Welcome!

- To join the call dial (866) 740-1260, passcode 3754894#.
- All participants are placed on mute for the duration of the webinar.
- If you have questions, type them in the chat box at the bottom left hand side of your screen. They will be answered at the end of the presentation.
- This conference is being recorded for future use.
- The recording will be made available on the ASPHO website afterwards.

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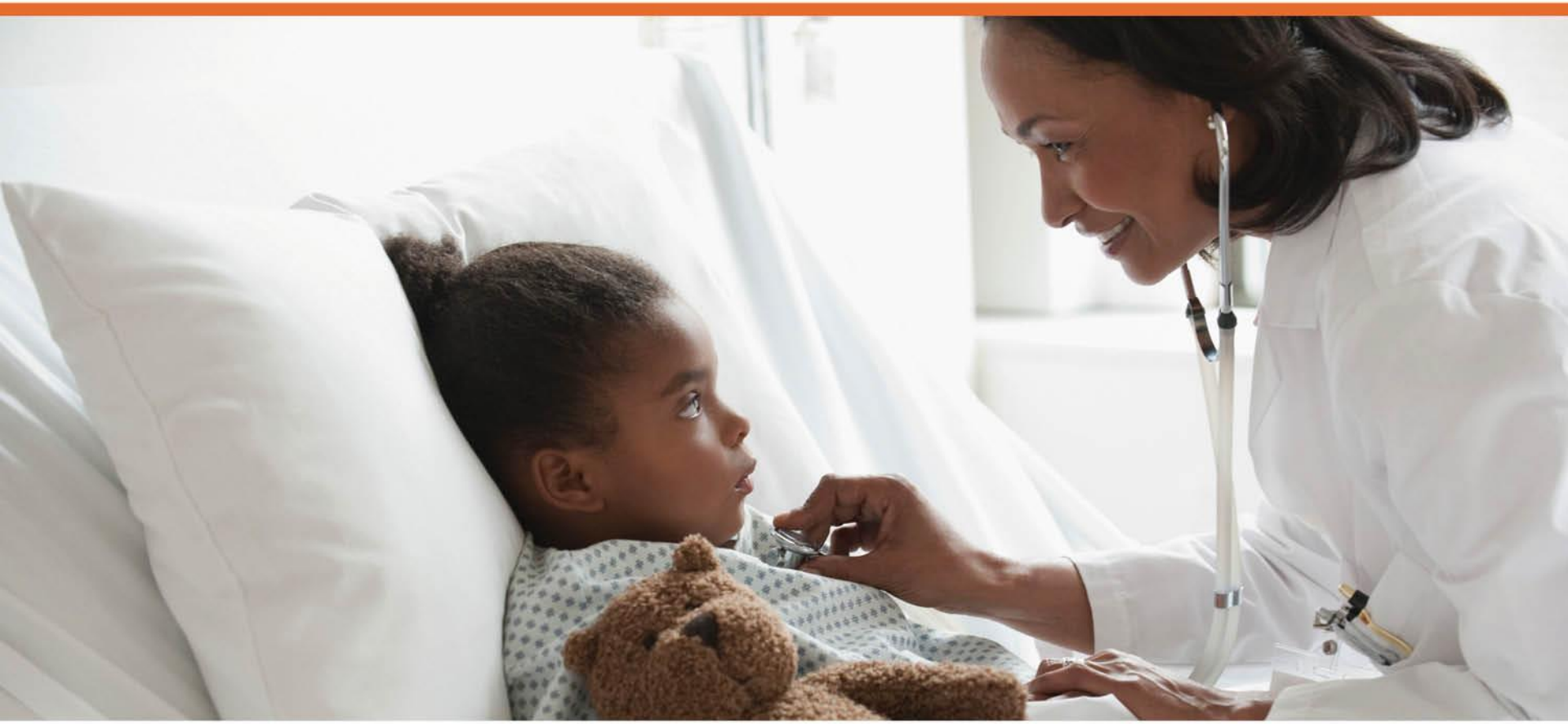
Every Vascular Tumor is NOT a Hemangioma What the Hematologist/Oncologist needs to know about Rare Vascular Tumors



Moderator: Denise Adams, MD

Speakers: Sandra P. D'Angelo, MD; Brian Rubin, MD, PhD

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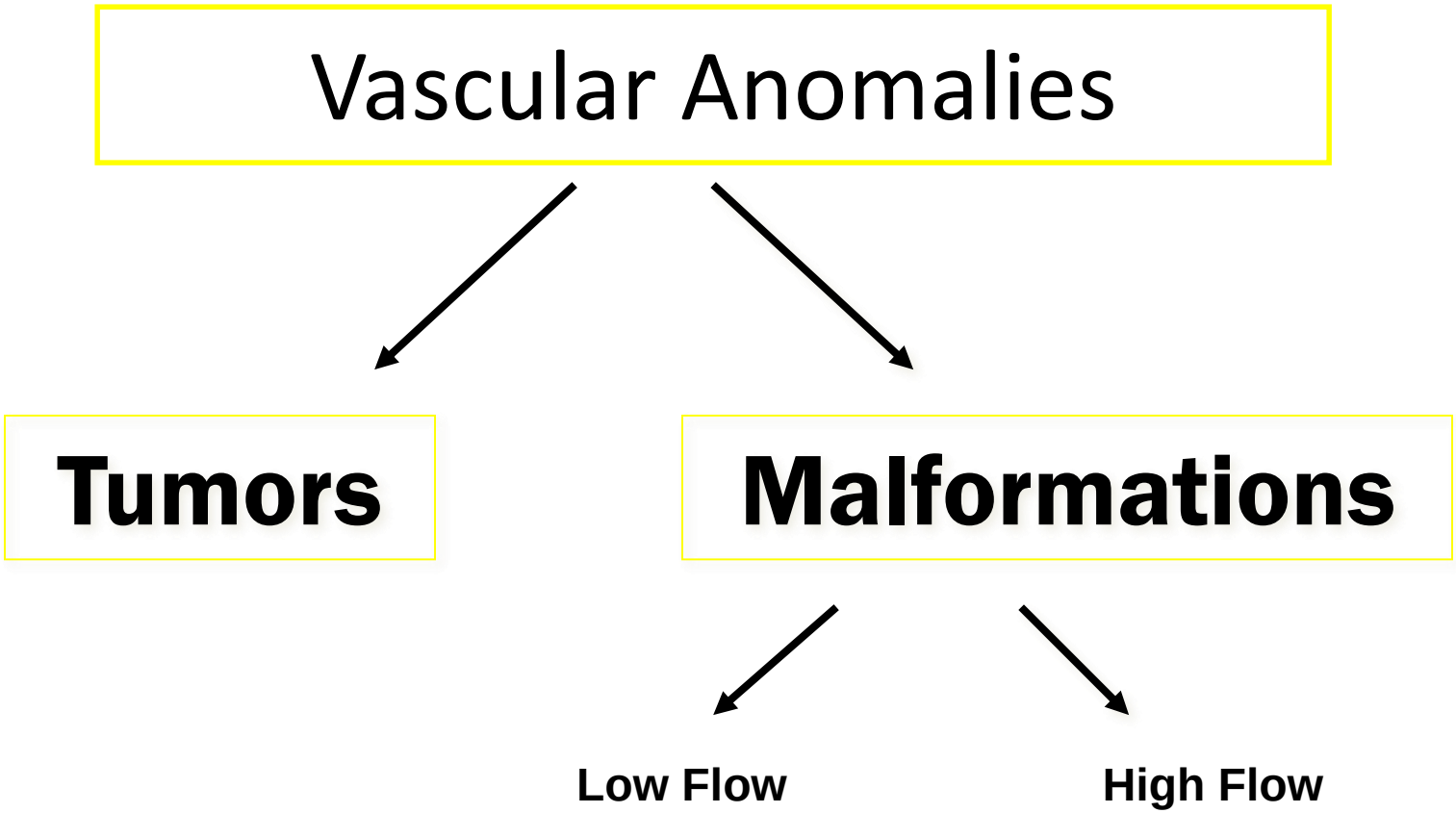
Outline

- Classification of Pediatric Vascular Tumors
- Current Update on therapy for Angiosarcomas
- Current Update on Epithelioid Hemangioendotheliomas

Mulliken & Glowacki. *Plast Recon Surg* 1982



ISSVA Classification - 1996

Table 1.: ISSVA Classification of Vascular Anomalies

Vascular Tumors	Vascular Malformations		
	Simple	Complex	Flow
Hemangioma Pyogenic granuloma Hemangiopericytoma	Capillary (CM) Venous (VM) Lymphatic (LM)	Lymphatico-Venous (LVM) Capillary-Lymphatico-Venous ...	S L O W
Hemangioendothelioma Tufted angioma	Arterial Arteriovenous (AVM)	Capillary-Arterio-Venous ...	F A S T

ISSVA = International Society for the Study of Vascular Anomalies

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ISSVA Classification – 2014

(Wassaf et al *Pediatrics* Vol 136 Number 1, July 2015)

ISSVA classification for vascular anomalies

(Approved at the 20th ISSVA Workshop, Melbourne, April 2014)

Overview table

Vascular anomalies				
Vascular tumors	**Vascular malformations**			
	Simple	**Combined** °	**of major named vessels**	**associated with other anomalies**
Benign Locally aggressive or borderline Malignant	Capillary malformations Lymphatic malformations Venous malformations Arteriovenous malformations* Arteriovenous fistula*	CVM, CLM LVM, CLVM CAVM* CLAVM* others	See details	See list

° defined as two or more vascular malformations found in one lesion

* high-flow lesions

N.B. The classification tables do not list exhaustively all known vascular anomalies. Some rare "dermatologic" vascular anomalies will be found in dermatology textbooks.

The tumor or malformation nature or precise classification of some lesions is still unclear. These lesions appear in a separate provisional list.

Abbreviations used

For more details, click on the underlined links

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Vascular Tumors

ISSVA Classification

- **Benign**
  - -Infantile Hemangioma
  - -Congenital Hemangioma
  - -Tufted Angioma
  - -Spindle Cell Hemangioma
  - -Pyogenic Granuloma
  - -Other
- **Locally Aggressive/Borderline**
  - -Kaposiform hemangioendothelioma
  - -Retiform hemangioendothelioma
  - -Papillary intralymphatic angioendothelioma (PILA), Dabska tumor
  - -Composite hemangioendothelioma
  - -Kaposi sarcoma
  - -Others
- **Malignant**
  - **-Epithelioid Hemangioendothelioma**
  - **-Angiosarcoma**
  - **-Other**

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Rare Vascular Tumors

- Classification of vascular tumors can be very difficult
- Uncommon tumors
- Clinical behavior varies
- Morphologic appearance varies
- Difficulty distinguishing benign vs. malignant lesions
- Pediatric tumors are not independently stratified

Pediatric Angiosarcoma

Angiosarcoma

- Extremely rare, aggressive malignant soft tissue neoplasm
- Very poor prognosis
- Comprises 1-2 % of liver tumors in children
- Five year overall survival is 20 – 35%

Hepatic Angiosarcoma

- Less than 50 cases of pediatric hepatic angiosarcoma in the literature
- Series of 8 patients, 1 presented at birth, average age of presentation 3 years (abdominal distention)
- Poor classification system.
- Nomenclature such as Type I, Type II and Type III hemangioendothelioma is confusing. Type II lesions are low grade angiosarcomas and NOT hemangiomas (7 of the patients noted were diagnosed as “hemangiomas” initially. One patient clearly had transformation.
- 20% are Glut – 1 positive

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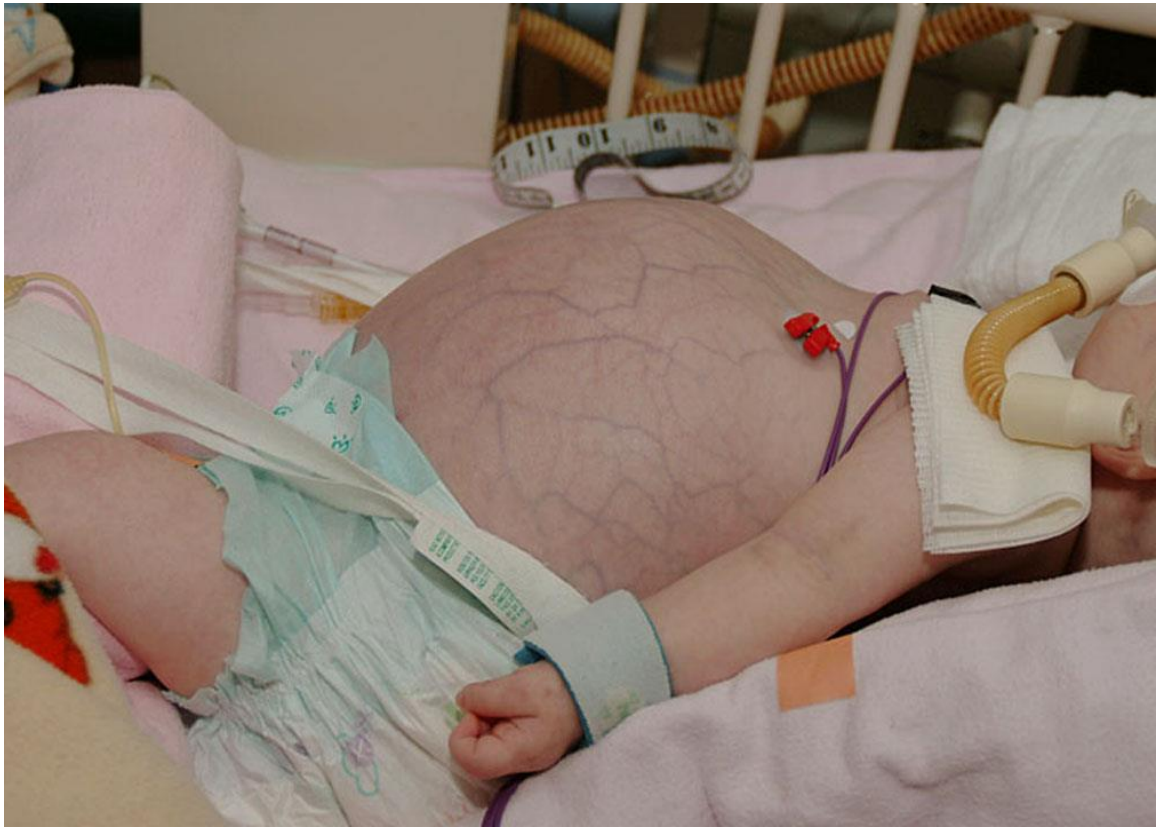
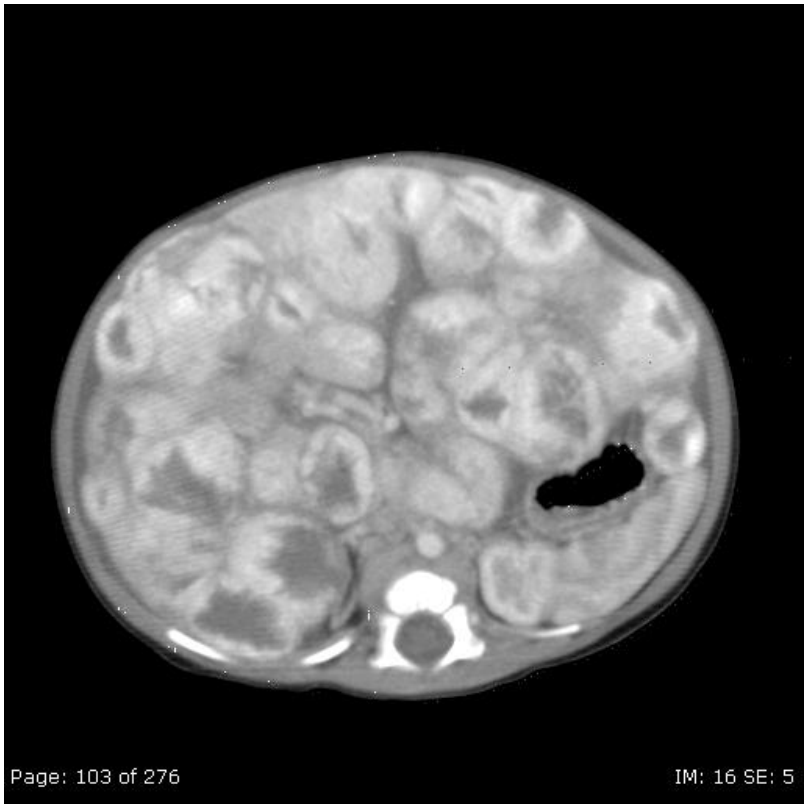
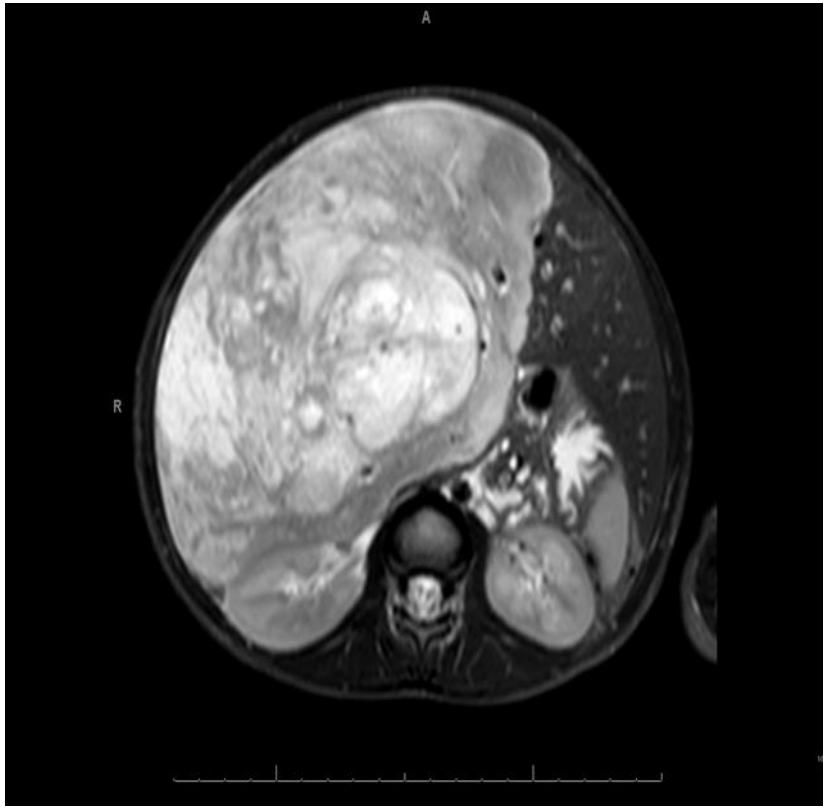
Patient with enlarging abdominal mass



Diffuse Liver Hemangioma





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Current Update on Metastatic Angiosarcoma

