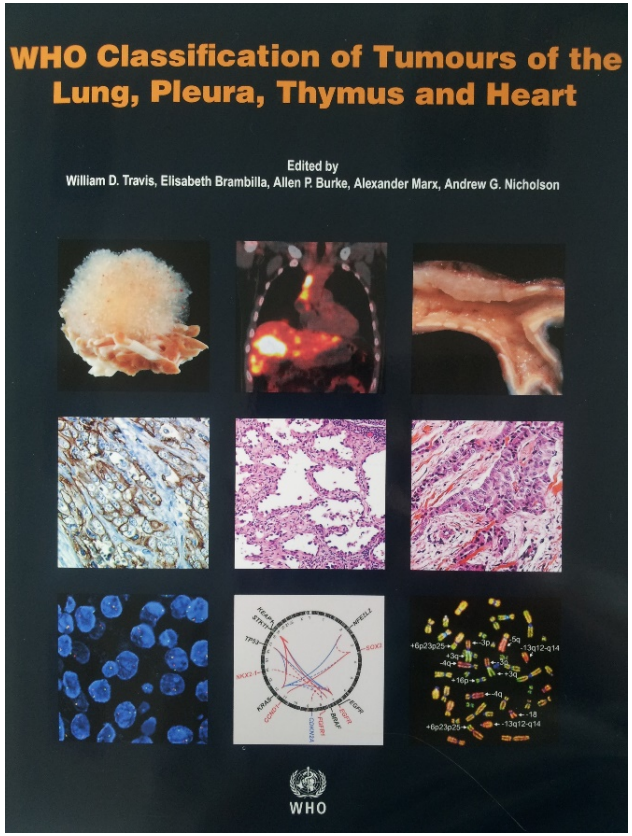
Update of the WHO Classification of Thymic Epithelial Tumors

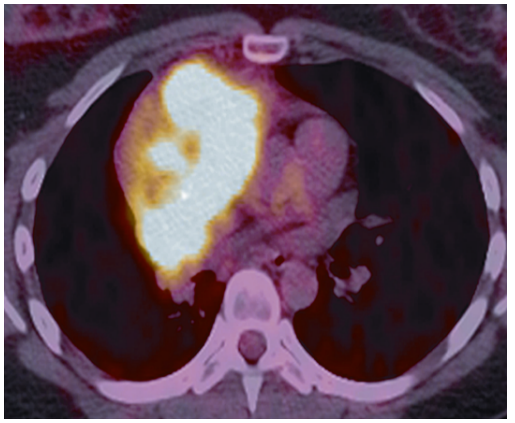


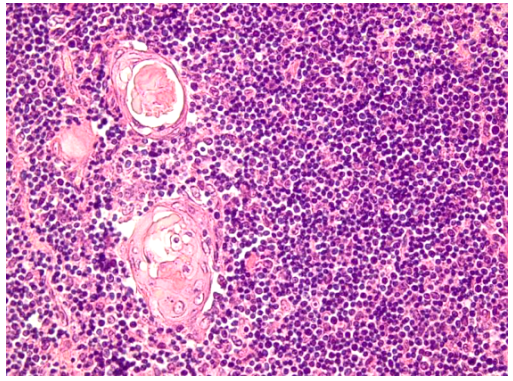
Alexander Marx

Institute of Pathology

University Medical Centre Mannheim

University of Heidelberg





Norddeutsche Bronchialkarzinom Arbeitsgruppe e.V.
Hamburg, 23.06.2017

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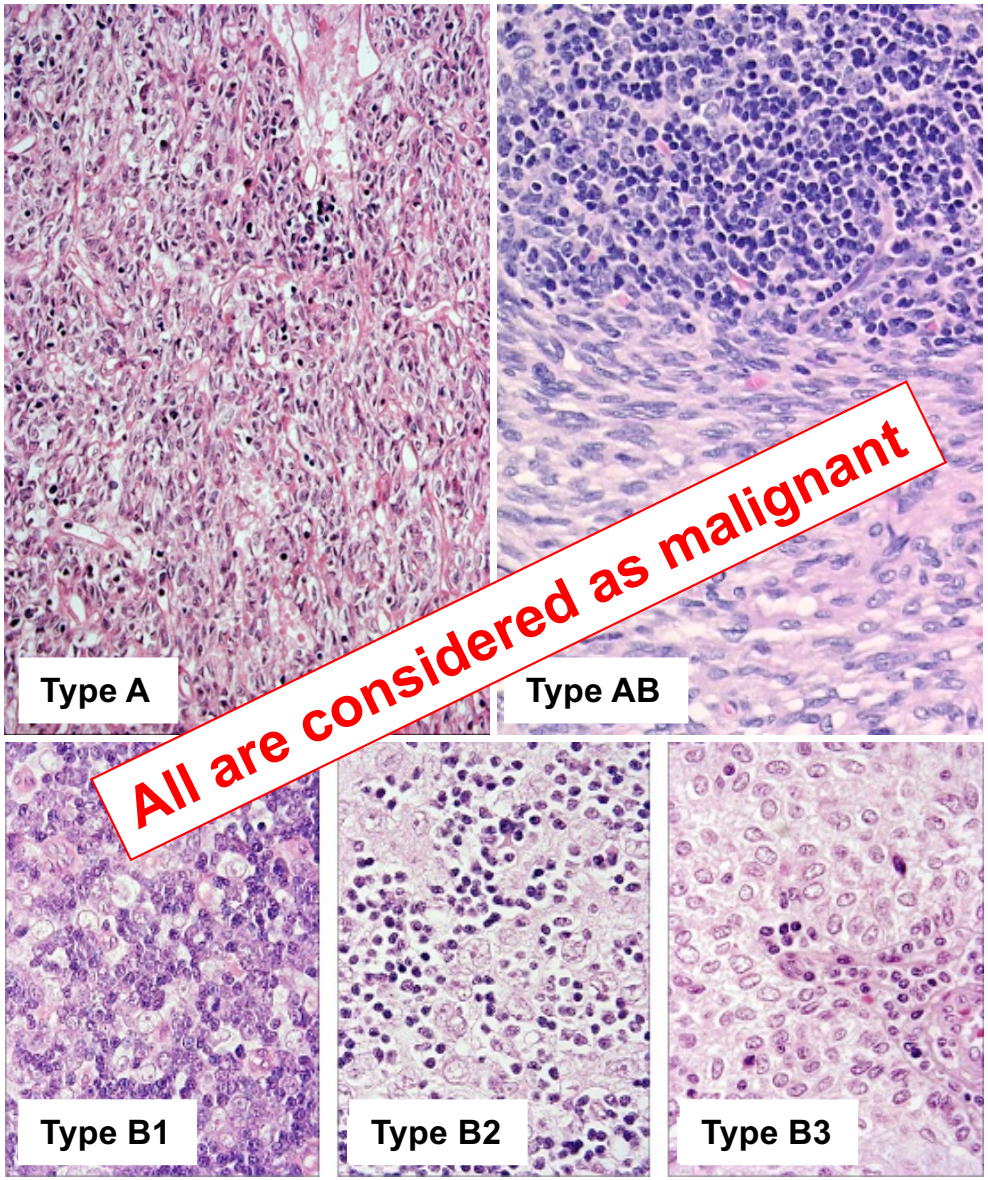
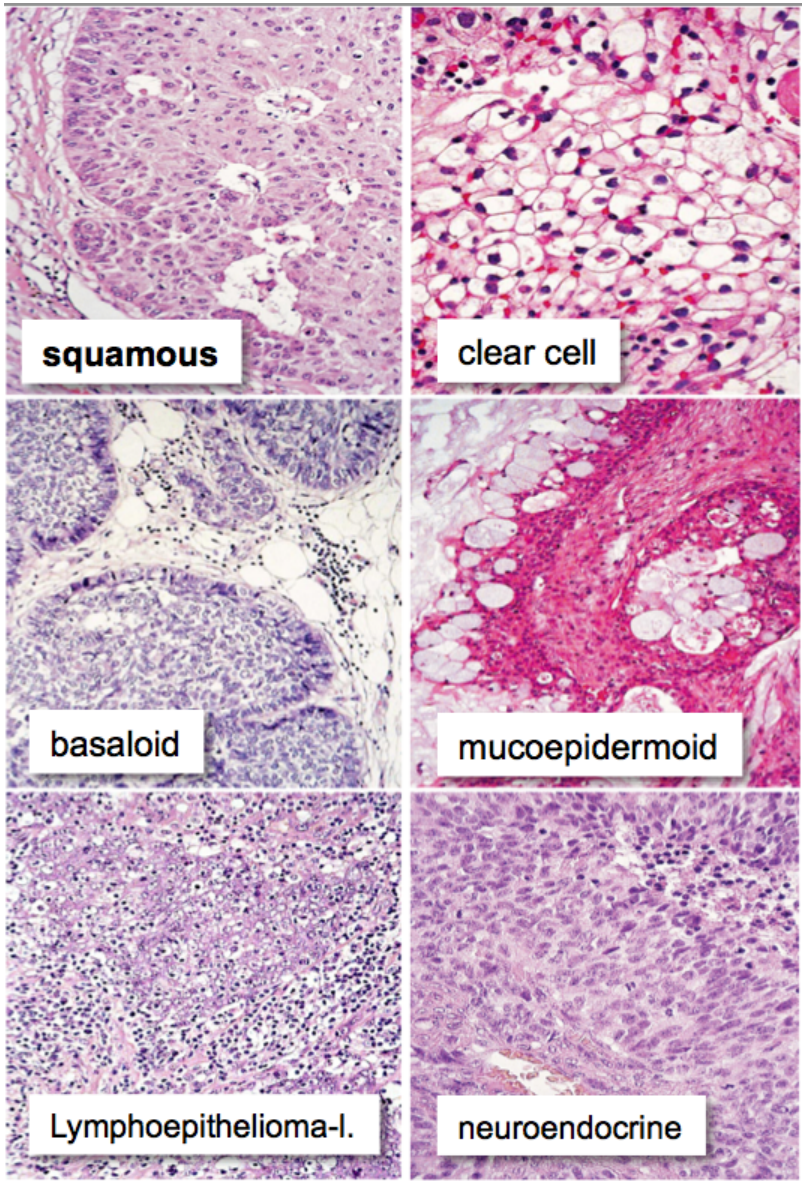
Conceptual change #1: Type A – B3 and metaplastic thymomas are now considered as malignant tumors – relevance for ICD-O codes

