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Staying Up-to-Date with Upper Gastrointestinal Malignancies

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OBJECTIVES

1. Identify how the histologic differences across the upper gastrointestinal (GI) cancers affect incidence of various biomarkers (P/T).
2. Determine an appropriate first-line treatment regimen for early-stage or metastatic upper GI cancers based on recent literature.
3. Construct a supportive care prevention and management plan for patients with upper GI cancers receiving newer systemic therapies.

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DISCLOSURE

The following relevant financial relationships from the past 24 months have been identified and disclosed for the following faculty of this CE activity:

- Courtney C. Cavalieri: Advisory Board, Pfizer

No relevant financial relationships from the past 24 months have been identified and disclosed for the following planners of this CE activity:

- Tahsin Imam, PharmD
- Daisy Doan, PharmD
- Kelly Brunk, PharmD, BCOP

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Abbreviations

- **ADR:** adverse drug reaction
- **BRAF:** B-Raf proto-oncogene
- **CLDN18.2:** claudin 18.2
- **EGJ:** esophagogastric junction
- **ERBB2:** Erythroblastic Oncogene B 2
- **G-CSF:** granulocyte-colony stimulating factor
- **HER2:** human epidermal growth factor receptor 2
- **irAE:** immune-related adverse effect
- **MMR:** DNA mismatch repair
- **MSI:** microsatellite instability
- **NTRK:** neurotrophic tropomyosin receptor kinase
- **OS:** overall survival
- **PD-L1:** programmed death ligand 1
- **PFS:** progression-free survival
- **RET:** rearranged during transfection
- **TMB:** tumor mutation burden

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Background

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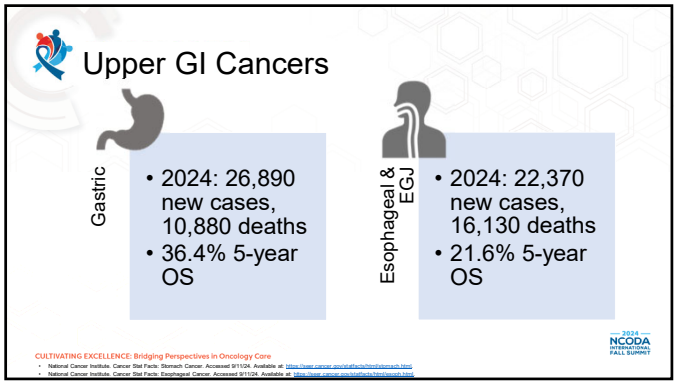
Upper GI Cancers
Gastric
• 2024: 26,890 new cases, 10,880 deaths
• 36.4% 5-year OS
Esophageal & EGJ
• 2024: 22,370 new cases, 16,130 deaths
• 21.6% 5-year OS
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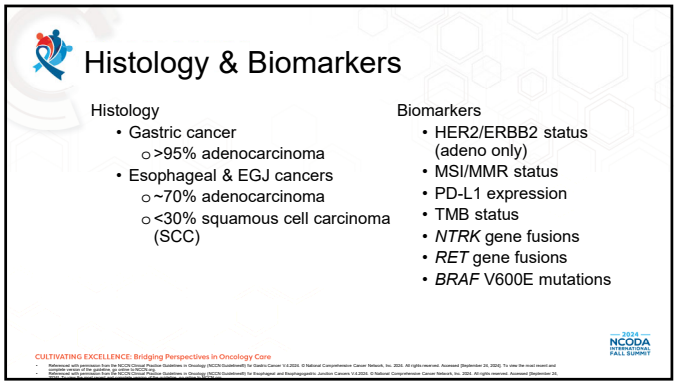
Histology & Biomarkers
Histology
• Gastric cancer
o >95% adenocarcinoma
• Esophageal & EGJ cancers
o ~70% adenocarcinoma
o <30% squamous cell carcinoma (SCC)
Biomarkers
• HER2/ERBB2 status (adeno only)
• MSI/MMR status
• PD-L1 expression
• TMB status
• *NTRK* gene fusions
• *RET* gene fusions
• *BRAF* V600E mutations
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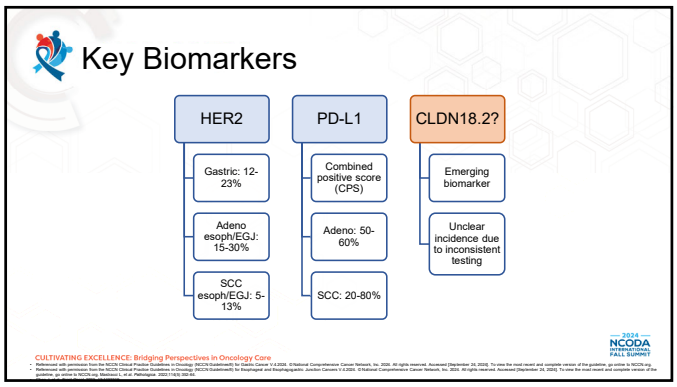
Key Biomarkers
HER2
Gastric: 12-23%
Adeno esoph/EGJ: 15-30%
SCC esoph/EGJ: 5-13%
PD-L1
Combined positive score (CPS)
Adeno: 50-60%
SCC: 20-80%
CLDN18.2?
Emerging biomarker
Unclear incidence due to inconsistent testing
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QUESTION 1

