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ORIGINAL ARTICLE

A randomized, open-label study of the efficacy and safety of AZD4547 monotherapy versus paclitaxel for the treatment of advanced gastric adenocarcinoma with *FGFR2* polysomy or gene amplification

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Background: Approximately 5%–10% of gastric cancers have a fibroblast growth factor receptor-2 (*FGFR2*) gene amplification. AZD4547 is a selective FGFR-1, 2, 3 tyrosine kinase inhibitor with potent preclinical activity in *FGFR2* amplified gastric adenocarcinoma SNU16 and SGC083 xenograft models. The randomized phase II SHINE study (NCT01457846) investigated whether AZD4547 improves clinical outcome versus paclitaxel as second-line treatment in patients with advanced gastric adenocarcinoma displaying *FGFR2* polysomy or gene amplification detected by fluorescence *in situ* hybridization.

Patients and methods: Patients were randomized 3:2 (*FGFR2* gene amplification) or 1:1 (*FGFR2* polysomy) to AZD4547 or paclitaxel. Patients received AZD4547 80 mg twice daily, orally, on a 2 weeks on/1 week off schedule of a 21-day cycle or intravenous paclitaxel 80 mg/m^2 administered weekly on days 1, 8, and 15 of a 28-day cycle. The primary end point was progression-free survival (PFS). Safety outcomes were assessed and an exploratory biomarker analysis was undertaken.

Results: Of 71 patients randomized (AZD4547 $n = 41$, paclitaxel $n = 30$), 67 received study treatment (AZD4547 $n = 40$, paclitaxel $n = 27$). Among all randomized patients, median PFS was 1.8 months with AZD4547 and 3.5 months with paclitaxel (one-sided $P = 0.9581$); median follow-up duration for PFS was 1.77 and 2.12 months, respectively. The incidence of adverse events was similar in both treatment arms. Exploratory biomarker analyses revealed marked intratumor heterogeneity of *FGFR2* amplification and poor concordance between amplification/polysomy and *FGFR2* mRNA expression.

Conclusions: AZD4547 did not significantly improve PFS versus paclitaxel in gastric cancer *FGFR2* amplification/polysomy patients. Considerable intratumor heterogeneity for *FGFR2* gene amplification and poor concordance between *FGFR2* amplification/polysomy and *FGFR2* expression indicates the need for alternative predictive biomarker testing. AZD4547 was generally well tolerated.

Key words: AZD4547, clinical efficacy, fibroblast growth factor receptor, gastric cancer, fluorescence *in situ* hybridization

Introduction

Fibroblast growth factors (FGFs) and their receptors (FGFRs) are instrumental in a number of normal biologic processes, and their dysregulation by mechanisms including activating gene mutations, gene amplification, and gene fusions is believed to drive human cancers, including gastric cancer (GC) [1–3]. Approximately 5%–10% of gastric tumors have an *FGFR2* amplification [4, 5], which appears to confer poor prognosis [5–7].

AZD4547 is a selective FGFR-1, 2, 3 tyrosine kinase inhibitor that has displayed potent activity in preclinical studies. Cell lines of gastric adenocarcinoma possessing *FGFR2* amplification were sensitive to AZD4547, resulting in reduced cell proliferation and cell death [8]. Additionally, AZD4547 induced rapid tumor regression in two *in vivo* models of *FGFR2*-amplified GC [8].

The primary hypothesis of the SHINE study was that AZD4547 has the potential to provide clinical benefit in patients with advanced gastric adenocarcinoma with tumors displaying *FGFR2* polysomy or gene amplification selected by centralized fluorescence *in situ* hybridization (FISH) testing. Exploratory biomarker analyses were carried out to further assess *FGFR2* amplification heterogeneity within tumor sections and concordance with *FGFR2* expression.

Materials and methods

Study design and patient selection

SHINE was a multicenter, randomized, open-label study carried out in 56 centers in Asia, North America, and Europe (ClinicalTrials.gov registration: NCT01457846; National Cancer Institute protocol ID: D2610C00004).

Patients were recruited with locally advanced or metastatic GC with radiologically confirmed progression after one prior chemotherapy regimen. Tumors were required to display either *FGFR2* polysomy or amplification determined from archival tumor block or fresh tumor biopsy. Patients with prior exposure to AZD4547 or any other FGFR inhibitor were excluded. Patients in the *FGFR2* amplification cohort were randomized 3:2 to AZD4547 or paclitaxel. Patients in the *FGFR2* polysomy cohort were randomized 1:1 to AZD4547 or paclitaxel.

Tumor FGFR status was determined by centralized FISH screening using a non-commercial kit (DAKO). FGFR2 amplification and polysomy were classified as follows:

- *FGFR2* amplification: *FGFR2*/Spectrum Green-labeled centromere of chromosome 10 (CEN10) ratio ≥2 or *FGFR2* gene clusters in ≥ 10% tumor cells.
- High polysomy: *FGFR2*/CEN10 ratio <2 and ≥4 copies of *FGFR2* in ≥ 40% tumor cells.
- Low polysomy: *FGFR2*/CEN10 ratio <2 and ≥4 copies of *FGFR2* in 10%–39% tumor cells.

