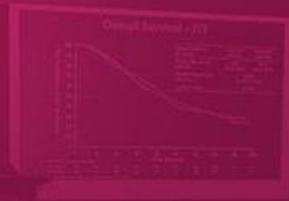
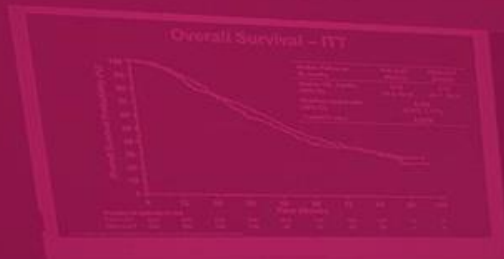


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Comitê de mama da SBOC
Diretoria do Grupo EVA

REALIZAÇÃO



Conflitos de interesses

- Participo de estudos clínicos patrocinado pelas empresas Lilly, Daiichi, Roche;
- Participo como speaker de eventos das empresas AstraZeneca, MSD, Novartis, Roche, Pfizer, Daiichi;
- Participo de Advisory Boards das empresas AstraZeneca, Gilead, GSK, Sanofi. MSD;
- Não tenho ações de quaisquer destas companhias;
- Meus pré-requisitos para participar destas atividades são a autonomia do pensamento científico, a independência de opiniões e a liberdade de expressão.

Phase 3 Study of Neoadjuvant Pembrolizumab or Placebo Plus Chemotherapy, Followed by Adjuvant Pembrolizumab or Placebo Plus Endocrine Therapy for Early-Stage High-Risk ER+/HER2– Breast Cancer: KEYNOTE-756

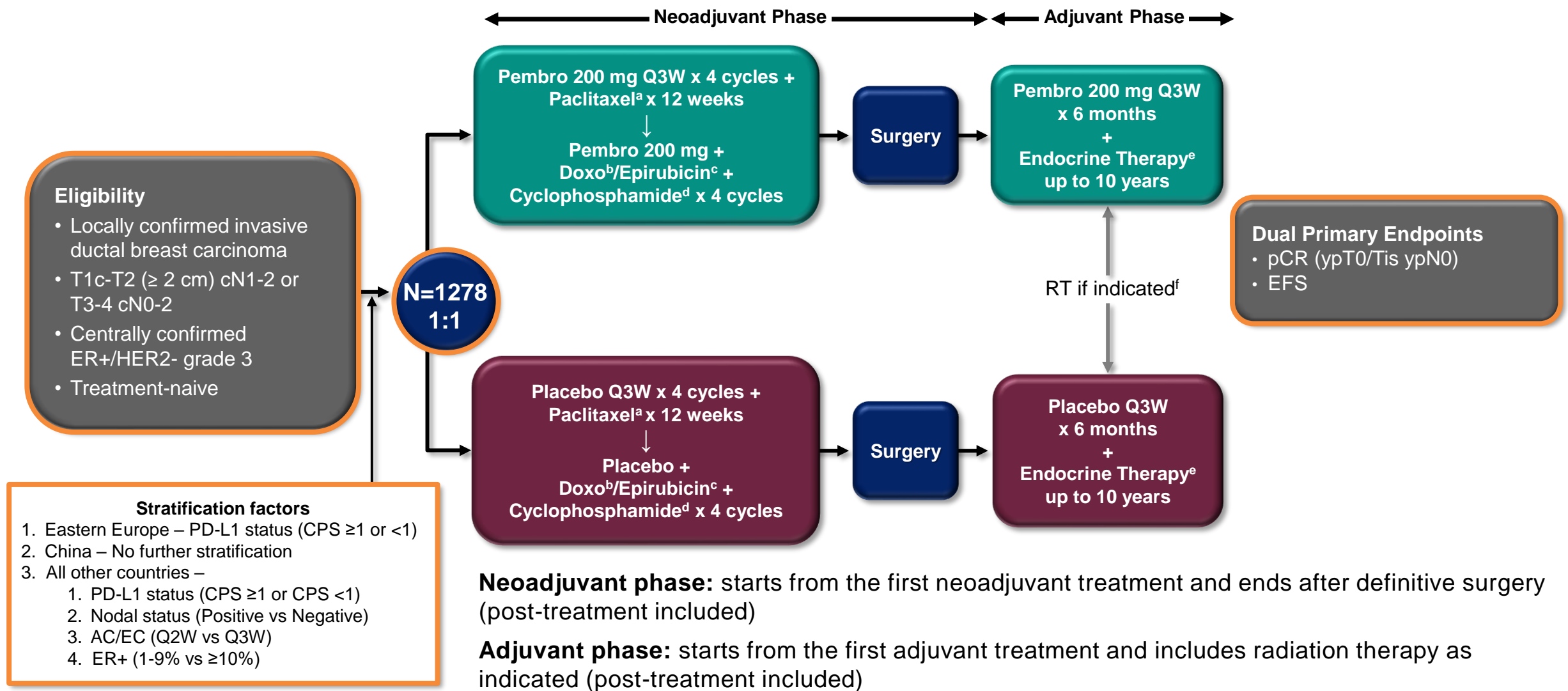
Fatima Cardoso¹; Joyce O'Shaughnessy²; Heather McArthur³; Peter Schmid⁴; Javier Cortes⁵; Nadia Harbeck⁶; Melinda L. Telli⁷; David W. Cescon⁸; Peter A. Fasching⁹; Zhimin Shao¹⁰; Delphine Loirat¹¹; Yeon Hee Park¹²; Manuel Gonzalez Fernandez¹³; Gábor Rubovszky¹⁴; Seock-Ah Im¹⁵; Rina Hui^{16,17}; Toshimi Takano¹⁸; Fabrice André¹⁹; Hiroyuki Yasojima²⁰; Zhenzhen Liu²¹; Yu Ding²²; Liyi Jia²²; Vassiliki Karantza²²; Konstantinos Tryfonidis²²; Aditya Bardia²³

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Background

- ER+/HER2– breast cancer is a heterogenous disease with different clinical behaviors and outcomes with standard treatment
- Although patients with early-stage ER+/HER2– breast cancer generally have a better prognosis than those with other breast cancer subtypes, there is a high-risk subpopulation for whom neoadjuvant chemotherapy is indicated
- Pembrolizumab combined with neoadjuvant chemotherapy improves pCR rates and event-free survival (EFS) in patients with early-stage TNBC^{1,2}
- The phase 3 KEYNOTE-756 study demonstrated that, in patients with high-risk, high-grade, early-stage ER+/HER2– breast cancer, addition of pembrolizumab to neoadjuvant chemotherapy led to a statistically significant increase in pCR (ypT0/Tis ypN0) in the ITT population, regardless of tumor PD-L1 expression status³
- Herein, we present additional pCR results from analyses of various subgroups in the KEYNOTE-756 study

KEYNOTE-756 Study Design (NCT03725059)



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)

^aPaclitaxel dose was 80 mg/m² QW. ^bDoxorubicin dose was 60 mg/m² Q3W. ^cEpirubicin dose was 100 mg/m² Q3W. ^dCyclophosphamide dose was 600 mg/m² Q3W or Q2W.

