Phase 1b/2 KEYNOTE-365 cohort I: Pembrolizumab plus carboplatin/etoposide or carboplatin/etoposide alone for patients with metastatic neuroendocrine prostate cancer

Evan Y. Yu[1]; Anthony M. Joshua[2]; Gero Kramer[3]; Neal D. Shore[4]; Haixia Hu[5]; Christian H. Poehlein[5]; Charles Schloss[5]; Johann S. de Bono[6]

[1]University of Washington, Seattle, WA, USA; [2]St Vincent's Hospital Sydney, Sydney, NSW, Australia; [3]Medical University of Vienna, Vienna, Austria; [4]Carolina Urologic Research Center, Myrtle Beach, SC, USA; [5]Merck & Co., Inc., Rahway, NJ, USA; [6]The Royal Marsden NHS Foundation Trust, London, United Kingdom

Clinical trial registry: NCT02861573

Background: Treatment-emergent neuroendocrine (t-NE) or de novo metastatic neuroendocrine prostate cancer is often treated with platinum-based chemotherapy but has no standard-of-care treatment. The PD-1 inhibitor pembrolizumab has shown antitumor activity and manageable safety in patients with metastatic castration-resistant prostate cancer (mCRPC) previously treated with docetaxel and targeted endocrine therapy. Cohort I of the multicohort, open-label, phase 1b/2 KEYNOTE-365 study (NCT02861573) will evaluate the efficacy and safety of pembrolizumab plus carboplatin/etoposide in patients with neuroendocrine mCRPC.

Methods: Eligible patients are adults with metastatic t-NE or de novo metastatic neuroendocrine prostate cancer (defined by ≥1% of neuroendocrine cells in discrete regions of a recent biopsy specimen), disease progression ≤6 months of screening, ECOG performance status of 0 or 1, and prior treatment with androgen deprivation therapy for metastatic disease; ≤2 prior chemotherapies for mCRPC and ≤2 prior next-generation hormonal agents for mCRPC are permitted. Prior docetaxel for metastatic disease is permitted. Patients are randomly assigned 1:1 to receive 4-6 cycles (per local standard of care) of chemotherapy (carboplatin area under the concentration-time curve of 5 IV on day 1 of each 3-week cycle plus etoposide 100 mg/m^2 IV on days 1-3 of each 3-week cycle) with or without pembrolizumab 200 mg IV on day 1 of each 3-week cycle for ≤35 cycles. Randomization is stratified by ECOG performance status (0 vs 1). Approximately 40-100 patients will be enrolled per arm. Primary end points are safety and tolerability, prostate-specific antigen (PSA) response rate (PSA decline of ≥50% from baseline), and objective response rate (ORR) per RECIST version 1.1 by blinded independent central review (BICR). Secondary end points include time to PSA progression; radiographic progression-free survival, ORR, duration of response, and disease control rate per Prostate Cancer Working Group 3-modified RECIST version 1.1 by BICR; and overall survival. Enrollment is ongoing.

Funding: Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

Conflicts of interest disclosure:

Evan Y. Yu reports consulting or advisory role for AADi, Advanced Accelerator Applications, Bayer, Bristol Myers Squibb, Janssen, Loxo Oncology/Eli Lilly, Merck, and Oncternal Therapeutics and research funding to his institution from Bayer, Blue Earth Diagnostics, Daiichi Sankyo, Dendreon, Lantheus Medical Imaging, Merck, Seagen, Surface Oncology, Taiho Pharmaceutical, and Tyra Biosciences.

Anthony M. Joshua holds stock or other ownership interests in Pricilium Therapeutics; has performed a consulting or advisory role for Astellas Pharma, AstraZeneca; Bayer; Bristol Myers Squibb, Eisai, IDEAYA Biosciences, Ipsen, IQVIA, Janssen Oncology, Merck Serono, Novartis, Pfizer, and Sanofi; reports research funding to his institution from AstraZeneca, Bayer, Bristol Myers Squibb, Corvus Pharmaceuticals, Janssen Oncology, Eli Lilly, Mayne Pharma, MSD, Pfizer, and Roche/Genentech; and has patents, royalties, or other Intellectual property for cancer therapeutic methods.

Gero Kramer has performed a consulting or advisory role for Astellas Pharma, AstraZeneca, Bayer, Ferring, Janssen, MSD, Life Science Foundation, Novartis, and Sandoz-Novartis and has received support for travel, accommodations, or expenses from Bayer and Janssen.

