Non-Interventional Study (NIS) Report

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Title:	Assessment of Real-World Outcomes Associated with Afatinib (Gilotrif) Use in Patients with Solid Tumors Harboring NRG1 Gene Fusions
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Research question and objectives:	Research Questions: 1. What are the characteristics of patients with NRG1 gene fusion-positive solid tumors treated with afatinib, and what are the characteristics of those treated with another systemic therapy? Study Objectives: 1. To describe the demographic and clinical characteristics of patients with *NRG1* gene fusion-positive solid tumors treated with afatinib and of patients with *NRG1* gene fusion-positive solid tumors treated with other systemic therapy.

	2. To calculate the objective response rate (ORR) and duration of response (DOR) among patients with *NRG1* gene fusion-positive solid tumors treated with afatinib and among patients with *NRG1* gene fusion-positive solid tumors treated with other systemic therapy 3. To estimate PFS (and TOT, TTP) among patients with *NRG1* gene fusion-positive solid tumors treated with afatinib and among patients with *NRG1* gene fusions treated with other systemic therapy 4. To estimate OS among patients with *NRG1* gene fusion-positive solid tumors treated with afatinib and among patients with *NRG1* gene fusion-positive solid tumors treated with other systemic therapy 5. To describe the incidence and severity of adverse events (AEs) among patients with *NRG1* gene fusion-positive solid tumors while on treatment with afatinib or other systemic therapy
Country(-ies) of study:	United States (U.S.)
Authors:	Andrew J. Klink, PhD, MPH Director, Real-World Evidence & Insights Cardinal Health Specialty Solutions andrew.klink@cardinalhealth.com Kristin M. Zimmerman Savill, PhD Senior Scientist, Real-World Evidence & Insights Cardinal Health Specialty Solutions kristin.savill@cardinalhealth.com Danielle Gentile, PhD Scientist, Real-World Evidence & Insights Cardinal Health Specialty Solutions danielle.gentile@cardinalhealth.com
Marketing authorisation holder(s):	Boehringer Ingelheim Pharmaceuticals, Inc.Ridgefield, CT 06877 USA
MAH contact person:	N/A
Date	17 September 2021
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1. ABSTRACT

Name of company:		Boehringer Ingelheim	
Name of finished medicinal product:		Gilotrif	
Name of active ingredient:		Afatinib Antineoplastic agents, tyrosinekinase inhibitors ATC code: L01XE13	
Report date: 17 SEP 2021	**Study number:** CTMS 1200.335	**Version/Revision:** CTMS 1200.335	**Version/Revision date:** 9/17/2021
Title of study:	Assessment of Real-World Outcomes Associated with Afatinib (Gilotrif) Use in Patients with Solid Tumors Harboring *NRG1* Gene Fusions		
Keywords:	Real-world, afatinib, NRG1		
Rationale and background:	The first neuregulin 1 (*NRG1)* fusion was reported by Fernandez-Cuesta et al in 2014 when they identified five *CD74-NRG1* fusions in invasive mucinous adenocarcinoma (IMA). Multiple tumor types with *NRG1* fusions have been described, including other lung, renal, head and neck, pancreatic, breast, ovarian, uterine, and prostate. The *CD74-NRG1* fusion provides an extracellular anchor for the epidermal growth factor (*EGF*) domain of *NRG1* to bind to ErbB3 (human epidermal growth factor receptor 3 (HER3]), leading to HER3 heterodimerization and activation of downstream signaling pathways resulting in oncogenesis. As such, targeted treatment with inhibitors of this pathway represents a possible therapeutic strategy. Afatinib, a pan-ErbB inhibitor, has been evaluated in preclinical models and in several case reports in patients with tumors harboring *NRG1* fusions who have achieved durable benefit with afatinib. *NRG1* fusions are rare, with an estimated overall frequency of ~0.2% to 0.8% across solid tumors and have a reported prevalence of up to 31% in lung IMA, making prospective clinical trials challenging. Obtaining real-world data describing the real-world outcomes associated with afatinib in patients with *NRG1* fusion-positive solid tumors is valuable, and such data may be used to explore potential use of afatinib in other indications through label expansion requests to the U.S. Food and Drug Administration (FDA) and other agencies.		

Research questionand objectives:	**Research Questions:** 1. What are the characteristics of patients with *NRG1* gene fusion-positive solid tumors treated with afatinib, and what are the characteristics of those treated with another systemic therapy? **Study Objectives:** 1. To describe the demographic and clinical characteristics of patients with NRG1 gene fusion-positive solid tumors treated with afatinib and of patients with NRG1 gene fusion-positive solid tumors treated with other systemic therapy. 2. To calculate the objective response rate (ORR) and duration of response (DOR) among patients with NRG1 gene fusion-positive solid tumors treated with afatinib and among patients with NRG1 gene fusion-positive solid tumors treated with other systemic therapy 3. To estimate progression-free survival PFS, time on treatment (TOT), and time to progression (TTP) among patients with NRG1 gene fusion-positive solid tumors treated with afatinib and among patients with NRG1 gene fusions treated with other systemic therapy 4. To estimate OS among patients with NRG1 gene fusion-positive solid tumors treated with afatinib and among patients with NRG1 gene fusion-positive solid tumors treated with other systemic therapy 5. To describe the incidence and severity of adverse events (AEs) among patients with NRG1 gene fusion-positive solid tumors while on treatment with afatinib or other systemic therapy
Study design:	This retrospective cohort study was conducted via a multi-site medical chart review of patients with *NRG1* gene fusion-positive solid tumors. Two cohorts of patients were identified: the first includes any patient with *NRG1* gene fusion-positive solid tumors who has received afatinib in any line of therapy (afatinib cohort). The second includes any patient with *NRG1* gene fusion-positive solid tumors who has not received afatinib in any line of therapy (other systemic therapy cohort). All patients must have initiated treatment after 01/01/2017 and before 03/31/2020. To remove potential bias, patients who died prior to 3 months following treatment initiation were still eligible. Data was collected between 11/30/2020 and 1/20/2021. Demographics, clinical characteristics, safety, and clinical outcomes (ORR, DOR, DOCB, TOT, TTP, PFS, OS, and AEs were described for both patient cohorts.
Population	**Inclusion Criteria:** • Adults, 18 years of age or older, at the time of diagnosis with any solid tumor. • Confirmed *NRG1* gene fusion in any solid tumor.

	• Initiated afatinib or other systemic therapy (in any line of therapy) for treatment of a solid tumor with *NRG1* gene fusion on or after 01/01/2017 and before 03/31/2020. • Followed up for ≥3 months after initiation of afatinib or other systemic therapy (unless deceased prior to 3 months of follow-up). **Exclusion Criteria:** • Treatment with any tyrosine kinase inhibitor (TKI)/ErbB-directed therapy other than afatinib
Setting:	Providers from the Cardinal Health Oncology Provider Extended Network (OPEN) were recruited to identify patients and complete electronic case report forms (eCRFs) of patients meeting the study selection criteria. All patients were required to have a confirmed NRG1 gene fusion in any solid tumor, initiated afatinib or other systemic therapy (in any line of therapy) for treatment of a solid tumor with *NRG1* gene fusion on or after 01/01/2017 through 03/31/2020, and followed up for ≥3 months after initiation of afatinib or other systemic therapy (unless deceased prior to 3 months of follow-up). Data collection began on 11 NOV 2020 and concluded on 11 JAN 2021.
Subjects and studysize, including dropouts:	72 afatinib patients and 38 non-afatinib patients were included for a total sample size of 110.
Variables	The primary exposure of interest was treatment with afatinib. Two unmatched cohorts of patients were created: the afatinib-treated cohort includes patients with an *NRG1* gene fusion who received afatinib in any line of therapy; the second cohort includes any patient with an *NRG1* gene fusion who had never received afatinib prior to the date of data collection. Demographic and clinical characteristics (e.g., sex, age, payer type, US region, race/ethnicity, tumor type/characteristics, comorbidities, ECOG PS, *NRG1* gene fusion testing (e.g., timing, lab/location, results/partner), tumor-specific testing of interest (e.g., EGFR) were described in each cohort of patients at initiation of index therapy (i.e., afatinib or for those not treated with non-afatinib, the treatment received after NRG1 testing). Clinical outcomes measured in this study included ORR, DOR, DOCB, TOT, TTP, PFS, OS, and AEs.

Data sources	De-identified, patient-level data was obtained from providers in the Cardinal Health Oncology Provider Extended Network (OPEN) who completed an eCRF for eligible patients. CHSS research operations recruited providers from OPEN to participate. OPEN is a community of over 7,000 oncologists, hematologists and urologists from across the U.S., with varying levels of time in practice, from practices both within and outside of group purchasing organizations. A subset of this provider group (~800) participates in retrospective observational research studies. All provider participation in the study was voluntary. Providers abstracted clinical and treatment related data as available from the patient's electronic health record (EHR) from the time of diagnosis of their primary malignancy through the last date of follow-up with the patient or death. Providers completed an eCRF for all eligible patients and were instructed to begin data abstraction with the first eligible patients, subsequently selecting consecutive patients moving forward. Required data elements were specified in the study inclusion/exclusion criteria; non-required data elements may have been missing/unknown. Providers may have abstracted data into the eCRF for both patients they personally managed/treated or those managed/treated by other providers within their practice. Providers were compensated for their time completing data abstraction into the eCRF only after subsequent data verification, as necessary. No source documents were provided to CHSS for verification; however, CHSS required duplicate data entry for a sample of patients' initial data collection to verify data point accuracy.
Results:	A total of 110 patients, n=72 afatinib, and n=38 non-afatinib were included in the final analytic dataset. In terms of demographic characteristics, the majority of patients within the afatinib cohort were male (58.3%) and White (66.7%), with the highest representation from the Northeast (36.1%) and West (36.1%) and a median age of 62 years at initiation of index therapy. . Within the non-afatinib cohort, the majority of patients were male (52.6%) and White (57.9%), with the highest percentages of patients were from the South (63.2%). In regard to clinical characteristics among afatinib-treated patients, the majority (70.8%) received afatinib as the second line (2L) of therapy. Most had an Eastern Cooperative Oncology Group (ECOG) score of 2 or greater (69.4%), had a past history of smoking (52.8%), and were stage IV at initial diagnosis (90.3%). Approximately 40% of patients had hypertension, 22.2% had chronic pulmonary disease, and 20.8% did not have any comorbidities. Among all non-afatinib-treated patients, the majority received their index systemic therapy (i.e., time at which patient and treatment characteristics were collected) as the first line (1L) of therapy (94.7%). Further, the majority of patients had an ECOG score of 0 or 1 or greater (68.4%), had a

	past history of smoking (57.9%), and were stage IV at initial diagnosis (89.5%). The most common comorbidities in non-afatinib-treated patients were hypertension (55.3%), cardiovascular disease (36.8%), diabetes with chronic complications (31.6%) and chronic pulmonary disease (31.6%). 26.3% of non-afatinib-treated patients did not have any comorbidities. Keeping in mind most afatinib-treated patients received afatinib in 2L, the charted ORR to afatinib in any line was 37.5% (n=27). The calculated best response based on imaging was 34.7% (n=25). The DOR was 5.58 months. Keeping in mind most non-afatinib-treated patients were index in 1L, the ORR to index therapy was 76.3% (n=29). The calculated best response based on imaging was 71.1% (n=27). The DOR was 13.38 months. Among all afatinib-treated patients, median PFS was 4.49 months, median TOT was 5.42 months, and TTP was 5.49 months. For all non-afatinib-treated patients, median PFS was 12.89 months, median TOT was 5.08 months, and median TTP was 12.89 months. Median OS was 7.16 months in afatinib patients and 22.55 months in non-afatinib patients. In terms of adverse events, among all afatinib-treated patients during index treatment, 9.7% (n=7) experienced an adverse drug reaction ADR with a median 1 ADR. The first ADR reported was diarrhea, which was moderate in 57.1% of cases and severe in 42.9% of cases. All (100%) cases were attributed to treatment. For those that experienced the ADR, 85.7% (n=6) had a dose hold, dose delay, or schedule change, 42.9% (n=3) had a dose reduction, 14.3% (n=1) had a discontinuation of treatment, and 14.3% (n=1) had an unscheduled office visit or treatment. Among all non-afatinib patients during index treatment line, 21.1% (n=8) experienced an ADR with a median 1 ADR. Reported ADRs included febrile neutropenia (n=2, 25%), nausea/vomiting (n=1, 12.5%), neuropathy (n=1, 12.5%), neutropenia (n=2, 25%), and thrombocytopenia (n=2, 25%). Febrile neutropenia resulted in dose hold, dose delay, or schedule change for 1 patient, death in 1 patient, and inpatient hospitalization in 1 patient. Nausea/vomiting resulted in an unscheduled office visit for 1 patient. Neuropathy resulted in dose hold, dose delay, or schedule change for 1 patient. Neutropenia for dose reduction, dose hold/dose delay/schedule change, and inpatient hospitalization for 1 patient in each outcome. Thrombocytopenia resulted in dose hold/dose delay/schedule change for 2 patients.

	There was an imbalance in line of treatment across the cohorts, rendering the non-afatinib cohort of limited context for the afatinib cohort. The majority of afatinib patients were on 2L therapy (70.8%) and the non-afatinib patients were largely on 1L therapy (94.7%). The current study had lower rates of adverse drug events

	(ADRs) compared to the randomized controlled trial for afatinib, although low severity ADRs which were not charted may have been missed. Both the non-afatinib and afatinib cohorts appear to have directionally better outcomes compared to comparators in the literature, although no statistical tests were performed and the current study examined tumor site groups with 20 or fewer patients. The real-world data gathered by this study including demographic and clinical characteristics, outcomes, and adverse events of both afatinib and non-afatinib patients may be useful for informing prospective clinical trials of NRG1 fusion-driven tumors treated with afatinib.
Discussion:	This non-comparative, retrospective observational study identified patients with NRG1 positive solid tumors who had been treated with afatinib or another systemic therapy. The study provided new information as to the demographics and clinical characteristics of patients who were treated with afatinib or another systemic therapy in routine clinical practice. Across both afatinib and non-afatinib patients, the majority were White and male. There was an imbalance in line of treatment across the cohorts. The majority of afatinib patients were on 2L therapy (70.8%) and the non-afatinib patients were largely on 1L therapy (94.7%). Without formal comparisons performed, it appears that overall, there were lower rates of ADRs in the current study compared to the randomized controlled trial for afatinib, although less severe ADRs may not have been charted and therefore not captured in this study. Both the non-afatinib and afatinib cohorts appear to have directionally better outcomes compared to comparable extant literature, although no statistical tests were performed, and the current study examined tumor site groups with 20 or fewer patients. Future research is warranted to generate evidence comparing afatinib and non-afatinib patient cohorts. Additional research is needed to examine if gene fusion status may possibly be prognostic. Prospective clinical trials with large numbers of NRG1 fusion-driven tumors of diverse origins treated with afatinib are also warranted.
Marketing Authorisation Holder(s):	Boehringer Ingelheim Pharmaceuticals, Inc.Ridgefield, CT 06877 USA
Names and affiliations of principal investigators:	**Andrew J. Klink, PhD, MPH** Director, Real-World Evidence & Insights Cardinal Health Specialty Solutions andrew.klink@cardinalhealth.com **Kristie Fernamberg** Associate Director, CDMA Boehringer Ingelheim kristie.fernamberg@boehringer-ingelheim.com

2. LIST OF ABBREVIATIONS

Abbreviation	Definition
1L	First-line (therapy)
2L	Second line therapy
AACR	American Association for Cancer Research
ADR	Adverse drug reaction
AE	Adverse event
BI	Boehringer Ingelheim Pharmaceuticals
CHSS	Cardinal Health Specialty Solutions
CI	Confidence interval
CR	Complete response
CTCAE	Common Terminology Criteria for Adverse Event
DOCB	Duration of clinical benefit
DOR	Duration of response
ECOG PS	Eastern Cooperative Oncology Group Performance Status
eCRF	Electronic Case Report Form
EHR	Electronic Health Record
EMR	Electronic Medical Record
FAE	Fatal adverse event
FDA	United States Food & Drug Administration
HIPAA	Health Insurance Portability and Accountability Act
IRB	Institutional Review Board
ISPE	International Society for Pharmacoepidemiology
NIS	Non-interventional study
NRG1	Neuregulin-1
OPEN	Cardinal Health Oncology Provider Extended Network
ORR	Objective response rate
OS	Overall survival
PHI	Protected Health Information
PFS	Progression-free survival
PR	Partial response
PS	Performance Status
RECIST	Response Evaluation Criteria In Solid Tumors
RCT	Randomized controlled trial
RWD	Real-world data
RWE	Real-world evidence
SAE	Serious adverse event
SD	Standard deviation
SE	Standard Error
TKI	Tyrosine kinase inhibitor
TOT	Time on treatment
TTP	Time to progression
US	United States

3. INVESTIGATORS

Principal/ Co Investigators	Andrew J. Klink, PhD, MPH Director, Real-World Evidence & Insights Cardinal Health Specialty Solutions andrew.klink@cardinalhealth.com
Clinical Investigators	Dr. Ajeet Gajra, MD, FACP Vice President and Senior Medical Director Cardinal Health Specialty Solutions ajeet.gajra@cardinalhealth.com Claas Frohn, MD Team Leader Medicine Boehringer Ingelheim claas.frohn@boehringer-ingelheim.com Agnieszka Cseh, MD Senior Global Medical Advisor Boehringer Ingelheim agnieszka.cseh@boehringer-ingelheim.com
Project Manager	Hsing-Ting Yu, MPH Manager, Real-World Evidence & Insights Cardinal Health Specialty Solutions hsingting.yu@cardinalhealth.com
BI NIS Lead	Lori Minasi, PhD Executive Director Boehringer Ingelheim Pharmaceuticals, Inc.900 Ridgebury Road Ridgefield, CT 06877 P: 203 791 6452 lori.minasi@boehringer-ingelheim.com

4. OTHER RESPONSIBLE PARTIES

Study Statistician	Harlen Hays, MPH Director, Research Analytics Cardinal Health Specialty Solutions Harlen.hays@cardinalhealth.com
Research Manager	Talia Miller, MPH, MSW Consultant, Research Operations Cardinal Health Specialty Solutions talia.miller@cardinalhealth.com
Clinical Analyst	JaLyna Laney, RN Director, Research Operations Cardinal Health Specialty Solutions jalyna.laney@cardinalhealth.com

5. MILESTONES

Milestone	Planned date	Actual date	Comments
Start of data collection	5/22/2020	11/20/2020	
End of data collection	6/19/2020	1/11/2021	
Study progress report: Final report of study results (PowerPoint format)	9/11/2020	8/27/2021	
Final report of study results (Word format)	7/30/2021	8/6/2021	

6. RATIONALE AND BACKGROUND

The epidermal growth factor receptor (EGFR) signaling pathway regulates apoptosis and proliferation in normal cells. An EGFR family component of the of tyrosine kinase ligands, neuregulin-1 (NRG1), induces the proliferation, differentiation, and survival of cells in epithelial, neuronal, and myocytic tissue types, among others. The first NRG1 fusion was reported by Fernandez-Cuesta et al. in 2014 when they identified five CD74-NRG1 fusions in invasive mucinous adenocarcinoma (IMA).[1]The CD74-NRG1 fusion provides an extracellular anchor for the epidermal growth factor (EGF) domain of NRG1 to bind to ErbB3 (human epidermal growth factor receptor 3 (HER3]) leading to HER3 heterodimerization and activation of downstream signaling pathways leading to oncogenesis.[2] As such, targeted treatment with inhibitors of this pathway represents a possible therapeutic strategy. Afatinib, a pan-ErbB inhibitor has been evaluated in preclinical models [3] and in several case reports in patients with tumors harboring a NRG1 fusions that achieved durable benefit with afatinib.[4-6]

NRG1 fusions are rare, with an estimated overall frequency of ~0.2% across solid tumors [7] and have a reported prevalence of up to 31% in lung IMA [8] making prospective clinical trials challenging. In addition to IMA, other tumor types with NRG1 gene fusions that have been described include cholangiocarcinoma (0.8% of cases tested), thyroid cancer (0.7%), ovarian cancer (0.5%), pancreatic cancer (0.4%), non-small cell lung cancer (NSCLC; 0.3%), breast cancer (0.2%), sarcomas (0.2%), and sinonasal teratocarcinoma, [9] as well as renal cell carcinoma, head and neck cancer, uterine cancer, and prostate cancer.[10] While the incidence of NRG1 gene fusions is only around 0.2% of all solid tumors, this represents approximately 3,500 new cases per year.

Results presented at the American Association for Cancer Research (AACR) Annual Meeting 2019 showed the hypoxia-activated pan-HER kinase inhibitor tarloxotinib to be active against NRG1 gene fusion cancers, irrespective of site of origin. Afatinib has been proposed to have similar activity across sites of cancer associated with NRG1 gene fusions. Recent case reports presented some of the first evidence that patients with NRG1 gene fusions who were treated with afatinib had durable responses.[5] While the first reports emerged in lung cancer, [5] further research has implicated other solid tumors.[6] These findings indicate that malignancies associated with NRG1 gene fusions may benefit from treatment with afatinib.

Other therapies which are appropriate in tumor agnostic settings include VITRAKVI (larotrectinib) and KEKYTRUDA (pembrolizumab).[11]

GILOTRIF (Afatinib) was initially approved in 2013 by the U.S. Food & Drug Administration (FDA) for the first-line treatment of patients with metastatic NSCLC whose tumors have EGFR exon 19 deletions or exon 21 (L858R) substitution mutations; this indication was broadened in 2018 to include non-resistant EGFR mutations. Additionally, afatinib was approved in 2016 for the treatment of patients with metastatic squamous NSCLC progressing after platinum-based chemotherapy. Obtaining real-world data describing the real-world outcomes associated with afatinib use in patients with NRG1 fusion-positive across a range of solid tumors may be used in supplemental applications for label expansion requests to the FDA and other agencies. This study aims to provide real-world evidence on the real-world clinical outcomes associated with afatinib use among patients with NRG1 gene fusions across a range of solid tumors, as well as real-world data among patients with NRG1 gene fusions treated with other systemic therapies.

7. RESEARCH QUESTION AND OBJECTIVES

Limited data on durable responses in patients with *NRG1* gene fusion-positive solid tumors have been reported with afatinib. Beyond these data, no comprehensive evaluation has been conducted of patients harboring *NRG1* gene fusions treated with afatinib or other systemic therapy, in any line of therapy, to describe patient characteristics and clinical outcomes associated with afatinib use. This study aimed to answer these questions by achieving the objectives stated below. As this study was descriptive in nature, no *a priori* hypotheses were tested.

Research Questions:

1. What are the characteristics of patients with *NRG1* gene fusion-positive solid tumors treated with afatinib, and what are the characteristics of those treated with another systemic therapy?

Study Objectives:

1. To describe the demographic and clinical characteristics of patients with *NRG1* gene fusion-positive solid tumors treated with afatinib and of patients with *NRG1* gene fusion-positive solid tumors treated with other systemic therapy.
2. To calculate ORR and duration of response (DOR) among patients with *NRG1* gene fusion-positive solid tumors treated with afatinib and among patients with *NRG1* gene fusion-positive solid tumors treated with other systemic therapy
3. To estimate progression-free survival (PFS) (and time on treatment (TOT], time to progression (TTP]) among patients with *NRG1* gene fusion-positive solid tumors treated with afatinib and among patients with *NRG1* gene fusions treated with other systemic therapy
4. To estimate overall survival (OS) among patients with *NRG1* gene fusion-positive solid tumors treated with afatinib and among patients with *NRG1* gene fusion-positive solid tumors treated with other systemic therapy
5. To describe the incidence and severity of adverse events (AEs) among patients with *NRG1* gene fusion-positive solid tumors while on treatment with afatinib or other systemic therapy

8. AMENDMENTS AND UPDATES

None.

9. RESEARCH METHODS

9.1 STUDY DESIGN

This was a non-interventional, retrospective, US, multi-site, cohort study based on existing data from medical records of patients with *NRG1* gene fusion-positive solid tumors treated with afatinib or other systemic therapy. Two cohorts of patients were identified. The first included any patient with *NRG1* gene fusion-positive solid tumors who received afatinib in any line of therapy (afatinib cohort) between 01/01/2017 and 03/31/2020. The second included any patient with *NRG1* gene fusion-positive solid tumors who did not receive afatinib in any line of therapy (other systemic therapy cohort) during the same period and no history of afatinib use. A minimum follow-up of 3 months after initiation of afatinib or other systemic therapy was required, unless a patient died prior to 3 months of follow-up.

In total, a sample size of 120 patients with *NRG1* gene fusion-positive solid tumors was targeted for this study (roughly 70 afatinib-treated and up to 50 treated with other systemic therapy). Study objectives were to describe these patients and calculate the ORR in each group, as well as to estimate PFS, TOT, TTP, OS, DOR, and duration of clinical benefit (DOCB) along with describing the incidence and severity of AEs among patients in the two cohorts. Data collected through this medical chart review included patient demographics, clinical characteristics at the time of diagnosis/initiation of a line of therapy, treatment-related data points (dates of initiation, discontinuation, dosing), AEs occurring during therapy, disease response, date of progression and/or death.

Given the small number of patients targeted for study inclusion and anticipated differences in baseline characteristics between afatinib-treated and patients treated with other systemic therapies, statistical comparisons were not planned. In lieu of statistical comparisons between cohorts, the non-afatinib arm provided context for interpreting results among those treated with afatinib. Specifically, this context included what patients with *NRG1* gene fusions not treated with afatinib look like, how they are managed and treated, and what their clinical outcomes look like. The non-afatinib arm provided a broader understanding of *NRG1* gene fusions among patients with solid tumors

Data collection occurred in the fourth quarter of 2020 and first quarter of 2021, allowing for a minimum follow-up period of 3 months. All patients were required to have initiated index therapy (i.e., afatinib in any line; other systemic therapy among those without any history of afatinib) between 01/01/2017 and 03/31/2020. As such, the maximum follow-up period is approximately 39 months. The index date was defined as the date of initiation of afatinib or other systemic therapy between 01/01/2017 and 03/31/2020 for the other systemic therapy cohort.

9.2 SETTING

Providers from Cardinal Health's proprietary Oncology Provider Extended Network (OPEN) participated in this research study. To minimize potential bias, the maximum number of patients each provider was able to select and complete data abstraction for was capped at 30; for any provider who submitted >10 patients, their data were reviewed in detail by a clinician and analyst to identify any data quality issues (see Section **9.10 Quality Control** for further details on data quality assurance and control measures). Data were collected through an electronic case report form (eCRF) completed by the patients' providers who volunteered to participate in the study. Providers were compensated at fair market value for the time to complete data abstraction and quality control procedures, which were estimated to take up to 1 hour per patient.

Recruitment of providers was conducted electronically. Providers who responded to an initial feasibility request and reported treating potentially eligible patients were contacted and invited to participate. Recruitment to fill the up-to-120-patient quota was anticipated to run for 4 weeks from the date of recruitment launch. During that time, the per-cohort quotas were electronically monitored to ensure that the final number of patients achieves up to 70 patients with *NRG1* gene fusion-positive solid tumors treated with afatinib and up to 50 with an *NRG1* gene fusion-positive solid tumor not treated with afatinib at the time of data collection. Data collection took place over 8 weeks, from 11/20/20 to 1/11/21. Once recruitment for a cohort was completed, no further patient data entry were allowed for that cohort; however, providers actively completing an eCRF at the time of quota close for a cohort were allowed to complete that eCRF, and the total number of patients per cohort may have exceeded the quotas.

