(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
14 February 2013 (14.02.2013)

WIPO | PCT

(10) International Publication Number
WO 2013/022935 A1

(51) **International Patent Classification:**
G01N33/574 (2006.01)

(21) **International Application Number:**
PCT/US2012/049941

(22) **International Filing Date:**
8 August 2012 (08.08.2012)

(25) **Filing Language:** English

(26) **Publication Language:** English

(30) **Priority Data:**
61/522,596 11 August 2011 (11.08.2011) US
61/560,555 16 November 2011 (16.11.2011) US

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(81) **Designated States** *(unless otherwise indicated, for every kind of national protection available):* AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) **Designated States** *(unless otherwise indicated, for every kind of regional protection available):* ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

— *as to the identity of the inventor (Rule 4.17(i))*

Published:

— *with international search report (Art. 21(3))*

— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*

(54) **Title:** PREDICTORS FOR CANCER TREATMENT

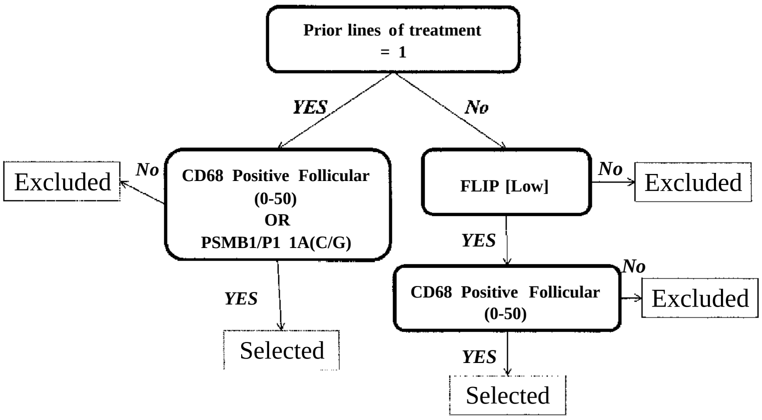

Figure 1.

(57) **Abstract:** The present invention provides methods of predicting a response to a cancer treatment by determining CD68 level or PSMB1 (P11A) polymorphism in a biological sample and the presence or quantity of a second biomarker in the patient. The invention also provides kits and methods for treating cancer.

PREDICTORS FOR CANCER TREATMENT

CROSS REFERENCE TO RELATED APPLICATIONS

This application claims priority to provisional application Serial Number 61/522,596, filed August 11, 2011 and provisional application Serial Number 61/560,555, filed November 16, 2011, both of which are incorporated herein by reference in their entirety.

FIELD OF THE INVENTION

The invention is related to treatment of cancer patients.

BACKGROUND OF THE INVENTION

While advances in development of successful cancer therapies progress, only a subset of patients respond to any particular therapy. With the narrow therapeutic index and the toxic potential of many available cancer therapies, such differential responses potentially contribute to patients undergoing unnecessary, ineffective and even potentially harmful therapy regimens.

One way to optimize therapy to treat individual patients is to determine whether the patient one or more predictors that correlate with a particular outcome in response to therapy. *See,* e.g., WO2004/053066; WO2006/133420; WO2008/021183; and WO2009/148528. The ability to predict drug sensitivity in patients is particularly challenging because drug responses reflect both the properties intrinsic to the target cells and also a host's metabolic properties.

There is a need to identify further predictive markers to identify particular cancer patients who are expected to have a favorable outcome when administered particular cancer therapies.

SUMMARY OF THE INVENTION

The invention provides a method for identifying whether a patient has an increased chance for a favorable outcome in response to a cancer treatment, comprising: determining the presence, absence or quantity of one or more predictors in the patient, wherein the presence, absence or quantity of the predictor correlates with at least one favorable outcome.

The presence of predictors may be determined by obtaining a biological sample from said patient. The cancer treatment may comprise administration of a proteasome inhibitor, such as bortezomib. The predictors may be one or more of low CD68, PSMBl (PI 1A), PSMB5 (R24C), P65, time since last cancer treatment, one prior treatment, low FLIPI score, age (65 or younger), and low tumor burden.

Also provided are diagnostic kits for identifying patients likely to have a positive outcome in response to a cancer treatment.

The invention also provides methods for treating cancer patients by determining the presence, absence or quantity of one or more predictors in the patient, and selecting a method of treatment dependent on whether the patient is likely to respond to the treatment.

Also provided are uses for proteasome inhibitors for the treatment of cancer, wherein the patients are characterized by one or more of: low CD68, PSMBl (PI 1A), PSMB5 (R24C), P65, time since last cancer treatment, one prior treatment, low FLIPI score, age, and low tumor burden.

DESCRIPTION OF THE FIGURES

Figures 1-8 show decision trees for determining whether a particular patient will have an increased chance for favorable outcome in response to treatment. "Selected" means that the patient will have an increased chance for favorable outcome in response to treatment.

DETAILED DESCRIPTION OF THE INVENTION

The present invention describes predictors that serve as useful tools for the prognosis and planning for the treatment of cancer. The predictors are predictive of whether there will be a favorable outcome in response to a particular treatment, for example, treatment with a proteasome inhibitor.

Without limitation, the present invention provides (a) methods for a predicting response to a treatment in a cancer patient by determining presence or quantity of one or more predictors, (b) kits useful in determination of the presence or quantity of the one or more predictors, (c) methods for treating cancer by selecting patients based on presence or quantity of one or more predictors and (d) treating cancer in patients with one or more predictors.

In certain embodiments, a method is provided for predicting response to a cancer treatment (for example, treatment with a proteasome inhibitor such as bortezomib) in a cancer patient comprising determining the presence or quantity of a predictor in a patient or a biological sample from the patient; and wherein the presence or quantity of the predictor is correlated with at least one positive outcome. Certain embodiments comprise determining the presence or quantity of a second predictor in the patient or a biological sample from the patient, wherein the presence or quantity of the second predictor is correlated with at least one positive outcome.

The present invention involves the identification of predictors also referred to herein as "variants", "markers" "biomarkers" and/or "factors", that correlate with an increased probability of favorable response to a cancer treatment. The association of patient response to a cancer treatment with these predictors can increase of higher confidence in the safety and/or efficacy with the particular treatment. The predictors may be a gene, protein, patient characteristic, or aspect of the patient history.

Predictors according to this invention which correlate with at least one favorable outcome include low CD68, PSMB1 (P1 1A) polymorphism, PSMB5 (R24C) polymorphism, P65, age (under 65), one prior treatment, low Follicular Lymphoma International Prognostic Index (FLIPI) score, time since last anti-cancer treatment and low tumor burden. Preferably, the patient has low CD68 or PSMB1 (P1 1A) and the presence of at least one other predictor. In one embodiment, the patient has low CD68 and PSMB1 (P1 1A) polymorphism. Predictor pairs according to this invention which correlate with at least one favorable outcome include those shown in Tables 6 and 7.

By "low CD68" is meant that the subject or biological sample from the patient shows less CD68 quantity than the average patient or biological samples from an average patient who has the same disease. In certain embodiments, low CD68 means that 25% or less of the cells in a biological sample express CD68; 50% or less of the cells in a biological sample express CD68; 25% or less of the follicular cells in a biological sample express CD68; 50% or less of the follicular cells in a biological sample express CD68; 25% or less of the perifollicular cells in a biological sample express CD68; or 50% or less of the perifollicular cells in a biological sample express CD68.

By "low FLIPI" score is meant a score of 0 or 1 factor on the Follicular Lymphoma International Prognostic Index (FLIPI score). To determine FLIPI score, one point is assigned to each of: age greater than 60 years, Stage III or IV disease, greater than 4 lymph node groups involved, serum hemoglobin less than 12 g/dL and elevated serum LDH.

As used herein, the terms "comprising", "containing", "having" and "including" are used in their open, non-limiting sense.

"Quantity" may mean the value, intensity, concentration, amount, degree, or expression level. For example, quantity of a gene may be the number of times a gene or portion thereof is present in a subject's genome or in the cells of the subject. Quantity may also mean the number of cells in a biological sample expressing a marker, or the overall expression level or intensity of the marker in a biological sample. Quantity may also refer to the number of types or lines of therapy the patient to which the patient may previously been exposed. The quantity may be in comparison to an absolute number, in comparison to a reference sample from a healthy patient, in comparison to an average number from healthy patients, or in comparison to an average number from patients with similar disease.

The cancer treatment may include administration of a single drug or treatment, or a combination treatment comprising administration of more than one drug or treatment. The cancer treatment may be administration of chemotherapy, radiotherapy, or immunotherapy; or the cancer treatment may be a bone marrow transplant.

In certain embodiments, the cancer treatment comprises administering a proteasome inhibitor to a patient. A proteasome inhibitor is any substance which inhibits enzymatic activity of the 20S or 26S proteasome in vitro or in vivo. In some embodiments, the proteasome inhibitor is a peptidyl boronic acid. Peptidyl boronic acids include bortezomib. Proteasome inhibitors include those compounds disclosed in U.S. Patents Nos. 5,756,764; 5,693,617; 6,831,099; 6,096,778; 6,075,150; 6,018,020; 7,1 19,080; 6,747,150; 6,617,317; 6,548,668; 6,465,433; 6,297,217; 6,083,903; 6,066,730; 5,780,454; 7,422,830; 7,109,323; 6,958,319; 6,713,446; and 6,699,835. The proteasome inhibitor may be bortezomib.

In certain embodiments, the cancer treatment comprises treatment with anti-cancer agents, including but not limited to, acemannan, aclarubicin, aldesleukin, alemtuzumab, alitretinoin, altretamine, amifostine, aminoglutethimide, amsacrine, anagrelide, anastrozole, ancestim, asparaginase, bevacizumab, bexarotene, broxuridine, capecitabine, celmoleukin, cetrorelix, cetuximab, cladribine, clofarabine, clotrimazole, daclizumab, dexrazoxane, dilazep, docosanol, doxifluridine, bromocriptine, carmustine, cyclophosphamide, cytarabine, diclofenac, edelfosine, edrecolomab, eflomithine, emitefur, exemestane, exisulind, fadrozole, filgrastim, finasteride, fludarabine phosphate, formestane, fotemustine, gallium nitrate, gemcitabine, glycopine, heptaplatin, hydroxyurea, ibandronic acid, imiquimod, iobenguane, irinotecan, irsogladine, lanreotide, leflunomide, lenograstim, lentinan sulfate, letrozole, liarozole, lobaplatin, lonidamine, masoprocol, melarsoprol, melphalan, mercaptopurine, methotrexate, metoclopramide, mifepristone, miltefosine, mirimostim, mitoguazone, mitolactol, mitomycin, mitoxantrone, molgramostim, nafarelin, nartograstim, nedaplatin, nilutamide, noscapine, oprelvekin, osaterone, oxaliplatin, pamidronic acid, pegaspargase, pentosan polysulfate sodium, pentostatin, picibanil, pirarubicin, porfimer sodium, prednisone, raloxifene, raltitrexed, rasburicase, rituximab, romurtide, sargramostim, sizofuran, sobuzoxane, sonermin, steroids, suramin, tasonermin, tazarotene, tegafur, temoporfin, temozolomide, teniposide, tetrachlorodecaoxide, thalidomide, thymalfasin, thyrotropin alfa, topotecan, toremifene, trastuzumab, treosulfan, tretinoin, trilostane, trimetrexate, ubenimex, valrubicin, verteporfin, vincristine, vinblastine, vindesine, and vinorelbine. In a preferred embodiment, the cancer treatment comprises rituximab. In other preferred embodiments, the cancer treatment comprises melphalin or prednisone, or a combination of melphalin and prednisone.

In certain embodiments, the cancer treatment is a combination treatment. The combination treatment may comprise treatment with a proteasome inhibitor and another cancer treatment or anti-cancer agent. In certain embodiments, the other anti-cancer agent is a monoclonal antibody, e.g., rituximab. In other embodiments, the other anti-cancer agent is melphalin, prednisone, or a combination of melphalin and prednisone.

The favorable outcome may be an overall response rate, overall survival rate, overall complete response rate, duration of response, longer time to next therapy, treatment free interval, positive response to treatment, a longer time-to-progression, longer term survival and/or longer progression-free survival. The favorable outcome may be dose-dependent or dose-independent. The favorable outcome may favorable be in comparison to no treatment, or in comparison to another cancer treatment or cancer treatment(s).

"Cancer" or "tumor" is intended to include any neoplastic growth in a patient, including an initial tumor and any metastases. The cancer can be of the hematological or solid tumor type. Hematologic cancers include such as myelomas e.g., multiple myeloma), leukemias (e.g., Waldenstrom's syndrome, acute myelogenous leukemia, chronic lymphocytic leukemia, granulocytic leukemia, monocytic leukemia, lymphocytic leukemia), and lymphomas (e.g., follicular lymphoma, mantle cell lymphoma, diffuse large B cell lymphoma, malignant lymphoma, plasmocytoma, reticulum cell sarcoma, Hodgkin's disease, non-Hodgkin's lymphoma or follicular B-cell non-Hodgkin's lymphoma). Solid tumors can originate in organs, and include cancers such as brain, skin, lung, breast, prostate, ovary, colon, kidney, and liver. The cancer may be at the primary site, a metastasis, refractory (e.g. refractory to one or more lines of treatment) and/or recurring. In certain embodiments, the cancer is follicular B-cell non-Hodgkin's lymphoma or multiple myeloma.

When the predictor is present within the patient's body, the presence, absence or quantity of the predictor may be assessed by obtaining a biological sample from a patient and determining whether said biological sample contains the predictor or in what amounts the biological sample contains the predictor. A "biological sample" as used herein refers to a sample containing or consisting of tissues, cells, biological fluids and isolates thereof, isolated from a subject, as well as tissues, cells and fluids present within a subject. Examples of biological samples include, for example, sputum, blood, blood cells (e.g., white blood cells), amniotic fluid, plasma, serum, semen, saliva, bone marrow, tissue or fine-needle biopsy samples, urine, peritoneal fluid, pleural fluid, and cell cultures. Biological samples may also include sections of tissues such as frozen sections taken for histological purposes. In certain embodiments, the biological sample may be or include tumor cells. Biological samples from a hematological tumor may include bone marrow and/or peripheral blood.

Detection of predictor in a biological sample may be performed by any conventional method for detecting the type of predictor, e.g., direct measurement, immunohistochemistry, immunoblotting, immunoflourescense, immunoabsorbence, immunoprecipitations, protein array, flourescence in situ hybridization, FACS analysis, hybridization, in situ hybridization, Northern blots, Southern blots, Western blots, ELISA, radioimmunoassay, gene array/chip, PCR, RT-PCR, or cytogenetic analysis.

When the predictor is based on a particular genotype or polymorphism, the biological sample may be analyzed by genotyping. The term "genotype" refers to the alleles present in DNA from a subject or patient, where an allele can be defined by the particular nucleotide(s) present in a nucleic acid sequence at a particular site(s). Often a genotype is the nucleotide(s) present at a single polymorphic site known to vary in the human population. "Genotyping" refers to the process of determining the genotype of an individual by the use of biological assays. Current methods of doing this include PCR, DNA sequencing, antisense oligonucleotide probes, and hybridization to DNA microarrays or beads.

A "single nucleotide polymorphism" (SNP, pronounced snip) is a DNA sequence variation occurring when a single nucleotide - A, T, C, or G - in the genome (or other shared sequence) differs between members of a species (or between paired chromosomes in an individual). For example, two sequenced DNA fragments from different individuals, AAGCCTA to AAGCTTA, contain a difference in a single nucleotide. In this case it is said that there are two alleles: C and T. Almost all common SNPs have only two alleles.

The detection of the presence or absence of at least one genotype variance involves contacting a nucleic acid sequence corresponding to one of the genes identified herein or a product of such a gene with a probe. The probe is able to distinguish a particular form of the gene or gene product or the presence or a particular variance or variances, e.g., by differential binding or hybridization.

When the predictor is the presence or quantity (including the expression level) of a particular gene or protein, the presence or quantity (including the expression level) may be determined by immunohistochemistry of a biological sample.

In certain embodiments, a kit is provided for identifying patients who are candidates for a cancer treatment comprising a first reagent for detecting the presence or quantity of one of the predictors of the invention in a biological sample and a second reagent for detecting the presence or quantity of a second predictor of the invention in a biological sample, and instructions for employing the predictors to identify patients who are candidates for the treatment. In certain embodiments, the first reagent detects CD68 quantity and the second reagent detects PSMB1 (P1 1A) polymorphism or PSMB5 (R24C) polymorphism. The reagents may be antibodies (for example, when testing CD68) or they may be probes or arrays of probes (for example, when detecting gene polymorphism)

In certain embodiments, a method for treating a patient for cancer comprising: determining the presence or quantity of a first predictor in patient or a biological sample from said patient; and determining the presence or quantity of a second predictor in said patient or a biological sample from said patient; and selecting a method of treatment dependent on whether said patient is likely to respond to said treatment.

The invention also provides uses of proteasome inhibitors for the treatment of cancer in a patient, where the patient is characterized by the presence, absence, or quantity of at least one predictor correlated with at least one positive outcome in response to the proteasome inhibitor.

All publications cited herein are hereby incorporated by reference. Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood to one of ordinary skill in the art to which this invention pertains.

EXAMPLE 1.

Non-Hodgkin lymphoma (NHL) encompasses several unique malignant lymphoid disease entities that vary in clinical behavior, morphologic appearance, immunologic, and molecular phenotype. Follicular lymphoma (FL), the most common indolent NHL, exhibits similar variability with some patients exhibiting very slow disease course while others progress and die within only 5 year (Dave 2004). A randomized, open-label, active-controlled, multicenter, multinational, prospective study to compare the efficacy and safety of the combination of bortezomib and rituximab (Vc-R) to single-agent rituximab in subjects who have relapsed or refractory, rituximab-naive or -sensitive follicular B-cell NHL was performed.

Subjects were centrally randomized to Treatment Groups A (Vc-R) or B (rituximab) in a 1:1 ratio taking into account the following stratification factors:

•Follicular Lymphoma International Prognostic Index (FLIPI) score (low [0 or 1 factor], intermediate [2 factors], high [>3 factors]);

•Prior rituximab therapy (yes, no);

•Time since last dose of anti-lymphoma therapy (<1 year, > 1 year);

•Region (United States/Canada, European Union, Rest of World).

Tumor samples for DNA and protein analysis and a blood sample for DNA analysis were collected.

Protein candidates selected were NF-κB (RELA/p65), PSMA5, p27, and CD68. These proteins are attenuated by bortezomib treatment (NF-κB (RELA/p65); PSMA5, p27), regulated by the ubiquitin proteasome pathway (p27), or associated with poor prognosis in lymphoma (CD68). Elevated expression levels of NF-κB (RELA/p65) were associated with longer time-to-progression (TTP) in mantle cell lymphoma (MCL) and in multiple myeloma (Goy 2010, Mulligan 2007, and Keats 2007). Low level expression of PSMA5 was associated with longer TTP in MCL (Goy 2010). Survival analysis in the MCL study also showed that high levels of p27 correlated with better overall survival (OS) (Goy 2010). CD68 was also prespecified and has recently been reported to be a prognostic marker for poor outcome in lymphoma and is also associated with response to rituximab. Candidate genes selected for somatic mutation analysis were Bcl-2 and Notch-1. Other candidates were considered, but were not included because the frequency of the known mutations was less then 10% in the lymphoma setting. Additionally, small amounts of DNA were recovered from collected samples, so the analyses were limited to these two candidates. Bcl-2 has mutation frequencies of 23% in B-cell lymphoma and 50% in follicular lymphoma (Arif 2009) and Notch-1 has a mutation frequency of 24%. Bcl-2 is an important anti-apoptotic protein frequently over expressed in aggressive lymphomas and previous reports have suggested that bortezomib overcomes Bcl-2-mediated protection (Fischer 2005, Yin 2005, Yeung 2006, Mitsiades 2002 and Wojcik 2002). Notch-1 has been shown to increase the residence time of NF-κB (RELA/p65) in the nucleus (Shin 2006). This acts in direct opposition to bortezomib, which prevents NF-κB from reaching the nucleus by inhibiting proteasomal degradation of I-kappa-B proteins, whose role is to retain NF-κB in the cytoplasm. Notch 1-mediated increased residence time of NF-κB in the nucleus activates the transcription of the cell cycle regulators, eg, cyclins D1 and D2, which may contribute to the up-regulation of genes involved in immune and inflammatory processes (Karin 2002). Mutations found in functional sequences of these two genes were hypothesized to contribute to inter-individual responses to treatment with bortezomib.

Drug target candidate genes were included for both bortezomib (PSMB1, 2, 5, 6, 8, 9) and rituximab (FCGR2A, FCGR3A). The chemical structure of bortezomib interacts with PSMB subunits 1, 2, and 5 and there is documented evidence of polymorphisms in these subunits as well as in PSMB6, 7, and 8. Polymorphisms within the subunits may affect the ability of the drug to bind effectively or may prevent autocatalytic processing of pro-sequences that could lead to variability in levels of proteasomes and/or response to bortezomib in individual patients. For rituximab, the presence of single nucleotide polymorphisms (SNPs) corresponding to phenotypic expression of valine (V) or phenylalanine (F) at amino acid 158 of FCGR3A and of histidine (H) or arginine (A) at amino acid 131 of FCG2A greatly influences the affinity of IgG for the Fey receptor (Binstadt 2003, Wu 1997). Expression of the high-affinity V allele at 158 results in tighter binding of FCG3A to IgGl and IgG3, whereas the low-affinity F allele is associated with decreased binding of FCG3A to IgG. Similarly, the high-affinity H allele at 131 results in greater affinity of FCGR2A for IgG2, whereas the low-affinity A allele correlates with decreased binding. Correlation of these low-affinity polymorphisms has been associated with worse clinical response and progression-free survival (PFS) after rituximab therapy in studies of NHL (Cartron 2002). Therefore, we examined whether subjects with these polymorphisms were responsive to treatment with Vc-R as this may be an alternative therapy for patients with limited treatment options.

The exploratory objectives in this study were to identify patient populations who were more or less likely to respond to Vc-R or rituximab alone by:

-Performing association analyses of CD68, NF-κB (RELA/p65), PSMA5, and p27 protein expression levels with selected clinical study endpoints

-Performing association analyses of Notch-1 and Bcl-2 somatic mutations (single and in combination) with selected clinical study endpoints

- Performing association analyses of FCGR2A and FCGR3A polymorphisms (SNPs) with selected clinical study endpoints

-PSMB1, PSMB2, PSMB5, PSMB6, PSMB8, and PSMB9 polymorphisms (SNPs) with selected clinical study endpoints

-Performing combinations of biomarkers with selected clinical study endpoints.

Multiple testing corrections were done using the false discovery rate (FDR) method for pair-wise comparisons and by forward selection when multiple biomarker combinations were compared. In practical terms, the FDR is the expected proportion of false positives; for example, if 1000 observations were predicted to be different, and the FDR for these observations was 0.10, then 100 of these observations would be expected to be false positives. Over-fitting is controlled by cross validation and independent validation within the analysis.

Genes with sufficient variation include:

FCGR2A (H166R, Q62R, Q62X)

FCGR3A (V212F)

PSMB1 (P1 1A)

PSMB5 (R24C)

PSMB8 (G8R)

PSMB9 (R60H, V32I)

PSMA (positive nuclear and cytoplasmic staining)

CD68 (overall positive, positive follicular, positive peri-follicular)

P27 (nuclei positive, intensity score)

RELA/p65 (positive nuclear and cytoplasmic staining, intensity score).

The intent-to-treat (ITT) population was defined as all subjects who were randomized. Subjects in this population were analyzed according to the treatment to which they were randomized. Biomarker evaluations were done on this population when biomarker data was generated for the clinical study endpoints.

Protein marker expression levels (CD68, NF-κB (P65), PSMA5, P27) were determined by immunohistochemistry (IHC). The expression level cut-points for single-marker analyses were:

CD68:

% positive follicular (0-25, 26-50, 51-75, >75),
% positive peri-follicular (0-25, 26-50, 51-75, >75),
overall % positive (0-25, 26-50, 51-75, >75)

NF-κB (p65):

% positive cytoplasmic signal (<90%, >91% cutoffs) ,
% positive nuclear signal (0, <5%, >5%)
Nuclear staining intensity (<1+, >2+)

PSMA5:

% positive cytoplasmic signal (0-20, 30-50, 60-70, 80-90)
% positive nuclear signal (0-20, 30-50, 60-70, 80-90)
Cytoplasmic staining intensity (<2+, 3+)
Nuclear positive vs. all other

P27:

% positive nuclear staining (0-20, 30-50, 60-70, 80-100)
Nuclear signal intensity (<1+, >2+)

Cut-points selected for pair-wise comparisons were chosen to reduce the total number of comparisons that would be done. The selected cut-points are found in Table 1:

Table 1:Cut-Points for Protein Markers Included in the Pair-Wise Comparisons

Protein Marker	Cutoff
20S (PSMA5) % nuclear staining	≤20 vs. >20
20S (PSMA5) % positive cytoplasmic signal	≤90 vs. >90
20S intensity cytoplasmic signal	≤2+ vs. >2
CD68 overall positive	≤50 vs. >50
CD68 positive follicular	≤50 vs. >50
CD68 positive perifollicular	≤50 vs. >50
P27 % nuclei positive	≤70 vs. >70
P27 signal intensity	<1+ vs. > 1
P65 (NF-KB) % nuclear staining	0 vs. >0
P65 (NF-KB) % positive cytoplasmic signal	≤90% vs. >90%
P65 (NF-KB) intensity cytoplasmic signal	<1+ vs. > 1

Germline SNP data for PSMB subunits and FCGR2A and FCGR3A genes were generated by standard polymerase chain reaction (PCR) methodologies. Alleles detected in these assays are found in Table 2:

Table 2: Alleles for PSMB Subunits and FCGR2A and FCGR3A Genes

FCGR2A	FCGR3A	PSMB1	PSMB2	PSMB5	PSMB6	PSMB8	PSMB9
H166R (aka H131R)	D118N	A171S	E49X	L206M	A234D	G8R	G9E
P273L	D183G	I208N	G187V	R24C	P107A	R141C	R60H
Q62R	E63V	P11A	L159F	-	-	V182M	V32I
Q62X	H194Y	P193L	-	-	-	-	-
V217I	L102R	-	-	-	-	-	-
-	L281F	-	-	-	-	-	-

-	R270X	-	-	-	-	-	-
-	S231A	-	-	-	-	-	-
-	S72R	-	-	-	-	-	-
-	VI421	-	-	-	-	-	-
-	V212F (aka V158F)	-	-	-	-	-	-

The following clinical endpoints were included in the analysis within each treatment group and an overall comparison was made with the biomarker-related endpoints: Progression-free survival, defined as the interval between the date of randomization and the date of progressive disease (PD) or death, whichever is first reported in the ITT population; overall survival; overall response rate (complete response [CR] + CR unconfirmed [CRu] + partial response [PR]); overall CR rate (CR + CRu); duration of response; time to next anti-lymphoma therapy; and treatment free interval.

Subjects from who met all of the following criteria were included in the analysis: subjects in the ITT population; subjects with evaluable biomarker data determined by IHC- or PCR-based methodologies; and subjects with clinical data for at least one of the clinical endpoints listed above.

The primary biomarker analysis was aimed at identification of differentially expressed proteins, mutations, or genotypes that were associated with clinical study endpoints. Covariates included in the analysis were: FLIPI score (low [0 or 1 factor], intermediate [2 factors], high [>3 factors]); prior rituximab therapy (yes, no); time since last dose of anti-lymphoma therapy (≤1 year, >1 year); region (United States/Canada, European Union, Rest of World), age, sex, race, Ann Arbor stage (I, II, III, IV), Number of prior lines of therapy (1, 2 and more), and high tumor burden (yes, no).

For single-marker association analyses and pair-wise comparisons, a log rank test and Cox proportional hazard model was utilized for assessments of PFS, TTP, and OS between the treatment groups. Kaplan-Meier curves were utilized to estimate the distribution differences between groups in the time-to-event analyses. Comparison of the response rates between the treatment groups was conducted using the Fishers exact test. Single-marker association analyses were stratified by the covariates.

For pair-wise comparison analysis, biomarker pairs were formed by combinations of two markers. A log rank test was utilized for assessments of PFS, TTP, and OS between the treatment groups in the subpopulation defined by biomarker pairs. Kaplan-Meier curves were utilized to estimate the distribution differences between groups in the time-to-event analyses. Comparison of the response rates between the treatment groups was conducted using the Fishers exact test. Methods of Analysis for the multiple biomarker comparison models can be found in section 4.6.

For each analysis, demographic and baseline characteristic variables were to be summarized for the biomarker population as follows. Descriptive statistics (mean, standard deviation, median, and range) were calculated for baseline demographic data (including: age (year), age category (>65 years and ≤65 years), sex (male, female), race (White, Asian/Pacific Islander, and Black/Other), FLIPI score (low [0 or 1 factor], intermediate [2 factors], high [>3 factors]); prior rituximab therapy (yes, no); time since last dose of anti-lymphoma therapy (≤1 year, >1 year); Ann Arbor stage (I, II, III, IV), number of prior lines of therapy (1, 2 and more), high tumor burden (yes, no), and region (United States/Canada, European Union, Rest of World) and were compared with summary statistics from the clinical trial data sets.

The stratified log rank test and Cox proportional hazard model was utilized for assessments of PFS between the treatment groups. The Kaplan-Meier method was to be used to estimate the distribution of overall PFS for each treatment group in the biomarker population, and overall; stratified by expression level, SNP, or mutation (or covariate groups as noted above). The hazard ratio and 95% confidence interval was based on a stratified Cox's proportion hazard model with treatment as the explanatory variable. Analyses were done for the population overall and by treatment group, and each of these analyses were also stratified by the following factors if sufficient sample size existed:

FLIPI score (low [0 or 1 factor], intermediate [2 factors], high [>3 factors])

Prior rituximab therapy (yes, no)

Time since last dose of anti-lymphoma therapy (≤ 1 year, > 1 year)

Region (United States/Canada, European Union (Belgium, Czech Republic, Finland, France, Germany, Great Britain, Greece, Hungary, Italy, Poland, Portugal, Slovakia, Spain, and Sweden), Rest of World (Argentina, Australia, Brazil, India, Israel, Mexico, China, Korea, Romania, Russia, South Africa, Thailand, and Ukraine))

Age (<65, >65)

Sex

Race

Ann Arbor stage (I, II, III, IV)

Number of prior lines of therapy (1, 2 and more)

High tumor burden (yes, no)

Overall Survival was measured from the date of randomization to the date of the subject's death. If the subject was alive or the vital status was unknown, it was censored at the date that the subject was last known to be alive. Similar to PFS and TTP, the Cox proportional hazard model was used to evaluate the association between biomarker endpoints and OS. Kaplan-Meier survival curves were presented. Analyses were done for the population overall and by treatment group, and each of these analyses was stratified by the covariates used for PFS.

Comparison of the response rates between the treatment groups was conducted using the Fishers Exact Test. Duration of response, time to response, and time to clinical relapse were analyzed descriptively, where appropriate, and the biomarker subset was compared (if appropriate, determined as per the initial analysis) to the overall clinical cohort, by treatment group and overall. An exploratory estimate of the response rates in each treatment group was presented with 2-sided 95% confidence intervals. The number and percentage of subjects falling into each response category was descriptively tabulated.

Analyses were done for the population overall and by treatment group. Each of these analyses were stratified by the same covariates utilized for PFS assessment.

Further analyses were planned because of the number of pair-wise comparisons that were significant prior to FDR corrections and because these pairs selected unique individuals with longer PFS and a trend for longer survival. These analyses sought to identify a single biomarker classifier that selected for a large PFS benefit and an OS benefit (or trend) with a high population frequency. The dataset was utilized whereby discovery and confirmation test sets within the same population were defined. The study was conducted as follows:

Subjects with no missing biomarker values (n=354) were assigned in a ratio of 7:3 into a discovery and confirmation set using simple randomization. The balance demographic factors and clinical covariates listed previously were confirmed using either the t-test or Mann- Whitney test. The discovery set (67%) was used for identification of biomarkers with significant association with PFS; subjects included had no missing biomarker data. The confirmation set (33%) was used for independent validation. Subjects with missing data were included in the confirmation dataset provided that significant biomarker data identified in the discovery phase was available. Additionally, evaluable sample from China were also included in the confirmation set.

As in the initial analyses, if all subjects have the same protein expression level for a particular biomarker, that biomarker was removed from the analysis. If all subjects had the same mutation, no mutation, or 1 mutation level represented >90% of the samples, then either that mutation or that gene was removed from the analysis.

In the discovery phase of biomarker combination analysis, all subjects that had missing values for any biomarker specified in Section 2 were excluded. Samples with missing data were included in the confirmation set provided that the missing data was not part of the associated dataset. Samples with missing biomarker data were considered "unevaluable" and were excluded from the confirmation set, all other samples not used in the discovery set were included in the confirmation set.

Biomarker outliers were not removed from the analysis.

Demographic and baseline covariates were to be compared using the t-test or Mann-Whitney test to ensure that there were no statistically significant differences between the discovery and confirmation sets. Demographic and baseline characteristics were to be summarized for the discovery and confirmation sets and overall. Subjects excluded in the final analysis were not to be evaluated in this data comparison. Descriptive statistics (mean, standard deviation, median, and range) were to be calculated for the baseline demographic data and comparison between the demographic and test set were to be made to ensure there were no significant differences between them.

Covariates included in the analysis were: FLIPI score (low [0 or 1 factor], intermediate [2 factors], high [>3 factors]); prior rituximab therapy (yes, no); time since last dose of anti-lymphoma therapy (≤ 1 year, > 1 year), age, Ann Arbor stage (I, II, III, IV), Number of prior lines of therapy (1, 2 and more), high tumor burden (yes, no), region (United States/Canada, European Union, Rest of World), sex, and race.

All markers and covariates were to be treated as categorical variables in the analysis. Protein biomarkers were to be dichotomized. The cut-points for protein markers were to be optimized based on enrichment of responders vs. non-responders and reasonable population size. Specifically, for each biomarker, number of responders and non-responders (based on overall response) and their percentages in the evaluable population were to be determined using every potential cut-point listed in the Table 3. Summary tables with potential cut-points, number of responders, number of non-responders, and their percentages were to be generated for each biomarker.

Table 3: Response by Cut-Point (Evaluable Population)

Protein Marker	Cutoff
20S (PSMA5) % nuclear staining	20%, 50%, 70%, 90%
20S (PSMA5) % positive cytoplasmic signal	20%, 50%, 70%, 90%
20S intensity cytoplasmic signal	0, 1, 2
CD68 overall positive	25, 50, 75, 90
CD68 positive follicular	25, 50, 75, 90
CD68 positive perifollicular	25, 50, 75, 90
P27 % nuclei positive	20%, 50%, 70%, 90%
P27 signal intensity	0, 1, 2
P65 (NF-KB) % nuclear staining	0, 1, 5, 10, 20
P65 (NF-KB) % positive cytoplasmic signal	20%, 50%, 70%, 90%
P65 (NF-KB) intensity cytoplasmic signal	0, 1, 2

All genotypes were to be considered separately in the analysis (eg, C/C, C/T, T/T):

FCGR2A (H166R, Q62R, Q62X)

FCGR3A (V212F)

PSMB1 (P11A)

PSMB5 (R24C)

PSMB8 (G8R)

PSMB9 (R60H,V32I).

Evaluation and Ranking of Single-Marker Associations with PFS (Discovery set)

The initial step of the analysis was selection and ranking of markers that were to be used in subsequent multiple comparison analysis. All protein, SNPs with greater than 10% genotype variability, and clinical covariates listed were to be included as categorical variables. The evaluation was to include the following steps:

Biomarkers (including clinical covariates) that showed improvement of PFS from prior single-marker association analysis ($p<0.2$) were reported. Only analyses that were done using IRC review were used.

Each biomarker and clinical covariate was evaluated by Cox regression to assess the importance of biomarkers with respect to PFS. The P-values and weights/odds ratios of all markers in the Cox model were reported.

To evaluate correlation among biomarkers, a pairwise correlation matrix was generated using Spearman correlation method. Biomarkers that showed high correlation ($p<0.05$ and correlation coefficient >0.7) were highlighted. Markers that had high correlation were re-analyzed in a Cox regression model with their interaction terms.

An interim summary of this analysis was generated for selecting markers that were used in multiple comparison analysis. The markers that were selected were based on the following criteria:

Relatively lower P-values in Cox regression for marker effect on PFS.

PFS benefit in Vc-R arm compared to R arm that were based on interaction with treatment in Cox regression or single marker logrank tests.

If multiple markers are highly correlated and have high ranks from Cox regression, representative marker(s) that have the highest rank from Cox regression with interaction terms were used. Subpopulations of samples showing a large PFS benefit in Vc-R arm compared to the Pv arm were to be identified by an exhaustive search of "AND" combination of biomarkers. Specifically, subpopulations of patients were formed from "AND" combinations of any two or three biomarkers selected in section 4.6.1. The difference of PFS for the patient subsets defined by the markers was evaluated using the log-rank test with PFS as response variable and 5-fold cross-validation as described below.

The discovery set was randomly split into 5 subsets with 20% of subjects in each subset. An 80% subset was formed by combining 4 of the 5 subsets. Using the 80%> subset, subpopulations of patients were formed from "AND" combinations of biomarkers. If the number of samples (N) in either Vc-R or R is < 5 for the subpopulation, the subpopulation was skipped. For subpopulations with N ≥ 5 in both arms, the difference in PFS for the patient subsets defined by the two markers was evaluated using the log-rank test. A looser P-value cutoff was applied because of the exploratory nature of this analysis. The PFS benefit was subsequently tested on the remaining 20% subset.

The remaining 4 cross validation sets were tested similarly (P value cutoff was not applied due to small sample size). Specifically, a different 20% subset from above and a new 80% subset formed with remaining subjects was used to repeat logrank tests until all 5 20% subsets were tested. The proportion of iterations with large PFS benefit in both 90% subset and 10%, subset were reported.

Biomarker combinations were merged and evaluated again for PFS benefit and statistical significance with cross validation. For subpopulations formed from merging of marker combinations, if the size of the subpopulation is ≤ 10% of the discovery set, no statistical test will be performed. Exhaustive merging of marker pairs and assessment of PFS benefit was performed. Only marker combinations or merging of marker combinations that were significant were reported to save computational time. Results were saved after each iteration.

For top ranked marker combinations, decision rules for defining selected patient subpopulations were established using Classification and Regression Tree. Association of the selected patient subpopulations for other clinical endpoints was also evaluated. Performance of PFS and OS in the confirmation set was evaluated by testing the association of biomarkers identified in the discovery set using the decision rules defined. The PFS of both biomarker positive and negative subgroups was reported for both study arms in the confirmation set. P-value cutoff was not applicable due to a small sample size, but was still reported.

Samples included in the independent confirmation set may have missing values for biomarkers not found to associate with PFS, however, subjects who could not be classified due to missing values of the selected biomarkers were regarded as "unevaluable" and were excluded.

Initial analyses focused on single-marker associations stratified by covariates. Significant associations were found in the single marker association analysis including CD68, PSMB1 (PI 1A), P65 and PSMB5 (R24C). Subsequent pair-wise analysis identified a biomarker pair with significantly longer PFS and a trend for an OS benefit. Because there were no data sets available for independent confirmation of this finding, dataset was split into the Discovery and Confirmation sets described above. As part of that analysis, multiple biomarker combinations were compared and other significant combinations were identified. The association deemed to be most clinically appropriate from all analyses was the PSMB P11A heterozygote in combination with CD68 Low (0-50%) expression. Sub-populations of clinical interest are subjects with high tumor burden, prior rituximab and one or two prior lines of therapy.

Pair-wise combinations of markers were conducted using the stratified log rank test for each potential pair to determine differences in PFS between the Vc-R and rituximab only treatment groups. One-hundred and two biomarker pairs had a log rank p<0.05. Of these, 97 pairs had a >1% population frequency. Fourteen pairs also showed a PFS improvement of ≥6 months. In this analysis, 1,140pair-wise comparisons were made (covariates were paired with each individual marker to supplement the analyses). Following FDR correction, 1 pair was significant (FDR=0.051). This biomarker pair identified 33% of the biomarker evaluable population that had a 7.5 month PFS advantage when treated with Vc-R compared with rituximab alone (Table 4) and a trend for better OS (p=0.055, HR: 0.426 [0.174, 1.046] This pair is composed of PSMB1 P11A (C/G heterozygote) and CD68 Low expression defined as 0-50 positively stained cells. Following, this pair will be referred to as the biomarker positive subgroup. The biomarker negative subgroup does not have this biomarker pair and has a different PSMB1 genotype and CD68 expression level.

Table 4: Comparison of Biomarker Positive Population With Biomarker Negative Population for PFS and OS

		Biomarker Positive (N=118)		Biomarker Negative (N=238)		Total (N=356)	
		Vc-R	Rituximab	Vc-R	Rituximab	Vc-R	Rituximab
PFS	N	57	61	118	120	175	181
	Median (months)	16.6	9.1	12.5	12.5	13.6	11.3
	95% CI	(0.26-0.639)		(0.759-1.425)		(0.621-1.032)	
	p-value	0.0001		0.8097		0.0855	
	HR	0.407		1.04		0.801	
		Vc-R	Rituximab	Vc-R	Rituximab	Vc-R	Rituximab
OS	N	57	61	118	120	175	181
	Median (months)	NA	NA	NA	NA	NA	NA
	95% CI	(0.174-1.046)		(0.617-1.658)		(0.527-1.239)	
	p-value	0.0550		0.9645		0.3270	
	HR	0.426		1.011		0.808	

Biomarker positive=PSMB P11A heterozygote and CD68 "Low" biomarker pair, Biomarker negative^ all subjects without this pair, Vc-R=Bortezomib+Rituximab, PFS=progression free survival, OS=overall survival, CI=confidence interval, HR=hazard ratio

Importantly, biomarker positive subgroup (PSMB1 P11A heterozygote and CD68 Low expression) also had a significantly better overall response rate 73.7% for those treated with Vc-Pv compared to 47.5% with R alone (p=0.0077), and a longer time to next treatment (p=0.0013) and duration of treatment free interval (p=0.0017).

Similar AE profiles were observed in the biomarker positive and biomarker negative populations. Similar treatment exposure was observed in the biomarker positive and biomarker negative populations. Subjects treated with rituximab in the biomarker positive population had a median dose of 2941 mg/m^2 compared to 2940 mg/m^2 in the biomarker negative population. Subjects treated with Vc-R in the biomarker positive population had a median dose of 31.1 mg/m^2 compared to 30 mg/m^2 in the biomarker negative population. Total number of doses, duration of exposure, dose intensity, relative dose intensity and maximum number of cycles received also showed very similar differences.

Subjects treated with Bortezomib + rituximab maintained longer PFS when biomarker positive and stratified by any FLIPI score, by tumor burden, by Ann Arbor score, by age, by region, by sex, and by race. In patients with higher risk and poor prognosis, e.g. high tumor burden, medium or high FLIPI, older than 65, or with prior rituximab treatment, greater PFS improvement were observed in patients when biomarker positive comparing to when biomarker negative. Longer PFS was maintained regardless of time from last treatment or number of previous treatments by prior rituximab or by number of rituximab treatments less than or equal to 2.

Subjects treated with Bortezomib + rituximab maintained longer overall survival when biomarker positive and stratified by FLIPI score, by tumor burden, by Ann Arbor score, by age, by region, by sex, and by race. Subjects treated with Velcade + rituximab maintained longer PFS when positive for CD68 low (0-50) and stratified by any FLIPI score, by tumor burden, by Ann Arbor score, by age, by region, by sex, and by race. When CD68 high, they did better on rituximab alone as expected. Subjects treated with Velcade + rituximab maintained longer PFS when positive for PSMB P11A heterozygote and stratified by any FLIPI score, by tumor burden, by Ann Arbor score, by age, by region, by sex, and by race. When CD68 high, they did better on rituximab alone as expected.

A trend for a longer OS was found for biomarker positive subjects (p=0.055, HR 0.426. When the biomarker contributions are examined individually, this trend is less distinguishable. For subjects that are PSMB1 P11A C/G heterogygotes, the significance is p=0.2525 and HR=0.673 while subjects that are CD68 positive (0-50), the significance is p=0.0714 and HR=0.615.

Subjects treated with Velcade + rituximab had a trend for better OS when positive for CD68 low (0-50) and stratified by any FLIPI score, by tumor burden, by Ann Arbor score, by age, by region, by sex, and by race. Subjects treated with Velcade + rituximab had a trend for better OS when positive for PSMB1 P11A heterozygote and stratified by any FLIPI score, by tumor burden, by Ann Arbor score, by age, by region, by sex, and by race.

Following cross validation, the pair previously described (CD68 Low and PSMB P11A) was found to be significant in the smaller discovery cohort (p=0.0003, 14.2 months for Vc-R vs 8.5 months for R, HR=0.4 (0.24, 0.67)). There was still a trend for longer OS in the biomarker positive population (p=0. 1291), HR=0.47(0.17, 1.27). Although the number of subjects in the confirmation cohorts is small, the positive trend in both PFS and OS was found to be maintained. In confirmation cohort 1 (n=106), subjects treated with Vc-R had approximately 18.2 mo PFS while those treated with R alone had 9.5 months PFS (p= 0.0817, HR=0.44). In confirmation cohort 2 (n=426), subjects treated with Vc-R had 13.9 months median PFS while those treated with R had 9.5 months median PFS (p=0.0878, HR=0.49). The trend in OS was also maintained

It was of interest to determine the individual contributions of each biomarker to the PFS benefit found in subjects with both biomarkers (PSMB1 P11A heterozygote and CD68 Low). Within the biomarker positive population, subjects with PSMB1 P11A (C/G) had 16.6 months median PFS when treated with Vc-R compared to 9.5 months median PFS when treated with R alone, showing a 7.1 month PFS advantage when the combination was used. This benefit was not seen in biomarker negative subjects with Vc-R. Consistent with prior publication on CD68 and rituxan, this study shows that subjects with higher CD68 expression do better on rituximab alone (16.2 months median PFS) than those with lower CD68 expression (9.3 months median PFS). However, these subjects with low CD68 (0-50) had significantly longer PFS (14 months median) when treated with the combination compared to similar patients treated with R alone (9.3 months median); this is a 4.7 month PFS advantage (HR=0.64 (95% CI: 0.475-0.864).

These results suggest that patient subgroups can be identified prior to therapy that have significantly longer PFS and a trend for better OS when treated with combination Vc-R compared to R alone. One biomarker pair that maintains significance after multiple comparison corrections (FDR=0.051) includes a proteasomal subunit SNP [PSMB1 P11A heterozygote] and CD68 with low (0-50) expression. Three hundred fifty six subjects were evaluable for both of these biomarkers within this study. Additionally, this biomarker pair had a high population frequency with approximately one third of the evaluable subjects having both of these biomarkers. Subjects with this biomarker pair had a longer PFS interval when treated with Vc-R (16.6 months) compared to rituximab alone (9.1 months) demonstrating a PFS benefit of approximately 7.5 months with the combination. This group also appears to have an OS benefit with Vc-R that clearly trends toward significance (HR: 0.426 (0.174-1.046) P = 0.0550), a higher ORR (73.7% on Vc-R vs 47.5% on rituximab alone, p=0.0077), a longer time to next treatment interval (33.1 mo on Vc-R vs 14.8 mo on rituximab alone, p=0.0013) and a longer duration of treatment free interval (27.8 mo vs 10.1 mo, p=0.0017).

Importantly, the CD68/PSMB P11A biomarker positive cohort was representative of the overall trial population with regard to demographics and clinical characteristics. Of note, approximately half of this cohort was represented by subjects with high risk disease and poor prognostic features. In patients with higher tumor burden (-54%), medium or high FLIPI (~76%>), older age (> 65) (~25%>), with prior Rituximab treatment (~46%>), or with two (~26%)

or more than two (-30%) lines of prior therapy the PFS benefit of the CD68/PSMB P11A biomarker positive cohort appears to be maintained. These patients are generally regarded as "high risk" with limited treatment options and these preliminary findings suggest that biomarker positive subjects with high risk features may benefit from Vc-R.

Polymorphisms in PSMB1 and PSMB5 were found to have significant associations with clinical endpoints as single markers. The combination of PSMB1 [P11A] with CD68 was found to be synergistic and present in a high proportion of the study cohort. PSMB1 P11A is a polymorphism found in the leader sequence of the proteasome PSMB1 gene (Chen 1996). The leader sequence is responsible for appropriate subunit assembly and it has been reported that alterations of charged amino acids reduces the efficiency of subunit assembly (Schmidt 1999). Once assembled autocatalysis allows removes the leader sequence. The second biomarker in the pair is CD68 expressing tumor infiltrating macrophages. Previous reports have shown that high levels of CD68 associate with better response to rituximab (Taskinen 2007).

Importantly, this study has shown that subjects with low levels of CD68 expression have longer PFS and better overall response to Vc-R compared to R alone especially when present with PSMB1 P11A heterozygote as discussed above. Following cross validation, the pair previously described (CD68 Low and PSMB P11A) was found to be significant in the smaller discovery cohort (p=0.0003, 14.2 months for Vc-R vs 8.5 months for rituximab alone, HR=0.4 (0.24, 0.67)). There was still a trend for longer OS in the biomarker positive population (p=0.1291), HR=0.47(0.17, 1.27). Although the number of subjects in the confirmation cohorts was small, the positive trend in both PFS and OS was found to be maintained. In confirmation cohort 1 (which excludes subjects from China; n=106), subjects treated with Vc-R had approximately 18.2 mo PFS while those treated with R alone had 9.5 months PFS (p= 0.0817, HR=0.44). In confirmation cohort 2 (which includes China subjects and subjects with missing data; n=126), subjects treated with Vc-R had 13.9 months median PFS while those treated with R had 9.5 months median PFS (p=0.0878, HR=0.49). The trend in OS was also maintained.

EXAMPLE 2.

Single predictors which correlated with a positive response are shown in Table 5.

Table 5. Single predictors.

