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Adding atezolizumab to adjuvant chemotherapy for stage II and III triple-negative breast cancer is unlikely to improve efficacy: interim analysis of the ALEXANDRA/IMpassion030 phase 3 trial

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Michail Ignatiadis

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Background

- Triple-negative breast cancer (TNBC) is an aggressive and immunogenic breast cancer subtype[1,2,3].
- The anti-PD-L1 inhibitor atezolizumab plus nab-paclitaxel has been approved by Health Authorities for PD-L1-positive, metastatic TNBC[4,5].
- Pivotal studies of adjuvant immunotherapy for early-stage disease have improved outcomes in other solid tumors[6].
- When Alexandra/IMpassion030 was designed, the optimal timing of PD-(L)1 inhibitor administration in combination with chemotherapy in early TNBC was unknown.
- This study investigates the value of adding atezolizumab to standard anthracycline- and taxane-based adjuvant chemotherapy in TNBC.

[1]Bianchini G et al Nat Rev Clin Oncol 2016, [2]Loi S et al J Clin Oncol 2013; 31:860-7. [3]Ignatiadis M et al J Clin Oncol 2012; 30:1996-2004. [4]P Schmid et al, NEJM 2018; 379:2108-2121, [5]Tecentriq® SmPC, Japanese-PI, South Korean Product Information, Brazilian Healthcare Professional Leaflet [6]Weber J et al NEJM 2017;377:1824-1835,

Alexandra/IMpassion030 phase 3 open-label study design

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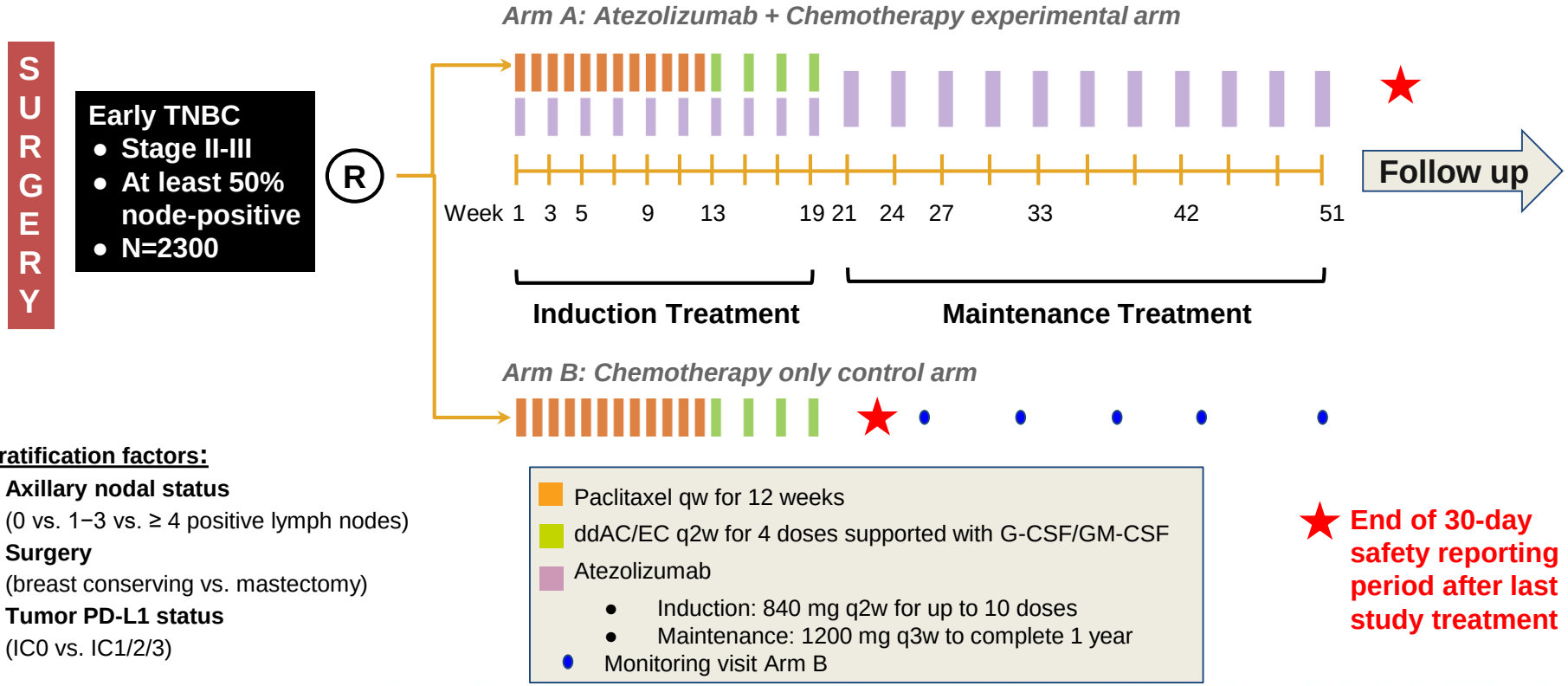

Stratification factors:

Axillary nodal status
(0 vs. 1−3 vs. ≥ 4 positive lymph nodes)
Surgery
(breast conserving vs. mastectomy)
Tumor PD-L1 status
(IC0 vs. IC1/2/3)

Endpoints

Primary efficacy endpoint

Invasive Disease-Free Survival (iDFS) in the intent to treat (ITT) population

Secondary efficacy endpoints

iDFS in the PD-L1-positive subpopulation

iDFS in the node-positive subpopulation

iDFS including second primary non-breast invasive cancer

Overall Survival (OS)

Relapse-Free Interval (RFI)

Distant Relapse-Free Interval (DRFI)

Disease-free survival (DFS)

Statistical analysis considerations

Health Authority request for additional interim and a futility analysis

Initial Statistical Analysis Plan:	**Updated Statistical Analysis Plan*:**
• 2300 patients and primary endpoint iDFS • One planned interim analysis at 80% information (310 iDFS events)	• At the SAP amendment 2199 patients had been randomized • Two planned interim analyses at 62% and 80% information (242 and 312 iDFS events) • Futility boundary added at a Hazard Ratio (HR) > 1
• Final analyses at 388 iDFS events ○ Two-sided, stratified log-rank test with alpha 0.05, power 80%, hazard ratio 0.75, ITT population	• Final analyses at 390 iDFS events ○ Two-sided, stratified log-rank test with alpha 0.05, power 80%, hazard ratio 0.75, ITT population

* *Main statistical design considerations, with the addition of one interim and futility analysis, remained the same as for the initial statistical analysis plan*

Data which follows is based upon clinical cut-off date of 17 February 2023, extracted from a dataset which was not fully cleaned to meet the Health Authority timeline requirement to perform the interim analysis that followed the iDMC recommendation to halt recruitment (temporarily).

ALEXANDRA/IMpassion030 interim analysis consort diagram

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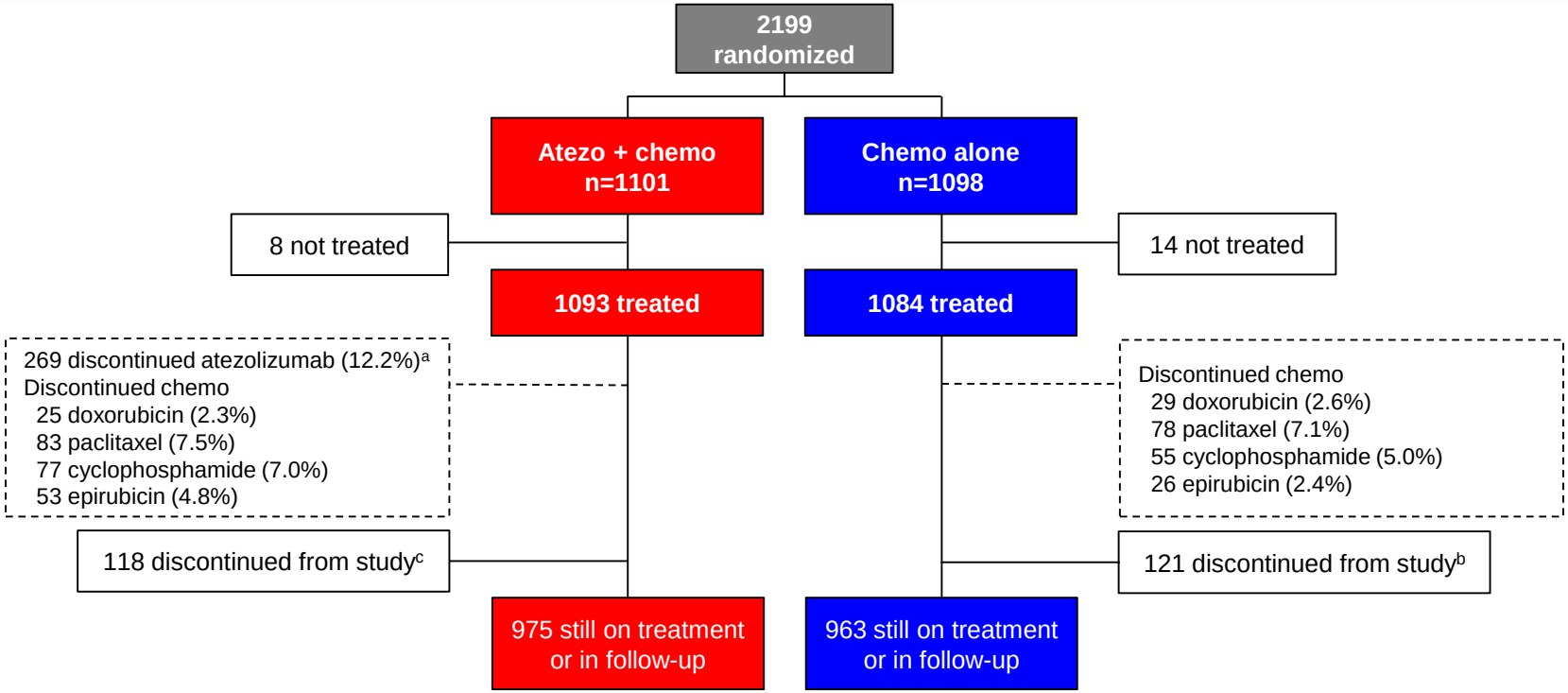


