

AACR-NCI-EORTC Virtual International Conference on

# MOLECULAR TARGETS AND CANCER THERAPEUTICS

October 7-10, 2021



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## Pharmacological inhibition of IRAK4 with CA-4948 is beneficial in marginal zone lymphoma models with secondary resistance to PI3K and BTK inhibitors

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## Financial relationships to disclose

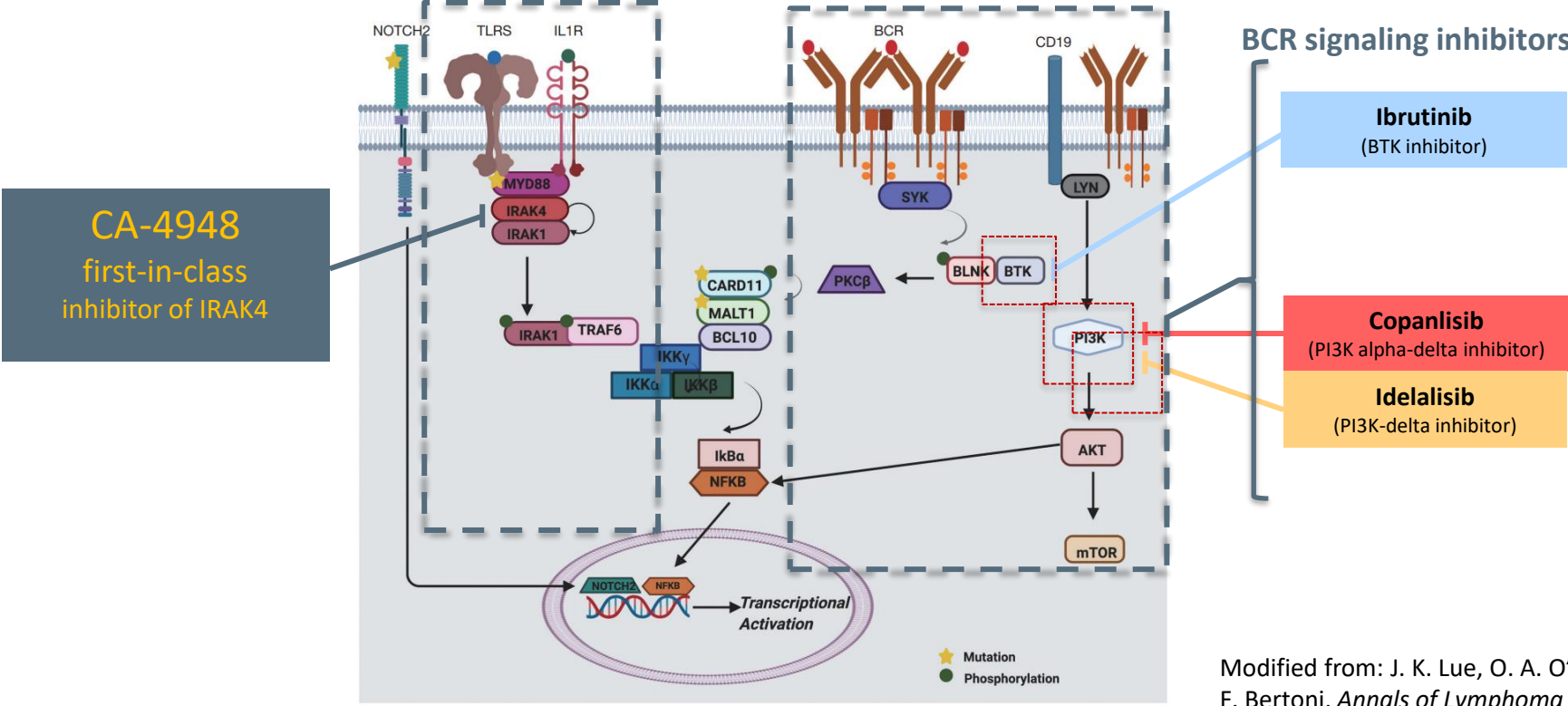


Speaker Name: Francesca Guidetti

Francesco Bertoni received institutional funds from Curis, Inc, Lexington, MA, USA

