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Basic & Translational Science

Efficacy of **GDC-0980 (Apitolisib)** in the Treatment of Cholangiocarcinoma: A Preclinical Study

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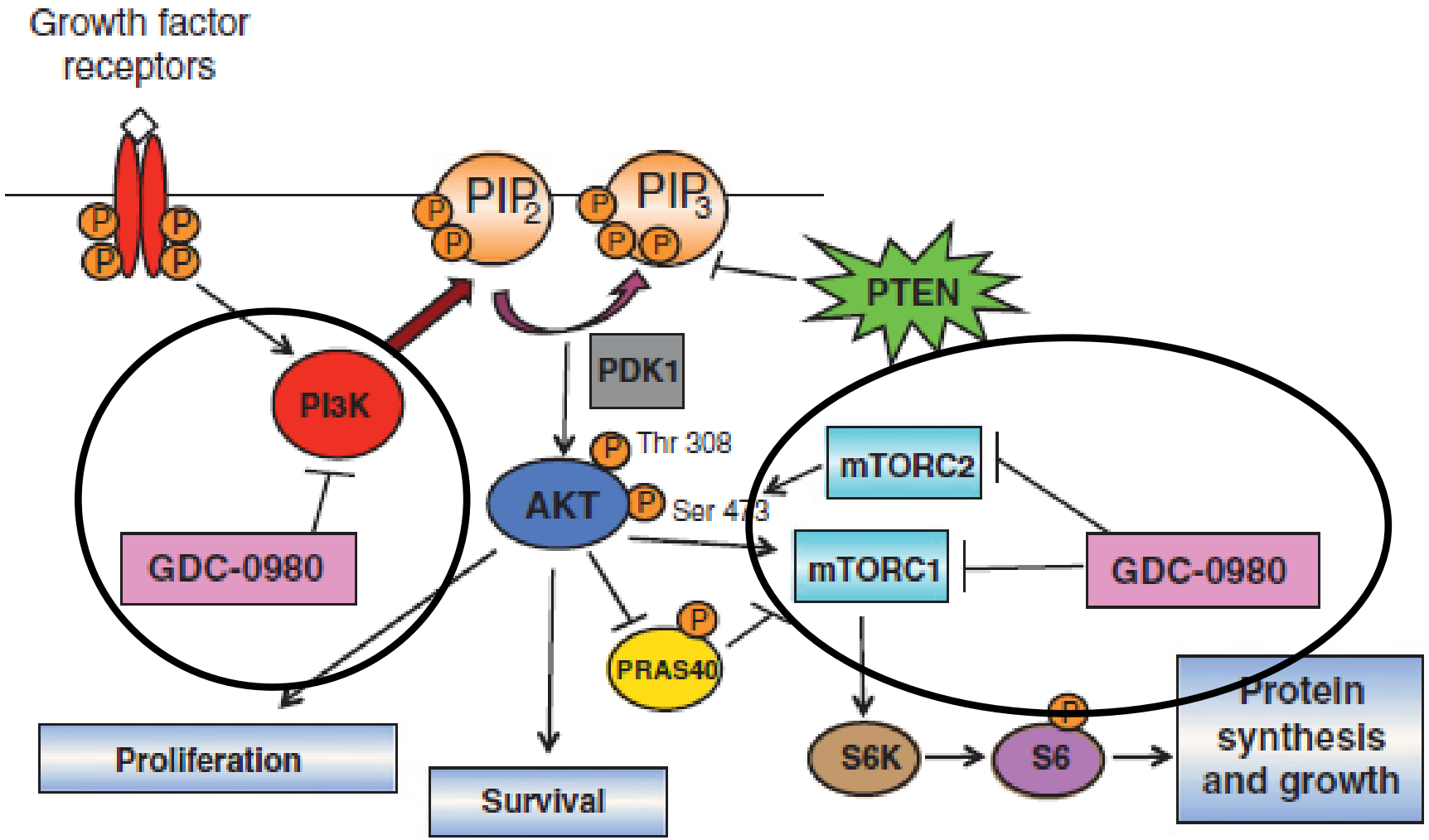
Disclosures

- The authors declare no potential conflicts of interest.

Highlights

- Activation of the **PI3K/Akt/mTOR** pathway is frequently observed in cholangiocarcinoma (CCA).
- Evidence on the efficacies of inhibitors for this pathway in CCA is lacking.
- Dual targeting of **PI3K/mTOR** using **apitolisib** reduced CCA cell growth.
- Cytotoxic effects of cisplatin and/or gemcitabine were enhanced by **apitolisib**.

