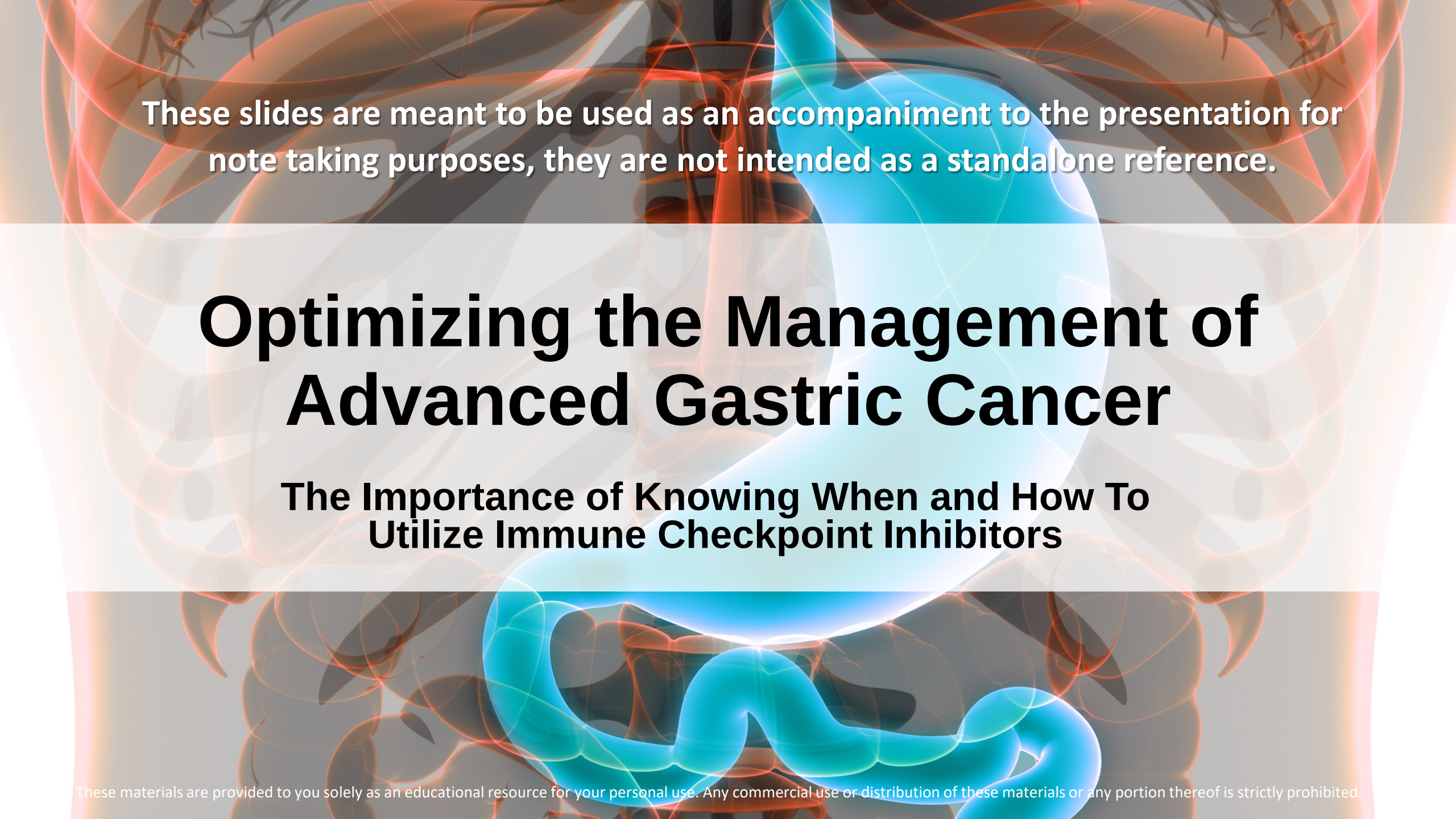
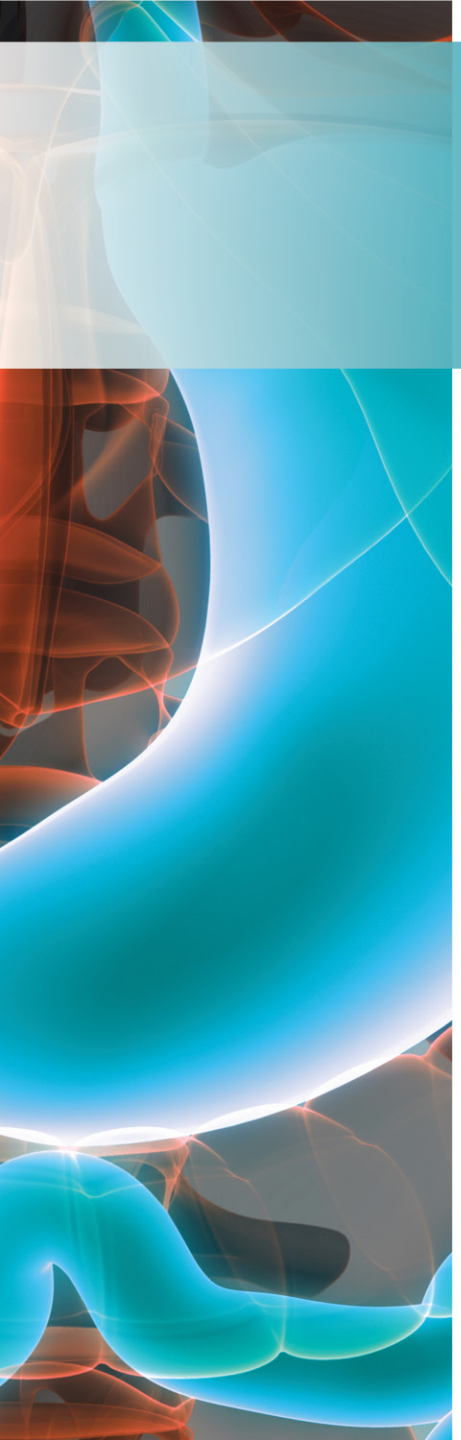


These slides are meant to be used as an accompaniment to the presentation for note taking purposes, they are not intended as a standalone reference.

Optimizing the Management of Advanced Gastric Cancer

The Importance of Knowing When and How To Utilize Immune Checkpoint Inhibitors



This educational activity is jointly accredited for physicians, nurses, and pharmacists and is supported by an independent educational grant from Bristol Myers Squibb.

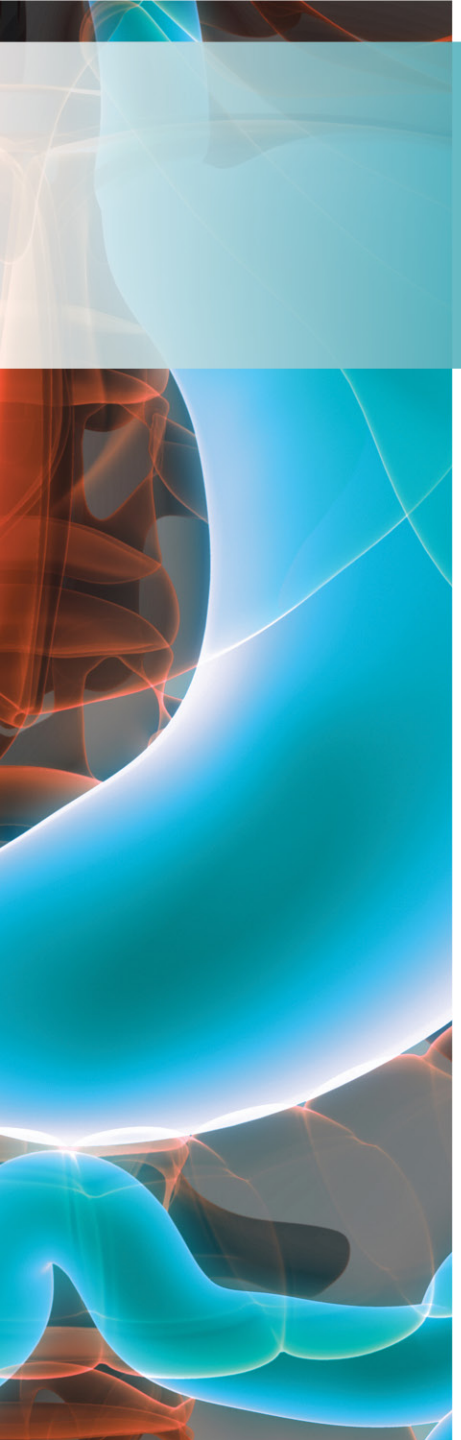
Faculty

Jennifer L. Zadlo, PharmD, BCOP
Oncology Clinical Pharmacy Specialist
Gastrointestinal Medical Oncology and Endocrine Neoplasias
The University of Texas MD Anderson Cancer Center
Houston, TX

Dr Zadlo earned her Doctor of Pharmacy from the University of the Sciences – Philadelphia College of Pharmacy in 2010, followed by a brief inpatient pharmacist stint at Monmouth Medical Center in Long Branch, NJ. Dr Zadlo completed a PGY1 Pharmacy Residency at Penn State Hershey Medical Center and a PGY2 Oncology Pharmacy Residency at MD Anderson Cancer Center before being permanently hired in outpatient gastrointestinal (GI) medical oncology in 2013. More recently, her clinical specialist role at MD Anderson has expanded to included GI Medical oncology and complex endocrine neoplasia.

Improving patient-related outcomes, patient safety, and building patient empowerment through direct patient care and education are included in her professional interest projects. She is particularly skilled in making difficult clinical topics approachable for both colleagues and patients, respectively.

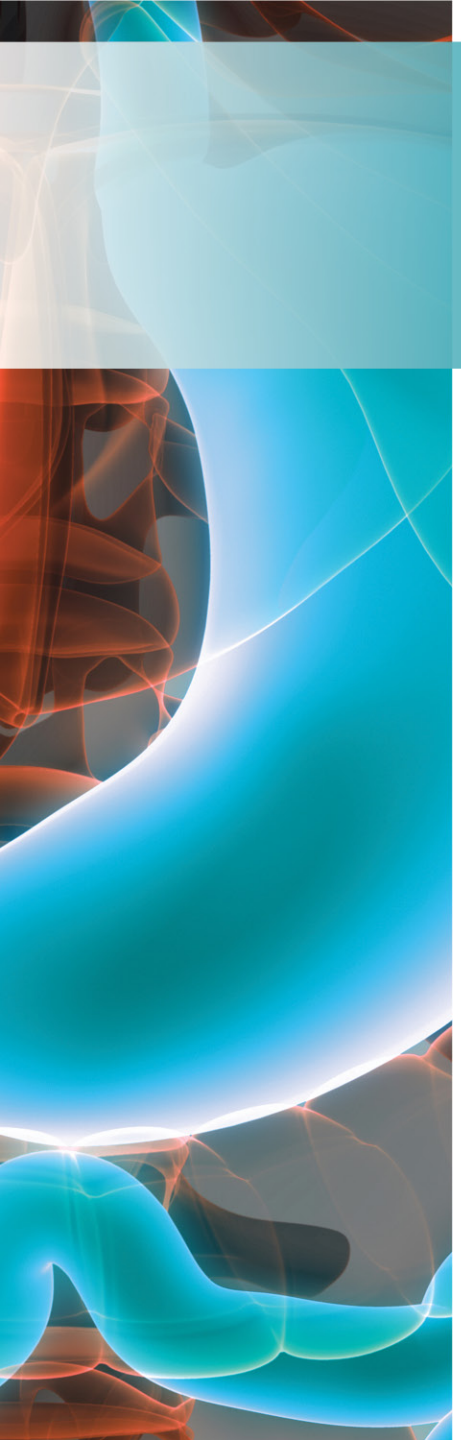
Faculty



Harry H. Yoon, MD, MHS
Chair, Gastroesophageal Cancer Disease Group
Mayo Clinic Comprehensive Cancer Center
Consultant, Department of Oncology
Mayo Clinic, Associate Professor of Oncology
Mayo Clinic College of Medicine
Rochester, MN

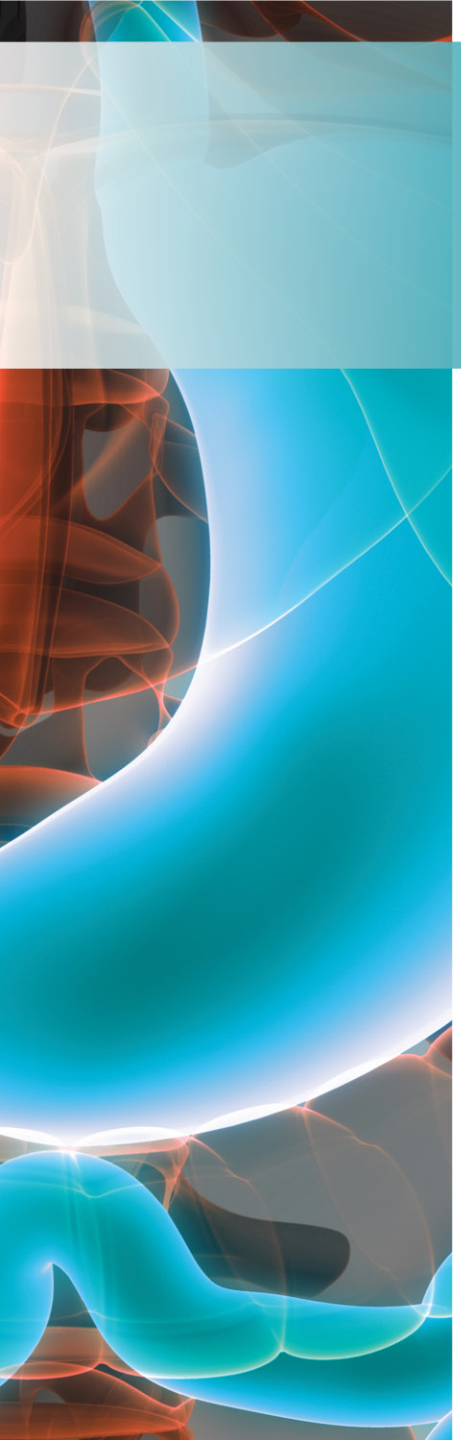
Dr Yoon is a GI oncologist and clinical/translational researcher at the Mayo Clinic, where he has been on faculty since 2008. He leads an R01-funded clinical/translational research program from the US National Institutes of Health that seeks to understand the impact of immunotherapy on host immune responses in patients with gastroesophageal cancer. He also serves on the guidelines panel of the National Comprehensive Cancer Network (NCCN) for gastric/esophageal cancer and on steering committees of global registrational trials. Dr Yoon is a graduate of Yale School of Medicine (MD), Johns Hopkins Schools of Medicine and Public Health (MHS); and Yale College (BS in Molecular Biophysics and Biochemistry).

Faculty



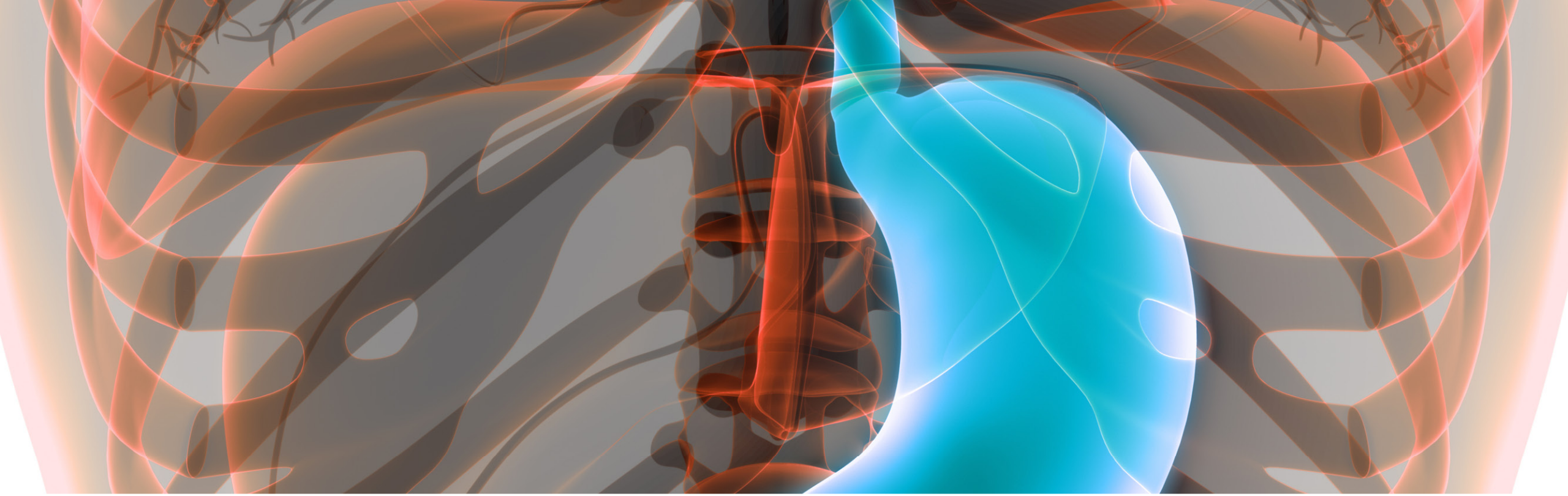
Sharon L. Cavone, RN, BSN, OCN
Clinical Content Developer
CAREVIVE Systems, Inc.
Oncology Nurse Navigator (Former)
PENN Medicine Princeton Healthcare

Ms Cavone is an oncology nurse with many years of experience caring for people on the cancer journey. She has administered treatments and provided education, symptom management, and decision support to countless numbers of patients and their families. In her role as nurse navigator, she worked to reduce barriers to optimal cancer care. Currently, she works as a clinical content developer for Carevive Systems - an oncology data health company focusing on amplifying the patient voice through their remote symptom monitoring platform.



Learning Objectives

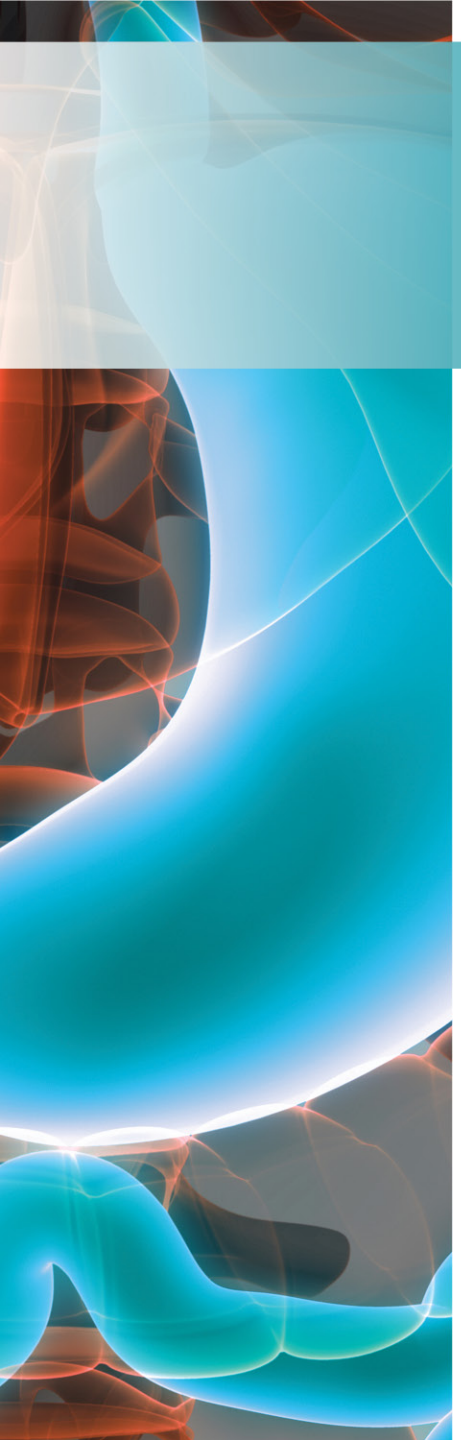
- **Describe** emerging evidence for immune checkpoint inhibitors in advanced gastric cancer
- **Recognize** appropriate biomarker assessment for timely initiation of immune checkpoint inhibitors for advanced gastric cancer
- **Develop** a patient-specific treatment plan for a patient with advanced gastric cancer
- **Formulate** approaches to optimally manage a patient with advanced gastric cancer on immune checkpoint inhibitors



Case 1

PD-L1 CPS 10+ HER2-negative

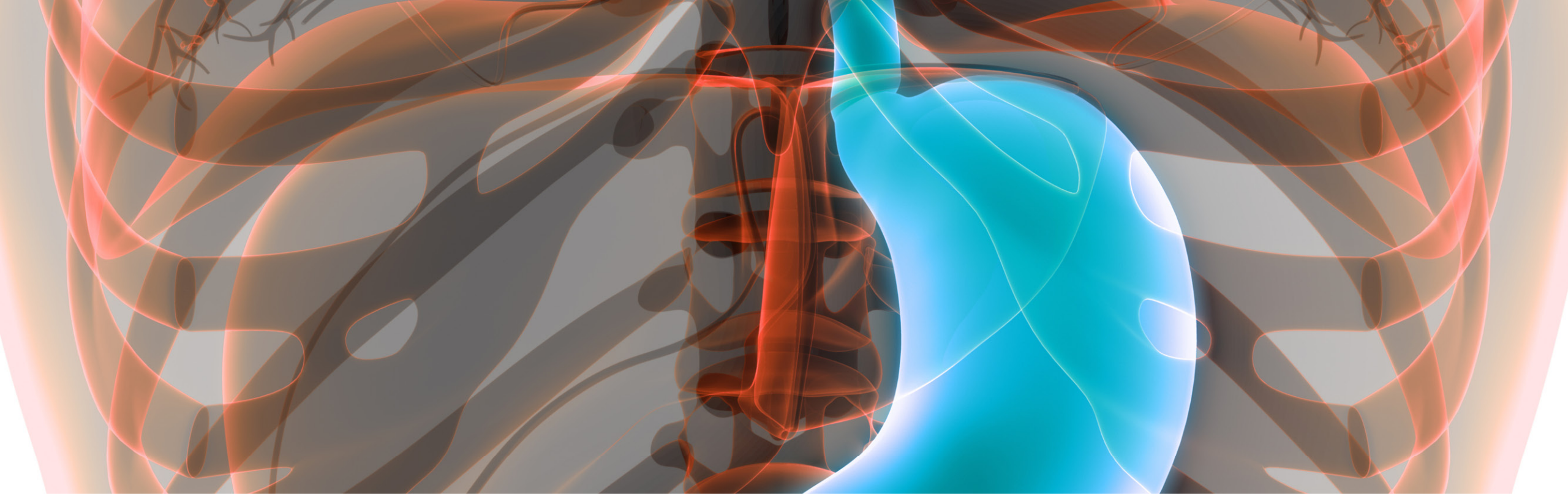
Abbreviations: CPS, combined positive score; PD-L1, programmed death ligand



Case 1

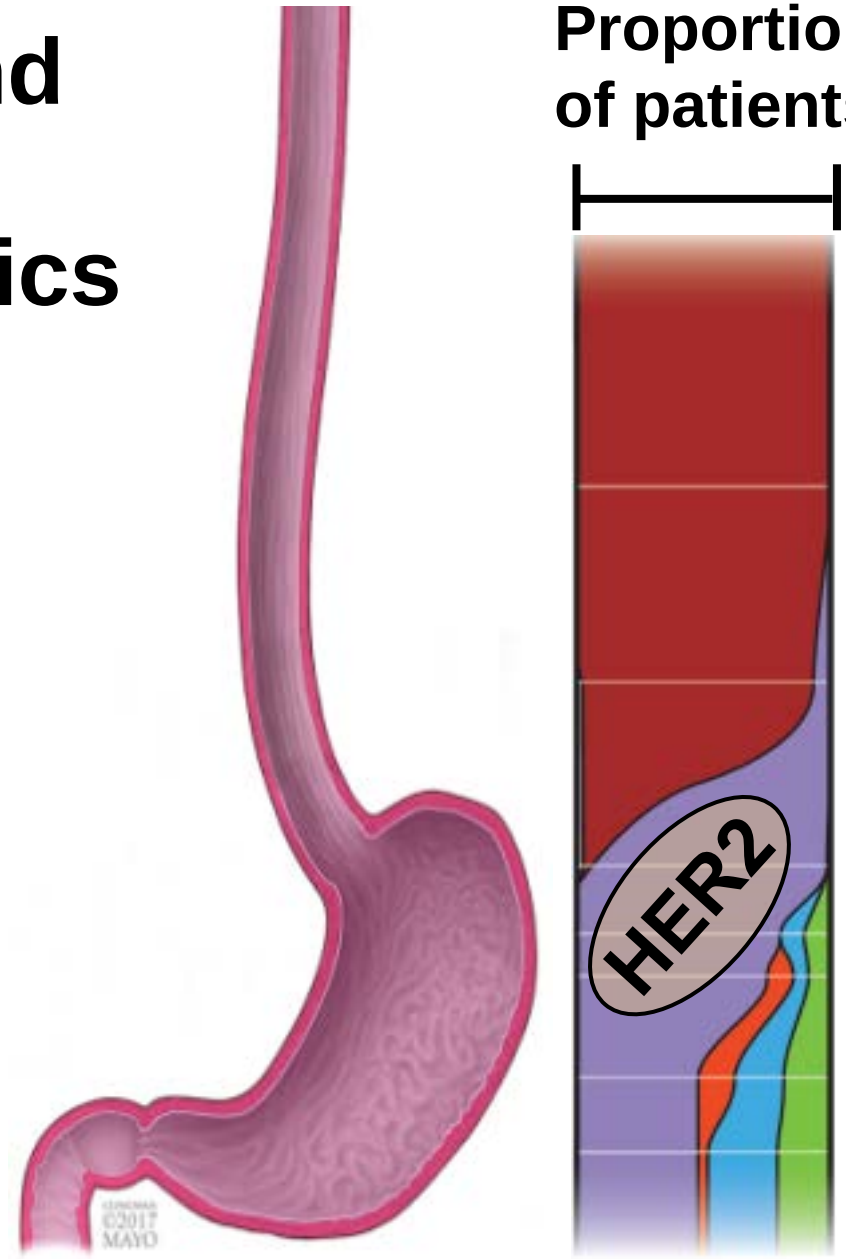
EM presents at your clinic with his son to discuss a new diagnosis of gastric cancer.

He had a recent ED visit and subsequent hospital work up for abdominal pain, nausea, and vomiting, and unintentional weight loss of more than 35 lbs.



What is the 30,000-ft overview of gastric cancer?

