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Précis: Tissue-specific BCL-2 family member expression in squamous cell carcinoma underlies resistance to HDAC and BCL-2 inhibitors and imparts sensitivity to combination therapy.

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Précis: BRAF-mutant melanoma cells lacking NF1 develop resistance to RAF and MEK blockade via sustained MAPK signaling but retain sensitivity to both ERK and irreversible RAF inhibitors.

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Puissant and colleagues screened a compendium of cancer cell lines to identify those most sensitive to the bromodomain and extraterminal domain (BET) protein inhibitor JQ1. Neuroblastoma cell lines were among the most JQ1-sensitive cell lines, and MYCN amplification, which is commonly observed in high-risk neuroblastoma, was the feature most predictive of JQ1 sensitivity. JQ1 displaced the BET family member BRD4 from the MYCN promoter, leading to decreased expression of MYCN and MYCN target genes, and significantly prolonged survival in several MYCN-amplified neuroblastoma models. These findings thus implicate MYCN amplification as a genetic predictor of BET inhibitor sensitivity and provide support for the development of BET inhibitors in MYCN-amplified neuroblastoma. For details, please see the article by Puissant and colleagues on page 308.