Allegheny Health Network

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

AHN Presenter: Diane BuchBarker, MD

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, Quirón Group; Vall d'Hebron Institute of Oncology (VHIO), Madrid & Barcelona, Spain; 30. Baylor University Medical Center, Texas Oncology, US Oncology, Dallas, TX, USA

Allegheny Health Network

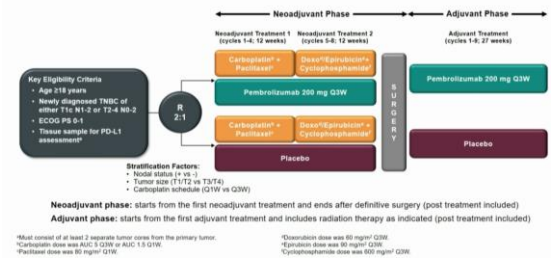
Background

- Patients with TNBC who achieve pathological complete response (pCR) after neoadjuvant chemotherapy have sustained clinical benefit[1,2]
- Taxane- and anthracycline-based neoadjuvant regimens produce pCR rates of ~40%[3]; addition of platinum increases pCR rates to ~50-55%[4-7]
- Meta-analysis of individual patient data showed a strong association of pCR after neoadjuvant chemotherapy with improved long-term EFS (HR 0.24) and OS (HR 0.16) benefit[8]
- Neoadjuvant pembrolizumab + chemotherapy showed manageable safety and antitumor activity in early TNBC[9,10]

1. Cortazar P et al. *Lancet* 2014;384:164-72. 2. Huang M et al. Poster. ESMO Breast Cancer; May 2-4, 2019; Berlin, Germany. 3. Lobl S et al. *Ann Oncol* 2013;30:1279-88. 4. von Minckwitz G et al. *Lancet Oncol* 2014;15:747-56. 5. Sikov WM et al. *J Clin Oncol* 2015;33:13-21. 6. Petrelli F et al. *Breast Cancer Res Treat* 2014;14:223-32. 7. Lobl S et al. *Lancet Oncol* 2018;19:497-509. 8. Spring LM et al. *Cancer Research* 2019;79:Abstract GS2-03. 9. Schmid P et al. *J Clin Oncol* 2017;35(15S):Abstract 506. 10. Nanda R et al. *J Clin Oncol* 2017;35(15S):Abstract 506.

Allegheny Health Network

KEYNOTE-522 Study Design (NCT03036488)



Allegheny Health Network

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]

In this analysis of KEYNOTE-522, we present the rates of pCR in key patient subgroups and by treatment exposure, RCB and immune-mediated AEs

[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.

Allegheny Health Network

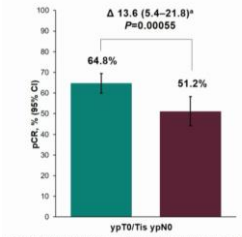
Baseline Characteristics, ITT Population

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.

Allegheny Health Network

Definitive pCR Analysis

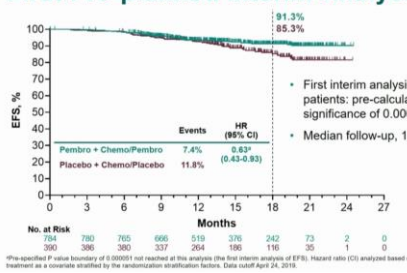


- Definitive pCR analysis to test primary hypothesis of pCR based on prespecified first 602 patients (pre-calculated P value boundary for significance of 0.003)
- Consistent benefit seen with pCR defined as ypT0 ypN0 and ypT0/Tis

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

Allegheny Health Network

First Pre-planned Interim Analysis for EFS

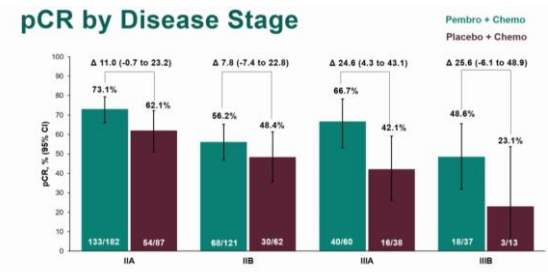


- First interim analysis of EFS based on 1174 patients: pre-calculated P value boundary for significance of 0.000051 (HR <0.4)
- Median follow-up, 15.5 months

ªPre-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.

