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LMS-04 study: A randomised, multicenter, phase III study comparing doxorubicin alone versus doxorubicin with trabectedin followed by trabectedin in non-progressive patients as first-line therapy, in patients with metastatic or unresectable leiomyosarcoma - A French Sarcoma Group study

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Background

Doxorubicin (Dox) alone remains the standard 1st-line treatment for unresectable or metastatic (met) leiomyosarcoma (LMS). The LMS02 study reported very encouraging results of a doxorubicin + trabectedin (Dox+Trab) combination in 1st-line therapy for met LMS with median progression-free survival (PFS) of 10.1 months (mo), and median overall survival (OS) of 34.4 mo.

Methods

The LMS-04 trial compared, as 1st-line treatment for patients (pts) with met or unresectable LMS, up to 6 cycles (cy) of Dox (75 mg/m^2) (arm A) *vs* up to 6 cy of Dox (60 mg/m^2) + Trab (1.1 mg/m^2) q 3w followed by maintenance with Trab alone for non-progressive pts (up to 17cy) (arm B). Surgery for residual disease was allowed in both arms after 6 cy. Primary endpoint is PFS (according to RECIST 1.1); the objective was to improve median PFS, from 6 mo in arm A to 9.7 mo in arm B. Pts were stratified by tumour location (uterine U-LMS *vs* soft tissue ST-LMS).

Results

Between January 2017 and March 2019, 150 pts with LMS (U-LMS: n=67; ST-LMS: n=83) with a median age of 61 years (range 30-86) and mostly metastatic diseases (90%) were enrolled: 76 in arm A and 74 in arm B. Median follow-up in August 2021 was 37 months (mo); 74% of arm B pts received at least 1 cy of Trab in maintenance. Grade 3-4 toxicities were reported in 46% of arm A pts *vs* 81% of arm B pts, mostly hematologic and digestive, with 1 toxic death due to infection (arm A). Primary end-point has significantly improved with Dox+Trab *vs* Dox, with median PFS of 13.5 mo [95% CI : 11.3-16.7] *vs* 7.3 mo [95% CI : 6.2-8.3], with adjusted HR : 0.384 [0.27;0.55] and p<.0001. The overall response rate (ORR) is 13% [10 PR] with Dox and 38% [4 CR + 24 PR] with Dox+Trab; 6 pts (arm A) and 14 pts (arm B) underwent surgery after 6 cy. Median OS rates are 24.1 mo with Dox and 30.5 mo with Dox+Trab (HR: 0.74 [0.49;1.12]).

Conclusions

Dox+Trab combination in 1st-line therapy increases significantly the PFS of met LMS compared to Dox alone, though at the cost of additional expected and manageable toxicity. Benefit in ORR and OS is also observed.

Clinical trial identification

NCT02997358.

Legal entity responsible for the study

Institut Gustave-Roussy.

Funding

PharmaMar.

Disclosure

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