5	0.63
	White (n = 655)	14.0	11.1	0.71
	Other (n = 64)	9.8	10.6	0.93
Region	Asia (n = 228)	15.6	11.8	0.64
	US/Canada (n = 137)	16.8	12.6	0.67
	ROW (n = 590)	13.6	10.4	0.74
ECOG PS	0 (n = 397)	17.6	13.8	0.79
	1 (n = 557)	12.6	8.8	0.63
Primary tumor location	GC (n = 667)	15.0	10.5	0.66
	GEJC (n = 170)	14.2	13.1	0.84
	EAC (n = 118)	11.2	11.3	0.78
Tumor cell PD-L1 expression	< 1% (n = 724)	14.2	11.6	0.75
	≥ 1% (n = 230)	16.2	8.8	0.56
Liver metastases	Yes (n = 408)	13.1	9.8	0.63
	No (n = 518)	15.5	12.0	0.76
Signet ring cell carcinoma	Yes (n = 141)	12.1	9.0	0.71
	No (n = 814)	15.1	11.3	0.69
MSI status	MSS (n = 846)	14.4	11.1	0.73
	MSI-H (n = 34)	Not reached	8.8	0.33
Chemotherapy regimen	FOLFOX (n = 479)	14.3	11.3	0.71
	XELOX (n = 454)	15.0	11.0	0.69



Moehler M, et al. ESMO 2020. Abstract LBA6_PR.

PD-L1 Testing

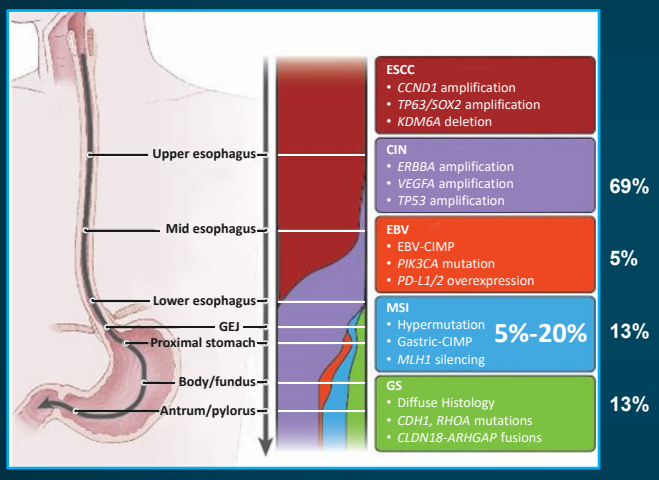
The FDA-approved anti-PD1 drug and PD-L1 assessment

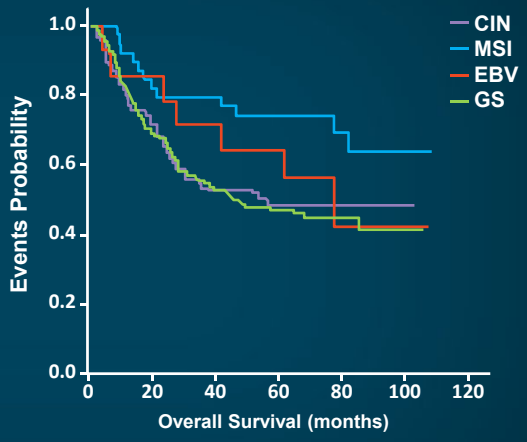
mAb	Drug	FDA approval	Scoring assessment	Overall response score
22C3 pharmDx (Dako North America, Inc)	Pembrolizumab	NSCLC	TPS <1%: No PD-L1 expression TPS = 1-49%: PD-L1 expression TPS ≥50%: High PD-L1 expression	NCT02007070 TPS ≥1%: 15.4% (95% CI: 4.4-34.9%) TPS ≥50%: 27.3% (95% CI: 6.0-61.0%)
		Gastric or GEJ adenocarcinoma	CPS <1: No PD-L1 expression CPS ≥1: PD-L1 expression	NCT02335411 CPS ≥1: 13.3% (95% CI: 8.2-20.0%)
28-8 pharmDx (Dako North America, Inc)	Nivolumab	Melanoma	TC <1%: No PD-L1 expression TC ≥1%: PD-L1 expression	NCT01721746 PD-L1 ≥5%: 5.49% (95% CI: 1.92-19.08%) PD-L1 <5%: 1.13% (95% CI: 0.44-3.16%)
		Non-squamous NSCLC	TC <1%: No PD-L1 expression TC ≥1%: PD-L1 expression	NCT01673867 PD-L1 ≥1% 30.9% (95% CI: 22.9-39.9%) PD-L1 <1%: 9.3% (95% CI: 45-16.4%)
SP 142 Assay (VENTANA MEDICAL SYSTEMS, INC)	Atezolizumab	NSCLC	TC ≥50%: PD-L1 expression IC ≥10%: PD-L1 expression TC <50% and IC <10%: PD-L1 expression	NCT01846416 PD-L1 expression: 16.1% (95% C19.32 to 25.2%)
SP263 Assay (VENTANA MEDICAL SYSTEMS, INC)	Durvalumab	Urothelial Carcinoma	TC ≥25%: High PD-L1 expression ICP >1% and IC+ ≥25%: High PD-L1 expression ICP = 1% and IC+ = 100%: High PD-L1 expression None of the criteria for PD-L1 High Status are met: Low/negative PD-L1 expression	NCT01693562 High PD-L1: 27.6% (95% CI: 19.0-37.5%) Low/negative PD-L1: 5.1% (1.4-12.5%)

E1L3N (Leica Bond RX) IHC with PD-L1 clone E1L3N (Cell Signaling) has been validated against clone 22C3 (pharmDx) and found to be comparable.

Ma J, et al. *Diagn Pathol*. 2018;13:91.

