ETEROGENEITA' TUMORALE

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UNIVERSITÀ DI ROMA

Modulo dichiarazione conflitto di interessi

Tutti i rapporti finanziari intercorsi negli ultimi due anni devono essere dichiarati.

☒ Non ho rapporti (finanziari o di altro tipo) con le Aziende del farmaco

"Tumor Heterogeneity" ⟷ "Tumor Evolution"

Intra-tumor Heterogeneity

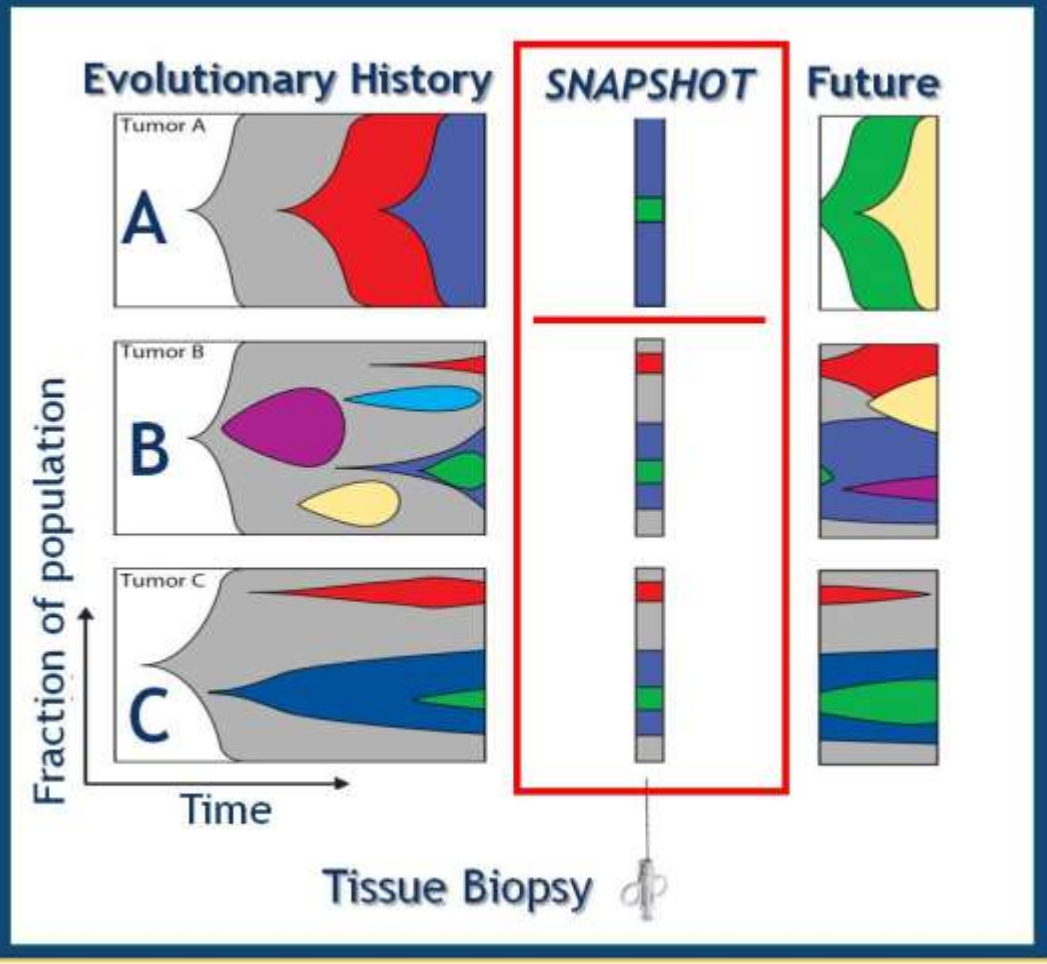
- heterogeneity within tumor
- spatial and temporal
- genetic, epigenetic, transcriptomic, proteomic

Inter-tumor Heterogeneity

- heterogeneity btw. patients

Heterogeneity in Interactions

with TME, external stresses

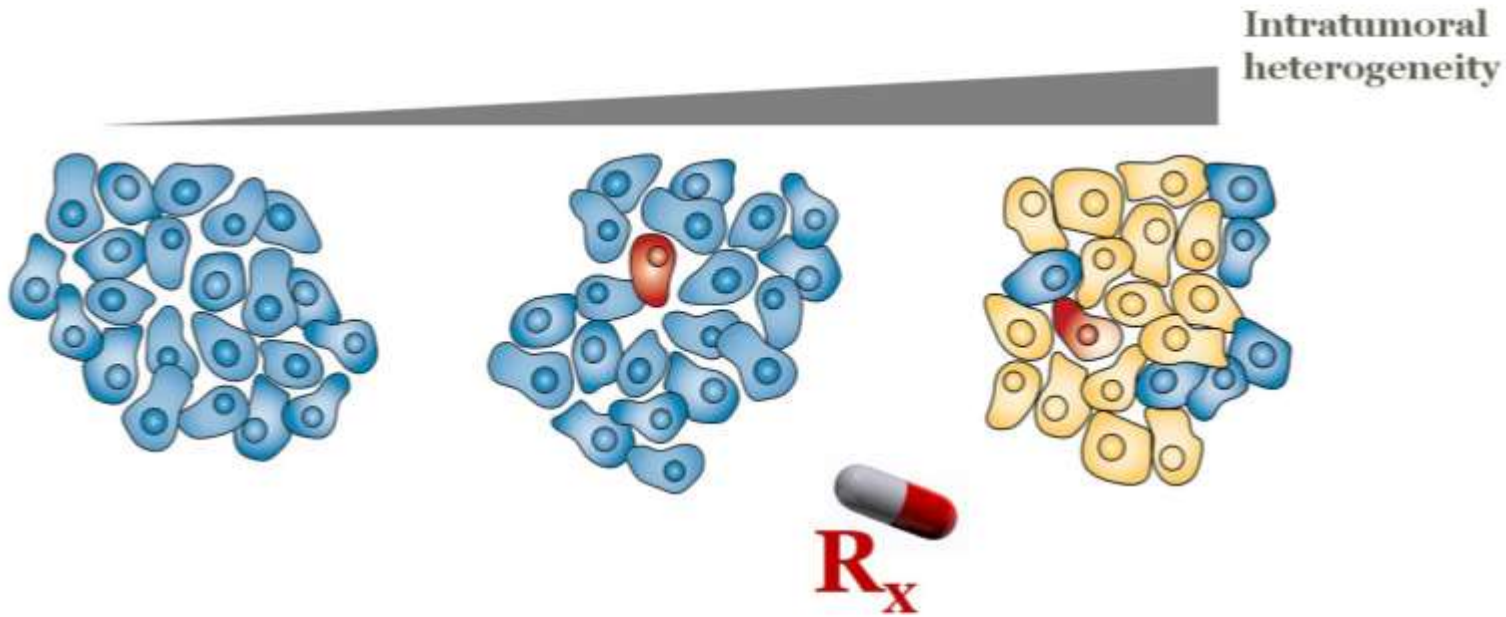


Hiley C et al. *Genome Biol*. 2014; 15(8): 453.

Presented By Patrick Ma at 2018 ASCO Annual Meeting

A cruel truth of many solid tumors

From modest to extensive intratumoral heterogeneity, the rule rather than exception



Presented By Barry Taylor at 2017 ASCO Annual Meeting

Which therapies cause heterogeneity?

"Chemotherapy"
Platinums
- **Carboplatin**
- **Cisplatin**

Other chemos
- Etoposide
- Vinorelbine
- Gemcitabine
- Irinotecan
- Topotecan
- Paclitaxel
- Docetaxel
- Pemetrexed
- Nab-paclitaxel

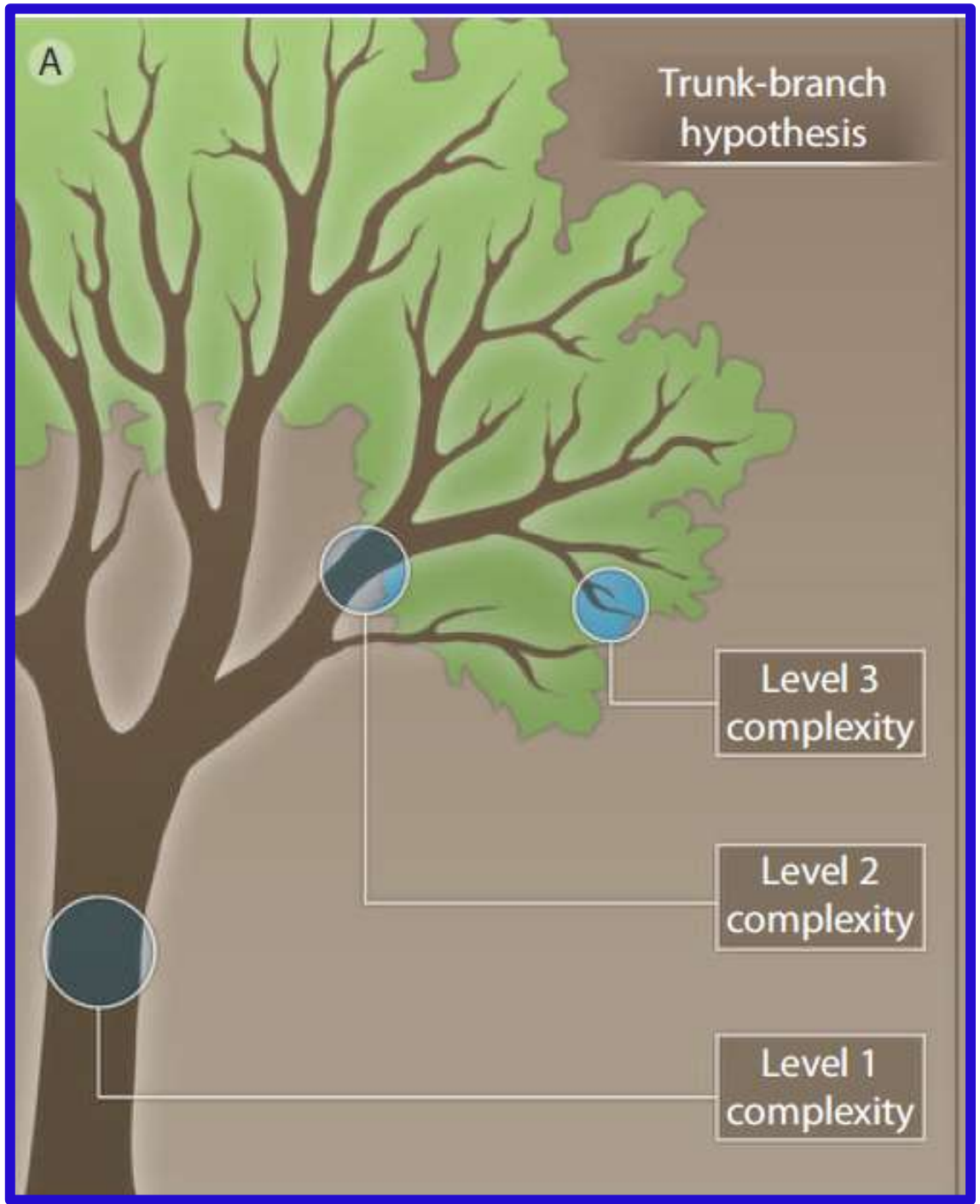
"Targeted Therapy"
VEGF Drugs
- Bevacizumab
- Ramucirumab

EGFR Drugs
- Erlotinib
- Afatinib
- Gefitinib
- Osimertinib
- Necitumumab

ALK/ROS1 Drugs
- Crizotinib
- Ceritinib
- Alectinib
- Brigatinib

"Immunotherapy"
Checkpoint inhibitors
- Nivolumab
- Pembrolizumab
- Atezolizumab

Presented By Joel Neal at 2017 ASCO Annual Meeting


A
Trunk-branch hypothesis
Level 3 complexity
Level 2 complexity
Level 1 complexity

A

Trunk-branch hypothesis

Level 3 complexity

Level 2 complexity

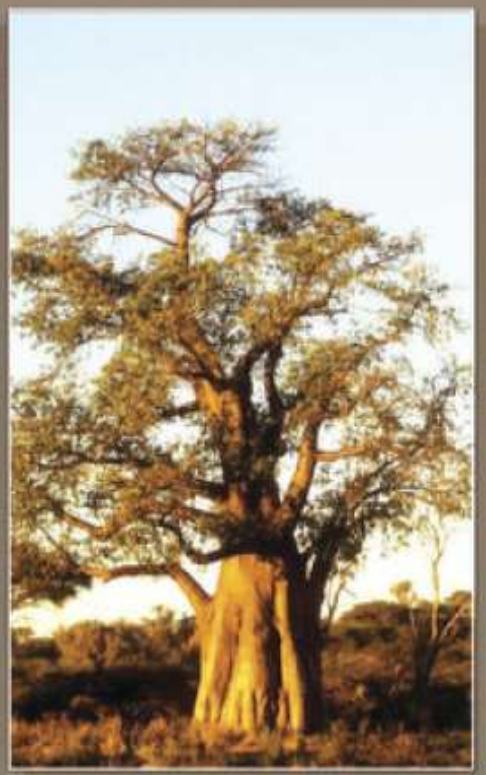
Level 1 complexity

B

Clonal architecture as a biomarker

Palm tree

Chestnut tree



Baobab tree

Risk of treatment failure ?

Tumor Heterogeneity: Will It Change What Pathologists Do

J Clin Pathol. 2018 Apr; 71(4): 285–290.
Published online 2017 Nov 7. doi: 10.1136/jclinpath-2017-204821
PMCID: PMC5868526
PMID: 29113995

Time for change: a new training programme for morpho-molecular pathologists?

What Are the Consequences of Molecular Tumor Heterogeneity in Daily Diagnostic Pathology Practice?

