Supplementary Table S1: Description of major clinical trials assessing ICIs in metastatic TNBC with biomarkers assessment.

	PCD4989g	TONIC	Keynote 086	Keynote 119	Keynote 355	IMpassion 130	IMpassion 131
Study Design	Phase Ib	Phase II	Phase II	Phase III	Phase III	Phase III	Phase III
	NCT01375842	NCT02499367	NCT02447003	NCT02555657	NCT02819518	NCT02425891	NCT03125902
	Atezolizumab monotherapy	Randomization into 5 arms: -Nivolumab without induction -Radiotherapy + nivolumab -Cyclophosphamide + nivolumab -Cisplatine + nivolumab -Doxorubicine + nivolumab	Pembrolizumab monotherapy	Pembrolizumab monotherapy vs chemotherapy of choice of investigator (capecitabine, eribulin, gemcitabine, or vinorelbine)	Pembrolizumab and chemotherapy of choice of investigator (nabpaclitaxel, paclitaxel, or gemcitabine plus carboplatin) vs placebo and chemotherapy)	Atezolizumab and nab-paclitaxel vs nab-paclitaxel and placebo	Atezolizumab and paclitaxel vs paclitaxel and placebo
	N = 116	N = 70 Maximum of 3 previous line of systemic treatment	N = 254 (all patients) Cohort A (previously treated patients), N = 170 Cohort B (previously untreated patients and PD-L1 positive tumor), N = 84	N = 622 Previously treated patients with an anthracycline or a taxane in the (neo)adjuvant or metastatic setting	N = 847 Previously treated patients with (neo)adjuvant setting allowed	N = 902	N = 651
Prior line(s) of therapy in metastatic setting	No prior therapy: N = 21 (18%) 1 prior therapy: N = 28 (24%) ≥ 2 prior therapies: N = 67 (58%)	No prior therapy: N = 17 (24%) 1 prior therapy: N = 34 (49%) ≥ 2 prior therapies: N = 19 (27%)	1 prior therapy: N = 53 (31.2%) 2 prior therapies: N = 43 (25.3%) ≥3 prior therapies: N = 74 (43.5%)	1 prior therapy: N = 374 (60%) 2 prior therapies: N = 247 (40%)	No previous chemotherapy or targeted therapy for metastatic TNBC	No previous chemotherapy or targeted therapy for metastatic TNBC	No previous chemotherapy or targeted therapy for metastatic TNBC
Biopsy requirement for	Newly collected biopsy or archival tissue	Newly collected biopsy at baseline, post-induction and	Newly collected biopsy (mostly from metastases): N = 146 (75%)	Newly collected biopsy or archival tissue allowed	Newly collected biopsy or archival tissue	Newly collected biopsy or archival tissue:	Newly collected biopsy or archival tissue:

biomarker assessment		during immunotherapy	Archival tissue (mostly from primary breast tumors): N = 47 (25%)			Primary breast tumor samples: N = 563 Metastatic tumor samples: N = 337	Primary breast tumor samples: N = 336 Metastatic tumor samples: N = 315
PD-L1 testing and scoring	IHC Ventana SP142 PD-L1 scored on ICs: IC0 <1% IC1 ≥1% and <5% IC2 ≥ 5% and <10% IC3 ≥ 10%	IHC 22C3	IHC 22C3 Positive if CPS ≥ 1	IHC 22C3 Positive if CPS ≥1	IHC 22C3 Positive if CPS ≥ 1 and CPS ≥ 10	IHC Ventana SP142 Positive if PD-L1 IC ≥ 1%	IHC Ventana SP142 Positive if PD-L1 IC ≥ 1%
PD-L1 population	IC0: N = 21 (18%) IC1: N = 17 (15%) IC2: N = 49 (42%) IC3: N = 25 (22%)	PD-L1 IC ≥ 1%: N = 60 (86%) PD-L1 IC ≥ 5%: N = 47 (67%) PD-L1 TC ≥ 1%: N = 44 (63%) PD-L1 TC ≥ 5 %: N = 23 (33%)	Cohort A CPS ≥ 1: N = 105 (62%) Cohort B CPS ≥ 1: N = 84 (100%)	CPS < 1: N = 217 (35%) CPS ≥1: N = 405 (65%) CPS ≥ 10: N = 194 (31%) CPS ≥ 20: N = 109 (18%)	CPS < 1: N = 211 (25%) CPS ≥ 1: N = 636 (75%) CPS ≥ 10: N = 323 (38%)	PD-L1 IC ≥ 1%: N = 368 (41%) PD-L1 IC ≥1% and <5%: N = 243 (27%) PD-L1 IC ≥ 5%: N = 125 (14%) Primary breast tumor samples N = 563 PD-L1 ≥ 1%: N = 247 (44%) Metastatic tumor samples N = 337 PD-L1 ≥ 1%: N = 121 (36%)	PD-L1 IC ≥ 1%: N = 292 (44.8%) Primary breast tumor samples N = 336 PD-L1 ≥ 1%: N = 161 (48%) Metastatic tumor samples N = 315 PD-L1 ≥ 1%: N = 132 (42%)
TILs population	N = 110 Median IC level distribution 10% (range = 0.5-60%)	sTILs ≥ 5%: N = 39	Median sTILs level = 17.5% (range 6.2-57.5%)	N = 536 Median sTILs distribution 5% (IQR = 14%)	NR	N = 892 Median sTILs distribution 5% (IQR = 3%-10%; range = 0%-90%)	NR
ORR	All lines: 10% Atezolizumab as first line therapy: 24%	20%	Cohort A: 5.3% Cohort B : 21.4%	Pembrolizumab arm : 9.6%	Pembrolizumab arm: 40.8% Placebo arm : 37.0%	Atezolizumab arm : 56% Placebo arm : 45.9%	Atezolizumab arm : 54% Placebo arm : 47%

