Allegheny
Health Network

NRG-BR004: A Randomized, Double-blind, Phase III Trial of Taxane/Trastuzumab/Pertuzumab with Atezolizumab or Placebo in First-line Her2-positive Metastatic Breast Cancer

Background/Rationale

The CLEOPATRA trial established trastuzumab/pertuzumab with docetaxel (THP) as SOC for 1st line HER2+ MBC, with a 6-month improvement in median PFS and a remarkable improvement in median OS to 56.1 months with the addition of pertuzumab.[1]

An important component of activity of HER2-directed monoclonal antibodies is mediated through the adaptive immune system initially by antibody-dependent cell-mediated cytotoxicity (ADCC).[2]

In a preclinical study, an anti-PD-1 monoclonal antibody significantly improved the activity of an anti-HER-2 antibody.[3]

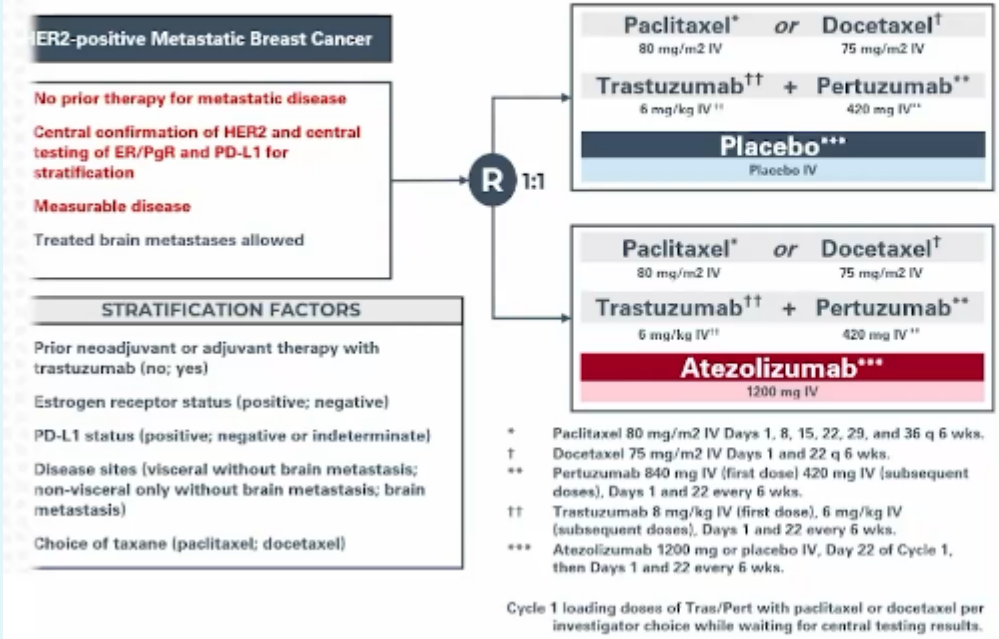
Treatment with trastuzumab increases NK cell activity and response correlates with the intensity of ADCC.[4]

In the NeoSphere trial, increased PD-L1 expression was associated with reduced pathologic complete response, suggesting PD-L1 inhibition might improve activity.[5]

BR004 was designed to determine if addition of the PD-L1 inhibitor atezolizumab to standard THP could improve outcomes with an acceptable safety profile.

3R004 Study Design

udy was designed to enroll 600 patients and activated on March 12, 2019.

