Micvotabart pelidotin in combination with EGFR-targeted therapy improves duration of response in HNSCC PDX models

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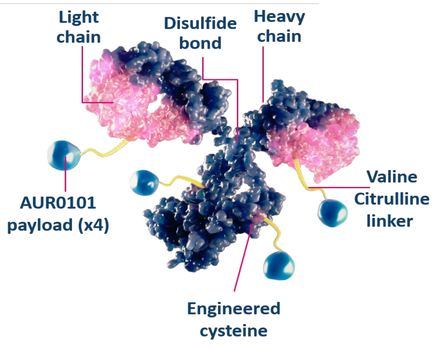
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Abstract: 79

Micvotabart pelidotin (MICVO, formerly PYX-201), a first-in-concept antibody-drug conjugate (ADC) targeting extradomain-B of fibronectin (EDB+FN)

MICVO structure

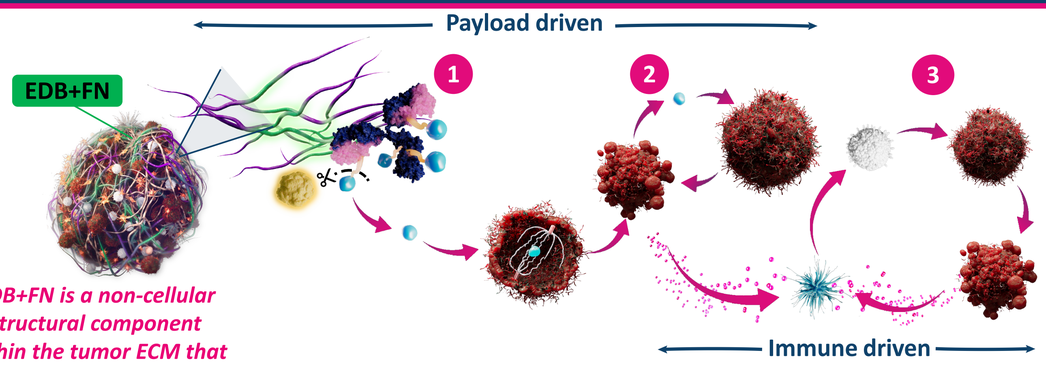


MICVO is composed of a fully human IgG1 monoclonal antibody (mAb) derived from the L19 clone. The mAb was engineered with cysteines κK183C and K290C for site-specific conjugation. The optimized auristatin payload Aur0101 was conjugated to the mAb via the PABC spacer and a mc-Val-Cit linker [1]

Key potential advantages

PURPOSE-BUILT	• Structural integrity with **high avidity-driven binding** • **Site-specific, extracellular cleavable Valine Citrulline linkers**
PREDICTABLE	• **Uniform DAR* of 4** provides improved therapeutic window • **Reduced free payload in serum,** C_{max} ~4 days post administration
POTENT	• Four **optimized auristatin 0101** microtubule directed payloads • Maximize **broad tumor-killing and biological potency**
PERMEABLE	• Optimized membrane diffusion to enable **bystander killing** • **Fast payload clearance to reduce off-target effects**

MICVO delivers potent antitumor activity through a three-pronged mechanism of action (MOA)



EDB+FN is a non-cellular structural component within the tumor ECM that is highly expressed in tumors compared to normal adult tissues [9]. MICVO is designed for extracellular linker cleavage in the acidic TME which initiates the MOA.

1 **Direct cancer cell killing[1-4]:** MICVO designed to bind to EDB+FN and release payload within tumor ECM

2 **Bystander cancer cell killing[5]:** Cancer cell dies releasing payload for additional cycles of cancer cell killing

3 **Immunogenic cell death[6-8]:** Cancer cell death releases immune stimulatory molecules leading to T-cell activation



