Titel der Studie

LEONIS pNET: A prospective, non-interventional study in patients with neuroendocrine tumors for evaluation of the treatment with everolimus (Afinitor®): Compliance, quality of life and prospective pharacoeconomics (CRAD001PDE46)

Zielsetzung/Fragestellung

The objective of this study was to obtain data on clinical treatment of patients with progressive pancreatic neuroendocrine tumors (pNET) on treatment with Afinitor®. Parameters of particular interest were compliance, quality of life, pharmacoeconomics, safety and tolerability, effectiveness and number of patients prematurely terminating treatment.

Indikation

Patients with progressive pancreatic neuroendocrine tumors

Wirkstoff

Everolimus

Marke/Handelsname

Afinitor®

Anzahl der vorgesehenen Studienzentren/Praxen in Deutschland

50

Angestrebte Fallzahl beteiligter Patienten

100

Beginn der Studie

14.05.2012

Geplante Dauer der Studie

3 years

Studiennummer

CRAD001PDE46

Unternehmen

Novartis Pharma GmbH
Roonstr. 25
90429 Nürnberg
Deutschland

Stand der Information

27.11.2015

Status der Studie

Study completed

Zusammenfassung der Ergebnisse

Methodologie

This was a multicentric NIS according to § 4 section 23 item 3 of the German Drug Law (AMG) in patients with progressive pNET who were treated with Afinitor®. Only patients who provided informed consent at baseline visit were included in this study. Within the scope of this NIS, only diagnostic procedures as well as medically indicated examinations being conducted according to daily medical routine were documented.

Analysierte Anzahl der Patienten

63

Diagnose und Einschlußkriterium

informed consent form and for whom treatment with Afinitor® according to item 4.1 of the relevant Summary of Product Characteristics (SmPC) was indicated.

Wirkliche Dauer der Studie

3 years

Wirksamkeit unter Alltagsbedingungen

provide information on the application in real-life settings. The objective of this study was to obtain data on clinical treatment of patients with progressive pancreatic neuroendocrine tumors (pNET) on treatment with Afinitor®. Parameters of particular interest were compliance, quality of life, pharmacoeconomics, safety and tolerability, effectiveness and number of patients prematurely terminating treatment.

Sicherheit

Adverse Event (AE)
An "adverse event“ (AE) is defined as every untoward medical condition occurring in a patient after the administration of a drug or treatment, irrespective of whether or not a causal relationship with the drug or treatment was suspected (4th Announcement on the Reporting of Adverse Events and Drug Abuse according to Section 63b(1-8) of the German Drug Law). All AEs occurring in patients had to be documented on the "Adverse Event Report", including the type of the event, its first occurrence and its duration.
Furthermore, the doctor had to document whether or not he suspected a relationship to any of the drugs or treatments the patient had received. Additionally, he was required to report countermeasures taken as well as the outcome of the event.
Serious Adverse Events (SAE)
Using the definitions denoted in §3 Par. 8 of the Guidelines for Good Clinical Practice, GCP, (dated August 9th, 2004), a serious adverse event (SAE) is any untoward medical occurrence which
• Is fatal or life-threatening,
• Requires inpatient hospitalization or prolongation of existing hospitalization
• Results in persistent or significant disability or incapacity
• Results in a congenital anomaly or a birth defect.

Methoden

The planned observation period of patients on treatment with Afinitor® was 12 months. Data were docu¬mented at baseline visit and follow-up visits at month 3, month 6, month 9 and month 12. Only data submitted via the web-based NIS data base until 31 May 2015 or were sent to Winicker Norimed GmbH until 30 September 2015 were included in the statistical analyses. Participating physicians were informed by the Medical Lead of the LEONIS pNET study about the tasks and modalities of this NIS.

Ergebnisse zur Wirksamkeit unter Alltagsbedingungen

Compliance

Compliance was evaluated via the MMAS-8 questionnaire by patients and, separately, by the treating physician via direct questioning (figure 4). Predominantly, compliance is evaluated as “high” by patients (best adherence for FAS 75.5% “high”, 22.6% “medium”) and “very good”(63.5%) or “sufficient” (28.6%) by investigators, respectively.

Efficacy

Disease control rates (CR+PR+SD) were 56.7% (FAS), 65.0% (FASp; full analysis set, patiens pretreated with everolimus) and 52.5% (FASs; full analysis set, everolimus-naïve patiens), as calculated using the investigator`s assessment of overall response rate at the end of study (FAS 11.7%, FASp 5.0% and FASs 15.0%). PFS was calculated as date of death or first progression minus date of baseline

plus 1. In case no death or progression have occurred, PFS was censored with the date of last dose of EVE (in case of premature discontinuation) or the date of final documentation. 35 events (56.5%) of death or progression had occurred in FAS, 12 (57.1%) in FASp and 23 (56.1%) in FASs, respectively. 43.5% (n=27) patients have been censored for FAS, 42.9% (n=9) in FASp and 43.9% (n=18) in FASs.

