Title

THE BCL-2 INHIBITOR ABT-199 (GDC-0199) IS ACTIVE AND WELL-TOLERATED IN ULTRA HIGH-RISK RELAPSED/REFRACTORY CHRONIC LYMPHOCYTIC LEUKEMIA (CLL)

Journal

HAEMATOLOGICA, 98

ISSN

0390-6078

Authors

Roberts, A

Davids, M

Pagel, J

et al.

Publication Date

2013-06-12

Chronic lymphocytic leukemia - Clinical studies

S1146

THE BCL-2 INHIBITOR ABT-199 (GDC-0199) IS ACTIVE AND WELL-TOLERATED IN ULTRA HIGH-RISK RELAPSED/REFRACTORY CHRONIC LYMPHOCYTIC LEUKEMIA (CLL)

A Roberts[1,*], M Davids[2], J Pagel[3], B Kahl[4], W Wierda[5], T Miller[6], J Gerecitano[7], T Kipps[8], M Anderson[1], D Huang[1], D Darden[9], L Gressick[9], C Nolan[9], J Yang[9], T Busman[9], A Graham[9], E Cerri[9], S Enschede[9], R Humerickhouse[9], J Seymour[10]
[1]Walter and Eliza Hall Institute of Medical Research, Melbourne, Australia, [2]Dana-Farber Cancer Institute, Boston, MA, [3]University of Washington, Seattle, WA, [4]University of Wisconsin, Madison, WI, [5]University of Texas, Houston, TX, [6]University of Arizona, Tucson, AZ, [7]Memorial Sloan-Kettering Cancer Center, New York, NY, [8]University of California San Diego, San Diego, CA, [9]AbbVie Inc., North Chicago, IL, United States, [10]Peter MacCallum Cancer Centre, Melbourne, Australia

Background: Patients (pts) with CLL and deletions of chromosome 17p (del(17p)) or whose disease is refractory to fludarabine (F) are considered to have ultra high-risk CLL. The median life expectancy of these pts is less than 2 to 3 years with standard therapy; therefore novel agents are urgently needed, particularly for this subgroup. Overexpression of BCL-2 and failure to trigger upstream pro-apoptotic pathways underpin resistance to apoptosis in these patients. *In vitro,* this block to apoptosis can be overcome by targeting mitochondria through BCL-2 inhibition. The first-generation BCL-2 inhibitor, navitoclax, achieved partial remissions (PRs) in 35% of pts with relapsed/refractory (R/R) CLL, however concomitant inhibition of BCL-X_L resulted in dose-limiting thrombocytopenia (TCP). ABT-199 is a second generation inhibitor with greater affinity for BCL-2, but 500-fold less affinity for BCL-X_L, than navitoclax. We hypothesized that selective BCL-2 inhibition with ABT-199 would demonstrate significant clinical efficacy, including in pts with ultra high-risk disease.
Aims: The primary objectives of this phase-I dose-escalation study are to evaluate the safety and pharmacokinetics (PK) of ABT-199, determine a maximum tolerated dose and recommended phase-2 dose, and assess efficacy and biomarkers in pts with R/R CLL. In this analysis, we have sought to determine if pts with ultra-high risk CLL have similar response rates to the overall study population.
Methods: Pts with ECOG performance status ≤1 and adequate marrow function received a single dose of ABT-199 on Week1 Day -3 or -7 (W1D-3, W1D-7), followed by continuous once-daily dosing from W1D1, until disease progression or unacceptable toxicity. After cohort1, the initial dose was reduced and daily dosing modified to include a 2 or 3 step dose-escalation to the target dose for each cohort. Evaluations included adverse events (AE; NCI-CTCAE-V4), PK parameters and disease response (IWCLL 2008).
Results: As of January 2013, 56 pts have been enrolled (see Table 1) in cohorts assessing doses from 150mg to 1200mg. Sixteen (29%) had del(17p) and 18 (32%) F-refractory CLL (see Table 1). The most common non-haematologicalAEs (>15% pts) were nausea (36%), diarrhea (30%), fatigue (25%), upper respiratory tract infection (23%), and cough (16%). Grade 3/4 AEs occurring in ≥5 pts were neutropenia 21(38%), thrombocytopenia 6 (11%) and tumour lysis syndrome (TLS) 5 (9%). The thrombocytopenia was not dose-related. With initial dosing, TLS occurred in 3/3 pts in cohort 1 and 2/53 pts with the modified dosing schedule (both were DLTs). Additionally, 1 fatal AE occurred within 48 hrs of dose-escalation to 1200 mg in a pt with laboratory evidence of TLS (DLT). 13 pts have discontinued, 7 due to progression, 6 for other reasons: TLS (2), other illness (2), thromboembolic event (1), consent withdrawal (1). After a single dose of ABT-199 with a low-fat meal, T_{max} and $T_{1/2}$ values were approximately 7 and 17 hrs, respectively, a pattern supporting daily dosing. Preliminary efficacy data are summarised (Table 1).

