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Dana-Farber
Cancer Institute

**Loss-of-function of GABARAP drives tumor resistance to
bortezomib-induced immunogenic cell death in multiple
myeloma**

18th International Myeloma Workshop

Annamaria Gulla', MD

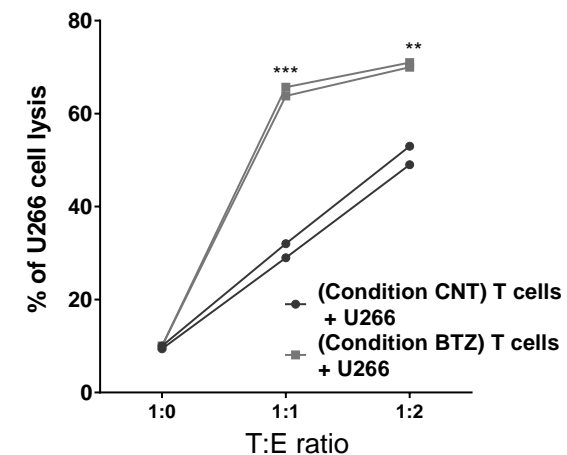
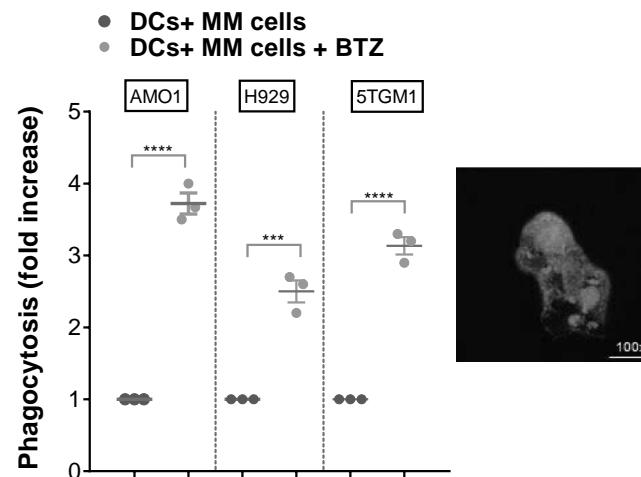
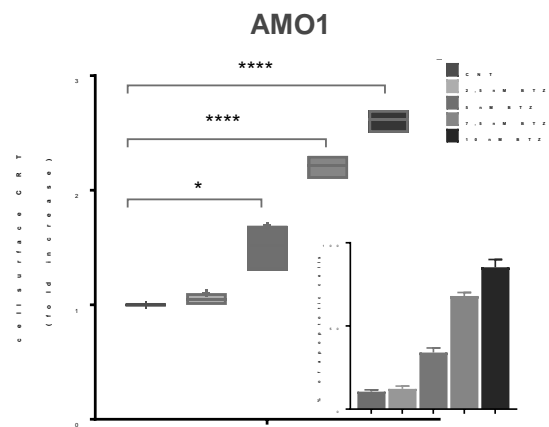
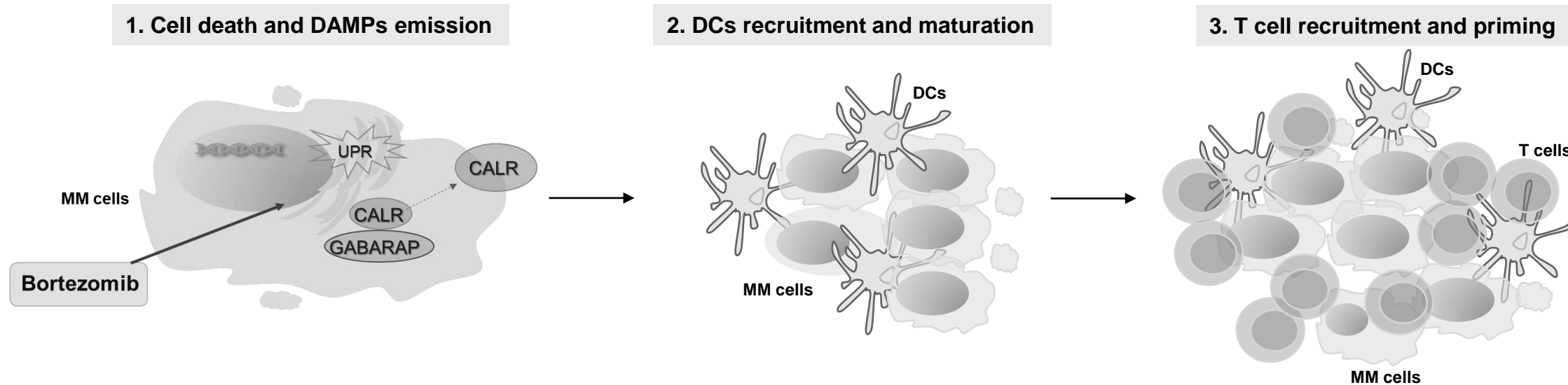
Kenneth Anderson lab

Disclosure

- **I do not have conflicts of interest**

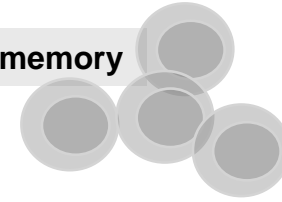
Overcoming immune dysfunction in myeloma

