**Table S1. Summary of safety in Phase 1**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Patients  N (%) | Abivertinib dose cohort (BID) | | | | | | | |
| 50 mg | 100 mg | 150 mg | 200 mg | 250 mg | 300 mg | 350 mg | Total |
| (n=3) | (n=23) | (n=20) | (n=20) | (n=23) | (n=45) | (n=6) | (n=140) |
| **Any AE  (all grades)** | 3 (100.0) | 21 (91.3) | 19 (95.0) | 20 (100.0) | 23 (100.0) | 45 (100.0) | 6 (100.0) | 137 (97.9) |
| **Any Grade 3/4 AE** | 0 | 5 (21.7) | 4 (20.0) | 5 (25.0) | 10 (43.5) | 21 (46.7) | 4 (66.7) | 49 (35.0) |
| **Any treatment-related Grade 3/4 AE** | 0 | 3 (13.0) | 3 (15.0) | 2 (10.0) | 7 (30.4) | 12 (26.7) | 4 (66.7) | 31 (22.1) |
| **Any Grade 5 AE** | 0 | 2 (8.7) | 1 (5.0) | 1 (5.0) | 2 (8.7) | 4 (8.9) | 0 | 10 (7.1) |
| **Treatment-related Grade 5 AE** | 0 | 0 | 0 | 0 | 0 | 1 (2.2) | 0 | 1 (0.7) |
| **Dose interruption due to any AEs** | 0 | 1 (4.3) | 4 (20.0) | 3 (15.0) | 5 (21.7) | 15 (33.3) | 4 (66.7) | 32 (22.9) |
| **Dose interruption due to treatment related AEs** | 0 | 0 | 2 (10.0) | 2 (10.0) | 4 (17.4) | 7 (15.6) | 4 (66.7) | 19 (13.6) |
| **Any SAEb** | 1 (33.3) | 3 (13.0) | 2 (10.0) | 3 (15.0) | 7 (30.4) | 15 (33.3) | 1 (16.7) | 32 (22.9) |
| **Treatment-related SAEa,b** | 1 (33.3) | 0 | 0 | 0 | 2 (8.7) | 3 (6.7) | 0 | 6 (4.3) |
| **Treatment-related AEs (all grades) a,c,d** | 3 (100.0) | 20 (87.0) | 18 (90.0) | 18 (90.0) | 21 (91.3) | 42 (93.3) | 6 (100.0) | 128 (91.4) |
| ALT increase | 0 | 7 (30.4) | 13 (65.0) | 9 (45.0) | 13 (56.5) | 25 (55.6) | 5 (83.3) | 72 (51.4) |
| AST increase | 0 | 7 (30.4) | 9 (45.0) | 8 (40.0) | 14 (60.9) | 27 (60.0) | 6 (100.0) | 71 (50.7) |
| Diarrhea | 1 (33.3) | 13 (56.5) | 5 (25.0) | 4 (20.0) | 12 (52.2) | 26 (57.8) | 4 (66.7) | 65 (46.4) |
| Rash | 1 (33.3) | 7 (30.4) | 2 (10.0) | 9 (45.0) | 8 (34.8) | 12 (26.7) | 4 (66.7) | 43 (30.7) |
| QT prolongation | 2 (66.7) | 4 (17.4) | 5 (25.0) | 5 (25.0) | 10 (43.5) | 10 (22.2) | 2 (33.3) | 38 (27.1) |
