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Preclinical Antitumor and Immunomodulatory Activity of ARV-6723, a PROTAC HPK1 Degrader, Versus ICIs

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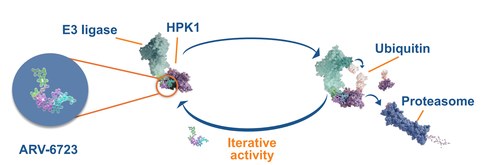
Background

- HPK1 is a serine/threonine protein kinase encoded by *MAP4K1* that is almost exclusively expressed in hematopoietic-derived cells[1,2]
- HPK1 negatively regulates proximal TCR signaling and is associated with decreased T-cell activation and proliferation and increased T-cell dysfunction and exhaustion[3,4]
- HPK1 also regulates other immune cells (eg, B cells, NK cells, and dendritic cells) through less well-characterized suppressive mechanisms[5-9]
- Immune checkpoint inhibitors (ICIs, eg, anti-PD-1 and anti-CTLA-4 antibodies) have demonstrated robust and durable responses in multiple solid tumor types; however, a high unmet medical need remains, as resistance mechanisms (eg, immunosuppressive tumor microenvironments) contribute to disease progression in most patients[10,11]
- ARV-6723 is a potent and selective orally bioavailable PROTAC HPK1 degrader being studied for its potential as an immunotherapy for advanced solid tumors[12,13]

Mechanism of action of ARV-6723[a]



[a]General PROTAC protein degrader is shown.

- The PROTAC mechanism of action and associated iterative activity offers advantages over inhibitors, as evidenced by:
  - Deeper, sustained degradation and more complete and durable pathway engagement with ARV-6723 vs an investigational HPK1 inhibitor in vitro and in vivo[12]
  - Enhanced immunomodulatory activity, including increased cytokine production and enhanced immune-cell function, with ARV-6723 vs an investigational HPK1 inhibitor[12,13]
  - Greater antitumor activity with ARV-6723 than with single-agent anti-PD-1 antibody or an investigational HPK1 inhibitor in multiple syngeneic mouse models[12,13]

Scan to view previously presented ARV-6723 preclinical data[12,13]

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Objectives

- To evaluate the preclinical antitumor activity of ARV-6723 in syngeneic models with distinct mechanisms of ICI resistance
- To compare immunological changes induced by ARV-6723 vs standard-of-care ICI agents (anti-PD-1 antibody alone or in combination with an anti-CTLA-4 antibody) or an investigational HPK1 inhibitor and identify immune features unique to ARV-6723 responses

