Triple Negative Breast Cancer: SABCS 2023 Updates

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Disclosures

I have no conflicts of interest to disclose

Learning objectives

1. Identify the potential role of ICI (pembrolizumab) and parp inhibition in BRCA wild-type and any PD-L1 score within advanced TNBC
2. Identify considerations in the sequenced use of ADC's within (HER2-low) advanced TNBC
3. Recognize that adjuvant ICI (atezolizumab) did not improve outcomes when added to CT in early-stage TNBC
4. Recognize that neoadjuvant ICI (nivolumab) given as a lead-in followed by CT vs concurrent with CT did not improve pCR in early-stage TNBC
5. Recognize older patients $\geq$ 65 years have improved total mortality with adjuvant systemic treatments vs no treatments in early-stage TNBC

Agenda

Advanced TNBC

1. Abstract GS01-05: Keylynk-009
2. Abstract PS08-02: ADC after ADC

Early-Stage TNBC

1. Impassion-030
2. IBCSG61-20 NeoN
3. PS13-07

Advanced TNBC

1. Keylynk-009
2. PS08-02

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Keylynk-009

Pembrolizumab Plus Olaparib vs Pembrolizumab Plus Chemotherapy After Induction With Pembrolizumab Plus Chemotherapy for Locally Recurrent Inoperable or Metastatic TNBC: Randomized, Open-Label, Phase 2 KEYLYNK-009 Study

Hope S. Rugo[1]; Mark Robson[2]; Seock-Ah Im[3]; Florence Dalenc[4]; Eduardo Yañez Ruiz[5]; Young-Hyuck Im[6]; Sergii Kulyk[7]; Oleksandr Dudnichenko[8]; Néstor Llinás-Quintero[9]; Shigehira Saji[10]; Yasuo Miyoshi[11]; Nadia Harbeck[12]; Li Fan[13]; Jaime A. Mejia[13]; Vassiliki Karantza[13]; David W. Cescon[14]

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Background

- Pembrolizumab plus chemotherapy showed statistically significant improvements in PFS and OS vs placebo plus chemotherapy for previously untreated, locally recurrent inoperable or metastatic TNBC and PD-L1 CPS ≥10 in the phase 3 KEYNOTE-355 study[1,2]
- There is a need for tolerable and effective regimens in this setting that maintain the clinical benefit achieved after induction therapy
- Evidence suggests that combination maintenance therapy with an anti-PD-(L)1 antibody and PARP inhibitor may provide therapeutic benefit
- In preclinical tumor models, PARP inhibitors activated the STING pathway, upregulated PD-L1 expression, and had synergistic antitumor activity when combined with anti-PD-(L)1 antibodies regardless of *BRCA* status[3,4]

1. Cortes J, et al. *Lancet.* 2020;396:1817–28. 2. Cortes J, et al. *N Engl J Med.* 2022;387:217–26. 3. Jiao S, et al. *Clin Cancer Res*. 2017;23:3711-3720. 4. Wang Z, et al. *Sci Rep*. 2019;9:1853.

Background (cont'd)

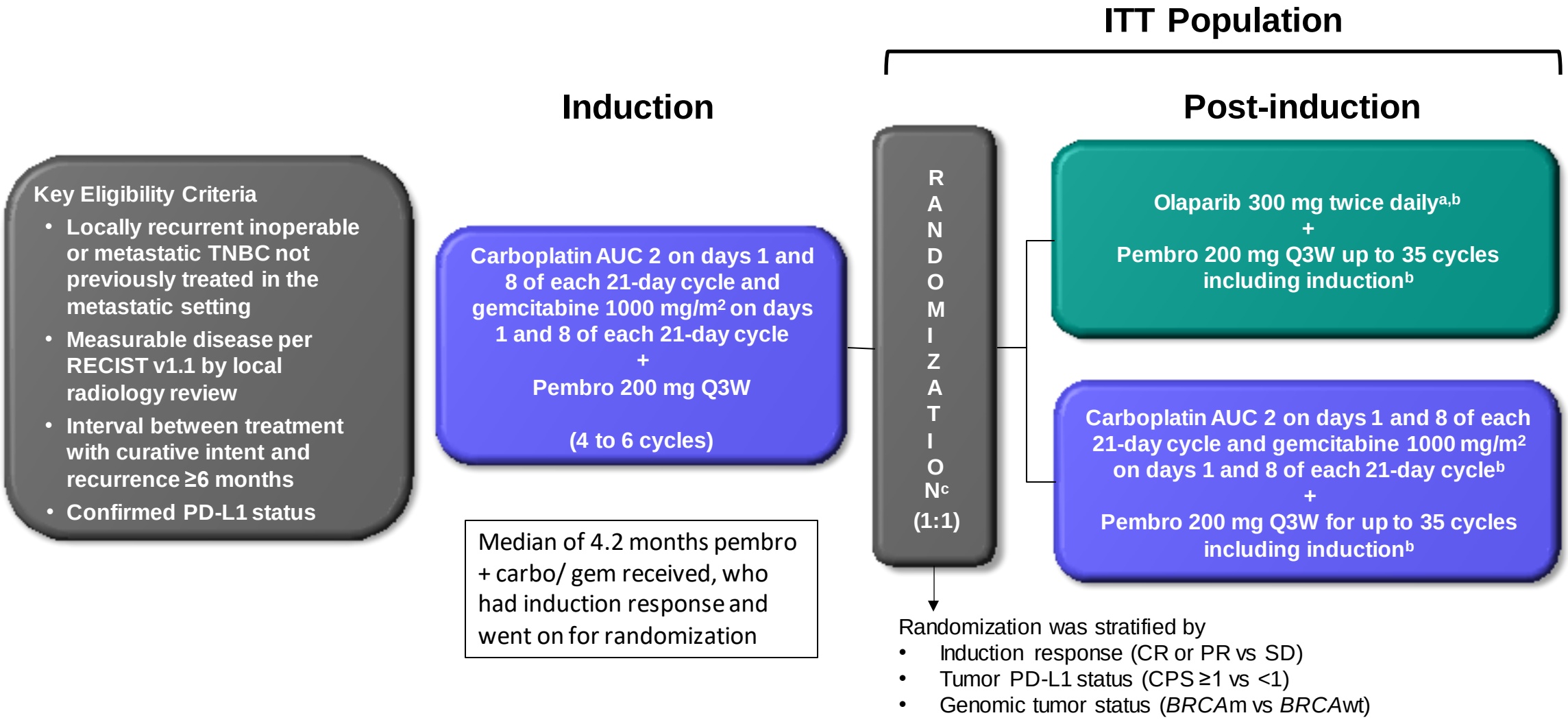
- Phase 1 trials with anti-PD-(L)1 antibodies plus PARP inhibitors demonstrated tolerable safety and promising antitumor activity in patients with advanced TNBC[1,2]

- The PARP inhibitor olaparib is an established maintenance therapy for platinum-sensitive ovarian cancer, regardless of *BRCA* status[3,4]

- In the phase 2 KEYLYNK-009 study (NCT04191135), we evaluated the efficacy and safety of maintenance pembrolizumab plus olaparib vs pembrolizumab plus chemotherapy for patients with locally recurrent inoperable or metastatic TNBC who had clinical benefit from induction with 1L pembrolizumab plus platinum-based chemotherapy

1. Domchek SM, et al. *Lancet Oncol.* 2020;21:1155–64. 2. Vinayak S, et al. *JAMA Oncol.* 2019;5:1132–40. 3. Olaparib Prescribing Information 2023. 4. Olaparib Summary of Product Characteristics 2023.

KEYLYNK-009 (NCT04191135): Study Design

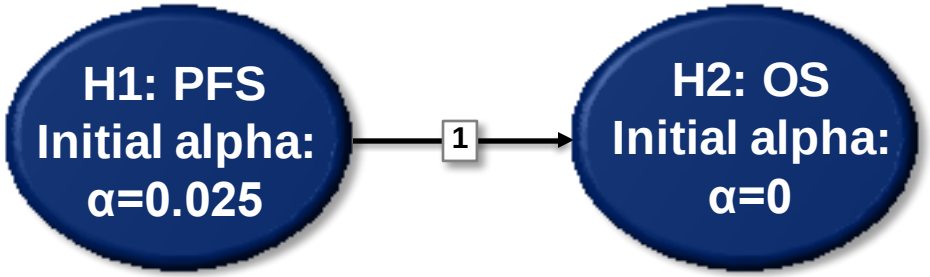


[a]Olaparib was administered postinduction and given concurrently with pembrolizumab. [b]Until disease progression or unacceptable toxicity. [c]ITT population was determined from randomization (not from the time of enrollment).

Study Endpoints

- Primary Endpoints[a]
  - PFS per RECIST v1.1 by BICR in ITT population
  - OS in ITT population
- Secondary Endpoints[a]
  - PFS in PD-L1 CPS ≥10 tumors and t*BRCA*m populations[b]
  - OS in PD-L1 CPS ≥10 tumors and t*BRCA*m populations[b]
  - Safety

Multiplicity:



All α=2.5% will be allocated to PFS first, and if superiority is demonstrated, the full alpha 2.5% from the superiority test for PFS will be passed to the superiority test for OS

[a]Assessed from the time of randomization. [b]PD-L1 and *BRCA* status were centrally confirmed; PD-L1 was assessed using PD-L1 IHC 22C3 pharmDx and measured using the combined positive score (CPS; number of PD-L1–positive tumor cells, lymphocytes, and macrophages divided by total number of tumor cells x 100).

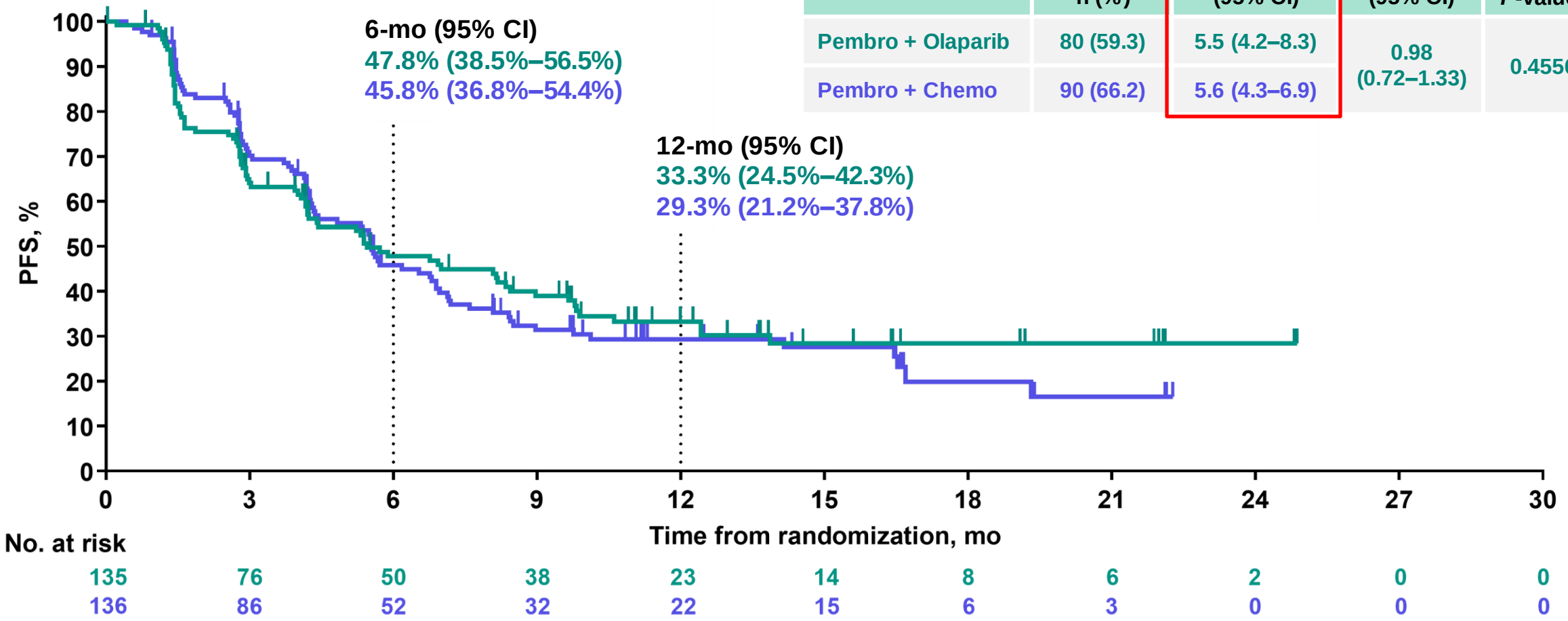
Baseline Characteristics: ITT Population

Characteristic, n (%)	Pembro + Olaparib n = 135	Pembro + Chemo n = 136
Age, median (range), y	54 (25–82)	52 (30–80)
ECOG PS 1	48 (35.6)	45 (33.1)
Postmenopausal	96 (71.1)	94 (69.1)
PD-L1 status[a]		
PD-L1 CPS ≥1	106 (78.5)	105 (77.2)
PD-L1 CPS <1	29 (21.5)	31 (22.8)
PD-L1 CPS ≥10	65 (48.1)	65 (47.8)
PD-L1 CPS <10	69 (51.1)	71 (52.2)
BRCA mutation[b]	29 (21.5)	30 (22.1)
HRD ≥33[c]	83 (61.5)	77 (56.6)
Disease status		
Metastatic, de novo	47 (34.8)	37 (27.2)
Metastatic, recurrence	87 (64.4)	96 (70.6)
Locally recurrent inoperable	1 (0.7)	3 (2.2)
Response at randomization		
CR/PR	95 (70.4)	96 (70.6)
SD	39 (28.9)	40 (29.4)

[a]PD-L1 assessed at a central laboratory using PD-L1 IHC 22C3 pharmDx and measured using the combined positive score (CPS; number of PD-L1 positive tumor cells, lymphocytes, and macrophages divided by the total number of tumor cells × 100). [b]BRCA status was determined in tumor for the purpose of this analysis; blood testing will be conducted at a later time. [c]Myriad MyChoice CDx® Plus was used to determine HRD; ≥33 is used as a cutoff for HRD based on Merck internal validation.

