

# KRYSTAL-16: A Phase 1/1b Trial of Adagrasib (MRTX849) in Combination with Palbociclib in Patients with Advanced Solid Tumors with KRAS<sup>G12C</sup> Mutation

Poster # CT242

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\*Weining Volinn is replacing Xuesong Guan, who we acknowledge for contributions to the abstract.

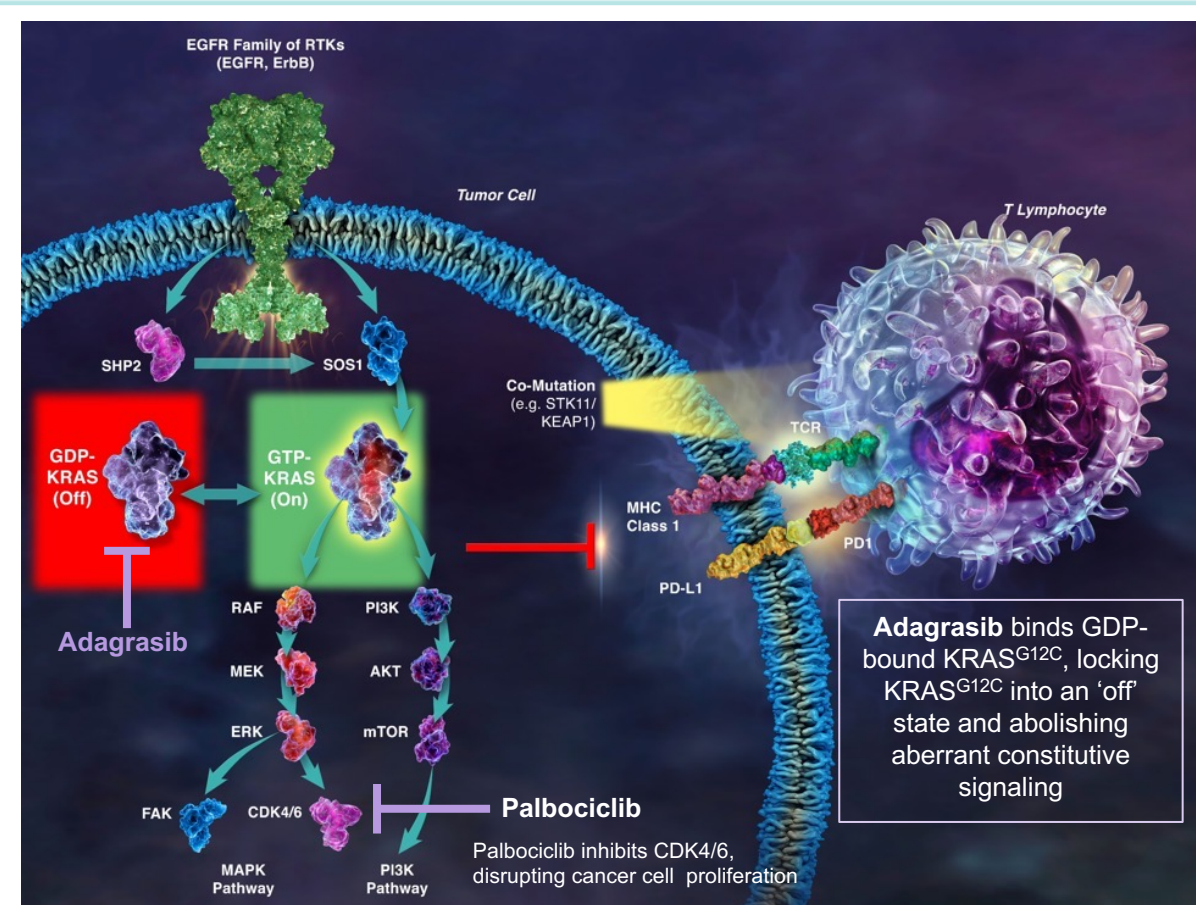
## Background

- KRAS is the most frequently mutated oncogene in cancer and is a key mediator of the RAS/MAPK signaling cascade promoting cellular growth and proliferation<sup>1</sup>
- KRAS<sup>G12C</sup> mutations occur in ~14% of non-small cell lung cancer (NSCLC), 3–5% of colorectal cancer (CRC), and 1–2% of other tumors<sup>2,3</sup>
- Adagrasib, an investigational agent, is a potent, covalent inhibitor of KRAS<sup>G12C</sup> that irreversibly and selectively binds to KRAS<sup>G12C</sup> and locks it in its inactive state (Figure 1)<sup>4,5</sup>
- Adagrasib was optimized for desired biochemical and pharmacokinetic (PK) properties, including:
  - Potent inhibition of KRAS<sup>G12C</sup> (cellular IC<sub>50</sub>: ~5–14 nM)<sup>4,5</sup>
  - High selectivity (>1000X) for the mutant KRAS<sup>G12C</sup> protein vs wild type KRAS<sup>4</sup>