Marker A	Marker Subtype	PFS Vc+R vs. R median days	N Vc+R vs. R	Logrank P-value	% N in ITT
CD68 OVERALL POSITIVE	0-25	11.5 mo vs 10.6 mo 0.9 mo PFS improvement	40 vs 44	0.422	12.4
CD68 OVERALL POSITIVE	26-50	12.1 mo vs 9.3 mo 2.8 mo PFS improvement	114 vs 108	0.0588	32.9
CD68 POSITIVE FOLLICULAR	0-25	14.1 mo vs 9.3 mo 4.8 mo PFS improvement	50 vs 60	0.0934	16.3
CD68 POSITIVE FOLLICULAR	26-50	13.4 mo vs 9.1 mo 4.3 mo PFS improvement	84 vs 91	0.0289	25.9
P65 INTENSITY CYTOPLASMIC SIGNAL	<=1+	11.6 mo vs 9.3 mo 2.3 mo PFS improvement	41 vs 43	0.2455	12.4
PSMB1/P11A	C/G	14 mo vs 9.3 mo 4.7 mo improvement	115 vs 127	0.0218	35.9
PSMB5/R24C	C/T	17.6 mo vs 9.3 mo 8.3 mo improvement	41 vs 41	0.4016	12.1

EXAMPLE 3.

Predictor pairs which correlated with a positive response are shown in Tables 6 and 7.

Table 6. Significant marker pairs.

Marker A	**Marker B**	**PFS Vc-R vs. R median month**	**N Vc-R vs. R**	**Logrank P-value**	**FDR**
PSMB5/R24C C/T	P65 INTENSITY CYTOPLASMIC SIGNAL <=1+	27 mo vs. 10.4 mo 16.6 mo improvement	5 vs. 7	0.0439	0.489
PSMB1/P11A C/G	20S % POSITIVE CYTOPLASMIC SIGNAL: >90	18.9 mo vs. 9.5 mo 9.4 improvement	50 vs 50	0.0145	0.447
PSMB1/P11A C/G	CD68 POSITIVE FOLLICULAR: 0-50	16.6 mo vs. 9.1 mo 7.5 mo improvement	57 vs 61	0.0001	0.051
PSMB1/P11A C/G	CD68 POSITIVE PERIFOLLICULAR: >50	16.6 mo vs. 9.2 mo 7.4 improvement	24 vs 28	0.0365	0.471
PSMB9/R60H G/G	P65 % NUCLEAR STAINING: >0	16.2 mo vs. 9.5 mo 6.7 improvement	35 vs 28	0.0303	0.455
PSMB5/R24C C/T	CD68 POSITIVE FOLLICULAR: 0-50	13.7 mo vs. 7.2 mo 6.5 mo improvement	18 vs 21	0.0220	0.447
HI Tumor BD NO	CD68 OVERALL POSITIVE: 0-50	22.8 mo vs. 16 mo 6.8 mo improvement	64 vs 68	0.0177	0.447
HI Tumor BD NO	CD68 POSITIVE FOLLICULAR: 0-50	20.5 mo vs. 13.8 mo 6.7 mo improvement	64 vs 66	0.0310	0.455
Prior RX: 1	CD68 POSITIVE FOLLICULAR: 0-50	18.2 mo vs. 9.3 mo 8.9 mo improvement	63 vs 69	0.0129	0.447
PSMB1/P11A C/G	Time since last Rx: > 1 year	18.2 mo vs. 10.7 mo 7.5 mo improvement	72 vs 74	0.0198	0.447
Prior Ritutux NO	CD68 POSITIVE FOLLICULAR: 0-50	15.9 mo vs. 9.2 mo 6.7 mo improvement	73 vs 86	0.0066	0.437

Table 6. Significant marker pairs.

Marker A	Marker B	PFS Vc-R vs. R median month	N Vc-R vs. R	Logrank P-value	FDR
PSMB1/P11A C/G	Age group: <=65	15.3 mo vs. 9.2 mo 6.1 mo improvement	86 vs 96	0.0071	0.437
Sex MALE	20S % NUCLEAR STAINING: >20	13.7 mo vs. 7.7 mo 6 mo improvement	63 vs 48	0.0050	0.437
Race Group OTHER	20S % NUCLEAR STAINING: >20	11.4 mo vs. 3.8 mo 7.6 mo improvement	11 vs 7	0.0320	0.455
PSMB1/P11A C/G	PSMB5/R24C C/T	13.7 mo vs. 7.8 mo 5.9 mo improvement	7 vs. 7	0.0221	0.4468

Table 7. Significant marker pairs

Combination	PFS Vc-R vs. R median month	Logrank P-value
P65 Cytoplasmic signal >90% & 1 prior treatment*	23.6 vs. 10.6 mo (13mo)	0.0132
	16 vs. 8.9 mo (7.1mo)	n.s.
CD68 Pos Follic (0-50) & P11A[C/G]**	14.2 vs 8.5 mo (5.7 mo)	0.0025
	14.4 vs 9.2 mo (5.2 mo)	n.s.

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EXAMPLE 4.

Appendix 2 presents an overall summary of the single-marker associations with clinical endpoint other than PFS and stratified by clinical covariates from the previous examples.

Appendix 3 outlines the data for all significant pair-wise combinations from the previous examples. Note: Selected = Biomarker positive, Not Selected=Biomarker negative.

EXAMPLE 5

The VISTA study was an open-label, randomized study of VELCADE/Melphalan/Prednisone versus Melphalan/Prednisone in subjects with previously untreated multiple myeloma. San Miguel, *N. Engl. J. Med.* 2008 Aug 28;359(9):906-17. The primary efficacy objective of this study was to determine whether the addition of VELCADE (Bortezomib for Injection) to standard melphalan/prednisone (MP) therapy improves the time to disease progression (TTP) in subjects with previously untreated multiple myeloma.

The exploratory objectives in biomarker analysis from the the VISTA study were to identify patient populations that are more or less likely to respond to VELCADE/Melphalan/Prednisone versus Melphalan/Prednisone alone by:

- Confirming the finding (from lymphoma studies) of a single marker association of PSMB1 P11A and PSMB5 R24C with PFS and OS.

'Association with other clinical endpoints including: time to progression (TTP), complete response (CR), Overall response rate, time to response and duration of response.

Association of PSMB1 P11A and PSMB5 R24C individually or in combination with TTP, PFS, and OS were estimated using the log rank test between treatment groups for biomarker positive and negative populations. The overall biomarker population by treatment arm had similar associations made. Medians of TTP, PFS, and OS, difference in median TTP, PFS, and OS between treatment groups, log rank P-value, hazard ratio and its 95% confidence intervals and frequencies of events were reported. Kaplan-Meier plots were presented for each biomarker. When positive associations were found for TTP, OS or PFS, then the other clinical endpoints were tested with similar methods and output. For ORR, Fishers exact test was used. The number and percentage of subjects falling into each response category were descriptively tabulated.

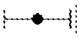
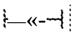
Table 8 shows the progression free survival benefit of 5.3 months with VELCADE-MP vs. MP alone in patients with PSMBl PI 1A (C/G) marker.

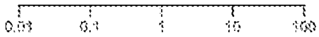
	Biomarker Positive		**Biomarker Negative**		**Total**	
Statistic	**Vmp**	**mp**	**Vmp**	**mp**	**Vmp**	**mp**
Event/Total (%)	39/82 (47.6)	61/89 (68.5)	47/87 (54.0)	68/94 (72.3)	86/169 (50.9)	129/183 (70.5)
Median (95%CI)	20.3 mo (556,873)	15 mo (253,511)	17.7 mo (459,610)	11.2 mo (254,436)	19 mo (533,662)	12.6 mo (279,463)
HR (Vmp vs mp)	0.44 (0.29,0.67)		0.62 (0.43,0.90)		0.54 (0.41,0.71)	
HR p-Value (Vmp vs mp)	<.0001		0.0117		<.0001	

Table 9 shows the overall survival benefit of 6 months with VELCADE-MP vs. MP alone in patients with PSMBl PI1A (C/G) marker.

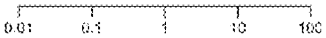
	Biomarker Positive		**Biomarker Negative**		**Total**	
Statistic	**Vmp**	**mp**	**Vmp**	**mp**	**Vmp**	**mp**
Event/Total (%)	47/82 (57.3)	65/89 (73.0)	42/87 (48.3)	55/94 (58.5)	89/169 (52.7)	120/183 (65.6)
Median (95%CI)	52 (1322,1845)	39 (893,1412)	58 (1318,-)	46 (965,1745)	56 (1372,1845)	42 (1014,1470)
HR Vmp vs mp)	0.63 (0.44,0.92)		0.81 (0.54,1.22)		0.72 (0.55,0.95)	
HR p-Value (Vmp vs mp)	**0.0167**		0.3153		0.0179	

Appendix 2, Table 2.1: Overall survival (OS) by Protein Expression and by Covariate, IRC Review (Significant [p ≤0.05], Frequency of ≥10% or Higher)

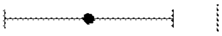
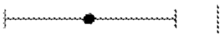
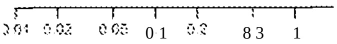
Marker: Level	Subgroup	HR (95% CI)	HR (log scale)	R Evt/ N	R Median	Vc-R Evt/ N	Vc-R Median	Marker: Subgroup N Total
20S % POSITIVE CYTOPLASMIC SIGNAL: 0-20	2 Prior Lines of Therapy	8.28 (0.85,80.83)		1/10	-	3/4	809	122
20S % POSITIVE CYTOPLASMIC SIGNAL: 95-100	2 Prior Lines of Therapy	0.42 (0.17,1.00)		14/35	1205	9/40	-	122
CD68 OVERALL POSITIVE: 26-50	2 Prior Lines of Therapy	0.33 (0.12,0.87)		13/26	1205	7/30	-	111
CD68 POSITIVE PERIFOLLICULAR : 26-50	2 Prior Lines of Therapy	0.30 (0.09,1.04)		7/16	1205	5/27	-	98
P65 % POSITIVE CYTOPLASMIC SIGNAL: >90%	2 Prior Lines of Therapy	0.42 (0.19,0.97)		19/52	-	9/44	-	125
P65 INTENSITY CYTOPLASMIC SIGNAL: >2+	2 Prior Lines of Therapy	0.35 (0.14,0.88)		19/55	-	7/43	-	125
CD68 OVERALL POSITIVE: 26-50	No High Tumor Burden	0.21 (0.06,0.72)		14/54	-	3/46	-	204
CD68 POSITIVE PERIFOLLICULAR : 26-50	No High Tumor Burden	0.11 (0.01,0.82)		10/41	-	1/33	-	182
P27 % NUCLEI POSITIVE: 0-20	No High Tumor Burden	3.91 (0.98,15.69)		3/29	-	6/17	-	215
20S INTENSITY CYTOPLASMIC SIGNAL: <2+	Intermediate FLIPI Score	5.43 (1.17,25.14)		2/48	-	9/41	-	168
P65 INTENSITY CYTOPLASMIC SIGNAL: ≤1+	Intermediate FLIPI Score	6.84 (0.80,58.74)		1/17	-	5/13	-	170
CD68 POSITIVE FOLLICULAR: 0-25	No Prior Rituximab Therapy	0.21 (0.05,0.97)		11/36	-	3/25	1343	210
CD68 POSITIVE FOLLICULAR: 0-25	<65 years old	0.29 (0.10,0.83)		14/46	-	5/41	-	292
20S INTENSITY CYTOPLASMIC SIGNAL: >3+	Male	0.30 (0.12,0.77)		10/27	-	8/62	-	204
CD68 POSITIVE PERIFOLLICULAR : 26-50	Male	0.29 (0.10,0.83)		11/30	-	5/39	-	169
P27 % NUCLEI POSITIVE: 60-70	Male	0.09 (0.01,0.93)		4/12	-	1/14	-	202
CD68 OVERALL POSITIVE: 51-75	Ann Arbor Stage III	6.24 (1.25,31.02)		2/21	-	6/13	1078	144
20S % POSITIVE	Ann Arbor	7.22		1/15	-	4/11	1103	236

CYTOPLASMIC SIGNAL: 0-20	Stage IV	(0.80,65.02)						
20S % POSITIVE CYTOPLASMIC SIGNAL: 95-100	Ann Arbor Stage IV	0.50 (0.27,0.91)		25/56	1205	19/75	1343	236
								

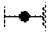
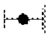
Appendix 2, Table 2.2: OS by Germlme Genetic Variant nd by Covariate, IRC Review (Significant [p<0.05], Frequency of ≥10% or Higher)

Marker: Level	Subgroup	HR (95% CD	HR (log scale)	R Evt/N	R Median	Vc-R Evt/N	Vc-R Median	Marker: Subgroup N Total
PSMB9/R60H : A/A	3 Prior Lines of Therapy	6.92 (0.79,60.79)		1/6	-	5/7	846	85
PSMB5/R24C : C/T	Intermedial e FLIPI Score	0.10 (0.01,0.97)		4/10	971	1/16	-	186
PSMB5/R24C : C/T	Ann Arbor Stage IV	0.22 (0.07,0.66)		9/15	717	5/28	-	270
								

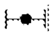
Appendix 2, Table 2.3: OS by Somatic Mutation and by Covariate, IRC Review (Significant [p<0.05], Frequency of ≥ 10% or Higher)

Marker: Level	Subgroup	HR (95% CI)	HR (log scale)	R Evt/ N	R Median	Vc-R Evt/ N	Vc-R Median	Marker: Subgroup N Total
NOTCH/X28DEL: MND	2 Prior Lines of Therapy	0.44 (0.20,0.97)		20/56	-	10/48	-	109
NOTCH/P2513L: MD	No High Tumor Burden	0.14 (0.02,1.15)		7/26	-	1/21	-	163
BCL2/P59L: MD	High Tumor Burden	0.17 (0.04,0.65)		5/6	282	4/14	-	172
BCL2/P59L: MD	High FLIPI Score	0.21 (0.05,0.86)		6/6	282	4/7	843	125
BCL2/P59L: MD	No Prior Rituximab Therapy	0.12 (0.03,0.48)		5/5	174	4/13	-	178
BCL2/P59L: MD	Rest of World	0.22 (0.06,0.84)		4/5	174	5/12	-	152
NOTCH/P2513L: MD	> 65 years old	0.30 (0.09,1.03)		8/13	795	4/13	-	92
BCL2/P59L: MD	Female	0.26 (0.07,0.92)		6/8	536	4/14	-	180
BCL2/R106H: MD	Male	0.25 (0.07,0.84)		8/10	318	4/12	-	169
NOTCH/Q2460X: MD	Male	0.11 (0.02,0.70)		3/3	595	5/12	-	142
NOTCH/X28DEL: MND	Male	0.57 (0.32,1.00)		26/75	-	22/97	-	180
BCL2/P59L: MD	Ann Arbor Stage IV	0.12 (0.03,0.50)		5/5	174	4/12	-	149
								

Appendix 2, Table 2.4: Time to Progression (TTP), by Protein Expression and by Covariate, IRC Review (Significant [p<0.05], Frequency of ≥ 10% or Higher)

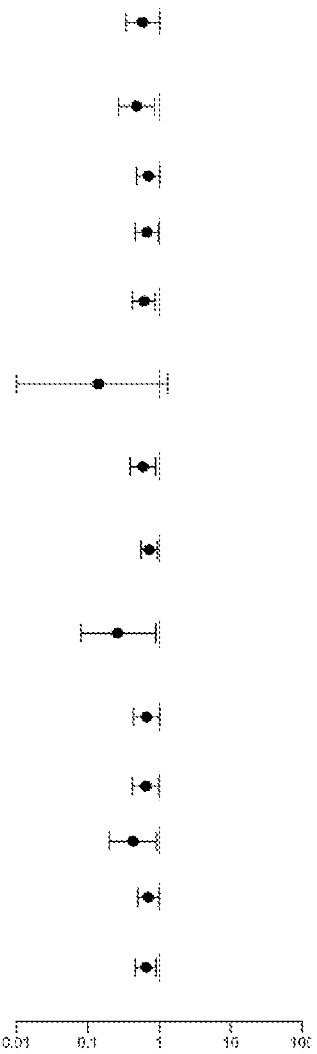
Marker: Level	Subgroup	HR (95% CI)	HR (log scale)	R Evt/N	R Median	Vc-R Evt/N	Vc-R Median	Marker: Subgroup N Total
CD68 POSITIVE FOLLICULAR: 26-50	No Subgroup	0.66 (0.45,0.96)		65/91	277	48/84	414	387
P65 % POSITIVE CYTOPLASMIC SIGNAL: >90%	No Subgroup	0.75 (0.59,0.96)		139/204	334	116/186	414	470
CD68 POSITIVE FOLLICULAR: 26-50	1 Prior Line of Therapy	0.51 (0.27,0.94)		26/39	349	18/40	881	176
CD68 POSITIVE PERIFOLLICULAR: >75	1 Prior Line of Therapy	0.24 (0.09,0.65)		13/18	275	7/16	716	174
P65 % POSITIVE CYTOPLASMIC SIGNAL: >90%	1 Prior Line of Therapy	0.67 (0.45,0.98)		56/89	349	48/88	506	203
20S % NUCLEAR STAINING: 30-50	2 Prior Lines of Therapy	0.41 (0.18,0.95)		11/13	239	13/22	431	122
CD68 OVERALL POSITIVE: 0-25	2 Prior Lines of Therapy	0.22 (0.05,0.90)		6/8	142	4/7	771	111
CD68 POSITIVE PERIFOLLICULAR: 0-25	2 Prior Lines of Therapy	0.13 (0.03,0.64)		7/8	70	4/7	771	98
CD68 POSITIVE FOLLICULAR: 51-75	3 Prior Lines of Therapy	9.40 (1.13,78.09)		1/4	-	8/8	276	60
P27 SIGNAL INTENSITY: >2+	4 Prior Lines of Therapy	3.02 (1.09.8.34)		9/15	348	8/10	144	32
CD68 OVERALL POSITIVE: 26-50	No High Tumor Burden	0.50 (0.29,0.86)		37/54	357	22/46	881	204
CD68 POSITIVE FOLLICULAR: 26-50	No High Tumor Burden	0.50 (0.27,0.93)		29/44	351	17/39	881	182
CD68 OVERALL POSITIVE: 26-50	High FLIPI Score	0.58 (0.36,0.94)		36/45	277	35/52	366	181
CD68 POSITIVE FOLLICULAR: 26-50	High FLIPI Score	0.57 (0.33,0.97)		31/37	205	25/36	347	156
P65 % POSITIVE CYTOPLASMIC SIGNAL: >90%	High FLIPI Score	0.65 (0.45,0.94)		61/83	239	53/77	358	193
P65 INTENSITY CYTOPLASMIC SIGNAL: >2+	High FLIPI Score	0.67 (0.46,0.98)		60/80	275	51/76	358	193
P27 % NUCLEI POSITIVE: 60-70	Intermediale FLIPI Score	3.34 (1.20.9.30)		6/13	513	10/11	215	165
P65 % POSITIVE	Intermedial	2.77		5/16	567	15/19	351	170

Appendix 2, Table 2.4: Time to Progression (TTP), by Protein Expression and by Covariate, IRC Review (Significant [p≤0.05], Frequency of ≥ 10% or Higher)

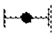
Marker: Level	Subgroup	HR (95% CI)	HR (log scale)	R Evt/N	R Median	Vc-R Evt/N	Vc-R Median	Marker: Subgroup N Total
CYTOPLASMIC SIGNAL: <90%	e FLIPI Score	(1.00,7.64)						
P65 % NUCLEAR STAINING: 0	No Prior Rituximab Therapy	0.69 (0.49,0.97)		77/102	322	55/92	426	255
P65 % POSITIVE CYTOPLASMIC SIGNAL: >90%	No Prior Rituximab Therapy	0.68 (0.49,0.95)		80/112	345	61/105	463	255
CD68 OVERALL POSITIVE: 0-25	≤ 1 year since last anti-lymphoma treatment	2.66 (1.02,6.96)		11/18	424	11/13	202	173
CD68 POSITIVE FOLLICULAR: 0-25	> 1 year since last anti-lymphoma treatment	0.49 (0.26,0.91)		23/34	357	20/33	519	235
P65 % POSITIVE CYTOPLASMIC SIGNAL: >90%	> 1 year since last anti-lymphoma treatment	0.69 (0.49,0.96)		77/117	357	61/112	519	288
CD68 OVERALL POSITIVE: 26-50	Rest of World	0.63 (0.40,1.00)		40/51	277	34/52	367	198
CD68 OVERALL POSITIVE: 26-50	<65 years old	0.65 (0.44,0.95)		57/77	278	50/84	414	329
CD68 POSITIVE FOLLICULAR: 26-50	<65 years old	0.55 (0.36,0.86)		52/67	270	34/62	406	292
CD68 POSITIVE PERIFOLLICULAR: >75	<65 years old	0.46 (0.22,0.98)		17/23	275	12/23	506	289
P27 SIGNAL INTENSITY: >2+	<65 years old	0.73 (0.55,0.97)		104/153	281	91/149	406	344
P65 % NUCLEAR STAINING: 0	<65 years old	0.72 (0.53,0.98)		97/138	287	71/118	414	349
P65 % POSITIVE CYTOPLASMIC SIGNAL: >90%	<65 years old	0.66 (0.50,0.89)	M I	108/154	278	83/142	422	349
P65 INTENSITY CYTOPLASMIC SIGNAL: >2+	<65 years old	0.74 (0.55,0.98)		105/152	287	85/139	406	349
20S % POSITIVE CYTOPLASMIC SIGNAL: 0-20	> 65 years old	0.14 (0.02,1.21)		5/6	278	4/7	738	118
CD68 POSITIVE FOLLICULAR: 51-75	Female	2.38 (1.11,5.13)		14/26	708	13/14	324	217
20S % NUCLEAR STAINING: 60-70	Male	0.37 (0.17,0.84)		13/16	212	15/20	358	204

Appendix 2, Table 2.4: Time to Progression (TTP), by Protein Expression and by Covariate, IRC Review (Significant [p≤0.05], Frequency of ≥ 10% or Higher)

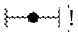
Marker: Level	Subgroup	HR (95% CI)	HR (log scale)	R Evt/N	R Median	Vc-R Evt/N	Vc-R Median	Marker: Subgroup N Total
20S INTENSITY CYTOPLASMIC SIGNAL: >3+	Male	0.58 (0.34,1.00)		20/27	280	39/62	422	204
CD68 POSITIVE PERIFOLLICULAR: 26-50	Male	0.48 (0.27,0.86)		22/30	239	26/39	429	169
P27 SIGNAL INTENSITY: >2+	Male	0.70 (0.48,1.00)		52/72	280	69/101	360	202
P65 % NUCLEAR STAINING: 0	Male	0.67 (0.46,0.98)		56/74	280	56/84	358	207
P65 % POSITIVE CYTOPLASMIC SIGNAL: >90%	Male	0.61 (0.42,0.87)		54/72	271	65/97	414	207
CD68 POSITIVE PERIFOLLICULAR: 26-50	Other	0.14 (0.01,1.31)		4/4	128	4/5	346	22
CD68 POSITIVE FOLLICULAR: 26-50	White	0.59 (0.39,0.89)		53/77	334	39/73	463	335
P65 % POSITIVE CYTOPLASMIC SIGNAL: >90%	White	0.72 (0.55,0.94)		119/179	345	99/162	426	406
P65 INTENSITY CYTOPLASMIC SIGNAL: ≤ 1+	Ann Arbor Stage III	0.26 (0.08,0.90)		7/11	204	7/11	464	151
20S % POSITIVE CYTOPLASMIC SIGNAL: 95-100	Ann Arbor Stage IV	0.66 (0.43,1.00)		43/56	278	47/75	414	236
CD68 OVERALL POSITIVE: 26-50	Ann Arbor Stage IV	0.65 (0.42,0.99)		44/56	277	45/68	366	222
P27 % NUCLEI POSITIVE: 30-50	Ann Arbor Stage IV	0.43 (0.20,0.92)		15/19	278	13/23	485	237
P27 SIGNAL INTENSITY: >2+	Ann Arbor Stage IV	0.70 (0.50,0.99)		64/85	283	73/113	358	237
P65 % POSITIVE CYTOPLASMIC SIGNAL: >90%	Ann Arbor Stage IV	0.65 (0.46,0.91)		67/87	275	66/104	366	240



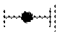
Appendix 2, Table 2.5: TTP by Germline Genetic Variant and by Covariate, IRC review (Significant [p≤0.05], Frequency of ≥10% or Higher)

Marker: Level	Subgroup	HR (95% CI)	HR (log scale)	R Evt/N	R Median	Vc-R Evt/N	Vc-R Median	Marker: Subgroup N Total
PSMB1/P1 1A: C/G	No Subgroup	0.70 (0.5 1,0.96)		82/127	288	74/1 15	426	542
PSMB9/V32I: C/C	No Subgroup	0.80 (0.65,0.99)		177/266	345	157/254	417	542
PSMB5/R24C: C/T	2 Prior Lines of Therapy	0.32 (0.1 1,0.95)		8/10	280	6/12	534	142
PSMB1/A171S: G/G	High Tumor Burden	0.74 (0.57.0.97)		110/147	273	107/149	344	296
PSMB 1/I208N: T/T	High Tumor Burden	0.74 (0.57,0.97)		110/147	273	107/149	344	296
PSMB1/P1 1A: C/G	High Tumor Burden	0.66 (0.44,0.99)		52/72	253	44/65	358	296
PSMB1/P193L: C/C	High Tumor Burden	0.74 (0.57,0.97)		110/147	273	107/149	344	296
PSMB2/E49X: G/G	High Tumor Burden	0.74 (0.57.0.97)		110/147	273	107/149	344	296
PSMB2/G187V: G/G	High Tumor Burden	0.74 (0.57,0.97)		110/147	273	107/149	344	296
PSMB2/L159F: C/C	High Tumor Burden	0.74 (0.57,0.97)		110/147	273	107/149	344	296
PSMB5/L206M: C/C	High Tumor Burden	0.74 (0.57.0.97)		110/147	273	107/149	344	296
PSMB5/R24C: C/T	High Tumor Burden	0.39 (0. 19,0.77)		17/21	275	18/24	352	296
PSMB6/A234D: C/C	High Tumor Burden	0.74 (0.57,0.97)		110/147	273	107/149	344	296
PSMB8/G8R: G/G	High Tumor Burden	0.73 (0.56,0.96)		104/140	271	105/145	344	296
PSMB8/R141C: C/C	High Tumor Burden	0.74 (0.57.0.97)		110/147	273	107/149	344	296
PSMB8/V182M: G/G	High Tumor Burden	0.74 (0.57,0.97)		110/147	273	107/149	344	296
PSMB9/G9E: G/G	High Tumor Burden	0.74 (0.56,0.96)		110/145	271	107/148	344	296

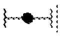
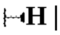
Appendix 2, Table 2.5: TTP by Germlme Genetic Variant and by Covariate, IRC review (Significant [p≤0.05], Frequency of ≥ 10% or Higher)

Marker: Level	Subgroup	HR (95% CD	HR (log scale)	R Evt/N	R Median	Vc-R Evt/N	Vc-R Median	Marker: Subgroup N Total
PSMB9/V32I: C/C	High Tumor Burden	0.73 (0.56,0.96)		108/142	273	101/142	331	296
PSMB1/A171S : G/G	High FLIPI Score	0.68 (0.49,0.92)		84/112	273	75/110	350	222
PSMB1/I208N: T/T	High FLIPI Score	0.68 (0.49,0.92)		84/112	273	75/110	350	222
PSMB1/P193L : C/C	High FLIPI Score	0.68 (0.49,0.92)		84/112	273	75/110	350	222
PSMB2/E49X: G/G	High FLIPI Score	0.68 (0.49,0.92)		84/112	273	75/110	350	222
PSMB2/G187 V: G/G	High FLIPI Score	0.68 (0.49,0.92)		84/112	273	75/110	350	222
PSMB2/L159F : C/C	High FLIPI Score	0.68 (0.49,0.92)		84/112	273	75/110	350	222
PSMB5/L206 M: C/C	High FLIPI Score	0.68 (0.49,0.92)		84/112	273	75/110	350	222
PSMB6/A234 D: C/C	High FLIPI Score	0.68 (0.49,0.92)		84/112	273	75/110	350	222
PSMB6/P107A : C/C	High FLIPI Score	0.68 (0.49,0.93)		851/107	275	74/108	350	222
PSMB8/G8R: G/G	High FLIPI Score	0.69 (0.50,0.95)		77/105	273	73/107	350	222
PSMB8/R141C : C/C	High FLIPI Score	0.68 (0.49,0.92)		84/112	273	75/110	350	222
PSMB8/V182 M: G/G	High FLIPI Score	0.68 (0.49,0.92)		84/112	273	75/110	350	222
PSMB9/G9E: G/G	High FLIPI Score	0.69 (0.50,0.94)		84/111	273	75/109	348	222
PSMB9/V32I: C/C	High FLIPI Score	0.65 (0.47,0.89)		80/105	239	71/105	348	222
PSMB1/P11A: C/G	No Prior Rituximab Therapy	0.64 (0.43,0.98)		49/68	330	43/70	464	287
PSMB9/V32I: C/C	No Prior Rituxima	0.73 (0.55,0.99		98/138	351	79/136	483	287

Appendix 2, Table 2.5: TTP by Germlme Genetic Variant and by Covariate, IRC review (Significant [p≤0.05], Frequency of ≥ 10% or Higher)

Marker: Level	Subgroup	HR (95% CD	HR (log scale)	R Evt/N	R Median	Vc-R Evt/N	Vc-R Median	Marker: Subgroup p N Total
	b Therapy	)						
PSMB1/A171S : G/G	> 1 year since last anti-lymphoma treatment	0.71 (0.54,0.94)		104/165	381	91/166	529	331
PSMB1/I208N: T/T	> 1 year since last anti-lymphoma treatment	0.71 (0.54,0.94)		104/165	381	91/166	529	331
PSMB1/P1 1A: C/G	> 1 year since last anti-lymphoma treatment	0.60 (0.39,0.91)		47/74	338	42/72	576	331
PSMB1/P193L : C/C	> 1 year since last anti-lymphoma treatment	0.71 (0.54,0.94)		104/165	381	91/166	529	331
PSMB2/E49X: G/G	> 1 year since last anti-lymphoma treatment	0.71 (0.54,0.94)		104/165	381	91/166	529	331
PSMB2/G187 V: G/G	> 1 year since last anti-lymphoma treatment	0.71 (0.54,0.94)		104/165	381	91/166	529	331
PSMB2/L159F : C/C	> 1 year since last anti-lymphoma treatment	0.71 (0.54,0.94)		104/165	381	91/166	529	331
PSMB5/L206 M: C/C	> 1 year since last anti-lymphoma treatment	0.71 (0.54,0.94)		104/165	381	91/166	529	331
PSMB6/A234	> 1 year	0.71		104/16	381	91/166	529	331

Appendix 2, Table 2.5: TTP by Germlme Genetic Variant and by Covariate, IRC review (Significant [p≤0.05], Frequency of ≥10% or Higher)

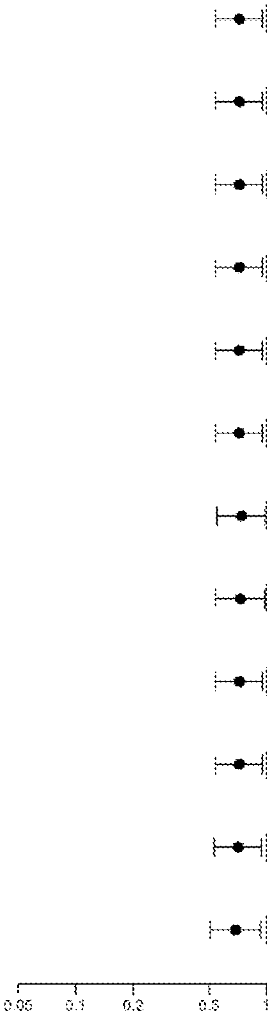
Marker: Level	Subgroup	HR (95% CD	HR (log scale)	R Evt/N	R Median	Vc-R Evt/N	Vc-R Median	Marker: Subgroup N Total
D: C/C	since last anti-lymphoma treatment	(0.54,0.94)		5				
PSMB6/P107A: C/C	> 1 year since last anti-lymphoma treatment	0.71 (0.53,0.94)		103/159	381	90/162	519	331
PSMB8/G8R: G/G	> 1 year since last anti-lymphoma treatment	0.73 (0.55,0.98)		96/155	414	86/159	519	331
PSMB8/R141C: C/C	> 1 year since last anti-lymphoma treatment	0.71 (0.54,0.94)		104/165	381	91/166	529	331
PSMB8/V182M: G/G	> 1 year since last anti-lymphoma treatment	0.71 (0.54,0.94)		104/165	381	91/166	529	331
PSMB9/G9E: G/G	> 1 year since last anti-lymphoma treatment	0.70 (0.53,0.93)		104/163	381	91/165	519	331
PSMB9/V32I: C/C	> 1 year since last anti-lymphoma treatment	0.69 (0.51,0.92)		102/160	379	86/158	529	331
PSMB1/A171S: G/G	<65 years old	0.71 (0.55,0.91)		131/198	326	115/194	435	392
PSMB1/I208N: T/T	<65 years old	0.71 (0.55,0.91)		131/198	326	115/194	435	392
PSMB1/P11A: C/G	<65 years old	0.58 (0.40,0.85)		62/96	288	50/86	506	392
PSMB1/P193L	<65 years	0.71		131/19	326	115/19	435	392

Appendix 2, Table 2.5: TTP by Germline Genetic Variant and by Covariate, IRC review (Significant [p≤0.051, Frequency of >10% or Higher)

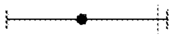
Marker: Level	Subgroup	HR (95% CI)	HR (log scale)	R Evt/N	R Median	Vc-R Evt/N	Vc-R Median	Marker: Subgroup P N Total
: C/C	old	(0.55,0.91)		8		4		
PSMB2/E49X: G/G	<65 years old	0.71 (0.55,0.91)	├◆┤	131/198	326	115/194	435	392
PSMB2/G187V: G/G	<65 years old	0.71 (0.55,0.91)	HH	131/198	326	115/194	435	392
PSMB2/L159F: C/C	<65 years old	0.71 (0.55,0.91)	HH	131/198	326	115/194	435	392
PSMB5/L206M: C/C	<65 years old	0.71 (0.55,0.91)	HH	131/198	326	115/194	435	392
PSMB5/R24C: C/C	<65 years old	0.71 (0.55,0.93)	├●┤	115/170	334	103/167	429	392
PSMB6/A234D: C/C	<65 years old	0.71 (0.55,0.91)	├●┤	131/198	326	115/194	435	392
PSMB6/P107A: C/C	<65 years old	0.71 (0.55,0.92)	├●┤	126/189	330	113/190	435	392
PSMB8/G8R: G/G	<65 years old	0.72 (0.56,0.93)	├●┤	124/189	330	111/186	422	392
PSMB8/R141C: C/C	<65 years old	0.71 (0.55,0.91)	HH	131/198	326	115/194	435	392
PSMB8/V182M: G/G	<65 years old	0.71 (0.55,0.91)	HH	131/198	326	115/194	435	392
PSMB9/G9E: G/G	<65 years old	0.70 (0.55,0.90)	HH	131/196	326	115/193	431	392
PSMB9/R60H: G/G	<65 years old	0.69 (0.50,0.96)	├●┤	79/119	330	68/113	487	392
PSMB9/V32I: C/C	<65 years old	0.69 (0.53,0.89)	HH	129/192	326	108/186	435	392
PSMB9/R60H: A/G	Male	0.54 (0.31,0.94)	├●┤	22/28	273	34/48	351	241
PSMB1/A171S: G/G	Ann Arbor Stage IV	0.72 (0.54,0.95)	├●┤	95/127	278	93/143	360	270
PSMB1/I208N: T/T	Arm Arbor Stage IV	0.72 (0.54,0.95)	├●┤	95/127	278	93/143	360	270
PSMB1/P11A:	Ann	0.64	├●┤	46/59	235	48/68	351	270

Appendix 2, Table 2.5: TTP by Germlme Genetic Variant and by Covariate, IRC review (Significant [p≤0.05], Frequency of ≥ 10% or Higher)

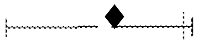
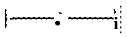
Marker: Level	Subgroup	HR (95% CD	HR (log scale)	R Evt/N	R Median	Vc-R Evt/N	Vc-R Median	Marker: Subgroup N Total
C/G	Arbor Stage IV	(0.42,0.96)						
PSMB1/P193L : C/C	Ann Arbor Stage IV	0.72 (0.54,0.95)		95/127	278	93/143	360	270
PSMB2/E49X: G/G	Ann Arbor Stage IV	0.72 (0.54,0.95)		95/127	278	93/143	360	270
PSMB2/G187 V: G/G	Ann Arbor Stage IV	0.72 (0.54,0.95)		95/127	278	93/143	360	270
PSMB2/L159F : C/C	Ann Arbor Stage IV	0.72 (0.54,0.95)		95/127	278	93/143	360	270
PSMB5/L206 M: C/C	Ann Arbor Stage IV	0.72 (0.54,0.95)		95/127	278	93/143	360	270
PSMB6/A234 D: C/C	Ann Arbor Stage IV	0.72 (0.54,0.95)		95/127	278	93/143	360	270
PSMB6/P107A : C/C	Ann Arbor Stage IV	0.74 (0.55,0.99)		92/124	279	92/140	358	270
PSMB8/G8R: G/G	Ann Arbor Stage IV	0.73 (0.54,0.98)		88/120	279	88/138	352	270
PSMB8/R141C : C/C	Ann Arbor Stage IV	0.72 (0.54,0.95)		95/127	278	93/143	360	270
PSMB8/V182 M: G/G	Ann Arbor Stage IV	0.72 (0.54,0.95)		95/127	278	93/143	360	270
PSMB9/G9E: G/G	Ann Arbor Stage IV	0.71 (0.53,0.94)		95/126	278	93/142	358	270
PSMB9/V32I: C/C	Ann Arbor Stage IV	0.69 (0.5 1,0.93)		93/123	277	89/138	363	270



Appendix 2, Table 2.6: TTP by somatic mutation and by covariate, IRC review (Significant [p≤0.05], Frequency of ≥10% and Higher)

Marker: Level	Subgroup	HR (95% CI)	HR (log scale)	R Evt/N	R Median	Vc-R Evt/N	Vc-R Median	Marker: Subgroup N Total
BCL2/A43G: MND	No Subgroup	0.73 (0.55,0.95)		110/161	334	96/154	435	315
BCL2/C.-1 10T: MND	No Subgroup	0.77 (0.60,1.00)		130/192	334	113/179	422	390
BCL2/E29K: MND	No Subgroup	0.71 (0.53,0.95)		102/150	326	87/139	435	318
BCL2/P46S: MND	No Subgroup	0.73 (0.55,0.97)		100/147	287	92/147	429	310
BCL2/P59S: MND	No Subgroup	0.73 (0.55,0.97)		100/145	288	94/147	429	309
BCL2/Q52P: MND	No Subgroup	0.73 (0.55,0.96)		105/153	288	97/154	429	307
BCL2/R106H: MND	No Subgroup	0.72 (0.55,0.95)		112/162	338	94/151	422	372
NOTCH/X28DEL: MND	No Subgroup	0.78 (0.61,1.00)		133/194	334	120/189	414	400
NOTCH/X28INS: MND	No Subgroup	0.75 (0.59,0.96)		138/198	334	123/195	414	401
BCL2/A43G: MND	1 Prior Line of Therapy	0.62 (0.40,0.97)		45/72	349	35/67	624	139
BCL2/P59L: MD	1 Prior Line of Therapy	0.14 (0.02,0.83)		3/3	398	6/11	553	139
NOTCH/X28INS: MND	1 Prior Line of Therapy	0.65 (0.44,0.97)		53/84	365	47/88	553	178
BCL2/P46L: MD	2 Prior Lines of Therapy	0.14 (0.02,1.28)		5/5	226	2/4	-	83
BCL2/R106H: MND	6 or More Prior Lines of Therapy	0.11 (0.01,1.04)		4/4	50	4/5	305	11
NOTCH/G _A1702P: MND	6 or More Prior Lines of Therapy	0.13 (0.01,1.19)		5/6	70	4/5	305	11
NOTCH/I1681N: MND	6 or More Prior Lines of	0.13 (0.01,1.19)		5/6	70	4/5	305	11

Appendix 2, Table 2.6: TTP by somatic mutation and by covariate, IRC review (Significant [p<0.05]. Frequency of >10% and Higher)

Marker: Level	Subgroup	HR (95% CI)	HR (log scale)	R Evt/N	R Median	Vc-R Evt/N	Vc-R Median	Marker: Subgroup N Total
	Therapy							
NOTCH/L1679P: MND	6 or More Prior Lines of Therapy	0.13 (0.01,1.19)		5/6	70	4/5	305	11
NOTCH/L1679Q: MND	6 or More Prior Lines of Therapy	0.13 (0.01,1.19)		5/6	70	4/5	305	11
NOTCH/P25 15FS4: MND	6 or More Prior Lines of Therapy	0.13 (0.01,1.19)		5/6	70	4/5	305	11
NOTCH/X26DEL: MND	6 or More Prior Lines of Therapy	0.14 (0.01,1.31)		4/5	130	4/5	305	10
NOTCH/X26INS: MND	6 or More Prior Lines of Therapy	0.14 (0.01,1.31)		4/5	130	4/5	305	10
NOTCH/X28DEL: MND	6 or More Prior Lines of Therapy	0.13 (0.01,1.25)		4/5	70	4/5	305	11
NOTCH/X28INS: MND	6 or More Prior Lines of Therapy	0.12 (0.01,1.10)		5/6	70	4/5	305	11
NOTCH/X26DEL: MND	No High Tumor Burden	0.65 (0.43,1.00)		56/87	422	36/71	630	163
NOTCH/X28INS: MND	No High Tumor Burden	0.62 (0.42,0.93)		62/98	422	41/82	630	184
BCL2/A43G: MND	High Tumor Burden	0.65 (0.46,0.92)		63/83	241	64/90	352	173
BCL2/E29K: MND	High Tumor Burden	0.63 (0.43,0.90)		59/79	239	57/82	358	174
BCL2/P46L: MND	High Tumor Burden	0.61 (0.42,0.90)		50/67	241	59/83	352	173
BCL2/P46S: MND	High Tumor Burden	0.61 (0.42,0.88)		55/73	239	63/89	348	170
BCL2/P59L: MD	High Tumor Burden	0.21 (0.05,0.86)		4/6	137	11/14	506	172

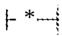
Appendix 2, Table 2.6: TTP by somatic mutation and by covariate, IRC review
(Significant [p≤0.05], Frequency of ≥10% and Higher)

Marker: Level	Subgroup	HR (95% CI)	HR (log scale)	R Evt/N	R Median	Vc-R Evt/N	Vc-R Median	Marker: Subgroup N Total
BCL2/P59L: MND	High Tumor Burden	0.64 (0.44,0.94)		54/72	241	56/80	344	172
BCL2/P59S: MND	High Tumor Burden	0.60 (0.42,0.87)		56/73	241	62/87	358	170
BCL2/Q52P: MND	High Tumor Burden	0.60 (0.42,0.85)		58/76	239	65/92	352	168
BCL2/R106H: MND	High Tumor Burden	0.66 (0.46,0.93)		63/83	241	64/93	352	209
NOTCH/F1593S: MND	High Tumor Burden	0.68 (0.48,0.98)		57/77	253	64/91	358	168
NOTCH/G_A1702P: MND	High Tumor Burden	0.68 (0.49,0.95)		68/90	241	69/96	348	187
NOTCH/I1681N: MND	High Tumor Burden	0.69 (0.49,0.96)		68/90	241	70/97	348	187
NOTCH/L1575P: MND	High Tumor Burden	0.69 (0.48,0.99)		56/76	253	64/91	358	168
NOTCH/L1586P: MND	High Tumor Burden	0.68 (0.48,0.98)		57/77	253	64/91	358	168
NOTCH/L1586Q: MND	High Tumor Burden	0.68 (0.48,0.96)		58/78	241	67/94	352	172
NOTCH/L1594P: MND	High Tumor Burden	0.68 (0.48,0.98)		57/77	253	64/91	358	168
NOTCH/L1597H: MND	High Tumor Burden	0.68 (0.48,0.96)		58/78	241	67/94	352	172
NOTCH/L1597_S15981 NSG: MND	High Tumor Burden	0.68 (0.48,0.98)		57/77	253	64/91	358	168
NOTCH/L1601P: MND	High Tumor Burden	0.67 (0.47,0.96)		57/77	253	63/90	358	168
NOTCH/L1679P: MND	High Tumor Burden	0.69 (0.49,0.96)		68/90	241	70/97	348	187
NOTCH/L1679Q: MND	High Tumor Burden	0.69 (0.49,0.96)		68/90	241	70/97	348	187
NOTCH/L2458V: MND	High Tumor	0.70 (0.49,0.9		61/83	253	68/95	352	178

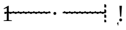
Appendix 2, Table 2.6: TTP by somatic mutation and by covariate, IRC review
(Significant [$p \leq 0.05$], Frequency of ≥10% and Higher)

Marker: Level	Subgroup	HR (95% CI)	HR (log scale)	R Evt/N	R Median	Vc-R Evt/N	Vc-R Median	Marker: Subgroup N Total
	Burden	9)						
NOTCH/P25 13L: MND	High Tumor Burden	0.66 (0.45,0.96)		57/76	253	51/71	358	198
NOTCH/P25 15FS4: MND	High Tumor Burden	0.69 (0.49,0.96)		68/90	241	70/98	352	189
NOTCH/Q2441X: MND	High Tumor Burden	0.70 (0.49,0.99)		61/83	253	68/95	352	178
NOTCH/Q2460X: MND	High Tumor Burden	0.69 (0.48,1.00)		57/79	270	60/87	360	181
NOTCH/R1599>QS: MND	High Tumor Burden	0.68 (0.48,0.98)		57/77	253	64/91	358	168
NOTCH/R1599P: MND	High Tumor Burden	0.68 (0.48,0.96)		58/78	241	67/94	352	172
NOTCH/V1579DEL: MND	High Tumor Burden	0.68 (0.48,0.98)		57/77	253	64/91	358	168
NOTCH/V1579E: MND	High Tumor Burden	0.68 (0.48,0.96)		58/78	241	67/94	352	172
NOTCH/V1579G: MND	High Tumor Burden	0.68 (0.48,0.98)		57/77	253	64/91	358	168
NOTCH/X28INS: MND	High Tumor Burden	0.73 (0.53,0.99)		76/100	253	82/113	324	217
BCL2/A43G: MND	High FLIPI Score	0.63 (0.41,0.95)		47/66	239	43/61	358	127
BCL2/E29K: MND	High FLIPI Score	0.64 (0.41,0.99)		43/62	239	39/55	366	128
BCL2/P46L: MND	High FLIPI Score	0.60 (0.38,0.95)		37/53	210	40/55	352	124
BCL2/P59L: MND	High FLIPI Score	0.64 (0.41,1.00)		40/57	239	39/55	358	125
BCL2/P59S: MND	High FLIPI Score	0.63 (0.41,0.97)		42/59	224	41/57	352	123
BCL2/Q52P: MND	High FLIPI Score	0.62 (0.41,0.95)		44/61	224	43/60	352	121
BCL2/R106H: MND	High	0.60		50/68	239	38/57	366	151

Appendix 2, Table 2.6: TTP by somatic mutation and by covariate, IRC review (Significant [p≤0.05], Frequency of ≥10% and Higher)

Marker: Level	Subgroup	HR (95% CI)	HR (log scale)	R Evt/N	R Median	Vc-R Evt/N	Vc-R Median	Marker: Subgroup N Total
	FLIPI Score	(0.39,0.92)						
NOTCH/G_A1702P: MND	High FLIPI Score	0.67 (0.45,0.99)		52/72	212	49/67	346	139
NOTCH/I1681N: MND	High FLIPI Score	0.67 (0.45,0.99)		52/72	212	49/67	346	139
NOTCH/L1679P: MND	High FLIPI Score	0.67 (0.45,0.99)		52/72	212	49/67	346	139
NOTCH/L1679Q: MND	High FLIPI Score	0.67 (0.45,0.99)		52/72	212	49/67	346	139
NOTCH/P25 15FS4: MND	High FLIPI Score	0.66 (0.45,0.99)		52/72	239	47/67	358	141
NOTCH/X28DEL: MND	High FLIPI Score	0.66 (0.45,0.96)		60/81	239	50/73	352	159
NOTCH/X28INS: MND	High FLIPI Score	0.61 (0.42,0.89)		61/81	239	52/76	352	160
BCL2/R106H: MD	Intermediate FLIPI Score	3.47 (1.07,11.29)		4/10	924	10/11	281	130
BCL2/P46S: MND	Low FLIPI Score	0.51 (0.27,1.00)		24/38	349	14/38	-	83
BCL2/Q52P: MND	Low FLIPI Score	0.53 (0.28,1.00)		26/41	349	15/40	508	81
NOTCH/G_A1702P: MND	Low FLIPI Score	0.52 (0.28,0.97)		28/43	381	15/41	-	84
NOTCH/I1681N: MND	Low FLIPI Score	0.52 (0.28,0.97)		28/43	381	15/41	-	84
NOTCH/L1679P: MND	Low FLIPI Score	0.52 (0.28,0.97)		28/43	381	15/41	-	84
NOTCH/L1679Q: MND	Low FLIPI Score	0.52 (0.28,0.97)		28/43	381	15/41	-	84
NOTCH/X28INS: MND	Low FLIPI Score	0.56 (0.32,1.00)		30/48	349	19/48	771	98
BCL2/A43G: MND	No Prior Rituximab Therapy	0.69 (0.48,0.99)		69/98	345	52/85	485	183

Appendix 2, Table 2.6: TTP by somatic mutation and by covariate, IRC review
(Significant [p≤0.05], Frequency of ≥10% and Higher)

