

Preclinical evaluation of ODM-212 in solid tumor models alone and in combination with chemotherapy

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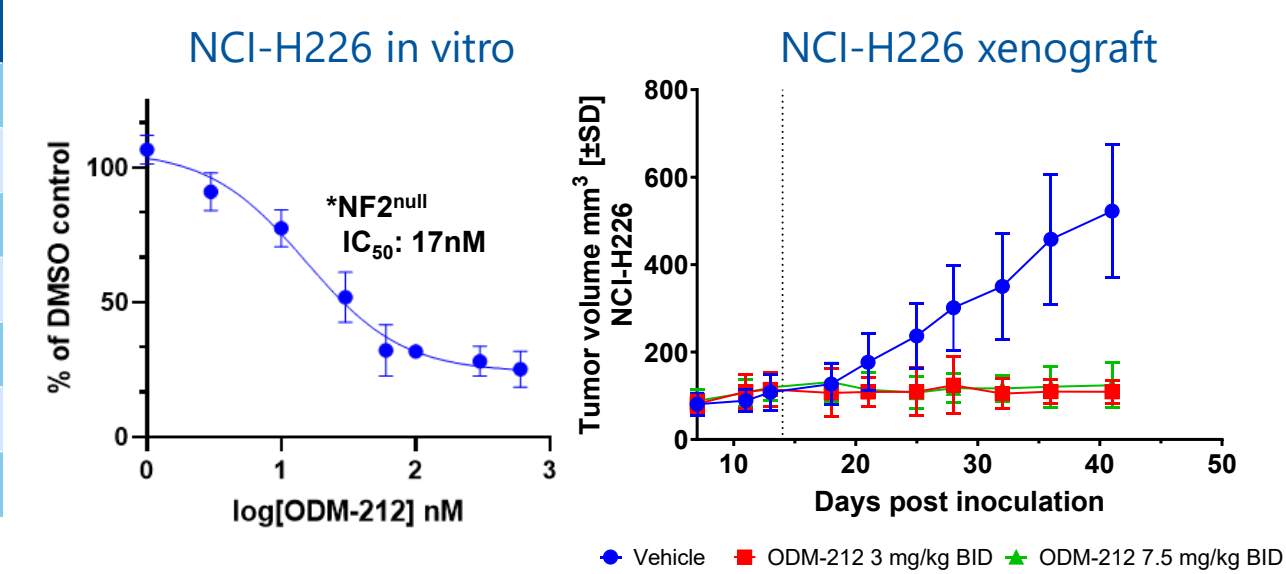
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Introduction

The Hippo signaling pathway is a conserved regulator of tissue homeostasis and organ size. Its core downstream effectors, YAP and TAZ, are frequently activated in cancers to drive proliferation and survival. In addition to their direct oncogenic activity in Hippo pathway-altered cancers, YAP/TAZ-TEAD contributes to the intrinsic and acquired tumor resistance that undermines a wide variety of antitumor treatments including chemotherapy. The possibility of combining TEAD inhibitors with other agents to eradicate drug-tolerant persister cells is therefore gaining increased attention [1]. Combining TEAD inhibitor with chemotherapy presents thus a promising strategy to enhance treatment efficacy in cancers where the Hippo pathway is dysregulated. Here, we present results from translational preclinical *in vitro* and *in vivo* studies exploring the efficacy of ODM-212, a novel pan-TEAD inhibitor [2], alone and in combination with traditional chemotherapy agents providing promising evidence for activity across various indications.

