SUPPLEMENTARY FILE

Nivolumab Combined with Ibrutinib for Patients with Diffuse Large B-cell Richter Transformation of CLL

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1.0: Inclusion and Exclusion Criteria

1.1. Inclusion Criteria

1. Patients with a diagnosis of Richter transformation (RT), refractory to and/or relapsed after at least one prior standard therapy or untreated with del(17p) by FISH (high-risk cytogenetics)
2. Age 18 years or older
3. Eastern Cooperative Oncology Group (ECOG) Performance Status ≤2
4. Patients must have adequate renal and hepatic function

   - Total bilirubin ≤1.5 x upper limit of normal (ULN). For patients with Gilbert's disease, total bilirubin up to ≤3 x ULN is allowed provided normal direct bilirubin.

   - Serum creatinine ≤1.5 x ULN

   - ALT and AST ≤3 x ULN
5. Females of childbearing potential must have a negative serum or urine beta human chorionic gonadotrophin (β-hCG) pregnancy test result within 24 hours prior to the first dose of treatment and must agree to use an effective contraception method during the study and for 23 weeks following the last dose of the study drugs. Females of non-childbearing potential are those who are postmenopausal greater than 1 year or who have had a bilateral tubal ligation or hysterectomy. Males who have partners of childbearing potential must agree to use an effective contraceptive method during the study and for 31 weeks following the last dose of study drugs
6. Patients or their legally authorized representative must provide written informed consent.

1.2. Exclusion Criteria

1. History of another primary invasive malignancy that has not been definitively treated or in remission for at least 2 years. Patients with non-melanoma skin cancers or with carcinomas in situ are eligible regardless of the time from diagnosis (including concomitant diagnoses). If patients have another malignancy that was treated within the last 2 years, such patients may be enrolled if the likelihood of requiring systemic therapy for this other malignancy within 2 years is less than 10%, as determined by an expert in that particular

malignancy at MD Anderson Cancer Center and after consultation with the Principal Investigator

2. Any major surgery, radiotherapy, cytotoxic chemotherapy, biologic therapy, immunotherapy, immunomodulatory drugs, experimental therapy within 4 weeks prior to the first dose of the study drugs. Note: Prior therapy with anti CD20 monoclonal antibody, anti CD52 monoclonal antibody, and lenalidomide are allowed. For oral targeted therapies (such as idelalisib, venetoclax), a washout of 3 days is allowed.
3. Significant cardiovascular disease such as uncontrolled or symptomatic arrhythmias, congestive heart failure, or myocardial infarction within 2 months of screening, or any Class 3 or 4 cardiac disease as defined by the New York Heart Association Functional Classification.
4. History of stroke or cerebral hemorrhage within previous 2 months.
5. Patients who have uncontrolled hypertension (defined as sustained systolic blood pressure ≥ 160 mmHg or diastolic ≥ 100 mmHg)
6. Known evidence of active cerebral/meningeal CLL. Patients may have history of CNS leukemic involvement if definitively treated with prior therapy and no evidence of active disease at the time of registration.
7. Active, uncontrolled autoimmune hemolytic anemia or immune thrombocytopenia requiring steroid therapy.
8. Patients with autoimmune diseases are excluded: Patients with a history of Inflammatory Bowel Disease (including Crohn's disease and ulcerative colitis) are excluded from this study as are patients with a history of autoimmune disease (e.g., rheumatoid arthritis, systemic progressive sclerosis, systemic lupus erythematosus, Wegener's granulomatosis).
9. Patients with previous allogeneic stem cell transplant (SCT) within 6 months or with active acute or chronic graft-versus host disease are excluded. Patients must be off immunosuppression for GVHD for at least 30 days before cycle 1 day 1.
10. Patients with organ allografts (such as renal transplant) are excluded.
11. History of interstitial lung disease or pneumonitis.
12. Patients who are on high dose steroids (>10mg daily of prednisone or equivalent) or immune suppression medications. Note: Patients on high-dose steroids (doses >10mg/day of prednisone or equivalent) or immune suppression medications are eligible provided these drugs are discontinued at least 3 days prior to starting on the study drugs.
13. Patients with uncontrolled active infection (viral, bacterial, and fungal) are not eligible.
14. Current or chronic hepatitis B or C infection or known seropositivity for HIV.
15. Patient is pregnant or breast-feeding.
16. Concurrent use of investigational therapeutic agent.
17. Malabsorption syndrome or other condition that precludes enteral route of administration.

