Supplementary Online Content

Hortobagyi GN, Van Poznak C, Harker WG, et al. Continued treatment effect of zoledronic acid dosing every 12 vs 4 weeks in women with breast cancer metastatic to bone: the OPTIMIZE-2 randomized clinical trial. *JAMA Oncol.* Published online January 19, 2016. doi:10.1001/jamaoncol.2016.6316

This supplementary material has been provided by the authors to give readers additional information about their work.

eMethods. Additional Details of the Study Methods

History of protocol amendments

The final protocol was very different from the original protocol due to several major amendments. The first and the second amendment changed the inclusion criteria, allowing patients who were treated at least 9 doses over the prior 10 to15 months to enter the trial, with no upper limit (was previously 9 to 12 doses over the prior 10 to 12 months); The second amendment removed the placebo arm which was included in the original protocol, and the primary efficacy variable was changed from 'time-to-first Skeletal-Related Events (SRE)' to 'the proportion of patients with at least 1 SRE'. Also, the efficacy comparisons were changed from the original superiority design (zoledronic acid arms versus placebo, and zoledronic acid q4 weeks versus q12 weeks) to the non-inferiority design (zoledronic acid q4 weeks versus q12 weeks). The third amendment reduced the frequency of bone survey tests from once every 3 months to once every 6 months during the study. The fourth amendment reduced the sample size from a total of 705 patients to a total of 423 patients.

Additional details on blinding

Patients in the q12 weeks treatment arm received placebo infusions between active drug doses to maintain the blinding.

Additional details on study design amendment and sample size calculation

The study was designed to include a placebo arm, with a randomization ratio of 2:2:1 for zoledronic acid q4 weeks, q12 weeks and placebo arms, respectively. Consequently, 13 patients were randomly assigned to the placebo arm. Subsequently, with the approval of bisphosphonates, the placebo arm was dropped. All patients who were randomly assigned to the placebo arm were switched to zoledronic acid every 4 weeks; their efficacy data were analyzed separately and were not reported in this paper. Analysis was done at 52 weeks, with treatment duration of 48 weeks.

No SRE data from the second year of treatment with zoledronic acid versus placebo was available at the time of designing this trial. Eventually, the data from the ZOOM trial, which had a similar trial design, reported a SRE incidence which was much lower than the assumed SRE incidence in the OPTIMIZE-2 protocol. Hence, the pooled blinded SRE rate in OPTIMIZE-2 was evaluated at a data cut-off date of December 10, 2010. The pooled SRE rate was 21%, which was substantially lower than the previous SRE rate assumption (48%). The sample size was re-estimated with no change to the statistical requirements (type I error, type II error, and the non-inferiority margin). The new revised sample size was 206 patients per treatment arm plus 11 patients who were assigned to the placebo arm (total N = 423) with an allocation ratio of 1:1.

Additional statistical analysis methodology

At the time this study was designed, no data was available from trials that had randomized patients (who had been pre-treated for one year) into placebo versus continuation of zoledronic acid. The 10% non-inferiority margin as well as the sample size was therefore determined, based on SRE rate data from the first year of treatment. For the sample size, an SRE rate of 48% in the q4 weeks was assumed, and the initial sample size of OPTIMIZE-2 was calculated to be N = 705. While OPTIMIZE-2 was ongoing, data from the ZOOM study became available, and the overall pooled SRE rate (15%) was much lower than expected. A blinded look at the pooled SRE data of OPTIMIZE-2 was conducted and showed the rate of 21%. Based on this lower SRE rate, the sample-size of OPTIMIZE-2 was re-estimated to N = 423 (including the 13 patients who had initially been randomized to placebo, for whom the results are not reported in this paper. This new sample size had a power of 80% to detect the non-inferiority with the non-inferiority margin of ten, with one-sided 5% significance level. However, a decision was made to use the one-sided 2.5% significance level for the analysis i.e. to use the two-sided 95% confidence interval for the SRE rate difference to compare with the non-inferiority margin.

