BRIEF REPORT

Phase 2 Study of the HSP-90 Inhibitor AUY922 in Previously Treated and Molecularly Defined Patients with Advanced Non–Small Cell Lung Cancer

Enriqueta Felip, MD, PhD,[a,*] Fabrice Barlesi, MD, PhD,[b] Benjamin Besse, MD,[c] Quincy Chu, MD,[d] Leena Gandhi, MD, PhD,[e] Sang-We Kim, MD, PhD,[f] Enric Carcereny, MD,[g] Lecia V. Sequist, MD, MPH,[h] Paal Brunsvig, MD, PhD,[i] Christos Chouaid, MD, PhD,[j] Egbert F. Smit, MD, PhD,[k] Harry J. M. Groen, MD, PhD,[l] Dong-Wan Kim, MD, PhD,[m] Keunchil Park, MD, PhD,[n] Emin Avsar, PhD,[o] Sebastian Szpakowski, PhD,[p] Mikhail Akimov, MD, PhD,[q] Edward B. Garon, MD[r]

[a]*Vall d'Hebron University Hospital and Vall d'Hebron Institute of Oncology, Barcelona, Spain*
[b]*Multidisciplinary Oncology and Therapeutic Innovations Department, Aix-Marseille University, Assistance Publique Hôpitaux de Marseille, Marseille, France*
[c]*Gustave Roussy Cancer Campus, Villejuif, France, and Paris-Sud University, Le Kremlin-Bicêtre, France*
[d]*Cross Cancer Institute, Edmonton, Canada*
[e]*New York University Perlmutter Cancer Center, New York, New York*
[f]*Oncology, Asan Medical Center, Seoul, Republic of Korea*
[g]*Catalan Institute of Oncology, Hospital Germans Trias i Pujol, Badalona, Spain*
[h]*Massachusetts General Hospital Cancer Center, Boston, Massachusetts*
[i]*Department of Oncology, Oslo University Hospital, Oslo, Norway*
[j]*Department of Pulmonology, Centre Hospitalier Intercommunal de Créteil, Créteil, France*
[k]*Department of Pulmonary Diseases, VU University Medical Center, Amsterdam, The Netherlands*
[l]*Department of Pulmonary Diseases, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands*
[m]*Seoul National University Hospital, Seoul, Republic of Korea*
[n]*Innovative Cancer Medicine Institute, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea*
[o]*Novartis Pharma, East Hanover, New Jersey*
[p]*Novartis Institutes for Biomedical Research, Cambridge, Massachusetts*
[q]*Novartis Pharma AG, Basel, Switzerland*
[r]*David Geffen School of Medicine at University of California, Los Angeles, Los Angeles, California*

Received 20 July 2017; revised 10 November 2017; accepted 24 November 2017
Available online - 13 December 2017

*Corresponding author.

Disclosure: Dr. Felip reports personal fees from Boehringer-Ingelheim, Eli Lilly, Pfizer, Roche, Merck Sharp and Dohme (consulting fees), Astra-Zeneca, Bristol-Myers Squibb, and Novartis (lecture fees) and outside the submitted work. Dr. Barlesi reports personal fees from Astra-Zeneca, Bristol-Myers Squibb, Boehringer-Ingelheim, Clovis Oncology, Eli Lilly Oncology, Roche, Novartis, Merck, Merck Sharp and Dohme, Pierre Fabre, and Pfizer outside the submitted work. Dr. Besse reports grants (to his institution) from Novartis during the conduct of the study. Dr. Gandhi reports participation in scientific advisory boards for Merck, Genentech/Roche, Abbvie, Astra-Zeneca, and Pfizer; honoraria for a lecture on lung cancer management from Merck (2015); and research funding from Bristol-Myers Squibb IION foundation. Dr. Sequist reports grants (to her institution) from Novartis during the conduct of the study and has done consulting for AstraZeneca, Bristol-Myers Squibb, Ariad, and Genentech, as well as uncompensated consulting for Boehringer-Ingelheim, Clovis, Novartis, and Merrimack outside the submitted work. Dr. Chouaid reports personal fees from Novartis outside the submitted work. Dr. Smit reports personal fees from Eli Lilly, grants (to his institution) from Boehringer Ingelheim Bayer, Roche/Genentech and Astra-Zeneca outside the submitted work. Dr. Groen reports grants (to his institution) from Roche and advisory boards for Roche, Eli Lilly, and Bristol-Myers Squibb outside the submitted work. Dr. Park reports advisory board for Novartis outside the submitted work. Dr. Avsar was an employee of Novartis during conduct of the study and owns Novartis stocks. Dr. Szpakowski is an employee of Novartis. Dr. Akimov is an employee of Novartis and owns Novartis stock. Dr. Garon reports grants (to his institution) from Bristol-Myers Squibb, Astra-Zeneca, Boehringer-Ingelheim, Genentech, Eli Lilly, Merck, Pfizer, Novartis, and Mirati outside the submitted work. The remaining authors declare no conflict of interest.

Trial registration: A Study of AYU922 in Non-Small Cell Lung Cancer Patients Who Have Received Previous Two Lines of Chemotherapy. NCT01124864.

