Supplementary information

Methods

Inclusion criteria

1. Men and women who are ≥18 years old at signing of informed consent.

2. Histologically confirmed cancers in patients with activating *ERBB* mutations and who are refractory to standard therapy or for which standard or curative therapy does not exist or is not considered sufficient or appropriate by the Investigator.

3. At the time of screening, a previously documented mutation: *HER2* mutation in breast, bladder/urinary tract, biliary tract, colorectal, endometrial, gastroesophageal, lung, ovarian, and any other cancers.

4. At least one measurable lesion, preferably as defined by Response Evaluation Criteria in Solid Tumors (version 1.1)[1].

5. Left ventricular ejection fraction ≥50% measured by multiple-gated acquisition scan or echocardiogram.

6. Eastern Cooperative Oncology Group performance status of 0–2.

7. Female patients with cancers known to secrete β-human chorionic gonadotropin (β-hCG), ie, germinomas, are eligible if the pattern of serum β-hCG is suggestive of the malignancy and the pelvic ultrasound is negative for pregnancy.

8. Men must agree and commit to use a barrier method of contraception while on treatment and for 3 months after the last dose of the investigational product. Women of child-bearing potential must agree and commit to the use of a highly effective double-barrier method of contraception (eg, a combination of male condom with an intravaginal device such as the cervical cap, diaphragm, or vaginal sponge with spermicide) or a non-hormonal method, from the signing of the informed consent until:

    i. 28 days after the last dose of neratinib monotherapy, or

    ii. 6 months after the last dose of paclitaxel, or

    iii. 1 year after the last dose of fulvestrant.

9. Provide written informed consent to participate in the study and follow the study procedures.

Exclusion criteria

1. Prior treatment with any *HER2*-directed tyrosine kinase inhibitor (eg, lapatinib, afatinib, dacomitinib, neratinib) with the exception of patients with non-small cell lung cancer (NSCLC) who may have received afatinib and remain eligible.

2. Not recovered to at least grade 1 or baseline (National Cancer Institute [NCI] Common Terminology Criteria for Adverse Events [CTCAE] version 4.0) from all clinically significant adverse events related to prior therapies (excluding alopecia).

3. Received chemotherapy or biologic therapy ≤2 weeks or five half-lives of the agent used, whichever is shorter, prior to the start of neratinib.

4. Received radiation therapy ≤14 days prior to initiation of investigational product, except primary brain tumour patients.

5. Patients who are receiving any other anticancer agents with the exception of patients on (1) a stable dose of bisphosphonates or denosumab or (2) sex hormone therapy in the case of breast, prostate, or gynaecological cancers.

6. Received prior therapy resulting in a cumulative epirubicin dose >900 mg/m^2 or cumulative doxorubicin dose >450 mg/m^2. If another anthracycline or more than one anthracycline has been used, the cumulative dose must not exceed the equivalent of 450 mg/m^2 doxorubicin.

7. Symptomatic or unstable brain metastases. (Note: Asymptomatic patients with metastatic brain disease who have been on a stable dose of corticosteroids for treatment of brain metastases for at least 14 days are eligible to participate in the study.) Patients with primary central nervous system tumours are eligible.

8. Active uncontrolled cardiac disease, including cardiomyopathy, congestive heart failure (New York Heart Association functional classification of ≥2), unstable angina (symptomatic angina pectoris within the past 180 days that required the initiation of or increase in anti-anginal medication or other intervention), myocardial infarction within 12 months of enrolment, or ventricular arrhythmia (except for benign premature ventricular contractions). For patients with NSCLC, the following are additionally excluded: conduction abnormality requiring a pacemaker; supraventricular and/or nodal arrhythmias not controlled with medication; valvular disease with documented compromise in cardiac function; symptomatic pericarditis; any history of myocardial infarction documented by elevated cardiac enzymes or persistent regional wall abnormalities on assessment of left ventricular function; any history of documented congestive heart failure and/or cardiomyopathy.

9. Demonstrates a QTc interval >450 ms for men or >470 ms for women or known history of congenital QT prolongation or torsade de pointes.

10. Inadequate bone marrow, renal, or hepatic function as defined on screening laboratory assessments.

11. Uncontrolled concurrent malignancy (early-stage or chronic disease is allowed if not requiring active therapy or intervention and is under control).

12. Active infection or unexplained fever >38.5°C (101.3°F).

13. Women who are pregnant, are planning on becoming pregnant, or are breast-feeding.

14. Significant chronic gastrointestinal disorder with diarrhoea as a major symptom (eg, Crohn's disease, malabsorption, or grade ≥2 NCI CTCAE [version 4.0] diarrhoea of any aetiology at baseline).

15. Clinically active infection with a hepatitis virus.

16. Evidence of significant medical illness, abnormal laboratory finding, or psychiatric illness/social situations that could, in the Investigator's judgement, make the patient inappropriate for this study.

17. Known hypersensitivity to any component of the investigational product, required combination therapy, or loperamide.

18. Unable or unwilling to swallow tablets.

19. Patients bearing certain somatic *HER* mutations, such as those that are subclonal in nature, or resulting in the expression of truncated proteins including alterations that result in a premature stop codon or a change in reading frame (ie, frameshift mutations) may not be considered for eligibility.