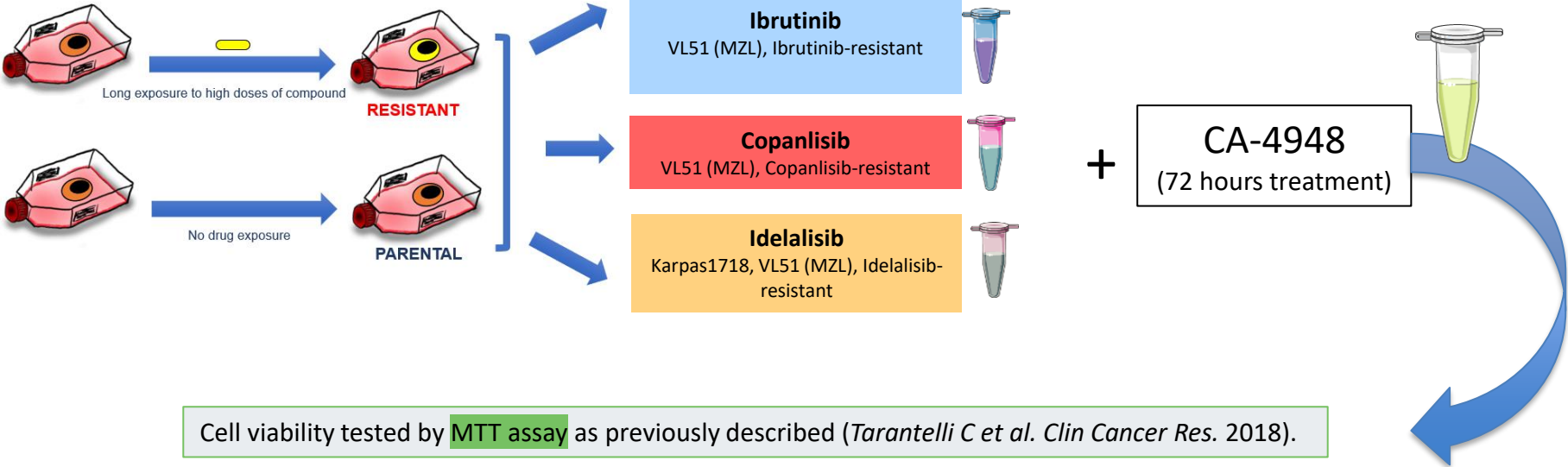
Reinhard von Roemeling , Elizabeth Martinez are employees of Curis Inc, Lexington, MA, USA

# Targeting pathogenic mechanisms in marginal zone lymphoma



Modified from: J. K. Lue, O. A. O'Connor, F. Bertoni. *Annals of Lymphoma* (2020)

# Pharmacological screening of IRAK4 inhibition with CA-4948

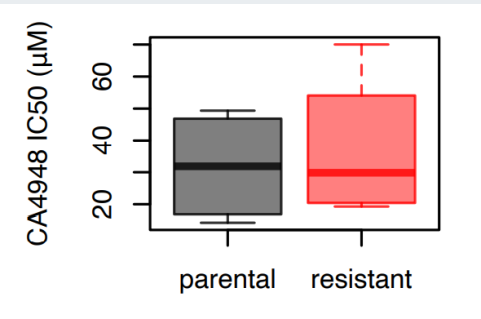
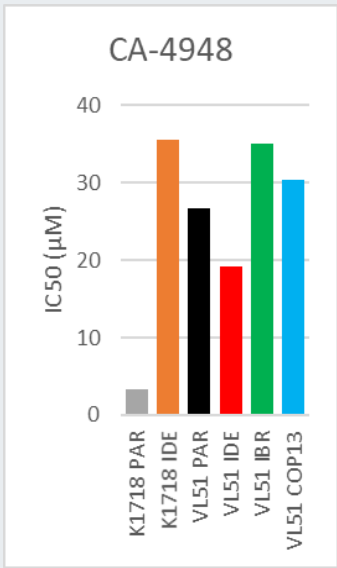


Cell viability tested by **MTT assay** as previously described (*Tarantelli C et al. Clin Cancer Res. 2018*).

