1483PD Imatinib in combination with everolimus in patients with progressive advanced chordoma: results form an Italian phase 2 clinical trial

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Background: To evaluate the antitumor activity of imatinib in combination with everolimus in patients (pts) with advanced PDGFB- and/or PDGFRB-positive chordomas with evidence of mTOR and/or of its effectors (i.e. S6, 4EBP1) activation.

Methods: Within an Italian academic prospective phase II clinical study carried out from January 2011 to March 2015, 45 patients with advanced PDGFB/PDGFRB and mTOR/S6/4EBP1 positive chordoma received imatinib 400 mg/day in combination with everolimus at the starting dose of 2.5 mg/day, until progression or limiting toxicity. Eligible pts had to have evidence of progression in the 6 months prior to study entry. The primary endpoint was overall tumor response rate (ORR), defined by the Choi criteria applied also to MRI. Secondary endpoints were RECIST response, progression-free survival (PFS), overall survival (OS).

Results: Fifteen of 45 pts included in the study were pretreated with imatinib (as a single agent). All pts completed their treatment (22 progression; 16 toxicity; 7 other). Among 38/46 patients evaluable by Choi criteria, the best response was: 8 partial response (PR) (ORR, 21%), 23 stable disease (60%) and 7 progression. 42/46 pts were evaluable by RECIST with 1 PR (2%), 36 SD (85%) and 3. Median PFS by Choi criteria was 10 months (range 1-45), with 36% and 17% pts disease-free at 12 and 24 mos, respectively. Median PFS by RECIST was 13 months. At a median follow-up of 31 months, median OS was 47 months.

Conclusions: Although formally negative (the planned target was a Choi ORR $\geq$60%), this study showed that imatinib + everolimus is active in a proportion of progressive advanced chordoma pts. Major dimensional responses were uncommon but disease stabilization was apparently longer than observed with imatinib as a single agent. Toxicity was not negligible.

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