Bortezomib induces calreticulin-dependent immunogenic cell death (ICD) in MM



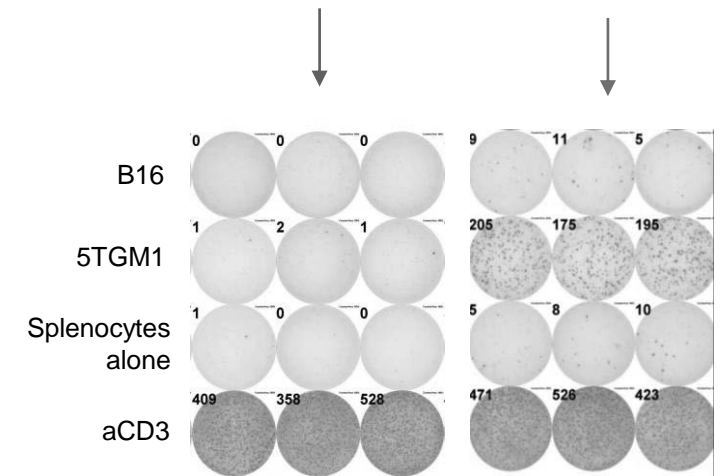
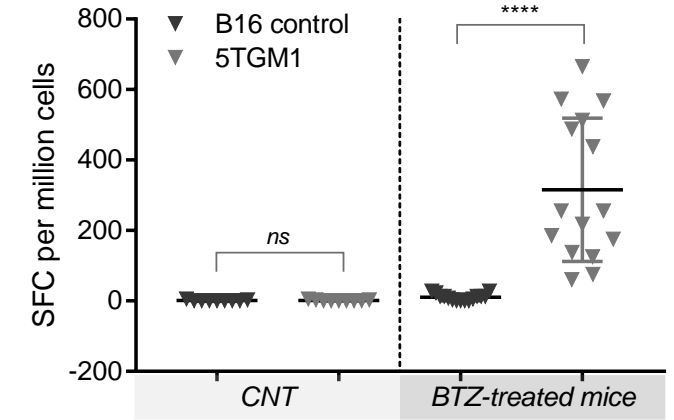
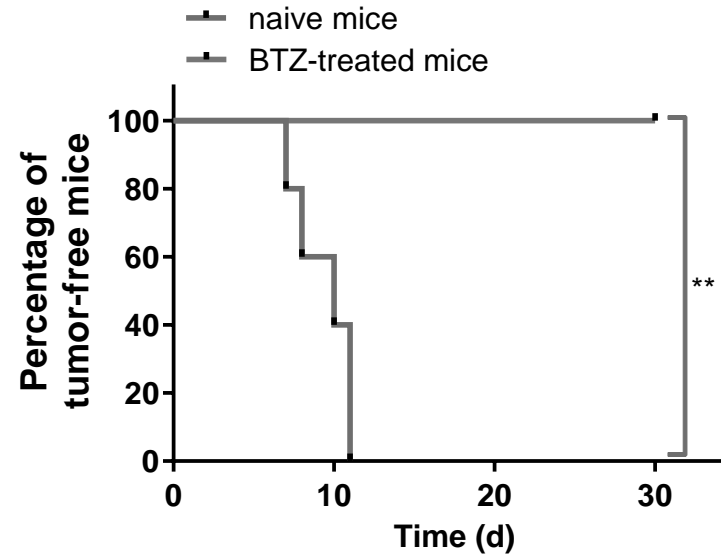
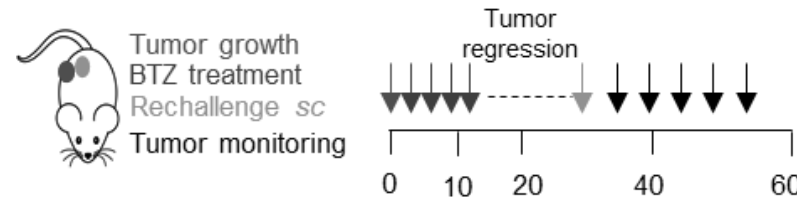
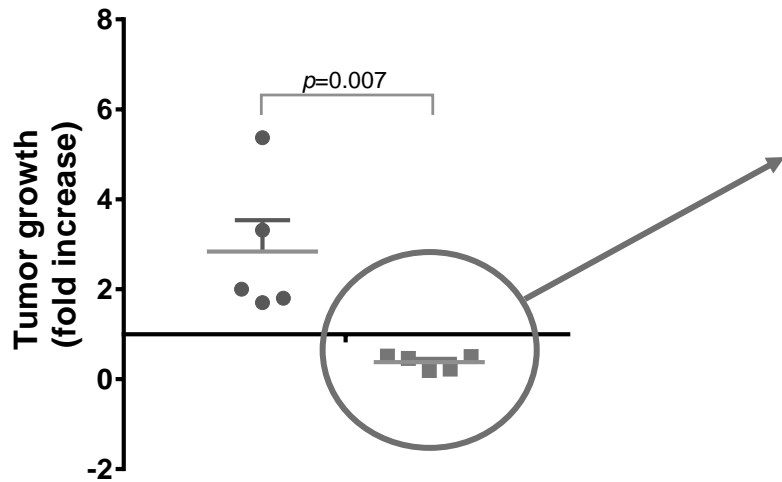
Bortezomib-induced ICD stimulates a potent antitumor immune response *in vivo*

