Oncology Clinical Pathways

Malignant Melanoma

March 2024 – V1.2024

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Malignant Melanoma – 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.

Gulf War and Post 9/11 Veterans

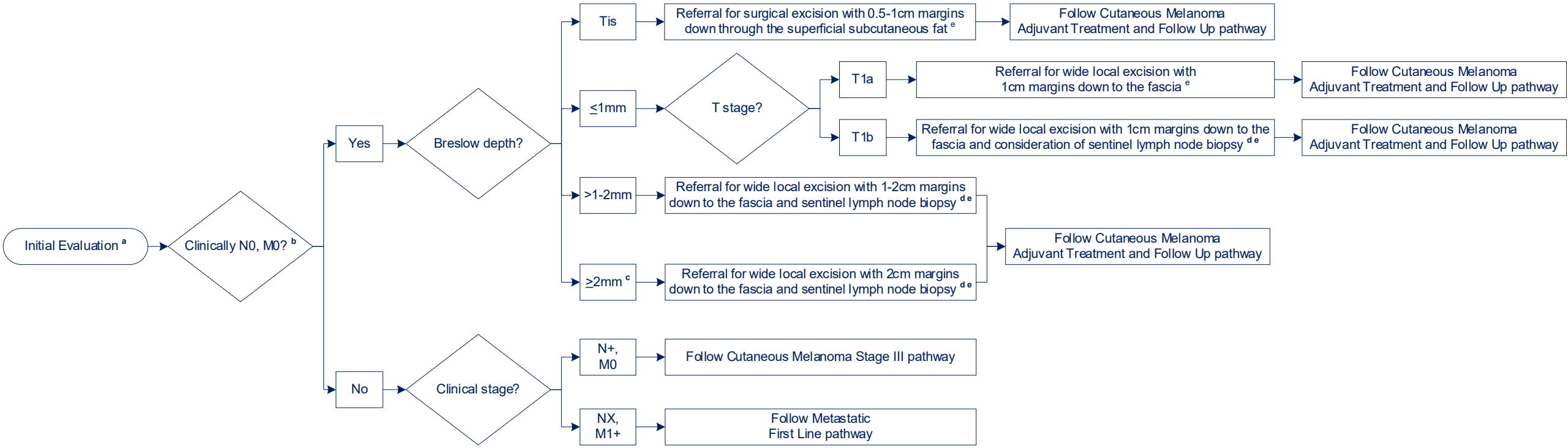
If the patient served on or after Sept. 11, 2001, in Afghanistan, Djibouti, Egypt, Jordan, Lebanon, Syria, Uzbekistan, or Yemen or if you served in the *Southwest Asia theater of operations, or Somalia, on or after Aug. 2, 1990, specific conditions include:

- Melanoma

* 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)

Malignant Melanoma – Initial Evaluation



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

[a] **Initial Evaluation** diagnosis of cutaneous melanoma should be obtained by a method to adequately assess depth

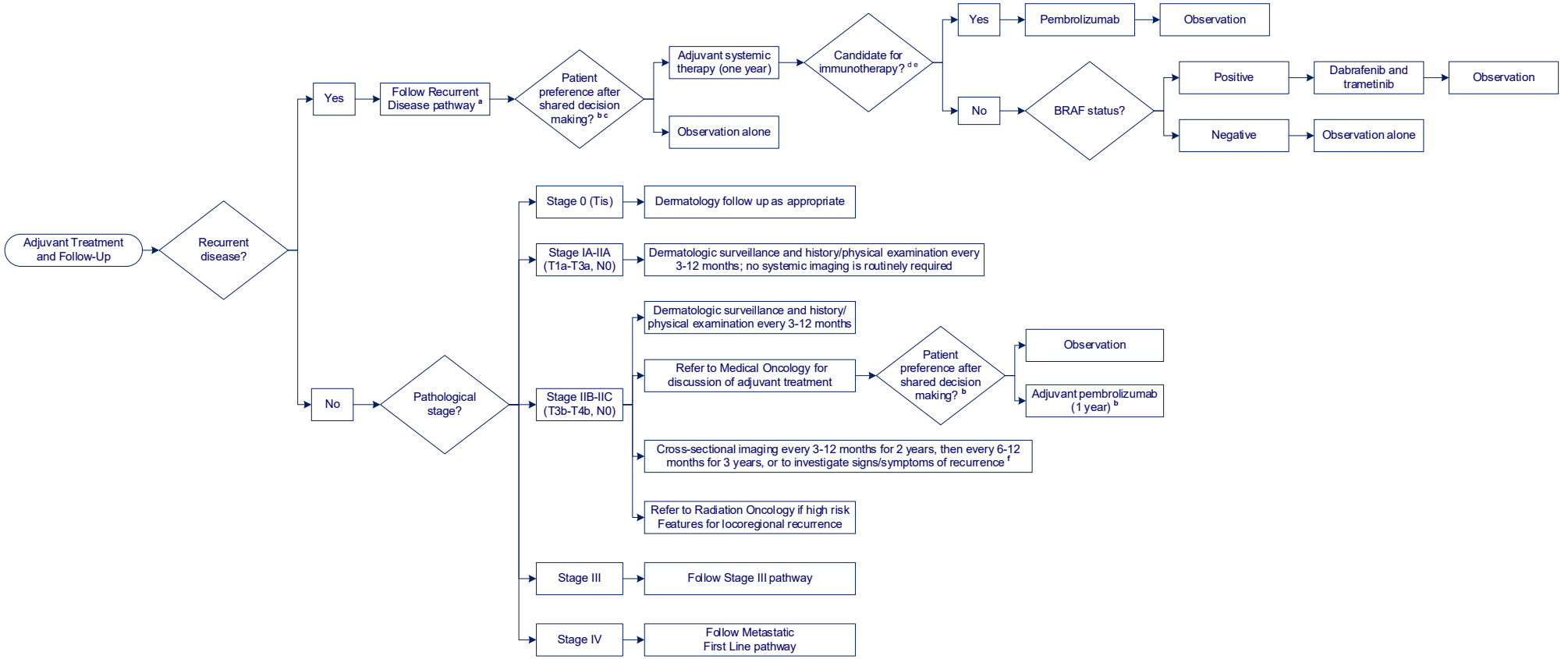
[b] **Microsatellitosis or Satellitosis** is N1c disease

