Clinical Benefit in Biomarker-Positive Patients (pts) With Locally Advanced or Metastatic Solid Tumors Treated With the PARP1/2 Inhibitor Pamiparib in Combination With Low-Dose (LD) Temozolomide (TMZ)

Agostina Stradella[1], Melissa Johnson[2], Sanjay Goel[3], Sreenivasa R. Chandana[4], Matthew D. Galsky[5], Emiliano Calvo[6], Victor Moreno[7], Haeseong Park[8], Tobias Arkenau[9], Andrés Cervantes[10], Lorena Fariñas-Madrid[11], Linda Mileshkin[12], Siqing Fu[13], Ruth Plummer[14], Jeff Evans[15], Lisa Horvath[16], Amy Prawira[17], Kunbin Qu[18], Robert J. Pelham[19], and Minal Barve[20]

[1]Institut Catala, Barcelona, Spain; [2]Sarah Cannon Research Institute, Tennessee Oncology, Nashville, TN, USA; [3]Medical Oncology, Montefiore Medical Center, Bronx, NY, USA; [4]START Midwest, Grand Rapids, Michigan, USA; [5]Hematology and Medical Oncology, Icahn School of Medicine at Mount Sinai, New York, NY, USA; [6]START Madrid - CIOCC, Centro Integral Oncológico Clara Campal, Hospital Madrid Norte Sanchinarro, Madrid, Spain; [7]START Madrid - FJD, Hospital Fundación Jiménez Díaz, Madrid, Spain; [8]Medical Oncology, Washington University, St. Louis, MO, USA; [9]Sarah Cannon Research Institute, London, UK; [10]Medical Oncology, Biomedical Research Institute, Incliva, and University of Valencia, Valencia, Spain; [11]Vall d'Hebron, Barcelona, Spain; [12]Peter MacCallum Cancer Centre, Melbourne, Australia; [13]Department of Investigational Cancer Therapeutics, Division of Cancer Medicine, MD Anderson, Houston, TX, USA; [14]Sir Bobby Robson Cancer Trials Research Centre, Translational and Clinical Research Institute, Newcastle University, Newcastle UK; [15]Beatson West of Scotland Cancer Centre, University of Glasgow, Glasgow, UK; [16]Chris O'Brien Lifehouse, Sydney, Australia; [17]St Vincent's Hospital, Sydney, Australia; [18] Biomarker Development & Translational Research, BeiGene USA, Inc., San Mateo, CA, USA; [19]CDx and Biomarker Development, BeiGene USA, Inc., San Mateo, CA, USA; [20]Medical Oncology, Mary Crowley Cancer Research, Dallas, TX, USA

Background: DNA damage caused by the alkylator TMZ can sensitize tumors to PARP inhibitors. Pamiparib, an investigational oral PARP1/2 inhibitor, has shown PARP-DNA complex trapping activity, brain penetration, and synergistic cytotoxicity with LD TMZ in nonclinical studies and preliminary antitumor activity in pts with solid tumors.

Methods: This ongoing phase 1b study consists of a dose-escalation (3+3 design) and dose-expansion phase. In dose escalation, pts received pamiparib 60 mg PO BID on Days 1-28 and LD TMZ at escalating doses PO QD on Days 1-7, 1-14, or 1-28 of each 28-day cycle. Dose-expansion pts, including pts with gastric cancer and SCLC with 1-2 prior lines of chemotherapy, were treated at the recommended phase 2 dose of pamiparib 60 mg PO BID on Days 1-28 and LD TMZ 60 mg PO QD on Days 1-7. Tumor assessments occurred every 8 weeks. Endpoints were safety/tolerability (CTCAE v4.03) and antitumor activity (RECIST v1.1). Biomarker assessments included determination of DDR mutational status (SNV/CNV homozygous loss) of 16 core DDR genes in circulating tumor DNA and genomic instability score (GIS) by the Myriad myChoice® HRD test. Herein, we present data from the biomarker analysis.

Results: As of 10 April 2020, 114 pts were enrolled (n=66, dose escalation; n=48, dose expansion). Median follow-up was 8.5 mo (range: 0.3, 26.5). Of 36 pts analyzed for GIS, 11

(31%) were GIS positive (GIS^+ ≥33), with an ORR of 82% and disease control rate (DCR) of 91% across multiple tumor types. Antitumor activity was observed in $BRCA^m$/GIS^+ (n=5; ORR and DCR, 100%) and $BRCA^{wt}$/GIS^+ pts (n=6; ORR, 67%; DCR, 83%). Responses were observed in 3 GIS^- pts with pancreatic cancer, pheochromocytoma, and nonsquamous NSCLC (ORR=12%; DCR, 52%). Of 104 pts analyzed for DDR mutational status, 27 (26%) were DDR^+, with an ORR of 26% and DCR of 52%. In DDR^- pts, ORR was 14% and DCR was 67%. Five pts were both GIS^+ and DDR^+.

Conclusions: In this limited subset of pts analyzed for GIS status, GIS^+ pts derived superior benefit from pamiparib + LD TMZ, irrespective of *BRCA* status. GIS status appears to be the most robust biomarker to predict response to pamiparib + LD TMZ.

Clinical trial registry number: NCT03150810