	Atezolizumab as second line or beyond: 11%			Chemotherapy arm : 10.6%			
mPFS	1.4 months (95% CI 1.3-1.6)	1.9 months (95% CI 1.8-2.0)	Cohort A : 2.0 months (95% CI 1.9-2.0) Cohort B : 2.1 months (95% CI 2.0-2.2)	Pembrolizumab arm : 2.1 months Chemotherapy arm : 3.3 months HR = 1.60 (95% CI 1.33-1.92)	Pembrolizumab arm : 7.5 months Placebo arm : 5.6 months HR = 0.82 (95% CI: 0.69-0.97)	Atezolizumab arm : 7.2 months Placebo arm : 5.5 months HR = 0.79 (95% CI 0.69-0.91) P = 0.002	Atezolizumab arm : 5.7 months Placebo arm : 5.6 months HR = 0.86(95% CI 0.70-1.05)
mOS	8.9 months (95% CI 7.0-12.6)		Cohort A : 9.0 months (95% CI 7.6-11.2) Cohort B : 18.0 months (95% CI 12.9-23.0)	Pembrolizumab arm : 9.9 months Chemotherapy arm 10.8 months HR = 0.97 (95% CI 0.82-1.15)	Pembrolizumab arm : 17.2 months Placebo arm : 15.5 months HR = 0.89 (95% CI 0.76-1.05)	Atezolizumab arm 21 months Placebo arm 18.7 months HR = 0.86 (95% CI 0.72-1.02)	Atezolizumab arm : 22.1 months Placebo arm 28.3 months HR = 1.11 (95% CI 0.76-1.64)
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PD-L1	IC 0/1 or IC 2/3	Responders or non-responders	Cohort A: CPS ≥ 1 or < 1	CPS ≥ 1, 10 or 20: Pembrolizumab vs chemo arm	CPS ≥ 1 or ≥10: Pembrolizumab vs placebo arm	IC ≥ 1% or < 1%: Atezolizumab vs placebo arm	IC ≥ 1%: Atezolizumab vs placebo arm
ORR	IC 0/1: ORR = 5% (95% CI 1.0-18.0) IC 2/3: ORR = 12% (95% CI 6.0-22.0)	Responders: PD-L1 IC ≥ 1% = 15% Non-responders: PD-L1 IC ≥ 1% = 5% P = 0.02 Responders: PD-L1 TC ≥ 1% = 1% Non-responders: PD-L1 TC ≥ 1% = 1% P = 0.4	CPS ≥ 1: ORR = 5.7% (95% CI 2.4-12.2) CPS < 1: ORR = 4.7% (95% CI 1.1-13.4)	CPS ≥ 1: ORR = 12.3 vs 9.4 % CPS ≥ 10: ORR = 17.7 vs 9.2% CPS ≥ 20: ORR = 26.3 vs 11.5 %	CPS ≥ 1: ORR = 44.9 vs 38.9% CPS ≥ 10: ORR = 52.7 vs 40.8%	PD-L1 IC ≥ 1%: ORR = 58.9% vs 42.6% HR = 1.96 95% CI 1.29-2.98	PD-L1 IC ≥ 1%: ORR = 63% vs 55%
mPFS	IC 0/1: mPFS = 1.4 months (95% CI 1.3-1.5) IC 2/3: mPFS = 1.4 months (95% CI 1.3-1.9) IC 1/2/3: mPFS = 1.4 months (95% CI 1.3-1.9)	NR	CPS ≥ 1: mPFS = 2.0 months (95% CI 1.9-2.1) CPS < 1: mPFS = 1.9 months (95% CI 1.7-2.0)	CPS ≥ 1: mPFS = 2.1 vs 3.1 months HR = 1.35 (95% CI 1.08-1.68) CPS ≥ 10: mPFS = 2.1 vs 3.4 months	CPS <1: mPFS = 6.3 vs 6.2 months HR = 1.08 (95% CI 0.77-1.53) CPS ≥ 1: mPFS = 7.6 vs 5.6 months	PD-L1 IC ≥ 1%: mPFS = 7.6 vs 5.3 months HR = 0.65 (95% CI 0.52-0.82) PD-L1 IC <1%: mPFS = 5.6 vs 5.6 months	PD-L1 ≥ 1%: mPFS = 6 vs 5.7 months HR = 0.82 (95% CI 0.60-1.12)