[c] **≥2mm** systemic imaging can be considered for very high risk features prior to excision

[d] **Sentinel Lymph Node Biopsy** age and fragility of the patient may be considered when deciding to pursue sentinel lymph node biopsy

[e] **Alternatives** consider Mohs depending on location; primary radiation may be considered if not a surgical candidate

Malignant Melanoma – Adjuvant Treatment and Follow-Up



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[a] **Recurrent Disease Pathway** use of neoadjuvant immunotherapy may be considered based on clinical scenario

[b] **Stage II Adjuvant Treatment** with pembrolizumab in Stage II melanoma has not yet been associated with improvements in overall survival and have been approved based on improvements in recurrence free survival alone; discussions of this should be highlighted with patients, and observation is a reasonable approach

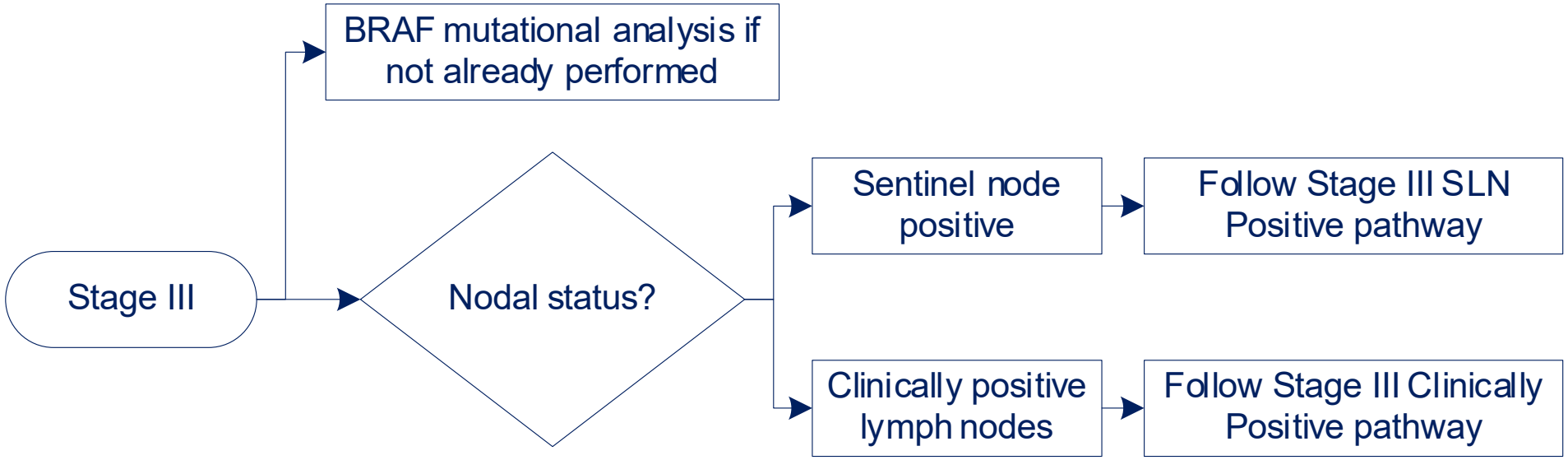
[c] **Stage III Adjuvant Treatment** with pembrolizumab in Stage III melanoma has been associated with improvements in relapse free survival compared to placebo and compared to ipilimumab (known to improve overall survival in adjuvant treatment); for patients with small burden Stage IIIA disease (non-ulcerated primary and <1mm in a LN), observation is reasonable

[d] **Candidate for Immunotherapy** patient without active autoimmune disease, primary immune deficiency, concurrent immunosuppression (including prednisone equivalent >10mg/day) or prior allogeneic hematopoietic stem cell transplantation or solid organ transplant

[e] **Second Regimen** of systemic adjuvant treatment following a recurrence preceded by initial systemic adjuvant therapy is to be considered on a case by case basis

[f] **Cross-Sectional Imaging** includes PET/CT or CT imaging of the chest, abdomen, and pelvis; neck or brain imaging may be considered as necessary

Malignant Melanoma – Stage III



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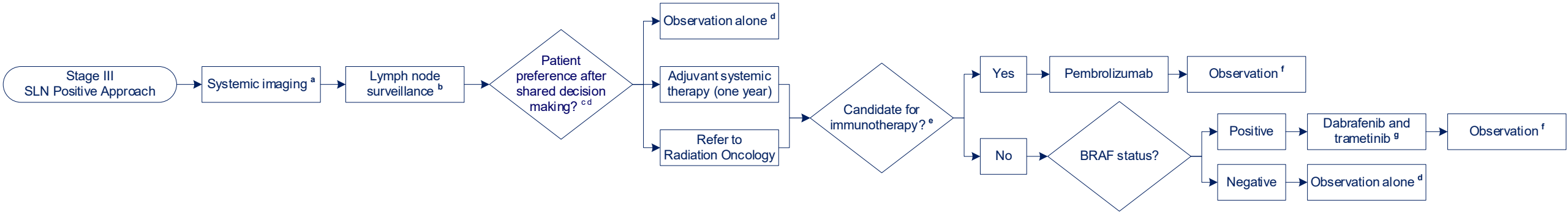
Malignant Melanoma – Stage III SLN Positive Approach



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[a] **Systemic Imaging** to include whole body PET/CT, or CT imaging and brain MRI

[b] **Lymph Node Surveillance** to include ultrasound every 4 months for the first 2 years (involved LN basin ultrasound if possible at local center), otherwise cross-sectional imaging appropriate; observe to 5 years with imaging as directed by symptoms or at least every 6 months for 3 years, then at least yearly to 5 years, observation should be a component of any treatment strategy; LN dissection may be considered in high risk clinical scenarios

