Supplementary Data

Table S1. Expansion cohorts (mobocertinib 160 mg daily): cohort-specific inclusion criteria and number of patients enrolled

Cohort number	Description, inclusion criteria	n[a]
1	Patients with NSCLC with *EGFR* exon 20 activating insertions, who have either not received or not shown an objective response to an EGFR TKI, and who have no active, measurable CNS metastases Inclusion criteria: 1. Have a documented *EGFR* in-frame exon 20 insertion by a local test, including A763_Y764insFQEA, V769_D770insASV, D770_N771insNPG, D770_N771insSVD, H773_V774insNPH, or any other in-frame exon 20 insertion mutation. The *EGFR* exon 20 insertion mutation can be either alone or in combination with other *EGFR* or *HER2* mutations 2. Previously treated with one or more regimens of systemic therapy for locally advanced or metastatic disease 3. Prior treatment with an EGFR TKI is allowed unless the patient had an objective response and subsequent progression as assessed by the investigator or treating physician during treatment with that prior TKI 4. Not eligible for Expansion Cohort 3	22
2	Patients with NSCLC with *HER2* exon 20 activating insertions or point mutations and no active, measurable CNS metastases Inclusion criteria: 1. Have one of the following documented by a local test: a. A *HER2* exon 20 insertion including A775_G776insYVMA, G776_V777insVC, or P780_Y781insGSP, or any other in-frame exon 20 insertion mutation b. An activating point mutation in *HER2* including, but not limited to, L755S, G776V, and V777L 2. The *HER2* exon 20 insertion mutation or point mutation can be either alone or in combination with other *EGFR* mutations except *EGFR* exon 20 insertion mutations 3. Previously treated with one or more regimens of systemic therapy for locally advanced or metastatic disease 4. Prior treatment with a pan-HER TKI (e.g., afatinib, neratinib, or dacomitinib) is allowed unless the patient had an objective response and subsequent progression as assessed by the investigator or treating physician during treatment with that prior TKI 5. Not eligible for Expansion Cohort 3	21
3	Patients with NSCLC with *EGFR* exon 20 activating insertions or *HER2* exon 20 activating insertions or point mutations and active, measurable CNS metastases Inclusion criteria: 1. Have one of the following documented by a local test:	8

Cohort number	Description, inclusion criteria	n[a]
	a. An *EGFR* exon 20 insertion: A763_Y764insFQEA, V769_D770insASV, D770_N771insNPG, D770_N771insSVD, H773_V774insNPH, or any other in-frame exon 20 insertion mutation b. A *HER2* exon 20 insertion: A775_G776insYVMA, G776_V777insVC, P780_Y781insGSP, or any other in-frame exon 20 insertion mutation c. An activating point mutation in HER2 including, but not limited to, L755S, G776V, and V777L The above mutations can be either alone or in combination with other *EGFR* mutations 2. Previously treated with one or more regimen of systemic therapy for locally advanced or metastatic disease. 3. For patients with an *EGFR* exon 20 insertion: prior treatment with an EGFR TKI is allowed unless the patient had an objective response and subsequent progression as assessed by the investigator or treating physician during treatment with that prior TKI 4. For patients with a *HER2* exon 20 insertion or *HER2* activating point mutation: prior treatment with a pan-HER TKI (e.g., afatinib, neratinib, or dacomitinib) is allowed unless the patient had an objective response and subsequent progression as assessed by the investigator or treating physician during treatment with that prior TKI 5. Have either previously untreated intracranial CNS metastases or previously treated intracranial CNS metastases with radiologically documented new or progressing CNS lesions 6. Have at least one target (i.e., measurable) intracranial CNS lesion (≥10 mm in longest diameter by contrast enhanced magnetic resonance imaging [MRI]). Lesions previously treated by stereotactic radiosurgery (SRS) or surgical resection should not be included as a target lesion. Lesions previously treated with whole brain radiation therapy (WBRT) may be included as a target lesion if (1) the last administration of WBRT was >3 months prior to the first dose of mobocertinib and (2) unequivocal radiological progression of the lesion has been observed.	
4	Patients with NSCLC with other targets against which mobocertinib is active (examples include *EGFR* exon 19 deletions or exon 21 substitutions [with or without T790M mutations] and other uncommon *EGFR* activating mutations), without active CNS metastases Inclusion criteria: 1. Have one of the following documented by a local test: an activating mutation in *EGFR* including exon 19 deletions or exon 21 L858R substitution (with or without T790M), or an uncommon activating mutation other than exon 20 insertion including, but not limited to, G719X (where X is any other amino acid), S768I, L861Q, or L861R 2. Treatment naive for locally advanced or metastatic disease or previously treated with one or more regimens of systemic therapy for locally advanced or metastatic disease	29
5	Patients with NSCLC with *EGFR* exon 20 activating insertions, who have previously shown an objective response to or SD with an EGFR TKI and subsequently progressed, without active CNS metastases Inclusion criteria: 1. Have a documented *EGFR* in-frame exon 20 insertion by a local test, including A763_Y764insFQEA, V769_D770insASV, D770_N771insNPG, D770_N771insSVD, H773_V774insNPH, or any other in-frame exon 20 insertion mutation. The *EGFR* exon 20 insertion mutation can be either alone or in combination with other *EGFR* or *HER2* mutations 2. Previously treated with one or more regimens of systemic therapy for locally advanced or metastatic disease	19

