Allegheny
Health Network

A Randomized Double-Blind Phase III Clinical Trial of Neoadjuvant Chemotherapy with Atezolizumab or Placebo Followed by Adjuvant Atezolizumab or Placebo in Patients with Stage II and III Triple Negative Breast Cancer

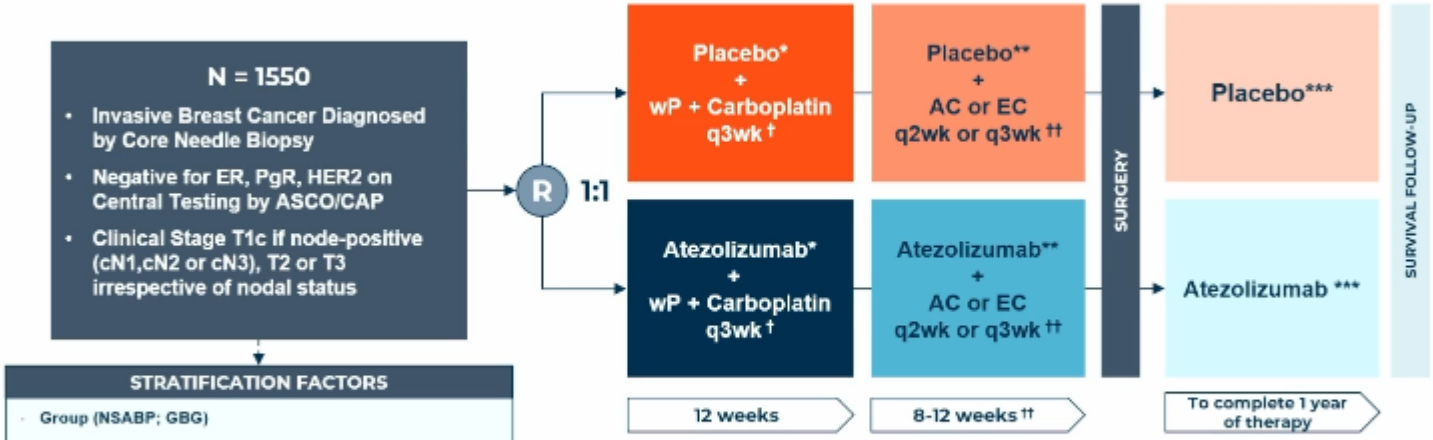
Study Rationale

- Triple-negative breast cancer (TNBC) is an aggressive subtype with high tumor mutational burden and potential susceptibility to immune checkpoint inhibitors.[1,2]
- Atezolizumab, an anti-PD-L1 antibody, improved the pCR rate of early-stage TNBC when added to neoadjuvant chemotherapy and significantly improved PFS when added to chemotherapy in metastatic TNBC.[3, 4]
- Atezolizumab can be combined with standard chemotherapy with manageable toxicities.[3,4,5]
- NSABP B-59/GBG-96-GeparDouze was designed to determine if the addition of atezolizumab to neoadjuvant chemotherapy would improve outcomes in stages II and III TNBC.

[1] Bianchini G, et al. *Nat Rev Clin Oncol* 2016:13, 674-690. [2] Ignatiadis M, et al. *JCO* 2012: 30;1996-2004. [3] Mittendorf EA, et al. *Lancet* 2020:396:1090-1100.
[4] Schmid P, et al. *NEJM* 2018:379;2108-2121. [5] Schmid P, et al. *Lancet* 2020:21;44-59.

Study Design

SAN ANTONIO BREAST CANCER SYMPOSIUM



∅ PD-L1 status was not available at randomization for 374 patients enrolled prior to amendments in July 2019.
* Atezolizumab (atezo) 1200 mg or placebo IV Day 1 every 3 wks for 4 doses.
† Paclitaxel 80 mg/m2 IV weekly x 12 doses (WP) + Carboplatin AUC of 5 IV Day 1 every 3 wks for 4 cycles.
** Atezo 1200 mg or placebo IV Day 1 every 3 wks for 3 to 4 doses depending on AC/EC schedule used.
†† Doxorubicin (A) 60 mg/m2 IV + cyclophosphamide (C) 600 mg/m2 IV Day 1 every 2 or 3 wks for 4 cycles. OR Epirubicin (E) 90 mg/m2 IV + cyclophosphamide (C) 600 mg/m2 IV Day 1 every 2 or 3 wks for 4 cycles.
*** Atezo 1200 mg or placebo IV Day 1 every 3 wks after surgery until 1 yr after the first dose. Adjuvant capecitabine was allowed for non-pCR as of February 2020 and olaparib as of December 2021.

