VIRTUAL 2020 ESMO congress

IMpassion031: results from a Phase III study of neoadjuvant atezolizumab + chemotherapy in early triple-negative breast cancer

Nadia Harbeck,[1] Hong Zhang,[2] Carlos H Barrios,[3] Shigehira Saji,[4] Kyung Hae Jung,[5] Roberto Hegg,[6] Andreas Koehler,[7] Joohyuk Sohn,[8] Hiroji Iwata,[9] Melinda L. Telli,[10] Cristiano Ferrario,[11] Kevin Punie,[12] Frédérique Penault-Llorca,[13] Shilpen Patel,[14] Anh Nguyen Duc,[15] Mario Liste-Hermoso,[15] Vidya Maiya,[14] Luciana Molinero,[14] Stephen Y. Chui,[14] Elizabeth A. Mittendorf[16]

[1]Breast Center, Department of OB/GYN and CCC LMU, LMU University Hospital, Munich, Germany; [2]Memorial Sloan Kettering Cancer Center, New York, NY, USA; [3]Centro de Pesquisa em Oncologia HSL, PUCRS, Porto Alegre, RS, Brazil; [4]Fukushima Medical University, Fukushima, Japan; [5]Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea; [6]University of São Paulo, São Paulo, Brazil; [7]Gemeinschaftspraxis für Haematologie und Onkologie Langen, Langen, Germany; [8]Yonsei Cancer Center, Yonsei University Health System, Seoul , Korea; [9]Aichi Cancer Center Hospital, Nagoya, Japan; [10]Stanford University School of Medicine, Stanford, USA; [11]Jewish General Hospital–McGill University, Montréal, QC, Canada; [12]Department of General Medical Oncology and Multidisciplinary Breast Centre, Leuven Cancer Institute, University Hospitals Leuven, Leuven, Belgium; [13]Department of Biopathology, Centre Jean Perrin and University Clermont Auvergne/INSERM U1240, Clermont-Ferrand, France; [14]Genentech, Inc., South San Francisco, CA, USA; [15]F. Hoffmann-La Roche, Ltd., Basel, Switzerland; [16]Dana-Farber/Brigham and Women's Cancer Center, Boston, MA, USA

Disclosures

- Honoraria for lectures and/or consulting: Agendia, Amgen, AstraZeneca, BMS, Celgene, Daiichi-Sankyo, Genomic Health, Lilly, MSD, Novartis, Odonate, Pierre Fabre, Pfizer, Roche, Samsung, Sandoz/Hexal, Seattle Genetics
- Institution: clinical phase II-IV trials
- Other: co-Director West German Study Group (WSG)

Background

- Stage I-III TNBC accounts for 10%-20% of new diagnoses of early breast cancer[1]
- IMpassion130 showed that atezolizumab combined with nab-paclitaxel provided PFS benefit and a clinically meaningful OS benefit for PD-L1–positive[a] metastatic TNBC with an acceptable safety profile vs nab-paclitaxel alone[2]
- IMpassion031 (NCT03197935) is a phase III trial evaluating the efficacy and safety of atezolizumab vs placebo in combination with neoadjuvant chemotherapy consisting of sequential nab-paclitaxel and doxorubicin-cyclophosphamide for treatment of early-stage TNBC

OS, overall survival; PD-L1, programmed death-ligand 1; PFS, progression-free survival; TNBC; triple-negative breast cancer.
[a] PD-L1–expressing immune cells covering ≥ 1% of tumour area (VENTANA SP142 assay).

1. Howlader N, et al. *SEER Cancer Statistics Review, 1975-2014*. Bethesda, MD: National Cancer Institute: 2017.
2. Schmid P, et al. *N Engl J Med.* 2018;379:2108-2121.

IMpassion031: Phase III atezolizumab neoadjuvant study in eTNBC[1,2]

A randomised, multicentre, international, double-blind, placebo-controlled trial

N = 333

- TNBC, with primary tumour > 2 cm
- cT2-cT4, cN0-cN3, cM0
- Known PD-L1 status (IHC)
- No prior therapy for treatment or prevention of BC
- ECOG PS 0 or 1

Stratification Factors:
- Stage II vs Stage III
- PD-L1 IC < 1% vs IC ≥ 1%

R 1:1

Atezolizumab 840 mg IV q2w + *nab*-paclitaxel 125 mg/m² IV qw	Atezolizumab 840 mg IV q2w + Doxorubicin 60 mg/m² IV q2w Cyclophosphamide 600 mg/m² IV q2w	SURGERY	Atezolizumab 1200 mg IV q3w x 11 doses	Survival follow-up[a]
Placebo + *nab*-paclitaxel 125 mg/m² IV qw	Placebo + Doxorubicin 60 mg/m² IV q2w Cyclophosphamide 600 mg/m² IV q2w		Observation[a]	
12 weeks	8 weeks	*pCR*	≤ 1 year from start	

Co-primary endpoints: pathologic complete response (pCR, ypT0/is ypN0) in ITT and PD-L1–positive (IC ≥ 1%) subpopulation