2.0 Treatment plan

Study drugs	C1D1	C1D15	C2D1	C2D15	C3D1 and then Q2 weeks for a total of 96 weeks	After 96 weeks
Nivolumab*	3 mg/kg IV	3 mg/kg IV	3 mg/kg IV	3 mg/kg IV	3 mg/kg IV	—
Ibrutinib	—	—	Begin 420 mg orally once daily			

Each cycle was 28 days. Patients received nivolumab (3mg/kg IV over approximately 1 hour) monotherapy for the first cycle. Nivolumab continued for up to 24 cycles (96 weeks; 48 infusions). Treatment with ibrutinib was initiated on C2D1 and continued until disease progression, study termination, or a patient experiences a toxicity that requires discontinuation of ibrutinib. Ibrutinib could be introduced earlier than start of cycle 2, in case of worsening disease, after discussion with study PI.

3.0 Supplementary tables and figures

3.1 Supplementary Table 1

Details of prior therapy for CLL and RT

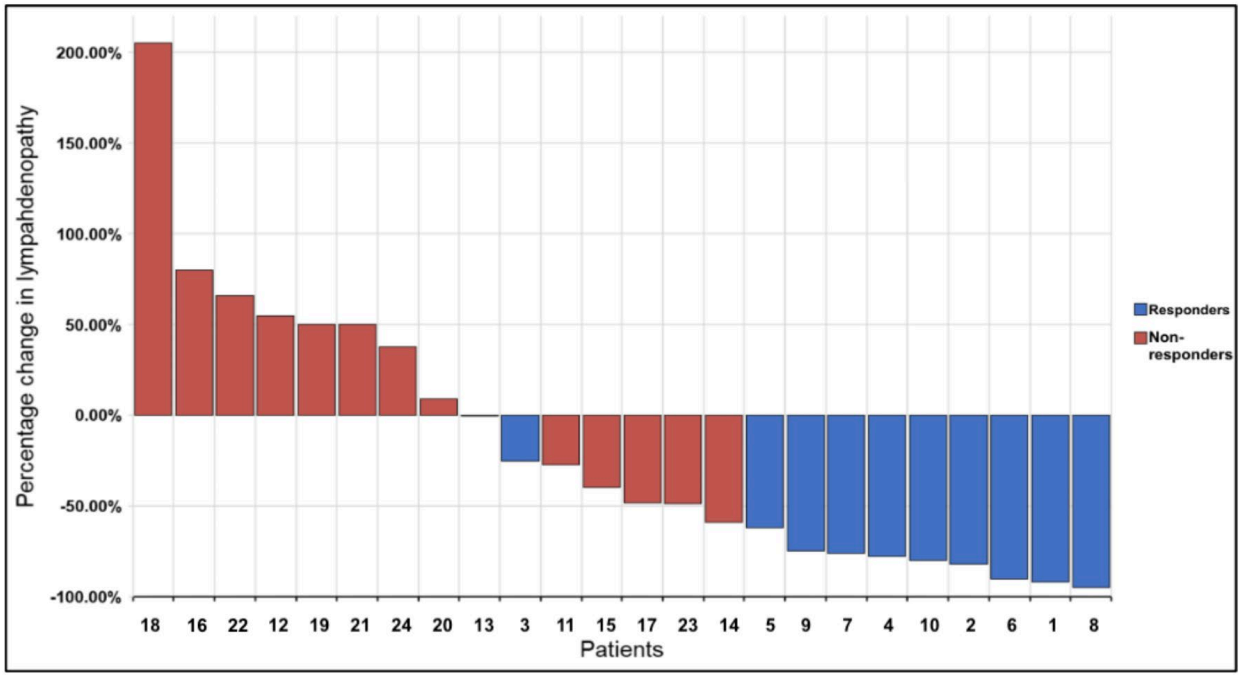
	Prior therapy for CLL	**Prior therapy for RT**
Responders		
Patient 1	Rituximab, FCR	-
Patient 2	FCR, BR, G + HDMP, Idelasilib+ R	-
Patient 3	FR, BR, Ibrutinib	-
Patient 4	PCR, BR, Ibrutinib	-
Patient 5	FCR	-
Patient 6	-	R-CHOP, R-ICE
Patient 7	-	R-CHOP, Auto-SCT
Patient 8	FCR, Alemtuzumab, Allo-SCT, R+ HDMP, Acalabrutinib, Idelasilib+ G, Venetoclax+ G,	Blinatumomab
Patient 9	-	-
Patient 10	BR	-
Non-responders		
Patient 11	Lenalidomide	-
Patient 12	FCR, Ibrutinib, Venetoclax	-
Patient 13	BR, Ibrutinib, Idelasilib	R-Hyper-CVAD
Patient 14	FR, FCR, BR, Ibrutinib+ R	-
Patient 15	FCR, RCD, Ibrutinib+ R	R-CD, G
Patient 16	FCR, Umbralisib + Ublituximab	R-EPOCH, Allo-SCT, OFAR, Venetoclax+ G
Patient 17	BR, Chlorambucil, R+ HDMP, Ibrutinib, Ofatumumab	-
Patient 18	FMD, R+FMD, BR	CD-19 mAb, R-ICE, R-DHAP, R-Hyper-CVAD, Allo-SCT, Ibrutinib
Patient 19	Ibrutinib	-
Patient 20	Ibrutinib	-
Patient 21	BR	R-EPOCH, R-ICE
Patient 22	-	R-CHOP
Patient 23	Ibrutinib+ Venetoclax	-
Patient 24	C+ prednisone, FCR, Ibrutinib+ R, Bendamustine +G	R-Hyper-CVAD+ Venetoclax