				HR = 1.14 (95% CI 0.82-1.59) CPS ≥ 20: mPFS = 3.4 vs 2.4 months HR = 0.76 (95% CI 0.49-1.18)	HR = 0.74 (95% CI 0.61-0.90) CPS ≥ 10: mPFS = 9.7 vs 5.6 months HR = 0.66 (95% CI 0.50-0.88)	HR = 0.92 (95% CI 0.77-1.10)	
mOS	IC 0/1: mOS = 7.0 months (95% CI 5.1-12.6) IC 2/3: mOS = 10.5 months (95% CI 7.1-14.7)	NR	CPS ≥ 1: mOS = 8.8 months (95% CI 7.1-11.2) CPS < 1: mOS = 9.7 months (95% CI 6.2-12.6)	CPS ≥ 1: mOS = 10.7 vs 10.2 months HR 0.86 (95% CI 0.69-1.06) P = 0.073 CPS ≥ 10: mOS = 12.7 vs 11.6 months HR 0.78(95% CI 0.57-1.06) P = 0.057 CPS ≥ 20: mOS = 14.9 vs 12.5 months HR = 0.58 (95% CI 0.38-0.88) P = 0.50	CPS < 1: mOS = 16.2 vs 14.7 months HR = 0.97 (95% CI 0.72-1.32) CPS ≥ 1: mOS = 17.6 vs 16.0 months HR = 0.86 (95% CI 0.72-1.04) P= 0.0563 CPS ≥ 10: mOS = 23 vs 16.1 months HR = 0.73 (95% CI 0.55-0.95)	PD-L1 IC ≥ 1%: mOS = 25.0 vs 18.0 months HR = 0.71 (95% CI 0.54-0.94) PD-L1 IC <1%: mOS = 19.7 vs 19.6 months HR = 0.97 (95% CI 0.78-1.20)	PD-L1 ≥ 1%: mOS = 15.2 vs 15.8 months HR = 1.11 (95% CI 0.76-1.64)
TILs	ICs level > 10% or ≤ 10%	Responders or non-responders	TILs ≥ or < median	TILs as continous variable	NR	sTIL ≥ 10% or < 10%: Atezolizumab vs placebo arm	NR
ORR	Median ICs level > 10%: ORR = 13% (95% CI 4.0-22.0) Median ICs level ≤ 10%: ORR = 7% (95% CI 0-14.0)	Responders: sTILs = 22.5% Non-responders: sTILs = 5% P = 0.004	Cohort A : Median Tils = 5% Median sTILs 5%: ORR = 6% Median sTILs < 5%: ORR = 2% Cohort B: Median sTILs = 17.5% Median sTILs ≥ 17.5%: ORR = 39% Median sTILs < 17.5%: ORR = 9%	Pembrolizumab arm ORR = 9.2% P = 0.0007 Chemotherapy arm: ORR = 11% P = 0.18	NR	NR	NR

