“Confirmational Proteomics ….. Is It Time?”

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“44 Years Down the IHC Highway …..”

- Transition from frozen tissue to formalin-fixed, paraffin-embedded tissue (avidin-biotin complex detection)
- The introduction of heat-induced epitope retrieval (HIER)
- Automation
- First- and second- generation polymer detection
- Going from “RUO” status to selecting cancer patients for targeted therapy based on IHC testing

FOUNDATIONONE®CDx

PATIENT [redacted]

TUMOR TYPE
Liver mixed hepatocellular cholangiocarcinoma
COUNTRY CODE
US

REPORT DATE
08 May 2020

ORDERED TEST #
ORD-0801087-01

ABOUT THE TEST FoundationOne®CDx is the first and only FDA-Approved comprehensive companion diagnostic for all solid tumors.

Interpretive content on this page and subsequent pages is provided as a professional service, and is not reviewed or approved by the FDA.

PATIENT

DISEASE Liver mixed hepatocellular cholangiocarcinoma
NAME [redacted]
DATE OF BIRTH 15 November 1952
SEX Male
MEDICAL RECORD # 2001136007

PHYSICIAN

ORDERING PHYSICIAN [redacted]
MEDICAL FACILITY Hartford Healthcare
ADDITIONAL RECIPIENT None
MEDICAL FACILITY ID 200579
PATHOLOGIST Cartun, Richard

SPECIMEN

SPECIMEN SITE Liver
SPECIMEN ID HS20-1980 ET
SPECIMEN TYPE Block
DATE OF COLLECTION 28 January 2020
SPECIMEN RECEIVED 28 April 2020

Biomarker Findings

Microsatellite status - Cannot Be Determined
Tumor Mutational Burden - 4 Muts/Mb

Genomic Findings

For a complete list of the genes assayed, please refer to the Appendix

ERBB2 amplification
MYC amplification
FANCC R548*
TERT promoter -124C>T
TP53 Y234H

8 Therapies with Clinical Benefit
0 Therapies with Lack of Response
18 Clinical Trials

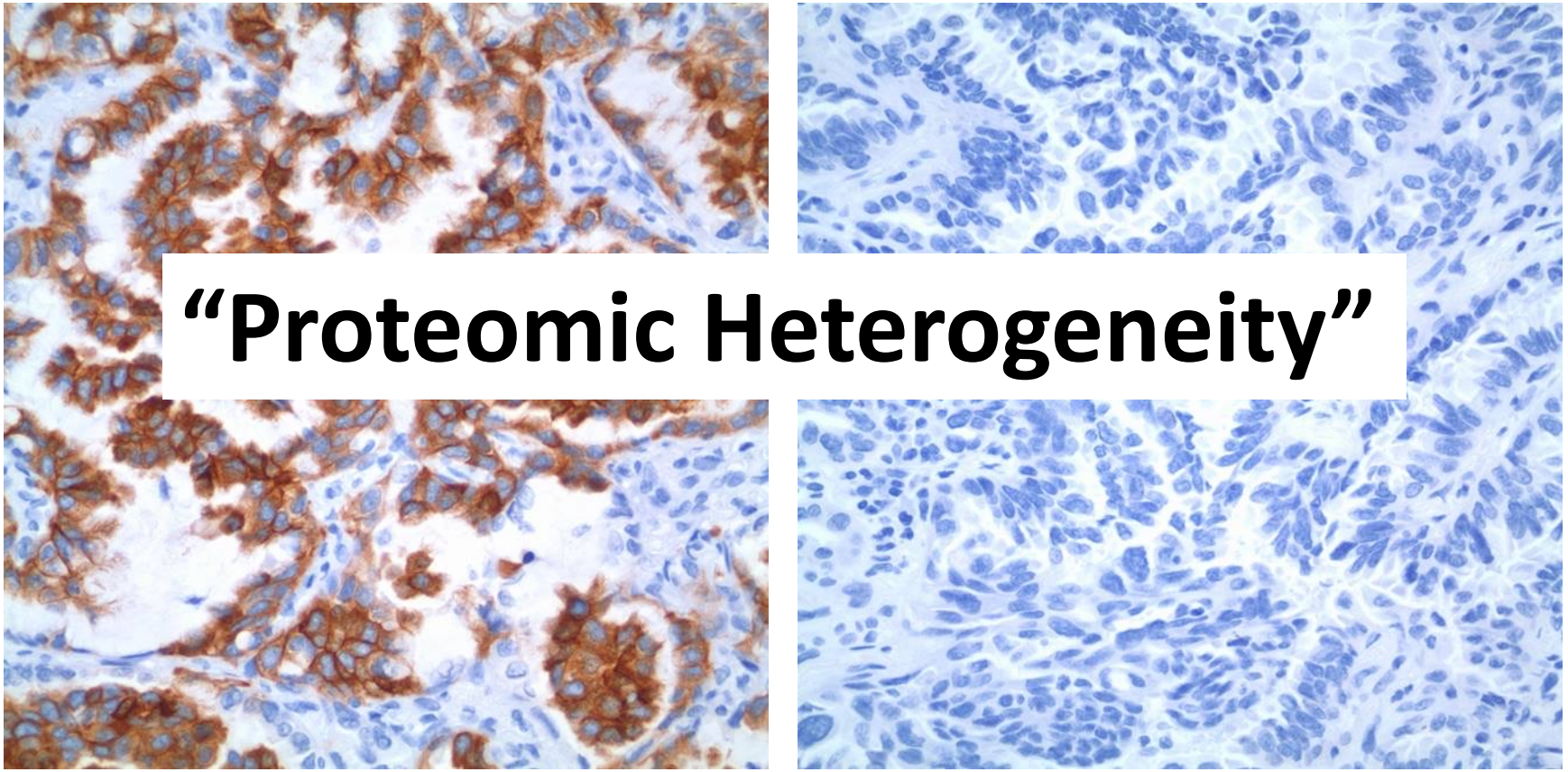
Order: HER2, c-Myc, p53 > Rec'd 5/13/20

BIOMARKER FINDINGS	ACTIONABILITY
Microsatellite status - Cannot Be Determined	No therapies or clinical trials. see Biomarker Findings section
Tumor Mutational Burden - 4 Muts/Mb	No therapies or clinical trials. see Biomarker Findings section

GENOMIC FINDINGS	THERAPIES WITH CLINICAL BENEFIT (IN PATIENT'S TUMOR TYPE)	THERAPIES WITH CLINICAL BENEFIT (IN OTHER TUMOR TYPE)
ERBB2 - amplification	none	Ado-trastuzumab emtansine
		Afatinib
		Dacomitinib
		Fam-trastuzumab deruxtecan
		Lapatinib
		Neratinib
		Pertuzumab
		Trastuzumab

10 Trials see p. 11

EGFR L858R Mutation-Specific mAb



“Proteomic Heterogeneity”

Clone 43B2; 20x

Is Next Generation Sequencing (NGS) the last stop for the Pathology Train?

What is this HER2 IHC slide doing in my box?

