(S807) A PHASE IB/II STUDY OF DUVELISIB IN COMBINATION WITH FCR (DFCR) FOR FRONTLINE THERAPY OF YOUNGER CLL PATIENTS

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Abstract: S807

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Background

FCR is a common initial therapy for younger CLL patients (pts); however, only about 20% will achieve CR/CRi with MRD negativity in the bone marrow (BM-MRD-). Duvelisib (formerly IPI-145) is a delta/gamma PI3K inhibitor with promising efficacy in CLL. We report on an investigator-initiated, phase Ib/II study of dFCR as initial treatment for younger CLL pts (NCT02158091).

Aims

The primary objectives in phase Ib were to determine duvelisib safety and the RP2D, and in phase II to assess the rate of CR/CRi with BM MRD- after dFCR. Secondary objectives included efficacy assessments.

Methods

A standard 3 + 3 phase I design included 2 dose levels of duvelisib (25 mg qd and 25 mg bid). Duvelisib was given for 1 week with FCR added on day 8. Up to 6 cycles of dFCR were given, followed by up to 2 years of duvelisib maintenance. Growth factor support, antimicrobial prophylaxis, and CMV monitoring were mandatory. Eligibility criteria included: age ≤ 65, requiring treatment by IW-CLL criteria, ECOG PS ≤1, and adequate organ function. Toxicity evaluations were performed by CTCAE v4.03/IW-CLL. Response evaluations by 2008 IW-CLL criteria occurred after 3 cycles, 2 months after final FCR, and q6 months thereafter. MRD was assessed by four-color flow cytometry (sensitivity of 10^{-4}).

Results

32 pts were enrolled, including 6 pts treated with duvelisib 25 mg QD and 26 pts treated with duvelisib 25 mg bid. The median age at enrollment was 55 yrs (range 45-65). By FISH, 8 pts (25%) had del(11q), and 3 (9%) had del(17p). Unmutated *IGHV* was present in 18 pts (56%) and *TP53* mutation in 2 pts (6%). Gr3 febrile neutropenia at 25 mg QD (n=1) was the only DLT, and the RP2D of duvelisib was 25 mg bid. Heme toxicity included thrombocytopenia (69%; 34% gr 3-4), neutropenia (56%; 47% gr 3-4), and anemia (34%, 16% gr 3). Non-heme toxicities included nausea (72%, all gr 1/2), fatigue (69%, 3% gr 3), fever (53%, all gr 1/2), diarrhea (47%, 3% gr 3), transaminitis (34%, 28% gr 3/4), anorexia (34%, all gr 1/2), vomiting (28%, all gr 1/2), pruritus (16%, 3% gr 3), and inflammatory arthritis (9%, all gr 2). SAEs included transaminitis (n=5 gr 3, n=4 gr 4), febrile neutropenia (n=7, all gr 3), pneumonia (n=6, including 3 cases of PJP despite planned prophylaxis), colitis (n=1 gr 2, n=1 gr 3), gr 3 pruritus and gr 3 CMV infection (n=1 each). A median of 5.5 cycles of FCR were given, and 10 pts (31%) discontinued chemotherapy early due to toxicity. Nine pts (28%) required duvelisib dose-reduction. In the 29 pts evaluable for post-FCR response, the ORR was 97%, with 28% achieving CR (n=4) or CRi (n=4), and 69% achieving PR. The best rate of MRD- in the BM in pts with at least one evaluation was 21/26 (81%). The rate of CR/CRi with BM-MRD- (primary efficacy endpoint) was 28%. Two pts with del(17p) achieved MRD+ PR and one achieved MRD+ CR after 12 mo. of duvelisib maintenance. With a median follow-up among survivors of 21 mo. (range 6-42), 2 pts have progressed, including 1 with asymptomatic progression 6 mo. after maintenance ended and 1 with baseline del(17p) and complex karyotype who developed Richter's Syndrome and died 29 mo. after starting on study. Two other pts died, including 1 with metastatic melanoma (at 15 mo.) and 1 with glioblastoma (at 36 mo.). 2-year PFS and OS are both 97%. 8 pts have now completed 2 yrs of duvelisib maintenance.

Conclusion

dFCR is an effective regimen for the initial therapy of younger, fit CLL pts, leading to a high rate of BM-MRD negativity of 81%, although infectious and immune-mediated toxicities were observed.

Session topic: 6. Chronic lymphocytic leukemia and related disorders - Clinical
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