Marker: Level	Subgroup	HR (95% CI)	HR (log scale)	R Evt/N	R Median	Vc-R Evt/N	Vc-R Median	Marker: Subgroup N Total
BCL2/E29K: MND	No Prior Rituximab Therapy	0.65 (0.45,0.96)		65/93	345	46/76	508	186
BCL2/P46S: MND	No Prior Rituximab Therapy	0.66 (0.45,0.97)		60/87	287	48/79	508	175
BCL2/Q52P: MND	No Prior Rituximab Therapy	0.68 (0.47,0.99)		63/91	287	51/83	485	174
BCL2/R106H: MND	No Prior Rituximab Therapy	0.67 (0.46,0.98)		66/95	351	46/79	483	213
NOTCH/X28INS: MND	No Prior Rituximab Therapy	0.71 (0.51,1.00)		79/112	357	64/107	463	226
BCL2/P46L: MD	> 1 year since last anti-lymphoma treatment	0.20 (0.05,0.72)		10/10	408	4/10	637	180
NOTCH/X28INS: MND	> 1 year since last anti-lymphoma treatment	0.72 (0.51,1.00)		75/113	379	67/119	506	237
BCL2/E29K: MND	Rest of World	0.65 (0.43,0.98)		55/75	241	41/63	415	154
BCL2/R106H: MND	Rest of World	0.66 (0.44,0.97)		60/83	275	42/69	422	184
NOTCH/X28INS: MND	Rest of World	0.68 (0.48,0.96)		72/97	275	59/92	406	194
BCL2/A43G: MND	<65 years old	0.63 (0.46,0.87)		89/124	277	67/115	483	239
BCL2/C.-110T: MND	≤65 years old	0.69 (0.52,0.93)		102/147	278	81/135	429	296
BCL2/E29K: MND	≤65 years old	0.60 (0.43,0.84)		83/117	275	59/103	485	241
BCL2/P46L: MD	≤65 years old	0.40 (0.16,0.99)		13/14	226	8/15	485	238
BCL2/P46L: MND	<65 years old	0.66 (0.47,0.9		74/105	277	62/104	429	238

Appendix 2, Table 2.6: TTP by somatic mutation and by covariate, IRC review
(Significant $[p \leq 0.05]$, Frequency of $\geq 10\%$ and Higher)

Marker: Level	Subgroup	HR (95% CI)	HR (log scale)	R Evt/N	R Median	Vc-R Evt/N	Vc-R Median	Marker: Subgroup N Total
		3)						
BCL2/P46S: MND	<65 years old	0.62 (0.45,0.87)	├●┤	80/111	275	66/113	456	236
BCL2/P59L: MND	<65 years old	0.64 (0.45,0.89)	├●┤	80/112	277	59/103	431	237
BCL2/P59S: MND	<65 years old	0.63 (0.45,0.87)	├●┤	81/110	275	69/114	435	235
BCL2/Q52P: MND	<65 years old	0.63 (0.46,0.86)	├●┤	85/117	275	69/117	435	234
BCL2/R106H: MND	<65 years old	0.60 (0.44,0.83)	├●┤	89/124	275	64/112	483	281
NOTCH/F1593S: MND	<65 years old	0.69 (0.50,0.95)	├●┤	84/117	277	66/110	429	227
NOTCH/G_A1702P: MND	<65 years old	0.66 (0.48,0.89)	├●┤	96/133	277	72/121	429	255
NOTCH/I1681N: MND	<65 years old	0.66 (0.49,0.90)	├●┤	96/133	277	73/122	422	255
NOTCH/L1575P: MND	<65 years old	0.70 (0.50,0.96)	├●┤	83/116	277	66/110	429	227
NOTCH/L1586P: MND	<65 years old	0.69 (0.50,0.95)	├●┤	84/117	277	66/110	429	227
NOTCH/L1586Q: MND	<65 years old	0.69 (0.50,0.95)	├●┤	86/120	277	69/114	422	234
NOTCH/L1594P: MND	<65 years old	0.69 (0.50,0.95)	├●┤	84/117	277	66/110	429	227
NOTCH/L1597H: MND	<65 years old	0.69 (0.50,0.95)	├●┤	86/120	277	69/114	422	234
NOTCH/L1597_S15981 NSG: MND	<65 years old	0.69 (0.50,0.95)	├●┤	84/117	277	66/110	429	227
NOTCH/L1601P: MND	<65 years old	0.68 (0.49,0.94)	├●┤	84/117	277	65/109	431	227
NOTCH/L1679P: MND	<65 years old	0.66 (0.49,0.90)	├●┤	96/133	277	73/122	422	255
NOTCH/L1679Q:	<65 years	0.66	├●┤	96/13	277	73/12	422	255

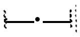
Appendix 2, Table 2.6: TTP by somatic mutation and by covariate, IRC review
(Significant [p<0.05], Frequency of >10% and Higher)

Marker: Level	Subgroup	HR (95% CD	HR (log scale)	R Evt/N	R Median	Vc-R Evt/N	Vc-R Median	Marker: Subgroup N Total
MND	old	(0.49,0.90)		3		2		
NOTCH/L2458V: MND	<65 years old	0.67 (0.49,0.92)		86/120	275	71/117	422	237
NOTCH/P25 13L: MND	<65 years old	0.59 (0.41,0.84)		77/107	275	51/90	429	269
NOTCH/P25 15FS4: MND	<65 years old	0.67 (0.49,0.90)		96/134	278	74/123	431	259
NOTCH/Q2441X: MND	<65 years old	0.67 (0.49,0.92)		86/120	275	71/115	422	237
NOTCH/Q2460X: MND	<65 years old	0.64 (0.45,0.90)		78/110	275	60/104	422	239
NOTCH/R1599>QS: MND	<65 years old	0.69 (0.50,0.95)		84/117	277	66/110	429	227
NOTCH/R1599P: MND	<65 years old	0.69 (0.50,0.95)		86/120	277	69/114	422	234
NOTCH/V1579DEL: MND	<65 years old	0.69 (0.50,0.95)		84/117	277	66/110	429	227
NOTCH/V1579E: MND	<65 years old	0.69 (0.50,0.95)		86/120	277	69/114	422	234
NOTCH/V1579G: MND	<65 years old	0.69 (0.50,0.95)		84/117	277	66/110	429	227
NOTCH/X26DEL: MND	<65 years old	0.70 (0.52,0.94)		96/137	281	78/132	431	273
NOTCH/X26INS: MND	<65 years old	0.68 (0.51,0.92)		97/138	281	78/133	435	273
NOTCH/X28DEL: MND	<65 years old	0.66 (0.50,0.89)		106/149	278	83/140	422	298
NOTCH/X28INS: MND	<65 years old	0.64 (0.48.0.85)		109/149	277	85/143	429	298
NOTCH/P25 13L: MND	> 65 years old	1.96 (1.03,3.75)		16/33	616	24/33	414	92
BCL2/P59L: MD	Female	0.28 (0.08,0.95)		6/8	398	9/14	512	180

Appendix 2, Table 2.6: TTP by somatic mutation and by covariate, IRC review (Significant [p≤0.05], Frequency of ≥10% and Higher)

Marker: Level	Subgroup	HR (95% CI)	HR (log scale)	R Evt/N	R Median	Vc-R Evt/N	Vc-R Median	Marker: Subgroup N Total
BCL2/P59S: MND	Female	0.66 (0.44,0.97)		66/97	348	42/73	512	178
BCL2/Q52P: MND	Female	0.68 (0.46,1.00)		67/100	348	43/76	553	176
BCL2/R106H: MND	Female	0.65 (0.44,0.98)		65/96	357	38/70	506	203
BCL2/A43G: MND	Male	0.60 (0.40,0.91)		43/59	273	51/76	414	135
BCL2/E29K: MND	Male	0.60 (0.39,0.93)		40/55	271	46/68	414	138
BCL2/P46S: MND	Male	0.64 (0.42,0.98)		37/52	241	52/75	360	133
BCL2/Q52P: MND	Male	0.64 (0.42,0.97)		38/53	271	54/78	360	131
NOTCH/G_A1702P: MND	Male	0.66 (0.44,0.98)		44/63	241	56/81	360	145
NOTCH/I1681N: MND	Male	0.67 (0.45,1.00)		44/63	241	57/82	360	145
NOTCH/L1679P: MND	Male	0.67 (0.45,1.00)		44/63	241	57/82	360	145
NOTCH/L1679Q: MND	Male	0.67 (0.45,1.00)		44/63	241	57/82	360	145
NOTCH/L2458V: MND	Male	0.63 (0.42,0.95)		42/59	241	56/80	360	139
NOTCH/P2513L: MND	Male	0.58 (0.38,0.91)		39/54	239	42/63	414	155
NOTCH/P2515FS4: MND	Male	0.65 (0.43,0.96)		44/62	273	57/84	406	148
NOTCH/Q2441X: MND	Male	0.64 (0.42,0.95)		42/59	241	56/79	360	139
NOTCH/Q2460X: MND	Male	0.61 (0.40,0.94)		41/57	241	47/70	414	142
NOTCH/X28DEL: MND	Male	0.69 (0.48,1.0		54/75	275	65/97	352	180

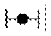
Appendix 2, Table 2.6: TTP by somatic mutation and by covariate, IRC review (Significant [p<0.05], Frequency of >10% and Higher)

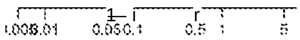
Marker: Level	Subgroup	HR (95% CI)	HR (log scale)	R Evt/N	R Median	Vc-R Evt/N	Vc-R Median	Marker: Subgroup N Total
		0)						
NOTCH/X28INS: MND	Male	0.68 (0.47,0.97)		57/78	275	67/100	358	181
BCL2/A43G: MND	White	0.72 (0.54,0.97)		93/140	345	84/139	483	279
BCL2/E29K: MND	White	0.70 (0.51,0.96)		85/129	345	77/127	506	282
BCL2/P46L: MD	White	0.38 (0.16,0.88)		18/21	346	8/16	512	279
BCL2/P46S: MND	White	0.69 (0.51,0.94)		87/130	334	79/131	463	275
BCL2/P59L: MND	White	0.73 (0.53,0.99)		85/129	334	74/123	431	278
BCL2/P59S: MND	White	0.69 (0.51,0.94)		87/128	334	80/130	463	274
BCL2/Q52P: MND	White	0.69 (0.51,0.93)		91/135	334	83/137	463	272
NOTCH/P25 15FS4: MND	White	0.75 (0.57,1.00)		102/154	348	91/148	431	304
NOTCH/X28INS: MND	White	0.75 (0.57,0.97)		119/174	345	107/171	422	352
NOTCH/P25 13L: MD	Ann Arbor Stage III	0.40 (0.17,0.95)		13/15	345	12/14	414	116
BCL2/A43G: MND	Ann Arbor Stage IV	0.61 (0.41,0.89)		57/71	275	52/83	414	154
BCL2/C.-1 10T: MND	Ann Arbor Stage IV	0.66 (0.47,0.94)		66/84	277	64/100	358	193
BCL2/E29K: MND	Ann Arbor Stage IV	0.58 (0.39,0.87)		53/67	275	44/73	415	154
BCL2/P46L: MND	Ann Arbor Stage IV	0.59 (0.38,0.91)		40/52	253	47/74	360	148
BCL2/P46S: MND	Ann Arbor Stage IV	0.62 (0.42,0.93)		48/61	253	53/81	358	147
BCL2/P59L: MND	Ann	0.63		46/59	273	45/73	352	149

Appendix 2, Table 2.6: TTP by somatic mutation and by covariate, IRC review
(Significant [p≤0.05], Frequency of ≥10% and Higher)

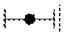
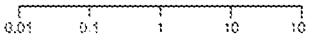
Marker: Level	Subgroup	HR (95% CI)	HR (log scale)	R Evt/N	R Median	Vc-R Evt/N	Vc-R Median	Marker: Subgroup N Total
	Arbor Stage IV	(0.42,0.96)						
BCL2/P59S: MND	Ann Arbor Stage IV	0.64 (0.43,0.97)		45/58	273	51/79	360	147
BCL2/Q52P: MND	Ann Arbor Stage IV	0.60 (0.41,0.90)		49/62	273	53/83	360	145
BCL2/R106H: MND	Ann Arbor Stage IV	0.57 (0.39,0.84)		57/72	274	51/83	414	186
NOTCH/F1593S: MND	Ann Arbor Stage IV	0.64 (0.43,0.95)		50/64	253	52/79	360	143
NOTCH/G_A1702P: MND	Ann Arbor Stage IV	0.61 (0.42,0.88)		59/75	273	57/87	360	163
NOTCH/I1681N: MND	Ann Arbor Stage IV	0.62 (0.43,0.89)		59/75	273	58/88	358	163
NOTCH/L1575P: MND	Ann Arbor Stage IV	0.64 (0.43,0.95)		50/64	253	52/79	360	143
NOTCH/L1586P: MND	Ann Arbor Stage IV	0.64 (0.43,0.95)		50/64	253	52/79	360	143
NOTCH/L1586Q: MND	Ann Arbor Stage IV	0.64 (0.44,0.94)		52/67	273	55/83	360	150
NOTCH/L1594P: MND	Ann Arbor Stage IV	0.64 (0.43,0.95)		50/64	253	52/79	360	143
NOTCH/L1597H: MND	Ann Arbor Stage IV	0.64 (0.44,0.94)		52/67	273	55/83	360	150
NOTCH/L1597_SI5981 NSG: MND	Ann Arbor Stage IV	0.64 (0.43,0.95)		50/64	253	52/79	360	143
NOTCH/L1601P: MND	Ann Arbor Stage IV	0.64 (0.43,0.95)		50/64	253	52/79	360	143
NOTCH/L1679P: MND	Ann Arbor Stage IV	0.62 (0.43,0.89)		59/75	273	58/88	358	163
NOTCH/L1679Q: MND	Ann Arbor Stage IV	0.62 (0.43,0.89)		59/75	273	58/88	358	163
NOTCH/L2458V: MND	Ann Arbor Stage IV	0.61 (0.42,0.90)		53/68	273	56/86	360	154

Appendix 2, Table 2.6: TTP by somatic mutation and by covariate, IRC review (Significant [p≤0.05], Frequency of ≥10% and Higher)

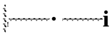
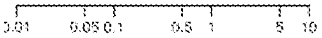
Marker: Level	Subgroup	HR (95% CI)	HR (log scale)	R Evt/N	R Median	Vc-R Evt/N	Vc-R Median	Marker: Subgroup N Total
NOTCH/P25 13L: MND	Ann Arbor Stage IV	0.55 (0.36,0.84)		48/61	273	41/69	414	176
NOTCH/P25 15FS4: MND	Ann Arbor Stage IV	0.61 (0.42,0.88)		58/74	273	58/91	366	167
NOTCH/Q2441X: MND	Ann Arbor Stage IV	0.61 (0.42,0.90)		53/68	273	56/85	360	154
NOTCH/Q2460X: MND	Ann Arbor Stage IV	0.57 (0.38,0.86)		49/64	273	49/79	414	156
NOTCH/R1599>QS: MND	Ann Arbor Stage IV	0.64 (0.43,0.95)		50/64	253	52/79	360	143
NOTCH/R1599P: MND	Ann Arbor Stage IV	0.64 (0.44,0.94)		52/67	273	55/83	360	150
NOTCH/V1579DEL: MND	Ann Arbor Stage IV	0.64 (0.43,0.95)		50/64	253	52/79	360	143
NOTCH/V1579E: MND	Ann Arbor Stage IV	0.64 (0.44,0.94)		52/67	273	55/83	360	150
NOTCH/V1579G: MND	Ann Arbor Stage IV	0.64 (0.43,0.95)		50/64	253	52/79	360	143
NOTCH/X26DEL: MND	Ann Arbor Stage IV	0.65 (0.45,0.92)		61/76	275	66/101	360	180
NOTCH/X26INS: MND	Ann Arbor Stage IV	0.64 (0.45,0.91)		62/79	275	66/101	360	180
NOTCH/X28DEL: MND	Ann Arbor Stage IV	0.64 (0.46,0.91)		67/85	275	65/103	358	195
NOTCH/X28INS: MND	Ann Arbor Stage IV	0.60 (0.42,0.84)		70/87	274	66/105	358	196



Appendix 2, Table 2.7: Duration of response by protein expression and by covariate, IRC review. * **(All** reported groups are significant (p ≤0.05) and with a frequency ≥10%)

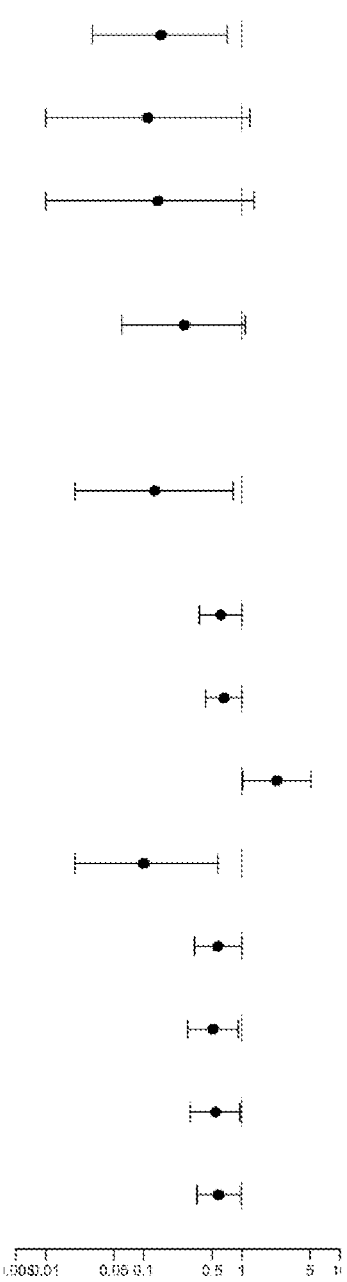
Marker: Level	Subgroup	HR (95% CD	HR (log scale)	R Evt/N	R Median	Vc-R Evt/N	Vc-R Median	Marker: Subgroup N Total
CD68 OVERALL POSITIVE: 0-25	High FLIPI Score	3.66 (1.10,12.16)		7/11	423	7/8	202	91
P27 % NUCLEI POSITIVE: 60-70	High FLIPI Score	0.14 (0.03,0.74)		7/9	337	3/6	1162	96
20S INTENSITY CYTOPLASMIC SIGNAL: <2+	Intermediate FLIPI Score	2.39 (1.08,5.26)		9/25	554	20/26	264	99
20S INTENSITY CYTOPLASMIC SIGNAL: >3+	Intermediate FLIPI Score	0.38 (0.17,0.84)		17/25	352	10/23	813	99
20S INTENSITY CYTOPLASMIC SIGNAL: >3+	No Prior Rituximab Therapy	0.53 (0.29,0.97)		22/32	427	20/43	638	155
20S % NUCLEAR STAINING: 30-50	Prior Rituximab Therapy	2.39 (0.97,5.86)		9/13	356	13/14	245	97
CD68 OVERALL POSITIVE: 0-25	≤1 year since last anti-lymphoma treatment	9.97 (1.13,88.13)		5/7	354	5/5	145	79
20S INTENSITY CYTOPLASMIC SIGNAL: >3+	<65 years old	0.55 (0.31,0.98)		28/39	417	20/44	654	177
CD68 POSITIVE FOLLICULAR: 0-25	Female	0.38 (0.15, 1.01)		12/20	354	8/15	648	131
CD68 OVERALL POSITIVE: 51-75	Male	0.27 (0.07, 1.03)		5/7	279	6/12	784	98
CD68 OVERALL POSITIVE: >75	Male	0.10 (0.01, 1.02)		3/3	284	2/7	-	98
CD68 POSITIVE PERIFOLLICULAR: >75	Male	0.11 (0.01, 1.11)		3/3	284	2/7	-	86
P27 % NUCLEI POSITIVE: 60-70	Male	0.29 (0.08, 1.08)		5/6	281	7/9	502	99
P65 INTENSITY CYPTOPLASMIC SIGNAL: ≤1+	Ann Arbor Stage III	0.16 (0.02, 1.19)		2/4	173	5/8	474	87
								

Appendix 2, Table 2.8: Duration of Response by Germline Genetic Variant and by Covariate, IRC Review. (All Reported Groups are Significant (p ≤0.05) and at a Frequency ≥10%)

Marker: Level	Subgroup	HR (95% CI)	HR (log scale)	R Evt/N	R Median	Vc-R Evt/N	Vc-R Median	Marker: Subgroup N Total
PSMB9/R60H : A/G	Male	0.42 (0.19,0.94)		*10/11*	*211*	*19/28*	*351*	*120*
PSMB5/R24C : C/C	Ann Arbor Stage II	3.29 (1.07, 10.09)		4/18	-	13/20	438	43
								

Appendix 2, Table 2.9: Duration of Response by Somatic Mutation and by Covariate, IRC Review. (All Reported Groups are Significant (P ≤0.05) and at a Frequency ≥10%)

Marker: Level	Subgroup	HR (95% CI)	HR (log scale)	R Evt/N	R Median	Vc-R Evt/N	Vc-R Median	Marker: Subgroup N Total
BCL2/P59L: MD	No Subgroup	0.15 (0.03,0.71)		4/5	343	9/15	488	177
BCL2/P59L: MD	1 Prior Line of Therapy	0.11 (0.01,1.21)		2/2	345	5/10	488	82
BCL2/P59L: MD	Prior Rituximab Therapy	0.14 (0.01,1.33)		3/3	330	4/5	372	68
BCL2/P46L: MD	> 1 year since last anti-lymphoma treatment	0.26 (0.06,1.09)		5/5	356	4/8	502	115
BCL2/P59L: MD	> 1 year since last anti-lymphoma treatment	0.13 (0.02,0.82)		3/4	330	6/10	502	116
BCL2/E29K: MND	<65 years old	0.61 (0.37,1.00)		32/49	353	32/66	648	128
NOTCH/X28INS: MND	<65 years old	0.66 (0.43,1.00)		44/64	369	45/84	490	152
NOTCH/P2513L: MND	> 65 years old	2.28 (1.02,5.09)		10/23	948	18/22	356	62
BCL2/P59L: MD	White	0.10 (0.02,0.57)		4/5	343	8/14	488	163
BCL2/A43G: MND	Ann Arbor Stage IV	0.57 (0.33,1.00)		23/28	353	29/50	488	78
BCL2/E29K: MND	Ann Arbor Stage IV	0.51 (0.28,0.93)		21/26	344	23/43	490	78
BCL2/R106H: MND	Ann Arbor Stage IV	0.54 (0.30,0.96)		21/26	352	27/48	423	90
NOTCH/X28INS: MND	Ann Arbor Stage IV	0.58 (0.35,0.98)		26/31	353	35/58	423	91



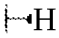
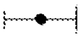
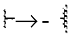
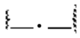
Appendix 2, Table 2.10: Time to Next Anti-Lymphoma Therapy by Protein Expression and by Covariate, IRC Review.

(All Reported Groups are Significant (p≤0.05) and at a Frequency ≥10%)

Marker: Level	Subgroup	HR (95% CI)	HR (log scale)	R Evt/N	R Median	Vc-R Evt/N	Vc-R Median	Marker: Subgroup N Total
CD68 OVERALL POSITIVE: 0-25	No Subgroup	0.41 (0.23,0.73)		30/44	409	19/41	1047	442
CD68 POSITIVE FOLLICULAR: 0-25	No Subgroup	0.54 (0.33,0.88)		40/60	462	29/5 1	834	387
CD68 POSITIVE PERIFOLLICULAR: 0-25	No Subgroup	0.48 (0.27,0.87)		26/39	374	20/41	1103	384
P27 SIGNAL INTENSITY: >2+	No Subgroup	0.77 (0.60,0.99)		127/199	533	114/196	700	463
P65 % POSITIVE CYTOPLASMIC SIGNAL: >90%	No Subgroup	0.75 (0.58,0.96)		129/204	505	108/1S6	726	470
CD68 POSITIVE PERIFOLLICULAR: >75	1 Prior Line of Therapy	0.43 (0.19,0.97)		15/18	437	10/16	744	174
P27 % NUCLEI POSITIVE: 0-20	1 Prior Line of Therapy	0.38 (0.15,0.97)		19/26	434	6/16	1047	204
P65 % NUCLEAR STAINING: 0	1 Prior Line of Therapy	0.63 (0.41,0.95)		54/79	546	39/73	841	203
P65 % POSITIVE CYTOPLASMIC SIGNAL: >90%	1 Prior Line of Therapy	0.61 (0.42,0.90)		59/89	550	47/88	841	203
P65 INTENSITY CYTOPLASMIC SIGNAL: >2+	1 Prior Line of Therapy	0.64 (0.43,0.95)		54/85	568	47/91	841	203
CD68 OVERALL POSITIVE: 0-25	2 Prior Lines of Therapy	0.20 (0.04,1.04)		6/8	204	2/7	1005	111
CD68 POSITIVE PERIFOLLICULAR: 0-25	2 Prior Lines of Therapy	0.09 (0.01,0.81)		6/8	171	1/7	-	98
P65 % NUCLEAR STAINING: <5%	2 Prior Lines of Therapy	0.31 (0.10,0.92)		7/9	225	7/12	705	125
P27 % NUCLEI POSITIVE: 60-70	3 Prior Lines of Therapy	8.15 (0.93,71.30)		1/6	-	5/5	227	74
P27 SIGNAL INTENSITY: >2+	5 Prior Lines of Therapy	0.20 (0.04,1.02)		5/6	228	3/8	939	16
P65 % NUCLEAR STAINING: <5%	5 Prior Lines of Therapy	0.13 (0.01,1.34)		3/3	235	2/4	1235	16
CD68 OVERALL POSITIVE: 0-25	No High Tumor	0.23 (0.07,0.79		8/14	552	5/19	1235	204

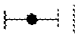
Appendix 2, Table 2.10: Time to Next Anti-Lymphoma Therapy by Protein Expression and by Covariate, IRC Review.

(All Reported Groups are Significant (p≤0.05) and at a Frequency ≥10%)

Marker: Level	Subgroup	HR (95% CI)	HR (log scale)	R Evt/N	R Median	Vc-R Evt/N	Vc-R Median	Marker: Subgroup P N Total
	Burden	)						
CD68 OVERALL POSITIVE: 51-75	No High Tumor Burden	2.27 (0.98,5.28)		10/25	-	12/18	511	204
CD68 POSITIVE FOLLICULAR: 0-25	No High Tumor Burden	0.38 (0.17,0.87)		14/22	573	12/25	939	182
CD68 POSITIVE PERIFOLLICULAR: 0-25	No High Tumor Burden	0.22 (0.06,0.74)		8/13	501	5/16	1235	182
P27 % NUCLEI POSITIVE: 0-20	High Tumor Burden	0.54 (0.30,0.98)		23/27	220	23/31	503	248
P27 % NUCLEI POSITIVE: 30-50	High Tumor Burden	0.45 (0.22,0.93)		17/22	421	13/25	599	248
P27 SIGNAL INTENSITY: ≤1+	High Tumor Burden	0.42 (0.19,0.93)		16/18	220	11/17	975	248
CD68 OVERALL POSITIVE: 0-25	Intermediate FLIPI Score	0.27 (0.08,0.96)		7/11	485	5/15	1235	159
CD68 POSITIVE FOLLICULAR: 0-25	Intermediate FLIPI Score	0.44 (0.19,1.01)		14/20	421	11/20	939	141
CD68 POSITIVE PERIFOLLICULAR: 0-25	Intermediate FLIPI Score	0.27 (0.08,0.95)		7/13	501	5/17	1235	139
CD68 OVERALL POSITIVE: 0-25	Low FLIPI Score	0.32 (0.10,0.99)		8/10	422	5/11	1075	102
CD68 OVERALL POSITIVE: 0-25	No Prior Rituximab Therapy	0.36 (0.14,0.93)		12/19	533	7/21	1103	241
CD68 POSITIVE FOLLICULAR: 0-25	No Prior Rituximab Therapy	0.40 (0.19,0.84)		23/36	485	10/25	1103	210
CD68 POSITIVE PERIFOLLICULAR: 0-25	No Prior Rituximab Therapy	0.33 (0.11,0.95)		12/18	533	5/15	-	208
20S % NUCLEAR STAINING: 60-70	Prior Rituximab Therapy	0.39 (0.15,1.00)		17/21	343	6/12	1075	212
CD68 OVERALL POSITIVE: 0-25	Prior Rituximab Therapy	0.41 (0.19,0.89)		18/25	235	12/20	834	201
P27 SIGNAL INTENSITY: >2+	Prior Rituximab Therapy	0.64 (0.44,0.94)		60/88	421	48/85	718	210
P65 %	Prior	0.29		16/21	232	13/27	975	215

Appendix 2, Table 2.10: Time to Next Anti-Lymphoma Therapy by Protein Expression and by Covariate, IRC Review.

(All Reported Groups are Significant (p<0.05) and at a Frequency >10%)

Marker: Level	Subgroup	HR (95% CI)	HR (log scale)	R Evt/N	R Median	Vc-R Evt/N	Vc-R Median	Marker: Subgroup N Total
NUCLEAR STAINING: <5%	Rituximab Therapy	(0.14,0.64)						
CD68 OVERALL POSITIVE: 0-25	> 1 year since last anti-lymphoma treatment	0.26 (0.11,0.60)		17/26	409	9/28	1235	269
CD68 POSITIVE FOLLICULAR: 0-25	> 1 year since last anti-lymphoma treatment	0.48 (0.25,0.93)		22/34	550	16/33	1005	235
CD68 POSITIVE PERIFOLLICULAR: 0-25	> 1 year since last anti-lymphoma treatment	0.40 (0.18,0.88)		15/24	533	11/27	1235	234
P65 % POSITIVE CYTOPLASMIC SIGNAL: >90%	> 1 year since last anti-lymphoma treatment	0.68 (0.48,0.98)		69/117	593	54/112	983	288
20S INTENSITY CYTOPLASMIC SIGNAL: >3+	European Union	0.58 (0.34,0.97)		34/52	533	25/52	1075	214
CD68 OVERALL POSITIVE: 0-25	European Union	0.40 (0.18,0.90)		14/22	374	11/25	1103	211
CD68 POSITIVE PERIFOLLICULAR: >75	European Union	0.35 (0.13,0.96)		13/17	675	7/14	1185	185
P27 % NUCLEI POSITIVE: 80-100	European Union	0.59 (0.35,1.00)		29/41	655	27/51	939	214
P27 SIGNAL INTENSITY: >2+	European Union	0.67 (0.46,0.99)		57/89	649	49/91	939	214
P65 % POSITIVE CYTOPLASMIC SIGNAL: >90%	European Union	0.67 (0.46,0.99)		57/92	552	48/87	975	216
P65 INTENSITY CYTOPLASMIC SIGNAL: ≤1+	European Union	0.45 (0.19,1.02)		13/18	409	11/21	1005	216
CD68 OVERALL POSITIVE: 0-25	<65 years old	0.38 (0.20,0.73)		24/34	374	15/32	1005	329
CD68 POSITIVE FOLLICULAR: 0-25	<65 years old	0.45 (0.26,0.77)		33/46	332	24/41	764	292
CD68 POSITIVE	<65 years	0.48		20/31	332	13/29	1075	289

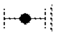
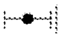
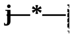
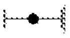
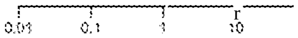
Appendix 2, Table 2.10: Time to Next Anti-Lymphoma Therapy by Protein Expression and by Covariate, IRC Review.

(All Reported Groups are Significant (p≤0.05) and at a Frequency ≥10%)

Marker: Level	Subgroup	HR (95% CI)	HR (log scale)	R Evt/N	R Median	Vc-R Evt/N	Vc-R Median	Marker: Subgroup N Total
PERIFOLLICULAR: 0-25	old	(0.24,0.98)						
CD68 POSITIVE PERIFOLLICULAR: >75	<65 years old	0.45 (0.22,0.91)		19/23	437	13/23	726	289
P27 % NUCLEI POSITIVE: 0-20	<65 years old	0.52 (0.29,0.96)		26/34	327	19/32	834	344
P27 SIGNAL INTENSITY: >2+	<65 years old	0.74 (0.56,0.98)		103/153	484	90/149	672	344
P65 % NUCLEAR STAINING: <5%	<65 years old	0.54 (0.29,1.00)		19/29	374	22/43	975	349
P65 % POSITIVE CYTOPLASMIC SIGNAL: >90%	<65 years old	0.71 (0.53,0.94)		103/154	484	84/142	719	349
P65 INTENSITY CYTOPLASMIC SIGNAL: >2+	<65 years old	0.72 (0.54,0.96)		101/152	484	82/139	718	349
20S % NUCLEAR STAINING: 0-20	Female	0.53 (0.30,0.93)		35/61	568	19/49	-	259
CD68 OVERALL POSITIVE: 0-25	Female	0.27 (0.10,0.76)		16/26	434	5/18	1103	242
CD68 POSITIVE FOLLICULAR: 0-25	Female	0.45 (0.21,0.96)		23/37	462	10/22	1103	217
CD68 POSITIVE PERIFOLLICULAR: 0-25	Female	0.29 (0.11,0.79)		19/28	374	5/17	1107	215
P65 INTENSITY CYTOPLASMIC SIGNAL: >2+	Female	0.68 (0.46,1.00)		74/129	537	41/87	1047	263
20S % NUCLEAR STAINING: 60-70	Male	0.42 (0.19,0.93)		14/16	247	12/20	518	204
20S INTENSITY CYTOPLASMIC SIGNAL: >3+	Male	0.58 (0.34,1.00)		20/27	421	37/62	764	204
CD68 OVERALL POSITIVE: 0-25	Male	0.46 (0.22,0.99)		14/18	251	14/23	975	200
CD68 OVERALL POSITIVE: >75	Male	0.23 (0.07,0.79)		8/9	427	4/11	-	200
P65 % POSITIVE CYTOPLASMIC SIGNAL: >90%	Male	0.68 (0.47,0.98)		51/72	427	62/97	726	207

Appendix 2, Table 2.10: Time to Next Anti-Lymphoma Therapy by Protein Expression and by Covariate, IRC Review.

(All Reported Groups are Significant (p≤0.05) and at a Frequency ≥10%)

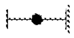
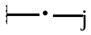
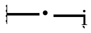
Marker: Level	Subgroup	HR (95% CI)	HR (log scale)	R Evt/N	R Median	Vc-R Evt/N	Vc-R Median	Marker: Subgroup N Total
CD68 POSITIVE FOLLICULAR: 0-25	Asian	0.13 (0.01,1.09)		5/6	220	2/6	-	30
CD68 POSITIVE PERIFOLLICULAR: 26-50	Other	0.14 (0.01,1.31)		4/4	341	4/5	658	22
CD68 OVERALL POSITIVE: 0-25	White	0.38 (0.20,0.72)		24/35	409	16/35	1075	385
CD68 POSITIVE FOLLICULAR: 0-25	White	0.57 (0.34,0.98)		32/48	462	25/42	834	335
CD68 POSITIVE PERIFOLLICULAR: 0-25	White	0.43 (0.22,0.82)		19/27	501	19/39	1103	332
P27 SIGNAL INTENSITY: >2+	White	0.75 (0.57,0.98)		113/177	533	99/170	718	403
P65 % POSITIVE CYTOPLASMIC SIGNAL: >90%	White	0.73 (0.56,0.96)		113/179	505	95/162	744	406
P65 INTENSITY CYTOPLASMIC SIGNAL: >2+	White	0.75 (0.57,0.99)		109/176	533	94/165	744	406
CD68 OVERALL POSITIVE: 0-25	Ann Arbor Stage III	0.35 (0.14,0.92)		12/16	276	9/12	905	144
CD68 POSITIVE FOLLICULAR: 0-25	Ann Arbor Stage III	0.40 (0.19,0.83)		19/24	332	13/li ;	764	135
P27 % NUCLEI POSITIVE: 0-20	Ann Arbor Stage III	0.42 (0.17,1.00)		14/16	418	12/15	613	149
P65 INTENSITY CYTOPLASMIC SIGNAL: ≤1+	Ann Arbor Stage III	0.36 (0.13,0.99)		10/11	261	7/11	834	151
CD68 OVERALL POSITIVE: 0-25	Ann Arbor Stage IV	0.37 (0.15,0.92)		15/22	434	8/23	1047	222
CD68 POSITIVE PERIFOLLICULAR: 0-25	Ann Arbor Stage IV	0.37 (0.14,0.96)		11/15	374	8/22	1107	183
								

Appendix 2, Table 2.11: Time to Next Anti-Lymphoma Therapy by Germline Genetic Variant and by Covariate, IRC Review.

(All Reported Groups are Significant (p <0.05) and at a Frequency of >10%)

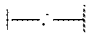
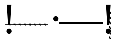
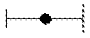
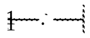
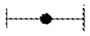
Marker: Level	Subgroup	HR (95% CI)	HR (log scale)	R Evt/N	R Median	Vc-R Evt/N	Vc-R Median	Marker: Subgroup N Total
PSMB1/A171S : G/G	No Subgroup	0.78 (0.63,0.97)		173/276	546	152/266	719	542
PSMB1/I208N: T/T	No Subgroup	0.78 (0.63,0.97)		173/276	546	152/266	719	542
PSMB1/P11A: C/G	No Subgroup	0.68 (0.48,0.94)		78/127	550	63/115	939	542
PSMB1/P11A: G/G	No Subgroup	0.57 (0.34,0.97)		30/37	436	26/43	613	542
PSMB1/P193L : C/C	No Subgroup	0.78 (0.63,0.97)		173/276	546	152/266	719	542
PSMB2/E49X: G/G	No Subgroup	0.78 (0.63,0.97)		173/276	546	152/266	719	542
PSMB2/G187V : G/G	No Subgroup	0.78 (0.63,0.97)		173/276	546	152/266	719	542
PSMB2/L159F : C/C	No Subgroup	0.78 (0.63,0.97)		173/276	546	152/266	719	542
PSMB5/L206M : C/C	No Subgroup	0.78 (0.63,0.97)		173/276	546	152/266	719	542
PSMB5/R24C: C/C	No Subgroup	0.78 (0.62.0.99)		147/235	546	127/223	719	542
PSMB6/A234D : C/C	No Subgroup	0.78 (0.63,0.97)		173/276	546	152/266	719	542
PSMB6/P107A : C/C	No Subgroup	0.79 (0.63,0.98)	N	167/265	550	150/261	717	542
PSMB8/G8R: G/G	No Subgroup	0.77 (0.61,0.96)		165/264	537	144/256	719	542
PSMB8/R141C : C/C	No Subgroup	0.78 (0.63,0.97)		173/276	546	152/266	719	542
PSMB8/V182M : G/G	No Subgroup	0.78 (0.63,0.97)		173/276	546	152/266	719	542
PSMB9/G9E: G/G	No Subgroup	0.78 (0.63,0.97)		172/274	546	152/265	718	542
PSMB9/V32I: C/C	No Subgroup	0.79 (0.63,0.99		167/266	546	146/254	717	542

Appendix 2, Table 2.11: Time to Next Anti-Lymphoma Therapy by Germline Genetic Variant and by Covariate, IRC Review.
(All Reported Groups are Significant (p ≤0.05) and at a Frequency of ≥10%)

Marker: Level	Subgroup	HR (95% CI)	HR (log scale)	R Evt/N	R Median	Vc-R Evt/N	Vc-R Median	Marker: Subgroup N Total
		)						
PSMB1/A171S: G/G	1 Prior Line of Therapy	0.70 (0.50,0.98)		72/113	673	61/118	841	231
PSMB1/I208N: T/T	1 Prior Line of Therapy	0.70 (0.50,0.98)		72/113	673	61/118	841	231
PSMB1/P11A: C/G	1 Prior Line of Therapy	0.56 (0.34,0.95)		32/51	621	27/55	1047	231
PSMB1/P11A: G/G	1 Prior Line of Therapy	0.35 (0.13,0.93)		11/11	443	7/14	700	231
PSMB1/P193L: C/C	1 Prior Line of Therapy	0.70 (0.50,0.98)		72/113	673	61/118	841	231
PSMB2/E49X: G/G	1 Prior Line of Therapy	0.70 (0.50,0.98)		72/113	673	61/118	841	231
PSMB2/G187V: G/G	1 Prior Line of Therapy	0.70 (0.50,0.98)		72/113	673	61/118	841	231
PSMB2/L159F: C/C	1 Prior Line of Therapy	0.70 (0.50,0.98)		72/113	673	61/118	841	231
PSMB5/L206M: C/C	1 Prior Line of Therapy	0.70 (0.50,0.98)		72/113	673	61/118	841	231
PSMB6/A234D: C/C	1 Prior Line of Therapy	0.70 (0.50,0.98)		72/113	673	61/118	841	231
PSMB6/P107A: C/C	1 Prior Line of Therapy	0.70 (0.49,0.99)		70/108	673	60/116	841	231
PSMB8/G8R: G/G	1 Prior Line of Therapy	0.68 (0.47,0.97)		69/109	673	55/111	852	231
PSMB8/R141C: C/C	1 Prior Line of Therapy	0.70 (0.50,0.98)		72/113	673	61/118	841	231
PSMB8/V182M: G/G	1 Prior Line of Therapy	0.70 (0.50,0.98)		72/113	673	61/118	841	231
PSMB9/G9E: G/G	1 Prior Line of Therapy	0.71 (0.50,1.00)		71/112	673	61/118	841	231
PSMB1/A171S: G/G	5 Prior Lines of Therapy	0.29 (0.08,0.99)		7/9	235	6/12	939	21
PSMB1/I208N:	5 Prior	0.29		7/9	235	6/12	939	21

Appendix 2, Table 2.11: Time to Next Anti-Lymphoma Therapy by Germline Genetic Variant and by Covariate, IRC Review.

(All Reported Groups are Significant (p ≤0.05) and at a Frequency of ≥10%)

Marker: Level	Subgroup	HR (95% CI)	HR (log scale)	R Evt/N	R Median	Vc-R Evt/N	Vc-R Median	Marker: Subgroup N Total
T/T	Lines of Therapy	(0.08,0.99)						
PSMB1/P193L: C/C	5 Prior Lines of Therapy	0.29 (0.08,0.99)		7/9	235	6/12	939	21
PSMB2/E49X: G/G	5 Prior Lines of Therapy	0.29 (0.08,0.99)		7/9	235	6/12	939	21
PSMB2/G187V: G/G	5 Prior Lines of Therapy	0.29 (0.08,0.99)		7/9	235	6/12	939	21
PSMB2/L159F: C/C	5 Prior Lines of Therapy	0.29 (0.08,0.99)		7/9	235	6/12	939	21
PSMB5/L206M: C/C	5 Prior Lines of Therapy	0.29 (0.08,0.99)		7/9	235	6/12	939	21
PSMB5/R24C: C/C	5 Prior Lines of Therapy	0.16 (0.03,0.79)		6/7	235	4/9	1235	21
PSMB6/A234D: C/C	5 Prior Lines of Therapy	0.29 (0.08,0.99)		7/9	235	6/12	939	21
PSMB6/P107A: C/C	5 Prior Lines of Therapy	0.29 (0.08,0.99)		7/9	235	6/12	939	21
PSMB8/G8R: G/G	5 Prior Lines of Therapy	0.29 (0.08,1.00)		7/9	235	6/11	939	21
PSMB8/R141C: C/C	5 Prior Lines of Therapy	0.29 (0.08,0.99)		7/9	235	6/12	939	21
PSMB8/V182M: G/G	5 Prior Lines of Therapy	0.29 (0.08,0.99)		7/9	235	6/12	939	21
PSMB9/G9E: G/G	5 Prior Lines of Therapy	0.29 (0.08,0.99)		7/9	235	6/12	939	21
PSMB9/V32I: C/C	5 Prior Lines of Therapy	0.25 (0.07,0.86)		7/8	228	5/11	1235	21
PSMB1/A171S: G/G	High Tumor Burden	0.72 (0.55,0.95)		108/147	396	98/149	521	296
PSMB1/I208N: T/T	High Tumor Burden	0.72 (0.55,0.95)		108/147	396	98/149	521	296
PSMB1/P11A: C/G	High Tumor Burden	0.63 (0.41,0.96)		49/72	358	38/65	675	296

Appendix 2, Table 2.11: Time to Next Anti-Lymphoma Therapy by Germline Genetic Variant and by Covariate, IRC Review.

(All Reported Groups are Significant (p ≤0.05) and at a Frequency of ≥10%)

Marker: Level	Subgroup	HR (95% CI)	HR (log scale)	R Evt/N	R Median	Vc-R Evt/N	Vc-R Median	Marker: Subgroup N Total
PSMB1/P193L : C/C	High Tumor Burden	0.72 (0.55,0.95)		108/147	396	98/149	521	296
PSMB2/E49X: G/G	High Tumor Burden	0.72 (0.55,0.95)		108/147	396	98/149	521	296
PSMB2/G187V: G/G	High Tumor Burden	0.72 (0.55,0.95)		108/147	396	98/149	521	296
PSMB2/L159F : C/C	High Tumor Burden	0.72 (0.55,0.95)		108/147	396	98/149	521	296
PSMB5/L206M: C/C	High Tumor Burden	0.72 (0.55,0.95)		108/147	396	98/149	521	296
PSMB5/R24C: C/T	High Tumor Burden	0.46 (0.24,0.89)		19/21	317	18/24	536	296
PSMB6/A234D: C/C	High Tumor Burden	0.72 (0.55,0.95)		108/147	396	98/149	521	296
PSMB6/P107A : C/C	High Tumor Burden	0.73 (0.55,0.96)		104/140	380	97/146	518	296
PSMB8/G8R: G/G	High Tumor Burden	0.69 (0.52,0.91)	N	104/140	374	94/145	521	296
PSMB8/R141C : C/C	High Tumor Burden	0.72 (0.55,0.95)		108/147	396	98/149	521	296
PSMB8/V182M: G/G	High Tumor Burden	0.72 (0.55,0.95)		108/147	396	98/149	521	296
PSMB9/G9E: G/G	High Tumor Burden	0.72 (0.55,0.95)	N	107/145	396	98/148	518	296
PSMB9/V32I: C/C	High Tumor Burden	0.71 (0.54,0.94)		106/142	396	94/142	521	296
PSMB1/A171S : G/G	> 1 year since last anti-lymphoma treatment	0.69 (0.51,0.93)		98/165	688	80/166	969	331
PSMB1/I208N: T/T	> 1 year since last anti-lymphoma	0.69 (0.51,0.93)		98/165	688	80/166	969	331

Appendix 2, Table 2.11: Time to Next Anti-Lymphoma Therapy by Germline Genetic Variant and by Covariate, IRC Review.

(All Reported Groups are Significant (p <0.05) and at a Frequency of >10%)

Marker: Level	Subgroup	HR (95% CI)	HR (log scale)	R Evt/N	R Median	Vc-R Evt/N	Vc-R Median	Marker: Subgroup N Total
PSMB1/P11A: G/G	treatment > 1 year since last anti-lymphoma	0.47 (0.23,0.97)		17/20	429	13/25	872	331
PSMB1/P193L: C/C	treatment > 1 year since last anti-lymphoma	0.69 (0.51,0.93)		98/165	688	80/166	969	331
PSMB2/E49X: G/G	treatment > 1 year since last anti-lymphoma	0.69 (0.51,0.93)		98/165	688	80/166	969	331
PSMB2/G187V: G/G	treatment > 1 year since last anti-lymphoma	0.69 (0.51,0.93)		98/165	688	80/166	969	331
PSMB2/L159F: C/C	treatment > 1 year since last anti-lymphoma	0.69 (0.51,0.93)		98/165	688	80/166	969	331
PSMB5/L206M: C/C	treatment > 1 year since last anti-lymphoma	0.69 (0.51,0.93)		98/165	688	80/166	969	331
PSMB5/R24C: C/C	treatment > 1 year since last anti-lymphoma	0.70 (0.51,0.97)		51/137	649	68/141	983	331
PSMB6/A234D: C/C	treatment > 1 year since last anti-lymphoma	0.69 (0.51,0.93)		98/165	688	80/166	969	331
PSMB6/P107A	treatment > 1 year	0.70		95/159	702	79/162	969	331

Appendix 2, Table 2.11: Time to Next Anti-Lymphoma Therapy by Germline Genetic Variant and by Covariate, IRC Review.

(All Reported Groups are Significant (p ≤0.05) and at a Frequency of ≥10%)

Marker: Level	Subgroup	HR (95% CI)	HR (log scale)	R Evt/N	R Median	Vc-R Evt/N	Vc-R Median	Marker: Subgroup N Total
: C/C	since last anti-lymphoma treatment	(0.52,0.94)						
PSMB8/G8R: G/G	> 1 year since last anti-lymphoma treatment	0.69 (0.51,0.93)	●	91/155	702	74/159	1005	331
PSMB8/R141C : C/C	> 1 year since last anti-lymphoma treatment	0.69 (0.51,0.93)	●	98/165	688	80/166	969	331
PSMB8/V182M: G/G	> 1 year since last anti-lymphoma treatment	0.69 (0.51,0.93)	●	98/165	688	80/166	969	331
PSMB9/G9E: G/G	> 1 year since last anti-lymphoma treatment	0.69 (0.51,0.93)	●	97/163	688	80/165	969	331
PSMB9/V32I: C/C	> 1 year since last anti-lymphoma treatment	0.68 (0.50,0.91)	●	96/160	649	76/158	969	331
PSMB1/A171S : G/G	European Union	0.71 (0.51,0.99)	●	75/119	675	66/122	939	241
PSMB1/I208N: T/T	European Union	0.71 (0.51,0.99)	●	75/119	675	66/122	939	241
PSMB1/P11A: C/G	European Union	0.56 (0.34,0.92)	⊢●⊣	34/49	462	29/51	1005	241
PSMB1/P193L : C/C	European Union	0.71 (0.51,0.99)	●	75/119	675	66/122	939	241
PSMB2/E49X: G/G	European Union	0.71 (0.51,0.99)	●	75/119	675	66/122	939	241

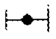
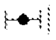
Appendix 2, Table 2.11: Time to Next Anti-Lymphoma Therapy by Germline Genetic Variant and by Covariate, IRC Review.

(All Reported Groups are Significant (p ≤0.05) and at a Frequency of >10%)

Marker: Level	Subgroup	HR (95% CI)	HR (log scale)	R Evt/N	R Median	Vc-R Evt/N	Vc-R Median	Marker: Subgroup N Total
PSMB2/G187V: G/G	European Union	0.71 (0.51,0.99)		75/119	675	66/122	939	241
PSMB2/L159F: C/C	European Union	0.71 (0.51,0.99)		75/119	675	66/122	939	241
PSMB5/L206M: C/C	European Union	0.71 (0.51,0.99)		75/119	675	66/122	939	241
PSMB6/A234D: C/C	European Union	0.71 (0.51,0.99)		75/119	675	66/122	939	241
PSMB8/G8R: G/G	European Union	0.71 (0.50, 1.00)		70/111	649	62/117	939	241
PSMB8/R141C: C/C	European Union	0.71 (0.51,0.99)		75/119	675	66/122	939	241
PSMB8/V182M: G/G	European Union	0.71 (0.51,0.99)		75/119	675	66/122	939	241
PSMB9/G9E: G/G	European Union	0.71 (0.51,0.99)		75/119	675	66/122	939	241
PSMB1/A171S: G/G	<65 years old	0.72 (0.56,0.92)		130/198	489	112/194	719	392
PSMB1/I208N: T/T	<65 years old	0.72 (0.56,0.92)		130/198	489	112/194	719	392
PSMB1/P11A: C/G	<65 years old	0.62 (0.42,0.91)		63/96	546	47/86	764	392
PSMB1/P11A: G/G	<65 years old	0.40 (0.21,0.78)		21/25	409	16/30	834	392
PSMB1/P193L: C/C	<65 years old	0.72 (0.56,0.92)		130/198	489	112/194	719	392
PSMB2/E49X: G/G	<65 years old	0.72 (0.56,0.92)		130/198	489	112/194	719	392
PSMB2/G187V: G/G	<65 years old	0.72 (0.56,0.92)		130/198	489	112/194	719	392
PSMB2/L159F: C/C	<65 years old	0.72 (0.56,0.92)		130/198	489	112/194	719	392
PSMB5/L206M: C/C	<65 years old	0.72 (0.56,0.92		130/198	489	112/194	719	392

Appendix 2, Table 2.11: Time to Next Anti-Lymphoma Therapy by Germline Genetic Variant and by Covariate, IRC Review.

