

Supplemental Tables

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Supplemental Table 1. Serious Toxicities Phase I Lenalidomide/Rituximab Trial

Pt No.	Lenalidomide Dose Level (mg/day)	Months on Lenalidomide Monotherapy	Months on Lenalidomide /Rituximab	Grade 3 or 4 Adverse Events
1	10	2	4	None
2	10	1	0	None
3	10	21	0	None
4	20	48 +	0	None
5	20	2	0.5	Gr. 3 Infection
6	20	1.75	0	Gr. 3 Confusion (DLT)
7	20	1	0.5	Gr. 3 Neutropenia
8	20	9	0.25	None
9	20	0.25	0	Not evaluable
10	20	18	0	Gr. 4 Infection (DLT)
11	15	1	0	Gr. 5 Tumor Progression
12	15	1	2	Gr. 3 Neutropenia, Gr. 4 Pneumonia
13	15	13	0	Gr. 4 Neutropenia, Gr. 3 Zoster
14	15	21+	0	None

Supplemental Table 2. Mini-Mental Status Score Results for Phase I Trial Subjects at Baseline and for the first five months of study treatment with lenalidomide and/or lenalidomide/rituximab.

Pt	Baseline	Month 1	Month 2	Month 3	Month 4	Month 5
1	30	30	30	30	30	30
2	28	28				
3	28	29	30	30	30	30
4	30	30	30	30	30	30
5	17	17	21	22		
6	23	14	7			
7	27	27	26			
8	28	30	28	30	29	30
9	26					
10	23	28	26	29	26	22
11	20	0				
12	17	20	21	17		
13	30	30	30	30	30	30
14	25	30	30	30	30	30

Supplemental Table 3. Control and CNS Lymphoma Subjects: CSF Metabolomic Discovery Set (from Figure 2).

Group	Non-Neoplastic Controls	
	Age/Sex	Diagnosis
A1	65/M	Staging, Myelodysplastic Syndrome
A2	65/M	Inflammatory Arthritis
A3	73/F	Staging, AML
A4	39/F	Staging, AML
A5	45/F	Staging, ALL
A6	59/M	Staging, Systemic DLBCL
A7	44/M	Limbic Encephalitis
A8	43/M	Multiple Sclerosis
A9	17/M	Staging, ALL
A10	20/M	Staging, ALL
A11	73/M	Staging, AML
A12	65/M	Staging, AML
A13	65/M	Staging, AML
A14	38/M	Multiple Sclerosis
Group	CNS Lymphoma	
	Age/Sex	Diagnosis
B1	82/M	PCNSL/DLBCL
B2	84/M	PCNSL/DLBCL
B3	63/M	PCNSL/DLBCL
B4	68/F	PCNSL/DLBCL, + Malignant Cytology
B5	71/M	PCNSL/DLBCL, + Malignant Cytology
B6	63/M	PCNSL/DLBCL
B7	68/F	PCNSL/DLBCL
B8	72/M	PCNSL/DLBCL, + Malignant Cytology
B9	60/F	PCNSL/DLBCL, + Malignant Cytology
B10	75/F	PCNSL/DLBCL
B11	69/F	Relapsed PCNSL/DLBCL, + Malignant Cytology
B12	63/F	Relapsed PCNSL/DLBCL, + Malignant Cytology
B13	73/M	Relapsed SCNSL/Marginal Zone Lymphoma, + Malignant Cytology
B14	55/M	Relapsed PCNSL/DLBCL, + Malignant Cytology

Supplemental Table 4. PCNSL Cases used to evaluate IDO1 Expression by Immunohistochemistry.