Providers were asked to identify all eligible patients, and starting with the earliest index date, chronologically select consecutive patients meeting the eligibility criteria and complete the data abstraction. The eCRF was structured to allow data collection regarding patient clinical history at the time of initial diagnosis of their solid tumor, initiation of index therapy (including dates of dose starts, stops, and interruptions), response to therapy, dates of disease progression, AEs, (including dates of onset, recovery, and reported deaths).

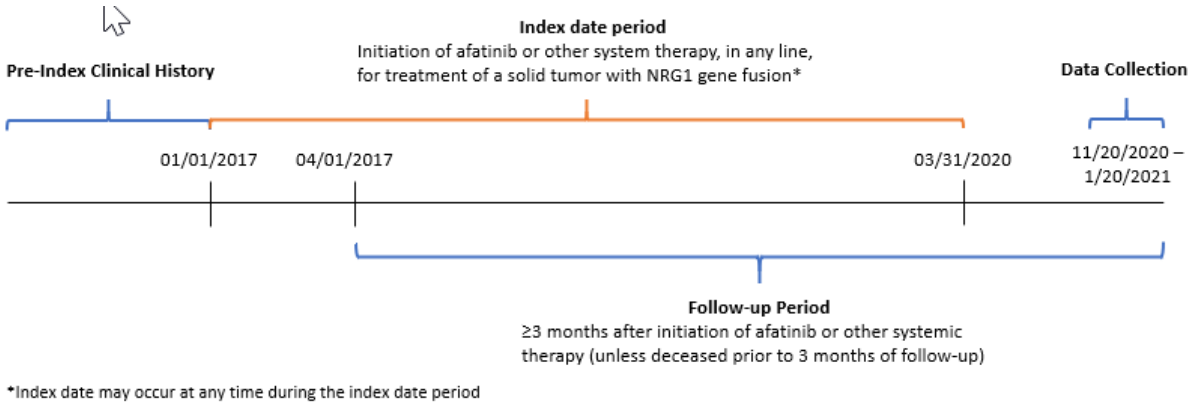
9.3 SUBJECTS

The sample size was determined *a priori* to be up to 120 patients, including up to 70 patients with an NRG1 gene fusion-positive solid tumor treated with afatinib and up to 50 patients with an NRG1 gene fusion-positive solid tumor who had not received afatinib at the time of data collection. The target number of patients was based on the results of a pilot feasibility study conducted by CHSS with BI. No substantial deviation from the sample size occurred.

9.3.1 Selection Criteria

All patients were required to have a confirmed NRG1 gene fusion in any solid tumor, initiated afatinib or other systemic therapy (in any line of therapy) for treatment of a solid tumor with *NRG1* gene fusion on or after 01/01/2017 through 03/31/2020, and followed up for ≥3 months after initiation of afatinib or other systemic therapy (unless deceased prior to 3 months of follow-up).

Figure 1. Study Period



9.3.1.1 Provider Selection Criteria

Providers were eligible to participate in this research study if they met the following criteria:

- Board-certified hematologist/oncologist.
- Had treated/was treating at least two patients with an NRG1 fusion-positive solid tumor.
- Was able to participate in research approved by an external/central institutional review board (IRB).
- Agreed to participate in data quality assurance/control processes.

9.3.1.2 Patient Selection Criteria

Providers selected patients meeting the study eligibility criteria as described below. Providers were asked to select eligible patients chronologically, starting with the first patient who first initiated any line of afatinib or chemotherapy on or after 01/01/2017 through 03/31/2020.

Inclusion Criteria:

- Adults, 18 years of age or older at the time of diagnosis with any solid tumor
- Confirmed NRG1 gene fusion in any solid tumor
- Initiated afatinib or other systemic therapy (in any line of therapy) for treatment of a solid tumor with NRG1 gene fusion on or after 01/01/2017 and before 03/31/2020
- Followed up for ≥3 months after initiation of afatinib or other systemic treatment

Exclusion Criteria:

- Treatment with any tyrosine kinase inhibitor (TKI)/ErbB-directed therapy other than afatinib

9.4 VARIABLES

The patient's treating/managing provider was the chart data abstractor in this study. The provider reviewed the patient's electronic health record (EHR) and abstracted the data points described below from the EHR into the eCRF. Source documents (e.g., the structured fields of the EHR database) were not provided to Cardinal Health. The data points described below were collected for each of the study cohorts (afatinib-treated cohort included patients with an *NRG1* gene fusion-positive solid tumor who had received afatinib in any line of therapy and non-

afatinib-treated cohort included patients with an *NRG1* gene fusion-positive solid tumor who had not received afatinib prior to the date of data collection) through the eCRF. All variables captured were transformed into a series of questions that the providers answered by entering the relevant data into the eCRF. Data points listed below were abstracted by the providers.

9.4.1 Provider Characteristics

- Provider characteristics: practice location, practice size, urban versus rural location, years in practice, number of eligible patients treated/treating, medical specialty

9.4.2 Patient Demographics/Clinical Characteristics

Demographic and clinical characteristics were described in each cohort of patients at initiation of index therapy (i.e., afatinib or for those not treated with non-afatinib, the treatment received after NRG1 testing).

- Patient demographics: sex as charted, age at solid tumor diagnosis and initiation of afatinib or other systemic therapy, region ofprimary residence, race, ethnicity (Hispanic or non-Hispanic)
- Tumor type of primary tumor
- Eastern Cooperative Oncology Group Performance Status (ECOG PS)
- Comorbidities at initiation of afatinib or other systemic therapy, following Charlson comorbidity index
- Tumor stage at initiation of afatinib or other systemic therapy
- NRG1 results: Date of NRG1 gene fusion test; laboratory performing test (e.g., academic, reference, in-house lab; name of lab); NRG1 gene fusion partner
- Other biomarkers: Tumor-specific biomarkers tested and their results (e.g., microsatellite instability (MSI]/mismatch repair (MMR], EGFR, human epidermal growth factor receptor 2 (HER2])

9.4.3 Patient Treatment Regimens

- Treatment history (i.e., regimens, duration, number of cycles, sequence)
- Starting dose of afatinib or other systemic therapy
- Dose modifications of afatinib or other systemic therapy (i.e., dose reductions and their timing, dose increases and their timing, dose delays and their duration and timing)
- Rationale for afatinib or other systemic therapy discontinuation

9.4.4 AEs

- Severity of AE: mild, moderate, or severe
- Resolution
- Outcome
- End date of AE
- Causal relationship of AE to treatment

Providers were only queried if the severe AEs listed above occurred during therapy. No other severe AEs were captured in structured fields of the eCRF. If the provider notified Cardinal Health of another ADR/AE, these ADRs/AEs/SAEs were reported by Cardinal Health according to Boehringer Ingelheim reporting requirements (see Annex 5).

9.4.5 Exposure(s)

The primary exposure of interest was treatment with afatinib. Two cohorts of patients were created: the afatinib-treated cohort included patients with an NRG1 gene fusion-positive solid tumor who had received afatinib in any line of therapy; the second cohort included patients with an NRG1 gene fusion-positive solid tumor who had not received afatinib prior to the date of data collection. Patients treated with afatinib or another systemic therapy and their outcomes were described in addition to the two main aforementioned treatment groups.

9.4.6 Outcome(s)

9.4.6.1 Primary outcome(s)

(objective 1) To describe the demographic and clinical characteristics of patients receiving afatinib or non-afatinib therapy, all variables listed as patient demographics/clinical characteristics were reported using counts and frequencies for categorical variables and means or medians (as appropriate) for continuous variables for those treated with afatinib and separately for those treated with other systemic therapy (i.e., did not receive afatinib in any line during the study period).

(objective 2) ORR was defined as the proportion of patients with a complete response (CR) or partial response (PR) out of all patients (CR+PR/all patients) at initial response assessment and best response. DOR was calculated as the time from initial response (for any patient with a complete, partial, or stable disease response initially) until the earliest of either disease progression or death. Patients who discontinued therapy due to a reason other than progression were censored on the date of discontinuation. Patients still on therapy at the time of data cut-off were censored on their last visit date.

(objective 3) PFS was defined as the time from initiation of a line of therapy until disease progression or death; patients on therapy at the time of data cut-off were censored on the last date of treatment. Patients who discontinued a line of therapy for a reason other than disease progression but who subsequently die prior to the receipt of any other therapy were considered an event on the date of death. TOT was defined as the time from initiation of a line of therapy until discontinuation for any reason; patients on therapy at the time of data cut-off were censored on the last date of treatment. was defined as the time from initiation of a line of therapy until discontinuation due to disease progression; patients on therapy or those who discontinued due to a reason other than disease progression were censored on the last date of treatment.

(objective 4) OS was defined as the time from initiation of any therapy in the metastatic setting until death; patients alive at the time of data cut-off were censored on the last date the patient was seen by the provider/clinic.

(objective 5) ADRs and Fatal AEs (FAEs) are reported in this Clinical Study Report. Providers were shown information describing what constitutes an AE/ADR/SAE/FAE per BI policies. The processes for safety reporting and analysis of the safety data were implemented and conducted as per the BI non-interventional study (NIS) standard operating procedures. The provider completing the chart data abstraction completed any reporting of events to BI per event reporting protocols.

The diagnosis, time, attribution (treatment-related or not, per provider interpretation) and severity of the reported AEs were collected. Severity was captured as serious and/or fatal by providers abstracting the data according to guidance on these determinations. If death was cited as the rationale for discontinuation, the provider abstracted data related to the date and cause of death. Providers were informed that should they be notified of another ADR/AE, the procedures outlined in NIS study protocol section 11 Management and Reporting of Adverse Events/Adverse Reactions were to be followed.

9.4.6.2 Secondary outcome(s)

None.

9.4.6.3 Further outcome(s)

None.

9.4.7 ADVERSE EVENTS/ADVERSE REACTIONS

This retrospective, non-interventional, non-randomized study used data contained in structured and unstructured areas of the patients' EHRs, which were previously collected as part of routine clinical care. Chart abstractors (i.e., the patient's treating physician) were asked to abstract information regarding all AEs, both serious and non-serious for both patients treated with afatinib in 2L and those treated with another systemic therapy. Abstractors collected the severity, resolution, outcome, end date, and causal relationship of each AE to treatment.

9.5 DATA SOURCES AND MEASUREMENT

All study data were entered into the eCRF. The eCRF captured data for each of the study variables described in **Section 9.4 – Variables**. The eCRF is a custom data abstraction tool that allows physicians to input deidentified data directly from patient EHR into a secure, is a web-based survey platform (Qualtrics) designed to allow providers to efficiently move through the patient chart/EHR to enter data on the patient journey that document the course of disease. Through the chart review approach, data elements contained in unstructured fieldsof the EHR were collected (e.g., clinical progress notes, radiologic scans/reports, pathology reports) as well as data requiring provider interpretation (e.g., date of disease progression rationale for treatment discontinuation). Patient demographics, clinical characteristics, treatments, and outcomes (e.g., disease response, date of progression) were collected through the date of last follow-up with the patient or death from any cause. The data abstractors for this study had been instructed to consult all available sources and indicate whether data points were substantiated by source materials in the EHR. No source document verification was conducted by Cardinal Health; however, data QC, QA, and validation processes were performed as described in **Section 9.10**. These processes and systems were vetted during field testing with volunteer physicians. In cases where patient data could not be verified, records were excluded from the analytic dataset.

The eCRF format conforms to the rules and regulations of the Health Insurance Portability and Accountability Act (HIPAA) of 1996 governing the abstraction and storage of protectedhealth information (PHI). The CHSS research team was responsible for the programming, testing, and hosting of data from submitted eCRFs. All data are stored on encrypted, password-protected, and HIPAA-compliant servers housed within the Cardinal Health electronic data

storage infrastructure.

9.6 BIAS

Provider and patient selection bias may exist in this study. Provider selection bias was minimized by only allowing providers to contribute up to 30 patients each. Patient selection bias was minimized to the extent possible by requesting providers complete eCRFs for eligible patients starting chronologically with the earliest patient meeting the criteria and selecting patients consecutively thereafter. To assess the degree of selection made by the participating provider, the total number of patients meeting the study selection criteria were collected (e.g., 5 patients meet study inclusion/exclusion criteria) were compared to the number of patients contributed to the study (e.g., 3 patients submitted as CRFs).

In addition, the extent of both provider and patient selection bias is likely minimized by the stringent study selection criteria. Because of the relative rarity of *NRG1* fusion-positive histology, the total prevalence of this patient population is likely small, minimizing potential selection biases.

9.7 STUDY SIZE

As a descriptive study, no formal *a priori* hypothesis testing or statistical comparisons were planned for evaluating outcomes between cohorts, subgroups, or in relation to randomized controlled trials. The sample size was determined based on the resources available to conduct the study and the pre-planned sample size was up to120 patients, including up to 70 patients with an NRG1 gene fusion-positive solid tumor treated with afatinib and up to 50 patients with an NRG1 gene fusion-positive solid tumor who had not received afatinib at the time of data collection.

9.8 DATA TRANSFORMATION

Following protocol finalization, study variables were captured and transformed into a text version of the CRF. Variables were captured in numeric and text format, as appropriate, and grouped according to the study objectives as described in the protocol. The Qualtrics interface used for data entry and management provides screens for data entry and includes study-specific programming checks to help control for data quality, consistency, and validity.The raw data entered into Qualtrics were vetted through QA, QC, and validation procedures, and a CHSS analyst exported them into SAS v9.4 for data transformation and analysis. All manipulations of data were conducted in SAS v9.4.

9.9 STATISTICAL METHODS

9.9.1 Main summary measures

Main outcome measures were:

- Profiles of patients treated with afatinib or another systemic therapy including demographic characteristics, clinical characteristics including tumor histology, and the outcomes defined in **Table 1**.

Table 1. Main study outcomes and definitions

Outcome	Definition
ORR	Proportion of patients with a complete response (CR) or partial response (PR) out of all patients (CR+PR/all patients) at initial response assessment and best response
DOCB	Duration of clinical benefit (DOCB) was calculated as the time from initial response (for any patient with a complete, partial, or stable disease response initially) until the earliest of either disease progression or death. Patients who discontinued therapy due to a reason other than progression were censored on the date of discontinuation. Patients still on therapy at the time of data cut-off were censored on their last visit date.
DOR	Duration of response was calculated as the time from initial response (for any patient with a complete or partial response initially) until the earliest of either disease progression or death. Patients who discontinued therapy due to a reason other than progression were censored on the date of discontinuation. Patients still on therapy at the time of data cut-off were censored on their last visit date.
TOT	Time from initiation of a line of therapy until discontinuation for any reason; patients on therapy at the time of data cut-off were censored on the last date of treatment.
TTP	Time from initiation of a line of therapy until discontinuation due to disease progression; patients on therapy or those who discontinued due to a reason other than disease progression were censored on the last date of treatment.
PFS	Time from initiation of a line of therapy until disease progression or death; patients on therapy at the time of data cut-off were censored on the last date of treatment. Patients who discontinued a line of therapy for a reason other than disease progression but who subsequently died prior to the receipt of any other therapy were considered an event on the date of death.
OS	Time from initiation of any therapy in the metastatic setting until death; patients alive at the time of data cut-off were censored on the last date the patient was seen by the provider/clinic.
AE	An adverse event was defined as any untoward medical occurrence in a patient administered a medicinal product and which does not necessarily have a causal relationship with this treatment. AEs from a prepopulated list (including “other, please specify”) during each line of therapy.

9.9.2 Main statistical methods

The results were stratified separately for afatinib and non-afatinib index therapy patients. Results were also separated into tumor type for those types with 3 or more patients. These tumor types included NSCLC, pancreatic cancer, bladder cancer, cholangiocarcinoma, renal cell cancer, colorectal cancer, ovarian cancer, and sarcoma. Furthermore, results were stratified by line of therapy (e.g., 1L, 2L, 3L) through the fourth line of therapy. Additionally, results were stratified by known or unknown NRG1 gene fusion partner status.

Demographic and clinical characteristics were reported via descriptive analyses, including counts and frequencies for dichotomous and categorical variables, while measures of centrality (mean, median) and spread (min, max, standard deviation, interquartile range, as appropriate) were used for continuous variables. These characteristics were described at the time of initial diagnosis of advance/metastatic disease and at the time of initiation of each line of therapy received.

For disease response, the point estimate for ORR and associated 95% confidence interval were calculated for each cohort. The Kaplan-Meier method was used to estimate any time to event outcome including DOR, DOCB, TOT, TTP, PFS, and OS to account for any right censoring (e.g., patient had not discontinued therapy, patient had not progressed or died).

Given the small number of patients targeted for study inclusion and anticipated differences in baseline characteristics between afatinib-treated and patients treated with other systemic therapies, statistical comparisons were not planned. In lieu of statistical comparisons between cohorts, the non-afatinib cohort provided context for interpreting results among those treated with afatinib. Specifically, this context includes what patients with *NRG1* gene fusions not treated with afatinib look like, how they are managed and treated, and what their clinical outcomes look like. The non-afatinib cohort provided a broader understanding of *NRG1* gene fusions among patients with solid tumors, for which limited evidence currently exists.

Incidence and severity of AEs were summarized and displayed in number/percentage. All safety endpoints were analyzed descriptively.

9.9.3 Missing values

The numbers of missing and unknown observations were described for both categorical and continuous variables. No data imputation was conducted. Patients with missing/unknown data were reported as such.

9.9.4 Subgroup analyses

None.

9.9.5 Amendments to the statistical analysis plan

None.

9.10 QUALITY CONTROL

CHSS conducted all data quality assurance and control activities. The following sections outline the data quality assurance and control measures implemented throughout data collection, management, and inspection, prior to constructing a final analytic data file. These procedures were conducted from a programming standpoint (e.g., logic checks built into the data collection tool) via statistical analysis to identify patterns and outliers, and by clinical review to identify implausible data or incongruent data points on a given patient.

Prior to data collection and during the field test, CHSS tested the eCRF. This quality control process began with extensive testing of the eCRF to ensure functionality across web-based user environments, looping logic to ensure proper alignment of data-related fields (required responses to certain fields prior to entering data into subsequent field), and other programmatic checks to ensure the reduction of the input of erroneous data (such as specifying maximums for year of birth or initiation of treatment within the dates of the enrollment period). Only data ranges consistent with known clinical parameters were allowed to be entered into the eCRF.

In addition, the eCRF was field-tested among four providers to ensure its functionality, the correct interpretation of the questions in relation to the data points of interest, and the length of time required for completion for a single patient. Field-testing includes a CHSS researcher viewing the screen of the provider completing the eCRF with actual patient data and asking probing questions regarding the functionality, interpretability (variables are aligned with clinical definitions or clinical interpretations), and availability of the variables requested. No data from the pre-testing phase was used in the analysis for this research. Pre-testing of the eCRF did not commence until IRB approval for the conduct of the study was received. The pre-test results were reviewed by BI with CHSS; however, BI did not have access to the individual data collected. Changes made to the eCRF document as a result of the pre-test required the resubmission of the eCRF and study protocol to the IRB.

9.10.1 Other Aspects

This study was designed, implemented, and reported in accordance with the Guidelines for Good Pharmacoepidemiology Practices (GPP) of the International Society for Pharmacoepidemiology (ISPE 2008), the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines, and with the ethical principles laid down in the Declaration of Helsinki. All study materials, including the research protocol and paper-version of the CRF, were reviewed by a central IRB prior to any data abstraction, including pre-testing (field testing by physicians) of the eCRF (described above). Providers were required to be able to participate in research covered by a central IRB. At all times, patients' PHI was kept confidential in accordance with HIPAA. The eCRF did not capture any data related to the patient's name, full date of birth, social security number, health insurance plan number, medical record number, or other such PHI. However, date of disease diagnosis, date(s) of treatment(s) administered (including dates of dosage changes), dates of development of health states of interest (e.g., AE/toxicity, disease progression), and dates of death (if available) were collected. These items are considered PHI under HIPAA. At no time was Boehringer Ingelheim provided with PHI in the form of a dataset or otherwise, however, and all study results were reported in aggregate.

Serious adverse event (SAE)

A serious adverse event (SAE) is defined as any AE that:

- results in death
- is life-threatening
- requires in-patient hospitalisation, or prolongation of existing hospitalisation
- results in persistent or significant disability or incapacity, or
- is a congenital anomaly/birth defect

Life-threatening in this context refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if more severe.

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious events, such as important medical events that might not be immediately life-threatening or result in death or hospitalisation but may jeopardise the patient or might require intervention to prevent one of the other outcomes listed above.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation or development of drug dependency or drug abuse. Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

The study design is of non-interventional nature, and the study was conducted within the conditions of the approved marketing authorisation. Sufficient data from controlled interventional trials are available to support the evidence on the safety and efficacy of the afatinib. For this reason, the following AE collection and reporting requirements have been defined.

The following were collected by the investigator in the eCRF from start of data extraction once informed consent was signed (if required) onwards until the end of data extraction:

- all ADRs (serious and non-serious)
- all AEs with fatal outcome

The investigator carefully assessed whether an AE constitutes an ADR using the information covered in Section 9.4.6.1.

10. RESULTS

10.1 PARTICIPANTS

10.1.1 Physician and Practice Characteristics

The highest percentage of physicians were mostly from medium -sized private community practices (6-10 physicians) (n=4, 30.8%) and large private community practices (>10 physicians) (n=4, 30.8%). Geographic practice settings were comprised of physicians from the South (n=4, 30.8%), West (n=4, 30.8%), Northeast (n=4, 30.8%), and Midwest (n=4, 30.8%). Physicians were from urban (n=6, 46.2%), suburban (n=6, 46.2%), and rural settings (n=1, 7.7%). Years in practice was a median of 14 years (**Table 2**).

Table 2. Physician and practice characteristics (n=13)

	All physicians (n=13)
Primary practice setting, n (%)	
Solo practitioner	0 (0.0%)
Small private community practice (2-5 physicians)	1 (7.7%)
Medium-sized private community practice (6-10 physicians)	4 (30.8%)
Large private community practice (>10 physicians)	4 (30.8%)
Community-based hospital	1 (7.7%)
Academic medical center	2 (15.4%)
Affiliated teaching hospital	1 (7.7%)
VA/military hospital/DOD	0 (0.0%)
Geographic practice setting, n (%)[1]	
Northeast	3 (23.1%)
Midwest	2 (15.4%)
South	4 (30.8%)
West	4 (30.8%)
Practice location, n (%)	
Urban	6 (46.2%)
Suburban	6 (46.2%)
Rural	1 (7.7%)
Years in practice	
mean, SD	14.9, (6.8%)
min, max	4, 28
median, 25th/75th	14, 10/17
Specialty, n (%)[2]	
Medical Oncology	4 (30.8%)
Hematology/Oncology	10 (76.9%)
Gynecological Oncology	0 (0.0%)
Pediatric Hematology/Oncology	0 (0.0%)
Radiation Oncology	0 (0.0%)
Surgical Oncology	0 (0.0%)

Notes: [1]Northeast includes Connecticut, Delaware, Massachusetts, Maine, Maryland, New Hampshire, New Jersey, New York, Pennsylvania, Rhode Island, Vermont; Midwest includes Iowa, Illinois, Indiana, Kansas, Michigan, Minnesota, Missouri, North Dakota, Nebraska, Ohio, South Dakota, Wisconsin; South includes Arkansas, Alabama, District of Columbia, Georgia, Florida, Kentucky, Louisiana, Mississippi, North Carolina, Oklahoma, South Carolina, Tennessee, Texas, Virginia, West Virginia; West includes Alaska, Arizona, California, Colorado, Idaho, Hawaii, Montana, New Mexico, Nevada, Oregon, Utah, Washington, Wyoming.
[2]Physicians were required to be board certified/eligible in medical oncology and/or hematology/oncology to participate.
Abbreviation: VA= Veterans Affairs; DOD= Department of Defense; SD= standard deviation; 25th/75th= interquartile range.

Thirteen (13) physicians representing 13 sites contributed 110 patients to the study. The mean number of patients each provider contributed to the sample was 8.5 (**Table 3**).

Table 3. Number of patients submitted per physician (n=13)

Physician number	Number of patients submitted
1	1
2	1
3	12
4	11
5	30
6	5
7	11
8	4
9	10
10	2
11	15
12	5
13	3

10.1.2 All Patients

A total of 114 eCRFs were submitted that met the study selection criteria. Of the 114 patients submitted, 4 patient records were removed from the analytic dataset during the QA/QC process (due to the chart abstractor not completing data validation for the patient), leaving a final analytic sample of 110 total patients that comprised the 72 afatinib-treated and 38 in the non-afatinib treated group. The 110 total patients were submitted by 13 unique providers from unique community practices across the U.S. Regional distribution of practice locations was 30.8% South, 30.8% West, 23.1% Northeast, and 15.4% Midwest. The mean time in practice was 14.9 years and the mean number of patients each provider contributed to the sample was 11.6.

At the time of data collection, 81.9% of the afatinib cohort and 36.8% of the non-afatinib cohort were deceased. Among the patients alive at the time of data collection, 11/13 (84.6%) in the afatinib cohort were receiving active therapy and 22/24 (91.7%) of the non-afatinib cohort were still receiving active therapy. Mean (std) follow-up from initiation of index therapy was 8.8 months (5.9) in the afatinib cohort and 11 months (6.4) in the non-afatinib cohort **(Table 4)**.

Table 4. Patient disposition at the time of data collection

	Afatinib (n=72)	Non-afatinib (n=38)
Disposition at data collection, n (%)		
Alive	13 (18.1%)	24 (63.2%)
Alive and receiving active therapy	11 (84.6%)	22 (91.7%)
Deceased	59 (81.9%)	14 (36.8%)
Months follow-up from initiation of index therapy, mean (SD)	8.8 (5.9)	11 (6.4)

Abbreviation: SD= standard deviation.

10.2 DESCRIPTIVE DATA

The full dataset of patient demographic and clinical characteristics are available in full study Tables, Listings, and Figures (Annex 3). Key data points of interest were summarized here. Of note, the results in this report summarize characteristics and outcomes of patients in their index line of therapy. For afatinib-treated patients, this was largely in 2L; for non-afatinib patients, this was largely 1L. This imbalance in the line of therapy in which these two groups were indexed should be considered when reviewing results below. For characteristics and outcomes for each line of therapy, see the full study compendium.

***Objective 1**: To describe the demographic and clinical characteristics of patients with NRG1 gene fusion-positive solid tumors treated with afatinib and of patients with NRG1 gene fusion-positive solid tumors treated with other systemic therapy.*

Among all afatinib patients, the majority were male (58.3%) and White (66.7%). The highest percentages of patients were from the Northeast (36.1%) and West (36.1%). The median follow-up from initiation of index therapy was 7.2 months **(Table 5)**.

Table 5. All afatinib patient baseline demographics (n=72)

	Afatinib patients (n=72)
Age (years) at initiation of index therapy, median (IQR)	62 (58-68)
Sex, n (%)	
Female	30 (41.7%)
Male	42 (58.3%)
Race, n (%)	
White	48 (66.7%)
Asian	6 (8.3%)
Black-African American	16 (22.2%)
Native Hawaiian of Other Pacific Islander	1 (1.4%)
American Indian or Alaska Native	1 (1.4%)
Geographic Region, n (%)	
Northeast	26 (36.1%)
Midwest	5 (6.9%)
South	15 (20.8%)
West	26 (36.1%)
Follow-up (months) from initiation of index therapy, median (IQR)	7.2 (5.4-10.1)

Abbreviations: IQR= interquartile range.

Among all non-afatinib patients, the majority were male (52.6%) and White (57.9%). The highest percentages of patients were from the South (63.2%). The median follow-up from initiation of index therapy was 9.3 months **(Table 6)**.

