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Breast Cancer Immunotherapy Today and Tomorrow: Sharing clinical experiences

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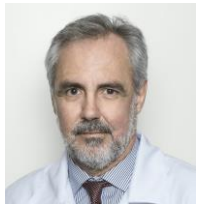
POTENTIAL CONFLICTS OF INTEREST 2019

- **Clinical Research**: AbbVie, Amgen, Astellas Pharma, AstraZeneca, Bristol-Myers Squibb, Celgene, Covance, Lilly, Medivation, Merck Serono, Merck Sharp Dohme (MSD), Novartis, Pfizer, PharmaMar, Roche/Genentech.
- **Academic Research Projects:** CPO, PUCRS, LACOG, GBECAM, INCA-Brazil.
- **Advisory Boards and Consulting**: Boehringer-Ingelheim, GSK, Novartis, Pfizer, Roche/Genentech, Eisai.
- **No financial conflicts to declare.**



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Conflict of Interest Statement

This presentation reflects my personal opinion, and not that of my employer or the sponsor of this activity. Its main objective is to stimulate independent scientific discussion and does not intend to promote a specific product or indication. The information presented may be different from the local/regional label of some of the medications. Please refer to your local label for further clarification.

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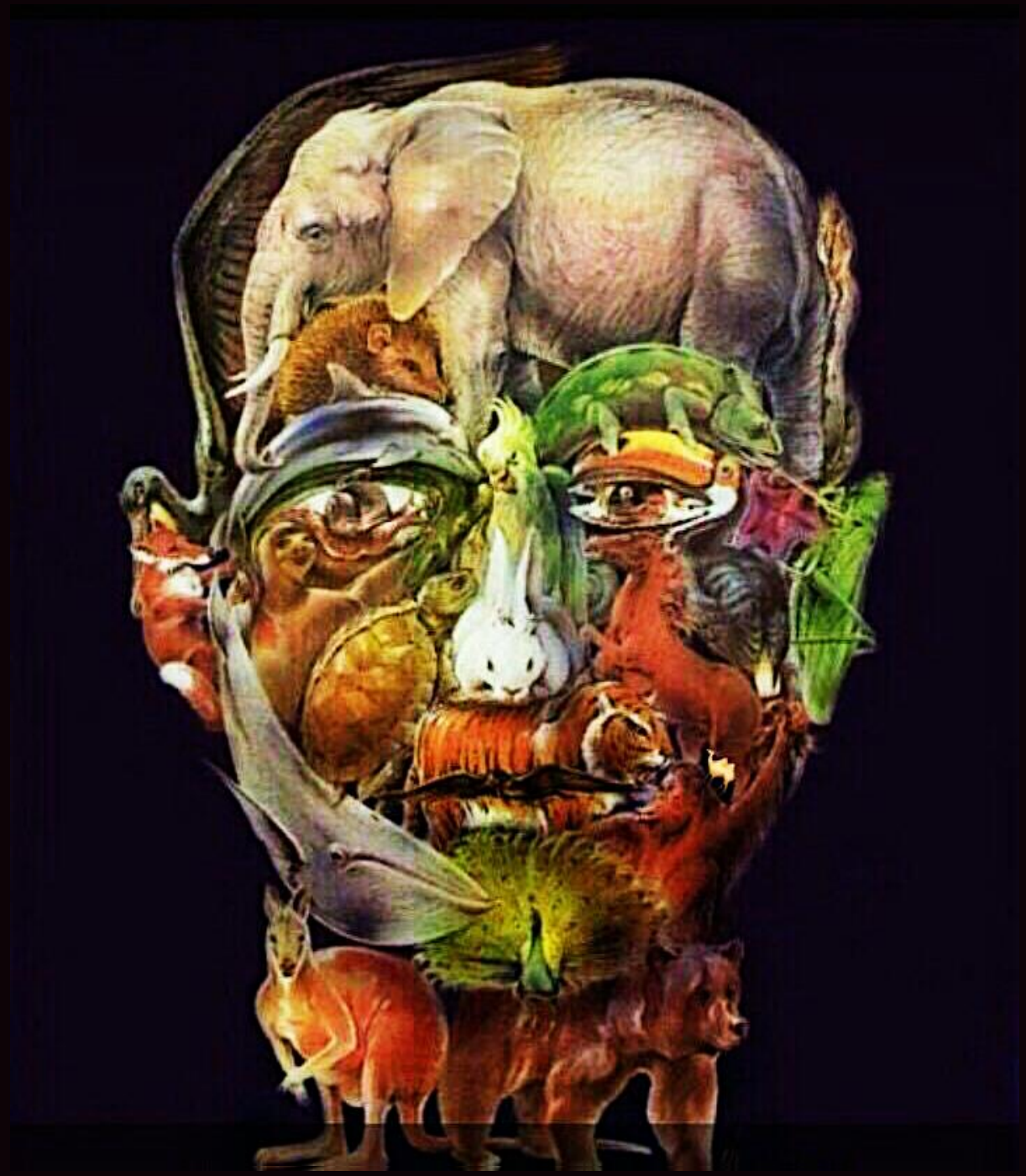
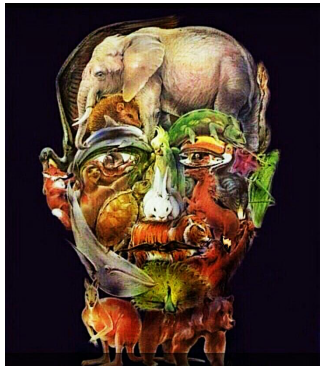
Real World Data on OS in MBC

	Year of Diagnosis					
OS (m)	2008	2009	2010	2011	2012	2013
HR+ HER2- (N=9.908)	43.7 (40.2-46.6)	42.0 (38.9-44.6)	40.9 (38.0-43.4)	42.0 (39.2-45.0)	44.5 (41.8-47.3)	40.3 (37.8-ND)
HER2+ (N=2.861)	38.6 (33.6-44.6)	42.3 (38.3-50.8)	40.1 (35.2-45.6)	42.3 (36.5-49.8)	51.1 (46.5-ND)	Not Reached
HR- HER2- (N=2.317)	15.1 (12.7-16.4)	15.1 (13.0-17.4)	14.7 (13.2-17.0)	14.0 (11.4-15.9)	13.9 (11.4-15.9)	14.1 (12.5-15.5)

Delaloge S, et al. ASCO 2017.



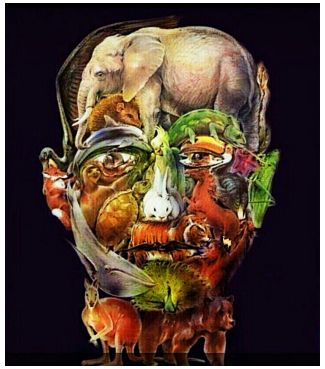
What Is TNBC?



- “Triple negative” - ER negative, PgR negative, HER2 negative
- TNBC accounts for 10% to 17% of all breast carcinomas
- Heterogeneous group of diseases, in general, with significantly more aggressive behavior than other molecular subtypes
- Majority are Grade 3 tumors
- Histologically, most frequently high-grade invasive ductal carcinomas of no special type

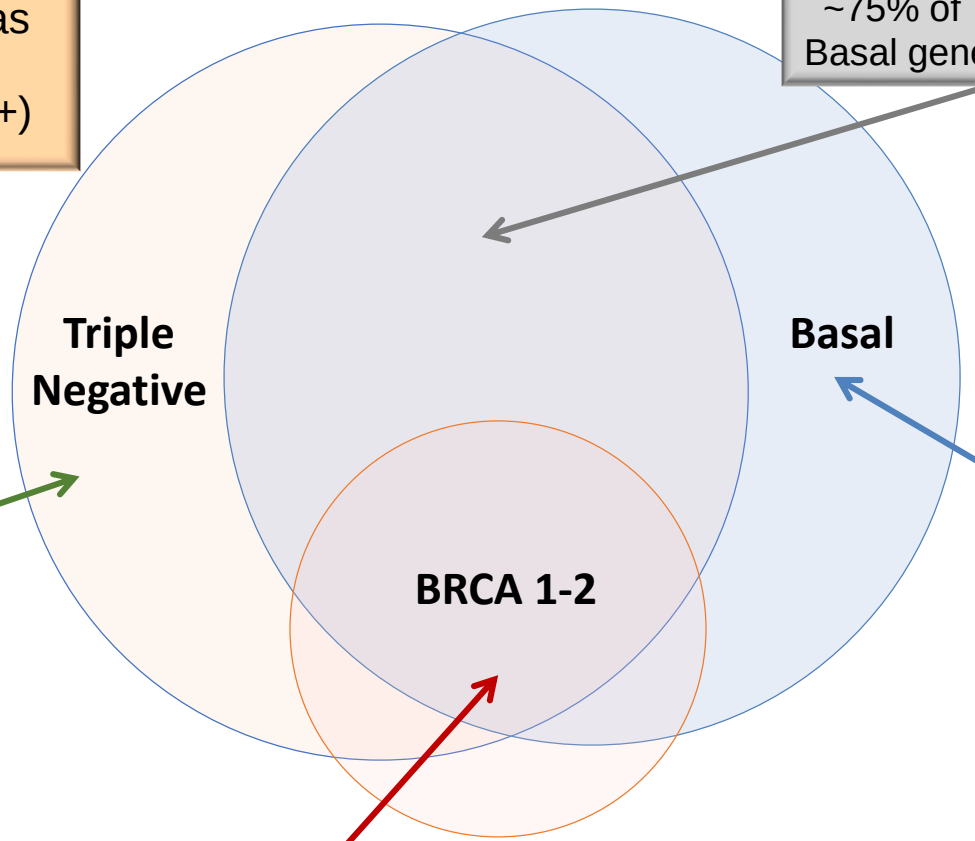
Boyle P. Ann Oncol. 2012;23(suppl 6):vi7-vi12.
Anders CK, et al. Clin Breast Cancer. 2009;9(suppl 2):S73-S81.

Triple-Negative vs. Basal-Like: Definitions



- ER- / PR- / HER2-
- ~15% of all breast carcinomas
- Poorly differentiated
- Express CK 5/6, 17, EGFR (+)

~75% of TNBC have Basal gene expression



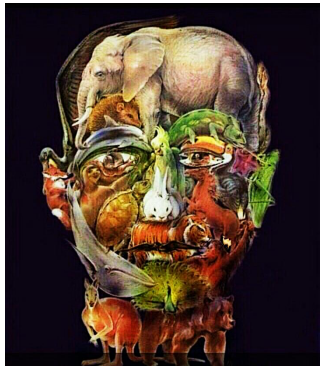
- **Triple negative** but not basal
- Definition by IHC
- Includes other histologies (medullar, adenoid cystic)
- 10-30% can also include "claudin-low," a subtype notable for high expression of stem cell markers
- 90% of TNBC do not have BRCA mutations

- **Basal** but not triple negative
- Definition by gene expression
- Includes some if not most of BRCA1 mutated tumors
- 15-40% are ER+, PR+ or HER2+

- BRCA1-2 mutated tumors
- ~5% of Breast Cancer
- 50% BRCA-1 carriers are basal-like

Pal & Mortimer. Maturitas 2009;
Gluz et al. Ann Oncol 2009;
Ander & Carey. Oncology 2008.
Young et al. BMC Cancer 2009
Schneider, B. P. et al. Clin Cancer Res 2008;14:8010-8018

Proposed Clinically Relevant TNBC Subgroups



Germline *BRCA1/2* and HR pathway gene mutation testing

(Somatic *BRCA* mutation testing)

(HRD score, HRD scar biomarkers)

Histologic examination f tumor-infiltrat lymphocytes (

(Immune signat by gene expres microarray)

Carbop Cispla Oxalip Olaparib Talazoparib

Atezolizumab Pertuzuma Avelumab Nivolumab

Enzalutamide

Anthracyclines Taxanes Vinorelbine Eribulin Others

ertib nserti

Sacituzumab Govitecan Other ADC

Tested negative

Defective DNA repair:	Inflamed phenotype:	Androgen receptor–positive:	*PI3K/AKT/PTEN* altered:	Unique antigen-expressing:	Unclassified TNBCs:
platinums and PARP inhibitors	immunotherapy	androgen blockade	AKT inhibitors	antibody-drug conjugates	chemotherapy and clinical trials

Chan JJ, et al. *J Oncol Pract.* 2018;14(5):281-289.

IMpassion130 study design

- Histologically documented[b] metastatic or inoperable locally advanced TNBC
- No prior therapy for advanced TNBC[c]
- Evaluable sample for PD-L1 testing
- ECOG PS 0-1

Stratification factors:

- Prior taxane use (y vs n)
- Liver metastases (y vs n)
- PD-L1 status on IC (positive [≥1%] vs negative [<1%])[d]

R

A - nabPx arm:
Atezolizumab
840 mg IV (days 1 and 15)[f]
+ *Nab*-paclitaxel
100 mg/m^2 IV (days 1, 8 and 15)

Double-blind; no crossover permitted

P - nabPx arm:
Placebo
IV (days 1 and 15)
+ *Nab*-paclitaxel
100 mg/m^2 IV (days 1, 8 and 15)

RECIST v1.1
PD or toxicity

Key study endpoints

- Co-primary: PFS (ITT and PD-L1 IC+)
  OS (ITT and PD-L1 IC+)
- Secondary: ORR and DOR
- Safety and tolerability

[a] ClinicalTrials.gov: NCT02425891. [b] Per ASCO-CAP guidelines (local). [c] Neoadjuvant treatment allowed if treatment-free interval ≥ 1 year.
[d] Per VENTANA SP142 immunohistochemistry assay. [e] Radiologic endpoints were Investigator assessed (per RECIST v1.1). [f] Cycle: 28 d.