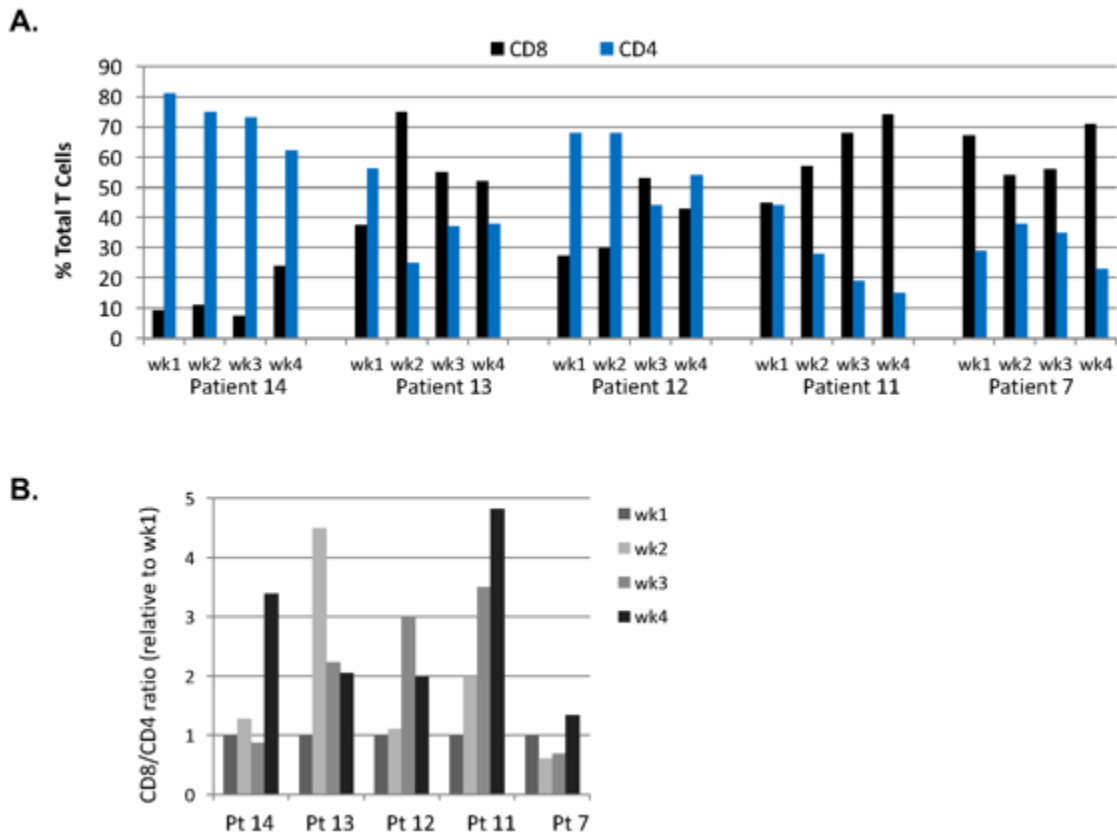
Case	Diagnosis	Age/Sex	IDO1 Immunoreactivity
1	PCNSL/DLBCL	85/M	5%, lymphoma cells only
2	PCNSL/DLBCL	68/F	5%, lymphoma cells only
3	PCNSL/DLBCL	74/M	100%, tumor-associated macrophages only
4	PCNSL/DLBCL	72/F	5%, lymphoma cells only
5	PCNSL/DLBCL	60/F	100%, tumor-associated macrophages only
6	PCNSL, DLBCL, EBV+	67/F	>40%, lymphoma and tumor macrophages
7	PCNSL/DLBCL	63/M	>40%, lymphoma and tumor macrophages
8	PCNSL/DLBCL	80/F	>40%, lymphoma and tumor macrophages
9	PCNSL/DLBCL	66/F	Negative immunoreactivity
10	PCNSL/DLBCL	54/F	>40%, lymphoma and tumor macrophages
11	PCNSL/DLBCL	41/M	>40%, lymphoma and tumor macrophages
12	PCNSL/DLBCL	48/F	>40%, lymphoma and tumor macrophages
13	PCNSL/DLBCL	70/M	>40%, lymphoma and tumor macrophages
14	PCNSL/DLBCL	61/F	>40%, lymphoma and tumor macrophages
15	PCNSL/DLBCL	65/M	100%, tumor-associated macrophages only
16	PCNSL/DLBCL	63/M	>40%, lymphoma and tumor macrophages
17	PCNSL/DLBCL	71/M	>40%, lymphoma and tumor macrophages
18	PCNSL, lymphoblastic	54/M	>40%, lymphoma and tumor macrophages
19	PCNSL/DLBCL	54/F	100% tumor-associated macrophages only
20	PCNSL/DLBCL	86/F	>40%, lymphoma and tumor macrophages