Anatomic and Genomic Characteristics



Esophageal SCC signature — **PD-L1 enriched**

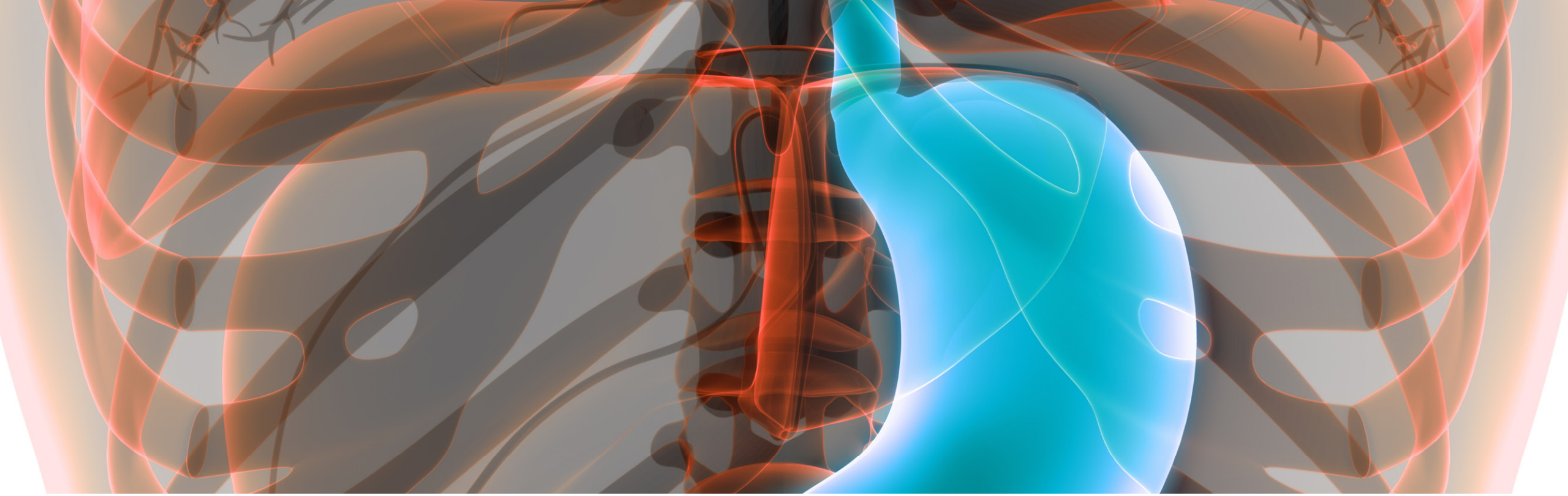
Chromosomal instability (CIN) — **RTKs**

EBV, **MSI** — **T-cell inflamed**

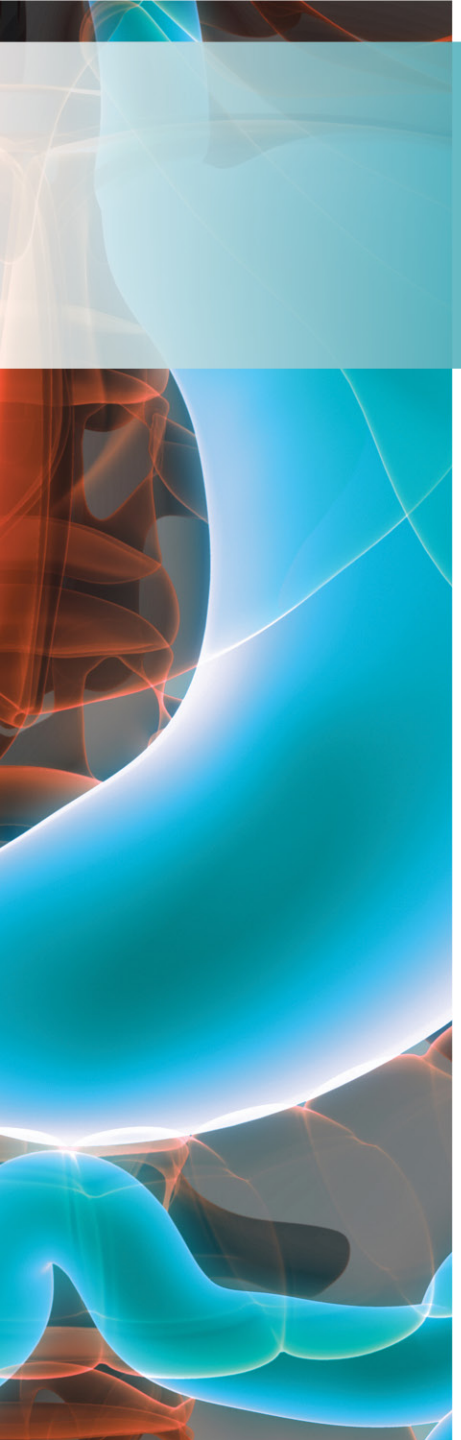
Genomically stable — **Few known actionable targets**

TCGA, *Nature* 2017

Abbreviations: CIN, chromosomal instability; EBV, Epstein Barr virus; MSI, microsatellite instability; RTKs, receptor tyrosine kinases; SCC, squamous cell carcinoma.



What are the next steps in diagnosis?



Case 1

CT CAP: multiple hepatic metastases; peritoneal thickening concerning for peritoneal carcinomatosis

Pathology: poorly differentiated adenocarcinoma of the gastric cardia; MSS

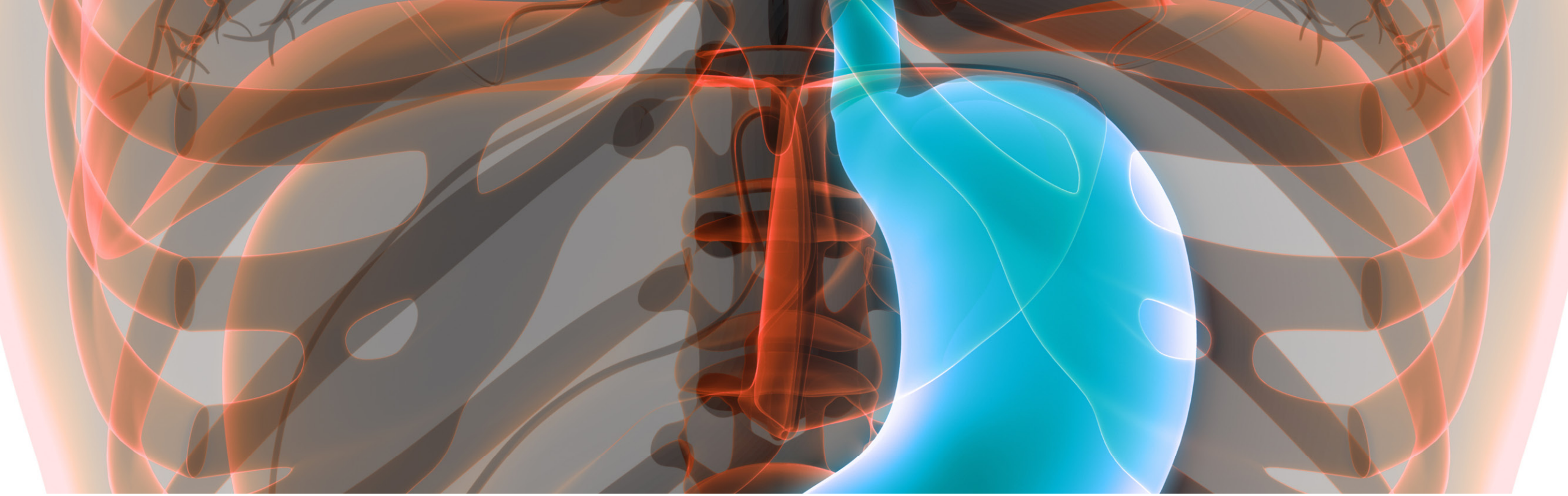
Biomarker testing:

HER2-negative

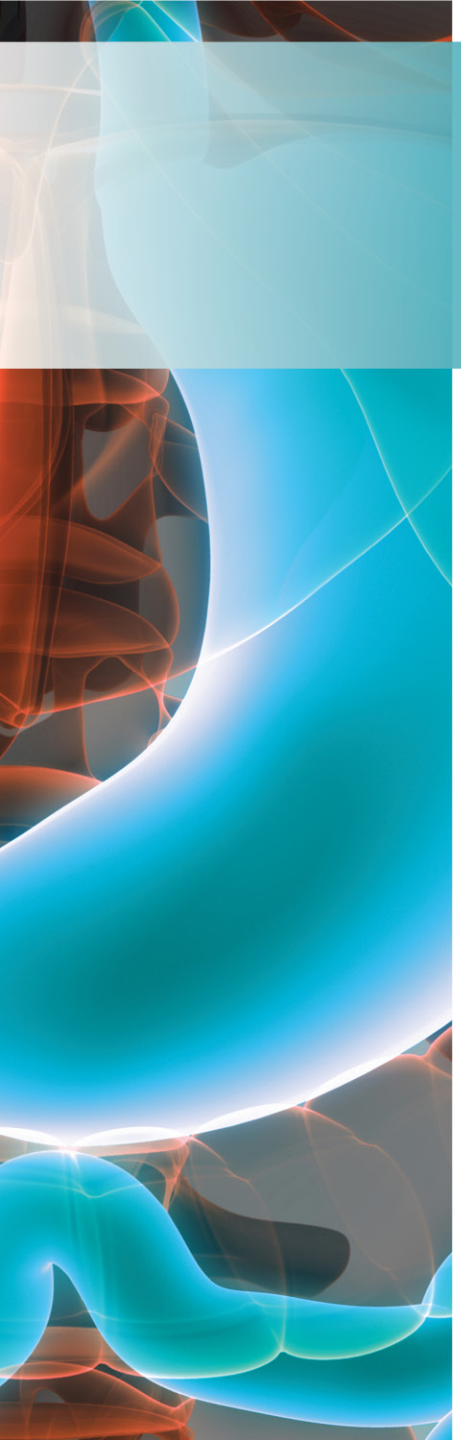
PD-L1 CPS = 10

Additional: EM regularly takes medication for diabetes and hypertension but has not been to the medical clinic in almost 1 year.

Abbreviations: MSS, microsatellite stability biomarker.



What are the necessary biomarkers of interest?



Necessary Biomarkers

- **HER2** – order IHC first, reflex to FISH if IHC 2+
- **PD-L1** – order IHC (28-8 [nivolumab], 22C3 [pembrolizumab])
- **MSI** – order MMR by IHC
- Other:
  - NTRK fusion
  - TMB
- **Alternate approach: NGS plus PD-L1**
  - Advantage: more targets tested, TMB
  - Disadvantage: more tissue depleted, unevaluable, delay
- If above not available or as complement: **ctDNA**

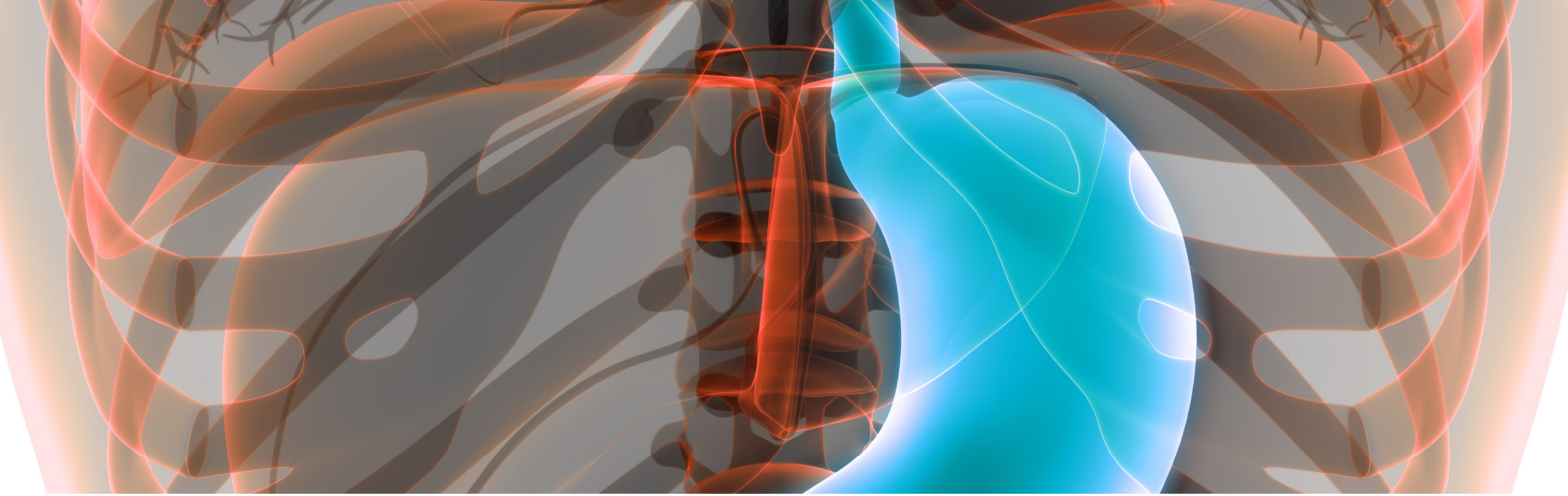
Definition of HER2 positive

IHC 3+, or IHC2+ with FISH+

Definition of MMR-deficient

Loss of 1 or more MMR proteins

Abbreviations: ctDNA, circulating tumor DNA; FISH, fluorescence in situ hybridization; IHC, immunohistochemistry; MMR, mismatch repair; NGS, next-generation sequencing.



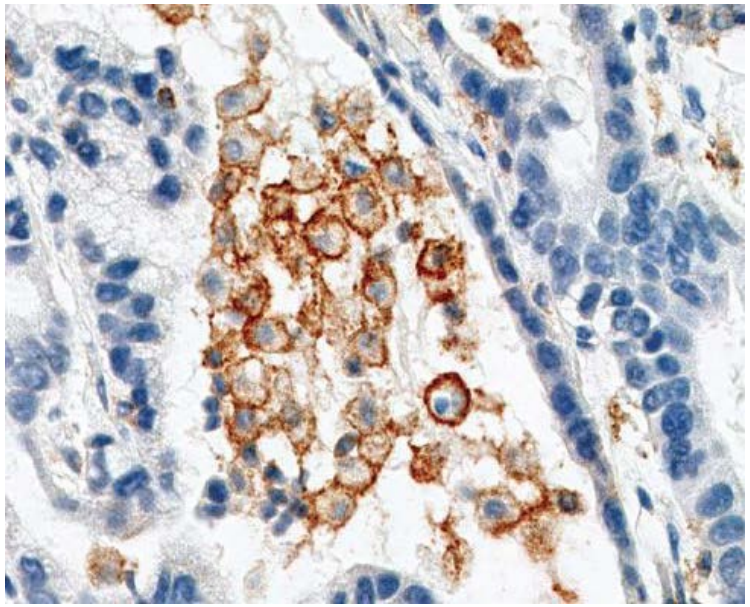
What is the difference between PD-L1 CPS and TPS?

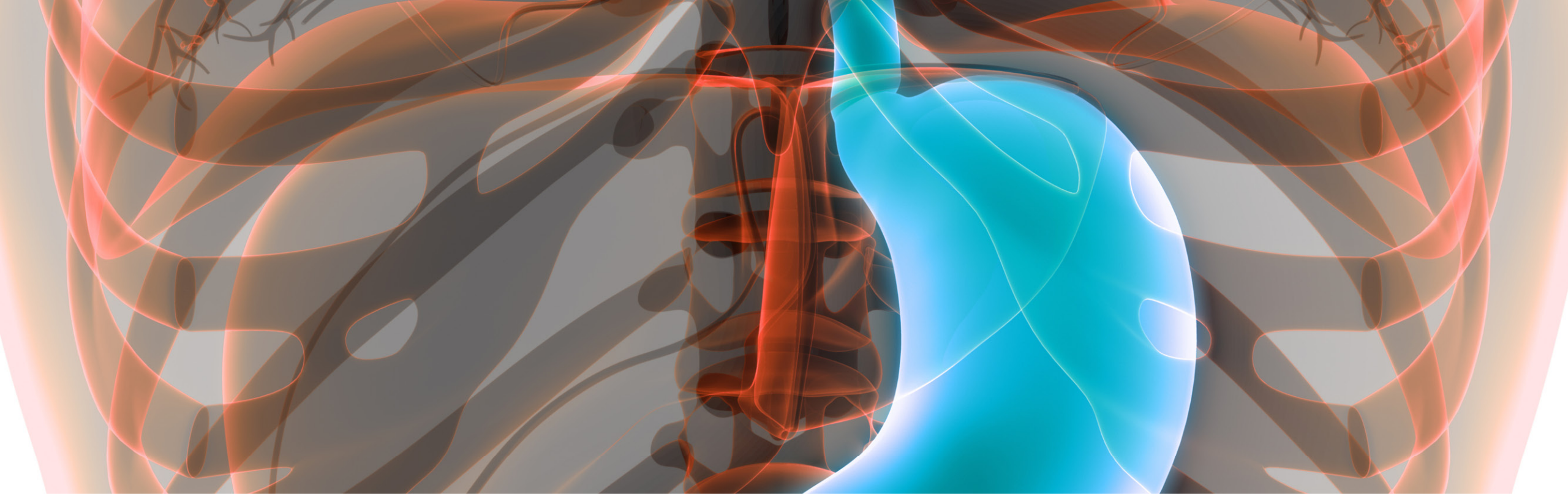
Abbreviation: TPS, tissue polypeptide specific antigen.

PD-L1 CPS vs TPS

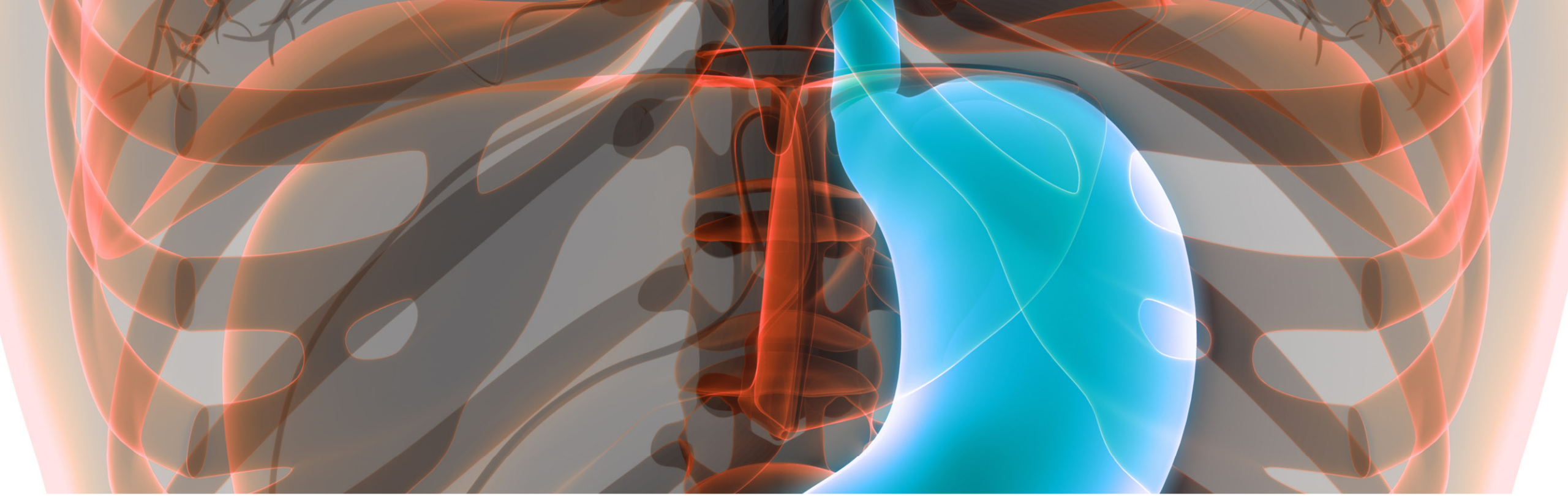
$$\textbf{CPS} = \frac{\text{\# of } \textbf{\textit{macrophages}}\textbf{, }\textbf{\textit{lymphocytes}}\text{, or tumor cells that express PD-L1}}{\text{\# of tumor cells evaluated}} \times 100$$

$$\textbf{TPS} = \frac{\text{\# of tumor cells that express PD-L1}}{\text{\# of tumor cells evaluated}} \times 100$$





EM and son wish to discuss first-line treatment of metastatic gastric cancer



What does the “big picture” treatment of gastric cancer look like?

2022 Treatment Landscape for Fit Patient With Advanced Gastric Cancer: First-line

NCCN (Category 1 or 2A)

HER2-pos
pembrolizumab + trastuzumab + platin/fluoropyrimidine (KN811)

HER2-neg, PD-L1 CPS ≥ 5
nivolumab + platin/fluoropyrimidine (CM649)

HER2-neg, PD-L1 CPS 0-4
platin/fluoropyrimidine (CM649)

FDA

HER2-pos
pembrolizumab + trastuzumab + platin/fluoropyrimidine (KN811)

HER2-neg
nivolumab + platin/fluoropyrimidine (CM649)

NOTE: Oxaliplatin is preferred over cisplatin.

NOTE: For adenoca with MSI, nivo + platin/FP, or pembro or nivo or nivo + IPI

Abbreviations: FDA, Food and Drug Administration; NCCN, National Comprehensive Cancer Network.

NCCN and FDA

NCCN's rationale to withhold ICI in patients with PD-L1-low tumors

1. Prior phase 3 data (eg, KN-181, KN-061)
   - Lack of benefit in PD-L1-low patients with stage IV gastroesophageal cancer
2. Current 2 Phase 3 trials (CM-649, KN-590)
   - Lack of benefit in PD-L1-low patients with treatment-naïve stage IV gastroesophageal cancer
3. Large sample size of PD-L1-low subgroups
   - n = 606 (CM-649); n = 347 (KN-590)
3. Toxicities appeared higher in ICI arm

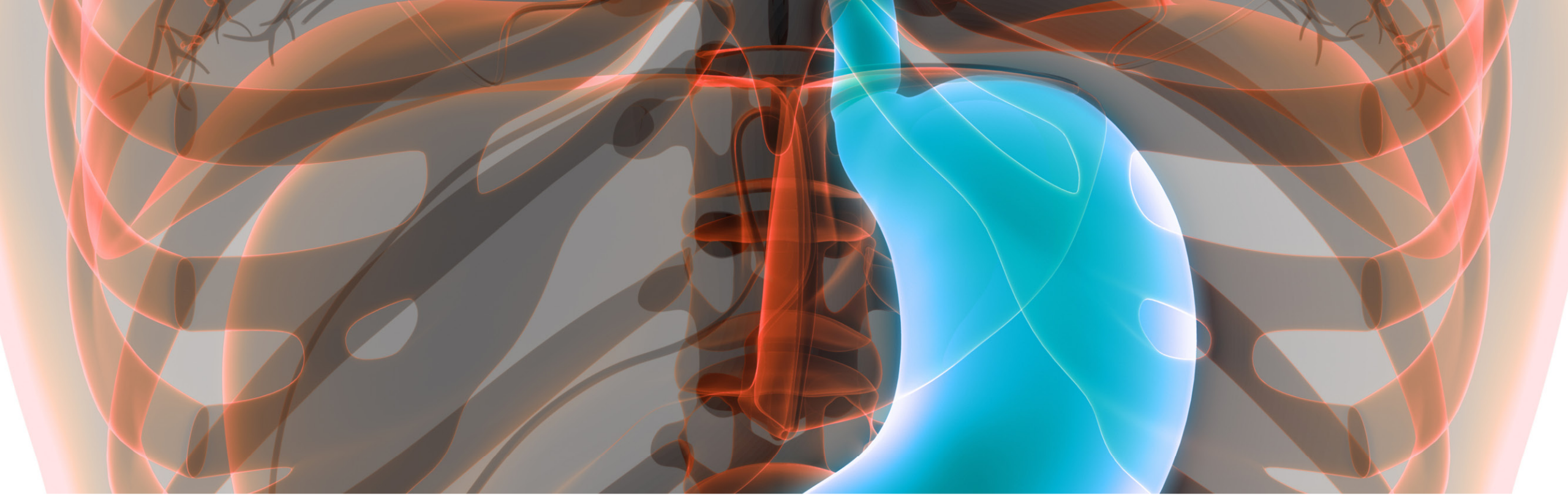
vs

FDA's possible rationale for broad approval

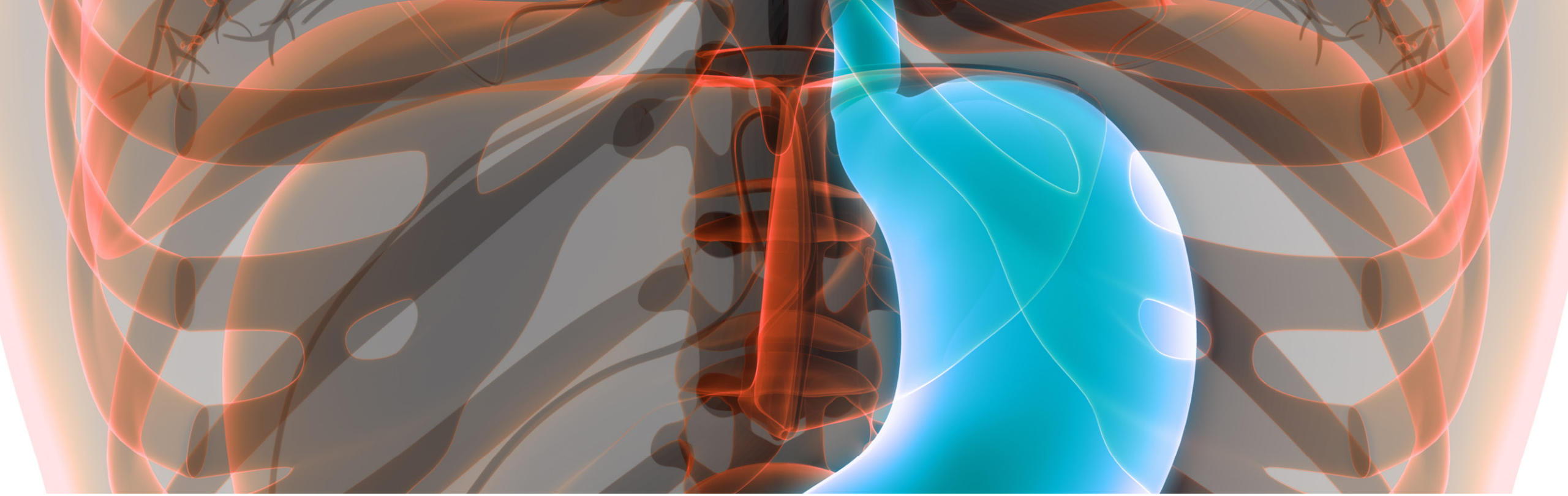
1. Inter-lab variability of PD-L1 scoring (?)
2. Keeping abreast of latest PD-L1 cutpoints is challenging in busy practice
3. Patients will "vote with their feet"

[1] Accelerated approval, https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/125554s091lbl.pdf

Abbreviation: ICI, immune checkpoint inhibitors.