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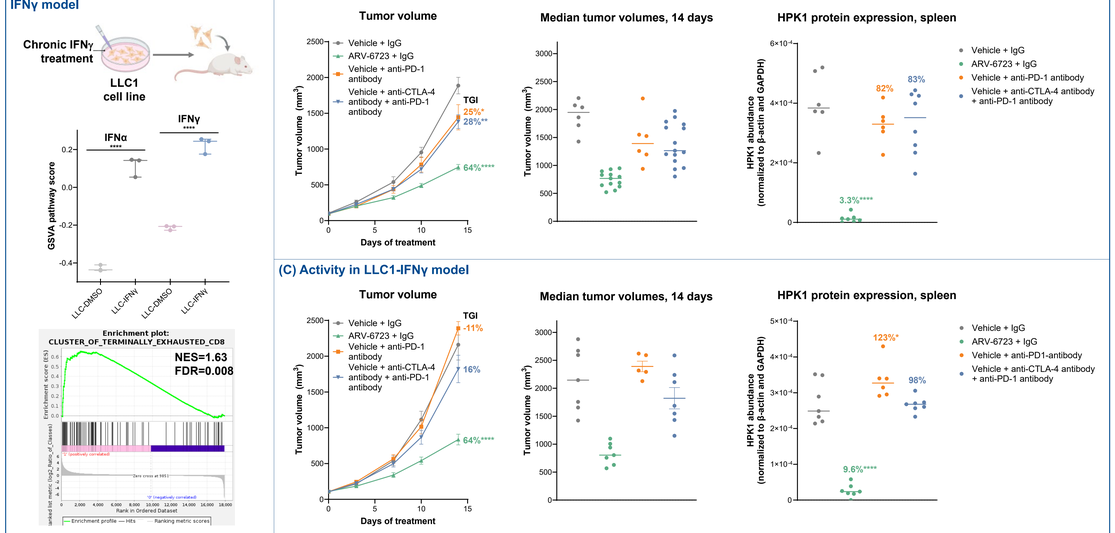
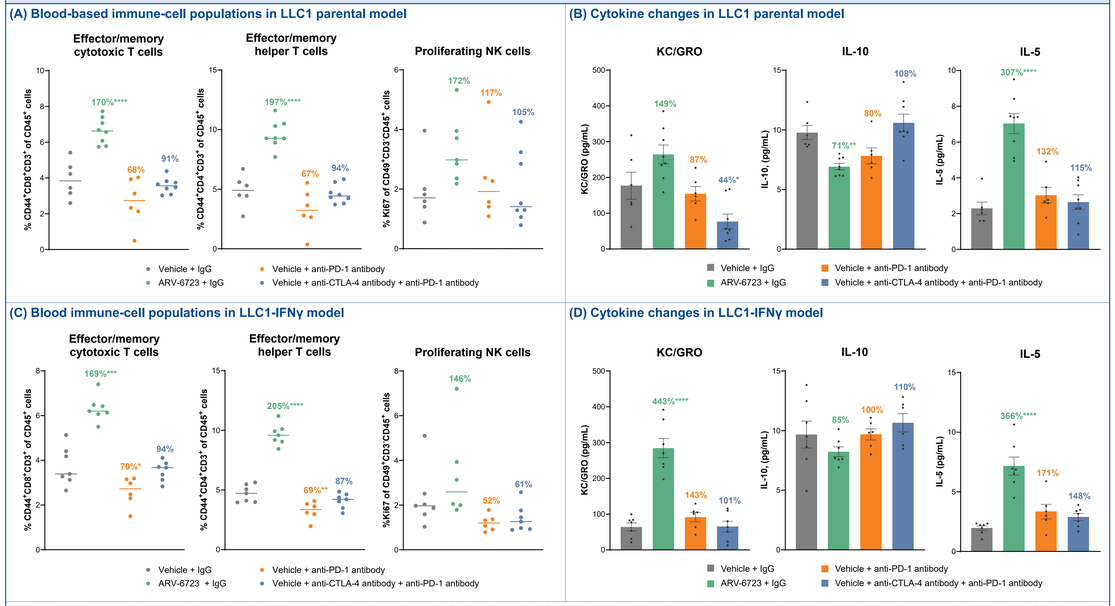
Figure 1: Antitumor activity of ARV-6723 vs anti-PD-1 ± anti-CTLA-4 antibodies in an ICI-resistant lung cancer model of T-cell dysfunction/exhaustion (LLC1-IFNγ)



(**A**) Schematic of the generation of LLC1-IFNγ mouse model through chronic in vitro treatment of LLC1 cell line with IFNγ. Validation of LLC1-IFNγ model with bulk RNA sequencing compared with parental line. Results were consistent with Menom et al. 2024.[11] In vivo RNA sequencing data showed a positive enrichment of 'Cluster of Terminally Exhausted CD8' for LLC1-IFNγ tumors vs LLC1 parental tumors. (**B**-**C**) Tumor volume growth curve, median terminal tumor volume, and HPK1 levels in spleen lysates from C57BL/6 mice implanted subcutaneously with (**B**) LLC1 or (**C**) LLC1-IFNγ and dosed with vehicle + IgG, ARV-6723 (30 mg/kg PO QD) + IgG, vehicle + anti-PD-1 antibody (10 mg/kg IP BIW), or vehicle + anti-CTLA-4 antibody (10 mg/kg IP BIW) + anti-PD-1 antibody (10 mg/kg IP BIW) during a 14-day study (n=8–10 per group). HPK1 protein levels were normalized to β-actin and GAPDH levels and quantified by targeted mass spectrometry. Quartile analysis was performed to exclude outliers. Percentage values shown are the mean percent change. *P*-values were calculated using a one-way ANOVA with Dunnett's multiple comparisons (mean vs vehicle). **P*<0.05; ***P*<0.01; *****P*<0.0001.