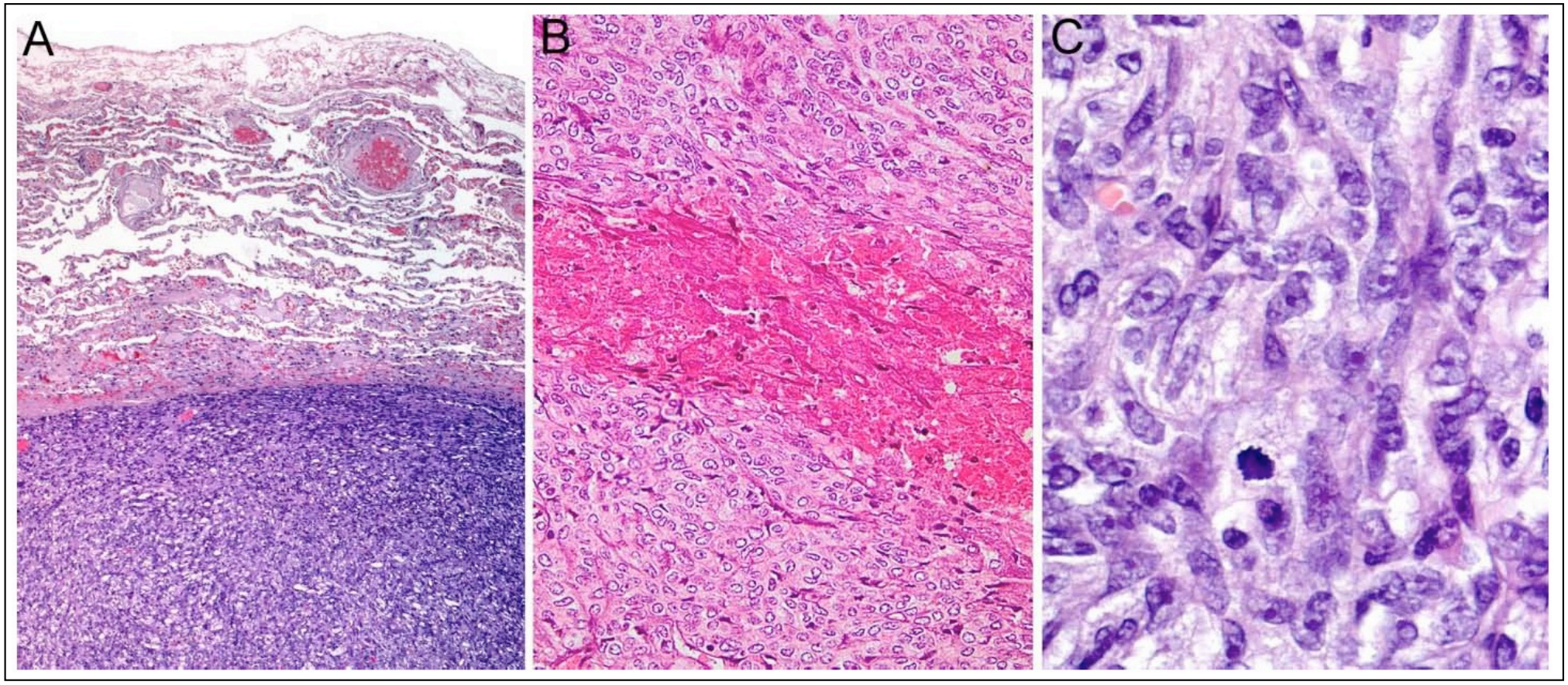
Thymomas

Thymic carcinomas / NETs





Atypical type A (and AB) thymoma: new aggressive variants

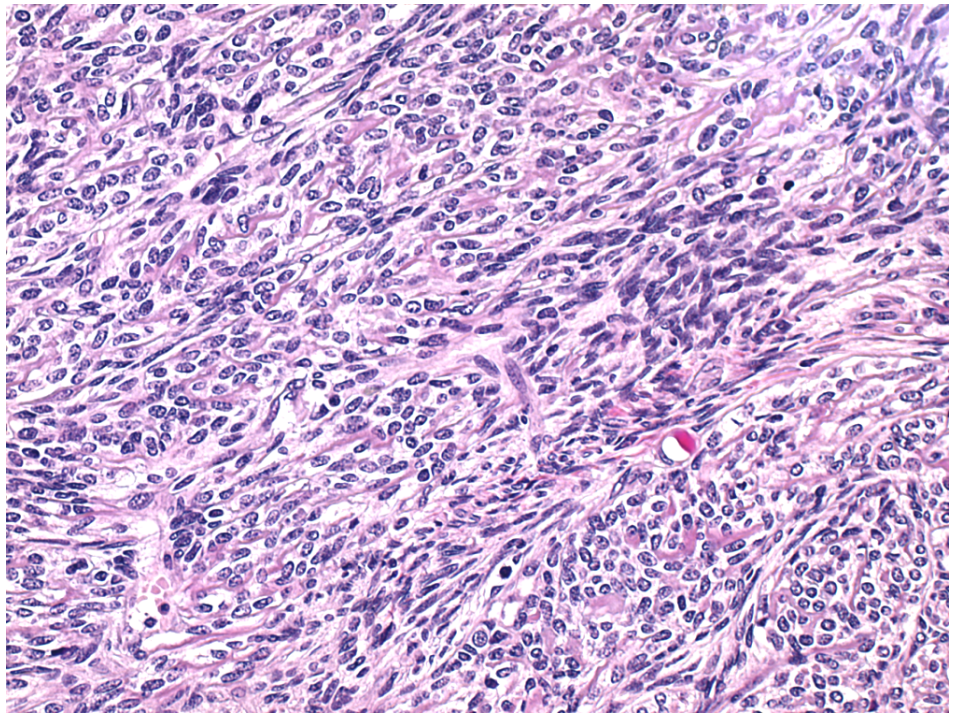


Nonaka and Rosai AJSP 36(6): 889, 2012
Vladislav IT Mod Pathol 26(8):1059, 2013
Green et al Histopathol 66(6);884, 2015

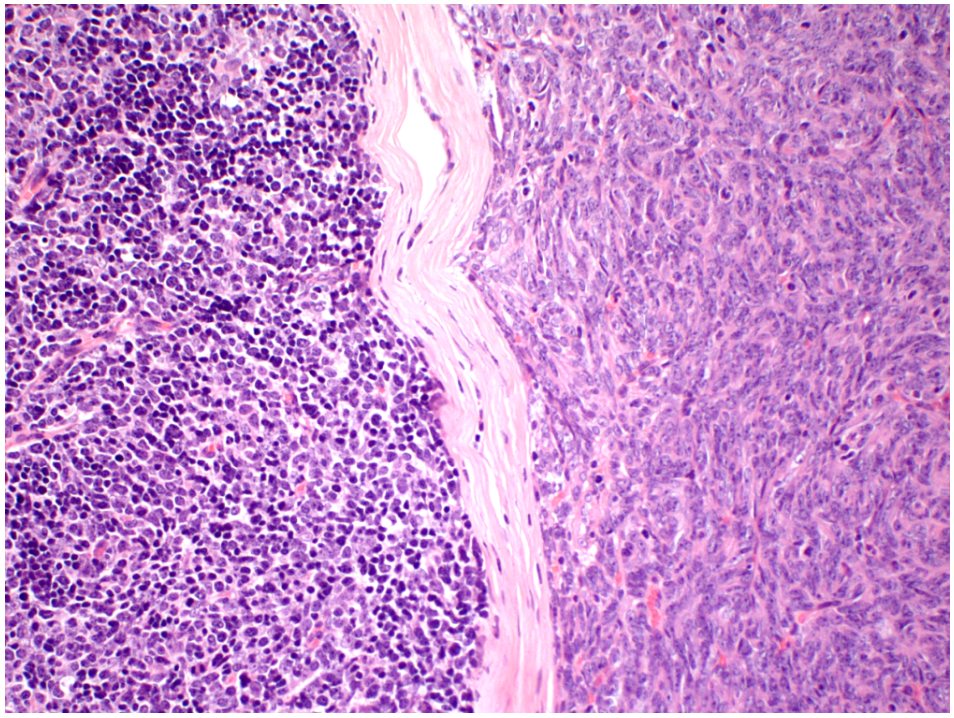
Necrosis is the best marker of clinical aggressiveness

Conceptual change #2: Obligatory and optional criteria

Classical Type A Thymoma



Classical Type AB Thymoma



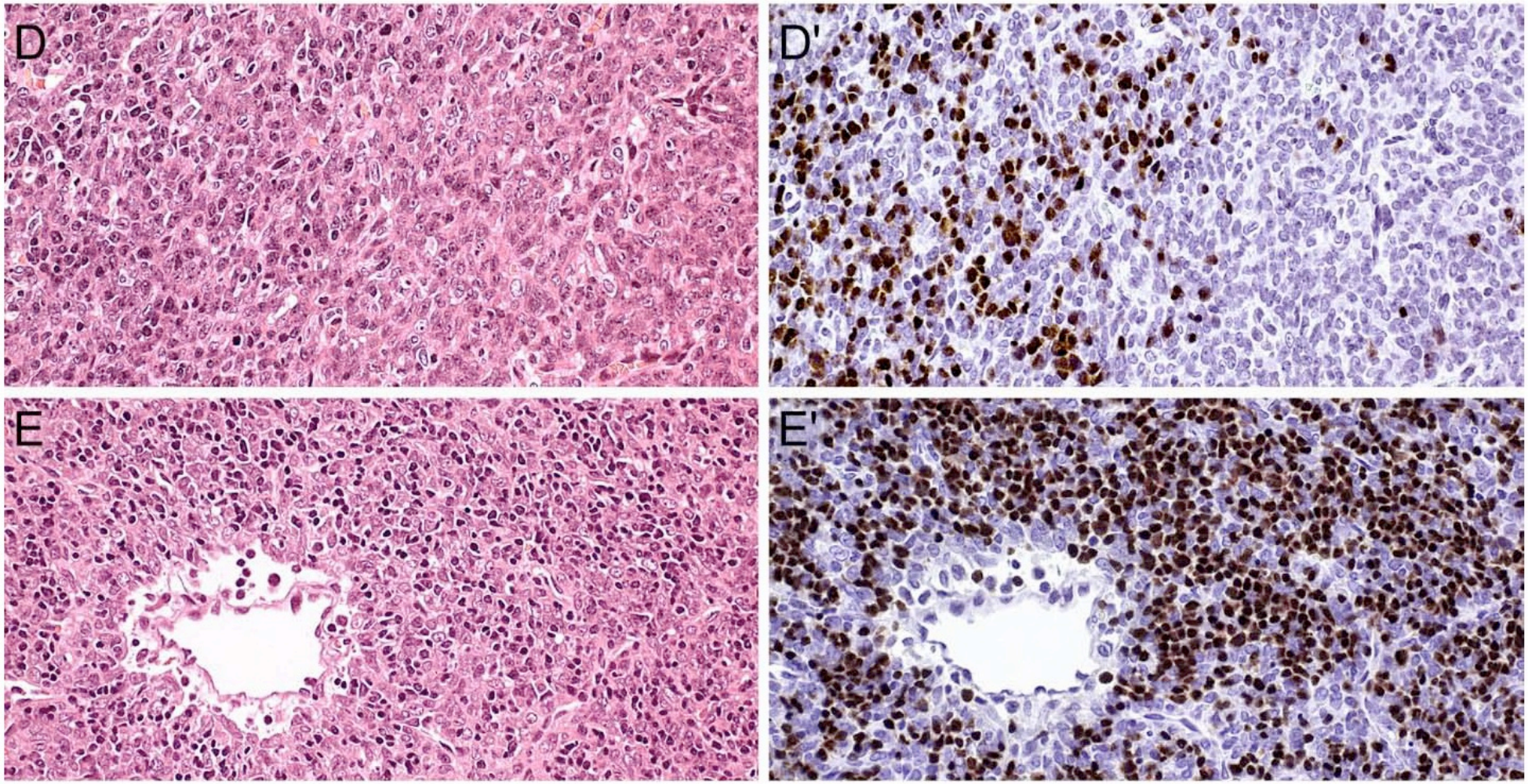
	Classical Type A Thymoma	Classical Type AB Thymoma
Obligatory:	Spindle cells (focally) present	Spindle cells (focally) present
	Paucity of lymphocytes	Abundance of lymphocytes
Optional:	Polygonal epithelial cells	Polygonal epithelial cells

Conceptual change #3: Introduction of immunohistochemistry

Moderate no. of TdT+ T cells

Type A if in 0-10% of tumor area

Type AB if in >10% of tumor area



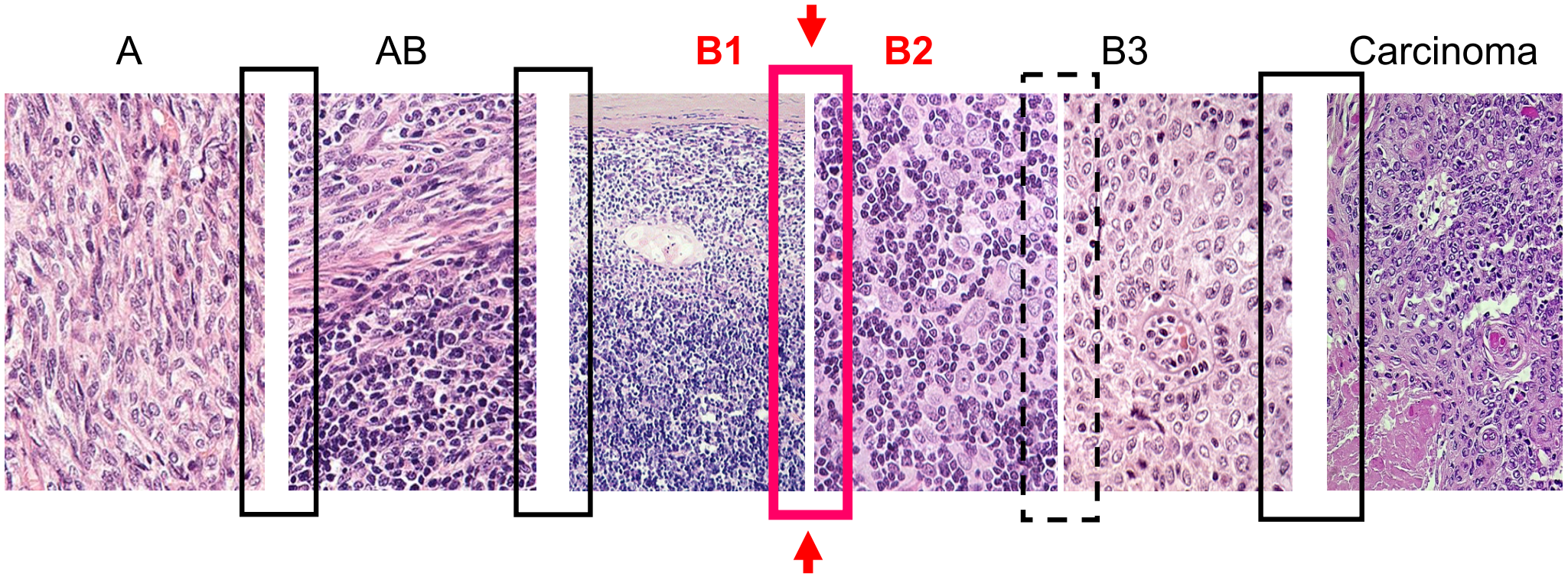
„Crowded“ TdT+ cells exclude diagnosis of type A thymoma

→ Diagnosis: Type AB thymoma

Difficult but relevant separation of B1 from B2 thymoma

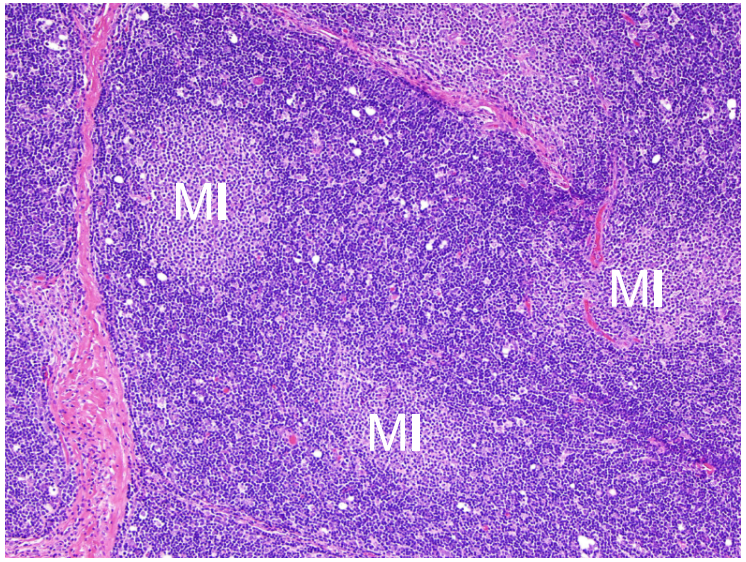
Reported relative incidence of B1 compared to B2: 0.3 to 3.0