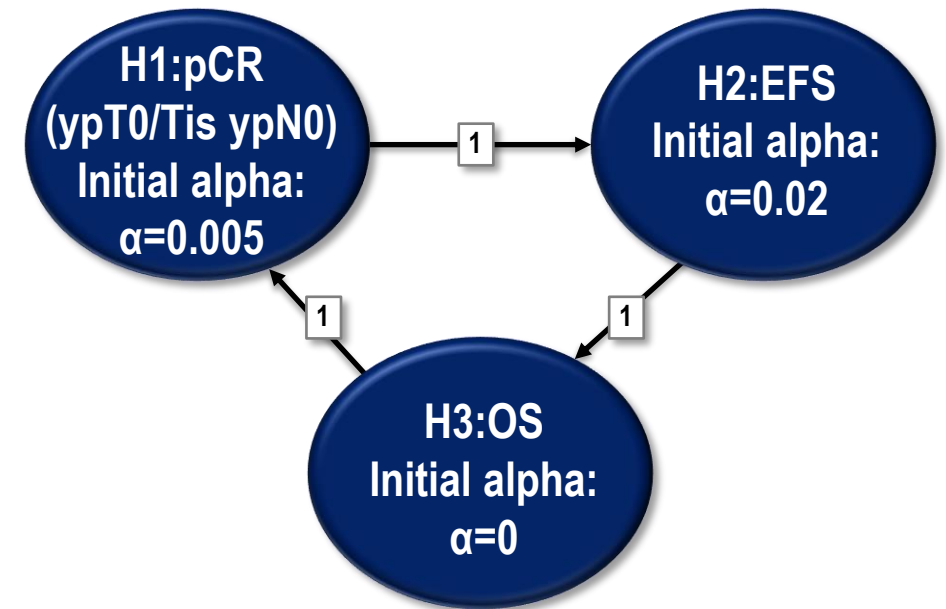
^eEndocrine therapy was administered according to institution guidelines. ^fRadiation therapy (concurrent or sequential) was administered according to institution guidelines.

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Study Endpoints

- Primary Endpoints
 - pCR (ypT0/Tis ypN0)^a assessed by the local pathologist at the time of definitive surgery in the ITT population
 - Event-free survival (EFS)^b assessed by the investigator in the ITT population
- Secondary Endpoints
 - pCR as per alternative definitions (ypT0 ypN0 and ypT0/Tis)^a
 - Overall survival (OS)^c
 - pCR^a, EFS^b and OS^c in the PD-L1^d CPS ≥ 1 population
 - Safety in all treated patients
- Exploratory Endpoint
 - Residual cancer burden (RCB)^e

Multiplicity:

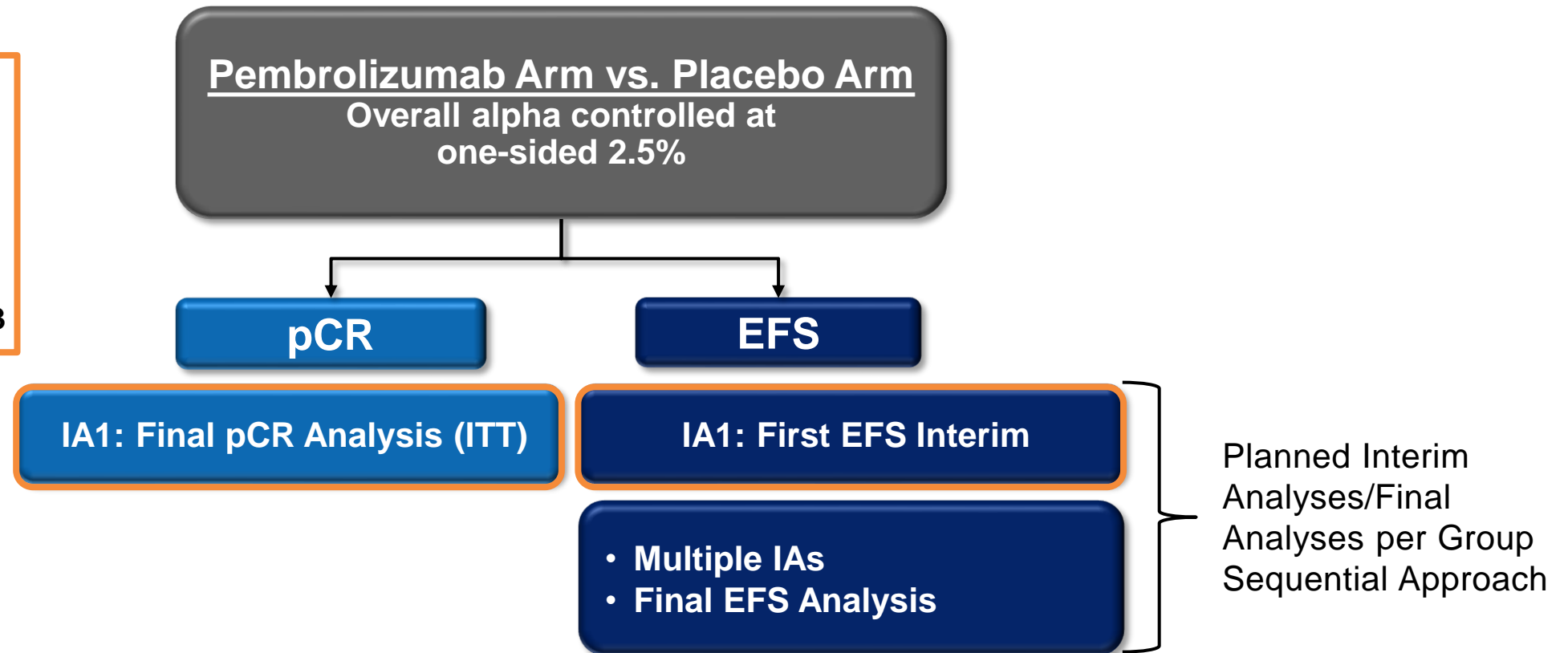


Prespecified analysis plan allows alpha passing from successful endpoint(s) to other(s)

^aParticipants without pCR data for any reason or who received neoadjuvant chemotherapy not specified in the protocol were counted as non-pCR. ^bTo be presented at a later date. ^cTested only when EFS succeeds; to be presented at a later date. ^dPD-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 total number of tumor cells x 100). ^eAssessed by local pathologist at time of surgery.

