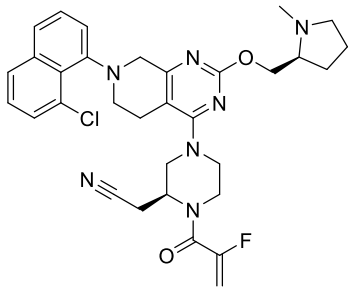
Product data sheet

MedKoo Cat#: 207112 Name: MRTX849 CAS#: 2326521-71-3 Chemical Formula: $C_{32}H_{35}ClFN_7O_2$ Exact Mass: 603.2525 Molecular Weight: 604.13	
Product supplied as:	Powder
Purity (by HPLC):	≥ 98%
Shipping conditions	Ambient temperature
Storage conditions:	Powder: -20°C 3 years; 4°C 2 years.
	In solvent: -80°C 3 months; -20°C 2 weeks.

1. Product description:
Adagrasib, also known as MRTX849, is a potent, highly selective, oral available KRAS G12C inhibitor. MRTX849 maximizes inhibition by irreversibly locking the KRAS molecule in its inactive state, thereby preventing tumor cell growth which results in tumor cell death. MRTX849 exhibited significantly improved half-life and penetration into the tumor, shutting down KRAS signaling for the entire dosing interval, and showing a higher degree of antitumor activity than previous KRAS mutant-selective inhibitors.

2. CoA, QC data, SDS, and handling instruction
SDS and handling instruction, CoA with copies of QC data (NMR, HPLC and MS analytical spectra) can be downloaded from the product web page under "QC And Documents" section. Note: copies of analytical spectra may not be available if the product is being supplied by MedKoo partners. Whether the product was made by MedKoo or provided by its partners, the quality is 100% guaranteed.

3. Solubility data

Solvent	Max Conc. mg/mL	Max Conc. mM
DMSO	1.0	1.7

4. Stock solution preparation table:

Concentration / Solvent Volume / Mass	1 mg	5 mg	10 mg
1 mM	1.66 mL	8.28 mL	16.55 mL
5 mM	0.33 mL	1.66 mL	3.31 mL
10 mM	0.17 mL	0.83 mL	1.66 mL
50 mM	0.03 mL	0.17 mL	0.33 mL

5. Molarity Calculator, Reconstitution Calculator, Dilution Calculator
Please refer the product web page under section of "Calculator"

6. Recommended literature which reported protocols for in vitro and in vivo study
In vitro study

1. Hallin J, Engstrom LD, Hargis L, Calinisan A, Aranda R, Briere DM, Sudhakar N, Bowcut V, Baer BR, Ballard JA, Burkard MR, Fell JB, Fischer JP, Vigers GP, Xue Y, Gatto S, Fernandez-Banet J, Pavlicek A, Velastagui K, Chao RC, Barton J, Pierobon M, Baldelli E, Patricoin EF 3rd, Cassidy DP, Marx MA, Rybkin II, Johnson ML, Ou SI, Lito P, Papadopoulos KP, Jänne PA, Olson P, Christensen JG. The KRASG12C Inhibitor MRTX849 Provides Insight toward Therapeutic Susceptibility of KRAS-Mutant Cancers in Mouse Models and Patients. Cancer Discov. 2020 Jan;10(1):54-71. doi: 10.1158/2159-8290.CD-19-1167. Epub 2019 Oct 28. PMID: 31658955; PMCID: PMC6954325.

In vivo study

1. Hallin J, Engstrom LD, Hargis L, Calinisan A, Aranda R, Briere DM, Sudhakar N, Bowcut V, Baer BR, Ballard JA, Burkard MR, Fell JB, Fischer JP, Vigers GP, Xue Y, Gatto S, Fernandez-Banet J, Pavlicek A, Velastagui K, Chao RC, Barton J, Pierobon M, Baldelli E, Patricoin EF 3rd, Cassidy DP, Marx MA, Rybkin II, Johnson ML, Ou SI, Lito P, Papadopoulos KP, Jänne PA, Olson P, Christensen JG. The KRASG12C Inhibitor MRTX849 Provides Insight toward Therapeutic Susceptibility of KRAS-Mutant Cancers in Mouse Models and Patients. Cancer Discov. 2020 Jan;10(1):54-71. doi: 10.1158/2159-8290.CD-19-1167. Epub 2019 Oct 28. PMID: 31658955; PMCID: PMC6954325.

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7. Bioactivity

Biological target:

MRTX849 is a potent, orally-available, and mutation-selective covalent inhibitor of KRAS G12C with potential antineoplastic activity.