Neal D. Shore reports employment with GenesisCare; leadership role at Alessa Therapeutics and Photocure; consulting or advisory role for Abbvie, Alkido Pharma, Amgen, Arquer Diagnostics, Asieris Pharmaceuticals, Astellas Pharma, AstraZeneca, Bayer, Boston Scientific, Bristol Myers Squibb/Sanofi, CG Oncology, Clarity Pharmaceuticals, Clovis Oncology, Dendreon, Exact Imaging, Exact Sciences, FerGene, Ferring, Fize Medical, Foundation Medicine, Genesis Cancer Care, Genzyme, Guardant Health, ImmunityBio, Incyte, InVitae, Janssen Scientific Affairs, Lantheus Medical Imaging, Eli Lilly, MDxHealth, Medivation/Astellas, Merck, Minomic, Myovant Sciences, Myriad Genetics, NGM Biopharmaceuticals, Nonagen Bioscience, Novartis, Nymox, Pacific Edge Biotechnology, Peerview, Pfizer, Phosphorus, Photocure, PlatformQ Health, Profound Medical, Promaxo, Propella Therapeutics, Protara Therapeutics, Sanofi, Sesen Bio, Specialty Networks, Telix Pharmaceuticals, Tempus, Tolmar, Urogen Pharma, Vaxiion, and Vessi Medical; speaker's bureau for Astellas Pharma, AstraZeneca, Bayer, Clovis Oncology, Dendreon, Foundation Medicine, Guardant Health, Janssen, Merck, and Pfizer; research funding from Abbvie, Advantagene, Amgen, Aragon Pharmaceuticals, Astellas Pharma, AstraZeneca, Bayer, Boston Scientific, Bristol Myers Squibb/Pfizer, CG Oncology, Clovis Oncology, Dendreon, DisperSol, Endocyte, Exact Imaging, Exelixis, Ferring, FKD Therapies, Forma Therapeutics, Foundation Medicine, Genentech, Guardant Health, InVitae, Istari Oncology, Janssen, Jiangsu Yahong Meditech, MDxHealth, Medivation, Merck, MT Group, Myovant Sciences, Myriad Genetics, Novartis, Nymox, OncoCellMDx, ORIC Pharmaceuticals, pacific edge, Palette Life Sciences, Pfizer, Plexxikon, POINT Biopharma, Propella

Therapeutics, Propella Therapeutics, RhoVac, Sanofi, Seagen, Sesen Bio, Steba Biotech, Theralase, Tolmar, UroGen Pharma, Urotronic, US Biotest, Vaxiion, Veru, and Zenflow; expert testimony for Ferring; and other relationships with Alessa Therapeutics and Photocure.

Haixia, Hu, Christian H. Poehlein, and Charles Schloss are employees of Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA, and have stock in Merck & Co., Inc., Rahway, NJ, USA.

Johann S. de Bono reports honoraria from Amgen, Astellas Pharma, AstraZeneca, Bayer, Daiichi Sankyo, Genentech/Roche, GlaxoSmithKline, ImCheck therapeutics, Janssen Oncology, Merck Serono, MSD, Pfizer, and Sanofi; consulting or advisory role for Amgen, Astellas Pharma, AstraZeneca, Bayer, BioXcel Therapeutics, Boehringer Ingelheim, CellCentric, Crescendo Biologics, Daiichi Sankyo, Dark Blue Therapeutics, Eisai, Genentech/Roche, Genmab, GlaxoSmithKline, Harpoon therapeutics, ImCheck therapeutics, Immunic Therapeutics, Janssen Oncology, Merck Serono, MSD, MetaCurUm, Myricx Pharma, Novartis, Nurix, Oncternal Therapeutics, Orion, Pfizer, Qiagen, Sanofi Aventis GmbH, Sierra Oncology, Taiho Oncology, Takeda, and Tango Therapeutics; speakers' bureau for AstraZeneca; research funding to institution from Amgen, Astellas Pharma, Astex Pharmaceuticals, AstraZeneca, Bayer, CellCentric, Crescendo Biologics, Daiichi Sankyo, Genentech/Roche, Genmab, GlaxoSmithKline, Harpoon, Immunic Therapeutics, Janssen, Merck Serono, Merck Sharp & Dohme, MetaCurUm, Myricx, Nurix, Oncternal Therapeutics, Orion, Pfizer, Sanofi Aventis GmbH, Taiho Pharmaceutical; the following patents, royalties, or other intellectual property: abiraterone rewards to inventors; CHK1 inhibitor, PARP inhibitors and DNA repair defects, and targeting of IL23 in prostate cancer; and support for travel, accommodations or expenses from Amgen, Astellas Pharma, AstraZeneca, Bayer, CellCentric, Daiichi Sankyo, Genentech/Roche, GlaxoSmithKline, Halda Therapeutics, Merck Serono, MSD, Orion, Pfizer, and Sanofi.