| Positive occult blood | 2 (66.7) | 4 (17.4) | 6 (30.0) | 3 (15.0) | 7 (30.4) | 8 (17.8) | 4 (66.7) | 34 (24.3) |
| Platelet count decreased | 1 (33.3) | 5 (21.7) | 3 (15.0) | 1 (5.0) | 8 (34.8) | 11 (24.4) | 4 (66.7) | 33 (23.6) |
| Neutrophil count decreased | 0 | 3 (13.0) | 4 (20.0) | 2 (10.0) | 6 (26.1) | 13 (28.9) | 2 (33.3) | 30 (21.4) |
| Leukocyte count decreased | 0 | 3 (13.0) | 4 (20.0) | 2 (10.0) | 7 (30.4) | 9 (20.0) | 1 (16.7) | 26 (18.6) |
| Nausea | 0 | 4 (17.4) | 4 (20.0) | 4 (20.0) | 2 (8.7) | 10 (22.2) | 2 (33.3) | 26 (18.6) |
| γ-GT increased | 0 | 1 (4.3) | 4 (20.0) | 5 (25.0) | 8 (34.8) | 4 (8.9) | 3 (50.0) | 25 (17.9) |
| Vomiting | 1 (33.3) | 1 (4.3) | 6 (30.0) | 2 (10.0) | 5 (21.7) | 9 (20.0) | 1 (16.7) | 25 (17.9) |
| Anemia | 0 | 1 (4.3) | 2 (10.0) | 3 (15.0) | 6 (26.1) | 8 (17.8) | 4 (66.7) | 24 (17.1) |
| Blood alkaline phosphatase increased | 1 (33.3) | 2 (8.7) | 2 (10.0) | 2 (10.0) | 7 (30.4) | 4 (8.9) | 4 (66.7) | 22 (15.7) |
| Uric acid increased | 0 | 1 (4.3) | 4 (20.0) | 3 (15.0) | 3 (13.0) | 2 (4.4) | 2 (33.3) | 15 (10.7) |
| **Treatment-related AEs (Grade ≥ 3)a,c,e** | 0 | 3 (13.0) | 3 (15.0) | 2 (10.0) | 7 (30.4) | 12 (26.7) | 4 (66.7) | 31 (22.1) |
| ALT increase | 0 | 0 | 2 (10.0) | 1 (5.0) | 1 (4.3) | 4 (8.9) | 2 (33.3) | 10 (7.1) |
| AST increase | 0 | 0 | 1 (5.0) | 1 (5.0) | 0 | 3 (6.7) | 3 (50.0) | 8 (5.7) |
| Diarrhea | 0 | 1 (4.3) | 0 | 0 | 1 (4.3) | 2 (4.4) | 0 | 4 (2.9) |
| Rash | 0 | 0 | 0 | 0 | 1 (4.3) | 3 (6.7) | 0 | 4 (2.9) |
| Platelet count decreased | 0 | 1 (4.3) | 0 | 0 | 1 (4.3) | 2 (4.4) | 0 | 4 (2.9) |
| γ-GT increased | 0 | 0 | 0 | 1(5.0) | 1 (4.3) | 0 | 1 (16.7) | 3 (2.1) |
| Leukocyte count decreased | 0 | 0 | 0 | 0 | 1 (4.3) | 1 (2.2) | 1 (16.7) | 3 (2.1) |
| Anemia | 0 | 1 (4.3) | 0 | 0 | 1 (4.3) | 0 | 0 | 2 (1.4) |
| QT prolongation | 0 | 0 | 1 (5.0) | 0 | 0 | 1 (2.2) | 0 | 2 (1.4) |

