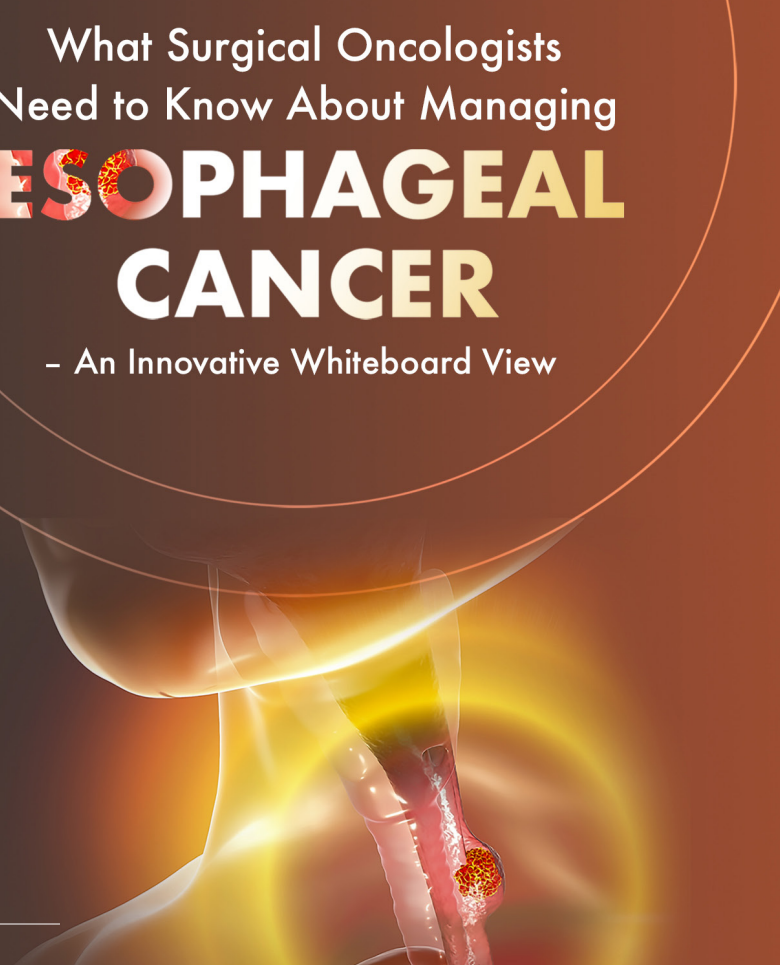
What Surgical Oncologists Need to Know About Managing

ESOPHAGEAL CANCER

– An Innovative Whiteboard View



FRIDAY, MARCH 19, 2021

FACULTY

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This presentation was selected by the Society of Surgical Oncology as an independent educational activity held in conjunction with SSO 2021. This presentation is not sponsored or endorsed by the Society of Surgical Oncology.

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.

AGENDA

I. **Esophageal Cancer (EC): An Overview**
   a. Epidemiology, incidence, and prevalence
   b. Presentation of esophageal squamous cell carcinoma (ESCC) and esophageal adenocarcinoma (EAC)
   c. Whiteboard animation: Pathophysiology of ESCC and EAC
   d. Burden of disease

II. **EC Screening and Surveillance**
   a. Disease course and progression
   b. Risk factors for disease progression
   c. Best practices in screening and surveillance

III. **The Use of Immune Checkpoint Inhibitors (ICIs) for the Treatment of EC**
   a. Current standards of care for EC
      i. Chemotherapy
      ii. Radiation
   b. Whiteboard animation: Mechanism of action of ICIs in EC
   c. Clinical trial data on the efficacy and safety of ICIs as adjuvant therapy for patients with EC
   d. Clinical profiles of ICIs used alone, in combination, and in combination with chemo- and radiotherapy for the treatment of patients with EC across lines of therapy

IV. **The Important Roles for Surgical Oncologists in the Management of EC**
   a. Clinical responsibilities: Surgical and non-surgical
   b. Incorporating ICIs into clinical practice
   c. Educational responsibilities

V. **Case Study**
VI. **Conclusions**
VII. **Questions and Answers**
VIII. **Adjournment**

What Surgical Oncologists Need to Know About Managing Esophageal Cancer – An Innovative Whiteboard View

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PROGRAM OVERVIEW

This case-based activity will explore the role of surgical oncologists in the management of esophageal cancer, review emerging clinical trial data on the use of immune checkpoint inhibitors as adjuvant therapy, and examine strategies to appropriately sequence therapies using patient-specific factors.

TARGET AUDIENCE

This educational activity is specifically designed for US-based surgical oncologists and other healthcare professionals involved in the treatment of patients with esophageal cancer.

LEARNING OBJECTIVES

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

- Describe the role of surgical oncologists in esophageal cancer (EC) screening and surveillance
- Review data from clinical trials on the efficacy and safety of immune checkpoint inhibitors (ICIs) for the treatment of patients with advanced EC across lines of therapy
- Discuss clinical trial data 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 Esophageal Cancer.
CNE Credits: 1.0 ANCC Contact Hour.

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Dr. Molena is a consultant for Intuitive, Johnson & Johnson, Boston Scientific, Urogen, and AstraZeneca.

CME Content Review
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The reviewer of this activity has nothing to disclose.

CNE Content Review
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2. Participate in the activity.
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Disclosures

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- Dr. Molena is a consultant for Intuitive, Urogen, Johnson & Johnson, and Boston Scientific. She serves on the steering committee at AstraZeneca.
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Learning Objectives

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

Screening and Surveillance of Esophageal Cancer

Dr. Daniela Molena

Esophageal Squamous Cell Carcinoma (ESCC)

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.

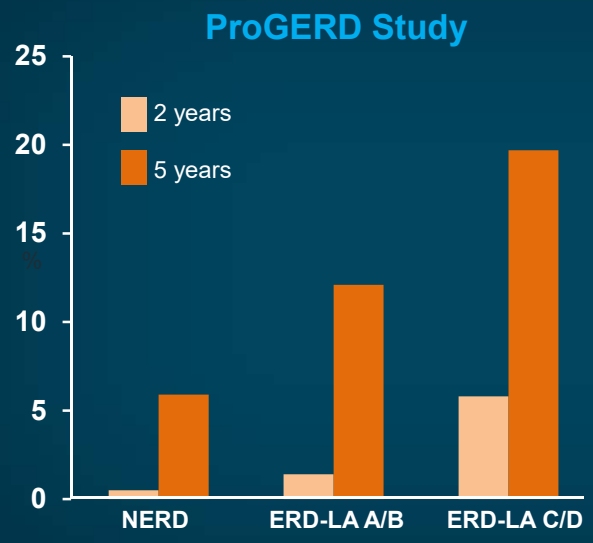
Screening Recommendation for Esophageal Cancer

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.

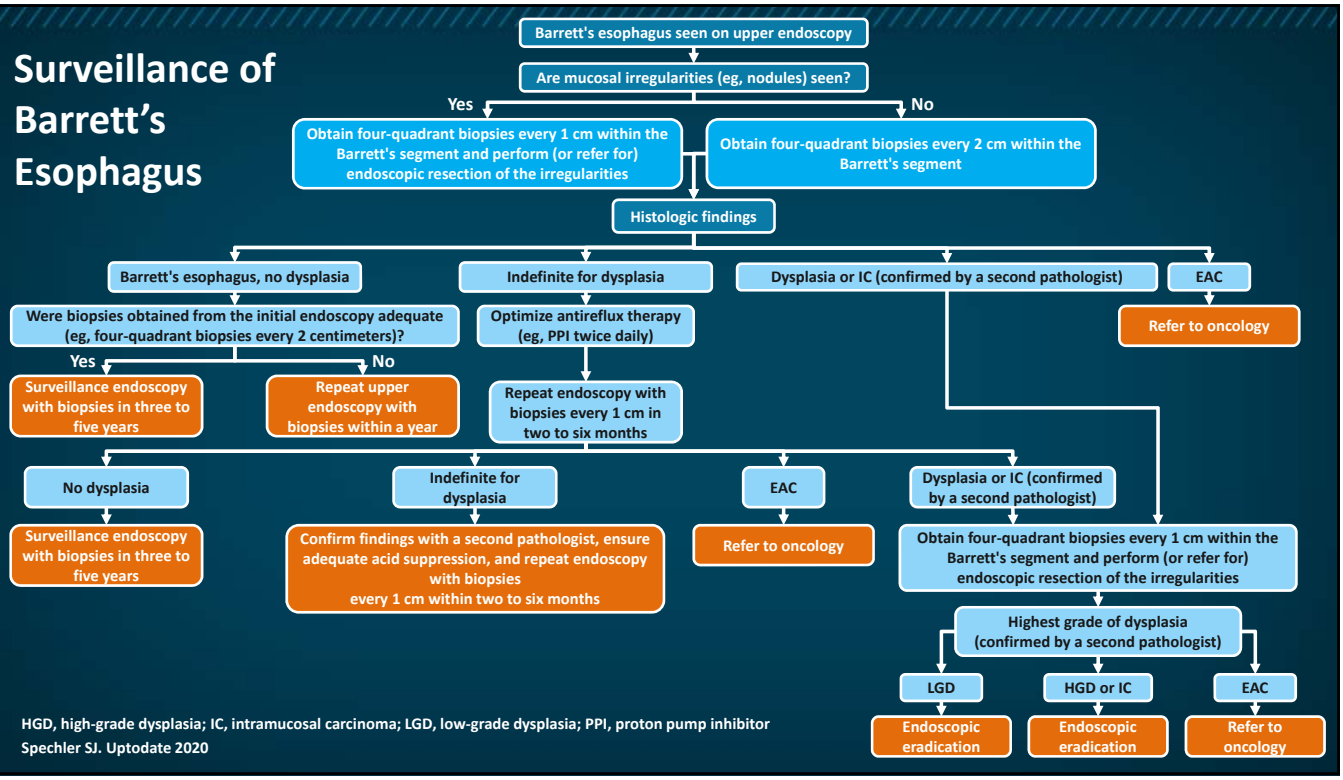
ASGE Guideline on Screening and Surveillance of BE

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.