Study Endpoints

Primary efficacy endpoint

- **Event-free survival (EFS)**

Secondary efficacy endpoints

- **Overall survival (OS)**
- **Pathologic complete response (pCR) in the breast and lymph nodes (ypT0/Tis ypN0)**
- Distant disease-free survival (DDFS)
- Disease-free survival (DFS)
- **Toxicity**

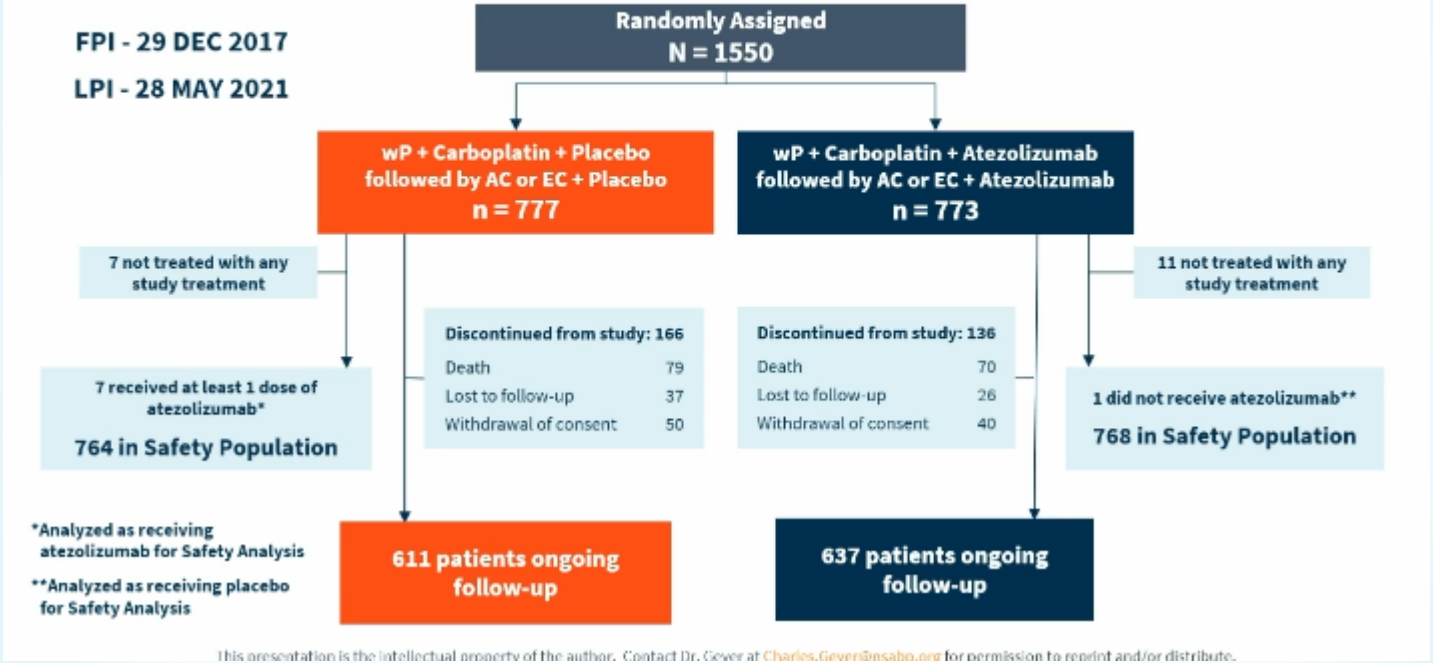
Exploratory Endpoints

- Nodal status conversion rate
- Recurrence-free interval (RFI)
- Brain metastases-free survival
- EFS and pCR in patients with pathogenic variants in germline *BRCA1, BRCA2, PALB2*

Statistical Considerations

- Study designed to detect HR of 0.7 for EFS between the atezolizumab arm and the placebo arm with 252 EFS confirmed events and to provide 80% power at overall 2-sided alpha level of 0.05.
- Planned interim analysis (IA) was performed in July 2023 when 196 EFS events had been confirmed.
- Due to consistently low monthly event rates in 2024, the study SAP was modified to allow definitive analysis to proceed when at least 242 EFS events were confirmed.
- At data base lock on 10/30/2024, 243 EFS events were confirmed. Controlling the overall type I error at 0.05, the 2-sided superiority boundary for this primary analysis is 0.04444.
- If primary EFS analysis reached a significant result, formal IA for OS would be performed.

