Oncology Clinical Pathways

Esophageal Cancer

April 2025 – V2.2025

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Esophageal Cancer – Presumptive Conditions

VA automatically presumes that certain disabilities were caused by military service. This is because of the unique circumstances of a specific Veteran's military service. If a presumed condition is diagnosed in a Veteran within a certain group, they can be awarded disability compensation.

Atomic Veterans – Exposure to Ionizing Radiation

- Cancer of the esophagus

Gulf War and Post 9/11 Veterans

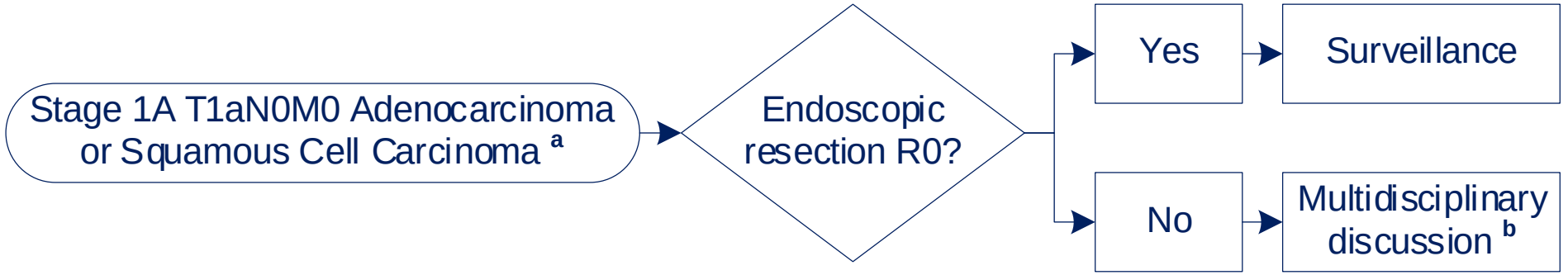
If the patient served on or after Sept. 11, 2001, in Afghanistan, Djibouti, Egypt, Jordan, Lebanon, Syria, Uzbekistan, or Yemen or if you served in the *Southwest Asia theater of operations, or Somalia, on or after Aug. 2, 1990, specific conditions include:

- Gastrointestinal cancer of any type

* The Southwest Asia theater of operations refers to Iraq, Kuwait, Saudi Arabia, the neutral zone between Iraq and Saudi Arabia, Bahrain, Qatar, the United Arab Emirates, Oman, the Gulf of Aden, the Gulf of Oman, the Persian Gulf, the Arabian Sea, the Red Sea, and the airspace above these locations.

For more information, please visit U.S. Department of Veterans Affairs - Presumptive Disability Benefits (va.gov)

Esophageal Cancer – Stage 1A T1aN0M0 Adenocarcinoma or Squamous Cell Carcinoma



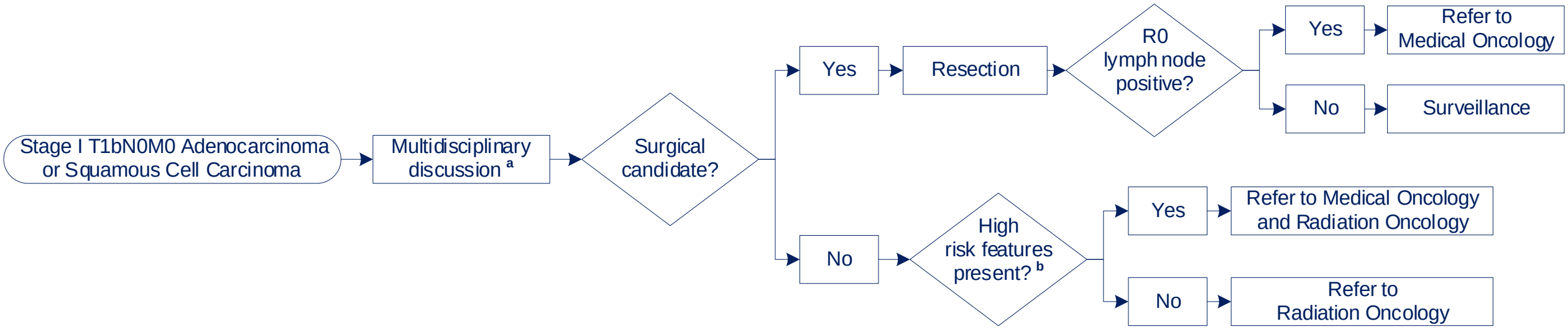
Clinical trial(s) always considered on pathway. For assistance finding a clinical trial, email CancerClinicalTrialsNavigation@va.gov.