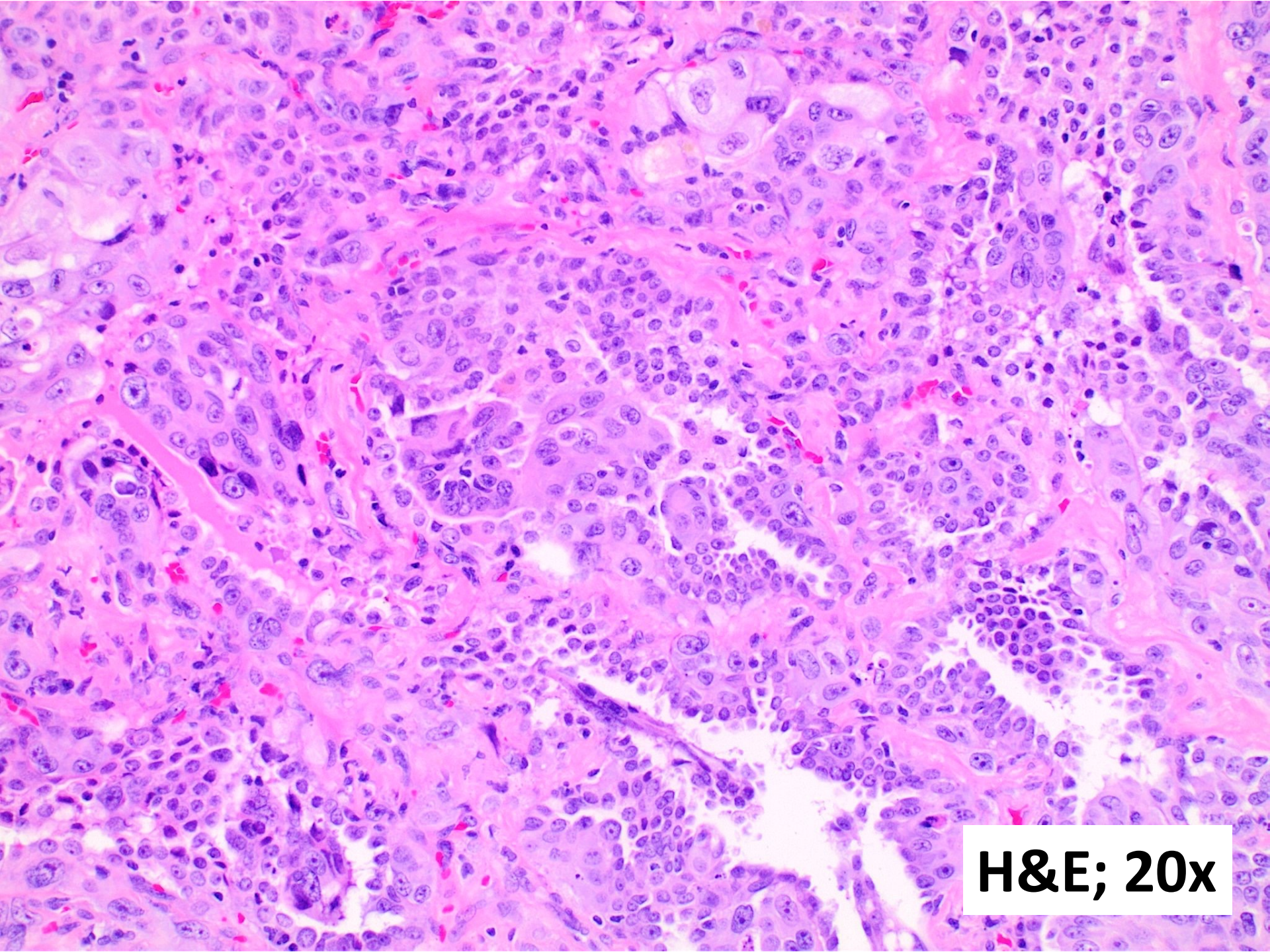
Case Study

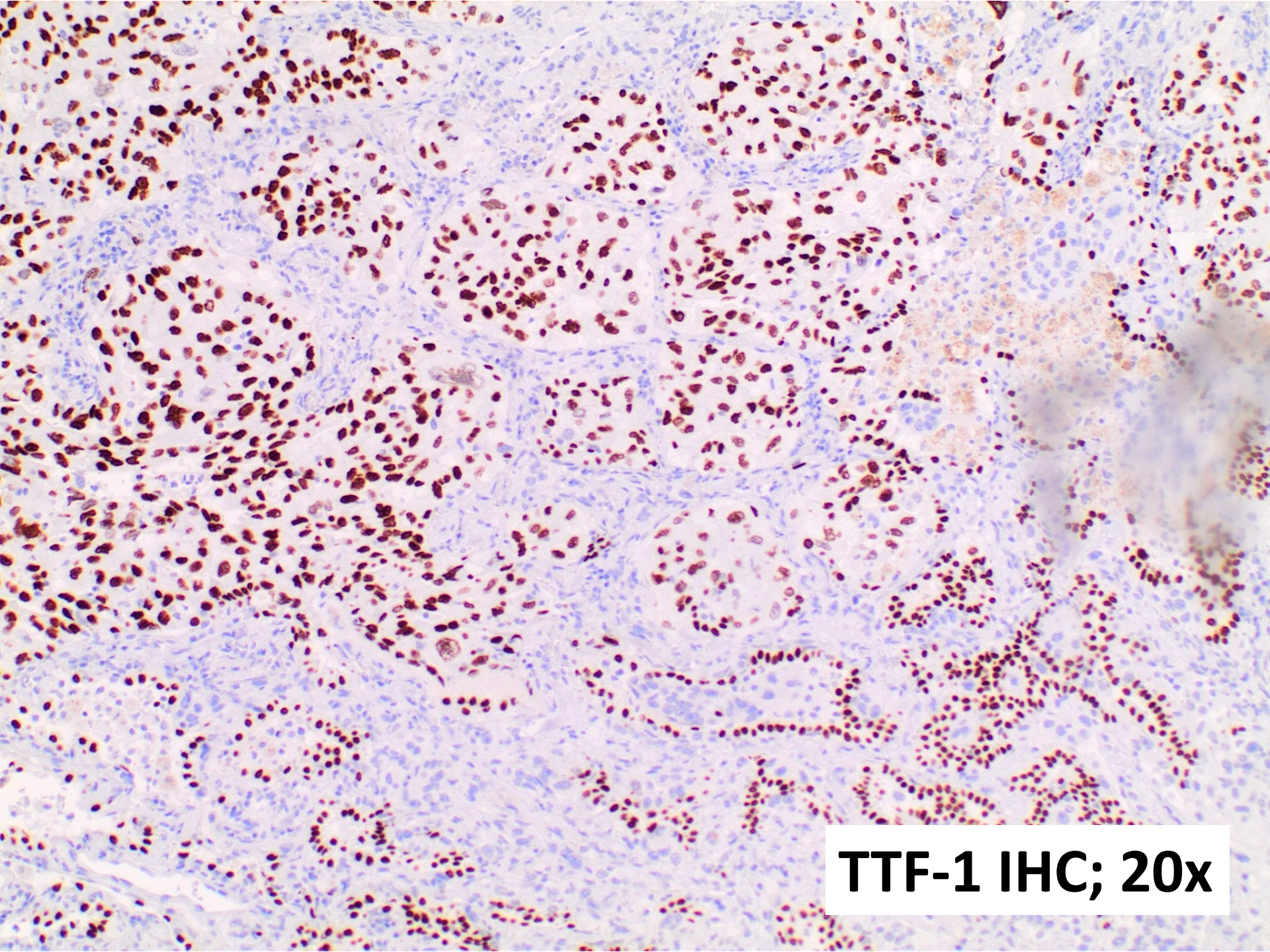
- 54 year-old male
- Malignant neoplasm of upper lobe of left lung
- Left upper lobe apical resection
- Invasive adenocarcinoma of lung with one positive station 5 lymph node
- IHC and molecular testing performed