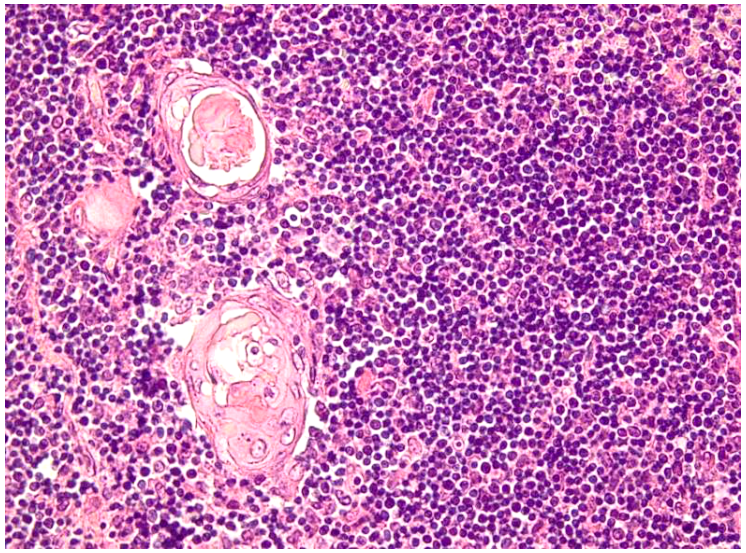
Indolent clinical course **Aggressive clinical course**



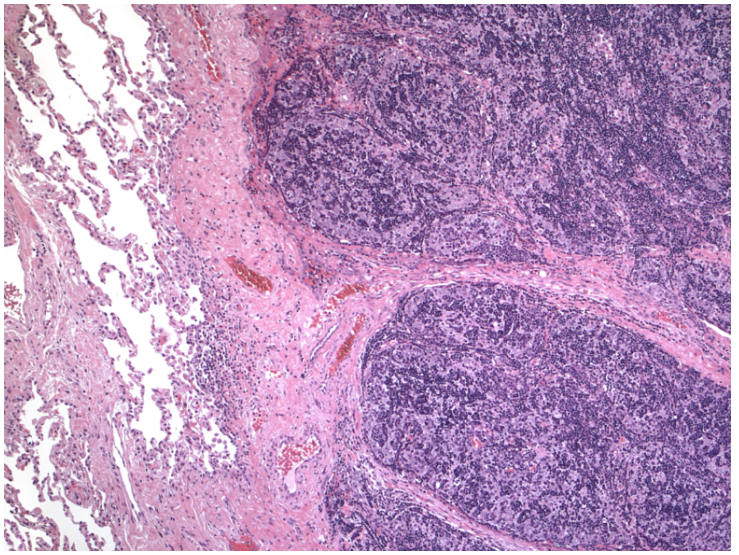
Cortex-/medulla-specific IHC markers (b5t, PRSS16, Claudin 4, CD40, Aire)

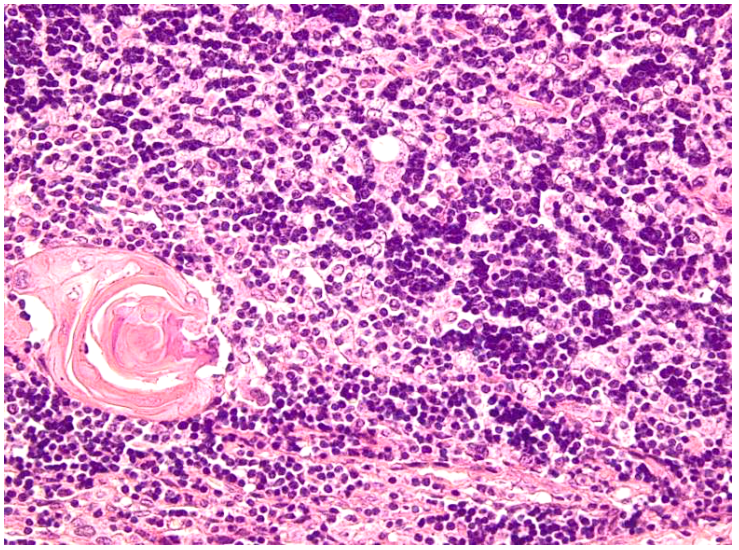
Classical Type B1





Classical Type B2

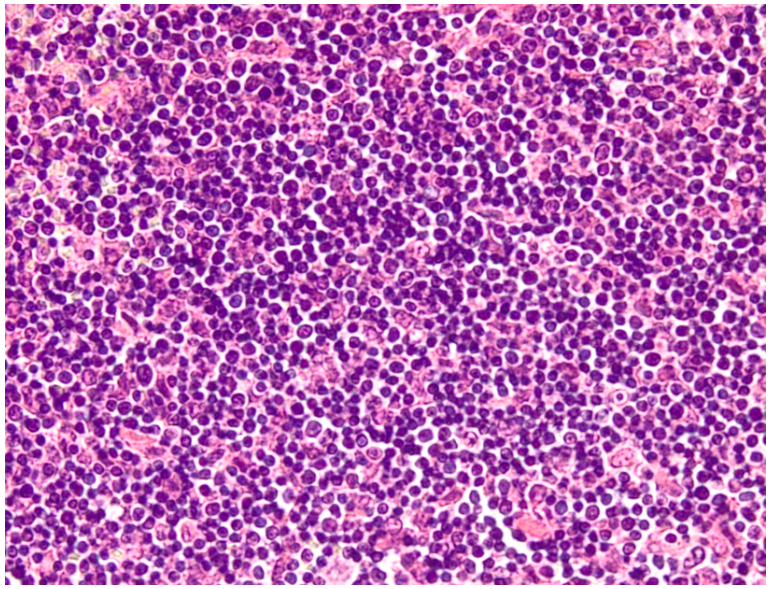


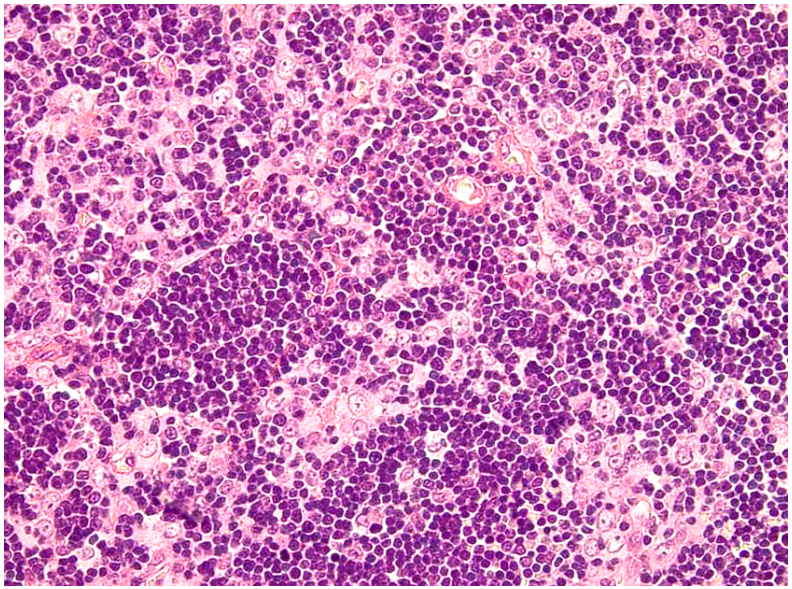


Organoid architecture:	Obligatory	Optional
Medullary islands (MI):	Obligatory	Optional
Hassall‘s corpuscles:	Optional	Optional

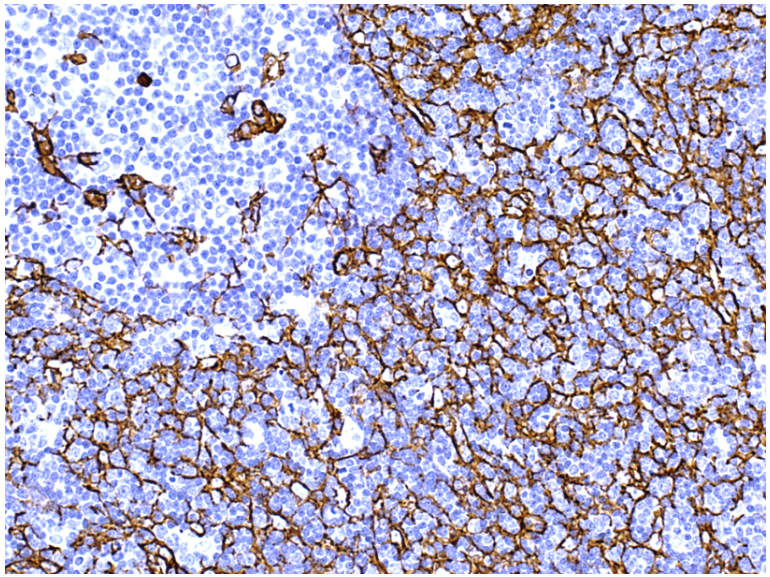
Classical Type B1

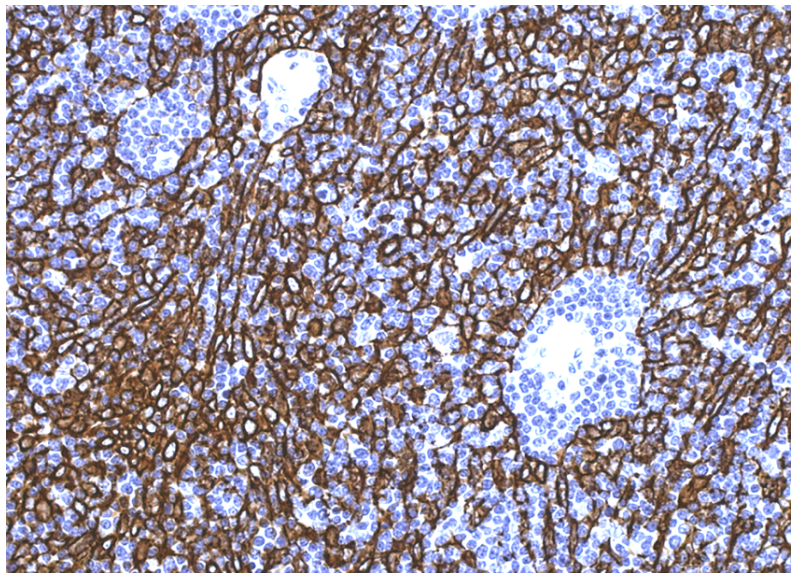
Classical Type B2





CK19

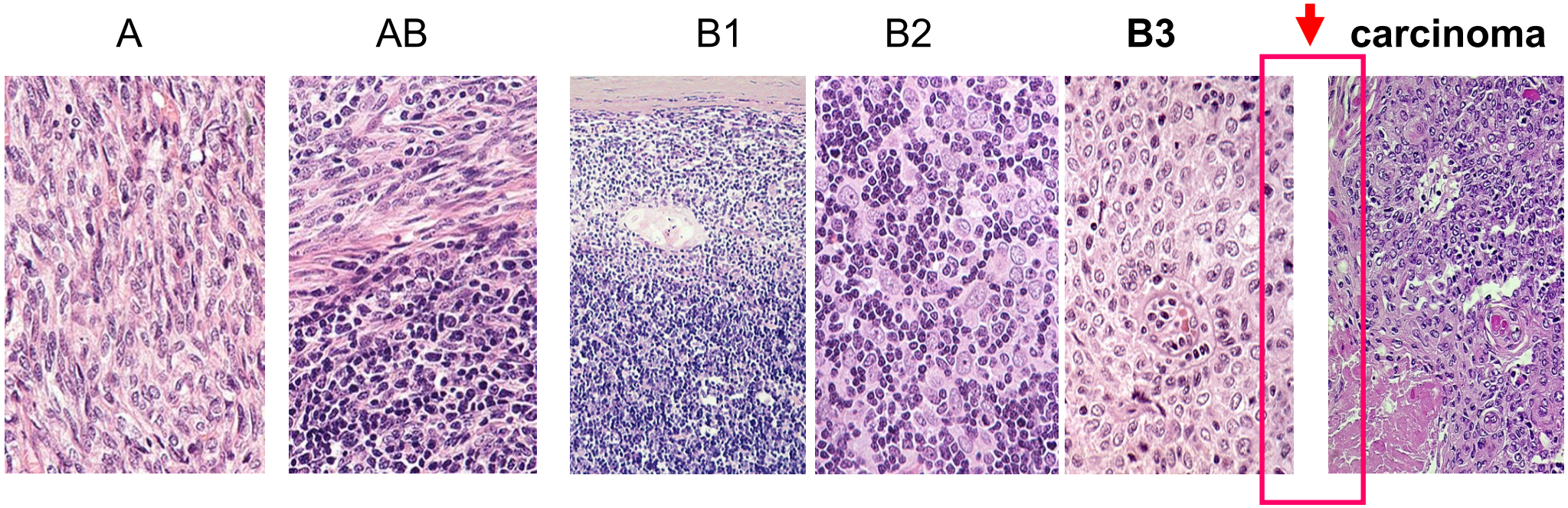




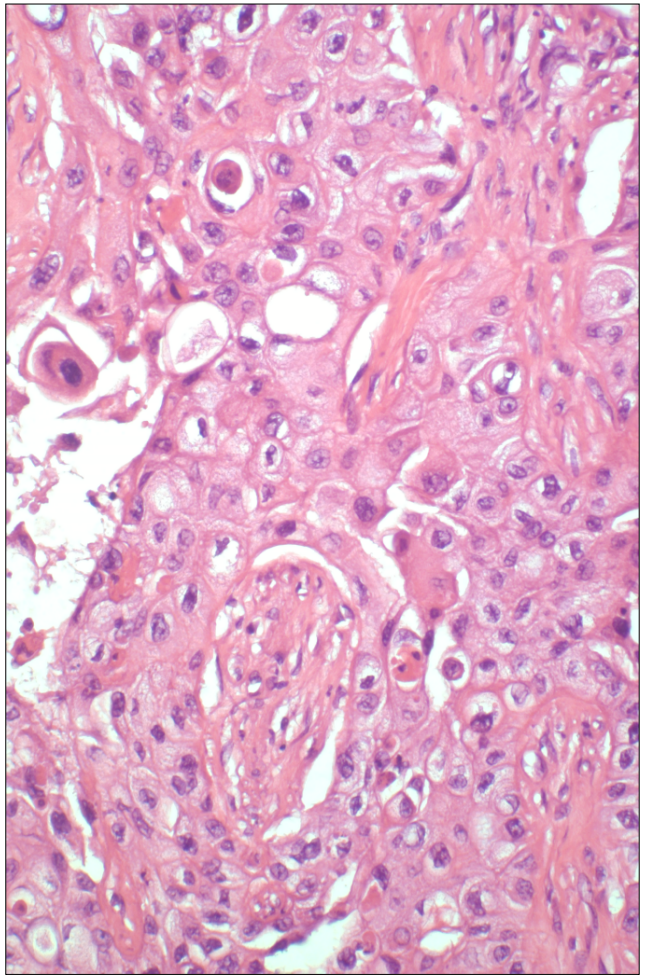
Epithelial cell content:	Pediatric thymus-like	Increased
Epithelial cell clusters:	None (obligatory)	Optional

