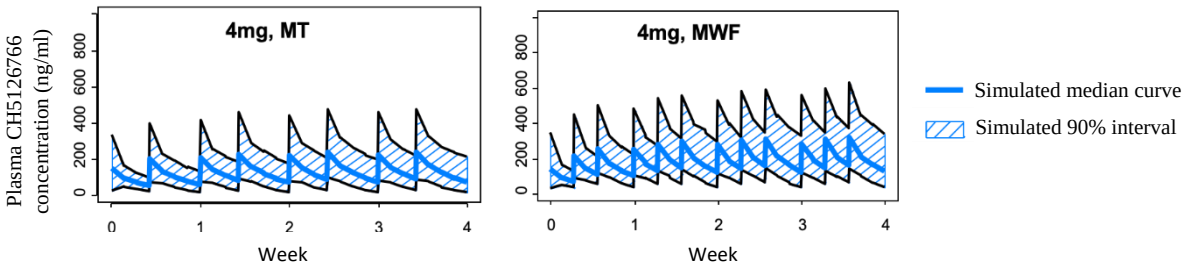
Supplementary Information

Table S1: Prior therapy in patients who achieved partial responses

Tumour type	Mutation	Prior therapy	Number of cycles or duration of treatment	Best response
Non-small cell lung cancer	*KRAS*^{G12V}	Cisplatin + pemetrexed	3 cycles	SD
Non-small cell lung cancer	*KRAS*^{G12R}	Carboplatin + pemetrexed	4 cycles	PR
Non-small cell lung cancer	*KRAS*^{G12V}	Carboplatin + pemetrexed	6 cycles	PR
		Pemetrexed (maintenance)	5 cycles	NA
		Docetaxel	8 cycles	SD
Low-grade serous ovarian cancer	*BRAF*^{V600E}	Carboplatin + paclitaxel	6 cycles	SD
		Letrozole	2 months	PD
		Paclitaxel (weekly)	7 months	PR
		Vemurafenib	17 months	PR
		MEK inhibitor + PI3K inhibitor	9 months	PR
		Paclitaxel + FAS inhibitor	2 months	PD
Endometrial adenocarcinoma	*KRAS*^{G12V}	Carboplatin + paclitaxel	6 cycles	PR
		Anastrazole	1 month	NA
Low-grade serous ovarian cancer	*KRAS*^{G12D}	Carboplatin + paclitaxel	6 cycles	PR
		Liposomal doxorubicin	3 cycles	PD
		Selumetinib + AKT inhibitor	18 months	SD
		MEK inhibitor + PI3K inhibitor	12 months	PR
		Olaparib	7 months	SD
Multiple myeloma (lambda light chain)	*KRAS*^{G12V}	Cyclophosphamide, thalidomide, dexamethasone	2 months	NA
		High-dose melphalan followed by autologous stem cell transplant	NA	NA
		Lenalidomide	3.5 years	PR
		Cyclophosphamide, bortezomib, dexamethasone	5 months	NA
		High-dose melphalan followed by autologous stem cell transplant	NA	NA

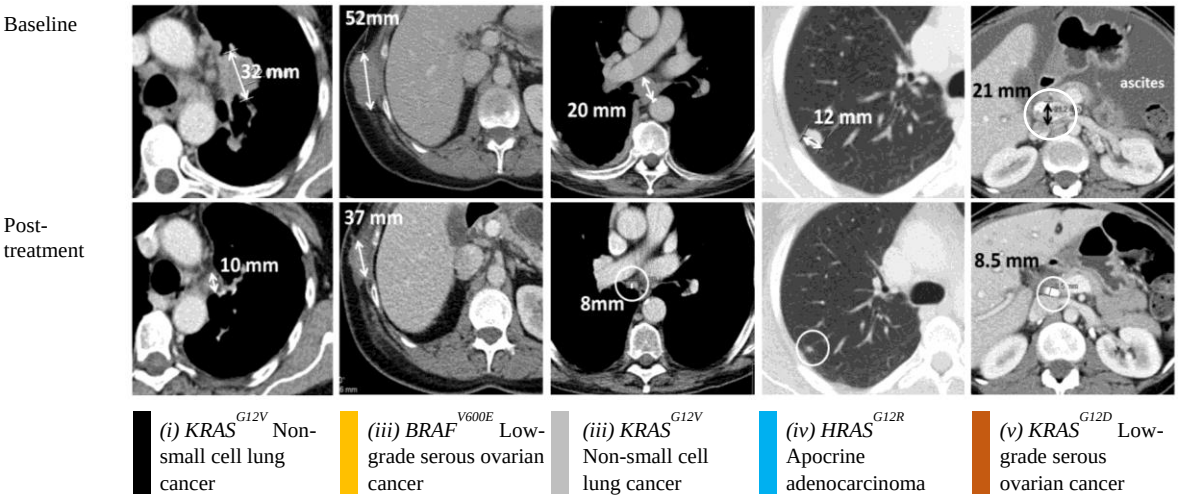
NA = not available

Figure S1: Simulated pharmacokinetics of intermittent dosing schedules.



