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EVENT-FREE SURVIVAL, OVERALL SURVIVAL, AND SAFETY OF ADDING VELIPARIB PLUS CARBOPLATIN OR CARBOPLATIN ALONE TO NEOADJUVANT CHEMOTHERAPY IN TRIPLE-NEGATIVE BREAST **CANCER AFTER ≥4 YEARS OF FOLLOW**-UP: BRIGHTNESS, A RANDOMIZED PHASE 3 TRIAL

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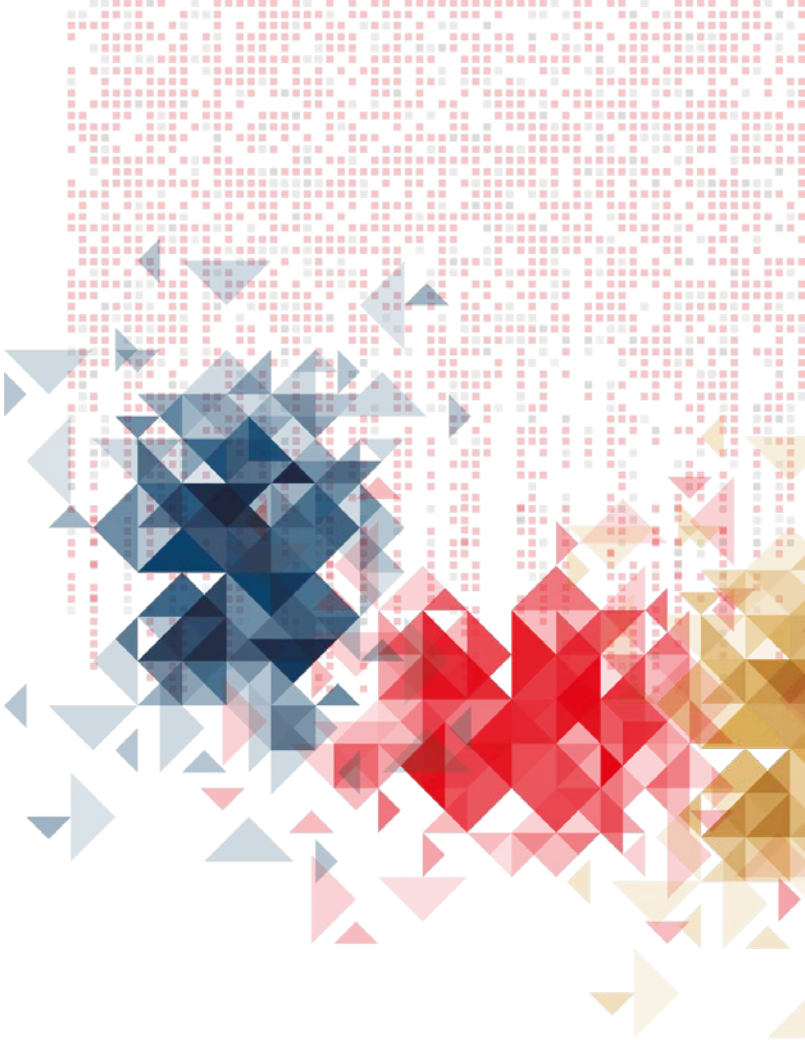