[a]5 death, 44 disease relapse, 144 adverse events, 1 lost to follow-up, 3 non-compliance, 7 physician decision, 56 patient withdrawal, 9 other
[b]49 death, 5 lost to follow-up, 4 physician decision, 63 patient withdrawal
[c]60 death, 5 lost to follow-up, 3 physician decision, 50 patient withdrawal
Analyses based on all randomized patients per intention-to-treat principle

Baseline characteristics, ITT population (1)

Characteristic, n (%)	Atezo + chemo (n=1101)	Chemo alone (n=1098)	Total (N=2199)
Age (years), median (range)	53 (24–86)	53 (23–79)	53 (23–86)
Age Group (years)			
<65	916 (83.2)	904 (82.3)	1820 (82.8)
≥65	185 (16.8)	194 (17.7)	379 (17.2)
Race			
White	554 (50.3)	564 (51.4)	1118 (50.8)
Asian	423 (38.4)	401 (36.5)	824 (37.5)
American Indian or Alaska Native	28 (2.5)	27 (2.5)	55 (2.5)
Black or African American	8 (0.7%)	2 (0.2)	10 (0.5)
Other[1]	2 (0.2)	6 (0.5)	8 (0.4)
Unknown	86 (7.8)	98 (8.9)	184 (8.4)
ECOG Score at baseline			
0	887 (80.6)	895 (81.5)	1782 (81.0)
1	214 (19.4)	203 (18.5)	417 (19.0)

[1] Race category 'Other' includes 'Native Hawaiian or other pacific islander' and 'Multiple'

Baseline characteristics, ITT population (2)

Characteristic, n (%)	Atezo + chemo (n=1101)	Chemo alone (n=1098)	Total (N=2199)
Histology			
Ductal, NOS	823 (74.9)	793 (72.2)	1616 (73.6)
Lobular	39 (3.5)	54 (4.9)	93 (4.2)
Metaplastic	50 (4.5)	46 (4.2)	96 (4.4)
Other[1]	211 (19.2)	241 (21.9)	452 (20.6)
Histological Grade at Screening			
Well Differentiated	60 (5.5)	75 (6.8)	135 (6.1)
Moderately Differentiated	205 (18.6)	233 (21.2)	438 (19.9)
Poorly Differentiated	686 (62.4)	653 (59.5)	1339 (60.9)
Anaplastic	3 (0.3)	3 (0.3)	6 (0.3)
Unknown	146 (13.3)	134 (12.2)	280 (12.7)

[1] Histological Subtype category 'Other' includes 'Tubular', 'Mucinous', 'Ductal with medullary features' and 'Other'

Baseline characteristics, ITT population (3)