Address for correspondence: Enriqueta Felip, MD, PhD, Department of Medical Oncology, Oncology Service, Vall d'Hebron University Hospital, P. Vall d'Hebron, 119-129, 08035, Barcelona, Spain. E-mail: efelip@vhio.net

ISSN: 1556-0864

https://doi.org/10.1016/j.jtho.2017.11.131

ABSTRACT

Introduction: In this phase 2 study, we evaluated the activity of AUY922 in pretreated patients with stage IV NSCLC.

Methods: Patients with advanced NSCLC were divided into molecularly defined strata based on mutations in the *EGFR* gene, the ALK receptor tyrosine kinase gene (*ALK*), the *KRAS* gene, or the wild type of all three. All patients must have received more than two prior lines of therapy, except for those in a fifth stratum for a less pretreated *EGFR* cohort (*EGFR*<2). In the *EGFR*-mutant and *ALK*-rearranged strata, prior platinum therapy was not required. Patients with *EGFR* mutation must have received an EGFR tyrosine kinase inhibitor unless they had de novo resistance (e.g., T790M or exon 20 insertions). Eligible patients received weekly intravenous AUY922, 70 mg/m^2. The primary objective was to estimate efficacy (complete or partial response, or in the absence of complete or partial response, stable disease) at 18 weeks, by the Response Criteria in Solid Tumors.

Results: A total of 153 patients from 21 global centers were enrolled from October 2010 to November 2014. The investigator-assessed overall response rate and stable disease rate at 18 weeks were 31.8% and 9.1% in the *ALK*-rearranged stratum, 17.1% and 8.6% in *EGFR*-mutant stratum, 9.7% and 22.6% in the *EGFR*<2 stratum, 0% and 7.1% in *KRAS*-mutant stratum, and 8.8% and 8.8% in wild-type stratum. Biomarker data showed activity of AUY922 in *EGFR*-mutant patients with exon 19 deletion, T790M mutation, and exon 20 insertion. The most common (≥40%) all-causality adverse events were diarrhea, nausea, and decreased appetite. Visual-related disorders were reported in 79.7% of patients (most were grade 1/2). Thirty-five patients (22.9%) reported night blindness.

Conclusion: AUY922 is active in patients with NSCLC, particularly among patients with *ALK* rearrangements and *EGFR* mutations.

Keywords: NSCLC; AUY922; HSP90 inhibitor; *EGFR* mutation; *KRAS* mutation; *ALK* rearrangement

Introduction

Heat-shock protein90 (HSP90) is an adenosine triphosphate–dependent, molecular chaperone involved in the maintenance, maturation, and functioning of several oncogenic client proteins relevant in the pathogenesis of NSCLC.[1] Studies on resected NSCLC tumor specimens have shown that a lower expression of the gene encoding HSP90 correlates with better prognosis.[2] Inhibition of HSP90 has also been shown to induce apoptosis in NSCLC cells.[1]

AUY922 is a highly potent, adenosine triphosphate-competitive, nongeldanamycin HSP90 inhibitor. It potently inhibits growth in most NSCLC cell lines in vitro and in a variety of tumor xenografts in vivo.[3–6] The first-in-human, phase 1 dose-escalation study of AUY922, which was conducted in patients with advanced solid tumors demonstrated acceptable tolerability at the recommended dose of 70 mg/m^2.[7] These preclinical and clinical studies provided the rationale for the current phase 2 study of AUY922 in patients with advanced NSCLC with different tumor molecular etiologies.

Patients and Methods

Study Design

This was a global, multicenter, open label phase 2 study of AUY922 that was conducted in 21 global centers between October 2010 and November 2014. Patients with advanced NSCLC were divided into molecularly defined strata based on mutations in the *EGFR* gene, the ALK receptor tyrosine kinase gene (*ALK*), the *KRAS* gene, or the wild-type of all three. All patients must have received more than 2 prior lines of therapy, except for those in a fifth stratum for a less pretreated *EGFR* cohort (EGFR<2). In the *EGFR*-mutant and *ALK*-rearranged strata, prior platinum therapy was not required. Patients with *EGFR* mutation must have received an EGFR tyrosine kinase inhibitor (TKI) unless they had de novo resistance.

The primary objective was to estimate efficacy as assessed by the Response Criteria in Solid Tumors, classified as complete or partial response (overall response rate [ORR]) or in the absence of complete or partial response, as stable disease or no clinical benefit (NCB) for each study stratum at 18 weeks after treatment initiation. NCB is defined as development of progressive disease in within 18 weeks after the patient had started receiving treatment. Secondary objectives included assessment of overall survival (OS), progression-free survival (PFS), safety, and pharmacokinetics. An exploratory objective was included to examine molecular markers of response. Further details are provided in the Supplementary Materials and Methods.

Results

Patient Disposition and Characteristics

Of a total of 153 patients,150 were assigned to five strata, *ALK*-rearranged (n = 22), *EGFR*- mutant (n = 35), *EGFR*<2 (n = 31), *KRAS*- mutant (n = 28), and wild-type (n = 34), and three patients were classified as "unknown" because the tumor tissue from them was not of a quality acceptable for molecular determination. Of the

153 patients, 151 (98.7%) discontinued treatment, most (73.2%) because of disease progression.