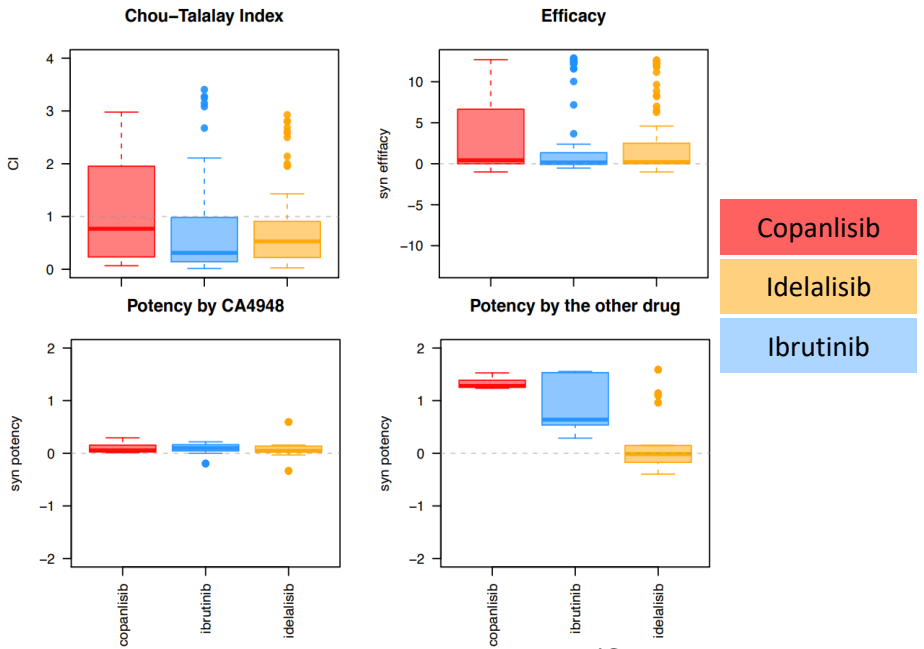
The beneficial effect of the combinations versus the single agents was considered both as synergism according to the **Chou-Talalay combination index** (*Chou TC Cancer Res 2010*) and as potency and efficacy according to the **MuSyC algorithm** (*Meyer et al. Cell Syst 2019*).

# Pharmacological screening of IRAK4 inhibition with CA-4948

## CA-4948 treatment as single agent in resistant and parental *in vitro* models



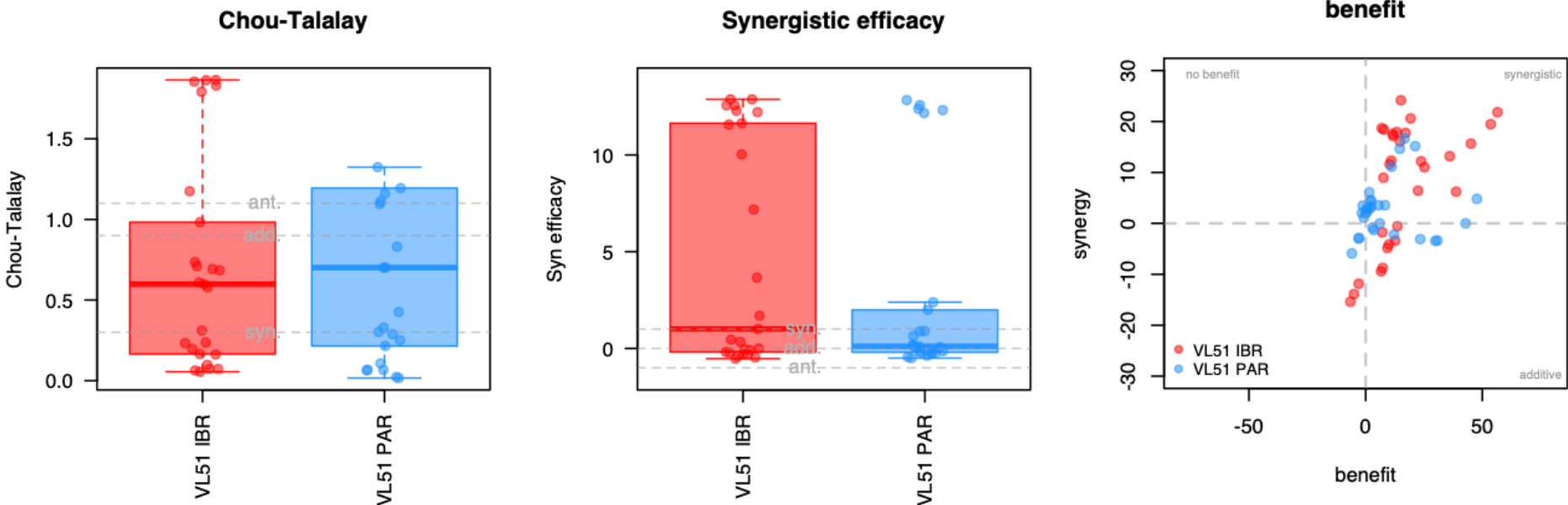
## CA-4948 72h treatment in combination to PI3K/BTK inhibitors in resistant and parental *in vitro* models



(Guidetti et al, on-going)