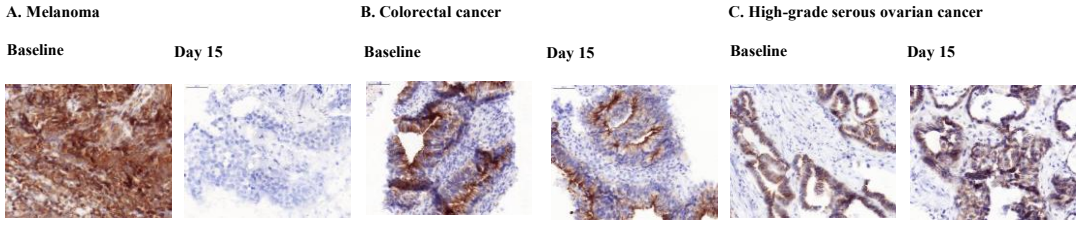
Pharmacokinetics simulation showed that administration of the CH5126766 4·0 mg twice-weekly (Mon/Thu [MT]) or 4·0 mg thrice-weekly (Mon/Wed/Fri [MWF]) achieved similar drug exposure to continuous daily dosing

Figure S2: Radiologic response in long-term responders



Representative computer tomography of responses in all five long-term responders with solid tumours harbouring RAS-RAF-MEK pathway mutations: (i) partial response in a left hilar metastasis of a patient with *KRAS*^{G12V} non-small cell lung cancer after four cycles of treatment; (ii) partial response in a subcutaneous metastasis of a patient with *BRAF*^{V600E} low-grade serous ovarian cancer after four cycles of treatment; (iii) partial response in a mediastinal lymph node of a patient with *KRAS*^{G12V} non-small cell lung cancer after two cycles of treatment; (iv) partial response in a lung metastasis of a patient with *HRAS*^{G12R} apocrine adenocarcinoma of the scalp after two cycles of treatment; (v) partial response in a celiac lymph node and resolution of ascites in a patient with *KRAS*^{G12D} low-grade serous ovarian cancer after 12 cycles of treatment.

Figure S3: Pharmacodynamic studies



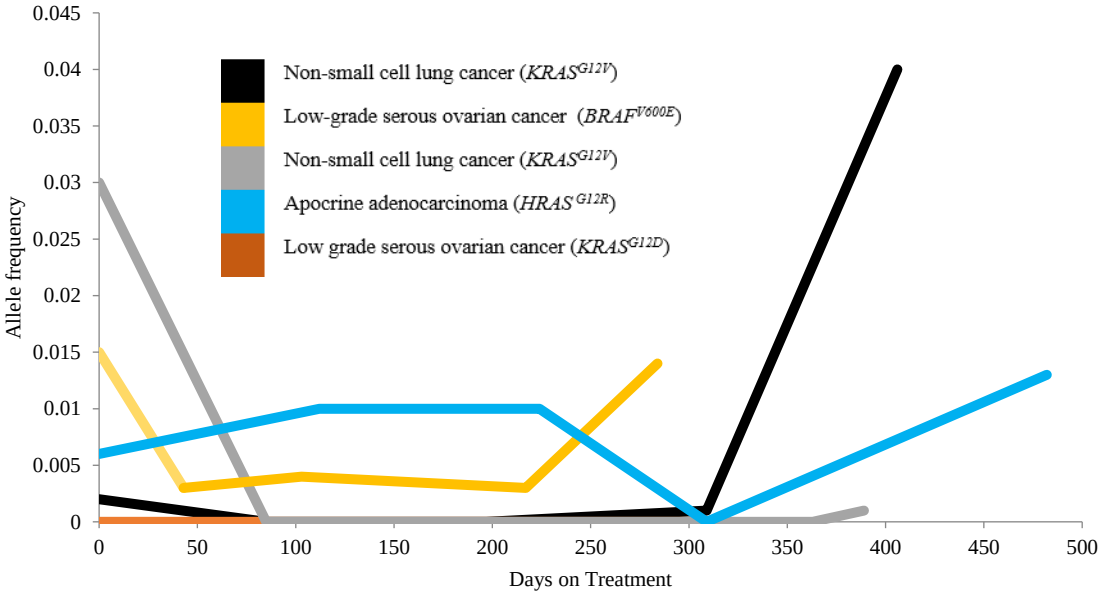
H scores	Baseline	Day 15	Baseline	Day 15	Baseline	Day 15
Membrane	0	0	208	116	93	85
Cytoplasm	168	43	185	125	130	115
Nuclear	57	0	0	0	0	0