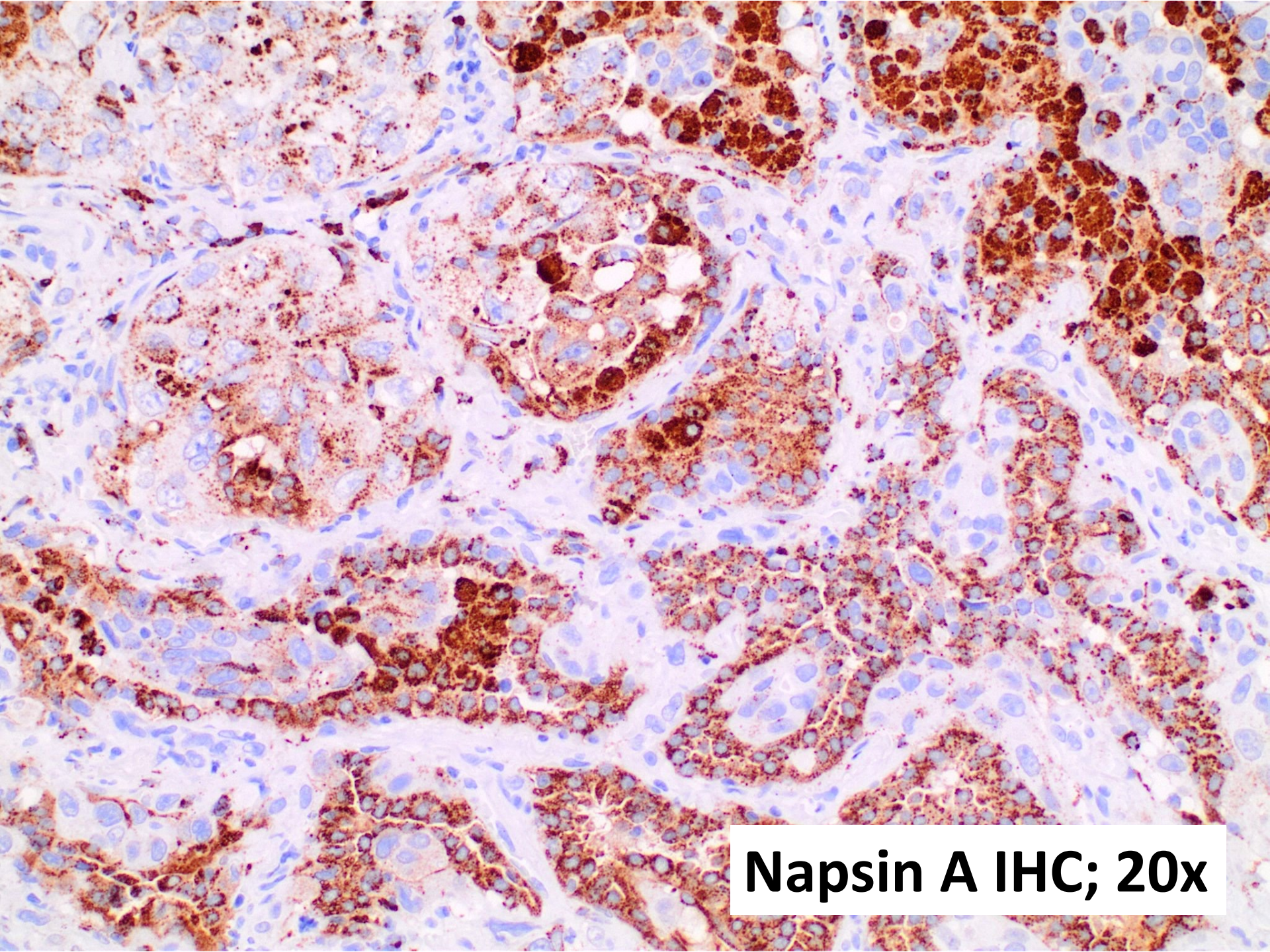
F – LEFT UPPER LOBE APICAL RESECTION: INVASIVE ADENOCARCINOMA OF LUNG. SEE SYNOPTIC REPORT.

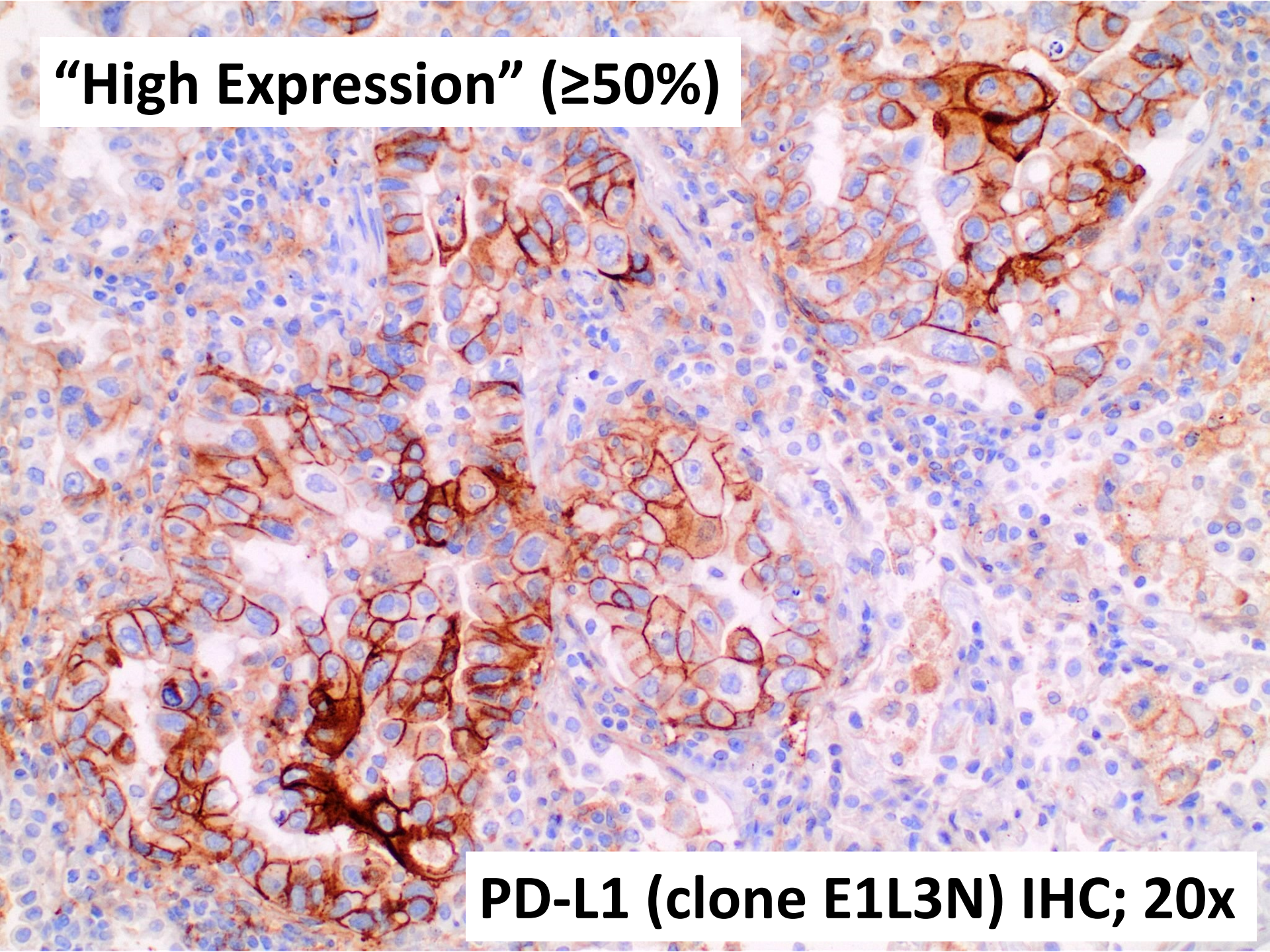
Synoptic Report:
Specimen
Procedure: Wedge resection
Specimen Laterality: Left
Tumor
Tumor Site: Upper lobe of lung
Histologic Type: Invasive adenocarcinoma, acinar predominant
Histologic Type Comments: TTF-1 is present focally within tumor cells, as is napsin, supportive of pulmonary primary.
Percentage of Lepidic: 0 %
Percentage of Acinar: 50 %
Percentage of Papillary: 0 %
Percentage of Micropapillary: 10 %
Percentage of Solid: 40 %
Histologic Grade: G3: Poorly differentiated
Spread Through Air Spaces (STAS): Present

