Penn Medicine

2020 “International Meetings” Breast Cancer Review: Triple Negative Breast Cancer

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Division of Hematology/Oncology

Conflicts of Interest

- None

Overview

- Abstract 507: Phase III trial of metronomic capecitabine maintenance after standard treatment in operable triple-negative breast cancer (SYSUCC-001).

- Abstract 1000: KEYNOTE-355: Randomized, double-blind, phase III study of pembrolizumab + chemotherapy versus placebo + chemotherapy for previously untreated locally recurrent inoperable or metastatic triple-negative breast cancer.

- Abstract 1001: Results of a phase II randomized trial of cisplatin +/- veliparib in metastatic triple-negative breast cancer (TNBC) and/or germline *BRCA*-associated breast cancer (SWOG S1416).

Please note that some of the studies reported in this presentation were published as abstracts only and/or presented at a conference. These data and conclusions are included because expert faculty found them to be important scientific contributions but should be considered to be preliminary until published in a peer-reviewed journal.

Phase III Trial of Metronomic Capecitabine Maintenance after Standard Treatment in Early Triple-Negative Breast Cancer (SYSUCC-001)

Xi Wang, Shu-Sen Wang, Heng Huang, Rou-Jun Peng, Li Cai, Li Zhao, Yin Lin, Jian Zeng, Le-Hong Zhang, Jun Tang, Yong-Li Ke, Xian-Ming Wang, Xin-Mei Liu, Qian-Jun Chen, An-Qin Zhang, Yan-Xia Shi, Ye Cao, Dan-Mei Pang, Fei Xu, Jia-Jia Huang, Cong Xue, Xin An, Wen Xia, Ruo-Xi Hong, **Zhong-Yu Yuan**; on behalf of the South China Breast Cancer Group (SCBCG)

(NCT01112826)

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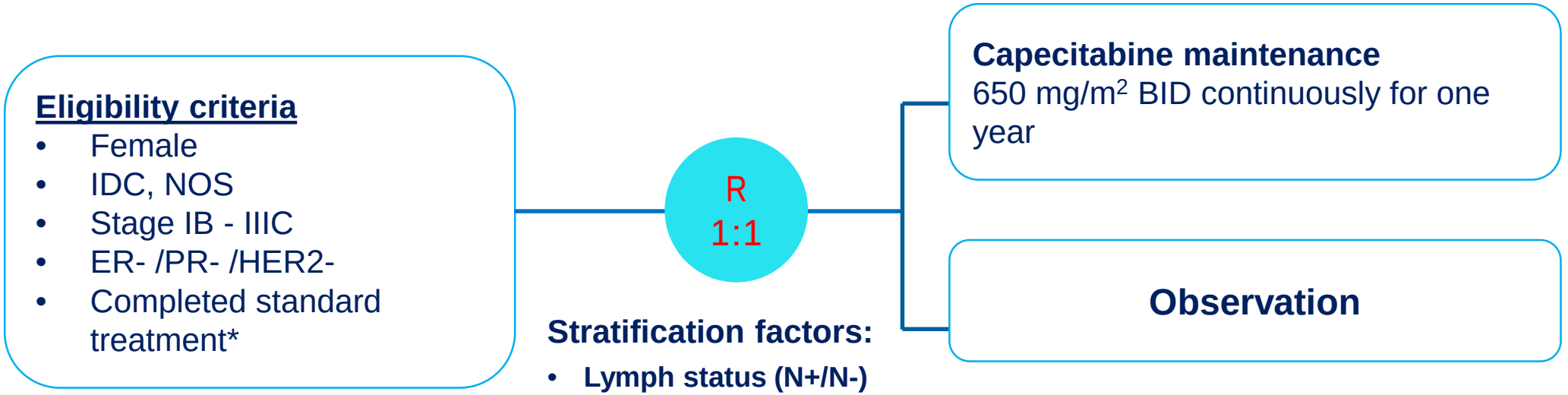
Study Design and Patient Population



*surgery, (neo)adjuvant chemotherapy (A and/or T based), RT

89% received A+T

93% received adjuvant chemotherapy

Primary endpoint: DFS
Secondary Endpoint: OS, distant DFS, safety

443 patients randomized with a median follow up of 57 months

Patient characteristics	
Age	Mean 46 years
Lymph node status	62% node negative
Tumor size	25% ≤2cm, 57% 2.1-5 cm
Pathologic stage	26% stage I; 54% stage II; 19% stage III

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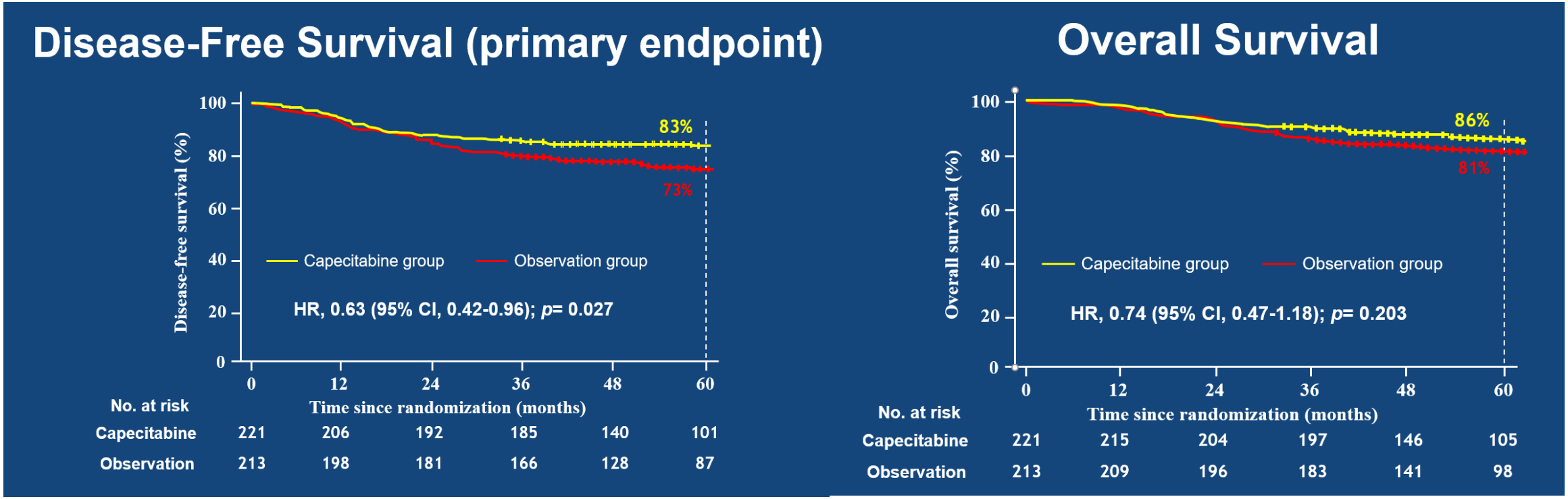
SYSUCC-001: Study Results



- 5y improvement in DFS with capecitabine vs observation: **83% vs 73%, HR 0.63 (95% CI, 0.42-0.96); p= 0.027**
- No significant improvement in OS

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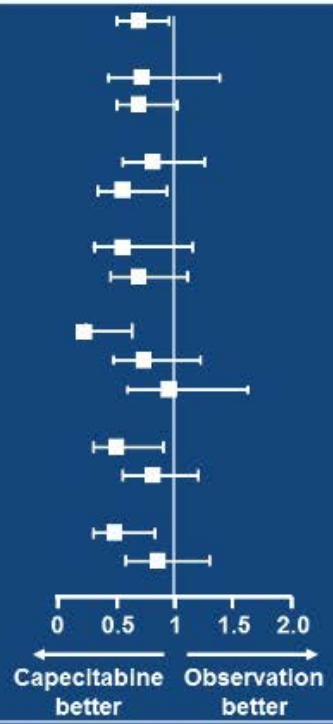
Subgroup Analysis of DFS