[a] **Staging** confirmed during EMR or ESD

[b] **Multidisciplinary Discussion** includes surgery, radiation oncology, and medical oncology

EMR Endoscopic Mucosal Resection
ESD Endoscopic Submucosal Dissection

Esophageal Cancer – Stage I T1bN0M0 Adenocarcinoma or Squamous Cell Carcinoma



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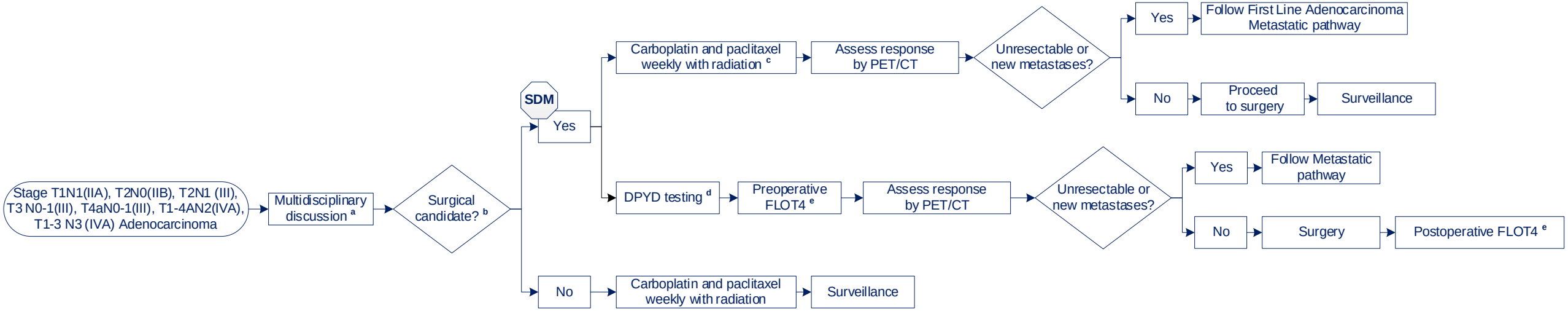
[a] **Multidisciplinary Discussion** confirm stage

[b] **High Risk Features** include lymphovascular invasion, poorly differentiated tumors, tumor size ≥ 2cm, SM1, SM2, or positive margin on EMR

EMR Endoscopic Mucosal Resection

Esophageal Cancer – Stage T1N1(IIA), T2N0(IIB), T2N1 (III), T3 N0-1(III), T4aN0-1(III), T1-4AN2(IVA), T1-3 N3 (IVA) Adenocarcinoma



Clinical trial(s) and shared decision making are always considered on pathway. For assistance finding a clinical trial, email CancerClinicalTrialsNavigation@va.gov.

[a] **Multidisciplinary Discussion** includes surgery, radiation oncology, and medical oncology

[b] **Surgical Candidate** discussion with or evaluation by a surgeon

[c] **Carboplatin and Paclitaxel with Radiation** preferred treatment for predominantly esophageal tumors

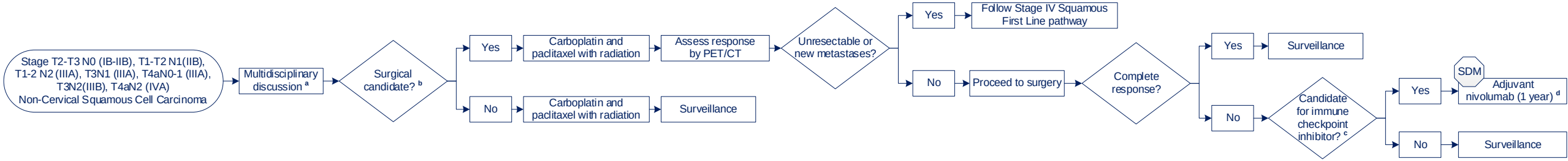
[d] **Perform DPYD Testing If Not Already Performed** if DPYD PGx results return predicted phenotypes of either intermediate or poor metabolizer, please consult your local PGx pharmacist or submit an IFC Pharmacogenomics e-consult for assistance with therapeutic recommendation; a clinician may proceed without DPYD results if withholding chemotherapy for 2-3 weeks may gravely endanger patient's life; for example, if the disease burden is very high and it involves a large portion of vital organs such as liver, etc.

[e] **FLOT4 Candidates** include fit patients with ECOG 0-1 due to expected Grade 3/4 toxicities of neutropenia, infection, diarrhea and peripheral neuropathy

SDM ESOPEC trial compared CROSS regimen to perioperative FLOT; ESOPEC trial showed improvement in OS with perioperative FLOT; however, the majority of patients on the trial had ECOG PS 0 with limited comorbidities and this might not be reflective of our patient population; PETCTs were not mandated for staging; only 67% of patients on the CROSS arm received all their weekly chemotherapy regimen; the CROSS arm underperformed potentially due to under treatment; we therefore recommend shared decision making when deciding optimal therapy for each patient; shared decision making is critical at the time of consideration of therapy

SDM Shared Decision Making

Esophageal Cancer – Stage T2-T3 N0 (IB-IIB), T1-T2 N1(IIB), T1-2 N2 (IIIA), T3N1 (IIIA), T4aN0-1 (IIIA), T3N2(IIIB), T4aN2 (IVA) Non-Cervical Squamous Cell Carcinoma



Clinical trial(s) always considered on pathway. For assistance finding a clinical trial, email CancerClinicalTrialsNavigation@va.gov.

