**Editorial Commentary**

# Eribulin Approval in Advanced Liposarcoma – Successful Drug or a Weaker Methodology?

## Background

Advanced soft tissue sarcoma is a complex and extremely heterogeneous disease with dismal survival outcomes. However, recent approval and success of newer therapies have generated a wave of enthusiasm among sarcoma medical oncologists across the world. Newer therapies can help us adopt a more flexible and individualized approach. Since benefit of therapies in soft tissue sarcoma is at best modest, we must analyze the trials carefully before the drugs are approved for our patients.

## The Eribulin Trial

We read with immense interest the recently published randomized controlled trial by Schoffski *et al.* published in Lancet and its accompanying thought provoking commentary.[1,2] In this randomized, open-label, multicenter, phase 3 study, patients with intermediate- or high-grade leiomyosarcoma and liposarcoma, who had received two previous lines of therapy were randomized to eribulin or dacarbazine in 1:1 fashion. Overall survival (OS), the primary end point, was significantly better in patients assigned to eribulin ($n$ = 228) compared with those assigned to dacarbazine ($n$ = 224) (median 13·5 months vs. 11·5 months; hazard ratio 0.77 [95% confidence interval (CI): 0.62–0.95]; $P$ = 0.0169). Not unexpectedly, the drug was approved by the US Food and Drug Administration (FDA) in January 2016 as the most coveted end point was met, i.e., improvement in OS. We wish to underscore a few points of interest pertinent to this study.

## Comments and Critical Analysis

First, regarding the reported prespecified subgroup analysis, interaction test is conspicuous by its absence. As a matter of fact, interaction test is grossly underreported in medical literature, even in reputed medical journals.[3] When significance of treatment effect is reported in individual subgroups, rates of false negative and false positive are extremely high.[4] This is evident by the lack of benefit in female subgroup in the trial, for which no plausible scientific explanation exists. The only reliable statistical approach is to test for a subgroup-treatment effect interaction.[3] In other words, the most useful tool for assessing subgroup analyses are statistical tests for interaction, which directly examine the strength of evidence for the treatment difference varying between subgroups. The subgroup analysis in this scenario begets more attention as this drug is now FDA approved in liposarcoma as directed by subgroup analysis; something that is still a matter of debate.[5] Since this trial was not powered to detect the efficacy of eribulin in

leiomyosarcoma or liposarcoma, we cannot rule out the efficacy of eribulin in leiomyosarcoma just on the basis of subgroup analysis and further trials need to explore this.

Second, we wonder if in a study OS is more than four times the progression-free survival (PFS), whether OS remains a valid end point as has been debated in recent times.[6] We anticipate that multiple lines of postprogression therapies would obscure the real effect of the study drug. In the wake of imperfection of OS as an end point in trials with multiple postprogression therapies, newer end points such as duration of disease control and time to failure of strategy (TFS) need to be explored in soft tissue sarcoma as well.[7] TFS allows better assessment of the effect treatment sequence and strategies on outcome than PFS. Recently, Morita *et al.* showed by their extensive simulation that it is a possibility that in breast cancer, the OS benefit of eribulin could be due to postprogression survival; and thus, we must use newer end points or choose end points more carefully in future trials.[8] Another way to overcome this conundrum is to predefine the poststudy treatment at study entry/randomization to eliminate bias introduced by such imbalances.

Third, as both eribulin and pazopanib influence the tumor microvasculature, there might exist an interaction between them that abrogates the effect of either of them if used sequentially. This could be a possible reason for failure of eribulin to show any effect on survival in leiomyosarcoma.

## Conclusion

In nutshell, we consider that the new drugs are promising in soft tissue sarcoma but as the sarcoma landscape is changing, we need to scrutinize these trials in detail so that further trials incorporate the inputs learned from the previous trial. OS has always eluded us in the previous trials and now when it has been achieved, we must not give into its glory but analyze if we have not been mistaken. Since sarcoma is a disease where subgroup analysis forms the backbone of the results, it must be planned by adhering to the recent guidelines including interaction testing.

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