November 2, 2016

Sandra P. D'Angelo

Assistant Attending

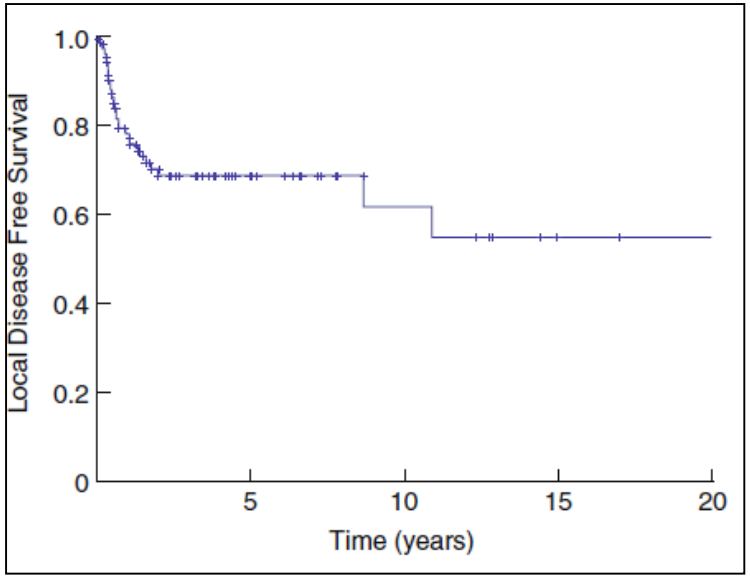
Sarcoma Medical Oncology Service

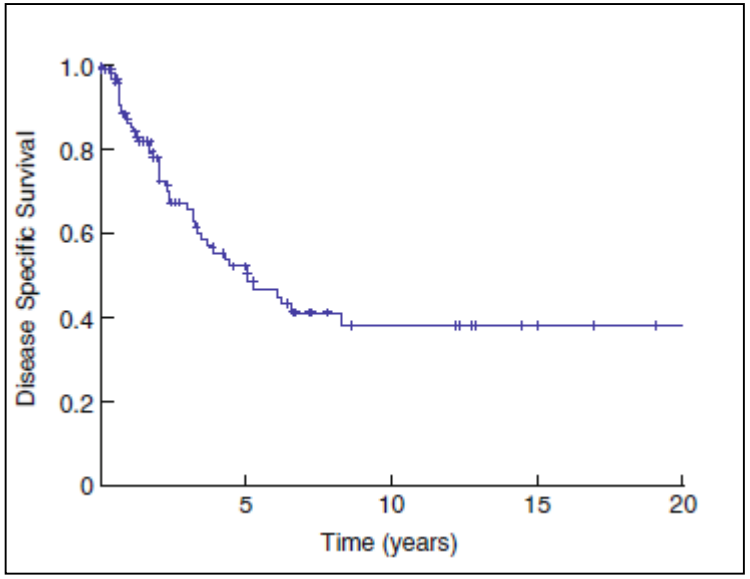
Outline

- Prognosis
- Genomic aberrations
- Treatment strategies

Management/Outcomes for Localized Disease

- Surgery +/- Radiation therapy
- Adjuvant chemotherapy Controversial

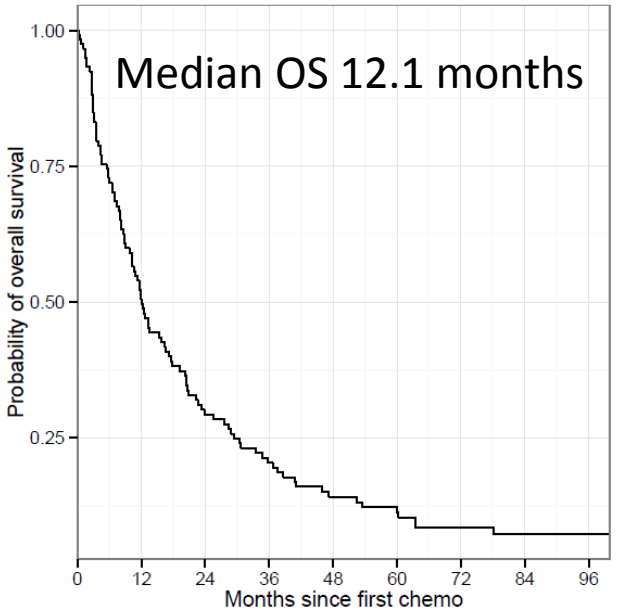




Brennan et. al. Management of STS. Springer 2012

Metastatic angiosarcoma: Poor Prognostic Factor includes Primary tumor size > 10cm

Variable	n	mOS/HR	p value
Univariate analysis			
Age	119	–	0.378
Gender			
Female	69	12.7	
Male	50	11.9	0.8606
Primary site			0.5588
Head/neck	24	20.5	
Extremities	17	11.6	
Trunk/breast	37	11.3	
Retroperitoneum	2	11.2	
Visceral primary	26	10.0	
Other	9	13.3	
Bone origin			0.9323
Yes	8	12.0	
No	111	12.3	
Cutaneous			0.4977
Yes	33	15.3	
No	83	10.9	
RT-associated			0.7565
Yes	28	10.8	
No	91	12.3	
Primary tumor size			0.0034
≤5 cm	43	15.8	
5.1–10 cm	33	12.0	
>10 cm	22	5.9	
Visceral metastases			0.0405
Yes	45	9.7	
No	66	17.2	
Bone metastases			0.6869
Yes	33	11.6	
No	78	16.6	
KPS			0.0485
≤70	18	10.5	
80–100	54	19.2	
First-line regimen			
Anthracycline-based	49	12.0	0.193
Taxane-based	45	11.6	
Other	25	17.8	
Single agent	95	12.0	0.7894
Combination	24	12.3	

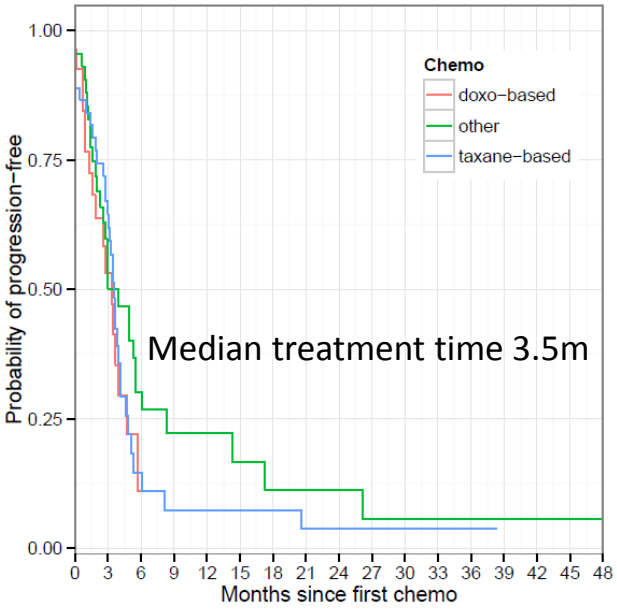


D'Angelo et al. Metastatic AS. Oncology 2016

Metastatic angiosarcoma: outcomes and response to chemotherapy

	n	mTTP
Doxo monotherapy	7	1.61
Doxo combo	22	3.49
Lipo doxo	22	2.93
Taxane monotherapy	40	3.45
Taxane combo	5	4.14
Vinorelabine	1	2.96
mTOR	1	14.31
Sorafenib	7	5.38
Sunitinib	1	8.36
Doxo + taxane	4	4.26
Other	9	2.01

	mTTP
doxo-based	3.39
other	3.91
taxane-based	3.59

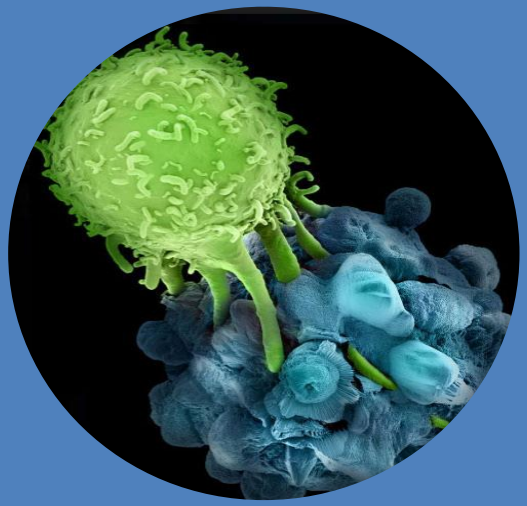


D'Angelo et al. Metastatic AS. Oncology 2016

Treatment Strategies for Metastatic Angiosarcoma

Targeted therapy

Standard Chemotherapy



Immunotherapy

Clinical Trials

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Metastatic Angiosarcoma

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2016
Soft Tissue Sarcoma

NCCN
Soft Tissue Sarcoma, 1

Angiosarcoma
- Paclitaxel[70,71]
- Docetaxel
- Vinorelbine[f]
- Sorafenib[72]
- Sunitinib[73]
- Bevacizumab[74]
- All other systemic therapy options as per Soft Tissue Sarcoma Subtypes with Non-Specific Histologies (SARC-E 1 of 6)

Soft Tissue Sarcoma Subtypes with Non-Specific Histologies

Combination regimens
- AD (doxorubicin, dacarbazine)[1-4]
- AIM (doxorubicin, ifosfamide, mesna)[3-6]
- MAID (mesna, doxorubicin, ifosfamide, dacarbazine)[3,4,7,8]
- Ifosfamide, epirubicin, mesna[9]
- Gemcitabine and docetaxel[10,11]
- Gemcitabine and vinorelbine[f,12]
- Gemcitabine and dacarbazine[13]

Single agents
- Doxorubicin[3,4,14]
- Ifosfamide[9,15]
- Epirubicin[16]
- Gemcitabine
- Dacarbazine
- Liposomal doxorubicin[17]
- Temozolomide[f,18]
- Vinorelbine[f,19]
- Pazopanib[f,g,20]
- Eribulin[f,21]
- Trabectedin[f,22,23,24]

Authors	Year	n	Treatment regimen	ORR	mTTP/mPFS, months	mOS, months
Retrospective studies						
Schlemmer et al. [8]	2008	32	Single-agent P (weekly or q3w)	62%	7.6	NI
Stacchiotti et al. [11]	2011	25	Gemcitabine	64%	7.0	17.0
Penel et al. [24]	2012	149	A-based (46.9%) P (31.5%) Other (sorafenib, platinum-based, vinorelbine, ifosfamide, etc.)	A-based 30.9% P 45.5% Overall	A-based 3.9 P 5.6 3.2	 11.0
Italiano et al. [23]	2012	117	Single-agent P (64%)/single-agent Dox (36%)	Dox 29.5% P 53% Overall	Dox 3.0 P 5.8 4.9	Dox 5.5 P 10.3 8.5
This study	2014	119	A-based T-based Other (sorafenib, platinum-based, vinorelbine, ifosfamide, etc.)	A-based 30% T-based 31% Overall 30%	3.4 3.6 3.9	12.0 11.6 12.1
Prospective clinical trials						
Penel et al. [27]	2008	30	WP	19%	4.0	8.0
Maki et al. [26]	2009	37	Sorafenib	14%	3.8	14.9
Ray-Coquard et al. [10]	2012	41	Sorafenib	14.6%	2.0	9.7
Agulnik et al. [25]	2013	23	Bev	9%	3.0	13.2
D'Angelo et al. [29]	2014	16	Trebananib (AMG386)	0%	1.7	7.0
Penel et al. [28]	2014	50	WP WP + Bev	50% 40%	6.8 6.9	19.5 15.9

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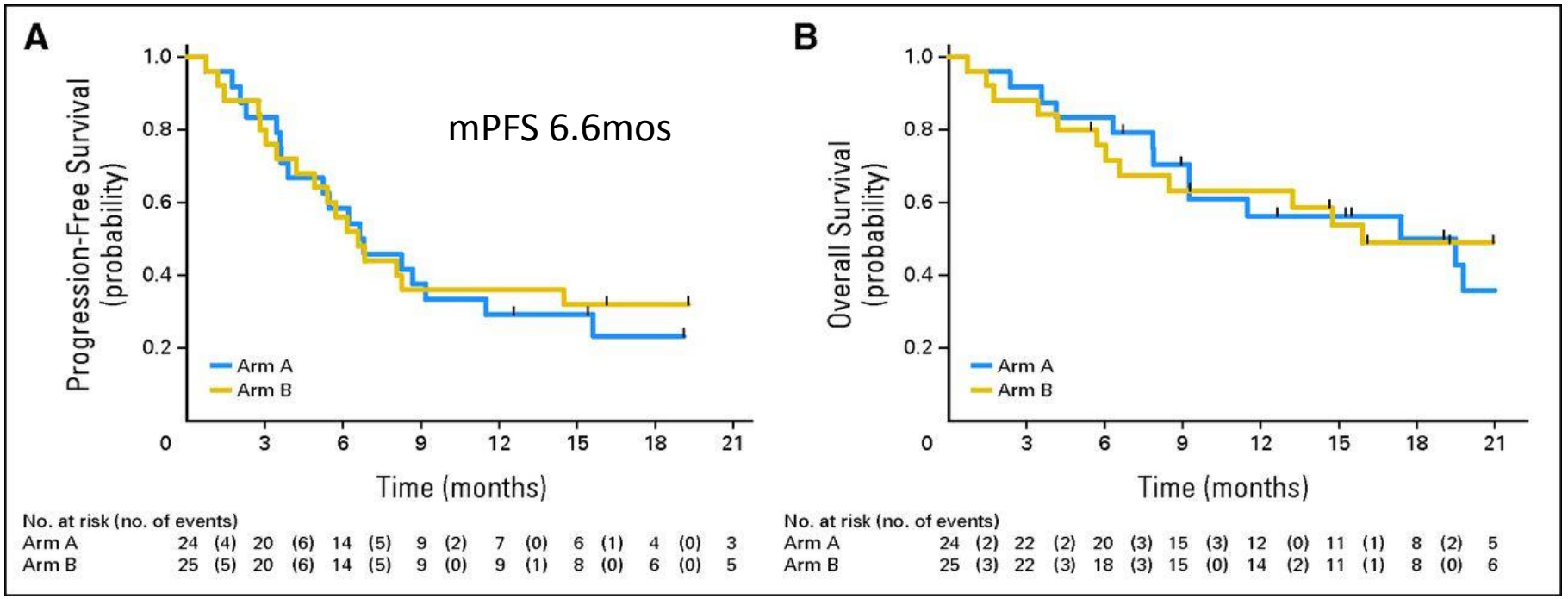
Paclitaxel +/- Bevacizumab



Isabelle L. Ray-Coquard et al. JCO
doi:10.1200/JCO.2015.60.8505

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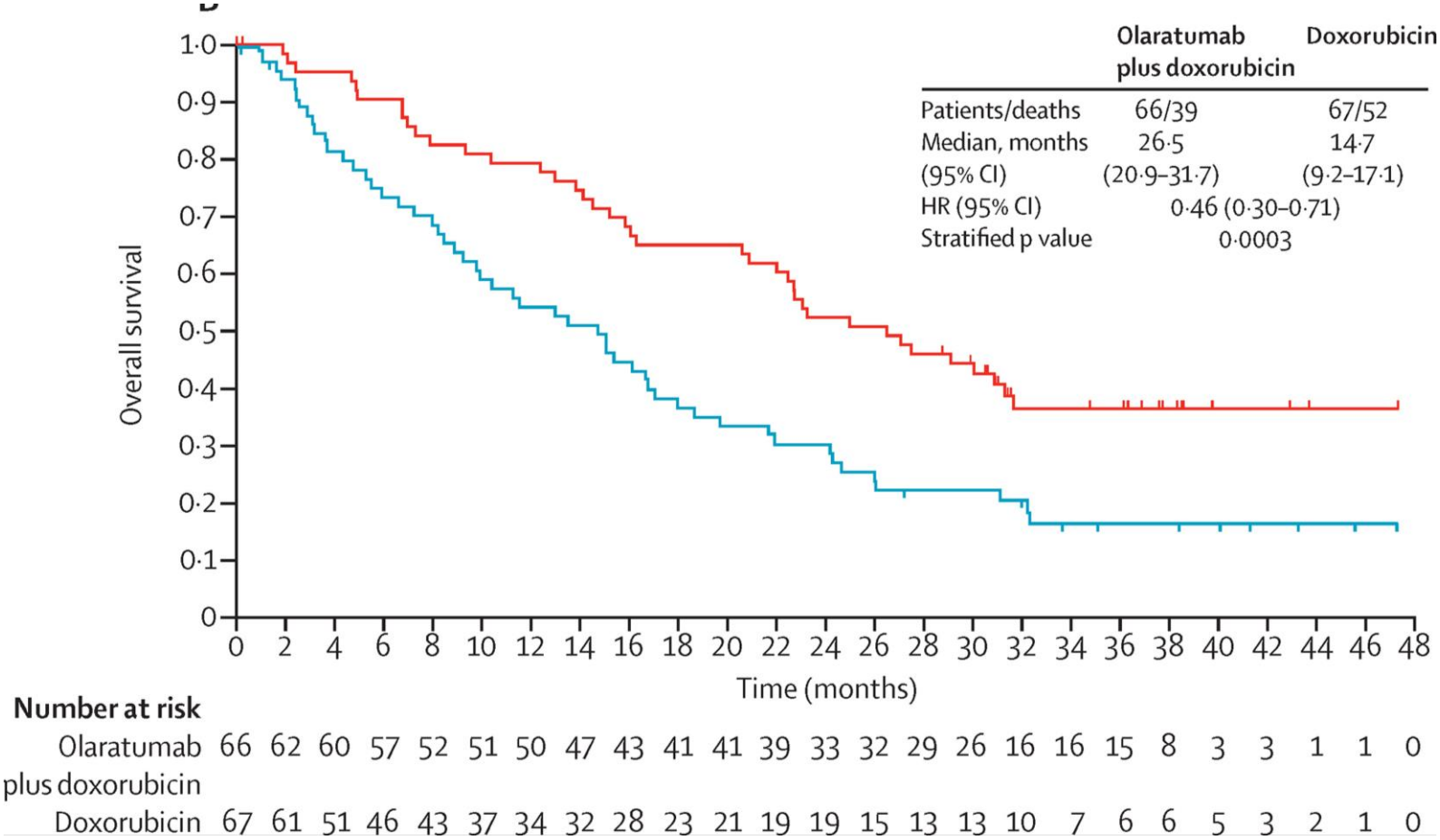
Doxorubicin +/- Olaratumab (PDGFRα inhibitor)

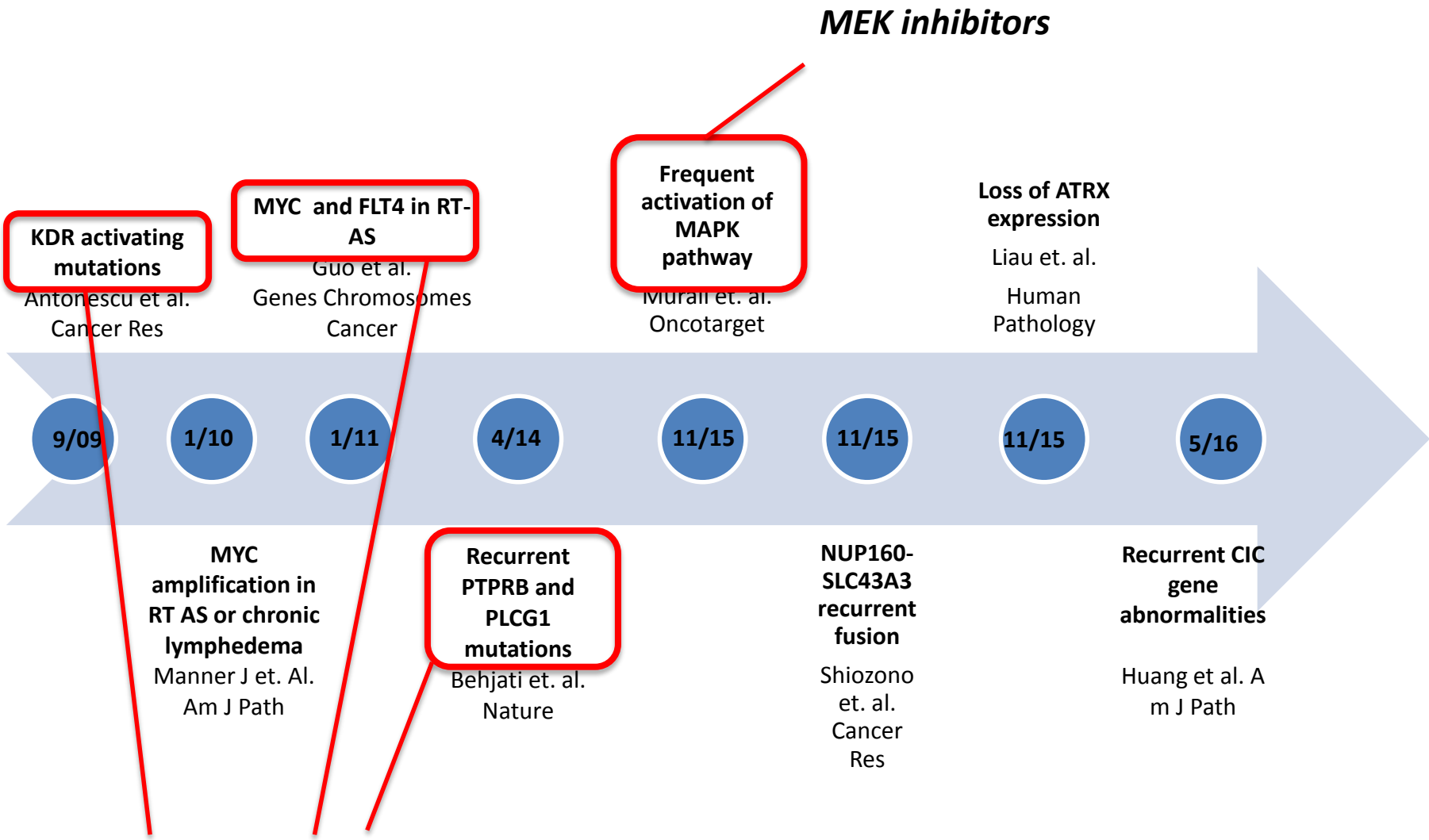


Tap WD, Lancet 2016

Pazopanib + TRC105 (endoglin)