Additional details on assays used for bone marker assessments

uNTX was measured by the Vitros ECi system (Ortho Clinical Diagnostics), using a CLIA (ChemiLuminescent ImmunoAssay) method and BSAP was measured by the Access Immunoassay system (Beckman Coulter) using a CLIA method.

eMaterial. List of Independent Ethics Committees (IECs) or Institutional Review Boards (IRBs) by Study Center

Center No.	Ethics Committee or Institutional Review Board	Department/Organization	City, State/Province, Postal Code	Country
0501	McLaren Regional Medical Center, IRB	McLaren Regional Medical Center	Flint, MI 48532	USA
0504	Sterling Institutional Review Board	Highlands Oncology Group	Atlanta, GA 30339	USA
0506	Sterling Institutional Review Board	Wilshire Oncology Medical Group, Inc	Atlanta, GA 30339	USA
0510	Sterling Institutional Review Board	Gabrail Cancer Center	Atlanta, GA 30339	USA
0511	Sterling Institutional Review Board	Florida Cancer Specialists	Atlanta, GA 30339	USA
0512	Sterling Institutional Review Board	Clintell, Inc	Atlanta, GA 30339	USA
0514	Sterling Institutional Review Board	Bay Area Cancer Research Group, LLC	Atlanta, GA 30339	USA
0515	Western Institutional Review Board	South Texas Oncology and Hematology, PA	Olympia, WA 98502	USA
0517	Main Line Hospitals Institutional Review Board	Lankenau Hospital	Wynnewod, PA 19096	USA
0521	Sterling Institutional Review Board	Southwest Oncology Associates	Atlanta, GA 30339	USA
0522	Sterling Institutional Review Board	Southbay Oncology Hematology Partners	Atlanta, GA 30339	USA
0525	Sterling Institutional Review Board	Ventura County Hematology-Oncology Specialists	Atlanta, GA 30339	USA
0531	St Luke's Hospital Duluth IRB #1	St Luke's Hospital Association of Duluth, Inc	Duluth, MN 55805	USA
0532	Western Institutional Review Board	Providence Everett Medical Center	Olympia, WA 98502	USA
0533	CHRISTUS St Frances Cabrini Hospital Institutional Review Board	CHRISTUS St FrancesCabrini Hospital	Alexandria, LA 71301	USA
0537	Sterling Institutional Review Board	Capitol Comprehensive Cancer Care Clinic	Atlanta, GA 30339	USA
0538	Sterling Institutional Review Board	Hematology Oncology Consultants, Inc	Atlanta, GA 30339	USA
0541	Human Research Protections Office	University of Maryland Greenebaum Cancer Center	Baltimore, MD 21201	USA
0542	Sterling Institutional Review Board	Cotton-O'Neil Cancer Center	Atlanta, GA 30339	USA
0544	St Joseph's Mercy Health Center IRB	St Joseph's Mercy Clinic	Hot Springs, AR 71913	USA
0547	St Barnabas Medical Center Institutional Review Board	St Barnabas Medical Center	Livingston, NJ 07039	USA
0549	Sterling Institutional Review Board	Medical Oncology Care Associates	Atlanta, GA 30339	USA
0552	Research Subject's Protection Program	Institutional Review Board: Human Subjects Committee Fairview Southdale Medical	Minneapolis, MN 55420	USA

		Oncology		
0553	Sterling Institutional Review Board	Magee-Women's Hospital	Atlanta, GA 30339	USA
0554	Western Institutional Review Board	Cancer Care Center, Inc	Olympia, WA 98502	USA
0556	Sterling Institutional Review Board	Lancaster Cancer Center, Ltd	Atlanta, GA 30339	USA
0557	Sterling Institutional Review Board	Eastern Connecticut Hematology and Oncology Associates	Atlanta, GA 30339	USA
0558	Sterling Institutional Review Board	Cancer Care Centers of South Texas	Atlanta, GA 30339	USA
0562	Western Institutional Review Board	HUX Cancer Center	Olympia, WA 98508	USA
0563	Sterling Institutional Review Board	Kentucky Cancer Clinic	Atlanta, GA 30339	USA
0566	Sterling Institutional Review Board	Investigative Clinical Research of Indiana, LLC	Atlanta, GA 30339	USA
0570	Sterling Institutional Review Board	Santee Hematology/Onocology	Atlanta, GA 30339	USA
0571	Siouxland Institutional Review Board	Siouxland Hematology-Oncology Associates, LLP	Sioux City, IA 51101	USA
0572	Wayne State University IRB	Karmanos Cancer Institute	Detroit, MI 48201	USA
0573	Committee for the Protection of Human Subjects in Research	St Peter's University Hospital Somerset Hematology Oncology Associates, PA	New Brunswick, NJ 08901	USA
0575	Guthrie Healthcare Institutional Review Board	Robert Packer Hospital	Sayre, PA 18840	USA
0576	Research Subjects' Protection Program University of Minnesota	University of Minnesota Medical Center	Minneapolis, MN 55455	USA
0577	Sterling Institutional Review Board	Cancer Center of Kansas	Atlanta, GA 30339	USA
0578	Frederick Memorial Hospital Healthcare System, IRB	Frederick Memorial Hospital	Frederick, MD 21701	USA
0583	Sterling Institutional Review Board	Barberton Citizens Hospital Cancer Center	Atlanta, GA 30339	USA
0585	Sterling Institutional Review Board	Ohio Cancer Specialists, Inc	Atlanta, GA 30339	USA
0587	Sterling Institutional Review Board	Arena Oncology Associates, PC	Atlanta, GA 30339	USA
0590	Western Institutional Review Board	Anchorage Oncology Centre	Puyallup, WA 98374	USA
0591	Caritas St Elizabeth's Medical Center Institutional Review Board, HOQ326	Caritas Holy Family Hospital	Boston, MA 02135	USA
0593	Baptist Medical Center Institutional Review Board	Baptist Cancer Institute	Jacksonville, FL 32207	USA
0594	Sterling Institutional Review Board	Oncology Care Associates, PLLC	Atlanta, GA 30339	USA
0596	COMIRB/UCDHSC, MS F490 DHMC	Hematology/Oncology	Aurora, CO 80045	USA

