Supplementary material

1: full eligibility criteria

1.1 Inclusion Criteria

[1] Willingness and ability to provide written informed consent and to comply with the study protocol as judged by the investigator

Disease Characteristics:

[2] Pathologically confirmed Mantle Cell Lymphoma (MCL) which is relapsed or refractory to at least one chemotherapy containing regimen

a. Presence of cyclin D1 expression and/or t(11;14) by FISH or cytogenetics is required

[3] Subjects must have measurable or evaluable disease:

a. Evaluable disease must be evidenced by CT or PET scans (Abnormal PET scans may be used as long as the CT portion is of diagnostic quality)
b. Subject must have at least one objective measurable disease parameter:
    i. measurable disease on cross sectional imaging that is ≥ 2 cm in the longest diameter and measurable in 2 perpendicular dimensions
    ii. Splenomegaly > 13 cm in cranio-caudal dimension as measured by CT

Subject Characteristics:

[4] ECOG Performance Status of 0-2

[5] Age ≥ 18 years

[6] Subject must be referred for treatment with ibrutinib.

[7] Demonstrate adequate organ function as defined in Table 3, all screening labs should be performed within 28 days of treatment initiation and confirmed on C0D1.

Table 1. Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	≥ 1000 cells/ mm^3 (or ≥ 750 in subjects with bone marrow involvement)
Platelets	≥ 50,000 cells/ mm^3
PT and aPTT INR	≤ 1.5 X institutional upper limit of normal (IULN) ≤ 1.5 X institutional upper limit of normal (IULN)
Hemoglobin	≥ 8g/dL
Renal	
Measured or calculated[a] creatinine clearance	≥ 50 mL/min
Hepatic	
AST (SGOT) and ALT (SGPT)	≤ 3.0 X IULN

Bilirubin	≤ 1.5 X IULN[b]
[a]Creatinine clearance should be calculated using modified Cockcroft-Gault equation (using Ideal Body Mass [IBM] instead of mass). Direct measured creatinine clearance (i.e. 24h urine or other method) can be substituted if calculated creatinine clearance is thought to be inadequate per treating physician. [b]Bilirubin > 1.5 × ULN is allowed in subjects with conjugated bilirubin disorder or Gilbert's syndrome	

[8] Women of childbearing potential and men must agree to use adequate contraception prior to study entry and for at least 30 days following last dose of ABT-199.

a. Women of childbearing potential (WOCBP) includes any female who has experienced menarche and who has not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation or bilateral oophorectomy) or is not postmenopausal [defined as amenorrhea ≥ 12 consecutive months; or women on hormone replacement therapy (HRT) with documented serum follicle stimulating hormone (FSH) level > 35 mIU/mL]

i. Prior to study enrollment, WOCBP must be advised of the importance of avoiding pregnancy during trial participation and the potential risk factors for an unintentional pregnancy

ii. The following birth control methods are allowed during the study:

1. Barrier methods:
    a. Intra-uterine device (IUD)
    b. Diaphragm with spermicide
    c. Cervical cap with spermicide
    d. Condom with spermicide
2. Hormonal method:
    a. Hormonal contraceptives (such as the birth control pill)
3. Abstinence (no heterosexual activity)

b. Non-vasectomized males must agree to use adequate contraception for at least 30 days after the last dose of ABT-199

i. The following birth control methods are allowed during the study:

1. Partner is not WOCBP or is taking hormonal contraceptives
2. Barrier methods:
    e. Intra-uterine device (IUD)
    f. Diaphragm with spermicide
    g. Cervical cap with spermicide
    h. Condom with spermicide
3. Abstinence (no heterosexual activity)

ii. Males must also abstain from sperm donations for at least 90 days after the last dose of ABT-199

1.2 Exclusion Criteria

[1] Active second malignancy requiring treatment or that would interfere with assessment of response of the lymphoma per investigator's discretion