Allegheny Health Network

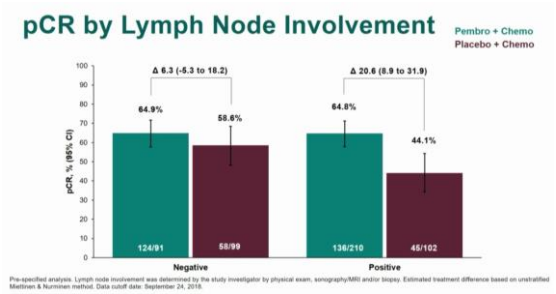
pCR by Disease Stage



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

Allegheny Health Network

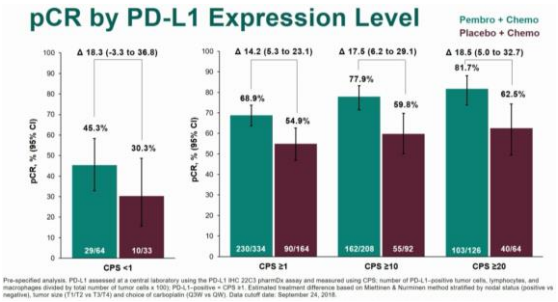
pCR by Lymph Node Involvement



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.

Allegheny Health Network

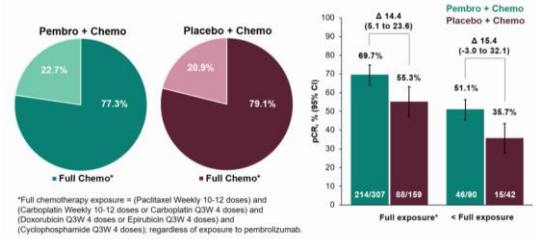
pCR by PD-L1 Expression Level



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.

Allegheny Health Network

pCR by Exposure to Chemotherapy

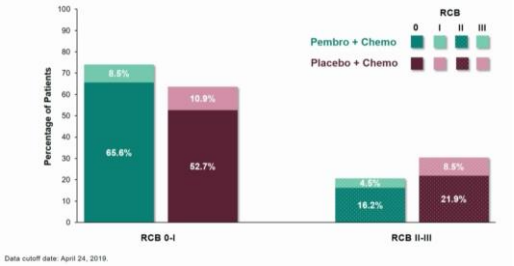


*Full chemotherapy exposure = (Paclitaxel Weekly 10-12 doses) and (Carboplatin Weekly 10-12 doses or Carboplatin Q3W 4 doses) and (Doxorubicin Q3W 4 doses or Epirubicin Q3W 4 doses) and (Cyclophosphamide Q3W 4 doses); regardless of exposure to pembrolizumab.

Post-hoc analysis. Data cutoff date: September 24, 2018.

Allegheny Health Network

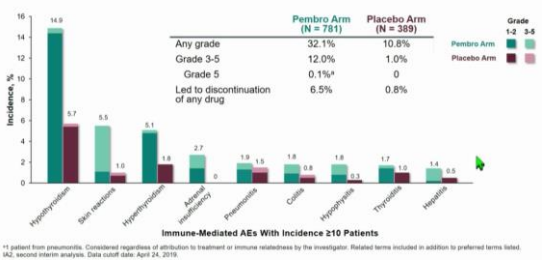
Residual Cancer Burden



Data cutoff date: April 24, 2019.

Allegheny Health Network

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%

Grade 1-2 3-5
Pembro Arm
Placebo Arm

[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.

Allegheny Health Network

Summary

- Neoadjuvant pembro + chemo provided a larger magnitude of pCR benefit versus chemo alone in patients with stage III and/or node positive early TNBC
- The benefit of neoadjuvant pembro + chemo on pCR was also observed in patients who received less than the planned chemo (although absolute pCR rates were lower), and regardless of CPS threshold
- Neoadjuvant pembro + chemo was associated with a higher rate of RCB 0-1
- Immune-mediated adverse event rates were consistent with the known profiles of each regimen and represent no new safety concern
- Further follow-up needed to confirm EFS benefit and the long-term safety profile
- Additional biomarker analyses planned, including TILs and BRCA

Allegheny Health Network