Analysis Populations



Patient Characteristics (1/3)

SAN ANTONIO BREAST CANCER SYMPOSIUM®

Parameter	Chemo/Placebo n = 777	Chemo/Atezolizumab n = 773	Total N = 1550
Age			
Median	49.0	49.0	49.0
Range	23, 77	22, 79	22, 79
Race			
American Indian or Alaskan native	2 (0.3%)	2 (0.3%)	4 (0.3%)
Asian	13 (1.7%)	18 (2.3%)	31 (2.0%)
Black or African American	40 (5.1%)	42 (5.4%)	82 (5.3%)
Native Hawaiian or Other Pacific Islander	0 (0%)	1 (0.1%)	1 (0.1%)
White	702 (90.3%)	692 (89.5%)	1394 (89.9%)
Other/Multiple/Unknown/Missing	20 (2.5%)	18 (2.3%)	38 (2.4%)
Ethnicity			
Hispanic or Latino	54 (6.9%)	41 (5.3%)	95 (6.1%)
Not Hispanic or Latino	693 (89.2%)	695 (89.9%)	1388 (89.5%)
Unknown/Missing	30 (3.9%)	37 (4.8%)	67 (4.3%)
Sex			
Female	776 (99.9%)	773 (100%)	1549 (99.9%)
Male	1 (0.1%)	0 (0%)	1 (0.1%)

Characteristics by Stratification Factors (2/3)

SAN ANTONIO BREAST CANCER SYMPOSIUM

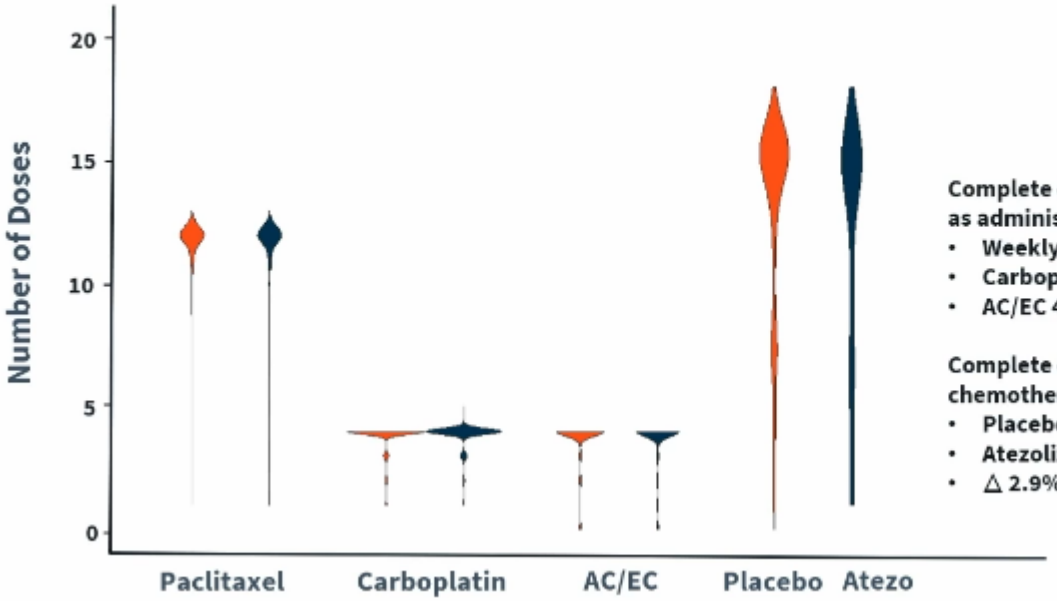
Parameter	Chemo/Placebo n = 777	Chemo/Atezolizumab n = 773	Total N = 1550
Group			
GBG	490 (63.1%)	488 (63.1%)	978 (63.1%)
NSABP	287 (36.9%)	285 (36.9%)	572 (36.9%)
Nodal Status			
Negative	459 (59.1%)	452 (58.5%)	911 (58.8%)
Positive	318 (40.9%)	321 (41.5%)	639 (41.2%)
Clinical Size of the Primary Tumor			
1.1–3.0 cm	457 (58.8%)	453 (58.6%)	910 (58.7%)
>3 cm	320 (41.2%)	320 (41.4%)	640 (41.3%)
PDL1 Status			
Negative/Indeterminate/Not Available	496 (63.8%)	493 (63.8%)	989 (63.8%)
Positive	281 (36.2%)	280 (36.2%)	561 (36.2%)
AC/EC Schedule			
Every 2 weeks (q2w)	495 (63.7%)	489 (63.3%)	984 (63.5%)
Every 3 weeks (q3w)	282 (36.3%)	284 (36.7%)	566 (36.5%)