GDC-0980 (Apitolisib): A novel **PI3K/mTOR** dual inhibitor



Jeffrey J et al., *Molecular Cancer Therapeutics.* 2011

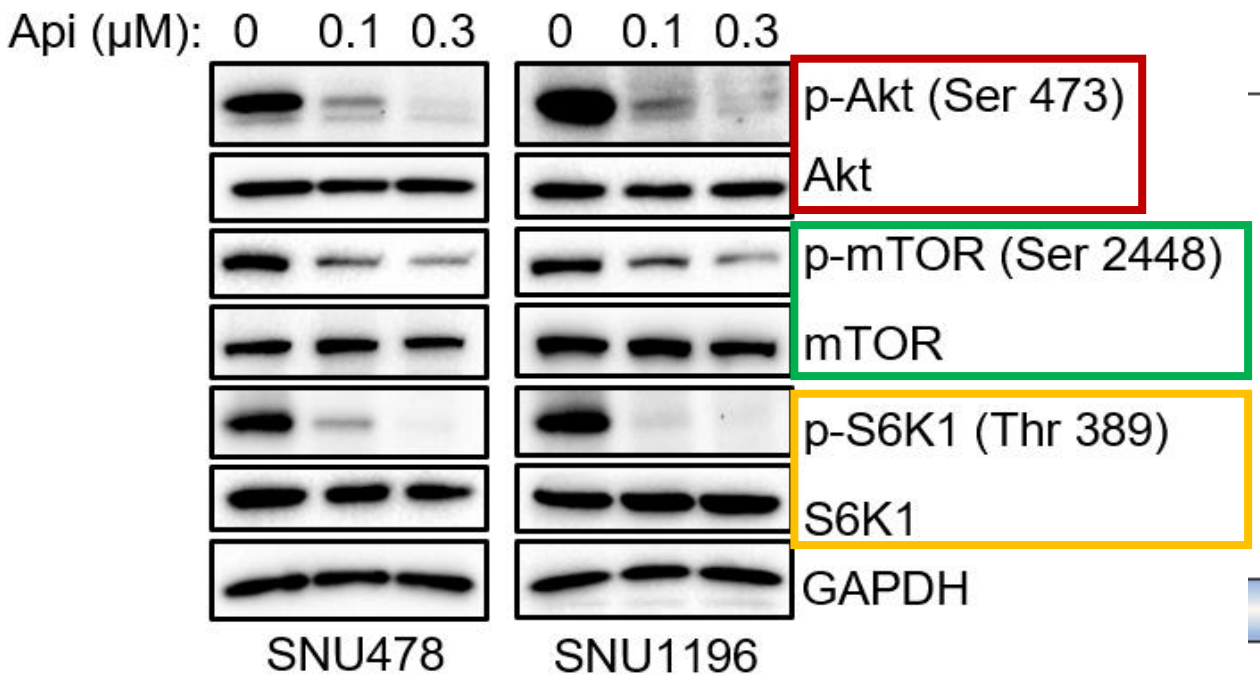
Hypothesis/Aim

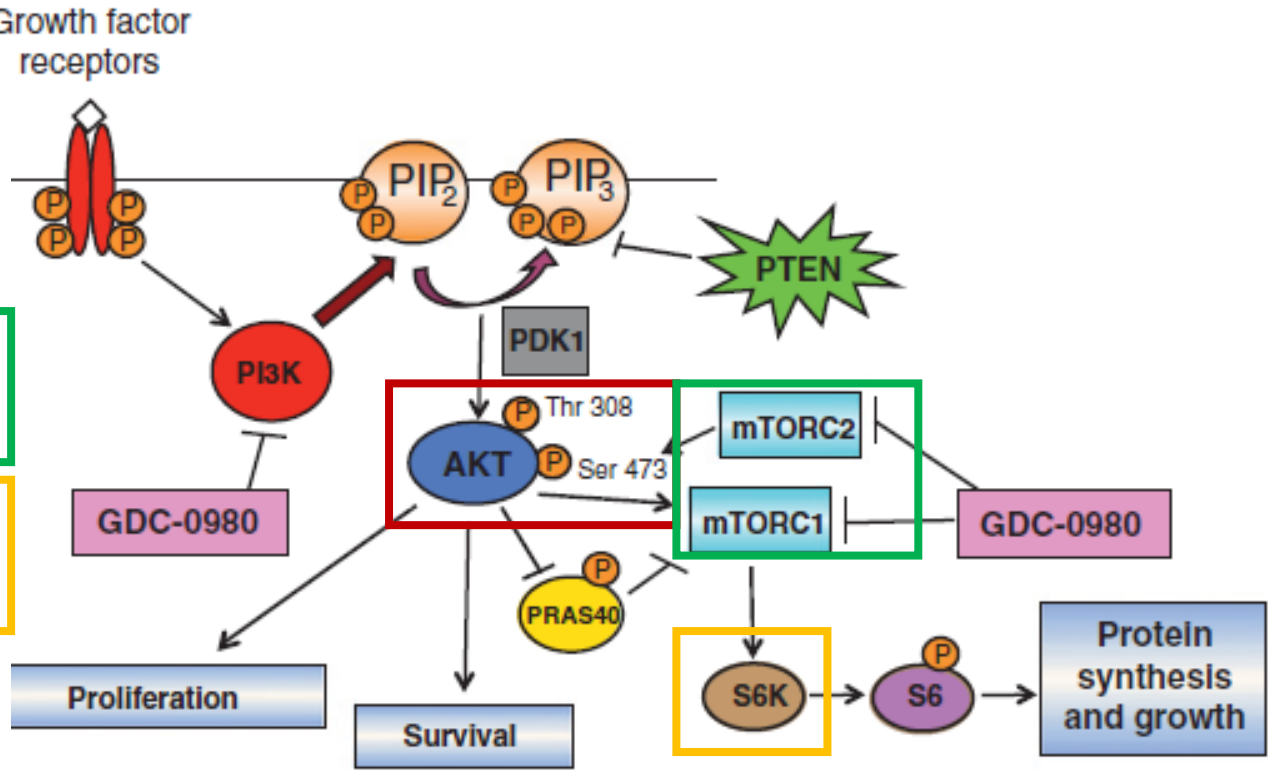
- GDC-0980 (apitolisib), a dual inhibitor for both PI3K and mTOR, can exert a potent effect by inhibiting **two** parts of the **PI3K/Akt/mTOR pathway.**

This study was to examine the effects of apitolisib on CCA cells *in vitro* and *in vivo*.

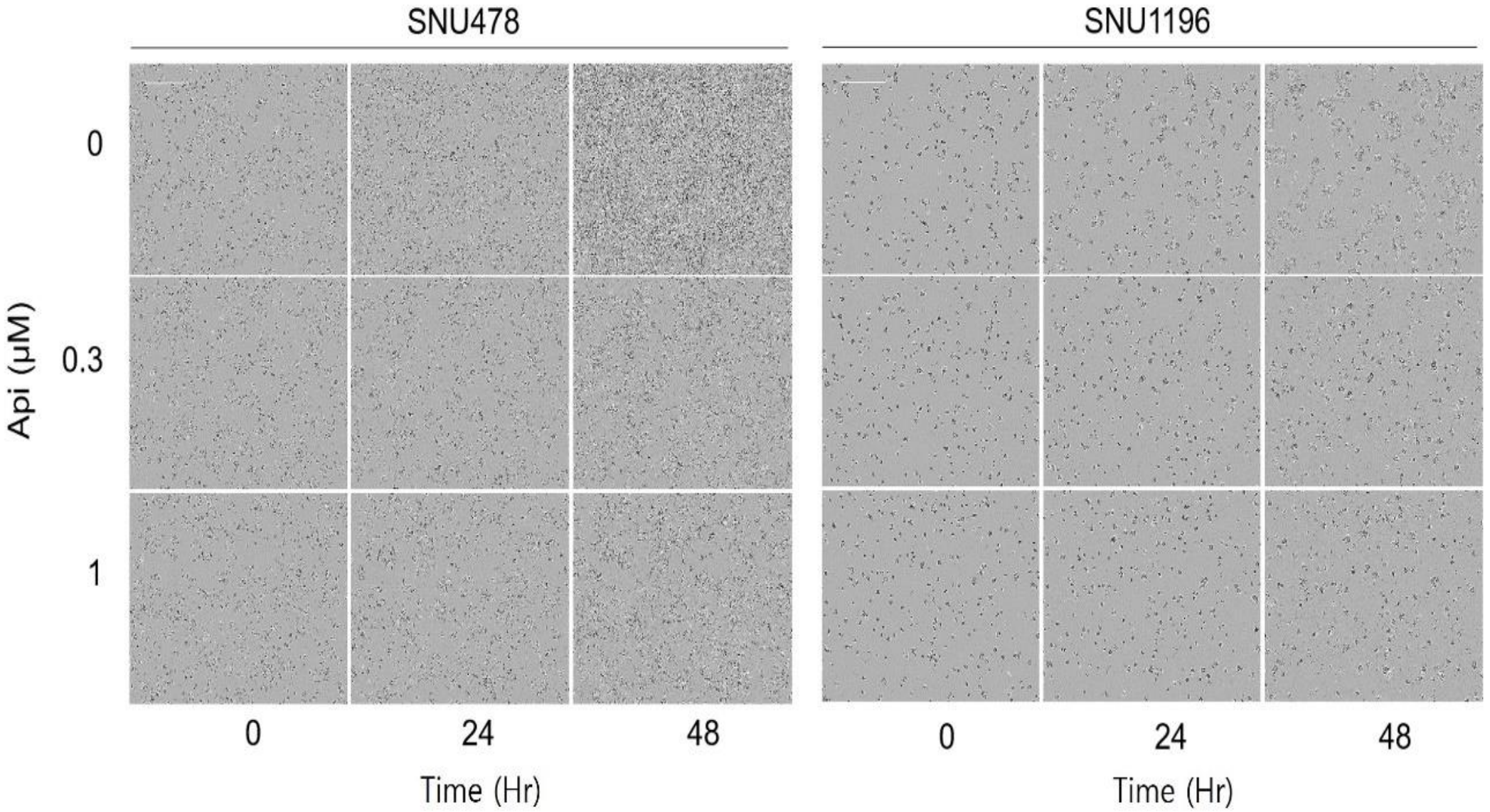
Also to evaluate the effects co-administering apitolisib and conventional chemotherapeutic agents (**cisplatin and/or gemcitabine**).