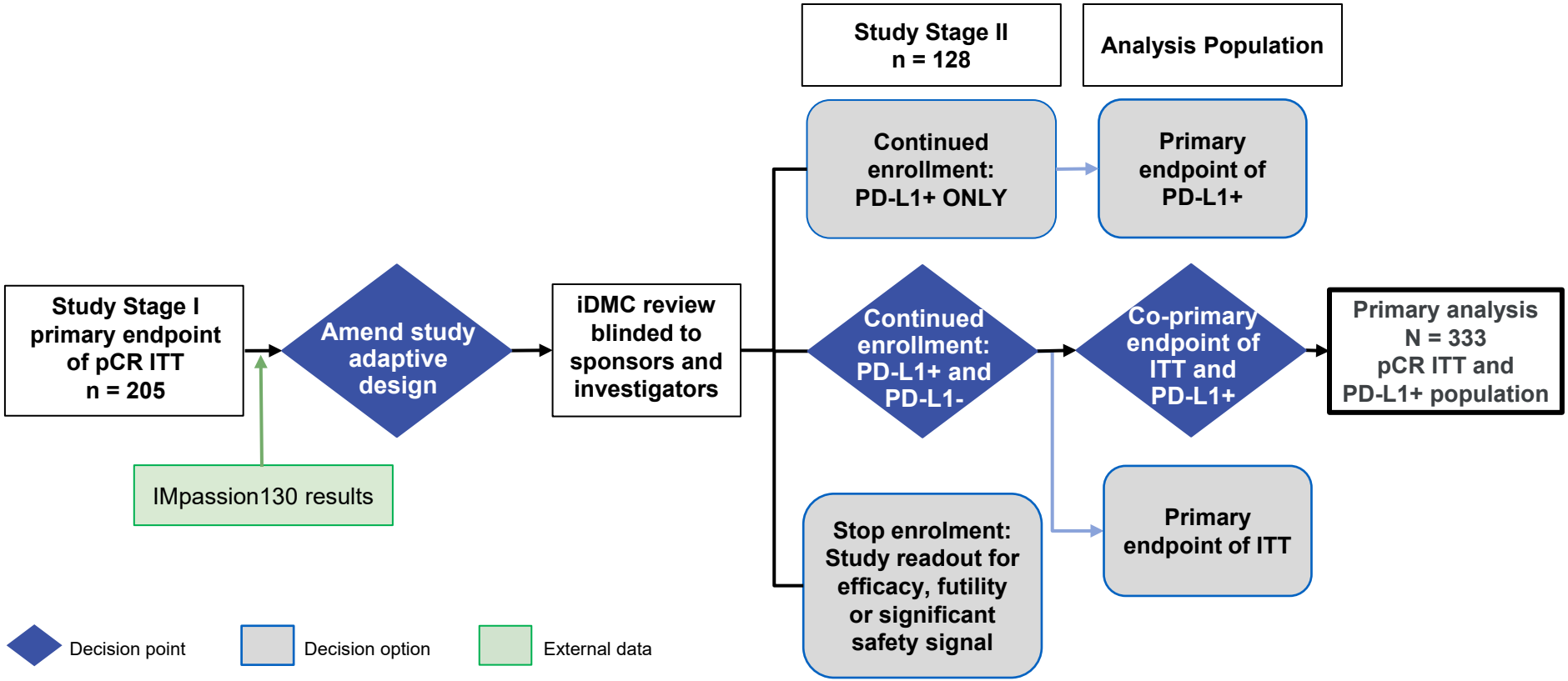
Secondary endpoints: EFS, DFS, and OS in ITT and in PD-L1–positive subpopulation, safety, PROs

[a] Postsurgical management of patients was at the discretion of the treating investigator and based on local practice guidelines.

pCR, pathologic complete response; PD-L1 IC, PD-L1–expressing tumor-infiltrating immune cells as percentage of tumor area using the VENTANA SP142 assay; PRO, patient-reported outcome; q2w, every 2 weeks, q3w, every 3 weeks, qw, every week.

1. Mittendorf E, et al. SABCS 2017 [abstract 17-OT2-07-03]. 2. ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/study/NCT03197935. Accessed 11 August 2020.

