Progetto CANOA
26 Marzo 2021

Setting metastatico: dalle evidenze della letteratura alla pratica clinica

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DISCLOSURES

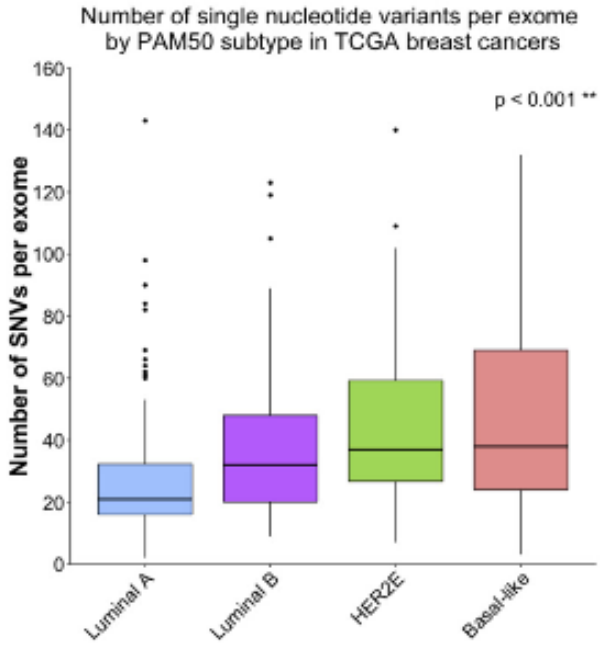
Advisory Board: EliLilly, Novartis, Roche, MSD
Speaker’s Bureau: EliLilly, Novartis
Research Grant (Institutional): Roche

IMMUNOTHERAPY FOR TN METASTATIC BREAST CANCER

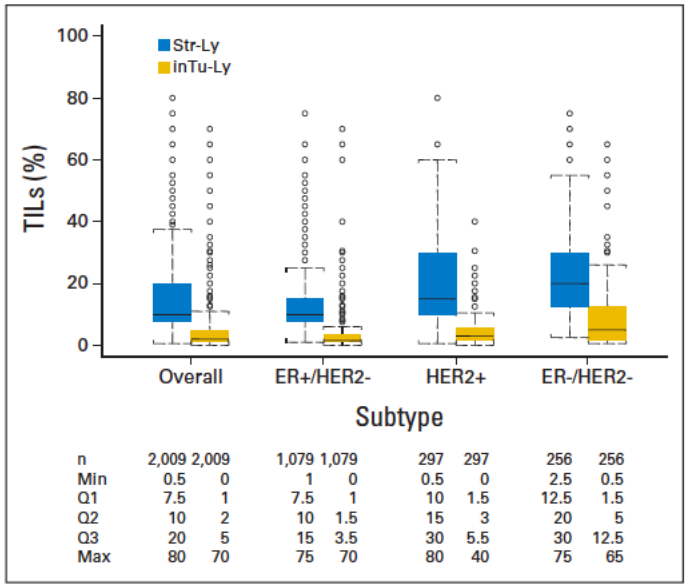
- The Past: an unmet clinical need but, given the biology, a very strong candidate for IO clinical investigation
- The Present: lights (and shadows) from RCT
- The Monday Clinic: harmonizing PDL1 assessment
- The Future: exploring new combinations

RATIONALE FOR IMMUNOTHERAPY IN TNBC

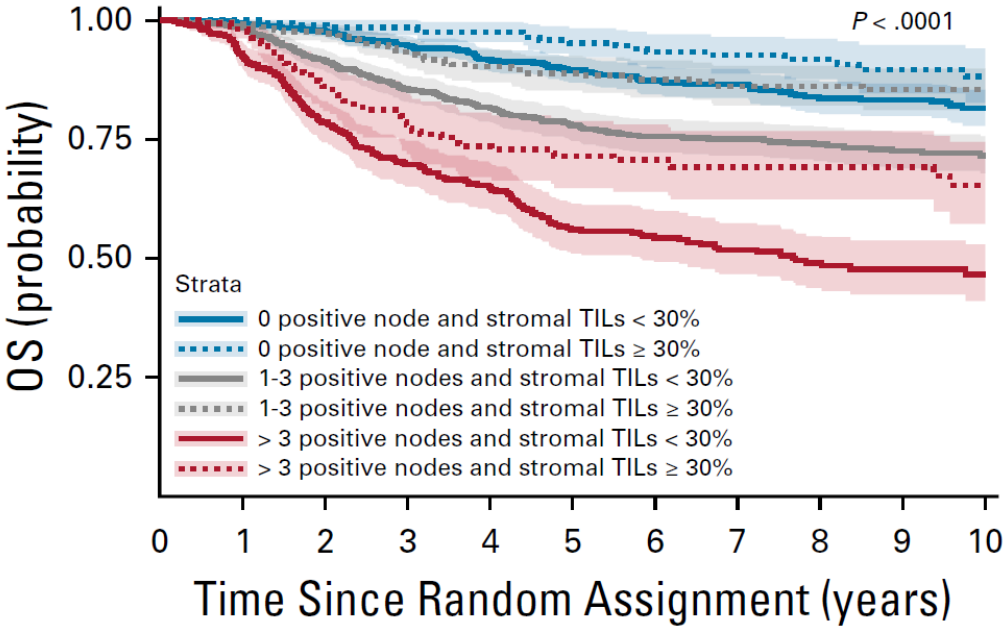
Mut load across BC subtypes



TILs across BC subtypes



Prognostic role of TILs in TNBC



Prognostic role of additional immune markers in TNBC

Model variables	Likelihood ratio χ^2	P value
CP + TILs + PD-L1 vs CP + TILs	6.50	0.011
CP + TILs + CD8 vs CP + TILs	5.89	0.015
CP + TILs + FOXP3 vs CP + TILs	3.95	0.047

Luen S et al, Breast 2016; Loi S et al, J Clin Oncol 2013;
Loi S et al, J Clin Oncol 2019; Dieci MV et al, Eur J Cancer 2020

