Biomarqueurs et cancer infiltrant du sein: quoi de neuf ?

Biomarqueurs émergents

Dr Magali LACROIX-TRIKI

Pathologiste

Carrefour Pathologie – 7 novembre 2019

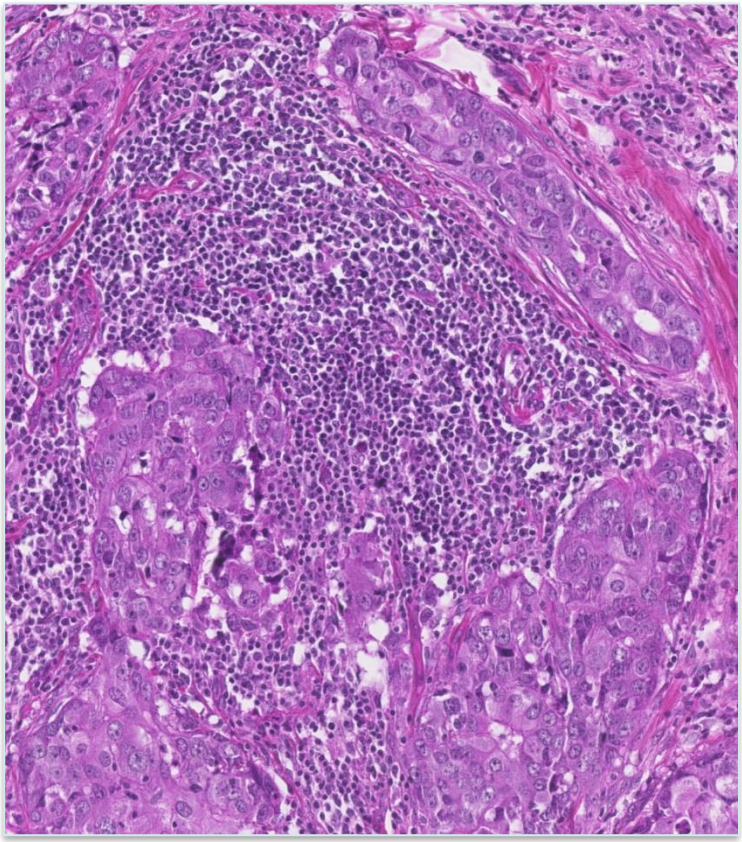
GUSTAVE ROUSSY
CANCER CAMPUS
GRAND PARIS

Liens d’intérêts

- Roche
- Roche diagnostics
- Myriad Genetics
- Genomic Health
- MyPL

Microenvironnement tumoral

- TILs : pronostique++
- PD-L1 : prédictif++

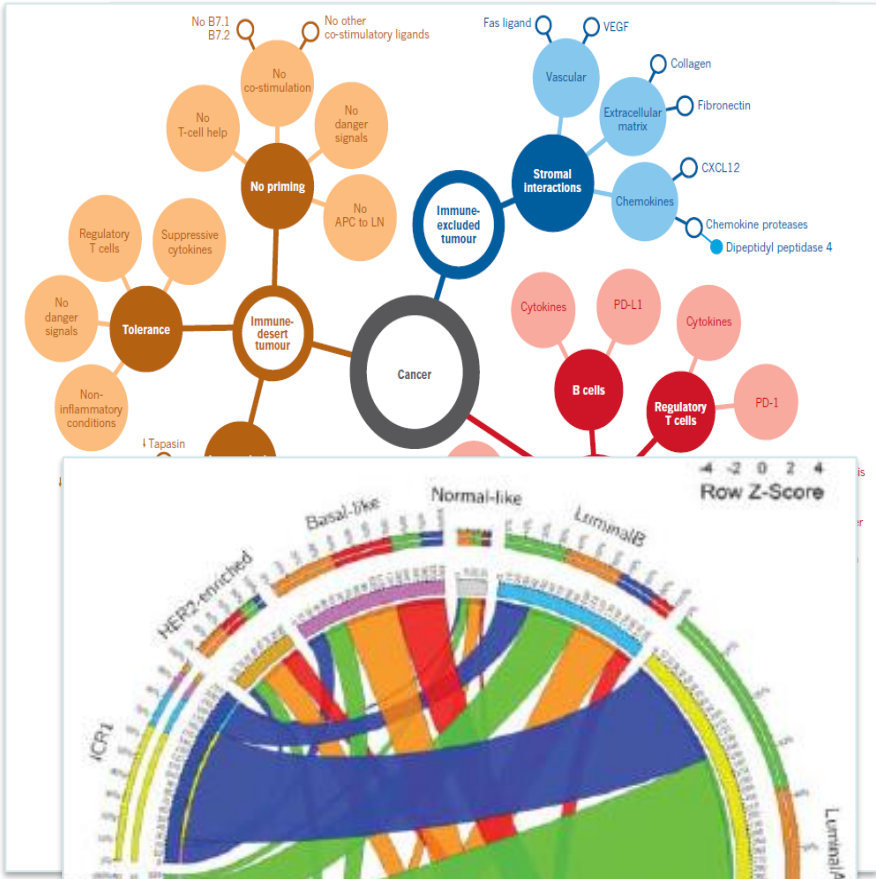


Portrait immunitaire

- RNA seq., TCGA n=1004, (cohorte indépendante n=1954)
- 4 phénotypes immunitaires
  - ICR1: le moins activé
  - ICR4: signature Th1, up-régulation *PDL1*, *FOXP3*, *CTLA4*

→ **Enflammé («chaud»)**
→ Exclu (cellules immunitaires exclues)
→ **Désert immunitaire («froid»)**

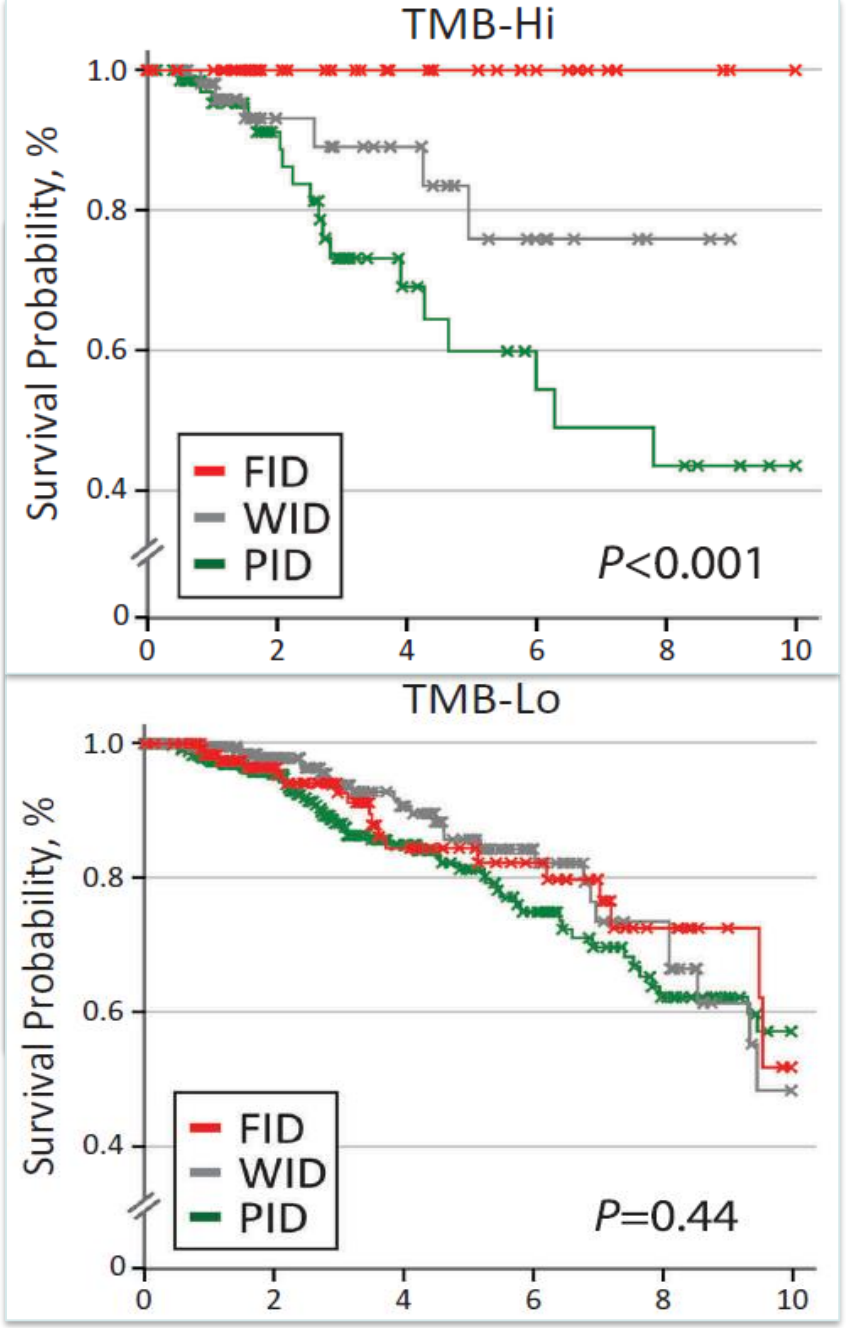
- Distribution hétérogène selon les types moléculaires



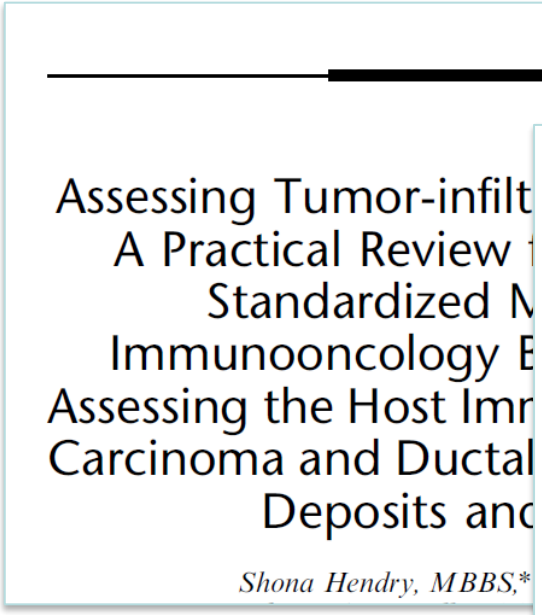
Hendrickx W et al. Oncoimmunology 2017;6:e1253654
Chen DS. Nature 2017;541:321-30