Tumor Size
Tumor Size: 2.2 Centimeters (cm)
Tumor Focality: Single focus
Direct Invasion of Adjacent Structures: Adjacent structures present and involved
Involved Adjacent Structures: Parietal pleura
Visceral Pleura Invasion: Present
Lymphovascular Invasion: Not identified


H&E; 20x


TTF-1 IHC; 20x


Napsin A IHC; 20x


“High Expression” (≥50%)
PD-L1 (clone E1L3N) IHC; 20x

One H&E-stained slide (marked) and 5 H&E-stained slides (no cloverslips) were submitted to our Molecular Pathology Laboratory for NGS and RNA fusion panel testing.

NGS Solid Tumor Combined Varient Plex and RNA Fusion Panel

LUL Apical Resection block F7 was collected on 1/11/21. See pathology report HS21-557.

Diagnosis/Indication: Lung adenocarcinoma
Specimen: Left upper lobe apical resection, estimated tumor cellularity (**40%**)

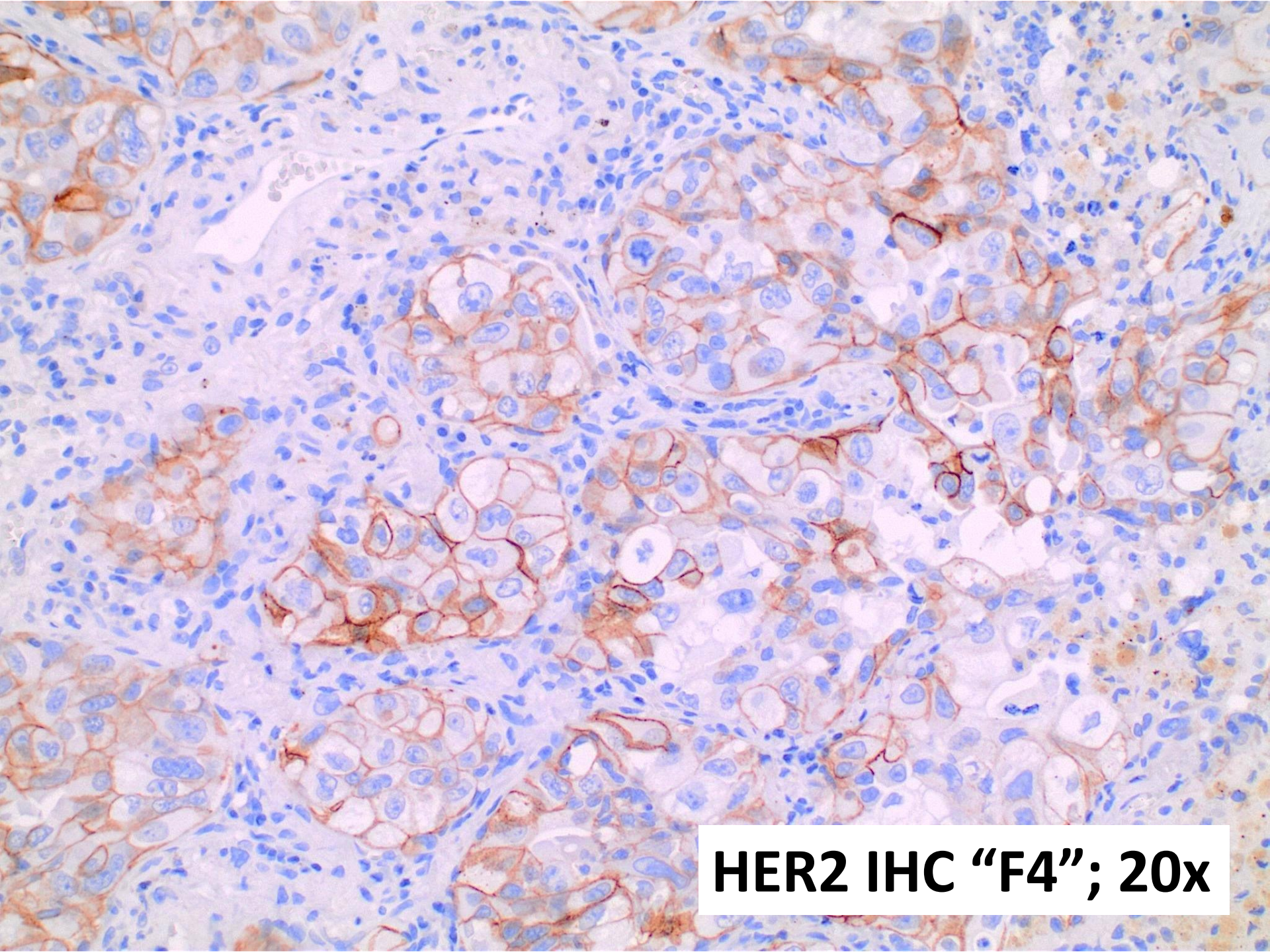
POSITIVE:
Tier II (variants of potential clinical significance):
***ERBB2 GENE* COPY NUMBER GAIN (1.84 Fold Change) = 4 COPIES** **(see comment)**