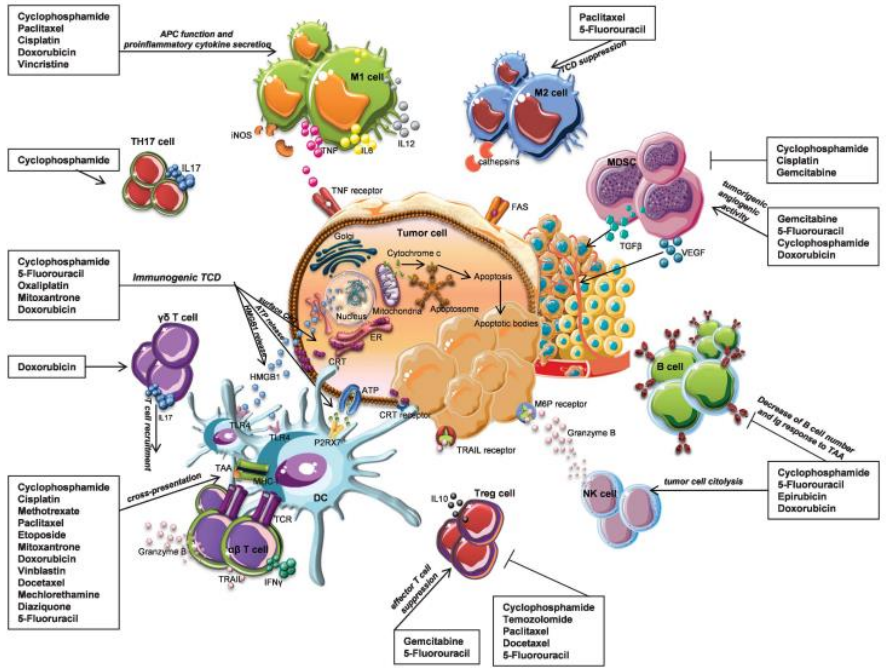
CT AS A TRIGGER FOR IMMUNE ACTIVATION

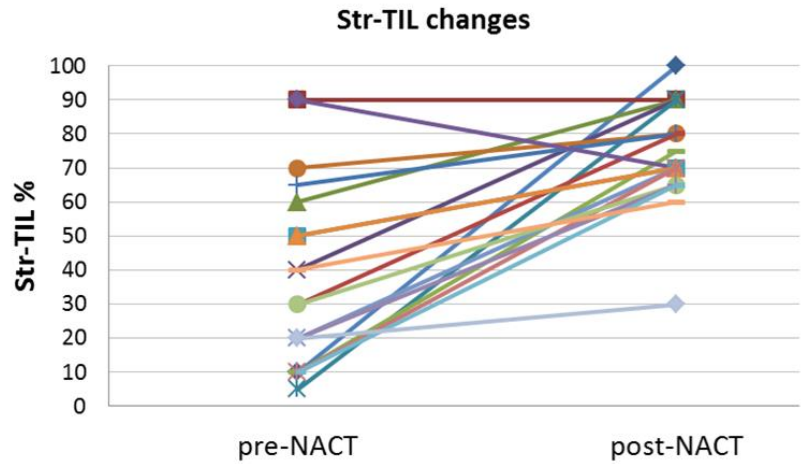
Lessons from pivotal trials

Modest activity as monotherapy

PDL1 status matters

Line of therapy matters





Bracci L, et al. *Cell Death Differ 2014*

Dieci MV, et al. *Ann Oncol*. 2014

IMMUNOTHERAPY FOR TN METASTATIC BREAST CANCER

- The Past: an unmet clinical need but, given the biology, a very strong candidate for IO clinical investigation
- The Present: lights (and shadows) from RCT
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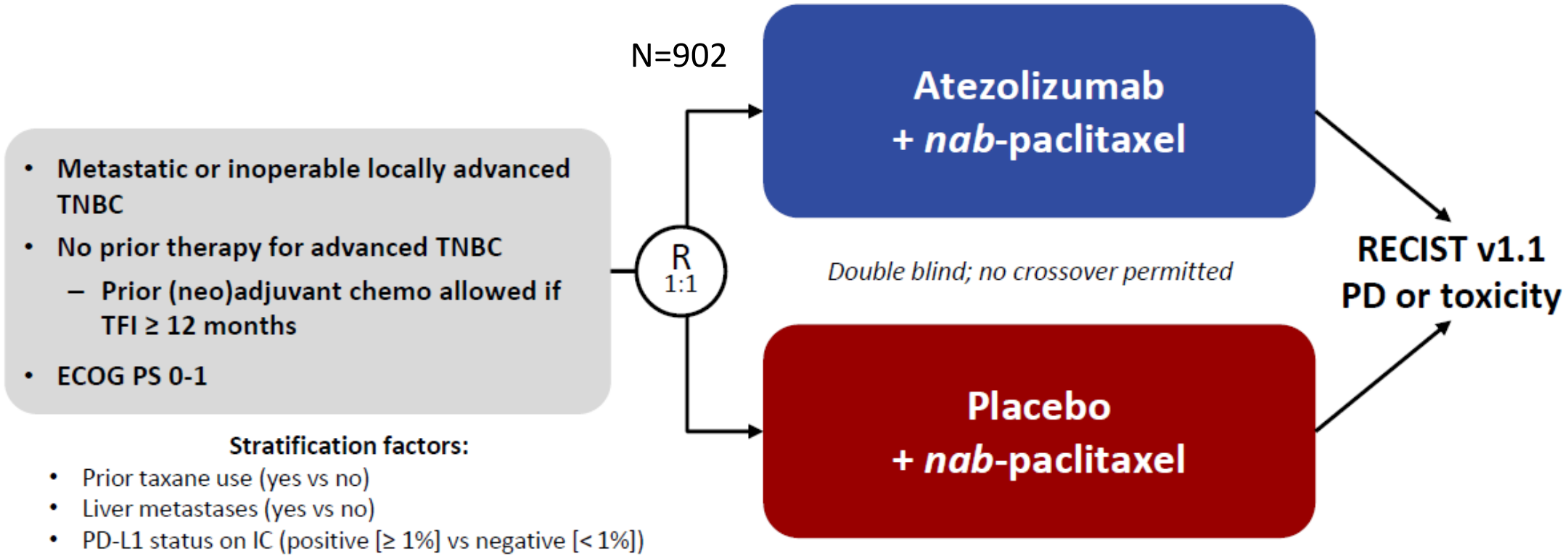
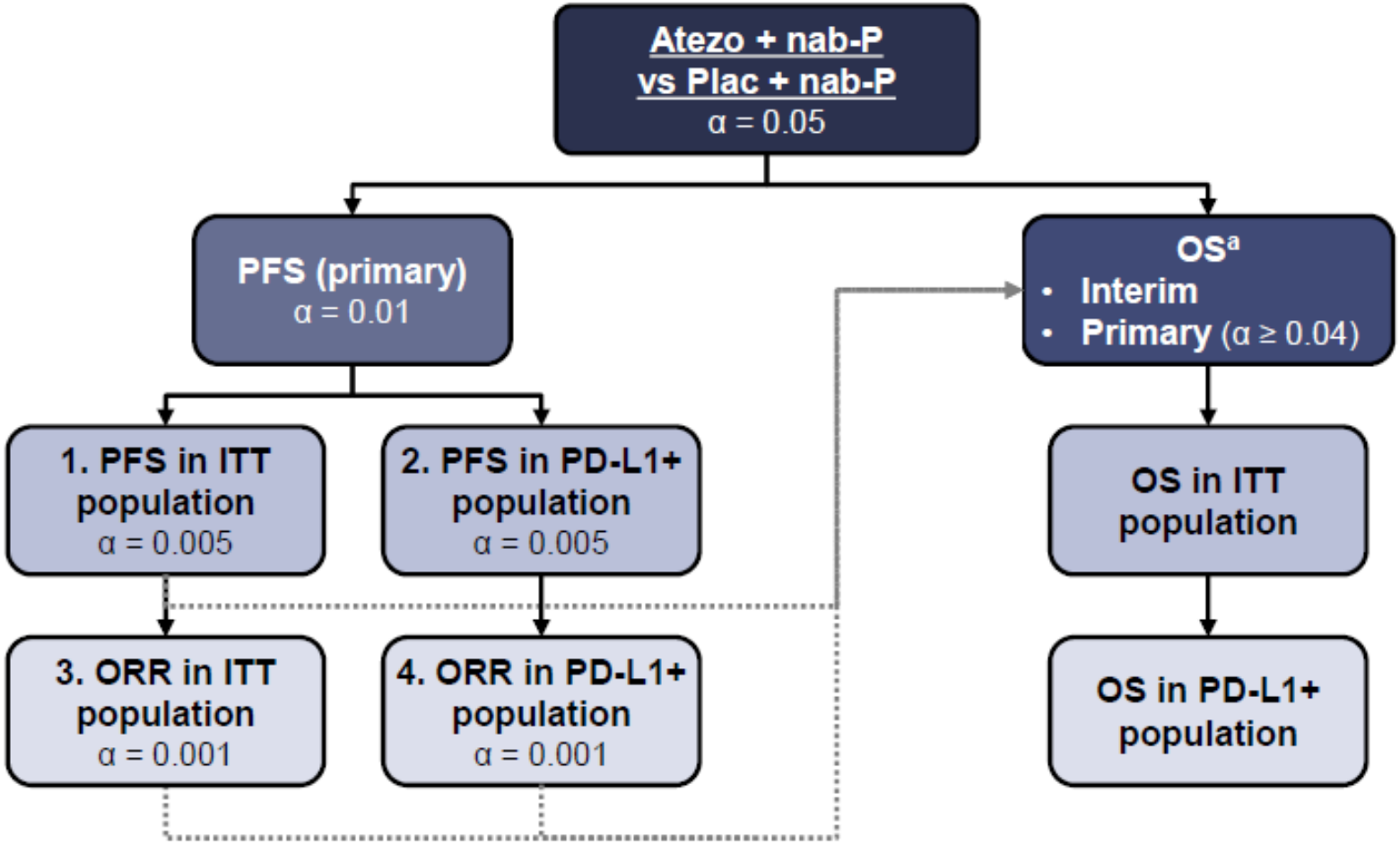
ATEZOLIZUMAB + NabPACLITAXEL AS 1L: IMPASSION 130



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

Schmid P, NEJM 2018

IMPASSION 130 STATISTICAL TESTING



- Primary PFS analysis (PFS tested in ITT and PD-L1+ populations)
- First interim OS analysis (OS tested in ITT population, then, if significant, in PD-L1+ population)

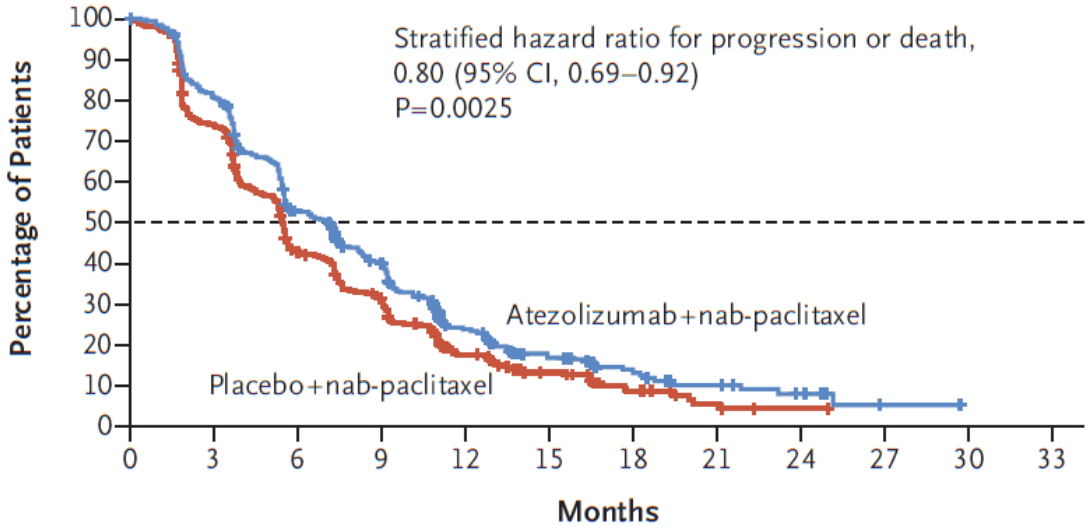
[a] α recycled if PFS/ORR testing is significant. Hazard ratio (HR)/*P* value–stopping boundaries are dependent on the OS analysis timing.

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

IMPASSION 130: PROGRESSION-FREE SURVIVAL

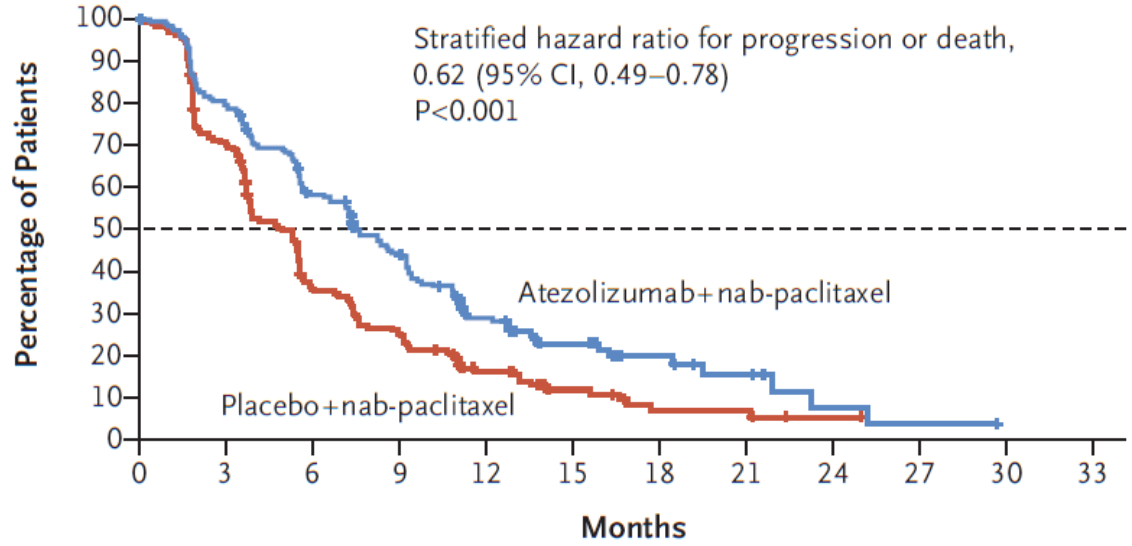
ITT population

	No. of Events/ No. of Patients	Median Progression-free Survival (95% CI)	1-Yr Rate of Progression-free Survival (95% CI)
		mo	%
Atezolizumab+Nab-Paclitaxel	358/451	7.2 (5.6–7.5)	23.7 (19.6–27.9)
Placebo+Nab-Paclitaxel	378/451	5.5 (5.3–5.6)	17.7 (14.0–21.4)