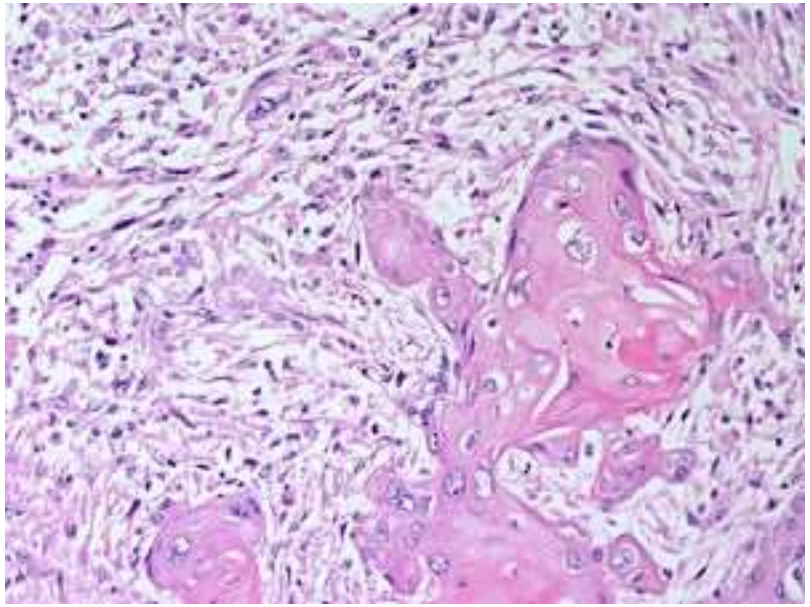
Front Med (Lausanne). 2017; 4: 227.
Published online 2017 Dec 8. doi: 10.3389/fmed.2017.00227

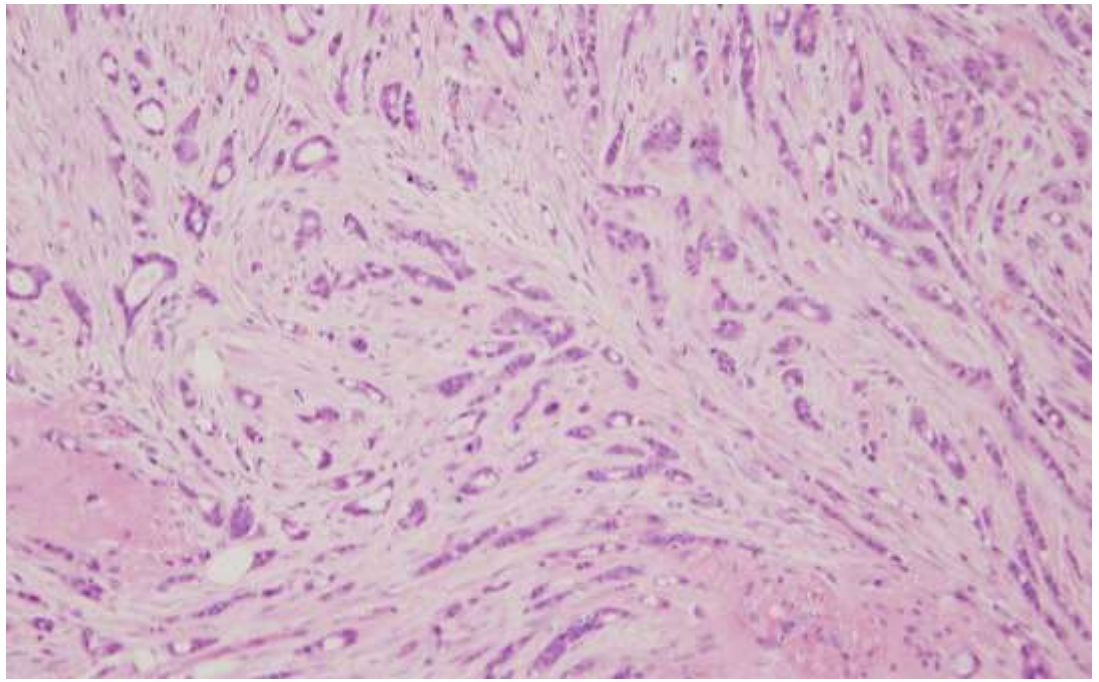
Tumor Heterogeneity in Breast Cancer

Gulisa Turashvili[1] and Edi Brogi[1,*]

ETEROGENEITA’ INTRATUMORALE

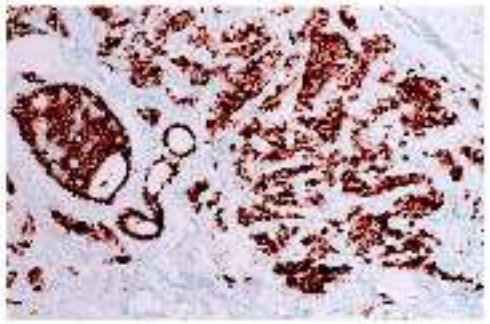
- Istopatologica





ETEROGENEITA' INTRATUMORALE: biomarcatori

ER/PG

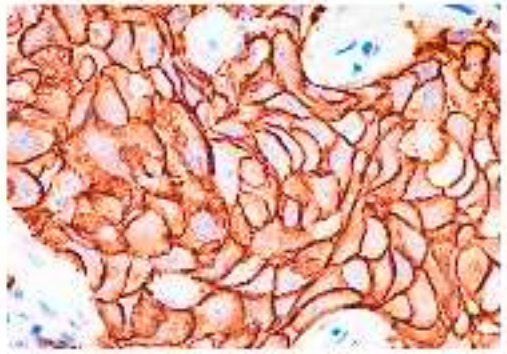


ASCO/CAP Guideline Recommendations for Immunohistochemical Testing of Estrogen and Progesterone Receptors in Breast Cancer. *Hammond et al 2010.*

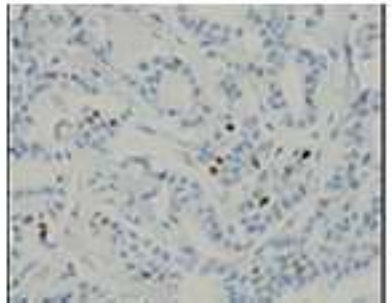
>=1%

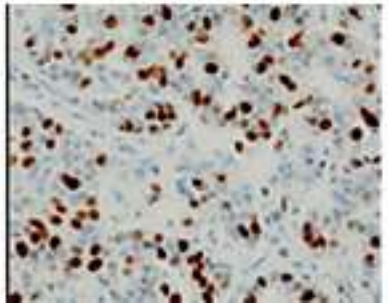
GLI IMPRESCINDIBILI!

Her2



Ki67





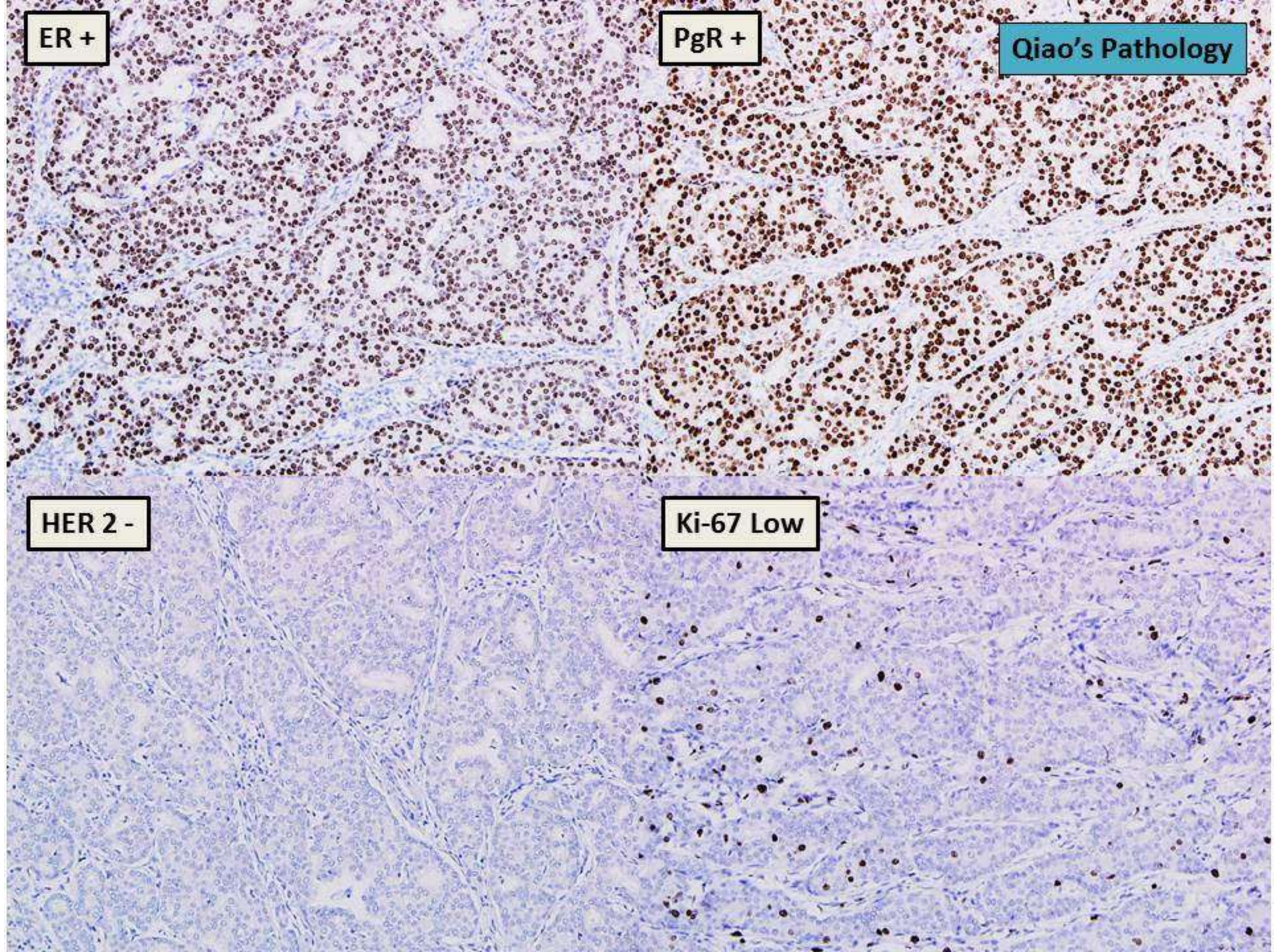
Conversione dei biomarkers tra PT e MT

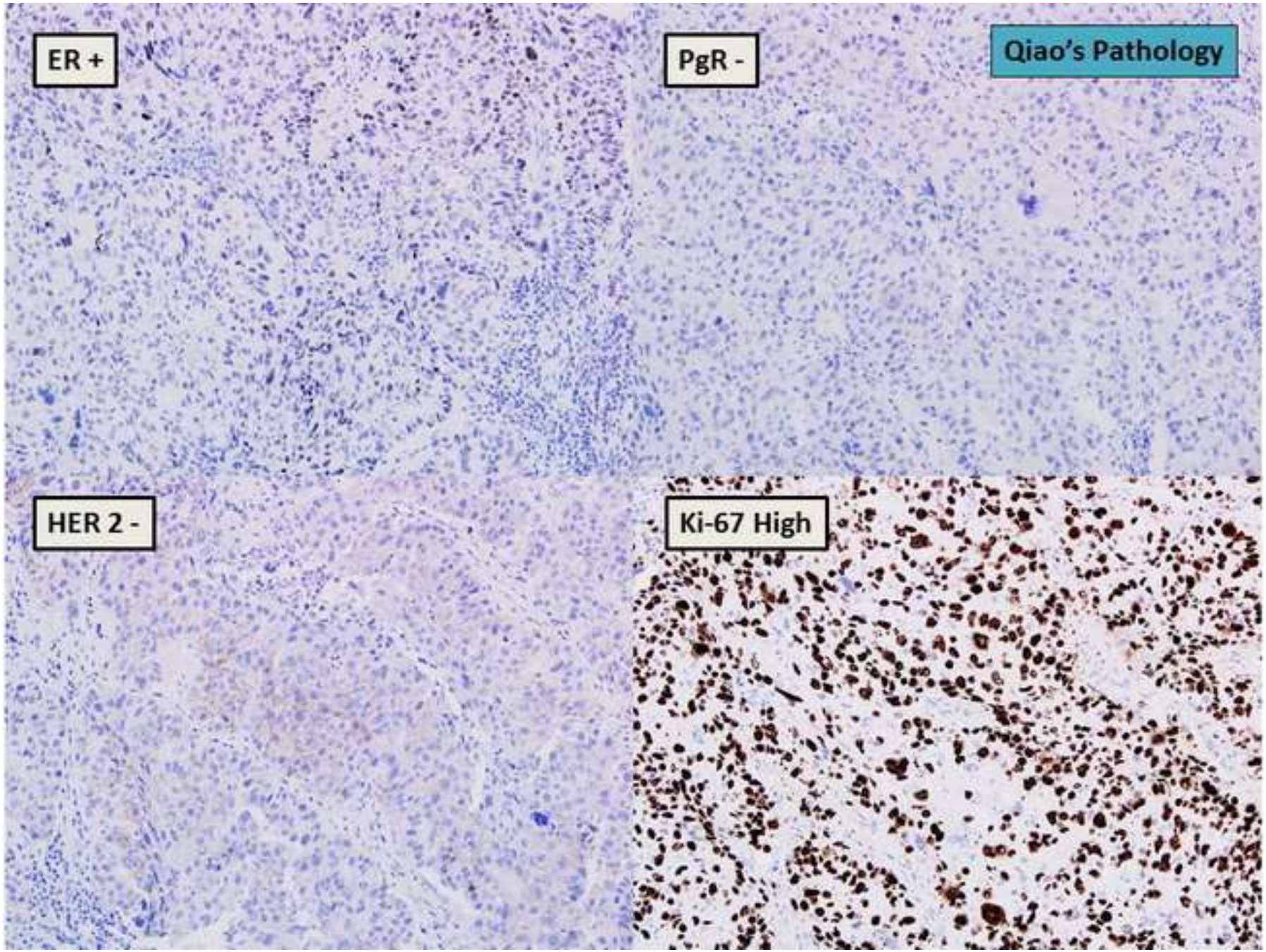
- La negativizzazione dei ER/PG e l'incremento del Ki67 si associa a prognosi peggiore
- ER: 6-40%; PG: 21-41%; Her2/Neu: 1-41% (*Criscitiello C et al; Breast Cancer Res. 2014*)
- Meta-analisi di 48 studi: tasso di discordanza per ER, PG, Her2 dell'8-23% (*Aurilio G et al; Eur J Cancer. 2014*)
- Iperespressione di Her2/Neu nei MT nelle metastasi cerebrali e ossee di TNBC (*Wallwiener M et al; Oncotarget 2017*)

Mod Pathol. 2016 Dec;29(12):1460-1470. doi: 10.1038/modpathol.2016.116. Epub 2016 Aug 26.

Influence of decalcification procedures on immunohistochemistry and molecular pathology in breast cancer.

Schrijver WA[1], van der Groep P[1,2], Hoefnagel LD[1], Ter Hoeve ND[1], Peeters T[1], Moelans CB[1], van Diest PJ[1].


ER +
PgR +
Qiao's Pathology
HER 2 -
Ki-67 Low


ER +
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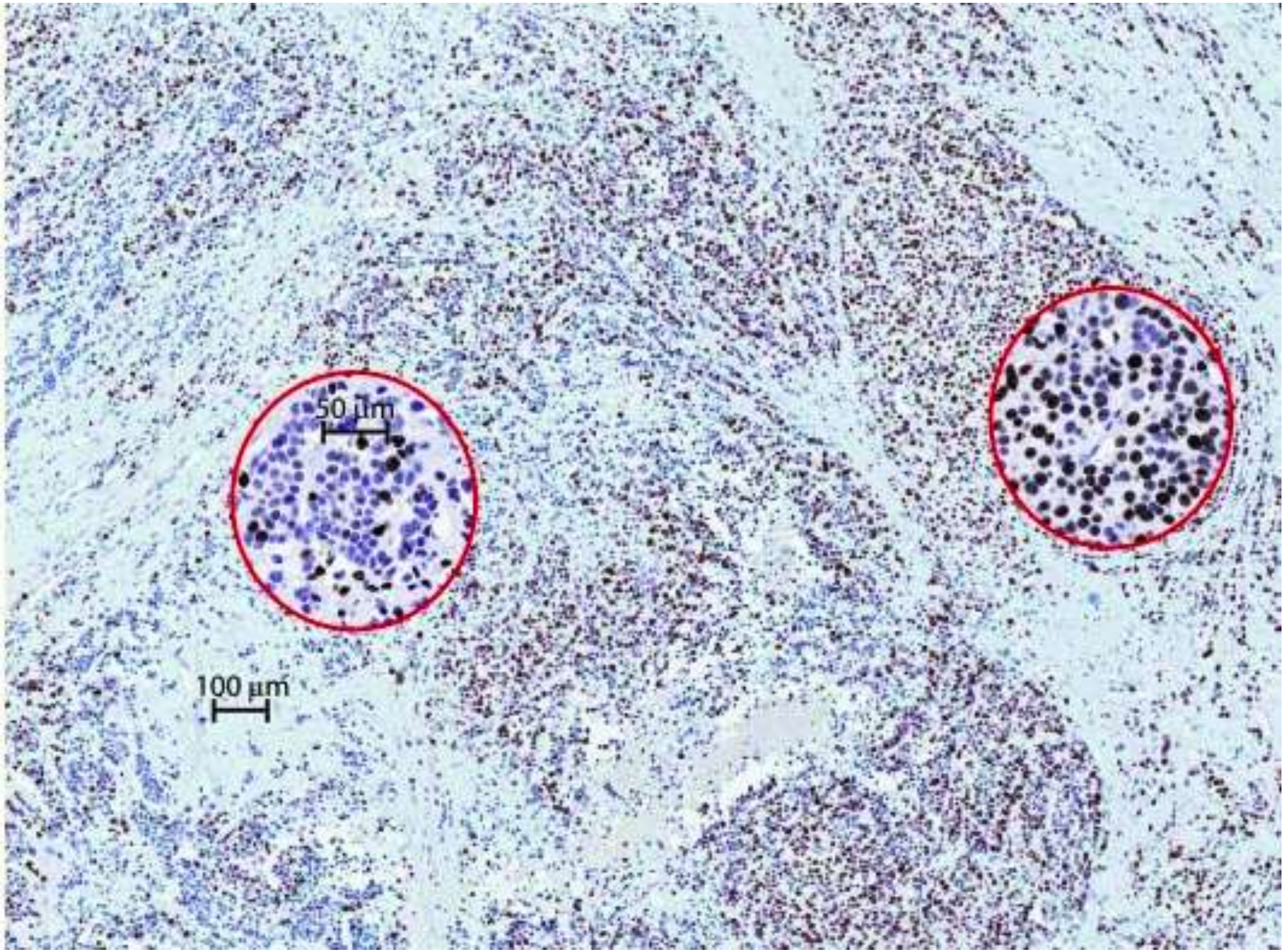
HER 2 -
Ki-67 High