Baseline demographics and disease characteristics are presented in Table 1. All patients had received one or more prior antineoplastic medications, including chemotherapy in 92.2% of patients and targeted therapy in 63.3%. Among these, four patients (2.6%), 31 (20.3%), and 40 (26.1%) received more than four, four, and three previous regimens, respectively, whereas the remaining 78 patients (51%) received one or two previous regimens. At baseline, TKIs were administered to nearly all patients in the *EGFR*-mutant (97.1%) and

Table 1. Baseline Demographics and Clinical Characteristics

Characteristic	No. of patients (%)						
	ALK-Rearranged (n = 22)	*EGFR*-Mutant (n = 35)	*EGFR*<2-Mutant (n = 31)	Wild-Type (n = 34)	*KRAS*-Mutant (n = 28)	Unknown (n = 3)	All Patients (N = 153)
Age, y							
Median	53.0	63.0	56.0	62.5	60.0	66.0	59.0
Range	37-73	33-80	40-76	40-73	39-72	48-67	33-80
<65, n (%)	18 (81.8)	21 (60.0)	25 (80.6)	23 (67.6)	20 (71.4)	1 (33.3)	108 (70.6)
≥65, n (%)	4 (18.2)	14 (40.0)	6 (19.4)	11 (32.4)	8 (28.6)	2 (66.7)	45 (29.4)
Female	15 (68.2)	25 (71.4)	19 (61.3)	18 (52.9)	11 (39.3)	0.0	88 (57.5)
Race, n (%)							
White	16 (72.7)	25 (71.4)	16 (51.6)	23 (67.6)	25 (89.3)	2 (66.7)	107 (69.9)
Asian	6 (27.3)	10 (28.6)	13 (41.9)	9 (26.5)	2 (7.1)	1 (33.3)	41 (26.8)
Black	0	0	0	1 (2.9)	0	0	1 (0.7)
Other	0	0	2 (6.5)	1 (2.9)	1 (3.6)	0	4 (2.6)
WHO performance status, n (%)							
0	9 (40.9)	13 (37.1)	11 (35.5)	10 (29.4)	10 (35.7)	1 (33.3)	54 (35.3)
1	11 (50.0)	19 (54.3)	20 (64.5)	21 (61.8)	18 (64.3)	2 (66.7)	91 (59.5)
2	2 (9.1)	3 (8.6)	0.0	3 (8.8)	0.0	0.0	8 (5.2)
Smoking status, n (%)							
Current smoker	2 (9.1)	1 (2.9)	1 (3.2)	2 (5.9)	3 (10.7)	1 (33.3)	10 (6.5)
Ex-smoker	5 (22.7)	12 (34.3)	16 (51.6)	18 (52.9)	21 (75.0)	0.0	72 (47.1)
Never smoked	15 (68.2)	22 (62.9)	14 (45.2)	14 (41.2)	4 (14.3)	2 (66.7)	71 (46.4)
Median time since initial diagnosis to first dose of study drug (range), mo	22.37 (2.9-64.1)	24.61 (7.6-32.8)	19.15 (3.1-65.1)	18.00 (4.0-65.7)	19.91 (5.1-43.5)	18.79 (8.0-27.1)	20.83 (2.9-132.8)
No. of prior regimens, n (%)							
1	2 (9.1)	2 (5.7)	13 (41.9)	0.0	1 (3.6)	0.0	18 (11.8)
2	4 (18.2)	14 (40.0)	18 (58.1)	16 (47.1)	8 (28.6)	0.0	60 (39.2)
3	7 (31.8)	12 (34.3)	0.0	5 (14.7)	14 (50.0)	2 (66.7)	40 (26.1)
4	7 (31.8)	7 (20.0)	0.0	12 (35.3)	4 (14.3)	1 (33.3)	31 (20.3)
>4	2 (9.1)	0.0	0.0	1 (2.9)	1 (3.6)	0.0	4 (2.6)
Therapy type at last regimen, n (%)							
Chemotherapy	13 (59.1)	19 (54.3)	11 (35.5)	25 (73.5)	22 (78.6)	2 (66.7)	92 (60.1)
Hormonal therapy	0	0	1 (3.2)	0	0	0	1 (0.7)
Immunotherapy	0	0	1 (3.2)	1 (2.9)	1 (3.6)	0	3 (2.0)
Targeted therapy	9 (40.9)	18 (51.4)	19 (61.3)	11 (32.4)	6 (21.4)	1 (33.3)	64 (41.8)
Other	0	1 (2.9)	1 (3.2)	1 (2.9)	0	0	3 (2.0)
Tumor histologic/cytologic type, (%)							
Adenocarcinoma	20 (90.9)	32 (91.4)	30 (96.8)	28 (82.4)	23 (82.1)	3 (100.0)	136 (88.9)
Squamous cell carcinoma	0	0	0	2 (5.9)	1 (3.6)	0	3 (2.0)
Adenosquamous cell carcinoma	0	0	0	2 (5.9)	0	0	2 (1.3)
Bronchioalveolar carcinoma	1 (4.5)	1 (2.9)	0	0	2 (7.1)	0	4 (2.6)
Large cell carcinoma	0	1 (2.9)	0	2 (5.9)	1 (3.6)	0	4 (2.6)
Other	1 (4.5)	1 (2.9)	1 (3.2)	0	1 (3.6)	0	4 (2.6)
Key metastatic site of cancer, n (%)							
Bone	11 (50.0)	15 (42.9)	13 (41.9)	15 (44.1)	9 (32.1)	2 (66.7)	65 (42.5)
Brain	4 (18.2)	6 (17.1)	2 (6.5)	5 (14.7)	6 (21.4)	0	23 (15.0)
Liver	5 (22.7)	9 (25.7)	4 (12.9)	8 (23.5)	4 (14.3)	1 (33.3)	31 (20.3)

ALK, ALK receptor tyrosine kinase gene; *EGFR*<2-Mutant, stratum of patients with *EGFR* mutation and fewer than two prior lines of therapy.