Attai S, ASCO 2016

Unraveling the genomics of angiosarcoma



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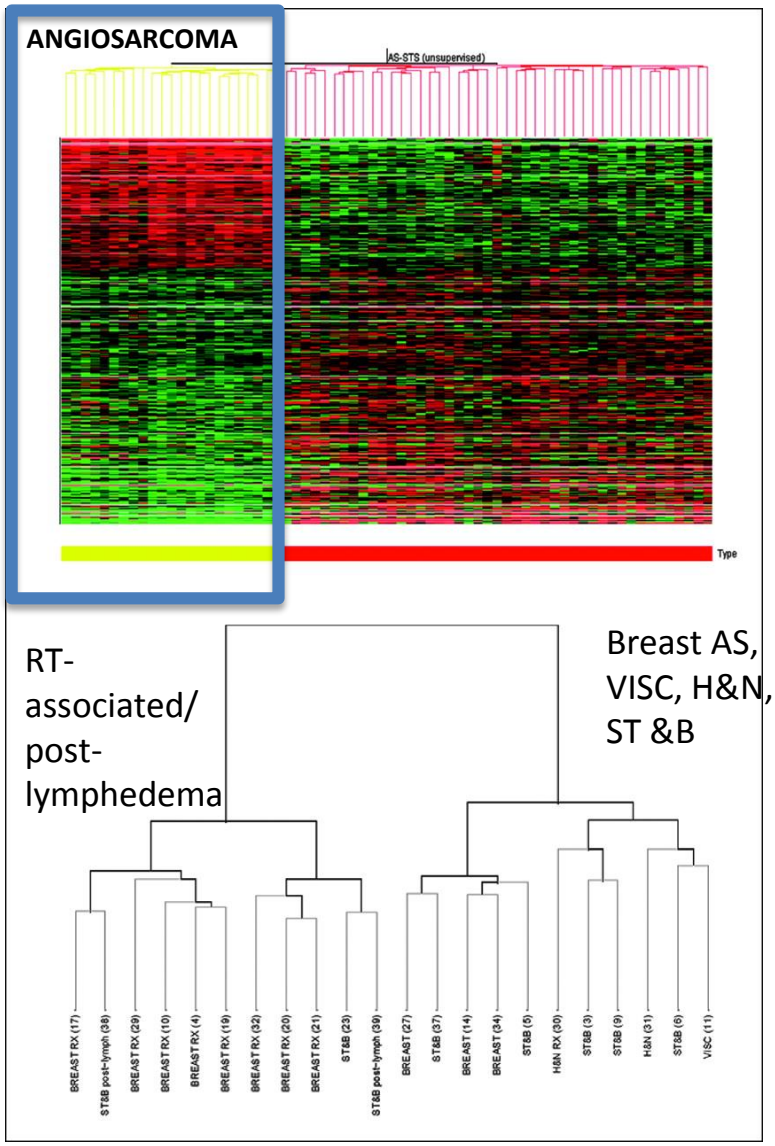
AS clusters into distinct genomic clusters



Antonescu et al. Cancer Res 2009;69:7175-7179

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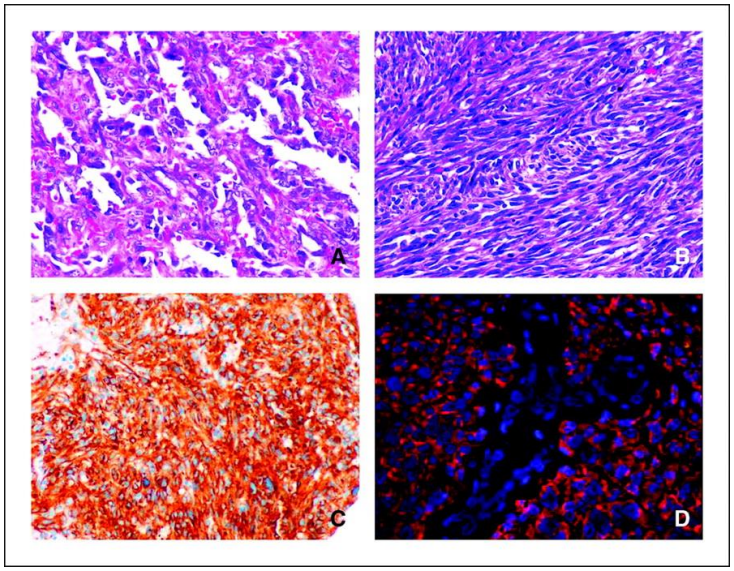
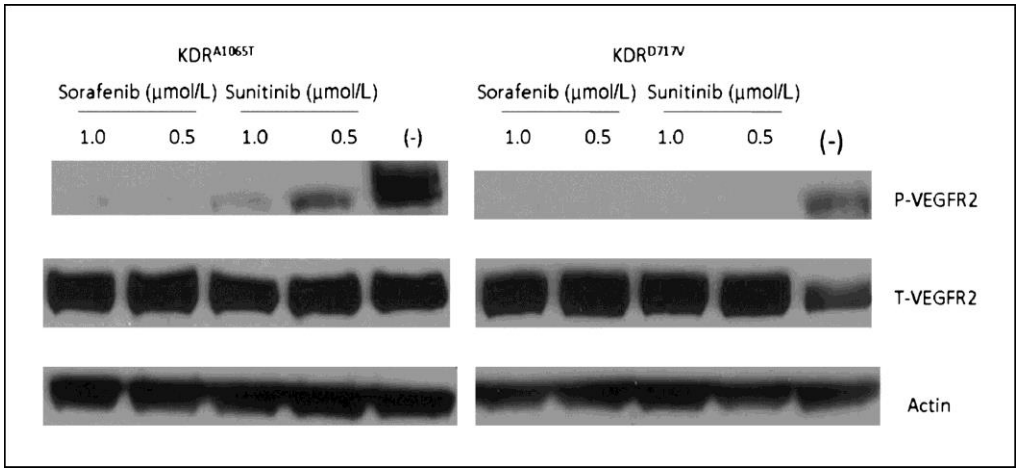
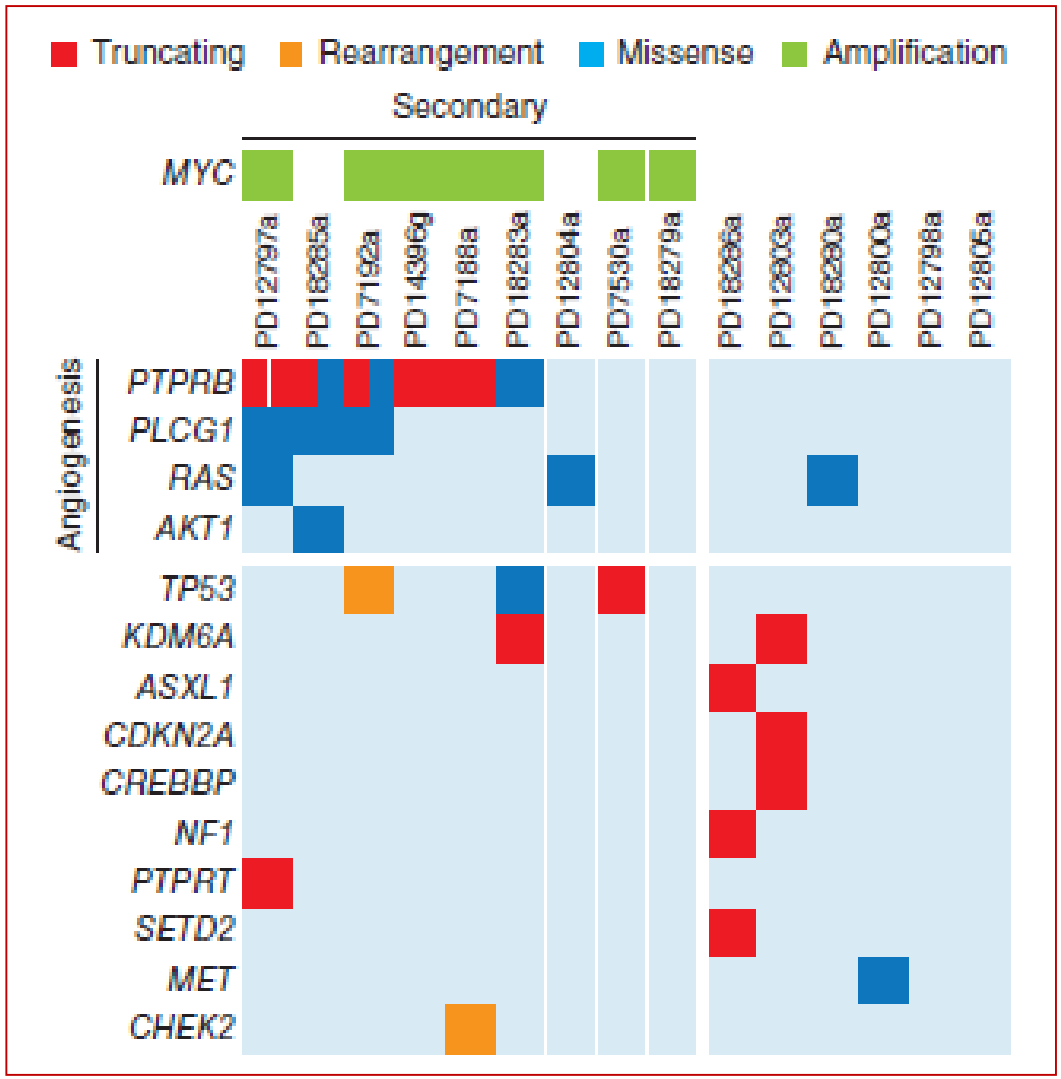
KDR mutation present in 10% of breast/chest wall and demonstrate sensitivity to KDR inhibitors





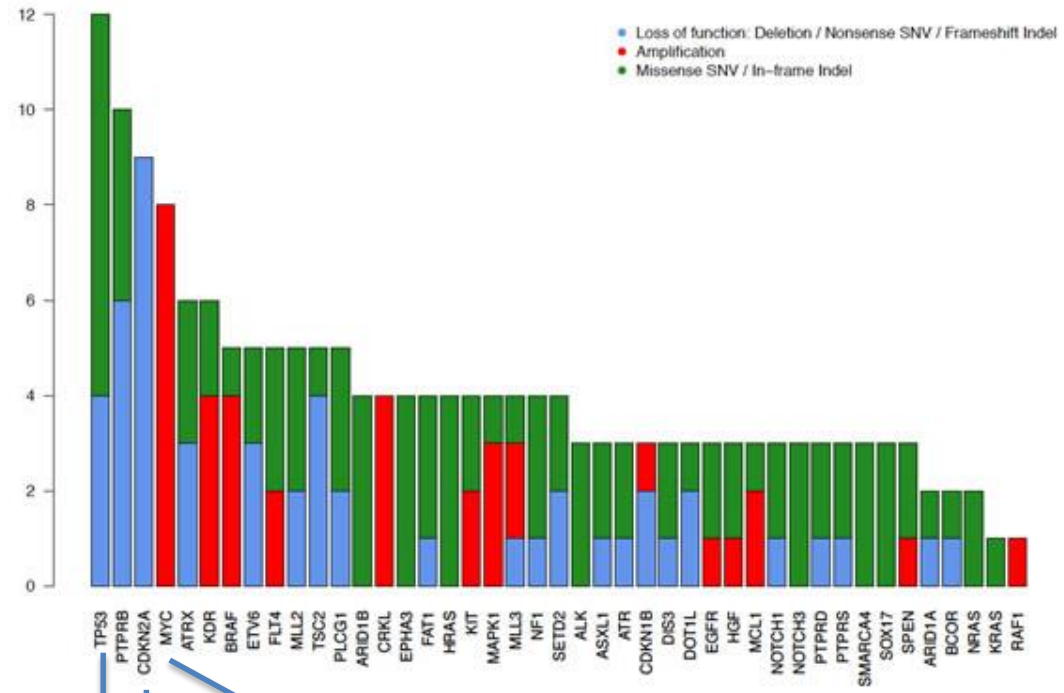
Antonescu et al. Cancer Res 2009;69:7175-7179

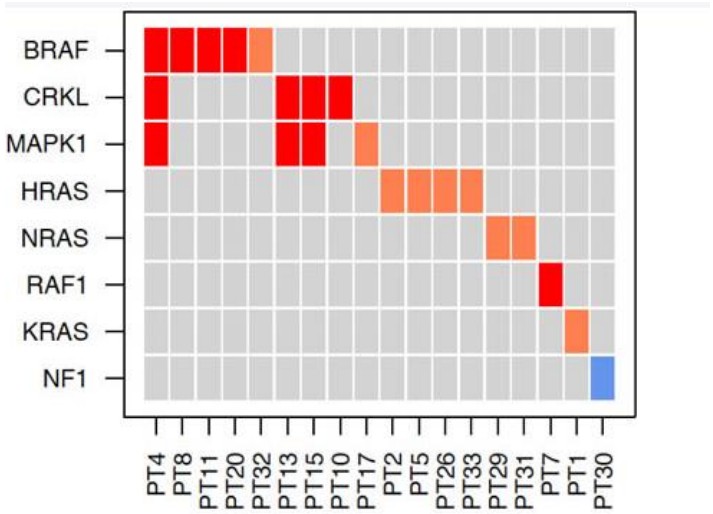
38% of angiosarcomas have at least 1 driver mutation in angiogenesis signaling gene in angiosarcoma



Behjati et al. Nat Genet. 2014

MAPK pathway mutations in 53% of Angiosarcoma





Loss CDKN2A 26%

MYC 24%, post RT

TP53 :35%

Moran et al. Oncotarget 2015.

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Clinical case #1: Primary breast angiosarcoma

- 47 yo woman w primary breast angiosarcoma,

POSITIVE FOR THE FOLLOWING SOMATIC ALTERATIONS IN THE CLINICALLY VALIDATED PANEL:
1. PIK3CA (NM_006218) exon8 p.C420R (c.1258T>C)
2. PIK3CA (NM_006218) exon21 p.H1047Y (c.3139C>T)

POSITIVE FOR THE FOLLOWING SOMATIC ALTERATIONS IN THE INVESTIGATIONAL PANEL:
3. KDR (NM_002253) exon14 splicing variant p.E685fs (c.2053_2134+57delGAAGTCTCATGCACGGCATCTGGGAATCCCCCTCCACAGATCATGTGGTTTAAAGATAATGAGACCCTTGTAGAAGACTCAGGTAAATAGAATTTGGCTATCACTCTTGGGTTGCAGAACTTTCCCAGGGATGTTATC)
4. MLL2 (NM_003482) exon31 p.R2635* (c.7903C>T)
Note: Copy number profile is suggestive of broad copy number loss on Chromosome arm 11q14-11q23.

MEAN OVERALL COVERAGE (SEQUENCING DEPTH) IN THIS SAMPLE: 300X
Unless specified, all exons tested had minimum depth of coverage of 100X.

5/5/2016 enrolled in clinical trial of a PI3K inhibitor

Initially treated with sorafenib from 10/1/2015 – 1/22/16

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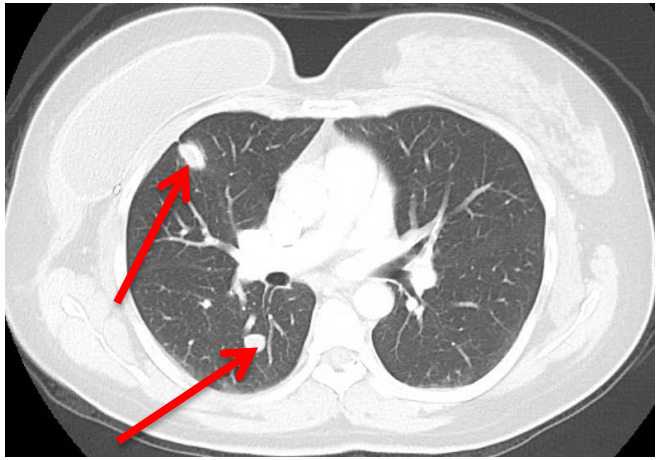

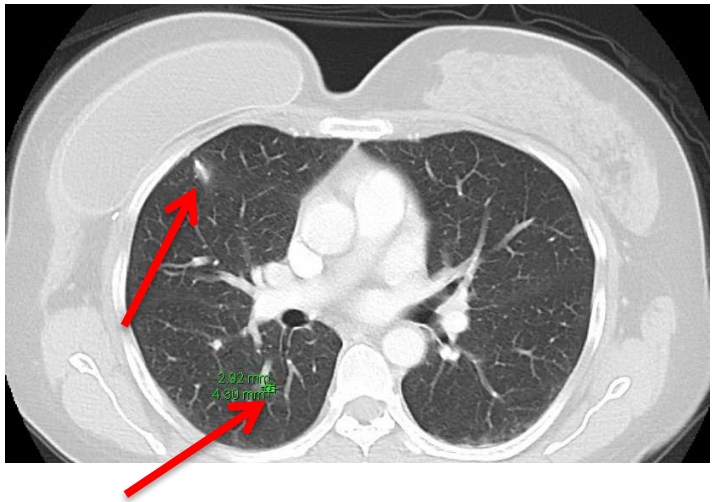

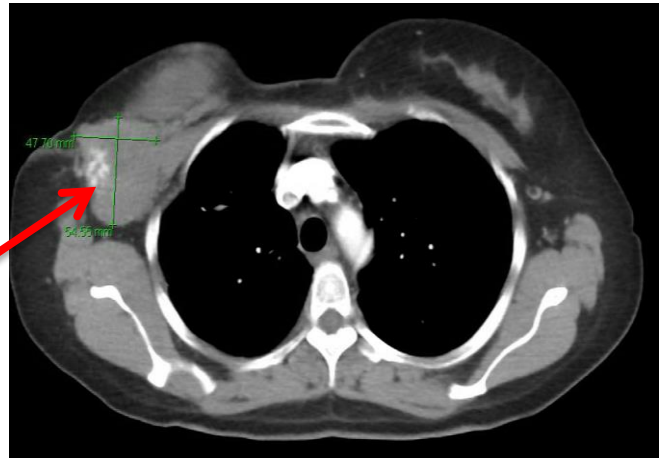

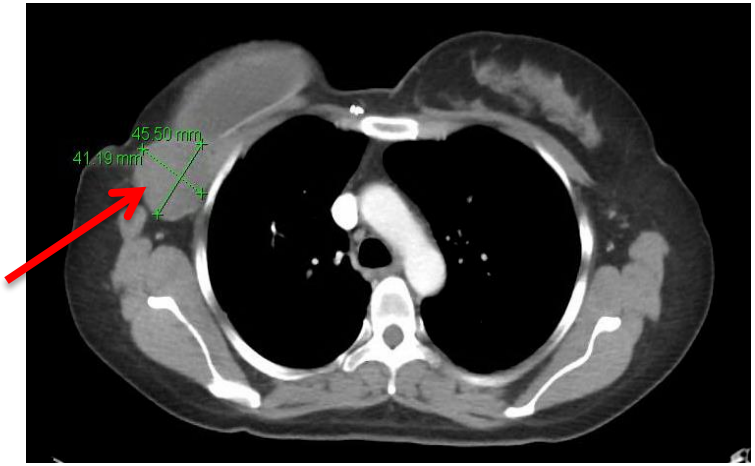

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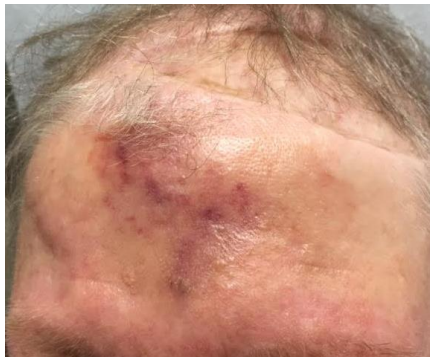
Clinical case #2: Scalp angiosarcoma