Subgroup	Capecitabine (events/ n)	Observation (events/ n)	Hazard Ratio (95% CI)	*p* value for interation
Overall	38/221	56/213	0.64 (0.42, 0.96)	0.031
Age, years				0.915
≤ 40	11/65	14/54	0.66 (0.30, 1.45)	
> 40	27/156	42/159	0.63 (0.39, 1.03)	
Menopause status				0.247
Premenopausal	27/157	30/133	0.78 (0.46, 1.31)	
Postmenopausal	11/64	26/80	0.46 (0.23, 0.93)	
Histological grade				0.429
1/ 2	6/57	14/61	0.45 (0.17, 1.17)	
3	21/129	27/108	0.64 (0.36, 1.13)	
Pathological stage				0.091
I	1/56	14/59	0.07 (0.009, 0.52)	
II	16/120	23/116	0.67 (0.35, 1.26)	
III	21/45	19/38	0.94 (0.50, 1.74)	
Tumor size				0.160
≤ 2 cm	8/79	19/79	0.39 (0.17, 0.89)	
> 2 cm	30/142	37/134	0.77 (0.47, 1.24)	
Lymph node status				0.052
Negative	9/135	23/133	0.37 (0.17, 0.80)	
Positive	29/86	33/80	0.82 (0.50, 1.37)	



- Subgroup analysis shows lower HR in more favorable risk patients: Stage I, <2cm tumors, LN negative
- Benefit of capecitabine not being driven by highest risk patients in this trial

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Tolerability and Toxicity

- 91.4% of patients completed one year of treatment
- 24.7% required at least 1 dose reduction

Toxicity	Any	Grade 3-4
Hand-foot syndrome	45.2%	7.7%
Leukopenia	23.5%	0
Elevated bilirubin	12.7%	0
Elevated ALT/AST	5.0%	0
Abdominal pain/Diarrhea	6.8%	0

Slide courtesy of Angie Demichele, MD

Context of Capecitabine adjuvant trials

CREATE-X (positive)	SYSUCC-001 (positive)	GEICAM (negative)
ER+/TNBC (32%)	TNBC	TNBC
Residual dx after NAC	93% adjuvant chemo	80% adjuvant chemo
1250 mg/m2 d1-14 q 3 wk for 6-8 cycles	650 mg/m^2 BID continuously for one year	1000mg/m2 day 1-14/q3 wks) x 8 cycles
95% anthracycline+taxane	89% anthracycline+taxane	67% anthracycline+taxane
57% pre-menopausal	67% pre-menopausal	32% pre-menopausal
NA	62% node negative	55% node negative
NA	73% grade 3	71% grade 3
unknown	unknown	26% non-basal
5 yr DFS/OS (control) 56%/70%	5 yr DFS/OS (control) 73%/81%	5 yr DFS/OS (control) 77%/86%
5 yr DFS/OS (cape) 70%/79%	5 yr DFS/OS (cape) 83%/86%	5 yr DFS/OS (cape) 80%/86%

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Adjuvant Capecitabine - Summary

- Maintenance metronomic capecitabine resulted in a statistically significant improvement in DFS among patients with TNBC
- This is in contrast to the results of the GEICAM study, which had a similar patient population, but different schedule and duration
- CREATE-X demonstrated an improvement in DFS and OS with adjuvant capecitabine in patients who fail to achieve a pCR to neoadjuvant chemotherapy
  - Capecitabine is appropriate in this setting
- Duration and side effects of 1 year of capecitabine may not be tolerable for many women who have just completed several months of adjuvant chemotherapy
- Await overall survival data before routinely incorporating this regimen into practice

KEYNOTE-355: Randomized, Double-Blind, Phase 3 Study of Pembrolizumab + Chemotherapy versus Placebo + Chemotherapy for Previously Untreated Locally Recurrent Inoperable or Metastatic Triple-Negative Breast Cancer

Javier Cortes[1], David W. Cescon[2], Hope S. Rugo[3], Zbigniew Nowecki[4], Seock-Ah Im[5], Mastura Md Yusof[6], Carlos Gallardo[7], Oleg Lipatov[8], Carlos H. Barrios[9], Esther Holgado[1], Hiroji Iwata[10], Norikazu Masuda[11], Marco Torregroza Otero[12], Erhan Gokmen[13], Sherene Loi[14], Zifang Guo[15], Jing Zhao[15], Gursel Aktan[15], Vassiliki Karantza[15], Peter Schmid[16]

[1]IOB Institute of Oncology, Quiron Group; Vall d'Hebron Institute of Oncology (VHIO), Madrid & Barcelona, Spain; [2]Princess Margaret Cancer Centre, Toronto, Ontario, Canada; [3]University of California San Francisco Comprehensive Cancer Center, San Francisco, CA, USA; [4]Maria Sklodowska-Curie Memorial Cancer Centre and Institute of Oncology, Warsaw, Poland; [5]Seoul National University Hospital, Cancer Research Institute, Seoul National University College of Medicine, Seoul, Korea; [6]Pantai Hospital, Kuala Lumpur, Malaysia; [7]Arturo Lopez Perez Foundation, Santiago, Chile; [8]Republican Clinical Oncology Dispensary, Republic of Bashkortostan, Russian Federation; [9]Oncology Research Unit, HSL, PUCRS, Porto Alegre, Brazil; [10]Aichi Cancer Center Hospital, Nagoya, Japan; [11]National Hospital Organization, Osaka National Hospital, Osaka, Japan; [12]Oncomedica S.A., Monteria, Colombia; [13]Ege University Medical Faculty, Izmir, Turkey; [14]Peter McCallum Cancer Centre, Melbourne, Australia; [15]Merck & Co., Inc., Kenilworth, NJ, USA; [16]Barts Cancer Institute, Centre for Experimental Cancer Medicine, London, UK

PRESENTED AT: 2020 ASCO ANNUAL MEETING #ASCO20
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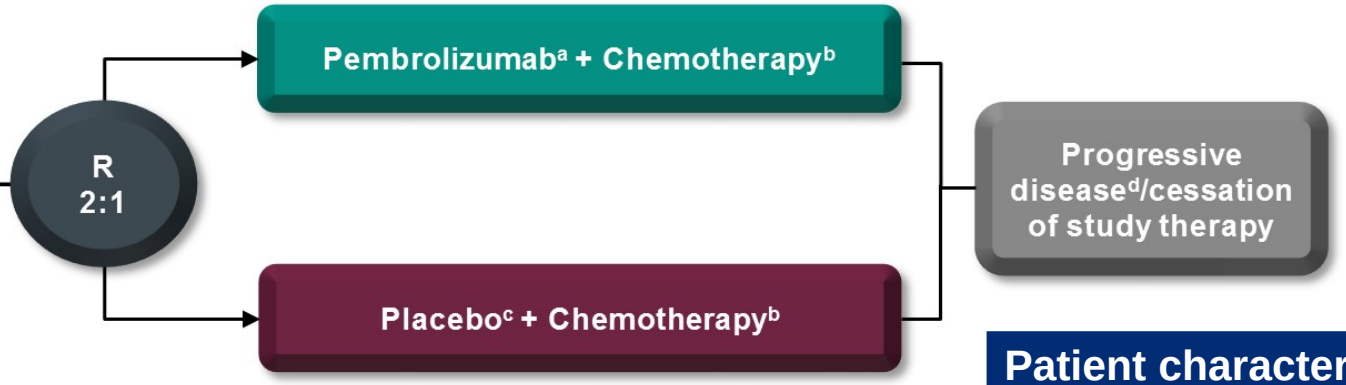
PRESENTED BY: Javier Cortes