The amplified cohort was further stratified into 'low' (*FGFR2*/CEN10 ratio ≥2 and <5) or 'high' (*FGFR2*/CEN10 ratio ≥5) strata. Subsequent changes to the scoring system are detailed in the supplementary material, available at *Annals of Oncology* online.

All patients gave written informed consent. The study was approved by the Institutional Review Board/Independent Ethics Committee at each study center and conducted in accordance with the Declaration of Helsinki.

Treatment schedule

Patients received either AZD4547 80 mg b.i.d., orally, on a 2 weeks on/1 week off schedule of a 21-day cycle or paclitaxel 80 mg/m^2 as a 1-h intravenous infusion weekly on days 1, 8, and 15 of a 28-day cycle. The dosing strategy for AZD4547 was based on a phase I dose-escalation study [9, 10].

Assessments

Patients underwent Response Evaluation Criteria In Solid Tumors (RECIST) assessments (ver. 1.1) at baseline and every 8 weeks thereafter using computerized tomography or magnetic resonance imaging. All assessments were carried out at the local sites and were not confirmed centrally.

Pharmacokinetic (PK) assessments included changes in blood-borne biomarkers (phosphates, basic FGF, and FGF23). Adverse events (AEs) and clinical laboratory values were monitored throughout the study.

End points

The primary end point was progression-free survival (PFS). Secondary end points included overall survival (OS), objective response rate (ORR), change in tumor size at 8 weeks, and the percentage of patients without progressive disease at 8 weeks.

Interim analysis

Prompted by slow recruitment, AstraZeneca and the Safety Review Committee agreed that it would be appropriate to conduct an unscheduled interim analysis of efficacy (based on average change in tumor size) and tolerability data. The results did not show superiority of AZD4547 over paclitaxel in patients with advanced GC tumors with *FGFR2* amplification and a decision was made to cease enrollment and close the study.

Exploratory biomarker analysis

FGFR2 expression in RNA extracted from tumor samples was analyzed using the nCounter® platform (NanoString Technologies® Inc., Seattle, WA).

For heterogeneity analysis, FISH-stained sections were scanned into the MIRAX Panoramic 250 Flash II (3D Histech) scanner at ×40 magnification in the x, y, and z planes and analyzed using custom HALO v1.9 software (Indica Labs). All cells within the tumor compartment were classified as amplified or nonamplified, based on target:control probe ratio thresholds (*FGFR2*:CEN10 probe signals where ratio <2.0 = nonamplified and ratio ≥2.0 = amplified) and a visual heterogeneity map generated.

