SUPPLEMENTARY MATERIALS

Evaluation of Cardiac Repolarization in the Randomized Phase 2 Study of Intermediate- or High-Risk Smoldering Multiple Myeloma Patients Treated with Daratumumab Monotherapy

Ajai Chari • Markus Munder • Katja Weisel • Matthew Jenner • Ceri Bygrave • Maria Teresa Petrucci • Mario Boccadoro • Michele Cavo • Niels W.C.J. van de Donk • Mehmet Turgut • Fatih Demirkan • Ihsan Karadogan • Edward Libby • Robert Kleiman • Steven Kuppens • Rajesh Bandekar • Tobias Neff • Christoph Heuck • Ming Qi • Pamela L. Clemens • Hartmut Goldschmidt

SUPPLEMENTARY METHODS

1.1 Additional Exclusion Criteria

Patients with renal insufficiency, anemia, and primary systemic AL (immunoglobulin light chain) amyloidosis were excluded from the study.

1.2 Electrocardiogram Interval Duration Assessment

Interval duration measurements of RR, PR, QRS, and QT were collected using computer-assisted caliper placements on 3 consecutive beats. Trained analysts reviewed all electrocardiograms (ECGs) for correct lead and beat placement and adjudicated the pre-placed algorithm calipers as necessary using a proprietary validated electronic caliper system applied on a computer screen (manual adjudication methodology). A cardiologist then verified the interval durations and performed the morphology analysis. The ECG interval duration measurements were performed in Lead II, Lead V5 when Lead II was not analyzable, Lead V2 when Lead V5 was not analyzable, followed by the most appropriate lead.

1.3 Statistical Analysis

1.3.1 ECG Central Tendency Analysis

The ECG analysis was based on defining the central tendency of all ECG interval parameter changes (heart rate, PR, QRS, QT, and QT interval corrected by Fridericia's formula [QTcF]) as a change from baseline. A mixed effects general linear model was fit with QTc as the dependent variable, scheduled time point of measurement as the fixed effect, and patient as a random effect. Using the means and intrapatient variance obtained from this model, 2-sided 90% confidence intervals (CIs) were calculated for the difference in the mean QTc from baseline at each

scheduled time point. An effect on QTc was ruled out if the upper bound of the 90% CI for the difference in means between the post-baseline QTc (at each time point) and baseline QTc was <20 ms. Descriptive statistics were used to summarize the ECG variable parameters and the corresponding changes from the mean baseline to each time point for the time-point analysis. Two-sided 90% (1-sided 95%) CIs were produced for the change from baseline data.

Two sets of time-matched analyses were performed using different definitions of baseline. For the primary time-matched by time-point analyses, the baseline was defined as the mean of the ECG interval duration and heart rate measurements of the triplicate ECGs, recorded either at Screening or Cycle 1 Dose 1 pre-dose, which most closely matched the clock time of each set of the Cycle 1 Dose 1 end of infusion (EOI) and Cycle 1 Dose 8 ECGs. It was possible that, for a specific patient, different baselines might be used for each of the on-treatment ECG time points (Cycle 1 Dose 1 EOI, Cycle 1 Dose 8 pre-dose, Cycle 1 Dose 8 EOI, and Cycle 1 Dose 8 1 hour after EOI). For the by time-point analyses, the baseline ECGs were compared to each time point separately for all ECG intervals.

1.3.2. Outlier Analyses

The outlier analysis supplements the central tendency analysis by determining if patients had an exaggerated effect on any ECG interval that would not be revealed in a mean change from baseline central tendency analysis. Criteria defined for these analyses included heart rate, PR interval, QRS interval, QT interval, and QTcF. The categorical outlier analysis was exploratory, and data are presented as a percentage of patients who met the criteria as defined for this analysis.

1.3.3 Pharmacokinetic-Pharmacodynamic Analysis

Pharmacokinetic-pharmacodynamic (PK/PD) concentration response analysis was performed using baseline-adjusted QTc (ΔQTcF), serum concentration of daratumumab, and time [1]. The primary endpoint was change from baseline in QTcF. For the primary analysis, a time-matched baseline was used, as described for the central tendency analyses. A negative result (ie, no evidence of a QTc prolongation) was defined as a model based upper bound of the 2-sided 90% CI of the predicted mean ΔQTcF <20 ms at the observed mean C_{max} for the therapeutic dose of daratumumab.