Immuno-Oncology Context

Setting	Study	Design	Results
Neoadjuvant	KEYNOTE-522	Carbo/paclitaxel +/- **pembro**→AC/FEC→surgery→ Pembro v. placebo	Increase in pCR with P regardless of PD-L1 (64.8% v. 51.2%)
	NeoTRIPa PDL1	Carbo/paclitaxel +/- **atezo**→surgery→AC/FEC	NO significant increase in pCR with A (43.5% v. 40.8%)
1st Line mTNBC	IMPASSION 130	Nab-paclitaxel +/- **Atezolizumab**	PFS (ITT) HR 0.80, p=0.0025 PFS (PD-L1+) HR 0.62, p<0.0001 ORR (ITT): 56% v. 46% ORR (PD-L1+): 59% v. 43%
	KEYNOTE-355	Taxane or carbo/gem +/- **Pembrolizumab**	??
2nd - 3rd Line mTNBC	KEYNOTE-119	**Pembrolizumab** v. chemotherapy (capecitabine, Eribulin,	No improvement in OS ORR (ITT): 9.6% v. 10.6% ORR (CPS≥10): 17.7% v. 9.2%

KEYNOTE-355 Study Design (NCT02819518)

Key Eligibility Criteria
- Age ≥18 years
- Central determination of TNBC and PD-L1 expression
- Previously untreated locally recurrent inoperable or metastatic TNBC
- Completion of treatment with curative intent ≥6 months prior to first disease recurrence
- ECOG performance status 0 or 1
- Life expectancy ≥12 weeks from randomization
- Adequate organ function
- No systemic steroids
- No active CNS metastases
- No active autoimmune disease



Stratification Factors:
- Chemotherapy on study (taxane vs gemcitabine/carboplatin)
- PD-L1 tumor expression (CPS ≥1 vs CPS <1)
- Prior treatment with same class chemotherapy in the neoadjuvant or adjuvant setting (yes vs no)

Patient characteristics	
Age	Median 53 years
PD-L1 + CPS ≥1	75.1%
PD-L1 + CPS ≥10	36.7 – 38.9%
Chemo on study	45% Taxane 55% Gem/carbo

Primary Endpoint: PFS and OS in PD-L1+ tumors and ITT population
Secondary EP: ORR, DOR, DCR, safety

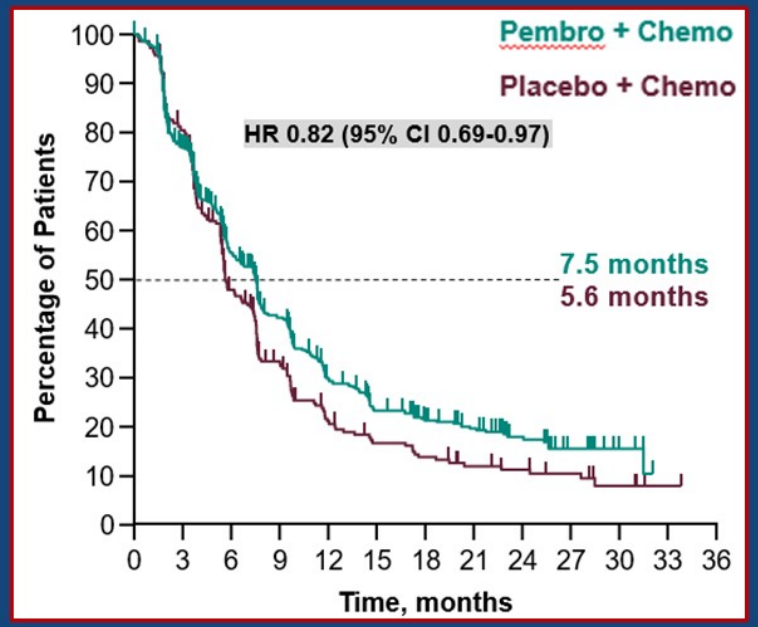
847 pts randomized 2:1 with median f/u ~26m

3W)
y 28 days
ays
and 8 every 21 days

[c]Normal saline
[d]Treatment may be continued until confirmation of progressive disease
CNS=central nervous system; ECOG=Eastern Cooperative Oncology Group; PD-L1=programmed death ligand 1; R=randomized; TNBC=triple-negative breast cancer
CPS=combined positive score

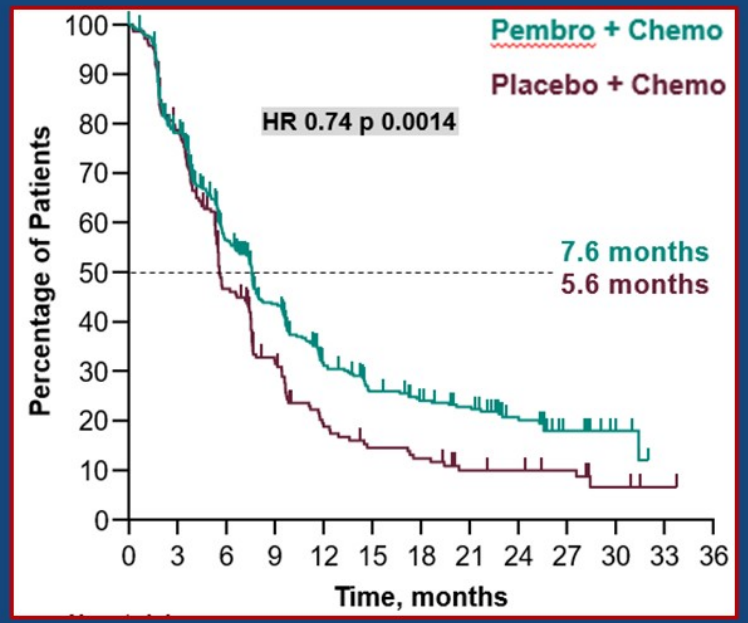
KEYNOTE 355: Progression-free survival

ITT



Statistical significance was not tested due to the prespecified hierarchical testing strategy

