Supplementary Appendix

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

Supplement to: Yu AL, Gilman AL, Ozkaynak MF, et al. Anti-GD2 antibody with GM-CSF, interleukin-2, and isotretinoin for neuroblastoma. N Engl J Med 2010;363:1324-34.

Supplemental data

Table S1. List of COG participating institutions

COG Participating Institutions
A.B. Chandler Medical Center - University of Kentucky, Lexington
A.I. duPont Hospital for Children, Wilmington
Albany Medical Center, Albany
Alberta Children's Hospital, Calgary
All Children's Hospital, St. Petersburg
Allan Blair Memorial Clinic
Backus Children's Hospital at MHUMC, Savannah
Baptist Children's Hospital, Miami
Baylor College of Medicine
Baystate Medical Center, Springfield
Bellin Memorial Hospital
Boston Floating Hospital
British Columbia's Children's Hospital, Vancouver
Broward General Medical Center, Ft. Lauderdale
C.S. Mott Children's Hospital, Ann Arbor
CancerCare Manitoba, Winnipeg
Cardinal Glennon Children’s Medical Center, St. Louis
Carolinas Medical Center, Charlotte
Cedars-Sinai Medical Center, Los Angeles
Centre Hospitalier Universitaire de Quebec, Quebec
Children's Healthcare of Atlanta, Emory University, Atlanta
Children's Hem/Onc Team @ Covenant Children's Hosp, Lubbock
Children's Hospital Cent Georgia
Children's Hospital Central California, Madera
Childrens Hospital Los Angeles, Los Angeles
Childrens Hospital Medical Center-Akron, Ohio, Akron
Childrens Hospital Oakland, Oakland
Children's Hospital of Eastern Ontario, Ottawa
Children's Hospital of Michigan, Detroit
Childrens Hospital of Orange County, Orange
Childrens Hospital of Philadelphia, Philadelphia
Children's Hospital of the Greenville Hospital System, Greenville
Children's Hospital, London Health Sciences Centre, London
Childrens Hospital-King's Daughters, Norfolk
Childrens Hospitals and Clinics of Minnesota, Minneapolis
Children's Medical Center Dayton, Dayton
Children's Memorial Medical Center at Chicago, Chicago
Children's National Medical Center - D.C., Washington
Children's of New Orleans/LSUMC CCOP, New Orleans
Cincinnati Children's Hospital Medical Center, Cincinnati
City of Hope National Medical Center, Duarte
Connecticut Children's Medical Center, Hartford

Cook Children's Medical Center, Fort Worth
Dakota Midwest Cancer Institute
Dana-Farber Cancer Institute and Children's Hosp, Boston
Dartmouth-Hitchcock Medical Center, Lebanon
Dell Children's Medical Center of Central Texas, Austin
Doernbecher Children's Hospital
Driscoll Children's Hospital, Corpus Christi
Duke University Medical Center, Durham
East Tennessee Childrens Hospital, Knoxville
Eastern Maine Medical Center, Bangor
Emanuel Hospital-Health Center, Portland
Florida Hospital Cancer Institute, Orlando
Geisinger Medical Center, Danville
Georgetown University Medical Center
Hackensack University Medical Center, Hackensack
Helen DeVos Children's Hospital, Grand Rapids
Hopital Sainte-Justine, Montreal
Hospital for Sick Children, Toronto
Hurley Medical Center, Flint
Indiana University - Riley Childrens Hospital, Indianapolis
Inova Fairfax Hospital, Fairfax
IWK Health Centre, Halifax
Janeway Child Health Centre, St. John's
Joe DiMaggio Children's Hospital at Memorial , Hollywood
Johns Hopkins Hospital, Baltimore
Kaiser Permanente Medical Group, Inc., Northern CA, Sacramento
Kalamazoo Center for Medical Studies
Kosair Childrens Hospital, Louisville
Lee Memorial Health System, Ft. Myers
Lehigh Valley Hospital - Muhlenberg, Bethlehem
Loma Linda University Medical Center, Loma Linda
M.D. Anderson Cancer Center Orlando, Orlando
M.U.S. Carolina
Marshfield Clinic, Marshfield
Mayo Clinic, Rochester
McMaster University, Hamilton
Medical City Children's Hospital, Dallas
Mercy Children's Hospital, Toledo
Methodist Children's Hospital of South Texas, San Antonio
Miami Children's Hospital
Michigan State University, East Lansing
Midwest Children's Cancer Center, Milwaukee
Miller Children's Hospital/Harbor-UCLA, Long Beach
Mission Hospitals, Asheville
Montefiore Medical Center, Bronx
Mount Sinai Medical Center, New York
Nationwide Children's Hospital, Columbus