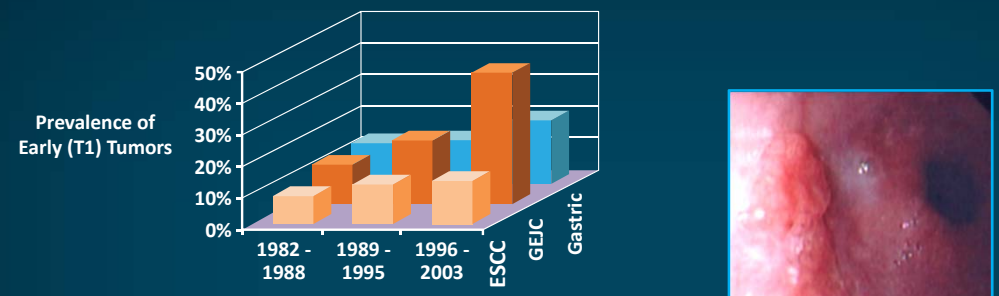
Surveillance of Barrett's Esophagus

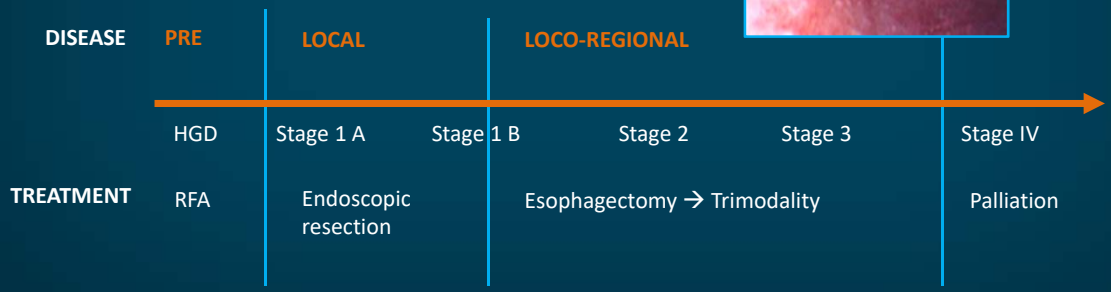


HGD, high-grade dysplasia; IC, intramucosal carcinoma; LGD, low-grade dysplasia; PPI, proton pump inhibitor

Spechler SJ. Uptodate 2020

Esophageal Cancer: A Diverse Disease

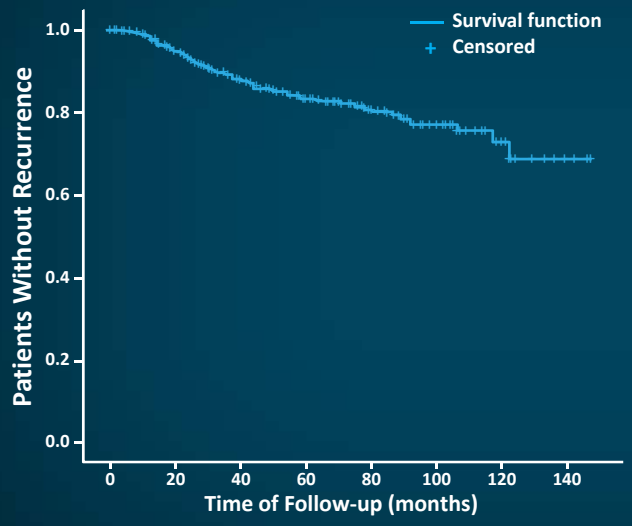




HGD, high-grade dysplasia; RFA, radiofrequency ablation.

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

Endoscopic Resection for T1a EAC



Complete Response in 96.3% of Patients

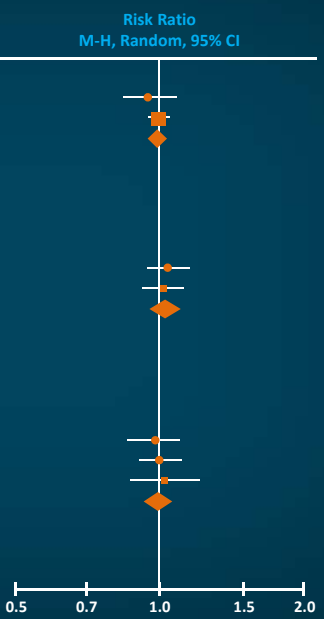
Patients	1000 (86% males)
SSBE/LSBE	481/519
Well/Mod/Poor Differentiated	691/255/54
Median # resections	1 (range 1-3)
Complications	14 bleeding, 1 perforation
Metachronous lesions or cancer recurrence	14.5%
Treatment failure	4.2% (26 esophagectomy)
DFS at 5 years	87.1%

DFS, disease-free survival; SSBE, short-segment Barrett's esophagus; LSBE, long-segment Barrett's esophagus.

Pech O, et al. *Gastroenterol*. 2014;146:652-660.

Endotherapy versus Esophagectomy: Overall Survival

Study or Subgroup	Endotherapy Events	Endotherapy Total	Surgery Events	Surgery Total	Weight	Risk Ratio M-H, Random, 95% CI
1 year survival						
Pacifico 2003	22	24	62	64	6.5%	0.95 (0.83, 1.08]
Pech 2011	75	76	38	38	47.2%	0.99 (0.95, 1.04]
Subtotal (95% CI)		100		102	53.8%	0.99 [0.94, 1.03]
Total events	97		100			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.81$, df= 1 (P=0.37); $I^2 = 0\%$						
Test for overall effect: Z = 0.55 (P=0.58)						
3 years survival						
Pech 2011	73	76	35	38	10.0%	1.04 (0.94, 1.16]
Zehetner 2011	38	40	57	61	11.3%	1.02 (0.92, 1.12]
Subtotal (95% CI)		116		99	21.3%	1.03 [0.96, 1.10]
Total events	111		92			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.12$, df= 1 (P=0.72); $I^2 = 0\%$						
Test for overall effect: Z = 0.79 (P=0.43)						
5 years survival						
Pech 2011	68	76	35	38	7.3%	0.97 (0.86, 1.10]
Prasad 2007	118	129	64	70	13.5%	1.00 [0.92, 1.09]
Prasad 2009	109	132	37	46	4.1%	1.03 (0.87, 1.21]
Subtotal (95% CI)		337		154	24.9%	1.00 (0.93, 1.06]
Total events	295		136			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.33$, df= 2 (P=0.85); $I^2 = 0\%$						
Test for overall effect: Z = 0.12 (P=0.90)						



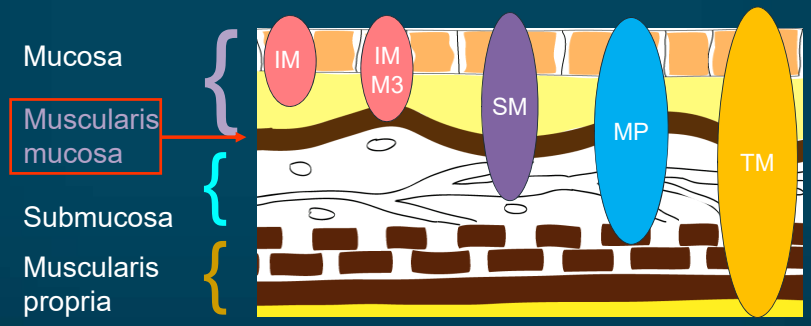
M-H, Mantel Haenszel.

Wu J, et al. *Gastrointest Endosc*. 2014;79:233-241.

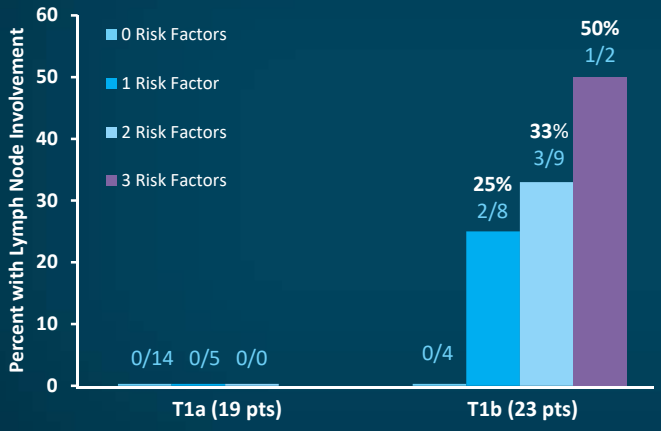
Depth of Invasion and Risk of Node Metastases

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%



Gauging the Risk of Lymph Node Metastases in Endoscopically Resected Submucosal EAC

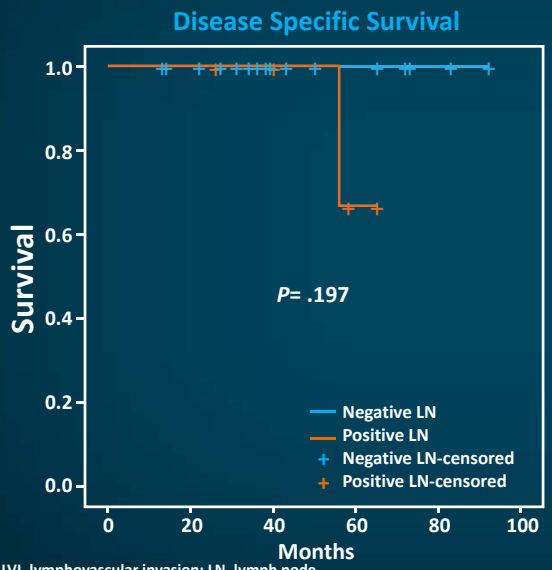


Risk factors:

- Poor differentiation
- Lymphovascular invasion
- Submucosal invasion > 500 µ

Boys JA, et al. *J Gastroenterol Surg*. 2016;20:6-12.