DECLARATION OF INTERESTS

Sibylle Loibl: Paid to institute unless otherwise stated. Grant: AbbVie, Amgen, AstraZeneca, Celgene, Daiichi-Sankyo, Immunomedics/Gilead, Novartis, Pfizer, Roche, and Vifor; Honorarium for advisory boards: AbbVie, Amgen, AstraZeneca, Bayer, BMS, Celgene, Daiichi-Sankyo, Eirgenix, GSK, Lilly, Merck kG, Novartis, Pfizer, Pierre Fabre, Prime/Medscape, Puma, Roche, and Seagen; Lectures: Chugai (personal), Daiichi-Sankyo, Novartis, Pfizer, Pierre Fabre, PriME/Medscape, Roche, and Samsung; Medical writing role: AbbVie, Amgen, AstraZeneca, Celgene, Daiichi-Sankyo, Novartis, Pfizer, and Roche. **William M. Sikov:** Unpaid member of the Steering Committee: AbbVie. **Jens Huober:** Research funding: Celgene, Hexal, Lilly, and Novartis; Honoraria: AbbVie, AstraZeneca, Celgene, Eisai, Gilead, Lilly, MSD, Novartis, Pfizer, Roche, and Seagen; Consulting and advisory role: AbbVie, AstraZeneca, Celgene, Hexal, Lilly, Gilead, MSD, Novartis, Pfizer, Roche, and Seagen; Travel expenses: Celgene, Daiichi, Novartis, Pfizer, and Roche. **Hope S. Rugo:** Research support for clinical trials through the University of California: AstraZeneca, Boehringer Ingelheim, Daiichi, Genentech, Immunomedics, Lilly, Macrogenics, Merck, Novartis, Odonate, Pfizer, Polyphor, Seattle Genetics, and Sermonix; Honoraria: Mylan, Puma, and Samsung. **Joyce O'Shaughnessy:** Honoraria for consulting and/or advisory boards: AbbVie, Agendia, and Amgen Biotechnology, Aptitude Health, AstraZeneca, Bayer, Bristol-Myers Squibb, Celgene Corporation, Clovis Oncology, Daiichi Sankyo, Eisai, G1 Therapeutics, Genentech, Gilead Sciences, GRAIL, Halozyme Therapeutics, Heron Therapeutics, Immunomedics, Ipsen Biopharmaceuticals, Lilly, Merck, Myriad, Nektar Therapeutics, Novartis, Pfizer, Pharmacyclics, Pierre Fabre Pharmaceuticals, Prime Oncology, Puma Biotechnology, Roche, Samsung Bioepis, Sanofi, Seagen, Syndax Pharmaceuticals, Taiho Oncology, Takeda, and Synthon. **David Maag, Martin Dunbar:** AbbVie employee and may hold stock or options. **Michael Untch:** Lectures and advisory boards: AbbVie, Agendia, Amgen, Astra Zeneca, BioNTech, BMS, Celgene, Daiichi-Sankyo, Eisai, GSK, Jansen Cilag, Johnson & Johnson, Lilly, Molecular Health, MSD, Mundipharma, Myriad, Novartis, Pfizer, Pierre Fabre, Roche, and Seagen; Consulting role: AbbVie. **Mehra Golshan:** Unpaid member of the Steering Committee: AbbVie; Research funding: Breast Cancer Research Foundation. **Jose Ponce Lorenzo:** Honoraria for consulting and/or advisory boards: Seagen, Novartis, Pfizer, Astra Zeneca, Lilly, and Roche. **Otto Metzger:** Research and honoraria for consulting activities: AbbVie. **W. Fraser Symmans:** Founder shares: Delphi Diagnostics; Intellectual property: Delphi Diagnostics; Public company shares: Eiger Biopharmaceuticals and IONIS Pharmaceuticals; Compensated advisory board: Merck; Uncompensated advisory boards: Delphi Diagnostics and Roche. **Charles E Geyer Jr:** Travel funding: Genentech, Roche, Daiichi-Sankyo, and AstraZeneca; Medical writing role: Roche and AbbVie; Uncompensated advisory boards: Genentech, Roche, Daiichi-Sankyo, and Seattle Genetics; Compensated advisory boards: Exact Sciences; Uncompensated consulting role: Daiichi-Sankyo; Compensated consulting role: Athenex. **Norman Wolmark**: None to disclose.