Patient and Tumor Characteristics (3/3)

SAN ANTONIO BREAST CANCER SYMPOSIUM®

Parameter	Chemo/Placebo n = 777	Chemo/Atezolizumab n = 773	Total N = 1550
Histological Tumor Type			
Invasive Ductal/Invasive Carcinoma of No Special Type (NST)	740 (95.2%)	729 (94.3%)	1469 (94.8%)
Invasive Lobular Carcinoma or Mixed Lobular Carcinoma	10 (1.3%)	9 (1.2%)	19 (1.2%)
Other	27 (3.5%)	35 (4.5%)	62 (4.0%)
Grade			
1	9 (1.2%)	7 (0.9%)	16 (1.0%)
2	135 (17.4%)	140 (18.1%)	275 (17.7%)
3	631 (81.2%)	626 (81.0%)	1257 (81.1%)
Unknown/Missing	2 (0.3%)	0 (0%)	2 (0.1%)
Stromal TILs Category on Baseline Specimen (%)			
<30%	480 (61.8%)	480 (62.1%)	960 (61.9%)
≥30%	295 (38.0%)	288 (37.3%)	583 (37.6%)
Germline Pathogenic Variant Status			
BRCA1 Pathogenic Variant	62 (8.0%)	67 (8.7%)	129 (8.3%)
BRCA2 Pathogenic Variant	16 (2.1%)	22 (2.8%)	38 (2.5%)
PALB-2 Pathogenic Variant	4 (0.5%)	9 (1.2%)	13 (0.8%)
Wild Type for *BRCA1*, *BRCA2* and *PALB-2*	425 (54.7%)	394 (51.0%)	819 (52.8%)
Missing *BRCA* Germline Testing Status	275 (35.4%)	294 (38%)	569 (36.7%)

Drug Delivery by Treatment Arm



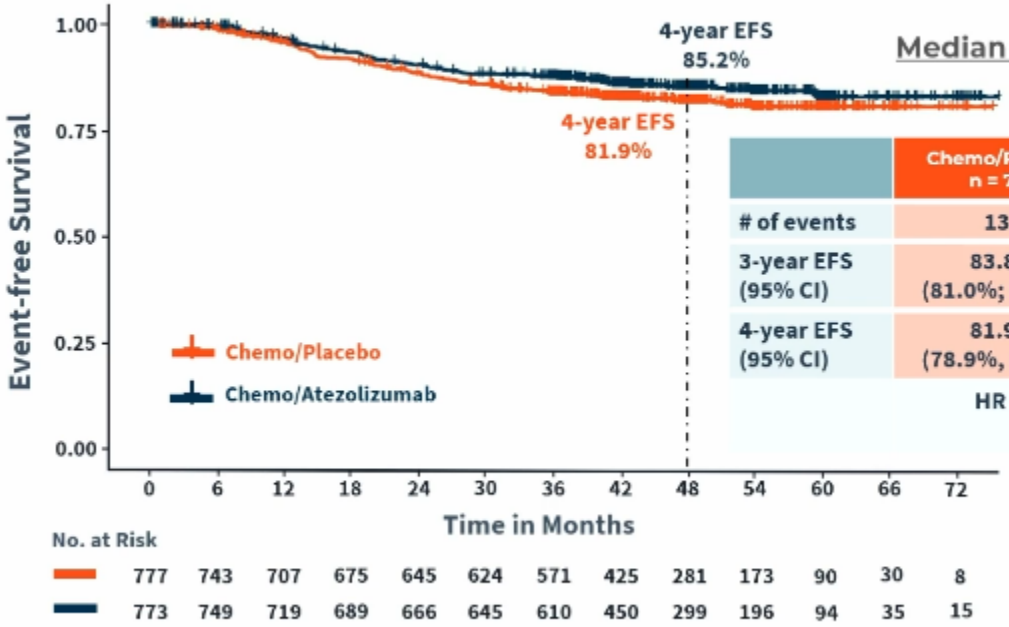
Complete delivery of chemo defined as administration of the following:

- **Weekly Paclitaxel ≥ 10 doses**
- **Carboplatin 4 doses**
- **AC/EC 4 doses**

Complete delivery of planned chemotherapy by arm:

- **Placebo arm 632/777 (81.3%)**
- **Atezolizumab arm 606/773 (78.4%)**
- **Δ 2.9%**

Event-free Survival



Median follow-up 46.9 months

	Chemo/Placebo n = 777	Chemo/Atezolizumab n = 773
# of events	133	110
3-year EFS (95% CI)	83.8% (81.0%; 86.3%)	87.7% (85.1%; 89.9%)
4-year EFS (95% CI)	81.9% (78.9%, 84.6%)	85.2% (82.4%, 87.7%)

HR = 0.8 (95% CI = 0.62, 1.03)
Log rank p = 0.08

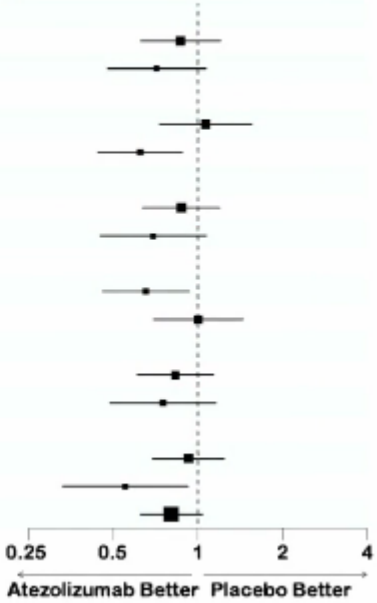
Types of First EFS Events

Parameter	Chemo/Placebo n = 777	Chemo/Atezolizumab n = 773
Neoadjuvant Progression	1 (0.1%)	0 (0%)
Ipsilateral Breast Tumor Recurrence	20 (2.6%)	15 (1.9%)
Local Recurrence Following Mastectomy	4 (0.5%)	7 (0.9%)
Regional Recurrence	13 (1.7%)	9 (1.2%)
Distant Recurrence Distant Recurrence Involving CNS Distant Recurrence Not Involving CNS	77 (9.9%) 24 (3.1%) 53 (6.8%)	58 (7.5%) 29 (3.8%) 29 (3.8%)
Contralateral Invasive Breast Cancer	3 (0.4%)	5 (0.6%)
Second Non-breast Primary Cancer	7 (0.9%)	10 (1.3%)
Death as First EFS Event	8 (1.0%)	6 (0.8%)

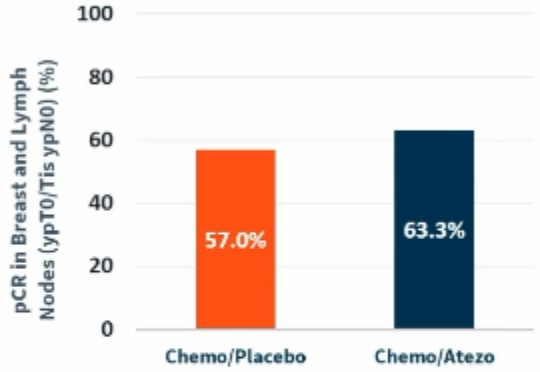
EFS Subgroup Analysis

Subgroup	N events/patients	HR (95% CI)	P	P for interaction
Group				0.457
GBG	146/978	0.868 (0.627, 1.202)	0.395	
NSABP	97/572	0.714 (0.478, 1.067)	0.100	
Clinical Nodal Status				0.039
Negative	109/901	1.066 (0.732, 1.552)	0.739	
Positive	134/649	0.623 (0.441, 0.879)	0.007	
AC/EC Schedule				0.401
Every 2 weeks	159/996	0.872 (0.638, 1.191)	0.389	
Every 3 weeks	84/554	0.694 (0.450, 1.069)	0.097	
Clinical Size of Primary Tumor				0.098
> 3.0 cm	128/647	0.653 (0.459, 0.929)	0.018	
1.1–3.0 cm	115/903	1.003 (0.696, 1.446)	0.986	
PD-L1 status				0.712
Negative/indeterminate/not available	160/853	0.831 (0.609, 1.135)	0.244	
Positive	83/697	0.752 (0.487, 1.160)	0.198	
TIL Category				0.086
<30%	180/960	0.925 (0.690, 1.239)	0.560	
>=30%	63/583	0.551 (0.330, 0.920)	0.023	
Overall	243/1550	0.805 (0.626, 1.037)	0.093	

X-axis is under log scale.