Table 2. Summary of Response Assessment by Study Stratum, as per Investigator Assessment and Central Radiological Review

	No. of patients (%)						
Response	*ALK*-Rearranged (n = 22)	*EGFR*-Mutant (n = 35)	*EGFR*<2-Mutant (n = 31)	Wild-type (n = 34)	*KRAS*-Mutant (n = 28)	Unknown (n = 3)	All patients (N = 153)
Primary assessment: investigator assessment							
ORR (CR + PR) at 18 wk, n (%) (95% CI)	7 (31.8) (13.9-54.9)	6 (17.1) (6.6-33.6)	3 (9.7) (2.0-25.8)	3 (8.8) (1.9-23.7)	0 (0-12.3)	1 (33.3) (0.8-90.6)	20 (13.1) (8.2-19.5)
Stable disease at 18 wk, n (%)	2 (9.1)	3 (8.6)	7 (22.6)	3 (8.8)	2 (7.1)	0	17 (11.1)
NCB, n (%)	13 (59.1)	26 (74.3)	21 (67.7)	28 (82.4)	26 (92.9)	2 (66.7)	116 (75.8)
Secondary assessment: central radiological review							
ORR (CR + PR) at 18 weeks, n (%) (95% CI)	6 (27.3) (10.7-50.2)	5 (14.3) (4.8-30.3)	1 (3.2) (0.1-16.7)	3 (8.8) (1.9-23.4)	0 (0-12.3)	0 (0-70.8)	15 (9.8) (5.6-15.7)
Stable disease at 18 wk, n (%)	1 (4.5)	1 (2.9)	7 (22.6)	4 (11.8)	3 (10.7)	1 (33.3)	17 (11.1)
NCB, n (%)	15 (68.2)	29 (82.9)	23 (74.2)	27 (79.4)	25 (89.3)	2 (66.7)	121 (79.1)

ALK, ALK receptor tyrosine kinase gene; *EGFR*<2-Mutant, stratum of patients with *EGFR* mutation and fewer than two prior lines of therapy; ORR, overall response rate; CR, complete response; PR, partial response; CI, confidence interval; NCB, no clinical benefit.

EGFR<2 (90.3%) strata, most commonly erlotinib. Among patients with *ALK* rearrangement who had received at least one prior regimen, 77.3% had received the anaplastic lymphoma kinase (ALK) inhibitor crizotinib.

Efficacy

Overall, 20 patients achieved an investigator-assessed tumor response (ORR of 13.1%) and 17 patients (11.1%) had stable disease at 18 weeks. The investigator-assessed ORR and stable disease at 18 weeks among the five strata are reported in Table 2. Most of the patients (75.8%) showed NCB, as they did not have a radiological response per the Response Criteria in Solid Tumors and progressed within 18 weeks of study treatment. Overall, on the basis of central radiological review, 15 patients (9.8%) had a radiological response, 17 patients (11.1%) had stable disease at 18 weeks, and the remainder (79.1%) showed NCB (see Table 2).

Bayesian analysis of the ORR and NCB rates demonstrated (1) a high probability of improved efficacy (on the basis of predefined thresholds) in the *ALK*-rearranged (0.899) and *EGFR*-mutant (0.832) strata, (2) a low probability of improved efficacy in the wild-type (0.346) and *EGFR*<2-mutant strata (0.185), and (3) a high probability of no efficacy in the *KRAS*-mutant stratum (0.036) (Supplementary Table 1).

Investigator-assessed disease control rate was highest in the *EGFR*<2-mutant (71.0% [95% confidence interval (CI): 52.0–85.8]), *ALK*-rearranged (59.1% [95% CI: 36.4–79.3]), and *EGFR*-mutant (57.1% [95% CI: 39.4–73.7]) strata (Supplementary Table 2). Three of the seven patients who had a response to treatment had received prior crizotinib-based treatment.

Next-generation sequencing data were successfully generated for 54 patients (35% because of limited tissue availability), including 11 of 31 patients (35%) assigned to the *EGFR*<2 stratum and 14 of 35 patients (40%) assigned to the *EGFR*-mutant stratum (Table 3). Among the *EGFR*<2-mutant patients, seven had two mutations each (exon 19 deletions and T790M mutations [n = 6] or L858R and T790M [n = 1]). Among the *EGFR*-mutant patients who received more than two lines of therapy,

Table 3. Summary of Mutations and Responses in Patients in the Less Pretreated *EGFR*-Mutant and *EGFR*-Mutant Strata by Next-Generation Sequencing

Study Stratum	Mutation Type	No. of Patients	No. of Responders (PR/CR)
EGFR<2-mutant	Exon 19 deletion and T790M	6	1
	Exon 19 deletion	3	0
	Exon 21 L858R and T790M	1	0
	Not detected	1	1
	Not sequenced	20	Not applicable
EGFR-mutant	Exon 19 deletion	4	1
	Exon 19 deletion and T790M	4	2
	Exon 20 insertion	2	1
	Exon 21 L858R	1	0
	Exon 21 L858R and S768I	1	0
	Exon 21 L861Q	1	0
	L747P	1	0
	Not sequenced	21	Not applicable

CR, complete response; PR, partial response; *EGFR*<2-mutant, stratum of patients with *EGFR* mutation and fewer than two prior lines of therapy.