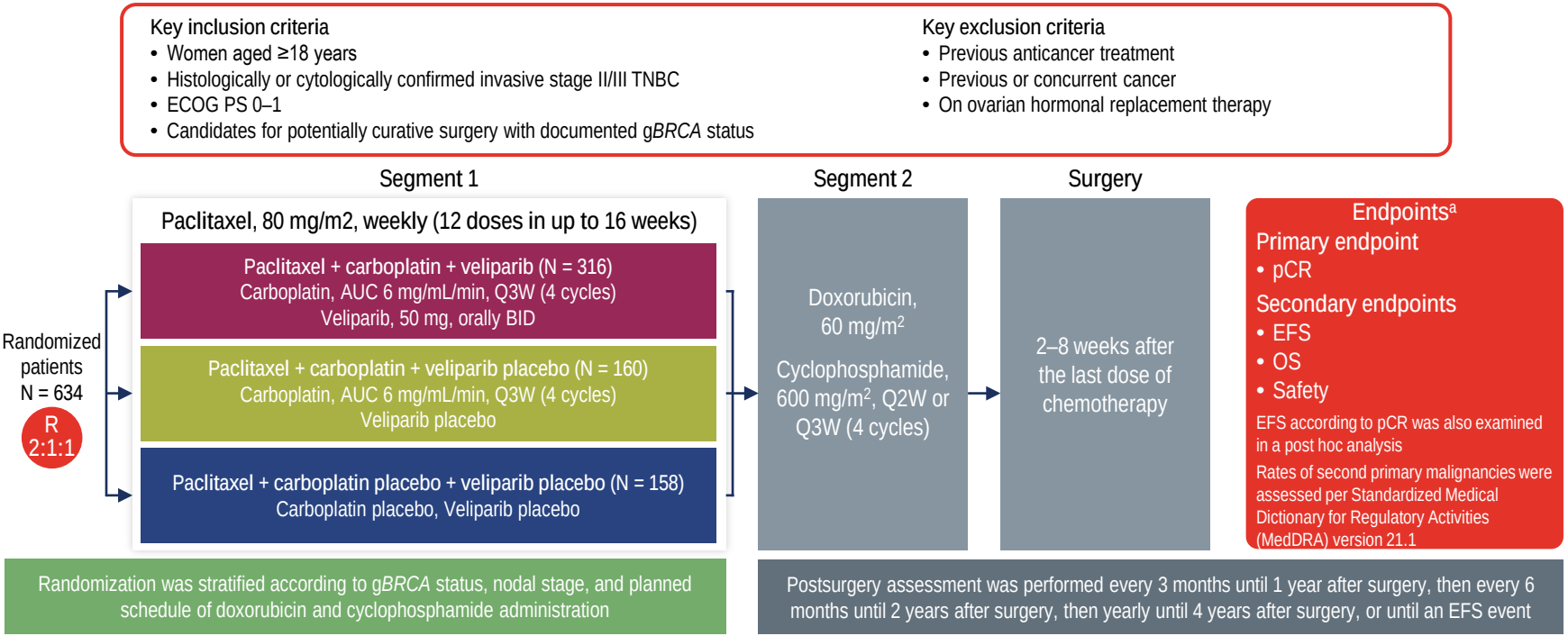
BACKGROUND

- Triple-negative breast cancer (TNBC) has higher risk of recurrence and worse overall prognosis and survival than other breast cancers[1,2]
- Due to a lack of targeted options, neoadjuvant chemotherapy (NACT) followed by surgery has become a standard treatment for patients with stage II-III TNBC[3-5]
- In the phase 3 **BrighTNess trial** (NCT02032277), carboplatin, with or without veliparib demonstrated[6]:
  - Significantly improved pathological complete response (pCR) in patients with operable TNBC compared with standard NACT alone (53% and 58%, respectively, versus 31%[a])
  - An acceptable safety profile in patients with operable TNBC
- Increased pCR rates with addition of carboplatin to NACT were also reported in other randomized breast cancer trials[7,8]
  - **CALGB 40603/Alliance:** 54% with carboplatin added to paclitaxel versus 41%[a] with conventional regimen +/- bevacizumab
  - **GeparSixto**: 53% with carboplatin added to paclitaxel and liposomal doxorubicin plus bevacizumab versus 43%[a] with chemotherapy plus bevacizumab
- Impact of neoadjuvant carboplatin on long-term outcomes remains uncertain

[a]Using a definition of pCR as ypT0/is ypN0.