GJ presents to the medical oncology clinic to discuss treatment of a new diagnosis of metastatic squamous cell carcinoma of the esophagus. The oncologist is going to acquire next-generation sequencing to check for any pertinent biomarkers.

Which of the following biomarkers will be most relevant to GJ's diagnosis for first-line treatment?

a. EGFR
b. HER2
c. PD-L1
d. BRAF V600E

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Early-Stage Esophageal Cancer Updates

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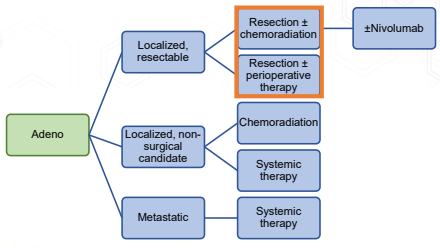
Overview of Treatment: Esophageal & EGJ



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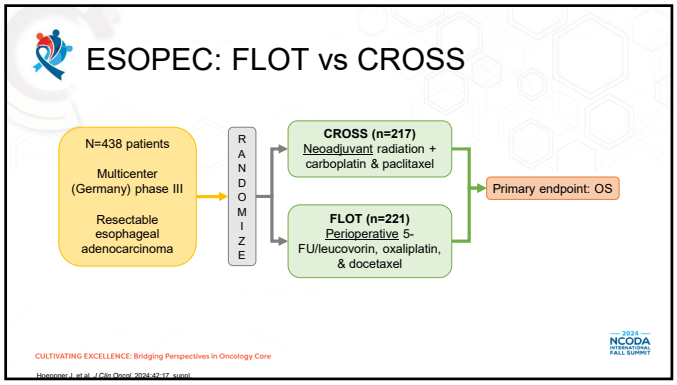

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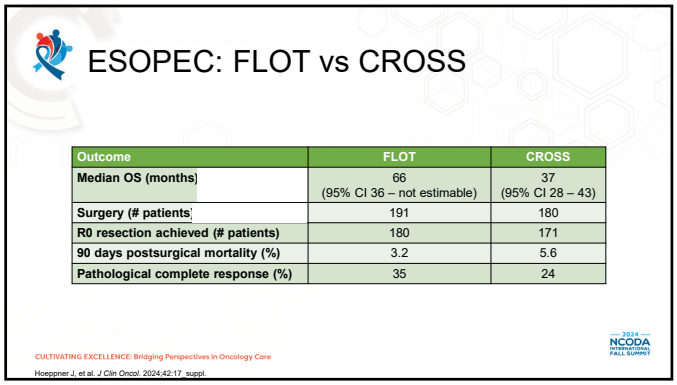

Outcome	FLOT	CROSS
Median OS (months)	66 (95% CI 36 – not estimable)	37 (95% CI 28 – 43)
Surgery (# patients)	191	180
R0 resection achieved (# patients)	180	171
90 days postsurgical mortality (%)	3.2	5.6
Pathological complete response (%)	35	24