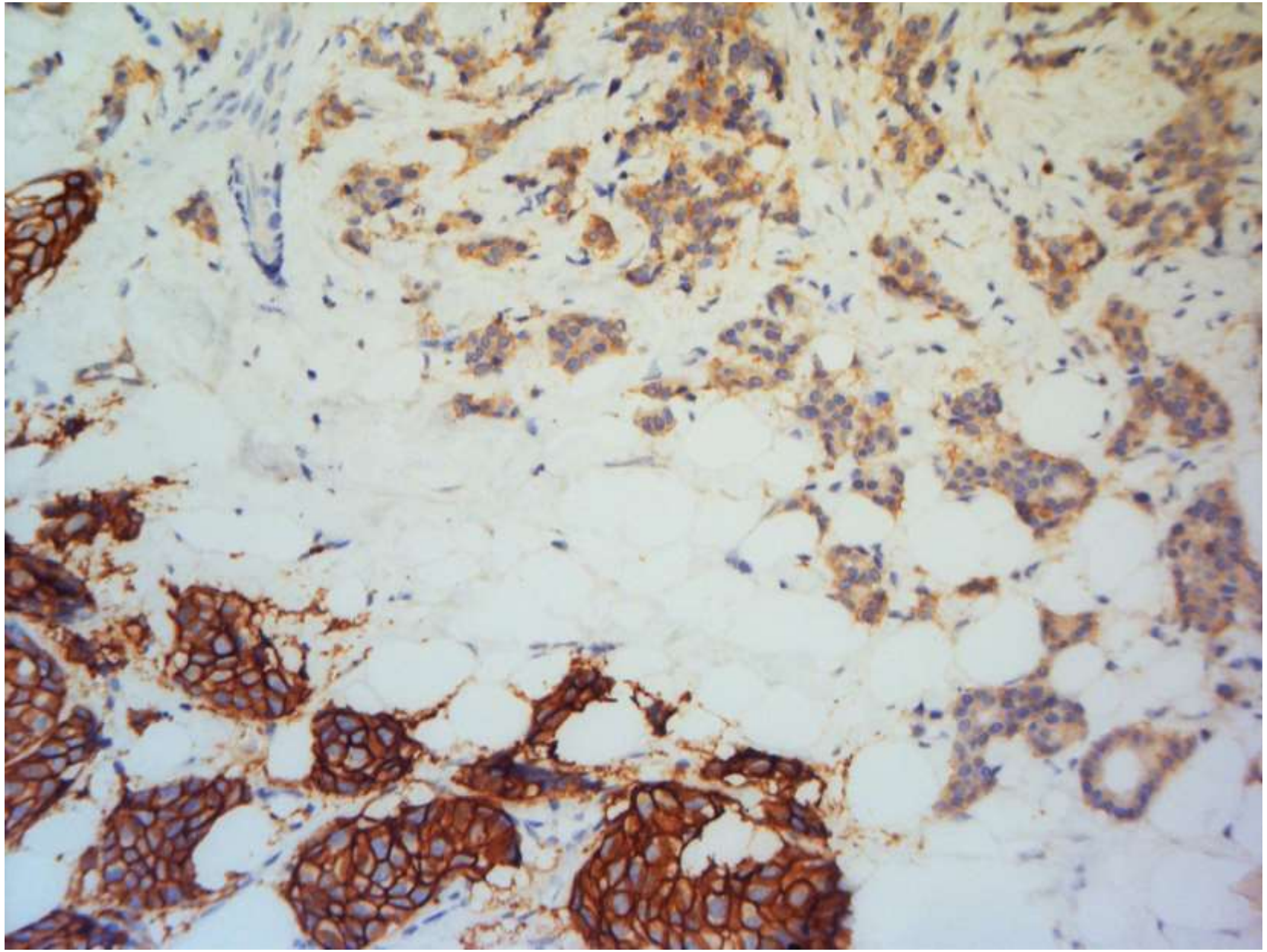

50 µm
100 µm

Interpretation and scoring

- In full sections, at least three high-power (×40 objective) fields should be selected to represent the spectrum of staining seen on initial overview of the whole section.
- For the purpose of prognostic evaluation, the invasive edge of the tumor should be scored.
- If pharmacodynamic comparisons must be between core cuts and sections from the excision, assessment of the latter should be across the whole tumor.
- If there are clear hot spots, data from these should be included in the overall score.
- Only nuclear staining is considered positive. Staining intensity is not relevant.
- Scoring should involve the counting of at least 500 malignant invasive cells (and preferably at least 1000 cells) unless a protocol clearly states reasons for fewer being acceptable.
- Image analysis methods for Ki67 remain to be proven for use in clinical practice.

Data handling

- The Ki67 score or index should be expressed as the percentage of positively staining cells among the total number of invasive cells in the area scored.
- Statistical analysis should take account of the log-normal distribution generally followed by Ki67 measurement.
- The most appropriate endpoint in comparative studies of treatment efficacy or response is the percentage suppression of Ki67-positive cells.
- The most appropriate endpoint for assessing residual risk of recurrence is the on-treatment proportion of Ki67-positive cells.
- Cut points for prognosis, prediction, and monitoring should only be applied if the results from local practice have been validated against those in studies that have defined the cutoff for the intended use of the Ki67 result.



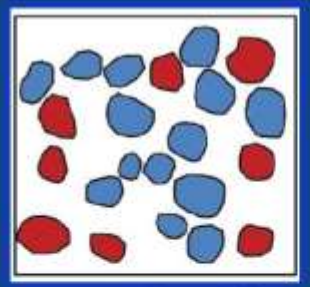
HER2 heterogeneity as a predictor of response to neoadjuvant T-DM1 plus pertuzumab: Results from a prospective clinical trial.

June 3, 2019

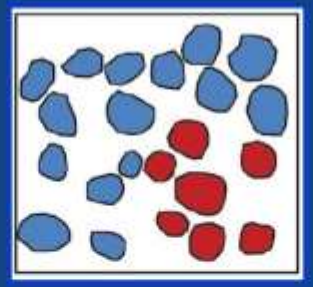
Otto Metzger Filho, Giuseppe Viale, Lorenzo Trippa, Tianyu Li, Denise A. Yardley, Ingrid A. Mayer, Vandana Gupta Abramson, Carlos L. Arteaga, Laura Spring, Adrienne Gropper Waks, Michalina Janiszewska, Eileen Wrabel, Michelle Demeo, Aditya Bardia, Tari A. King, Kornelia Polyak, Eric P. Winer, Ian E. Krop; Dana-Farber.

Background: HER2 Heterogeneity

- HER2 heterogeneity is defined by the presence of at least two distinct clones of cells with different levels of HER2 amplification within a tumor
- Estimates of prevalence of heterogeneity: 10-30% (depends on definition, population)



Scattered amplified cells (red)



Cluster of amplified cells (red)

Vance GH et al. Arch Pathol Lab Med 2009
Viale et al. Modern Pathology 2013
Lee, HJ. Am J Clin Pathol 2014
Lee, HJ. Am J Clin Pathol 2015

Study Hypothesis and Rationale

- HER2 heterogeneity is associated with inferior pathologic complete response (pCR) rate to neoadjuvant targeted anti-HER2 therapy

Investigating the impact of HER2 heterogeneity on response to therapy is an important step while we try to de-escalate chemotherapy and rely on HER2-targeted Rx

Study Design

- Centrally-confirmed HER2+ BC
- Stage II and III (N = 164)

Single Arm

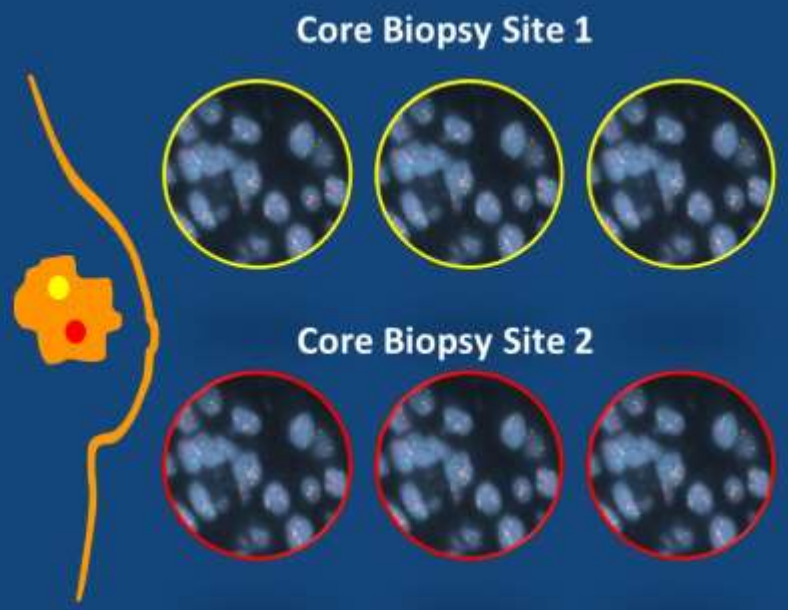
T-DM1 + Pertuzumab q3w x 6

SURGERY

● ● Image-guided research biopsies

Presented By Otto Metzger Filho at 2019 ASCO Annual Meeting

HER2 Heterogeneity: Method of Evaluation



HER2 Heterogeneity defined as either

1) HER2 positivity by FISH in > 5% and < 50% of tumor cells (i.e., CAP guideline)
2) An area of tumor that tested HER2 negative.

Assessment performed by central laboratory (European Institute of Oncology, Milan) and blinded to treatment outcome

Vance GH et al. Arch Pathol Lab Med 2009
Bartlett JM et al. J Clin Pathol 2011

Objectives

Primary

To investigate the relationship between pCR (defined as Residual Cancer Burden = 0) and intratumor heterogeneity of HER2 amplification

Secondary

Safety and tolerability
Objective response rate
Disease-free survival and overall survival

Translational

Digital Spatial Profiling (DSP) of HER2 heterogeneity

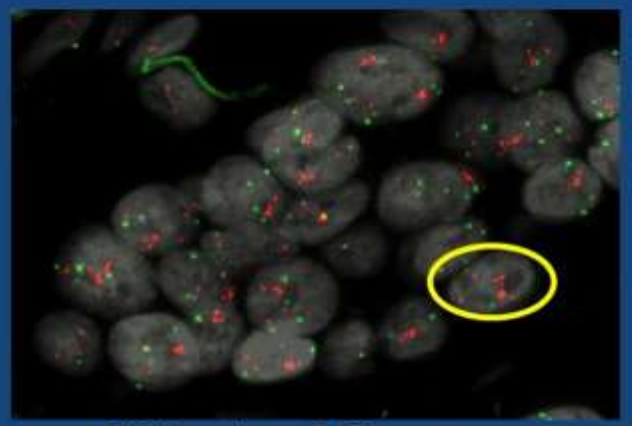
Baseline Characteristics

Characteristic N (%)	T-DM1 plus Pertuzumab N = 163
Median tumor size (IQR)	2.8 cm (2.1-3.8 cm)
Hormone receptor status, n (%)	
ER+ and/or PR+	112 (68.7%)
ER- and PR-	51 (31.3%)
Clinical stage	
I	1 (0.6%)
II	138 (84.7%)
III	24 (14.7%)
HER2 IHC (central evaluation)	
2+	40 (24.5%)
3+	121 (74.2%)
Missing	2 (1.2%)

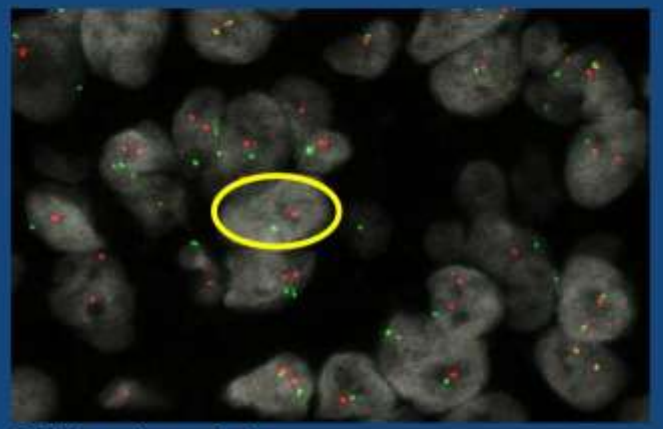
Results: Prevalence of Heterogeneity

- 16/157(10%) of evaluable cases were classified as HER2 heterogenous
  - 13 (81%) hormone receptor positive and 3 (19%) hormone receptor negative

Example: Core biopsy site 1 amplified and site 2 non-amplified



FISH ratio = 3.85



FISH ratio = 1.1

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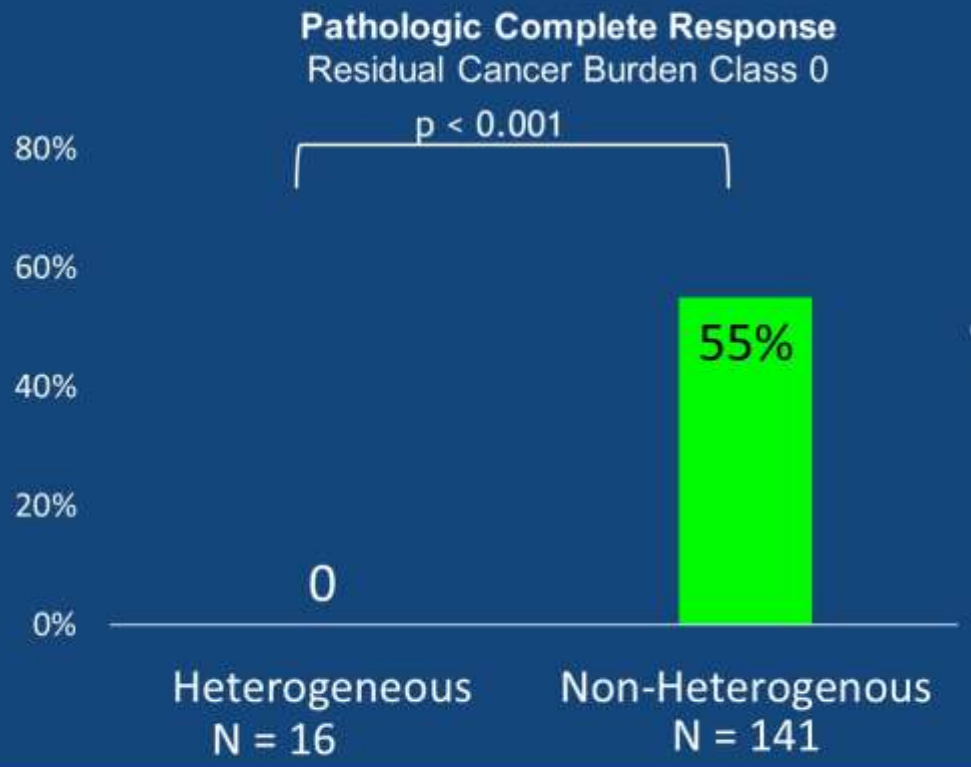
Effect of Heterogeneity on pCR