  - Long half-life (~24 h),<sup>4,5</sup> dose-dependent PK,<sup>4,6</sup> and central nervous system penetration<sup>6</sup>
- Palbociclib, a CDK4/6 inhibitor, disrupts cancer cell proliferation by preventing the G1 to S phase transition, inducing cell-cycle arrest<sup>7</sup>

## Adagrasib Monotherapy

- Initial results from KRYSTAL-1, a phase 1/2 study, demonstrated the preliminary antitumor activity and tolerability of adagrasib monotherapy across multiple tumor types harboring KRAS<sup>G12C</sup> mutations, including patients with NSCLC previously treated with at least 1 standard therapy<sup>6</sup>
  - In patients with NSCLC, the confirmed objective response rate (ORR) was 45%, and clinical benefit (disease control) was observed in 96% of patients<sup>6</sup>
  - In patients with CRC, the confirmed ORR was 22%, and clinical benefit was observed in 87% of patients<sup>8</sup>
  - In patients with other gastrointestinal (GI) cancers, the ORR was 41% (50% in pancreatic ductal adenocarcinoma, 35% in other GI cancers); the disease control rate was 100%<sup>9</sup>
- In a safety analysis of patients (n=110) from KRYSTAL-1, adagrasib was well tolerated, with a low incidence of grade 3–4 treatment-related adverse events (TRAEs)<sup>6</sup>
  - The most common TRAEs included nausea, diarrhea, vomiting, and fatigue