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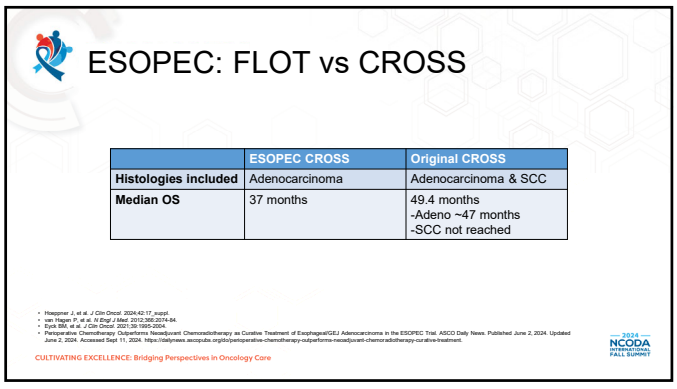

	ESOPEC CROSS	Original CROSS
Histologies included	Adenocarcinoma	Adenocarcinoma & SCC
Median OS	37 months	49.4 months -Adeno ~47 months -SCC not reached

- Hoeppner J, et al. *J Clin Oncol*. 2024;42:17_suppl.
- van Hagen P, et al. *N Engl J Med*. 2012;366:2074-84.
- Eyck BM, et al. *J Clin Oncol*. 2021;39:1995-2004.
- Perioperative Chemotherapy Outperforms Neoadjuvant Chemoradiotherapy as Curative Treatment of Esophageal/GEJ Adenocarcinoma in the ESOPEC Trial. ASCO Daily News. Published June 2, 2024. Updated June 2, 2024. Accessed Sept 11, 2024. https://dailynews.ascopubs.org/do/perioperative-chemotherapy-outperforms-neoadjuvant-chemoradiotherapy-curative-treatment.

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QUESTION 2

You are part of the gastrointestinal tumor treatment board conference. UH is a patient with newly diagnosed, early-stage esophageal adenocarcinoma. The decision has been made that he is resectable.

What is the most appropriate systemic therapy to include with his resection to maximize his survival?

a. Perioperative FLOT (5-FU, oxaliplatin, docetaxel)

b. Neoadjuvant chemoradiation with carboplatin and paclitaxel

c. Adjuvant nivolumab

d. Neoadjuvant FOLFOX (5-FU, oxaliplatin) and pembrolizumab

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Metastatic Disease Updates

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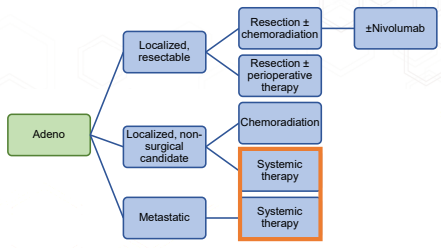
Overview of Treatment: Esophageal & EGJ