1.3.4 Sensitivity Analyses

As a sensitivity analysis, central tendency, outlier, and PK/PD analyses were repeated using a time-averaged baseline. Baseline was defined as the mean of the measurement values of the up to 3 ECGs recorded pre-dose at Cycle 1 Dose 1. For any patients who did not have any Cycle 1 Dose 1 pre-dose ECGs, the baseline for this sensitivity analysis was instead the mean of the measurement values of the Screening ECGs that most closely matched the clock time of the Cycle 1 Dose 1 EOI ECGs. For the outlier sensitivity analyses, the maximum change from baseline values were compared to the subject's time-averaged baseline mean value. PK/PD sensitivity analysis used the time-averaged baseline to calculate a change from baseline, and this was matched to the concentration sample after the start of dosing.

Reference

1. Garnett C, Needleman K, Liu J, Brundage R, Wang Y. Operational characteristics of linear concentration-QT models for assessing QTc interval in the thorough QT and phase I clinical studies. Clin Pharmacol Ther. 2016;100:170–178

Supplementary Table 1 Institutional Review Boards or Ethics Committees at Each CENTAURUS Study Site

Region	Institutional Review Board/Ethics Committee
Australia	Alfred Health Human Ethics Committee 55 Commercial Rd Melbourne, VIC, 3004 Australia
	Monash Health 246 Clayton Rd Clayton, Victoria, 3168 Australia
	Central Adelaide Local Health Network Level 4 Womens Health Centre North Terrace, SA, 5000 Australia
	Concord Repatriation General Hospital Research Office Building 20 Hospital Road Concord, NSW, 2139 Australia
	Eastern Health Human Research Ethics Committee Arnold Street Level 2 Number 5 Box Hill, Victoria, 3128 Australia
Canada	UHN Research Ethics Board 700 University Avenue Hydro Building, 10th Floor Suite 1056 Toronto, Ontario, M5G 1Z5 Canada
	Health Research Ethics Board of Alberta Clinical Trials Committee 1500,10104 - 103 Avenue NW Edmonton, Alberta, T5J 4A7 Canada
Czech Republic	Lokalni Eticka komise FN Brno Eticka komise Fakultni nemocnice Brno Jihlavska 20 BRNO, N/A, 625 00 Czech Republic
France	CPP OUEST I Hopital Bretonneau servive de Radiologie Batiment B1A Tours, 37044 France
	CPP Tours - Région Centre (Ouest-1) Département de Radiologie

	Adultes - Bât. B1A Hôpital Bretonneau - CHRU TOURS Tours Cedex 9, 37044 France
Germany	Ethikkommission der Medizinischen Fakultät der Universität Heidelberg Alte Glockengießerei 11/1 Heidelberg, 69115 Germany
	Ethik-Kommission der Medizinischen Fakultät der Universität Duisburg-Essen Robert-Koch-Str. 9-11 Ethik- Kommission der Med. Fakultät d. Universität Essen, 45147 Germany
	Landesamt für Gesundheit und Soziales, Geschäftsstelle der Ethik-Kommission des Landes Berlin Fehrbelliner Platz 1 BERLIN, 10707 Germany
	Ethikkommission der Landesärztekammer Rheinland-Pfalz Deutschhausplatz 3 Mainz, 55116 Germany
	Ethikkommission an der Med. Fakultät der Eberhard-Karls- Universität Tübingen Gartenstr. 47 Tübingen, 72074 Germany
	Ethikkommission bei der Bayerischen Landesärztekammer Mühlbaurstr. 16 München, 81677 Germany
	Ethikkommission der Sächsischen Landesärztekammer Schützenhöhe 16-18 Dresden, 01099 Germany
Great Britain	West Midlands - Edgbaston Research Ethics Committee The Old Chapel Royal Standard Place Nottingham, NG1 6FS Great Britain