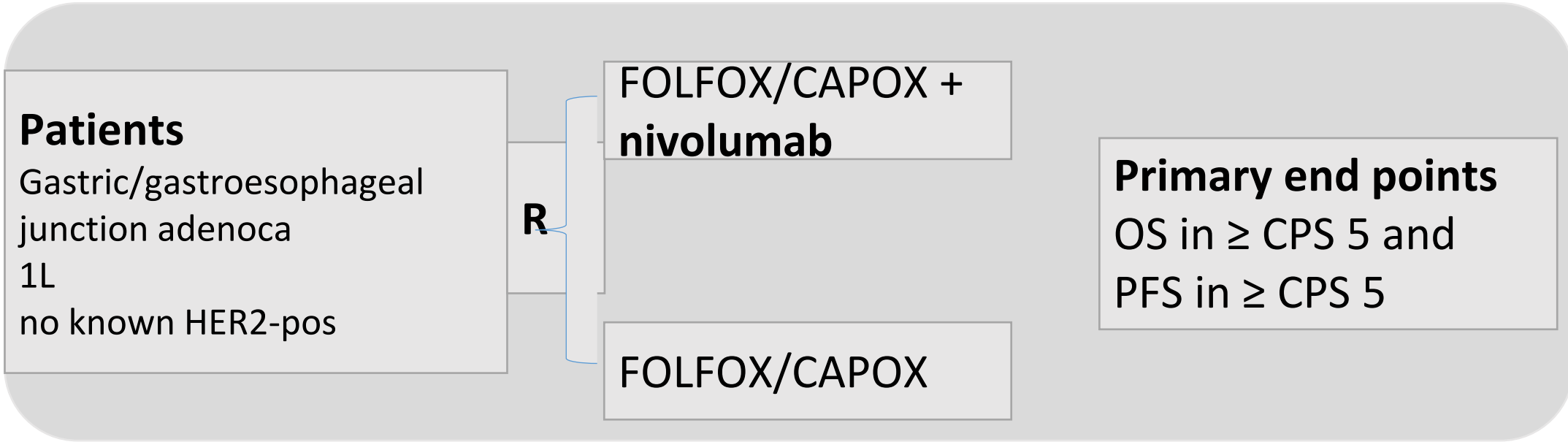


First-line unresectable/metastatic gastric cancer consists of the chemotherapy backbone +/- targeted therapy



What data support the use of chemotherapy + immunotherapy in a HER2-negative patient like EM?

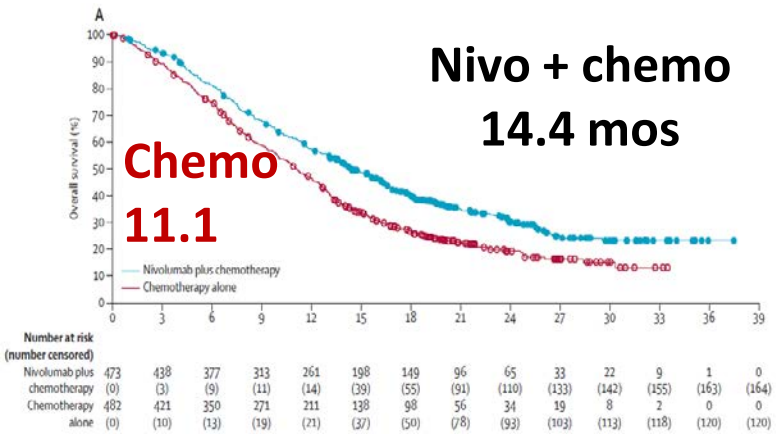
CM-649



CM-649: Overall Survival

PD-L1 CPS ≥ 5 (n = 955)

HR 0.71 0.59–0.86

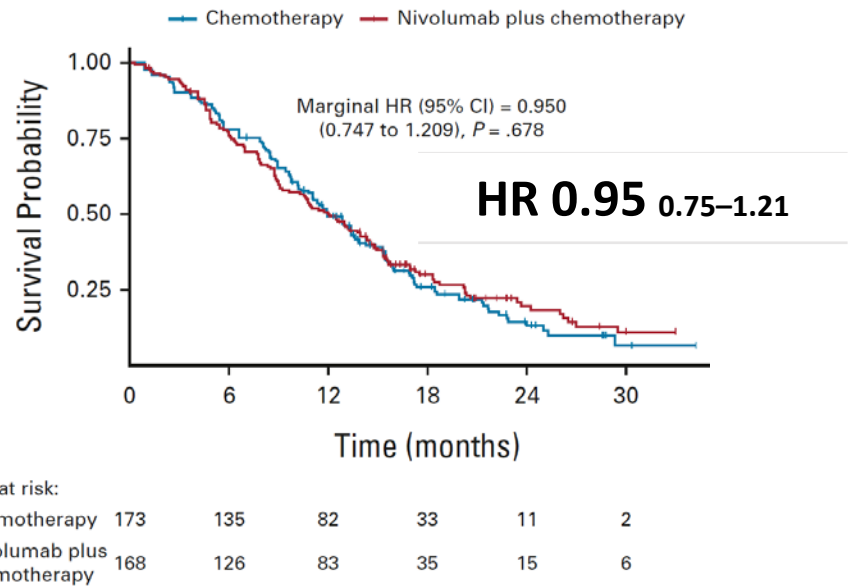


Nivo + chemo 14.4 mos

Chemo 11.1

Janjigian YY, et al. *Lancet*. 2021;398(10294):27-40.

PD-L1 CPS 1-4 (n = 341)

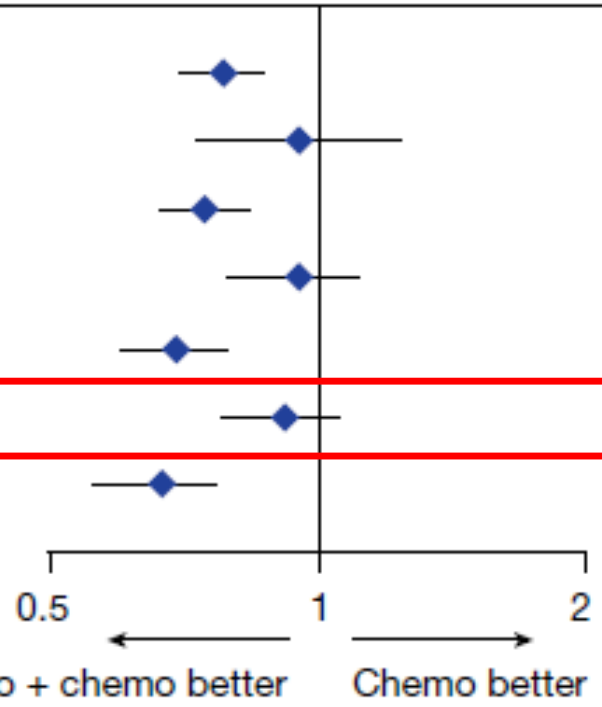


Zhao JJ, et al. *J Clin Oncol*. 2021:40(4):392-402.

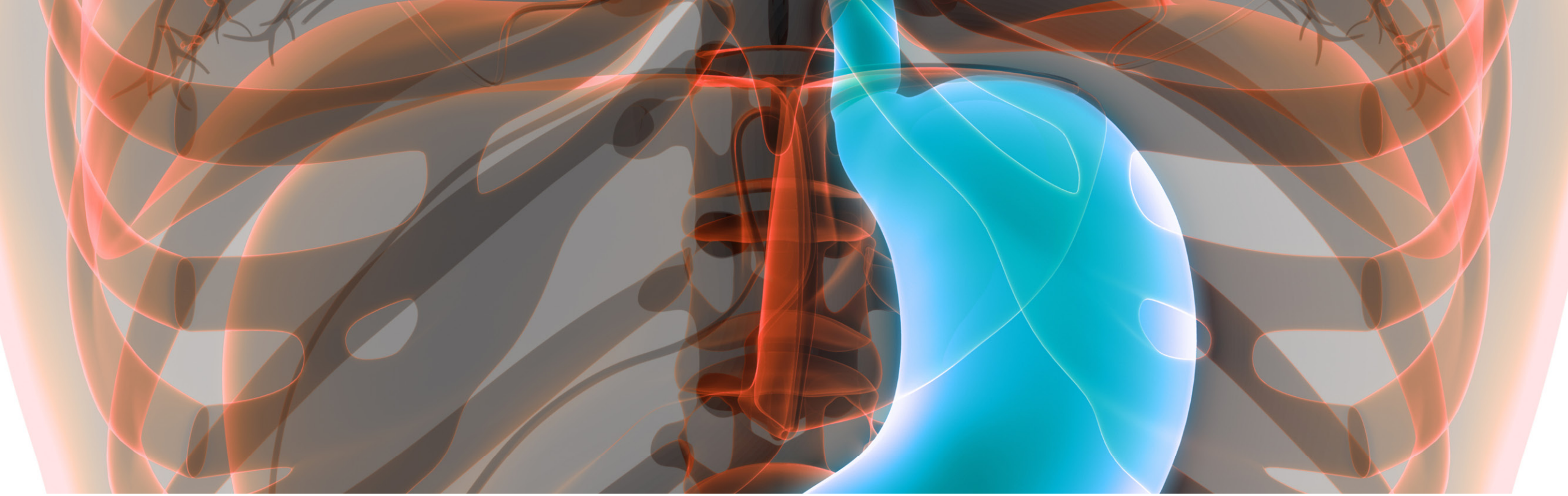
CM-649: Overall survival

Median overall survival (month)

Population	Nivolumab plus chemotherapy	Chemotherapy	Unstratified HR for death (95% CI)
Overall (*n* = 1,581)	13.8	11.6	0.78 (0.70, 0.87)
PD-L1 CPS <1 (*n* = 265)	13.1	12.5	0.95 (0.73, 1.24)
PD-L1 CPS ≥1 (*n* = 1,297)	13.8	11.3	0.74 (0.66, 0.84)
PD-L1 CPS <5 (*n* = 607)	12.4	12.3	0.94 (0.79, 1.11)
PD-L1 CPS ≥5 (*n* = 955)	14.4	11.1	0.69 (0.60, 0.79)
PD-L1 CPS <10 (*n* = 795)	12.4	12.5	0.91 (0.78, 1.06)
PD-L1 CPS ≥10 (*n* = 767)	15.0	10.9	0.66 (0.56, 0.77)



Shitara K, et al. *Nature*. 2022;603(7903):942-948.



What is the toxicity profile per data?

Higher G3-5 Toxicity

	Nivo + Chemo	Chemo
Any G3-5	**60%** 1.3x	**44%** ref
Serious G3-5	**17%** 1.7x	**10%** ref
G3-4 discontinued	**17%** 1.9x	**9%** ref
Tx duration	**6.8 m** 1.4x	**4.9 m** ref

G3-4 discontinued = G3-4 toxicity leading to treatment discontinuation

Checkmate 649

Checkmate 649 Toxicities

Toxicities	Nivolumab + chemo; n = 782	Chemo alone; n = 767
Events leading to death	16 (2%)	4 (< 1%)
AE leading to discontinuation related to treatment • Grade ≥ 3	284 (36%) • 140 (18%)	181 (24%) • 67 (9%)
Serious AE related to treatment • Grade ≥ 3	172 (22%) • 135 (17%)	93 (12%) • 77 (10%)
Any AE related to treatment • Grade ≥ 3	738 (94%) • 466 (60%)	679 (89%) • 341 (44%)

Janjigian YY, et al. *Lancet*. 2021;398(10294):27-40.

CheckMate 649: Most Common AEs in ≥ 10% of Treated Patients in Either Group

Event	Nivolumab + chemo n = 782 Any grade	Chemo alone n = 767 Any grade
Nausea	42%	38%
Vomiting	25%	22%
Diarrhea	33%	28%
Peripheral neuropathy	29%	25%
Fatigue	26%	23%
Anemia	**27%**	24%
Decreased appetite	20%	18%

Bolded = Grade ≥ 3 in ≥ 5% of patients

Janjigian YY, et al. *Lancet*. 2021;398(10294):27-40.

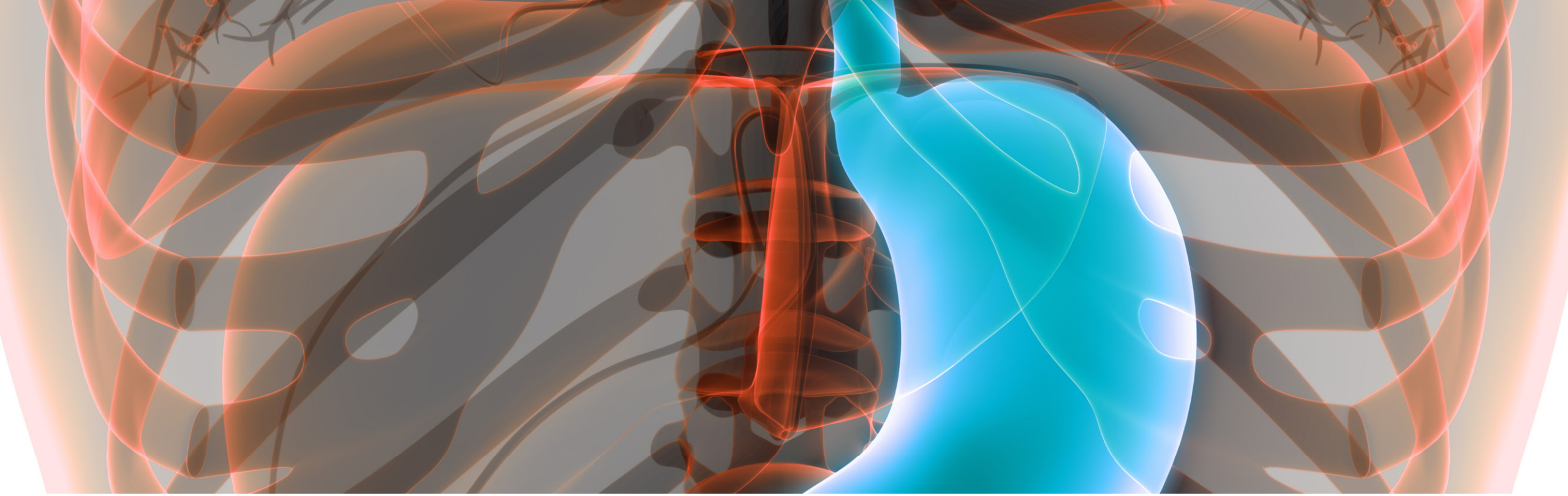
CheckMate 649: Most Common AEs in ≥ 10% of Treated Patients in Either Group

Event	Nivolumab + chemo n = 782 Any grade	Chemo alone n = 767 Any grade
Thrombocytopenia	21%	20%
Platelet count decreased	20%	16%
AST increased	16%	9%
ALT increased	12%	7%
Hand-foot syndrome	12%	11%
WBC decreased	15%	11%
Neutrophil count decreased	**21%**	**16%**
Neutropenia	**24%**	**23%**
Asthenia	9%	11%
Lipase increased	**11%**	5%

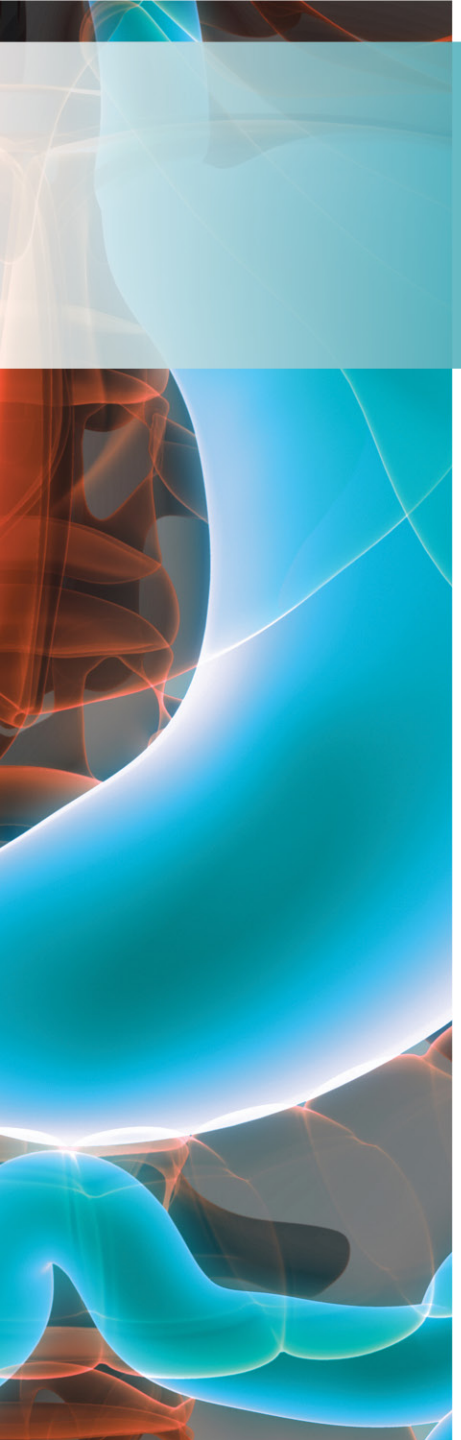
Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; WBC, white blood cell.

Bolded = Grade ≥3 in ≥ 5% of patients

Janjigian YY, et al. *Lancet*. 2021;398(10294):27-40.

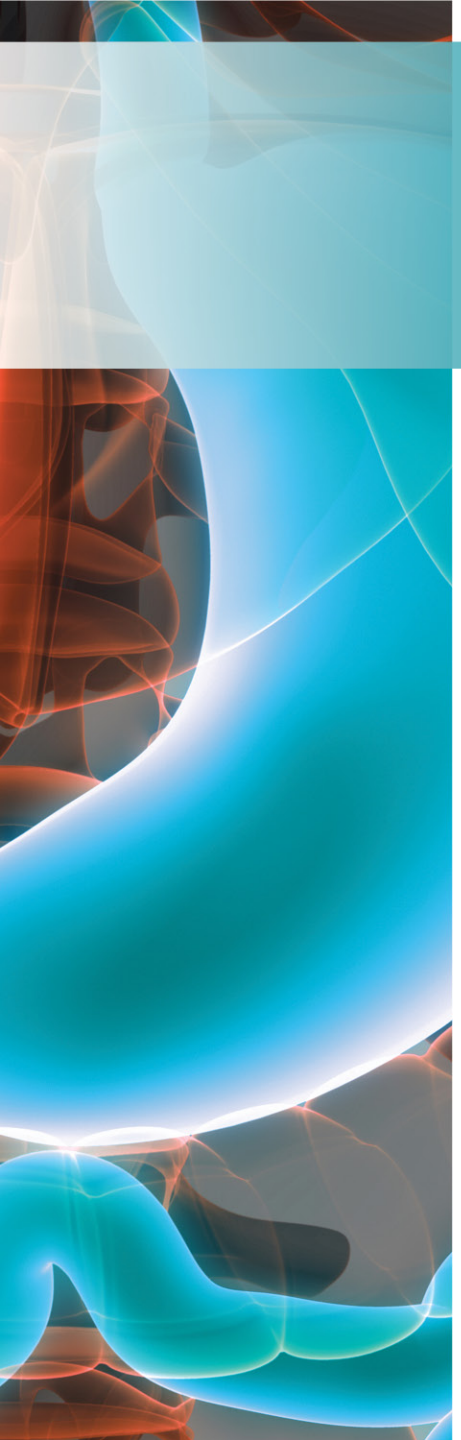


Considerations that may influence treatment decisions for EM



Considerations Checklist

- [x] Medical comorbidities
- [x] Performance status
- [x] Toxicity profile of therapy
- [x] Insurance status (including immigrant status)
- [x] Therapy logistics
- [x] Patient’s wishes/goals of care



Case 1 Additional Information

EM is a 75-year-old widower who emigrated from Mexico 4 years ago to live with his son and daughter in law.

He does not have US citizenship but is pending a green card, has been a local town resident, and worked on and off at small jobs in that time.

EM regularly takes medication for diabetes and hypertension; however, these have been on hold since his ER visit.

Case 1 Additional Information

EM is a 75-year-old widower who **emigrated from Mexico** 4 years ago to live with his son and daughter in law.

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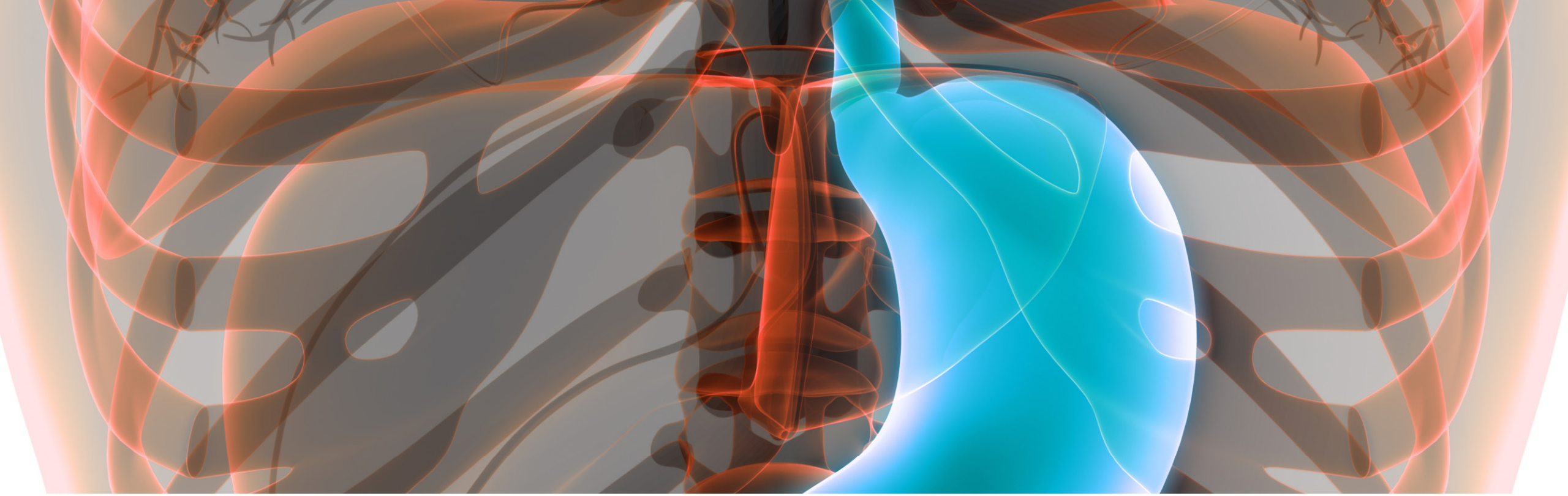
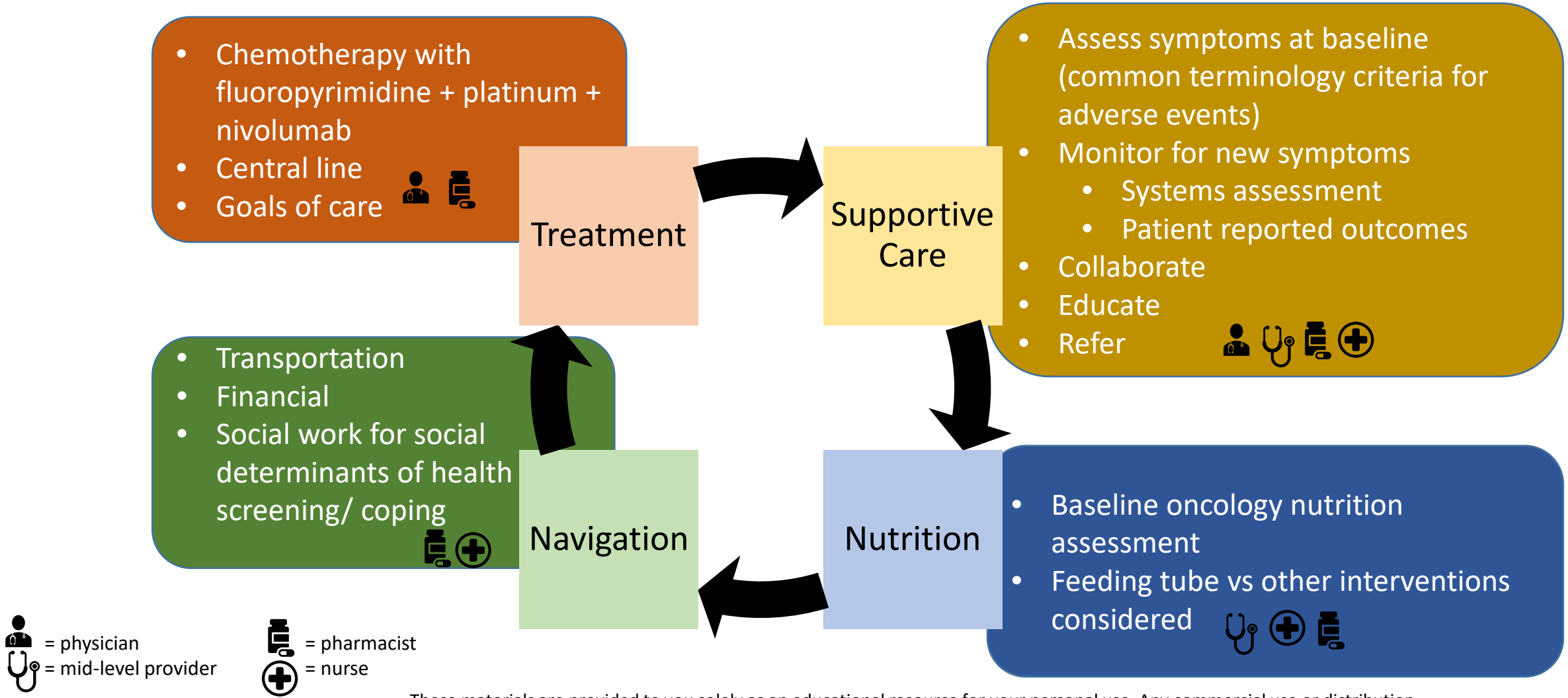
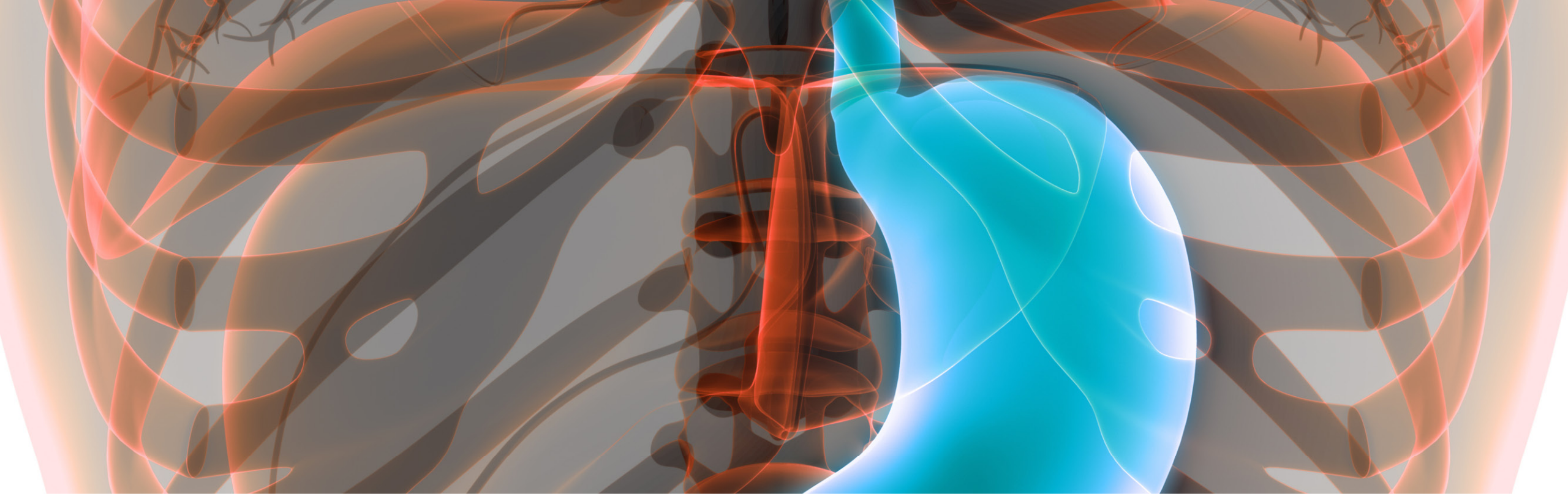


What is our plan?