4. Immunological memory



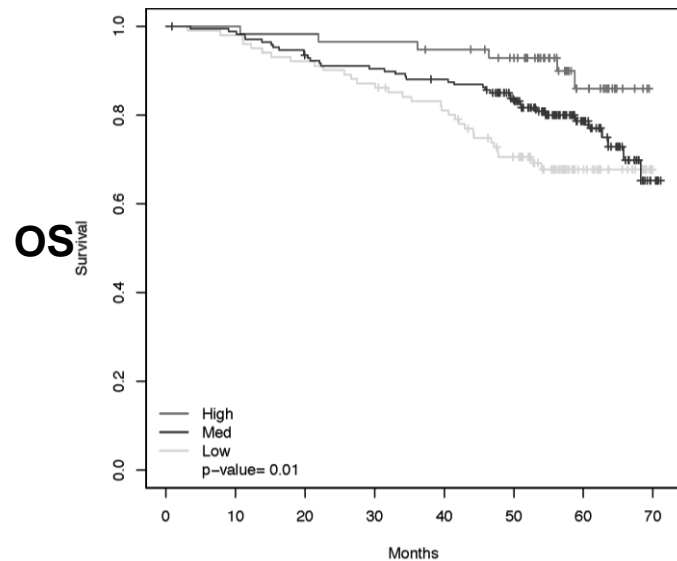
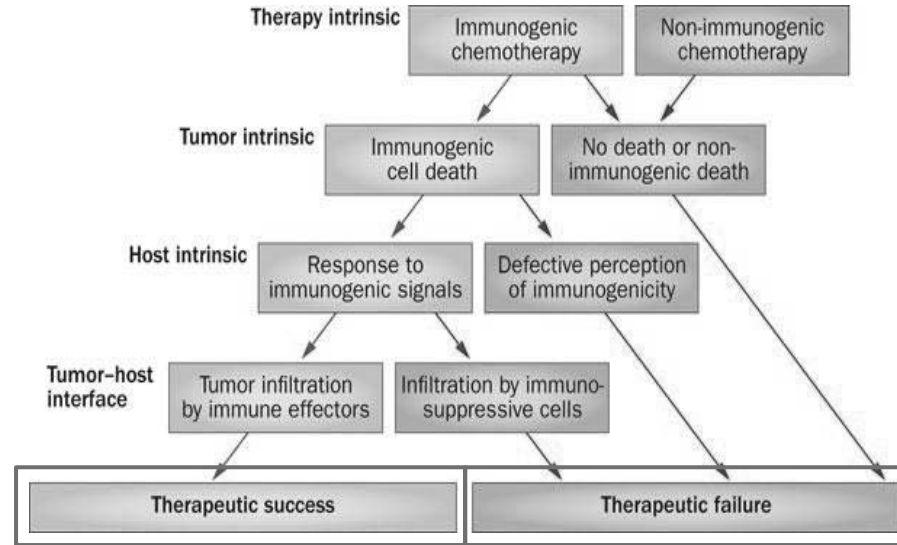
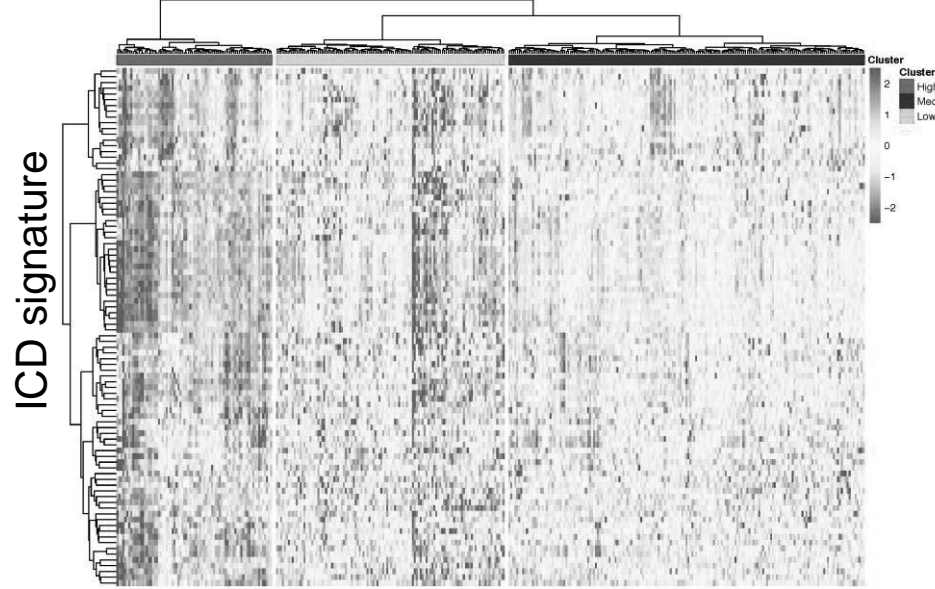
Immunocompetent mice