Schmid P, et al. IMpassion130. ESMO 2018 (abs LBATBC).
Emens LA, et al. IMpassion130 biomarkers. SABCS 2018 (program #GS1-04).
Schmid P, et al. NEJM, October 20, 2018. DOI: 10.1056/NEJMoa1809615.

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- Speaker for Roche/Ventana in scientific meetings
- No financial conflicts to declare.
- The concepts issued are the speaker responsibility and do not necessarily reflect the opinion of Roche.

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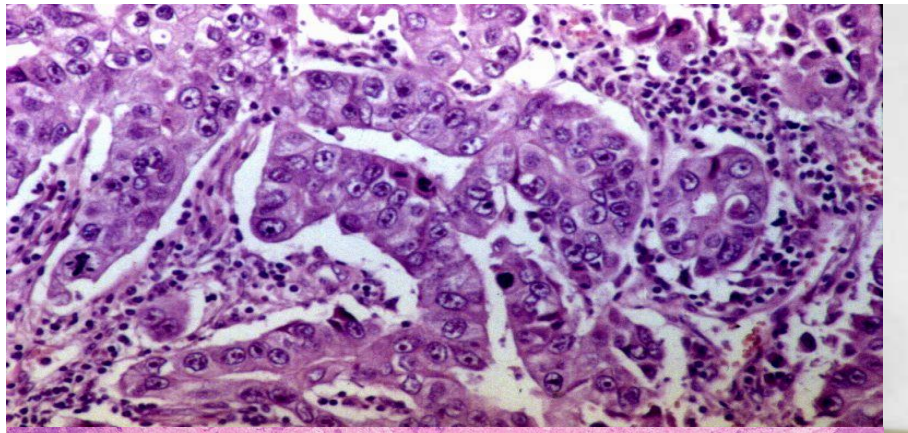
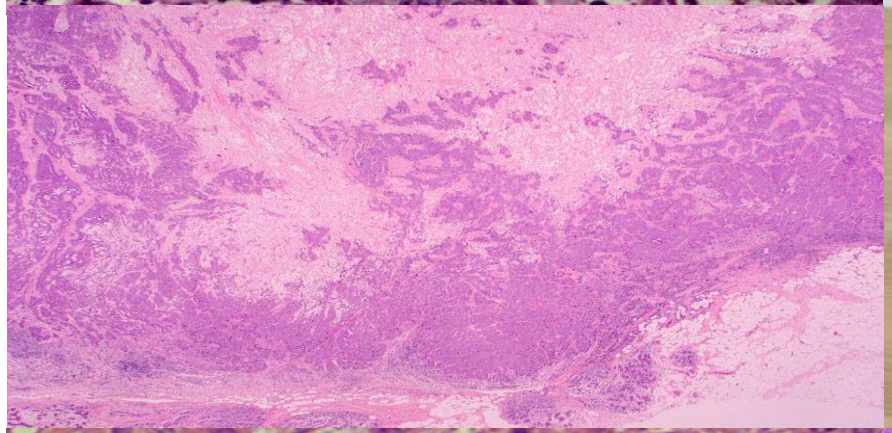
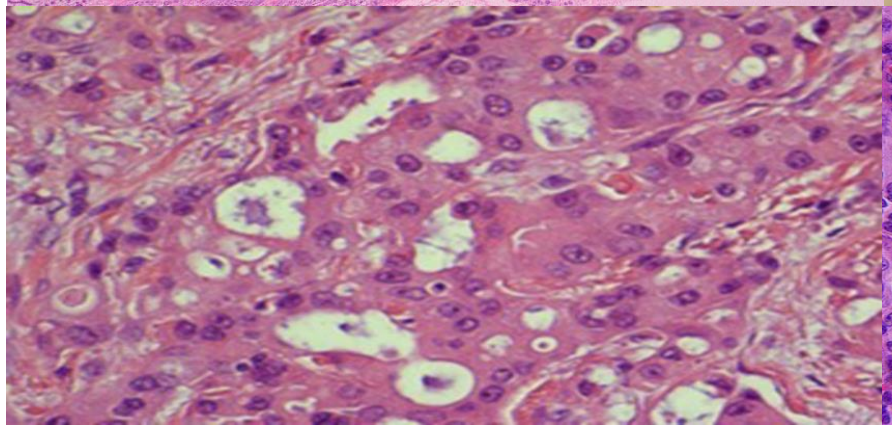
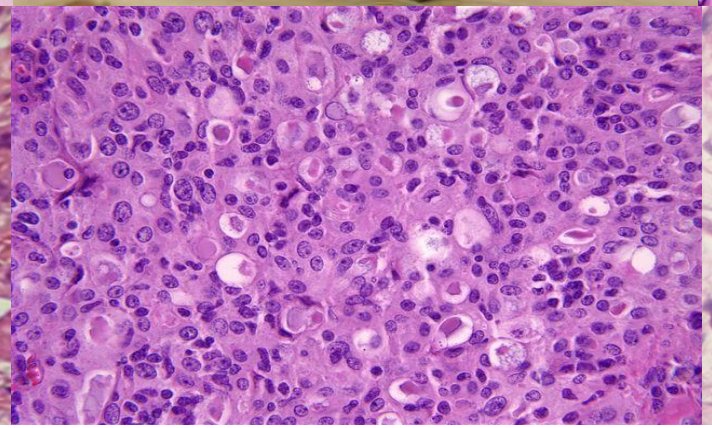
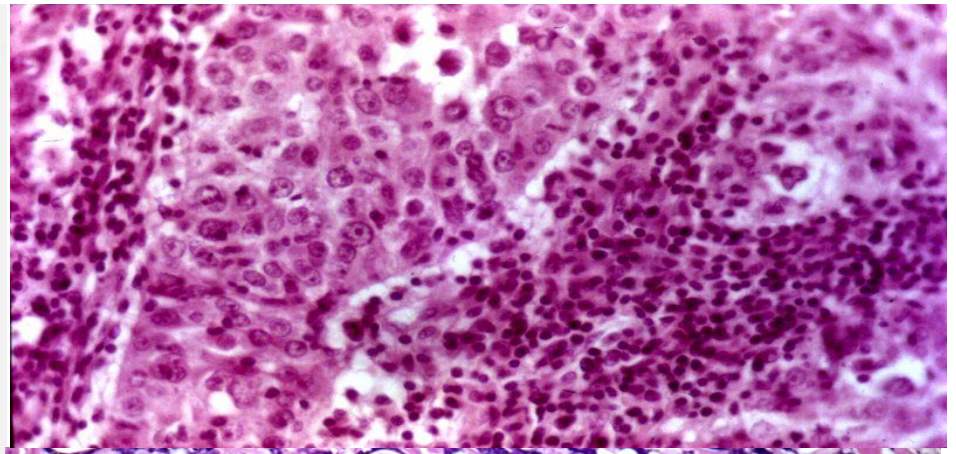
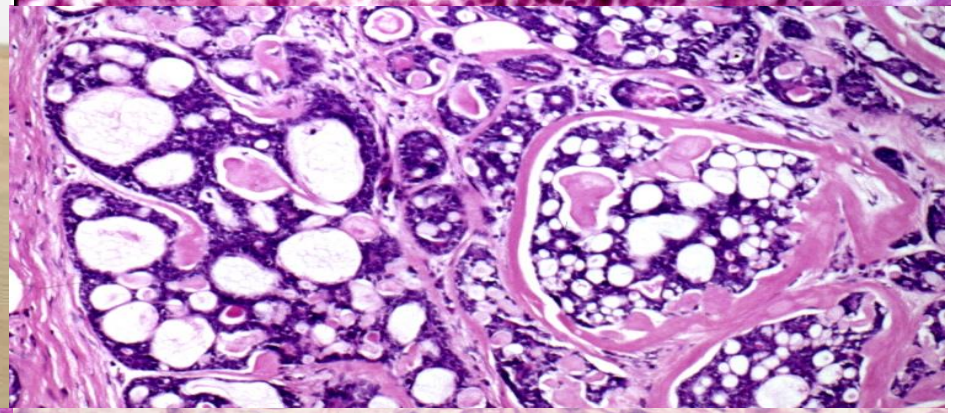
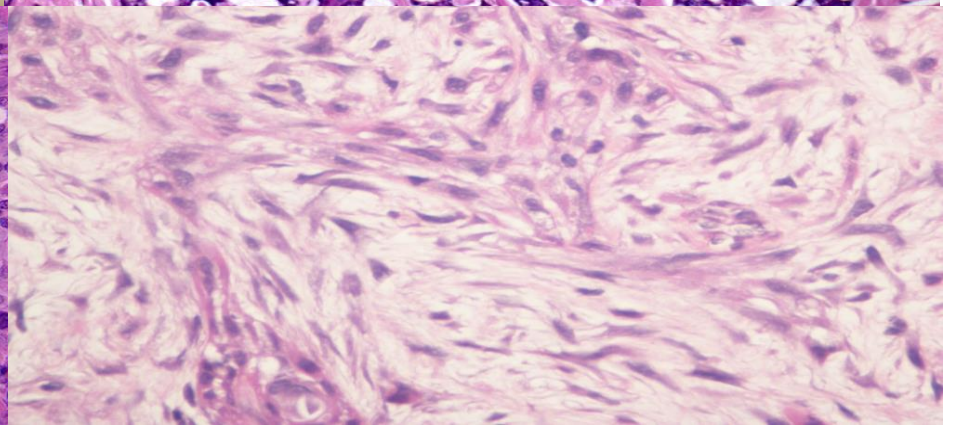
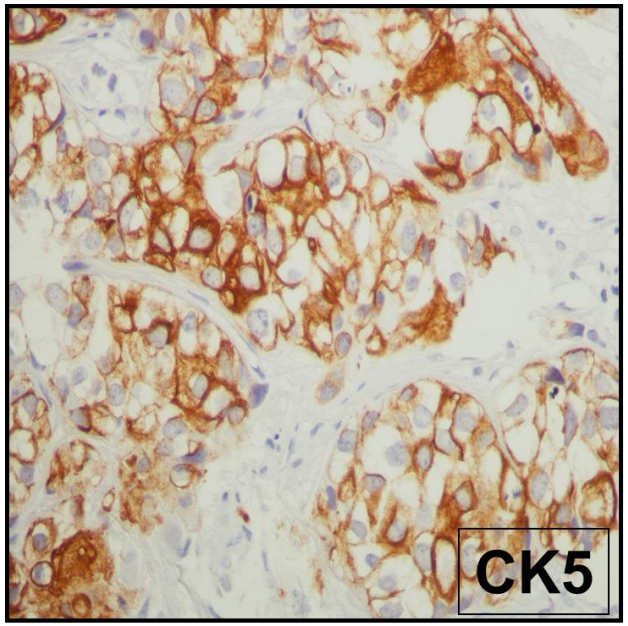
Morphological Heterogeneity of TNBC

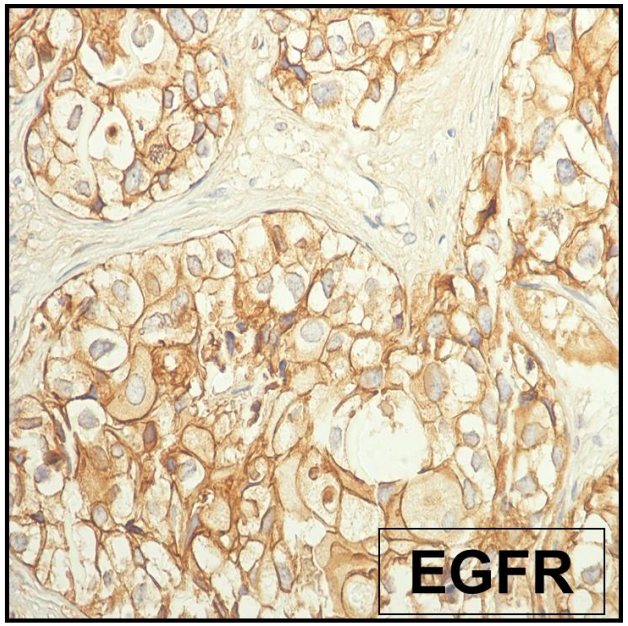




Basal-like Breast Cancer (BLBC)

