

Broad Activity of APTO-253 in AML and Other Hematologic Malignancies Correlates with KLF4 Expression Level

Abstract
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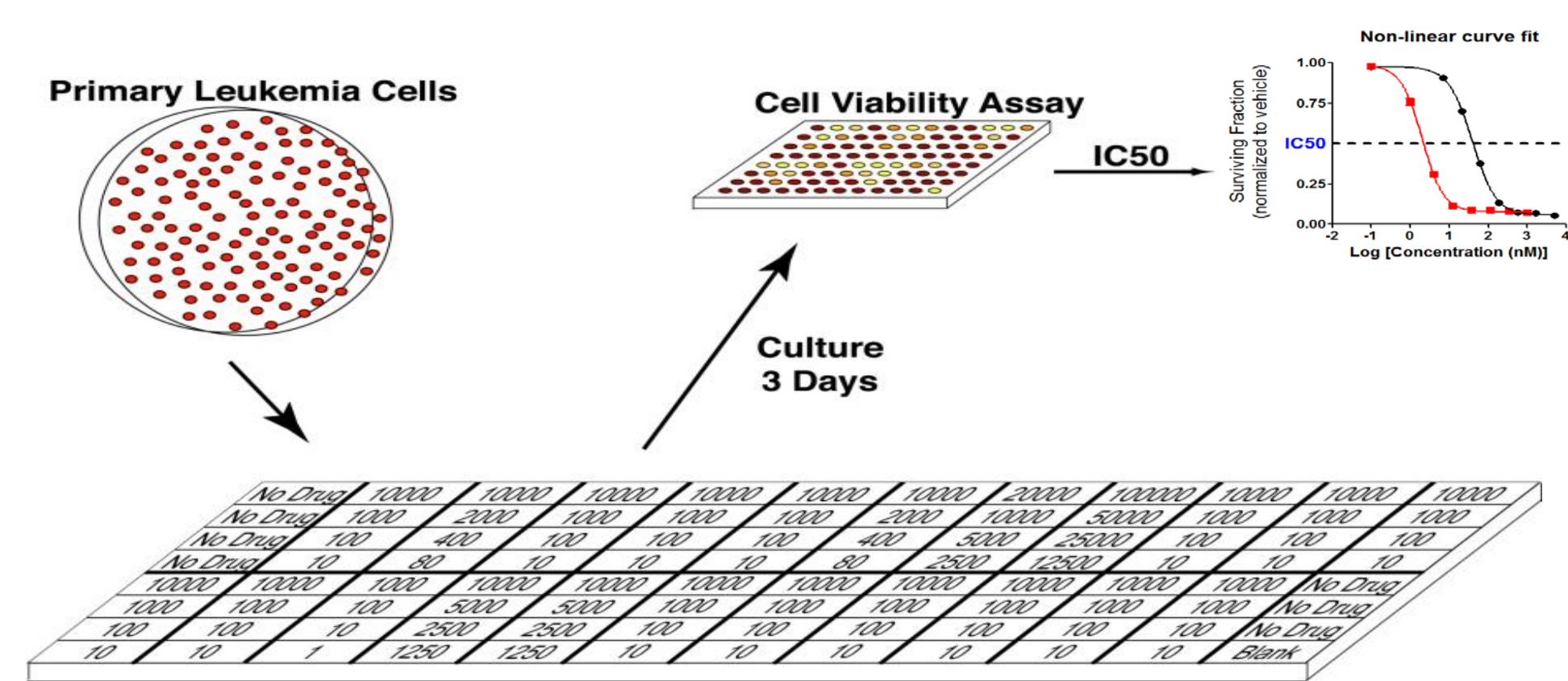
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INTRODUCTION

- Aberrant expression of the homeodomain transcription factor CDX2 has recently been reported in a large proportion of AML cases. One consequence of CDX2 deregulation appears to be repressed expression of the transcription factor KLF4.
- Repression of KLF4 was shown to be critical for CDX2-mediated tumorigenesis, and forced genetic de-repression of KLF4 led to apoptosis of AML cells.
- We evaluated the activity of APTO-253, a novel small-molecule that induces KLF4 expression, on primary specimens from patients with AML, CLL, CML, and MDS/MPN as a single agent and in combination with two emerging targeted therapies, the BET bromodomain inhibitor JQ1 and the FLT3 inhibitor quizartinib.