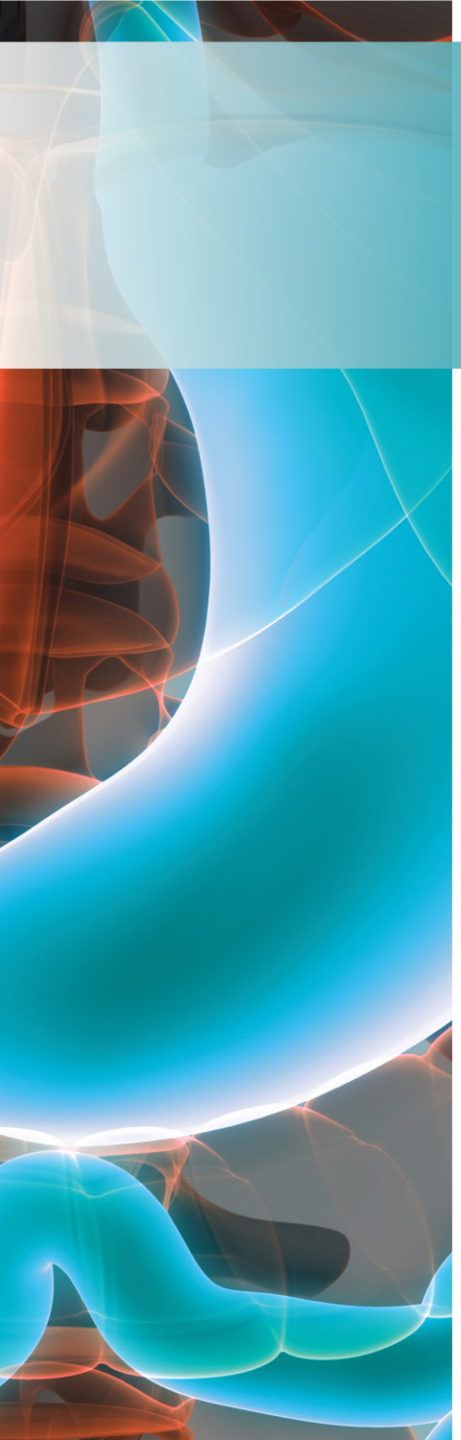
Multidisciplinary Team Approach





Case 2

HER2+ (+/- PD-L1 positive)



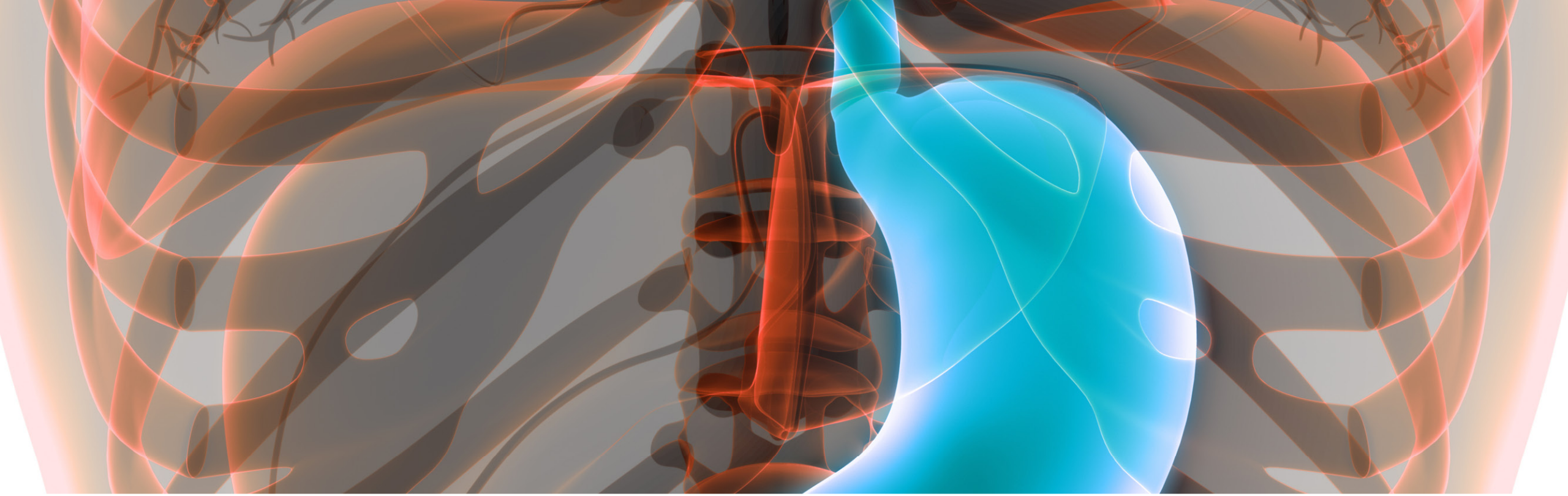
Case 2

MJ, a 52-year-old woman, presents with newly diagnosed metastatic gastric cancer, HER2-positive, PD-L1-CPS pending. She presents to clinic to discuss treatment options.

Past Medical History:
Hodgkin's Lymphoma s/p ABVD + radiation; in her 20s
Menopause (48 yo)
Hypothyroidism

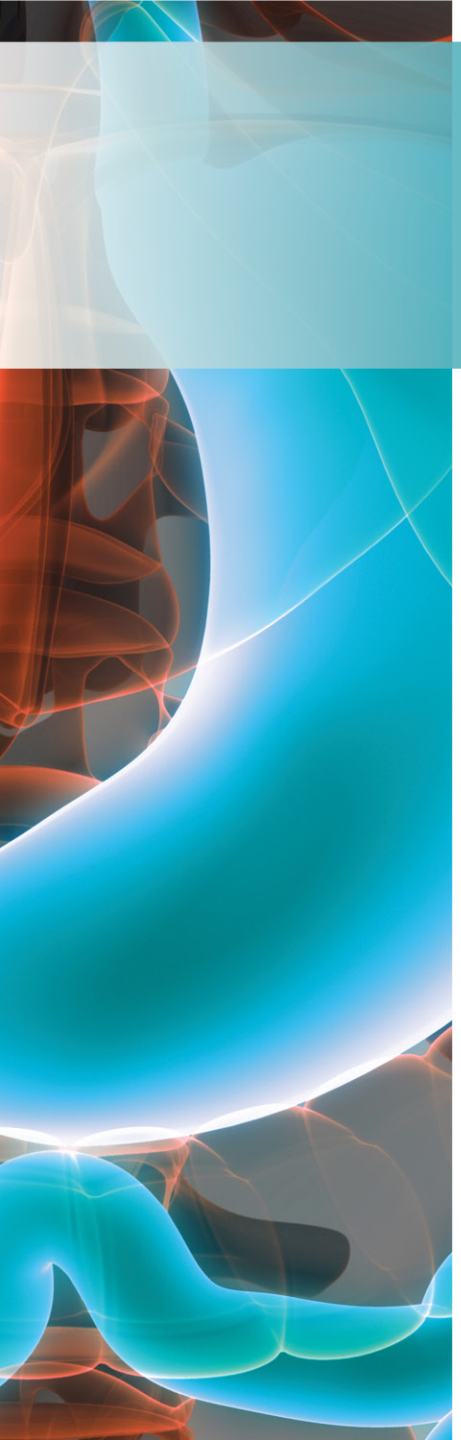
Baseline LVEF: 55%

Abbreviations: ABVD, Adriamycin, bleomycin sulfate, vinblastine sulfate, and dacarbazine; LVEF, left ventricular ejection fraction.



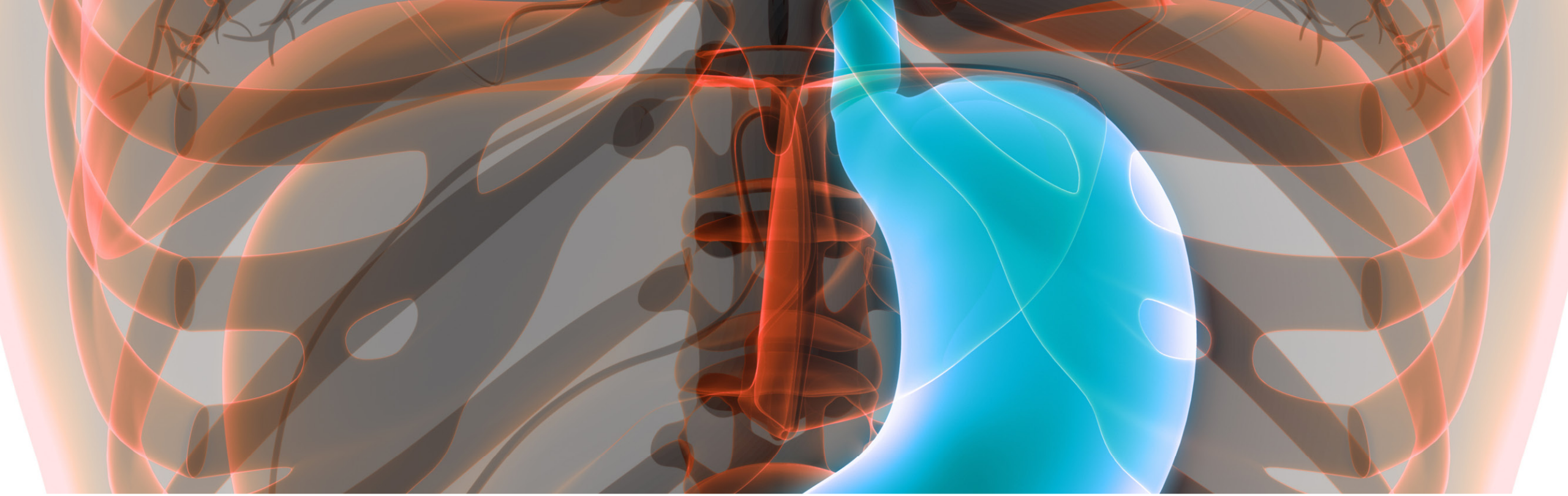
HER2-positive gastric cancer

Quick Facts



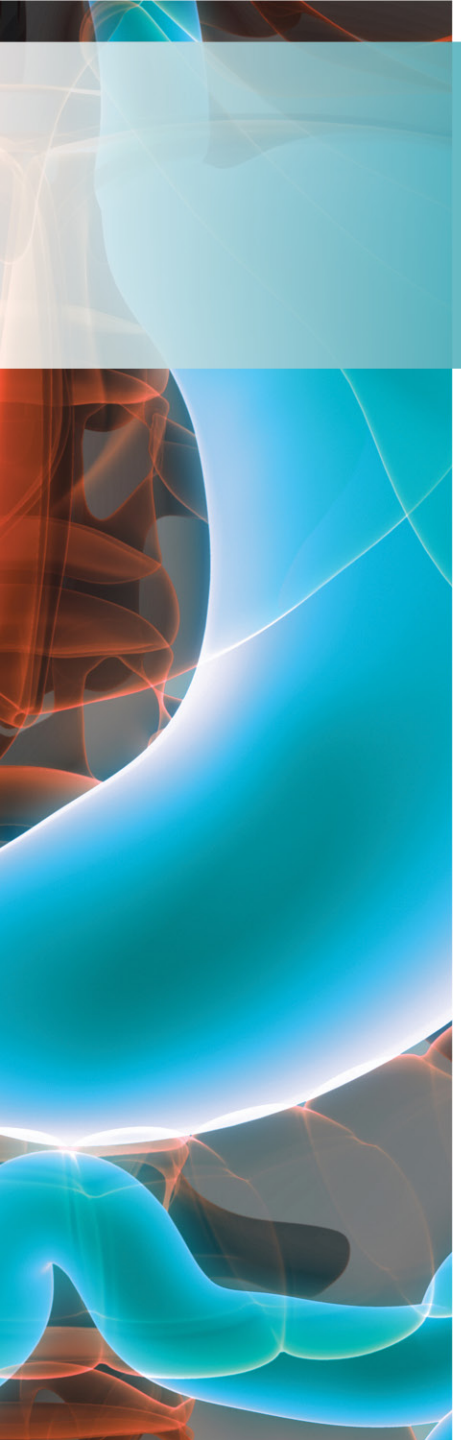
HER2-Positive Gastric Cancer

- Frequency of HER2 positivity: 10-20%
- IHC scoring system is different for gastric (vs breast) cancer → ensure that gastric criteria are used
- HER2 positivity is more frequent in intestinal-type or Barrett's type pathology
- ~ 30% of patients "lose" HER2 positive status over time



What is the treatment landscape for HER2-positive gastric cancer?

(and how does it differ from HER2-negative?)



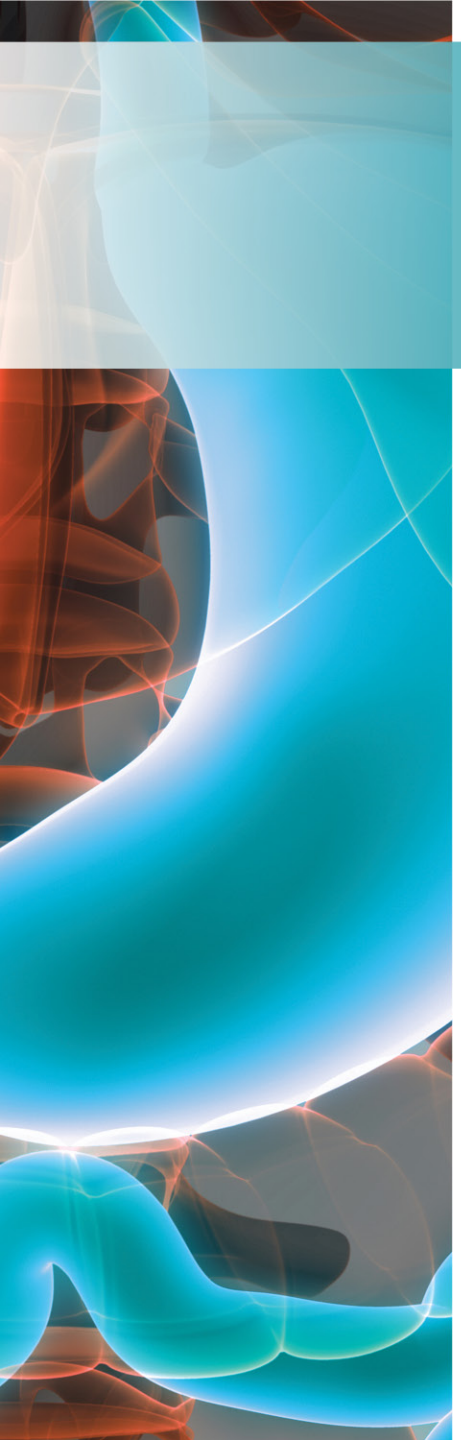
HER2-Positive Treatment Pathway

Dr Yoon's general approach (simplification of NCCN)

- **1st Line**
- FOLFOX + trastuzumab
- Add pembrolizumab generally, especially if PD-L1 CPS 1+

- **2nd Line**
- Consider trastuzumab deruxtecan
- Same as HER2-negative:
  - Paclitaxel + Ramucirumab
  - FOLFIRI +/- Ramucirumab

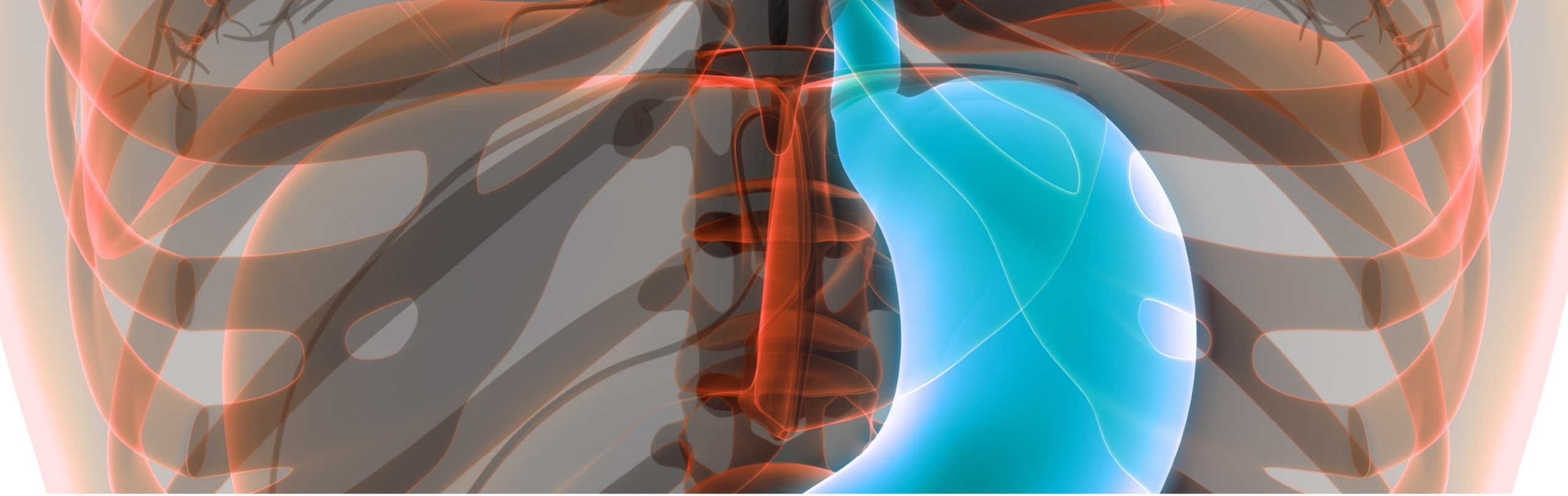
- **3rd Line**
- Consider trastuzumab deruxtecan



Case 2 Continued

MJ initiated systemic treatment with FOLFOX + trastuzumab and has received 1 cycle. Her tumor PD-L1-CPS = 30.

Should you consider adding immunotherapy to MJ's existing regimen?



What data exist for using immunotherapy in combination with HER2-directed therapies?

KN-811: Pembro increases RR in HER2+ GEJ/GC

Primary end point: OS and PFS (not reported to date)
Pre-specified interim analysis of first 264 patients

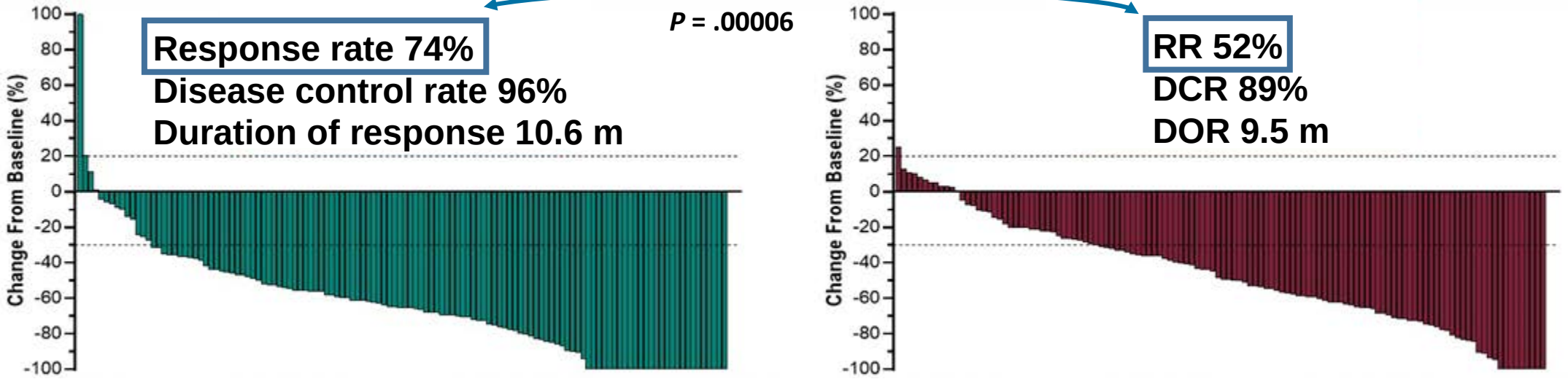
Pembro + tras + platin/FP
(mostly CAPOX)

Response rate 74%
Disease control rate 96%
Duration of response 10.6 m

***P* = .00006**

Placebo + tras + platin/FP
(mostly CAPOX)

RR 52%
DCR 89%
DOR 9.5 m



Δ RR between arms by PD-L1 status

- **CPS ≥ 1 (n = 229): 25.2%** (95% CI -12.8, 36.9)
- **CPS < 1 (n = 35): 4.6%** (95% CI -27.6, 35.4)

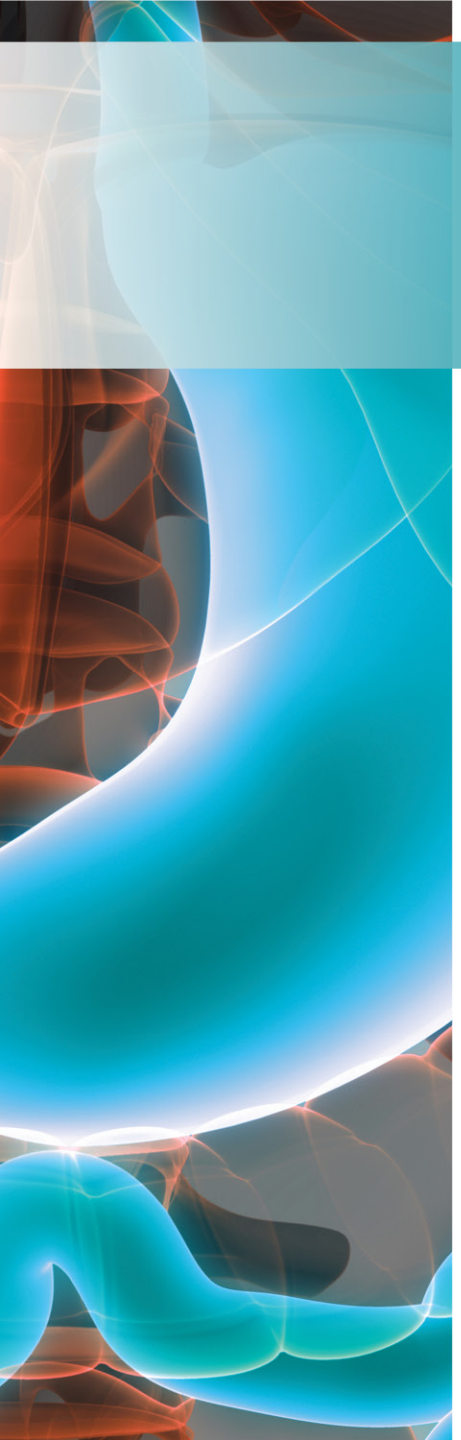
Accelerated FDA approval
NCCN Cat 1 and 2A approval

Janjigian YY et al. ASCO Annual Meeting 2021 (PowerPoint slides); Janjigian YY, et al. *Nature*. 2021. doi.org/10.1038/s41586-021-04161-3.

Keynote 811 Toxicities

Toxicities	Pembrolizumab + trastuzumab + chemo; n = 217	Placebo + trastuzumab + chemo; n = 216
Events leading to death	3.2%	4.6%
AEs leading to discontinuation related to treatment	24.4%	25.9%
Grade 3-5 AEs	57.1%	57.4%

Janjigian YY, et al. *Nature*. 2021;600(7890):727-730.



Keynote 811: Most Common AEs in ≥ 20% of Treated Patients in Either Group

Event	Pembrolizumab + tras + chemo; n = 217	Placebo + tras + chemo; n = 216
Diarrhea	**52.5%**	**44.4%**
Nausea	48.8%	**44.4%**
Anemia	**41%**	**44%**
Decreased appetite	30.9%	31.9%
Vomiting	30.9%	27.3%
Platelet count decreased	**24.4%**	**28.2%**
Fatigue	23.5%	19.9%
Neutrophil count decreased	**23.5%**	**24.5%**
Peripheral sensory neuropathy	23%	18.5%
AST increased	20.7%	13%

Janjigian YY, et al. *Nature*. 2021;600(7890):727-730.