PD-L1 positive subgroup

	No. of Events/ No. of Patients	Median Progression-free Survival (95% CI)	1-Yr Rate of Progression-free Survival (95% CI)
		mo	%
Atezolizumab+Nab-Paclitaxel	138/185	7.5 (6.7–9.2)	29.1 (22.2–36.1)
Placebo+Nab-Paclitaxel	157/184	5.0 (3.8–5.6)	16.4 (10.8–22.0)

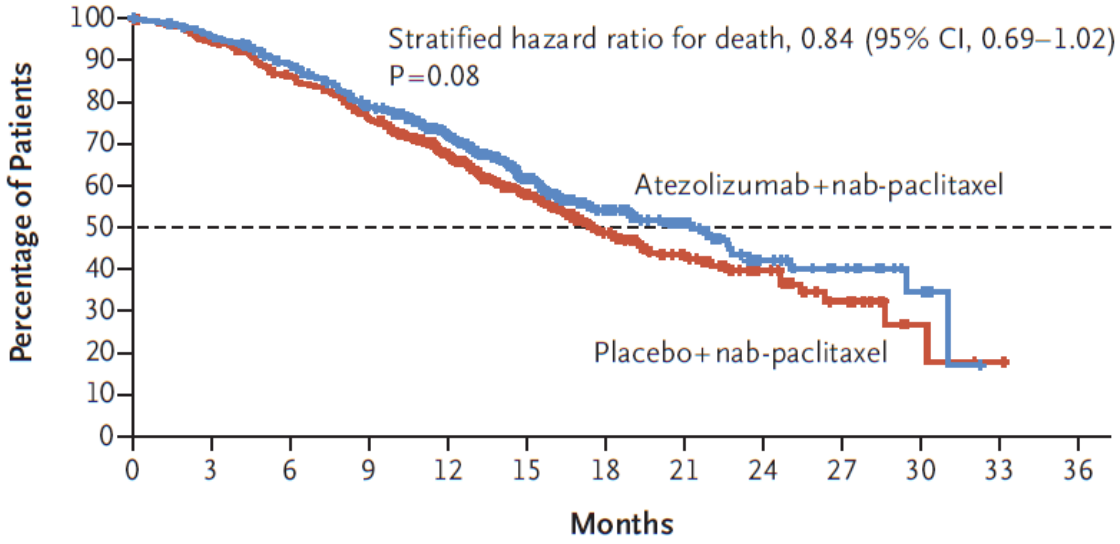


Schmid P, NEJM 2018

IMPASSION 130: OVERALL SURVIVAL

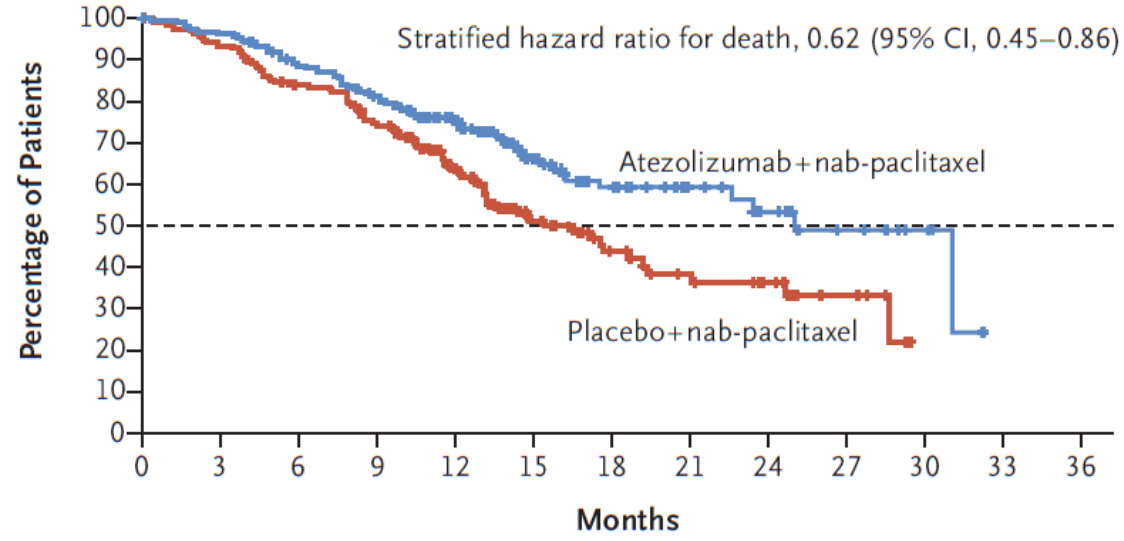
ITT population

	No. of Events/ No. of Patients	Median Overall Survival (95% CI)	2-Yr Rate of Progression-free Survival (95% CI)
		mo	%
Atezolizumab+Nab-Paclitaxel	181/451	21.3 (17.3–23.4)	42.1 (34.3–49.9)
Placebo+Nab-Paclitaxel	208/451	17.6 (15.9–20.0)	39.7 (33.2–46.3)



PD-L1 positive subgroup

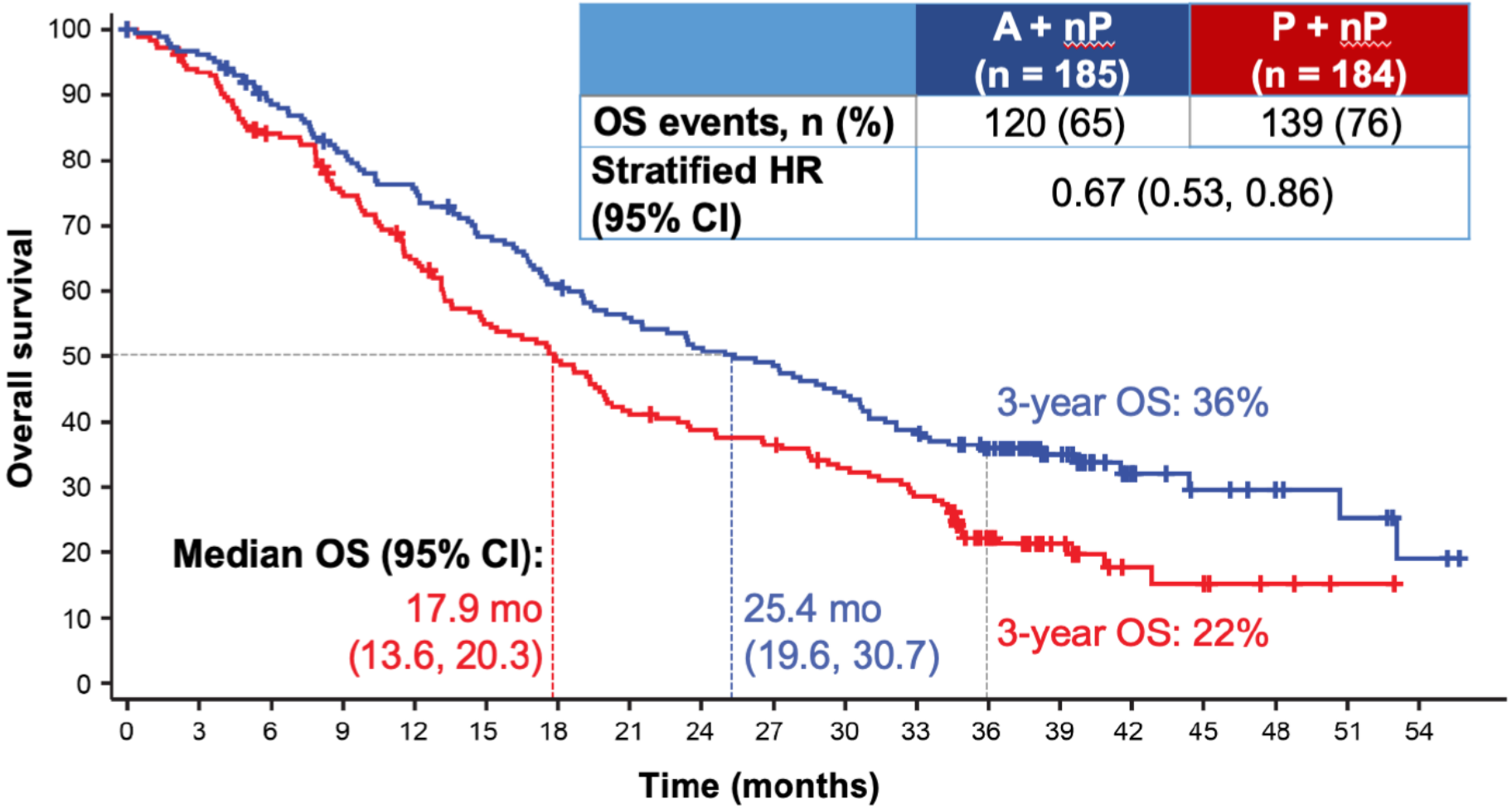
	No. of Events/ No. of Patients	Median Overall Survival (95% CI)	2-Yr Rate of Progression-free Survival (95% CI)
		mo	%
Atezolizumab+Nab-Paclitaxel	64/185	25.0 (22.6–NE)	53.5 (42.3–64.6)
Placebo+Nab-Paclitaxel	88/184	15.5 (13.1–19.4)	36.6 (26.4–46.7)



Schmid P, NEJM 2018

IMPASSION 130: OS IN PDL1+ AT 20 MOS FUP

	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)	



△ mOS = 7.5m

ITT population:
18.7 vs 21.0m;
no impact in PDL1-

Emens, ESMO 2020

IMpassion131 trial design

Double-blind placebo-controlled randomised phase 3 trial

- 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/m^2 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/m^2 d1, 8 & 15

Stratification:

- Prior taxane (yes vs no)
- Tumour PD-L1 status (IC <1% vs ≥1%)[a]
- Liver metastases (yes vs no)
- Geographical region (N America vs W Europe/Australia vs E Europe/Asia Pacific vs S America)

Primary endpoint: PFS (investigator assessed)
Secondary endpoints include:

- OS, ORR, PFS (IRC assessed)
- PROs
- Safety
- Translational research

[a]PD-L1 IC: area of PD-L1-stained tumour-infiltrating ICs as a percentage of tumour area by VENTANA SP142 immunohistochemistry assay. eBC = early breast cancer; ECOG PS = Eastern Cooperative Oncology Group performance status; IC = immune cell; IRC = independent review committee; ORR = objective response rate; PRO = patient-reported outcome; q28d = every 28 days; R = randomisation

Statistical design and study conduct

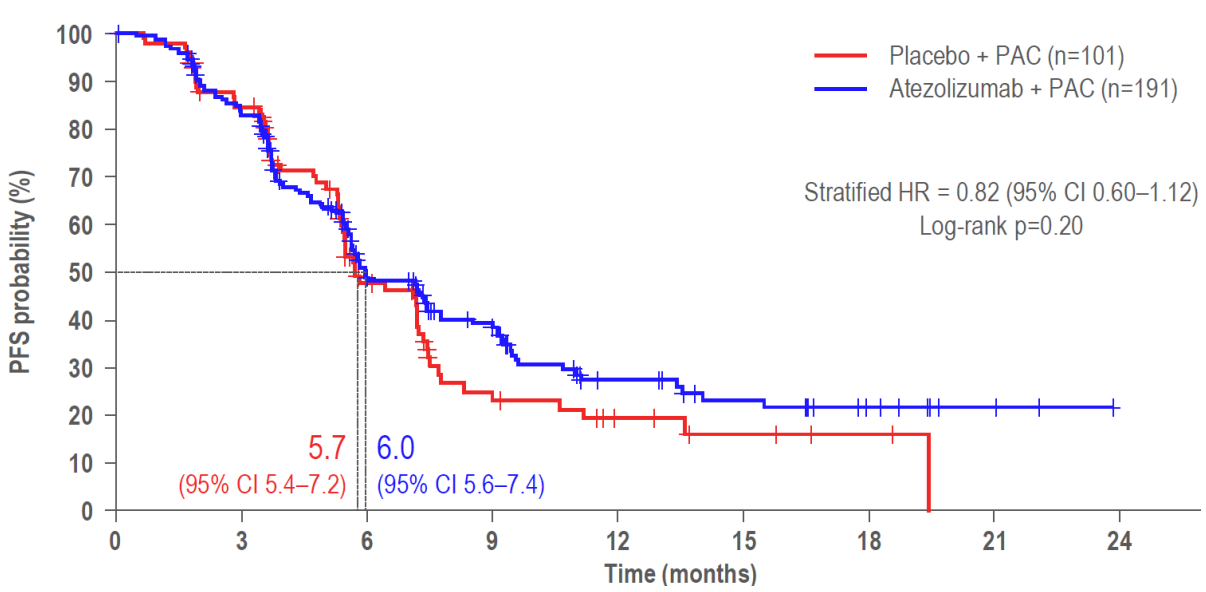
- Hierarchical testing informed by results from IMpassion130[1]
- Primary endpoint: Investigator-assessed PFS
  - Tested first in PD-L1+ population (defined as IC ≥1%)
  - Target HR 0.62 (median PFS 5.0 → 8.0 months); 5% 2-sided alpha and 80% power; 155 PFS events in PD-L1+ population
  - If significant in PD-L1+, PFS tested in the ITT population
- Data cut-off for primary PFS and first planned interim OS analysis: 15 November 2019
- Secondary endpoints tested only if all previous tests are significant:
  - OS (PD-L1+ then ITT population)
  - ORR (PD-L1+ then ITT population)
- Data cut-off for updated interim OS analysis: 19 August 2020
- Final OS analysis planned after deaths in 122 (51%) of anticipated 240 patients with PD-L1+ TNBC