Table 6. All non-afatinib patient baseline demographics (n=38)

	Non-afatinib patients (n=38)
Age (years) at initiation of index therapy, median (IQR)	66 (59-71)
Sex, n (%)	
Female	18 (47.4%)
Male	20 (52.6%)
Race, n (%)	
White	22 (57.9%)
Asian	0 (0%)
Black/African American	16 (42.1%)
Native Hawaiian of Other Pacific Islander	0 (0%)
American Indian or Alaska Native	0 (0%)
Geographic Region, n (%)	
Northeast	10 (26.3%)
Midwest	4 (10.5%)
South	24 (63.2%)
West	0 (0%)
Follow-up (months) from initiation of index therapy, median (IQR)	9.3 (7.9-12)

Abbreviations: IQR= interquartile range.

Among all afatinib patients, the majority received afatinib as the second line of therapy (70.8%) **(Table 7)**. The majority of patients had an ECOG score of 2 or greater (69.4%), had a past history of smoking (52.8%), and had a tumor stage of four or greater (90.3%). Approximately forty percent of patients had hypertension, 22.2% had chronic pulmonary disease, and 20.8% did not have any comorbidities. Additional comorbidities can be referred to in Annex 3.

Table 7. All afatinib patient baseline clinical characteristics (n=72)

	Afatinib patients (n=72)
Line of therapy in which afatinib (index therapy) was received, n (%)	
1L	16 (22.2%)
2L	51 (70.8%)
3L +	5 (7%)
ECOG-PS, n (%)	
0,1	22 (30.6%)
2+	94 (69.4%)
Smoking status, n (%)	
Never smoked	32 (44.4%)
Current smoker	2 (2.8%)
Past history of smoking	38 (52.8%)
Tumor stage at initiation of index therapy, n (%)	
Stage I	0 (0%)
Stage II	1 (1.4%)
Stage III	6 (8.3%)
Stage IV	65 (90.3%)
Comorbidities, n (%)	
Hypertension	29 (40.3%)
Chronic pulmonary disease	16 (22.2%)
None of the above	15 (20.8%)

Abbreviations: 1L= first-line therapy, 2L= second-line therapy, 3L= third-line therapy, ECOG-PS= Eastern Cooperative Oncology Group Performance Status.

Among all non-afatinib patients, the majority received a systemic therapy as the first line of therapy (94.7%). The majority of patients had an ECOG score of 0 or 1 (68.4%), had a past history of smoking (57.9%), and had a tumor stage of four or greater (89.5%). The most common comorbidities were hypertension (55.3%), cardiovascular disease (36.8%), diabetes with chronic complications (31.6%) and chronic pulmonary disease (31.6%). Approximately one-quarter (26.3%) did not have any comorbidities. Additional comorbidities can be referred to in Annex 3 **(Table 8)**.

Table 8. All non-afatinib patient baseline clinical characteristics (n=38)

	Non-afatinib patients (n=38)
Line of therapy in which afatinib (index therapy) was received, n (%)	
1L	36 (94.7%)
2L	2 (5.3%)
3L +	0 (0%)
ECOG-PS, n (%)	
0,1	26 (68.4%)
2+	12 (31.6%)
Smoking Status, n (%)	
Never smoked	14 (36.8%)
Current smoker	2 (5.3%)
Past history of smoking	22 (57.9%)
Tumor stage at initiation of index therapy, n (%)	
Stage I	0 (0%)
Stage II	3 (7.9%)
Stage III	1 (2.6%)
Stage IV	34 (89.5%)
Comorbidities, n (%)	
Hypertension	21 (55.3%)
Cardiovascular disease	14 (36.8%
Diabetes with chronic complications	12 (31.6%)
Chronic pulmonary disease	12 (31.6%)
None of the above	10 (26.3%)

Abbreviations: 1L= first-line therapy, 2L= second-line therapy, 3L= third-line therapy, ECOG-PS= Eastern Cooperative Oncology Group Performance Status.

Among afatinib patients, NRG1 testing location was mostly from Foundation One (40.3%). The gene testing lab was mostly Foundation Medicine (64.3%) (**Table 9**).

Table 9. Testing patterns – afatinib patients (n=72)

***NRG1* testing characteristics**	**Afatinib (n=72)**
NRG1 testing location, n (%)	
Caris Life Sciences	15 (20.8%)
Foundation One	29 (40.3%)
Other	3 (4.2%)
Specialty gene testing lab	11 (15.3%)
Tempus	3 (4.2%)
Unknown	11 (15.3%)
Gene testing lab, n (%)	
Foundation Medicine	9 (12.5%)
Neogenomics	4 (5.6 %)
STRATA	1 (1.4%)

Abbreviation: NRG1= Neuregulin 1.

Among non-afatinib patients, *NRG1* testing location was mostly from Foundation One (71.1%). The gene testing lab was Neogenomics for all patients in this cohort **(Table 10)**.

Table 10. Testing patterns – non-afatinib patients (n=38)

***NRG1* testing characteristics**	**Non-afatinib patients (n=38)**
NRG1 testing location, n (%)	
Caris Life Sciences	0 (0%)
Foundation One	27 (71.1%)
Other	1 (2.6%)
Specialty gene testing lab	7 (18.4%)
Tempus	0 (0%)
Unknown	3 (7.9%)
Gene testing lab, n (%)	
Foundation Medicine	0 (0%)
Neogenomics	8 (21.1%)
STRATA	0 (0%)

Abbreviation: NRG1= Neuregulin 1.

10.3 OUTCOME DATA

Objective 2*: To calculate the ORR and DOR among patients with NRG1 gene fusion-positive solid tumors treated with afatinib and among patients with NRG1 gene fusion-positive solid tumors treated with other systemic therapy*

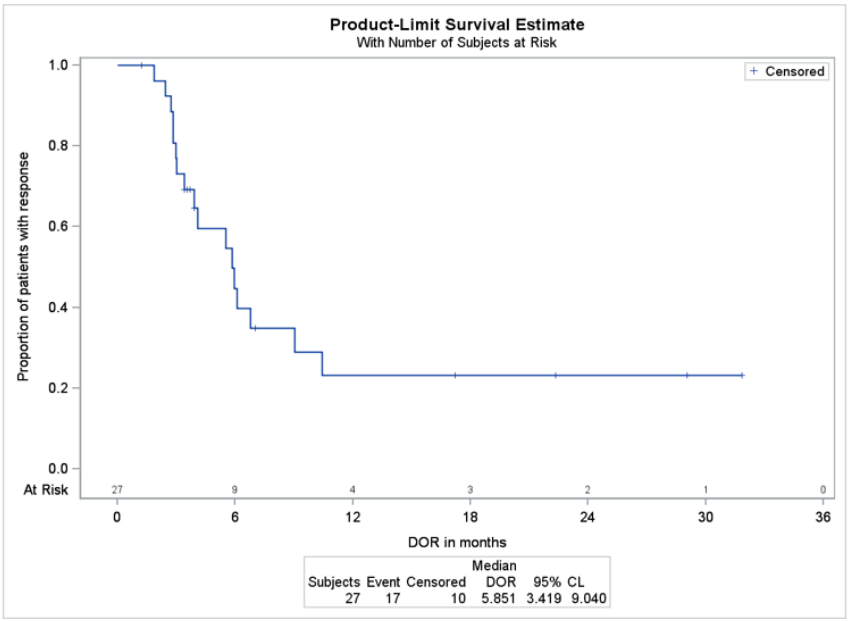
Keeping in mind most patients treated with afatinib received afatinib in 2L, among all afatinib patients, the charted best response to afatinib in any line overall response rate was 37.5% (n=27). The calculated best response based on imaging was 34.7% (n=25) **(Table 11)**. The DOR was 5.85 months **(Figure 2)**. ORR to each line of therapy is available in the complete study compendium.

Table 11. Overall ORR, any line, of all afatinib patients (n=72)

	Afatinib patients (n=72)
Charted best response to therapy ORR, n (%)	27 (37.5%)
Calculated best response based on imaging ORR, n (%)	25 (34.7%)

Abbreviation: charted ORR= overall response rate, imaging ORR= objective response rate.

Figure 2. DOR, any line, of afatinib patients, all tumor types (n=72)



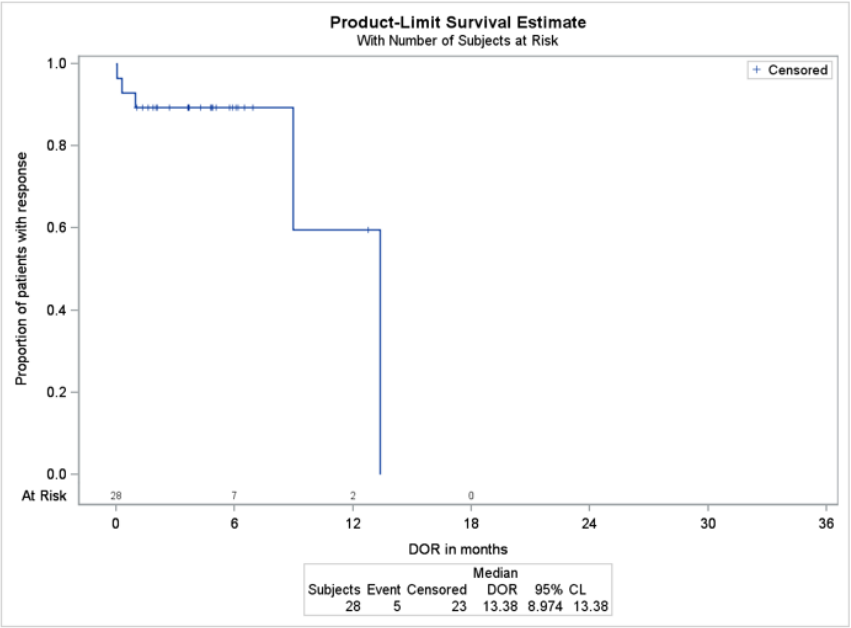
Keeping in mind most patients who were not treated with afatinib were index in 1L, among all non-afatinib patients, the charted ORR was 76.3% (n=29). The calculated best response based on imaging was 71.1% (n=27) **(Table 12)**. The DOR was 13.38 months **(Figure 3)**.

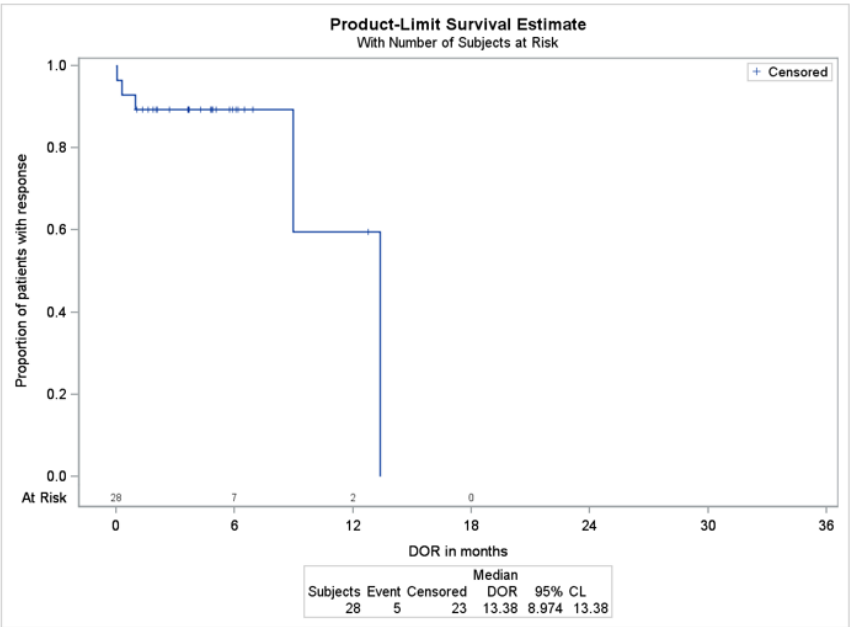
Table 12. ORR, any line, of all non-afatinib patients (n=38)

	Non-afatinib patients (n=38)
Charted best response to therapy ORR n (%)	29 (76.3%)
Calculated best response based on imaging ORR n (%)	27 (71.1%)

Abbreviation: charted ORR= overall response rate, imaging ORR= objective response rate.

Figure 3. DOR of non-afatinib patients, all tumor types (n=38)





***Objective 3**: To estimate PFS (and TOT, TTP) among patients with NRG1 gene fusion-positive solid tumors treated with afatinib and among patients with NRG1 gene fusions treated with other systemic therapy*

Across tumor types, median TOT of prior 1L therapy was 3.88 months among patients who received afatinib as 2L, 8.48 months among patients who received afatinib as 3L, and 4.67 months among those who received afatinib as 4L. Across tumor types, TOT of prior 2L therapy was 3.68 months among patients who received afatinib as 3L, and 11.31 months among those who received afatinib as 4L. Across tumor types, TOT of prior 3L therapy was 3.02 months among those who received afatinib as 4L (**Table 13**).

Table 13. TOT for prior lines of therapy by cancer type – afatinib (n=72)

Line of index therapy	TOT (KM estimate)					
	1L		2L		3L	
	Median	95% CI	Median	95% CI	Median	95% CI
2L (months)	3.88	3.52-4.83				
NSCLC	6.07	3.22-6.94				
Pancreatic cancer	3.71	1.41-5.23				
Bladder cancer	4.17	1.87-6.05				
Cholangiocarcinoma	3.60	2.10-3.71				
Sarcoma	2.68	2.10-3.71				
Renal cell carcinoma	4.67	1.84-12.69				
Colorectal cancer	7.79	NR-NR				
3L (months)	8.48	3.19-13.15	3.68	2.60-5.56		
NSCLC	8.17	3.19-13.15	3.05	2.60-3.49		
Cholangiocarcinoma	4.83	NR-NR	3.88	NR-NR		
Colorectal cancer	12.13	NR-NR	5.56	NR-NR		
4L (months)	4.67	NR-NR	11.31	NR-NR	3.02	NR-NR
NSCLC	4.67	NR-NR	11.31	NR-NR	3.02	NR-NR

Abbreviations: 1L= first-line therapy, 2L= second-line therapy, 3L= third-line therapy, 4L= fourth-line therapy, CI= confidence interval, KM= Kaplan-Meier, NSCLC= non-small cell lung cancer, TOT= time on therapy.

Across tumor types, median TOT of prior 1L therapy was 6.94 months among patients who received non-afatinib therapy as 2L (**Table 14**).

Table 14. TOT for prior lines of therapy by cancer type – non-afatinib (n=38)

	TOT 1L (KM estimate)	
	Median	95% CI
Index Therapy: Second line	6.94	2.79-11.08
Colorectal Cancer	6.94	2.79-11.08

Abbreviations: 1L= first-line therapy, CI= confidence interval, KM= Kaplan-Meier, TOT= time on therapy.

Keeping in mind most patients treated with afatinib received afatinib in 2L, among all afatinib patients, the PFS among all afatinib patients was 4.49 months **(Figure 4)**, TOT was 5.42 months (**Figure 5**) and TTP was 5.49 months (**Figure 6**).

Figure 4. PFS, any line, all afatinib patients (n=72)

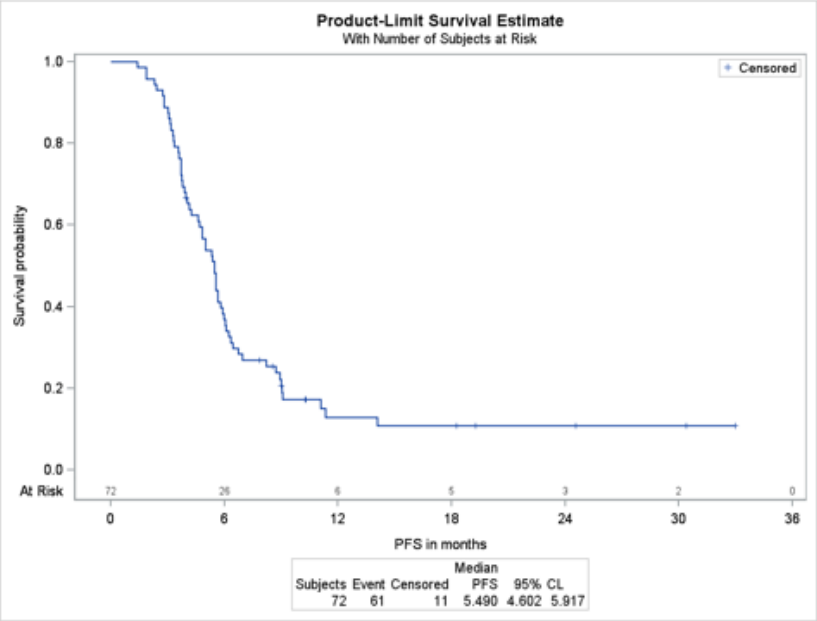


Figure 5. TOT – all afatinib patients (n=38)

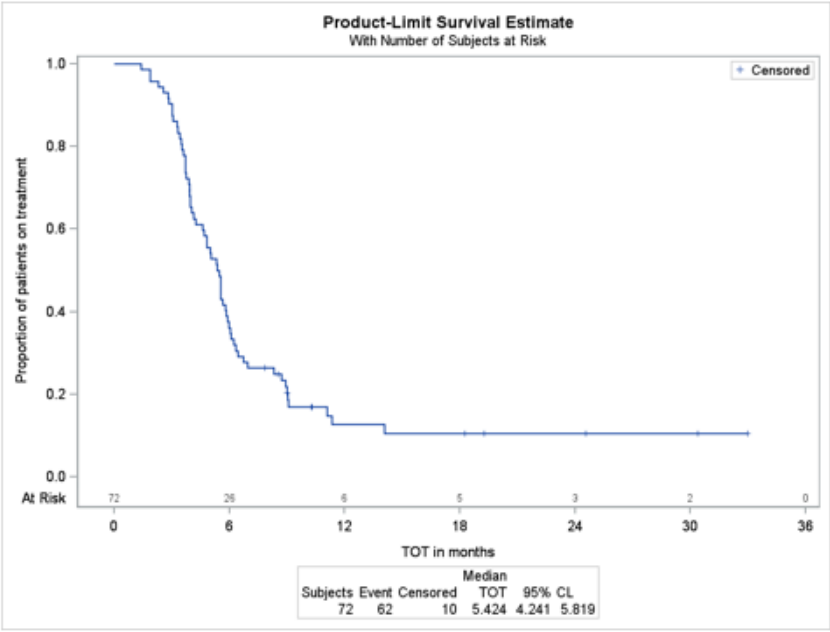


Figure 6. TTP – all afatinib patients (n=72)

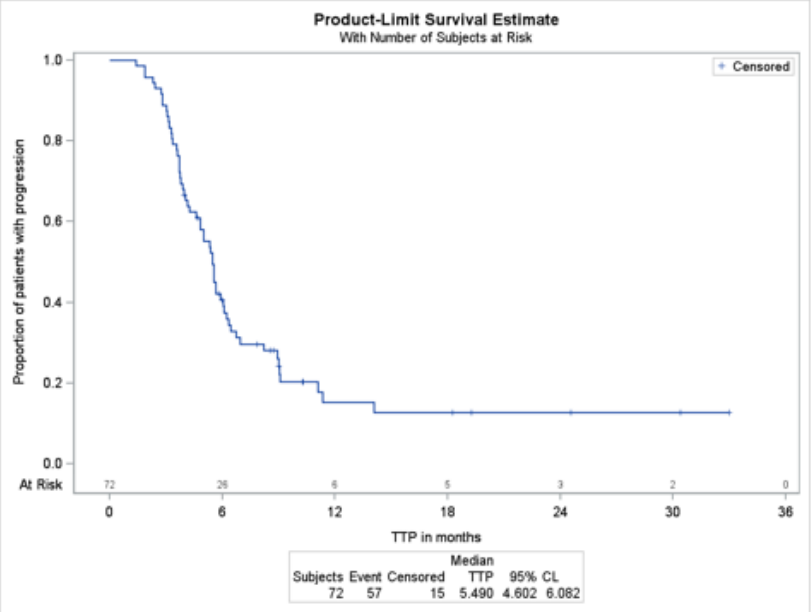


Table 15. Treatment response in all afatinib patients (n=72)

	All afatinib patients (n=72)	2L afatinib patients with known gene fusion partner (n=43)
Charted best response to therapy ORR, n (%)	27 (37.5%)	16 (37.2%)
Calculated best response based on imaging ORR, n (%)	25 (4.7%)	15 (34.9%)
DOCB (months), median (95% CI)	5.85 (2.99-9.04)	5.52 (2.83-6.11)
DOR (months), median (95% CI)	5.85 (3.42-9.04)	5.52 (2.83-6.11)

Abbreviations: 2L=second line therapy, CI= confidence interval, charted ORR=overall response rate, imaging ORR= objective response rate, DOCB= duration of clinical benefit, DOR= duration of response

Figure 7. PFS in afatinib NSCLC patients (n=29)

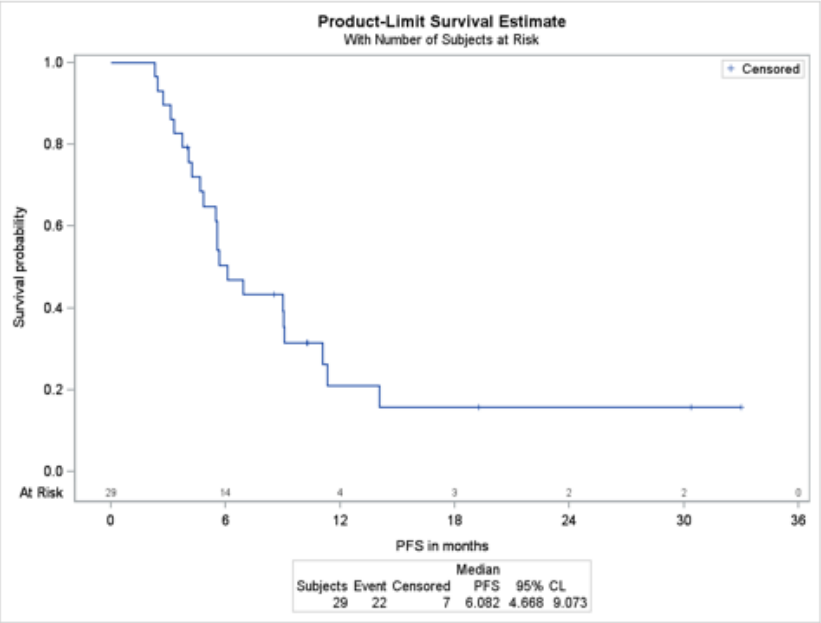


Figure 8. TOT in afatinib NSCLC patients (n=29)

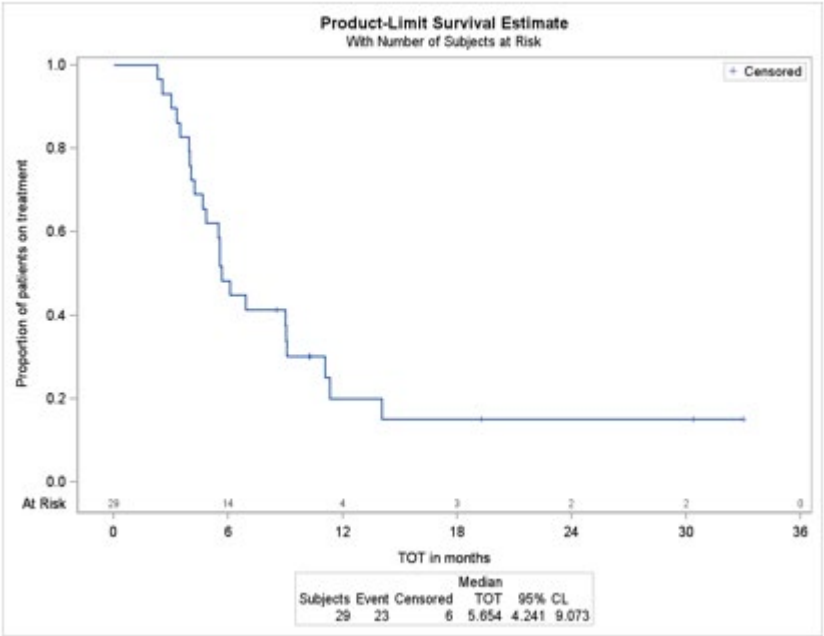
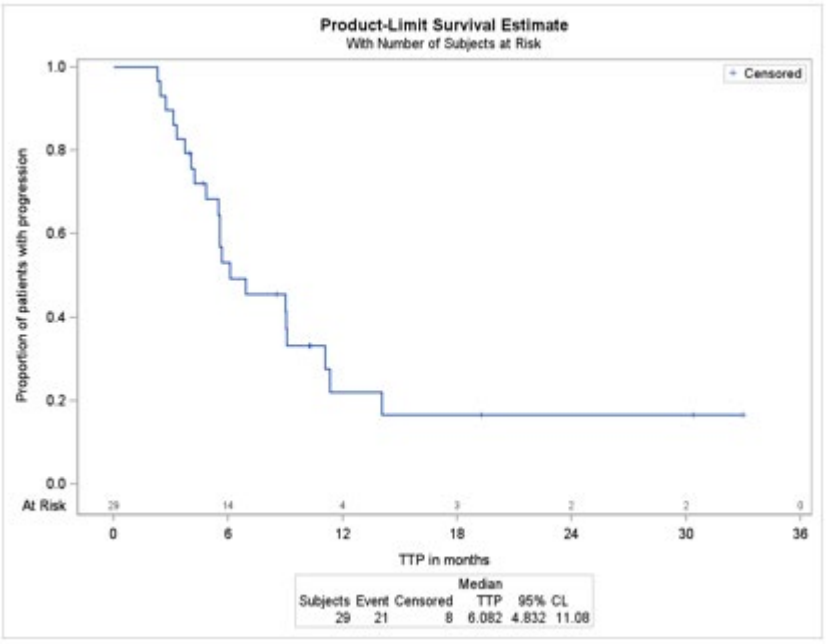


Figure 9. TTP in afatinib NSCLC patients (n=29)



Within patients treated with afatinib, median PFS ranged from 3.12 months in bladder cancer to 6.14 months in sarcoma. Median TOT ranged from 3.28 months in bladder cancer to 6.15 months in sarcoma. Median TTP ranged from 3.12 months in bladder cancer to 6.4 months in renal cell carcinoma. Among all afatinib cancer patients (n=72), the largest proportion had 2L afatinib with a known NRG1 gene fusion partner (n=43). This pattern was also observed among afatinib patients of specific cancer types where the largest proportions had 2L afatinib with a known gene fusion partners in all cancer types examined: NSCLC, pancreatic cancer, bladder cancer, cholangiocarcinoma, renal cell carcinoma, colorectal cancer and sarcoma.

