

Challenges for biomarkers in clinical trials (patient selection, stratification, primary analysis)

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EORTC

Chair of the Innovation and Biomarkers in Cancer Drug Development (IBCD)-meeting

Disclaimer

Advisory Board/consultancy role for BMS, Exact Sciences, Roche, Astra Zeneca, Daicchi Sankyo, Owkin, Case45.

Research funding by Roche, Puma, Merck, BMS.

I have **no** conflicts of interests related to the current work presented at this lecture.

We need to develop those studies, including the selection of biomarkers, that inform the mindset of the clinician when he/she is in front of their patient

= The First narrative of this lecture, to discuss some regulatory and industry implications, we will discuss through a patient's perspective

I have Four narratives for today

- **Narrative 1:**

- Will in pharma-driven drug trials prognostic factors ever be used for NOT given adjuvant therapy in this (and other) settings?

What can the regulatory do?
What can patients do?

- **Narrative 2:**

- Will the sponsor in pharma-driven drug trials ever formally and publicly claim that what is most important is the validation of the assay, irrespective whether it's a CdX or not?

I believe that a clinical trial serves to validate a biomarker, and not a vendor-specific assay.

What are the regulatory implications of these notions?

- **Narrative 3:**

- Does FDA-approval of a CdX equal biomarker level of evidence?
Is it always evidence of the highest standard of performance?

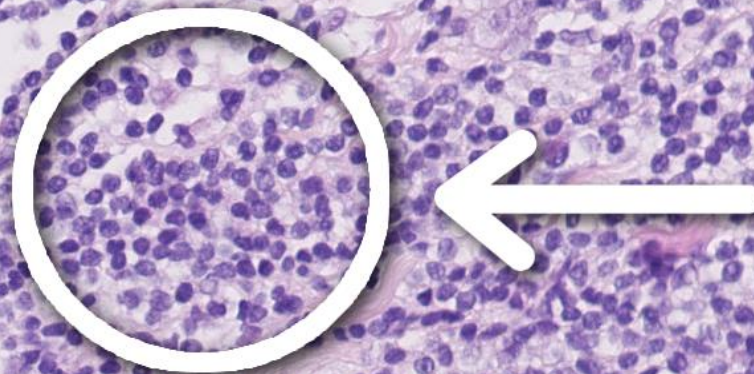
- **Narrative 4:**

- That's for the end.

Three narratives

- The emerging importance of morphological biomarkers in clinical trials (using AI).
- Does a clinical trial serves to validate a biomarker and a drug, and does not serve to validate an assay Are CdX always the best performing assays?

**lymphocytes / plasma cells
= TILs**





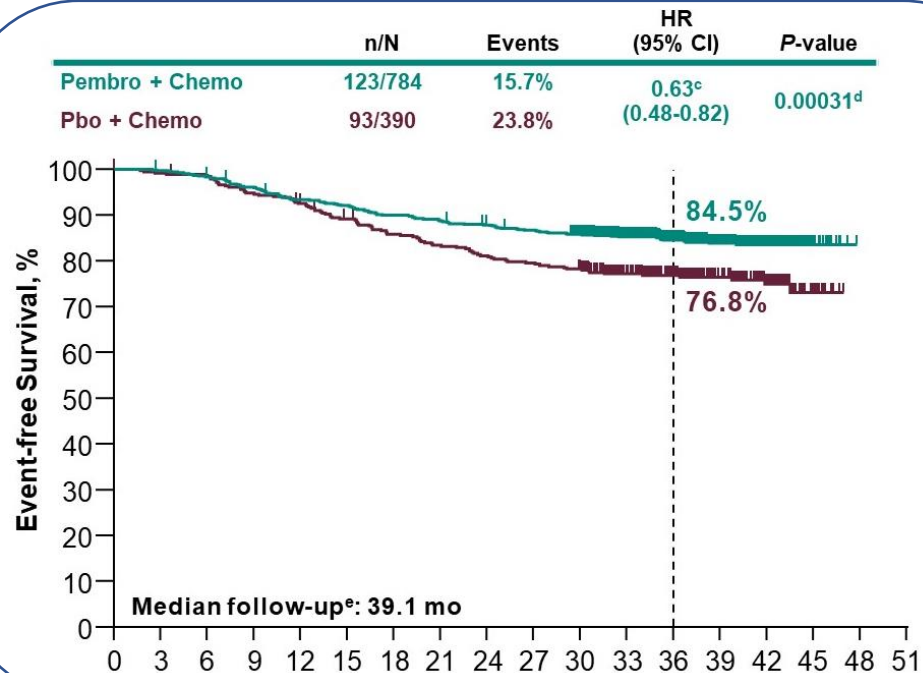
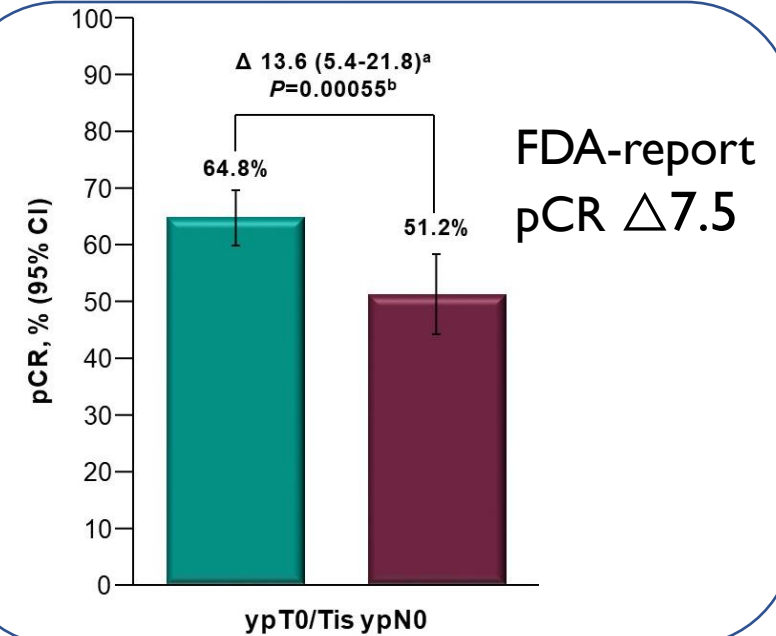
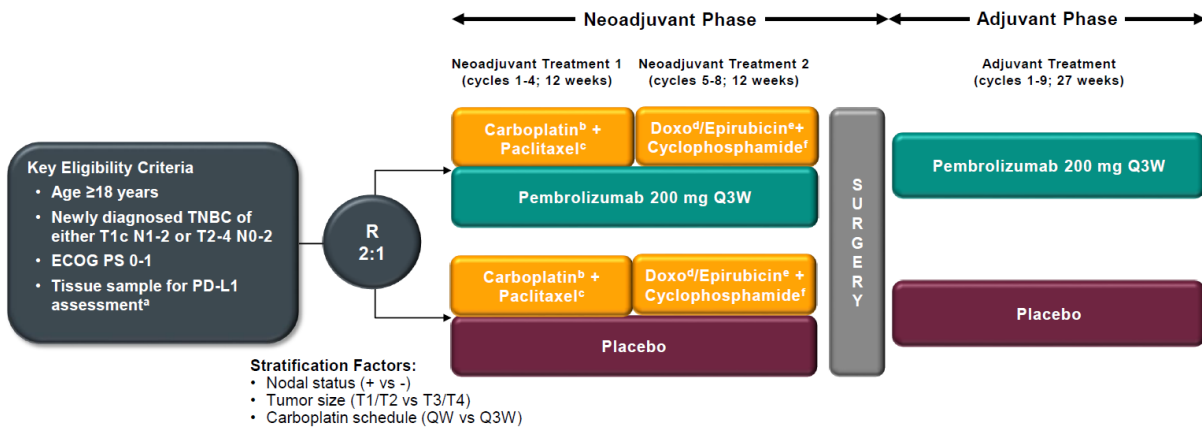
Erin's journey