mPFS	ICs level > 10% vs ≤ 10% HR = 0.76 (95% CI 0.51-1.14) P = 0.1855	NR	NR	NR		sTILs ≥ 10%: mPFS = 8.3 vs 6.1 months HR = 0.64 (95% CI 0.50-0.84) sTILs < 10%: mPFS = 5.6 vs 5.4 months HR = 0.86 (95% CI 0.73-1.02)	NR
mOS	ICs level > 10% vs ≤ 10% HR = 0.63 (95% CI 0.40-0.98) P = 0.0406	NR	NR	sTILs < 5% or ≥ 5%: Pembrolizumab vs chemo arm TILs < 5%: mOS = 5.9 vs 8.8 months TILs ≥ 5%: mOS = 12.5 vs 11.3 months	NR	sTILs ≥ 10%: mOS = 25 vs 20 months HR = 0.75 (95% CI 0.54-1.03) sTILs < 10%: mOS = 19.2 vs 18.1 months HR = 0.88 (95% CI 0.72-1.08)	NR
CD8	CD8+ ≥ 1.35% or < 1.35%	Responders or non-responders	NR	NR	NR	CD8+ ≥ 0.5% vs < 0.5%: Atezolizumab vs placebo arm	NR
ORR	CD8+ ≥ 1.35%: ORR = 14% (95% CI 4.0-23.0) CD8+ < 1.35%: ORR = 6% (95% CI 0-12.0)	Responders: CD8+ counts per mm^2 = 49.3 Non-responders: CD8+ counts per mm^2 = 25.5 P = 0.01	NR	NR	NR	NR	NR
mPFS	HR = 0.85 95% CI 0.55-1.31 P = 0.46	NR	NR	NR	NR	CD8+ ≥ 0.5%: mPFS = 7.4 vs 5.5 months HR = 0.75 (95% CI 0.62-0.91) CD8+ < 0.5%: mPFS = 5.6 vs 5.6 months HR = 0.86 (95% CI 0.65-1.14)	NR
mOS	HR = 0.68 (95% CI 0.41-1.12) P = 0.13	NR	NR	NR	NR	CD8+ ≥ 0.5%: mOS = 22.6 vs 18.1 months	NR

						HR = 0.69 (95% CI 0.54-0.87) CD8+ < 0.5%: mOS = 16.3 vs 22.3 months HR = 1.16 (95% CI 0.81-1.65)	
TMB	NR	Responders or non-responders	NR	Pembrolizumab or chemo arm	NR	NR	NR
ORR	NR	Responders: median TMB (mut/Mb) = 1.2 Non-responders: median TMB (mut/Mb) = 1.9 P = 0.1	NR	Pembro arm: ORR= 0.58 (95% CI 0.43-0.73) P = 0.154 Chemo arm: ORR=0.43 (95% CI 0.27-0.59) P=0.114	NR	NR	NR
mPFS	NR	NR	NR	NR	NR	PD-L1 positive or negative PD-L1 positive: HR=0.31 95% CI 0.17-0.57 PD-L1 negative: HR=0.84 95% CI 0.48, 1.47	NR

TNBC Triple negative breast cancer ; IHC immunohistochemistry ; CPS Combined positive score ; TC Tumor cells ; IC Immune cells ; TILs Tumor infiltrating lymphocytes ; H&E Hematoxylin and eosin ; ORR Overall response rate ; mPFS median Progression free survival ; mOS median overall survival ; sTILs stroma TILs; TMB = tumor mutational burden, NR : not reported

Supplementary Table S2: Description of major clinical trials assessing ICIs as neoadjuvant treatment in TNBC with biomarkers assessment.

	GeparNuevo	**NeoTRIPaPDL1**	**Impassion 031**	**Keynote 522**
Study Design	Phase II Neoadjuvant nab-paclitaxel and durvalumab vs nab-paclitaxel and placebo followed by adjuvant anthracycline and cyclophosphamide chemotherapy Window cohort with one injection of durvalumab before combination therapy	Phase III Neoadjuvant Carboplatin, nab-paclitaxel in association with atezolizumab vs placebo followed by adjuvant anthracycline based chemotherapy	Phase III Neoadjuvant nab-paclitaxel and atezolizumab vs nab-paclitaxel and placebo followed by adjuvant anthracycline and cyclophosphamide	Phase III Neoadjuvant paclitaxel and carboplatine in association with pembrolizumab vs placebo followed adjuvant anthracycline and cyclophosphamide
Population	N = 174 cT2 to cT4a-d	N = 280 All stage	N = 333 cT2–T4 and cN0–cN3	N = 1174 T1cN1-2 or T2-4N0-2
Biopsy requirement for biomarker assessment	Pre-treatment biopsy Post-treatment biopsies after durvalumab in window cohort	Pre-treatment, on-treatment (day 1, cycle 2) biopsy and surgery	Pre-treatment biopsy and surgery	Pre-treatment biopsy and surgery
PD-L1 testing and scoring	IHC Ventana SP263 Positive if PD-L1 TC or IC ≥ 1%	IHC Ventana SP142 PD-L1 scored on IC and TC: IC0 <1% IC1 ≥1% and <5% IC2 ≥ 5% and <10% IC3 ≥ 10%	IHC Ventana SP142 Positive if PD-L1 IC ≥ 1%	IHC 22C3 Positive if CPS ≥ 1
PD-L1 population	PD-L1 positive: N = 138 (87%)	IC1: N = 91 (32.5%) IC2: N = 48 (17%)	PD-L1 positive: N = 152 (46%)	PD-L1 positive: N = 973 (83%)