Table 16. Treatment response in afatinib NSCLC patients (n=29)

	All afatinib NSCLC Patients (n=29)	2L afatinib NSCLC patients with known gene fusion partner (n=19)
Charted best response to therapy ORR, n (%)	2 (50%)	10 (52.6%)
Calculated best response based on imaging ORR, n (%)	16 (55.2%)	12 (63.2%)
DOCB (months), median (95% CI)	6.77 (3.42-NR)	6.11 (2.73-NR)
DOR (months), median (95% CI)	6.77 (3.42-10.45)	6.11 (2.73-10.45)

Abbreviations: 2L= second-line therapy, CI= confidence interval, charted ORR= overall response rate, imaging ORR= objective response rate, DOCB= duration of clinical benefit, DOR= Duration of response, NSCLC= non-small lung cancer, NR=not reached,

Figure 10. PFS in afatinib pancreatic patients (n=11)

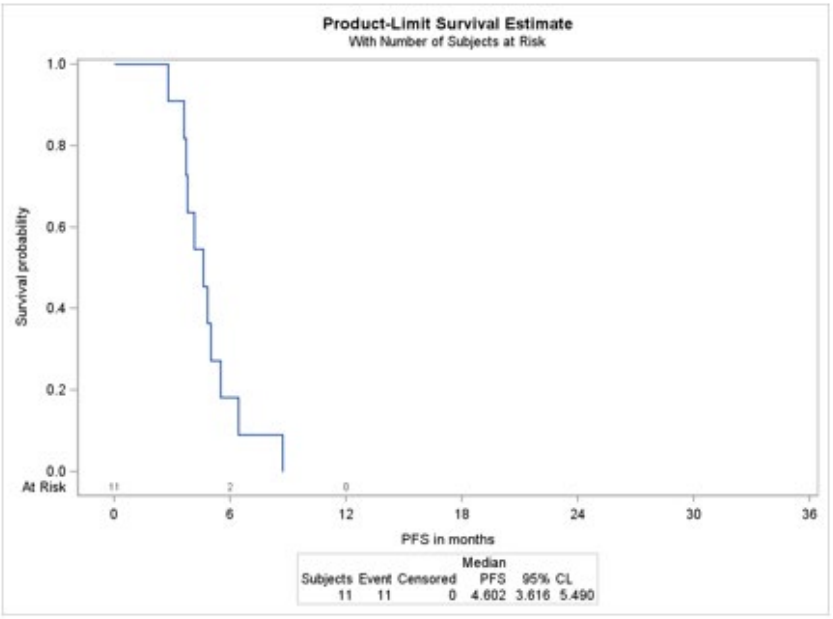


Figure 11. TOT in afatinib pancreatic patients (n=11)

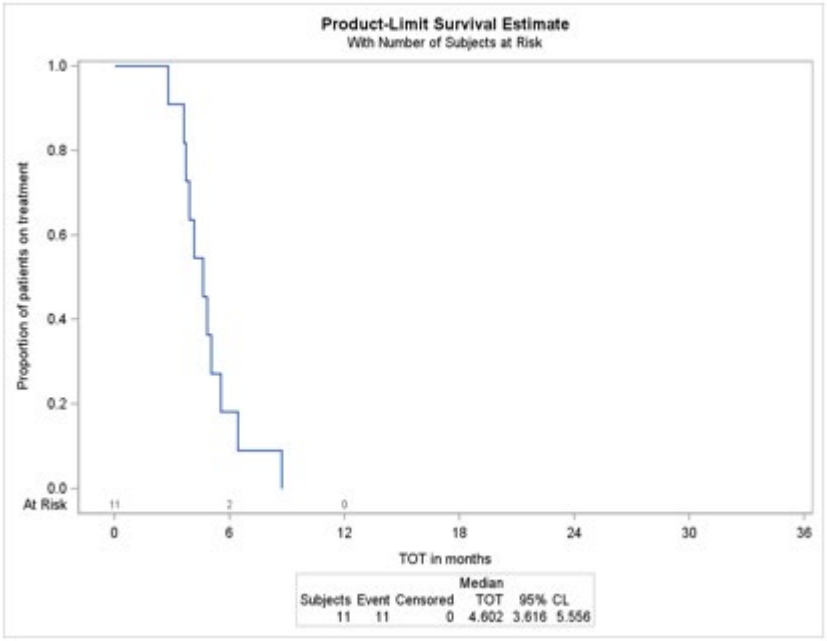


Figure 12. TTP in afatinib pancreatic patients (n=11)

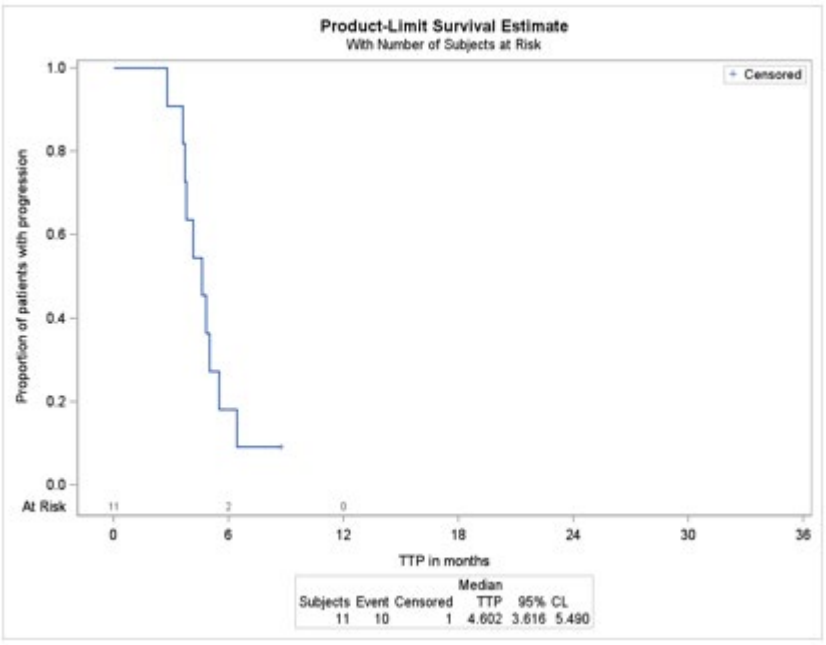


Table 17. Treatment response in afatinib pancreatic cancer patients (n=11)

	All afatinib pancreatic patients (n=11)	**2L afatinib pancreatic patients with known gene fusion partner (n=7)**
Charted best response to therapy ORR, n (%)	4 (36.4%)	3 (42.9%)
Calculated best response based on imaging ORR, n (%)	4 (36.4%)	3 (42.9%)
DOCB (months), median (95% CI)	2.43 (1.87-NR)	2.04 (1.87-2.83)
DOR (months), median (95% CI)	NR (NR-NR)	- (- -)

Abbreviations: 2L= second-line therapy, CI= confidence interval, charted ORR= overall response rate, imaging ORR= objective response rate, DOCB= duration of clinical benefit, DOR= duration of response, NR= not reached.

Figure 13. PFS in afatinib bladder cancer patients (n=8)

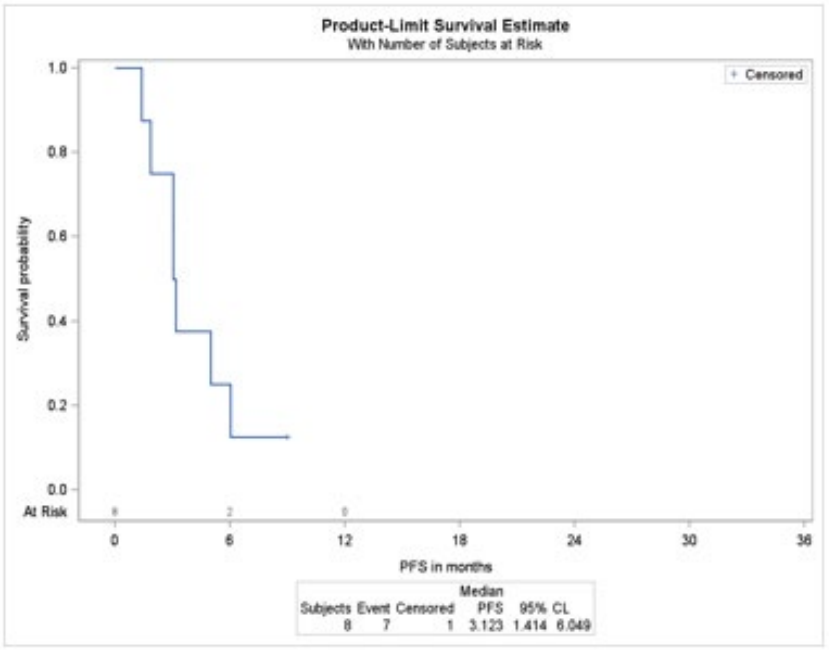


Figure 14. TOT in afatinib bladder cancer patients (n=8)

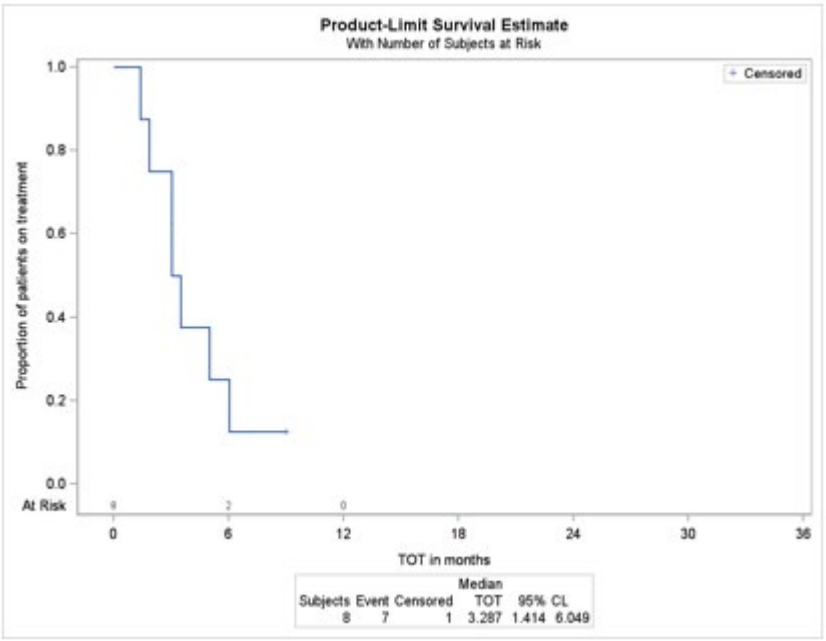


Figure 15. TTP in afatinib bladder cancer patients (n=8)

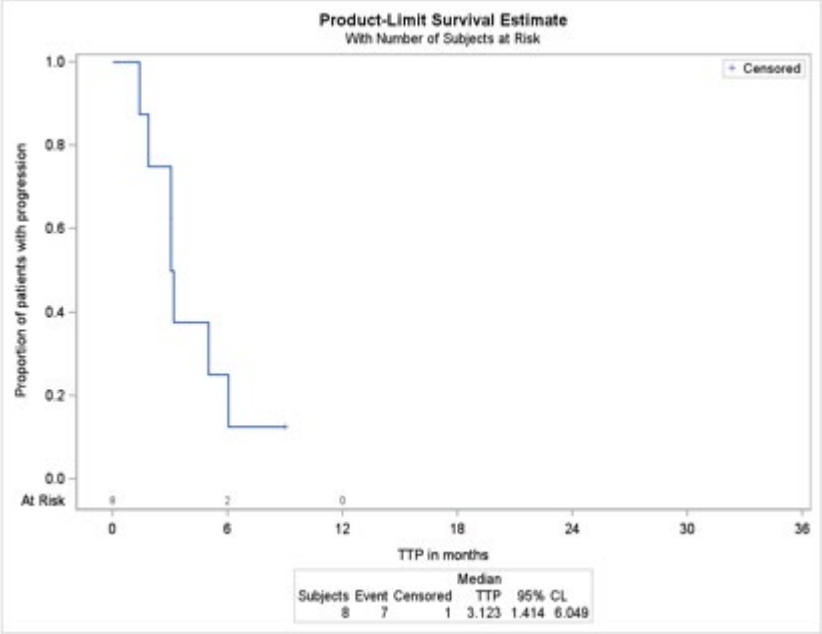


Table 18. Treatment response in afatinib bladder cancer patients (n=8)

	All afatinib bladder cancer patients (n=8)	2L afatinib bladder cancer patients with known gene fusion partner (n=6)
Charted best response to therapy ORR, n (%)	2 (25%)	1 (16.7%)
Calculated best response based on imaging ORR, n (%)	2 (25%)	1 (16.7%)
DOCB (months), median (95% CI)	NR (2.83-NR)	2.83 (NR-NR)
DOR (months) median (95% CI)	NR (2.83-NR)	2.83 (NR-NR)

Abbreviations: 2L= second-line therapy, CI= confidence interval, charted ORR= overall response rate, imaging ORR= objective response rate, DOCB= duration of clinical benefit, DOR= Duration of response, NR= not reached.

Figure 16. PFS in afatinib cholangiocarcinoma patients (n=8)

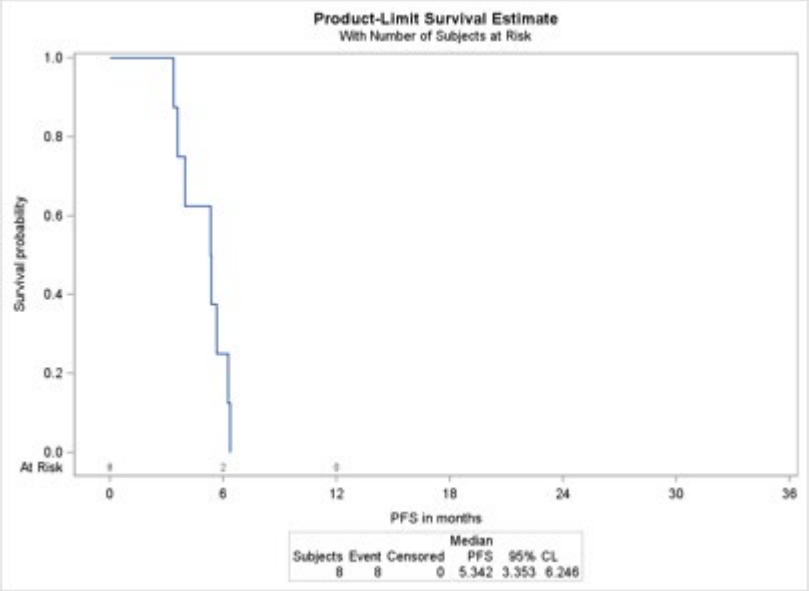


Figure 17. TOT in afatinib cholangiocarcinoma patients (n=8)

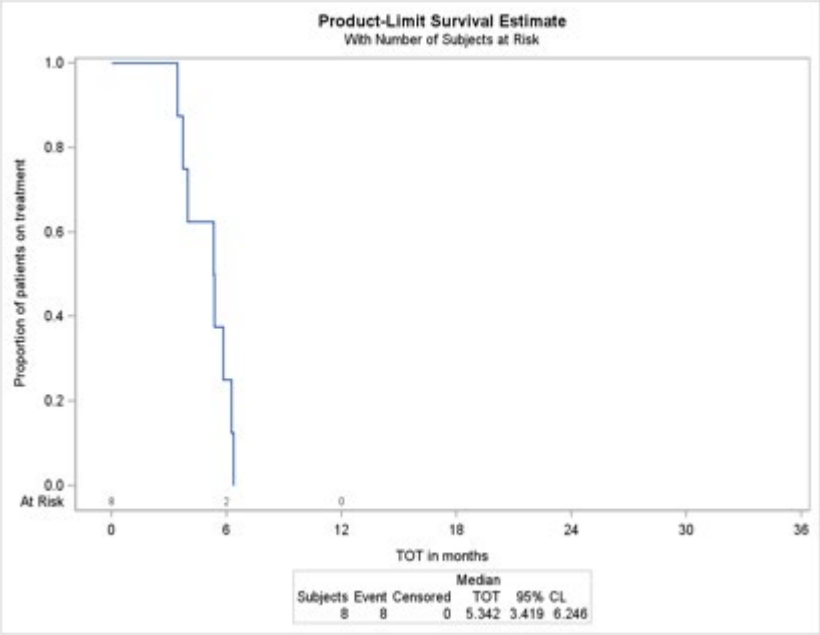


Figure 18. TTP in afatinib cholangiocarcinoma pancreatic patients (n=8)

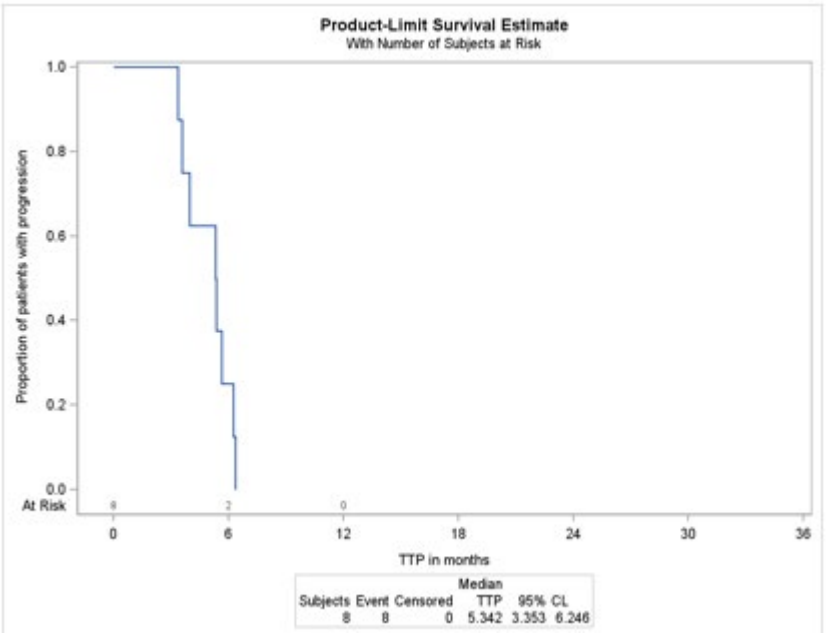


Table 19. Treatment response in afatinib cholangiocarcinoma patients (n=8)

	All afatinib cholangiocarcinoma Patients (n=8)	2L afatinib cholangiocarcinoma patients with known gene fusion partner (n=3)
Charted best response to therapy ORR, n (%)	4 (50%)	2 (66.7%)
Calculated best response based on imaging ORR, n (%)	1 (12.5%)	0 (0%)
DOCB (months), median (95% CI)	2.71 (1.87-3.91)	2.43 (1.87-2.99)
DOR (months), median (95% CI)	2.71 (1.87-3.91)	2.43 (1.87-2.99)

Abbreviations: 2L= second-line therapy, CI= confidence interval, charted ORR= overall response rate, imaging ORR= objective response rate, DOCB= duration of clinical benefit, DOR= duration of response.

Figure 19. PFS in afatinib renal cell carcinoma patients (n=4)

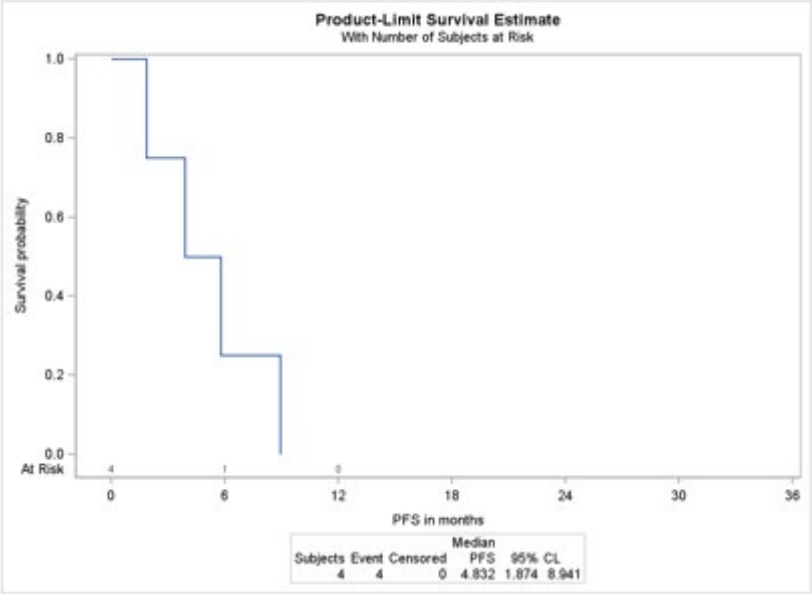


Figure 20. TOT in afatinib renal cell carcinoma patients (n=4)

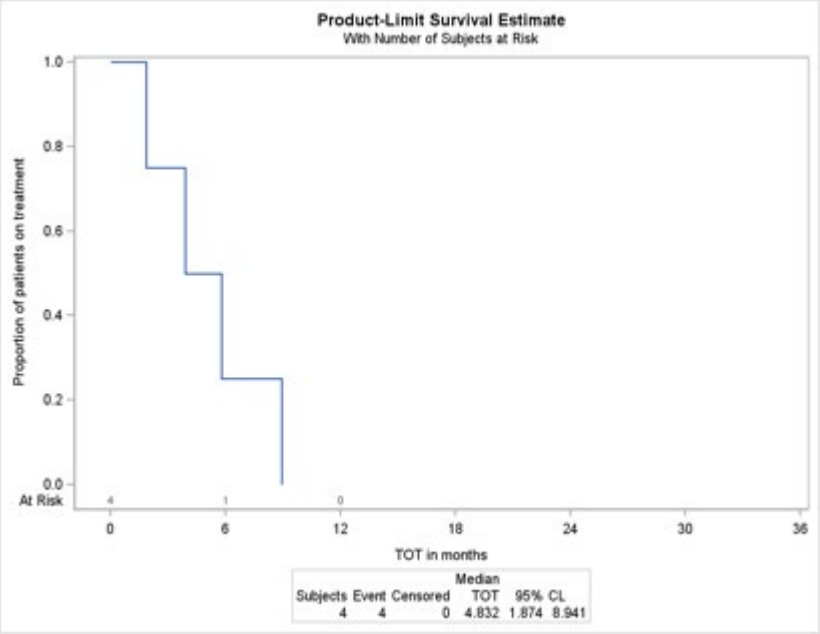


Figure 21. TTP in afatinib renal cell carcinoma patients (n=4)

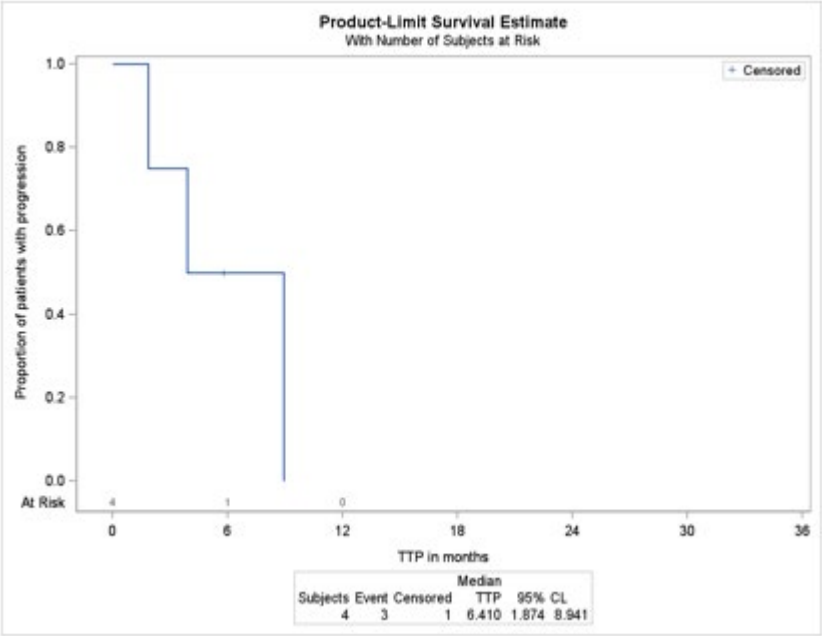


Table 20. Treatment response in renal cell carcinoma patients (n=4)

	All renal cell carcinoma patients (n=4)	2L afatinib renal cell carcinoma patients with known gene fusion partner (n=3)
Charted best response to therapy ORR, n (%)	1 (25%)	1 (33.3%)
Calculated best response based on imaging ORR, n (%)	0 (0%)	1 (33.3%)
DOCB (months), median (95% CI)	5.79 (NR-NR)	5.79 (NR-NR)
DOR (months), median (95% CI)	3.02 (NR-NR)	3.02 (NR-NR)

Abbreviations: 2L= second-line therapy, CI= confidence interval, charted ORR= overall response rate, imaging ORR= objective response rate, DOCB= duration of clinical benefit, DOR= duration of response.

Figure 22. PFS in afatinib colorectal cancer patients (n=3)

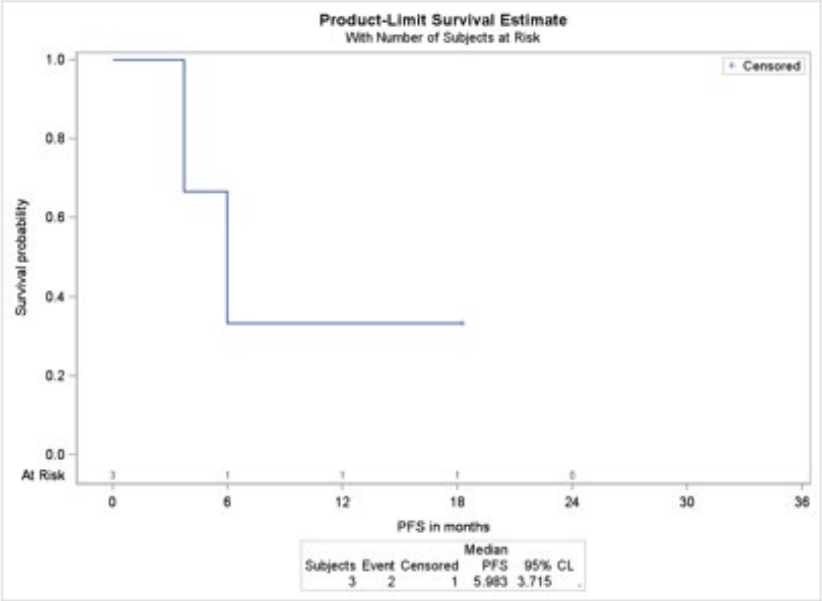


Figure 23. TOT in afatinib colorectal cancer patients (n=3)

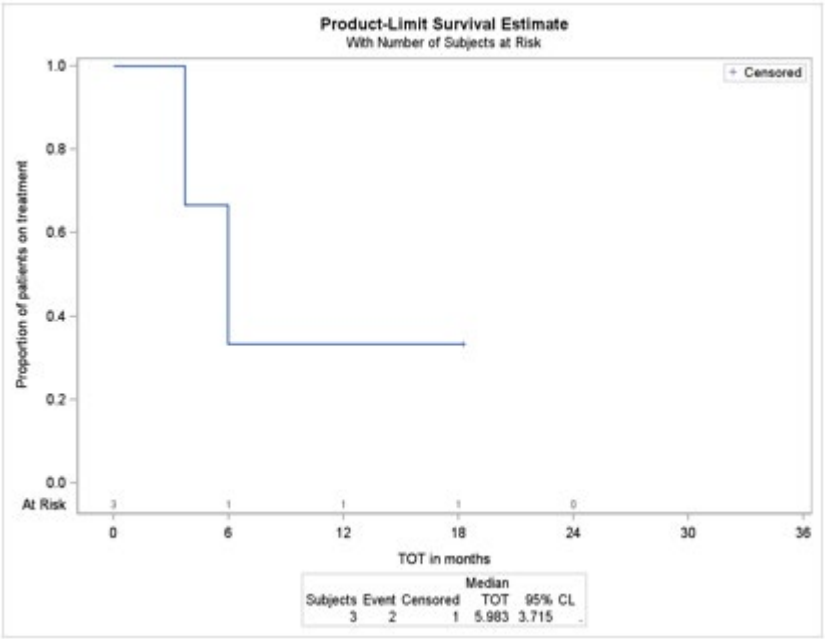


Figure 24. TTP in afatinib colorectal cancer patients (n=3)

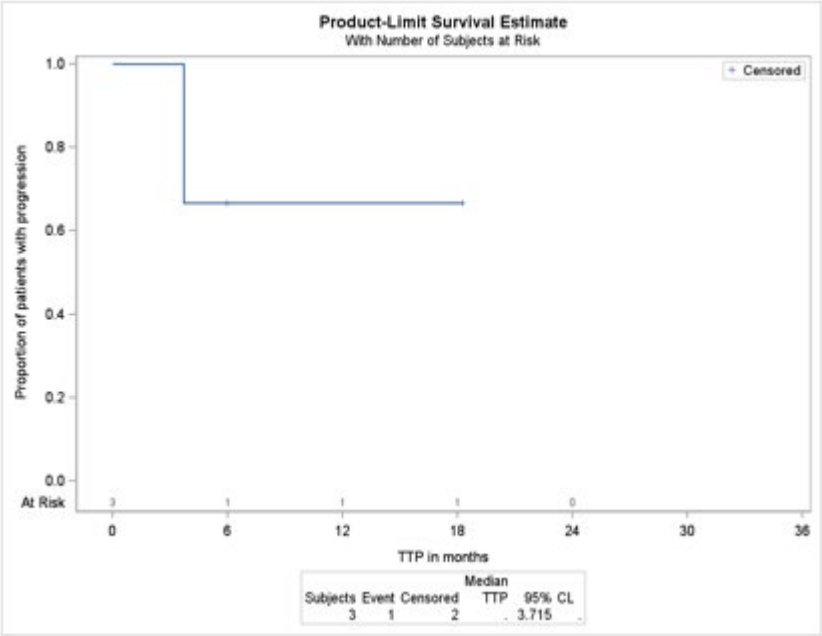


Table 21. Treatment response in afatinib renal colorectal cancer patients (n=3)

	All afatinib colorectal cancer patients (n=3)	2L afatinib colorectal cancer patients with known gene fusion partner (n=1)
Charted best response to therapy ORR, n (%)	2 (66.7%)	1 (100%)
Calculated best response based on imaging ORR, n (%)	2 (66.7%)	1 (100%)
DOCB (months), median (95% CI)	NR (5.95-NR)	5.95 (NR-NR)
DOR (months), median (95% CI)	NR (5.95-NR)	5.9, (NR-NR)

Abbreviations:2L= second-line therapy, CI= confidence interval, charted ORR= overall response rate, imaging ORR= objective response rate, DOCB= duration of clinical benefit, DOR= duration of response, NR= not reached.