20. Patients with known activating *KRAS* mutations.

Reference

1. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur. J. Cancer* **45(2),** 228–247 (2009).

Supplementary Table 1 Central confirmation of *HER2* mutations.

Patient ID	Enrolment assay	*HER2* mutation code	Confirmed by *HER2* targeted sequencing (Custom-seq)	Confirmed by MSK-IMPACT	Confirmed by MSK-ACCESS	Additional *HER2* mutations found	Best objective response
1	MDA Solid Tumor Genomic Assay	V777L	NA	NA	V777L		NE
2	Brigham and Women's in-house	L755S	NA	L755S	NA		SD
3	Guardant360	V777L	NA	V777L[a]	NA		PR
4	SNaPshot	V777L	NA	NA	NA		PD
5	FoundationOne	L755S	NA	NA	NA		PD
6	FoundationOne	G776C; H878Y	NA	NA	G776C; H878Y		SD
7	Guardant360	S310F	NA	NA	S310F[a]	D277Y	PD
8	Caris MiProfile	D769Y	NA	NA	D769Y		SD
9	FoundationOne	S310F	NA	NA	S310F		PD
10	FoundationOne	S310F	NA	NA	S310F		NE
11	Pangaea Sanger exon 8, 19−21	S310F	NA	S310F	NA		PD
12	RT-PCR	V842I	Inconclusive	Not confirmed	NA		NE
13	Oncomine	V842I	NA	V842I	NA		NE
14	FoundationOne	T733I	NA	T733I	NA		SD
15	MSK-IMPACT	S310F	S310F	S310F	NA		PR
16	MSK-IMPACT	S310F	S310F	S310F	NA		PD
17	MSK-IMPACT	S310Y	NA	S310Y	NA		SD
18	MSK-IMPACT	S310Y	NA	S310Y	NA		SD
19	Peter Mac somatic panel (tissue)	V659E	V695E	V695E	NA	V842I	uPR
20	AmpliSeq comprehensive cancer panel	S310F	NA	NA	S310F	L253V[a]	SD
21	AmpliSeq colon and lung cancer panel	V777L	NA	NA	V777L		PR
22	FoundationOne CDx	R678Q	NA	R678Q	NA		NE
23	FoundationOne CDx	S310F; V777L	NA	S310F; V777L	NA		PD
24	FoundationOne	R678Q	NA	R678Q	NA		NE
25	Stanford STAMP	S310F	NA	S310F	NA		PR

[a]Alteration at or near limit of detection of the assay, underwent manual re-review to confirm accuracy of alteration.

MDA MD Anderson, *MSK-ACCESS* Memorial Sloan Kettering-Analysis of Circulating cfDNA to Evaluate Somatic Status, *MSK-IMPACT* Integrated Mutation Profiling of Actionable Cancer Targets, *NA* not available, *NE* not evaluable, *PD* progressive disease, *PR* partial response, *RT-PCR* reverse transcription polymerase chain reaction, *SD* stable disease, *STAMP* Solid Tumor Actionable Mutation Panel, *uPR* unconfirmed partial response.

Supplementary Table 2 Serious adverse events.

Adverse event	Biliary tract (n=25)
Patients with ≥1 reported serious adverse event	16 (64%)
Dehydration	3 (12%)
Abdominal pain	2 (8%)
Diarrhoea	2 (8%)
Pyrexia	2 (8%)
Sepsis	2 (8%)
Acute kidney injury	1 (4%)
Anaemia	1 (4%)
Asthenia	1 (4%)
Bacteraemia	1 (4%)
Bile duct stone	1 (4%)
Blood bilirubin increased	1 (4%)
Decreased appetite	1 (4%)
Device-related infection	1 (4%)
Encephalopathy	1 (4%)
Gallbladder obstruction	1 (4%)
Gastric ulcer	1 (4%)
General physical health deterioration	1 (4%)
Hypotension	1 (4%)
International normalised ratio increased	1 (4%)
Large intestinal haemorrhage	1 (4%)
Liver abscess	1 (4%)
Malnutrition	1 (4%)
Nausea	1 (4%)
Obstruction gastric	1 (4%)
Respiratory failure	1 (4%)
Small intestinal obstruction	1 (4%)
Vomiting	1 (4%)

Data are n (%).

Supplementary Table 3 Characteristics of diarrhoea.

Characteristic	Biliary tract cancer (n=25)
Diarrhoea incidence	
Any grade	14 (56%)
Grade 1	3 (12%)
Grade 2	5 (20%)
Grade 3	6 (24%)
Action taken for diarrhoea	
Concomitant medication	10 (40%)
Leading to temporary dose hold	3 (12%)
Leading to hospitalisation	1 (4%)
Diarrhoea episodes	
Median time to first grade 3 diarrhoea, days (range)	7 (3–28)
Median duration per episode of grade 3 diarrhoea, days (range)	5.5 (1–56)

Data are n (%) unless otherwise stated.