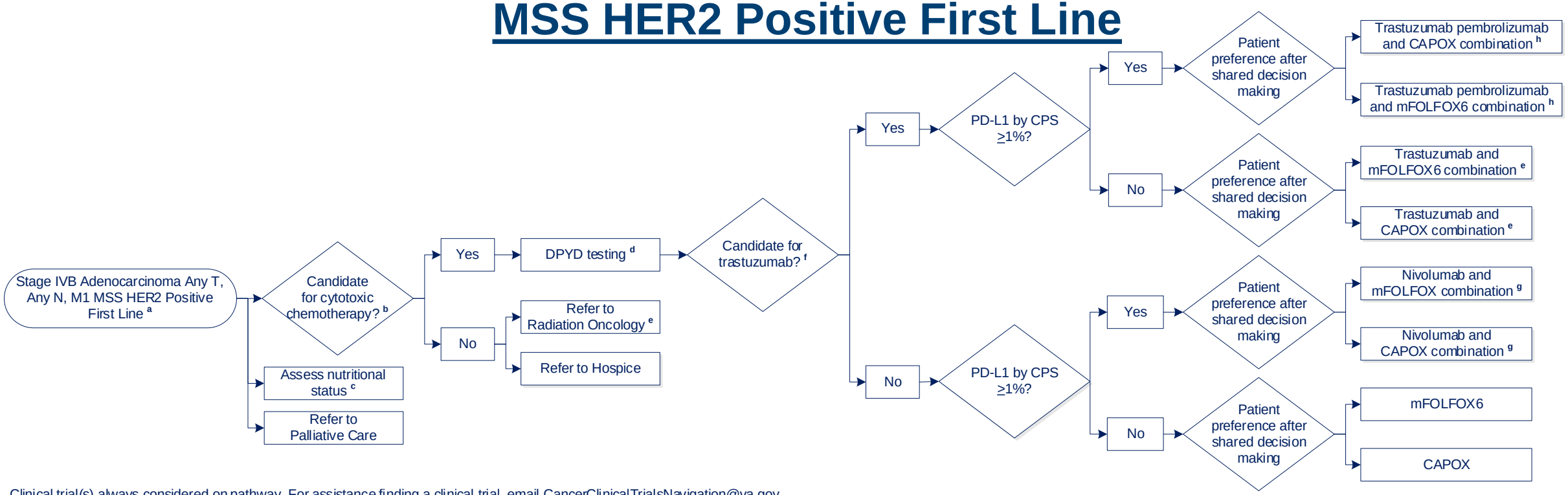
[a] **Multidisciplinary Discussion** includes surgery, radiation oncology, and medical oncology

[b] **Surgical Candidate** discussion with or evaluation by a surgeon

[c] **Qualify for Immune Checkpoint Inhibitor** patient without active autoimmune disease, primary immune deficiency, concurrent immunosuppression (including prednisone equivalent >10mg/day) or prior allogeneic HSCT/solid organ transplant

[d] **SDM Adjuvant Nivolumab** is a consideration based on improvement disease free survival noted on CheckMate 577; however, no overall survival data is yet available, with overall survival as the gold standard for adjuvant trials; only 7% of patients on the placebo arm received immunotherapy at progression

Esophageal Cancer – Stage IVB Adenocarcinoma Any T, Any N, M1 MSS HER2 Positive First Line



Clinical trial(s) always considered on pathway. For assistance finding a clinical trial, email CancerClinicalTrialsNavigation@va.gov.

[a] **HER2 Positive** considered IHC score +3 or an IHC score of +2 and FISH/ISH positive

[b] **Candidate for Cytotoxic Chemotherapy** consider if patient can tolerate a platinum- and fluoropyrimidine-based doublet

[c] **Assess Nutritional Status** and consider palliative stent or other nutritional support modalities when clinically appropriate

[d] **Perform DPYD Testing If Not Already Performed** if DPYD PGx results return predicted phenotypes of either intermediate or poor metabolizer, please consult your local PGx pharmacist or submit an IFC Pharmacogenomics e-consult for assistance with therapeutic recommendation; a clinician may proceed without DPYD results if withholding chemotherapy for 2-3 weeks may gravely endanger patient's life; for example, if the disease burden is very high and it involves a large portion of vital organs such as liver, etc.

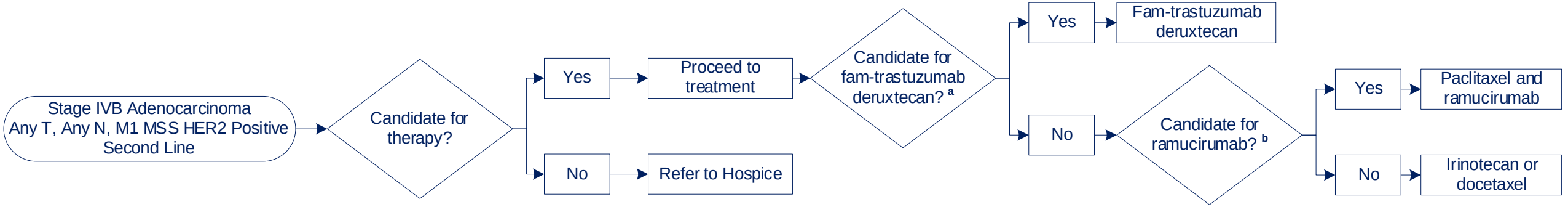
[e] **Radiation Oncology** consider palliative radiation when clinically appropriate

