CLUSTER: A biomarker-integrated targeted therapy study in patients with advanced non-small cell lung cancer

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Abstract

The CLUSTER umbrella trial simultaneously investigated the efficacy of multiple targeted therapies in Chinese patients with advanced non-small cell lung cancer and pre-specified genetic alterations. Patients were assigned to receive capmatinib (METi), ceritinib (ALKi), binimetinib (MEKi), or alpelisib (PI3Kαi) matched to their genetic alteration. The overall response rate (ORR) and safety of each treatment were determined. Ceritinib met the pre-specified statistical threshold for efficacy with an ORR of 73%, whereas an ORR of 19% and 9% were attained with capmatinib and binimetinib, respectively. Although not a predefined endpoint, a post-hoc analysis of the overall anti-tumor activity in all treated patients showed encouraging results. Despite the limited number of patients in some of the treatment arms and the stringent criteria for preliminary activity, these findings confirm the feasibility of conducting biomarker-integrated studies in China, and warrant the implementation of further umbrella trials to simultaneously evaluate the efficacy of multiple targeted treatments.

Trial registration number: NCT02276027

Introduction

Lung cancer is the leading cause of cancer deaths worldwide[1,2], and non-small cell lung cancer (NSCLC) accounts for ~85% of all lung cancer diagnoses[2]. More than 50% of patients with lung cancer are diagnosed with metastatic NSCLC, with 5-year survival rates of less than 5%[3]. Compared with the rest of the world, China has the highest lung cancer incidence and mortality; the incidence is expected to increase by a further 65% by 2040[1,4].

Even though the distribution of NSCLC histologic subtypes is similar between Chinese and non-Asian patients, with adenocarcinomas representing ~40% of cases, the prevalence of oncogenic mutations varies substantially between these populations[2,5,6]. Overall, there is a higher incidence of oncogenic mutations in Asian patients compared with non-Asian patients (84% vs. 61%)[6]. At least 50% of lung adenocarcinomas in Asian patients have one or more known oncogenic driver mutations, with a higher frequency of actionable alterations in patients who have never smoked compared with those with a history of smoking[7,8]. In a study of 1200 Chinese patients with NSCLC, 73.9% harbored at least one of the actionable genomic alterations recommended for molecular testing by the National Comprehensive Cancer Network (NCCN) guidelines[9]. Similar findings emerged from a retrospective study of 280 Chinese patients with NSCLC[10].

Several studies reported differences in the genomic profiles of driver mutations, etiology, and the ability to tolerate different treatments between Chinese and Western patients with NSCLC[9,11]. Epidermal growth

factor receptor (*EGFR)* is the most frequently identified mutated gene in NSCLC regardless of ethnicity, but its mutation occurs with a higher frequency in Asian patients (30–40%) than in patients in the United States (U.S.) and Europe (10–15%)[10,12-14]. Approximately 8% of Chinese patients with NSCLC have anaplastic lymphoma kinase (*ALK)* rearrangement, which is a significantly higher proportion than in the non-Asian population[9]. Other oncogenic drivers, including *KRAS* (14–21%), phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha (*PIK3CA*; 5–10%), translocation proto-oncogene receptor tyrosine kinase rearrangement (*ROS1*; 2–5%), *MET* alterations (*MET* amplification: 1.5 – 4.5%; *MET*ex14: ~1%; *MET* rearrangement: 0.2%), and serine/threonine protein kinase B-Raf (*BRAF*; 4%), are among the ten most frequently identified mutated genes in Chinese patients with NSCLC[10,15-19]. As such, understanding the genomic characteristics of NSCLC in Chinese populations is of great importance for the management of advanced NSCLC.

Certain genomic alterations are common across different tumor types; hence, specific subsets of patients may benefit from novel agents already in development. With advancements in genotyping and biomarker screening, biomarker-integrated trials, such as umbrella trials, have been developed under the master protocol framework[20]. Umbrella trials can effectively investigate multiple therapeutic agents and hypotheses by screening tumors for multiple genomic alterations and allocating patients to one of several genotype-matched therapeutic agents in individual treatment arms[20,21]. In addition, the umbrella trial design offers a more ethical approach to trial evaluation by minimizing risks for participants and maximizing the expected benefits[21,22].

The CLUSTER (NCT02276027) trial is one of the first umbrella trials conducted in China. Based on their specific molecular alteration, patients with advanced NSCLC were allocated to four individual treatment arms to evaluate the anti-tumor activity of capmatinib, ceritinib, binimetinib, and alpelisib.

Results

Patients and genetic characteristics

Recruitment for the CLUSTER study (January 2015 – October 2019; China, Guangdong) was halted prematurely because of challenges in identifying patients under the prevailing treatment paradigm for NSCLC in China at the time. Based on the eligibility criteria, the trial enrolled a total of 66 patients harboring *MET* amplification or MET overexpression (*n* = 16), *ALK* or *ROS1* rearrangement (*n* = 26, *KRAS/*neuroblastoma RAS viral oncogene homolog (*NRAS*)*/BRAF* (*n* = 22) mutations, and *PIK3CA* mutations and/or amplification (*n* = 2) who were assigned to receive capmatinib, ceritinib, binimetinib, and alpelisib, respectively. Patients with co-existing mutations were eligible for enrollment but ultimately no such patients were enrolled. The median age of the enrolled patients was 58 years. Most patients

(94%) enrolled into the trial had an Eastern Cooperative Oncology Group (ECOG) performance status of 1. Overall, 52% of patients were treatment-naïve, and a substantial proportion (23%) was heavily pre-treated with two or more lines of prior treatment. All patients enrolled in the capmatinib, ceritinib, and binimetinib arms had adenocarcinoma, whereas both patients in the alpelisib arm had squamous cell carcinoma. Patient baseline characteristics are summarized in **Table 1**.

Treatment and outcomes

Of the overall trial population, 24 (36.4%) patients attained confirmed partial response (PR) to their assigned targeted agents. Among the remaining patients, 21 (31.8%) and 13 (19.7%) attained stable disease (SD) and progressive disease (PD), respectively. Responses were unknown for the remaining 8 (12.1%) patients. Forty-five (68.2%) of 66 patients experienced tumor shrinkage (**Table 2, Fig. 1a**). The median progression-free survival (PFS) calculated for 56 patients (10 patients were censored) was 5.4 months (95% confidence interval [CI], 3.6–6.7), with a 12-month Kaplan–Meier estimate of 22.4% (95% CI, 13.0–33.4; **Fig. 2a**). The median overall survival (OS) calculated for 46 patients (20 patients were censored) was 14.0 months (95% CI, 10.4–21.0), with a 12-month Kaplan–Meier estimate of 57.0% (95% CI, 44.1–68.0; **Fig. 3a**).

