Supplementary Contents

Supplementary Methods

Vitamin D Assay Details

Baseline measurement of vitamin D2 and D3 by liquid chromatography – tandem mass spectrometry was performed centrally by the University of Rochester Central Laboratory. In brief, serum specimens were placed on protein crash plates with a precipitating solvent (acetonitrile and internal standard). The plate was mixed and placed on a positive pressure manifold to transfer supernatant to the collection plate. The collection plates were put directly on the HPLC autosampler for analysis. The samples were injected onto a high-flow HPLC column and then into the tandem mass spectrometer ionization source. Ions specific to the analytes and internal standards were monitored and their abundance indicated the amount of analyte molecules present. Quantitation was achieved by reference to calibrators of known concentration, which were analyzed with the patient samples.

The multiplex analyzer (LCMS5) uses two HPLC platforms, two autosamplers, and one mass spectrometer - API 4000 Qtrap. The multiplex software allows for injecting another sample while the prior sample is going through the mass spectrometer, thus maximizing the analyzer throughput. Samples are injected onto a C18 Monolithic silica HPLC column equilibrated to 30% methanol. After a short wash step, the methanol concentration is rapidly increased to 80% and then slowly ramped to 90% to elute the 25-OH-Vitamin D2 and D3. A diverter valve re-directs the flow from waste to tandem mass spectrometer. Analytes elute into the Atmospheric Pressure Chemical Ionization (APCI) source where the molecules ionize and are drawn into the mass spectrometer.

In this assay, the masses corresponding to the protonated molecule minus a water molecule (M+H+-18) are selected in the first set of quadrupoles (Q1). Q1 masses are 395·4, 383·4, and 389·4 for 25-OH-Vitamin D2, 25-OH-Vitamin D3, and hexadeuterium-25-OH-Vitamin D3 respectively. Ions are fragmented in the collision chamber and specific fragments are selected for detection in the third set of quadrupoles (Q3). Q3 masses are 209·1, 211·3, and 211·3 for 25-OH-Vitamin D2, 25-OH-Vitamin D3, and hexadeuterium-25-OH-Vitamin D3 respectively. Quantitation is based on the integrated peak areas of the fragment ions detected. After elution is complete, the column switching valves allow a sample to be injected onto the second column, while the first column is washed with 95% methanol to remove any interfering compounds and re-equilibrated at 30% methanol.

PTH Assay Details

PTH was measured at baseline centrally by the University of Rochester Central Laboratory. Electrochemiluminescence immunoassays (Elecsys PTH STAT) were performed using the automated Roche Cobas e602 via (Roche Diagnostics, Indianapolis, IN).