- CNT
- BTZ 0.5 mg/kg



Clinical benefit of ICD induction in MM patients

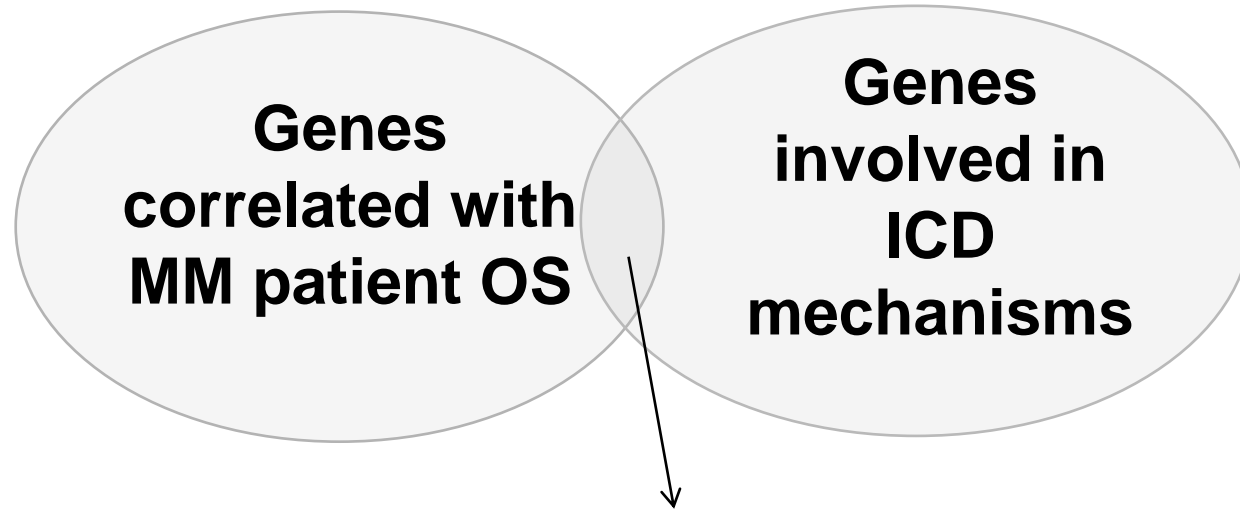
IFM-DFCI 2009 clinical trial



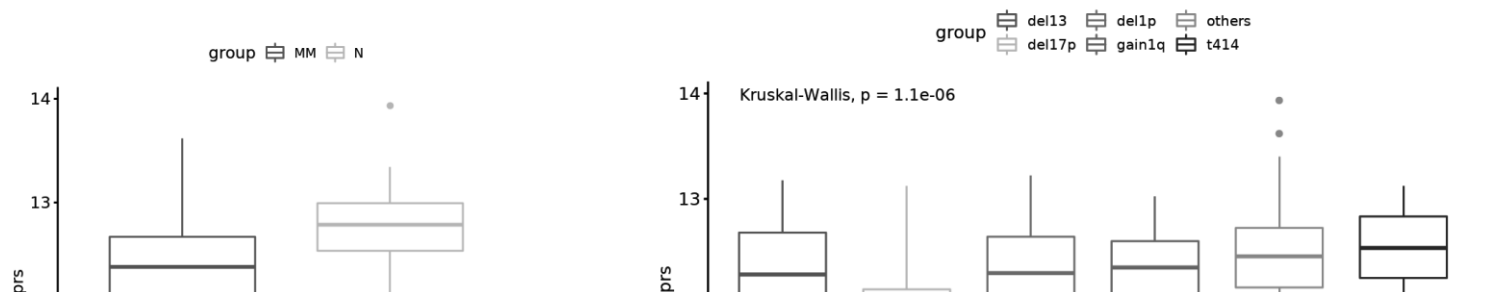
To investigate the mechanisms of resistance to BTZ-induced ICD

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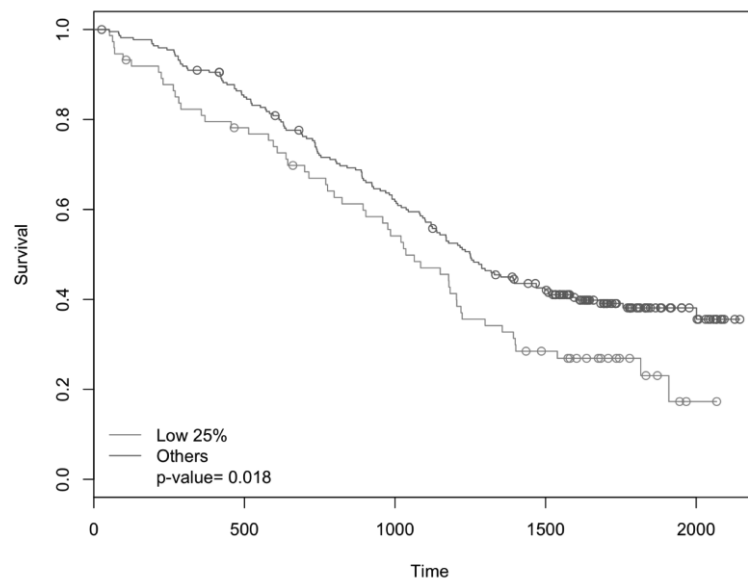
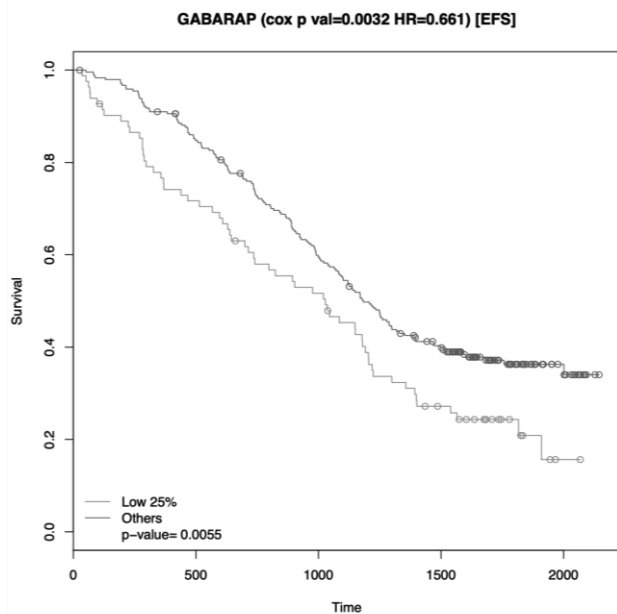
Newly diagnosed MM patients (IFM/DFCI)
LongTermSurvival (>5years)
versus
ShortTermSurvival (<1.5years)
↓
differentially expressed genes



GABARAP expression levels impact on clinical outcome of MM patients



Patients with low GABARAP, particularly those with del(17p), may not undergo ICD upon BTZ treatment