Figure 1. Mechanism of Action of Adagrasib and Palbociclib<sup>10</sup>



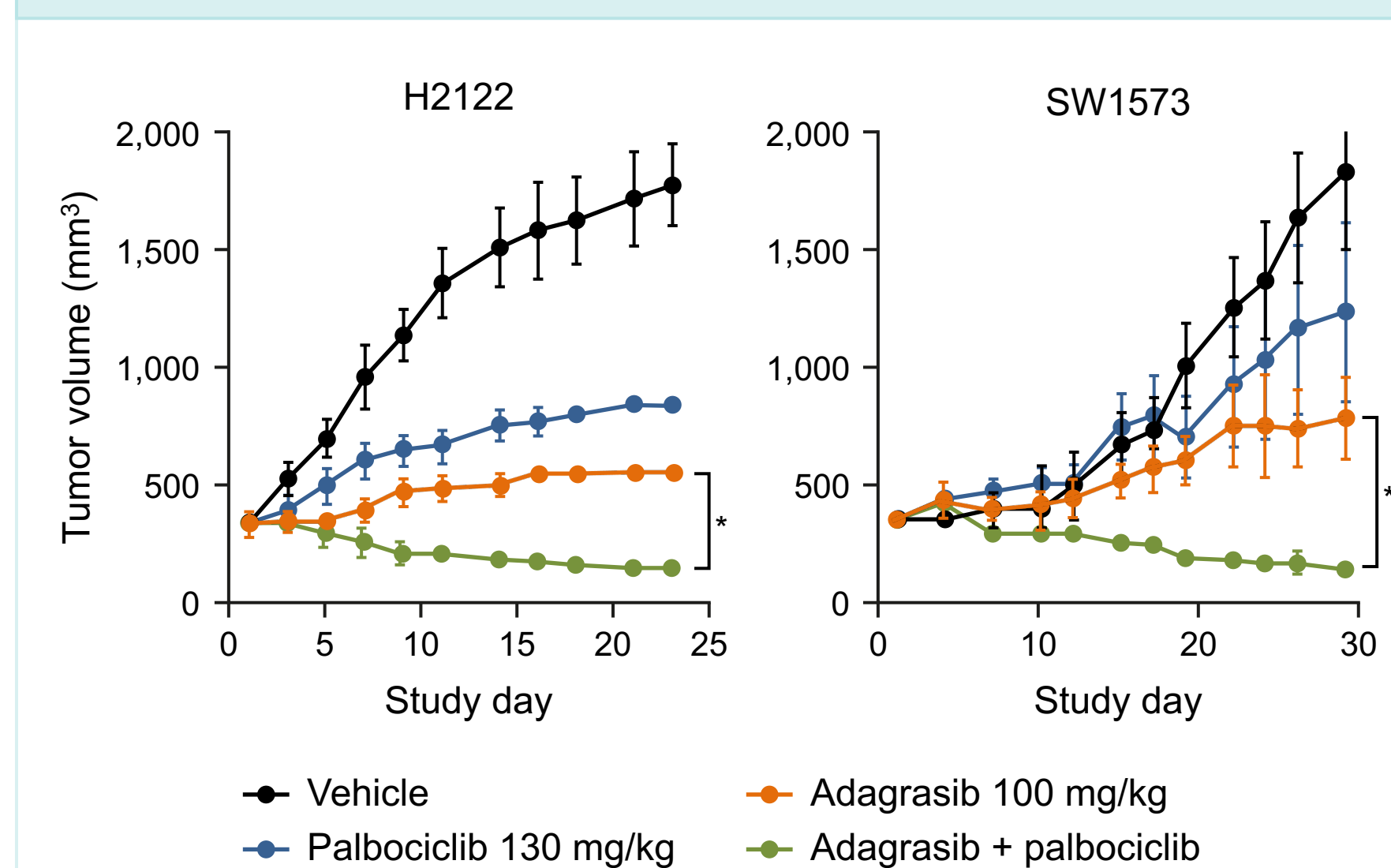
AKT, gene on chromosome 14q32.32/14q32.32 that encodes protein kinase B; CDK4/6, cyclin-dependent kinase 4/6; EGFR, epidermal growth factor receptor; ERK, extracellular signal-regulated kinase; FAK, focal adhesion kinase; GDP, guanosine diphosphate; GTP, guanosine triphosphate; HP2, Src homology phosphatase 2; KEAP1, Kelch-like ECH-associated protein 1; KRAS, Kirsten rat sarcoma; MAPK, mitogen-activated protein kinase; MEK, mitogen-activated protein kinase Ketch; MHC, major histocompatibility complex; mTOR, mechanistic target of rapamycin; PD-1, programmed cell death protein 1; PD-L1, programmed cell death-ligand 1; PI3K, phosphatidylinositol-3-kinase; RAF, rapidly accelerating fibrosarcoma; RTK, receptor tyrosine kinase; SOS1, son of sevenless isoform 1; STK11, serine/threonine kinase 11.

## Background

### Rationale for Combining Adagrasib and Palbociclib

- Cyclin D1 and CDK4/6 are downstream of signaling pathways that lead to cellular proliferation<sup>1,11</sup>
- Signaling through KRAS is known to mediate cell proliferation partly through regulation of the Cyclin D family and RB/E2F-dependent entry of cells into the cell cycle<sup>11</sup>
- Preclinical data in KRAS<sup>G12C</sup> mouse models of NSCLC suggested increased antitumor activity when adagrasib and palbociclib were combined compared with either agent as monotherapy (Figure 2)<sup>4</sup>

Figure 2. Preclinical Experiments on the Combination of Adagrasib and Palbociclib in Mouse Models<sup>4</sup>