IMpassion031: Adaptive enrichment design



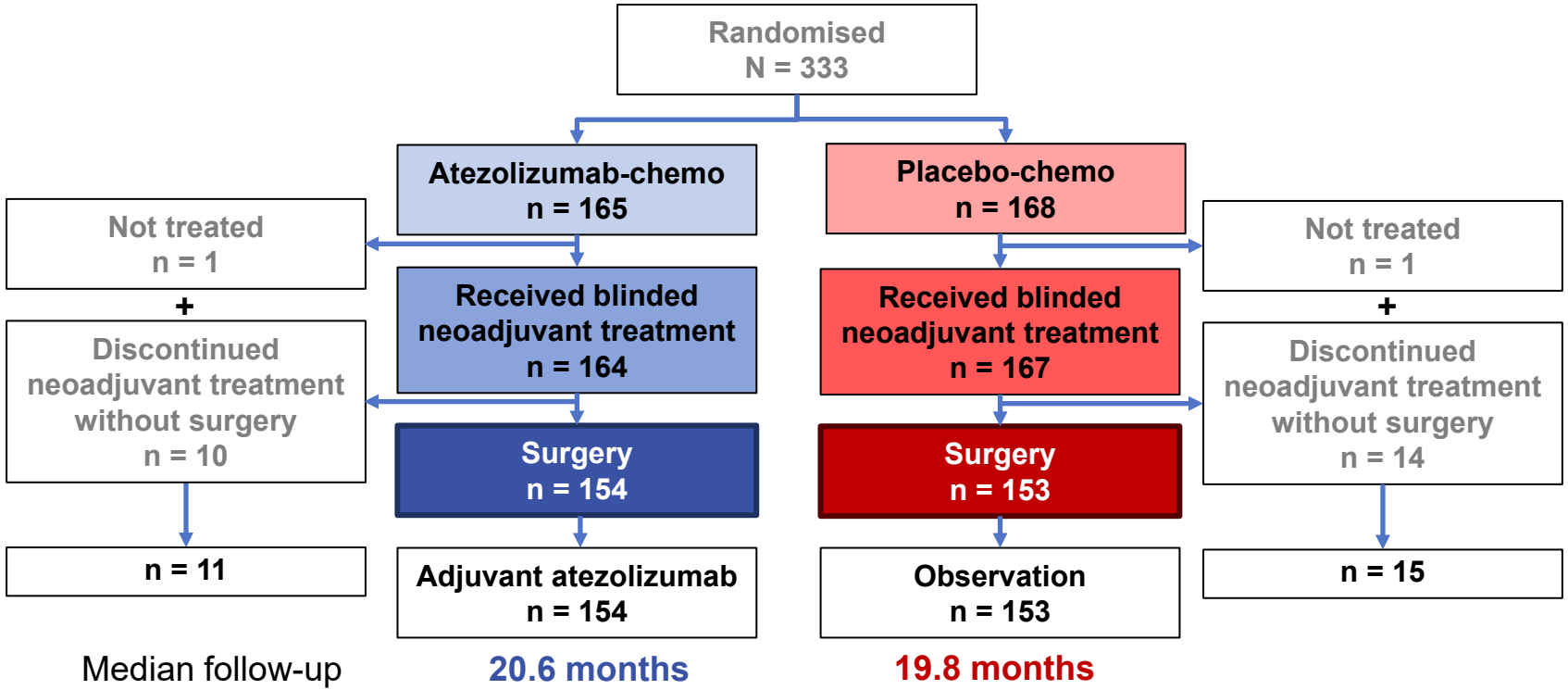
iDMC, independent data monitoring committee.

IMpassion031: Baseline characteristics (ITT)

Characteristic		Atezolizumab-Chemo (n = 165)	Placebo-Chemo (n = 168)
Age, median (range), years		51.0 (22-76)	50.5 (26-78)
ECOG PS, n (%)	0	156 (94.5)	153 (91.1)
	1	8 (4.8)	14 (8.3)
	Missing	1 (0.6)	1 (0.6)
Race, n (%)	White	102 (61.8)	108 (64.3)
	Asian	47 (28.5)	41 (24.4)
	Black or African American	9 (5.5)	15 (8.9)
	Unknown	3 (1.8)	4 (2.4)
	Multiple	4 (2.4)	0
AJCC stage, n (%)[a,b]	II	126 (76.4)	129 (76.8)
	III	38 (23.0)	39 (23.2)
PD-L1, n (%)[b]	IC < 1%	87 (52.7)	92 (54.8)
	IC ≥ 1%	78 (47.3)	76 (45.2)
Staging of primary tumour, n (%)	T2	116 (70.3)	123 (73.2)
	T3/T4	49 (29.7)	45 (26.8)
Staging of regional lymph nodes, n (%)	N0	109 (66.1)	96 (57.1)
	N1/N2/N3	56 (33.9)	72 (42.9)
Histological subtype[c]	Ductal	141 (85.5)	140 (83.3)
	Lobular	1 (0.6)	4 (2.4)
	Tubular	1 (0.6)	4 (2.4)
	Other	15 (9.1)	13 (7.7)
	NOS	17 (10.3)	18 (10.7)

[a] One patient in the atezolizumab arm was enrolled with Stage IV disease and was discontinued due to protocol deviation before starting study treatment.
[b] Stratification factor.
[c] One patient can have ≥ 1 subtype.
AJCC, American Joint Committee on Cancer; NOS, not otherwise specified.

IMpassion031: Patient disposition (ITT)



