Supporting Information

Discovery of (*S*)-1-(1-(4-Chloro-3-fluorophenyl)-2-hydroxyethyl)-4-(2-((1-methyl-1*H*-pyrazol-5-yl)amino)pyrimidin-4-yl)pyridin-2(1*H*)-one (GDC-0994), an Extracellular Signal-Regulated Kinase 1/2 (ERK1/2) Inhibitor in Early Clinical Development

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Contents: Experimental procedures for the crystal structure determination of ERK2 and CDK2 complexes with **22**.

Crystal structure determination

The diffraction data set of ***22*** with ERK2 was collected at Advanced Light Source beamline 5.0.1. The diffraction data set of ***22*** with CDK2 was collected at Advanced Phonto Source beamline 22ID. The data set was processed with the HKL2000 package (Z. Otwinowski and W. Minor, " Processing of X-ray Diffraction Data Collected in Oscillation Mode ", Methods in Enzymology, Volume 276: Macromolecular Crystallography, part A, p.307-326, 1997). Data collection and structure refinement statistics are summarized in Tables 1.

The structure of **22** with ERK2 was solved by molecular replacement (MR) with known ERK2 structure (PDB code:1ERK) as the search model using the program Phaser. The structure of **22** with CDK2 was solved by molecular replacement (MR) with known CDK2 structure (PDB code:1AQ1) as the search model using the program Phaser. The structure was further refined with program REFMAC5 (Murshudov GN et al, Acta Crystallogr. D Biol. Crystallogr. 53, 240–255, 1997) and BUSTER (Smart

OS, Womack TO, Flensburg C, Keller P, Paciorek W, Sharff A, Vonrhein C, Bricogne G: Exploiting structure similarity in refinement: automated NCS and target-structure restraints in BUSTER. Acta Crystallogr D Biol Crystallogr 2012, 68:368-380) using the maximum likelihood target functions, anisotropic individual B-factor refinement method, and TLS refinement method, to achieve convergence. The data and refinement statistics are shown in Table S1.

Table S1. X-ray crystallography data processing and structure refinement statistics

	22/CDK2	**22/ERK2**
Space group	$P2_12_12_1$	$P4_12_12$
Unit cell	a=53.6Å,b=71.7Å,c=72.2Å, α= β=γ=90°	a=b=83.2Å,c=274.5Å, α= β=γ=90°
Resolution	1.60 Å	2.57 Å
Total number of reflections	36822 (3640) [a]	31284 (3067) [a]
Completeness (%)	98.4 (98.8)	99.1 (99.9)
Redundancy	4.8 (4.3)	7.2 (7.3)
I/σ	12.7 (3.0)	19.8 (2.4)
Rsym[b]	0.109 (0.493)	0.098 (0.956)
Resolution range	50 – 1.60 Å	50-2.57 Å
Rcryst[c] / Rfree[d]	0.175/0.223	0.210/0.244
Non-hydrogen atoms	2559	5789
Water molecules	237	120

	22/CDK2	**22/ERK2**
Average B, Overall	23.32	82.76
r.m.s.d. bond lengths	0.022 Å	0.009 Å
r.m.s.d. angles	1.889°	1.050°
Ramachandran (C/A/G/D)	0.914/0.078/0.008/0	0.847/0.143/0.007/0.003

[a]Values in parentheses are of the highest resolution shell. [b]Rsym = $\Sigma|I_{hi} - I_h|/\Sigma I_{hi}$, where I_{hi} is the scaled intensity of the *i*th symmetry-related observation of reflection *h* and I_h is the mean value. [c]Rcryst = $\Sigma_h|F_{oh} - F_{ch}| /\Sigma_h F_{oh}$, where F_{oh} and F_{ch} are the observed and calculated structure factor amplitudes for reflection *h*. [d]Value of Rfree is calculated for 5% randomly chosen reflections not included in the refinement.