Figure 25. PFS in afatinib sarcoma patients (n=6)

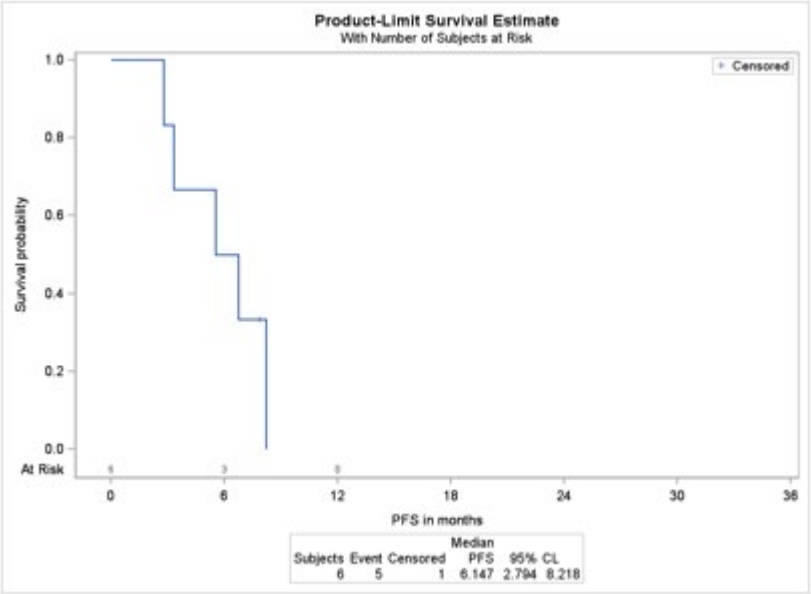


Figure 26. TOT in afatinib sarcoma patients (n=6)

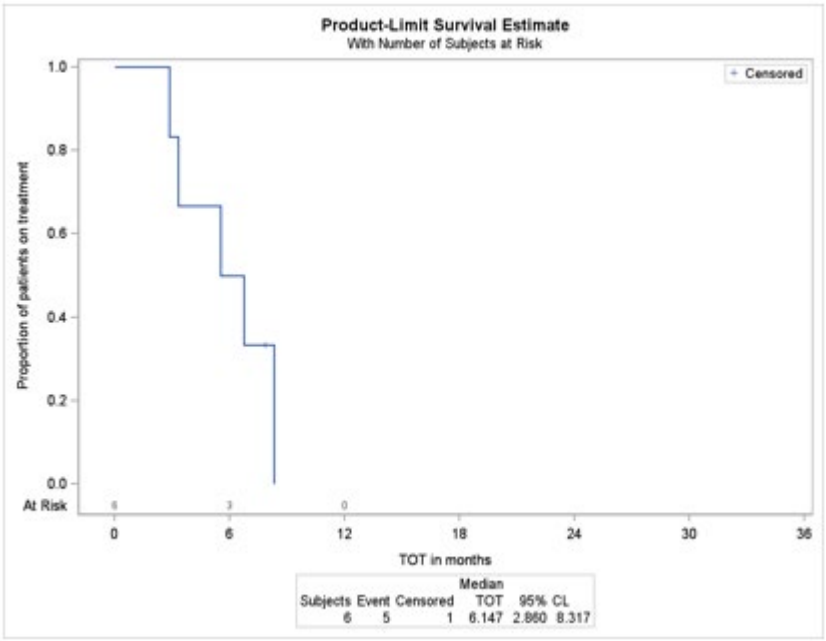


Figure 27. TTP in afatinib sarcoma patients (n=6)

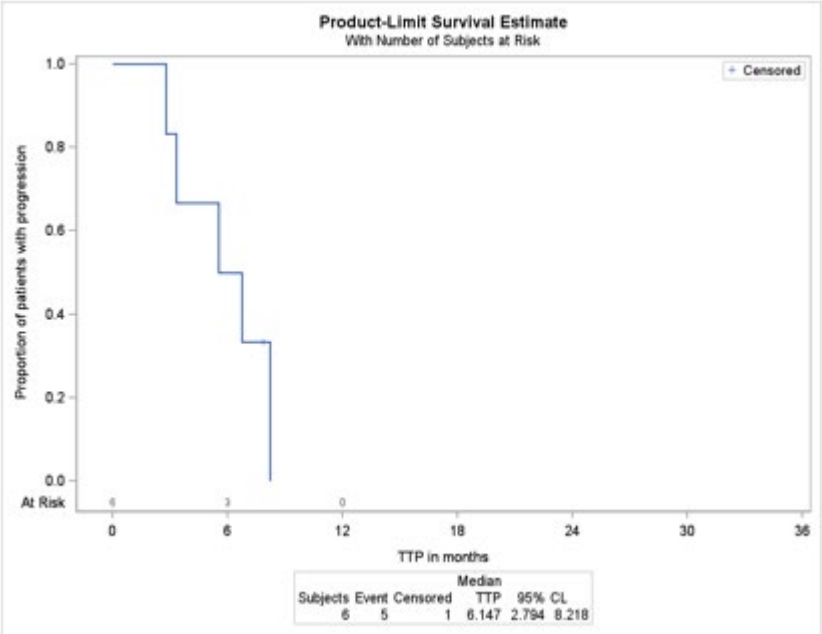


Table 22. Treatment response in afatinib sarcoma cancer patients (n=6)

	All afatinib sarcoma patients (n=6)	2L afatinib sarcoma patients with known gene fusion partner (n=3)
Charted best response to therapy ORR, n (%)	2 (33.3%)	1 (33.3%)
Calculated best response based on imaging ORR, n (%)	1 (16.7%)	0 (0%)
DOCB (months), median (95% CI)	5.52 (NR-NR)	5.52 (NR-NR)
DOR (months), median (95% CI)	5.52 (NR-NR)	5.52 (NR-NR)

Abbreviations: CI= confidence interval, charted ORR= overall response rate, imaging ORR= objective response rate, DOCB= duration of clinical benefit, DOR= duration of response, NR= no response.

Keeping in mind that most patients who did not receive afatinib were indexed in 1L, among all non-afatinib patients, PFS was 12.89 months **(Figure 28)**, TOT was 5.08 months **(Figure 29)**, and TTP was 12.89 months **(Figure 30)**.

Figure 28. PFS in all non-afatinib patients (n=72)

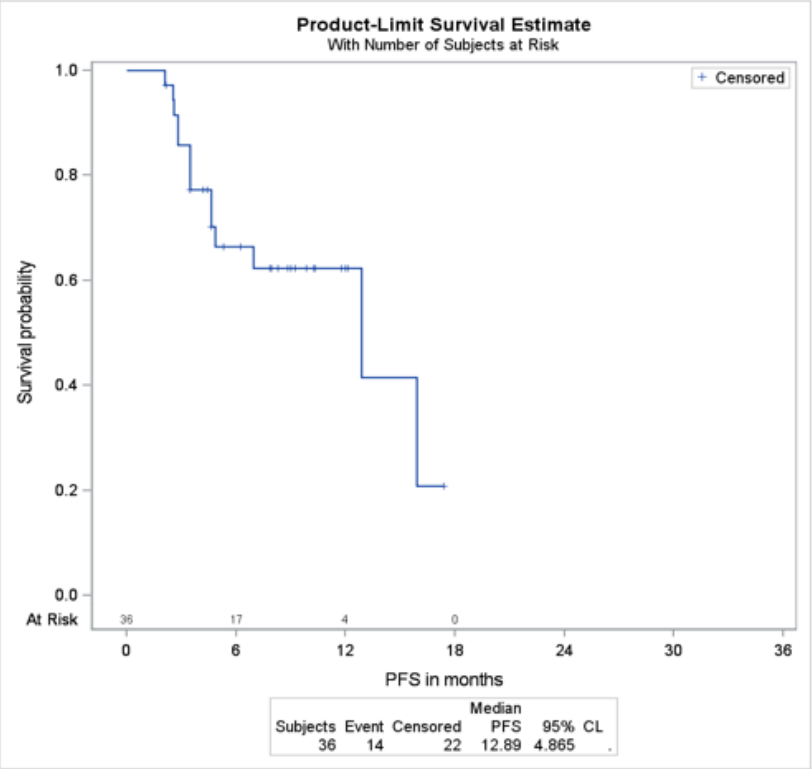


Figure 29. TOT in all non-afatinib patients (n=72)

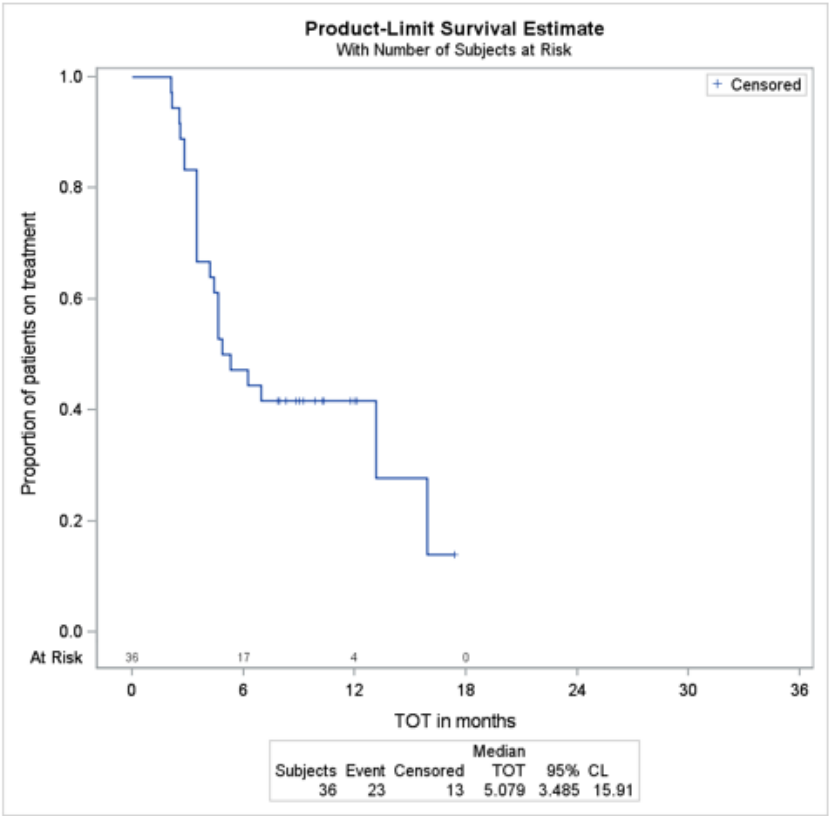


Figure 30. TTP in all non-afatinib patients (n=72)

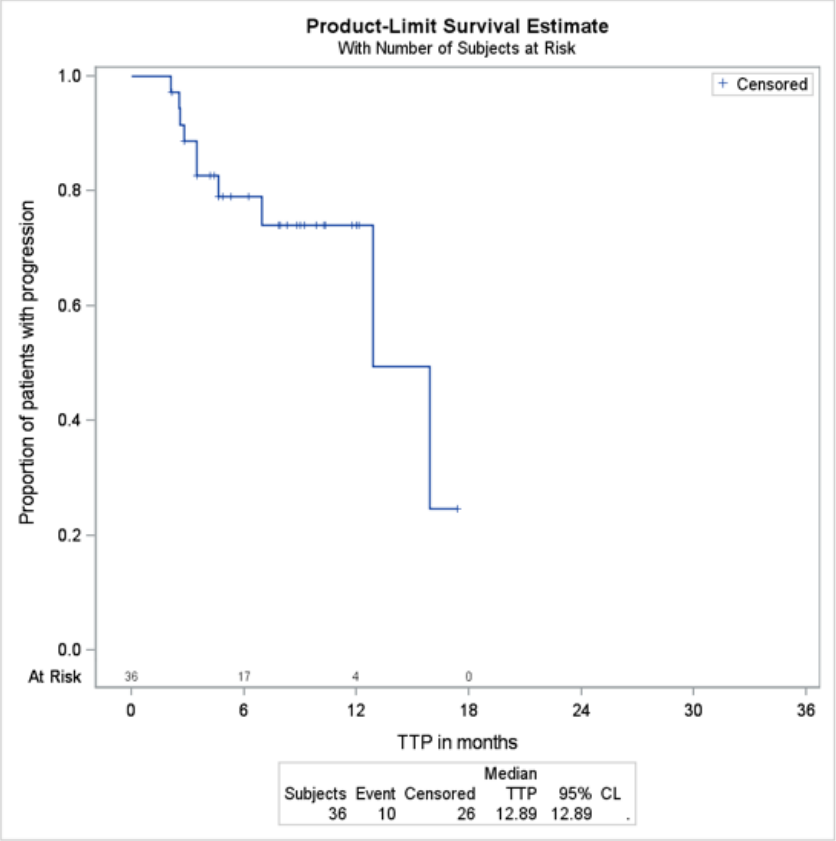


Table 23. Treatment response in all non-afatinib patients (n=38)

	All non-afatinib patients (n=36)	1L non-afatinib patients with known gene fusion partner (n=18)	1L non-afatinib patients with unknown gene fusion partner (n=18)
Charted best response to therapy ORR, n (%)	29 (76.3%)	13 (72.2%)	15 (83.3%)
Calculated best response based on imaging ORR, n (%)	27 (71.1%)	13 (72.2%)	13 (72.2%)
DOCB, months median (95% CI)	13.3 (8.97-13.38)	8.97 (2.10-13.38)	NR (1.81 NR)
DOR, months median (95% CI)	13.38 (8.97-13.38)	8.97 (8.97-13.38)	NR (NR-NR)

Abbreviations: CI= confidence interval, charted ORR= overall response rate, imaging ORR= objective response rate, DOCB= duration of clinical benefit, DOR= duration of response, NR= not reached.

Figure 31. PFS in non-afatinib NSCLC patients (n=11)

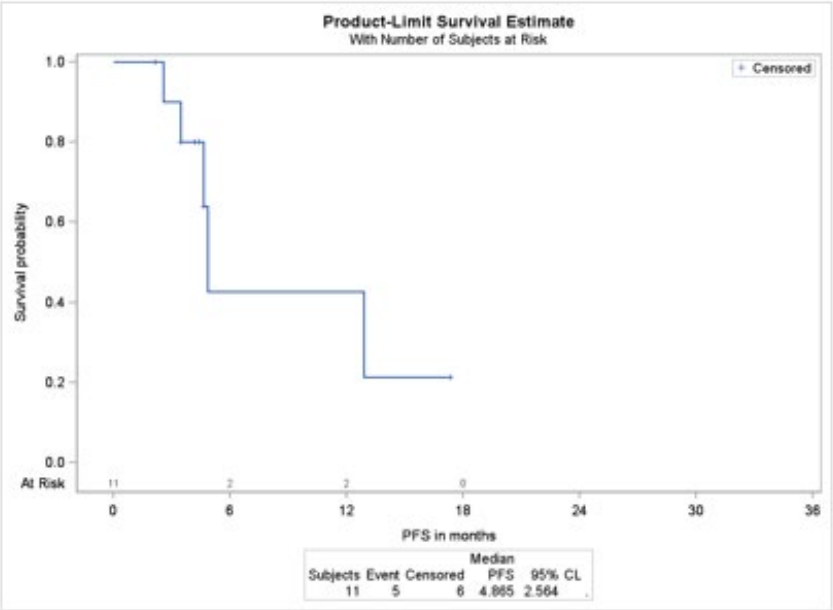


Figure 32. TOT in non-afatinib NSCLC patients (n=11)

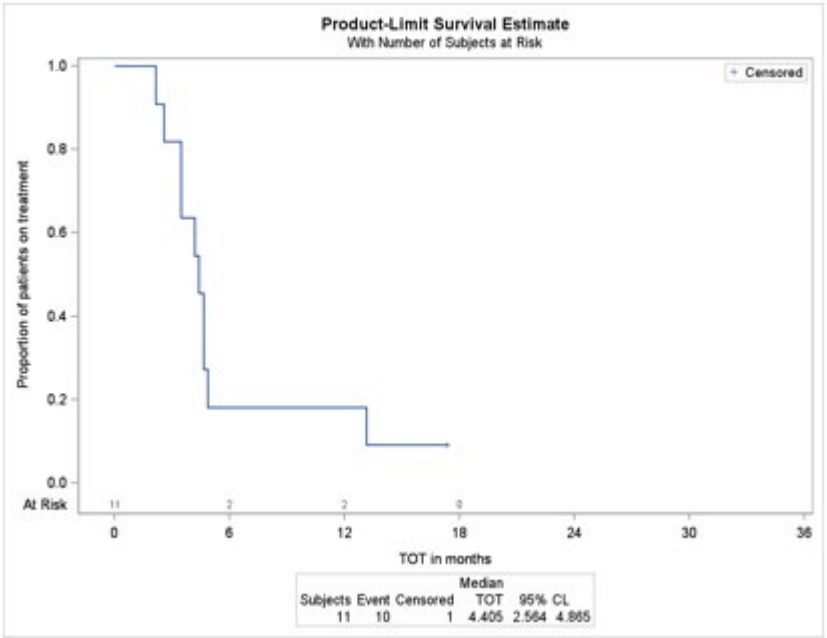
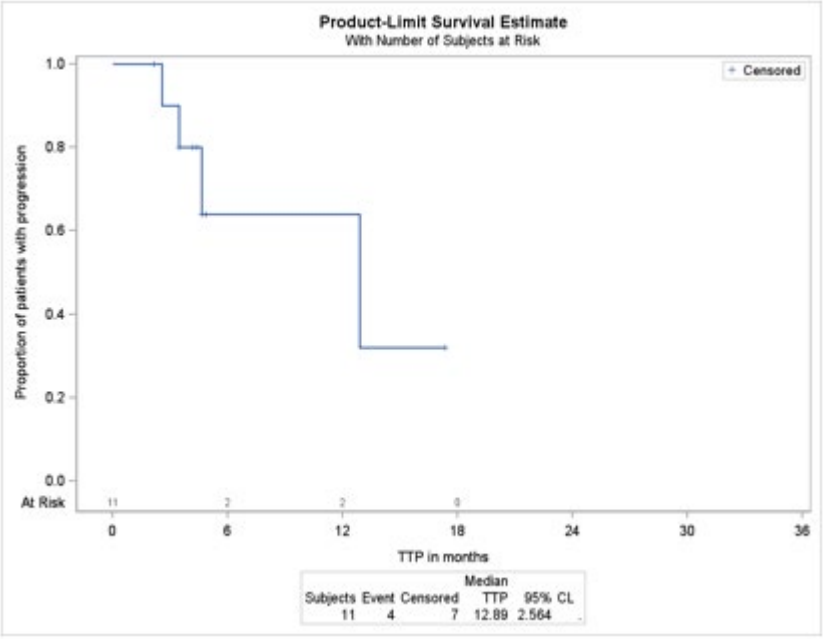


Figure 33. TTP in non-afatinib NSCLC patients (n=11)



Within patients not treated with afatinib, median PFS ranged from 3.14 months in cholangiocarcinoma to 15.91 months in renal cell cancer. Median TOT ranged from 3.13 months in cholangiocarcinoma to 15.91 months in renal cell cancer. Median TTP ranged from 12.89 months in NSCLC to 15.91 months in renal cell cancer. KM curves for PFS, TOT, and TTP were not possible for non-afatinib ovarian cancer patients (n=3) and non-afatinib colorectal cancer patients (n=3) due to small sample size. Among all non-afatinib cancer patients (n=38), there was an equal proportion who had 1L non-afatinib therapy with a known gene fusion partner (n=18) and an unknown gene fusion partner (n=18). There was a lack of pattern observed among the non-afatinib specific cancer types. There was a mixture of 1L and 2L therapies and known and unknown gene partners.

Table 24. Treatment response in non-afatinib NSCLC patients (n=11)

	All non-afatinib NSCLC patients (n=11)	**1L non-afatinib NSCLC patients with known gene fusion partner (n=19)**
Charted best response to therapy ORR, n (%)	8 (72.7%)	5 (83.3%)
Calculated best response based on imaging ORR, n (%)	8 (72.7%)	0 (0%)
DOCB (months), median (95% CI)	13.38 (1.81-13.38)	11.18 (8.97-13.38)
DOR (months), median (95% CI)	13.38 (8.97-13.38)	11.18 (8.97-13.38)

Abbreviations:1L= first-line therapy, CI= confidence interval, charted ORR= overall response rate, imaging ORR= objective response rate, DOCB= duration of clinical benefit, DOR= duration of response.

Figure 34. PFS in non-afatinib pancreatic cancer patients (n=6)

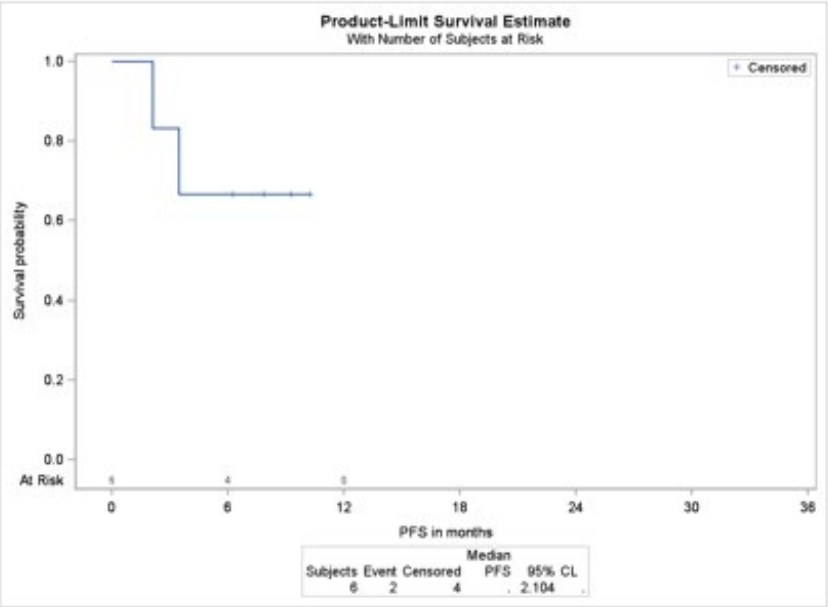


Figure 35. TOT in non-afatinib pancreatic cancer patients (n=6)

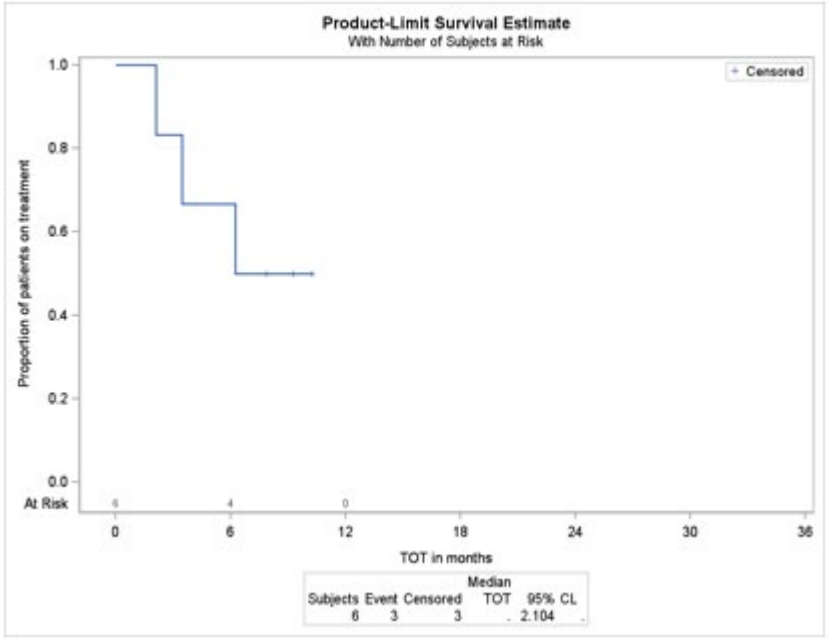


Figure 36. TTP in non-afatinib pancreatic cancer patients (n=6)

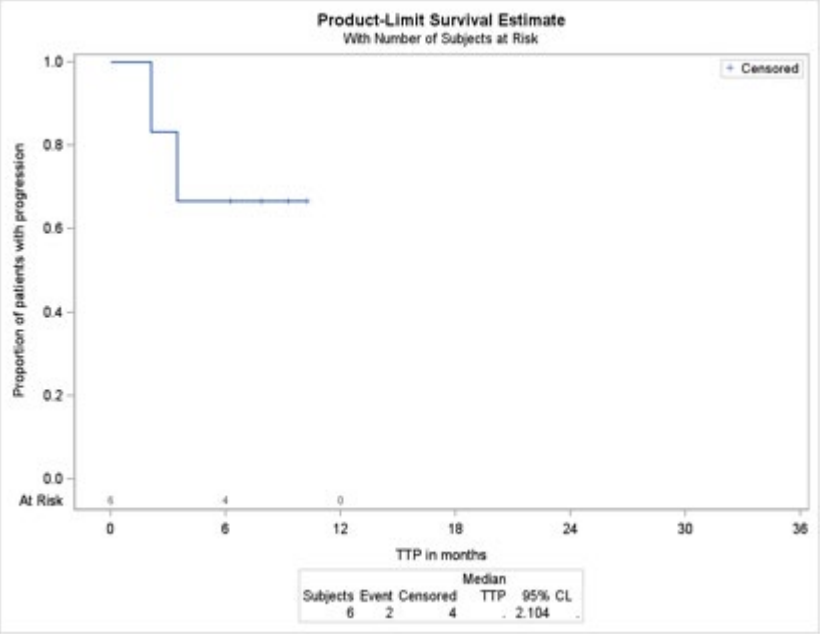


Table 25. Treatment response in non-afatinib pancreatic cancer patients (n=6)