[c] **Stage III Adjuvant Treatment** with pembrolizumab in Stage III melanoma has been associated with improvements in relapse free survival compared to placebo and compared to ipilimumab (known to improve overall survival in adjuvant treatment); for patients with small burden Stage IIIA disease (non-ulcerated primary and <1mm in a LN), observation is reasonable

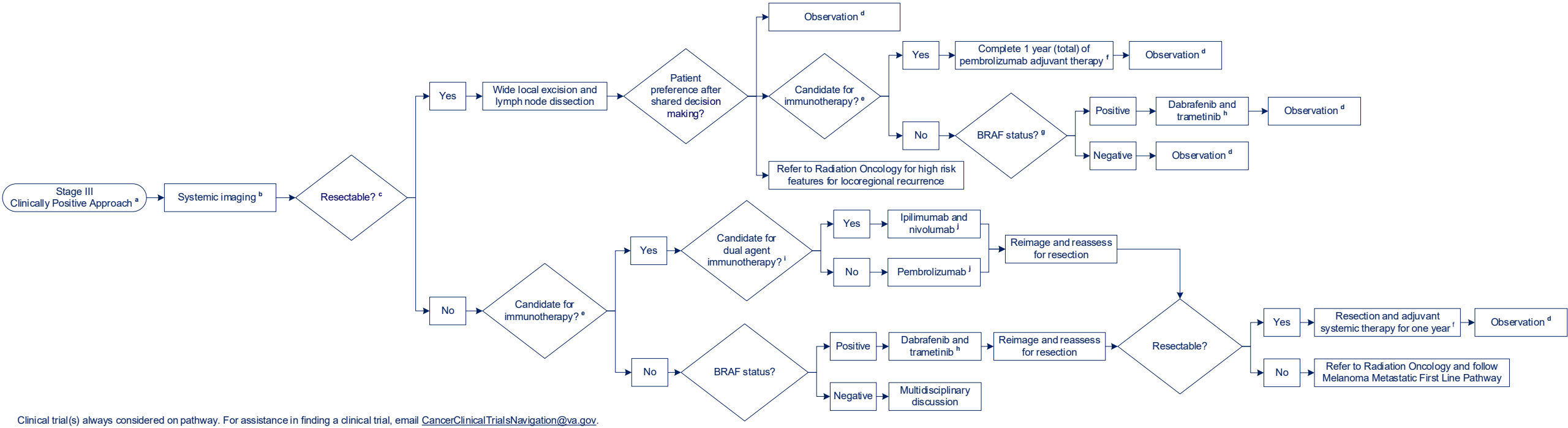
[d] **Observation Alone** if Stage IIIA if small volume sentinel lymph node disease (< 1mm) observation is reasonable and often preferred

[e] **Candidate for Immunotherapy** patient without active autoimmune disease, primary immune deficiency, concurrent immunosuppression (including prednisone equivalent >10mg/day) or prior allogeneic hematopoietic stem cell transplantation or solid organ transplant

[f] **Observation if Stage IIIA** includes: PET/CT or CT imaging (every 6-12 months for up to five years); **Stage IIIB** includes: PET/CT or CT imaging and CNS imaging as necessary (every 6-12 months for up to five years); **Stage IIIC/IIID**: PET/CT or CT imaging and CNS imaging as necessary (every 3-12 months for up to five years)

[g] **Dabrafenib and Trametinib** alternate BRAF inhibitors may be considered for patient intolerance or preference (encorafenib and binimetinib or vemurafenib and cobimetinib)

Malignant Melanoma – Stage III Clinically Positive Approach



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

[a] **Clinically Positive** defined as palpable lymph node or found on imaging and pathologically confirmed

[b] **Systemic Imaging** to include whole body PET/CT, or CT imaging and brain MRI

[c] **Resectable** neoadjuvant immunotherapy consisting of 3 doses of pre-operative pembrolizumab has been associated with significant improvements in event free survival for patients with clinical or radiographically evident and resectable stage III and IV melanoma in the randomized phase II SWOG S1801 study; this approach may be reasonable for some patients after discussion, but has not yet been associated with improved overall survival and is not FDA approved in this manner

[d] **Observation if Stage IIIA** includes PET/CT or CT imaging (every 6-12 months for up to five years); **Stage IIIB** includes PET/CT or CT imaging and CNS imaging as necessary (every 6-12 months for up to five years); **Stage IIIC/IID** includes PET/CT or CT imaging and CNS imaging as necessary (every 3-12 months for up to five years)

[e] **Candidate for Immunotherapy** patient without active autoimmune disease, primary immune deficiency, concurrent immunosuppression (including prednisone equivalent >10mg/day) or prior allogeneic hematopoietic stem cell transplantation/solid organ transplant

[f] **Adjuvant Therapy** choice should consider prior lines, toxicities, and duration since prior treatment; options include pembrolizumab, nivolumab, dabrafenib/trametinib (if BRAF V600E/K +), ipilimumab, discussion of locoregional therapy, and observation

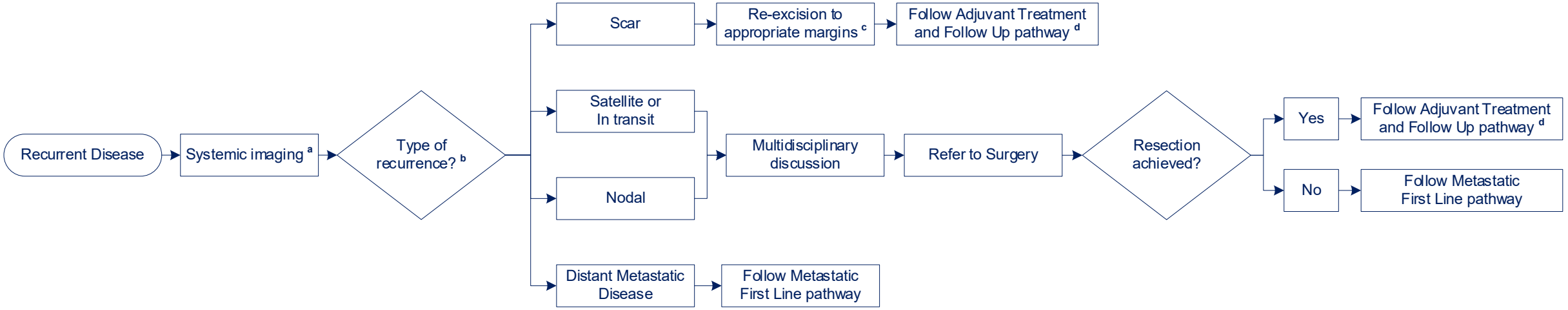
[g] **Targeted Therapy after Neoadjuvant Immunotherapy** the use of adjuvant targeted therapy following neoadjuvant immunotherapy is not standard but can be considered in appropriate situations for those no longer eligible for completion of adjuvant immunotherapy or poor responders