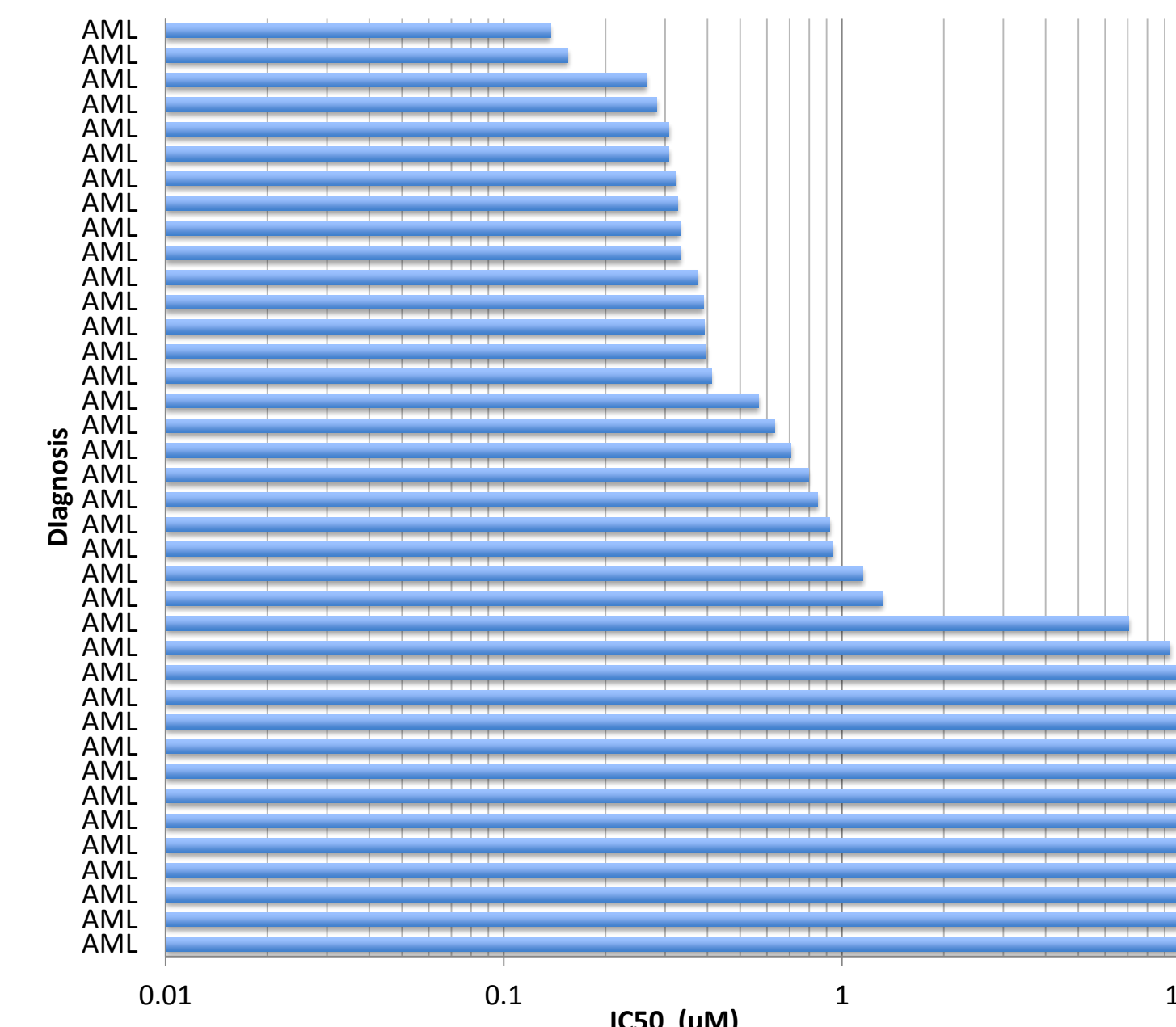
Ex Vivo Drug Sensitivity Assay

- We evaluated specimens from 177 patients with a variety of hematologic malignancy diagnoses.
- We used an *ex vivo* drug sensitivity assay to determine the activity of APTO-253, JQ1, and quizartinib across graded concentrations of each agent with a maximal dose of 10 μ M. Combinations were tested at a fixed, equimolar ratio over the same dose range. Cell viability was assessed using a colorimetric, tetrazolium-based MTS assay after a 3-day culture, and IC50 values were calculated. RNA-seq was performed on AML specimens to evaluate correlation of drug sensitivity with gene expression levels.