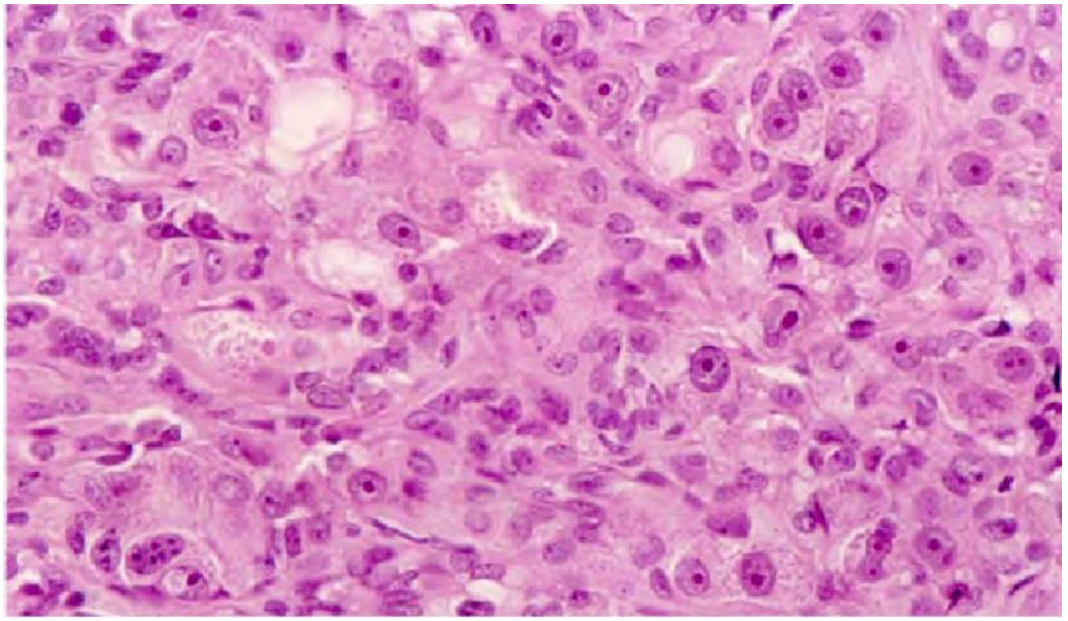
- Among TNBC: 15% are basal-like. Around 70-85% of BLBC are triple negative.
- BLBC are also a heterogeneous group based on morphology and biological behavior and includes: IBC-NST, medullary, metaplastic, secretory and adenoid cystic.
- Basal-like breast cancers are defined by IHC based on expression of HMW-CK (CK5, CK5/6, CK14) and/or EGFR
- When testing TNBC for basal markers ? Clinical indication for better categorization

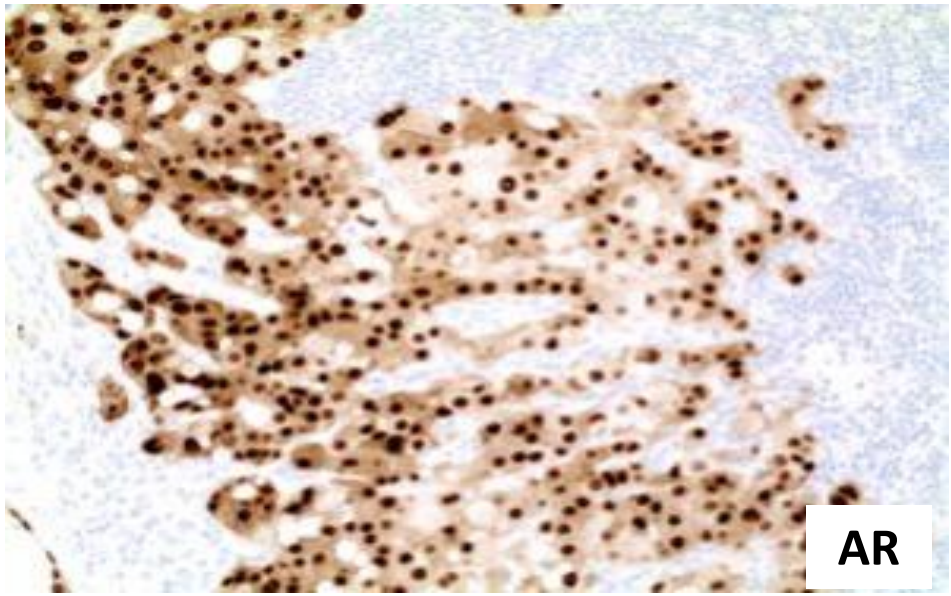




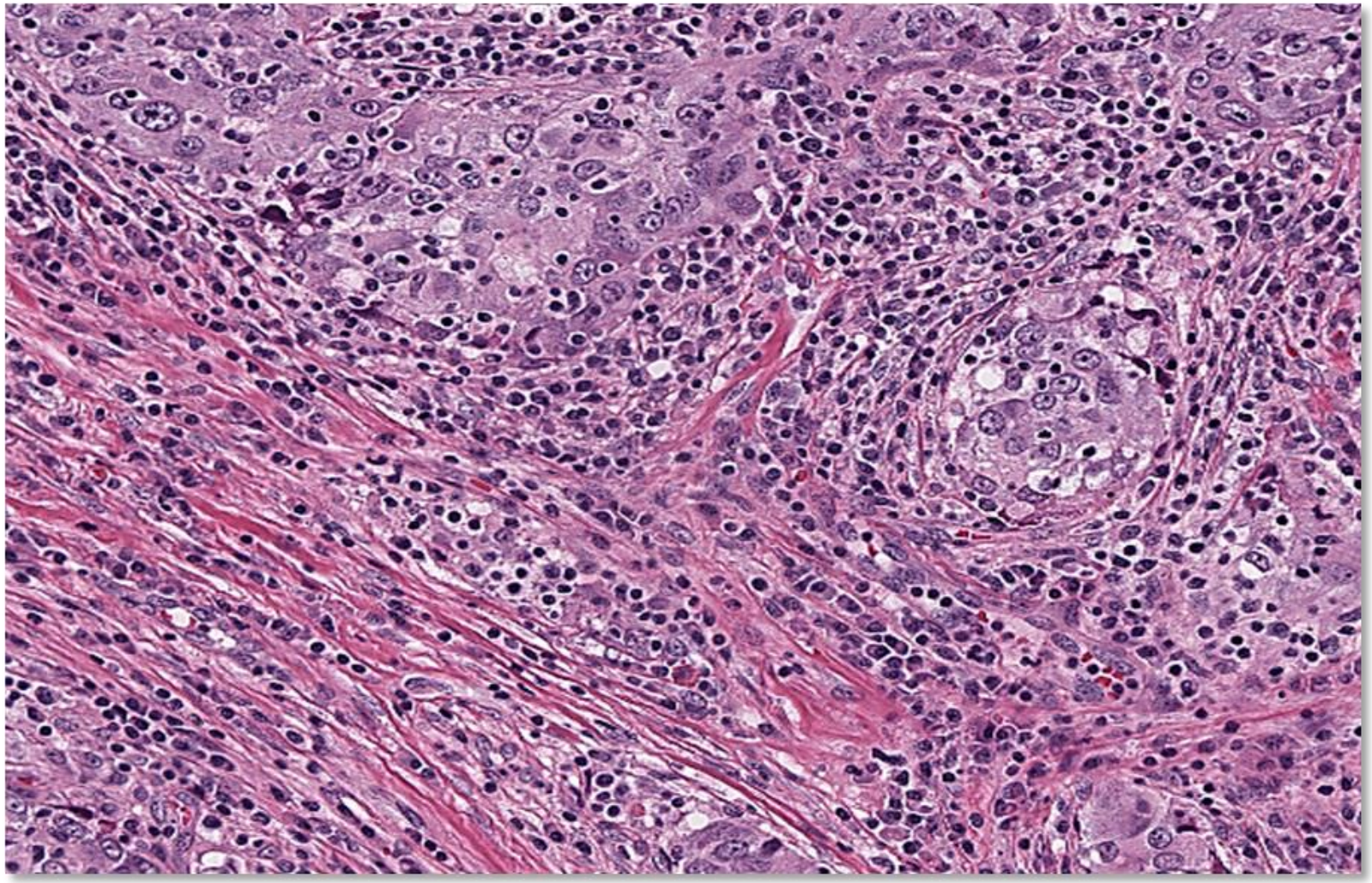
Apocrine Breast Cancer and Androgen Receptor Testing

- Apocrine cancers are frequently triple negative, but majority are positive for androgen receptor (AR).
- AR stimulates cellular proliferation in TNBC and treatment with AR antagonists reduces the tumor growth.
- But there is no consensus about routine testing of apocrine cancers for AR





TNBC are well known to be associated with inflammatory infiltrate



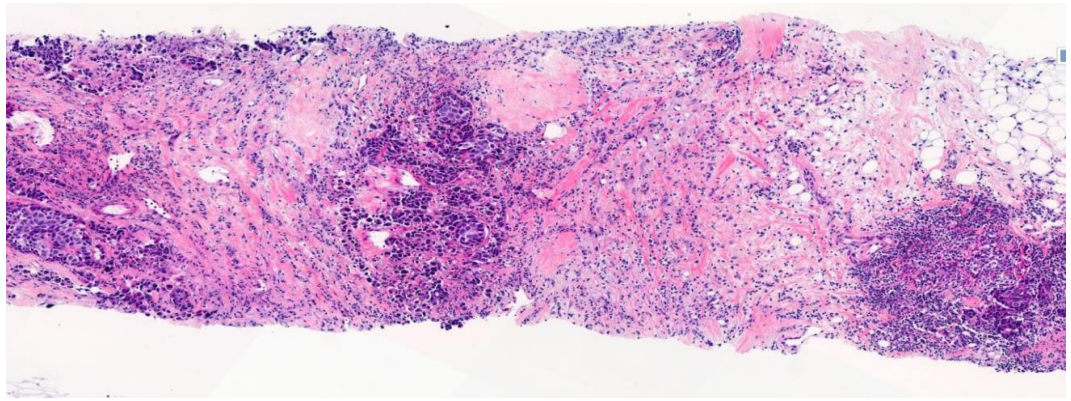
When testing TNBC for PDL1?

- Local advanced and metastatic TNBC are elegible for imunotherapy
- Although there is already FDA and ANVISA approval for immunotherapy, there is still no indication for routine evaluation of PD-L1 in TNBC
- Pathologists are still awaiting oncologist´s request for PD-L1 testing in TNBC

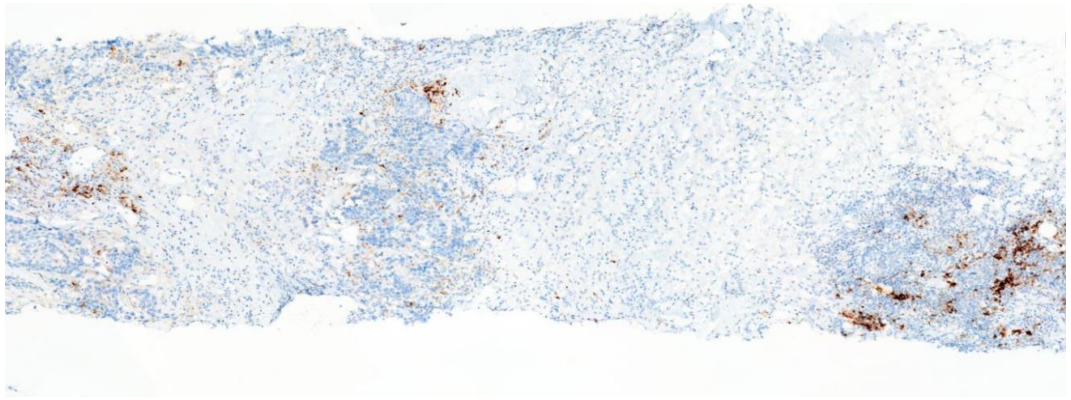
PD-L1 expression in metastatic TNBC

In the IMpassion130 study ~40% of cases were positive for PD-L1 in immune cells (≥1%)

H&E



VENTANA SP142 PD-L1 positive staining



1, Schmid, I. New England Journal of Medicine 379,22 (2018): 2108-2121

Commercially Available Assays for Evaluation of PD-L1 by IHC

Ensaio (clone de anticorpo)	Ensaio VENTANA PD-L1 IHC (SP142) [1,2]	Ensaio VENTANA PD-L1 IHC (SP263) [3]	Agilent/Dako PD-L1 IHC (22C3) pharmDx[4,5]	Agilent/Dako PD-L1 IHC (28-8) pharmDx[6]
Droga Anti-PD-1/PD-L1	TECENTRIQ (atezolizumabe) – R/G	IMFINZI (durvalumabe) – AZ	KEYTRUDA (pembrolizumabe) – MSD	OPDIVO (nivolumabe) – BMS
Fabricante e plataforma Dx	VENTANA BenchMark ULTRA	VENTANA BenchMark ULTRA	Dako Link 48 Autostainer	Dako Link 48 Autostainer
Origem	Monoclonal de coelho vs C-terminus	Monoclonal de coelho vs C-terminus	Monoclonal de camundongo vs N-terminus	Monoclonal de coelho vs N-terminus
Tipo de células do algoritmo de classificação e valores de corte	▪ CPNPC: TC1/2/3 (≥1%, ≥10%, ≥50% ou IC1/2/3 (≥1%, ≥5%, ≥10%) ▪ mUC: IC1/2/3 (≥1%, ≥5%, ≥10%)	▪ CPNPC: TC ≥25% ▪ mUC: TC ou IC ≥25%	▪ CPNPC: TC ≥1%, ≥5% e ≥10% ▪ mUC: TC ≥1%, ≥5%	TC <1% TC ≥1% TC ≥5% TC ≥10%