Supplemental Table 5. Restaging Studies During Lenalidomide Maintenance

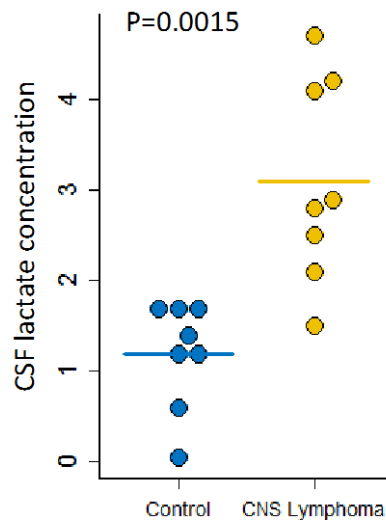
Pt	Response Duration	Restaging Studies During Lenalidomide Maintenance
1	12 months	7 Brain MRI, 1 Ophthalmologic examination
2	39 months+	9 Brain MRI
3	8 months	3 Brain MRI, 2 Ophthalmologic examinations
4	32 months+	7 Brain MRI, 3 Ophthalmologic examinations
5	9 months	3 Brain MRI, 5 Ophthalmologic examinations
6	13 months	3 Brain MRI
7	2 months	1 Brain MRI
8	6 months	2 Brain MRI
9	25 months+	4 Brain MRI, 6 Ophthalmologic examinations
10	14 months+	3 Brain MRI, 8 Ophthalmologic examinations

Supplemental Figure 1. Lenalidomide induces an increase in the CD8:CD4 T-cell ratio in CSF in CNS lymphoma patients.

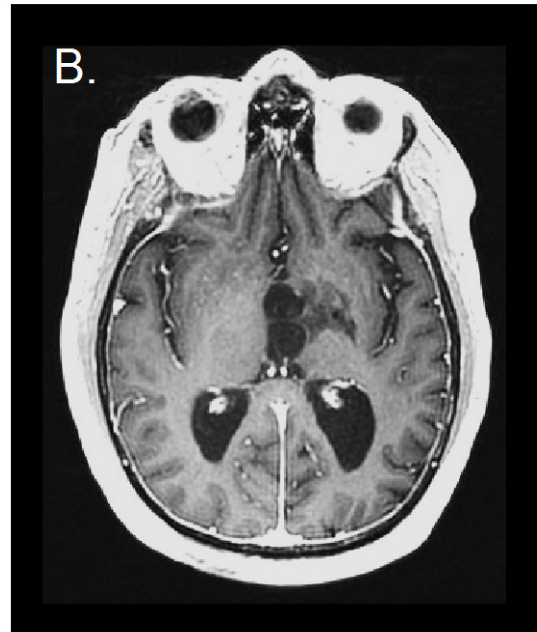
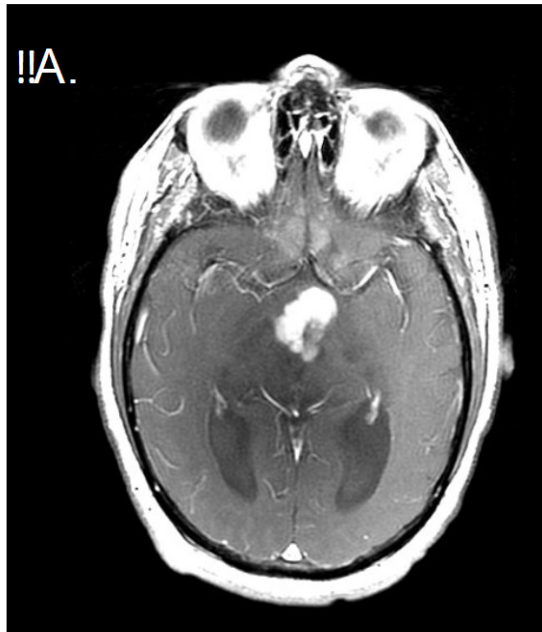
Application of multicolor flow-cytometry to analyze T cell subsets in CSF ([66] during the first four weeks of cycle 1 lenalidomide monotherapy demonstrated reproducible increases in the ratio of CD8+ relative to CD4+ T cells, compared to week 1, pretreatment baseline, in four out of five relapsed, refractory CNS lymphoma patients. (1A). Of note, the normal CD4:CD8 ratio in the CSF of HIV negative, healthy subjects is approximately 3:1 [66]. (1B).