1. Bianchini G et al. Nat Rev Clin Oncol 2016; 13(11): 674-90; 2. Otto H et al. BMC Genomics 2005; 6: 139; 3. Korde LA et al. J Clin Oncol 2021: Jco2003399; 4. Cardoso F et al. Ann Oncol 2019; 30(8): 1194-220;5. Thomssen C et al. Breast Care (Basel) 2021; 16(2): 135-43; 6. Loibl S et al. Lancet Oncol 2018; 19(4): 497-509; 7. von Minckwitz G et al. Lancet Oncol 2014; 15(7): 747-56; 8. Sikov WM et al. J Clin Oncol 2015; 33(1): 13-21.

STUDY DESIGN



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[a]Efficacy was assessed in all randomized patients and safety in all patients who received ≥1 dose

AUC, area under the curve; BID, twice a day; ECOG PS, Eastern Cooperative Oncology Group performance status; EFS, event-free survival; OS, overall survival; pCR, pathological complete response; Q2W, every 2 weeks; Q3W, every 3 weeks; R, randomization; TNBC, triple negative breast cancer.

ENDPOINT ASSESSMENT

The primary (pCR) and secondary (EFS and OS) endpoints used fixed-sequence testing* that ordered:

1. Paclitaxel + carboplatin + veliparib versus paclitaxel, then;
2. Paclitaxel + carboplatin + veliparib versus paclitaxel + carboplatin

*Both co-primary endpoints needed to be statistically significant to continue formally testing secondary endpoints

In primary analyses[1], paclitaxel + carboplatin + veliparib was:

- **Superior** to paclitaxel alone but;
- **Not superior** to paclitaxel + carboplatin

Thus, subsequent secondary analyses are descriptive with nominal P-values.

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EFS, event-free survival; OS, overall survival; pCR, pathological complete response.

1. Loibl S et al. Lancet Oncol 2018; 19(4): 497-509.

SECONDARY ENDPOINT ANALYSIS

Here we report:

- Long-term EFS
- Long-term OS
- Rate of second malignancies at 4 years postsurgery

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EFS, event-free survival; OS, overall survival.

PATIENT CHARACTERISTICS

	Paclitaxel + carboplatin + veliparib (n=316)	Paclitaxel + carboplatin (n=160)	Paclitaxel (n=158)
Age, median (range), years	51 (26–79)	49 (23–76)	50 (22–75)
Age ≤50 years	151 (48)	87 (54)	81 (51)
Age >50 years	165 (52)	73 (46)	77 (49)
Recruitment region			
North America	140 (44)	73 (46)	79 (50)
Europe	119 (38)	65 (41)	58 (37)
Asia-Pacific	57 (18)	22 (14)	21 (13)
Germline *BRCA* status			
Deleterious mutations	43 (14)	25 (16)	22 (14)
No deleterious mutations	273 (86)	135 (84)	136 (86)
Tumor stage			
T1	37 (12)	20 (13)	15 (9)
T2	229 (72)	108 (68)	117 (74)
T3–4a	50 (16)	32 (20)	26 (16)

	Paclitaxel + carboplatin + veliparib (n=316)	Paclitaxel + carboplatin (n=160)	Paclitaxel (n=158)
Lymph node stage			
N0[a]	180 (57)	92 (58)	94 (59)
N1–N2	136 (43)	68 (43)	64 (41)
Planned schedule of AC			
Every 2 weeks	173 (55)	88 (55)	89 (56)
Every 3 weeks	140 (44)	70 (44	69 (44)
Missing	3 (1)	2 (1)	0
Histological primary tumor grade			
High	190 (60)	97 (61)	92 (58)
Intermediate	70 (22)	32 (20)	30 (19)
Low	18 (6)	10 (6)	7 (4)
Unknown/not reported	38 (12)	29 (18)	21 (13)