Capmatinib

Three patients treated with capmatinib, including 1 patient with *MET* immunohistochemistry (IHC) intensity 3+ in ≥50% of tumor cells and 2 patients with *MET* gene copy number (GCN) ≥5 by fluorescence *in situ* histochemistry (FISH) attained confirmed PR, giving an ORR of 18.8% (**Table 2, Fig. 1b)**. No patient attained a complete response (CR). The ORR in capmatinib-treated patients with *MET* alterations did not fulfill the predefined statistical parameters for preliminary efficacy. Among the 16 patients treated with capmatinib, the median PFS was 1.5 months (95% CI, 0.8–5.4) with a 4-month Kaplan–Meier estimated rate of 31.3% (95% CI, 11.4–53.7) (**Fig. 2b**). The median OS was 13.3 months (95% CI, 1.2–23.3) (**Fig. 3b**). Seven out of 16 patients experienced SD or better, giving a disease control rate (DCR) of 43.8%. The median duration of response (DOR) was 3.8 months (95% CI, 3.8–5.6).

Ceritinib

Confirmed PR was observed in 19 out of 26 patients treated with ceritinib. No patient achieved a CR, which means an ORR of 73.1% was attained (**Table 2, Fig. 1c**). The ORR to ceritinib in patients with *ALK* or *ROS1* rearrangement met the predefined statistical threshold for preliminary activity. The estimated ORR posterior median was above the 55% threshold at 68.8%, while the posterior probability of being in the unacceptable efficacy category was below the 5% threshold at 0.02%. The median PFS was 14.4 months (95% CI, 7.3–40.6) in patients treated with ceritinib. The Kaplan–Meier estimate for PFS rate was 84.6% (95% CI, 64.0–94.0) at 4 months, and 53.3% (95% CI, 32.6–70.3) at 12 months (**Fig. 2c**). The median OS was not reached (**Fig. 3c**). DCR was 92.3%, with 24 out of 26 patients who attained SD or better. The median DOR was 35.0 months (95% CI, 7.6–not estimated).

Binimetinib

Binimetinib treatment resulted in an ORR of 9.1%, with PR confirmed in 2 of the 22 patients treated (**Table 2, Fig. 1d**). The ORR to binimetinib in patients with *KRAS*, *NRAS,* or *BRAF* mutations did not fulfill the predefined statistical parameters for preliminary efficacy. The median PFS and OS were 3.8 months (95% CI, 1.6–5.4; **Fig. 2d**) and 9.2 months (95% CI, 3.5–12.0; **Fig. 3d**), respectively. A DCR of 59.1% was attained because 13 patients achieved SD or better. The median DOR was 5.5 months (95% CI, 3.6–7.4).

Alpelisib

In the alpelisib treatment arm, none of the two patients enrolled attained a CR or PR, although one of the patients attained SD. Because only two patients were enrolled in this arm, Kaplan–Meier estimates for PFS and OS were not generated. In the absence of a response, the DOR for alpelisib could not be determined.

Pharmacokinetics

Pharmacokinetics (PK) parameters were evaluated for all treatment arms after a single-dose administration on cycle 1, day 1 (alpelisib arm only) and/or multiple-dose administration on cycle 1, day 15. After multiple-dose administration, the geo-mean (coefficient of variation [CV]%) area under the plasma concentration-time curve (AUC) from time zero to time of last measurable concentration (AUC_{last}) and maximum (peak) plasma drug concentration (C_{max}) were 26614 ng´hr/mL (35.2%) and 7224 ng/mL (54.4%) for capmatinib tablet; 27610 ng´hr/mL (19.2%) and 1351 ng/mL (13.9%) for ceritinib, 2463 ng´hr/mL (41.9%) and 561 ng/mL (33.3%) for binimetinib, and 23721 ng´hr/mL and 2630 ng/mL for one of the patients in the alpelisib arm, respectively. The median time to reach maximum (peak) plasma concentration following drug administration (T_{max}) was 1 hour for capmatinib tablet and binimetinib, 2 hours for alpelisib, and 6 hours for ceritinib.

Safety

This study included a pooled safety evaluation across all study patients, as well as the safety profile of the individual study arms. For the overall study population, the most frequent (³25%) all-grade treatment-related adverse events (AEs) were diarrhea (60.6%), increased aspartate aminotransferase (AST; 54.5%) and alanine aminotransferase (ALT; 50.0%), vomiting (43.9%), rash (40.9%), increased blood creatine phosphokinase (CPK; 33.3%), increased blood alkaline phosphatase (ALP; 31.8%), increased gamma-glutamyl transferase (GGT; 31.8%), nausea (30.3%), decreased appetite (30.3%), and upper abdominal pain (25.8%). Overall, 56.1% of patients experienced grade 3 or 4 treatment-related AEs. The most frequent grade 3 or 4 treatment-related AEs were increased ALT, which occurred in 10 (15.2%) patients, followed by increased GGT in 9 (13.6%) patients, and increased blood CPK in 8 (12.1%) patients (**Table 3**). PD was the most frequent reason for study drug discontinuation in each treatment arm.

Patients treated with capmatinib had a median duration of exposure (DOE) of 7.2 weeks. Most patients (81.3%) discontinued treatment because of PD. Most AEs were grade 1 or 2 and did not require discontinuation (**Table 3**). AEs leading to study drug discontinuation were reported in 2 (12.5%) patients (both grade 3/4). The most frequent (³25%) all-grade treatment-related AEs were anemia, nausea, diarrhea, vomiting, decreased appetite, peripheral edema, and ALT elevation (**Table 4**). Grade 3/4 treatment-related AEs (³5%) included neutropenia, peripheral edema, increased ALT, increased GGT, increased amylase, and interstitial lung disease, which occurred in 1 (6.3%) patient each. Pneumonia (12.5%) was the most frequently reported AE (³10%) that required dose adjustment/interruption.