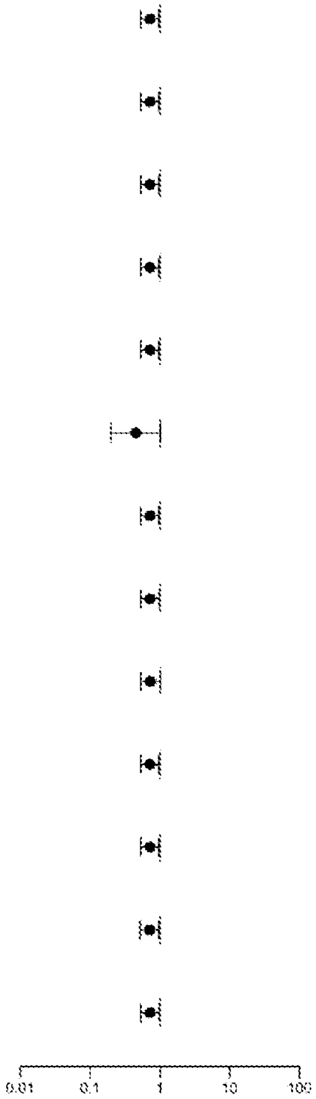
(All Reported Groups are Significant (p ≤0.05) and at a Frequency of ≥10%)

Marker: Level	Subgroup	HR (95% CI)	HR (log scale)	R Evt/N	R Median	Vc-R Evt/N	Vc-R Median	Marker: Subgroup N Total
PSMB5/R24C: C/C	<65 years old	) 0.71 (0.54,0.93		113/170	489	97/167	719	392
PSMB6/A234D: C/C	<65 years old	) 0.72 (0.56,0.92		130/198	489	112/194	719	392
PSMB6/P107A: C/C	<65 years old	) 0.72 (0.56.0.93	Hi	125/189	504	110/190	718	392
PSMB8/G8R: G/G	<65 years old	) 0.72 (0.55.0.93	Hi	123/189	504	106/186	719	392
PSMB8/R141C: C/C	<65 years old	) 0.72 (0.56,0.92		130/198	489	112/194	719	392
PSMB8/V182M: G/G	<65 years old	) 0.72 (0.56,0.92		130/198	489	112/194	719	392
PSMB9/G9E: G/G	<65 years old	) 0.72 (0.56,0.93		129/196	489	112/193	719	392
PSMB9/V32I: C/C	<65 years old	) 0.72 (0.56,0.93		127/192	489	107/186	718	392
PSMB1/P11A: C/G	Female	) 0.58 (0.36,0.93		42/75	546	30/66	1103	301
PSMB8/G8R: G/G	Female	) 0.72 (0.52.0.98		94/160	649	65/131	939	301
PSMB1/P11A: G/G	Male	) 0.50 (0.25, 1.01		17/19	421	15/25	631	241
PSMB9/R60H: A/G	Male	) 0.43 (0.24,0.76		22/28	380	30/48	764	241
PSMB1/P11A: C/G	Other	) 0.07 (0.01,0.81		2/3	164	6/9	557	27
PSMB1/P11A: C/G	White	) 0.68 (0.47,0.97		67/111	581	54/97	975	473
PSMB1/P11A: G/G	White	) 0.54 (0.31,0.94		27/32	421	25/39	599	473
PSMB1/A171S: G/G	Ann Arbor Stage IV	) 0.72 (0.53.0.97		86/127	457	78/143	639	270
PSMB1/I208N:	Ann	) 0.72		86/127	457	78/143	639	270

Appendix 2, Table 2.11: Time to Next Anti-Lymphoma Therapy by Germline Genetic Variant and by Covariate, IRC Review.

(All Reported Groups are Significant (p ≤0.05) and at a Frequency of ≥10%)

Marker: Level	Subgroup	HHRR ((9955%% CI)	H R (log scale)	R Evt/N	R MMeeddiiaa n	VVcc--RR Evt/N	Vc-R Media n	Marker: Subgroup N Total
T7T	Arbor Stage IV	(0.53,0.97)						
PSMB1/P193L : C/C	Ann Arbor Stage IV	0.72 (0.53,0.97)		86/127	457	78/143	639	270
PSMB2/E49X: G/G	Ann Arbor Stage IV	0.72 (0.53,0.97)		86/127	457	78/143	639	270
PSMB2/G187 V : G/G	Ann Arbor Stage IV	0.72 (0.53,0.97)		86/127	457	78/143	639	270
PSMB2/L159F : C/C	Ann Arbor Stage IV	0.72 (0.53,0.97)		86/127	457	78/143	639	270
PSMB5/L206 M : C/C	Ann Arbor Stage IV	0.72 (0.53,0.97)		86/127	457	78/143	639	270
PSMB5/R24C: C/T	Ann Arbor Stage IV	0.45 (0.20,1.01)		11/15	421	13/28	991	270
PSMB6/A234 D : C/C	Ann Arbor Stage IV	0.72 (0.53,0.97)		86/127	457	78/143	639	270
PSMB6/P107A : C/C	Ann Arbor Stage IV	0.72 (0.53,0.98)		84/124	485	77/140	602	270
PSMB8/G8R: G/G	Ann Arbor Stage IV	0.73 (0.53,1.00)		80/120	457	74/138	602	270
PSMB8/R141C : C/C	Ann Arbor Stage IV	0.72 (0.53,0.97)		86/127	457	78/143	639	270
PSMB8/V182 M : G/G	Ann Arbor Stage IV	0.72 (0.53,0.97)		86/127	457	78/143	639	270
PSMB9/G9E: G/G	Ann Arbor Stage IV	0.71 (0.52,0.97)		86/126	457	78/142	602	270
PSMB9/V32I: C/C	Ann Arbor Stage IV	0.72 (0.53,0.98)		84/123	457	76/138	639	270

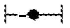
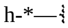
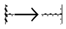
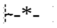


Appendix 2, Table 2.12: Time to Next Anti-Lymphoma Therapy by Somatic Mutation and by Covariate, IRC review.

(All Reported Groups are Significant (p ≤0.05) and at a Frequency of ≥10%)

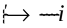
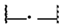
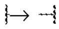
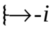
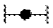
Marker: Level	Subgroup	HR (95% CI)	HR (log scale)	R Evt/N	R Median	Vc-R Evt/N	Vc-R Median	Marker: Subgroup N Total
BCL2/A43G: MND	No Subgroup	0.66 (0.49,0.88)	MM	104/161	501	84/154	791	315
BCL2/C.-1 10T: MND	No Subgroup	0.71 (0.54,0.92)	├●┤	127/192	501	102/179	719	390
BCL2/E29K: MND	No Subgroup	0.64 (0.47,0.86)	HH	98/150	484	77/139	791	318
BCL2/P46L: MND	No Subgroup	0.70 (0.51,0.95)	├●┤	86/135	504	77/139	743	314
BCL2/P46S: MND	No Subgroup	0.73 (0.54,0.98)	├●┤	92/147	504	84/147	751	310
BCL2/P59S: MND	No Subgroup	0.72 (0.53,0.96)	H•┤	92/145	504	84/147	751	309
BCL2/Q52P: MND	No Subgroup	0.71 (0.53,0.95)	├●┤	97/153	501	88/154	751	307
BCL2/R106H: MND	No Subgroup	0.66 (0.50,0.88)	├●┤	108/162	489	84/151	751	372
NOTCH/G _A1702P: MND	No Subgroup	0.73 (0.55,0.96)	HH	113/175	501	93/161	726	337
NOTCH/I1681N: MND	No Subgroup	0.73 (0.56,0.97)	├●┤	113/175	501	94/162	719	337
NOTCH/L1679P: MND	No Subgroup	0.73 (0.56,0.97)	├●┤	113/175	501	94/162	719	337
NOTCH/L1679Q: MND	No Subgroup	0.73 (0.56,0.97)	├●┤	113/175	501	94/162	719	337
NOTCH/L2458V: MND	No Subgroup	0.75 (0.56,0.99)	├●┤	104/162	501	92/157	719	319
NOTCH/P25 13L: MND	No Subgroup	0.69 (0.50,0.95)	i●-i	90/140	501	67/123	791	361
NOTCH/P25 15FS4: MND	No Subgroup	0.70 (0.53,0.92)	├●┤	114/176	501	92/166	751	344
NOTCH/Q2441X: MND	No Subgroup	0.75 (0.57,1.00)	├●┤	103/161	501	92/155	719	319
NOTCH/Q2460X: MND	No Subgroup	0.72 (0.53,0.9	HH	98/151	489	82/143	726	324

Appendix 2, Table 2.12: Time to Next Anti-Lymphoma Therapy by Somatic Mutation and by Covariate, IRC review.
(All Reported Groups are Significant (p ≤0.05) and at a Frequency of ≥10%)

Marker: Level	Subgroup	HR (95% CI)	HR (log scale)	R Evt/N	R Median	Vc-R Evt/N	Vc-R Median	Marker: Subgroup N Total
		6)						
NOTCH/X26DEL: MND	No Subgroup	0.74 (0.57,0.97)		112/175	505	102/178	744	361
NOTCH/X26INS: MND	No Subgroup	0.74 (0.56,0.96)		114/179	505	103/180	744	361
NOTCH/X28DEL: MND	No Subgroup	0.72 (0.56,0.93)		128/194	503	109/189	719	400
NOTCH/X28INS: MND	No Subgroup	0.70 (0.55,0.90)		132/198	501	112/195	719	401
BCL2/A43G: MND	1 Prior Line of Therapy	0.54 (0.34,0.86)		46/72	550	30/67	991	139
BCL2/C.-1 10T: MND	1 Prior Line of Therapy	0.61 (0.40,0.92)		57/86	568	38/78	988	170
BCL2/E29K: MND	1 Prior Line of Therapy	0.54 (0.34,0.88)		41/64	546	29/62	991	139
BCL2/P46L: MND	1 Prior Line of Therapy	0.59 (0.37,0.97)		37/58	589	30/63	991	140
BCL2/P46S: MND	1 Prior Line of Therapy	0.61 (0.38,0.97)		40/64	550	33/68	991	138
BCL2/P59S: MND	1 Prior Line of Therapy	0.62 (0.39,0.99)		41/66	573	32/66	988	138
BCL2/Q52P: MND	1 Prior Line of Therapy	0.62 (0.39,0.97)		42/67	550	35/71	988	138
BCL2/R106H: MND	1 Prior Line of Therapy	0.58 (0.37,0.90)		49/73	550	33/68	991	162
NOTCH/P25 15FS4: MND	1 Prior Line of Therapy	0.62 (0.40,0.97)		48/75	573	35/72	988	149
NOTCH/X28DEL: MND	1 Prior Line of Therapy	0.67 (0.45,1.00)		56/85	568	44/84	756	177
NOTCH/X28INS: MND	1 Prior Line of Therapy	0.63 (0.42,0.93)		56/84	568	45/88	841	178
BCL2/C.-1 10T: MND	5 Prior Lines of Therapy	0.17 (0.03,1.05)		3/3	221	3/7	939	11
NOTCH/X28DEL:	5 Prior	0.20		4/4	342	3/7	939	11

Appendix 2, Table 2.12: Time to Next Anti-Lymphoma Therapy by Somatic Mutation and by Covariate, IRC review.

(All Reported Groups are Significant (p ≤0.05) and at a Frequency of ≥10%)

Marker: Level	Subgroup	HR (95% CI)	HR (log scale)	R Evt/N	R Median	Vc-R Evt/N	Vc-R Median	Marker: Subgroup N Total
MND	Lines of Therapy	(0.04,1.12)						
BCL2/A43G: MND	No High Tumor Burden	0.61 (0.37,0.98)		42/78	774	27/64	-	142
BCL2/R106H: MND	No High Tumor Burden	0.60 (0.37,0.98)		46/79	690	26/58	1185	163
NOTCH/P2513L: MD	No High Tumor Burden	0.44 (0.19,0.99)		17/26	593	9/21	-	163
NOTCH/X28INS: MND	No High Tumor Burden	0.63 (0.41,0.96)		55/98	734	37/82	1107	184
BCL2/A43G: MND	High Tumor Burden	0.60 (0.42,0.86)		62/83	380	57/90	534	173
BCL2/C.-110T: MND	High Tumor Burden	0.65 (0.47,0.90)		76/101	380	69/107	484	217
BCL2/E29K: MND	High Tumor Burden	0.56 (0.38,0.81)		60/79	374	52/82	542	174
BCL2/P46L: MND	High Tumor Burden	0.57 (0.38,0.84)		51/67	374	51/83	534	173
BCL2/P46S: MND	High Tumor Burden	0.63 (0.43,0.92)		52/73	374	56/89	488	170
BCL2/P59L: MND	High Tumor Burden	0.66 (0.44,0.97)		52/72	396	50/80	455	172
BCL2/P59S: MND	High Tumor Burden	0.62 (0.42,0.90)		53/73	396	54/87	534	170
BCL2/Q52P: MND	High Tumor Burden	0.62 (0.42,0.89)		55/76	374	58/92	534	168
BCL2/R106H: MND	High Tumor Burden	0.59 (0.41,0.84)		62/83	380	58/93	542	209
NOTCH/F1593S: MND	High Tumor Burden	0.69 (0.48,1.00)		55/77	410	60/91	488	168
NOTCH/G_A1702P: MND	High Tumor Burden	0.62 (0.44,0.88)		67/90	374	62/96	534	187
NOTCH/I1681N: MND	High Tumor Burden	0.63 (0.45,0.89)		67/90	374	63/97	534	187

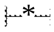
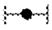
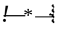
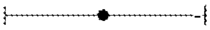
Appendix 2, Table 2.12: Time to Next Anti-Lymphoma Therapy by Somatic Mutation and by Covariate, IRC review.

(All Reported Groups are Significant (p ≤0.05) and at a Frequency of ≥10%)

Marker: Level	Subgroup	HR (95% CI)	HR (log scale)	R Evt/N	R Median	Vc-R Evt/N	Vc-R Median	Marker: Subgroup N Total
NOTCH/L1586P: MND	High Tumor Burden	0.69 (0.48,1.00)	├●-	55/77	410	60/91	488	168
NOTCH/L1586Q: MND	High Tumor Burden	0.65 (0.45,0.94)	HH	56/78	396	60/94	534	172
NOTCH/L1594P: MND	High Tumor Burden	0.69 (0.48,1.00)	├●–	55/77	410	60/91	488	168
NOTCH/L1597H: MND	High Tumor Burden	0.65 (0.45,0.94)	HH	56/78	396	60/94	534	172
NOTCH/L1597 _S15981 NSG: MND	High Tumor Burden	0.69 (0.48,1.00)	├→–	55/77	410	60/91	488	168
NOTCH/L1601P: MND	High Tumor Burden	0.68 (0.47,0.98)	HH	55/77	410	59/90	488	168
NOTCH/L1679P: MND	High Tumor Burden	0.63 (0.45,0.89)	HH	67/90	374	63/97	534	187
NOTCH/L1679Q: MND	High Tumor Burden	0.63 (0.45,0.89)	HH	67/90	374	63/97	534	187
NOTCH/L2458V: MND	High Tumor Burden	0.64 (0.45,0.91)	HH	61/83	380	61/95	534	178
NOTCH/P25 13L: MND	High Tumor Burden	0.54 (0.36,0.80)	├–●–┤	58/76	380	43/71	542	198
NOTCH/P25 15FS4: MND	High Tumor Burden	0.61 (0.43,0.87)	HH	67/90	380	61/98	534	189
NOTCH/Q2441X: MND	High Tumor Burden	0.64 (0.45,0.91)	r●┤	61/83	380	61/95	534	178
NOTCH/Q2460X: MND	High Tumor Burden	0.61 (0.42,0.88)	HH	59/79	380	54/87	542	181
NOTCH/R1599>QS: MND	High Tumor Burden	0.69 (0.48,1.00)	├→ -	55/77	410	60/91	488	168
NOTCH/R1599P: MND	High Tumor Burden	0.65 (0.45,0.94)	HH	56/78	396	60/94	534	172
NOTCH/V1579DEL: MND	High Tumor Burden	0.69 (0.48,1.00)	├–*–	55/77	410	60/91	488	168
NOTCH/V1579E: MND	High Tumor	0.65 (0.45,0.9	HH	56/78	396	60/94	534	172

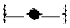
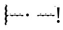
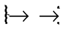
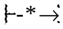
Appendix 2, Table 2.12: Time to Next Anti-Lymphoma Therapy by Somatic Mutation and by Covariate, IRC review.

(All Reported Groups are Significant ($p \leq 0.05$) and at a Frequency of ≥10%)

Marker: Level	Subgroup	HR (95% CI)	HR (log scale)	R Evt/N	R Median	Vc-R Evt/N	Vc-R Median	Marker: Subgroup N Total
	Burden	4)						
NOTCH/V1579G: MND	High Tumor Burden	0.69 (0.48,1.00)		55/77	410	60/91	488	168
NOTCH/X26DEL: MND	High Tumor Burden	0.67 (0.47,0.94)		63/88	396	68/107	518	198
NOTCH/X26INS: MND	High Tumor Burden	0.66 (0.47,0.93)		64/89	396	68/107	518	198
NOTCH/X28DEL: MND	High Tumor Burden	0.64 (0.46,0.89)		74/99	374	72/111	488	216
NOTCH/X28INS: MND	High Tumor Burden	0.64 (0.47,0.88)		77/100	343	75/113	474	217
BCL2/P59L: MD	High FLIPI Score	0.18 (0.03,1.06)		4/6	211	6/7	658	125
BCL2/A43G: MND	Intermediate FLIPI Score	0.60 (0.36,1.00)		34/53	504	26/52	939	105
BCL2/C.-110T: MND	Intermediate FLIPI Score	0.59 (0.38,0.93)		44/66	504	33/63	939	136
BCL2/P46S: MND	Intermediate FLIPI Score	0.59 (0.35,1.00)		31/50	505	26/52	988	105
BCL2/P59S: MND	Intermediate FLIPI Score	0.60 (0.35,1.00)		31/48	505	27/52	939	105
BCL2/Q52P: MND	Intermediate FLIPI Score	0.60 (0.36,0.99)		32/51	505	28/54	988	105
BCL2/R106H: MND	Intermediate FLIPI Score	0.51 (0.31,0.82)		40/55	501	28/54	988	130
NOTCH/X28DEL: MND	Intermediate FLIPI Score	0.65 (0.42,1.00)		44/65	505	38/70	756	143
BCL2/E29K: MND	No Prior Rituximab Therapy	0.65 (0.43,0.97)		57/93	534	41/76	883	186
BCL2/P59L: MD	No Prior Rituximab Therapy	0.15 (0.03,0.80)		3/5	211	7/13	947	178
BCL2/A43G: MND	Prior Rituximab Therapy	0.59 (0.38,0.92)		44/63	428	37/69	719	132
BCL2/C.-110T: MND	Prior	0.58		57/78	396	43/77	718	165

Appendix 2, Table 2.12: Time to Next Anti-Lymphoma Therapy by Somatic Mutation and by Covariate, IRC review.

(All Reported Groups are Significant (p ≤0.05) and at a Frequency of ≥10%)

Marker: Level	Subgroup	HR (95% CI)	HR (log scale)	R Evt/N	R Median	Vc-R Evt/N	Vc-R Median	Marker: Subgroup N Total
	Rituximab Therapy	(0.39,0.86)						
BCL2/E29K: MND	Prior Rituximab Therapy	0.59 (0.37,0.92)		41/57	428	36/63	719	132
BCL2/P59S: MND	Prior Rituximab Therapy	0.60 (0.38,0.95)		39/56	450	37/69	719	133
BCL2/R106H: MND	Prior Rituximab Therapy	0.54 (0.36,0.83)		50/67	421	39/72	719	159
NOTCH/G _A1702P: MND	Prior Rituximab Therapy	0.60 (0.40,0.91)		51/72	434	41/74	719	147
NOTCH/I1681N: MND	Prior Rituximab Therapy	0.61 (0.41,0.93)		51/72	434	42/75	719	147
NOTCH/L1586Q: MND	Prior Rituximab Therapy	0.63 (0.41,0.97)		44/63	443	41/73	719	136
NOTCH/L1597H: MND	Prior Rituximab Therapy	0.63 (0.41,0.97)		44/63	443	41/73	719	136
NOTCH/L1679P: MND	Prior Rituximab Therapy	0.61 (0.41,0.93)		51/72	434	42/75	719	147
NOTCH/L1679Q: MND	Prior Rituximab Therapy	0.61 (0.41,0.93)		51/72	434	42/75	719	147
NOTCH/L2458V: MND	Prior Rituximab Therapy	0.61 (0.40,0.93)		47/66	443	42/75	719	141
NOTCH/P2513L: MND	Prior Rituximab Therapy	0.57 (0.35,0.95)		39/57	450	25/51	751	154
NOTCH/P2515FS4: MND	Prior Rituximab Therapy	0.61 (0.41,0.92)		51/72	434	42/77	719	149
NOTCH/Q2441X: MND	Prior Rituximab Therapy	0.61 (0.40,0.93)		47/66	443	42/73	719	141
NOTCH/Q2460X: MND	Prior Rituximab Therapy	0.58 (0.37,0.90)		45/62	434	36/66	719	143
NOTCH/R1599P: MND	Prior Rituximab Therapy	0.63 (0.41,0.97)		44/63	443	41/73	719	136
NOTCH/V1579E: MND	Prior Rituximab Therapy	0.63 (0.41,0.97)		44/63	443	41/73	719	136

Appendix 2, Table 2.12: Time to Next Anti-Lymphoma Therapy by Somatic Mutation and by Covariate, IRC review.

(All Reported Groups are Significant (p ≤0.05) and at a Frequency of ≥10%)

Marker: Level	Subgroup	HR (95% CI)	HR (log scale)	R Evt/N	R Median	Vc-R Evt/N	Vc-R Median	Marker: Subgroup N Total
NOTCH/X26DEL: MND	Prior Rituximab Therapy	0.65 (0.44,0.98)	├-●-┤	50/70	434	46/82	718	158
NOTCH/X26INS: MND	Prior Rituximab Therapy	0.64 (0.43,0.94)	├-●-┤	52/74	434	47/84	719	158
NOTCH/X28DEL: MND	Prior Rituximab Therapy	0.61 (0.42,0.89)	├-●-┤	60/83	427	49/86	672	175
NOTCH/X28INS: MND	Prior Rituximab Therapy	0.60 (0.41,0.87)	├-*-┤	62/86	427	50/88	672	175
BCL2/A43G: MND	> 1 year since last anti-lymphoma treatment	0.63 (0.43,0.94)	├-●-┤	57/91	589	44/94	878	185
BCL2/C.-1 10T: MND	> 1 year since last anti-lymphoma treatment	0.62 (0.44,0.138)	├-●M	73/112	560	55/112	878	233
BCL2/E29K: MND	> 1 year since last anti-lymphoma treatment	0.59 (0.39,0.90)	├-●-┤	52/82	550	39/83	883	185
BCL2/R106H: MND	> 1 year since last anti-lymphoma treatment	0.57 (0.39,0.133)	├-●-┤	65/96	534	45/94	878	217
NOTCH/P25 13L: MND	> 1 year since last anti-lymphoma treatment	0.60 (0.39,0.92)	├-●-┤	50/78	560	37/81	878	213
NOTCH/P25 15FS4: MND	> 1 year since last anti-lymphoma treatment	0.65 (0.44,0.94)	├-●-┤	64/102	593	48/102	878	205
NOTCH/Q2460X: MND	> 1 year since last	0.66 (0.44,0.9	├-●-┤	53/84	573	43/86	841	185

Appendix 2, Table 2.12: Time to Next Anti-Lymphoma Therapy by Somatic Mutation and by Covariate, IRC review.

(All Reported Groups are Significant (p ≤0.05) and at a Frequency of ≥10%)

Marker: Level	Subgroup	HR (95% CI)	HR (log scale)	R Evt/N	R Median	Vc-R Evt/N	Vc-R Median	Marker: Subgroup N Total
	anti-lymphoma treatment	9)						
NOTCH/X26INS: MND	> 1 year since last anti-lymphoma treatment	0.69 (0.48,1.00)	├●┤	62/102	643	54/110	883	212
NOTCH/X28DEL: MND	> 1 year since last anti-lymphoma treatment	0.70 (0.49,0.99)	├●┤	70/112	589	58/116	872	236
NOTCH/X28INS: MND	> 1 year since last anti-lymphoma treatment	0.64 (0.45,0.90)	├●┤	73/113	573	59/119	872	237
BCL2/A43G: MND	European Union	0.53 (0.33,0.84)	├●┤	41/66	649	32/72	1103	138
BCL2/C.-110T: MND	European Union	0.57 (0.38,0.86)	├●┤	53/79	505	41/83	983	169
BCL2/E29K: MND	European Union	0.58 (0.36,0.94)	├◆┤	37/61	533	32/67	1075	138
BCL2/P46L: MND	European Union	0.58 (0.35,0.96)	├·┤	34/56	533	29/64	1185	139
BCL2/P46S: MND	European Union	0.59 (0.37,0.94)	├●┤	37/61	504	33/68	1075	136
BCL2/P59S: MND	European Union	0.60 (0.37,0.96)	├●┤	36/60	505	34/69	983	136
BCL2/Q52P: MND	European Union	0.60 (0.38,0.94)	├●┤	38/63	504	36/73	983	136
BCL2/R106H: MND	European Union	0.57 (0.36,0.89)	├*┤	44/65	533	35/70	1005	160
NOTCH/G_A1702P: MND	European Union	0.61 (0.39,0.95)	├●┤	44/72	533	36/74	983	147
NOTCH/I1681N: MND	European	0.63	├●┤	44/72	533	37/75	983	147

Appendix 2, Table 2.12: Time to Next Anti-Lymphoma Therapy by Somatic Mutation and by Covariate, IRC review.

(All Reported Groups are Significant (p <0.05) and at a Frequency of >10%)

Marker: Level	Subgroup	HR (95% CI)	HR (log scale)	R Evt/N	R Median	Vc-R Evt/N	Vc-R Median	Marker: Subgroup N Total
	Union	(0.40,0.97)						
NOTCH/L1586Q: MND	European Union	0.63 (0.40,0.99)	├─●─┤	40/66	505	36/72	983	138
NOTCH/L1597H: MND	European Union	0.63 (0.40,0.99)	├─●─┤	40/66	505	36/72	983	138
NOTCH/L1679P: MND	European Union	0.63 (0.40,0.97)	├─●─┤	44/72	533	37/75	983	147
NOTCH/L1679Q: MND	European Union	0.63 (0.40,0.97)	├─●─┤	44/72	533	37/75	983	147
NOTCH/P25 13L: MND	European Union	0.47 (0.28,0.80)	├──●──┤	39/59	504	22/52	-	159
NOTCH/P25 15FS4: MND	European Union	0.58 (0.38,0.90)	├─●─┤	48/77	533	36/77	1075	155
NOTCH/R1599P: MND	European Union	0.63 (0.40,0.99)	├─●─┤	40/66	505	36/72	983	138
NOTCH/V1579E: MND	European Union	0.63 (0.40,0.99)	├─●─┤	40/66	505	36/72	983	138
NOTCH/X26DEL: MND	European Union	0.64 (0.42,0.99)	├─●─┤	44/72	552	42/84	1005	159
NOTCH/X26INS: MND	European Union	0.63 (0.42,0.96)	├─●─┤	46/74	552	42/84	1005	159
NOTCH/X28DEL: MND	European Union	0.62 (0.41,0.92)	├─●─┤	53/82	533	45/87	983	177
NOTCH/X28INS: MND	European Union	0.61 (0.41,0.90)	├─●─┤	56/85	533	46/89	983	177
BCL2/A43G: MND	<65 years old	0.66 (0.48,0.91)	├●┤	84/124	484	65/115	743	239
BCL2/C.-1 10T: MND	<65 years old	0.70 (0.52,0.94)	├●┤	101/147	484	81/135	718	296
BCL2/E29K: MND	<65 years old	0.60 (0.43,0.85)	├●┤	81/117	450	58/103	751	241
BCL2/P46L: MND	<65 years old	0.69 (0.48,0.97)	├●┤	71/105	485	59/104	743	238

Appendix 2, Table 2.12: Time to Next Anti-Lymphoma Therapy by Somatic Mutation and by Covariate, IRC review.

(All Reported Groups are Significant (p ≤0.05) and at a Frequency of ≥10%)

Marker: Level	Subgroup	HR (95% CI)	HR (log scale)	R Evt/N	R Median	Vc-R Evt/N	Vc-R Median	Marker: Subgroup N Total
BCL2/P46S: MND	<65 years old	0.71 (0.51,0.99)	HH	73/111	489	66/113	726	236
BCL2/P59S: MND	<65 years old	0.71 (0.51,0.99)	|-●-|	74/110	489	68/114	726	235
BCL2/Q52P: MND	<65 years old	0.71 (0.51,0.98)	HH	78/117	485	69/117	726	234
BCL2/R106H: MND	<65 years old	0.61 (0.44,0.84)	HH	86/124	450	61/112	751	281
NOTCH/G _A1702P: MND	<65 years old	0.69 (0.51,0.95)	HH	91/133	462	71/121	719	255
NOTCH/I1681N: MND	<65 years old	0.70 (0.51,0.96)	HH	91/133	462	72/122	719	255
NOTCH/L1679P: MND	<65 years old	0.70 (0.51,0.96)	HH	91/133	462	72/122	719	255
NOTCH/L1679Q: MND	<65 years old	0.70 (0.51,0.96)	HH	91/133	462	72/122	719	255
NOTCH/L2458V: MND	<65 years old	0.71 (0.52,0.98)	HH	82/120	462	70/117	719	237
NOTCH/P25 13L: MND	<65 years old	0.62 (0.43,0.89)	HH	74/107	462	50/90	751	269
NOTCH/P25 15FS4: MND	<65 years old	0.67 (0.49,0.92)	H●-|	92/134	484	70/123	726	259
NOTCH/Q2441X: MND	<65 years old	0.72 (0.52,0.99)	HH	82/120	462	70/115	719	237
NOTCH/Q2460X: MND	<65 years old	0.68 (0.48,0.95)	|-●-|	77/110	449	61/104	719	239
NOTCH/X26DEL: MND	<65 years old	0.70 (0.52,0.95)	HH	92/137	489	76/132	726	273
NOTCH/X26INS: MND	<65 years old	0.70 (0.52,0.95)	HH	93/138	501	77/133	726	273
NOTCH/X28DEL: MND	<65 years old	0.68 (0.51,0.90)	|-●-|	104/149	462	83/140	719	298
NOTCH/X28INS: MND	<65 years old	0.67 (0.50,0.8	HH	106/149	462	85/143	718	298

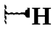
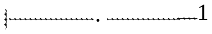
Appendix 2, Table 2.12: Time to Next Anti-Lymphoma Therapy by Somatic Mutation and by Covariate, IRC review.

(All Reported Groups are Significant (p ≤0.05) and at a Frequency of ≥10%)

Marker: Level	Subgroup	HR (95% CI)	HR (log scale)	R Evt/N	R Median	Vc-R Evt/N	Vc-R Median	Marker: Subgroup N Total
		9)						
BCL2/P46L: MND	Female	0.61 (0.39,0.96)	├─●─┤	51/86	535	31/68	1185	180
BCL2/P59S: MND	Female	0.65 (0.43,1.00)	├─●─	57/97	533	36/73	947	178
BCL2/R106H: MND	Female	0.65 (0.42,0.99)	H H	58/96	534	35/70	883	203
BCL2/A43G: MND	Male	0.55 (0.36,0.82)	HH	45/59	343	47/76	743	135
BCL2/C.-110T: MND	Male	0.62 (0.43,0.90)	HH	57/77	380	58/93	651	182
BCL2/E29K: MND	Male	0.51 (0.33,0.77)	H H	43/55	337	43/68	743	138
BCL2/P46L: MD	Male	0.11 (0.02,0.63)	├────────· ────────i	4/4	382	6/10	878	134
BCL2/P46S: MND	Male	0.64 (0.42,0.99)	H H	38/52	396	49/75	695	133
BCL2/Q52P: MND	Male	0.62 (0.41,0.95)	├─●─┤	39/53	396	50/78	695	131
BCL2/R106H: MND	Male	0.61 (0.41,0.90)	├─· ─┤	50/66	396	49/81	695	169
NOTCH/G_A1702P: MND	Male	0.60 (0.40,0.89)	├─●─┤	47/63	337	51/81	726	145
NOTCH/I1681N: MND	Male	0.61 (0.41,0.90)	H H	47/63	337	52/82	695	145
NOTCH/L1586Q: MND	Male	0.65 (0.43,0.98)	├─●─┤	41/56	396	51/79	695	135
NOTCH/L1597H: MND	Male	0.65 (0.43,0.98)	H H	41/56	396	51/79	695	135
NOTCH/L1679P: MND	Male	0.61 (0.41,0.90)	H H	47/63	337	52/82	695	145
NOTCH/L1679Q: MND	Male	0.61 (0.41,0.90)	H H	47/63	337	52/82	695	145
NOTCH/L2458V: MND	Male	0.60	H H	44/59	337	51/80	695	139

Appendix 2, Table 2.12: Time to Next Anti-Lymphoma Therapy by Somatic Mutation and by Covariate, IRC review.

(All Reported Groups are Significant (p ≤0.05) and at a Frequency of ≥10%)

Marker: Level	Subgroup	HR (95% CI)	HR (log scale)	R Evt/N	R Median	Vc-R Evt/N	Vc-R Median	Marker: Subgroup N Total
		(0.40,0.91)						
NOTCH/P25 13L: MND	Male	0.52 (0.33,0.82)		41/54	343	37/63	791	155
NOTCH/P25 15FS4: MND	Male	0.57 (0.38,0.85)		47/62	380	51/84	743	148
NOTCH/Q2441X: MND	Male	0.61 (0.40.0.91)		44/59	337	51/79	695	139
NOTCH/Q2460X: MD	Male	0.14 (0.03,0.71)		3/3	127	8/12	645	142
NOTCH/Q2460X: MND	Male	0.60 (0.39,0.93)		42/57	343	43/70	726	142
NOTCH/R1599P: MND	Male	0.65 (0.43.0.98)		41/56	396	51/79	695	135
NOTCH/V1579E: MND	Male	0.65 (0.43,0.98)		41/56	396	51/79	695	135
NOTCH/X26DEL: MND	Male	0.58 (0.39,0.85)		49/65	396	58/95	726	162
NOTCH/X26INS: MND	Male	0.56 (0.38.0.82)		50/66	396	58/95	743	162
NOTCH/X28DEL: MND	Male	0.63 (0.44,0.91)		56/75	396	61/97	695	180
NOTCH/X28INS: MND	Male	0.62 (0.44,0.89)		59/78	396	63/100	651	181
BCL2/A43G: MND	White	0.67 (0.49,0.91)		89/140	504	76/139	834	279
BCL2/C.-1 10T: MND	White	0.70 (0.53,0.93)		110/168	504	90/158	726	342
BCL2/E29K: MND	White	0.63 (0.46,0.87)		83/129	485	70/127	834	282
BCL2/P46L: MND	White	0.68 (0.49,0.95)		74/117	505	68/125	791	279
BCL2/P46S: MND	White	0.70 (0.51.0.96)		81/130	505	74/13j	834	275

Appendix 2, Table 2.12: Time to Next Anti-Lymphoma Therapy by Somatic Mutation and by Covariate, IRC review.

(All Reported Groups are Significant ($p < 0.05$) and at a Frequency of ≥10%)

Marker: Level	Subgroup	HR (95% CI)	HR (log scale)	R Evt/N	R Median	Vc-R Evt/N	Vc-R Median	Marker: Subgroup N Total
BCL2/P59L: MND	White	0.72 (0.52,0.99)	├●┤	80/129	533	69/123	791	278
BCL2/P59S: MND	White	0.68 (0.50,0.94)	├●┤	81/128	505	73/130	834	274
BCL2/Q52P: MND	White	0.69 (0.50,0.94)	├●┤	85/135	504	77/137	834	272
BCL2/R106H: MND	White	0.68 (0.50,0.92)	├●┤	93/140	501	77/135	743	327
NOTCH/G_A1702P: MND	White	0.72 (0.54,0.97)	├●┤	97/152	504	82/143	743	295
NOTCH/I1681N: MND	White	0.72 (0.54,0.97)	├●┤	97/152	504	82/143	743	295
NOTCH/L1679P: MND	White	0.72 (0.54,0.97)	├●┤	97/152	504	82/143	743	295
NOTCH/L1679Q: MND	White	0.72 (0.54,0.97)	├●┤	97/152	504	82/143	743	295
NOTCH/L2458V: MND	White	0.73 (0.54,0.99)	├●┤	89/140	504	81/139	743	279
NOTCH/P2513L: MND	White	0.67 (0.48,0.94)	├●┤	78/122	504	59/108	841	319
NOTCH/P2515FS4: MND	White	0.68 (0.50,0.91)	├●┤	99/154	505	81/148	834	304
NOTCH/Q2441X: MND	White	0.74 (0.54,1.00)	├●─	88/139	501	81/137	726	279
NOTCH/Q2460X: MND	White	0.70 (0.51,0.96)	├●┤	85/131	501	73/127	743	284
NOTCH/X26DEL: MND	White	0.73 (0.55,0.97)	├●┤	99/155	505	91/158	751	321
NOTCH/X26INS: MND	White	0.72 (0.54,0.96)	├●┤	101/159	533	92/160	751	321
NOTCH/X28DEL: MND	White	0.73 (0.55,0.95)	├●┤	111/169	504	98/167	726	351
NOTCH/X28INS: MND	White	0.70 (0.53,0.9	├●┤	115/174	504	99/171	743	352

Appendix 2, Table 2.12: Time to Next Anti-Lymphoma Therapy by Somatic Mutation and by Covariate, IRC review.

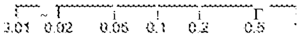
(All Reported Groups are Significant (p ≤0.05) and at a Frequency of ≥10%)

Marker: Level	Subgroup	HR (95% CI)	HR (log scale)	R Evt/N	R Median	Vc-R Evt/N	Vc-R Median	Marker: Subgroup N Total
		2)						
BCL2/A43G: MND	Ann Arbor Stage IV	0.60 (0.40,0.91)	├─●─┤	48/71	450	42/83	658	154
BCL2/C.-1 10T: MND	Ann Arbor Stage IV	0.64 (0.44,0.93)	├─●─┤	60/84	450	54/10 Q	639	193
BCL2/E29K: MND	Ann Arbor Stage IV	0.59 (0.38,0.91)	├─●- i	46/67	450	37/73	651	154
BCL2/P46L: MND	Ann Arbor Stage IV	0.62 (0.39,0.99)	├─*─┤	35/52	449	38/74	651	148
BCL2/P59L: MD	Ann Arbor Stage IV	0.17 (0.03,0.88)	├──────●──────┤	3/5	182	8/12	725	149
BCL2/R106H: MND	Ann Arbor Stage IV	0.59 (0.39,0.89)	├─●─┤	50/72	449	42/83	651	186
NOTCH/G _A1702P: MND	Ann Arbor Stage IV	0.61 (0.41,0.90)	├─●─┤	52/75	428	47/87	649	163
NOTCH/I1681N: MND	Ann Arbor Stage IV	0.62 (0.42,0.92)	├─●─┤	52/75	428	48/88	649	163
NOTCH/L1679P: MND	Ann Arbor Stage IV	0.62 (0.42,0.92)	├─●─i	52/75	428	48/88	649	163
NOTCH/L1679Q: MND	Ann Arbor Stage IV	0.62 (0.42,0.92)	├─●─┤	52/75	428	48/88	649	163
NOTCH/L2458V: MND	Ann Arbor Stage IV	0.63 (0.42,0.95)	├─●─┤	46/68	434	46/86	651	154
NOTCH/P25 13L: MND	Ann Arbor Stage IV	0.55 (0.35,0.87)	├─●─┤	42/61	449	34/69	791	176
NOTCH/P25 15FS4: MND	Ann Arbor Stage IV	0.59 (0.39,0.87)	├─●─┤	51/74	434	46/91	658	167
NOTCH/Q2441X: MND	Ann Arbor Stage IV	0.63 (0.42,0.95)	├─●─┤	46/68	434	46/85	651	154
NOTCH/Q2460X: MND	Ann Arbor Stage IV	0.61 (0.39,0.93)	├─●─┤	43/64	449	41/79	658	156
NOTCH/X26DEL: MND	Ann Arbor Stage IV	0.63 (0.43,0.93)	├─●─┤	53/76	457	54/10 1	65 1	180
NOTCH/X26INS: MND	Ann	0.63	├─●─┤	54/79	450	54/10	651	180

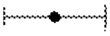
Appendix 2, Table 2.12: Time to Next Anti-Lymphoma Therapy by Somatic Mutation and by Covariate, IRC review.

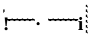
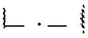
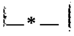
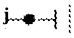
(All Reported Groups are Significant (p ≤0.05) and at a Frequency of ≥10%)

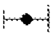
Marker: Level	Subgroup	HR (95% CI)	HR (log scale)	R Evt/N	R Median	Vc-R Evt/N	Vc-R Median	Marker: Subgroup N Total
	Arbor Stage IV	(0.43,0.91)				1		
NOTCH/X28DEL: MND	Ann Arbor Stage IV	0.63 (0.44,0.91)		61/85	449	56/103	644	195
NOTCH/X28INS: MND	Ann Arbor Stage IV	0.60 (0.42,0.86)		64/87	434	57/105	644	196



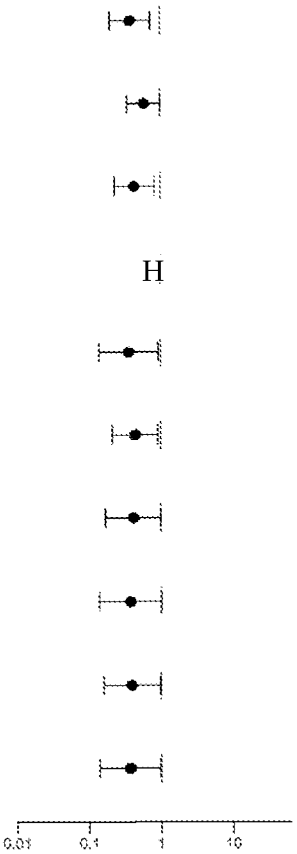
Appendix 2, Table 2.13: Treatment Free Interval by Protein Expression and by Covariate, IRC Review. (All Reported Groups are Significant (p ≤0.05) and at a Frequency of ≥10%)

Marker: Level	Subgroup	HR (95% CI)	HR (log scale)	R Evt/N	R Median	Vc-R Evt/N	Vc-R Median	Marker: Subgroup N Total
CD68 OVERALL POSITIVE: 0-25	No Subgroup	0.42 (0.23,0.75)		30/44	269	19/41	883	442
CD68 POSITIVE FOLLICULAR: 0-25	No Subgroup	0.56 (0.34,0.90)		40/60	307	29/51	671	387
CD68 POSITIVE PERIFOLLICULAR: 0-25	No Subgroup	0.49 (0.27,0.89)		26/39	234	20/41	924	384
P65 % POSITIVE CYTOPLASMIC SIGNAL: >90%	No Subgroup	0.77 (0.60,1.00)		129/204	363	108/li 6	581	470
CD68 POSITIVE PERIFOLLICULAR: >75	1 Prior Line of Therapy	0.45 (0.20,1.01)		15/18	297	10/16	587	174
P27 % NUCLEI POSITIVE: 0-20	1 Prior Line of Therapy	0.40 (0.16,1.01)		19/26	293	6/16	883	204
P65 % NUCLEAR STAINING: 0	1 Prior Line of Therapy	0.66 (0.43,0.99)		54/79	406	39/73	673	203
P65 % POSITIVE CYTOPLASMIC SIGNAL: >90%	1 Prior Line of Therapy	0.63 (0.43,0.93)		59/89	409	47/88	673	203
P65 INTENSITY CYTOPLASMIC SIGNAL: >2+	1 Prior Line of Therapy	0.66 (0.45,0.98)		54/85	427	47/91	673	203
CD68 OVERALL POSITIVE: 0-25	2 Prior Lines of Therapy	0.20 (0.04,1.02)		6/8	80	2/7	844	111
CD68 POSITIVE PERIFOLLICULAR: 0-25	2 Prior Lines of Therapy	0.09 (0.01,0.81)		6/8	64	1/7	-	98
P65 % NUCLEAR STAINING: <5%	2 Prior Lines of Therapy	0.32 (0.11,0.96)		7/9	85	7/12	542	125
P27 % NUCLEI POSITIVE: 60-70	3 Prior Lines of Therapy	8.31 (0.95,72.50)		1/6	-	5/5	65	74
P27 SIGNAL INTENSITY: >2+	5 Prior Lines of Therapy	0.22 (0.04,1.13)		5/6	88	3/8	778	16
P65 % NUCLEAR STAINING: <5%	5 Prior Lines of Therapy	0.13 (0.01,1.34)		3/3	95	2/4	1058	16
CD68 OVERALL POSITIVE: 0-25	No High Tumor Burden	0.23 (0.07,0.80)		8/14	411	5/19	-	204
CD68 OVERALL POSITIVE: 51-75	No High Tumor Burden	2.33 (1.00,5.41)		10/25	-	12/18	349	204

CD68 POSITIVE FOLLICULAR: 0-25	No High Tumor Burden	0.40 (0.18,0.91)		14/22	432	12/25	1058	182
CD68 POSITIVE PERIFOLLICULAR: 0-25	No High Tumor Burden	0.23 (0.07,0.78)		8/13	361	5/16	1058	182
P27 % NUCLEI POSITIVE: 30-50	High Tumor Burden	0.49 (0.24,1.01)		17/22	280	13/25	483	248
P27 SIGNAL INTENSITY: ≤1+	High Tumor Burden	0.45 (0.20,1.00)		16/18	122	11/17	818	248
CD68 OVERALL POSITIVE: 0-25	Intermediate FLIPI Score	0.27 (0.08,0.98)		7/11	343	5/15	1058	159
CD68 POSITIVE PERIFOLLICULAR: 0-25	Intermediate FLIPI Score	0.27 (0.08,0.95)		7/13	361	5/17	1058	139
CD68 OVERALL POSITIVE: 0-25	Low FLIPI Score	0.32 (0.10,1.01)		8/10	281	5/11	907	102
CD68 OVERALL POSITIVE: 0-25	No Prior Rituximab Therapy	0.38 (0.15,0.99)		12/19	393	7/21	942	241
CD68 POSITIVE FOLLICULAR: 0-25	No Prior Rituximab Therapy	0.41 (0.19,0.87)		23/36	344	10/25	942	210
CD68 POSITIVE PERIFOLLICULAR: 0-25	No Prior Rituximab Therapy	0.33 (0.12,0.97)		12/18	393	5/15	-	208
20S % NUCLEAR STAINING: 60-70	Prior Rituximab Therapy	0.40 (0.16,1.02)		17/21	190	6/12	907	212
CD68 OVERALL POSITIVE: 0-25	Prior Rituximab Therapy	0.42 (0.20,0.90)		18/25	115	12/20	671	201
P27 SIGNAL INTENSITY: >2+	Prior Rituximab Therapy	0.67 (0.46,0.98)		60/88	272	48/85	554	210
P65 % NUCLEAR STAINING: <5%	Prior Rituximab Therapy	0.31 (0.14,0.67)		16/21	93	13/27	818	215
CD68 OVERALL POSITIVE: 0-25	> 1 year since last anti-lymphoma treatment	0.27 (0.12,0.63)		17/26	269	9/28	1058	269
CD68 POSITIVE FOLLICULAR: 0-25	> 1 year since last anti-lymphoma treatment	0.50 (0.26,0.97)		22/34	409	16/33	907	235
CD68 POSITIVE PERIFOLLICULAR: 0-25	> 1 year since last anti-lymphoma treatment	0.42 (0.19,0.92)		15/24	393	11/27	1058	234

20S INTENSITY CYTOPLASMIC SIGNAL: >3+	European Union	0.59 (0.35,0.99)		34/52	393	25/52	907	214
CD68 OVERALL POSITIVE: 0-25	European Union	0.41 (0.18,0.92)		14/22	234	11/25	942	211
CD68 POSITIVE PERIFOLLICULAR: >75	European Union	0.37 (0.14,1.00)		13/17	533	7/14	1023	185
CD68 OVERALL POSITIVE: 0-25	<65 years old	0.39 (0.20,0.76)		24/34	234	15/32	844	329
CD68 POSITIVE FOLLICULAR: 0-25	<65 years old	0.46 (0.27,0.78)		33/46	190	24/41	603	292
CD68 POSITIVE PERIFOLLICULAR: 0-25	<65 years old	0.50 (0.24,1.01)		20/31	143	13/29	907	289
CD68 POSITIVE PERIFOLLICULAR: >75	<65 years old	0.46 (0.22,0.94)		19/23	297	13/23	587	289
P27 % NUCLEI POSITIVE: 0-20	<65 years old	0.53 (0.29,0.97)		26/34	187	19/32	671	344
P65 % NUCLEAR STAINING: <5%	<65 years old	0.54 (0.29,1.00)		19/29	234	22/43	818	349
P65 % POSITIVE CYTOPLASMIC SIGNAL: >90%	<65 years old	0.73 (0.55,0.97)		103/154	343	84/142	557	349
P65 INTENSITY CYTOPLASMIC SIGNAL: >2+	<65 years old	0.74 (0.55,0.99)		101/152	343	82/139	554	349
20S % NUCLEAR STAINING: 0-20	Female	0.55 (0.32,0.97)		35/61	427	19/49	-	259
CD68 OVERALL POSITIVE: 0-25	Female	0.28 (0.10,0.76)		16/26	293	5/18	942	242
CD68 POSITIVE FOLLICULAR: 0-25	Female	0.46 (0.22,0.96)		23/37	307	10/22	942	217
CD68 POSITIVE PERIFOLLICULAR: 0-25	Female	0.28 (0.10,0.77)		19/28	234	5/17	942	215
20S % NUCLEAR STAINING: 60-70	Male	0.43 (0.20,0.95)		14/16	110	12/20	390	204
CD68 OVERALL POSITIVE: >75	Male	0.25 (0.07,0.87)		8/9	272	4/11	-	200
CD68 POSITIVE FOLLICULAR: 0-25	Asian	0.13 (0.02,1.17)		5/6	148	2/6	-	30
CD68 POSITIVE PERIFOLLICULAR: 26-50	Other	0.14 (0.01,1.31)		4/4	217	4/5	495	22