HR = hazard ratio; ITT = intent-to-treat

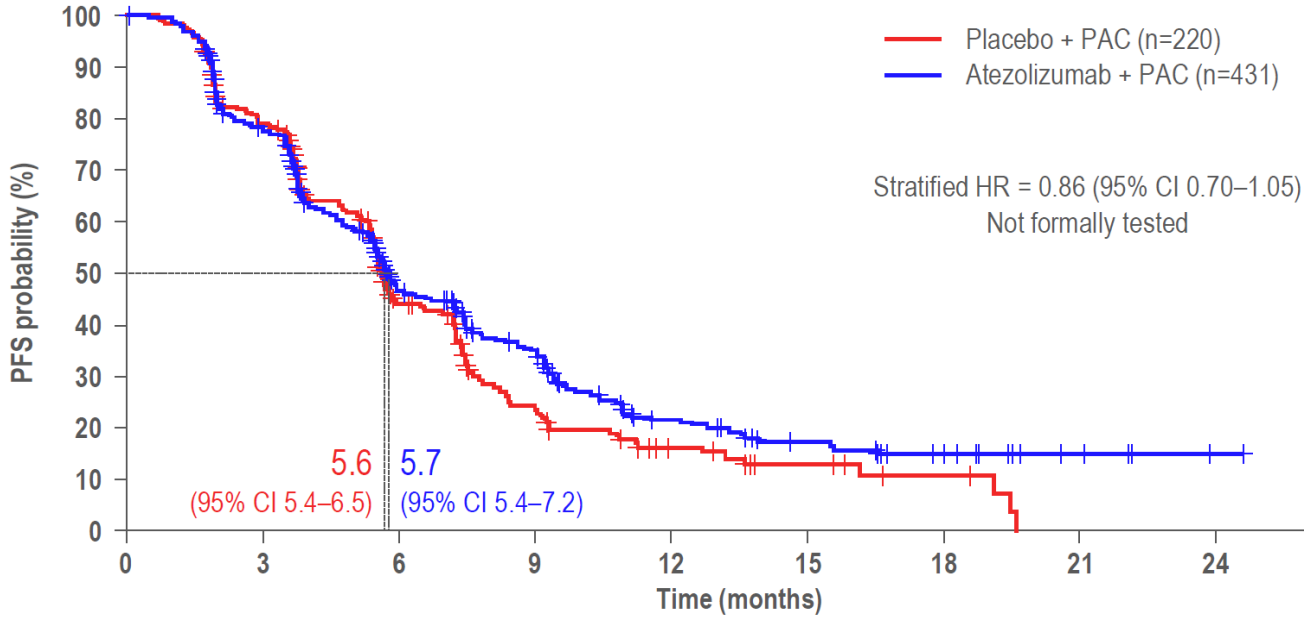
[1]Schmid P et al. NEJM 2018

IMPASSION 131: primary analysis

PFS in the PD-L1+ population

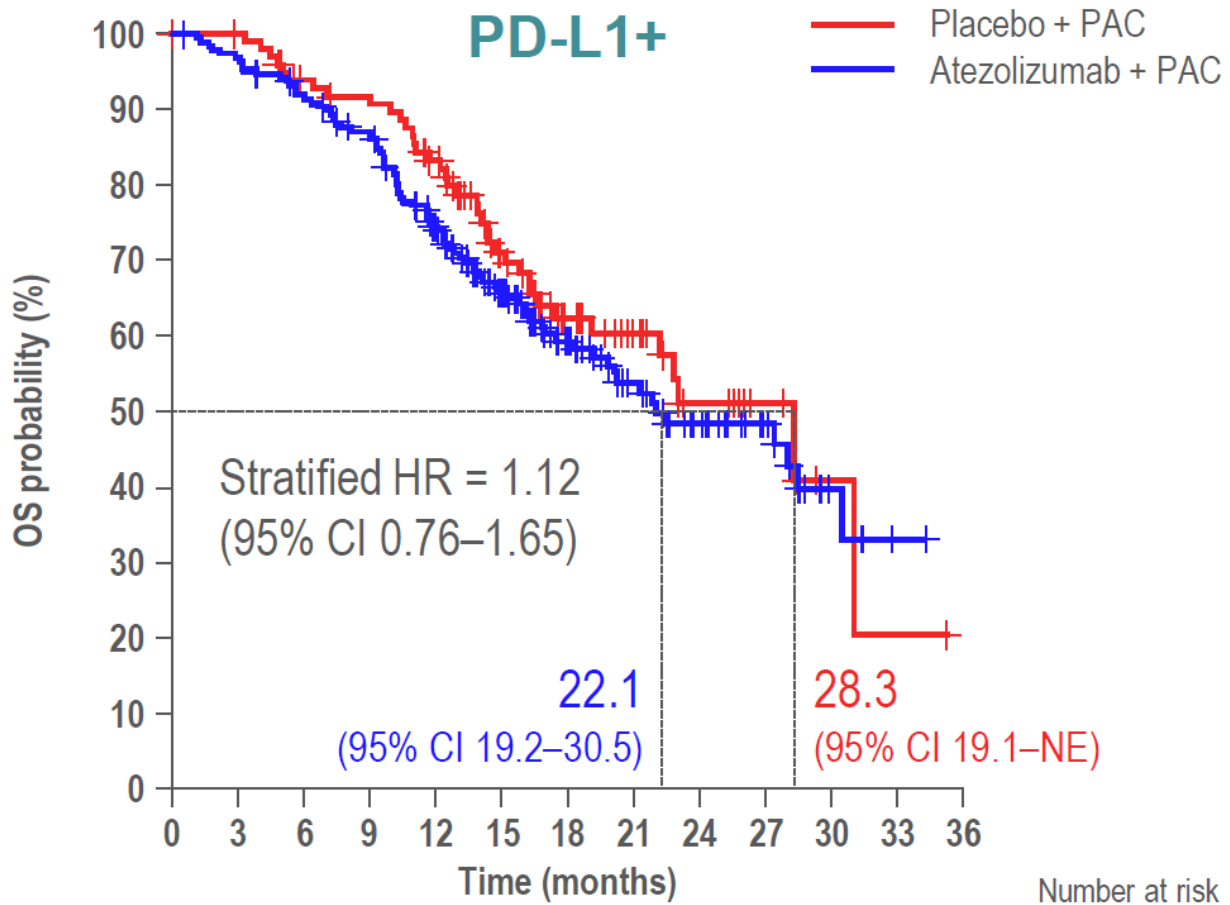


PFS in the ITT population

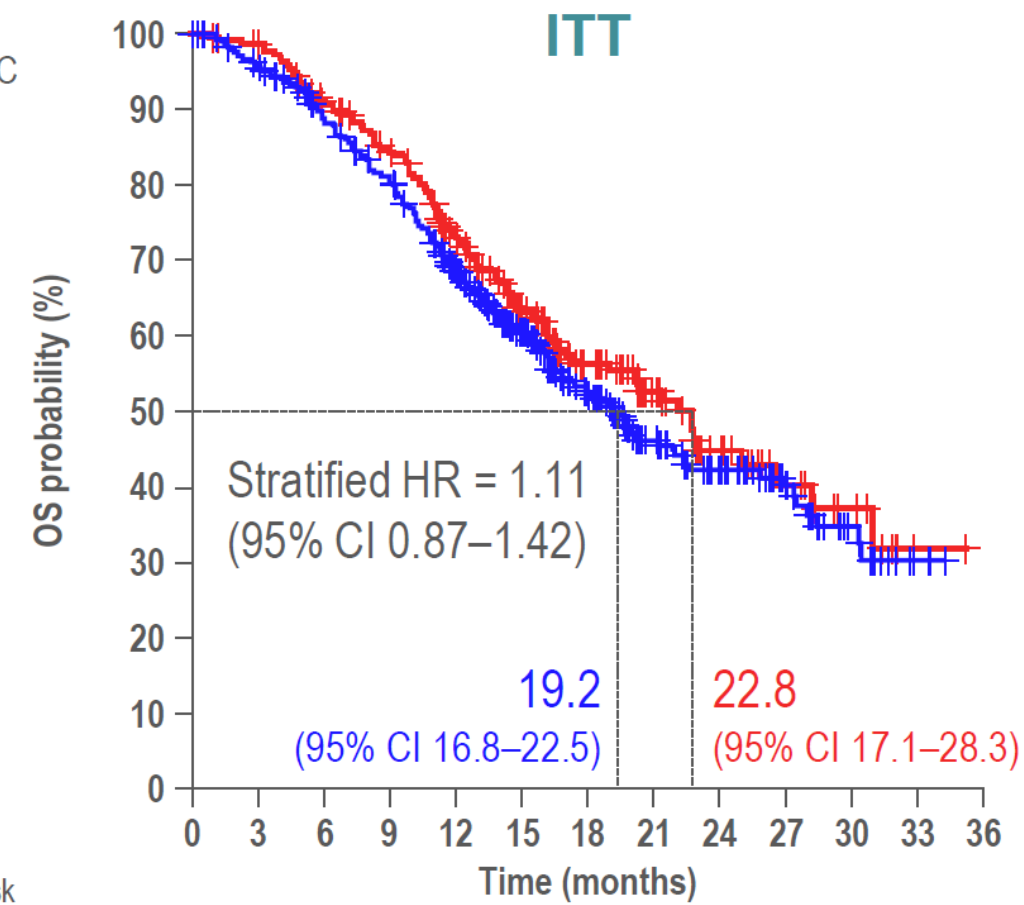


Updated OS

Data cut-off 19 Aug 2020

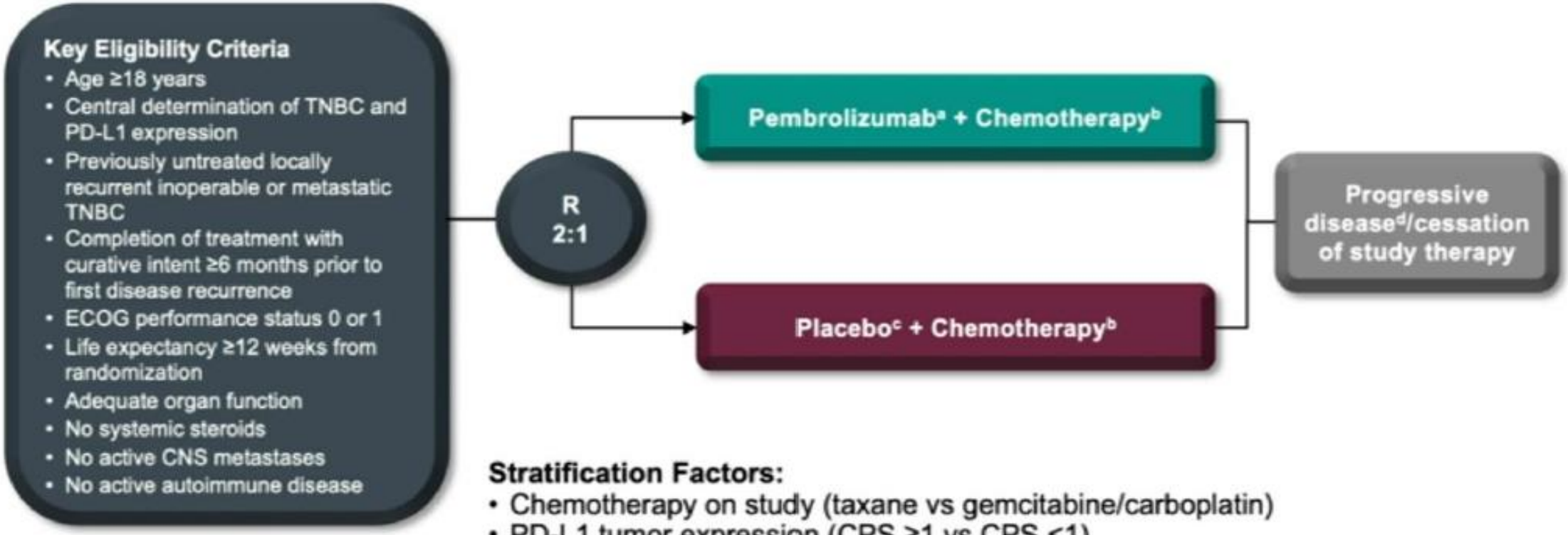


Number at risk													
Placebo + PAC	101	99	89	86	75	53	34	25	12	6	2	1	0
Atezolizumab + PAC	191	184	171	160	129	95	60	43	30	19	6	1	0



Number at risk													
Placebo + PAC	220	213	191	174	141	102	71	50	27	15	9	1	0
Atezolizumab + PAC	431	406	366	331	267	194	126	76	56	35	16	3	0

PEMBROLIZUMAB + CT FOR 1L: KEYNOTE 355

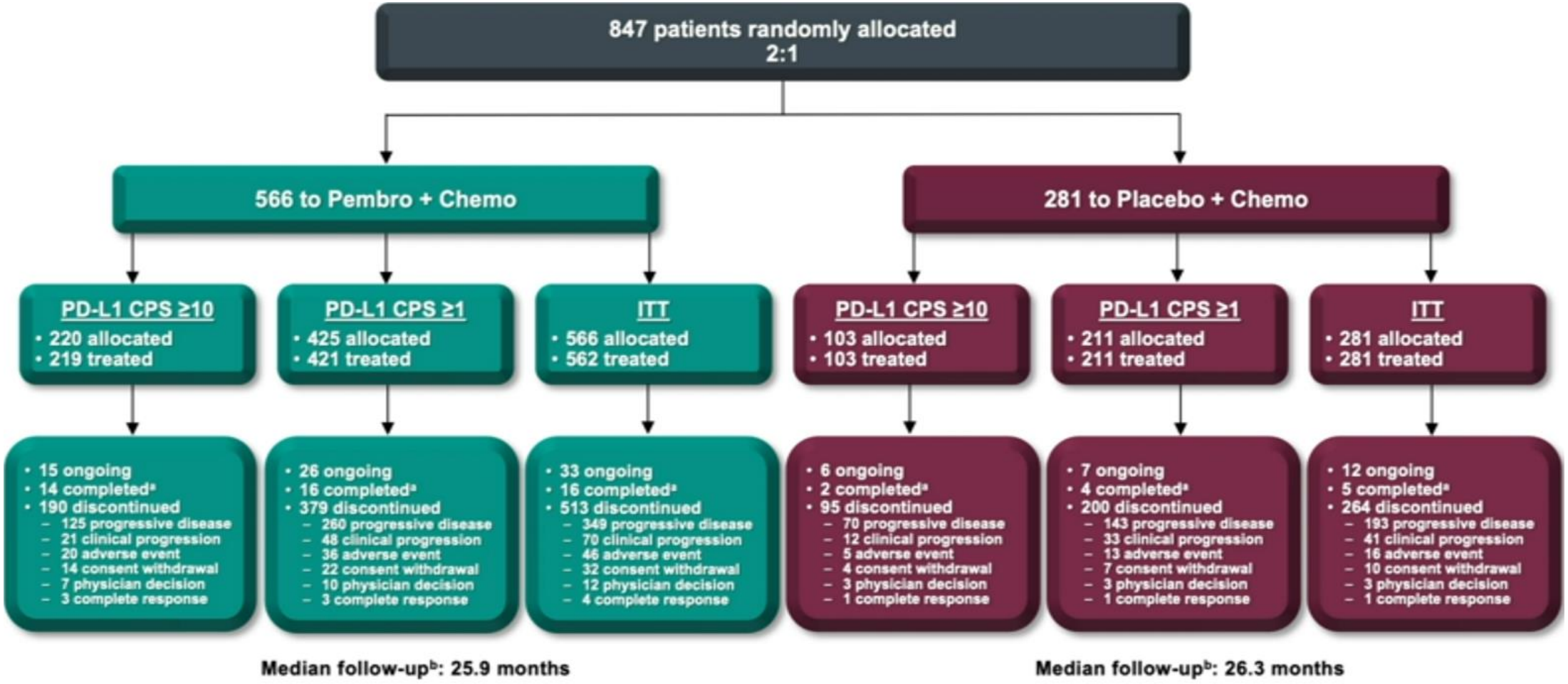


Stratification Factors:
- Chemotherapy on study (taxane vs gemcitabine/carboplatin)
- PD-L1 tumor expression (CPS ≥1 vs CPS <1)
- Prior treatment with same class chemotherapy in the neoadjuvant or adjuvant setting (yes vs no)

[a]Pembrolizumab 200 mg intravenous (IV) every 3 weeks (Q3W)
[b]Chemotherapy dosing regimens are as follows:
Nab-paclitaxel 100 mg/m² IV on days 1, 8, and 15 every 28 days
Paclitaxel 90 mg/m² IV on days 1, 8, and 15 every 28 days
Gemcitabine 1000 mg/m²/carboplatin AUC 2 on days 1 and 8 every 21 days

- Primary Endpoints
  - PFS[a] in patients with PD-L1–positive tumors[b] (CPS ≥10 and CPS ≥1) and in the ITT population
  - OS[c] in patients with PD-L1–positive tumors[b] (CPS ≥10 and CPS ≥1) and in the ITT population