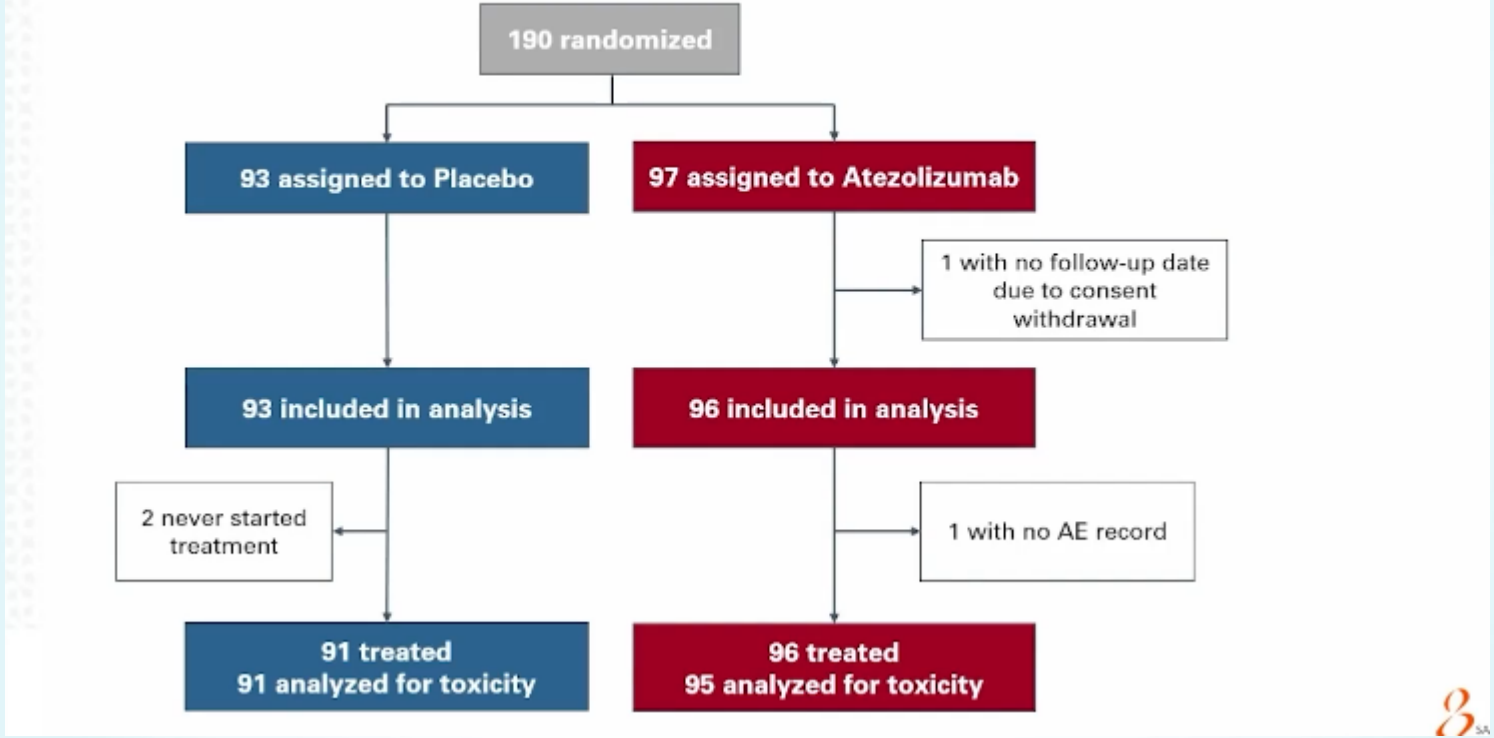


* Paclitaxel 80 mg/m2 IV Days 1, 8, 15, 22, 29, and 36 q 6 wks.
† Docetaxel 75 mg/m2 IV Days 1 and 22 q 6 wks.
** Pertuzumab 840 mg IV (first dose) 420 mg IV (subsequent doses), Days 1 and 22 every 6 wks.
†† Trastuzumab 8 mg/kg IV (first dose), 6 mg/kg IV (subsequent doses), Days 1 and 22 every 6 wks.
*** Atezolizumab 1200 mg or placebo IV, Day 22 of Cycle 1, then Days 1 and 22 every 6 wks.

Cycle 1 loading doses of Tras/Pert with paclitaxel or docetaxel per investigator choice while waiting for central testing results.

- **In late April of 2022, imbalance in deaths on treatment was identified.**
- Accrual was placed on hold on April 29, 2022.
- **Accrual was permanently discontinued on May 20, 2022; Patients were unblinded.**
- Details were reported at SABCS 2022.[1]
- **Protocol was amended to follow enrolled patients for progression-free survival (PFS) and overall survival (OS) through April 2024.**
- Median follow-up for PFS is 31.9 months and for OS is 35.9 months.