The Genomic Spectrum of Esophagogastric Cancer

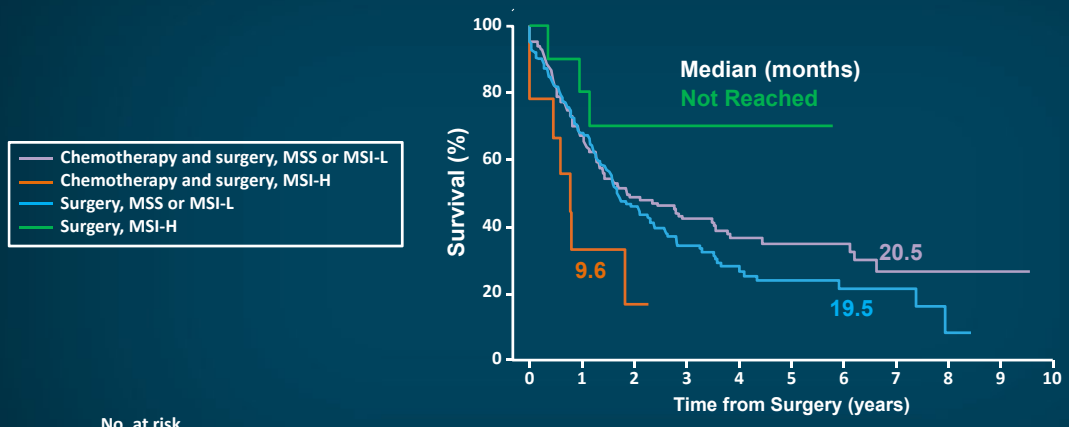




CIN, chromosomal instability; EBV, Epstein-Barr; MSI, microsatellite instability; GS, genomic stability.
TCGA Research Network. *Nature.* 2017;541:169-175. Cristescu R, et al. *Nature Medicine.* 2015; 21:449-456.

MSI-H Esophagogastric Tumors Are Chemotherapy Resistant

OS in ADJUVANT MAGIC STUDY



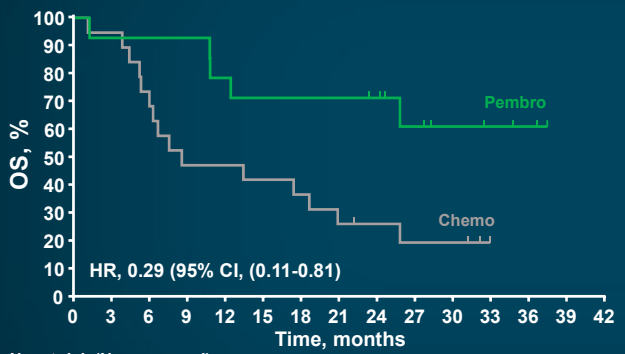
No. at risk											
Chemotherapy and surgery, MSI-negative patients	129	85	58	42	27	22	15	6	3	1	0
Chemotherapy and surgery, MSI-positive patients	9	3	1	0	0	0	0	0	0	0	0
Surgery, MSI-negative patients	151	100	58	37	21	13	9	7	1	0	0
Surgery, MSI-positive patients	10	8	6	3	1	1	0	0	0	0	0

Smyth EC, et al. *JAMA Oncology.* 2017;3:1197-1203.

The KEYNOTE-062 Phase 3 Randomized Clinical Trial

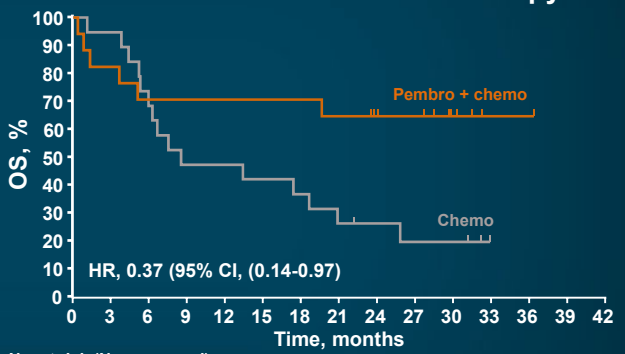
Overall Survival in Patients With MSI-H Tumors and PD-L1 CPS of 1 or Greater

Pembrolizumab



No. at risk (No. censored)								
	14 (0)	13 (0)	11 (0)	10 (0)	9 (0)	4 (3)	2 (6)	0 (9)
	19 (0)	13 (0)	9 (0)	7 (0)	4 (0)	3 (1)	0 (4)	0 (4)

Pembrolizumab and Chemotherapy



No. at risk (No. censored)								
	14 (0)	12 (0)	12 (0)	12 (0)	9 (0)	4 (3)	1 (10)	0 (11)
	19 (0)	13 (0)	9 (0)	7 (0)	4 (0)	3 (1)	0 (4)	0 (4)

Shitara K, et al. *JAMA Oncol*. 2020;6:1571-1580.

CheckMate 577: Study Design

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

Key Eligibility Criteria
- Stage II/III EC/GEJC
- Adenocarcinoma or squamous cell carcinoma
- Neoadjuvant CRT + surgical resection (R0, 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%)

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

Primary endpoint:
- DFS

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

- Median follow-up was 24.4 months (range, 6.2–44.9)
- Geographical regions: Europe (38%), US and Canada (32%), Asia (13%), rest of the world (16%)

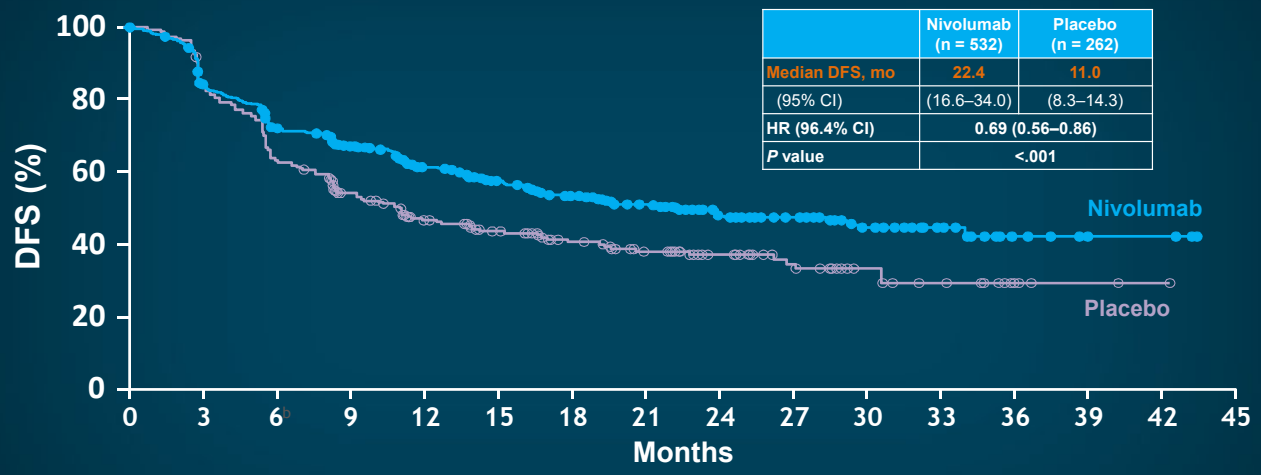
Kelly RJ, et al. ESMO 2020. Abstract LBA9_PR. Kelly RJ, et al. *N Engl J Med.* 2021;384:1191-1203.