Marqueur pronostique

- Signature immunitaire Th1 (ICR4) : meilleure survie
- Rôle pronostique de la « disposition immunitaire »: dépendant de la charge mutationnelle (*Tumor Mutational Burden, TMB*), élevée ++ dans HER2+ et basal-like
- ↗TILs : bon pronostic dans triple négatifs et HER2+ *(Adams S. JCO 2014, Loi S. JCO2013, Loi S. JCO 2019, Salgado R. JAMA oncol 2015)*
- Moins clair pour RE+/HER2- (mauvais pronostic ?) *(Denkert C. Lancet oncol 2018)*



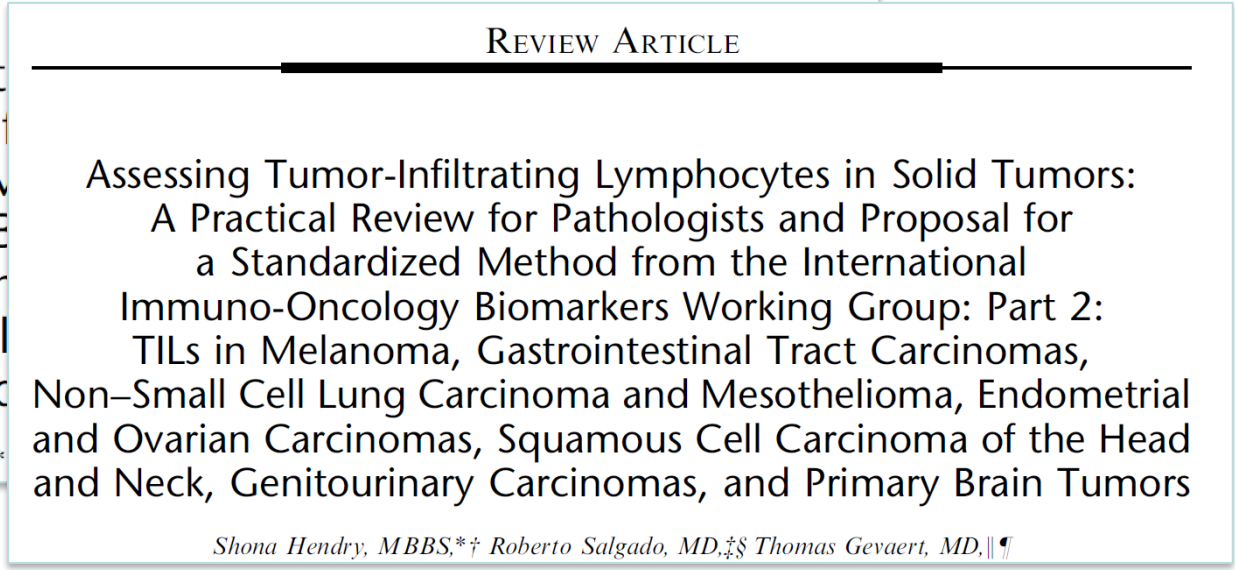
Hendrickx W et al. Oncoimmunology 2017;6:e1253654
Thomas A et al. Oncoimmunology 2018;7:e1490854


REVIEW ARTICLE

Assessing Tumor-infilt
A Practical Review
Standardized M
Immunooncology E
Assessing the Host Imr
Carcinoma and Ductal
Deposits and

*Shona Hendry, MBBS,**

Adv Anat Pathol 2017

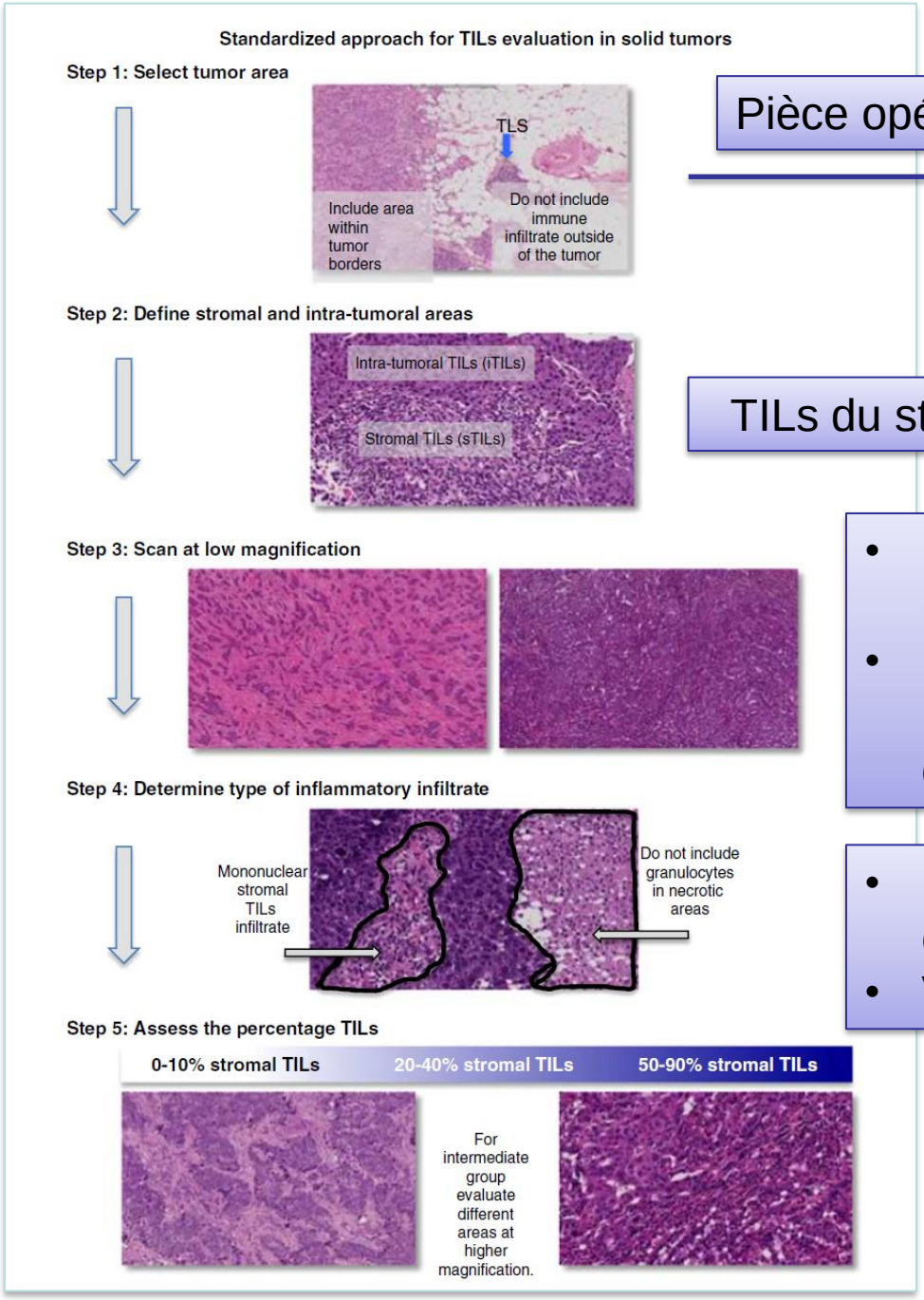

REVIEW ARTICLE

Assessing Tumor-Infiltrating Lymphocytes in Solid Tumors: A Practical Review for Pathologists and Proposal for a Standardized Method from the International Immuno-Oncology Biomarkers Working Group: Part 2: TILs in Melanoma, Gastrointestinal Tract Carcinomas, Non–Small Cell Lung Carcinoma and Mesothelioma, Endometrial and Ovarian Carcinomas, Squamous Cell Carcinoma of the Head and Neck, Genitourinary Carcinomas, and Primary Brain Tumors

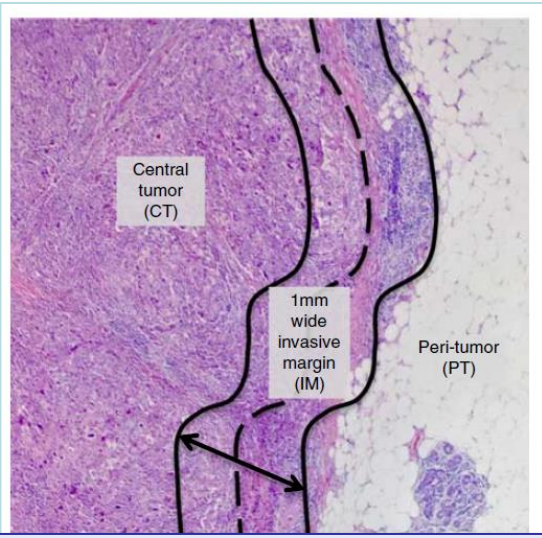
Shona Hendry, MBBS,† Roberto Salgado, MD,‡§ Thomas Gevaert, MD,‖¶*

- Groupe international (pathologistes, oncologues, biostatisticiens, biologistes)
- TILs sur H&E: semi-quantitatitif, adapté à la recherche et à la pratique clinique, universel, simple et faible coût
- Revue de la littérature et recommandations pour standardiser la méthode de lecture
- Décrit initialement pour le cancer du sein (2015) puis étendu aux autres types de tumeur solide avec quelques spécificités

