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Trial in Progress: A Phase 1/2 Open-label Study of ARV-6723, an Oral PROTAC HPK1 Degrader, as Monotherapy or in Combination With an Anti-PD-1 Antibody in Patients With Advanced Solid Tumors

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Objective

To evaluate ARV-6723, a PROTAC HPK1 degrader, as monotherapy and in combination with an anti-PD-1 antibody in patients with advanced solid tumors and prior exposure to IO therapy

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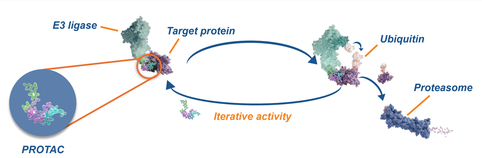
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Background

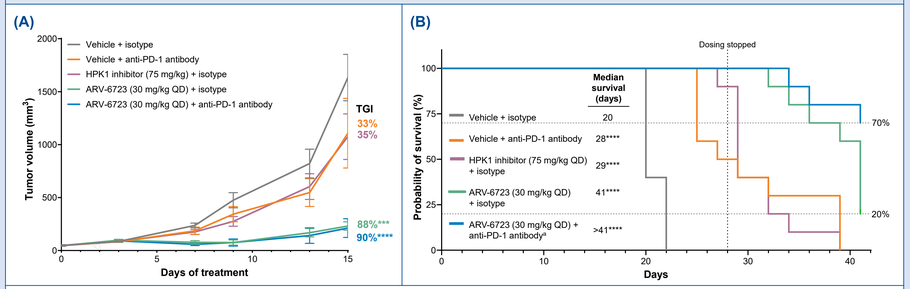
- Although ICIs have transformed the treatment paradigm for advanced solid tumors, only a subset of patients respond and most eventually develop treatment resistance
- Many IO strategies have been tried and failed to demonstrate meaningful clinical benefit in patients with ICI-resistant tumors, highlighting the need for new approaches to overcome resistance[1]
- HPK1 (encoded by *MAP4K1*) is a multifunctional signaling protein that regulates adaptive and innate immune cell activation through kinase-dependent and kinase-independent scaffolding mechanisms, serving as a critical negative regulator of T-cell, B-cell, dendritic-cell, and natural killer-cell signaling and antitumor immune responses[2,3]
- ARV-6723, a potent, selective, oral PROTAC HPK1 degrader, forms a trimer complex with HPK1 and an E3 ubiquitin ligase, inducing HPK1 ubiquitination and proteasomal degradation (**Figure 1**)
- ARV-6723, alone or combined with an anti–PD-1 antibody, demonstrated greater antitumor activity than anti–PD-1 monotherapy or an investigational HPK1 inhibitor in preclinical models (**Figure 2**)[4]
  - In the highly immunogenic CT26 syngeneic mouse model, CRs occurred in 5 of 10 mice treated with ARV-6723 combined with an anti-PD-1 antibody vs 0 of 10 mice treated with anti-PD-1 antibody alone and led to immunological memory[4]

Figure 1: PROTAC mechanism of action



- In several ICI-resistant mouse models characterized by T-cell dysfunction, exhaustion, or exclusion, ARV-6723 monotherapy demonstrated greater antitumor activity than an anti–PD-1 antibody or an investigational HPK1 inhibitor and induced distinct proinflammatory effects across innate and adaptive immune-cell populations[4-6]
- These preclinical findings support the clinical investigation of ARV-6723, alone or in combination with ICIs, as a novel IO approach to overcoming ICI resistance

Figure 2: ARV-6723 efficacy in highly immunogenic CT26 syngeneic colon cancer model[4]



BALB/c mice were implanted subcutaneously with CT26 syngeneic tumor line; tumors were given time to establish, and then mice were randomized to receive listed treatment. (**A**) Mice were dosed with specified treatment for 15 days; tumor volumes were measured twice weekly and percentage TGI was calculated. (**B**) Mice were continually dosed with specified treatment until day 28 post-randomization when treatments were discontinued; survival was assessed using maximum allowable tumor volume as a surrogate for death and median survival was calculated. ***P<0.001 and ****P<0.0001 by 1-way ANOVA.
[a]Figure has been updated from its original presentation[4] to show data for the cohort treated with ARV-6723 in combination with an anti-PD-1 antibody.