Bolded = Grade ≥3 in ≥ 5% of patients

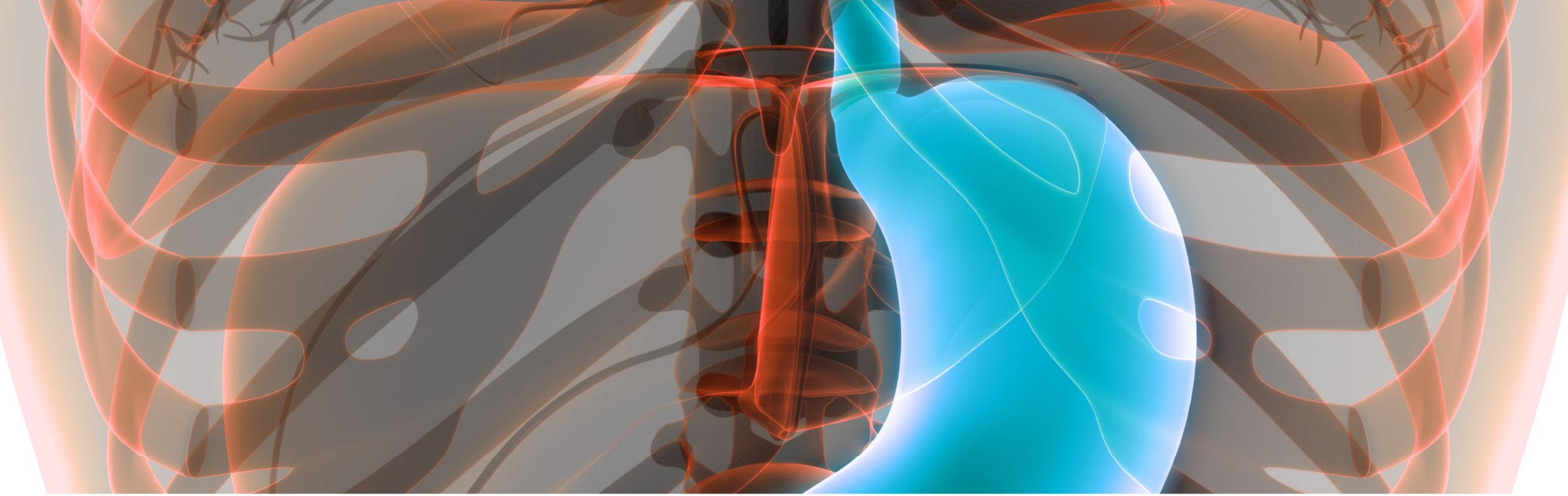
Keynote 811 : Adverse Events in > 1% of Patients with a Possible Immune-Mediated Cause

Event	Pembrolizumab + tras + chemo; n = 217	Placebo + tras + chemo; n = 216
Infusion-related reaction	**18%**	**13%**
Pneumonitis	**5.1%**	1.4%
Colitis	**4.6%**	**1.9%**
Hypothyroidism	4.6%	2.8%
Hyperthyroidism	3.7%	3.2%
Hypophysitis	**1.4%**	0

Other AEs with a possible immune-mediated cause in < 1% of patients in either treatment arm: hepatitis, severe skin reactions, nephritis, thyroiditis, type 1 diabetes mellitus, uveitis, myocarditis

Bolded = Grade ≥ 3 in ≥ 1 patient(s)

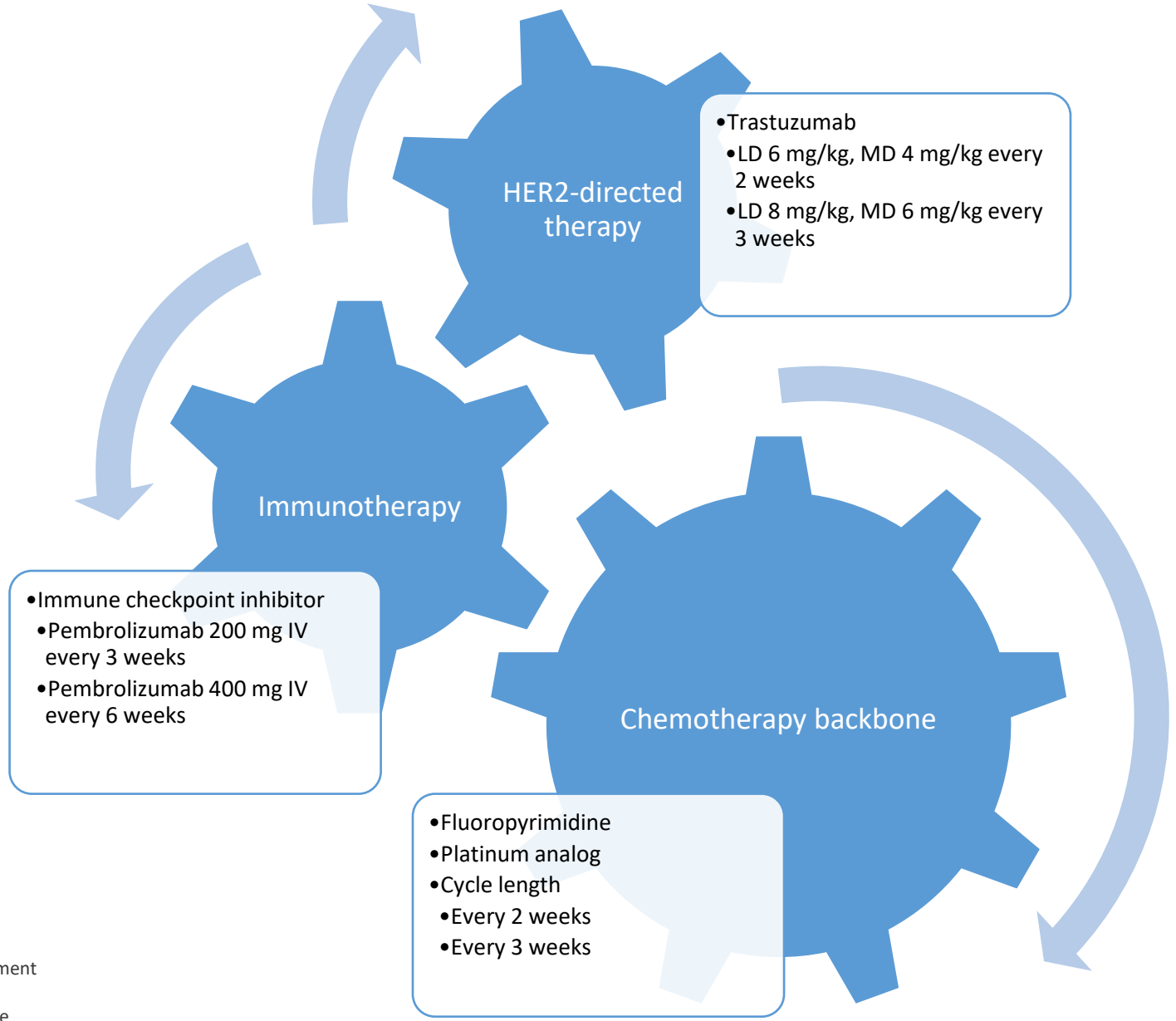
Janjigian YY, et al. *Nature*. 2021;600(7890):727-730.



Design a systemic regimen for MJ

(agents, doses, route, frequency)

Flexibility with regimen design



Flexibility with regimen design

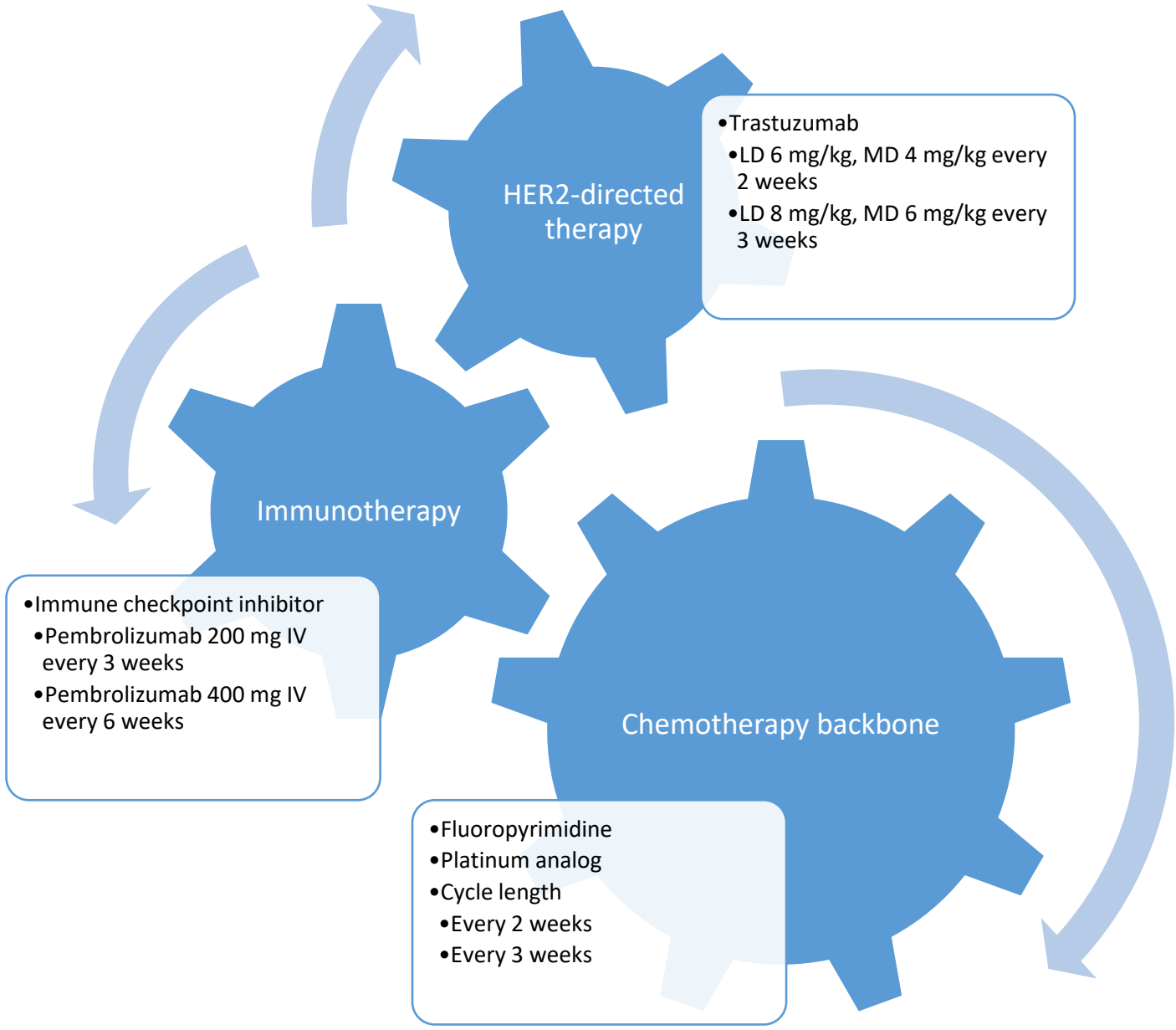
- FOLFOX
  - Oxaliplatin 85 mg/m^2 IV, Leucovorin 400 mg/m^2 IV, 5FU 400 mg/m^2 bolus over 15 min, 5FU 2400 mg/m^2 via continuous infusion over 46-48 hours
  - Every 2 weeks

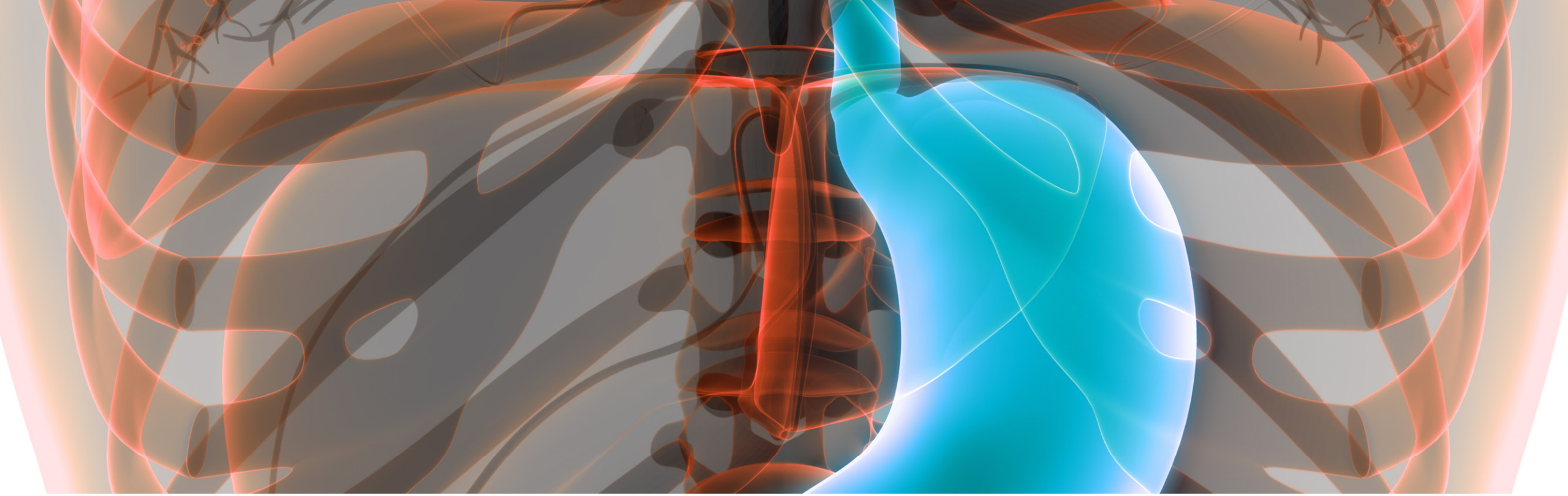
+

- Trastuzumab
  - LD 6 mg/kg, followed by MD 4 mg/kg IV
  - Every 2 weeks

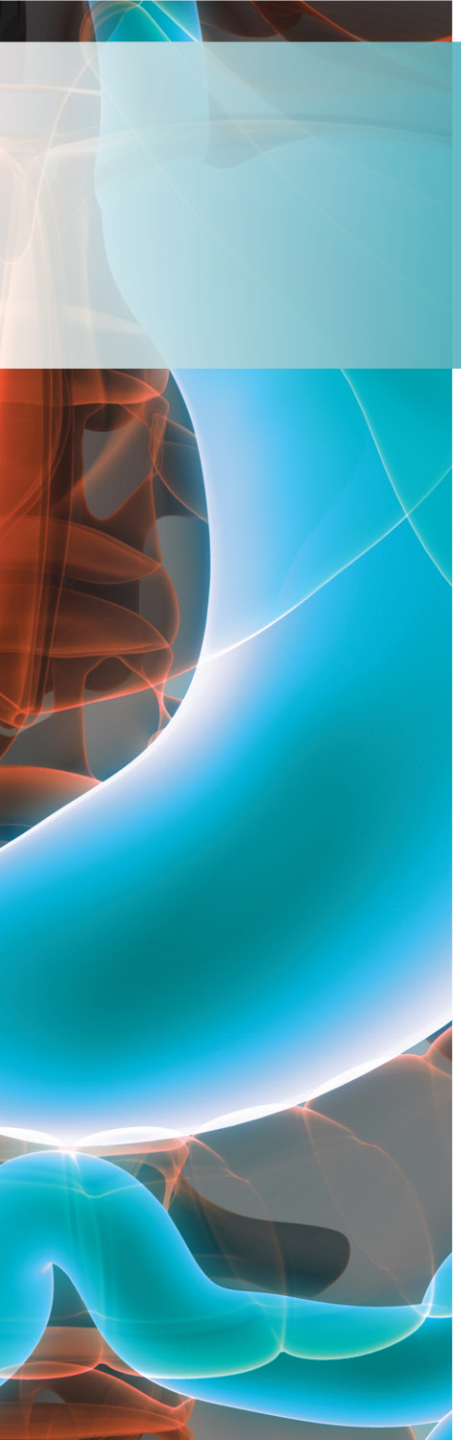
+

- Pembrolizumab
  - 400 mg IV every 6 weeks



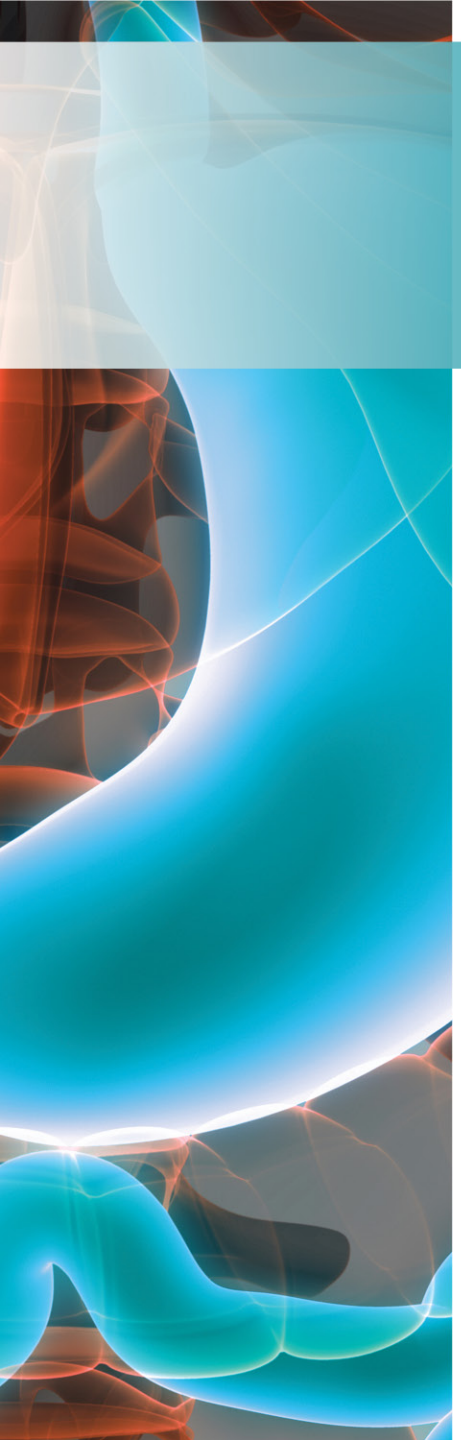


What is the appropriate monitoring for a patient receiving immunotherapy?



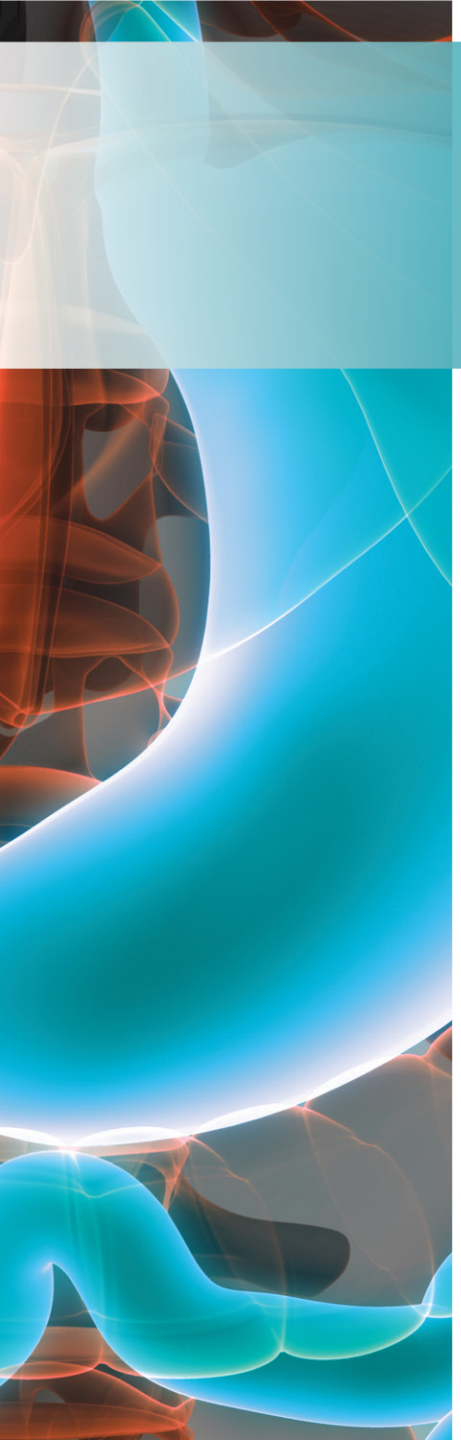
Routine Monitoring

System	Subjective	Objective	Frequency
Skin (Dermatitis)	Rash- flat/ raised/ bumpy Itching - with or without rash Mouth sores Sunburn Discoloration	Examination of skin and mucosa % of body surface area with rash – law of 9s	Periodically throughout treatment or as symptoms arise
Gastrointestinal (Colitis)	Quantity of stool Quality of stool Blood/ mucus in stool Abdominal pain, cramping, urgency	Weight Serum chemistry (dehydration) Stool culture (rule out infectious process)	Periodically throughout treatment or as symptoms arise
Pulmonary (Pneumonitis)	Dry cough Shortness of breath – with activity, at rest, while talking	Pulmonary function tests Oxygen saturation Chest imaging	Baseline for high risk; as symptoms arise



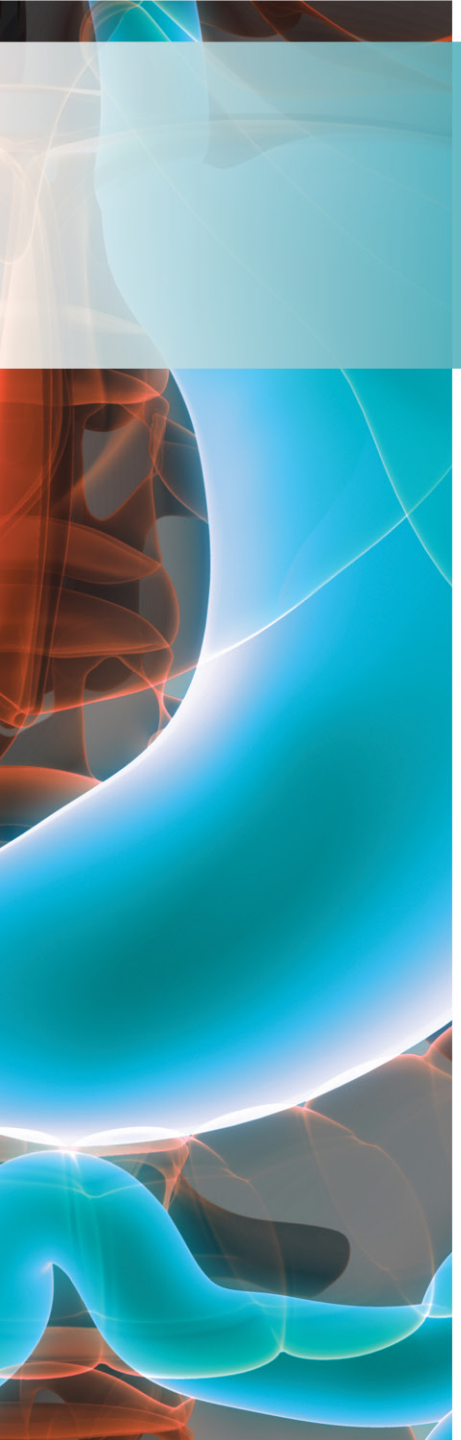
Routine Monitoring

(See pocket guide)	Subjective	Objective	Frequency
Endocrine: Thyroiditis	Fatigue Lethargy Cold sensitivity Constipation Tachycardia Tremor Anxiety	Thyroid-stimulating hormone test Free T4	Every 4-6 weeks on therapy; every 12 weeks after discontinuation, as indicated
Endocrine: Pituitary/Adrenal (Hypophysitis)	Acute onset headache Photophobia Fatigue Muscle weakness Nausea/vomiting Sexual dysfunction	Morning cortisol	Every 4-6 weeks on therapy; every 12 weeks after discontinuation, as indicated



Routine Monitoring

(See pocket guide)	Subjective	Objective	Frequency
Vision	Blurred/distorted vision Blind spots Changes in color perception Floaters Eye redness, tenderness, pain	None required	As symptoms arise
Cardiac (myocarditis)	Chest pain/pressure Shortness of breath Fatigue Syncope Heart palpitations Irregular heartbeat	Electrocardiogram	Periodically throughout treatment or as symptoms arise



Routine Monitoring

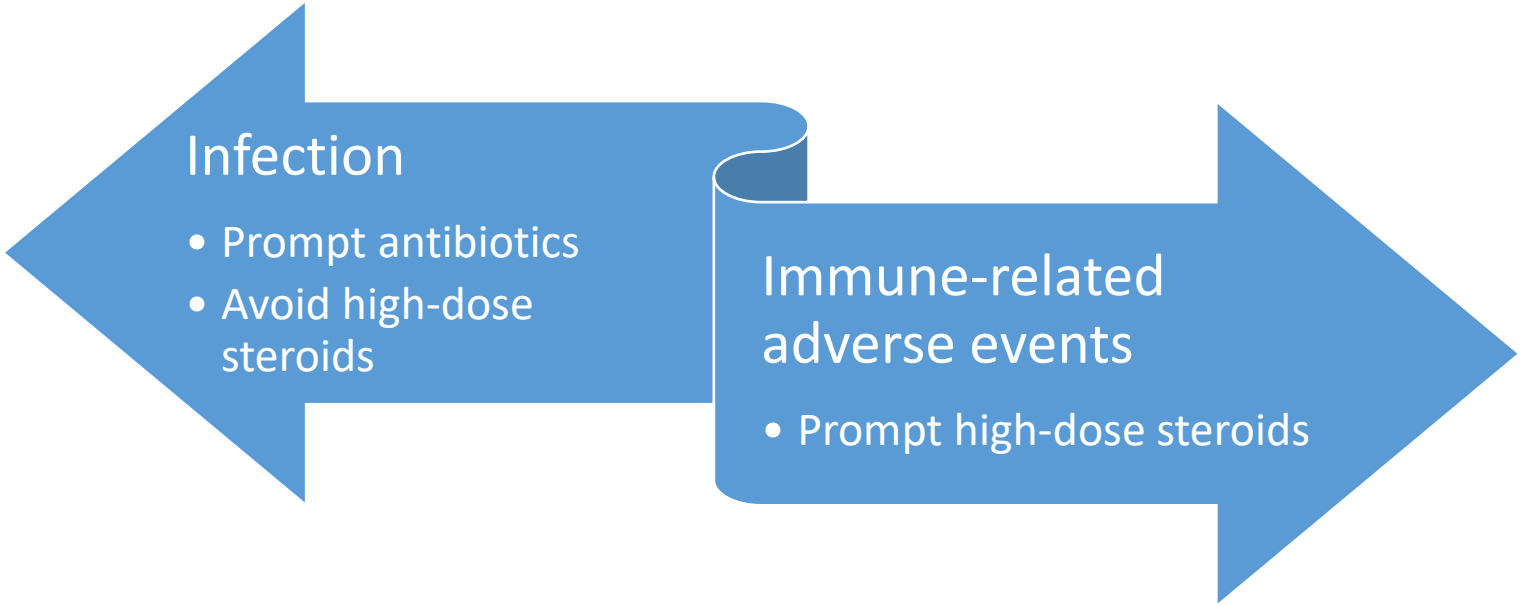
(See pocket guide)	Subjective	Objective	Frequency
Muscle/joint (arthritis, myositis) Nerve	Joint pain and/or swelling Stiffness after inactivity Muscle pain Jaw claudication Tenderness Muscle weakness Sensory-motor deficits	Joint examination/functional assessment Deep tendon reflexes	None required; as symptoms arise
Neurological	Confusion Headaches Altered behavior Seizure Speech abnormality Weakness	None required	None required; as symptoms arise