CD68 OVERALL POSITIVE: 0-25	White	0.38 (0.20,0.73)	24/35	269	16/35	907	385
CD68 POSITIVE FOLLICULAR: 0-25	White	0.59 (0.35,1 .00)	32/48	307	25/42	671	335
CD68 POSITIVE PERIFOLLICULAR: 0-25	White	0.43 (0.23,0.83)	19/27	361	19/39	924	332
P65 % POSITIVE CYTOPLASMIC SIGNAL: >90%	White	0.76 (0.58,1 .00)	113/179	363	95/162	587	406
CD68 OVERALL POSITIVE: 0-25	Ann Arbor Stage III	0.36 (0.14.0.92)	12/16	135	9/12	745	144
CD68 POSITIVE FOLLICULAR: 0-25	Ann Arbor Stage III	0.44 (0.21,0.90)	19/24	190	13/18	603	135
P27 % NUCLEI POSITIVE: 0-20	Ann Arbor Stage III	0.42 (0.17, 1.00)	14/16	275	12/15	449	149
P65 INTENSITY CYTOPLASMIC SIGNAL: ≤ 1+	Ann Arbor Stage III	0.38 (0.14,1 .02)	10/1 1	119	7/1 1	671	151
CD68 OVERALL POSITIVE: 0-25	Ann Arbor Stage IV	0.39 (0.16,0.97)	15/22	293	8/23	883	222
CD68 POSITIVE PERIFOLLICULAR: 0-25	Aim Arbor Stage **rV**	0.37 (0.14,0.96)	11/15	234	8/22	924	183



Appendix 2, Table 2.14: Treatment Free Interval by Germline Genetic Variant and by Covariate, IRC Review. (All Reported Groups are Significant (p ≤0.05) and at a Frequency of ≥10%)

Marker: Level	Subgroup	HR (95% CI)	HR (log scale)	R Evt/N	R Median	Vc-R Evt/N	Vc-R Median	Marker: Subgroup N Total
PSMB1/A171S: G/G	No Subgroup	0.80 (0.65, 1.00)		173/276	406	152/266	581	542
PSMB1/I208N: T/T	No Subgroup	0.80 (0.65,1.00)		173/276	406	152/266	581	542
PSMB1/P11A: C/G	No Subgroup	0.69 (0.50,0.97)		78/127	409	63/115	778	542
PSMB1/P193L: C/C	No Subgroup	0.80 (0.65,1.00)		173/276	406	152/266	581	542
PSMB2/E49X: G/G	No Subgroup	0.80 (0.65,1.00)		173/276	406	152/266	581	542
PSMB2/G187V: G/G	No Subgroup	0.80 (0.65,1.00)		173/276	406	152/266	581	542
PSMB2/L159F: C/C	No Subgroup	0.80 (0.65,1.00)		173/276	406	152/266	581	542
PSMB5/L206M: C/C	No Subgroup	0.80 (0.65,1.00)		173/276	406	152/266	581	542
PSMB6/A234D: C/C	No Subgroup	0.80 (0.65,1.00)		173/276	406	152/266	581	542
PSMB8/G8R: G/G	No Subgroup	0.79 (0.63,0.99)		165/264	396	144/256	581	542
PSMB8/R141C: C/C	No Subgroup	0.80 (0.65,1.00)		173/276	406	152/266	581	542
PSMB8/V182M: G/G	No Subgroup	0.80 (0.65,1.00)		173/276	406	152/266	581	542
PSMB1/P11A: C/G	1 Prior Line of Therapy	0.58 (0.35,0.97)		32/51	480	27/55	883	231
PSMB1/P11A: G/G	1 Prior Line of Therapy	0.37 (0.14,0.98)		11/11	302	7/14	522	231
PSMB8/G8R: G/G	1 Prior Line of Therapy	0.70 (0.49,0.99)		69/109	533	55/111	690	231
PSMB1/A171S: G/G	5 Prior Lines of Therapy	0.29 (0.08,1.01)		7/9	95	6/12	778	21
PSMB1/I208N: T/T	5 Prior Lines of Therapy	0.29 (0.08, 1.01)		7/9	95	6/12	778	21

Appendix 2, Table 2.14: Treatment Free Interval by Germline Genetic Variant and by Covariate, IRC Review. (All Reported Groups are Significant (p ≤0.05) and at a Frequency of ≥10%)

Marker: Level	Subgroup	HR (95% CI)	HR (log scale)	R Evt/N	R Median	Vc-R Evt/N	Vc-R Median	Marker: Subgroup N Total
PSMB1/P193L: C/C	5 Prior Lines of Therapy	0.29 (0.08,1.01)		7/9	95	6/12	778	21
PSMB2/E49X: G/G	5 Prior Lines of Therapy	0.29 (0.08,1.01)		7/9	95	6/12	778	21
PSMB2/G187V: G/G	5 Prior Lines of Therapy	0.29 (0.08,1.01)		7/9	95	6/12	778	21
PSMB2/L159F: C/C	5 Prior Lines of Therapy	0.29 (0.08,1.01)		7/9	95	6/12	778	21
PSMB5/L206M: C/C	5 Prior Lines of Therapy	0.29 (0.08,1.01)		7/9	95	6/12	778	21
PSMB5/R24C: C/C	5 Prior Lines of Therapy	0.17 (0.03,0.86)		6/7	95	4/9	1058	21
PSMB6/A234D: C/C	5 Prior Lines of Therapy	0.29 (0.08,1.01)		7/9	95	6/12	778	21
PSMB6/P107A: C/C	5 Prior Lines of Therapy	0.29 (0.08,1.01)		7/9	95	6/12	778	21
PSMB8/G8R: G/G	5 Prior Lines of Therapy	0.29 (0.08,1.01)		7/9	95	6/11	778	21
PSMB8/R141C: C/C	5 Prior Lines of Therapy	0.29 (0.08,1.01)		7/9	95	6/12	778	21
PSMB8/V182M: G/G	5 Prior Lines of Therapy	0.29 (0.08,1.01)		7/9	95	6/12	778	21
PSMB9/G9E: G/G	5 Prior Lines of Therapy	0.29 (0.08,1.01)		7/9	95	6/12	778	21
PSMB9/V32I: C/C	5 Prior Lines of Therapy	0.25 (0.07,0.87)		7/8	88	5/11	1058	21
PSMB1/A171S: G/G	High Tumor Burden	0.75 (0.57,0.99)		108/147	234	98/149	366	296
PSMB1/I208N: T/T	High Tumor Burden	0.75 (0.57,0.99)	N	108/147	234	98/149	366	296
PSMB1/P11A: C/G	High Tumor Burden	0.65 (0.42,1.00)		49/72	218	38/65	499	296
PSMB1/P193L: C/C	High Tumor Burden	0.75 (0.57,0.99)		108/147	234	98/149	366	296

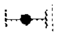
Appendix 2, Table 2.14: Treatment Free Interval by Germline Genetic Variant and by Covariate, IRC Review. (All Reported Groups are Significant (p ≤0.05) and at a Frequency of ≥10%)

Marker: Level	Subgroup	HR (95% CI)	HR (log scale)	R Evt/N	R Median	Vc-R Evt/N	Vc-R Median	Marker: Subgroup N Total
PSMB2/E49X: G/G	High Tumor Burden	0.75 (0.57,0.99)		108/147	234	98/149	366	296
PSMB2/G187V: G/G	High Tumor Burden	0.75 (0.57,0.99)		108/147	234	98/149	366	296
PSMB2/L159F: C/C	High Tumor Burden	0.75 (0.57,0.99)		108/147	234	98/149	366	296
PSMB5/L206M: C/C	High Tumor Burden	0.75 (0.57,0.99)		108/147	234	98/149	366	296
PSMB5/R24C: C/T	High Tumor Burden	0.48 (0.25,0.93)		19/21	148	18/24	391	296
PSMB6/A234D: C/C	High Tumor Burden	0.75 (0.57,0.99)		108/147	234	98/149	366	296
PSMB6/P107A: C/C	High Tumor Burden	0.76 (0.57,1.00)		104/140	234	97/146	365	296
PSMB8/G8R: G/G	High Tumor Burden	0.71 (0.54,0.94)		104/140	218	94/145	390	296
PSMB8/R141C: C/C	High Tumor Burden	0.75 (0.57,0.99)		108/147	234	98/149	366	296
PSMB8/V182M: G/G	High Tumor Burden	0.75 (0.57,0.99)		108/147	234	98/149	366	296
PSMB9/G9E: G/G	High Tumor Burden	0.75 (0.57,0.99)		107/145	234	98/148	365	296
PSMB9/V32I: C/C	High Tumor Burden	0.74 (0.56,0.98)		106/142	234	94/142	366	296
PSMB1/A171S: G/G	> 1 year since last anti-lymphoma treatment	0.71 (0.53,0.95)		98/165	547	80/166	800	331
PSMB1/I208N: T/T	> 1 year since last anti-lymphoma treatment	0.71 (0.53,0.95)		98/165	547	80/166	800	331
PSMB1/P193L: C/C	> 1 year since last anti-	0.71 (0.53,0.95)		98/165	547	80/166	800	331

Appendix 2, Table 2.14: Treatment Free Interval by Germline Genetic Variant and by Covariate, IRC Review. (All Reported Groups are Significant (p ≤0.05) and at a Frequency of >10%)

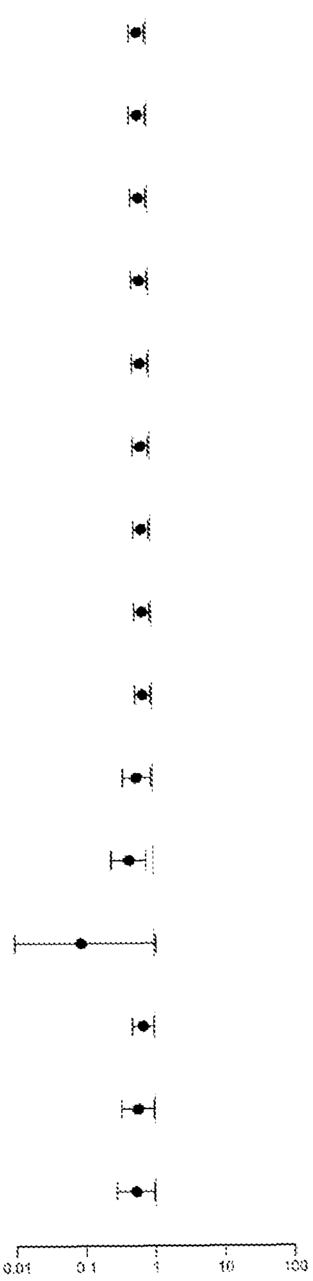
Marker: Level	Subgroup	HR (95% CI)	HR (log scale)	R Evt/N	R Median	Vc-R Evt/N	Vc-R Median	Marker: Subgroup N Total
	lymphoma treatment							
PSMB2/E49X: G/G	> 1 year since last anti-lymphoma treatment	0.71 (0.53,0.95)		98/165	547	80/166	800	331
PSMB2/G187V: G/G	> 1 year since last anti-lymphoma treatment	0.71 (0.53,0.95)		98/165	547	80/166	800	331
PSMB2/L159F: C/C	> 1 year since last anti-lymphoma treatment	0.71 (0.53,0.95)		98/165	547	80/166	800	331
PSMB5/L206M: C/C	> 1 year since last anti-lymphoma treatment	0.71 (0.53,0.95)		98/165	547	80/166	800	331
PSMB5/R24C: C/C	> 1 year since last anti-lymphoma treatment	0.72 (0.52.1 .00)		81/137	507	68/141	843	331
PSMB6/A234D: C/C	> 1 year since last anti-lymphoma treatment	0.71 (0.53,0.95)		98/165	547	80/166	800	331
PSMB6/P107A: C/C	> 1 year since last anti-lymphoma treatment	0.72 (0.53,0.97)		95/159	561	79/162	800	331
PSMB8/G8R: G/G	> 1 year since last anti-lymphoma treatment	0.71 (0.52.0.96)	N	91/155	562	74/159	843	331

Appendix 2, Table 2.14: Treatment Free Interval by Germline Genetic Variant and by Covariate, IRC Review. (All Reported Groups are Significant (p ≤0.05) and at a Frequency of ≥10%)

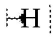
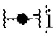
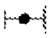
Marker: Level	Subgroup	HR (95% CD	HR (log scale)	R Evt/N	R Median	Vc-R Evt/N	Vc-R Median	Marker: Subgroup N Total
PSMB8/R141C : C/C	> 1 year since last anti-lymphoma treatment	0.71 (0.53,0.95)		98/165	547	80/166	800	331
PSMB8/V182 M: G/G	> 1 year since last anti-lymphoma treatment	0.71 (0.53,0.95)		98/165	547	80/166	800	331
PSMB9/G9E: G/G	> 1 year since last anti-lymphoma treatment	0.71 (0.53,0.96)		97/163	547	80/165	800	331
PSMB9/V32I: C/C	> 1 year since last anti-lymphoma treatment	0.70 (0.51,0.94)		96/160	507	76/158	800	331
PSMB1/P1 1A: C/G	European Union	0.56 (0.34,0.93)		34/49	309	29/51	844	241
PSMB 1/A171S : G/G	<65 years old	0.74 (0.57,0.95)		130/198	344	112/194	557	392
PSMB 1/I208N: T/T	<65 years old	0.74 (0.57,0.95)		130/198	344	112/194	557	392
PSMB 1/P1 1A: C/G	<65 years old	0.63 (0.43,0.92)		63/96	406	47/86	603	392
PSMB 1/P1 1A: G/G	<65 years old	0.42 (0.22,0.81)		21/25	269	16/30	671	392
PSMB 1/P193L : C/C	<65 years old	0.74 (0.57,0.95)		130/198	344	112/194	557	392
PSMB2/E49X: G/G	<65 years old	0.74 (0.57,0.95)		130/198	344	112/194	557	392
PSMB2/G187 V: G/G	<65 years old	0.74 (0.57,0.95)		130/198	344	112/194	557	392
PSMB2/L159F : C/C	<65 years old	0.74 (0.57,0.95)		130/198	344	112/194	557	392

Appendix 2, Table 2.14: Treatment Free Interval by Germline Genetic Variant and by Covariate, IRC Review. (All Reported Groups are Significant (p <0.05) and at a Frequency of ≥10%)

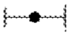
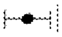
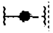
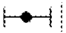
Marker: Level	Subgroup	HR (95% CI)	HR (log scale)	R Evt/N	R Median	Vc-R Evt/N	Vc-R Median	Marker: Subgroup N Total
PSMB5/L206M: C/C	<65 years old	0.74 (0.57,0.95)		130/198	344	112/194	557	392
PSMB5/R24C: C/C	<65 years old	0.73 (0.56,0.96)		113/170	344	97/167	581	392
PSMB6/A234D: C/C	<65 years old	0.74 (0.57,0.95)		130/198	344	112/194	557	392
PSMB6/P107A: C/C	<65 years old	0.74 (0.57,0.96)		125/189	363	110/190	554	392
PSMB8/G8R: G/G	<65 years old	0.74 (0.57,0.96)		123/189	344	106/186	581	392
PSMB8/R141C: C/C	<65 years old	0.74 (0.57,0.95)		130/198	344	112/194	557	392
PSMB8/V182M: G/G	<65 years old	0.74 (0.57,0.95)		130/198	344	112/194	557	392
PSMB9/G9E: G/G	<65 years old	0.74 (0.57,0.95)		129/196	344	112/193	557	392
PSMB9/V32I: C/C	<65 years old	0.74 (0.57,0.96)		127/192	344	107/186	554	392
PSMB1/P1 1A: C/G	Female	0.59 (0.37,0.95)		42/75	406	30/66	924	301
PSMB9/R60H: A G	Male	0.45 (0.25,0.79)		22/28	234	30/48	603	241
PSMB 1/P1 1A: C/G	Other	0.09 (0.01,1.06)		2/3	76	6/9	394	27
PSMB1/P1 1A: C/G	White	0.69 (0.48,0.99)		67/1 11	432	54/97	818	473
PSMB1/P1 1A: G/G	White	0.57 (0.33,0.98)		27/32	272	25/39	449	473
PSMB1/P1 1A: C/G	Ann Arbor Stage III	0.53 (0.28,0.98)		29/44	206	16/28	818	172



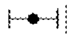
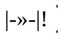
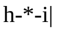
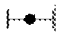
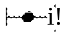
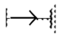
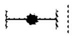
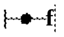
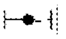
Appendix 2, Table 2.15: Treatment-Free Interval by Somatic Mutation and by Covariate, IRC Review. (All Reported Groups are Significant (p ≤0.05) and at a Frequency of ≥10%)

Marker: Level	Subgroup	HR (95% CI)	HR (log scale)	R Evt/N	R Median	Vc-R Evt/N	Vc-R Median	Marker: Subgroup N Total
BCL2/A43G: MND	No Subgroup	0.67 (0.50,0.90)		104/161	344	84/154	649	315
BCL2/C.-110T: MND	No Subgroup	0.72 (0.56,0.94)		127/192	361	102/179	587	390
BCL2/E29K: MND	No Subgroup	0.65 (0.48,0.87)		98/150	343	77/139	649	318
BCL2/P46L: MND	No Subgroup	0.72 (0.53,0.98)		86/135	362	77/139	595	314
BCL2/P59S: MND	No Subgroup	0.73 (0.54,0.99)		92/145	362	84/147	629	309
BCL2/Q52P: MND	No Subgroup	0.73 (0.55,0.97)		97/153	361	88/154	629	307
BCL2/R106H: MND	No Subgroup	0.68 (0.51,0.90)		108/162	344	84/151	629	372
NOTCH/G_A1702P: MND	No Subgroup	0.74 (0.57,0.98)		113/175	361	93/161	589	337
NOTCH/I1681N: MND	No Subgroup	0.75 (0.57,0.99)		113/175	361	94/162	587	337
NOTCH/L1679P: MND	No Subgroup	0.75 (0.57,0.99)		113/175	361	94/162	587	337
NOTCH/L1679Q: MND	No Subgroup	0.75 (0.57,0.99)		113/175	361	94/162	587	337
NOTCH/P2513L: MND	No Subgroup	0.71 (0.52,0.97)		90/140	360	67/123	649	361
NOTCH/P2515FS4: MND	No Subgroup	0.71 (0.54,0.94)		114/176	361	92/166	629	344
NOTCH/Q2460X: MND	No Subgroup	0.74 (0.55,0.99)		98/151	344	82/143	589	324
NOTCH/X26DEL: MND	No Subgroup	0.76 (0.58,0.99)		112/175	363	102/178	595	361
NOTCH/X26INS: MND	No Subgroup	0.75 (0.58,0.99)		114/179	363	103/180	595	361
NOTCH/X28DEL: MND	No Subgroup	0.74 (0.57,0.96)		128/194	361	109/li[illegible]9	583	400

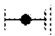
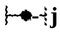
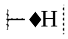
Appendix 2, Table 2.15: Treatment-Free Interval by Somatic Mutation and by Covariate, IRC Review. (All Reported Groups are Significant (p ≤0.05) and at a Frequency of ≥10%)

Marker: Level	Subgroup	HR (95% CI)	HR (log scale)	R Evt/N	R Median	Vc-R Evt/N	Vc-R Median	Marker: Subgroup N Total
NOTCH/X28INS: MND	No Subgroup	0.72 (0.56,0.93)		132/198	361	112/195	583	401
BCL2/A43G: MND	1 Prior Line of Therapy	0.55 (0.35,0.88)		46/72	409	30/67	907	139
BCL2/C.-1 10T: MND	1 Prior Line of Therapy	0.63 (0.42,0.95)		57/86	427	38/78	827	170
BCL2/E29K: MND	1 Prior Line of Therapy	0.56 (0.34,0.90)		41/64	406	29/62	828	139
BCL2/P46L: MND	1 Prior Line of Therapy	0.61 (0.38, 1.00)		37/58	449	30/63	828	140
BCL2/P46S: MND	1 Prior Line of Therapy	0.62 (0.39,0.99)		40/64	409	33/68	828	138
BCL2/Q52P: MND	1 Prior Line of Therapy	0.63 (0.40,0.99)		42/67	409	35/71	827	138
BCL2/R106H: MND	1 Prior Line of Therapy	0.59 (0.38,0.92)		49/73	409	33/68	828	162
NOTCH/P2 5 15FS 4: MND	1 Prior Line of Therapy	0.64 (0.41,0.99)		48/75	432	35/72	827	149
NOTCH/X28INS: MND	1 Prior Line of Therapy	0.65 (0.44,0.96)		56/84	427	45/88	673	178
BCL2/A43G: MND	No High Tumor Burden	0.61 (0.38, 1.00)		42/78	632	27/64	-	142
BCL2/R106H: MND	No High Tumor Burden	0.61 (0.38,0.99)		46/79	549	26/58	1023	163
NOTCH/P25 13L: MD	No High Tumor Burden	0.45 (0.20, 1.01)		17/26	452	9/21	-	163
NOTCH/X28INS: MND	No High Tumor Burden	0.64 (0.42,0.98)		55/98	592	37/82	924	184
BCL2/A43G: MND	High Tumor Burden	0.62 (0.43,0.89)		62/83	234	57/90	379	173
BCL2/C.-1 10T: MND	High Tumor Burden	0.68 (0.49,0.94)		76/101	234	69/107	326	217
BCL2/E29K: MND	High Tumor Burden	0.57 (0.40,0.84)		60/79	234	52/82	392	174

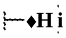
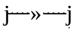
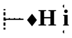
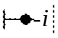
Appendix 2, Table 2.15: Treatment-Free Interval by Somatic Mutation and by Covariate, IRC Review.
(All Reported Groups are Significant (p ≤0.05) and at a Frequency of ≥10%)

Marker: Level	Subgroup	HR (95% CI)	HR (log scale)	R Evt/N	R Median	Vc-R Evt/N	Vc-R Median	Marker: Subgroup N Total
BCL2/P46L: MND	High Tumor Burden	0.59 (0.40,0.87)		51/67	234	51/83	379	173
BCL2/P46S: MND	High Tumor Burden	0.64 (0.44,0.94)		52/73	234	56/89	337	170
BCL2/P59L: MND	High Tumor Burden	0.67 (0.45,0.99)		52/72	254	50/80	318	172
BCL2/P59S: MND	High Tumor Burden	0.63 (0.43,0.93)		53/73	254	54/87	379	170
BCL2/Q52P: MND	High Tumor Burden	0.63 (0.44,0.92)		55/76	234	58/92	379	168
BCL2/R106H: MND	High Tumor Burden	0.61 (0.43,0.88)		62/83	234	58/93	392	209
NOTCH/G_A1702P: MND	High Tumor Burden	0.64 (0.45,0.91)		67/90	234	62/96	379	187
NOTCH/I1681N: MND	High Tumor Burden	0.65 (0.46,0.92)		67/90	234	63/97	379	187
NOTCH/L1586Q: MND	High Tumor Burden	0.67 (0.47,0.97)		56/78	254	60/94	379	172
NOTCH/L1597H: MND	High Tumor Burden	0.67 (0.47,0.97)		56/78	254	60/94	379	172
NOTCH/L1679P: MND	High Tumor Burden	0.65 (0.46,0.92)		67/90	234	63/97	379	187
NOTCH/L1679Q: MND	High Tumor Burden	0.65 (0.46,0.92)		67/90	234	63/97	379	187
NOTCH/L2458V: MND	High Tumor Burden	0.66 (0.46,0.94)		61/83	234	61/95	379	178
NOTCH/P2513L: MND	High Tumor Burden	0.56 (0.37,0.83)		58/76	234	43/71	392	198
NOTCH/P2515FS4: MND	High Tumor Burden	0.63 (0.45,0.90)		67/90	234	61/98	379	189
NOTCH/Q2441X: MND	High Tumor Burden	0.66 (0.46,0.94)		61/83	234	61/95	379	178
NOTCH/Q2460X: MND	High Tumor Burden	0.63 (0.43,0.91)		59/79	234	54/87	392	181

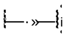
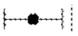
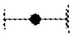
Appendix 2, Table 2.15: Treatment-Free Interval by Somatic Mutation and by Covariate, IRC Review. (All Reported Groups are Significant (p ≤0.05) and at a Frequency of ≥10%)

Marker: Level	Subgroup	HR (95% CI)	HR (log scale)	R Evt/N	R Median	Vc-R Evt/N	Vc-R Median	Marker: Subgroup N Total
NOTCH/R1599P: MND	High Tumor Burden	0.67 (0.47,0.97)		56/78	254	60/94	379	172
NOTCH/V1579E: MND	High Tumor Burden	0.67 (0.47,0.97)		56/78	254	60/94	379	172
NOTCH/X26DEL : MND	High Tumor Burden	0.69 (0.49,0.98)		63/88	254	68/107	379	198
NOTCH/X26INS: MND	High Tumor Burden	0.68 (0.49,0.96)		64/89	254	68/107	379	198
NOTCH/X28DEL : MND	High Tumor Burden	0.67 (0.48,0.92)		74/99	234	72/111	326	216
NOTCH/X28INS: MND	High Tumor Burden	0.67 (0.49,0.92)		77/100	190	75/113	318	217
BCL2/A43G: MND	Intermediate FLIPI Score	0.60 (0.36, 1.00)		34/53	362	26/52	778	105
BCL2/C.-1 10T: MND	Intermediate FLIPI Score	0.60 (0.38,0.95)		44/66	362	33/63	778	136
BCL2/R106H: MND	Intermediate FLIPI Score	0.52 (0.32,0.84)		40/55	361	28/54	671	130
BCL2/E29K: MND	No Prior Rituximab Therapy	0.66 (0.44,0.98)		57/93	393	41/76	718	186
BCL2/P59L: MD	No Prior Rituximab Therapy	0.17 (0.03,0.91)		3/5	217	7/13	779	178
BCL2/A43G: MND	Prior Rituximab Therapy	0.62 (0.40,0.96)		44/63	287	37/69	589	132
BCL2/C.-1 10T: MND	Prior Rituximab Therapy	0.60 (0.40,0.89)		57/78	254	43/77	554	165
BCL2/E29K: MND	Prior Rituximab Therapy	0.62 (0.39,0.97)		41/57	287	36/63	581	132
BCL2/P59S: MND	Prior Rituximab Therapy	0.63 (0.40,0.98)		39/56	307	37/69	589	133
BCL2/R106H: MND	Prior Rituximab Therapy	0.57 (0.38,0.88)		50/67	272	39/72	581	159
NOTCH/G_A1702P: MND	Prior Rituximab Therapy	0.62 (0.41,0.94)		51/72	288	41/74	589	147

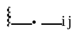
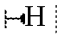
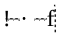
Appendix 2, Table 2.15: Treatment-Free Interval by Somatic Mutation and by Covariate, IRC Review. (All Reported Groups are Significant (p ≤0.05) and at a Frequency of ≥10%)

Marker: Level	Subgroup	HR (95% CI)	HR (log scale)	R Evt/N	R Median	Vc-R Evt/N	Vc-R Median	Marker: Subgroup N Total
NOTCH/I1681N: MND	Prior Rituximab Therapy	0.64 (0.42,0.96)		51/72	288	42/75	581	147
NOTCH/L1679P: MND	Prior Rituximab Therapy	0.64 (0.42,0.96)		51/72	288	42/75	581	147
NOTCH/L1679Q: MND	Prior Rituximab Therapy	0.64 (0.42,0.96)		51/72	288	42/75	581	147
NOTCH/L2458V: MND	Prior Rituximab Therapy	0.63 (0.41,0.96)		47/66	302	42/75	581	141
NOTCH/P2513L: MND	Prior Rituximab Therapy	0.59 (0.36,0.98)		39/57	307	25/51	649	154
NOTCH/P2515FS4: MND	Prior Rituximab Therapy	0.63 (0.42,0.96)		51/72	288	42/77	581	149
NOTCH/Q2441X: MND	Prior Rituximab Therapy	0.63 (0.42,0.97)		47/66	302	42/73	581	141
NOTCH/Q2460X: MND	Prior Rituximab Therapy	0.60 (0.39,0.93)		45/62	288	36/66	589	143
NOTCH/X26INS: MND	Prior Rituximab Therapy	0.66 (0.45,0.98)		52/74	288	47/84	581	158
NOTCH/X28DEL: MND	Prior Rituximab Therapy	0.64 (0.43,0.93)		60/83	280	49/86	554	175
NOTCH/X28INS: MND	Prior Rituximab Therapy	0.62 (0.43,0.91)		62/86	280	50/88	554	175
BCL2/A43G: MND	> 1 year since last anti-lymphoma treatment	0.65 (0.44,0.96)		57/91	449	44/94	716	185
BCL2/C.-110T: MND	> 1 year since last anti-lymphoma treatment	0.64 (0.45,0.90)		73/112	419	55/112	716	233
BCL2/E29K: MND	> 1 year since last anti-lymphoma treatment	0.60 (0.40,0.91)		52/82	409	39/83	718	185
BCL2/R106H: MND	> 1 year since last anti-	0.58 (0.40,0.85)		65/96	392	45/94	716	217

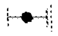
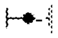
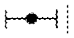
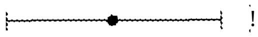
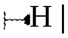
Appendix 2, Table 2.15: Treatment-Free Interval by Somatic Mutation and by Covariate, IRC Review. (All Reported Groups are Significant (p <0.05) and at a Frequency of ≥10%)

Marker: Level	Subgroup	HR (95% CI)	HR (log scale)	R Evt/N	R Median	Vc-R Evt/N	Vc-R Median	Marker: Subgroup N Total
	lymphoma treatment							
NOTCH/P25 13L: MND	> 1 year since last anti-lymphoma treatment	0.61 (0.40,0.94)		50/78	419	37/81	716	213
NOTCH/P25 15FS4: MND	> 1 year since last anti-lymphoma treatment	0.66 (0.45,0.96)		64/102	452	48/102	716	205
NOTCH/X28INS: MND	> 1 year since last anti-lymphoma treatment	0.66 (0.47,0.93)		73/113	432	59/119	709	237
BCL2/A43G: MND	European Union	0.54 (0.34,0.86)		41/66	507	32/72	942	138
BCL2/C.-1 10T: MND	European Union	0.58 (0.38,0.87)		53/79	363	41/83	843	169
BCL2/E29K: MND	European Union	0.60 (0.37,0.96)		37/61	393	32/67	907	138
BCL2/P46L: MND	European Union	0.59 (0.36,0.97)		34/56	393	29/64	1023	139
BCL2/P46S: MND	European Union	0.60 (0.37,0.96)		37/61	362	33/68	907	136
BCL2/P59S: MND	European Union	0.61 (0.38,0.97)		36/60	363	34/69	843	136
BCL2/Q52P: MND	European Union	0.61 (0.38,0.96)		38/63	362	36/73	843	136
BCL2/R106H: MND	European Union	0.58 (0.37,0.90)		44/65	393	35/70	844	160
NOTCH/G_A1702P: MND	European Union	0.62 (0.40,0.96)		44/72	393	36/74	843	147
NOTCH/I1681N: MND	European Union	0.64 (0.41,0.99)		44/72	393	37/75	843	147
NOTCH/L1679P: MND	European Union	0.64 (0.41,0.99)		44/72	393	37/75	843	147
NOTCH/L1679Q:	European	0.64		44/72	393	37/75	843	147

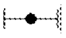
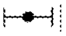
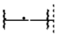
Appendix 2, Table 2.15: Treatment-Free Interval by Somatic Mutation and by Covariate, IRC Review. (All Reported Groups are Significant (p ≤0.05) and at a Frequency of ≥10%)

Marker: Level	Subgroup	HR (95% CI)	HR (log scale)	R Evt/N	R Median	Vc-R Evt/N	Vc-R Median	Marker: Subgroup N Total
MND	Union	(0.41,0.99)						
NOTCH/P2513L: MND	European Union	0.48 (0.28,0.81)		39/59	362	22/52	942	159
NOTCH/P2515FS4: MND	European Union	0.59 (0.38,0.91)		48/77	393	36/77	907	155
NOTCH/X26INS: MND	European Union	0.64 (0.42,0.98)		46/74	411	42/84	844	159
NOTCH/X28DEL: MND	European Union	0.63 (0.42,0.94)		53/82	393	45/87	843	177
NOTCH/X28INS: MND	European Union	0.62 (0.42,0.91)		56/85	393	46/89	843	177
BCL2/A43G: MND	<65 years old	0.67 (0.48,0.93)		84/124	343	65/115	595	239
BCL2/C.-110T: MND	<65 years old	0.72 (0.54,0.96)		101/147	341	81/135	554	296
BCL2/E29K: MND	<65 years old	0.61 (0.44,0.86)		81/117	307	58/103	649	241
BCL2/P46L: MND	<65 years old	0.70 (0.49,0.99)		71/105	344	59/104	589	238
BCL2/Q52P: MND	<65 years old	0.72 (0.52,1.00)		78/117	344	69/117	589	234
BCL2/R106H: MND	<65 years old	0.62 (0.44,0.86)		86/124	309	61/112	649	281
NOTCH/G_A1702P: MND	<65 years old	0.71 (0.52,0.96)		91/133	309	71/121	587	255
NOTCH/I1681N: MND	<65 years old	0.72 (0.52,0.98)		91/133	309	72/122	581	255
NOTCH/L1679P: MND	<65 years old	0.72 (0.52,0.98)		91/133	309	72/122	581	255
NOTCH/L1679Q: MND	<65 years old	0.72 (0.52,0.98)		91/133	309	72/122	581	255
NOTCH/L2458V: MND	<65 years old	0.73 (0.53,1.00)		82/120	309	70/117	581	237
NOTCH/P2513L:	<65 years	0.63		74/107	309	50/90	649	269

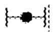
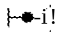
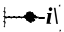
Appendix 2, Table 2.15: Treatment-Free Interval by Somatic Mutation and by Covariate, IRC Review. (All Reported Groups are Significant (p ≤0.05) and at a Frequency of ≥10%)

Marker: Level	Subgroup	HR (95% CI)	HR (log scale)	R Evt/N	R Median	Vc-R Evt/N	Vc-R Median	Marker: Subgroup N Total
MND	old	(0.44,0.91)						
NOTCH/P2515FS4: MND	<65 years old	0.68 (0.50,0.93)		92/134	341	70/123	589	259
NOTCH/Q2460X: MND	<65 years old	0.69 (0.49,0.96)		77/110	307	61/104	581	239
NOTCH/X26DEL: MND	<65 years old	0.71 (0.53,0.97)		92/137	344	76/132	595	273
NOTCH/X26INS: MND	<65 years old	0.72 (0.53,0.97)		93/138	344	77/133	589	273
NOTCH/X28DEL: MND	<65 years old	0.69 (0.52,0.93)		104/149	309	83/140	581	298
NOTCH/X28INS: MND	<65 years old	0.68 (0.51,0.91)		106/149	309	85/143	554	298
BCL2/P46L: MND	Female	0.62 (0.40,0.98)		51/86	393	31/68	1023	180
BCL2/A43G: MND	Male	0.56 (0.37,0.84)		45/59	215	47/76	587	135
BCL2/C.-110T: MND	Male	0.63 (0.44,0.92)		57/77	234	58/93	534	182
BCL2/E29K: MND	Male	0.52 (0.34,0.79)		43/55	190	43/68	587	138
BCL2/P46L: MD	Male	0.11 (0.02,0.63)		4/4	244	6/10	716	134
BCL2/Q52P: MND	Male	0.64 (0.42,0.98)		39/53	254	50/78	543	131
BCL2/R106H: MND	Male	0.62 (0.42,0.93)		50/66	254	49/81	543	169
NOTCH/G_A1702P: MND	Male	0.61 (0.41,0.91)		47/63	190	51/81	581	145
NOTCH/I1681N: MND	Male	0.62 (0.42,0.92)		47/63	190	52/82	543	145
NOTCH/L1679P: MND	Male	0.62 (0.42,0.92)		47/63	190	52/82	543	145
NOTCH/L1679Q:	Male	0.62		47/63	190	52/82	543	145

Appendix 2, Table 2.15: Treatment-Free Interval by Somatic Mutation and by Covariate, IRC Review. (All Reported Groups are Significant (p ≤0.05) and at a Frequency of ≥10%)

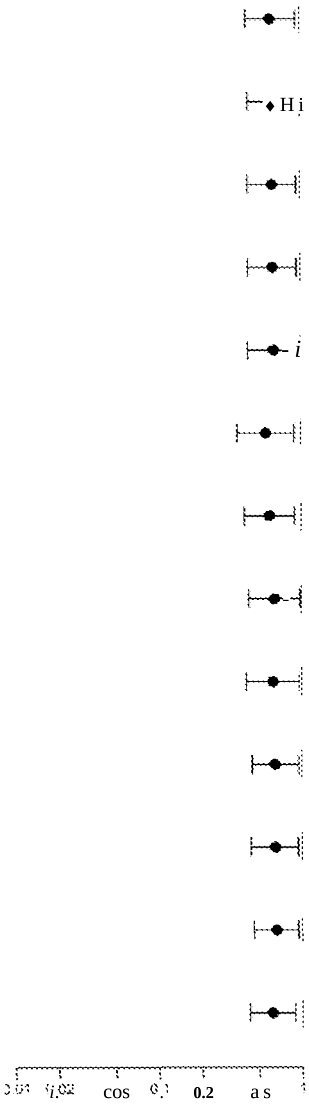
Marker: Level	Subgroup	HR (95% CI)	HR (log scale)	R Evt/N	R Median	Vc-R Evt/N	Vc-R Median	Marker: Subgroup N Total
MND		(0.42,0.92)						
NOTCH/L2458V: MND	Male	0.62 (0.41,0.93)		44/59	190	51/80	543	139
NOTCH/P2513L: MND	Male	0.54 (0.35,0.85)		41/54	190	37/63	629	155
NOTCH/P2515FS4: MND	Male	0.58 (0.39,0.87)		47/62	234	51/84	587	148
NOTCH/Q2441X: MND	Male	0.62 (0.41,0.93)		44/59	190	51/79	543	139
NOTCH/Q2460X: MD	Male	0.14 (0.03,0.71)		3/3	55	8/12	504	142
NOTCH/Q2460X: MND	Male	0.62 (0.40,0.95)		42/57	190	43/70	581	142
NOTCH/X26DEL: MND	Male	0.59 (0.40,0.87)		49/65	254	58/95	583	162
NOTCH/X26INS: MND	Male	0.57 (0.39,0.84)		50/66	234	58/95	583	162
NOTCH/X28DEL: MND	Male	0.65 (0.45,0.94)		56/75	254	61/97	543	180
NOTCH/X28INS: MND	Male	0.64 (0.45,0.91)		59/78	234	63/100	534	181
BCL2/A43G: MND	White	0.68 (0.50,0.93)		89/140	361	76/139	671	279
BCL2/C.-1 10T: MND	White	0.72 (0.54,0.95)		110/168	362	90/158	589	342
BCL2/E29K: MND	White	0.64 (0.47,0.88)		83/129	344	70/127	671	282
BCL2/P46L: MND	White	0.70 (0.50,0.97)		74/117	363	68/125	649	279
BCL2/P46S: MND	White	0.71 (0.52,0.98)		81/130	363	74/131	671	275
BCL2/P59S: MND	White	0.70 (0.51,0.96)		81/128	363	73/130	671	274
BCL2/Q52P:	White	0.70		85/135	362	77/137	671	272

Appendix 2, Table 2.15: Treatment-Free Interval by Somatic Mutation and by Covariate, IRC Review. (All Reported Groups are Significant (p ≤0.05) and at a Frequency of >10%)

Marker: Level	Subgroup	HR (95% CI)	HR (log scale)	R Evt/N	R Median	Vc-R Evt/N	Vc-R Median	Marker: Subgroup N Total
MND		(0.51 .0.96)						
BCL2/R106H: MND	White	0.70 (0.51,0.94)		93/140	361	77/135	629	327
NOTCH/G_A1702P: MND	White	0.73 (0.55,0.99)		97/152	362	82/143	629	295
NOTCH/I1681N: MND	White	0.73 (0.55,0.99)		97/152	362	82/143	629	295
NOTCH/L1679P: MND	White	0.73 (0.55,0.99)		97/152	362	82/143	629	295
NOTCH/L1679Q: MND	White	0.73 (0.55,0.99)		97/152	362	82/143	629	295
NOTCH/P2513L: MND	White	0.69 (0.49,0.96)		78/122	362	59/108	673	319
NOTCH/P2515FS4: MND	White	0.69 (0.51,0.93)		99/154	363	81/148	671	304
NOTCH/Q2460X: MND	White	0.71 (0.52,0.98)		85/131	361	73/127	589	284
NOTCH/X26DEL: MND	White	0.75 (0.56.0.99)		99/155	363	91/158	649	321
NOTCH/X26INS: MND	White	0.74 (0.56,0.98)		101/159	392	92/160	649	321
NOTCH/X28DEL: MND	White	0.75 (0.57.0.98)		111/169	362	98/167	587	351
NOTCH/X28INS: MND	White	0.72 (0.55,0.94)		115/174	362	99/171	589	352
BCL2/A43G: MND	Ann Arbor Stage IV	0.62 (0.41,0.93)		48/71	309	42/83	495	154
BCL2/C.-110T: MND	Ann Arbor Stage IV	0.66 (0.46,0.95)		60/84	309	54/100	471	193
BCL2/E29K: MND	Ann Arbor Stage IV	0.60 (0.39,0.93)		46/67	307	37/73	490	154
BCL2/P59L: MD	Ann Arbor Stage IV	0.19 (0.03, 1.00)		3/5	145	8/12	562	149
BCL2/R106H:	Ann Arbor	0.60		50/72	307	42/83	490	186

Appendix 2, Table 2.15: Treatment-Free Interval by Somatic Mutation and by Covariate, IRC Review. (All Reported Groups are Significant (p <0.05) and at a Frequency of ≥10%)

Marker: Level	Subgroup	HR (95% CI)	HR (log scale)	R Evt/N	R Median	Vc-R Evt/N	Vc-R Median	Marker: Subgroup N Total
MND	Stage IV	(0.40,0.91)						
NOTCH/G_A1702P: MND	Ann Arbor Stage IV	0.62 (0.42,0.93)		52/75	287	47/87	487	163
NOTCH/I1681N: MND	Ann Arbor Stage IV	0.64 (0.43,0.94)		52/75	287	48/88	487	163
NOTCH/L1679P: MND	Ann Arbor Stage IV	0.64 (0.43,0.94)		52/75	287	48/88	487	163
NOTCH/L1679Q: MND	Ann Arbor Stage IV	0.64 (0.43,0.94)		52/75	287	48/88	487	163
NOTCH/L2458V: MND	Ann Arbor Stage IV	0.65 (0.43,0.98)		46/68	293	46/86	490	154
NOTCH/P2513L: MND	Ann Arbor Stage IV	0.57 (0.36,0.90)		42/61	307	34/69	629	176
NOTCH/P2515FS4: MND	Ann Arbor Stage IV	0.60 (0.40,0.90)		51/74	293	46/91	495	167
NOTCH/Q2441X: MND	Ann Arbor Stage IV	0.65 (0.43,0.98)		46/68	293	46/85	490	154
NOTCH/Q2460X: MND	Ann Arbor Stage IV	0.63 (0.41,0.96)		43/64	307	41/79	495	156
NOTCH/X26DEL: MND	Ann Arbor Stage IV	0.65 (0.45,0.95)		53/76	317	54/101	490	180
NOTCH/X26INS: MND	Ann Arbor Stage IV	0.65 (0.44,0.94)		54/79	309	54/101	490	180
NOTCH/X28DEL: MND	Ann Arbor Stage IV	0.66 (0.46,0.94)		61/85	307	56/103	483	195
NOTCH/X28INS: MND	Ann Arbor Stage IV	0.62 (0.43,0.89)		64/87	293	57/105	483	196



APPENDIX 3. PAIR-WISE COMBINATIONS OF MARKERS

The following table outlines the data for all significant pair-wise combinations.