\*Adjusted  $p < 0.05$ .  
Reprinted from Cancer Discovery, 2020, 10/1, 54–71, Hallin et al. The KRASG12C Inhibitor MRTX849 Provides Insight toward Therapeutic Susceptibility of KRAS-Mutant Cancers in Mouse Models and Patients, with permission from AACR

## Methods

### Study Design

- KRYSTAL-16 (NCT05178888) is a multicenter, open-label study evaluating the safety, PK, pharmacodynamics (PD) and preliminary clinical activity of the combination of adagrasib and palbociclib in patients with advanced solid tumors with a KRAS<sup>G12C</sup> mutation (Figure 3)
- Approximately 50 patients will be enrolled in 2 phases:
  - PK lead-in
  - Dose escalation using the modified Toxicity Probability Interval (mTPI-2) design

### Primary Endpoints

- Safety and tolerability of adagrasib in combination with palbociclib
- PK of adagrasib and palbociclib in combination
- Maximum tolerated dose (MTD) and/or recommended phase 2 dose (RP2D) of the combination

## Methods

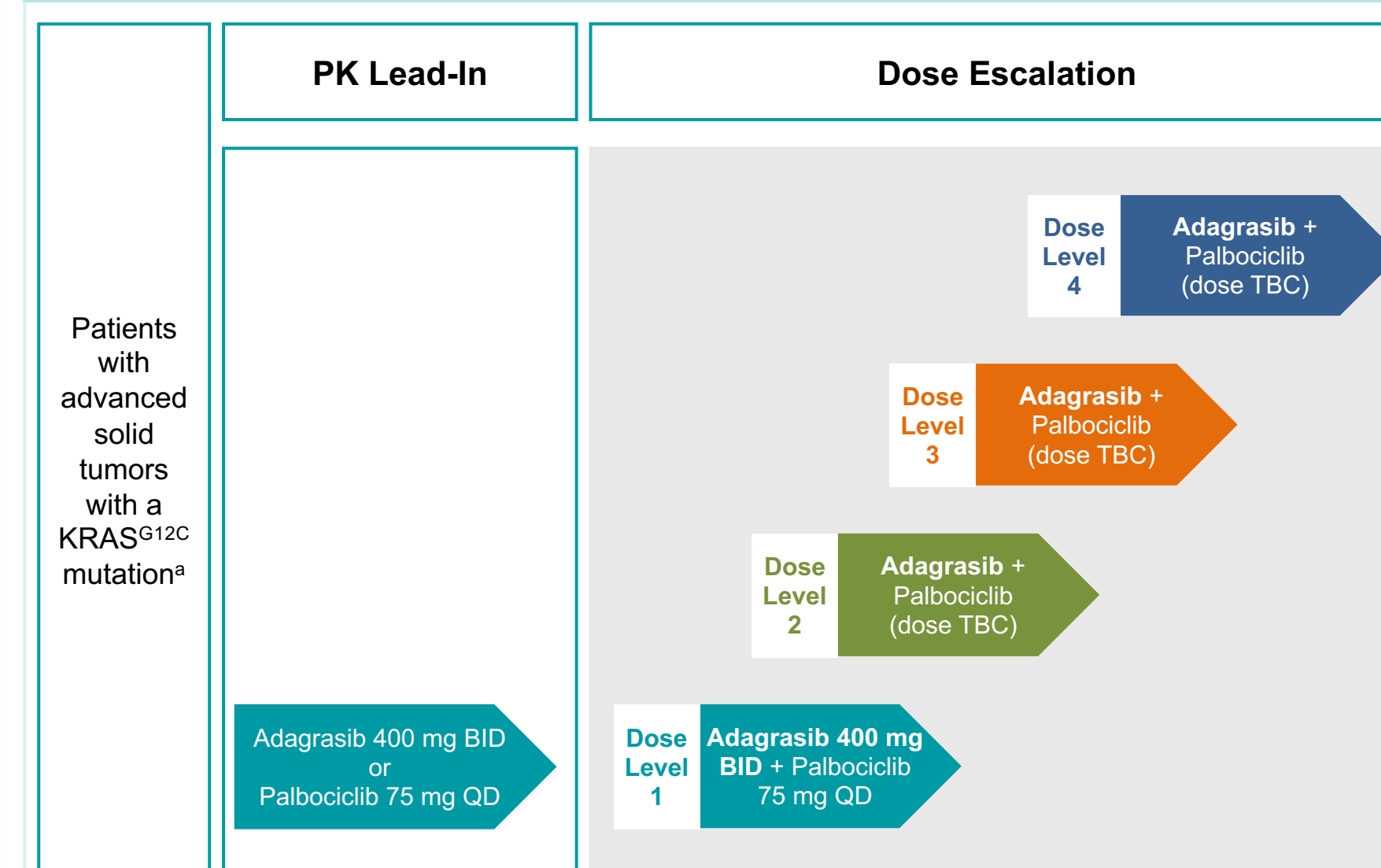
### Secondary Endpoints

- Clinical activity, including ORR, duration of response (DOR), progression-free survival (PFS), and overall survival (OS)

### Exploratory Endpoints

- PD parameters of KRAS and/or CDK4/6 inhibition
- Dynamics of gene alterations in tumor tissue and circulating tumor DNA (ctDNA)

Figure 3. KRYSTAL-16 Study Design



\*Detected in tumor tissue or ctDNA.  
BID, twice daily; ctDNA, circulating tumor DNA; PK, pharmacokinetics; QD, once daily.  
Adagrasib is given orally in a continuous dosing regimen; palbociclib is given orally in a 21 days on/7 days off regimen. Patients will receive study treatment at the discretion of the Investigator until disease progression, unacceptable adverse events, patient refusal, or death.

### Key Inclusion Criteria

- Histologically confirmed diagnosis of unresectable or metastatic solid tumor malignancy with KRAS<sup>G12C</sup> mutation
- At least 1 prior treatment for advanced or metastatic disease, with no further available treatment with curative intent
- Age ≥18 years and Eastern Cooperative Oncology Group performance status (ECOG PS) 0 or 1