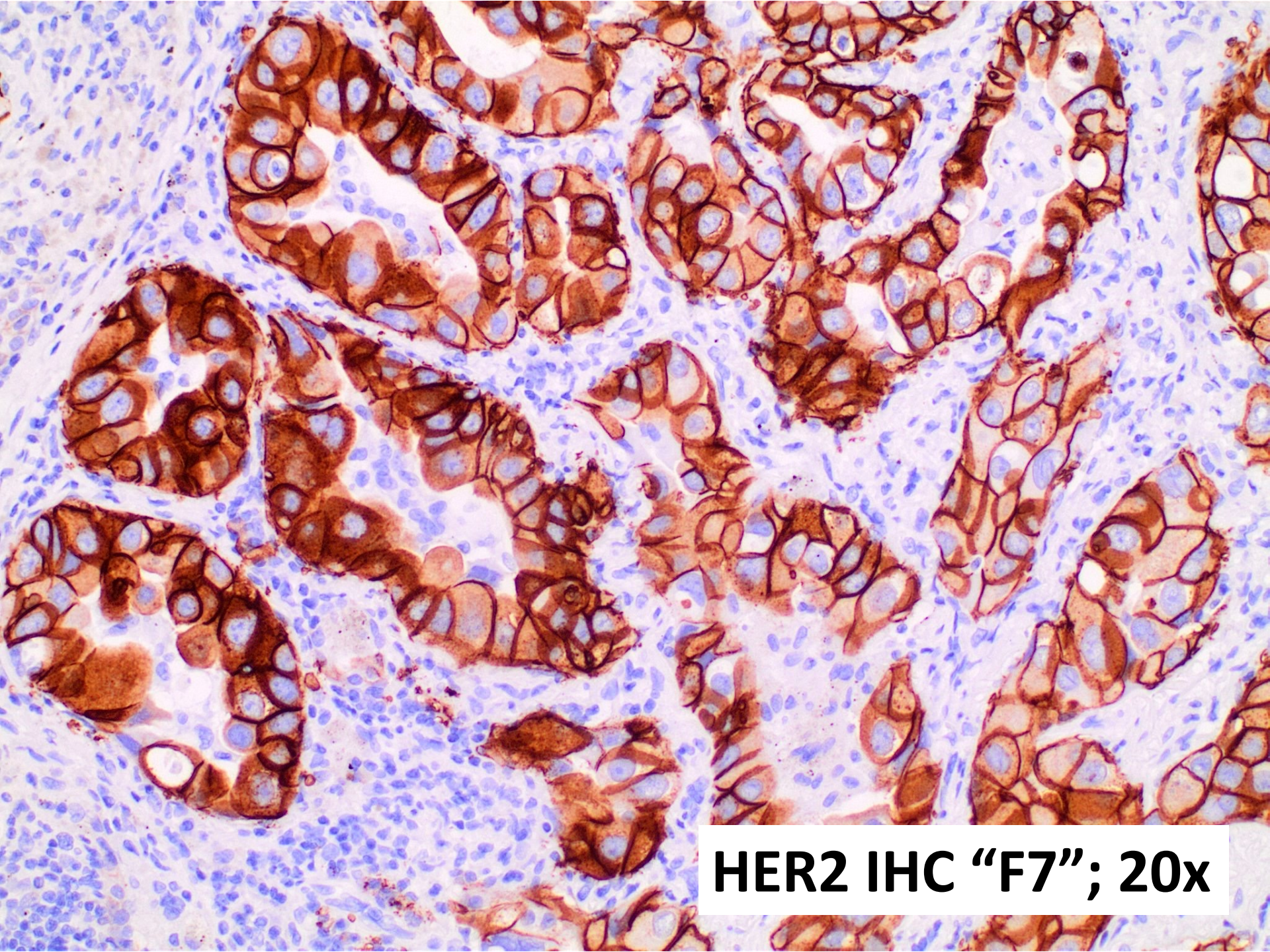
***MET* GENE COPY NUMBER GAIN (1.72 Fold Change) = 3-4 COPIES** **(see comment)**

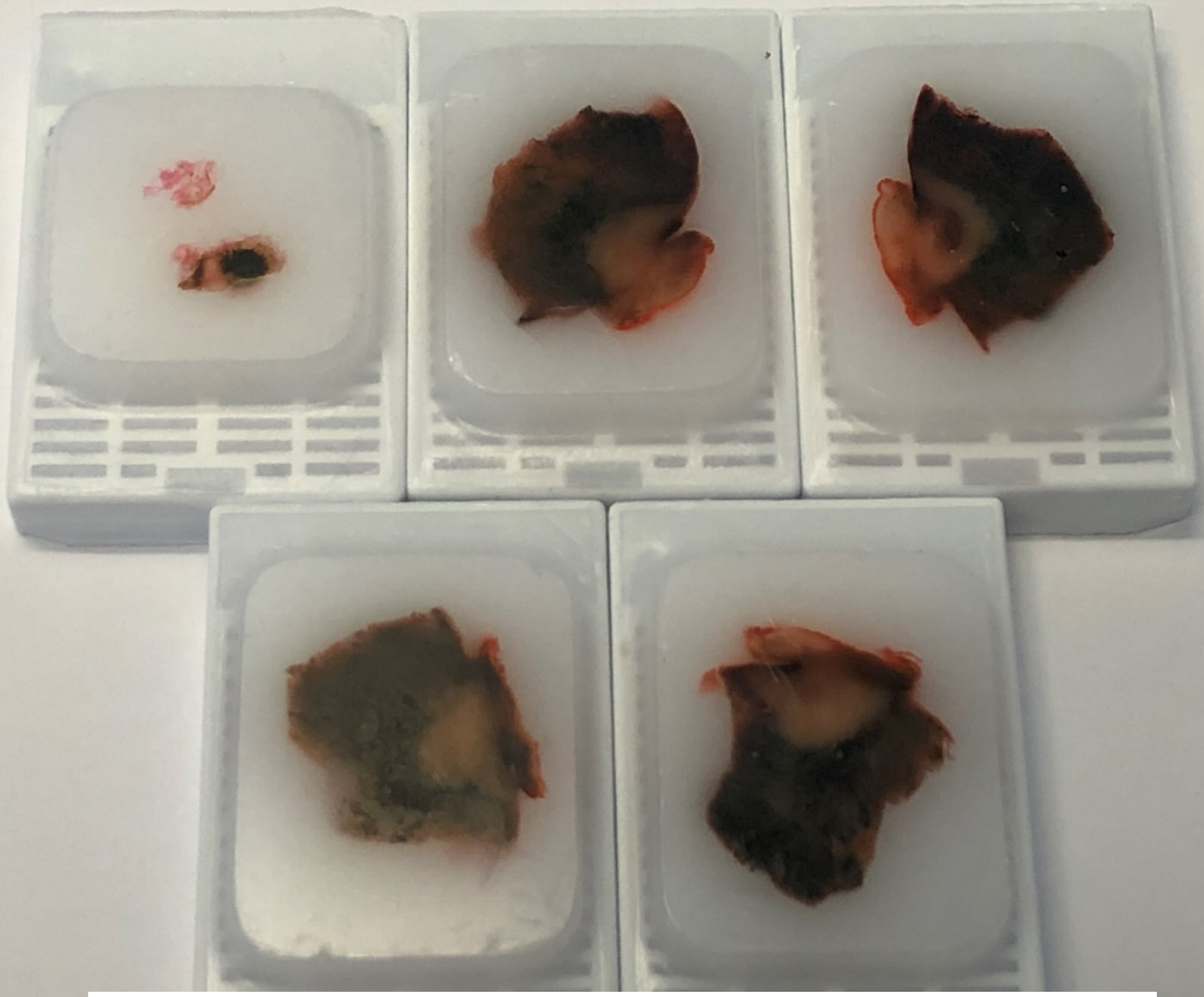
***TP53*: NM_000546.5, c.673-5_681del14, splice acceptor disruption, VAF=15.7%** **(see comment)**

See below for a complete list of genes covered by the assay.

