SYNOPSIS

Title of the study:	Randomized Phase 3 Trial of Gemcitabine/Carboplatin with or without Iniparib (SAR240550) (a PARP1 Inhibitor) in Subjects with Previously Untreated Stage IV Squamous Non-Small-Cell Lung Cancer (NSCLC) (EFC11553; 20090321)
Investigator(s):	[redacted]
Study center(s):	138 study centers in Belgium, Canada, France, Germany, Hungary, Israel, Italy, Luxembourg, Netherlands, Poland, Romania, Spain, United Kingdom, and United States
Publications (reference):	Spigel DR, Harper PG, Hainsworth JD, De Marinis F, Kabbinavar FF, Kim ES, et al. Randomized phase III trial of gemcitabine/carboplatin with or without iniparib (BSI-201) in patients with previously untreated stage IV squamous non-small cell lung cancer (NSCLC) [abstract]. J Clin Oncol. 2011;29 Suppl:TPS220. Spigel D, Kim ES, Lynch T, Mccleod M, Waterhouse D, Paz-Ares L, et al. Randomized phase III trial of gemcitabine (G)/carboplatin (C) with or without iniparib (I) in patients (PTS) with previously untreated stage IV squamous lung cancer [abstract O15.06]. J Thoracic Oncol. 2013:8(2 Suppl):S193-S194.
Study period:	Date first patient enrolled: 05 March 2010 Date last patient completed: 11 April 2013
Phase of development:	Phase 3
Objectives:	Primary: To evaluate the overall survival (OS) of patients with stage IV squamous non-small cell lung cancer (NSCLC) receiving gemcitabine/carboplatin either with (GCI) or without (GC) iniparib Secondary: To evaluate the following in patients with stage IV squamous NSCLC receiving gemcitabine/carboplatin either with or without iniparib: • Progression-free survival (PFS) • Time to progression (TTP) • Objective response rate (ORR) • Safety and tolerability of the treatment regimen • Quality of life (QOL) as measured by European Organization for the Research and Treatment of Cancer (EORTC) Quality-of-Life Questionnaire (QLQ)-C30 and QLQ-LC13 Exploratory substudy: • Global gene expression profiling was performed in search of a predictive signature correlated with the efficacy of (or lack of) the treatment. No new tumor biopsy was requested, but access to the archived tissue was mandatory unless national/local regulations prohibited any of the key steps of the process to evaluate the sample as described in the protocol. Cytology was not usable for this substudy. • Optionally (specific consent required), genomic DNA from peripheral blood was obtained and stored to evaluate biomarkers that may predict response (or lack of) to the treatment and/or toxicity. For similar purposes, serum collection (optional) was to be requested at baseline and at several time points during the treatment.

Methodology: This was a randomized, Phase 3, open-label, parallel, 2-arm study in patients with stage IV squamous NSCLC. Eligible patients were randomly assigned via a central interactive voice response system (IVRS) in a 1:1 ratio to receive either GCI or GC as follows:

- GCI arm: Gemcitabine (1000 mg/m^2; intravenously [IV]) on Day 1 and Day 8, carboplatin (area under the plasma concentration-time curve [AUC] 5; IV) on Day 1, and iniparib (5.6 mg/kg; IV) on Days 1, 4, 8, and 11 of each 21-day cycle
- GC arm: Gemcitabine (1000 mg/m^2; IV) on Day 1 and Day 8 and carboplatin (AUC 5; IV) on Day 1 of each 21-day cycle

Patients received treatment (6 planned cycles) with GCI or GC as long as there was no evidence of disease progression, unacceptable toxicity, or any other criteria for discontinuation or withdrawal. Patients could remain on study treatment beyond 6 cycles if there was no evidence of disease progression or the presence of dose-limiting toxicities per Investigator assessment.

Disease assessments were evaluated by Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1, every 6 weeks (±1 week) during study treatment. Quality-of-life assessments were to be performed at baseline, after 6 weeks of treatment, and at end of treatment. Toxicity was assessed on an ongoing basis.