- 65 yo woman initially presented 6/2014 w scalp angiosarcoma. She initiated treatment w paclitaxel and had a near CR. Had residual disease resected in 12/2014. A 2.5cm residual angiosarcoma was excised.
- 2/15, she developed recurrent disease in the scalp

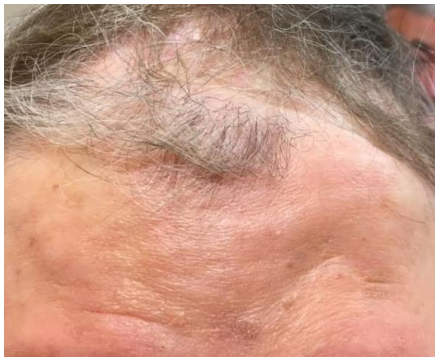
POSITIVE FOR THE FOLLOWING SOMATIC ALTERATIONS IN THE CLINICALLY VALIDATED PANEL:
1. TP53 (NM_000546) exon8 p.R280G (c.838A>G)

POSITIVE FOR THE FOLLOWING SOMATIC ALTERATIONS IN THE INVESTIGATIONAL PANEL:
2. FLT4 (NM_182925 - 5q35.3) Amplification (Fold Change: 2.7)
3. VHL (NM_000551 - 3p25.3) Amplification (Fold Change: 2.3)
4. RAF1 (NM_002880 - 3p25.2) Amplification (Fold Change: 2.3)
5. POLE (NM_006231 - 12q24.33) Deletion (Fold Change: -2.6)
6. NF1 (NM_001042492 - 17q11.2) Deletion (Fold Change: -2.6)
7. SUZ12 (NM_015355 - 17q11.2) Deletion (Fold Change: -2.6)
8. STK11 (NM_000455 - 19p13.3) Deletion (Fold Change: -2.5)
9. TCF3 (NM_001136139 - 19p13.3) Deletion (Fold Change: -2.5)
10. DOT1L (NM_032482 - 19p13.3) Deletion (Fold Change: -2.5)
11. GNA11 (NM_002067 - 19p13.3) Deletion (Fold Change: -2.5)
12. NPM1 (NM_002520 - 5q35.1) Deletion (Fold Change: -2.3)
13. CCNE1 (NM_001238 - 19q12) Deletion (Fold Change: -2.2)
14. ATRX (NM_000489 - Xq21.1) Deletion (Fold Change: -2.1)
15. EPHA3 (NM_005233) exon14 p.I796K (c.2387T>A)
16. FOXA1 (NM_004496) exon2 p.P86S (c.256C>T)
17. MTOR (NM_004958) exon11 p.L552F (c.1653_1654delinsTT)
18. PDGFRB (NM_002609) exon4 p.P129S (c.385C>T)

Note: Copy number profile is suggestive of a fragmented genome.



7/9/15 started sorafenib



11/15

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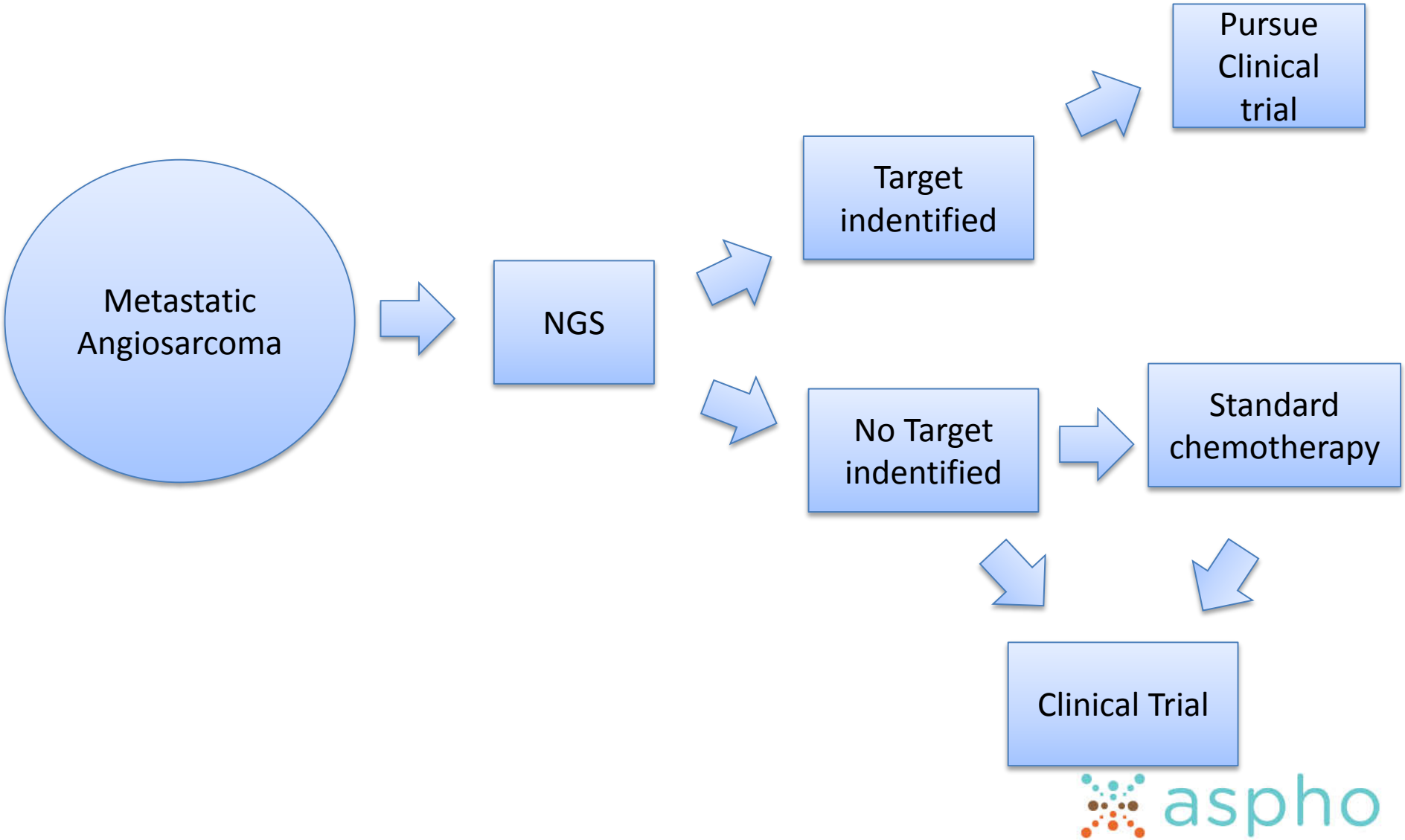
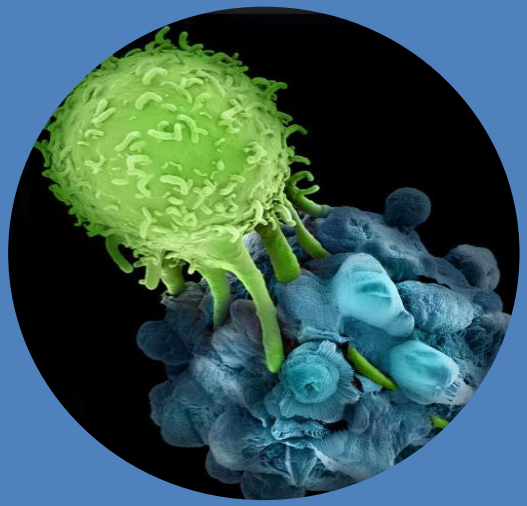
Treatment Approach



Treatment Strategies for Metastatic Angiosarcoma

Targeted therapy

Standard Chemotherapy



Immunotherapy

Clinical Trials

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Conclusions

- Metastatic angiosarcoma is a rare malignancy with poor prognosis
- Next generation sequencing has identified aberrations in vascular genesis pathways in 40% of patients providing new potential therapeutic options
- Role of immunotherapy as a mechanism to treat has not yet been defined
- Enrolling patients in clinical trials remains essential

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Update on Epithelioid Hemangioendothelioma (EHE)

Brian Rubin, MD, PhD
Professor of Pathology
Director, Soft Tissue Pathology
Vice-Chair of Research
Robert J. Tomsich Pathology and Laboratory Medicine Institute
Cleveland Clinic
Department of Cancer Biology
Lerner Research Institute

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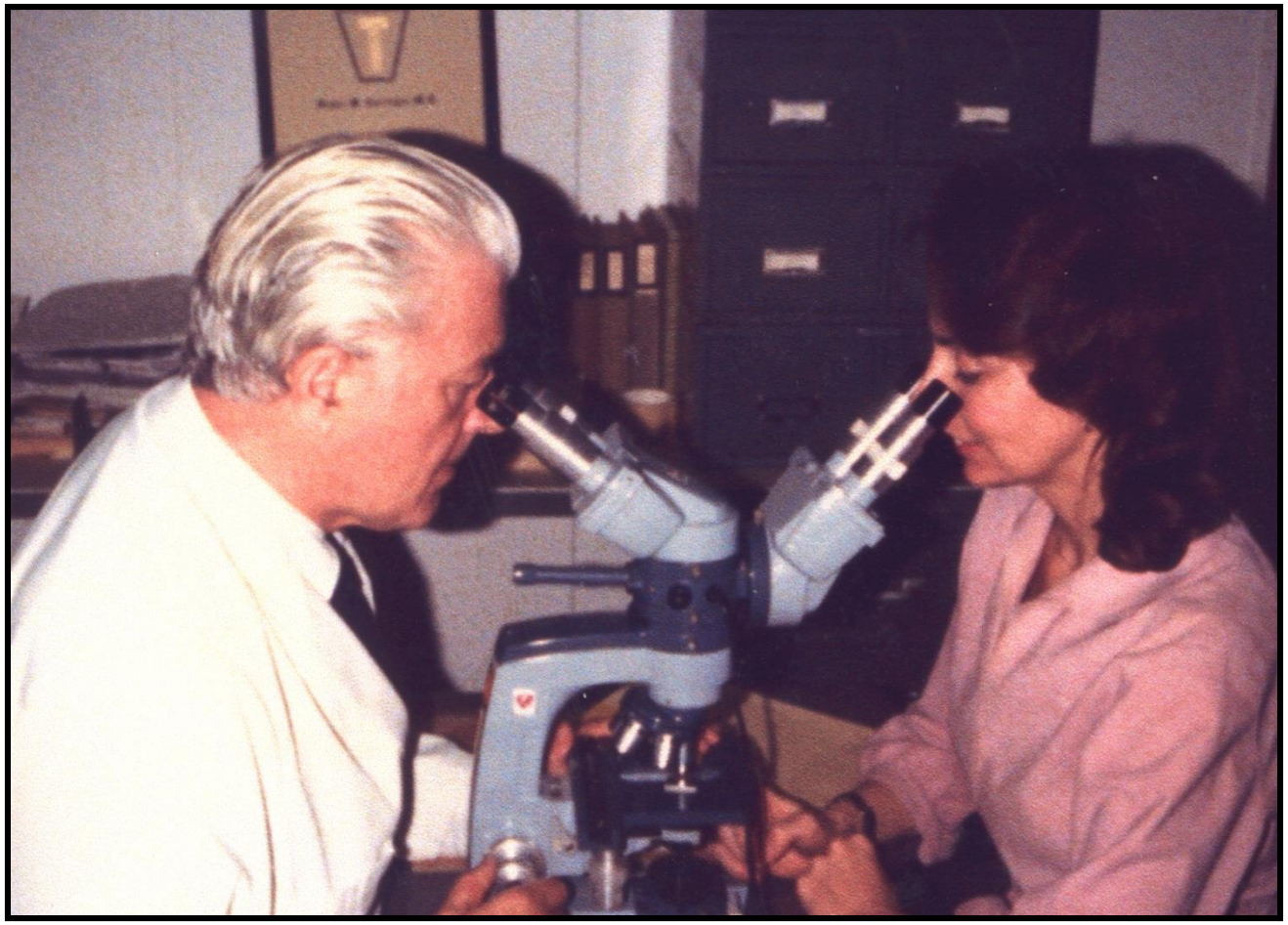
Epithelioid Hemangioendothelioma (EHE)

First described as a distinct vascular tumor of soft tissue by Weiss and Enzinger in 1982



Weiss SW, Enzinger FM. Epithelioid hemangioendothelioma: a vascular tumor often mistaken for a carcinoma. Cancer 50: 970-981 (1982).

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EHE – Clinical

- Malignant vascular neoplasm (sarcoma with endothelial differentiation)
- Estimated prevalence - 1 in 1 million (approx 100-200 new cases in USA each year)
- Age range 7-83 years (rare in children).
- Median onset of 36 years.
- Usual age at diagnosis between 20-60 years.
- F:M = 4:1
- Usually presents incidentally (50-76%)
- Chest pain and abdominal pain are symptomatic presentations due to lung and liver involvement respectively.
- Can present with bone pain due to path fracture.

EHE – Clinical

- Most common EHE presentations:
  - Liver alone (21%)
  - Liver plus lung (18%)
  - Lung alone (12%)
  - Bone alone (14%)
- Very heterogeneous and can involve numerous soft tissue and visceral sites: brain and meninges, head and neck, mediastinum, skin, stomach, retroperitoneum, ovary, prostate – essentially any site can be involved
- Can also present as primary neoplasm of lymph node.

EHE – Clinical

- Soft tissue lesions usually solitary
- Lung, liver and bone lesions usually metastatic at presentation
- Mean survival is 4.6 years (6 months to 24 years).
- Mortality varies depending on site of origin:
  - Soft tissue – 13%
  - Liver – 35%
  - Lung – 65%
- 1 year and 5 year overall survival is 90% and 73% respectively

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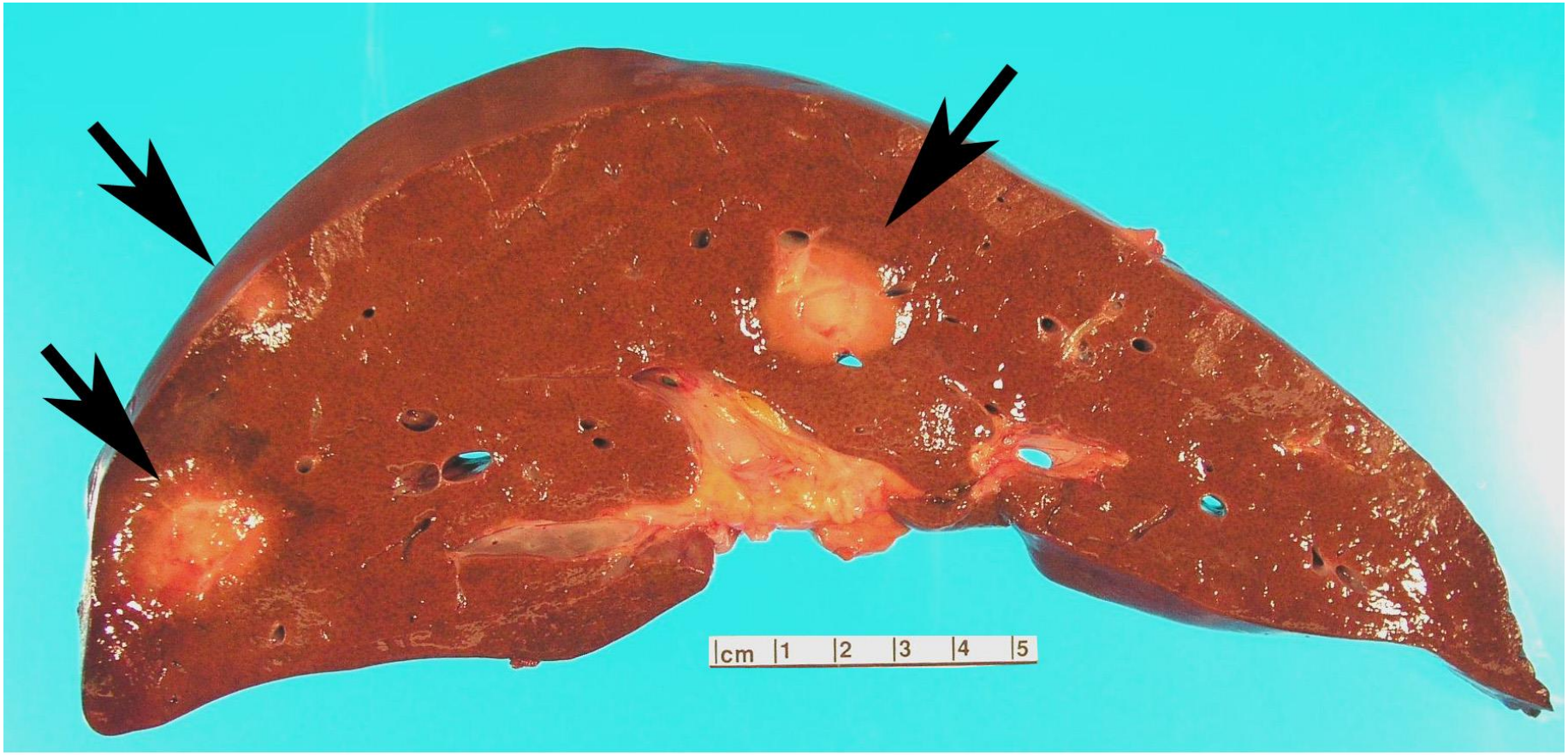
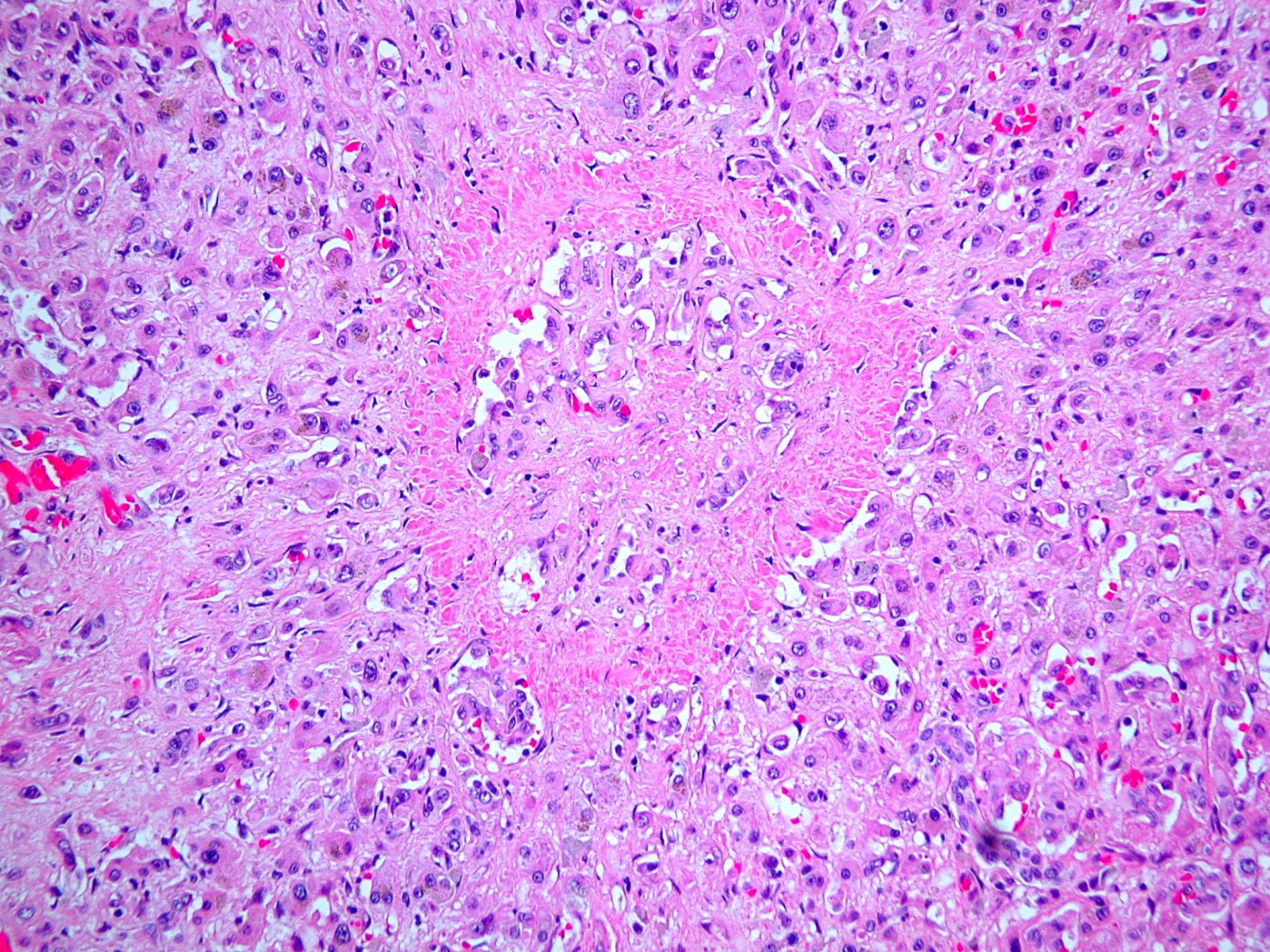
EHE – Clinical