Naval Medical Center/Portsmouth (USOC), Portsmouth
Nemours Children's Clinic-Jacksonville, Jacksonville
Nemours Children's Clinic-Orlando, Orlando
Nevada Cancer Research Foundation - CCOP, Las Vegas
New York Medical College, Valhalla
Newark Beth Israel Medical Center, Newark
Penn State Children's Hospital, Hershey Med Center, Hershey
Phoenix Childrens Hospital, Phoenix
Presbyterian Hospital, Charlotte
Primary Childrens Medical Center, Salt Lake City
Princess Margaret Hospital for Children, Perth
Rady Children's Hospital San Diego, San Diego
Rainbow Babies Hospital
Raymond Blank Children's Hospital, Des Moines
Rhode Island Hospital, Providence
Roswell Park Cancer Institute/WCHOB, Buffalo
Royal Children's Hospital, Brisbane, Brisbane
Sacred Heart Children's Hospital, Spokane
Sacred Heart Hospital, Pensacola
Saint Peter's University Hospital, New Brunswick
San Jorge Children's Hospital
Sanford Children’s Specialty Clinics, Sioux Falls
Saskatoon Cancer Center, Saskatoon
Seattle Children's, Seattle
Sinai Hospital of Baltimore, Baltimore
South Carolina Cancer Center, Columbia
Southern California Permanente Medical Group, Downey
Southern Illinois University School of Medicine, Springfield
St John Hospital and Medical Center, Grosse Point Woods
St. Christopher's Hospital for Children, Philadelphia
St. Jude Children's Research Hospital Memphis, Memphis
St. Jude Midwest Affiliate, Peoria
St. Mary's Hospital, West Palm Beach
St. Vincent Children's Hospital - Indiana, Indianapolis
St. Vincent Hospital - Wisconsin, Green Bay
Stanford University Medical Center, Palo Alto
Stollery Children's Hospital, Edmonton
SUNY Upstate Medical University, Syracuse
Sutter Medical Center, Sacramento, Sacramento
T.C. Thompson Children's Hospital, Chattanooga
Tampa Children's Hospital, Tampa
The Children's Hospital - Denver, CO, Aurora
The Children's Hospital at The Cleveland Clinic, Cleveland
The Children's Hospital at Westmead, Westmead
The Childrens Mercy Hospital, Kansas City
The University of Chicago Comer Children's Hosp, Chicago
Tod Children's Hospital-Forum