Statistical Considerations

Interim Completed:
 First IA (IA1) performed
 ~10 months after last
 participant randomized
 and included all
 randomized participants
 Data Cutoff: **May 25, 2023**



pCR (ypT0/Tis ypN0) at IA1 (final analysis of pCR): pre-specified P value boundary for significance of 0.005
 EFS at IA1 (first interim analysis of EFS): pre-calculated P value boundary for significance of 0.000459

Summary of Study Treatment and Analysis Populations

1278 participants randomized 1:1

Pembrolizumab Arm

- 635 allocated
- 634 (99.8%) started paclitaxel
- 598 (94.2%) started AC or EC
- 614 (96.7%) had documented surgery^b
- 478 (75.3%) started adjuvant treatment

Analysis Populations

- ITT: N = 635
- Safety-evaluable: N = 634^c

Placebo Arm

- 643 allocated
- 641 (99.7%) started paclitaxel
- 612 (95.2%) started AC or EC
- 631 (98.1%) had documented surgery^b
- 524 (81.5%) started adjuvant treatment

Analysis Populations

- ITT: N = 643
- Safety-evaluable: N = 642^c

14 (2.2%) discontinued neoadjuvant treatment due to PD^a

13 (2.0%) discontinued neoadjuvant treatment due to PD^a

Median follow-up^d: 33.2 mo (range, 9.7-51.8)

^aIncludes radiographic PD. ^bParticipants did not have to complete all neoadjuvant therapy to undergo surgery. ^cIncludes all participants who received ≥1 dose of study treatment or underwent surgery. ^dDefined as the time from randomization to database cutoff date of May 25, 2023.

Baseline Characteristics, ITT Population

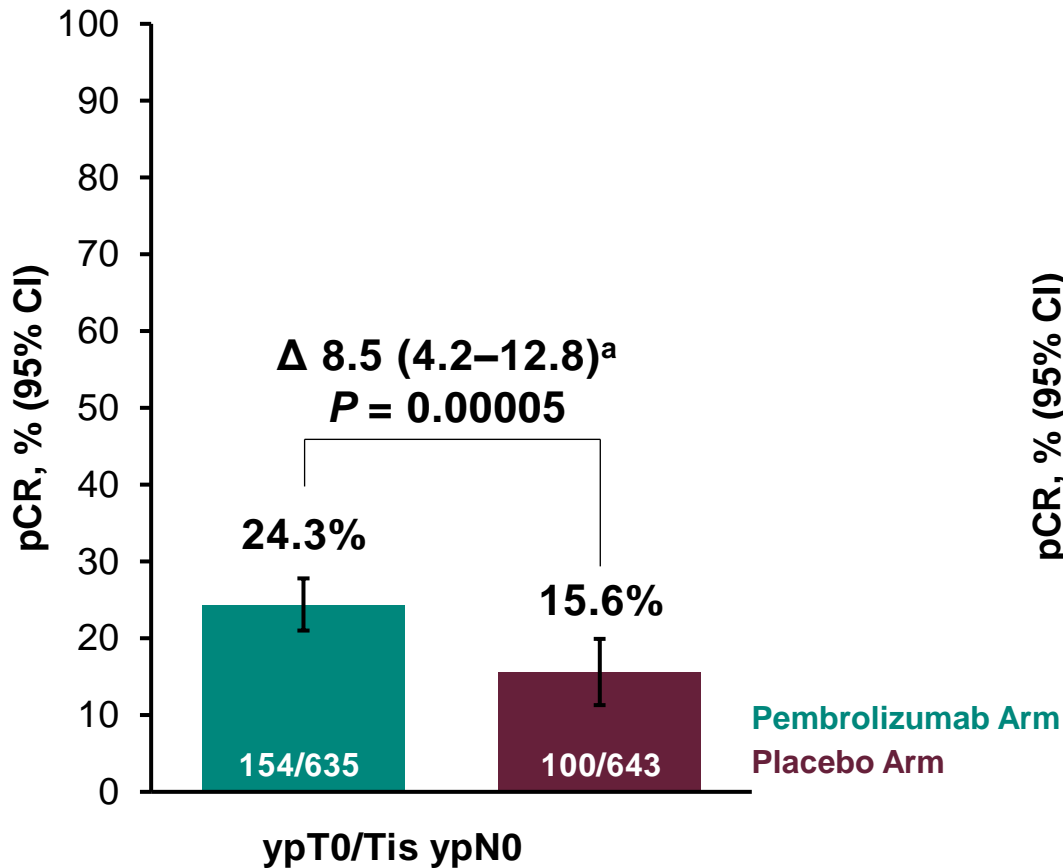
Characteristic, n (%)	All Participants ^a , N = 1278	
	Pembrolizumab Arm N = 635	Placebo Arm N = 643
Age, median (range), yrs	49 (24-82)	49 (19-78)
ECOG PS 1	65 (10.2)	55 (8.6)
PD-L1 ^b CPS ≥1	482 (75.9)	489 (76.0)
PD-L1 CPS ≥10	253 (39.8)	259 (40.3)
China / Eastern Europe / all other countries	88 (13.9) / 139 (21.9) / 408 (64.3)	91 (14.2) / 130 (20.2) / 422 (65.6)
Overall disease stage		
II	399 (62.8)	408 (63.5)
III	236 (37.2)	235 (36.5)
Anthracycline schedule		
Q3W	415 (65.4)	425 (66.1)
Q2W	183 (28.8)	187 (29.1)
Not started	37 (5.8)	31 (4.8)
Tumor size		
T1/T2	402 (63.3)	413 (64.2)
T3/T4	233 (36.7)	230 (35.8)
Nodal involvement (clinically assessed)		
Positive	570 (89.8)	582 (90.5)
Negative	65 (10.2)	61 (9.5)
ER positivity ≥10%	601 (94.6)	600 (93.3)

^aAll participants had centrally confirmed grade 3 disease. ^bPD-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). Data cutoff date: May 25, 2023.