Case Presentation & Timeline:

- 48 y/o Athletic Female, Emergency Room Physician, Metabolic Health Coach
- Oct. 26: **Biopsy confirms TNBC with Medullary Features., Marked Tumor Infiltrating Lymphocytes (later called "a ton of TILs")**
- Nov. 16: MRI reveals two Local Masses (~24mm and ~10mm)
- Nov. 28: Pet/CT Scan & subsequent follow-up MRI show no nodal activity and no distant disease.
- Dec. 5: Erin may have Flammer's Syndrome, associated with breast cancer that might stem from Flammer's-related hypoxic conditions.
- Dec. 7: Tempus Labs Tumor Report: PD-L1+ with CPS = 30
- Dec. 21 (Wed.): **Keynote-522 Regimen Commences**
- Notes after 4+ wks of treatment as of (Jan 16):
 - Patient fasts 24 hours prior and post chemo-therapy..
 - Patient doing hyperbaric oxygen therapy 3x per week to counteract cancer-favoring hypoxic conditions
 - Side effects: flush facial skin managed by Zyrtec, diarrhea (one day per week), constipation, fatigue, hair loss.
 - All side effects have been manageable to date.
 - **Patient's self-examinations suggest tumors have disappeared and have remained gone since Week3.**



Neoadjuvant aPD1



**The great news is that the tumor has shrunk already!!
So, that has us thinking about de-escalation strategies**

(mail Adam/Erin on January 4th, 2023).

Unfortunately, our oncologist team remains very reluctant to de-escalate Keynote-522.

(Mail Adam/Erin January 31st, 2023)

Marked TILs? A ton of TILs?

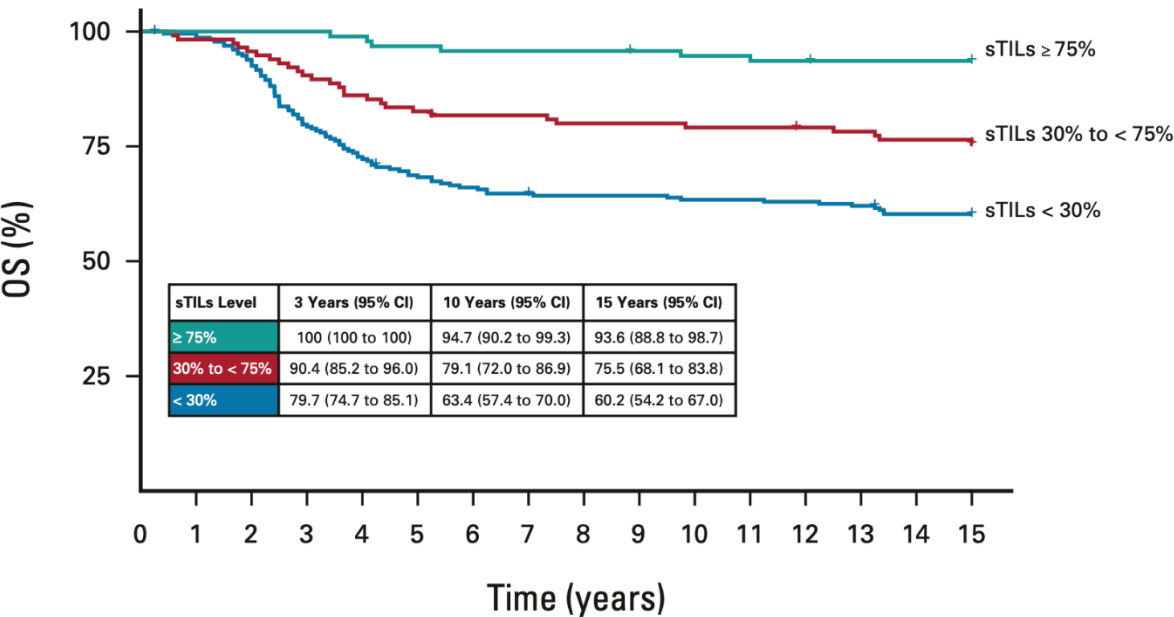
Our pathologist read de Jong et al. (2022) and reviewed Salgado R from the Annals of Oncology on the matter (2014). She got back to us, and she and her partner say

“We believe that your core biopsies show 80-85% TILs”.

(Mail Adam/Erin January 31st, 2023)

sTILs >=75%, 15-ylrs OS 94% with only 2% distant metastasis

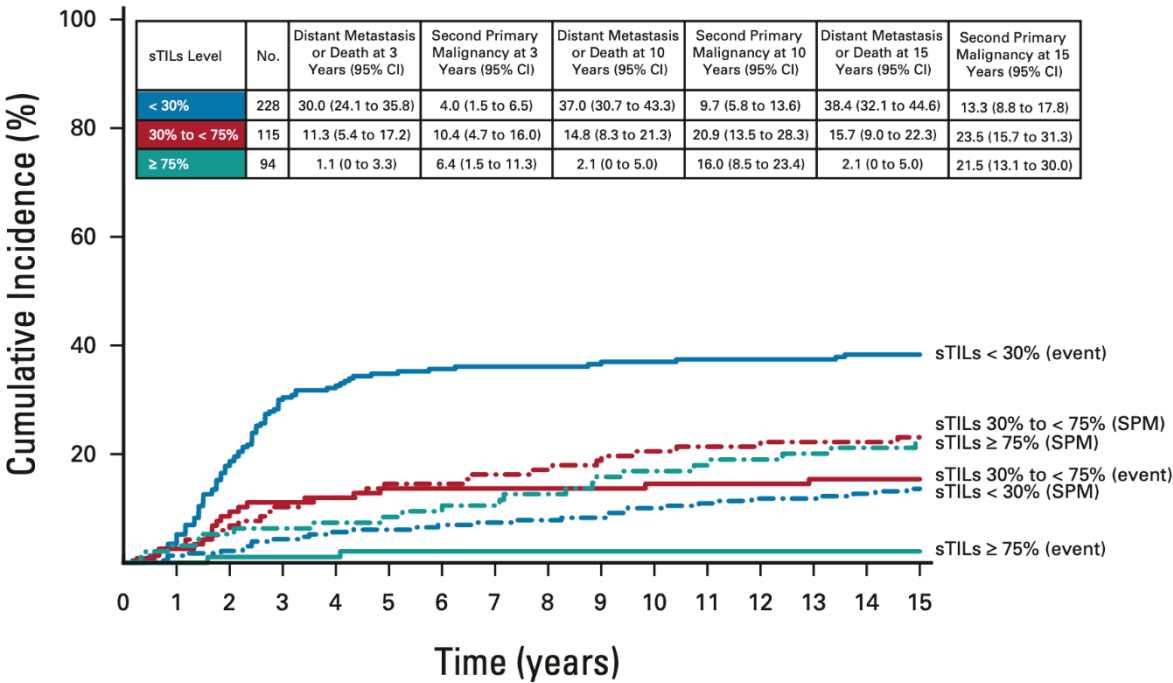
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No. at risk:

sTILs < 30%	228	225	212	181	165	154	149	146	144	144	142	142	141	139	134	134
sTILs 30% to < 75%	115	113	110	104	99	95	93	93	91	91	90	90	89	88	86	85
sTILs ≥ 75%	94	94	94	94	93	91	90	90	90	89	88	88	87	86	86	86

A



**The great news is that the tumor has shrunk already!!
So, that has us thinking about de-escalation strategies**

(mail Adam/Erin on January 4th, 2023).