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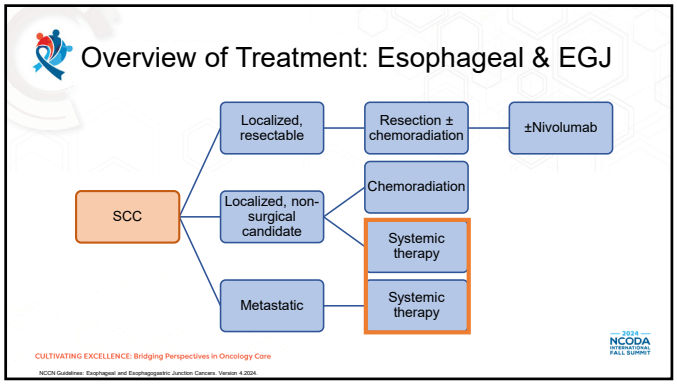
Overview of Treatment: Esophageal & EGJ
Localized, resectable
Resection ± chemoradiation
±Nivolumab
SCC
Localized, non-surgical candidate
Chemoradiation
Systemic therapy
Metastatic
Systemic therapy
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NCCN Guidelines: Esophageal and Esophagogastric Junction Cancers, Version 4.2024.
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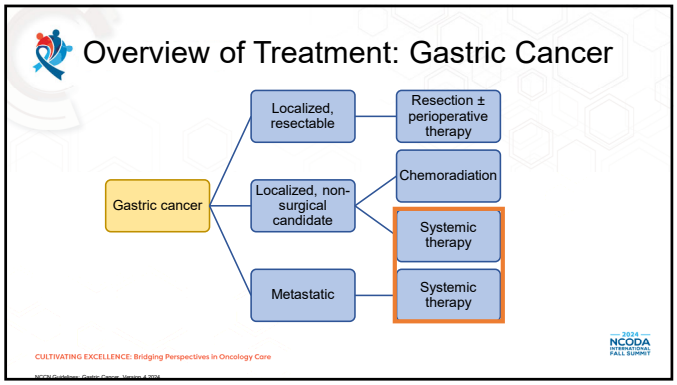
Overview of Treatment: Gastric Cancer
Localized, resectable
Resection ± perioperative therapy
Gastric cancer
Localized, non-surgical candidate
Chemoradiation
Systemic therapy
Metastatic
Systemic therapy
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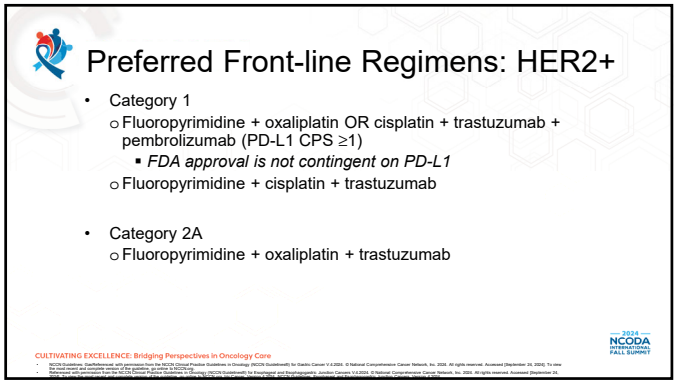
Preferred Front-line Regimens: HER2+
Category 1
Fluoropyrimidine + oxaliplatin OR cisplatin + trastuzumab + pembrolizumab (PD-L1 CPS ≥1)
FDA approval is not contingent on PD-L1
Fluoropyrimidine + cisplatin + trastuzumab
Category 2A
Fluoropyrimidine + oxaliplatin + trastuzumab
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Preferred Front-line Regimens: HER2-

	Gastric	Adeno esophageal/EGJ	SCC esophageal/EGJ
F + oxaliplatin + nivolumab	HER2-, category 1 for PD-L1 ≥5	Category 1 for PD-L1 ≥5 Category 2B for PD-L1 <5	Category 1
F + cisplatin + nivolumab	X	X	Category 1
F + oxaliplatin + pembrolizumab	Category 1 for PD-L1 ≥10 Category 2A for PD-L1 ≥1 Category 2B for PD-L1 1 to <10		Category 2A for PD-L1 ≥10 Category 2B for PD-L1 <10
F + cisplatin + pembrolizumab			Category 1 for PD-L1 ≥10 Category 2B for PD-L1 <10
F + oxaliplatin or cisplatin	Category 2A		
Nivolumab + ipilimumab	X		Category 2A

F = fluoropyrimidine; 5-fluorouracil or capecitabine

All regimens are FDA approved for respective indications regardless of PD-L1 status

- Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Gastric Cancer V.4.2024. © National Comprehensive Cancer Network, Inc. 2024. All rights reserved. Accessed [September 24, 2024]. To view the most recent and complete version of the guideline, go online to NCCN.org.
- Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Esophageal and Esophagogastric Junction Cancers V.4.2024. © National Comprehensive Cancer Network, Inc. 2024. All rights reserved. Accessed [September 24, 2024]. To view the most recent and complete version of the guideline, go online to NCCN.org.

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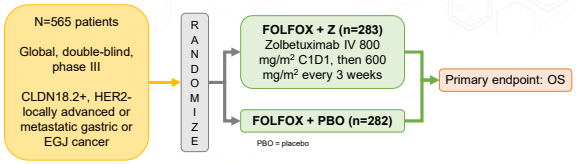
SPOTLIGHT: Zolbetuximab



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- Shitara K, et al. *J Clin Oncol*. 2024;42:16_suppl.
- Shitara K, et al. *Lancet*. 2023;401:1655-68.