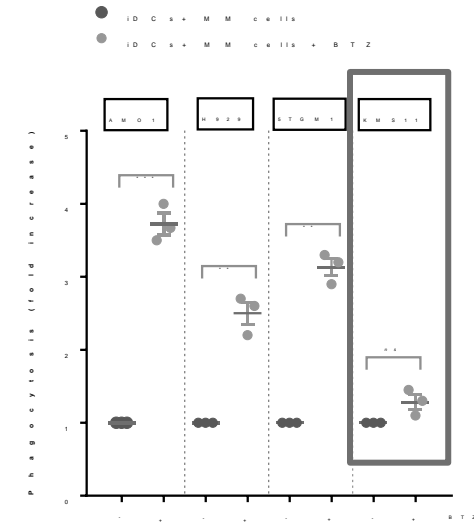
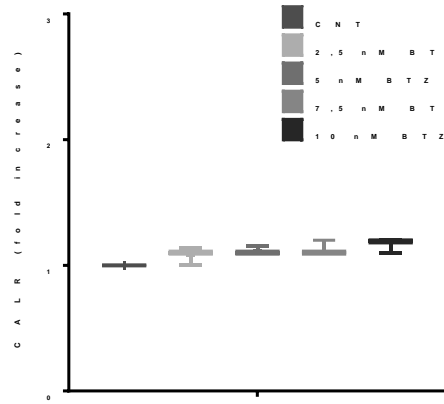
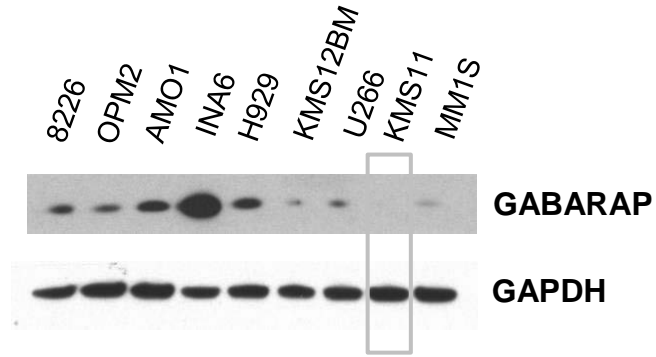


No patients with del(17p)

BTZ does not induce ICD in low-GABARAP MM cells

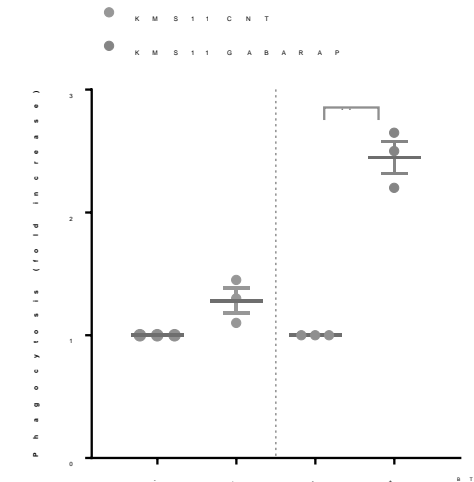
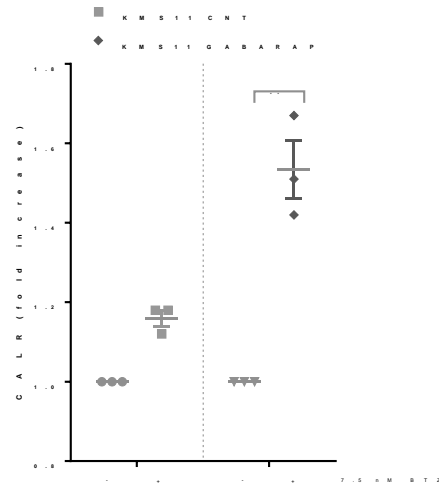
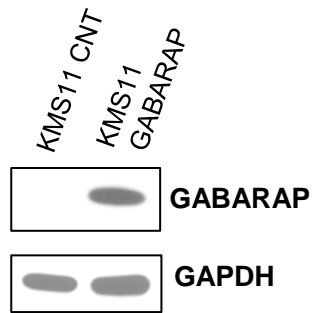
Calreticulin

Phagocytosis

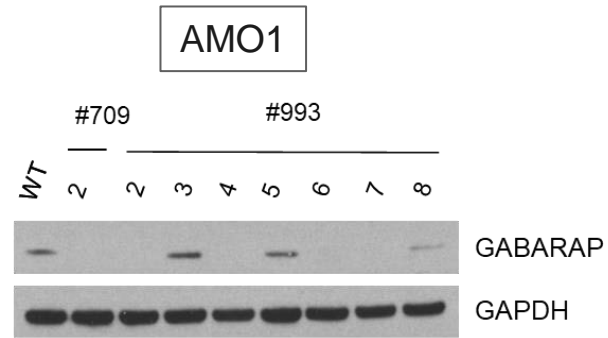


Calreticulin

Phagocytosis

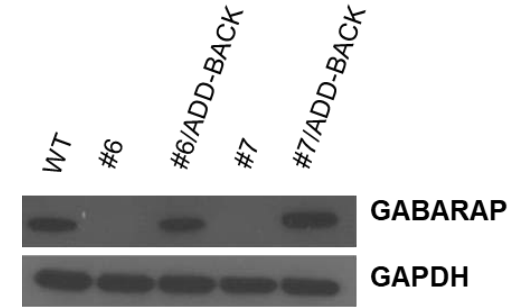
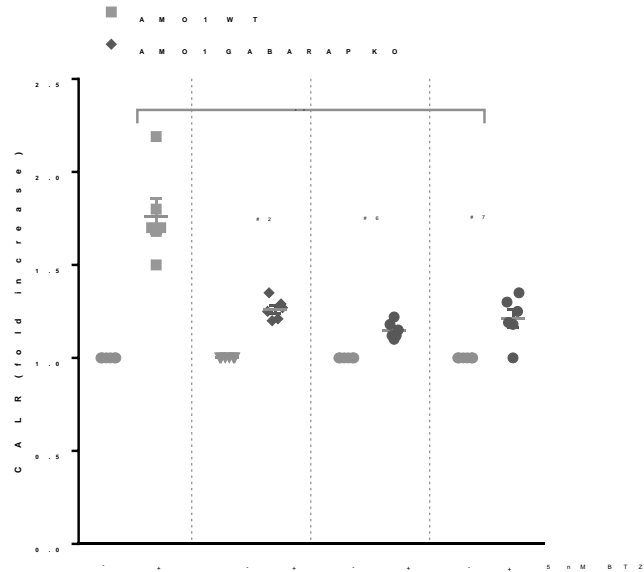


