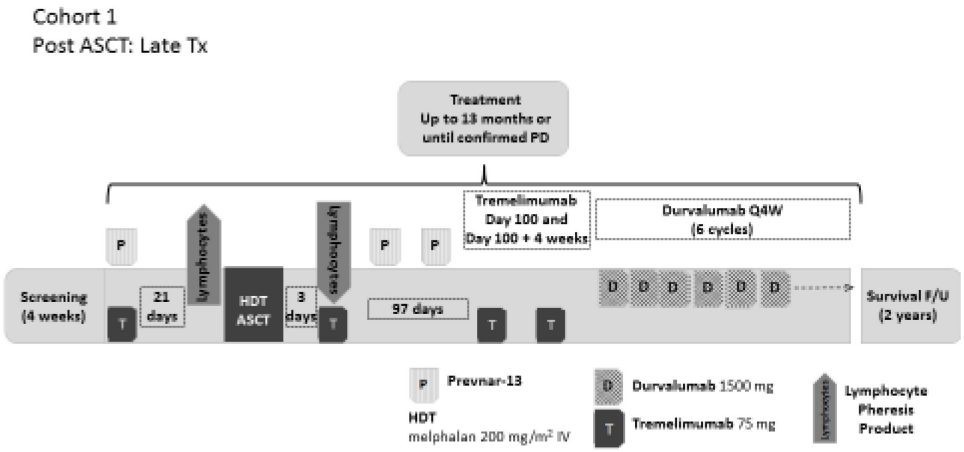
LUD2014-010 (NCT02716805). A Phase 1 Study to Assess Safety and Tolerability of Tremelimumab and Durvalumab, Administered with High Dose Chemotherapy and Autologous Stem Cell Transplant (HDT/ASCT)

Expanded Access Protocol for LUD2014-010 Cohort 1 Subjects Continuing Tremelimumab Treatment 12September2017

LUD2014-010 was initiated under IND 129021 for durvalumab.

Six subjects have been enrolled into Cohort 1. One subject [redacted] has discontinued therapy due to disease progression as discussed below. Five subjects remain on study. The dosing scheme for Cohort 1 is provided below.



A partial clinical hold on this study issued by FDA on September 1, 2017. LICR has implemented this partial clinical hold with the following immediate actions:

- The Principal Investigators at the two participating sites have been notified and they have informed their IRBs.
- No new patients will be entered into this study.
- Durvalumab will be discontinued in Subject [redacted], and durvalumab will not be started in any other patient.
- A decision to amend or discontinue this protocol will be made at a later date.
- All subjects will be informed of the results of the pembrolizumab clinical studies in Multiple Myeloma, the FDA partial clinical hold and, if applicable, reconsented prior to additional study treatment.
- Ongoing subjects receiving clinical benefit may remain on study treatment with tremelimumab.

In discussions with the two Principal Investigators as well as the study chair for this study, it was their desire and recommendation that the 4 ongoing subjects who are now in the transplant phase of the study be permitted to continue the tremelimumab treatment portion of the study after being informed of the data from the two pembrolizumab studies in Multiple Myeloma and re-consented. These subjects will be treated in accordance with this expanded access protocol as outlined in the flowchart provided in ***Figure 1***.

This addendum references version 3 of the LUD2014-010 protocol, the most recent version submitted to IND 129021 and approved by the IRBs. This protocol will be followed, superseded by the updated information in this expanded access protocol including the schedule of events, as the LUD2014-010 protocol has information that would be referenced, such as preparation and administration of tremelimumab, AE reporting, toxicity management, and other important guidance.

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In **Table 1** on the following page, detailed information on the 4 subjects including their disease stage and prior therapies as well as the dates on the next protocol-scheduled treatment is provided.

These four subjects have received tremelimumab pre-transplant and 3 of them have also received the tremelimumab together with the lymphocyte re-infusions on day 3 post-transplant. Based on discussions with the Principal Investigators at the two study sites as well as the study chair, it is believed that these subjects are obtaining clinical benefit from this treatment and therefore would like to continue treatment with tremelimumab up to and including the day 100 and day 100 + 4 weeks dosing and followed as per ***Figure 1***. No durvalumab will be administered in cycles 3-8. These subjects may receive lenalidomide maintenance after Cycle 3 at the investigator's discretion.