Esophagectomy Following Endoscopic Resection of Submucosal EAC: Highly Curative Even with Nodal Metastases



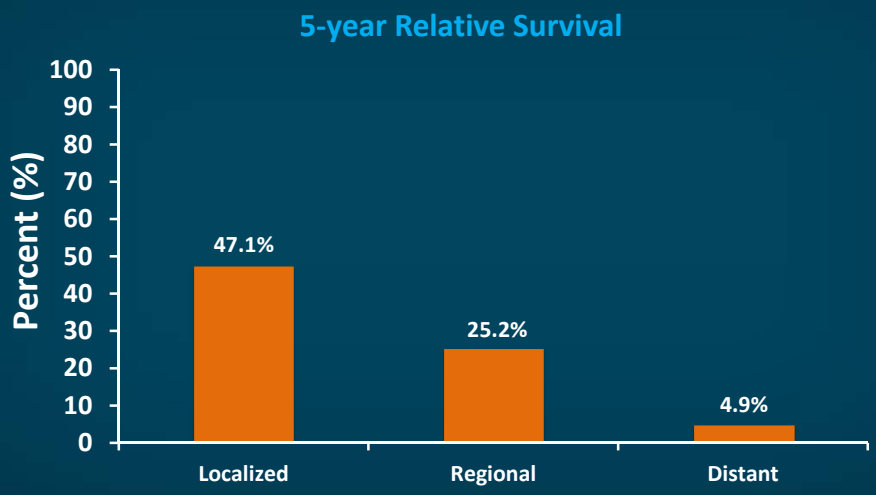
- 26% of patients (6/23) had nodal metastases
  - N1 in 5, N2 in 1 (3 nodes)
- Disease-specific 5-year survival: 88%
  - 67% in patients with positive nodal metastases
  - 100% in those without

Patient with positive nodes	Poor differentiation	LVI	Depth invasion ≥500 µm	Positive nodes	Residual tumor
1 (alive)	No	No	Yes	1	T1a
2 (dead)	No	Yes	No	1	T0
3 (alive)	Yes	No	Yes	1	T0
4 (alive)	Yes	No	Yes	1	T1a
5 (alive)	No	Yes	Yes	1	T0
6 (alive)	Yes	Yes	Yes	3	T1b

LVI, lymphovascular invasion; LN, lymph node.

Molena D, et al. *J Gastrointest Surg*. 2017;21:62-67.

Outcomes of Esophageal Cancer Remain Poor

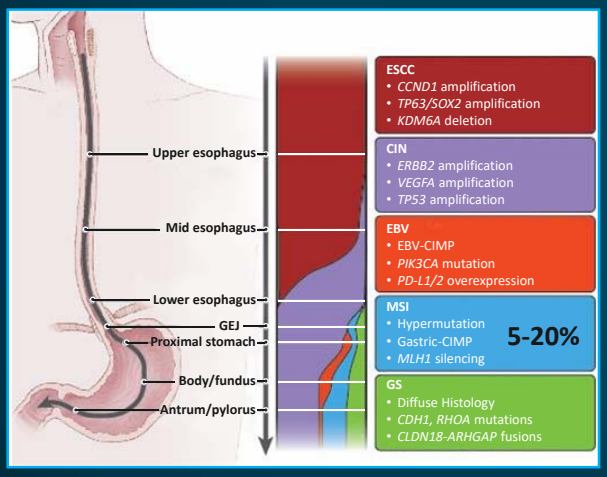


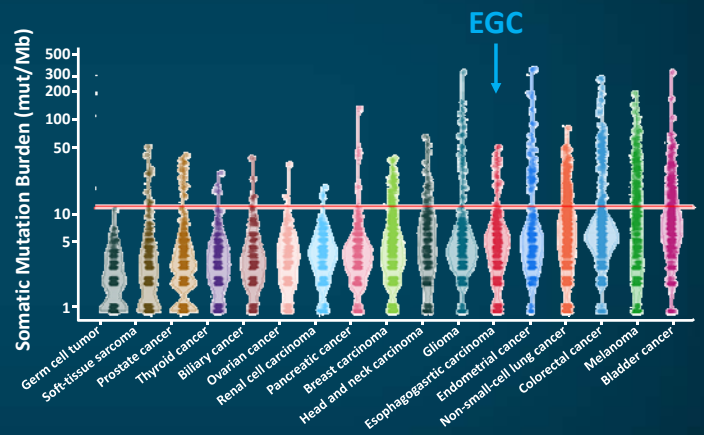
SEER. Cancer Stat Facts: Esophageal Cancer. https://seer.cancer.gov/statfacts/html/esoph.html

Whiteboard Animation:
Pathophysiology 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

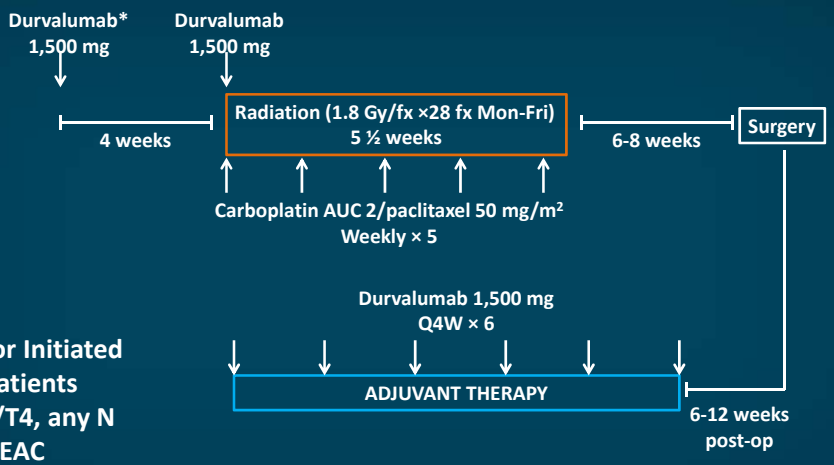
→ CheckMate-649

→ KEYNOTE-590

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

*Off-label or investigative use.

Phase I Neoadjuvant trial



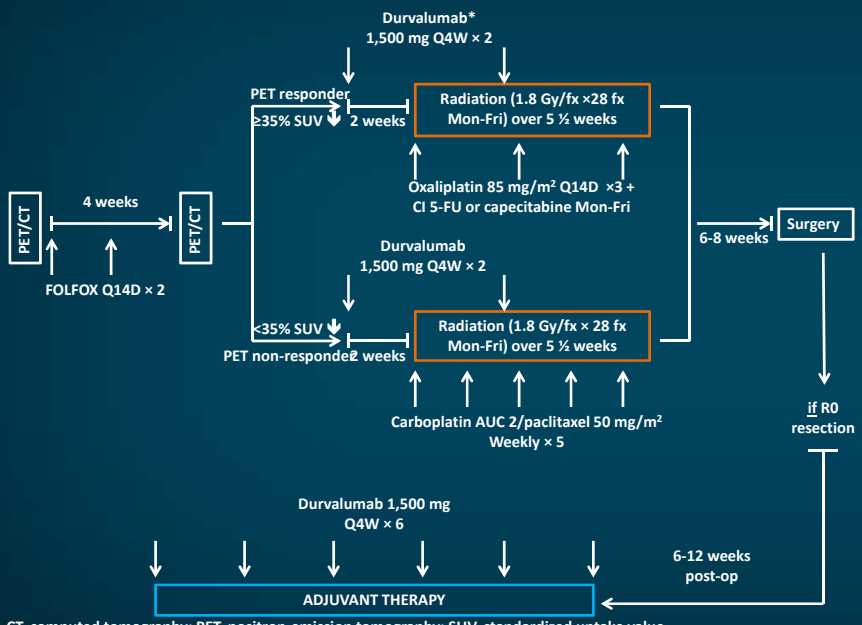
- MSK Investigator Initiated
- Phase I, N = 5 patients
- Any T, N+ or T3/T4, any N
- Siewert I and II EAC

AUC, area under the curve; fx, fraction; Gy, Gray; MSK, Memorial Sloan-Kettering; N, node; Q4W, every 4 weeks; T, tumor.

Sihag S, et al. *J Thorac Cardiovasc Surg*. 2021;161:836-843.e1.

*Off-label or investigative use.

Phase II Neoadjuvant trial

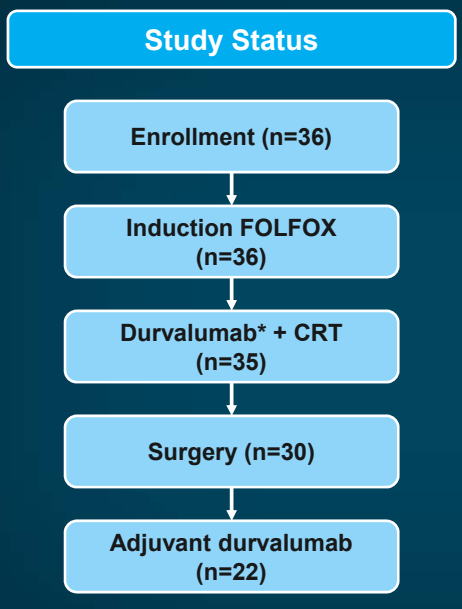


- Incorporates CALGB 80803 trial
- Phase II, N = 36 patients
- Any T, N+ or T3/T4, any N
- Esophageal and EGJ

CT, computed tomography; PET, positron-emission tomography; SUV, standardized uptake value.

Sihag S, et al. *J Thorac Cardiovasc Surg*. 2021;161:836-843.e1.

*Off-label or investigative use.



	Demographics	
Age (years)	Median Range	63 25-73
Sex	Male Female	30 (83%) 6 (17%)
Primary Tumor Location	Esophageal Siewert Type I Siewert Type II Siewert Type III GEJ — Unspecified	11 (31%) 4 (11%) 9 (25%) 3 (8%) 9 (25%)
TNM Stage	T1-T2 N+ T3-T4 NO T3-4 N+ T3 NX	3 (8%) 12 (33%) 20 (56%) 1 (3%)
MMR Status	MMR proficient MMR deficient MMR status pending	32 (89%) 3 (8%) 1 (3%)

Ku GY, et al. GI ASCO 2021

*Off-label or investigative use.

