SABCS 2019 Update

Triple-negative and hereditary breast cancer

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Disclosures

- Advisory Role: Aduro, Celldex, Celgene, Daiichi Sankyo, Genentech/Roche, Immunomedics, Lilly, Merck, Pfizer, PharmaMar, Tesaro, Vertex
- DSMC: G1 Therapeutics, Immunomedics
- Contracted Research: AstraZeneca, Bayer, Biothera, Calithera, EMD Serono, Genentech/Roche, Merck, OncoSec, Pfizer, PharmaMar, Tesaro, Vertex

Triple-negative breast cancer

Abstract	Presenter	Title
GS3-02	Dalenc	Durvalumab compared to maintenance chemotherapy in patients with metastatic breast cancer: Results from phase II randomized trial SAFIR02-IMMUNO
GS3-03	Schmid	Keynote-522 study of neoadjuvant pembrolizumab + chemotherapy vs placebo + chemotherapy, followed by adjuvant pembrolizumab vs placebo for early triple-negative breast cancer: pathologic complete response in key subgroups and by treatment exposure, residual cancer burden, and breast-conserving surgery
GS3-04	Gianni	Pathologic complete response (pCR) to neoadjuvant treatment with or without atezolizumab in triple negative, early high-risk and locally advanced breast cancer. NeoTRIPaPDL1 Michelangelo randomized study

Role of maintenance PD-L1 inhibition in 1st & 2nd line HER2- MBC?

Role of neoadjuvant PD-1/PD-L1 addition in early stage TNBC?

Hereditary breast cancer

Abstract	Presenter	Title
GS6-03	Tung	TBCRC 031: A randomized phase II study of preoperative cisplatin (CDDP) vs doxorubicin & cyclophosphamide (AC) in germline *BRCA* mutation carriers with newly diagnosed breast cancer (INFORM)
PD4-01	Arun	First-line veliparib plus carboplatin/paclitaxel in patients with HER2-negative advanced/metastatic *gBRCA*-associated breast cancer: planned subgroup analysis from the phase 3 BROCADE3 trial

Role of neoadjuvant platinum monotherapy in early stage gBRCA1/2 breast cancer?

Role of chemotherapy + PARPi in 1st-3rd line gBRCA1/2 MBC?

IMpassion130 study design

Key IMpassion130 eligibility criteria[a]:

- Metastatic or inoperable locally advanced TNBC
  - Histologically documented[b]
- No prior therapy for advanced TNBC
  - Prior chemo in the curative setting, including taxanes, allowed if TFI ≥ 12 mo
- ECOG PS 0-1

Stratification factors:

- Prior taxane use (yes vs no)
- Liver metastases (yes vs no)
- PD-L1 status on IC (positive [≥ 1%] vs negative [< 1%])[c]

R 1:1

Atezo + nab-P arm:

Atezolizumab 840 mg IV
- On days 1 and 15 of 28-day cycle

+ *nab*-paclitaxel 100 mg/m^2 IV
- On days 1, 8 and 15 of 28-day cycle

Double blind; no crossover permitted

Plac + nab-P arm:

Placebo IV
- On days 1 and 15 of 28-day cycle

+ *nab*-paclitaxel 100 mg/m^2 IV
- On days 1, 8 and 15 of 28-day cycle

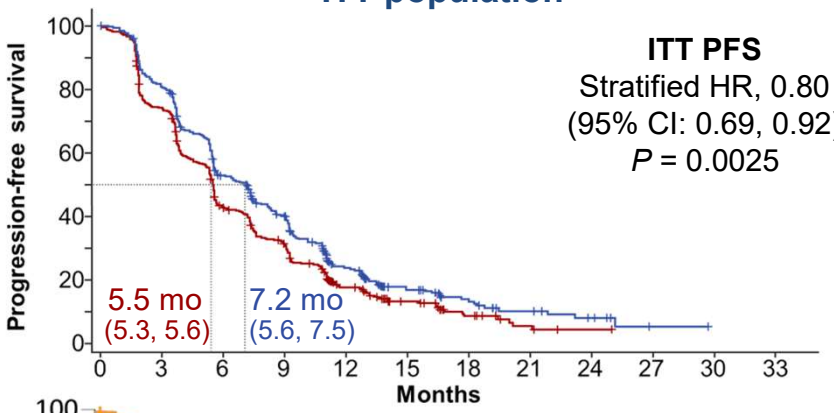
RECIST v1.1
PD or toxicity

- Co-primary endpoints were PFS and OS in the ITT and PD-L1+ populations[d]
  - Key secondary efficacy endpoints (ORR and DOR) and safety were also evaluated

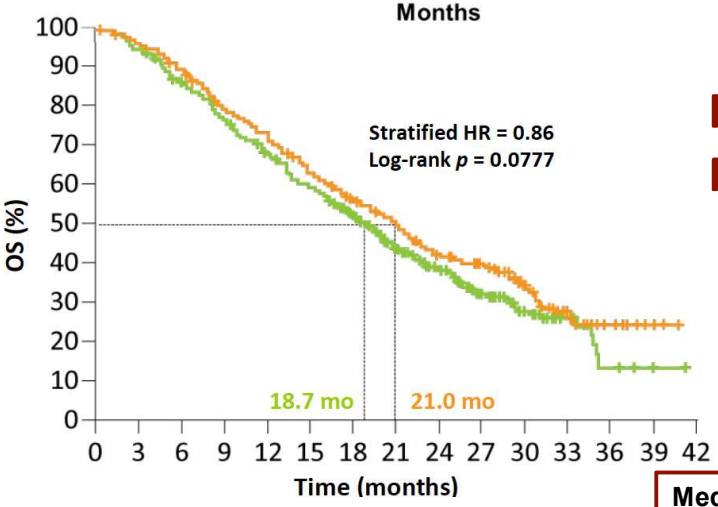
IC, tumour-infiltrating immune cell; TFI, treatment-free interval. [a] ClinicalTrials.gov: NCT02425891. [b] Locally evaluated per ASCO–College of American Pathologists (CAP) guidelines. [c] Centrally evaluated per VENTANA SP142 IHC assay (double blinded for PD-L1 status). [d] Radiological endpoints were investigator assessed (per RECIST v1.1).

IMpassion130 primary analysis

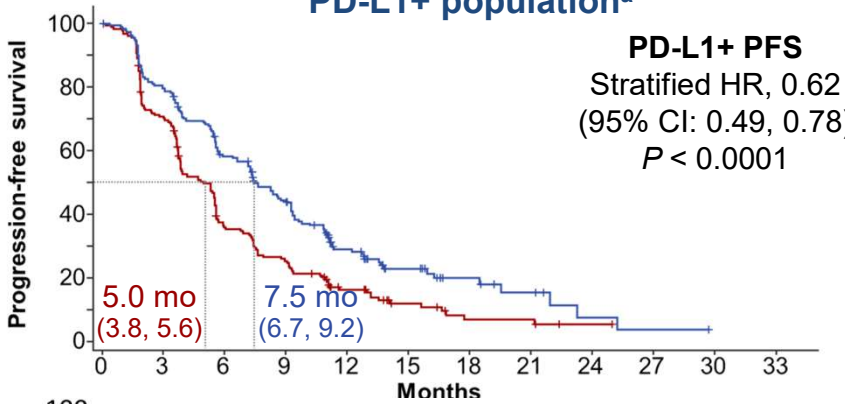
ITT population



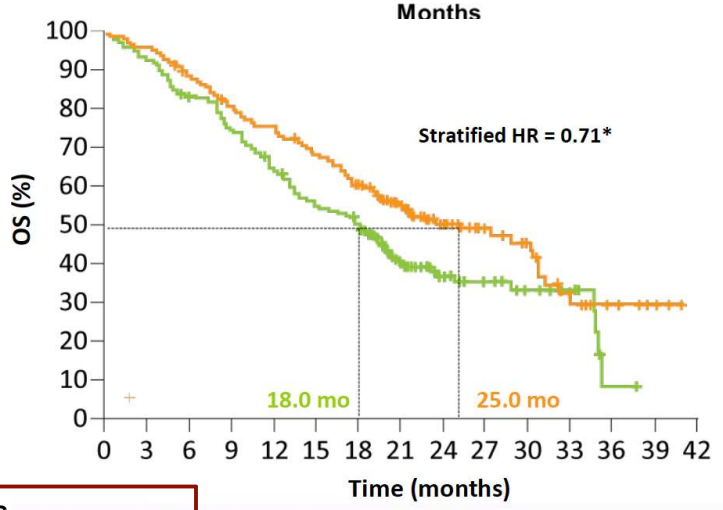
ITT PFS
Stratified HR, 0.80
(95% CI: 0.69, 0.92)
P = 0.0025



PD-L1+ population[a]



PD-L1+ PFS
Stratified HR, 0.62
(95% CI: 0.49, 0.78)
P < 0.0001



FDA approved March 8, 2019

Median follow-up = 18 months

2nd Interim OS ~ 80% of required events

Emens LA, et al. SABCS 2018
Schmid P et al. ASCO 2019

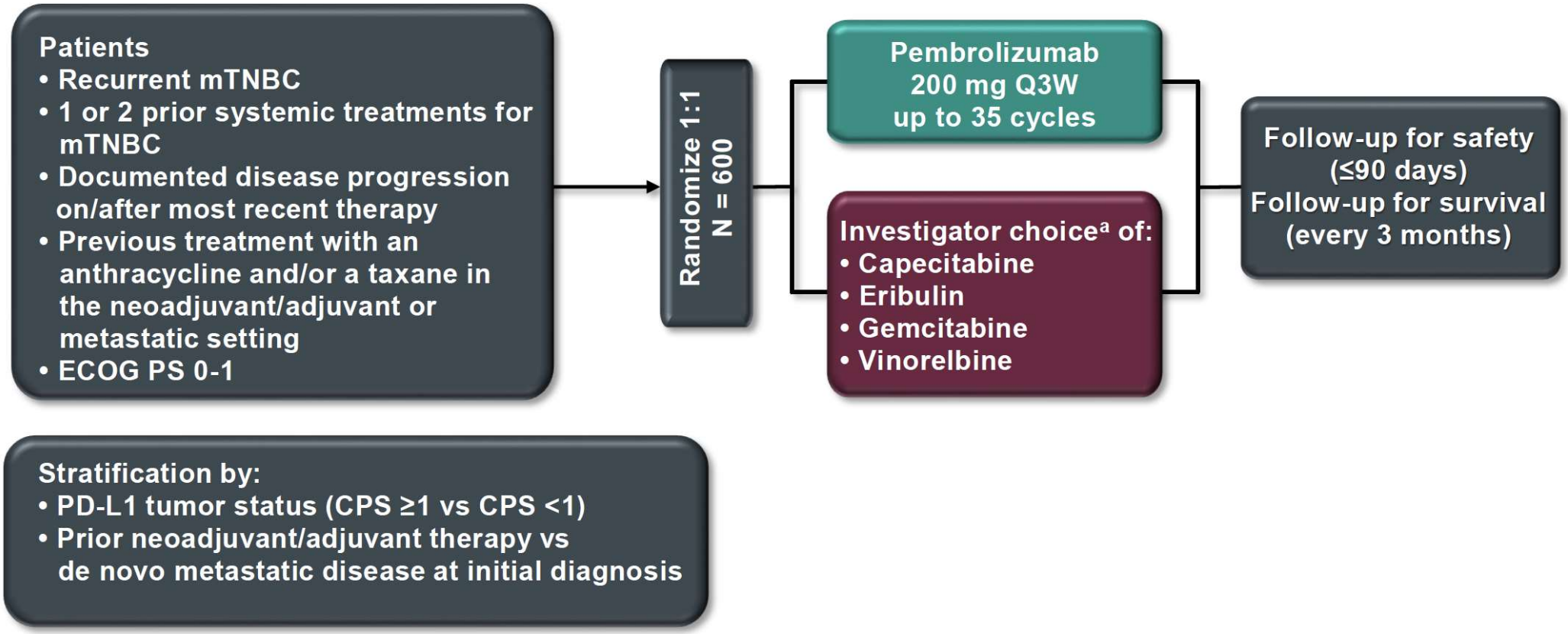
BARCELONA 2019 ESMO congress

KEYNOTE-119: Phase 3 Study of Pembrolizumab versus Single-Agent Chemotherapy for Metastatic Triple-Negative Breast Cancer (mTNBC)

Javier Cortes[1], Oleg Lipatov[2], Seock-Ah Im[3], Anthony Goncalves[4], Keun Seok Lee[5], Peter Schmid[6], Kenji Tamura[7], Laura Testa[8], Isabell Witzel[9], Shoichiro Ohtani[10], Stefania Zambelli[11], Nadia Harbeck[12], Fabrice Andre[13], Rebecca Dent[14], Xuan Zhou[15], Vassiliki Karantza[15], Jaime Mejia[15], Eric P. Winer[16]

1. IOB Institute of Oncology, Quiron Group; Vall d'Hebron Institute of Oncology (VHIO), Madrid & Barcelona, Spain; 2. Republican Clinical Oncology Dispensary, Republic of Bashkortostan, Russian Federation; 3. Seoul National University, Seoul, Republic of Korea; 4. Institut Paoli-Calmettes, Marseille, France; 5. National Cancer Center, Goyang, Republic of Korea; 6. Barts Cancer Institute, Queen Mary University London, London, UK; 7. National Cancer Center Hospital, Tokyo, Japan; 8. Instituto do Câncer do Estado de São Paulo - Faculdade de Medicina da Universidade do Estado do São Paulo, São Paulo, Brazil; 9. University Medical Center Hamburg, Hamburg, Germany; 10. Hiroshima City Hiroshima Citizens Hospital, Hiroshima, Japan; 11. IRCCS Ospedale San Raffaele, Milan, Italy; 12. Breast Center, University of Munich (LMU), Munich, Germany; 13. Faculté de Medicine Paris-Sud XI, Gustave Roussy, Villejuif, France; 14. University of Toronto, Toronto, Ontario, Canada; 15. Merck & Co., Inc., Kenilworth, NJ, USA; 16. Dana-Farber Cancer Institute, Boston, MA, USA

KEYNOTE-119 Study Design (NCT02555657)



ECOG PS = Eastern Cooperative Oncology Group performance status; mTNBC = metastatic triple-negative breast cancer; PD-L1 = programmed death ligand 1; Q3W = every 3 weeks.
[a]Maximum enrollment cap of 60% of total enrollment for each chemotherapy drug.

Study End Points

Primary

- OS in patients with PD-L1 positive tumors (CPS ≥10)[a]
- OS in patients with PD-L1 positive tumors (CPS ≥1)[a]
- OS in all patients

Key Secondary

- PFS in all patients
- ORR in all patients[b]
- Safety and tolerability

Additional Secondary

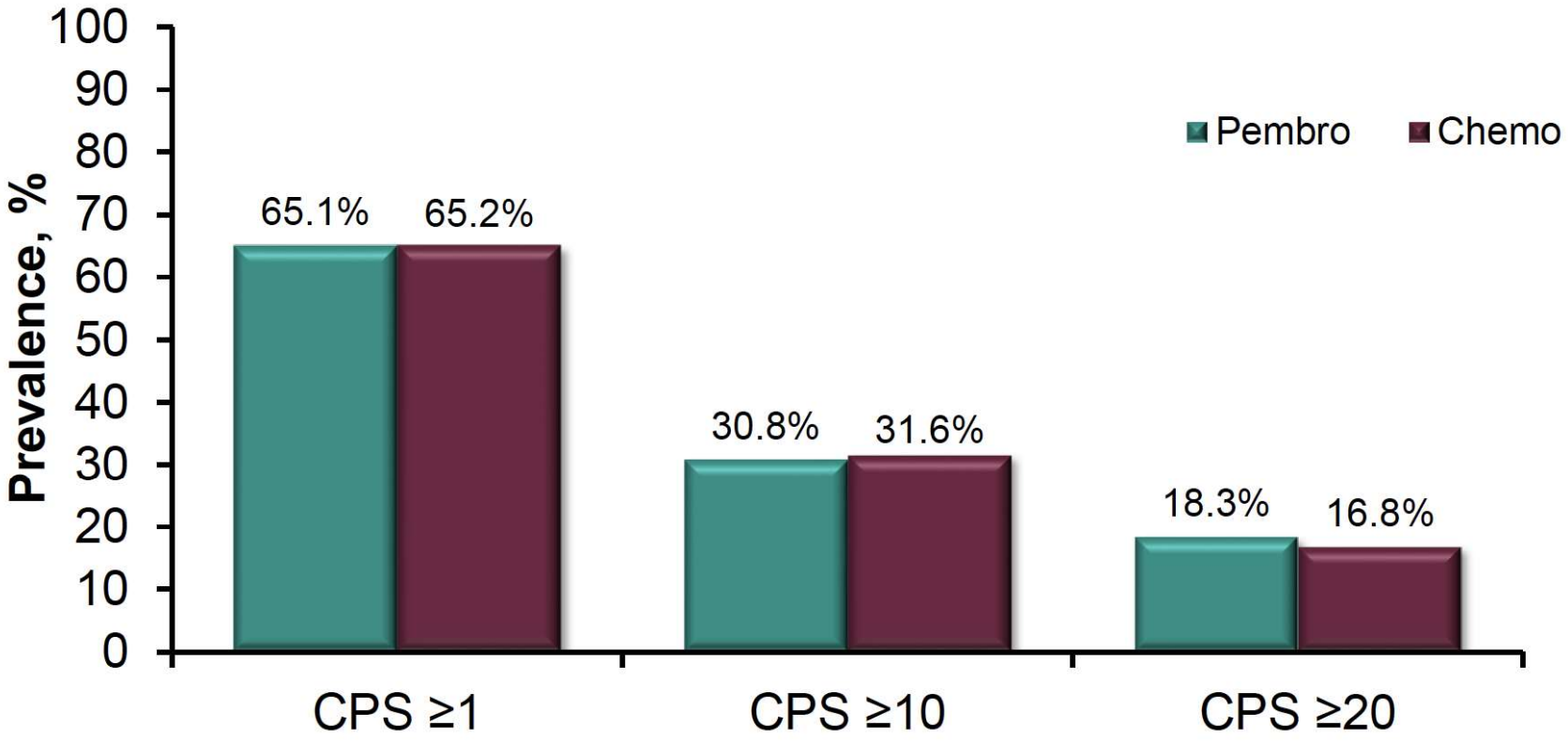
- DCR and DOR in all patients and patients with PD-L1 positive tumors (CPS ≥1 or CPS ≥10)[a]

Exploratory

- OS, PFS, ORR, and DOR in patients with PD-L1 positive tumors using additional CPS cutpoints

[a]Assessed at a central laboratory using the PD-L1 IHC 22C3 pharmDx assay defined as the combined positive score (CPS), the number of PD-L1–positive cells (tumor cells, lymphocytes, macrophages) divided by total number of tumor cells × 100.
[b]Assessed per RECIST v1.1 by blinded, independent central review.