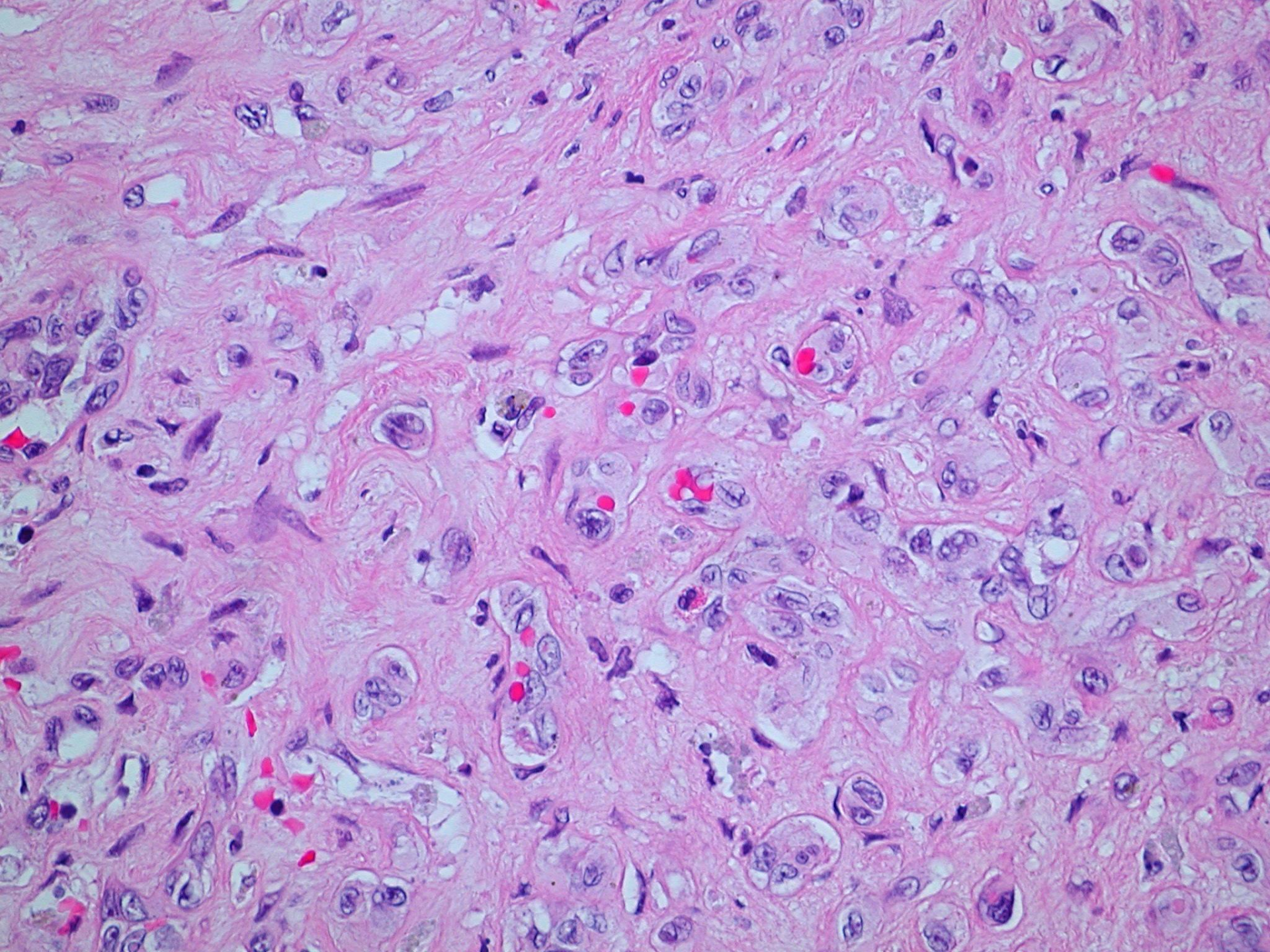
- With metastatic disease the 1 and 5 year overall survival is 53% and 24% respectively.
- Asymptomatic patients have a median survival of 180 months.
- Adverse prognostic factors:
  - Alveolar hemorrhage
  - Hemoptysis
  - Pleural effusion
  - Anemia
  - Lymph node involvement
  - Ascites
  - Weight loss

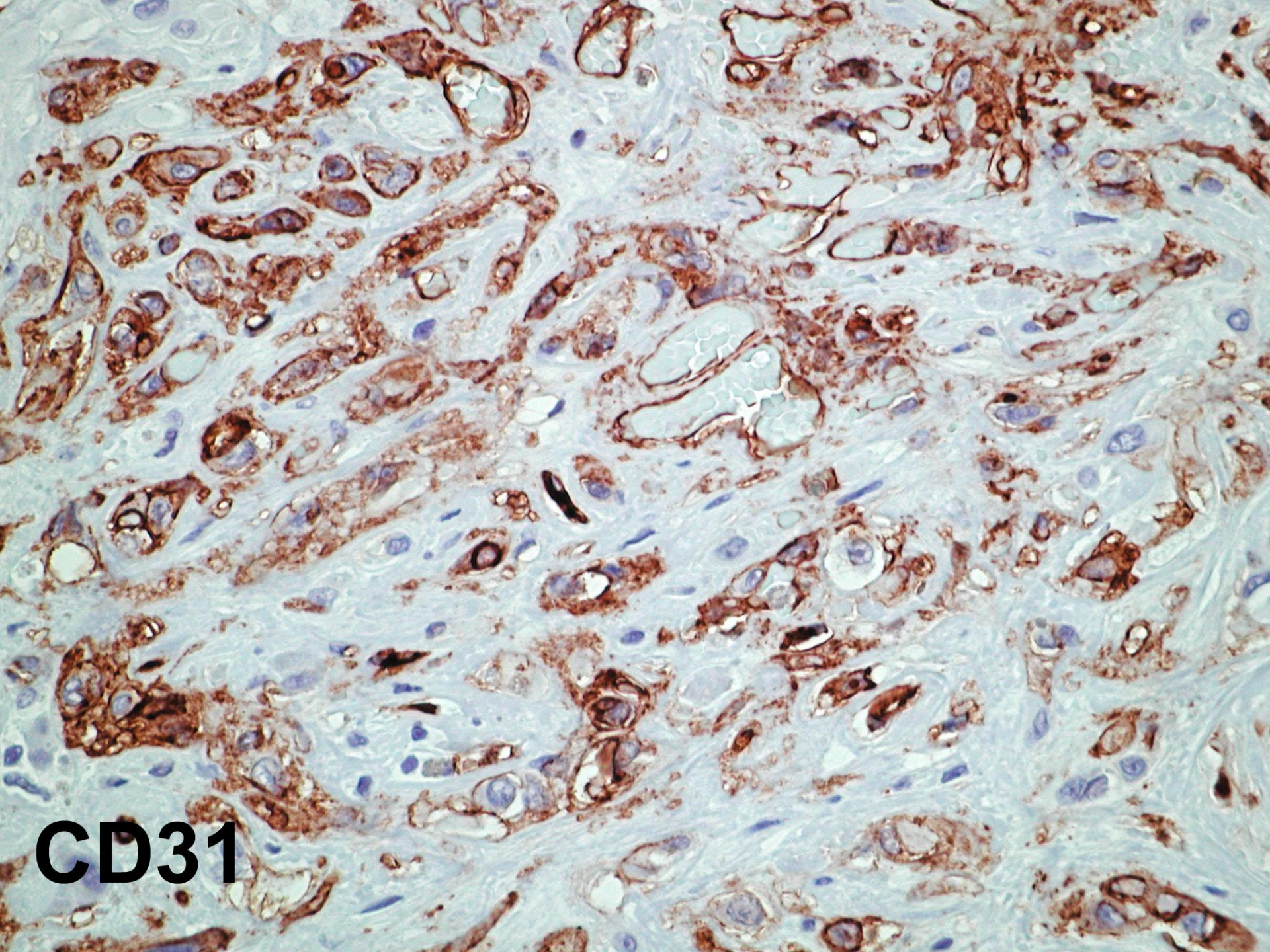
Epithelioid Hemangioendothelioma (EHE)

Multiple liver nodules

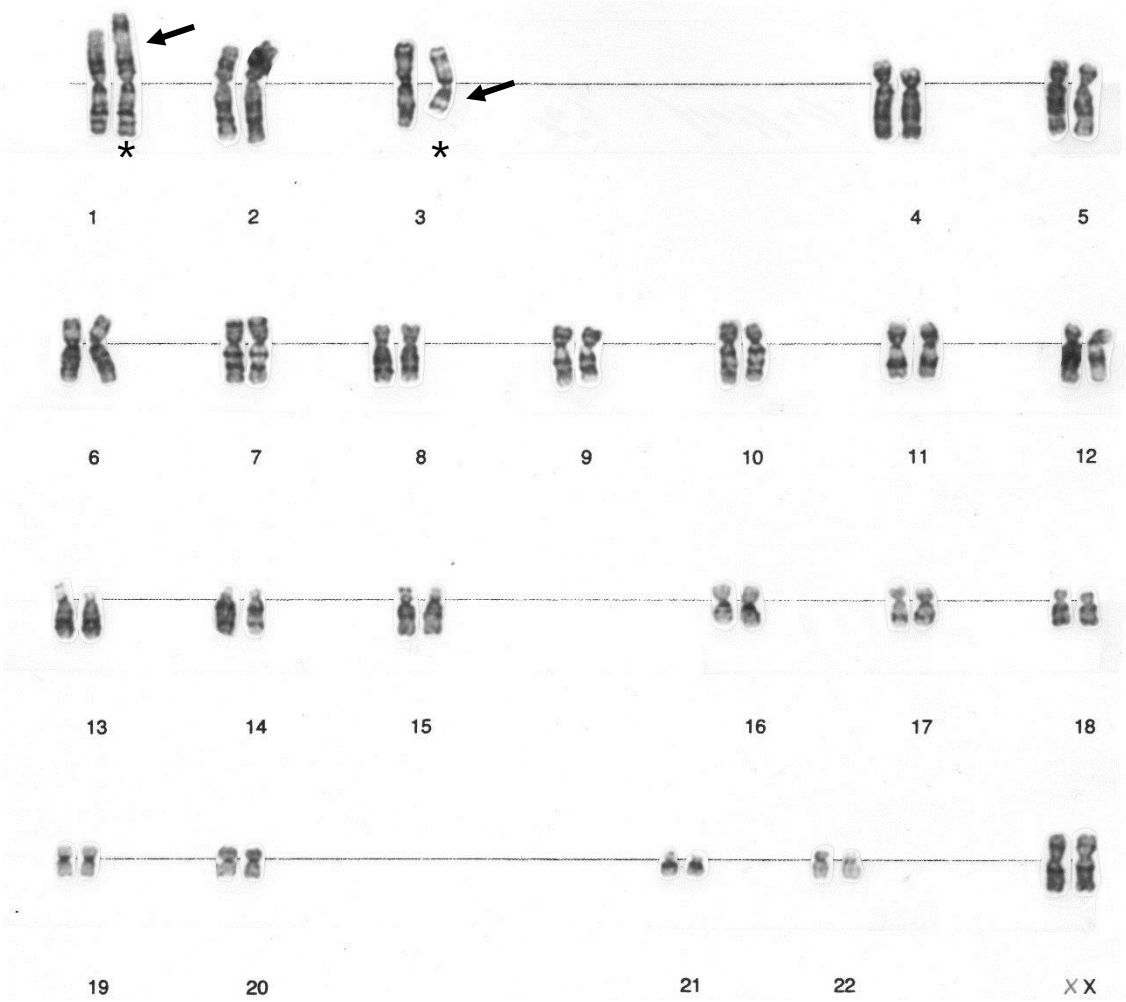


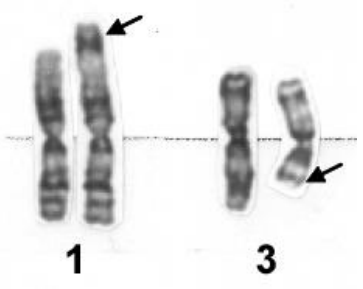





CD31

EHE Cytogenetics





46, XX, t(1;3)(p36.3;q25)

Mendlick et al. Am J Surg Pathol. 25:684;2001.

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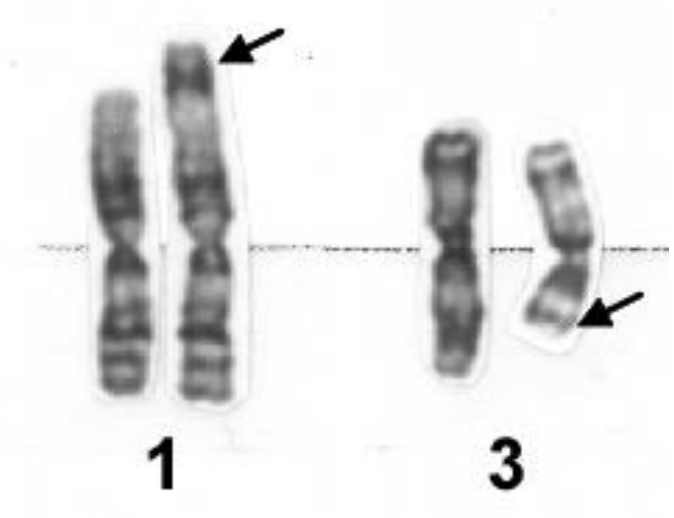
Results of mRNA-Seq analyzed by FusionSeq Algorithm



67	0.189	0.189	0.704	10	inter	chr1:6767970-7752351	CAMTA1 (KIAA0833)	chr3:150720721-150903805	WWTR1

CAMTA1 on Chromosome 1 and WWTR1 on Chromosome 3

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FISH results in 47 EHE

Site	WWTR1	CAMTA1
Liver (EHE 1)	(+)	(+)
Liver (EHE 2)	(+)	(+)
Lung (EHE 3)	(+)	(+)
Liver (EHE 4)	(+)	(+)
Liver (EHE 5)	(+)	(+)
Submandibular region	(+)	(+)
Shoulder	(+)	(+)
Leg	(+)	(+)
Thigh	(+)	(+)
Skin, thigh	(+)	(+)
Mediastinum	(+)	(+)
Occiput	(+)	(+)
Thigh-subcutaneous	(+)	(+)
Thigh	(+)	(+)
Back	(+)	(+)
N/A	(+)	(+)
Lung,multiple	(+)	(+)
N/A	(+)	(+)
N/A	(+)	(+)
Liver	(+)	(+)
L4 verteb	(+)	(+)
Inguinal lymph node	(+)	(+)
Left calf-soft tissue	(+)	(+)
Lung/pleura	(+)	(+)
Liver	(+)	(+)

Site	WWTR1	CAMTA1
Retroperitoneum	(+)	(+)
Liver	(+)	(+)
Thigh/deep	(+)	(+)
Liver	(+)	(+)
C1 vertebrae	(+)	(+)
N/A	(+)	(+)
Liver	(+)	(+)
Toe	(+)	(+)
Lung	(+)	(+)
Liver	(+)	(+)
Neck	(+)	(+)
Groin	(+)	(NF)
Liver	(+)	(NF)
Soft tissue, NOS	(+)	(+)
Liver	(+)	(+)
Mediastinum	(+)	(+)
Lung	(+)	(-)
Acetabulum	(-)	(-)
Tongue	(-)	(-)
Lung	(-)	(-)
Heel	(-)	(-)
Rectovaginal septum	(-)	(-)
Positive cases/Total	42/47	39/45
% cases positive	89%	87%

Translocation present in essentially all EHE!

EHE from both visceral locations and soft tissue harbor the translocation

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FISH results for 165 vascular neoplasms

	WWTR1		CAMTA1	
	Positive /Total	%	Positive /Total	%
Epithelioid hemangioendothelioma	42/47	89%	39/45	87%
Angiosarcoma, NOS	0/42	0%	0/39	0%
Epithelioid angiosarcoma	0/7	0%	0/7	0%
Intimal sarcoma	0/5	0%	0/3	0%
Kaposi's sarcoma	0/4	0%	0/4	0%
Malignant hemangioendothelioma, NOS	0/1	0%	0/1	0%
Retiform hemangioendothelioma	0/1	0%	0/1	0%
Kaposiform hemangioendothelioma	0/3	0%	0/2	0%
Epithelioid hemangioma	0/5	0%	0/4	0%
Arteriovenous malformation	0/2	0%	0/2	0%
Angiomatosis	0/1	0%	0/1	0%
Hemangioma, NOS	0/3	0%	0/3	0%
Capillary/pyogenic hemangioma	0/5	0%	0/5	0%
Cavernous hemangioma	0/5	0%	0/5	0%
Juvenile hemangioma	0/1	0%	0/1	0%
Spindle cell hemangioma	0/4	0%	0/4	0%
Synovial hemangioma	0/1	0%	0/1	0%
Intramuscular hemangioma	0/6	0%	0/5	0%
Littoral cell hemangioma	0/6	0%	0/2	0%
Malignant hemangiopericytoma	0/1	0%	0/1	0%
Hemangiopericytoma, NOS	0/1	0%	0/1	0%
Sinonasal hemangiopericytoma	0/1	0%	0/1	0%
Glomus tumor	0/1	0%	0/1	0%
Atypical glomus tumor	0/2	0%	0/2	0%
Lymphangioma	0/7	0%	0/7	0%
Lymphangioleiomyomatosis	0/1	0%	0/1	0%
Papillary endothelial hyperplasia	0/2	0%	0/2	0%
Total cases	165		151	

No other vascular neoplasm harbored rearrangement of *WWTR1* or *CAMTA1*!