Patients treated with ceritinib had a median DOE of 63.5 weeks. PD (46.2%) was the most frequent reason for discontinuation of ceritinib. Most AEs were grade 1 or 2 and did not lead to discontinuation (**Table 3**). AEs leading to ceritinib discontinuation were reported in 8 (30.8%) patients (grade 3/4 events in 5 [19.2%] patients). The most frequent (³25%) all-grade treatment-related AEs were anemia, nausea, diarrhea, vomiting, decreased appetite, abdominal pain, upper abdominal pain, asthenia, ALT/AST elevation, increased blood ALP and GGT, prolonged electrocardiogram (ECG) QT (per ECGs performed at local institutions), pruritus, and rash (**Table 4**). Grade 3/4 treatment-related AEs (³5%) included increased ALT in 9 (34.6%) patients; increased GGT in 7 (26.9%) patients; prolonged ECG QT in 4 (15.4%) patients; increased blood ALP and AST in 3 (11.5%) patients each; asthenia and hyperglycemia in 2 (7.7%) patients each. The most frequently reported AEs that required dose adjustment/interruption (³10%) included increased ALT (42.3%), increased AST (23.1%), increased blood ALP (19.2%), prolonged ECG QT (11.5%), increased GGT (19.2%), and decreased appetite (15.4%).

Patients treated with binimetinib had a median DOE of 14.8 weeks. PD (63.6%) was most common reason for discontinuation of binimetinib. Most AEs were grade 1 or 2 and did not require discontinuation (**Table 3**). AEs leading to study drug discontinuation were reported in 2 (9.1%) patients (both grade 3/4). The most frequent (³25%) all-grade treatment-related AEs were diarrhea, mouth ulceration, AST elevation, increased blood CPK, and rash (**Table 4**). Grade 3/4 treatment-related AEs (³5%) included increased blood CPK in 8 (36.4%) patients, prolonged ECG QT interval in 2 (9.1%) patients, and mouth ulceration, increased GGT, and hypertension in 1 (4.5%) patient each. Increased blood CPK was the most frequently reported AE (³10%) that required dose adjustment/interruption (27.3%).

The median DOE to alpelisib was 8.5 weeks. One patient discontinued treatment because of PD. None of the observed treatment-related AEs led to study drug discontinuation (**Table 3**). The AEs related to alpelisib were of grade 1; malaise and dysgeusia were reported for 1 patient, and hyperglycemia in the other patient.

Discussion

The CLUSTER study confirmed the feasibility of conducting a biopsy-mandated, biomarker-integrated clinical trial in patients with advanced NSCLC at a large institution in China. Identifying patients with the protocol-prescribed molecular alterations was generally feasible. Although PIK3CA alterations occur at a relatively higher frequency compared with the other oncogenic alterations investigated in this study, recruitment of patients with PIK3CA alterations turned out to be challenging: before enrollment was halted, only two such patients had been enrolled which renders the findings inconclusive. Tumor shrinkage was observed in 1 patient treated with alpelisib. Beyond advanced NSCLC, alpelisib has demonstrated efficacy in the treatment of patients with PIK3CA-mutated breast cancer when combined with fulvestrant. In addition, findings from a phase Ib study in patients with platinum-resistant BRCA-wild type epithelial ovarian cancer showed activity when alpelisib was combined with PARP inhibitor olaparib, compared with either olaparib or alpelisib monotherapy.[28]

Response to ceritinib in this study was found to be consistent with other reported studies in patients with *ALK*-rearranged advanced NSCLC[23,24]. The majority of these patients (69%) received ceritinib in the first-line setting, while the remaining patients were treated in the second-line setting (12%) or beyond. The ORR of capmatinib in this study was 18.8%. Pre-selection for capmatinib treatment was based upon *MET* amplification or overexpression because *MET* exon 14 skipping alteration (*MET*ex14*)* was not a validated biomarker at the time of patient enrollment. The phase II GEOMETRY mono-1 (Clinical Study of Oral cMET Inhibitor INC280 in Adult Patients With EGFR Wild-type Advanced Non-small Cell Lung Cancer) trial has since demonstrated the safety and efficacy of capmatinib in patients with treatment-naïve advanced *MET*ex14 NSCLC[25,26]. Data from this study showed a 68% ORR in the treatment naive patients and 41% ORR in pre-treated patients with *MET*ex14. In addition, the GEOMETRY mono-1 study provided preliminary evidence of efficacy in patients with high *MET* amplification. In patients with GCN ≥10, an ORR of 29% in the second- and third-line, and 40% in the first-line settings were reported. The GEOMETRY mono-1 results suggest that the efficacy of capmatinib is dependent on the type of *MET* alteration (i.e., *MET*ex14 vs. *MET* amplification), on the GCN cutoff threshold, and on the extent of prior treatment. Thus, findings of the CLUSTER study are consistent with initial clinical studies using treatments targeting *MET* alterations, in which no distinction was made between the subtype of *MET* alteration or the level of *MET* amplification[25]. The overall response rate to binimetinib in this study was 9%. It should be noted that findings from recently completed or ongoing studies of binimetinib in combination with chemotherapy or immune checkpoint inhibitors are expected.

Overall, there were few episodes of dose adjustment/interruption or discontinuation with capmatinib, alpelisib, and binimetinib, which were all well tolerated. Most treatment-related dose adjustment/interruptions and discontinuation due to AEs occurred in 17 (65%) and 6 (23%) patients treated with ceritinib, respectively.

The advantages of the umbrella trial design include the opportunity to assess treatment effects on multiple biomarker subgroups and the logistic efficiency of using a master protocol. Its design allows adding or removing biomarkers when justified[29]. Within the umbrella master protocol, many trial logistics (e.g., eligibility criteria, follow-up schedule during treatment, long-term follow-up) are harmonized across treatment groups[30]. However, umbrella trials should ideally utilize a standard biomarker testing method, such as next generation sequencing (NGS). Enrollment to this study was slow because NGS was not routinely used in clinical practice at the time of study conduct; therefore, some tissue specimens had to undergo serial biomarker testing. In addition, the availability of tumor tissue and the turnaround time for testing became critical issues. In some instances, there were insufficient tumor specimens to enable biomarker assessment. Because of the aggressive nature of NSCLC, patients eligible for enrollment needed to commence treatment swiftly and could not wait for an extended period for their biomarker results to be available. Finally, the small overall and individual cohort sample size, as well as the descriptive nature of the findings, limit the interpretation of the findings of this study.