Whole Exome Sequencing and Polymorphism Analysis

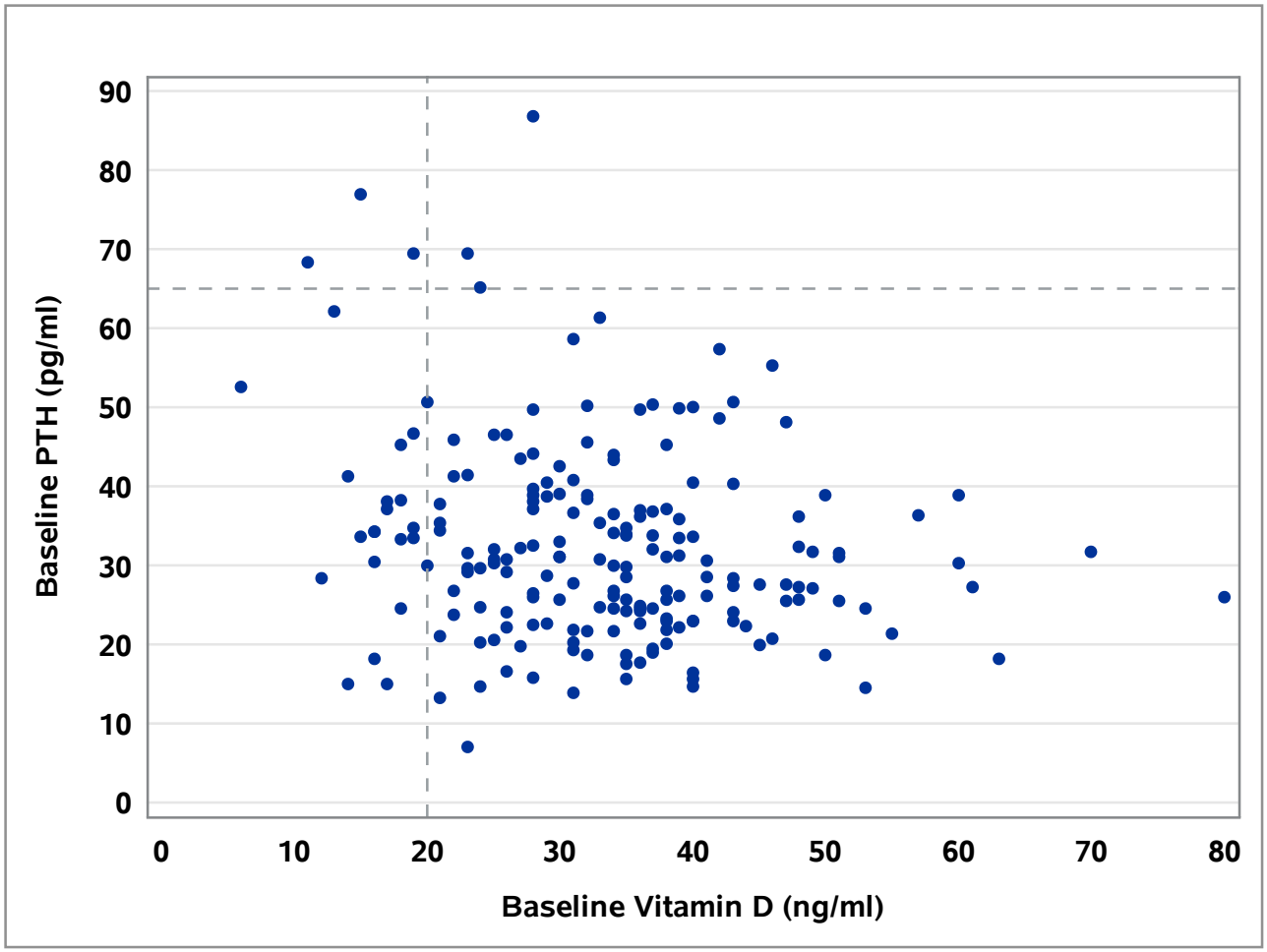
Saliva was collected for the isolation of germline DNA using Oragene collection kits, OGR-500, and extracted using the prepIT DNA recovery kits (both from DNA Genotek, Ottawa, Canada). Purified genomic DNA was quantified using the Qubit Flourometer (ThermoFisher, Waltham, MA) and quality was assessed with the gDNA tapestation assay (Agilent Technologies, Santa Clara, CA). Whole exome libraries were generated using SureSelectXT Whole Exome v6 (+UTRs) per manufacturer's recommendations (Agilent Technologies). Briefly, 4µg of genomic DNA was sheared with Covaris S2 (Covaris, Woburn, MA) to an average peak size of 250bp followed by end repair, poly adenylation, Illumina adaptor ligation, and purification with AmpureXP (Beckman Coulter, Brea, CA). Library amplification was carried out with 250ng of purified DNA with 4 cycles of PCR followed by AmpureXP purification (Beckman Coulter). Exome probe hybridization capture was performed per manufacturer's protocols. Exome target enriched samples were quantified using the Qubit Flourometer (ThermoFisher) and library sizing was assessed with the high sensitivity Bioanalyzer 2100 DNA assay (Agilent Technologies). Whole exome libraries were normalized, pooled and 2x150 pair end sequencing was performed with the NovaSeq 6000 (Illumina, San Diego, CA).

Supplementary Table 1. Week 13 Overall and Complete Response Rates by Arm and Histology