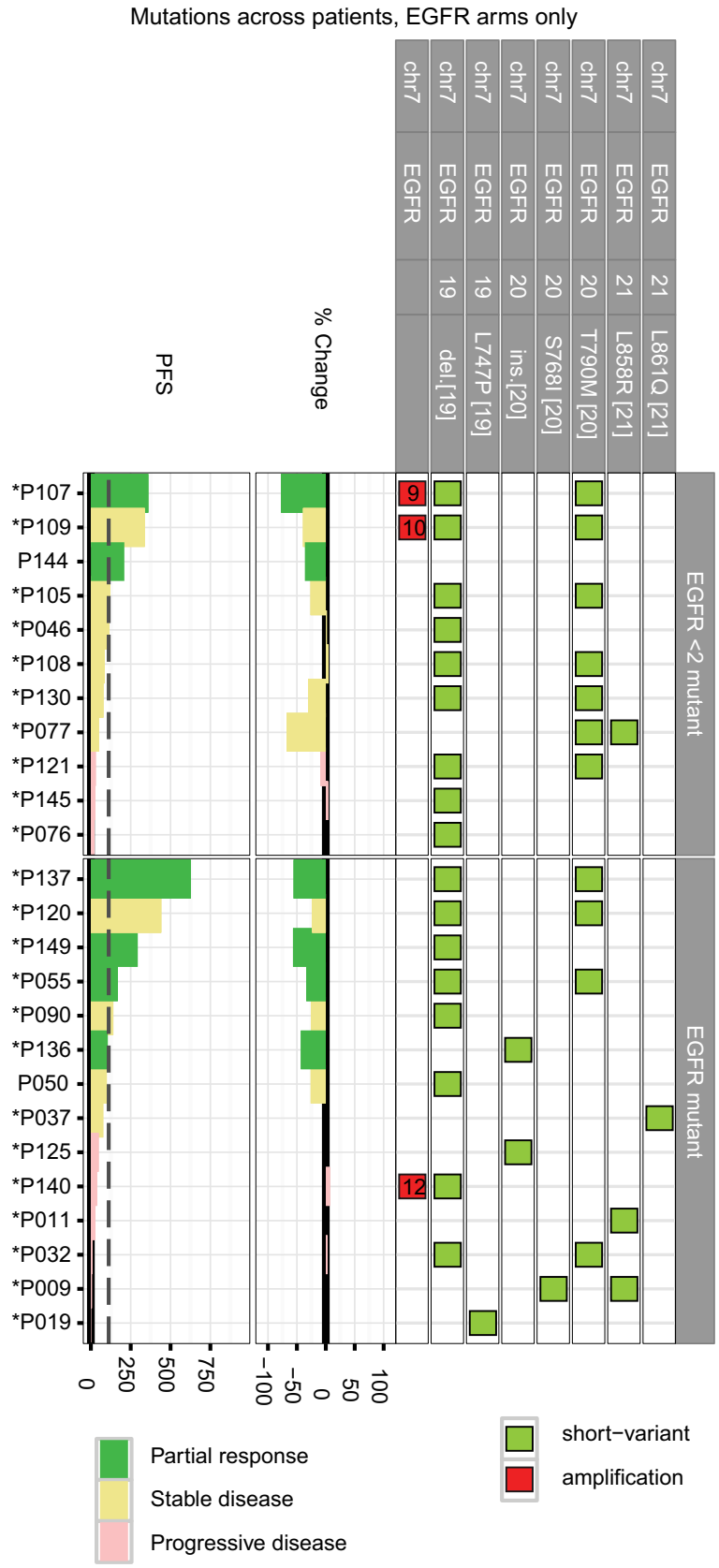

Figure 1. Mutations across patients with clinical variables (EGFR, all patients). PFS, progression-free survival.

