Title

ABT-199 (GDC-0199) COMBINED WITH RITUXIMAB (R) IN PATIENTS (PTS) WITH RELAPSED / REFRACTORY (R/R) CHRONIC LYMPHOCYTIC LEUKEMIA (CLL): INTERIM RESULTS OF A PHASE 1B STUDY

Journal

HAEMATOLOGICA, 99

ISSN

0390-6078

Authors

Roberts, AW

Ma, S

Kipps, T

et al.

Publication Date

2014-06-01

Chronic lymphocytic leukemia and related disorders - Clinical 1

S702

ABT-199 (GDC-0199) IN RELAPSED/REFRACTORY CHRONIC LYMPHOCYTIC LEUKEMIA AND SMALL LYMPHOCYTIC LYMPHOMA: HIGH RESPONSE RATES AMONG PATIENTS WITH HIGH RISK DISEASE FEATURES INCLUDING UNMUTATED IGHV

JF Seymour[1,*] MS Davids[2], JM Pagel[3], BS Kahl[4], WG Wierda[5], S Puvvada[6], JF Gerecitano[7], TJ Kipps[8], MA Anderson[9], DC Huang[10], NK Rudersdorf[11], LA Gressick[11], NP Montalvo[11], J Yang[11], M Zhu[11], M Dunbar[11], E Cerri[11], SH Enschede[11], RA Humerickhouse[11], AW Roberts[9]
[1]Peter MacCullum Cancer Center, Melbourne, Australia, [2]Dana Farber Cancer Institute, Boston, [3]University of Washington, Seattle, [4]University of Wisconsin, Madison, [5]University of Texas, Houston, [6]The University of Arizona, Tucson, [7]Memorial Sloan-Kettering Cancer Center, New York, [8]The University of California San Diego, San Diego, United States, [9]Royal Melbourne Hospital and Walter and Eliza Hall Institute of Medical Research, [10]Walter and Eliza Hall Institute of Medical Research, Melbourne, Australia, [11]AbbVie, North Chicago, United States

Background: Overexpression of BCL-2 in relapsed/refractory (R/R) Chronic Lymphocytic Leukemia (CLL) and Small Lymphocytic Lymphoma (SLL) is associated with resistance to both chemotherapy and apoptosis. ABT-199 is an orally bioavailable, selective BCL-2 inhibitor that triggers apoptosis of CLL cells *in vitro* and *in vivo*, independent of TP53 functional status, making it a promising agent for the treatment of patients (pts) with CLL/SLL, including those with high-risk disease features.
Aims: The primary objectives of this phase I study were to evaluate the safety and pharmacokinetics (PK) and to determine the maximum tolerated dose and a recommended phase 2 dose (RP2D) of ABT-199 monotherapy. A secondary objective was to assess preliminary efficacy.
Methods: Pts received daily oral ABT-199 until progressive disease (PD), intolerance or withdrawal. Following events of tumor lysis syndrome (TLS) early in the trial, a schedule with weekly dose increases to the target cohort dose (150-1200 mg) was implemented. Pts are now being enrolled in the safety expansion (SE) cohort incorporating a weekly ramp-up period from 20, 50, 100, 200 mg to the final RP2D of 400 mg.
Results: As of January 17, 2014, 93 pts (37 in the SE) were enrolled with a median time on study of 6.1 (range, 0 - 27) months. Twenty-three (24%) pts had del(17p), 55 (59%) had fludarabine (F)-refractory CLL, 32 of the 42 pts with available status have unmutated *IGHV*. The median number of prior therapies was 4 (range 1-11). The most common treatment-emergent AEs (>25% pts) of any grade were neutropenia (39%), diarrhea (36%), nausea (35%), upper respiratory tract infection (31%), and fatigue (27%). Grade 3/4 AEs (>5% pts) were neutropenia (36%), anemia (10%), TLS (8%, including 1 Gr5), thrombocytopenia (7%), hyperglycemia (7%), and febrile neutropenia and hypokalemia (6% each). Thirty-one pts discontinued treatment: 20 for progressive disease, 9 for AEs, and 2 for other reasons. Preliminary efficacy results are detailed in the Table 1.

