Targeted therapy to treat cervical cancer: Alpelisib, Inavolisib, and Capivasertib, PI3-kinase and AKT inhibitors, suppress PIK3CA-mutated cervical cells, and potentiate immunotherapy

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Introduction and Background

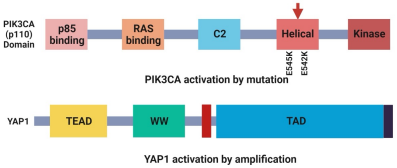
- Cervical cancer is the **4th most common cancer in women**
- The highest rates in incidence and mortality are in sub-Saharan Africa, Central America, Southeast Asia, and low-resource environments. **However, over 4000 women in the US die of this cancer**

Objectives

- Cervical cancer therapy involves surgery, chemoradiation, and, more recently, immune checkpoint inhibitors.
- **We aimed to identify targeted therapies to improve outcomes.**

Methodology

- Long-read whole-genome sequencing on 28 cervical cancer cell lines.
- Mutations in *PIK3CA*, deletions of *STK11*, and amplifications of the YAP1 oncogene were identified.
- Cell proliferation after PI3K and AKT inhibitor treatment was monitored with an Agilent xCELLigence instrument.
- Protein levels were determined by Western blot.
- Cells were treated with activated T cells from normal donors.
- Validation used data from Caris Life Sciences, TCGA, AACR Project Genie, and the Guatemalan Cervical Cohort.



Molecular stratification identifies ~30% of cervical cancers as candidates for PI3K-targeted therapy and rational combination immunotherapy.

Results

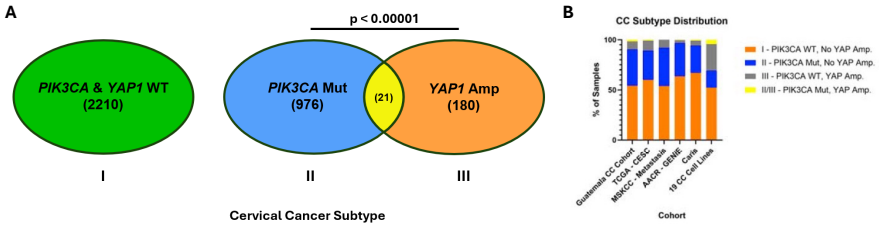


Figure 1. Three molecular subtypes of cervical cancer are defined

Table 1. Response of cell lines to PI3K and AKT inhibitors

Cell Line	HPV Type	PIK3CA Status	Alpelisib	Inavolisib	Capivasertib
CaSki	HPV16	E545K	Mod Inh	Mod Inh	Mod Inh
SNU17	HPV16	E545K/E726K	Strong Inh	Strong Inh	
C33A	None	R88Q	Strong Inh	Strong Inh	
SNU902	HPV16	Q546L	Strong Inh		
ME180	HPV68	E545K	Strong Inh	Strong Inh	Strong Inh
JHUCS-3	None	R88Q	Strong Inh		
SiHa	HPV16	WT	No Inh	No Inh	Strong Inh
HeLa	HPV18	WT	No Inh*		

Cell lines and their HPV types and PIK3CA mutation statuses are shown.

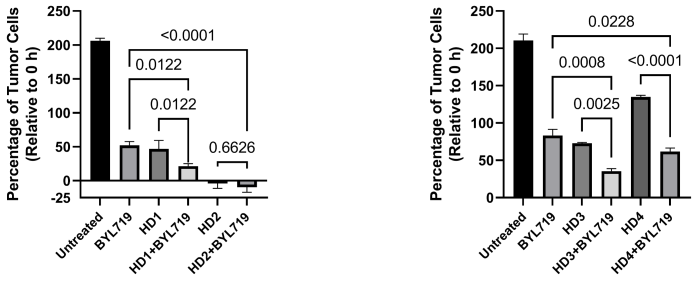
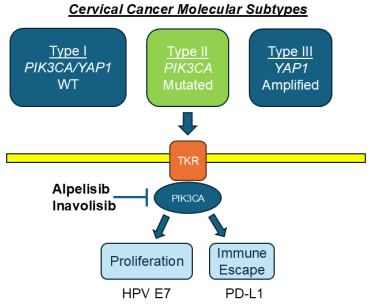


Figure 2. CaSki cells were cultured alone, with either BYL-719 (5μM) (A and B) or BYL-719 (1μM) (C) with T cells (E:T ratio – 2.5:1-10:1), or with BYL-719 plus T cells for 48h or 24h, respectively.

Conclusions



- Orally available PI3K and AKT inhibitors are viable options for cervical cancer and may enhance immunotherapies.
- Our cell line panel enables the testing of additional therapeutics targeting YAP1 and other pathways, thereby expanding treatment options.

Future Directions

- A Phase 2 trial of PI3K inhibitors in mutated cervical tumor patients.
- In vitro testing of YAP1/HIPPO pathway inhibitors on YAP1 amplified cell lines