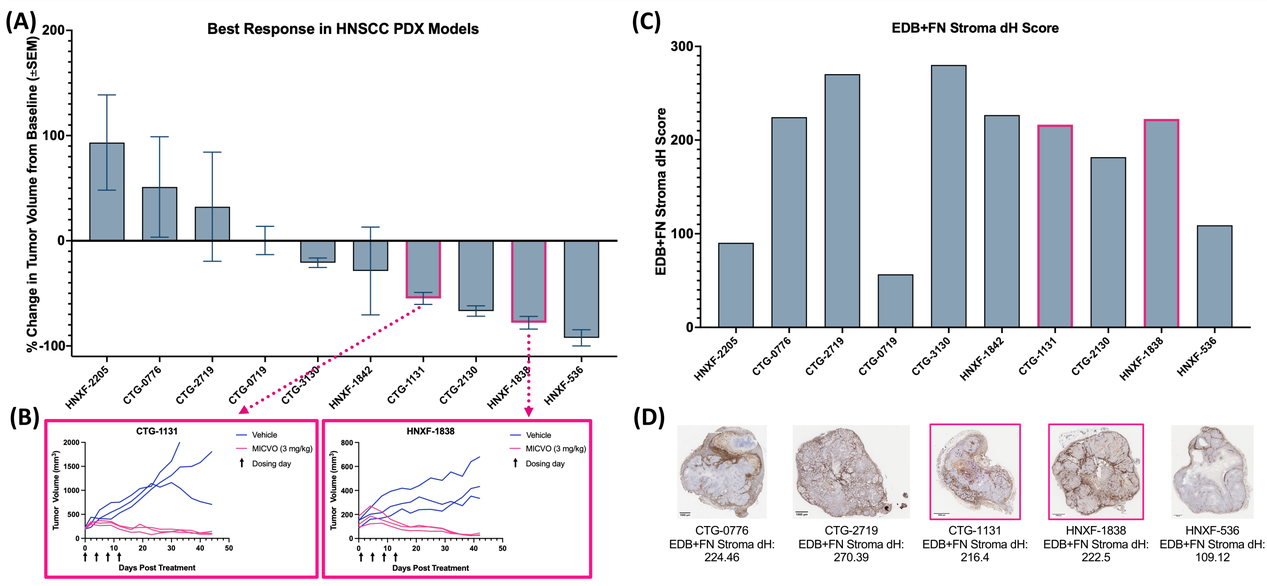
Objectives

- Recurrent or metastatic (R/M) head and neck squamous cell carcinoma (HNSCC) has limited treatment options [10,11]
- EGFR is overexpressed in over 90% of head and neck tumors [12]. Cetuximab is the only FDA-approved EGFR-targeted therapy for HNSCC, with several other next-generation EGFR-targeted therapies in clinical development aiming to improve upon the low response rate of cetuximab in HNSCC [10,11].
- EDB+FN is upregulated in various solid tumors including HNSCC [9]. Preclinical studies have demonstrated broad antitumor activity of MICVO across multiple solid tumor mouse models including HNSCC patient-derived xenograft (PDX) models [4,5]. In addition, a mouse analog of MICVO sensitized an immunotherapy refractory syngeneic HNSCC model, MOC-2, to anti-PD-1 treatment [13].
- The objective of this poster is to evaluate the combinatorial potential of MICVO with EGFR-targeted therapies. The combination of MICVO and cetuximab was evaluated in 2 HNSCC PDX models.

Methods

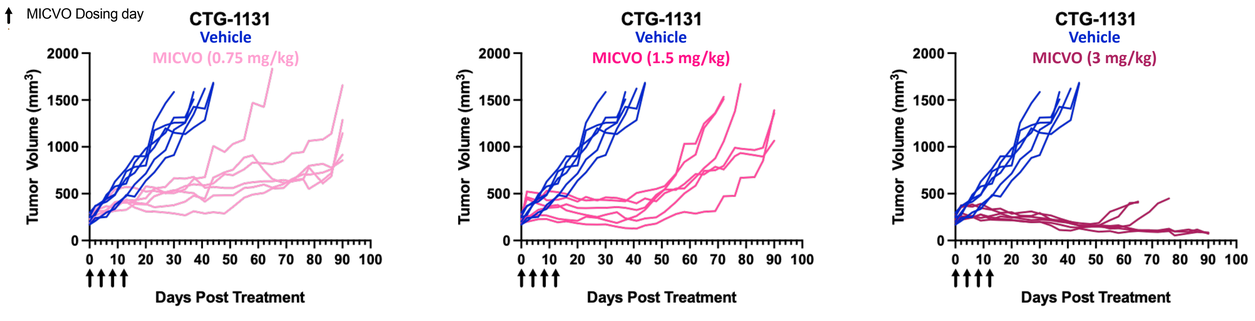
- **MICVO monotherapy evaluation in HNSCC PDX models.** 10 HNSCC PDX models were selected to test antitumor activity of MICVO. The PDX models were developed by Champions Oncology or IQVIA Laboratories (FKA Charles River Laboratories Germany GmbH). HNSCC PDX models with EDB+FN protein detected by immunohistochemistry (IHC) were selected. Mice were dosed with either vehicle or MICVO i.v. q4dx4 at 3 mg/kg and tumor volume and body weights were measured. For all 10 HNSCC PDX models, a satellite tumor was collected from one mouse at randomization size. This tumor was analyzed with IHC staining to measure EDB+FN protein expression. In one PDX model, MICVO was also tested at lower doses of 0.75 mg/kg and 1.5 mg/kg in addition to the 3 mg/kg dose level in order to study dose-response and durability over 90 days.
- **MICVO + cetuximab combination activity in PDX models.** 2 HNSCC PDX models from the monotherapy PDX study were selected for combination testing. Mice were dosed with either vehicle, MICVO i.v. q4dx4 at 1.5 mg/kg, cetuximab i.p. q4dx4 at 10 mg/kg, or the combination of both MICVO and cetuximab and tumor volume and body weights were measured (n=10 mice per group). In order to compare the difference in activity between groups, tumor regression was defined as a reduction in tumor volume compared to baseline and following regression, a tumor relapse was defined as growth beyond the baseline tumor volume.