End-of-treatment assessments were performed 30 days after the last dose of study treatment. For all randomized patients, follow-up visits were performed up to the final analysis cut-off date (ie, the date when 561 deaths had been observed) or death, whichever was first. If, at the time of the final analysis cut-off date, there were patients in the GCI arm who were still on treatment and who continued to experience a clinical benefit per the treating clinician, they could be offered enrollment in a treatment extension protocol sponsored by Sanofi (LTS12674).

A Data and Safety Monitoring Board periodically evaluated the safety of the trial and also reviewed unblinded efficacy information for the interim analysis.

Number of patients:

Planned: 780 (390 in the GCI arm and 390 in the GC arm)

Evaluated:
Efficacy (randomized, intent-to-treat [ITT]): 780 (390 in the GCI arm and 390 in the GC arm)

Safety: 763 (383 in the GCI arm and 380 in the GC arm)

Diagnosis and criteria for inclusion:

- Patients must have had newly diagnosed, stage IV (UICC TNM 7th edition) squamous NSCLC. This included patients who presented with disseminated metastases and those with a malignant pleural or pericardial effusion (ie, formerly stage IIIB in the TNM 6th edition staging system).
- Patients who had received prior adjuvant therapy for early-stage lung cancer were eligible if at least 12 months had elapsed since that treatment.
- Patients must have had an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1.
- Patients with previous thoracic radiotherapy as definitive therapy for locally advanced NSCLC were eligible as long as the recurrence was outside the original radiation therapy port. Radiation therapy was to have been completed >4 weeks prior to the initiation of study treatment. Patients who had received chemotherapy/radiation for locally advanced NSCLC were not eligible. Patients who had received palliative radiation therapy for symptomatic metastases must have completed treatment >14 days prior to initiation of study treatment.
- Patients with treated brain metastases were eligible if (1) radiation therapy had been completed at least 2 weeks prior to study treatment, (2) follow-up scan showed no disease progression, and (3) patient did not require steroids.

Study treatments

Investigational medicinal product(s): iniparib (SAR240550; BSI-201)

Formulation: 10 mg/mL iniparib in 25% hydroxypropylbetacyclodextrin/10.8 mM phosphate buffer at a pH of 7.3 ± 0.3.

Route(s) of administration: IV infusion (over 60 ±10 minutes)

Dose regimen: 5.6 mg/kg on Days 1, 4, 8, and 11 of each 21-day cycle (GCI arm only)

Batch number(s): [redacted]

Noninvestigational medicinal product(s): gemcitabine and carboplatin

Formulation: Available commercial supplies of gemcitabine and carboplatin were used for this study where applicable; otherwise, each was repackaged and relabeled according to Good Manufacturing Practice guidelines before supplies were provided to the study sites.

Route(s) of administration: IV (according to institutional standards)

Dose regimen: Gemcitabine 1000 mg/ m^2 on Days 1 and 8 and carboplatin AUC 5 on Day 1 of each 21-day cycle (GCI and GC treatment arms)

Duration of treatment: Patients received study treatment for 6 cycles as long as there was no evidence of disease progression, unacceptable toxicity, or any other criteria for discontinuation or withdrawal. Patients could remain on study treatment beyond 6 cycles if there was no evidence of disease progression or the presence of dose-limiting toxicities per Investigator assessment. Patients who remained on treatment were to continue to receive their assigned treatment combination or any components contained therein.

Duration of observation: End-of-treatment assessments were performed 30 days after the last dose of study treatment. For all randomized patients, follow-up visits were performed up to the final analysis cut-off date (ie, the date when 561 deaths had been observed) or death, whichever was first. Patients who discontinued study treatment prior to the occurrence of disease progression (including patients randomized and not treated) were to be assessed every 6 weeks (±1 week) during Year 1, every 3 months during Year 2, every 6 months during Years 3 to 5, and annually thereafter for toxicity and disease progression. After disease progression, patients were to be assessed every 3 months (including patients randomized and not treated) for survival status and anticancer therapies.