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SPOTLIGHT: Zolbetuximab

- Median OS: 18.23 vs 15.57 months (95% CI 0.644-0.954; p=0.0075)
- Median PFS: 11.04 vs 8.94 months (95% CI 0.591-0.910; p=0.0024)
- ORR: 48.1% vs 47.5%
- Safety
  - Most common ADRs: nausea, vomiting, decreased appetite
  - Discontinuation due to ADRs: 14% vs 2%

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- Shitara K, et al. *J Clin Oncol*. 2024;42:16_suppl.
- Shitara K, et al. *Lancet*. 2023;401:1655-68.

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Zolbetuximab & CLDN18.2

- Claudin → family of 27 transmembrane proteins
- Claudin 18 → major component of tight junctions
  - Plays a tumor suppressor role in gastric cancer
- CLDN18.2 → protein isoform specifically expressed in stomach tissue
  - Involved in regulating ion permeability
  - Deficiency leads to neutrophil recruitment and inflammation
- Zolbetuximab → binds with high affinity to cells expressing CLDN18.2
  - Induces antibody-dependent cytotoxicity

Chen J, et al. *Front Oncol*. 2023;13:1132319.

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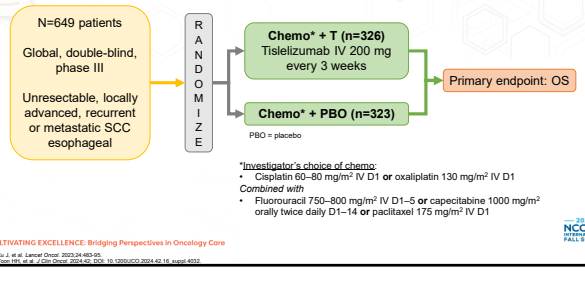
RATIONALE-306: Tislelizumab + chemo



*Investigator's choice of chemo:
- Cisplatin 60–80 mg/m² IV D1 **or** oxaliplatin 130 mg/m² IV D1

Combined with
- Fluorouracil 750–800 mg/m² IV D1–5 **or** capecitabine 1000 mg/m² orally twice daily D1–14 **or** paclitaxel 175 mg/m² IV D1

- Xu J, et al. *Lancet Oncol*. 2023;24:483-95.
- Yoon HH, et al. *J Clin Oncol*. 2024;42. DOI: 10.1200/JCO.2024.42.16_suppl.4032.

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RATIONALE-306: Tislelizumab + chemo

- Median OS: 17.2 vs 10.6 months (HR 0.70, 95% CI 0.59 to 0.83)
  - 36-month OS: 22.1 vs 14.1 months
- Median PFS: 7.3 vs 5.6 months (HR 0.62, 95% CI 0.52 to 0.75)
  - 36-month PFS: 15.0 vs 2.9 months
- Any-grade (96.6% vs 96.3%) or grade ≥3 (67.0% vs 64.5%) treatment-related adverse events were comparable

- Xu J, et al. *Lancet Oncol*. 2023;24:483-95.
- Yoon HH, et al. *J Clin Oncol*. 2024;42. DOI: 10.1200/JCO.2024.42.16_suppl.4032.

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PD-L1 status

- KEYNOTE-590 (pembrolizumab + chemo), CheckMate 648 (nivolumab + chemo), and RATIONALE-306 included all patients regardless of PD-L1 status
  - PD-L1 <1 patients consistently did not benefit from addition of checkpoint inhibitors
  - NCCN Guidelines took PD-L1 cutoffs into consideration, FDA approvals did not
- **9/26/24**: FDA Oncologic Drugs Advisory Committee (ODAC) voted against the risk:benefit profile of anti–PD-1 therapy in first-line metastatic esophageal SCC with a PD-L1 <1

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Wahner A. ODAC Votes Against Risk-Benefit Profile of Frontline Anti–PD-1 Therapy in Metastatic/Unresectable ESCC With a PD-L1 Expression Under 1. OncLive. Updated 9/26/24. Accessed 9/26/24. Available at: https://www.onclive.com/view/odac-votes-against-risk-benefit-profile-of-frontline-anti-pd-1-therapy-in-metastatic-unresectable-escc-with-a-pd-l1-expression-under-1