	All non-afatinib pancreatic cancer patients (n=6)	2L non-afatinib pancreatic cancer patients with unknown gene fusion partner (n=3)	1L Non-Afatinib Pancreatic Cancer Patients with Known gene fusion partner (n=3)
Charted best response to therapy ORR, n (%)	4 (66.7%)	1 (33.3%)	3- (100%)
Calculated best response based on imaging ORR, n (%)	4 (66.7%)	1 (33.3%)	3 (100%)
DOCB (months), median (95% CI)	NR (2.10-NR)	NR (2.10-NR)	NR (NR-NR)
DOR (months), median (95% CI)	NR (NR-NR)	NR (NR-NR)	NR (NR-NR)

Abbreviations: 1L= first line therapy, 2L=second line therapy, CI=confidence interval, charted ORR=overall response rate, imaging ORR= objective response rate, DOCB=duration of clinical benefit, DOR=Duration of response, NR= not reached

Figure 37. PFS in non-afatinib bladder cancer patients (n=6)

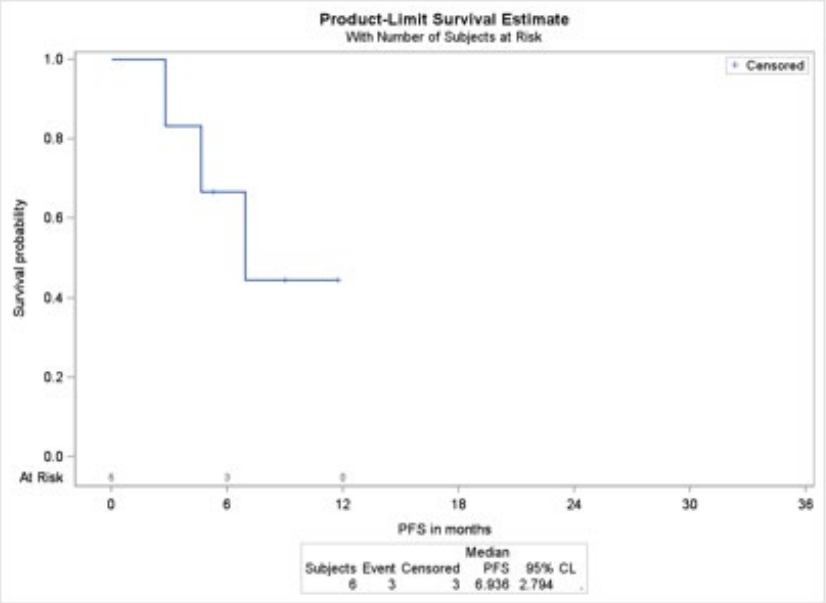


Figure 38. TOT in non-afatinib bladder cancer patients (n=6)

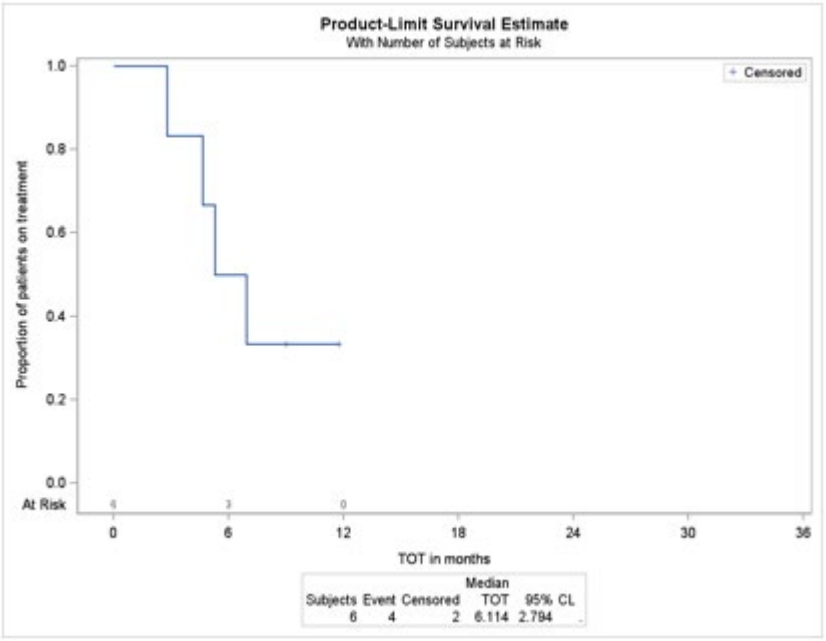


Figure 39. TTP in non-afatinib bladder cancer patients (n=6)

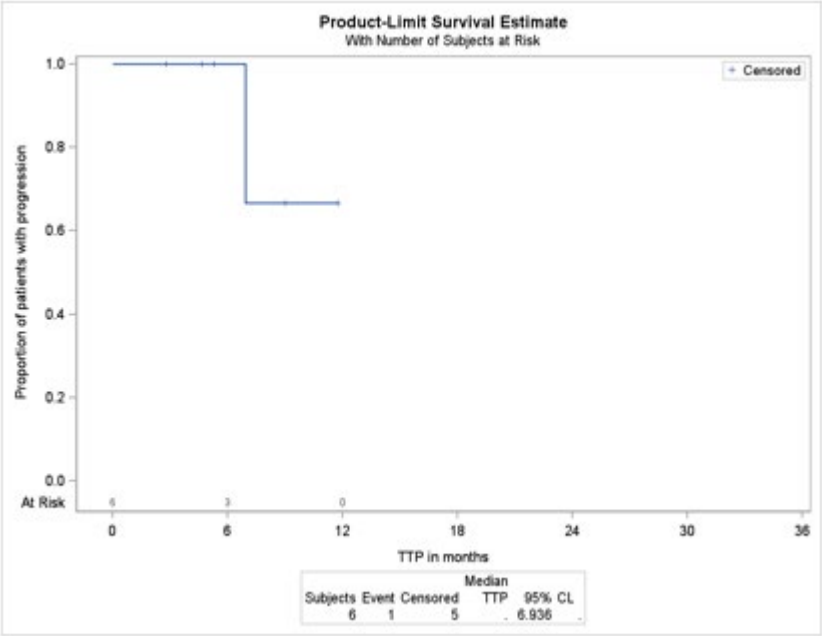


Table 26. Treatment response in non-afatinib bladder cancer patients (n=6)

	All non-afatinib bladder cancer patients (n=6)	1L non-afatinib bladder cancer patients with known gene fusion partner (n=4)
Charted best response to therapy ORR, n (%)	4 (66.7%)	3 (75%)
Calculated best response based on imaging ORR, n (%)	4 (66.7%)	3 (75%)
DOCB (months), median (95% CI)	NR (0.46-NR)	NR (NR-NR)
DOR (months), median (95% CI)	NR (NR-NR)	NR (NR-NR)

Abbreviations: 1L= first-line therapy, CI= confidence interval, charted ORR= overall response rate, imaging ORR= objective response rate, DOCB=duration of clinical benefit, DOR= duration of response, NR=no response.

Figure 40. PFS in non-afatinib cholangiocarcinoma patients (n=4)

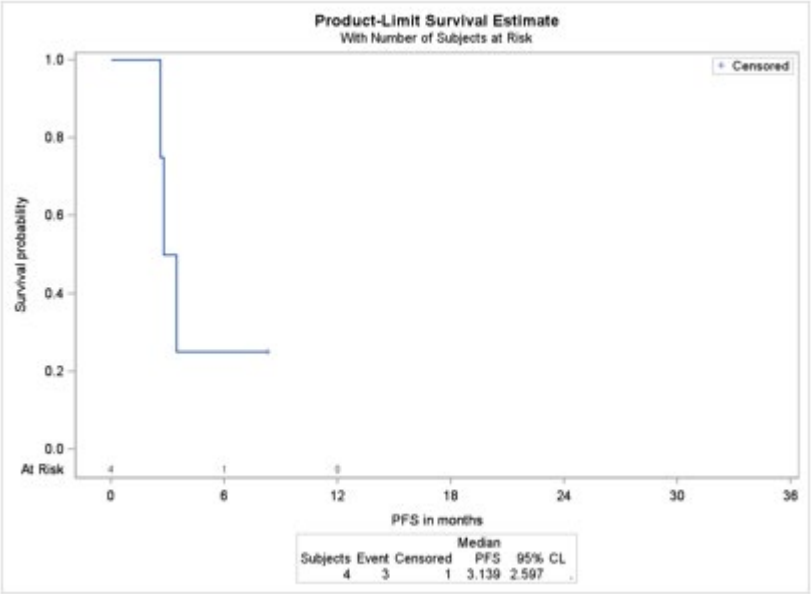


Figure 41. TOT in non-afatinib cholangiocarcinoma patients (n=4)

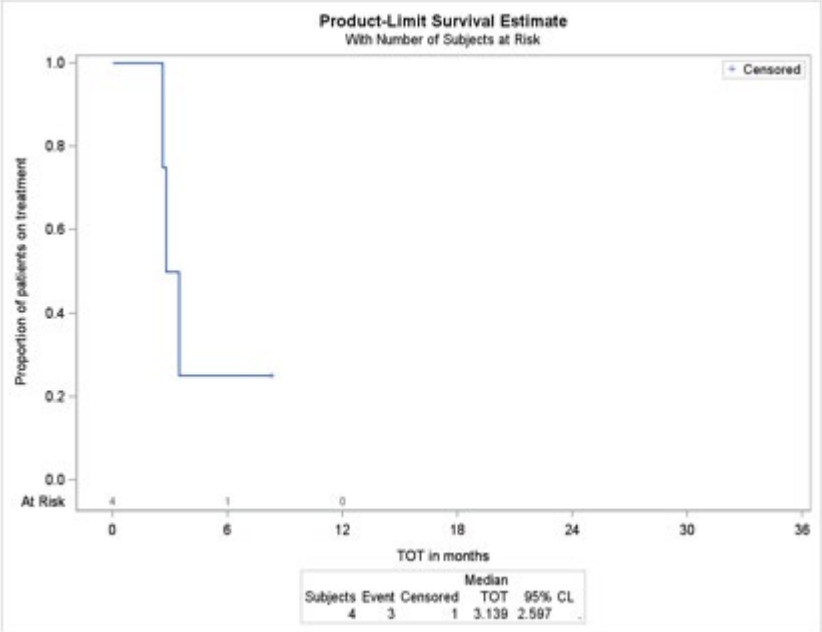


Figure 42. TTP in non-afatinib cholangiocarcinoma patients (n=4)

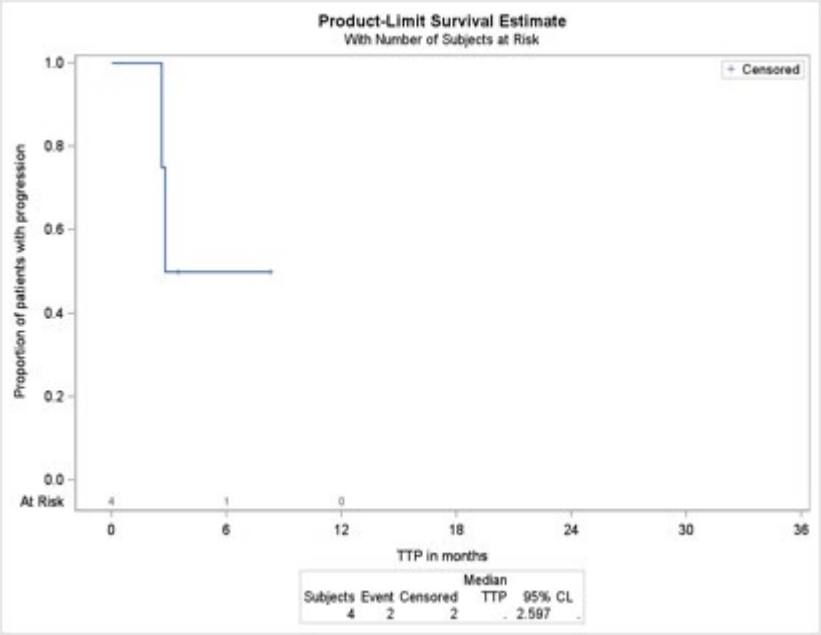


Table 27. Treatment response in non-afatinib cholangiocarcinoma patients (n=4)

	All non-afatinib cholangiocarcinoma patients (n=4)	2L non-afatinib cholangiocarcinoma patients with unknown gene fusion partner (n=3)
Charted best response to therapy ORR, n (%)	3 (75%)	3 (100%)
Calculated best response based on imaging ORR, n (%)	1 (25%)	1 (33.3%)
DOCB (months), median (95% CI)	0.99 (0.3-NR)	0.99 (0.3-NR)
DOR (months), median (95% CI)	0.99 (0.3-NR)	0.99 (0.3-NR)

Abbreviations: 2L= second-line therapy, CI= confidence interval, charted ORR= overall response rate, imaging ORR= objective response rate, DOCB= duration of clinical benefit, DOR= duration of response, NR= not reached.

Figure 43. PFS in non-afatinib renal cell carcinoma patients (n=3)

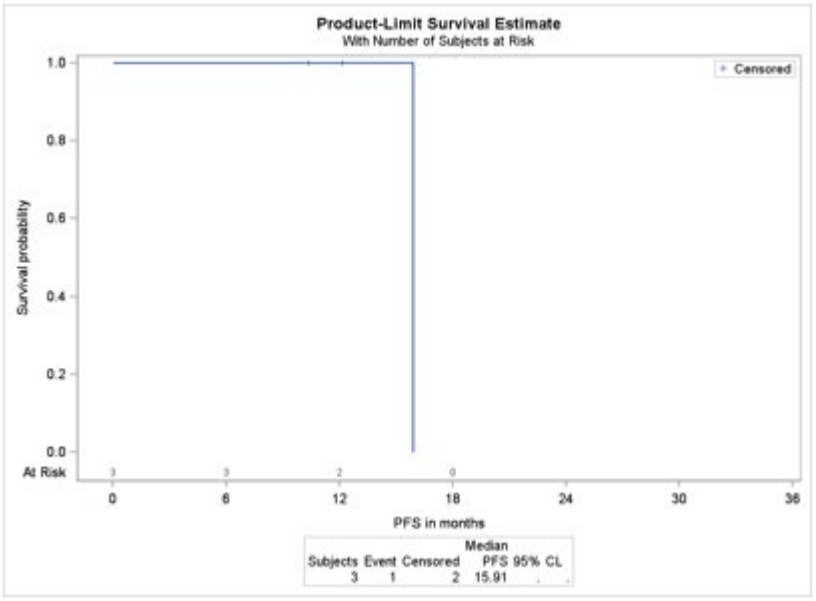


Figure 44. TOT in non-afatinib renal cell carcinoma patients (n=3)

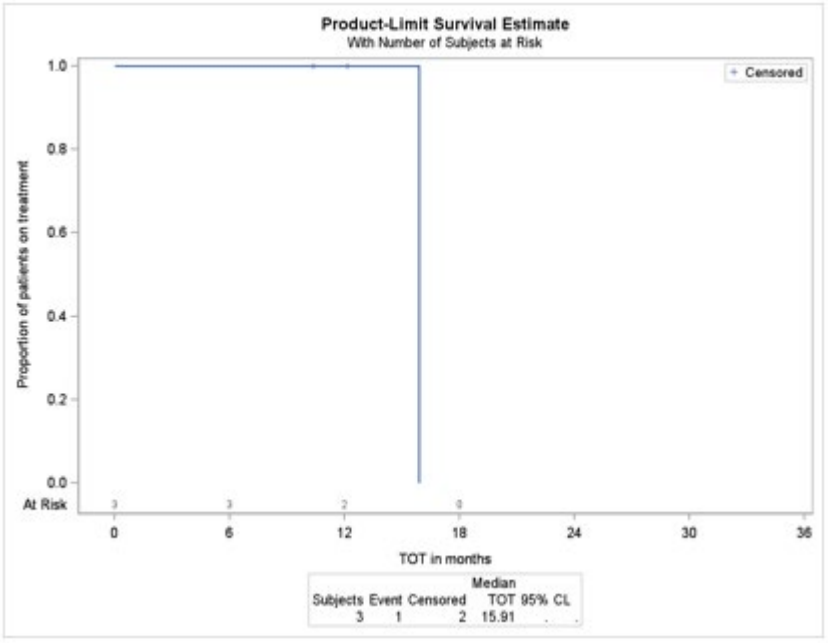


Figure 45. TTP in non-afatinib renal cell carcinoma patients (n=3)

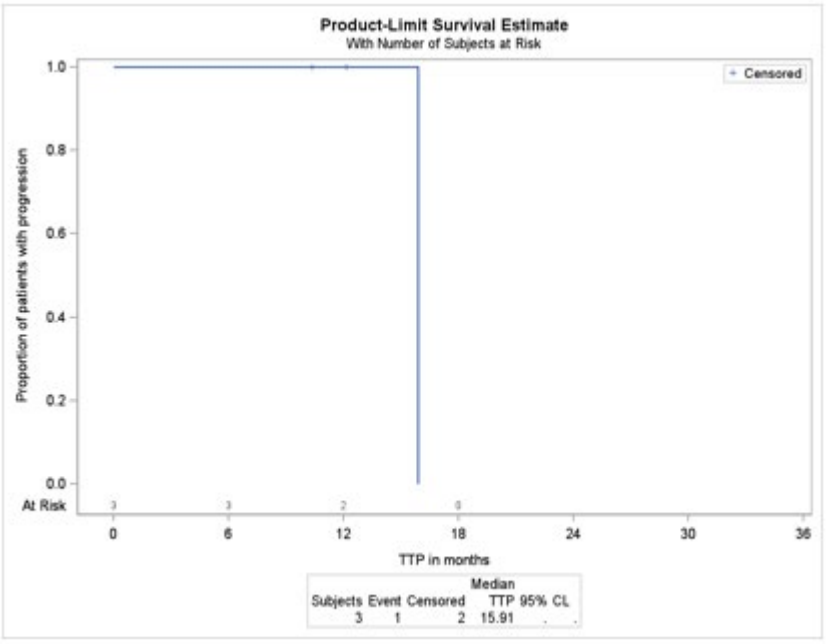


Table 28. Treatment response in non-afatinib renal cell carcinoma patients (n=3)

	All non-afatinib renal cell carcinoma patients (n=3)	2L non-afatinib renal cell carcinoma patients with unknown gene fusion partner (n=2)
Charted best response to therapy ORR, n (%)	3 (100%)	2 (100%)
Calculated best response based on imaging ORR, n (%)	3 (100%)	2 (100%)
DOCB (months), median (95% CI)	NR (0.03-NR)	NR (NR-NR)
DOR (months), median (95% CI)	NR (0.0-NR)	NR (NR-NR)

Abbreviations: 2L= second-line therapy, CI= confidence interval, ORR= objective response rate, DOCB= duration of clinical benefit, DOR= duration of response, NR= not reached.

Table 29. Treatment response in non-afatinib colorectal patients (n=3)

	All non-afatinib colorectal cancer patients (n=3)	2L non-afatinib colorectal cancer Patients with known and unknown gene fusion partner (n=1)
Charted best response to therapy ORR, n (%)	2 (66.7%)	1 (100%)
Calculated best response based on imaging ORR, n (%)	2 (66.7%)	1 (100%)
DOCB (months), median (95% CI)	NR, (NR-NR)	NR, (NR-NR)
DOR (months), median (95% CI)	NR, (NR-NR)	NR, (NR-NR)

Abbreviations: 2L= second-line therapy, CI= confidence interval, ORR= objective response rate, DOCB= duration of clinical benefit, DOR= duration of response, NR= not reached.

Table 30. Treatment response in non-afatinib ovarian cancer patients (n=3)

	All afatinib ovarian cancer patients (n=3)	1L afatinib ovarian cancer patients with known gene fusion partner (n=2)
Charted best response to therapy ORR, n (%)	3 (100%)	2 (100%)
Calculated best response based on imaging ORR, n (%)	3 (100%)	2 (100%)
DOCB (months), median, (95% CI)	NR (NR-NR)	NR (NR-NR)
DOR (months), median, (95% CI)	NR (NR-NR)	NR (NR-NR)

Abbreviations: 1L= first-line therapy, CI= confidence interval, ORR= objective response rate, DOCB= duration of clinical benefit, DOR= duration of response, NR= no response.

Objective 4*: To estimate OS among patients with NRG1 gene fusion-positive solid tumors treated with afatinib and among patients with NRG1 gene fusion-positive solid tumors treated with other systemic therapy*

Among all afatinib patients, median OS was 7.16 months **(Figure 46)** and among all non-afatinib patients, median OS was 22.55 months **(Figure 47)**.

Figure 46. OS for all afatinib patients (n=72)

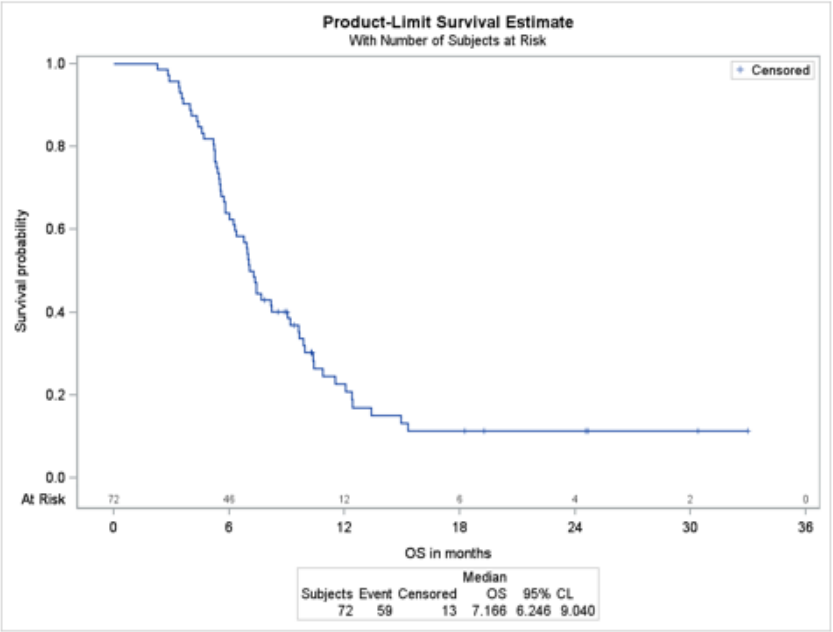
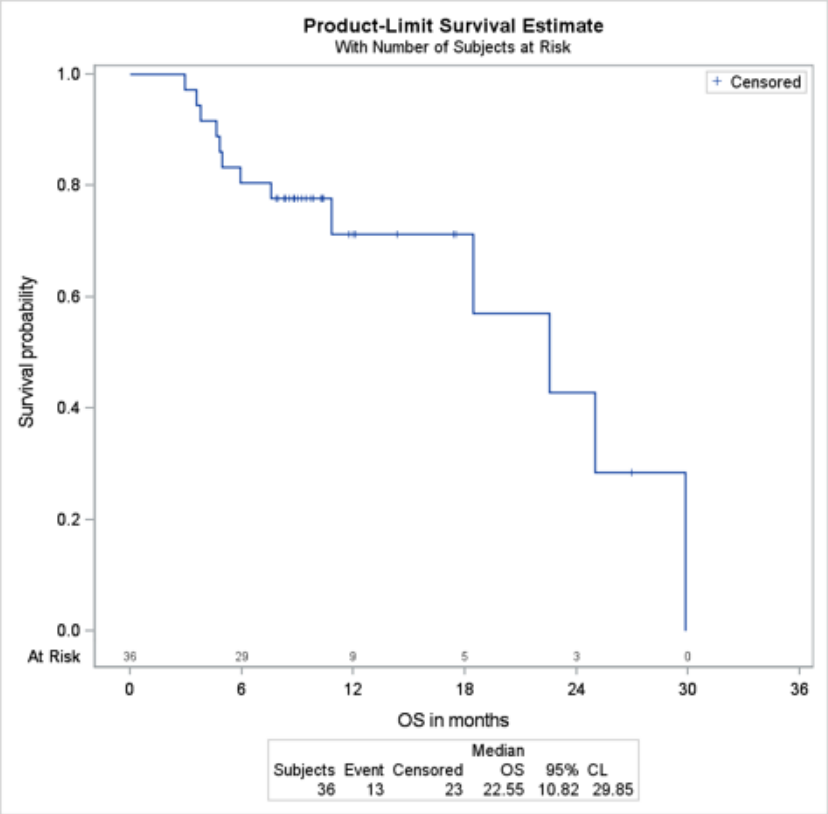


Figure 47. OS for all non-afatinib patients (n=38)



10.3.1 Secondary Outcome(s)

Not applicable.

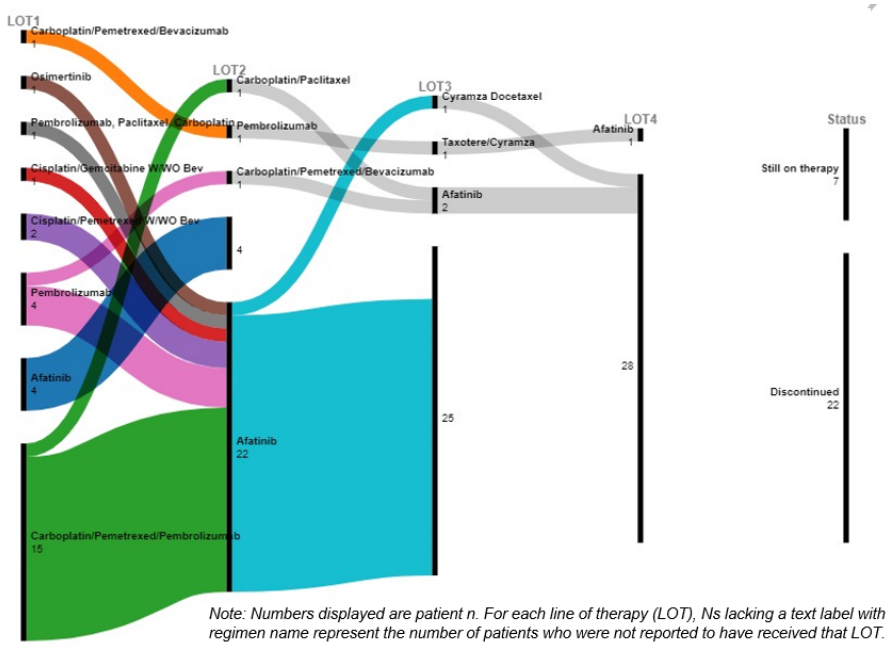
10.3.2 Further Outcome(s)

Not applicable.

10.5 OTHER ANALYSES

Among 29 patients with NSCLC: For the 4 patients who received afatinib as 1L, no subsequent therapy was reported following afatinib. For the 22 patients who received afatinib as 2L, for all but one patient, no subsequent therapy was reported following afatinib. Pre-afatinib therapy included carboplatin/pemetrexed/pembrolizumab for 15 patients (68%), pembrolizumab for 4 patients (18%), cisplatin/pemetrexed with or without bevacizumab for 2 patients, pembrolizumab/paclitaxel/carboplatin for 1 patient, and cisplatin/gemcitabine with or without bevacizumab for 1 patient. For 1 patient, osimertinib was received prior to afatinib and ramucirumab/docetaxel was received following afatinib. For the 2 patients who received afatinib as 3L, no subsequent therapy was reported following afatinib. 1 patient each received carboplatin/pemetrexed/bevacizumab, pembrolizumab, and ramucirumab/docetaxel prior to afatinib. For the 1 patient who received afatinib as 4L, no subsequent therapy was reported following afatinib. 1 patient each received docetaxel/ramucirumab, pembrolizumab, and carboplatin/pemetrexed/bevacizumab prior to afatinib (**Figure 48**).

