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Lurbinectedin Inactivates the Ewing Sarcoma Oncoprotein EWS-FLI1 by Redistributing It within the Nucleus.

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Abstract

There is a great need to develop novel approaches to target oncogenic transcription factors with small molecules. Ewing sarcoma is emblematic of this need, as it depends on the continued activity of the EWS-FLI1 transcription factor to maintain the malignant phenotype. We have previously shown that the small molecule trabectedin interferes with EWS-FLI1. Here, we report important mechanistic advances and a second-generation inhibitor to provide insight into the therapeutic targeting of EWS-FLI1. We discovered that trabectedin functionally inactivated EWS-FLI1 by redistributing the protein within the nucleus to the nucleolus. This effect was rooted in the wild-type functions of the EWSR1, compromising the N-terminal half of the chimeric oncoprotein, which is known to be similarly redistributed within the nucleus in the presence of UV light damage. A second-generation trabectedin analogue lurbinectedin (PM01183) caused the same nuclear redistribution of EWS-FLI1, leading to a loss of activity at the promoter, mRNA, and protein levels of expression. Tumor xenograft studies confirmed this effect, and it was increased in combination with irinotecan, leading to tumor regression and replacement of Ewing sarcoma cells with benign fat cells. The net result of combined lurbinectedin and irinotecan treatment was a complete reversal of EWS-FLI1 activity and elimination of established tumors in 30% to 70% of mice after only 11 days of therapy. Our results illustrate the preclinical safety and efficacy of a disease-specific therapy targeting the central oncogenic driver in Ewing sarcoma. Cancer Res; 76(22); 6657-68. ©2016 AACR.