Salgado R et al, Ann Oncol 2015
Hendry S et al, Adv Anat Pathol 2017



Pièce opératoire

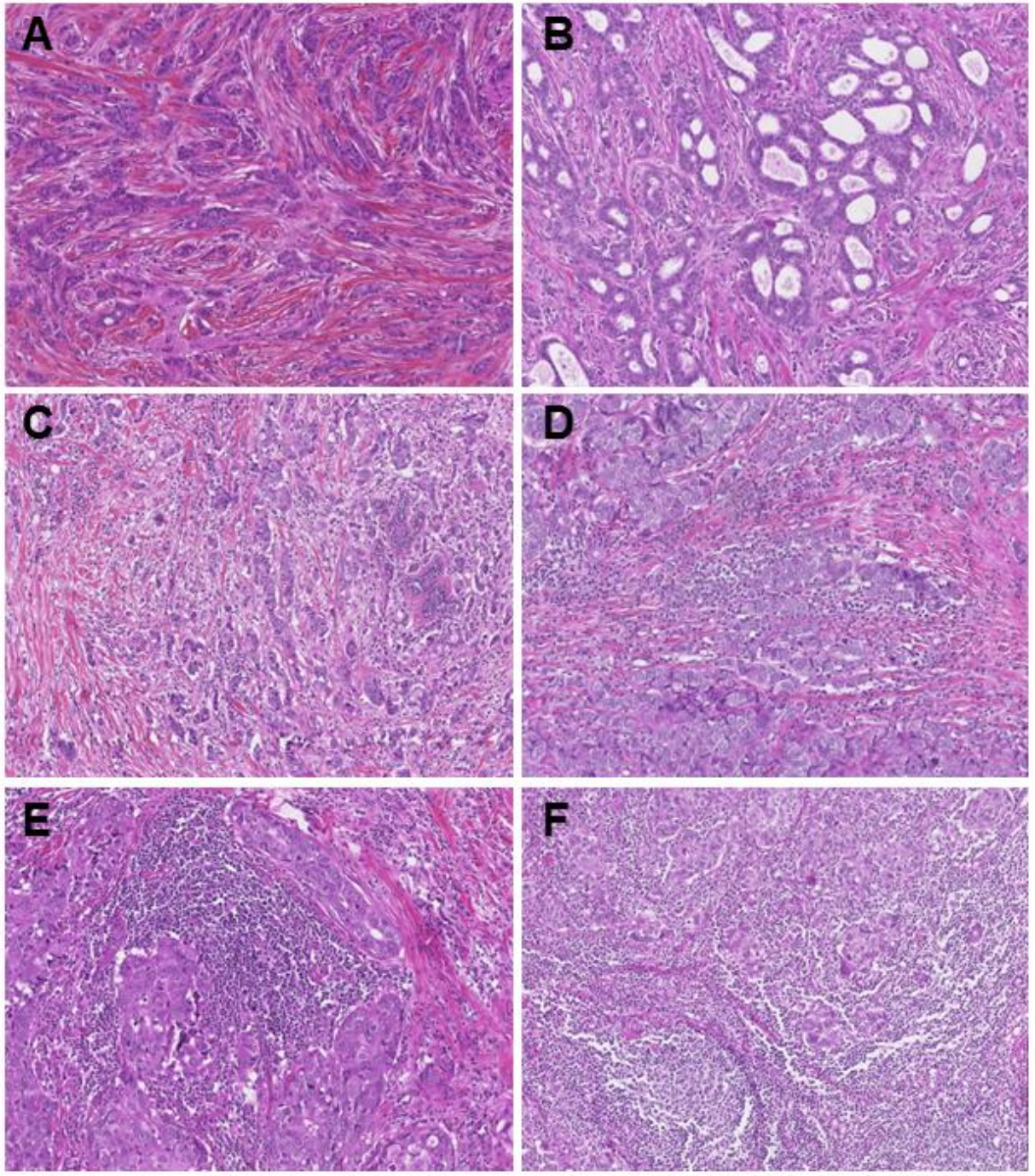


TILs du stroma

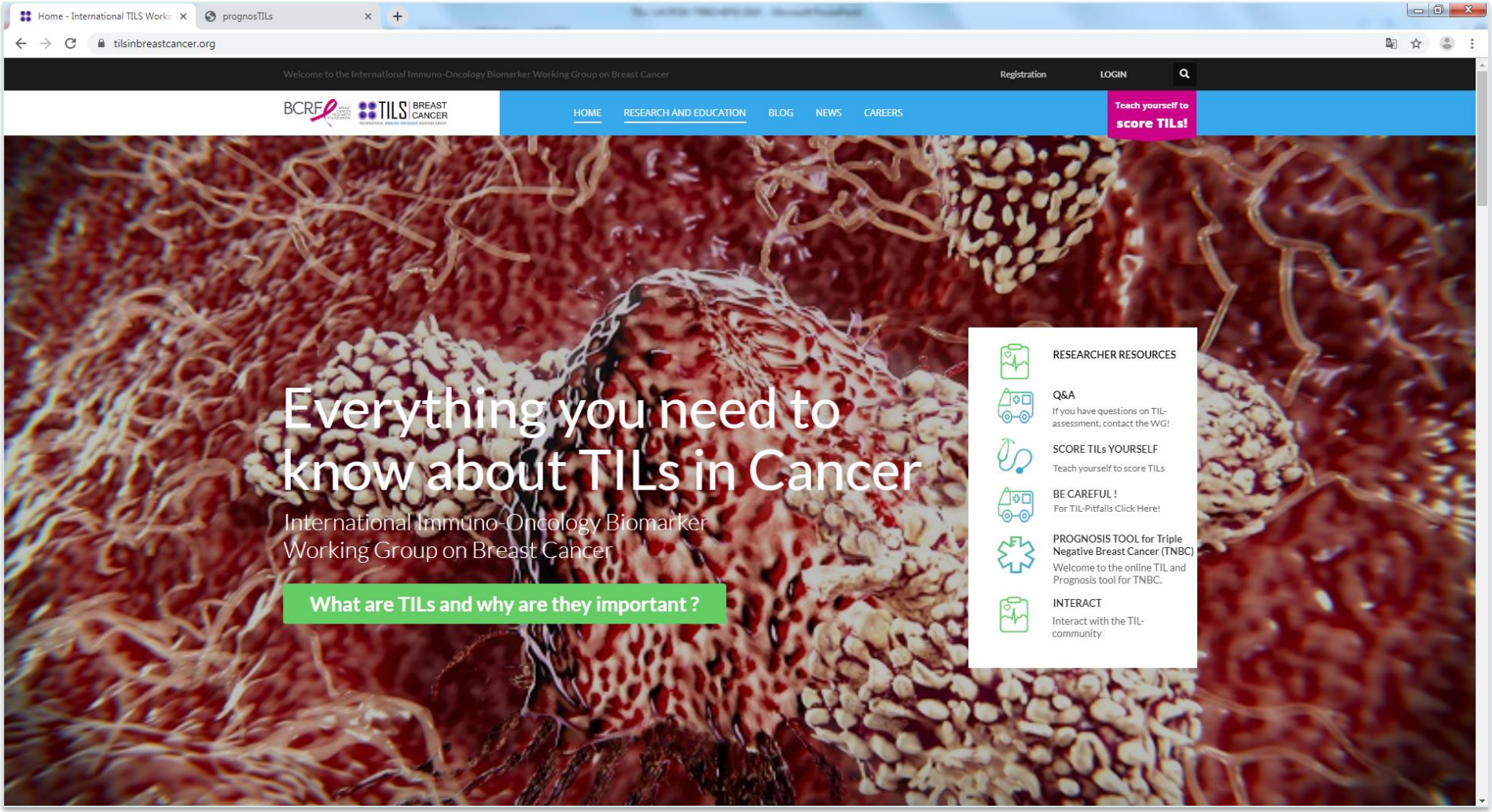
- Moyenne sur toute la zone tumorale (pas hot spots)
- Hors artéfacts écrasement, nécrose, hyalinisation régressive (centrale), sites de biopsie

- Évaluer les TILs en % de **surface** occupée par les cellules mononucléées
- Variable continue (arrondir à 5% près)

- Riche en TILs (prédominance lymphocytaire) = ≥50-60% sTILs
- Pas de cut-off défini à ce stade
- S'aider de grilles visuelles



Joyon N et al, Ann Pathol 2017; 37:127-32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prognosTILs
tilsinbreastcancer.org
Welcome to the International Immuno-Oncology Biomarker Working Group on Breast Cancer
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BCRF
TILS BREAST CANCER
HOME
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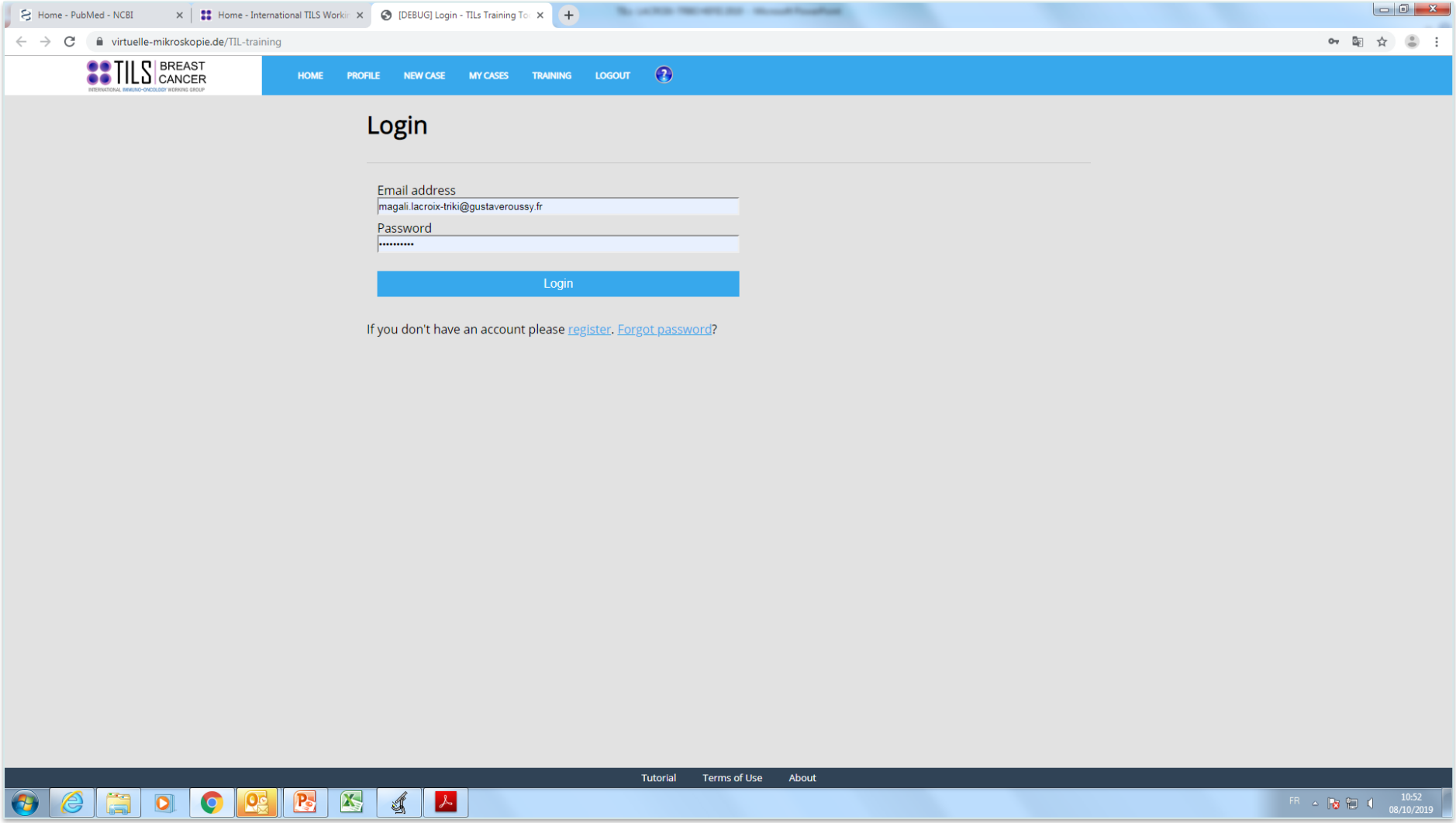
BLOG
NEWS
CAREERS
Teach yourself to score TILs!
Everything you need to know about TILs in Cancer
International Immuno-Oncology Biomarker Working Group on Breast Cancer
What are TILs and why are they important ?
RESEARCHER RESOURCES
Q&A
If you have questions on TIL-assessment, contact the WG!
SCORE TILs YOURSELF
Teach yourself to score TILs
BE CAREFUL !
For TIL-Pitfalls Click Here!
PROGNOSIS TOOL for Triple Negative Breast Cancer (TNBC)
Welcome to the online TIL and Prognosis tool for TNBC.
INTERACT
Interact with the TIL-community