GABARAP^{KO} blocks CALR exposure upon BTZ in MM cells



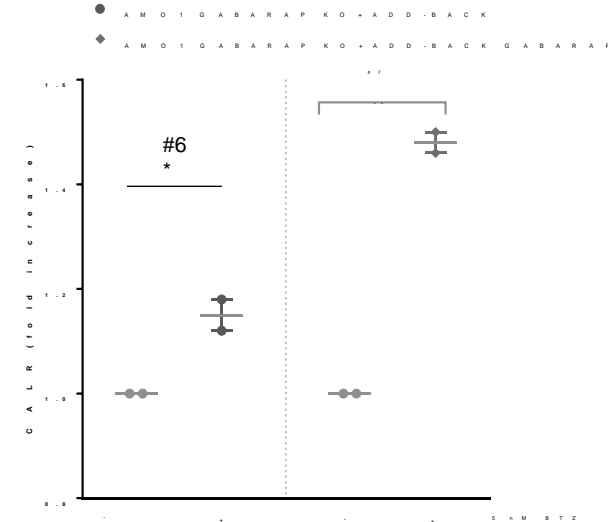
GABARAP^{KO}

Calreticulin

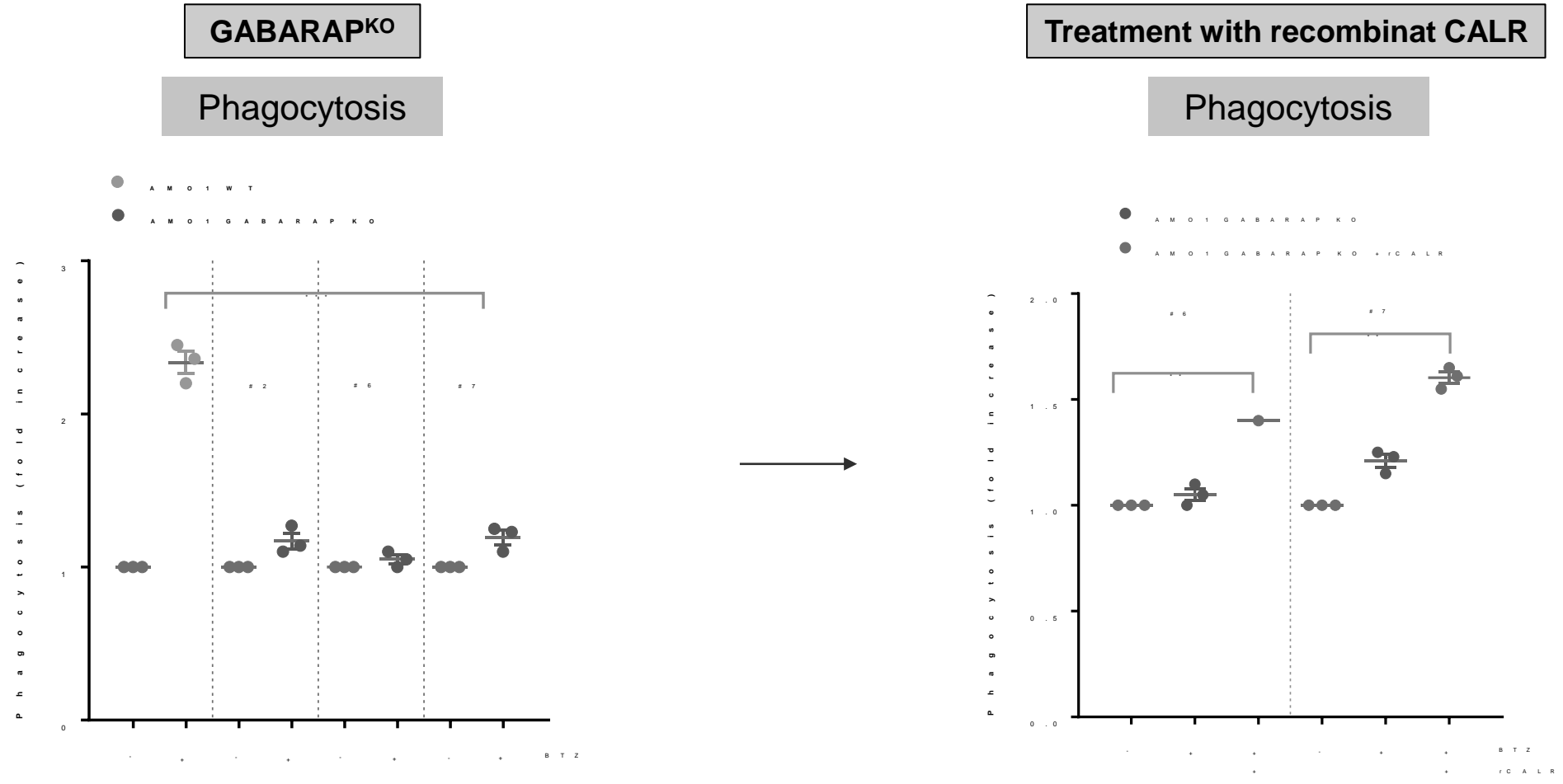


GABARAP add-back