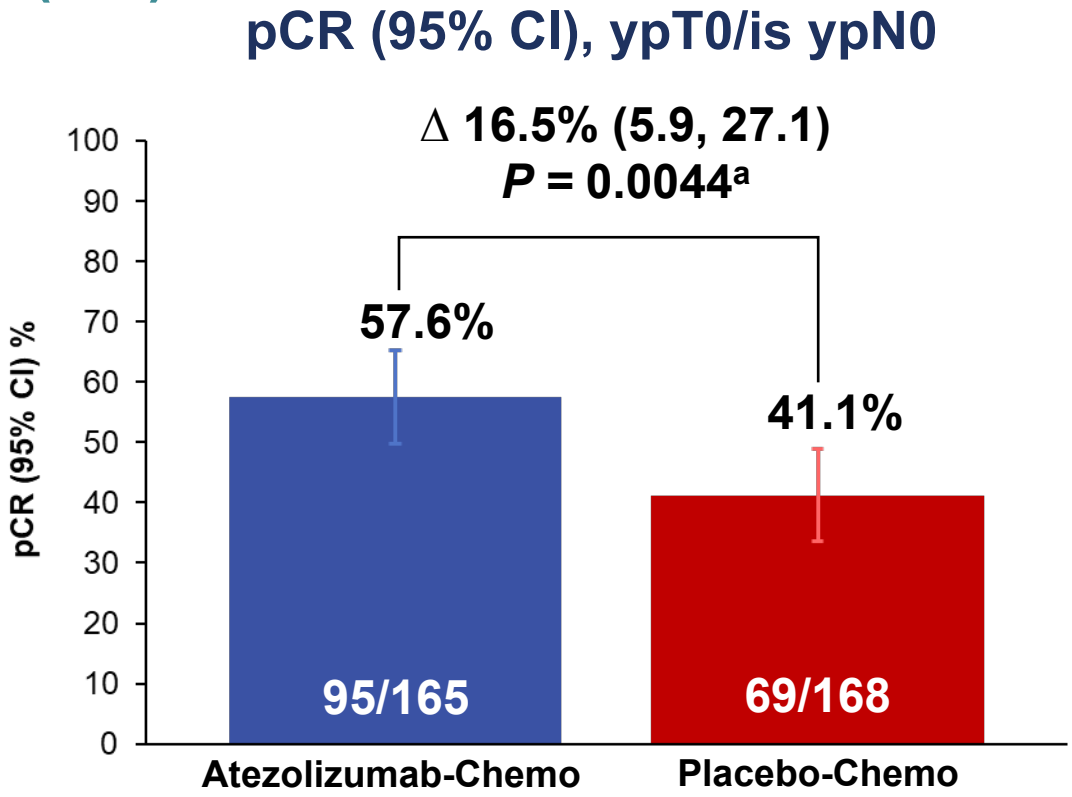
Clinical cutoff: April 3, 2020

IMpassion031: Patients without surgery or missing pathologic complete response assessment (ITT)

Reason, n (%)	Atezolizumab-Chemo (n = 165)	Placebo-Chemo (n = 168)
Not treated or discontinued treatment	**11 (6.7)**	**15 (8.9)**
Protocol deviation	1[a] (0.6)	0
Death	1 (0.6)	1 (0.6)
Progressive disease	5 (3.0)	7 (4.2)
Withdrawal by patient	1 (0.6)	6 (3.6)
Physician decision	1 (0.6)	1 (0.6)
Surgery ≥ 4 months after last dose	1[b] (0.6)	0
Adverse event	1 (0.6)	0

AE, adverse event.
[a] Patient had metastatic disease at entry.
[b] Patient had surgery delayed due to AE.

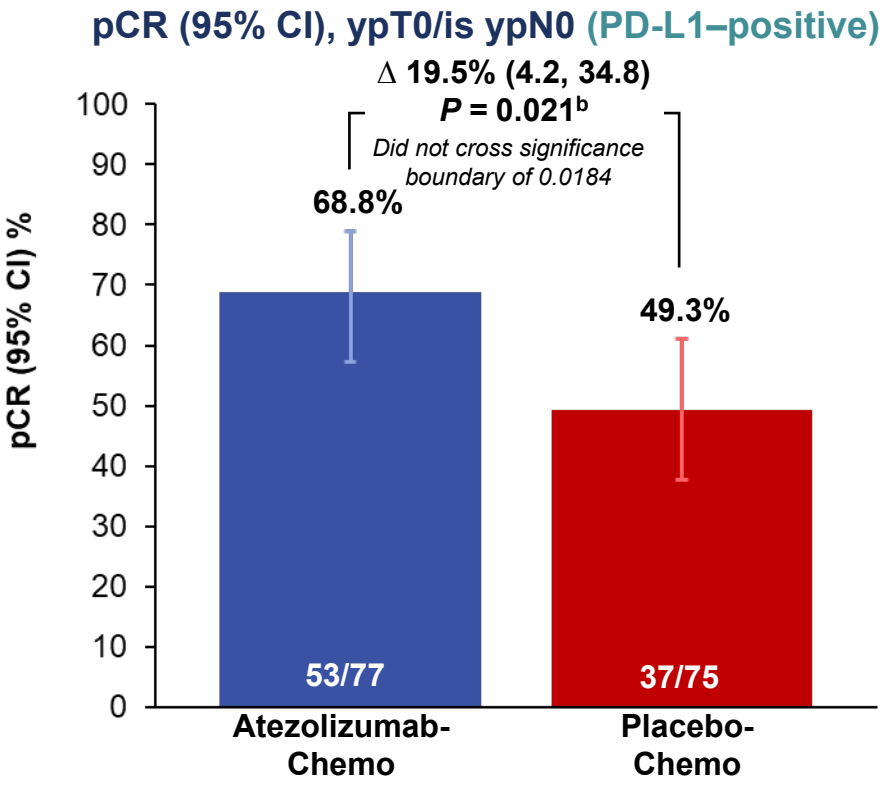
IMpassion031: Co-primary endpoint pathologic complete response (ITT)

