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Afatinib for advanced cancers carrying an EGFR, HER2 or HER3 mutation: an open label, phase II, Belgian Precision study

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ABSTRACT (words 292)

Background

The Belgian Precision project aims to implement tumor-agnostic next generation sequencing (NGS) in advanced cancer patients and expand genotype-matching drug availability. The current investigator-driven trial aimed to investigate the efficacy of afatinib in advanced solid tumors with HER2, EGFR or HER3 mutation.

Methods

This is an open-label phase II trial with three cohorts: HER2, HER2 and HER3-mutated previously treated solid tumors. The primary endpoint was objective response rate (ORR). For each cohort a Simon two-stage design was used. Observation of ≥2 responses in the first ten patients prompted a further 19 to be included. Secondary endpoints were disease control rate (DCR), duration of response (DOR), progression-free survival (PFS), overall survival (OS) and safety.

Results

A total of 45 patients were included in this study with median age 62 years. Recruitment was hampered because of low incidence of mutations in different tumor types, absence of systematic NGS testing in at the start of the trial as well as the COVID pandemic.

For the HER2 cohort (n=30), ORR was 3.3% (one partial response) and DCR was 23.3%.

In the EGFR cohort a total of seven patients were included resulting in an ORR in 2/7 (28.6%) patients with duration of response of respectively 6.6 and 15.4 months.

In the HER3 cohort, a total of eight patients were included but none demonstrated an objective response.

Safety data were consistent with the known safety profile of afatinib.

Conclusion

The present phase II study investigating afatinib in HER2, EGFR or HER3 mutant, pretreated solid tumors did not reach its primary endpoint in the HER2 cohort. Both the EGFR and HER3 cohort did not

reach full accrual, but clinical meaningful responses were observed in two EGFR mutated patients. Further exploration of HER targeting in solid tumors is warranted.

KEYWORDS: afatinib, EGFR, HER2, HER3, precision

BODY TEXT ()

INTRODUCTION

The introduction of Next-Generation Sequencing (NGS) in routine clinical practice has uncovered a myriad of cancer gene mutations across different solid tumor types. It is estimated that >50% of cancers could harbour an actionable mutation[1]. Targeted therapy, specifically directed against such an activating genomic alteration, could lead to greater benefit for the patient than conventional systemic therapy[2,3]. However, most of the genomic alterations are present in very low frequencies insufficient to organize prospective pharma-driven, clinical trials[4,5,6]

The Belgian Society of Medical Oncology (BSMO) launched a national Precision initiative to provide access to NGS for different tumor types as well as access to biomarker matching drugs by means of tumor agnostic basket phase II trials[7,8,9]. One of these studies investigated the efficacy of afatinib, a selective and irreversible erbB family blocker, in advanced cancers harboring EGFR, HER2 or HER3 mutations

Afatinib is approved for the treatment of EGFR mutant non-small cell lung cancer (NSCLC), resulting in improvement of objective response rate (ORR) and progression free survival (PFS) compared to chemotherapy[10]. In cancers, other than NSCLC, EGFR mutations are rare (1.6%)[5]. Mutations of HER2 and HER3, other targets of afatinib, are equally rare, ≤5% and ≤1% respectively[11]. Nevertheless, patients with these rare mutations may derive important benefit from targeted therapy.

The aim of the present phase II trial is to investigate the clinical activity of afatinib in advanced, pretreated solid tumors harboring an EGFR, a HER2 or a HER3 mutation.

PATIENTS AND METHODS

Study design and patients

This open label phase II study was conducted from October 2017 to July 2021 in nine Belgian hospitals. The objective of the study was to evaluate the efficacy and safety of afatinib in patients with advanced, previously treated solid tumors with EGFR, HER2, or HER3 mutations. Patients with advanced cancers were assigned to one of the following three cohorts: Cohort 1 EGFR mutations, except for EGFR-mutated non-squamous NSCLC; cohort 2 HER2 mutations and cohort 3 HER3 mutations.