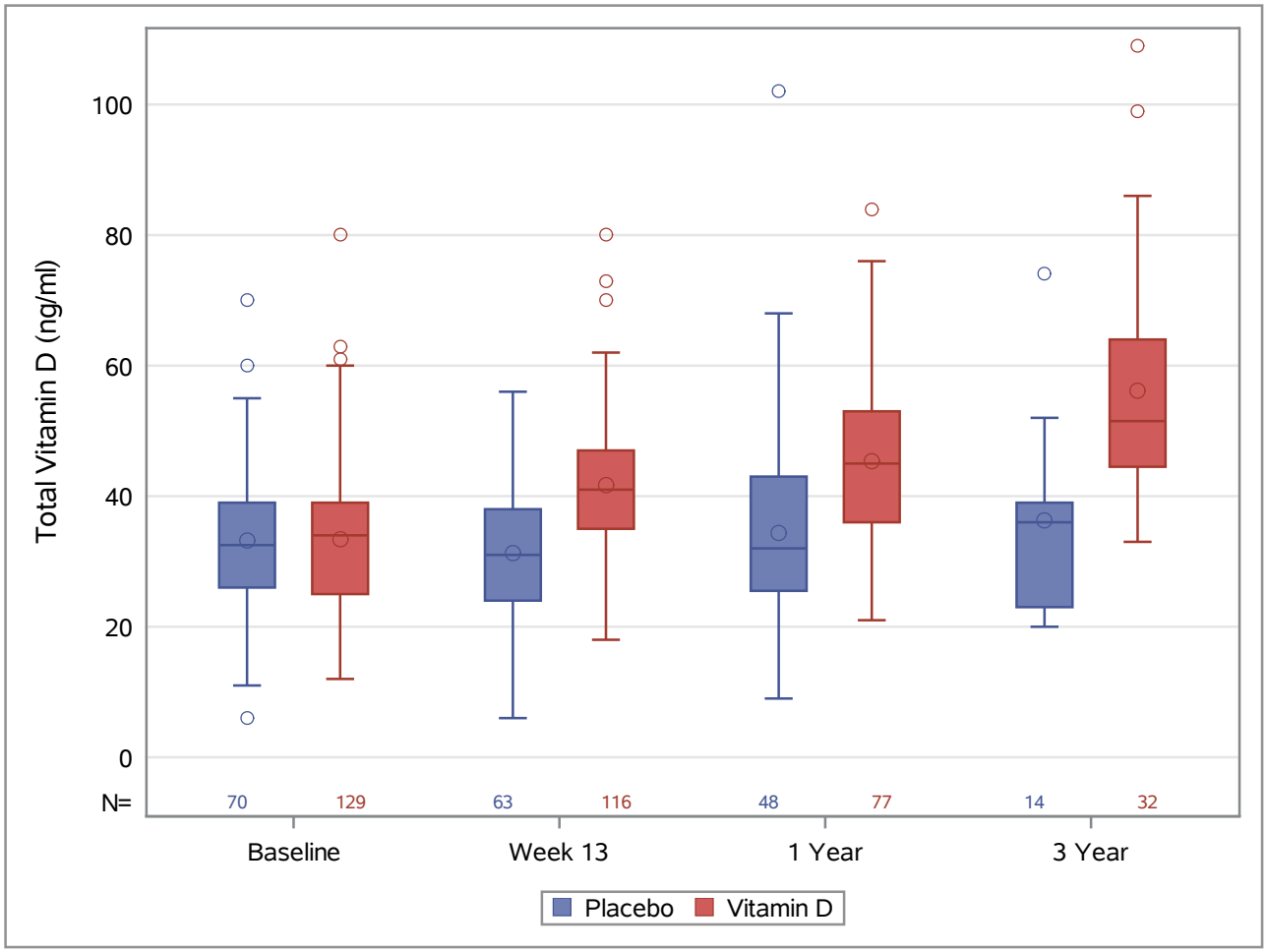
	Vitamin D Arm			Placebo Arm		
	N	**ORR (%)**	**CR (%)**	**N**	**ORR (%)**	**CR (%)**
All Histologies	135	113 (84)	70 (52)	70	59 (84)	40 (57)
Follicular	89	83 (93)	50 (56)	48	44 (92)	29 (60)
SLL	13	8 (62)	6 (46)	8	3 (38)	3 (38)
Marginal Zone	33	22 (67)	14 (42)	14	12 (86)	8 (57)

No treatment comparisons of response rates were statistically significant (P > 0·25 for all)

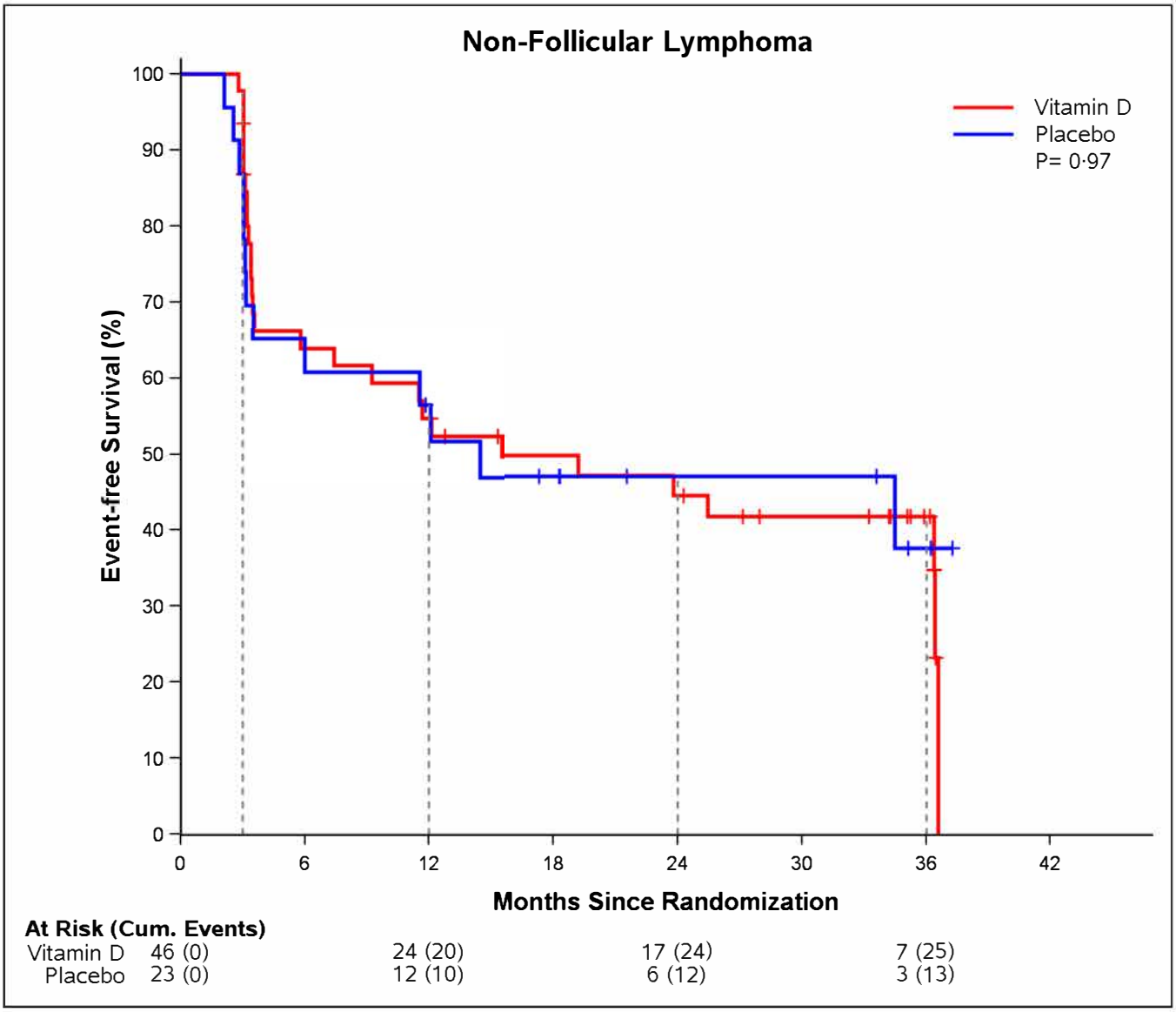
Supplementary Figure 1. Association Between Baseline Vitamin D and PTH