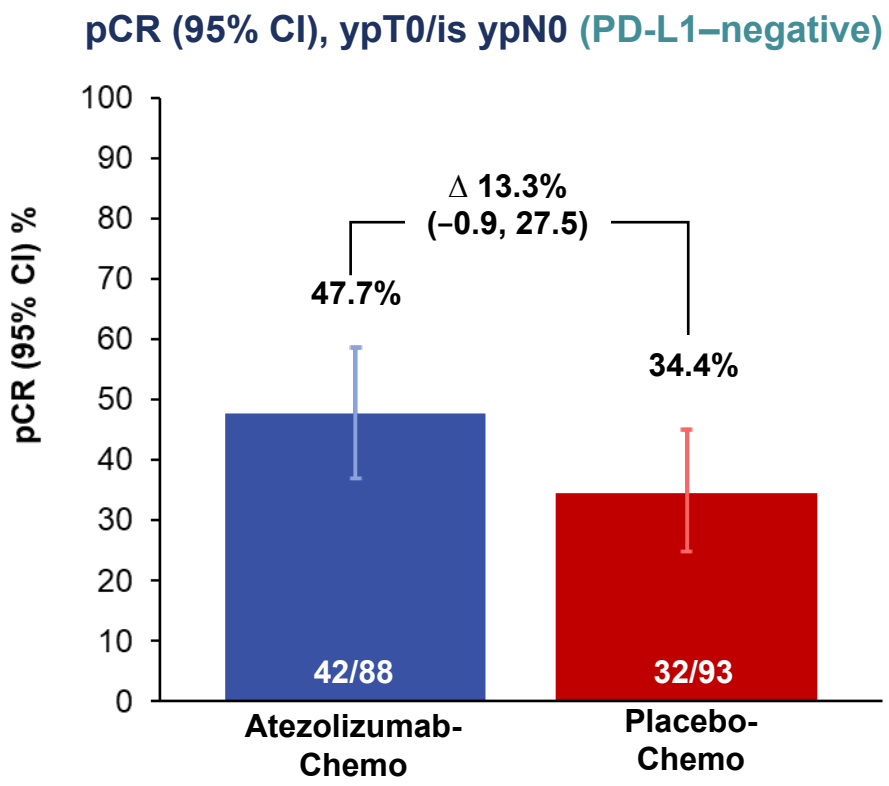


[a] One-sided significance boundary *P* = 0.0184 (accounting for the adaptive enrichment design). *P* = 0.0085 for the intersection hypothesis of pCR in the ITT and PD-L1–positive population.

Harbeck et al. IMpassion031 Primary Analysis https://bit.ly/3ji97cn

IMpassion031: Co-primary endpoint pathologic complete response in PD-L1 positive tumours[a]





[a] PD-L1+, PD-L1 IC ≥ 1%; PD-L1–, PD-L1 IC < 1%.
[b] One-sided significance boundary *P* = 0.0184 (accounting for the adaptive enrichment design). *P* = 0.0085 for the intersection hypothesis of pCR in the ITT and PD-L1–positive population.

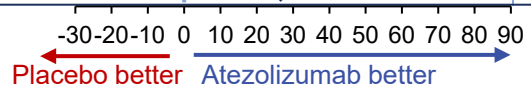
Harbeck et al. IMpassion031 Primary Analysis https://bit.ly/3ji97cn

IMpassion031: Pathologic complete response (ITT)

Subgroup analysis

Stratification factors

Subgroup	Atezolizumab-Chemo		Placebo-Chemo			
	pCR (%)	n/n	pCR (%)	n/n	Difference in pCR (95% CI)	Δ (%)	95% CI
Overall	57.6	95/165	41.1	69/168		16.5	5.9, 27.1
AJCC BC Stage							
II	61.9	78/126	46.5	60/129		15.4	3.3, 27.5
III	44.7	17/38	23.1	9/39		21.7	1.1, 42.3
PD-L1 status[a]							
PD-L1-positive	68.8	53/77	49.3	37/75		19.5	4.2, 34.8
PD-L1-negative	47.7	42/88	34.4	32/93		13.3	−0.9, 27.5
Age group							
< 40 years	58.8	20/34	35.7	15/42		23.1	1.1, 45.1
≥ 40 years	57.3	75/131	42.9	54/126		14.4	2.3, 26.5
Race							
White	57.8	59/102	44.4	48/108		13.4	0, 26.8
Black	44.4	4/9	26.7	4/15		17.8	−21.7, 57.2
Asian	57.4	24/47	34.1	14/41		23.3	3.0, 43.6
ECOG PS							
0	57.7	90/156	43.1	66/153		14.6	3.5, 25.6
1	62.5	5/8	21.4	3/14		41	1.2, 80.9
Regional lymph node							
LN-negative	57.8	63/109	49	47/96		8.8	−4.8, 22.5
LN-positive	57.1	32/56	30.6	22/72		26.6	9.8, 43.4



[a] PD-L1–positive, PD-L1 IC ≥ 1%; PD-L1–negative, PD-L1 IC < 1%.

IMpassion031: Secondary time-to-event endpoints (ITT)[a]