The data cutoff time of Phase 1 was March 05, 2018.

a Investigator assessed as ‘certainly’, ‘probably’ or ‘cannot judge’ related to study medication

b SAEs were identified per investigator assessment

c Total number of patients with AEs, each patient may have experienced one or more AEs

d All-grade treatment-related AEs are reported which occurred in ≥10% of patients

e Grade ≥3 treatment-related AEs are reported which occurred in ≥1% (n=2) of patients

Note: Dose interruption presented includes dose reduction, dose interruption and dose discontinuation.

Abbreviation: BID, twice daily; AE, adverse event; SAE, serious adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; γ-GT, gamma glutamyl transferase

**Table S2. Confirmeda best overall response and progression free survival (efficacy evaluable patientsb with EGFR T790M-positive tumors; N=132) in Phase 1**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Abivertinib dose cohorts (BID)** | | | | | | |
| **Patients** | **50 mg** | **100 mg** | **150 mg** | **200 mg** | **250 mg** | **300 mg** | **350 mg** |
| **n (%)** | **(N=3)** | **(N=23)** | **(N=20)** | **(N=20)** | **(N=22)** | **(N=38)** | **(N=6)** |
| **Objective response** | 0 | 1 (4.3) | 7 (35.0) | 8 (40.0) | 4 (18.2) | 15 (39.5) | 0 |
| (95% CI) | (0, 70.8) | (0.1, 21.9) | (15.4, 59.2) | (19.1, 63.9) | (5.2, 40.3) | (24.0, 56.6) | (0, 45.9) |
| CR | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| PR | 0 | 1 (4.3) | 7 (35.0) | 8 (40.0) | 4 (18.2) | 15 (39.5) | 0 |
| SD | 2 (66.7) | 17 (73.9) | 12 (60.0) | 6 (30.0) | 17 (77.3) | 19 (50.0) | 6 (100.0) |
| PD | 1 (33.3) | 5 (21.7) | 1 (5.0) | 6 (30.0) | 1 (4.5) | 4 (10.5) | 0 |
| **Disease control** | 2 (66.7) | 18 (78.3) | 19 (95.0) | 14 (70.0) | 21 (95.5) | 34 (89.5) | 6 (100.0) |
| 95% CI | (9.4, 99.2) | (56.3, 92.5) | (75.1, 99.9) | (45.7, 88.1) | (77.2, 99.9) | (75.2, 97.1) | (54.1, 100.0) |
| **Median DOR (months)** | – | 6.1 | 8.0 | 11.3 | 8.1 | 8.0 | – |
| 95% CI | – | NR, NR | 3.0, NR | 3.9, 14.0 | 4.0, 16.0 | 4.8, 20.1 | – |
| **Median PFS (months)c** | 15.0 d | 3.0 | 4.5 | 5.0 | 7.0 | 6.9 | 4.1 |
| 95% CI | 1.0, 15.0 | 2.0, 7.0 | 3.0, 9.0 | 1.0, 12.3 | 4.3, 9.0 | 3.0, 9.0 | 2.6, NR |

The data cutoff time of Phase 1 was March 05, 2018.

a Confirmed according to the requirements of RECIST version 1.1.  
b Response was evaluated in all patients who received ≥1 dose of abivertinib and had a baseline and ≥1 on-treatment RECIST assessment  
c Data for 12% (16 of 132) patients were censored.

d Two patients without disease progression or death from total three patients at 50mg cohort were censored.

Abbreviation: BID, twice daily; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; DOR, duration of response; PFS, progression-free survival; NR, not reached

**Table S3. Descriptive summary of plasma pharmacokinetic parameters of abivertinib after multiple dose oral administration**

| Parameter, Unit | Parameter summary statisticsa by abivertinib treatment | | | | | | |
| --- | --- | --- | --- | --- | --- | --- | --- |
| 50 mg BID | 100 mg BID | 150 mg BID | 200 mg BID | **250 mg BID** | **300 mg BID** | **350 mg BID** |
| N | 3 | 6 | 6 | 6 | 6 | 6 | 6 |
| Tmax, hr | 4.0 (2.0-6.0) | 2.5 (1.0-3.0) | 2.0 (1.0-4.0) | 2.0 (2.0-3.0) | 2.5 (2.0-3.0) | 3.0 (2.0-4.0) | 1.5 (0.0-3.1) |
| T1/2, hr | 5.46 (9.9) | 5.69 (19.9) | 7.03 (27.6) | 6.3 (24.7) | 7.52 (22.6) | 6.03 (18.6) | 5.78 (12.1) |
| Cmax, ng/mL | 415.84 (30.9) | 1075.74 (68.9) | 1890.09 (71) | 2528.01 (25.3) | 1902.55 (72.3) | 3088.86 (14) | 2498.44 (19.1) |
| Cmin, ng/mL | 75.7 (31.2) | 240.52 (113.6) | 379.76 (89) | 505.68 (55.2) | 632.87 (93.3) | 723.21 (33.4) | 754.47 (36.6) |
| AUCss, ng\*hr/mL | 3005.48 (27.9) | 7747.26 (96.1) | 11985.87 (72.4) | 14611.27 (18.8) | 14613.34 (80.4) | 22574.78 (21.1) | 19163.03 (16.1) |
| CL/F, L/hr | 17.7 (32.5) | 26.1 (97) | 20.64 (78.3) | 14.11 (19.4) | 24.25 (50.3) | 13.72 (18.9) | 19.04 (18.2) |
| Robs2b | 1.52 (21.3) | 0.98 (55) | 1.27 (44.7) | 1.17 (77.7) | 1.31 (45.1) | 1.77 (62.7) | 1.3 (39.9) |
| AUCss, area under the concentration-time curve at steady-state; BID, twice daily; CL/F, apparent oral clearance; Cmax, maximum plasma concentration; Cmin, minimum plasma concentration; %CV, coefficient of variation; MAD, multiple-ascending dose; N, number of subjects; T1/2, elimination half-life; Tmax, time to peak plasma concentration.  a Arithmetric mean (%CV) for all except for median (range) for Tmax.  b Robs2, defined as area under the concentration-time curve accumulation ratio for BID. | | | | | | | |

