A novel small molecule activator of the integrated stress response kinase GCN2 shows potent preclinical antitumor activity as monotherapy and in combination with standard of care agents

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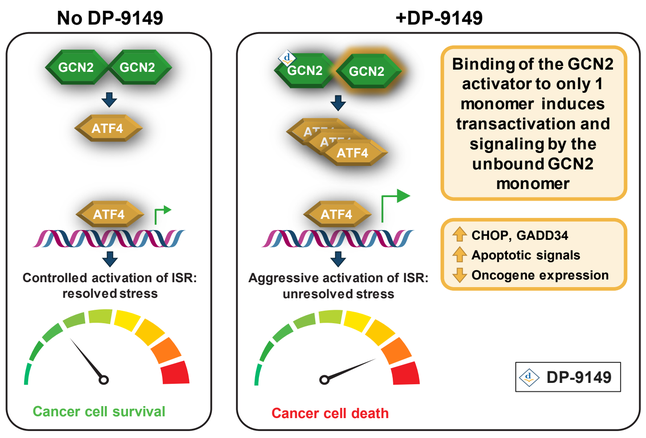
Abstract: 29

INTRODUCTION

- The Integrated Stress Response (ISR) is a major adaptive stress response pathway in cancer and plays an important role in cell fate determination[1-4]
- Cancer cells experience high extrinsic and intrinsic stress and are dependent on a balanced ISR to survive in the context of uncontrolled growth[1-4]
- The ISR is tightly regulated by several kinases, including GCN2
- Pharmacological activation of GCN2 and its downstream pathways can induce apoptosis in tumor cells reliant on a balanced ISR[1-4]
- DP-9149 is a novel, selective, and potent activator of GCN2 kinase activity and the ISR pathway in cancer cells[5]
- Treatment with DP-9149 led to a significant increase in ATF4 and subsequent induction of apoptotic cell death in clear cell renal cell carcinoma (ccRCC), bladder cancer, and non–small cell lung cancer (NSCLC) cell lines
- Oral dosing with DP-9149 resulted in tumor growth inhibition (TGI) in mouse xenograft models for multiple human cancers (ccRCC, bladder cancer, and KRAS^{G12C}-mutant NSCLC) and augmented the anticancer effect of standard of care (SOC) therapy resulting in tumor regression in most models



METHODS

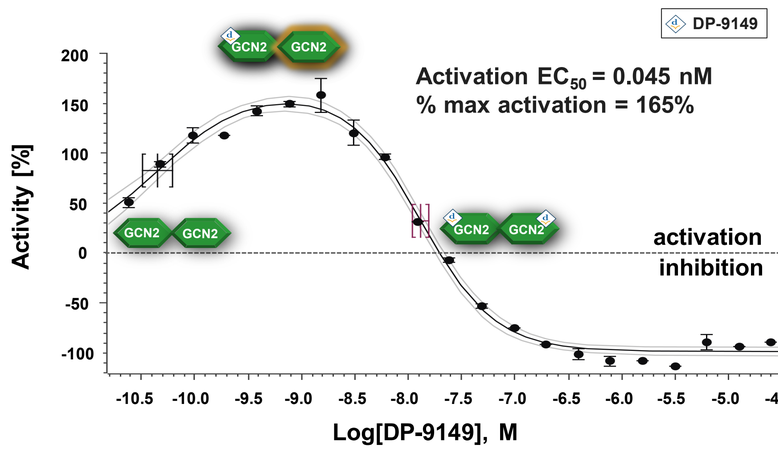
- Activation of ISR kinases was characterized using enzymatic assays
- Cellular modulation of the ISR pathway (phospho-GCN2, ATF4, CHOP, or the apoptosis pathway [c-PARP and c-caspase 3/7]) was assessed via Western blot or ELISA
- In vivo upregulation of tumoral ATF4 was determined in an RCC PK/PD xenograft model
- In vivo inhibition of tumor growth was determined in solid tumor xenografts
- TGI and regression were calculated at the end of dosing