Abbreviations: CLL, chronic lymphocytic leukemia; RT, Richter transformation; FCR, fludarabine, cyclophosphamide, rituximab; BR, bendamustine, rituximab; G, obinutuzumab; HDMP, high dose methyl prednisone; R, rituximab; PCR; pentostatin, cyclophosphamide, rituximab; R-CHOP, rituximab, cyclophosphamide, vincristine, prednisone; R-ICE, rituximab, ifosfamide, cisplatin, etoposide; Auto-SCT,

autologous stem cell transplantation; Allo-SCT, allogeneic stem cell transplantation; R-hyper-CVAD, rituximab with hyper fractionated cyclophosphamide, vincristine, adriamycin and dexamethasone alternating with methotrexate and cytarabine; RCD, rituximab, cyclophosphamide, dexamethasone; R-EPOCH, rituximab, etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin; OFAR, oxaliplatin, fludarabine, cisplatin, rituximab; FMD, fludarabine, mitoxantrone, dexamethasone; CD-19 mAb, anti-CD-19 monoclonal antibody (not blinatumomab); C, cyclophosphamide

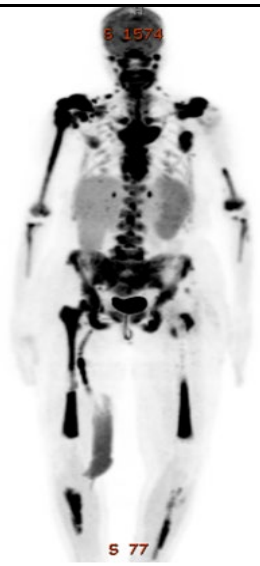
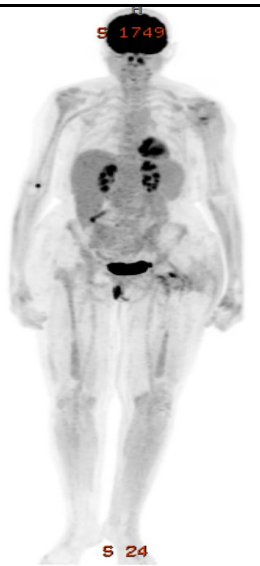
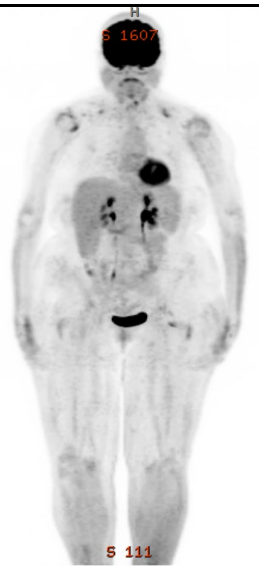
3.2 Supplementary Figure 1