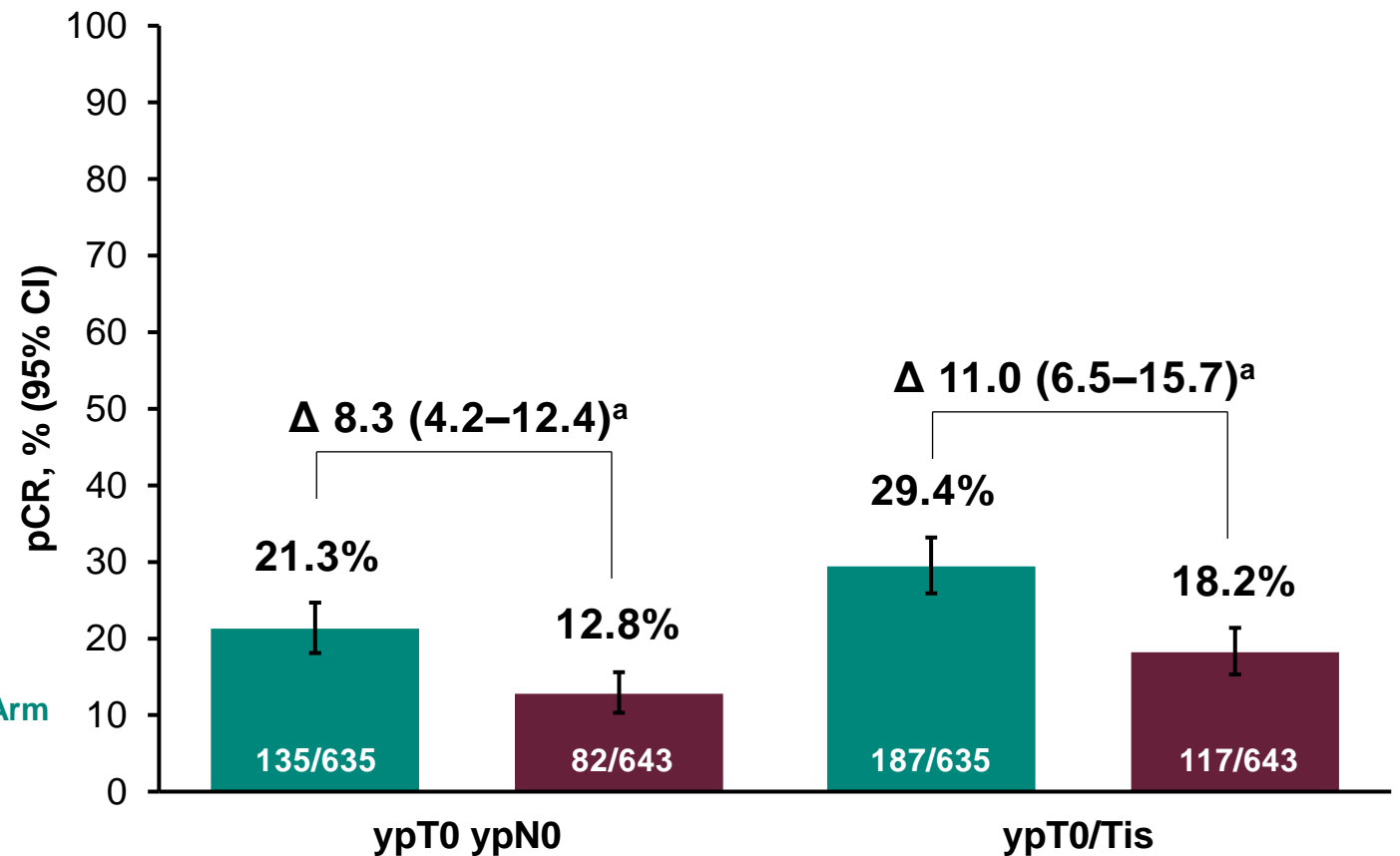
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Pathological Complete Response at IA1

Primary Endpoint



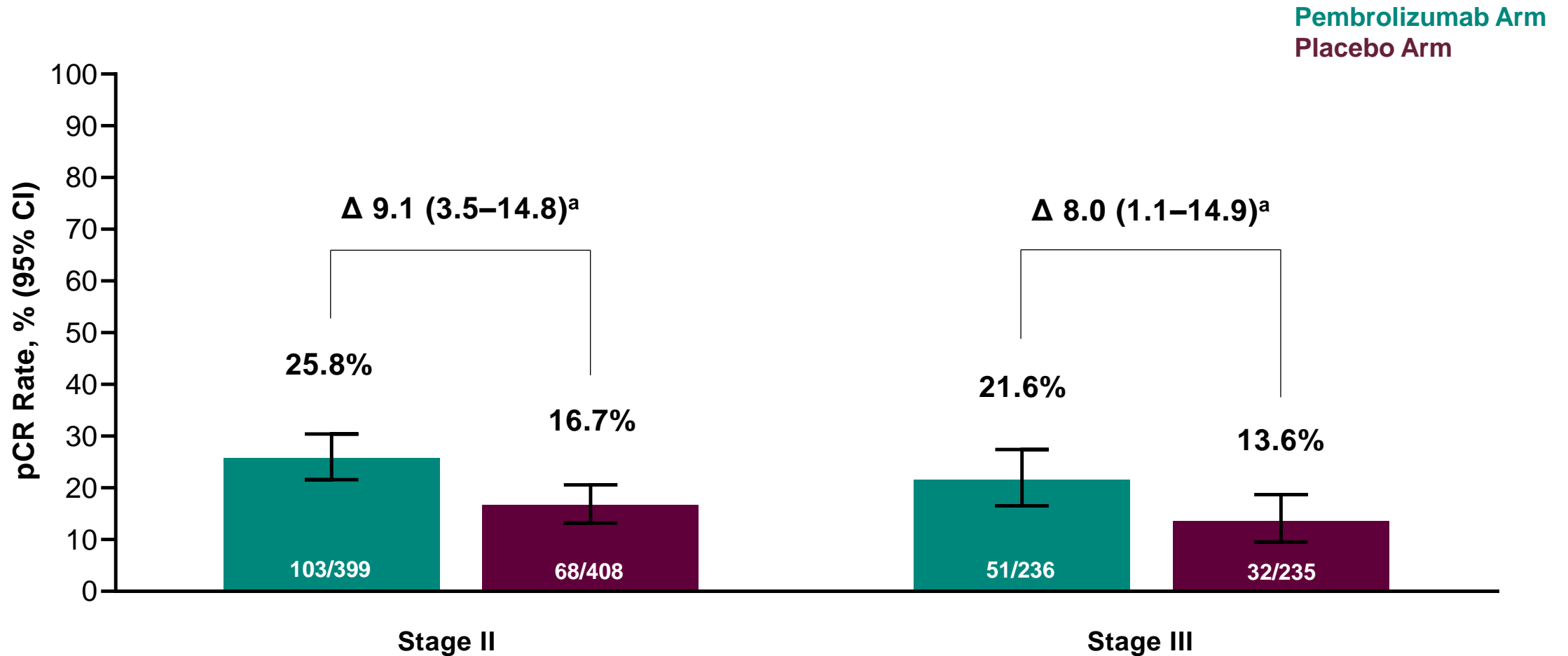
Secondary Endpoints: Other pCR Definitions



