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NMS-812, a clinical stage dual PERK and GCN2 modulator, with activity in Multiple Myeloma, AML and solid tumors

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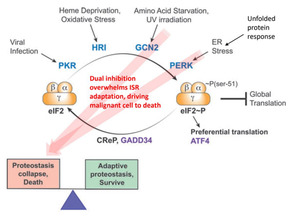
INTRODUCTION

- **PERK** and **GCN2** are eIF2α ser-thr kinases activated by endoplasmic reticulum (ER) stress and aminoacid deficiency, respectively. PERK regulates the **Unfolded Protein Response (UPR)** and GCN2 the aminoacid response (AAR), pathways of the broader **Integrated Stress Response (ISR)**.
- Cancer cells exploit ISR to survive and adapt to harsh conditions, such as lack of O_2 and nutrients or treatment with chemotherapies, by a **transient arrest of protein synthesis,** that provides the cell time to respond to stress; in parallel, the **induction of the transcription factor ATF4** occurs to activate the transcription of several genes involved in stress response.
- ATF4 plays a role in survival and cell death, depending on the context and extent of stress. ER stress is also affecting the immune system and PERK/GCN2 modulation may represent a promising therapeutic approach to target tumors dependent on ISR.



Adapted from Wek et al 2023

AIM

Here we describe the *in vitro* mechanism of action and the *in vivo* efficacy in different tumors of **NMS-812**, a very potent ATP-competitive dual PERK/GCN2 inhibitor.

RESULTS

- In **Multiple Myeloma (MM)**, a highly protein-secreting tumor, NMS-812 is active *in vitro* by the dual inhibition of PERK and GCN2, impeding their crosstalk and pro-survival effect.
- In **Acute Myeloid Leukemia (AML)** and **Clear Cell Ovarian Cancer model (OCCC)**, NMS-812 shows potent activity as single agent and in combination with standards of care (SOCs).
  - *In vitro*, NMS-812 induces ATF4 and, in parallel, ecto-calreticulin, a marker of immunogenic cell death (ICD), and apoptosis.
  - *In vivo*, NMS-812 induces tumor regression as single agent and is synergic with SOCs; ATF4 induction was also confirmed *ex-vivo*.
- NMS-812 also showed antitumor activity on the CT26 murine colorectal model implanted in immunocompetent mice, while its activity was abolished when CT26 were implanted in immunodeficient mice, suggesting that in this case the *in vivo* efficacy is reliant on the immune system.

NMS-812

NMS-812 is a potent dual PERK/GCN2 inhibitor

	PERK	GCN2
compound	Ki (nM)	Ki (nM)
NMS-812	0.149 ± 0.019	2.23 ± 0.85
GSK-157	0.318 ± 0.164	>3000

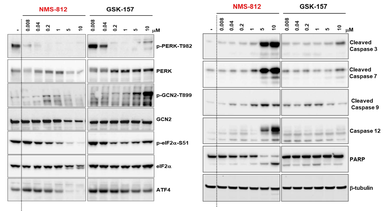
	PERK		GCN2	
compound	Kd[a] (nM)	τ (min)	Kd[a] (nM)	τ (min)
NMS-812	0.23	71	0.55	67

[a] HTRF binding assay – Enzymlogic (Spain)

NMS-812 and GSK-157 have similar potency on PERK. NMS-812 also shows significant activity on GCN2 while GSK-157 is inactive

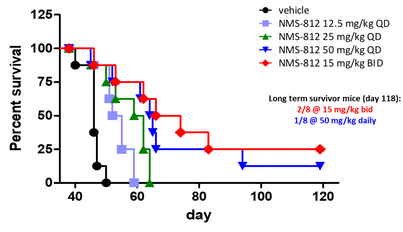
Multiple Myeloma

NMS-812 modulates PERK/GCN2 pathway and induces apoptosis *in vitro* in KMS-11 multiple myeloma cell line



KMS-11 multiple myeloma cells treated with different doses of NMS-812 for 48h

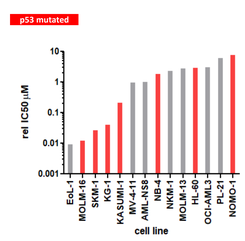
NMS-812 is efficacious *in vivo* as monotherapy in KMS-11 multiple myeloma model



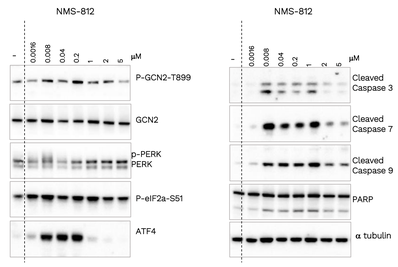
NMS-812 showed significant dose-dependent median survival time prolongation in KMS-11 MM orthotopic xenograft model without toxicity (treatment days 7-26)