PFS per RECIST v1.1 by BICR: ITT Population

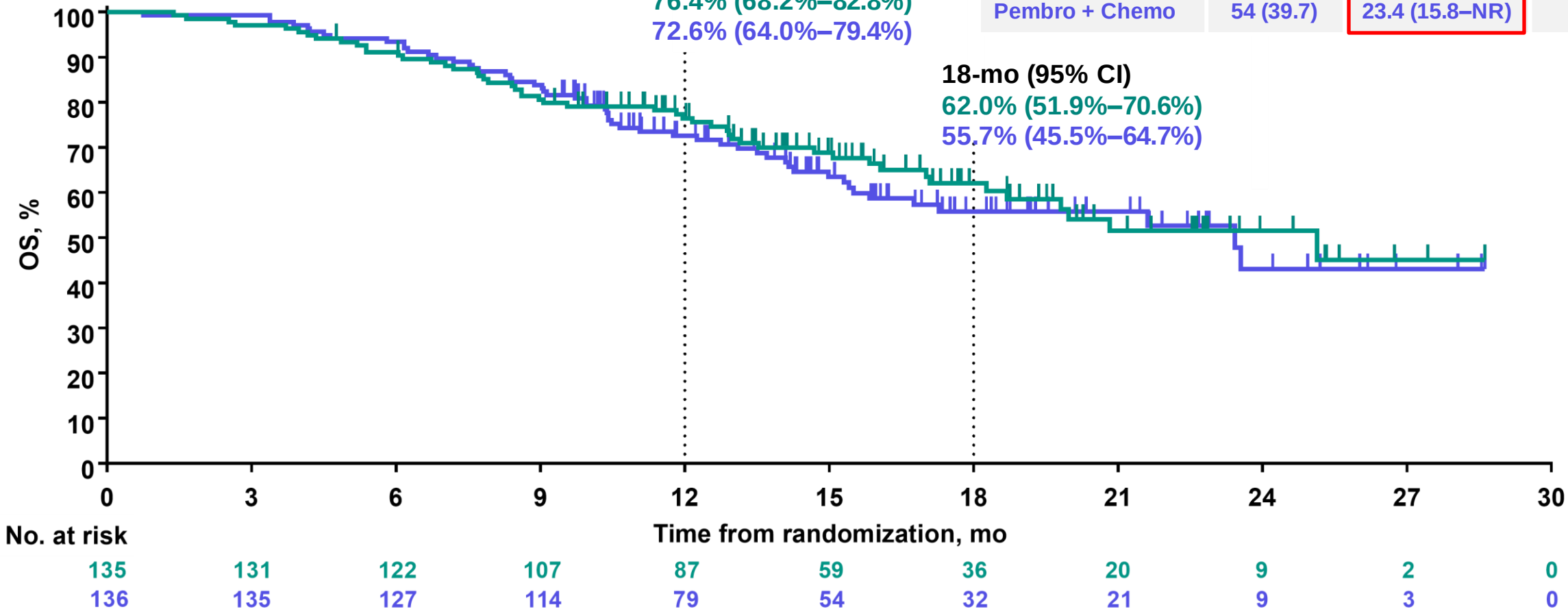
	Events, n (%)	Median, mo (95% CI)	HR[a] (95% CI)	*P*-value[b]
Pembro + Olaparib	80 (59.3)	5.5 (4.2–8.3)	0.98 (0.72–1.33)	0.4556
Pembro + Chemo	90 (66.2)	5.6 (4.3–6.9)		



[a]HR (pembro + olaparib vs pembro + chemo) based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by response to induction therapy, tumor PD-L1 status, and *BRCA* status. [b]One-sided and based on log-rank test stratified by response to induction therapy, tumor PD-L1 status, and *BRCA* status.

Estimates of OS: ITT Population

	Events, n (%)	Median, mo (95% CI)	HR[a] (95% CI)
Pembro + Olaparib	50 (37.0)	25.1 (18.3–NR)	0.95 (0.64–1.40)
Pembro + Chemo	54 (39.7)	23.4 (15.8–NR)	

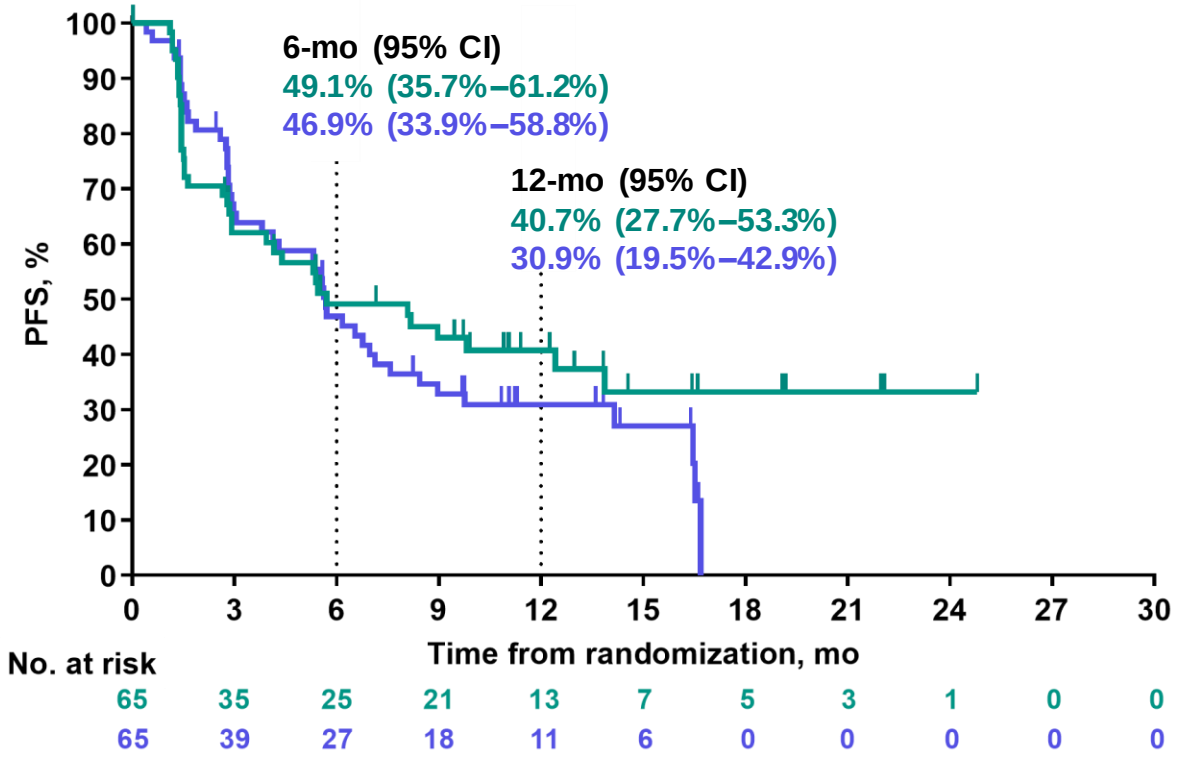


NR, not reached. [a]HR (pembro + olaparib vs pembro + chemo) based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by response to induction therapy, tumor PD-L1 status, and *BRCA* status.

PFS per RECIST v1.1 by BICR: PD-L1 CPS ≥10 and t*BRCA*m

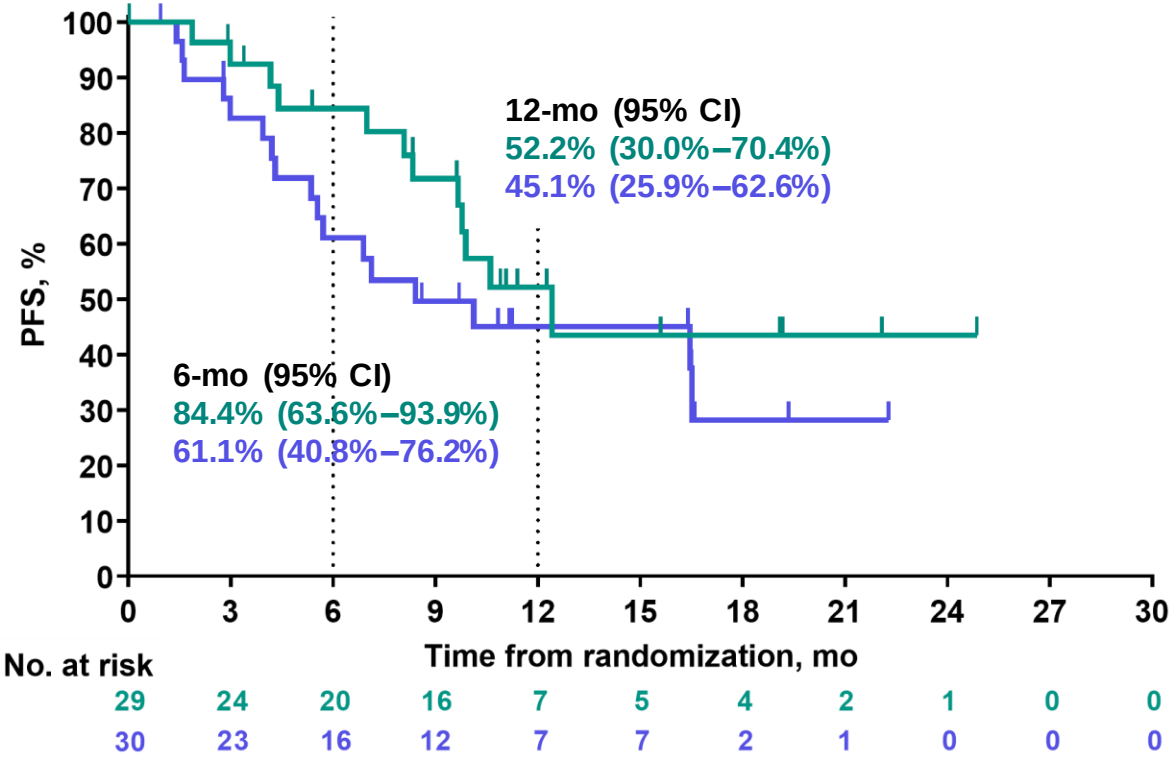
Tumor PD-L1 CPS ≥10 Population

	Events, n (%)	Median, mo (95% CI)	HR[a] (95% CI)
Pembro + Olaparib	36 (55.4)	5.7 (2.9–13.9)	0.92 (0.59–1.43)
Pembro + Chemo	45 (69.2)	5.7 (3.8–7.6)	



t*BRCA*m Population

	Events, n (%)	Median, mo (95% CI)	HR[b] (95% CI)
Pembro + Olaparib	12 (41.4)	12.4 (8.3–NR)	0.70 (0.33–1.48)
Pembro + Chemo	17 (56.7)	8.4 (5.4–NR)	

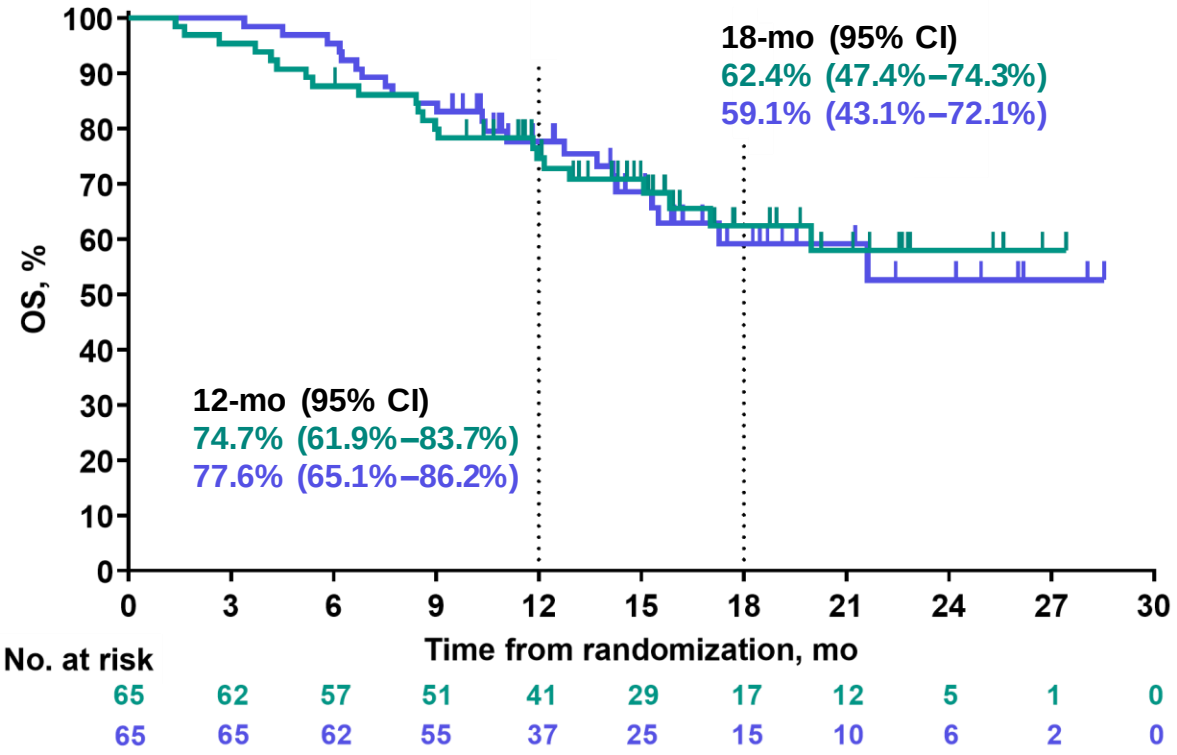


NR, not reached; t*BRCA*m, tumor *BRCA* mutation (includes germline and somatic mutations). [a]HR (pembro + olaparib vs pembro + chemo) based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by response to induction therapy and *BRCA* status. [b]HR (pembro + olaparib vs pembro + chemo) based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by response to induction therapy and tumor PD-L1 status.

Estimates of OS: PD-L1 CPS ≥10 and t*BRCA*m

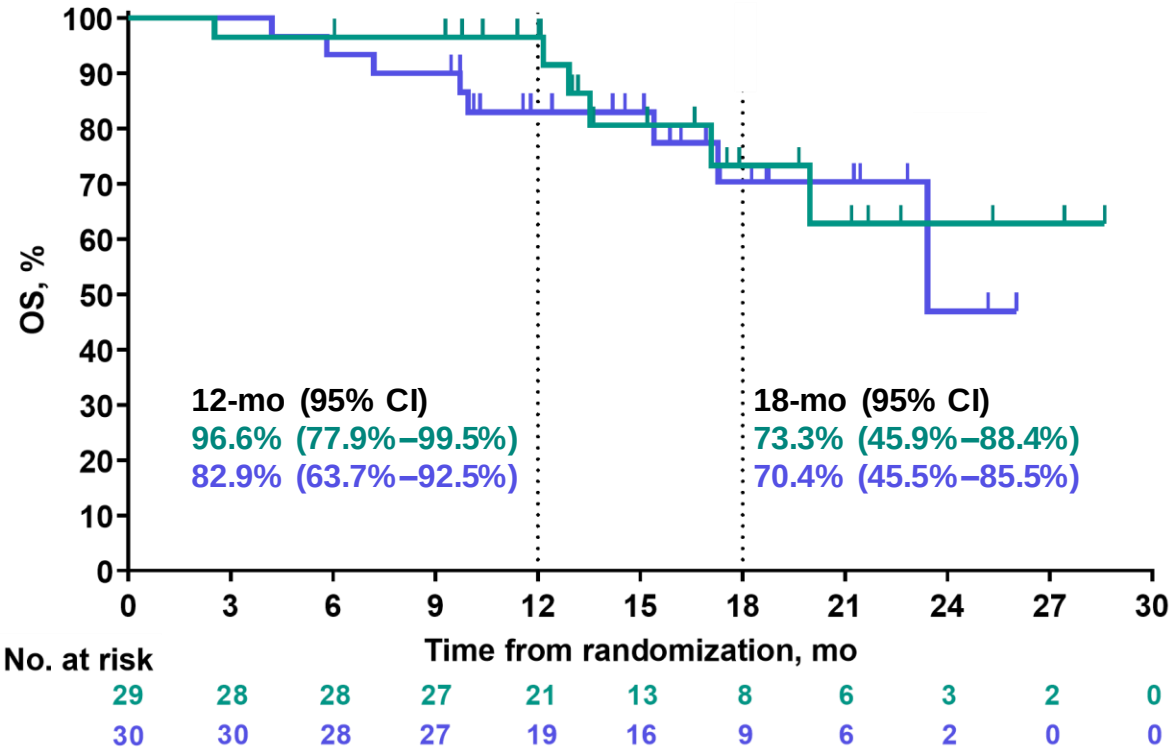
Tumor PD-L1 CPS ≥10 Population

	Events, n (%)	Median, mo (95% CI)	HR[a] (95% CI)
Pembro + Olaparib	22 (33.8)	NR (17.0–NR)	0.97 (0.53–1.76)
Pembro + Chemo	22 (33.8)	NR (15.5–NR)	