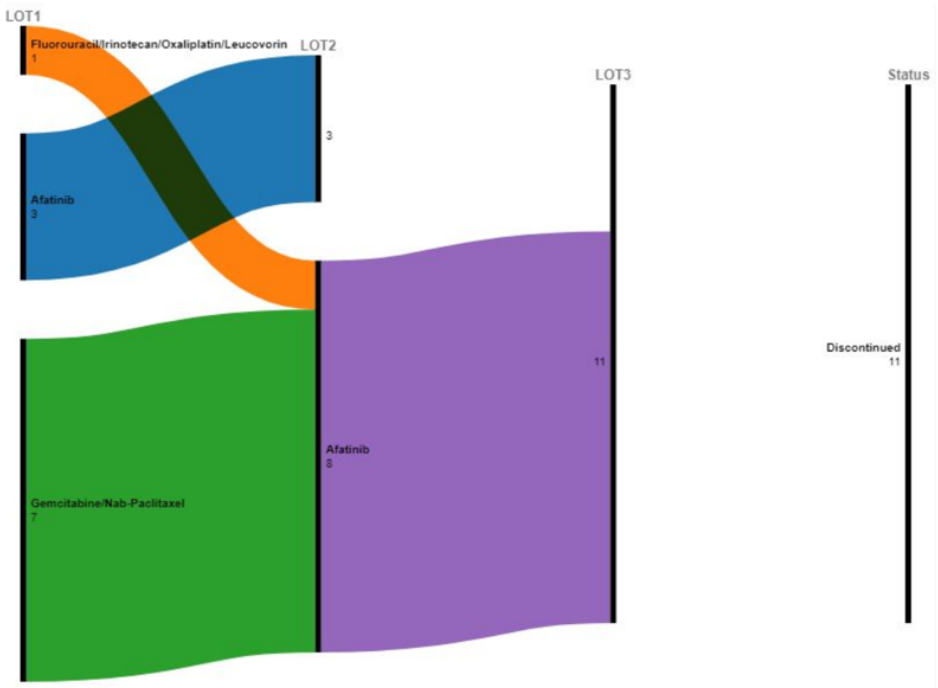
Figure 48. Treatment sequencing – afatinib NSCLC patients



Note: Numbers displayed are patient n. For each line of therapy (LOT), Ns lacking a text label with a regimen name represent the number of patients who were not reported to have received that LOT.

Among 11 patients with pancreatic cancer, for the 3 patients who received afatinib as 1L, no subsequent therapy was reported. For the 8 patients who received afatinib as 2L, no subsequent therapy was reported. Of these 8 patients, 7 received gemcitabine/nab-paclitaxel as 1L and 1 received fluorouracil/irinotecan/oxaliplatin/leucovorin as 1L (**Figure 49**).

Figure 49. Treatment sequencing – afatinib pancreatic cancer patients

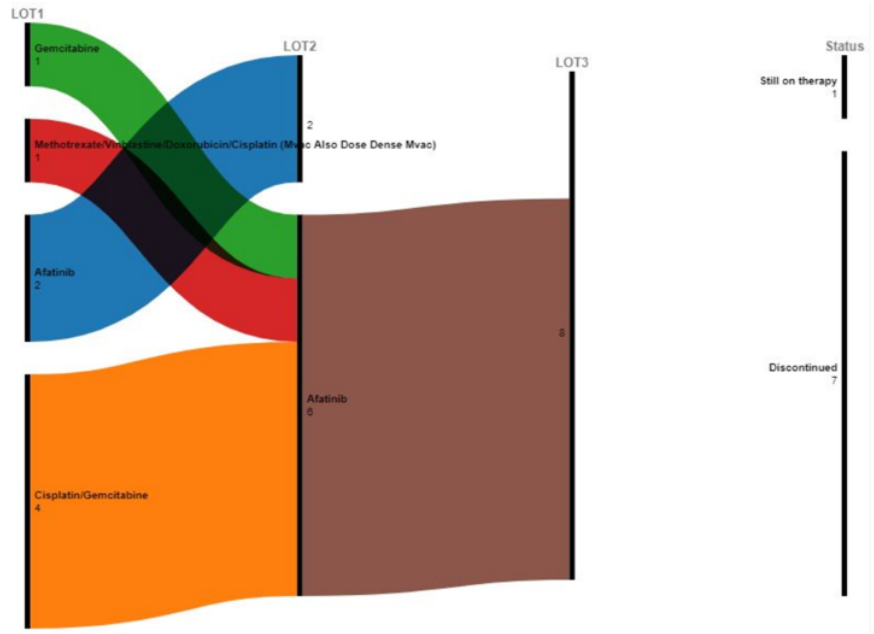


Note: Numbers displayed are patient n. For each line of therapy (LOT), Ns lacking a text label with a regimen name represent the number of patients who were not reported to have received that LOT.

Among 8 patients with bladder cancer, for the 2 patients who received afatinib as 1L, no

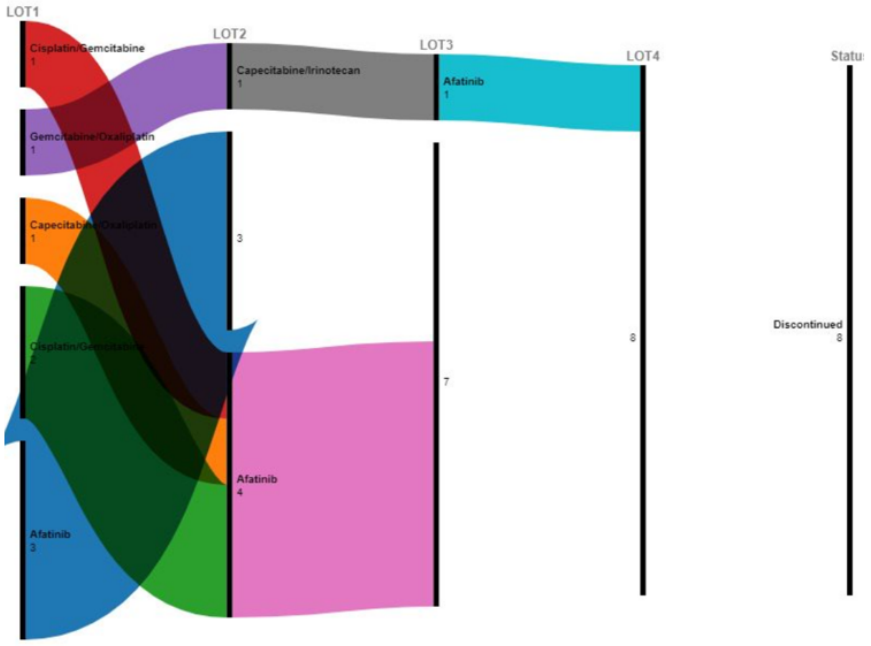
subsequent therapy was reported. For the 6 patients who received afatinib as 2L, no subsequent therapy was reported. Of these 6 patients, 4 received cisplatin/gemcitabine as 1L, 1 received gemcitabine as 1L, and 1 received methotrexate/vinblastine/doxorubicin/cisplatin as 1L (**Figure 50**).

Figure 50. Treatment sequencing – afatinib bladder cancer patients



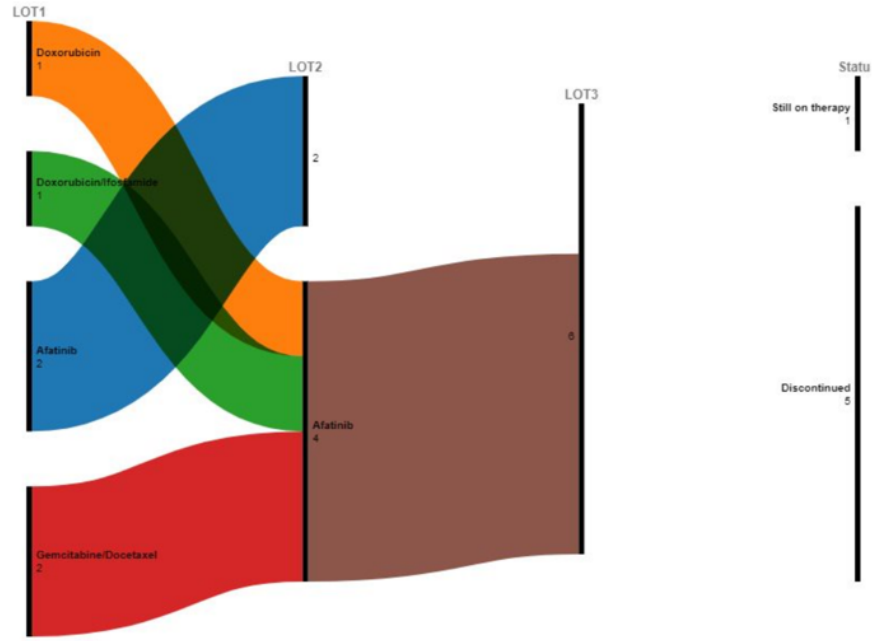
Note: Numbers displayed are patient n. For each line of therapy (LOT), Ns lacking a text label with a regimen name represent the number of patients who were not reported to have received that LOT.

Figure 51. Treatment sequencing – afatinib cholangiocarcinoma patients



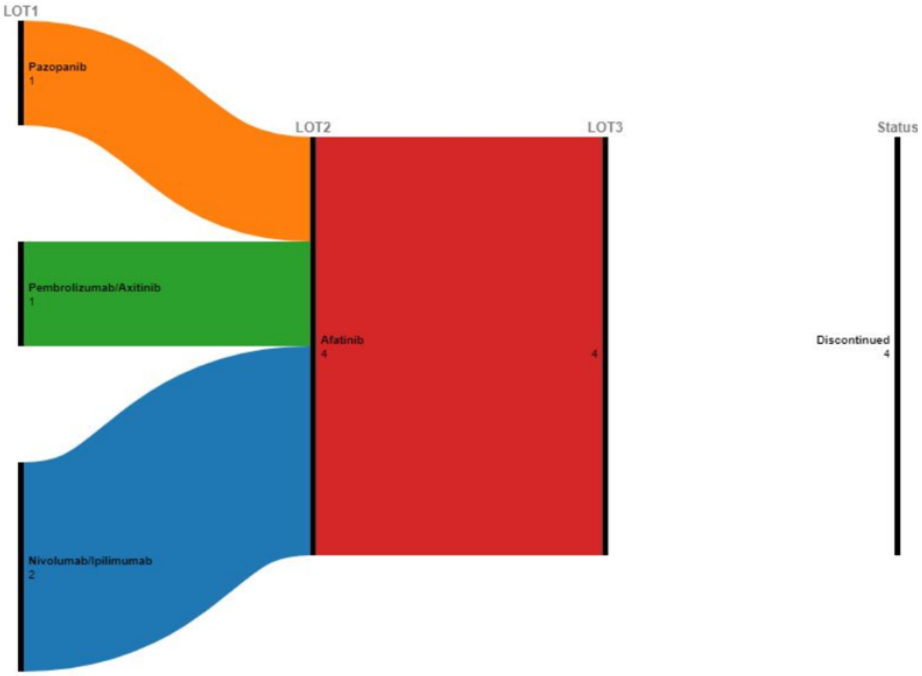
Note: Numbers displayed are patient n. For each line of therapy (LOT), Ns lacking a text label with a regimen name represent the number of patients who were not reported to have received that LOT.

Figure 52. Treatment sequencing – afatinib sarcoma patients



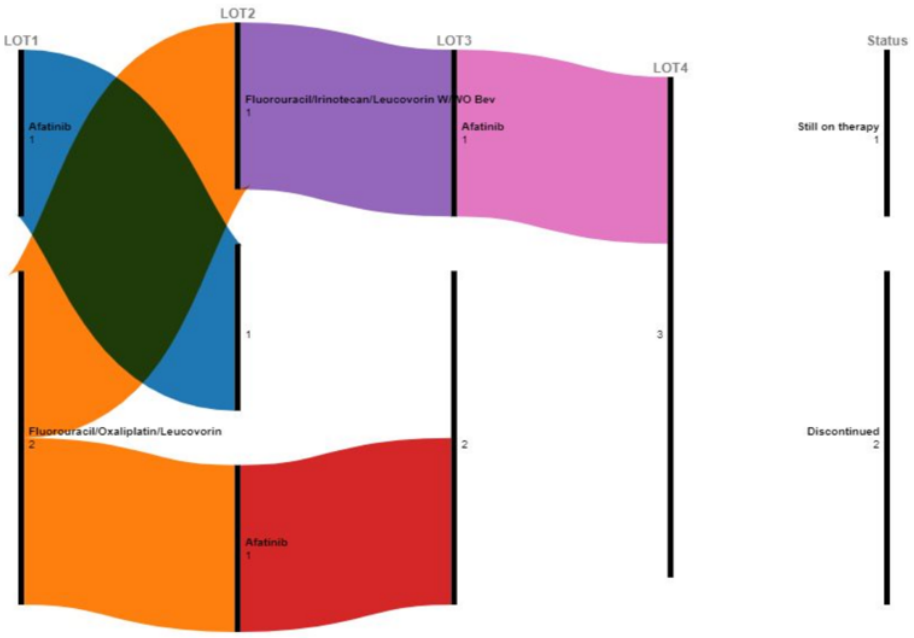
Note: Numbers displayed are patient n. For each line of therapy (LOT), Ns lacking a text label with a regimen name represent the number of patients who were not reported to have received that LOT.

Figure 53. Treatment Sequencing – afatinib renal cell cancer patients



Note: Numbers displayed are patient n. For each line of therapy (LOT), Ns lacking a text label with a regimen name represent the number of patients who were not reported to have received that LOT.

Figure 54. Treatment Sequencing – afatinib colorectal cancer patient

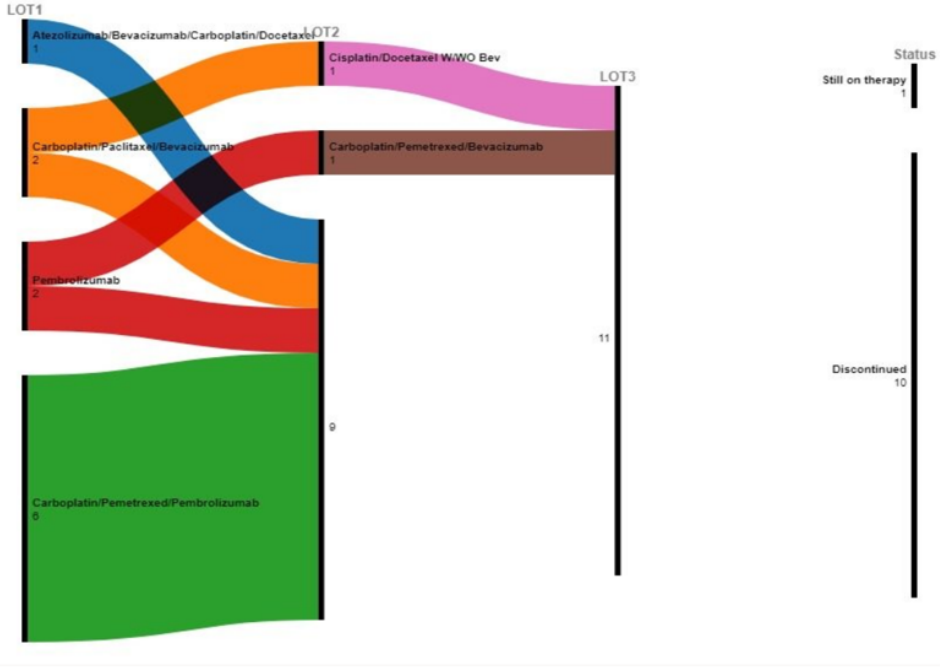


Note: Numbers displayed are patient n. For each line of therapy (LOT), Ns lacking a text label with a regimen name represent the number of patients who were not reported to have received that LOT.

S

Among 11 non-afatinib patients with NSCLC: 6 patients received carboplatin/pemetrexed/pembrolizumab, 2 patients received pembrolizumab and carboplatin/paclitaxel/bevacizumab, and 1 patient received atezolizumab/bevacizumab/carboplatin/docetaxel as 1L. For the 6 patients who received carboplatin/pemetrexed/pembrolizumab as 1L, no subsequent therapy was reported. of the 2 pembrolizumab 1L patients, 1 reported no additional therapy and 1 received carboplatin/pemetrexed/bevacizumab as 2L therapy. Of the 2 carboplatin/paclitaxel/bevacizumab 1L patients, 1 reported no additional therapy and 1 received cisplatin/docetaxel/bevacizumab as 2L therapy. The 1 patient who received atezolizumab/bevacizumab/carboplatin/docetaxel reported no subsequent therapy. 1 patient received cisplatin/docetaxel/bevacizumab and 1 patient received carboplatin/pemetrexed/bevacizumab as 2L therapy both of these patients reported no subsequent therapy (**Figure 55**).

Figure 55. Treatment sequencing – non-afatinib NSCLC patients



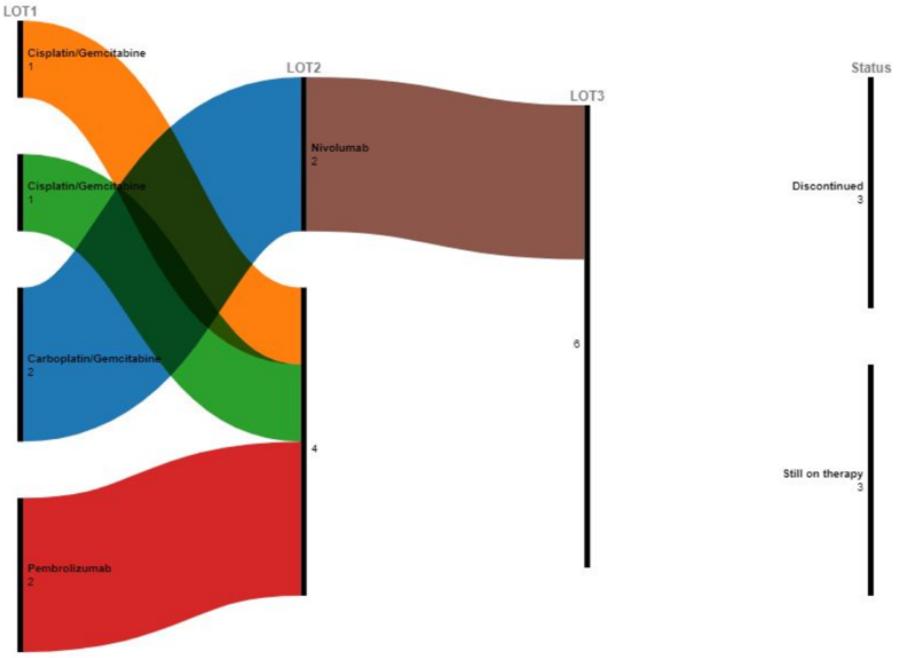
Note: Numbers displayed are patient n. For each line of therapy (LOT), Ns lacking a text label with a regimen name represent the number of patients who were not reported to have received that LOT.

Among 6 non-afatinib patients with pancreatic cancer, 4 patients received gemcitabine/nab-paclitaxel as 1L. 1 patient was still on therapy at the end of the observation period, and 3 patients were discontinued at the end of the observation period. 2 patients received fluorouracil/irinotecan/oxaliplatin/leucovorin as 1L. Both of these patients were still on therapy at the end of the observation period (**Figure 56).**

Figure 56. Treatment sequencing – non-afatinib pancreatic cancer patients

Among 6 non-afatinib patients with bladder cancer, 2 patients received pembrolizumab as 1L, 2 patients received carboplatin/gemcitabine as 1L, and 2 patients received cisplatin/gemcitabine. Only those 2 patients who received carboplatin/gemcitabine as 1L went on to receive a subsequent line of therapy, which was nivolumab as 2L.
all other patients reported no subsequent therapy after 1L (**Figure 57**).

Figure 57. Treatment Sequencing – non-afatinib bladder cancer patients



Note: Numbers displayed are patient n. For each line of therapy (LOT), Ns lacking a text label with a regimen name represent the number of patients who were not reported to have received that LOT.

Figure 58. Treatment sequencing – non-afatinib cholangiocarcinoma patients

Figure 59. Treatment sequencing – non-afatinib ovarian cancer patients

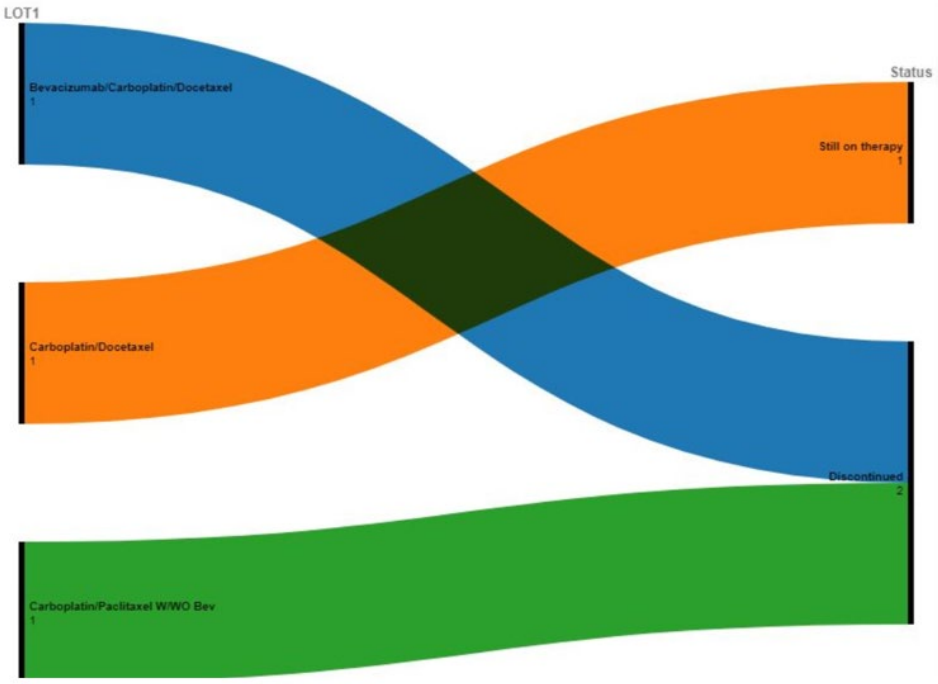
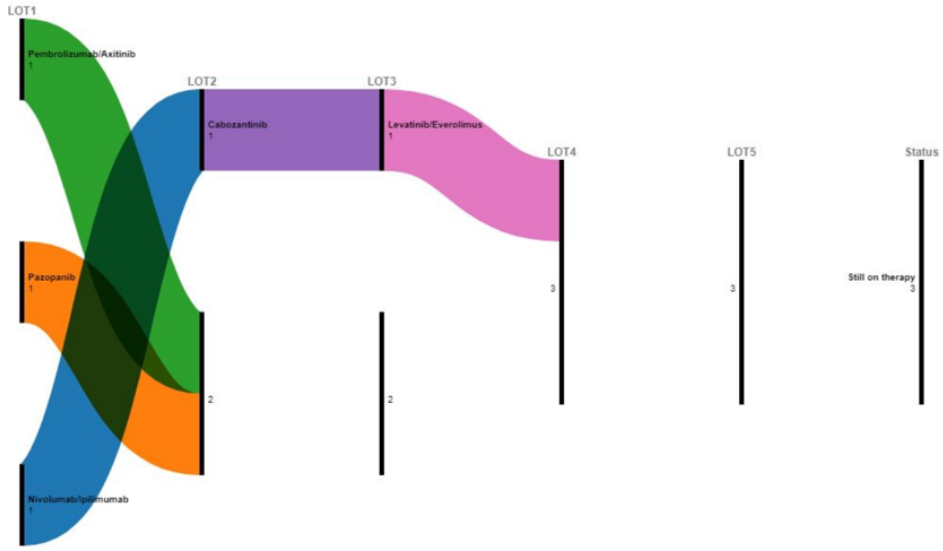
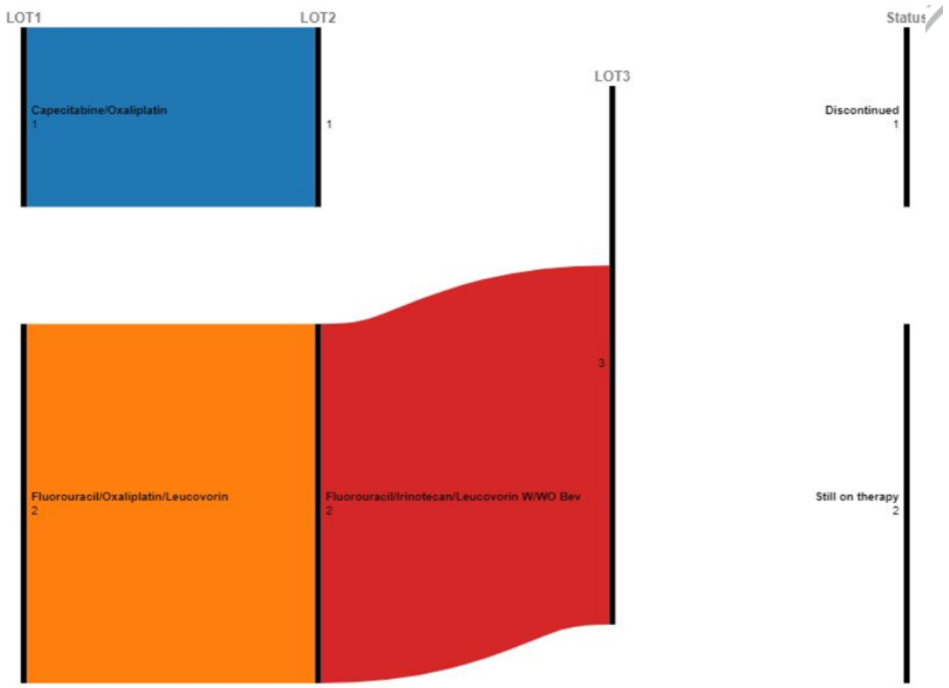


Figure 60. Treatment sequencing – non-afatinib renal cell cancer patients



Note: Numbers displayed are patient n. For each line of therapy (LOT), Ns lacking a text label with a regimen name represent the number of patients who were not reported to have received that LOT.

Figure 61. Treatment sequencing – non-afatinib colorectal cancer patients



Note: Numbers displayed are patient n. For each line of therapy (LOT), Ns lacking a text label with a regimen name represent the number of patients who were not reported to have received that LOT.