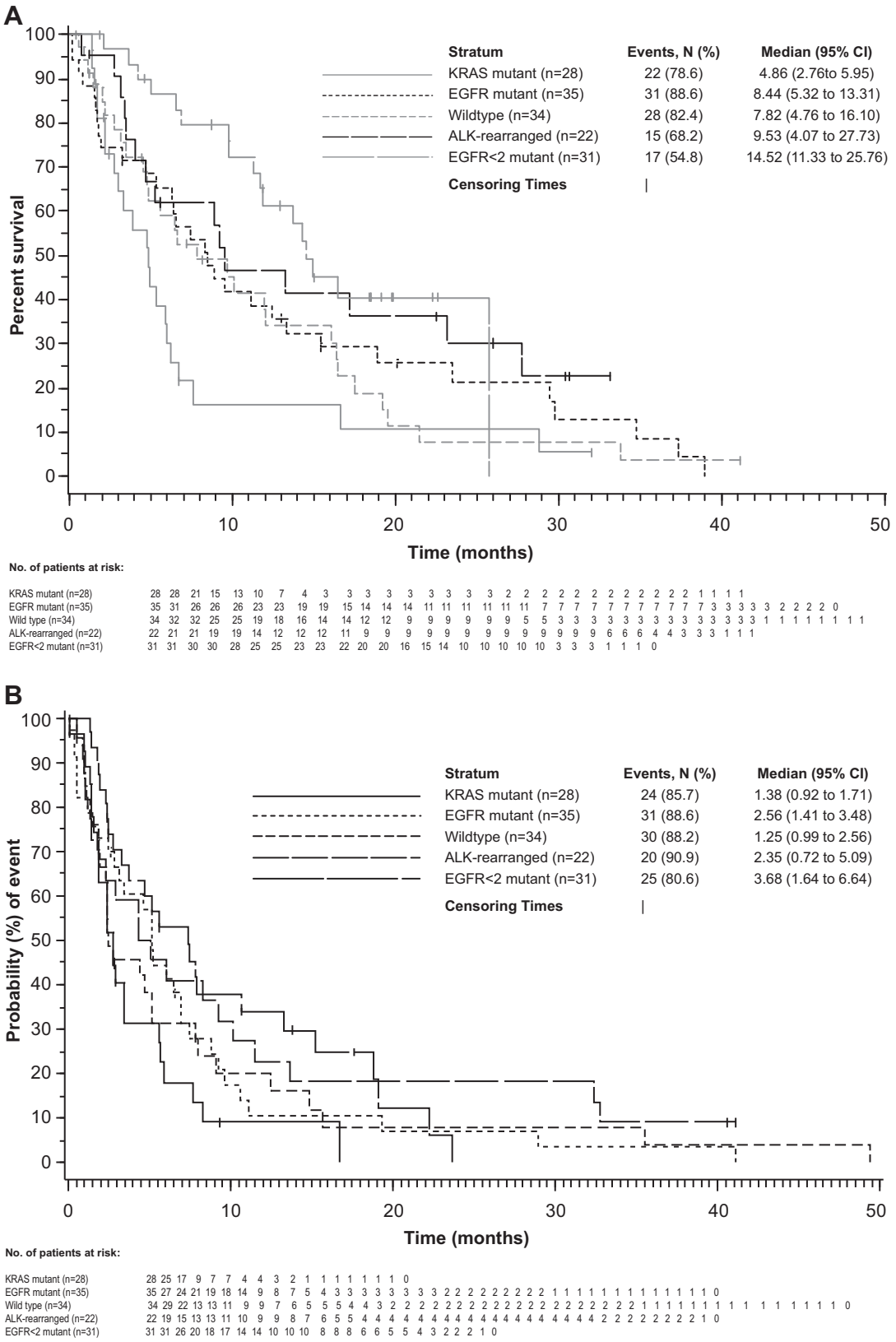

Figure 2. Kaplan-Meier estimates of progression-free survival (*A*) and overall survival (*B*) by study stratum. *ALK*, ALK receptor tyrosine kinase gene; CI, confidence interval; *EML4*, echinoderm microtubule association protein like 4 gene.

Table 4. Most Common All-Causality Adverse Events by Study Stratum

Preferred Term	No. of patients (%)						
	ALK-Rearranged, n (%) (n = 22)	*EGFR*-Mutant, n (%) (n = 35)	*EGFR*<2-Mutant, n (%) (n = 31)	*KRAS*-Mutant, n (%) (n = 28)	Wild-Type, n (%) (n = 34)	Unknown, n (%) (n = 3)	All Patients, n (%) (N = 153)
Diarrhea	17 (77.3)	24 (68.6)	24 (77.4)	25 (89.3)	25 (73.5)	3 (100.0)	118 (77.1)
Nausea	10 (45.5)	19 (54.3)	12 (38.7)	16 (57.1)	13 (38.2)	1 (33.3)	71 (46.4)
Decreased appetite	7 (31.8)	15 (42.9)	10 (32.3)	17 (60.7)	12 (35.3)	1 (33.3)	62 (40.5)
Asthenia	10 (45.5)	14 (40.0)	4 (12.9)	13 (46.4)	11 (32.4)	1 (33.3)	53 (34.6)
Headache	13 (59.1)	8 (22.9)	13 (41.9)	8 (28.6)	8 (23.5)	2 (66.7)	52 (34.0)
Fatigue	3 (13.6)	9 (25.7)	15 (48.4)	7 (25.0)	14 (41.2)	0 (0.0)	48 (31.4)
Vomiting	9 (40.9)	14 (40.0)	4 (12.9)	13 (46.4)	4 (11.8)	2 (66.7)	46 (30.1)
Cough	7 (31.8)	8 (22.9)	8 (25.8)	5 (17.9)	9 (26.5)	1 (33.3)	38 (24.8)
Dyspnea	3 (13.6)	13 (37.1)	2 (6.5)	7 (25.0)	9 (26.5)	1 (33.3)	35 (22.9)
Night blindness	5 (22.7)	10 (28.6)	10 (32.3)	3 (10.7)	6 (17.6)	1 (33.3)	35 (22.9)
Photopsia	10 (45.5)	5 (14.3)	6 (19.4)	3 (10.7)	10 (29.4)	0 (0.0)	34 (22.2)
Back pain	3 (13.6)	5 (14.3)	7 (22.6)	8 (28.6)	8 (23.5)	0 (0.0)	31 (20.3)
Vision blurred	6 (27.3)	6 (17.1)	6 (19.4)	5 (17.9)	7 (20.6)	0 (0.0)	30 (19.6)
Visual impairment	6 (27.3)	8 (22.9)	7 (22.6)	6 (21.4)	3 (8.8)	0 (0.0)	30 (19.6)
Constipation	4 (18.2)	6 (17.1)	5 (16.1)	6 (21.4)	5 (14.7)	0 (0.0)	26 (17.0)
Visual acuity reduced	7 (31.8)	6 (17.1)	5 (16.1)	1 (3.6)	7 (20.6)	0 (0.0)	26 (17.0)
Pyrexia	6 (27.3)	3 (8.6)	4 (12.9)	5 (17.9)	4 (11.8)	2 (66.7)	24 (15.7)
Abdominal pain	5 (22.7)	5 (14.3)	2 (6.5)	5 (17.9)	4 (11.8)	0	21 (13.7)
Myalgia	5 (22.7)	4 (11.4)	6 (19.4)	0	4 (11.8)	1 (33.3)	20 (13.1)
Insomnia	5 (22.7)	3 (8.6)	4 (12.9)	0	6 (17.6)	0	18 (11.8)
Anemia	3 (13.6)	3 (8.6)	4 (12.9)	2 (7.1)	5 (14.7)	0	17 (11.1)
Retinal disorder	5 (22.7)	3 (8.6)	7 (22.6)	1 (3.6)	1 (2.9)	0	17 (11.1)
Dry mouth	0	4 (11.4)	1 (3.2)	5 (17.9)	6 (17.6)	0	16 (10.5)
Hypertension	3 (13.6)	5 (14.3)	5 (16.1)	0	3 (8.8)	0	16 (10.5)
Ocular toxicity	3 (13.6)	4 (11.4)	3 (9.7)	4 (14.3)	1 (2.9)	1 (33.3)	16 (10.5)