CheckMate 577: Baseline Characteristics

		Nivolumab (n = 532)	Placebo (n = 262)
Median age (range), years		62.0 (26–82)	61.0 (26–86)
Male, %		84	85
Race, %	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, %	≥ 1%	17	15
	< 1%	70	75
	Indeterminate/nonevaluable	13	10

Kelly RJ, et al. *N Engl J Med.* 2021;384:1191-1203.

CheckMate 577: Disease-Free Survival



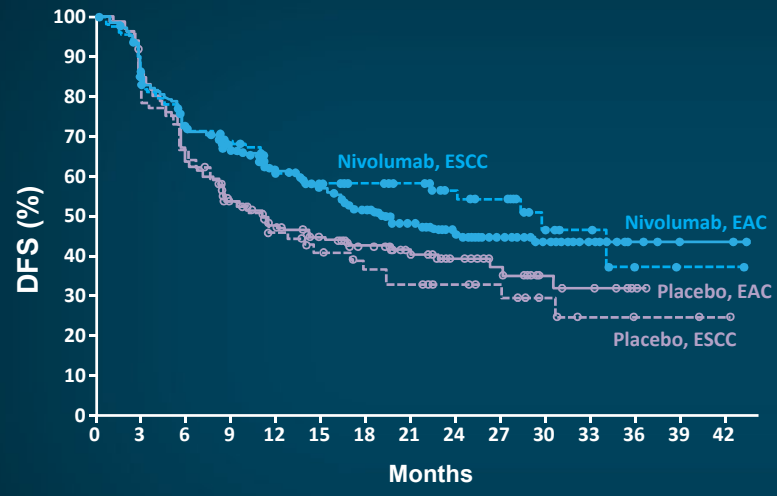
	Nivolumab (n = 532)	Placebo (n = 262)
Median DFS, mo	22.4	11.0
(95% CI)	(16.6–34.0)	(8.3–14.3)
HR (96.4% CI)	0.69 (0.56–0.86)	
P value	<.001	

- Nivolumab provided superior DFS with a 31% reduction in the risk of recurrence or death and a doubling in median DFS versus placebo

DFS, disease-free survival.

Kelly RJ, et al. *N Engl J Med.* 2021;384:1191-1203.

CheckMate 577: DFS According to Histologic Type



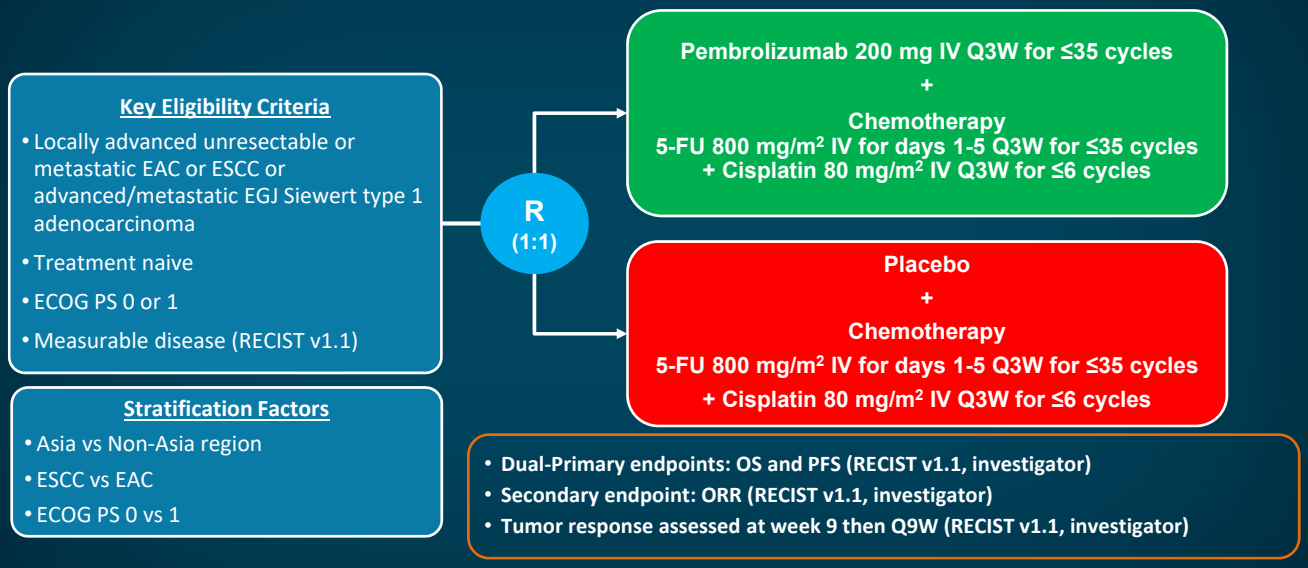
EAC	Nivolumab (n = 376)	Placebo (n = 187)
Median DFS, mo	19.4	11.1
(95% CI)	(15.9-29.4)	(8.3-16.8)
HR (95% CI)	0.75 (0.59-0.96)	

ESCC	Nivolumab (n = 155)	Placebo (n = 75)
Median DFS, mo	29.7	11.0
(95% CI)	(14.4-NE)	(7.6-17.6)
HR (96.4% CI)	0.61 (0.42-0.88)	

- DFS benefit with nivolumab was observed regardless of histologic type and in patients with PD-L1 CPS ≥5 and <5

Kelly RJ, et al. *N Engl J Med.* 2021;384:1191-1203.

KEYNOTE-590 Study Design (NCT03189719)



Kato K, et al. *Ann Oncol*. 2020;31(suppl_4):S1142-S1215.