- A mouse model of ICI-resistant lung cancer with a T-cell exhaustion phenotype was developed by chronic in vitro treatment of the LLC1 cell line with IFNγ followed by implantation into mice[11]; bulk RNA-sequencing confirmed an increase in the IFNγ- and IFNα-response gene signature scores in cell lines, and derived tumors showed positive enrichment of terminally exhausted CD8+ cell signatures (Figure 1A)
- ARV-6723 demonstrated significant antitumor activity (TGI: 64%) in the LLC1 parental model (Figure 1B) and the LLC1-IFNγ model (Figure 1C), whereas an anti-PD-1 antibody alone or combined with an anti-CTLA-4 antibody had modest antitumor activity (TGI: 25% and 28%, respectively) in the parental model and minimal activity in the LLC1-IFNγ model (TGI: -11% and 16%, respectively)

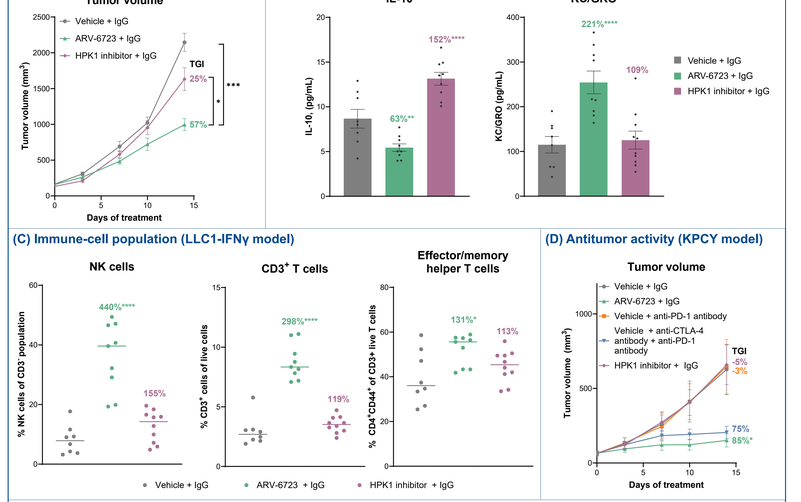
Figure 2: Immunomodulatory effects of ARV-6723 vs anti-PD-1 ± anti-CTLA-4 antibodies in an ICI-resistant lung cancer model of T-cell dysfunction/exhaustion (LLC1-IFNγ)



C57BL/6 mice were implanted subcutaneously with (**A**-**B**) LLC1 or (**C**-**D**) LLC1-IFNγ and dosed with vehicle + IgG, ARV-6723 (30 mg/kg PO QD) + IgG, vehicle + anti-PD-1 antibody (10 mg/kg IP BIW), or vehicle + anti-CTLA-4 antibody (10 mg/kg IP BIW) + anti-PD-1 antibody (10 mg/kg IP BIW) during a 14-day study (n=8–10 per group). Blood was collected at terminal timepoint. Immunophenotypic changes in blood immune cells were characterized by flow cytometry (**A**, **C**), and plasma cytokine and chemokine analysis was performed by Meso Scale Discovery V-PLEX mouse kit. (**B**,**D**). Percentage values shown are the mean percent difference compared with the vehicle group. Quartile analysis was performed to exclude outliers. *P*-values were determined by a one-way ANOVA with Dunnett's multiple comparisons (mean vs vehicle). **P*<0.05; ***P*<0.01; ****P*<0.001; *****P*<0.0001.

- Flow cytometric immunophenotyping of peripheral blood in LLC1 parental and LLC1-IFNγ models revealed consistent changes following ARV-6723 treatment compared with ICI treatment, including increases in the proportions of effector/memory cytotoxic and helper T cells and proliferating NK cells (Figure 2A and 2C), demonstrating persistence of these antitumor immune-cell types
- Cytokine analysis showed an increase in proinflammatory cytokines (IL-5 and KC/GRO) and a decrease in an anti-inflammatory cytokine (IL-10) following ARV-6723 treatment across both models (Figure 2B and 2D)

Figure 3: Antitumor activity and immunomodulatory effects of ARV-6723 vs an investigational HPK1 inhibitor in an ICI-resistant lung cancer model of T-cell dysfunction/exhaustion (LLC1-IFNγ), and antitumor activity in an ICI-resistant pancreatic cancer model of T-cell exclusion/low T-cell infiltration (KPCY)