Study Design

- This multicenter, first-in-human study (NCT07749586) will evaluate ARV-6723 as monotherapy and in combination with an anti-PD-1 antibody in patients with advanced solid tumors and prior ICI exposure
- Key eligibility criteria are listed in **Table 1**

Table 1: Key eligibility criteria[a]

Inclusion criteria

- Adults aged ≥18 years with unresectable or metastatic solid tumors
- Prior treatment with ≥1 ICI or T-cell costimulatory agent
- Radiographic disease progression
- ≥1 measurable lesion (RECIST v1.1)
- ECOG PS 0–1[b]
- Adequate bone marrow, renal, and hepatic function

Exclusion criteria

- Active brain metastases or carcinomatous meningitis; treated brain metastases permitted if stable
- Active or potentially relapsing autoimmune disease requiring immunosuppression
- Prior severe, unresolved, or high-risk immune-related adverse events
- Clinically significant pulmonary disease, including interstitial lung disease/pneumonitis or impaired pulmonary function
- Recent or clinically significant cardiovascular, cerebrovascular, bleeding, or pancreatic disease
- Active uncontrolled infection
- Prior HPK1-targeted therapy or allogeneic stem-cell/organ transplantation

[a]This is not the complete list of inclusion/exclusion criteria.
[b]ECOG PS 2 may be permitted after discussion with the sponsor.

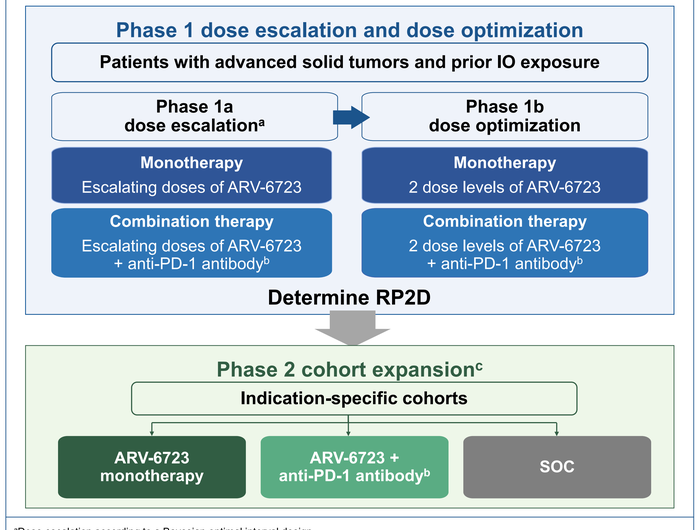
- In phase 1a, patients will receive escalating oral doses of ARV-6723 as monotherapy or in combination with an approved anti-PD-1 antibody to identify 2 doses for phase 1b optimization (**Figure 3**)
- The phase 2 portion will further evaluate ARV-6723 alone, ARV-6723 in combination with anti-PD-1 therapy, and/or SOC therapy in selected solid tumors
- Primary, secondary, and exploratory outcome measures are listed in **Table 2**

Table 2: Outcome measures

Endpoints	Phase 1a	Phase 1b	Phase 2
Primary	• DLTs • Safety and tolerability	• Safety and tolerability • ORR per RECIST v1.1[a]	• ORR per RECIST v1.1[a]
Secondary	• Pharmacokinetics • ORR, and DCR per RECIST v1.1 and iRECIST[a]	• ORR per iRECIST[a] • DCR per RECIST v1.1 and iRECIST[a]	• ORR per iRECIST[a] • PFS, TTR, and DOR per RECIST v1.1 and iRECIST[a] • Safety and tolerability
Exploratory	• PFS, TTR, and DOR per RECIST v1.1 and iRECIST[a] • Overall survival • Pharmacodynamic biomarkers (eg, change in HPK1 protein levels in PBMCs and tumor tissue)		• Overall survival • Biomarkers • Plasma concentrations of ARV-6723

[a]Responses assessed by CT/MRI per investigator assessment.

Figure 3: Trial schema



[a]Dose escalation according to a Bayesian optimal interval design.
[b]An approved anti-PD-1 antibody to be administered at the standard dose and schedule.
[c]Patients will be randomized to one of the following treatment arms: ARV-6723 monotherapy, ARV-6723 + anti-PD-1 antibody, or SOC.

Study Status

- Enrollment is currently ongoing
- To view currently recruiting sites, visit clinicaltrials.gov (NCT07749586)

Scan this QR code to view the clinicaltrials.gov page for this study.

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Abbreviations
CT=computed tomography; DCR=disease control rate; DLT=dose-limiting toxicity; DOR=duration of response; ECOG PS=Eastern Cooperative Oncology Group performance status; HPK1=hematopoietic progenitor kinase 1; ICI=immune checkpoint inhibitor; IO=immuno-oncology; iRECIST=immune Response Evaluation Criteria in Solid Tumors; MAP4K1=mitogen-activated protein kinase kinase kinase kinase 1; MRI=magnetic resonance imaging; ORR=objective response rate; PBMC=peripheral blood mononuclear cell; PD-1=programmed cell death protein 1; PFS=progression-free survival; PROTAC=proteolysis-targeting chimera; QD=once daily; RECIST=Response Evaluation Criteria in Solid Tumors; RP2D=recommended phase 2 dose; SOC=standard of care; TTR=time to response.

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