Pharmacoeconomics

Mean numbers of visits related to pNET therapy do not increase significantly during study as compared to the six months before enrollment (assessed at baseline visit). Notably, LEONIS patients do not utilize psychological or psychiatric support.

Quality of Life

Data on QoL were collected every 3 months via the patient questionnaires EORTC QLQ-C30, EORTC QLQ-G.I.NET21 and EQ-5D. Figure 5 displays median values for QoL as assessed per EQ-5D visual analogue scale.

Ergebnisse zur Sicherheit

A total of 52 FAS patients (82.5%) experienced at least one AE during the observational period, and the proportion of patients with AEs was lower in the FASp than in the FASs (66.7% vs. 90.5%). At least 1 serious AE experienced 23 patients (36.5% overall; FASp: 28.6%, FASs: 40.5%), and 12 patients (19.0%) died. Thirty-nine patients (61.9%; FASp: 47.6%, FASs: 69.0%) experienced AEs, which were assessed as non-serious ADRs (nsADRs) and which were causally related to the treatment with Afinitor®. Serious ADRs (SADRs) affected 10 patients (15.9%; FASp: 4.8%, FASs: 21.4%). None of the SADRs was fatal. No pregnancies were reported (post-text Listing 14.3.2-4).

Table 4 summarizes all patients with at least one adverse event with and without relationship to EVE (FAS and subgroups FASs and FASp). Pretreated patients (FASp) were less likely to experience any AE (66.7%) than patients without pretreatment (90.5%). Serious adverse events related to EVE (SADR) occurred in EVE naïve patients more frequently (21.4%) than in pretreated patients (4.8%). The same was true for non-serious AEs related to EVE.

Schlussfolgerungen

Overall, the results of the study in the FAS imply a high level of treatment compliance which was accompanied by a maintenance of the patients' quality of life. In general, compliance according the MMAS-8 and quality of life were higher in patients who received Afinitor® already before study participation (FASp) than in patients who started intake of Afinitor® with study entry (FASs). This indicates that current Afinitor® treatment settings are particularly appropriate and accepted among patients after long-term treatment.

Along with the relative better compliance, primarily patients in the FASp experienced improve¬ments in their QoL. These trends were seen in all QoL measures applied in this NIS.

Although none of the patients achieved complete response, nearly 60% of the patients had at least stable disease, at least at some time point during the study, which confirms the beneficial effect of Afinitor® treatment in patients with progressive pNET. Moreover, effectiveness appeared to be more pronounced in FASp patients than in FASs patients. Specifically, the estimated progression-free survival time (i.e., the time to either progression or death) was numerically longer in FASp patients than in FASs patients, although numbers of patients were too low to draw reliable conclusions.

The safety data obtained in this NIS were in accordance with the known safety profile of Afinitor®, and again the data were in favor of the FASp. Both non-serious and serious ADRs were less frequent in this subgroup than in the FASs. It may be speculated that these data are to some extend biased by the selection of the pre-treated patients, as the discontinuation rate due to AEs was markedly higher in the FASs (64.3% vs. 52.4% in the FASp) during the NIS. This means that patients susceptible for ADRs had already discontinued the treatment with Afinitor® prior to enrolment in this NIS. However, the overall incidence rates of ADRs were as expected in this patient population, irrespective of the treatment duration.

In summary, these results suggest that Afinitor® performs well regarding compliance, quality of life, safety and tolerability and effectiveness particularly after long-term treatment (i.e., longer than 1 year) than in short-term treatment (i.e., for less than 1 year), although FASs patients felt increasingly bothered by cancer treatment. Result suggest that current pNET treatment settings used in clinical practice in Germany are safe and widely accepted by patients. The results suggest that treatment of ADRs of Afinitor® in pNET patients is well-established and typical ADRs occur mainly at the beginning of Afinitor® therapy.

Pharmacoeconomics analyses indicated that changes in treatment methods during Afinitor® therapy changed only marginally (if at all) throughout the study, i.e., results suggest that the overall frequencies of applied treatment methods were time-invariant or nearly time-invariant over the 12-month observation period of Afinitor® therapy. Most patients were treated by physicians who held an agreement "treatment of an oncology patient (86512)" with the Federal Association of Statutory Health Insurance Physicians (KBV). The prevailing radiological action applied was CT.