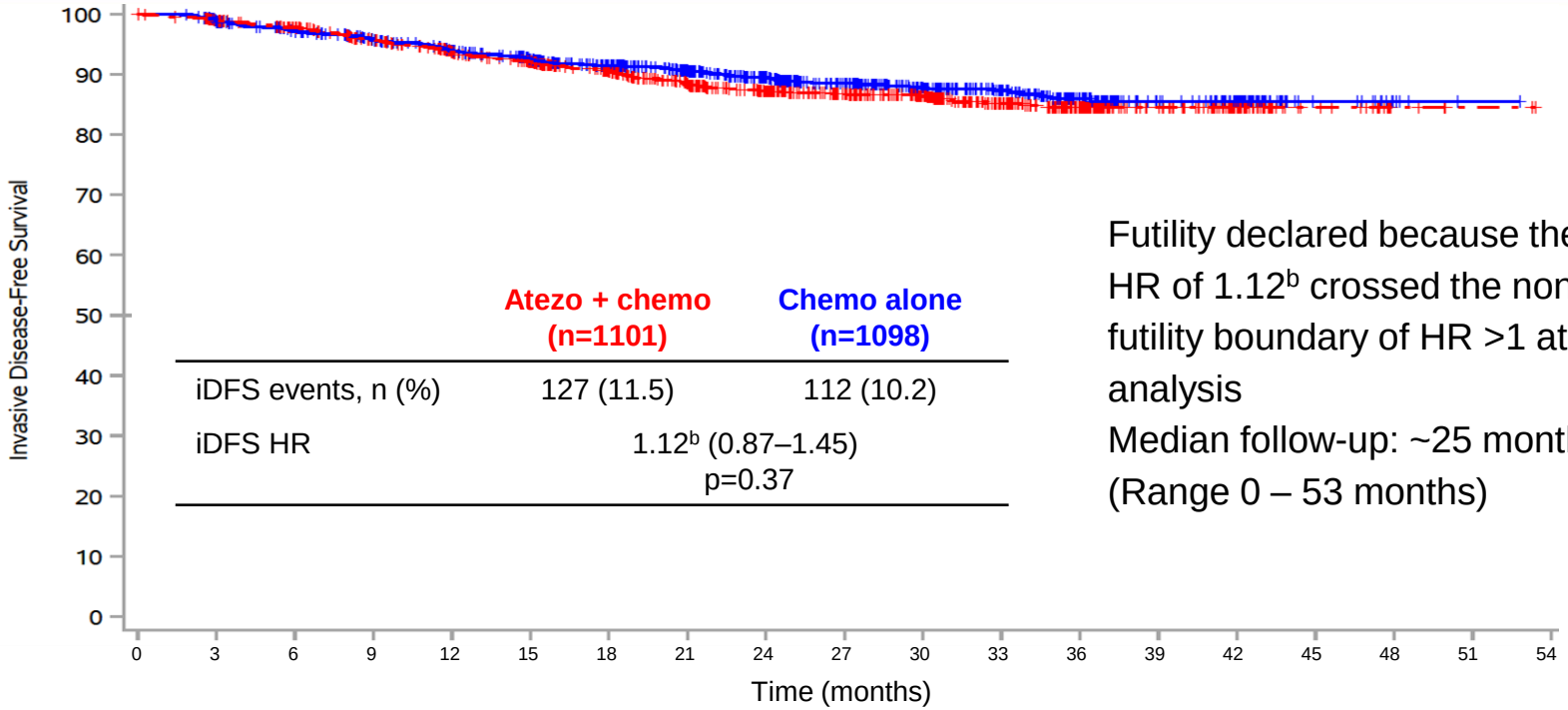
Characteristic, n (%)	Atezo + chemo (n=1101)	Chemo alone (n=1098)	Total (N=2199)
Primary Tumor Stage			
pT1-pT2	1024 (93.0)	1045 (95.2)	2069 (94.1)
pT3	71 (6.4)	51 (4.6)	122 (5.5)
Other[1]	6 (0.5)	2 (0.2)	8 (0.4)
Axillary Nodal Status (IxRS)			
0	577 (52.4)	573 (52.2)	1150 (52.3)
1-3	390 (35.4)	390 (35.5)	780 (35.5)
≥4	134 (12.2)	135 (12.3)	269 (12.2)
AJCC Stage at Surgery			
Stage II	935 (84.9)	940 (85.6)	1875 (85.3)
Stage III	161 (14.6)	157 (14.3)	318 (14.5)
Other[2]	5 (0.5)	1 (<0.1)	6 (0.3)

[1]Primary Tumor Stage category 'Other' includes 'pT0', 'pTis', 'pT4', 'pT4b' and missing
[2]AJCC Stage category 'Other' includes 'Stage I' and missing

Baseline characteristics, ITT population (4)

Characteristic, n (%)	Atezo + chemo (n=1101)	Chemo alone (n=1098)	Total (N=2199)
PD-L1 Status (IxRS)			
IC 0	316 (28.7)	316 (28.8)	632 (28.7)
IC 1/2/3	785 (71.3)	782 (71.2)	1567 (71.3)
Surgery (IxRS)			
Breast conserving	524 (47.6)	523 (47.6)	1047 (47.6)
Mastectomy	577 (52.4)	575 (52.4)	1152 (52.4)

Primary efficacy endpoint: iDFS[a] (ITT population)