Patients were eligible for enrolment in case of histologically confirmed advanced cancer with mutations in EGFR, HER2, or HER3 after at least one standard treatment administered previously, and no possibility for inclusion in any other trial available for the tumor type. Patients had to be at least 18 years of age, have an ECOG performance status of 0-2, and have a life expectancy of at least 3 months according to the treating physician. Eligible patients had adequate organ function with ANC > 1500/mm^3, platelet count > 75,000/mm^3, and creatinine clearance > 45 ml/min. Toxicity from any prior therapy must be resolved to a grade of 1 or lower.

Written informed consent was obtained from all patients prior to inclusion in the study. The study was approved by the ethics committees of all hospitals (EC-2016-392) and was conducted in accordance with the Declaration of Helsinki.

Study treatment

Afatinib was administered orally at an initial dose of 40 mg once daily. Treatment continued until disease progression, the occurrence of intolerable toxicity, or voluntary withdrawal by the patient from the study. Treatment interruptions and dose adjustments were permitted according to pre-specified rules to manage adverse events. Adjustments were made for improving tolerability and for patient safety, with the potential for increase to 50 mg or decrease to 30 mg or 20 mg as needed. Upon progression, paclitaxel chemotherapy could be added to last tolerated dosing of afatinib.

Paclitaxel was administered intravenously once a week with a dose of 80 mg/m² for three weeks every four-week period.

Efficacy and safety measures

Tumor evaluations were performed using CT imaging according to the RECIST version 1.1 criteria. Evaluations occurred at baseline, during screening within 28 days of the first dose of treatment, and repeated every 8 weeks up to cycle 7, followed by every 12 weeks for the remainder of the treatment and follow-up.

Adverse events were recorded and graded at each patient visit using the CTCAE criteria, version 4.0, as specified in the study protocol.

Outcomes

Efficacy results were analyzed for each cohort separately. Safety profile was analyzed for the three cohorts together.

The primary objective of this clinical trial was the objective response rate (ORR), which is characterized as the percentage of patients who attain either a Complete Response (CR) or a Partial Response (PR) as per the RECIST 1.1 criteria, for each cohort separately. Disease control rate was defined as the sum of patients with an ORR and patients with a stable disease (SD) lasting for six months or more.

Secondary objectives were progression-free survival (PFS), defined as the time from the start of treatment to the occurrence of either documented disease progression or death due to any cause, whichever occurs first, overall survival (OS), defined as the time from initiation of treatment to death of any cause, safety profile as well as ORR when adding paclitaxel to afatinib.

Statistical analysis

Sample size calculation

For each cohort an optimal Simon's two-stage design was used. The null hypothesis of a true response rate of 10% was tested against a one-sided alternative of a true response rate of 30%. In the first stage,

10 patients were accrued in each cohort. If there was one or fewer responses in these ten patients, that cohort was stopped. Otherwise, 19 additional patients were accrued for a total of 29. The null hypothesis was rejected if six or more responses were observed in 29 patients. This design yielded a type I error rate of 5% and a power of 80% when the true response rate was 30%.

Data were analyzed using SPSS version 30.

Descriptive statistics (%, range) were used for patient characteristics and ORR. PFS and OS were calculated using Kaplan Meier survival analysis.

RESULTS

Patient characteristics

A total of 45 patients were enrolled in this study: 30 in the HER2 cohort, seven in the EGFR cohort and eight in the HER3 cohort. Patient characteristics for each cohort are represented in table I.

Efficacy

HER2 cohort

In the HER2 cohort, the ORR was 3.3% with one patient out of 30 obtaining a PR, which lasted for 8.5 months. This was a NSCLC patient with a HER2 exon 20 insertion who was received three previous treatment lines. One patient initially classified as a PR was later reclassified as SD, explaining why this cohort proceeded to the second stage of patient inclusion. A total of 14 patients (46.7%) obtained a SD which lasted for more than six months in six patients. These six patients had either mutations in the kinase domain of HER2 (two with exon 20 insertions, one lung and one pancreas, and one with unspecified mutation (breast) or in the extracellular domain with S310 mutations in exon 8 (one cervix, one breast and one kidney). The DCR was therefore 23.3% (7/30).