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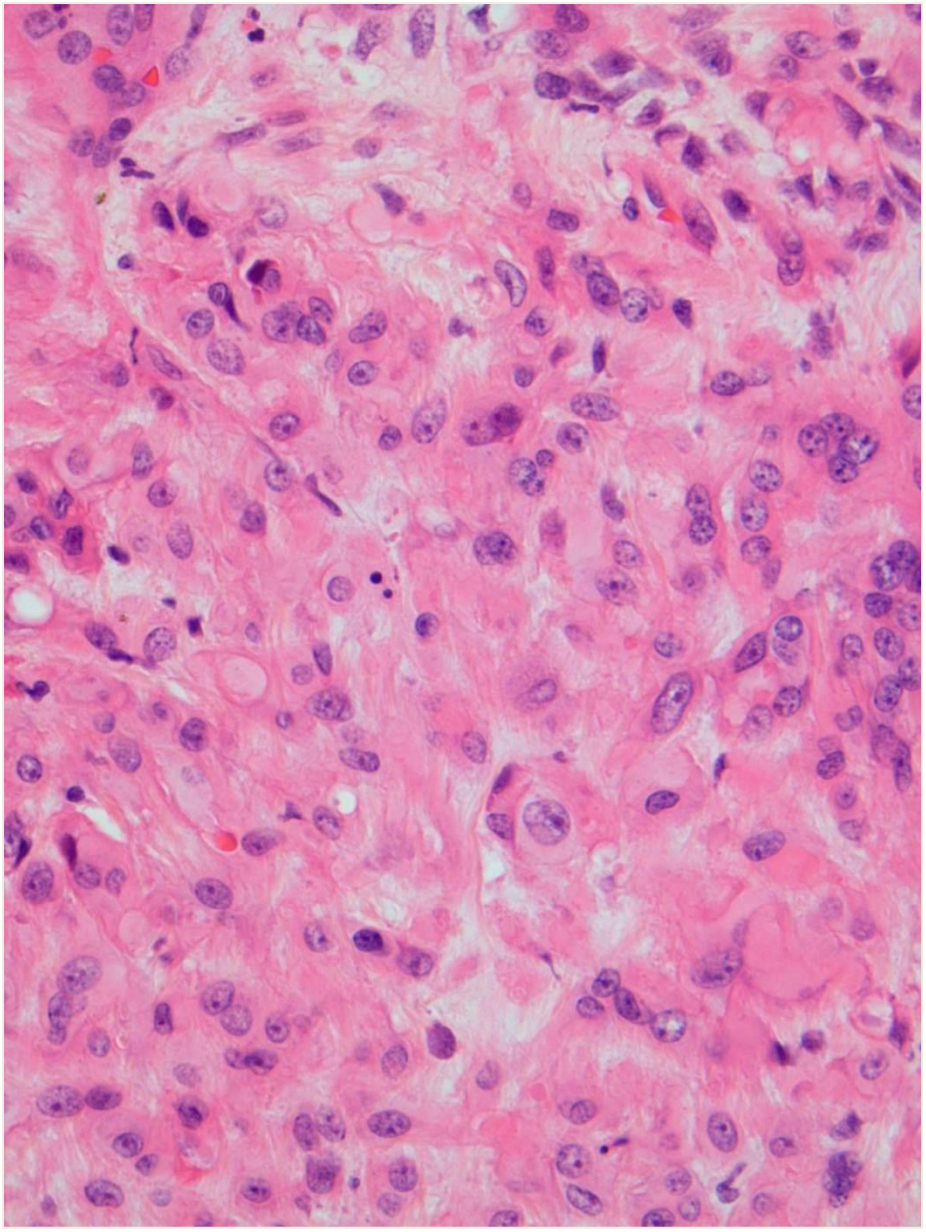
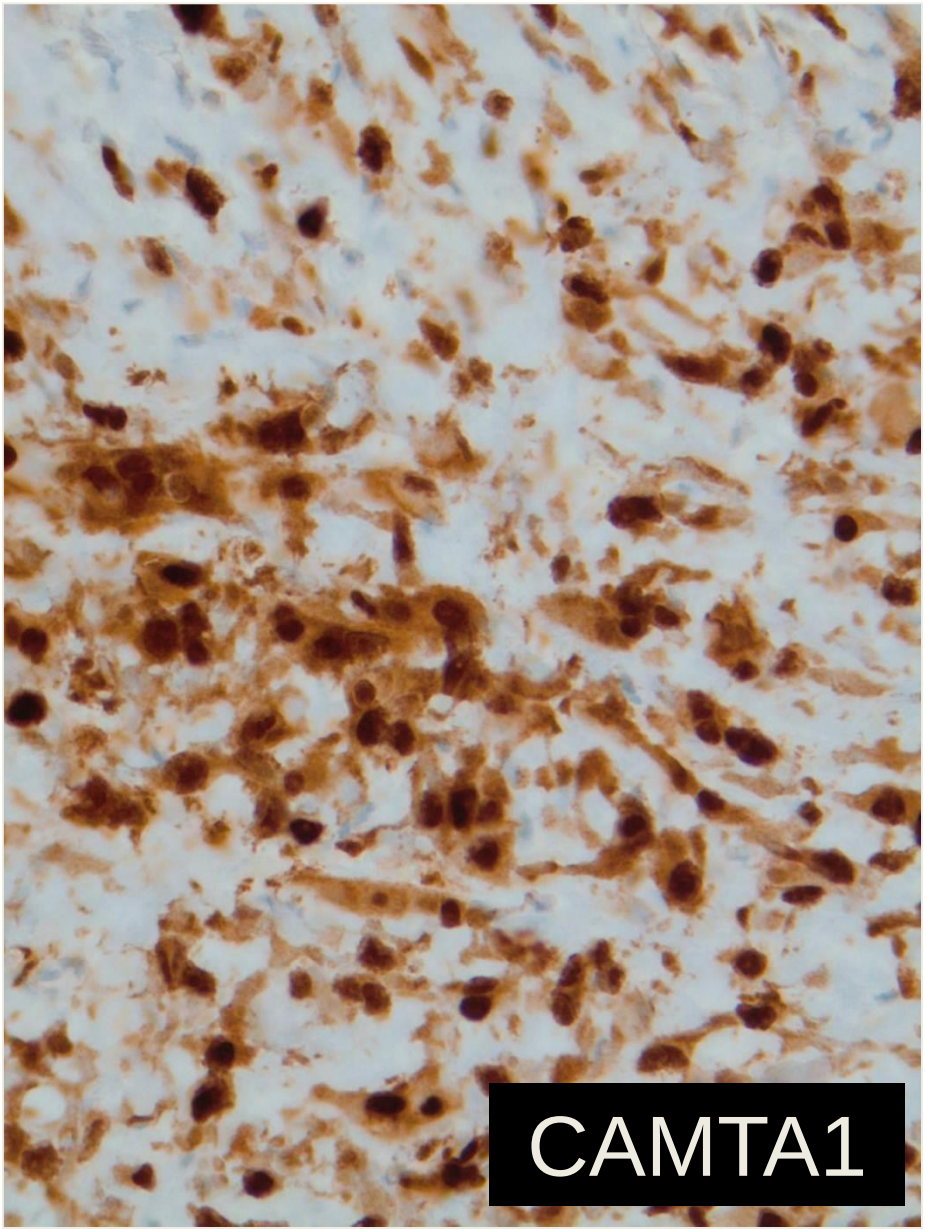
CAMTA1 IHC sensitive and specific for EHE





Novel *YAP1-TFE3* Fusion Defines a Distinct Subset of Epithelioid Hemangioendothelioma

Cristina R. Antonescu,[1*] Francois Le Loarer,[1] Juan-Miguel Mosquera,[2] Andrea Sboner,[2,3] Lei Zhang,[1] Chun-Liang Chen,[1] Hsiao-Wei Chen,[1] Nursat Pathan,[4] Thomas Krausz,[5] Brendan C. Dickson,[6] Ilan Weinreb,[7] Mark A. Rubin,[2] Meera Hameed,[1] and Christopher D. M. Fletcher[8*]

Genes , Chromosomes & Cancer 52:775-784 (2013)

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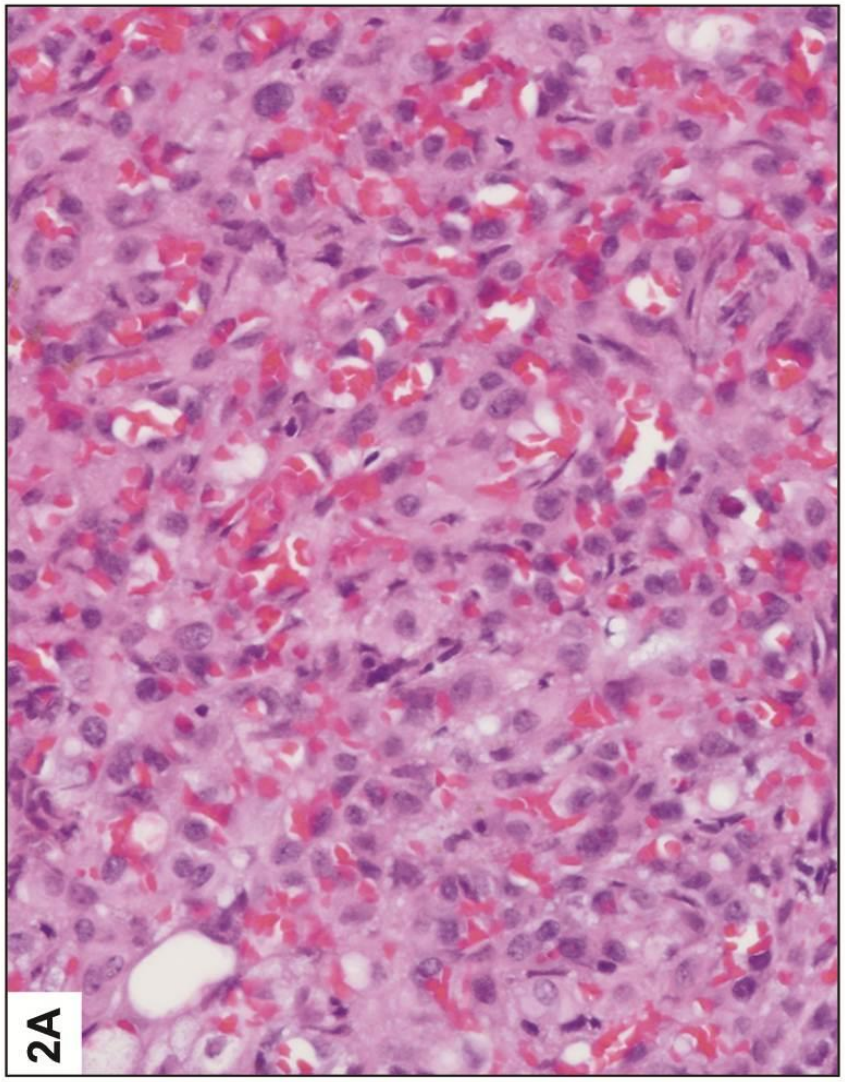
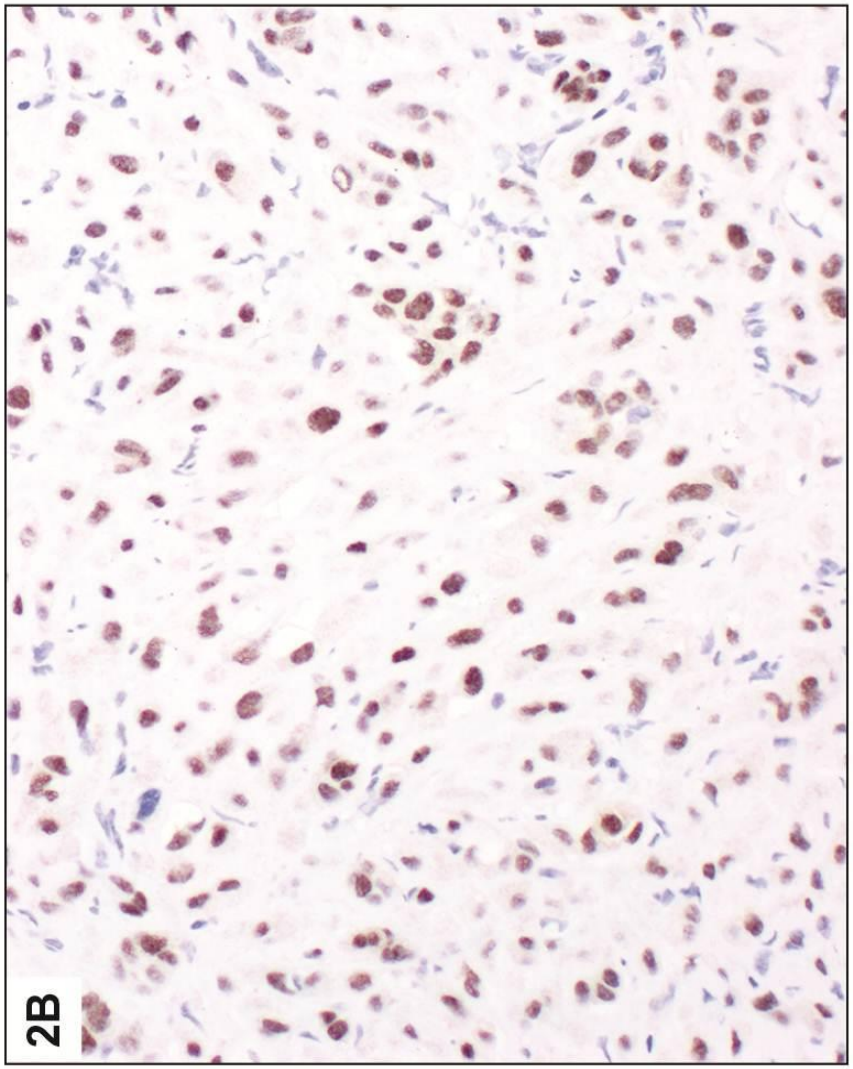
Example of *YAP1-TFE3* "EHE"
Not EHE

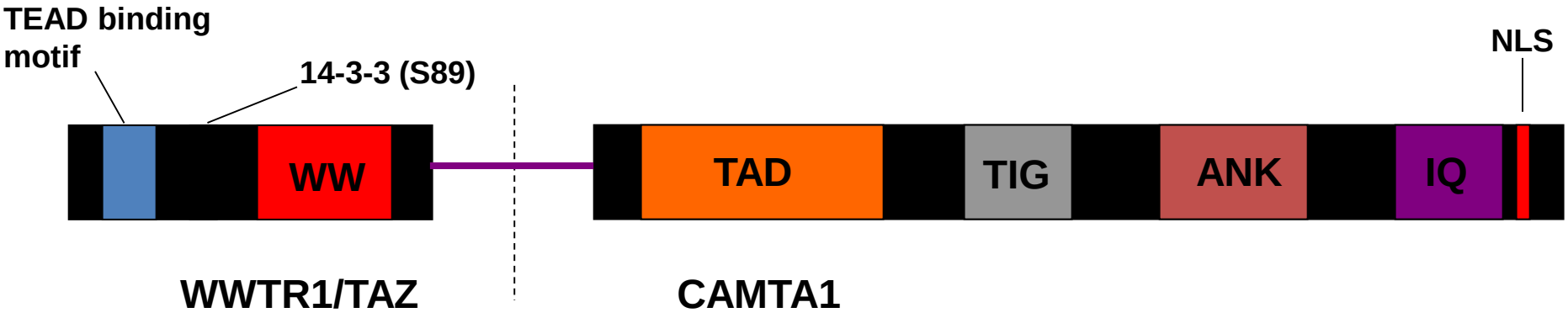
Well-formed vascular structures



TFE3 IHC



Composition of WWTR1(TAZ)/CAMTA1 fusion protein (W/C)



- 1595 Amino Acids (173 kDa)
- 90% of fusion protein is CAMTA1
- Key features
  - TEAD binding motif mediates DNA binding
  - Transcriptional activating domain of CAMTA1 replaces TAD of WWTR1

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Modeling EHE in vitro

Cell types:

HUVECs

Immortalized HUVECs

Immortalized human fibroblasts

Human mammary epithelial cells

MCF10A

HEK293

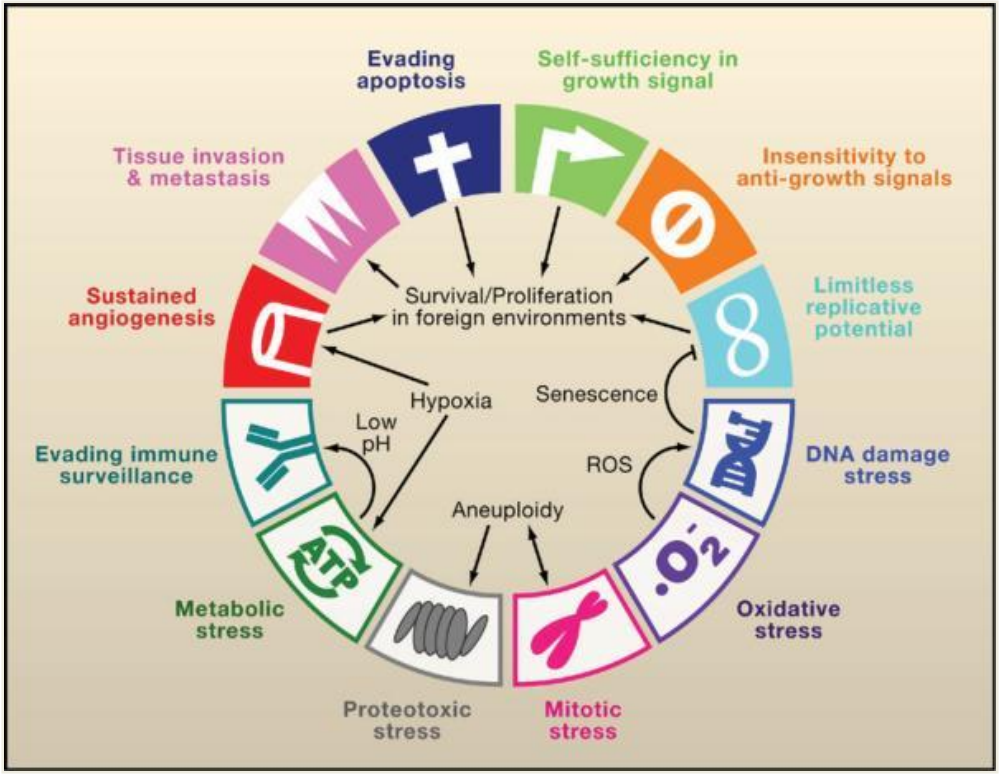
NIH-3T3 cells

Assays:

Proliferation

Anchorage independent growth

Migration/Invasion



Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. Cell 144(5):646-74 (2011).