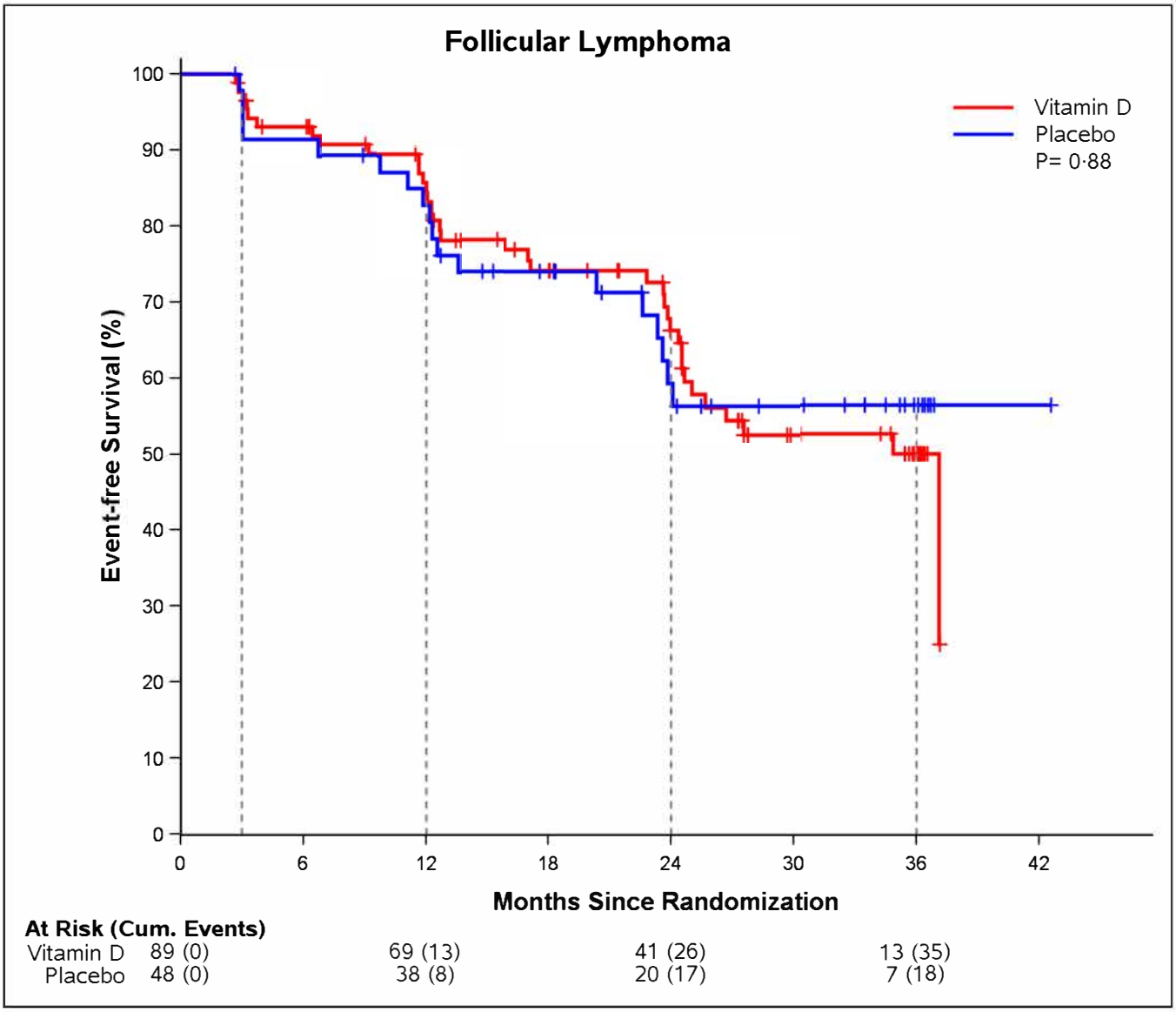
Supplementary Figure 2. Serum Vitamin D Levels by Arm Over Time