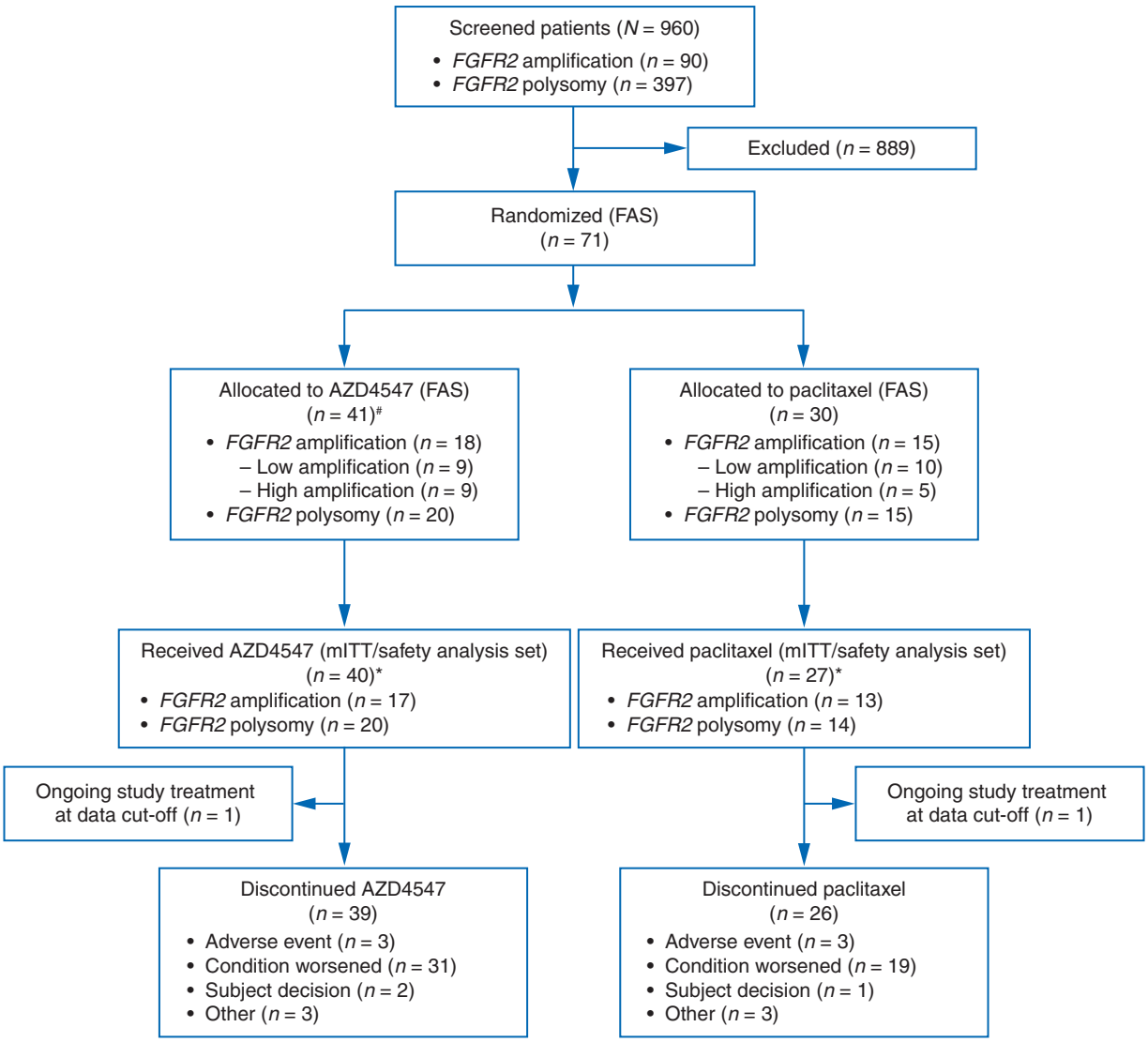
Statistical analysis

PFS, OS, and ORR in all randomized patients were analyzed using Cox proportional hazards models with covariates for *FGFR2* strata and treatment. PFS, OS, and ORR within *FGFR2* strata were estimated from Cox proportional hazards models fitted in the overall population with covariates for *FGFR2* stratum, treatment, and the treatment by *FGFR2* stratum interaction. The effect of AZD4547 on change in tumor size in all randomized patients, and within each of the *FGFR2* strata, was estimated from an analysis of covariance model that included terms for baseline tumor size (log transformed), time from baseline scan to randomization, *FGFR2* stratum, treatment, and the treatment by *FGFR2* interaction, where appropriate.

Results

Participants

A total of 960 patients had to be prescreened for *FGFR2* status to enable 71 patients to be randomized (AZD4547 $n = 41$ [57.7%]; paclitaxel $n = 30$ [42.3%]; full analysis set (FAS); Figure 1).



*Three patients did not receive study therapy because they died prior to administration (one in the AZD4547 arm and two in the paclitaxel arm); One patient in the paclitaxel arm had 'Other' recorded with no further details;
#Including three patients who no longer met the criteria for polysomy or amplification.

Figure 1. CONSORT diagram. FAS, full analysis set; *FGFR2*, fibroblast growth receptor-2.

Table 1. Median PFS and OS stratified by *FGFR2* low and high amplification, and polysomy (FAS)

	AZD4547				Paclitaxel			
	Amplification (*n* = 38)			Polysomy (*n* = 20)	Amplification (*n* = 30)			Polysomy (*n* = 15)
	Total (*n* = 18)	Low (*n* = 9)	High (*n* = 9)		Total (*n* = 15)	Low (*n* = 10)	High (*n* = 5)	
PFS								
Median PFS (months)	1.5	1.4	2.0	1.9	2.3	1.9	3.7	3.5
No. of events	17	9	8	19	13	10	3	13
Duration of follow-up (months)	1.46	–	–	1.86	1.87	–	–	3.52
OS								
Median OS (months)	4.9	4.9	10.5	6.3	4.6	3.5	NC	7.2
No. of deaths	12	6	6	15	9	8	1	9
Duration of follow-up (months)	3.0	2.0	3.4	6.0	3.9	3.5	6.5	6.6

FAS, full analysis set; *FGFR2*, fibroblast growth factor receptor-2; NC, noncalculable; OS, overall survival; PFS, progression-free survival.