KEYNOTE-590: Baseline Characteristics (ITT)

Characteristic, n (%)	Pembro + Chemo N = 373	Chemo N = 376
Median age, years (range)	64.0 (28-94)	62.0 (27-89)
≥65 years	172 (46)	150 (40)
Male	306 (82.0)	319 (84.8)
Asia Region	196 (52.5)	197 (52.4)
ECOG PS 1	223 (59.8)	225 (59.8)
Metastatic disease	344 (92.2)	339 (90.2)
Unresectable/locally advanced	29 (7.8)	37 (9.8)
Squamous-cell carcinoma	274 (73.5)	274 (72.9)
Adenocarcinoma	99 (26.5)	102 (27.1)
Esophageal	58 (15.5)	52 (13.8)
EGJ	41 (11.0)	50 (13.3)
PD-L1 CPS ≥10	186 (49.9)	197 (52.4)

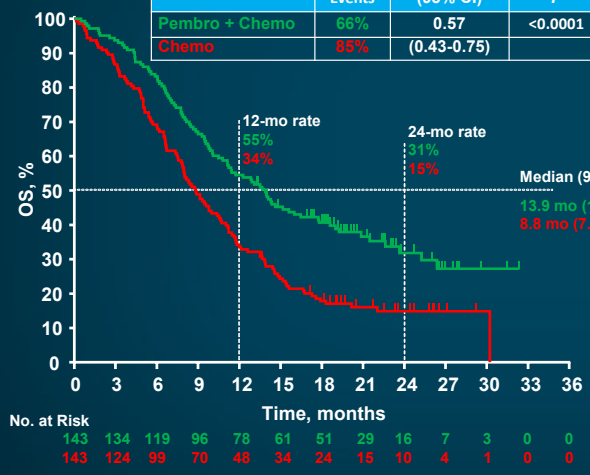
ITT, intent-to-treat

Kato K, et al. *Ann Oncol*. 2020;31(suppl_4):S1142-S1215.

KEYNOTE-590: ESCC Overall Survival

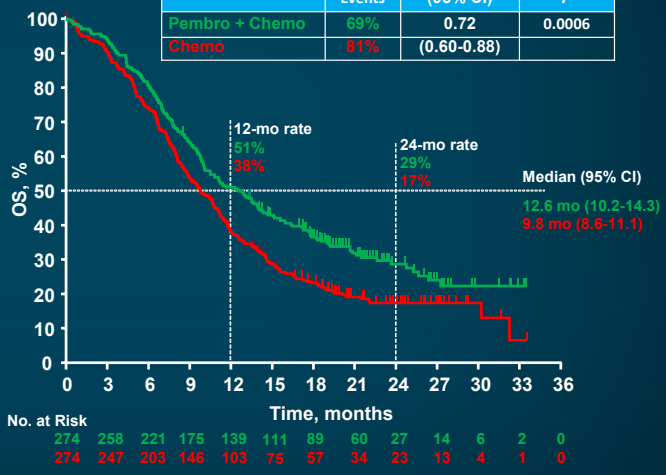
ESCC PD-L1 CPS ≥10

	Events	HR (95% CI)	P
Pembro + Chemo	66%	0.57	<0.0001
Chemo	85%	(0.43-0.75)	



ESCC

	Events	HR (95% CI)	P
Pembro + Chemo	69%	0.72	0.0006
Chemo	81%	(0.60-0.88)	

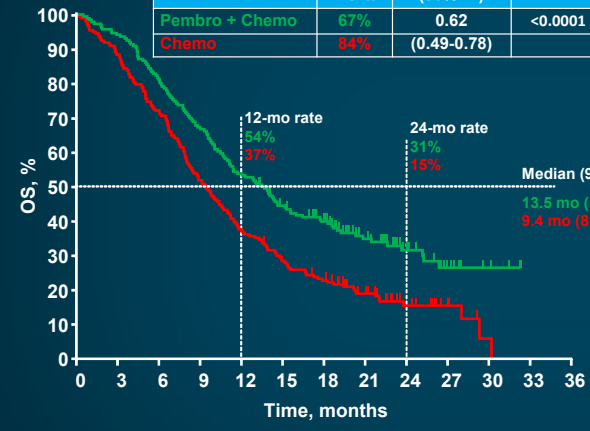


Kato K, et al. *Ann Oncol*. 2020;31(suppl_4):S1142-S1215.
Data cut-off: July 2, 2020.

KEYNOTE-590: Overall Survival

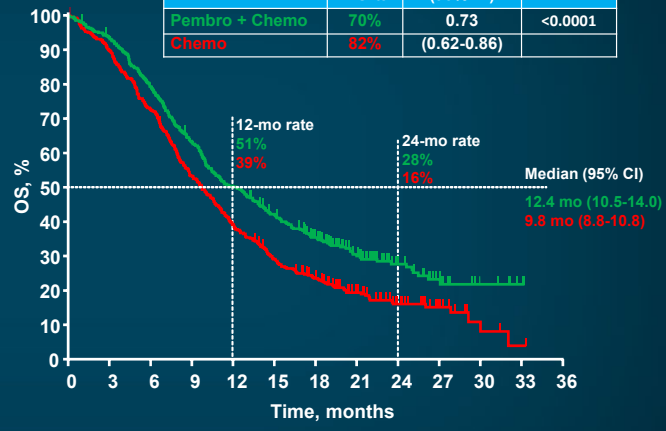
PD-L1 CPS ≥10

	Events	HR (95% CI)	P
Pembro + Chemo	67%	0.62	<0.0001
Chemo	84%	(0.49-0.78)	



All Patients

	Events	HR (95% CI)	P
Pembro + Chemo	70%	0.73	<0.0001
Chemo	82%	(0.62-0.86)	

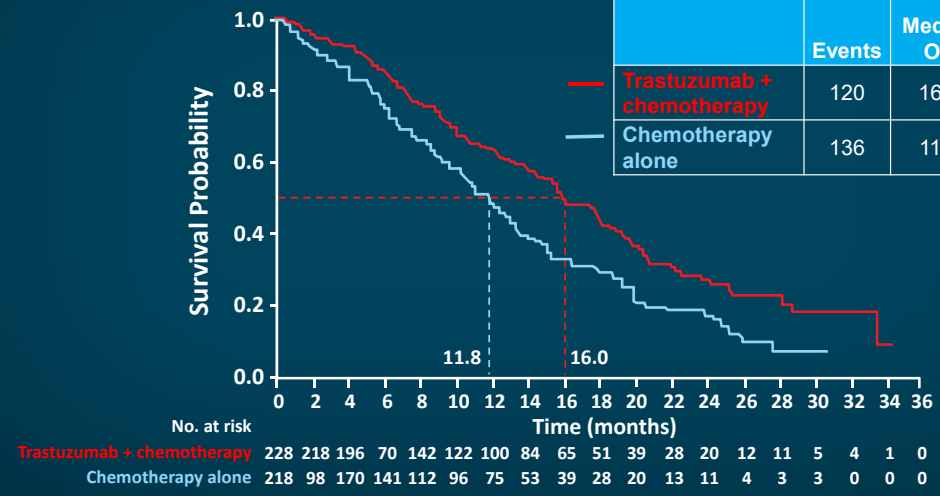


Pembrolizumab approved in combination with platinum and fluoropyrimidine-based chemo for patients with metastatic or locally advanced esophageal or GEJ carcinoma who are not candidates for surgical resection or definitive chemoradiation

Kato K, et al. *Ann Oncol*. 2020;31(suppl_4):S1142-S1215.
Data cut-off: July 2, 2020.