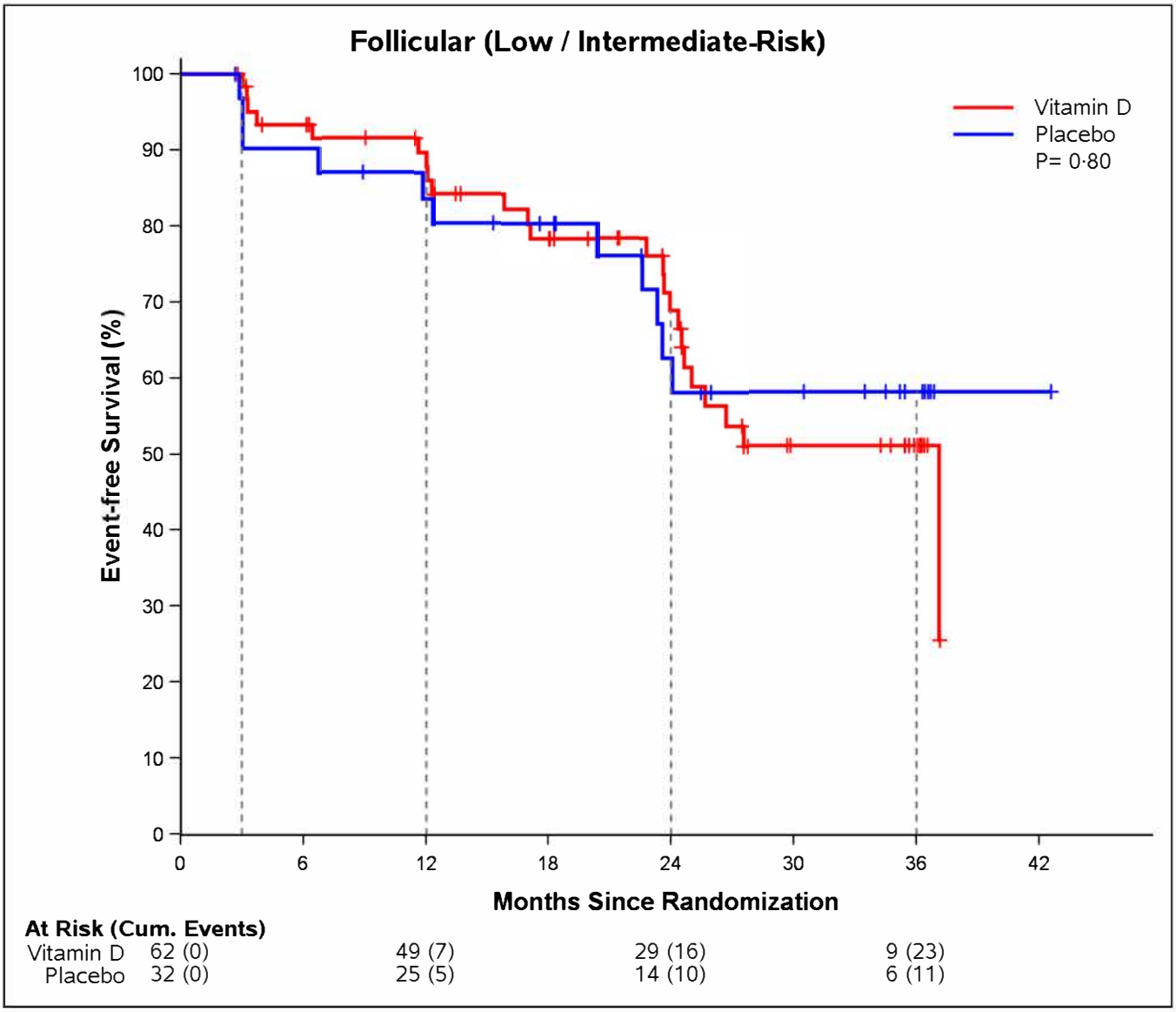
Supplementary Figure 3. Event-Free Survival by Arm in Patients with Non-Follicular Lymphoma