[2] Known CNS lymphoma

[3] Prior or concomitant treatments:

a. Prior treatment with ibrutinib

b. The following cancer treatments:
    i. chemotherapy or biological therapy within 14 days prior to start of treatment
    ii. immunological therapy, radiation therapy, or hormonal therapy within 7 days prior to start of treatment
    iii. major surgery within 15 days prior to start of treatment
    iv. subjects who have unresolved toxicity (≥ grade 2) from prior anti-cancer therapy, unless that event is thought to be due to disease progression

c. Any investigational agent, including small molecule agents, within 30 days prior to start of study treatment

d. Any of the following with 7 days prior to start of study treatment:
    - B-cell receptor pathway inhibitor;
    - CYP3A inhibitors (such as fluconazole, ketoconazole, and clarithromycin);
    - Potent CYP3A inducers (e.g., rifampin, phenytoin, carbamazepine or St. John's Wort);
    - Warfarin or requires the use of warfarin (due to potential drug-drug interactions that may potentially increase the exposure of warfarin and complications of this effect);
    - Antiretroviral medications
    - Antibiotics, antifungals, or antivirals to treat an active infection (prophylactic antibiotics allowed)

e. Subjects who are unable or unwilling to discontinue use of prohibited medications, including medications with CYP450 interactions (see Section 4.5.1)

f. Subject has received prior treatment with allogeneic stem cell transplant or solid organ transplant (except for cornea) for any indication

[4] Subject meets one of the following criteria:

a. Evidence of active TLS (per criteria outlined in Appendix E) during screening

b. a measurable lymph node with diameter ≥ 10 cm, or

c. a measurable lymph node with diameter ≥ 5 cm and an absolute lymphocyte count (including atypical lymphocytes and circulating lymphoma cells) ≥ 25 × 10^9/L

[5] Subject has malabsorption syndrome or other condition which may affect an enteral route of administration

[6] Subject has known contraindication or allergy to both xanthine oxidase inhibitors and rasburicase

[7] Significant history of uncontrolled cardiac disease defined as uncontrolled arrhythmias, unstable angina, myocardial infarction within the last 4 months, and uncontrolled congestive heart failure or any Class 2 - 4 New York Heart Association Classification cardiac disease (see Appendix B)

[8] Significant screening electrocardiogram (ECG) abnormalities including left bundle branch block, 2nd degree AV block type II, 3rd degree block, bradycardia, or corrected QT interval (Fridericia's correction; QTcF) > 470 msec

[9] Subject is unable or unwilling to participate a study related procedure

[10] Subject has an active infection

[11] Subject is pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the study

[12] Known history of Human Immunodeficiency Virus (HIV) (HIV 1/2 antibodies).

[13] Known active Hepatitis B (e.g., HBsAg reactive) or Hepatitis C (e.g., HCV RNA [qualitative] is detected)

[14] History or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the trial, interfere with the subject's participation for the full duration of the trial, or is not in the best interest of the subject to participate, in the opinion of the treating investigator

[15] A serious uncontrolled medical disorder that in the opinion of the Investigator would impair the ability of the subject to receive protocol therapy

2: baseline characteristics pre and post amendment

Demographics for eligible subjects		Arm					Time											
							Pre amendment						Post amendment					
								Arm						Arm				
	Total	A	B	C	D	E	Total	A	B	C	D	E	Total	A	B	C	D	E
	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
RACE																		
Asian	1	1	0	0	0	0	1	1	0	0	0	0	0	0	0	0	0	0
Unknown	2	0	1	0	0	1	0	0	0	0	0	0	2	0	1	0	0	1
White	32	1	15	8	4	4	14	1	3	5	2	3	18	0	12	3	2	1
ETHNICITY																		
Hispanic or Latino	2	0	0	0	1	1	2	0	0	0	1	1	0	0	0	0	0	0
Non-Hispanic	31	2	15	8	3	3	12	2	3	5	1	1	19	0	12	3	2	2
Unknown	2	0	1	0	0	1	1	0	0	0	0	1	1	0	1	0	0	0
GENDER																		
F	6	0	2	2	1	1	2	0	0	1	1	0	4	0	2	1	0	1
M	29	2	14	6	3	4	13	2	3	4	1	3	16	0	11	2	2	1
ECOG																		
0 - Fully Active	14	2	8	0	2	2	4	2	2	0	0	0	10	0	6	0	2	2
1 - Restricted	20	0	8	7	2	3	11	0	1	5	2	3	9	0	7	2	0	0
2 - Ambulatory	1	0	0	1	0	0	0	0	0	0	0	0	1	0	0	1	0	0
Total	35	2	16	8	4	5	15	2	3	5	2	3	20	0	13	3	2	2