The study met its primary endpoint by demonstrating a significant association between HER2 heterogeneity and pCR adjusted by ER status (p < 0.001)

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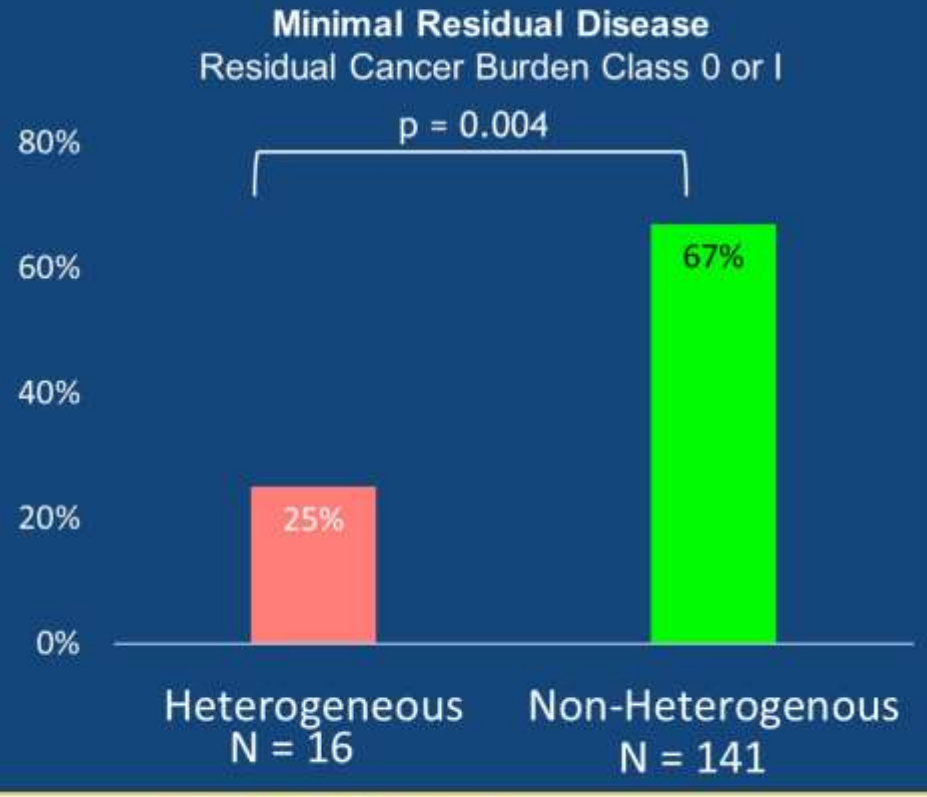
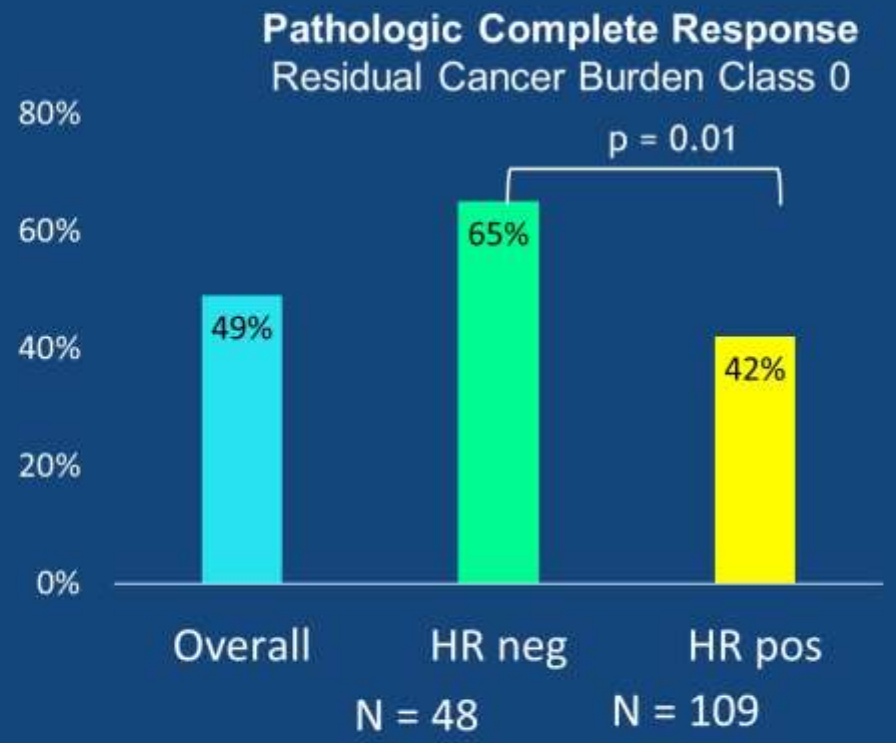
Effect of Heterogeneity on RCB 0 or I



Significant association between heterogeneity and RCB 0 or I adjusted by ER status (OR = 5.6, p = 0.004)

pCR by Hormone Receptor Status



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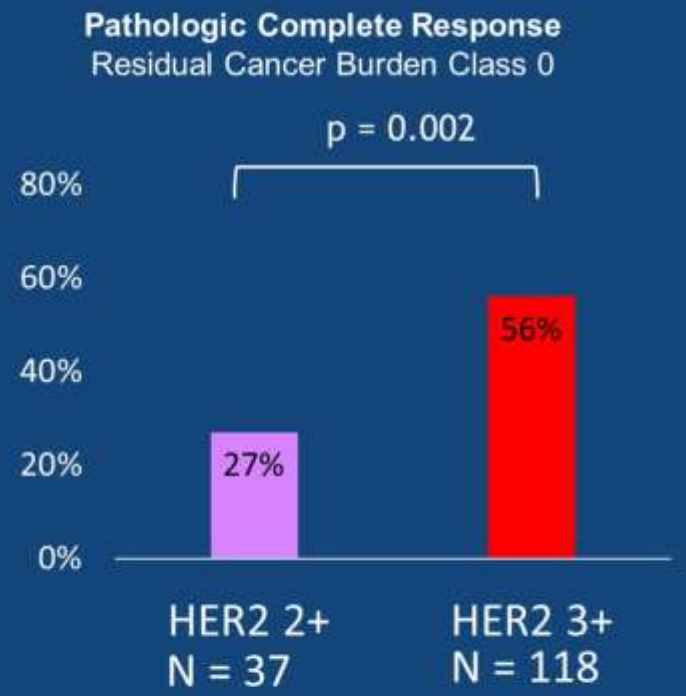
Exploratory Analyses: pCR by HER2 IHC



The association between HER2 heterogeneity and pCR remained significant when adjusted by ER status and HER2 IHC status (p = 0.002)

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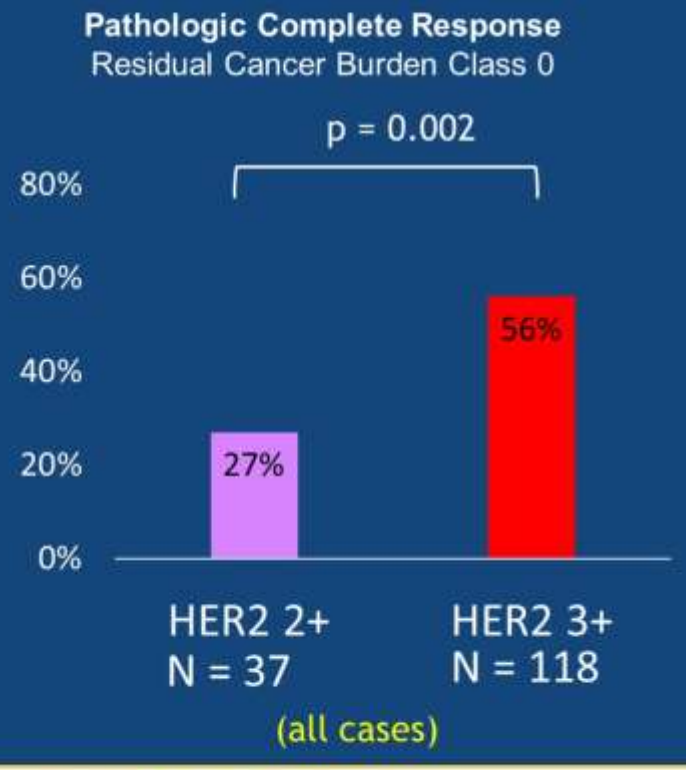
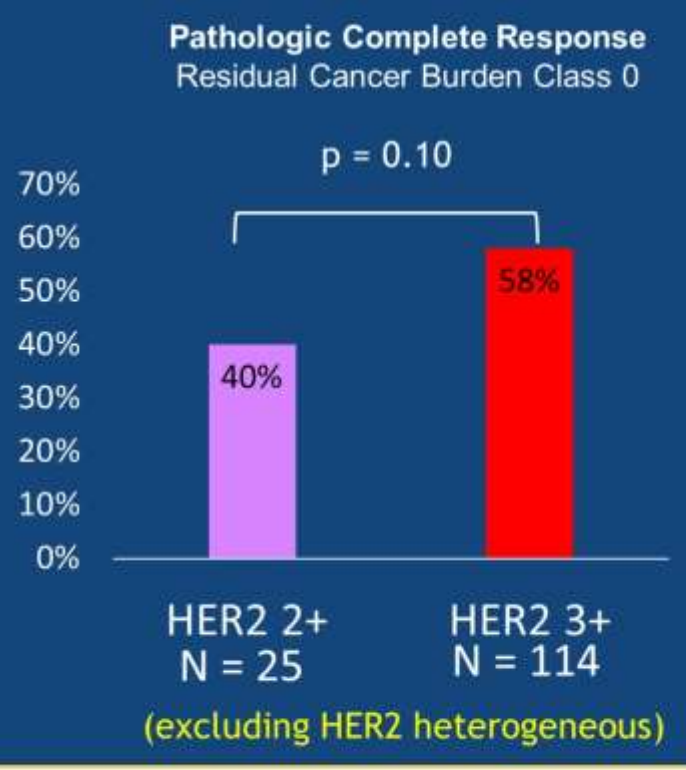
Exploratory Analyses: pCR by HER2 IHC





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Translational Research: Digital Spatial Profiling

Measurement of HER2 protein level in multiple areas of each case

- FFPE slides stained with oligonucleotides antibodies (i.e. HER2)
- Pan-CK to select regions of interest (ROIs)
- Quantification via nCounter Assay (NanoString Technologies)

Patient Selection

- 30 cases
- Heterogeneous and non-heterogeneous cases (with or without pCR)
- Core biopsy site 1 and 2 profiled
- 3-4 Regions of Interest (ROI) per site

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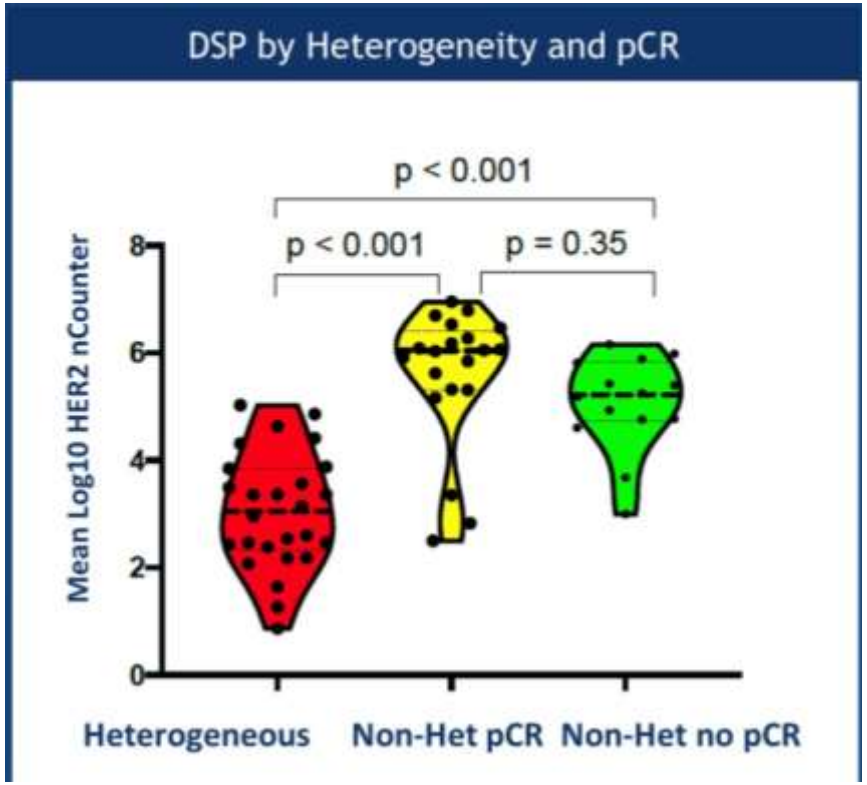
Digital Spatial Profiling - Results



Conclusions

- Our study met its primary endpoint by demonstrating a significant association between HER2 heterogeneity and pCR
  - This effect was independent of ER status and HER2 protein expression by IHC
- The use of a clinical definition of HER2 heterogeneity defined by FISH should facilitate efforts to validate in other studies
- T-DM1 plus Pertuzumab is a well tolerated regimen with 95% of pts completing six cycles of tx
  - In the non-heterogeneous group pCR rate is 55%
- HER2 heterogeneous cancers may represent a distinct subset of HER2+ breast cancer
  - Lower rates of pCR
  - Lower levels of HER2 protein expression
  - Possibly require different treatment approaches

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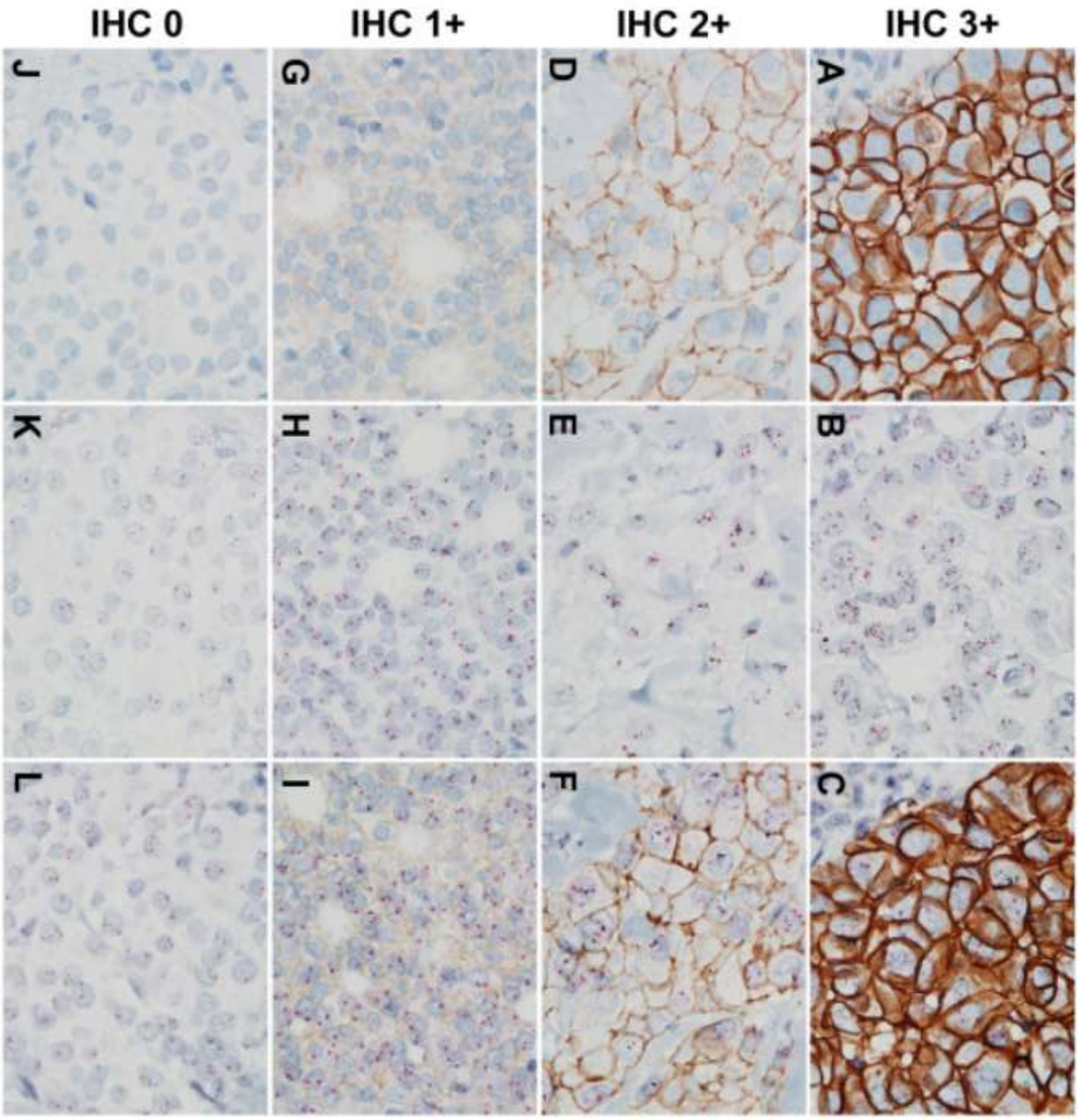