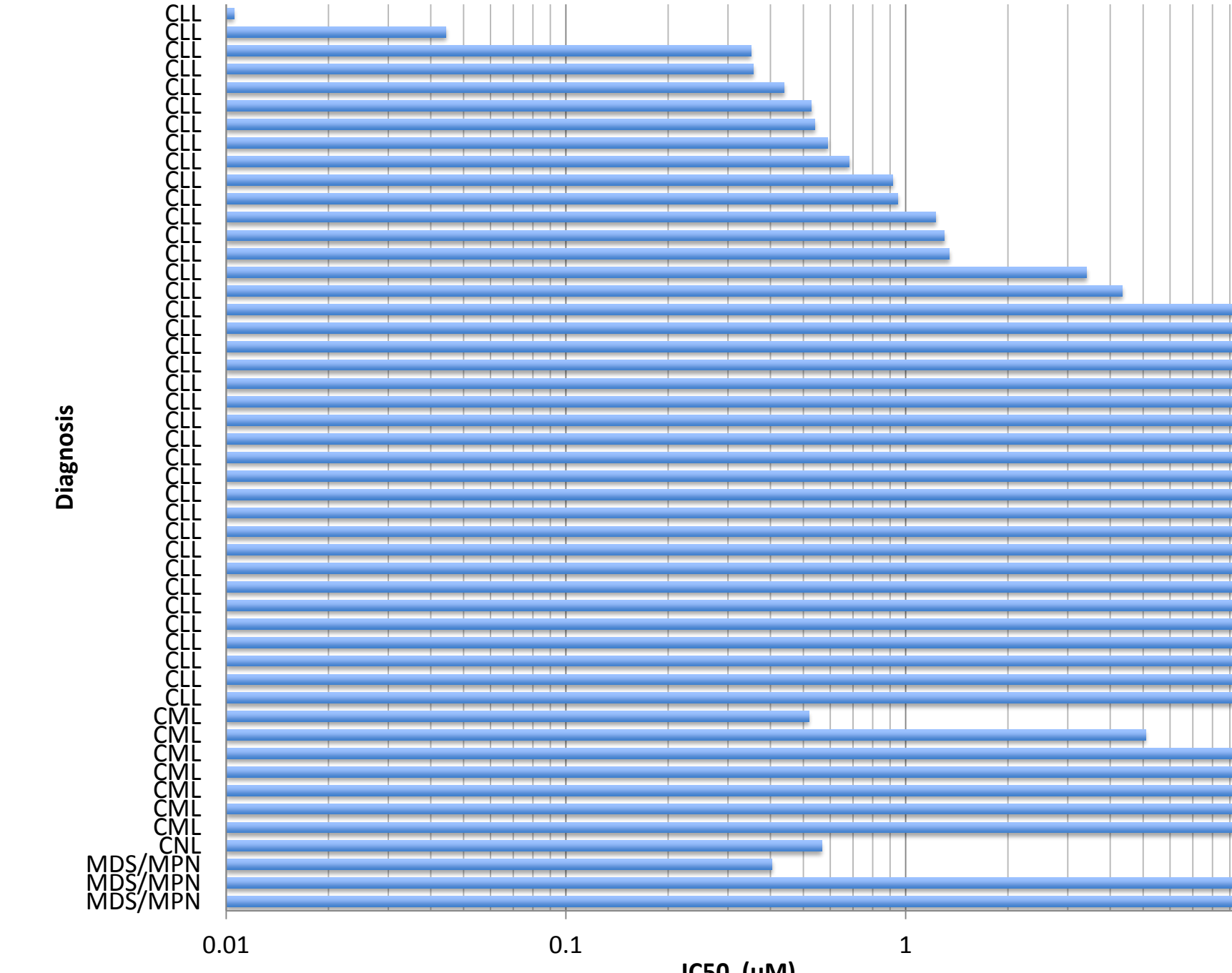
Primary AML Patient Samples Are Sensitive to Single-Agent APTO-253

- AML cases showed the highest frequency of APTO-253 sensitivity, with 43/80 (54%) cases exhibiting an IC50 of less than 1 μ M.