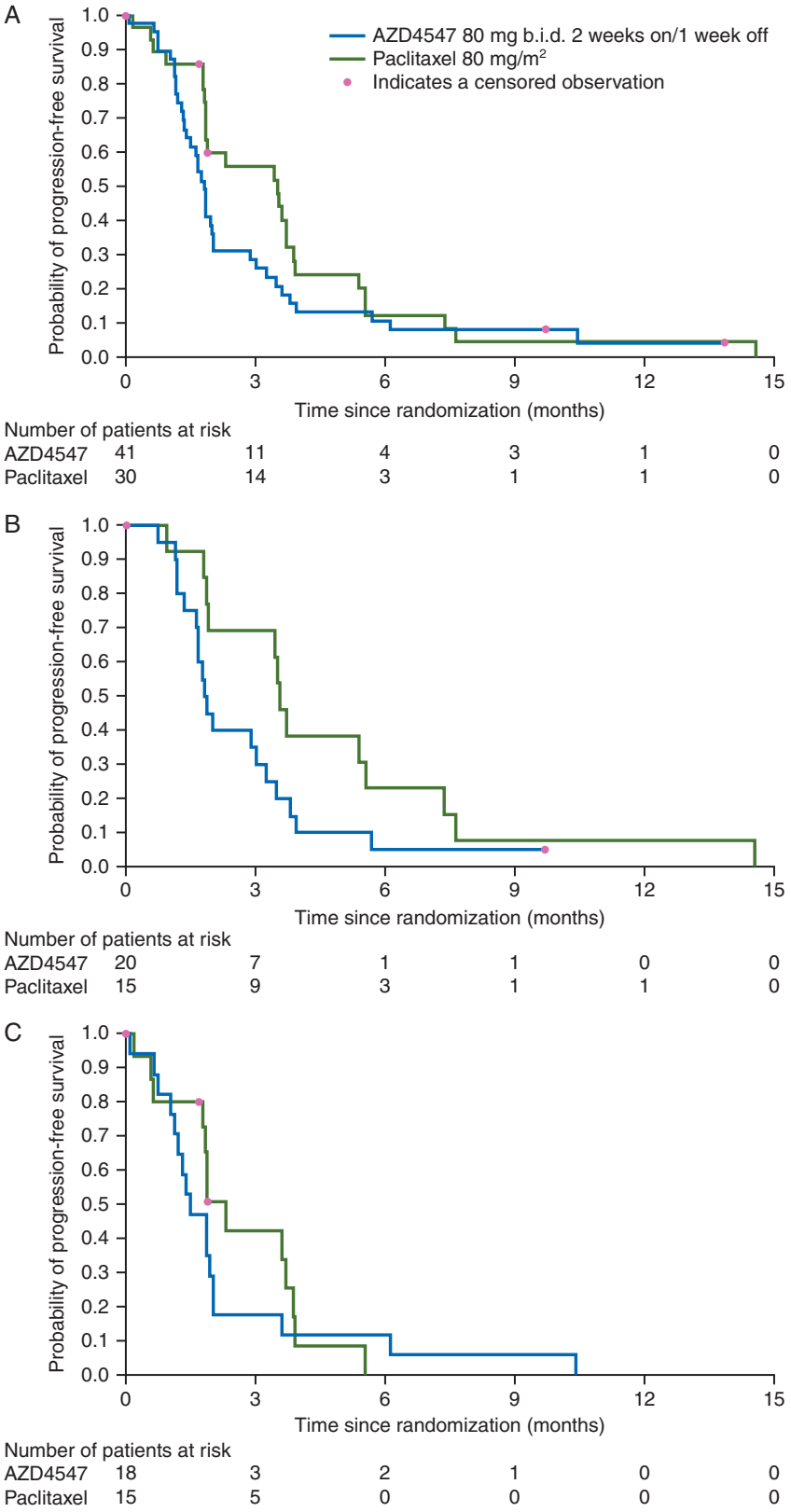


Figure 2. Progression-free survival Kaplan–Meier plots (full analysis set): overall population (A), *FGFR2* polysomy population (B), and *FGFR2* amplification population (C). *FGFR2*, fibroblast growth receptor-2.

Table 2. Best objective response stratified by *FGFR2* low and high amplification, and polysomy (FAS[a])

	AZD4547			Paclitaxel		
	Low amplification ($n = 9$)	High amplification ($n = 9$)	Polysomy ($n = 20$)	Low amplification ($n = 10$)	High amplification ($n = 5$)	Polysomy ($n = 15$)
Response						
Complete response, *n* (%)	0	0	0	0	0	0
Partial response, *n* (%)	0	0	1 (5.0)	1 (10.0)	2 (40.0)	4 (26.7)
Nonresponse						
Stable disease ≥8 weeks, *n* (%)	1 (11.1)	2 (22.2)	5 (25.0)	3 (30.0)	2 (40.0)	5 (33.3)
Progression, *n* (%)	8 (88.9)	6 (66.7)	14 (70.0)	6 (60.0)	1 (20.0)	4 (26.7)
RECIST progression	6 (66.7)	5 (55.6)	13 (65.0)	2 (20.0)	1 (20.0)	4 (26.7)
Death	2 (22.2)	1 (11.1)	1 (5.0)	4 (40.0)	0	0
Not evaluable, *n* (%)	0	1 (11.1)	0	0	0	2 (13.3)

[a]FISH rescoring (removal of the cluster rule) to detect *FGFR2* amplification resulted in the identification of three patients in the FAS who no longer met the criteria for polysomy or amplification.