IHC 0
IHC 1+
IHC 2+
IHC 3+
J
G
D
A
K
H
E
B
L
I
F
C

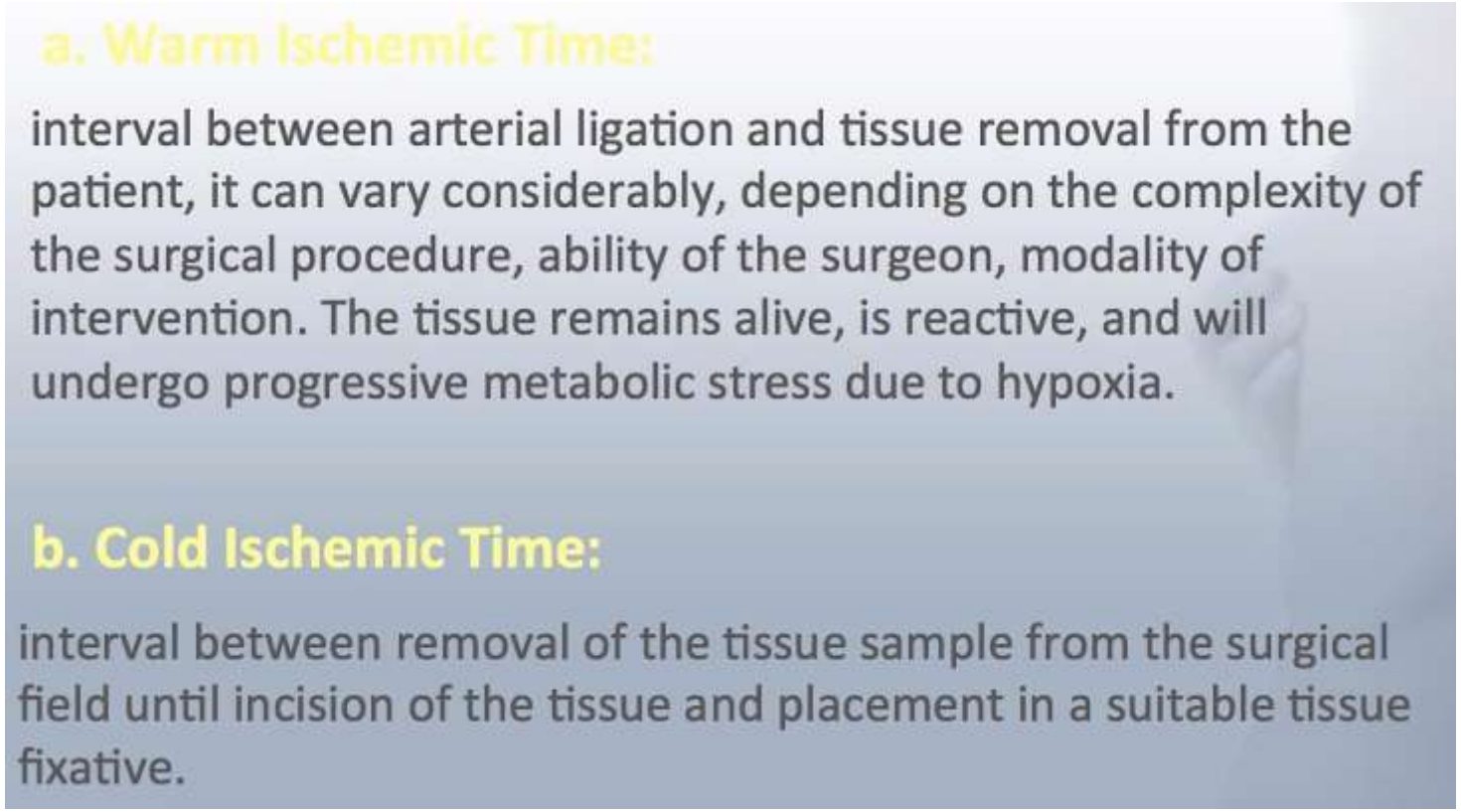
Un evergreen:
la corretta fissazione!

- «breast biopsies and excised breast tissue samples be assessed grossly as rapidly as possible, sectioned and placed in formalin, ideally **within 1 h** from excision and removal from the patient, and that these times be recorded for each specimen»
- «biopsies fixed for intervals shorter than 6 hours or longer than 72 hours»
- «surgical sample fixed <24h and/or >72h»

«Examples of circumstances that may lead to uninterpretable results include:

testing of needle biopsies or cytology samples fixed in alcohol, use of fixatives other than 10% neutral buffered formalin, samples where fixation was delayed for more than 1 hour»

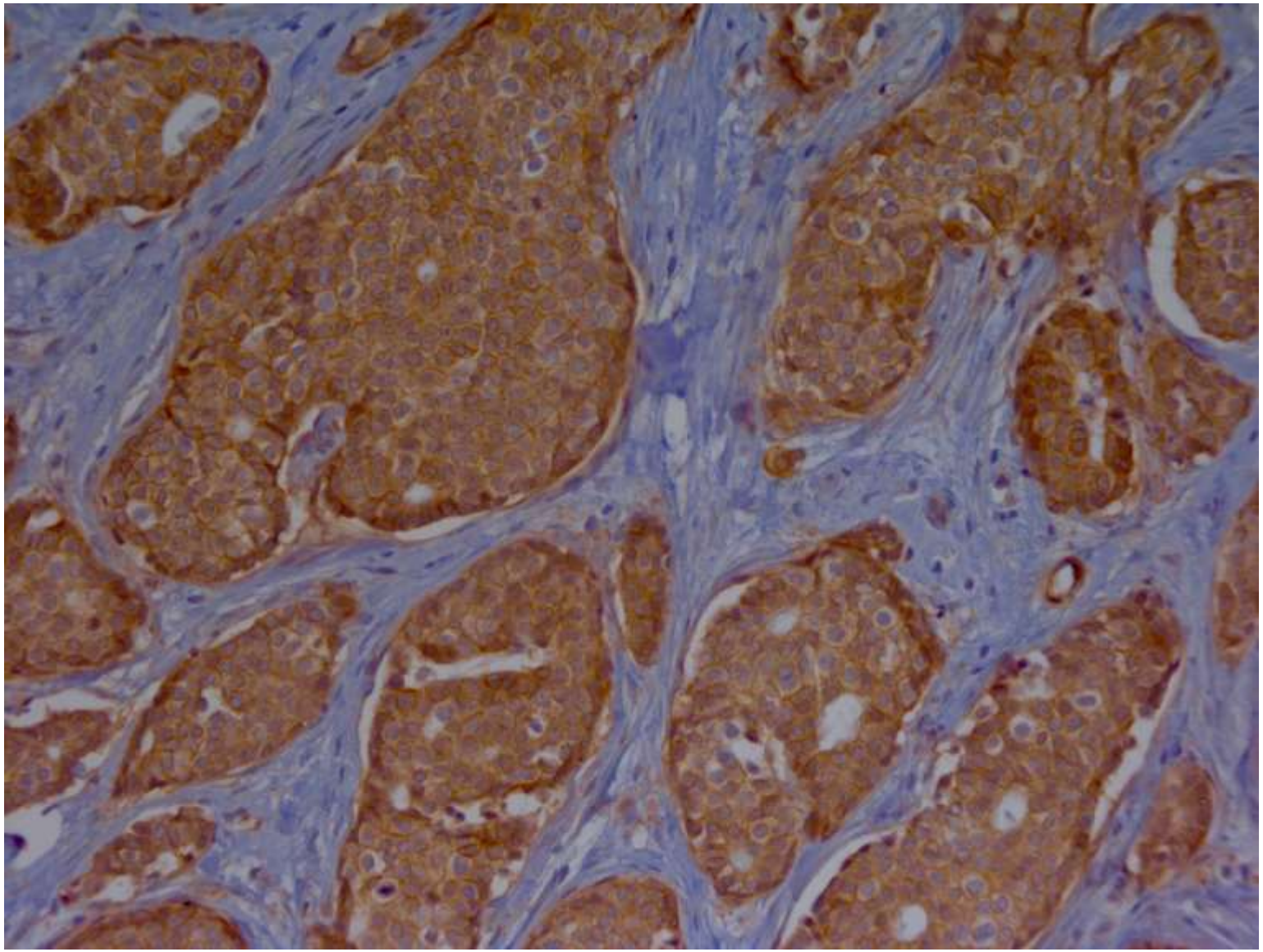
Hammond et al. 2010; Wolff et al. 2014; Taylor et al 2006; Goldstein NS et al 2003.

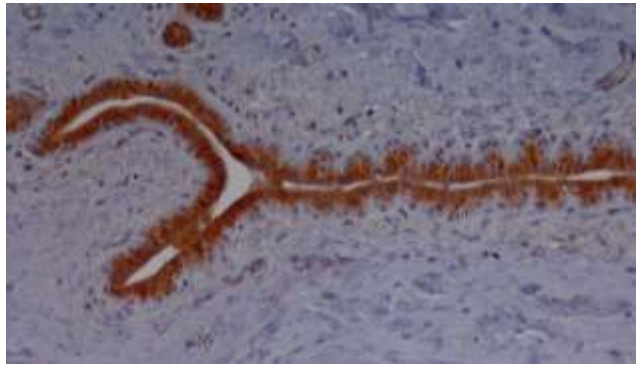


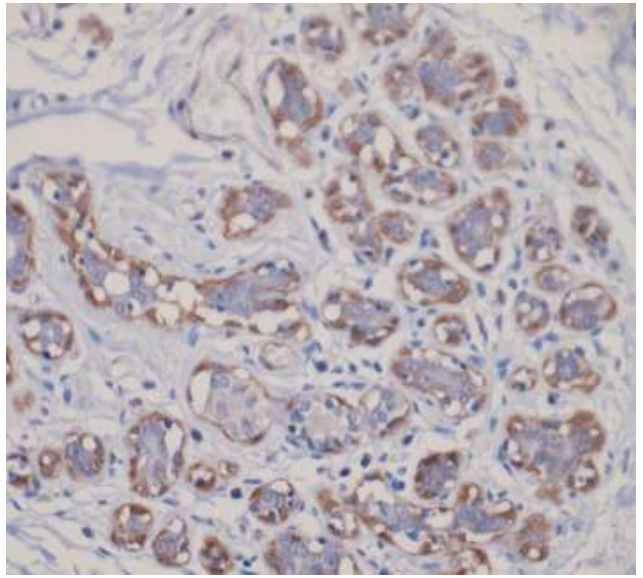
«important variables in the analysis of labile macromolecules such as proteins, RNA, and DNA from clinical tissue samples».

American Society of Clinical Oncology/College of American Pathologists Guideline Recommendations for Immunohistochemical Testing of Estrogen and Progesterone Receptors in Breast Cancer. Hammond et al 2010.

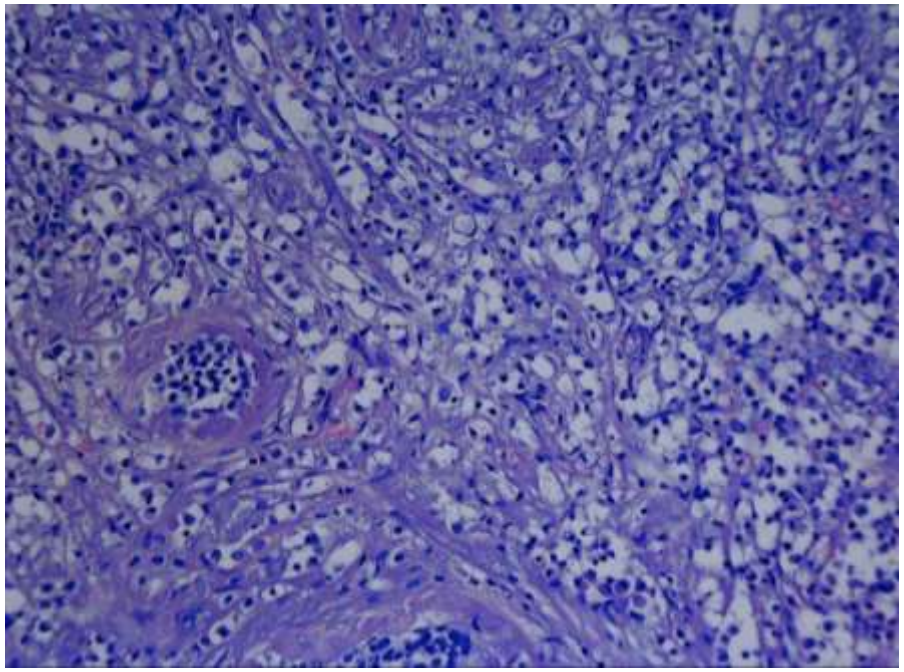
HER2 3+?