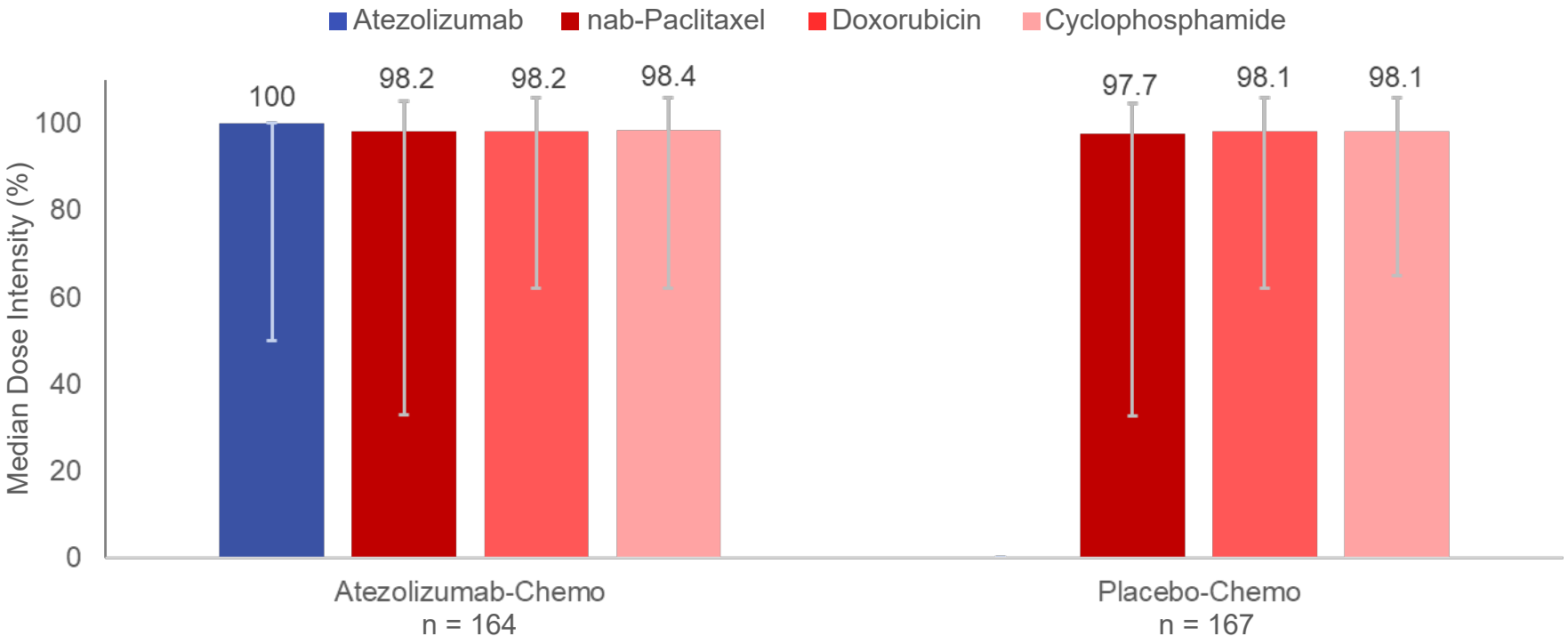
		Atezolizumab-Chemo	Placebo-Chemo
EFS	Events, n/N (%)	17/165 (10.3%)	22/168 (13.1%)
	Median (95% CI)	NE (NE, NE)	NE (NE, NE)
	Stratified HR (95% CI)	**0.76** (0.40, 1.44)	
DFS	Events, n/N (%)	10/154[b] (6.5%)	13/153[b] (8.5%)
	Median (95% CI)	NE (NE, NE)	NE (NE, NE)
	Stratified HR (95% CI)	**0.74** (0.32, 1.70)	
OS	Events, n/N (%)	7/165 (4.2%)	9/168 (5.4%)
	Median (95% CI)	NE (27.40, NE)	NE (NE, NE)
	Stratified HR (95% CI)	**0.69** (0.25, 1.87)	

- EFS, DFS and OS trends support the pCR benefit seen for atezolizumab-chemo
- EFS, DFS and OS are immature and will continue to be collected until the final analysis per protocol

NE, not estimable.
[a] This study was not formally powered for long-term secondary efficacy time-to-event endpoints.
[b] Only patients having surgery are included.

IMpassion031: Treatment exposure in the neoadjuvant phase

Median dose intensity[a]



Dose intensity for a patient is defined as the total dose received over all planned cycles divided by the total planned dose.

[a] Error bars indicate range.