[h] **Dabrafenib and Trametinib** alternate BRAF inhibitors may be considered for patient intolerance or preference (encorafenib and binimetinib or vemurafenib and cobimetinib)

[i] **Candidate for Dual Agent Immunotherapy** patients with ECOG performance status 0-1, good social support and ability to recognize toxicity, lack of active autoimmune disease, primary immune deficiency, concurrent immunosuppression (including prednisone equivalent >10mg/day) or prior allogeneic hematopoietic stem cell transplantation or solid organ transplant

[j] **Stage III Adjuvant Therapy** adjuvant therapy with pembrolizumab in Stage III melanoma has been associated with improvements in relapse free survival compared to placebo and compared to ipilimumab (known to improve overall survival in adjuvant treatment); for patients with small burden Stage IIIA disease (non-ulcerated primary and <1mm in a LN), observation is reasonable

Malignant Melanoma – Recurrent Disease



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

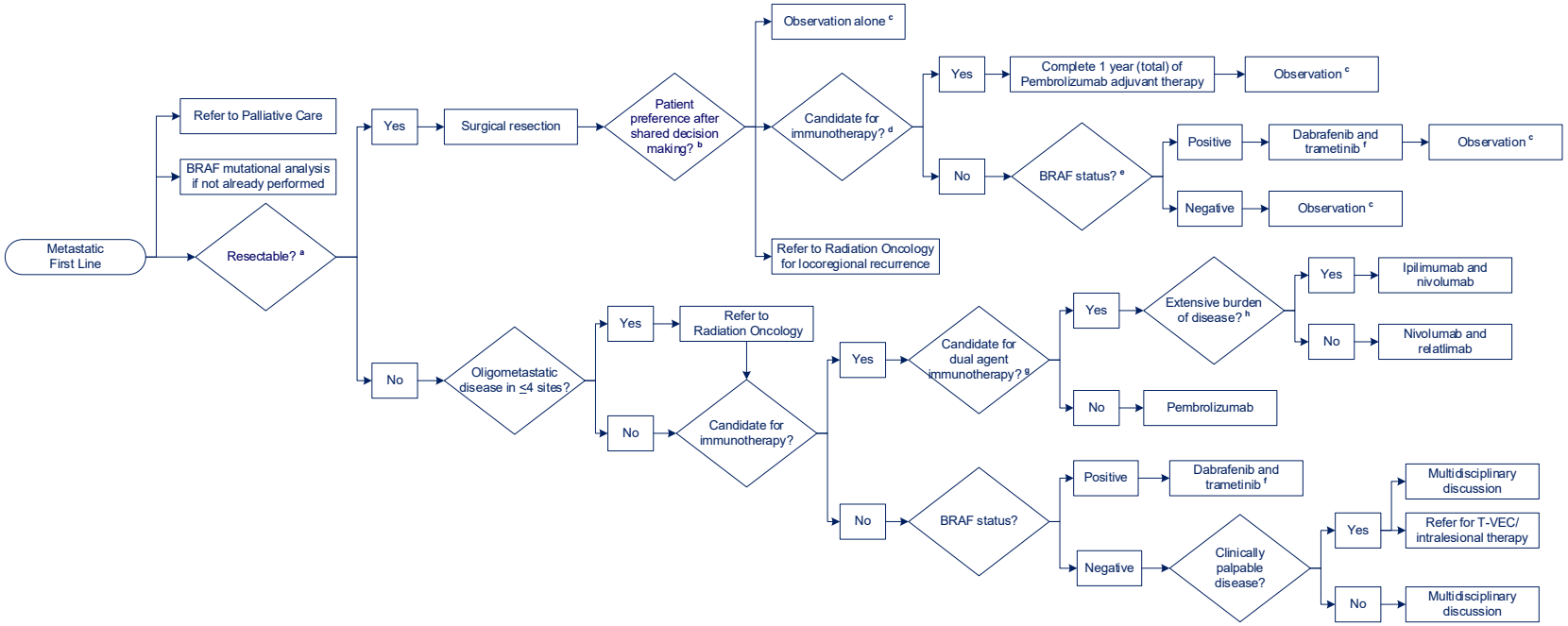
[a] **Systemic Imaging** to include PET/CT, or CT imaging and brain MRI ongoing observation (5 years); scar recurrences may not require full systemic imaging,

[b] **Recurrent Disease** use of neoadjuvant therapy may be considered based on clinical scenario

[c] **Re-Excise to Appropriate Margins** consider sentinel lymph node biopsy

[d] **Adjuvant Therapy** choice should consider prior lines and timing of potential adjuvant treatment include pembrolizumab, nivolumab, dabrafenib/trametinib if BRAF V600E/K + observation; discussion of locoregional therapy ipilimumab if prior PD-1

Malignant Melanoma – Metastatic First Line



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

[a] **Neoadjuvant pembrolizumab** use of neoadjuvant immunotherapy should consider the clinical situation and progression to immediate resection is appropriate in some patients; neoadjuvant immunotherapy consisting of 3 doses of pre-operative pembrolizumab has been associated with significant improvements in event free survival for patients with clinical or radiographically evident and resectable stage III and IV melanoma in the randomized phase II SWOG S1801 study; this approach may be reasonable for some patients after discussion, but has not yet been associated with improved overall survival and is not FDA approved in this manner