Western blot



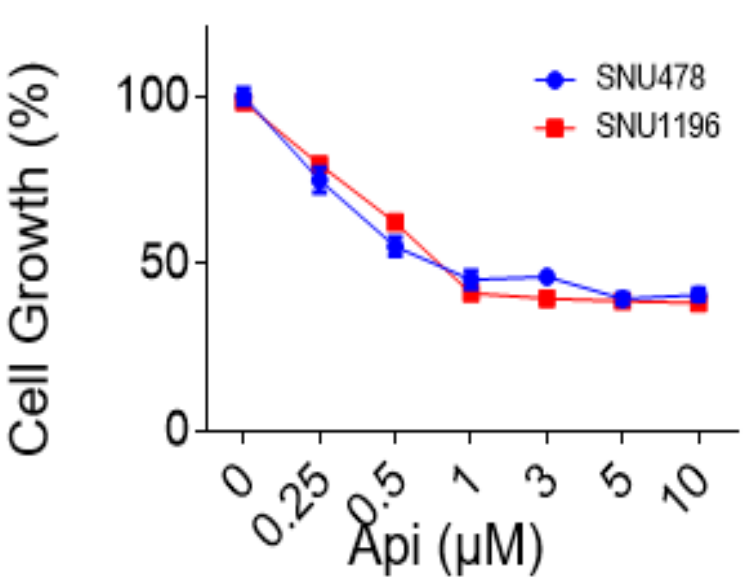


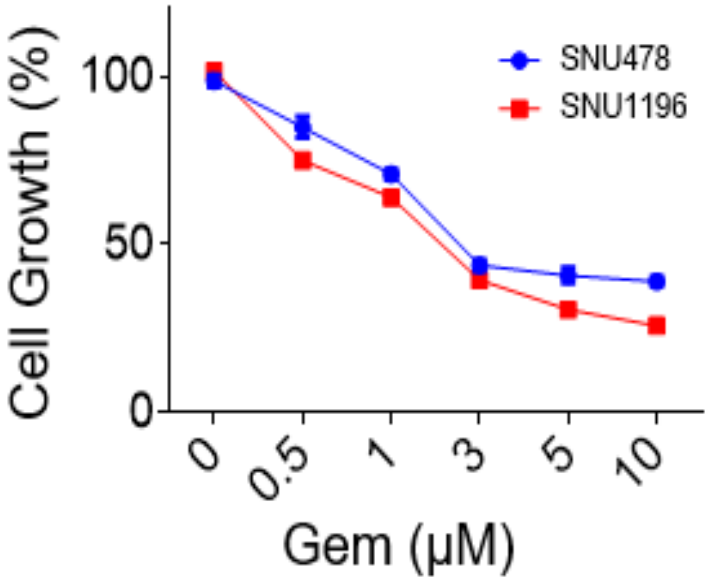
Live-cell Imaging

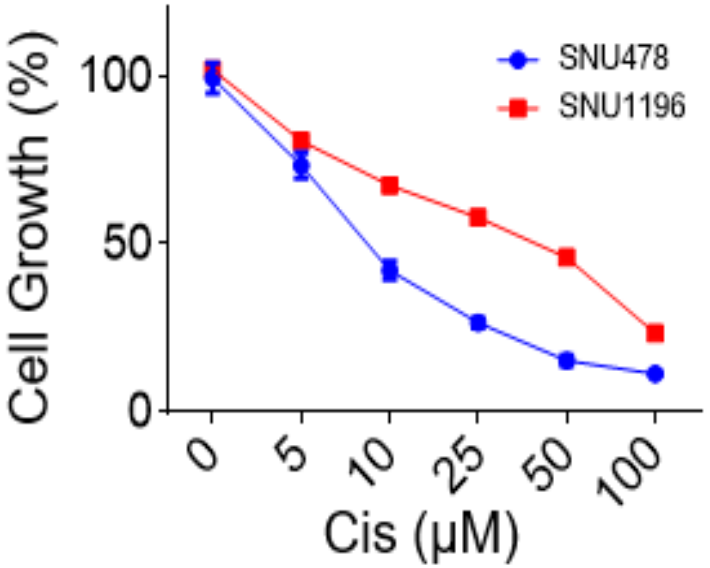


Cell proliferation assay (SNU478 & SNU1196)