Harbeck et al. IMpassion031 Primary Analysis https://bit.ly/3ji97cn

IMpassion031: Overall safety profile in the neoadjuvant phase

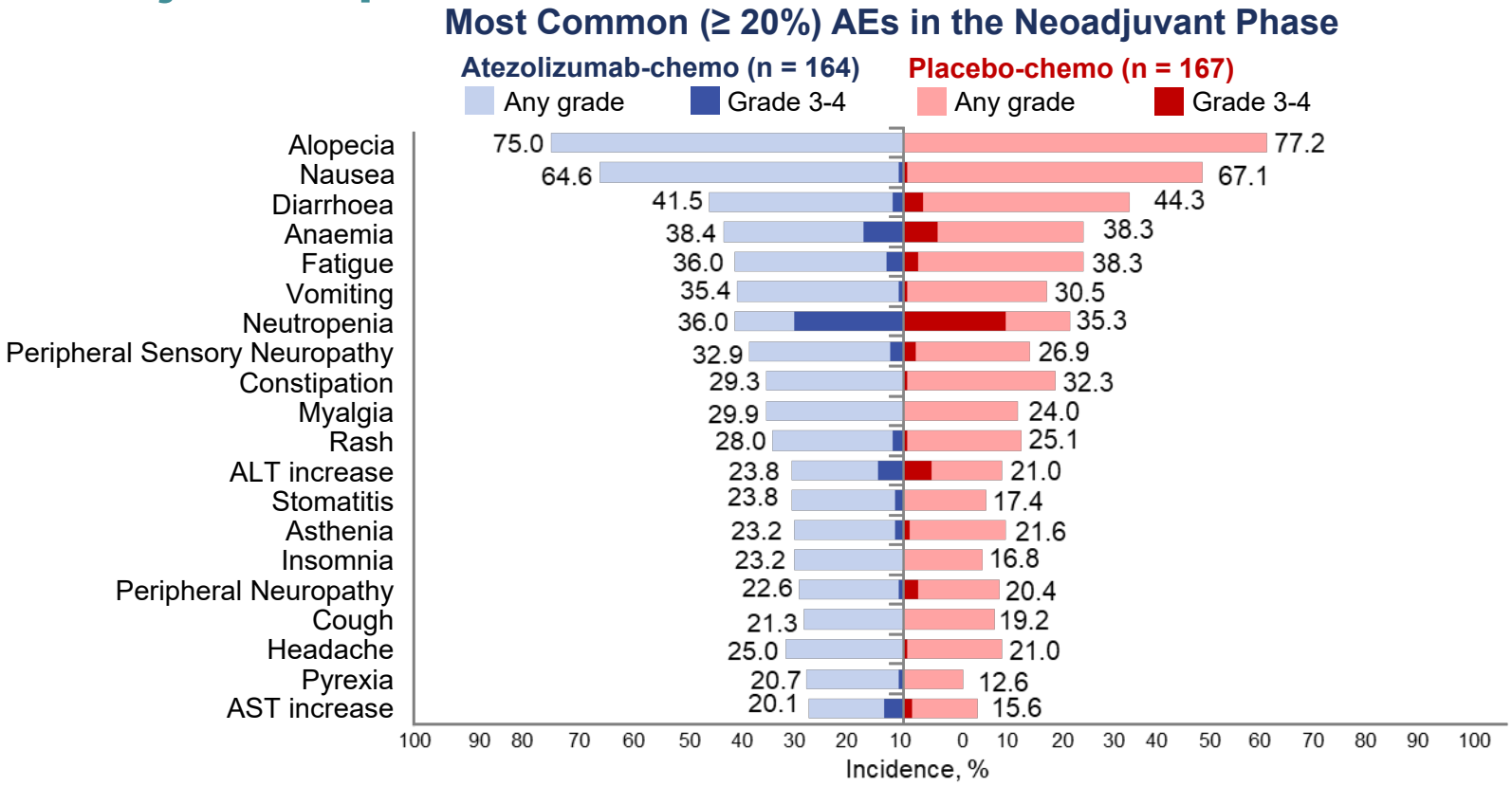
	Atezolizumab-Chemo (n = 164)	Placebo-Chemo (n = 167)
Number of patients ≥ 1 AE, n (%)	163 (99.4)	167 (100)
Grade 3-4, n (%)	103 (62.8)	101 (60.5)
Treatment-related Grade 3-4 AE	93 (56.7)	89 (53.3)
Grade 5, n (%)[a]	1 (0.6)	1 (0.6)
Serious AE, n (%)	50 (30.5)	30 (18.0)
Treatment-related SAE	37 (22.6)	26 (15.6)
AE leading to any treatment discontinuation, n (%)	37 (22.6)	33 (19.8)
Of atezolizumab/placebo	21 (12.8)	19 (11.4)
Of nab-paclitaxel	27 (16.5)	23 (13.8)
Of doxorubicin	8 (4.9)	10 (6.0)
Of cyclophosphamide	8 (4.9)	10 (6.0)

- Rates of treatment-related serious AEs were higher in the atezolizumab-chemo arm
- Grade 3-4 AEs and discontinuation rates were well balanced

[a] One unrelated Grade 5 AE each occurred in the atezolizumab-chemo arm (road traffic accident) and the placebo-chemo arm (pneumonia).

Harbeck et al. IMpassion031 Primary Analysis https://bit.ly/3ji97cn

IMpassion031: Most common (≥ 20%) AEs in the neoadjuvant phase



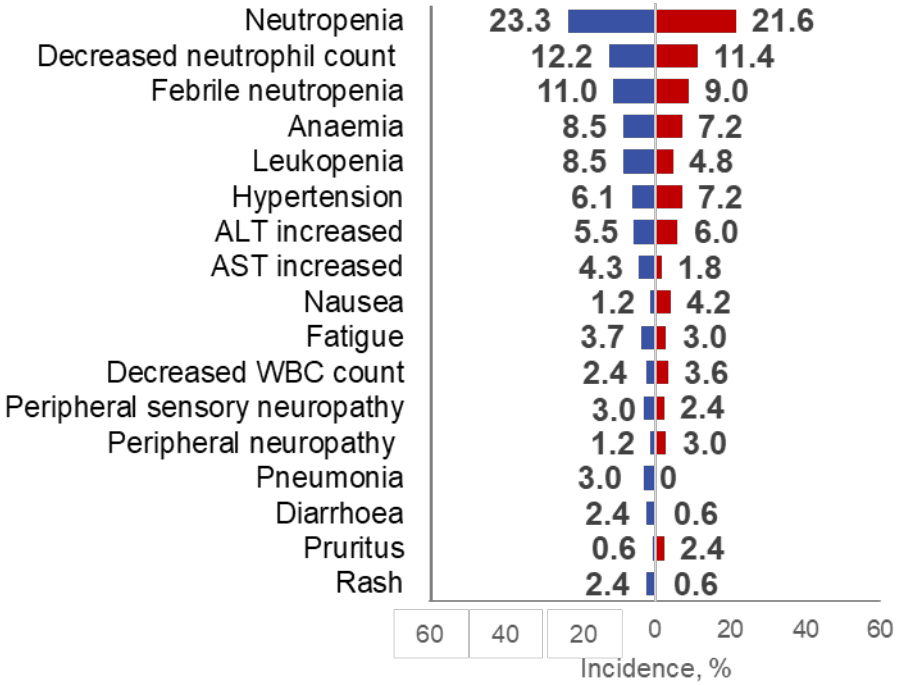
ALT, alanine aminotransferase; AST, aspartate aminotransferase.