[f] **Candidate for Trastuzumab or Biosimilar** patient with HER2-positive disease and no clinically significant CV disease (defined as LVEF< 50%, MI within prior 6 months, symptomatic CHF (NYHA class II to IV), unstable angina or cardiac arrhythmia requiring therapy)

[g] **Candidate for Immune Checkpoint Inhibitor** patient without active autoimmune disease, primary immune deficiency, concurrent immunosuppression (including prednisone equivalent >10mg/day) or prior allogeneic HSCT/solid organ transplant

[h] **Pembrolizumab** for two years

Esophageal Cancer – Stage IVB Adenocarcinoma Any T, Any N, M1 MSS HER2 Positive Second Line

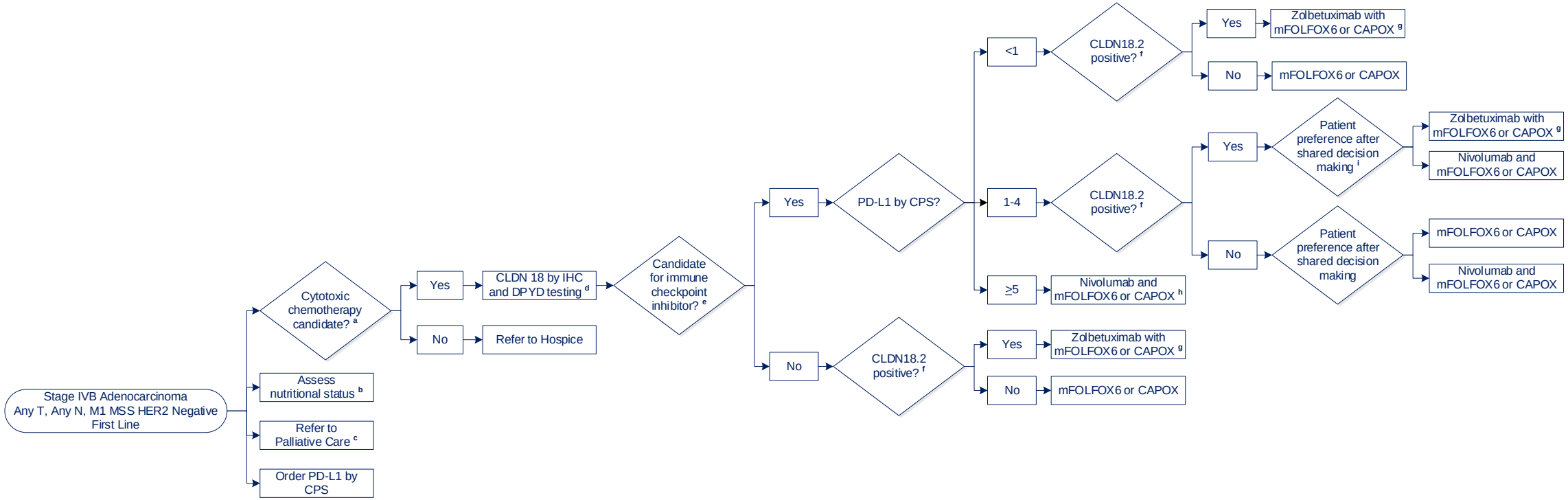


Clinical trial(s) always considered on pathway. For assistance finding a clinical trial, email CancerClinicalTrialsNavigation@va.gov.

[a] **Candidate for Fam-Trastuzumab Deruxtecan** received trastuzumab in the first-line setting; baseline LVEF ≥ 50% and/or no clinically significant cardiac disease (defined as LVEF< 50%, MI within prior 6 months, symptomatic CHF (NYHA class II to IV), unstable angina or cardiac arrhythmia requiring therapy); no ILD or pneumonitis; ANC ≥ 1500/mm^3

[b] **Candidate for Ramucirumab** received fluoropyrimidine and platinum agent in the first-line setting; ECOG PS 0-2; ANC ≥ 1500/mm^3. Note: Due to anti-VEGF effects patients with the following should not receive ramucirumab: non-healing wound/fracture, major surgery in prior 4 weeks, bleeding disorder or coagulopathy, recent history of GI perforation, unstable cardiac condition (uncontrolled HTN, arterial thromboembolism, symptomatic CHF (NYHA II-IV) or arrhythmia), or active cocaine use

Esophageal Cancer – Stage IVB Adenocarcinoma Any T, Any N, M1 MSS HER2 Negative First Line



Clinical trial(s) always considered on pathway. For assistance finding a clinical trial, email CancerClinicalTrialsNavigation@va.gov.

[a] **Candidate for Cytotoxic Chemotherapy** consider if patient can tolerate a platinum- and fluoropyrimidine-based doublet

[b] **Assess Nutritional Status** consider palliative stent or other nutritional support modalities when clinically appropriate

[c] **Assess Palliative Care** consider palliative radiation when clinically appropriate

[d] **Perform DPYD Testing If Not Already Performed** if DPYD PGx results return predicted phenotypes of either intermediate or poor metabolizer, please consult your local PGx pharmacist or submit an IFC Pharmacogenomics e-consult for assistance with therapeutic recommendation; a clinician may proceed without DPYD results if withholding chemotherapy for 2-3 weeks may gravely endanger patient's life; for example, if the disease burden is very high and it involves a large portion of vital organs such as liver, etc.

