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ORIGINAL REPORT

Phase I/II Study of HSP90 Inhibitor AUY922 and Erlotinib for *EGFR*-Mutant Lung Cancer With Acquired Resistance to Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitors

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Terms in blue are defined in the glossary, found at the end of this article and online at www.jco.org.

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ABSTRACT

Purpose
AUY922 is an HSP90 inhibitor that causes degradation of HSP chaperones and their client proteins, including epidermal growth factor receptor. We conducted a phase I/II trial to evaluate AUY922 and erlotinib for patients with *EGFR*-mutant lung cancer and disease progression during erlotinib treatment.

Patients and Methods
All patients had developed acquired resistance after treatment with erlotinib and underwent repeat tumor biopsies before study entry to assess for *EGFR* T790M. In phase I, 18 patients were treated with AUY922 intravenously once per week and erlotinib once per day in 28-day cycles using a 3 + 3 dose-escalation design. In phase II, 19 additional patients were treated at the maximum-tolerated dose. The primary end point of the phase II trial was complete plus partial response rate.

Results
In phase I (n = 18), three patients were treated in each cohort, except the highest-dose cohort (AUY922 70 mg and erlotinib 150 mg), which expanded to six patients because of a dose-limiting toxicity (ie, junctional cardiac rhythm). Common drug-related adverse events were diarrhea, skin rash, hyperglycemia, and night blindness. All patients treated at maximum-tolerated dose (n = 25) were evaluable for response. The partial response rate was 16% (four of 25 patients; 95% CI, 5% to 36%) and was independent of tumor T790M status.

Conclusion
Partial responses were observed, but the duration of treatment with AUY922 and erlotinib was limited by toxicities, especially night blindness. This phase II study of AUY922 and erlotinib did not meet its primary end point.

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INTRODUCTION

Patients with *EGFR*-mutant lung cancer often have dramatic initial responses when treated with a small-molecule tyrosine kinase inhibitor (TKI), such as erlotinib, gefitinib, or afatinib.[1-4] However, virtually all patients develop progressive disease, or acquired resistance, within a median of 9 to 14 months after initiation of these agents.[5-7] Sixty percent of patients with acquired resistance develop a secondary gatekeeper mutation, *EGFR* T790M, which interferes with TKI binding.[8-10] Other patients may develop resistance by alternative mechanisms, such as additional second site mutations within *EGFR*, upregulation of parallel signaling pathways (MET, human epidermal growth factor receptor 2, AXL),[11-13] additional acquired secondary mutations (*PIK3CA*, *BRAF*), or histologic changes (small cell or epithelial to mesenchymal transitions).[14-16] There are no approved targeted therapies for patients once acquired resistance occurs, although third-generation epidermal growth factor receptor (EGFR) TKIs, developed to specifically target *EGFR* T790M, have shown significant activity.[17-19]

EGFR is a client of chaperone protein HSP90.[20,21] AUY922 is an isoxazolyl resorcinol–based HSP90 inhibitor, chemically distinct from parent compound geldanamycin and first-generation HSP90 inhibitors 17-AAG and 17-DMAG.[22] AUY922 induces apoptosis in TKI-sensitive and TKI-resistant *EGFR*-mutant cell lines and slows growth of xenografts harboring *EGFR* T790M.[23,24] In phase I

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clinical trials, the recommended phase II dose for AUY922 was 70 mg/m^2.[22] In a phase II trial evaluating single-agent AUY922 for patients with recurrent lung cancer, including patients with *EGFR*-mutant lung cancer previously treated with EGFR TKIs, 18% (12 of 66) had a partial response to single-agent AUY922.[25,26]

Patients with *EGFR*-mutant lung cancer may develop acquired resistance variably throughout their tumors, so some subclones retain sensitivity to EGFR TKI therapies, even as other parts of the tumor become resistant.[27] When first-line TKIs are discontinued after the development of EGFR TKI resistance, patients can develop rapid, symptomatic disease flare manifested as hospitalization or death as a result of progressive cancer.[28,29] To avoid this rapid disease progression, EGFR TKIs may be administered concomitantly with the introduction of second-line therapies.[27-29] We used this strategy in a phase I/II study that combined AUY922 and erlotinib for patients with lung adenocarcinoma and acquired resistance to EGFR TKIs.