FAS, full analysis set; *FGFR2*, fibroblast growth factor receptor-2; FISH, fluorescence *in situ* hybridization; RECIST, Response Evaluation Criteria In Solid Tumors.

FISH rescoring to detect *FGFR2* amplification identified three patients in the FAS who no longer met polysomy or amplification criteria and were excluded from the efficacy analysis that included *FGFR2* stratum as a factor in the statistical model.

Treatment groups were generally well balanced with respect to demographic characteristics (supplementary Table S1, available at *Annals of Oncology* online).

Efficacy

PFS and disease outcome. Disease progression was reported in 36 of the 38 patients (94.7%) in the AZD4547 arm and 26 of the 30 patients (86.7%) in the paclitaxel arm.

In the FAS, median PFS was 1.8 months in the AZD4547 arm and 3.5 months in the paclitaxel arm, with a median duration of follow-up of 1.77 and 2.12 months, respectively (see Table 1 for amplified and polysomy cohorts). The difference in PFS was not statistically significant in favor of AZD4547 at the one-sided 10% level (*P*-value from Cox proportional hazards model = 0.9581). The observed hazard ratio (HR) was 1.57 (80% CI, 1.12–2.21) for AZD4547 compared with paclitaxel (Figure 2).

The observed HRs for the polysomy and amplified groups were 1.87 (80% CI, 1.17–3.06) and 1.30 (80% CI, 0.81–2.12), respectively. No statistically significant difference in PFS in favor of AZD4547 was observed for AZD4547 versus paclitaxel in either the polysomy or amplified groups (one-sided $P = 0.9562$ and $P = 0.7590$, respectively).

Complete response was not reported in any patient (Table 2). In the overall population, the ORR was 2.6% in the AZD4547 arm and 23.3% in the paclitaxel arm (0% and 20.0%, respectively [amplified cohort] and 5.0% and 26.7%, respectively [polysomy cohort]). The difference in ORR was not statistically significant in favor of AZD4547 at the one-sided 10% level (odds ratio 0.09, 80% CI, 0.02–0.35, one-sided $P = 0.9970$).

There were a total of 27 deaths (71.1%) in the AZD4547 arm and 18 deaths (60.0%) in the paclitaxel arm. In the FAS, median OS was 5.5 and 6.6 months for AZD4547 and paclitaxel arms, respectively, with a median duration of follow-up of 4.8 and 5.1 months, and the difference in OS was not statistically significant (Figure 3; HR 1.31; 80% CI, 0.89–1.95, one-sided $P = 0.8156$). In the amplified and polysomy cohorts, there was no difference between treatment groups in terms of median OS (Table 1; HR 1.26; 80% CI, 0.72–2.25, one-sided $P = 0.7006$ for the amplified cohort and HR 1.36; 80% CI, 0.80–2.38, one-sided $P = 0.7697$ for the polysomy cohort).

Analysis of the percentage change in tumor size at week 8 did not show any statistically significant difference in favor of the AZD4547 arm compared with the paclitaxel arm (difference 39.44; 80% CI, 25.18–55.33, one-sided $P = 0.9999$). Similar results were observed in the amplified (difference 39.21; 80% CI, 19.43–62.26, one-sided $P = 0.9965$) and polysomy (difference 39.68; 80% CI, 19.38–63.45, one-sided $P = 0.9961$) cohorts.

Safety

For those patients who received treatment, the median total duration of treatment was 50.5 days in the AZD4547 arm and 57.0 days in the paclitaxel arm. AEs and serious AEs related to study treatment occurred at similar rates in both treatment arms (supplementary Table S2, available at *Annals of Oncology* online).

Biomarker analysis

PK findings were consistent with previous studies of AZD4547 [9] (see supplementary Figure S1, available at *Annals of Oncology* online).

FGFR2 expression was assessed by nanostring analysis of RNA from 73 archival tumor samples, comprised of 56 tumor samples from patients randomized to AZD4547 or paclitaxel ($n = 35$ and $n = 21$, respectively), and an additional 17 samples from prescreened patients who were not randomized (*FGFR2* copy number normal [CNN]). Overall, the analysis set consisted of 24 amplified, 29 polysomy, and 20 CNN samples.