Prevalence of PD-L1 CPS Categories

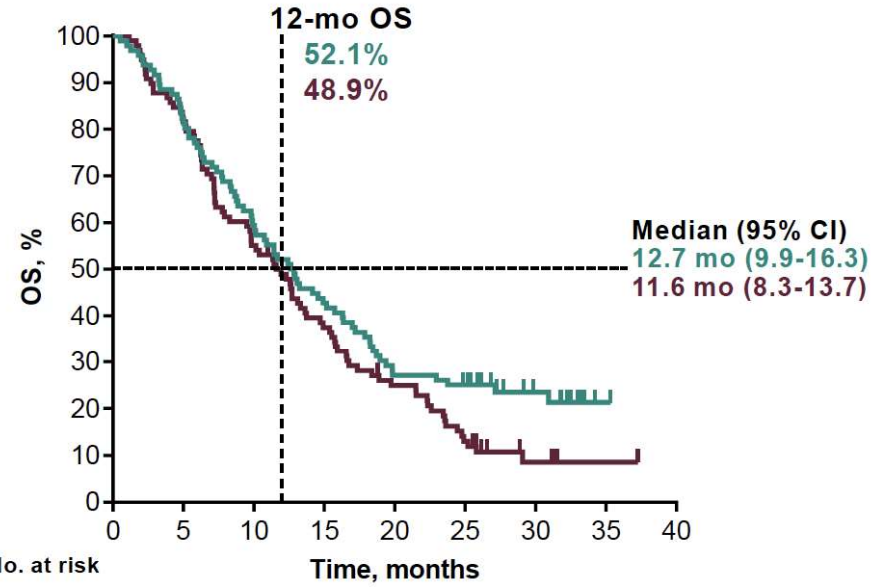


CPS = combined positive score defined as the number of PD-L1–positive cells (tumor cells, lymphocytes, macrophages) divided by total number of tumor cells × 100.
Data cutoff date: April 11, 2019.

Overall Survival: Primary Endpoints

CPS ≥10

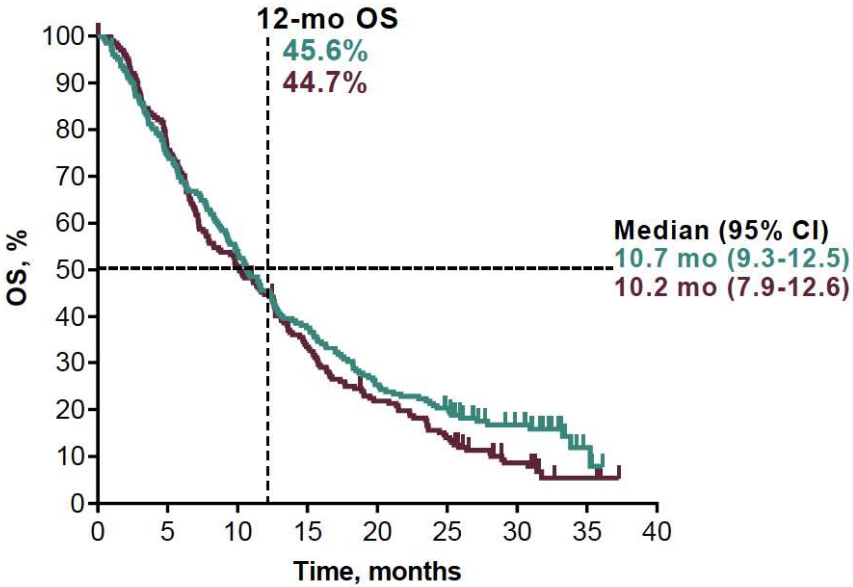
Events	HR (95% CI)	*P*
77.1%	0.78	0.057
88.8%	(0.57-1.06)	



No. at risk									
Pembro	96	79	57	41	26	23	11	1	0
Chemo	98	80	54	36	23	12	4	1	0

CPS ≥1

Events	HR (95% CI)	*P*
84.2%	0.86	0.073
90.6%	(0.69-1.06)	

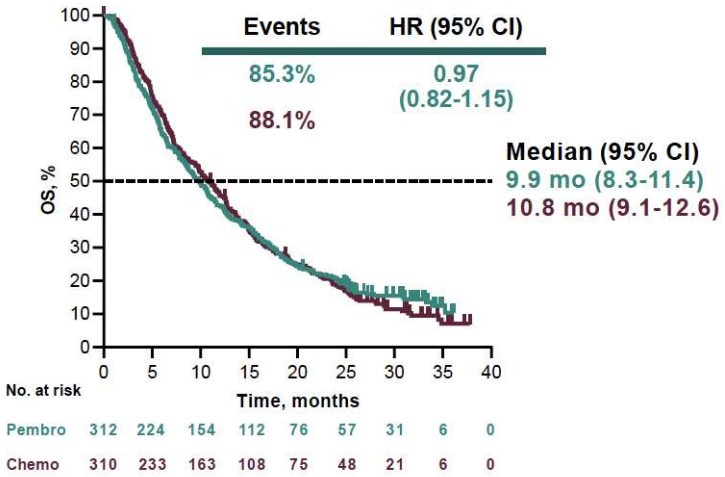


	203	151	109	76	51	40	20	3	0
	202	152	102	66	42	27	12	3	0

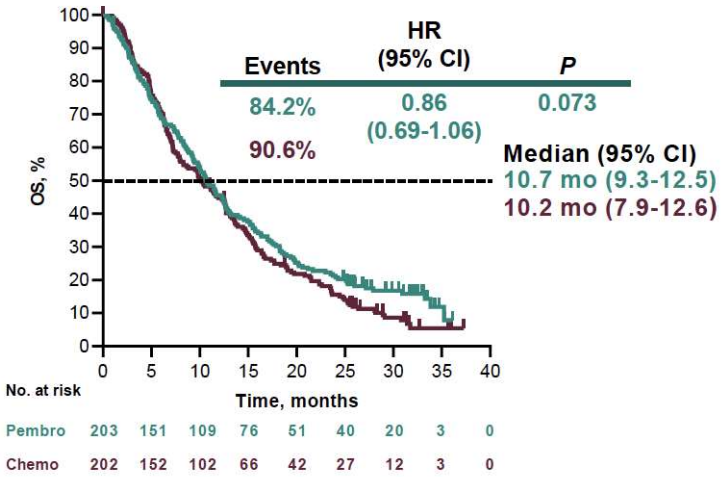
Data cutoff date: April 11, 2019.

Overall Survival by PD-L1 CPS

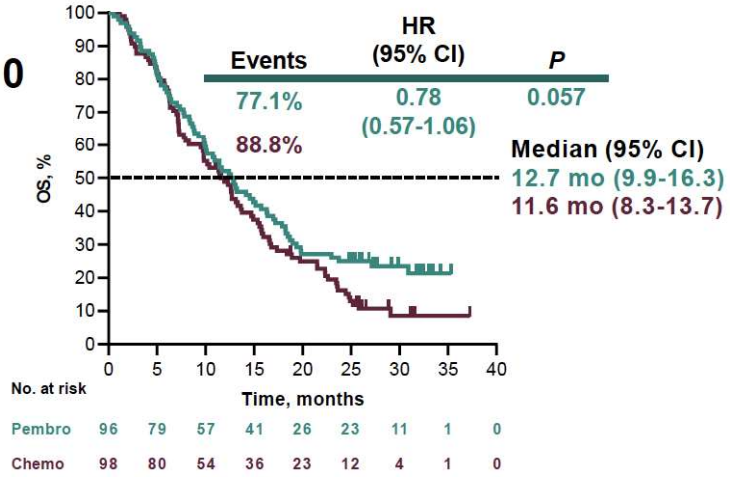
ITT



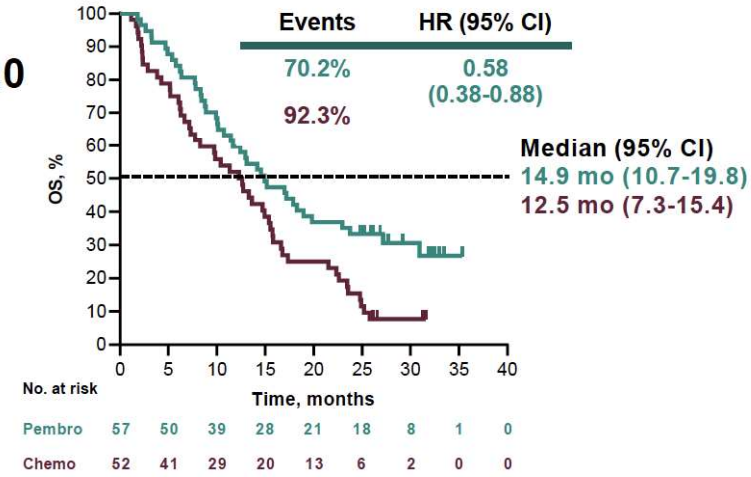
CPS ≥1



CPS ≥10



CPS ≥20



OS in the ITT, CPS ≥1 and CPS ≥10 populations were primary endpoints; OS in the CPS ≥20 population was an exploratory endpoint. Data cutoff date: April 11, 2019

Durvalumab compared to maintenance chemotherapy in patients with metastatic breast cancer : Results from phase II randomized trial SAFIR02-IMMUNO

Florence Dalenc[1], Thomas Bachelot[2], Thomas Filleron[1], Amélie Lusque[1], Monica Arnedos[3], Mario Campone[4] , Marie Paule Sablin[5], Hervé Bonnefoi[6], Marta Jimenez[7], Alexandra Jacquet[7], Fabrice André[3]

[1] Institut Claudius Regaud, IUCT-O, Toulouse; [2] Centre Léon Bérard, Lyon, [3] Gustave Roussy, Villejuif ; [4] ICO- Centre René Gauducheau, Nantes & Paul Papin, Angers; [5] Institut Curie, Paris; [6] Institut Bergonié, Bordeaux; [7] UNICANCER R&D, Paris,

San Antonio Breast Cancer Symposium, 10-14 December 2019

SAFIR-02 BREAST : Study Design

Metastatic breast cancer or locally advanced disease

HER-2 negative

Resistant to endocrine therapy if ER+*

1st or 2nd line chemotherapy (CT)

n=1462 patients

Frozen or FFPE or ctDNA sample (collected before C3 chemotherapy).

NGS (50-70 genes) CGH array

CR/PR/SD after 6-8 CT cycles (or 4 cycles if stopped for tox)

Targetable molecular alteration ?

YES

R

2:1

Targeted therapy matched to genomics

Maintenance CT without switch

1ry objective N=240 Ongoing

NO

SABCS2019

R

2:1

Durvalumab 10 mk/kg every 14 days

Maintenance CT without switch

Stratification :
- 1st or 2nd line CT
- CR/PR or SD

Secondary objective N=199

*: progression during endocrine therapy

Patient characteristics

Characteristics	Durvalumab arm A (n=131)	Control arm B (n=68)	p value
Median age	56 (27-79)	56 (24-77)	p = 0.5308
ECOG= 0	72 (59.5%)	37 (56.1%)	p = 0.6481
≥ 3 metastatic sites	55 (42.0%)	30 (44.1%)	p = 0.7730
Liver metastases	61 (46.6%)	34 (50.0%)	p = 0.6454
Lung metastases	35 (26.7%)	20 (29.4%)	p = 0.6869
IHC subtypes defined on primary tumor (n=192) TNBC HR+/HER2- HER2+	 47 (37.6%) 76 (60.8%) 2 (1.6%)	 35 (52.2%) 32 (47.8%) 0 (0.0%)	p = 0.0918
PDL1 expression (≥ 1% IC, SP142) (n=133)	28 (32.6%)	16 (34.0%)	
1st Line CT	118 (90.1%)	61 (89.7%)	
CT regimen in the maintenance arm	NA	No maintenance n=10 Paclitaxel n=16 Capecitabine n=10 (F)EC n=10	
Objective response to induction CT	52 (39.7%)	29 (42.6%)	

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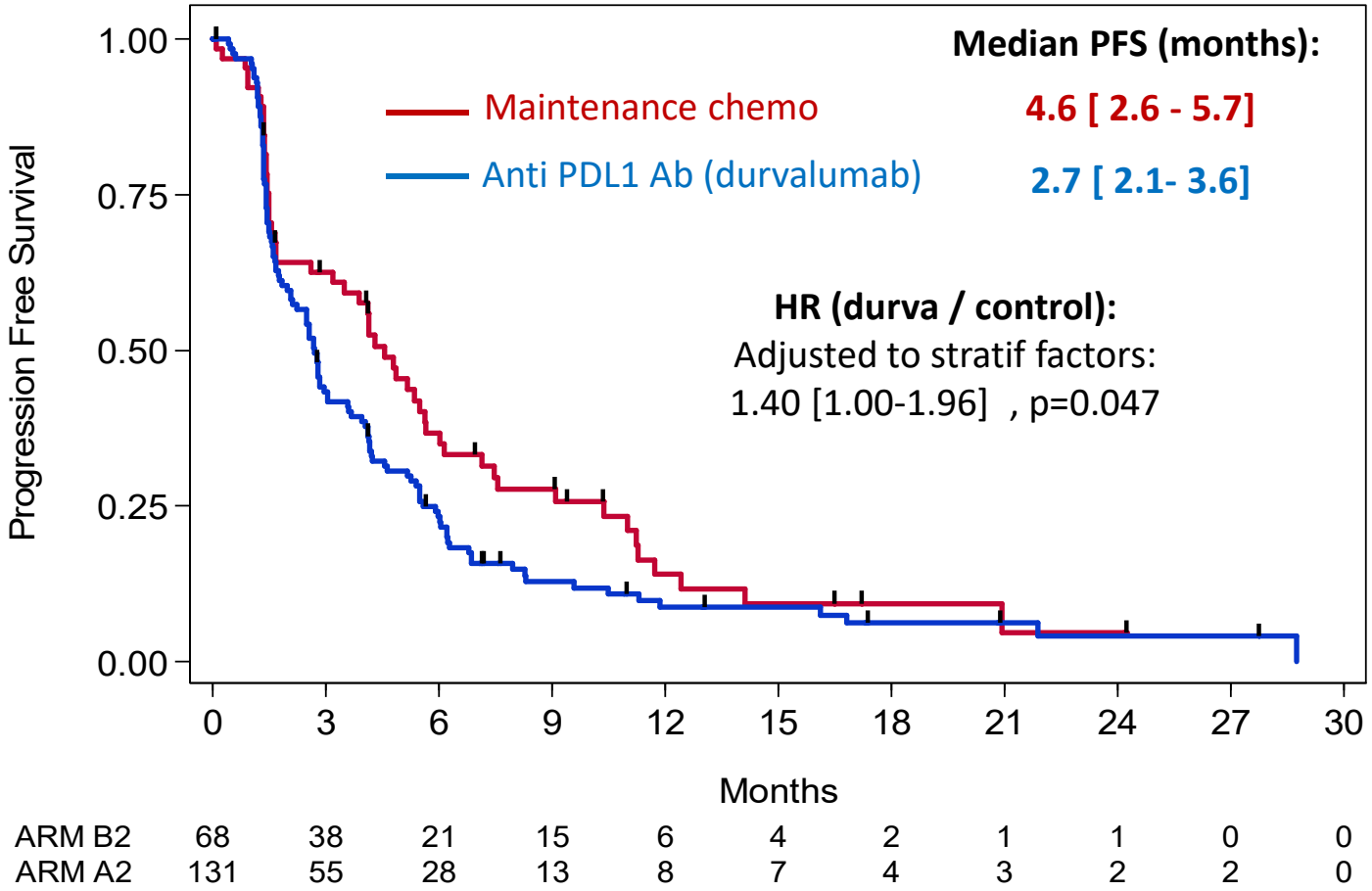
Description of PDL1 status