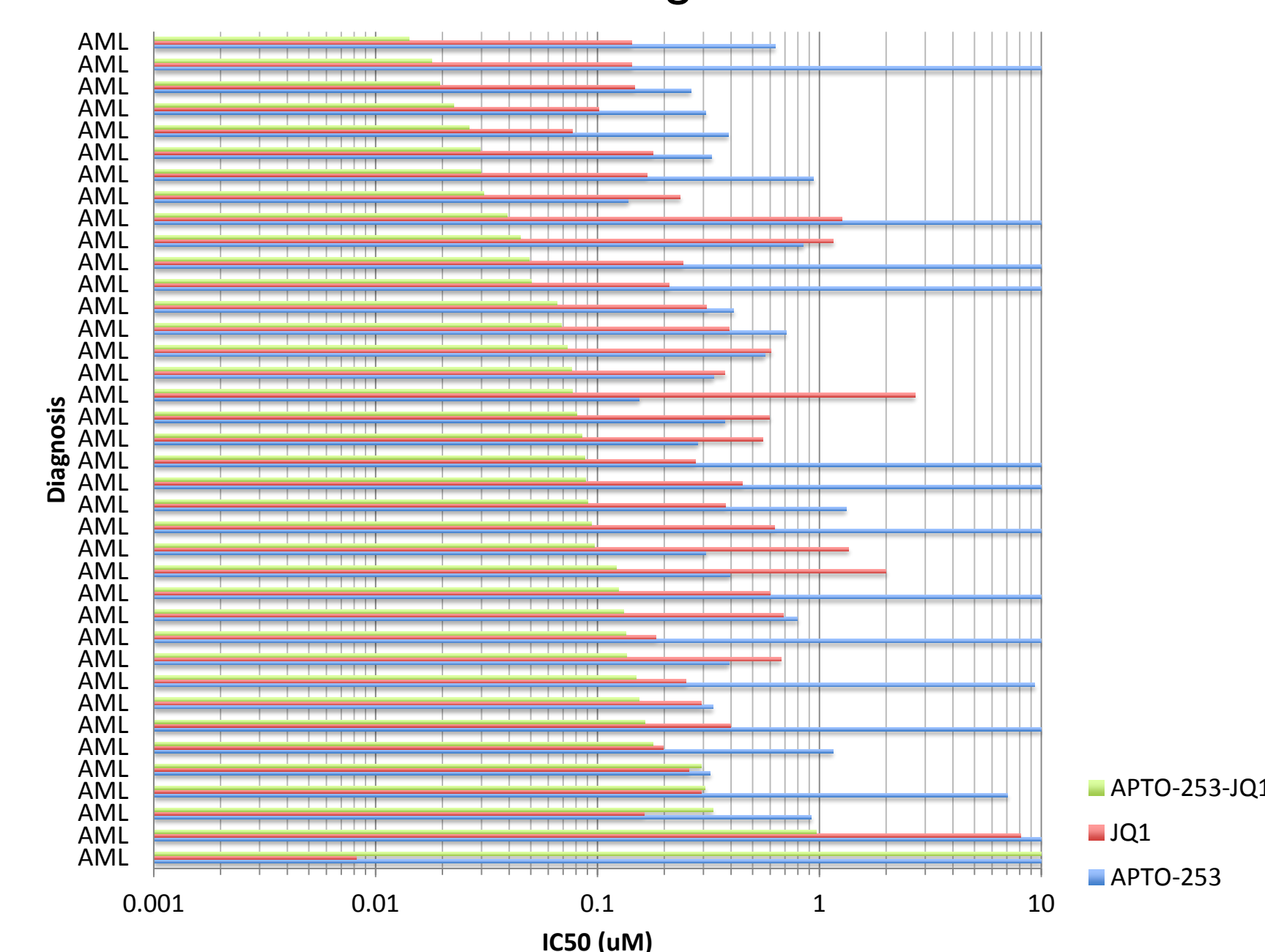
Primary Non-AML Patient Samples Are Sensitive to Single-Agent APTO-253

- CLL cases exhibited sensitivity at a frequency of 25/72 (35%), and MDS/MPN at a frequency of 3/25 (12%).