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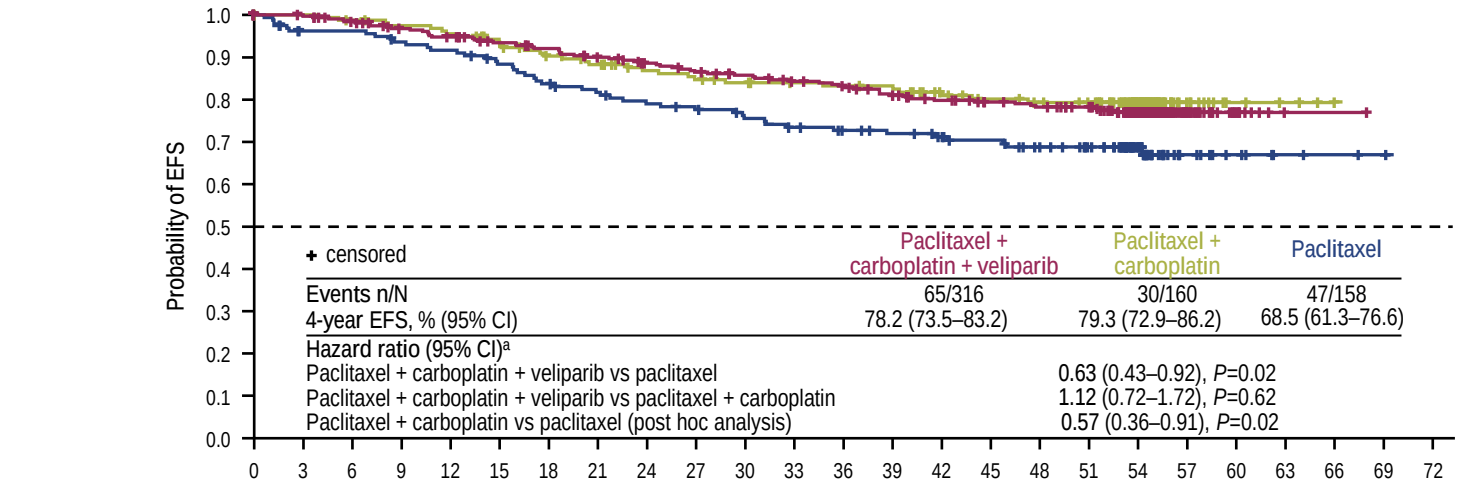
Data are median (range) unless otherwise indicated. [a]N0 category included patients without suspicious nodes on examination or ultrasound, plus patients with suspicious nodes that showed no evidence of tumor cell on needle biopsy. All patients classified as lymph node stage N1–N2 were histologically confirmed per protocol.

Loibl S et al. Lancet Oncol 2018; 19(4): 497-509.

STRATIFIED ANALYSIS OF EFS WITH MEDIAN FOLLOW-UP OF 4.5 YEARS



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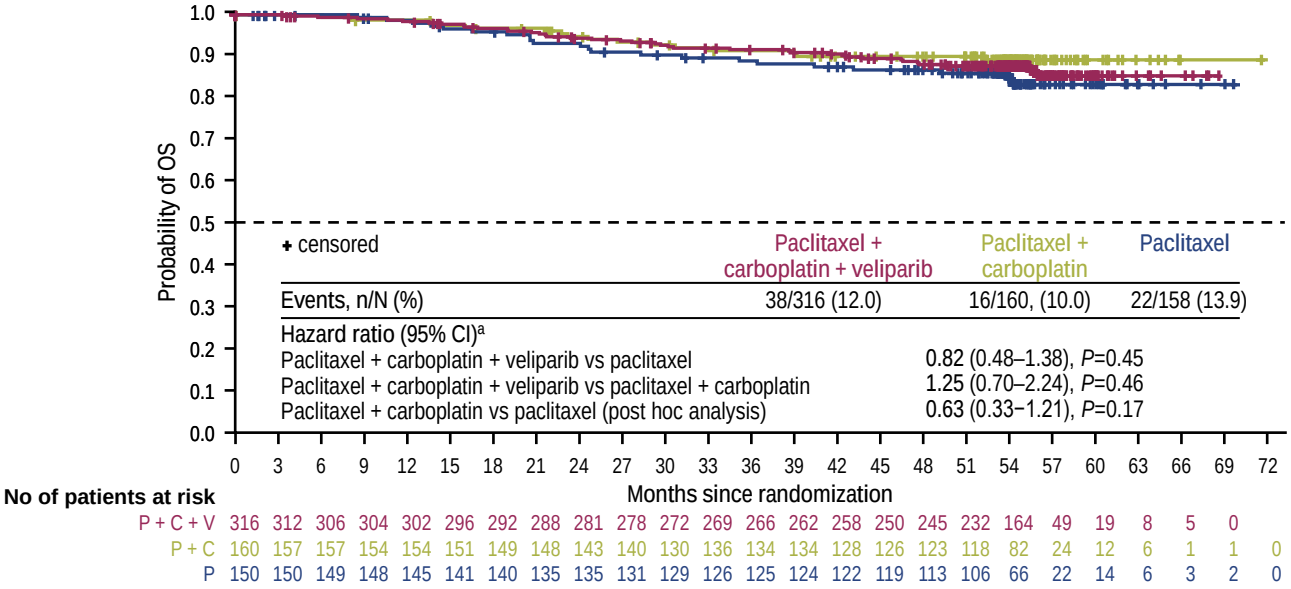
[a]Stratified by *BRCA* status, lymph node status, and planned doxorubicin/cyclophosphamide dose intensity.
C, carboplatin; CI, confidence interval; EFS, event-free survival; HR, hazard ratio; P, paclitaxel; V, veliparib.