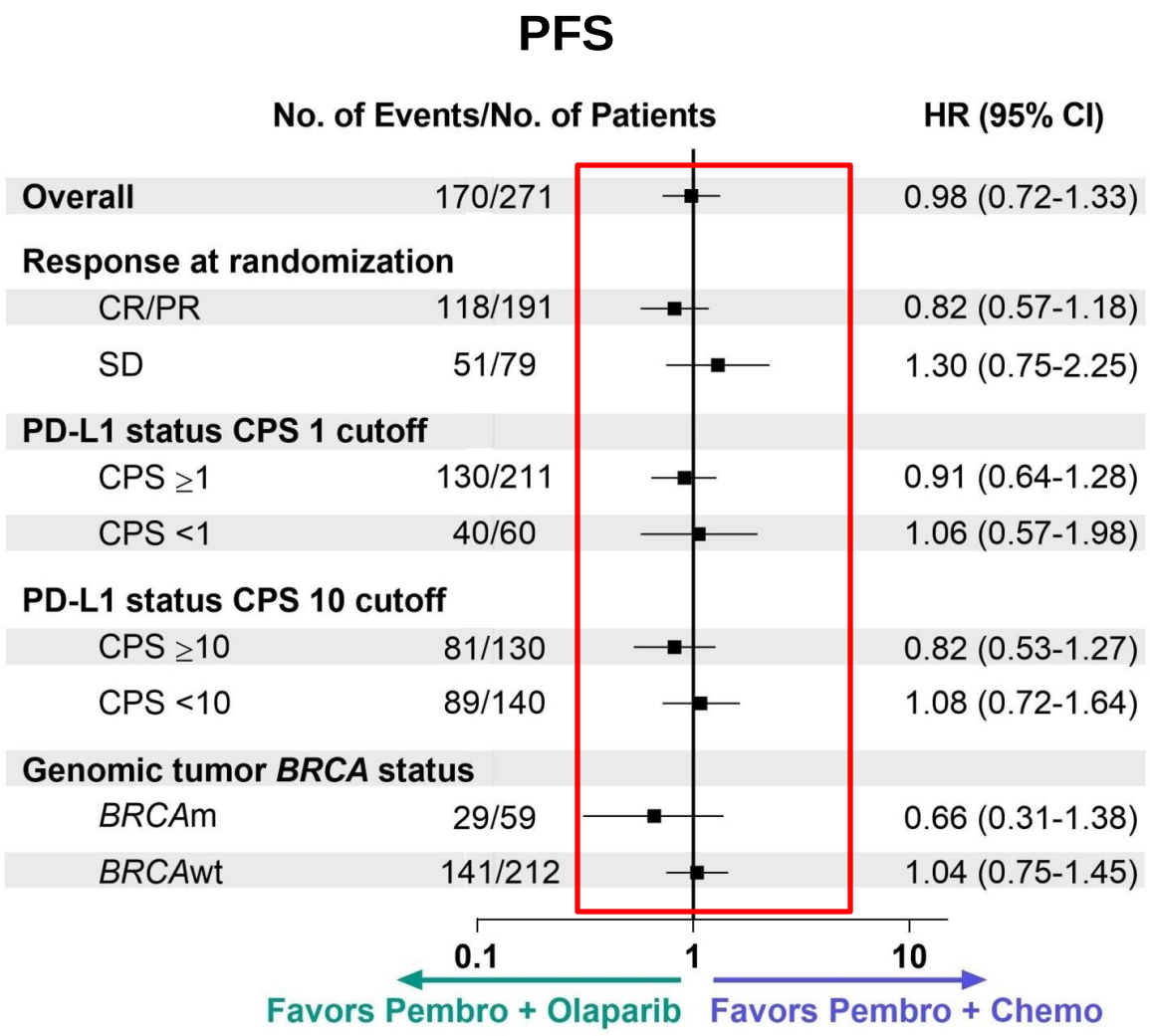
t*BRCA*m Population

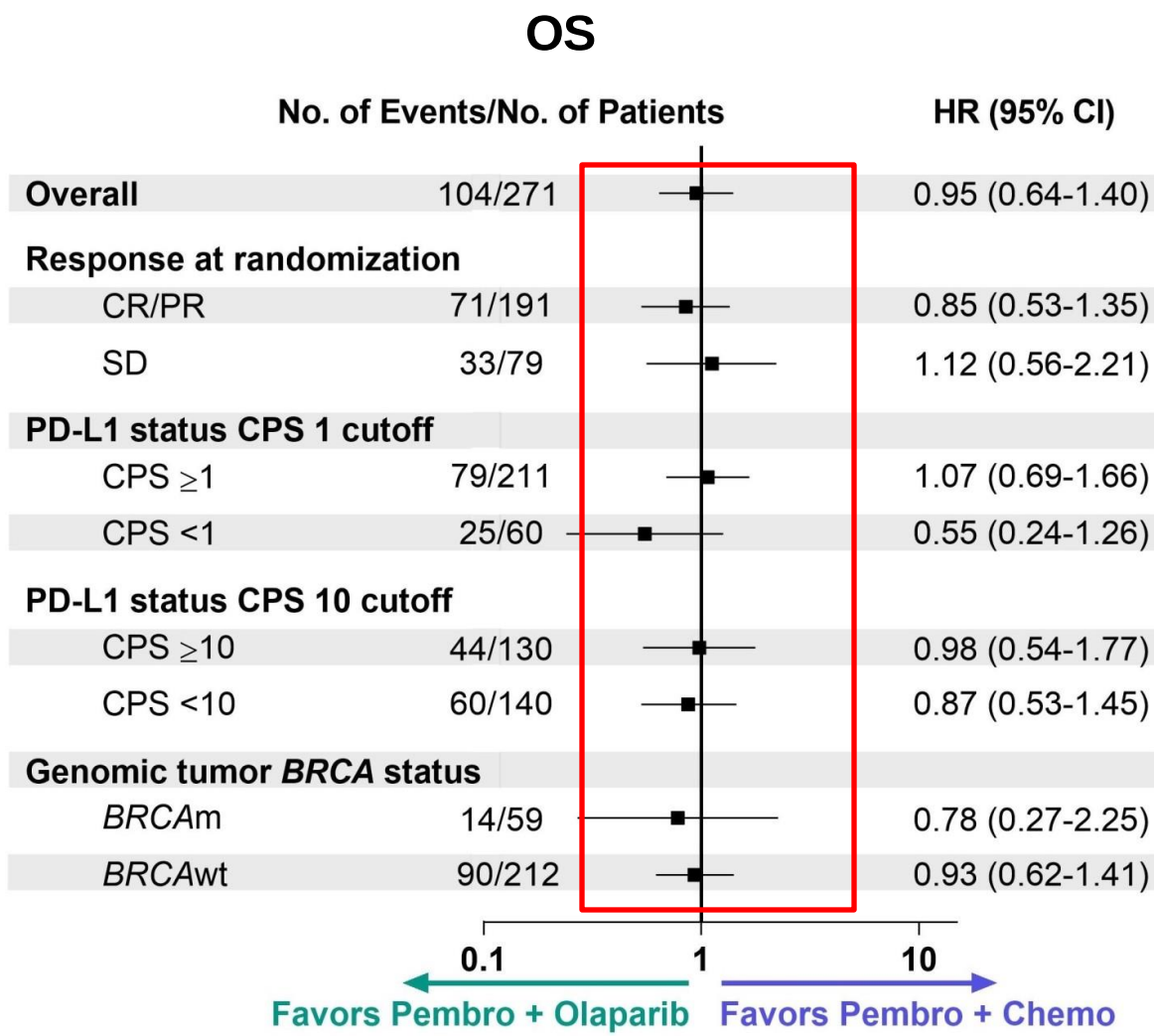
	Events, n (%)	Median, mo (95% CI)	HR[b] (95% CI)
Pembro + Olaparib	6 (20.7)	NR (17.1–NR)	0.81 (0.28–2.37)
Pembro + Chemo	8 (26.7)	23.4 (17.3–NR)	



NR, not reached. [a]HR (pembro + olaparib vs pembro + chemo) based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by response to induction therapy and *BRCA* status. [b]HR (pembro + olaparib vs pembro + chemo) based on Cox regression model with Efron's method of tie handling with treatment as a covariate stratified by response to induction therapy and tumor PD-L1 status.

PFS and OS in Key Patient Subgroups: ITT Population





Adverse Events Summary (As-Treated Population)

	Pembro + Olaparib n = 135	Pembro + Chemo n = 133
Treatment-related AEs		
Any grade treatment-related AEs	114 (84.4)	128 (96.2)
Grade 3–5 treatment-related AEs	44 (32.6)[a]	91 (68.4)[b]
Treatment-related AEs leading to discontinuation of any treatment	12 (8.9)	26 (19.5)
Immune-Mediated AEs and Infusion Reactions[c]		
Any grade	26 (19.3)	31 (23.3)
Grade 3/4[d]	6 (4.4)	6 (4.5)
Led to discontinuation of any treatment	0	4 (3.0)

Data are n (%) of patients.

[a]There were no grade 5 events in the pembro + olaparib group.

[b]2 patients had grade 5 events in the pembro + chemo group (gastrointestinal hemorrhage and thrombotic thrombocytopenic purpura, n = 1 each).

[c]Immune-mediated AEs and infusion reactions were based on a list of preferred terms intended to capture known risks of pembrolizumab and were considered regardless of attribution to study treatment by the investigator.

[d]There were no grade 5 events in either group.

Discussion: Keylynk-009

- In responders after pembro + CT induction for metastatic TNBC, maintenance of pembro + olaparib vs pembro + CT did not improve outcomes
- Non-chemotherapy approach as maintenance strategy led to same PFS and OS outcomes in the ITT group
- More favorable safety profile with pembro + olaparib → Much lower incidence of TRAE in pembro + olaparib arm

Key Questions:

1. Is the benefit to pembro + olaparib as maintenance in any BRCA status, similar to platinum sensitive ovarian cancer?
2. In tumor BRCA mutated: Numeric benefit in survival outcomes with pembro + olaparib over pembro + CT
   - Consistent with TBCRC 048[1] analysis: benefit with parp inhibitor in mBC with gPALB2 and somatic BRCA1/2 carriers
   - Small subgroup- only 58 with tumor BRCA mutation
   - May be a less toxic maintenance treatment strategy for this population
3. CPS score did not lead to difference in response between maintenance treatment arms; same median survivals with pembro + CT or pembro + olaparib
   - CPS is a surrogate for ICI response
   - Is the pembro the reason for response?
     - Keynote- 355 subgroup analysis update from ESMO 2023[2]:

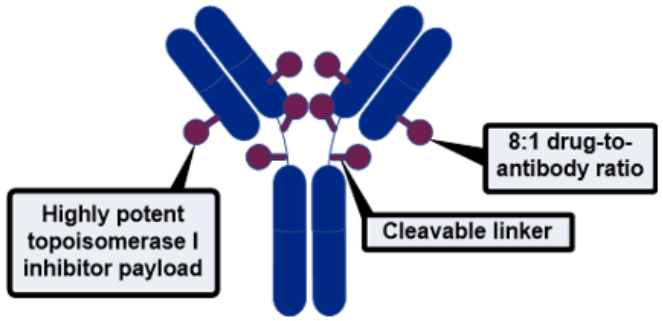
1. Tung et al, TBCRC-048: olaparib in MBC and mutations in HRD genes, JCO 2020.
2. Rugo et al, Keynote0-355: outcomes in patients who discontinued CT before pembro and in patients with IMAE. Abstract 191MO. ESMO 2023.

ADC after ADC

Current ADC's for HER2-negative MBC

Trastuzumab deruxtecan (T-DXd)

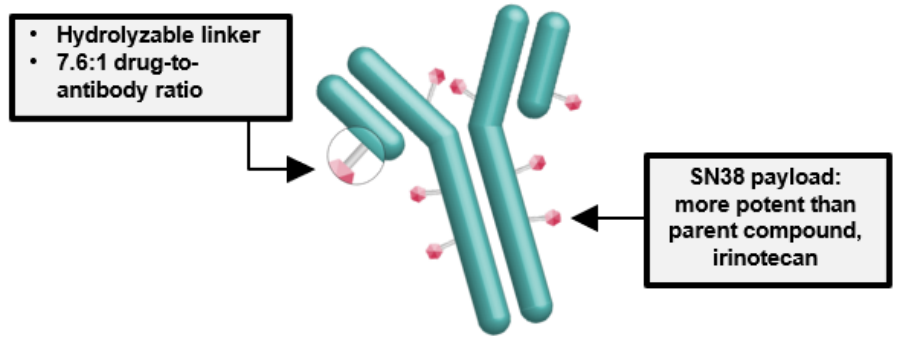
HER2-directed ADC



Unresectable or metastatic **HER2-low** breast cancer (IHC 1+ or IHC 2+/ISH-) after a prior chemotherapy in the metastatic setting or disease recurrence during or within 6 months of completing adjuvant chemotherapy

Sacituzumab govitecan (SG)

TROP2-directed ADC



Unresectable locally advanced or metastatic **HR+/HER2-** breast cancer after endocrine therapy and ≥2 additional systemic therapies for metastatic disease

Unresectable locally advanced or metastatic **TNBC** after ≥2 prior systemic therapies, at least one of them for metastatic disease

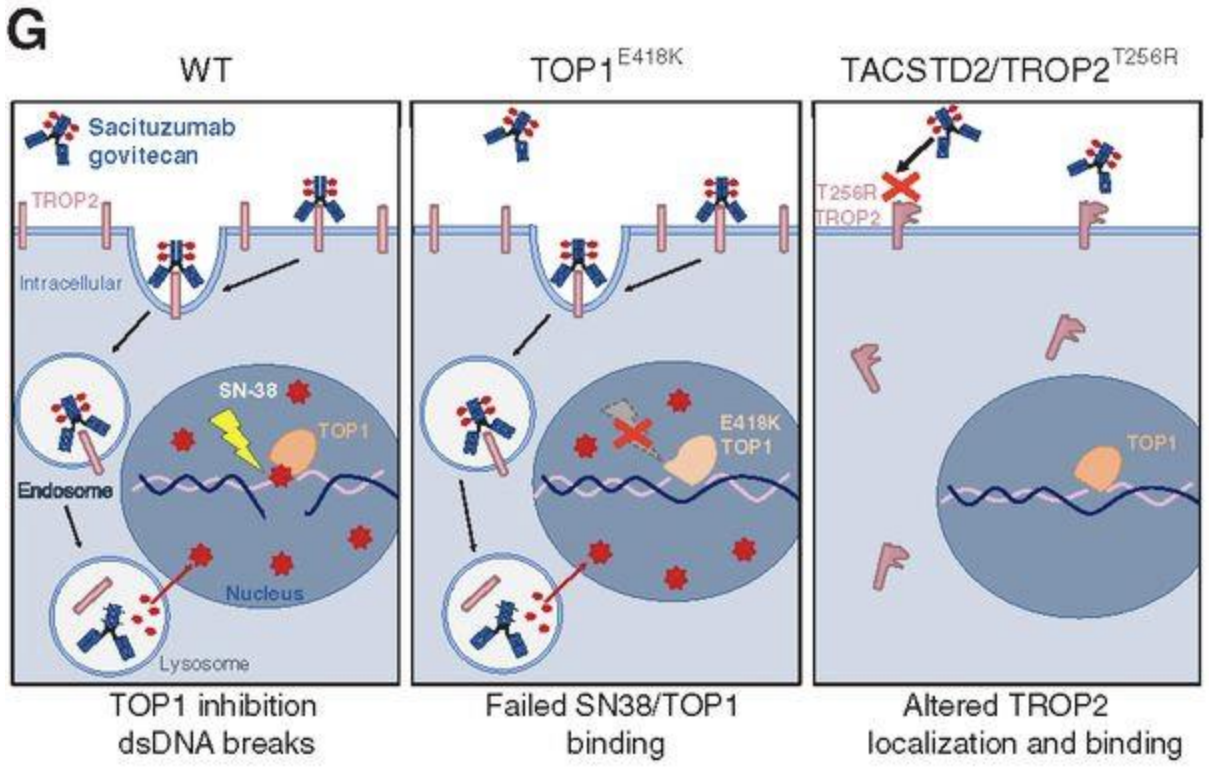
Bardia A et al. ESMO 2020.
Modi S et al. ASCO 2022.