[b] **Stage IV, Resected Adjuvant Therapy** has been associated with improvement in overall survival in a small Phase II study with ipilimumab and nivolumab, but has not shown clear overall survival improvements with single agent PD-1 treatment; single agent PD-1 treatment has shown relapse free survival improvements in resected Stage IV disease; discussions with patients about benefits and risks are suggested

[c] **Observation** if Stage IIIA includes PET/CT or CT imaging (every 6-12 months for up to five years); **Stage IIIB** includes PET/CT or CT imaging and CNS imaging as necessary (every 6-12 months for up to five years); **Stage IIIC/IID/IV** PET/CT or CT imaging and CNS imaging as necessary (every 3-12 months for up to five years)

[d] **Candidate for Immunotherapy** patient without active autoimmune disease, primary immune deficiency, concurrent immunosuppression (including prednisone equivalent >10mg/day) or prior allogeneic hematopoietic stem cell transplantation or solid organ transplant

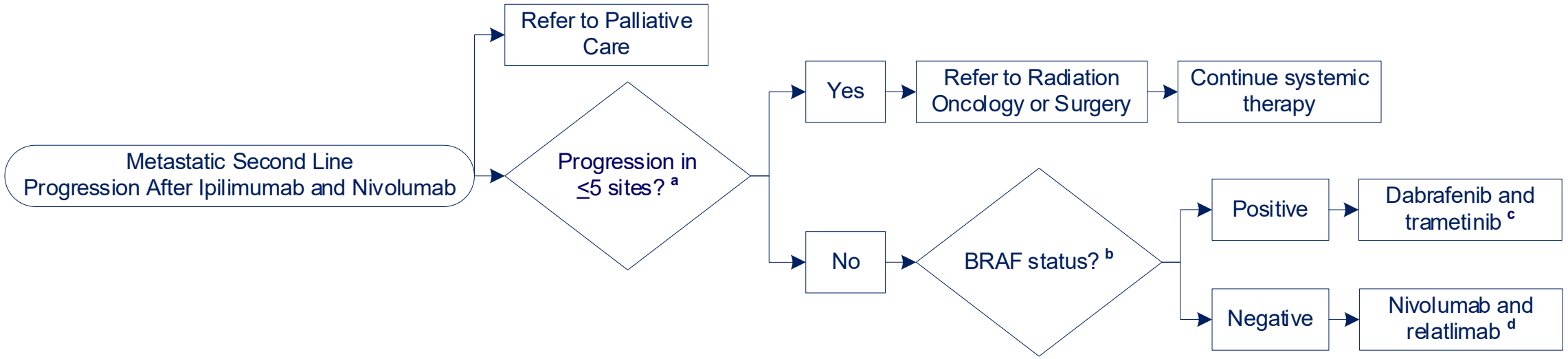
[e] **Targeted Therapy after Neoadjuvant Immunotherapy** the use of adjuvant targeted therapy following neoadjuvant immunotherapy is not standard but can be considered in appropriate situations for those no longer eligible for completion of adjuvant immunotherapy or poor responders

[f] **Dabrafenib and Trametinib** alternate BRAF inhibitors may be considered for patient intolerance or preference (encorafenib and binimetinib or vemurafenib and cobimetinib)

[g] **Candidate for Dual Agent Immunotherapy** patients with ECOG performance status 0-1, lack of active autoimmune disease, primary immune deficiency, concurrent immunosuppression (including prednisone equivalent >10mg/day) or prior allogeneic hematopoietic stem cell transplantation or solid organ transplant

[h] **Extensive Disease Burden** presence of brain metastases or clinically symptomatic sites of disease

Malignant Melanoma – Metastatic Second Line Progression After Ipilimumab and Nivolumab



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

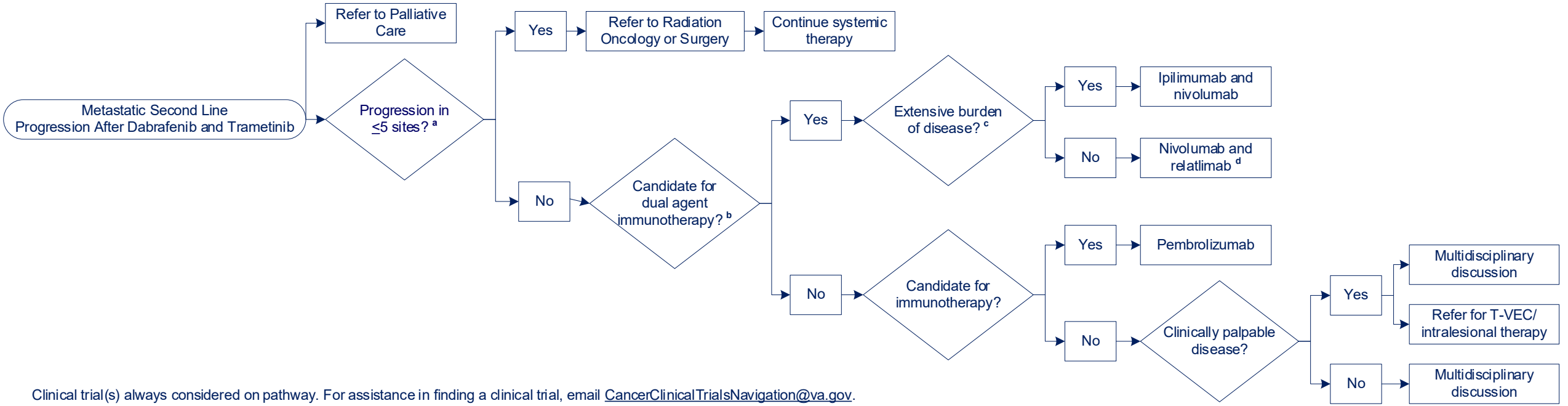
[a] **Progression** time, rate, and site of progression should be considered when deciding on change in systemic treatment or locoregional treatment