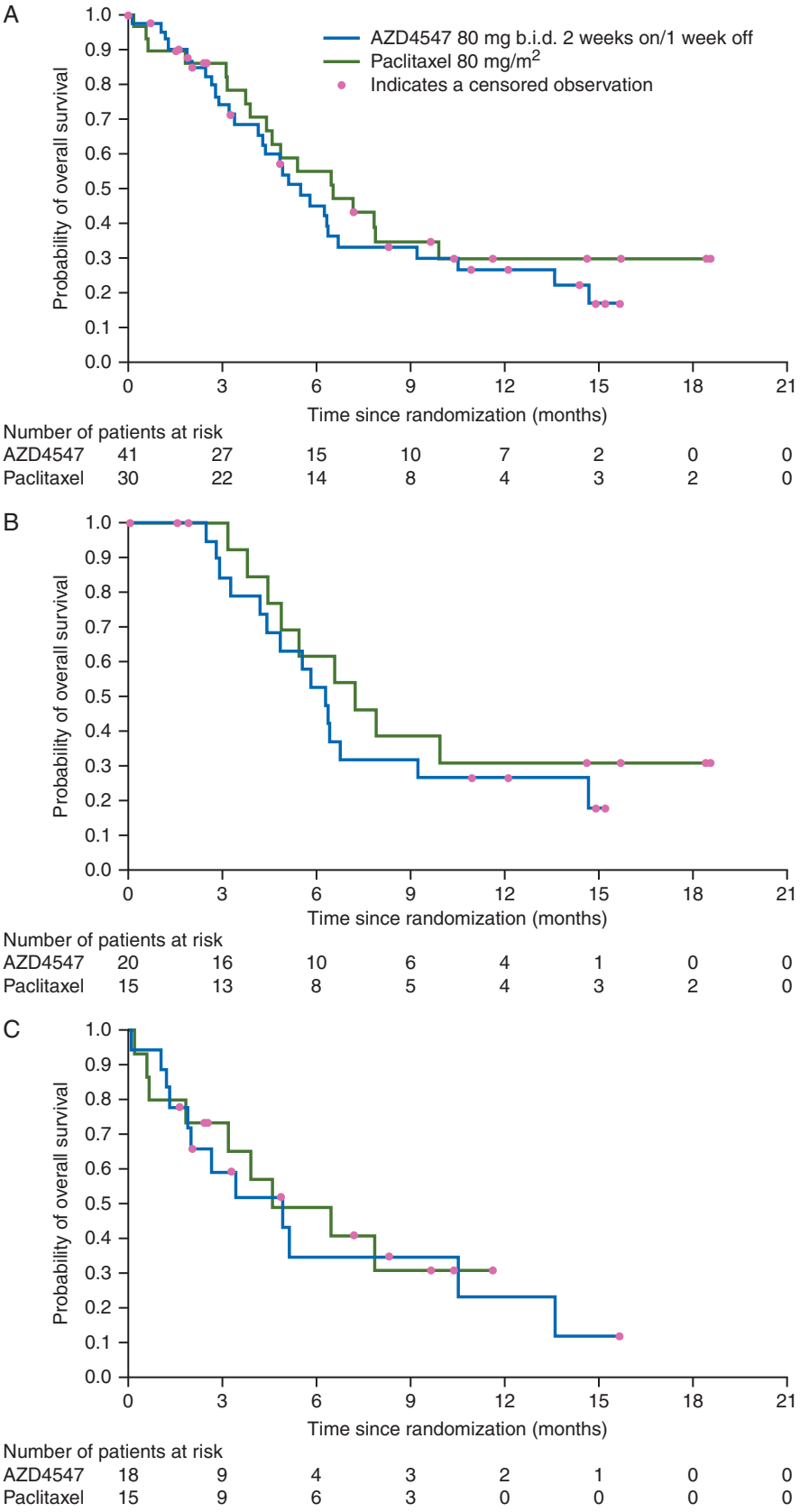
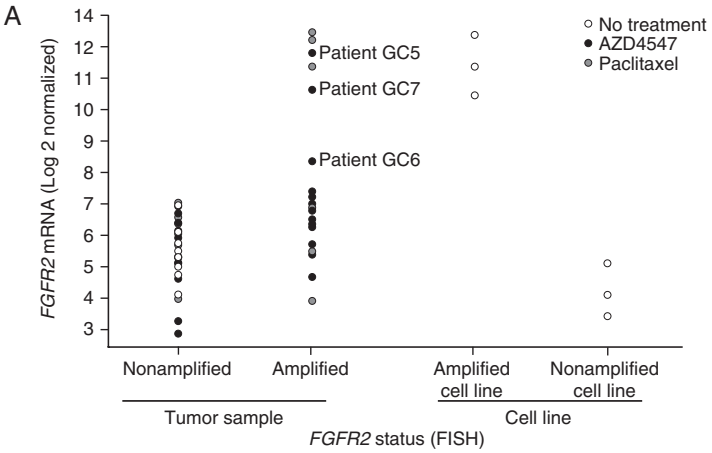
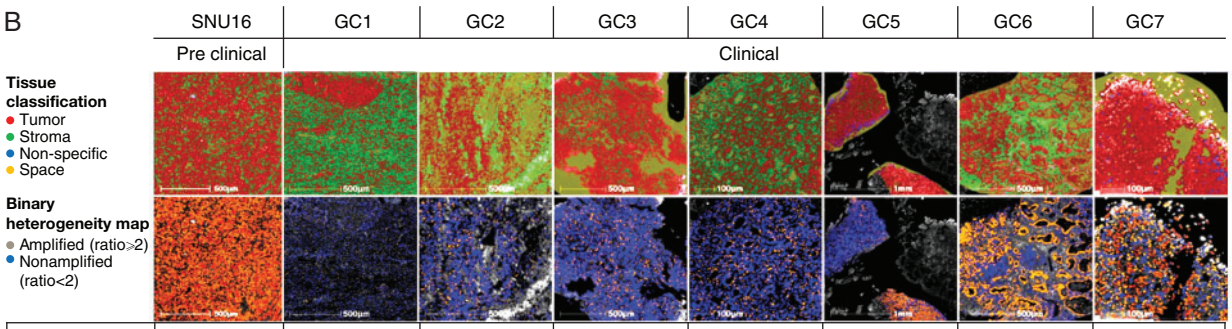