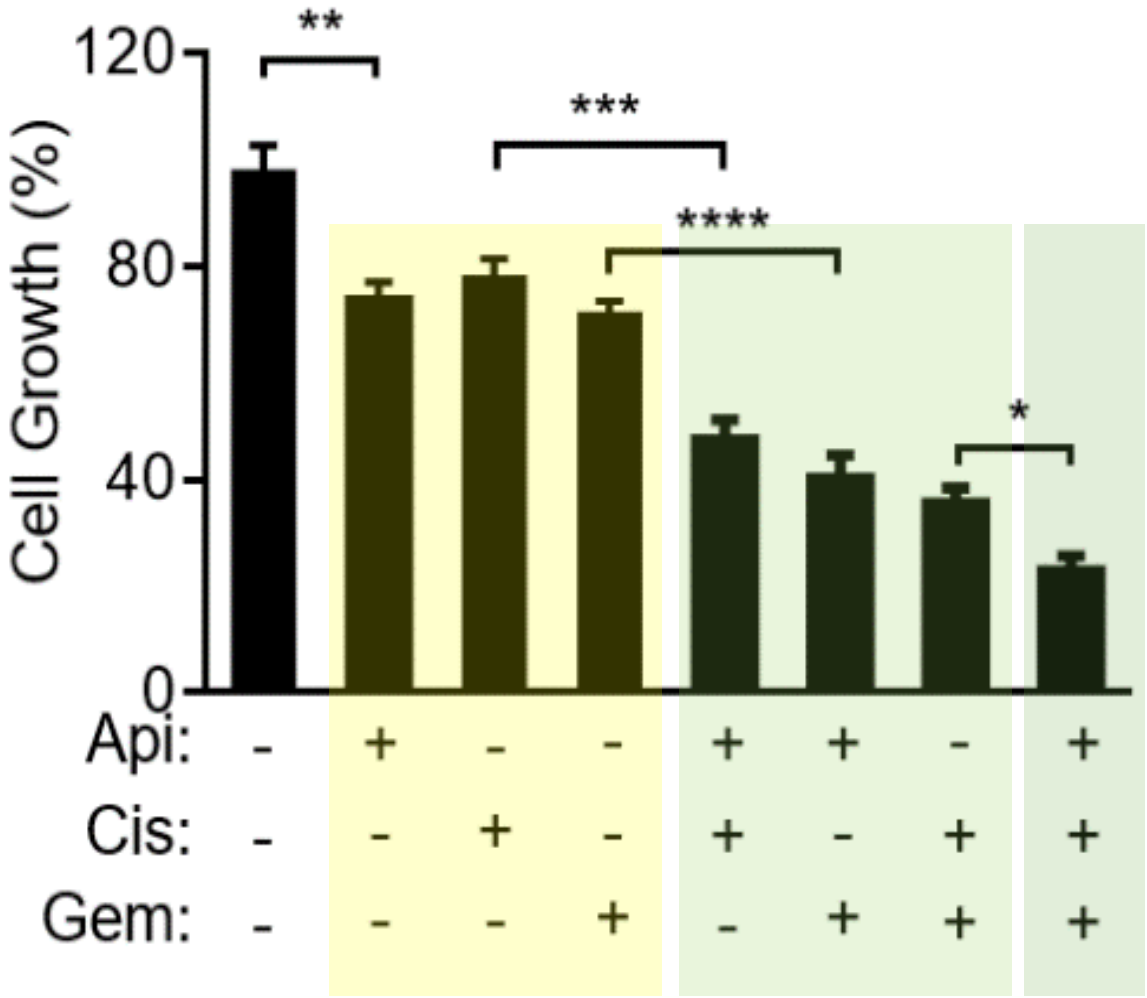
Direct cell counting – trypan blue exclusion







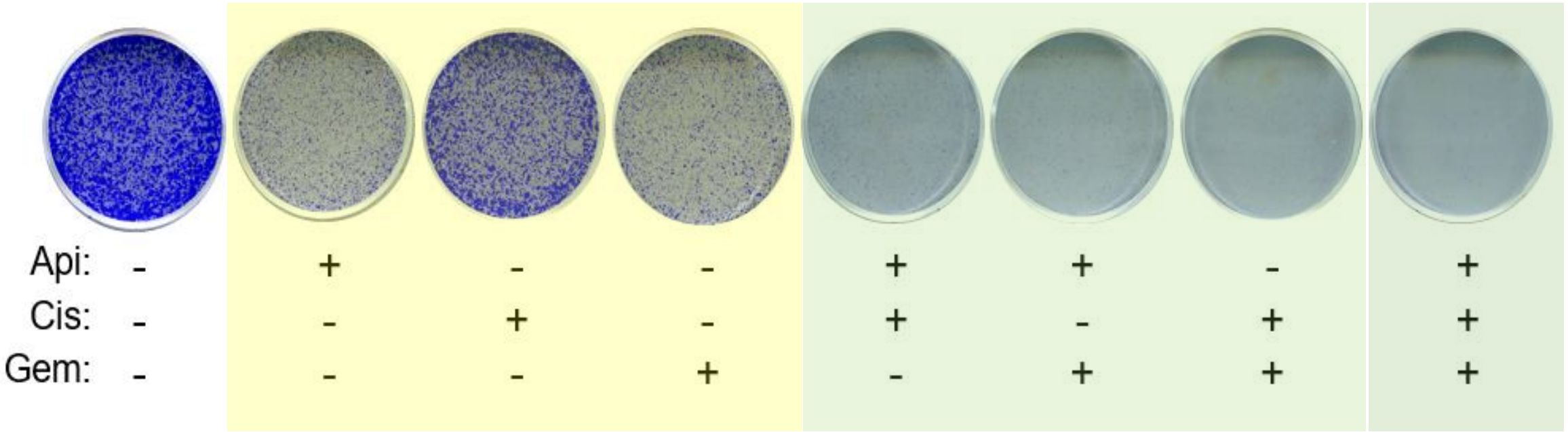
Cell proliferation assay (SNU478)



*p: 0.0061
**p: 0.0026
***p: 0.0006
****p: 0.0005

Apitolisib (Api, 0.3 μM) for 48 hr
Cisplatin (Cis, 10 μM) for 48 hr
Gemcitabine (Gem, 1 μM) for 48 hr