[b] **BRAF Status** decision between second line targeted therapy and escalation to dual agent immunotherapy (nivolumab and relatlimab or ipilimumab and nivolumab) should take into account disease burden, rate of progression, and tolerance of prior lines of therapy

[c] **Dabrafenib and Trametinib** alternate BRAF inhibitors may be considered for patient intolerance or preference (encorafenib and binimetinib or vemurafenib and cobimetinib)

[d] **Nivolumab and Relatlimab** although this combination has been approved in the first line setting, it is reasonable to use in the appropriate relapsed setting, published data support activity in the second-line

Malignant Melanoma – Metastatic Second Line Progression After Dabrafenib and Trametinib



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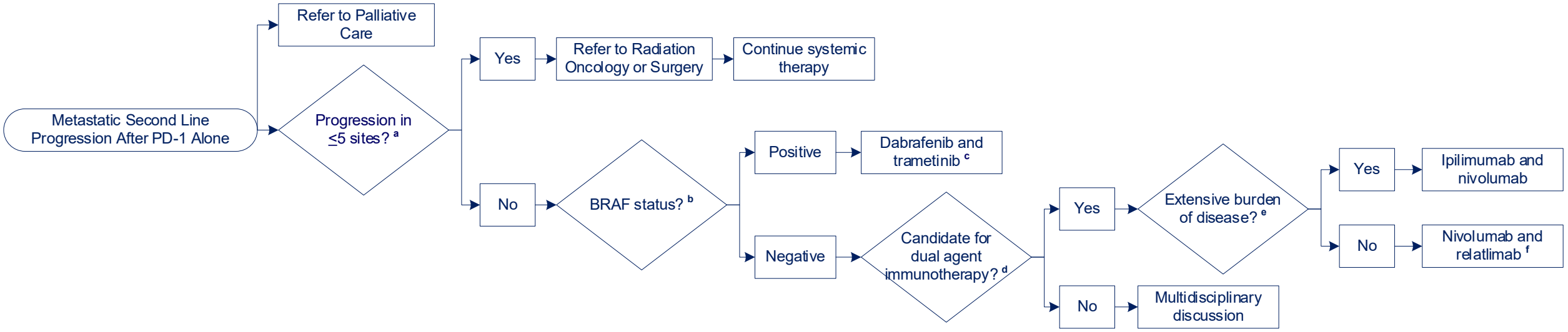
[a] **Progression** time, rate, and site of progression should be considered when deciding on change in systemic treatment or locoregional treatment

[b] **Candidate for Dual Agent Immunotherapy** patients with ECOG performance status 0-1, lack of active autoimmune disease, primary immune deficiency, concurrent immunosuppression (including prednisone equivalent >10mg/day) or prior allogeneic hematopoietic stem cell transplantation or solid organ transplant

[c] **Extensive Disease Burden** presence of brain metastases or clinically symptomatic sites of disease

[d] **Nivolumab and Relatlimab** although this combination has been approved in the first line setting, it is reasonable to use in the appropriate relapsed setting

Malignant Melanoma – Metastatic Second Line Progression After PD-1 Alone



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[a] **Progression** time, rate, and site of progression should be considered when deciding on change in systemic treatment or locoregional treatment

[b] **BRAF Status** decision between second line targeted therapy and escalation to dual agent immunotherapy (nivolumab and relatlimab or ipilimumab and nivolumab) should take into account disease burden, rate of progression, and tolerance of prior lines of therapy

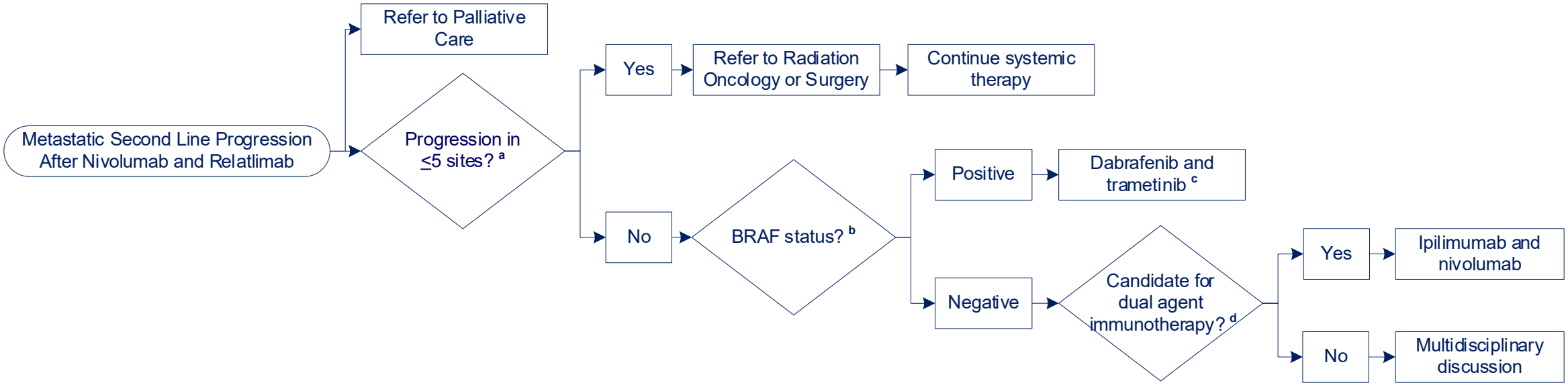
[c] **Dabrafenib and Trametinib** alternate BRAF inhibitors may be considered for patient intolerance or preference (encorafenib and binimetinib or emurafenib and cobimetinib)

[d] **Candidate for Dual Agent Immunotherapy** patients with ECOG performance status 0-1, lack of active autoimmune disease, primary immune deficiency, concurrent immunosuppression (including prednisone equivalent >10mg/day) or prior allogeneic hematopoietic stem cell transplantation or solid organ transplant

[e] **Extensive Disease Burden** presence of brain metastases or clinically symptomatic sites of disease

[f] **Nivolumab and Relatlimab** although this combination has been approved in the first line setting, it is reasonable to use in the appropriate relapsed setting

