XXIV

SIMPOSIO DE REVISIONES EN CÁNCER

"Tratamiento médico del cáncer en el año 2022"

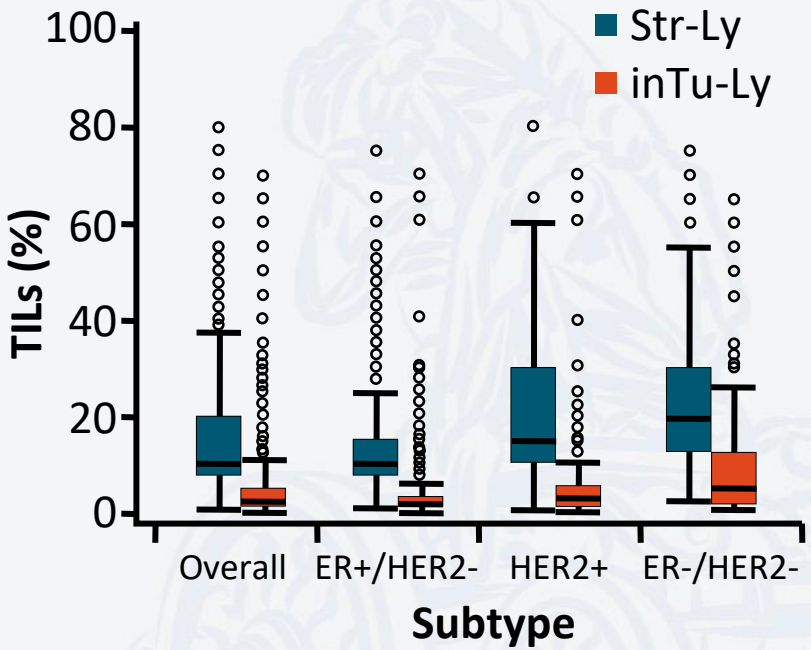
Avances de la inmunoterapia en cáncer de mama triple negativo en estadio avanzado

Begoña Bermejo de las Heras
HCUValencia

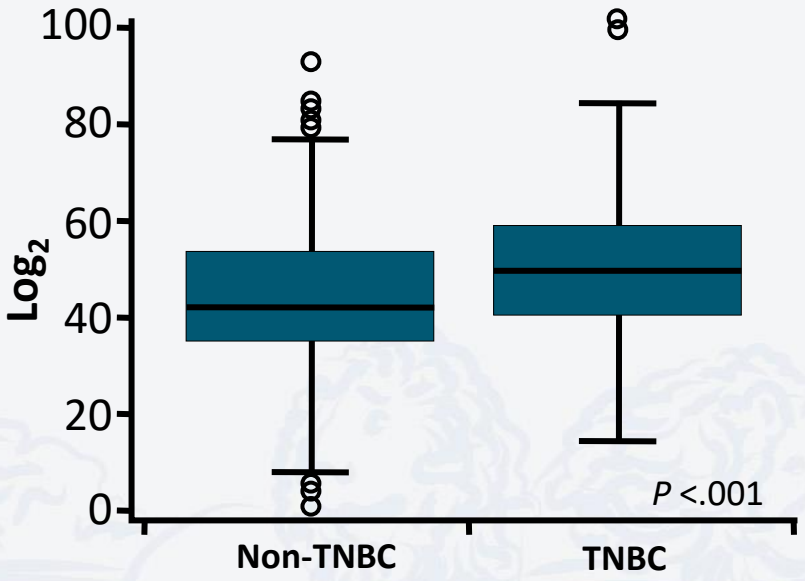
ARÁN

Immune Checkpoint Inhibition in TNBC: Rationale

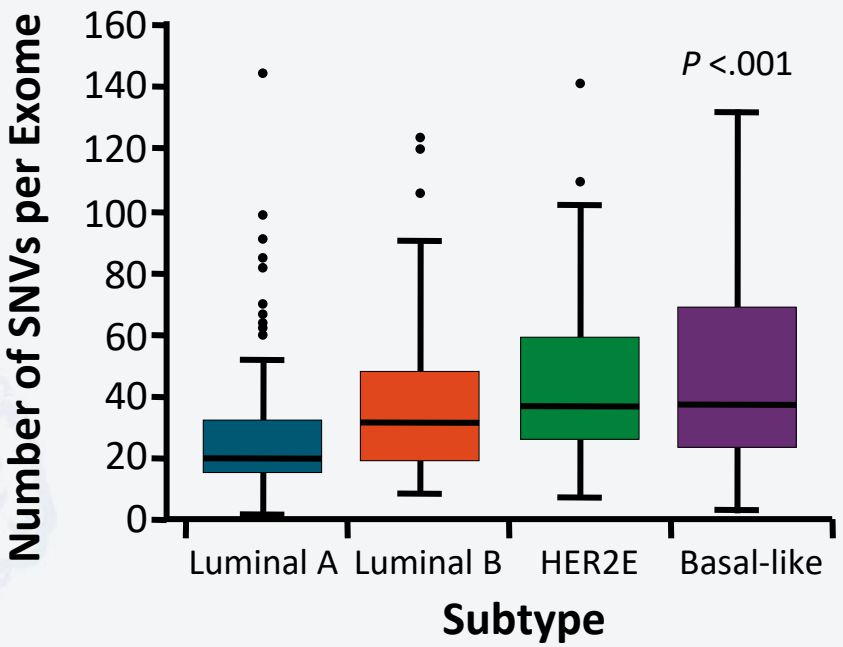
Tumor-Infiltrating Lymphocytes[1]



PD-L1 Expression[2]



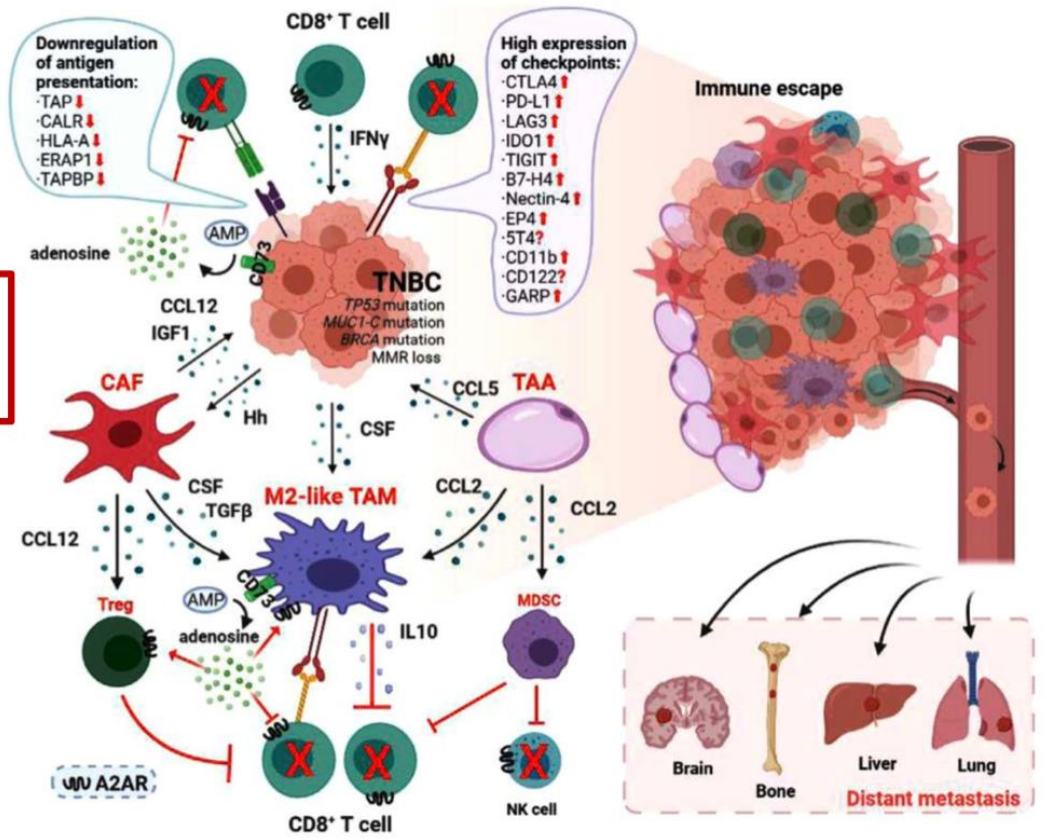
Non synonymous Mutations[3]



1. Loi. JCO. 2013;31:860. 2. Mittendorf. Cancer Immunol Res. 2014;2:361. 3. Luen. Breast. 2016;29:241.

The Immune Portrait of TNBC

High mutation rate vs. other BCs

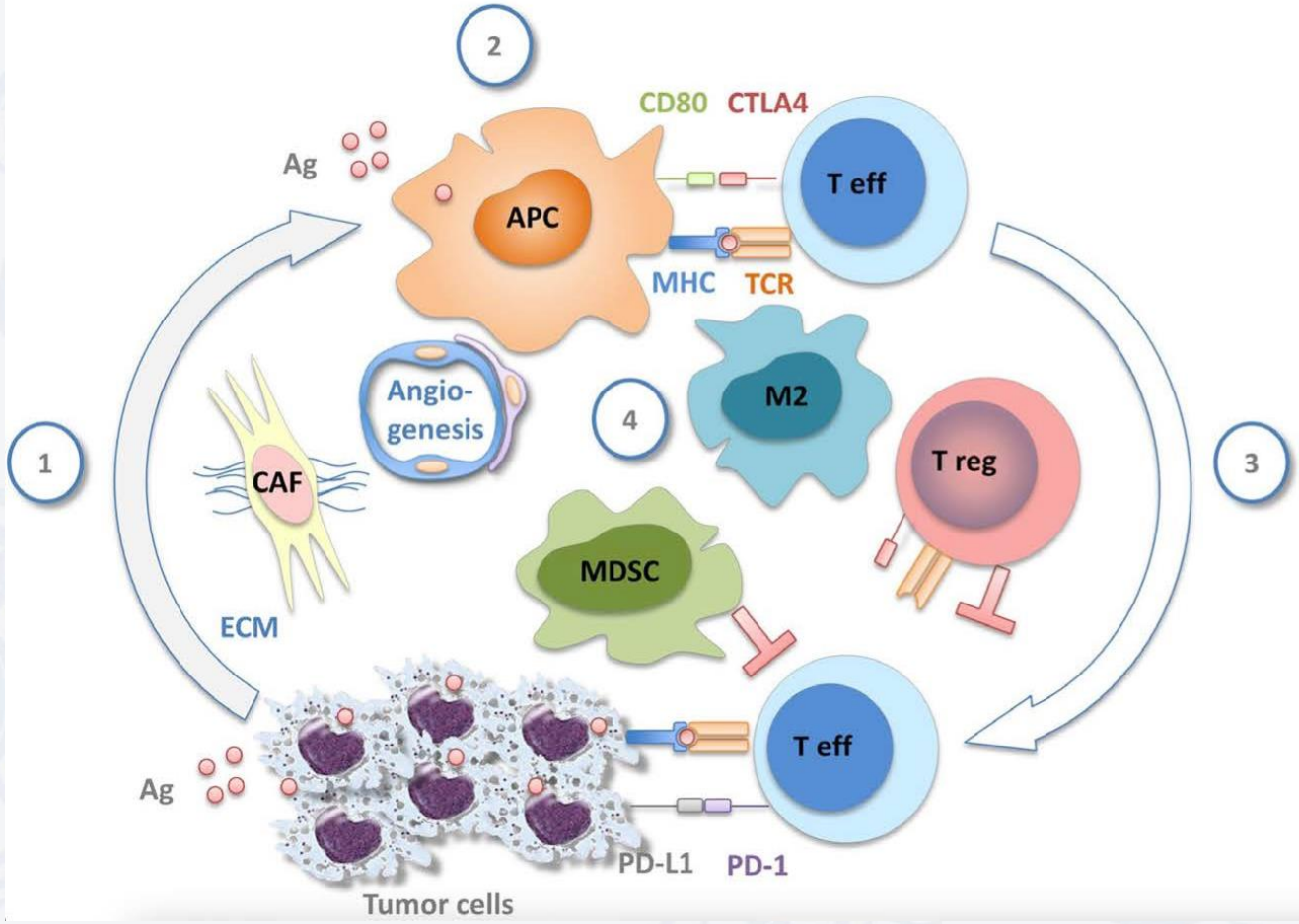


T-cell infiltration

PD-L1 expression

Bai X et al. JNCC 2021

Turning 'cold' tumours into hot

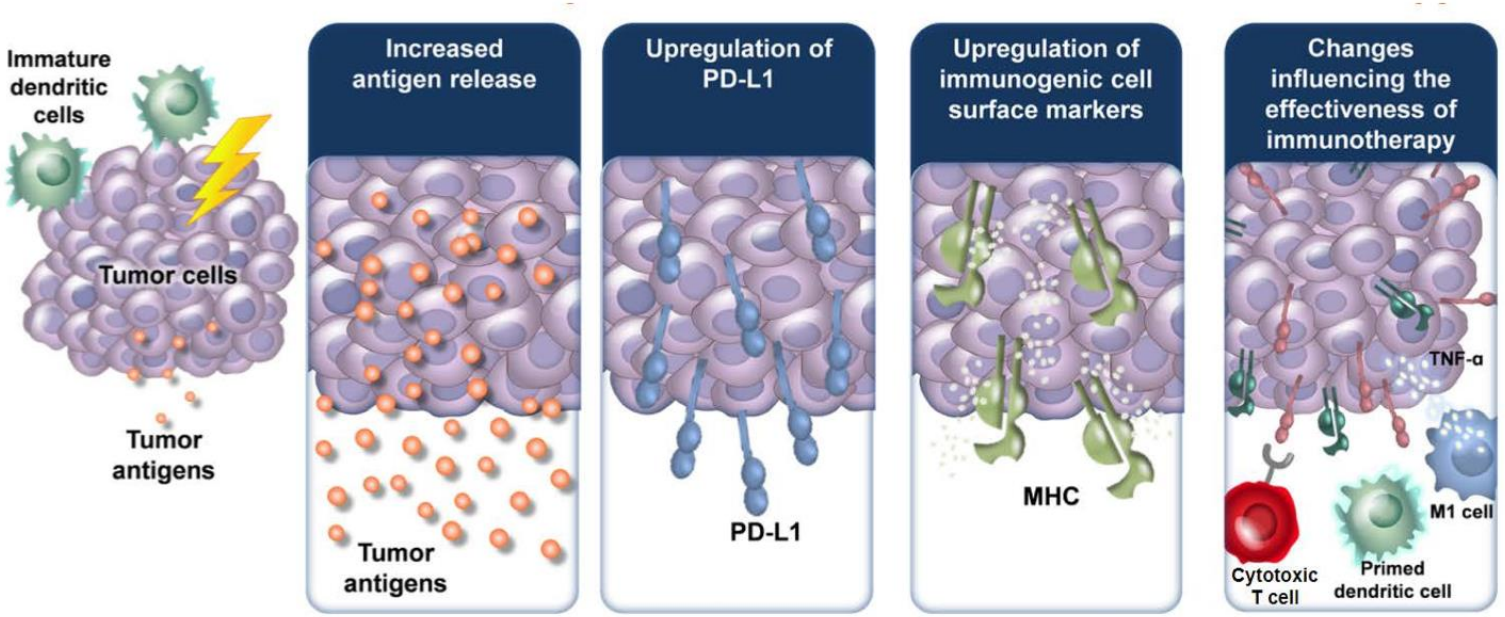


1. Promoting antigen presentation
2. Engaging Antigen Presentation Cells
3. Stimulating, enabling and reprogramming T cells
4. Reprograming the innate immunity compartment

Gerrard Ca Treat Rev 2021

Activity of anti-PD1/PD-L1 & chemotherapy in TNBC

Chemotherapy induces multiple immunomodulatory changes in the tumor microenvironment that may influence the effectiveness of immunotherapy



1. Daly ME, et al. J Thorac Oncol 2015; 2. Kaur P, et al. Front Oncol 2012; 3. Deng L, et al. J Clin Invest 2014

SITUACIÓN ACTUAL

IMpassion130 study design

Key IMpassion130 eligibility criteria[a]:

- Metastatic or inoperable locally advanced TNBC
  - Histologically documented[b]
- 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%])[c]

R 1:1

Atezo + nab-P arm:

Atezolizumab 840 mg IV
- On days 1 and 15 of 28-day cycle

+ *nab*-paclitaxel 100 mg/m^2 IV
- On days 1, 8 and 15 of 28-day cycle

Plac + nab-P arm:

Placebo IV
- On days 1 and 15 of 28-day cycle

+ *nab*-paclitaxel 100 mg/m^2 IV
- On days 1, 8 and 15 of 28-day cycle

Double blind; no crossover permitted

RECIST v1.1
PD or toxicity

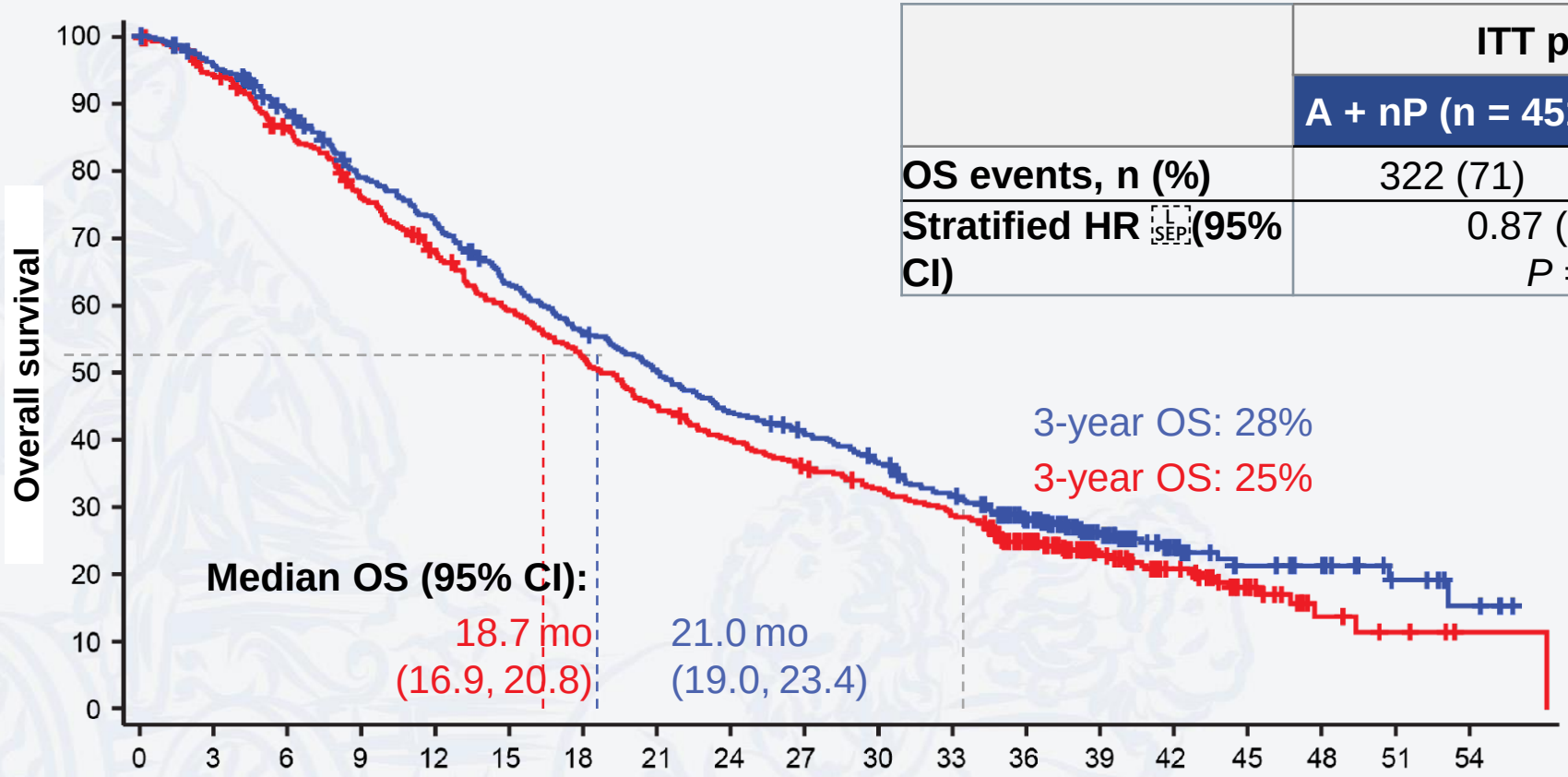
- Co-primary endpoints were PFS and OS in the ITT and PD-L1+ populations[d]
  - Key secondary efficacy endpoints (ORR and DOR) and safety were also evaluated

IC, tumour-infiltrating immune cell; TFI, treatment-free interval. [a] ClinicalTrials.gov: NCT02425891. [b] Locally evaluated per ASCO–College of American Pathologists (CAP) guidelines. [c] Centrally evaluated per VENTANA SP142 IHC assay (double blinded for PD-L1 status). [d] Radiological endpoints were investigator assessed (per RECIST v1.1).

Schmid P, et al. IMpassion130 ESMO 2018 (LBA1_PR)
http://bit.ly/2DMhayg

OS in the ITT population

	ITT population	
	A + nP (n = 451)	P + nP (n = 451)
OS events, n (%)	322 (71)	344 (76)
Stratified HR (95% CI)	0.87 (0.75, 1.02) *P* = 0.077	



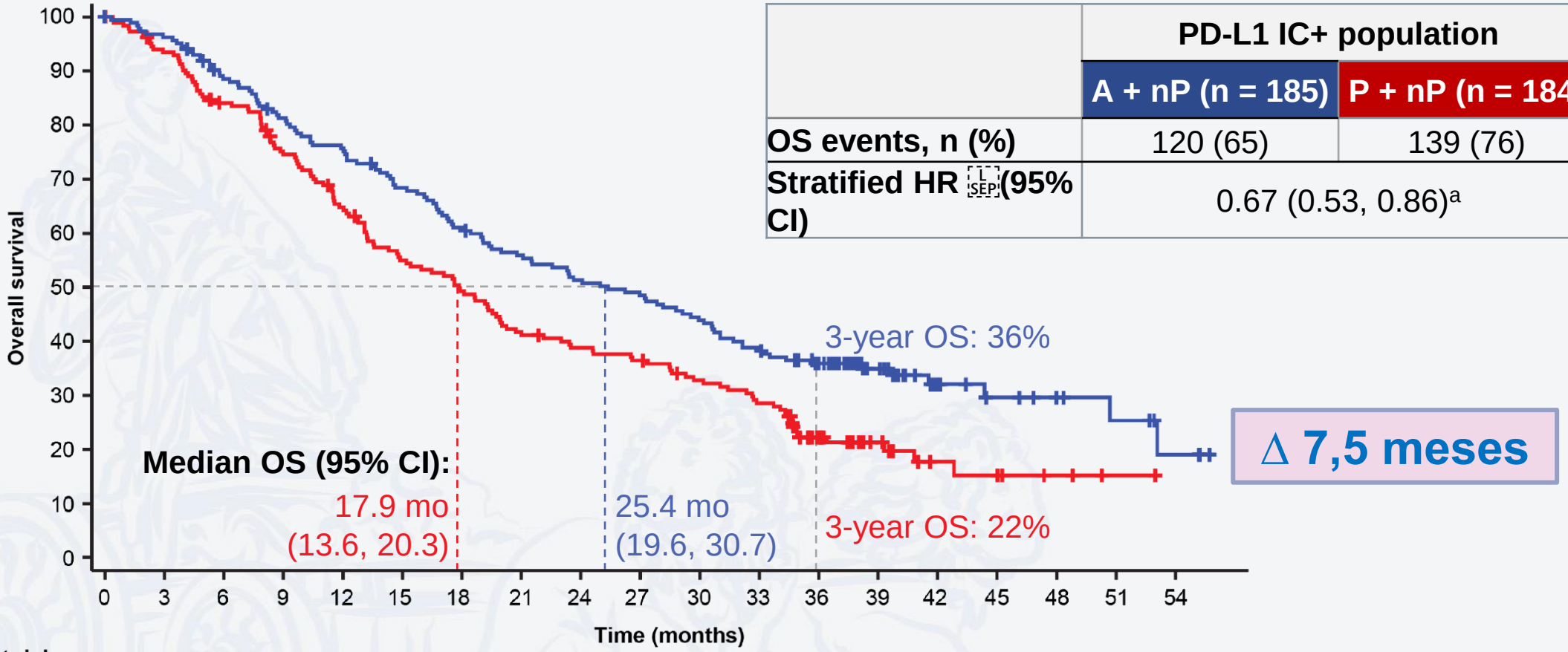
No. at risk (ITT population):																			
A + nP	451	426	389	342	312	270	240	214	188	172	152	130	99	58	33	20	16	8	4
P + nP	451	420	379	332	294	255	225	194	172	153	138	121	89	52	35	20	7	4	1

Data cutoff, 14 April 2020. Median survival follow-up, 18.8 months (all patients). HR, hazard ratio.

Emens LA. ESMO 2020.
IMpassion130 Final OS.

OS in the PD-L1 IC+ population

	PD-L1 IC+ population	
	A + nP (n = 185)	P + nP (n = 184)
OS events, n (%)	120 (65)	139 (76)
Stratified HR (95% CI)	0.67 (0.53, 0.86)[a]	



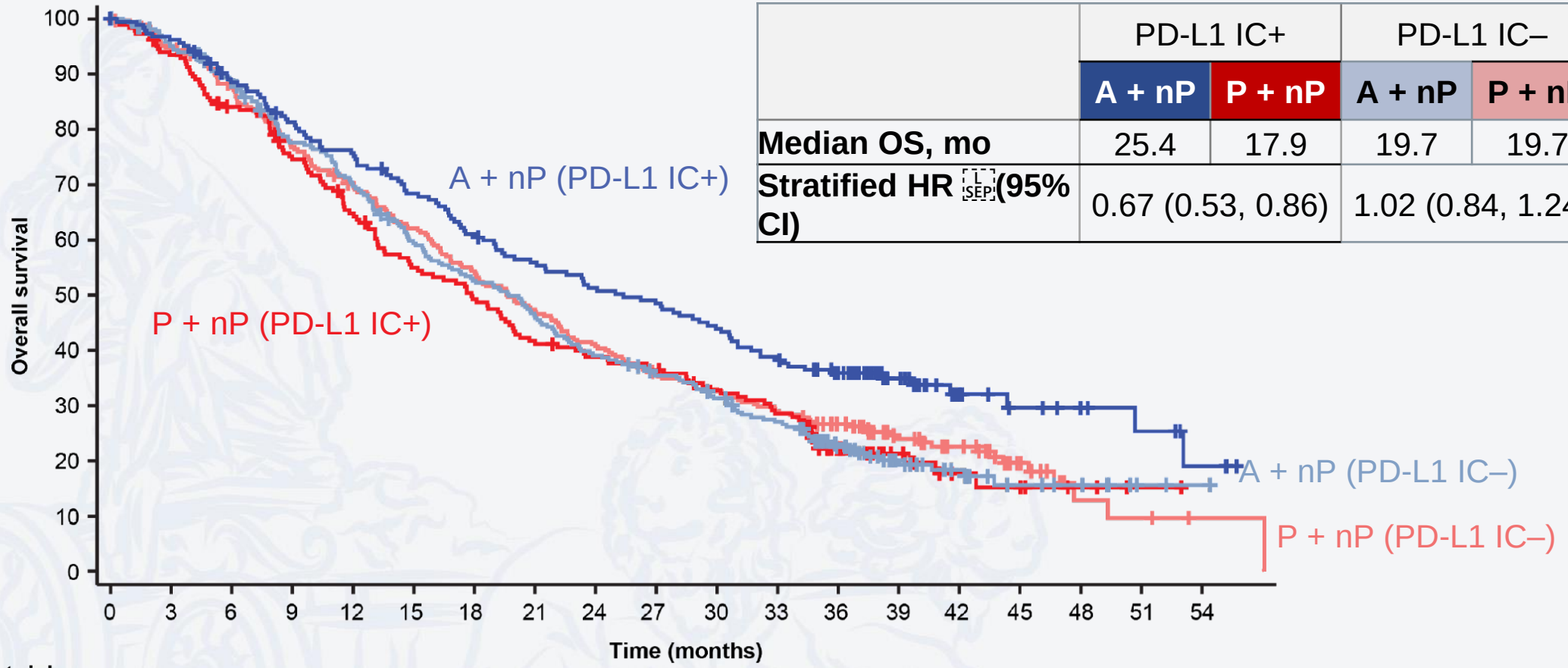
Δ 7,5 meses

Data cutoff, 14 April 2020. NE, not estimable.
[a] *P* value not displayed since OS in the PD-L1+ population was not formally tested due to the hierarchical study design.

Emens LA. ESMO 2020.
IMpassion130 Final OS.

OS by PD-L1 IC status (PD-L1 IC+ vs PD-L1 IC–)

	PD-L1 IC+		PD-L1 IC–	
	A + nP	P + nP	A + nP	P + nP
Median OS, mo	25.4	17.9	19.7	19.7
Stratified HR (95% CI)	0.67 (0.53, 0.86)		1.02 (0.84, 1.24)	



Patients at risk

ıab + *nab*-Paclitaxel (PD-L1+)	185	177	160	145	135	121	108	98	90	86	77	67	56	32	17	11	9	6	3
ıab + *nab*-Paclitaxel (PD-L1–)	266	249	229	197	177	149	132	116	98	86	75	63	43	26	16	9	7	2	1
ɛbo + *nab*-Paclitaxel (PD-L1+)	184	170	150	132	113	95	85	72	66	62	54	47	28	14	7	6	3	1	NE
ɛbo + *nab*-Paclitaxel (PD-L1–)	267	250	229	200	181	160	140	122	106	91	84	74	61	38	28	14	4	3	1

Data cutoff, 14 April 2020.

Emens LA. ESMO 2020. IMpassion130 Final OS.

IMpassion130: summary

- Here we report mature OS data from the prespecified final OS analysis
  - The OS boundary for statistical significance was not crossed in the ITT population, precluding further formal testing
  - Clinical meaningful OS was observed in the PD-L1 IC+ population
    - Final OS HR, 0.67 (95% CI: 0.53, 0.86) and a +7.5-mo median OS improvement with A + nP vs P + nP
  - OS results in the PD-L1 IC+ population were consistent with the first and second interim analyses
    - OS HR, 0.62 (95% CI: 0.45, 0.86) in the first interim analysis and 0.71 (95% CI: 0.54, 0.93) in the second interim analysis
- With additional follow-up, A + nP remained safe and tolerable
  - The safety profile was consistent with those of the individual treatment components
  - No new safety signals were identified
- **These results support a positive benefit-risk profile for A + nP as first-line therapy in patients with PD-L1 IC+ mTNBC**

Emens LA. ESMO 2020. IMpassion130 Final OS.

IMpassion131

- Metastatic or unresectable locally advanced TNBC
- No prior chemotherapy or targeted therapy for advanced TNBC
- Previous eBC treatment completed ≥12 months before randomisation
- Taxane eligible
- Measurable disease
- ECOG PS 0/1

R
2:1

Atezolizumab 840 mg d1 & 15 + paclitaxel 90 mg/m² d1, 8 & 15

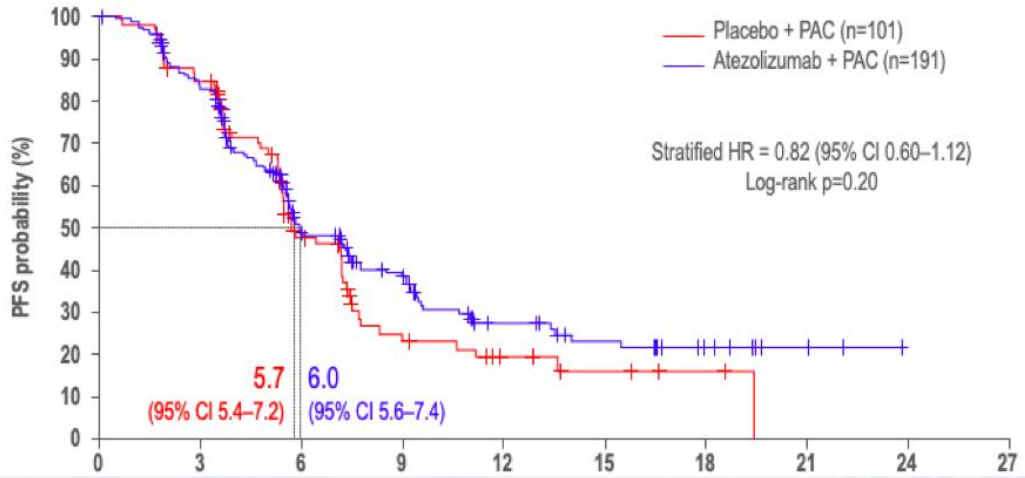
8–10 mg dexamethasone or equivalent for at least the first 2 infusions, cycles repeated q28d

Placebo d1 & 15 + paclitaxel 90 mg/m² d1, 8 & 15

VIRTUAL 2020 ESMO congress

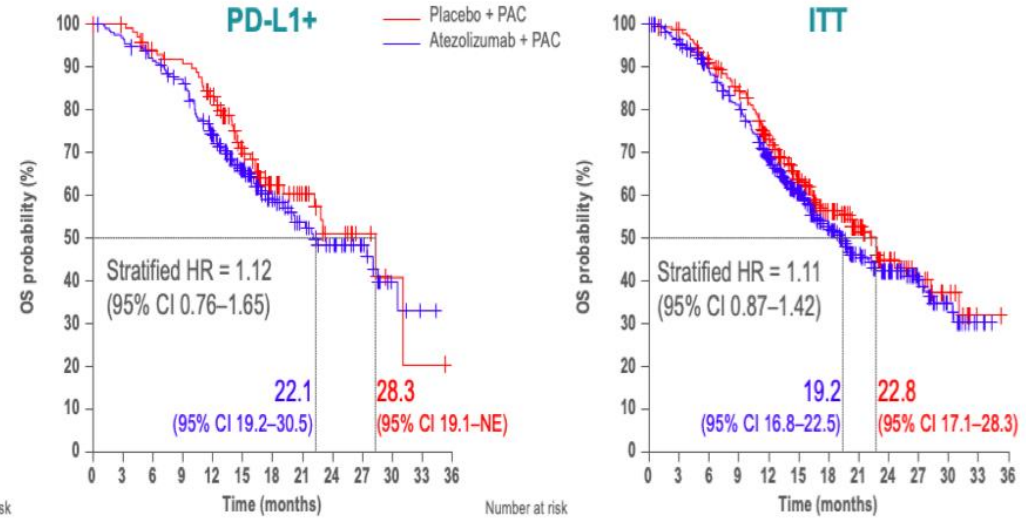
Primary analysis: PFS in the PD-L1+ population

Events in 61% of patients (data cut-off: 15 Nov 2019)



VIRTUAL 2020 ESMO congress

- Updated OS
- Data cut-off 19 Aug 2020



Miles et al. Annals Oncol 2021

Aprobaciones Tecentriq mTNBC

2019

JAN | FEB | MAR | APR | MAY | JUN | JUL | AUG | SEP | OCT | NOV | DEC

8 Marzo 2019 – **Aprobación FDA**

29 Agosto 2019 – **Aprobación EMA**

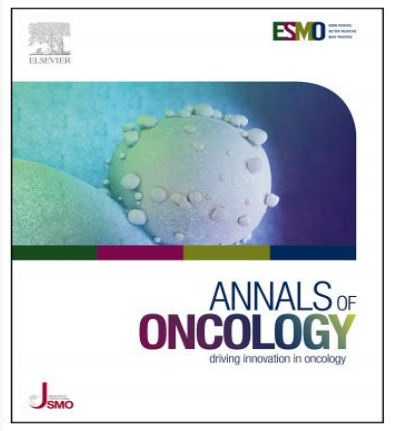
1 de Agosto 2021 **-Precio reembolso (acuerdo de pago por resultados)**

Tecentriq® en combinación con nab-paclitaxel está indicado para el tratamiento de pacientes adultos con **cáncer de mama triple negativo (CMTN)** localmente avanzado irresecable o metastásico cuyos tumores tengan una expresión de PD-L1 ≥ 1% y que no hayan recibido quimioterapia previa frente a la metástasis.[3]

- La FDA también aprobó el **Test de VENTANA (SP142) como test validado para seleccionar pacientes para Tecentriq en CMTNm**

1. https://www.fda.gov/drugs/drug-approvals-and-databases
2. https://www.roche.com/media/releases/med-cor-2019-08-29.htm
3. Ficha técnica Tecentriq

Inclusión en guías



5th ESO-ESMO international consensus guidelines for advanced breast cancer[3]

Atezolizumab + nab-paclitaxel is an option for first-line therapy for PD-L1-positivea triple-negative
ABC, either de novo or at least 12 months since (neo)adjuvant ChT. ESMO-MCBS v1.1 score: 3. LoE/GoR:1/B

AGO
ARBEITSGEMEINSCHAFT GYNÄKOLOGISCHE ONKOLOGIE E.V.