CONSORT Diagram



SYMPOSIUM

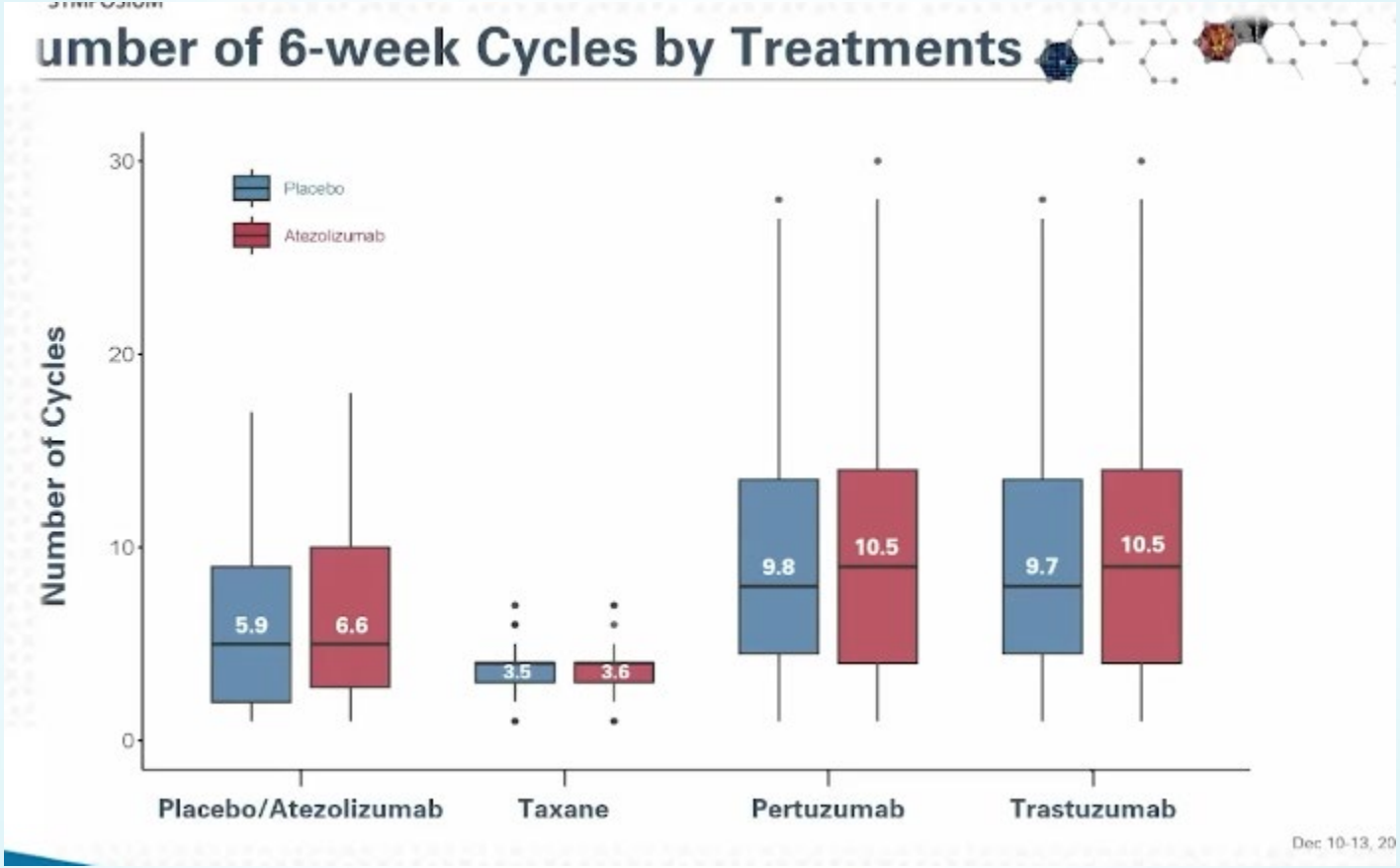
Patient Characteristics

	Placebo (n=93)	Atezolizumab (n=97)
ge, n (%)		
<40 years	17 (18.3%)	18 (18.6%)
40-50 years	20 (21.5%)	24 (24.7%)
50-60 years	29 (31.2%)	25 (25.8%)
60+ years	**27 (29.0%)**	**30 (30.9%)**
ender, n (%)		
Female	90 (96.8%)	96 (99.0%)
Male	3 (3.2%)	1 (1.0%)
ace, n (%)		
White	76 (81.7%)	70 (72.2%)
Black	8 (8.6%)	11 (11.3%)
Others	9 (9.7%)	16 (16.5%)