The distinction between type B3 thymomas and thymic carcinomas is relevant for „targeted therapies" with RTK, angiogenesis, immune checkpoint inhibitors…

---	CD117	++/-
---	CD5	++/-
heterogeneous	Glut-1	homog.
+/-	TdT	---/+



However… Conceptual Change #4



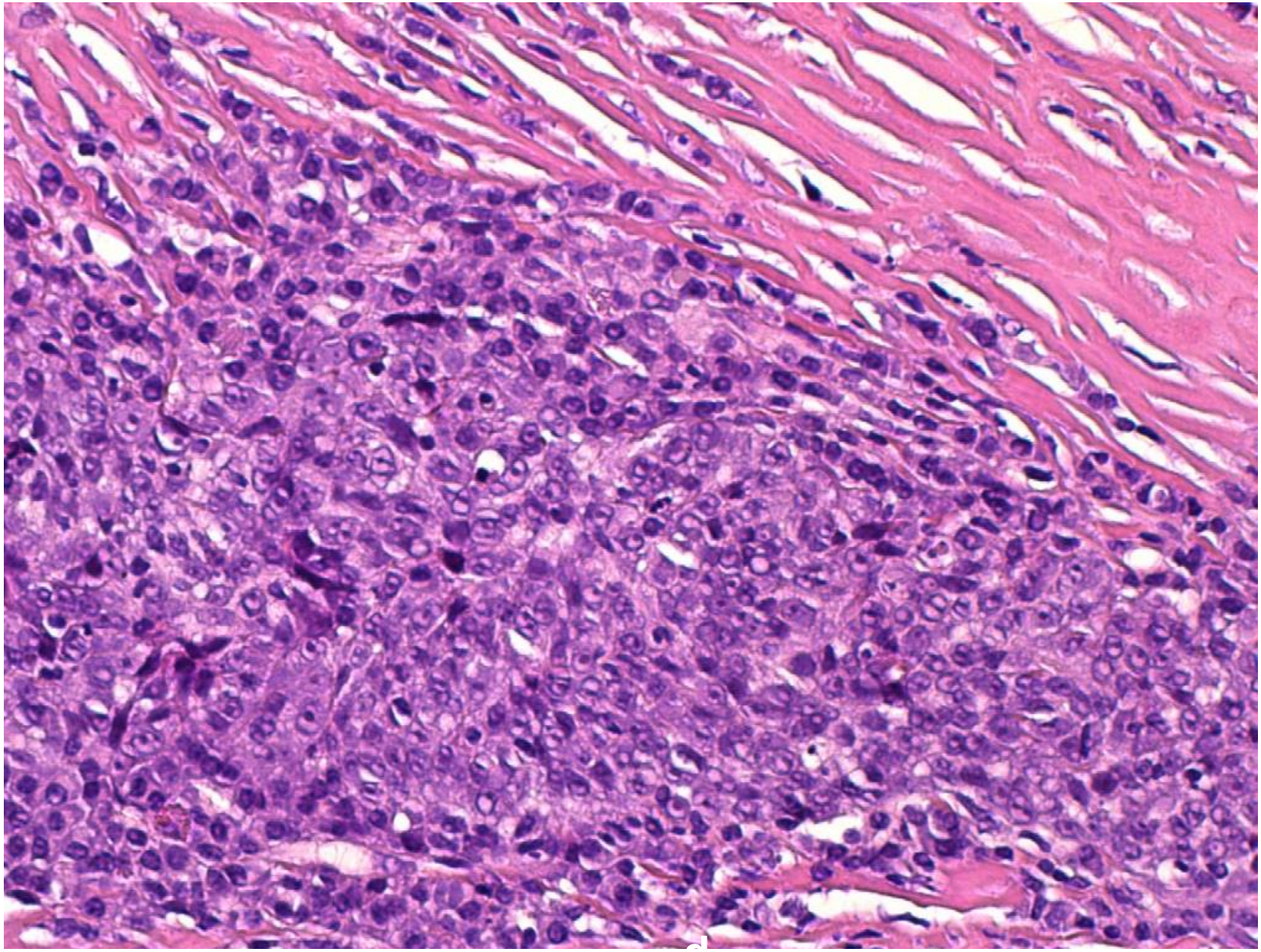
TSQCC

- **Type B3 thymomas rarely show – usually focal – expression of CD5 and CD117**
- **Thymic squamous cell carcinomas rarely harbour - usually few - immature TdT+ T cells**

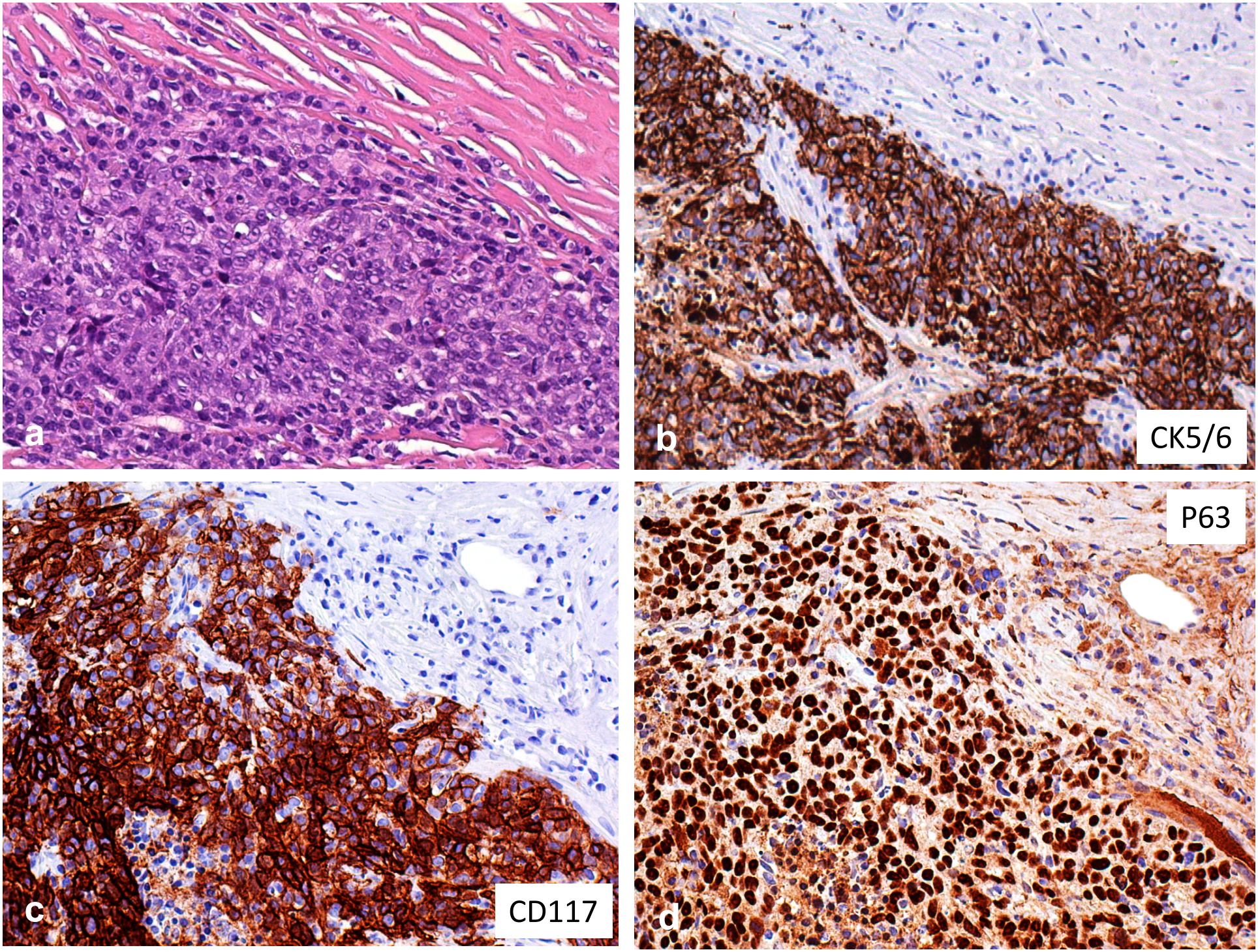
In such cases H&E histology "trumps" immunohistochemical features

(different from WHO lung carcinoma classification)

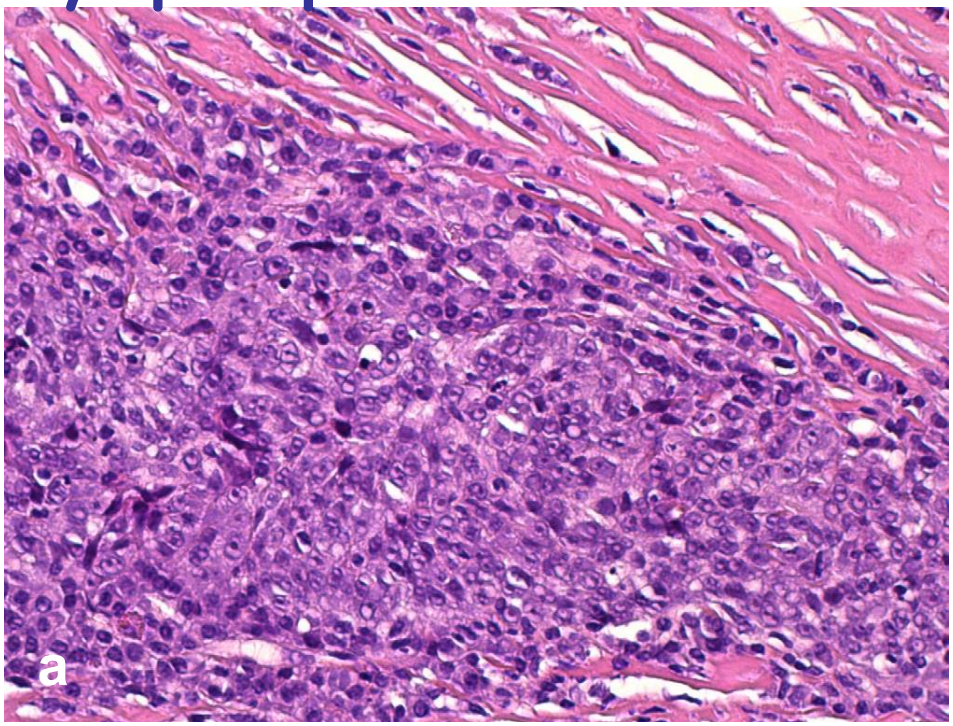
Is IHC dispensible in thymic carcinoma classification?

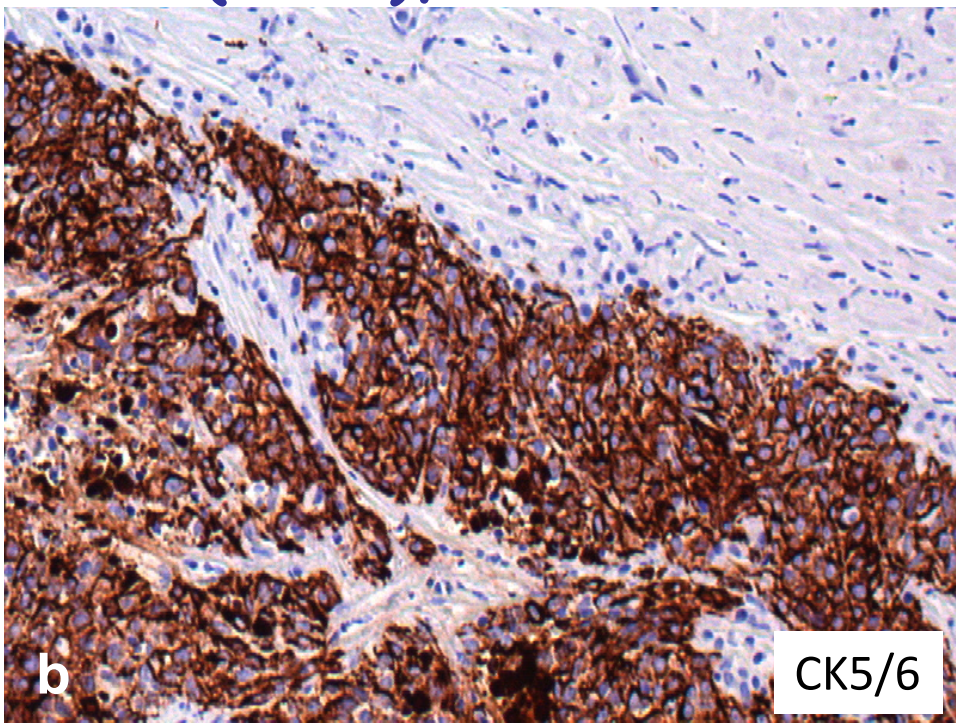


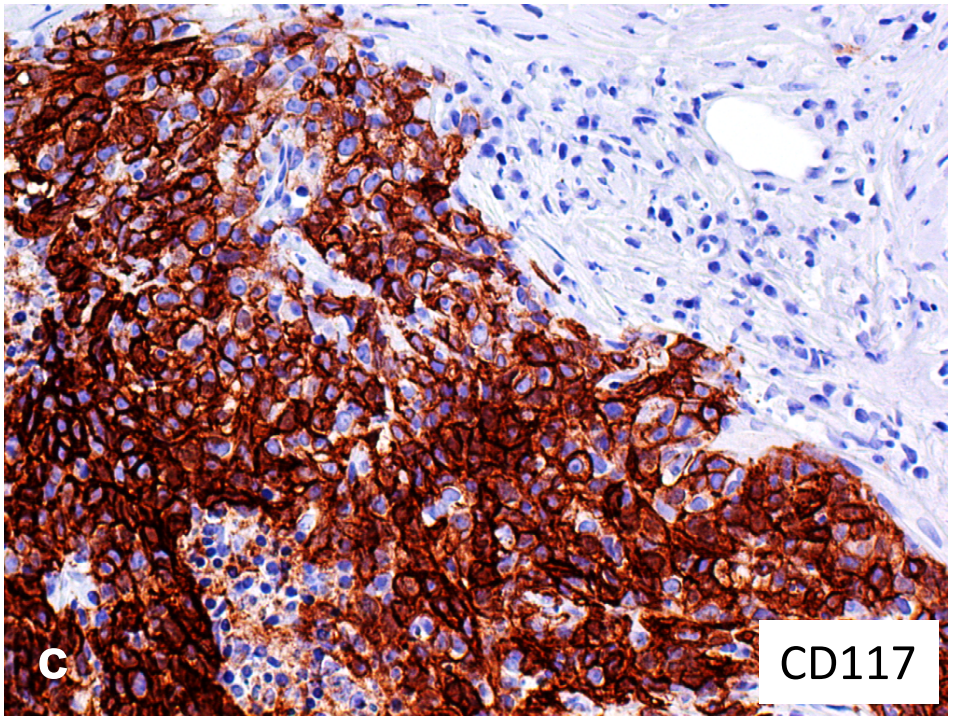
Poorly differentiated Thymic Squamous Cell Carcinoma?