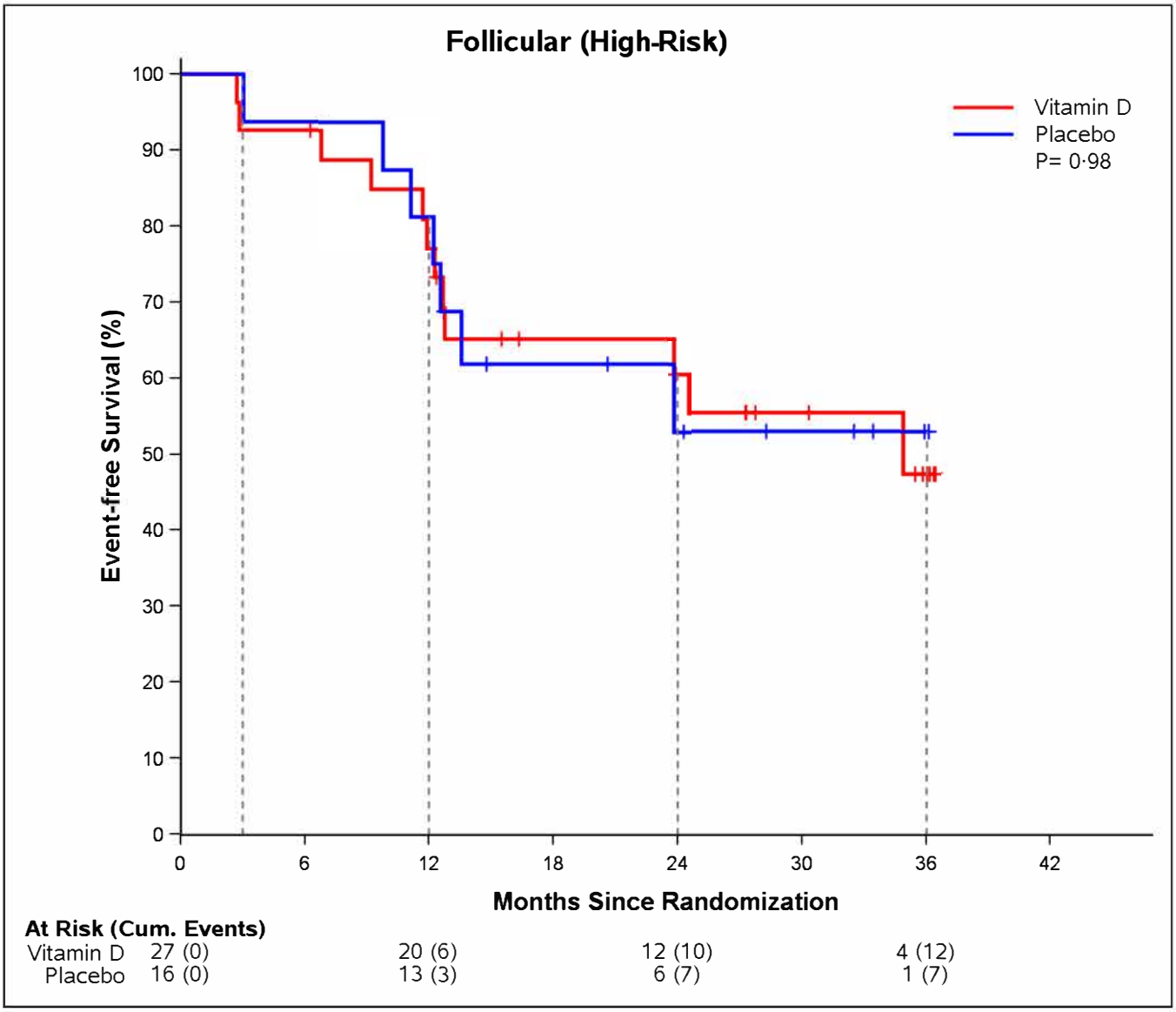
Supplementary Figure 4. Event-Free Survival by Arm in Patients with Follicular Lymphoma



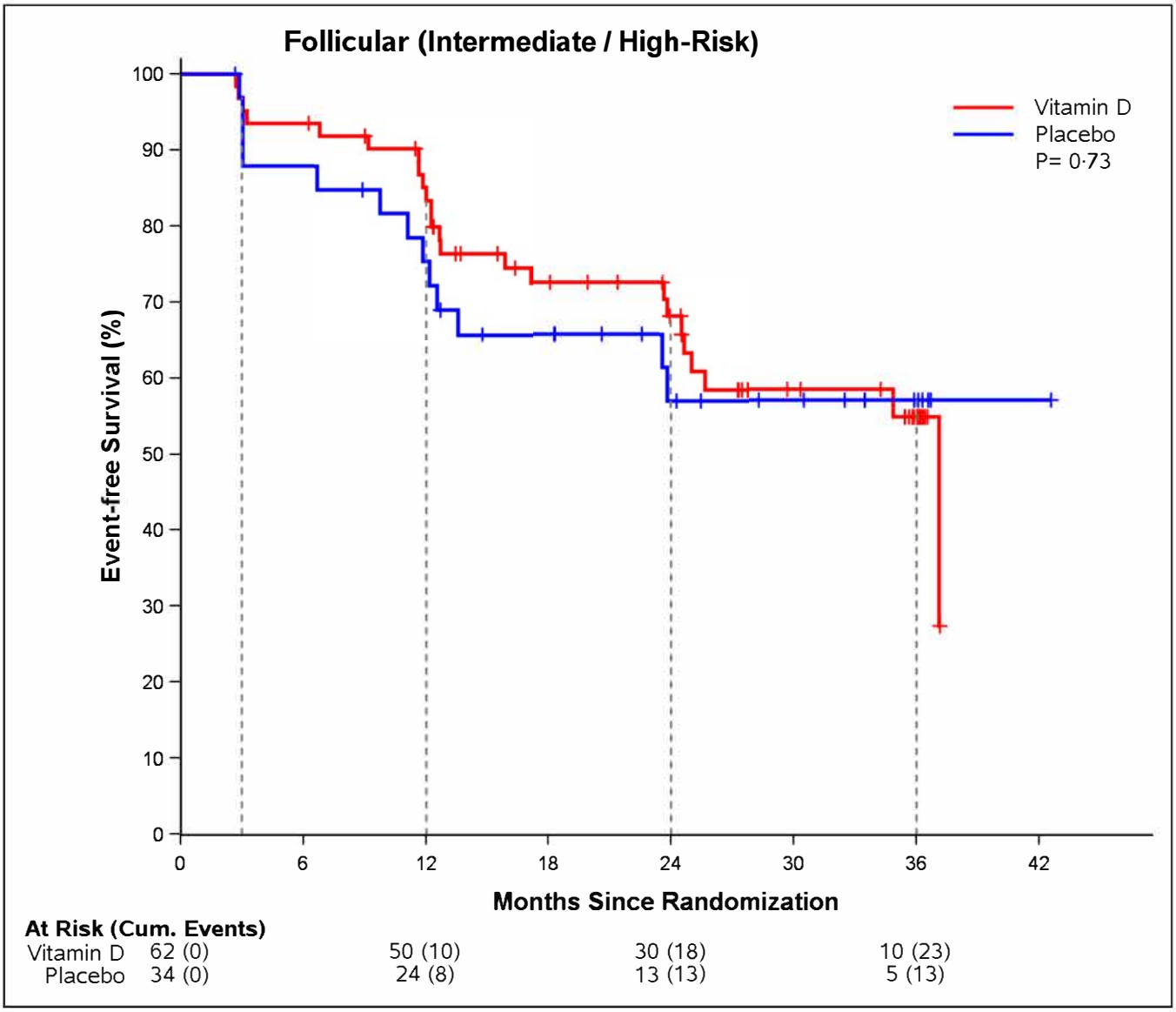
Supplementary Figure 5. Event-Free Survival by Arm in Patients with Low/Intermediate Risk Follicular Lymphoma