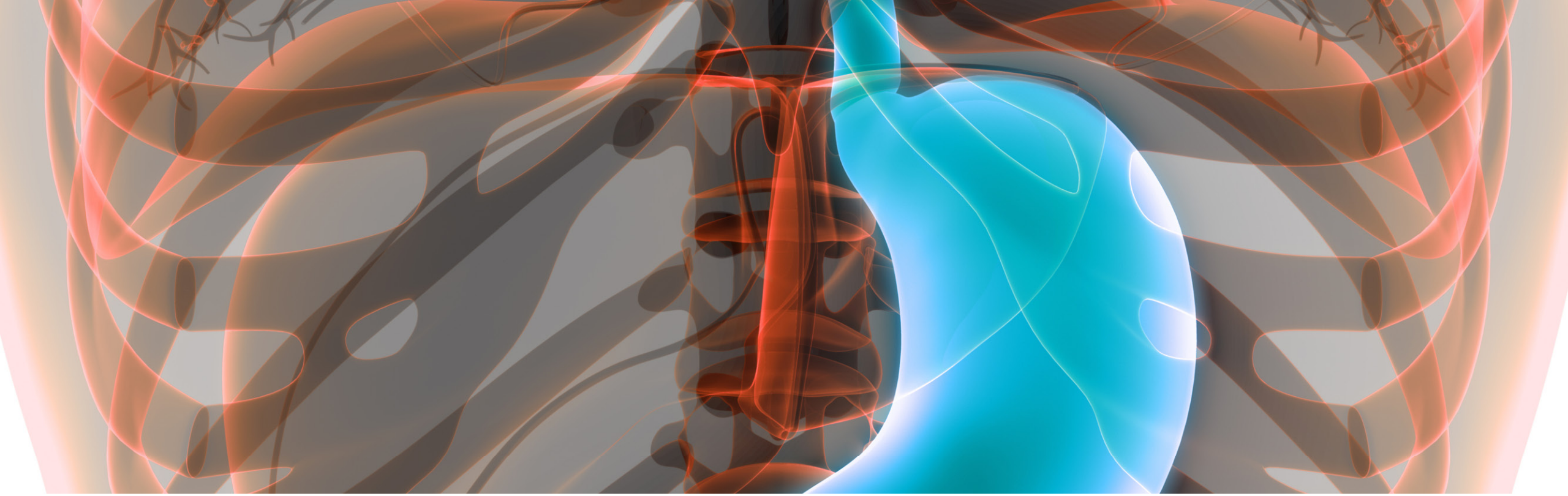
Routine Monitoring

(See pocket guide)	Subjective	Objective	Frequency
Liver (hepatitis)	Pain/tenderness in upper abdomen Yellowing of skin/eyes Pale stool, dark urine	Comprehensive metabolic panel	Prior to each treatment; every 6-12 weeks; as indicated
Pancreas (diabetes mellitus, pancreatitis)	Excessive thirst Frequent urination Diabetic ketoacidosis-related signs and symptoms Epigastric pain Nausea Abdominal pain	Baseline not required Blood glucose	None required; as symptoms arise
Kidney (nephritis)	Change in urine output	Comprehensive metabolic panel	Prior to each treatment; every 6-12 weeks; as indicated

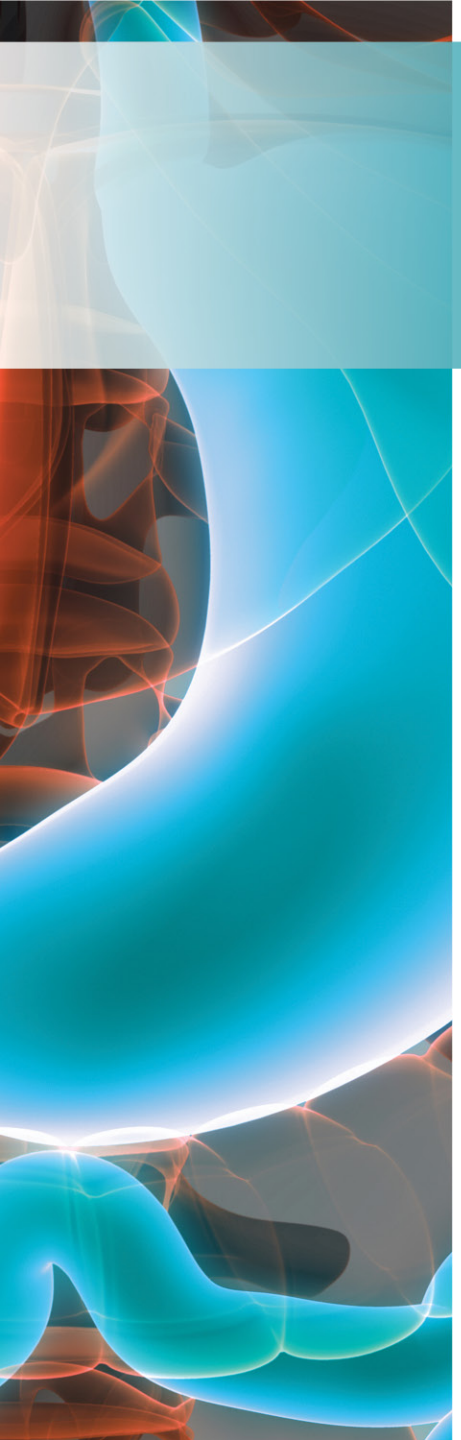
Monitoring Clinical Conundrum

- Important to rule-out infection
- Higher rates of infection in patients treated with chemo + immunotherapy?





Develop a monitoring plan for MJ



Monitoring Considerations for MJ

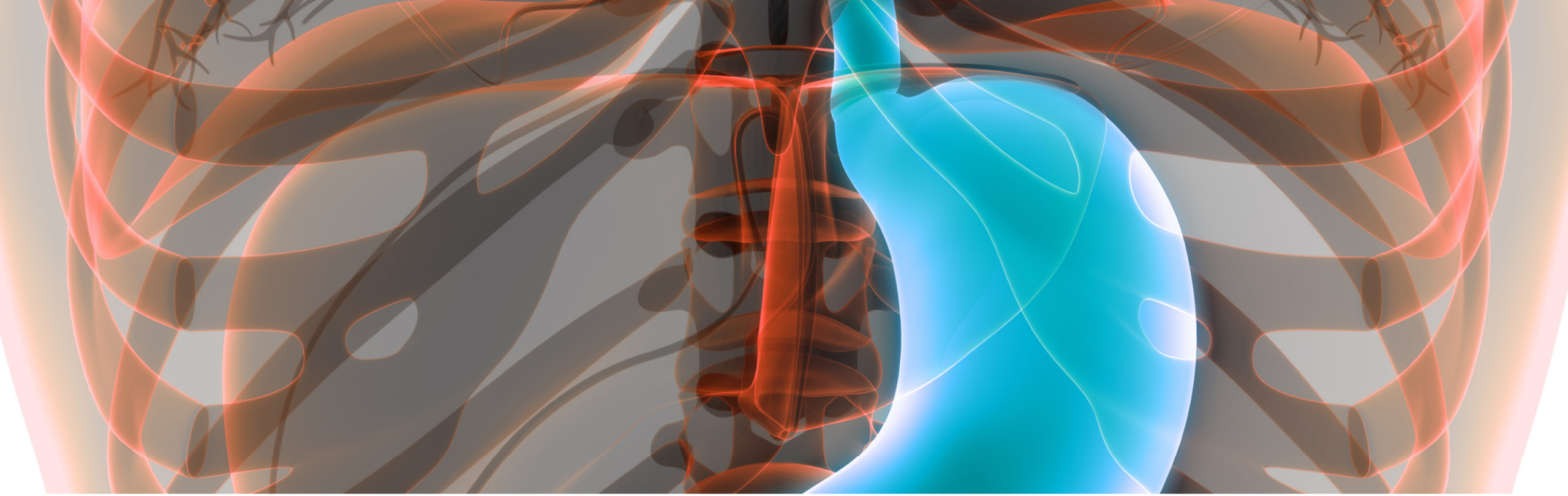
- MJ is at elevated risk of cardiac symptoms: HER2 treatment, previous anthracycline, and radiation to chest.

- Cardiac symptoms in females assigned at birth:
  - Can differ from males assigned at birth – genetic differences in muscle, ventricle, blood vessel size
  - May reflect disease location, comorbid conditions, treatment side effects, gender related, anxiety

  - GI: indigestion/nausea/vomiting, left upper quadrant abdominal pain
  - Pain: chest, neck/throat, back/shoulders, jaw, upper arms, legs
  - Hot flashes/dizziness, syncope, unusual fatigue

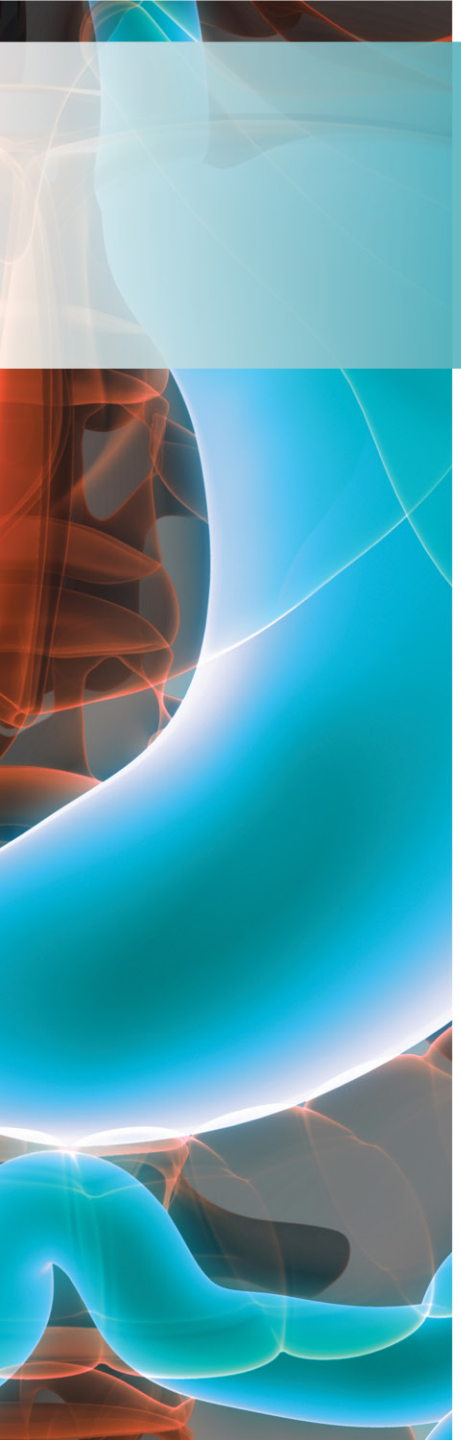
MJ's Monitoring Plan

System	Monitoring	Frequency	Other considerations
Cardiovascular	Echocardiogram	Baseline, every 3 months	• Get cardiology on board • Trastuzumab potential for decreased LVEF • If cardiac symptoms manifest: immunotherapy vs fluoropyrimidine-induced cardiac vasospasms
	EKG	Baseline	
	Troponins	Baseline, weekly x 6 weeks, then every 2 weeks (until week 22), then monthly through duration of treatment	
	Brain natriuretic peptide	Baseline, as symptoms arise	
Pulmonary	Pulmonary function tests	Baseline, as symptoms arise	• Prior radiation to chest • Prior exposure to bleomycin
	Oxygen saturation	Baseline, at each visit	
	Chest imaging	Baseline	
Thyroid	TSH, free T4	Baseline, every 4-6 weeks on treatment	
All others	Complete blood count with diff, comprehensive metabolic panel, review of systems	Baseline, prior to each treatment	• Consider morning cortisol level



Case 3

After 1L therapy- 3L pembro (removed) and prior therapies



Case 3

BC, a 62-year-old man with metastatic gastric cancer, PD-L1 CPS 10, was treated with FOLFOX. Then disease progressed.

- Which anticancer agents are recommended?
- Is there a role for immunotherapy? In 2nd Line? In 3rd Line?
- What if PD-L1 CPS 0?
- Should PD-L1 be rechecked on a new specimen?

2022 Treatment Landscape for Fit Patient with Advanced Gastric Cancer: 2nd Line or Later

2nd Line	3rd Line or later
HER2-positive consider TDXD	Trifluridine-tipiracil
Other ram + paclitaxel FOLFIRI +/- ram	Agents not previously used

[a] For adenoca with MSI: nivo + platin/FP, or pembro

Abbreviations: ram, ramucirumab; TDXD, trastuzumab deruxtecan.

Is there data to support the use of immunotherapy for metastatic gastric cancer beyond 1st Line?

ICI in 2nd Line or later

- No data to support ICI after progression on ICI in 1st Line
  - Deficient MMR is arguably an exception
- If a patient never received prior ICI and has high PD-L1 (eg, CPS 10+), whether to give ICI is controversial.
- Limited quality data show activity for ICI + chemo

Rogers JE, Xiao L, Trail A, et al. **Nivolumab** in combination with irinotecan and 5-fluorouracil **(FOLFIRI)** for refractory advanced gastroesophageal cancer. *Oncology*. 2020;98(5):289-294.

Herbst RS, et al. Ramucirumab plus pembrolizumab in patients with previously treated advanced non-small-cell lung cancer, gastro-oesophageal cancer, or urothelial carcinomas (JVDF): a multicohort, non-randomised, open-label, phase 1a/b trial. *Lancet Oncol*. 2019;20(8):1109-1123.

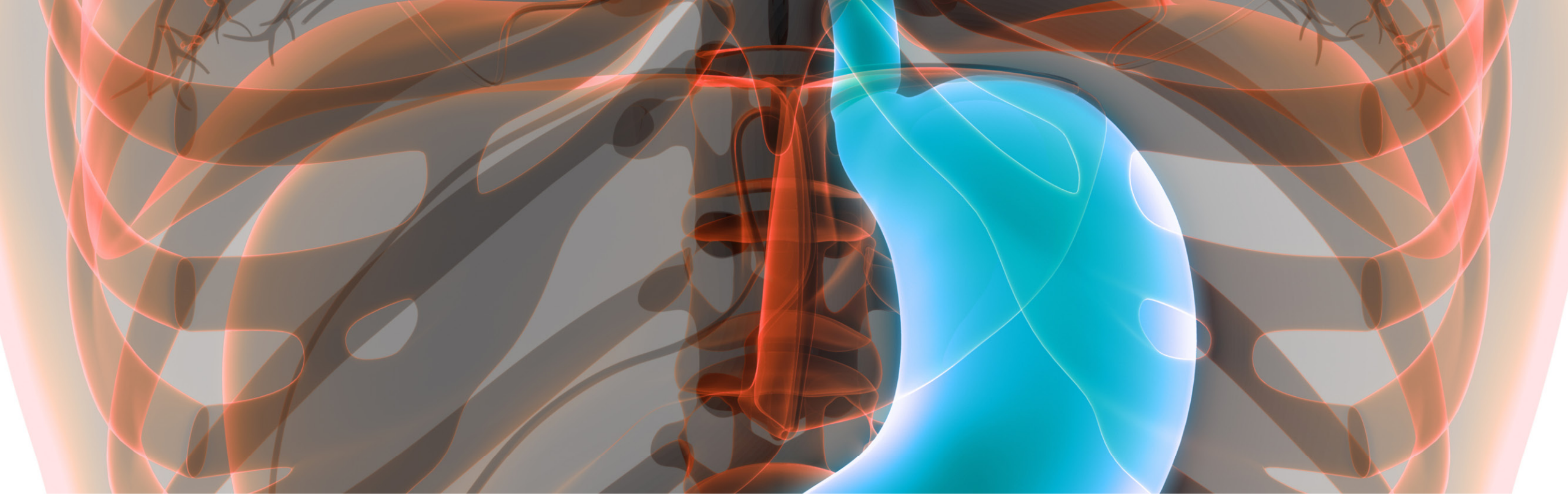
Nakajima TE, et al. Multicenter phase I/II study of nivolumab combined with paclitaxel plus ramucirumab as second-line treatment in patients with advanced gastric cancer. *Clin Cancer Res*. 2021;27(4):1029-1036.

Kang YK, et al. **Nivolumab** in patients with advanced gastric or gastro-oesophageal junction cancer refractory to, or intolerant of, at least two previous chemotherapy regimens (ONO-4538-12, ATTRACTION-2): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet*. 2017;390(10111):2461-2471.

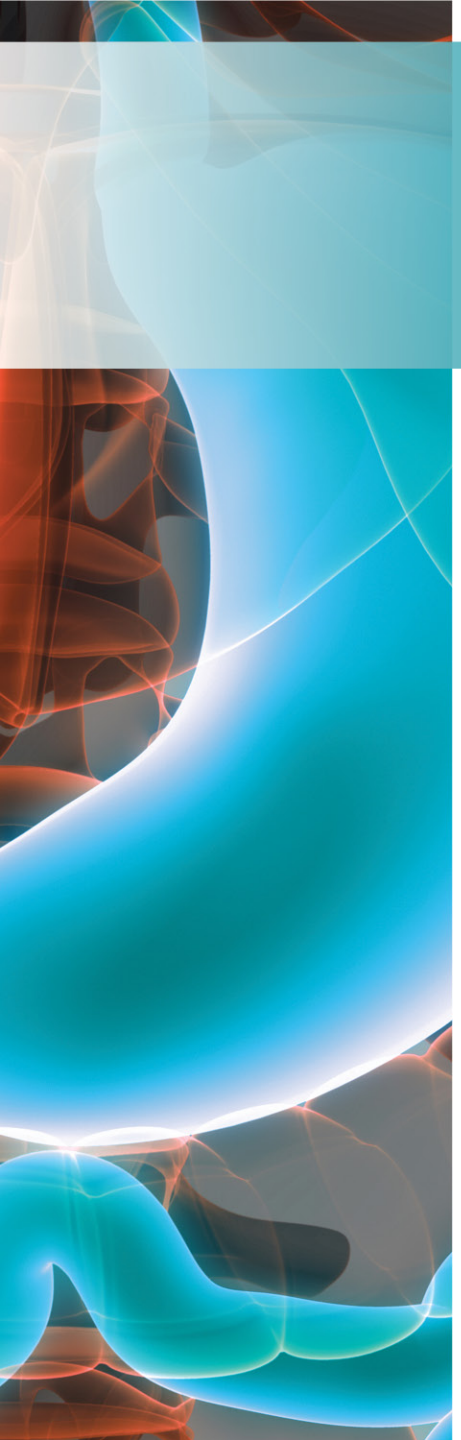
Kato K, et al. A subanalysis of Japanese patients in a randomized, double-blind, placebo-controlled, phase 3 trial of nivolumab for patients with advanced gastric or gastro-esophageal junction cancer refractory to, or intolerant of, at least two previous chemotherapy regimens (ONO-4538-12, ATTRACTION-2). *Gastric Cancer*. 2019;22(2):344-354.

Shitara K, et al. Pembrolizumab versus paclitaxel for previously treated, advanced gastric or gastro-oesophageal junction cancer (KEYNOTE-061): a randomised, open-label, controlled, phase 3 trial. *Lancet*. 2018;392(10142):123-133. doi: 10.1016/S0140-6736(18)31257-1. Epub 2018 Jun 4. PMID: 29880231.

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(10):1571-1580. doi: 10.1001/jamaoncol.2020.3370. PMID: 32880601; PMCID: PMC7489405.

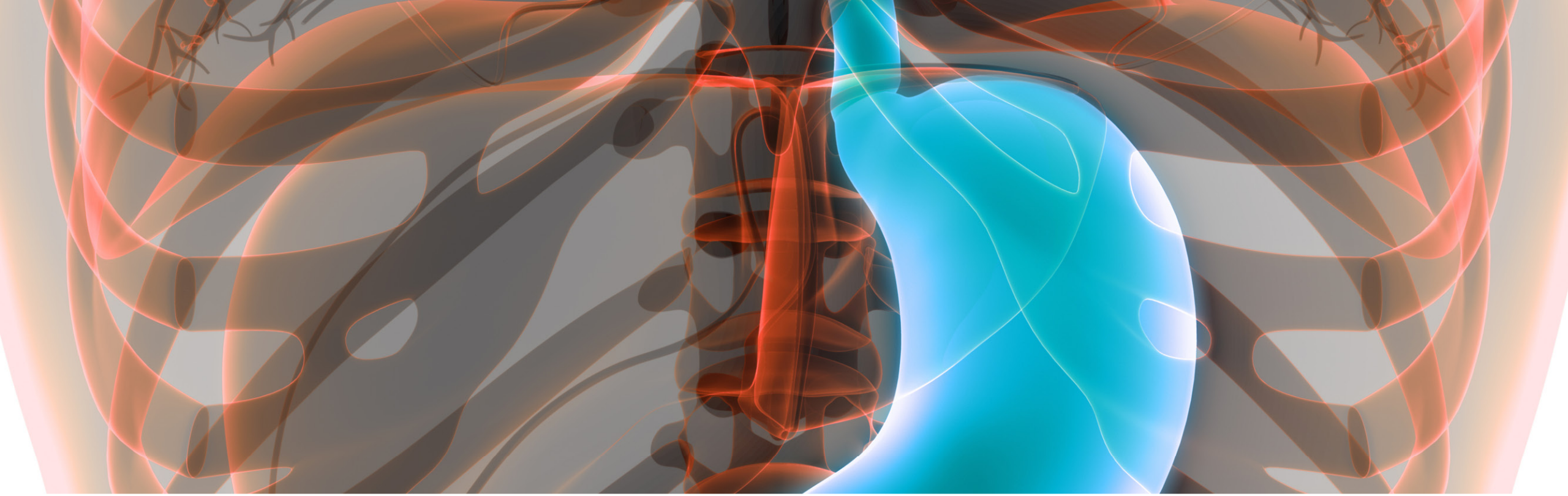


Considerations that may influence treatment decisions for BC

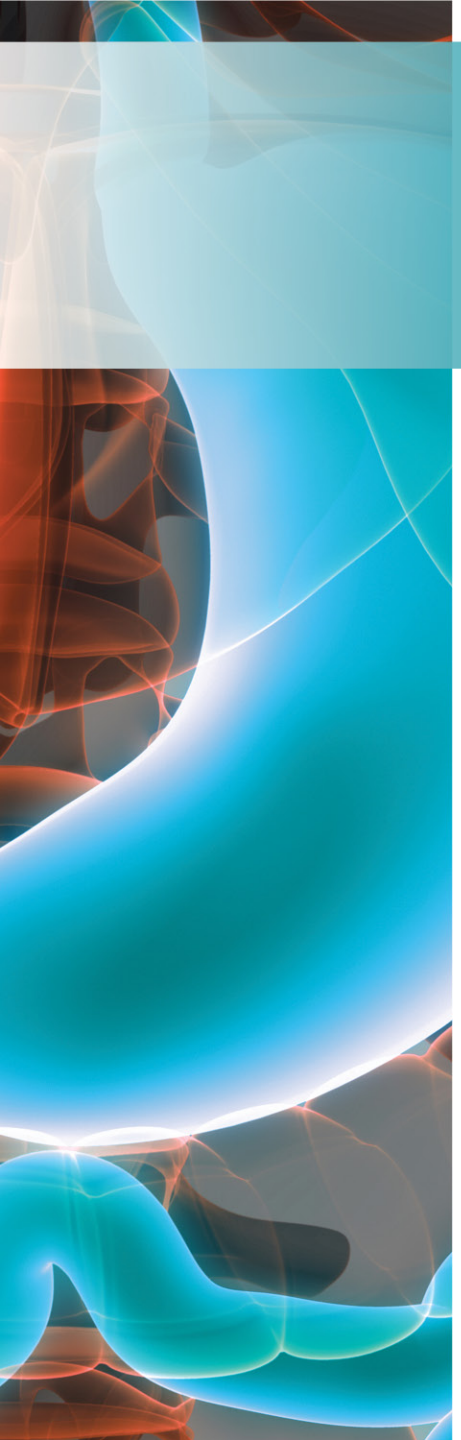


Considerations Checklist

- [x] Medical comorbidities
- [x] Performance status
- [x] Toxicity profile of therapy
- [x] Insurance status (including immigrant status)
- [x] Therapy logistics
- [x] Patient’s wishes/goals of care

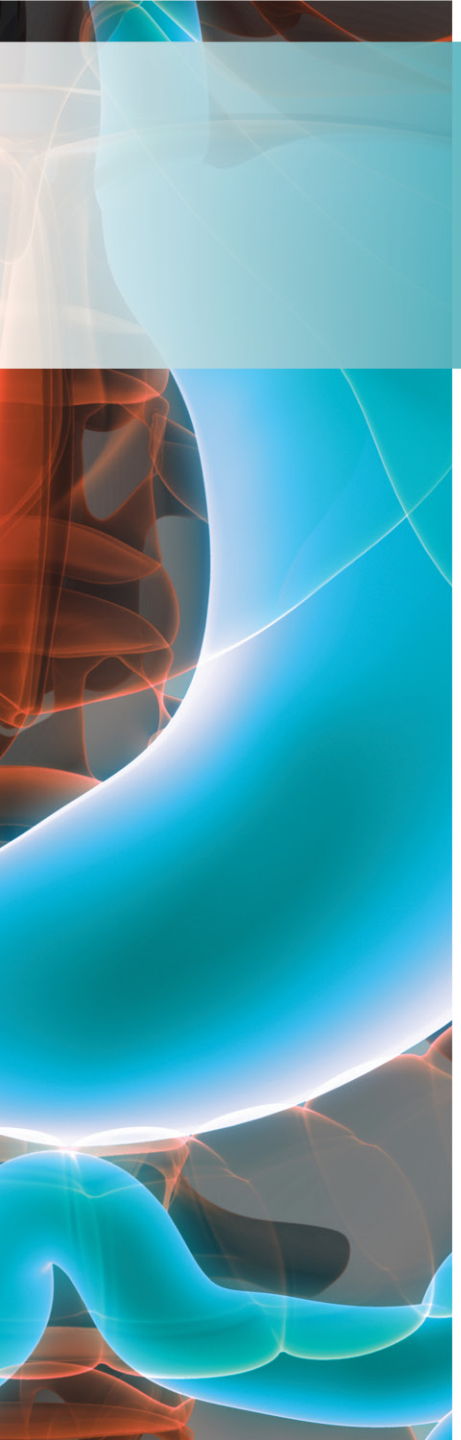


There is more to treatment than just efficacy data



Disease vs Person Management

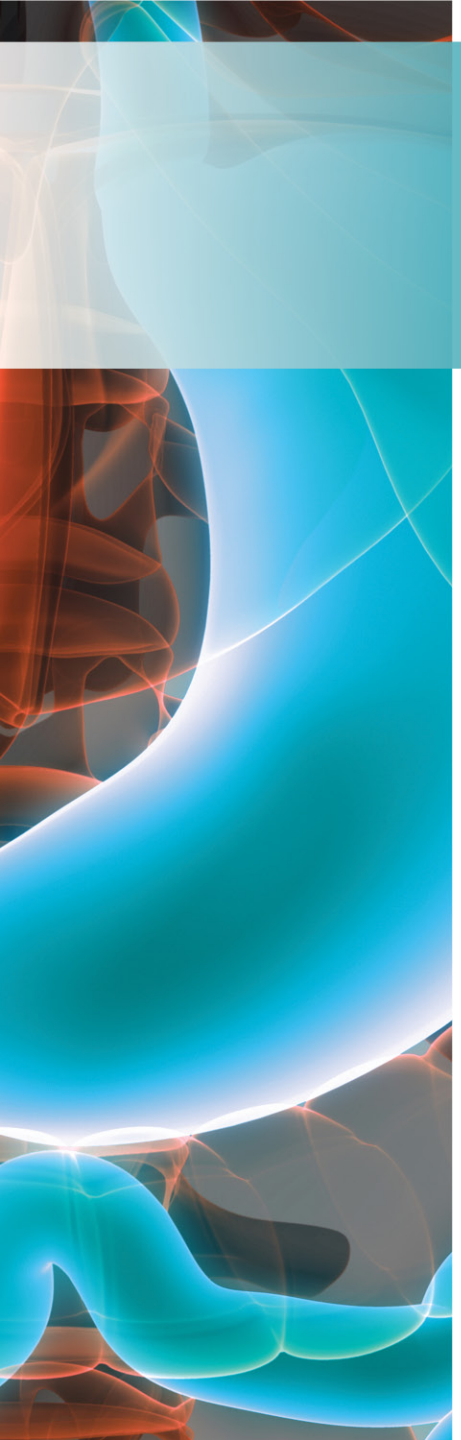
- At 62 years old, BC is still working but considering early retirement as his symptoms result in work absences.
- He is worried about obtaining care if no longer receiving health insurance through his employer.
- BC asks to speak to someone about financial help.