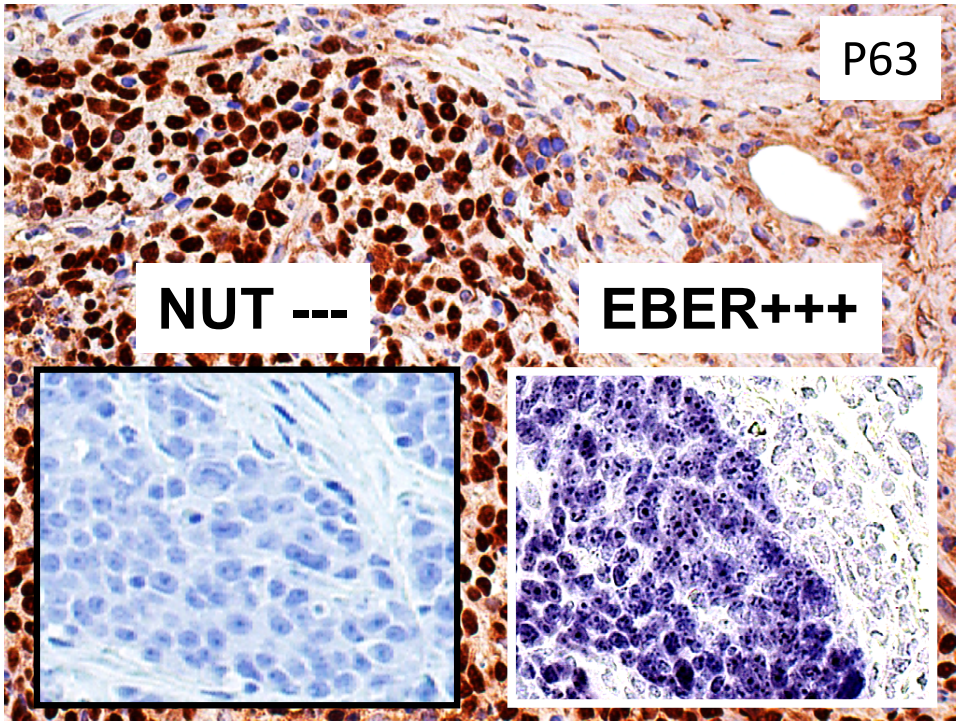


Lymphoepithelioma-like carcinoma (LELC), solid variant

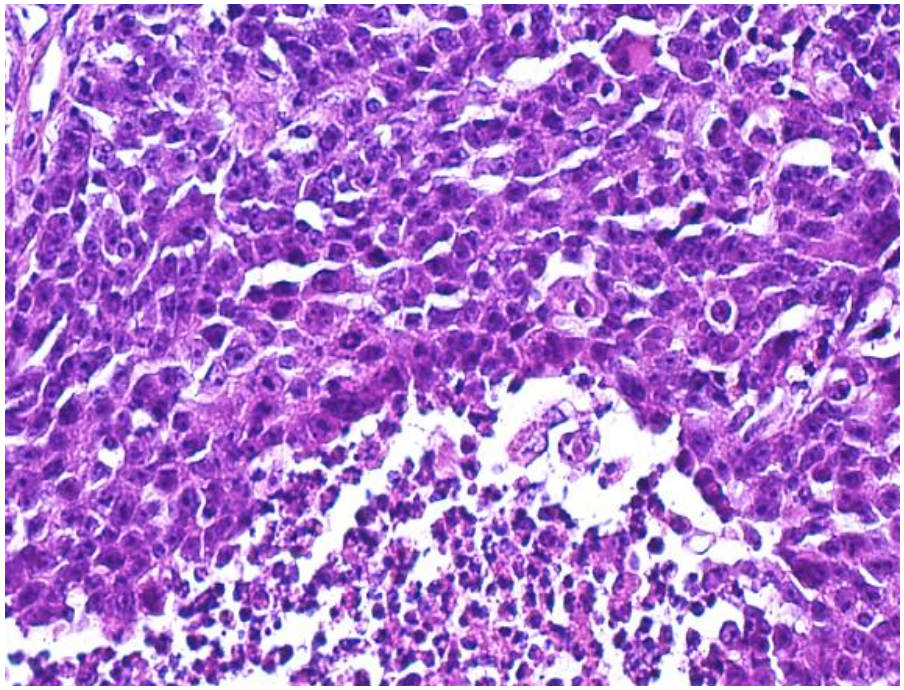


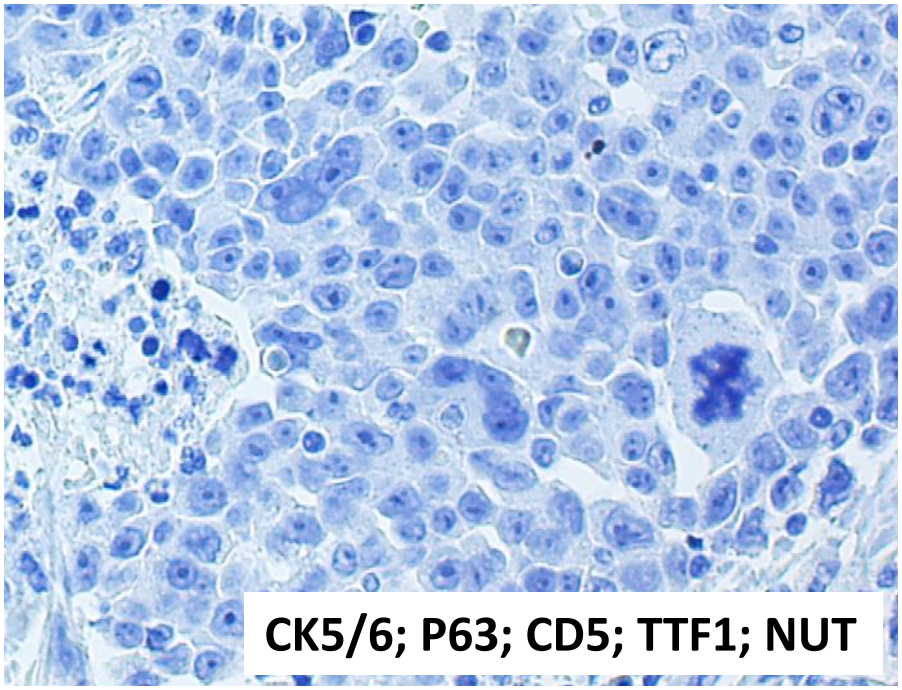


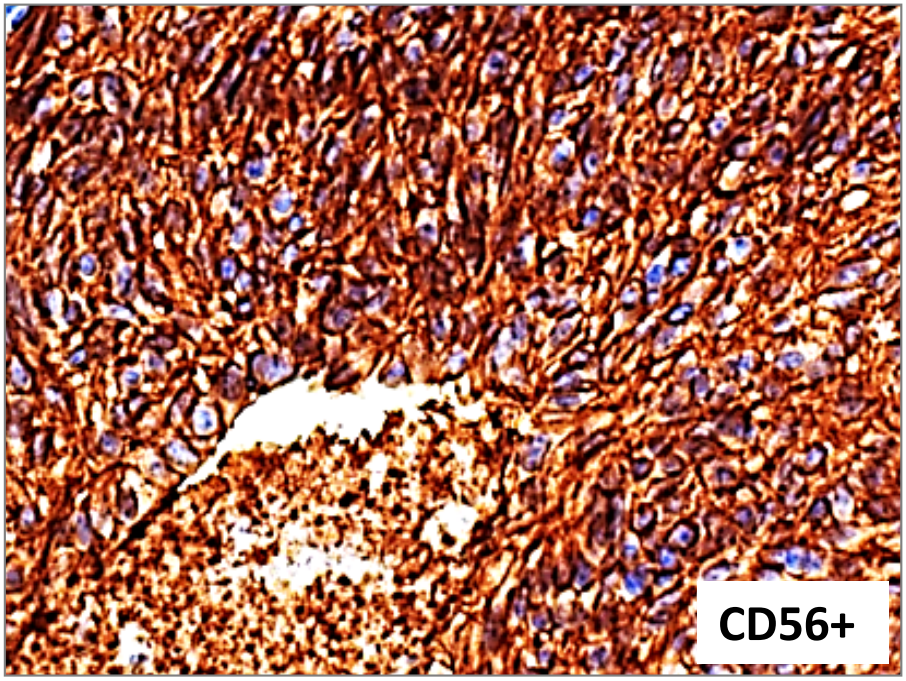


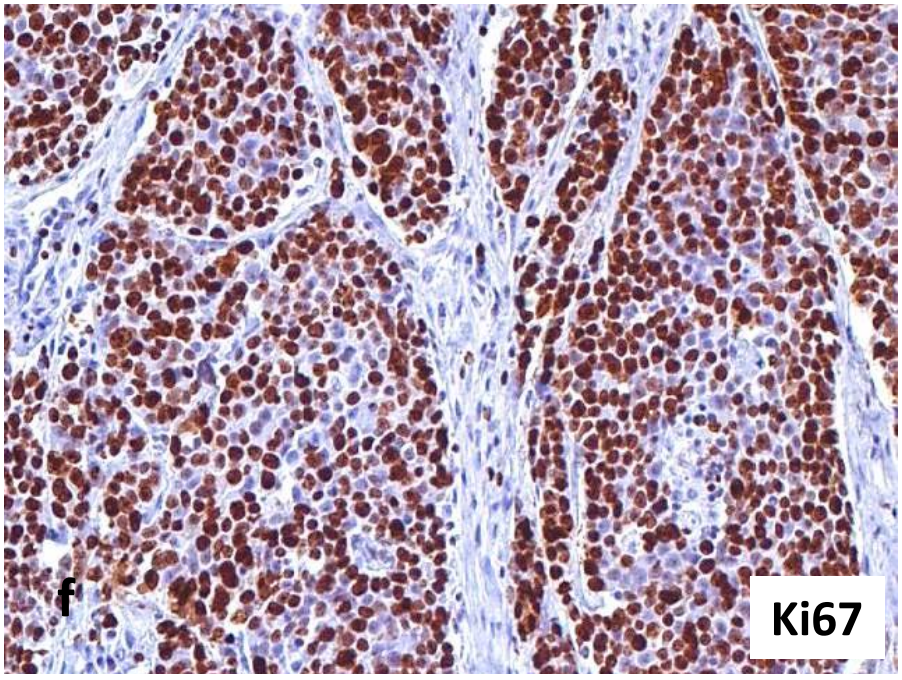


LCNEC

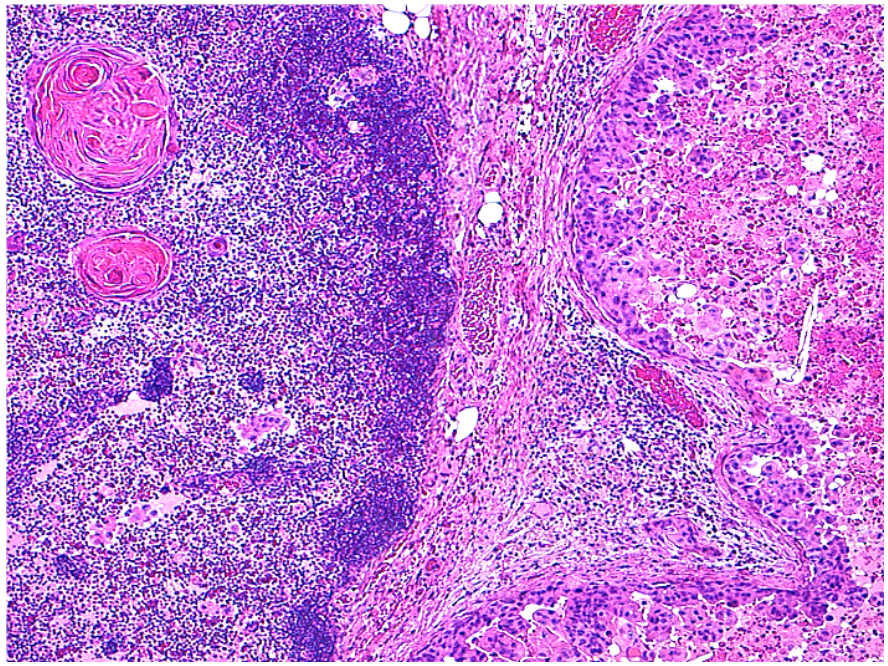


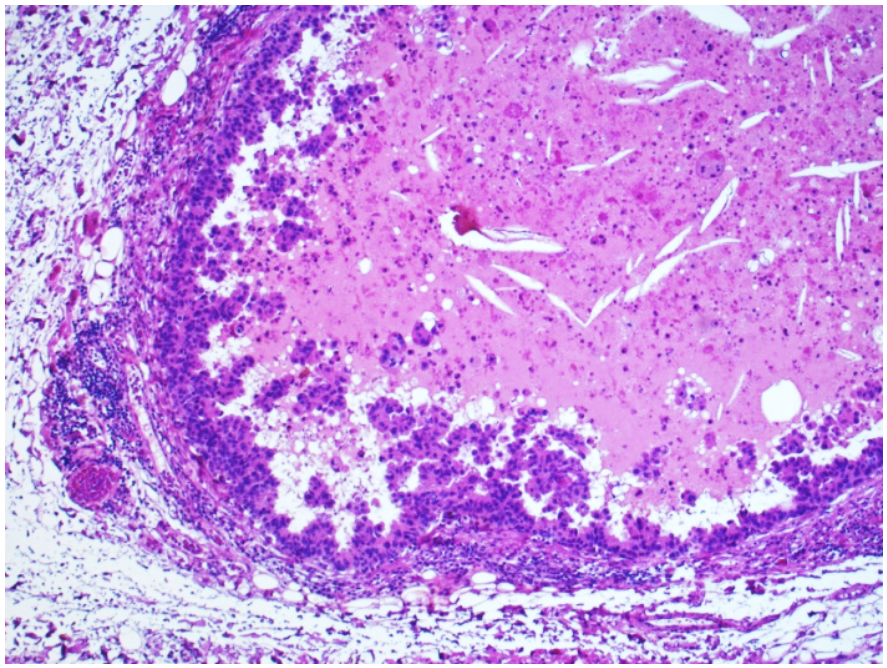


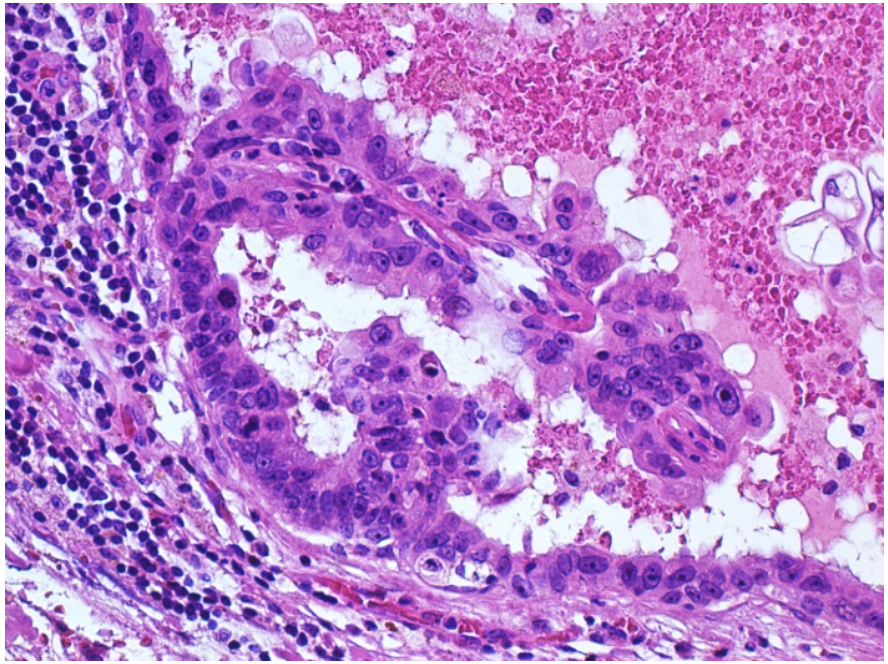


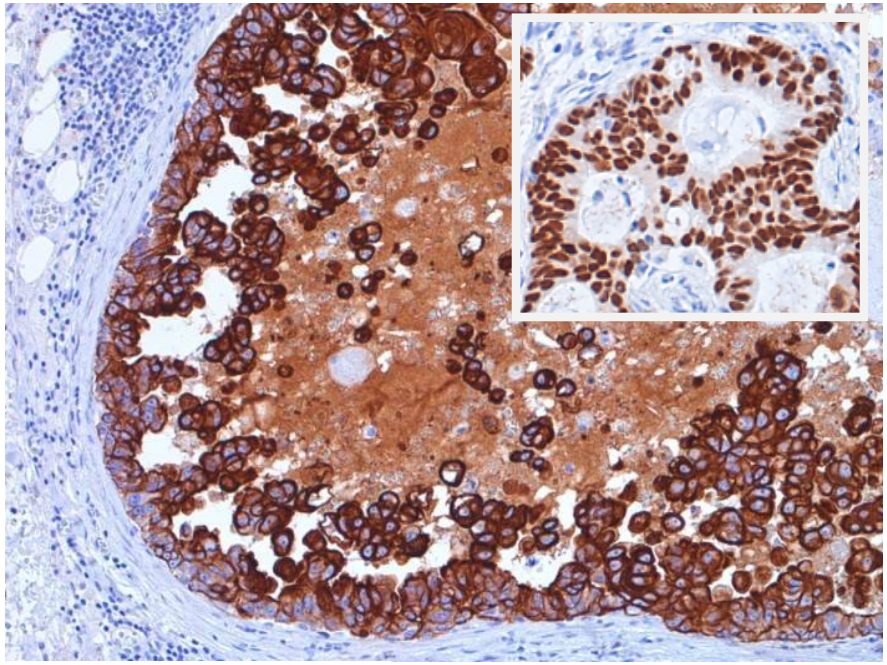


Thymic papillary adenocarcinoma, enteric type = new variant



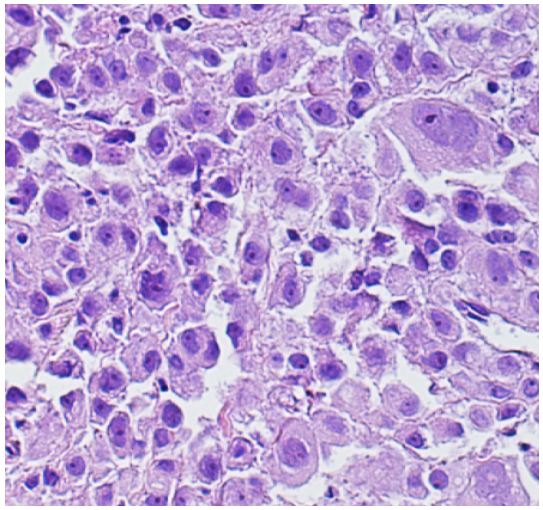






CK20+/CDX2+

“Carcinoma w/o clear-cut differentiation”



DD

Thymic squamous cell carcinoma (TSQCC)
(CD5+ or -; CK5/6+; p40/p63+; NUT-, EBER-)

NUT carcinoma
(looks like TSCC or UTC or SCC but NUT+)

Solid variant of LELC
(looks like TSQCC or UTC but EBER+)

Clinicopathological correlation needed

Solid adenocarcinoma
