ORAL 11 - Clinical Trials 1 (ID 100)

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Session Type Oral Session

Coordinates WCLC 2015, 09/07/2015, 10:45 AM - 12:15 PM, 702+704+706

ORAL11.02 - Phase I Study of Anti-Mesothelin Antibody Drug Conjugate Anetumab Ravtansine (ID 1574)

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Topic Thymoma, Mesothelioma and Other Thoracic Malignancies

PRESENTATION | **ABSTRACT**

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Background

Anetumab ravtansine (BAY 94-9343) is a novel fully humanized anti-mesothelin IgG1 antibody conjugated to a ravtansine, a maytansine derivative DM4 antitubulin cytotoxic agent. We report results from a phase I study evaluating the safety, PK and tumor response in patients (pts) with advanced solid tumors treated with anetumab, with a particular focus on patients with mesothelioma.

Methods

Anetumab was given IV every 21 days (q3w) in 77 pts: 45 pts in 10 dose escalation cohorts from 0.15 to 7.5 mg/kg (21 mesothelioma, 9 pancreatic, 5 breast, 4 ovarian, 6 other), and 32 pts in 2 expansion cohorts (12 mesothelioma and 20 ovarian); 38 pts were treated at MTD in escalation and expansion cohorts (16 mesothelioma, 21 ovarian, 1 breast). Clinical and laboratory safety assessments were made on D1, D8 and D15 in C1-C3 and on D1 in subsequent cycles. Tumor assessments were made q6wks up to C8 and q12wks thereafter. Mesothelin expression in archival tumor samples was assessed retrospecively by IHC (SP74, Ventana).

Results

Thirty-two males and 45 females were treated [mean age 62 yrs (range, 18-84 yrs), body weight 77 kg (44-113 kg), ECOG ≤1, median prior cytotoxic regimens: overall 4 (1-9), mesothelioma 1 (1-4)]. Non-tolerated anetumab dose was 7.5 mg/kg (DLTs: 1 pt with G2 keratitis and G3 neuropathy, 1 pt with G4 keratitis and G2 neuropathy). Anetumab MTD was 6.5 mg/kg (DLT: G3 AST increase). Only one DLT occurred at doses below MTD (G3 hyponatremia, 5.5 mg/kg). No drug-related deaths and few drug-related SAEs (7 total and 5 at MTD) were reported. Seventeen of 38 (45%) pts total or 7 of 16 (44%) mesothelioma pts at MTD had drug-related AE requiring dose reduction (G1-4 keratitis, G2-3 neuropathy, G3 fatigue, anorexia, asthenia, diarrhea, N&V, AST increase). LFT increases were the most common drug-related laboratory abnormality at MTD: AST in 7 pts (2 G3), ALT in 6 pts (no G3), alkaline phosphatase in 4 pts (one G3) and bilirubin increase in 1 pt (no G3). There were no drug-related G3 hematological abnormalities at any dose. Fourteen of 38 (37%) pts total or 4 of 16 (25%) mesothelioma pts at MTD had G1-4 keratitis (worst G3-4 in 3 pts, blurred vision in 10, dose reduction in 8, dose delay in 11, all fully reversible). Anetumab at the MTD showed a PR in 6 pts (19%) and SD in 18 pts (47%) overall. Five of 16 (31%) mesothelioma pts at the MTD had durable PR (>600 days in 4 pts) and 7 (44%) had SD. Five PRs occurred in 11 mesothelioma pts who received anetumab as second line treatment (45% response rate).

Conclusion

Anetumab at the MTD (6.5 mg/kg) showed encouraging efficacy with durable PR in pts with advanced mesothelioma. At the MTD, all drug-related AEs were reversible and non-life-threatening but required dose reduction in about half of pts, most commonly due to G1-4 keratitis and G2-3 peripheral neuropathy. Given this benefit-risk ratio, the recommended phase II dose of anetumab in second line treatment of advanced mesothelioma is 6.5 mg/kg IV q3w.