Unfortunately, our oncologist team remains very reluctant to de-escalate Keynote-522.

(Mail Adam/Erin January 31st, 2023)

“I do have good news for you! My initial surgery on July 5 revealed excellent results:

First of all, my surgeon was able to choose a nipple sparing bilateral mastectomy after my MRI revealed no residual cancer. Initially, my lesion was so close to the nipple that we did not think this would be possible . Obviously, this will lead to a better cosmetic result overall.

The breast tissue that was removed, as well as 2 axillary lymph nodes (including the sentinel node) on the left all showed no cancer. Complete PCR!”

(mail Adam/Erin on August 8th, 2023).

“The universal response was “you are handling the treatment well, so no reason to stop now”.

“Handling it well” included immediate loss of my thyroid function (another good indicator) after suffering through severe hyperthyroid symptoms, tremendous fatigue, dehydration, confusion, nausea, explosive diarrhea, severe thrush, sleep disruption, night sweats, hair loss, scalp tenderness, bone pain, joint pain, muscle pain... This is aside from loss of salary due to inability to work, inability to drive due to brain fog, loss of independence, loss of confidence, loss of high-level reasoning, loss of mobility... just to name a few. “

“I have opted to stop with post operative immunotherapy. This is, of course, going against the current standard , laid out in the Keynote protocol. Both of my oncologists frowned upon this decision. However, I feel confident in quitting based on my pathology, my results, and other studies. My decision to stop immunotherapy was due to ongoing exhaustion, along with pain in my muscles, bones, and tendons. I am not experiencing these symptoms anymore. I will remain on levothyroxine, likely for life, due to the side effects of immunotherapy.

Unfortunately, I have had several setbacks this Summer with the surgical reconstructive process that have been frustrating. The expander placed on my left side has been infected twice and removed both times. I will be returning for surgery to try again at the end of September.”

(mail Adam/Erin on August 8th, 2023).

Narrative 1

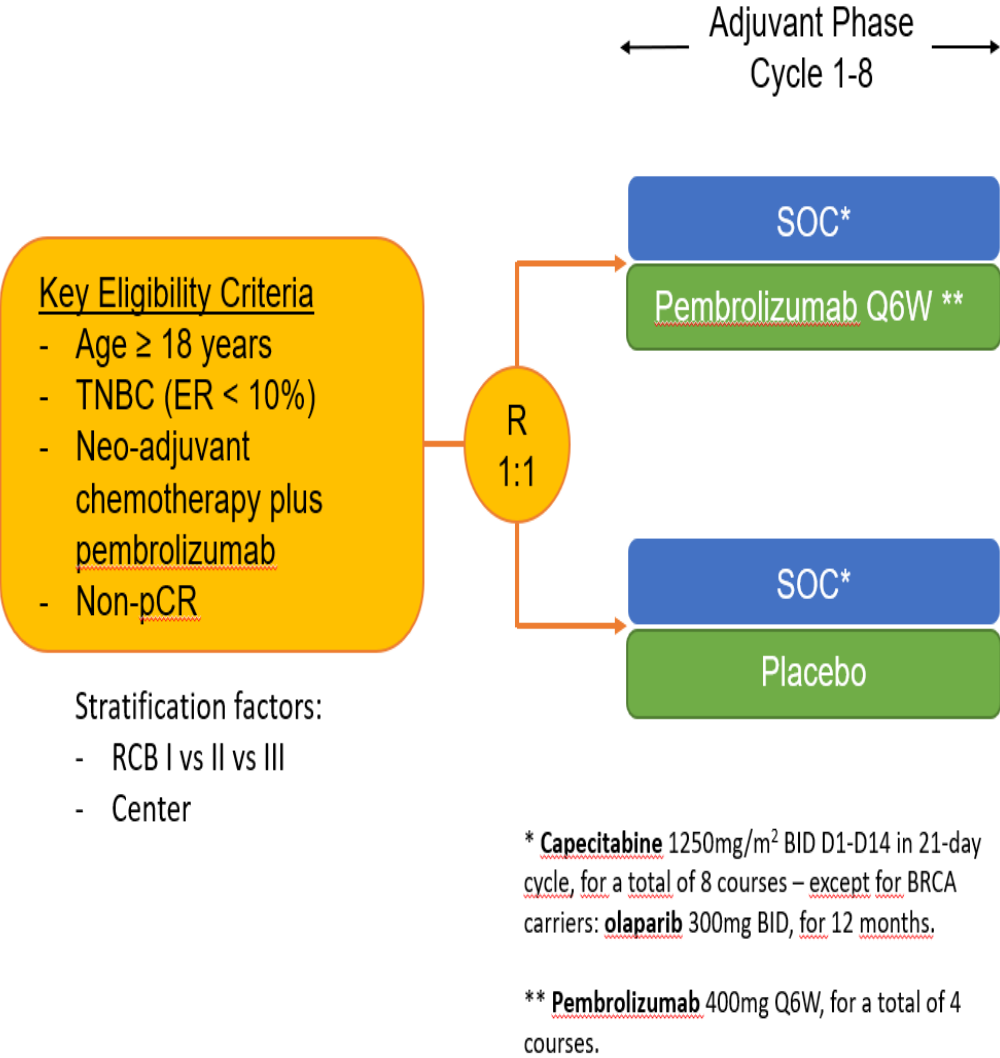
- **Will in pharma-driven drug trials prognostic factors ever be used for NOT given adjuvant therapy in this (and other) settings?**

What can the regulatory do?

What can patients do?

Can a prognostic factor be a CdX, formally speaking? Eg Ki67, how scientifically valid is this?

PembroLizumab Adjuvant in patients with stage II-III Triple NEgative breast cancer with residual disease after neoadjuvant pembrolizumab plus chemotherapy – the multicenter, randomized, phase III, pragmatic, return-on-investment PLANET trial



Population: Patients with early TNBC (defined as ER<10%, HER2-negative) and with residual disease after neoadjuvant pembrolizumab plus chemotherapy (i.e., Non-pCR after neoadjuvant pembrolizumab and chemotherapy).

Intervention: Adjuvant intravenous pembrolizumab (outpatient clinic) plus oral capecitabine (OR oral olaparib for BRCA1/2 carriers).