Israel	Helsinki Committee - Rabin Medical Center Jabotinky 39 Street Pob 85 Beilinson Campus Petach- Tikva, 35254 Israel
	Helsinki committee - Rambam MC Rambam Medical Center 8 Haaliya Hashniya street Bat Galim Haifa, 31096 Israel
	Helsinki Committee - Sourasky Medical Center 6 Weitzman Street Tel Aviv, 64239 Israel
	Helsinki Committee (IRB) of Hadassah Medical Organization Kiryat Hadassah Jerusalem Jerusalem Israel
Italy	COMITATO ETICO DELL`AZIENDA POLICLINICO UMBERTO I DI ROMA Viale Policlinico 155 N/A N/A Roma, RM, 00161 Italy
	Comitato Etico Regione Liguria c/o IRCCS Az. Ospedaliera Universitaria San Martino IST Istituto Nazionale per la Ricerca sul Cancro Largo Rosanna Benzi, 10 Genova, 16132 Italy
	COMITATO ETICO INTERAZIENDALE AOU CITTA' DELLA SALUTE E DELLA SCIENZA DI TORINO Corso Bramante 88/90 Dipartimento di Oncologia Medica Torino, TO, 10126 Italy
	COMITATO ETICO INDIPENDENTE DELL'AZIENDA OSPEDALIEROUNIVERSITARIAPOLICLINI CO S. ORSOLA-MALPIGHI VIA MASSERENTI 9 BOLOGNA, 40138

	Italy
The Netherlands	Medisch Ethische Toetsingscommissie VU Medisch Centrum de Boelelaan 1117 AMSTERDAM, N/A, 1081 HV Netherlands
Russia	Independent Interdisciplinary Committee on Ethics Expertise of Clinical Trials 51 Leningradsky prospect Moscow, 125468 Russia
Turkey	On Dokuz Mayıs Üniversitesi Tıp Fakültesi Klinik Araştırmalar Etik Kurulu On Dokuz Mayıs Üniversitesi Tıp Fakültesi 1. Kat Özel servis karşısı SAMSUN Turkey
United States	University of Pennsylvania Office of Regulatory Affairs IRB 3624 Market Street - ST. 301-S Suite 301 S Philadelphia, PA, 19104 USA
	Washington University in St. Louis Human Research Protection Office 660 S. Euclid Avenue., Box 8089 Human Research Protection Office (IRB) St. Louis, MO, 63110 USA
	Memorial Sloan-Kettering Cancer Center IRB/Privacy Board 1275 York Avenue New York, NY, 10065 USA
	Western Institutional Review Board 3535 Seventh Avenue SW Olympia, WA, 98502 USA
	BRANY (Biomedical Research Alliance of New York) 1981 Marcus Ave Suite 210 Lake Sucess, NY, 11041 USA
	Western Institutional Review Board

	1019 39th Ave. SE Suite 120 Puyallup, WA, 98374 USA
	IRBMED, University of Michigan 2800 Plymouth Rd Building 200, Room 2086 Ann Arbor, MI, 48109 USA
	Dana-Farber Cancer Institute IRB 450 Brookline Ave. OS-229 Boston, MA, 02215 USA
	Emory University IRB 1599 Clifton Road NE 5th Floor Atlanta, GA, 30322 USA
	Mayo Clinic IRB 200 First Street S W / 20 Rochester, MN, 55905 USA
	NYU School of Medicine IRB 550 1ST Ave N/A N/A New York, NY, 10016 USA
	University of Arkansas for Medical Sciences IRB Institutional Review Board Office of Reserach and Sponsored Programs Sherman Allen, Ph.D., Chairman 4301 West Markham,#636 Little Rock, AK, 72205 USA
	The University of North Carolina of Chapel Hill Office of Human Research Ethics Medical Building 52 Mason Farm Road, CB#7097 Chapel Hill, NC, 27599 USA

IRB institutional review board.

Supplementary Table 2 Mean change from baseline in QTcF interval by timepoint

Time point	n	QTcF Change from Baseline (ms)	90% Confidence Interval (ms)
C1D1 Post-infusion	27	9.1	4.1-14.1
C1D8 Pre-infusion	29	0.3	-4.3-4.9
C1D8 Post-infusion	28	6.9	3.2-10.6
C1D8 1 h Post-infusion	27	7.4	2.7-12.1

QTcF interval QT interval corrected for heart rate using Fridericia's formula, *C* cycle, *D* day.