Figure 3. Overall survival Kaplan–Meier plot (full analysis set) overall population (A), *FGFR2* polysomy population (B), and *FGFR2* amplification population (C). *FGFR2*, fibroblast growth receptor-2.





Sample	SNU16	GC1	GC2	GC3	GC4	GC5	GC6	GC7
Cells analyzed	41670	99875	41763	10340	10330	5339	3177	1537
% cells amplified (r≥2)	100	10	8	16	23	52	59	70
Average ratio score	38	0.9	1.1	1.1	1.1	7.8	3.6	7.7

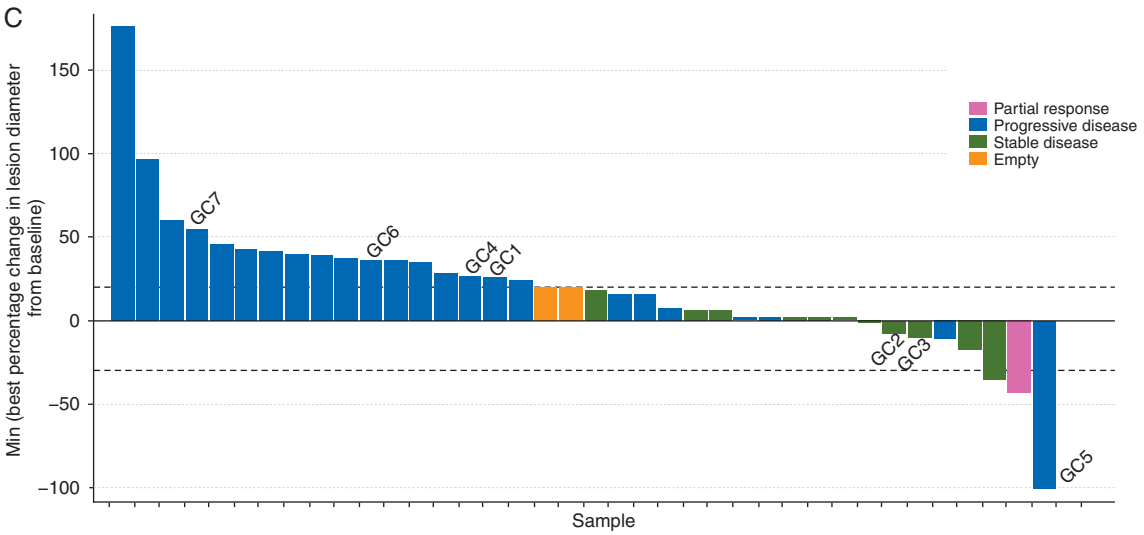


Figure 4. Analysis of formalin-fixed, paraffin-embedded archival tumor samples from patients with advanced gastric cancer (GC) in SHINE showing: (A) *FGFR2* expression (log_2 normalized data) of archival tumor sections compared with amplified (SNU16, KATOIII, and SUM52) and nonamplified (AGS, SNU-216, and SNU-620) cell lines; (B) *in situ* heterogeneity mapping of seven patient samples and an SNU16 GC xenograft section showing tissue classifications and binary heterogeneity maps (nonamplified = blue; amplified = orange) for a large representative field of view for each tumor. The table shows cell count, % amplification (based on ratio ≥2) and average ratio score; and (C) a waterfall plot showing best change in target lesion size for SHINE patients who received AZD4547. *FGFR2*, fibroblast growth receptor-2.

A range of overlapping *FGFR2* expression levels were observed between the amplified and nonamplified tumor samples (Figure 4A), with only 6 of 24 amplified tumors having elevated *FGFR2* expression and, of these, only 5 having expression levels overlapping with SNU16- and KATOIII *FGFR2*-amplified GC cell lines, which are highly sensitive to AZD4547-induced growth inhibition [11]. There was no evidence of elevated *FGFR2* expression outside the amplified cohort (Figure 4A).