Comparator: Standard of care adjuvant oral capecitabine (OR oral olaparib for BRCA1/2 carriers)

Outcome: Primary objective is to evaluate the additive value of adjuvant pembrolizumab in TNBC patients with residual disease after neoadjuvant chemo+pembro (primary endpoint 3-yrs DFS). Secondary objectives are: i) to evaluate the additive value of adjuvant pembrolizumab in TNBC patients with residual disease after neoadjuvant chemo+pembro (iDFS, OS); ii) to evaluate the additive value of adjuvant pembrolizumab in RCB I, II, III patients, respectively; **iii) to evaluate the additive value of adjuvant pembrolizumab in TNBC patients with residual disease according to TIL levels (TIL baseline and residual TIL).**

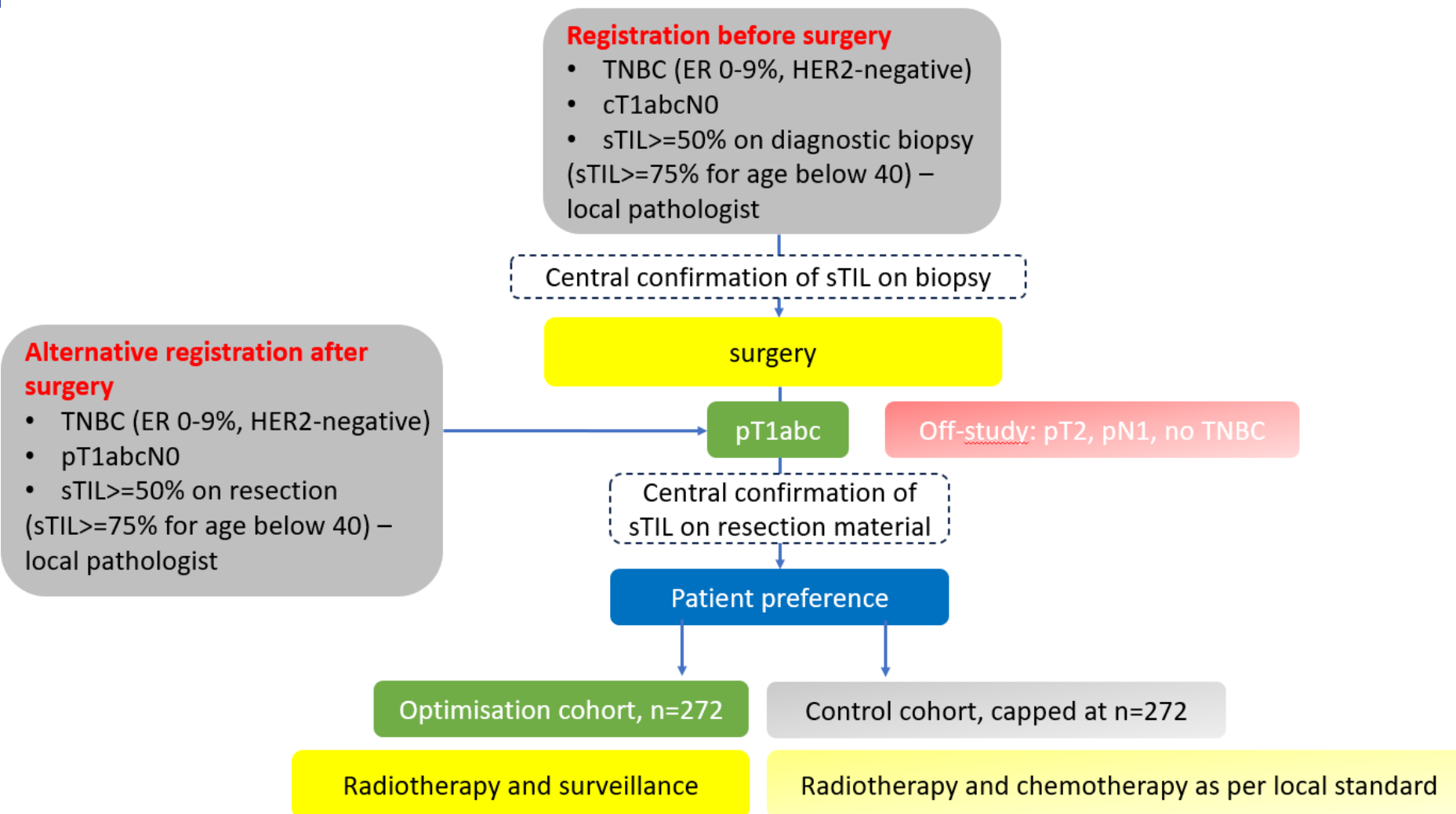
OPTimal: OPTimisation of treatMent for pAtients with low stage triple-negative breast cancer patients with high sTIL

Study coordinator: Dr Marleen Kok (NKI)

Young Study Coordinator: Dr. Gil Awada (NKI)

Study co-coordinator: Prof dr Sabine Linn (NKI)

Key pathologist: dr Roberto Salgado (GZA Antwerp)



A close monitoring on a 3-4 monthly basis will be performed during the first two years, then on a 6-monthly basis until the analysis of primary endpoint (i.e. up to 3 years), then annual survival sweep up to 10 years.

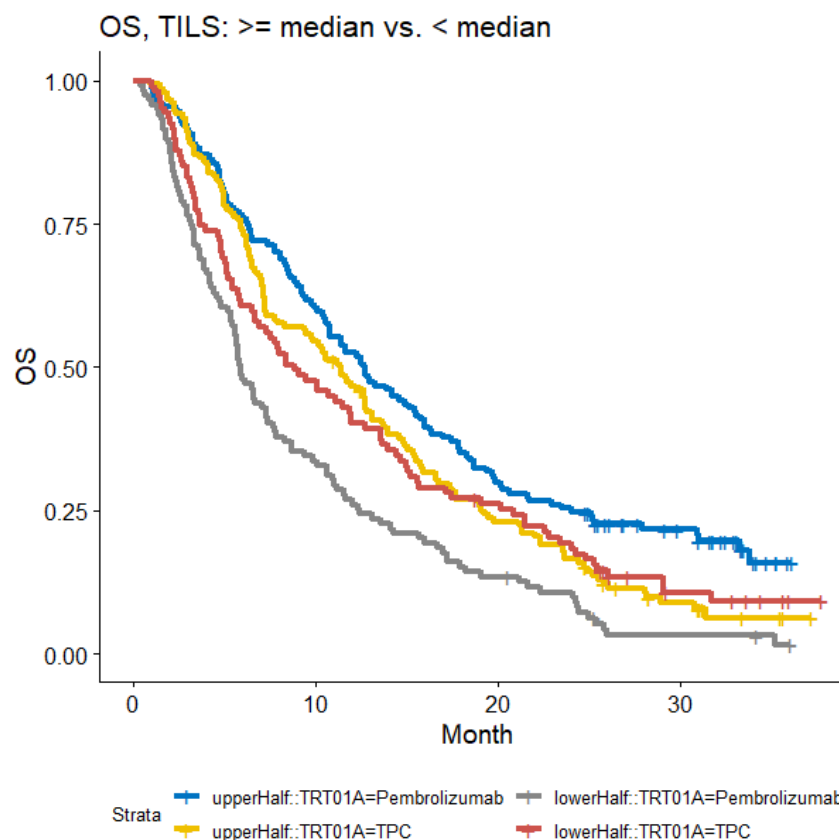
Relationship Between Tumor-Infiltrating Lymphocytes and Outcomes in the KEYNOTE-119 Study of Pembrolizumab Versus Chemotherapy for Previously Treated, Metastatic Triple-Negative Breast Cancer