10.6 ADVERSE EVENTS/ADVERSE REACTIONS (ADRs)

Objective 5*: To describe the incidence and severity of AEs among patients with NRG1 gene fusion-positive solid tumors while on treatment with afatinib or other systemic therapy*

Among all afatinib patients during index treatment line, 10.3% (n=3) experienced an ADR with a median 1 ADR. The first ADR reported was diarrhea, which was moderate in 57.1% of cases and severe in 42.9% of cases. 100% of cases were attributed to treatment. For those that experienced the ADR, 85.7% (n=6) had a dose hold, dose delay, or schedule change, 42.9% (n=3) had a dose reduction, 14.3% (n=1) had a discontinuation of treatment, and 14.3% (n=1) had an unscheduled office visit or treatment **(Table 31).**

Among all non-afatinib patients during index treatment line, 21.1% (n=8) experienced an ADR with a median 1 ADR. Reported ADRs included febrile neutropenia (n=2, 25%), nausea/vomiting (n=1, 12.5%), neuropathy (n=1, 12.5%), neutropenia (n=2, 25%), and thrombocytopenia (n=2, 25%). Febrile neutropenia resulted in dose hold, dose delay, or schedule change for 1 patient, death in 1 patient, and inpatient hospitalization in 1 patient. Nausea/vomiting resulted in an unscheduled office visit for 1 patient. Neuropathy resulted in dose hold, dose delay, or schedule change for 1 patient. Neutropenia for dose reduction, dose hold/dose delay/schedule change, and inpatient hospitalization for 1 patient in each outcome. Thrombocytopenia resulted in dose hold/dose delay/schedule change for 2 patients **(Table 32).**

Table 31**.** All afatinib patients ADRs (n=72)

	Afatinib patients (n=72)
Patient experienced any ADR during index treatment line, n (%)	
Yes	3 (10.3%)
No	26 (89.7%)
Median number of ADRs experienced during index treatment line, median (25^{th}-75th)	1 (1-2)
1st ADR experienced during index treatment line, n (%)	3 (100%)
Diarrhea	
Outcome of ADR, n (%)	
Diarrhea	
Dose reduction	1 (33.3%)
Dose hold/dose delay/schedule change	3 (100%)
Unscheduled office visit/treatment	1 (33.3%)

Table 32. All non-afatinib patients ADRs (n=38)

	Non-afatinib patients (n=38)
Patient experienced any ADR during index treatment line, n (%)	
Yes	8 (21.1%)
No	30 (78.9%)
Median number of ADRs experienced during index treatment line, median (25^{th}-75^{th})	1 (1-2)
1st ADR experienced during index treatment line, n (%)	
Febrile neutropenia	2 (25%)
Nausea/vomiting	1 (12.5%)
Neuropathy	1 (12.5%)
Neutropenia	2 (25%)
Thrombocytopenia	2 (25%)
Outcome of ADR, n (%)	
Febrile neutropenia, n (%)	
Dose hold/dose delay/schedule change	1 (50%)
Resulting in death	1 (50%)
Inpatient hospitalization	1 (50%)
Nausea/vomiting, n (%)	
Unscheduled office visit/treatment	1 (100%)
Neuropathy, n (%)	
Dose hold/dose delay/schedule change	1 (100%)
Neutropenia, n (%)	
Dose reduction	1 (50%)
Dose hold/dose delay/schedule change	1 (50%)
Inpatient hospitalization	1 (50%)
Thrombocytopenia, n (%)	
Dose hold/dose delay/schedule change	2 (100%)

AEs evaluated in this study met the criteria for an event as would be defined in a prospective clinical trial.

11. DISCUSSION

11.1 KEY RESULTS

This non-comparative, retrospective observational study identified patients with NRG1 positive solid tumors who had been treated with afatinib or another systemic therapy. A total of 110 patients, 72 afatinib and 38 non-afatinib were included in the final analytic dataset. Demographics within the afatinib cohort were majority male (58.3%) and White (66.7%), with the highest representation from the Northeast (36.1%) and West (36.1%) and a median age of 62 at initiation of index therapy. Within the non-afatinib cohort, the majority were male (52.6%) and White (57.9%) with the highest percentages of patients were from the South (63.2%).

In regard to clinical characteristics among afatinib patients, the majority received afatinib as the second line of therapy (70.8%). Most had an ECOG score of 2 or greater (69.4%), had a past history of smoking (52.8%), and were stage IV at initial diagnosis (90.3%). Approximately 40% of patients had hypertension, 22.2% had chronic pulmonary disease, and

20.8% did not have any comorbidities. Among all non-afatinib patients, the majority received a systemic therapy as the first line of therapy (94.7%). The majority of patients had an ECOG score of 0 or 1 or greater (68.4%), had a past history of smoking (57.9%), and had a tumor stage of four or greater (89.5%). The most common comorbidities were hypertension (55.3%), cardiovascular disease (36.8%), diabetes with chronic complications (31.6%) and chronic pulmonary disease (31.6%). Approximately one-quarter (26.3%) did not have any comorbidities.

Most patients treated with afatinib received afatinib in 2L, among all afatinib patients, the charted ORR to afatinib in any line was 37.5% (n=27). The calculated best response based on imaging was 34.7% (n=25). The DOR was 5.58 months. Keeping in mind that most patients who did not receive afatinib were indexed in 1L, among all non-afatinib patients, the charted ORR to index therapy was 76.3% (n=29). The calculated best response based on imaging was 71.1% (n=27). The DOR was 13.38 months. Among all afatinib patients, median PFS was 4.49 months, median TOT was 5.42 months and TTP was 5.49 months. For all non-afatinib patients, median PFS was 12.89 months, median TOT was 5.08 months, and median TTP was 12.89 months. Median OS was 7.16 months in afatinib patients and 22.55 months in non-afatinib patients.

Concerning adverse events, among all afatinib patients during index treatment line (largely 2L), 9.7% (n=7) experienced an ADR with a median 1 ADR. The first ADR reported was diarrhea, which was moderate in 57.1% of cases and severe in 42.9% of cases. 100% of cases were attributed to treatment. For those that experienced the ADR, 85.7% (n=6) had a dose hold, dose delay, or schedule change, 42.9% (n=3) had a dose reduction, 14.3% (n=1) had a discontinuation of treatment, and 14.3% (n=1) had an unscheduled office visit or treatment.

Among all non-afatinib patients during index treatment line (largely 1L), 21.1% (n=8) experienced an ADR with a median 1 ADR. Reported ADRs included febrile neutropenia (n=2, 25%), nausea/vomiting (n=1, 12.5%), neuropathy (n=1, 12.5%), neutropenia (n=2, 25%), and thrombocytopenia (n=2, 25%). Febrile neutropenia resulted in dose hold, dose delay, or schedule change for 1 patient, death in 1 patient, and inpatient hospitalization in 1 patient. Nausea/vomiting resulted in an unscheduled office visit for 1 patient. Neuropathy resulted in dose hold, dose delay, or schedule change for 1 patient. Neutropenia for dose reduction, dose hold/dose delay/schedule change, and inpatient hospitalization for 1 patient in each outcome. Thrombocytopenia resulted in dose hold/dose delay/schedule change for 2 patients.

11.2 LIMITATIONS

In this study, limitations existed as a result of the methodology (retrospective, observational) and of the data that were collected specific to this study. In terms of the methodology, retrospective, observational studies may suffer from selection biases.This may limit the external generalizability of the results depending upon the extent of the bias. This study employed purposive sampling that selected physicians and patients based on pre-specified selection criteria, and hence this may not be representative of all patients diagnosed with NRG1 gene fusions treated with the drugs of interest or representative of all physicians treating these types of patients. No data are available to describe non-participating providersor non-selected patients.

Mitigation of this bias was attempted by asking providers to report on consecutive patients,

starting with the earliest and capping the maximum number of patient charts submitted per provider to 30. Any provider who submitted >10 patients had their data reviewed in detail by a clinician and analyst to identify any data quality issues.

Next, as an exploratory, retrospective, non-randomized study with a total sample size of 110 patients, the study was not powered to compare outcomes between the cohorts. In addition to the sample size, adjustments were not made to address any imbalance in patient characteristics across the two treatment cohorts. Consequently, no interpretation of the comparative effectiveness of afatinib versus other systemic therapies should be made from the findings of this study as the sample size and heterogeneity precludes any matched analysis. Future research should explore the feasibility of obtaining a larger sample of patients with NRG1 gene fusion-positive tumors or implementing additional inclusion criteria in order to achieve two cohorts that may be more similar in terms of baseline characteristics.

Loss to follow-up during the study period may also have occurred if patients transferred care to other providers or clinics. As such, treatments, visits, and outcomes occurring after the date of last visit may be missing. Additionally, AEs may have been detected, but not necessarily reported, if the information was not included in the patient's medical record. In general AEs may be underreported/under-documented in a routine clinical setting due to their occurrence outside of the office setting if they do not require clinical/medical intervention (e.g., a dose modification if low grade).

11.3 INTERPRETATION

This retrospective, observational study examined patients with NRG1 positive gene fusion solid tumors treated with either afatinib or another systemic therapy. The study provided new information as to the demographics and clinical characteristics of patients who were treated with afatinib or another systemic therapy in routine clinical practice. Across both afatinib and non-afatinib patients, the majority were White and male. There was an imbalance in line of treatment across the cohorts. The majority of afatinib patients were on 2L therapy (70.8%) and the non-afatinib patients were largely on 1L therapy (94.7%). Given the small number of potentially eligible patients and the observed amount of heterogeneity in patient characteristics across treatment groups, matching or additional restriction to a particular line of therapy was not possible in the present study. Future research is warranted to generate evidence comparing afatinib and non-afatinib patient cohorts. Across both cohorts, the majority had a past history of smoking and hypertension and cardiovascular disease and chronic pulmonary disease. Among patients who received afatinib, the majority received afatinib on 2L therapy and had a known NRG1 gene fusion partner. Non-afatinib patients did not have a distinct majority for which line of therapy the systemic therapy was received in or whether the gene fusion was known or unknown. There was a mixture of known/unknown NRG1 gene fusions and line of therapy when systemic therapy was received.

The cohort used in the present study differs from the closest comparator in extant literature. Drilon et al., (2021)[12] examined a homogenous cohort of patients with *NRG1* fusion-positive lung cancers while the present study examined a heterogeneous cohort of patients with any solid tumor (e.g., non-small cell lung cancer, pancreatic, bladder, and renal cancers) with a confirmed *NRG1* gene fusion. Baseline characteristics differed from the Drilon cohort (n=110 lung cancer patients) and the current real-world data (RWD) NSCLC cohort (afatinib, n=29; non-afatinib, n=11). The median ages also varied slightly. The current research has a median of 62 years in afatinib and 66 years in non-afatinib compared to 64 years in Drilon,

The Drilon cohort had a subgroup of patients treated with systemic therapy in the metastatic setting. Of those patients with metastatic disease, 20 received afatinib, and 36 received non-afatinib (9 with pembrolizumab + premetrexed + carboplatin). In the current RWD cohort, 9 of the 11 non-afatinib NSCLC patients were treated with pembrolizumab (7 in combination with premetrexed + carboplatin); 2 of the 11 were treated with a platinum-based chemotherapy (i.e., bevacizumab + carboplatin + paclitaxel; atezolizumab + bevacizumab + carboplatin + docetaxel).

ORR to platinum-doublet or taxane-based chemotherapy was 13%-14% in the Drilon cohort (n=22). Of the 9 Drilon patients receiving IO plus chemo, 0 had CR+PR and median PFS was 3.3 months. ORR to afatinib (n=20) was 25%; in the RWD cohort, ORR to 1L non-afatinib (largely chemo-IO) was 73% (all PRs, no CRs), and ORR to 2L afatinib (n=22) was 59% in the current RWD cohort. In the Drilon cohort, the median PFS in platinum-doublet or taxane-based chemotherapy was 4.0-5.8 months, and median PFS from initiation of afatinib (n=20) was 2.8 months. In our RWD cohort, median PFS from initiation of 1L non-afatinib (n=11) was 4.9 months (95% CI, 2.6-NE); median PFS from initiation of 2L afatinib (n=22) was 6.1 months (95% CI, 4.0-11.1).

In summary, both the non-afatinib and afatinib cohorts appear to have directionally better outcomes compared to Drilon patients (e.g., RWD afatinib vs Drilon afatinib; RWD non-afatinib vs Drilon non-afatinib, and in particular the 9 chemo-IO patients), although no statistical tests were performed and the current study examined tumor site groups with 20 or fewer patients.

Without formal comparisons performed, it appears that overall, there were lower rates of ADRs in the current study compared to the randomized controlled trial for afatinib where the most common adverse reactions (≥20%) were diarrhea, rash/acneiform dermatitis, stomatitis, paronychia, dry skin, decreased appetite, nausea, vomiting, and pruritus. The current chart review, however may have lower rates of ADRs because ADRs of lower severity not requiring medical intervention may not have been charted and therefore not able to be abstracted and captured. [13, 14]

Jones et al., (2017) reported on one patient with lung adenocarcinoma and one with cholangiocarcinoma who were both treated with pan HER-TKIs for the treatment of NRG1 fusion positive tumors. Both patients displayed significant and durable responses to treatment, which suggests that NRG1 fusion-positive cancers may benefit from pan HER-TKIs regardless of their site of origin. [15] Although this study did not examine afatinib specifically, it may provide evidence for afatinib as a TKI treatment for expanded tumor types. A case series by Cadrenal et al., (2021) summarized six cases of metastatic NRG1 positive tumors treated with afatinib including colorectal cancer, nonmucinous adenocarcinoma, invasive nonmucinous adenocarcinoma, and invasive mucinous adenocarcinoma with encouraging levels of response. [16] Soria et al., 2015 conducted a randomized trial (n=795) comparing patients with squamous cell carcinoma of the lung treated with afatinib vs. erlotinib and found improvements in PFS and OS in the afatinib arm. [6]

11.4 GENERALISABILITY

As only providers who met the study eligibility requirements and who volunteered to

participate in the study were known to CHSS, the representativeness of the providers for all oncologists in the U.S. cannot be verified directly. In addition, the representativeness of the patients treated at the participating practices cannot be verified directly. Nevertheless, the relatively large sample size in this study vis-à-vis the rareness of this population (i.e., patients with NRG1 gene fusion-positive tumors) increases the generalizability of this study (e.g., the 110 patients in this study represent a greater proportion of the target population, given the relatively small target population in the US).

Further research is needed to identify and characterize patients with NRG1 gene fusion-positive tumors who are not treated with afatinib to better assess whether the patients included in this study who were not treated with afatinib are representative of this underlying patient population. The same can be said for those treated with afatinib: additional real-world evidence among patients with NRG1 gene fusion-positive tumors who were treated with afatinib would allow for a better assessment of generalizability of the afatinib-treated cohort in the present study.

12. OTHER INFORMATION

Not applicable.

13. CONCLUSION

Afatinib is currently approved for the treatment of patients with metastatic NSCLC, and limited data exist on its impact on tumor sites other than NSCLC. Other therapies which have gained FDA approval in the tumor agnostic setting include but are not limited to VITRAKVI (larotrectinib) and KEYTRUDA (pembrolizumab). Additional research is needed to examine if gene fusion status may possibly be prognostic. Prospective clinical trials with large numbers of NRG1 fusion-driven tumors of diverse origins treated with afatinib are also warranted.

14. REFERENCES

14.1 PUBLISHED REFERENCES

1. Stinchcombe, T.E., *Unmet needs in squamous cell carcinoma of the lung: potential role for immunotherapy.* Medical Oncology, 2014. **31**(5).
2. Hirsh, V., *New developments in the treatment of advanced squamous cell lung cancer: focus on afatinib.* OncoTargets and Therapy, 2017. **Volume 10**: p. 2513-2526.
3. Schiller, J.H., et al., *Comparison of Four Chemotherapy Regimens for Advanced Non–Small-Cell Lung Cancer.* New England Journal of Medicine, 2002. **346**(2): p. 92-98.
4. Davis, K.L., et al., *Real-world treatment patterns and costs in a US Medicare population with metastatic squamous non-small cell lung cancer.* Lung Cancer, 2015. **87**(2): p. 176-85.
5. Goss, G.D., et al., *Association of ERBB Mutations With Clinical Outcomes of Afatinib- or Erlotinib-Treated Patients With Lung Squamous Cell Carcinoma.* JAMA Oncology, 2018. **4**(9): p. 1189.
6. Soria, J.-C., et al., *Afatinib versus erlotinib as second-line treatment of patients with advanced squamous cell carcinoma of the lung (LUX-Lung 8): an open-label*

randomised controlled phase 3 trial. The Lancet Oncology, 2015. **16**(8): p. 897-907.
7. Paz-Ares, L., et al., *Pembrolizumab plus Chemotherapy for Squamous Non–Small-Cell Lung Cancer.* New England Journal of Medicine, 2018. **379**(21): p. 2040-2051.
8. Paz-Ares, L.G., et al., *Phase 3 study of carboplatin-paclitaxel/nab-paclitaxel (Chemo) with or without pembrolizumab (Pembro) for patients (Pts) with metastatic squamous (Sq) non-small cell lung cancer (NSCLC).* Journal of Clinical Oncology, 2018. **36**(15_suppl): p. 105-105.
9. Ettinger, D.S., et al., *NCCN Guidelines Insights: Non-Small Cell Lung Cancer, Version 5.2021.* J Natl Compr Canc Netw, 2021. **19**(3): p. 254-266.
10. Schoenfeld, A.J., et al., *Severe immune-related adverse events are common with sequential PD-(L)1 blockade and osimertinib.* Annals of Oncology, 2019. **30**(5): p. 839-844.
11. Oncology Nursing Society VOICE, *Larotrectinib and Other Tumor-Agnostic Targeted Therapies Are Leading Cancer Care Into the Next Frontier*. 2021.
12. Drilon, A., et al., *Clinicopathologic Features and Response to Therapy of NRG1 Fusion-Driven Lung Cancers: The eNRGy1 Global Multicenter Registry.* J Clin Oncol, 2021: p. JCO2003307.
13. *Gilotrif (afatinib) tablets, for oral use: US prescribing information*. 2018, Ridgefield: Boehringer Ingelheim Pharmaceuticals, Inc.
14. Deeks, E.D. and G.M. Keating, *Afatinib in advanced NSCLC: a profile of its use.* Drugs & Therapy Perspectives, 2018. **34**(3): p. 89-98.
15. Jones, M.R., et al., *Successful targeting of the NRG1 pathway indicates novel treatment strategy for metastatic cancer.* Annals of Oncology, 2017. **28**(12): p. 3092-3097.
16. Cadranel, J., et al., *Therapeutic Potential of Afatinib in NRG1 Fusion-Driven Solid Tumors: A Case Series.* The Oncologist, 2021. **26**(1): p. 7-16.

14.1 UNPUBLISHED REFERENCES

None.

APPENDICES

ANNEX 1. LIST OF STANDALONE DOCUMENTS

Number	Document reference number	Date	Title
Annex 2		1/9/2020	Study protocol
Annex 3		5/8/2020	Tables, Listings and Figures
Annex 4		2/25/2020	Case Report Form
Annex 5		3/26/2020	Adverse Event Rules and Reporting

ANNEX 2. STUDY PROTOCOL

ANNEX 3. TABLES, LISTINGS, AND FIGURES

ANNEX 4. CASE REPORT FORM

ANNEX 5. ADVERSE EVENT RULES AND REPORTING

Adverse event (AE)

An adverse event (AE) is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a medicinal product and that does not necessarily have a causal relationship with this treatment.

An AE can therefore be any unfavourable and unintended sign (e.g., abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, regardless of whether it was considered related to the medicinal product.

Adverse drug reaction (ADR)

An adverse drug reaction (ADR) is defined as a response to a medicinal product that is noxious and unintended. Response in this context means that a causal relationship between a medicinal product and an AE is at least a reasonable possibility. An ADR may arise from the use of the product within or outside the terms of the marketing authorisation or from occupational exposure. Conditions of use outside the marketing authorisation include off-label use, overdose, misuse, abuse, and medication errors.

Causal relationship of AE

The definition of an adverse reaction implies at least a reasonable possibility of a causal relationship between a suspected medicinal product and an AE. An adverse reaction, in contrast to an AE, is characterised by the fact that a causal relationship between a medicinal product and an occurrence is suspected.

Medical judgment should be used to determine the relationship, considering all relevant factors, including the pattern of reaction, temporal relationship, de-challenge or re-challenge, confounding factors such as concomitant medication, concomitant diseases, and relevant history.

Arguments that may suggest a reasonable causal relationship could be:

- The event is **consistent with the known pharmacology** of the drug
- The event is known to be caused by or **attributed to the drug class**
- A **plausible time to onset of the event** relative to the time of drug exposure
- Evidence that the **event is reproducible** when the drug is re-introduced
- **No medically sound alternative etiologies** that could explain the event (e.g., pre-existing or concomitant diseases, or co-medications)
- The event is typically **drug-related and infrequent in the general population** not exposed to drugs (e.g., Stevens-Johnson syndrome)
- An indication of dose-response (i.e., greater effect size if the dose is increased,smaller effect size if the dose is diminished)

Arguments that may suggest that there is no reasonable possibility of a causal relationship could be:

- No plausible time to onset of the event relative to the time of drug exposure is evident (e.g., pre-treatment cases, diagnosis of cancer or chronic disease within days/weeks of drug administration; an allergic reaction weeks after discontinuation of the drug concerned)
- Continuation of the event despite the withdrawal of the medication, taking into account the pharmacological properties of the compound (e.g., after 5 half-lives). Of note, this criterion may not apply to events whose time course is prolonged despite removing the original trigger.
- Additional arguments amongst those stated before, like alternative explanation (e.g., situations where other drugs or underlying diseases appear to provide a more likely explanation for the observed event than the drug concerned).
- Disappearance of the event even though the study drug treatment continues or remainsunchanged.

Intensity of AE

The intensity of AEs should be classified and recorded according to the Common Terminology Criteria for Adverse Events (CTCAE) criteria *version 5.0* in the eCRF.

Pregnancy

In rare cases, pregnancy might occur in a study. Once a subject has been enrolled into the study, after having taken afatinib, the investigator must report any drug exposure during pregnancy that occurred in a female subject or a partner to a male subject to the Sponsor by means of Part A of the Pregnancy Monitoring Form. The outcome of the pregnancy associated with drug exposure during pregnancy must be followed up and reported by means of Part B of the Pregnancy Monitoring Form.

In the absence of a reportable AE, only the Pregnancy Monitoring Form must be completed. Otherwise, the NIS AE form is to be completed and forwarded as well within the respective timelines.

Expedited reporting of AEs and drug exposure during pregnancy

The following must be reported by the investigator on the NIS AE form and/or Pregnancy Monitoring Form from start of data extraction once informed consent is signed (if required) onwards until the end of data extraction and provide to BI unique entry point:

Type of Report	Timeline
All **serious ADRs** associated with afatinib	immediately within 24 hours
All **AEs with fatal outcome** in patients exposed to afatinib *Exemption applies	immediately within 24 hours
All **non-serious ADRs** associated with afatinib	7 calendar days
Drug exposure during pregnancy	7 calendar days

The same timelines apply if follow-up information becomes available for the respective events. In specific occasions, the Investigator could inform the Sponsor upfront via telephone. This does not replace the requirement to complete and fax and/or email the NIS AE form.

*Exemption

Death due to disease progression of the underlying malignancy is a study endpoint and the natural course of the disease. As such it is exempted from reporting as an SAE. Progression of the subject's underlying malignancy were recorded on the appropriate pages of the eCRF only and will not be reported on the NIS AE Form. However, when there is evidence suggesting a causal relationship between afatinib and the progression of the underlying malignancy, the event must be reported as an SAE on the NIS AE Form and on the eCRF.

Information required

For each reportable AE, the investigator should provide the information requested on the appropriate CRF pages and the NIS AE form.

Reporting of related AEs associated with any other BI drug

The investigator is encouraged to report all AEs related to any BI drug other than afatinib according to the local regulatory requirements for spontaneous AE reporting at the investigator's discretion by using the locally established routes and AE report forms. The term AE includes drug exposure during pregnancy, and, regardless of whether an AE occurred, any abuse, off-label use, misuse, medication error, occupational exposure, lack of effect, and benefit. AE reporting to regulatory agencies were done by the Marketing Authorisation Holder(MAH) according to local and international regulatory requirements.

ANNEX 6: Selected Outcomes, Treatment, and Clinical Characteristics of 11 Non-Afatinib NSCLC Patients

Patient #	Line of therapy	Stage at diagnosis	Charted best response	Calculated best response	Duration of clinical benefit (months)	Duration of response (months)	Time to progression (months)	Progression free survival (months)	Time on treatment (months)	Regimen
Patient 1	First line	Stage IVB	Partial response	Partial response	1.05	1.05	4.17	4.17	4.17	Carboplatin/Pemetrexed/ Pembrolizumab
Patient 2	First line	Stage IVB	Progressive disease	Progressive disease			4.64	4.64	4.64	Carboplatin/Pemetrexed/ Pembrolizumab
Patient 3	First line	Stage IVB	Partial response	Partial response	6.05	6.05	2.14	2.14	2.14	Carboplatin/Pemetrexed/ Pembrolizumab
Patient 4	First line	Stage IVB	Progressive disease	Progressive disease			2.56	2.56	2.56	Carboplatin/Pemetrexed/ Pembrolizumab
Patient 5	First line	Stage IVA	Partial response	Partial response	6.51	6.51	3.48	3.48	3.48	Atezolizumab/Bevacizumab/Carboplatin/Docetaxel
Patient 6	First line	Stage IVA	Partial response	Partial response	13.38	13.38	3.48	3.48	3.48	Carboplatin/Paclitaxel/Bevacizumab
Patient 7	First line	Stage IVB	Partial response	Partial response	8.97	8.97	12.89	12.89	13.15	Pembrolizumab
Patient 8	First line	Stage IVB	Partial response	Partial response	1.35	1.35	4.41	4.41	4.41	Carboplatin/Pemetrexed/ Pembrolizumab
Patient 9	First line	Stage IVB	Stable disease	Stable disease	1.81		4.87	4.87	4.87	Carboplatin/Paclitaxel/Bevacizumab
Patient 10	First line	Stage IVA	Partial response	Partial response	1.61	1.61	4.64	4.64	4.64	Carboplatin/Pemetrexed/ Pembrolizumab
Patient 11	First line	Stage IVB	Partial response	Partial response	12.75	12.75	17.36	17.36	17.36	Pembrolizumab

ANNEX 7: Selected Outcomes, Treatment, and Clinical Characteristics of 11 Non-Afatinib NSCLC Patients

Cancer Type	N	Unadjusted Mean		Adjusted Mean (From KM Analysis)		Unadjusted Median		Adjusted Median (From KM Analysis)	
		PFS	TOT	PFS	TOT	PFS	TOT	PFS	TOT
Overall	36	6.8	6.8	10.7	8.5	5.1	5.1	12.9	5.1
Bladder cancer	6	6.7	6.7	5.9	5.9	6.1	6.1	6.9	6.1
Breast cancer	2	10.4	10.4	NR	NR	10.4	10.4	NR	NR
Cholangiocarcinoma	4	4.3	4.3	3.1	3.1	3.1	3.1	3.1	3.1
Colorectal cancer	1	9.9	9.9	NR	NR	9.9	9.9	NR	NR
Non-small cell lung cancer	11	5.9	5.9	7.9	5.5	4.4	4.4	4.9	4.4
Ovarian cancer	3	5.0	5.0	NR	3.5	3.5	3.5	NR	3.5
Pancreatic cancer	6	6.5	6.5	3.3	5.1	7.1	7.1	NR	NR
Renal cell cancer	3	12.8	12.8	15.9	15.9	12.1	12.1	15.9	15.9

Cancer Type	N	PFS				TOT			
		Mean	Median	95% CI		Mean	Median	95% CI	
All	36	10.7	12.9	4.9	NR	8.5	5.1	3.5	15.9
All except Renal	33	9.1	12.9	4.6	NR	7.3	4.6	3.5	13.1
All except Pancreatic	30	10.7	12.9	4.6	NR	8.3	4.8	3.5	15.9
All except Ovarian	33	10.5	12.9	4.6	NR	8.6	5.3	4.2	15.9
All except NSCLC	25	11.8	15.9	4.6	15.9	10.2	15.9	3.5	15.9
All except Colorectal	35	10.6	12.9	4.9	NR	8.3	4.9	3.5	15.9
All except Cholangiocarcinom	32	11.4	12.9	6.9	NR	8.8	5.8	4.2	15.9
All except Breast	34	10.5	12.9	4.6	NR	8.1	4.8	3.5	13.1
All except Bladder	30	9.9	12.9	4.6	NR	8.0	4.8	3.5	13.1

Study title: Assessment of Real-World Outcomes Associated with Afatinib (Gilotrif) Use in Patients with Solid Tumors Harboring NRG1 Gene Fusions

Study number: CTMS 1200.335
Report version: V1

I herewith certify that I agree to the content of the study report and to all documents referenced in the study report.

Position:	Name/Date:	
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