Table 1.

Characteristic	All CLL n=56	del (17p) n=16*	F-refractory n=18*
Age (yr)†	67 [36-86]	69 [47-80]	66 [36-78]
Male#	41 (73)	11 (69)	12 (67)
Number of prior therapies†	3.5 [1-10]	4 [2-9]	5 [1-10]
Bulky disease >= 5 cm#	28 (50)	6 (38)	10 (56)
Bulky disease >= 10 cm#	8 (14)	0 (0)	4 (22)
Time on study (days)†	190 [1-495]	159 [33-495]	203 [1-484]
Response			
Time to first 50% reduction in nodes (days)†	43 [20-417]	43 [33-81]	44 [20-88]
Best response‡	n=54	n=16	n=18
CR/CRi	7 (13)	1 (6)	3 (17)
PR	39 (72)	13 (81)	11 (61)
SD	4 (7)	1 (6)	1 (6)
PD	0 (0)	0 (0)	0 (0)
D/C prior to first (W6) assessment	4 (7)	1 (6)	3 (17)
Response Rate (CR + PR)	85%	88%	78%

†median [range]; #n(%);*6 pts had both del(17p) and F-refractory disease
‡Evaluable pts either 1) completed at least a W6 assessment or 2) discontinued (D/C) prior to W6

Summary and Conclusions: ABT-199 is highly active in ultra high-risk CLL, achieving a response rate of 88% in del(17p) and 78% in F-refractory pts, comparable to the 85% response rate in the whole study population Additional dosing and scheduling modifications are currently being explored to minimise the risk of TLS while preserving efficacy. (study status see clinicaltrials.gov)

S1147

RANDOMISED COMPARISON OF FCR-LITE AND CLR (CHLORAMBUCIL PLUS RITUXIMAB) REGIMENS IN ELDERLY PATIENTS WITH CHRONIC LYMPHOCYTIC LEUKEMIA

E Nikitin[1,*], D Kisilichina[2], O Zakharov[3], S Lugovskaya[2], E Varlamova[4], T Obukhova[5], B Biderman[6], I Kaplanskaya[7], E Naumova[2], M Pochtar[2], A Sudarikov[6], E Domracheva[5], V Ivanova[8], L Kovaleva[1], V Ptushkin[9]
[1]Outpatient department, Hematology Research Center of Russia, [2]Department of Clinical Laboratory Diagnostics, Russian Medical academy of postgradual education, [3]Outpatient department, City Hospital N150, [4]Laboratory of immunochemistry, [5]Laboratory of Cytogenetics, [6]Laboratory of Molecular Hematology, [7]Department of Pathology, Hematology Research Center of Russia, [8]Outpatient department, City hospital named after Sergei Botkin, [9]Oncology and hematology dpt. for adolescents and young adults, Federal Scientific and Clinical Centre of Pediatric Hematology, Oncology and Immunology named after Dmitriy Rogachev, Moscow, Russian Federation