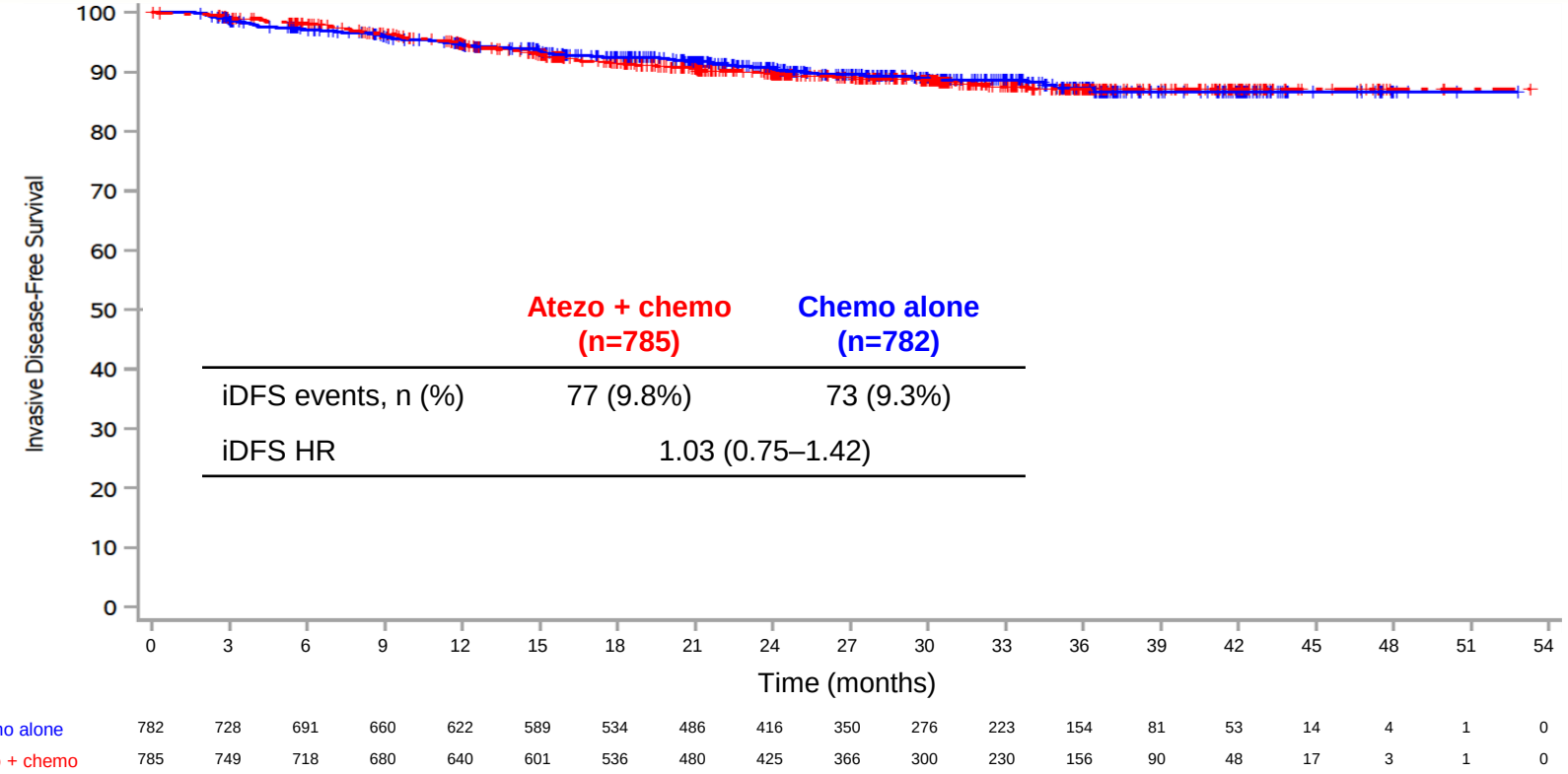
	Atezo + chemo (n=1101)	Chemo alone (n=1098)
iDFS events, n (%)	127 (11.5)	112 (10.2)
iDFS HR	1.12[b] (0.87–1.45) p=0.37	

Futility declared because the observed HR of 1.12[b] crossed the non-binding futility boundary of HR >1 at this interim analysis

Median follow-up: ~25 months (Range 0 – 53 months)

[a]Defined as the interval from randomization until date of first occurrence of an iDFS event, [b]stratified by PD-L1 status, Surgery, and Axillary Nodal Status

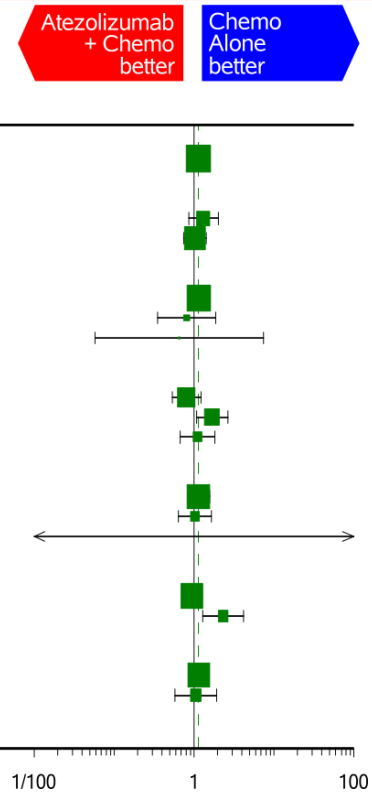
Key secondary efficacy endpoint: iDFS in the PD-L1+ subgroup (71%)



	Atezo + chemo (n=785)	Chemo alone (n=782)
iDFS events, n (%)	77 (9.8%)	73 (9.3%)
iDFS HR	1.03 (0.75–1.42)	