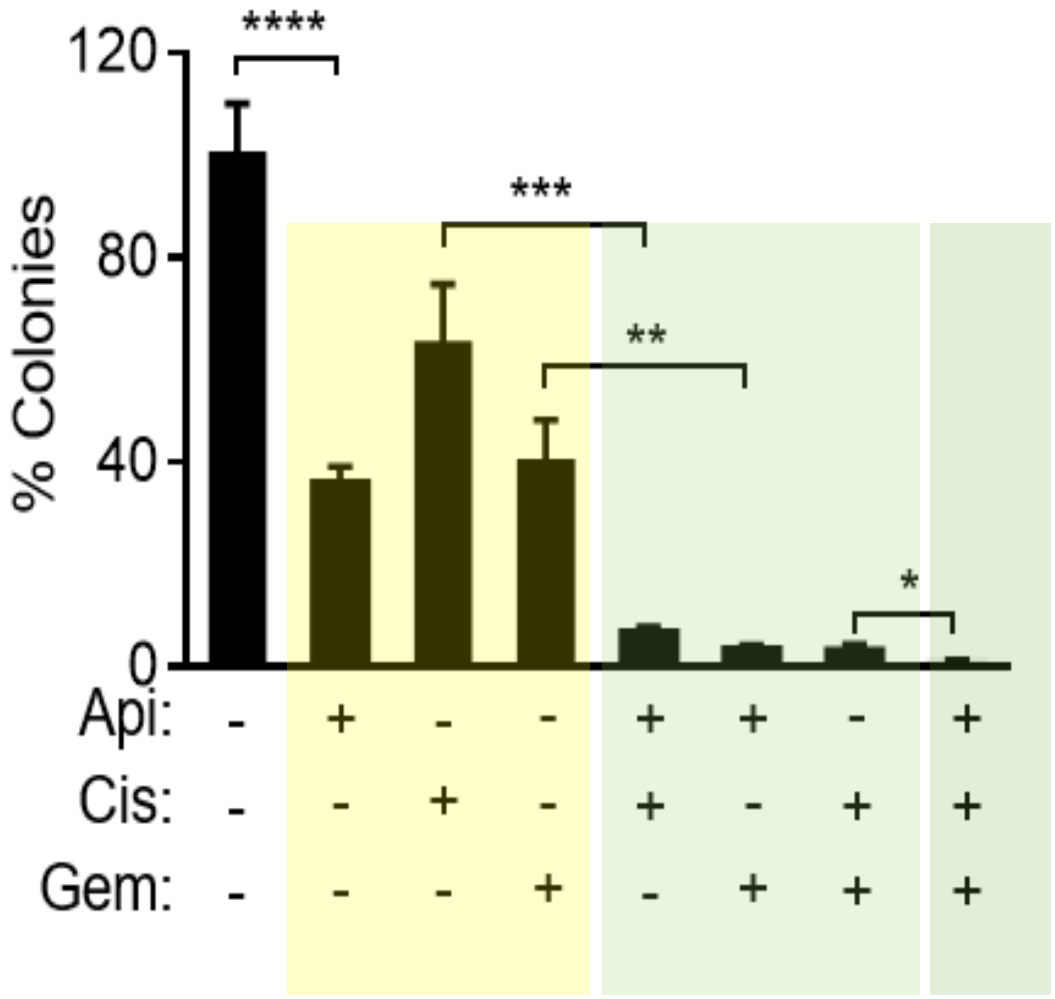
Colony formation assay (SNU478)



Apitolisib (Api, 0.3 μM)
Cisplatin (Cis, 10 μM)
Gemcitabine (Gem, 1 μM)

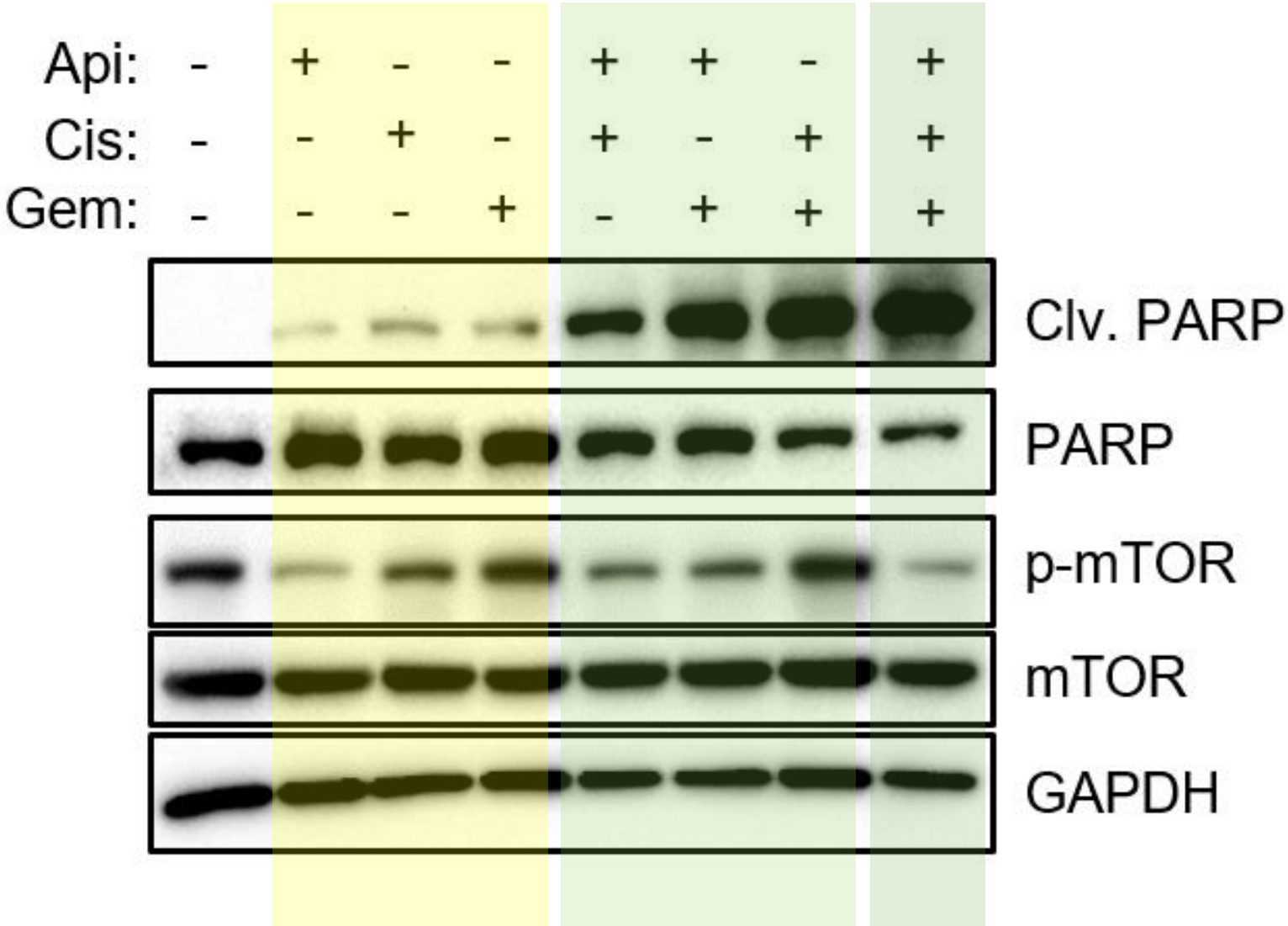
Colony formation was assessed by crystal violet staining after 10 days