0598	Research Institute NorthShore University HealthSystem	Evanston Hospital	Evanston, IL 60201	USA
0601	Sterling Institutional Review Board	Center for Cancer and Blood Disorders	Atlanta, GA 30339	USA
0604	Sterling Institutional Review Board	Jackson Oncology Associates	Atlanta, GA 30339	USA
0607	Sterling Institutional Review Board	Nevada Cancer Centers	Atlanta, GA 30339	USA
0611	Sterling Institutional Review Board	The Corvallis Clinic, PC	Atlanta, GA 30339	USA
0612	Sterling Institutional Review Board	Nebraska Hematology-Oncology, PC	Atlanta, GA 30339	USA
0613	Human Subjects Review Committee University of California, Davis	University of California, Davis Medical Center	Sacramento, CA 95817	USA
0614	Sterling Institutional Review Board	Gwinnett Hospital System, Inc dba The Center for Cancer		
Care	Atlanta, GA 30339	USA		
0615	The University of Texas MD Anderson Cancer Center Institutional Review Board Box 198	The University of Texas MD Anderson Cancer Center	Houston, TX 77030	USA
0617	Sterling Institutional Review Board	Pacific Coast Hematology/Oncology Medical Group, Inc	Atlanta, GA 30339	USA
0618	Sterling Institutional Review Board	Metropolitan Hematology/Oncology Medical Group	Atlanta, GA 30339	USA
0619	Sterling Institutional Review Board	Pacific Cancer Medical Center, Inc	Atlanta, GA 30339	USA
0620	Alamance Regional Medical Center IRB	Alamance Regional Medical Center and Cancer Center	Burlington, NC 27215	USA
0622	MedStar Research Institute Georgetown University Oncology Institutional Review Board	Georgetown University Medical Center Lombardi Comprehensive Cancer Center	Washington, DC 20057	USA
0623	Sterling Institutional Review Board	Kansas City Cancer Center, LLC	Atlanta, GA 30339	USA
0626	Edward Hospital IRB	Edward Cancer Center	Naperville, IL 60540	USA
0635	North Memorial Health Care Institutional Review Board	Hubert H Humphrey Cancer Center	Robbinsdale, MN 55422	USA
0638	Sterling Institutional Review Board	North Valley Hematology/Oncology Medical Care Center	Atlanta, GA 30339	USA
0642	University of Michigan Institutional Review Board IRBMED	University of Michigan Comprehensive Cancer Center	Ann Arbor, MI 48109	USA
0651	Sterling Institutional Review Board	Desert Cancer Care, Inc	Atlanta, GA 30339	USA
0653	Sterling Institutional	Hudson Valley Oncology,	Atlanta, GA	USA