Acute Myeloid Leukemia (AML)

NMS-812 is active *in vitro* on AML cell lines

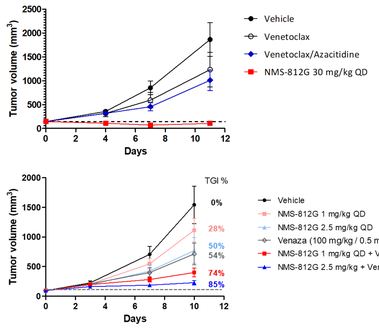


NMS-812 affects AML cell proliferation. Most sensitive cell lines are FLT3 wild type, p53 mutated

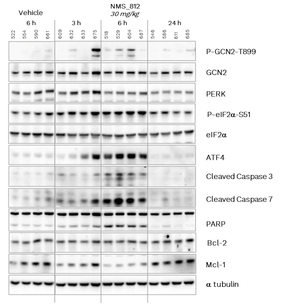


***In vitro* MoA of AML MOLM16 cell lines treated for 4h with different concentrations of NMS-812**

NMS-812 is efficacious *in vivo* as single agent and in combination with SOCs in MOLM16 AML model



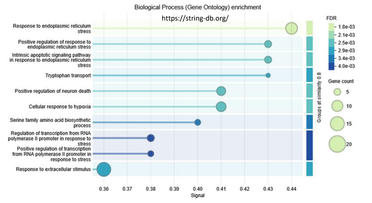
NMS-812 activates ATF4 and induces apoptosis *in vivo*



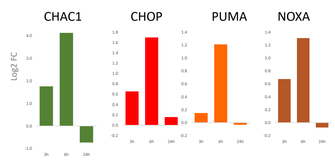
***Ex-vivo* MoA of AML MOLM16 tumors at 3-6-24 h after a single treatment with NMS-812 30 mg/kg**

NMS-812 induces a terminal integrated stress response and cell death *in vivo*

Ex-vivo transcriptomics analysis (differential gene expression of NMS-812 6h-treated vs control tumors)



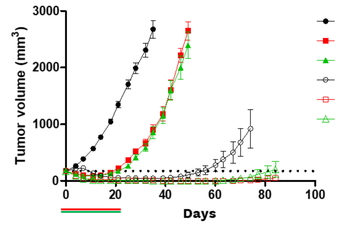
Functional enrichment of modulated pathways after 6h single treatment (30 mg/kg) NMS-812 in AML MOLM16 model



- **NMS-812 disturbs ISR homeostasis and induces ATF4**
- **ATF4 induces CHAC1 and CHOP transcription**
- **CHAC1 increases the oxidative stress**
- **CHOP induces pro-apoptotic genes such as Puma and Noxa**
- **A terminal ISR and cell death are induced**

Clear Cell Ovarian Cancer

NMS-812 is efficacious *in vivo* as single agent and in combination with SOCs in Tov21G clear cell ovarian cancer model

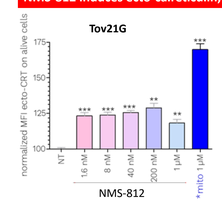


End of observation day 108:
SN38* s.a. 1/8 tumor free mice
Combo 15 BID 4/8 tumor free mice
Combo 30 QD 7/9 tumor free mice

*SN38 is the active metaolite of irinotecan

Immune system

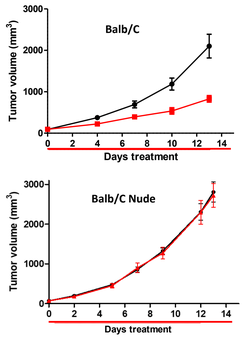
NMS-812 induces ecto-calreticulin, a marker of immunogenic cell death



Increase in ecto-calreticulin (CRT) measured on live cells by MFI (Median Fluorescence Intensity) after 24h treatment
*mitoxanthrone (positive control)

Increase in ecto-calreticulin (CRT) measured on live cells by % of positive cells after 24h treatment

NMS-812G shows efficacy on syngeneic CT26* colon cancer model only in the presence of an intact immune system



*CT26 *in vitro* IC50 >10 µM

CONCLUSIONS

PERK and GCN2 are involved in tumor growth and resistance to chemotherapies. NMS-812, a dual PERK/GCN2 inhibitor, is endowed with antitumor activity as single agent and in combination with SOC, suggesting that PERK/GCN2 modulation by NMS-812 can thwart resistance to chemotherapies. NMS-812 has also immune-modulatory properties with ICD induction and anti-tumor activity relying on the immune system. Based on these results, a Ph1 study in AML was started with the possibility to expand to solid tumors.

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