1, Fehrenbacher, et al. Lancet 2016; 2, Rosenberg, et al. Lancet 2016; 3, VENTANA PD-L1 (SP263) interpretation guide; 4, Herbst, et al. Lancet 2016; 5, Balar, et al. ESMO 2016 (Abstract LBA32_PR); 6, Borghaei, et al. N Engl J Med 2015

OBS: Os resultados de IMpassion130 não estão validados em nenhum outro ensaio, a não ser no ensaio VENTANA SP142

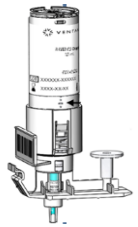
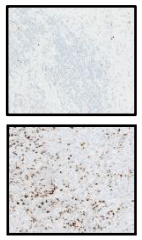
Accepted Specimens

- Formalin fixed paraffin embeded tissues
- Fresh or archived samples from resections, excisional and needle biopsies
- Metastatic or primary tumors
- Adequacy: at least 50 viable tumor cells in the sample

- *** It is necessary to have tumor associated stroma in other to evaluate the sample for PD-L1 in immune cells**

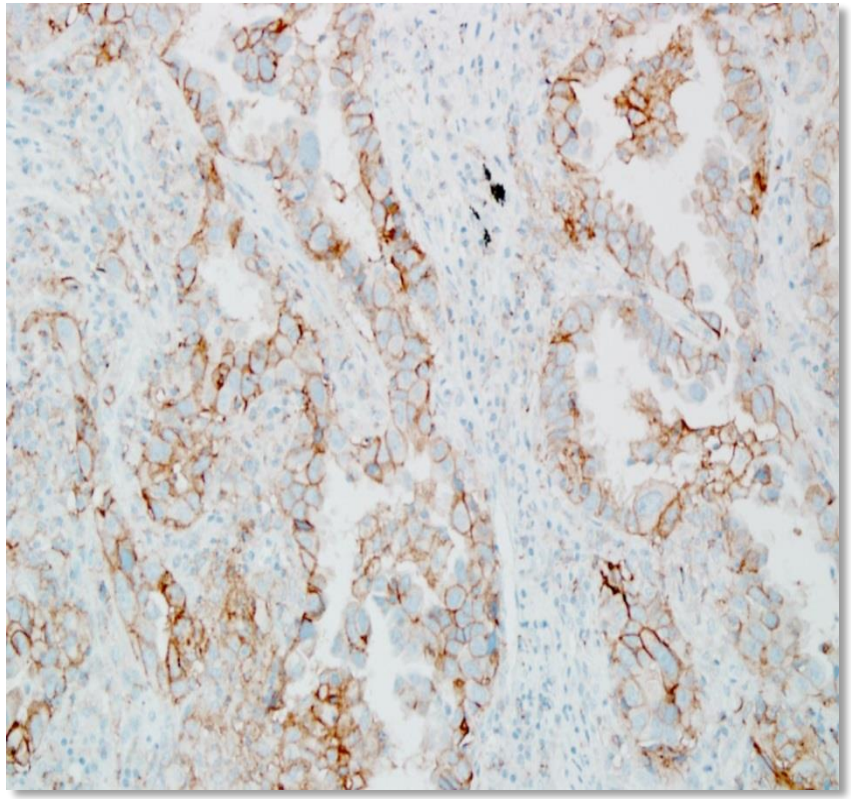
VENTANA PD-L1 (SP142) Assay

Assay consisting of: antibody SP142, detection kit, classification method, internal control from the system, all instrumetns necessary to perform the test., FDA aproved.

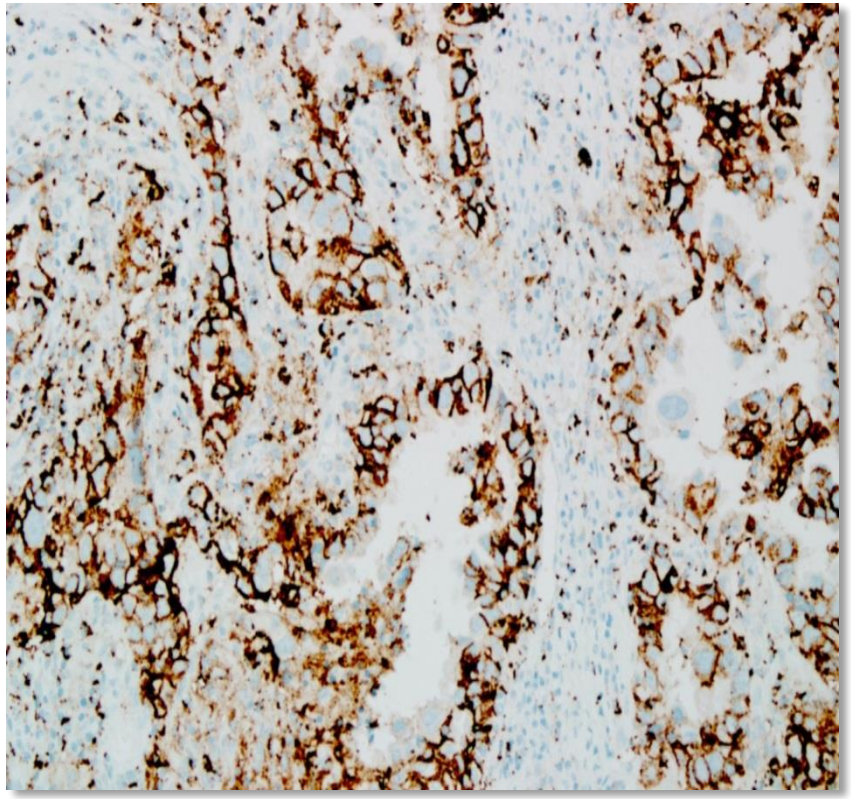
Reagent Kit		▪ It supplies 50 tests of SP142 clone of rabbit anti-PD-L1 monoclonal antibody ▪ Detection system ptiView DAB with amplication step ▪ Specification sheet
Staining Platform		▪ BenchMark ULTRA instrument ▪ System Controls (slides/tissues) ▪ Staining protocol BenchMark
Reproducible Results	 IC<1% IC≥1%	▪ Types of cells: immune cells infiltrating tumor (IC) and tumor cells (TC) ▪ Classification system/ Interpretation guide manual ▪ Pathologist's Instruction Materials

Source: Roche/Ventana

Ventana PD-L1 (SP142) Assay: Amplification Effect



Without Amplification

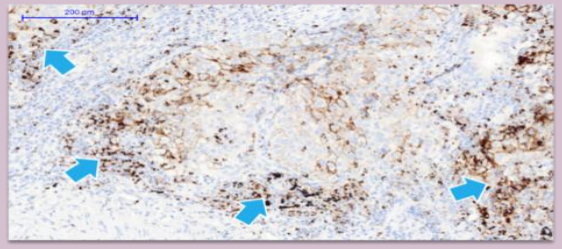


With Amplification

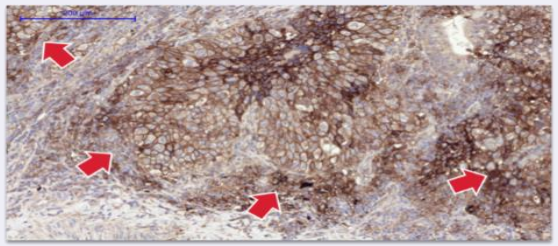
Pathologists Need Specific Training to Evaluate PD-L1 in TNBC

SP142 assay was developed to offer better visual contrast in other to better classify PD-L1 expression in immune cells

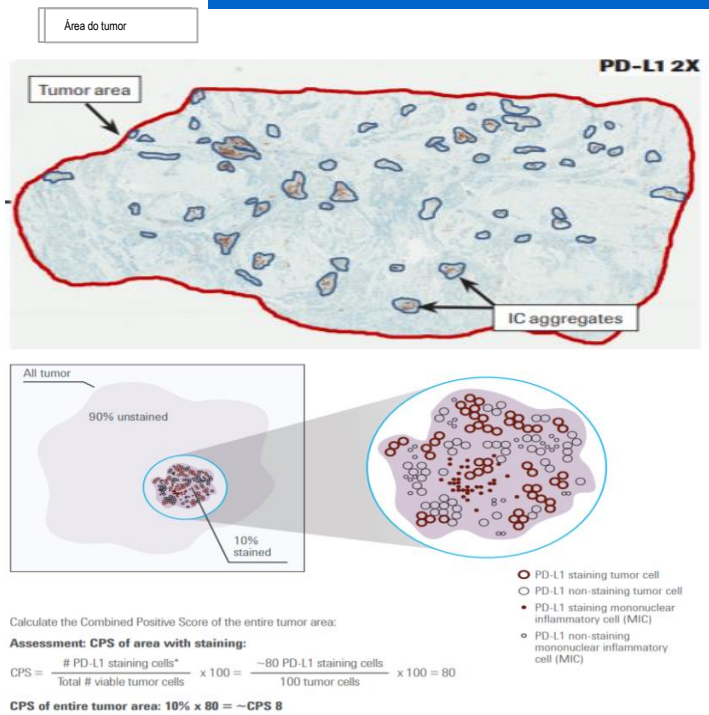
SP142



22c3



PD-L1 testing is indicated to select patients for treatment with atezolizumabe + nab-paclitaxel



Tumors are classified as positive when the area occupied by immune cells expressing **PD-L1 is ≥ 1%**

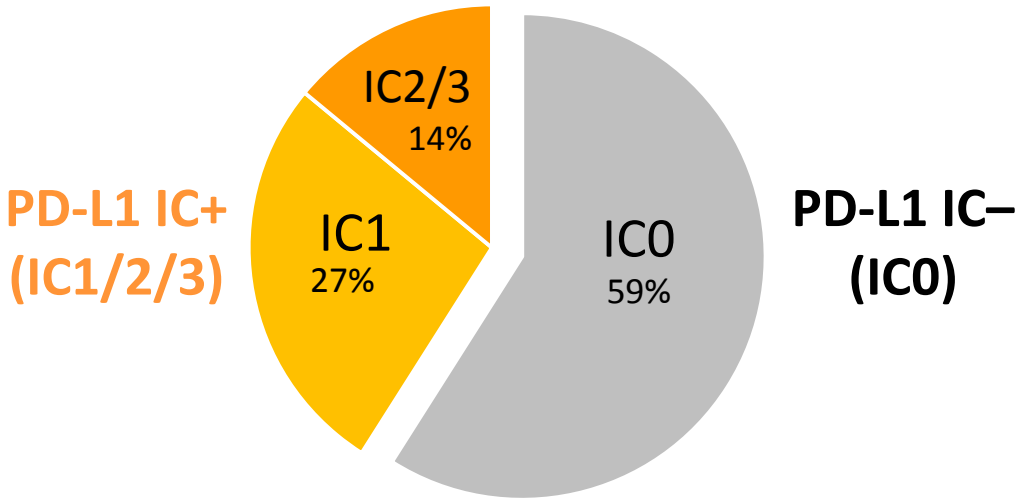
PD-L1 Classification Algorithm for TNBC using Ventana Assay (SP142)

Criteria/ Staining Characteristics	PD-L1 Expression
Staining for PD-L1 absent or completely negative OR Presense of PD-L1 staining with variable intensity in immune cells of intra and peritumoral stroma in < 1% of total tumor area	< 1% IC
Presence of positive staining for PD-L1 with variable intensity in immune cells of intra and peritumoral stroma in ≥1% of total tumor area	≥ 1% IC

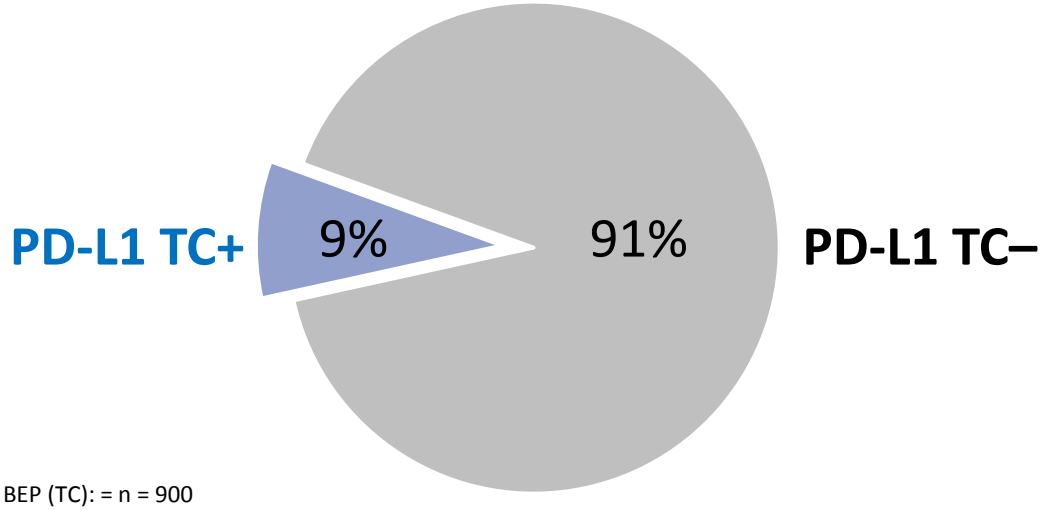
Only staining of immune cells is counted as part of the algorithm for PD-L1 in TNBC

In IMpassion130, PD-L1 in TNBC is expressed mainly on tumour-infiltrating immune cells