Criteria for evaluation:

Efficacy:

Primary endpoint: The primary efficacy endpoint was OS, which was defined as the time (months) from randomization until death (from any cause).

Secondary endpoints:

- PFS, defined as the time from randomization until objective tumor progression (as assessed by the Investigator per RECIST 1.1) or death, whichever was earlier
- TTP, defined as the time from randomization until objective tumor progression
- ORR, defined as the proportion of patients achieving complete response (CR) or partial response (PR) as assessed by the Investigator per RECIST 1.1. Confirmation of response by repeated scans was not required. Tumor assessments after the initiation of further anticancer therapy were excluded for the assessment of best overall response.
- Patient-reported QOL as measured by the EORTC QLQ-C30 and QLQ-LC13

Safety: Safety endpoints included adverse events (AEs) monitored throughout the study period according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.02, clinical laboratory tests (hematology and serum chemistry), vital signs (resting heart rate, blood pressure, respiratory rate, temperature), and physical examinations. Eastern Cooperative Oncology Group PS was also assessed.

Pharmacokinetic/pharmacodynamic sampling times and bioanalytical methods: Formalin-fixed, paraffin-embedded pretreatment tumor samples were collected and stored for gene expression profiling at the level of transcript diversity on a whole-genome scale. Correlations were to be established between the profile and clinical outcome variables. Because none of the efficacy endpoints were met for this clinical trial, this investigation was not pursued.

Serum and genomic DNA were obtained and stored on an optional basis to evaluate biomarkers that could predict response (or lack thereof) to the treatment and/or toxicity. This exploratory research was not performed.

Statistical methods:

Sample size determination: The primary outcome variable for this study was OS. Based on a group sequential design with 1 interim analysis and the use of a 1-sided log-rank test at an overall significance level of 0.025, approximately 561 death events were needed to provide 89% power to detect a hazard ratio (HR) of 0.75. The median OS in the GC arm was estimated at 8.0 months. The addition of iniparib to the gemcitabine/carboplatin regimen was hypothesized to improve median OS to approximately 10.7 months. It was assumed that the hazards of death between treatment arms were nonproportional with survival curves less separated in the first 4 months after randomization (HR=0.99) compared with later time points (HR=0.61). It should be noted that this nonproportional hazards assumption replaced the proportional hazards assumption in protocol amendment 6 based on data from Phase 3 studies in NSCLC[1,2,3] and the preliminary results of an ongoing Phase 2 study of iniparib in NSCLC (TCD11420). An overall sample size of approximately 780 patients (390 in the GCI arm and 390 in the GC arm) was determined to provide the required number of events and reasonable follow-up.

Analysis populations:

Intent-to-treat population: All randomized patients (ie, the set of patients who had provided informed consent and who were allocated to a randomized treatment through the IVRS, regardless of whether the treatment was actually administered). This population was used for all efficacy analyses, based on the treatment arm assigned by the IVRS.

Safety population: The subset of randomized patients who actually received at least part of 1 dose (even incomplete) of the study treatments (iniparib, gemcitabine, or carboplatin). This population was used for the safety analysis. All analyses using this population were based on the actual treatment received.

Analysis of primary efficacy endpoint:

Overall survival was estimated using the Kaplan-Meier method, based on the ITT population. The survival curves were provided, as well as the median survival and probabilities of surviving at 3, 6, 9, and 12 months. The HR and the corresponding 95% confidence intervals (CI) were estimated using a Cox proportional hazards model. The log-rank test was used to test the difference in OS between the treatment arms. Median follow-up time for OS was provided for each treatment arm.

One interim analysis of efficacy and futility based on OS was performed when 185 deaths (about one-third of total 561 events) had been observed. A group sequential design was used to control the overall Type I error.