In vitro activity

To evaluate the breadth of MRTX849 activity, its effect on cell viability was determined across a panel of 17 KRASG12C-mutant and three non-KRASG12C-mutant cancer cell lines using 2D (3-day, adherent cells) and 3D (12-day, spheroids) cell growth conditions. MRTX849 potently inhibited cell growth in the vast majority of KRASG12C-mutant cell lines with IC50 values ranging between 10 and 973 nM in the 2D format and between 0.2 and 1042 nM in the 3D format (Table S4 and Figure 1F). In agreement with prior KRASG12C inhibitor studies [5], MRTX849 demonstrated improved potency in the 3D assay format, as all but one KRASG12C-mutant cell line exhibited an IC50 value below 100 nM. Although MRTX849 was broadly effective in inhibiting viability of KRASG12C-mutant cell lines, IC50 values varied across the cell panel by 100-fold suggesting a differential degree of sensitivity to treatment. All three non-KRASG12C-mutant cell lines tested demonstrated IC50 values greater than 1 μM in 2D conditions and greater than 3 μM in 3D conditions suggesting the effect of MRTX849 on cell viability was dependent on the presence of KRASG12C. To determine if the difference in sensitivity across the cell panel correlated with the ability of MRTX849 to bind to KRAS or inhibit KRAS-dependent signal transduction, seven KRASG12C-mutant cancer cell lines were selected from the panel for further evaluation. In each cell line, MRTX849 demonstrated a very similar concentration-dependent electrophoretic mobility shift (IC50) for KRASG12C protein migration suggesting that the ability to bind to and modify KRASG12C does not readily account for differences in response in viability studies (Figure 1B, ,1C,1C, S1B, S1C, S2A, and S2B). The effect of MRTX849 on selected phospho-proteins implicated in mediating KRAS-dependent signaling was also evaluated across the cell panel by immunoblot and/or reverse phase protein array (RPPA) following treatment for 6 or 24 hours. Notably, the concentration-response relationship and maximal effect of MRTX849 on inhibition of ERK and S6S235/236 phosphorylation varied across the cell panel (Figure S2A, S2C and Table S7). MRTX849 demonstrated only partial inhibition of phosphorylated ERK in KYSE-410 and SW1573 and a minimal effect on pS6S235/236 in SW1573, H2030, and KYSE-410 cells (Figure S2A and S2C). Each of these cell lines were among those that exhibited a submaximal response to MRTX849 in both 2D and 3D viability assays (Figure 1F). Although KRAS is implicated in mediating signal transduction through the PI3 Kinase and mTOR pathways, there was minimal evidence of a significant and/or durable effect of MRTX849 on Akt (S473, T308) or 4E-BP-1 (T37/T46, S65, T70) phosphorylation at any time point in any cell lines evaluated (Figure S2D). However, MRTX849 demonstrated concentration-dependent partial inhibition of the mTOR-dependent signaling targets, p70 S6 kinase (T412) and/or pS6 (S240/44), in the H358, MIA PaCa-2, H2122, and H1373 cell lines; each of which exhibited a maximal response to treatment.

Reference: Cancer Discov. 2020 Jan;10(1):54-71. https://www.ncbi.nlm.nih.gov/pmc/articles/pmid/31658955/

In vivo activity

Studies were conducted to evaluate MRTX849 anti-tumor activity along with its pharmacokinetic and pharmacodynamic properties in vivo both to understand the clinical utility of this agent and to provide insight toward response to treatment. MRTX849 demonstrated moderate plasma clearance and prolonged half-life following oral administration (Table S1 and Figure S3). To evaluate the pharmacodynamic response to MRTX849 and to correlate drug exposure with target inhibition, MRTX849 was administered via oral gavage over a range of dose levels to H358 xenograft-bearing mice, and plasma and tumors were collected at defined time points. The fraction of covalently-modified KRASG12C protein was proportional to the plasma concentration of MRTX849 (Figure 2A). When evaluated over time after a single oral dose at 30 mg/kg the modified fraction of KRASG12C was 74% at 6 hours post-dose and gradually decreased to 47% by 72 hours (Figure 2B). This extended pharmacodynamic effect, despite declining levels of MRTX849 in plasma, was consistent with the irreversible inhibition of KRASG12C by MRTX849 and the relatively long half-life for the KRASG12C protein (~24 – 48 hours) (Table S5). The modification of KRASG12C was maximized after repeated daily dosing for 3 days at 30 mg/kg (Figure 2B) and higher dose levels did not demonstrate additional KRASG12C modification in multiple tumor models (data not shown). The maximum level of modification of ~80%, despite increasing dose and plasma levels of MRTX849 suggests that accurate measurement of complete inhibition of KRASG12C utilizing LCMS may not be attainable potentially due to a pool of active, non-cycling, or unfolded KRASG12C protein in tumors. Together, these studies demonstrated a dose-dependent increase in covalent modification of KRASG12C by MRTX849 and that the majority of targetable KRAS was covalently modified by MRTX849 over a repeated administration schedule at dose levels at or exceeding 30 mg/kg.

Reference: Cancer Discov. 2020 Jan;10(1):54-71. https://www.ncbi.nlm.nih.gov/pmc/articles/pmid/31658955/

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Note: The information listed here was extracted from literature. MedKoo has not independently retested and confirmed the accuracy of these methods. Customer should use it just for a reference only.