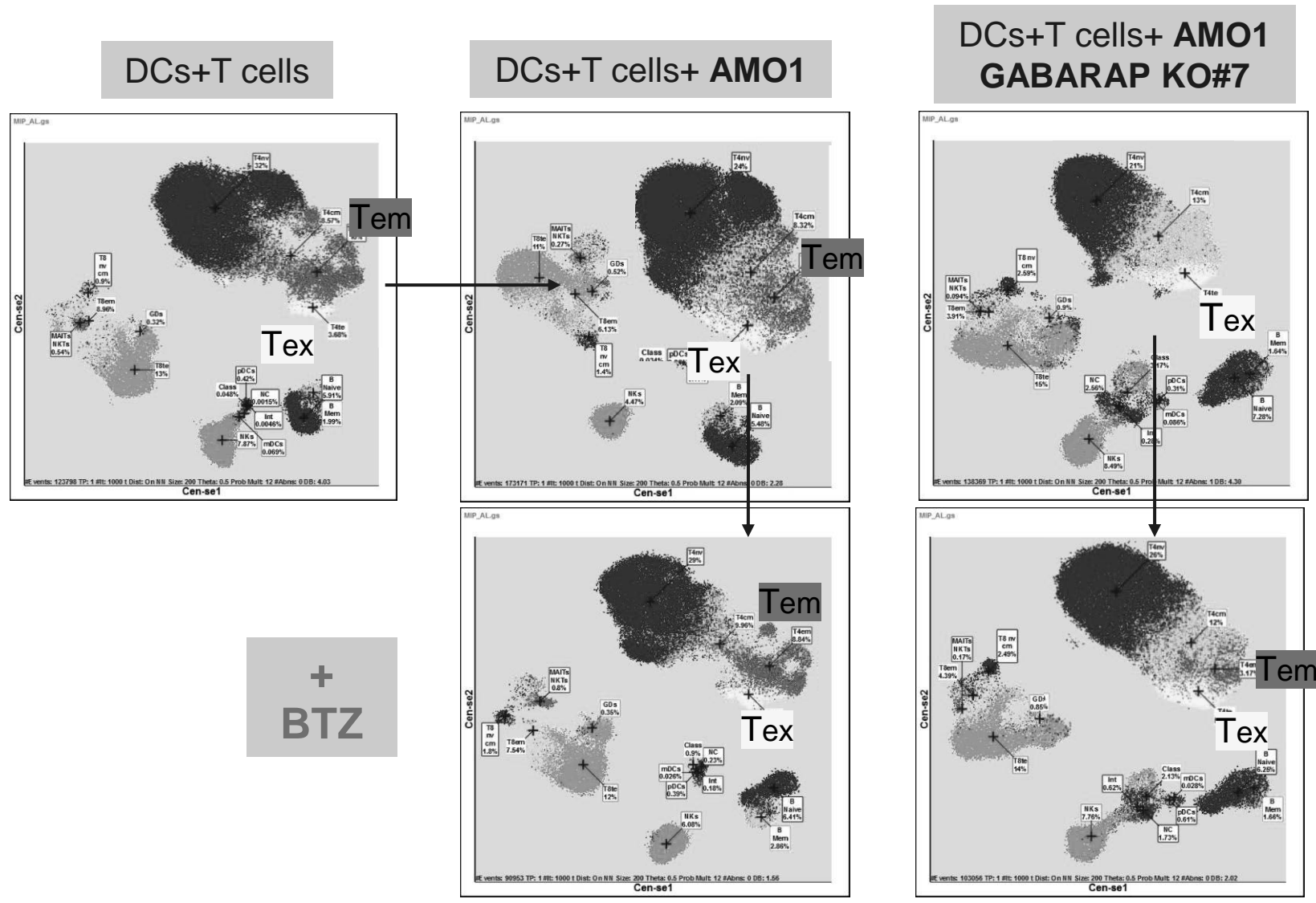
Calreticulin



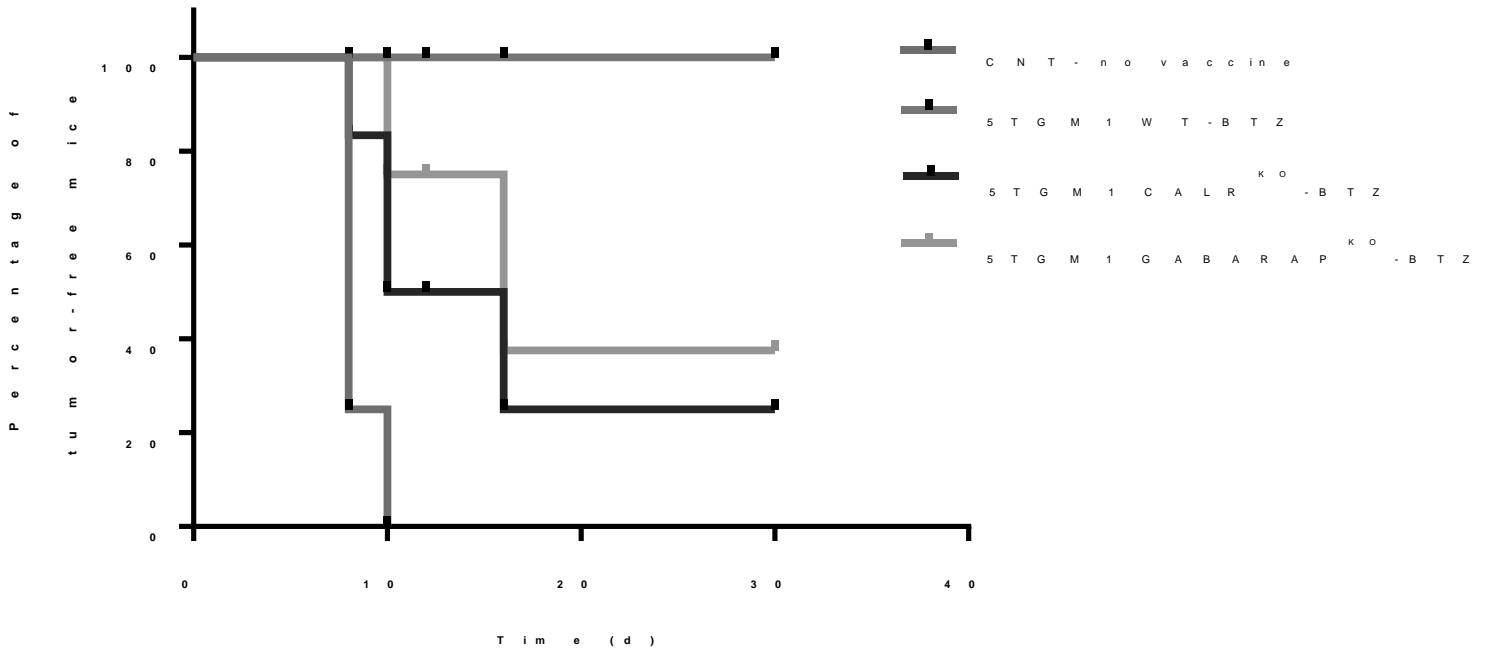
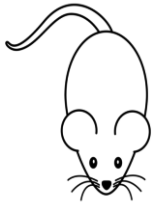
GABARAP^{KO} abrogates phagocytosis by DCs by inhibiting CALR exposure