RESULTS

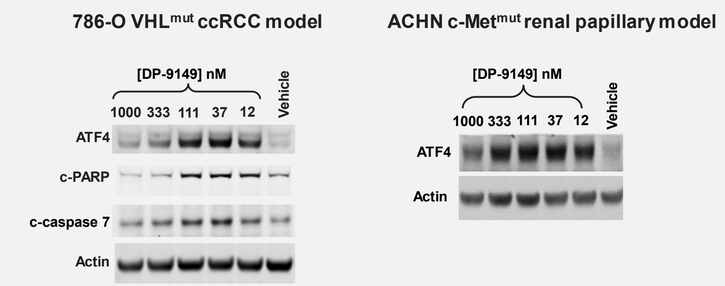
DP-9149 was designed as a selective and potent activator of GCN2

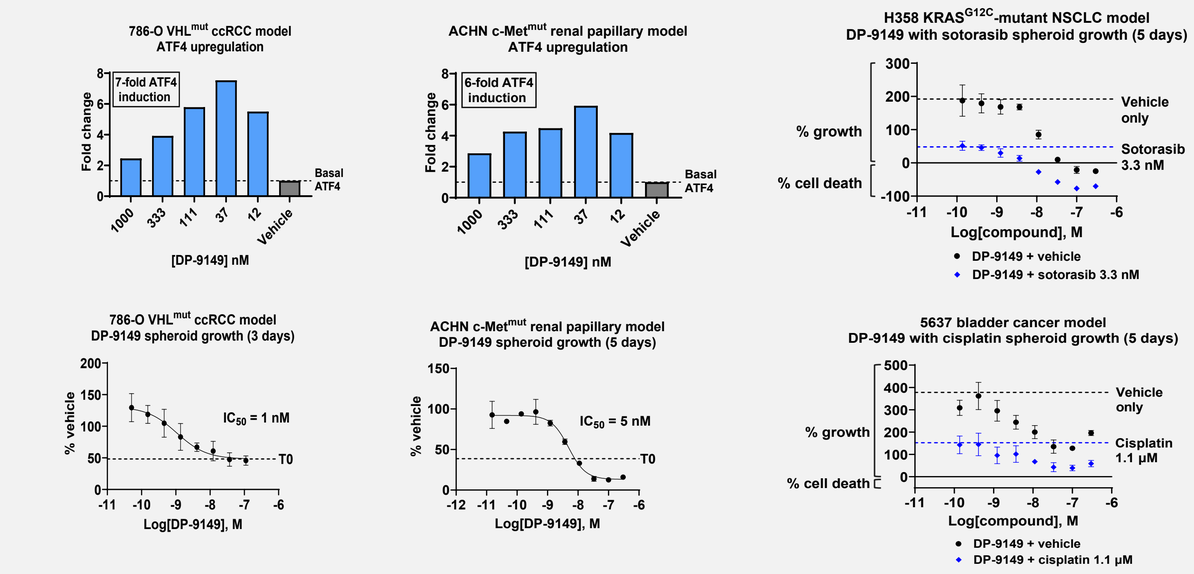
	Assay	DP-9149
Enzymatic	Recombinant GCN2 activation	EC_{50} = 0.045 nM
Cellular assays	ATF4 stimulation versus control 786-O (VHL^{mut} ccRCC model)	7-fold at 37 nM
	ATF4 stimulation versus control ACHN (c-Met^{mut} renal papillary model)	6-fold at 37 nM
In vivo PK/PD	Tumoral ATF4	Max activation >20-fold for 6 h at 25 mg/kg