(p40-; CD5+ or -; CK7+ or CK20+, CDX2+ or -)

Large cell NEC (any one of CD56, chromogranin or synaptophysin (+) in >50% of tumor cells)

Undifferentiated thymic carcinoma (UTC)
(AE1/3+; CK8/18+; CK5/6-; CD5-; p63-; EBER-)

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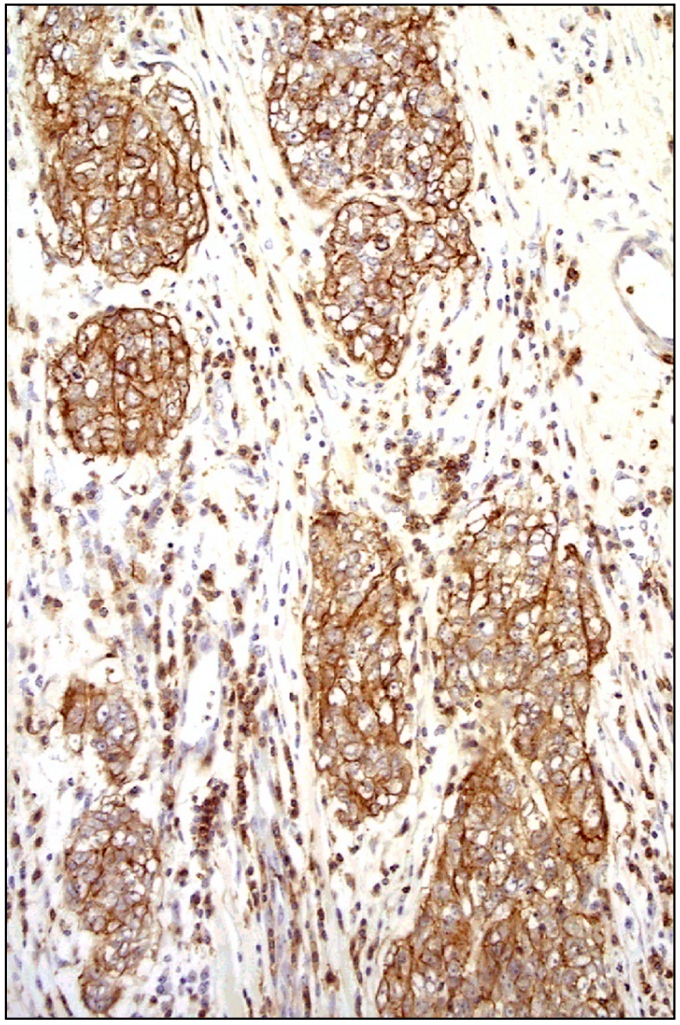
KIT protein expression has little predictive value for KIT mutation
Absence of KIT expression (20%) virtually excludes KIT mutations



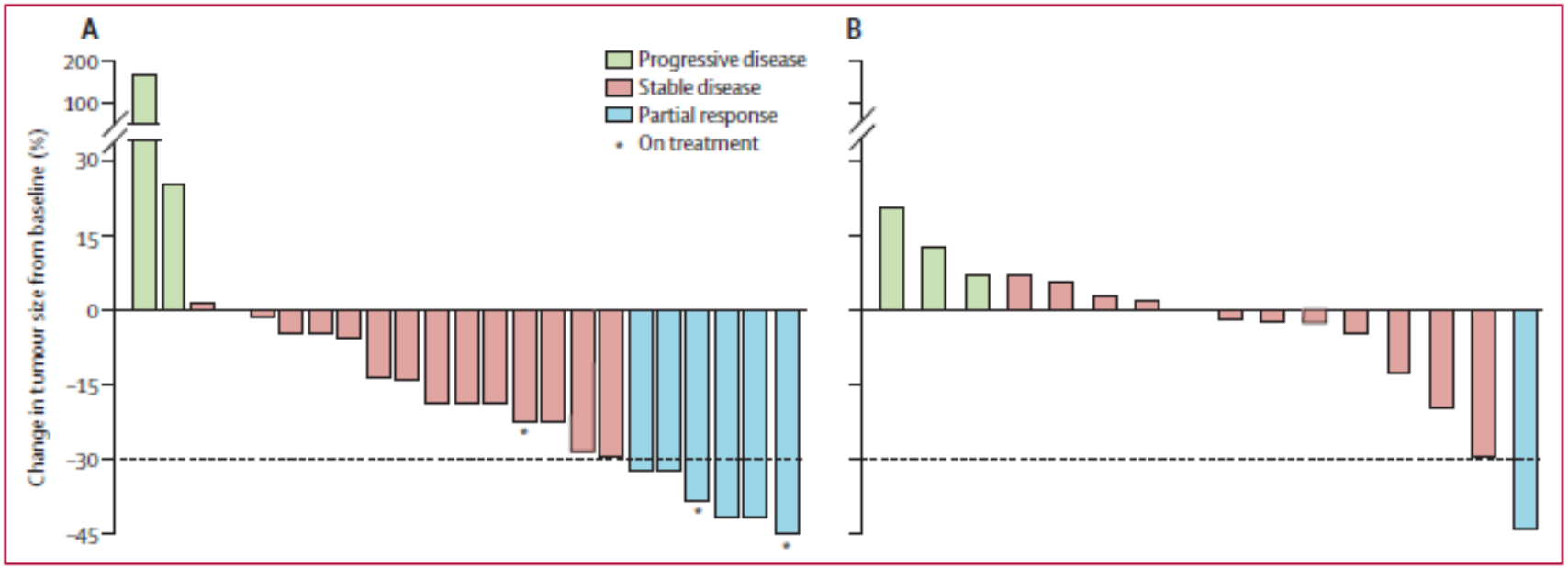
KIT(+) TSQCC

- Common: Exon 11 activating mutations*
- Rare: Exon 13 (K642E)**
  Exon 14 (H697Y)
  Exon 9 (E490K)
  Exon 17 (D820E)***

*Imatinib-sensitive Ströbel et al. 2004
Hagemann et al. 2014
Rossi V. et al. 2013
**Sorafenib-sensitive Catania et al. 2014
***Sunitinb-sensitive Pagano et al. 2014

Sunitinib in patients with chemotherapy-refractory thymoma and thymic carcinoma: an open-label phase 2 trial