	PDL1+	PDL1-
TNBC n=61	32 (52.4%)	29 (47.6%)
Non-TNBC n=67	10 (14.9%)	57 (85.1%)

PDL1 status was assessed by IHC using SP142 antibody, on a metastatic tumor sample and on tumor-infiltrating immune cells as a percentage of tumor area (≥ 1% [PDL1-positive]

For N=5 tumors, we don't have the HR status

PFS in the overall population of SAFIR02-Immuno



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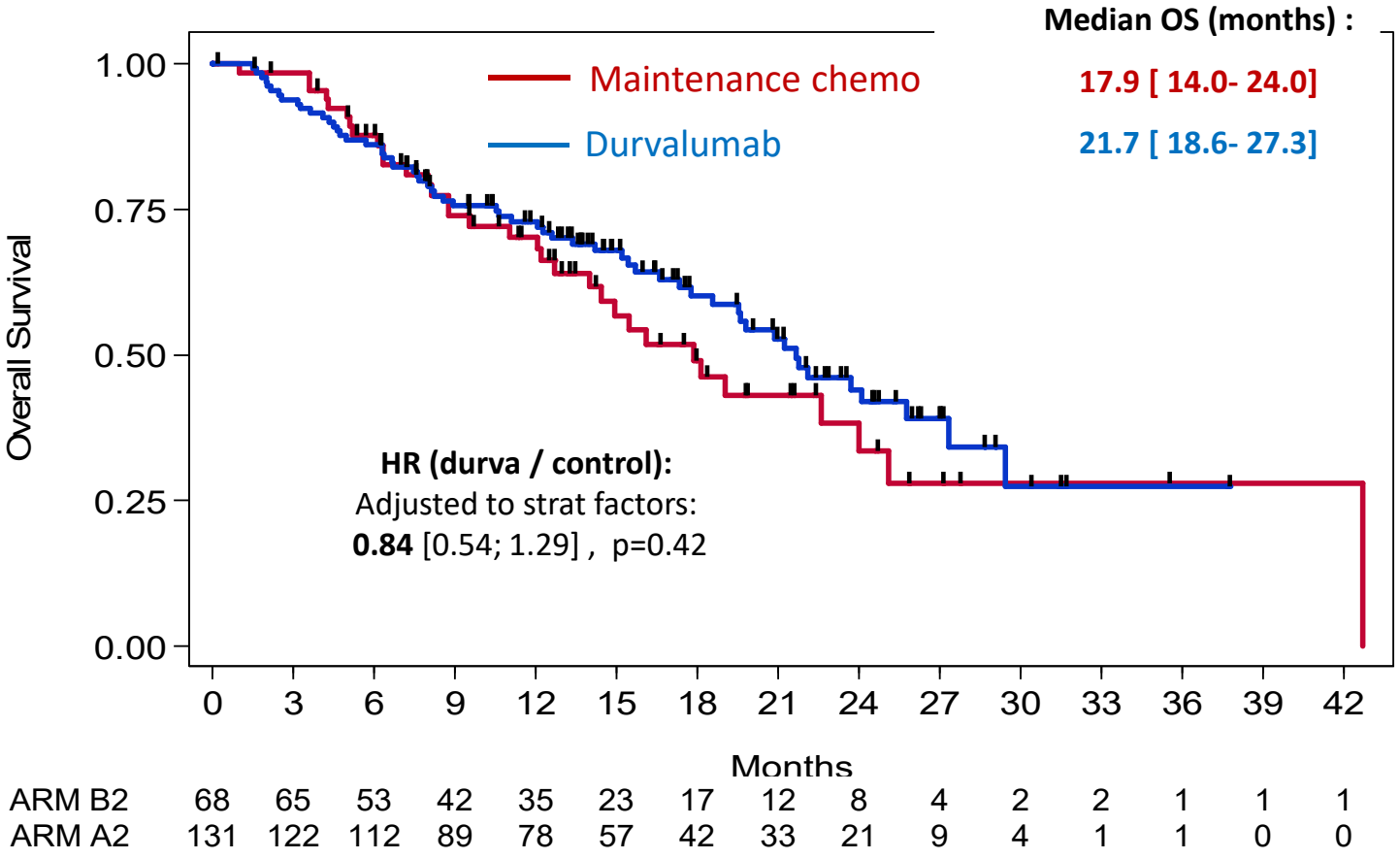
OS in the overall population of SAFIR02-Immuno



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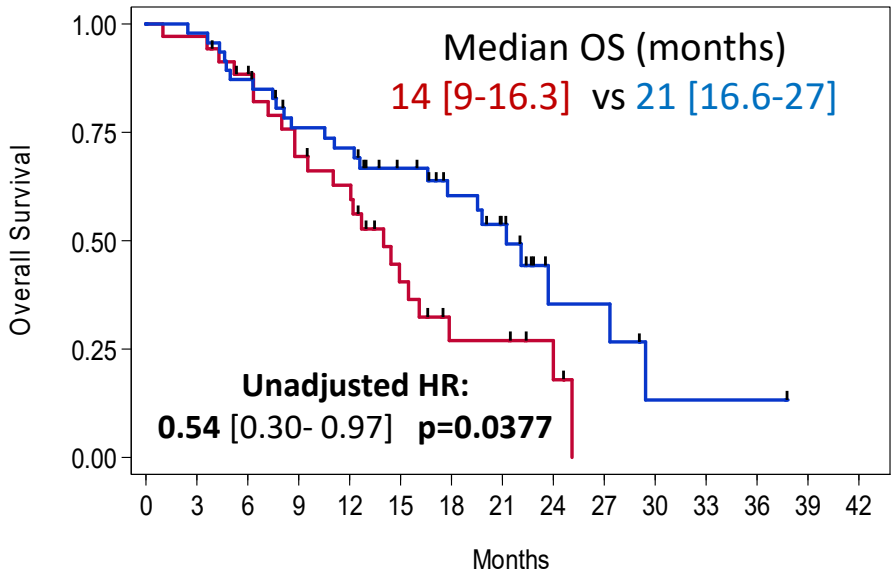
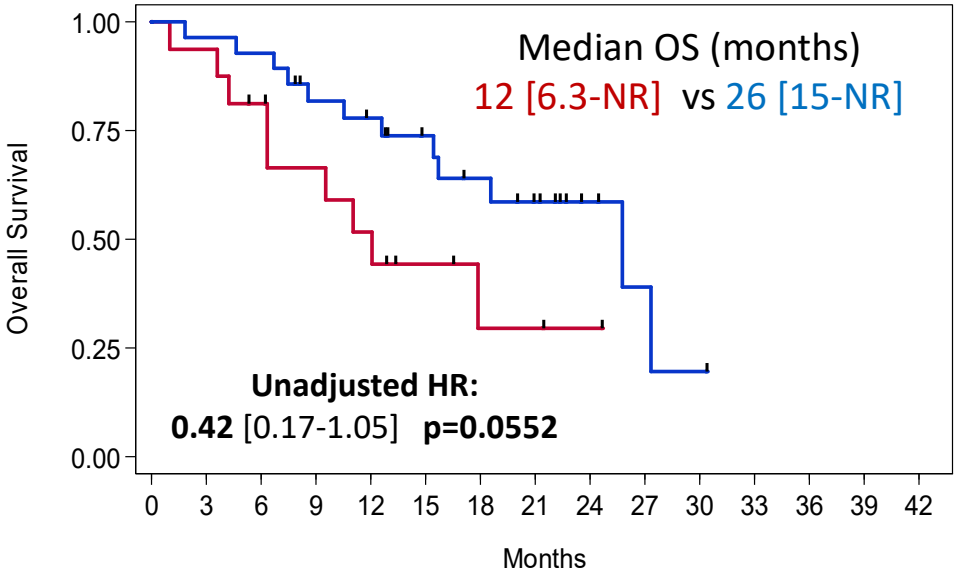
OS for patients with TNBC or PDL1+ tumors

TNBC (N=82)



ARM B2	35	34	28	22	19	10	5	5	3	0	0	0	0	0
ARM A2	47	46	41	33	31	24	18	13	4	4	1	1	1	0

PDL1+BC (N=44)



ARM B2	16	15	12	9	7	4	2	2	1	0	0	0		
ARM A2	28	27	26	21	19	15	12	9	4	2	1	0		

Maintenance CT

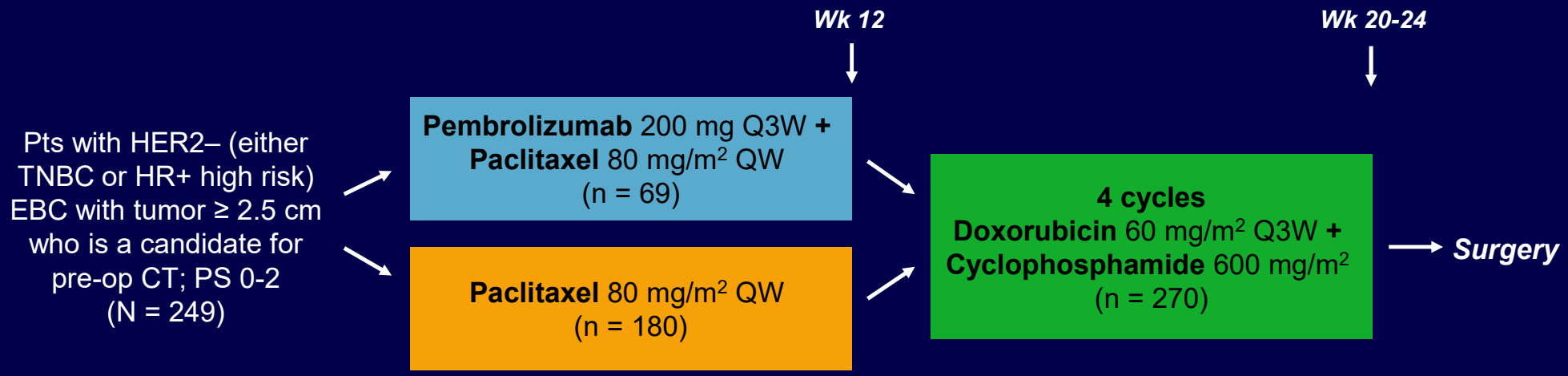
Durvalumab

Take Home Message – IO in mTNBC

- **Impassion 130 led to the approval of atezolizumab + nab-paclitaxel in PD-L1 positive mTNBC in the 1st line**
  - PFS advantage of 2.5 months in PD-L1+ (HR 0.62)
  - Interim OS advantage of 7 months in PD-L1+ (HR 0.71)
- **KEYNOTE-119 did not demonstrate improved overall survival with pembrolizumab monotherapy vs. chemotherapy in 2nd-3rd line mTNBC**
  - Suggestion of benefit in 22C3 CPS $\geq$ 20 in an exploratory analysis
- **The randomized phase II SAFIR-02 IMMUNO trial evaluated durvalumab maintenance vs. chemotherapy maintenance following 6-8 cycles of induction chemotherapy in 1st & 2nd line HER2- MBC**
  - Suggestion of improved OS in TNBC (HR 0.54) and PD-L1+ HER2- MBC (HR 0.42)
  - Should be further explored in a definitive trial
- **Still awaiting topline results from KEYNOTE-355**
  - Paclitaxel, nab-paclitaxel or gemcitabine/carboplatin + pembrolizumab or placebo

IO in the neoadjuvant treatment of TNBC

I-SPY 2 Pembrolizumab Randomization: Study Design



- Primary endpoint: pCR, no residual cancer in breast or lymph nodes (ypT0/is and ypN0)
  - Reported by Bayesian model that generates predictive probability of pCR rates
  - Reponses reported for HER2– "signatures": all HER2– pts; pts with TNBC; pts with HR+/HER2–

Nanda R, et al. ASCO 2017. Abstract 506.

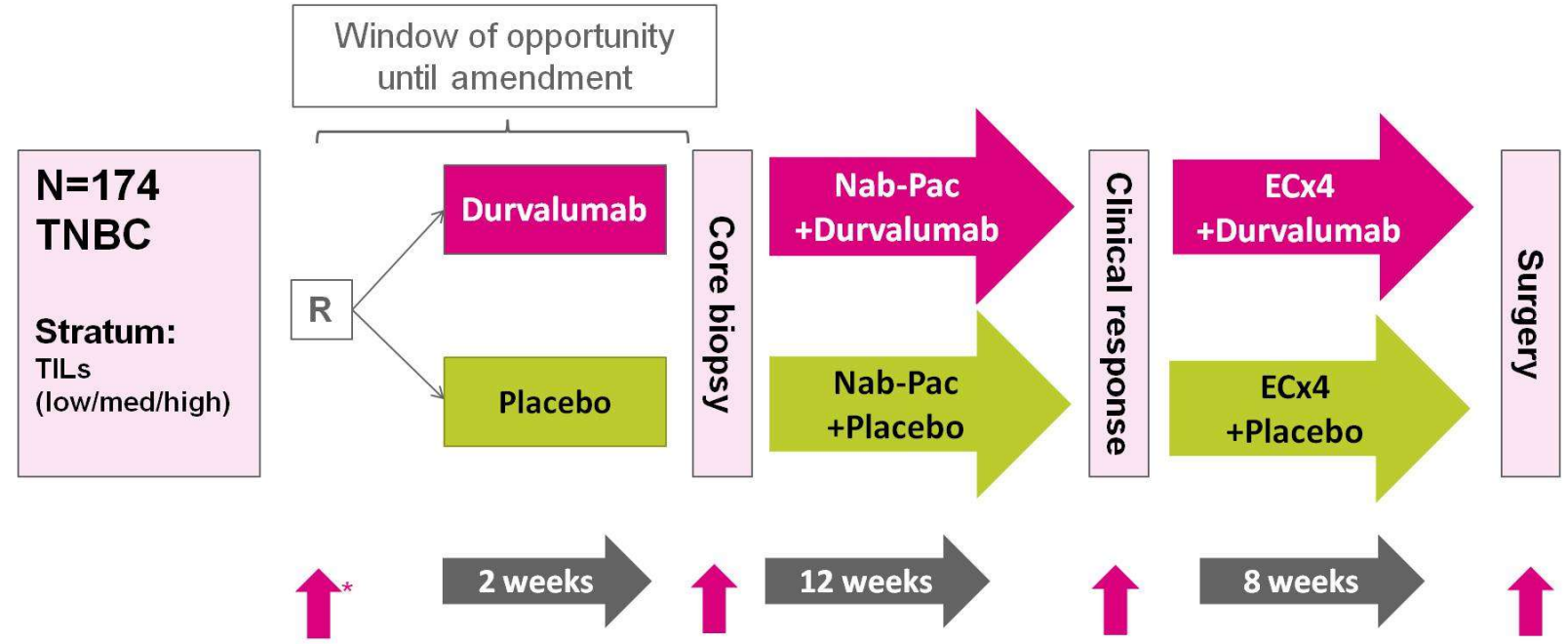
I-SPY 2 Pembrolizumab Randomization: Prediction of pCR (Primary Endpoint)

- I-SPY 2 uses Bayesian model to generate predictive probability of pCR rate by signature, actual pCR rates not reported
- Pembrolizumab + paclitaxel predicted to be superior to paclitaxel alone in these populations

HER2– Signature	Estimated pCR Rate (95% CI)		Probability of Superiority of Pembro + Paclitaxel vs Paclitaxel Alone	Predictive Probability of Success With Pembro + Paclitaxel in Phase III Trial
	Pembrolizumab + Paclitaxel	Paclitaxel Alone		
All HER2–	**0.46** (0.34-0.58)	**0.16** (0.06-0.27)	> 99%	99%
TNBC	**0.60** (0.43-0.78)	**0.20** (0.06-0.33)	> 99%	> 99%
HR+/HER2–	**0.34** (0.19-0.48)	**0.13** (0.03-0.24)	> 99%	88%

Nanda R, et al. ASCO 2017. Abstract 506.