MICVO demonstrated strong activity as a monotherapy in HNSCC PDX models



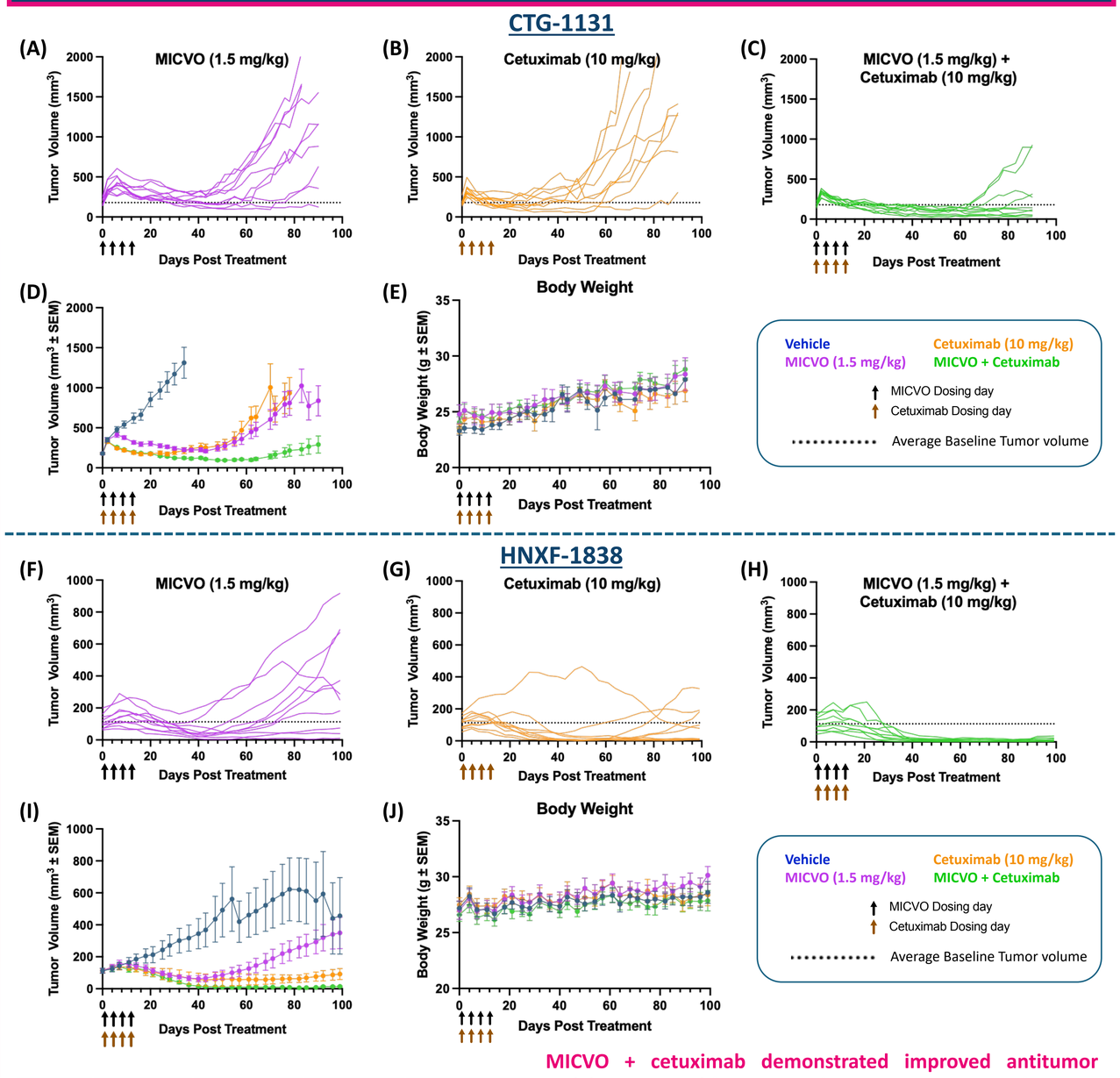
MICVO showed broad antitumor activity across HNSCC PDX models which did not correlate with stromal EDB+FN expression. (A) Best response of MICVO (3 mg/kg, q4dx4) was measured by % change in tumor volume compared to baseline and shows broad activity across 10 HNSCC PDX models (n=3 mice per group). (B) Tumor volume data comparing vehicle to MICVO-treated mice in selected models showed strong antitumor activity. (C) An IHC assay and digital pathology algorithm were used to quantify the intensity and distribution of EDB+FN expression in the stroma, reported as EDB+FN stroma dH scores [9]. Baseline satellite tumors from the HNSCC PDX models were evaluated for EDB+FN protein expression using this assay (models shown in order of best response). (D) Representative IHC images of EDB+FN expression.