^aEstimated treatment difference based on Miettinen & Nurminen method stratified by the analysis randomization stratification factors. Data cutoff date: May 25, 2023.

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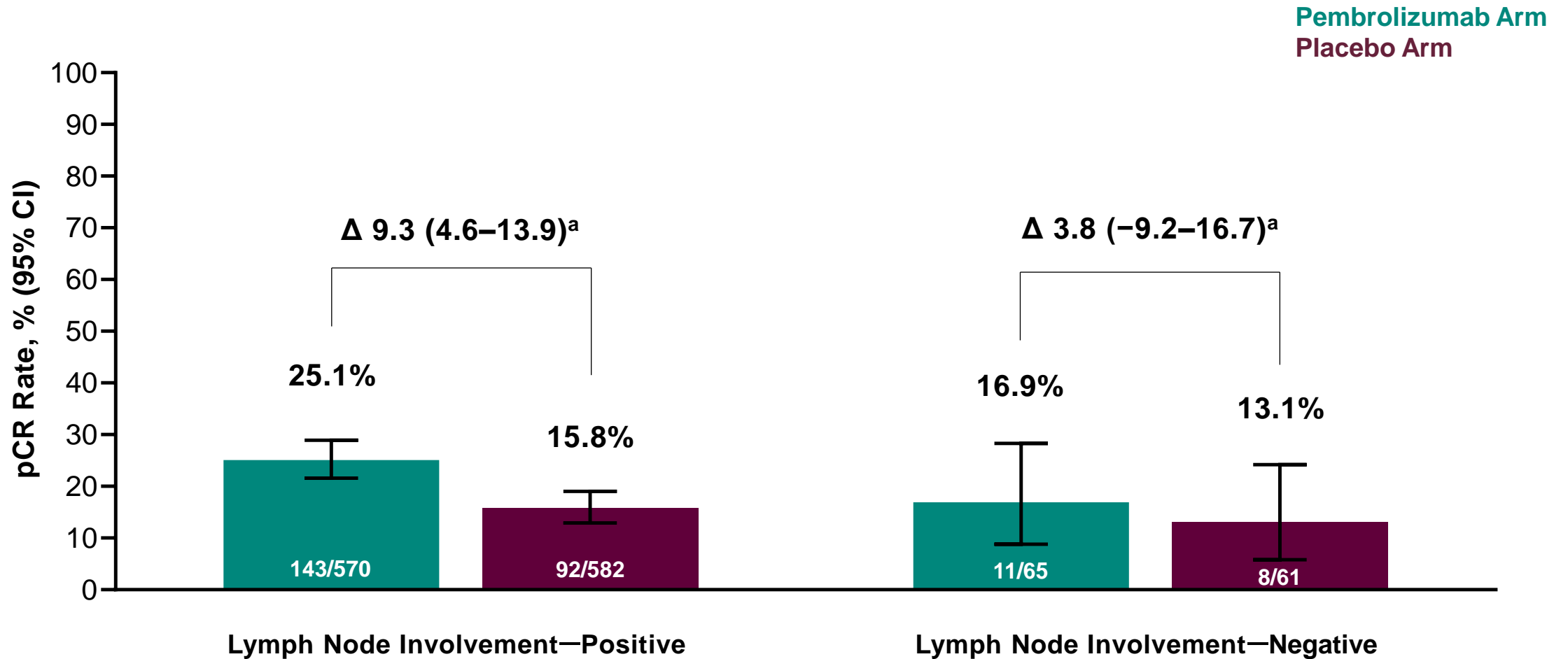
Pathological Complete Response at IA1 by Disease Stage



^aEstimated treatment difference based on Miettinen & Nurminen method (unstratified). Data cutoff date: May 25, 2023.