Note: Selected = Biomarker positive, Not Selected=Biomarker negative

Appendix 3, Table 3.1: Significant Pair-Wise Combinations

Marker A Type	Marker A	Marker A Level	Marker B Type	Marker B	Marker B Level	Combination	N Selected	N Excluded	N Unevaluable	N (Vc-R vs R)	% of ITT	Median PFS (Vc-R vs R)	PFS Difference	% PFS Difference	PFS Logrank P-value	PFS HR	Median OS (Vc-R vs R)	OS Logrank P-value	OS HR
B_DNA	PSMB1/P11A	C/G	Protein	CD68 POSITIVE FOLLICULAR	0-50	Selected	118	238	319	N: 57 vs 61	% in ITT: 17.5%	506d vs 277d	229	(82.7% improvement)	P-value = 1e-04	HR = 0.407 (0.26-0.639)	NAd vs NAd	0.0550	0.426 (0.174-1.046)
B_DNA	PSMB1/P11A	C/G	Protein	CD68 POSITIVE FOLLICULAR	0-50	Excluded	118	238	319	N: 118 vs 120	% in ITT: 35.3%	380d vs 381d	-1	(-0.3% improvement)	P-value = 0.8097	HR = 1.04 (0.759-1.425)	NAd vs NAd	0.9645	1.011 (0.617-1.658)
B_DNA	PSMB1/P11A	C/G	Protein	CD68 POSITIVE FOLLICULAR	0-50	Total	118	238	319	N: 175 vs 181	% in ITT: 52.7%	414d vs 345d	69	(20% improvement)	P-value = 0.0855	HR = 0.801 (0.621-1.032)	NAd vs NAd	0.3270	0.808 (0.527-1.239)
B_DNA	PSMB5/R24C	C/T	Protein	P65 INTENSITY CYTOPLASMIC SIGNAL	<=1+	Selected	12	425	238	N: 5 vs 7	% in ITT: 1.8%	827d vs 314.5d	512.5	(163% improvement)	P-value = 0.0439	HR = 0.149 (0.018-1.253)	NAd vs 717d	0.3026	0.333 (0.037-2.994)
B_DNA	PSMB5/R24C	C/T	Protein	P65 INTENSITY CYTOPLASMIC SIGNAL	<=1+	Excluded	12	425	238	N: 208 vs 217	% in ITT: 63%	406d vs 338d	68	(20.1% improvement)	P-value = 0.0641	HR = 0.803 (0.637-1.013)	NAd vs NAd	0.9151	0.979 (0.663-1.446)
B_DNA	PSMB5/R24C	C/T	Protein	P65 INTENSITY CYTOPLASMIC SIGNAL	<=1+	Total	12	425	238	N: 213 vs 224	% in ITT: 64.7%	414d vs 338d	76	(22.5% improvement)	P-value = 0.0354	HR = 0.782 (0.622-0.984)	NAd vs NAd	0.7048	0.929 (0.634-1.36)
B_DNA	PSMB1/P11A	C/G	Protein	20S % POSITIVE CYTOPLASMIC SIGNAL	95-100	Selected	100	330	245	N: 50 vs 50	% in ITT: 14.8%	576d vs 288d	288	(100% improvement)	P-value = 0.0145	HR = 0.543 (0.33-0.894)	NAd vs NAd	0.0949	0.516 (0.234-1.138)
B_DNA	PSMB1/P11A	C/G	Protein	20S % POSITIVE CYTOPLASMIC SIGNAL	95-100	Excluded	100	330	245	N: 159 vs 171	% in ITT: 48.9%	355d vs 346d	9	(2.6% improvement)	P-value = 0.3458	HR = 0.882 (0.679-1.145)	NAd vs NAd	0.5966	1.127 (0.723-1.758)
B_DNA	PSMB1/P11A	C/G	Protein	20S % POSITIVE CYTOPLASMIC SIGNAL	95-100	Total	100	330	245	N: 209 vs 221	% in ITT: 63.7%	406d vs 345d	61	(17.7% improvement)	P-value = 0.0397	HR = 0.785 (0.624-0.989)	NAd vs NAd	0.7080	0.929 (0.632-1.365)
Clinical	PRIORTX	1	Protein	CD68 POSITIVE FOLLICULAR	0-50	Selected	132	254	289	N: 63 vs 69	% in ITT: 19.6%	553d vs 282d	271	(96.1% improvement)	P-value = 0.0129	HR = 0.567 (0.36-0.893)	NAd vs NAd	0.3616	0.675 (0.288-1.58)
Clinical	PRIORTX	1	Protein	CD68 POSITIVE FOLLICULAR	0-50	Excluded	132	254	289	N: 127 vs 127	% in ITT: 37.6%	346d vs 348d	-2	(-0.6% improvement)	P-value = 0.9957	HR = 1 (0.746-1.339)	NAd vs NAd	0.6993	0.91 (0.566-1.466)
Clinical	PRIORTX	1	Protein	CD68 POSITIVE FOLLICULAR	0-50	Total	132	254	289	N: 190 vs 196	% in ITT: 57.2%	396d vs 346d	50	(14.5% improvement)	P-value = 0.1781	HR = 0.846 (0.663-1.08)	NAd vs NAd	0.4068	0.839 (0.554-1.27)
B_DNA	PSMB1/P11A	C/G	Clinical	TLAST	>1 year	Selected	146	396	133	N: 72 vs 74	% in ITT: 21.6%	554d vs 322d	232	(72% improvement)	P-value = 0.0198	HR = 0.615 (0.407-0.929)	NAd vs NAd	0.8289	1.091 (0.498-2.391)
B_DNA	PSMB1/P11A	C/G	Clinical	TLAST	>1 year	Excluded	146	396	133	N: 19	% in	352d vs	7	(2% improvement)	P-value	HR = 0.923	NA d vs	0.9430	1.014 (0.694-

Appendix 3, Table 3.1: Significant Pair-Wise Combinations

Marker A Type	Marker A	Marker A Level	Marker B Type	Marker B	Marker B Level	Combination	N Selected	N Excluded	N Unevaluable	N (Vc-R vs R)	% of ITT	Median PFS (Vc-R vs R)	PFS Difference	% PFS Difference	PFS Logrank P-value	PFS HR	Median OS (Vc-R vs R)	OS Logrank P-value	OS HR
										4 vs 202	ITT: 58.7%	345d			= 0.512	(0.726-1.174)	NAd		1.482)
B_DNA	PSMB1/P11A	C/G	Clinical	TLAST	> 1 year	Total	146	396	133	N: 266 vs 276	% in ITT: 80.3%	414d vs 345d	69	(20% improvement)	P-value = 0.0744	HR = 0.828 (0.673-1.019)	NAd vs NAd	0.8540	1.033 (0.734-1.453)
Clinical	RACEGRP	OTHER	Protein	20S % NUCLEAR STAINING	30-90	Selected	18	445	212	N: 11 vs 7	% in ITT: 2.7%	346d vs 114d	232	(203.5% improvement)	P-value = 0.032	HR = 0.272 (0.077-0.963)	928d vs NAd	0.7517	1.309 (0.246-6.958)
Clinical	RACEGRP	OTHER	Protein	20S % NUCLEAR STAINING	30-90	Excluded	18	445	212	N: 214 vs 231	% in ITT: 65.9%	396d vs 347d	49	(14.1% improvement)	P-value = 0.1229	HR = 0.836 (0.665-1.05)	NAd vs NAd	0.5139	0.879 (0.598-1.293)
Clinical	RACEGRP	OTHER	Protein	20S % NUCLEAR STAINING	30-90	Total	18	445	212	N: 225 vs 238	% in ITT: 68.6%	367d vs 345d	22	(6.4% improvement)	P-value = 0.1	HR = 0.83 (0.665-1.037)	NAd vs NAd	0.6640	0.921 (0.634-1.336)
B_DNA	PSMB1/P11A	C/G	Protein	CD68 POSITIVE PERIFOLLICULAR	>50	Selected	52	302	321	N: 24 vs 28	% in ITT: 7.7%	506d vs 280d	226	(80.7% improvement)	P-value = 0.0365	HR = 0.484 (0.241-0.971)	NAd vs 1175d	0.3998	0.648 (0.235-1.791)
B_DNA	PSMB1/P11A	C/G	Protein	CD68 POSITIVE PERIFOLLICULAR	>50	Excluded	52	302	321	N: 150 vs 152	% in ITT: 44.7%	414d vs 347d	67	(19.3% improvement)	P-value = 0.2937	HR = 0.862 (0.653-1.138)	NAd vs NAd	0.5170	0.855 (0.533-1.373)
B_DNA	PSMB1/P11A	C/G	Protein	CD68 POSITIVE PERIFOLLICULAR	>50	Total	52	302	321	N: 174 vs 180	% in ITT: 52.4%	417d vs 345d	72	(20.9% improvement)	P-value = 0.0849	HR = 0.8 (0.619-1.032)	NAd vs NAd	0.3311	0.809 (0.528-1.241)
Clinical	HITUBD	NO	Protein	CD68 OVERALL POSITIVE	0-50	Selected	132	309	234	N: 64 vs 68	% in ITT: 19.6%	693d vs 486d	207	(42.6% improvement)	P-value = 0.0177	HR = 0.576 (0.363-0.915)	NAd vs NAd	0.0204	0.316 (0.113-0.882)
Clinical	HITUBD	NO	Protein	CD68 OVERALL POSITIVE	0-50	Excluded	132	309	234	N: 153 vs 156	% in ITT: 45.8%	346d vs 287d	59	(20.6% improvement)	P-value = 0.5759	HR = 0.927 (0.712-1.207)	NAd vs NAd	0.6702	1.096 (0.718-1.674)
Clinical	HITUBD	NO	Protein	CD68 OVERALL POSITIVE	0-50	Total	132	309	234	N: 217 vs 224	% in ITT: 65.3%	360d vs 345d	15	(4.29999999999999% improvement)	P-value = 0.0864	HR = 0.819 (0.652-1.029)	NAd vs NAd	0.5387	0.887 (0.604-1.301)
B_DNA	PSMB9/R60H	G/G	Protein	P65 % NUCLEAR STAINING	>0	Selected	63	374	238	N: 35 vs 28	% in ITT: 9.3%	491d vs 288d	203	(70.5% improvement)	P-value = 0.0303	HR = 0.511 (0.275-0.952)	NAd vs NAd	0.3042	0.578 (0.2-1.667)
B_DNA	PSMB9/R60H	G/G	Protein	P65 % NUCLEAR STAINING	>0	Excluded	63	374	238	N: 178 vs 196	% in ITT: 55.4%	367d vs 345d	22	(6.4% improvement)	P-value = 0.1982	HR = 0.85 (0.664-1.088)	NAd vs NAd	0.9516	1.013 (0.673-1.525)
B_DNA	PSMB9/R60H	G/G	Protein	P65 % NUCLEAR STAINING	>0	Total	63	374	238	N: 213 vs 224	% in ITT: 64.7%	414d vs 338d	76	(22.5% improvement)	P-value = 0.0354	HR = 0.782 (0.622-0.984)	NAd vs NAd	0.7048	0.929 (0.634-1.36)
Clinical	HITUBD	NO	Protein	CD68 POSITIVE	0-50	Selected	130	256	289	N: 64	% in	624d vs	203	(48.2% improvement)	P-value	HR = 0.604	NAd vs	0.0222	0.288 (0.092-

Appendix 3, Table 3.1: Significant Pair-Wise Combinations

Marker A Type	Marker A	Marker A Level	Marker B Type	Marker B	Marker B Level	Combination	N Selected	N Excluded	N Unevaluable	N (Vc-R vs R)	% of ITT	Median PFS (Vc-R vs R)	PFS Difference	% PFS Difference	PFS Logrank P-value	PFS HR	Median OS (Vc-R vs R)	OS Logrank P-value	OS HR
				FOLLICULAR						vs 66	ITT: 19.3%	421d			= 0.031	(0.38-0.96)	NAd		0.896)
Clinical	HITUBD	NO	Protein	CD68 POSITIVE FOLLICULAR	0-50	Excluded	130	256	289	N: 126 vs 130	% in ITT: 37.9%	346d vs 283d	63	(22.3% improvement)	P-value = 0.8569	HR = 0.974 (0.729-1.3)	NAd vs NAd	0.8758	1.037 (0.657-1.636)
Clinical	HITUBD	NO	Protein	CD68 POSITIVE FOLLICULAR	0-50	Total	130	256	289	N: 190 vs 196	% in ITT: 57.2%	396d vs 346d	50	(14.5% improvement)	P-value = 0.1781	HR = 0.846 (0.663-1.08)	NAd vs NAd	0.4068	0.839 (0.554-1.27)
Clinical	PRITUX	NO	Protein	CD68 POSITIVE FOLLICULAR	0-50	Selected	159	227	289	N: 73 vs 86	% in ITT: 23.6%	483d vs 281d	202	(71.9% improvement)	P-value = 0.0066	HR = 0.586 (0.397-0.866)	NAd vs NAd	0.0713	0.53 (0.262-1.069)
Clinical	PRITUX	NO	Protein	CD68 POSITIVE FOLLICULAR	0-50	Excluded	159	227	289	N: 117 vs 110	% in ITT: 33.6%	346d vs 349d	-3	(-0.9% improvement)	P-value = 0.6451	HR = 1.079 (0.782-1.487)	NAd vs NAd	0.6426	1.134 (0.667-1.928)
Clinical	PRITUX	NO	Protein	CD68 POSITIVE FOLLICULAR	0-50	Total	159	227	289	N: 190 vs 196	% in ITT: 57.2%	396d vs 346d	50	(14.5% improvement)	P-value = 0.1781	HR = 0.846 (0.663-1.08)	NAd vs NAd	0.4068	0.839 (0.554-1.27)
B_DNA	PSMB5/R24C	C/T	Protein	CD68 POSITIVE FOLLICULAR	0-50	Selected	39	317	319	N: 18 vs 21	% in ITT: 5.8%	417d vs 220d	197	(89.5% improvement)	P-value = 0.022	HR = 0.415 (0.19-0.903)	NAd vs NAd	0.0557	0.247 (0.052-1.165)
B_DNA	PSMB5/R24C	C/T	Protein	CD68 POSITIVE FOLLICULAR	0-50	Excluded	39	317	319	N: 157 vs 160	% in ITT: 47%	414d vs 348d	66	(19% improvement)	P-value = 0.2328	HR = 0.849 (0.648-1.112)	NAd vs NAd	0.7320	0.924 (0.587-1.454)
B_DNA	PSMB5/R24C	C/T	Protein	CD68 POSITIVE FOLLICULAR	0-50	Total	39	317	319	N: 175 vs 181	% in ITT: 52.7%	414d vs 345d	69	(20% improvement)	P-value = 0.0855	HR = 0.801 (0.621-1.032)	NAd vs NAd	0.3270	0.808 (0.527-1.239)
B_DNA	PSMB1/P11A	C/G	Clinical	AGEGRP	<=65	Selected	182	360	133	N: 86 vs 96	% in ITT: 27%	464d vs 279d	185	(66.3% improvement)	P-value = 0.0071	HR = 0.605 (0.418-0.875)	NAd vs NAd	0.5650	0.822 (0.421-1.605)
B_DNA	PSMB1/P11A	C/G	Clinical	AGEGRP	<=65	Excluded	182	360	133	N: 180 vs 180	% in ITT: 53.3%	355d vs 348d	7	(2% improvement)	P-value = 0.766	HR = 0.962 (0.748-1.238)	NAd vs NAd	0.6392	1.1 (0.738-1.64)
B_DNA	PSMB1/P11A	C/G	Clinical	AGEGRP	<=65	Total	182	360	133	N: 266 vs 276	% in ITT: 80.3%	414d vs 345d	69	(20% improvement)	P-value = 0.0744	HR = 0.828 (0.673-1.019)	NAd vs NAd	0.8540	1.033 (0.734-1.453)
Clinical	SEX	MALE	Protein	20S % NUCLEAR STAINING	30-90	Selected	111	352	212	N: 63 vs 48	% in ITT: 16.4%	415d vs 235d	180	(76.6% improvement)	P-value = 0.005	HR = 0.534 (0.342-0.832)	NAd vs 1263d	0.0324	0.482 (0.243-0.955)
Clinical	SEX	MALE	Protein	20S % NUCLEAR STAINING	30-90	Excluded	111	352	212	N: 162 vs 190	% in ITT: 52.1%	360d vs 357d	3	(0.8% improvement)	P-value = 0.4394	HR = 0.903 (0.697-1.169)	NAd vs NAd	0.5157	1.16 (0.742-1.813)
Clinical	SEX	MALE	Protein	20S % NUCLEAR	30-90	Total	111	352	212	N: 22	% in	367d vs	22	(6.4% improvement)	P-value	HR = 0.83	NAd vs	0.6640	0.921 (0.634-

Appendix 3, Table 3.1: Significant Pair-Wise Combinations

Marker A Type	Marker A	Marker A Level	Marker B Type	Marker B	Marker B Level	Combination	N Selected	N Excluded	N Unevaluable	N (Vc-R vs R)	% of ITT	Median PFS (Vc-R vs R)	PFS Difference	% PFS Difference	PFS Logrank P-value	PFS HR	Median OS (Vc-R vs R)	OS Logrank P-value	OS HR
				STAINING						5 vs 238	ITT: 68.6%	345d			=0.1	(0.665-1.037)	NAd		1.336)
B_DNA	PSMB1/P11A	G/G	B_DNA	PSMB5/R24C	C/T	Selected	14	528	133	N: 7 vs 7	% in ITT: 2.1%	417d vs 237.5d	179.5	(75.6% improvement)	P-value = 0.0221	HR = 0.18 (0.035-0.921)	1037d vs NAd	0.6740	0.6 (0.054-6.662)
B_DNA	PSMB1/P11A	G/G	B_DNA	PSMB5/R24C	C/T	Excluded	14	528	133	N: 259 vs 269	% in ITT: 78.2%	414d vs 345d	69	(20% improvement)	P-value = 0.1175	HR = 0.845 (0.685-1.043)	NAd vs NAd	0.7952	1.047 (0.741-1.479)
B_DNA	PSMB1/P11A	G/G	B_DNA	PSMB5/R24C	C/T	Total	14	528	133	N: 266 vs 276	% in ITT: 80.3%	414d vs 345d	69	(20% improvement)	P-value = 0.0744	HR = 0.828 (0.673-1.019)	NAd vs NAd	0.8540	1.033 (0.734-1.453)
B_DNA	PSMB1/P11A	C/G	Protein	P27 % NUCLEI POSITIVE	0-70	Selected	110	320	245	N: 53 vs 57	% in ITT: 16.3%	444d vs 277d	167	(60.3% improvement)	P-value = 7e-04	HR = 0.456 (0.286-0.727)	NAd vs NAd	0.3082	0.67 (0.307-1.459)
B_DNA	PSMB1/P11A	C/G	Protein	P27 % NUCLEI POSITIVE	0-70	Excluded	110	320	245	N: 158 vs 162	% in ITT: 47.4%	360d vs 348d	12	(3.4% improvement)	P-value = 0.4399	HR = 0.9 (0.689-1.176)	NAd vs NAd	0.9580	0.988 (0.637-1.532)
B_DNA	PSMB1/P11A	C/G	Protein	P27 % NUCLEI POSITIVE	0-70	Total	110	320	245	N: 211 vs 219	% in ITT: 63.7%	396d vs 338d	58	(17.2% improvement)	P-value = 0.0319	HR = 0.777 (0.617-0.979)	NAd vs NAd	0.5987	0.903 (0.617-1.322)
B_DNA	PSMB1/P11A	C/G	Protein	P27 SIGNAL INTENSITY	>=2+	Selected	155	275	245	N: 75 vs 80	% in ITT: 23%	444d vs 280d	164	(58.6% improvement)	P-value = 0.0085	HR = 0.593 (0.4-0.879)	NAd vs NAd	0.3831	0.749 (0.391-1.436)
B_DNA	PSMB1/P11A	C/G	Protein	P27 SIGNAL INTENSITY	>=2+	Excluded	155	275	245	N: 136 vs 139	% in ITT: 40.7%	352d vs 346d	6	(1.69999999999999% improvement)	P-value = 0.4562	HR = 0.897 (0.674-1.194)	NAd vs NAd	0.9691	0.991 (0.618-1.589)
B_DNA	PSMB1/P11A	C/G	Protein	P27 SIGNAL INTENSITY	>=2+	Total	155	275	245	N: 211 vs 219	% in ITT: 63.7%	396d vs 338d	58	(17.2% improvement)	P-value = 0.0319	HR = 0.777 (0.617-0.979)	NAd vs NAd	0.5987	0.903 (0.617-1.322)
Clinical	TLAST	> 1 year	Protein	CD68 POSITIVE FOLLICULAR	0-50	Selected	176	210	289	N: 86 vs 90	% in ITT: 26.1%	519d vs 357d	162	(45.4% improvement)	P-value = 0.0185	HR = 0.633 (0.431-0.929)	NAd vs NAd	0.2048	0.587 (0.256-1.35)
Clinical	TLAST	> 1 year	Protein	CD68 POSITIVE FOLLICULAR	0-50	Excluded	176	210	289	N: 104 vs 106	% in ITT: 31.1%	346d vs 288d	58	(20.1% improvement)	P-value = 0.8222	HR = 1.038 (0.755-1.428)	NAd vs NAd	0.7189	0.915 (0.565-1.483)
Clinical	TLAST	> 1 year	Protein	CD68 POSITIVE FOLLICULAR	0-50	Total	176	210	289	N: 190 vs 196	% in ITT: 57.2%	396d vs 346d	50	(14.5% improvement)	P-value = 0.1781	HR = 0.846 (0.663-1.08)	NAd vs NAd	0.4068	0.839 (0.554-1.27)
B_DNA	PSMB1/P11A	C/G	Protein	20S % NUCLEAR STAINING	30-90	Selected	108	322	245	N: 45 vs 63	% in ITT: 16%	431d vs 275d	156	(56.7% improvement)	P-value = 0.0428	HR = 0.621 (0.39-0.989)	NAd vs NAd	0.1377	0.54 (0.236-1.234)
B_DNA	PSMB1/P11A	C/G	Protein	20S % NUCLEAR	30-90	Excluded	108	322	245	N: 16	% in	380d vs	34	(9.8% improvement)	P-value	HR = 0.849	NAd vs	0.6667	1.104 (0.704-

Appendix 3, Table 3.1: Significant Pair-Wise Combinations

Marker A Type	Marker A	Marker A Level	Marker B Type	Marker B	Marker B Level	Combination	N Selected	N Excluded	N Unevaluable	N (Vc-R vs R)	% of ITT	Median PFS (Vc-R vs R)	PFS Difference	% PFS Difference	PFS Logrank P-value	PFS HR	Median OS (Vc-R vs R)	OS Logrank P-value	OS HR
				STAINING						4 vs 158	ITT: 47.7%	346d			= 0.2311	(0.65-1.11)	NAd		1.729)
B_DNA	PSMB1/P11A	C/G	Protein	20S % NUCLEAR STAINING	30-90	Total	108	322	245	N: 209 vs 221	% in ITT: 63.7%	406d vs 345d	61	(17.7% improvement)	P-value = 0.0397	HR = 0.785 (0.624-0.989)	NAd vs NAd	0.7080	0.929 (0.632-1.365)
Clinical	AGEGRP	<=65	Protein	CD68 POSITIVE FOLLICULAR	0-50	Selected	215	171	289	N: 102 vs 113	% in ITT: 31.9%	429d vs 275d	154	(56% improvement)	P-value = 8e-04	HR = 0.57 (0.408-0.797)	NAd vs NAd	0.1020	0.62 (0.348-1.105)
Clinical	AGEGRP	<=65	Protein	CD68 POSITIVE FOLLICULAR	0-50	Excluded	215	171	289	N: 88 vs 83	% in ITT: 25.3%	348d vs 427d	-79	(-18.5% improvement)	P-value = 0.0837	HR = 1.383 (0.955-2.003)	NAd vs NAd	0.5681	1.196 (0.646-2.217)
Clinical	AGEGRP	<=65	Protein	CD68 POSITIVE FOLLICULAR	0-50	Total	215	171	289	N: 190 vs 196	% in ITT: 57.2%	396d vs 346d	50	(14.5% improvement)	P-value = 0.1781	HR = 0.846 (0.663-1.08)	NAd vs NAd	0.4068	0.839 (0.554-1.27)
B_DNA	PSMB1/P11A	C/G	Protein	P65 % POSITIVE CYTOPLASMIC SIGNAL	>90%	Selected	157	280	238	N: 75 vs 82	% in ITT: 23.3%	431d vs 278d	153	(55% improvement)	P-value = 0.0048	HR = 0.574 (0.389-0.848)	NAd vs NAd	0.2892	0.7 (0.361-1.358)
B_DNA	PSMB1/P11A	C/G	Protein	P65 % POSITIVE CYTOPLASMIC SIGNAL	>90%	Excluded	157	280	238	N: 138 vs 142	% in ITT: 41.5%	355d vs 348d	7	(2% improvement)	P-value = 0.513	HR = 0.909 (0.684-1.209)	NAd vs NAd	0.7743	1.071 (0.67-1.712)
B_DNA	PSMB1/P11A	C/G	Protein	P65 % POSITIVE CYTOPLASMIC SIGNAL	>90%	Total	157	280	238	N: 213 vs 224	% in ITT: 64.7%	414d vs 338d	76	(22.5% improvement)	P-value = 0.0354	HR = 0.782 (0.622-0.984)	NAd vs NAd	0.7048	0.929 (0.634-1.36)
B_DNA	PSMB9/R60H	A/G	Protein	20S % POSITIVE CYTOPLASMIC SIGNAL	95-100	Selected	89	341	245	N: 45 vs 44	% in ITT: 13.2%	426d vs 273d	153	(56% improvement)	P-value = 0.0222	HR = 0.544 (0.32-0.925)	NAd vs NAd	0.2901	0.659 (0.302-1.436)
B_DNA	PSMB9/R60H	A/G	Protein	20S % POSITIVE CYTOPLASMIC SIGNAL	95-100	Excluded	89	341	245	N: 164 vs 177	% in ITT: 50.5%	396d vs 347d	49	(14.1% improvement)	P-value = 0.2336	HR = 0.855 (0.661-1.106)	NAd vs NAd	0.9020	1.028 (0.659-1.603)
B_DNA	PSMB9/R60H	A/G	Protein	20S % POSITIVE CYTOPLASMIC SIGNAL	95-100	Total	89	341	245	N: 209 vs 221	% in ITT: 63.7%	406d vs 345d	61	(17.7% improvement)	P-value = 0.0397	HR = 0.785 (0.624-0.989)	NAd vs NAd	0.7080	0.929 (0.632-1.365)
B_DNA	PSMB1/P11A	C/G	Protein	20S INTENSITY CYTOPLASMIC SIGNAL	<=2+	Selected	108	322	245	N: 55 vs 53	% in ITT: 16%	431d vs 278d	153	(55% improvement)	P-value = 0.0269	HR = 0.601 (0.381-0.948)	NAd vs NAd	0.4710	0.724 (0.3-1.749)
B_DNA	PSMB1/P11A	C/G	Protein	20S INTENSITY CYTOPLASMIC SIGNAL	<=2+	Excluded	108	322	245	N: 154 vs 168	% in ITT: 47.7%	380d vs 345d	35	(10.1% improvement)	P-value = 0.2403	HR = 0.852 (0.651-1.114)	NAd vs NAd	0.9958	0.999 (0.651-1.533)
B_DNA	PSMB1/P11A	C/G	Protein	20S INTENSITY CYTOPLASMIC SIGNAL	<=2+	Total	108	322	245	N: 209 vs 221	% in ITT: 63.7%	406d vs 345d	61	(17.7% improvement)	P-value = 0.0397	HR = 0.785 (0.624-0.989)	NAd vs NAd	0.7080	0.929 (0.632-1.365)
B_DNA	PSMB9/R60H	A/G	Protein	CD68 POSITIVE	0-50	Selected	104	252	319	N: 51	% in	426d vs	153	(56% improvement)	P-value	HR = 0.592	NAd vs	0.1848	0.537 (0.211-

Appendix 3, Table 3.1: Significant Pair-Wise Combinations

Marker A Type	Marker A	Marker A Level	Marker B Type	Marker B	Marker B Level	Combination	N Selected	N Excluded	N Unevaluable	N (Vc-R vs R)	% of ITT	Median PFS (Vc-R vs R)	PFS Difference	% PFS Difference	PFS Logrank P-value	PFS HR	Median OS (Vc-R vs R)	OS Logrank P-value	OS HR
				FOLLICULAR						vs 53	ITT: 15.4%	273d			= 0.0339	(0.362-0.968)	NAd		1.366)
B_DNA	PSMB9/R60H	A/G	Protein	CD68 POSITIVE FOLLICULAR	0-50	Excluded	104	252	319	N: 124 vs 128	% in ITT: 37.3%	414d vs 349d	65	(18.6% improvement)	P-value = 0.435	HR = 0.888 (0.659-1.197)	NAd vs NAd	0.7690	0.93 (0.574-1.508)
B_DNA	PSMB9/R60H	A/G	Protein	CD68 POSITIVE FOLLICULAR	0-50	Total	104	252	319	N: 175 vs 181	% in ITT: 52.7%	414d vs 345d	69	(20% improvement)	P-value = 0.0855	HR = 0.801 (0.621-1.032)	NAd vs NAd	0.3270	0.808 (0.527-1.239)
B_DNA	PSMB9/R60H	G/G	Protein	20S % NUCLEAR STAINING	30-90	Selected	145	285	245	N: 74 vs 71	% in ITT: 21.5%	431d vs 280d	151	(53.9% improvement)	P-value = 0.0262	HR = 0.647 (0.439-0.953)	NAd vs NAd	0.2782	0.702 (0.368-1.336)
B_DNA	PSMB9/R60H	G/G	Protein	20S % NUCLEAR STAINING	30-90	Excluded	145	285	245	N: 135 vs 150	% in ITT: 42.2%	360d vs 345d	15	(4.29999999999999% improvement)	P-value = 0.3045	HR = 0.86 (0.644-1.148)	NAd vs NAd	0.7758	1.073 (0.661-1.741)
B_DNA	PSMB9/R60H	G/G	Protein	20S % NUCLEAR STAINING	30-90	Total	145	285	245	N: 209 vs 221	% in ITT: 63.7%	406d vs 345d	61	(17.7% improvement)	P-value = 0.0397	HR = 0.785 (0.624-0.989)	NAd vs NAd	0.7080	0.929 (0.632-1.365)
Protein	CD68 POSITIVE FOLLICULAR	0-50	Protein	P65 % POSITIVE CYTOPLASMIC SIGNAL	>90%	Selected	250	136	289	N: 114 vs 136	% in ITT: 37%	429d vs 279d	150	(53.8% improvement)	P-value = 0.0019	HR = 0.616 (0.452-0.839)	NAd vs NAd	0.0605	0.593 (0.342-1.029)
Protein	CD68 POSITIVE FOLLICULAR	0-50	Protein	P65 % POSITIVE CYTOPLASMIC SIGNAL	>90%	Excluded	250	136	289	N: 76 vs 60	% in ITT: 20.1%	324d vs 486d	-162	(-33.3% improvement)	P-value = 0.0545	HR = 1.52 (0.989-2.335)	NAd vs NAd	0.3261	1.408 (0.709-2.795)
Protein	CD68 POSITIVE FOLLICULAR	0-50	Protein	P65 % POSITIVE CYTOPLASMIC SIGNAL	>90%	Total	250	136	289	N: 190 vs 196	% in ITT: 57.2%	396d vs 346d	50	(14.5% improvement)	P-value = 0.1781	HR = 0.846 (0.663-1.08)	NAd vs NAd	0.4068	0.839 (0.554-1.27)
Clinical	AGEGRP	<=65	Protein	CD68 POSITIVE PERIFOLLICULAR	0-50	Selected	177	207	291	N: 89 vs 88	% in ITT: 26.2%	431d vs 281d	150	(53.4% improvement)	P-value = 0.0274	HR = 0.663 (0.458-0.959)	NAd vs NAd	0.7612	0.91 (0.496-1.67)
Clinical	AGEGRP	<=65	Protein	CD68 POSITIVE PERIFOLLICULAR	0-50	Excluded	177	207	291	N: 100 vs 107	% in ITT: 30.7%	348d vs 351d	-3	(-0.9% improvement)	P-value = 0.874	HR = 1.027 (0.739-1.428)	NAd vs NAd	0.3903	0.779 (0.44-1.379)
Clinical	AGEGRP	<=65	Protein	CD68 POSITIVE PERIFOLLICULAR	0-50	Total	177	207	291	N: 189 vs 195	% in ITT: 56.9%	406d vs 346d	60	(17.3% improvement)	P-value = 0.1772	HR = 0.845 (0.662-1.08)	NAd vs NAd	0.4116	0.841 (0.555-1.273)
Clinical	TLAST	> 1 year	Protein	P65 % POSITIVE CYTOPLASMIC SIGNAL	>90%	Selected	229	241	205	N: 112 vs 117	% in ITT: 33.9%	506d vs 357d	149	(41.7% improvement)	P-value = 0.0331	HR = 0.698 (0.5-0.973)	NAd vs NAd	0.3300	0.713 (0.36-1.413)
Clinical	TLAST	> 1 year	Protein	P65 % POSITIVE CYTOPLASMIC SIGNAL	>90%	Excluded	229	241	205	N: 117 vs 124	% in ITT: 35.7%	345d vs 280d	65	(23.2% improvement)	P-value = 0.6849	HR = 0.941 (0.699-1.266)	NAd vs NAd	0.9927	1.002 (0.644-1.557)
Clinical	TLAST	> 1 year	Protein	P65 % POSITIVE	>90%	Total	229	241	205	N: 22	% in	367d vs	22	(6.4% improvement)	P-value	HR = 0.826	NAd vs	0.6612	0.921 (0.636-

Appendix 3, Table 3.1: Significant Pair-Wise Combinations

Marker A Type	Marker A	Marker A Level	Marker B Type	Marker B	Marker B Level	Combination	N Selected	N Excluded	N Unevaluable	N (Vc-R vs R)	% of ITT	Median PFS (Vc-R vs R)	PFS Difference	% PFS Difference	PFS Logrank P-value	PFS HR	Median OS (Vc-R vs R)	OS Logrank P-value	OS HR
				CYTOPLASMIC SIGNAL						9 vs 241	ITT: 69.6%	345d			= 0.0902	(0.663-1.03)	NAd		1.332)
B_DNA	PSMB1/P11A	C/G	Protein	CD68 OVERALL POSITIVE	0-50	Selected	129	280	266	N: 64 vs 65	% in ITT: 19.1%	426d vs 278d	148	(53.2% improvement)	P-value = 0.0025	HR = 0.525 (0.343-0.804)	NAd vs NAd	0.2690	0.647 (0.297-1.409)
B_DNA	PSMB1/P11A	C/G	Protein	CD68 OVERALL POSITIVE	0-50	Excluded	129	280	266	N: 137 vs 143	% in ITT: 41.5%	355d vs 348d	7	(2% improvement)	P-value = 0.4433	HR = 0.894 (0.672-1.191)	NAd vs NAd	0.9914	1.002 (0.633-1.587)
B_DNA	PSMB1/P11A	C/G	Protein	CD68 OVERALL POSITIVE	0-50	Total	129	280	266	N: 201 vs 208	% in ITT: 60.6%	396d vs 345d	51	(14.8% improvement)	P-value = 0.0281	HR = 0.768 (0.606-0.973)	NAd vs NAd	0.5159	0.877 (0.591-1.302)
Protein	CD68 POSITIVE FOLLICULAR	0-50	Protein	CD68 POSITIVE PERIFOLLICULAR	0-50	Selected	193	191	291	N: 94 vs 99	% in ITT: 28.6%	429d vs 282d	147	(52.1% improvement)	P-value = 0.0075	HR = 0.625 (0.441-0.885)	NAd vs NAd	0.0947	0.596 (0.323-1.101)
Protein	CD68 POSITIVE FOLLICULAR	0-50	Protein	CD68 POSITIVE PERIFOLLICULAR	0-50	Excluded	193	191	291	N: 95 vs 96	% in ITT: 28.3%	344d vs 351d	-7	(-2% improvement)	P-value = 0.5972	HR = 1.098 (0.775-1.556)	NAd vs NAd	0.6374	1.148 (0.647-2.036)
Protein	CD68 POSITIVE FOLLICULAR	0-50	Protein	CD68 POSITIVE PERIFOLLICULAR	0-50	Total	193	191	291	N: 189 vs 195	% in ITT: 56.9%	406d vs 346d	60	(17.3% improvement)	P-value = 0.1772	HR = 0.845 (0.662-1.08)	NAd vs NAd	0.4116	0.841 (0.555-1.273)
Clinical	FLIPI	High	Protein	P27 % NUCLEI POSITIVE	0-70	Selected	113	350	212	N: 53 vs 60	% in ITT: 16.7%	358d vs 212d	146	(68.9% improvement)	P-value = 0.0156	HR = 0.588 (0.381-0.908)	1103d vs 1111d	0.8099	0.934 (0.539-1.619)
Clinical	FLIPI	High	Protein	P27 % NUCLEI POSITIVE	0-70	Excluded	113	350	212	N: 174 vs 176	% in ITT: 51.9%	406d vs 351d	55	(15.7% improvement)	P-value = 0.4522	HR = 0.905 (0.698-1.174)	NAd vs NAd	0.5519	0.859 (0.522-1.416)
Clinical	FLIPI	High	Protein	P27 % NUCLEI POSITIVE	0-70	Total	113	350	212	N: 227 vs 236	% in ITT: 68.6%	366d vs 345d	21	(6.1% improvement)	P-value = 0.0844	HR = 0.822 (0.659-1.027)	NAd vs NAd	0.5615	0.896 (0.62-1.297)
Clinical	SEX	MALE	Protein	P65 % POSITIVE CYTOPLASMIC SIGNAL	>90%	Selected	169	301	205	N: 97 vs 72	% in ITT: 25 %	414d vs 271d	143	(52.8% improvement)	P-value = 0.0094	HR = 0.622 (0.433-0.894)	NAd vs NAd	0.0574	0.571 (0.317-1.025)
Clinical	SEX	MALE	Protein	P65 % POSITIVE CYTOPLASMIC SIGNAL	>90%	Excluded	169	301	205	N: 132 vs 169	% in ITT: 44.6%	355d vs 375d	-20	(-5.3% improvement)	P-value = 0.4653	HR = 0.9 (0.678-1.194)	NAd vs NAd	0.4521	1.2 (0.746-1.931)
Clinical	SEX	MALE	Protein	P65 % POSITIVE CYTOPLASMIC SIGNAL	>90%	Total	169	301	205	N: 229 vs 241	% in ITT: 69.6%	367d vs 345d	22	(6.4% improvement)	P-value = 0.0902	HR = 0.826 (0.663-1.03)	NAd vs NAd	0.6612	0.921 (0.636-1.332)
B_DNA	PSMB1/P11A	C/G	B_DNA	PSMB9/R60H	G/G	Selected	150	392	133	N: 66 vs 84	% in ITT: 22.2%	431d vs 288d	143	(49.7% improvement)	P-value = 0.0335	HR = 0.65 (0.436-0.97)	NAd vs NAd	0.7239	0.888 (0.458-1.722)
B_DNA	PSMB1/P11A	C/G	B_DNA	PSMB9/R60H	G/G	Excluded	150	392	133	N: 20	% in	380d vs	34	(9.8% improvement)	P-value	HR = 0.906	NA d vs	0.6731	1.09 (0.73-

Appendix 3, Table 3.1: Significant Pair-Wise Combinations

Marker A Type	Marker A	Marker A Level	Marker B Type	Marker B	Marker B Level	Combination	N Selected	N Excluded	N Unevaluable	N (Vc-R vs R)	% of ITT	Median PFS (Vc-R vs R)	PFS Difference	% PFS Difference	PFS Logrank P-value	PFS HR	Median OS (Vc-R vs R)	OS Logrank P-value	OS HR
										0 vs 192	ITT: 58.1%	346d			= 0.4293	(0.71-1.157)	NAd		1.629)
B_DNA	PSMB1/P11A	C/G	B_DNA	PSMB9/R60H	G/G	Total	150	392	133	N: 266 vs 276	% in ITT: 80.3%	414d vs 345d	69	(20% improvement)	P-value = 0.0744	HR = 0.828 (0.673-1.019)	NAd vs NAd	0.8540	1.033 (0.734-1.453)
Clinical	AGEGRP	<=65	Protein	P27 % NUCLEI POSITIVE	0-70	Selected	194	269	212	N: 93 vs 101	% in ITT: 28.7%	422d vs 279d	143	(51.3% improvement)	P-value = 0.0458	HR = 0.7 (0.493-0.996)	NAd vs NAd	0.8473	0.946 (0.54-1.658)
Clinical	AGEGRP	<=65	Protein	P27 % NUCLEI POSITIVE	0-70	Excluded	194	269	212	N: 134 vs 135	% in ITT: 39.9%	352d vs 348d	4	(1.09999999999999% improvement)	P-value = 0.5904	HR = 0.923 (0.693-1.231)	NAd vs NAd	0.5476	0.86 (0.526-1.406)
Clinical	AGEGRP	<=65	Protein	P27 % NUCLEI POSITIVE	0-70	Total	194	269	212	N: 227 vs 236	% in ITT: 68.6%	366d vs 345d	21	(6.1% improvement)	P-value = 0.0844	HR = 0.822 (0.659-1.027)	NAd vs NAd	0.5615	0.896 (0.62-1.297)
Protein	20S % NUCLEAR STAINING	30-90	Protein	20S INTENSITY CYTOPLASMIC SIGNAL	>=3+	Selected	153	310	212	N: 79 vs 74	% in ITT: 22.7%	422d vs 280d	142	(50.7% improvement)	P-value = 0.0462	HR = 0.681 (0.467-0.994)	NAd vs NAd	0.0906	0.568 (0.292-1.103)
Protein	20S % NUCLEAR STAINING	30-90	Protein	20S INTENSITY CYTOPLASMIC SIGNAL	>=3+	Excluded	153	310	212	N: 146 vs 164	% in ITT: 45.9%	351d vs 347d	4	(1.2% improvement)	P-value = 0.5581	HR = 0.921 (0.7-1.213)	NAd vs NAd	0.5534	1.148 (0.727-1.815)
Protein	20S % NUCLEAR STAINING	30-90	Protein	20S INTENSITY CYTOPLASMIC SIGNAL	>=3+	Total	153	310	212	N: 225 vs 238	% in ITT: 68.6%	367d vs 345d	22	(6.4% improvement)	P-value = 0.1	HR = 0.83 (0.665-1.037)	NAd vs NAd	0.6640	0.921 (0.634-1.336)
B_DNA	PSMB9/R60H	A/G	Protein	CD68 OVERALL POSITIVE	0-50	Selected	112	297	266	N: 56 vs 56	% in ITT: 16.6%	414d vs 273d	141	(51.6% improvement)	P-value = 0.0031	HR = 0.501 (0.313-0.8)	NAd vs NAd	0.2509	0.61 (0.26-1.43)
B_DNA	PSMB9/R60H	A/G	Protein	CD68 OVERALL POSITIVE	0-50	Excluded	112	297	266	N: 145 vs 152	% in ITT: 44%	358d vs 349d	9	(2.6% improvement)	P-value = 0.3488	HR = 0.876 (0.665-1.155)	NAd vs NAd	0.9776	1.006 (0.644-1.573)
B_DNA	PSMB9/R60H	A/G	Protein	CD68 OVERALL POSITIVE	0-50	Total	112	297	266	N: 201 vs 208	% in ITT: 60.6%	396d vs 345d	51	(14.8% improvement)	P-value = 0.0281	HR = 0.768 (0.606-0.973)	NAd vs NAd	0.5159	0.877 (0.591-1.302)
B_DNA	PSMB5/R24C	C/C	Protein	20S % NUCLEAR STAINING	30-90	Selected	199	231	245	N: 95 vs 104	% in ITT: 29.5%	422d vs 281d	141	(50.2% improvement)	P-value = 0.0385	HR = 0.701 (0.5-0.983)	NAd vs NAd	0.6988	0.896 (0.513-1.563)
B_DNA	PSMB5/R24C	C/C	Protein	20S % NUCLEAR STAINING	30-90	Excluded	199	231	245	N: 114 vs 117	% in ITT: 34.2%	355d vs 346d	9	(2.6% improvement)	P-value = 0.384	HR = 0.869 (0.633-1.193)	NAd vs NAd	0.8760	0.958 (0.562-1.635)
B_DNA	PSMB5/R24C	C/C	Protein	20S % NUCLEAR STAINING	30-90	Total	199	231	245	N: 209 vs 221	% in ITT: 63.7%	406d vs 345d	61	(17.7% improvement)	P-value = 0.0397	HR = 0.785 (0.624-0.989)	NAd vs NAd	0.7080	0.929 (0.632-1.365)
B_DNA	PSMB1/P11A	C/G	Clinical	ANNARBOR	>=III	Selected	199	343	133	N: 96	% in	415d vs	140	(50.9% improvement)	P-value	HR = 0.639	NAd vs	0.7606	0.92 (0.536-

Appendix 3, Table 3.1: Significant Pair-Wise Combinations

Marker A Type	Marker A	Marker A Level	Marker B Type	Marker B	Marker B Level	Combination	N Selected	N Excluded	N Unevaluable	N (Vc-R vs R)	% of ITT	Median PFS (Vc-R vs R)	PFS Difference	% PFS Difference	PFS Logrank P-value	PFS HR	Median OS (Vc-R vs R)	OS Logrank P-value	OS HR
										vs 103	ITT: 29.5%	275d			= 0.0076	(0.459-0.89)	NAd		1.577)
B_DNA	PSMB1/P11A	C/G	Clinical	ANNARBOR	>=III	Excluded	199	343	133	N: 170 vs 173	% in ITT: 50.8%	414d vs 375d	39	(10.4% improvement)	P-value = 0.6023	HR = 0.931 (0.712-1.218)	NAd vs NAd	0.6663	1.102 (0.708-1.716)
B_DNA	PSMB1/P11A	C/G	Clinical	ANNARBOR	>=III	Total	199	343	133	N: 266 vs 276	% in ITT: 80.3%	414d vs 345d	69	(20% improvement)	P-value = 0.0744	HR = 0.828 (0.673-1.019)	NAd vs NAd	0.8540	1.033 (0.734-1.453)
Clinical	FLIPI	High	Protein	P65 % POSITIVE CYTOPLASMIC SIGNAL	>90%	Selected	160	310	205	N: 77 vs 83	% in ITT: 23.7%	352d vs 212d	140	(66% improvement)	P-value = 0.0168	HR = 0.644 (0.448-0.926)	1343d vs 1263d	0.4043	0.808 (0.49-1.333)
Clinical	FLIPI	High	Protein	P65 % POSITIVE CYTOPLASMIC SIGNAL	>90%	Excluded	160	310	205	N: 152 vs 158	% in ITT: 45.9%	429d vs 378d	51	(13.5% improvement)	P-value = 0.5531	HR = 0.919 (0.695-1.215)	NAd vs NAd	0.8360	1.06 (0.612-1.836)
Clinical	FLIPI	High	Protein	P65 % POSITIVE CYTOPLASMIC SIGNAL	>90%	Total	160	310	205	N: 229 vs 241	% in ITT: 69.6%	367d vs 345d	22	(6.4% improvement)	P-value = 0.0902	HR = 0.826 (0.663-1.03)	NAd vs NAd	0.6612	0.921 (0.636-1.332)
Clinical	AGEGRP	<=65	Protein	P65 % POSITIVE CYTOPLASMIC SIGNAL	>90%	Selected	296	174	205	N: 142 vs 154	% in ITT: 43.9%	415d vs 277d	138	(49.8% improvement)	P-value = 0.0078	HR = 0.684 (0.515-0.906)	NAd vs NAd	0.6825	0.907 (0.569-1.447)
Clinical	AGEGRP	<=65	Protein	P65 % POSITIVE CYTOPLASMIC SIGNAL	>90%	Excluded	296	174	205	N: 87 vs 87	% in ITT: 25.8%	352d vs 414d	-62	(-15% improvement)	P-value = 0.4179	HR = 1.159 (0.809-1.66)	NAd vs NAd	0.8391	0.94 (0.513-1.721)
Clinical	AGEGRP	<=65	Protein	P65 % POSITIVE CYTOPLASMIC SIGNAL	>90%	Total	296	174	205	N: 229 vs 241	% in ITT: 69.6%	367d vs 345d	22	(6.4% improvement)	P-value = 0.0902	HR = 0.826 (0.663-1.03)	NAd vs NAd	0.6612	0.921 (0.636-1.332)
Protein	20S % NUCLEAR STAINING	30-90	Protein	P65 % POSITIVE CYTOPLASMIC SIGNAL	>90%	Selected	232	231	212	N: 109 vs 123	% in ITT: 34.4%	414d vs 277d	137	(49.5% improvement)	P-value = 0.0249	HR = 0.7 (0.512-0.957)	NAd vs NAd	0.5718	0.86 (0.509-1.451)
Protein	20S % NUCLEAR STAINING	30-90	Protein	P65 % POSITIVE CYTOPLASMIC SIGNAL	>90%	Excluded	232	231	212	N: 116 vs 115	% in ITT: 34.2%	351d vs 419d	-68	(-16.2% improvement)	P-value = 0.9146	HR = 0.983 (0.714-1.353)	NAd vs NAd	0.9292	0.976 (0.571-1.668)
Protein	20S % NUCLEAR STAINING	30-90	Protein	P65 % POSITIVE CYTOPLASMIC SIGNAL	>90%	Total	232	231	212	N: 225 vs 238	% in ITT: 68.6%	367d vs 345d	22	(6.4% improvement)	P-value = 0.1	HR = 0.83 (0.665-1.037)	NAd vs NAd	0.6640	0.921 (0.634-1.336)
B_DNA	PSMB1/P11A	C/G	Protein	P65 % NUCLEAR STAINING	0	Selected	144	293	238	N: 70 vs 74	% in ITT: 21.3%	415d vs 279d	136	(48.7% improvement)	P-value = 0.0243	HR = 0.641 (0.434-0.947)	NAd vs NAd	0.5700	0.825 (0.424-1.605)
B_DNA	PSMB1/P11A	C/G	Protein	P65 % NUCLEAR STAINING	0	Excluded	144	293	238	N: 143 vs 150	% in ITT: 43.4%	406d vs 346d	60	(17.3% improvement)	P-value = 0.2722	HR = 0.853 (0.642-1.133)	NAd vs NAd	0.9159	0.975 (0.612-1.554)
B_DNA	PSMB1/P11A	C/G	Protein	P65 % NUCLEAR	0	Total	144	293	238	N: 21	% in	414d vs	76	(22.5% improvement)	P-value	HR = 0.782	NAd vs	0.7048	0.929 (0.634-

Appendix 3, Table 3.1: Significant Pair-Wise Combinations

Marker A Type	Marker A	Marker A Level	Marker B Type	Marker B	Marker B Level	Combination	N Selected	N Excluded	N Unevaluable	N (Vc-R vs R)	% of ITT	Median PFS (Vc-R vs R)	PFS Difference	% PFS Difference	PFS Logrank P-value	PFS HR	Median OS (Vc-R vs R)	OS Logrank P-value	OS HR
				STAINING						3 vs 224	ITT: 64.7%	338d			= 0.0354	(0.622-0.984)	NAd		1.36)
Protein	CD68 OVERALL POSITIVE	0-50	Protein	P65 % POSITIVE CYTOPLASMIC SIGNAL	>90%	Selected	255	185	235	N: 126 vs 129	% in ITT: 37.8%	414d vs 279d	135	(48.4% improvement)	P-value = 0.0086	HR = 0.671 (0.498-0.906)	NAd vs NAd	0.3681	0.798 (0.488-1.305)
Protein	CD68 OVERALL POSITIVE	0-50	Protein	P65 % POSITIVE CYTOPLASMIC SIGNAL	>90%	Excluded	255	185	235	N: 90 vs 95	% in ITT: 27.4%	352d vs 375d	-23	(-6.1% improvement)	P-value = 0.7752	HR = 1.052 (0.736-1.503)	NAd vs NAd	0.8468	1.062 (0.575-1.96)
Protein	CD68 OVERALL POSITIVE	0-50	Protein	P65 % POSITIVE CYTOPLASMIC SIGNAL	>90%	Total	255	185	235	N: 216 vs 224	% in ITT: 65.2%	366d vs 345d	21	(6.1% improvement)	P-value = 0.0769	HR = 0.814 (0.648-1.023)	NAd vs NAd	0.5608	0.892 (0.608-1.309)
Clinical	AGEGRP	<=65	Protein	CD68 OVERALL POSITIVE	0-50	Selected	226	215	234	N: 115 vs 111	% in ITT: 33.5%	414d vs 279d	135	(48.4% improvement)	P-value = 0.0104	HR = 0.658 (0.476-0.909)	NAd vs NAd	0.7470	0.915 (0.533-1.569)
Clinical	AGEGRP	<=65	Protein	CD68 OVERALL POSITIVE	0-50	Excluded	226	215	234	N: 102 vs 113	% in ITT: 31.9%	352d vs 351d	1	(0.299999999999989% improvement)	P-value = 0.8542	HR = 1.03 (0.745-1.424)	NAd vs NAd	0.5974	0.863 (0.499-1.492)
Clinical	AGEGRP	<=65	Protein	CD68 OVERALL POSITIVE	0-50	Total	226	215	234	N: 217 vs 224	% in ITT: 65.3%	360d vs 345d	15	(4.29999999999999% improvement)	P-value = 0.0864	HR = 0.819 (0.652-1.029)	NAd vs NAd	0.5387	0.887 (0.604-1.301)
Clinical	PRITUX	NO	Protein	P65 % NUCLEAR STAINING	0	Selected	194	276	205	N: 92 vs 102	% in ITT: 28.7%	422d vs 287d	135	(47% improvement)	P-value = 0.0407	HR = 0.702 (0.5-0.987)	NAd vs NAd	0.6357	0.877 (0.511-1.508)
Clinical	PRITUX	NO	Protein	P65 % NUCLEAR STAINING	0	Excluded	194	276	205	N: 137 vs 139	% in ITT: 40.9%	351d vs 346d	5	(1.4% improvement)	P-value = 0.6871	HR = 0.942 (0.703-1.262)	NAd vs NAd	0.9900	0.997 (0.601-1.653)
Clinical	PRITUX	NO	Protein	P65 % NUCLEAR STAINING	0	Total	194	276	205	N: 229 vs 241	% in ITT: 69.6%	367d vs 345d	22	(6.4% improvement)	P-value = 0.0902	HR = 0.826 (0.663-1.03)	NAd vs NAd	0.6612	0.921 (0.636-1.332)
Clinical	TLAST	> 1 year	Protein	CD68 OVERALL POSITIVE	0-50	Selected	189	252	234	N: 99 vs 90	% in ITT: 28 %	483d vs 348d	135	(38.8% improvement)	P-value = 0.0451	HR = 0.695 (0.486-0.994)	NAd vs NAd	0.4895	0.789 (0.402-1.549)
Clinical	TLAST	> 1 year	Protein	CD68 OVERALL POSITIVE	0-50	Excluded	189	252	234	N: 118 vs 134	% in ITT: 37.3%	347d vs 288d	59	(20.5% improvement)	P-value = 0.7048	HR = 0.944 (0.702-1.27)	NAd vs NAd	0.8742	0.963 (0.604-1.534)
Clinical	TLAST	> 1 year	Protein	CD68 OVERALL POSITIVE	0-50	Total	189	252	234	N: 217 vs 224	% in ITT: 65.3%	360d vs 345d	15	(4.29999999999999% improvement)	P-value = 0.0864	HR = 0.819 (0.652-1.029)	NAd vs NAd	0.5387	0.887 (0.604-1.301)
Protein	CD68 OVERALL POSITIVE	0-50	Protein	CD68 POSITIVE FOLLICULAR	0-50	Selected	231	155	289	N: 113 vs 118	% in ITT: 34.2%	414d vs 281d	133	(47.3% improvement)	P-value = 0.0037	HR = 0.63 (0.459-0.863)	NAd vs NAd	0.0725	0.604 (0.346-1.053)
Protein	CD68 OVERALL	0-50	Protein	CD68 POSITIVE	0-50	Excluded	231	155	289	N: 77	% in	380d vs	-1	(-0.3% improvement)	P-value	HR = 1.254	NA d vs	0.3788	1.331 (0.702-