Note: Occurring in at least 10% of all patients regardless of study drug relationship.
ALK, ALK receptor tyrosine kinase gene; *EGFR*<2-Mutant, stratum of patients with *EGFR* mutation and fewer than two prior lines of therapy.

five had two mutations each (exon 19 deletions and T790M mutations [n = 4] and S786I and L858R mutation [n = 1]). Overall in both of the *EGFR* mutation groups, six patients demonstrated partial response: three patients with both exon 19 deletions and T790M and one patient each with exon 19 deletion or exon 20 insertion (Fig. 1).

In the *ALK*-rearranged stratum, on the basis of investigator assessment, the median PFS was 2.35 months (95% CI: 0.72–5.09) (Fig. 2*A*) and the median OS was 9.53 months (95% CI: 4.07–27.73) (Fig. 2*B*). In the *EGFR*-mutant stratum, the median PFS was 2.56 months (95% CI: 1.41–3.48) (see Fig. 2*A*) and the median OS was 8.44 months (95% CI: 5.32–13.31) (see Fig. 2*B*). Similarly, in the *EGFR*<2-mutant stratum, the median PFS was 3.68 months (95% CI: 1.64–6.64) (see Fig. 2*A*) and the median OS was 14.52 months (95% CI: 11.33–25.76) (see Fig. 2*B*). The median PFS times for the *KRAS*-mutant and wild-type strata were 1.38 (95% CI: 0.92–1.71) and 1.25 months (95% CI: 0.99–2.56), respectively (see Fig. 2*A*). The overall survival times for the *KRAS*-mutant and wild-type strata were 4.86 (95% CI: 2.76–5.95) and 7.82 (95% CI: 4.76–16.10) months, respectively (see Fig. 2*B*).

Safety

Overall, the median duration of exposure was 7.0 weeks, with a longer duration observed in the following strata: *ALK*-rearranged (median 11.5 weeks, 41% treated past 18 weeks), *EGFR*<2 (median 12 weeks, 32% treated past 18 weeks), and *EGFR*-mutant (median 11 weeks, 23% treated past 18 weeks). Most patients (79.7%) did not require a dose reduction, and the rates of reduction were similar across all strata. Overall, 21 patients (13.7%) discontinued treatment because of adverse events (AEs); 10 patients (6.5%) discontinued

treatment because of AEs that were suspected to be related to the study drug.

All patients experienced one or more AE, regardless of causality. The most common all-causality AEs (≥10% incidence) are summarized in Table 4. Overall, 67.3% reported at least one grade 3 or 4 AE, regardless of causality, most frequently diarrhea (7.2%), dyspnea (7.2%), and asthenia (5.9%). The most frequently reported study drug–related AEs were diarrhea (69.9%), nausea (37.9%), asthenia (24.8%), fatigue (23.5%), night blindness (22.9%), photopsia (22.2%), and vomiting (20.9%).

Almost half of all patients (49.7%) experienced serious AEs, regardless of causality, with 16 of them (10.5%) experiencing a serious AE that was considered related to the study drug. There were no study drug–related deaths.