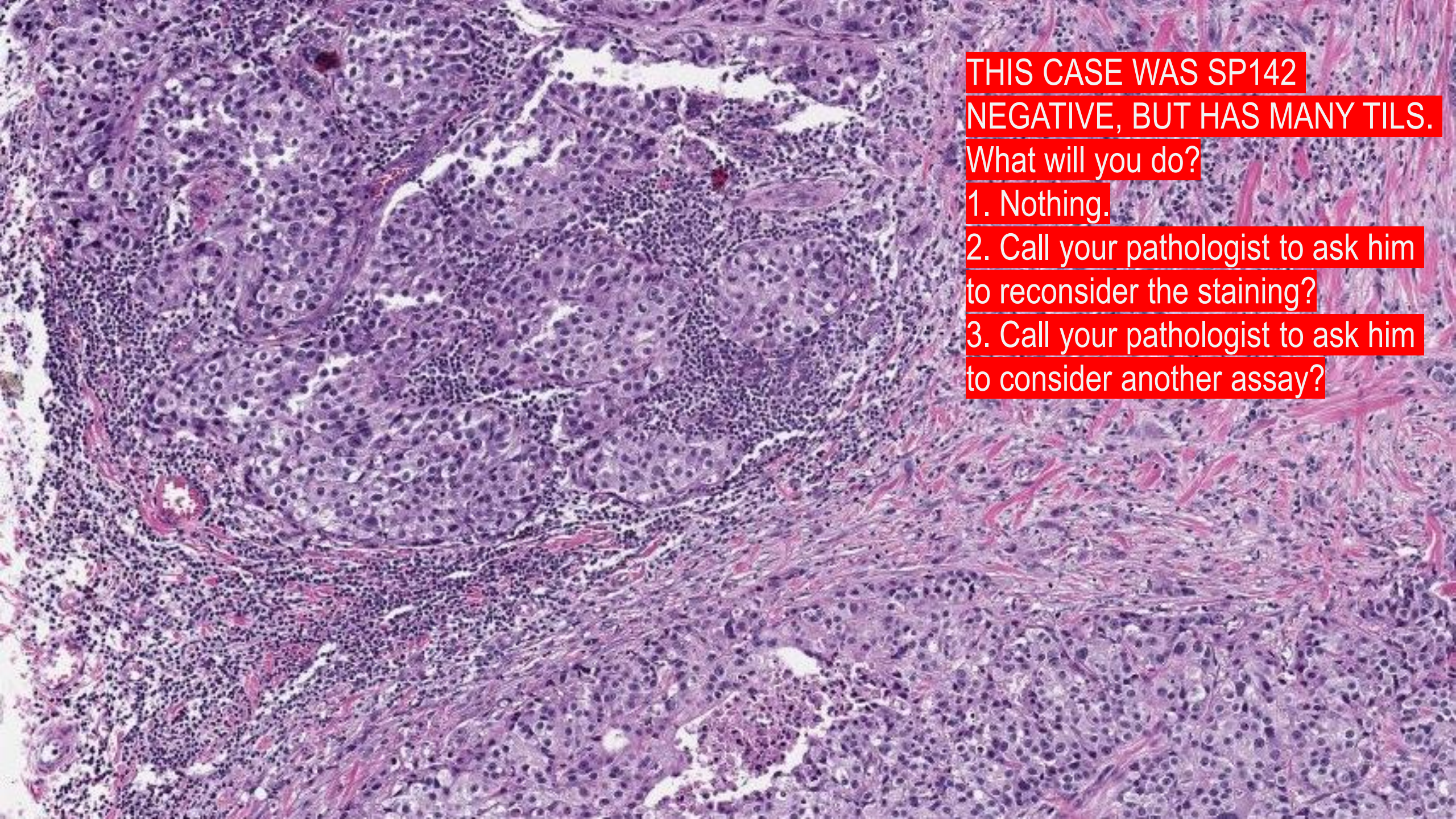
S. Loi¹, E. Winer², O. Lipatov³, S.-A. Im⁴, A. Gonçalves⁵, J. Cortes⁶, K. S. Lee⁷, P. Schmid⁸, L. Testa⁹, I. Witzel¹⁰, S. Ohtani¹¹, N. Turner¹², S. Zambelli¹³, N. Harbeck¹⁴, F. Andre¹⁵, R. Dent¹⁶, L. Huang¹⁷, J. Mejia¹⁸, V. Karantzis¹⁹, R. Salgado¹

¹Peter MacCallum Cancer Centre and University of Melbourne, Melbourne, VIC, Australia; ²Dana-Farber Cancer Institute, Boston, MA, USA; ³Republican Clinical Oncology Dispensary, Republic of Bashkortostan, Russian Federation; ⁴Seoul National University, Seoul, South Korea; ⁵Institut Paoli-Calmettes, Marseille, France; ⁶IOB Institute of Oncology, Quiron Group, Madrid, and Vall d'Hebron Institute of Oncology, Barcelona, Spain; ⁷National Cancer Center, Goyang, South Korea; ⁸Barts Cancer Institute, Centre for Experimental Cancer Medicine, London, United Kingdom; ⁹Instituto do Câncer do Estado de São Paulo – Faculdade de Medicina da Universidade do Estado de São Paulo, São Paulo, Brazil; ¹⁰University Medical Center Hamburg, Hamburg, Germany; ¹¹Hiroshima City Hiroshima Citizens Hospital, Hiroshima, Japan; ¹²The Royal Marsden NHS Foundation Trust, London, United Kingdom; ¹³San Raffaele Scientific Institute, Milan, Italy; ¹⁴Breast Center, University of Munich, Munich, Germany; ¹⁵Université Paris-Sud, Orsay, and Gustave Roussy, Villejuif, France; ¹⁶University of Toronto, Toronto, ON, Canada; ¹⁷Merck & Co., Inc., Kenilworth, NJ, USA

OS in subpopulation defined by TILs median cutpoint (TILs $\geq 5\%$ vs. $< 5\%$)

- For TPC arm, the yellow and red curves represent the TILs $\geq 5\%$ and TILs $< 5\%$, with little difference observed
- For Pembro arm, there is separation according to the median TILS cut-off consistent with testing as a continuous measure





THIS CASE WAS SP142
NEGATIVE, BUT HAS MANY TILS.

What will you do?