Treatment-Related Adverse Events with Durvalumab

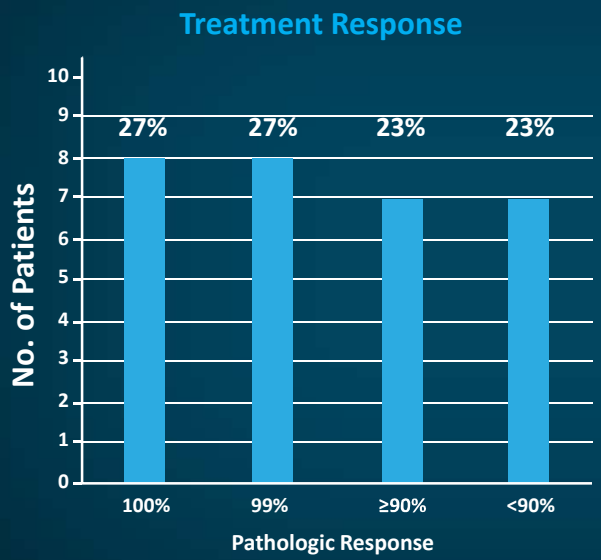
Adverse Events	Grade 1/2	Grade 3/4
Anemia	35 (97%)	7 (19%)
Neutropenia	17 (47%)	8 (22%)
Lymphopenia	35 (97%)	36 (100%)
Thrombocytopenia	34 (94%)	2 (6%)
Increased AST	26 (72%)	3 (8%)
Increased ALT	21 (58%)	3 (8%)
Increased amylase	11 (31%)	3 (8%)
Increased lipase	16 (44%)	3 (8%)
Rash	9 (25%)	–

Adverse Events	Grade 1/2	Grade 3/4
Dysphagia	33 (92%)	3 (8%)
Weight loss	18 (50%)	1 (3%)
Nausea	27 (75%)	2 (6%)
Vomiting	17 (47%)	2 (6%)
Diarrhea	21 (58%)	4 (11%)
Constipation	25 (69%)	–
Fatigue	32 (89%)	–
Neuropathy	12 (33%)	–
Pain	15 (42%)	1 (3%)

Immune Related Adverse Events	Grade 1/2	Grade 3/4
Colitis	1	2
Hepatitis	0	1
Dermatitis	2	0
Hypothyroidism	2	0

ALT, alanine aminotransferase; AST, aspartate aminotransferase. Ku GY, et al. GI ASCO 2021

Treatment Response at Surgery (n=30)



	≥99%	90-98%	<90%
PET responder (n = 23)	14 (61%)	5 (22%)	4 (17%)
PET non-responder (n = 7)	2 (29%)	2 (29%)	3 (43%)

1. A Pt with PET non-response (ASUV -31%) had significant clinical benefit to FOLFOX. He was considered a PET responder, received capecitabine/ oxaliplatin with RT and achieved a pCR
2. Of 3 dMMR Pts, 2 were PET responders (pCR and 99% response) and 1 was PET non-responder (90% response)

Ku GY, et al. GI ASCO 2021

Esophagectomy Peri-Operative Outcomes

Outcome	ICI (N=25)	Control (N=143)	*P*-value
Interval to Surgery (d)	54 (47-61)	53 (47-66)	0.6
Operative Time (min)	502 (419-560)	467 (419-533)	0.3
Length of Hospital Stay (d)	8 (7.0-9.0)	9.0 (7.0-11.0)	0.12
Intra-op Blood Loss (ml)	200 (150-300)	200 (100-350)	0.6
Peri-op Transfusion	2 (8%)	21 (15%)	0.5
30-day Readmission	4 (17%)	19 (13%)	0.7
30-day Mortality	0 (0%)	2 (1.4%)	1

ICI, immune checkpoint inhibitor.
Sihag S, et al. *J Thorac Cardiovasc Surg*. 2021;161:836-843.e1.

Overall Surgical Morbidity (N=30)

Outcome	
Median length of stay	8 days (6-57 days)
Respiratory failure	1 patient (7%)
Anastomotic leak	3 patients (10%) – 1 death after 73 days
Empyema	1 patient (7%)
Chylothorax	1 patient (7%)
Wound infection	2 patients (7%)

Ku GY, et al. GI ASCO 2021

Adjuvant Durvalumab* (n=36)

Number of Patients	Status of Adjuvant Durvalumab Therapy	
11	Completed 6 cycles of adjuvant durvalumab	
14	Did not initiate adjuvant durvalumab	
	3	Awaiting surgery
	5	Off study (1 Pt with G3 paclitaxel allergy, 2 Pt with G3/4 irAEs in pre-operative period, 2 developed metastatic disease)
	6	Pre-surgery/post-operative phase
11	Did not receive all six doses of adjuvant durvalumab	
	5	Currently receiving adjuvant durvalumab
	4	Stopped prematurely due to COVID-19 restrictions
	1	Discontinued for post-operative paraconduit hernia
	1	Discontinued for Grade 3 diarrhea (after 4th adjuvant durvalumab treatment)

Ku GY, et al. GI ASCO 2021

*Off-label or investigative use.

Is There a Role for 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.

Case Studies

Dr. Daniela Molena

Case Study 1

56 yo diagnosed with ESCC stage IV (+ adrenal met) in 2016, CPS = 15

↓

Chemotherapy for 1 year followed by CRT

↓

Attempted salvaged esophagectomy (R2 due to liver metastasis)

↓

Started on IO

↓

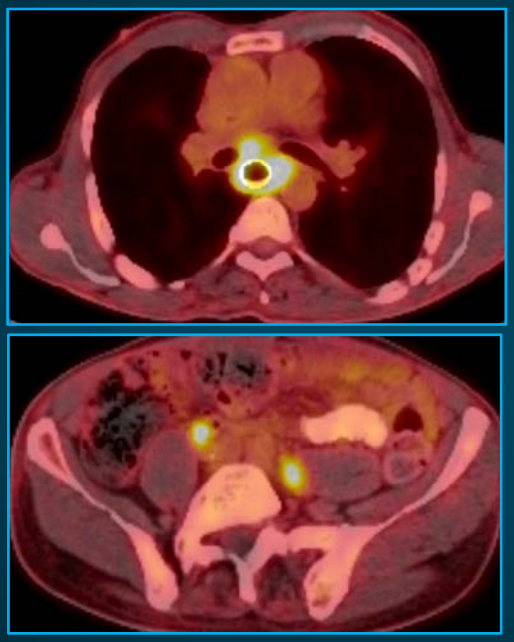
Salvage esophagectomy in 2018 (pCR on pathology)

↓

NED @ 1/06/2021

NED, no evidence of disease

Case Study 2



58 yo diagnosed with GEJ adenocarcinoma
stage IV (+ retroperitoneal nodes) in 2019
HER2 negative, CPS = 85

↓

IO for 1 year

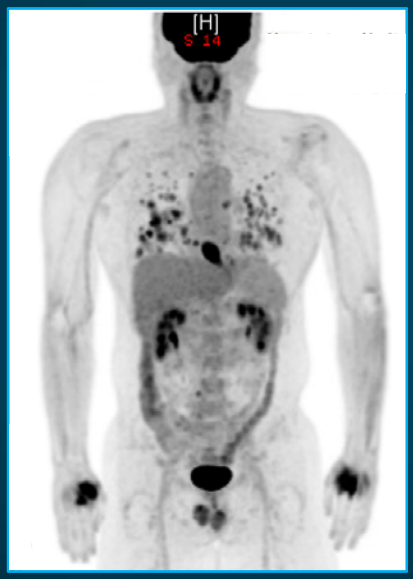
↓

Salvage esophagectomy with retroperitoneal dissection in 2020
(pCR on pathology)

↓

NED @ 1/20/2021

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 neoadjuvant IO for locally advanced disease is promising
- Esophagectomy after neoadjuvant treatment with IO appears to be safe and feasible
- Esophagectomy may have a role in advanced stage IV disease after good treatment response to IO

ICIs for the Management of Esophageal Cancer

Dr. Yelena Janjigian

Overview

- Summary outcomes for recent studies
  - CheckMate 649, CheckMate 577 and KEYNOTE-590
- Immunotherapy and HER2 directed therapy
- Review molecular features that affect response and inform treatment selection and timing
- Anti-PD-1 based combination strategies

Immunotherapy in Esophageal & Gastric Cancers

Adenocarcinoma

- Nivolumab approved in Asia irrespective of PD-L1 status in ≥3rd-line
- Pembrolizumab approved in ≥3rd line in the US
  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

ESMO 2020: Practice changing studies

NCCN Has Now Updated Compendium to Include Use of PD-1 Inhibitors in First Line and Postoperative Setting

Esophageal + Esophagogastric Junction Cancers as of 12-23-2020;
First line metastatic treatment for HER2 overexpression negative tumors

1. if CPS ≥5, Nivolumab + Fluoropyrimidine and Oxaliplatin
2. if CPS ≥ 10 Pembrolizumab + Fluoropyrimidine and Oxaliplatin
3. if CPS ≥10, Pembrolizumab + Fluoropyrimidine and Cisplatin

Gastric Cancers as of 12-23-2020
First line metastatic treatment for HER2 overexpression negative tumors if CPS ≥5, Nivolumab + Fluoropyrimidine and Oxaliplatin

First-Line Systemic Therapy for Unresectable Locally Advanced, Recurrent, or Metastatic Disease
• Oxaliplatin is generally preferred over cisplatin due to lower toxicity
Preferred Regimens • HER2 overexpression positive adenocarcinoma ▶ Fluoropyrimidine (fluorouracil or capecitabine) and oxaliplatin and trastuzumab ▶ Fluoropyrimidine (fluorouracil or capecitabine) and cisplatin and trastuzumab (category 1) • HER2 overexpression negative ▶ Fluoropyrimidine (fluorouracil or capecitabine), oxaliplatin, and nivolumab (PDL1 CPS 2 5) for adenocarcinoma only (category 1) ▶ Fluoropyrimidine (fluorouracil or capecitabine), oxaliplatin, and pembrolizumab (PDL1 CPS 2 10) ▶ Fluoropyrimidine (fluorouracil or capecitabine), cisplatin, and pembrolizumab (PDL1 CPS 2 10) (category 4) ▶ Fluoropyrimidine (fluorouracil or capecitabine) and oxaliplatin ▶ Fluoropyrimidine (fluorouracil or capecitabine) and cisplatin