DP-9149 directly binds to and activates recombinant GCN2 kinase

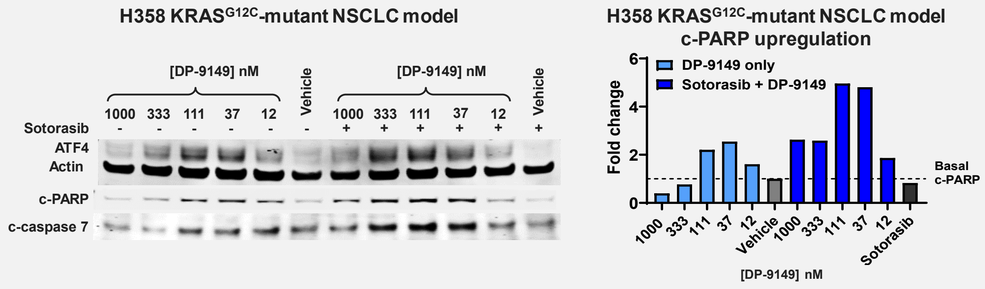


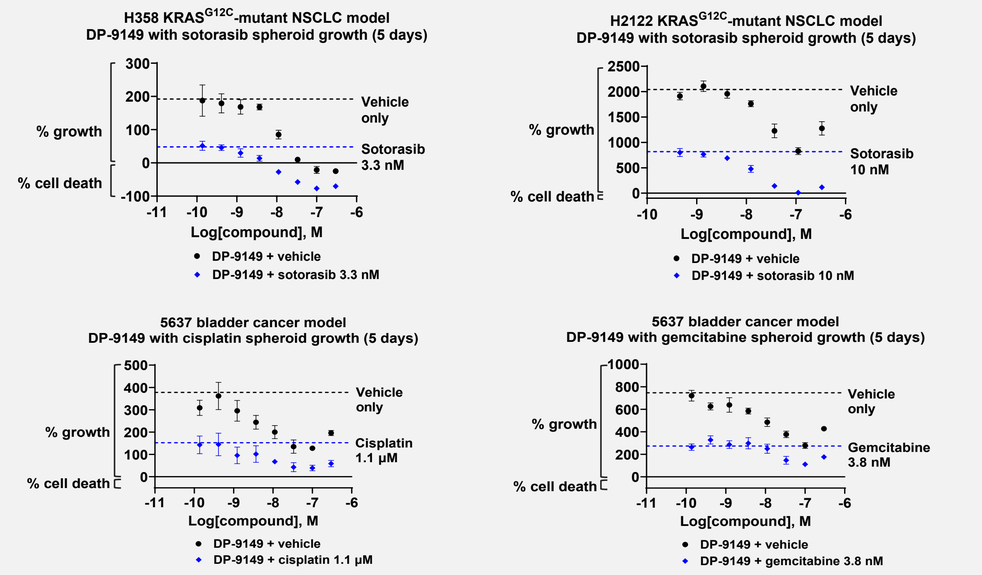
DP-9149 upregulates the ISR/apoptosis pathway and inhibits spheroid growth as a single agent in oncogene-driven solid tumors in vitro