- **ODM-212 is a novel pan-TEAD inhibitor**
- **ODM-212 binds to the central palmitate pocket of TEAD1-4**
- **ODM-212 inhibits TEAD transcriptional activity ($IC_{50} = 12nM$)**

Cell line	Hippo att.	IC ₅₀ (nM)
NCI-H226	NF2, LATS2	17
MSTO-211H	LATS1, LATS2	76
NCI-H2052	NF2, LATS2	54
C-33 A	LATS2	64
HEC-1-B	LATS1	33
HEC-251	LATS1	142
RL95-2	NF2, LATS1	38



Experimental approach

- ODM-212 was evaluated across a pan-cancer panel of human cancer model cell lines to profile the sensitivity to TEAD inhibition.
- 302 cell lines representing 22 anatomical cancer types were included in the screening panel to assess single agent efficacy (Misvik Biology and Oncolines).
- Drug combination assays with standard chemotherapies were used to assess therapeutic synergy with TEAD inhibition.
- Comparative transcriptomics analyses against reference TEAD inhibitors were conducted to verify the on-target effects of ODM-212 on YAP/TAZ-TEAD mediated transcriptional regulation.
- Cell line-derived xenograft (CDX) and patient-derived xenograft (PDX) studies were conducted to evaluate whether *in vitro* combination efficacy of ODM-212 with platinum-based chemotherapy translates to *in vivo* tumor models.

Figure 1. Preclinical evaluation of ODM-212, an orally bioavailable inhibitor of TEADs 1-4 in pan-cancer model cell lines