1. Nothing.

2. Call your pathologist to ask him
to reconsider the staining?

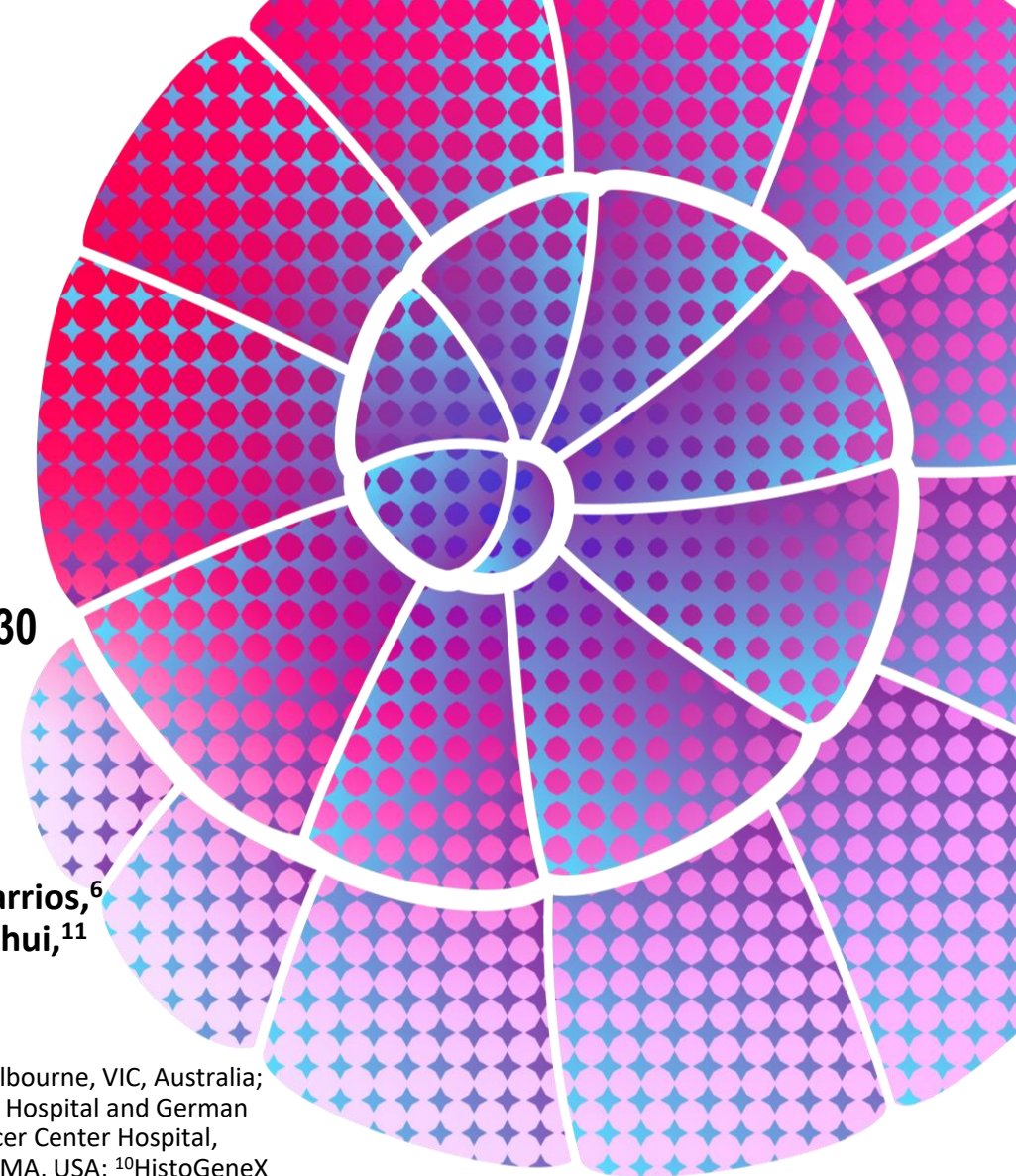
3. Call your pathologist to ask him
to consider another assay?

ESMO BREAST CANCER VIRTUAL MEETING

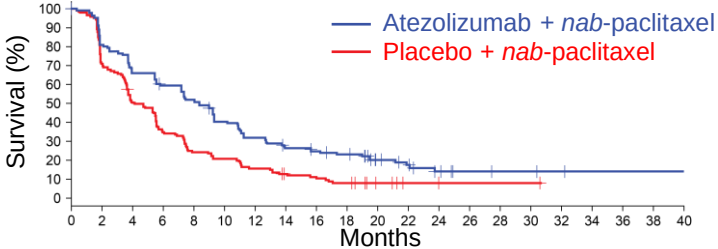
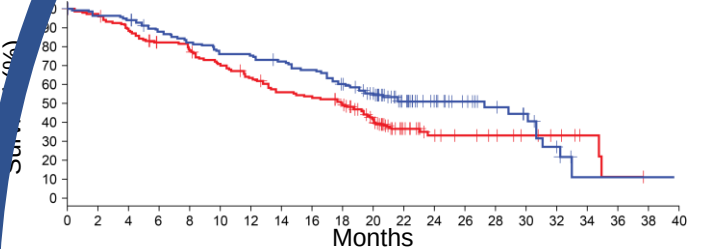
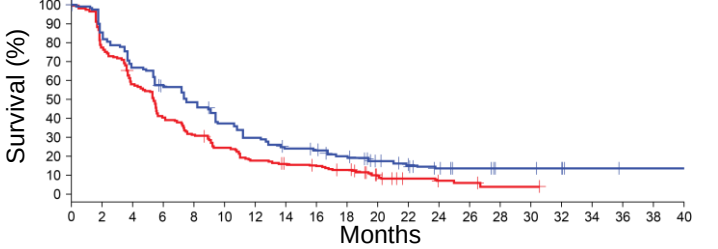
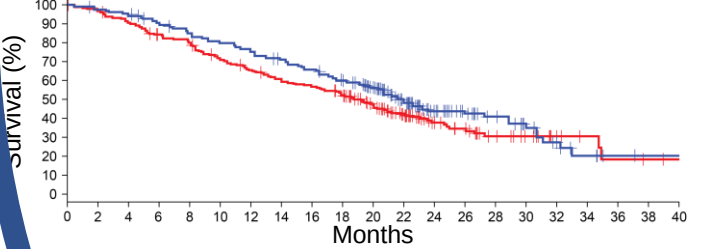
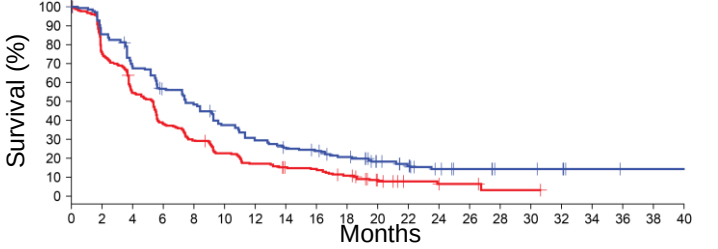
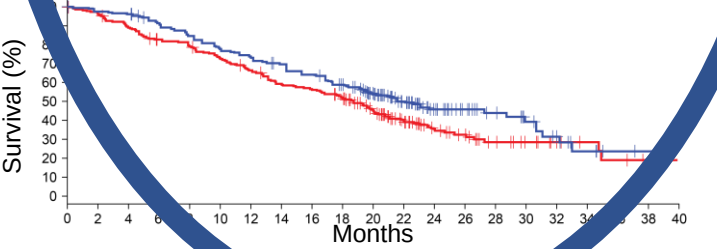
PERFORMANCE OF PD-L1 IMMUNOHISTOCHEMISTRY ASSAYS IN UNRESECTABLE LOCALLY ADVANCED OR METASTATIC TRIPLE-NEGATIVE BREAST CANCER: POST HOC ANALYSIS OF IMPASSION130

Hope S. Rugo,¹ Sherene Loi,² Sylvia Adams,³ Peter Schmid,⁴ Andreas Schneeweiss,⁵ Carlos H. Barrios,⁶
Hiroji Iwata,⁷ Véronique Diéras,⁸ Eric P. Winer,⁹ Mark M. Kockx,¹⁰ Dieter Peeters,¹⁰ Stephen Y. Chui,¹¹
Jennifer C. Lin,¹¹ Anh Nguyen Duc,¹¹ Giuseppe Viale,¹² Luciana Molinero,¹¹ Leisha A. Emens¹³

¹University of California San Francisco Comprehensive Cancer Center, San Francisco, CA, USA; ²Peter MacCallum Cancer Centre, Melbourne, VIC, Australia;
³NYU Langone Medical Center, New York, NY, USA; ⁴Barts Cancer Institute, Queen Mary University London, London, UK; ⁵University Hospital and German
Cancer Research Center Heidelberg, Heidelberg, Germany; ⁶Centro de Pesquisa Clínica, HSL, PUCRS, Porto Alegre, Brazil; ⁷Aichi Cancer Center Hospital,
Nagoya, Japan; ⁸Department of Medical Oncology, Centre Eugène Marquis, Rennes, France; ⁹Dana-Farber Cancer Institute, Boston, MA, USA; ¹⁰HistoGeneX
NV, Antwerp, Belgium; ¹¹Genentech, Inc., South San Francisco, CA, USA; ¹²University of Milan, European Institute of Oncology IRCCS, Milan, Italy;
¹³University of Pittsburgh Medical Center Hillman Cancer Center, Pittsburgh, PA, USA