Anish Thomas, Arun Rajan, Arlene Berman, Yusuke Tomita, Christina Brzezniak, Min-Jung Lee, Sunmin Lee, Alexander Ling, Aaron J Spittler, Corey A Carter, Udayan Guha, Yisong Wang, Eva Szabo, Paul Meltzer, Seth M Steinberg, Jane B Trepel, Patrick J Loehrer, Giuseppe Giaccone



No predictive marker identified*

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www.thelancet.com/oncology Vol 16 February 2015

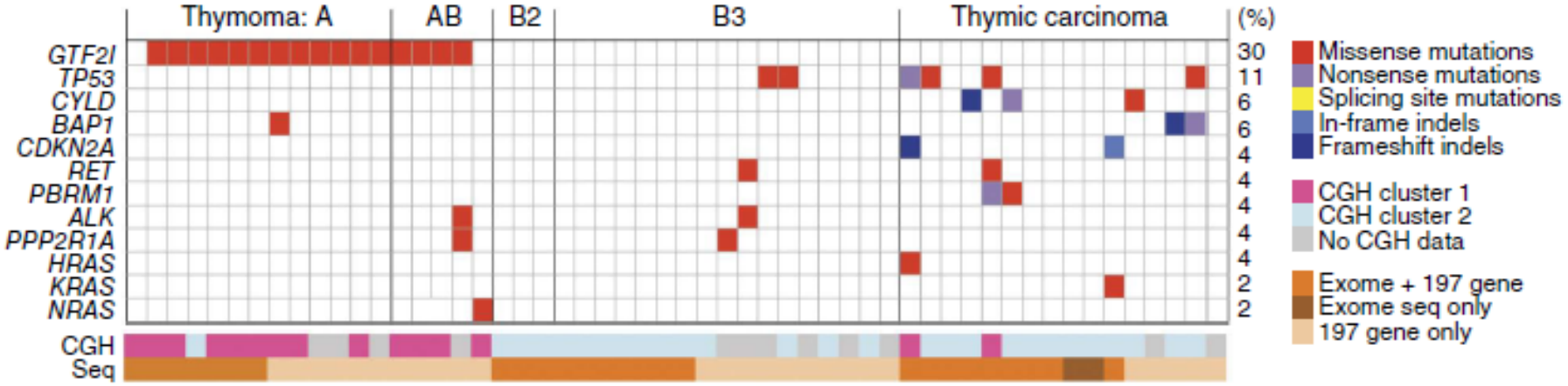
* Marx A, Weis CA, Lancet Oncolocy, 2015

Rare druggable targets in thymomas & TCs

nature genetics

A specific missense mutation in *GTF2I* occurs at high frequency in thymic epithelial tumors

Iacopo Petrini[1], Paul S Meltzer[2], In-Kyu Kim[3], Marco Lucchi[4], Kang-Seo Park[3], Gabriella Fontanini[5], James Gao[1], Paolo A Zucali[6], Fiorella Calabrese[7], Adolfo Favaretto[8], Federico Rea[9], Jaime Rodriguez-Canales[10], Robert L Walker[2], Marbin Pineda[2], Yuelin J Zhu[2], Christopher Lau[2], Keith J Killian[2], Sven Bilke[2], Donna Voeller[1], Sivanesan Dakshanamurthy[3], Yisong Wang[1,3] & Giuseppe Giaccone[1,3]



Potential new therapeutic targets: RET; ALK; PBRM1; BAP1 (?)

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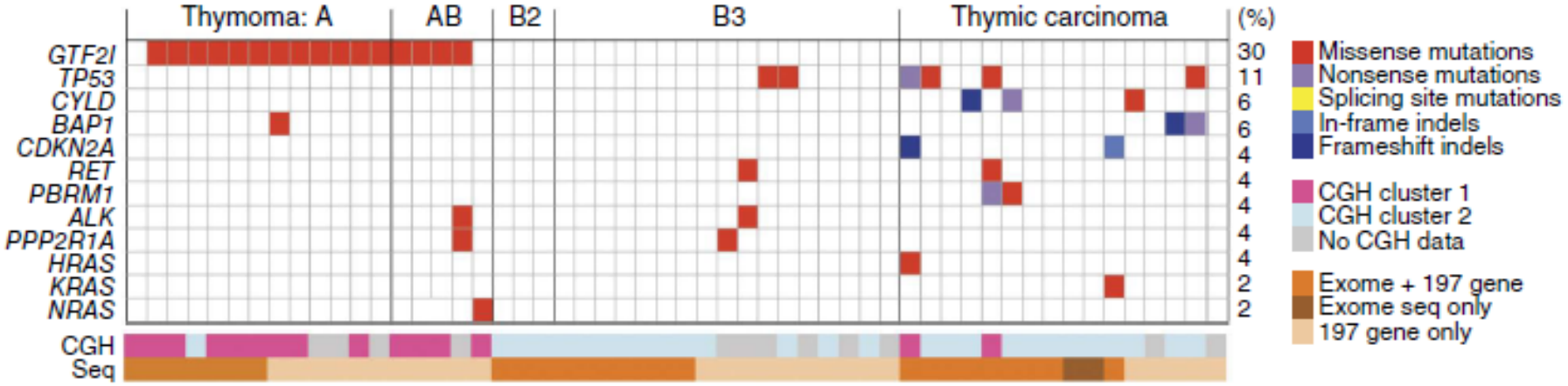

Potential new therapeutic targets: RET; ALK; PBRM1; BAP1 (?)

Is there a perspective for immunotherapies?

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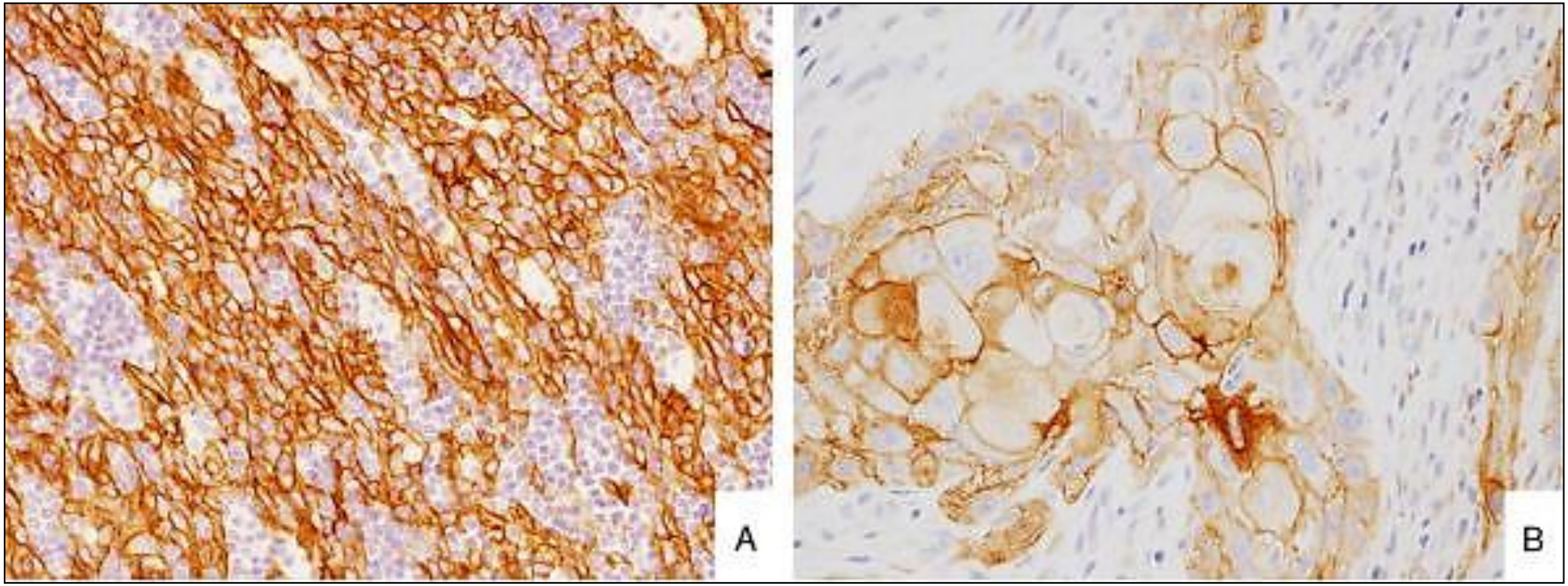
Thymoma is the #1 PD-L1 expressor among all epithelial tumors



Typ B2 thymoma

TSQCC

Thymoma	78.8%	
Thymic carcinoma		37.5%
Lung SQCC	58.9%	
Lung adenocarcinoma	21.9%	
Mesothelioma	30.1%	
CRC	12.8%	
Breast	5,8%	

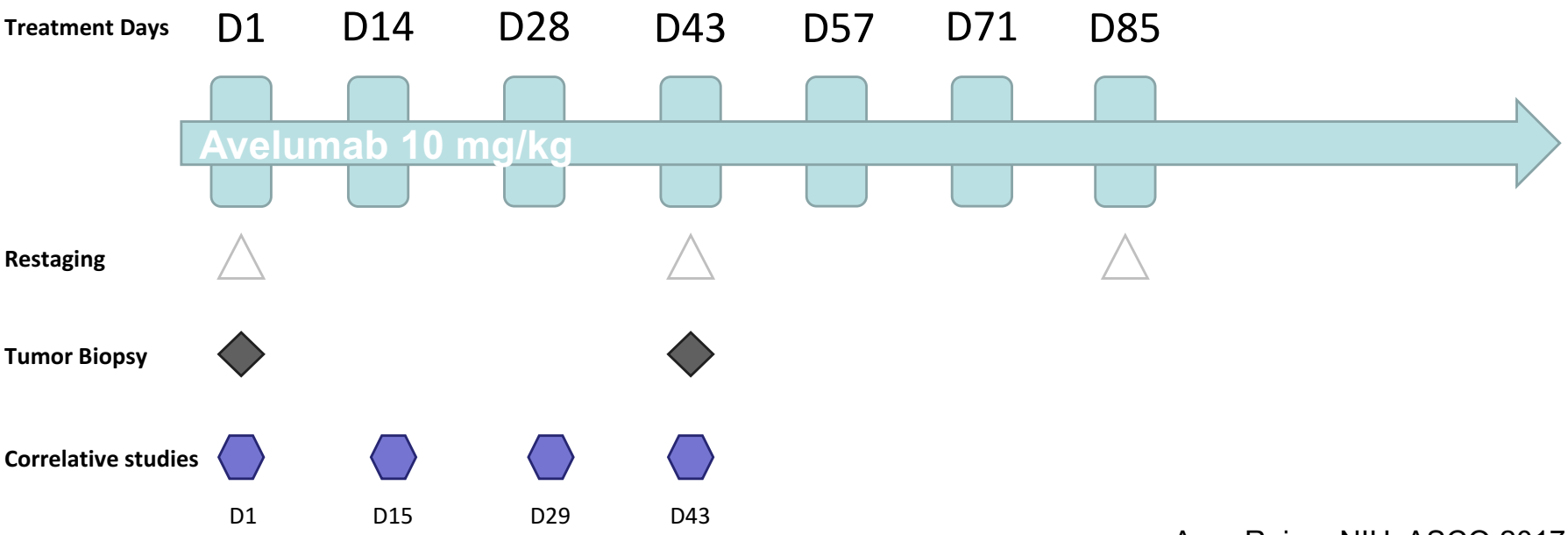
SQCC > Adenocarcinomas

Comprehensive Immunohistochemical Study of Programmed Cell Death Ligand 1 (PD-L1): Analysis in 5536 Cases Revealed Consistent Expression in Trophoblastic Tumors.
Inaguma, Shingo; Wang, Zengfeng; Lasota, Jerzy; Sarlomo-Rikala, Maarit; McCue, Peter; Ikeda, Hiroshi; Miettinen, Markku

American Journal of Surgical Pathology. 40(8):1133-1142, August 2016.
DOI: 10.1097/PAS.0000000000000653

A Pilot Study to Investigate the Safety and Clinical Activity of Avelumab (MSB0010718C) in Thymoma and TC after Progression on Platinum-Based Chemotherapy (NCT03076554)

Objectives	• Determine the safety and tolerability of avelumab in patients with relapsed thymoma and thymic carcinoma • Determine the objective response rate
Statistical Plan	• Pilot trial with an accrual ceiling of 12 patients with advanced thymoma • Enrollment of patients with thymic carcinoma will occur in parallel (accrual ceiling = 12) • If > 3 of 12 patients respond, study can be amended to a phase II trial
Correlative Studies	• Parameters of immune activation (Flow cytometry) • PD-1/PD-L1 expression and immune cell infiltrate (IHC) • Gene expression-based characterization of tumor microenvironment • RNA signatures: tumor-specific and immune-specific



Arun Rajan, NIH, ASCO 2017

ICI* Trials in Thymoma (and 1 Thymic Carcinoma) (TC) (A. Rajan, ASCO, 2017)

General requirements:

- Unresectable tumors with progression on platinum-based chemotherapy
- **No Myasthenia gravis; no active autoimmune disease under immunosuppression**
- No active acute or chronic infections (HBV; HCV; HIV) or post-transplant state

- **Avelumab (anti-PD-L1)*** phase 2 pilot study (thymoma and TC), NIH, (NCT03076554)

a. Seven patients with thymoma and one with TC
b. Partial responses in 4 thymomas (58%)
c. Stable disease in 2 thymomas and 1 TC
d. Progressive disease in 1 thymoma
e. No clear correlation with PD-L1 expression status (small number of cases)

f. Adverse effects (grade 3+4): In 5 thymomas and the 1 TC (75%)
In all 4 responders (!)
g. Adverse effects: **Myositis** > Enteritis

*ICI, Immune Chekpoint Inhibitor; fully human IgG1

Take Home Messages

- The vast **majority** of thymomas (>80%) can be diagnosed on the basis of H&E morphology (IHC only rarely needed)

- Only a **minority** of thymic carcinomas can be diagnose on the basis of H&E histology

- IHC, EBER-ISH …. are needed to properly distinguish poorly differentiated TSQCC, solid LELC, NUT carcinoma, undifferentiated TC and LCNEC

  …not to forget metastases, mesothelioma, sarcomas, germ cell tumors

- Immune checkpoint inhibitor therapy is an upcoming option in thymic epithelial tumors (if massive adverse affects can be harnessed)

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Thank you for your attention !