Table 1.

	Total N=93	*IGHV* Unmutated n=32 (42 assessed)	Del (17p) n=23	F-Refractory n=55
Gender M/F	68/25	22/10	18/5	40/14
Age (median)	66	64	66	66
Median Baseline Lymphocyte Count (x 10^9/L)	5.9	5.9	7.0	5.9
Responses				
Total Evaluable*	70	23	21	39
CR/CRi, n (%)	14 (20)	4 (17)	3 (14)	6 (15)
PR, n (%)	39 (56)	13 (57)	12 (57)	23 (59)
SD, n (%)	11 (16)	4 (17)	4 (19)	8 (21)
PD, n (%)	2 (3)	1 (4)	1 (5)	1 (3)
D/C, n (%)	4 (6)	1 (4)	1 (5)	1 (3)
Response Rate (ORR, CR+PR)	76%	74%	71%	74%

**Evaluable pts exclude those with unconfirmed PR and those not yet evaluable. D/C: Discontinued prior to week 6 assessment. The median duration of response (DOR) was 20.5 months [95% CI; 13.8, -] for the 53 responding pts. At 12 months, 91% of CR and 67% of PR pts remain progression-free. Of the 14 CR/CRi pts, 9 were evaluated in local labs by flow cytometry for minimal residual disease (MRD); 5 were MRD negative and of these, 2 were IGHV unmutated, 4 were F-refractory, and 1 had del(17p). Summary and Conclusions: ABT-199 induces a high rate of response in pts with R/R CLL, including those with unmutated IGHV, del(17p), and F-refractory disease. Responses appear to be durable, especially in the 21% who achieved CR/CRi. Several of these high-risk pts achieved MRD negativity. Enrollment continues in the safety expansion cohort to further define safety and efficacy.*

S703

ABT-199 (GDC-0199) COMBINED WITH RITUXIMAB (R) IN PATIENTS (PTS) WITH RELAPSED / REFRACTORY (R/R) CHRONIC LYMPHOCYTIC LEUKEMIA (CLL): INTERIM RESULTS OF A PHASE 1B STUDY

AW Roberts[1,*] S Ma[2], T Kipps[3], JC Barrientos[4], MS Davids[5], MA Anderson[1], C Tam[6], T Mason-Bright[7], NK Rudersdorf[7], J Yang[7], W Munasinghe[7], M Zhu[7], E Cerri[7], SH Enschede[7], RA Humerickhouse[7], JF Seymour[6]
[1]Royal Melbourne Hospital and Walter and Eliza Hall Institute of Medical Research, Melbourne, Australia, [2]Northwestern University, Chicago, [3]University of California San Diego, San Diego, [4]Hofstra North Shore-LIJ School of Medicine, New Hide Park, [5]Dana Farber Cancer Institute, Boston, United States, [6]Peter MacCullum Cancer Center, Melbourne, Australia, [7]AbbVie, North Chicago, United States