Analysis Variable : age_onstudy Age								
Time	Arm	N Obs	N Miss	Minimum	Maximum	Mean	Median	Std Dev
Pre amendment	A	2	0	69	82	75	75	9
	B	3	0	60	64	61	60	2
	C	5	0	49	72	63	66	9
	D	2	0	60	68	64	64	6
	E	3	0	50	58	54	56	4
Post amendment	B	13	0	54	76	62	61	6
	C	3	0	65	79	72	72	7
	D	2	0	53	66	59	59	9
	E	2	0	58	60	59	59	1
Pre amendment	Sub total	15	0	49	82	63	60	9
Post amendment	Sub total	20	0	53	79	63	62	7

Supplement Table 3: Trial conduct of CRM allocation								
			Study information available at the time of subject allocation to arm DLT in Bold (#/N available) ORR at 2 moths in italics (#/N available)					
Subject	Days from trial opening to allocation	Dose level allocation	A	B	C	D	E	F
Allocation Part 1: ordered, sequential Arm allocation								
1	30	A	NA	NA	NA	NA	NA	NA
2	169	B	**0/1**, *1/1*	NA	NA	NA	NA	NA
3	184	C	**0/1**, *1/1*	**0/0**, *0/0*	NA	NA	NA	NA
4	290	D	**0/1**, *1/1*	**0/1**, *1/1*	**0/1**, *1/1*	NA	NA	NA
5	305	E	**0/1**, *1/1*	**0/1**, *1/1*	**0/1**, *1/1*	**0/0**, *0/0*	NA	NA
6	330	E	**0/1**, *1/1*	**0/1**, *1/1*	**0/1**, *1/1*	**0/0**, *0/0*	**0/0**, *0/0*	NA
7	330	D	**0/1**, *1/1*	**0/1**, *1/1*	**0/1**, *1/1*	**0/0**, *0/0*	**0/0**, *0/0*	NA
Allocation Part 2 (triggered due to DLT on Arm E): arm allocation based on prior subjects 2 month ORR and DLT								
8	350	C	**0/1**, *1/1*	**0/1**, *1/1*	**0/1**, *1/1*	**0/1**, *0/0*	**1/1**, *0/0*	NA
9	375	C	**0/1**, *1/1*	**0/1**, *1/1*	**0/1**, *1/1*	**0/2**, *1/1*	**1/2**, *0/0*	NA
10	420	B	**0/1**, *1/1*	**0/1**, *1/1*	**0/2**, *2/2*	**0/2**, *1/2*	**1/2**, *0/1*	NA
11	435	C	**0/1**, *1/1*	**0/1**, *1/1*	**0/3**, *2/2*	**0/2**, *1/2*	**1/2**, *0/1*	NA
12	491	E	**0/1**, *1/1*	**0/2**, *2/2*	**0/4**, *2/3*	**0/2**, *1/2*	**1/2**, *0/1*	NA
13	532	B	**0/1**, *1/1*	**0/2**, *2/2*	**0/4**, *3/4*	**0/2**, *1/2*	**1/2**, *0/1*	NA
14	561	A	**0/1**, *1/1*	**0/2**, *2/2*	**0/4**, *3/4*	**0/2**, *1/2*	**1/3**, *1/2*	NA
15	561	C	**0/1**, *1/1*	**0/2**, *2/2*	**0/4**, *3/4*	**0/2**, *1/2*	**1/3**, *1/2*	NA
16	576	C-not treated	**0/1**, *1/1*	**0/3**, *2/2*	**0/4**, *3/4*	**0/2**, *1/2*	**1/3**, *1/2*	NA
17	578	C-not treated	**0/1**, *1/1*	**0/3**, *2/2*	**0/4**, *3/4*	**0/2**, *1/2*	**1/3**, *1/2*	NA