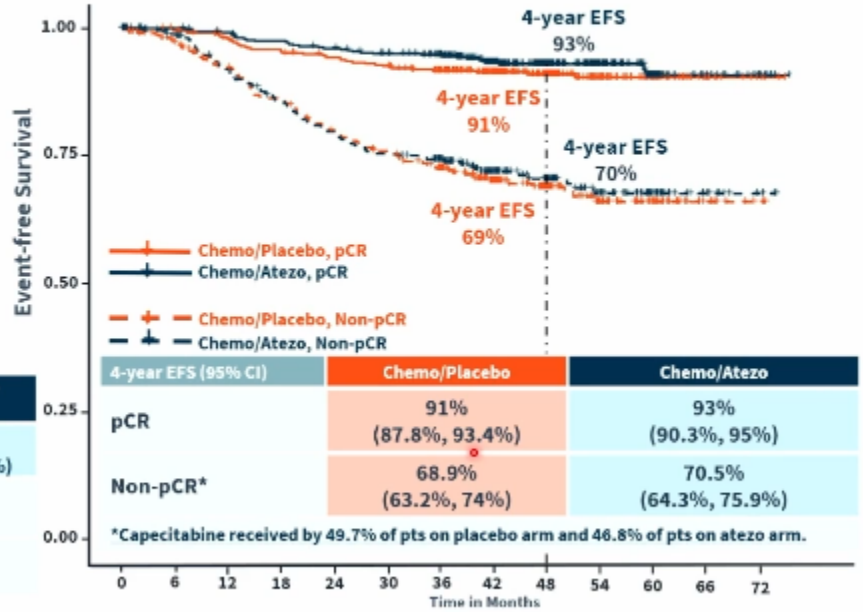


pCR by Arm and EFS by pCR Status



	Chemo/Placebo n = 777	Chemo/Atezo n = 773
% pCR [a] (95% CI)	57.0% (53.5%, 60.5%)	63.3% (59.9%, 66.7%)
Difference in % pCR (95% CI)	6.3% (1.4%, 11.1%)	
	(p_{adj} = 0.0091) [b]	

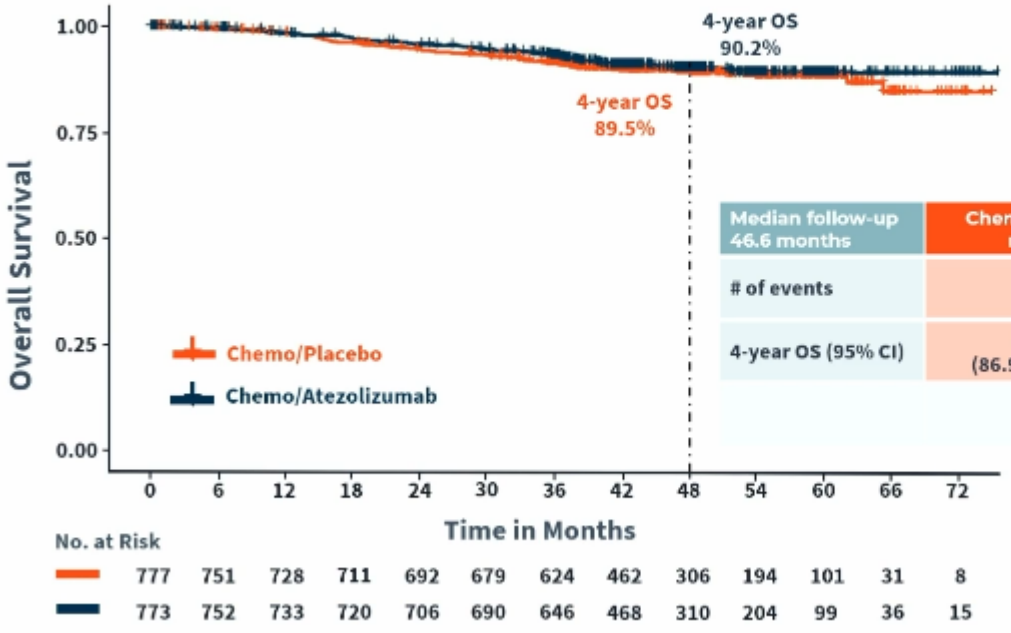
[a] Those with missing pCR status are considered as non-responders.
[b] 2-sided CMH test adjusted by stratification factors collapse of PD-L1 status.



4-year EFS (95% CI)	Chemo/Placebo	Chemo/Atezo
pCR	91% (87.8%, 93.4%)	93% (90.3%, 95%)
Non-pCR*	68.9% (63.2%, 74%)	70.5% (64.3%, 75.9%)

*Capecitabine received by 49.7% of pts on placebo arm and 46.8% of pts on atezo arm.