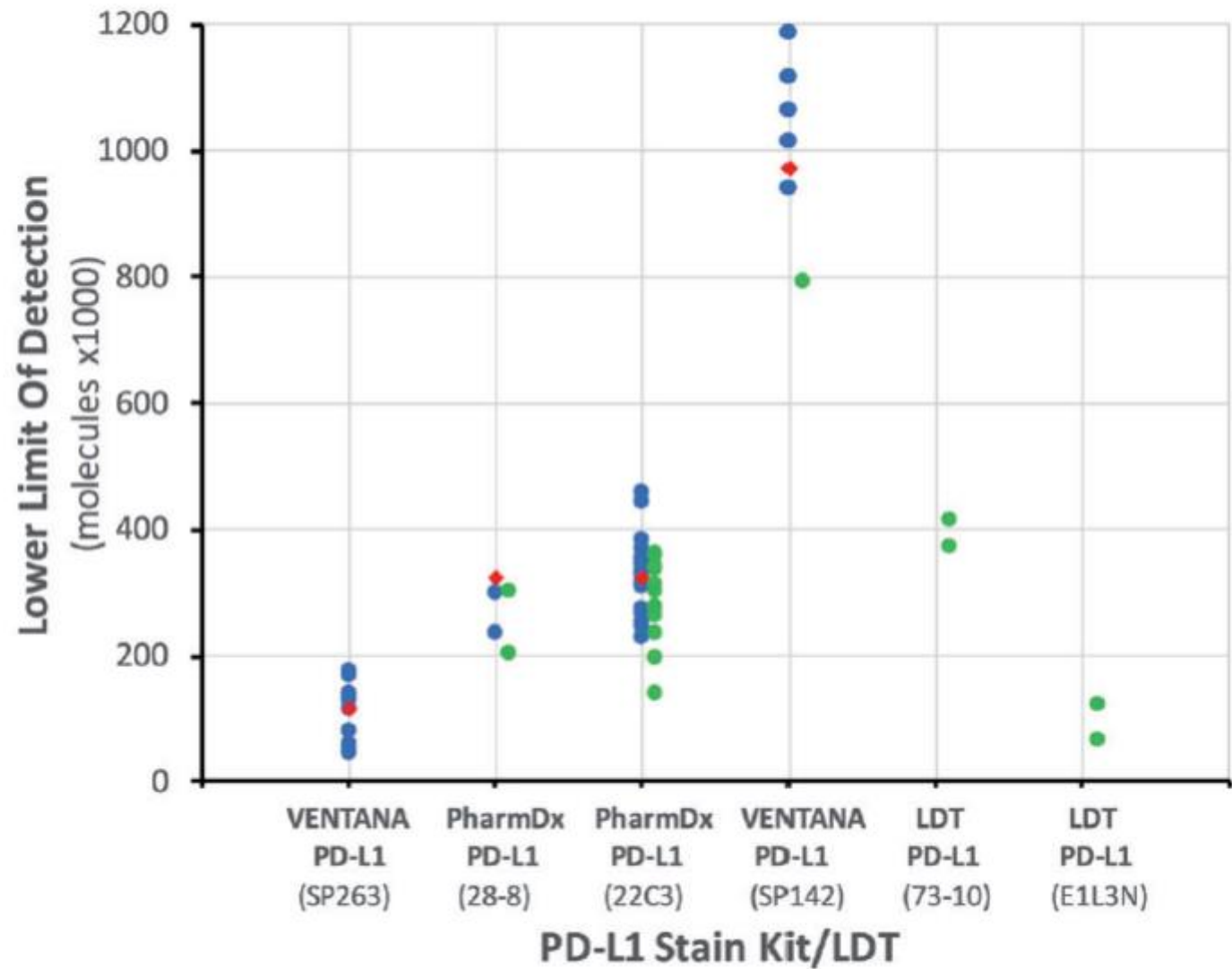


Clinical outcomes in PD-L1+ populations per SP142 (IC 1%), 22C3 (CPS 1) and SP263 (IC 1%)

Population	PFS				OS			
	Median PFS, mo			HR (95% CI)	Median OS, mo			HR (95% CI)
	A + nP	P + nP	Δ		A + nP	P + nP	Δ	
SP142 IC ≥ 1%: 46% (285/614)	8.3	4.1	4.2	0.60 (0.47, 0.78)	27.3	17.9	9.4	0.74 (0.54, 1.01)
								
22C3 CPS ≥ 1: 81% (497/614)	7.5	5.4	2.1	0.68 (0.56, 0.82)	21.6	19.2	2.4	0.78 (0.62, 0.99)
								
SP263 IC ≥ 1%: 75% (460/614)	7.5	5.3	2.2	0.64 (0.53, 0.79)	22.0	18.7	3.3	0.75 (0.59, 0.96)
								

HR adjusted for prior taxanes, presence of liver metastases, age and ECOG PS.

Limit of Detection (LOD) from Multiple Labs – Multiple Assays



Product Care

Vigilance Information

Tissue Diagnostics

15 November 2022

**Unacceptable Light Staining & review of negative results -
VENTANA PD-L1 (SP142) Assay Specific Lots**

Product Care

Vigilance Information

Tissue Diagnostics

15 November 2022

The clinical use of biomarkers to predict ICI therapy has been rapidly advancing in recent years. Patient eligibility for treatment with atezolizumab or with competitor immune checkpoint inhibitors

Pembrolizumab, Nivolumab, Cemiplimab, Avelumab and Durvalumab can be determined with other PD-L1 assays, 22C3 pharm Dx or VENTANA PD-L1 (SP263).

Narrative 2

- **Will the sponsor in pharma-driven drug trials ever formally and publicly claim that what is most important is the validation of the assay, irrespective whether it's a CdX or not?**

I believe that a clinical trial serves to validate a biomarker, and not a vendor-specific assay. What do you think?

What are the regulatory implications of these notions?

Narrative 3

- **Does FDA-approval of a CdX equal biomarker level of evidence?
Is it always evidence of the highest standard of performance?**

Levels of evidence?

FDA approves companion diagnostic to identify *NTRK* fusions in solid tumours for larotrectinib

 Right-click or tap and hold to download

On 23 October 2020, the US Food and Drug Administration (FDA) approved the next-generation sequencing (NGS)-based FoundationOne CDx test (Foundation Medicine, Inc.) as a companion diagnostic to identify fusions in neurotrophic receptor tyrosine kinase (*NTRK*) genes, *NTRK1*, *NTRK2*, and *NTRK3*, in DNA isolated from tumour tissue specimens from patients with solid tumours eligible for treatment with larotrectinib (VITRAKVI, Bayer Healthcare Pharmaceuticals, Inc.).

The FoundationOne CDx assay (F1CDx) approval as a companion diagnostic for larotrectinib was based on the retrospective testing with F1CDx of available tumour tissue samples from patients enrolled in the three clinical trials that supported the accelerated approval of larotrectinib.

**FDA-approval does NOT equate to biomarker level of evidence.
Is it NOT always evidence of the highest standard of performance?**

ARE WE REALLY SOLVING THE ISSUES THE COMMUNITY AND OUR PATIENTS ARE FACING?