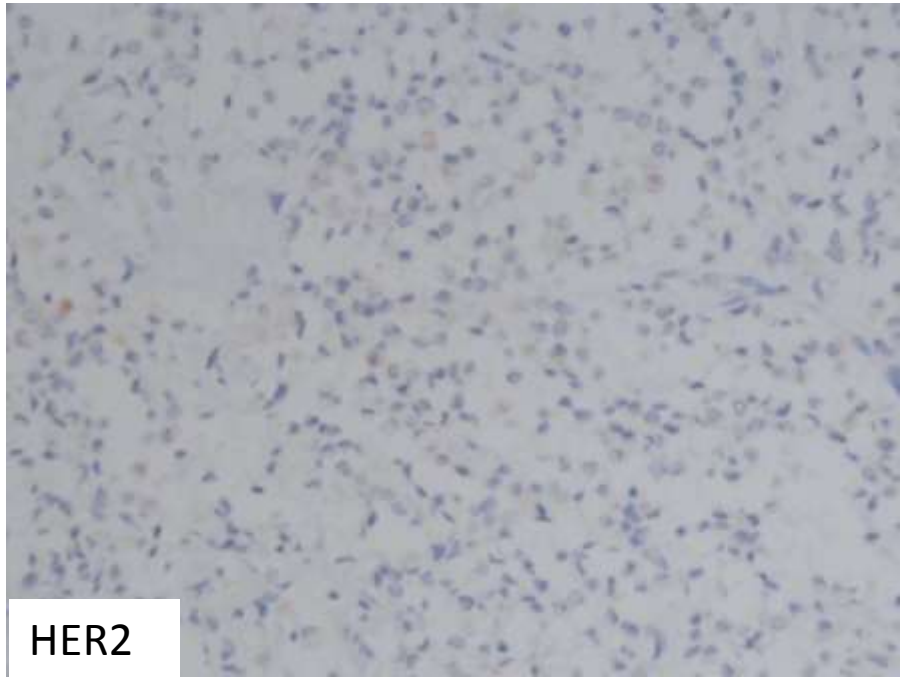




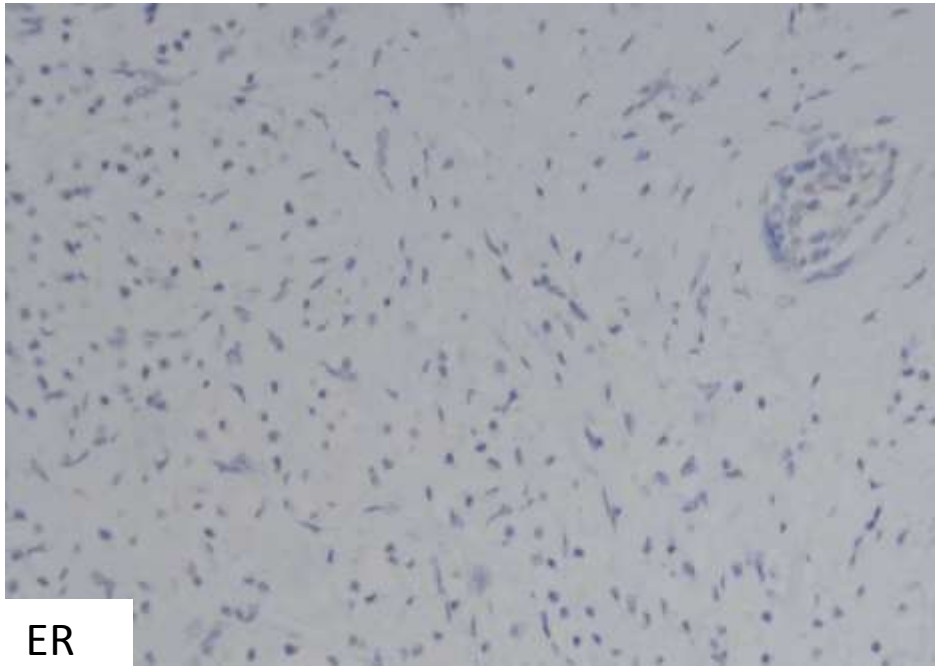


ARTEFATTI DA RITARDATA FISSAZIONE





HER2



ER

"Tumor Heterogeneity" ⟷ "Tumor Evolution"

Intra-tumor Heterogeneity

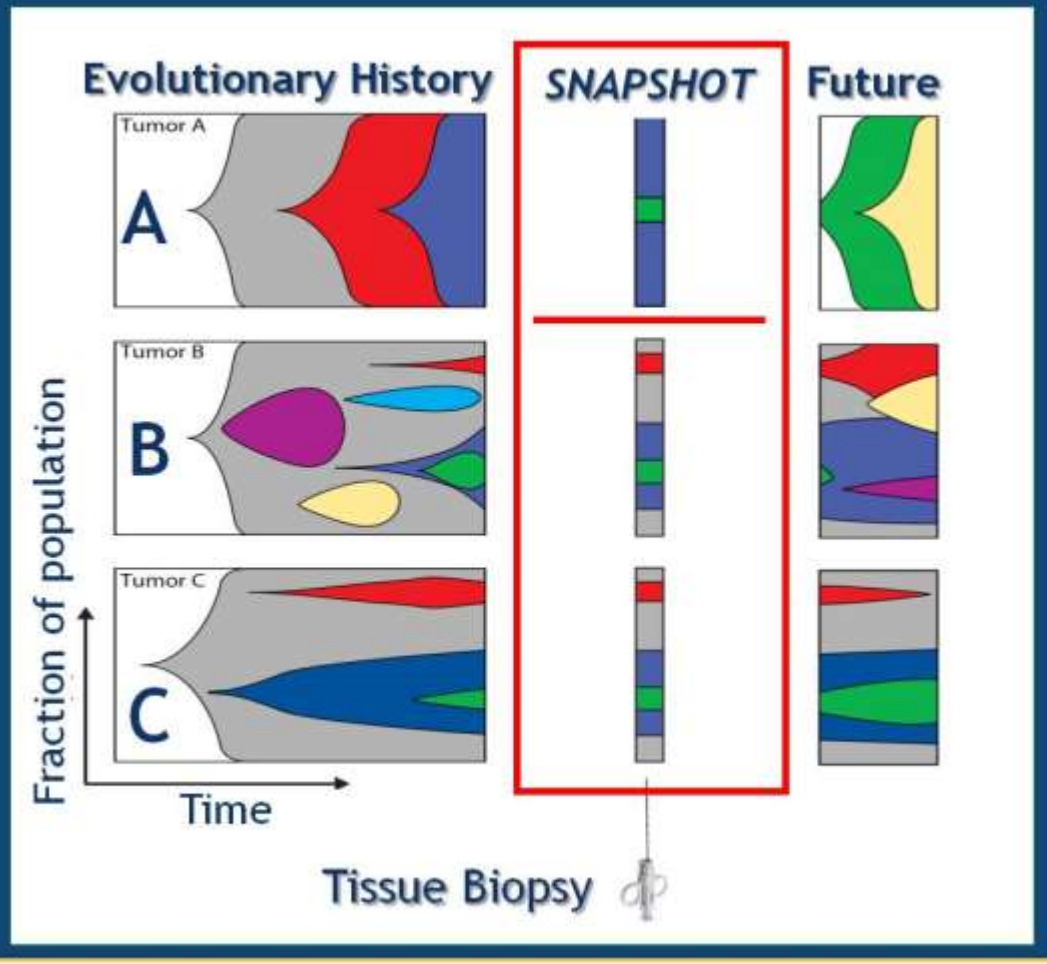
- heterogeneity within tumor
- spatial and temporal
- genetic, epigenetic, transcriptomic, proteomic

Inter-tumor Heterogeneity

- heterogeneity btw. patients

Heterogeneity in Interactions

with TME, external stresses



Hiley C et al. *Genome Biol*. 2014; 15(8): 453.

Presented By Patrick Ma at 2018 ASCO Annual Meeting

L’anticorpo primario

PD-L1 Assay Systems Used in the Blueprint Project				
Agent	**Nivolumab**	**Pembrolizumab**	**Atezolizumab**	**Durvalumab**
Primary antibody clone used in the assay system	28-8 (Dako)	22C3 (Dako)	SP142 (Ventana)	SP263 (Ventana)
Interpretive scoring	Tumor cell membrane	Tumor cell membrane	Tumor cell membrane Infiltrating immune cells	Tumor cell membrane
Instrument and detection systems required	EnVision Flex on AutostainerLink 48	EnVision Flex on AutostainerLink 48	OptiView detection and amplification on Benchmark ULTRA	OptiView detection on Benchmark ULTRA

PD-L1 Immunohistochemistry Assays for Lung Cancer: Results from Phase 1 of the Blueprint PD-L1 IHC Assay Comparison Project

Fred R. Hirsch, MD, PhD,[a,b,*] Abigail McElhinny, PhD,[c] Dave Stanforth, MBA,[d] James Ranger-Moore, PhD,[e] Malinka Jansson, MA,[d] Karina Kulangara, PhD,[d] William Richardson, BA,[e] Penny Towne, BS, MBA,[e] Debra Hanks, MD,[d] Bharathi Vennapusa, MD,[e] Amita Mistry, MD,[e] Rasika Kalamegham, PhD,[f,g] Steve Averbuch, MD,[h] James Novotny, PhD,[h] Eric Rubin, MD,[i] Kenneth Emancipator, MD,[j] Ian McCaffery, PhD,[j,k] J. Andrew Williams, PhD,[j] Jill Walker, PhD,[l] John Longshore, PhD,[m] Ming Sound Tsao, MD,[n] Keith M. Kerr, MB, FRCPath[o]

PD-L1 Immunohistochemistry Comparability Study in Real-Life Clinical Samples: Results of Blueprint Phase 2 Project

Ming Sound Tsao, MD,[a] Keith M. Kerr, MD,[b] Mark Kockx, MD, PhD,[c] Mary-Beth Beasley, MD,[d] Alain C. Borczuk, MD,[e] Johan Botling, MD,[f] Lukas Bubendorf, MD,[g] Lucian Chirieac, MD,[h] Gang Chen, MD,[i] Teh-Ying Chou, MD, PhD,[j] Jin-Haeng Chung, MD, PhD,[k] Sanja Dacic, MD, PhD,[l] Sylvie Lantuejoul, MD,[m] Mari Mino-Kenudson, MD,[n] Andre L. Moreira, MD,[o] Andrew G. Nicholson, DM,[p] Masayuki Noguchi, MD, PhD,[q] Giuseppe Pelosi, MD,[r] Claudia Poleri, MD,[s] Prudence A. Russell, MD,[t] Jennifer Sauter, MD,[u] Erik Thunnissen, MD, PhD,[v] Ignacio Wistuba, MD, PhD,[w] Hui Yu, MD, PhD,[x] Murry W. Wynes, PhD,[y] Melania Pintilie, MSc,[z] Yasushi Yatabe, MD, PhD,[aa] Fred R. Hirsch, MD, PhD[x,y,*]

Multicenter Comparison of 22C3 PharmDx (Agilent) and SP263 (Ventana) Assays to Test PD-L1 Expression for NSCLC Patients to Be Treated with Immune Checkpoint Inhibitors

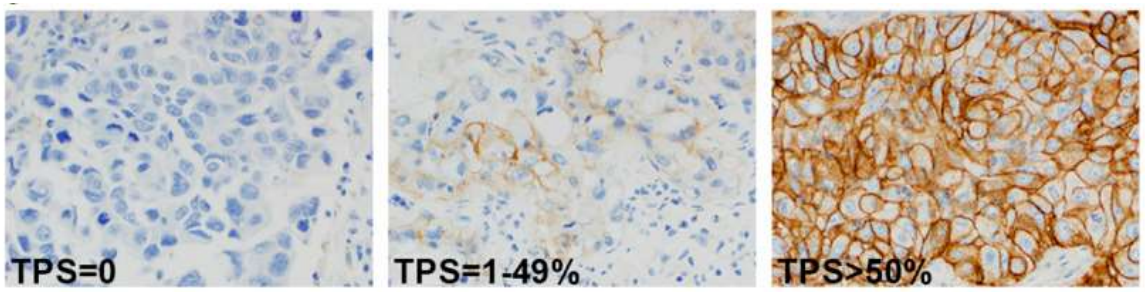
Antonio Marchetti, MD, PhD,[a,*] Massimo Barberis, MD,[b] Renato Franco, MD,[c] Graziano De Luca, MD,[a] Maria Vittoria Pace, PhD,[a] Stefania Staibano, MD,[d] Marco Volante, MD,[e] Fiamma Buttitta, MD, PhD,[a] Elena Guerini-Rocco, MD,[b] Luisella Righi, MD,[e] Tommaso D'antuono, BTech,[a] Giorgio V. Scagliotti, MD,[e] Carmine Pinto, MD,[f] Gaetano De Rosa, MD,[d] Mauro Papotti, MD[e]

La valutazione dell’espressione immunoistochimica di PD-L1 è un compito difficile…

PD-L1

TPS (tumour proportion score): LUNG (Pembro)

$$TPS = \left(\frac{\text{The number of viable tumor cells positive for PD-L1}}{\text{total number of viable neoplastic cells}}\right) \times 100\%.$$



Prevalence in non–small-cell lung cancer (NSCLC) tumor bank specimens stained with PD-L1 IHC 22C3. PD-L1 expression was detected over the entire dynamic range in NSCLC formalin-fixed paraffin-embedded specimens (A); using 50% tumor proportion score (TPS) as cut point, the percentage of clinical diagnostic positive cases was approximately 18.4% (B). Results were reported as the percentage of neoplastic cells showing membranous staining of PD-L1. Images shown are tumor samples obtained from patients with a TPS of <1%, a TPS of 1% to 49%, and a TPS of at least 50% (C).

PD-L1 BY IMMUNOHISTOCHEMISTRY:
OPTIONS FOR COMPANION AND COMPLEMENTARY DIAGNOSTIC ASSAYS

CLONE MCL TEST CODE	DRUG	TUMOR	SCORING INFORMATION
22C3	Pembrolizumab (Keytruda)	Non-small-cell lung cancer (NSCLC)	Companion diagnostic, scored with tumor proportion score (TPS)
		Urothelial carcinoma	Companion diagnostic, scored with combined positive score (CPS)
		Gastric or gastroesophageal junction adenocarcinoma	
		Cervical cancer	
SP263	Nivolumab (Opdivo)	NSCLC	Complementary diagnostic, scored with TPS
	Durvalumab (Imfinzi)	Urothelial carcinoma	Complementary diagnostic scored with tumor cells (TC) or tumor areas with immune cells present (ICP) and tumor infiltrating immune cells (IC)
SP142	Atezolizumab (Tecentriq)	NSCLC	Complementary diagnostic, scored with TPS
		Urothelial cancer	Companion diagnostic scored with IC
	Atezolizumab (Tecentriq) plus nab-paclitaxel (Abraxane)	Breast cancer (triple negative)	Companion diagnostic scored with IC

IC (PD-L1 immune cell): BREAST

PD-L1 BY IMMUNOHISTOCHEMISTRY:
OPTIONS FOR COMPANION AND COMPLEMENTARY DIAGNOSTIC ASSAYS

CLONE MCL TEST CODE	DRUG	TUMOR	SCORING INFORMATION
22C3	Pembrolizumab (Keytruda)	Non-small-cell lung cancer (NSCLC)	Companion diagnostic, scored with tumor proportion score (TPS)
		Urothelial carcinoma	Companion diagnostic, scored with combined positive score (CPS)
		Gastric or gastroesophageal junction adenocarcinoma	
		Cervical cancer	
SP263	Nivolumab (Opdivo)	NSCLC	Complementary diagnostic, scored with TPS
	Durvalumab (Imfinzi)	Urothelial carcinoma	Complementary diagnostic scored with tumor cells (TC) or tumor areas with immune cells present (ICP) and tumor infiltrating immune cells (IC)
SP142	Atezolizumab (Tecentriq)	NSCLC	Complementary diagnostic, scored with TPS
		Urothelial cancer	Companion diagnostic scored with IC
	Atezolizumab (Tecentriq) plus nab-paclitaxel (Abraxane)	Breast cancer (triple negative)	Companion diagnostic scored with IC