Appendix 3, Table 3.1: Significant Pair-Wise Combinations

Marker A Type	Marker A	Marker A Level	Marker B Type	Marker B	Marker B Level	Combination	N Selected	N Excluded	N Unevaluable	N (Vc-R vs R)	% of ITT	Median PFS (Vc-R vs R)	PFS Difference	% PFS Difference	PFS Logrank P-value	PFS HR	Median OS (Vc-R vs R)	OS Logrank P-value	OS HR
	POSITIVE			FOLLICULAR						vs 78	ITT: 23%	381d			= 0.257	(0.846-1.858)	NAd		2.524)
Protein	CD68 OVERALL POSITIVE	0-50	Protein	CD68 POSITIVE FOLLICULAR	0-50	Total	231	155	289	N: 190 vs 196	% in ITT: 57.2%	396d vs 346d	50	(14.5% improvement)	P-value = 0.1781	HR = 0.846 (0.663-1.08)	NAd vs NAd	0.4068	0.839 (0.554-1.27)
Protein	CD68 POSITIVE FOLLICULAR	0-50	Protein	P65 INTENSITY CYTOPLASMIC SIGNAL	>=2+	Selected	242	144	289	N: 114 vs 128	% in ITT: 35.9%	414d vs 281d	133	(47.3% improvement)	P-value = 0.0064	HR = 0.653 (0.48-0.89)	NAd vs NAd	0.0511	0.58 (0.333-1.009)
Protein	CD68 POSITIVE FOLLICULAR	0-50	Protein	P65 INTENSITY CYTOPLASMIC SIGNAL	>=2+	Excluded	242	144	289	N: 76 vs 68	% in ITT: 21.3%	351d vs 439d	-88	(-20% improvement)	P-value = 0.1744	HR = 1.334 (0.879-2.024)	NAd vs NAd	0.2917	1.432 (0.732-2.8)
Protein	CD68 POSITIVE FOLLICULAR	0-50	Protein	P65 INTENSITY CYTOPLASMIC SIGNAL	>=2+	Total	242	144	289	N: 190 vs 196	% in ITT: 57.2%	396d vs 346d	50	(14.5% improvement)	P-value = 0.1781	HR = 0.846 (0.663-1.08)	NAd vs NAd	0.4068	0.839 (0.554-1.27)
B_DNA	PSMB9/R60H	A/G	Protein	P65 % POSITIVE CYTOPLASMIC SIGNAL	>90%	Selected	130	307	238	N: 64 vs 66	% in ITT: 19.3%	406d vs 273d	133	(48.7% improvement)	P-value = 0.0268	HR = 0.616 (0.4-0.95)	NAd vs NAd	0.1673	0.589 (0.275-1.26)
B_DNA	PSMB9/R60H	A/G	Protein	P65 % POSITIVE CYTOPLASMIC SIGNAL	>90%	Excluded	130	307	238	N: 149 vs 158	% in ITT: 45.5%	414d vs 348d	66	(19% improvement)	P-value = 0.2491	HR = 0.853 (0.65-1.118)	NAd vs NAd	0.6468	1.11 (0.711-1.73)
B_DNA	PSMB9/R60H	A/G	Protein	P65 % POSITIVE CYTOPLASMIC SIGNAL	>90%	Total	130	307	238	N: 213 vs 224	% in ITT: 64.7%	414d vs 338d	76	(22.5% improvement)	P-value = 0.0354	HR = 0.782 (0.622-0.984)	NAd vs NAd	0.7048	0.929 (0.634-1.36)
Protein	CD68 POSITIVE FOLLICULAR	0-50	Protein	P27 SIGNAL INTENSITY	>=2+	Selected	251	135	289	N: 121 vs 130	% in ITT: 37.2%	414d vs 282d	132	(46.8% improvement)	P-value = 0.0058	HR = 0.651 (0.479-0.885)	NAd vs NAd	0.0695	0.612 (0.359-1.045)
Protein	CD68 POSITIVE FOLLICULAR	0-50	Protein	P27 SIGNAL INTENSITY	>=2+	Excluded	251	135	289	N: 69 vs 66	% in ITT: 20%	351d vs 465d	-114	(-24.5% improvement)	P-value = 0.1445	HR = 1.363 (0.898-2.07)	NAd vs NAd	0.2852	1.46 (0.726-2.936)
Protein	CD68 POSITIVE FOLLICULAR	0-50	Protein	P27 SIGNAL INTENSITY	>=2+	Total	251	135	289	N: 190 vs 196	% in ITT: 57.2%	396d vs 346d	50	(14.5% improvement)	P-value = 0.1781	HR = 0.846 (0.663-1.08)	NAd vs NAd	0.4068	0.839 (0.554-1.27)
Clinical	FLIPI	High	Protein	CD68 POSITIVE FOLLICULAR	0-50	Selected	119	267	289	N: 53 vs 66	% in ITT: 17.6%	347d vs 220d	127	(57.7% improvement)	P-value = 0.0481	HR = 0.655 (0.429-1)	NAd vs 1263d	0.2401	0.692 (0.374-1.282)
Clinical	FLIPI	High	Protein	CD68 POSITIVE FOLLICULAR	0-50	Excluded	119	267	289	N: 137 vs 130	% in ITT: 39.6%	431d vs 381d	50	(13.1% improvement)	P-value = 0.8607	HR = 0.974 (0.72-1.318)	NAd vs NAd	0.8997	1.038 (0.585-1.841)
Clinical	FLIPI	High	Protein	CD68 POSITIVE FOLLICULAR	0-50	Total	119	267	289	N: 190 vs 196	% in ITT: 57.2%	396d vs 346d	50	(14.5% improvement)	P-value = 0.1781	HR = 0.846 (0.663-1.08)	NAd vs NAd	0.4068	0.839 (0.554-1.27)
B_DNA	PSMB9/R60H	G/G	Clinical	AGEGRP	<=65	Selected	232	310	133	N: 11	% in	456d vs	126	(38.2% improvement)	P-value	HR = 0.706	NA d vs	0.9809	0.993 (0.574-

Appendix 3, Table 3.1: Significant Pair-Wise Combinations

Marker A Type	Marker A	Marker A Level	Marker B Type	Marker B	Marker B Level	Combination	N Selected	N Excluded	N Unevaluable	N (Vc-R vs R)	% of ITT	Median PFS (Vc-R vs R)	PFS Difference	% PFS Difference	PFS Logrank P-value	PFS HR	Median OS (Vc-R vs R)	OS Logrank P-value	OS HR
										3 vs 119	ITT: 34.4%	330d			= 0.032	(0.513-0.972)	NAd		1.72)
B_DNA	PSMB9/R60H	G/G	Clinical	AGEGRP	<=65	Excluded	232	310	133	N: 153 vs 157	% in ITT: 45.9%	355d vs 345d	10	(2.89999999999999% improvement)	P-value = 0.6085	HR = 0.931 (0.708-1.223)	NAd vs NAd	0.8407	1.046 (0.676-1.618)
B_DNA	PSMB9/R60H	G/G	Clinical	AGEGRP	<=65	Total	232	310	133	N: 266 vs 276	% in ITT: 80.3%	414d vs 345d	69	(20% improvement)	P-value = 0.0744	HR = 0.828 (0.673-1.019)	NAd vs NAd	0.8540	1.033 (0.734-1.453)
Protein	CD68 POSITIVE FOLLICULAR	0-50	Protein	P27 % NUCLEI POSITIVE	0-70	Selected	156	230	289	N: 66 vs 90	% in ITT: 23.1%	406d vs 281d	125	(44.5% improvement)	P-value = 0.034	HR = 0.655 (0.44-0.973)	NAd vs NAd	0.4918	0.796 (0.415-1.527)
Protein	CD68 POSITIVE FOLLICULAR	0-50	Protein	P27 % NUCLEI POSITIVE	0-70	Excluded	156	230	289	N: 124 vs 106	% in ITT: 34.1%	367d vs 365d	2	(0.499999999999989% improvement)	P-value = 0.9376	HR = 1.013 (0.738-1.39)	NAd vs NAd	0.6162	0.87 (0.505-1.499)
Protein	CD68 POSITIVE FOLLICULAR	0-50	Protein	P27 % NUCLEI POSITIVE	0-70	Total	156	230	289	N: 190 vs 196	% in ITT: 57.2%	396d vs 346d	50	(14.5% improvement)	P-value = 0.1781	HR = 0.846 (0.663-1.08)	NAd vs NAd	0.4068	0.839 (0.554-1.27)
B_DNA	PSMB1/P11A	C/G	Clinical	RACEGRP	WHITE	Selected	208	334	133	N: 97 vs 111	% in ITT: 30.8%	444d vs 326d	118	(36.2% improvement)	P-value = 0.0499	HR = 0.714 (0.509-1.001)	NAd vs NAd	0.6910	0.889 (0.498-1.589)
B_DNA	PSMB1/P11A	C/G	Clinical	RACEGRP	WHITE	Excluded	208	334	133	N: 169 vs 165	% in ITT: 49.5%	360d vs 345d	15	(4.29999999999999% improvement)	P-value = 0.3716	HR = 0.887 (0.68-1.155)	NAd vs NAd	0.6309	1.109 (0.726-1.695)
B_DNA	PSMB1/P11A	C/G	Clinical	RACEGRP	WHITE	Total	208	334	133	N: 266 vs 276	% in ITT: 80.3%	414d vs 345d	69	(20% improvement)	P-value = 0.0744	HR = 0.828 (0.673-1.019)	NAd vs NAd	0.8540	1.033 (0.734-1.453)
Clinical	AGEGRP	<=65	Protein	P27 SIGNAL INTENSITY	>=2+	Selected	302	161	212	N: 149 vs 153	% in ITT: 44.7%	396d vs 279d	117	(41.9% improvement)	P-value = 0.0348	HR = 0.742 (0.561-0.98)	NAd vs NAd	0.4996	0.855 (0.543-1.347)
Clinical	AGEGRP	<=65	Protein	P27 SIGNAL INTENSITY	>=2+	Excluded	302	161	212	N: 78 vs 83	% in ITT: 23.9%	355d vs 349d	6	(1.69999999999999% improvement)	P-value = 0.9982	HR = 1 (0.691-1.446)	NAd vs NAd	0.9211	0.968 (0.512-1.831)
Clinical	AGEGRP	<=65	Protein	P27 SIGNAL INTENSITY	>=2+	Total	302	161	212	N: 227 vs 236	% in ITT: 68.6%	366d vs 345d	21	(6.1% improvement)	P-value = 0.0844	HR = 0.822 (0.659-1.027)	NAd vs NAd	0.5615	0.896 (0.62-1.297)
Clinical	SEX	MALE	Protein	P27 % NUCLEI POSITIVE	0-70	Selected	120	343	212	N: 64 vs 56	% in ITT: 17.8%	351d vs 235d	116	(49.4% improvement)	P-value = 0.0331	HR = 0.639 (0.423-0.967)	NAd vs NAd	0.2905	0.703 (0.365-1.355)
Clinical	SEX	MALE	Protein	P27 % NUCLEI POSITIVE	0-70	Excluded	120	343	212	N: 163 vs 180	% in ITT: 50.8%	380d vs 351d	29	(8.3% improvement)	P-value = 0.2275	HR = 0.849 (0.651-1.107)	NAd vs NAd	0.8108	0.947 (0.605-1.482)
Clinical	SEX	MALE	Protein	P27 % NUCLEI	0-70	Total	120	343	212	N: 22	% in	366d vs	21	(6.1% improvement)	P-value	HR = 0.822	NA d vs	0.5615	0.896 (0.62-

Appendix 3, Table 3.1: Significant Pair-Wise Combinations

Marker A Type	Marker A	Marker A Level	Marker B Type	Marker B	Marker B Level	Combination	N Selected	N Excluded	N Unevaluable	N (Vc-R vs R)	% of ITT	Median PFS (Vc-R vs R)	PFS Difference	% PFS Difference	PFS Logrank P-value	PFS HR	Median OS (Vc-R vs R)	OS Logrank P-value	OS HR
				POSITIVE						7 vs 236	ITT: 68.6%	345d			= 0.0844	(0.659-1.027)	NAd		1.297)
Clinical	AGEGRP	<=65	Protein	P65 INTENSITY CYTOPLASMIC SIGNAL	>=2+	Selected	291	179	205	N: 139 vs 152	% in ITT: 43.1%	396d vs 281d	115	(40.9% improvement)	P-value = 0.0438	HR = 0.749 (0.564-0.993)	NAd vs NAd	0.6033	0.883 (0.551-1.413)
Clinical	AGEGRP	<=65	Protein	P65 INTENSITY CYTOPLASMIC SIGNAL	>=2+	Excluded	291	179	205	N: 90 vs 89	% in ITT: 26.5%	360d vs 349d	11	(3.2% improvement)	P-value = 0.9045	HR = 0.978 (0.685-1.395)	NAd vs NAd	0.9236	0.971 (0.534-1.767)
Clinical	AGEGRP	<=65	Protein	P65 INTENSITY CYTOPLASMIC SIGNAL	>=2+	Total	291	179	205	N: 229 vs 241	% in ITT: 69.6%	367d vs 345d	22	(6.4% improvement)	P-value = 0.0902	HR = 0.826 (0.663-1.03)	NAd vs NAd	0.6612	0.921 (0.636-1.332)
Protein	CD68 POSITIVE FOLLICULAR	0-50	Protein	P65 % NUCLEAR STAINING	0	Selected	208	178	289	N: 94 vs 114	% in ITT: 30.8%	396d vs 282d	114	(40.4% improvement)	P-value = 0.0366	HR = 0.699 (0.499-0.98)	NAd vs NAd	0.3965	0.78 (0.439-1.387)
Protein	CD68 POSITIVE FOLLICULAR	0-50	Protein	P65 % NUCLEAR STAINING	0	Excluded	208	178	289	N: 96 vs 82	% in ITT: 26.4%	406d vs 379d	27	(7.1% improvement)	P-value = 0.6341	HR = 1.094 (0.757-1.581)	NAd vs NAd	0.8015	0.925 (0.505-1.695)
Protein	CD68 POSITIVE FOLLICULAR	0-50	Protein	P65 % NUCLEAR STAINING	0	Total	208	178	289	N: 190 vs 196	% in ITT: 57.2%	396d vs 346d	50	(14.5% improvement)	P-value = 0.1781	HR = 0.846 (0.663-1.08)	NAd vs NAd	0.4068	0.839 (0.554-1.27)
Clinical	FLIPI	High	Protein	P65 INTENSITY CYTOPLASMIC SIGNAL	>=2+	Selected	156	314	205	N: 76 vs 80	% in ITT: 23.1%	352d vs 239d	113	(47.3% improvement)	P-value = 0.0229	HR = 0.653 (0.451-0.945)	1343d vs NAd	0.5476	0.856 (0.515-1.421)
Clinical	FLIPI	High	Protein	P65 INTENSITY CYTOPLASMIC SIGNAL	>=2+	Excluded	156	314	205	N: 153 vs 161	% in ITT: 46.5%	429d vs 348d	81	(23.3% improvement)	P-value = 0.5476	HR = 0.919 (0.697-1.211)	NAd vs NAd	0.9311	0.977 (0.57-1.674)
Clinical	FLIPI	High	Protein	P65 INTENSITY CYTOPLASMIC SIGNAL	>=2+	Total	156	314	205	N: 229 vs 241	% in ITT: 69.6%	367d vs 345d	22	(6.4% improvement)	P-value = 0.0902	HR = 0.826 (0.663-1.03)	NAd vs NAd	0.6612	0.921 (0.636-1.332)
B_DNA	PSMB1/P11A	C/G	Clinical	HITUBD	YES	Selected	137	405	133	N: 65 vs 72	% in ITT: 20.3%	351d vs 241d	110	(45.6% improvement)	P-value = 0.0273	HR = 0.643 (0.433-0.955)	NAd vs NAd	0.8487	0.942 (0.514-1.728)
B_DNA	PSMB1/P11A	C/G	Clinical	HITUBD	YES	Excluded	137	405	133	N: 201 vs 204	% in ITT: 60%	429d vs 375d	54	(14.4% improvement)	P-value = 0.3654	HR = 0.893 (0.7-1.14)	NAd vs NAd	0.7275	1.076 (0.711-1.629)
B_DNA	PSMB1/P11A	C/G	Clinical	HITUBD	YES	Total	137	405	133	N: 266 vs 276	% in ITT: 80.3%	414d vs 345d	69	(20% improvement)	P-value = 0.0744	HR = 0.828 (0.673-1.019)	NAd vs NAd	0.8540	1.033 (0.734-1.453)
Protein	20S INTENSITY CYTOPLASMIC SIGNAL	>=3+	Protein	CD68 POSITIVE FOLLICULAR	0-50	Selected	138	248	289	N: 66 vs 72	% in ITT: 20.4%	435d vs 326d	109	(33.4% improvement)	P-value = 0.048	HR = 0.657 (0.432-0.999)	NAd vs NAd	0.1965	0.624 (0.302-1.285)
Protein	20S INTENSIT	>=3+	Protein	CD68 POSITIVE	0-50	Excluded	138	248	289	N: 12	% in	352d vs	4	(1.09999999999999%	P-value	HR = 0.976	NAd vs	0.9537	0.985 (0.591-

Appendix 3, Table 3.1: Significant Pair-Wise Combinations

Marker A Type	Marker A	Marker A Level	Marker B Type	Marker B	Marker B Level	Combination	N Selected	N Excluded	N Unevaluable	N (Vc-R vs R)	% of ITT	Median PFS (Vc-R vs R)	PFS Difference	% PFS Difference	PFS Logrank P-value	PFS HR	Median OS (Vc-R vs R)	OS Logrank P-value	OS HR
	Y CYTOPLASMIC SIGNAL			FOLLICULAR						4 vs 124	ITT: 36.7%	348d		improvement)	= 0.8748	(0.721-1.322)	NAd		1.641)
Protein	20S INTENSITY CYTOPLASMIC SIGNAL	>=3+	Protein	CD68 POSITIVE FOLLICULAR	0-50	Total	138	248	289	N: 190 vs 196	% in ITT: 57.2%	396d vs 346d	50	(14.5% improvement)	P-value = 0.1781	HR = 0.846 (0.663-1.08)	NAd vs NAd	0.4068	0.839 (0.554-1.27)
Clinical	FLIPI	High	Protein	P27 SIGNAL INTENSITY	>=2+	Selected	164	299	212	N: 81 vs 83	% in ITT: 24.3%	346d vs 239d	107	(44.8% improvement)	P-value = 0.0449	HR = 0.694 (0.485-0.993)	1343d vs 1263d	0.2893	0.761 (0.459-1.262)
Clinical	FLIPI	High	Protein	P27 SIGNAL INTENSITY	>=2+	Excluded	164	299	212	N: 146 vs 153	% in ITT: 44.3%	429d vs 357d	72	(20.2% improvement)	P-value = 0.3899	HR = 0.883 (0.665-1.173)	NAd vs NAd	0.8014	1.072 (0.622-1.848)
Clinical	FLIPI	High	Protein	P27 SIGNAL INTENSITY	>=2+	Total	164	299	212	N: 227 vs 236	% in ITT: 68.6%	366d vs 345d	21	(6.1% improvement)	P-value = 0.0844	HR = 0.822 (0.659-1.027)	NAd vs NAd	0.5615	0.896 (0.62-1.297)
Clinical	PRITUX	NO	Protein	P65 % POSITIVE CYTOPLASMIC SIGNAL	>90%	Selected	217	253	205	N: 105 vs 112	% in ITT: 32.1%	426d vs 322d	104	(32.3% improvement)	P-value = 0.0193	HR = 0.677 (0.488-0.94)	NAd vs NAd	0.2559	0.732 (0.427-1.256)
Clinical	PRITUX	NO	Protein	P65 % POSITIVE CYTOPLASMIC SIGNAL	>90%	Excluded	217	253	205	N: 124 vs 129	% in ITT: 37.5%	345d vs 346d	-1	(-0.3% improvement)	P-value = 0.9336	HR = 0.987 (0.731-1.333)	NAd vs NAd	0.5660	1.161 (0.697-1.936)
Clinical	PRITUX	NO	Protein	P65 % POSITIVE CYTOPLASMIC SIGNAL	>90%	Total	217	253	205	N: 229 vs 241	% in ITT: 69.6%	367d vs 345d	22	(6.4% improvement)	P-value = 0.0902	HR = 0.826 (0.663-1.03)	NAd vs NAd	0.6612	0.921 (0.636-1.332)
B_DNA	PSMB1/P11A	C/G	Protein	P65 INTENSITY CYTOPLASMIC SIGNAL	>=2+	Selected	154	283	238	N: 73 vs 81	% in ITT: 22.8%	426d vs 322d	104	(32.3% improvement)	P-value = 0.027	HR = 0.645 (0.435-0.955)	NAd vs NAd	0.3233	0.71 (0.358-1.406)
B_DNA	PSMB1/P11A	C/G	Protein	P65 INTENSITY CYTOPLASMIC SIGNAL	>=2+	Excluded	154	283	238	N: 140 vs 143	% in ITT: 41.9%	360d vs 346d	14	(4% improvement)	P-value = 0.2961	HR = 0.86 (0.648-1.141)	NAd vs NAd	0.8398	1.049 (0.66-1.666)
B_DNA	PSMB1/P11A	C/G	Protein	P65 INTENSITY CYTOPLASMIC SIGNAL	>=2+	Total	154	283	238	N: 213 vs 224	% in ITT: 64.7%	414d vs 338d	76	(22.5% improvement)	P-value = 0.0354	HR = 0.782 (0.622-0.984)	NAd vs NAd	0.7048	0.929 (0.634-1.36)
B_DNA	PSMB1/P11A	C/G	Clinical	PRITUX	NO	Selected	138	404	133	N: 70 vs 68	% in ITT: 20.4%	426d vs 322d	104	(32.3% improvement)	P-value = 0.0388	HR = 0.658 (0.44-0.982)	NAd vs NAd	0.4750	0.786 (0.404-1.528)
B_DNA	PSMB1/P11A	C/G	Clinical	PRITUX	NO	Excluded	138	404	133	N: 196 vs 208	% in ITT: 59.9%	363d vs 345d	18	(5.2% improvement)	P-value = 0.3874	HR = 0.898 (0.705-1.145)	NAd vs NAd	0.5551	1.127 (0.757-1.68)
B_DNA	PSMB1/P11A	C/G	Clinical	PRITUX	NO	Total	138	404	133	N: 266 vs 276	% in ITT: 80.3%	414d vs 345d	69	(20% improvement)	P-value = 0.0744	HR = 0.828 (0.673-1.019)	NAd vs NAd	0.8540	1.033 (0.734-1.453)
B_DNA	PSMB9/R60H	G/G	Protein	CD68 POSITIVE	0-50	Selected	145	211	319	N: 66	% in	429d vs	103	(31.6% improvement)	P-value	HR = 0.641	NA d vs	0.1089	0.565 (0.279-

Appendix 3, Table 3.1: Significant Pair-Wise Combinations

Marker A Type	Marker A	Marker A Level	Marker B Type	Marker B	Marker B Level	Combination	N Selected	N Excluded	N Unevaluable	N (Vc-R vs R)	% of ITT	Median PFS (Vc-R vs R)	PFS Difference	% PFS Difference	PFS Logrank P-value	PFS HR	Median OS (Vc-R vs R)	OS Logrank P-value	OS HR
				FOLLICULAR						vs 79	ITT: 21.5%	326d			= 0.0269	(0.43-0.954)	NAd		1.146)
B_DNA	PSMB9/R60H	G/G	Protein	CD68 POSITIVE FOLLICULAR	0-50	Excluded	145	211	319	N: 109 vs 102	% in ITT: 31.3%	406d vs 347d	59	(17% improvement)	P-value = 0.7477	HR = 0.947 (0.677-1.324)	NAd vs NAd	0.9946	0.998 (0.576-1.731)
B_DNA	PSMB9/R60H	G/G	Protein	CD68 POSITIVE FOLLICULAR	0-50	Total	145	211	319	N: 175 vs 181	% in ITT: 52.7%	414d vs 345d	69	(20% improvement)	P-value = 0.0855	HR = 0.801 (0.621-1.032)	NAd vs NAd	0.3270	0.808 (0.527-1.239)
Protein	20S INTENSITY CYTOPLASMIC SIGNAL	>=3+	Protein	P65 % POSITIVE CYTOPLASMIC SIGNAL	>90%	Selected	195	268	212	N: 95 vs 100	% in ITT: 28.9%	435d vs 334d	101	(30.2% improvement)	P-value = 0.0304	HR = 0.681 (0.481-0.965)	NAd vs NAd	0.1802	0.66 (0.358-1.217)
Protein	20S INTENSITY CYTOPLASMIC SIGNAL	>=3+	Protein	P65 % POSITIVE CYTOPLASMIC SIGNAL	>90%	Excluded	195	268	212	N: 130 vs 138	% in ITT: 39.7%	351d vs 345d	6	(1.69999999999999% improvement)	P-value = 0.7745	HR = 0.959 (0.718-1.28)	NAd vs NAd	0.5860	1.141 (0.709-1.838)
Protein	20S INTENSITY CYTOPLASMIC SIGNAL	>=3+	Protein	P65 % POSITIVE CYTOPLASMIC SIGNAL	>90%	Total	195	268	212	N: 225 vs 238	% in ITT: 68.6%	367d vs 345d	22	(6.4% improvement)	P-value = 0.1	HR = 0.83 (0.665-1.037)	NAd vs NAd	0.6640	0.921 (0.634-1.336)
Clinical	RACEGRP	WHITE	Protein	CD68 POSITIVE FOLLICULAR	0-50	Selected	239	147	289	N: 114 vs 125	% in ITT: 35.4%	431d vs 334d	97	(29% improvement)	P-value = 0.0043	HR = 0.63 (0.458-0.868)	NAd vs NAd	0.0785	0.592 (0.328-1.069)
Clinical	RACEGRP	WHITE	Protein	CD68 POSITIVE FOLLICULAR	0-50	Excluded	239	147	289	N: 76 vs 71	% in ITT: 21.8%	324d vs 375d	-51	(-13.6% improvement)	P-value = 0.1919	HR = 1.294 (0.878-1.908)	NAd vs NAd	0.5253	1.215 (0.665-2.219)
Clinical	RACEGRP	WHITE	Protein	CD68 POSITIVE FOLLICULAR	0-50	Total	239	147	289	N: 190 vs 196	% in ITT: 57.2%	396d vs 346d	50	(14.5% improvement)	P-value = 0.1781	HR = 0.846 (0.663-1.08)	NAd vs NAd	0.4068	0.839 (0.554-1.27)
Protein	20S % NUCLEAR STAINING	30-90	Protein	CD68 OVERALL POSITIVE	0-50	Selected	168	271	236	N: 82 vs 86	% in ITT: 24.9%	367d vs 271d	96	(35.4% improvement)	P-value = 0.0181	HR = 0.647 (0.45-0.931)	NAd vs NAd	0.3345	0.753 (0.424-1.34)
Protein	20S % NUCLEAR STAINING	30-90	Protein	CD68 OVERALL POSITIVE	0-50	Excluded	168	271	236	N: 134 vs 137	% in ITT: 40.1%	355d vs 365d	-10	(-2.7% improvement)	P-value = 0.7301	HR = 0.949 (0.706-1.276)	NAd vs NAd	0.8394	1.055 (0.627-1.774)
Protein	20S % NUCLEAR STAINING	30-90	Protein	CD68 OVERALL POSITIVE	0-50	Total	168	271	236	N: 216 vs 223	% in ITT: 65 %	366d vs 345d	21	(6.1% improvement)	P-value = 0.0853	HR = 0.818 (0.651-1.029)	NAd vs NAd	0.6244	0.908 (0.618-1.335)
Clinical	AGEGRP	<=65	Protein	20S % NUCLEAR STAINING	30-90	Selected	193	270	212	N: 96 vs 97	% in ITT: 28.6%	367d vs 271d	96	(35.4% improvement)	P-value = 0.0413	HR = 0.703 (0.5-0.988)	NAd vs NAd	0.6180	0.865 (0.49-1.527)
Clinical	AGEGRP	<=65	Protein	20S % NUCLEAR STAINING	30-90	Excluded	193	270	212	N: 129 vs 141	% in ITT: 40 %	380d vs 357d	23	(6.4% improvement)	P-value = 0.6011	HR = 0.925 (0.689-1.241)	NAd vs NAd	0.8251	0.946 (0.576-1.552)
Clinical	AGEGRP	<=65	Protein	20S % NUCLEAR	30-90	Total	193	270	212	N: 22	% in	367d vs	22	(6.4% improvement)	P-value	HR = 0.83	NAd vs	0.6640	0.921 (0.634-

Appendix 3, Table 3.1: Significant Pair-Wise Combinations

Marker A Type	**Marker A**	**Marker A Level**	**Marker B Type**	**Marker B**	**Marker B Level**	**Combination**	**N Selected**	**N Excluded**	**N Unevaluable**	**N (Vc-R vs R)**	**% of ITT**	**Median PFS (Vc-R vs R)**	**PFS Difference**	**% PFS Difference**	**PFS Logrank P-value**	**PFS HR**	**Median OS (Vc-R vs R)**	**OS Logrank P-value**	**OS HR**
				STAINING						5 vs 238	ITT: 68.6%	345d			= 0.1	(0.665-1.037)	NAd		1.336)
Clinical	HITUBD	YES	Protein	P65 % POSITIVE CYTOPLASMIC SIGNAL	>90%	Selected	202	268	205	N: 100 vs 102	% in ITT: 29.9%	346d vs 253d	93	(36.8% improvement)	P-value = 0.0486	HR = 0.728 (0.531-0.999)	1343d vs NAd	0.7230	0.917 (0.567-1.481)
Clinical	HITUBD	YES	Protein	P65 % POSITIVE CYTOPLASMIC SIGNAL	>90%	Excluded	202	268	205	N: 129 vs 139	% in ITT: 39.7%	487d vs 422d	65	(15.4% improvement)	P-value = 0.4198	HR = 0.88 (0.646-1.199)	NAd vs NAd	0.6827	0.886 (0.496-1.584)
Clinical	HITUBD	YES	Protein	P65 % POSITIVE CYTOPLASMIC SIGNAL	>90%	Total	202	268	205	N: 229 vs 241	% in ITT: 69.6%	367d vs 345d	22	(6.4% improvement)	P-value = 0.0902	HR = 0.826 (0.663-1.03)	NAd vs NAd	0.6612	0.921 (0.636-1.332)
Protein	20S % NUCLEAR STAINING	30-90	Protein	CD68 POSITIVE FOLLICULAR	0-50	Selected	164	222	289	N: 75 vs 89	% in ITT: 24.3%	366d vs 274d	92	(33.6% improvement)	P-value = 0.0133	HR = 0.631 (0.437-0.911)	NAd vs NAd	0.2666	0.702 (0.374-1.315)
Protein	20S % NUCLEAR STAINING	30-90	Protein	CD68 POSITIVE FOLLICULAR	0-50	Excluded	164	222	289	N: 115 vs 107	% in ITT: 32.9%	422d vs 427d	-5	(-1.2% improvement)	P-value = 0.6841	HR = 1.072 (0.769-1.494)	NAd vs NAd	0.9562	0.984 (0.561-1.727)
Protein	20S % NUCLEAR STAINING	30-90	Protein	CD68 POSITIVE FOLLICULAR	0-50	Total	164	222	289	N: 190 vs 196	% in ITT: 57.2%	396d vs 346d	50	(14.5% improvement)	P-value = 0.1781	HR = 0.846 (0.663-1.08)	NAd vs NAd	0.4068	0.839 (0.554-1.27)
B_DNA	PSMB5/R24C	C/C	Clinical	AGEGRP	<=65	Selected	337	205	133	N: 167 vs 170	% in ITT: 49.9%	422d vs 330d	92	(27.9% improvement)	P-value = 0.0146	HR = 0.722 (0.555-0.939)	NAd vs NAd	0.9869	1.004 (0.638-1.579)
B_DNA	PSMB5/R24C	C/C	Clinical	AGEGRP	<=65	Excluded	337	205	133	N: 99 vs 106	% in ITT: 30.4%	355d vs 348d	7	(2% improvement)	P-value = 0.8278	HR = 1.037 (0.739-1.457)	NAd vs NAd	0.7965	1.071 (0.636-1.801)
B_DNA	PSMB5/R24C	C/C	Clinical	AGEGRP	<=65	Total	337	205	133	N: 266 vs 276	% in ITT: 80.3%	414d vs 345d	69	(20% improvement)	P-value = 0.0744	HR = 0.828 (0.673-1.019)	NAd vs NAd	0.8540	1.033 (0.734-1.453)
B_DNA	PSMB5/R24C	C/C	Protein	CD68 POSITIVE FOLLICULAR	0-50	Selected	225	131	319	N: 104 vs 121	% in ITT: 33.3%	426d vs 334d	92	(27.5% improvement)	P-value = 0.0247	HR = 0.691 (0.499-0.956)	NAd vs NAd	0.2817	0.729 (0.41-1.298)
B_DNA	PSMB5/R24C	C/C	Protein	CD68 POSITIVE FOLLICULAR	0-50	Excluded	225	131	319	N: 71 vs 60	% in ITT: 19.4%	414d vs 348d	66	(19% improvement)	P-value = 0.8308	HR = 1.046 (0.687-1.594)	NAd vs NAd	0.7179	0.888 (0.466-1.692)
B_DNA	PSMB5/R24C	C/C	Protein	CD68 POSITIVE FOLLICULAR	0-50	Total	225	131	319	N: 175 vs 181	% in ITT: 52.7%	414d vs 345d	69	(20% improvement)	P-value = 0.0855	HR = 0.801 (0.621-1.032)	NAd vs NAd	0.3270	0.808 (0.527-1.239)
Clinical	SEX	FEMALE	Protein	CD68 POSITIVE FOLLICULAR	0-50	Selected	163	223	289	N: 69 vs 94	% in ITT: 24.1%	435d vs 345d	90	(26.1% improvement)	P-value = 0.015	HR = 0.609 (0.406-0.913)	NAd vs NAd	0.5324	0.794 (0.385-1.639)
Clinical	SEX	FEMALE	Protein	CD68 POSITIVE	0-50	Excluded	163	223	289	N: 12	% in	352d vs	5	(1.4% improvement)	P-value	HR = 1.031	NA d vs	0.4476	0.821 (0.493-

Appendix 3, Table 3.1: Significant Pair-Wise Combinations

Marker A Type	Marker A	Marker A Level	Marker B Type	Marker B	Marker B Level	Combination	N Selected	N Excluded	N Unevaluable	N (Vc-R vs R)	% of ITT	Median PFS (Vc-R vs R)	PFS Difference	% PFS Difference	PFS Logrank P-value	PFS HR	Median OS (Vc-R vs R)	OS Logrank P-value	OS HR
				FOLLICULAR						1 vs 102	ITT: 33%	347d			= 0.854	(0.75-1.416)	NAd		1.368)
Clinical	SEX	FEMALE	Protein	CD68 POSITIVE FOLLICULAR	0-50	Total	163	223	289	N: 190 vs 196	% in ITT: 57.2%	396d vs 346d	50	(14.5% improvement)	P-value = 0.1781	HR = 0.846 (0.663-1.08)	NAd vs NAd	0.4068	0.839 (0.554-1.27)
B_DNA	PSMB9/R60H	A/G	Protein	P65 % NUCLEAR STAINING	0	Selected	120	317	238	N: 60 vs 60	% in ITT: 17.8%	366d vs 277d	89	(32.1% improvement)	P-value = 0.0212	HR = 0.6 (0.386-0.93)	NAd vs NAd	0.2104	0.635 (0.31-1.3)
B_DNA	PSMB9/R60H	A/G	Protein	P65 % NUCLEAR STAINING	0	Excluded	120	317	238	N: 153 vs 164	% in ITT: 47%	415d vs 348d	67	(19.3% improvement)	P-value = 0.2428	HR = 0.851 (0.65-1.115)	NAd vs NAd	0.7295	1.083 (0.689-1.704)
B_DNA	PSMB9/R60H	A/G	Protein	P65 % NUCLEAR STAINING	0	Total	120	317	238	N: 213 vs 224	% in ITT: 64.7%	414d vs 338d	76	(22.5% improvement)	P-value = 0.0354	HR = 0.782 (0.622-0.984)	NAd vs NAd	0.7048	0.929 (0.634-1.36)
Protein	20S % POSITIVE CYTOPLASMIC SIGNAL	95-100	Protein	CD68 POSITIVE FOLLICULAR	0-50	Selected	183	203	289	N: 90 vs 93	% in ITT: 27.1%	426d vs 338d	88	(26% improvement)	P-value = 0.0168	HR = 0.646 (0.449-0.928)	NAd vs NAd	0.0772	0.578 (0.313-1.069)
Protein	20S % POSITIVE CYTOPLASMIC SIGNAL	95-100	Protein	CD68 POSITIVE FOLLICULAR	0-50	Excluded	183	203	289	N: 100 vs 103	% in ITT: 30.1%	351d vs 347d	4	(1.2% improvement)	P-value = 0.7086	HR = 1.066 (0.762-1.49)	NAd vs NAd	0.5747	1.178 (0.664-2.09)
Protein	20S % POSITIVE CYTOPLASMIC SIGNAL	95-100	Protein	CD68 POSITIVE FOLLICULAR	0-50	Total	183	203	289	N: 190 vs 196	% in ITT: 57.2%	396d vs 346d	50	(14.5% improvement)	P-value = 0.1781	HR = 0.846 (0.663-1.08)	NAd vs NAd	0.4068	0.839 (0.554-1.27)
B_DNA	PSMB5/R24C	C/C	Protein	P65 % POSITIVE CYTOPLASMIC SIGNAL	>90%	Selected	300	137	238	N: 141 vs 159	% in ITT: 44.4%	422d vs 334d	88	(26.3% improvement)	P-value = 0.017	HR = 0.713 (0.54-0.943)	NAd vs NAd	0.6127	0.887 (0.558-1.411)
B_DNA	PSMB5/R24C	C/C	Protein	P65 % POSITIVE CYTOPLASMIC SIGNAL	>90%	Excluded	300	137	238	N: 72 vs 65	% in ITT: 20.3%	352d vs 347d	5	(1.4% improvement)	P-value = 0.8192	HR = 0.953 (0.633-1.435)	NAd vs NAd	0.9886	1.005 (0.513-1.972)
B_DNA	PSMB5/R24C	C/C	Protein	P65 % POSITIVE CYTOPLASMIC SIGNAL	>90%	Total	300	137	238	N: 213 vs 224	% in ITT: 64.7%	414d vs 338d	76	(22.5% improvement)	P-value = 0.0354	HR = 0.782 (0.622-0.984)	NAd vs NAd	0.7048	0.929 (0.634-1.36)
Protein	P27 SIGNAL INTENSITY	>=2+	Protein	P65 % POSITIVE CYTOPLASMIC SIGNAL	>90%	Selected	348	114	213	N: 168 vs 180	% in ITT: 51.6%	414d vs 326d	88	(27% improvement)	P-value = 0.0333	HR = 0.755 (0.583-0.979)	NAd vs NAd	0.2119	0.76 (0.493-1.171)
Protein	P27 SIGNAL INTENSITY	>=2+	Protein	P65 % POSITIVE CYTOPLASMIC SIGNAL	>90%	Excluded	348	114	213	N: 58 vs 56	% in ITT: 16.9%	347d vs 347d	0	(0% improvement)	P-value = 0.8643	HR = 1.04 (0.669-1.617)	NAd vs NAd	0.3256	1.455 (0.686-3.086)
Protein	P27 SIGNAL INTENSITY	>=2+	Protein	P65 % POSITIVE CYTOPLASMIC SIGNAL	>90%	Total	348	114	213	N: 226 vs 236	% in ITT: 68.4%	366d vs 345d	21	(6.1% improvement)	P-value = 0.0753	HR = 0.817 (0.654-1.021)	NAd vs NAd	0.5839	0.902 (0.623-1.305)
Clinical	HITUBD	YES	Protein	P27 % NUCLEI	0-70	Selected	148	315	212	N: 75	% in	324d vs	85	(35.6% improvement)	P-value	HR = 0.677	1343d vs	0.7672	0.918 (0.524-

Appendix 3, Table 3.1: Significant Pair-Wise Combinations

Marker A Type	Marker A	Marker A Level	Marker B Type	Marker B	Marker B Level	Combination	N Selected	N Excluded	N Unevaluable	N (Vc-R vs R)	% of ITT	Median PFS (Vc-R vs R)	PFS Difference	% PFS Difference	PFS Logrank P-value	PFS HR	Median OS (Vc-R vs R)	OS Logrank P-value	OS HR
				POSITIVE						vs 73	ITT: 21.9%	239d			= 0.0384	(0.466-0.982)	NAd		1.61)
Clinical	HITUBD	YES	Protein	P27 % NUCLEI POSITIVE	0-70	Excluded	148	315	212	N: 152 vs 163	% in ITT: 46.7%	426d vs 357d	69	(19.3% improvement)	P-value = 0.2588	HR = 0.852 (0.645-1.126)	NAd vs NAd	0.4225	0.817 (0.498-1.34)
Clinical	HITUBD	YES	Protein	P27 % NUCLEI POSITIVE	0-70	Total	148	315	212	N: 227 vs 236	% in ITT: 68.6%	366d vs 345d	21	(6.1% improvement)	P-value = 0.0844	HR = 0.822 (0.659-1.027)	NAd vs NAd	0.5615	0.896 (0.62-1.297)
Clinical	RACEGRP	WHITE	Protein	P65 % POSITIVE CYTOPLASMIC SIGNAL	>90%	Selected	341	129	205	N: 162 vs 179	% in ITT: 50.5%	417d vs 334d	83	(24.9% improvement)	P-value = 0.0163	HR = 0.725 (0.558-0.943)	NAd vs NAd	0.2846	0.783 (0.501-1.226)
Clinical	RACEGRP	WHITE	Protein	P65 % POSITIVE CYTOPLASMIC SIGNAL	>90%	Excluded	341	129	205	N: 67 vs 62	% in ITT: 19.1%	346d vs 378d	-32	(-8.5% improvement)	P-value = 0.4834	HR = 1.159 (0.767-1.752)	NAd vs NAd	0.5035	1.257 (0.643-2.455)
Clinical	RACEGRP	WHITE	Protein	P65 % POSITIVE CYTOPLASMIC SIGNAL	>90%	Total	341	129	205	N: 229 vs 241	% in ITT: 69.6%	367d vs 345d	22	(6.4% improvement)	P-value = 0.0902	HR = 0.826 (0.663-1.03)	NAd vs NAd	0.6612	0.921 (0.636-1.332)
Clinical	ANNARBOR	>=III	Protein	P65 % POSITIVE CYTOPLASMIC SIGNAL	>90%	Selected	321	149	205	N: 152 vs 169	% in ITT: 47.6%	360d vs 278d	82	(29.5% improvement)	P-value = 0.0306	HR = 0.75 (0.578-0.974)	NAd vs NAd	0.5983	0.891 (0.58-1.369)
Clinical	ANNARBOR	>=III	Protein	P65 % POSITIVE CYTOPLASMIC SIGNAL	>90%	Excluded	321	149	205	N: 77 vs 72	% in ITT: 22.1%	435d vs 432d	3	(0.69999999999999% improvement)	P-value = 0.78	HR = 1.063 (0.696-1.622)	NAd vs NAd	0.8428	1.077 (0 518-2.242)
Clinical	ANNARBOR	>=III	Protein	P65 % POSITIVE CYTOPLASMIC SIGNAL	>90%	Total	321	149	205	N: 229 vs 241	% in ITT: 69.6%	367d vs 345d	22	(6.4% improvement)	P-value = 0.0902	HR = 0.826 (0.663-1.03)	NAd vs NAd	0.6612	0.921 (0.636-1.332)
Clinical	REGION	REST OF WORLD	Protein	CD68 OVERALL POSITIVE	0-50	Selected	137	304	234	N: 67 vs 70	% in ITT: 20.3%	358d vs 277d	81	(29.2% improvement)	P-value = 0.0407	HR = 0.668 (0.452-0.987)	NAd vs NAd	0.2957	0.716 (0.382-1.341)
Clinical	REGION	REST OF WORLD	Protein	CD68 OVERALL POSITIVE	0-50	Excluded	137	304	234	N: 150 vs 154	% in ITT: 45%	380d vs 351d	29	(8.3% improvement)	P-value = 0.552	HR = 0.917 (0.691-1.217)	NAd vs NAd	0.9650	1.011 (0.621-1.645)
Clinical	REGION	REST OF WORLD	Protein	CD68 OVERALL POSITIVE	0-50	Total	137	304	234	N: 217 vs 224	% in ITT: 65.3%	360d vs 345d	15	(4.29999999999999% improvement)	P-value = 0.0864	HR = 0.819 (0.652-1.029)	NAd vs NAd	0.5387	0.887 (0.604-1.301)
Clinical	RACEGRP	WHITE	Protein	CD68 OVERALL POSITIVE	0-50	Selected	260	181	234	N: 132 vs 128	% in ITT: 38.5%	414d vs 334d	80	(24% improvement)	P-value = 0.0248	HR = 0.71 (0.526-0.959)	NAd vs NAd	0.1697	0.701 (0.421-1.167)
Clinical	RACEGRP	WHITE	Protein	CD68 OVERALL POSITIVE	0-50	Excluded	260	181	234	N: 85 vs 96	% in ITT: 26.8%	351d vs 348d	3	(0.89999999999999% improvement)	P-value = 0.9662	HR = 0.991 (0.696-1.411)	NAd vs NAd	0.4069	1.28 (0.713-2.299)
Clinical	RACEGRP	WHITE	Protein	CD68 OVERALL	0-50	Total	260	181	234	N: 21	% in	360d vs	15	(4.29999999999999%	P-value	HR = 0.819	NA d vs	0.5387	0.887 (0.604-

Appendix 3, Table 3.1: Significant Pair-Wise Combinations

Marker A Type	Marker A	Marker A Level	Marker B Type	Marker B	Marker B Level	Combination	N Selected	N Excluded	N Unevaluable	N (Vc-R vs R)	% of ITT	Median PFS (Vc-R vs R)	PFS Difference	% PFS Difference	PFS Logrank P-value	PFS HR	Median OS (Vc-R vs R)	OS Logrank P-value	OS HR
				POSITIVE						7 vs 224	ITT: 65.3%	345d		improvement)	= 0.0864	(0.652-1.029)	NAd		1.301)
Clinical	FLIPI	High	Protein	CD68 OVERALL POSITIVE	0-50	Selected	135	306	234	N: 67 vs 68	% in ITT: 20%	352d vs 273d	79	(28.9% improvement)	P-value = 0.0339	HR = 0.658 (0.446-0.971)	1343d vs NAd	0.2526	0.727 (0.421-1.257)
Clinical	FLIPI	High	Protein	CD68 OVERALL POSITIVE	0-50	Excluded	135	306	234	N: 150 vs 156	% in ITT: 45.3%	414d vs 357d	57	(16% improvement)	P-value = 0.4519	HR = 0.898 (0.677-1.191)	NAd vs NAd	0.9548	0.984 (0.574-1.687)
Clinical	FLIPI	High	Protein	CD68 OVERALL POSITIVE	0-50	Total	135	306	234	N: 217 vs 224	% in ITT: 65.3%	360d vs 345d	15	(4.29999999999999% improvement)	P-value = 0.0864	HR = 0.819 (0.652-1.029)	NAd vs NAd	0.5387	0.887 (0.604-1.301)
B_DNA	PSMB5/R24C	C/C	Clinical	ANNARBOR	>=III	Selected	375	167	133	N: 182 vs 193	% in ITT: 55.6%	360d vs 281d	79	(28.1% improvement)	P-value = 0.0395	HR = 0.776 (0.61-0.989)	NAd vs NAd	0.5509	1.127 (0.761-1.668)
B_DNA	PSMB5/R24C	C/C	Clinical	ANNARBOR	>=III	Excluded	375	167	133	N: 84 vs 83	% in ITT: 24.7%	512d vs 422d	90	(21.3% improvement)	P-value = 0.9843	HR = 0.996 (0.662-1.499)	NAd vs NAd	0.5602	0.814 (0.406-1.631)
B_DNA	PSMB5/R24C	C/C	Clinical	ANNARBOR	>=III	Total	375	167	133	N: 266 vs 276	% in ITT: 80.3%	414d vs 345d	69	(20% improvement)	P-value = 0.0744	HR = 0.828 (0.673-1.019)	NAd vs NAd	0.8540	1.033 (0.734-1.453)
B_DNA	PSMB5/R24C	C/T	Clinical	HITUBD	YES	Selected	45	497	133	N: 24 vs 21	% in ITT: 6.7%	352d vs 275d	77	(28% improvement)	P-value = 0.0054	HR = 0.383 (0.191-0.769)	NAd vs NAd	0.1763	0.496 (0.176-1.399)
B_DNA	PSMB5/R24C	C/T	Clinical	HITUBD	YES	Excluded	45	497	133	N: 242 vs 255	% in ITT: 73.6%	414d vs 347d	67	(19.3% improvement)	P-value = 0.1634	HR = 0.856 (0.688-1.065)	NAd vs NAd	0.5518	1.116 (0.777-1.605)
B_DNA	PSMB5/R24C	C/T	Clinical	HITUBD	YES	Total	45	497	133	N: 266 vs 276	% in ITT: 80.3%	414d vs 345d	69	(20% improvement)	P-value = 0.0744	HR = 0.828 (0.673-1.019)	NAd vs NAd	0.8540	1.033 (0.734-1.453)
Protein	CD68 OVERALL POSITIVE	0-50	Protein	P27 % NUCLEI POSITIVE	0-70	Selected	181	260	234	N: 85 vs 96	% in ITT: 26.8%	358d vs 282d	76	(27% improvement)	P-value = 0.0484	HR = 0.699 (0.488-1)	NAd vs NAd	0.5757	0.851 (0.485-1.496)
Protein	CD68 OVERALL POSITIVE	0-50	Protein	P27 % NUCLEI POSITIVE	0-70	Excluded	181	260	234	N: 132 vs 128	% in ITT: 38.5%	367d vs 349d	18	(5.2% improvement)	P-value = 0.4931	HR = 0.901 (0.669-1.213)	NAd vs NAd	0.7267	0.911 (0.539-1.538)
Protein	CD68 OVERALL POSITIVE	0-50	Protein	P27 % NUCLEI POSITIVE	0-70	Total	181	260	234	N: 217 vs 224	% in ITT: 65.3%	360d vs 345d	15	(4.29999999999999% improvement)	P-value = 0.0864	HR = 0.819 (0.652-1.029)	NAd vs NAd	0.5387	0.887 (0.604-1.301)
B_DNA	PSMB9/R60H	A/G	Clinical	SEX	MALE	Selected	76	466	133	N: 48 vs 28	% in ITT: 11.3%	348d vs 273d	75	(27.5% improvement)	P-value = 0.0491	HR = 0.583 (0.337-1.008)	NAd vs NAd	0.7868	0.879 (0.345-2.242)
B_DNA	PSMB9/R60H	A/G	Clinical	SEX	MALE	Excluded	76	466	133	N: 21	% in	422d vs	74	(21.3% improvement)	P-value	HR = 0.835	NA d vs	0.7578	1.06 (0.733-