# The combination of CA4948 and ibrutinib is synergistic in ibrutinib-resistant cells

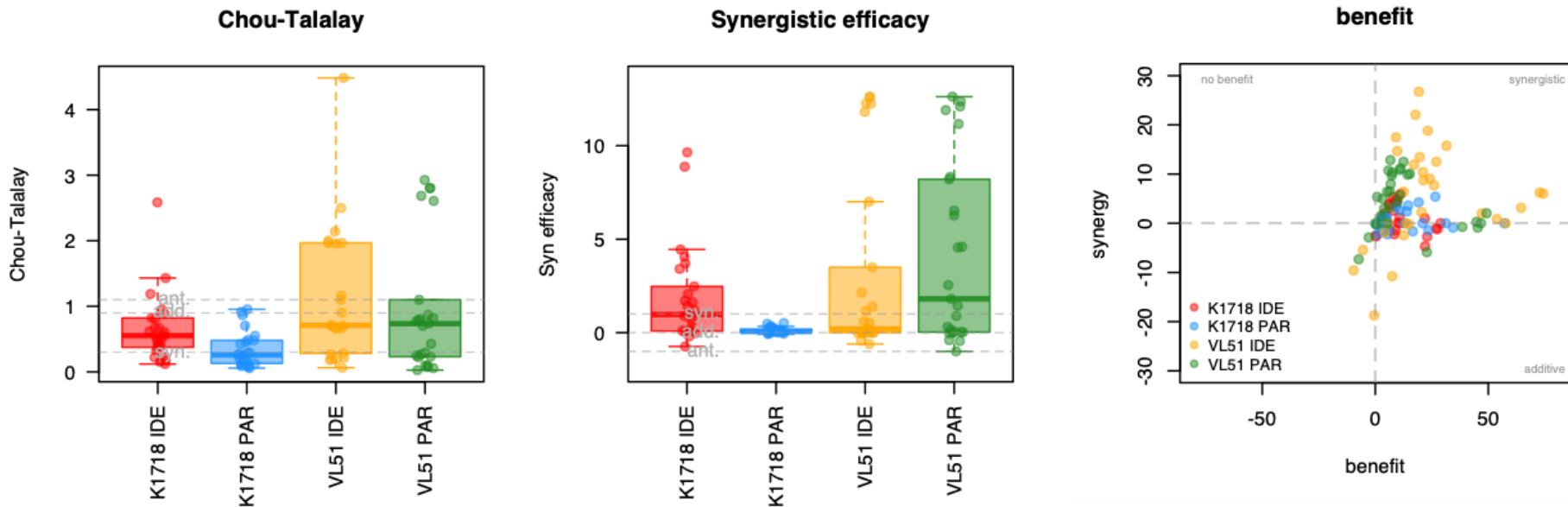
## CA-4948 in combination with ibrutinib in VL51 parental and ibrutinib resistant models



(Guidetti et al, on-going)

The combination of CA4948 and idelalisib is superior to single agents in resistant and parental models

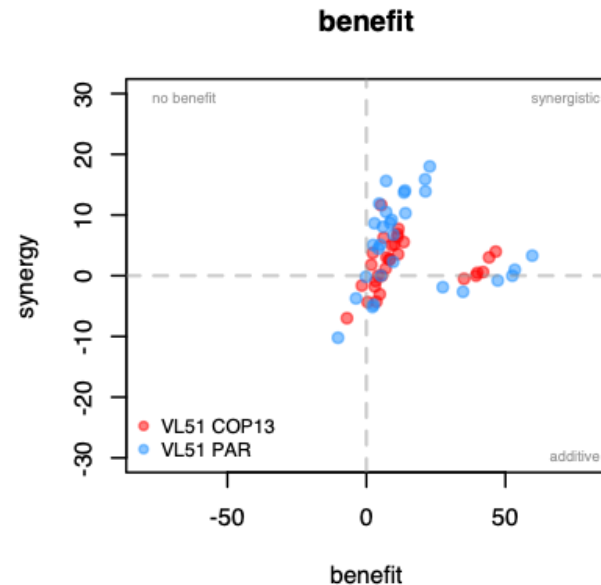
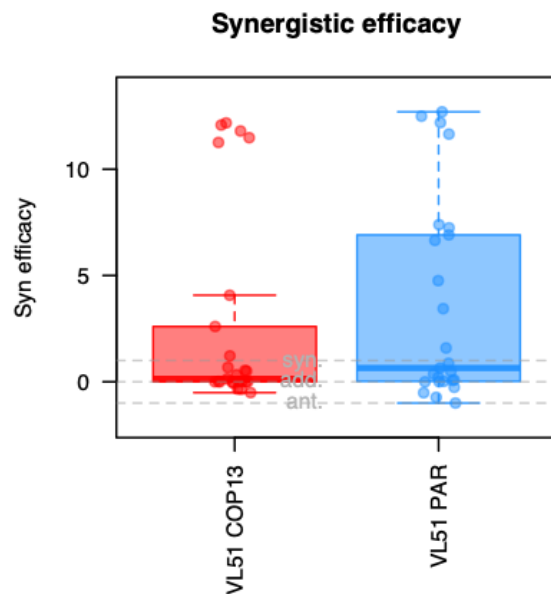
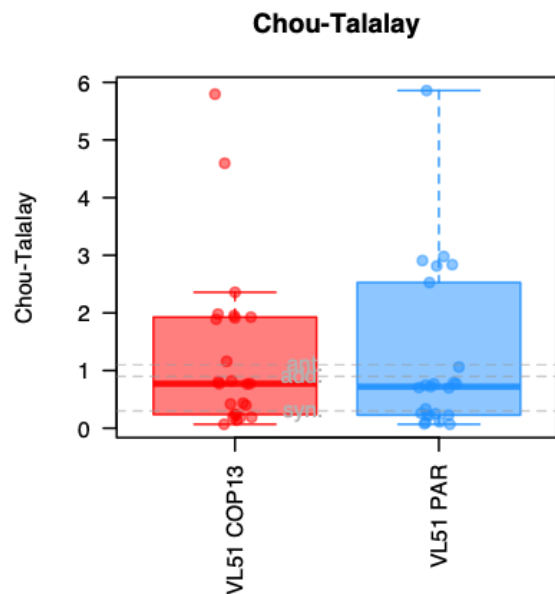
**CA-4948** in combination with **idelalisib** in  
VL51 and K1718 parental and idelalisib resistant models