Harbeck et al. IMpassion031 Primary Analysis https://bit.ly/3ji97cn

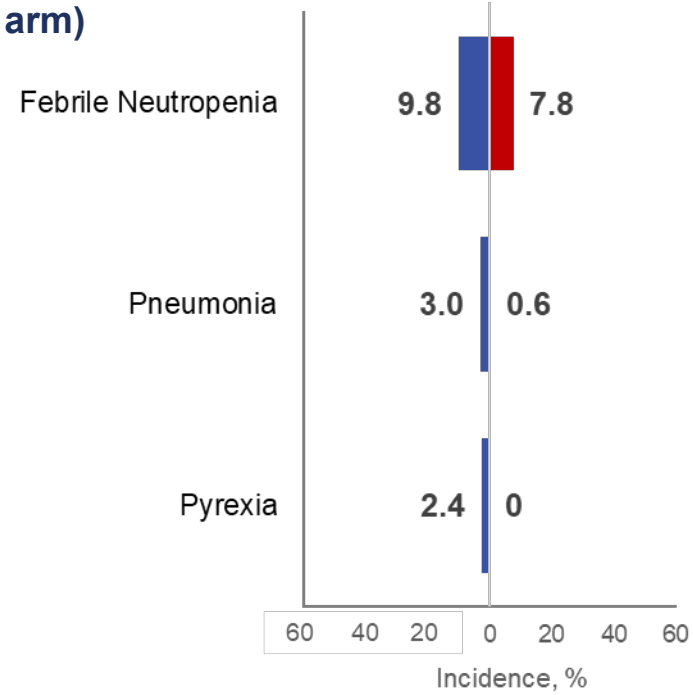
IMpassion031: Grade 3-4 AEs and serious AEs in the neoadjuvant phase

Atezolizumab-chemo (n = 164) Placebo-chemo (n = 167)

Grade 3-4 adverse events (≥ 2% in either arm)



Serious adverse events (≥ 2% in either arm)



WBC, white blood cell.

Harbeck et al. IMpassion031 Primary Analysis https://bit.ly/3ji97cn

IMpassion031: Adverse events of special interest (AESI) in the neoadjuvant phase[a]

Summary, n (%)	Atezolizumab-Chemo (n = 164)		Placebo-Chemo (n = 167)	
All AESIs	115 (70.1)		101 (60.5)	
Grade 3-4 AESI	24 (14.6)		20 (12.0)	
Serious AESI	11 (6.7)		5 (3.0)	
AESI requiring systemic corticosteroids	21 (12.8)		16 (9.6)	
Specific AESIs, n (%)	**Any Grade**	**Grade 3-4**	**Any Grade**	**Grade 3-4**
Hepatitis	2 (1.2)	0	1 (0.6)	0
Hypothyroidism	11 (6.7)	0	2 (1.2)	0
Hyperthyroidism	5 (3.0)	0	0	0
Adrenal insufficiency	0	0	1 (0.6)	0
Pneumonitis	2 (1.2)	1 (0.6)	2 (1.2)	0
Colitis	1 (0.6)	1 (0.6)	1 (0.6)	0
Guillain-Barré syndrome	0	0	2 (1.2)	1 (0.6)
Diabetes	1 (0.6)	0	1 (0.6)	0
Encephalitis[b]	1 (0.6)	1 (0.6)	0	0
Myositis	1 (0.6)	1 (0.6)	0	0
Rash	80 (48.8)	6 (3.7)	82 (49.1)	6 (3.6)
Infusion-related reactions	17 (10.4)	1 (0.6)	11 (6.6)	1 (0.6)
Ocular inflammatory toxicity	2 (1.2)	0	0	0
Severe cutaneous reactions	0	0	1 (0.6)	0

[a]AESI as medical concepts (grouped by MedDRA preferred terms) as defined by the sponsor.
[b]One additional case of photophobia in each arm not included.

IMpassion031: Summary

- Atezolizumab + chemotherapy resulted in a statistically significant and clinically meaningful +16.5% increase in pCR rate vs placebo + chemotherapy (57.6% vs 41.1%) in the ITT population (*P* = 0.0044)
  - Benefit was observed regardless of PD-L1 status and across clinical subgroups
- Although the data are immature, trends for EFS, DFS, and OS support the pCR benefit seen with atezolizumab + chemotherapy
- The safety profile of atezolizumab + chemotherapy (nab-paclitaxel/AC) was consistent with the known risks of the individual study drugs
  - Commonly reported AEs were relatively similar between arms and mostly driven by chemotherapy
- The combination of atezolizumab with neoadjuvant chemotherapy for stage II-III TNBC provides clinically meaningful pCR benefit with an acceptable safety profile independent of PD-L1 status
- This new combination therapy may offer an improved curative treatment option for this patient population with a high unmet medical need

Acknowledgements

- The patients and their families
- Participating study investigators and clinical sites
- This study is sponsored by F. Hoffmann-La Roche, Ltd.
- Medical writing assistance for this presentation was provided by Chris Lum, PhD, of Health Interactions and funded by F. Hoffmann-La Roche, Ltd.