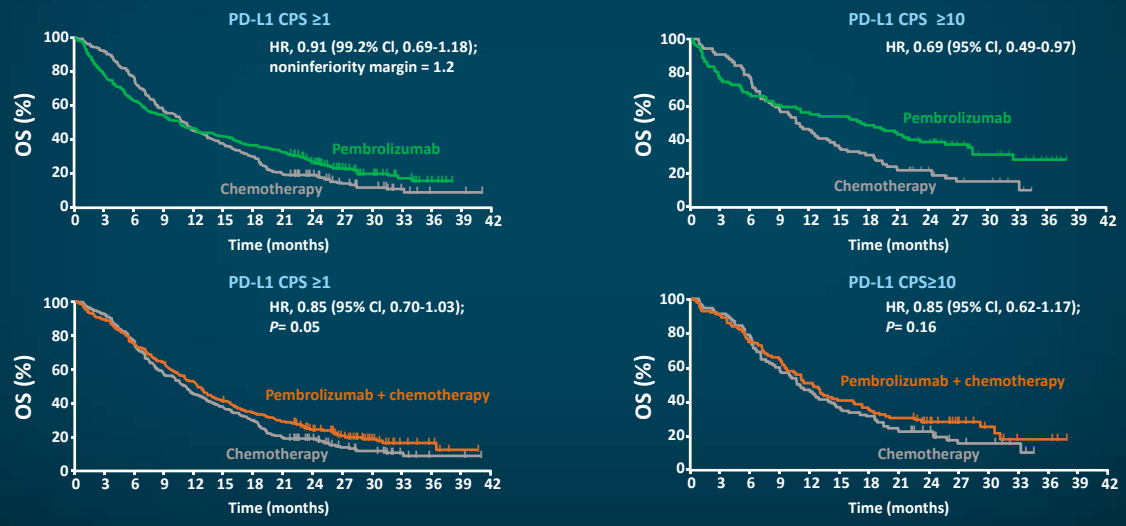
Postoperative Therapy
Preferred Regimens • Nivolumab only after preoperative chemoradiation with R0 resection and residual disease (category 1)
Other Recommended Regimens • Capecitabine and oxaliplatin • Fluorouracil and oxaliplatin

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

Whiteboard Animation:
Mechanism of Action of Immune Checkpoint Inhibitors as Adjuvant Therapy for EC

KEYNOTE-062: Efficacy and Safety of Pembrolizumab* or Pembrolizumab Plus Chemo vs Chemo Alone for Patients With First-line, Advanced Gastric Cancer

No benefit for pembrolizumab; CPS ≥10 is a unique population



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

*Off-label or investigative use.

CheckMate 649 Study Design

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

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

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

R 1:1:1

n = 789: **NIVO + IPI*** Q3W × 4 then NIVO 240 mg Q2W

n = 789: **NIVO*** 360 mg + **XELOX** Q3W or **NIVO*** 240 mg + **FOLFOX** Q2W

n = 792: **XELOX** Q3W or **FOLFOX** Q2W

N = 1581, including 955 patients (60%) with PD-L1 CPS ≥ 5

Dual primary endpoints:
- **OS** and **PFS** (PD-L1 CPS ≥5)

Secondary endpoints:
- **OS** (PD-L1 CPS ≥1 or all randomized)
- **OS** (PD-L1 CPS ≥10)
- **PFS** (PD-L1 CPS ≥10, 1, or all randomized)
- **ORR**

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

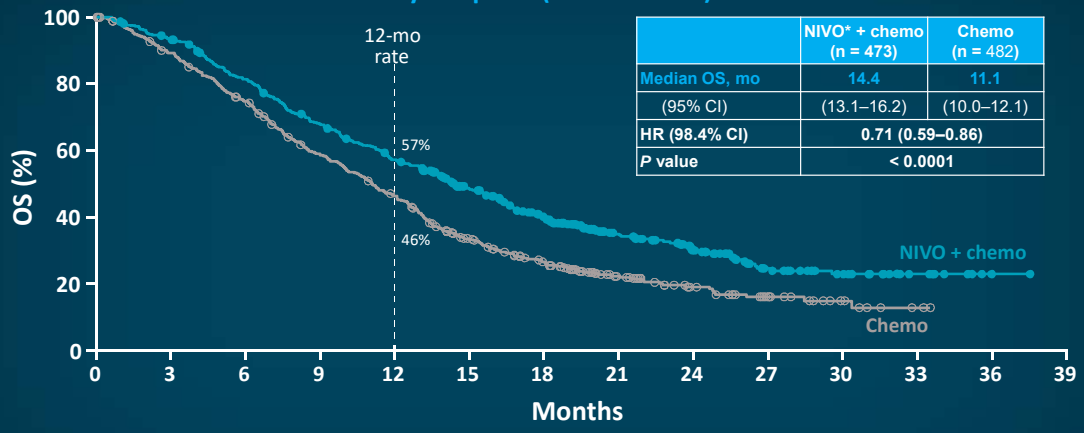
ECOG PS, Eastern Cooperative Oncology Group Performance Status; FOLFOX, 5-FU/leucovorin/oxaliplatin; IPI, ipilimumab; NIVO, nivolumab; ROW, rest of world; XELOX, capecitabine/oxaliplatin.

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

*Off-label or investigative use.

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	

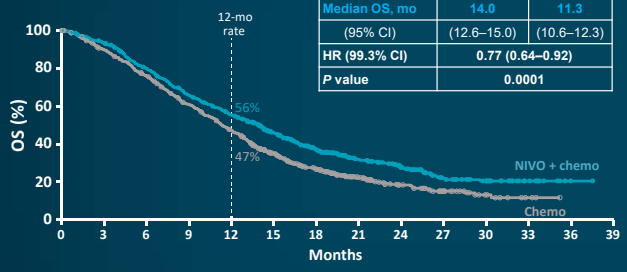
- Superior OS, 29% reduction in the risk of death, and a 3.3-month improvement in median OS with NIVO + chemo versus chemo in patients whose tumors expressed PD-L1 CPS ≥5

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

*Off-label or investigative use.

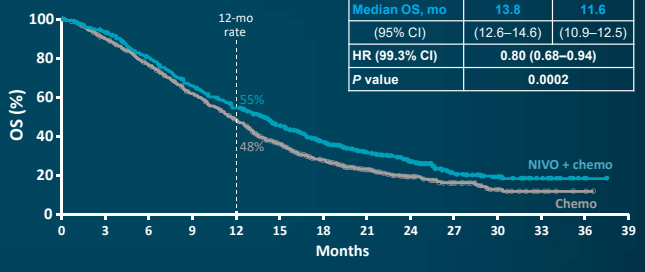
CheckMate 649: Overall Survival

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

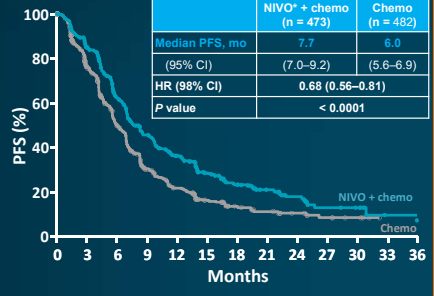
Moehler M, et al. ESMO 2020. Abstract LBA6_PR.

*Off-label or investigative use.

CheckMate 649: Progression-free Survival

Primary endpoint (PD-L1 CPS ≥5)

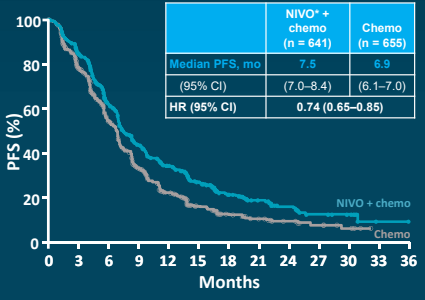
	NIVO* + chemo (n = 473)	Chemo (n = 482)
Median PFS, mo	7.7	6.0
(95% CI)	(7.0–9.2)	(5.6–6.9)
HR (98% CI)	0.68 (0.56–0.81)	
P value	< 0.0001	



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

PD-L1 CPS ≥1

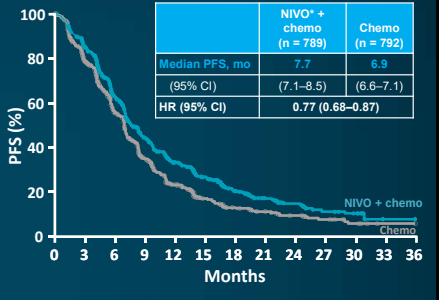
	NIVO* + chemo (n = 641)	Chemo (n = 655)
Median PFS, mo	7.5	6.9
(95% CI)	(7.0–8.4)	(6.1–7.0)
HR (95% CI)	0.74 (0.65–0.85)	



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.

*Off-label or investigative use.