Colony formation assay (SNU478)

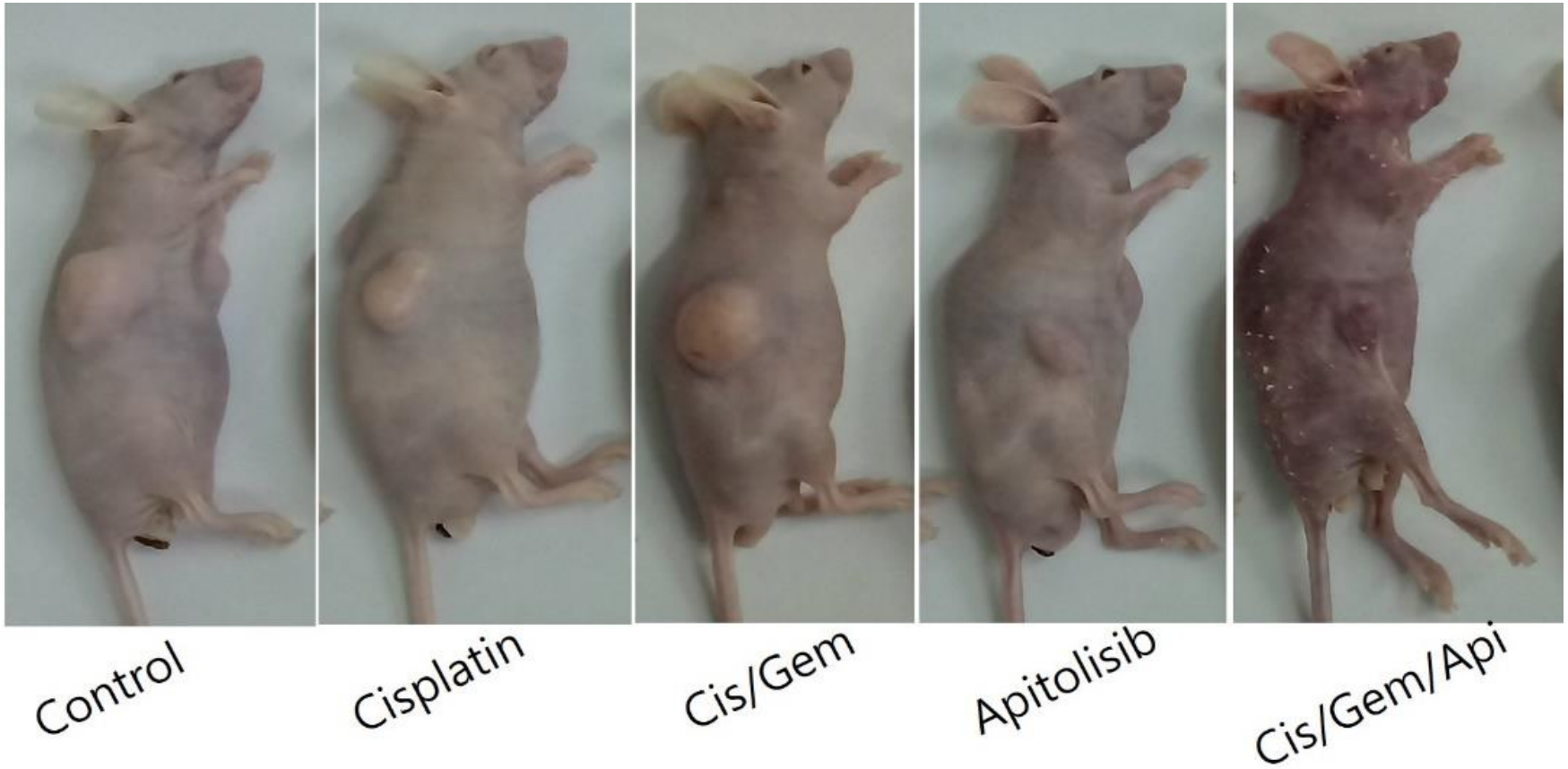


*p: 0.0223
**p: 0.0016
***p: 0.0012
****p: 0.0005

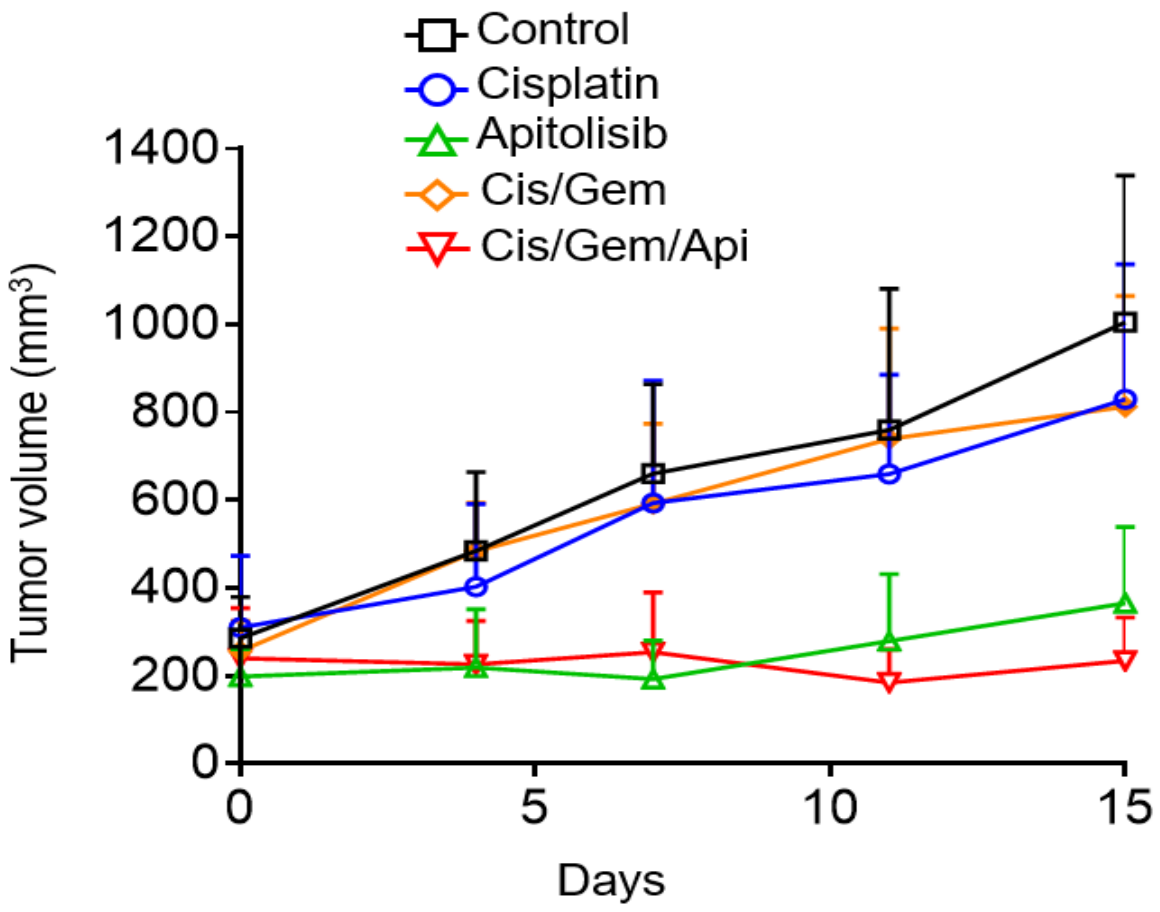
Western blot (SNU478)