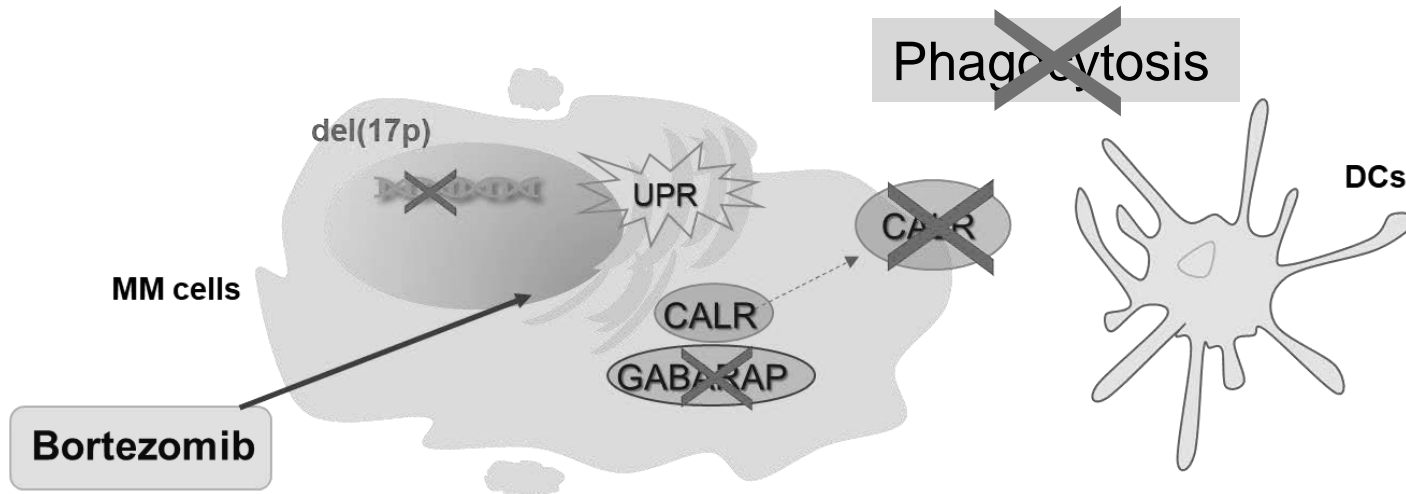
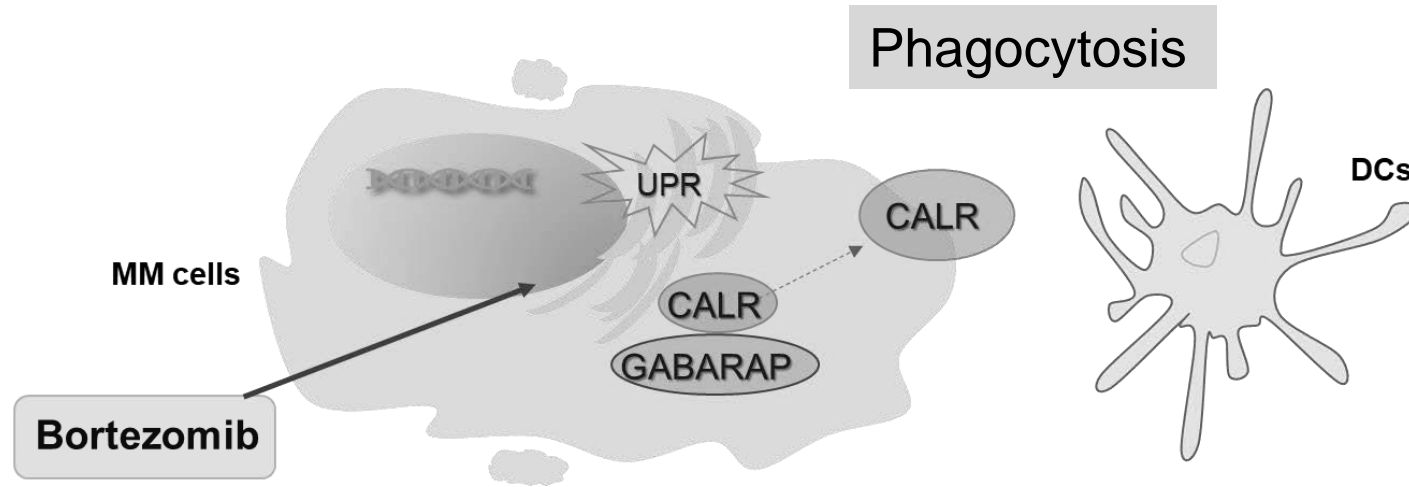
GABARAP^{KO} antagonizes BTZ-induced anti-tumor T cell response



GABARAP^{KO} cells treated with BTZ fail to protect against tumor rechallenge *in vivo*



Conclusions



- Loss-of-function of GABARAP, particularly in high-risk patients with 17p deletion, blocks CALR exposure upon BTZ treatment thus contributing to tumor immune evasion and ICD resistance.
- These studies provide the framework for novel combination treatments to restore anti-MM immunity and improve patient outcome in HR MM.

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All patients of IFM/DFCI clinical study!!



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