APPENDIX TABLES

Abemaciclib in combination with single-agent options in patients with stage IV non–small cell lung cancer (NSCLC): A phase 1b study

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Table S1. Treatments and dose escalation schedule

	Part A		Part B		Part C		
Combination drug	Pemetrexed [a]		Gemcitabine		Ramucirumab		
Dose	500 mg/m^2		1250 mg/m^2		8 or 10 mg/kg		
Administration	IV		IV		IV		
Dose frequency[b]	Day 1		Days 1and 8		Days 1 and 8, or Day 1		
Cohort no. and description	**No. of patients**	**Abemaciclib dose [c]**	**No. of patients**	**Abemaciclib dose [c]**	**No. of patients**	**Abemaciclib dose [c]**	**Ramucirumab dose**
1. Escalation	3-6	150 mg	3-6	150 mg	3-6	150 mg	10 mg/kg day 1
2. Escalation	3-6	200 mg	3-6	200 mg	3-6	200 mg	10 mg/kg day 1
3. Confirmation	12	200 mg or MTD	12	200 mg or MTD	12	200 mg or MTD	10 mg/kg day 1
4. Escalation	NA		NA		3-6	150 mg	8 mg/kg day 1,8
5. Escalation	NA		NA		3-6	150 mg	10 mg/kg day 1,8
6. Confirmation	NA		NA		12	150 mg	MTD days 1,8

[a] Prior to initiating pemetrexed, sites were instructed to administer supplementation with oral folic acid, intramuscular vitamin B12, and oral corticosteroids according to label recommendations.
[b] 21-day cycle.
[c] Administered orally every 12 hours (Q12H). Dose de-escalation to 100 mg abemaciclib was allowed.
Abbreviations: IV, intravenous; MTD, maximum tolerated dose; NA, not applicable (that is, there were no additional cohorts beyond cohorts 1–3); no, number.

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Table S2. Patient disposition

	Part A: Abemaciclib + Pemetrexed (N=23)		Part B: Abemaciclib + Gemcitabine (N=24)		Part C: Abemaciclib + Ramucirumab (N=39)			
Abemaciclib dose (Q12H) n (%)	150 mg n = 8	200 mg n = 15	150 mg n = 3	200 mg n = 21	150 mg; ram 10 mg, day 1 n = 4	200 mg; ram 10 mg, day 1 n = 19	150 mg; ram 8mg, days 1,8 n = 12	150 mg; ram 10mg, days 1,8 n = 4
Discontinued from study	8 (100)	15 (100)	3 (100)	21 (100)	4 (100)	19 (100)	7 (58)	4 (100)
On study	0	0	0	0	0	5 (42)	0	0
Reason for discontinuation								
AE	1 (13)	3 (20)	0	3 (14)	1 (25)	3 (16)	1 (8)	2 (50)
Death	0	1 (7)	0	3 (14)	1 (25)	2 (11)	0	1 (25)
Physician decision	3 (38)	3 (20)	0	2 (10)	0	5 (26)	0	0
Progressive disease	3 (38)	4 (27)	3 (100)	9 (43)	1 (25)	5 (26)	5 (42)	1 (25)
Subject decision	1 (13)	3 (20)	0	4 (19)	1 (25)	4 (21)	1 (8)	0

Abbreviation: AE, adverse event; n, number of patients; ram, ramucirumab

Table S3. Summary of abemaciclib exposure, dose adjustment and omissions

	Part A: Abemaciclib + Pemetrexed (N=23)		Part B: Abemaciclib + Gemcitabine (N=24)		Part C: Abemaciclib + Ramucirumab (N=39)			
Abemaciclib Dose (Q12H)	150 mg n = 8	200 mg n = 15	150 mg n = 3	200 mg n = 21	150 mg; ram 10mg, day 1 n = 4	200 mg; ram 10mg, day 1 n = 19	150 mg; ram 8mg, days 1,8 n = 12	150 mg; ram 10mg, days 1,8 n = 4
Median cycle number	2.5	3.0	3.0	2.0	1.5	3.0	3.0	1.5
Patients with ≥1 dose reduction, n (%)	5 (62.5)[a]	6 (40.0)[a]	1 (33.3)[b]	7 (33.3)[b]	1 (25.0)[c]	9 (47.4)[c]	2 (16.7)[c]	2 (50.0)[c]
Patients with ≥1 dose omission, n (%)	6 (60.0)[a]	9 (33.3)[a]	3 (100.0)[b]	12 (54.5)[b]	1 (25.0)[c]	13 (68.4)[c]	4 (33.3)[c]	3 (75)[c]
Relative dose intensity (%) Mean (SD)	78 (17)	82 (19)	81 (25)	76 (20)	75 (25)	77 (24)	93 (7)	82 (22)

[a] Among patients receiving the combination of abemaciclib and pemetrexed, neutropenia was the most common reason for dose reductions (4/11). Neutropenia (7/15) and vomiting (7/15) were most common reason for dose omission. Not represented in this table, a pemetrexed dose reduction was required for 30% (7/23) of patients receiving the combination of abemaciclib and pemetrexed; neutropenia led to 71% (5/7) of these reductions.

[b] Among patients receiving the combination of abemaciclib and gemcitabine, fatigue was most common reason for dose reductions (4/8). Diarrhea (4/15) and fatigue (3/15) were most common cause of abemaciclib dose omissions. Not represented in this table, the gemcitabine dose was also reduced among 42% (10/24) of patients, neutropenia led to 60% of the reductions and thrombocytopenia led to 30%.