Home - PubMed - NCBI
Home - International TILS Workin
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virtuelle-mikroskopie.de/TIL-training
TILS BREAST CANCER
INTERNATIONAL IMMUNO-ONCOLOGY WORKING GROUP
HOME
PROFILE
NEW CASE
MY CASES
TRAINING
LOGOUT
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Email address
magali.lacroix-triki@gustaveroussy.fr
Password
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If you don't have an account please register. Forgot password?
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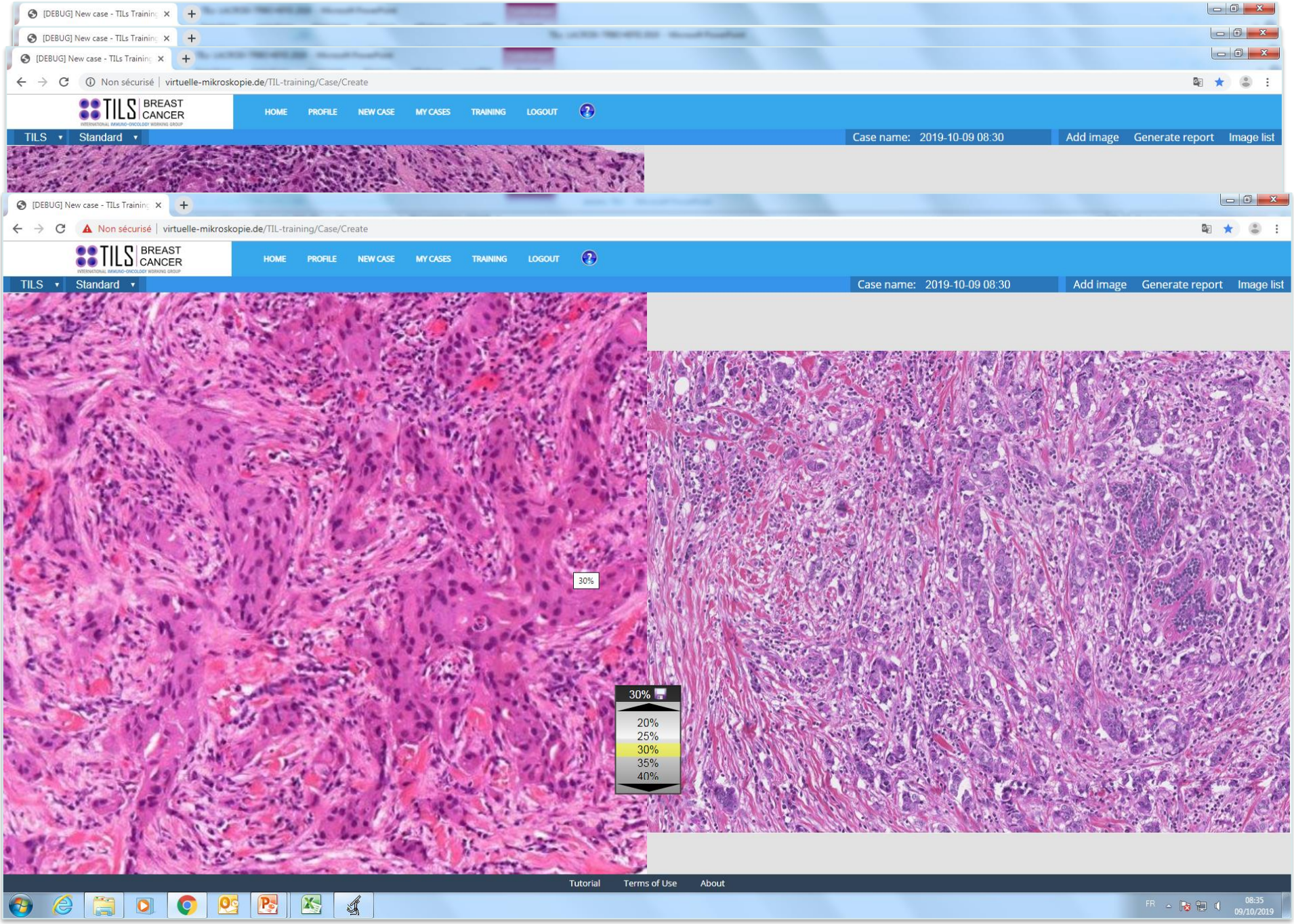
08/10/2019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TILS BREAST CANCER
INTERNATIONAL IMMUNO-ONCOLOGY WORKING GROUP
HOME
PROFILE
NEW CASE
MY CASES
TRAINING
LOGOUT
TILS
Standard
Case name: 2019-10-09 08:30
Add image
Generate report
Image list
30%
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30%
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40%
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08:35
09/10/2019

Home - International TILS Worki | prognosTILs

tilsinbreastcancer.org

Welcome to the International Immuno-Oncology Biomarker Working Group on Breast Cancer | Registration | LOGIN

Online TIL and Prognosis Tool - | prognosTILs

cesp-proxy2.vjf.inserm.fr/shiny/prognosTILs/

Predictions for patient series

Purpose

Using pooled individual data of 9 studies (n=2148 patients), we have developed an integrated survival prediction model for early stage triple negative breast cancer patients, based on standard clinicopathological factors and stromal tumour infiltrating lymphocytes (TILs). The model has been shown to have satisficatory discrimination and calibration across studies (see Loi et al 2018). This tool has been designed to facilitate the use of this predictive model.

Online TIL and Prognosis Tool - | prognosTILs

cesp-proxy2.vjf.inserm.fr/shiny/prognosTILs/

prognosTILs

- Home
- Obtain survival predictions
- Prepare a report
- Predictions for patient series

Predict the survival according stromal TILs

Print 95% confidence bands?

Would you compare to another profile? (max 3) | Reset profiles | Reset prediction table

Select type of survival function:

Survival

Select type of survival event:

iDFS

Which survival time (years):

0 5 10

Age (years):

20 50 85

Number of positive nodes:

0 20

Tumor size (cm):

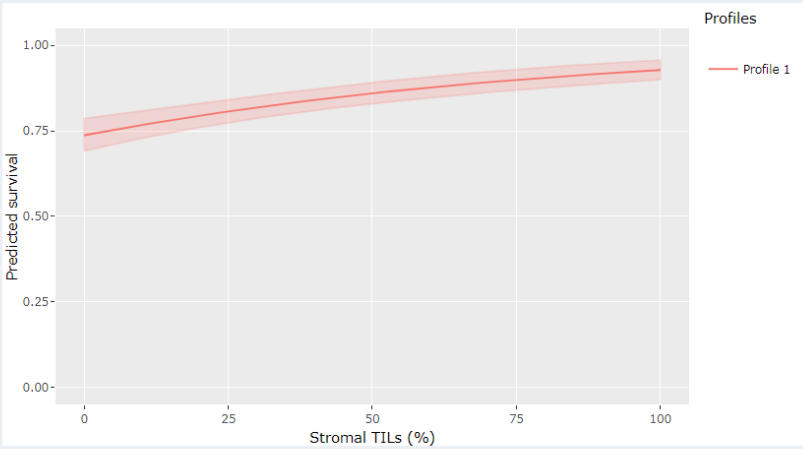
]0; 2]

Histological grade:

Grade 3

Treatment:

Anthracycline + Taxane



Get the prediction at a specific value of TILs?

60 | Get | Save comparison

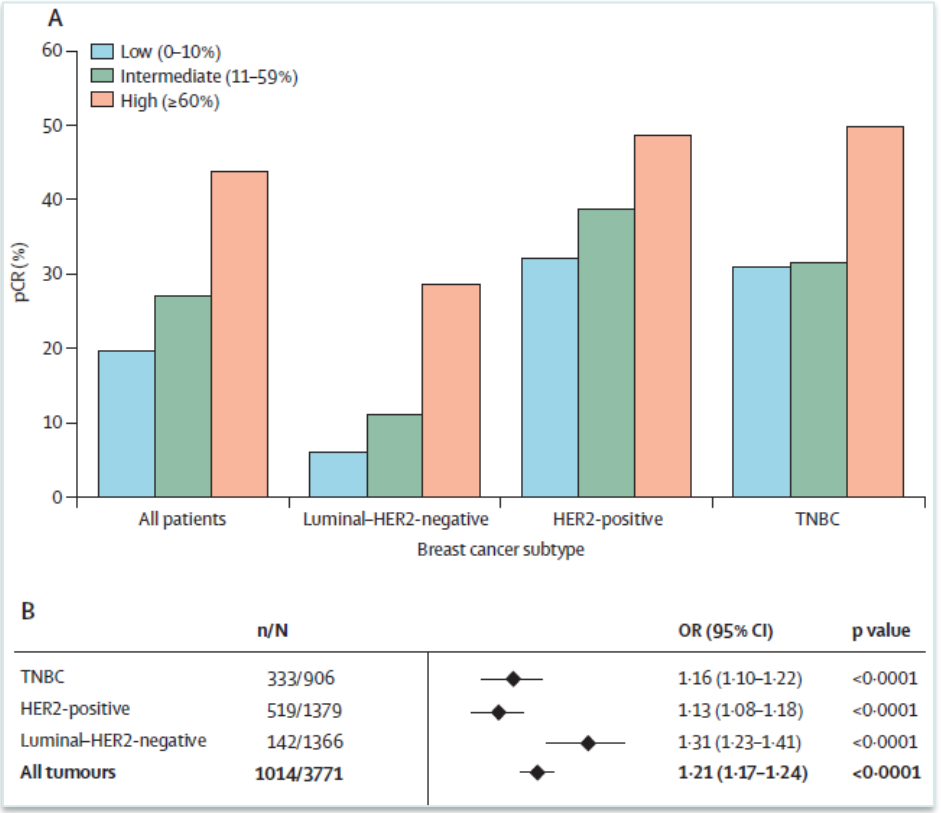
TIL	Profile1	Action
10	0.77 [0.73; 0.81]	×
60	0.88 [0.85; 0.91]	×

Previous 1 Next

FR 10:54 09/10/2019

Marqueur prédictif ?