*(Guidetti et al, on-going)*

# The combination of CA4948 and copanlisib is beneficial in copanlisib-resistant and parental models

## CA-4948 in combination with copanlisib in VL51 parental and copanlisib resistant models

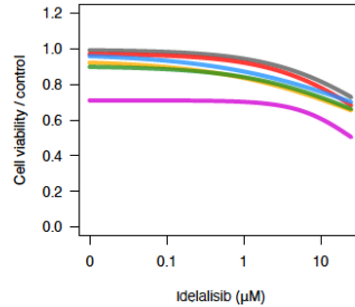


*(Guidetti et al, on-going)*



# Addition of CA4948 increases sensitivity to PI3K or BTK inhibitors

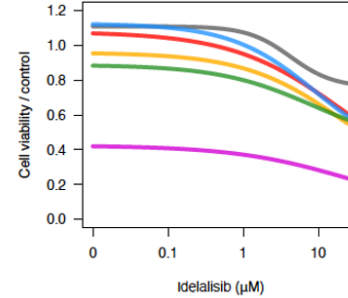
## Karpas1718 idelalisib-resistant



### legend

- Idelalisib single
- Idelalisib + 0.04 μM CA4948
- Idelalisib + 0.2 μM CA4948
- Idelalisib + 1 μM CA4948
- Idelalisib + 5 μM CA4948
- Idelalisib + 25 μM CA4948

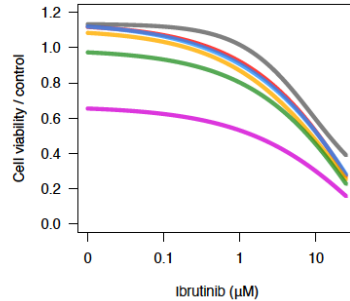
## VL51 idelalisib-resistant



### legend

- Idelalisib single
- Idelalisib + 0.04 μM CA4948
- Idelalisib + 0.2 μM CA4948
- Idelalisib + 1 μM CA4948
- Idelalisib + 5 μM CA4948
- Idelalisib + 25 μM CA4948

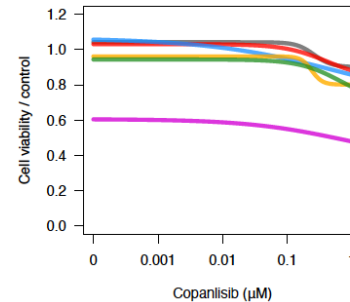
## VL51 ibrutinib-resistant



### legend

- Ibrutinib single
- Ibrutinib + 0.04 μM CA4948
- Ibrutinib + 0.2 μM CA4948
- Ibrutinib + 1 μM CA4948
- Ibrutinib + 5 μM CA4948
- Ibrutinib + 25 μM CA4948

## VL51 copanlisib-resistant



### legend

- Copanlisib single
- Copanlisib + 0.04 μM CA4948
- Copanlisib + 0.2 μM CA4948
- Copanlisib + 1 μM CA4948
- Copanlisib + 5 μM CA4948
- Copanlisib + 25 μM CA4948

(Guidetti et al, on-going)