A subgroup analysis of OS was performed based on the following baseline characteristics: age category, sex, race, ECOG PS, smoking history, presence/absence of prior treatment, region, hemoglobin concentration, albumin concentration, presence/absence of malignant pleural effusion at baseline, and presence/absence of bone/liver/brain metastasis at baseline. The median OS for each arm and the HR with corresponding 95% CI were provided.

Analyses of secondary efficacy endpoints:

Secondary efficacy endpoints (PFS and ORR) were analyzed at the final analysis using the ITT population. Data for the secondary endpoints of TTP and QOL were collected but were not analyzed for this synoptic report.

PFS: Progression-free survival was analyzed using the same methods as described above for OS.

ORR: The ORR and its corresponding 95% CI (based on normal approximation) were calculated based on the ITT population for each treatment arm. P-values based on the chi-square test for the percent difference between treatment arms were provided.

Safety analyses: All safety analyses were performed using the safety population. Only descriptive statistics were used for the safety analyses. All AEs were graded according to NCI-CTCAE version.4.02 and coded using Medical Dictionary for Regulatory Activities (MedDRA) version 15.1. Clinical laboratory parameters were graded per NCI-CTCAE version 4.02, when applicable.

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[1] Scagliotti GV, Parikh P, von Pawel J, Biesma B, Vansteenkiste J, Manegold C, et al. Phase III study comparing cisplatin plus gemcitabine with cisplatin plus pemetrexed in chemotherapy-naïve patients with advanced-stage non-small-cell lung cancer. J Clin Oncol. 2008;26(21):3543-51.

[2] Pirker R, Pereira JR, Szczesna A, von Pawel J, Krzakowski M, Ramlau R, et al. FLEX Study Team. Cetuximab plus chemotherapy in patients with advanced non-small-cell lung cancer (FLEX): an open-label randomised phase III trial. Lancet. 2009;373 (9674):1525-31.

[3] Sandler A, Gray R, Perry MC, Brahmer J, Schiller JH, Dowlati A, et al. Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer. N Engl J Med. 2006;355:2542-50.

Summary:

A total of 780 patients were randomized in the study (ITT population); 763 patients were treated and comprised the safety population (Table1).

Table 1 - Summary of analysis populations

	GC	GCI	All
Randomized patients	390 (100%)	390 (100%)	780 (100%)
Efficacy population - ITT population	390 (100%)	390 (100%)	780 (100%)
Safety population	380 (97.4%)	383 (98.2%)	763 (97.8%)

Abbreviations: GC = gemcitabine and carboplatin; GCI = gemcitabine, carboplatin, and iniparib; ITT = intent to treat.

Approximately half (51.7%) of all patients discontinued from the study due to disease progression (radiological or clinical) (Table 2). Other reasons for treatment discontinuation included AE (20.8%), treatment completion (14.6%), "other" reasons (10.4%), protocol compliance issues (0.3%), and loss to follow-up (0.1%).

Per protocol, the target duration of treatment was 6 cycles, but patients were allowed to continue receiving 1 or more components of the treatment beyond this point if the risk:benefit profile was positive. In the case of the GCI arm, a number of patients continued receiving iniparib single agent after GC discontinuation. In the case report form, the reason for discontinuation of the *last* component of the study drug regimen was reported, regardless of the reason for discontinuation of any other portion of the treatment regimen. For example, if a patient in the GCI arm were to discontinue gemcitabine and carboplatin due to an AE and then discontinue iniparib for disease progression, the reason for treatment discontinuation was to be documented as disease progression. The observed differences in the reasons for treatment discontinuation therefore are difficult to interpret.

All patients discontinued treatment under this protocol at the time of database lock. Three patients ([redacted]) continued to clinically benefit from the treatment and were rolled over into the treatment extension protocol (LTS12674).