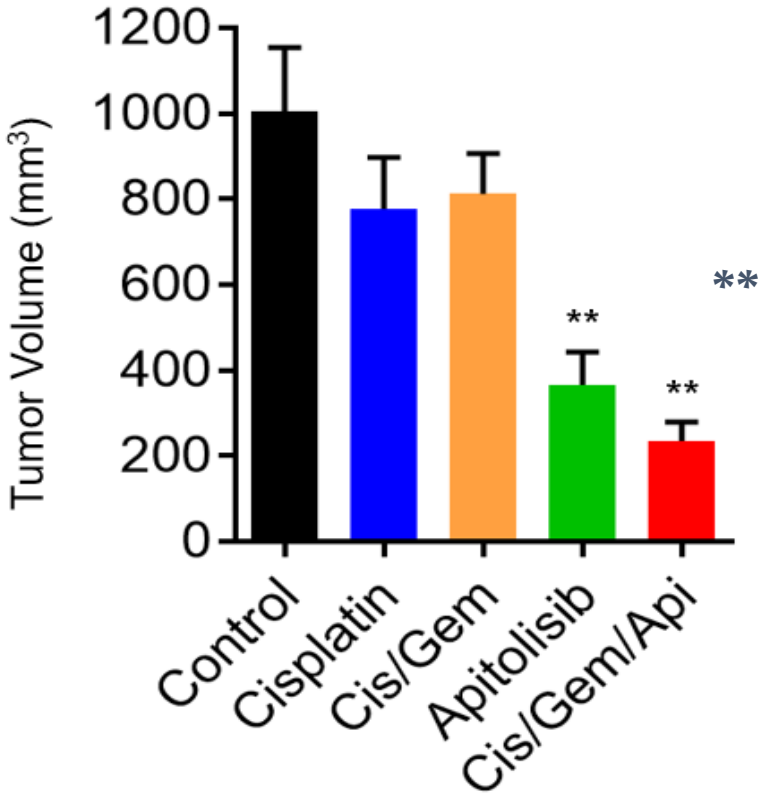


Mouse xenograft (SNU478)



Mouse xenograft (SNU478)

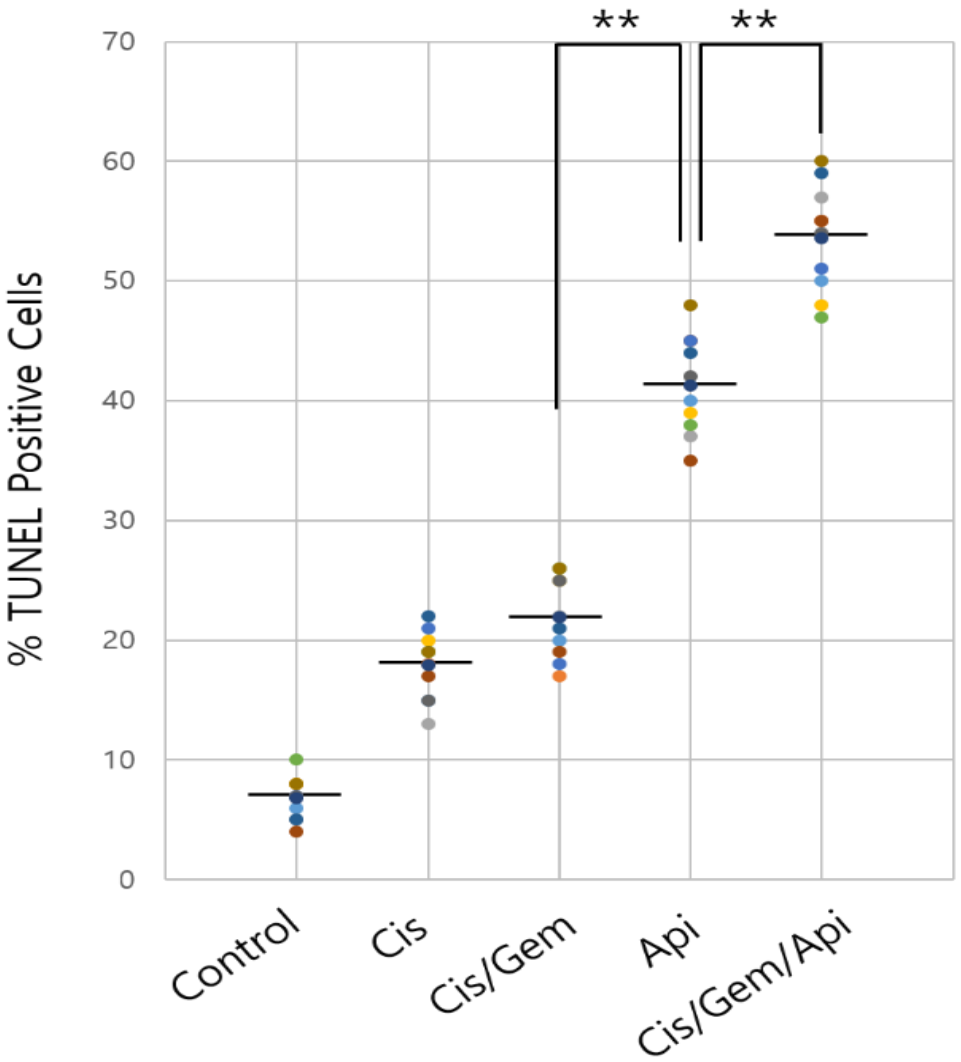




** $P < 0.01$

Five groups (five mice per group, **both flank** xenograft)
(1) Vehicle alone (control)
(2) Api (10 mg/kg via oral gavage)
(3) Cis (5 mg/kg via intraperitoneal injection)
(4) Gem (200 mg/kg via intraperitoneal injection) and Cis
(5) Gem, Cis, and Api.
* All chemicals were administered every 4 days for 2 weeks.