Treatment was stopped in 22 patients (73.3%) because of disease progression and in six patients (20%) because of AE. Median PFS was 3.8 months (95% CI 2.1;5.5) and median OS was 7.9 months (95% CI 7.0;8.8).

At progression, paclitaxel was added to afatinib in three patients. Two of these patients (one lung with exon 20 insertion and one breast with exon 8 mutation) demonstrated a SD on afatinib monotherapy lasting for 8.2 and 8.1 months respectively. When adding paclitaxel, these two patients developed a PR lasting for 11 and 5.5 months respectively. The third patient, a lung cancer with exon 20 mutation, had a PD on afatinib monotherapy and demonstrated further progression after addition of paclitaxel.

EGFR cohort

In the EGFR cohort the ORR was 28.6% with two out of seven patients achieving a PR. The first patient was a breast cancer with a point mutation in exon 20 (R776G) and the second a pancreatic cancer with a frameshift in exon 19. DOR was 6.6 and 15.4 months and PFS was 7.8 months and 17.1 months respectively for these two patients. One additional patient demonstrated a stable disease with a PFS of 3.7 months. All seven patients stopped afatinib treatment because of disease progression.

In one patient with initial PD, paclitaxel was added to afatinib after progression, but this combination was stopped prematurely because of AEs before an evaluation was performed.

HER3 cohort

Of the eight patients with a HER3 mutation, none developed an objective response. Five (62.5%) patients achieved a stable disease of which two lasted for more than six months. These two patients were one esophagus cancer with a S10496 HER3 mutation (PFS of 7.6 months) and one head and neck cancer with a D297Y mutation (PFS of 7.1 months).

Seven patients stopped afatinib treatment because of disease progression and one patient because of AEs. At progression, paclitaxel was added to afatinib in one patient with a colorectal cancer. This patient demonstrated a disease progression as best response to afatinib monotherapy and the addition of paclitaxel resulted in further disease progression.

Safety

All grades treatment related AEs appeared in 97.8% (44/45) patients with 17 (37.8) patients experiencing a grade 3/4 AE. Dose interruptions were necessary in 24/45 (53.3%) patients and dose reductions in 10/45 (22.2%) patients.

AEs observed in >10% of patients are listed in table 2. The most frequent AEs were diarrhea (91.1% with 20% grade ≥3), rash (80% with 4.4% grade≥3) and stomatitis (48.9% with 4.4% grade ≥3).

DISCUSSION

The present phase II trial is part of a Belgian Precision initiative aiming to increase access to molecular testing by NGS as well as access to targeted therapies if a molecular alteration was identified[7,8,9].

In the present study, patients with advanced tumors harboring either HER2, EGFR (except EGFR mutated NSCLC), or HER3 mutation were treated with afatinib. Recruitment in this trial was hampered initially by the lack of systematic NGS testing in all tumor types followed by the COVID crisis as well as the very low incidence of these mutations in different tumor types. As a result, only the HER2 cohort completed preplanned accrual, while the EGFR and HER3 cohort were closed prematurely because of slow patient accrual.

In the HER2 cohort (n=30), the most frequent tumors were NSCLC (36.7%) and breast cancer (26.7%). This HER2 cohort did not meet its primary endpoint with only one PR in a NSCLC and an additional six SD lasting for >6 months. Although previous case series as well as retrospective studies did report activity of afatinib in HER2 mutant NSCLC, other phase II studies with afatinib in this setting did not reach their primary endpoint of activity.[12-16] In our study out of 11 patients with NSCLC, one (9%) patient obtained a PR and one a SD (9%) lasting for more than six months, which is in line with results from the phase II studies[15,16]. Additionally, we did not observe significant activity across other tumor

types in our study, which is in line with the findings of the phase II ECOG-ACRIN trial[17]. More recently the registration of trastuzumab-deruxtecan for HER2 mutant NSCLC has offered new treatment options for this molecular subgroup of NSCLC patients.[18] In addition, a phase II trial of trastuzumab-deruxtecan in HER2 -expressing solid tumors reported promising activity with an ORR of 36.1% and median DOR of 11.3 months.[19] Both warrant further exploration of trastuzumab-deruxtecan in HER2 mutated solid tunors. In addition, novel tyrosine kinase inhibitors targeting HER2 are in clinical development and should be explored in HER2 mutated solid tumors, regardless of primary origin.