Background: Chlorambucil is still considered as standard of care in elderly and physically unfit patients with chronic lymphocytic leukemia (CLL). However, a considerable number of patients have insufficient or short responses to chlorambucil and there is a need to develop safe and more efficacious treatment approaches. Two regimens have been proposed for treatment of patients with comorbidities and elderly patients: FCR-Lite and CLR, both showing relatively high efficacy and good tolerability.
Aims: To compare in randomized trial FCR-Lite and CLR regimens in treatment of elderly patients with chronic lymphocytic leukemia.
Methods: Untreated CLL patients older than 71 years and physically unfit patients aged 61–70 years with cumulative illness rating score (CIRS) 7 and more were included into the trial. After Informed consent the patients were randomly assigned to receive either FCR-Lite (F oral 32 mg/m2 for three days, C oral 150 mg/m2 for three days) or CLR (Chl 10 mg/m2 for 7 days). Rituximab was given once in each cycle in both regimens (375 mg/m2 i.v. day 0 at first cycle and 500 mg/m2 day 1 all subsequent cycles). Cycles were repeated every 4 weeks.
Results: 97 patients have been included into the study. The patient's characteristics were relatively well balanced between arms with regard to age, stage, genomic aberrations and VH status. 72% were Binet B, 16% Binet C and 12% Binet A. The median age was 71 years (range 60 to 84), 47 patients were females (48%), the median CIRS score was 8 (range 1-18). The overall incidences of trisomy 12 and abnormalities of 13q, 11q23, and 17p13 detected by FISH were8,5%, 50%, 21,3%, and6,4%, respectively, with no statistically significant differences between treatment arms. One patient withdraw consent, 1 patient died from pneumonia before initiation of treatment, and 3 patients discontinued treatment due toxicity or worsening of concomitant condition. Ninety two patients were available for assessment. At the time of analysis, February 2013, the median observation time was 29.8 months. A mean number of 5.1 courses was given in the CLR arm *versus* 5.3 courses in the FCR-Lite arm. 72% (FCR-Lite) and 66% (CLR) of patients received 6 cycles. There was no significant differences in grade III–IV myelotoxicity in FCR-Lite and CLR arms: neutropenia was observed in 36% patients and 34% patients, anemia 4% and2,6% and thrombocytopenia in 8% and 13%, respectively. The incidence of CTC grade 3 or 4 infections was also not significantly different (17,7% in FCR-Lite arm *versus*14,8% in the CLR arm (P=0.9). The overall response rate of the FCR-Lite arm was 93% as compared to 85% in the CLR arm (P<0.35). The complete response rate was significantly higher in the FCR-Lite arm (42%; 19/45) compared to CLR (10,6%; 5/47) (P=0.001). Forteen patients (31%) in FCR-Lite arm achieved an MRD-negative CR while in CLR arm there were no MRD-negative cases. Median PFS in CLR arm was 25,3 months, while in FCR-Lite arm it was not reached (P=0,0042). PFS at 2 years in FCR-Lite arm was 72,6%. To date, 80 patients remain alive and 17 patients (17%) have died. In LR arm 6 patients died from progression, 2 from secondary tumors and 3 from other causes. In FCR-Lite arm there have been no deaths from progression, 3 patients died from secondary tumors and 3 from other causes.
Summary and Conclusions: Preliminary results show that FCR-Lite is more efficacious in terms of response and progression free survival without significant increase of toxicity.

S1148

RESULTS OF THE RANDOMISED PHASE II NCRI ADMIRE TRIAL OF FCR AND FCM-R IN PREVIOUSLY UNTREATED CLL: ORAL FCR IS HIGHLY EFFECTIVE AND SAFE BUT THE ADDITION OF MITOXANTRONE DOES NOT IMPROVE RESPONSES

P Hillmen[1,*], C Pocock[2], A Rawstron[3], L McParland[4], A Chalmers[4], A Varghese[1], A Smith[4], C Collett[4], M Hamblin[5], A Bloor[6], A Pettitt[7], C Fegan[8], J Blundell[9], J Gribben[10], W Gregory[4], D Phillips[4], D Cohen[4]