[c] Among patients receiving the combination of abemaciclib and ramucirumab, diarrhea (4/14) and fatigue (3/14) were the most common causes of dose reductions. Dose reductions due to diarrhea occurred only at the abemaciclib 200 mg dose level on the day 1 regimen. Not represented in this table, ramucirumab dose was reduced in 13% (3/23) of patients on the day 1 regimen (10 mg/kg) and 19% (3/16) on the days 1,8 regimen (8 or 10 mg/kg). The most common reason for reduction of ramucirumab dose was weight loss.

Abbreviations: n, number of patients; ram, ramucirumab; SD, standard deviation

Table S4. Summary of pharmacokinetic parameters for pemetrexed following intravenous infusions over 10 minutes in combination with abemaciclib in patients with stage IV NSCLC.

Pharmacokinetic parameter	Geometric mean (CV%)		
	First dose (Includes immediate post infusion data)* (n = 23)	First dose (Excludes immediate post infusion data)* (n = 23)	Second dose (n =11)
C_{max} (ng/mL)	94100 (30)	42800 (29)	41000 (23)
t_{max}[a] (hr)	0.25 (0.12 – 1.17)	1.23 (1.03 – 1.67)	1.17 (1.08 – 1.53)
C_{last} (ng/mL)	3600 (87)	3600 (87)	3700 (90)
t_{last}[a] (hr)	8.33 (7.17 – 10.17)	8.33 (7.17 – 10.17)	8.17 (6.53 – 9.92)
$AUC_{(0–tlast)}$ (ng·hr/mL)	184000 (27)	134000 (33)	123000 (27)
$AUC_{(0–\infty)}$ (ng·hr/mL)	200000 (30)	150000 (37)	142000 (32)[b]
$t_{1/2}$[c] (hr)	2.52 (1.73 – 3.89)	2.52 (1.73 – 3.89)	2.52 (1.76 – 3.09)[b]
CL (L/hr)	4.43 (32)	5.92 (37)	6.51 (22)[b]
Vss (L)	13.3 (36)	23.2 (35)	24.9 (19)[b]

[a]Median and range are provided for t_{max} and t_{last}.
[b]n = 10.
[c]Geometric mean and range are provided for $t_{1/2}$.
*Note: Immediate postdose samples were not collected following the second dose; hence, for comparison between the first and second dose, pemetrexed pharmacokinetic parameters were estimated with and without the immediate postdose sample concentration data.
Abbreviations: $AUC_{(0–tlast)}$, area under the concentration versus time curve from the time zero to t_{last}; CL, clearance after intravenous administration; C_{max}, maximum observed drug concentration; C_{last}, last quantifiable drug concentration; CV, coefficient of variation; hr, hour; n, number of observations; $t_{1/2}$, terminal elimination half-life; t_{last}, last time point where the concentration is above the limit of quantitation; t_{max}, time of maximum observed drug concentration; V_{ss}, volume of distribution at steady state following IV administration.

Table S5. Summary of pharmacokinetic parameters for gemcitabine metabolite (2′,2′-difluorodeoxyuridine) following intravenous infusions of gemcitabine over 30 minutes on days 1 and 8 of a 21-day cycle in combination with abemaciclib.

Pharmacokinetic parameter	Geometric mean (CV%)		
	First dose (Includes immediate post infusion data)* (n = 22)	First dose (Excludes immediate post infusion data)* (n = 22)	Third dose (n=6)
C_{max} (ng/mL)	41,700 (20)	33,600 (22)	33,600 (20)
t_{max}[a] (hr)	0.74 (0.50 – 1.67)	1.58 (0.98 – 2.65)	1.46 (1.02 – 1.60)
C_{last} (ng/mL)	8880 (41)	8880 (41)	10,300 (12)
t_{last}[a] (hr)	9.25 (8.22 – 10.95)	9.25 (8.22 – 10.95)	8.83 (8.02 – 10.42)
$AUC_{(0\text{-}tlast)}$ (ng·hr/mL)	178,000 (25)	158,000 (28)	167,000 (15)
$AUC_{(0\text{-}\infty)}$ (ng·hr/mL)	240,000[b] (30)	220,000[b] (32)	259,000 (9)
$t_{1/2}$[c] (hr)	4.53[b] (3.55 – 5.79)	4.53[b] (3.55 - 5.79)	5.87 (4.20 – 9.23)
CL (L/hr)	9.76[b] (37)	10.6[b] (38)	8.60 (17)
Vss (L)	62.0[b] (30)	73.7[b] (32)	72.5 (21)

[a] Median and range are provided for t_{max} and t_{last} .
[b] n=21.
[c] Geometric mean and range are provided for $t_{1/2}$.
* Immediate post dose samples were not collected following the second dose; hence, for comparison between the first and second dose, pemetrexed pharmacokinetic parameters were estimated with and without the immediate post dose sample concentration data.

Abbreviations: AUC(0-tlast) = area under the concentration versus time curve from the time zero to t_{last}; CL = clearance after intravenous administration; C_{max} = maximum observed drug concentration; C_{last} = last quantifiable drug concentration ; CV = coefficient of variation; h = hour; n = number of observations; $t_{1/2}$ = terminal elimination half-life; t_{last} = last time point where the concentration is above the limit of quantitation ; t_{max} = time of maximum observed drug concentration, V_{ss} = volume of distribution at steady state following iv administration