ToGA Trial: Overall Survival in HER2-Positive Advanced Gastric or GEJ Cancer

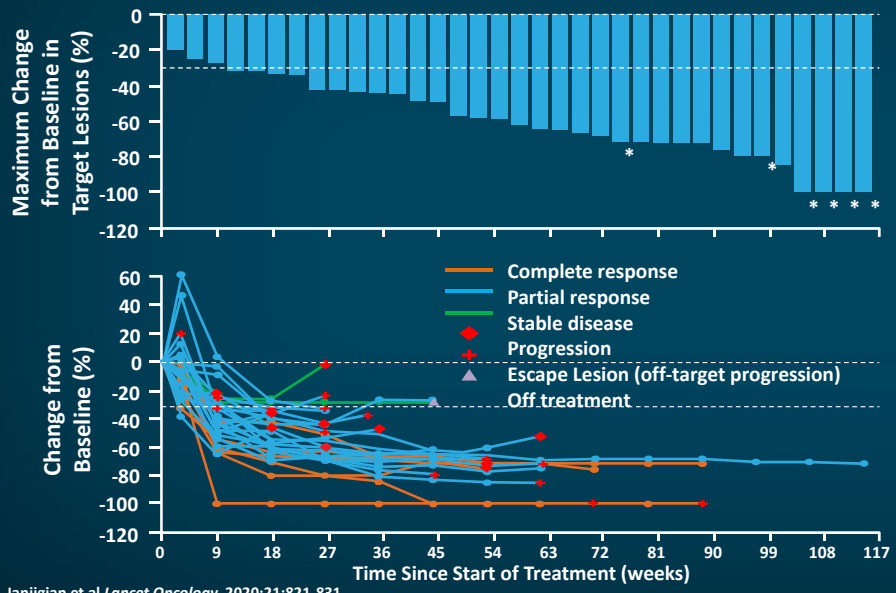
IHC 2+/FISH+ or IHC 3+



	Events	Median OS	HR	95% CI
Trastuzumab + chemotherapy	120	16.0	0.65	0.51, 0.83
Chemotherapy alone	136	11.8		

Bang Y-J, et al *Lancet.* 2010;376:687-697.

1st-line Capecitabine/Oxaliplatin/Pembrolizumab/Trastuzumab in HER2-Positive Esophageal, Gastric or GEJ Cancer

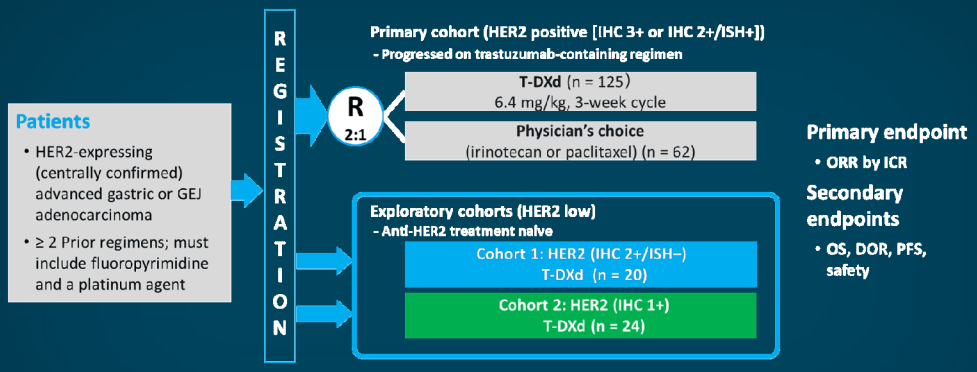


Best Response (n = 37)	Patients, n (%)
ORR, n (%)	32 (91%) 95% CI (78%, 97%)
CR PR SD PD	6 (17) 26 (74) 3 (9) 0
Disease Control Rate	100%

Janjigian et al *Lancet Oncology.* 2020;21:821-831.

DESTINY-Gastric01

An open-label, multicenter, randomized, phase 2 study



- All patients received T-DXd 6.4 mg/kg Q3W
  - Cohort 1 IHC 2+/ISH− (n = 20); cohort 2 IHC 1+ (n = 24)
- All patients had previously received anti-HER2 treatment
- Median of 2 prior lines of therapy for advanced/metastatic disease
  - 18% had irinotecan, 84% had ramucirumab, 32% had anti–PD-1/PD-L1
- At data cutoff (8 November 2019), no patients in cohort 1 and 2 in cohort 2 (8.3%) remained on treatment

T-DXd, trastuzumab deruxtecan.
Shitara K, et al. *N Engl J Med*. 2020;382:2419-2430.

Primary Endpoint: ORR

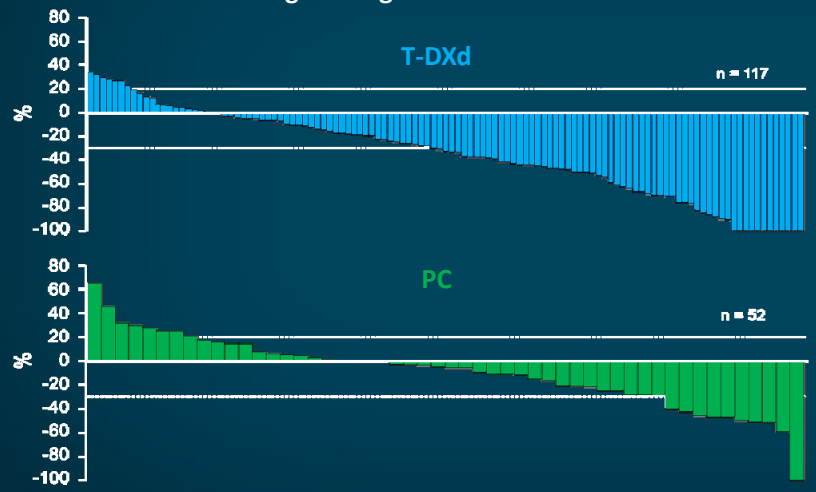
	Primary Cohort (PC)		Exploratory Cohorts	
	T-DXd (n = 119)	**PC Overall (n = 56)**	Cohort 1 IHC 2+/ISH− (n = 19)	**Cohort 2 IHC 1+ (n = 21)**
ORR by ICR (CR + PR)	**51.3% (n = 61) 95% CI, 41.9-60.5; *P* < .0001**	**14.3% (n = 8) 95% CI, 6.4-26.2**	**36.8% (n = 7) 95% CI, 16.3%-61.6%**	**19.0% (n = 4) 95% CI, 5.4%-41.9%**
Confirmed ORR by ICR (CR + PR)	**42.9% (n = 51) 95% CI, 33.8-52.3**	**12.5% (n = 7)** 95% CI, 5.2-24.1	**26.3% (n = 5) 95% CI, 9.1%-51.2%**	**9.5% (n = 2) 95% CI, 1.2%-30.4%**
CR	8.4% (n = 10)	0	0	0
PR	34.5% (n = 41)	12.5% (n = 7)	26.3% (n = 5)	9.5% (n = 2)
SD	42.9% (n = 51)	50.0% (n = 28)	63.2% (n = 12)	61.9% (n = 13)
PD	11.8% (n = 14)	30.4% (n = 17)	10.5% (n = 2)	28.6% (n = 6)
NE	2.5% (n = 3)	7.1% (n = 4)	0	0
Confirmed DCR (CR + PR + SD)	85.7% (n = 102) 95% CI, 78.1-91.5	62.5% (n = 35) 95% CI, 48.5-75.1	89.5% (n = 17) 95% CI, 66.9%-98.7%	71.4% (n = 15) 95% CI, 47.8%-88.7%
Median confirmed DOR	11.3 months 95% CI, 5.6 months-NE	3.9 months 95% CI, 3.0-4.9 months	7.6 months 95% CI, 4.1 months-NE	12.5 months 95% CI, NE-NE