Malignant Melanoma – Metastatic Second Line Progression After Nivolumab and Relatimab



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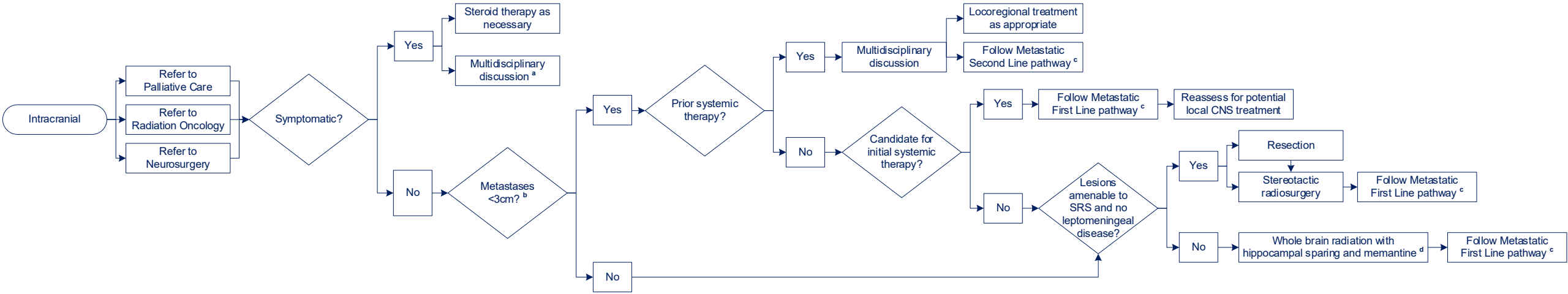
[a] **Progression** time, rate, and site of progression should be considered when deciding on change in systemic treatment or locoregional treatment

[b] **BRAF Status** decision between second line targeted therapy or immunotherapy (ipilimumab and nivolumab) should take into account disease burden, rate of progression, and tolerance of prior lines of therapy

[c] **Dabrafenib and Trametinib** alternate BRAF inhibitors may be considered for patient intolerance or preference (encorafenib and binimetinib or vemurafenib and cobimetinib)

[d] **Candidate for Dual Agent Immunotherapy** patients with ECOG performance status 0-1, lack of active autoimmune disease, primary immune deficiency, concurrent immunosuppression (including prednisone equivalent >10mg/day) or prior allogeneic hematopoietic stem cell transplantation or solid organ transplant

Malignant Melanoma – Intracranial



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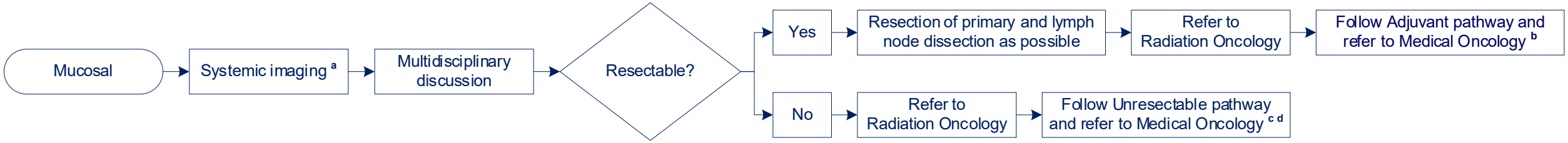
[a] **Multidisciplinary Discussion** to include Medical Oncology, Radiation Oncology, Palliative Care, and Neurosurgery

[b] **Asymptomatic Intracranial Metastases** < 3 cm in size can prompt consideration of upfront systemic therapy with monitoring by Neurosurgery and Radiation Oncology for potential of local therapy

[c] **Presence of Brain Metastases** should prompt strong consideration of ipilimumab and nivolumab as treatment option

[d] **Whole Brain Radiation Therapy** for low performance status patients (ECOG ≥3), consider whole brain radiation in consultation with Medical Oncology, Radiation Oncology, and Neurosurgery

Malignant Melanoma – Mucosal



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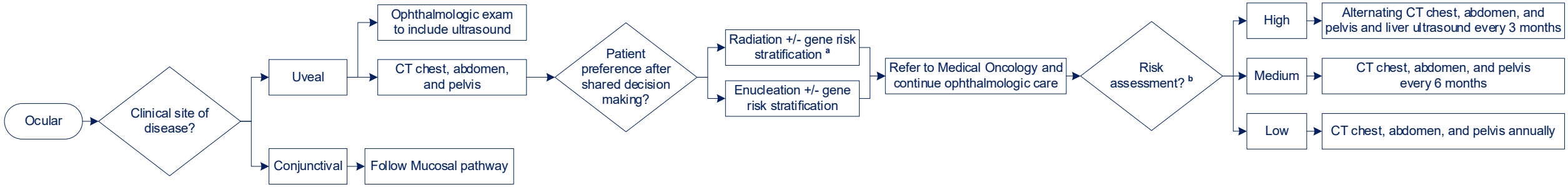
[a] **Systemic Imaging** to include whole body PET/CT, or CT imaging and brain MRI

[b] **Mucosal Melanoma Adjuvant Therapy** mucosal melanomas are not well represented on any large trials associated with FDA approvals; the decision to treat in an adjuvant manner off of a clinical trial should be considered carefully in depth with the patient

[c] **Assessment for KIT Mutations** complete assessment for KIT mutations and consider potential KIT targeting therapy for mucosal melanomas

[d] **Treatment of Metastatic Mucosal Melanoma** has limited clinical evidence but use of cutaneous melanoma pathways is appropriate; evidence suggest ipilimumab and nivolumab may have improved activity in mucosal melanomas