Waterfall plot showing the percentage change in the sum of product of diameter (SPD) of lymph nodes in responders (n=10) and non-responders (n=14). For responders, the best response in lymphadenopathy is denoted; and for non-responders the SPD at the time of going off protocol due to lack of response is denoted (Patients referenced according to the Swimmer's plot)



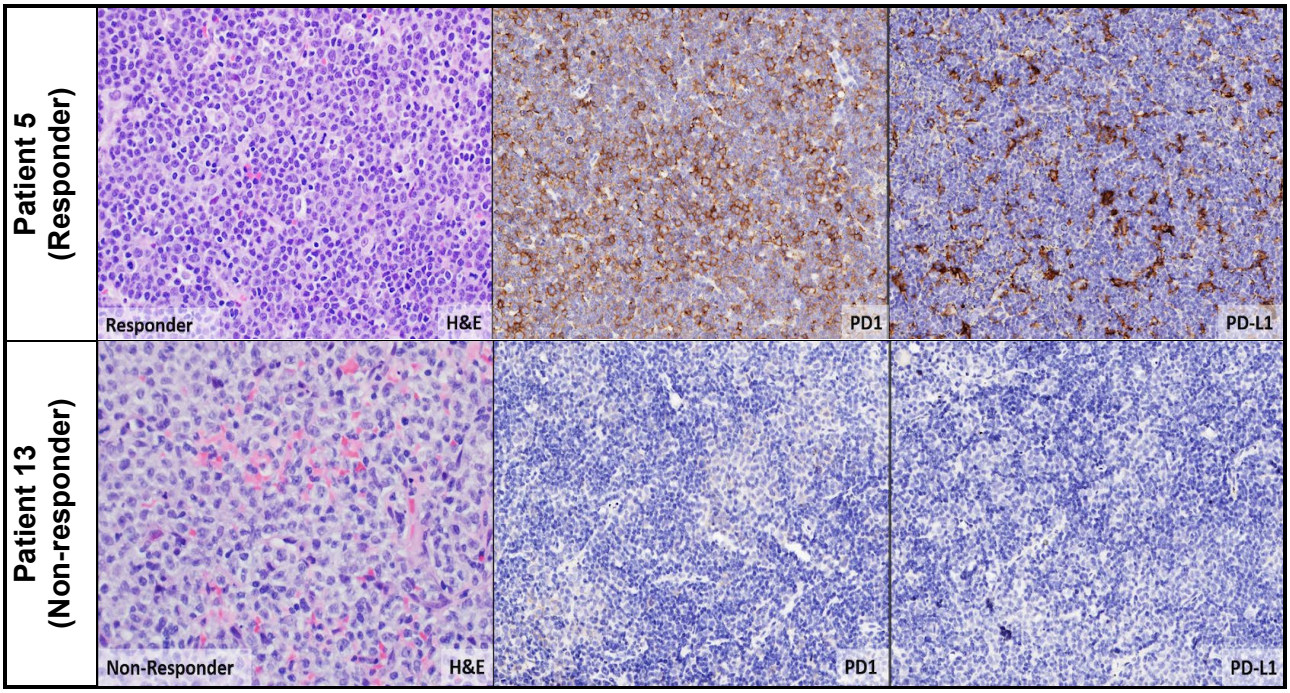
3.3 Supplementary Figure 2

Baseline (A) and follow up (B and C) PET scan images on study of a patient (Patient 8) with RT in the bone marrow and lymph nodes/spleen who had been heavily treated before for CLL/RT. The patient attained complete metabolic response of the RT after 3 months with disappearance of RT and CLL from the bone marrow.

Prior therapies FCR Alemtuzumab Hyper-CVAD Allo-SCT Rituximab + steroids Acalabrutinib Idelalisib + CD20 Venetoclax + CD20 Blinatumomab			
	A	**B**	**C**
	PET images		
Time points	Baseline	3 months	12 months
Bone marrow	80% RT + CLL	No RT, MRD+ CLL	No RT, U-MRD4 CLL

3.4 Supplementary Figure 3

Representative images of high expression of PD1 on the tumor cells of a responding patient and absent PD1 expression on a non-responding patient



3.5 Supplementary Figure 4: Flowchart representing disposition of the study patients