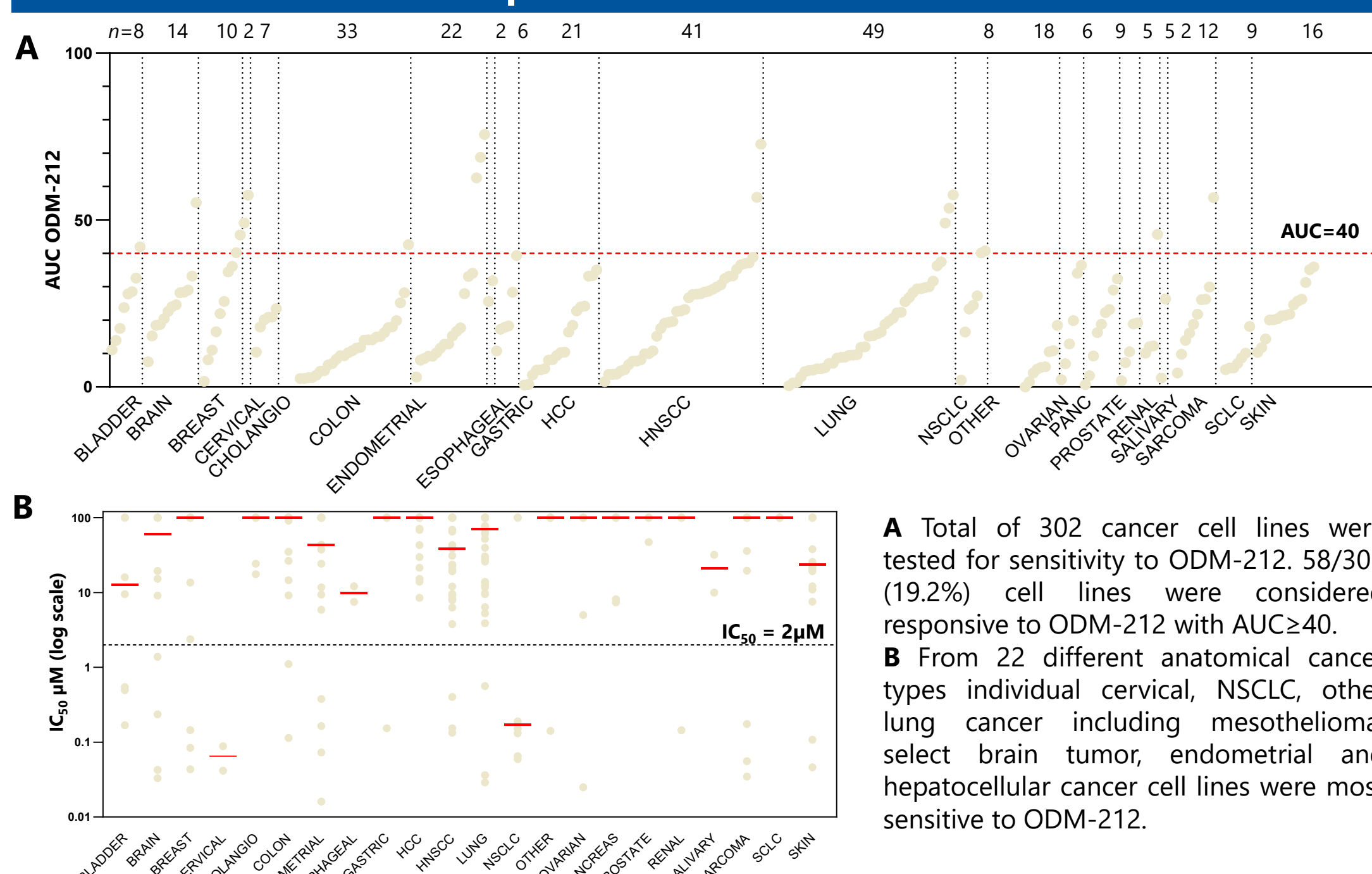
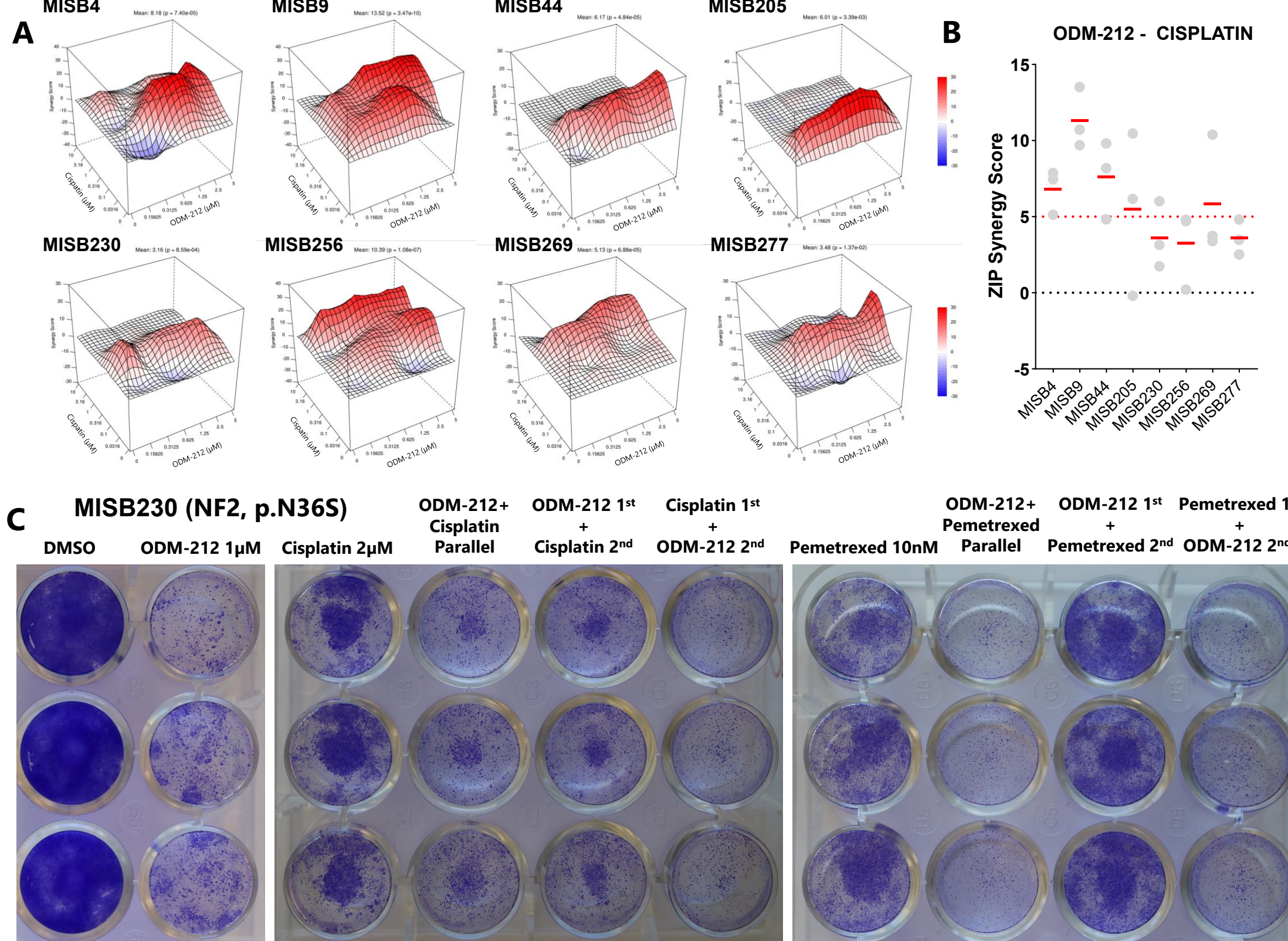