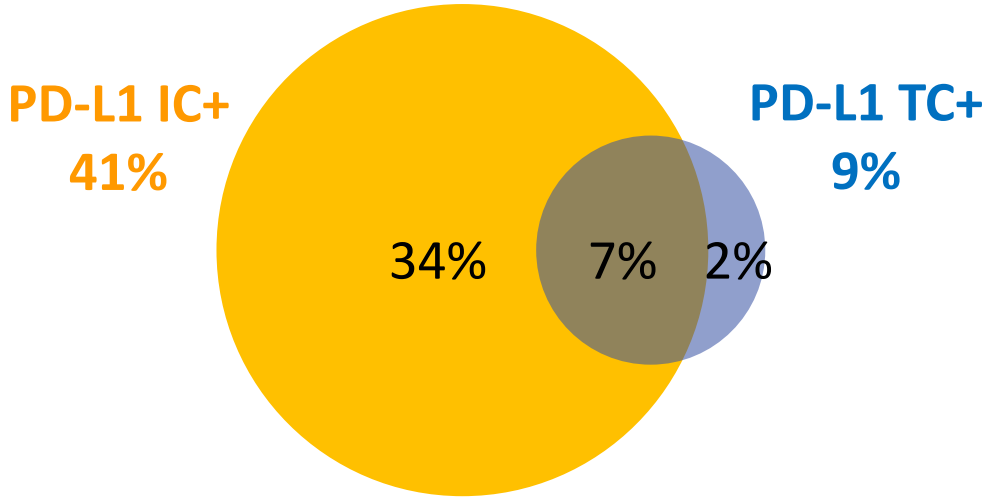
Prevalence of PD-L1 IC subgroups



Prevalence of PD-L1 TC subgroups



- **The majority of patients who express PD-L1 on TC are captured within the PD-L1 IC+ population**



BEP (TC): = n = 900
PD-L1 scoring: IC0: < 1%; IC1: ≥ 1% and < 5%; IC2: ≥ 5% and < 10%; IC3: ≥ 10%; TC–: < 1% PD-L1 on tumor cells; TC+: ≥ 1% PD-L1 on tumor cells.

Schmid P, et al. IMpassion130. ESMO 2018 (abs LBATBC).
Emens LA, et al. IMpassion130 biomarkers. SABCS 2018 (program #GS1-04).
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POTENTIAL CONFLICTS OF INTEREST 2019

- **Clinical Research**: AbbVie, Amgen, AstraZeneca, Lilly, Medivation, Merck Sharp Dohme (MSD), Novartis, Pierre Fabre, Pfizer, Roche/Genentech.
- **Advisory Boards and Consulting**: Novartis, Pierre Fabre, Pfizer, Roche/Genentech.
- **No financial conflicts to declare.**

- The concepts issued are the speaker responsibility and do not necessarily reflect the opinion of Roche.

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IMPASSION130 PATIENT POPULATION

Baseline characteristics (ITT population)

Characteristic	A- nabPx (n = 451)	P- nabPx (n = 451)
Median age (range)	55 y (20-82)	56 y (26–86)
Female sex	448 (99%)	450 (100%)
Race[a]		
White | Asian	308 (68%) | 85 (19%)	301 (67%) | 76 (17%)
Black or African American	26 (6%)	33 (7%)
Other or multiple	20 (4%)	26 (6%)
ECOG PS[b,c]		
0 | 1	256 (57%) | 193 (43%)	270 (60%) | 179 (40%)
Metastatic disease	404 (90%)	408 (91%)
Number of sites[d]		
0–3	332 (74%)	341 (76%)
≥4	118 (26%)	108 (24%)
Site of metastatic disease		
Lung | Bone	226 (50%) | 145 (32%)	242 (54%) | 141 (31%)
Liver | Brain	126 (28%) | 30 (7%)	118 (26%) | 31 (7%)
Lymph node only[d]	33 (7%)	23 (5%)
Prior neoadjuvant or adjuvant treatment	284 (63%)	286 (63%)
Prior taxane | anthracycline use	231 (51%) | 243 (54%)	230 (51%) | 242 (54%)

- **Characteristics were generally well balanced between arms**
- The PD-L1 population was representative of the ITT population

Data cut off: April 17, 2018. [a] Race was unknown in 12 patients in the A-nabPx arm and 15 in the P-nabPx arm. [b] n = 450 in each arm. [c] ECOG PS before start of treatment was 2 in 1 patient per arm. [d] n = 450 in A arm and 449 in P arm.

Schmid P, et al. IMpassion130. ESMO 2018 (abs LBATBC).
Emens LA, et al. IMpassion130 biomarkers. SABCS 2018 (program #GS1-04).
Schmid P, et al. NEJM, October 20, 2018. DOI: 10.1056/NEJMoa1809615.

IMpassion130 INCLUSION CRITERIA

- Histologically documented[b] metastatic or inoperable locally advanced TNBC
- No prior therapy for advanced TNBC[c]
- Evaluable sample for PD-L1 testing
- ECOG PS 0-1

Stratification factors:

- Prior taxane use (y vs n)
- Liver metastases (y vs n)
- PD-L1 status on IC (positive [≥1%] vs negative [<1%])[d]

[a] ClinicalTrials.gov: NCT02425891. [b] Per ASCO-CAP guidelines (local). [c] Neoadjuvant treatment allowed if treatment-free interval ≥ 1 year.
[d] Per VENTANA SP142 immunohistochemistry assay. [e] Radiologic endpoints were Investigator assessed (per RECIST v1.1). [f] Cycle: 28 d.

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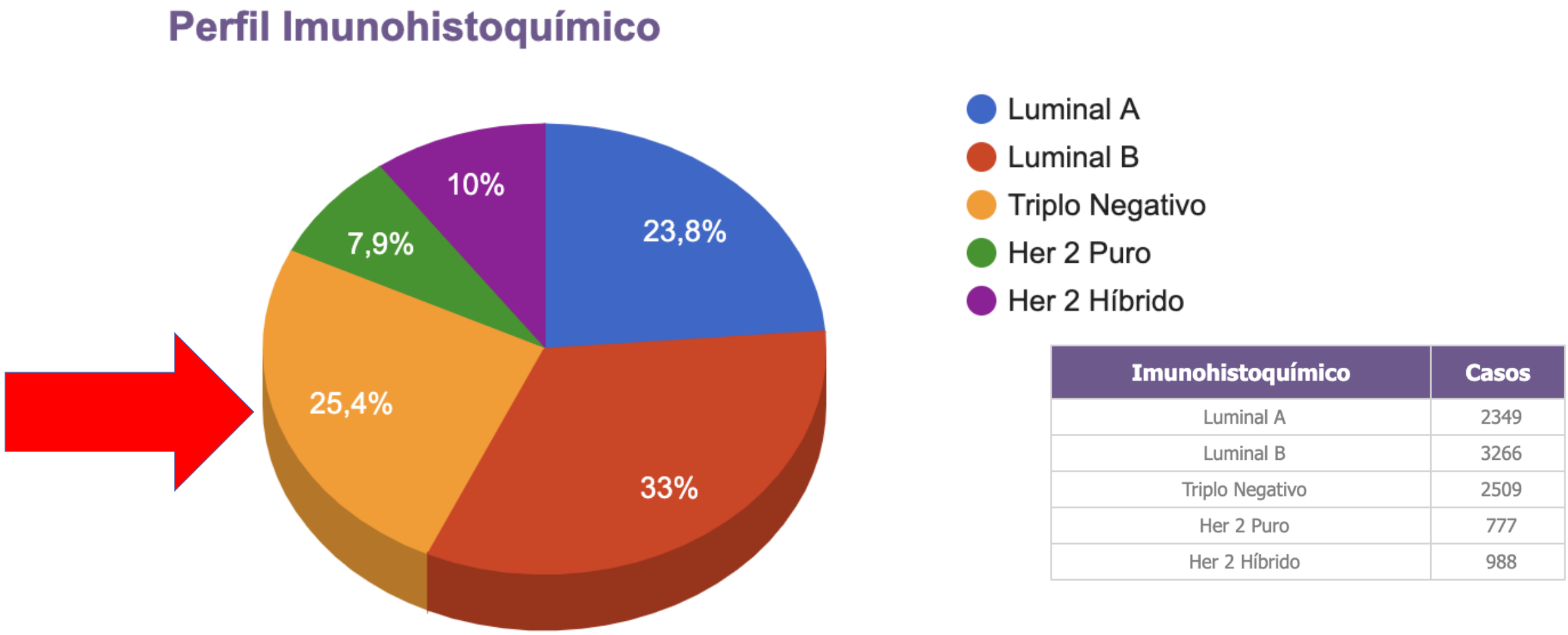
PEROLA BYIGTON HOSPITAL 2011-2018



Imunohistoquímico	Casos
Luminal A	2349
Luminal B	3266
Triplo Negativo	2509
Her 2 Puro	777
Her 2 Híbrido	988

N=9.889

SCREENING

- **HPB focused in Breast and Gynecological Cancer (SUS)**
  - **~ 1,000 new cases of Breast Cancer per year**

- **Patients are willing to accept**
  - **No better option available**
  - **Experience in Clinical Trials**

PERFORMANCE

22 enrolled

- 4 Screen Falures

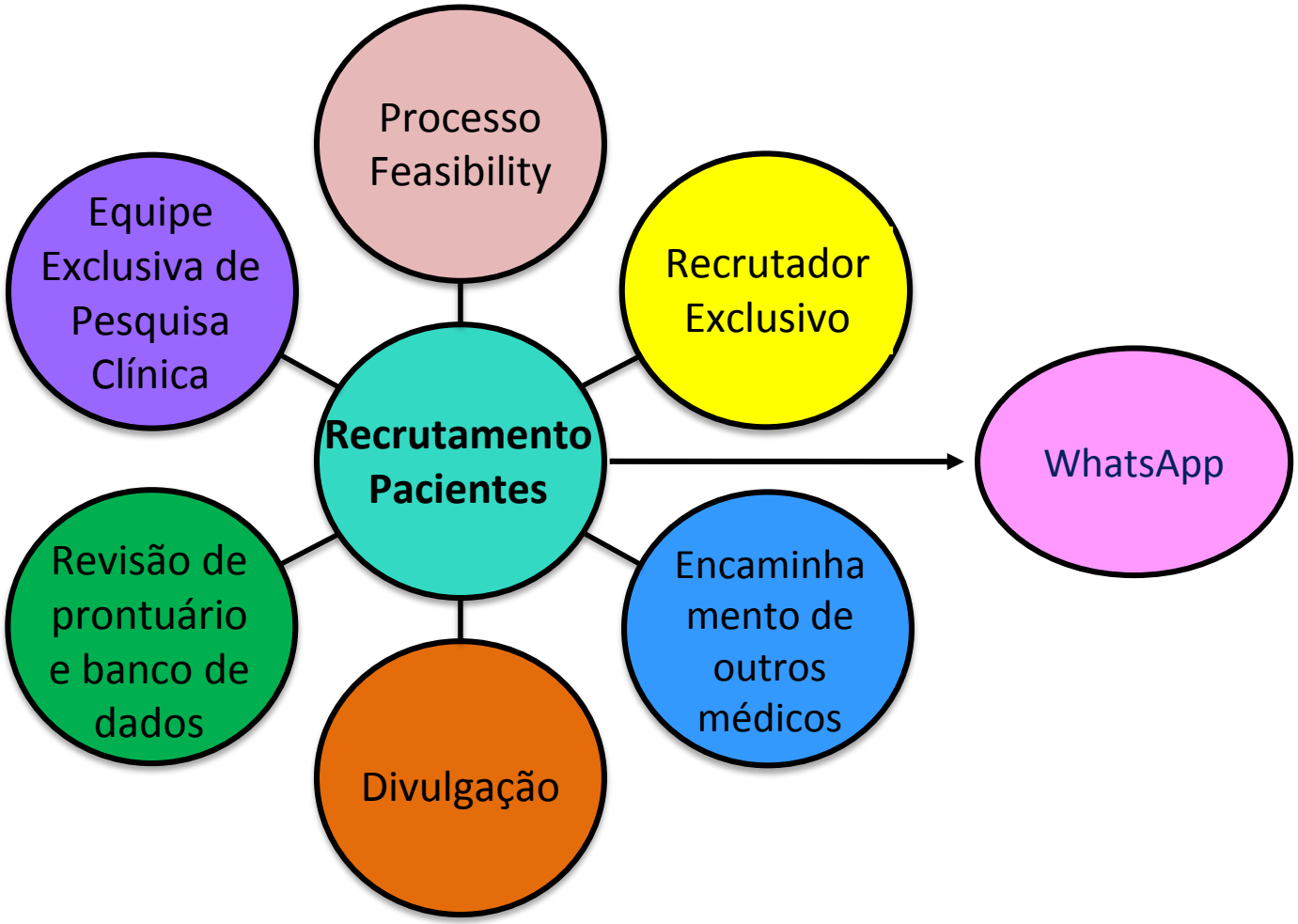
2 Brain Mets
1 PLD1
1 ER positive (5%)

18 randomised

2 still on treatment

Protocolo	Recrutamento	Randomizadas
IMpassion 130	22	18
IMpassion 131	7	6
IMpassion 132	5	3
IMpassion 031	41	32
IMpassion 050	14	10
		69