PD-L1

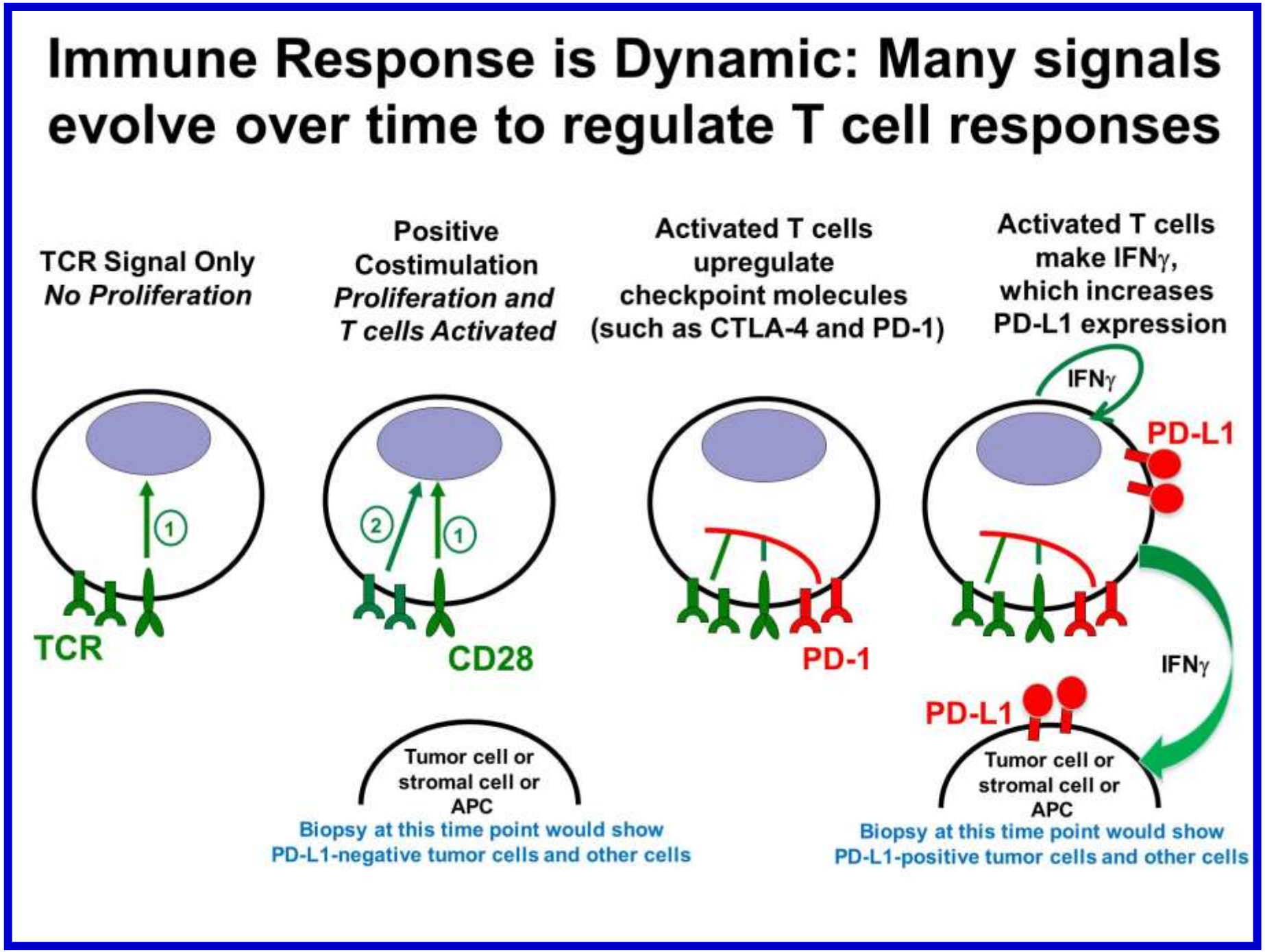
CPS (combined positive score): HEAD&NECK (Pembro)

Protocol-Specified Final Results of the KEYNOTE-048 Trial of Pembrolizumab as First-Line Therapy for Recurrent/ Metastatic Head and Neck Squamous Cell Carcinoma (R/M HNSCC)

Danny Rischin[1], Kevin Harrington,[2] Richard Greil,[3] Denis Soulières,[4] Makoto Tahara,[5] Gilberto de Castro,[6] Amanda Psyrri,[7] Neus Basté,[8] Prakash Neupane,[9] Åse Bratland,[10] Thorsten Fuereder,[11] Brett GM Hughes,[12] Ricard Mesia,[13] Nuttapong Ngamphaiboon,[14] Tamara Rordorf,[15] Wan Zamaniah Wan Ishak,[16] Yayan Zhang,[17] Fan Jin,[17] Burak Gumuscu,[17] Barbara Burtness[18]

[1]Peter MacCallum Cancer Centre, Melbourne, VIC, Australia; [2]The Institute of Cancer Research/The Royal Marsden NHS Foundation Trust National Institute of Health Research Biomedical Research Centre, London, UK; [3]Paracelsus Medical University, Salzburg Cancer Research Institute, and Cancer Cluster Salzburg, Salzburg, Austria; [4]Centre Hospitalier de l'Université de Montréal, Montréal, QC, Canada; [5]National Cancer Center Hospital East, Kashiwa, Japan; [6]Instituto do Cancer do Estado de Sao Paulo, Sao Paulo, Brazil; [7]National Kapodistrian University of Athens, Attikon University Hospital, Athens, Greece; [8]Vall d'Hebron University Hospital, Barcelona, Spain; [9]University of Kansas Medical Center, Kansas City, KS, USA; [10]Oslo University Hospital, Oslo, Norway; [11]Medical University of Vienna, Vienna, Austria; [12]Royal Brisbane and Women's Hospital and University of Queensland, Brisbane, QLD, Australia; [13]Catalan Institute of Oncology, Hospitalet de Llobregat, Barcelona, Spain; [14]Ramathibodi Hospital, Mahidol University, Bangkok, Thailand; [15]University Hospital, Zurich, Switzerland; [16]University Malaya, Kuala Lumpur, Malaysia; [17]Merck & Co., Inc., Kenilworth, NJ, USA; [18]Yale School of Medicine and Yale Cancer Center, New Haven, CT, USA

Dinamico


Immune Response is Dynamic: Many signals evolve over time to regulate T cell responses
TCR Signal Only
No Proliferation
Positive Costimulation
Proliferation and T cells Activated
Activated T cells upregulate checkpoint molecules (such as CTLA-4 and PD-1)
Activated T cells make IFNγ, which increases PD-L1 expression
IFNγ
PD-L1
1
2
1
TCR
CD28
PD-1
IFNγ
PD-L1
Tumor cell or stromal cell or APC
Biopsy at this time point would show PD-L1-negative tumor cells and other cells
Tumor cell or stromal cell or APC
Biopsy at this time point would show PD-L1-positive tumor cells and other cells

OPEN ISSUES

Dove

Biopsia vs CAMPIONE OPERATORIO

Annals of Oncology 27: 147–153, 2016
doi:10.1093/annonc/mdv489
Published online 19 October 2015

Comparative study of the PD-L1 status between surgically resected specimens and matched biopsies of NSCLC patients reveal major discordances: a potential issue for anti-PD-L1 therapeutic strategies

M. Ilie[1,2], E. Long-Mira[1,2], C. Bence[1], C. Butori[1], S. Lassalle[1,2], L. Bouhlel[2,3], L. Fazzalari[2], K. Zahaf[1], S. Lalvée[1], K. Washetine[4], J. Mouroux[2,5], N. Vénissac[5], M. Poudenx[3], J. Otto[6], J. C. Sabourin[7], C. H. Marquette[2,3], V. Hofman[1,2,4] & P. Hofman[1,2,4*]

[1]*Laboratory of Clinical and Experimental Pathology, Pasteur Hospital, Nice;* [2]*IRCAN Team 3, INSERM U1081/UMR CNRS 7284, Faculty of Medicine of Nice, University of Nice Sophia Antipolis, Nice;* [3]*Department of Pneumology;* [4]*Hospital-Related Biobank BB-0033-00025;* [5]*Department of Thoracic Surgery, Pasteur Hospital, Nice;* [6]*Department of Pneumology, Centre Antoine Lacassagne, Nice;* [7]*Laboratory of Cancer Genetics, Department of Pathology, Rouen University Hospital, Rouen, France*

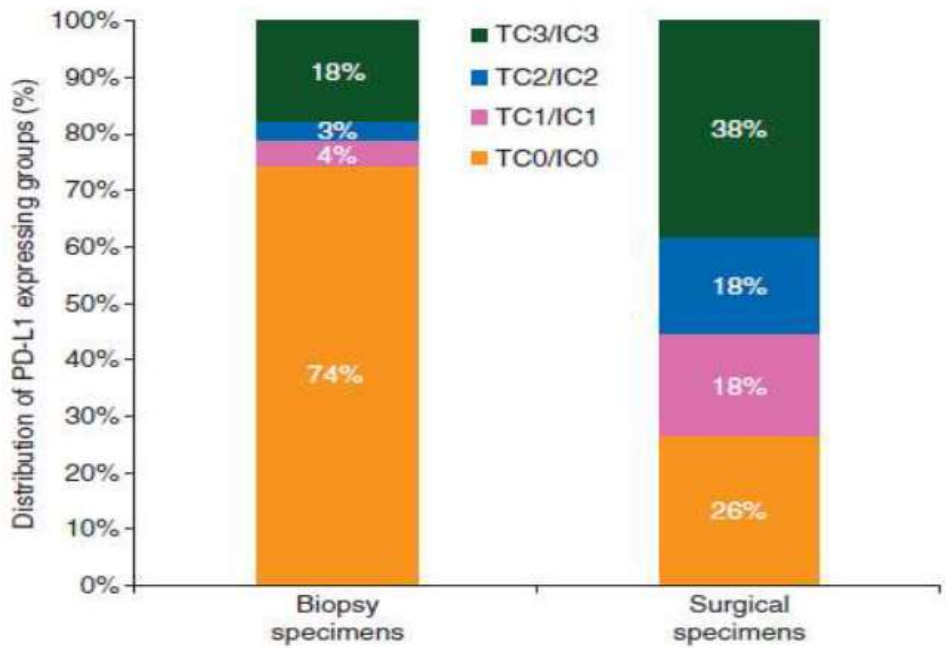
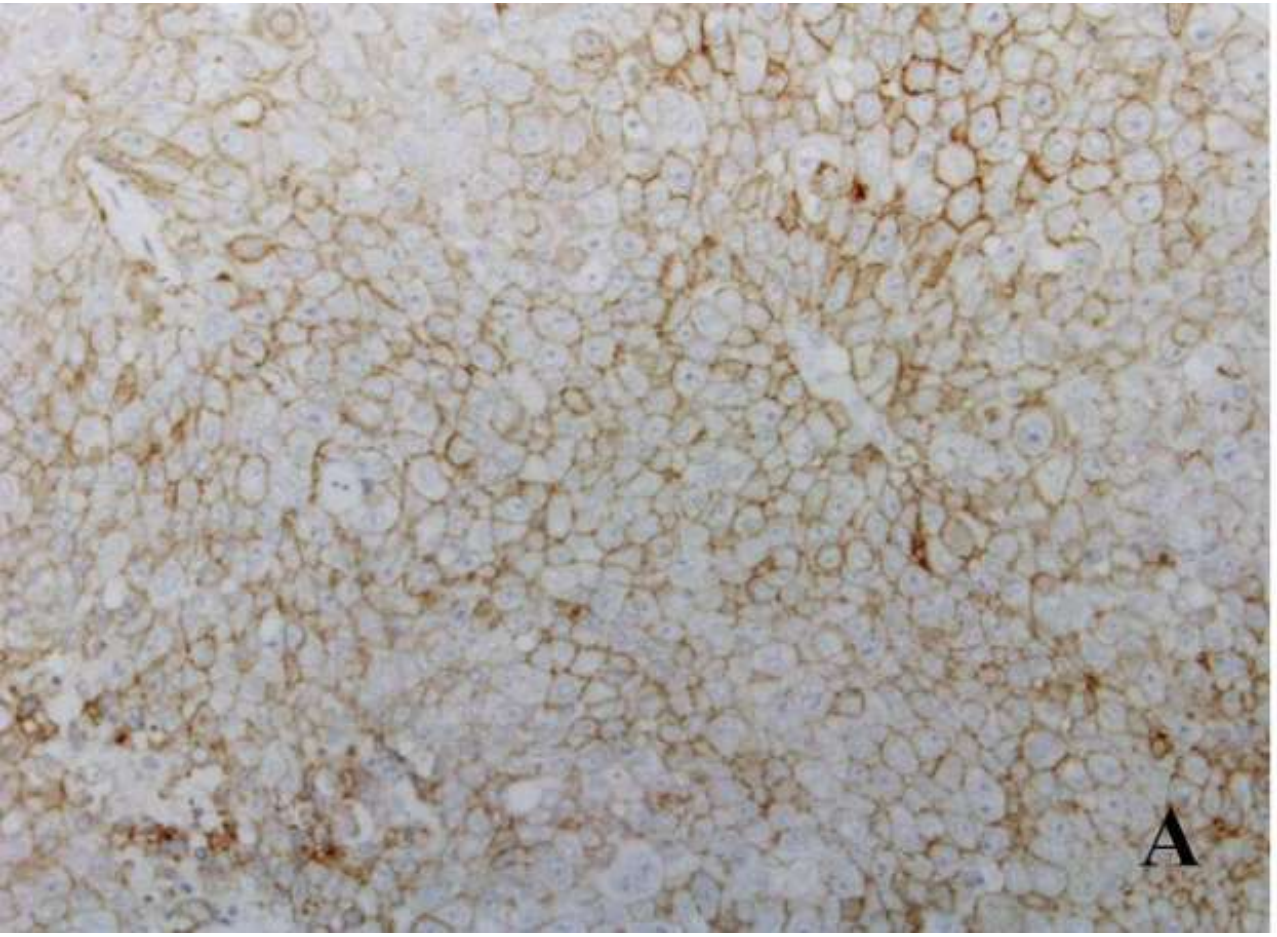
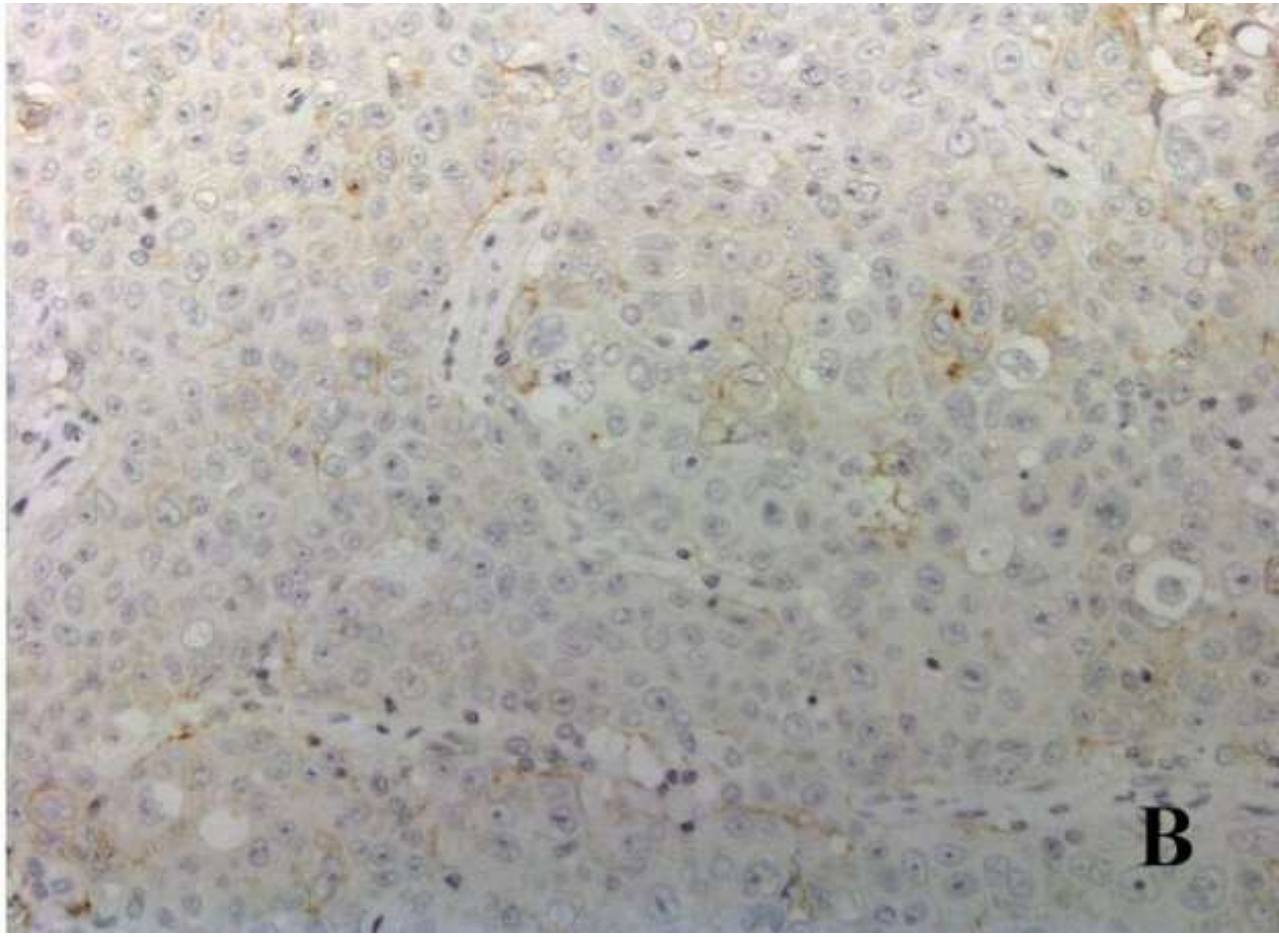


Figure 1. Distribution (%) of 160 NSCLC patients included in the study according to the expression of PD-L1 in tumor cells (TC) and immune cells (IC) in either surgical specimens or matched biopsy specimens.