- TILs : prédiction de la pCR en néoadjuvant *(Denkert C. JCO 2010, Denkert C. Lancet Oncol 2018)*
- Prédiction de la réponse (ou associée à la réponse) aux thérapies ciblées anti-HER2 (trastuzumab, lapatinib) dans le cancer HER2+ *(Loi S. Ann Oncol 2014, Salgado R. JAMA oncol 2015, Kim RS. JNCI 2019)*
- Exploré dans les essais cliniques avec immunothérapies → PD-L1 *(Savas P. Nat Rev 2016;13:228-41, Schmid P et al. NEJM 2018)*



Denkert C et al. Lancet Oncol 2018;19:40-50

The NEW ENGLAND JOURNAL of MEDICINE

2018

ORIGINAL ARTICLE

Atezolizumab and Nab-Paclitaxel in Advanced Triple-Negative Breast Cancer

P. Schmid, S. Adams, H.S. Rugo, A. Schneeweiss, C.H. Barrios, H. Iwata, V. Diéras, R. Hegg, S.-A. Im, G. Shaw Wright, V. Henschel, L. Molinero, S.Y. Chui, R. Funke, A. Husain, E.P. Winer, S. Loi, and L.A. Emens, for the IMpassion130 Trial Investigators*

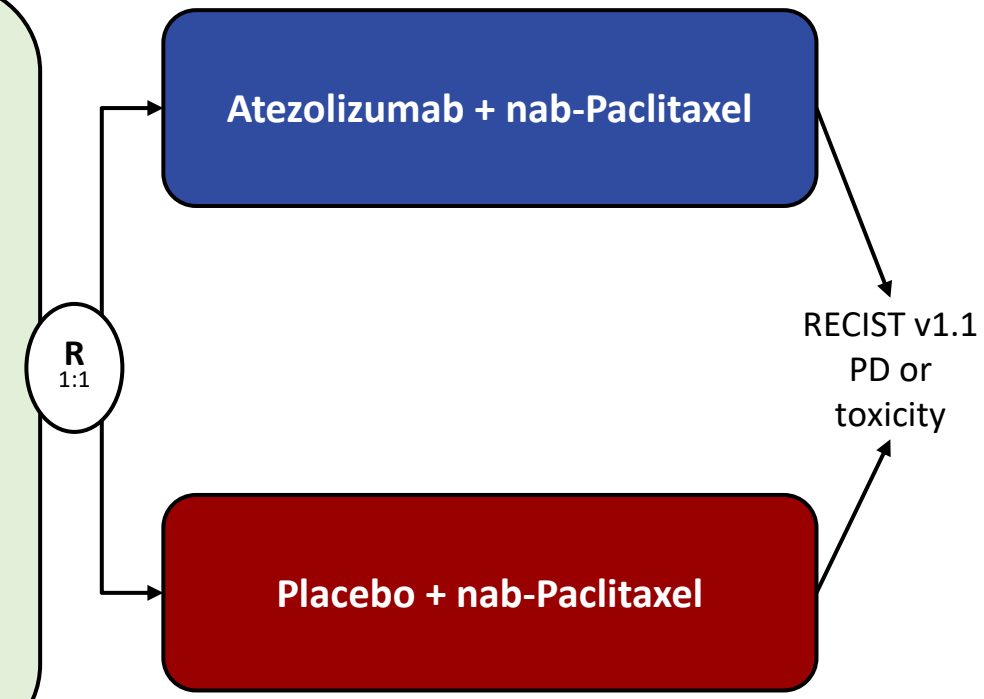
IMpassion130 Study Design

Key eligibility criteria:

- Metastatic or inoperable locally advanced TNBC
  - Histologically documented
- No prior therapy for advanced TNBC
  - Prior chemo in the curative setting, including taxanes, allowed if TFI ≥ 12 mo
- ECOG PS 0-1

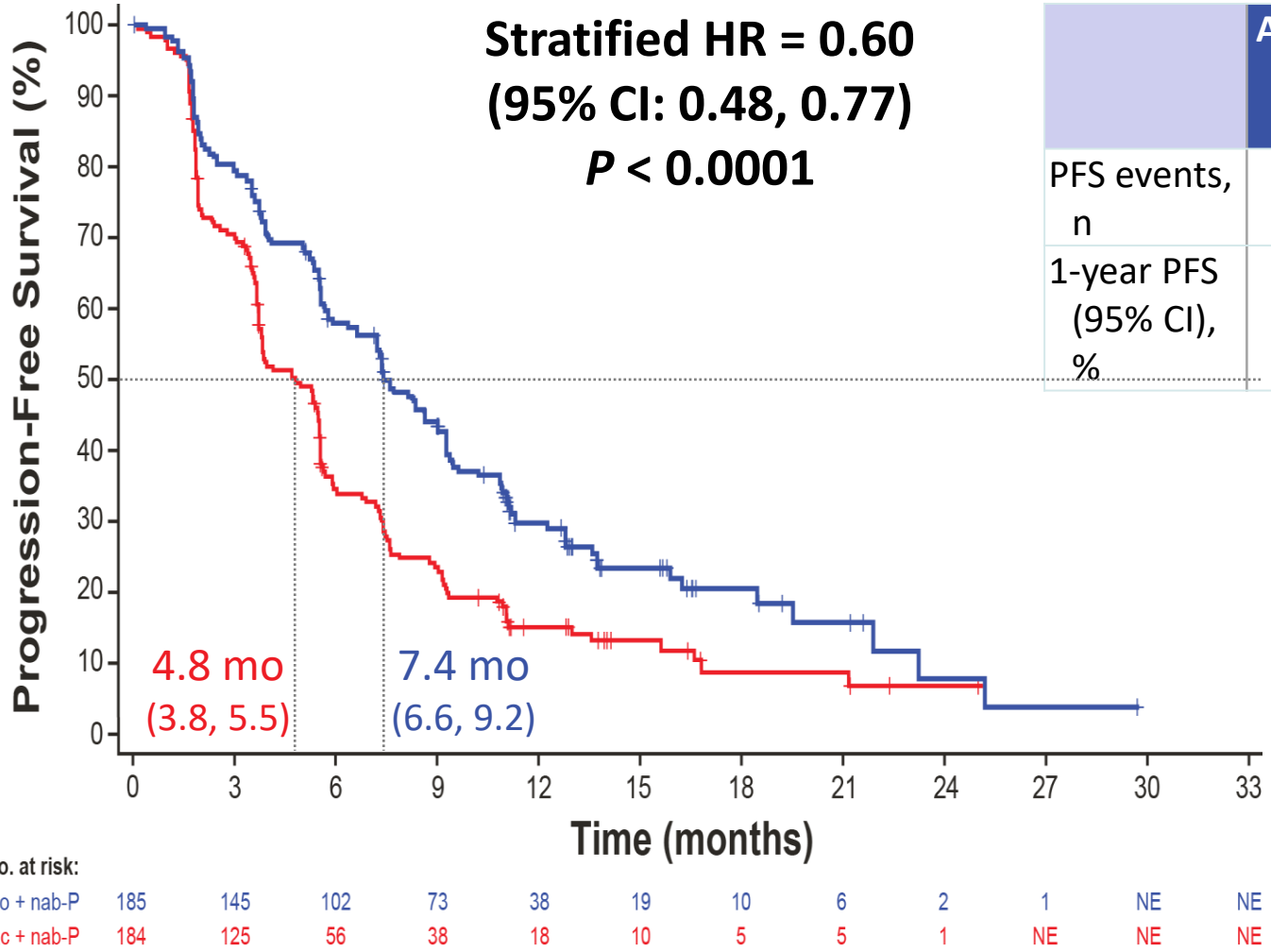
Stratification factors:

- Prior taxane use (yes vs no)
- Liver metastases (yes vs no)
- PD-L1 status on IC (positive [≥ 1%] vs negative [< 1%])



→ Co-primary endpoints were **PFS** and **OS** in the **ITT and PD-L1+ populations**

PFS analysis: PD-L1 + population



	Atezo + nab-Pac (N = 185)	Plac + nab-Pac (N = 184)
PFS events, n	136	151
1-year PFS (95% CI), %	30% (23, 37)	15% (10, 21)

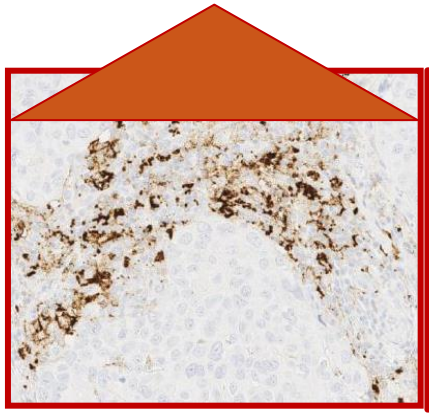
Data cutoff: 17 April 2018. Median PFS durations (and 95% CI) are indicated on the plot. [a] US censoring method.

IMpassion130 Study Results

PFS subgroup analysis:[a] ITT population

Atezolizumab and Nab-Paclitaxel in Advanced Triple-Negative Breast Cancer

Characteristic		Patients	HR(95% CI)[b]
All		902	0.80 (0.69, 0.92)
Baseline liver metastases	Yes	244	0.79 (0.60, 1.03)
	No	658	0.78 (0.65, 0.93)
Prior taxane use	Yes	461	0.78 (0.64, 0.96)
	No	441	0.81 (0.65, 1.00)
PD-L1 status	PD-L1+ (IC1/2/3)	369	0.62 (0.49, 0.79)
	PD-L1– (IC0)	533	0.96 (0.79, 1.16)
Age group	18-40 y	114	0.79 (0.53, 1.16)



PD-L1+

- Cellules immunitaires
- ≥1% (IC1/2/3)
- Clone SP142
- Testing central

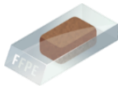
A + nab-Pac ← → P + nab-Pac

a US censoring method.
b Unstratified HRs are shown; 95% CIs are plotted as error bars. Dashed vertical line represents value in ITT population.
c Patients with ECOG PS 2 not plotted.
d Excludes patients with unknown/other values

- **Approbation FDA (8 mars 2019), EMA**
- **ATU en France pour atezolizumab (Tecentriq) depuis 08/2019**

Test PD-L1

Échantillons acceptés



- Tissu fixé au formol (4-6µ, lames blanches < 2mois)
- Biopsies ou pieces opératoires, tumeur primitive ou méta (pas de recommandations spécifiques)
- Au moins 50 cellules tumorales viables