Toledo Children's Hospital, Toledo
Tulane Univ./Tulane Univ. Hospital and Clinic, New Orleans
UCLA David Geffen School of Medicine, Los Angeles
UCSF School of Medicine, San Francisco
University of Alabama at Birmingham, Birmingham
University of Arizona Health Sciences Center, Tucson
University of California, Davis, Sacramento
University of Florida, Gainesville
University of Hawaii/Kapiolani Medical Center
University of Illinois, Chicago
University of Iowa Hospitals & Clinics, Iowa City
University of Minnesota Cancer Center, Minneapolis
University of Mississippi Medical Center Children's Hospital, Jackson
University of Nebraska Medical Center, Omaha
University of New Mexico School of Medicine, Albuquerque
University of North Carolina at Chapel Hill, Chapel Hill
University of Oklahoma Health Sciences Center, Oklahoma City
University of Pittsburgh, Pittsburgh
University of Rochester Medical Center, Rochester
University of Vermont College of Medicine, Burlington
University of Virginia
University of Wisconsin-AFCH
UT Southwestern Medical Center, Dallas
Vanderbilt Children's Hospital, Nashville
Via Christian Regional Medical Center
Virginia Commonwealth University Health System-MCV, Richmond
Wake Forest University School of Medicine, Winston-Salem
Washington University Medical Center, St. Louis
Wesley Medical Center
Winthrop University Hospital, Mineola

Table S2. Baseline characteristics for 25 eligible patients nonrandomly assigned to immunotherapy on COG study ANBL0032

Characteristic		Immunotherapy n (%)*
Age	< 18 mo	0 (0)
	≥ 18 mo	25 (100)
INSS stage	2	0 (0)
	3	2 (8)
	4s	0 (0)
	4	23 (92)
MYCN status	Not amplified	15 (71)
	Amplified	6 (29)
	unknown	*4*
Histology	Favorable	0 (0)
	Unfavorable	16 (100)
	unknown	*9*
Ploidy	Hyperdiploid	8 (40)
	Diploid	12 (60)
	unknown	*5*
Pre-ASCT Response	CR	0 (0)
	VGPR	4 (16)
	PR	21 (84)
Number of ASCTs	1	24 (96)
	2	1 (4)

* column percentage; percentage missing or unknown shown in *italics*. Number missing or unknown have been excluded from the calculation of the percentages.

Supplemental Figure Legends

Figure S1 Immunotherapy Treatment Schema

Figure S2. Group sequential Lan-DeMets upper monitoring boundary and observed z-scores over time (black line with triangles). Time is measured on the x-axis by the fraction of information [proportion of events] observed. The efficacy boundary was generated using an alpha x time^2 spending function for a cumulative alpha level of 0.025 (blue line with blue diamonds).
The 0.025 monitoring boundary was reached after observation of 61% of the expected number of events.

Figure S3. EFS and OS for 25 patients non-randomly assigned to receive immunotherapy. Kaplan-Meier curves for OS and EFS are shown for the 25 patients non-randomly assigned to immunotherapy because of biopsy-proven neuroblastoma following ASCT. The numbers of patients at risk for an event (EFS) or death (OS) at a given timepoint are provided below the x-axis.

Figure S1. Immunotherapy Treatment Schema

Figure S1A. Overall schedule of ch14.18, GM-CSF, IL2 and 13cisRA

Course 1	**Course 2**	**Course 3**	**Course 4**	**Course 5**	**Course 6**
Ch14.18	Ch14.18	Ch14.18	Ch14.18	Ch14.18	
GM-CSF	IL-2	GM-CSF	IL-2	GM-CSF	
13cisRA	13cisRA	13cisRA	13cisRA	13cisRA	13cisRA

Ch14.18: 25mg/m^2 x 4 days, q 4 weeks

Courses 1, 3, 5: GM-CSF 250 mcg/m^2 x 14 days, starting 3 days before ch14.18

Courses 2, 4: IL2 3.0 x10^6 IU/m^2 x 4 days on week one, IL2 4.5 x x10^6 IU/m^2 x 4 days on week two with ch14.18.