Cohort number	Description, inclusion criteria	n[a]
	3. Previously showed an objective response to an EGFR TKI or SD for at least 6 months with an EGFR TKI, then subsequently progressed as assessed by the investigator or treating physician	
6	Patients with NSCLC with *EGFR* exon 20 activating insertions, who have not received prior systemic anticancer treatment for locally advanced or metastatic disease, without active CNS metastases Inclusion criteria: 1. Have a documented *EGFR* in-frame exon 20 insertion by a local test, including A763_Y764insFQEA, V769_D770insASV, D770_N771insNPG, D770_N771insSVD, H773_V774insNPH, or any other in-frame exon 20 insertion mutation. The *EGFR* exon 20 insertion mutation can be either alone or in combination with other *EGFR* or *HER2* mutations. 2. No prior systemic treatment for locally advanced or metastatic disease (with the exception below): Prior adjuvant chemotherapy for Stage I to III or combined modality chemotherapy/radiation for locally advanced disease is allowed if completed >12 months prior to the first dose of mobocertinib	29
7	Patients with solid tumors other than NSCLC with *EGFR/HER2* mutations against which mobocertinib is active, without active CNS metastases Inclusion criteria: 1. Have a locally advanced or metastatic solid tumor that is not NSCLC, including, but not limited to, bladder/urinary tract cancer, breast cancer, gastric/esophageal cancer, biliary tract cancer, and head and neck cancer. 2. Is refractory to standard therapy. 3. Have a target against which mobocertinib is active, documented by a local test, including, but not limited to, the following: a. An activating mutation in *EGFR* including exon 20 insertions, exon 19 deletions or exon 21 L858R substitution (with or without T790M), or an uncommon activating mutation including G719X (where X is any other amino acid), S768I, L861Q, or L861R b. An *HER2* exon 20 insertion: A775_G776insYVMA, G776_V777insVC, P780_Y781insGSP, or any other in-frame exon 20 insertion mutation c. An activating point mutation in *HER2* including, but not limited to, L755S, G776V, and V777L	2