AGO - German Gynecological Oncology Group[2]

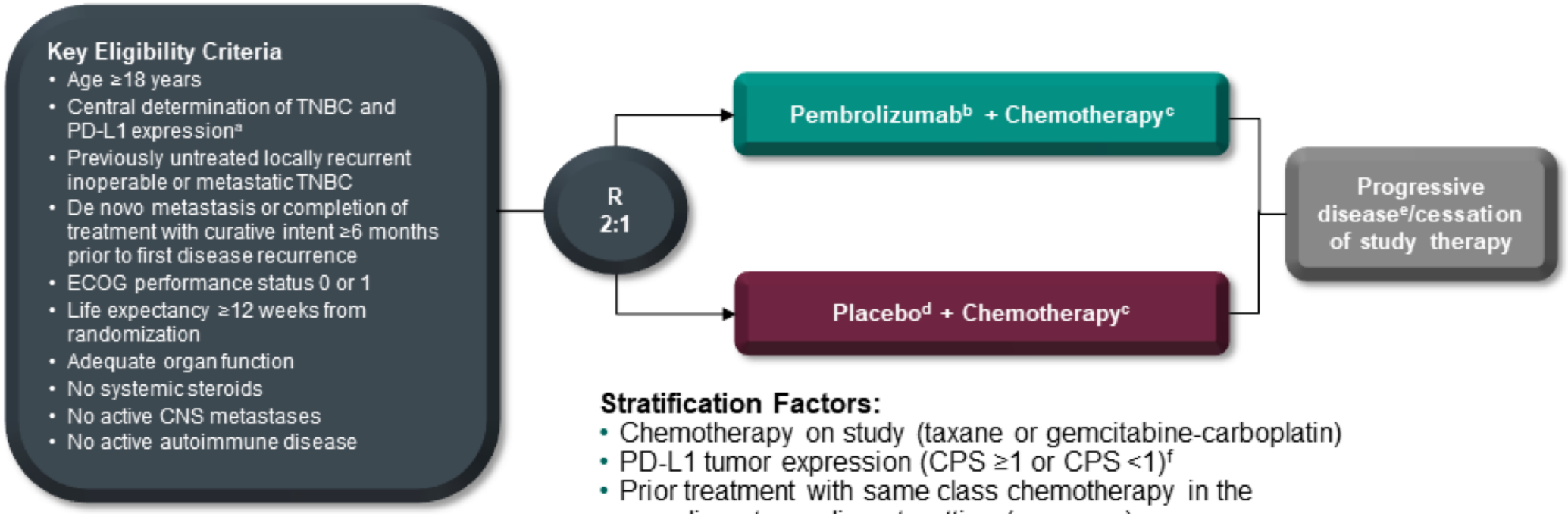
para el tratamiento de pacientes adultos con cáncer de mama triple negativo (CMTN) localmente avanzado irresecable o metastásico

2.German Gynecological Oncology Group. Guidelines of the AGO Breast Committee
3.Annals of oncology : official journal of the European Society for Medical Oncology, 2020

NUEVOS AVANCES

ESTRATEGIAS TERAPEUTICAS

KEYNOTE-355 Study Design (NCT02819518)



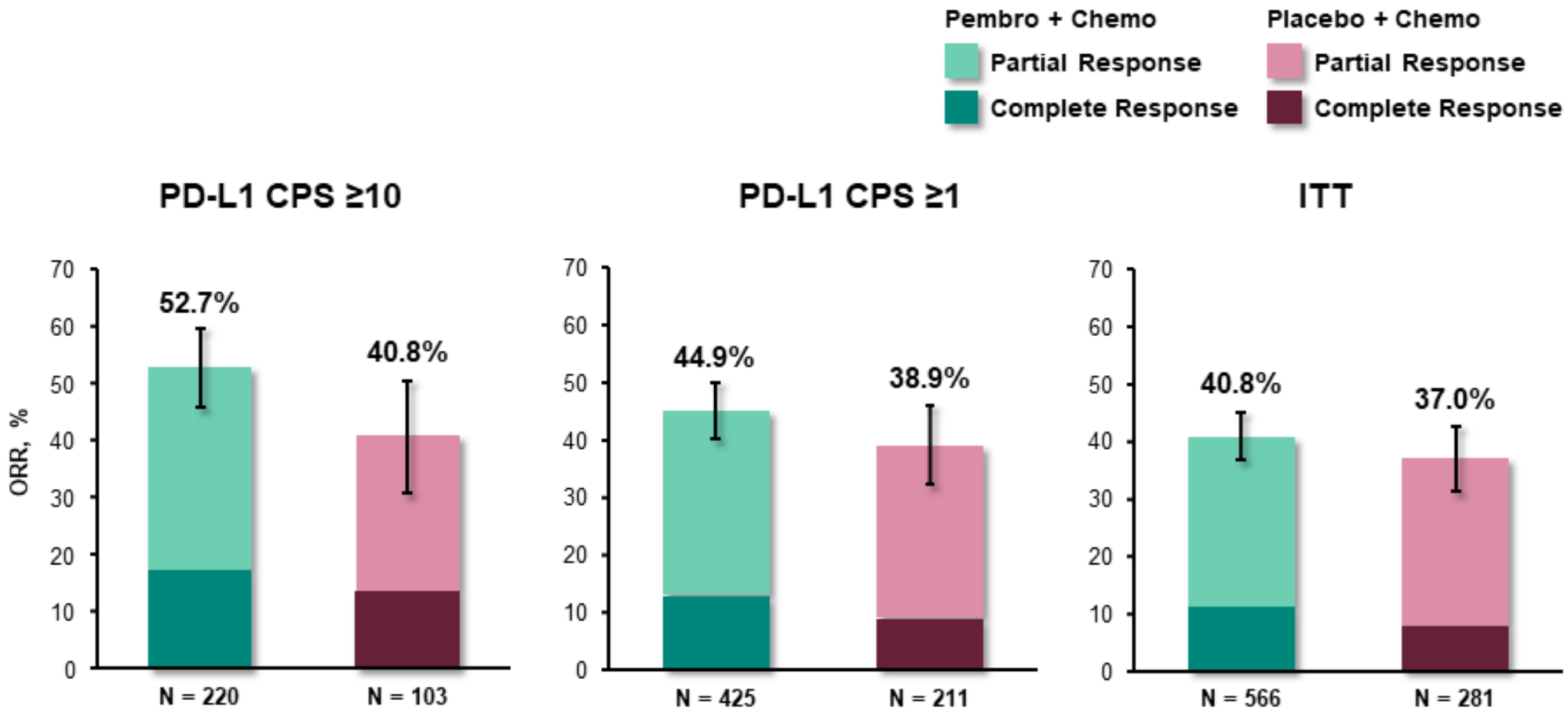
[c]Nab-paclitaxel 100 mg/m^2 IV on days 1, 8, and 15 every 28 days. [c]Paclitaxel 90 mg/m^2 IV on days 1, 8, and 15 every 28 days. [d]Gemcitabine and carboplatin: 1000 mg/m^2 and AUC 2 on days 1 and 8 every 21 days.

- Primary Endpoints
  - PFS[a] in PD-L1 CPS ≥10, CPS ≥1, and ITT populations
  - OS in PD-L1 CPS ≥10, CPS ≥1, and ITT populations

Secondary Endpoints
- ORR[a]
- DOR[a]
- DCR[a,b]
- Safety in all treated patients

H. Rugo KN355 ESMO 2021

Objective Response Rate



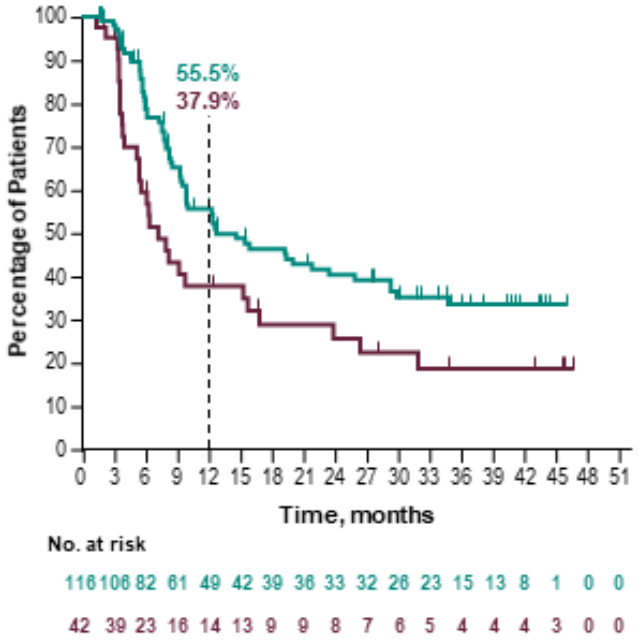
Data cutoff: June 15, 2021.

H. Rugo KN355 ESMO 2021

Duration of Response

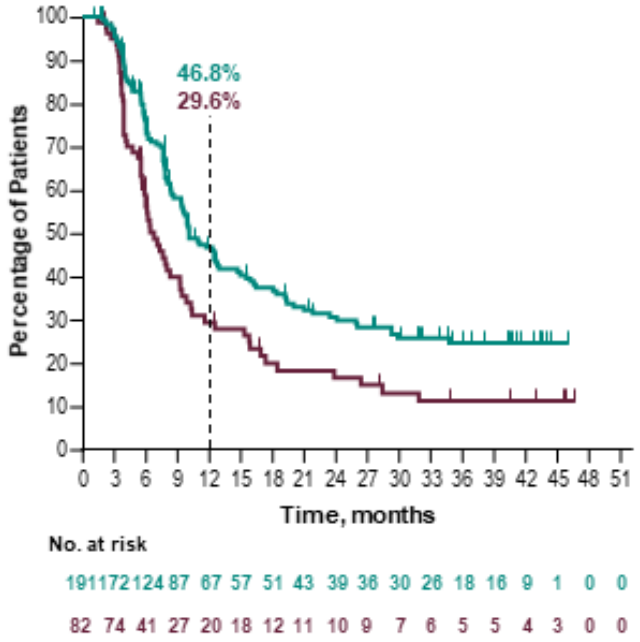
PD-L1 CPS ≥10

Duration of Response	Median, mo (range)
Pembro + Chemo	12.8 (1.6+ to 45.9+)
Placebo + Chemo	7.3 (1.5 to 46.6+)



PD-L1 CPS ≥1

Duration of Response	Median, mo (range)
Pembro + Chemo	10.1 (1.0+ to 45.9+)
Placebo + Chemo	6.8 (1.5 to 46.6+)



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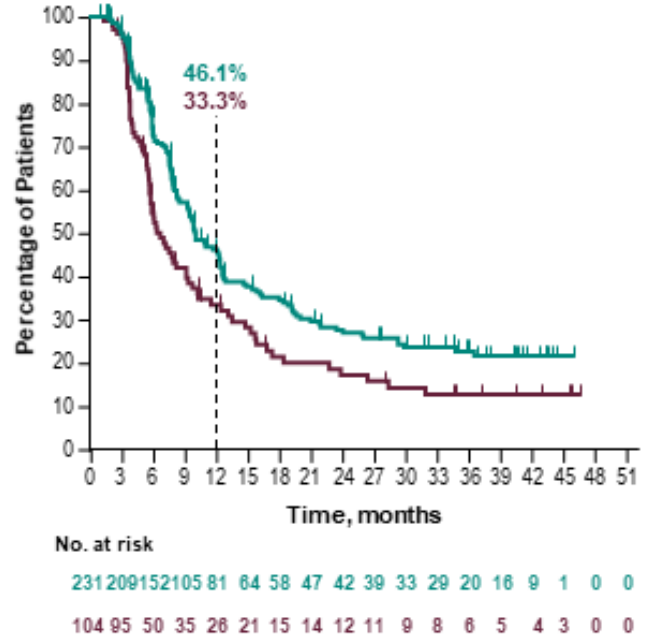
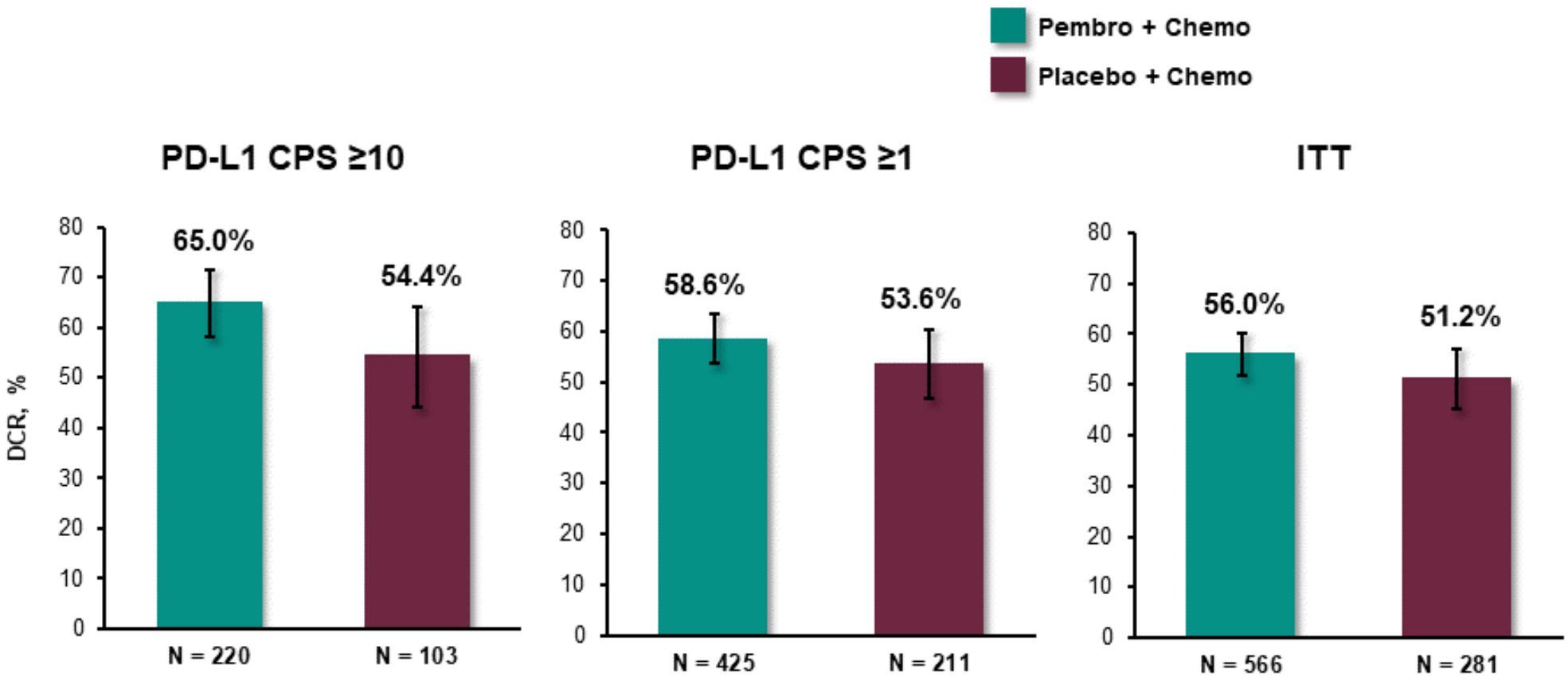
Duration of Response	Median, mo (range)
Pembro + Chemo	10.1 (1.0+ to 45.9+)
Placebo + Chemo	6.5 (1.5 to 46.6+)



"+" indicates there is no progressive disease by the time of last disease assessment. Data cutoff: June 15, 2021.

H. Rugo KN355 ESMO 2021

Disease Control Rate



DCR = CR+PR+SD ≥24 weeks. Data cutoff: June 15, 2021.

EFFICACY FINAL ANALYSIS

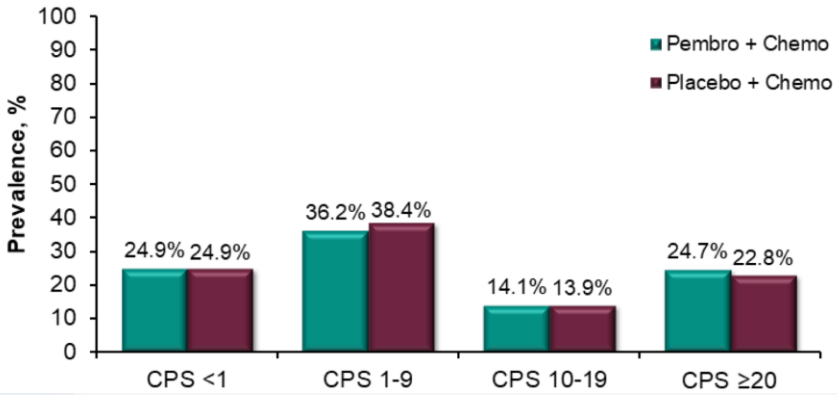
Baseline Characteristics: ITT

Characteristic, n (%)	All Patients, N = 847	
	Pembro + Chemo N = 566	Placebo + Chemo N = 281
Age, median (range), yrs	53 (25-85)	53 (22-77)
ECOG PS 1	232 (41.0)	108 (38.4)
PD-L1–positive CPS ≥1	425 (75.1)	211 (75.1)
PD-L1–positive CPS ≥10	220 (38.9)	103 (36.7)
Chemotherapy on study		
Taxane	255 (45.1)	127 (45.2)
Gemcitabine/Carboplatin	311 (54.9)	154 (54.8)
Prior same-class chemotherapy		
Yes	124 (21.9)	62 (22.1)
No	442 (78.1)	219 (77.9)
Disease-free interval		
de novo metastatic disease	168 (29.7)	84 (29.9)
<12 months	125 (22.1)	50 (17.8)
≥12 months	270 (47.7)	147 (52.3)

Data cutoff: June 15, 2021.