DCR, disease control rate; DOR, duration of response; ICR, independent central review; IHC, immunohistochemistry; ISH, in situ hybridization; NE, not estimable.
Shitara K, et al. *N Engl J Med*. 2020;382:2419-2430.

DESTINY-Gastric01: Response Rate IHC3+ or IHC2+/ISH+

Trastuzumab deruxtecan (T-DXd)

Best Percentage Change from Baseline in Tumor Size

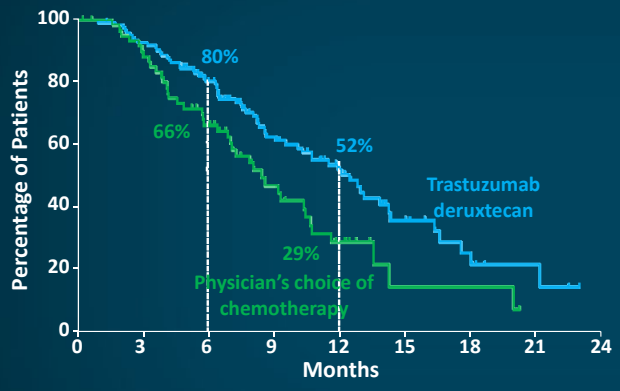


	T-DXd (n = 119)	PC (n = 56)
ORR	51.3%	14.3%
Confirmed ORR	42.9%	12.5%
CR	8.4%	0%
PR	34.5%	12.5%
SD	42.9%	50.0%

Shitara K, et al. *N Engl J Med*. 2020;382:2419-2430.

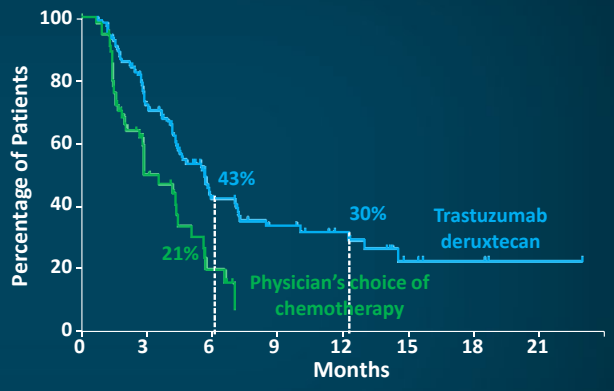
DESTINY-Gastric01: Survival

OS



mOS, 12.5 v 8.4 mos
HR, 0.59 (95% CI 0.39 – 0.88)
P = .01

PFS

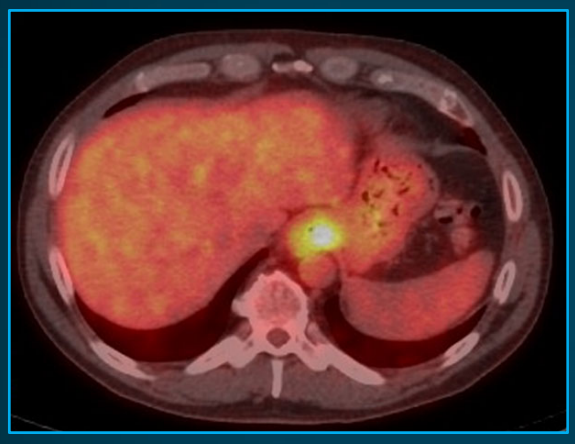


mPFS, 5.6 v 3.5 mos
HR, 0.47 (95% CI 0.31 – 0.71)

Shitara K, et al. *N Engl J Med*. 2020;382:2419-2430.

Case Studies

Case Study 1



50 y/o man with 3 months of progressive dysphagia – biopsy adenocarcinoma

↓

EUS: uT3N1M0, PET: no evidence of metastases

↓

Chemoradiation – radiation to 5040 cGy + paclitaxel + carboplatin

↓

Esophagectomy

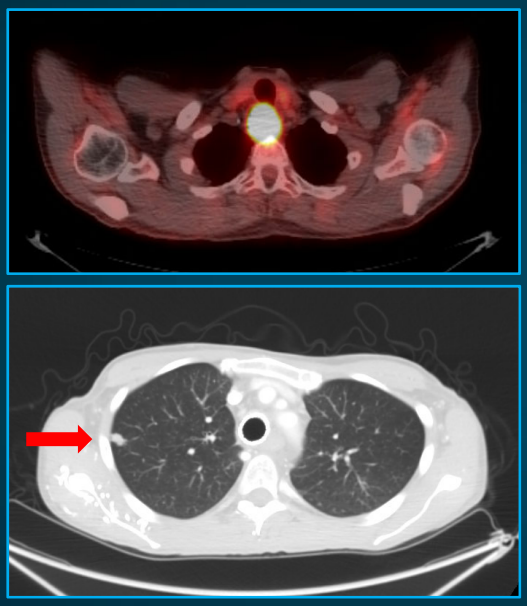
↓

Surveillance

↓

NED @ 2/1/2021

Case Study 2



8/2019 - 69 y/o woman with SCC of the cervical esophagus, uT3N1M0

↓

Induction FOLFOX x 2 cycles

↓

Definitive chemoradiation: carboplatin/paclitaxel + radiation therapy to 60 Gy in 30 fractions

