Supplementary Materials

Additional eligibility criteria

Patients who had controlled central nervous system metastases for longer than 4 weeks prior to study entry were eligible for enrollment. However, patients with symptomatic central nervous system metastases who were neurologically unstable or required increasing doses of steroids within 4 weeks prior to study entry were excluded. Other exclusion criteria included radiation therapy within ≤4 weeks prior to study entry; any other malignancies (except adequately treated carcinoma *in situ* of the cervix, or basal or squamous cell skin cancer; human immunodeficiency virus positivity) within the last 5 years before study start; major surgery ≤2 weeks prior to study entry; anti-cancer therapies ≤4 weeks prior to the first dose of study treatment, and any of the following laboratory values at baseline: hemoglobin <9 g/dL, platelet count <100×109/L, absolute neutrophil count <1.5×109/L, serum albumin <2.5 g/dL, total bilirubin >1.5×upper limit of normal (ULN), AST/serum glutamic-oxaloacetic transaminase test or ALT/serum glutamic-pyruvic transaminase test >3.0×ULN or >5.0×ULN when liver metastases present, serum creatinine >1.5×ULN or calculated creatinine clearance by Cockcroft-Gault formula <50 mL/min, serum calcium, potassium, and magnesium less than lower limit of normal, and positive urine beta human chorionic gonadotropin test.

Study endpoints analysis

For each treatment arm, individual lesion measurements and overall response at each assessment were recorded for each patient. The best overall response (BOR) is the best response recorded from the start of the treatment until disease progression or recurrence. However, assessments taken more than 28 days after the last dose of study treatment were excluded from the BOR derivation. Moreover, if any alternative cancer therapy was received while on study, any subsequent assessments were excluded from the BOR determination. Patients with missing BOR were considered as non-responders for the primary ORR analysis and were censored. The ORR is the proportion of subjects with BOR of either CR or PR among all subjects in the respective FAS.

Patients with symptoms of rapidly progressing disease without radiologic evidence were

classified as progression only when clear evidence of clinical deterioration was documented

and/or discontinued due to disease progression or death due to study indication.

A patient with documented PD as per RECIST was not considered for clinical progression and the date of PD was regarded as the date of disease progression per RECIST.

The DOR was censored at the date of the last adequate tumor assessment, when a subject did not experience a documented progression, or death due to the underlying cancer. When a subject discontinued trial treatment and received a new anti-neoplastic therapy prior to disease progression, the DOR was censored at the start date of the new therapy. The correlations between exposures and efficacy and safety endpoints were evaluated as exploratory objectives. Because not every patient contributed to PK sampling and, in some treatment arms, the response rates were too low for such analyses to be conducted, the later analyses were not performed.

PK assessments were performed for each study treatment. Serial, intensive sampling of patients’ blood was performed for 2 patients treated with alpelisib on cycle 1 day 1 and 1 patient on cycle 1 day 15; and for at least 6 patients from the other 3 treatment arms on cycle 1 day 15. Sparse PK blood samples were collected for the remaining patients from each treatment arm. A blood sample volume of 3 mL was collected at each visit.

Supplementary Table S1 Parameters of prior distributions and thresholds for posterior distributions of overall response rate

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Treatment arm** | | **Prior distribution** | | | **Threshold** | | |
| *i* | Component | *ai* | *bi* | Median | 90% credible interval | *Li* | *Mi* |
| Capmatinib | 1 | 0.3654 | 1 | 15% | (0.03–87%) | 7.5% | 17.5% |
| Binimetinib | 1 | 0.3654 | 1 | 15% | (0.03–87%) | 7.5% | 17.5% |
| Ceritinib | 1a (80%) | 6.9374 | 5.2562 | 57% | (34–79%) | 40% | 55% |
| 2 (20%) | 1 | 0.7565 | 60% | (7–98%) |
| Mixture |  |  | 58% | (26–87%) |
| Alpelisib | 1 | 0.3654 | 1 | 15% | (0.03–87%) | 7.5% | 17.5% |

aComponent derived from meta-analytic-predictive approach.

Supplementary Table S2 Posterior summaries of true objective response rate

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | Capmatinib  400/600 mg BIDa  *n* = 16 | Ceritinib  750 mq QD  *n* = 26 | Binimetinib  45 mg BID  *n* = 22 | Alpelisib  350 mg QD  *n* = 2 |
| Posterior distribution | | | | |
| *n* (%) | 3 (18.75) | 19 (73.08) | 2 (9.09) | 0 |
| Mean | 0.194 | 0.685 | 0.101 | 0.109 |
| Median | 0.182 | 0.688 | 0.090 | 0.043 |
| Standard deviation | 0.092 | 0.076 | 0.061 | 0.149 |
| 90% credible interval | 6.45−36.39 | 55.41−80.32 | 2.33−21.80 | 0.01−43.88 |
| Interval probabilitiesb (%) | | | | |
| Unacceptable efficacy | 7.46 | 0.02 | 39.50 | 60.21 |
| Limited efficacy | 39.57 | 4.59 | 48.39 | 17.61 |
| Clinically relevant efficacy | 52.97 | 95.39 | 12.11 | 22.18 |
| aOne patient received capmatinib 600 mg BID capsules; 15 patients received capmatinib 400 mg BID tablets; bTrue ORR intervals for capmatinib, binimetinib, and alpelisib: unacceptable efficacy 0−7.5%, limited efficacy: 7.5−17.5%, and clinically relevant efficacy: 17.5−100%. True ORR interval for ceritinib: unacceptable efficacy 0−40%, limited efficacy: 40−55%, and clinically relevant efficacy: 55−100%. | | | | |

References