	Placebo (n=93)	Atezolizumab (n=97)
Estrogen Receptor, n (%)		
Negative	31 (33.3%)	34 (35.1%)
Positive	62 (66.7%)	63 (64.9%)
Disease Site, n (%)		
Any visceral without brain metastasis	75 (80.6%)	74 (76.3%)
Brain metastasis	2 (2.2%)	5 (5.2%)
Non visceral only without brain metastasis	16 (17.2%)	18 (18.6%)
Prior Trastuzumab, n (%)		
No	**75 (80.6%)**	**79 (81.4%)**
Yes	18 (19.4%)	18 (18.6%)
PD-L1 Status, n (%)		
Indeterminate	10 (10.8%)	11 (11.3%)
Negative	**71 (76.3%)**	**71 (73.2%)**
Positive	12 (12.9%)	15 (15.5%)

Play

umber of 6-week Cycles by Treatments



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Overall AE and Selected SOC by Arm

Six Deaths on Treatment (Atezolizumab)

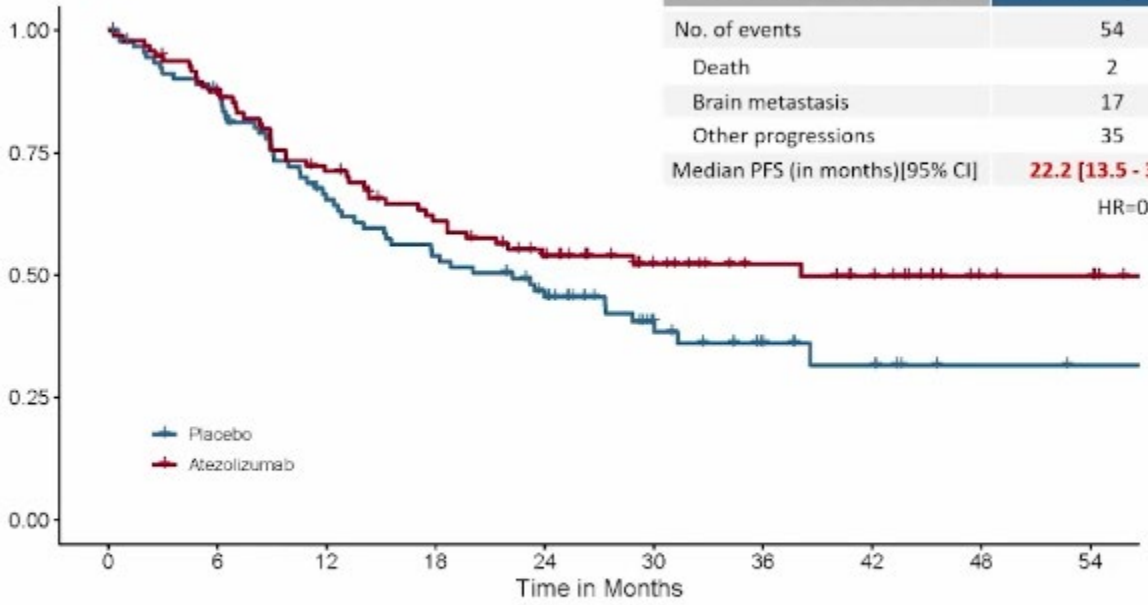
Date of Death	Adverse Event	Interpretation by DMC
05/20/2020	Hepatic failure due to rapid disease progression	Unrelated to treatment
10/25/2020	Diarrhea complicated by non-neutropenic sepsis	Probably related to treatment
08/24/2021	Respiratory failure due to pneumonia complicating admission for adrenal insufficiency	Related to treatment
08/27/2021	Sudden death NOS following discharge after 2nd hospitalization for immune colitis	Related to treatment
02/26/2022	Non-neutropenic sepsis	Related to treatment
04/22/2022	Heart failure due to progressive mitral valve disease	Not directly related to treatment though possibly aggravated by treatment