GeparNUEVO Study Design



*Tissue: FFPE, fresh frozen;
Liquid biopsies: full blood; plasma, serum;

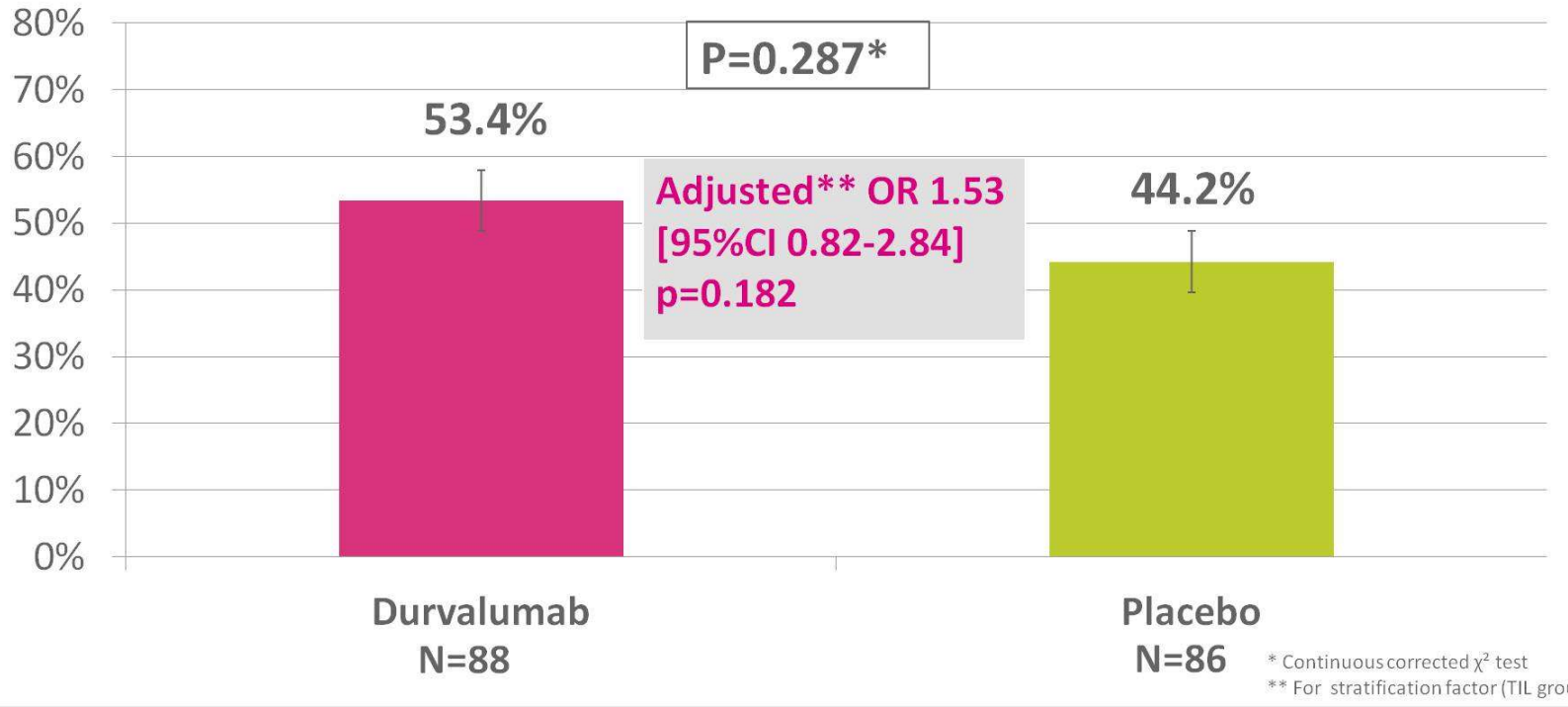
Durvalumab (0.75g) 1.5g d1q28

nab-Paclitaxel 125mg/m² weekly

Epirubicin 90mg/m²;
Cyclophosphamide 600mg/m² d1q14

Presented By Sibylle Loibl at 2018 ASCO Annual Meeting

Primary Endpoint - pathological complete response
pCR – ypT0, ypN0



* Continuous corrected χ^2 test
** For stratification factor (TIL groups)

Presented By Sibylle Loibl at 2018 ASCO Annual Meeting

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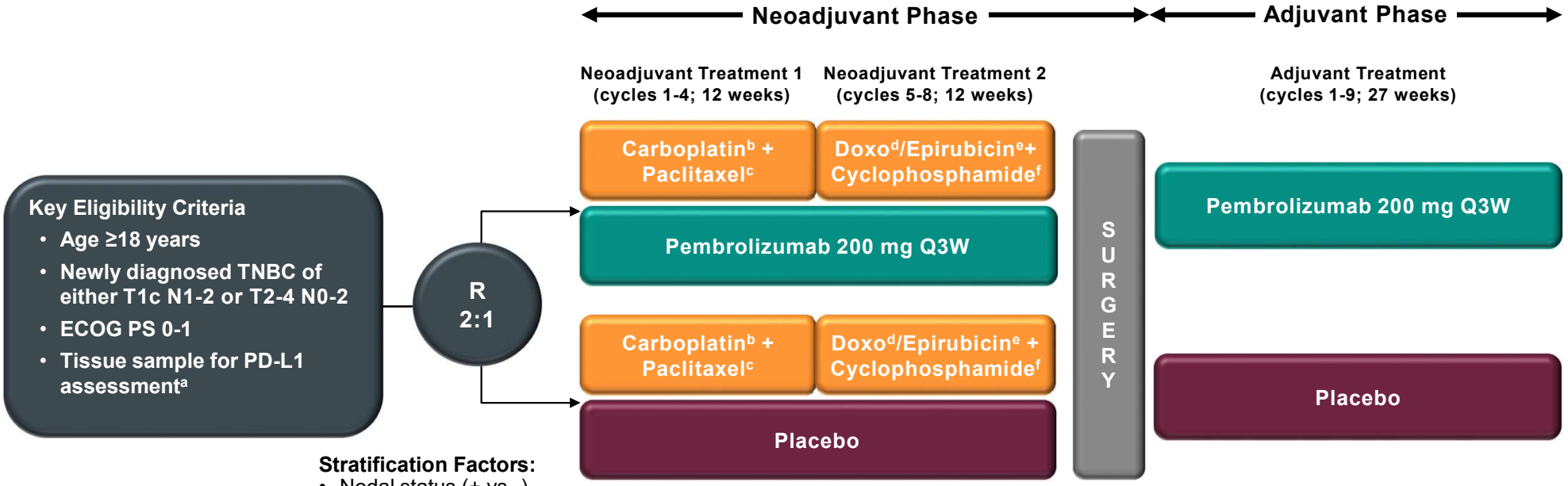
KEYNOTE-522: Phase 3 Study of Neoadjuvant Pembrolizumab + Chemotherapy versus Placebo + Chemotherapy, Followed by Adjuvant Pembrolizumab versus Placebo for Early Triple-Negative Breast Cancer: Pathologic Complete Response in Key Subgroups and by Treatment Exposure and Residual Cancer Burden

Peter Schmid[1], Yeon Hee Park[2], Marta Ferreira[3], Marie-Ange Mouret-Reynier[4], Seock-Ah Im[5], Jin-Hee Ahn[6], Maria Gion[7], Rina Hui[8], Sally Baron-Hay[9], Jean-Francois Boileau[10], Mei-Ching Liu[11], Nadia Harbeck[12], Masato Takahashi[13], Theodoros Foukakis[14], Peter A. Fasching[15], Fatima Cardoso[16], Jay Andersen[17], Michael Untch[18], Margarita Tokar[19], Florence Dalenc[20], Michael Danso[21], Debra Patt[22], Sherko Kümmel[23], Carsten Denkert[24], Lajos Pusztai[25], Jonas Bergh[14], Heather McArthur[26], Liyi Jia[27], Gursel Aktan[27], Vassiliki Karantza[27], Rebecca Dent[28], Javier Cortes[29], Joyce O'Shaughnessy[30]

1. Barts Cancer Institute, Centre for Experimental Cancer Medicine, London, UK; 2. Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea; 3. Instituto Português de Oncologia do Porto Francisco Gentil (IPO-Porto), Porto, Portugal; 4. Centre Jean-Perrin, Clermont-Ferrand, France; 5. Seoul National University Hospital, Cancer Research Institute, Seoul National University College of Medicine, Seoul, Republic of Korea; 6. Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea; 7. Ramon y Cajal University Hospital, Madrid, Spain; 8. Westmead Breast Cancer Institute, Westmead Hospital and the University of Sydney, Sydney, NSW, Australia; 9. Royal North Shore Hospital, Sydney, NSW, Australia; 10. McGill University, Jewish General Hospital Segal Cancer Centre, Montréal, Québec, Canada; 11. Koo Foundation Sun Yat-Sen Cancer Center, Taipei, Taiwan, Republic of China; 12. Breast Center, University of Munich (LMU), Munich, Germany; 13. Hokkaido Cancer Center, Sapporo, Japan; 14. Department of Oncology-Pathology, Karolinska Institutet and Breast Cancer Centre, Cancer theme, Karolinska University Hospital, Solna, Sweden; 15. University Hospital Erlangen, Comprehensive Cancer Center Erlangen-EMN, Erlangen, Germany; 16. Breast Unit, Champalimaud Clinical Center/Champalimaud Foundation, Lisbon, Portugal; 17. Compass Oncology, US Oncology, Portland, OR; 18. Breast Cancer Center, Helios Klinikum Berlin Buch, Berlin, Germany; 19. Soroka University Medical Center, Ben-Gurion University of the Negev, Beer-Sheva, Israel; 20. Institut Claudius-Regaud, IUCT-oncopôle, Toulouse, France; 21. Virginia Oncology Associates, Norfolk, VA, USA; 22. Texas Oncology, Austin, TX, USA; 23. Kliniken Essen-Mitte, Essen, Germany; 24 Philipps-University Marburg and University Hospital Marburg (UKGM), Marburg, Germany; 25. Yale School of Medicine, Yale Cancer Center, New Haven, CT, USA; 26. Cedars-Sinai Medical Center, Los Angeles, CA, USA; 27. Merck & Co., Inc., Kenilworth, NJ, USA; 28. National Cancer Center Singapore, Duke-NUS Medical School, Singapore; 29. IOB Institute of Oncology, Quiron Group; Vall d'Hebron Institute of Oncology (VHIO), Madrid & Barcelona, Spain; 30. Baylor University Medical Center, Texas Oncology, US Oncology, Dallas, TX, USA

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

KEYNOTE-522 Study Design (NCT03036488)



Stratification Factors:
- Nodal status (+ vs -)
- Tumor size (T1/T2 vs T3/T4)
- Carboplatin schedule (Q1W vs Q3W)

Neoadjuvant phase: starts from the first neoadjuvant treatment and ends after definitive surgery (post treatment included)

Adjuvant phase: starts from the first adjuvant treatment and includes radiation therapy as indicated (post treatment included)

[a]Must consist of at least 2 separate tumor cores from the primary tumor.
[b]Carboplatin dose was AUC 5 Q3W or AUC 1.5 Q1W.
[c]Paclitaxel dose was 80 mg/m^2 Q1W.
[d]Doxorubicin dose was 60 mg/m^2 Q3W.
[e]Epirubicin dose was 90 mg/m^2 Q3W.
[f]Cyclophosphamide dose was 600 mg/m^2 Q3W.

Study Endpoints

- Primary Endpoints
  - pCR (ypT0/Tis ypN0) assessed by local pathologist in ITT[a]
  - Event-free survival (EFS) assessed by investigator in ITT
- Secondary Endpoints
  - pCR as per alternative definitions (ypT0 ypN0 and ypT0/Tis)
  - Overall survival (OS)[b]
  - pCR, EFS[a] and OS[b] in the PD-L1–positive population[c]
  - Safety in all treated patients
- Exploratory Endpoints
  - Residual cancer burden (RCB)
  - pCR by patient subgroups
  - EFS by pCR[b]
  - pCR and EFS by TILs[b]

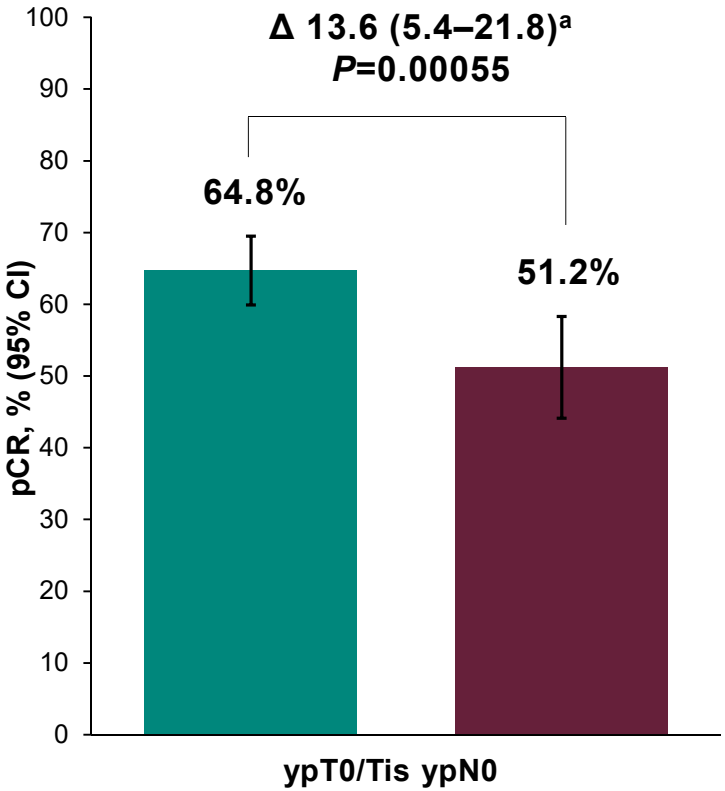
[a]Subjects without pCR data due to any reason or who received neoadjuvant chemotherapy not specified in the protocol were counted as non-pCR. [b]To be presented at a later date. [c]PD-L1 assessed at a central laboratory using the PD-L1 IHC 22C3 pharmDx assay and measured using the combined positive score (CPS; number of PD-L1–positive tumor cells, lymphocytes, and macrophages divided by total number of tumor cells x 100); PD-L1–positive = CPS ≥1.

Baseline Characteristics, ITT Population

Characteristic, n (%)	All Subjects, N = 602	
	Pembro + Chemo N = 401	Placebo + Chemo N = 201
Age, median (range), yrs	49 (22-80)	48 (24-79)
ECOG PS 1	73 (18.2)	28 (13.9)
PD-L1–positive[a]	334 (83.3)	164 (81.6)
Carboplatin schedule		
Q1W	167 (41.6)	83 (41.3)
Q3W	234 (58.4)	118 (58.7)
Tumor size		
T1/T2	296 (73.8)	148 (73.6)
T3/T4	105 (26.2)	53 (26.4)
Nodal involvement		
Positive	208 (51.9)	104 (51.7)
Negative	193 (48.1)	97 (48.3)

[a]PD-L1 assessed at a central laboratory using the PD-L1 IHC 22C3 pharmDx assay 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); PD-L1–positive = CPS ≥1. Data cutoff date: September 24, 2018.

Definitive pCR Analysis



- Definitive pCR analysis to test primary hypothesis of pCR based on prespecified first 602 patients (pre-calculated P value boundary for significance of 0.003)
- Consistent benefit seen with pCR defined as ypT0 ypN0 and ypT0/Tis

[a]Estimated treatment difference based on Miettinen & Nurminen method stratified by randomization stratification factors. Data cutoff date: September 24, 2018.