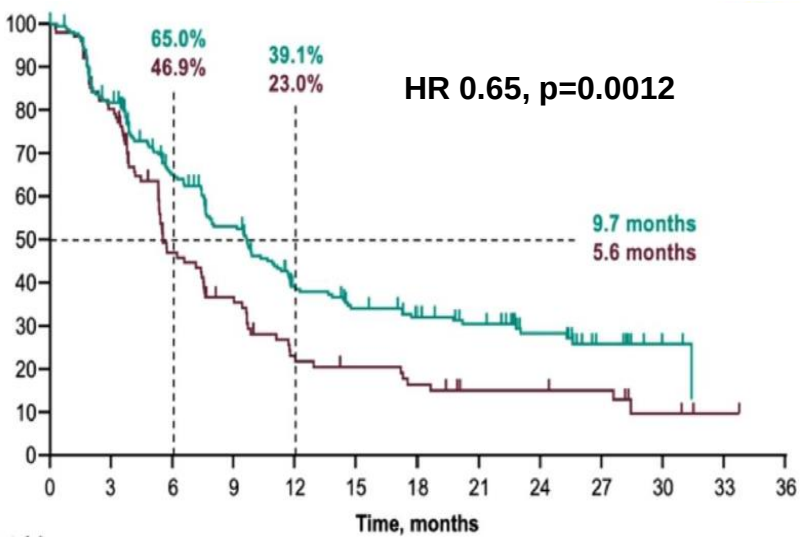
KEYNOTE 355: PATIENT DISPOSITION



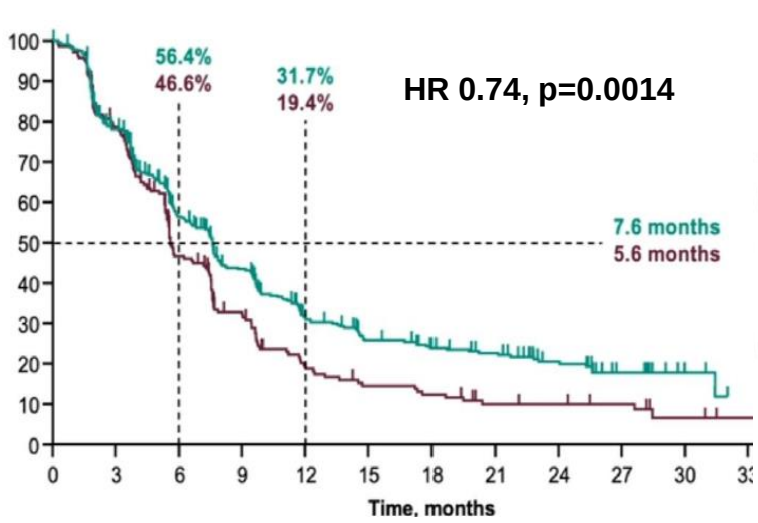
[a]Includes all patients who received 35 administrations of pembrolizumab or placebo and discontinued from chemotherapy; [b]Defined as the time from randomization to the database cutoff date of December 11, 2019.

Cortes J, et al. ASCO 2020

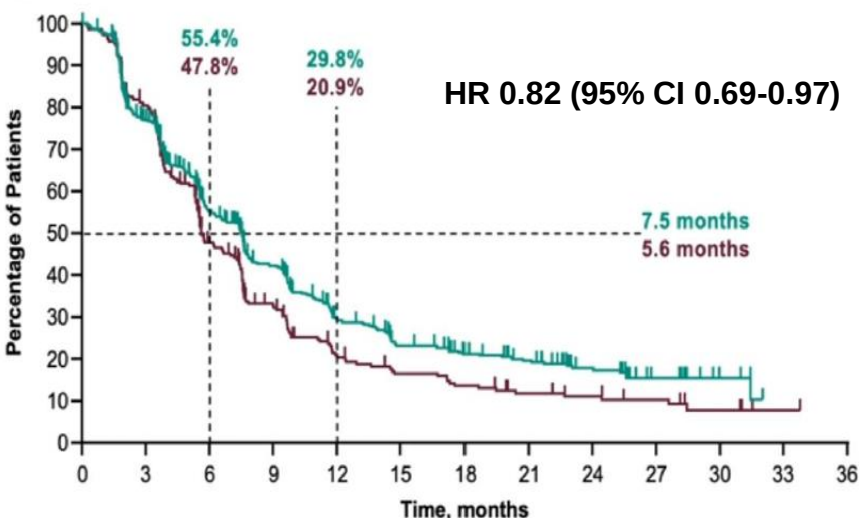
KEYNOTE 355:PROGRESSION-FREE SURVIVAL



CPS score ≥ 10 (38% of patients)
Pre-specified p-value boundary of 0.00411 met



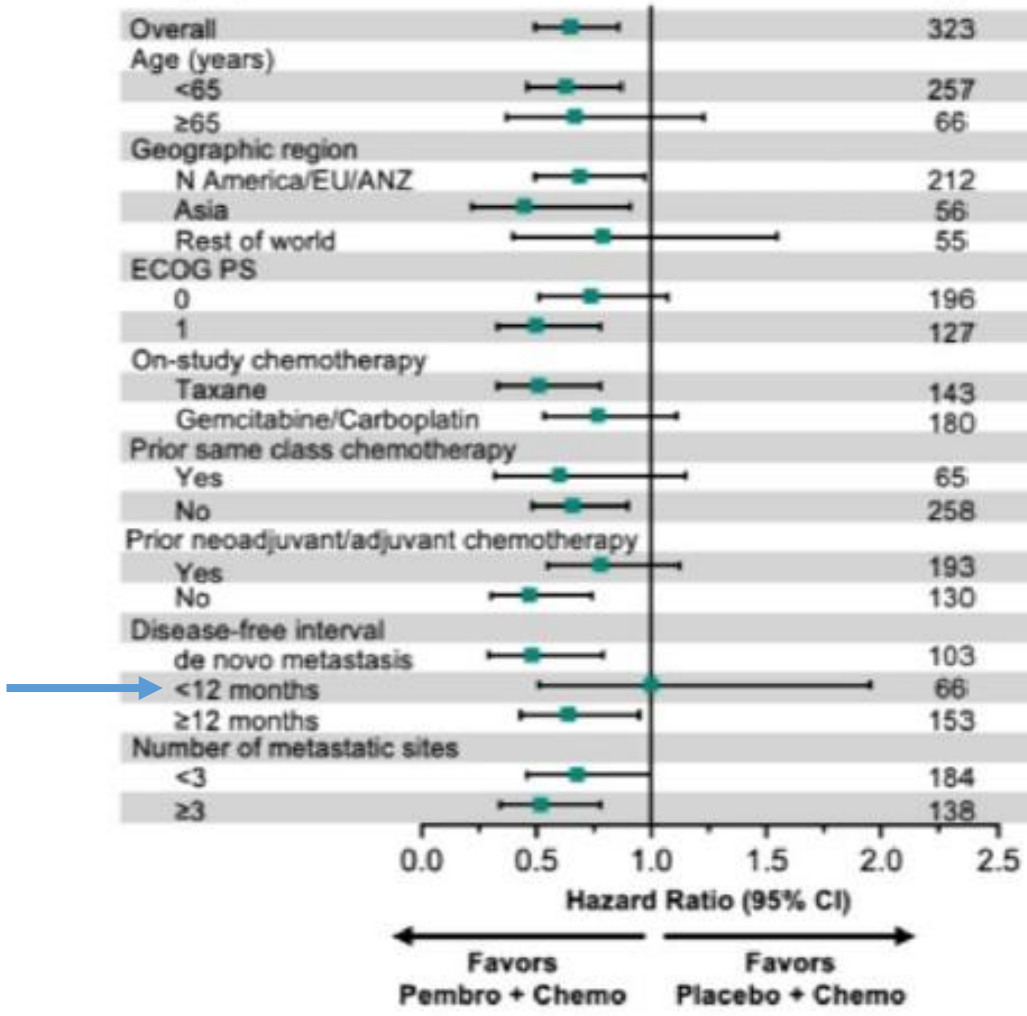
CPS score ≥ 1 (75% of patients)
Pre-specified p-value boundary of 0.00111 not met



ITT population
Statistical significance not tested due to the pre-specified hierarchical testing strategy

Cortes J, et al. ASCO 2020

PROGRESSION-FREE SURVIVAL IN SUBGROUPS:PD-L1 CPS≥10



Subgroup	N	Median PFS (mo)		Hazard Ratio for Progression or Death (95% CI)
		Pembro + Chemo	Placebo + Chemo	
Overall	323	9.7	5.6	0.65 (0.49 to 0.86)
Age (years)				
<65	257	9.5	5.5	0.63 (0.46 to 0.87)
≥65	66	10.7	7.6	0.67 (0.37 to 1.23)
Geographic region				
N America/EU/ANZ	212	9.6	5.7	0.69 (0.49 to 0.97)
Asia	56	17.3	5.6	0.45 (0.22 to 0.91)
Rest of world	55	7.6	6.2	0.65 (0.40 to 1.56)
ECOG PS				
0	196	9.8	7.5	0.74 (0.51 to 1.07)
1	127	7.6	3.9	0.50 (0.33 to 0.78)
On-study chemotherapy				
Taxane	143	9.9	5.4	0.51 (0.33 to 0.78)
Gemcitabine/Carboplatin	180	8.0	7.2	0.77 (0.53 to 1.11)
Prior same class chemotherapy				
Yes	65	7.5	5.4	0.60 (0.32 to 1.15)
No	258	9.9	5.7	0.66 (0.48 to 0.90)
Prior neoadjuvant/adjuvant chemotherapy				
Yes	193	7.9	5.7	0.78 (0.55 to 1.12)
No	130	11.0	5.4	0.47 (0.30 to 0.74)
Disease-free interval				
de novo metastasis	103	9.7	5.3	0.48 (0.29 to 0.79)
<12 months	66	7.5	7.2	1.00 (0.51 to 1.95)
≥12 months	153	9.9	6.6	0.64 (0.43 to 0.95)
Number of metastatic sites				
<3	184	11.8	9.0	0.68 (0.46 to 1.00)
≥3	138	7.6	4.5	0.52 (0.34 to 0.78)

Data cutoff December 11, 2019.

