First-in-human phase 1 study of CC-94676, a first-in-class androgen receptor (AR) ligand-directed degrader (LDD), in patients (pts) with metastatic castration-resistant prostate cancer (mCRPC).

Dana E. Rathkopf, Manish R. Patel, Atish Dipankar Choudhury, Drew W. Rasco, Nehal J. Lakhani, Jessica E. Hawley, Ana Aparicio, Vivek Narayan, Sandy Srinivas, Karie Runcie, Hamid Emamkhoo, Zachery R Reichert, Michael Anthony Carducci, Amber L. Wells, Can Liu, Raju Kandimalla, Jiaju Wu, Marie Huong Nguyen, Michael Pourdehnad, Andrew J. Armstrong; Memorial Sloan Kettering Cancer Center, New York, NY; Sarah Cannon Research Institute/Florida Cancer Specialists, Sarasota, FL; Dana-Farber Cancer Institute, Boston, MA; START Center for Cancer Care, San Antonio, TX; Cancer & Hematology Centers of Western Michigan, Grand Rapids, MI; University of Washington Medical Center, Seattle, WA; The University of Texas MD Anderson Cancer Center, Houston, TX; University of Pennsylvania-Abramson Cancer Center, Philadelphia, PA; Stanford University Medical Center, Stanford, CA; Columbia University Irving Medical Center, New York, NY; Carbone Cancer Center, University of Wisconsin-Madison, Madison, WI; University of Michigan Medical School, Ann Arbor, MI; The Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins University, Baltimore, MD; Bristol Myers Squibb, San Francisco, CA; Bristol Myers Squibb, Princeton, NJ; Duke Cancer Institute Center for Prostate and Urologic Cancers, Durham, NC

Background: Androgen receptor (AR) signaling is the principal driver of PC at all stages. CC-94676 (BMS-986365) is a heterobifunctional, first-in-class, orally bioavailable AR LDD designed to induce rapid, sustained, and highly selective AR degradation in pts who progressed on standard of care therapies. We report initial results from an open-label, multicenter study, NCT04428788, evaluating CC–94676 in pts with progressive mCRPC. Methods: Pts with mCRPC who progressed on androgen deprivation therapy, $\geq$ 1 second generation hormonal therapy (eg, enzalutamide [enza], abiraterone [abi], darolutamide, and apalutamide) and taxane chemotherapy (chemo) (unless refused or not indicated) were enrolled to evaluate the safety, tolerability, PK/PD, and preliminary efficacy of CC-94676. Escalation doses evaluated were 100–1200 mg QD and 600–900 mg BID; expansion doses were 600 mg QD and 400–900 mg BID. Results: As of Aug 21, 2023, 95 pts received CC-94676 (median age 71 yrs) with a median of 5 (range 2–12) prior therapies, including enza (80%), abi (72%), both enza & abi (56%), and chemo (56%) (docetaxel 55%; cabazitaxel 20%). There were no Grade (G) 4 treatment-related adverse events (TRAEs) or discontinuations due to TRAEs. Of 27 pts treated in escalation, treatment (Tx) was well tolerated; 2 pts had non-serious G3 TRAEs at doses $\geq$ 800 mg QD, which were manageable with dose modifications. One dose-limiting toxicity of asymptomatic QTc prolongation was observed at 900 mg BID and resolved with dose interruption. The maximum tolerated dose was not reached. Of 68 pts treated in expansion, the most common TRAEs were dose-dependent: QTc prolongation (asymptomatic) (43%; G3: 9%), bradycardia (31%; G3: none), and fatigue (24%; G3: none). G3 TRAEs were manageable with dose modifications. The rate of pts with confirmed PSA reductions $\geq$ 30% (PSA30) increased dose-dependently from 400 to 900 mg BID. 23/68 (34%) pts across all dose levels achieved $\geq$ PSA30. At 900 mg BID, 11/20 (55%) pts showed PSA30; 7/20 (35%) and 2/20 (10%) had confirmed PSA declines of $\geq$50% and $\geq$90%, respectively. PSA responses and radiographic tumor shrinkage occurred across all dose levels, including in pts with AR wildtype (WT), amplifications, and mutations (by cfDNA), and in heavily pretreated pts who progressed on abi, enza, and chemo. At 900 mg BID, the median duration of Tx was 182 days (range 21–448) and 9/20 (45%) pts remained free of radiographic progression with treatment ongoing at 6 months. Conclusions: CC-94676 is well tolerated with a manageable safety profile. CC-94676 shows promising and prolonged clinical activity in heavily pretreated mCRPC pts who progressed on abi, enza, and chemo with activity seen in pts with tumors expressing WT and mutant ARs. Selection of the recommended phase 2 dose is ongoing. Clinical trial information: NCT04428788. Research Sponsor: Celgene/BMS.