↓

9/2020 – solitary lung metastasis – NED at primary site and elsewhere

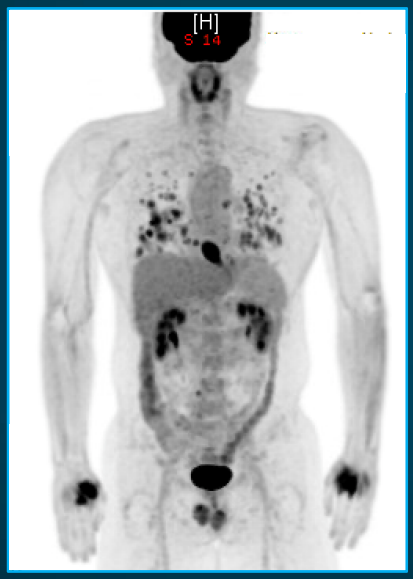
↓

VATS resection of lung nodule

↓

On observation, NED

Case Study 3



46 yo diagnosed with GEJ adenocarcinoma stage IV (+ lung metastasis) in 2018
HER2 positive, CPS = 2

↓

IO + chemo + trastuzumab for 2.5 years

↓

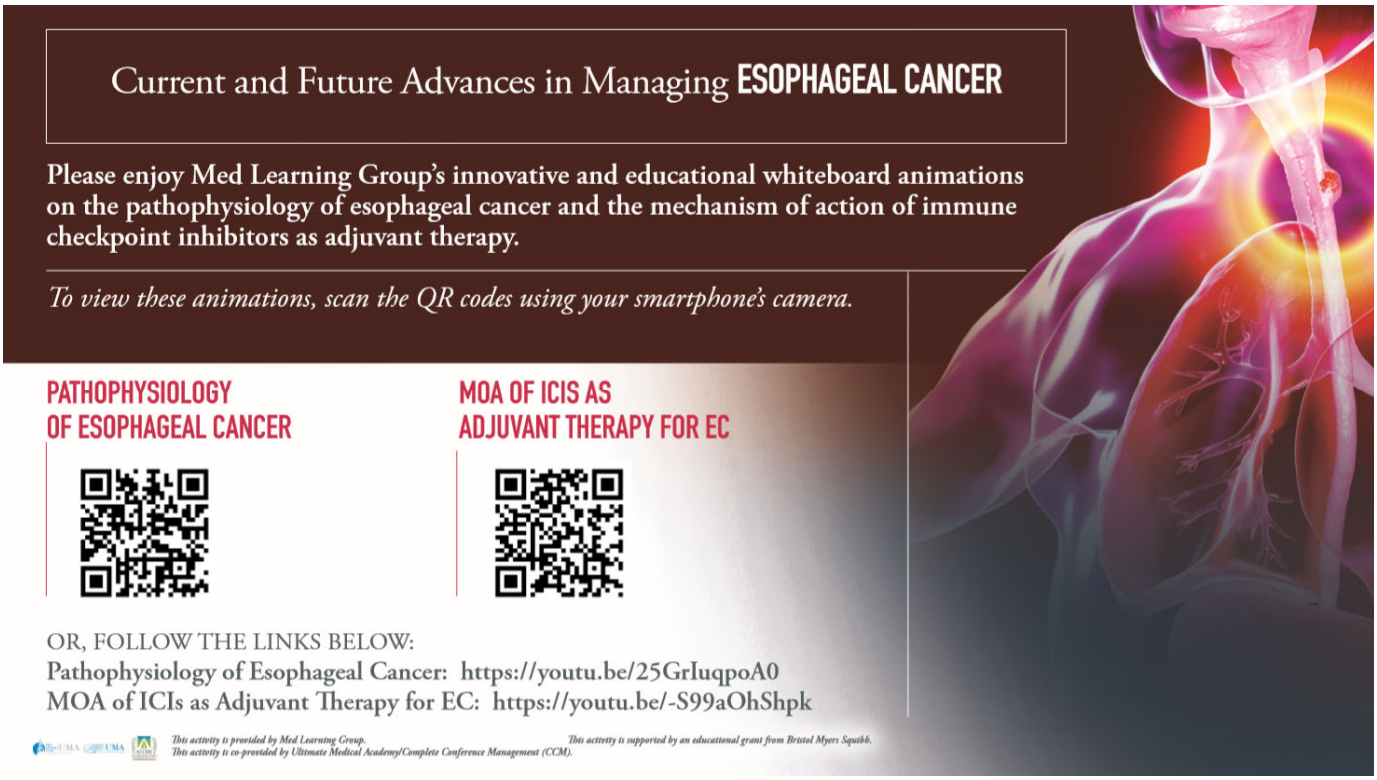
Salvage esophagectomy in 2020
(ypT2N0 on pathology)