In this analysis, we assessed outcomes in subgroups of patients by additional CPS cut-offs

Prevalence of Additional PD-L1 CPS Subgroups



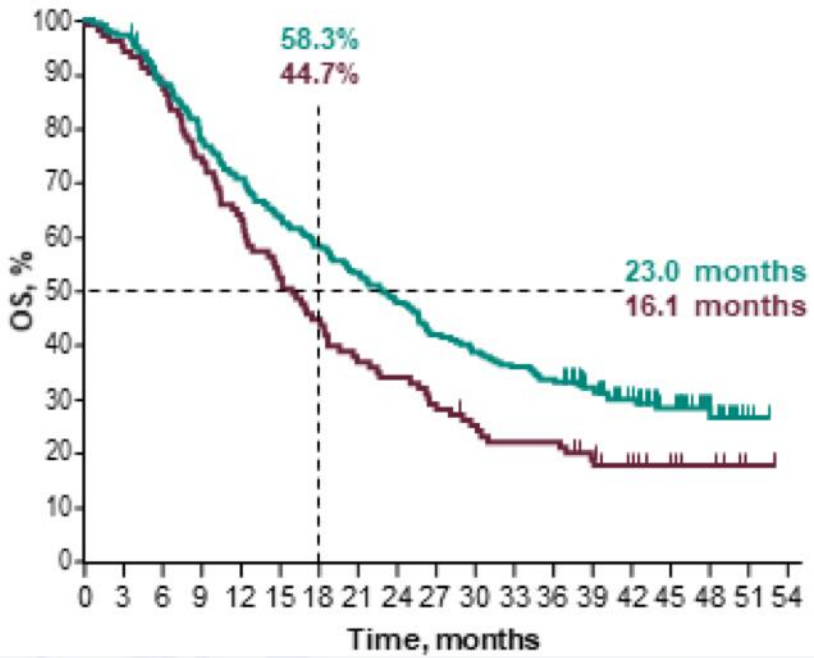
San Antonio Breast Cancer Symposium®, December 7-10, 2021

J Cortes KN355 SABCS 2021

Overall Survival at Final Analysis

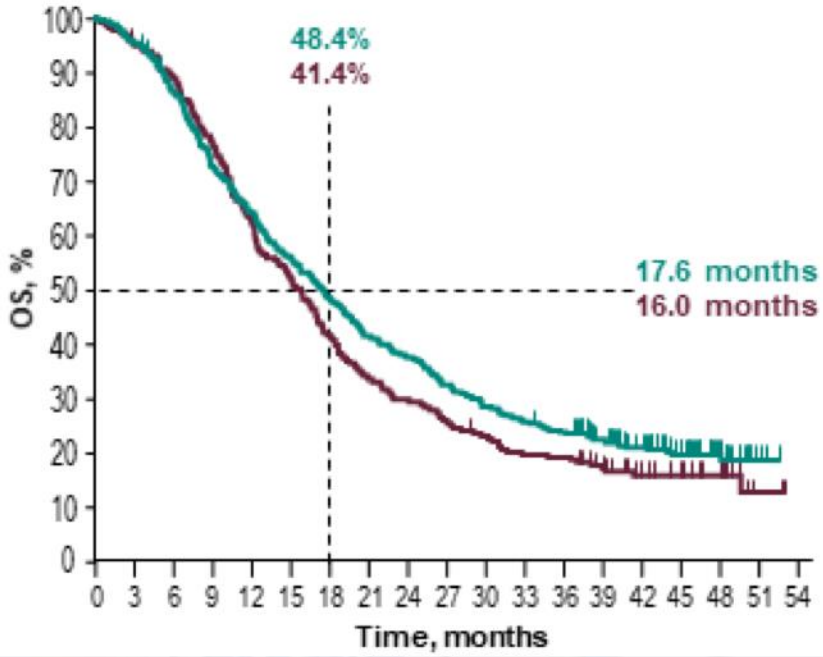
PD-L1 CPS ≥10

	n/N	Events	HR (95% CI)	*P*-value (one-sided)
Pembro + Chemo	155/220	70.5%	0.73 (0.55-0.95)	0.0093[a]
Placebo + Chemo	84/103	81.6%		



PD-L1 CPS ≥1

	n/N	Events	HR (95% CI)	*P*-value (one-sided)
Pembro + Chemo	336/425	79.1%	0.86 (0.72-1.04)	0.0563[b]
Placebo + Chemo	177/211	83.9%		



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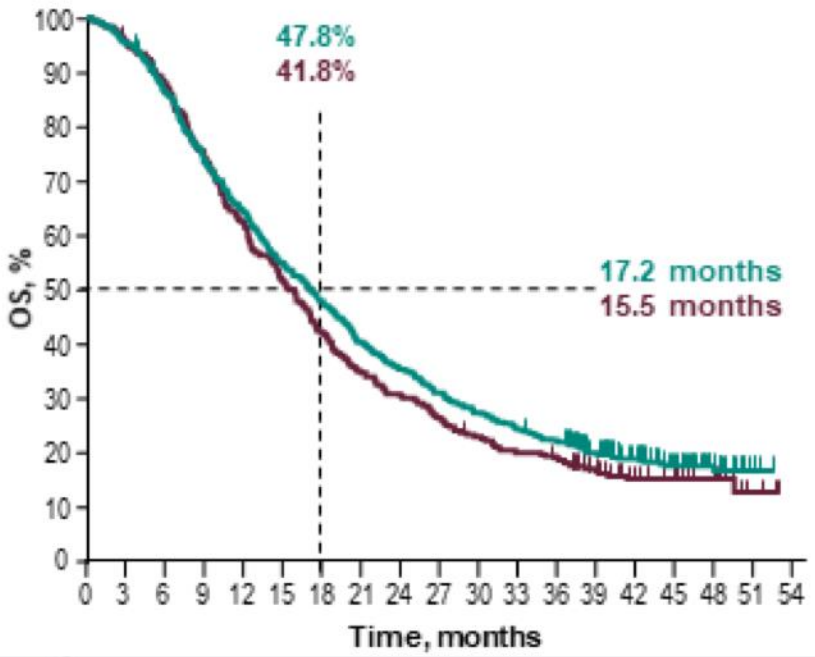
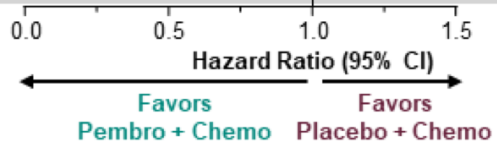
	n/N	Events	HR (95% CI)
Pembro + Chemo	460/566	81.3%	0.89 (0.76-1.05)[c]
Placebo + Chemo	238/281	84.7%	

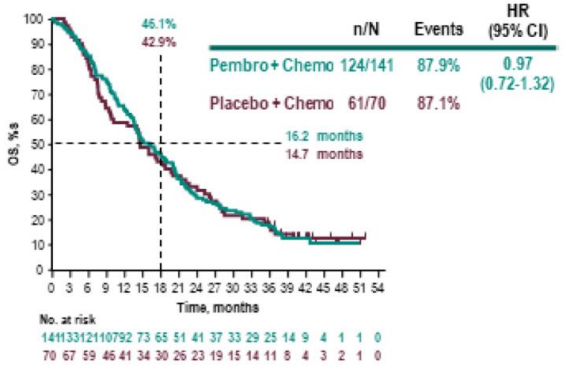


Overall Survival in Additional PD-L1 CPS Subgroups

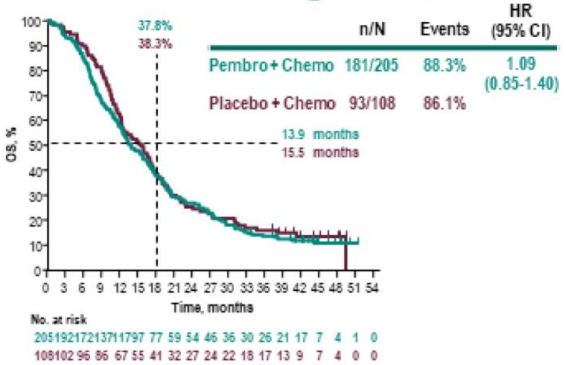
Subgroup	Median OS (mo) Patients *n*	Pembro + Chemo	Patients *n*	Placebo + Chemo	Hazard Ratio (95% CI)
Overall	566	17.2	281	15.5	0.89 (0.76 to 1.05)
PD-L1 CPS <1	141	16.2	70	14.7	0.97 (0.72 to 1.32)
PD-L1 CPS 1-9	205	13.9	108	15.5	1.09 (0.85 to 1.40)
PD-L1 CPS 10-19	80	20.3	39	17.6	0.71 (0.46 to 1.09)
PD-L1 CPS ≥20	140	24.0	64	15.6	0.72 (0.51 to 1.01)



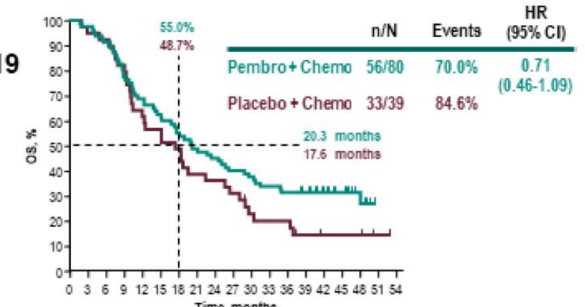
PD-L1 CPS <1



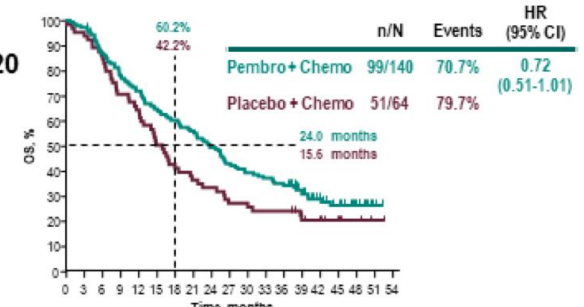
PD-L1 CPS 1-9



PD-L1 CPS 10-19



PD-L1 CPS ≥20



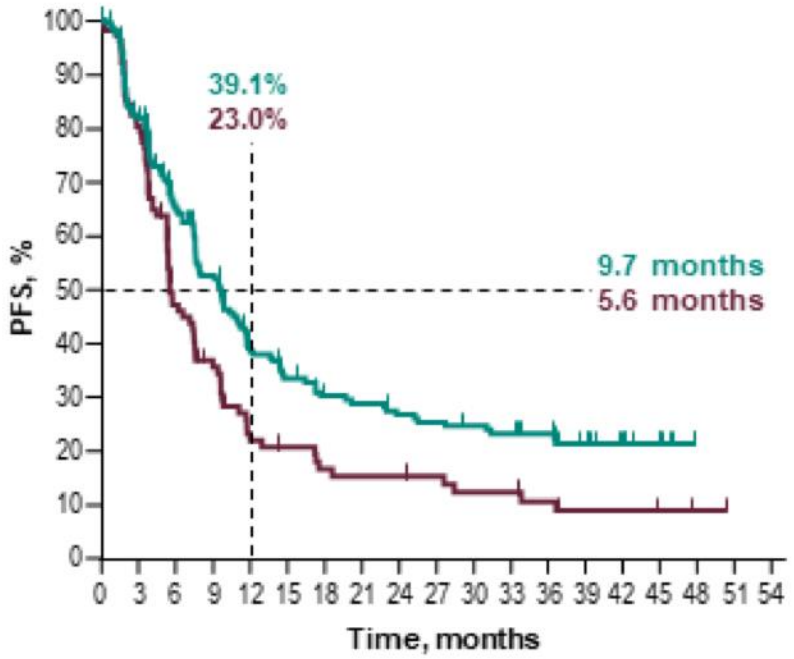
San Antonio Breast Cancer Symposium®, December 7-10, 2021

J Cortes KN355 SABCS 2021

Progression-Free Survival at Final Analysis

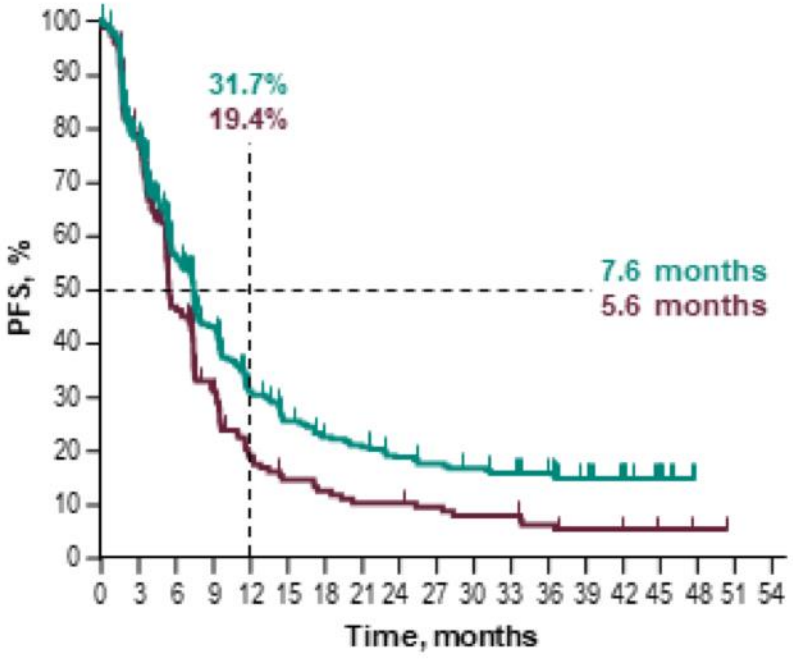
PD-L1 CPS ≥10

	n/N	Events	HR (95% CI)
Pembro + Chemo	144/220	65.5%	0.66 (0.50-0.88)
Placebo + Chemo	81/103	78.6%	



PD-L1 CPS ≥1

	n/N	Events	HR (95% CI)
Pembro + Chemo	299/425	70.4%	0.75 (0.62-0.91)
Placebo + Chemo	166/211	78.7%	



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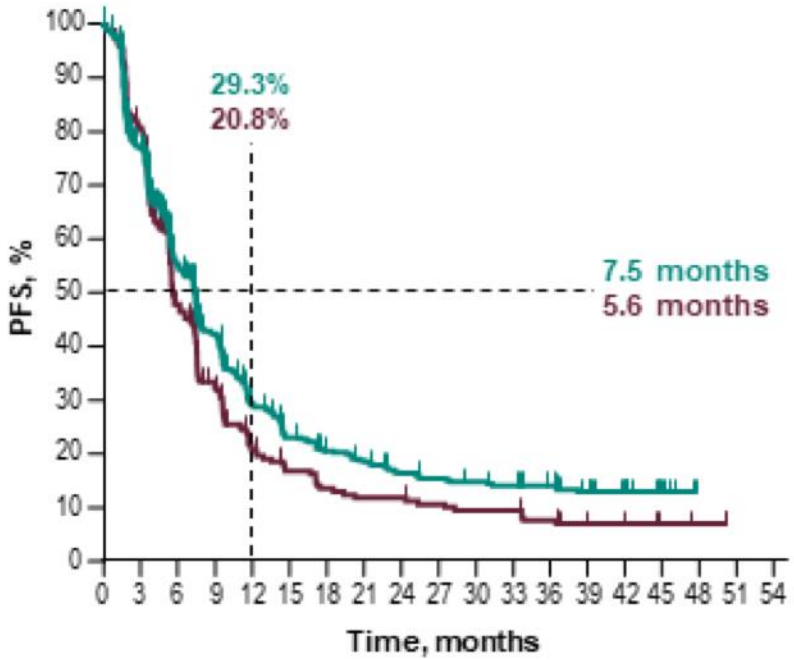
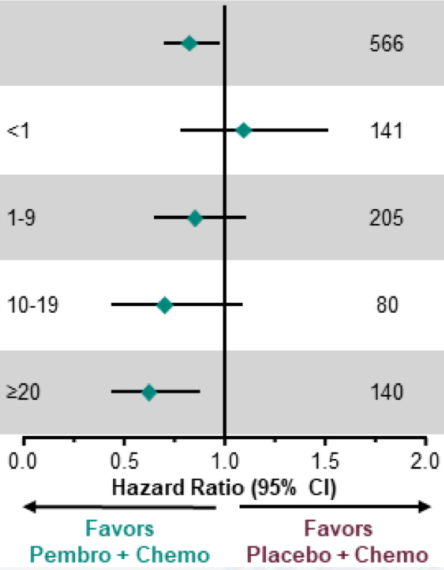
	n/N	Events	HR (95% CI)
Pembro + Chemo	406/566	71.7%	0.82 (0.70-0.98)
Placebo + Chemo	217/281	77.2%	



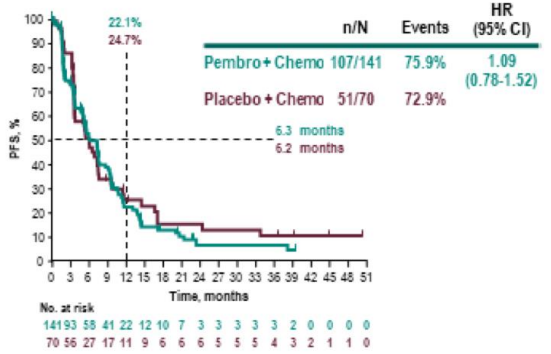
Progression-Free Survival in Additional PD-L1 CPS Subgroups

"Tratamiento médico del cáncer en el año 2022"