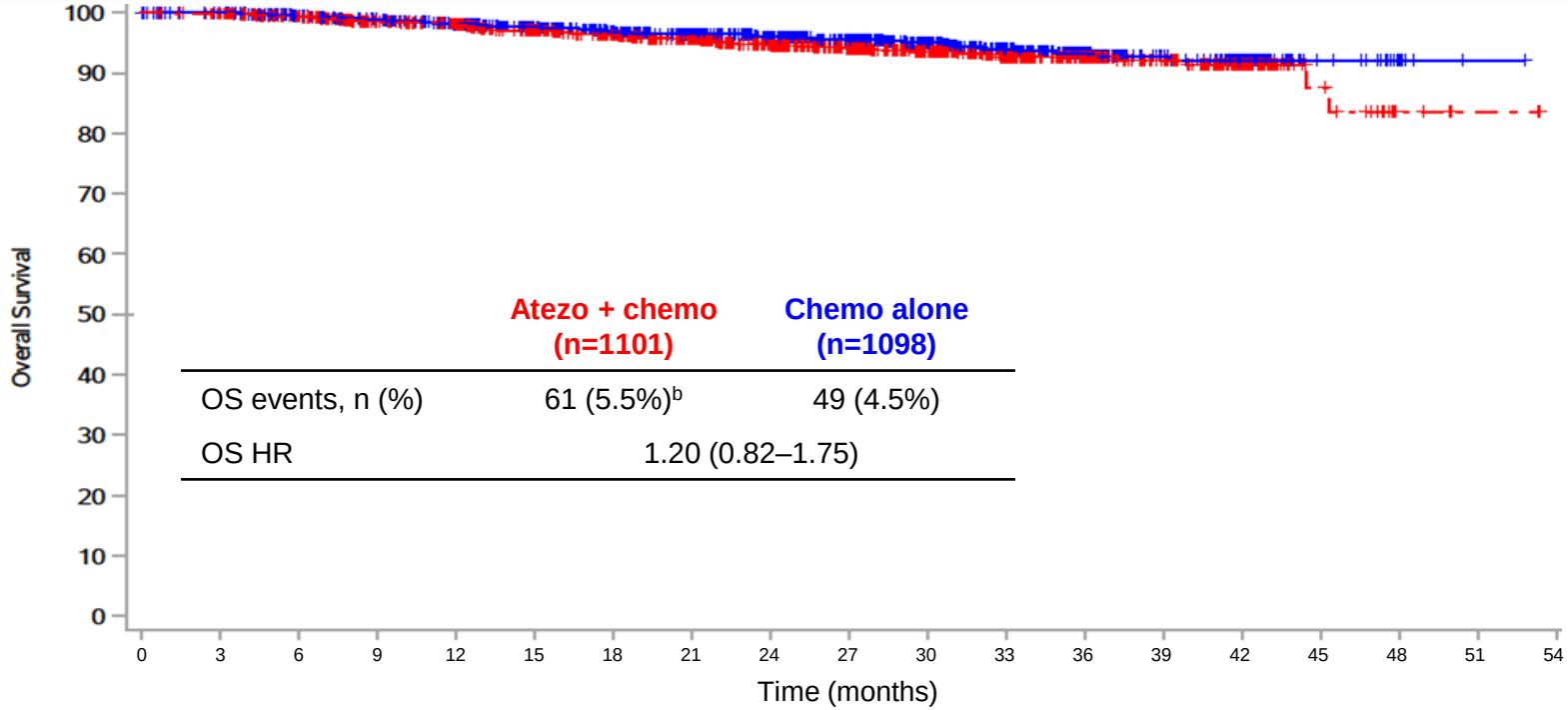
iDFS subgroup analysis (ITT Population)

Baseline Risk Factors	Total n	Atezolizumab + Chemo (N=1101) n	Atezolizumab + Chemo (N=1101) Median (Months)	Chemo Alone (N=1098) n	Chemo Alone (N=1098) Median (Months)	Hazard Ratio	95% Wald CI
All Patients	2199	1101	NE	1098	NE	1.13	(0.87, 1.45)
PD-L1 Status (IxRS)							
IC 0	632	316	NE	316	NE	1.32	(0.87, 2.01)
IC 1/2/3	1567	785	NE	782	NE	1.03	(0.75, 1.43)
Primary Tumor Stage at First Diagnosis (Grouped)							
pT1-pT2	2069	1024	NE	1045	NE	1.15	(0.88, 1.51)
pT3	122	71	NE	51	NE	0.81	(0.35, 1.86)
Other	8	6	23.7	2	NE	0.66	(0.06, 7.54)
Axillary Nodal Status (IxRS)							
0	1150	577	NE	573	NE	0.81	(0.54, 1.22)
1-3	780	390	NE	390	NE	1.69	(1.08, 2.64)
>=4	269	134	NE	135	NE	1.12	(0.68, 1.85)
AJCC Stage at Surgery (Grouped)							
Stage II	1875	935	NE	940	NE	1.15	(0.85, 1.56)
Stage III	318	161	NE	157	NE	1.03	(0.64, 1.65)
Other	6	5	NE	1	NE	>999.99	(0.00, NE)
Pooled Age Group 1							
<65	1820	916	NE	904	NE	0.95	(0.71, 1.26)
>=65	379	185	NE	194	NE	2.33	(1.28, 4.24)
Baseline ECOG Assessment Score							
0	1782	887	NE	895	NE	1.15	(0.87, 1.51)
1	417	214	NE	203	NE	1.06	(0.58, 1.95)



Hazard ratios and the associated Wald confidence intervals were estimated using *unstratified* Cox regression.
The vertical dashed line indicates the hazard ratio for all patients.
The size of the symbol is proportional to the size of the population in the subgroup.