TILs population	sTILs 0-10%: N = 66 (38%) sTILs 11-59%: N = 83 (48%) sTILs ≥ 60%: N = 25 (14%)	sTILs ≥ 40%: N = 59 (34%)		
pCR rate	Durvalumab vs Placebo Whole cohort 53.4 vs 44.2 % OR = 1.45 (95% CI 0.80–2.63) P = 0.224 Window cohort 61 % vs 41.4 % OR = 2.22 (95% CI 1.06–4.64) P = 0.035 No window cohort 37.9% vs 50% OR = 0.61 (95% CI 0.21–4.17) P = 0.360	Atezolizumab vs Placebo 52.3 vs 47.7 % P = 0.46	Atezolizumab vs Placebo 58% vs 41% P = 0.0044	Pembrolizumab vs Placebo 64.8% vs 51.2% (95% CI 5.4 - 21.8) P < 0.001
mDFS	NR	NR	HR = 0.74 95% CI 0.32-1.70 P = NS	DFS at 18 months: 91.3% vs 85.3% HR = 0.63 95% CI 0.43 - 0.93
mOS	NR	NR	HR = 0.69 95% CI 0.25-1.87 P = NS	
pCR, SUBGROUPS ANALYSIS				

PD-L1	Durvalumab arm: PD-L1 positive vs negative 58% vs 44.4% OR = 1.72 (95% CI 0.43-6.98) P = 0.445 Placebo arm: PD-L1 positive vs negative 50.7% vs 18.2 % OR = 4.63 (95% CI 0.93-23.01) P = 0.061	Atezolizumab vs Placebo arm IC0 : 35.1% vs 41.1% IC1 : 56,2% vs 44% IC2/3 : 87% vs 72%	PD-L1 positive: Atezolizumab vs Placebo arm 69% vs 49% P = 0.021 PD-L1 negative: Atezolizumab vs Placebo arm 48% vs 34% P = NS	PD-L1 positive : Pembrolizumab vs Placebo arm 68.9% vs 54.9% PD-L1 negative: Pembrolizumab vs Placebo arm 45.3% vs 30.3%
TILs	Durvalumab arm Baseline sTILs as continuous marker OR = 1.23 (95% CI 1.04-1.6) P = 0.019 Baseline iTILs as continuous marker OR = 1.58 (95% CI 0.85-2.97) P = 0.150 Placebo arm Baseline sTILs as continuous marker OR = 1.39 (95% CI 1.12-1.74) P = 0.003 Baseline iTILs as continuous marker OR = 0.94 (95% CI 0.73-1.22) P = 0.636	Atezolizumab arm sTIls high vs low OR = 3.41 (95% CI 1.32-8.82) P = 0.01 sTILs Intermediate vs low OR = 1.62 (95% CI 0.71-3.74) P = 0.25 iTILs high vs low OR = 6.84 (95% CI: 2.60-18.01) P = 0.0001 iTILs intermediate vs low OR = 2.66 (95% CI: 1.13-6.30) P = 0.03 Placebo arm sTIls high vs low OR = 1.76 (95% CI 0.75-4.17) P = 0.19	NR	NR

		sTILs Intermediate vs low OR = 0.63 (95% CI 0.26-1.55) P = 0.3 iTILs high vs low OR = 2.22 (95% CI 0.95-5.22) P = 0.06 iTILs intermediate vs low OR = 1.44 (95% CI 0.59-3.49) P = 0.3		

IHC immunohistochemistry ; TC Tumor cells ; IC Immune cells ; CPS Combined positive score ; TILs Tumor infiltrating lymphocytes ; H&E Hematoxylin and eosin ; pCR pathologic complete response ; OR Odd Ratio ; mDFS median Disease free survival ; NS not significant ; mOS median overall survival ; sTILs stroma TILs ; iTILS intra-tumor TILs ;