[e] **Qualify for Immune Checkpoint Inhibitor** no active autoimmune disease, primary immune deficiency, concurrent immunosuppression (including prednisone equivalent >10mg/day) or prior allogeneic HSCT/solid organ transplant

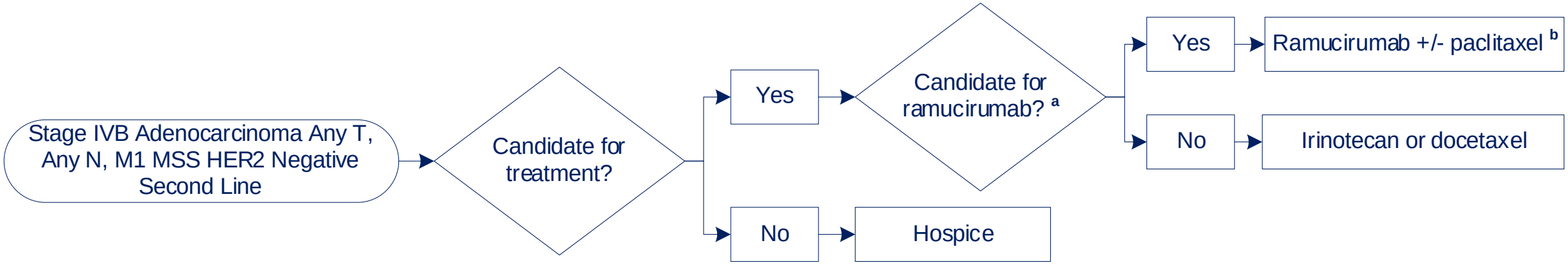
[f] **CLDN18.2 Positivity** defined as ≥ 75% of tumor cells demonstrating moderate to strong membranous CLDN18 IHC

[g] **Zolbetuximab** acute nausea and/or vomiting may occur within 1 hour of zolbetuximab infusion; management includes a slower infusion rate and combination antiemetics (i.e. 5-HT3 receptor antagonist, NK-1 receptor blockers, dexamethasone, etc.)

[h] **CPS ≥5** there is longer follow up data with nivolumab and chemotherapy in the metastatic first line setting of esophageal cancer; the largest benefit of adding immune therapy to chemotherapy is in the CPS ≥5 patient population

[i] **CPS 1-4 and CLDN18.2 Positive** there is no head to head comparison between zolbetuximab and chemotherapy or immunotherapy and chemotherapy; toxicity profiles are different, therefore discussion with patients that quality for either regimens is recommended

Esophageal Cancer – Stage IVB Adenocarcinoma Any T, Any N, M1 MSS HER2 Negative Second Line

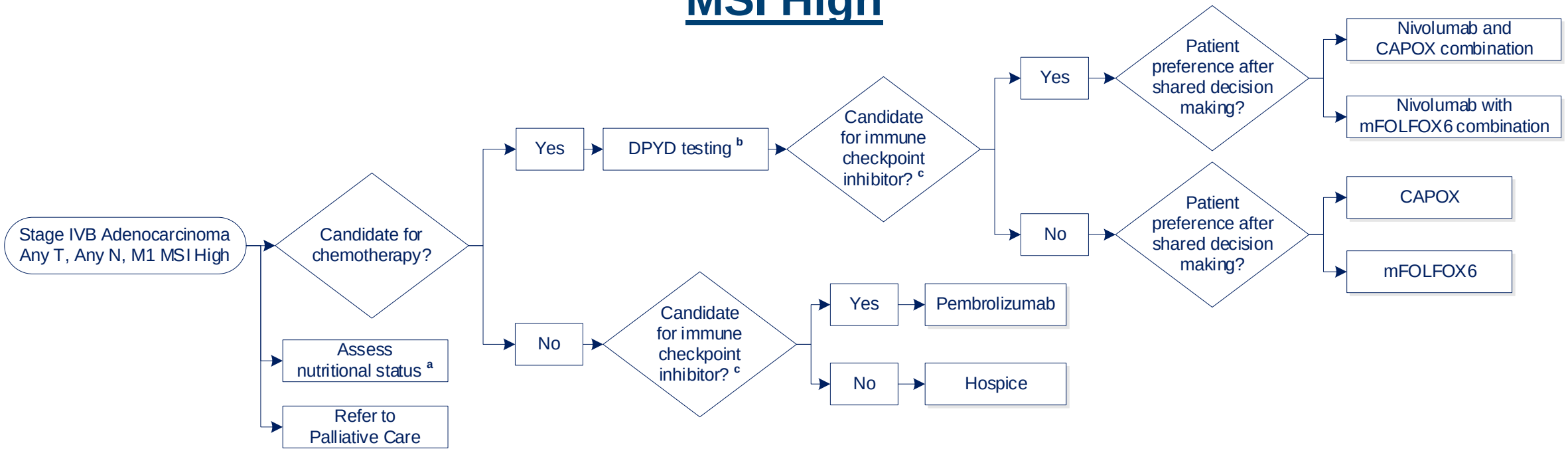


Clinical trial(s) always considered on pathway. For assistance finding a clinical trial, email CancerClinicalTrialsNavigation@va.gov.