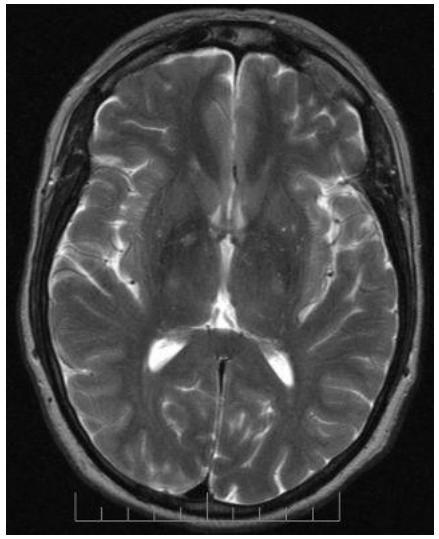
Estratégias de Recrutamento de Pacientes



ENVOLVIMENTO E COMPROMETIMENTO PI

Screen Failures

MRI



Patients in real world

PDL1 status

Old Blocs

Screen Failures

ORIGINAL ARTICLE

Estrogen and progesterone receptor testing in breast carcinoma: concordance of results between local and reference laboratories in Brazil

Teste de receptores de estrógeno e progesterona em carcinoma de mama: concordância dos resultados entre laboratórios locais e de referência no Brasil

Sheila Cristina Lordelo Wludarski[I], Lisandro Ferreira Lopes[I], Ívison Xavier Duarte[I], Filomena Marino Carvalho[II], Lawrence Weiss[III], Carlos Eduardo Bacchi[IV]

Pathology Consultancy, Botucatu, São Paulo, Brazil

Table 4. Comparison of the concordance results for estrogen (ER) and progesterone (PgR) receptors between reference/central and local laboratories reported in the literature and by the present study

Authors, country and year of publication	ER concordance	PgR concordance
Viale et al.,[22] 25 countries, 2007	6058/6205 (97.6%)	4202/5237 (80.2%)
Badve et al.,[23] USA, 2008	694/769 (90.2%)	649/769 (84.4%)
Gelber et al.,[27] several countries, 2009	4323/4931 (87.6%)	-
Wludarski et al., Brazil, 2011 (present study)	447/500 (89.4%)	425/500 (85.0%)

HER2 Testing in Breast Carcinoma

Very Low Concordance Rate Between Reference and Local Laboratories in Brazil

Sheila Cristina Lordelo Wludarski, MD,† Lisandro Ferreira Lopes, MD, PhD,* Tácio R. Berto e Silva, MD,* Filomena M. Carvalho, MD, PhD,† Lawrence M. Weiss, MD,‡ and Carlos E. Bacchi, MD, PhD*†*

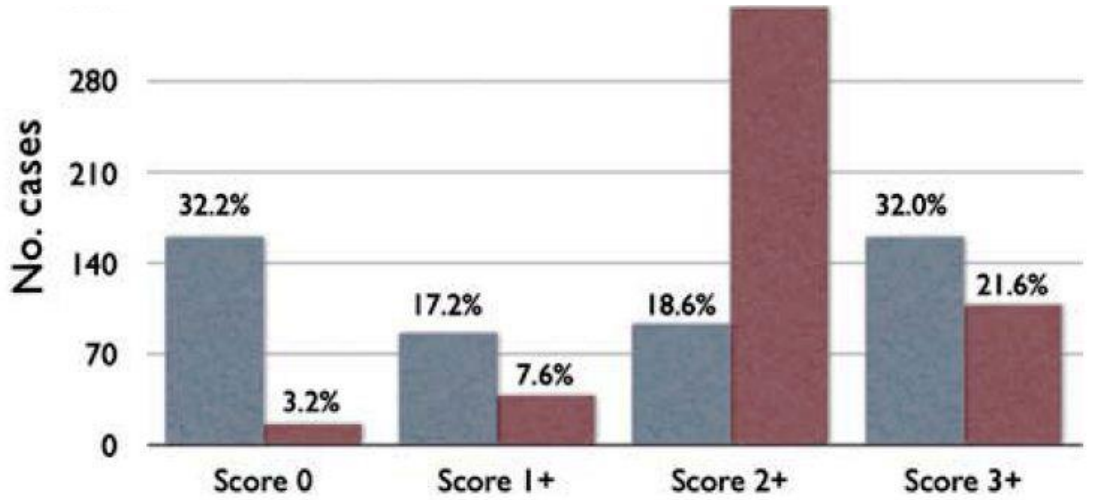
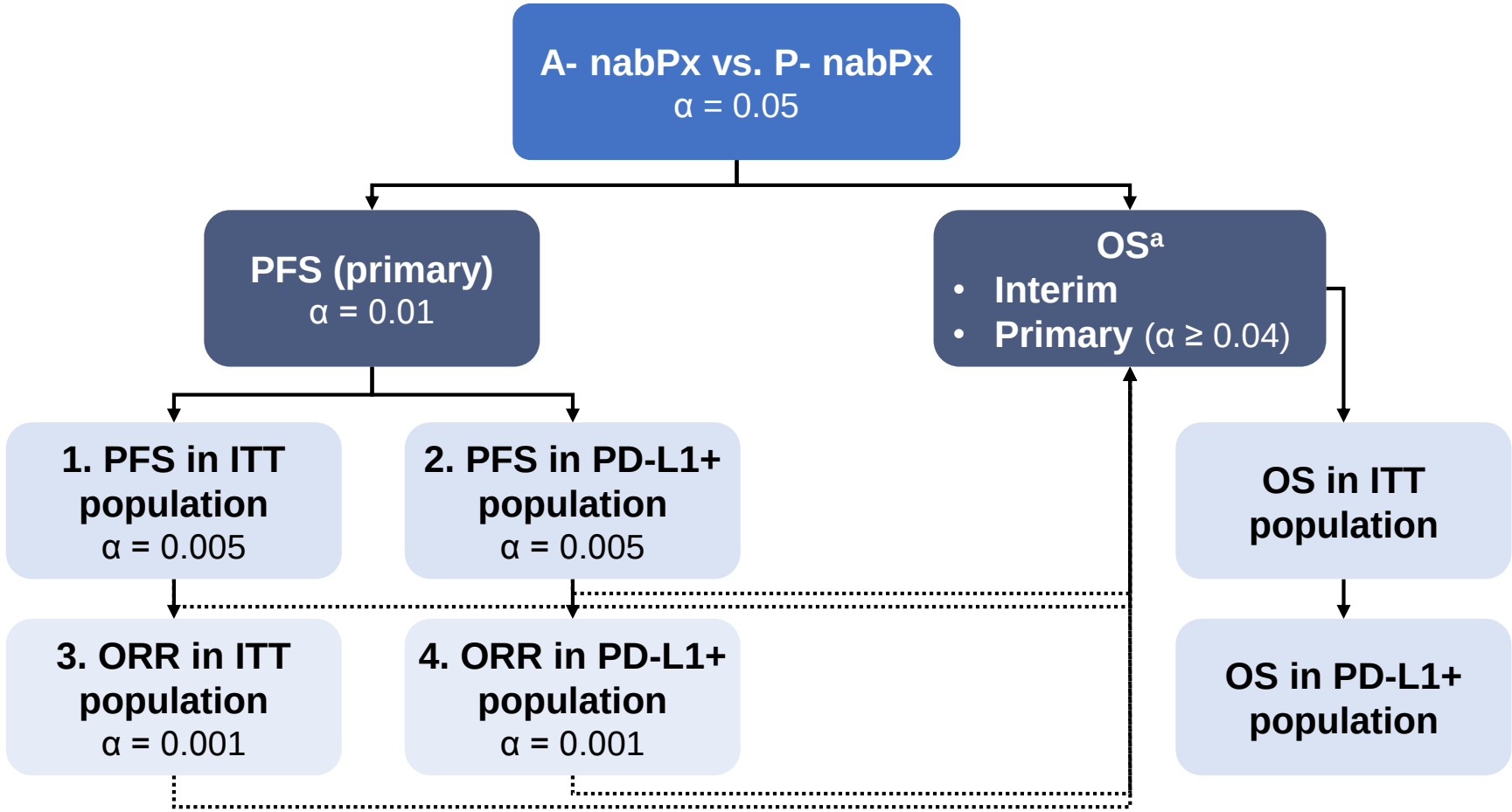


FIGURE 1. Frequency of cases per HER2 scores by reference and local laboratories.

IMPASSION130 STATISTICAL TESTING



- At the Apr 17, 2018 data cut off:
  - PFS tested in ITT and PD-L1+ populations (primary analysis)
  - OS tested first in ITT pts, then if significant OS benefit seen, in PD-L1+ population

[a] OS α levels determined based on outcome of PFS/ORR testing. HR/*P* value stopping boundaries are dependent on the OS analysis timing.

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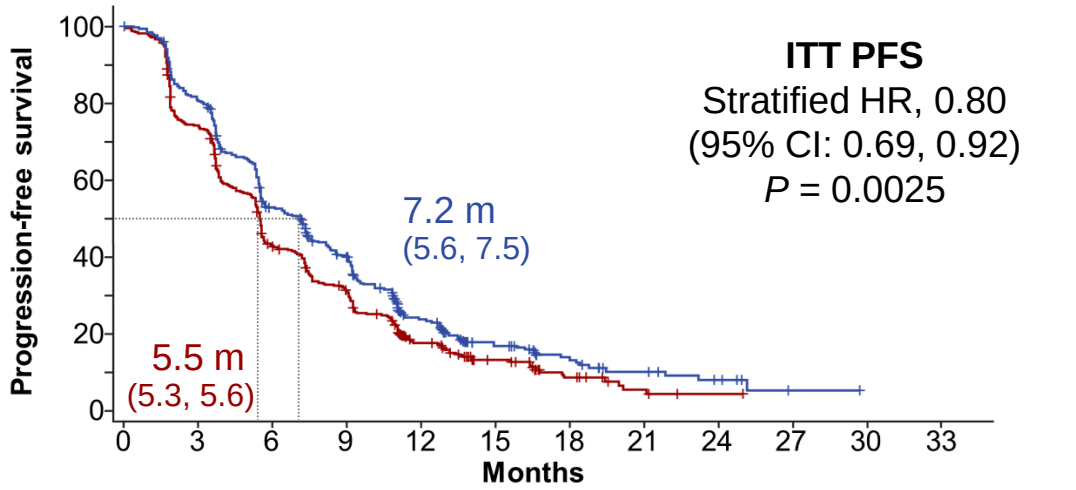
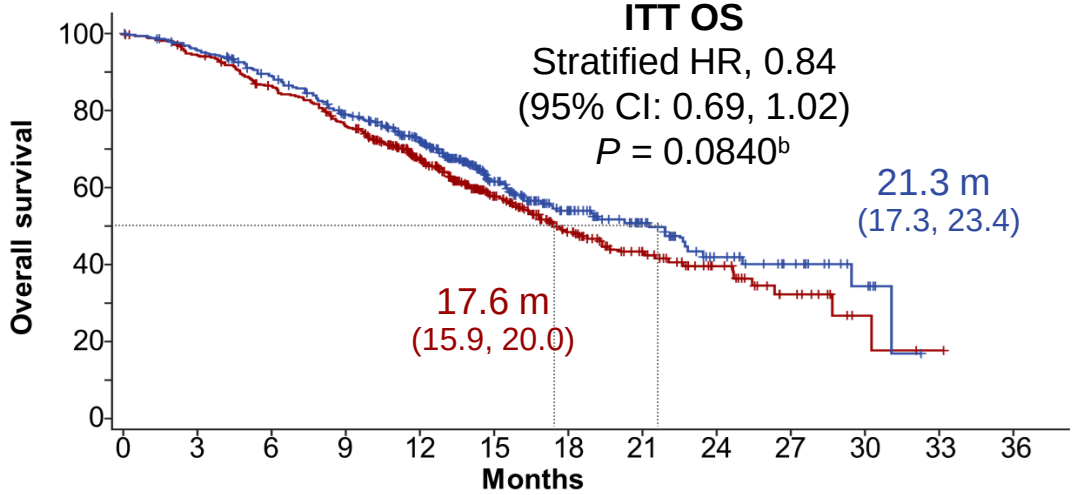
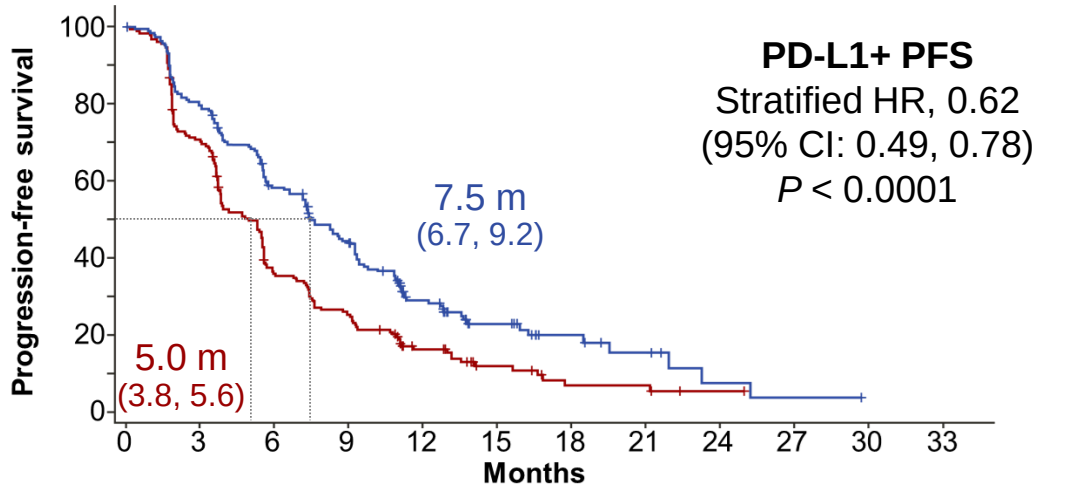
IMpassion130 primary analysis[1,2]: Clinically meaningful PFS and OS benefit in the PD-L1+ population