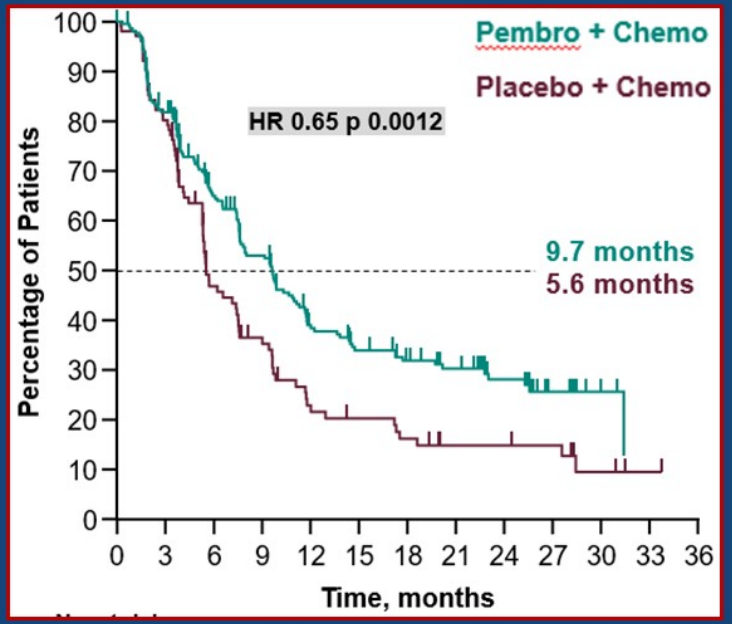
PD-L1 CPS ≥1



Prespecified *P* value boundary of 0.00111 not met

75% of pts

PD-L1 CPS ≥10



Prespecified *P* value boundary of 0.00411 met

38% of pts

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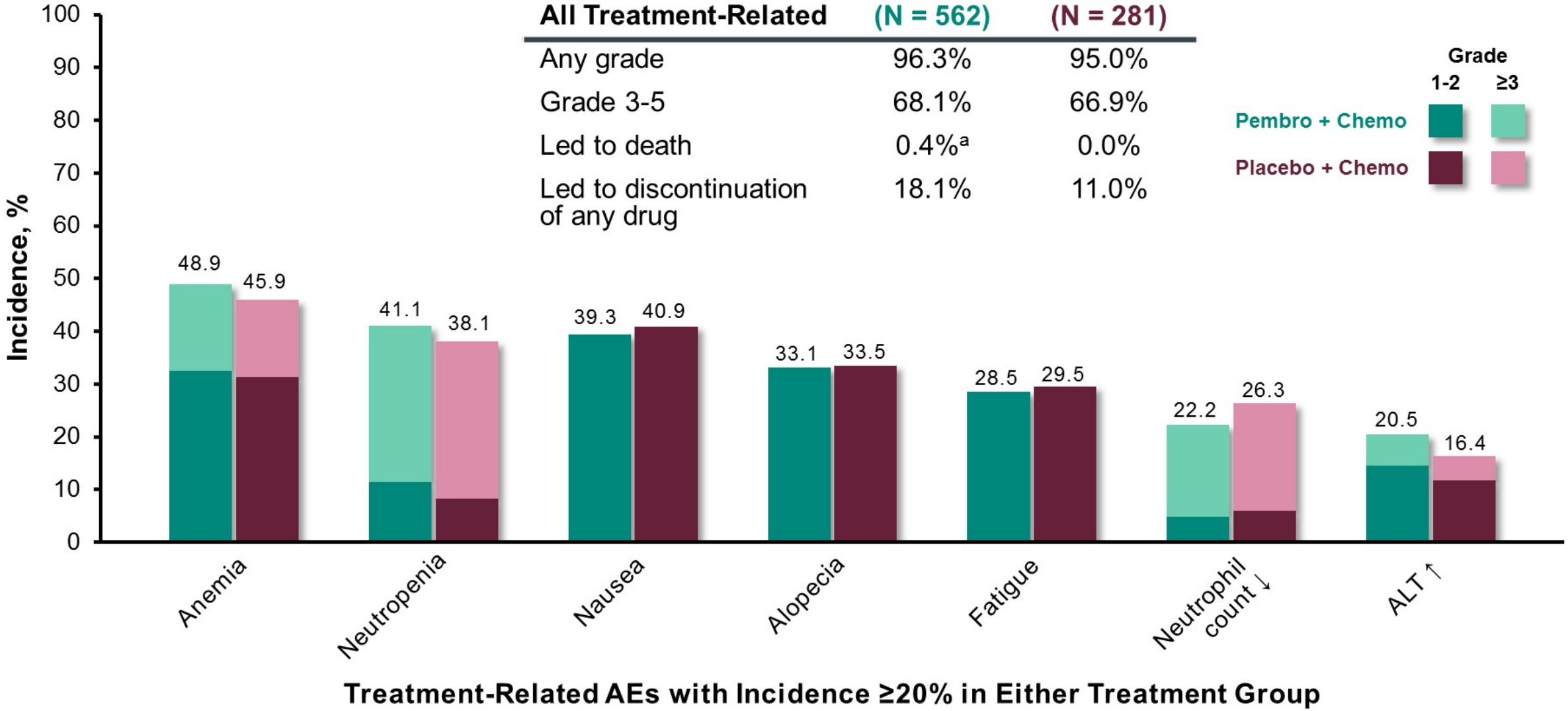
Treatment-Related AEs

All Treatment-Related	Pembro + Chemo (N = 562)	Placebo + Chemo (N = 281)
Any grade	96.3%	95.0%
Grade 3-5	68.1%	66.9%
Led to death	0.4%[a]	0.0%
Led to discontinuation of any drug	18.1%	11.0%



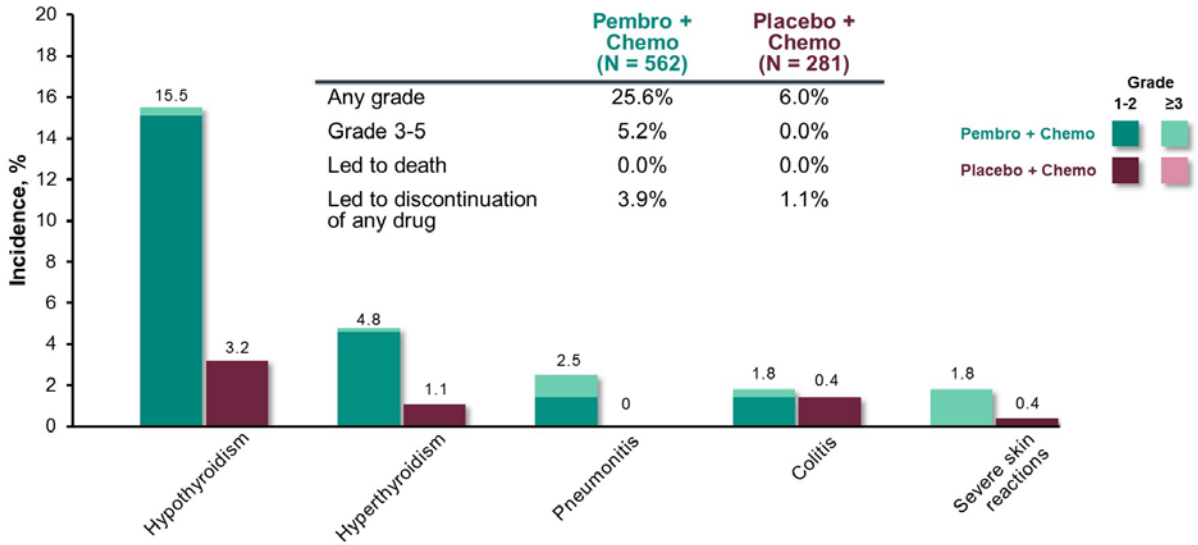
Treatment-Related AEs with Incidence ≥20% in Either Treatment Group

[a]1 patient from acute kidney injury and 1 patient from pneumonia. Data cutoff date: December 11, 2019.

Immune-Mediated AEs

Keynote-355

Immune-Mediated AEs



	Pembro + Chemo (N = 562)	Placebo + Chemo (N = 281)
Any grade	25.6%	6.0%
Grade 3-5	5.2%	0.0%
Led to death	0.0%	0.0%
Led to discontinuation of any drug	3.9%	1.1%

Immune-Mediated AEs with Incidence ≥10 Patients in Either Treatment Group[a]