Overall Survival



Median follow-up 46.6 months	Chemo/Placebo n = 777	Chemo/Atezolizumab n = 773
# of events	79	70
4-year OS (95% CI)	89.5% (86.9%, 91.5%)	90.2% (87.7%, 92.3%)

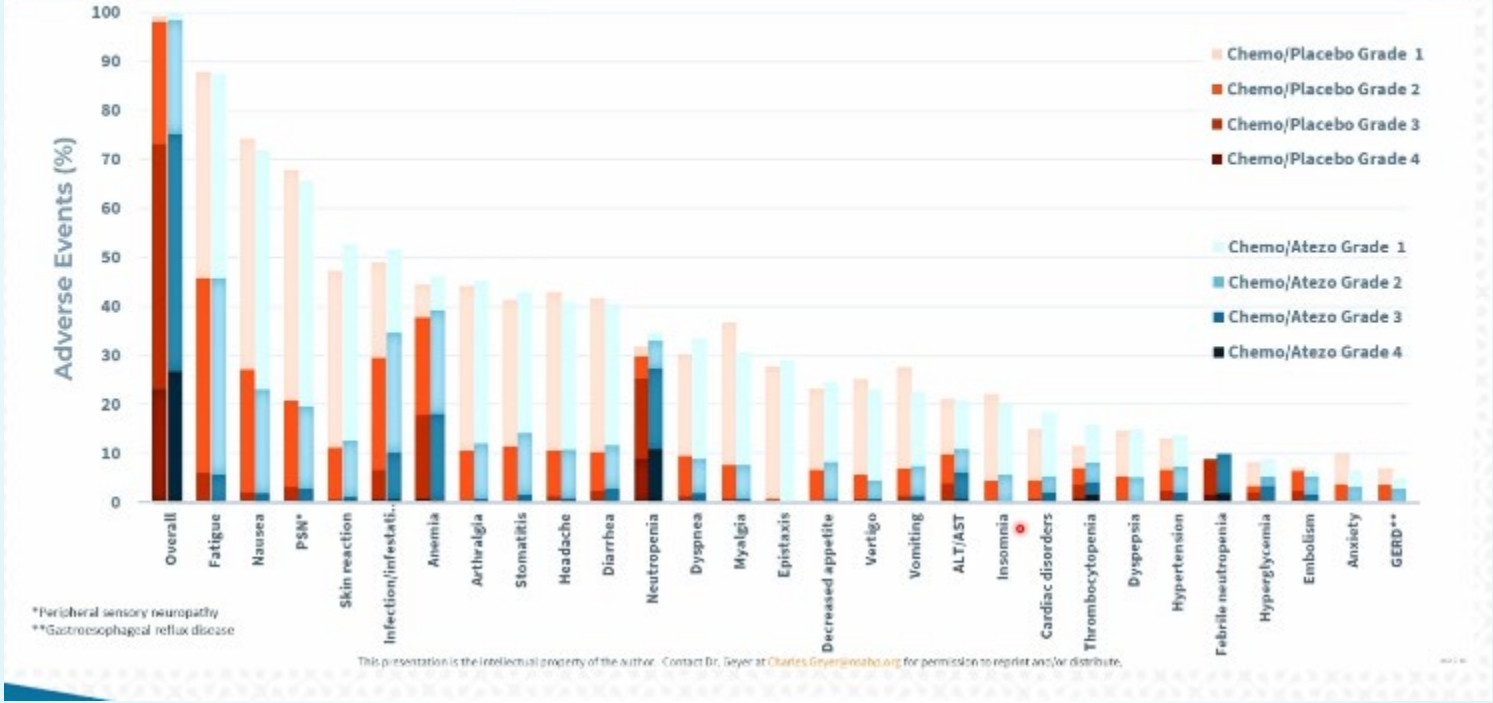
HR = 0.86 (95% CI = 0.62, 1.19)