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Table 1: LUD2014-010 Subjects Continuing Tremelimumab Therapy

Subject Age/Gender	Site	Date of Enrollment	Tremelimumab 75 mg Administration	Next steps
[redacted]	[redacted]	22-Aug-17	1 dose Pre ASCT Day -31	3 doses tremelimumab Day 3, day 100 and day 128 Next dose tremelimumab 9/28/2017
Background/reason for continuing treatment	Initially diagnosed with ISS I, IgA kappa MM in January 2012 after presenting with neck/back pain secondary to a C3 plasmacytoma, s/p corpectomy, laminectomy with fixation from C3-C5, then RT, induction therapy with Velcade, thalidomide, and dexamethasone, and ASCT with melphalan, with overall VGPR. In June 2016, relapsed with new bone lesions and treated with ixazomib, Revlimid, and dexamethasone with PR. In December 2016, progression of disease (POD) and switched to carfilzomib, pomalidomide, and dexamethasone, achieving a VGPR. In May 2017, POD with rising serum markers, rib/back pain, multiple FDG-avid plasmacytomas, and high-risk cytogenetics. Received VD-PACE x2 (May and June 2017) with excellent response (near resolution of FDG-avid plasmacytomas) and enrolled on the study. The patient has aggressive, multiply relapsed disease that is still chemosensitive, proving rationale for salvage ASCT with melphalan. However, due to the nature of his disease, he is at extremely high risk for early relapse after transplant. The addition of an immune modulatory agent, like tremelimumab, offers the potential to improve his response to salvage ASCT, beyond the limited benefits of available standard treatments. The patient is extremely motivated to participate and specifically requested this study during his initial transplant consultation at our center.			

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Subject Age/Gender	Site	Date of Enrollment	Tremelimumab 75 mg Administration	Next steps
[redacted]	[redacted]	4-May-17	2 doses Pre ASCT Day -31 PBL Day 3	2 doses tremelimumab days 100 and 128. Next dose tremelimumab 10/20/2017
Background/reason for continuing treatment	Primary Dx: IgG Lambda MM diagnosed in 2011. BMBx with monotypic plasma cells,85% overall cellularity. Normal Karyotype 46, XX. Fish : gain of IGH and TP53 and trisomy 13 associated with intermediate prognosis in multiple myeloma 1. First line tx- VRD x3 Melphalan with ASCT and maintenance Revlimid 15 mg. Rev reduced to 10 mg and then 5 mg due to cytopenias. Then off treatment until first relapse. 2. Second line treatment- Ludwig protocol LUD2014-010 Reason for continuing treatment-: Patient has responded very well to transplant with intermediate risk genetics. FLC have dropped from 201.75 to 9.28 and M-Spike has dropped from 0.94 to 0.00 on 60 days post-transplant without any SAE			
[redacted]	[redacted]	7-Jun-17	2 doses Pre ASCT Day -31 PBL Day 3	2 doses tremelimumab days 100 and 128. **Next Dose tremelimumab 9/21/2017**
Background/reason for continuing treatment	IgM Kappa MM, initially diagnosed ISS stage 1, DS stage II. Presented w/ T2 plasmacytoma. BMBx 5/16/16 with 5% PCs. FISH +TP53 deletion, monosomy 12 and gain 1q25. First Line- induction KRDx4/with Ludwig protocol LUD2014-010. Reason for continuing treatment: Patient has high-risk genetics that have possible early relapse with relatively chemo resistance clone could have better clinical benefit with the addition of immunomodulatory agents and transplant. Patient has 0.00 m-spike 30 days post-transplant and did not have any SAE during infusion.			

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Subject Age/Gender	Site	Date of Enrollment	Tremelimumab 75 mg Administration	Next steps
[redacted]	[redacted]	27-Jun-17	2 doses Pre ASCT Day -31 PBL Day 3	2 doses tremelimumab days 100 and 128. Next dose tremelimumab 11/13/2017
Background/reason for continuing treatment	Smoldering multiple myeloma IgA Lambda, diagnosed in July 9, 2013. Progressive increase in paraprotein without CRAB symptoms. Bone marrow on December 20, 2013. ISS stage I; Durie-Salmon stage IA. The result is abnormal and indicates a plasma cell clone with a 1q duplication, monosomy 13, and FGFR3/IGH fusion, t(4;14). At diagnosis, t(4;14) and 1q duplication are associated with an intermediate prognosis in multiple myeloma 1. First Line Therapy January 13, 2014: VRD x 5 cycles; CR 04/01/14. R25/D20 beginning 07/16/2014 for 6 cycles. R10/D4 maintenance. 2. Biochemical Relapse March 2017. Ludwig Protocol LUD2014-010 Reason for continuing treatment: Patient has responded very well to transplant with greater than low risk genetics. M-spike prior to transplant was 0.63 which has dropped to 0.0 after 30 days post-transplant. Patient has not had any SAE with infusion treatments.			