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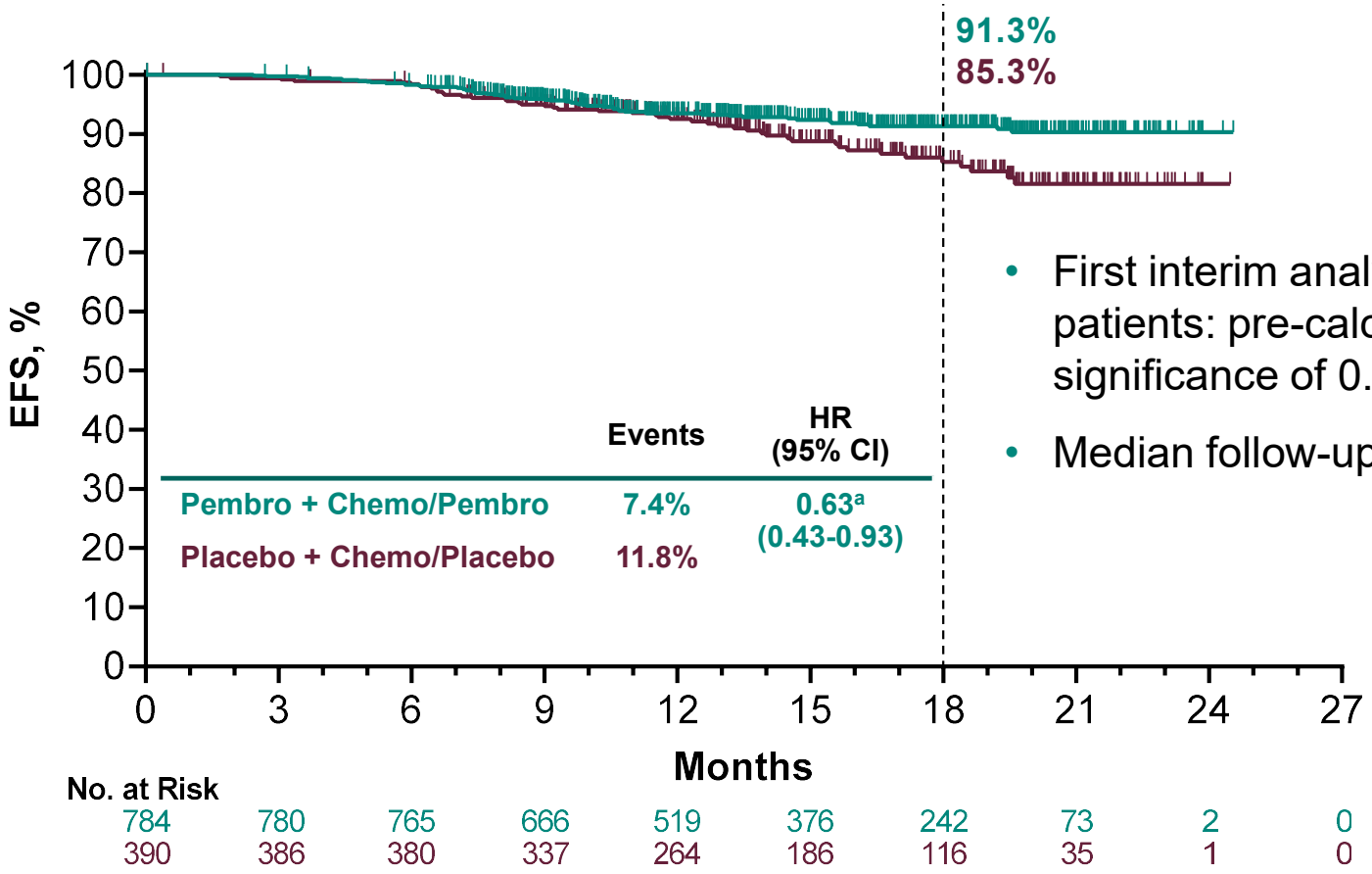
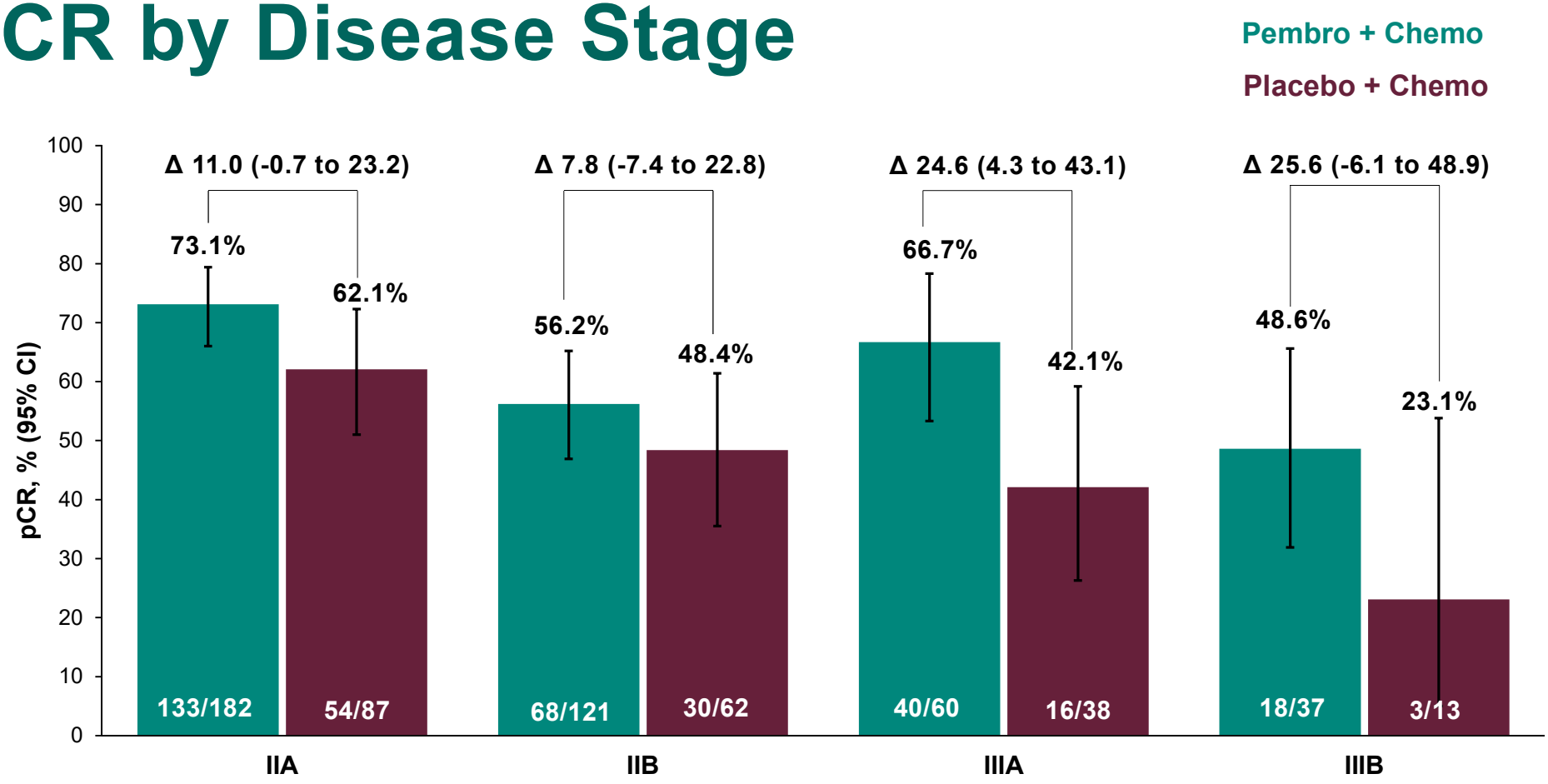
First Pre-planned Interim Analysis for EFS



- First interim analysis of EFS based on 1174 patients: pre-calculated P value boundary for significance of 0.000051 (HR <0.4)
- Median follow-up, 15.5 months

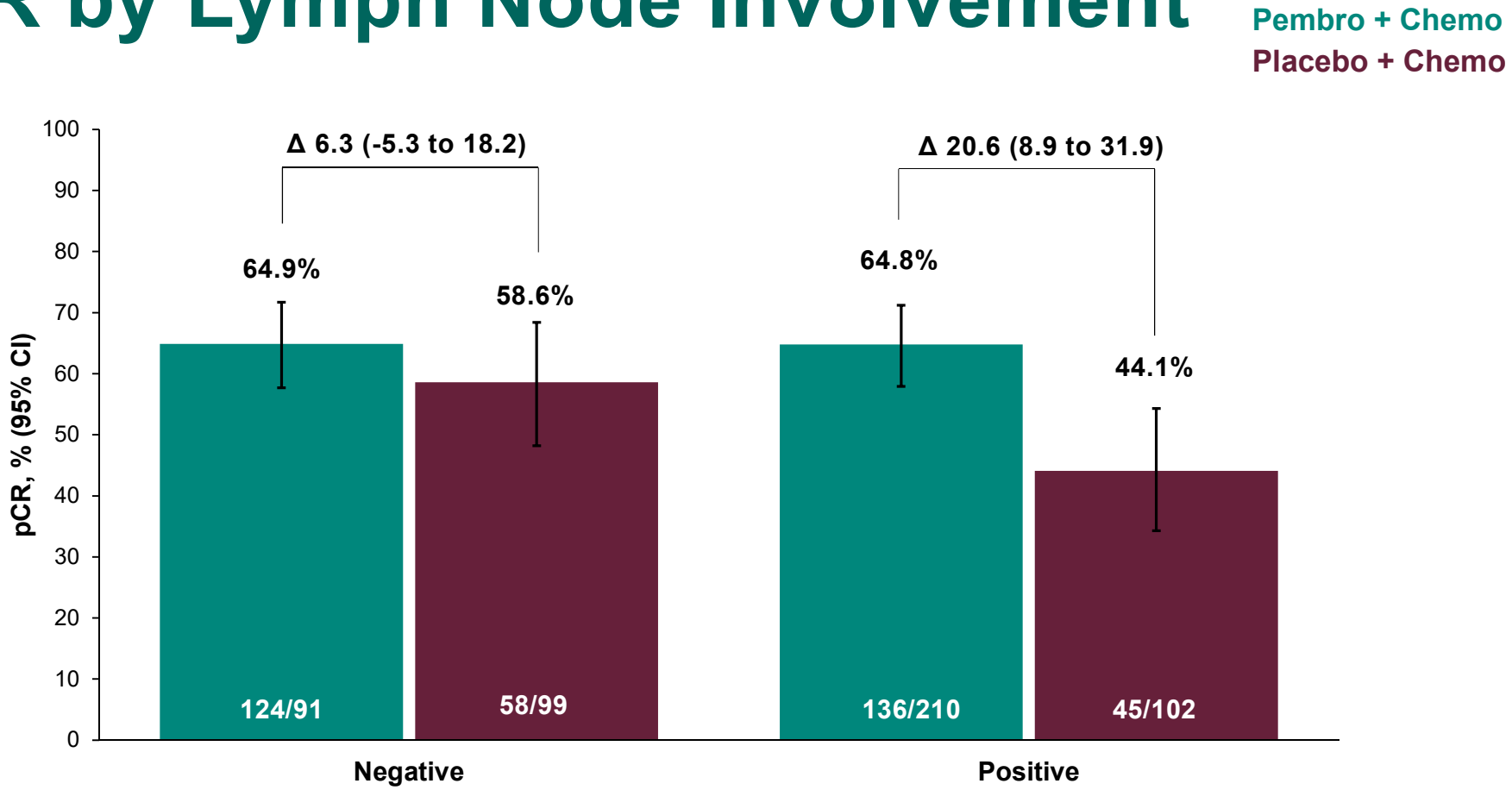
[a]Pre-specified P value boundary of 0.000051 not reached at this analysis (the first interim analysis of EFS). Hazard ratio (CI) analyzed based on a Cox regression model with treatment as a covariate stratified by the randomization stratification factors. Data cutoff April 24, 2019.

pCR by Disease Stage



Post-hoc analysis. Estimated treatment difference based on unstratified Miettinen & Nurminen method. Data cutoff date: September 24, 2018.

pCR by Lymph Node Involvement



Pre-specified analysis. Lymph node involvement was determined by the study investigator by physical exam, sonography/MRI and/or biopsy. Estimated treatment difference based on unstratified Miettinen & Nurminen method. Data cutoff date: September 24, 2018.

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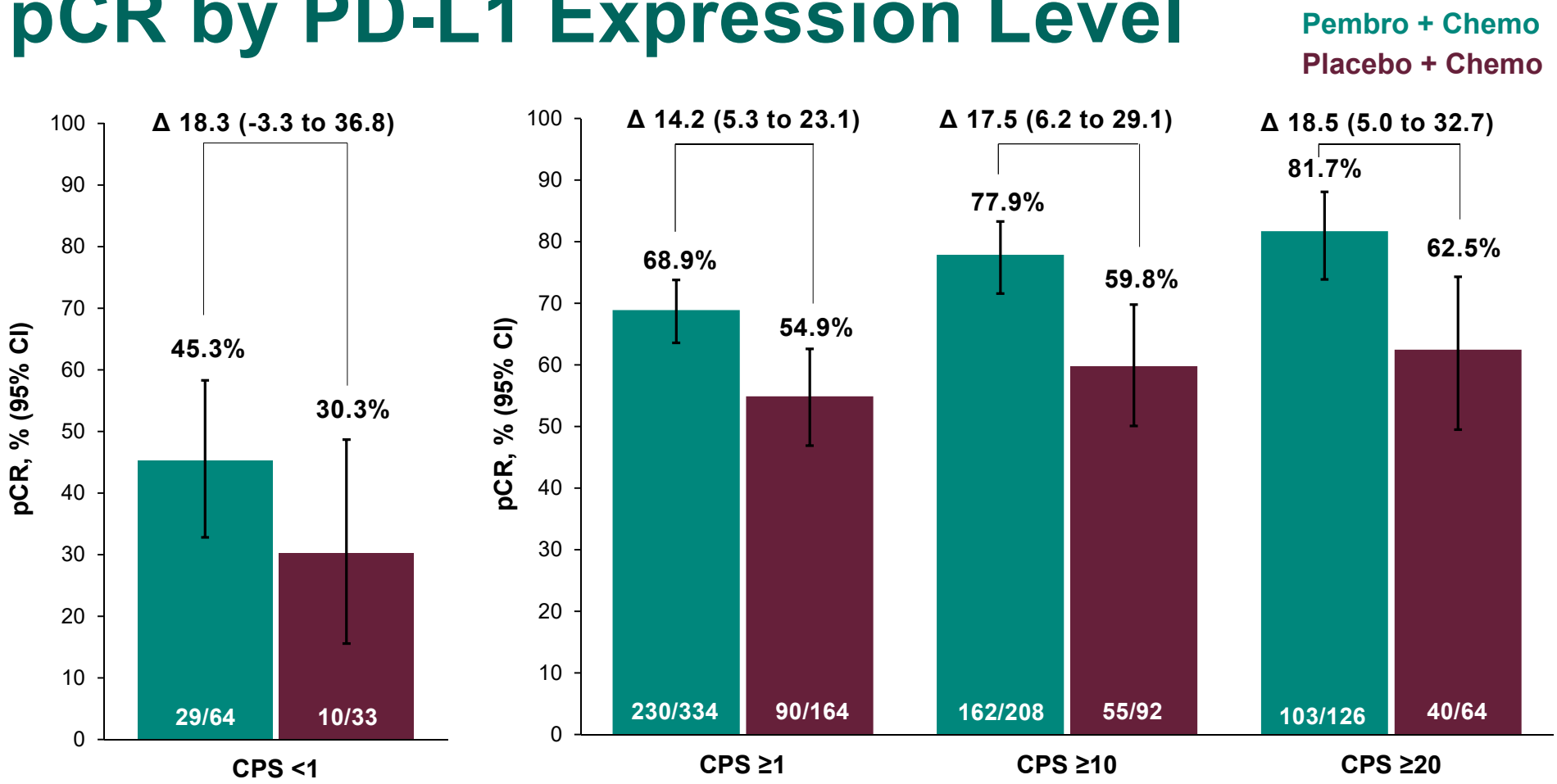
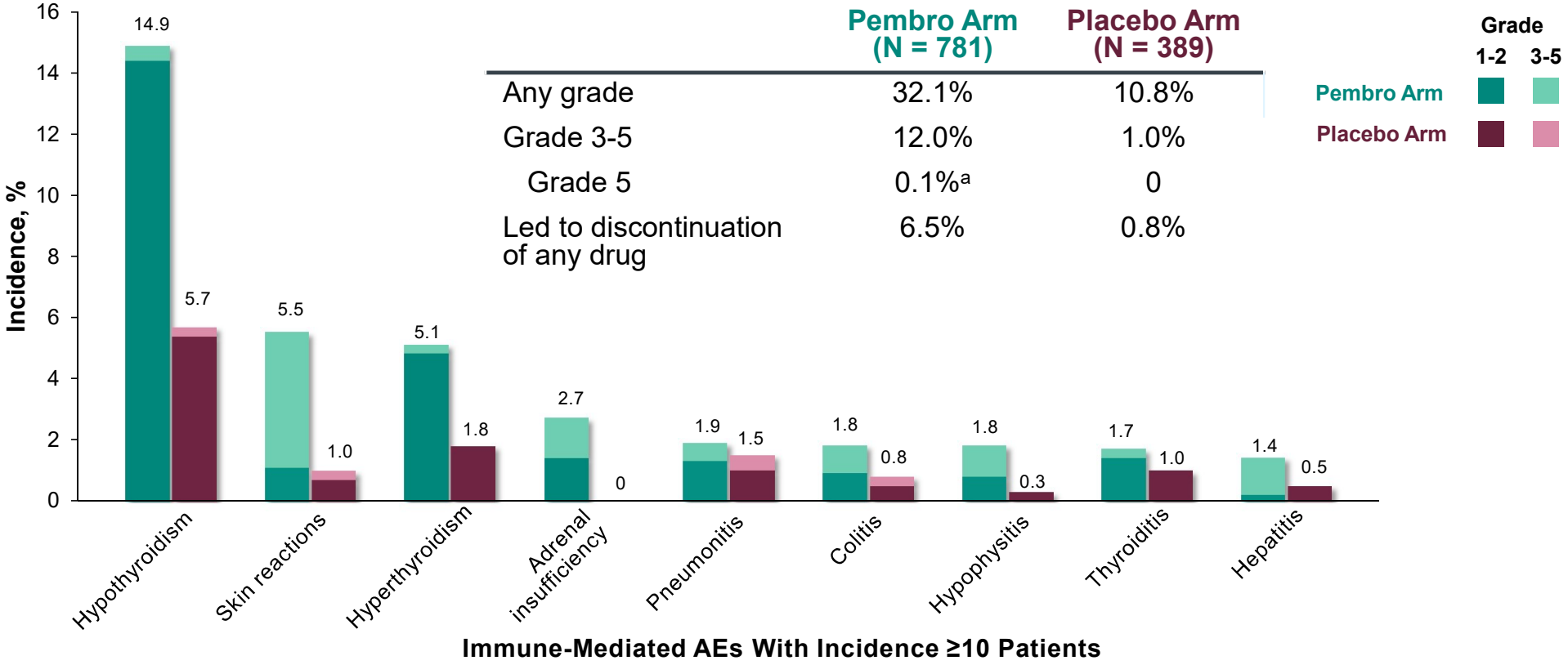
pCR by PD-L1 Expression Level



Pre-specified analysis. PD-L1 assessed at a central laboratory using the PD-L1 IHC 22C3 pharmDx assay and measured using CPS; number of PD-L1–positive tumor cells, lymphocytes, and macrophages divided by total number of tumor cells x 100); PD-L1–positive = CPS ≥1. Estimated treatment difference based on Miettinen & Nurminen method stratified by nodal status (positive vs negative), tumor size (T1/T2 vs T3/T4) and choice of carboplatin (Q3W vs QW). Data cutoff date: September 24, 2018.