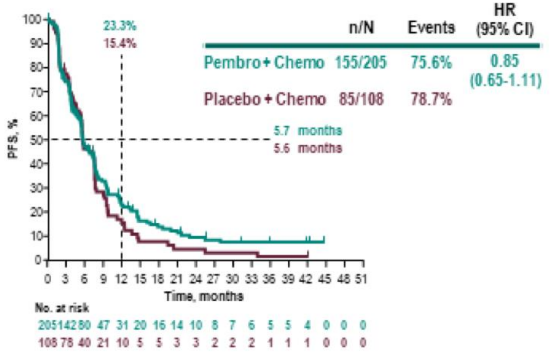
Subgroup	Patients *n*	Median PFS (mo) Pembro + Chemo	Patients *n*	Median PFS (mo) Placebo + Chemo	Hazard Ratio (95% CI)
Overall	566	7.5	281	5.6	0.82 (0.70 to 0.98)
PD-L1 CPS <1	141	6.3	70	6.2	1.09 (0.78 to 1.52)
PD-L1 CPS 1-9	205	5.7	108	5.6	0.85 (0.65 to 1.11)
PD-L1 CPS 10-19	80	9.9	39	7.6	0.70 (0.44 to 1.09)
PD-L1 CPS ≥20	140	9.2	64	5.4	0.62 (0.44 to 0.88)



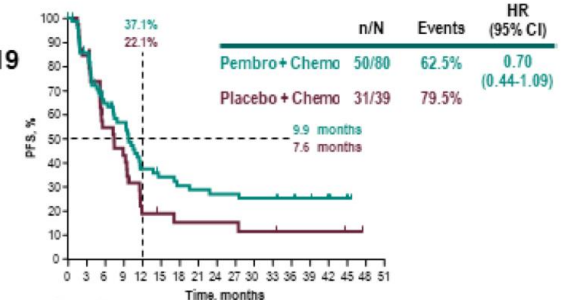
PD-L1 CPS <1



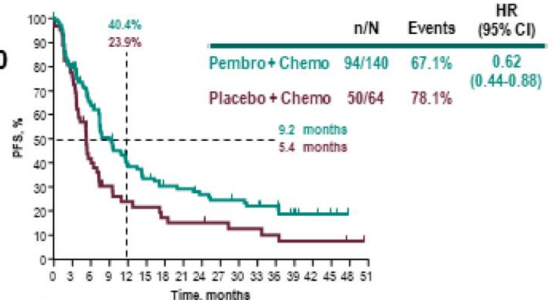
PD-L1 CPS 1-9



PD-L1 CPS 10-19



PD-L1 CPS ≥20



Summary and Conclusions

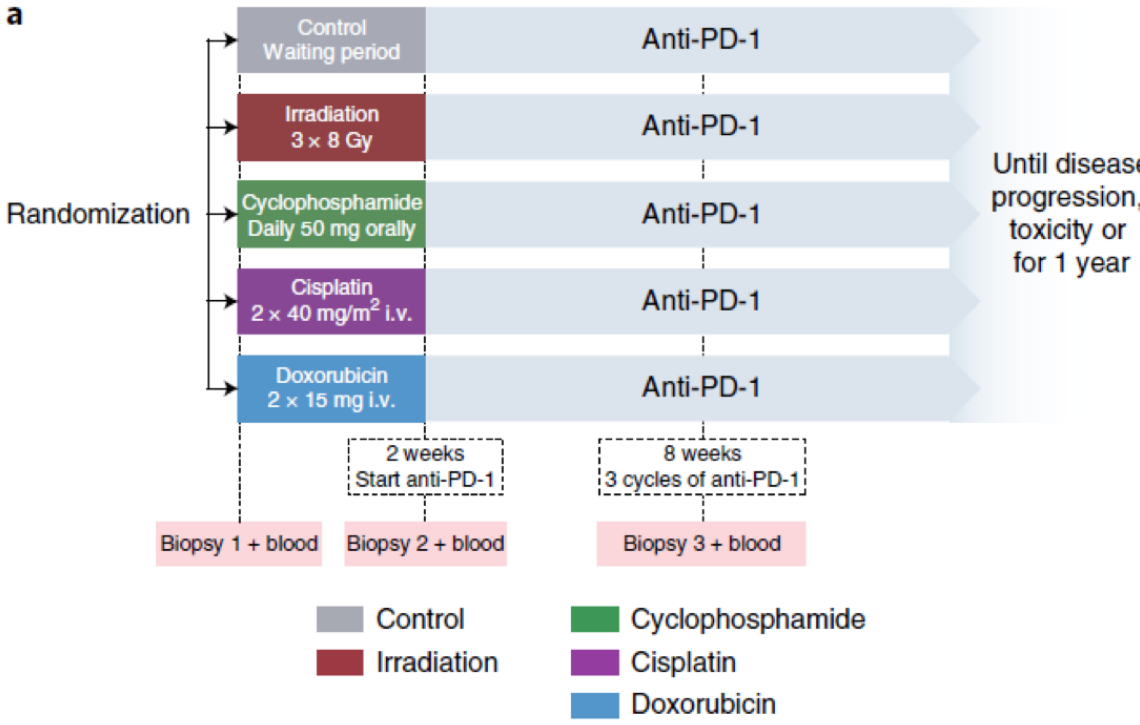
- Pembrolizumab + chemotherapy resulted in statistically significant and clinically meaningful improvements in PFS and OS versus chemotherapy alone for the first-line treatment of PD-L1 CPS ≥10 metastatic TNBC, meeting the dual primary study endpoints
- CPS ≥10 is a reasonable cut-off to define the population of patients with metastatic TNBC expected to derive treatment benefit from pembrolizumab + chemotherapy
- Safety was consistent with the known profiles of each regimen, with no new safety concerns
- These results provide further support for pembrolizumab in combination with chemotherapy as a new standard-of-care treatment regimen for patients with locally recurrent unresectable or metastatic TNBC whose tumors express PD-L1 (CPS ≥10)

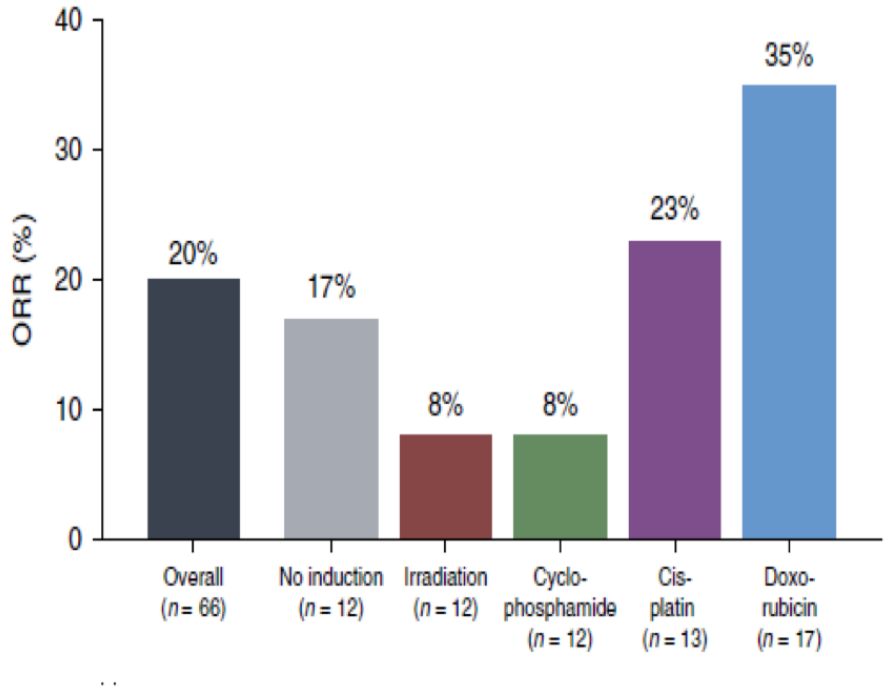
¿Qué INMUNOTERAPIA? ¿ Qué QUIMIOTERAPIA? ¿ Cómo SELECCIONAMOS? ¿ Biomarcadores?……

¿ QUÉ QUIMIOTERAPIA?

Which is the ideal partner?

The TONIC trial





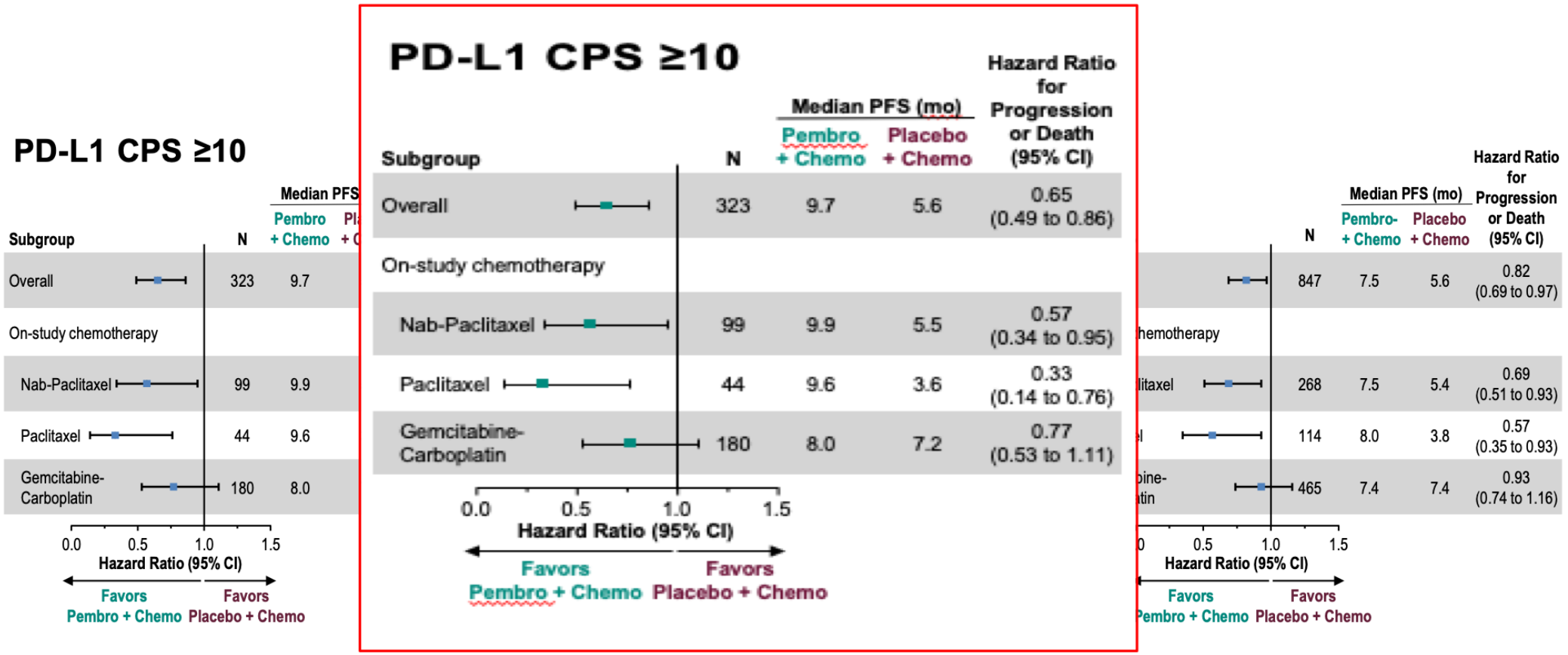
Voorwerk L, et al. Nat Med 2019

Immunotherapy: First-Line Rx for mTNBC

	IMPASSION 131	IMPASSION 130	KEYNOTE 355
N (PD-L1+)	943 (292, 45%) ≥1%	902 (369, 41%) ≥1%	847 (332, 38%) CPS≥10
Randomization and Treatment	2:1 Paclitaxel 90 mg/m2 Atezolizumab **NEGATIVO**	1:1 nab-Paclitaxel 100 mg/m2 Atezolizumab	2:1 Pac/nab/gem+carbo Pembrolizumab
de novo	28-30%	~37% (no chemo)	30%
Prior taxane	51-53%	51%	45%
PFS in PD-L1+	5.7 → 6 mo HR 0.82 P=0.2	5 → 7.5mo HR 0.62 P<0.0001	5.6 → 9.7mo HR0.65 P=0.0012
OS benefit	No	7 + mo	7 + mo!

Miles et al, Ann Oncol 2021; Schmid et al, NEJM 2018 & Emens et al, Ann Oncol 2021; Cortes et al, Lancet 2020; Rugo ESMO 2021

Progression-Free Survival in Subgroups by On-Study



Rugo H SABCS 2020

San Antonio Breast Cancer Symposium®, December 7-10, 2021 J Cortes KN355 SABCS 2021

Baseline Characteristics: ITT

Characteristic, n (%)	All Patients, N = 847	
	Pembro + Chemo N = 566	Placebo + Chemo N = 281
Age, median (range), yrs	53 (25-85)	53 (22-77)
ECOG PS 1	232 (41.0)	108 (38.4)
PD-L1–positive CPS ≥1	425 (75.1)	211 (75.1)
PD-L1–positive CPS ≥10	220 (38.9)	103 (36.7)
Chemotherapy on study		
Taxane	255 (45.1)	127 (45.2)
Gemcitabine/Carboplatin	311 (54.9)	154 (54.8)
Prior same-class chemotherapy		
Yes	124 (21.9)	62 (22.1)
No	442 (78.1)	219 (77.9)
Disease-free interval		
de novo metastatic disease	168 (29.7)	84 (29.9)
<12 months	125 (22.1)	50 (17.8)
≥12 months	270 (47.7)	147 (52.3)

Data cutoff: June 15, 2021.

KEYNOTE 355

IMPASSION 130

Characteristic, n (%)		PD-L1+ population		ITT population	
		Placebo + PAC (n=101)	Atezo + PAC (n=191)	Placebo + PAC (n=220)	Atezo + PAC (n=431)
Median (range) age, years		53 (25–78)	55 (23–83)	53 (25–81)	54 (22–85)
ECOG PS	0	59 (58)	118 (62)	130 (59)	262 (61)
	1	42 (42)	73 (38)	90 (41)	169 (39)
Liver metastases		24 (24)	37 (19)	61 (28)	118 (27)
>3 metastatic sites		13 (13)	35 (18)	48 (22)	105 (24)
PD-L1+[a]		101 (100)	191 (100)	101 (46)	191 (44)
Prior taxane		54 (53)	97 (51)	107 (49)	208 (48)
Prior anthracycline		50 (50)	98 (51)	110 (50)	212 (49)
de novo mBC		30 (30)	53 (28)	69 (31)	131 (30)

¿ QUÉ QT ASOCIAR A IO?

- In actual clinical scenario (prior taxane/platinum in neo-adj setting):

- Keynote355 and IMpassion130 included pts with taxanes in neo-adjuvant setting > 6 mo or > 12 mo respectively

- Could rechallenge with taxane, but no data on rechallenge with platinum

-Consider Nab-paclitaxel + Pembrolizumab or Atezolizumab (or Platinum if > 12 m ???)

- In chemo naive, de novo 1st line MBC TNBC setting, no known best chemotherapy backbone at present

TOXICIDAD

Toxicities IO & chemotherapy: Immune-Mediated Adverse Events

IMpassion 130[1]

G≥3 AESI: 9%

AE (medical concept), n (%)[a]	Atezolizumab + *nab*-paclitaxel (n = 460)		Placebo + *nab*-paclitaxel (n = 430)	
	Any grade	Grade 3-4	Any grade	Grade 3-4
Hepatitis (diagnosis)[b]	11 (2)	7 (2)	7 (2)	1 (< 1)
Hypothyroidism	84 (18)	0	19 (4)	0
Hyperthyroidism	22 (5)	1 (< 1)	5 (1)	0
Adrenal insufficiency	5 (1)	1 (< 1)	0	0
Pneumonitis	18 (4)	2 (< 1)	1 (< 1)	0
Colitis	7 (2)	2 (< 1)	3 (1)	1 (< 1)
Pancreatitis[c]	2 (< 1)	1 (< 1)	0	0
Diabetes mellitus	1 (< 1)	1 (< 1)	3 (1)	2 (< 1)
Hypophysitis	1 (< 1)	1 (< 1)	0	0
Myositis	3 (1)	1 (< 1)	1 (< 1)	1 (< 1)
Rash	165 (36)	5 (1)	112 (26)	2 (1)
Severe cutaneous reactions	4 (1)	1 (< 1)	3 (1)	0

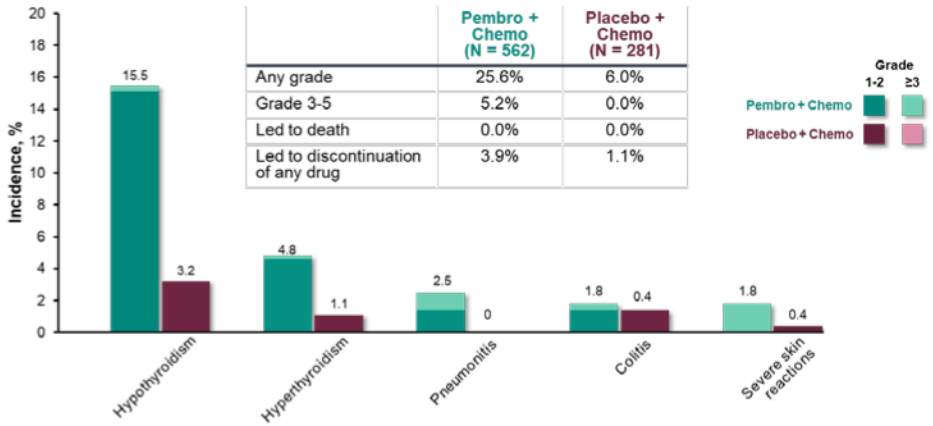
IMpassion 131[2]

G≥3 AESI: 10.2%

Immune-mediated AEs by medical concept, n (%)	Placebo + PAC (n=218)		Atezo + PAC (n=431)	
	Any grade	Grade 3/4[a]	Any grade	Grade 3/4[a]
Hepatitis (diagnosis)[b]	1 (0.5)	0	7 (1.6)	2 (0.5)
Pneumonitis	2 (0.9)	0	16 (3.7)	3 (0.7)
Hypothyroidism	9 (4.1)	0	55 (12.8)	0
Hyperthyroidism	0	0	22 (5.1)	0
Diabetes mellitus	2 (0.9)	2 (0.9)	4 (0.9)	3 (0.7)
Adrenal insufficiency	0	0	2 (0.5)	0
Infusion-related reactions	8 (3.7)	0	14 (3.2)	2 (0.5)
Pancreatitis	1 (0.5)	1 (0.5)	6 (1.4)	6 (1.4)
Colitis	2 (0.9)	2 (0.9)	3 (0.7)	1 (0.2)
Rash	67 (30.7)	2 (0.9)	137 (31.8)	4 (0.9)
Ocular inflammatory toxicity	1 (0.5)	0	4 (0.9)	0
Severe cutaneous reactions	3 (1.4)	0	1 (0.2)	0
Myositis	0	0	2 (0.5)[c]	0