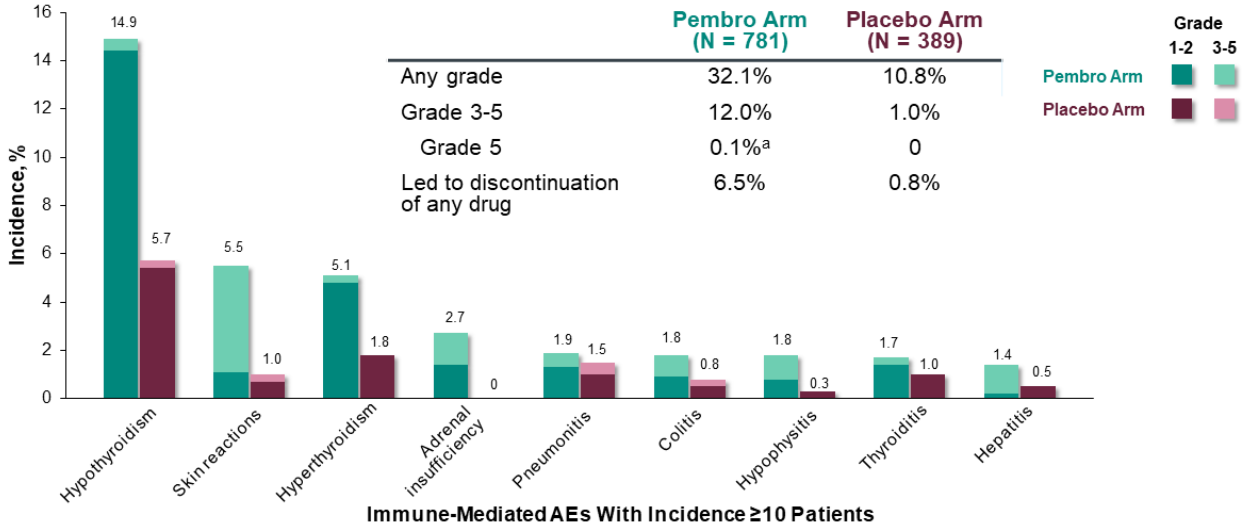
[a]Based on a list of terms prespecified by the sponsor and included regardless of attribution to study treatment or immune relatedness by the investigator; related terms included. Data cutoff date: December 11, 2019.

NAC Keynote-522

San Antonio Breast Cancer Symposium®, December 10-14, 2019

Schmid KN522 SABCS 20

Immune-Mediated AEs in Combined Phases



	Pembro Arm (N = 781)	Placebo Arm (N = 389)
Any grade	32.1%	10.8%
Grade 3-5	12.0%	1.0%
Grade 5	0.1%[a]	0
Led to discontinuation of any drug	6.5%	0.8%

Immune-Mediated AEs With Incidence ≥10 Patients

[a]1 patient from pneumonitis. Considered regardless of attribution to treatment or immune relatedness by the investigator. Related terms included in addition to preferred terms listed. IA2, second interim analysis. Data cutoff date: April 24, 2019.

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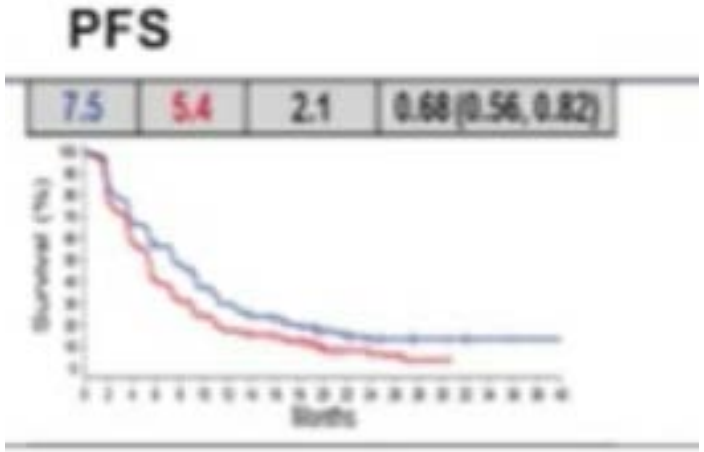
Immuno-Oncology Context

Setting	Study	Design	Results
Neoadjuvant	KEYNOTE-522	Carbo/paclitaxel +/- **pembro**→AC/FEC→surgery→ Pembro v. placebo	Increase in pCR with P regardless of PD-L1 (64.8% v. 51.2%)
	NeoTRIPa PDL1	Carbo/paclitaxel +/- **atezo**→surgery→AC/FEC	NO significant increase in pCR with A (43.5% v. 40.8%)
1st Line mTNBC	IMPASSION 130	Nab-paclitaxel +/- **Atezolizumab**	PFS (ITT) HR 0.80, p=0.0025 PFS (PD-L1+) HR 0.62, p<0.0001 ORR (ITT): 56% v. 46% ORR (PD-L1+): 59% v. 43%
	KEYNOTE-355	Taxane or carbo/gem +/- **Pembrolizumab**	PFS (ITT) HR 0.82 (0.69-0.97) PFS (CPS≥10) HR 0.64; p=0.0012 (5.6→9.7m)
2nd - 3rd Line mTNBC	KEYNOTE-119	**Pembrolizumab** v. chemotherapy (capecitabine, Eribulin, gemcitabine, vinorelbine)	No improvement in OS ORR (ITT): 9.6% v. 10.6% ORR (CPS≥10): 17.7% v. 9.2%

KEYNOTE 355 Conclusions

- KEYNOTE 355 met its primary endpoint, extending PFS in CPS ≥10 from 5.6 months to 9.7 months
  - Results are consistent with IMPASSION 130, which showed a PFS benefit with the addition of Atezolizumab to chemotherapy (nab-paclitaxel)
  - CPS ≥1 in 81% of IMPASSION130 population v. 75% in KN 355



- No benefit seen if CPS <1 – consistent with IMPASSION130, but distinct from KEYNOTE 522 (NAC)
  - PD-L1 status may be more important in metastatic disease than early stage disease

➢ Safety was consistent with known profiles of each regimen

➢ Unanswered questions: Optimal PD-L1 assay, optimal cut-off for IO, optimal chemo partner; why the difference between primary and metastatic disease?

Phase II Randomized Placebo-Controlled Trial of Cisplatin With or Without Veliparib in Metastatic Triple-Negative Breast Cancer and/or *BRCA* Mutation-Associated Breast Cancer (SWOG 1416)

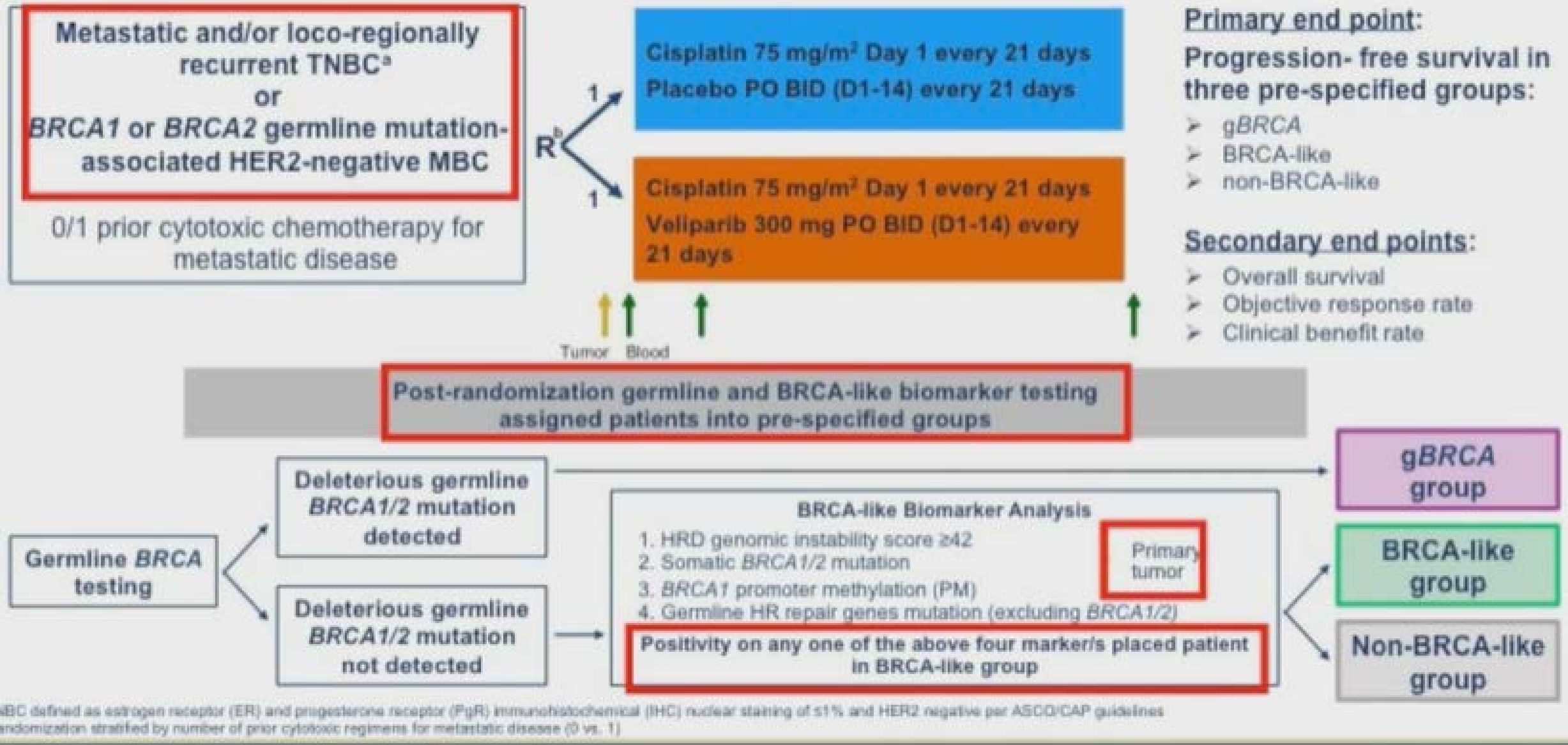
Priyanka Sharma[1*], Eve Rodler[2*], William Barlow, Julie R. Gralow, Shannon L. Puhalla, Carey K. Anders, Lori Goldstein, Ursa A. Brown-Glaberman, Thu-Tam Huynh, Christopher S. Szyarto, Andrew K. Godwin, Harsh B. Pathak, Elizabeth Swisher, Marc R. Radke, Kirsten M. Timms, Danika Lew, Jieling Miao, Lajos Pusztai, Daniel F. Hayes, Gabriel N. Hortobagyi.