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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Pathologic complete response (pCR) to neoadjuvant treatment with or without atezolizumab in triple negative, early high-risk and locally advanced breast cancer. NeoTRIPaPDL1 Michelangelo randomized study

Luca Gianni, Chiun-Sheng Huang, Daniel Egle, Begoña Bermejo, Claudio Zamagni, Marc Thill, Anton Anton, Stefania Zambelli, Giampaolo Bianchini, Stefania Russo, Eva Maria Ciruelos, Richard Greil, Vladimir Semiglazov, Marco Colleoni, Catherine Kelly, Gabriella Mariani, Lucia Del Mastro, Ilaria Maffeis, Pinuccia Valagussa, Giuseppe Viale

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

Design of the NeoTRIP trial

*HER-2 negative, ER and PgR negative early high-risk **(T1cN1; T2N1; T3N0)** or locally advanced unilateral breast cancer

R

Carboplatin (AUC2) + *nab*-paclitaxel (125 mg/m²) weekly for 2 wks every 3; 8 cy → **S**

Carboplatin (AUC2) + *nab*-paclitaxel (125 mg/m²) weekly for 2 wks every 3; 8 cy **+ Atezolizumab (1200 mg)** day 1 every 3 wks for 8 cycles → **S**

*Estrogen receptor, progesterone receptor, HER2 and PD-L1 were centrally assessed before randomization

Tumour & Blood banked for correlative studies

Aims of Study

Open-label, randomized phase III trial

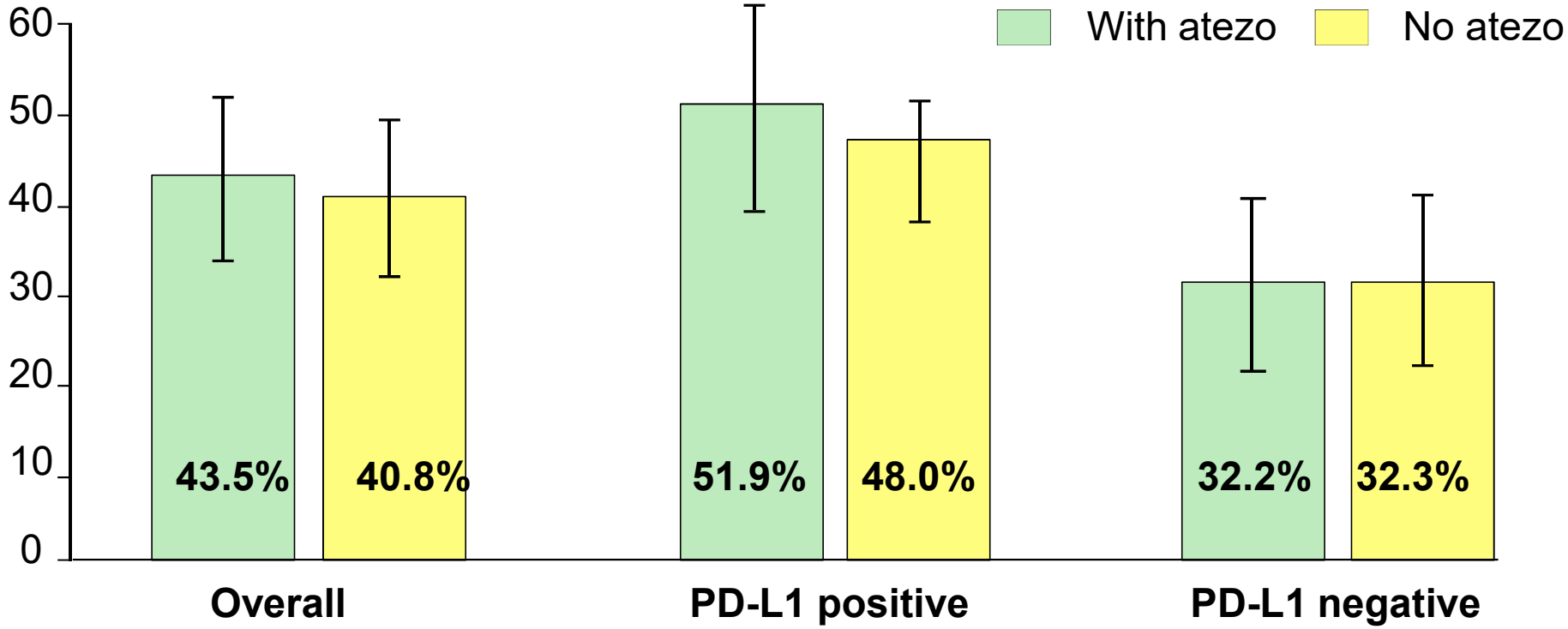
- ***Primary aim*:*** event-free survival (**EFS**) at 5 years after randomization of the last patient
- ***Key secondary aim: rate of pCR*** (as absence of invasive cells in breast and lymph nodes).
- The primary population for all efficacy endpoints is the **ITT (intent-to-treat) population**
- Other secondary aims: tolerability of the regimens; studies on putative predictive markers of benefit and/or resistance to the study regimens

**** Sample size was calculated for the primary endpoint of EFS***

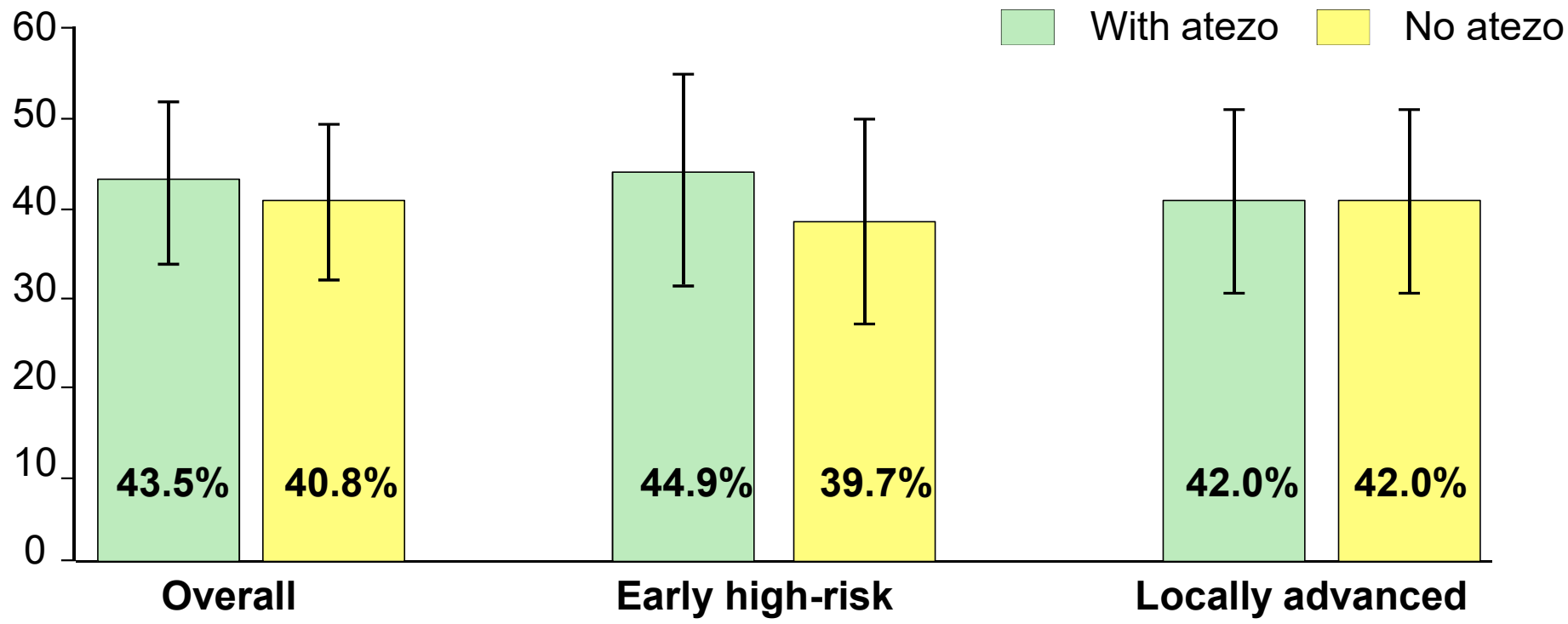
Main Characteristics at Randomization - ITT

		No atezo (142)	With atezo (138)	Total (280)
Disease stage	Early high-risk	73 (51%)	69 (50%)	142 (51%)
	Locally advanced	69 (49%)	69 (50%)	138 (49%)
PD-L1	Positive	77 (54%)	79 (57%)	156 (56%)
	Negative	65 (46%)	59 (43%)	124 (44%)
Median age in yr (range)		50 (24-77)	49.5 (25-79)	50 (24-79)
T stage	cT1c	8 (6%)	13 (9%)	21 (7.5%)
	cT2	75 (53%)	61 (44%)	136 (49%)
	cT3	41 (29%)	47 (34%)	88 (31%)
	cT4a-d	18 (13%)	17 (12%)	35 (12.5%)
Nodal status	cN0	19 (13%)	18 (13%)	37 (13%)
	cN1	79 (56%)	85 (62%)	164 (59%)
	cN2	22 (15.5%)	16 (12%)	38 (14%)
	cN3	22 (15.5%)	19 (14%)	41 (15%)

pCR rate and *PD-L1 expression*



pCR rate and *disease stage*



Safety

	With atezo	No atezo
ITT population	138	142
Safety population (all patients who received ≥ 1 dose)	138	140
Treatment-related AEs		
- Any grade	97.8%	98.6%
- Grade ≥ 3	77.5%	70.0%
- Serious Adverse Events	18.1%*	5.7%*
- Led to death (unknown causes)	0.7%	-
- Led to treatment discontinuation	25.4%	25.0%
(median # cycles before discontinuation with ranges)	6 (1-7)	6 (1-7)

*P = 0.003

Take Home Message:

- **Role of PD-1/PD-L1 addition in the neoadjuvant treatment of TNBC remains undefined**

- **KEYNOTE-522 demonstrated a 13.6% improvement in pCR with pembrolizumab addition**
  - EFS 91.3% vs. 85.3% at 18 mos -> PRELIMINARY, longer term FU needed
  - PD-L1 positive tumors achieved higher rates of pCR
  - Relative benefit of pembrolizumab was higher in PD-L1 negative

- **NeoTRIP showed no pCR benefit with atezolizumab addition**
  - Evaluated an anthracycline-free chemotherapy backbone, included more locally advanced disease
  - Is PD-L1 inhibition different to PD-1 inhibition?

- **Cost, risk of overtreatment & potential lifelong toxicities are major concerns**

Hereditary Breast Cancer

Abstract	Presenter	Title
GS6-03	Tung	TBCRC 031: A randomized phase II study of preoperative cisplatin (CDDP) vs doxorubicin & cyclophosphamide (AC) in germline *BRCA* mutation carriers with newly diagnosed breast cancer (INFORM)
PD4-01	Arun	First-line veliparib plus carboplatin/paclitaxel in patients with HER2-negative advanced/metastatic *gBRCA*-associated breast cancer: planned subgroup analysis from the phase 3 BROCADE3 trial

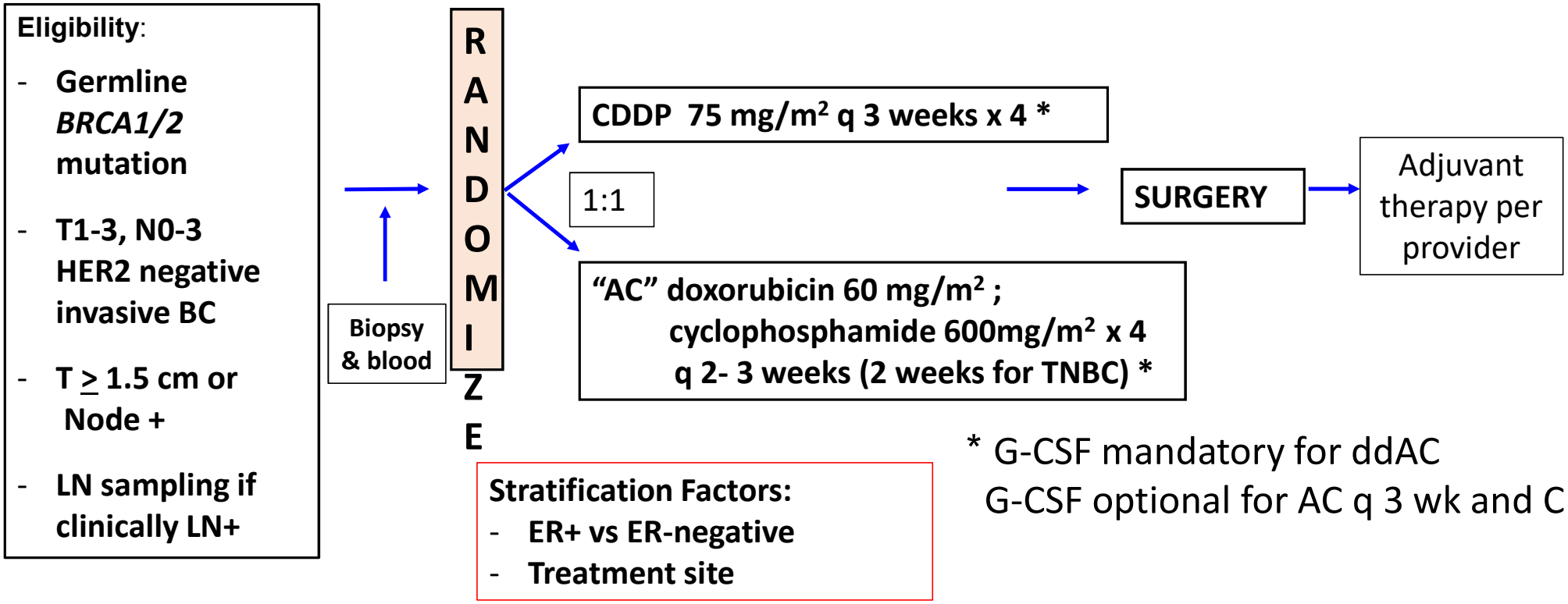
Role of neoadjuvant platinum monotherapy in early stage gBRCA1/2 breast cancer?

Role of chemotherapy + PARPi in 1st-3rd line gBRCA1/2 MBC?