Addition of JQ-1 Enhances Sensitivity to APTO-253

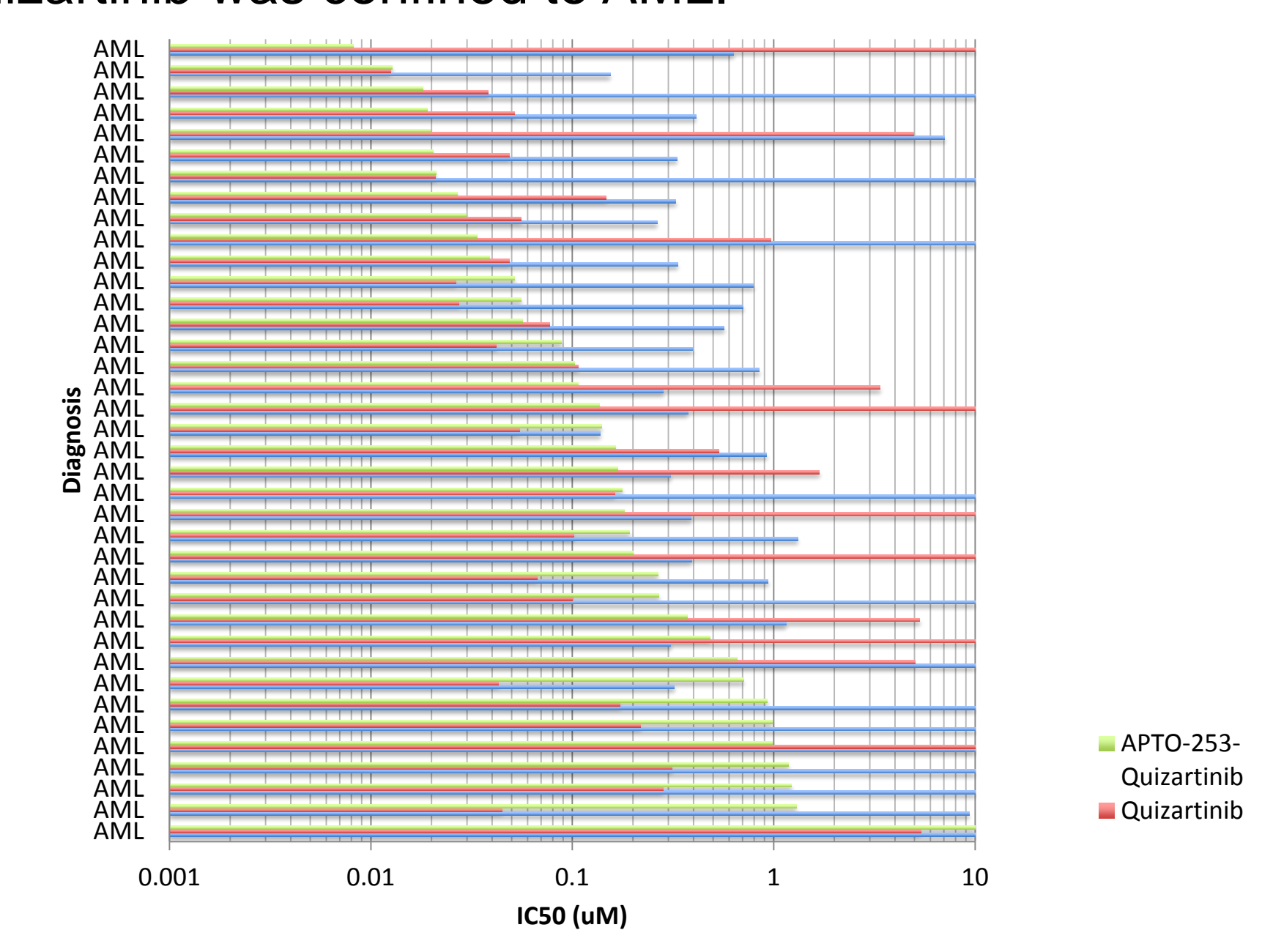
- Results:** Approximately 65% (56/87) of AML samples tested with a combination of APTO-253 and JQ1 showed the combination IC50 to be at least 2-fold lower than the IC50 of either single agent. This enhanced efficacy of APTO-253 with JQ1 was observed across diagnostic subsets.



- Rationale:** APTO-253 exerts anti-AML effect at least partly by upregulating KLF4, a master transcription factor involved in regulation of key cell identity and fate genes. APTO-253 also alters levels of histone methylation concomitant with altered expression profiles of key genes. Potential synergy was thus anticipated with agents that also affect transcriptional regulation, including bromodomain inhibitors.