Discussion

This study evaluated activity of AUY922 across a broad range of mutations (*ALK*, *EGFR*, and *KRAS*) in pretreated patients with advanced NSCLC. Our results show that AUY922 is active in those with *ALK* rearrangement and *EGFR* mutations. Despite preclinical evidence suggesting that KRAS-mutant models are sensitive on the basis of downstream proteins that are clients of HSP90, we did not observe any clinical benefit for patients with *KRAS* mutations.[8]

Development of resistance occurs in most patients treated with ALK TKIs.[9,10] AUY922 showed activity in both ALK inhibitor–naive and ALK inhibitor–pretreated patients. Similar prior studies with the single-agent HSP90 inhibitors ganetespib and IPI-504 showed responses in patients with NSCLC who had *ALK* rearrangement.[11,12]

Responses in *EGFR*-mutant patients with other HSP90 inhibitors, ganetespib and IPI-504, have been limited.[11,12] In our study, clinical activity was observed in patients with *EGFR* mutations, including exon 19 deletions and exon 20 insertions, and in patients with acquired T790M mutations. Differences in EGFR TKI response based on *EGFR* mutation have been reported previously.[13] Similar to our results described here, an ongoing phase 2 study of AUY922 in patients with NSCLC with exon 20 insertions demonstrated an ORR of 32%.[14]

The safety data were similar in patients with advanced solid tumors in the phase 1 trial.[7] Low-grade ocular toxicity was common but effectively managed with dose reductions and dose interruptions. The rate of discontinuation due to AEs was lower in the *ALK*-rearranged and *EGFR*<2 strata than in the other groups, indicating that these patients may not have many disease-related comorbidities or that the AEs may have been deemed more tolerable in patients who were benefiting from therapy.

In summary, AUY922 had a manageable safety profile and is active in patients with *ALK* rearrangement and *EGFR* mutations, including T790M, which had de novo resistance to EGFR TKIs. Future clinical studies are required to address subsequent overlap between different biomarkers to allocate the right therapy to the right group of patients.

Acknowledgments

This study was funded by Novartis Pharmaceuticals Corporation. The authors thank the participating patients, their families, all study co-investigators and research coordinators. Medical writing support was provided by Shiva Krishna Rachamadugu and Pushkar Narvilkar, Novartis HealthCare Private Limited (Hyderabad, India) and Andy Gannon, QXV Comms (New York, New York), an Ashfield business that is part of UDG Healthcare plc, and it was fully funded by the Novartis Pharmaceuticals Corporation.

Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the *Journal of Thoracic Oncology* at www.jto.org and at https://doi.org/10.1016/j.jtho.2017.11.131.

References

1. Banerji U. Heat shock protein 90 as a drug target: some like it hot. *Clin Cancer Res*. 2009;15:9–14.
2. Gallegos Ruiz MI, Floor K, Roepman P, et al. Integration of gene dosage and gene expression in non-small cell lung cancer, identification of HSP90 as potential target. *PloS One*. 2008;3:e0001722.
3. Brough PA, Aherne W, Barril X, et al. 4,5-diarylisoxazole Hsp90 chaperone inhibitors: potential therapeutic agents for the treatment of cancer. *J Med Chem*. 2008;51:196–218.
4. Eccles SA, Massey A, Raynaud FI, et al. NVP-AUY922: a novel heat shock protein 90 inhibitor active against xenograft tumor growth, angiogenesis, and metastasis. *Cancer Res*. 2008;68:2850–2860.
5. Jensen MR, Schoepfer J, Radimerski T, et al. NVP-AUY922: a small molecule HSP90 inhibitor with potent antitumor activity in preclinical breast cancer models. *Breast Cancer Res*. 2008;10:R33.
6. Gaspar N, Sharp SY, Eccles SA, et al. Mechanistic evaluation of the novel HSP90 inhibitor NVP-AUY922 in adult and pediatric glioblastoma. *Mol Cancer Ther*. 2010;9:1219–1233.
7. Sessa C, Shapiro GI, Bhalla KN, et al. First-in-human phase I dose-escalation study of the HSP90 inhibitor AUY922 in patients with advanced solid tumors. *Clin Cancer Res*. 2013;19:3671–3680.

8. Acquaviva J, Smith DL, Sang J, et al. Targeting KRAS-mutant non-small cell lung cancer with the Hsp90 inhibitor ganetespib. *Mol Cancer Ther*. 2012;11:2633–2643.
9. Katayama R, Shaw AT, Khan TM, et al. Mechanisms of acquired crizotinib resistance in ALK-rearranged lung cancers. *Sci Transl Med*. 2012;4:120ra117.
10. Shaw AT, Kim D-W, Mehra R, et al. Ceritinib in ALK-rearranged non–small-cell lung cancer. *N Engl J Med*. 2014;370:1189–1197.
11. Socinski MA, Goldman J, El-Hariry I, et al. A multicenter phase II study of ganetespib monotherapy in patients with genotypically defined advanced non-small cell lung cancer. *Clin Cancer Res*. 2013;19:3068–3077.
12. Sequist LV, Gettinger S, Senzer NN, et al. Activity of IPI-504, a novel heat-shock protein 90 inhibitor, in patients with molecularly defined non-small-cell lung cancer. *J Clin Oncol*. 2010;28:4953–4960.
13. Zhu JQ, Zhong WZ, Zhang GC, et al. Better survival with EGFR exon 19 than exon 21 mutations in gefitinib-treated non-small cell lung cancer patients is due to differential inhibition of downstream signals. *Cancer Lett*. 2008;265:307–317.
14. Piotrowska Z, Smit E, Costa DB, et al. Activity of AUY922 in NSCLC patinets with EGFR exon 20 insertions. Paper presented at: 16th World Conference on Lung Cancer. September 6–9, 2015; Denver, CO.