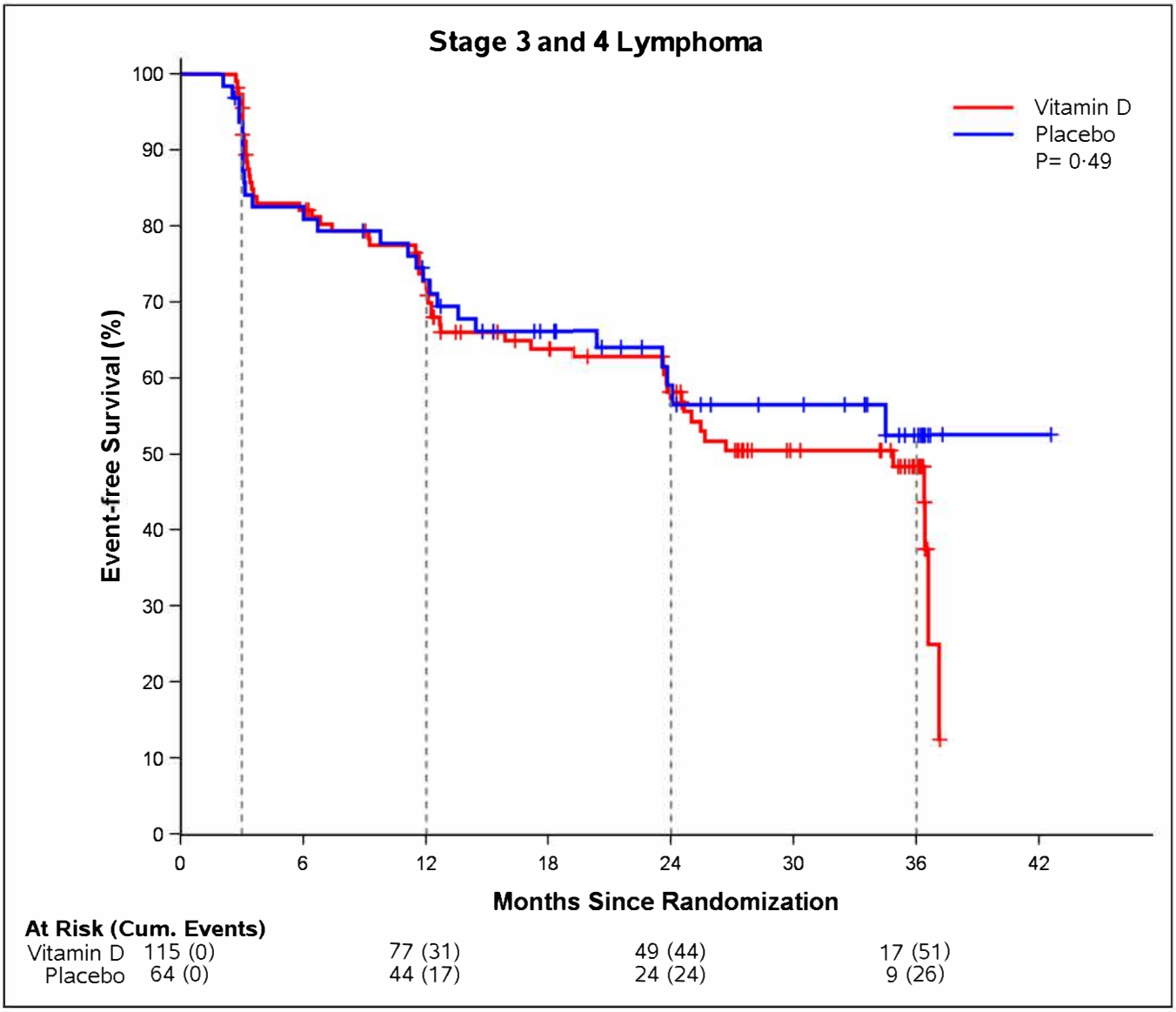
Supplementary Figure 6. Event-Free Survival by Arm in Patients with High-Risk Follicular Lymphoma