Background: ABT-199 is a selective, orally bioavailable BCL-2 antagonist that induces rapid apoptosis of CLL cells and an approximately 80% response rate as monotherapy in pts with R/R CLL. As with DNA damaging chemotherapy, R synergizes with ABT-199 in preclinical models of CD20+ lymphoid cancers.
Aims: Objectives were to evaluate the safety, pharmacokinetics (PK), preliminary efficacy and to determine a maximum tolerated dose (MTD) / recommended phase 2 dose (RPTD) for ABT-199+R.
Methods: Pts began daily ABT-199 at 50 mg (modified to 20 mg) with weekly increases to a final cohort dose (200-600mg). R was then administered at a starting dose of 375 mg/m^2 then 500mg/m^2 monthly for total of 6 doses (cohort 1-2 had 2 additional weekly doses in month 1) with continuation of daily ABT-199 until progressive disease (PD). The MTD/RPTD for the combination will be determined by the Bayesian Continual Reassessment Method. Pts were assessed by CT scan at month 3 (followed by confirmation CT for responders per IWCLL 2008) and by CT scan and bone marrow (BM) biopsy after the end of combination therapy.
Results: As of Jan 17, 2014, 37 pts were enrolled in 5 cohorts (median age 68, 14/23 F/M) with a median time on study: 4.8 (range 0 - 15.2) months, median number of prior therapies: 2 (range 1 - 5); 9 pts were fludarabine-refractory, 9 R-refractory, and 9 had del(17p). Six pts discontinued: 4 due to PD (3 Richter's transformation, 1 progressive CLL), 1 withdrew consent, 1 due to fatal hyperkalemia in the setting of tumor lysis syndrome (TLS) at 1st dose (50 mg) prior to dose modification. The most common treatment-emergent adverse events (AEs, >25% pts) were neutropenia (43%), nausea (38%), diarrhea (30%). The most common grade (G) 3/4 AEs were neutropenia (43%), thrombocytopenia (16%), and anemia (11%). Nine pts had G4 AEs with 14 events (9 neutropenia, 4 thrombocytopenia, 1 hemophagocytic syndrome), of these, 6 pts had interruptions or reductions. All but 1, maintained at a reduced dose of 200 mg, resumed treatment at the final cohort dose. Two G4 events were dose limiting toxicities occurring on combination therapy (in cohort 2): thrombocytopenia (300mg/375mg/m^2) and hemophagocytic syndrome (300mg/500mg/m^2). Preliminary PK data suggest a negligible effect of R on ABT-199 exposure. Of 18 pts who have completed combination therapy or discontinued prior to completion, 7 (39%) achieved complete remission (CR/CRi) and 7 (39%) partial remission (PR). Minimal residual disease (MRD) was quantified by local laboratory in 6/7 CR pts: 4 pts are MRD negative in BM (3 at 10^{-4} and 1 at 10^{-3} sensitivity) and 1 in peripheral blood (10^{-3} sensitivity). Additional results are included in the Table 1 below:

Table 1.

Cohort	Dose	N	Months on Study (median)	Assessment	Responses
Pts evaluable for CR (≥6 mo or PD)					
1	200	6	14	CT & BM	2 CR/CRi, 4 PR
2	300	10	10	CT & BM	5 CR/CRi, 3 PR, 2 PD
3	400	1	-	-	
1 DC					
Pts not yet evaluable for CR (<6 mo)					
3	400	7	5	CT	2 PR, 4 uPR, 1 DC
4	500	6	3	CT	2 PR, 4 uPR

**uPR: unconfirmed partial remission; DC: discontinued*

Summary and Conclusions: To date, the RPTD of R+ABT-199 has not been determined and dose escalation continues. No additional toxicities have been identified when compared to ABT-199 monotherapy. The combination is active in R/R CLL, with a number of patients achieving CR with MRD negativity. A fatal episode of TLS occurred during the ABT-199 lead-in period (prior to R). Following dosing and monitoring modifications, no further TLS events were reported.

S704

SECOND INTERIM ANALYSIS OF A PHASE 3 STUDY EVALUATING IDELALISIB AND RITUXIMAB FOR RELAPSED CLL

SE Coutre[1,*] RR Furman[2], JP Sharman[3], BD Cheson[4], JM Pagel[5], P Hillmen[6], JC Barrientos[7], AD Zelenetz[8], TJ Kipps[9], IW Flinn[10], P Ghia[11], HA Eradat[12], N Lamanna[13], B Coiffier[14], A Pettitt[15], X Li[16], TM Jahn[16], SM O'Brien[17], MJ Hallek[18]