Cortes J, et al. ASCO 2020

Baseline Characteristics, ITT

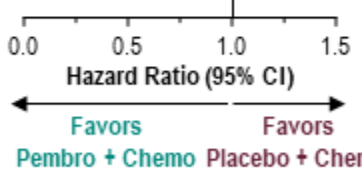
Characteristic, n (%)	All Subjects, N = 847	
	Pembro + Chemo N = 566	Placebo + Chemo N = 281
Age, median (range), yrs	53 (25-85)	53 (22-77)
ECOG PS 1	232 (41.0)	108 (38.4)
PD-L1–positive CPS ≥1	425 (75.1)	211 (75.1)
PD-L1–positive CPS ≥10	220 (38.9)	103 (36.7)
Chemotherapy on study		
Nab-Paclitaxel	173 (30.6)	95 (33.8)
Paclitaxel	82 (14.5)	32 (11.4)
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 metastasis	167 (29.5)	84 (29.9)
<12 months	126 (22.3)	50 (17.8)
≥12 months	270 (47.7)	147 (52.3)

Data cutoff December 11, 2019.

Progression-Free Survival in Subgroups by On-Study Chemotherapy

PD-L1 CPS ≥10

Subgroup	N	Median PFS (mo) Pembro + Chemo	Median PFS (mo) Placebo + Chemo	Hazard Ratio for Progression or Death (95% CI)
Overall	323	9.7	5.6	0.65 (0.49 to 0.86)
On-study chemotherapy				
Nab-Paclitaxel	99	9.9	5.5	0.57 (0.34 to 0.95)
Paclitaxel	44	9.6	3.6	0.33 (0.14 to 0.76)
Gemcitabine-Carboplatin	180	8.0	7.2	0.77 (0.53 to 1.11)

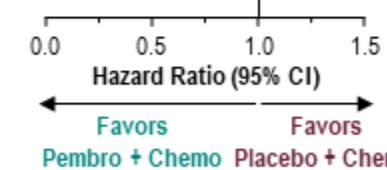


PD-L1 CPS ≥1

Subgroup	N	Median PFS (mo) Pembro + Chemo	Median PFS (mo) Placebo + Chemo	Hazard Ratio for Progression or Death (95% CI)
Overall	636	7.6	5.6	0.74 (0.61 to 0.90)
On-study chemotherapy				
Nab-Paclitaxel	204	6.3	5.3	0.66 (0.47 to 0.92)
Paclitaxel	84	9.4	3.8	0.46 (0.26 to 0.82)
Gemcitabine-Carboplatin	348	7.5	7.5	0.86 (0.66 to 1.11)

ITT

Subgroup	N	Median PFS (mo) Pembro- + Chemo	Median PFS (mo) Placebo + Chemo	Hazard Ratio for Progression or Death (95% CI)
Overall	847	7.5	5.6	0.82 (0.69 to 0.97)
On-study chemotherapy				
Nab-Paclitaxel	268	7.5	5.4	0.69 (0.51 to 0.93)
Paclitaxel	114	8.0	3.8	0.57 (0.35 to 0.93)
Gemcitabine-Carboplatin	465	7.4	7.4	0.93 (0.74 to 1.16)



The PFS treatment effect was assessed in subgroups descriptively using hazard ratios and 95% CIs; although subgroup analyses by on-study chemotherapy were pre-specified, the trial was not powered to compare efficacy among treatment groups by different chemotherapy regimens. Steroid premedication for paclitaxel was given according to local guidelines and practices and was not restricted by the protocol. Steroid use was also allowed for the management of immune-mediated AEs across the study. Data cutoff December 11, 2019.

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- The Past: an unmet clinical need but, given the biology, a very strong candidate for IO clinical investigation
- The Present: lights (and shadows) from RCT
- The Monday Clinic: harmonizing PDL1 assessment
- The Future: exploring new combinations

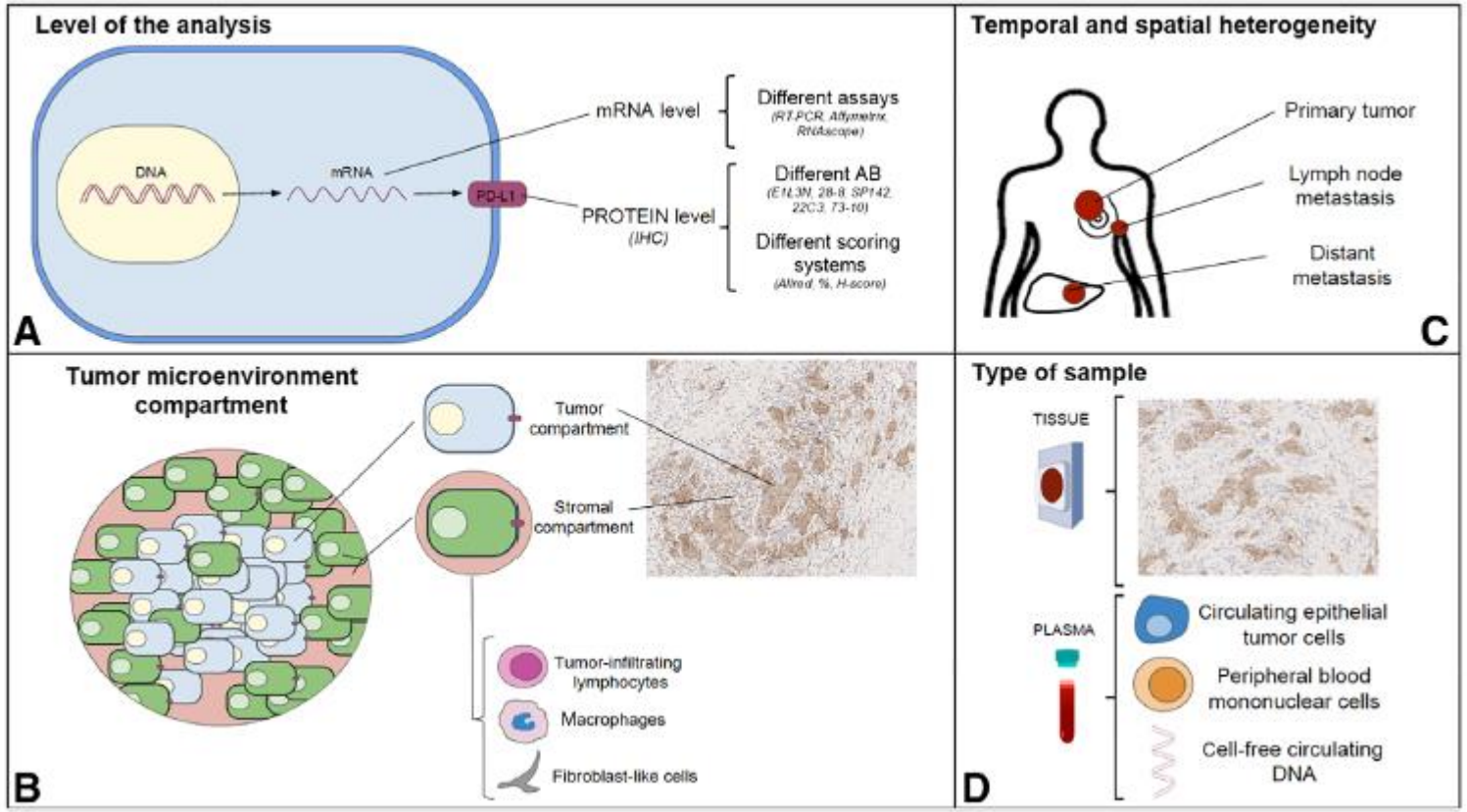
The Oncologist®

Breast Cancer

Programmed Cell Death Ligand 1 in Breast Cancer: Technical Aspects, Prognostic Implications, and Predictive Value

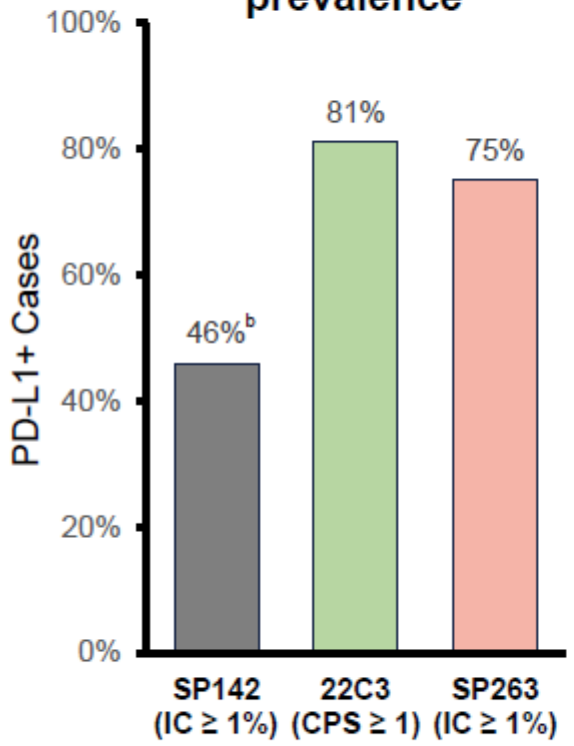
Federica Miglietta,[a,b] Gaia Griguolo,[a,b] Valentina Guarneri,[a,b] Maria Vittoria Dieci[a,b]

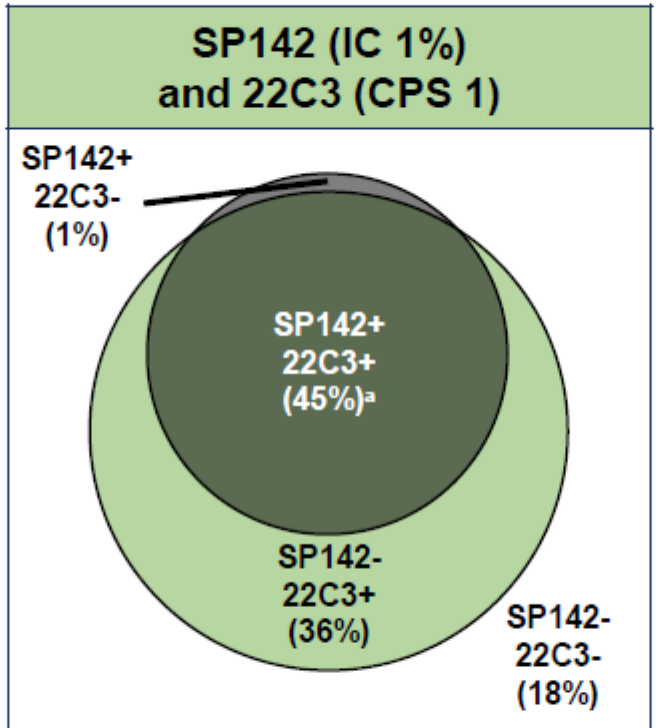
[a]Department of Surgery, Oncology and Gastroenterology, University of Padova, Padova, Italy; [b]Division of Medical Oncology 2, Istituto Oncologico Veneto IRCCS, Padova, Italy