Current landscape of ADCs in HER2-negative MBC

	HR+/HER2- BC			TNBC	
ADC trials in MBC	**DESTINY-Breast04**	**TROPION-Breast01**	**TROPiCS-02**	**DESTINY-Breast04**	**ASCENT**
Treatment arms	T-DXd (HER2) vs TPC	Dato-DXd (TROP2) vs TPC	SG (TROP2) vs TPC	T-DXd (HER2) vs. TPC	SG (TROP2) vs. TPC
HER2 status	1+, 2+/ISH-	0, 1+, 2+/ISH-	0, 1+, 2+/ISH-	1+, 2+/ISH-	0, 1+, 2+/ISH-
Prior chemotherapy for MBC	1-2	1-2	2-4	1-2	≥1
Median PFS HR (95% CI)	9.6 vs 4.2 mo. HR 0.37 (0.30-0.56)	6.9 vs 4.9 mo. HR 0.63 (0.52-0.76)	5.5 vs 4.0 mo. HR 0.65 (0.53-0.81)	6.3 vs 2.9 mo. HR 0.29 (0.15-0.57)	5.6 vs 1.7 mo. HR: 0.41 (0.32-0.52)
Median OS HR (95% CI)	23.9 vs 17.6 mo. HR 0.69 (0.55-0.87)	N/A HR 0.84 (0.62–1.14)	14.5 vs 11.2 mo. HR 0.79 (0.65-0.95)	17.1 vs 8.3 mo. HR 0.58 (0.31-1.08)	12.1 vs 6.7 mo. 0.48 (0.38-0.59)
ORR	52.6% vs 16.3%	36.4% vs 22.9%	21% vs 14%	50.0% vs 16.7%	35% vs 5%

Modi S et al. ESMO 2023; Bardia A et al. ESMO 2023; Tolaney S et al. ASCO 2023; Bardia A et al. NEJM 2021.

Potential ADC Mechanism of Resistance



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AACR American Association for Cancer Research

Efficacy of Sacituzumab Govitecan (SG) post Trastuzumab Deruxtecan (T-DXd) and vice versa for HER2-low advanced or metastatic breast cancer (MBC): a French multicentre retrospective study.

F. Poumeaud[1], M. Morisseau[2], L. Cabel[3], A. Gonçalves [4], C. Rivier[5], O. Trédan[5], E. Volant[6], J-S. Frenel[6], S. Ladoire[7], W. Jacot[8], M. Jamelot[9], H. Fokatichoue[10], A. Patsouris[11], L. Teixeira[12], F-C. Bidard[3], D. Loirat[3], M. Brunet[13],C. Levy[14], A. Deleuze[15], L. Drouin[12], B.Cabarrou[2], L. Uwer[16], E. Deluche[17], T. Grellety[18], F. Fiteni[19], H. Bischoff[20], R. Vion[21], M. Pagliuca[22], B. Verret[22], S. Becourt[23], T. Reverdy[24], A. de Nonneville[4], F. Dalenc[1].

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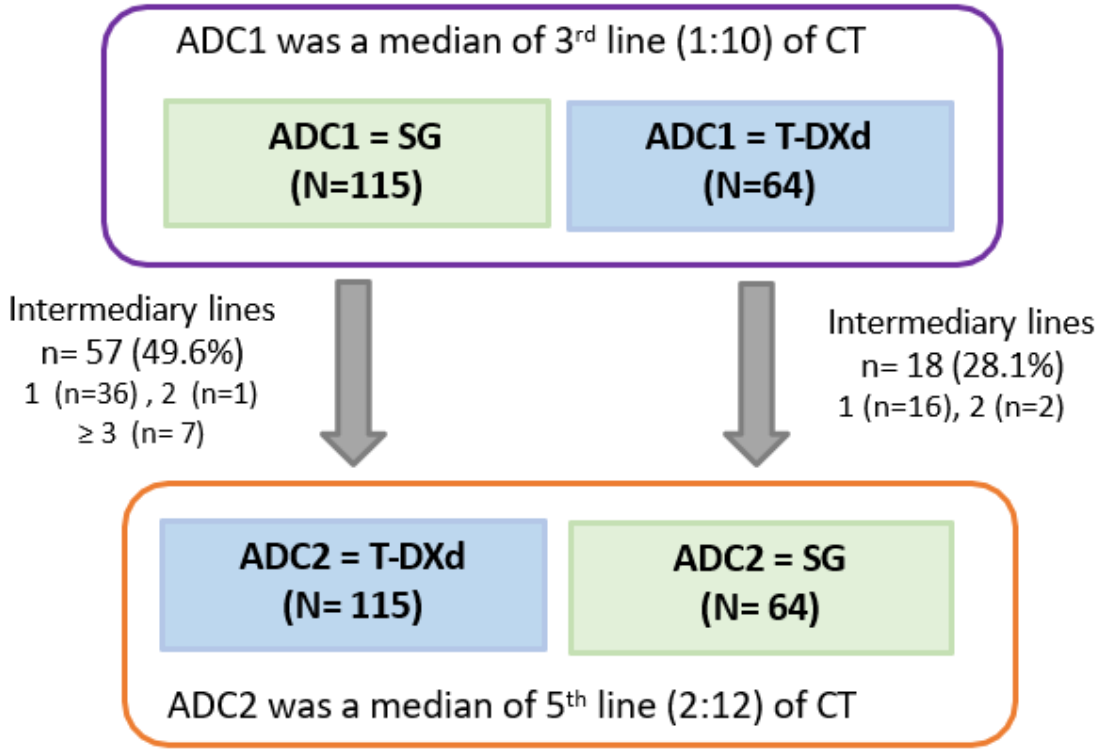
Objectives and Methods

- **ADC Low** is a **French**, **multicentric** and **retrospective** study including 179 pts. It was designed to **evaluate the efficacy and safety of one ADC after another**.
- Primary endpoint: **ADC2 PFS2** in the whole population.
- Secondary endpoints: **PFS2** by subgroups, **ADC1 PFI1** and **OS** in whole population and subgroups.

Table 2: ADC treatment

Characteristics	ADC1	ADC2
Previous CT regimens in metastatic setting, median (range)	2 (0-9)	4 (1-11)
Dose reduction after C1, n (%)	43 (24.3)	33 (19.2)
Ongoing treatment, n (%)		
Yes	0 (0)	57 (31.8)
No	100 (100)	122 (68.2)
Cause of interruption, n (%)		
Progressive disease	175 (97.8)	103 (85.8)
Toxicity	3 (1.7)	5 (4.2)
Death not related to ADC	0 (0)	9 (7.5)
ECOG 0-1, n (%)	166 (93.8)	137 (77.0)
Metastatic sites, n (%)		
Visceral	111 (62)	127 (70.9)
Cerebral and/or meningeal	27 (15.1)	34 (15.8)



*32% still receiving ADC2 at time of analysis

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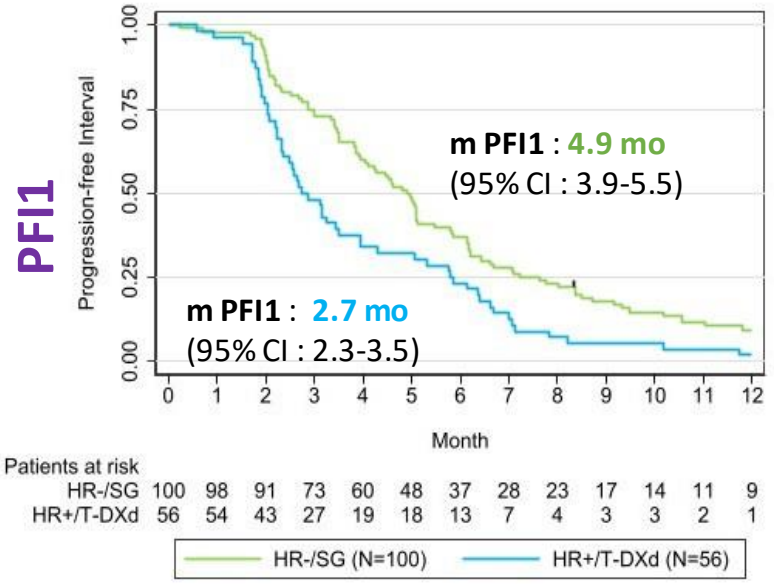
Results

PFI1

By HR/ADC combination



PFS2

All patients

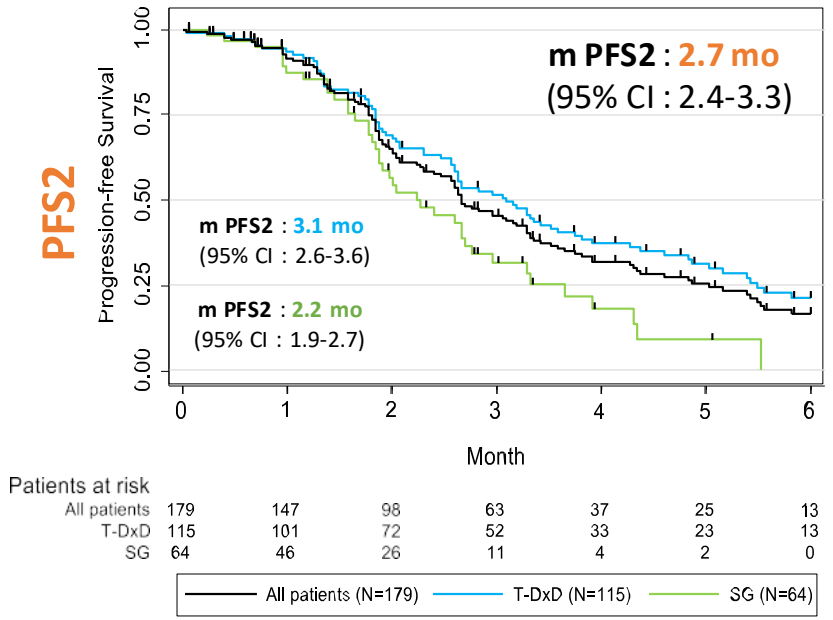


Table 3: Multivariate analysis

	HR [95%CI]	p-value
ECOG at initiation of ADC2		
0-1	1.00	
>1	1.45 [0.93; 2.26]	0.099
HR status		
HR +	1.00	
HR -	0.87 [0.50; 1.53]	0.631
Consecutive ADCs		
No	1.00	
Yes	0.76 [0.51; 1.14]	0.188
Therapeutic sequence		
T-DXd ➔ SG	1.00	
SG ➔ T-DXd	**0.57 [0.32; 1.03]**	**0.063**

m PFS2 is short (**2.7 mo**), **ADC post ADC** including the same payload **seems to be debatable** in these population of **heavily pre-treated patients**.

Conclusions

- Exposition to ADC2 after ADC1 is associated with **increased primary resistant pts** (**40.4%** and **54.4%** respectively for **ADC1** and **ADC2**), including 50% of pts with **secondary resistance** to **ADC1.**

  ➔ **These pts may have acquired payload cross-resistance at ADC1 progression.**

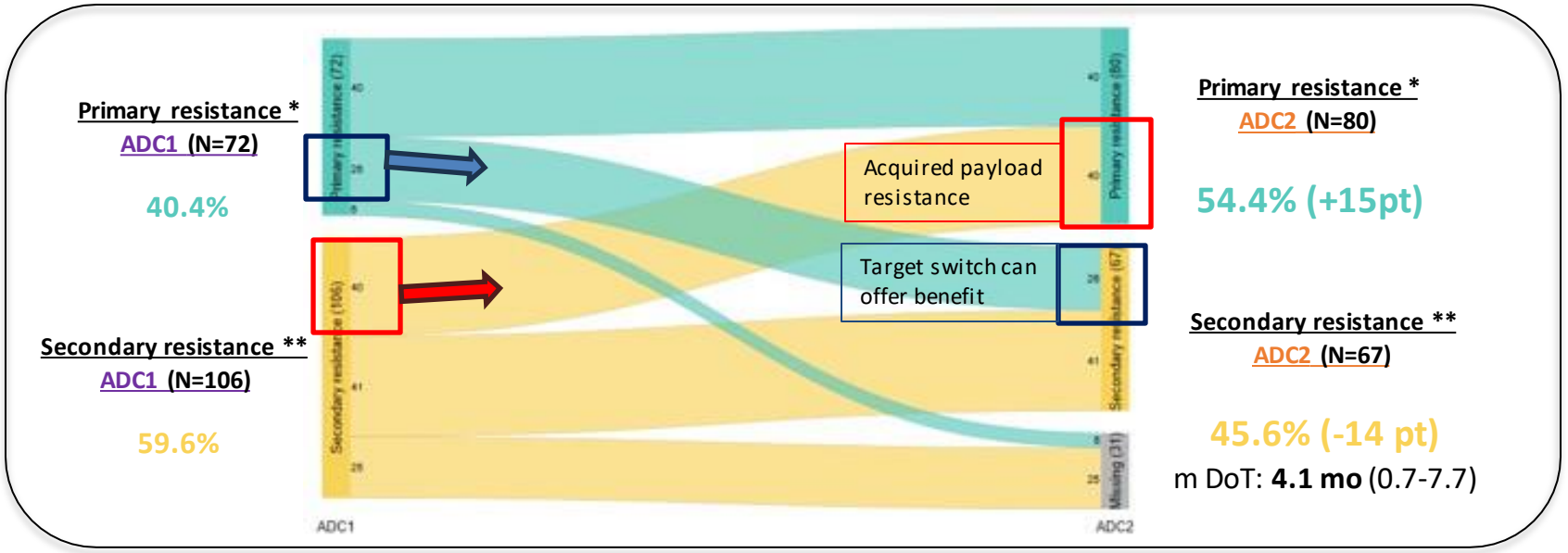
- ADC2 was effective for a short time for 39% of pts with primary resistance to **ADC1 .**

  ➔ **Switch of antibody target may be relevant for some pts.**

- **Additional studies** to understand resistance mechanisms are needed. Prospective studies must be planned.