Non validé

Cytology samples*

Decalcified metastatic bone lesions*

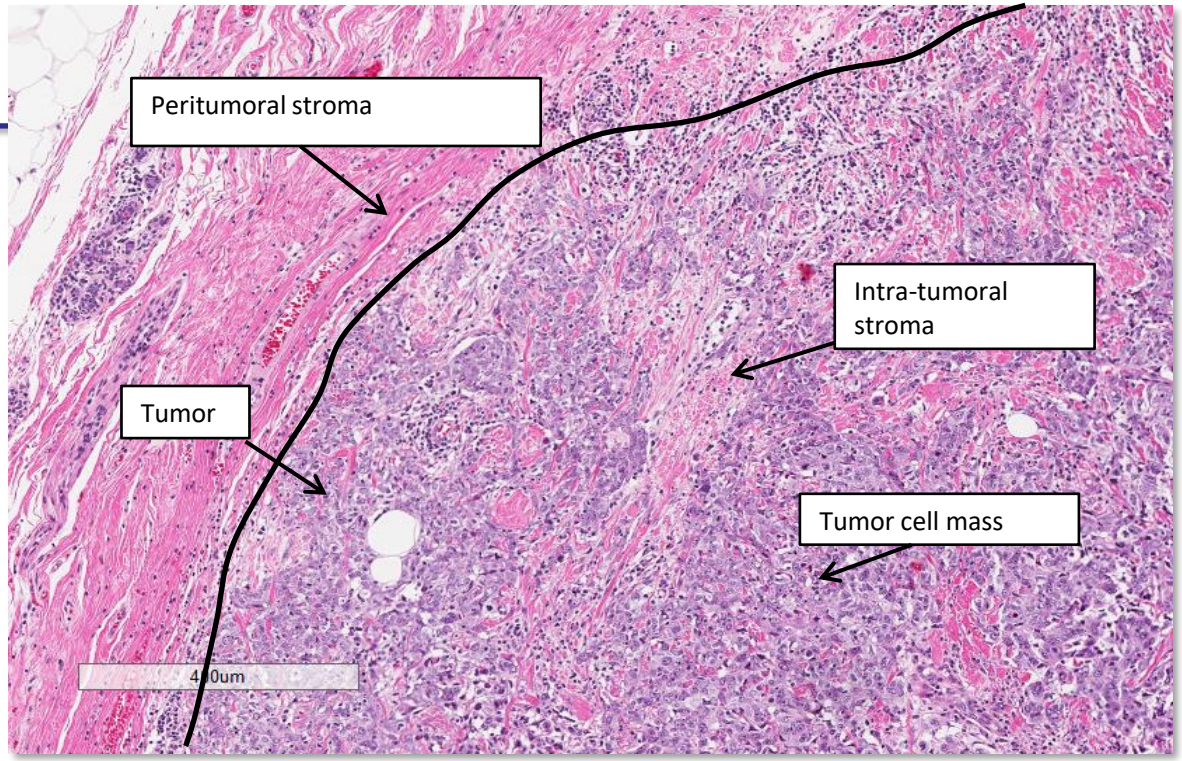
La presence de stroma associé à la tumeur est essentielle pour l’analyse des IC

Test PD-L1 (SP142)

Workflow

Lecture lame HE

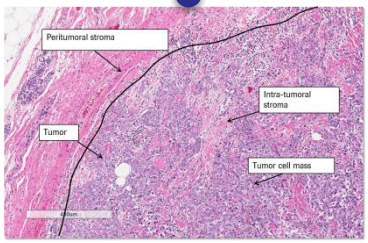
- Présence de la tumeur
- Identification de la surface tumorale (occupée par les cellules tumorales et le stroma)



Test PD-L1 (SP142)

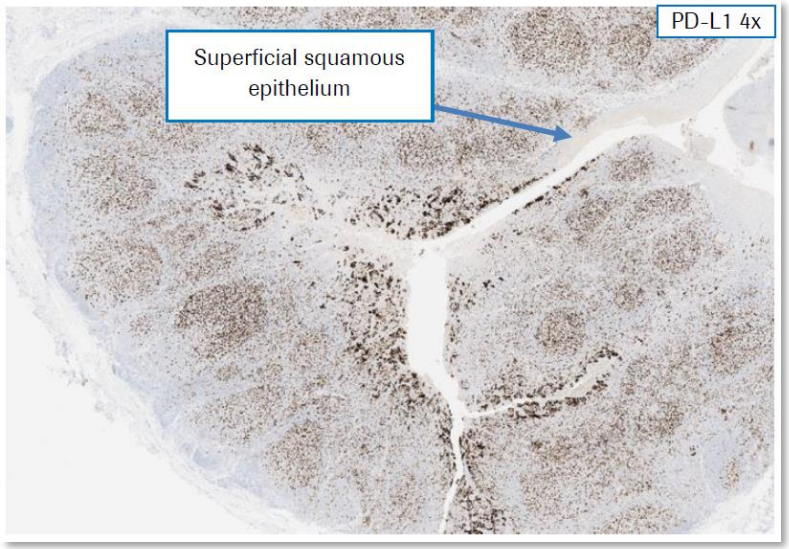
Workflow

Lecture lame HE



Contrôle positif (amygdale)

- Marquage des centres germinatifs et de l'épithélium des cryptes
- Négatif dansles zones inter-folliculaires et l'épithélium de surface

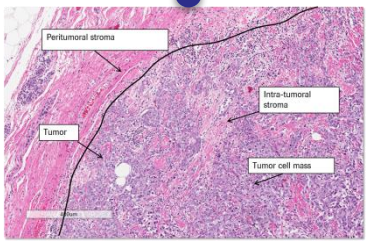


Lecture lame PD-L1

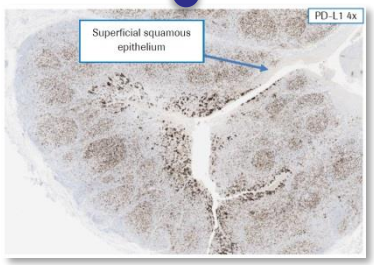
Test PD-L1 (SP142)

Workflow

Lecture lame HE

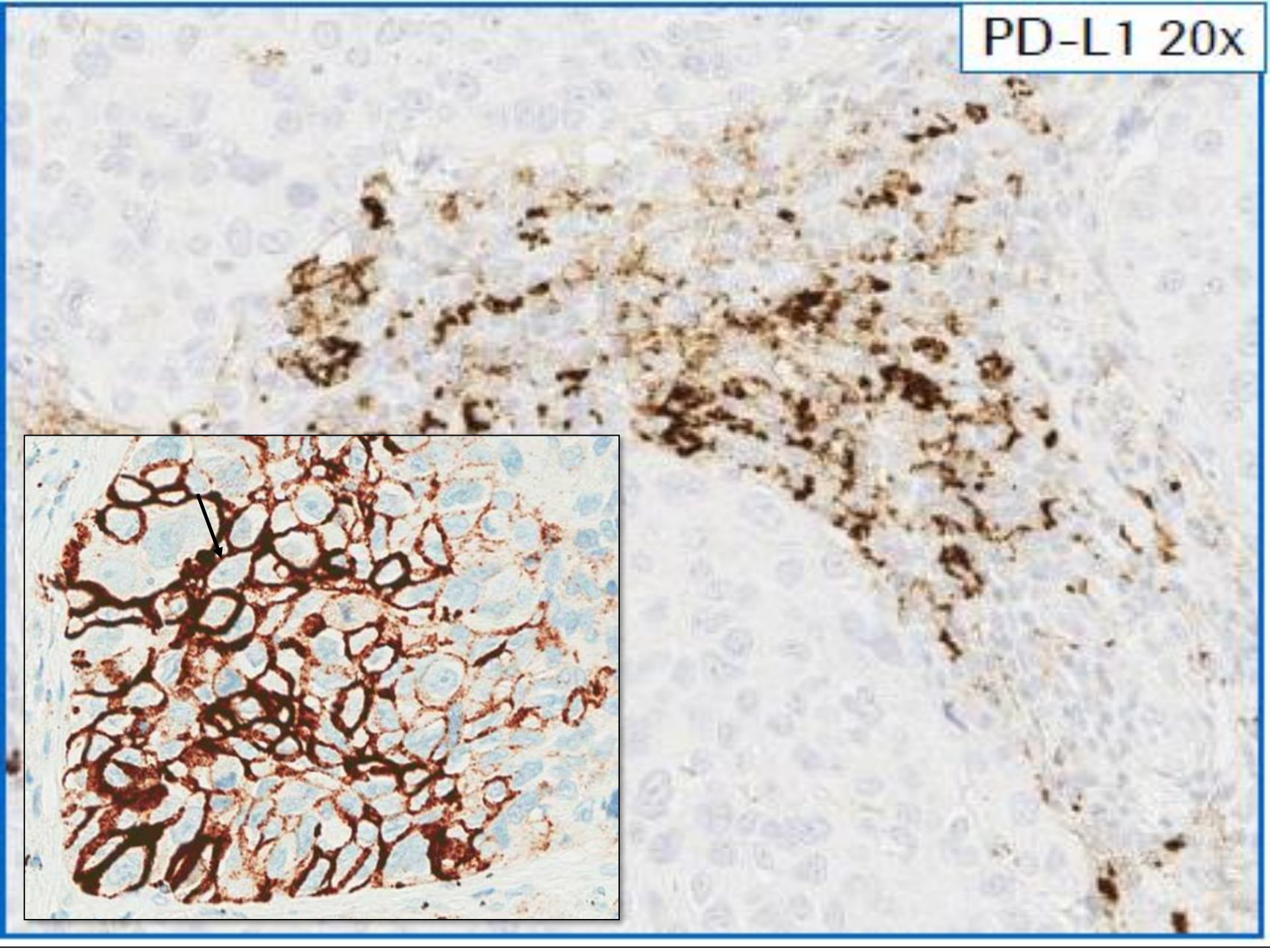


Contrôle positif (amygdale)