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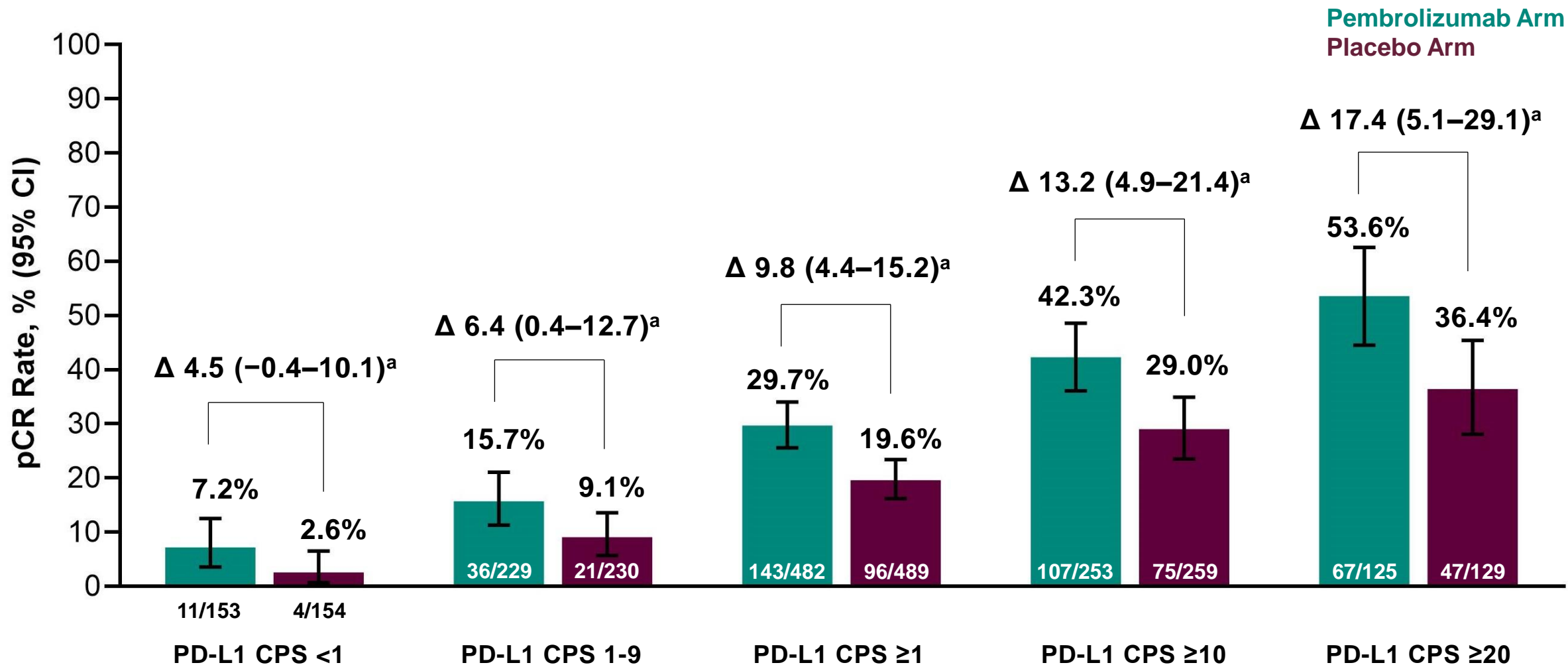
Pathological Complete Response at IA1 by Baseline Clinical Lymph Node Involvement



^aEstimated treatment difference based on Miettinen & Nurminen method (unstratified). Data cutoff date: May 25, 2023.

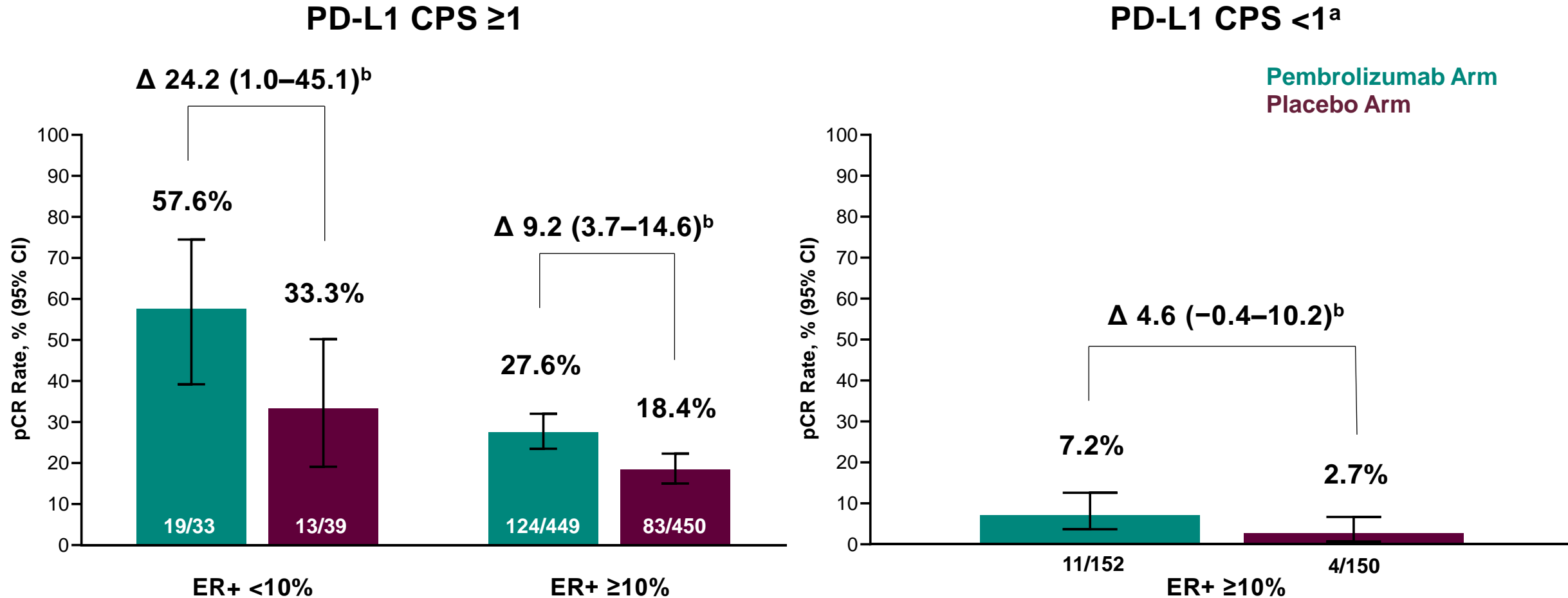
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Pathological Complete Response at IA1 by PD-L1 Expression Level



^aEstimated treatment difference based on Miettinen & Nurminen method stratified by geographic region (China vs Eastern Europe vs all other countries). Data cutoff date: May 25, 2023. This presentation is the intellectual property of the author/presenter. Contact them at Joyce.OShaughnessy@USONCOLOGY.COM for permission to reprint and/or distribute.