Eterogeneità del biomarcatore:



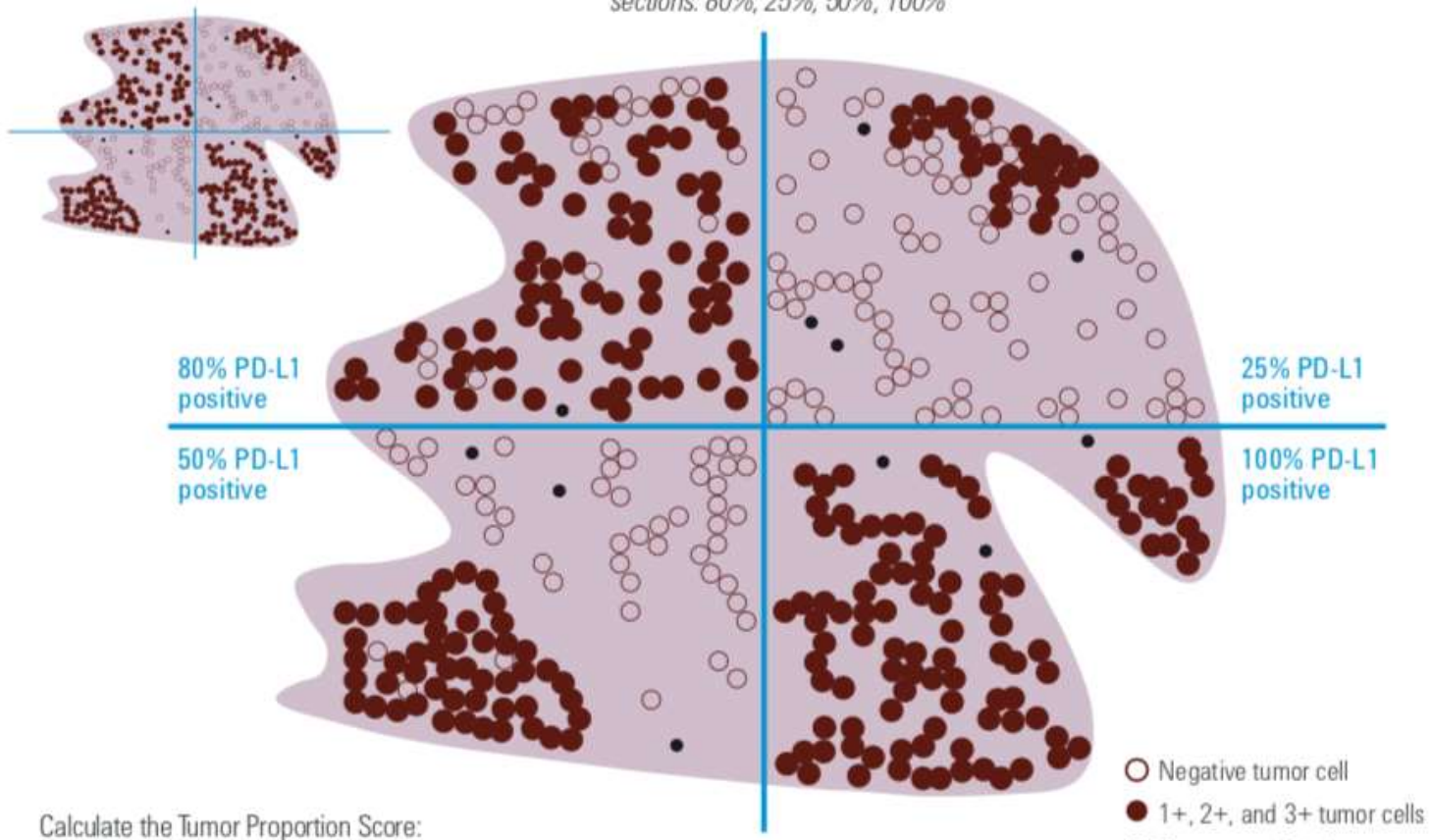


Example 2: Calculation of Tumor Proportion Score in a Heterogeneous Tumor Area

At lower magnification: Visually divide the tumor area into sections.

At higher magnification: Observe tumor areas with cell membrane staining for percentage of stained cells in each section.

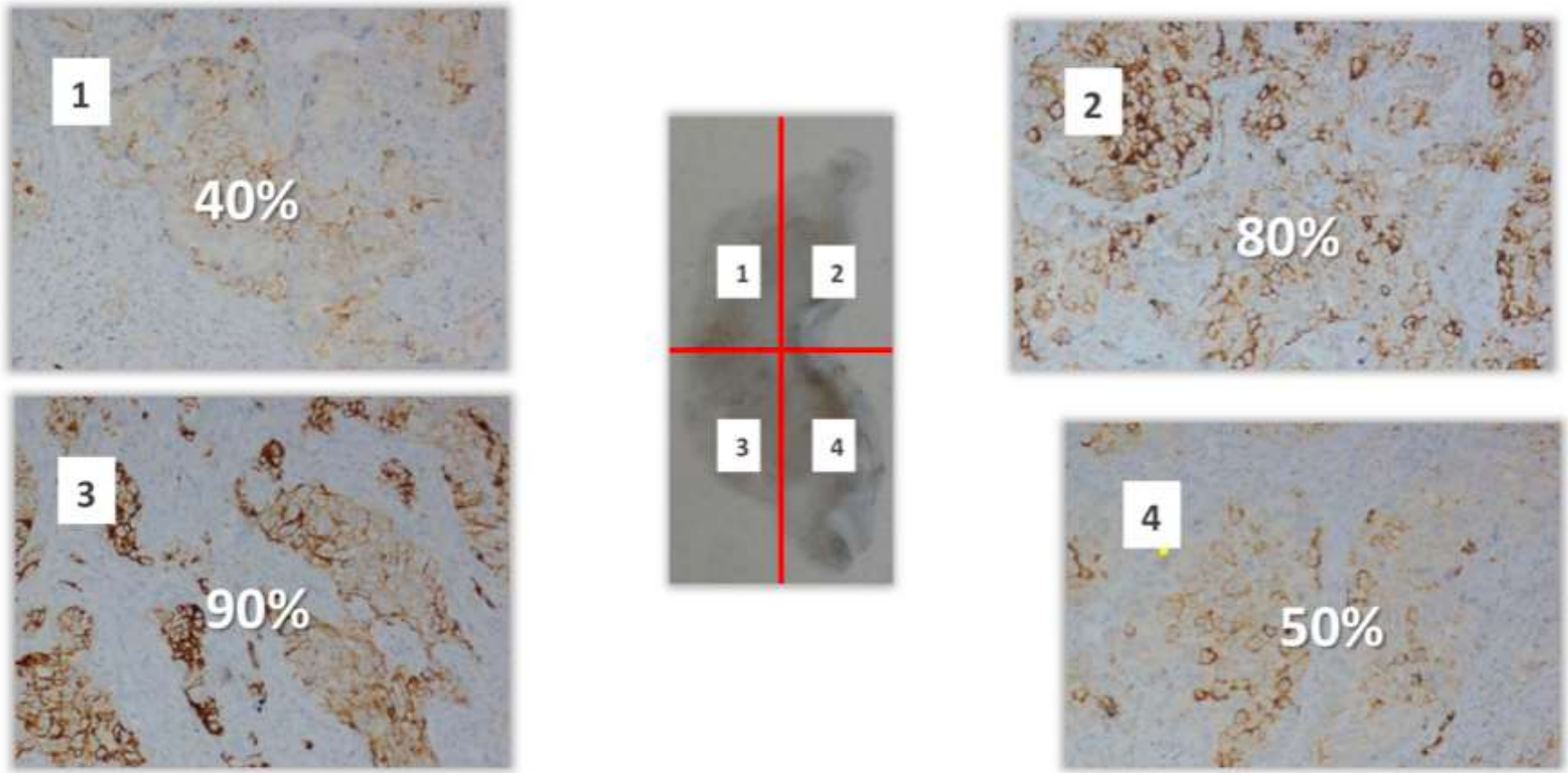
Assessment: *Staining of tumor cells in each of the four respective sections: 80%, 25%, 50%, 100%*



Calculate the Tumor Proportion Score: Determine the overall percentage of stained tumor cells.

Assessment: Tumor Proportion Score:
(80% + 25% + 50% + 100%) / 4 = ≥ 60%

Interpretazione dei preparati e scoring

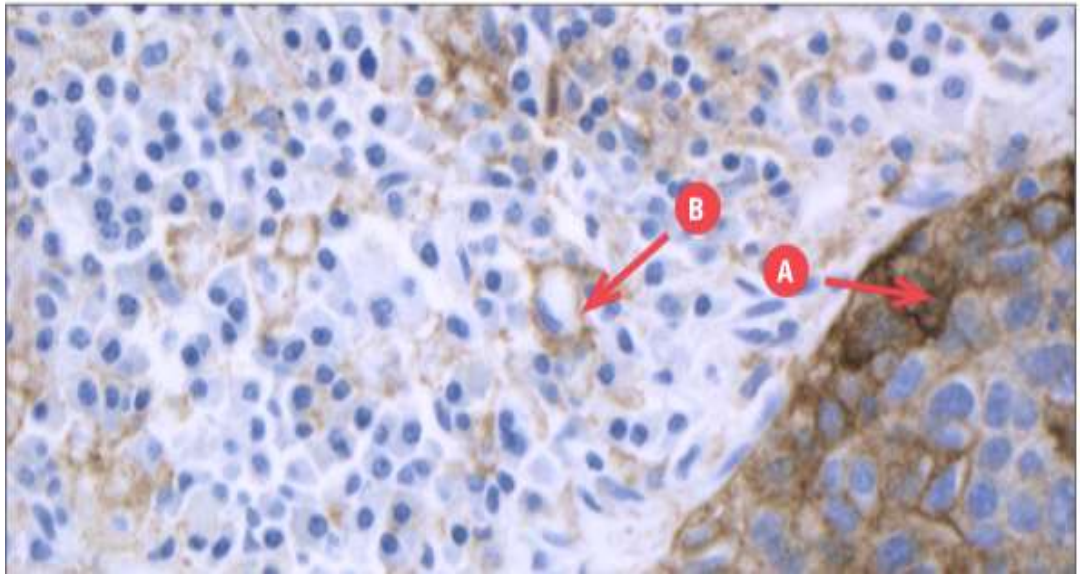


(40%+80%+90%+50%):4= 65%

Eterogeneità del biomarcatore

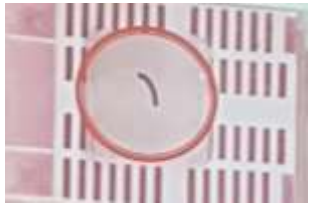
L’espressione di PD-L1 può essere maggiore all’interfaccia fra stroma e tumore, come esito dell’attivazione della risposta immunitaria

E nelle piccole biopsie??

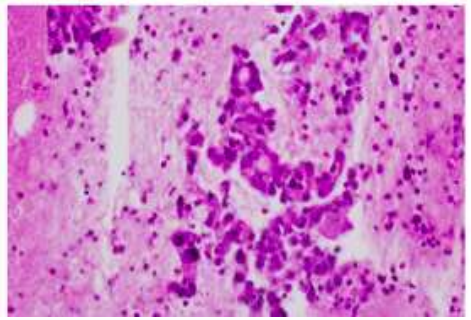


Eterogeneità del biomarcatore

- In oltre il 70% dei casi, il carcinoma del polmone si manifesta in uno stadio avanzato di malattia

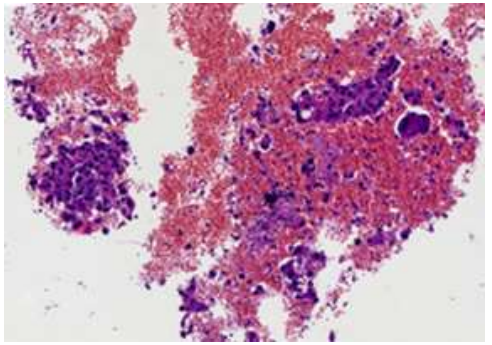


- Di conseguenza, il materiale biologico ottenibile per la tipizzazione delle neoplasie è rappresentato da piccole biopsie o da campioni citologici



- Proprio per questo, il materiale ottenuto potrebbe non essere rappresentativo del reale stato del biomarcatore

- Il fatto che circa il 10% dei NSCLC risponda agli inibitori dell'asse PD-L1/PD-1 nonostante l'assenza di espressione del biomarcatore potrebbe essere parzialmente spiegato dai risultati falsi negativi dei campioni bioptici di tumori PD-L1 positivi in modo eterogeneo



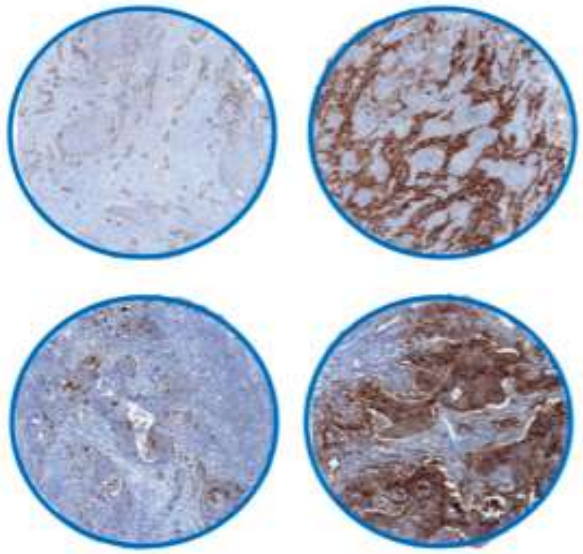
Eterogeneità del biomarcatore

Solo pochi studi hanno affrontato la tematica relativa all'impatto delle piccole biopsie nel determinare l'eleggibilità al trattamento con pembrolizumab nei pazienti con NSCLC e hanno ripotato risultati controversi:

- *Kitazono et al*. (2015) Hanno studiato l'espressione immunoistochimica di PD-L1 in 79 casi di NSCLC sia sulle biopsie che sui campioni chirurgici (45 adenoarcinomi, 23 carcinomi squamosi e 11 altri istotipi); usando un cut-off ≥ 1% hanno riscontrato una concordanza pari al 92.4% mentre, usando un cut-off ≥ 50% hanno riscontrato una concordanza pari al 83.5%

- In un altro studio, *Ilie et al* (2016) hanno valutano l'espressione immunoistochimica di PD-L1 in 160 casi di NSCLC sia sulle biopsie che sui campioni chirurgici (33 carcinomi squamosi e 127 adenocarcinomi); usando un cut-off ≥ 1% hanno riscontrato una concordanza, molto inferiore, pari al 52%

Eterogeneità del biomarcatore



Research Paper

PD-L1 expression heterogeneity in non-small cell lung cancer: evaluation of small biopsies reliability

Enrico Munari[1,2], Giuseppe Zamboni[1], Marcella Marconi[1], Marco Sommaggio[1], Matteo Brunelli[2], Guido Martignoni[2,3], George J. Netto[4], Francesca Moretta[5], Maria Cristina Mingari[6], Matteo Salgarello[7], Alberto Terzi[8], Vincenzo Picece[9], Carlo Pomari[10], Gianluigi Lunardi[9], Alberto Cavazza[11], Giulio Rossi[12], Lorenzo Moretta[13] and Giuseppe Bogina[1]

We observed a discordance rate of 20% and 7.9% and a Cohen's κ value of 0.53 (moderate) and 0,48 (moderate) for ≥ 1% and ≥ 50% cutoffs, respectively.

Il numero minimo 4 biopsie sarebbe necessario per avere una rappresentazione adeguata dell'eterogeneità del biomarcatore


12
123
18
17
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15

GRAZIE PER L’ATTENZIONE