Key secondary efficacy endpoint: OS[a], ITT population



	Atezo + chemo (n=1101)	Chemo alone (n=1098)
OS events, n (%)	61 (5.5%)[b]	49 (4.5%)
OS HR	1.20 (0.82–1.75)	

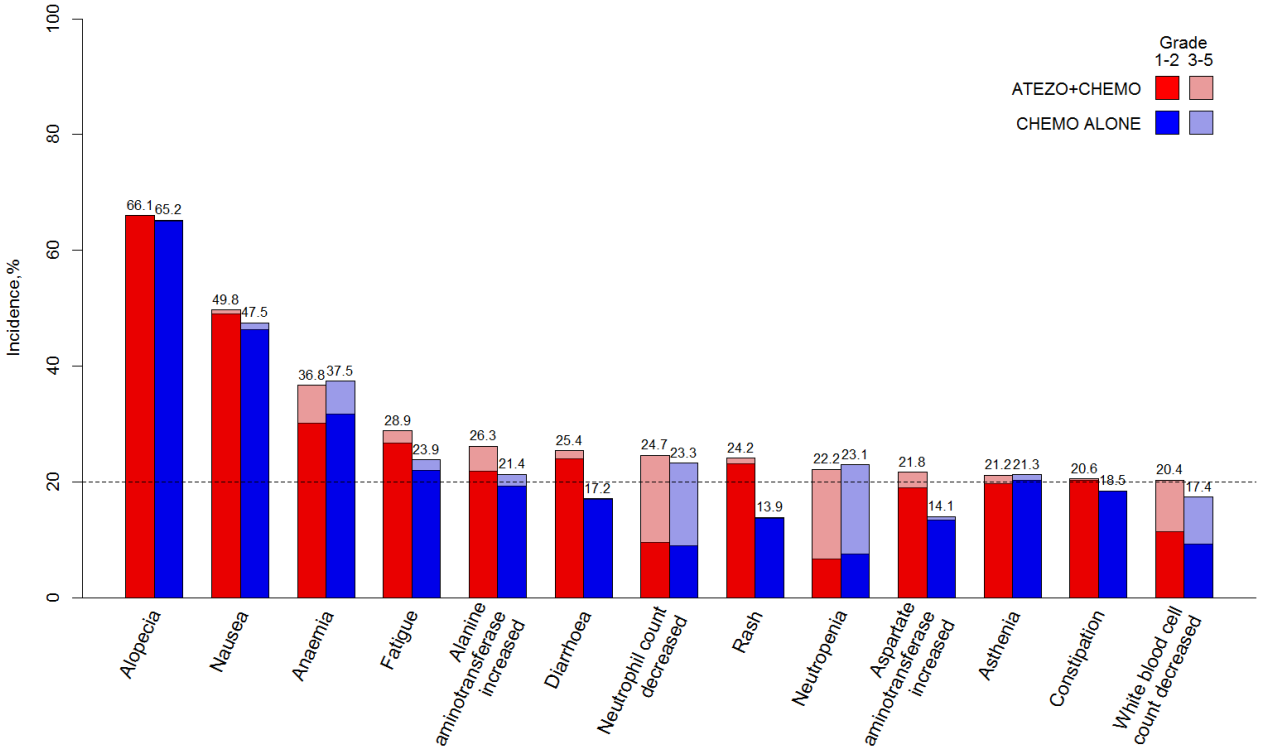
[a]Defined as the interval between randomization until death from any cause. [b]One patient in the atezo arm who died 25 Dec 2022 not taken into account (data issue).

Overview of number of patients with at least one AE

AE Overview*, n (%)	Atezo + chemo (n=1093)	Chemo alone (n=1084)	Total (N=2177)
TEAEs[1]	1090 (99.7)	1073 (99.0)	2163 (99.4)
TRAEs[2] All Grade	1083 (99.1)	1066 (98.3)	2149 (98.7)
TRAEs Grade 3 - 4	587 (53.7)	472 (43.5)	1059 (48.6)
TRSAE	198 (18.1)	107 (9.9)	305 (14.0)
Treatment related Deaths	2 (0.2)	1 (<0.1)	3 (0.1)
AE leading to any treatment discontinuation	185 (16.9)	60 (5.5)	245 (11.3)
AEs leading to discontinuation of:			
Atezolizumab	144 (13.2)	0 (0)	144 (6.6)
Epirubicin	30 (2.7)	12 (1.1)	42 (1.9)
Doxorubicin	14 (1.3)	17 (1.6)	31 (1.4)
Cyclophosphamide	43 (3.9)	30 (2.8)	73 (3.4)
Paclitaxel	54 (4.9)	33 (3.0)	87 (4.0)

[1]TEAE=Treatment Emergent Adverse Event
[2]TRAE=Treatment Related Adverse Event
*Safety follow-up period collects all AEs until 30 days after last dose of study treatment therefore atezo + chemo arm had longer safety FU due to the continued atezo dosing during maintenance phase. During the maintenance phase, the chemo arm had ½ the frequency of visits.