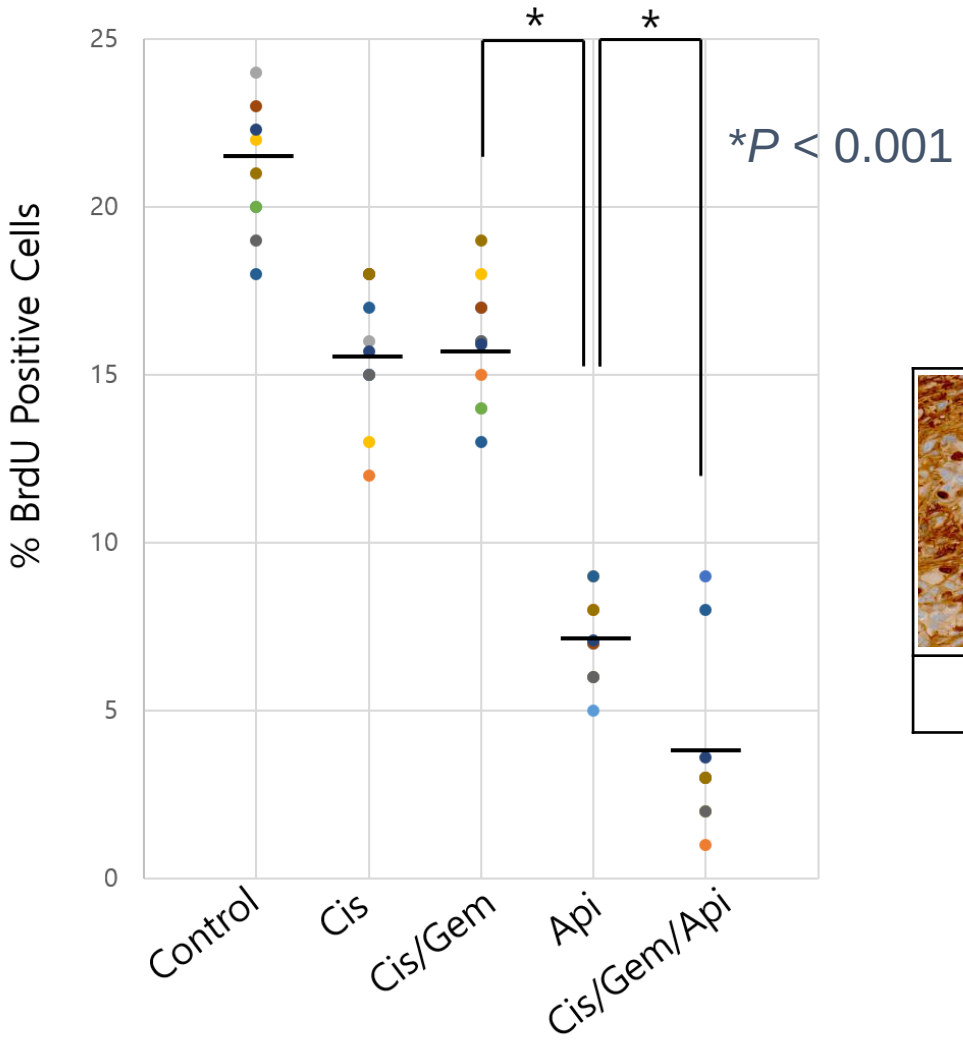
Xenograft tumor tissue – TUNEL assay



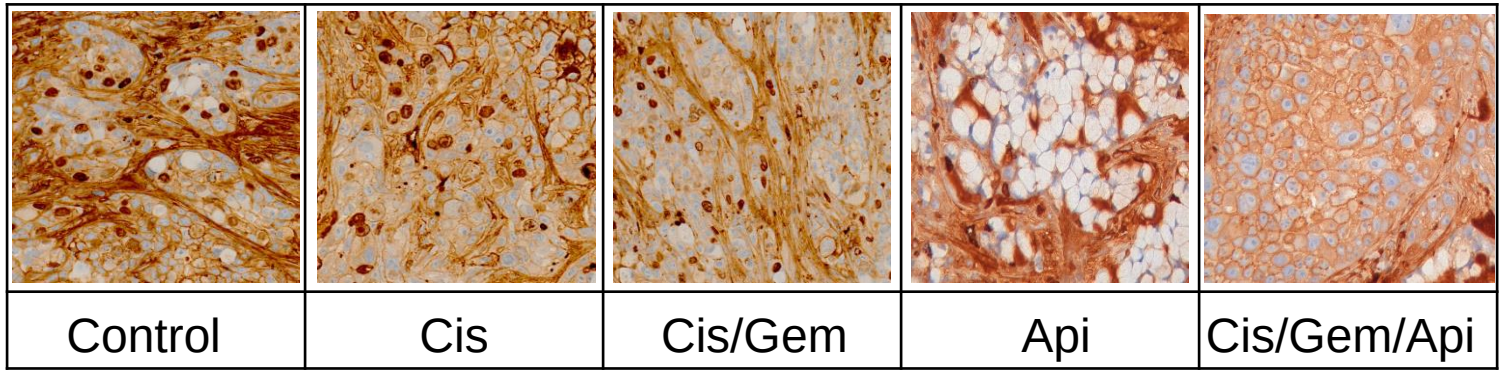
$^{**}P < 0.05$

The number of **TUNEL**-positive cells per 100 tumor cell in 10 random microscopic fields (400×).

Xenograft tumor tissue – BrdU assay



The number of **BrdU**-positive cells per 100 tumor cell in 10 random microscopic fields (400×).



Summary/Conclusion

- Dual targeting of PI3K/mTOR using **apitolisib** and cisplatin or cisplatin plus gemcitabine dose- and time-dependently reduced CCA **cell growth**, **viability**, and **colony formation**. In addition, the cytotoxic effects of cisplatin and/or gemcitabine were **enhanced** by apitolisib.

- Combinatorial treatments showed apitolisib enhanced these effects, which suggests the use of apitolisib in combination with conventional agents (gemcitabine, cisplatin) in clinical practice might enhance therapeutic effects.

- We suggest a clinical trial be conducted to determine the efficacy of gemcitabine/cisplatin/apitolisib combination therapy in CCA, but caution that **toxicity** concerns be fully addressed.