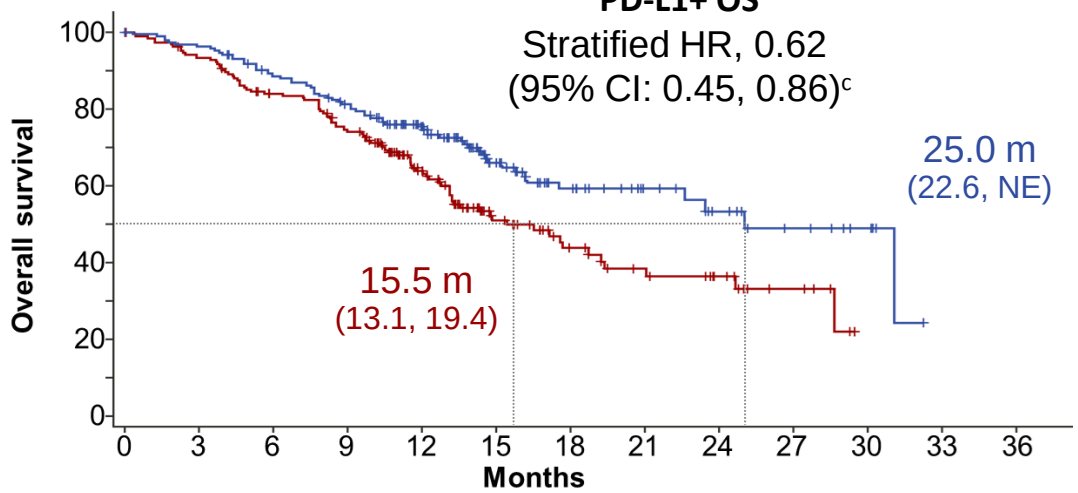
ITT population





PD-L1+ population[a]





NE, not estimable.
Median follow-up (ITT): 12.9 months.
[a] PD-L1+: PD-L1 in ≥ 1% of IC. [b] Not significant. [c] Not formally tested per hierarchical study design.
1. Schmid *N Engl J Med* 2018. 2. Schmid ESMO 2018 [LBA1_PR].

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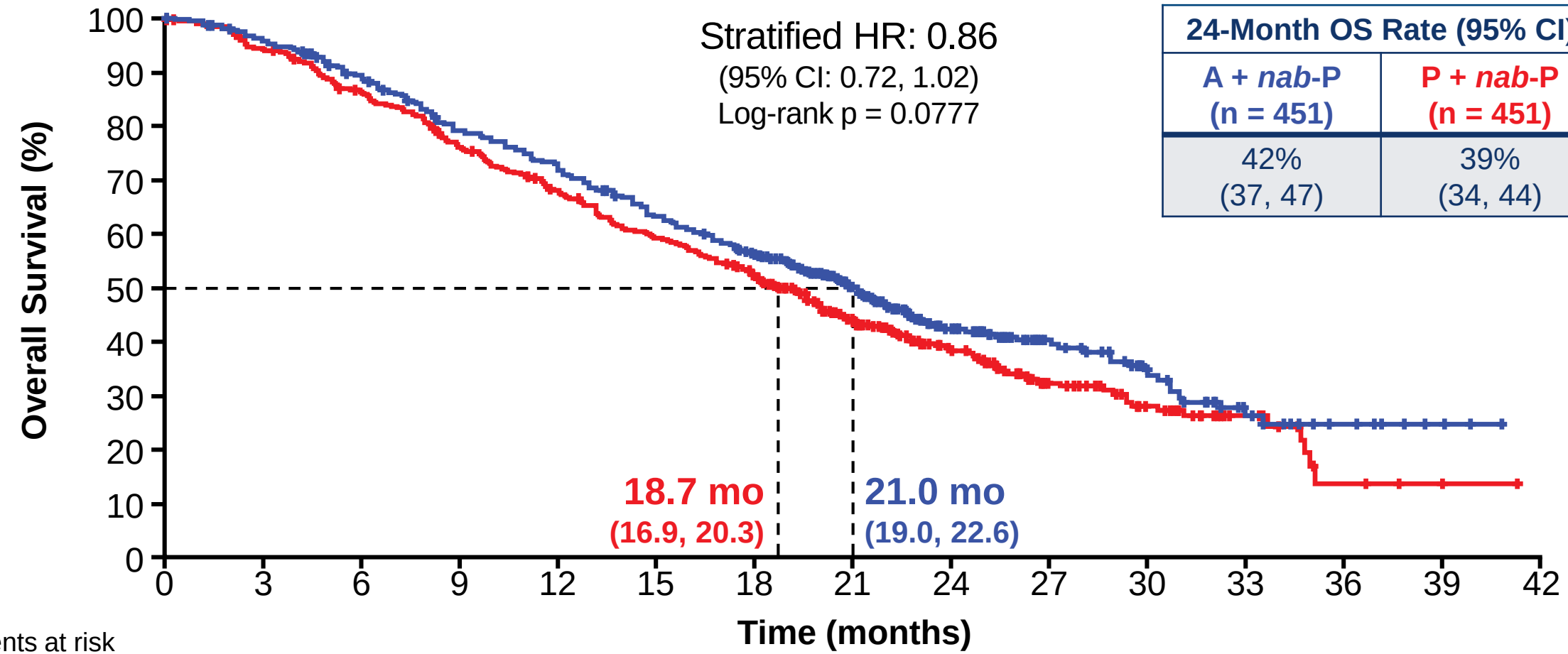
Overall Survival in ITT Population



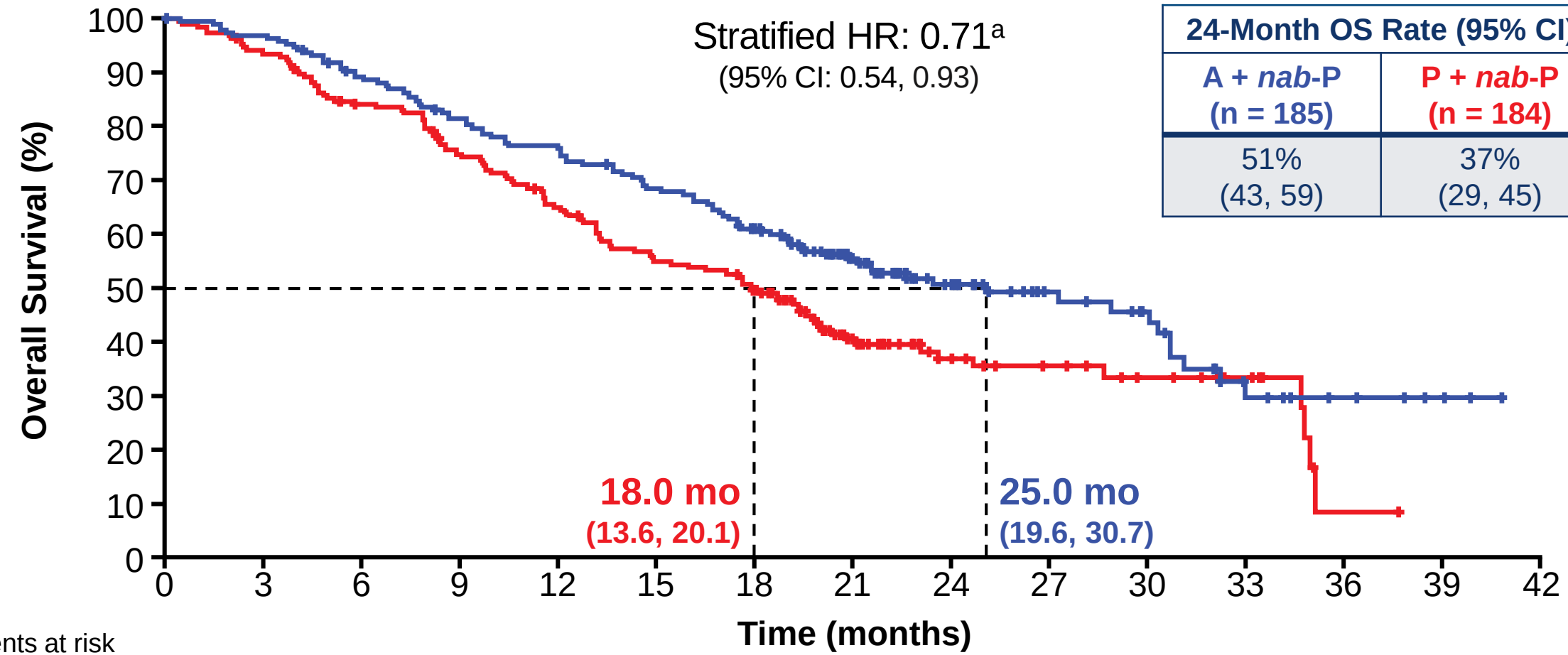
24-Month OS Rate (95% CI)	
A + *nab*-P (n = 451)	P + *nab*-P (n = 451)
42% (37, 47)	39% (34, 44)

Patients at risk

A + *nab*-P	451	426	389	342	312	270	235	162	88	56	35	19	8	3	NE
P + *nab*-P	451	420	376	329	291	252	216	145	87	51	33	17	4	1	NE

Clinical cutoff date: Jan 2, 2019. Median PFS (95% CI) are indicated on the plot. Median FU (ITT): 18.0 mo.

Overall Survival in PD-L1+ Population



24-Month OS Rate (95% CI)	
A + *nab*-P (n = 185)	P + *nab*-P (n = 184)
51% (43, 59)	37% (29, 45)

Patients at risk

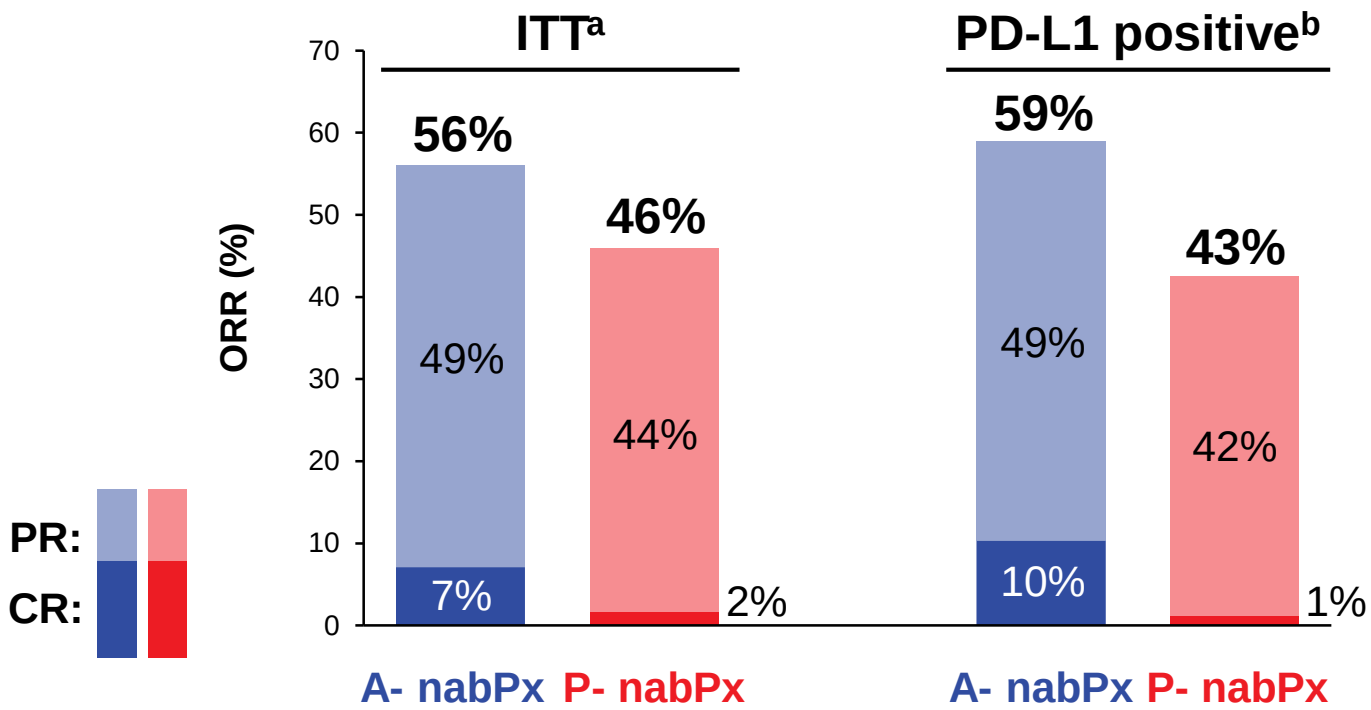
A + *nab*-P	185	177	160	145	135	121	106	69	43	28	21	10	6	3	NE
P + *nab*-P	184	170	147	129	111	93	81	47	26	20	15	10	1	NE	NE

[a] Not formally tested due to pre-specified hierarchical analysis plan.