SUMMARY OF EFS EVENTS

	Paclitaxel + carboplatin + veliparib (n=316)	Paclitaxel + carboplatin (n=160)	Paclitaxel (n=158)
Patients with EFS event[a]	65 (21)[b]	30 (19)[c]	47 (30)[d]
PD prior to surgery	2 (1)	1 (1)	6 (4)
Any recurrence	50 (16)	26 (16)	35 (22)
Distant	22 (7)	12 (8)	14 (9)
Local	16 (5)	10 (6)	10 (6)
Ipsilateral breast	6 (2)	4 (3)	5 (3)
Regional	4 (1)	3 (2)	11 (7)
Contralateral breast cancer	2 (1)	1 (1)	4 (3)
Second non-breast cancer	14 (4)	3 (2)	5 (3)
AML/MDS	4 (1)	2 (1)	2 (1)
Other	10 (3)	1 (1)	3 (2)
Death as first event	13 (4)	3 (2)	6 (4)

Data are n (%); [a]EFS events were summarized by first documented event. Patients may have had multiple events reported on the same day; [b]Patients with >1 EFS event, n=37; [c]Patients with >1 EFS event, n=16; [d]Patients with >1 EFS event, n=25.
AML, acute myeloid leukemia; EFS, event-free survival; MDS, myelodysplastic syndromes; PD, progressive disease.

STRATIFIED ANALSYIS OF OS AFTER MEDIAN FOLLOW-UP OF 4.5 YEARS



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[a]Stratified by *BRCA* status, lymph node status, and planned doxorubicin/cyclophosphamide dose intensity.
C, carboplatin; CI, confidence interval; HR, hazard ratio; OS, overall survival; P, paclitaxel; V, veliparib.

FREQUENCY OF MDS, AML, AND OTHER SECOND PRIMARY MALIGNANCIES

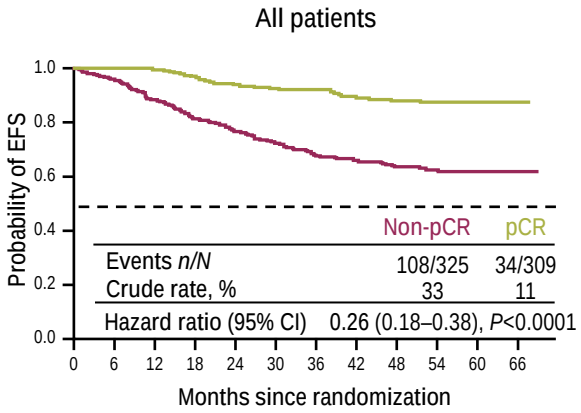
	Paclitaxel + carboplatin + veliparib (n=313)	Paclitaxel + carboplatin (n=158)	Paclitaxel (n=157)
MDS SMQ	5 (2)	3 (2)	1 (<1)
Pancytopenia	4 (1)	3 (2)	0
MDS	1 (<1)	0	1 (<1)
Secondary malignancy SMQ	6 (2)	6 (4)	4 (3)
Acute leukemia	1 (<1)	0	0
AML	2 (<1)	3 (2)	1 (<1)
CML	1 (<1)	0	0
Lung neoplasm	1 (<1)	0	0
Malignant melanoma	1 (<1)	0	0
Basal cell carcinoma	0	1 (<1)	0
Colon cancer	0	1 (<1)	0
Pancreatic carcinoma	0	0	2 (1)