FGFR2 amplification was assessed in sections from seven tumor samples from the high amplification (*FGFR2*:CEN10 ratio >5) AZD4547 arm, as this represented the patient group most likely to respond to treatment. As a benchmark, image analysis of a tumor section from the AZD4547-sensitive SNU16 tumor xenograft model revealed that 100% of tumor cells displayed *FGFR2* amplification with a mean *FGFR2*:CEN10 ratio of 38. In the seven patient tumor sections examined, the number of tumor cells ranged from approximately 1500 to >41000, and representative FISH-stained sections revealed marked sub-clonal heterogeneity, with between 8% and 70% of the tumor cells displaying *FGFR2* amplification (Figure 4B). However, there was no clear correlation between the extent of sub-clonal heterogeneity and tumor shrinkage in response to AZD4547 (Figure 4C).

Exploratory survival analysis

Details of the exploratory survival analysis of nonrandomized patients who underwent FISH prescreening in the SHINE study are shown in supplementary Figure S2, available at *Annals of Oncology* online.

Discussion

The efficacy of paclitaxel monotherapy in the SHINE study was consistent with data from other studies in a second-line setting. Median PFS and OS in the paclitaxel arm was similar to outcomes reported previously [12–16]. The trend towards shorter PFS and OS observed in the *FGFR2* amplified group, is in agreement with earlier studies in patients with *FGFR2* amplification [5–7].

In the current study, AZD4547 was not superior to paclitaxel, in contrast to preclinical findings [8, 17]. The poor association between *FGFR2* amplification and elevated *FGFR2* expression observed in the SHINE study, together with marked sub-clonal heterogeneity of *FGFR2* amplification in tumor sections, contrasts markedly with the high and homogenous amplification and high *FGFR2* expression observed in the SNU16 model. Although no correlation was observed between the level of sub-clonal heterogeneity and tumor shrinkage, the failure to adequately enrich for clonally amplified tumors is likely to be a factor in the failure to translate the preclinical efficacy of AZD4547 to the clinic and this is supported by results from a translational clinical study in which patients with high and clonal *FGFR2* amplification responded to AZD4547 [18]. It is possible that a high threshold exists for clonality of *FGFR2* amplification to sensitize to AZD4547.

Heterogeneity of gene amplification does not necessarily result in lack of clinical efficacy as *HER2* amplification and expression is heterogeneous in GC [19], yet patients with *HER2* amplification benefit from treatment with trastuzumab [20]. Hence, the impact of heterogeneity on the predictive nature of a gene amplification biomarker may be target dependent. A limitation of this study is that the archival diagnostic tissue samples screened by FISH and the *FGFR2* status may not reflect the status of metastatic tumor sites at study entry. Clearly, tumors with *FGFR2* amplification leading to elevated *FGFR2* expression do exist, but this appears to be at a very low prevalence. Consequently, there is a need for alternative predictive biomarker testing to more effectively enrich for this population before assessment of FGFR therapies.

Elevated plasma phosphate is a pharmacodynamic marker of interrupting FGF23 signaling through FGFR inhibition in the kidney [21, 22] and has been observed for other FGFR inhibitors [23, 24]. The intermittent dosing schedule allowed for elevations in plasma concentrations of phosphate during the on-drug period to normalize during the off-drug period.

This study illustrates the considerable operational challenge associated with recruitment of low prevalence patient groups into clinical studies. Centralized FISH testing identified patients with *FGFR2* amplification at an actual prevalence of 9%. However, attrition between FISH prescreening and randomization resulted in an operational prevalence of 1%. Follow-up of screened patients showed a trend for *FGFR2* amplification being associated with poor prognosis which may have contributed to the higher than expected attrition rate.

The AE profiles for AZD4547 and paclitaxel were consistent with their known pharmacologic effects. The AZD4547 80 mg b.i.d. 2 weeks on/1 week off schedule was well tolerated and no new safety signals were identified compared with previous studies [9, 11, 25].

Conclusion

Treatment with AZD4547 did not improve PFS compared with paclitaxel in the overall population or in patients with *FGFR2* amplification or polysomy according to FISH selection. The safety profile demonstrated that AZD4547 is generally well tolerated. Exploratory analysis revealed discordance between *FGFR2* expression and *FGFR2* amplification in gastric tumors selected using focal FISH testing, which to a large extent reflected considerable intratumor heterogeneity. Failure to enrich for a clonally amplified population may have contributed to the failure of the SHINE study to demonstrate superiority of AZD4547 compared with paclitaxel.

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Disclosure

EVC received research funding from AstraZeneca. Y-JB has received consultancy fees and research funding from AstraZeneca. RDP has received consultancy fees, travel grants, and honoraria from Lilly, travel grants from Merck and Bayer, and research funding from AstraZeneca and Roche. DC has received research funding from AstraZeneca. DRF has received honoraria from AstraZeneca. WM has received consultancy fees, travel grants, and honoraria from Lilly. YC received research funding from AstraZeneca. NRS, PF, JR, PKS, EK, and DL are employees of AstraZeneca. EK and PF hold AstraZeneca shares. PKS holds AstraZeneca shares.

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