Table 2 - Summary of patient disposition – ITT population

	GC (N=390)	GCI (N=390)	All (N=780)
Randomized and not treated	10 (2.6%)	7 (1.8%)	17 (2.2%)
Randomized and treated	380 (97.4%)	383 (98.2%)	763 (97.8%)
Discontinued study treatment[a]	380 (97.4%)	383 (98.2%)	763 (97.8%)
Reason for treatment discontinuation			
Completed treatment	73 (18.7%)	41 (10.5%)	114 (14.6%)
Disease progression	158 (40.5%)	245 (62.8%)	403 (51.7%)
- RECIST progression	131 (33.6%)	198 (50.8%)	329 (42.2%)
- Clinical progression[b]	27 (6.9%)	47 (12.1%)	74 (9.5%)
Adverse event	100 (25.6%)	62 (15.9%)	162 (20.8%)
Poor compliance to protocol	1 (0.3%)	1 (0.3%)	2 (0.3%)
Lost to follow-up	1 (0.3%)	0	1 (0.1%)
Other reasons	47 (12.1%)	34 (8.7%)	81 (10.4%)

Abbreviations: GC = gemcitabine and carboplatin; GCI = gemcitabine, carboplatin, and iniparib; RECIST = Response Evaluation Criteria in Solid Tumors.
Note: Percentages are calculated using the number of patients randomized as denominator.
a For randomized and treated patients.
b Patients with clinical deterioration attributed to tumor progression in the absence of radiological progressive disease.

Population characteristics:

Demographic and baseline characteristics were well balanced between the 2 treatment arms and, from an epidemiological viewpoint, represented those typically expected for this patient population. The median age of the ITT population was 66 years (range, 21 to 86 years), and the majority (68.0%) of patients had an ECOG PS of 1 at baseline. About three-fourths (73.2%) of the patients were male. Only about 5% of the patients were never smokers.

In accordance with the protocol inclusion criteria, all patients' tumors had squamous or mixed squamous histology. Most (87.9%) patients had de novo Stage IV disease. Most (70.4%) patients had at least 3 organs involved at baseline. About one-third (29.2%) of patients presented with pleural effusion at baseline.

Few patients had received prior adjuvant or neoadjuvant systemic anticancer therapy (GCI 3.6% of patients, GC 2.8%), prior surgery for lung cancer (GCI 11.3%, GC 7.9%), or prior radiotherapy for lung cancer (GCI 16.7%, GC 13.6%).

Efficacy results:

Overall survival

As planned per protocol, the final analysis of OS was based on a total of 561 deaths (final analysis cut-off date: 05 December 2012).

There was no statistically significant difference in OS between the 2 treatment arms. The observed median OS was identical (8.9 months) in the GCI (95% CI: 8.1150 to 9.7577) and GC (95% CI: 7.9836 to 10.5791) treatment arms (HR: 1.083; 95% CI: 0.917 to 1.278; 2-sided p = 0.3475 by unstratified log-rank test) (Table 3).

The treatment effect was similar among the subgroups analyzed, including age, sex, race, baseline ECOG PS, smoking history, disease stage, region of habitation, baseline hemoglobin and albumin concentrations, presence of pleural effusion at baseline, and presence of bone, liver, or brain metastases at baseline.

Table 3 - Summary of analysis of overall survival - ITT population

	GC (N=390)	GCI (N=390)
Patient status		
Dead	271 (69.5%)	290 (74.4%)
Censored	119 (30.5%)	100 (25.6%)
Alive at cut-off date	109 (27.9%)	96 (24.6%)
Lost to follow-up/consent withdrawal	9 (2.3%)	4 (1.0%)
Last contact within 30 days before the cut-off date	1 (0.3%)	0
Overall survival [months]		
Number of events, n/N (%)	271/390 (69.5%)	290/390 (74.4%)
Median survival (95% CI) (months)	8.871 (7.9836 to 10.5791)	8.871 (8.1150 to 9.7577)
25% quartile (95% CI) (months)	4.402 (3.8768 to 5.1253)	5.060 (4.1396 to 5.7823)
75% quartile (95% CI) (months)	16.756 (15.7700 to 21.0924)	15.507 (14.0287 to 16.9856)
Probability of surviving (95% CI)		
3 months	0.850 (0.814 to 0.885)	0.862 (0.827 to 0.896)
6 months	0.651 (0.603 to 0.699)	0.686 (0.640 to 0.732)
9 months	0.496 (0.446 to 0.547)	0.487 (0.437 to 0.537)
12 months	0.405 (0.354 to 0.457)	0.359 (0.308 to 0.409)
Unstratified log-rank test p-value		
vs GC	-	0.3475
Unadjusted hazard ratio (95% CI)		
vs GC	-	1.083 (0.917 to 1.278)