13cisRA: 160mg/m^2 x 14 days

Figure S1B. Treatment schema for courses 1, 3, & 5 with GM-CSF (28 days per course)

Day	0	1	2	3	4	5	6	7	8	9	10-13	24
GM-CSF	X	X	X	X	X	X	X	X	X	X	X	
ch14.18				X	X	X	X					
13cisRA											X	
Begin Course 2&4												X

Figure S1C. Treatment Schema for Courses 2 & 4 with IL2

Day	0	1	2	3	4-6	7	8	9	10	11-13	14-27	28
IL2	X	X	X	X		X	X	X	X			
Ch14.18						X	X	X	X			
13cisRA											X	
Begin course 3&5												X

Figure S2. Group sequential Lan-DeMets upper monitoring boundaries

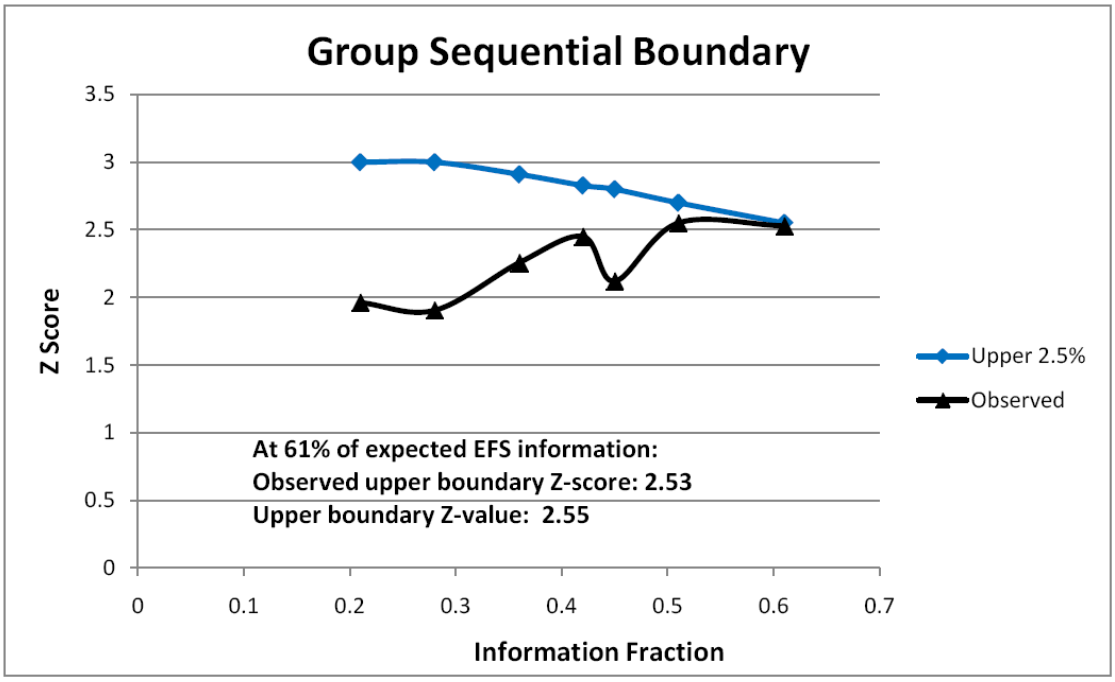
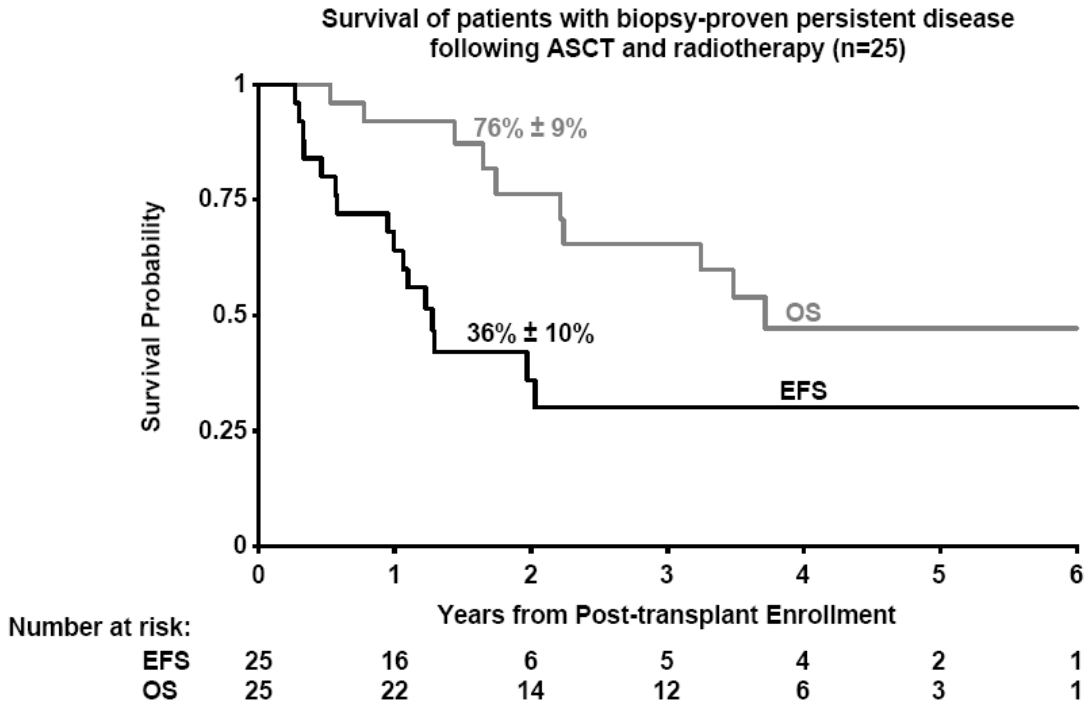