Figure 3. ODM-212 shows synergistic antiproliferative activity *in vitro* with cisplatin across multiple patient-derived HNSCC models



A 3D surface plots showing the ZIP synergy scores of ODM-212-Cisplatin combination across patient-derived HNSCC cell models. **B** Mean ZIP synergy scores across the HNSCC models and replicate experiments (ZIP ≥ 5 , 5/8 samples) **C** Colony forming efficiency assays were used to test alternate scheduling efficacy for ODM-212 in combination with cisplatin and pemetrexed.

RESULTS

Figure 2. Targeting YAP/TAZ mediated transcription with ODM-212 through inhibition of TEAD family of transcription factors

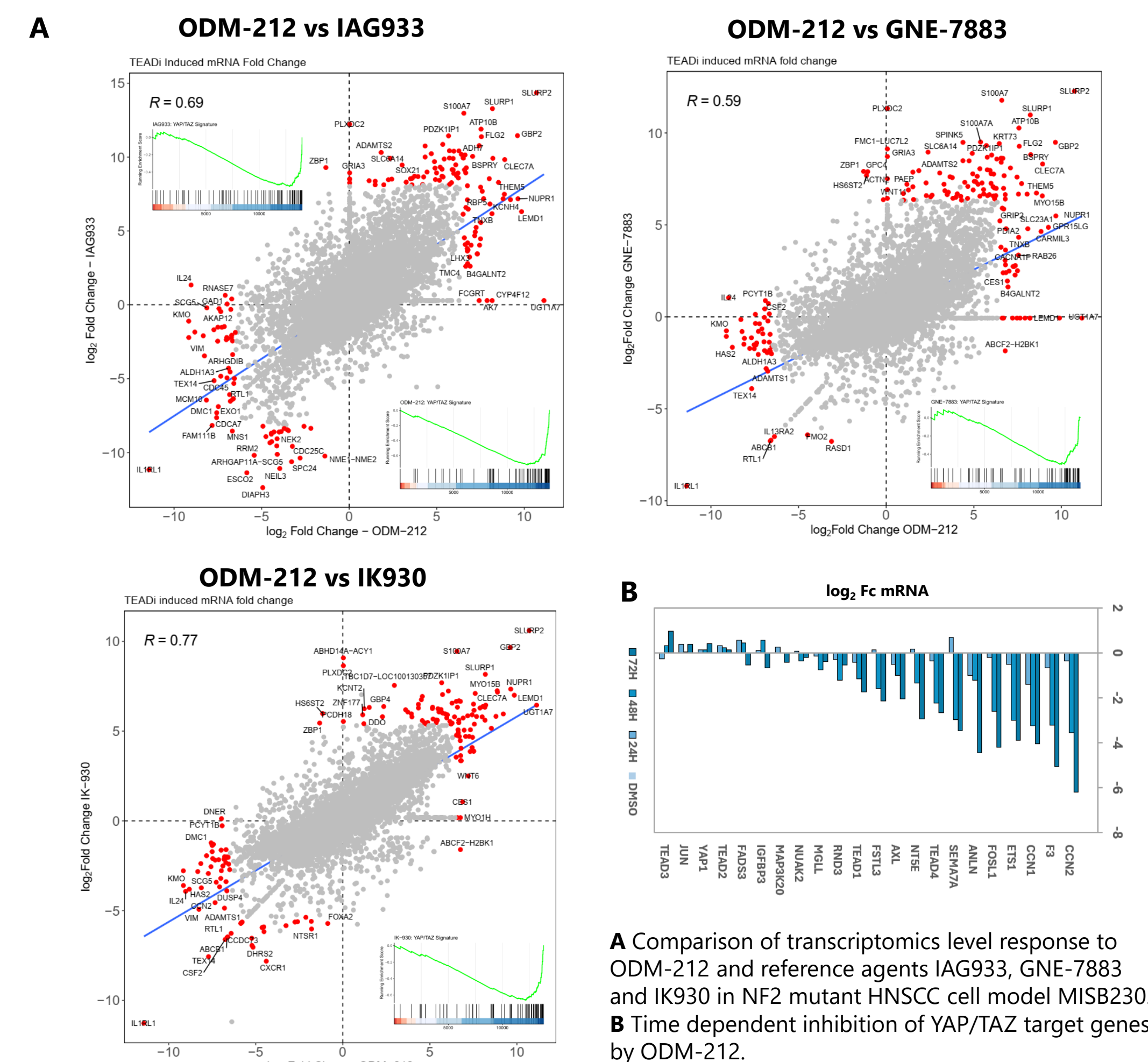
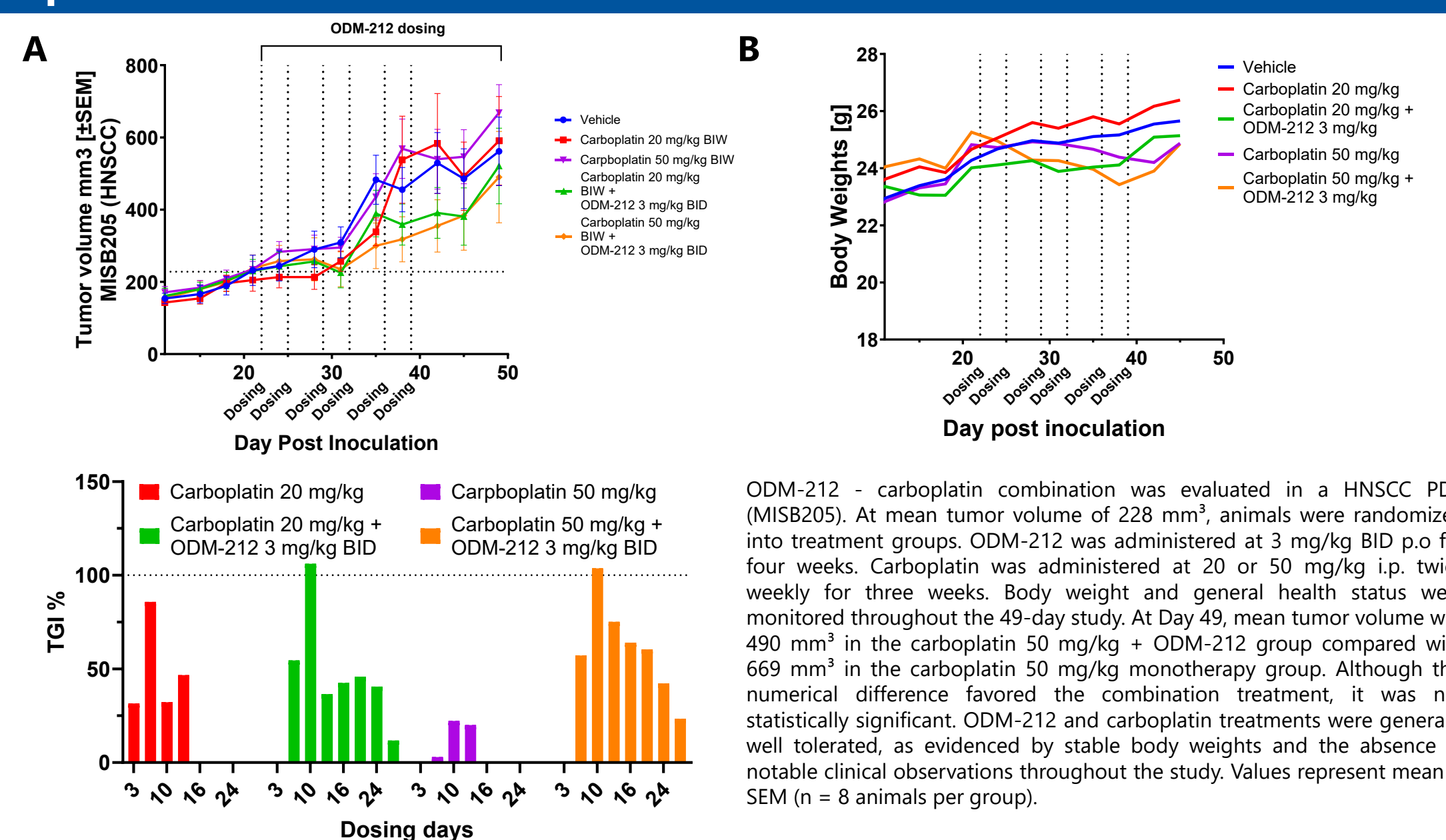