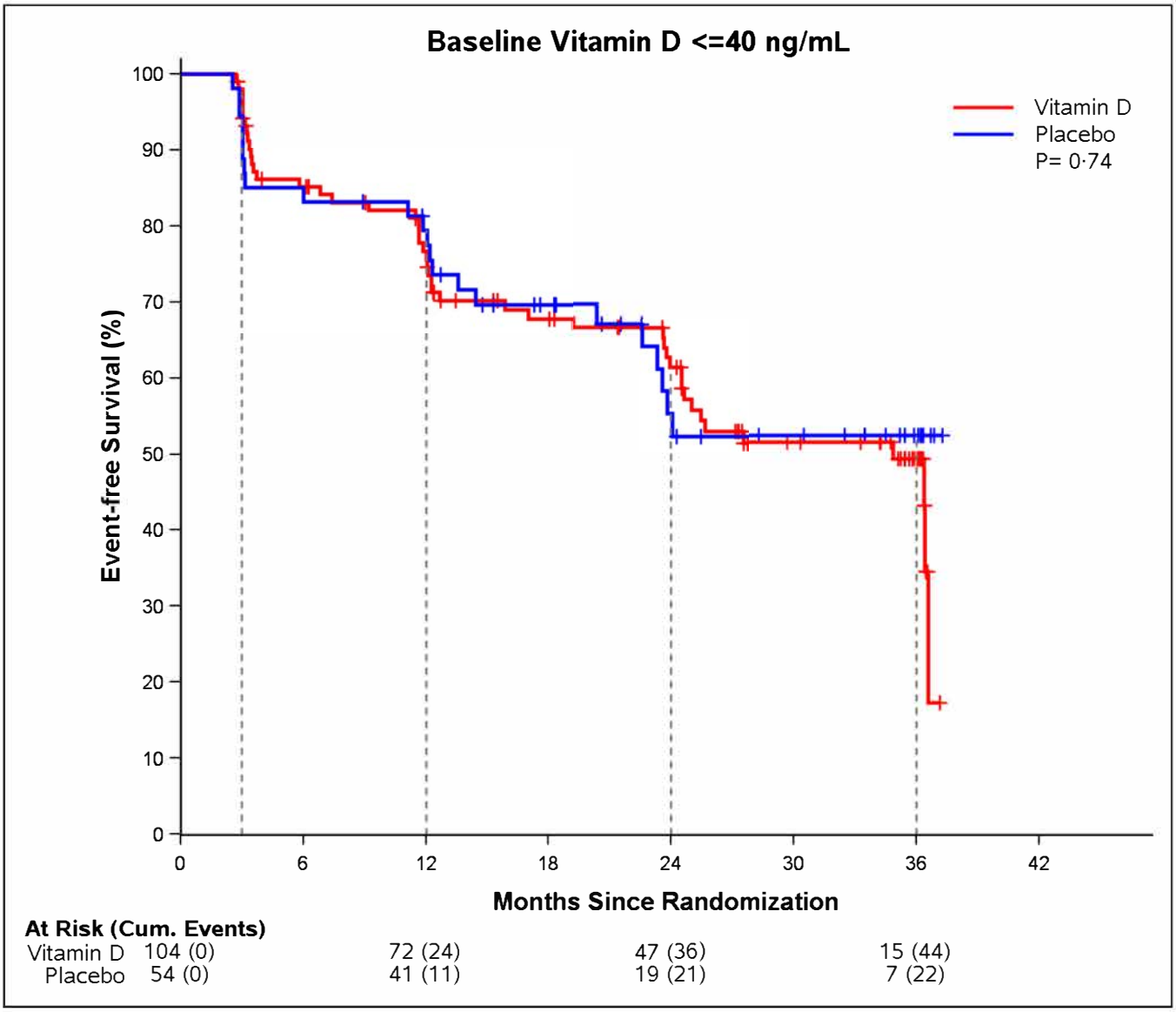
Supplementary Figure 7. Event-Free Survival by Arm in Patients with Intermediate and High-Risk Follicular Lymphoma



Supplementary Figure 8. Event-Free Survival by Arm in Patients with Stage 3 and 4 Lymphoma



Supplementary Figure 9. Event-Free Survival by Arm in Patients with Baseline Vitamin D Less Than or Equal to 40 ng/mL



Supplementary Figure 10. Overall Survival by Arm