PARP Inhibitors in TNBC

- 2 PARP inhibitors (olaparib and talozoparib) are approved for MBC associated with gBRCA1/2 mutations after studies showed an improvement in PFS compared to chemotherapy
- PARPi efficacy has been noted beyond gBRCA1/2 cancers, for example in ovarian cancer with homologous recombination deficiency (HRD)
- 40-60% of TNBC shows homologous recombination deficiencies, a so-called “BRCA-ness” or BRCA-like phenotype
- However, there has been limited evidence of efficacy of PARPi monotherapy beyond gBRCA in TNBC – raising the question that additional biomarkers and combinations with select DNA-damaging chemotherapeutic agents may be needed
- Combination of PARPi with chemo has been difficult due to toxicity
- Veliparib is an inhibitor of PARP-1 and -2 that can be safely combined with near maximal single-agent dose Cisplatin. SWOG 1416 evaluated whether the addition of veliparib to cisplatin is beneficial in BRCA-like, gBRCA negative TNBC

Robson et al, NEJM 2017; Litton et al, NEJM 2018

Study schema



[a]TNBC defined as estrogen receptor (ER) and progesterone receptor (PgR) immunohistochemical (IHC) nuclear staining of ≤1% and HER2 negative per ASCO/CAP guidelines
[b]Randomization stratified by number of prior cytotoxic regimens for metastatic disease (0 vs. 1)

Patient characteristics

Characteristic, no. (%)	All patients (N=321)	Cisplatin + Veliparib (N=161)	Cisplatin + Placebo (N=160)
Age (years)	56.2	55.9	56.5
Race			
White	245 (76%)	128 (80%)	117 (73%)
Black	51 (16%)	23 (14%)	28 (17%)
Asian	11 (3%)	6 (4%)	5 (3%)
Other/unk	14 (4%)	4 (2%)	10 (6%)
Ethnicity			
Hispanic	22 (7%)	15 (9%)	7 (4%)
ECOG performance status			
0	186 (58%)	95 (59%)	91 (57%)
1-2	135 (42%)	66 (41%)	69 (43%)
TNBC	305 (95%)	157 (98%)	148 (92%)

Characteristic, no. (%)	All patients (N=321)	Cisplatin + Veliparib (N=161)	Cisplatin + Placebo (N=160)
Prior lines of chemotherapy for metastatic disease			
0	221 (69%)	110 (68%)	111 (69%)
1	100 (31%)	51 (32%)	49 (31%)
Prior (neo)-adjuvant chemotherapy	236 (74%)	119 (74%)	117 (73%)
Prior carboplatin	32 (10%)	14 (9%)	18 (11%)
Measurable disease	270 (84%)	135 (84%)	135 (84%)
Visceral disease	212 (66%)	106 (66%)	106 (66%)
Prior biologic or immune checkpoint inhibitor therapy	12 (4%)	6 (4%)	6 (4%)

Distribution of patients in pre-defined groups

ITT
N=321

Blood not submitted N=27

Germline *BRCA* testing done (N=294)

Germline *BRCA* mutation positive
N=37

Germline *BRCA* mutation negative (N=257)

No/insufficient tissue N=32
Assay failure N=16

BRCA-like assessment (N=209)

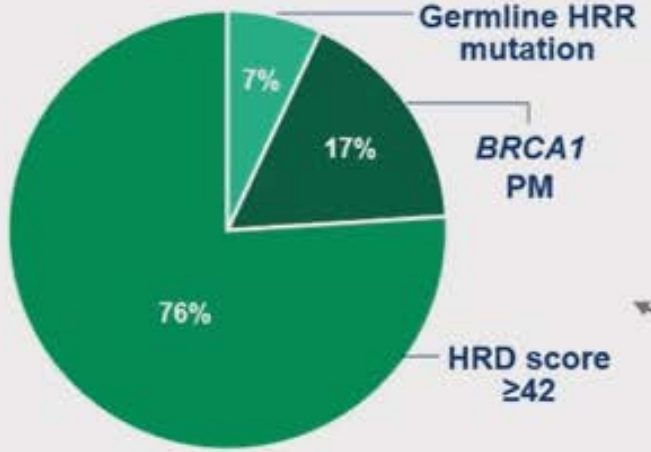
1. HRD genomic instability score ≥42 OR
2. Somatic *BRCA1/2* mutation OR
3. *BRCA1* promoter methylation (PM) OR
4. Germline HR repair genes mutation (excluding *BRCA1/2*)