Clinical cutoff date: Jan 2, 2019. Median PFS (95% CI) are indicated on the plot. Median FU (ITT): 18.0 mo.

IMPASSION130 SECONDARY EFFICACY DATA

ORR and DOR



	ITT[a]		PD-L1 positive[b]	
	A- nabPx	P- nabPx	A- nabPx	P- nabPx
DOR, median, m (95% CI)	7.4 (6.9, 9.0)	5.6 (5.5, 6.9)	8.5 (7.3, 9.7)	5.5 (3.7, 7.1)
No. of ongoing responses, n (%)[c]	**78 (31%)**	**52 (25%)**	**39 (36%)**	**19 (24%)**

- Responses, which appeared durable, were numerically more frequent in the A-nabPx arm
- The complete response rate was also higher in the A-nabPx arm
  - ITT population: 7% vs. 2%
  - PD-L1+ patients: 10% vs. 1%

Data cut off: April 17, 2018. Objective response–evaluable patients: [a] 450 in A-nabPx arm and 449 in P-nabPx arm.
[b] 185 in A-nabPx arm and 183 in P-nabPx arm. [c] No death or PD.

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IMPASSION130 SAFETY

Exposure and AE summary for safety-evaluable patients

AE	A- nabPx (n = 452)	P- nabPx (n = 438)
AEs regardless of attribution, any grade	449 (99%)	429 (98%)
Grade 3-4	220 (49%)	185 (42%)
Grade 5	6 (1%)	3 (1%)
Treatment-related AEs, any grade	436 (96%)	410 (94%)
Grade 3-4	179 (40%)	132 (30%)
Grade 5[a]	3 (1%)[a]	1 (< 1%)[a]
Serious AEs, any grade		
Serious AEs regardless of attribution	103 (23%)	80 (18%)
Treatment-related serious AEs	56 (12%)	32 (7%)
AEs leading to any treatment discontinuation, any grade	72 (16%)	36 (8%)
Leading to A or P discontinuation	29 (6%)	6 (1%)
Leading to nabPx discontinuation	72 (16%)	36 (8%)
AEs leading to any dose reduction or interruption, any grade	212 (47%)	177 (40%)
Leading to A or P dose interruption	139 (31%)	103 (24%)
Leading to nabPx dose reduction or interruption	195 (43%)	172 (39%)

- Median treatment duration:
  - A-nabPx arm: 24.1 weeks A and 22.1 weeks nabPx
  - P-nabPx arm, 22.1 weeks P and 21.8 weeks nabPx
- Atezolizumab did not compromise the dose intensity of nab-paclitaxel
- **A- nabPx was generally well tolerated with no new safety signals seen**

Data cut off: April 17, 2018. [a] Treatment-related deaths: autoimmune hepatitis, mucosal inflammation/death, septic shock (n = 1 each, A-nabPx arm); hepatic failure (n = 1, P-nabPx arm).

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IMPASSION130 SAFETY

Most common adverse events regardless of attribution

AE	A- nabPx (n = 452)		P- nabPx (n = 438)	
	Any Grade	Grade 3-4	Any Grade	Grade 3-4
Alopecia	255 (56%)	3 (1%)	252 (58%)	1 (< 1%)
Fatigue	211 (47%)	18 (4%)	196 (45%)	15 (3%)
Nausea[a]	208 (46%)	5 (1%)	167 (38%)	8 (2%)
Diarrhea	147 (33%)	6 (1%)	150 (34%)	9 (2%)
Anemia	125 (28%)	13 (3%)	115 (26%)	13 (3%)
Constipation	113 (25%)	3 (1%)	108 (25%)	1 (< 1%)
Cough[a]	**112 (25%)**	**0**	**83 (19%)**	**0**
Headache	105 (23%)	2 (< 1%)	96 (22%)	4 (1%)
Neuropathy peripheral	98 (22%)	25 (6%)	97 (22%)	12 (3%)
Neutropenia[a]	**94 (21%)**	**37 (8%)**	**67 (15%)**	**36 (8%)**
Decreased appetite	91 (20%)	3 (1%)	79 (18%)	3 (1%)
Peripheral sensory neuropathy	72 (16%)	9 (2%)	52 (12%)	8 (2%)
Neutrophil count decreased	57 (13%)	21 (5%)	48 (11%)	15 (3%)
Increased ALT	47 (10%)	8 (2%)	40 (9%)	5 (1%)

Data cut off: April 17, 2018. ALT, alanine aminotransferase. Includes all-grade AEs occurring in ≥ 20% and grade 3-4 AEs in ≥ 2% of patients in either arm. [a] AEs with ≥ 5% higher incidence in the A-nabPx arm vs P-nabPx arm; others include pyrexia and hypothyroidism (not shown in table because overall frequency < 20%).

- The most common AEs were generally similar between arms
  - Grade 3-4: mostly neutropenia, **decreased neutrophil count, peripheral neuropathy, fatigue, anemia**
  - Grade 3-4 AEs ≥ 2% higher in the A- nabPx arm included peripheral neuropathy (6% vs 3%)

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IMPASSION130 SAFETY

AESIs suggestive of potential immune-related etiology

AESI	A- nabPx (n = 452)		P- nabPx (n = 438)	
	Any Grade	Grade 3-4	Any Grade	Grade 3-4
All	259 (57%)	34 (8%)	183 (42%)	19 (4%)
Important AESIs[a]				
Immune-related hepatitis (all)	69 (15%)	23 (5%)	62 (14%)	13 (3%)
Immune-related hepatitis (diagnosis)	10 (2%)	6 (1%)	7 (2%)	1 (< 1%)
Immune-related hepatitis (lab abnormalities)	62 (14%)	17 (4%)	58 (13%)	12 (3%)
Immune-related hypothyroidism	78 (17%)	0	19 (4%)	0
Immune-related hyperthyroidism	20 (4%)	1 (< 1%)	6 (1%)	0
Immune-related pneumonitis	14 (3%)	1 (< 1%)	1 (< 1%)	0
Immune-related meningoencephalitis	5 (1%)	0	2 (< 1%)	0
Immune-related colitis	5 (1%)	1 (< 1%)	3 (1%)	1 (< 1%)
Immune-related adrenal insufficiency	4 (1%)	1 (< 1%)	0	0
Immune-related pancreatitis	2 (< 1%)	1 (< 1%)	0	0
Immune-related diabetes mellitus	1 (< 1%)	1 (< 1%)	2 (< 1%)	1 (< 1%)
Immune-related nephritis	1 (< 1%)	0	0	0
Other AESIs[a]				
Immune-related rash	154 (34%)	4 (1%)	114 (26%)	2 (< 1%)
Infusion-related reactions	5 (1%)	0	5 (1%)	0

- Hypothyroidism occurred at 17% (A- nabPx) vs. 4% (P- nabPx)
  - All grade 1-2; none led to discontinuation
- Pneumonitis was infrequent: 3% (A- nabPx) vs. < 1% (P- nabPx)
  - One grade 3-4 (A- nabPx)
- One related G5 event in each arm:
  - A- nabPx: autoimmune hepatitis
  - P- nabPx: hepatic failure

Data cut off: April 17, 2018. Includes all AESIs occurring in ≥1% of patients in either arm.

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Schmid P, et al. NEJM, October 20, 2018. DOI: 10.1056/NEJMoa1809615.

IMPASSION130 SAFETY ATEZO RELATED

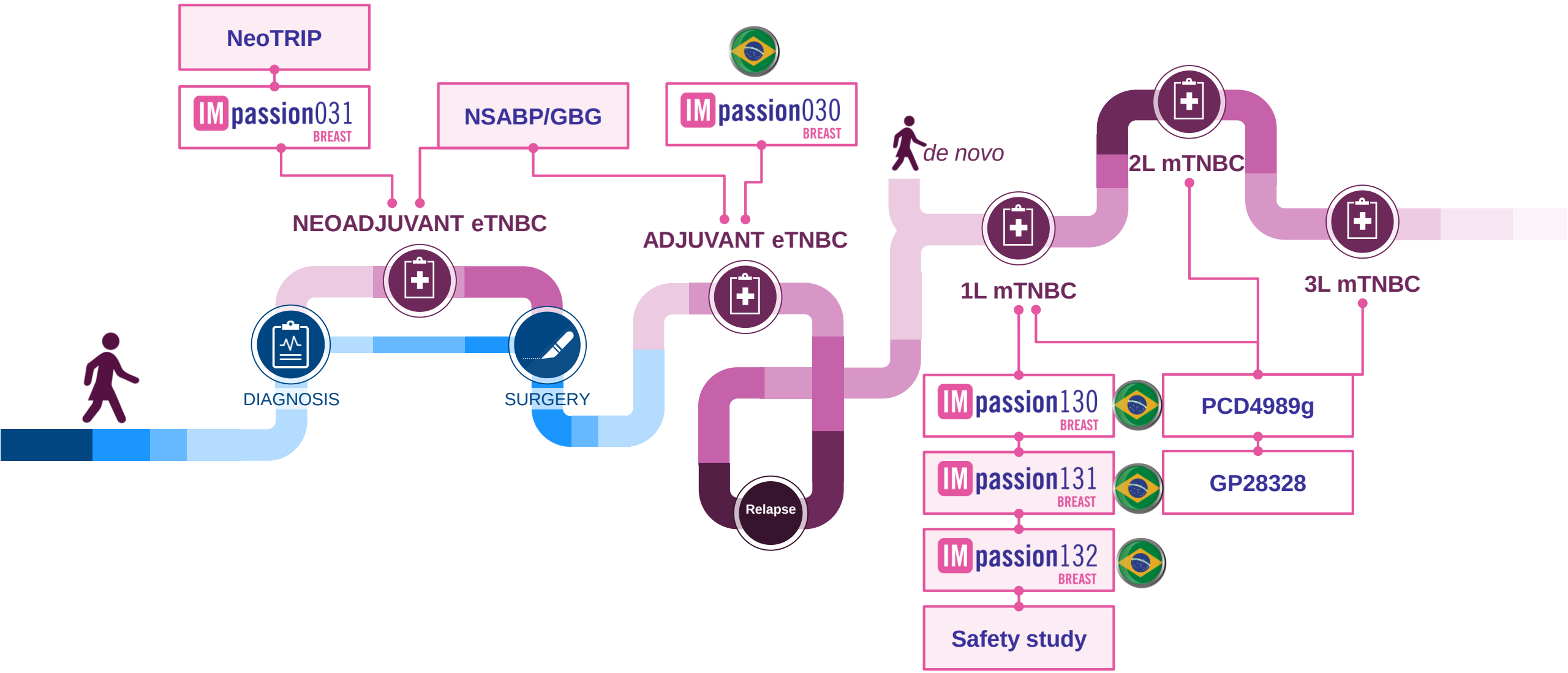
Personal Experience

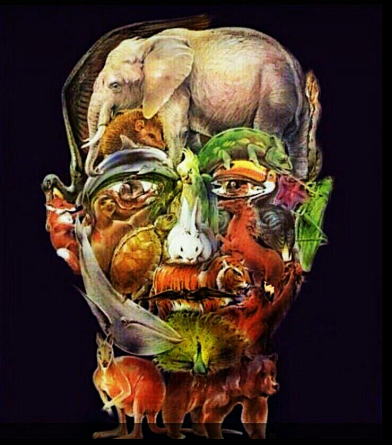
- Hypothyroidism 4 cases
- Hyperthyroidism 1 case
- Colitis 1 case (Impassion 031)

Impassion130 - Conclusions

- First positive phase 3 immunotherapy study in mTNBC
- 1L Atezo + nabPx resulted in **statistically significant PFS** benefit in the ITT and PD-L1 positive populations.
- **Clinically meaningful OS** improvement with a HR of 0.62 and a median OS improvement of 10 months in the PD-L1– positive population (first interim OS analysis).
- Atezo-nabPx was well tolerated with a safety profile consistent with each agent.

Atezolizumab in TNBC development programme





	Year of Diagnosis					
OS (m)	**2008**	**2009**	**2010**	**2011**	**2012**	**2013**
HR+ HER2- (N=9.908)	43.7 (40.2-46.6)	42.0 (38.9-44.6)	40.9 (38.0-43.4)	42.0 (39.2-45.0)	44.5 (41.8-47.3)	**40.3 (37.8-ND)**
HER2+ (N=2.861)	38.6 (33.6-44.6)	42.3 (38.3-50.8)	40.1 (35.2-45.6)	42.3 (36.5-49.8)	51.1 (46.5-ND)	**Not Reached**
HR- HER2- (N=2.317)	15.1 (12.7-16.4)	15.1 (13.0-17.4)	14.7 (13.2-17.0)	14.0 (11.4-15.9)	13.9 (11.4-15.9)	**14.1 (12.5-15.5)**

Delaloge S, et al. ASCO 2017.
Gobbini E, et al. European Journal of Cancer 2018, 96:17-24.