TEAEs ≥ 20% and Grading by Arm



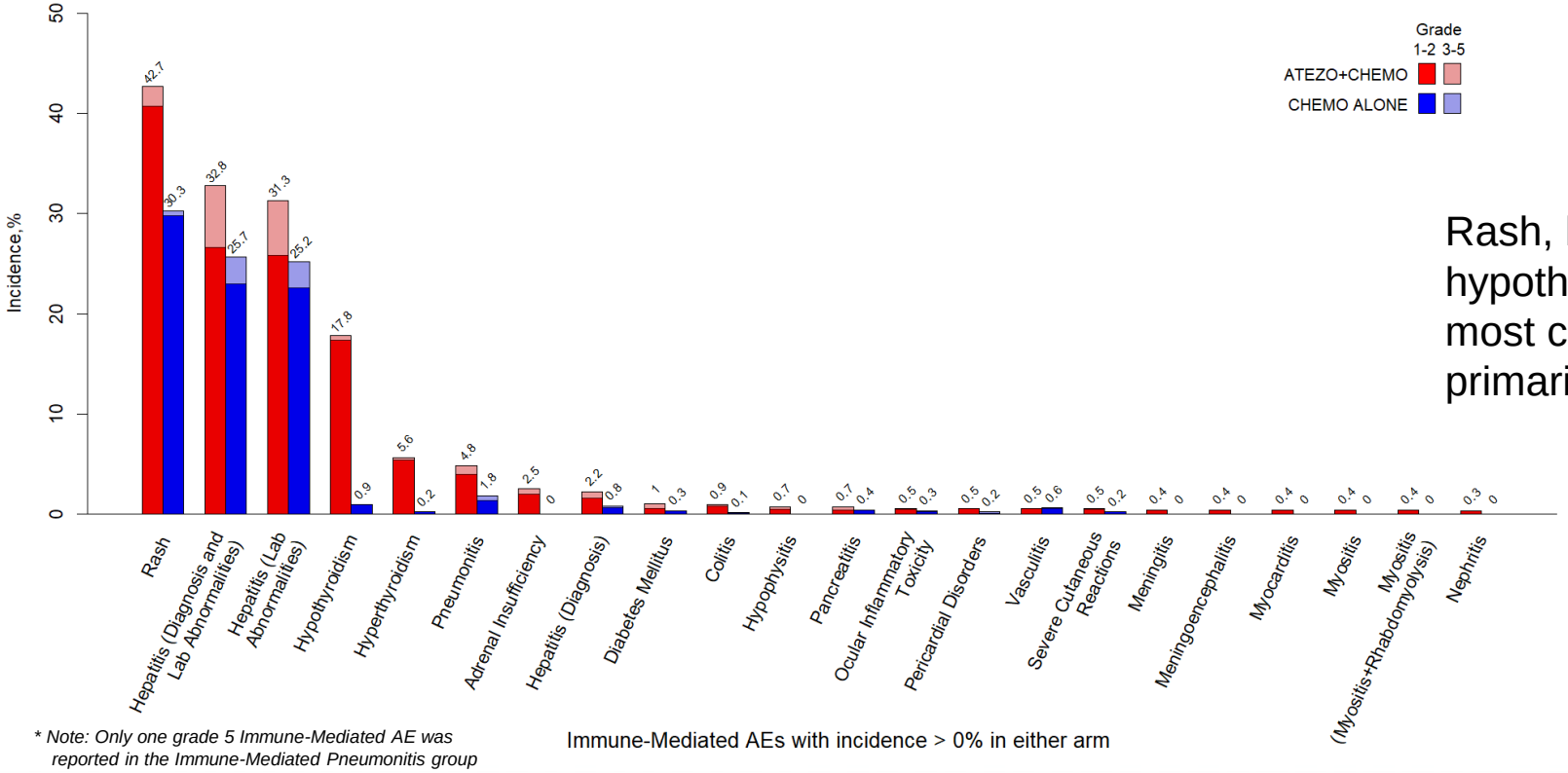
Treatment-Emergent AEs with incidence ≥ 20% in either arm

* *Note: No grade 5 TEAE were reported for AEs with incidence >= 20% in either arm*

*

Fatigue, diarrhea, rash and liver enzyme changes were numerically higher in the atezo arm

Immune-Mediated AEs



Immune-Mediated AEs with incidence > 0% in either arm

Rash, hepatitis and hypothyroidism were most common and primarily low grade

** Note: Only one grade 5 Immune-Mediated AE was reported in the Immune-Mediated Pneumonitis group*

Conclusions

- At the requested interim analysis of the phase 3 ALEXANDRA/IMpassion030 trial, HR for iDFS in the ITT population (primary endpoint) crossed the pre-specified futility boundary (HR>1), HR 1.12 [0.87–1.45].
- The primary endpoint together with secondary efficacy endpoints do not support the addition of atezolizumab to adjuvant chemotherapy in patients who have undergone primary surgery for early TNBC.
- Safety data were consistent with the known safety profile of atezolizumab in early TNBC (IMpassion031)[1] and across indications with numerically more AEs, grade 3/4 AEs and SAEs in the atezolizumab arm.
- Addition of atezolizumab did not compromise delivery of the SoC chemotherapy backbone.
- Study data are being updated to a clinical cut-off of 17 November 2023, and results will be published based on the final database. Moreover, the study partners will conduct translational research in this unique dataset.
- The ALEXANDRA/IMpassion030 trial contributes to an improved understanding about the optimal use of immunotherapy in patients with early TNBC.

[1] E A Mittendorf et al, The Lancet 2020; 396: 1090–100

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