Figure 1: Schedule of Procedures

Study Flowchart for Cohort 1	**Screening / Baseline**	**Treatment**										
		Pre ASCT			**HDT /ASCT**		**PBL**	**Post ASCT and PBL**			**Cycle 1**	**Cycle 2**
Treatment weeks (based on ASCT)	**-9 to -5**				**1**			**2**	**5**	**9**	**14**	**18**
Cycle Day											**1**	**1**
Treatment days (based on ASCT)	**-62 to -34**	**-33±2**	**-31±2**	**-10 to -3**	**-2**	**0**	**3**	**12 ±4**	**30 +10**	**60±4**	**100±10**	**128±4**
Study Drugs and PBL Administration												
Tremelimumab (75 mg)			X				X[2]				X	X
Melphalan					x							
Autologous Stem cell transplant (ASCT)						x						
Peripheral blood lymphocyte (PBL) pheresis				x								
PBL infusion							X[2]					
Prevnar - 13		X[1]							x[1]	x[1]		
Multiple Myeloma Tests												
PET/CT scan or MRI spine As clinically	X										x	
Myeloma serum tests[5]	X			x							x	x
Myeloma urine tests[5]	X			x							x	x
Study Procedures and Examinations												
Physical Exam (incl. weight and vitals)	X	X	x	x	x	x	x	x	x	x	x	x
12-Lead ECG	X											
ECHO- Heart Ultrasound	X											
Lung Function tests	X											
Routine Laboratory Samples												
Routine blood Test (chemistry and complete blood count)[3]	-40 to -33	X	x	x	x	x	x	x	x	x	x	x
Endocrine panel (Thyroid tests)[3]	-40 to -33				x						x	
Urinalysis[3]	-40 to -33	X	x	x	x	x	x	x	x	x	x	x
Serum pregnancy test (urine test only on Day -31)[3]	-40 to -33		x			x	x				x	x
Bone Marrow Samples												
Bone Marrow Sampling (tissue and aspirate) for routine and research laboratories	x										x	
Whole Blood for Research Labs												
Whole Blood Sampling for Research testing	X	X[3]	X[3]	X[4]	X[3]			X[3]	X[3]	X[3]	X[3]	X[3]

1. Prevnar dose and tremelimumab dose must be separated by a minimum of 48 hrs.
2. Tremelimumab must be infused within 24 hours following PBL infusion
3. Collect pre-dose (prior to drug administration) or other infusion. Note: It is strongly recommended that hematology, chemistry and pregnancy test (when applicable) results are reviewed before dosing.
4. Samples will be removed from the pheresis product
5. If serum and urine IF are positive, subsequent analysis is not necessary unless the subject achieves a response of VGPR or greater
6. For subjects who did not experience progression while on study

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Study Flowchart for Cohort 1 continued		**On Study Follow-up**			**Post Study Follow-up Every 6 months for up to 2 years from start of treatment**
	Cycle 3	**Cycle 3 or Last study drug +28 ±4 days**	**Cycle 3 or Last study drug +56 ±4 days**	**Cycle 3 or Last study drug +91 ±4 days End of Study**	
Treatment weeks (based on ASCT)	**22**				
Cycle Day	**1**				
Treatment days (based on ASCT)	**156 ±4**				
Multiple Myeloma Tests					
PET/CT scan or MRI spine As clinically		x			
Myeloma serum tests[5]	x	x			
Myeloma urine tests[5]	x	x			
Study Procedures and Examinations					
Physical Exam (incl. weight and vitals)	x	x	x	x	
12-Lead ECG		x			
ECHO- Heart Ultrasound					
Lung Function tests					
Routine Laboratory Samples					
Routine blood Test (chemistry and complete blood count)	x	x	x	x	
Endocrine panel (Thyroid tests)	x	x		x	
Urinalysis	x	x	x	x	
Serum pregnancy test (urine test only on Day -31)[3]		x		x	
Bone Marrow Samples					
Bone Marrow Sampling (tissue and aspirate) for routine and research laboratories		x			
Whole Blood for Research Labs					
Whole Blood Sampling for Research testing	x	x			
Long-Term Follow-up					
Overall Survival					x
Progression Free Survival[6]					x

1. Prevnar dose and tremelimumab dose must be separated by a minimum of 48 hrs.
2. Tremelimumab must be infused within 24 hours following PBL infusion
3. Collect pre-dose (prior to drug administration) or other infusion. Note: It is strongly recommended that hematology, chemistry and pregnancy test (when applicable) results are reviewed before dosing.
4. Samples will be removed from the pheresis product
5. If serum and urine IF are positive, subsequent analysis is not necessary unless the subject achieves a response of VGPR or greater
6. For subjects who did not experience progression while on study