[a] **Candidate for Ramucirumab** received fluoropyrimidine and platinum agent in the first-line setting; ECOG PS 0-2; ANC ≥ 1500/mm^3; due to anti-VEGF effects patients with the following should not receive ramucirumab: non-healing wound/fracture, major surgery in prior 4 weeks, bleeding disorder or coagulopathy, recent history of GI perforation, unstable cardiac condition (uncontrolled HTN, arterial thromboembolism, symptomatic CHF [NYHA II-IV] or arrhythmia), or active cocaine use

[b] **Ramucirumab** for patients that qualify for ramucirumab with paclitaxel, this combination is preferred based on the RAINBOW trial; ramucirumab alone is FDA approved based on REGARD trial, but should only be used in patients who do not qualify for the combination regimen; the majority of patients who have relapsed esophageal cancer are symptomatic, however, ramucirumab alone does not demonstrate partial or complete responses and only shows an increase to stable disease compared to placebo

Esophageal Cancer – Stage IVB Adenocarcinoma Any T, Any N, M1 MSI High



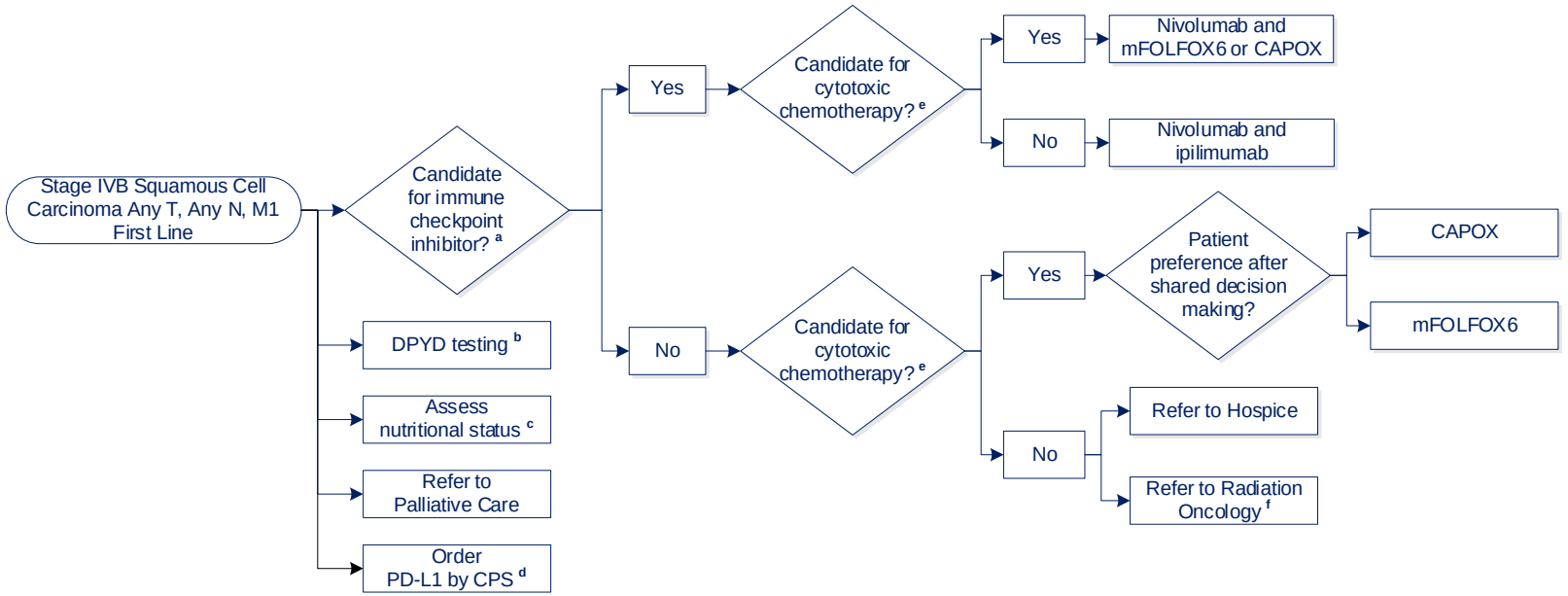
Clinical trial(s) always considered on pathway. For assistance finding a clinical trial, email CancerClinicalTrialsNavigation@va.gov.

[a] **Assess Nutritional Status** consider palliative stent or other nutritional support modalities when clinically appropriate

[b] **Perform DPYD Testing If Not Already Performed** if DPYD PGx results return predicted phenotypes of either intermediate or poor metabolizer, please consult your local PGx pharmacist or submit an IFC Pharmacogenomics e-consult for assistance with therapeutic recommendation; a clinician may proceed without DPYD results if withholding chemotherapy for 2-3 weeks may gravely endanger patient's life; for example, if the disease burden is very high and it involves a large portion of vital organs such as liver, etc.