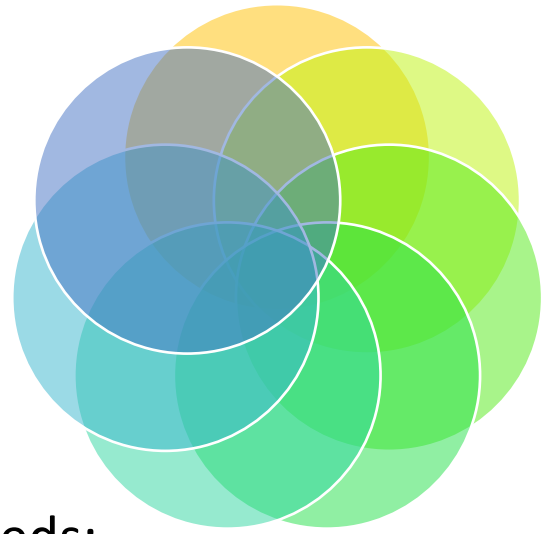


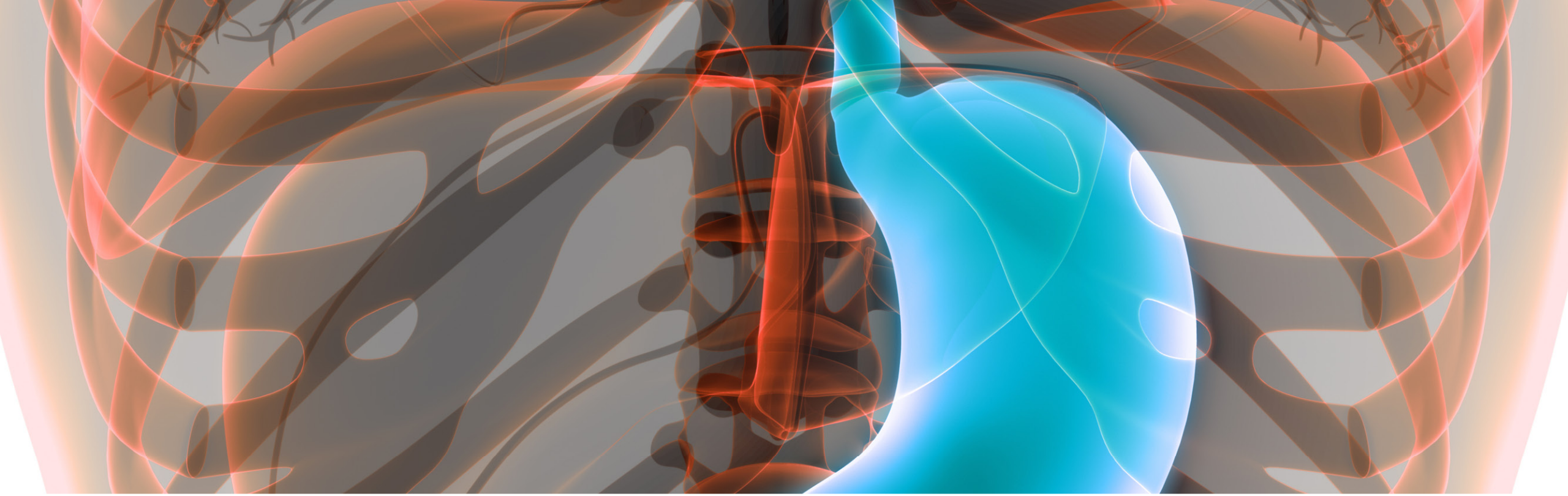
Financial Considerations

- Financial toxicities:
  - Employment change
    - Missed work; unanticipated retirement status; diminished income
  - Insurance gaps – prior to Medicare eligibility
  - Copays/coinsurance
  - Out of pocket maximum
  - Utilizing savings
  - Medical debt
  - Treatment complications
    - Hospital admission

Treatment Decision Considerations







What is the “take-home” message?

Multidisciplinary Approach to Treating Our Patient

Treatment

- Treatment regimen
- Assess symptoms at baseline (CTCAE)
- Monitor for new symptoms
- Follow up visits/phone/EMR portal
- Goals of therapy/care conversations

Navigation

- Care coordination
- Patient support organizations
- Transportation
- Financial

Social Work/ Financial

- SDOH assessment/ reassessment
- Distress screening
- Patient assistance programs
- Other (Insurance optimization)
- Transportation

Nutrition

- Baseline oncology nutrition assessment
- Feeding tube vs parenteral
- Ongoing assessment

Supportive Care

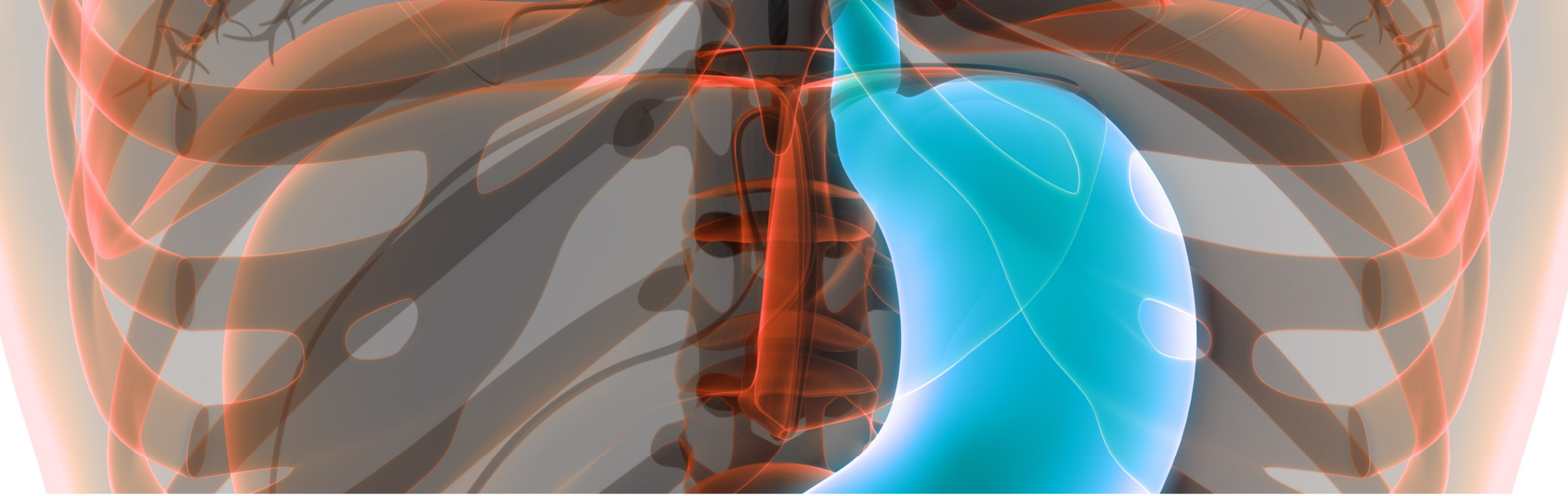
- Treatment-related symptom management
- Cancer-related symptom management

Payor

- Risk/benefit assessment
- Resource / benefit usage
- Determining financial liability

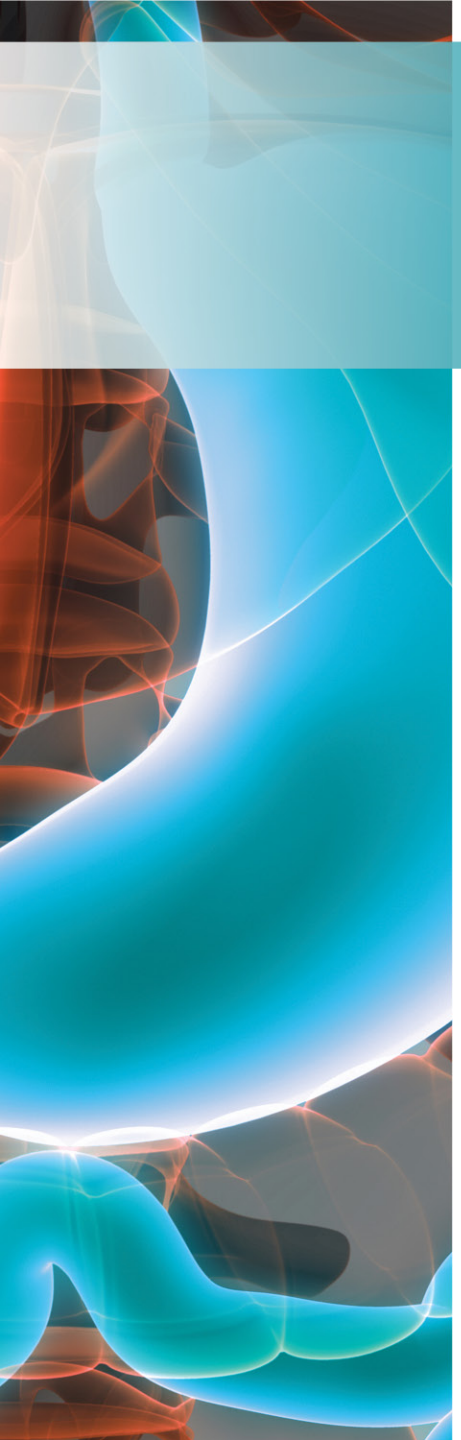
Health Care System

- Resource utilization
- Urgent/emergent care
- Reimbursement landscape



Case 4

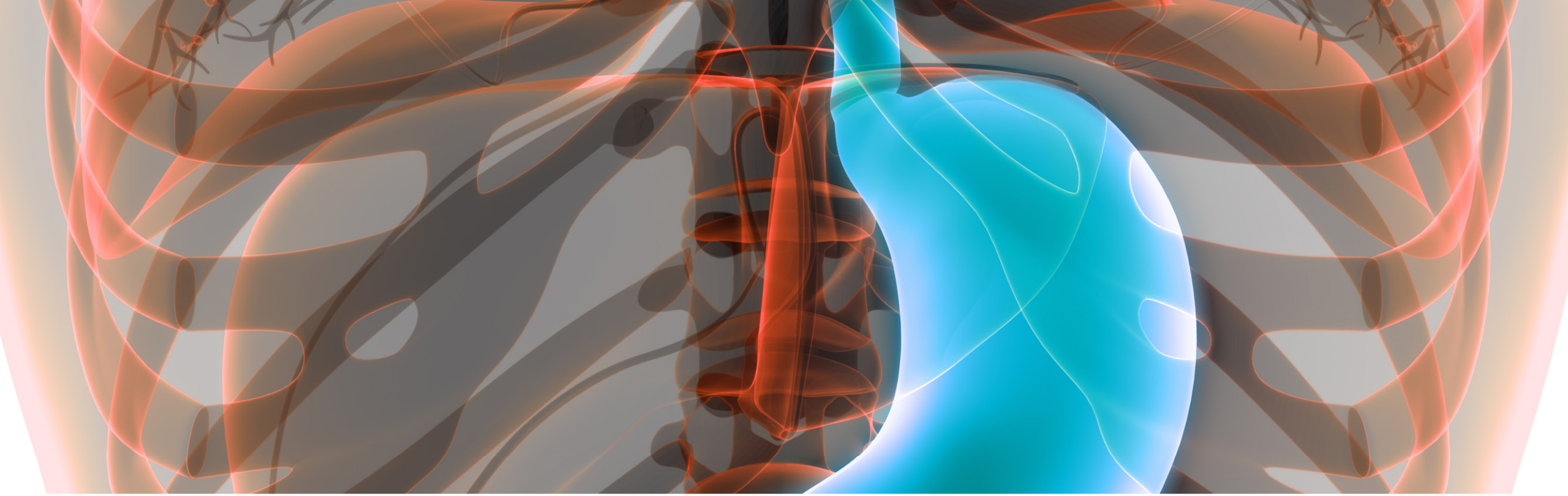
MSI high and TMB



CASE 4

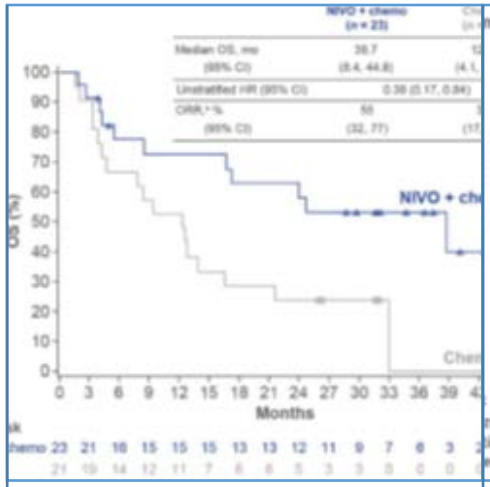
BW, a 42-year-old man, presents with metastatic gastric cancer, MSI-high.

- Which anticancer agents are recommended?
- How to treat TMB high, but MSI-low?

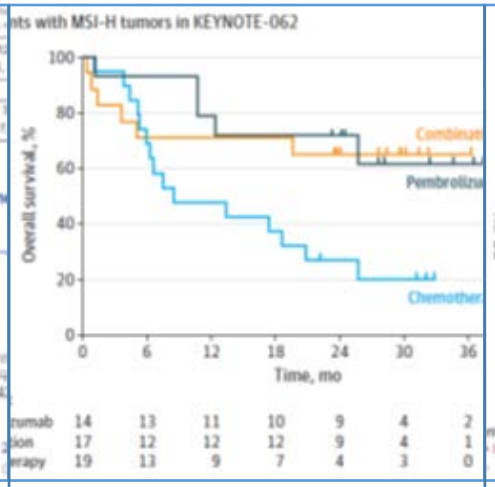


What are the data for using immunotherapy in MSI-high gastric cancer?

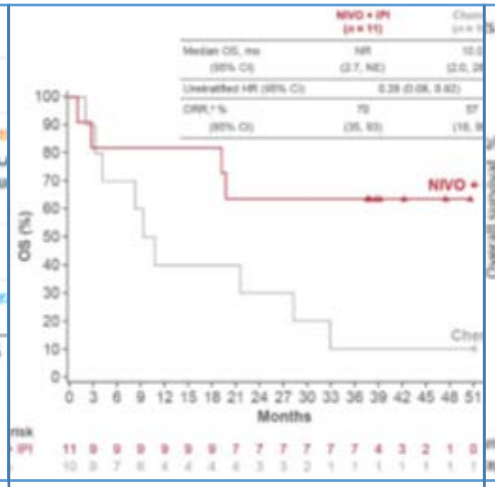
Evidence for ICI in dMMR/MSI-H



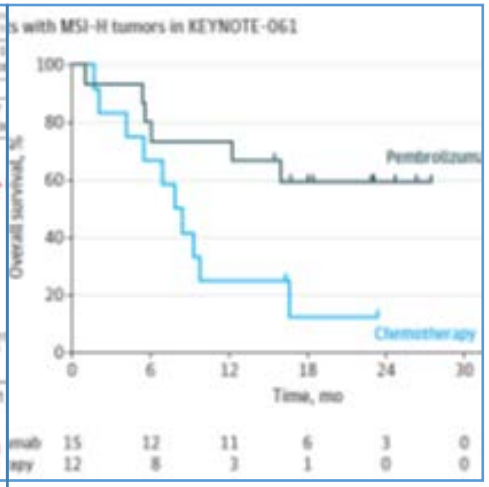
1st Line – nivo + FOLFOX (HR 0.38)



1st Line – pembro (24-mo OS = 65-71%)

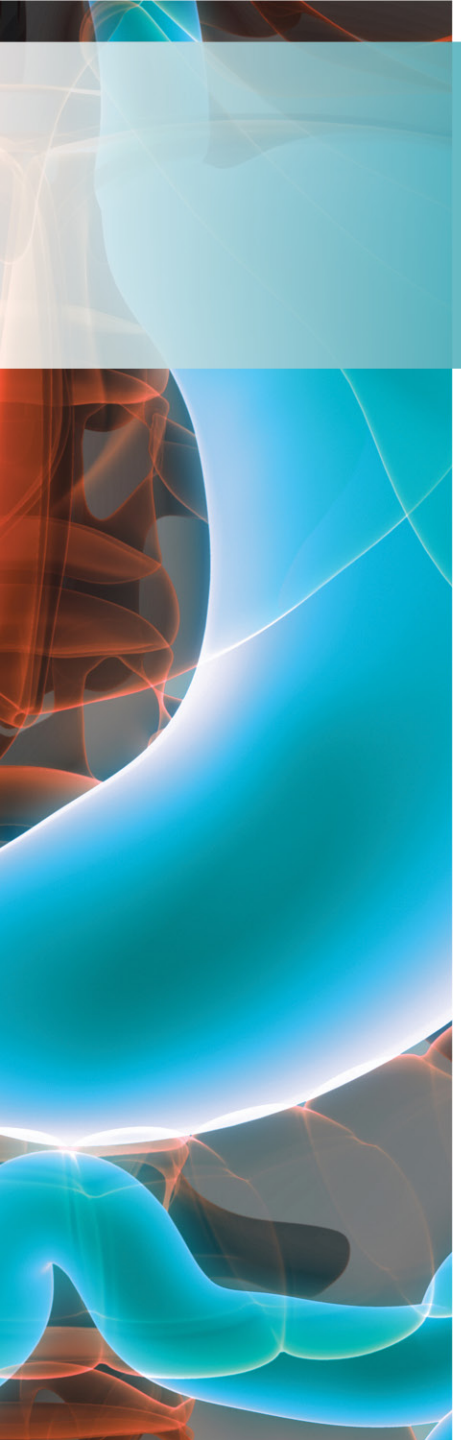


1st Line – nivo IPI (HR 0.28)



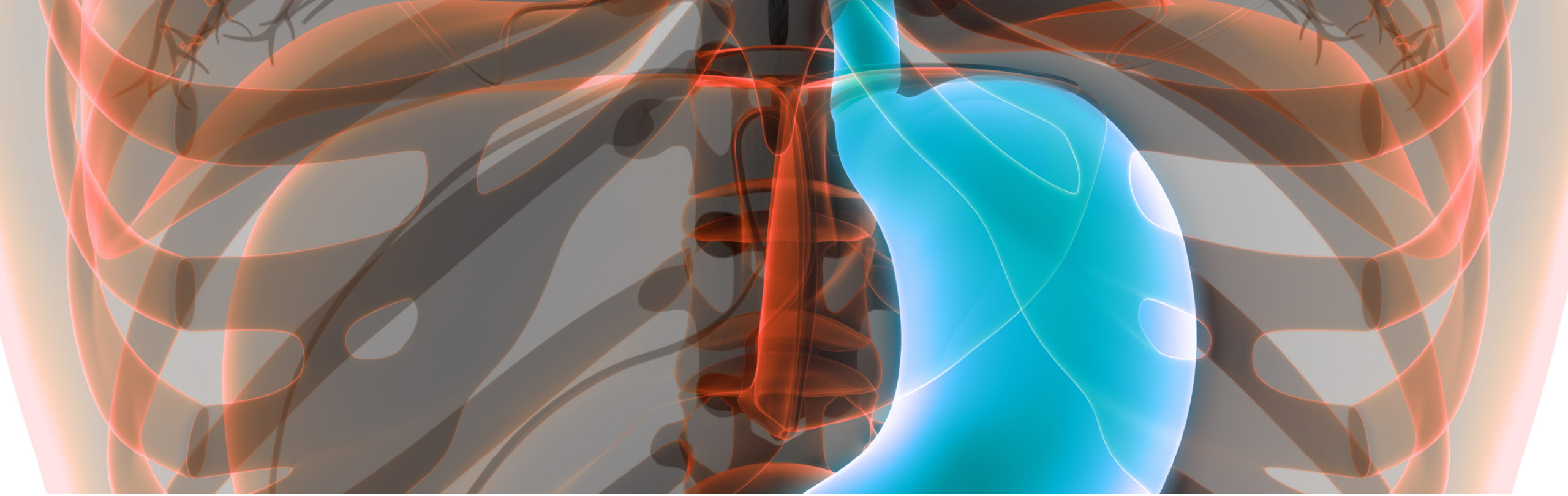
2nd Line – pembro (24-mo OS = 59%)

Chao J et al. *JAMA Oncol*. 2021;7(6):895-902.



Other Considerations for BW

- Family history
- Genetics consult



How do you educate the patient on irAEs?

Educating Patients about irAEs

Immunotherapies work differently than other treatments

Recognition of symptoms to report – include changes from baseline function and changes in ability to perform activities of daily living

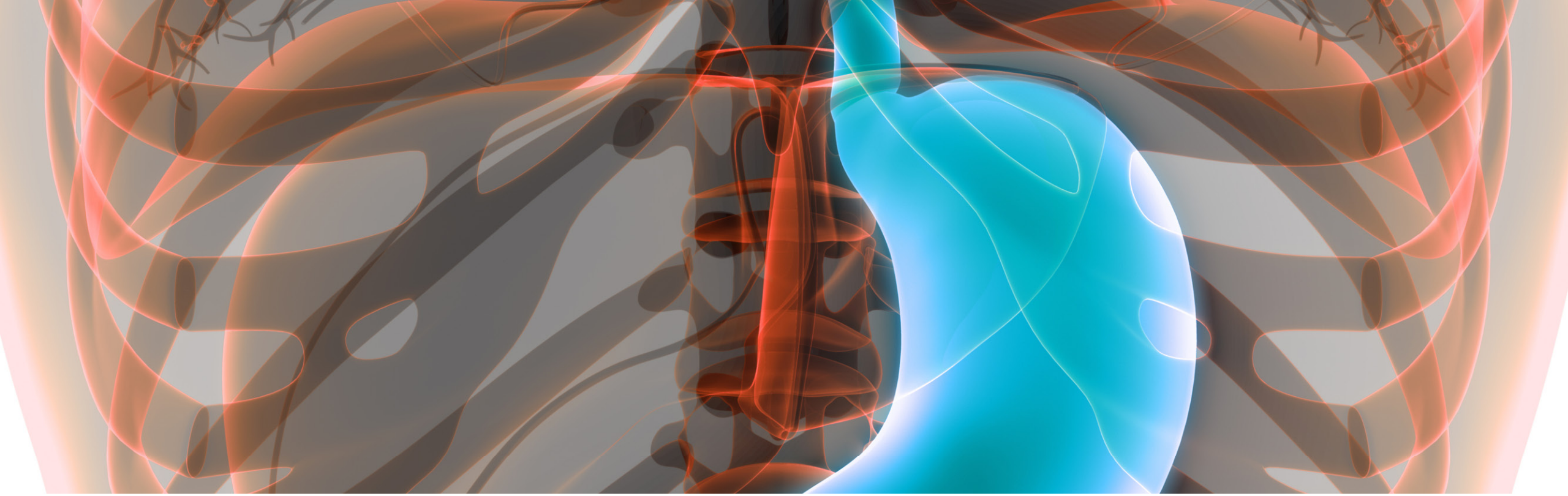
Know when to report, and how to reach treating team

IMMUNOTHERAPY WALLET CARDS to inform ALL health care providers, including ED/urgent care

https://www.ons.org/clinical-practice-resources/immunotherapy-patient-wallet-card

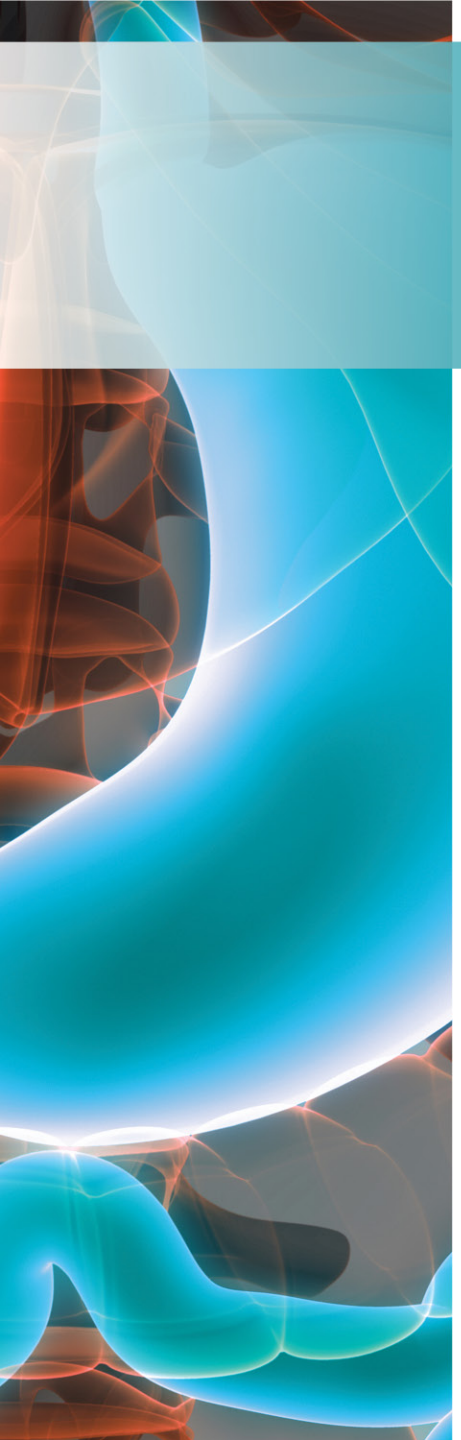
Treatment of irAEs often includes steroids; differs from other types of treatments for cancer

May include interruption in immunotherapy treatment



Patient calls RN triage line with complains of new rash

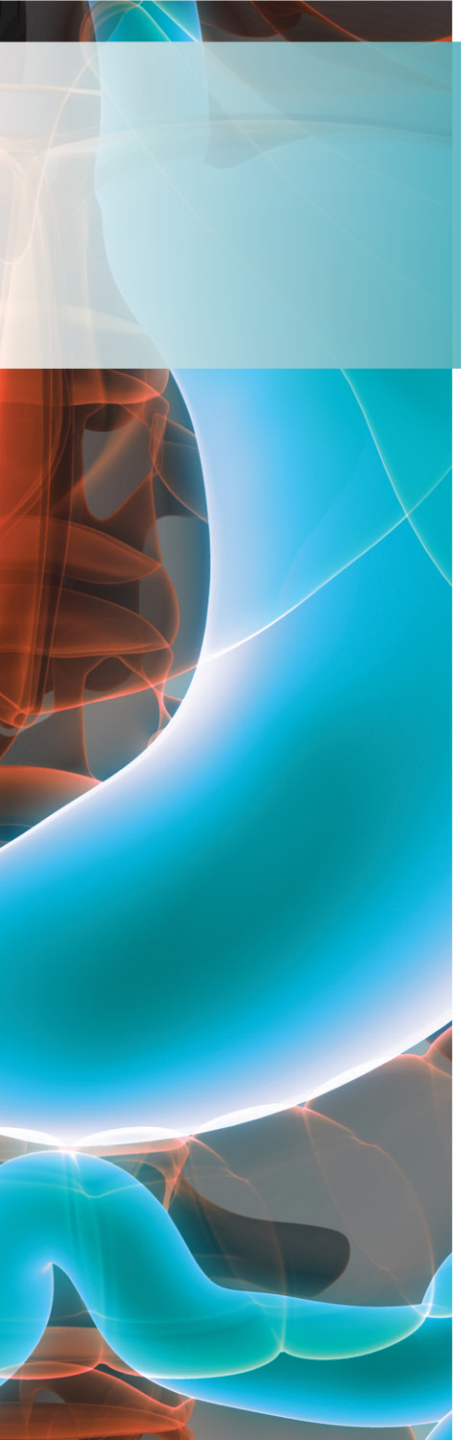
What information do you need to assess?