TBCRC 031: A randomized phase II study of preoperative cisplatin (CDDP) vs doxorubicin & cyclophosphamide (AC) in germline *BRCA* mutation carriers with newly diagnosed breast cancer (the INFORM trial)

Nadine Tung, Banu Arun, Erin Hofstatter, Michele R Hacker, Deborah L Toppmeyer, Steven J Isakoff, Virginia Borges, Robert D Legare, Claudine Isaacs, Antonio C. Wolff, Paul Kelly Marcom, Erica L Mayer, Paulina B Lange, Andrew J Goss, Colby Jenkins, Ian E Krop, Eric P Winer, Stuart J Schnitt, Judy E Garber

TBCRC 031 (INFORM): A randomized, multicenter phase II study of preoperative CDDP vs AC in gBRCA+ Breast Cancer



Baseline Clinical Characteristics

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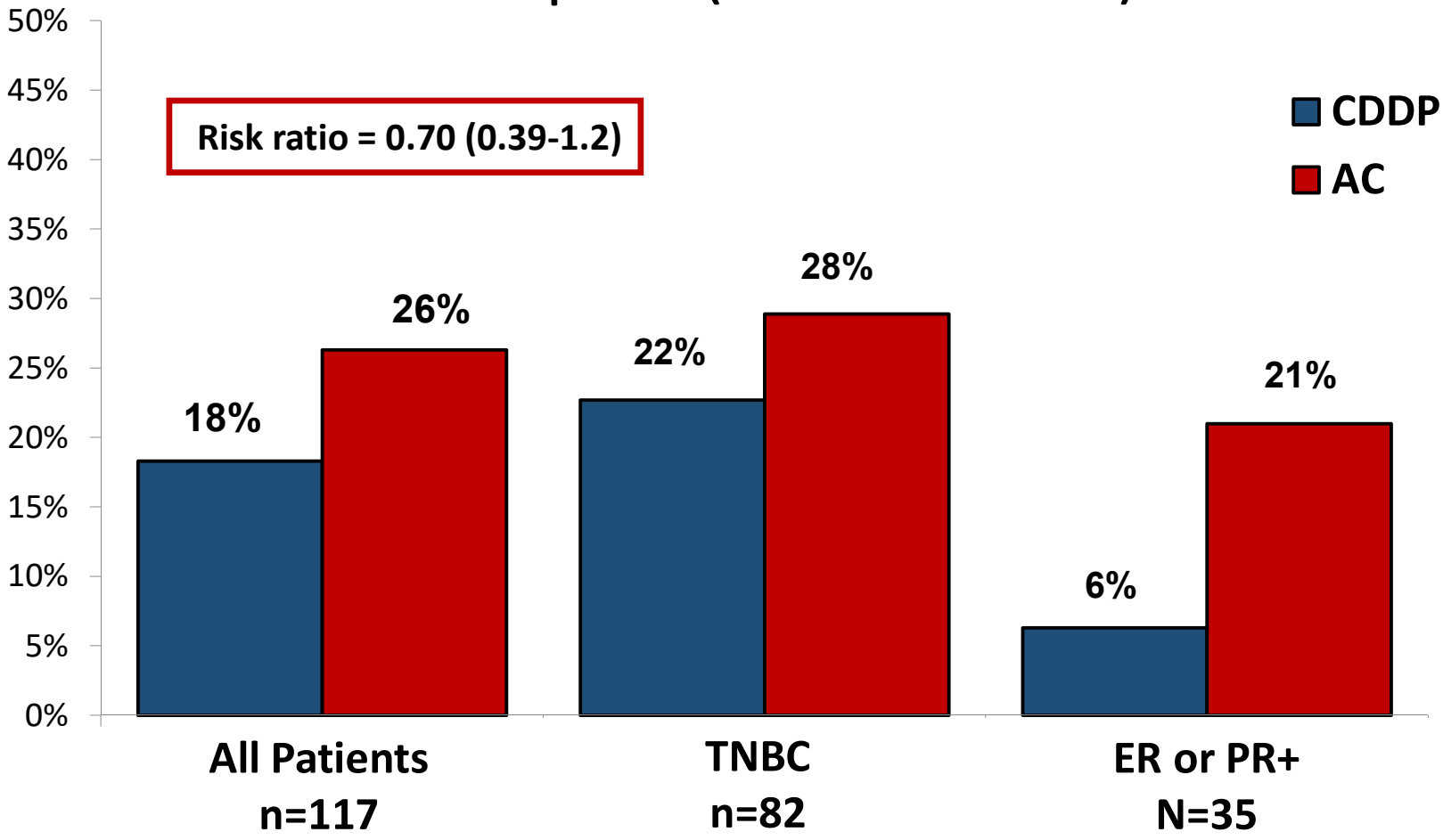
	All patients N=118	CDDP N=60	AC N=58
Age (yrs)—mean ±SD	42 ±10	40 ±9	44 ±10
BRCA status			
BRCA1	69%	73%	64%
BRCA2	30%	25%	34%
BRCA1 & BRCA2	2%	2%	2%
cT stage			
T1	25%	20%	29%
T2	56%	58%	53%
T3	19%	20%	17%
Node status			
Positive	45%	48%	41%
Negative	55%	52%	59%
Stage			
1	19%	13%	26%
2	63%	67%	59%
3	18%	20%	16%

Baseline Tumor Characteristics

	All patients N=118	CDDP N=60	AC N=58
ER/PR status (≤ or > 10%)			
TNBC	70%	73%	67%
ER or PR >10%	30%	27%	33%
Histology			
Invasive ductal	92%	95%	90%
Invasive lobular	3%	3%	3%
Mixed/other	4%	2%	7%
Histologic grade			
1	3%	3%	2%
2	19%	18%	21%
3	77%	77%	78%
Lymphocytic infiltrate			
Moderate/marked	36%	35%	38%
Scant/absent	58%	60%	57%
Stromal TILs (%)- median (IQR)	10 (1-20)	10 (3-30)	10 (1-20)

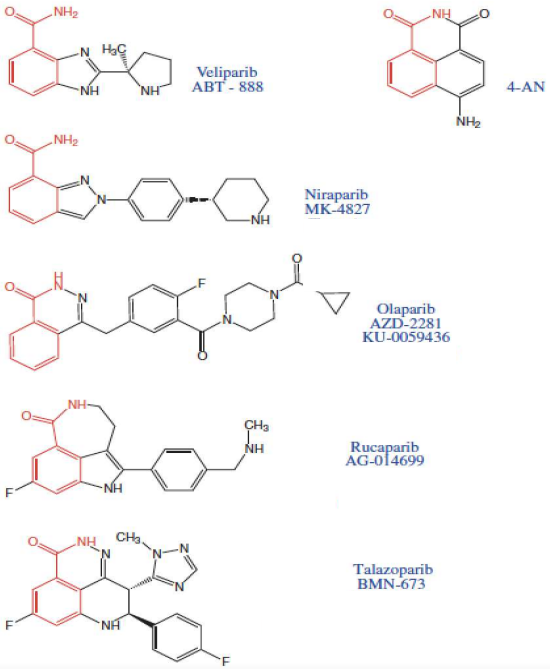
pCR (CDDP vs AC)



Highlights the importance of conducting randomized trials

PARP inhibition in *gBRCA1/2* mutant MBC

PARP Inhibitors



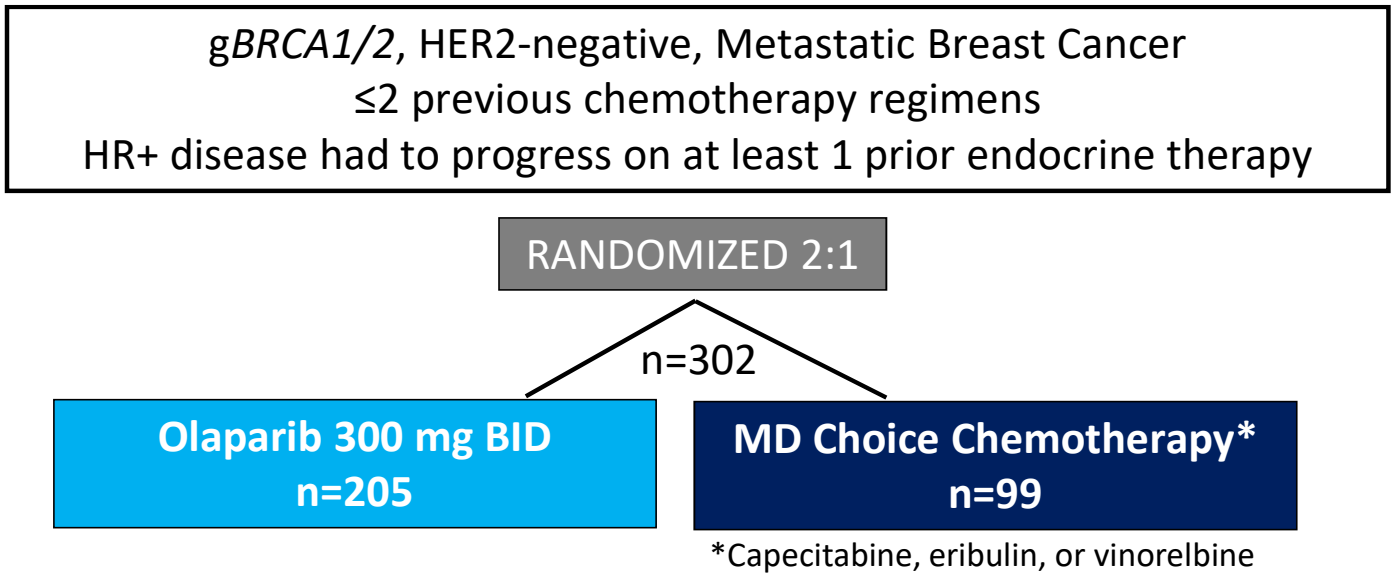
- **Veliparib – Phase III data presented 9/2019**
- **Niraparib**
- **Olaparib - Approved 1/12/2018**
- **Rucaparib**
- **Talazoparib - Approved 10/16/2018**

★ **NCCN guidelines now endorse germline *BRCA1/2* mutation testing for all HER2- MBC patients**

Murai J, Pommier Y. Classification of PARP Inhibitors Based on PARP Trapping and Catalytic Inhibition, and Rationale for Combinations with Topoisomerase I Inhibitors and Alkylating Agents. In: Curtin NJ, Sharma RA, eds. *PARP Inhibitors for Cancer Therapy*. New York: Springer International Publishing;2015:261-274.

Phase III OlympiAD Trial

Olaparib in gBRCA1/2 Mutant Advanced Breast Cancer



- **~50% TNBC**
- **27-29% Prior platinum**
- **Platinum resistant excluded**

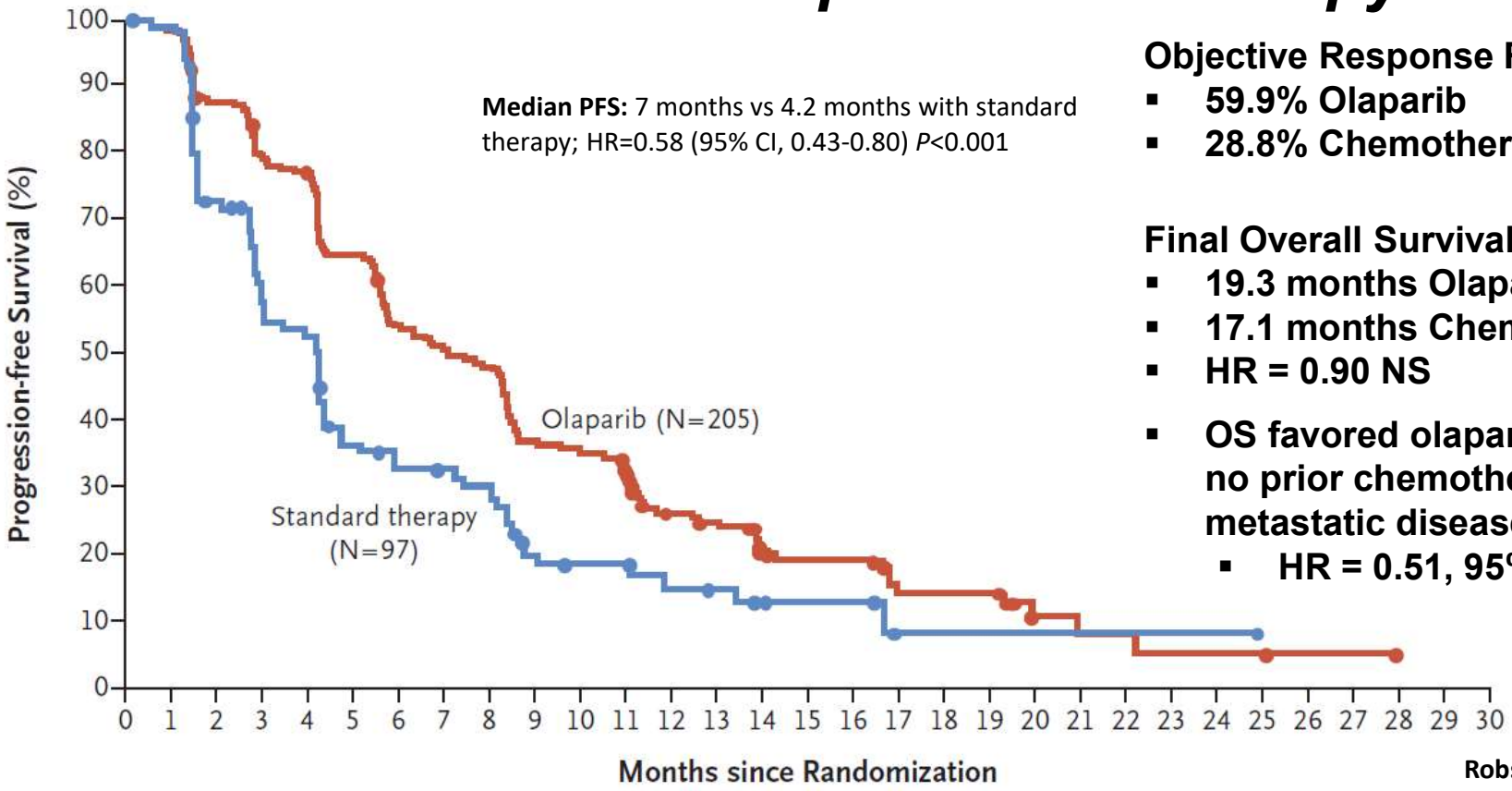
Primary endpoint: PFS (blinded central review)

Secondary endpoints: Safety, OS, ORR, and health-related QOL scores

Robson M, et al. *NEJM*. 2017.

Phase III OlympiAD Trial

PFS with Olaparib Monotherapy



Median PFS: 7 months vs 4.2 months with standard therapy; HR=0.58 (95% CI, 0.43-0.80) *P*<0.001

Objective Response Rate

- **59.9% Olaparib**
- **28.8% Chemotherapy**

Final Overall Survival

- **19.3 months Olaparib**
- **17.1 months Chemotherapy**
- **HR = 0.90 NS**
- **OS favored olaparib in patients with no prior chemotherapy for metastatic disease**
  - **HR = 0.51, 95% CI 0.29-0.90**

Robson M, et al. *NEJM,* 2017
Robson, M et al. *Ann Oncol*, 2019

Phase III EMBRACA Trial

Talazoparib in gBRCA1/2 Mutant Advanced Breast Cancer

g*BRCA1/2*, HER2-negative, Locally Advanced or Metastatic breast cancer
≤3 previous chemotherapy regimens
No limit on number of prior endocrine therapies

RANDOMIZED 2:1

N=431

Talazoparib 1 mg daily n=287

MD Choice Chemotherapy n=144**

**Capecitabine, eribulin, vinorelbine, or gemcitabine

- **~45% TNBC**
- **16-21% prior platinum**
- **Platinum resistant excluded**

Primary Endpoint: PFS (blinded central review)

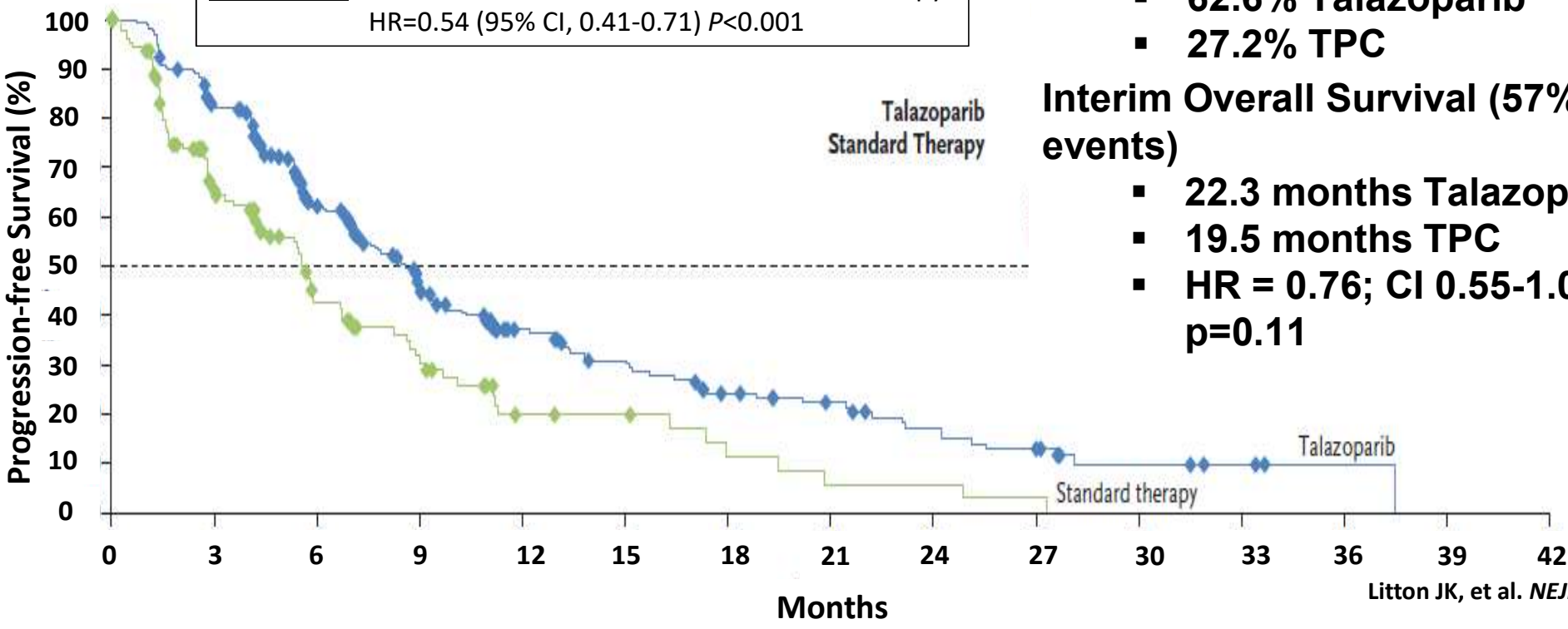
Secondary Endpoints: OS, ORR, CBR24, Safety

Litton J, et al. *NEJM, 2018*

Phase III EMBRACA Trial

PFS with Talazoparib Monotherapy

Median PFS: **8.6 months** vs **5.6 months** with standard therapy
HR=0.54 (95% CI, 0.41-0.71) *P*<0.001



Objective Response Rate

- **62.6% Talazoparib**
- **27.2% TPC**

Interim Overall Survival (57% of events)

- **22.3 months Talazoparib**
- **19.5 months TPC**
- **HR = 0.76; CI 0.55-1.06; p=0.11**

Litton JK, et al. *NEJM,* 2018.