[c] **Qualify for Immune Checkpoint Inhibitor** patient without active autoimmune disease, primary immune deficiency, concurrent immunosuppression (including prednisone equivalent >10mg/day) or prior allogeneic HSCT/solid organ transplant

Esophageal Cancer – Stage IVB Squamous Cell Carcinoma Any T, Any N, M1 First Line



Clinical trial(s) always considered on pathway. For assistance finding a clinical trial, email CancerClinicalTrialsNavigation@va.gov.

[a] **Qualify for Immune Checkpoint Inhibitor** patient without active autoimmune disease, primary immune deficiency, concurrent immunosuppression (including prednisone equivalent >10mg/day) or prior allogeneic HSCT/solid organ transplant

[b] **Perform DPYD Testing If Not Already Performed** if DPYD PGx results return predicted phenotypes of either intermediate or poor metabolizer, please consult your local PGx pharmacist or submit an IFC Pharmacogenomics e-consult for assistance with therapeutic recommendation; a clinician may proceed without DPYD results if withholding chemotherapy for 2-3 weeks may gravely endanger patient's life; for example, if the disease burden is very high and it involves a large portion of vital organs such as liver, etc.

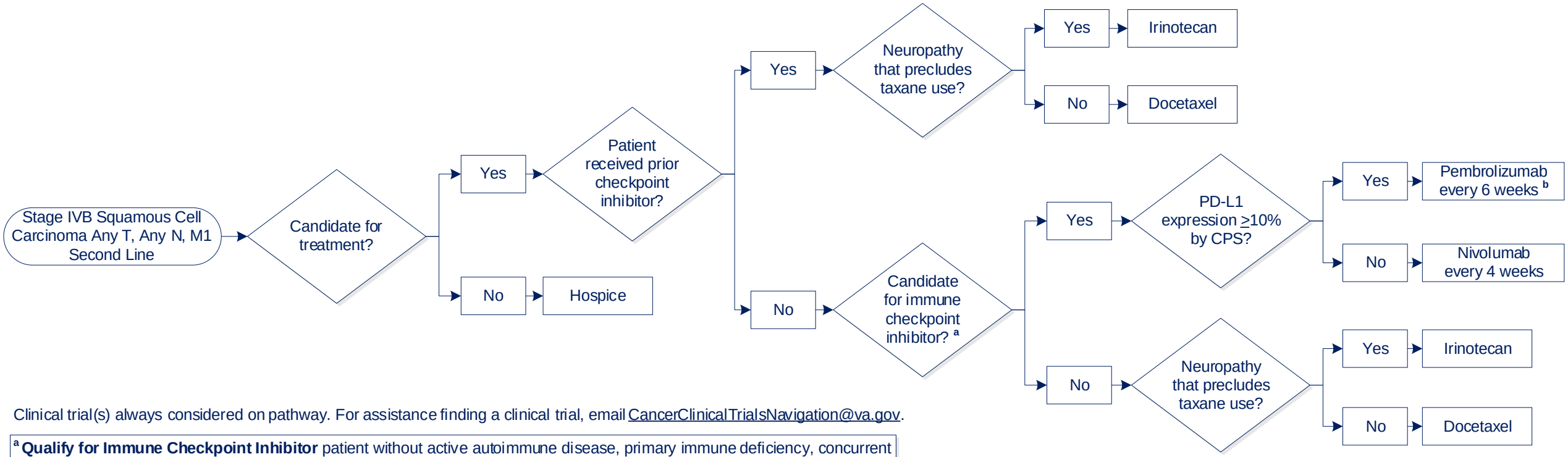
[c] **Assess Nutritional Status** consider palliative stent or other nutritional support modalities when clinically appropriate

[d] **PD-L1 by CPS** helpful biomarker regarding the potential benefit of the addition of nivolumab to chemotherapy; the number of patients with a PD-L1 score <1 was small on CheckMate 648, limiting the ability to make definite conclusions about the clinical value of adding nivolumab to FOLFOX in these patients, however, current FDA approval is not limited to PD-L1 positive patients

[e] **Candidate for Cytotoxic Chemotherapy** consider if patient can tolerate a platinum- and fluoropyrimidine-based doublet

[f] **Radiation Oncology** consider palliative or metastasis-directed radiation when clinically appropriate

Esophageal Cancer – Stage IVB Squamous Cell Carcinoma Any T, Any N, M1 Second Line

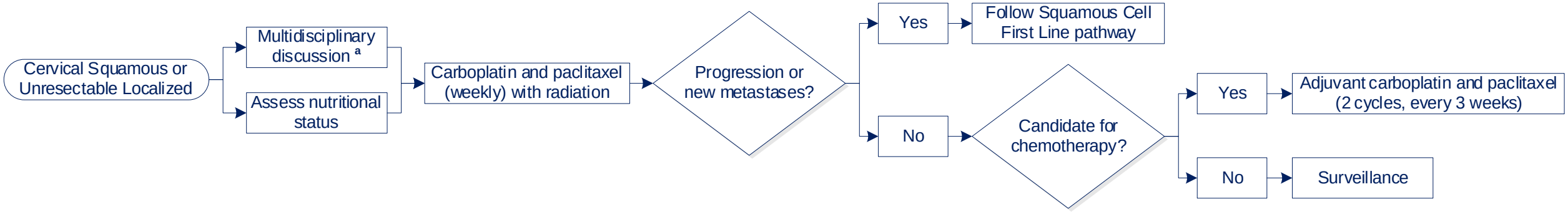


Clinical trial(s) always considered on pathway. For assistance finding a clinical trial, email CancerClinicalTrialsNavigation@va.gov.