The concept of biomarker-integrated master protocols has emerged as a feasible approach to accelerate oncology drug development and regulatory approval in biomarker-defined subgroups of cancer[31]. A few large-scale umbrella trials in NSCLC have been conducted in the U.S.[31,32]. The Lung-MAP (Biomarker-Targeted Second-Line Therapy in Treating Patients With Recurrent Stage IV Squamous Cell Lung Cancer) trial implemented the first biomarker-integrated master protocol within the National Cancer Institute to evaluate investigational agents in genomically defined subgroups of lung cancer[31]. The results have demonstrated the efficiency of such innovative study design, which provides the opportunity to expand the therapeutic development to underserved subgroups of patients with oncogene-driven NSCLC (such as *MET* and *BRAF*), less common histology, or early NSCLC[31,32]. For patients whose tissue biopsy samples are not available or accessible, liquid biopsy can provide a minimally invasive alternative test for determining targeted therapy or eligibility for inclusion in clinical trials. Moreover, liquid biopsy offers the opportunity to monitor treatment outcomes, in particular, the potential to provide early detection of tumor recurrence.

Many umbrella trials designed for solid tumors are currently in progress, with most master protocol trials being conducted in the U.S.[21]. Increased awareness and improved technical expertise in implementing master protocols in geographic regions outside the U.S. are needed to increase the opportunities for patients to access potentially efficacious therapies through participation in clinical research[21,33]. Considering the exponential advancements in the field of genomics, this is particularly relevant for China, where a high proportion of patients with oncogene-driven NSCLC may gain faster access to personalized treatment. Umbrella trial design could accelerate the discovery and development of targeted therapy to address the unmet need in this population.

Methods

Study objective

The primary study objective was to investigate the anti-tumor activity of targeted treatment with capmatinib, ceritinib, binimetinib, and alpelisib monotherapy in patients previously treated for advanced NSCLC harboring targetable molecular alterations.

Patients

Patients aged ≥18 years with an ECOG performance status ≤2 and histologically or cytologically confirmed stage IIIB or IV adenocarcinoma (all treatment arms) or squamous cell carcinoma (alpelisib treatment arm only) were pre-screened for *PIK3CA* and *MET* alterations, *ALK* or *ROS1* rearrangement, *KRAS*, *NRAS,* or *BRAF* mutations, from a newly obtained tumor sample, if available, or the most recently archived tumor sample. The study protocol was reviewed and approved by the institutional review board of the site. Written informed consent was obtained from each patient prior to conducting any study procedure. Patients with the pre-specified genetic mutations who met all other eligibility criteria were assigned to the treatment arm corresponding to the molecular alterations of their tumor. Additional eligibility criteria can be found in the **Supplementary Materials**.

Study design, treatment, and endpoints

Study design. The CLUSTER trial is a phase II umbrella four-arm, open-label study of capmatinib, ceritinib, binimetinib, and alpelisib monotherapy in patients with advanced NSCLC in whom prior treatment has failed (≥1 line of prior treatment) or in whom chemotherapy was considered unsuitable in the investigator's opinion, including patients who refused chemotherapy. All pre-screened patients were required to have measurable disease by Response Evaluation Criteria In Solid Tumors (RECIST) 1.1. Tumor lesions were assessed by computed tomography or magnetic resonance imaging performed at baseline and subsequently every 8 weeks from the start of cycle 3 until disease progression.

Treatment. At the time of conduct of this study, there was no regulatory approval for alpelisib. Initial studies in healthy males identified a recommended phase II dose (RP2D) of 400 mg QD alpelisib[34]. However, further data showed improved tolerability with 350 mg QD in Japanese patients with advanced solid malignancies.[35] Hence, patients with NSCLC who harbored *PIK3CA* mutations and/or amplification (defined as *PIK3CA* GCN ³4) received 350 mg alpelisib once daily (QD), a dose higher than the 300 mg QD currently approved for the treatment of metastatic breast cancer[36]. The capmatinib RP2D of 600 mg BID capsules was determined in the initial studies. Subsequently, capmatinib tablet formulation was developed for increased convenience of the study drug administration. Further studies showed improved pharmacokinetics with capmatinib 400 mg BID tablets compared with 600 mg BID capsules and the former dose was declared RP2D. Patients with *MET* amplification (defined as MET IHC intensity 3+ in ³50% of tumor cells,or MET IHC intensity score 2+ in ³50% of tumor cells and concurrent *MET* GCN ³5 by FISH), received a 600 mg capsule or 400 mg tablet twice daily (BID). Patients with GCN ³5 by FISH and

unknown MET IHC results, or with a *MET* mutation, could be enrolled at the discretion of the investigator. However, no patients harboring a *MET* mutation were enrolled. Dose selection for ceritinib and binimetinib were based on the highest dose with acceptable toxicity identified in the initial studies and confirmed in phase I studies in Japan. Patients with either *ALK* or *ROS1* rearrangement and those with either *KRAS*, *NRAS,* or *BRAF* were enrolled in the ceritinib 750 mg capsule QD or binimetinib 45 mg tablet BID arm, respectively (**Fig. 1**). Alpelisib is a PIK3 inhibitor and degrader approved for the treatment of advanced or metastatic breast cancer[36]. Capmatinib and ceritinib are selective tyrosine kinase inhibitors approved for the treatment of advanced NSCLC harboring *MET*ex14 and *ALK* alterations, respectively[26,37]. Binimetinib is a selective inhibitor of mitogen-activated extracellular signal regulated kinase 1/2 (ERK1/2) approved for the treatment of metastatic melanoma in combination with encorafenib[38].

Patients received their assigned study treatment until disease progression, death, unacceptable toxicity, or until treatment was discontinued by the investigator or withdrawal of consent by the patient. All patients were followed up for safety for a mandatory 30 days after receiving the last dose of study treatment. Patients who discontinued study treatment for reasons other than disease progression were followed up for progression of the underlying NSCLC. All patients were followed up for survival.

Study endpoints. The primary endpoint for all treatment arms was ORR per RECIST v1.1. Confirmation of CR or PR was required by repeat assessments to be performed no less than 4 weeks, and ideally no later than 5 weeks, after the criteria for response were first met. SD was defined as at least one SD assessment or better >6 weeks after start of study treatment and not qualifying for CR or PR. PD was defined as disease progression ≤12 weeks after start of study treatment and not qualifying for CR, PR, or SD. For all other cases not qualifying for confirmed CR or PR and without SD after more than 6 weeks or early progression within the first 12 weeks, the response was classified as “unknown”. The secondary endpoints were also identical for all study arms and included OS, PFS, DCR, and DOR, which were defined as the time from the first documented CR or PR (confirmed by the subsequent assessment) to the date of the first documented progression or death due to the underlying cancer. Additional details of the individual study endpoints and assessments can be found in the **Supplementary Materials**.