Figure S3. EFS and OS for 25 patients non-randomly assigned to receive immunotherapy.



Supplemental Explanatory Material:

Treatment prior to enrolling in this study:

During the first 6 years of this study, the majority of patients received induction and myeloablative therapy per the COG A3973 protocol. This consisted of an induction regimen with 4 cycles of cyclophosphamide, doxorubicin, vincristine, interspersed with 2 cycles of cisplatin and etoposide, and surgical resection of residual disease. This was followed by a conditioning regimen with carboplatin, etoposide, and melphalan (CEM) for ASCT. Since 2008, most patients received therapy per COG ANBL0532 which was activated in November 2007. It consists of the same induction therapy as A3973, except for substituting 2 cycles of dose intensive cyclophosphamide and topotecan for the initial 2 cycles of the A3973 induction. Following induction therapy, patients are randomized to either one myeloablative consolidation with CEM or two myeloablative consolidations. For the latter, the first conditioning regimen is Thiotepa plus cyclophosphamide and the second is the standard CEM Regimen. After ASCT, all patients received local irradiation before enrolling into this ANBL0032 study.

Follow up:

Median follow-up after randomization in patients alive without an event was 2.0 years (5 days to 6.5 years) and 2.1 years (4 days to 6.9 years) for the immunotherapy group and the standard therapy group, respectively.

Method of randomization:

Patients were stratified according to pre-autologous stem cell transplantation (ASCT) response ("complete" vs "very good partial" vs "partial"), stem cells received ("purged" vs "unpurged"), and frontline chemotherapy ("COG-A3973" vs. "POG 9341/9342" vs. "COG-ANBL02P1" vs "other therapy"). Patients in the first set of strata were randomized to immunotherapy or standard

therapy treatment arms. A further stratum consisted of patients with biopsy-confirmed post-ASCT persistent disease who were not randomized but assigned to the immunotherapy treatment."

Stratified permuted blocks were used for randomization. Procedurally this was accomplished by the COG Remote Data Entry (RDE1) system. The treatment group was assigned in real-time based on the balance existing at that time within "blocks", where blocks in this case were the study strata. The block size, or "margin" was set (margin=2 within each stratum) prior to the activation of the study. In this RDE approach, the treatment group assignment is random until such time as a margin within a stratum is exceeded, and only then does the method become deterministic. Once a randomized treatment group assignment was made for a given patient, that patient's treatment group was never changed for any reason.