Primary resistance: having progressive disease as the best response

Secondary resistance: stable disease or objective response on the ADC



Discussion: PS-082

1. ADC1 was given at median 3rd line and most commonly SG
2. ADC2 was given at median 5th line and was T-DXd
3. In HR- who received SG as ADC1, mPFI was 4.9 mo
4. ADC2 with T-DXd, mPFS2 3.1 mo
5. Acquired payload resistance observed in 50% where secondary resistance to ADC1 is followed by primary resistance to ADC2
6. Population of benefit in 40% where primary resistance to ADC1 is followed by secondary resistance to ADC2, suggesting target switch is beneficial

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Sequencing Antibody-Drug Conjugate after Antibody-Drug Conjugate in Metastatic Breast Cancer (A3 study): Multi-Institution Experience and Biomarker Analysis

Rachel O. Abelman, MD
Massachusetts General Hospital, Boston, MA

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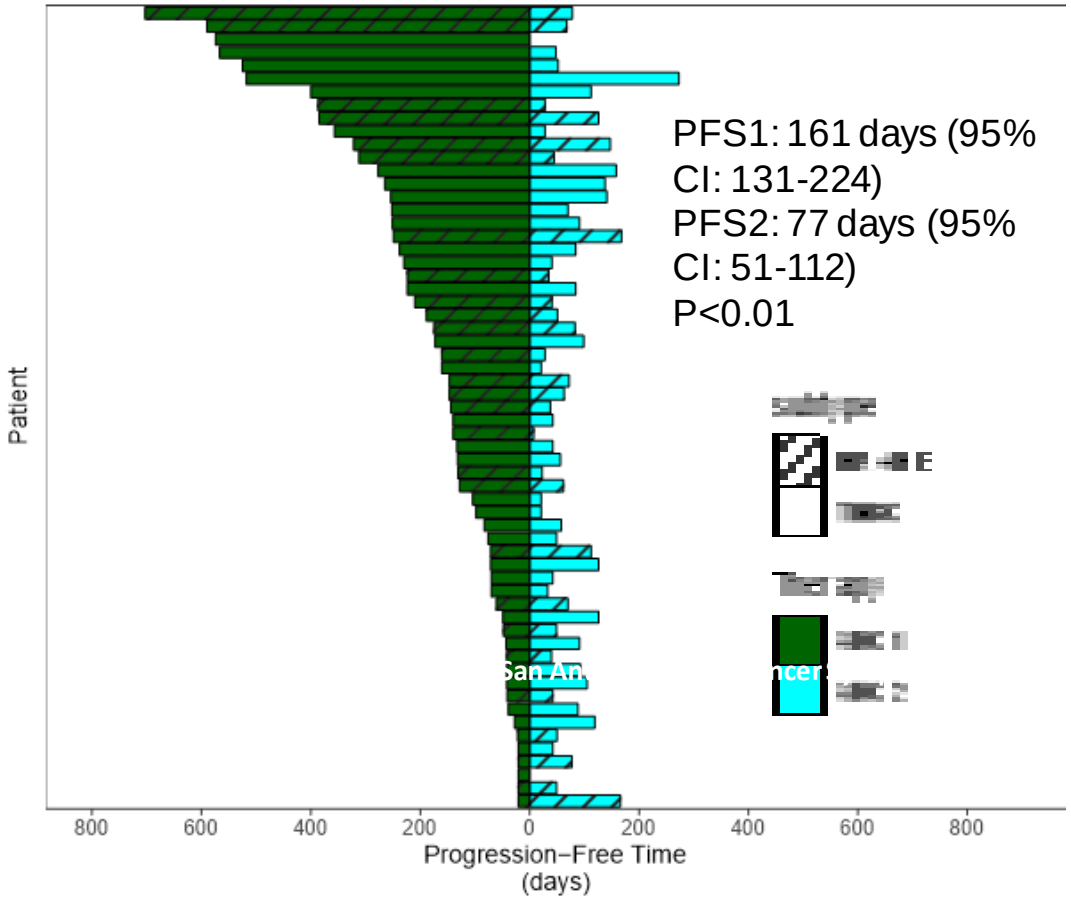
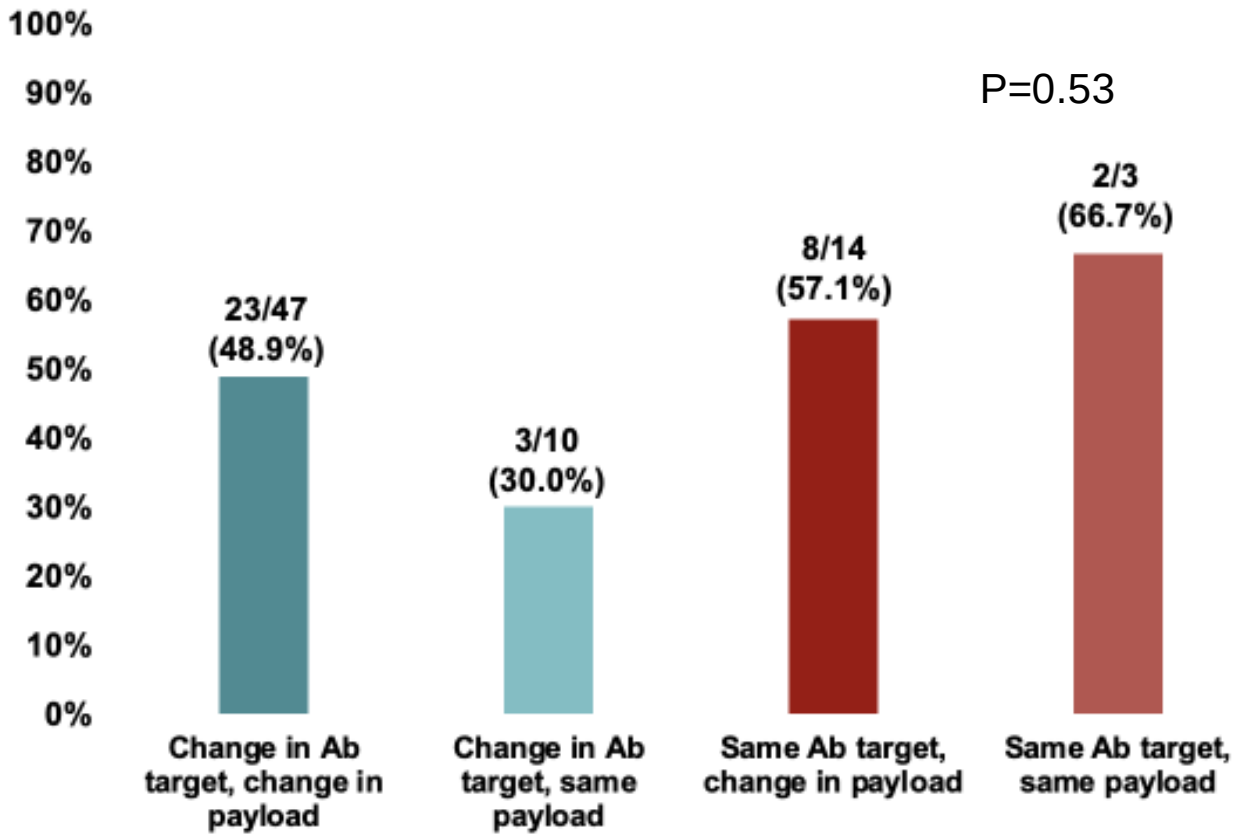
Results

Time To Progression ADC1 vs. ADC2



Cross-Resistance to Later ADC Based on ADC-to-ADC Characteristics



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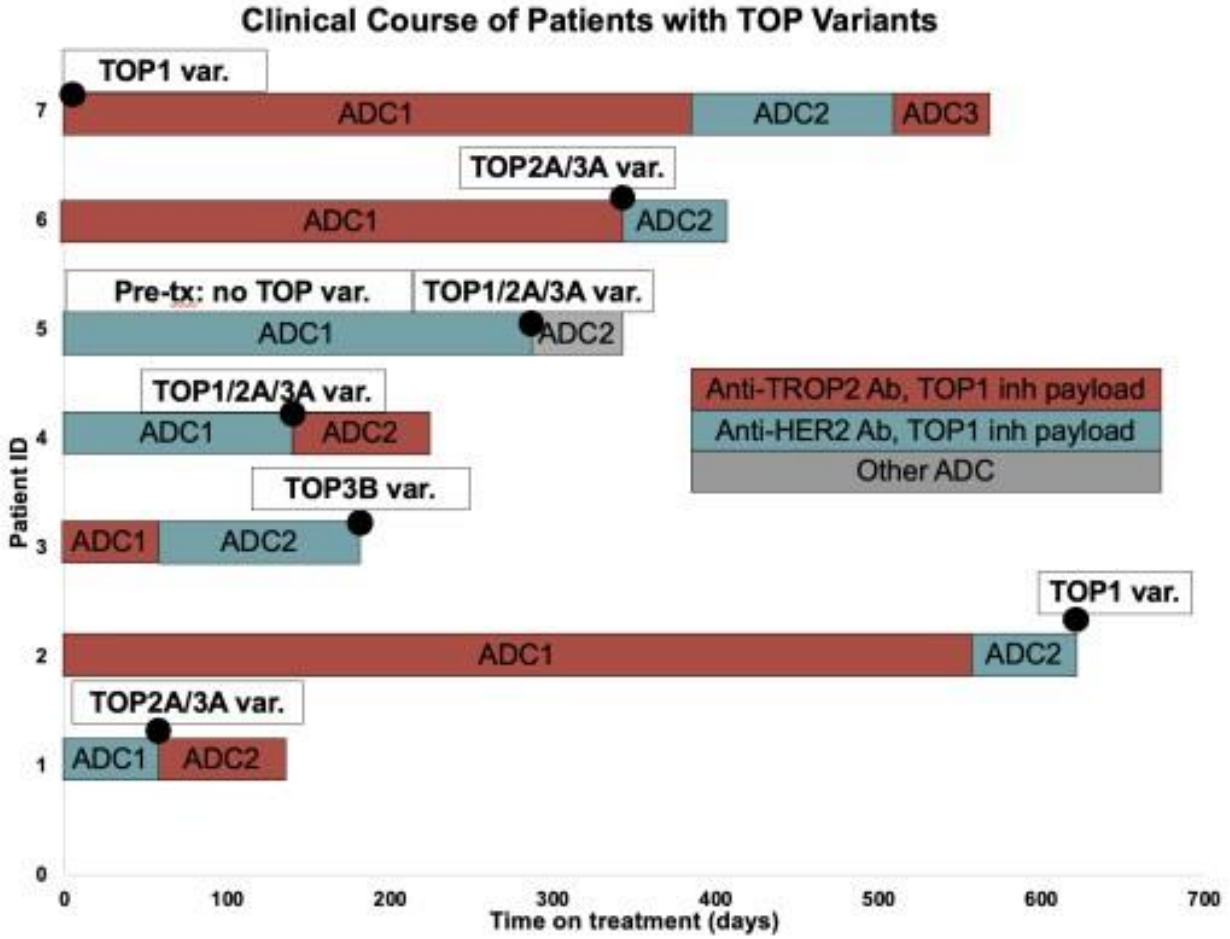
Conclusion/Future Directions



- Multi-institution update with biomarkers
- Cross-resistance to ADC2 driven by Ab target and payload
- *TOP* variants may drive resistance to topoisomerase-I inhibitor payloads
- Heterogeneity reflects ADC structure
- Tissue sequencing impactful in determining resistance mechanisms

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Discussion PS-08-03

- ADC1 time to progression, longer than ADC2 TTP
  - PFS1 161 days
  - PFS2 77 days
- Cross resistance to ADC2 most common when antibody target was the same
- Tissue sequencing demonstrated acquired Top 1 variant in one resistant sample, though also with existing Top1 variations and long duration of benefit on ADC1

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Multicenter retrospective cohort study of the sequential use of the antibody-drug conjugates (ADCs) trastuzumab deruxtecan (T-DXd) and sacituzumab govitecan (SG) in patients with HER2-low metastatic breast cancer (MBC)

Laura A. Huppert[1*], Reshma Mahtani[2*], Samantha Fisch[1], Naomi Dempsey[2], Sarah Premji[3], Angelina Raimonde[4], Saya Jacob[1], Laura Quintal[1], Michelle Melisko[1], Jo Chien[1], Ana Sandoval[2], Lauren Carcas[2], Manmeet Ahluwalia[2], Natasha Harpalani[2], Jenna Hoppenworth[3], Kelly Blum[1], Mi-Ok Kim[1], Dame Idossa[5], Ruta Rao[4], Karthik V. Giridhar[3], Hope S. Rugo[1]

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Disclosures:
LAH – Ad board: AstraZenica

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Background

- Two antibody drug conjugates (ADCs) are approved for patients with metastatic HR+/HER2- and triple negative breast cancer (TNBC):
  - Sacituzumab govitecan (SG) for HR+/HER2-[1] MBC and mTNBC[2]
  - Trastuzumab deruxtecan (T-DXd) for HER2-low MBC[3]
- Outstanding question: What is the safety and efficacy of these agents in a real-world setting, including in sequence?
- Study design: Retrospective multi-institutional cohort study at 5 academic centers. We identified patients with HER2-low MBC who had received both SG and T-DXd, in either order, per standard of care or on a clinical trial with ADC monotherapy.

1. Rugo et. al. JCO 2022
2. Bardia et. al. NEJM 2021
3. Modi et. al. NEMJ 2022

Demographic Data

	HR+/HER2-low MBC (n=56)	HR-/HER2-low MBC (n=28)
Demographic Data		
Median age at time of ADC #1, yrs (range)	60.4 (23.0-81.7)	54.0 (37.7-79.1)
Sex, n (%)		
Female	55 (98.2%)	28 (100.0%)
Male	1 (1.8%)	0 (0%)
Ethnicity, n (%)		
Non-Hispanic	47 (83.9%)	19 (67.9%)
Hispanic	8 (14.3%)	9 (32.1%)
Unknown	1 (1.8%)	0 (0%)
Race, n (%)		
White	44 (78.6%)	18 (64.3%)
Black	3 (5.4%)	5 (17.9%)
Asian	4 (7.1%)	3 (10.7%)
Other/unknown	5 (8.9%)	2 (7.1%)
Histology, n (%)		
Ductal	41 (73.2%)	23 (82.1%)
Lobular	7 (12.5%)	2 (7.1%)
Mixed ductal/lobular	5 (8.9%)	1 (3.6%)
Other/unknown	3 (5.4%)	2 (7.1%)
De novo metastatic disease, n (%)	12 (21.4%)	7 (25.0%)
Sites of metastatic disease prior to ADC #1		
Bone	41 (73.2%)	20 (71.4%)
Liver	34 (60.7%)	11 (39.3%)
Lung	20 (35.7%)	14 (50.0%)
CNS	8 (14.3%)	6 (21.4%)
Visceral disease prior to ADC #1	47 (83.9%)	18 (64.3%)
Treatment History		
Median time from MBC diagnosis to ADC1, months (range)	44.0 (0.7-199.3)	10.2 (0.5-59.6)
Median lines of MBC therapy prior to ADC1 by type:		
Medan lines endocrine therapy, number (range)	2 (0-6)	0 (0-1)
Median lines chemotherapy, number (range)	2 (0-7)	1 (0-4)
Median total lines of therapy, number (range)	4 (0-10)	2 (0-5)
Prior CDK4/6 inhibitor use	45 (80.4%)	
Median time on ET for MBC, months (range)	30.6 (0-145.0)	n/a

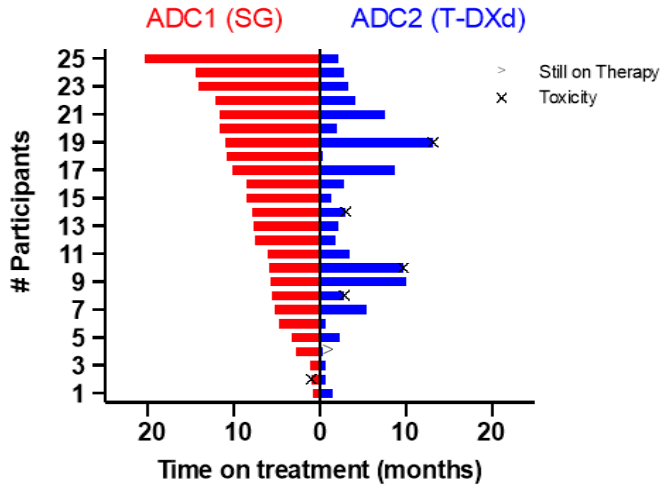
HR-/HER2-Low Efficacy Data (n=28)

SG → T-DXd (n=25, 89.3%)

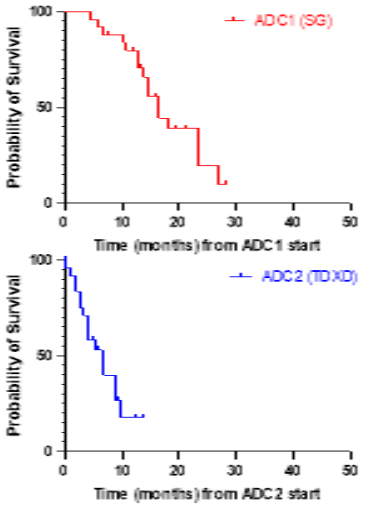
- Median lines of therapy for MBC prior to SG: 2.0 (range 0-5)
- Intervening therapies between ADCs: 40.0%