Statistical analyses

This study planned to enroll ~20–25 patients with advanced NSCLC to each treatment arm according to their molecular alteration (**Fig. 4**)[39]. For the alpelisib, capmatinib, and binimetinib treatment arms, a minimally informative unimodal Beta prior distribution for each arm i with parameters a_i and b_i that reflects the degree of uncertainty around ORR before starting the current trial was elicited[39]. Based on prior clinical assumption, the prior median of ORR of each treatment arm is obtained. If the prior median ORR was smaller than 50%, $b_i = 1$ and $a_i = \ln(0.5)/\ln(\text{median}_i)$; otherwise, $a_i = 1$ and $b_i = \ln(0.5)/\ln(1-$

median$_i$). The values of prior median$_i$, a_i, and b_i for the three treatment arms are listed in **Supplementary Table S1**.

For the ceritinib arm, a mixture of prior distributions with a component derived from relevant historical trials was used.

In order to reflect potential variability of the heterogeneity between trials, the heterogeneity parameter tau (τ) was given a half-normal distribution with scale 0.5. This distribution is right-skewed with median 0.34 and 95% probability interval (0.016–1.120). It allows the heterogeneity to vary from small to large but at the same time gives small probability to very large values of τ (τ >1). This component receives a prior weight of 80%.

The second minimally informative component is derived as described above for alpelisib, capmatinib, and binimetinib treatment arms, and receives a prior weight of 20%.

At time of analysis for each treatment arm, the respective prior distribution will be updated with all available data from patients in the respective full analysis set (FAS). Once updated, the posterior risks that the true ORR lies in the following efficacy intervals will be provided:

(0, L_i) unacceptable efficacy

(L_i, M_i) limited efficacy

(M_i, 100%) clinically relevant efficacy

The estimated ORR for each treatment arm was the median value of the respective posterior distribution. The values of thresholds L_i and M_i for the four treatment arms are listed in **Supplementary Table S1**. A study treatment was considered efficacious if the estimated ORR$_i$ was equal to or greater than M_i, and the posterior probability of being in the unacceptable efficacy (0, L_i) was lower than 5%. Otherwise, the inferential summaries for the three categories above will be assessed for further characterization of the efficacy. The posterior summaries of true ORR by treatment arm are given in **Supplementary Table S2**. Statistical analyses were performed using the Statistical Analysis System (SAS) version 9.4.

PK analyses were summarized using descriptive statistics. The primary PK parameters were AUC_{last}, AUC for a dosing interval (AUC_{tau}), C_{max}, and T_{max}. Descriptive statistics included arithmetic and geometric mean, median, standard deviation, CV, geometric CV, minimum, and maximum. PK parameters were calculated using non-compartmental methods with Phoenix WinNonlin version 6.2.

Declarations

Data availability

Novartis is committed to sharing access to patient-level data with qualified external researchers and supporting clinical documents from eligible studies. These requests are reviewed and approved by an independent review panel based on scientific merit. All data provided are anonymized to respect the privacy of patients who have participated in the trial in line with applicable laws and regulations. This trial data availability is according to the criteria and process described on **http://www.clinicalstudydatarequest.com**.

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Author contributions

All contributions from the authors have been declared.

Competing interests

The authors declare the existence of a financial/non-financial competing interests.

Tables

Table 1. Patient baseline characteristics

Characteristic	Capmatinib 400/600 mg BID[a] *n* = 16	Ceritinib 750 mg QD *n* = 26	Binimetinib 45 mg BID *n* = 22	Alpelisib 350 mg QD *n* = 2	All treatments *N* = 66
Mean age (standard deviation), years	58.2 (5.2)	49.4 (10.7)	60.3 (6.1)	53.0 (12.7)	55.3 (9.5)
Male, *n* (%)	11 (68.8)	11 (42.3)	19 (86.4)	2 (100)	43 (65.2)
Stage IV, *n* (%)	15 (93.8)	25 (96.2)	22 (100)	2 (100)	64 (97.0)
Median time since the initial diagnosis of primary site, months (range)	2.5 (1–121)	1.3 (1–75)	9.5 (1–96)	13.6 (10–17)	3.1 (1–121)
Histology, *n* (%)					
Adenocarcinoma	16 (100)	26 (100)	22 (100)	0	64 (97.0)
Squamous cell carcinoma	0	0	0	2 (100)	2 (3.0)
ECOG, *n* (%)					
1	13 (81.3)	26 (100)	22 (100)	1 (50.0)	62 (93.9)
2	3 (18.8)	0	0	1 (50.0)	4 (6.1)
Number of prior lines of therapy[b], *n* (%)					
0	9 (56.3)	18 (69.2)	7 (31.8)	0	34 (51.5)
1	7 (43.8)	4 (15.4)	6 (27.3)	0	17 (25.8)
2	0	3 (11.5)	7 (31.8)	2 (100)	12 (18.2)
≥3	0	1 (3.8)	2 (9.1)	0	3 (4.5)

[a]One patient was administered capmatinib capsules at 600 mg BID; 15 patients were administered capmatinib tablets at 400 mg BID; [b]Chemotherapy administered as adjuvant treatment more than 6 months prior to study enrollment was not considered as prior line of therapy.

Table 2. Best overall response

	Capmatinib 400/600 mg BID[a] *n* = 16	Ceritinib 750 mg QD *n* = 26	Binimetinib 45 mg BID *n* = 22	Alpelisib 350 mg QD *n* = 2	All treatments *N* = 66
Best overall response, n (%)					
Complete response	0	0	0	0	0
Partial response	3 (19)	19 (73)	2 (9)	0	24 (36)
Stable disease	4 (25)	5 (19)	11 (50)	1 (50)	21 (32)
Progressive disease	6 (38)	1 (4)	6 (27)	0	13 (20)
Unknown	3 (19)	1 (4)	3 (14)	1 (50)	8 (12)
Overall response rate[b]					
No. of patients with overall response	3	19	2	0	24
Percent of patients (95% CI)	19 (4–46)	73 (52–88)	9 (1–29)	0 (0–84)	36 (25–49)
Disease control[c]					
No. of patients with disease control	7	24	13	1	45
Percent of patients (95% CI)	44 (20–70)	92 (75–99)	59 (36–79)	50 (1–99)	68 (56–79)

[a]The data cutoff date was October 15, 2019. Percentages may not total 100 because of rounding. [b]Overall response was defined as a complete response or partial response. [c]Disease control was defined as a complete response, partial response, stable disease, non-complete response, or non-progressive disease.