MICVO demonstrated durable, dose-responsive activity in a HNSCC PDX model



MICVO showed dose-responsive and durable activity for over 90 days in a HNSCC PDX model. Antitumor activity of MICVO was monitored for over 90 days in mice treated with vehicle or MICVO at 0.75 mg/kg, 1.5 mg/kg, or 3 mg/kg in a HNSCC PDX model (CTG-1131) known to be MICVO-responsive (n=6 mice per group). These data demonstrated that antitumor activity of MICVO is long-lasting and dose-responsive. **Based on these data, a suboptimal dose of 1.5 mg/kg was selected for MICVO + cetuximab combination studies.**

The combination of MICVO + cetuximab improved antitumor activity compared to either monotherapy alone in HNSCC PDX models



PDX Model	Treatment group	# of Tumor regressions	# of Tumor relapse	Average day of tumor relapse
CTG-1131	Cetuximab	5/9	5/5	Day 57
	MICVO	5/10	4/5	Day 60
	MICVO + cetuximab	**10/10**	**4/10**	**Day 70**
HNXF-1838	Cetuximab	9/10	3/9	Day 77
	MICVO	9/10	6/9	Day 63
	MICVO + cetuximab	**9/9**	**0/9**	**Relapse not reached**

MICVO + cetuximab demonstrated improved antitumor activity over either monotherapy treatment alone at suboptimal dose levels in 2 HNSCC PDX models. (A-C) In the CTG-1131 model, the combination of MICVO + cetuximab resulted in an increased number of tumor regressions (10/10 mice) compared to either cetuximab (5/9) or MICVO alone (5/10). Additionally, fewer mice with regressions later demonstrated relapse (4/10) compared to either monotherapy alone. (D) Improved antitumor activity was observed as shown by average tumor volume (± SEM) between treatment groups. (F-H) In the HNXF-1838 model, the combination resulted in a similar number of regressions compared to monotherapies but demonstrated no tumor relapse (0/9) compared to 3/9 and 6/9 mice with relapse in the cetuximab and MICVO monotherapy groups, respectively. (I) Average tumor volume (± SEM) shown between treatment groups. (E, J) Body weight was normal across treatment groups in both models tested.

Conclusions

- MICVO monotherapy demonstrated strong, durable activity in HNSCC PDX models. No correlation was observed between the level of EDB+FN expression and MICVO response.
- The combination of MICVO and cetuximab improved duration of response in two MICVO-responsive HNSCC PDX models compared to either monotherapy alone and was well-tolerated based on body weight.
- Overall, these results suggest the potential to combine MICVO with EGFR-targeted therapies, including cetuximab, in HNSCC tumors.
- MICVO is in clinical development as a monotherapy (NCT05720117) and in combination with pembrolizumab (NCT06795412) as an investigational therapy for patients with difficult-to-treat cancers including HNSCC. Monotherapy R/M HNSCC clinical data to be presented during Plenary Session 3 (3LBA)

References

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