	ADC1 (SG)	ADC2 (T-DXd)
ORR (CR+PR) by investigator assessment, %	68.0%	35.0%
CBR (CR + PR + SD) by investigator assessment, %	80.0%	45.0%
Median rwPFS, months	7.8	2.8
Median rwOS from time of each ADC start, months	16.5	6.5

rwPFS



rwOS

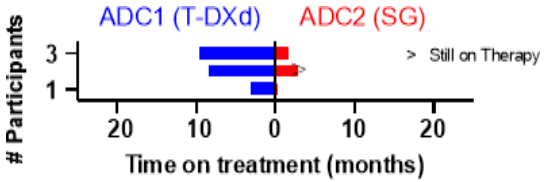


T-DXd → SG (n=3, 10.7%)

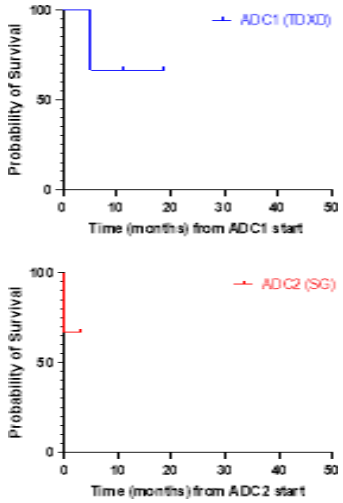
- Median lines of therapy for MBC prior to T-DXd: 3.0 (range 1-5)
- Intervening therapies between ADCs: 66.7%

	ADC1 (T-DXd)	ADC2 (SG)
ORR (CR+PR) by investigator assessment, %	33.3%	0.0%
CBR (CR + PR + SD) by investigator assessment, %	66.7%	50.0%
Median rwPFS, months	undetermined	
Median rwOS from time of each ADC start, months	undetermined	

rwPFS



rwOS



Discussion PS-084

- This study represents the largest multicenter series to date of patients treated with sequential ADCs for HR+/HER2-low or HR-/HER2-low MBC.
- ORR was higher and rwPFS was longer for ADC #1 than ADC #2 in all subgroups, regardless of HR+ status and ADC sequence order. However, there was a subset of patients with more durable responses to ADC2 compared to ADC1.
- Rates of ADC discontinuation and dose reduction in this real-world cohort show relatively low rates of discontinuation but higher rates of dose reduction. Most patients on SG needed growth factor; 16.7% of patients on T-DXd were diagnosed with any grade ILD.
- Future prospective studies are needed to further clarify the safety and efficacy of sequential ADC use and to identify biomarkers of response and mechanisms of resistance.

Early-Stage TNBC

1. Impassion-030
2. IBCSG61-20 NeoN
3. PS13-07: Adjuvant systemic tx in older patients

Impassion-030

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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

Michail Ignatiadis[1], MD, PhD, Andrew Bailey[2], Heather McArthur[3], MD, PhD Sarra El-Abed[4], Evandro De Azambuja[1], Otto Metzger[5], Stephen Y. Chui [6], Max Dieterich[7], Thomas Perretti[7], Guenther Steger[8], Jacek Jassem[9], Soo Chin Lee[10], Michaela Higgins[11], Jose Zarba[12], Marcus Schmidt[13], Henry Gomez[14], Angel Guerrero Zotano[15], Luca Moscetti[16], Joanne Chiu[17], Carter DuFrane[5], Vanessa Honvault[1], Rosa Altarcheh-Xifro[4], Luciana Molinero[6], Andrew Ellingson[2], Elisabetta Munzone[18], Noa Efrat Ben-Baruch[19], Emilio Bajetta[20], Shinji Ohno[21], Seock-Ah Im[22], Gustavo Werutsky[23], Einav Nili Gal-Yam[24], Xavier Gonzalez Farre[25], Ling-Ming Tseng [26], William Jacot[27], Oleg Gluz[28], Zhimin Shao[29], Yaroslav Shparyk[30], Ivan Sinielnikov[31], Anastasia Zimina[32], Vasiliev Aleksander [33], Esther Shearer-Kang[6], Eric Winer[5], Diogo Martins Branco[1], Shona Fielding[2], David Cameron[34], Giuseppe Viale[18], Shigehira Saji[35], Richard Gelber[2,5], Martine Piccart[1].

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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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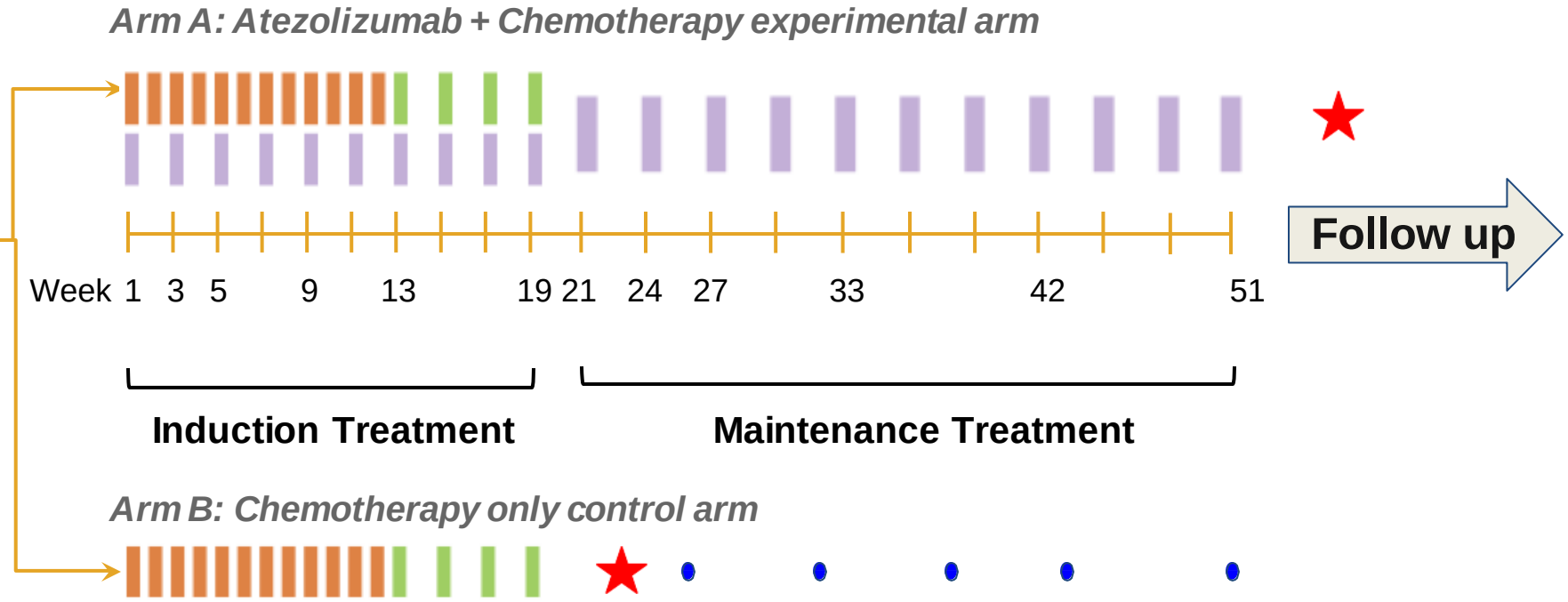
SURGERY

Early TNBC
- **Stage II-III**
- **At least 50% node-positive**
- **N=2300**

R



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)

- Paclitaxel qw for 12 weeks
- ddAC/EC q2w for 4 doses supported with G-CSF/GM-CSF
- Atezolizumab
  - Induction: 840 mg q2w for up to 10 doses
  - Maintenance: 1200 mg q3w to complete 1 year
- Monitoring visit Arm B

★ **End of 30-day safety reporting period after last study treatment**

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

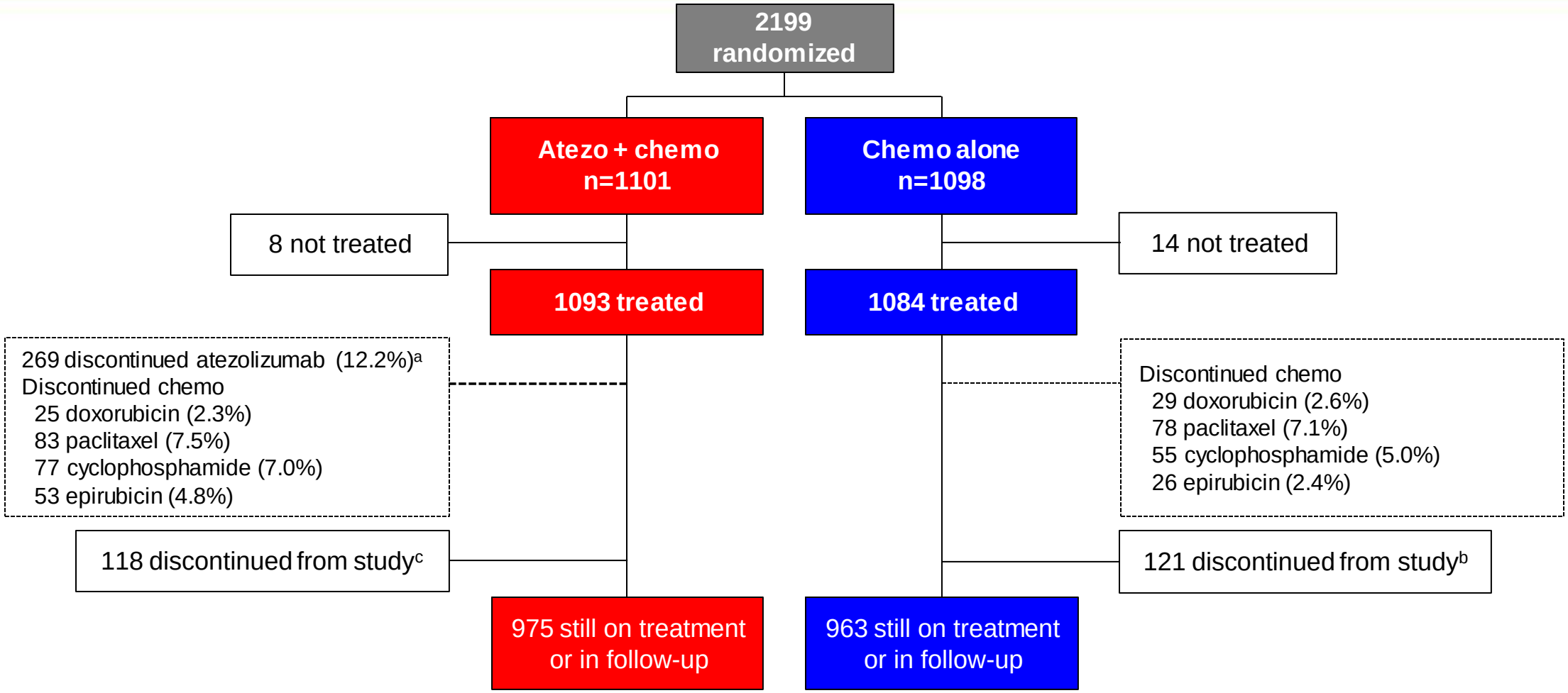
Overall Survival (OS)

Relapse-Free Interval (RFI)

Distant Relapse-Free Interval (DRFI)

Disease-free survival (DFS)

ALEXANDRA/IMpassion030 interim analysis consort diagram



[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)

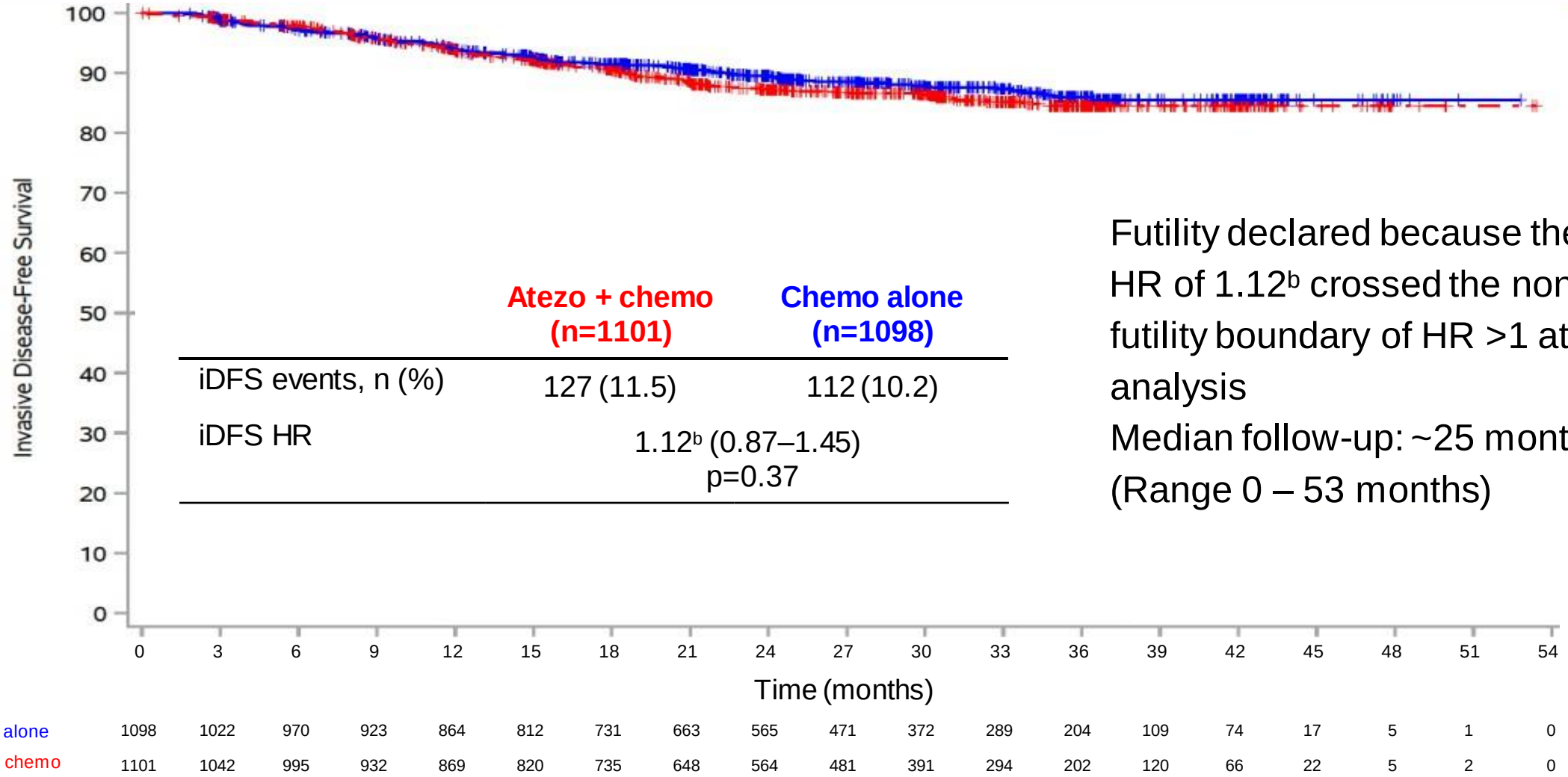
Characteristic, n (%)	Atezo + chemo (n=1101)	Chemo alone (n=1098)	Total (N=2199)
Primary Tumor Stage			
pT1-pT2	1024 (93.0)	1045 (95.2)	2069 (94.1)
pT3	71 (6.4)	51 (4.6)	122 (5.5)
Other[1]	6 (0.5)	2 (0.2)	8 (0.4)
Axillary Nodal Status (IxRS)			
0	577 (52.4)	573 (52.2)	1150 (52.3)
1-3	390 (35.4)	390 (35.5)	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)

[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)