Abbreviations: CI = confidence interval; GC = gemcitabine and carboplatin; GCI = gemcitabine, carboplatin, and iniparib.

Progression-free survival

There was no statistically significant difference for the secondary endpoint of PFS between the 2 treatment arms.

In the GCI arm, 294 (75.4%) patients had a PFS event, including 251 (64.4%) patients with radiological disease progression and 21 (5.4%) patients who died on study without disease progression (Table 4). In the GC arm, 272 (69.7%) patients had a PFS event, including 225 (57.7%) patients with radiological disease progression and 28 (7.2%) patients who died on study without disease progression.

The observed median PFS was identical (4.4 months) in the GCI (95% CI: 4.2053 to 5.0595) and GC (95% CI: 4.2382 to 5.0924) treatment arms (HR: 1.006; 95% CI: 0.853 to 1.186; 2-sided p = 0.9436 by unstratified log-rank test).

Table 4 - Summary of analysis of progression-free survival (PFS) - ITT population

	GC (N=390)	GCI (N=390)
Patient status		
PFS events [n(%)]	272 (69.7%)	294 (75.4%)
No post-baseline adequate tumor assessment and early death	19 (4.9%)	22 (5.6%)
Death without documented disease progression	28 (7.2%)	21 (5.4%)
Documented disease progression	225 (57.7%)	251 (64.4%)
Censored	118 (30.3%)	96 (24.6%)
No baseline tumor assessment	1 (0.3%)	0
No post-baseline adequate tumor assessment and no early death	29 (7.4%)	12 (3.1%)
Further anticancer therapy started	53 (13.6%)	58 (14.9%)
Death or progression after more than one missed tumor assessment	14 (3.6%)	12 (3.1%)
No progression and alive	21 (5.4%)	14 (3.6%)
PFS [months]		
Number of events, n/N(%)	272/390 (69.7%)	294/390 (75.4%)
Median survival (95% CI) (months)	4.435 (4.2382 to 5.0924)	4.435 (4.2053 to 5.0595)
25% quartile (95% CI) (months)	2.694 (2.0698 to 2.9240)	2.628 (2.0698 to 2.7598)
75% quartile (95% CI) (months)	6.374 (5.9466 to 6.9322)	6.735 (6.1766 to 7.4908)
Probability of surviving (95% CI)		
3 months	0.677 (0.627 to 0.727)	0.653 (0.603 to 0.702)
6 months	0.302 (0.248 to 0.356)	0.335 (0.282 to 0.387)
9 months	0.102 (0.063 to 0.142)	0.106 (0.066 to 0.145)
12 months	0.059 (0.025 to 0.093)	0.039 (0.013 to 0.066)
Unstratified log-rank test p-value		
vs GC	-	0.9436
Unadjusted hazard ratio (95% CI)		
vs GC	-	1.006 (0.853 to 1.186)

Abbreviations: CI = confidence interval; GC = gemcitabine and carboplatin; GCI = gemcitabine, carboplatin, and iniparib; PFS = progression-free survival.

Objective response rate

There was no statistically significant difference for the secondary endpoint of ORR between the 2 treatment arms.