Table 3. Overview of adverse events[a]

	Capmatinib 400/600 mg BID[a] *n* = 16		Ceritinib 750 mg QD *n* = 26		Binimetinib 45 mg BID *n* = 22		Alpelisib 350 mg QD *n* = 2		All treatments *N* = 66	
	Total	Gr. 3/4	Total	Gr. 3/4	Total	Gr. 3/4	Total	Gr. 3/4	Total	Gr. 3/4
Deaths (on treatment)	4 (25)		1 (4)		5 (23)		1 (50)		11 (17)	
AEs	16 (100)	11 (69)	26 (100)	23 (89)	55 (83)	20 (91)	2 (100)	1 (50)	66 (100)	55 (83)
Treatment-related AEs	14 (88)	5 (31)	26 (100)	20 (77)	37 (56)	12 (55)	2 (100)	0	64 (97)	37 (56)
Serious AEs	12 (75)	7 (44)	11 (42)	9 (35)	32 (49)	15 (68)	1 (50)	1 (50)	42 (64)	32 (49)
Treatment-related serious AEs	1 (6)	1 (6)	4 (15)	3 (12)	8 (12)	4 (18)	0	0	9 (14)	8 (12)
AEs leading to discontinuation	2 (13)	2 (13)	8 (31)	5 (19)	9 (14)	2 (9)	0	0	12 (18)	9 (14)
Treatment-related AEs leading to discontinuation	1 (6)	1 (7)	6 (23)	4 (15)	6 (9)	1 (5)	0	0	8 (12)	6 (9)
AEs leading to dose-adjustment or interruption	5 (31)		19 (73)		13 (59)		1 (50)		38 (58)	
Treatment-related AEs leading to dose-adjustment or interruption	2 (13)		17 (65)		6 (27)		0		25 (38)	

[a]The data cutoff date was October 15, 2019. All data are presented as n (%). Percentages may not total 100 because of rounding.

Table 4. Treatment-related adverse events[a]

Adverse event, All grades (preferred term), *n* (%)	Capmatinib *n* = 16	Ceritinib *n* = 26	Binimetinib *n* = 22	All treatments *N* = 66
Neutropenia	1 (6)	3 (12)	0	4 (6)
Asthenia	0	9 (35)	2 (9)	11 (17)
Edema peripheral	4 (25)	2 (8)	2 (9)	8 (12)
ALT increased	6 (38)	24 (92)	3 (14)	33 (50)
Anemia	5 (31)	8 (31)	3 (14)	16 (24)
GGT increased	5 (31)	14 (54)	2 (9)	21 (32)
ECG QT prolonged[b]	0	9 (35)	5 (23)	14 (21)
AST increased	2 (13)	24 (92)	10 (46)	36 (55)
Blood alkaline phosphatase increased	3 (19)	15 (58)	3 (14)	21 (32)
Amylase increased	4 (25)	6 (23)	5 (23)	15 (23)
Blood CPK increased	0	6 (23)	16 (73)	22 (33)
Interstitial lung disease	1 (6)	2 (8)	0	3 (5)
Dysgeusia[c]	0	1 (4)	0	2 (3)
Hyperglycemia[c]	0	3 (12)	0	4 (6)
Malaise[c]	0	1 (4)	0	2 (3)

Decreased appetite	5 (31)	11 (42)	4 (18)	20 (30)
Diarrhea	4 (25)	25 (96)	11 (50)	40 (61)
Nausea	6 (38)	11 (42)	3 (14)	20 (30)
Vomiting	5 (31)	19 (73)	5 (23)	29 (44)
Abdominal pain	0	11 (42)	2 (9)	13 (20)
Pruritis	2 (13)	7 (27)	3 (14)	12 (18)
Rash	0	12 (46)	15 (68)	27 (41)
Upper abdominal pain	0	15 (58)	2 (9)	17 (26)
Mouth ulceration	1 (6)	2 (8)	8 (36)	11 (17)

[a]The data cutoff date was October 15, 2019. Percentages may not total 100 because of rounding.

[b]Per ECGs performed at local institute. A patient with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment. [c]One AE occurred in the alpelisib arm.