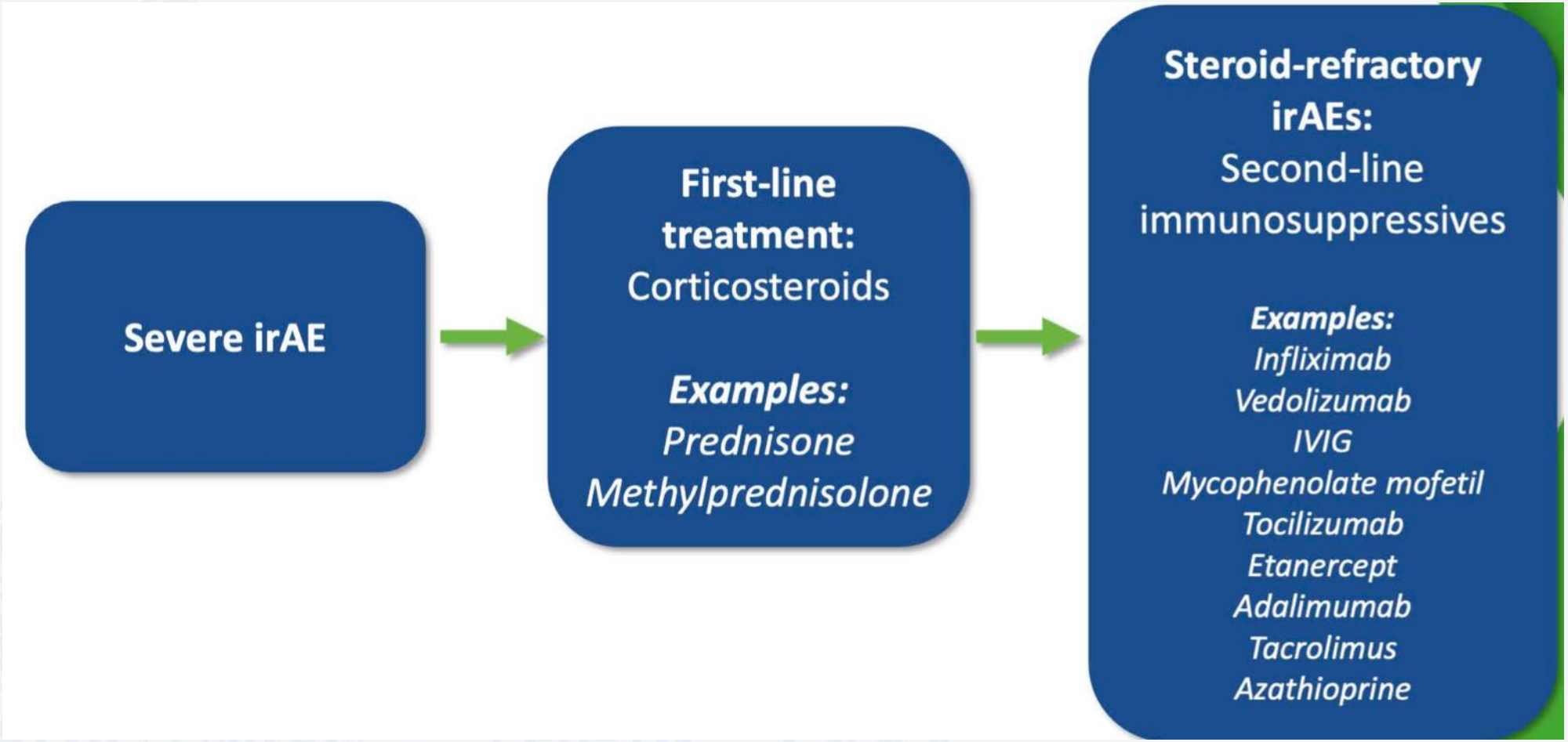
Keynote 355

G≥3 AESI: 5.2%



	Pembro + Chemo (N = 562)	Placebo + Chemo (N = 281)
Any grade	25.6%	6.0%
Grade 3-5	5.2%	0.0%
Led to death	0.0%	0.0%
Led to discontinuation of any drug	3.9%	1.1%

General irAE management



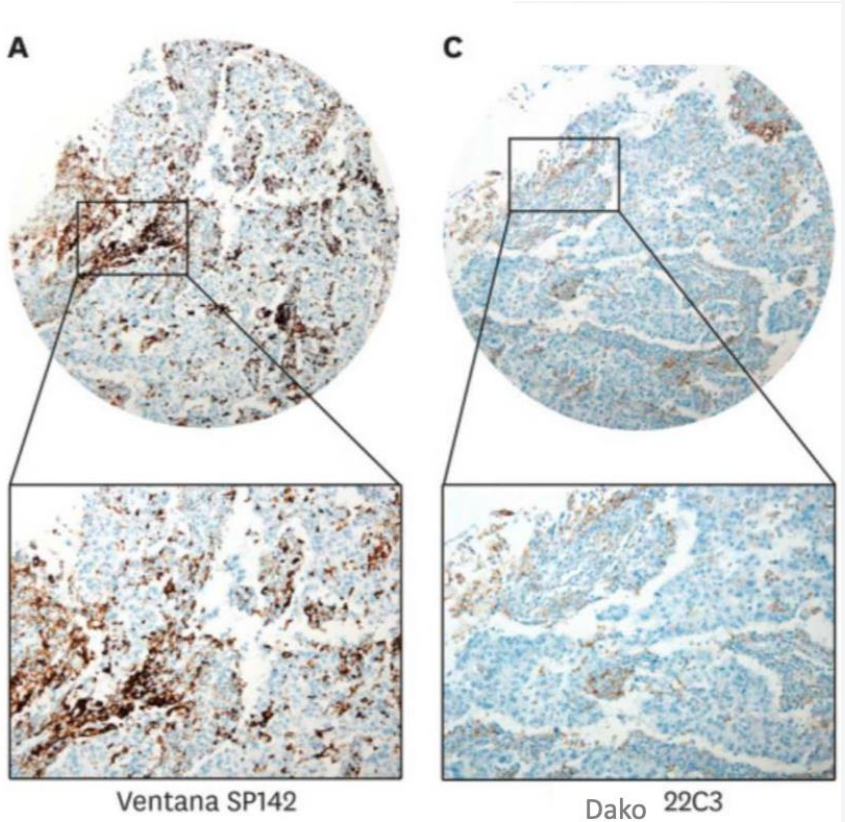
Brahmer, J Immunother Cancer 2021

DIAGNÓSTICO

PD-L1 assays in TNBC

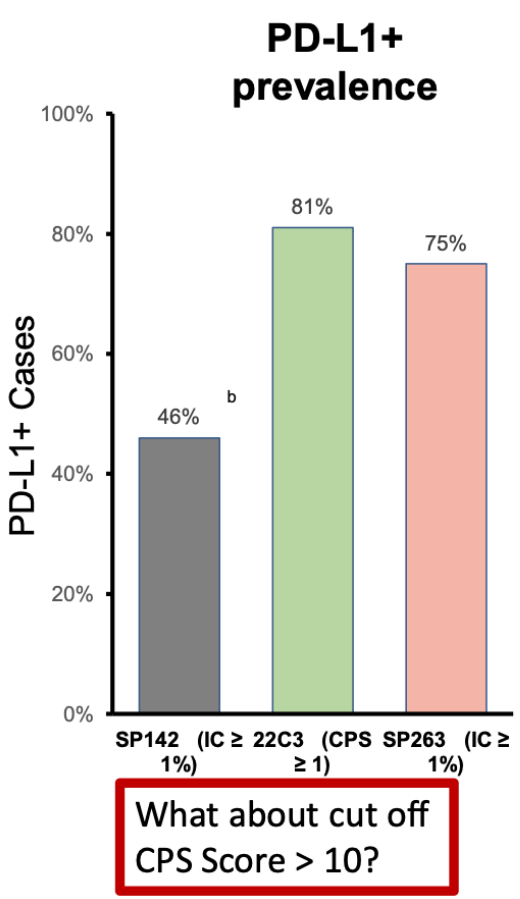
- **SP142**: IC ≥ 1%, companion diagnostic for atezolizumab
  Ventana (IC = immune cells)

- **22C3**: CPS ≥ 10, companion diagnostic for pembrolizumab
  Dako (CPS score)

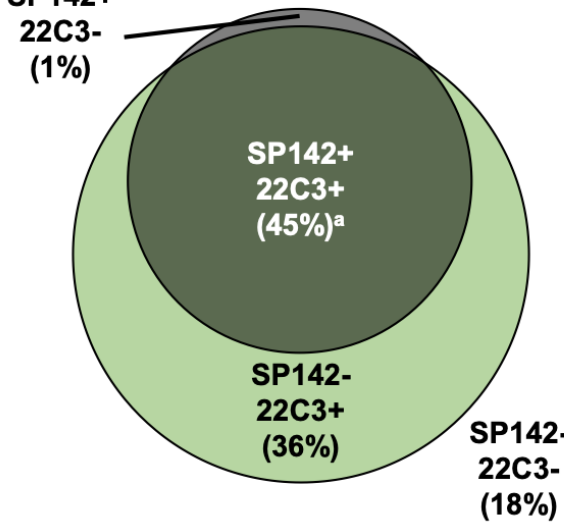


Lee J, Breast Cancer 2020

PD-L1 IHC assays: prevalence and analytical concordance

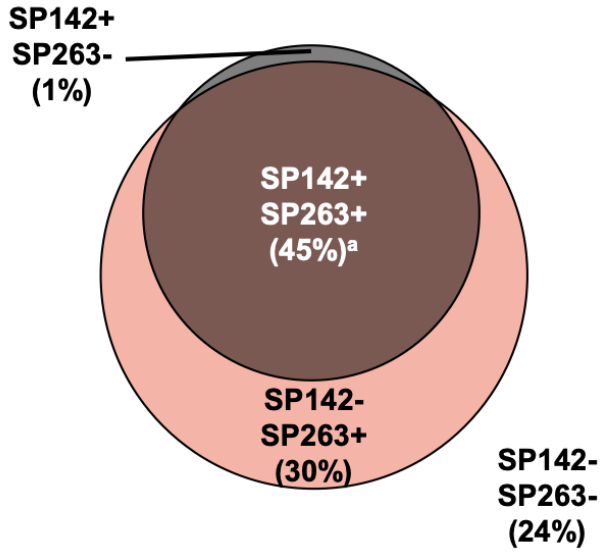


SP142 (IC 1%) and 22C3 (CPS 1)



OPA[c]	64%
PPA	98%
NPA	34%

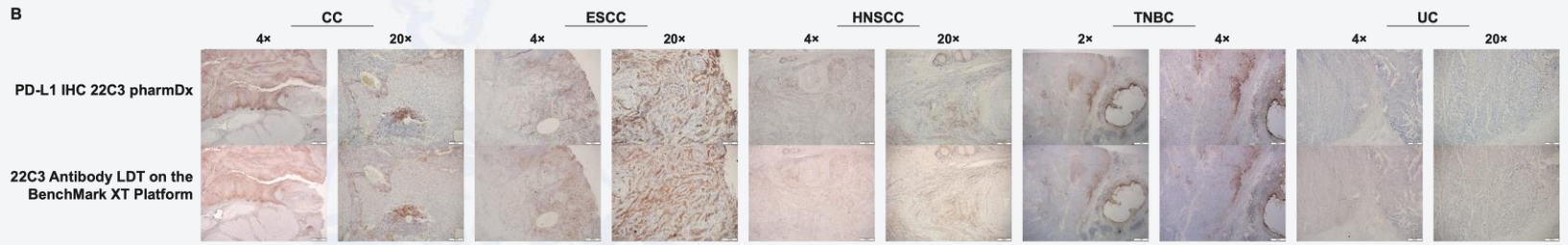
SP142 (IC 1%) and SP263 (IC 1%)



OPA[c]	69%
PPA	98%
NPA	45%

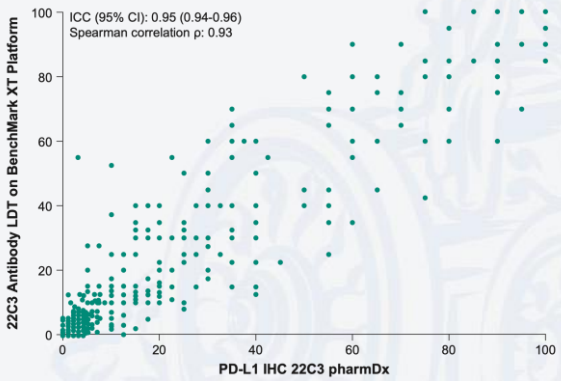
- USA: CPS score using 22C3 assay (as only pembrolizumab is now approved)
- Europa: SP 142 (Atezolizumab) and/or CPS score (22C3 assay), depending on country approval and reimbursement.

Analytical Comparison of a PD-L1 22C3 Antibody Laboratory-Developed Test Protocol on the Benchmark XT and PD-L1 IHC 22C3 pharmDx: Pan-Tumor and Triple-Negative Breast Cancer Samples

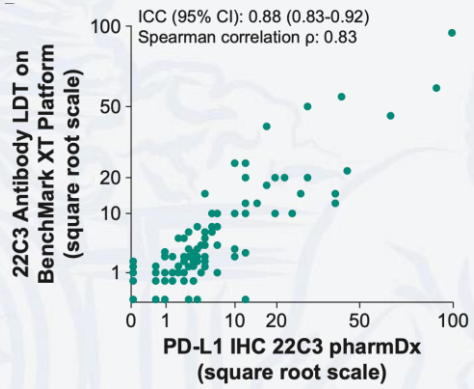


OBJETIVO: *To compare our PD-L1 22C3 antibody–based LDT on the BenchMark XT platform with the gold standard PD-L1 IHC 22C3 pharmDx,*

Pairwise Scatterplot Using the 22C3 Antibody LDT on the BenchMark XT Platform and PD-L1 IHC 22C3 pharmDx



Pan-Tumor (N = 522)



TNB(N=118)

CONCLUSIONES:

- Demostramos que nuestra LDT basada en anticuerpos 22C3 en la plataforma Ventana BenchMark XT arrojó una alta concordancia con el PD-L1 IHC 22C3 pharmDx aprobado por la FDA y/o con marca CE en un análisis pantumoral y cuando cada tipo de tumor se analizó por separado
- Estos hallazgos sugieren la comparabilidad de PD-L1 IHC 22C3 pharmDx con una LDT basada en el anticuerpo 22C3 en varios tipos de tumores

Presented at the Society for Immunotherapy Cancer 36th Annual Meeting & Pre-Conference Programs (SITC 2021); November 10-14, 2021; Washington, DC (Hybrid)

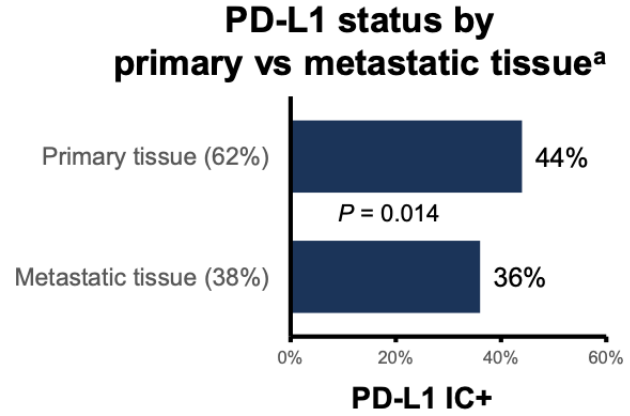
Laboratory-developed tests (LDTs)

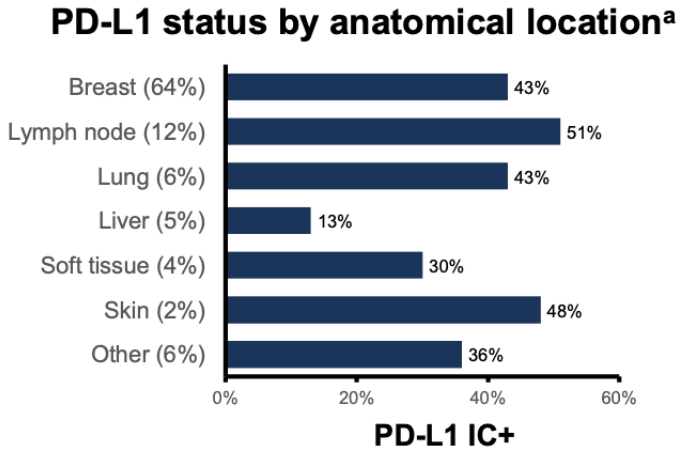
What site should I test for PD-L1?