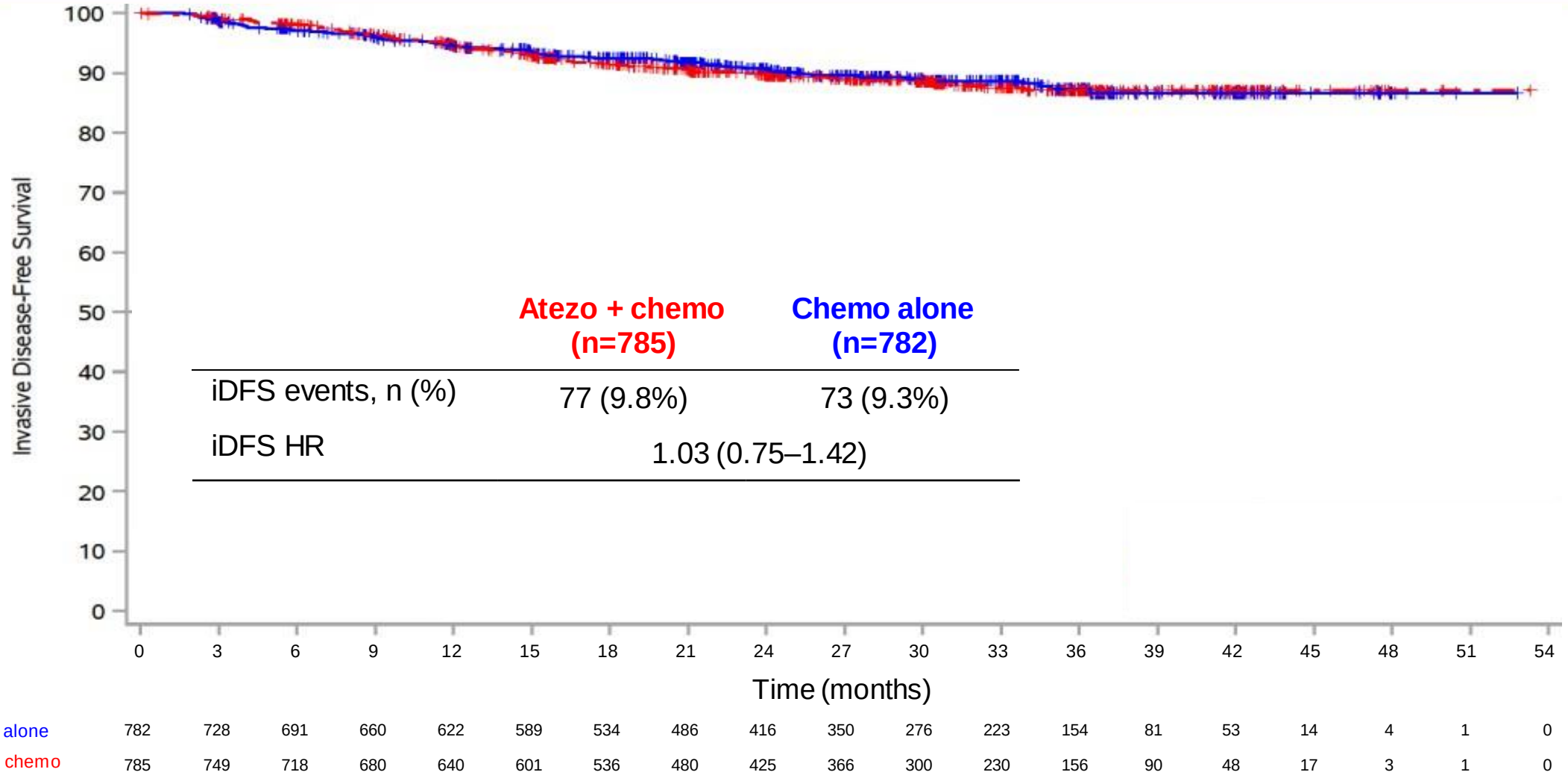
	Atezo + chemo (n=1101)	Chemo alone (n=1098)
iDFS events, n (%)	127 (11.5)	112 (10.2)
iDFS HR	1.12[b] (0.87–1.45) p=0.37	

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

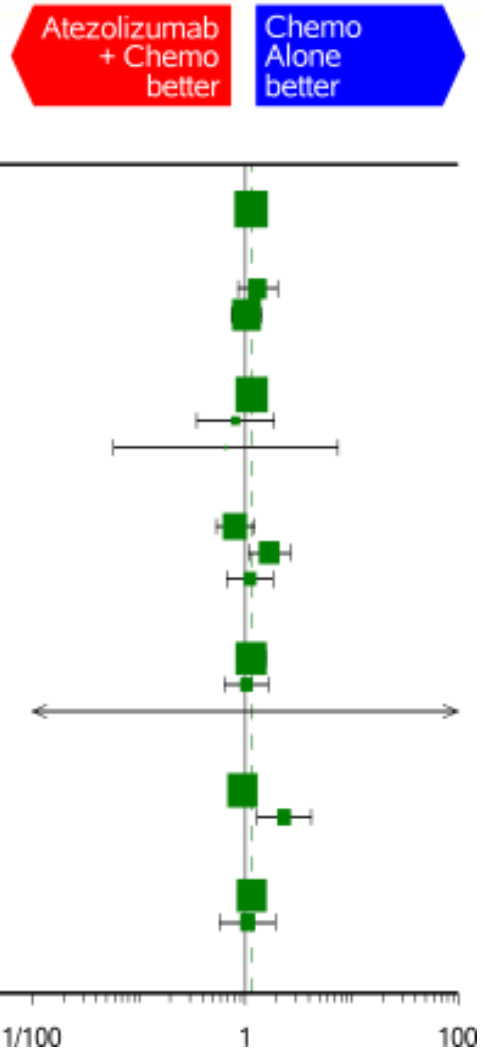
Key secondary efficacy endpoint: iDFS in the PD-L1+ subgroup (71%)



	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)	

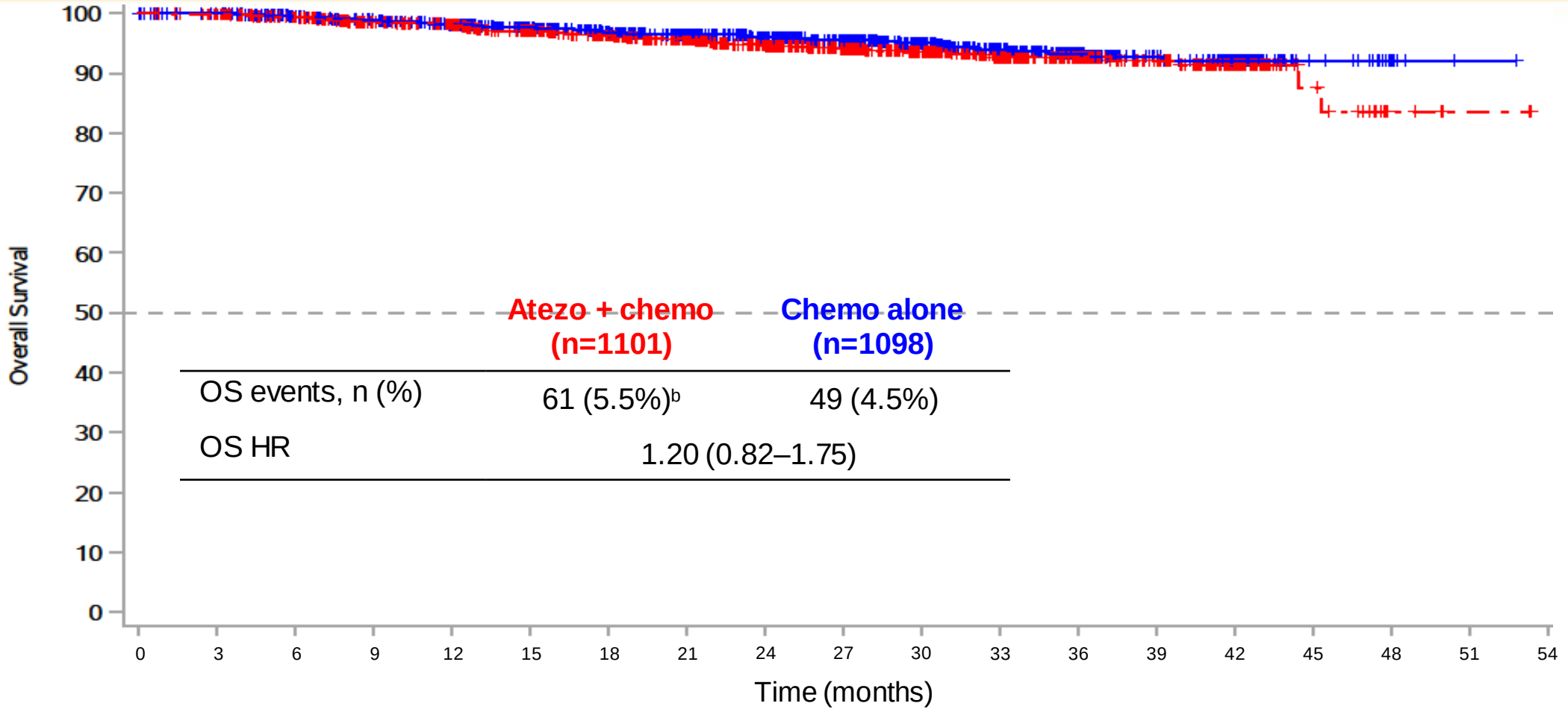
iDFS subgroup analysis (ITT Population)

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



[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.

Neo-N Trial

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Randomized Phase II Study of Neoadjuvant Nivolumab (N) monotherapy 2-week lead-in followed by 12 weeks of concurrent N+carboplatin plus paclitaxel (CbP) vs concurrent N+CbP in Triple Negative Breast Cancer (TNBC): (BCT1902/IBCSG 61-20 Neo-N)

Nicholas Zdenkowski, BMed, FRACP, PhD
University of Newcastle, NSW Australia; Breast Cancer Trials

Sherene Loi[1], Samuel M. Niman[2], Nicholas Zdenkowski[3], Prudence A. Francis[4], Sally Baron Hay[5], William Fox[6], Kevin Punie[7], Alexander M. Menzies[5], Rebecca Angus[8], Carlie Mavin[8], Lauren Rennie[8], Isobel Stoodley[8], G. Bruce Mann[9], Marion J.J Kuper-Hommel[10], Meredith M. Regan[2].

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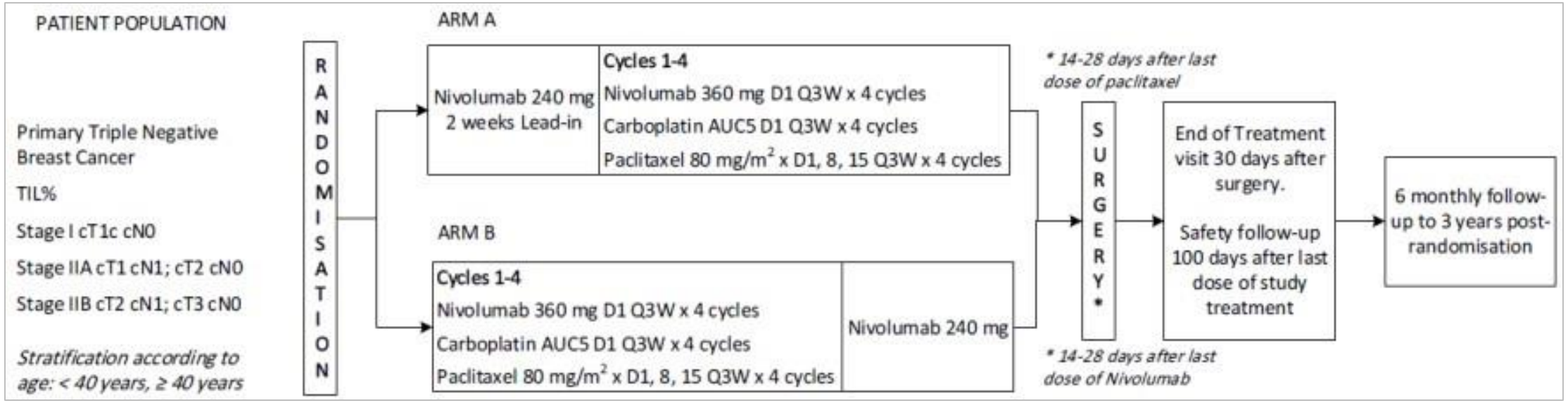
Background

- Neoadjuvant systemic therapy, including immunotherapy, is standard care for stage II/III TNBC[1]
- Not all patients require the full KN522 regimen[2]
- GeparNuevo: higher pCR with immunotherapy ‘lead-in’ vs concurrent chemo-IO (61% vs 38%)[3]
- Immune enriched tumors may have a greater response
- pCR is associated with good prognosis and may allow de-escalation of chemotherapy

1. Curigliano, Ann Onc 2023; 2. Schmid, NEJM 2022; 3. Loibl, Ann Onc 2019

Methods

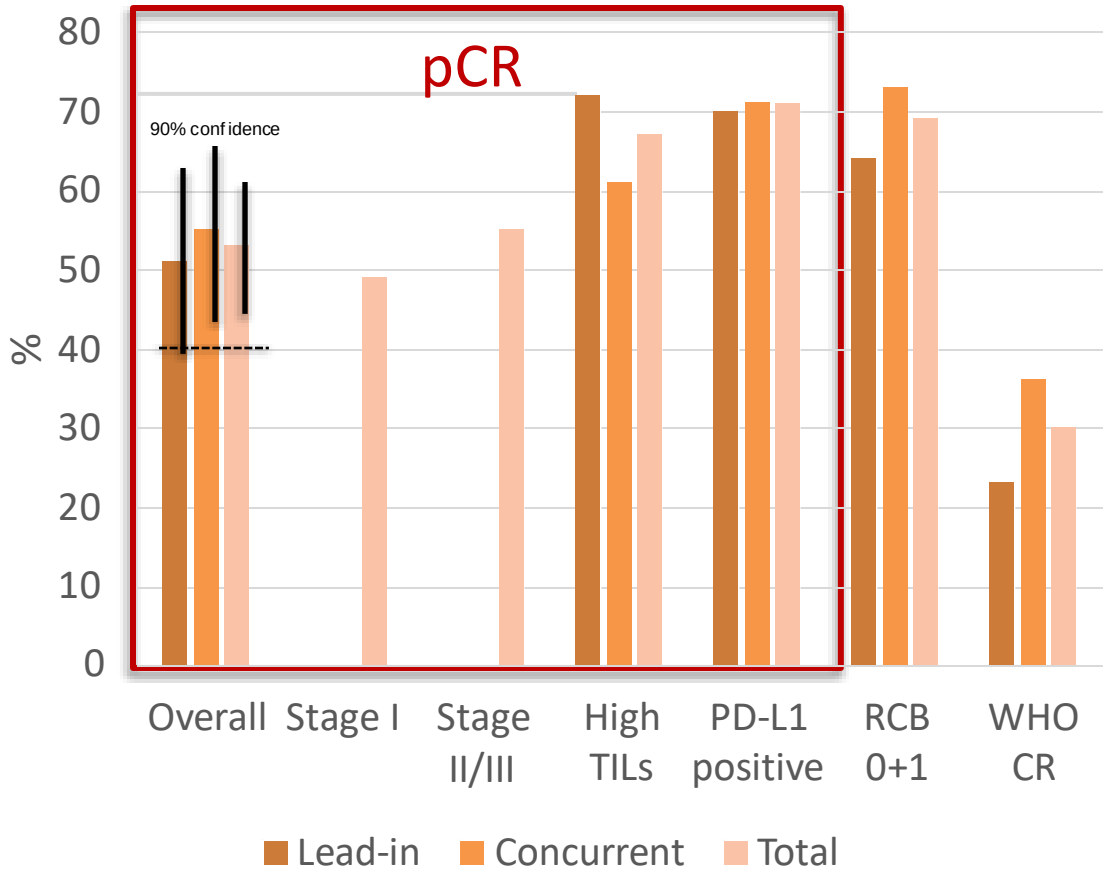
- Non-comparative, Simon 2-stage 'pick-the-winner' design
- Hypothesis: pCR=ypT0/is ypN0 (lower 90% CI, primary endpoint) greater than 40%
- Secondary endpoints: RCB, safety, pCR by PD-L1 (≥1% SP-142) and TILs (≥30%), EFS
- Adjuvant chemotherapy at investigators discretion



Results

Participants N=108*	Lead-in N=53	Concurrent N=55
Age <40	26%	16%
Pre/perimenopausal	53%	55%
Stage I	34%	35%
Stage II/III	66%	65%
TILs ≥30%	34%	33%
PDL1 +ve (≥1% SP-142)	43%	51%
Ki67% (median)	70%	70%

*110 enrolled, 2 not included (did not start treatment)



Multivariable logistic regression model (age, study cohort, stage, TILs): High TILs was only predictor of pCR (67 vs 46%; OR 2.47)

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Discussion:

- pCR rates exceeding 50% support a 12-week neoadjuvant non-anthracycline chemotherapy regimen with nivolumab for Stage I/II TNBC;
  - Total 53% (90%CI 44-61%)
  - Lead-in 51% (90%CI 39-63%)
  - Concurrent 55% (90%CI 43-66%)
  - PD-L1 71% positive vs 33% negative; sTILs 67% high vs 47% low
- No evidence of pCR advantage was seen with Lead-in N;
- Patients with immune enriched tumors, identified by high sTILs or PD-L1 positivity, had high pCR rates with just 12 weeks of treatment;
- Well tolerated, with no new safety signals seen;
- EFS results remain immature; Translational research is ongoing.