Figure 4. ODM-212 in combination with carboplatin in head and neck squamous cell carcinoma PDX model



Results

- Cancer cells bearing mutations in Hippo pathway exhibit sensitivity to ODM-212 both *in vitro* and *in vivo*.
- Therapeutic activity was observed in cell lines from multiple solid tumor lineages ($IC_{50} < 2 \mu M$, 58/302 samples). (**Figure 1A-B**)
- Targeting YAP/TAZ-mediated transcriptional regulation with ODM-212 resulted in dose- and time-dependent target gene repression consistent with inhibition of YAP/TAZ–TEAD signaling [3]. (**Fig. 2A-B**)
- ODM-212 combined with standard chemotherapeutics including cisplatin (**Figure 3A**) and pemetrexed resulted in synergistic therapeutic efficacy [4] in Hippo pathway-wild-type and mutant HNSCC cell models (ZIP Synergy Score ≥ 5 , 62.5% of samples). In colony forming assays with NF2 mutant patient derived HNSCC cells, ODM-212 in combination with cisplatin and pemetrexed delayed resumption of tumor cell growth after drug washout (**Figure 3B**).
- Xenograft studies in a patient-derived, Hippo pathway-wild-type HNSCC PDX model demonstrated that well-tolerated twice-daily oral dosing of ODM-212 in combination with carboplatin induced tumor growth inhibition (**Figure 4A**) and delayed tumor regrowth following treatment discontinuation. (**Figure 4B**)

Conclusions

- ODM-212 demonstrated anti-tumor activity across a pan-cancer panel of cancer cell lines representing 22 different anatomical cancer types, with sensitivity observed both in Hippo pathway mutant and –wild-type models.
- Comparative transcriptomic analyses showed that ODM-212 induces transcriptional changes consistent with TEAD inhibition and modulation of YAP/TAZ target gene expression in patient-derived HNSCC models.
- ODM-212 enhanced the anti-tumor activity of standard chemotherapies *in vitro*, demonstrating synergistic activity with cisplatin across multiple patient-derived HNSCC models.
- Observed therapeutic activity across solid tumor models provides a rationale for further evaluation in other tumor types and combinations with standard-of-care chemotherapy, which is currently being investigated in the TEADCO Phase I/II study [NCT07563738](#).

ODM-212 is an investigational compound. Its safety and efficacy have not been established, and it has not been approved by any regulatory authority

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A first-in-human Phase I/II clinical trial: TEADES, [NCT06725758](#), A 2-part Phase I/II Open-label Trial on ODM-212: TEADCO, [NCT07563738](#)

Disclosure statement: J.K. Rantala, Other, Institutional, Membership or affiliation: Orion Corporation & Misvik Biology Oy.

Study sponsored by Orion Corporation, Orion Pharma.

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