Journal for ImmunoTherapy of Cancer

Comparison of PD-L1 protein expression between primary tumors and metastatic lesions in triple negative breast cancers

Mariya Rozenblit,[1] Richard Huang,[2] Natalie Danziger,[2] Priti Hegde,[2] Brian Alexander,[2] Shakti Ramkissoon,[2,3] Kim Blenman ,[1] Jeffrey S Ross,[2,4] David L Rimm ,[1,5] Lajos Pusztai[1]





- Higher % of PD-L1 IC + primary 63.7% vs. mets 42.2%
- Lower positivity rates in liver (17.4%), skin (23.8%) and bone (16.7%) metastasis

San Antonio Breast Cancer Symposium®, December 2021

Panel recommendations for biomarkers in breast cancer

Journal for ImmunoTherapy of Cancer

Society for Immunotherapy of Cancer (SITC) clinical practice guideline on immunotherapy for the treatment of breast cancer

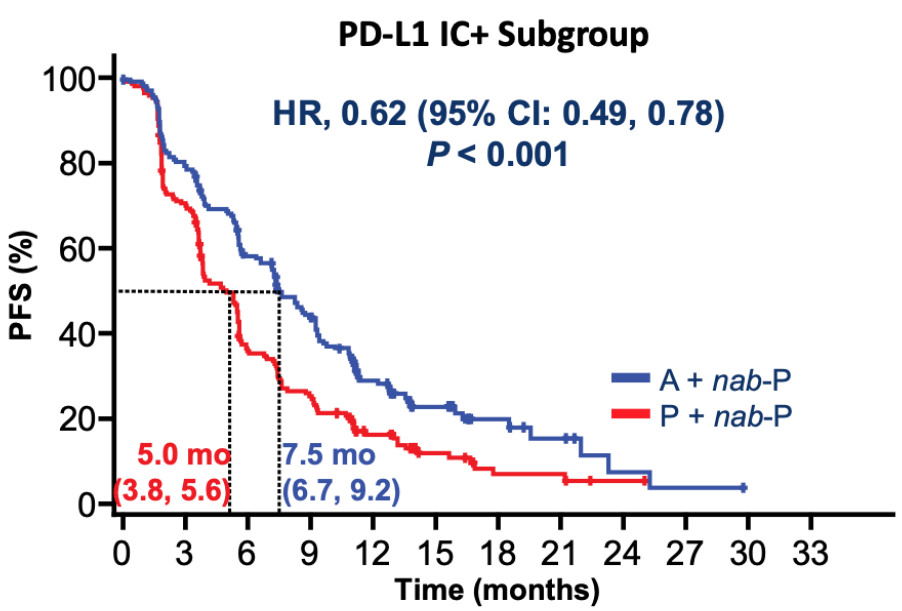
Leisha A Emens,[1] Sylvia Adams,[2] Ashley Cimino-Mathews,[3] Mary L Disis,[4] Margaret E Gatti-Mays,[5] Alice Y Ho,[6] Kevin Kalinsky,[7] Heather L McArthur,[8] Elizabeth A Mittendorf,[9,10] Rita Nanda,[11] David B Page,[12] Hope S Rugo,[13] Krista M Rubin,[14] Hatem Soliman,[15] Patricia A Spears,[16] Sara M Tolaney,[17] Jennifer K Litton[18]

- All patients with advanced TNBC should have tumor tissue tested for PD-L1, TMB and MSI by FDA-approved tests.
- All patients who are candidates for immunotherapy should have tumor tissue tested for PD-L1 at least once, irrespective of prior therapies.
- PD-L1 testing is not recommended for patients with early-stage breast cancer at this time.
- When considering metastatic sites to test for PD-L1, it is preferable to prioritize extrahepatic sites or the primary tumor, if available.
- Biomarker assessment, including repeat receptor profiles, PD-L1 and NGS should be considered at first relapse.

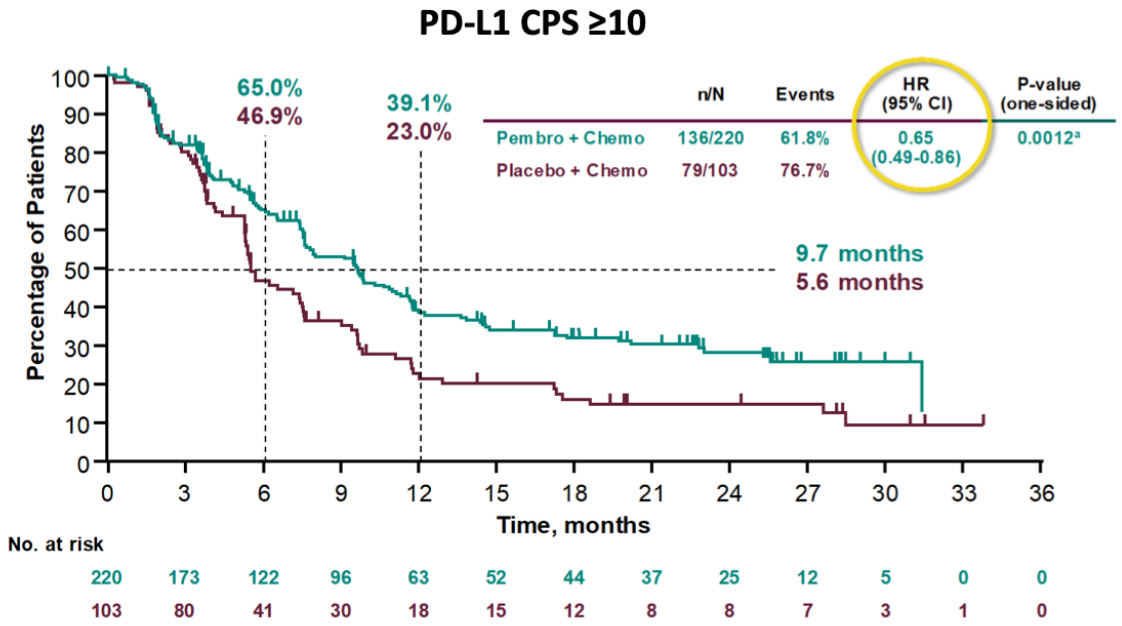
BIOMARCADORES: predictores de respuesta inmune.

PDL-1

PFS and OS benefit driven by PDL1+ subgroups



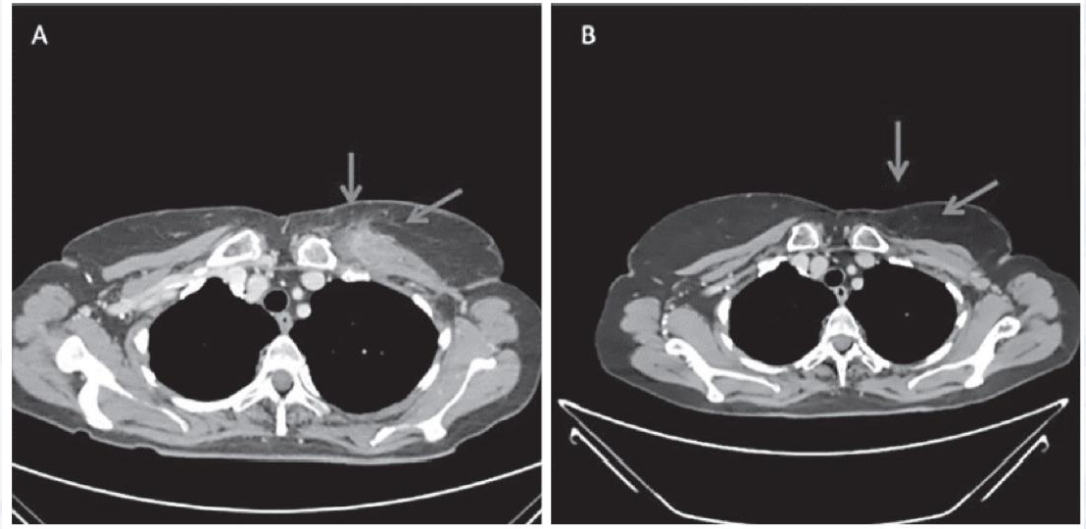
Schmid P, *New Engl J Med.* 2018

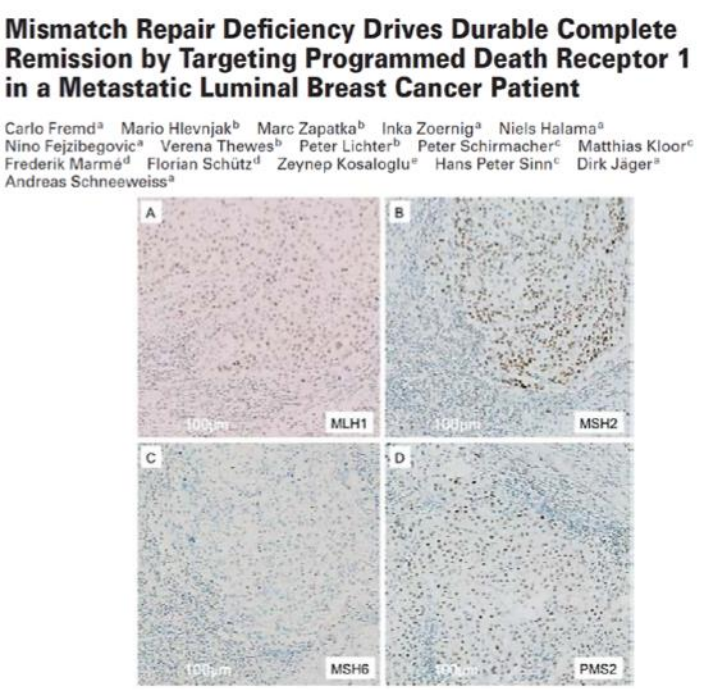


Cortes J, The Lancet 2021

MSI-H/dMMR

- En 2017, la FDA otorgó la aprobación acelerada a pembrolizumab para la primera indicación agnóstica de tumor agnostic (MSI-H tumores sólidos irresecables o metastásicos que habían progresado con terapias anteriores)
- • **Los cánceres de mama MSI-H/dMMR son muy raros: 2 % o menos, distribuidos en diferentes subtipos intrínsecos**
- • NGS como Foundation One CDx interroga 95 loci de microsatélites, pero fija su umbral contra los cánceres colorrectal y endometrial MSI-H.





TMB

Journal of Clinical Oncology > List of Issues > Volume 38, Issue 15_suppl >

BREAST CANCER—METASTATIC

Association of tumor mutational burden (TMB) and clinical outcomes with pembrolizumab (pembro) versus chemotherapy (chemo) in patients with metastatic triple-negative breast cancer (mTNBC) from KEYNOTE-119.

Eric P. Winer, Oleg Lipatov, Seock-Ah Im, Anthony Goncalves, Eva Muñoz-Couselo, Keun Seok Lee, ...

original reports

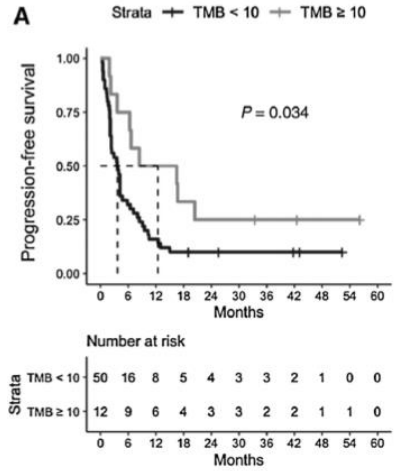
Pembrolizumab in Patients With Metastatic Breast Cancer With High Tumor Mutational Burden: Results From the Targeted Agent and Profiling Utilization Registry (TAPUR) Study

Ajjai S. Alva, MD[1]; Pam K. Mangat, MS[2]; Elizabeth Garrett-Mayer, PhD[2]; Susan Halabi, PhD[3]; Damien Hansra, MD[4]; Carmen J. Calfa, MD[5]; Maged F. Khalil, MD[6]; Eugene R. Ahn, MD[7]; Timothy L. Cannon, MD[8]; Pamela Crilley, DO[9]; Julie G. Fisher, MD[10]; Derrick S. Haslem, MD[11]; Sagun Shrestha, MD[12]; Kaitlyn R. Antonelli, BA[2]; Nicole L. Butler, MPH[2]; Sasha L. Warren, MS[2]; Andrew L. Rygiel, MPH[2]; Shamika Ranasinghe, MS[2]; Suanna S. Bruinooge, MPH[2]; and Richard L. Schilsky, MD[2]

CLINICAL CANCER RESEARCH | PRECISION MEDICINE AND IMAGING

Tumor Mutational Burden and *PTEN* Alterations as Molecular Correlates of Response to PD-1/L1 Blockade in Metastatic Triple-Negative Breast Cancer

Romualdo Barroso-Sousa[1,2], Tanya E. Keenan[1,2], Sonia Pernas[1,2,3], Pedro Exman[1,2], Esha Jain[1,4], Ana C. Garrido-Castro[1,2], Melissa Hughes[1], Brittany Bychkovsky[1,2], Renato Umeton[4,5], Janet L. Files[6], Neal I. Lindeman[6], Laura E. MacConaill[6], F. Stephen Hodi[1,2], Ian E. Krop[1,2], Deborah Dillon[6], Eric P. Winer[1,2], Nikhil Wagle[1,2], Nancy U. Lin[1,2], Elizabeth A. Mittendorf[2,7,8], Eliezer M. Van Allen[1,2,9], and Sara M. Tolaney[1,2]



- KEYNOTE-158 study that led to tissue agnostic FDA approval of Pembrolizumab for tumours with TMB>10 was not represented with breast cancers
- Recent studies seem to support the benefit of Pembrolizumab in metastatic breast cancers with TMB>10 where clinical response was demonstrated and improved PFS compared to chemotherapy.

San Antonio Breast Cancer Symposium®, December 7-10, 2021

SUSAN F. SMITH CENTER FOR WOMEN'S CANCERS
Dana-Farber Cancer Institute

HARVARD MEDICAL SCHOOL

NIMBUS: A phase II study of Nivolumab plus Ipilimumab in Metastatic hypermutated HER2-negative Breast cancer

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Dana-Farber Cancer Institute

Study Design: NIMBUS trial

Eligibility:

- Metastatic HER2- breast cancer
- 0-3 lines of prior chemotherapy
- TMB ≥ 9 mut/Mb as assessed by a CLIA-approved cancer-gene panel
- Measurable disease by RECIST 1.1
- Mandatory research biopsy if tumor safely accessible
- No prior checkpoint inhibition

REGISTRATION

Nivolumab 3 mg/kg Q2W
+
Ipilimumab 1 mg/kg Q6W

1 cycle = 42 days (6 weeks)

Duration of therapy

Treatment until progression, unacceptable toxicity or up to 24 months

Tumor assessment: Imaging will be performed at baseline and Q6W for 24 weeks, and then Q9W.

Biopsy #1
Stool #1
(Baseline)

Biopsy #2
Stool #2
(Cycle 1 day 29)

Biopsy #3
Stool #3
(End of treatment – optional)

Characteristic	(N=30)
Age, median (range), years	63.0 (36-72)
Female, %	100
Race, % White / Asian / Other	90.0 / 3.3 / 6.7
ECOG performance status 0 / 1, n (%)	22 (73.3) / 8 (26.7)
HR+/ TNBC, n (%)	21 (70.0) / 9 (30.0)
Prior lines of CT in the advanced setting, median (range) 0, n (%) 1, n (%) 2, n (%) 3, n (%)	1.5 (0-3) 8 (26.7) 7 (23.3) 8 (26.7) 7 (23.3)
PD-L1 status#, n (%) positive, n (%) negative, n (%) specimen not adequate for evaluation, n (%) missing samples, n (%)	 4 (13.3) 21 (70.1) 4 (13.3) 1 (3.3)
TMB* (mut/Mb), median (range) ≥ 9 - < 14, n (%) ≥ 14 - < 20, n (%) ≥ 20, n (%)	10.9 (9 - 110) 25 (83.3) 2 (6.7) 3 (10)

#Performed centrally CPS ≥10 using 22C3 DAKO; *no central testing for TMB

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Exploratory analysis

	Objective response	No response	Total	P value
Subtype	n = 5	n = 25	n = 30	0.6
TNBC, n (%)	2 (22)	7 (78)	n = 9	
HR+, n (%)	3 (14)	18 (86)	n = 21	
PD-L1 status	n = 4	n = 21	n = 25	1.0
Negative, n (%)	3 (14.3)	18 (85.7)	n = 21	
Positive, n (%)	1 (25)	3 (75)	n = 4	
Stromal TIL	n = 5	n = 23	n = 28	0.3
<10, n (%)	2 (11)	17 (89)	n = 19	
≥ 10, n (%)	3 (33)	6 (67)	n = 9	
TMB (Mut/Mb)	n = 5	n = 25	n = 30	0.02
<14, n (%)	2 (8)	23 (92)	n = 25	
≥14, n (%)	3 (60)	2 (40)	n = 5	

Patients with an objective response

ID	Tumor subtype	TMB (Mut/Mb)	PD-L1 CPS ≥ 10	Stromal TIL ≥ 10	IHC CD8 ≥ 10	Prior CT lines
1	HR+	110	Unknown	No	No	0
7	HR+	38	No	Yes	No	1
14	HR+	17.5	No	Yes	No	1
11	TNBC	10.9	Yes	Yes	Yes	3
28	TNBC	9.1	No	No	No	0

Objective Response Rate (ORR)

Confirmed ORR, n (%)	5 (16.7%)
CR, n (%)	0
PR, n (%)	5 (16.7%)
SD, n (%)	6 (20%)
PD, n (%)	16 (53.3%)
Not evaluable, n (%)	3 (10%)
CBR, n (%)	5 (16.7%)

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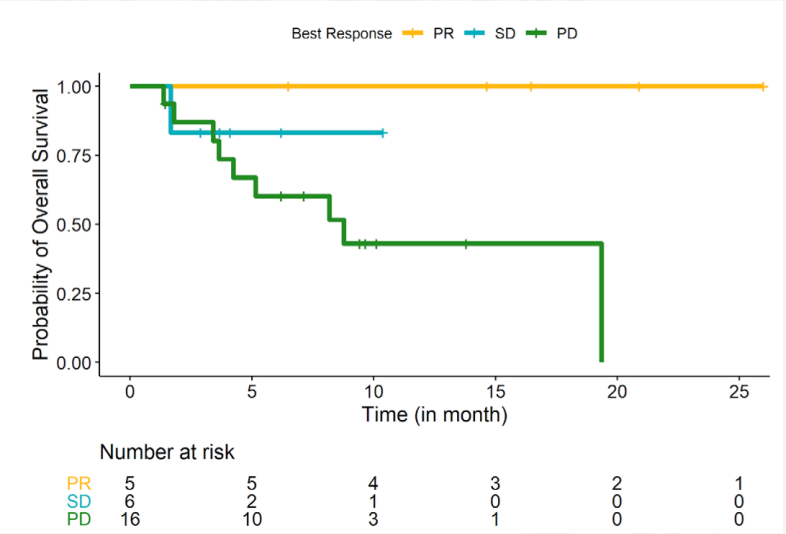
Overall survival according to best response