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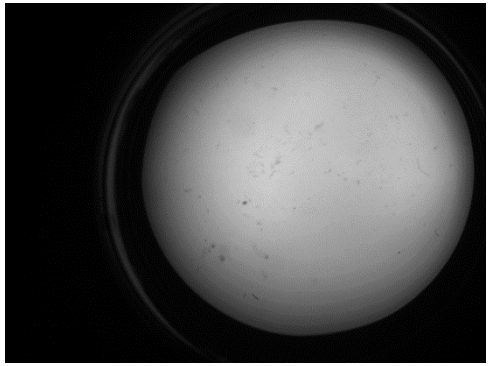
WC causes NIH-3T3 cells to grow in soft agar

Empty Vector



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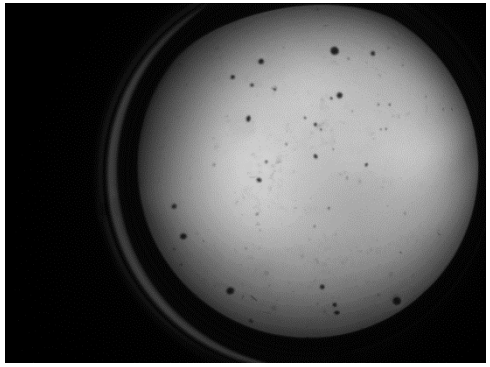
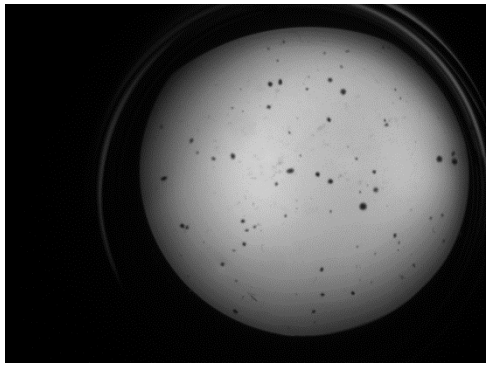
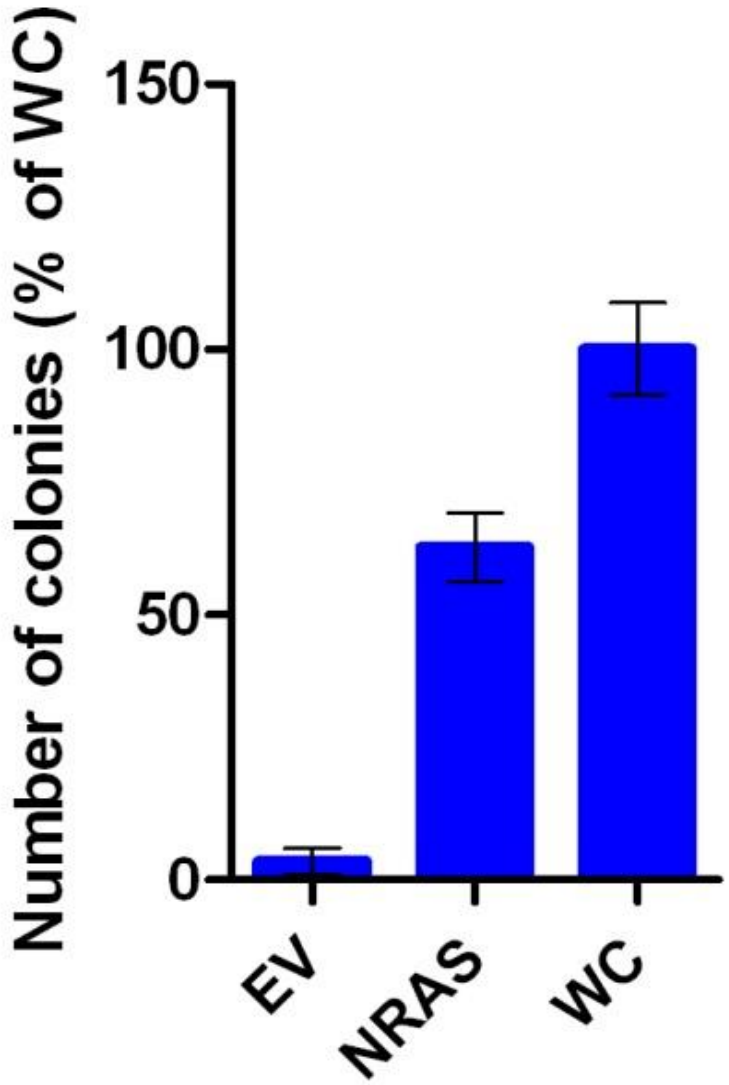
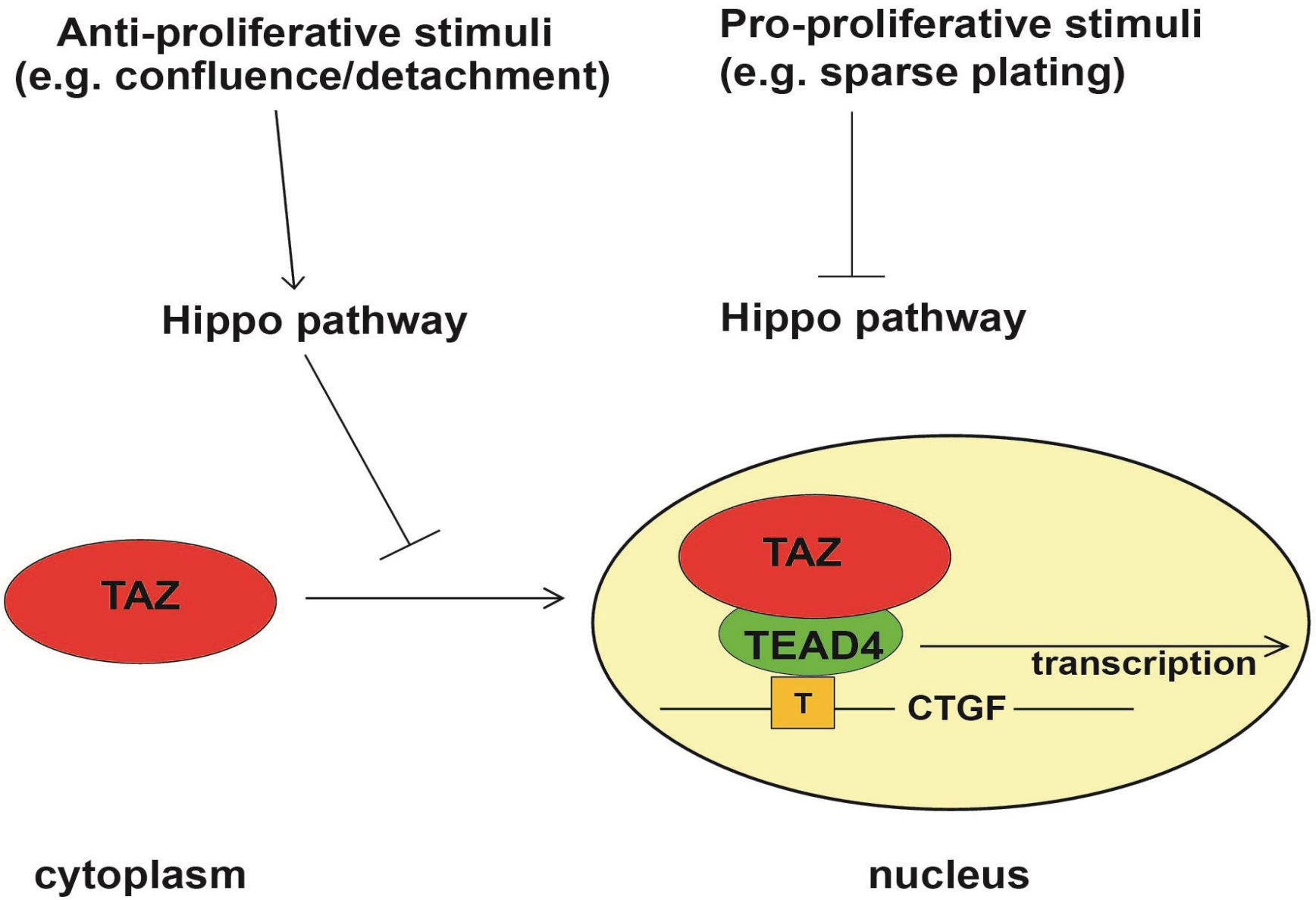


WC

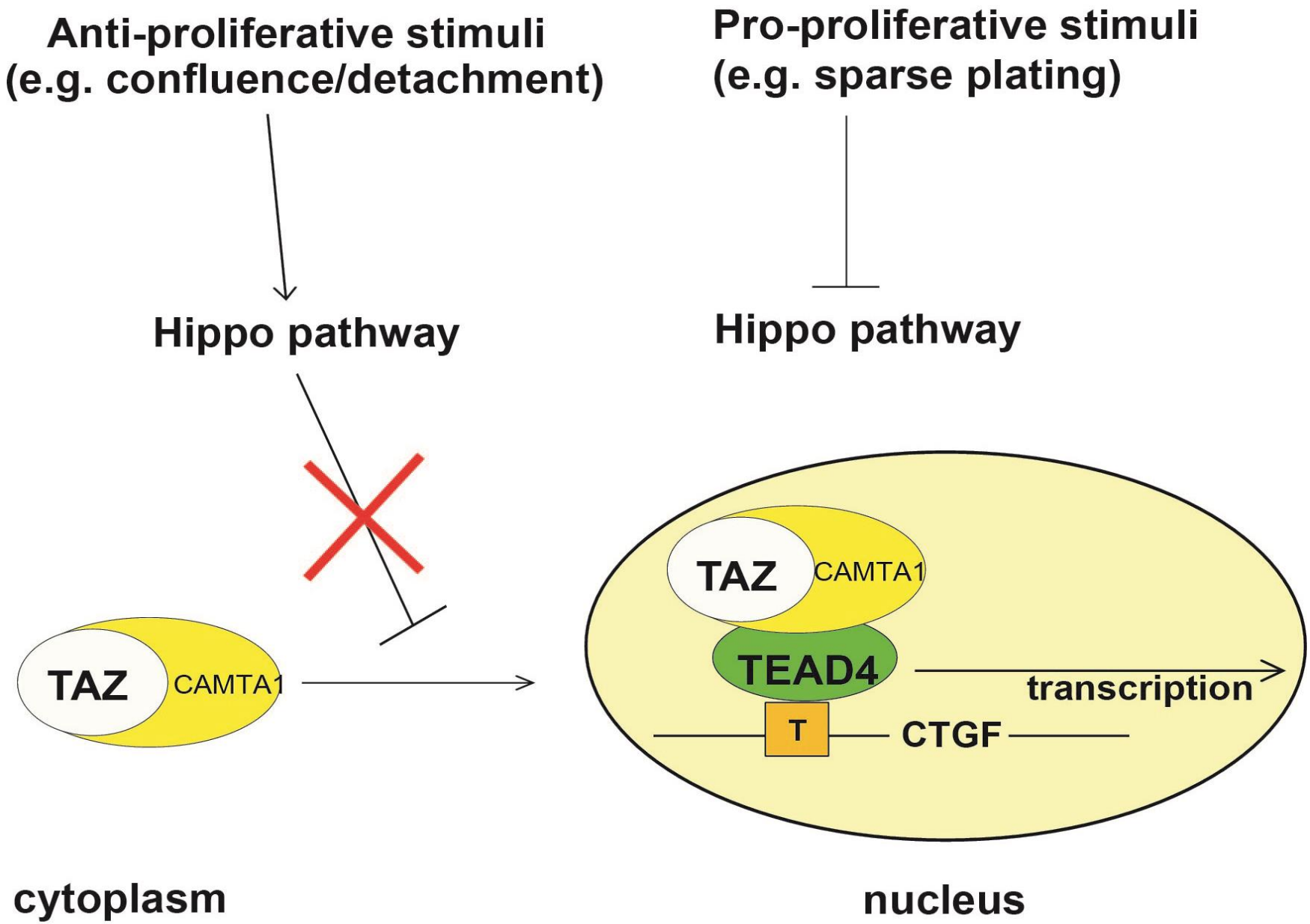




A working model of TC function



A working model of TC function



Lack of standard therapies for EHE

- Surgery and XRT used consistently
- Liver transplantation
- 2 responses and 4 SD in 7 patients treated with bevacizumab (phase II study)
- 2 PRs lasting 2 and 9 mos in 15 pts with sorafenib (phase II study)
- Case report responses with sunitinib and pazopanib
- Interferon, celecoxib, and thalidomide also have shown activity

Sirolimus for EHE

- Sirolimus in retrospective analysis of 18 patients showed 1 PR lasting > 3yrs, 12 SDs (75%) and 3 PDs.
- Minor tumor shrinkage in 4 cases
- Interval progression in 4/4 cases after stop and stabilization after re-challenge
- Median progression free survival was 12 months
- Four patients progression-free at 24 months
- Median OS was 16 months
- 7 patients had increased pleural and/or peritoneal effusions – 6 died at 1-8 months – only 2/7 had PD by RECIST!

Stacchiotti et al. *Ann Surg Oncol* 2016

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Treatment Recommendations

Major scenarios:

1. Isolated resectable lesion
   - Surgery and follow-up – staging
2. Isolated unresectable lesion
   - Follow for 3 months – serial CT - staging
   - If no growth continue to follow with CT
   - If growing then xrt/chemo - ? Sirolimus
3. Asymptomatic metastatic disease
   - Follow for 3 months – serial CT
   - If no growth continue to follow with CT
   - If growing then surgery/xrt/chemo
4. Symptomatic metastatic disease
   - Surgery/xrt/chemo - ? Sirolimus

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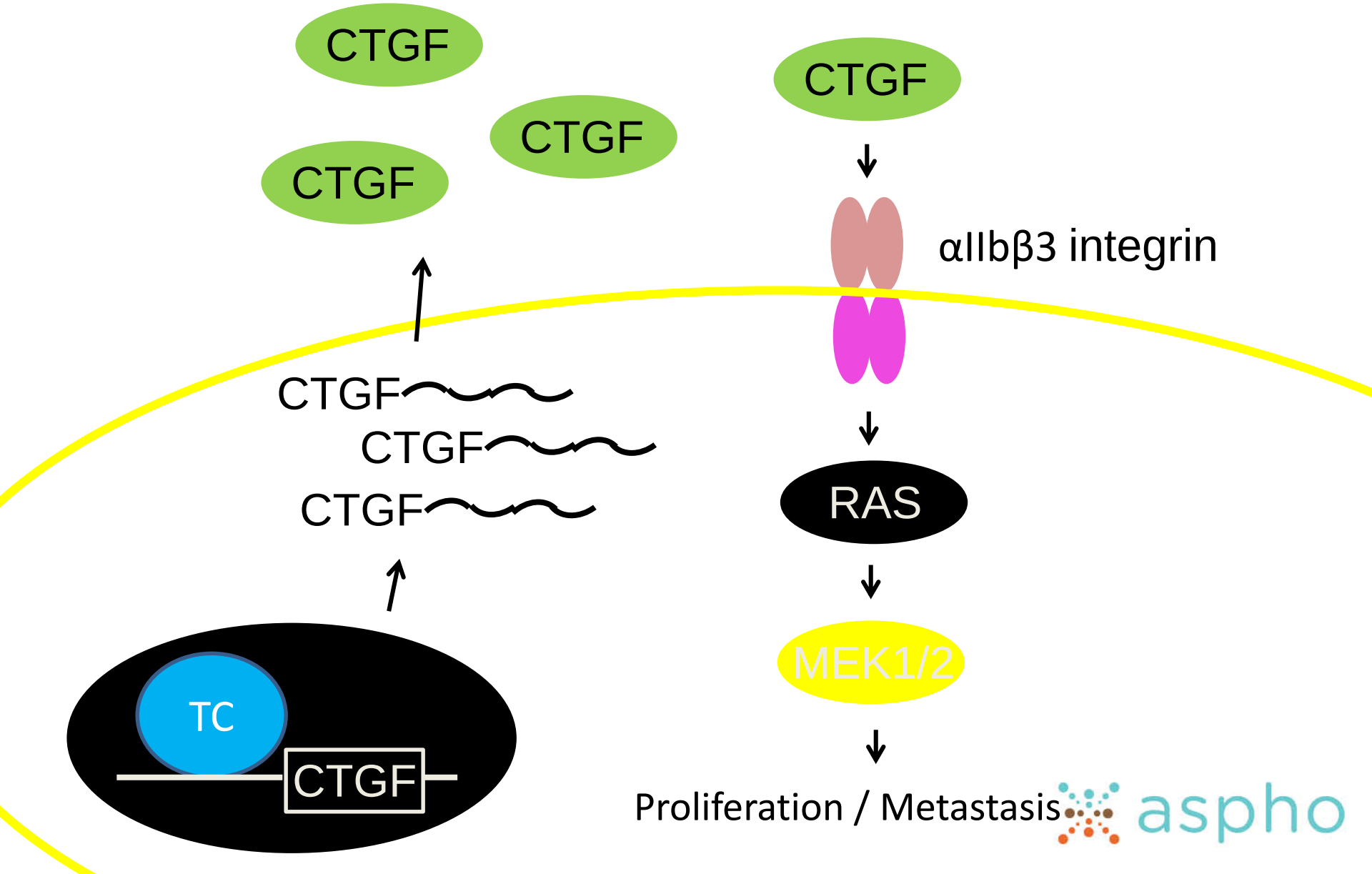
Molecular dissection of TC signaling



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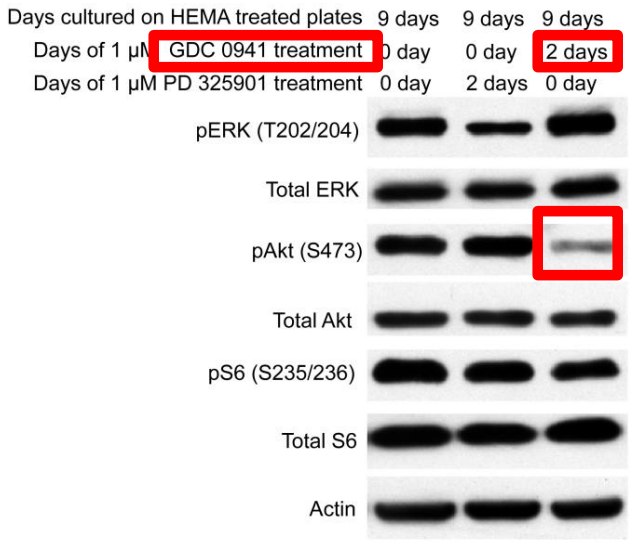
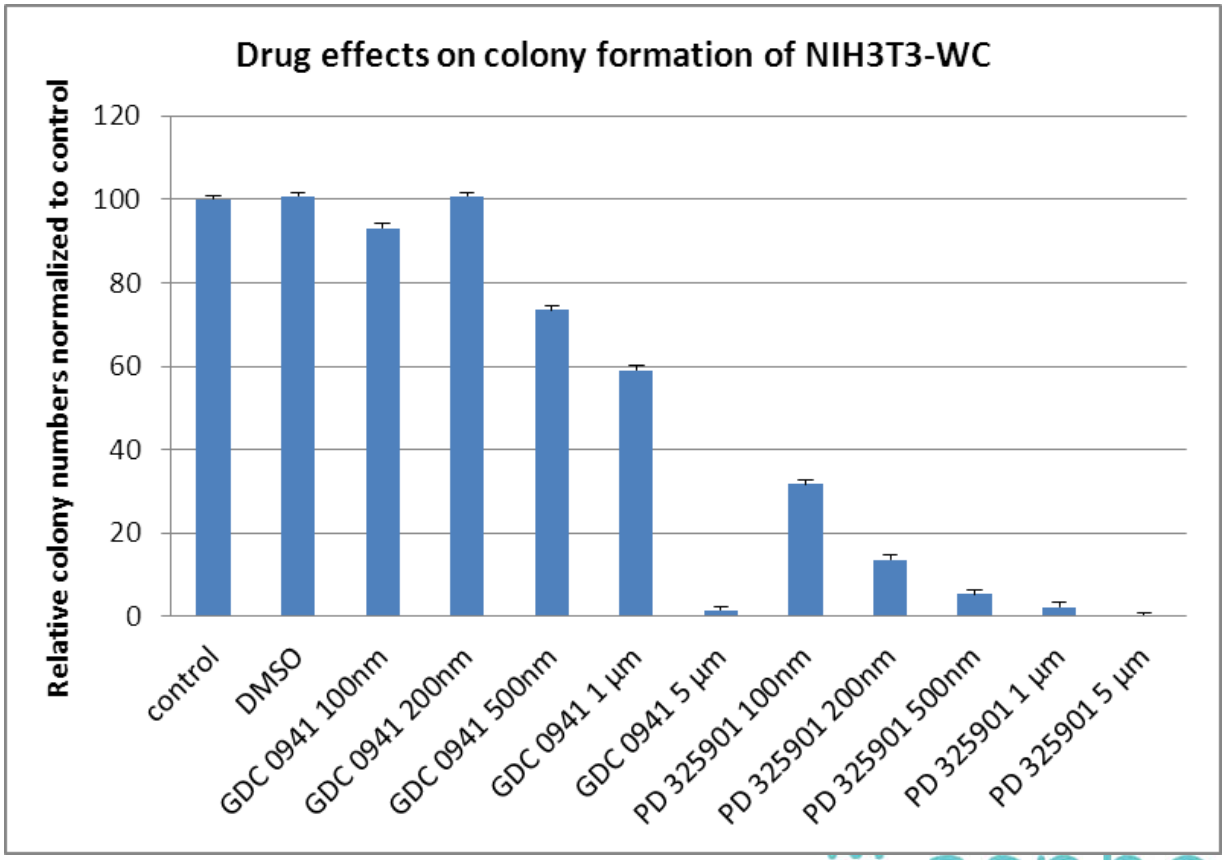
MEK but not PI3K inhibition interferes with colony formation in soft agar