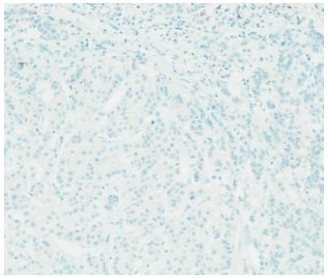
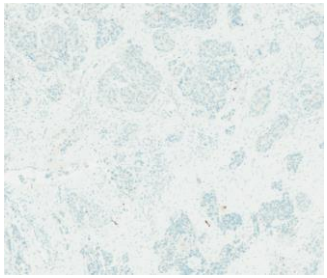
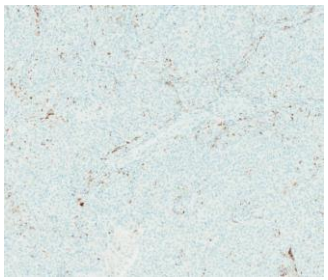
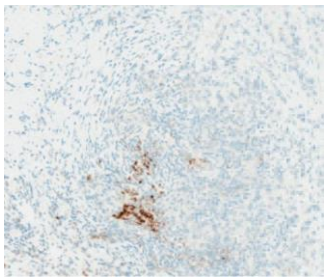
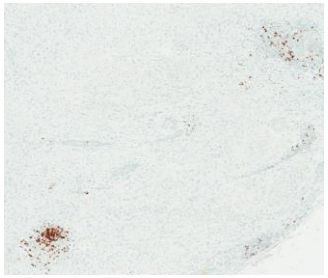
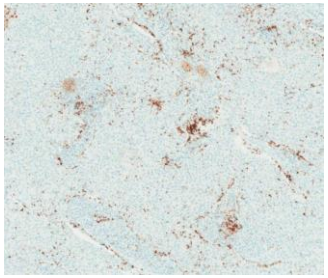
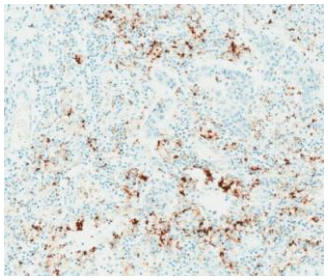
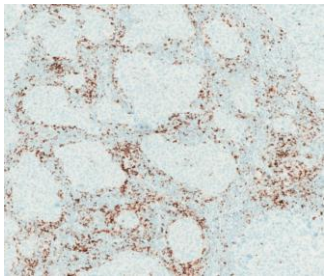


Lecture lame PD-L1

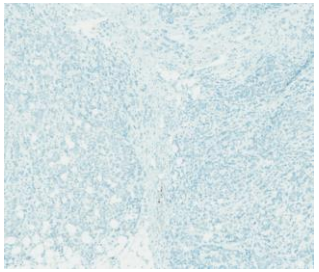
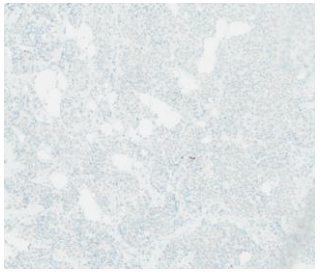
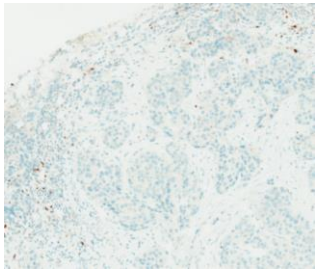
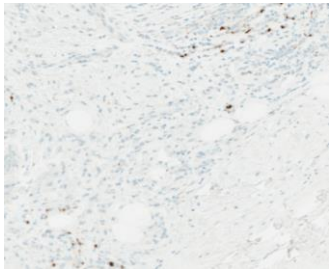
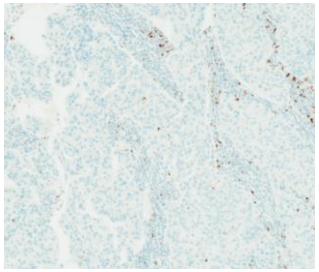
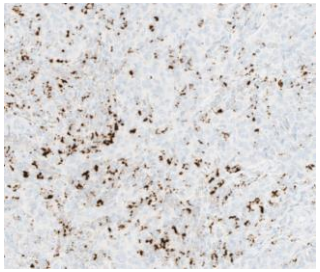
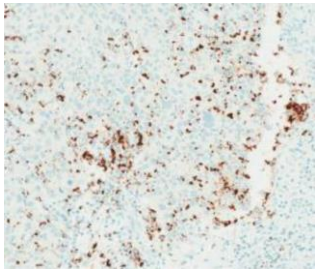
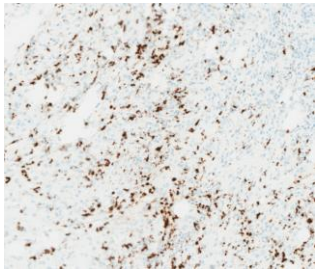
- Evaluer les cellules immunitaires (macrophages, lymphocytes, cellules dendritiques et polynucléaires)
- **Cut-off de positivité ≥1% de la surface tumorale occupée par IC PD-L1+**
- Lame de contrôle négatif utile (exclure les pigments d'hémosidérine et les marquages non spécifiques)


PD-L1 20x

Images de référence

IC Aggregates		
IC < 1%		
IC ≥ 1%		
		
		

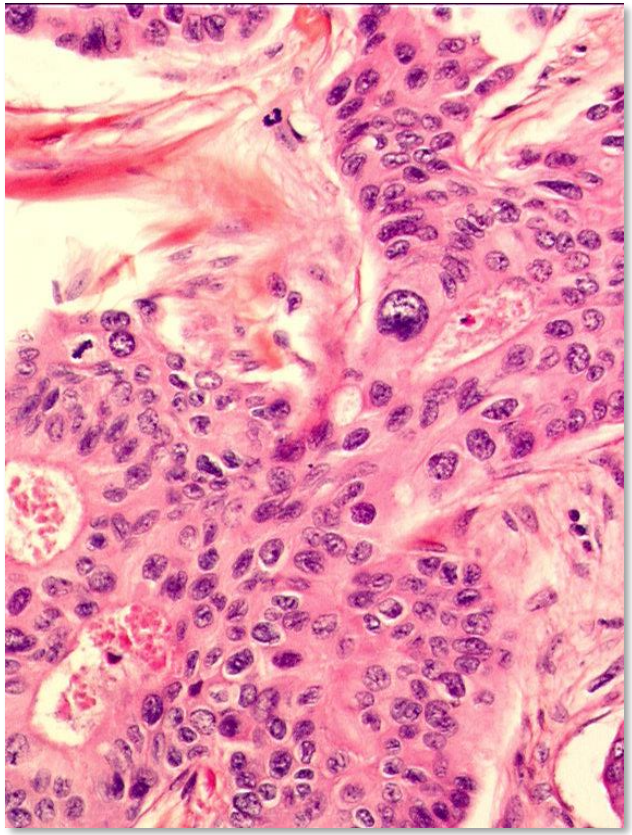
(all images 10X magnification)

IC Single-Cell Spread		
IC < 1%		
IC ≥ 1%		
		
		

(all images 10X magnification)

Cellules tumorales: nouvelles cibles thérapeutiques

- Récepteur des androgènes (IHC)
- Mutations somatiques (NGS)



Récepteur des androgènes (RA)

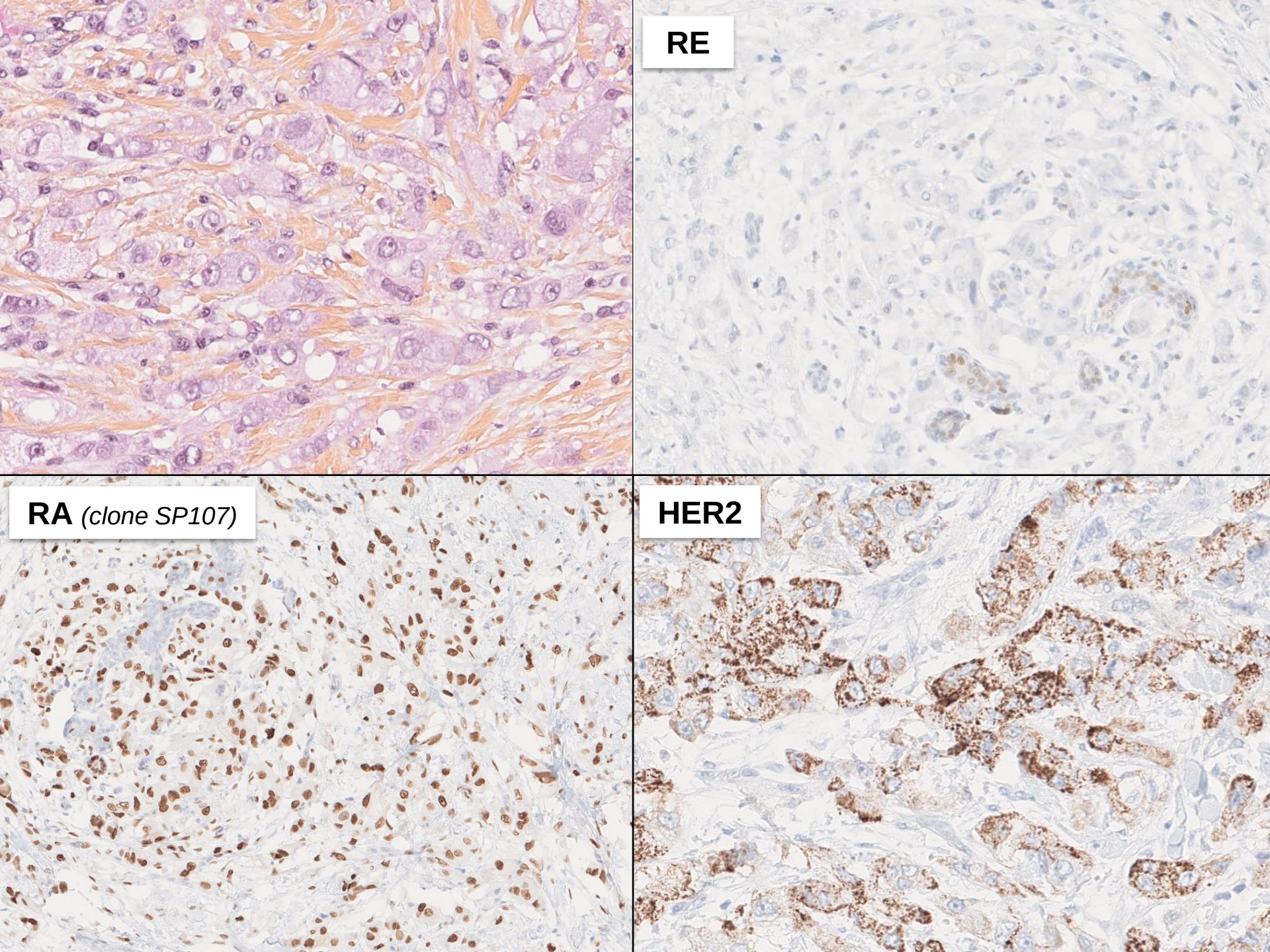
- Carcinomes infiltrants de type apocrine:
  phénotype RE- RP- RA+ HER2-/+ FOXA1+ GCDFP15+
- Mauvais pronostic *(Bonnefoi H et al. BJC 2019)*
- Biologie tumorale dépendante de la voie du RA, surexpression de *CHEK1*/chk1 dans les non répondeurs *(Grellety T et al. CCR 2019)*

  → **nouvelle(s) cible(s) thérapeutique(s)**

- Détecté par IHC dans les tumeurs triple-négatives (88% concordance avec définition moléculaire) *(Bonnefoi H et al. BJC 2019)*
- Cut-off de positivité : ≥10% (témoin interne: glandes normales)