Addition of Quizartinib Enhances Sensitivity to APTO-253

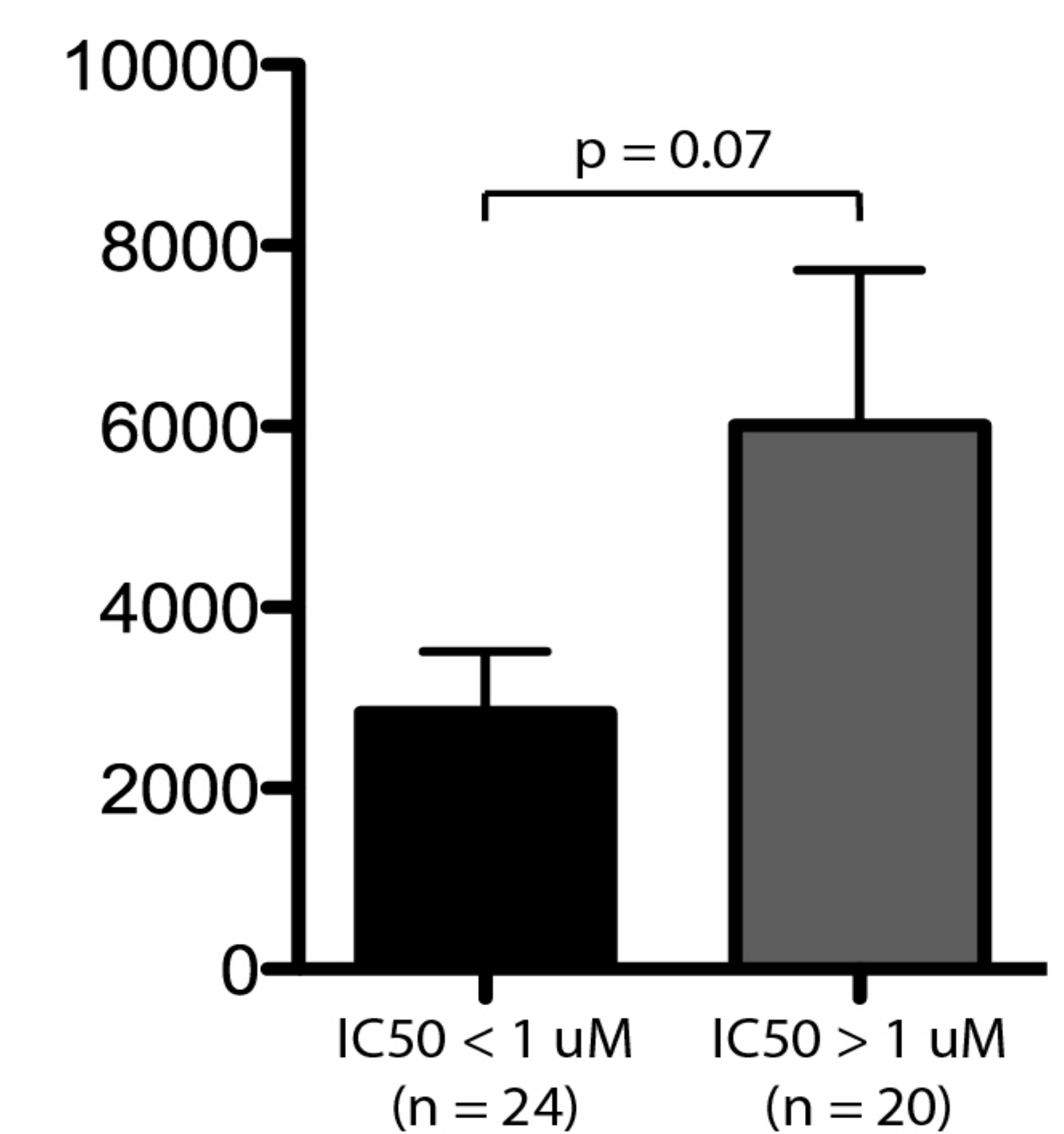
- Results:** Approximately 37% (14/38) of cases tested with a combination of APTO-253 and quizartinib showed the combination IC50 to be at least 2-fold lower than the IC50 of either single agent. This enhanced efficacy of APTO-253 with quizartinib was confined to AML.



- Rationale:** APTO-253 exerts anti-AML effect at least partly by upregulating KLF4, a master transcription factor involved in regulation of key cell identity and fate genes. APTO-253 also alters levels of histone methylation concomitant with altered expression profiles of key genes. Potential synergy was thus anticipated with agents that also affect transcriptional regulation, including bromodomain inhibitors.

KLF4 Expression Correlates with Sensitivity to APTO-253

- AML cases exhibiting sensitivity to APTO-253 had an average KLF4 expression level lower than non-sensitive cases.



CONCLUSIONS

- The KLF4 inducer APTO-253 is effective at killing tumor cells in a majority of AML cases; it is also active in CLL.
- Expression level of KLF4 may be one component of a biomarker for prediction of APTO-253 efficacy.
- Combinations of APTO-253 with the BET bromodomain inhibitor JQ1 and with the FLT3 inhibitor quizartinib suggest these classes of drugs as potential partners for APTO-253.

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