Pathologic Complete Response at IA1 by ER Status and PD-L1 Expression

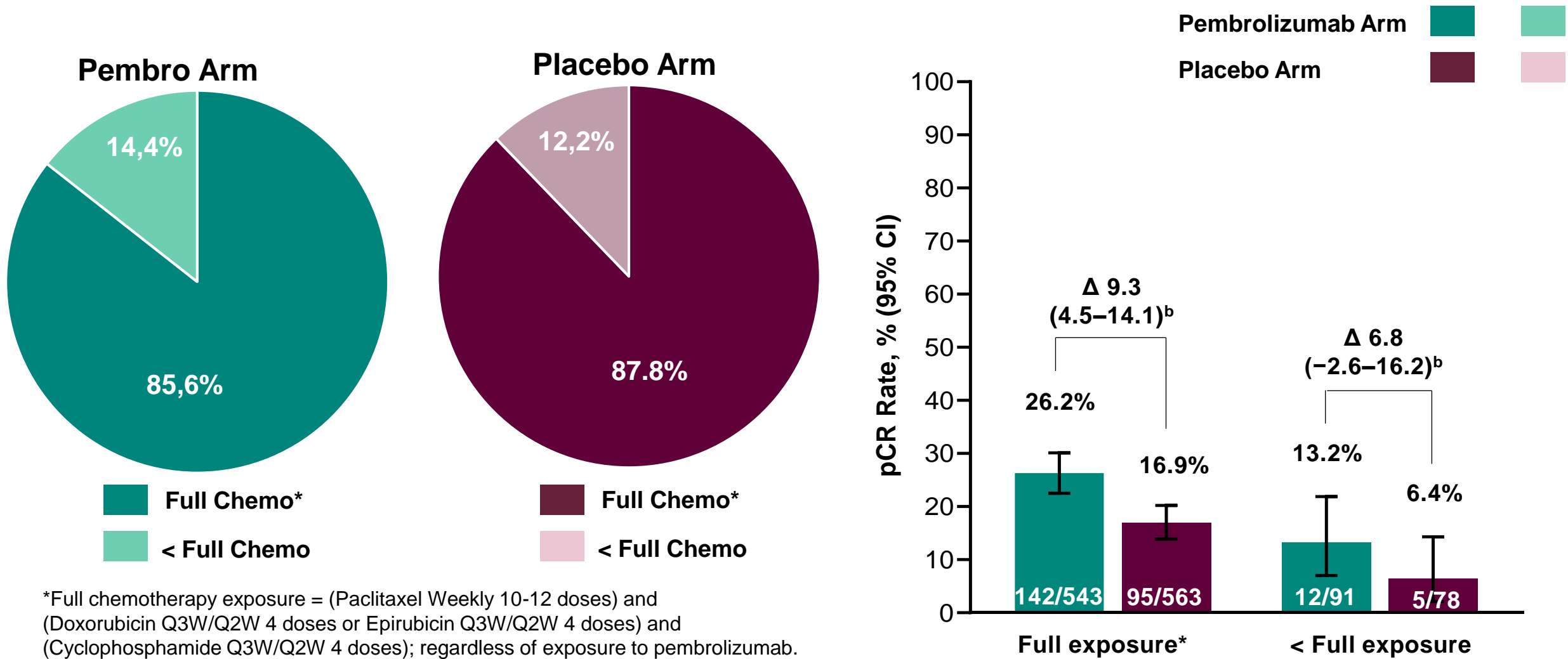


^aNo pCR in patients with a PD-L1 CPS < 1 with ER+ < 10% (pembrolizumab arm, n = 1; placebo arm, n = 4). ^bEstimated treatment difference based on Miettinen & Nurminen method (unstratified).

Data cutoff date: May 25, 2023.

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Pathological Complete Response at IA1 by Exposure to Chemotherapy^a

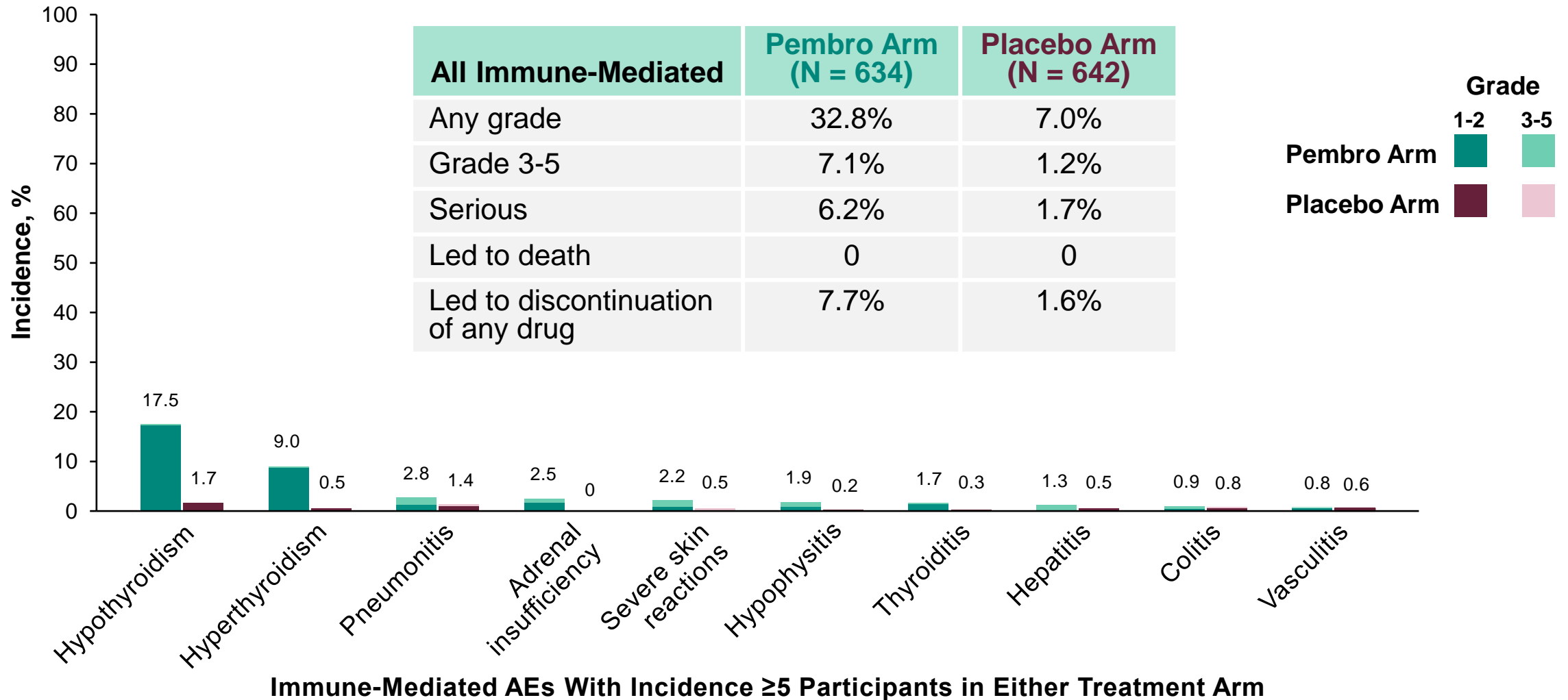


*Full chemotherapy exposure = (Paclitaxel Weekly 10-12 doses) and (Doxorubicin Q3W/Q2W 4 doses or Epirubicin Q3W/Q2W 4 doses) and (Cyclophosphamide Q3W/Q2W 4 doses); regardless of exposure to pembrolizumab.