(**A**) Tumor volume growth curve from C57BL/6 mice implanted subcutaneously with LLC1-IFNγ and dosed with vehicle + IgG, ARV-6723 (30 mg/kg PO QD) + IgG, or HPK1 inhibitor (75 mg/kg PO BID) + IgG during a 14-day study (n=8–10 per group). Blood was collected at terminal timepoint. (**B**) A subset of the blood was used for flow cytometry to characterize immunophenotypic changes. Percentage values shown are the mean percent difference compared with the vehicle group. *P*-values were adjusted for multiple comparisons using Tukey's method. **P*<0.05; ***P*<0.01; ****P*<0.001; *****P*<0.0001. (**D**) Tumor volume growth curve from C57BL/6 mice implanted subcutaneously with KPCY clone #2699 and dosed with vehicle + IgG, ARV-6723 (30 mg/kg PO QD) + IgG, vehicle + anti-PD-1 antibody (10 mg/kg IP BIW), vehicle + anti-CTLA-4 antibody (10 mg/kg IP BIW) + anti-PD-1 antibody (10 mg/kg IP BIW), or HPK1 inhibitor (75 mg/kg PO BID) + IgG during a 14-day study (n=8–10 per group). Quartile analysis was performed to exclude outliers. *P*-values were calculated using a one-way ANOVA with Dunnett's multiple comparisons (mean vs vehicle). **P*<0.05.

- ARV-6723 demonstrated significantly greater antitumor activity than an investigational HPK1 inhibitor in the LLC1-IFNγ model (TGI: 57% vs 25%; Figure 3A)
- ARV-6723 treatment induced proinflammatory effects on cytokine levels (Figure 3B) and peripheral immune-cell populations (Figure 3C) that were not observed with HPK1 inhibition
- Single-agent ARV-6723 demonstrated increased antitumor efficacy in an ICI-resistant pancreatic cancer model (KPCY) vs the investigational HPK1 inhibitor (TGI: 85% vs -5%), had similar activity to combination treatment with an anti-PD-1 antibody plus an anti-CTLA-4 antibody treatment (TGI: 75%; Figure 3D), and was accompanied by a significant reduction (-78%) in HPK1 protein levels in spleen (data not shown), consistent with the PROTAC mechanism of action and previous work[12]

Conclusions

- In ICI-resistant lung cancer models, ARV-6723 demonstrated greater antitumor activity than standard-of-care ICI (anti-PD-1 antibody alone or in combination with an anti-CTLA-4 antibody) or an investigational HPK1 inhibitor, with enhanced activity linked to distinct proinflammatory changes in cytokines and peripheral immune-cell populations
  - These findings indicate that PROTAC-mediated deep and sustained HPK1 degradation, unlike inhibition, boosts innate and adaptive immune activity even in the setting of T-cell exhaustion
- ARV-6723 demonstrated more robust antitumor activity than single-agent ICI (anti-PD-1 antibody) or an investigational HPK1 inhibitor in an ICI-resistant pancreatic cancer model characterized by T-cell exclusion and low T-cell infiltration
- These data highlight the potential for ARV-6723 to overcome ICI resistance, supporting its future investigation alone or in combination with ICIs in patients with solid tumors

Abbreviations

ANOVA=analysis of variance
BID=twice daily
BIW=twice weekly
CD=cluster of differentiation
CTLA-4=cytotoxic T-lymphocyte–associated protein 4
DMSO=dimethyl sulfoxide
FDR=false discovery rate
GAPDH=glyceraldehyde 3-phosphate dehydrogenase
GRO=growth-related oncogene
GSEA=gene set enrichment analysis
HPK1=hematopoietic progenitor kinase 1
ICI=immune checkpoint inhibitor
IFN=interferon
IgG=immunoglobulin
IL=interleukin
IP=intraperitoneally
KC=keratinocyte-derived chemokine
LLC1=Lewis lung carcinoma 1
NES=normalized enrichment score
NK=natural killer
PD-1=programmed cell death 1
PO=orally
PROTAC=PROteolysis TArgeting Chimera
pSLP76=phosphorylated SH2 domain-containing leukocyte protein of 76 kDa
TCR=T-cell receptor
TGI=tumor growth inhibition

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