Best overall response was CR for 1 (0.3%) patient in the GCI arm. Best response was PR for 125 (32.1%) patients in the GCI arm and 132 (33.8%) patients in the GC arm. Stable disease was achieved in 167 (42.8%) patients in the GCI arm and 150 (38.5%) patients in the GC arm. The ORR was similar in the GCI arm (32.3% [95% CI: 27.7% to 36.9%]) and the GC arm (33.8% [95% CI: 29.1% to 38.5%]).

Safety results:

Extent of exposure

Overall treatment exposure was slightly longer in the GCI arm (median, 5 cycles [range, 1 to 32 cycles]) than in the GC arm (median, 4 cycles [range, 1 to 26 cycles]). This difference is attributable to the continuation of treatment with iniparib single agent in a substantial number of patients in the GCI arm. Median exposure was identical between the 2 arms for both gemcitabine and carboplatin.

Adverse events

There were no clinically meaningful differences between the 2 arms in the frequency of TEAEs (GCI 99.2%, GC 98.7%), Grade 3 to 4 TEAEs (GCI 87.2%, GC 84.2%), related Grade 3 to 4 TEAEs (GCI 67.6%, GC 68.2%), TEAEs leading to death (GCI 11.2%, GC 11.1%), and TEAEs leading to permanent treatment discontinuation (GCI 28.7%, GC 32.1%).

The most frequently reported TEAEs (all grades, ≥20% of patients in either treatment arm) were anemia (GCI 57.4% of patients, GC 60.8%), neutropenia (GCI 49.1%, GC 44.2%), fatigue (GCI 47.5%, GC 42.4%), nausea (GCI 45.4%, GC 39.5%), thrombocytopenia (GCI 41.0%, GC 39.2%), constipation (GCI 33.4%, GC 30.0%), dyspnea (GCI 30.5%, GC 23.4%), decreased appetite (GCI 26.6%, GC 24.5%), asthenia (GCI 24.5%, GC 22.1%), and vomiting (GCI 21.4%, GC 15.5%). The most common Grade 3 to 4 TEAEs (≥20% of patients in either treatment arm) were neutropenia (GCI 34.5%, GC 31.3%), thrombocytopenia (GCI 27.7%, GC 26.6%), and anemia (GCI 25.8%, GC 27.9%). The incidence of TEAEs (all grades) of dyspnea, nausea, vomiting, fatigue, and weight decreased was >5% higher in the GCI arm than in the GC arm.

The overall incidence of serious TEAEs (all grades) was higher in the GCI arm (50.4%) than in the GC arm (41.3%), although for all reported preferred terms the difference between the 2 treatment arms was <5%. The most frequently reported serious TEAEs in the GCI arm were pneumonia (6.8% of patients for all grades and Grade 3 to 4), anemia (5.7% all grades, 3.9% Grade 3 to 4), thrombocytopenia (5.2% all grades and Grade 3 to 4), and disease progression (3.7% all grades and Grade 3 to 4), and in the GC arm, anemia (6.6% all grades, 5.5% Grade 3 to 4), pneumonia (4.5% all grades, 3.9% Grade 3 to 4), and thrombocytopenia (3.9% all grades and Grade 3 to 4).

A total of 42 (11.0%) patients in the GCI arm and 38 (10.0%) patients in the GC arm died during the on-treatment period. Most of these patients died due to an AE (GCI 6.0% of patients, GC 7.1%); the rest died as a result of disease progression (GCI 4.7%, GC 2.9%) or an "other" reason ([cystic fibrosis progression] GCI 0.3%).

Clinical laboratory evaluations

There were no meaningful differences between the 2 treatment arms in any hematologic or nonhematologic parameter (all grades and Grade 3 to 4). Specifically, Grade 3 to 4 neutropenia (GCI 50.1% of patients, GC 50.8%) and thrombocytopenia (GCI and GC 38.3%) occurred at a similar rate between the 2 treatment arms.

Conclusions: [redacted]

Date of report: 07-Apr-2014