When Two Broad Tumor Class Screening Markers are at Odds

(more generally, when markers for both of the entities in your differential are expressed):

- You have to solve the differential diagnosis
- The stronger marker often wins

Pattern	Principal Diagnostic Considerations	Initial Screening Panel
Epithelioid	Carcinoma, melanoma, large cell lymphoma	Broad-spectrum keratin, CD45, SOX10
Round cell	Round cell sarcoma, lymphoma, small cell carcinoma	CD99, NKX2.2, desmin, myogenin, CD45, TdT, INSM1, broad-spectrum keratin, SOX10
Spindle cell	Sarcomatoid carcinoma, sarcoma, spindle cell/desmoplastic melanoma	Broad-spectrum keratin, p40, SMSA, desmin, SOX1
Anaplastic	Anything (usually not lymphoma)	Broad-spectrum keratin, CD45, SOX10

S-100 Expression in Adenocarcinoma

	Primary Tumors	Metastatic Tumors
Salivary gland	80% (n=15)	75% (n=4)
Lung	7% (n=27)	12% (n=25)
Breast	60% (n=20)	62% (n=8)
Esophagus	0% (n=8)	0% (n=2)
Stomach	20% (n=10)	25% (n=8)
Gallbladder	0% (n=1)	0% (n=1)
Colorectum	25% (n=28)	23% (n=13)
Pancreas	0% (n=8)	0% (n=5)
Kidney	65% (n=23)	66% (n=3)
Endometrium	78% (n=36)	64% (n=14)
Ovary	84% (n=24)	87% (n=22)
Prostate	0% (n=27)	0% (n=8)
Unknown origin		22% (n=9)
Total	43% (n=228)	39% (n=122)

Keratin-Positivity in Melanoma

	Primary cutaneous melanoma (n=62)	Recurrent or metastatic melanoma (n=22)
Vimentin	100%	100%
S-100	95%	95%
NSE	87%	77%
HMB45	97%	64%
NKI-C3	97%	95%
Cytokeratin (KL1, CAM5.2, 35βH11)	0%	23%

EMA+ Only: Beware

EMA-Positive Hematolymphoid Neoplasms	LCA-Weak to Negative Hematolymphoid Neoplasms
	Lymphoblastic leukemia/lymphoma
	Classical Hodgkin lymphoma
Plasma cell neoplasm	**Plasma cell neoplasm**
Plasmablastic lymphoma	**Plasmablastic lymphoma**
Anaplastic large cell lymphoma	**Anaplastic large cell lymphoma**
ALK+ DLBCL	**ALK+ DLBCL**
Follicular dendritic cell sarcoma	**Follicular dendritic cell sarcoma**
T-cell/histiocyte rich DLBCL	
Primary effusion lymphoma	

Keratin-Positive Soft Tissue Tumors

- Chondroid lipoma
- Pleomorphic liposarcoma
- Desmoplastic fibroblastoma
- Solitary fibrous tumor
- Inflammatory myofibroblastic tumor
- Myxoinflammatory fibroblastic sarcoma
- **Leiomyosarcoma**
- Rhabdomyosarcoma
- Schwannoma (cross-reactivity with GFAP)
- Epithelioid hemangioma
- Pseudomyogenic hemangioendothelioma
- Epithelioid hemangioendothelioma
- **Angiosarcoma**
- Gastrointestinal stromal tumor
- Sclerosing perineurioma
- Dermal nerve sheath myxoma
- Epithelioid MPNST
- Ectopic hamartomatous thymoma
- Ossifying fibromyxoid tumor
- Myoepithelial tumors of soft tissue
- **Synovial sarcoma**
- **Epithelioid sarcoma**
- Desmoplastic small round cell tumor
- Extrarenal rhabdoid tumor
- Undifferentiated/unclassified sarcoma
- Chondroblastoma
- **Dedifferentiated chondrosarcoma**
- Conventional osteosarcoma
- Ewing sarcoma
- Chordoma
- Adamantinoma
- Osteofibrous dysplasia

Melanoma Markers in Variants

	Conventional	Spindle Cell	Desmoplastic
S-100	**95%**	**91%**	**96%**
SOX10	**97%**	**100%**	**92%**
Melan A	**85%**	44%	19%
HMB-45	**85%**	46%	9%
MiTF	**89%**	60%	9%
Tryrosinase	**93%**	46%	18%
MUM1	**92%**	67%	0%
BRAFV600E	50%	31%	5%

Weissinger SE, et al. *Mod Pathol*. 2014 Apr;27(4):524-34. PMID: 24051699

Initial Panel in a Small Round Blue Cell Tum

Marker	Expressed by	Also Expressed by
CD99	Ewing sarcoma	Lymphoblastic lymphoma; mesenchymal chondrosarcoma
NKX2.2	Ewing sarcoma	Olfactory neuroblastoma
Desmin	Rhabdomyosarcoma; Desmoplastic small round cell tumor	Triton tumor
Myogenin	Rhabdomyosarcoma (ARMS>>ERMS)	Atrophic skeletal muscle
CD45	Lymphoma	
TdT	Lymphoblastic lymphoma	
INSM1 (CgA/Syn)	Neuroendocrine carcinoma; neuroblastoma; ?DSRCT	Extraskeletal myxoid chondrosar
Pan-K	Carcinoma; Desmoplastic small round cell tumor	PD synovial sarcoma; occ. aberra expressed by sarcoma, melanom
SOX10	Melanoma, MPNST (<50%)	Tumors with myoepithelial

Stains I Hate

Stain I Hate	Undeserved Reputation	What to Use Instead	Comment
Vimentin	Sarcoma	MDM2/CDK4 in undiff. malignant neoplasm; otherwise, morphology-driven	Ubiquitously expressed by melanoma and often expressed by lymphoma and carcinoma; I DO use to support endometrial over endocervical AdCA
p63	Squamous cell CA	p40	Dangerously non-specific
CA125	Pan-Müllerian	PAX8	Broadly expressed by non-GYN CA
CA19-9	Pancreas CA	SMAD4; CDH17 in CK7+ only	Broadly expressed by non-pancreas CA
CK19	CholangioCA	BAP1 (iCC); SMAD4 (i and eCC)	Nearly ubiquitously expressed by non-HCC carcinomas
MOC-31	AdenoCA	There is no pan-AdCA marker	I DO use as a broad-spectrum epithelial marker
RCC	Renal cell CA	PAX8	Supplanted by much better marker
CEA	Colon CA	CDX2 homogeneous; SATB2	Broadly expressed by non-colon CA

SATB2: Will it Swiss Army? Yes

- Lower GI adenocarcinoma (specific)
- Undifferentiated GI carcinoma (sensitive)
- Osteoblastic differentiation
- Rectal/appendiceal NET marker
- Merkel cell carcinoma
- *BCOR*-rearranged sarcoma