^aPost-hoc analysis. ^bEstimated treatment difference based on Miettinen & Nurminen method (unstratified). Data cutoff date: May 25, 2023.

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Immune-Mediated AEs in Neoadjuvant Phase

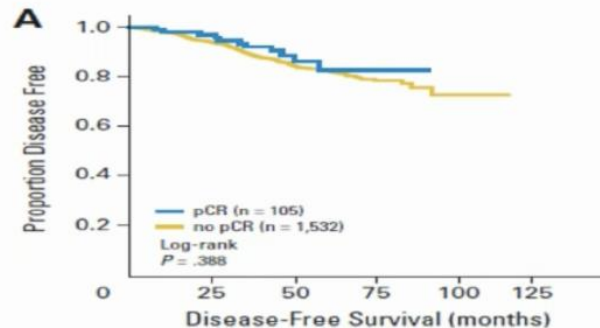


Summary

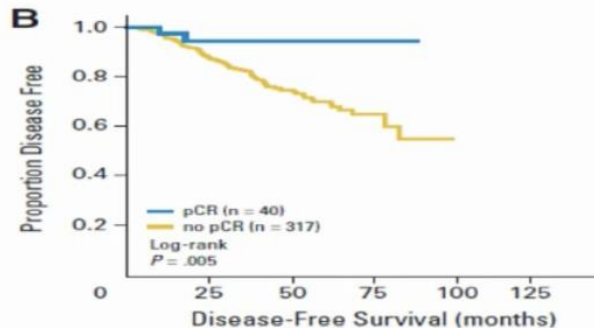
- Addition of pembrolizumab to neoadjuvant chemotherapy led to a statistically significant increase in pCR in the ITT population
- Addition of pembrolizumab increased pCR rates in subgroups defined by geography, stage, baseline clinical lymph node involvement, and different levels of PD-L1 expression
- A larger magnitude of pCR benefit was observed in patients with node-positive disease, higher PD-L1 CPS thresholds, and ER-low tumors (<10%)
- Patients who received less than the planned chemotherapy doses had lower pCR rates, although pCR rates were improved with pembrolizumab regardless of chemotherapy exposure (ie, full exposure or less than full exposure)
- Addition of pembrolizumab to neoadjuvant chemotherapy shifted more patients to lower residual cancer burden categories (RCB 0–1)
- Immune-mediated AE rates were consistent with the known toxicity profile of pembrolizumab plus neoadjuvant chemotherapy and no new safety concerns were observed
- The study is powered to evaluate EFS as the dual primary endpoint; EFS results are immature and continue to be evaluated

Neoadjuvant Chemotherapy: pCR & Prognosis (DFS) by Subtype

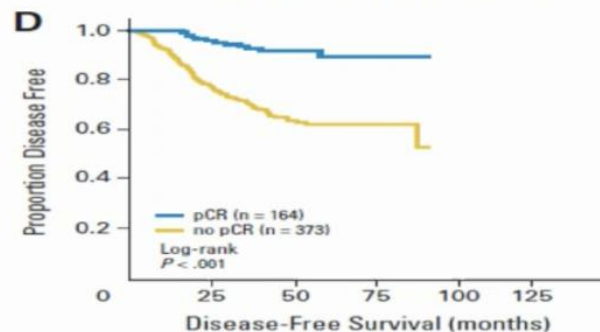
Luminal A ER+



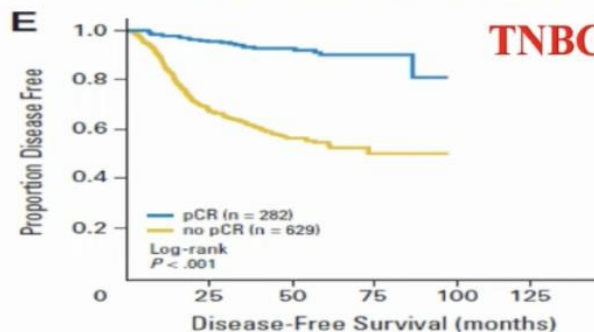
Luminal B ER+ HER2-neg



HER2-pos (non-lum)



TNBC



Stephen Johnston

Invited Discussant LBA20 and LBA21

14:00 - 15:40 Proffered Paper session - Breast cancer, early stage

CHAIRS : STEPHEN JOHNSTON, SARA TOLANEY

Neoadjuvant Immunotherapy for ER+ HER2- Early Breast Cancer

A New Paradigm ?

Can Neoadjuvant Immunotherapy improve pCR rates in ER+ HER2- EBC ?

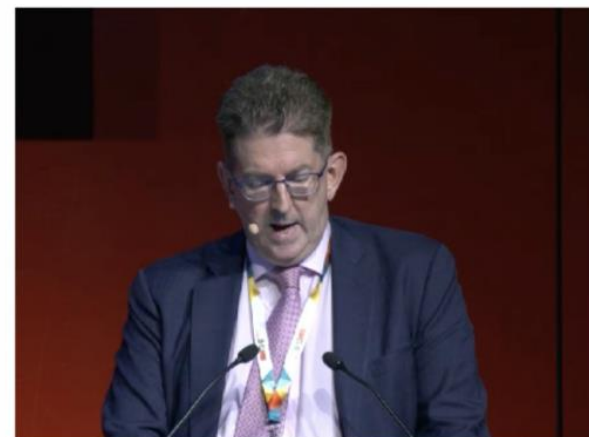
- Yes, significant improvement in pCR seen in 2 separate studies of PD1 inhibitors, albeit rates still only 24%
- Unclear if this will translate into improved EFS

Are there subgroups of ER+ HER2- EBC who benefit most ?

- Almost certainly – higher grade, luminal B, & possibly PD-L1 positive (assay dependent)
- Need to better evaluate if genomic & immune signatures can further define those with most to gain

Are the added toxicities worth it ?

- Added toxicities well known and important in “risk / benefit” decision making of “whom to treat”



Stephen Johnston

Invited Discussant LBA20 and LBA21

Obrigada!!

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