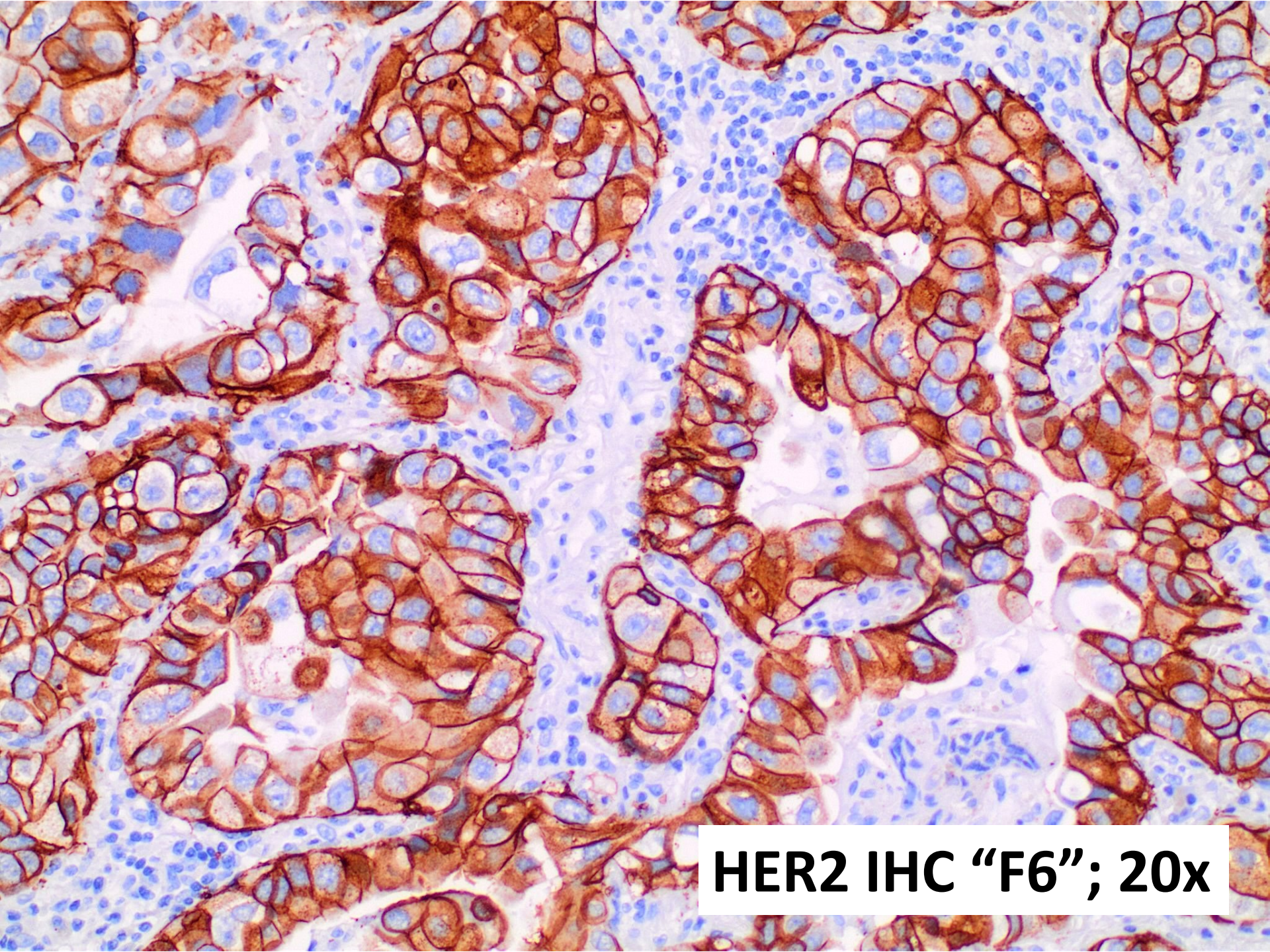
RNA FUSIONS:
NEGATIVE: NO FUSIONS WERE DETECTED
No pathogenic fusions were identified in targeted regions of 64 genes covered by this assay.
See below for a complete list of genes covered by the assay.