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Figures

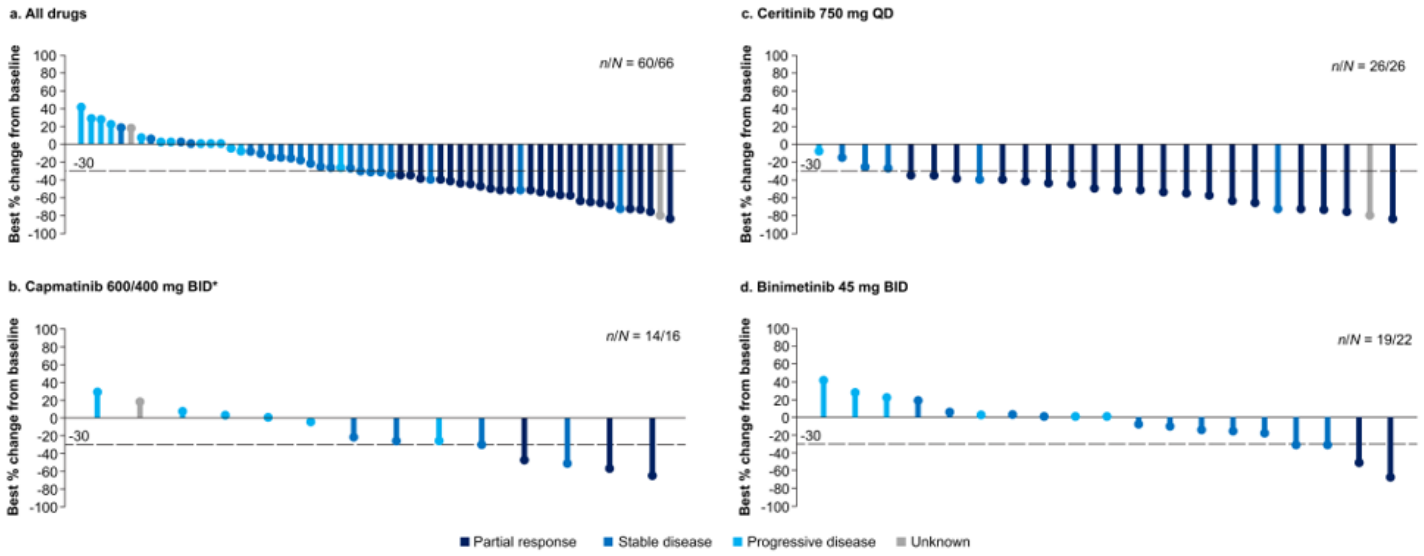

Figure 1

Tumor responses to targeted treatment

The best percentage change from baseline in the sum of the longest dimaters in patients who had measurable disease at baseline and at least one valid post-baseline assesement. The line at −30% corresponds to a change indicating a partial response. **a** All patients with either *MET* alterations, *ALK* or *ROS1* rearrangement, and *KRAS*, *NRAF* or *BRAF* mutations who received targeted treatment matching their molecular alteration. **b** Tumor responses to capmatinib in patients with *MET* alterations. **c** Tumor responses to ceritinib in patients with *ALK* or *ROS1* alterations. **d** Tumor responses to binimetinib in patients with *KRAS, NRAF* or *BRAF* mutations.

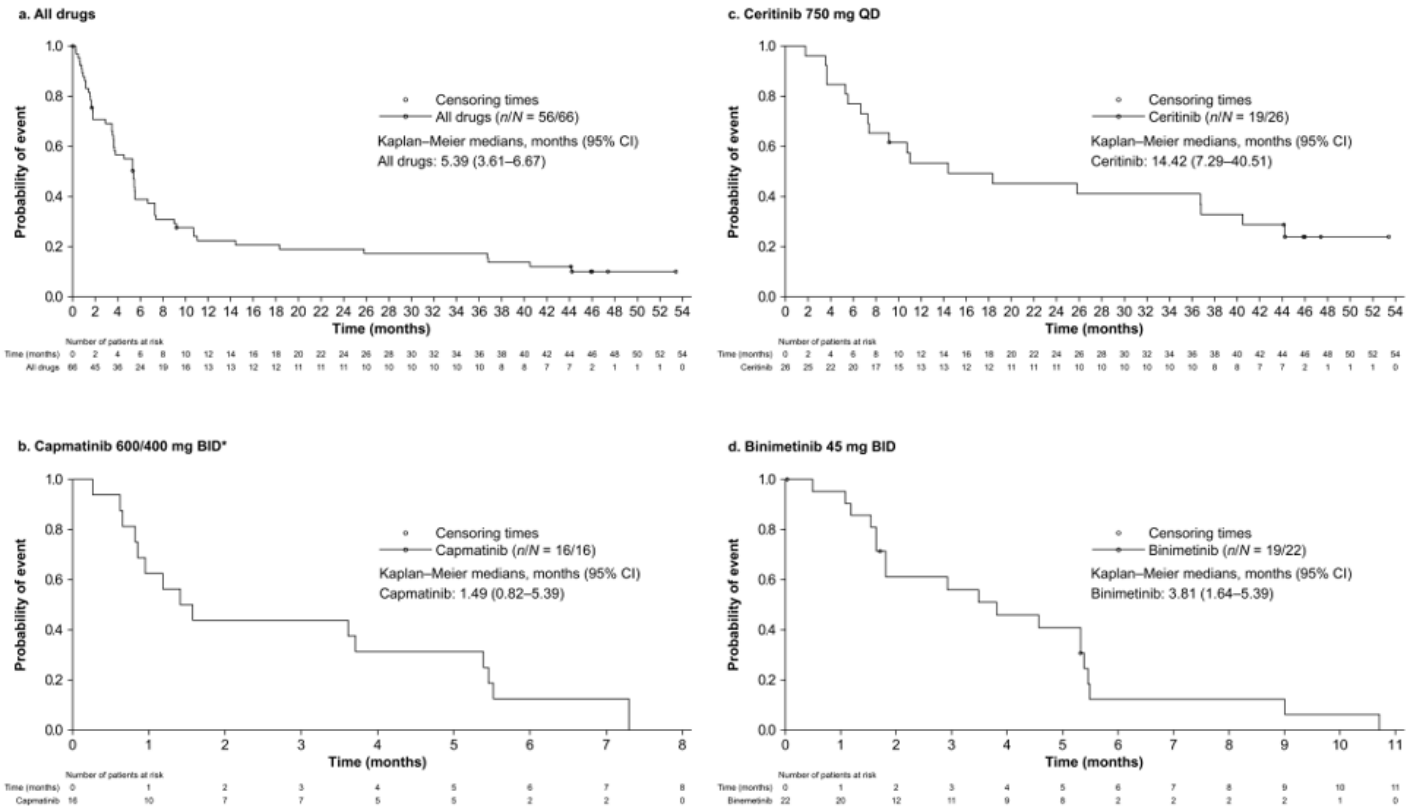

Figure 2

Kaplan–Meier curves of progression-free survival

Kaplan–Meier curves of progression-free survival (PFS) for all study patients and per treatment arm. **a** PFS plot for all patients with either *MET* alterations, *ALK* or *ROS1* rearrangement, and *KRAS*, *NRAF* or *BRAF* mutations who received targeted treatment matching their molecular alteration. **b** PFS plot in the capmatinib arm. **c** PFS plot in the ceritinib arm. **d** PFS plot in the binimetinib arm.