Phase III BROCADE 3 Trial

Carboplatin + Paclitaxel +/- Veliparib

Patient Population

- Advanced HER2-negative breast cancer
- Germline *BRCA1* or *BRCA2* mutation
- ≤2 prior lines cytotoxic therapy for metastatic disease
- ≤1 prior lines of platinum; no progression ≤12 months of completing

Stratification Factors

- Hormone Receptor Expression
- Prior Platinum
- CNS Metastasis

2:1 Randomization
N=513

Veliparib + Carboplatin/paclitaxel

Placebo + Carboplatin/paclitaxel

Treat to progression:
If carboplatin and paclitaxel were discontinued prior to progression, dosing of veliparib/placebo increased to 300mg BID continuous, and then 400mg BID if tolerated

Optional open-label crossover to veliparib

Primary Endpoint:
Investigator-assessed PFS per RECIST 1.1

21-Day Cycles:

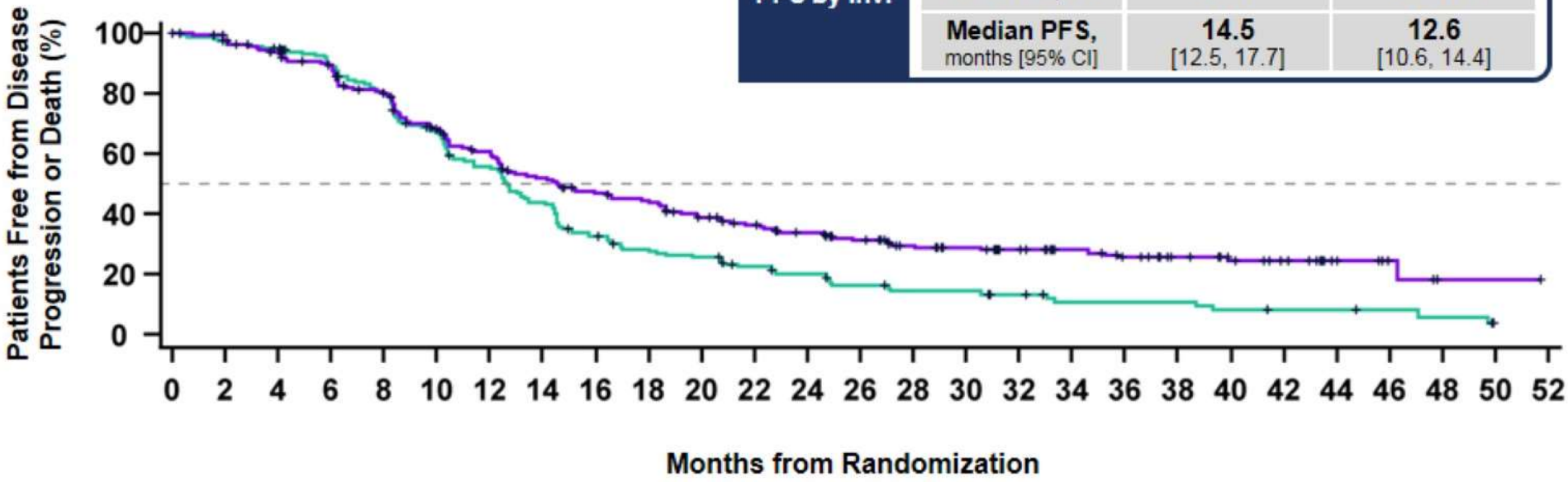
- Carboplatin (C): AUC 6 on Day 1
- Paclitaxel (P): 80 mg/m² on Days 1, 8, 15
- Veliparib or Placebo: 120mg BID on Days -2 to 5

Dieras V, et al. ESMO 2019

Primary Endpoint: PFS by Investigator Assessment

HR 0.705
[95% CI 0.566-0.877], p = 0.002

PFS by Inv.		Veliparib + C/P	Placebo + C/P
	PFS Events, n/N	217/337	132/172
	Median PFS, months [95% CI]	**14.5** [12.5, 17.7]	**12.6** [10.6, 14.4]

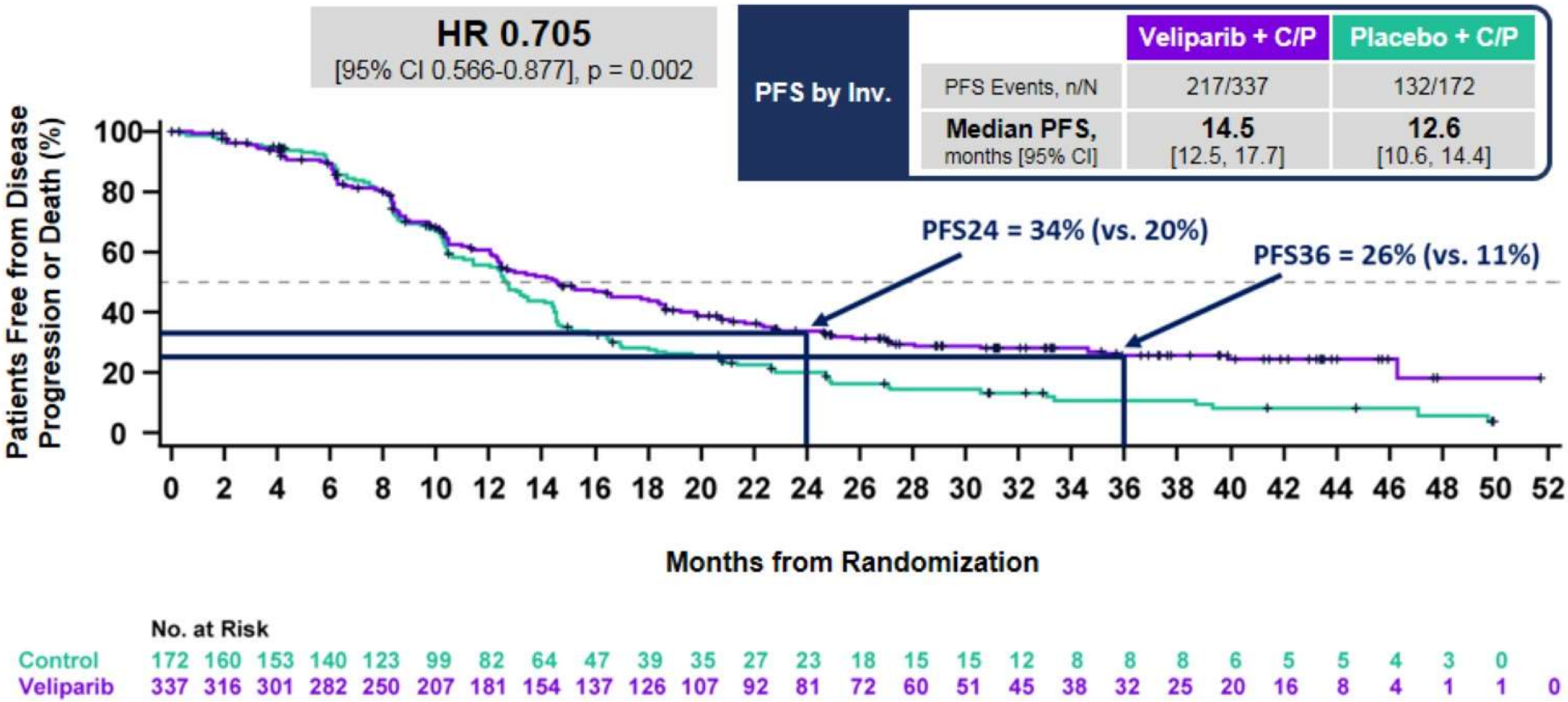


No. at Risk

Control	172	160	153	140	123	99	82	64	47	39	35	27	23	18	15	15	12	8	8	8	6	5	5	4	3	0	
Veliparib	337	316	301	282	250	207	181	154	137	126	107	92	81	72	60	51	45	38	32	25	20	16	8	4	1	1	0

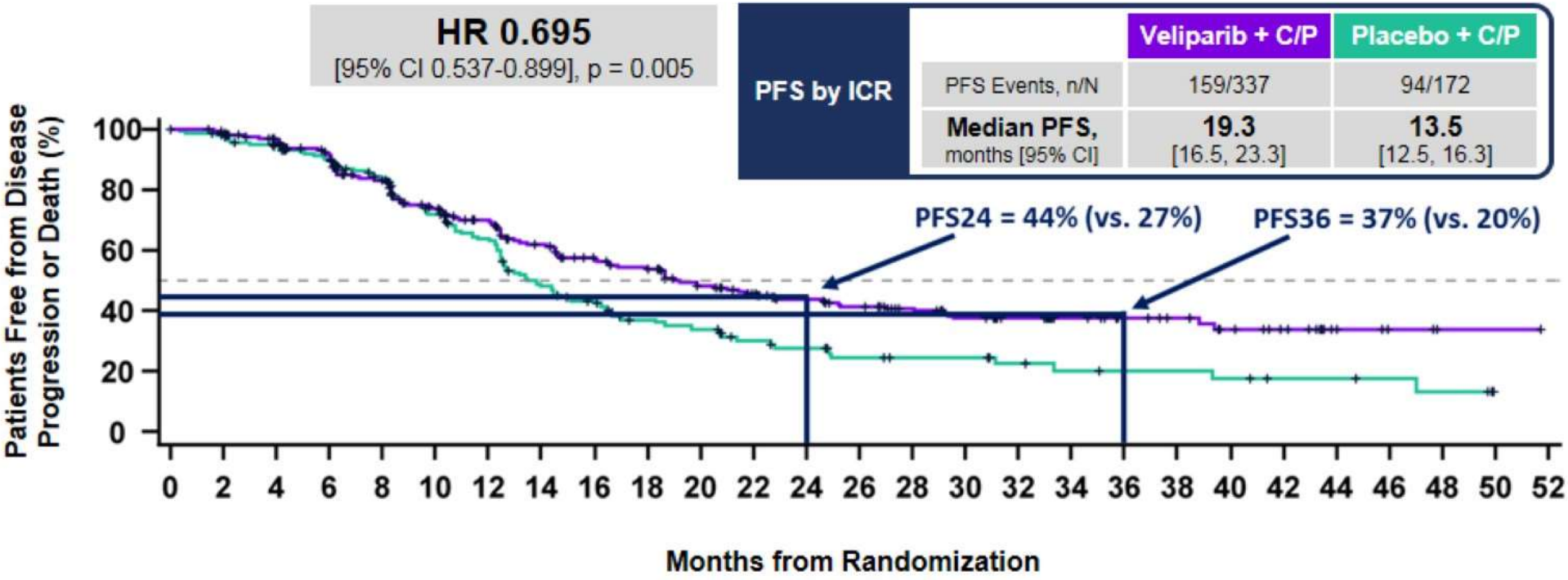
Dieras V, et al. ESMO 2019

Primary Endpoint: PFS by Investigator Assessment



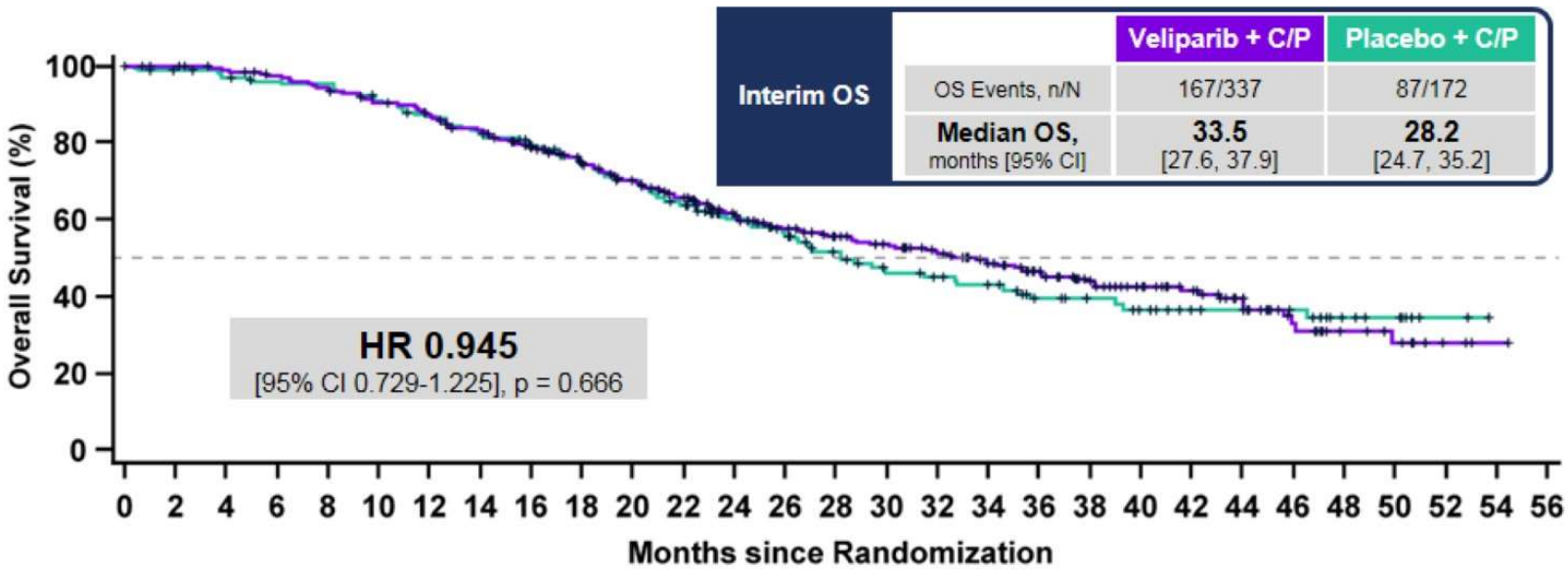
Dieras V, et al. ESMO 2019

Primary Endpoint: PFS by Independent Central Review



Dieras V, et al. ESMO 2019

Secondary Endpoint: Overall Survival (Interim Analysis)



No. at Risk

Control	172	166	162	158	157	149	141	134	125	111	102	90	75	68	57	47	44	40	32	29	25	19	18	15	9	7	2	0	
Veliparib	337	332	326	318	307	294	281	265	247	223	203	185	161	145	132	117	106	90	76	62	50	41	30	18	11	8	3	1	0

BARCELONA 2019 ESMO congress

C/P: Carboplatin and Paclitaxel

Crossover: 44% of ITT subjects randomized to placebo + C/P elected open-label veliparib as 1st subsequent therapy

Dieras V, et al. ESMO 2019

Does BROCADE 3 challenge current paradigms?

- **Olaparib and talazoparib monotherapy result in high rates of response**
  - **PROBLEM:** Responses are generally short-lived and rapid emergence of resistance is the biggest current challenge in the clinic
- **Carboplatin and paclitaxel control arm in BROCADE 3 was highly active**
  - Veliparib benefits emerged late and a significant proportion remained progression-free at 2 and 3 years
- **Ovarian cancer strategy of induction chemotherapy followed by maintenance PARPi may be superior to PARPi monotherapy**
  - Combination therapy appears to be delaying emergence of resistance

Thank you