### Key Exclusion Criteria

- History of significant or intolerable toxicity on prior CDK4/6 or KRAS<sup>G12C</sup> inhibitor
- Active brain metastases, unless adequately treated and neurologically stable, or carcinomatous meningitis

### Assessments

- Tumor assessments will be performed at 6-week intervals
- Adverse events (AEs) will be monitored throughout the study and graded according to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), version 5.0

## Methods

### Statistical Methods: Dose Escalation

- mTPI-2 design:<sup>12</sup> dose escalation steps for adagrasib and palbociclib will proceed until the MTD and/or RP2D for the combination is established (Figure 3)
- Dose level cohorts in the mTPI-2 model will include at least 3 patients

## Trial Progress

- The study is recruiting with 4 sites currently open in the United States: MD Anderson Cancer Center, Houston, TX; NEXT Oncology, San Antonio, TX; Sarah Cannon Research Institute, Nashville, TN; and Florida Cancer Specialists, Lake Nona, FL
- An additional 3 sites are planned

## Summary

- Adagrasib is a covalent inhibitor of KRAS<sup>G12C</sup> that irreversibly and selectively binds KRAS<sup>G12C</sup> and locks it in its inactive, GDP-bound state
- Palbociclib is a CDK4/6 inhibitor that induces cell cycle arrest in cancer cells
- The combination of adagrasib and palbociclib has been shown to increase antitumor activity in mouse models of KRAS<sup>G12C</sup>-mutated NSCLC
- KRYSTAL-16 is a multicenter, open-label, phase 1/1b study to evaluate the safety, PK, and preliminary clinical activity of the combination of adagrasib and palbociclib in patients with advanced solid tumors with a KRAS<sup>G12C</sup> mutation
- Clinical trial registry number: NCT05178888

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## Acknowledgments

- The clinical study teams for their work and contributions
- This study is sponsored by Mirati Therapeutics, Inc.
- All authors contributed to and approved this presentation; writing and editorial assistance were provided by Charlotte Kennerley, PhD, of Ashfield MedComms, an Ashfield Health company, funded by Mirati Therapeutics, Inc.

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