	Review Board	PC	30339	
0657	Sterling Institutional Review Board	Francisco Gonzalez, MD, PA	Atlanta, GA 30339	USA
0659	Sterling Institutional Review Board	Advanced Oncology Associates	Atlanta, GA 30339	USA
0660	Institutional Review Board Beth Israel Medical Center	Beth Israel Medical Center	New York, NY 10038	USA
0662	Penn State College of Medicine Penn State Milton S Hershey Medical Center Human Subjects Protection Office, A115	Penn State Milton S Hershey Medical Center	Hershey, PA 17033	USA
0664	MedStar Research Institute Georgetown University Oncology Institutional Review Board	Harry and Jeanette Weinberg Cancer Institute	Washington, DC 20057	USA
0671	Sterling Institutional Review Board	Swarna S Chanduri, MD	Atlanta, GA 30339	USA
0673	CHS Institutional Review Board	NorthEast Oncology		
Associates	Concord, NC 28025	USA		
0677	Western IRB	University of Iowa Hospitals and Clinics	Olympia, WA 98502	USA
0678	Sterling Institutional Review Board	Regional Cancer Care Associates Cherry Hill Division	Atlanta, GA 30339	USA
0679	Memorial Sloan-Kettering Cancer Center Institutional Review Board	Memorial Sloan-Kettering Cancer Center	New York, NY 10021	USA
0680	Sterling Institutional Review Board	Davood Vafai, MD	Atlanta, GA 30339	USA
0681	Office for the Protection of Research Subjects IRB	Northwestern University	Chicago, IL 60611	USA
0682	Sterling Institutional Review Board	Trilogy Cancer Center	Atlanta, GA 30339	USA
0683	Froedtert and Medical College of Wisconsin IRB	Froedtert and Medical College of Wisconsin	Milwaukee, WI 53226	USA
0687	Henry Ford Health System Institutional Review Board	Henry Ford Health System	Detroit, MI 48202	USA
0690	Sterling Institutional Review Board	Florida Cancer Research Institute	Atlanta, GA 30339	USA
0692	Sterling Institutional Review Board	Rockwood Clinic, PS	Atlanta, GA 30339	USA
0693	Sterling Institutional Review Board	St Agnes HealthCare, Inc	Atlanta, GA 30339	USA
0695	Western IRB	University of Rochester Medical Center	Olympia, WA 98508	USA
0698	Columbus Regional Institutional Review Committee	John B. Amos Cancer Center	Columbus, GA 31902	USA
0701	Sterling Institutional Review Board	United Cancer Specialists	Atlanta, GA 30339	USA

0703	Central Baptist Institutional Review Board	Central Baptist Hospital	Lexington, KY 40503	USA
0704	Sterling Institutional Review Board	Redwood Regional Medical Group	Atlanta, GA 30339	USA
0705	Sterling Institutional Review Board	Pacific Shores Medical Group	Atlanta, GA 30339	USA
0708	St John's Mercy Medical Center Institutional Review Board	St John's Mercy Medical Center	St Louis, MO 63141	USA
0709	Bay Area Hospital IRB #1	Bay Area Hospital	Coos Bay, OR 97420	USA
0710	Fred Hutchinson Cancer Research Center IRB	Seattle Cancer Center Alliance	Seattle, WA 98109	USA
0711	UT Southwestern Medical Center Institutional Review Board	UT Southwestern Medical Center	Dallas, TX 75390	USA
0714	MedStar Health Research Institute Georgetown University Oncology Institutional Review Board	Washington Cancer Institute at MedStar Washington Hospital Center	Washington, DC 20057	USA
0715	OV-UCLA Education and Research Institute	Olive View UCLA Medical Center	Sylmar, CA 91342	USA
0717	Sterling Institutional Review Board	Medical Associates Clinic, PC	Atlanta, GA 30339	USA
0718	Sterling Institutional Review Board	Cedar Valley Medical Specialists, PC	Atlanta, GA 30339	USA
0720	Summa Health System IRB	Summa Health System	Akron, OH 44304	USA
0723	Columbia University IRB	Columbia University Medical Center	New York, NY 10032	USA

eResults. Additional Details of the Study Results

Additional demographic and baseline data

The majority of patients were Caucasians (88%), with a mean age of 59 years. The mean baseline composite pain score was comparable between the q4 weeks group 2.03 (1.90) and the q12 weeks group 2.22 (2.09). Prior to the study, the majority of patients had been treated with IV bisphosphonates for more than 15 months (n = 226 [54.3%]) and had a uNTX/Cr level of less than 100 nmol BCE/mmol creatinine (n = 405 [97.4%]).