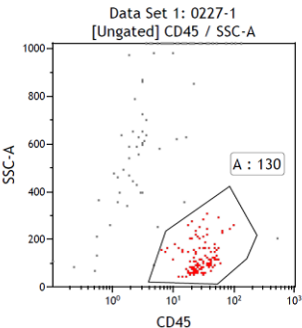
Supplemental Figure 2. Validation of elevated CSF lactate in CNS Lymphomas as determined by Beckman Coulter Clinical Chemistry Analyzer. **Controls.** CSF from 8 cases of non-neoplastic conditions (3M, 5F; median age 53, range 26-77; including negative staging AML (3 cases), multiple sclerosis (3 cases), amyotrophic lateral sclerosis (1 case), fibromyalgia (1 case): median CSF lactate concentration, controls: 1.3 mmole/l. **CNS lymphomas.** CSF from 8 independent cases of CNS DLBCL, four newly-diagnosed and four at relapse (4M, 4F; median age: 63, range 51-76): median CSF lactate concentration, CNS lymphoma: 2.85 mmole/l.



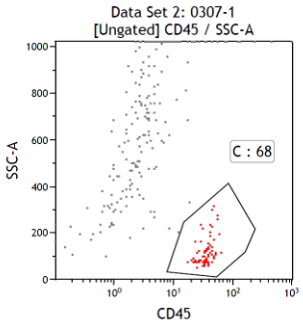
Supplemental Figure 3. Example of a durable remission with Lenalidomide maintenance: after fourth progression of methotrexate-resistant CNS lymphoma. A. MRI of relapsed PCNSL patient 4 (Table 3): one month after salvage high-dose methotrexate plus rituximab. (Longest previous response duration was 8 months (CR1)). B. After involved-field irradiation, CR5 was achieved as assessed by MRI, followed by lenalidomide maintenance, resulting in response duration ≥ 32 months.



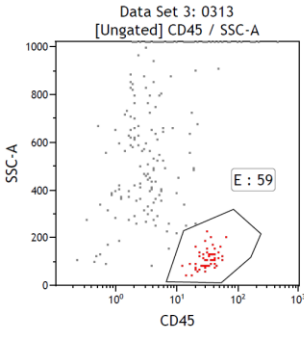
Supplemental Figure 4. Example of Resolution of Leptomeningeal Lymphoma Induced by Lenalidomide Monotherapy, Confirmed by Flow-Cytometry.



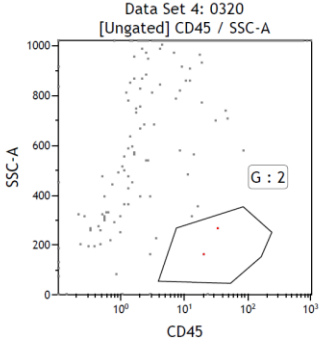
Baseline



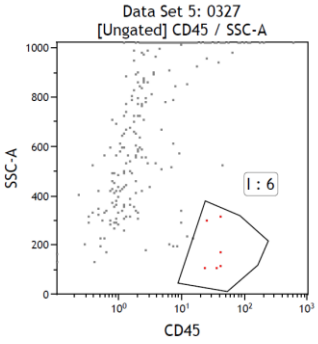
Wk1



Wk2



Wk3



Wk4