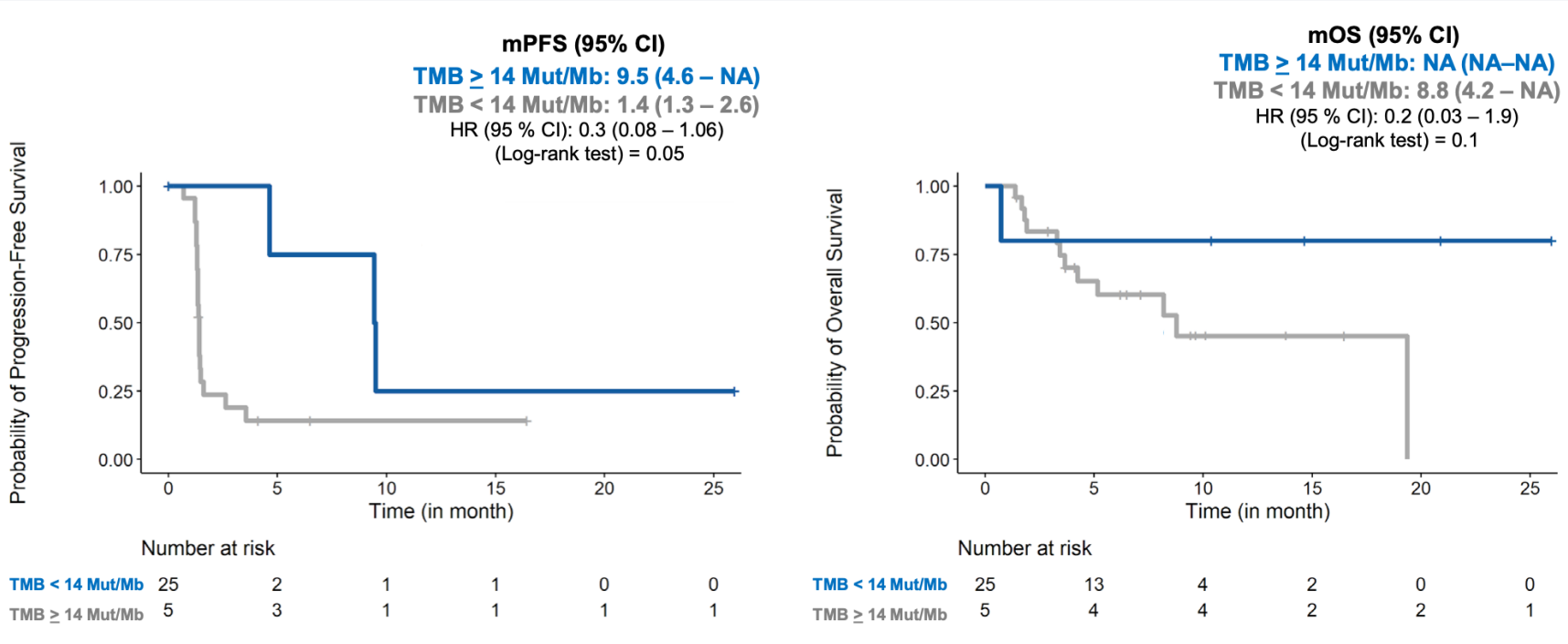
12 months OS rate

PR: 100%

SD: 80%

PD: 45%

Median PFS and OS according to TMB



- The combination of nivolumab plus ipilimumab in patients **with HER2-negative MBC and high TMB demonstrated an ORR of 16.7%, meeting the primary endpoint . In TN 2/9 PR**

- Patients with TMB > 14 Mut/Mb achieved ORR 60% and
  *further work is need to investigate the optimal TMB cutoff for selecting patients for receiving ICI.
- Work is ongoing to centrally confirm TMB in blood and tissue using the FoundationOne CDx assay.

FDA-approved immunotherapies for advanced TNBC

Regimen	Approved	Indication	Dose
Pembrolizumab + chemotherapy	2020	Locally recurrent/metastatic TNBC with PD-L1 CPS ≥ 10	200 mg Q3W or 400 mg Q6W
Pembrolizumab	2017/2020	MSI-H/dMMR or TMB-high solid tumors with progression on prior treatment	200 mg Q3W or 400 mg Q6W

Formerly approved regimen	Approved/ Withdrawn	Indication	Dose
Atezolizumab + nab-paclitaxel or paclitaxel protein-bound	2019	Advanced/metastatic TNBC with PD-L1 ≥1% immune cells	840 mg atezolizumab Q2W + 100 mg/m^2 nab-paclitaxel on days 1, 8, 15

Emens et al. J Immunotherap Cancer 2021

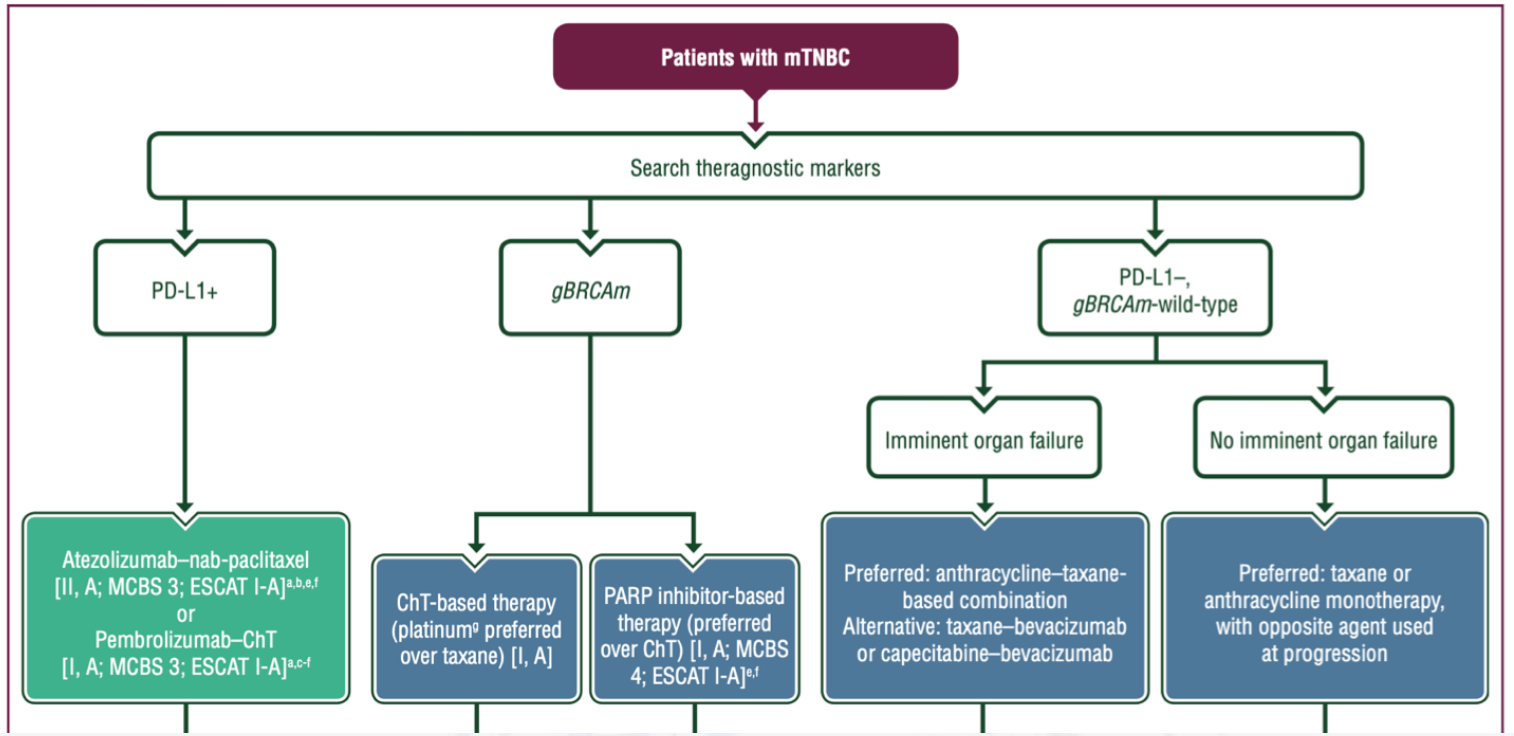
ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ANNALS OF ONCOLOGY
driving innovation in oncology

SPECIAL ARTICLE

ESMO Clinical Practice Guideline for the diagnosis, staging and treatment of patients with metastatic breast cancer☆

A. Gennari[1], F. André[2], C. H. Barrios[3], J. Cortés[4,5,6,7], E. de Azambuja[8], A. DeMichele[9], R. Dent[10], D. Fenlon[11], J. Gligorov[12], S. A. Hurvitz[13,14], S.-A. Im[15], D. Krug[16], W. G. Kunz[17], S. Loi[18], F. Penault-Llorca[19], J. Ricke[2,17], M. Robson[20], H. S. Rugo[21], C. Saura[22], P. Schmid[23], C. F. Singer[24], T. Spanic[25], S. M. Tolaney[26], N. C. Turner[27], G. Curigliano[28], S. Loibl[29], S. Paluch-Shimon[30] & N. Harbeck[31], on behalf of the ESMO Guidelines Committee*



This pre

IMMUNOTHERAPY FOR TRIPLE NEGATIVE ABC

Checkpoint inhibitors + chemotherapy (pembrolizumab + taxane or carboplatin/gemcitabine) is the preferred treatment option for 1st line therapy for most patients with PD-L1+* triple negative ABC, either de novo or diagnosed at least 6 months from (neo)adjuvant chemotherapy.

(LoE/GoR: I/A) (91%)

In countries where atezolizumab is available, its combination with nab-paclitaxel may be an option for 1st line therapy of patients with PD-L1+* triple negative ABC.

(LoE/GoR: II/B) (81%)

ESMO-MCBS: 3

CONCLUSIONES : Situación actual

- Dos estudios randomizados fase III confirman el beneficio en SG de Atezolizumab y Pembrolizumab en 1º linea mTNBC

- Determinación PD-L1 by IHC es un requisito imprescindible en el dx mTNBC
  -MUST use the PD-L1 result relevant to the therapeutic target (SP142 – Atezolizumab; 22C3 CPS score score > 10 - Pembrolizumab)

  *Likely better biomarker of benefit than PD-L1 – research in progress

- Quimioterapia de combinación?
  - Si Atezolizumab, datos solo con nab-paclitaxel
  - Si Pembrolizumab, datos para poder usar taxanos o carbo/gem (si platinos en precoz?)

- Vigilar efectos secundarios. Seguir las guias de manejo de toxicidad IO

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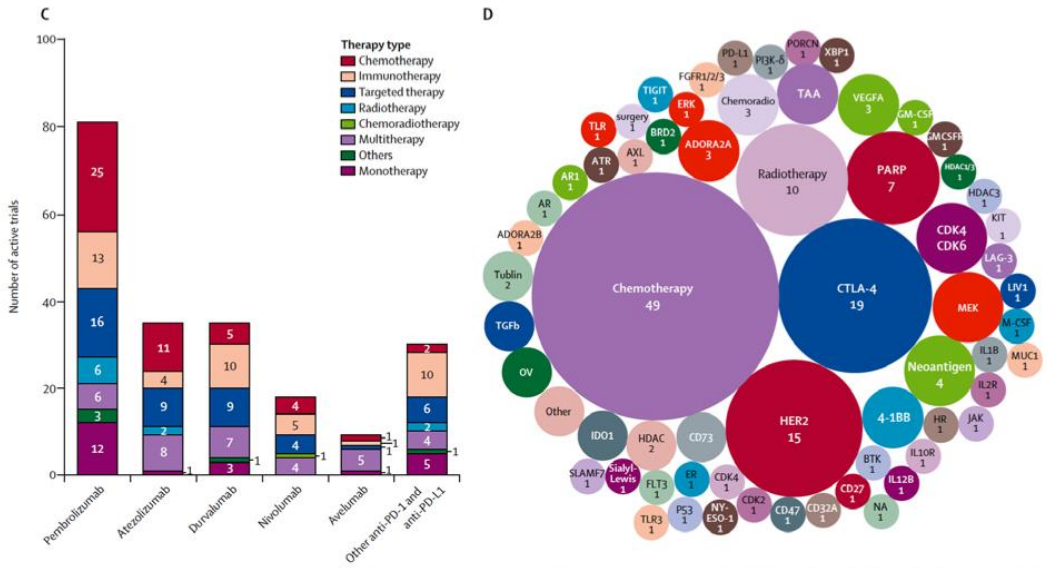
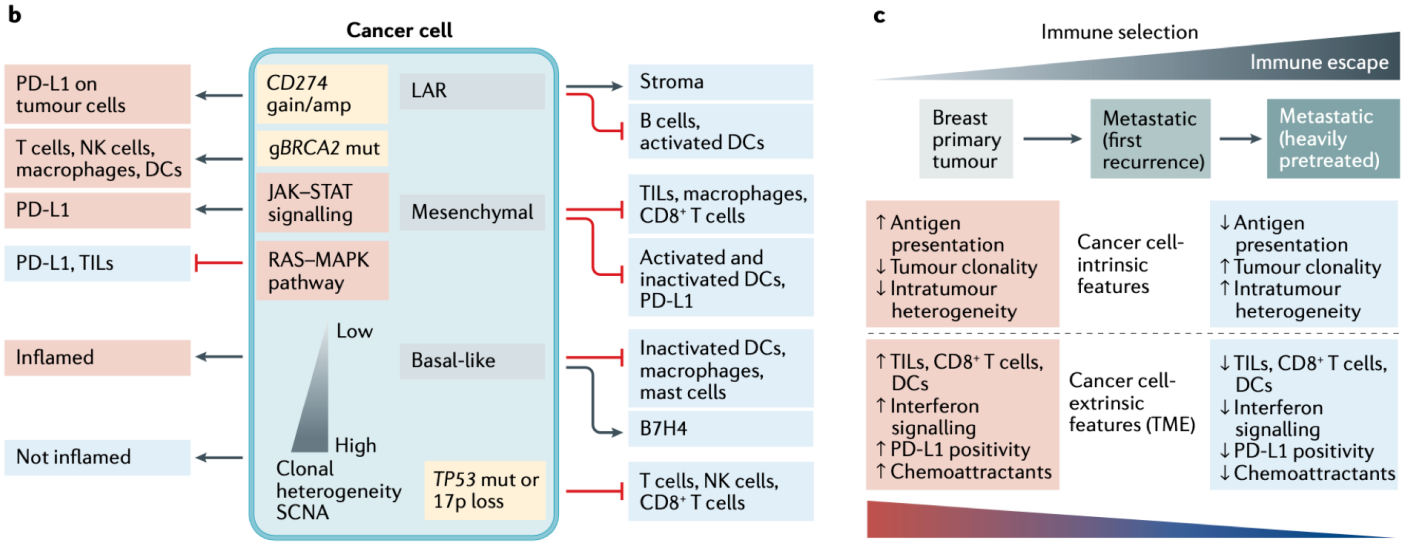
Futuro……

Immuno-oncology trials in Breast Cancer



Esteva FJ, et al. *Lancet Oncol*. 2019;20(3):e175–e186

The Immune Portrait of TNBC Remains Complex



Bianchini et al. Nature Reviews 2021

- ¿ Cómo ampliar la Respuesta Inmune ?

  -Dobletes de IO

  - IPARP + IO

  - Inhib PI3K/AKT/pTEN+ Inmunoterapia

    * Begonia , Morpheus (poca aportación del los inhib PI3K/AKT/pTEN)

- ¿ Cuanto tiempo mantener IO?

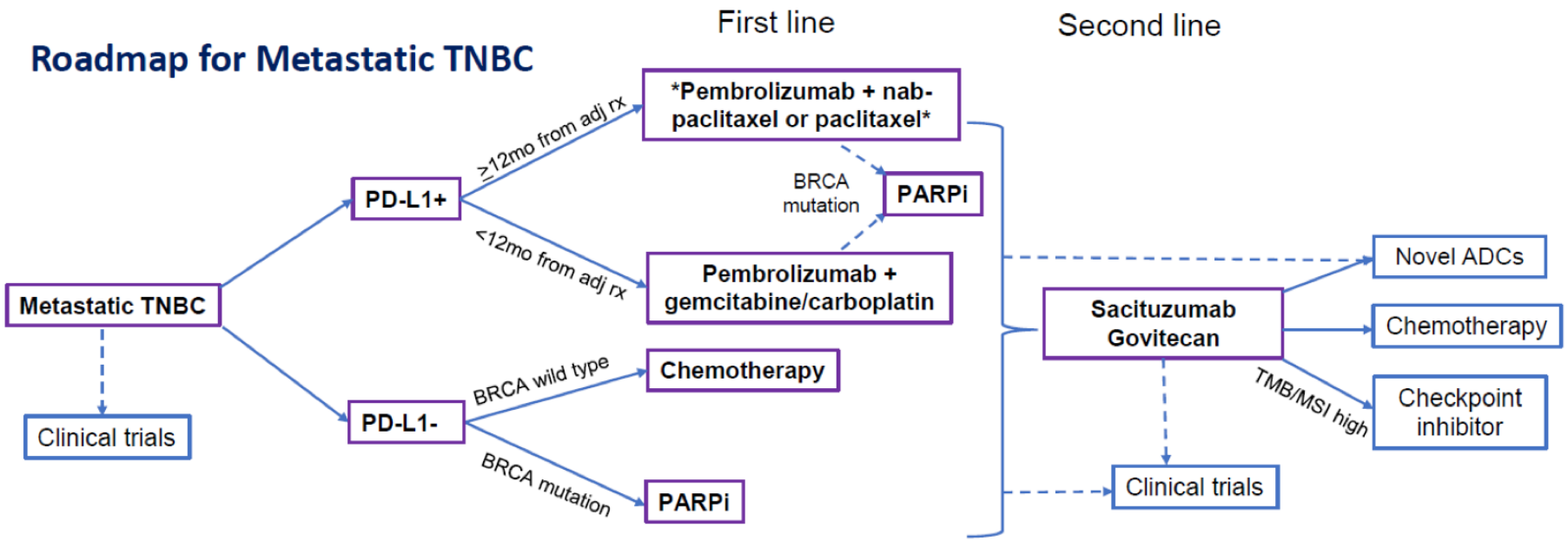
- ¿ Quién se beneficia IO?

• PDLI+

• OTROS: TMB…

mTNBC

ALWAYS CONSIDER CLINICAL TRIALS



**Pembrolizumab (CPS) or atezolizumab ex US (SP142), nab-paclitaxel only)*

PARPi: PARP inhibitor (olaparib, talazoparib)

Always consider clinical trials at each decision point

Rugo, SABCS 2021. GS1-03

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Gracias

ARÁN