[a] **Qualify for Immune Checkpoint Inhibitor** patient without active autoimmune disease, primary immune deficiency, concurrent immunosuppression (including prednisone equivalent >10mg/day) or prior allogeneic HSCT/solid organ transplant

[b] **Pembrolizumab** chosen due to FDA approval and patient convenience

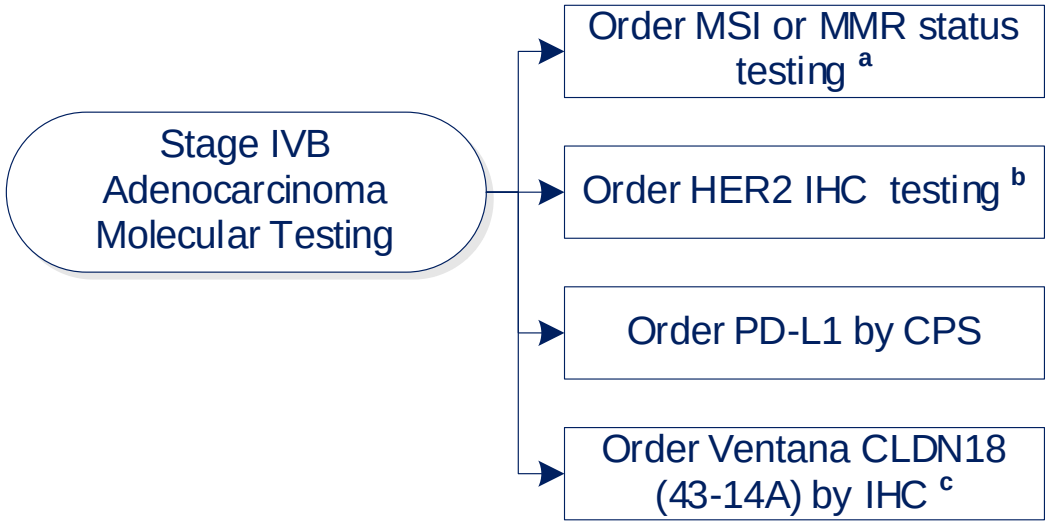
Esophageal Cancer – Cervical Squamous or Unresectable Localized



Clinical trial(s) always considered on pathway. For assistance finding a clinical trial, email CancerClinicalTrialsNavigation@va.gov.

[a] **Multidisciplinary Discussion** includes surgery, radiation oncology, and medical oncology; for mid-esophageal tumors, consider referral to Pulmonary to assess tracheal invasion

Esophageal Cancer – Stage IVB Adenocarcinoma Molecular Testing



Clinical trial(s) always considered on pathway. For assistance finding a clinical trial, email CancerClinicalTrialsNavigation@va.gov.

[a] **MSI or MMR** PCR or IHC; consider using both methods based on location or personal/family history

[b] **HER2 IHC** if results 2+, HER2 IHC with reflex to FISH required (in-situ hybridization)

[c] **Ventana CLDN18 (43-14A)** positivity is defined as ≥ 75% of tumor cells demonstrating moderate to strong membranous CLDN18 IHC

Esophageal Cancer – Molecular Testing Table

Eligibility	Test Category	Test Type	Recommended Vendors	NPOP Coverage	Specimen Type
Metastatic Esophageal Adenocarcinoma (Stage IVB)	IHC*	Mismatch repair (MMR) genes (MLH1, MSH2, MSH6, and PMS2).	Local VA or locally contracted vendor	No	Tumor Tissue
	PCR*	Microsatellite instability (MSI) status by PCR.	Regional Testing Center (GLA)	Yes	Tumor Tissue and Normal Tissue or Blood
	IHC	PD-L1 IHC (clone 22C3 with CPS score)	Local VA or locally contracted vendor	No	Tumor Tissue
	IHC	HER2 IHC with reflex to FISH if 2+ on IHC	Local VA or locally contracted vendor	No	Tumor Tissue
	FISH	HER2 FISH if 2+ on IHC	Local VA or locally contracted vendor	No	Tumor Tissue
Metastatic Esophageal Squamous Cell Carcinoma (Stage IVB)	IHC	PD-L1 IHC (clone 22C3 with CPS score)	Local VA or locally contracted vendor	No	Tumor Tissue
Deficient MMR or MSI-H Tumor	Germline NGS	If full germline testing not performed, perform Germline** testing if: 1) MSH2 or MSH6 loss by IHC or 2) MLH1 or PMS2 loss by IHC and MLH1 unmethylated or 3) MSI-H without IHC testing and MLH1 unmethylated	Fulgent Prevention Genetics	Yes Yes	Saliva, Blood
* Consider performing both IHC and PCR for MMR status if distal location or if there is a personal/family history suspicious for Lynch syndrome					
** Germline testing should include at minimum: EPCAM (deletion), MLH1, MSH2, MSH6, and PMS2; Alternatively, the VA Common Hereditary POC panel can be performed; For genetic online ordering, refer to CCGS page for further details					