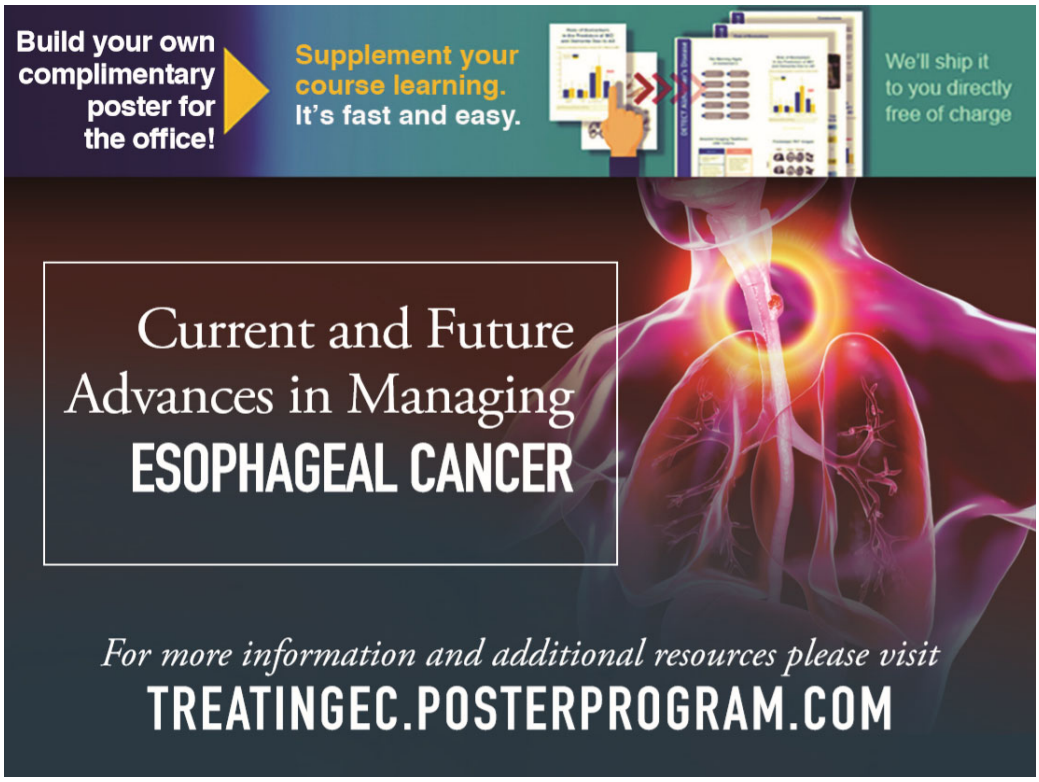
↓

NED @ 1/21/2021

Conclusions

- Early-stage EC is associated with favorable prognosis
  - Although screening is not recommended, BE surveillance can lead to identification of early-stage disease
- The role of adjuvant IO for locally advanced disease is promising (CheckMate 577)
- Esophagectomy after neoadjuvant chemoradiation followed by IO appears to be safe and feasible
- 5-FU/oxaliplatin + nivolumab is likely to replace SOC (CheckMate 649)
- Adjuvant nivolumab DFS benefit irrespective of PD-L1 and histology
- T-DXd approved after trastuzumab progression
- Order HER2, MSI and PD-L1 on all patients

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Resource	Address
ASGE STANDARDS OF PRACTICE COMMITTEE, Qumseya B, Sultan S, et al. **ASGE guideline on screening and surveillance of Barrett's esophagus.** *Gastrointest Endosc.* 2019;90:335-359.e2.	https://pubmed.ncbi.nlm.nih.gov/31439127/
Hoppo T, Jobe BA. **Personalizing therapy for esophageal cancer patients.** *Thoracic Surg Clin*. 2013;23:471-478.	https://pubmed.ncbi.nlm.nih.gov/24199697/
Rice TW, et al. **Cancer of the esophagus and esophagogastric junction: An eighth edition staging primer.** *J Thorac Oncol.* 2017;12:36-42.	https://pubmed.ncbi.nlm.nih.gov/27810391/
Van Hagen P, et al. **Preoperative chemoradiotherapy for esophageal or junctional cancer.** *N Engl J Med.* 2012;366:2074-2084.	https://pubmed.ncbi.nlm.nih.gov/22646630/
Shapiro J, et al. **Neoadjuvant chemoradiotherapy plus surgery versus surgery alone for oesophageal or junctional cancer (CROSS): Long-term results of a randomised controlled trial.** *Lancet Oncol*. 2015;16:1090-1098.	https://pubmed.ncbi.nlm.nih.gov/26254683/
Oppendijk V, et al. **Patterns of recurrence after surgery alone versus preoperative chemoradiotherapy and surgery in the CROSS trials.** *J Clin Oncol*. 2014;32:385-391.	https://pubmed.ncbi.nlm.nih.gov/24419108/
Al-Batran SE, et al. **Perioperative chemotherapy with fluorouracil plus leucovorin, oxaliplatin, and docetaxel versus fluorouracil or capecitabine plus cisplatin and epirubicin for locally advanced, resectable gastric or gastro-oesophageal junction adenocarcinoma (FLOT4): A randomised, phase 2/3 trial.** *Lancet.* 2019;393:1948-1957.	https://pubmed.ncbi.nlm.nih.gov/30982686/
Wu AJ, et al. **Expert Consensus Contouring Guidelines for Intensity Modulated Radiation Therapy in Esophageal and Gastroesophageal Junction Cancer.** *Int J Radiat Oncol Biol Phys*. 2015;92:911-920.	https://pubmed.ncbi.nlm.nih.gov/26104943/
The Cancer Genome Atlas (TCGA) Research Network. **Integrated genomic characterization of oesophageal carcinoma.** *Nature.* 2017;541:169-175.	https://pubmed.ncbi.nlm.nih.gov/28052061/
Moehler M, et al. **Nivolumab (nivo) plus chemotherapy (chemo) versus chemo as first-line (1L) treatment for advanced gastric cancer/gastroesophageal junction cancer (GC/GEJC)/esophageal adenocarcinoma (EAC): First results of the CheckMate 649 study.** Presented at ESMO 2020. Abstract LBA6_PR. *Ann Oncol*. 2020;31(suppl_4):S1142-S1215.	https://oncologypro.esmo.org/meeting-resources/esmo-virtual-congress-2020/nivolumab-nivo-plus-chemotherapy-chemo-versus-chemo-as-first-line-1l-treatment-for-advanced-gastric-cancer-gastroesophageal-junction-cancer

Kelly RJ, et al. **Adjuvant nivolumab in resected esophageal or gastroesophageal junction cancer.** *N Engl J Med.* 2021;384:1191-1203.	https://pubmed.ncbi.nlm.nih.gov/33789008/
Kato K, et al. **Pembrolizumab plus chemotherapy versus chemotherapy as first-line therapy in patients with advanced esophageal cancer: The phase 3 KEYNOTE-590 study.** Presented at ESMO 2020. Abstract LBA8_PR. *Ann Oncol*. 2020;31(suppl_4):S1142-S1215.	https://oncologypro.esmo.org/meeting-resources/esmo-virtual-congress-2020/pembrolizumab-plus-chemotherapy-versus-chemotherapy-as-first-line-therapy-in-patients-with-advanced-esophageal-cancer-the-phase-3-keynote-590-study
Bang YJ, et al. **Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): A phase 3, open-label, randomised controlled trial.** *Lancet.* 2010;376:687-697.	https://pubmed.ncbi.nlm.nih.gov/20728210/
Janjigian YY, et al. **First-line pembrolizumab and trastuzumab in HER2-positive oesophageal, gastric, or gastro-oesophageal junction cancer: an open-label, single-arm, phase 2 trial.** *Lancet Oncol.* 2020;21:821-831.	https://pubmed.ncbi.nlm.nih.gov/32437664/
Shitara K, et al. **Trastuzumab deruxtecan in previously treated HER2-positive gastric cancer.** *N Engl J Med*. 2020;382:2419-2430.	https://pubmed.ncbi.nlm.nih.gov/32469182/