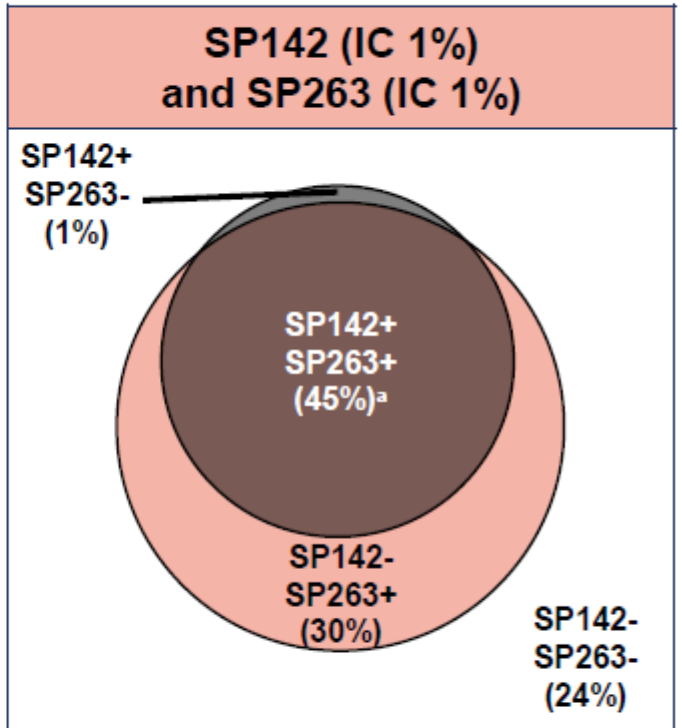
COMPARISON OF PD-L1 IHC ANTIBODIES IN TNBC

PD-L1 IHC assays: prevalence and analytical concordance





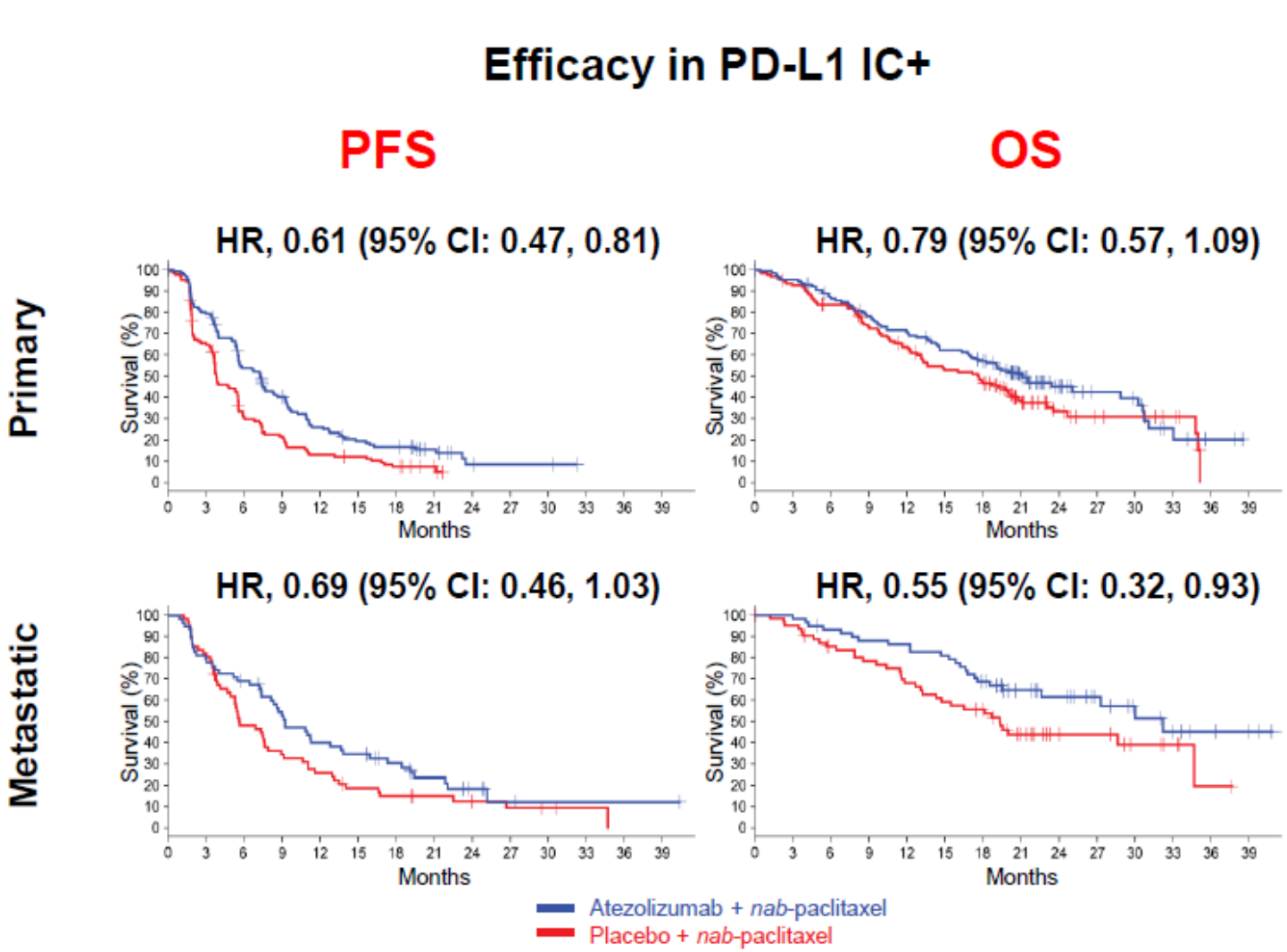
OPA[c]	64%
PPA	98%
NPA	34%

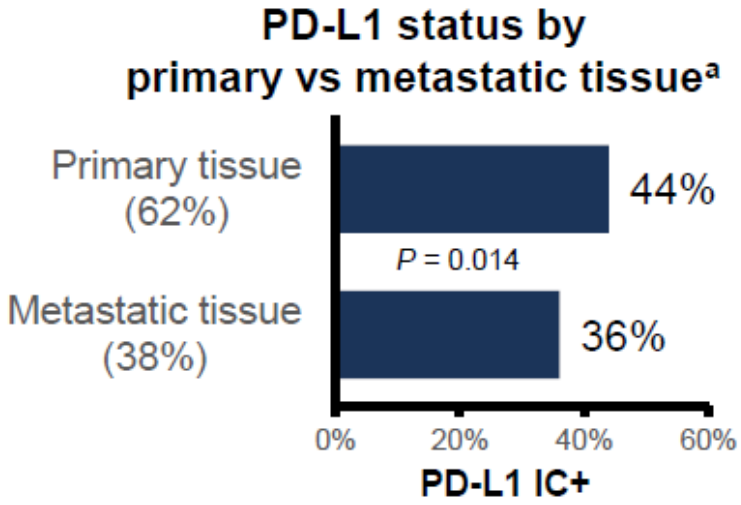


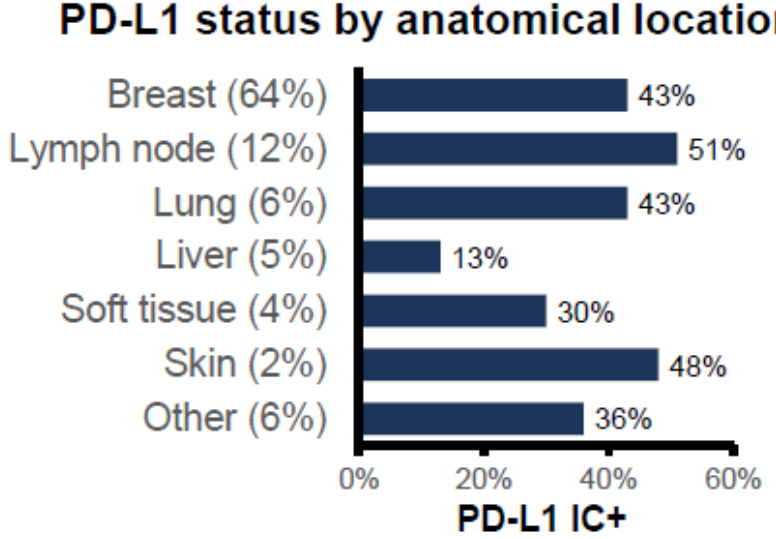
OPA[c]	69%
PPA	98%
NPA	45%

NPA, negative percentage agreement; OPA, overall percentage agreement; PPA, positive percentage agreement.
[a] > 97% of SP142+ samples included in 22C3+ or SP263+ samples. [b] Compared with 41% in ITT (Schmid, *New Engl J Med* 2018).
[c] ≥ 90% OPA, PPA *and* NPA required for analytical concordance.

IMPASSION 130: PD-L1 STATUS ASSESSMENT







[a] Evaluable population (n = 901). PD-L1 IC+: PD-L1 in ≥ 1% of IC as percentage of tumour area assessed with the VENTANA SP142 assay.
HRs adjusted for prior taxanes, presence of liver metastases, age and ECOG PS. Median time of sample collection to randomization: 61 days. No major differences were observed for clinical benefit in samples collected within 61 days

Rugo, et al ESMO 2019

IMMUNOTHERAPY FOR TN METASTATIC BREAST CANCER

- The Past: an unmet clinical need but, given the biology, a very strong candidate for IO clinical investigation
- The Present: lights (and shadows) from RCT
- The Monday Clinic: harmonizing PDL1 assessment
- The Future: exploring new combinations
  - Enhancing immune response (ladiratuzumab vedotin, Dectin-1 agonist Imprime PGG…)
  - Broadening the benefit of PARPi