Predictive Biomarker Evaluation and Molecular Differentiation for Imipridones ONC201 and ONC206

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Abstract

ONC201 and ONC206 Overview
ONC201/206 are imipridones with predicted antitumor activity in hypoxic and normoxic GBM cells. ONC201/206 have acceptable efficacies in human GBM cell lines in combination with a range of other commonly used drugs.

Background and Methods

ONC201/206 are imipridones with antitumor activity in GBM cell lines. ONC201/206 exhibit improved efficacy and reduced toxicity in human GBM xenograft and cell line models.

Results

Figure 1. (A) Fold change in gene expression fold (B) number of genes that exhibit a fold change upon treatment with ONC201 and ONC206 (drug IC50) in GBM cells.

Figure 2. (A) Cell viability upon treatment with ONC201, ONC206 and combinations. (B) Cell viability upon treatment with ONC201, ONC206 and combinations.

Figure 3. (A) Cell viability of (A) U87, (B) SF268, and (C) T98G cells treated under normoxic or hypoxic conditions with ONC201 (drug IC50) or indicated concentrations. Cell viability of (E) SF268, (F) T98G cells treated with ONC201 (drug IC50) or indicated concentrations.

Conclusions and Future Directions

- Gene expression profiling, GDC5 biomarker prioritization, acquired resistance and combinational synergy suggest that ONC201/206 significantly reduce tumor burden.
- GDC5 biomarkers exhibit distinct therapeutic properties relative to ONC201/206, which can be uniquely powered to address tumors that are not addressed by ONC201/206.
- GDC5 biomarkers indicate that single biomarkers do not completely capture the sensitivity profiles of ONC201/206 across tumor types and that combinations of biomarkers are needed to capture the synergy.
- GDC5 biomarkers for ONC201/206 that are sensitive to hypoxia and exhibit distinct correlations are likely to be related to the inherent hypoxic nature of tumors. This is a need for further understanding the biological mechanisms of biomarkers observed in the treatment settings for each compound.