ICI* Trials in Recurrent Thymic Carcinoma (TC) (G. Giaccone, ASCO, 2017)

- **Pembrolizumab (anti-PD-1)** phase 2 study, (NCT02364076)

  a. 40 patients with TC (but only 14 with thymic squamous cell carcinoma)
  b. Complete response in 1 patient (2.5%)
  c. Partial response in 8 patients (20%)
  d. Stable disease in 20 patients

  a. **No clear correlation with PD-L1 expression status**

  b. Immune related adverse effects (grade 3+4): In 6 patients (15%)
  Particularly in responders (!)
  g. **Adverse effects:** Myositis, **myocarditis**, hepatitis, pancreatitis, T1D, MG

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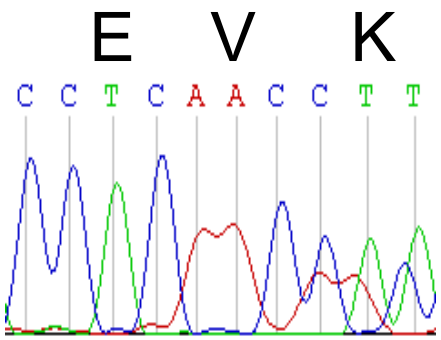
*ICI, Immune Chekpoint Inhibitor

5-10% of KIT+ Thymic Carcinomas show KIT Mutations

c-kit, Exon 11



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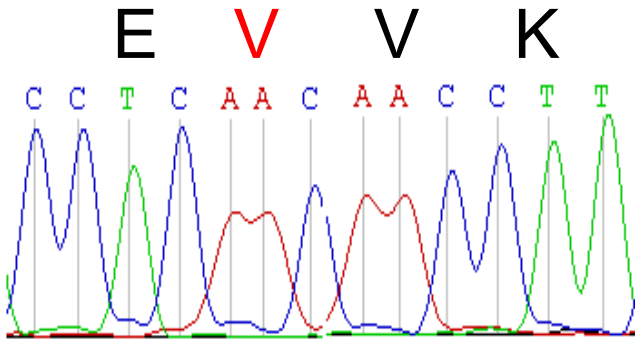
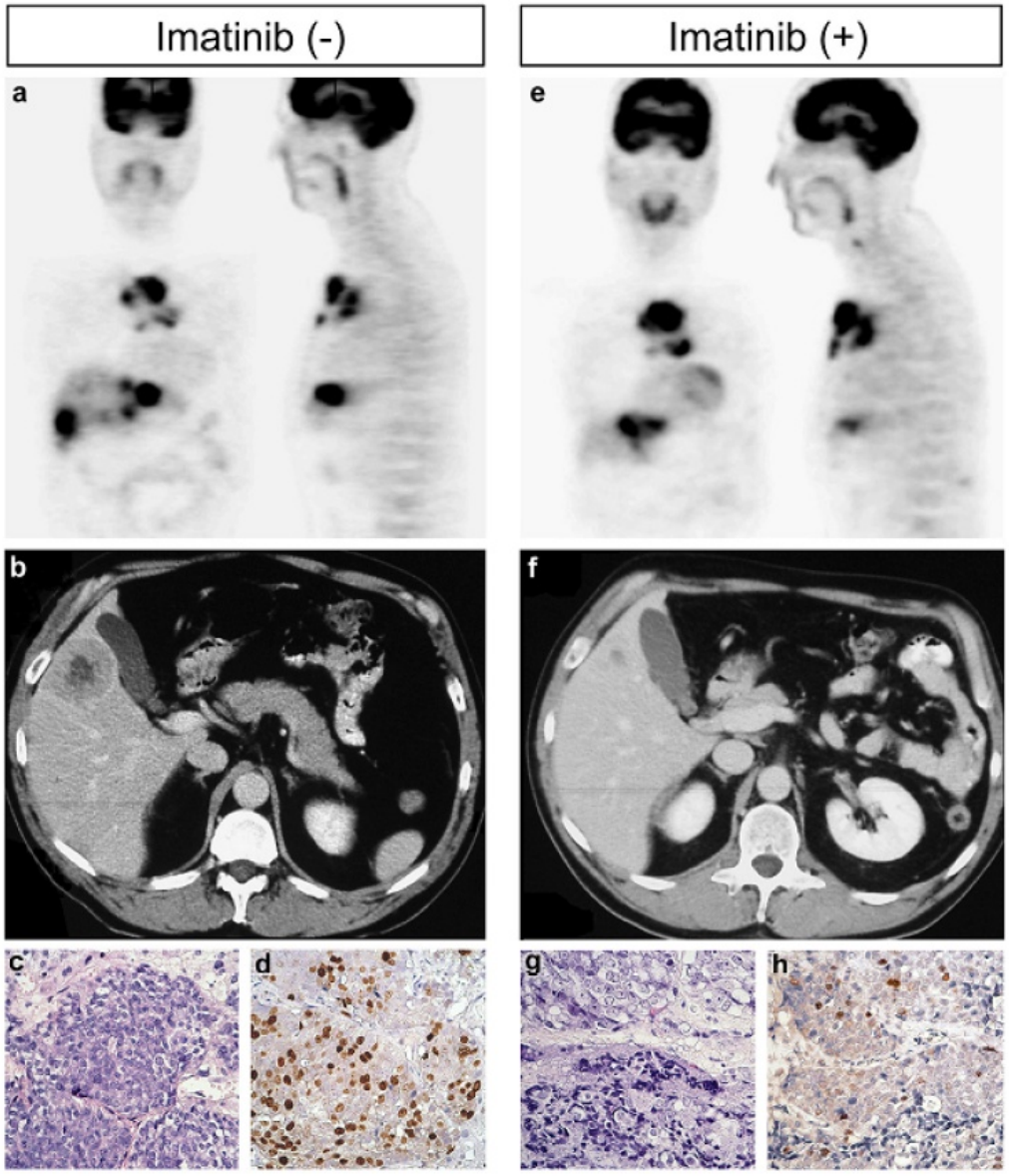
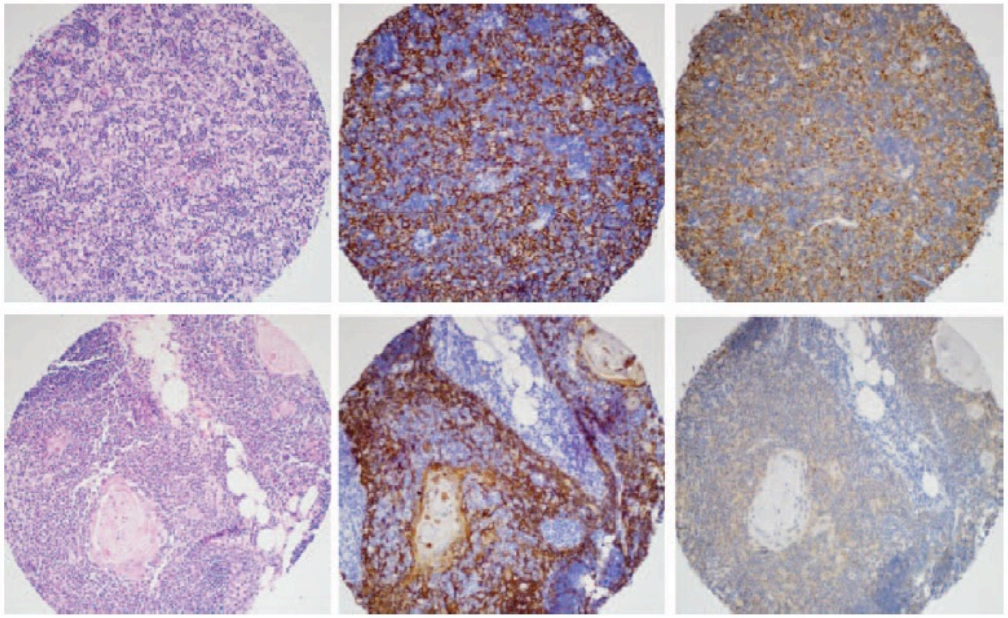


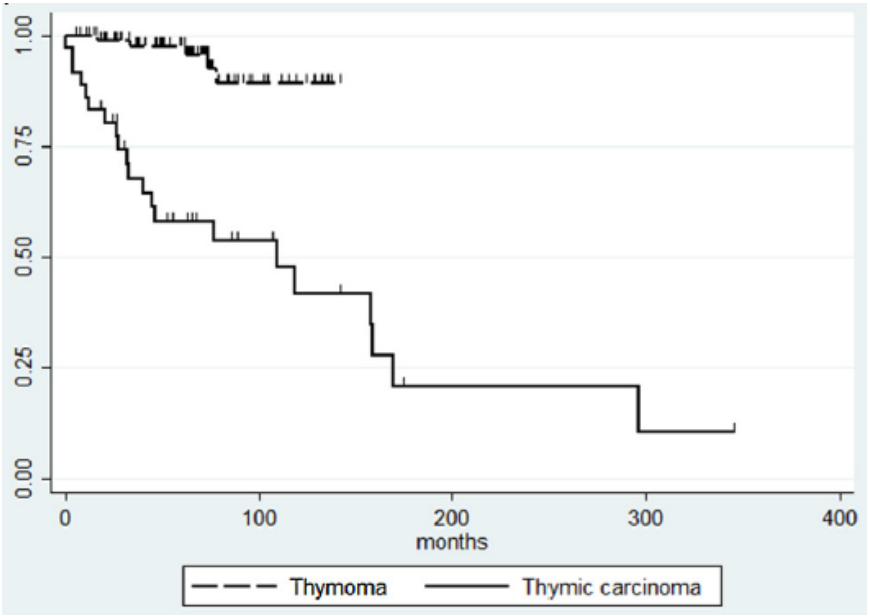
WT-Sequence

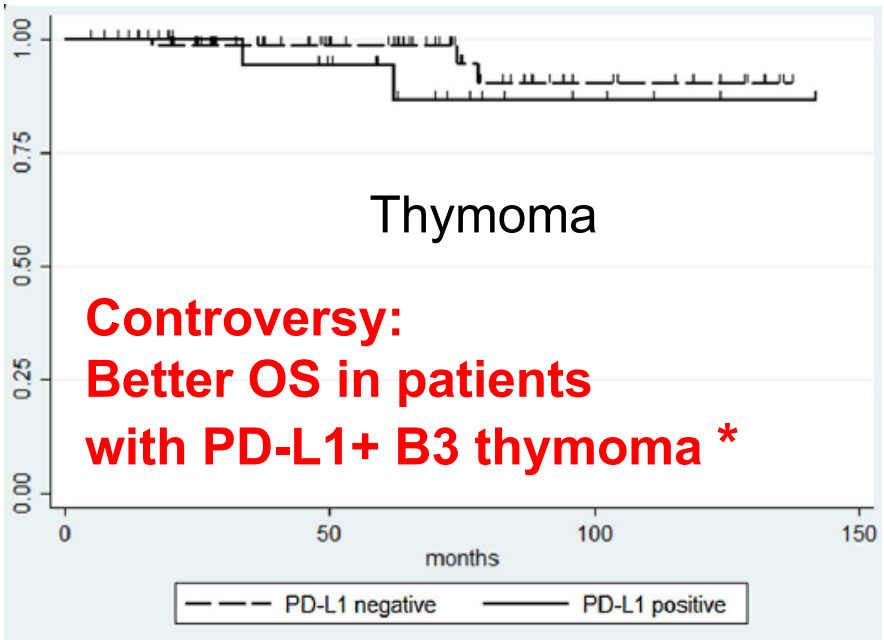


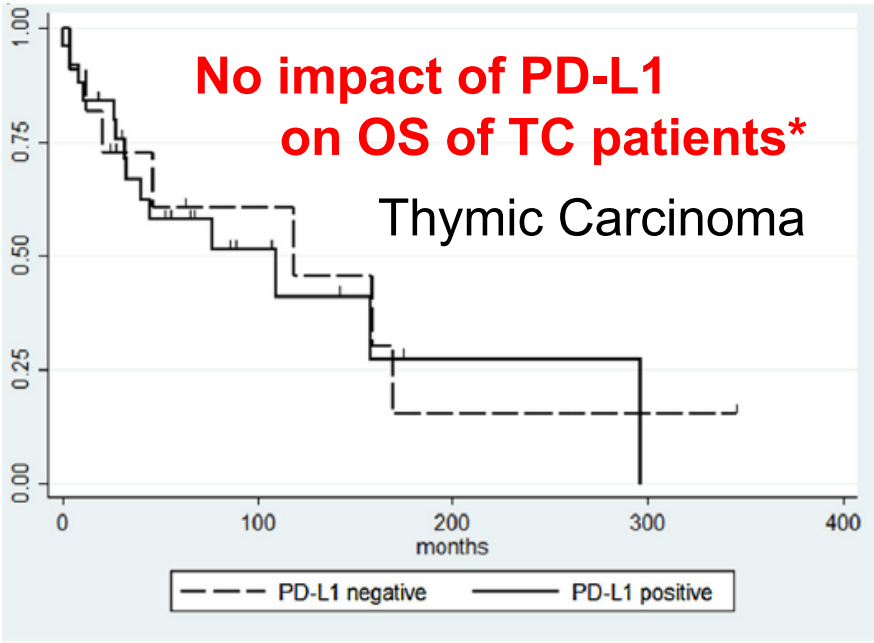
Ströbel et al. N Engl J Med. 2004

PD-L1 Expression in thymoma and TC: no or favourable impact on survival (?)









Padda SK et al. JTO, 2015; Katsuya Y et al. Lung Cancer 2015; *Taranchon-Clerment E et al. ASCO, 2017