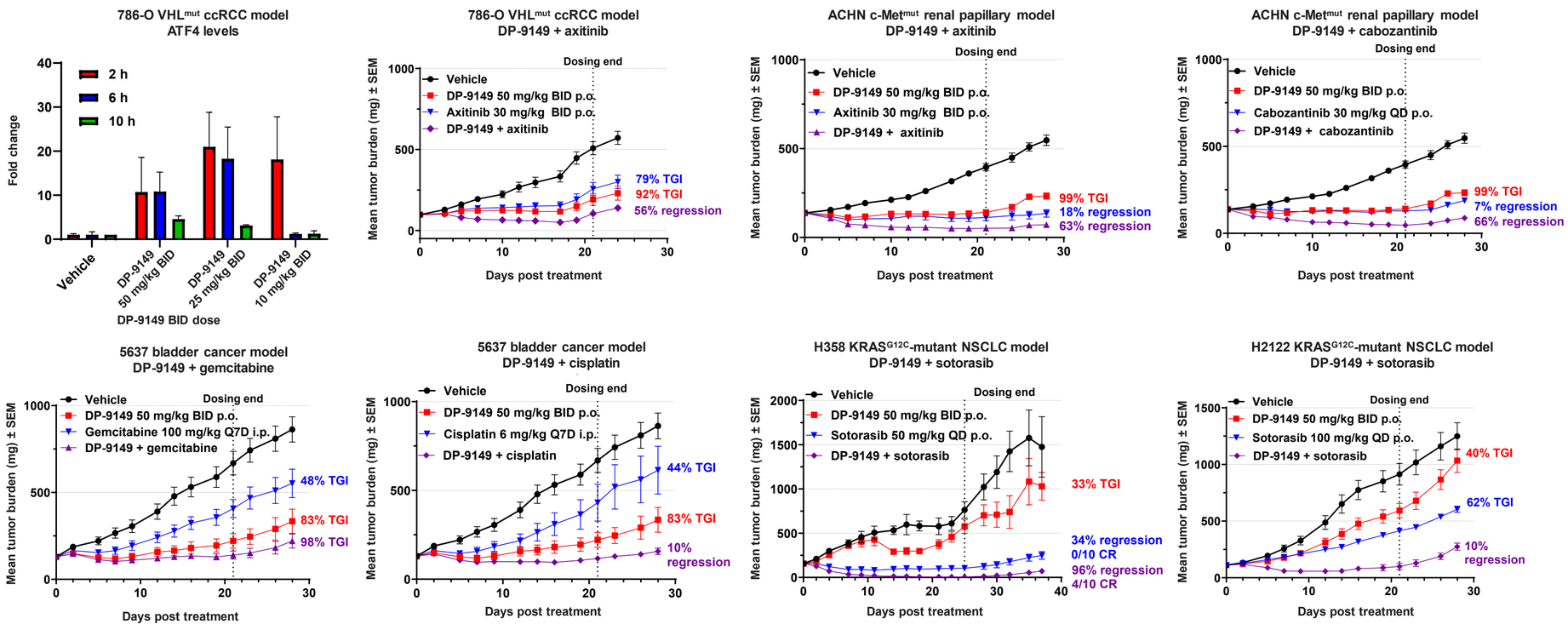


DP-9149 upregulates apoptosis and inhibits tumor cell growth in combination with SOC in NSCLC and bladder cancer cell lines





DP-9149 upregulates the ISR, inhibits tumor growth as a single agent, and combines with SOC therapy to induce tumor regression in solid tumor xenograft models in vivo



CONCLUSIONS

- DP-9149, a novel, potent, selective and orally bioavailable compound, activates GCN2, which upregulates the ISR pathway and induces anti-tumoral effects in solid tumors in vitro and in vivo through the induction of an unresolved stress response
- DP-9149 exhibited robust activity as a single agent and in combination with SOC agents in renal cell, bladder, and KRAS^{G12C}-mutant lung cancers in vivo

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DISCLOSURES

All authors are/were full time employees of Deciphera Pharmaceuticals, LLC.

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ABBREVIATIONS

ACHN, human renal adenocarcinoma cell line; ADP, adenosine diphosphate; ATF4, activating transcription factor 4; BID, twice daily; c-caspase, cleaved caspase; ccRCC, clear cell renal cell carcinoma; CHOP, CCAAT enhancer-binding protein homologous protein; c-Met, cleaved proto-oncogene encoding the hepatocyte growth factor receptor; c-PARP, cleaved poly-ADP ribose polymerase; CR, complete response; EC_{50}, half maximal effective concentration; ELISA, enzyme-linked immunosorbent assay; GADD34, growth arrest and DNA damage-inducible gene 34; GCN2, general control nonderepressible 2; GTPase, guanosine triphosphatase; IC_{50}, half maximal inhibitory concentration; i.p., intraperitoneally; ISR, integrated stress response; KRAS, Kirsten rat sarcoma small GTPase protein; mut, mutant; NSCLC, non–small cell lung cancer; PD, pharmacodynamic; PK, pharmacokinetic; p.o., orally; QD, once daily; Q7D, once every week; SEM, standard error of the mean; SOC, standard of care; T0, time zero; TGI, tumor growth inhibition; VHL, Von Hippel-Lindau.

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