Malignant Melanoma – Ocular



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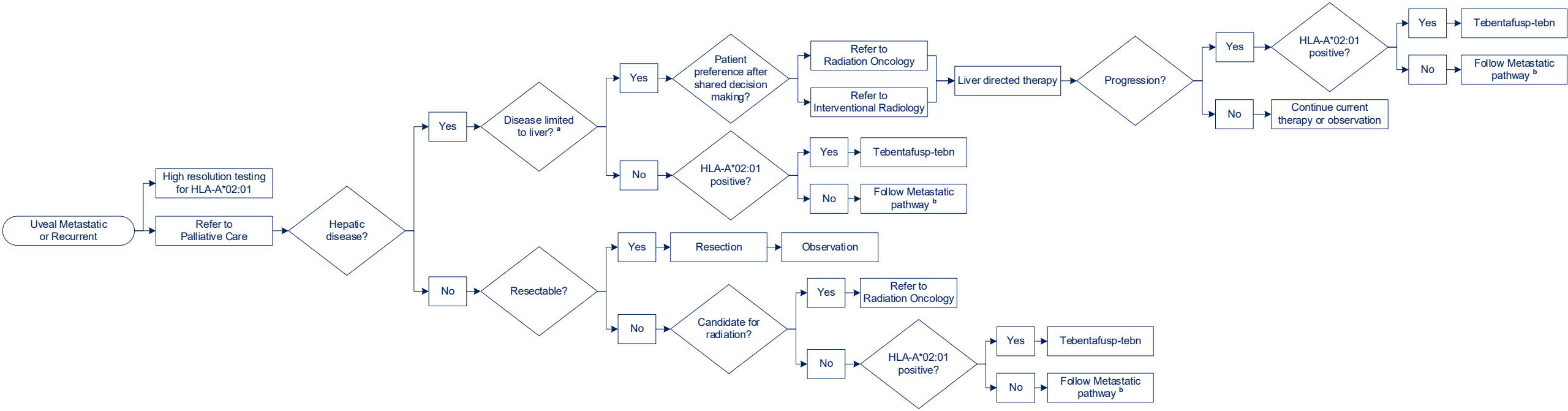
[a] **Radiation** if patient undergoes plaque brachytherapy, obtain CT of orbit with contrast prior to therapy

[b] **Risk Assessment** includes **Low Risk**: class IA, disomy 3, gain of chromosome 6p, EIF1AX mutation, T1 (AJCC); **Medium Risk**: Class IB, SF33B1 mutation, T2 and T3 (AJCC); **High Risk**: class II, monosomy 3, gain of chromosome 8q, BAP1 mutation, T4 (AJCC)

Malignant Melanoma – Uveal Metastatic or Recurrent



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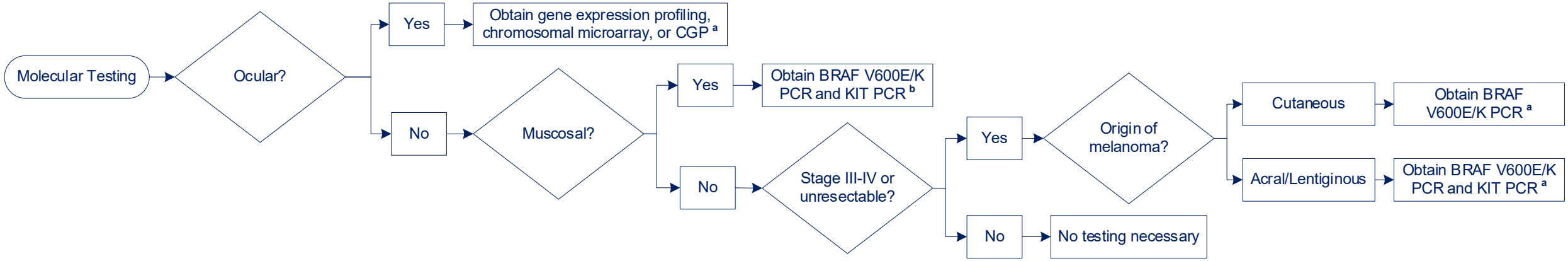
[a] **Disease Limited to Liver** in select situations, hepatic resection can be considered

[b] **Metastatic Uveal Melanoma** limited data suggest ipilimumab and nivolumab have improved activity in uveal melanoma

Malignant Melanoma – Molecular Testing



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[a] **Risk Stratification** may be obtained through either gene expression profiling analysis, chromosomal microarray, or CGP

[b] **BRAF Immunohistochemistry** for BRAF V600E may be obtained faster if clinically necessary

CGP Comprehensive Genetic Profiling

Malignant Melanoma – Molecular Testing Table

Eligibility	Test Category	Test Type	Recommended Vendors	NPOP Coverage	Specimen Type
Cutaneous Melanoma	Molecular Testing	BRAF V600E/K PCR	Local VA or locally contracted vendor	No	Tumor Tissue, Blood
	IHC	BRAF V600E mutation	Local VA or locally contracted vendor	No	Tumor Tissue
Mucosal Melanoma	Molecular Testing	BRAF V600E/K PCR KIT PCR	Local VA or locally contracted vendor	No	Tumor Tissue, Blood
	IHC	BRAF V600E mutation	Local VA or locally contracted vendor	No	Tumor Tissue
Ocular (Uveal) Melanoma	Gene Expression Profiling*	Gene expression profiling for risk stratification	Local VA or locally contracted vendor	No	Blood
	Chromosomal Micro Array*	Chromosomal micro array for risk stratification	Local VA or locally contracted vendor	No	Blood, Saliva
	Somatic NGS*	Comprehensive genomic profiling (CGP) for risk stratification including GNAQ, GNA11, BAP1, PLCB4, CYSLTR2, SF3B1, EIF1AX	Tempus Foundation Medicine	Yes Yes	Tumor Tissue, Blood
	Genotyping	High resolution testing for HLA-A*02:01 for recurrent metastatic uveal melanoma only	Local VA or locally contracted vendor	No	Blood, Saliva
Acral/Lentiginous Melanoma	Molecular Testing	BRAF V600E/K PCR KIT PCR	Local VA or locally contracted vendor	No	Tumor Tissue, Blood
	IHC	BRAF V600E mutation	Local VA or locally contracted vendor	No	Tumor Tissue
* Risk stratification for Ocular melanoma could be done either by gene expression profiling, chromosomal micro array or CGP					