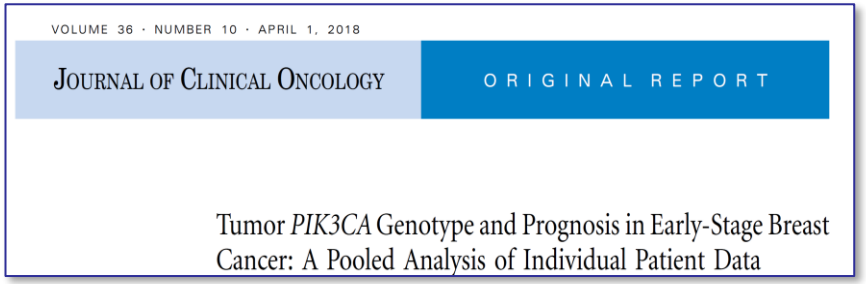
- Inhibiteurs du RA: abiratérone, darolutamide
- Essai clinique en phase métastatique :
  - AMA (UCBG 12-1): 20% de taux de bénéfice clinique à 6 mois (1 réponse complète et 5 cas stables) (*Bonnefoi H et al. Ann Oncol 2016*)
  - START (darolutamide): ouvert aux inclusions

unicancer


RE
RA (clone SP107)
HER2

Mutations de *PIK3CA*

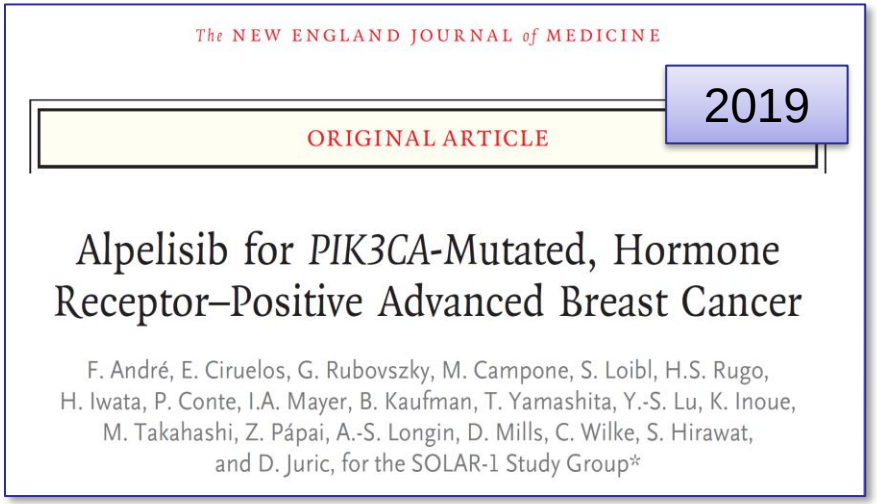
- Fréquentes (32%, n=10319), associées statut RE+, âge, bas grade, petite taille (p<0.001)
  - 18% RE-/HER2-
  - 22% HER2+
  - 37% RE+/HER2-
- Meilleur pronostic (IDFS) (up-régulation voie RE)


VOLUME 36 · NUMBER 10 · APRIL 1, 2018

JOURNAL OF CLINICAL ONCOLOGY | ORIGINAL REPORT

Tumor *PIK3CA* Genotype and Prognosis in Early-Stage Breast Cancer: A Pooled Analysis of Individual Patient Data

- Inhibiteur PI3Kα : alpelisib
- Associé fulvestrant
- n=572 RE+/HER2- traité par HT (341 *PIK3CA*^{mut})
- PFS 11mois *vs* 5.7mois dans le groupe *PIK3CA*^{mut}


The NEW ENGLAND JOURNAL of MEDICINE

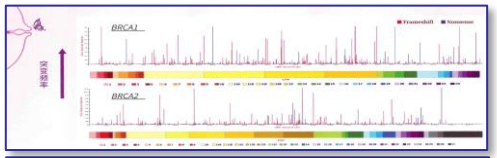
2019

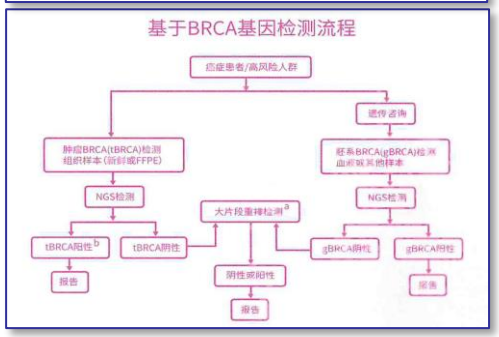
ORIGINAL ARTICLE

Alpelisib for *PIK3CA*-Mutated, Hormone Receptor–Positive Advanced Breast Cancer

F. André, E. Ciruelos, G. Rubovszky, M. Campone, S. Loibl, H.S. Rugo, H. Iwata, P. Conte, I.A. Mayer, B. Kaufman, T. Yamashita, Y.-S. Lu, K. Inoue, M. Takahashi, Z. Pápai, A.-S. Longin, D. Mills, C. Wilke, S. Hirawat, and D. Juric, for the SOLAR-1 Study Group*

➢ **AMM en cours, ATU (Protocole Utilisation Thérapeutique) alpelisib en cours**



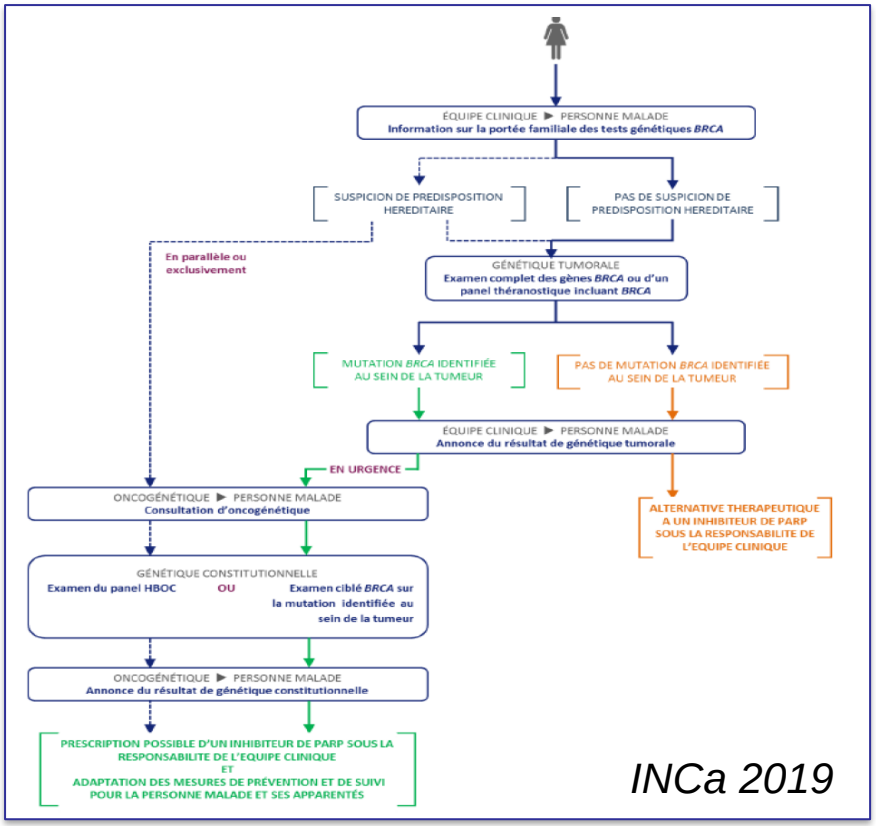


BRCA1/2 et HRD

- Défaut de réparation des cassures double-brin par recombinaison homologue (HRD)
- Inhibiteurs de PARP (réparation BER): principe de létalité synthétique

- **Olaparib**
- Étude OlympiAD
- Kc sein HER2-, gBRCA1/2^{mut}
- mPFS 7mois *vs* 4.2mois
- (Robson M et al. NEJM 2017)
- FDA en 2018

- **Talazoparib**
- Étude EMBRACA
- Kc sein HER2-, gBRCA1/2^{mut}
- PFS 8.6mois *vs* 5.6mois
- (Litton et al. NEJM 2018)
- FDA en 2018
- AMM Europe juin 2019



INCa 2019

➢ **Mutation germinale BRCA1/2 (mais screening somatique possible)**

En synthèse

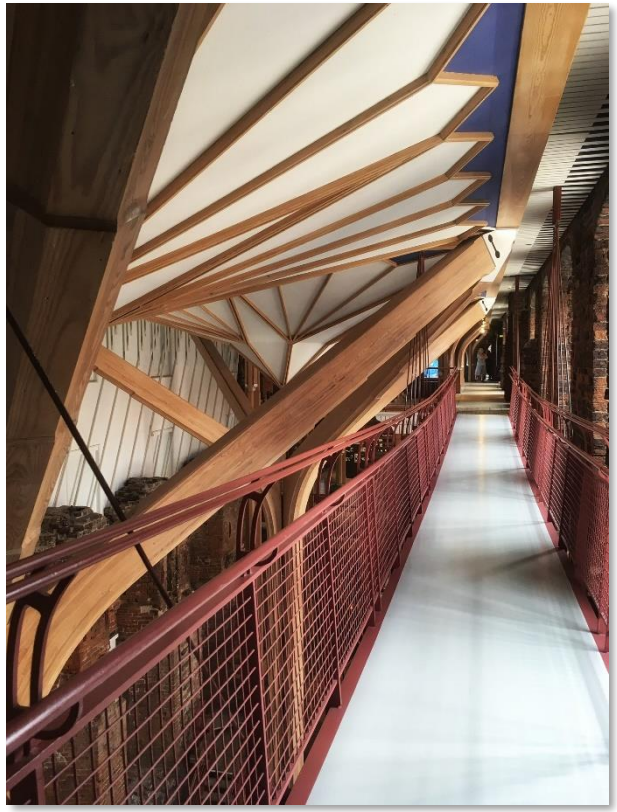
RE+/HER2-	RE-/HER2-	HER2+
TILs (?)	**TILs (pronostic)**	**TILs**
	PD-L1 (IHC, SP142)	
	RA (IHC)	
PIK3CA (tum ou ADNc) ***BRCA1/2***	***BRCA1/2***	
Perspectives		
AKT1 Panel HRD Panel cibles (*ESR1,**HER2**, FGFR, NTRK*…)	***AKT1*** Panel HRD Panel cibles (*ESR1,**HER2**, FGFR, NTRK*…)	

PROFILAGE MOLECULAIRE

- **Privilégier les biopsies de métastases (hors os+++), sinon tumeur primitive par défaut**
- **Information des patientes+++ (contexte oncogénétique éventuel)**

Merci !





Nos chemins parcourus (et à venir)…