Checklist – Questions to ask

Provocation/Palliation	Quality	Region/Radiation	Severity Scale	Timing
• What makes it better? • What makes it worse/does not help at all?	• What does it feel like? (hot, itchy, painful, etc) • What does it look like? (color, raised or flat, associated sores, blisters or peeling?, etc)	• Where is it? • Extent of body affected	• Does it prevent you from sleeping at night? • Does it impair your daily activities?	• When did it start? • What was the last treatment? • Changes in daily routine (new medications, change in soap, sunburn, etc)

Hui D, Bruera E. *J Clin Oncol*. 2014;32(16):1640-1646.

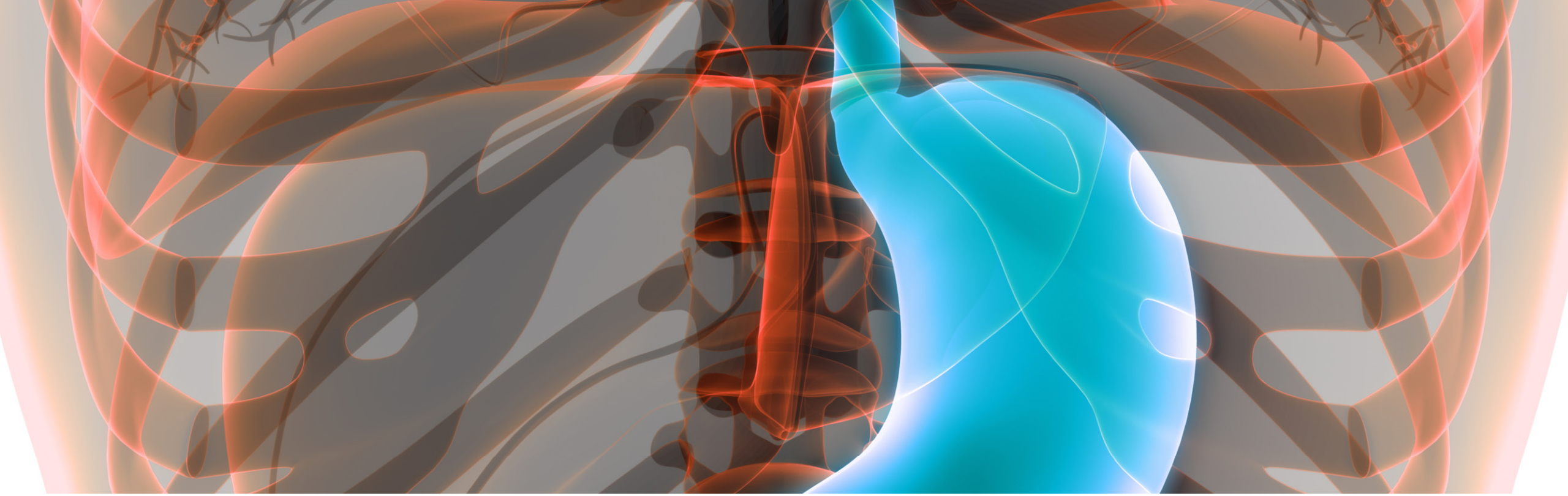


Checklist – BW Answers

Provocation/Palliation	Quality	Region/Radiation	Severity Scale	Timing

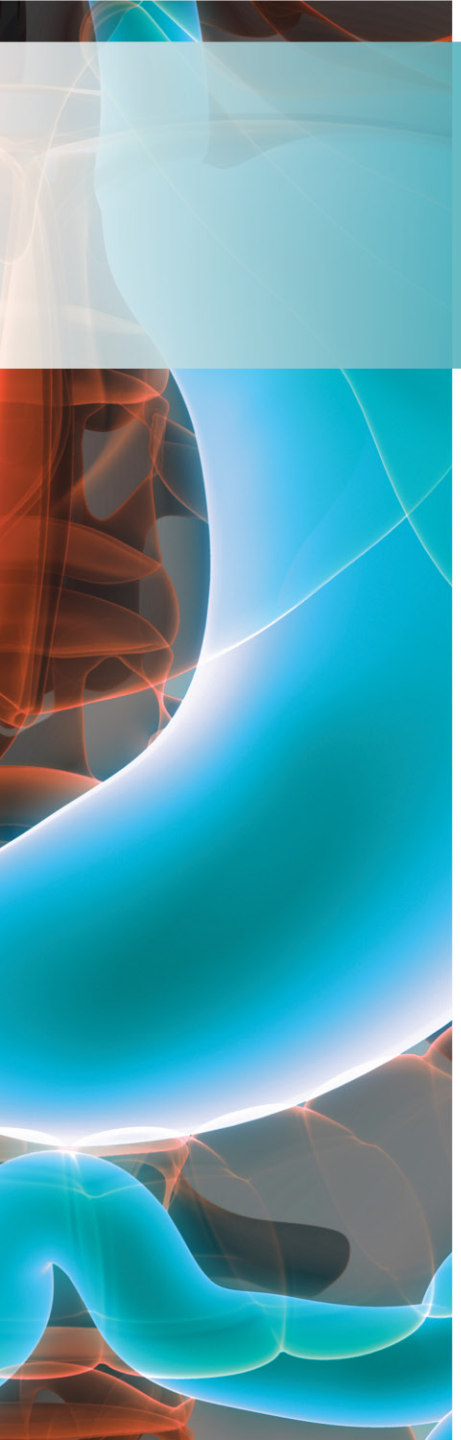
• What makes it better?
  • **OTC hydrocortisone cream**
• What makes it worse/does not help at all?
  • **Topical Calamine lotion**
	• What does it feel like? (hot, itchy, painful, etc)
	  • **Itchy**
	• What does it look like? (color, raised or flat, associated sores, blisters or peeling?, etc)
	  • **Red**
	  • **Raised and flat**
	  • **No blistering or peeling**
		• Where is it?
		  • **Forearms only**
			• Does it prevent you from sleeping at night?
			  • **Does not wake me up, but if I happen to wake up, it's hard to fall back asleep**
			• Does it impair your daily activities?
			  • **Manages through the itching**
				• When did it start?
				  • **Yesterday afternoon**
				• What was the last treatment?
				  • **Received cycle 2 of treatment 4 days ago**
				• Changes in daily routine (new medications, change in soap, sunburn, etc)
				  • **No changes**

Hui D, Bruera E. *J Clin Oncol*. 2014;32(16):1640-1646.



What is the plan?

Action Items



1 → 2 → 3 → 4 → 5

Step 1
- **Assess and grade according to CTCAE**
- **Discuss with team**

Step 2
- Evaluate if patient can be treated outpatient vs inpatient

Step 3
- HOLD therapy, if indicated

Step 4
- Consult referral to specialty service, if indicated
- Consider additional tests

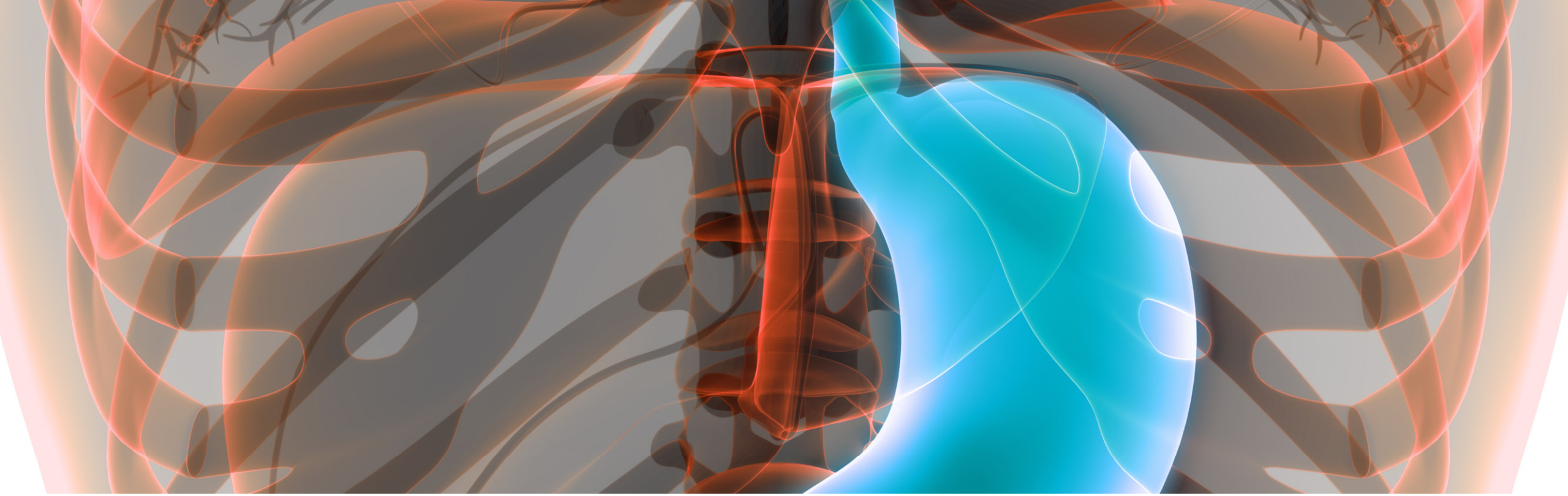
Step 5
- Initiate treatment according to evidence-based algorithms

Common Terminology Criteria for Adverse Events (CTCAE) Version 5. Published: November 27. US Department of Health and Human Services, National Institutes of Health, National Cancer Institute.

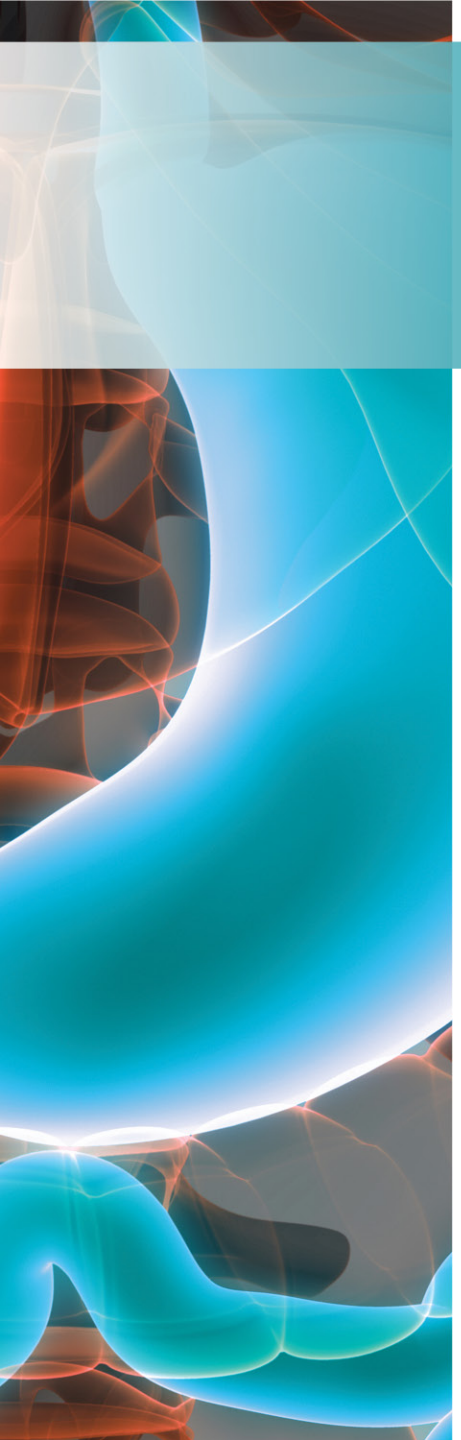
Action Items

1	2	3	4	5
Step 1 •**Assess and grade according to CTCAE** •**Discuss with team**	Step 2 •Evaluate if patient can be treated outpatient vs inpatient	Step 3 •HOLD therapy, if indicated	Step 4 •Consult referral to specialty service, if indicated •Consider additional tests	Step 5 •Initiate treatment according to evidence-based algorithms
• Grade 1-2	• Outpatient appropriate	• Hold not required	• Consider dermatology consult; not urgent	• Moderate-high potency topical steroid • Enough to cover area • PRN antihistamine

Common Terminology Criteria for Adverse Events (CTCAE) Version 5. Published: November 27. US Department of Health and Human Services, National Institutes of Health, National Cancer Institute.



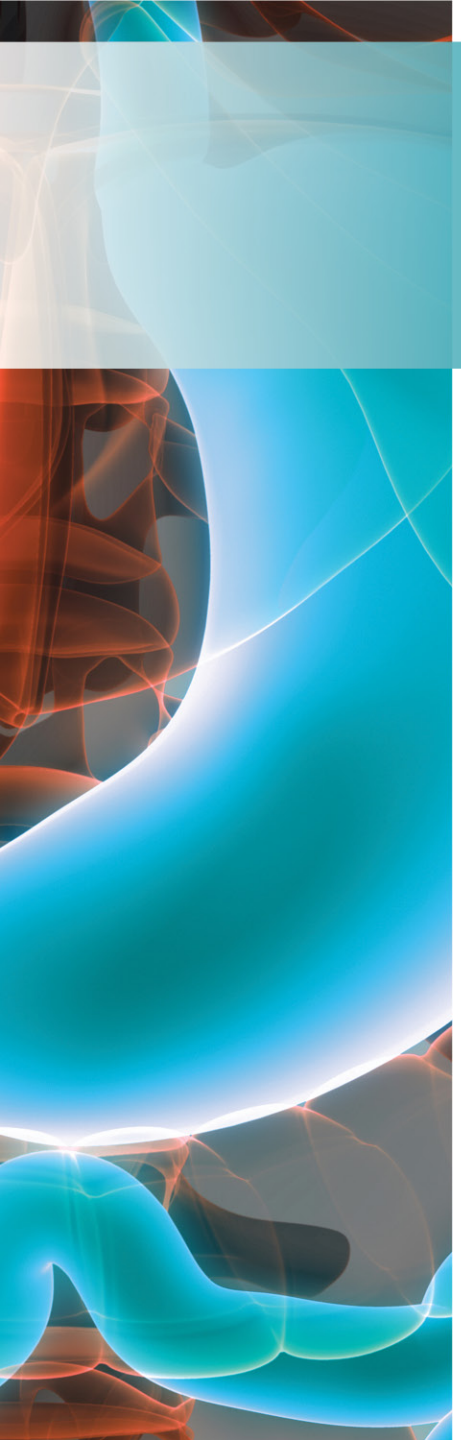
After cycle 6, rash worsens.



Checklist – Questions to ask

Provocation/Palliation	Quality	Region/Radiation	Severity Scale	Timing
• What makes it better? • What makes it worse/does not help at all?	• What does it feel like? (hot, itchy, painful, etc) • What does it look like? (color, raised or flat, associated sores, blisters or peeling?, etc)	• Where is it?	• Does it prevent you from sleeping at night? • Does it impair your daily activities?	• When did it start? • What was the last treatment? • Changes in daily routine (new medications, change in soap, sunburn, etc)

Hui D, Bruera E. *J Clin Oncol*. 2014;32(16):1640-1646.

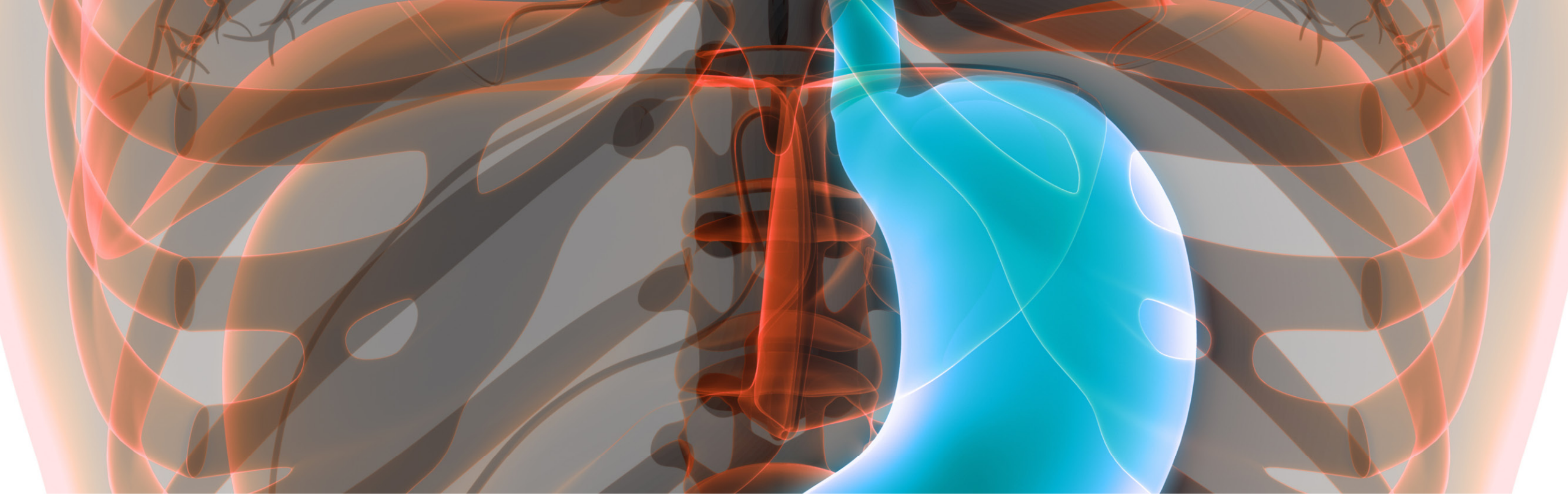


Checklist – BW Answers

Provocation/Palliation	Quality	Region/Radiation	Severity Scale	Timing

• What makes it better?
  • **Nothing. The prescription cream was working, but now there is just too much rash**
• What makes it worse/does not help at all?
  • **Not sure anymore**
	• What does it feel like? (hot, itchy, painful, etc)
	  • **Intense, unrelenting itching**
	• What does it look like? (color, raised or flat, associated sores, blisters or peeling?, etc)
	  • **Red**
	  • **"Angry"**
	  • **Raised**
	  • **No blistering or peeling**
		• Where is it?
		  • **Both arms**
		  • **Both legs**
		  • **Chest**
		  • **Abdomen**
		  • **Upper back**
			• Does it prevent you from sleeping at night?
			  • **Cannot sleep**
			• Does it impair your daily activities?
			  • **Cannot concentrate on any other tasks**
				• When did it start?
				  • **This morning**
				• What was the last treatment?
				  • **Cycle 6 was administered 3 days ago**
				• Changes in daily routine (new medications, change in soap, sunburn, etc)
				  • **No changes**

Hui D, Bruera E. *J Clin Oncol*. 2014;32(16):1640-1646.



What is the plan?

Stepwise Approach

1 → 2 → 3 → 4 → 5

Step 1

- **Assess and grade according to CTCAE**
- **Discuss with team**

Step 2

- Evaluate if patient can be treated outpatient vs inpatient

Step 3

- HOLD therapy, if indicated

Step 4

- Consult referral to specialty service, if indicated
- Consider additional tests

Step 5

- Initiate treatment according to evidence-based algorithms

Common Terminology Criteria for Adverse Events (CTCAE) Version 5. Published: November 27. US Department of Health and Human Services, National Institutes of Health, National Cancer Institute.

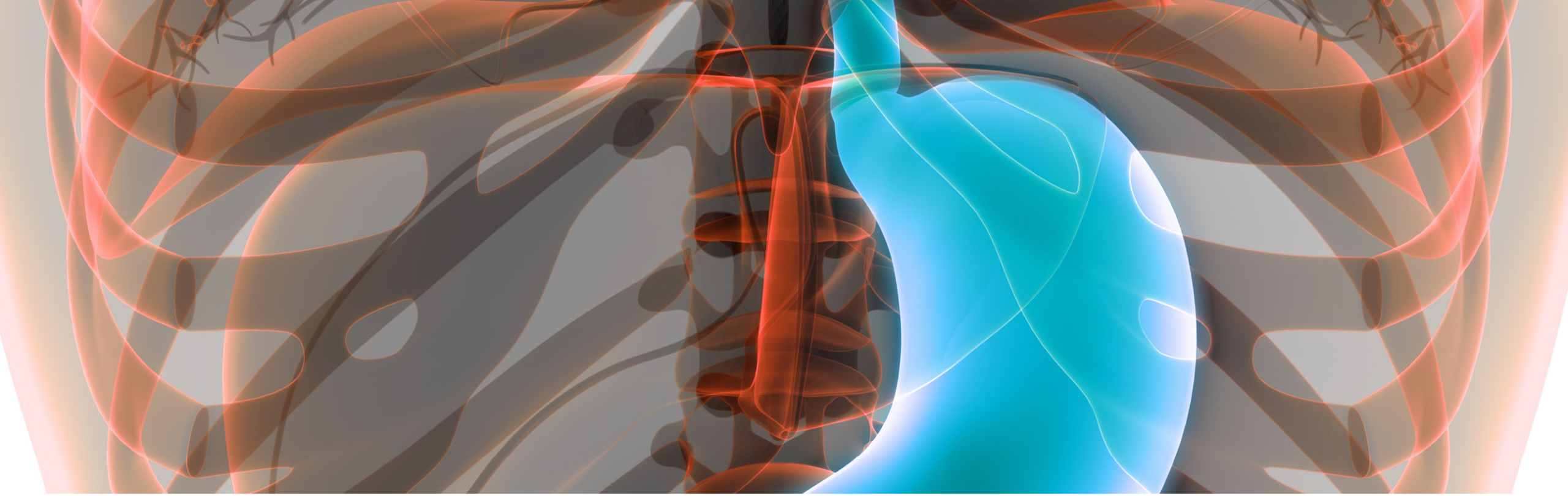
Stepwise Approach

1	2	3	4	5
Step 1 •**Assess and grade according to CTCAE** •**Discuss with team**	Step 2 •Evaluate if patient can be treated outpatient vs inpatient	Step 3 •HOLD therapy, if indicated	Step 4 •Consult referral to specialty service, if indicated •Consider additional tests	Step 5 •Initiate treatment according to evidence-based algorithms
• Grade 3	• Inpatient	• HOLD therapy • Reinforce education (fears)	• Consult Dermatology	• Systemic corticosteroids required • (See next slide)

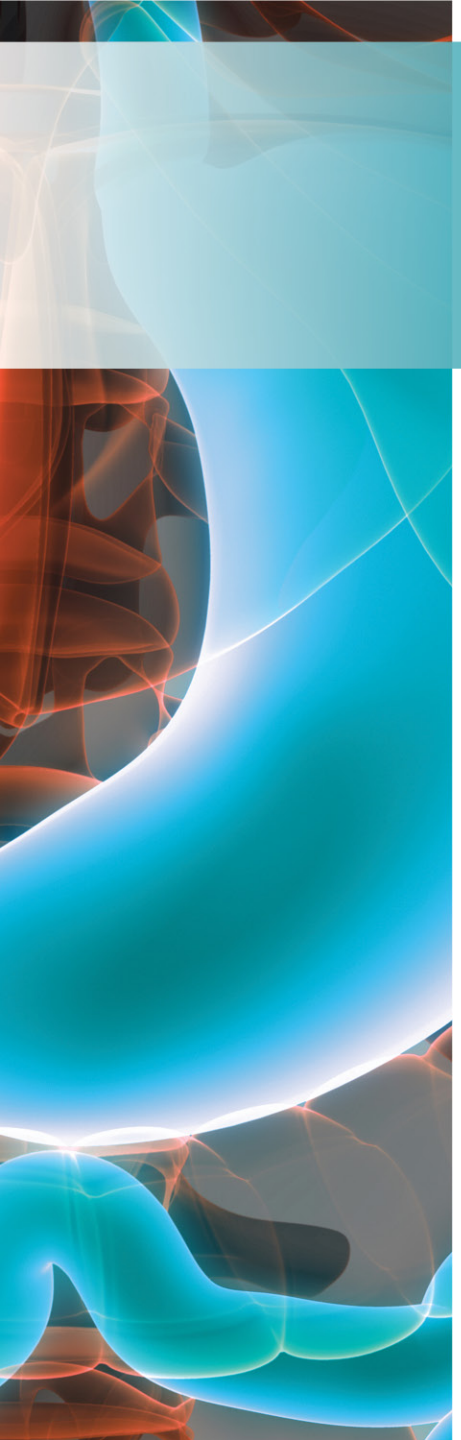
Common Terminology Criteria for Adverse Events (CTCAE) Version 5. Published: November 27. US Department of Health and Human Services, National Institutes of Health, National Cancer Institute.

Admission “To Do” Checklist

Inpatient admission	
Urgent consult to dermatology	
Consider skin biopsy	
Initiate systemic IV steroids	Prednisone 0.5-1 mg/kg/d
	GI prophylaxis
	Consider Prophylaxis for pneumocystis jirovecii pneumonia
High potency topical steroids to selected areas	Triamcinolone 0.5%
	Clobetasol 0.025%
	Betamethasone 0.05%
	Fluocinonide 0.05%
Antihistamine, as needed, for itching	
HOLD immunotherapy	



Future Directions



Some Areas of Research

- **Understanding impact of PD-1 blockade on immune microenvironment**
  - Sometimes conflicting (eg, balance of PD-1 expression on CD8+ T cells vs regulatory T cells, “hyper-progression”)
  - Discrepancy of PFS vs OS
- **Overcoming primary and acquired resistance to PD-1 blockade**
  - Targeting other immune checkpoints (eg, TIM3, TIGIT, LAG3)
  - Combination with anti-angiogenesis, anti-HER2 ADC
  - CAR-T (eg, Claudin18.2, HER2, CEA, MUC1, EpCAM, mesothelin)
- **Targeting growth pathways**
  - Anti-Claudin18.2 Ab
  - Anti-FGFR2
  - Anti-HER2 in “HER2-low”