Study Amendment due to toxicity								
18	766	C	**0/2**, *2/2*	**0/3**, *3/3*	**0/5**, *4/5*	**0/2**, *1/2*	**1/3**, *1/2*	NA
19	772	C	**0/2**, *2/2*	**0/3**, *3/3*	**0/5**, *4/5*	**0/2**, *1/2*	**1/3**, *1/2*	NA
20	815	B	**0/2**, *2/2*	**0/3**, *3/3*	**0/6**, *4/5*	**0/2**, *1/2*	**1/3**, *1/2*	NA
21	823	C	**0/2**, *2/2*	**0/3**, *3/3*	**0/7**, *4/5*	**0/2**, *1/2*	**1/3**, *1/2*	NA
22	861	B	**0/2**, *2/2*	**0/4**, *3/3*	**0/7**, *5/7*	**0/2**, *1/2*	**1/3**, *1/2*	NA
23	897	D	**0/2**, *2/2*	**0/4**, *4/4*	**0/8**, *6/8*	**0/2**, *1/2*	**1/3**, *1/2*	NA
24	913	D	**0/2**, *2/2*	**0/5**, *4/4*	**0/8**, *6/8*	**0/2**, *1/2*	**1/3**, *1/2*	NA
25	1016	E	**0/2**, *2/2*	**0/5**, *5/5*	**0/8**, *6/8*	**0/4**, *2/4*	**1/3**, *1/2*	NA
26	1037	E	**0/2**, *2/2*	**0/5**, *5/5*	**0/8**, *6/8*	**0/4**, *2/4*	**1/3**, *1/2*	NA
27	1064	B	**0/2**, *2/2*	**0/5**, *5/5*	**0/8**, *6/8*	**0/4**, *2/4*	**1/4**, *1/2*	NA
28	1081	B	**0/2**, *2/2*	**0/5**, *5/5*	**0/8**, *6/8*	**0/4**, *2/4*	**1/4**, *2/3*	NA
29	1103	B	**0/2**, *2/2*	**0/5**, *5/5*	**0/8**, *6/8*	**0/4**, *2/4*	**2/4**, *3/4*	NA
30	1113	B	**0/2**, *2/2*	**0/6**, *5/5*	**0/8**, *6/8*	**0/4**, *2/4*	**2/4**, *3/4*	NA
31	1179	B	**0/2**, *2/2*	**0/9**, *9/9*	**0/8**, *6/8*	**0/4**, *2/4*	**2/4**, *3/4*	NA
32	1198	B	**0/2**, *2/2*	**0/9**, *9/9*	**0/8**, *6/8*	**0/4**, *2/4*	**2/4**, *3/4*	NA
33	1261	B	**0/2**, *2/2*	**0/11**, *11/11*	**0/8**, *6/8*	**0/4**, *2/4*	**2/4**, *3/4*	NA
34	1257	B	**0/2**, *2/2*	**0/11**, *11/11*	**0/8**, *6/8*	**0/4**, *2/4*	**2/4**, *3/4*	NA
35*	1282	B	**0/2**, *2/2*	**0/11**, *11/11*	**0/8**, *6/8*	**0/4**, *2/4*	**2/4**, *3/4*	NA
36	1290	B	**0/2**, *2/2*	**0/11**, *11/11*	**0/8**, *6/8*	**0/4**, *2/4*	**2/4**, *3/4*	NA
37**	1295	B	**0/2**, *2/2*	**0/11**, *11/11*	**0/8**, *6/8*	**0/4**, *2/4*	**2/4**, *3/4*	NA
Final data and dose recommendation		B	**0/2**, *2/2*	**1/16**, *15/16*	**0/8**, *6/8*	**0/4**, *2/4*	**2/4**, *3/4*	**NA**