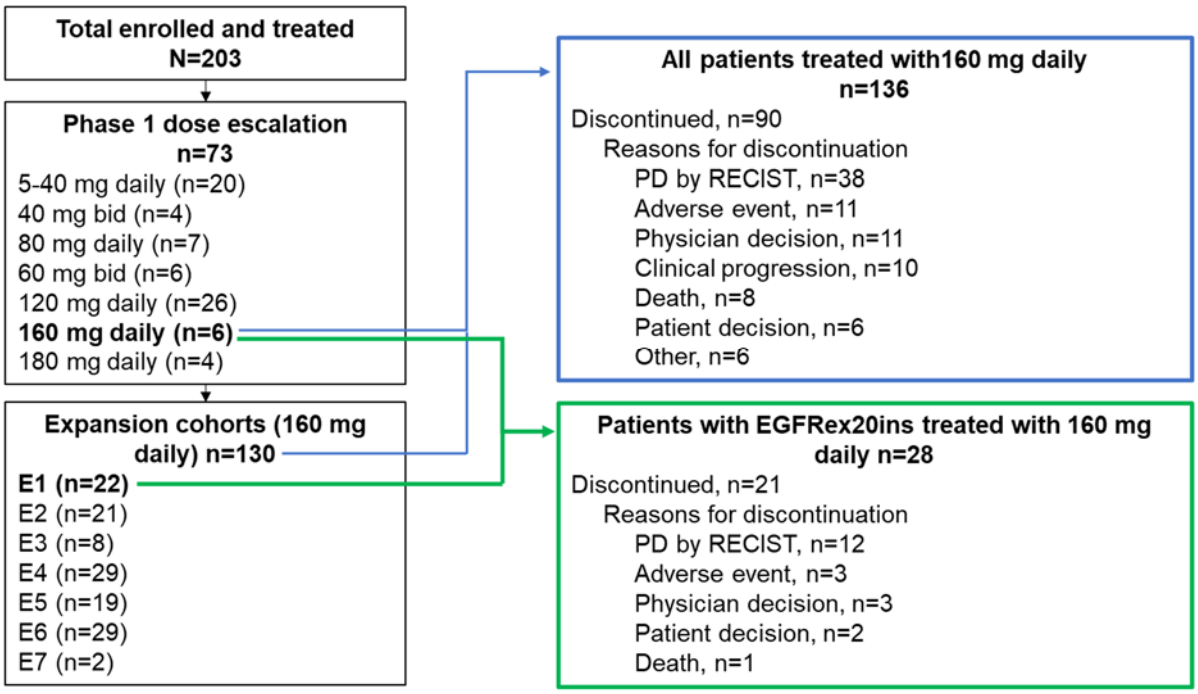
[a] Number of patients enrolled as of January 27, 2020.

CNS, central nervous system EGFR, epidermal growth factor receptor; HER, human epidermal growth factor receptor; HER2, human epidermal growth factor receptor-2; NSCLC, non–small cell lung cancer; SD, stable disease; TKI, tyrosine kinase inhibitor.

Supplementary Table S2. Blood sampling schedule for pharmacokinetic assessments in the dose escalation study

Cycle	Blood sampling schedule
Cycle 1	• Pre-dose (time 0), and at 0.5, 1 hour (±5 minutes), 2, 4, 6, 8 hours (±10 minutes), and 24 hours (±60 minutes) after the first dose on Cycle 1, Day 1 The 24-hour sample will be collected prior to drug administration on Cycle 1, Day 2 • Pre-dose on Cycle 1, Days 8, 15, and 22
Cycle 2	• Pre-dose and at 0.5, 1 hour (±5 minutes), 2, 4, 6, 8 hours (±10 minutes), and 24 hours (±60 minutes) after administration of mobocertinib on Cycle 2, Day 1 • The 24-hour sample will be collected prior to drug administration on Cycle 2, Day 2
Cycle 3	• Pre-dose on Cycle 3, Day 1

Supplementary Figure S1. Patient disposition.



Expansion cohorts: E1, Expansion cohort 1: Patients with NSCLC with activating *EGFR*ex20ins who have either not received or not shown an objective response to an EGFR TKI, and who have no active, measurable CNS metastases; E2, Expansion cohort 2: Patients with NSCLC with *HER2* exon 20 activating insertions or point mutations and no active, measurable CNS metastases; E3, Expansion cohort 3: Patients with NSCLC with activating *EGFR*ex20ins or *HER2* exon 20 activating insertions or point mutations and active, measurable CNS metastases; E4, Expansion cohort 4: Patients with NSCLC with other targets against which mobocertinib is active (examples include *EGFR* exon 19 deletions or exon 21 substitutions [with or without T790M mutations] and other uncommon *EGFR* activating mutations), without active CNS metastases; E5, Expansion cohort 5: Patients with NSCLC with activating *EGFR*ex20ins who have previously shown an objective response to or SD with an EGFR TKI and subsequently progressed, without active CNS metastases; E6, Expansion cohort 6: Patients with NSCLC with activating *EGFR*ex20ins mutations who have not received prior

systemic anticancer treatment for locally advanced or metastatic disease, without active CNS metastases; E7, Expansion cohort 7: Patients with solid tumors other than NSCLC with *EGFR/HER2* mutations against which mobocertinib is active, without active CNS metastases.

Abbreviations: bid, twice daily; CNS, central nervous system; *EGFR*ex20ins, epidermal growth factor receptor exon 20 insertions; *HER2*, human epidermal growth factor receptor-2; NSCLC, non–small cell lung cancer; PD, progressive disease; daily, once daily; RECIST, Response Evaluation Criteria in Solid Tumors version 1.1; SD, stable disease; TKI, tyrosine kinase inhibitor.