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

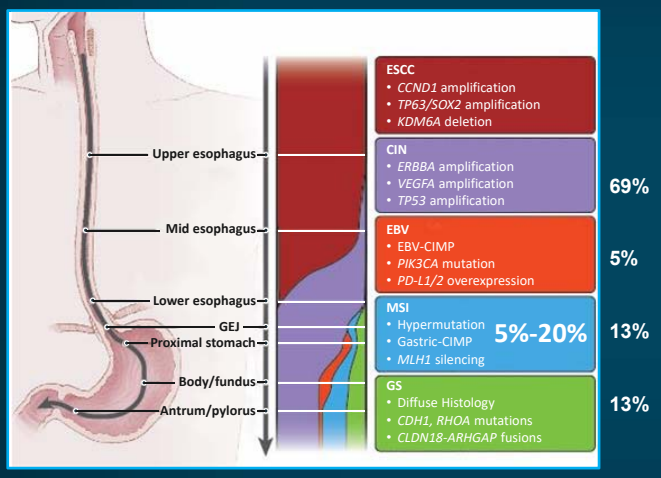
The FDA-approved anti-PD1 drug and PD-L1 assessment

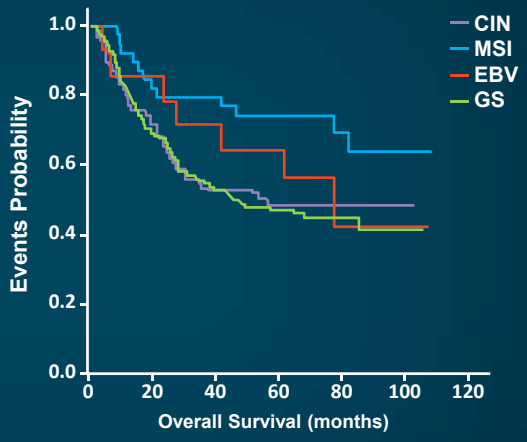
mAb	Drug	FDA approval	Scoring assessment	Overall response score
22C3 pharmDx (Dako North America, Inc)	Pembrolizumab	NSCLC	TPS <1%: No PD-L1 expression TPS = 1-49%: PD-L1 expression TPS ≥50%: High PD-L1 expression	NCT02007070 TPS ≥1%: 15.4% (95% CI: 4.4-34.9%) TPS ≥50%: 27.3% (95% CI: 6.0-61.0%)
		Gastric 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



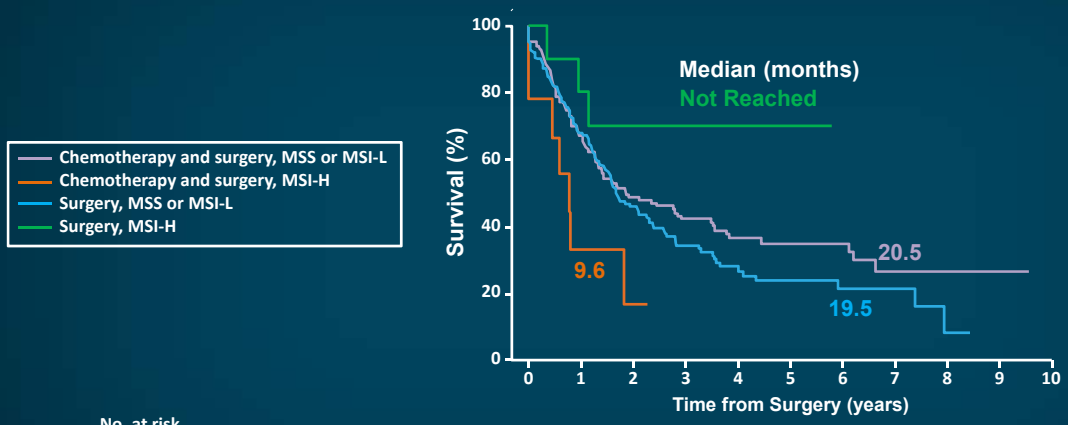


CIN, chromosomal instability; EBV, Epstein-Barr; MSI, microsatellite instability; GS, genomic stability.

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



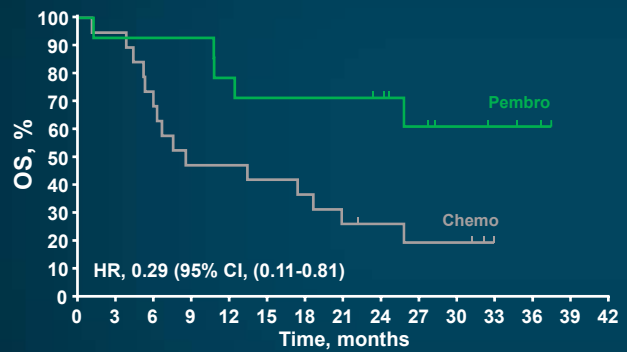
No. at risk											
Chemotherapy and surgery, MSI-negative patients	129	85	58	42	27	22	15	6	3	1	0
Chemotherapy and surgery, MSI-positive patients	9	3	1	0	0	0	0	0	0	0	0
Surgery, MSI-negative patients	151	100	58	37	21	13	9	7	1	0	0
Surgery, MSI-positive patients	10	8	6	3	1	1	0	0	0	0	0

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

The KEYNOTE-062 Phase 3 Randomized Clinical Trial

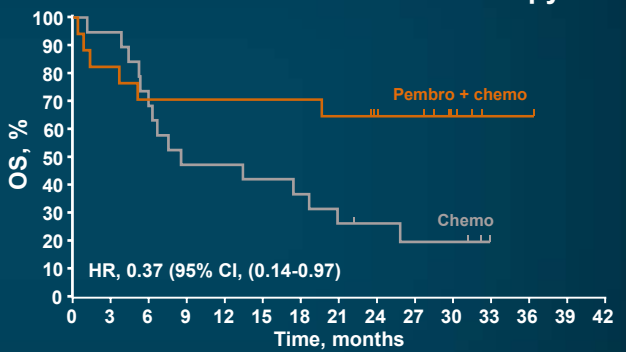
Overall Survival in Patients With MSI-H Tumors and PD-L1 CPS of 1 or Greater

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.

*Off-label or investigative use.

A Randomized Double-Blind Study of Adjuvant Pembrolizumab* vs Placebo in Patients with MSI-H Tumors with Persistent ctDNA Following Surgery (NCT03832569)

Patient with MSI-H Tumor → R0 Surgical Resection → SOC Adjuvant Therapy → ctDNA Analysis

- ctDNA+ CT - → Pembrolizumab N=24
- ctDNA- → Observation

R0 Surgical Resection → Tumor Sequencing

Year 1 Objective: To demonstrate clearance of ctDNA at 6 months.

Year 2, 3 and 5 Objectives: To demonstrate DFS and OS.

ctDNA, circulating tumor DNA; SOC, standard of care

Courtesy of PI Janjigian.

*Off-label or investigative use.

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%)

CRT, chemoradiation therapy

Kelly RJ, et al. ESMO 2020. Abstract LBA9_PR

*Off-label or investigative use.

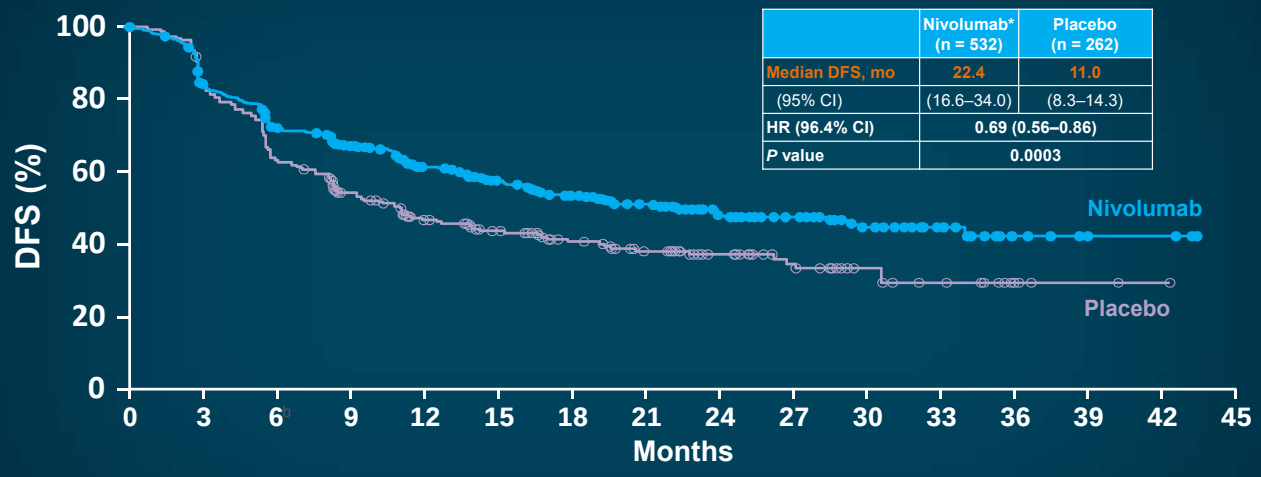
CheckMate 577: Baseline Characteristics

		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. ESMO 2020. Abstract LBA9_PR

*Off-label or investigative use.

CheckMate 577: Disease-free Survival



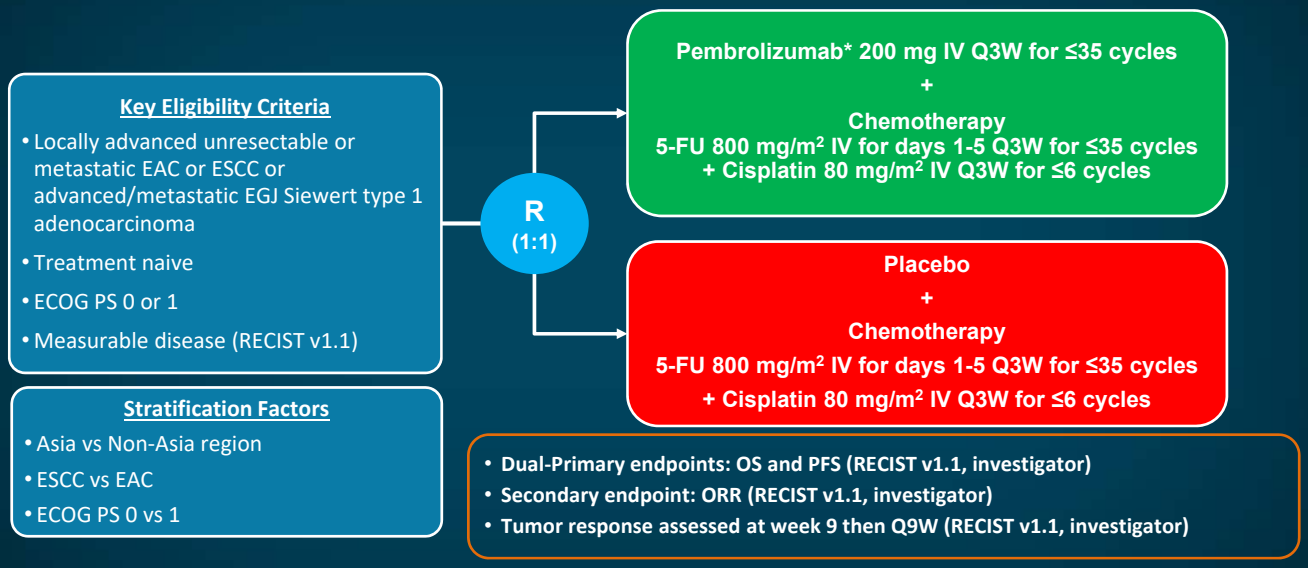
	Nivolumab* (n = 532)	Placebo (n = 262)
Median DFS, mo	22.4	11.0
(95% CI)	(16.6–34.0)	(8.3–14.3)
HR (96.4% CI)	0.69 (0.56–0.86)	
P value	0.0003	

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

Kelly RJ, et al. ESMO 2020. Abstract LBA9_PR

*Off-label or investigative use.