Additional details on cardiac adverse events

One patient in q4 weeks group and two patients in q12 weeks group experienced cardiac ischemic events. One patient in q4 weeks group and two patients in q12 weeks group experienced an atrial fibrillation TEAE.

eTable 1. Number of Infusions Before the Study

	Zoledronic acid every 4 weeks (n = 198)	**Zoledronic acid every 12 weeks (n = 202)**
Number of zoledronic acid infusions prior to study		
N	194	200
Mean (SD)	20.6 (14.02)	18.8 (12.29)
Median	15.0	14.0
Min, Max	1, 80	1, 74
Number of pamidronate infusions prior to study		
N	15	11
Mean (SD)	12.3 (10.07)	22.6 (27.30)
Median	11.0	13.0
Min, Max	1, 35	1, 93

SD= standard deviation

eTable 2. Renal Adverse Events

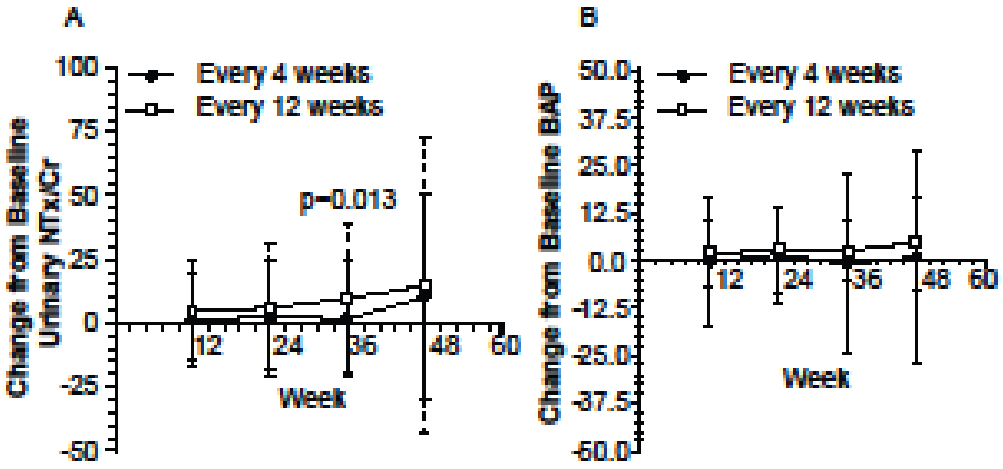
	Zoledronic acid every 4 weeks (n = 198)	**Zoledronic acid every 12 weeks (n = 202)**
Number of patients with at least one renal adverse event	19 (9.6%)	16 (7.9%)
Investigations	17 (8.6%)	8 (4.0%)
Blood creatinine increased	10 (5.1%)	4 (2.0%)
Creatinine renal clearance decreased	6 (3.0%)	5 (2.5%)
Blood urea increased	3 (1.5%)	1 (0.5%)
Creatinine renal clearance abnormal	1 (0.5%)	-
Glomerular filtration rate decreased	1 (0.5%)	-
Renal and urinary disorders	2 (1.0%)	9 (4.5%)
Renal failure	1 (0.5%)	5 (2.5%)
Renal failure acute	1 (0.5%)	2 (1.0%)
Azotaemia	-	1 (0.5%)
Renal impairment	-	1 (0.5%)

eTable 3. On-treatment Deaths

Cause of death	Zoledronic acid every 4 weeks (n = 10)	Zoledronic acid every 12 weeks (n = 7)	Placebo/ zoledronic acid (n = 1)[a]	Total (N = 18)
Metastatic disease	8	4	1	13
Sepsis	-	2	-	2
Multi-organ failure	1	-	-	1
Liver failure	1	-	-	1
Subdural hematoma		1	-	1

[a]The study was designed to include a placebo arm, with a randomization ratio of 2:2:1 for zoledronic acid q4 weeks, q12 weeks and placebo arms, respectively. Consequently, 13 patients were randomly assigned to the placebo arm. Subsequently, with the approval of bisphosphonates, the placebo arm was dropped. All patients who were randomly assigned to the placebo arm were switched to zoledronic acid q4 weeks; their efficacy data were analyzed separately and were not reported in this paper.

eFigure. Change From Baseline in Bone Biomarker Levels



(A) Urinary N- telopeptide normalized for urinary creatinine (uNTX/Cr) and (B) serum bone-specific alkaline phosphatase (BAP).