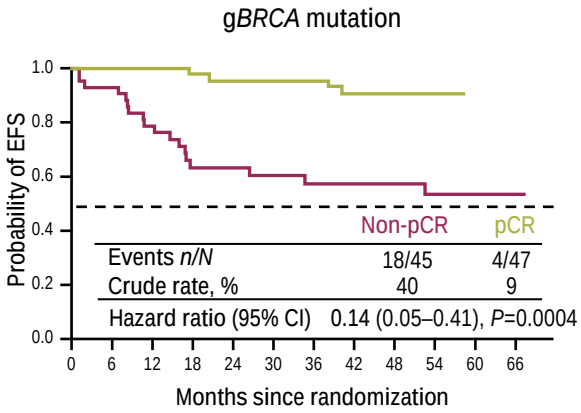
The rates of treatment-emergent and posttreatment-emergent MDS, AML, and secondary malignancies were similar between all treatment groups

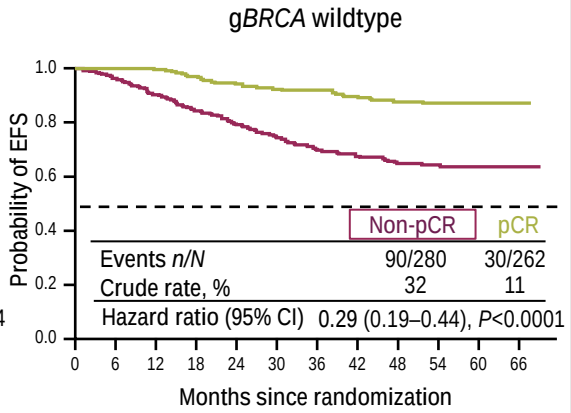
Data are n (%).

AML, acute myeloid leukemia; CML, chronic myeloid leukemia; MDS, myelodysplastic syndrome; MedDRA, Medical Dictionary for Regulatory Activities; SMQ, Standardized MedDRA Queries.

EFS BY pCR IN ALL PATIENTS AND SUBGROUPS BY g*BRCA* STATUS







Patients with pCR had improved EFS compared to those without pCR (HR 0.26, 95% CI 0.18–0.38; P<0.0001), regardless of *BRCA* mutation status

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[a]Stratified by *BRCA* status, lymph node status, and planned doxorubicin/cyclophosphamide dose intensity.
CI, confidence interval; EFS, event-free survival; HR, hazard ratio; pCR, pathological complete response.

CONCLUSIONS

- Adding carboplatin to paclitaxel followed by doxorubicin and cyclophosphamide improved pCR significantly[1] and translated into an improved EFS after a median follow-up of 4.5 years
- Addition of veliparib did not impact pCR, EFS, or OS
- Patients with pCR had significantly better EFS; this was similar in patients with and without g*BRCA* mutations
- Higher rates of hematologic AEs with the addition of carboplatin with or without veliparib (previously reported) did not compromise treatment delivery or the impact of this treatment on the study's primary (pCR) or secondary (EFS/OS) endpoints
- The regimens had manageable safety profiles without increased risk of MDS, AML, or other secondary malignancies
- These findings support the inclusion of carboplatin in neoadjuvant chemotherapy for stage II-III TNBC, irrespective of g*BRCA* status

AE, adverse event; AML, acute myeloid leukemia; EFS, event-free survival; OS, overall survival; MDS, myelodysplastic syndrome; pCR, pathological complete response; TNBC, triple negative breast cancer.

1. Loibl S et al. Lancet Oncol 2018; 19(4): 497-509.

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