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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Targeting pathogenic mechanisms in marginal zone lymphoma

CA-4948
first-in-class inhibitor of IRAK4

Pharmacological screening of IRAK4 inhibition with CA-4948

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 theMuSyC algorithm (Meyer et al. Cell Syst 2019).

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

(K7178 PAR, K7178 IDE, V151 PAR, V151 IDE, V151 B.R, V151 COP13)

CA-4948 IC50 (μM)

10 20 30 40

Parental Resistant

Chou–Talalay Index

Efficacy

Potency by CA4948

Potency by the other drug

(R) Copanlisib
(Idelalisib)
(Ibrutinib)

(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 (Guidetti et al, on-going).

**CA-4948** in combination with **idelalisib** in VL51 and K1718 parental and idelalisib resistant models.
The combination of CA4948 and copanlisib is beneficial in copanlisib-resistant and parental models (Guidetti et al, on-going)
Addition of CA4948 increases sensitivity to PI3K or BTK inhibitors

(Guidedti et al, on-going)