SYMPOSIUM

Progression-free Survival

Median follow-up 31.9 mos	Placebo (n=93)	Atezolizumab (n=97)
No. of events	54	44
Death	2	7
Brain metastasis	17	18
Other progressions	35	19
Median PFS (in months)[95% CI]	22.2 [13.5 - 30.0]	38.1 [18.6 -]

HR=0.73 (95% CI=0.49, 1.09)
Log rank p=0.12



Number at risk

Placebo	93	79	57	47	36	19	11	7	2	1
zolizumab	96	82	65	53	42	28	21	16	6	5

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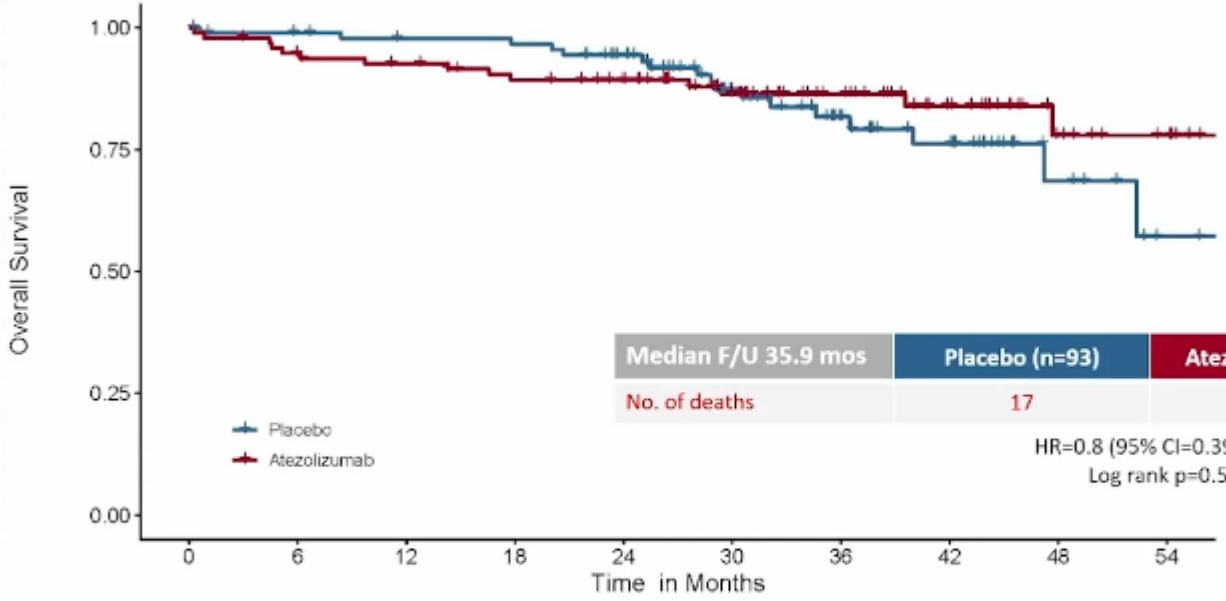
Overall Survival



Median F/U 35.9 mos	Placebo (n=93)	Atezolizumab (n=97)
No. of deaths	17	14

HR=0.8 (95% CI=0.39, 1.63)
Log rank p=0.53

Number at risk

Placebo	93	89	86	85	77	52	35	25	9	3
Atezolizumab	96	89	85	79	74	57	43	28	12	7

Dec 10-13, 2024

Summary and Conclusions

Due to an imbalance of deaths on atezolizumab, and persistently slow accrual, BR004 was closed early to accrual in April 2022. Atezolizumab/placebo was stopped, patients were unblinded, therapy continued per investigator discretion, and protocol was amended to provide follow-up through April 2024.

The incidence of Grade 3 and 4 events were not meaningfully different between the 2 arms and the delivery of THP was not impaired by the administration of atezolizumab.

With a median follow-up of 31.9 months for PFS superiority of atezolizumab relative to placebo could not be claimed with the small sample size.

- Stratified log-rank test p-value=0.12
- HR=0.73 (95% CI=0.49 -1.09)

OS was immature and underpowered, but there were fewer deaths in the atezolizumab arm.

Although results of BR004 do not support adding atezolizumab tp THP. However, the findings support a potential role for checkpoint inhibitors in patients with HER2+ MBC perhaps in combination with ADCs.