**Table S4. Summary of safety in Phase 2**

|  |  |
| --- | --- |
|  | **300 mg BID (n=227)** |
| **n (%) a** |
| Any AE (all grades) | 227 (100) |
| Treatment-related AEs (all grades) b | 220 ( 96.9) |
| Any Grade 3/4 AE | 117 ( 51.5) |
| Any treatment-related Grade 3/4 AE | 74 ( 32.6) |
| Any Grade 5 AE | 10 ( 4.4) |
| Treatment-related Grade 5 AE | 0 |
| Dose discontinuation due to any AEs | 28 ( 12.3) |
| Dose discontinuation due to treatment-related AEs | 17 ( 7.5) |
| Dose interruption due to any AEs | 88 ( 38.8) |
| Dose interruption due to treatment-related AEs | 67 ( 29.5) |
| Dose reduction due to any AEs | 14 ( 6.2) |
| Dose reduction due to treatment-related AEs | 14 ( 6.2) |
| Any SAEc | 77 ( 33.9) |
| Treatment-related SAEb,c | 31 ( 13.7) |

The data cutoff time of Phase 2 was March 15, 2019.

a Total number of patients with AEs, each patient may have experienced one or more AEs

b Investigator assessed as ‘certainly’, ‘probably’ or ‘cannot judge’ related to study medication

c SAEs were identified per investigator assessment

Abbreviation: BID, twice daily; AE, adverse event; SAE, serious adverse event

**Table S5. Most common treatment-emergent SAE (≥ 1%) in Phase 2**

|  |  |  |
| --- | --- | --- |
|  | **300mg BID (N=227)** | |
|  | **All, n (%)** | **Treatment-related, n (%)** |
| Interstitial lung cancer (ILD) | 10 (4.4) | 10 (4.4) |
| Infectious pneumonia | 6 (2.6) | 1 (0.4) |
| Lung infection | 6 (2.6) | 0 |
| Liver malfunction | 6 ( 2.6) | 5 ( 2.2) |
| Liver damage | 4 ( 1.8) | 3 (1.3) |
| Hemoptysis | 4 (1.8) | 0 |
| Vomiting | 3 (1.3) | 2 (0.9) |

The data cutoff time of Phase 2 was March 15, 2019.

Abbreviation: BID, twice daily; SAE, serious adverse event

**Table S6. Confirmeda best overall response and progression free survival (efficacy evaluable patientsb; N=209) in Phase 2**

|  |  |
| --- | --- |
|  | **300 mg BID** |
|  | **(N= 209)** |
| **Objective response, n (%)** | 109 ( 52.2) |
| (95% CI) | (45.2, 59.1) |
| CR | 0 |
| PR | 109 ( 52.2) |
| SD | 75 ( 35.9) |
| PD | 25 ( 12.0) |
|  |  |
| **Disease control, n (%)** | 184 ( 88.0) |
| 95% CI | (82.9, 92.1) |
| **Median DOR (months)** | 8.5 |
| 95% CI | 6.1, 9.2 |
| **Median PFS (months)c** | 7.5 |
| 95% CI | 6.0, 8.8 |
| **Median OS (months)d** | 24.9 |
| 95% CI | 22.4, NR |

The data cutoff time of Phase 2 was March 15, 2019.

a Confirmed according to the requirements of RECIST version 1.1.  
b Response was evaluated in all patients who received ≥1 dose of abivertinib and had a baseline and ≥1 on-treatment RECIST assessment  
c Data for 17.2% (36 of 209) patients were censored at the time of the data cutoff

d Data for 60.3% (126 of 209) patients were censored at the time of the data cutoff

Abbreviation: BID, twice daily; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; NE, not evaluable; DOR, duration of response; PFS, progression-free survival; OS, overall survival; NR, not reached