KEYNOTE-590 Study Design (NCT03189719)



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

*Off-label or investigative use.

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

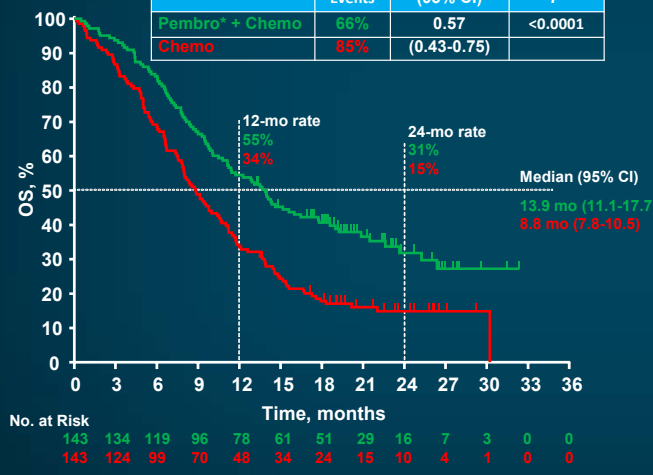
Kato K, et al. *Ann Oncol*. 2020;31(suppl_4):S1142-S1215.

*Off-label or investigative use.

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)	

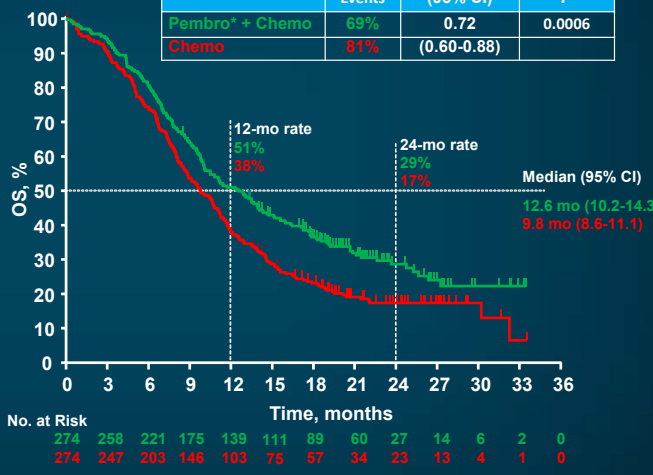


No. at Risk

143	134	119	96	78	61	51	29	16	7	3	0	0
143	124	99	70	48	34	24	15	10	4	1	0	0

ESCC

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



No. at Risk

274	258	221	175	139	111	89	60	27	14	6	2	0
274	247	203	146	103	75	57	34	23	13	4	1	0

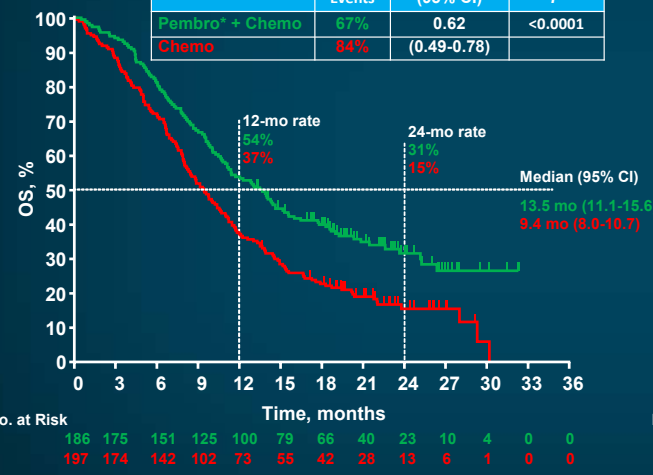
Kato K, et al. *Ann Oncol*. 2020;31(suppl_4):S1142-S1215.
Data cut-off: July 2, 2020.

*Off-label or investigative use.

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)	

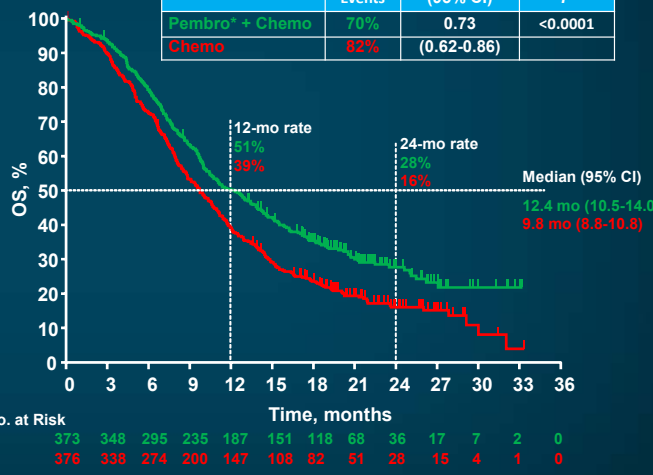


No. at Risk

186	175	151	125	100	79	66	40	23	10	4	0	0
197	174	142	102	73	55	42	28	13	6	1	0	0

All Patients

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



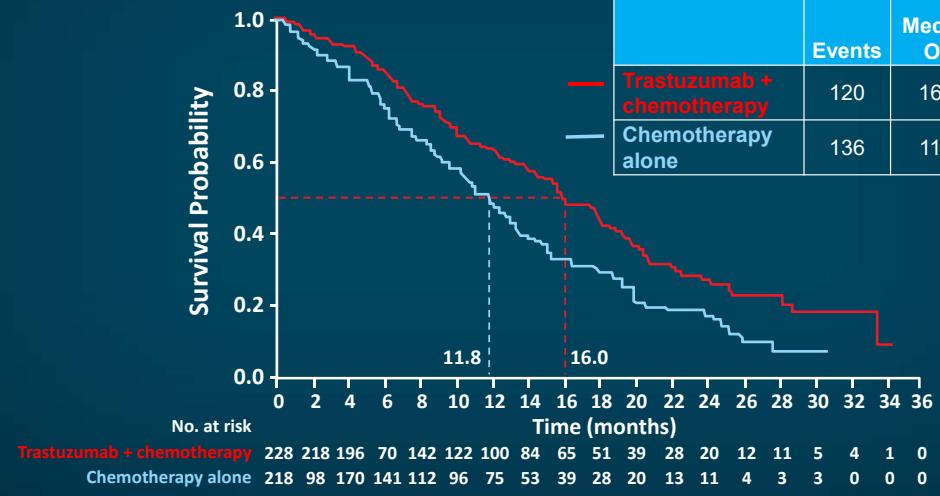
No. at Risk

373	348	295	235	187	151	118	68	36	17	7	2	0
376	338	274	200	147	108	82	51	28	15	4	1	0

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

*Off-label or investigative use.

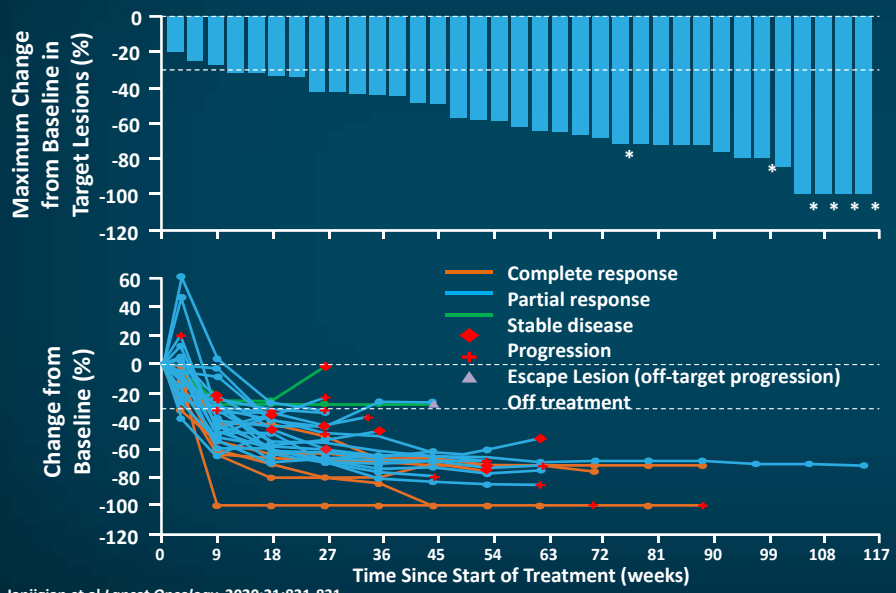
ToGA Overall Survival
IHC 2+/FISH+ or IHC 3+



	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



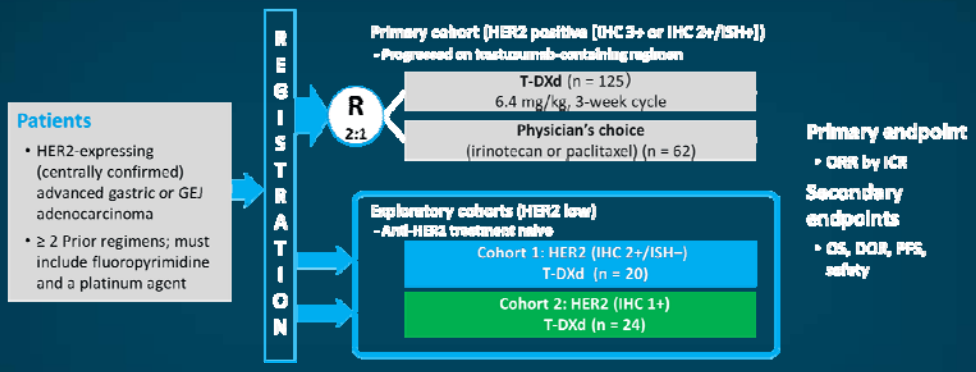
Best Response (n=37)	Patients, n (%)
ORR, n (%)	32 (91%) 95% CI (78%, 97%)
CR PR SD PD	6 (17) 26 (74) 3 (9) 0
Disease Control Rate	100%

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

*Off-label or investigative use.