Positivity on any one of the four marker/s placed patient in BRCA-like group

BRCA-like
N=99

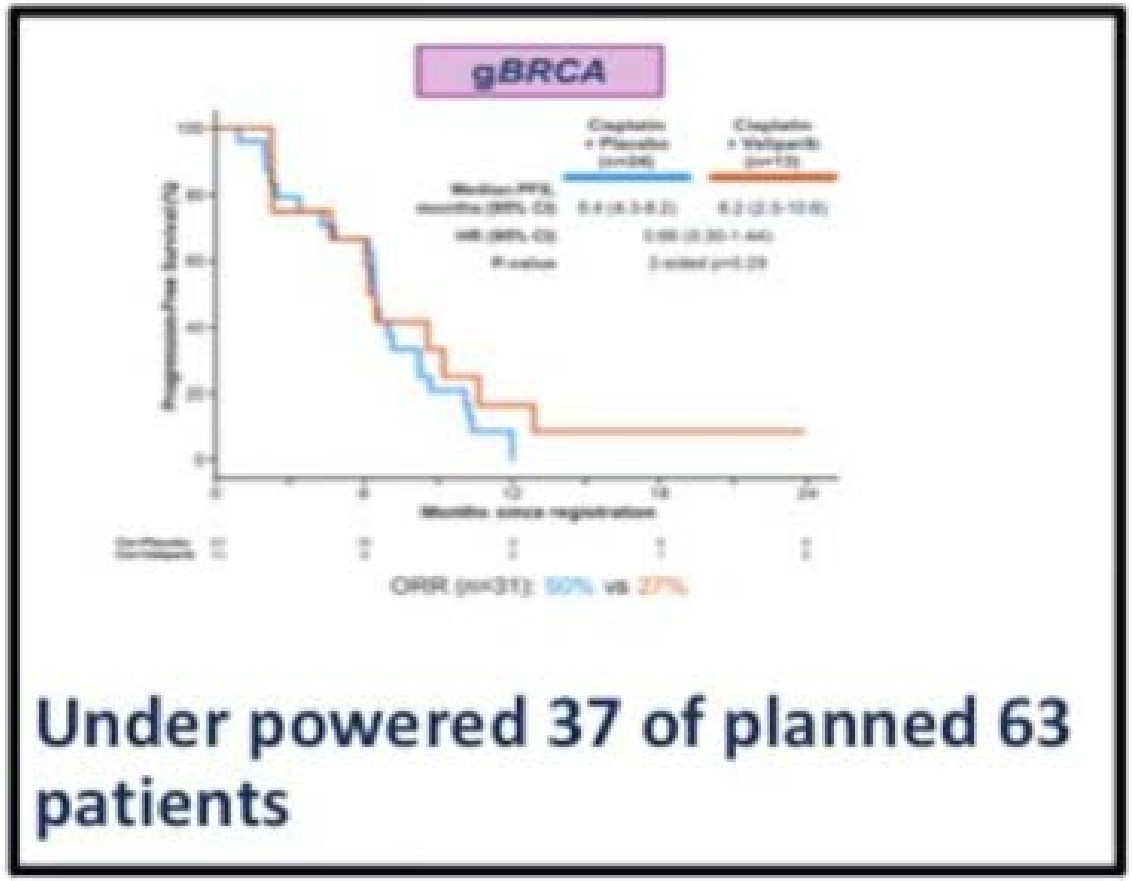
Non-BRCA-like
N=110

Marker distribution in BRCA-like group

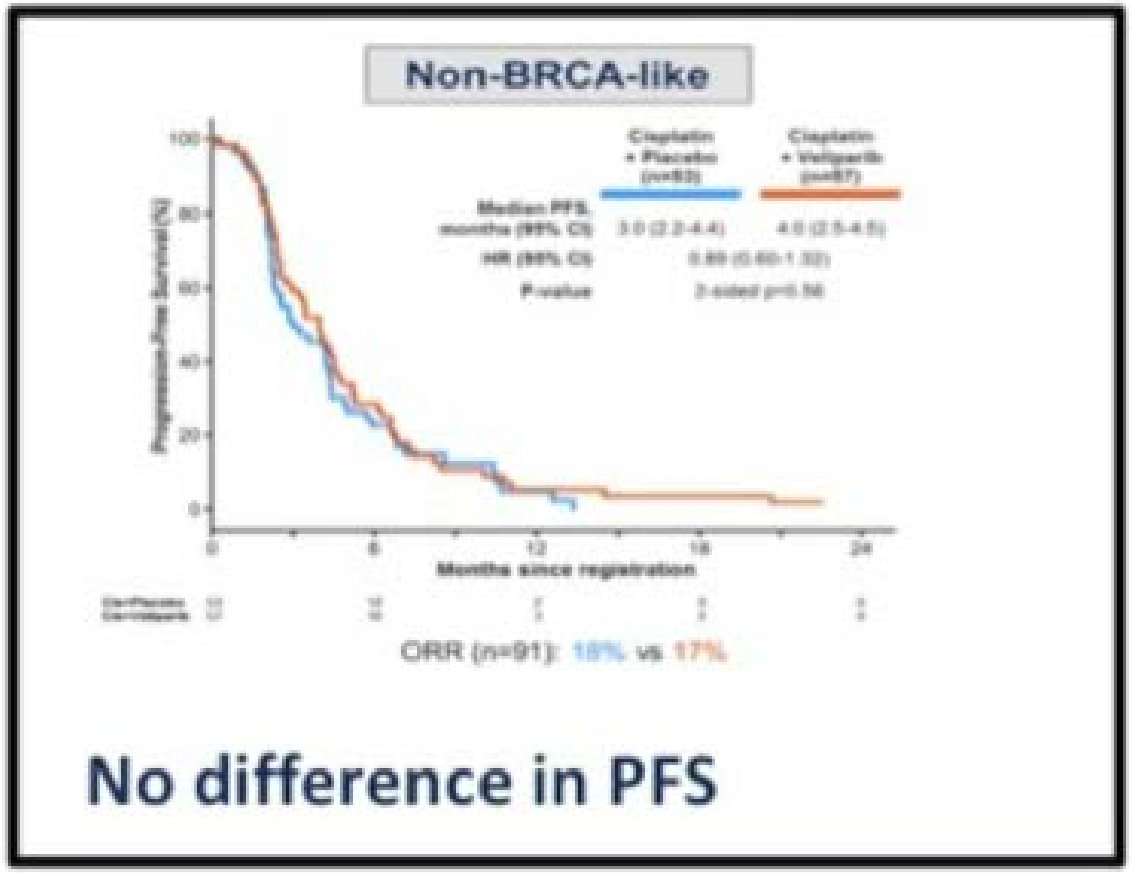


Somatic *BRCA1/2* mutation = 8% (all with HRD score ≥42)