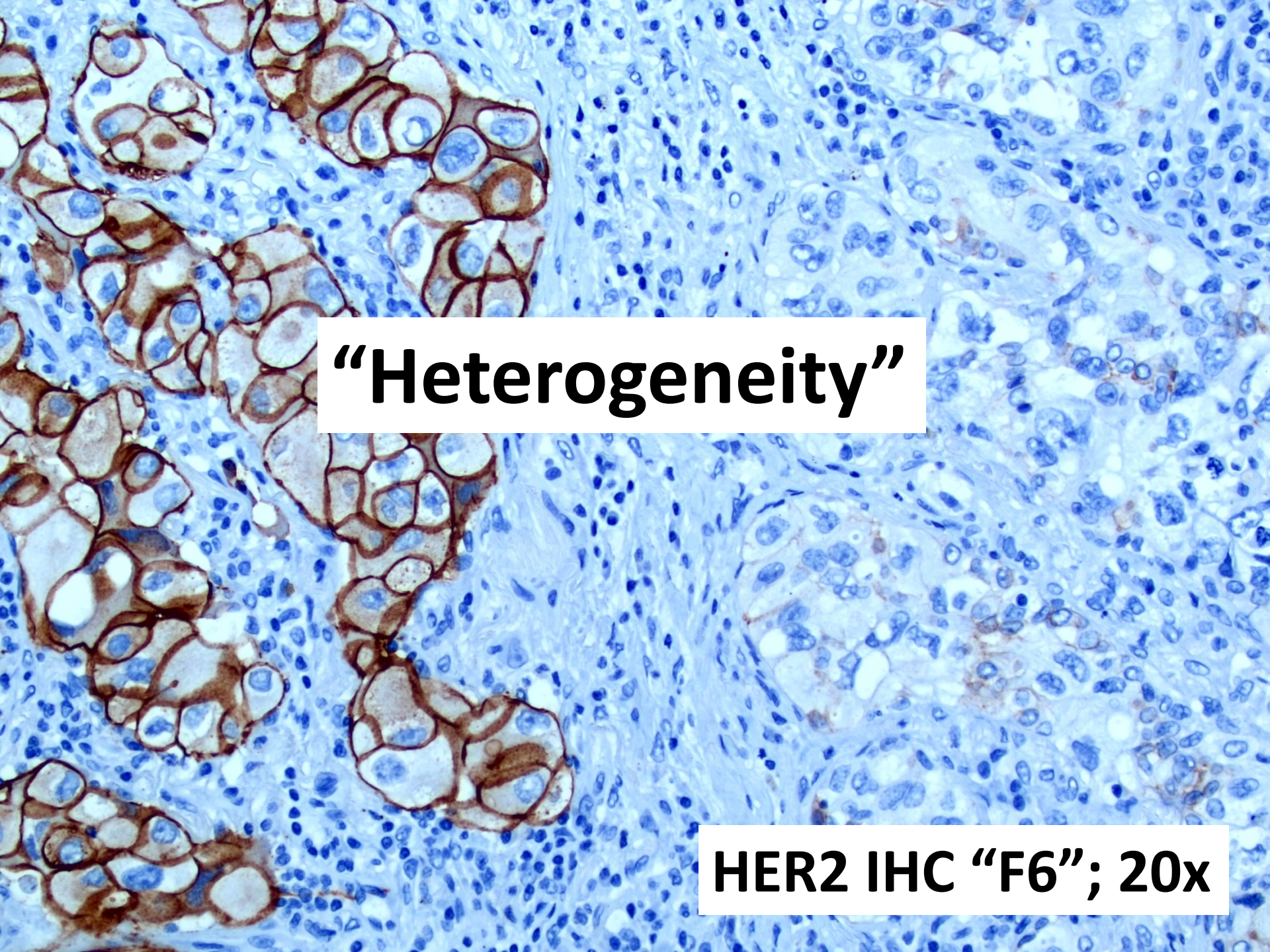

HER2 IHC “F4”; 20x

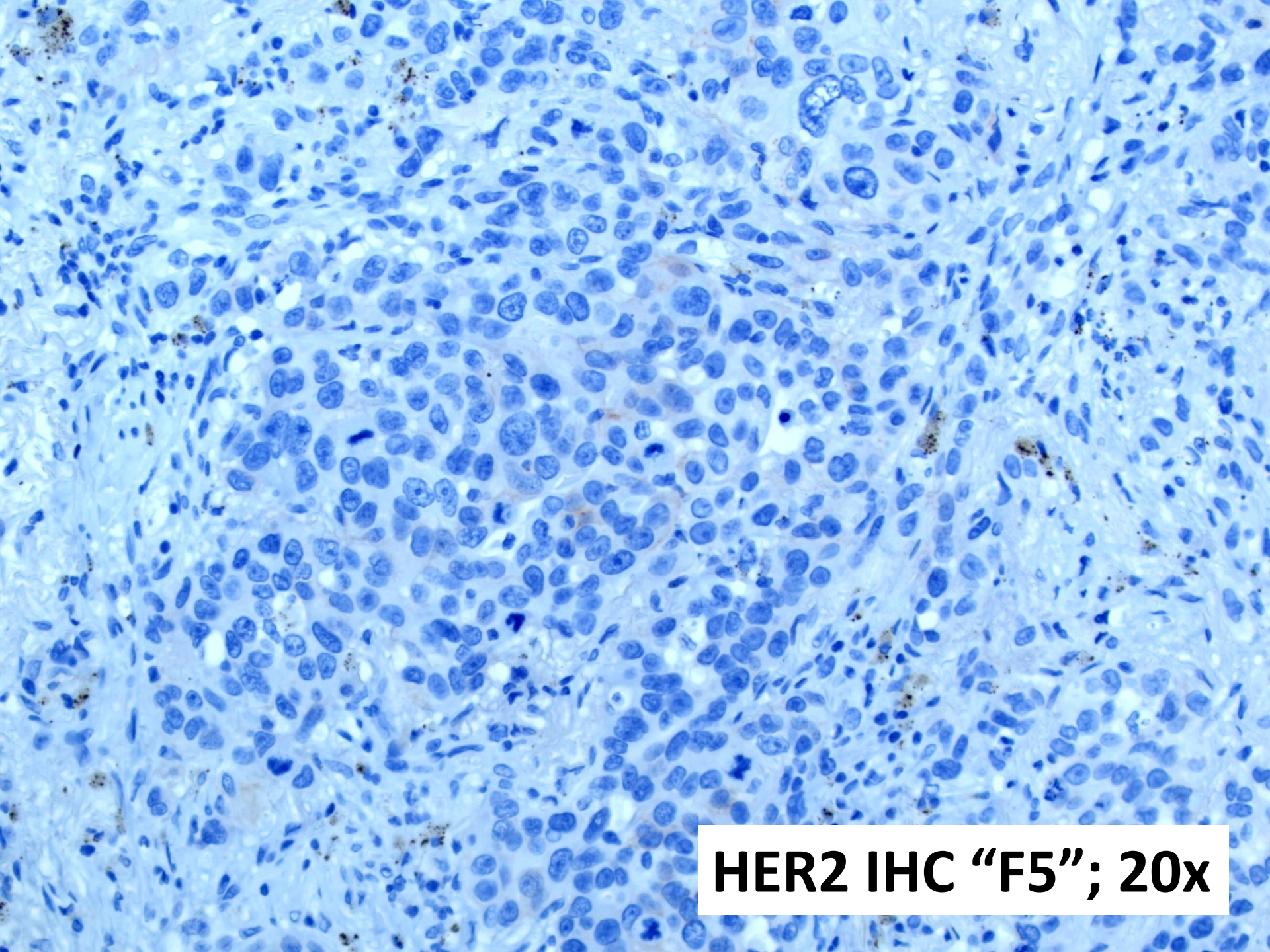

HER2 IHC “F7”; 20x

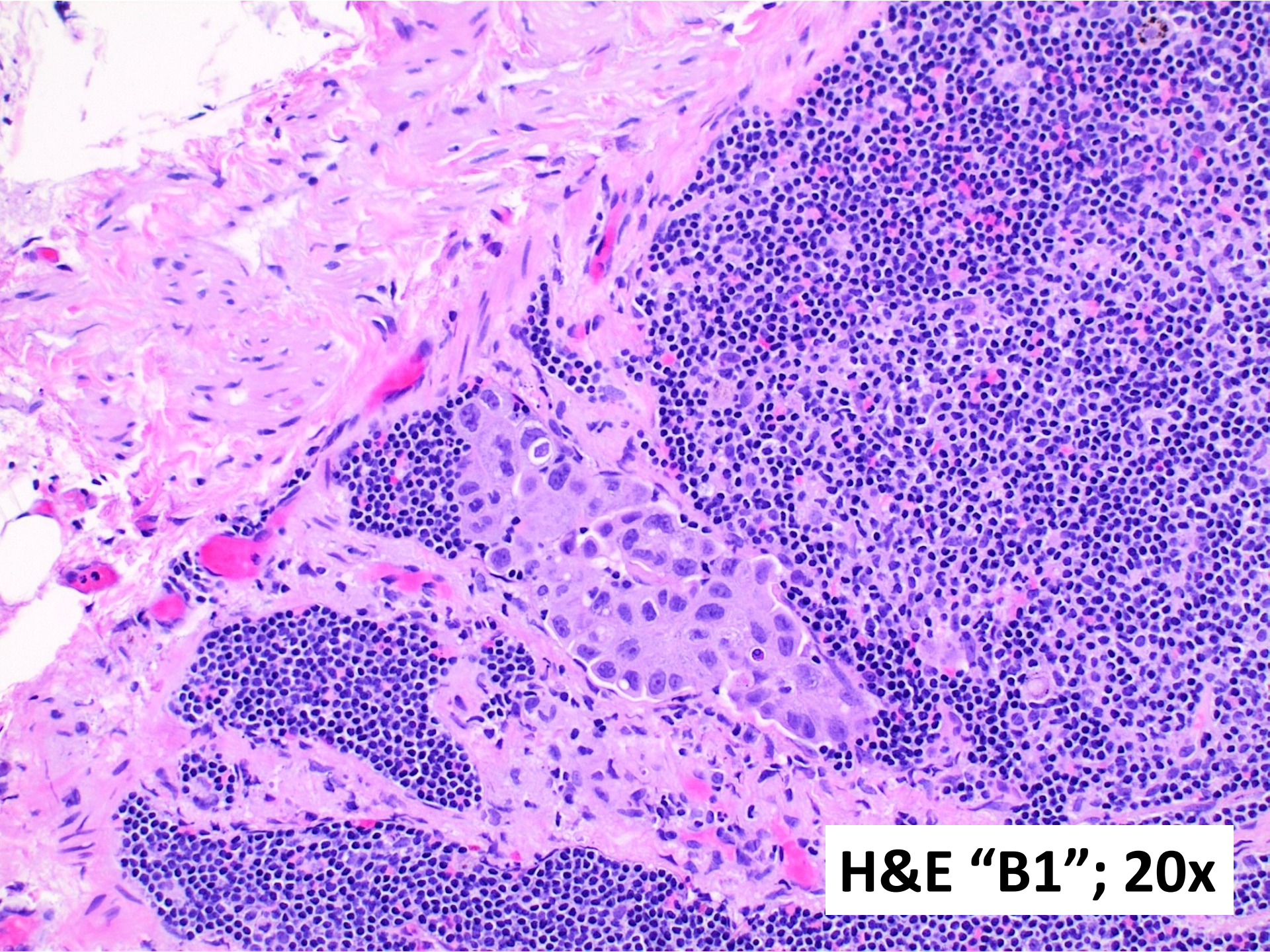


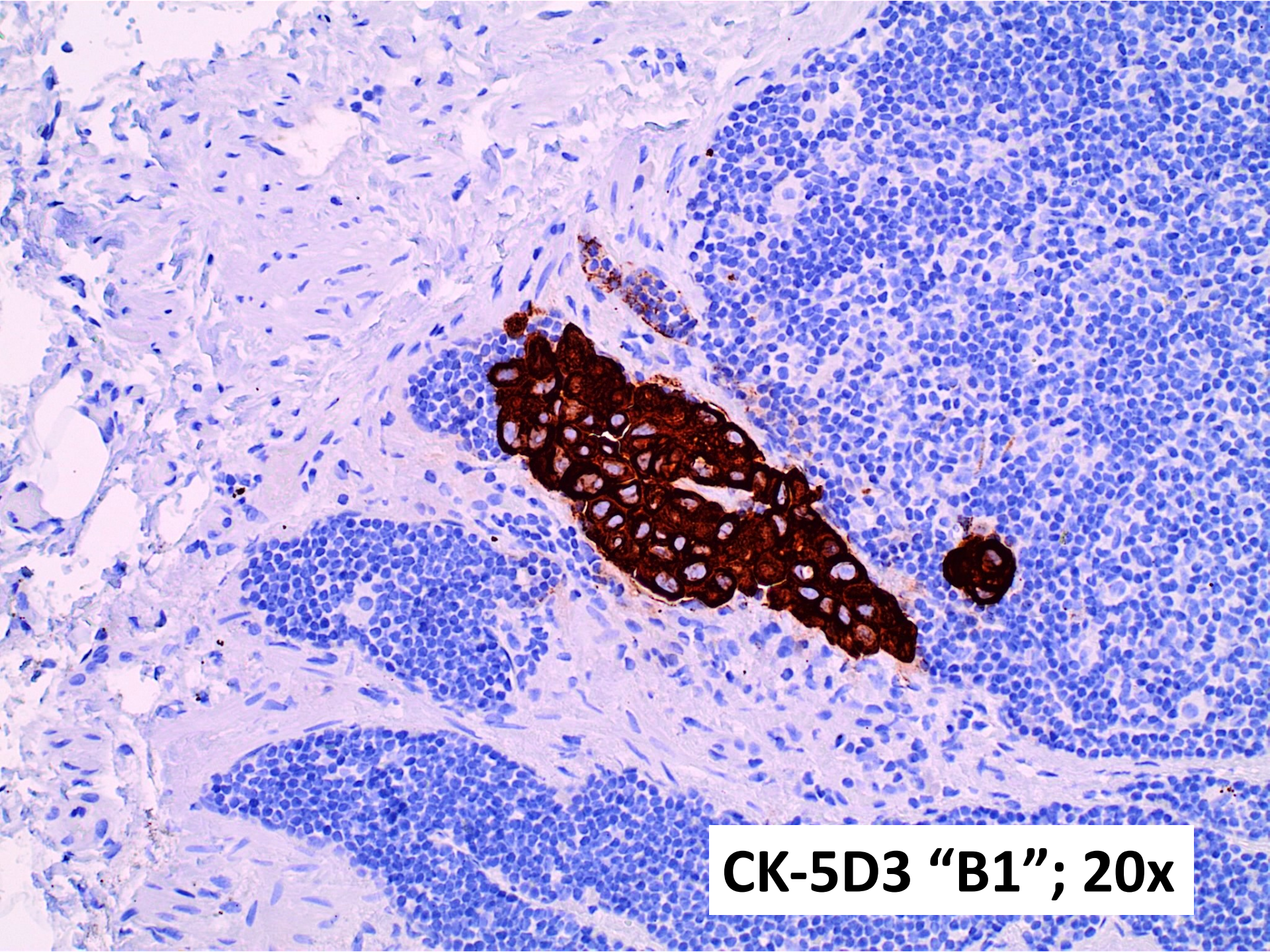
“5” Tissue Blocks With Tumor

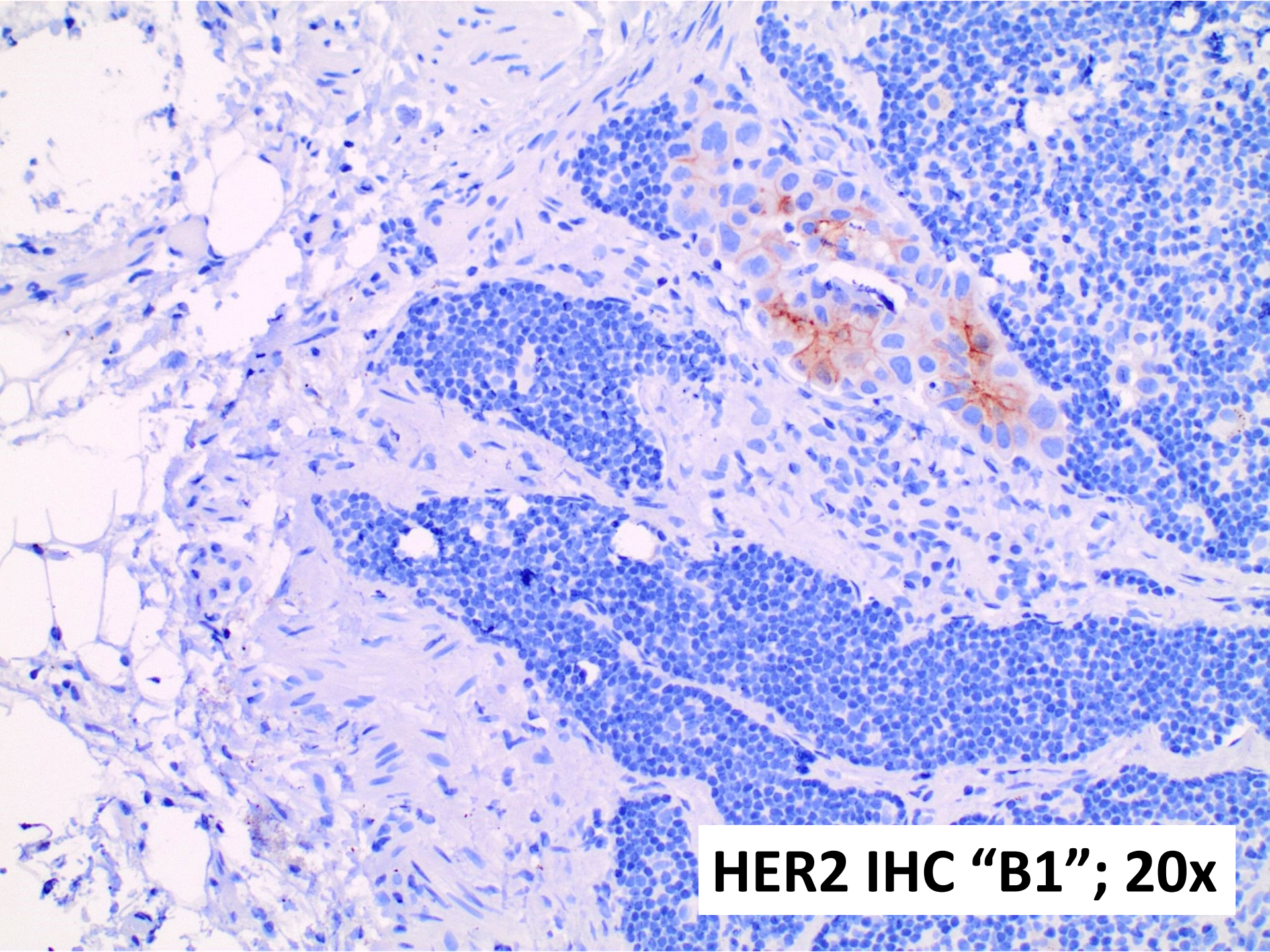

HER2 IHC “F6”; 20x


“Heterogeneity”
HER2 IHC “F6”; 20x


HER2 IHC “F5”; 20x


H&E “B1”; 20x


CK-5D3 “B1”; 20x


HER2 IHC “B1”; 20x

“Confirmational Proteomics”

- Immunohistochemical testing identifies protein overexpression that can result from genomic alterations, and that serves as a potential target for mAb-based targeted therapy.
- IHC testing may help to clarify the significance of certain genomic alterations based on the expression of the target protein.
- Heterogeneity remains a significant issue for ancillary testing that looks at “snapshots” of the cancer.
- Immunohistochemical testing evaluates the entire tumor “landscape” for proteomic expression and may help to predict response to targeted therapy inpatients with residual disease.

“To win the war on cancer, we need to put proteomics on an equal footing with genomics.”

Andreas Hühmer, Director, Thermo Fisher Scientific, USA