Appendix 3, Table 3.1: Significant Pair-Wise Combinations

Marker A Type	Marker A	Marker A Level	Marker B Type	Marker B	Marker B Level	Combination	N Selected	N Excluded	N Unevaluable	N (Vc-R vs R)	% of ITT	Median PFS (Vc-R vs R)	PFS Difference	% PFS Difference	PFS Logrank P-value	PFS HR	Median OS (Vc-R vs R)	OS Logrank P-value	OS HR
										8 vs 248	ITT: 69%	348d			= 0.1201	(0.666-1.048)	NAd		1.533)
B_DNA	PSMB9/R60H	A/G	Clinical	SEX	MALE	Total	76	466	133	N: 266 vs 276	% in ITT: 80.3%	414d vs 345d	69	(20% improvement)	P-value = 0.0744	HR = 0.828 (0.673-1.019)	NAd vs NAd	0.8540	1.033 (0.734-1.453)
Protein	CD68 OVERALL POSITIVE	0-50	Protein	P27 SIGNAL INTENSITY	>=2+	Selected	252	189	234	N: 129 vs 123	% in ITT: 37.3%	396d vs 322d	74	(23% improvement)	P-value = 0.0434	HR = 0.734 (0.543-0.992)	NAd vs NAd	0.1214	0.676 (0.411-1.113)
Protein	CD68 OVERALL POSITIVE	0-50	Protein	P27 SIGNAL INTENSITY	>=2+	Excluded	252	189	234	N: 88 vs 101	% in ITT: 28%	352d vs 348d	4	(1.09999999999999% improvement)	P-value = 0.7527	HR = 0.944 (0.665-1.34)	NAd vs NAd	0.3802	1.31 (0.715-2.402)
Protein	CD68 OVERALL POSITIVE	0-50	Protein	P27 SIGNAL INTENSITY	>=2+	Total	252	189	234	N: 217 vs 224	% in ITT: 65.3%	360d vs 345d	15	(4.29999999999999% improvement)	P-value = 0.0864	HR = 0.819 (0.652-1.029)	NAd vs NAd	0.5387	0.887 (0.604-1.301)
Clinical	ANNARBOR	>=III	Protein	CD68 POSITIVE FOLLICULAR	0-50	Selected	239	147	289	N: 110 vs 129	% in ITT: 35.4%	351d vs 278d	73	(26.3% improvement)	P-value = 0.0172	HR = 0.693 (0.512-0.939)	NAd vs NAd	0.2011	0.71 (0.419-1.203)
Clinical	ANNARBOR	>=III	Protein	CD68 POSITIVE FOLLICULAR	0-50	Excluded	239	147	289	N: 80 vs 67	% in ITT: 21.8%	435d vs 492d	-57	(-11.6% improvement)	P-value = 0.248	HR = 1.29 (0.837-1.989)	NAd vs NAd	0.6331	1.187 (0.586-2.406)
Clinical	ANNARBOR	>=III	Protein	CD68 POSITIVE FOLLICULAR	0-50	Total	239	147	289	N: 190 vs 196	% in ITT: 57.2%	396d vs 346d	50	(14.5% improvement)	P-value = 0.1781	HR = 0.846 (0.663-1.08)	NAd vs NAd	0.4068	0.839 (0.554-1.27)
Clinical	FLIPI	Intermediate	Protein	P65 % POSITIVE CYTOPLASMIC SIGNAL	<=90 %	Selected	35	435	205	N: 19 vs 16	% in ITT: 5.2%	351d vs 567d	-216	(-38.1% improvement)	P-value = 0.0277	HR = 2.941 (1.075-8.05)	NAd vs NAd	0.6255	1.524 (0.277-8.379)
Clinical	FLIPI	Intermediate	Protein	P65 % POSITIVE CYTOPLASMIC SIGNAL	<=90 %	Excluded	35	435	205	N: 210 vs 225	% in ITT: 64.4%	396d vs 326d	70	(21.5% improvement)	P-value = 0.0193	HR = 0.761 (0.605-0.957)	NAd vs NAd	0.5888	0.9 (0.616-1.317)
Clinical	FLIPI	Intermediate	Protein	P65 % POSITIVE CYTOPLASMIC SIGNAL	<=90 %	Total	35	435	205	N: 229 vs 241	% in ITT: 69.6%	367d vs 345d	22	(6.4% improvement)	P-value = 0.0902	HR = 0.826 (0.663-1.03)	NAd vs NAd	0.6612	0.921 (0.636-1.332)
B_DNA	PSMB9/R60H	A/A	Clinical	ANNARBOR	<=II	Selected	10	532	133	N: 2 vs 8	% in ITT: 1.5%	87d vs 347d	-260	(-74.9% improvement)	P-value = 0.01	HR = 12.341 (1.094-139.179)	140d vs NAd	0.0009	834275752.139 (0-Inf)
B_DNA	PSMB9/R60H	A/A	Clinical	ANNARBOR	<=II	Excluded	10	532	133	N: 264 vs 268	% in ITT: 78.8%	414d vs 334d	80	(24% improvement)	P-value = 0.0538	HR = 0.814 (0.66-1.004)	NAd vs NAd	0.9481	0.989 (0.7-1.396)
B_DNA	PSMB9/R60H	A/A	Clinical	ANNARBOR	<=II	Total	10	532	133	N: 266 vs 276	% in ITT: 80.3%	414d vs 345d	69	(20% improvement)	P-value = 0.0744	HR = 0.828 (0.673-1.019)	NAd vs NAd	0.8540	1.033 (0.734-1.453)
Clinical	AGEGRP	>65	Protein	CD68 POSITIVE	>50	Selected	25	361	289	N: 13	% in	324d vs	-384	(-54.2% improvement)	P-value	HR = 2.999	NAd vs	0.8613	0.895 (0.257-

Appendix 3, Table 3.1: Significant Pair-Wise Combinations

Marker A Type	Marker A	Marker A Level	Marker B Type	Marker B	Marker B Level	Combination	N Selected	N Excluded	N Unevaluable	N (Vc-R vs R)	% of ITT	Median PFS (Vc-R vs R)	PFS Difference	% PFS Difference	PFS Logrank P-value	PFS HR	Median OS (Vc-R vs R)	OS Logrank P-value	OS HR
				FOLLICULAR						vs 12	ITT: 3.7%	708d			= 0.0252	(1.095-8.21)	971d		3.112)
Clinical	AGEGRP	>65	Protein	CD68 POSITIVE FOLLICULAR	>50	Excluded	25	361	289	N: 177 vs 184	% in ITT: 53.5%	414d vs 338d	76	(22.5% improvement)	P-value = 0.0595	HR = 0.784 (0.608-1.011)	NAd vs NAd	0.4138	0.833 (0.536-1.293)
Clinical	AGEGRP	>65	Protein	CD68 POSITIVE FOLLICULAR	>50	Total	25	361	289	N: 190 vs 196	% in ITT: 57.2%	396d vs 346d	50	(14.5% improvement)	P-value = 0.1781	HR = 0.846 (0.663-1.08)	NAd vs NAd	0.4068	0.839 (0.554-1.27)
Clinical	RACEGRP	OTHER	Protein	20S % NUCLEAR STAINING	0-20	Selected	7	456	212	N: 2 vs 5	% in ITT: 1%	351d vs 763d	-412	(-54% improvement)	P-value = 0.0455	HR = 186167564.897 (0-Inf)	371d vs NAd	0.1573	28100816.562 (0-Inf)
Clinical	RACEGRP	OTHER	Protein	20S % NUCLEAR STAINING	0-20	Excluded	7	456	212	N: 223 vs 233	% in ITT: 67.6%	367d vs 338d	29	(8.6% improvement)	P-value = 0.072	HR = 0.815 (0.652-1.019)	NAd vs NAd	0.5543	0.893 (0.614-1.299)
Clinical	RACEGRP	OTHER	Protein	20S % NUCLEAR STAINING	0-20	Total	7	456	212	N: 225 vs 238	% in ITT: 68.6%	367d vs 345d	22	(6.4% improvement)	P-value = 0.1	HR = 0.83 (0.665-1.037)	NAd vs NAd	0.6640	0.921 (0.634-1.336)
Protein	20S INTENSITY CYTOPLASMIC SIGNAL	>=3+	Protein	P65 % POSITIVE CYTOPLASMIC SIGNAL	<=90 %	Selected	18	445	212	N: 12 vs 6	% in ITT: 2.7%	191d vs 708d	-517	(-73% improvement)	P-value = 0.0111	HR = 9.726 (1.204-78.546)	NAd vs 717d	0.3995	0.525 (0.114-2.411)
Protein	20S INTENSITY CYTOPLASMIC SIGNAL	>=3+	Protein	P65 % POSITIVE CYTOPLASMIC SIGNAL	<=90 %	Excluded	18	445	212	N: 213 vs 232	% in ITT: 65.9%	396d vs 338d	58	(17.2% improvement)	P-value = 0.033	HR = 0.781 (0.622-0.981)	NAd vs NAd	0.7212	0.932 (0.634-1.37)
Protein	20S INTENSITY CYTOPLASMIC SIGNAL	>=3+	Protein	P65 % POSITIVE CYTOPLASMIC SIGNAL	<=90 %	Total	18	445	212	N: 225 vs 238	% in ITT: 68.6%	367d vs 345d	22	(6.4% improvement)	P-value = 0.1	HR = 0.83 (0.665-1.037)	NAd vs NAd	0.6640	0.921 (0.634-1.336)
Clinical	SEX	FEMALE	Protein	CD68 POSITIVE FOLLICULAR	>50	Selected	54	332	289	N: 22 vs 32	% in ITT: 8%	344d vs 889d	-545	(-61.3% improvement)	P-value = 0.0156	HR = 2.293 (1.149-4.575)	1078d vs NAd	0.0178	3.398 (1.16-9.958)
Clinical	SEX	FEMALE	Protein	CD68 POSITIVE FOLLICULAR	>50	Excluded	54	332	289	N: 168 vs 164	% in ITT: 49.2%	414d vs 283d	131	(46.3% improvement)	P-value = 0.007	HR = 0.698 (0.537-0.908)	NAd vs NAd	0.0624	0.649 (0.41-1.026)
Clinical	SEX	FEMALE	Protein	CD68 POSITIVE FOLLICULAR	>50	Total	54	332	289	N: 190 vs 196	% in ITT: 57.2%	396d vs 346d	50	(14.5% improvement)	P-value = 0.1781	HR = 0.846 (0.663-1.08)	NAd vs NAd	0.4068	0.839 (0.554-1.27)
Protein	CD68 POSITIVE FOLLICULAR	>50	Protein	P65 % POSITIVE CYTOPLASMIC SIGNAL	<=90 %	Selected	8	378	289	N: 5 vs 3	% in ITT: 1.2%	487d vs 1083d	-596	(-55% improvement)	P-value = 0.0136	HR = 15582766.206 (0-Inf)	NAd vs NAd	0.1967	0 (0-Inf)
Protein	CD68 POSITIVE FOLLICULAR	>50	Protein	P65 % POSITIVE CYTOPLASMIC SIGNAL	<=90 %	Excluded	8	378	289	N: 185 vs 193	% in ITT: 56%	396d vs 345d	51	(14.8% improvement)	P-value = 0.1162	HR = 0.821 (0.641-1.051)	NAd vs NAd	0.5254	0.874 (0.576-1.325)
Protein	CD68 POSITIVE FOLLICULAR	>50	Protein	P65 % POSITIVE CYTOPLASMIC	<=90 %	Total	8	378	289	N: 190 vs	% in ITT:	396d vs 346d	50	(14.5% improvement)	P-value = 0.178	HR = 0.846 (0.663-1.08)	NAd vs NAd	0.4068	0.839 (0.554-1.27)

Appendix 3, Table 3.1: Significant Pair-Wise Combinations

Marker A Type	Marker A	Marker A Level	Marker B Type	Marker B	Marker B Level	Combination	N Selected	N Excluded	N Unevaluable	N (Vc-R vs R)	% of ITT	Median PFS (Vc-R vs R)	PFS Difference	% PFS Difference	PFS Logrank P-value	PFS HR	Median OS (Vc-R vs R)	OS Logrank P-value	OS HR
				SIGNAL						196	57.2%				1				
Protein	CD68 OVERALL POSITIVE	>50	Protein	P65 % POSITIVE CYTOPLASMIC SIGNAL	<=90 %	Selected	8	432	235	N: 5 vs 3	% in ITT: 1.2%	144d vs 751d	-607	(-80.8% improvement)	P-value = 0.0434	HR = 12170471.716 (0-Inf)	887d vs NAd	0.1970	7048571.582 (0-Inf)
Protein	CD68 OVERALL POSITIVE	>50	Protein	P65 % POSITIVE CYTOPLASMIC SIGNAL	<=90 %	Excluded	8	432	235	N: 211 vs 221	% in ITT: 64%	380d vs 345d	35	(10.1% improvement)	P-value = 0.0487	HR = 0.793 (0.63-0.999)	NAd vs NAd	0.3832	0.841 (0.57-1.242)
Protein	CD68 OVERALL POSITIVE	>50	Protein	P65 % POSITIVE CYTOPLASMIC SIGNAL	<=90 %	Total	8	432	235	N: 216 vs 224	% in ITT: 65.2%	366d vs 345d	21	(6.1% improvement)	P-value = 0.0769	HR = 0.814 (0.648-1.023)	NAd vs NAd	0.5608	0.892 (0.608-1.309)
Protein	CD68 POSITIVE FOLLICULAR	>50	Protein	CD68 POSITIVE PERIFOLLICULAR	0-50	Selected	45	339	291	N: 26 vs 19	% in ITT: 6.7%	344d vs 1083d	-739	(-68.2% improvement)	P-value = 0.0143	HR = 2.642 (1.182-5.908)	NAd vs NAd	0.3295	1.784 (0.548-5.8)
Protein	CD68 POSITIVE FOLLICULAR	>50	Protein	CD68 POSITIVE PERIFOLLICULAR	0-50	Excluded	45	339	291	N: 163 vs 176	% in ITT: 50.2%	414d vs 326d	88	(27% improvement)	P-value = 0.0227	HR = 0.739 (0.569-0.96)	NAd vs NAd	0.1951	0.743 (0.473-1.167)
Protein	CD68 POSITIVE FOLLICULAR	>50	Protein	CD68 POSITIVE PERIFOLLICULAR	0-50	Total	45	339	291	N: 189 vs 195	% in ITT: 56.9%	406d vs 346d	60	(17.3% improvement)	P-value = 0.1772	HR = 0.845 (0.662-1.08)	NAd vs NAd	0.4116	0.841 (0.555-1.273)
Protein	CD68 OVERALL POSITIVE	0-50	Protein	CD68 POSITIVE FOLLICULAR	>50	Selected	32	354	289	N: 19 vs 13	% in ITT: 4.7%	307d vs NAd	NA	(NA% improvement)	P-value = 0.0127	HR = 3.155 (1.22-8.164)	NAd vs NAd	0.4981	1.592 (0.41-6.178)
Protein	CD68 OVERALL POSITIVE	0-50	Protein	CD68 POSITIVE FOLLICULAR	>50	Excluded	32	354	289	N: 171 vs 183	% in ITT: 52.4%	406d vs 326d	80	(24.5% improvement)	P-value = 0.0309	HR = 0.755 (0.585-0.976)	NAd vs NAd	0.2670	0.779 (0.501-1.212)
Protein	CD68 OVERALL POSITIVE	0-50	Protein	CD68 POSITIVE FOLLICULAR	>50	Total	32	354	289	N: 190 vs 196	% in ITT: 57.2%	396d vs 346d	50	(14.5% improvement)	P-value = 0.1781	HR = 0.846 (0.663-1.08)	NAd vs NAd	0.4068	0.839 (0.554-1.27)
B_DNA	PSMB9/R60H	A/A	Clinical	REGION	UNITED STATES / CANADA	Selected	6	536	133	N: 2 vs 4	% in ITT: 0.9%	75d vs 346d	-271	(-78.3% improvement)	P-value = 0.0269	HR = 43248190.876 (0-Inf)	211d vs NAd	0.0177	62252190.678 (0-Inf)
B_DNA	PSMB9/R60H	A/A	Clinical	REGION	UNITED STATES / CANADA	Excluded	6	536	133	N: 264 vs 272	% in ITT: 79.4%	414d vs 338d	76	(22.5% improvement)	P-value = 0.052	HR = 0.814 (0.661-1.002)	NAd vs NAd	0.9831	1.004 (0.711-1.418)
B_DNA	PSMB9/R60H	A/A	Clinical	REGION	UNITED STATES / CANADA	Total	6	536	133	N: 266 vs 276	% in ITT: 80.3%	414d vs 345d	69	(20% improvement)	P-value = 0.0744	HR = 0.828 (0.673-1.019)	NAd vs NAd	0.8540	1.033 (0.734-1.453)

CLAIMS

1. A method for predicting response to a cancer treatment in a cancer patient, comprising: determining the level or quantity of a first predictor in a biological sample from said patient, wherein said first predictor is CD68 or PSMBl (PI 1A) polymorphism; and determining the presence or quantity of a second predictor in said patient; wherein low CD68 or presence of PSMBl (PI 1A) polymorphism is correlated with at least one positive outcome, and presence, absence, or quantity of said second predictor is correlated with at least one positive outcome.

2. The method of claim 1, wherein the first predictor is low CD68.

3. The method of claim 2, wherein low CD68 is 50% or less CD68-positive cells, as determined by immunohistochemistry.

4. The method of claim 1, wherein the first predictor is PSMBl (PI 1A) polymorphism.

5. The method of claim 1, wherein the second predictor is selected from the group consisting of: low CD68, PSMBl (PI 1A) polymorphism, PSMB5 (R24C) polymorphism, age of under 65, one prior treatment, low Follicular Lymphoma International Prognostic Index (FLIPI) score, and low tumor burden.

6. The method of claim 1, wherein the cancer is a hematological cancer.

7. The method of claim 6, wherein the hematological cancer is follicular B-cell non-Hodgkin lymphoma or multiple myeloma.

8. The method of claim 1, wherein said treatment comprises treatment with a proteasome inhibitor.

9. The method of claim 9, wherein said proteasome inhibitor is bortezomib.

10. The method of claim 1, wherein said treatment is a combination treatment.

11. The method of claim 10, wherein the combination treatment comprises a proteasome inhibitor.

12. The method of claim 11, wherein said proteasome inhibitor is bortezomib.

13. The method of claim 11, wherein said combination treatment further comprises rituximab.

14. A diagnostic kit or equivalent for identifying patients who are candidates for a particular cancer treatment comprising: a reagent for detecting quantity or presence of a first predictor in a biological sample; a reagent for detecting quantity or presence of a second predictor in a biological sample; and instructions for employing said predictors to identify patients who are candidates for said treatment; wherein said first predictor is selected from the group consisting of CD68 and PSMB1 (PI 1A) polymorphism.

15. The kit of claim 14, wherein the second predictor is selected from the group consisting of CD68, PSMB1 (PI 1A) polymorphism and PSMB5 (R24C) polymorphism.

16. A method for treating a patient for cancer comprising: determining the quantity or presence of a first predictor in a biological sample from said patient, wherein said first biomarker is selected from the group consisting of CD68 and PSMB1 (PI 1A); determining the presence or quantity of a second predictor in said patient; and selecting a method of treatment dependent on whether said patient is likely to respond to said treatment.

17. Use of a proteasome inhibitor for the treatment of cancer in a patient, wherein the patient is characterized by low CD68 quantity or presence of PSMB1 (PI 1A) polymorphism.

18. The use according to claim 17, wherein the patient is characterized by 0-50% CD68-positive follicular cells, as measured by immunohistochemistry.

19. The use according to claim 17, wherein the patient is further characterized by one or more predictors selected from the group consisting of: low CD68, PSMB1 (PI 1A) polymorphism; PSMB5 (R24C) polymorphism; one prior treatment; low Follicular Lymphoma International Prognostic Index (FLIPI) score; age under 65; and low tumor burden.

20. The use according to claim 17, wherein the cancer is a hematological cancer.

21. The use according to claim 20, wherein the hematological cancer is follicular B-cell non-Hodgkin lymphoma or multiple myeloma.

22. The use according to claim 17, wherein the proteasome inhibitor is bortezomib.

23. The use according to claim 17, wherein the proteasome inhibitor is used in combination with a second therapeutic agent.

24. The use according to claim 23, wherein the second therapeutic agent is rituximab, melphalan or prednisone.

25. A method for treating cancer in a patient characterized by low CD68 or PSMB1 polymorphism, comprising administering to the patient a proteasome inhibitor.

26. The method according to claim 26, wherein the patient is characterized by 0-50% CD68-positive follicular cells, as measured by immunohistochemistry.

27. The method according to claim 25, wherein the patient is further characterized by one or more predictors selected from the group consisting of: low CD68; PSMB1 (PI 1A) polymorphism; PSMB5 (R24C) polymorphism; one prior treatment; low Follicular Lymphoma International Prognostic Index (FLIPI) score; age under 65; and low tumor burden.

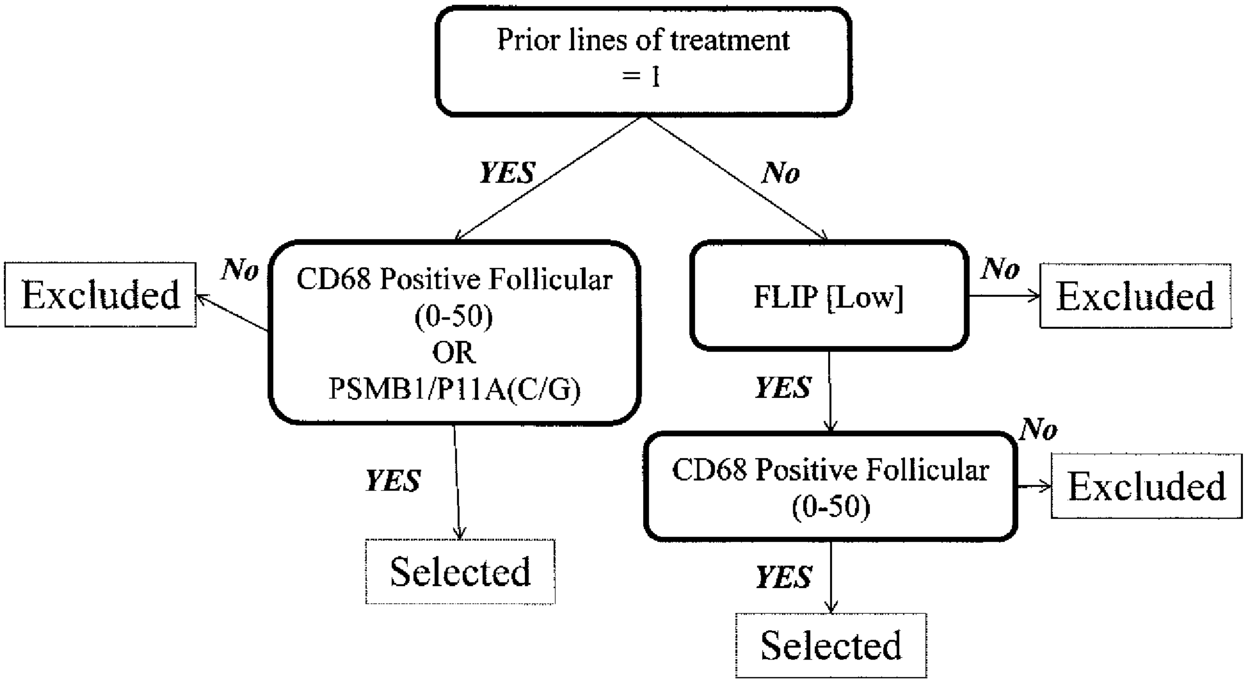
28. The method according to claim 25, wherein the cancer is a hematological cancer.

29. The method according to claim 28, wherein the hematological cancer is follicular B-cell non-Hodgkin lymphoma.

30. The method according to claim 25, wherein the proteasome inhibitor is bortezomib.

31. The method according to claim 25, wherein the proteasome inhibitor is used in combination with a second therapeutic agent.

32. The method according to claim 31, wherein the second therapeutic agent is rituximab, melphalan or prednisone.


Prior lines of treatment
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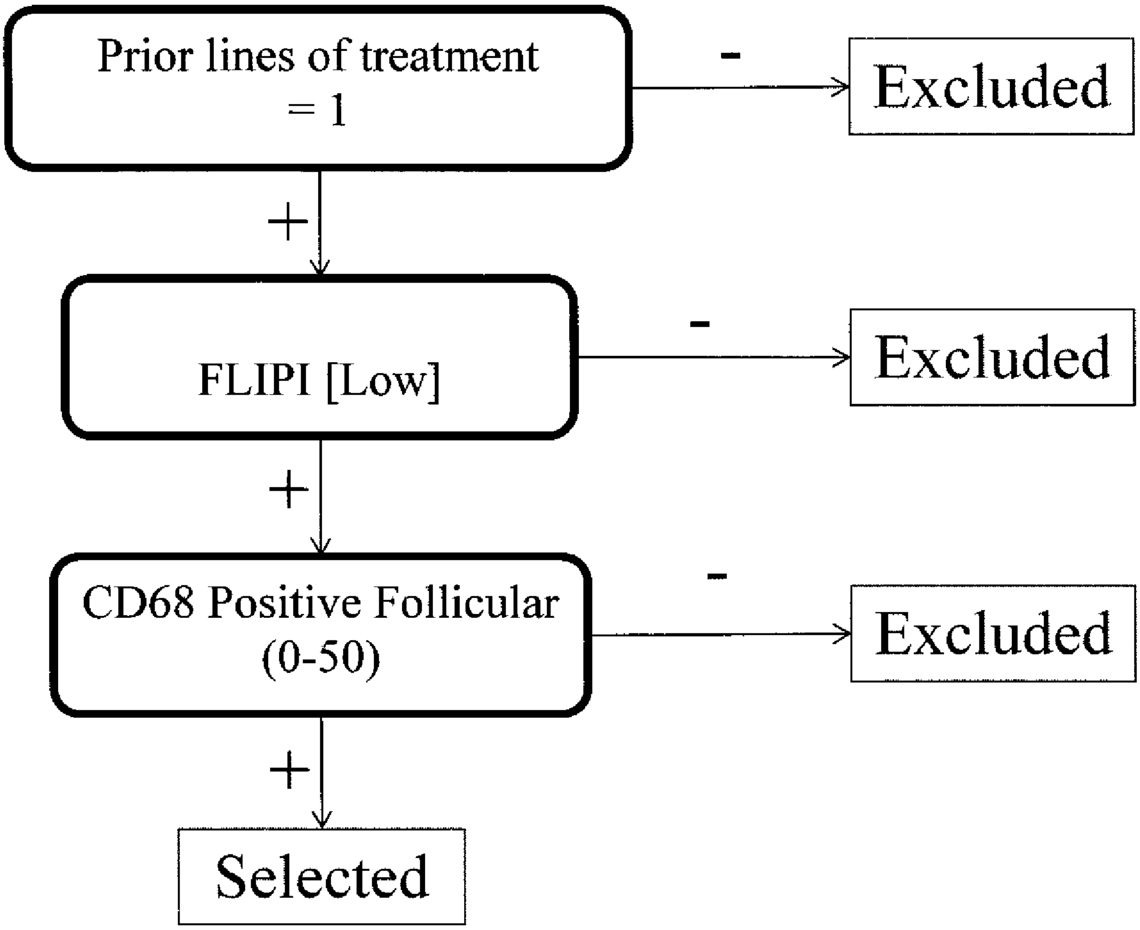
No
CD68 Positive Follicular
(0-50)
OR
PSMB1/P11A(C/G)
No
Excluded
YES
Selected
FLIP [Low]
No
Excluded
YES
CD68 Positive Follicular
(0-50)
No
Excluded
YES
Selected

Figure 1.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Excluded
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FLIPI [Low]
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Excluded
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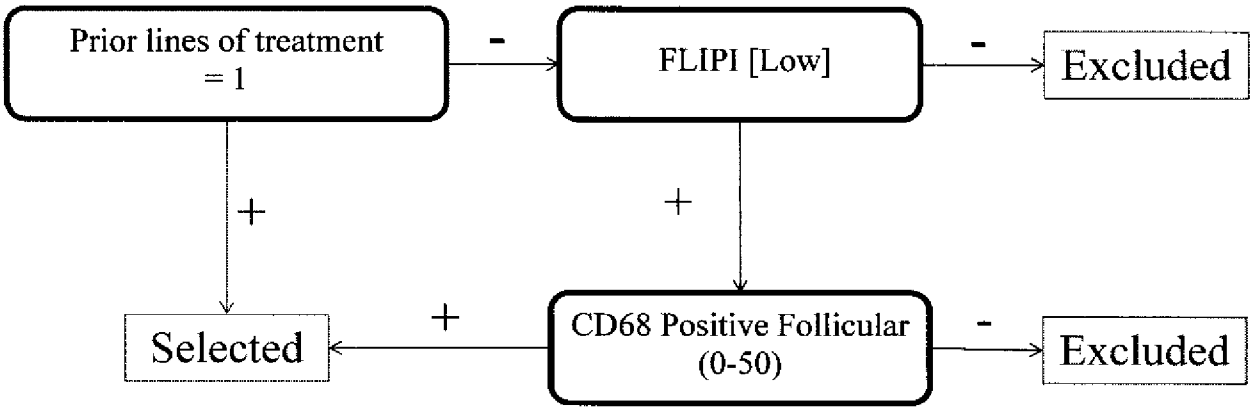
Excluded
+
Selected

Figure 2.


Prior lines of treatment = 1
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FLIPI [Low]
-
Excluded
+
+
Selected
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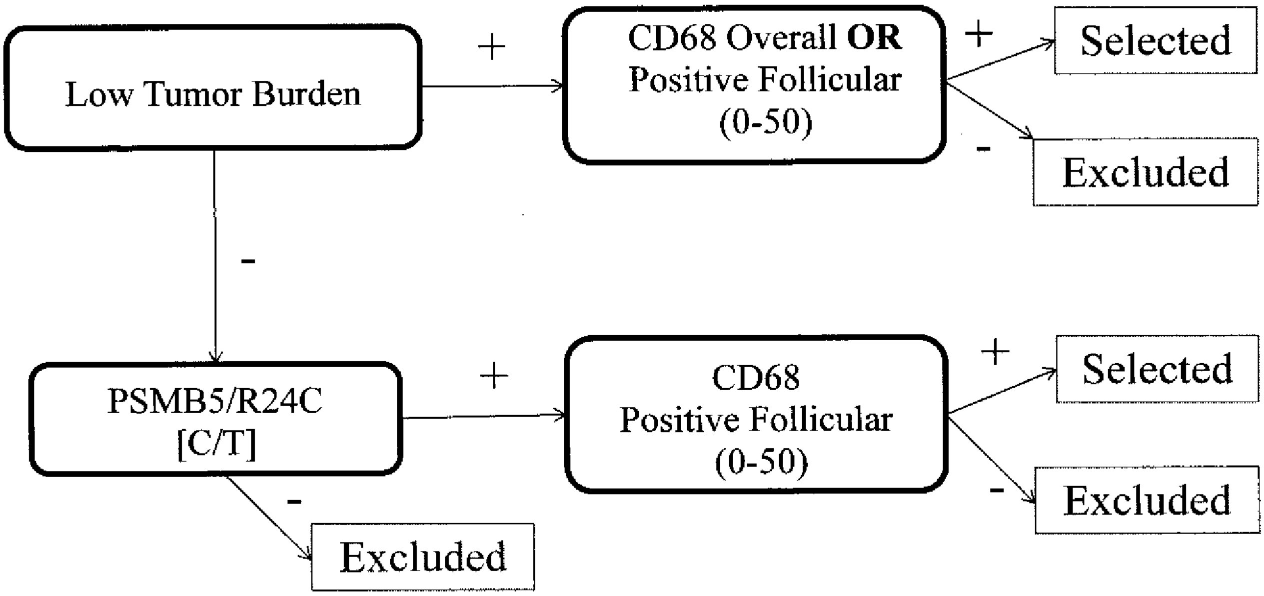
CD68 Positive Follicular (0-50)
-
Excluded

Figure 3.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CD68 Overall **OR** Positive Follicular (0-50)
+
Selected
-
Excluded
-
PSMB5/R24C [C/T]
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CD68 Positive Follicular (0-50)
+
Selected
-
Excluded
-
Excluded

Figure 4.

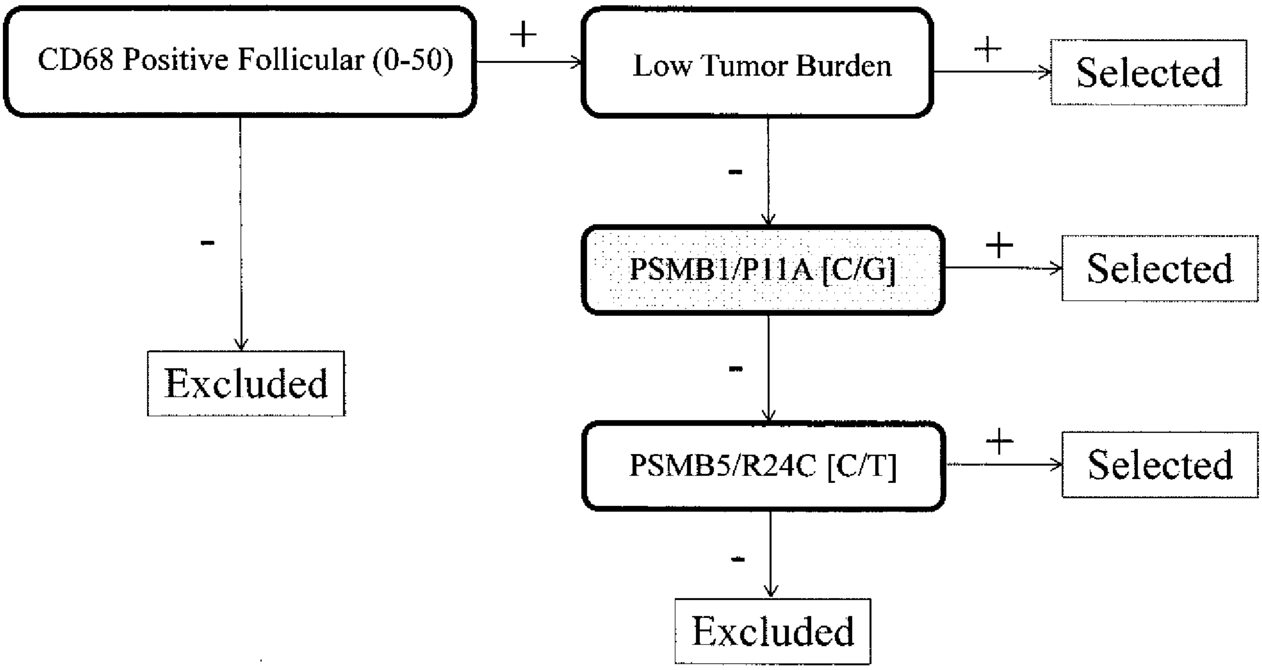
CD68 Positive Follicular (0-50)
+
Low Tumor Burden
+
Selected
-
Excluded
-
PSMB1/P11A [C/G]
+
Selected
-
PSMB5/R24C [C/T]
+
Selected
-
Excluded

Figure 5.

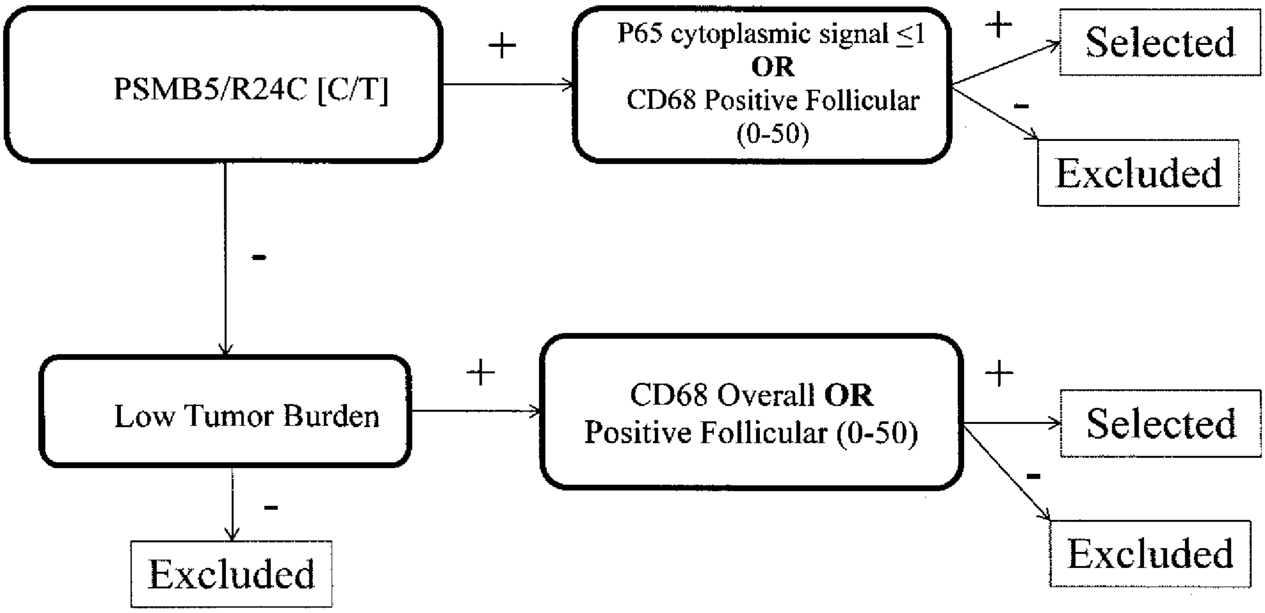
PSMB5/R24C [C/T]
+
P65 cytoplasmic signal ≤1
OR
CD68 Positive Follicular
(0-50)
+
Selected
-
Excluded
-
Low Tumor Burden
+
CD68 Overall OR
Positive Follicular (0-50)
+
Selected
-
Excluded
-
Excluded

Figure 6.

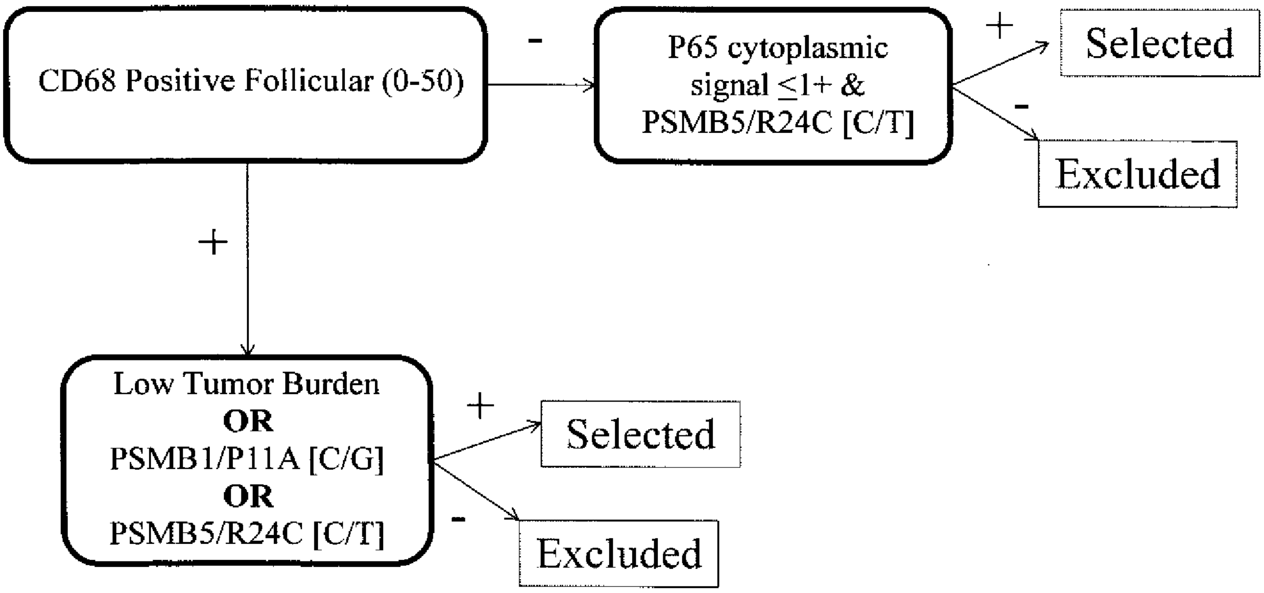
CD68 Positive Follicular (0-50)
-
P65 cytoplasmic signal ≤1+ & PSMB5/R24C [C/T]
+
Selected
-
Excluded
+
Low Tumor Burden
OR
PSMB1/P11A [C/G]
OR
PSMB5/R24C [C/T]
+
Selected
-
Excluded

Figure 7.

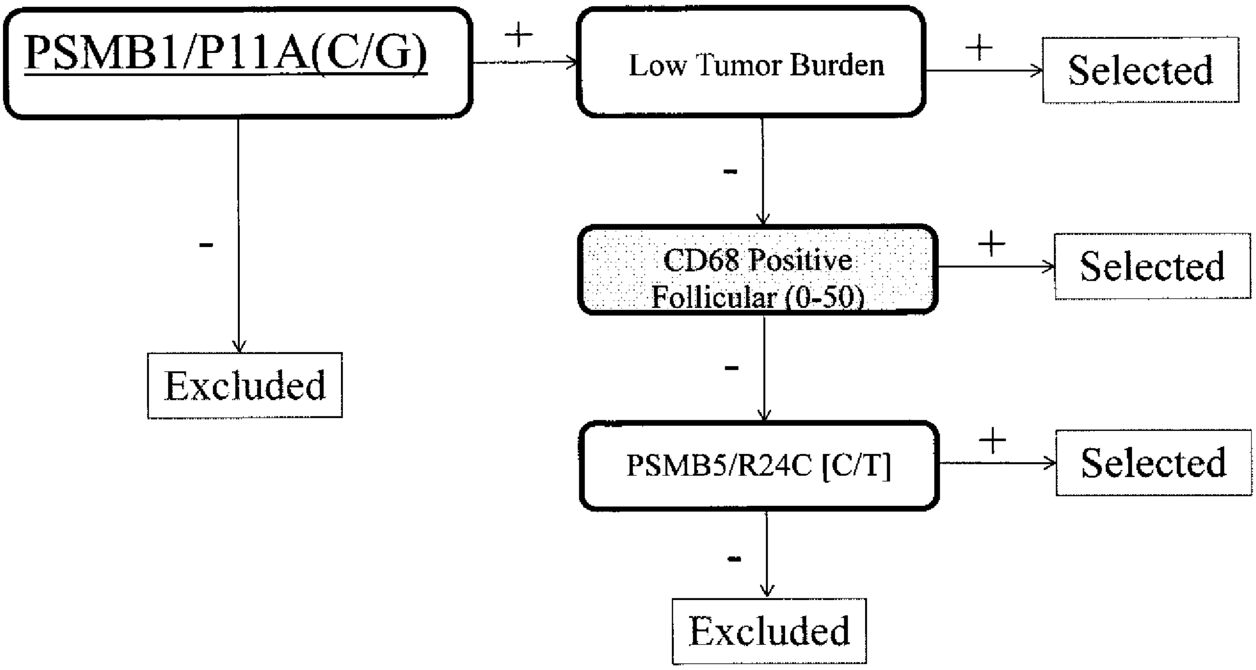
PSMB1/P11A(C/G)
+
-
Excluded
Low Tumor Burden
+
Selected
-
CD68 Positive Follicular (0-50)
+
Selected
-
PSMB5/R24C [C/T]
+
Selected
-
Excluded

Figure 8.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2012/049941

A. CLASSIFICATION OF SUBJECT MATTER
INV. G01N33/574
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
G01N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal , EMBASE, BIOSIS, FSTA, PAJ, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	M. TASKINEN ET AL: "A High Tumor-Associated Macrophage Content Predicts Favorable Outcome in Follicular Lymphoma Patients Treated with Rituximab and Cyclophosphamide-Doxorubicin-Vincristine-Prednisone", CLINICAL CANCER RESEARCH, vol. 13, no. 19, 1 October 2007 (2007-10-01), pages 5784-5789, XP55029715, ISSN: 1078-0432, DOI: 10.1158/1078-0432.CCR-07-0778 abstract ----- -/-	1-16

☒ Further documents are listed in the continuation of Box C.

☐ See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search 11 January 2013	Date of mailing of the international search report 28/01/2013
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Authorized officer Lunter, Pim

4

INTERNATIONAL SEARCH REPORT

International application No

PCT/US2012/049941

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CHRISTIAN STEIDL ET AL: "Tumor-Associated Macrophages and Survival in Classic Hodgkin's Lymphoma", NEW ENGLAND JOURNAL OF MEDICINE, vol. 362, no. 10, 11 March 2010 (2010-03-11), pages 875-885, XP55041466, ISSN: 0028-4793, DOI: 10.1056/NEJMoa0905680 abstract -----	1-16
X	D. DE JONG ET AL: "Impact of the tumor microenvironment on prognosis in follicular lymphoma is dependent on specific treatment protocols", HAEMATOLOGICA, vol. 94, no. 1, 1 January 2009 (2009-01-01), pages 70-77, XP55041470, ISSN: 0390-6078, DOI: 10.3324/haematol.13574 abstract -----	1-16
X	P. FARINHA: "Analysis of multiple biomarkers shows that lymphoma-associated macrophage (LAM) content is an independent predictor of survival in follicular lymphoma (FL)", BLOOD, vol. 106, no. 6, 15 September 2005 (2005-09-15), pages 2169-2174, XP55041472, ISSN: 0006-4971, DOI: 10.1182/blood-2005-04-1565 abstract -----	1-16
X	D. CANIONI ET AL: "High Numbers of Tumor-Associated Macrophages Have an Adverse Prognostic Value That Can Be Circumvented by Rituximab in Patients With Follicular Lymphoma Enrolled Onto the GELA-GOELAMS FL-2000 Trial", JOURNAL OF CLINICAL ONCOLOGY, vol. 26, no. 3, 20 January 2008 (2008-01-20), pages 440-446, XP55029717, ISSN: 0732-183X, DOI: 10.1200/JCO.2007.12.8298 abstract ----- -/--	1-16

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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DAVID P. STEENSMA ET AL: "Splenic histopathological patterns in chronic myelomonocytic leukemia with clinical correlations: reinforcement of the heterogeneity of the syndrome", LEUKEMIA RESEARCH, vol. 27, no. 9, 1 September 2003 (2003-09-01), pages 775-782, XP55041467, ISSN: 0145-2126, D0I: 10.1016/50145-2126(03)00006-7 abstract -----	1-16
X	P. KAMPER ET AL: "Tumor-infiltrating macrophages correlate with adverse prognosis and Epstein-Barr virus status in classical Hodgkin's lymphoma", HAEMATOLOGICA, vol. 96, no. 2, 11 November 2010 (2010-11-11), pages 269-276, XP55041465, ISSN: 0390-6078, D0I: 10.3324/haematol.2010.031542 abstract -----	1-16
X	C. STEIDL ET AL: "Macrophages predict treatment outcome in Hodgkin's lymphoma", HAEMATOLOGICA, vol. 96, no. 2, 31 January 2011 (2011-01-31), pages 186-189, XP55041473, ISSN: 0390-6078, D0I: 10.3324/haematol.2010.033316 page 188 -----	1-16
X	DING L ET AL: "Bortezomib in combination with IGEV chemotherapy regimen for a primary refractory Hodgkin's lymphoma of bone", LEUKEMIA RESEARCH, NEW YORK, NY, US, vol. 33, no. 9, 1 September 2009 (2009-09-01), pages el70-el72, XP026222057, ISSN: 0145-2126, D0I: 10.1016/J.LEUKRES.2009.03.036 [retrieved on 2009-04-28] page el70 - page el71 -----	17-32

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International application No
PCT/US2012/049941

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	RICCI DEBORAH S ET AL: "Pharmacogenomic (PGx) Analysis of Bortezomib-Associated Peripheral Neuropathy in the Phase 3 VISTA Trial of Bortezomib Plus Melphalan-Prednisone Versus Melphalan-Prednisone in Multiple Myeloma", BLOOD; 51ST ANNUAL MEETING OF THE AMERICAN-SOCIETY-OF-HEMATOLOGY; NEW ORLEANS, LA, USA; DECEMBER 05 -08, 2009, AMERICAN SOCIETY OF HEMATOLOGY, US, vol. 114, no. 22, 20 November 2009 (2009-11-20), page 1491, XP008124894, ISSN: 0006-4971 abstract -----	17-32
X	K. A. BLUM: "Upcoming Diagnostic and Therapeutic Developments in Classical Hodgkin's Lymphoma", HEMATOLOGY, vol. 2010, no. 1, 1 December 2010 (2010-12-01), pages 93-100, XP55049366, ISSN: 1520-4391, D0I: 10.1182/asheducation-2010.1.93 page 94; table 2 -----	17-32

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2012/049941

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☒ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos. :

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos. :

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☒ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-16

Method for predicting response to a cancer treatment comprising determining the level of CD68; kit; method for treating a patient for cancer

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2. claims: 17-32

use of a proteasome inhibitor; method for treating comprising administering a proteasome inhibitor

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