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Supportive Care

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CROSS & FLOT

CROSS	FLOT
Radiation complications	Neutropenia
Myelosuppression	Need for central access
Neuropathy	Neuropathy
Hypersensitivity	Hypersensitivity

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Checkpoint Inhibitors

- Pembrolizumab, nivolumab, ipilimumab, dostarlimab, tislelizumab
- Typically well-tolerated, but irAEs can be serious and fatal
- Variety of guidelines to aid in management:
  - NCCN Guidelines: Management of Immunotherapy-Related Toxicities
  - Management of Immune-Related Adverse Events in Patients Treated With Immune Checkpoint Inhibitor Therapy: ASCO Guideline Update
  - Management of toxicities from immunotherapy: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up

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- NCCN Guidelines: Management of Immunotherapy-Related Toxicities. Version 1.204.
- Schneider BJ, et al. J Clin Oncol. 2021;39:4073-126.
- Haanen J, et al. Ann Oncol. 2022;33:1217-38.

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Zolbetuximab

- Nausea increased by >20%: 77% vs 53%
- Vomiting increased by almost 40%: 64% vs 25%
- Incidence of nausea and vomiting were most common during the first treatment cycle (42 days) and decreased thereafter
- Analysis from SPOTLIGHT & GLOW trials
  - First episode of N/V occurred within 1 hour of zolbetuximab infusion
  - Incidence of nausea and vomiting dropped from the first infusion to the second: 58% vs 18% (nausea) and 43% vs 15% (vomiting)

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- Shitara K, et al. Lancet. 2023;401:1655-68.
- Shitara K, et al. J Clin Oncol. 2024;42:3. suppl.

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Zolbetuximab-Induced N/V

n (%)	5-HT3 only	5-HT3 + NK-1	5-HT3 + steroids	5-HT3 + NK-1 + steroids	5-HT3 + NK-1 + steroids + others
Nausea	16 (53)	95 (52)	58 (48)	34 (49)	15 (47)
Vomiting	15 (50)	63 (35)	44 (36)	23 (33)	10 (31)
N/V	11 (37)	48 (27)	32 (26)	19 (28)	8 (25)
No N/V	10 (33)	71 (39)	51 (42)	31 (45)	15 (47)

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QUESTION 3

KM is starting zolbetuximab + FOLFOX on a clinical trial.

Which of the following is the most appropriate statement to include in her counseling?

a. KM may experience immediate and severe diarrhea during the zolbetuximab infusion

b. Nausea and vomiting are pretty common with zolbetuximab, and KM may vomit within 1 hour of the infusion starting

c. KM will likely experience a severe hypersensitivity to zolbetuximab, so she will receive pre-medications to ameliorate this

d. Nausea and vomiting will likely become more severe as KM receives more infusions of zolbetuximab

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SUMMARY

- The treatment landscape of upper GI cancers is evolving, both in the early stage and metastatic space
- Healthcare providers need to consider multiple factors for upper GI patients to select the most appropriate treatment regimen, including histology, location of the disease, and pertinent biomarkers
- As new therapies are introduced, healthcare providers should be aware of unique toxicities in order to best care for patients

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QUESTION & ANSWERS

Staying Up-to-Date with Upper Gastrointestinal Malignancies

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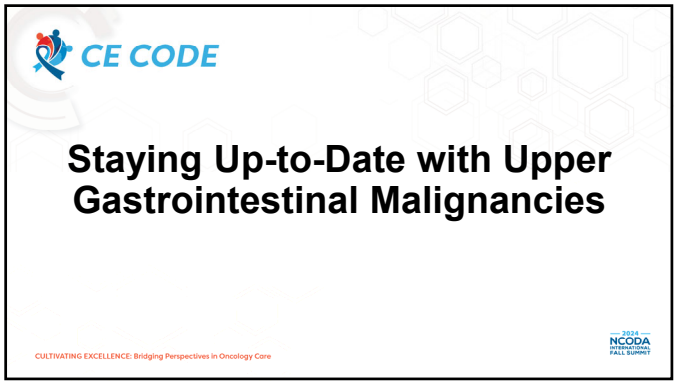
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