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)
- Patients had not 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

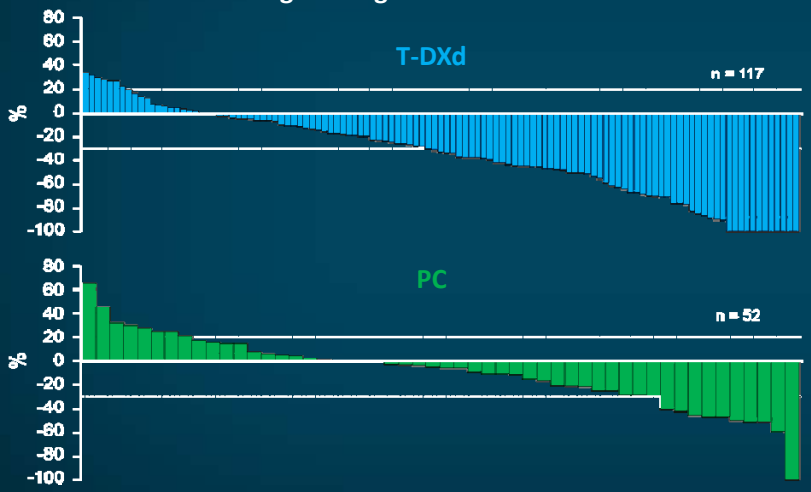
DCR, disease control rate; DOR, duration of response; ICR, independent central review; IHC, immunohistochemistry; ISH, in situ hybridization; NE, not estimable.

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

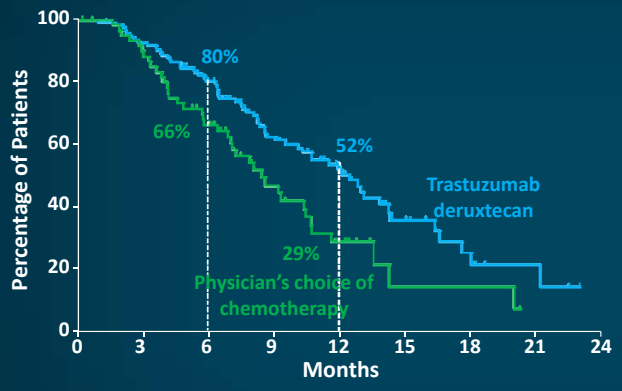


	T-DXd (n=119)	PC (n=56)
ORR	**51.3%**	**14.3%**
Confirmed ORR	**42.9%**	**12.5%**
CR	8.4%	0%
PR	34.5%	12.5%
SD	42.9%	50.0%

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

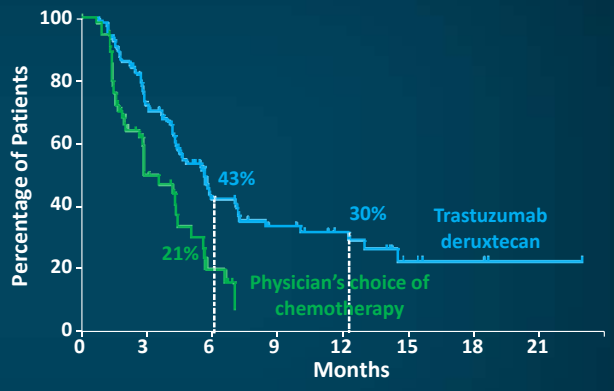
DESTINY-Gastric01: Survival

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.

Summary

- 5-FU/oxaliplatin + nivolumab is likely to replace SOC
- 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

Thank You

Q & A

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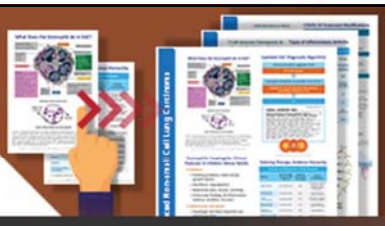

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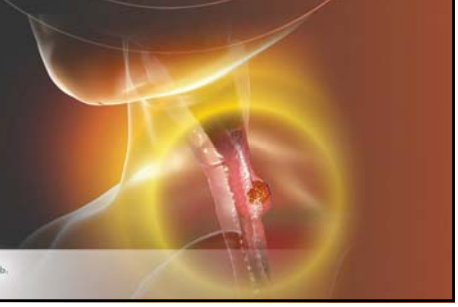
What Surgical Oncologists
Need to Know About Managing
ESOPHAGEAL CANCER
– An Innovative Whiteboard View



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What Surgical Oncologists
Need to Know About Managing
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– An Innovative Whiteboard View

PATHOPHYSIOLOGY OF ESOPHAGEAL CANCER

MOA OF ICIS AS ADJUVANT THERAPY FOR EC

OR, FOLLOW THE LINKS BELOW:

Pathophysiology of Esophageal Cancer: https://youtu.be/25GrIuqpoA0

MOA of ICIs as Adjuvant Therapy for EC: https://youtu.be/-S99aOhShpk

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What Surgical Oncologists Need to Know About Managing Esophageal Cancer – An Innovative Whiteboard View

Resource	Address
ASGE Standards of Practice Committee, Qumseya B, 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/
Pech O, et al. **Long-term efficacy and safety of endoscopic resection for patients with mucosal adenocarcinoma of the esophagus.** *Gastroenterol*. 2014;146:652-660.e1.	https://pubmed.ncbi.nlm.nih.gov/24269290/
Wu J, et al. **Endotherapy versus surgery for early neoplasia in Barrett's esophagus: a meta-analysis.** *Gastrointest Endosc*. 2014;79:233-241.	https://pubmed.ncbi.nlm.nih.gov/24079410/
Boys JA, et al. **Can the risk of lymph node metastases be gauged in endoscopically resected submucosal esophageal adenocarcinomas? A multi-center study.** *J Gastroenterol Surg*. 2016;20:6-12.	https://pubmed.ncbi.nlm.nih.gov/26408330/
Molena D, et al. **Esophagectomy following endoscopic resection of submucosal esophageal cancer: A highly curative procedure even with nodal metastases.** *J Gastrointest Surg*. 2017;21:62-67.	https://pubmed.ncbi.nlm.nih.gov/27561633/
Cancer Genome Atlas Research Network; Analysis Working Group: Asan University; BC Cancer Agency. **Integrated genomic characterization of oesophageal carcinoma.** *Nature.* 2017;541:169-175.	https://pubmed.ncbi.nlm.nih.gov/28052061/
Zehir A, et al. **Mutational landscape of metastatic cancer revealed from prospective clinical sequencing of 10,000 patients.** *Nat Med*. 2017;23:703-713.	https://pubmed.ncbi.nlm.nih.gov/28481359/
Sihag S, et al. **Safety and feasibility of esophagectomy following combined immunotherapy and chemoradiotherapy for esophageal cancer.** *J Thorac Cardiovasc Surg.* 2021;161:836-843.e1.	https://www.jtcvs.org/article/S0022-5223(20)33192-5/fulltext
Shitara K, et al. **Efficacy and safety of pembrolizumab or pembrolizumab plus chemotherapy vs chemotherapy alone for patients with first-line, advanced gastric cancer: The KEYNOTE-062 phase 3 randomized clinical trial.** *JAMA Oncol.* 2020;6:1571-1580.	https://jamanetwork.com/journals/jamaoncology/article-abstract/2769922
Moehler M, et al. **LBA6_PR - 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**	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

results of the CheckMate 649 study. Presented at ESMO 2020. *ANN Oncol.* 2020;31(suppl 4):S1142-S1215.	
Smyth EC, et al. **Mismatch repair deficiency, microsatellite instability, and survival: An exploratory analysis of the Medical Research Council Adjuvant Gastric Infusional Chemotherapy (MAGIC) Trial.** *JAMA Oncology.* 2017;3:1197-1203.	https://jamanetwork.com/journals/jamaoncology/fullarticle/2604821
Kelly RJ, et al. **LBA9_PR - Adjuvant nivolumab in resected esophageal or gastroesophageal junction cancer (EC/GEJC) following neoadjuvant chemoradiation therapy (CRT): First results of the CheckMate 577 study.** Presented at ESMO 2020. *Ann Oncol.* 2020;31(suppl 4):S1142-S1215.	https://oncologypro.esmo.org/meeting-resources/esmo-virtual-congress-2020/adjuvant-nivolumab-in-resected-esophageal-or-gastroesophageal-junction-cancer-ec-gejc-following-neoadjuvant-chemoradiation-therapy-crt-first-r
Kato K, et al. **LBA8_PR - 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. *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
Shitara K, et al. **Trastuzumab deruxtecan in previously treated HER2-positive gastric cancer.** *N Engl J Med*. 2020;382:2419-2430.	https://www.nejm.org/doi/full/10.1056/NEJMoa2004413