Comment

How current assay approval policies are leading to unintended imprecision medicine



Panel: Solutions to improve the current assay approval pathway

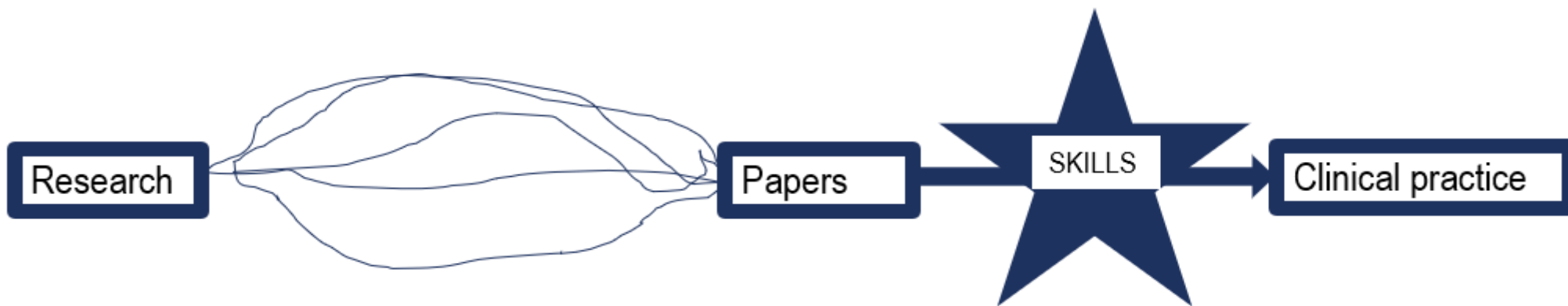
- Industry should be mandated to do concordance studies with other similar assays or standardised controls before a drug is approved
- Industry should support, in concert with all stakeholders, relabelling or revising approved companion diagnostics if evidence exists that the labelling might lead to uncertainty in the identification of patients for treatments
- Industry should support, in concert with all stakeholders, relabelling or revising of the companion diagnostics if equivalent clinical validity has been shown with other biomarkers or standards, providing access to clinical trial tissues to validate other assays
- Industry, when considering the incorporation of assays in their trials, should communicate and share assay information when using an assay that identifies the same molecule (eg, epitope, antigen, DNA, RNA) as in other competitive trials—eg, method information related to the binding sites of the antibodies used in the companion diagnostic assay should be made public, even if this information is commercially sensitive
- Pathways for regulatory acceptance of other assays that are equivalent, but less expensive and easier to implement in daily practice, should be developed by governments and regulatory agencies, ideally before a drug is labelled together with a companion diagnostic
- Early engagement by all stakeholders in external quality control schemes to allow rapid development of guidelines and quality standards is essential, preferably before an assay is approved by the regulatory agencies
- Clinical practice guidelines developed by professional organisations like the American Society of Clinical Oncology and the European Society for Medical Oncology should endorse not just a companion diagnostic assay used in the trial, but any rigorously and technically validated equivalent laboratory assays that can define essentially the same population as the companion diagnostic
- Regulators should require data confirmation of the analytical validity of the companion diagnostic in the distributed setting in which it would be applied, at a level of rigor similar to that required to show efficacy of the drug in question

The Main Narrative of this Lecture

We are too good in producing academic output.

We are not so good in changing clinical practice. A worldwide community effort, including patients and industry should drive interactions with FDA and CMS, and that should determine clinical practice.

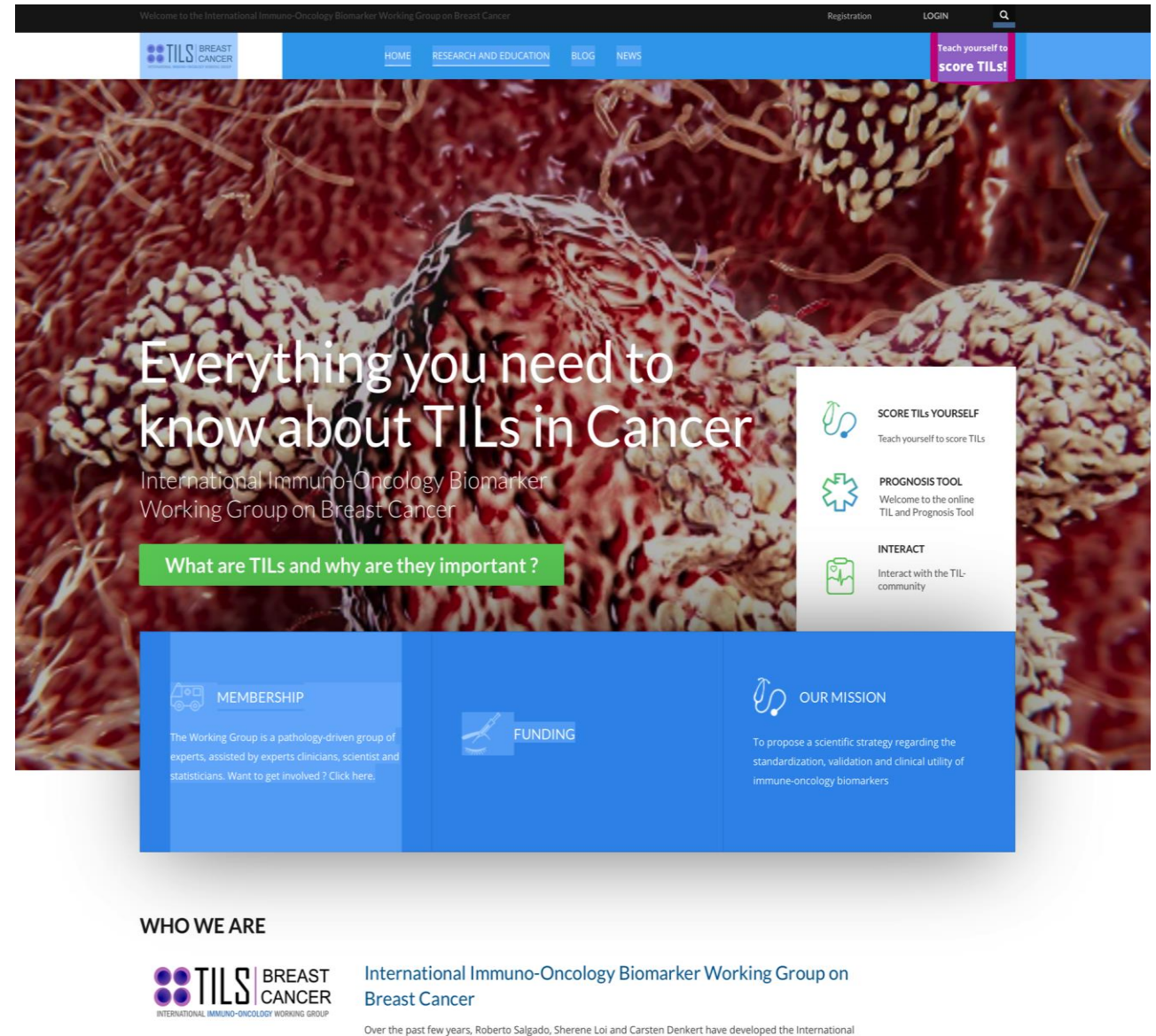
This goes beyond a “simple” notion of a CdX and an IVDR-label.



THANK YOU

Roberto@salgado.be

All welcome to join the TIL-WG
Just mail me



www.tilsinbreastcancer.org