GDC 0941: PI3K inhibitor, selectively binds to PI3K isoforms inhibiting the production of PIP3

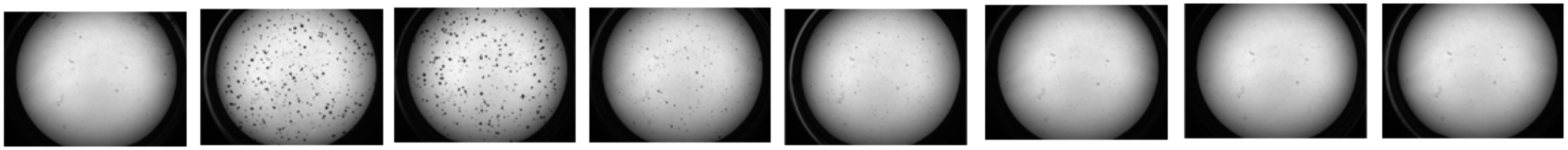
PD 325901: MEK1/2 inhibitor

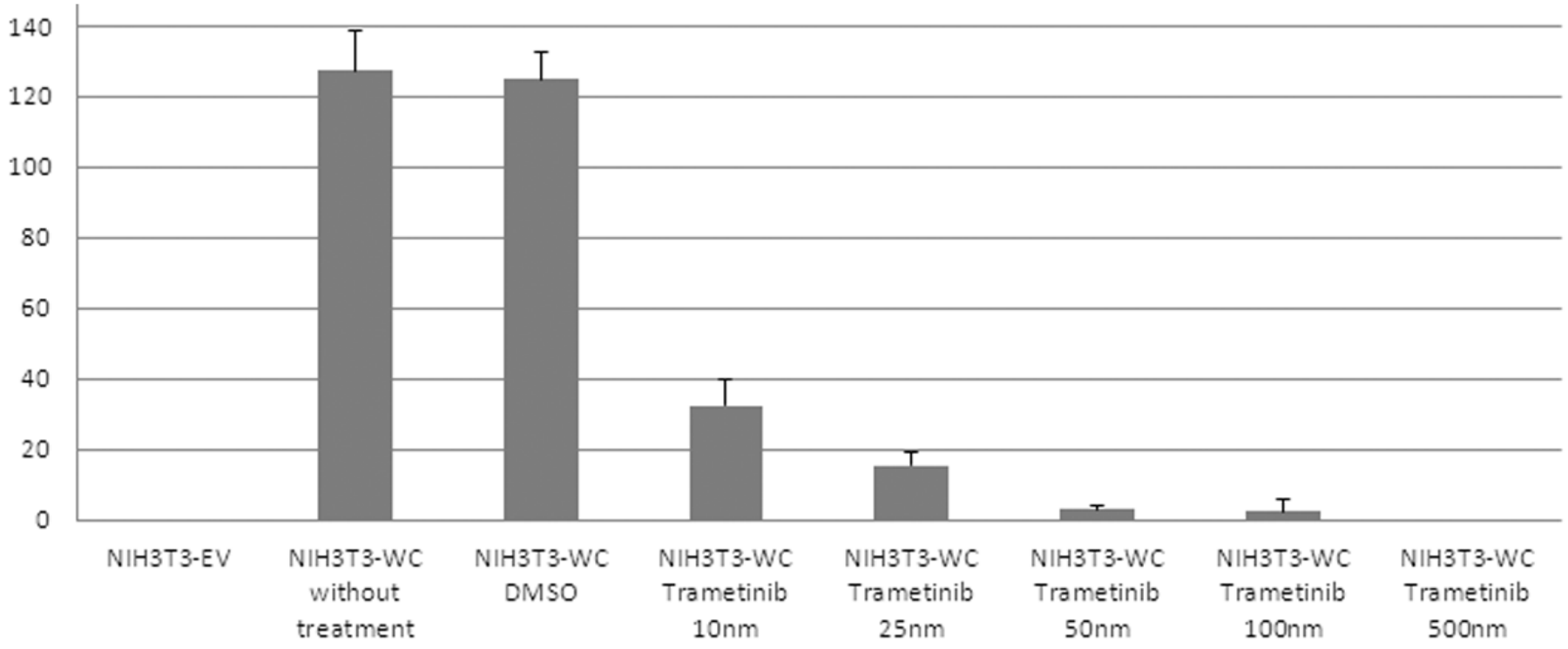




Trametinib interferes with colony formation in soft agar

Trametinib : MEK1/2 inhibitor





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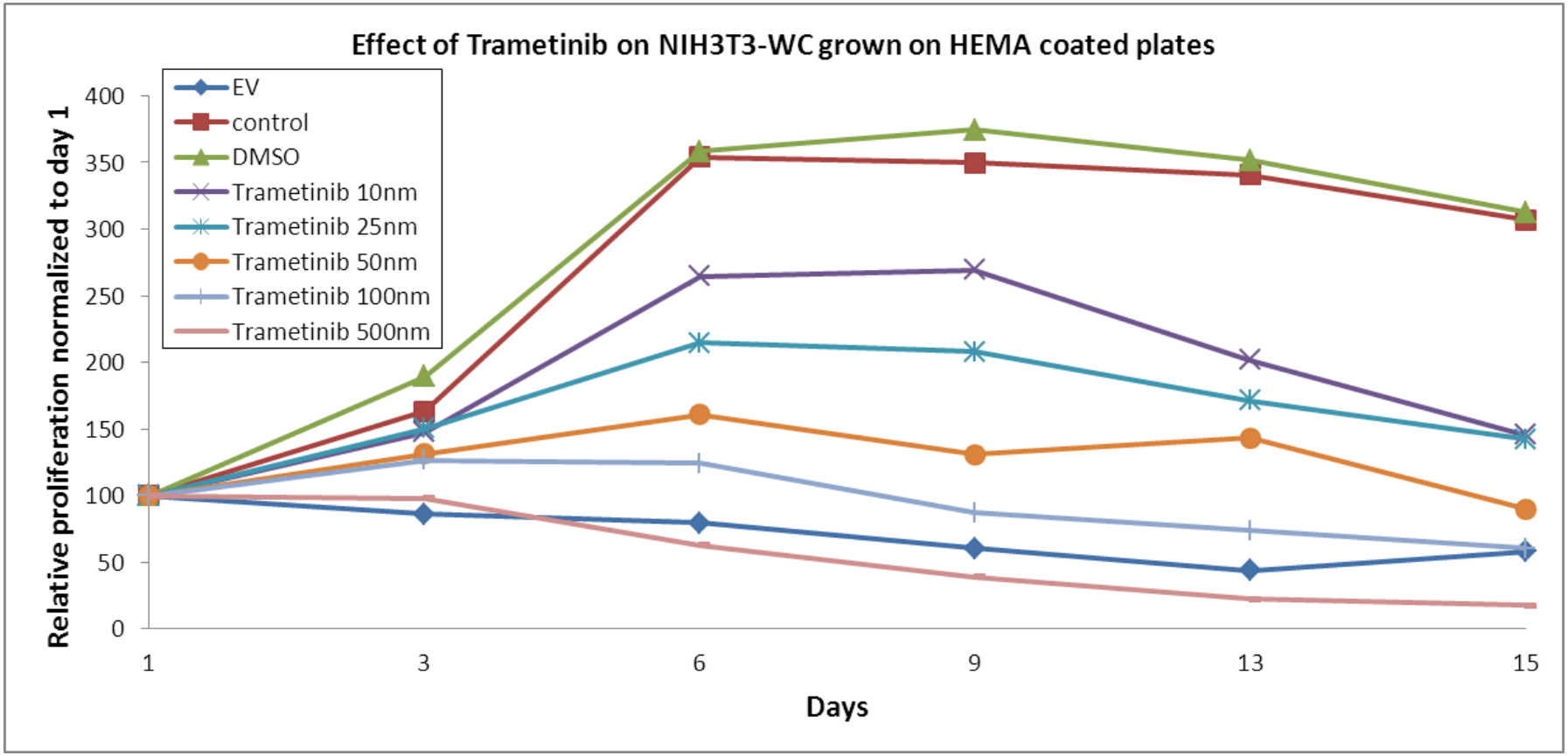
Trametinib inhibits anchorage-independent growth



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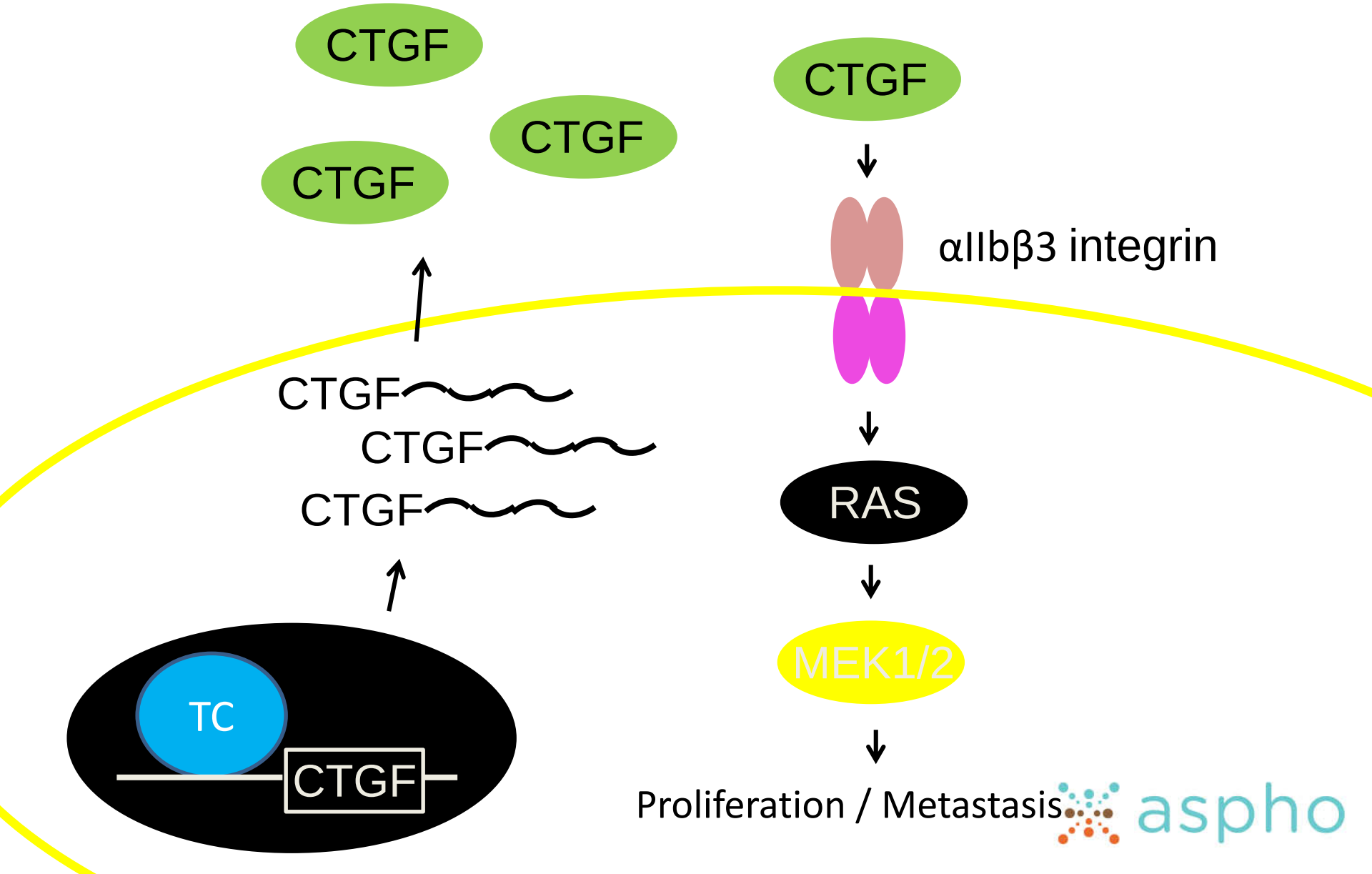
Molecular dissection of TC signaling



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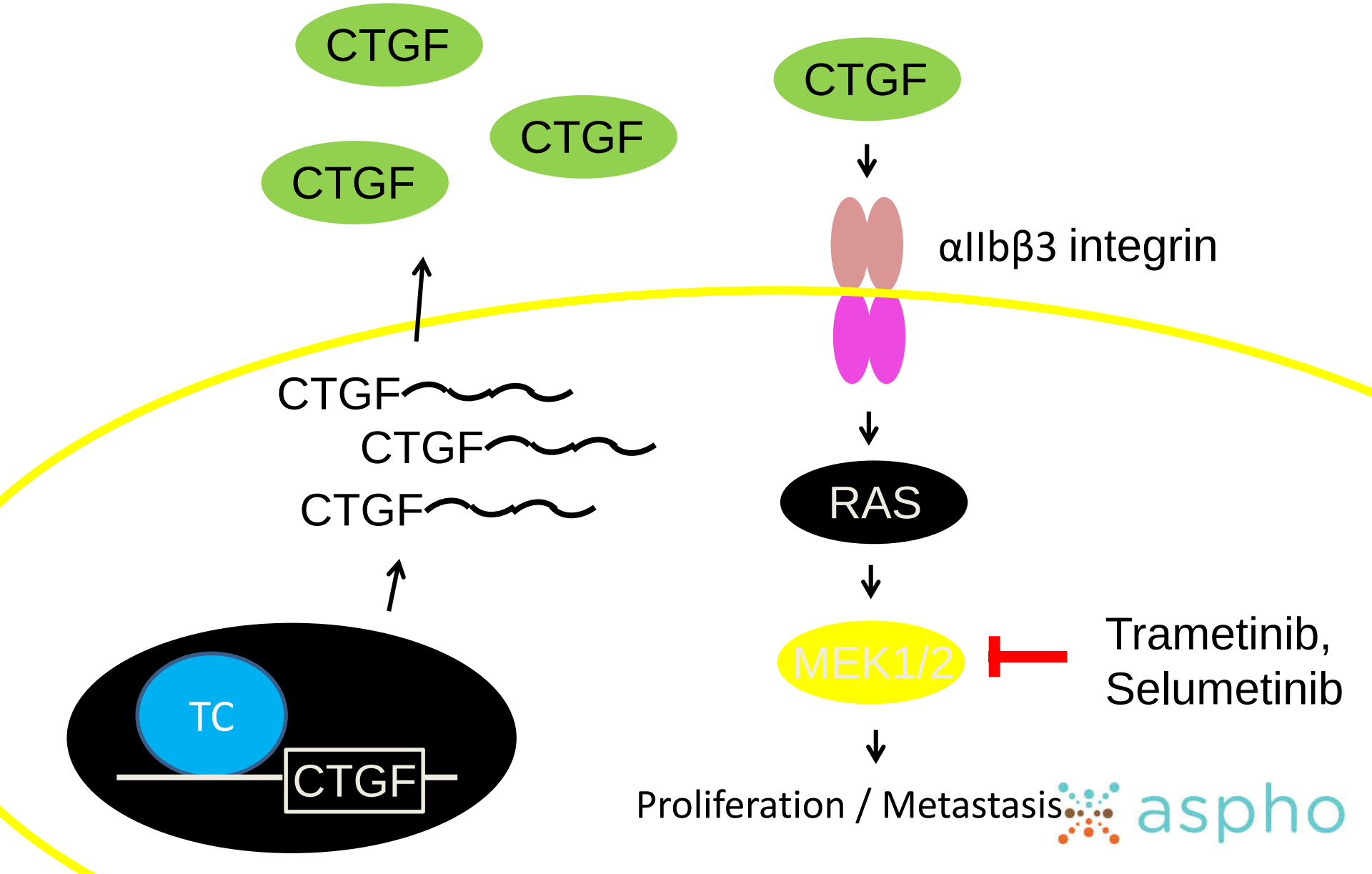
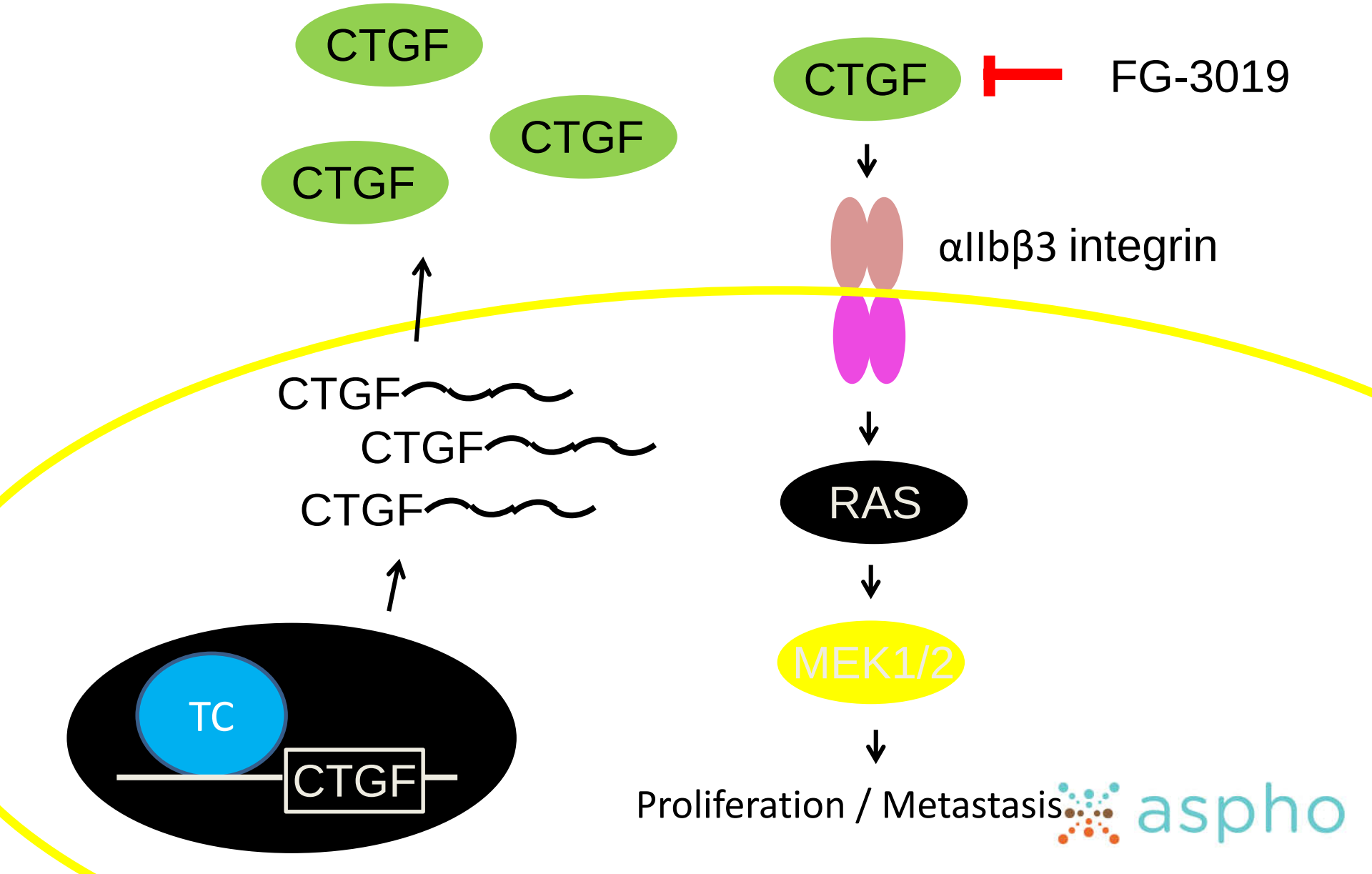
Molecular dissection of TC signaling



Molecular dissection of TC signaling



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Ashley Kendig

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The EHE Foundation
CRAVAT
National Cancer Institute
SARC Sarcoma Spore
The Liddy Shriver Sarcoma Initiative


Cure EHE

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