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Adjuvant systemic therapy and outcomes in ≥ 65 years with TNBC

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Systemic Therapy in Geriatric Patients with Triple Negative Breast Cancer: A National Cancer Database Analysis

Yolcar Chamorro, Muni Rubens, Mukesh Roy, Naomi Dempsey, Reshma Mahtani, Manmeet Ahluwalia, Lauren Carcas, Ana Sandoval-Leon

Disclosure Information

Ana Sandoval-Leon, MD

Consultant/advisory boards: AstraZeneca, Gilead, Guardant Health, Stemline, Merck, Oncocyte, Sanofi, Sermonix

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Background

- Despite the lower incidence of TNBC (12%-15%) the 5-year survival is 8% to 16% lower than in hormone receptor-positive BC .
- With the improved life expectancy in the US and the increased incidence of BC as patients (pts) age, guidance around optimal treatment for geriatric patients is lacking, given their underrepresentation in clinical trials.

Objective

To compare the survival of geriatric patients (≥65yrs old) with early stage (I-III) TNBC treated without chemotherapy or immunotherapy (No CT/IO) vs chemotherapy (CT) or CT in combination with immunotherapy (CT+IO) stratified by age.

Methods

- Retrospective analysis of data collected from the National Cancer Database (NCDB) for early stage (I-III) geriatric (≥65yrs) TNBC pts treated between 2004-2019.
- Pts were categorized into two treatment groups – those who were not treated with any systemic therapy (No-CT/IO) and those who received treatment with CT or CT in combination with IO (CT/CT+IO).
- Patients were excluded if treatment administered was unknown, if there was no follow-up time beyond diagnosis, or vital status.
- The main outcome was all-cause mortality.
- We used Cox regression to adjust for the covariates.
- Using the log rank P value, we identified the age cutoff over which the survival rates were not significantly different between two treatment groups.
- Based on this age cutoff, we further categorized patients into two groups- those between 65-80yrs and those ≥81yrs. We report 1- and 3-year survival rates.

Howard FM, Olopade OI; Epidemiology of Triple-Negative Breast Cancer: A Review. Cancer J 2021, 27(1):8-16.

Demographics by treatment type

Characteristics	No-CT/IO (n=4105, 36.0%)	CT/CT+IO (n=7311, 64.0%)	P-value
CT, n (%)	---	7080 (96.8%)	
CT/CT+IO, n (%)	---	231 (3.2%)	
Age, n (%)			<0.001
65-69yrs	731 (17.8%)	3076 (42.1%)	
70-74yrs	849 (20.7%)	2348 (32.1%)	
75-79yrs	864 (21.0%)	1275 (17.4%)	
80-84yrs	806 (19.6%)	487 (6.7%)	
≥85yrs	855 (20.8%)	125 (1.7%)	
Race, n (%)			0.152
White	2956 (77%)	5208 (75.84%)	
Black	743 (19.4%)	1405 (20.4%)	
Other	140 (3.6%)	258 (3.8%)	
Ethnicity, n (%)			0.070
Hispanic	151 (3.8%)	324 (4.5%)	
Non-Hispanic	3839 (96.2%)	6871 (95.5%)	
Insurance, n (%)			<0.001
Public	3636 (89.4%)	6314 (87.1%)	
Private	416 (10.2%)	905 (12.5%)	
None	13 (0.3%)	34 (0.5%)	
Charlson-Deyo score, n (%)			<0.001
0	2904 (70.7%)	5517 (75.5%)	
1	643 (15.7%)	1163 (15.9%)	
2	298 (7.3%)	354 (4.8%)	
3	260 (6.3%)	277 (3.8%)	
Stage			<0.001
I	2410 (58.7%)	3034 (41.5%)	
II	1089 (26.5%)	2549 (34.9%)	
III	606 (14.8%)	1728 (23.6%)	
Regional Lymph Node Surgery, n (%)	3245 (79.2%)	6805 (93.2%)	<0.001
Surgery, n (%)	3737 (91.2%)	7009 (96.0%)	<0.001
Radiation, n (%)	1848 (45.0%)	4803 (65.7%)	<0.001

RESULTS

1-year and 3-year survival rates by treatment and age categories

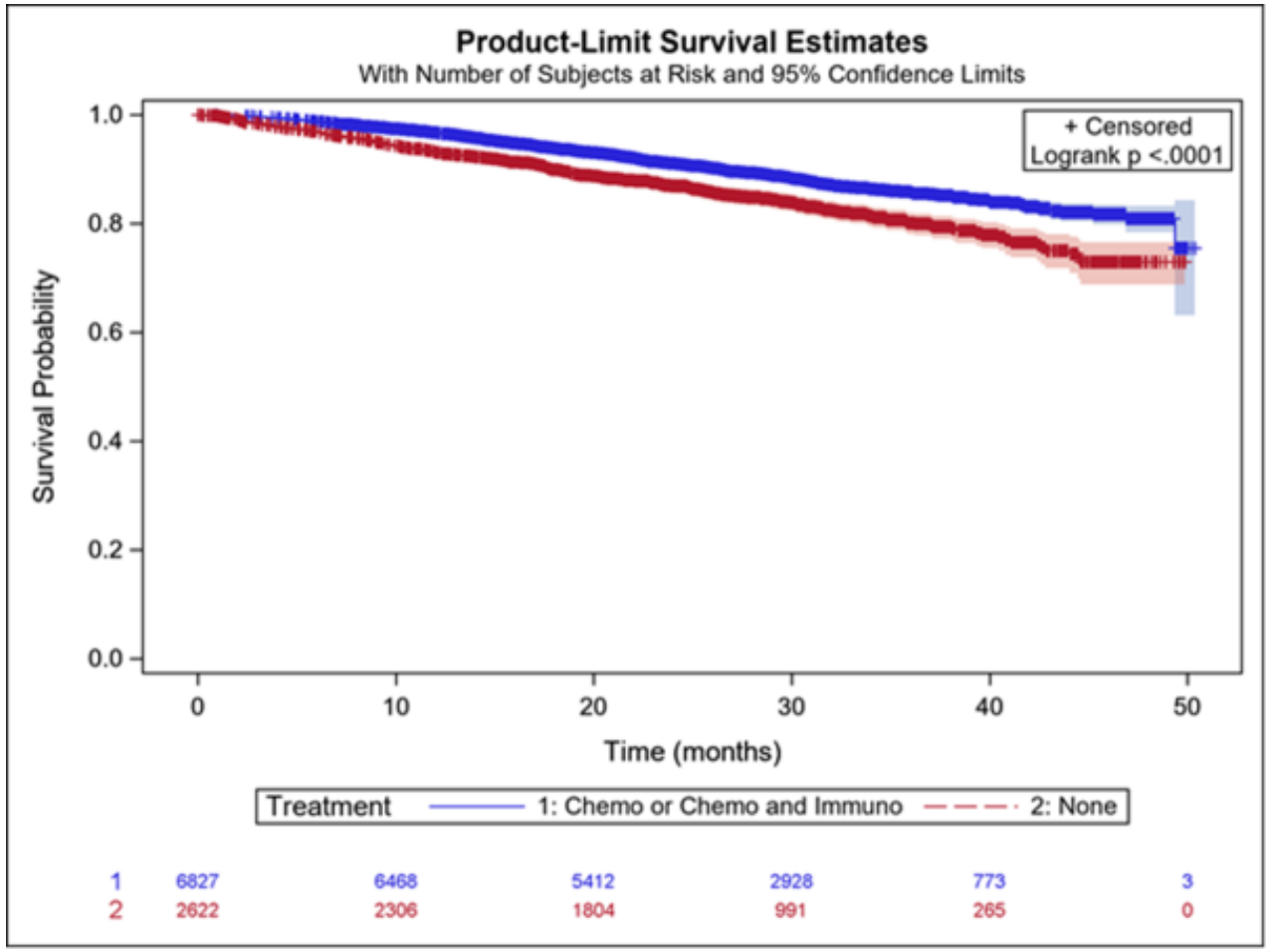
Histology types	1-year survival (95% CI)	3-year survival (95% CI)
No treatment		
65-80yrs	93.1% (92.1%-94.1%)	80.1% (78.1%-82.1%)
≥81yrs	85.0% (83.2%-86.9%)	58.0% (54.7%-61.3%)
CT/CT+IO		
65-80yrs	96.7% (96.3%-97.1%)	85.8% (84.7%-86.8%)
≥81yrs	87.1% (84.1%-90.1%)	62.3% (56.8%-67.7%)

Cox regression survival analysis showing factors associated with mortality by age and stage categories

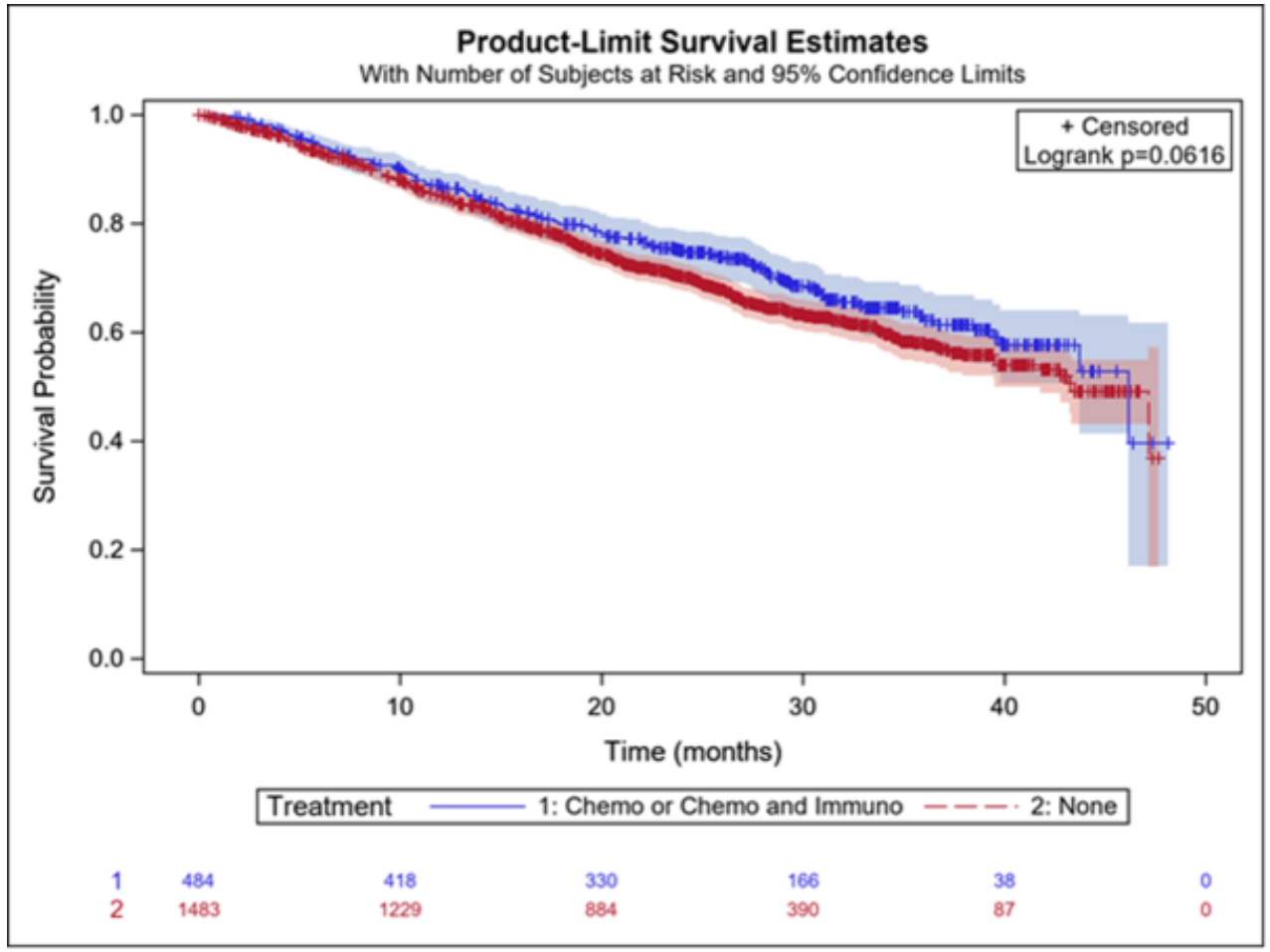
Variables	HR (95% CI)	*P* value
Model 1	0.52 (0.45-0.60)	<0.001
Model 2	0.84 (0.67-1.05)	0.131

Note: All models were adjusted for covariates
Reference: No treatment
Model1: 65-80
Model 2: ≥81 years
The model is adjusted for race, insurance, income, area, distance to hospital, facility type, facility location, Charlson-Deyo score, stage, regional lymph node surgery, surgery, radiation.

Kaplan Meier curves comparing mortality by treatment among patients aged 65-80yrs



Kaplan Meier curves comparing mortality by treatment among patients aged 81yrs and older



Conclusion

- Among geriatric pts who were between 65-80 yrs old and received treatment for early stage TNBC, there were significant improvements in mortality.
- Among pts who were ≥81yrs old there was no survival benefit in those who received CT or CT+IO as compared to those who received no treatment.
- This analysis highlights the importance of individualizing treatment recommendations in geriatric patients who may not garner the same benefit of treatment as younger patients and may experience higher toxicity.

Limitations

- The small number of pts ≥81yrs old who received CT/CT+IO that were included in this analysis, which could account for the lack of a statistically significant benefit of CT/CT+IO.
- We were not able to assess breast cancer specific mortality.

Future Directions

- Additional studies are required to clarify contributing factors and to help optimize the management of geriatric patients with TNBC.

Acknowledgement

The data used in the study are derived from a de-identified NCDB file. The American College of Surgeons and the Commission on Cancer have not verified and are not responsible for the analytic or statistical methodology employed, or the conclusions drawn from these data by the investigator.

Thank you

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