For the EGFR cohort, ORR was higher with two PR on a total of seven patients (28.6%). However, because of slow accrual this cohort could not proceed to the planned second stage of the Simon two stage design. Nevertheless, in the absence of other therapeutic options, further exploration of EGFR targeted strategies in EGFR mutant solid tumors, excluding NSCLC, is indicated.

Finally, in our study no response was observed in the HER3 mutated cohort of solid tumors, indicating a lack of activity although the cohort was not fully recruited. More recently antibody-drug conjugates targeting HER3 have shown activity in different solid tumors, but a biomarker of response is still lacking.[20] Further exploration of such treatments in HER3 mutated solid tumors may therefore be of interest.

In conclusion, the present phase II trial with afatinib in HER2, EGFR and HER3 mutated solid tumors did not reach its primary endpoint, although three patients did present a clinical meaningful benefit. With the introduction of broader and systematic agnostic NGS as well as the development of new agents including tyrosine kinase inhibitors and anti-body drug conjugates, further exploration of HER inhibition in solid tumors is warranted.

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Table I: Patient characteristics for the total population and for each cohort separately

Characteristics	Total population N=45	HER2 N=30	HER3 N=8	EGFR N=7
Age				
Median	62	62	67.5	60
Range	26-80	26-80	51-70	53-74
Sex M/F (%)				
Males (%)	13 (28.9)	8 (26.7)	3 (37.5)	2 (28.6)
Females (%)	32 (71.1)	22 (73.3)	5 (62.5)	5 (71.4)
Tumor subtype				
Breast cancer	11 (24.4)	8 (26.7)	2 (25)	1 (14.3)
Lung cancer	11 (24.4)	11 (36.7)	0	0
Pancreatic cancer	5 (11.1)	1 (3.3)	2 (25)	2 (28.6)
Head and Neck cancer	4 (8.9)	2 (6.7)	1 (12.5)	1 (14.3)
Cervical cancer	4 (8.9)	3 (10)	0	1 (14.3)
Colorectal cancer	3 (6.7)	2 (6.7)	1 (12.5)	0
Renal cancer	2 (4.4)	1 (3.3)	0	1 (14.3)
Endocrinal cancer	1 (2.2)	0	0	1 (14.3)
Genitourinary cancer	1 (2.2)	1 (3.3)	0	0
Oesophagus cancer	1 (2.2)	0	1 (12.5)	0
Stomach cancer	1 (2.2)	0	1 (12.5)	0
Hepatocellular carcinoma	1 (2.2)	1 (3.3)	0	0
Number of previous lines (%)				
1	13 (28.9)	9 (30)	3 (37.5)	1 (14.3)
2	11 (24.4)	8 (26.7)	0	3 (42.9)
3	11 (24.4)	9 (30)	2 (25)	0
≥4	10 (22.1)	4 (13.3)	3 (37.5)	3 (42.9)

Table II: All grades and grade 3/4 adverse events occuring in >10% of patients (n=45)

Adverse event	**All grades n (%)**	**Grade 3/4 n (%)**
All	44 (97.8)	17 (37.8)
Diarrhea	41 (91.1)	9 (20)
Rash	36 (80)	2 (4.4)
Stomatitis	22 (48.9)	2 (4.4)
Fatigue	16 (35.6)	1 (2.2)
Anorexia	13 (28.9)	2 (4.4)
Nausea	12 (26.7)	2 (4.4)
Epistaxis	9 (20)	0
Paronychia	8 (17.8)	0
Vomiting	7 (15.6)	1 (2.2)
Pruritus	6 (13.3)	0
Epigastric pain	5 (11.1)	0
Dysgeusia	5 (11.1)	0