Safety Overview TEAEs

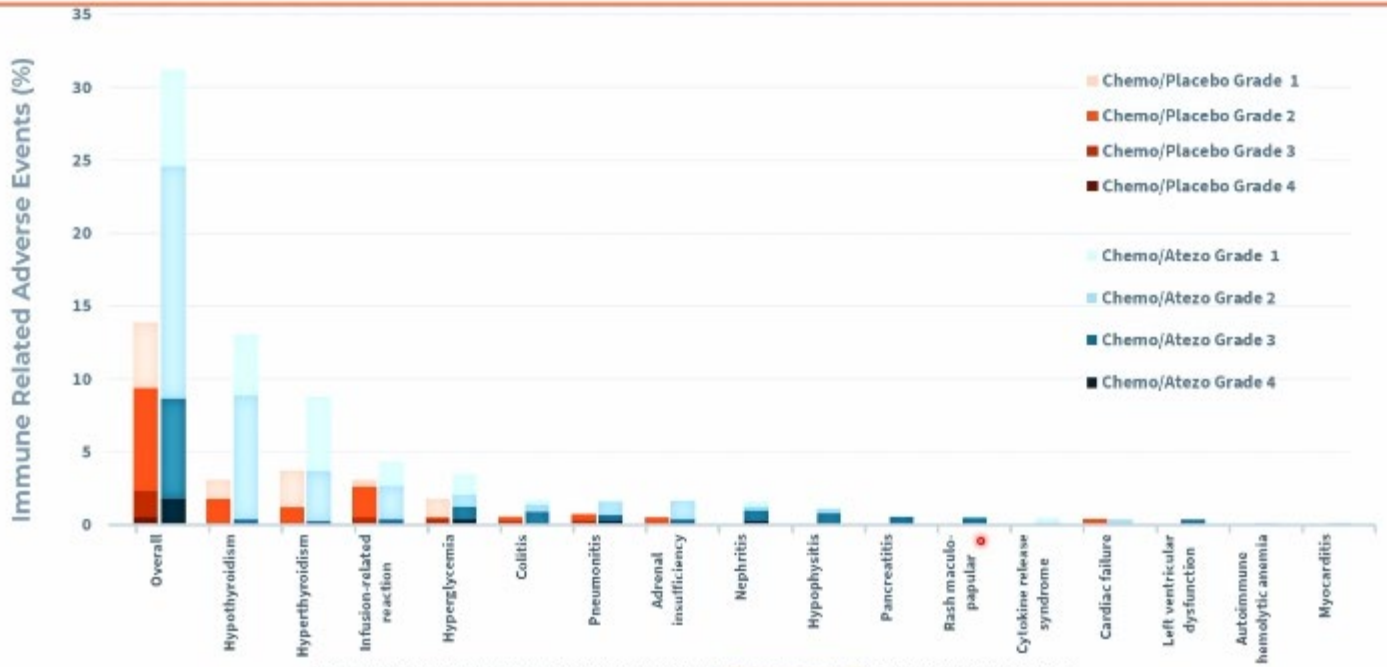
Parameter	Chemo/Placebo n = 764	Chemo/Atezolizumab n = 768	Total N = 1532
Treatment-emergent Adverse Events (TEAEs)	762 (99.7%)	768 (100%)	1530 (99.8%)
Grades 3 and 4 TEAEs	561 (73.4%)	578 (75.3%)	1139 (74.3%)
Serious TEAEs	231 (30.2%)	270 (35.2%)	501 (32.7%)
TEAEs Leading to Therapy Discontinuation			
Paclitaxel	87 (11.4%)	93 (12.1%)	180 (11.7%)
Carboplatin	56 (7.3%)	65 (8.5%)	121 (7.9%)
AC/EC	27 (3.5%)	40 (5.2%)	67 (4.4%)
Atezolizumab/Placebo	81 (10.6%)	163 (21.2%)	244 (15.9%)
TEAEs Leading to Death	3 (0.4%)*	2 (0.3%)**	5 (0.3%)

*Cause of deaths : sudden death, pneumonitis, and unknown
**Cause deaths: non-neutropenic sepsis and severe hyponatremia

TEAEs by Highest Grade in at Least 5% of Patients



Immune Related Adverse Events



Conclusions

- Addition of atezolizumab to neoadjuvant chemotherapy followed by adjuvant atezolizumab did not result in statistically significant improvement in EFS
  - HR = 0.8 (95% CI = 0.62, 1.03) log rank p = 0.08
  - 4-Year EFS was 85.2% for atezolizumab arm and 81.9% for control arm.
- Addition of atezolizumab to neoadjuvant chemotherapy increased pCR from 57% to 63%, an absolute improvement of 6%.
- Overall safety profile of atezolizumab with multiagent chemotherapy was in line with the known safety profiles in TNBC.
- While not meeting efficacy criteria for the primary endpoint, the results support translational studies for potential biomarkers to identify subsets of patients who may benefit from addition of checkpoint inhibitors to neoadjuvant/adjuvant therapy in TNBC.