H scores	Baseline	Day 15	Baseline	Day 15	Baseline	Day 15
Membrane	0	0	0	0	0	0
Cytoplasm	200	65	110	86	110	23
Nuclear	70	0	58	29	4	0

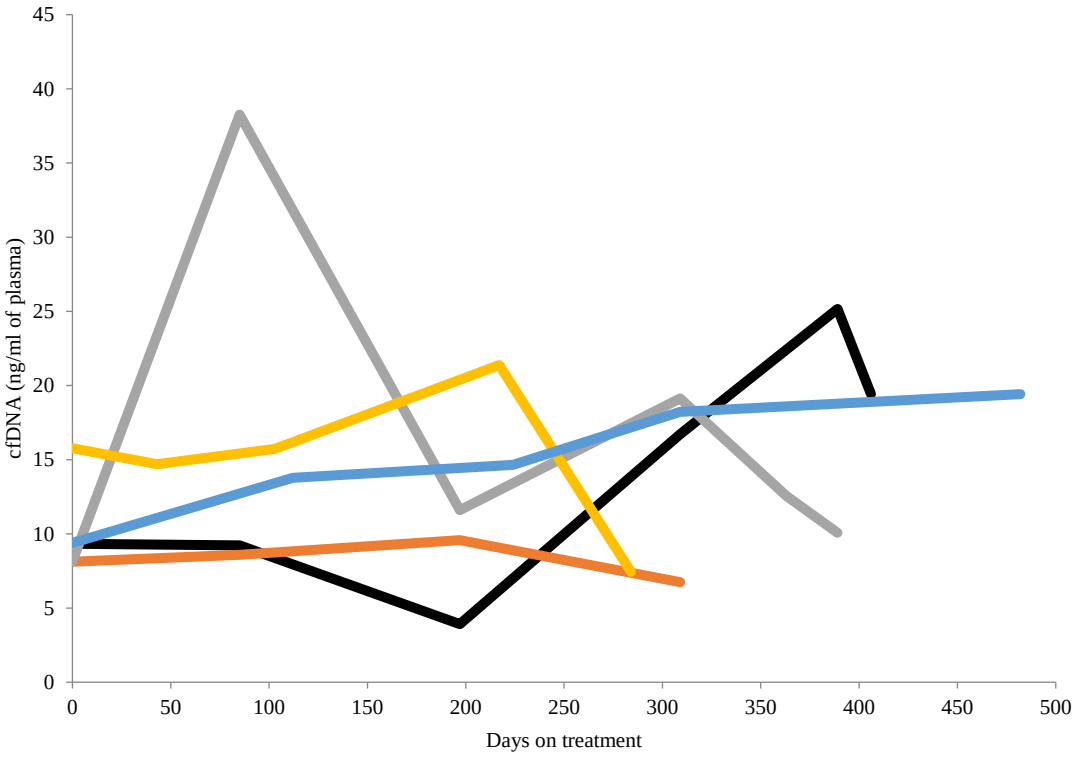
Immunohistochemical staining of phosphorylated MEK (pMEK) and phosphorylated ERK (pERK) with corresponding histo-scores (H-scores) of tumour biopsies collected pre- and approximately 15 days post-treatment from patients with: (A) NRASQ61R cutaneous melanoma, (B) NRASQ61R colorectal cancer, (C) high-grade serous ovarian cancer with PTEN loss.

Figure S4: Cell-free DNA (cfDNA) analyses in long-term responders

A.



B.



(A) Mutant alleles of driver *RAS* or *RAF* mutations were detectable in the cfDNA of four out of five long-term (> 6 months) responders. Mutant allele frequency decreased with response to treatment in all four patients. In three of out of four patients, mutant allele frequency increased at the time of disease progression. (B) Total cfDNA decreased in response to treatment in two of the five long-term responders.