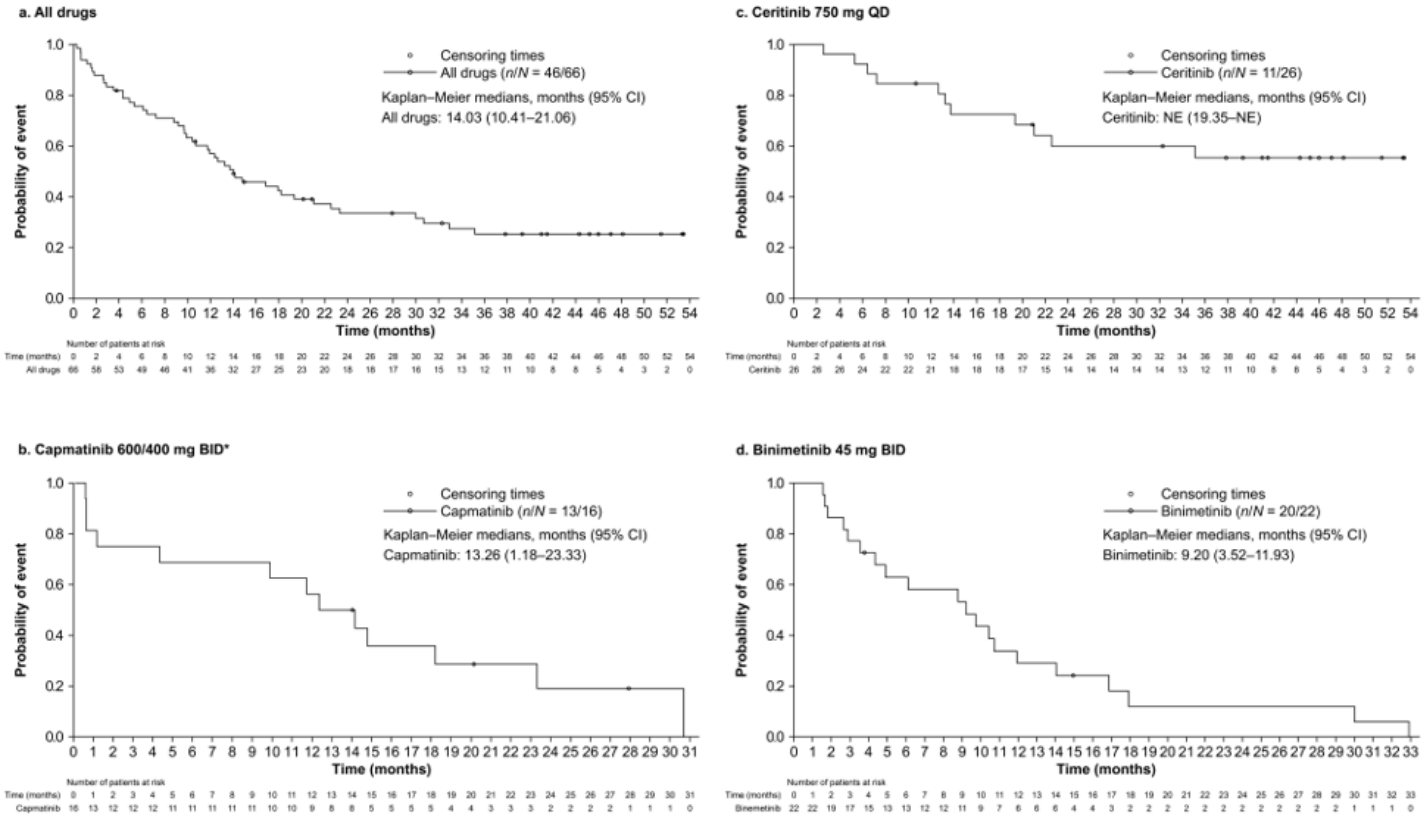

Figure 3

Kaplan–Meier curves of overall survival

Kaplan–Meier curves of overall survival (OS) for all study patients and per treatment arm. **a** OS plot for all patients with either *MET* alterations, *ALK* or *ROS1* rearrangement, and *KRAS*, *NRAF* or *BRAF* mutations who received targeted treatment matching their molecular alteration. **b** OS plot in the capmatinib arm. **c** OS plot in the ceritinib arm. **d** OS plot in the binimetinib arm.

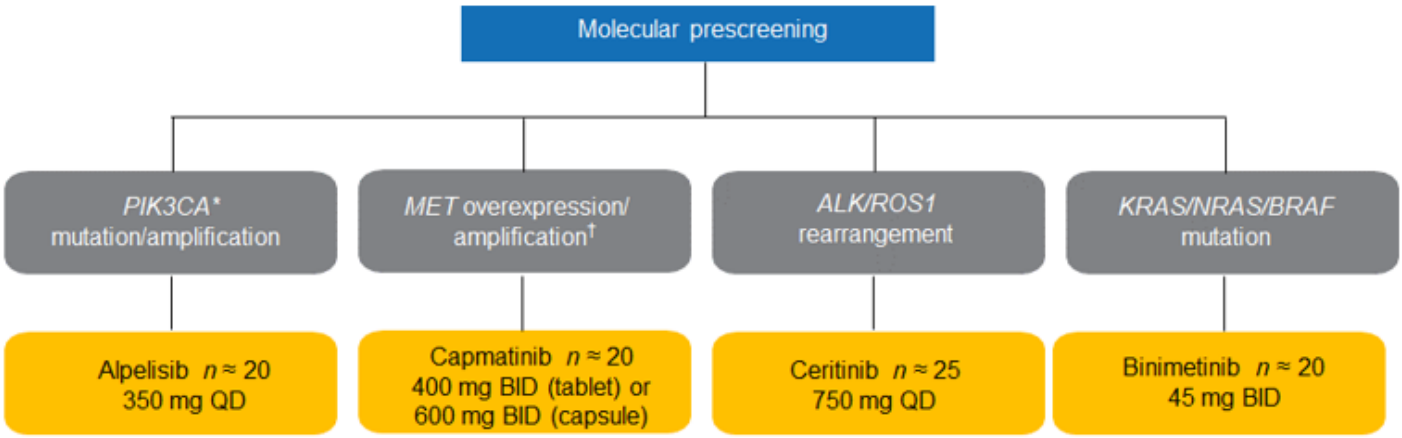

Figure 4

CLUSTER trial study design

[a]GCN ≥4; [†]IHC intensity 3+ in ≥50% of tumor cells or IHC intensity score 2+ in ≥50% of tumor cells and GCN ≥5 by FISH.

ALK, anaplastic lymphoma kinase; BID, twice daily; *BRAF*, serine/threonine protein kinase B-Raf; FISH, fluorescence *in situ* hybridization; GCN, gene copy number; IHC, immunohistochemistry; *KRAS*, Kristen *RAS* viral oncogene homolog; *MET*, mesenchymal epithelial transition; *NRAS*, neuroblastoma *RAS* viral oncogene homolog; *PIK3CA*, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; QD, once daily;

ROS1, translocation proto-oncogene receptor tyrosine kinase rearrangement.

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