Germline BRCA group and Non-BRCA-like group



Under powered 37 of planned 63 patients

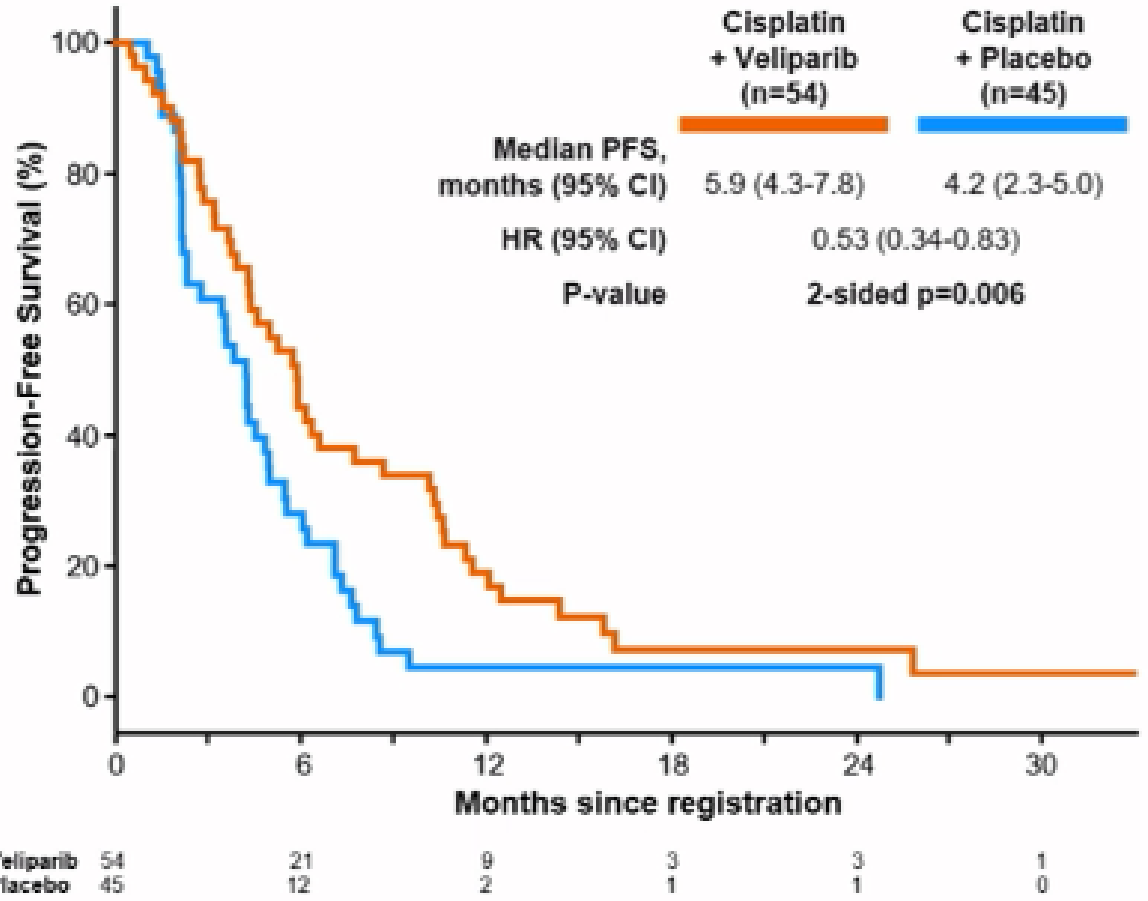


No difference in PFS

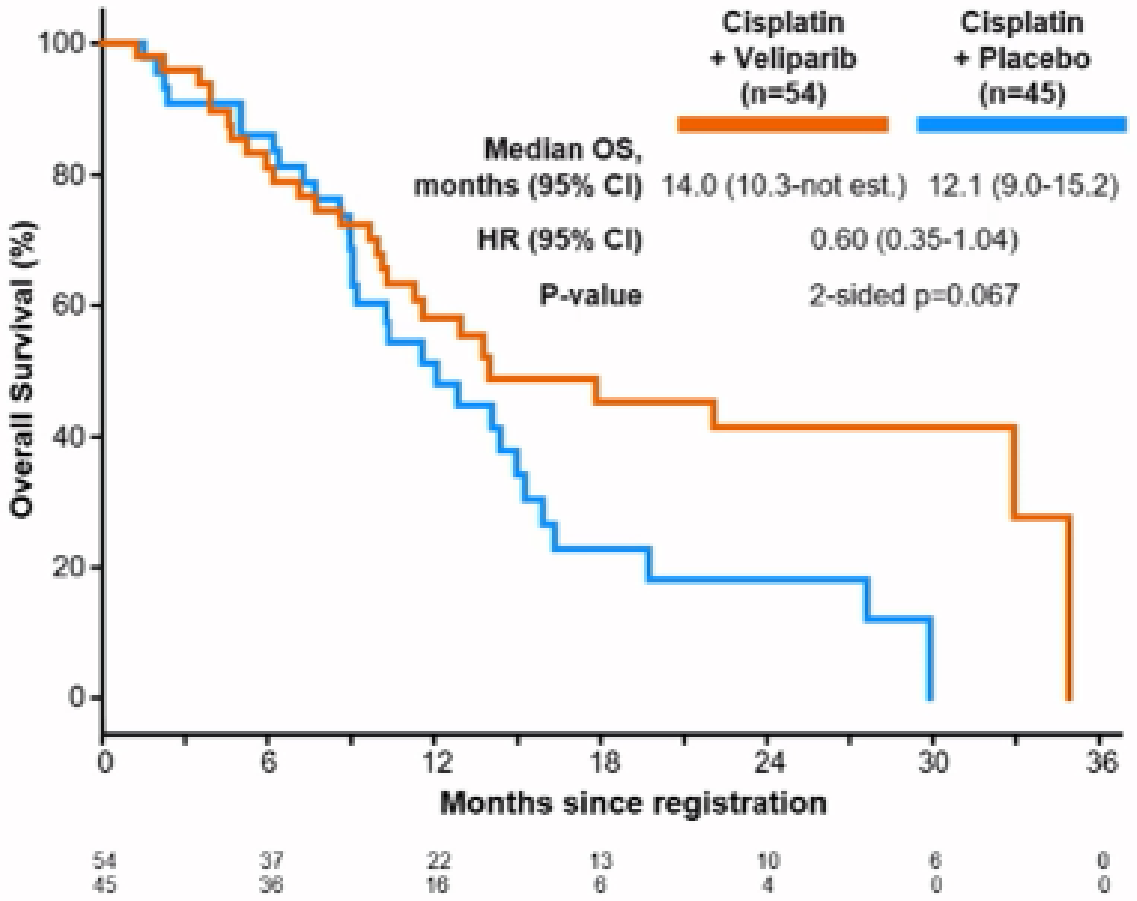
Slide by Catherine Margaret Kelly, FRCP

BRCA-like group

Progression-free survival



Overall survival



ORR (n=83): 45% vs 33%

Treatment-related adverse events

Adverse event	Cisplatin + Veliparib (N=154#)		Cisplatin + Placebo (N=149#)	
	All Grades, N (%)	Grade 3-4, N (%)	All Grades, N (%)	Grade 3-4, N (%)
Nausea	116 (75)	19 (12)	93 (62)	11 (7)
Fatigue	96 (62)	8 (5)	83 (56)	9 (6)
Anemia	94 (61)	35 (23)	84 (56)	11 (7)*
Neutropenia	91 (59)	71 (46)	63 (42)	29 (19)*
Leukopenia	82 (53)	42 (27)	69 (46)	11 (7)*
Vomiting	69 (45)	9 (6)	52 (35)	5 (3)
Thrombocytopenia	80 (52)	29 (19)	36 (24)	4 (3)*
Anorexia	44 (29)		35 (23)	
Peripheral sensory neuropathy	40 (26)		39 (26)	
Lymphocyte count decreased	37 (24)	11 (7)	40 (27)	9 (6)

Two treatment-related deaths: one on placebo arm (acute kidney injury due to cisplatin and heart failure from previous adriamycin exposure); one on Veliparib arm (sepsis)

Most common (>20% of patients) and grade 3-4 (>5% of patients)
#18 patients did not receive protocol therapy and are not included in toxicity assessment
* $p<0.001$

SWOG 1416 Conclusions

- In pts with gBRCA-negative mTNBC with BRCA-like phenotype, veliparib added to cisplatin improves PFS by 47% and shows a trend towards improved OS
  - All BRCA-like biomarker subgroups benefitted from veliparib but the benefit was primarily driven by the HRD biomarker group
- Addition of veliparib was not beneficial in patients with non-BRCA-like phenotype mTNBC
- No difference seen in germline BRCA group
  - Low accrual/insufficient power
  - Ph III BROCADE 3: Addition of veliparib to platinum-based chemo improves PFS in gBRCA-associated MBC
- Toxicity was manageable and no new signals noted
- About half of gBRCA-negative TNBCs demonstrated BRCA-like phenotype, with 2/3 having an elevated HRD genomic instability score
- Further research needed to identify optimal HRD biomarkers critical in early BC and MBC treatment

Overall Conclusions: TNBC

- Adjuvant capecitabine is currently appropriate for patients with TNBC who do not achieve a pathologic complete response to neoadjuvant chemotherapy
- Await mature overall survival results of SYSUCC-001 before routinely escalating adjuvant therapy in all TNBC
- PD-L1 testing should be routine on all metastatic TNBC biopsy specimens (incorporated into pathology workflows)
  - The optimal PD-L1 assay is unknown
- Patients with PD-L1+ positive tumors benefit from immune checkpoint inhibitor+chemotherapy in the first line setting
- PARP inhibitors are approved and appropriate for gBRCA mutation carriers
- BRCA-like biomarker analysis should be conducted as part of a broader sequencing approach increasingly being used in MBC
- MBC treatment will increasingly become more personalized, with tumor sequencing/biomarker assessment done routinely, and selection of therapy based on the presence of any number of biomarkers.

Thank you!

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