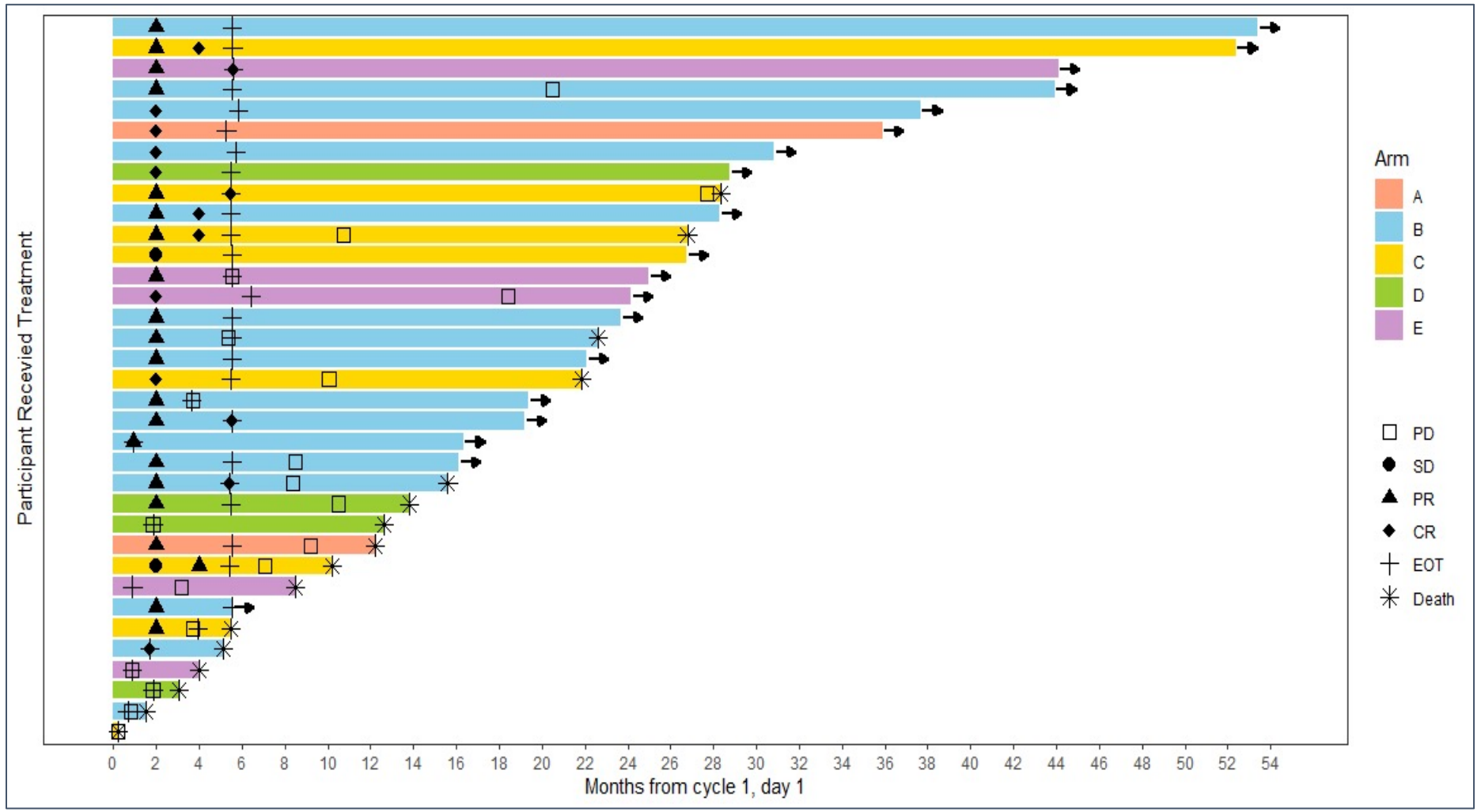
*later had a DLT

**later progressed

4: Dose Modifications

Arm	# pts with modification/n	ABT-199		Ibrutinib	
		# doses modified	# doses held or missed	# doses modified	# doses held or missed
A	2/2	0	5	1	5
B	6/16	3	16	2	17
C	8/8	1	8	0	14
D	3/4	0	3	0	2
E	2/5	0	2	0	2

Supplement Figure 4



Supplement Figure 1: Individual patient outcomes per swimmer plot for all participants. Each participant is a line on the plot and colors indicate the arm allocation. Arrows at the end of the lines represent ongoing follow up.