PATIENTS AND METHODS

Patient Population

Eligible patients for this study had advanced (stage IV) lung adenocarcinoma with EGFR TKI–sensitizing mutations (ie, G719X, exon 19 deletion, L858R, or L861). Per criteria developed by Jackman et al,[30] patients developed acquired resistance after at least 6 months of treatment with erlotinib. Patients were required to have measurable disease per RECIST (version 1.1). All patients had an Eastern Cooperative Oncology Group performance status of 0 to 2. Patients with preexisting diarrhea grade $\geq$ 1 (per Common Terminology Criteria for Adverse Events) or baseline QTc $\geq$ 450 milliseconds were excluded. All patients had a repeat tumor biopsy at a site of disease that had grown during previous treatment to ensure the highest chance that the sampled tumor tissue would demonstrate resistance mechanisms, such as *EGFR* T790M.

The study was conducted after approval from institutional review boards at Northwestern University and Memorial Sloan-Kettering Cancer Center. All patients provided written informed consent before participating.

Study Design

The phase I portion of this clinical trial was a standard 3 + 3 dose-escalation study to determine the maximum-tolerated dose (MTD) of AUY922 and erlotinib. In absence of dose-limiting toxicities (DLTs), three patients were treated in each dose cohort. DLTs were defined as grade 4 diarrhea (or grade 3 diarrhea refractory to antidiarrheal medication for $>$ 72 hours), grade 3 QTc prolongation, other grade 3 to 4 nonhematologic toxicities, grade 4 hematologic toxicities, or treatment-related deaths. Toxicity was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.0). If a DLT was observed in the initial cohort of three patients at a given dose, another three patients were added to the cohort. The MTD was determined as the highest dose where not more than one of six patients developed a DLT.

Treatment immediately before enrollment varied. Some had been treated with erlotinib monotherapy before study entry, whereas others had received multiple lines of therapy since developing acquired resistance, including cytotoxic chemotherapies or investigational agents. To standardize responses to the combination of agents and to eliminate the chance that re-response to erlotinib could be confused with response to the combination, patients treated with therapies other than erlotinib had a 1-month erlotinib lead-in before initiation of AUY922 (not required for patients previously treated with erlotinib-containing chemotherapy regimens or erlotinib alone). All patients had a baseline disease evaluation after the erlotinib lead-in and before starting AUY922.

AUY922 was administered intravenously (IV) once per week and erlotinib orally once per day in 28-day cycles. The phase I dose levels are summarized in Table 1. During the phase II study, additional patients were treated at the MTD (AUY922 70 mg/m^2 IV once per week and erlotinib 150 mg orally once per day). The primary objectives of the phase II trial were to determine the complete plus partial response rate and assess adverse effects. All patients treated at the MTD were evaluable for response, whereas all patients treated with any dose of erlotinib and AUY922 were evaluable for toxicity.

Table 1. Dose-Escalation Schema

Cohort	AUY922 IV Dose (once per week; mg/m^2)	Erlotinib Oral Dose (once per day; mg)	No. of Patients Enrolled
1	25	75	3
2	25	150	3
3	37.5	150	3
4	55	150	3
5	70	150	6

Abbreviation: IV, intravenous.

Toxicity Assessments

Patients were evaluated once per week for treatment-related toxicities throughout cycles one and two and at the beginning of each subsequent 28-day cycle. On day 1 of cycle one, ECGs were performed in triplicate: at 30 minutes, 1 hour, 4 hours, 24 hours, and 48 hours post-AUY922 infusion. ECGs were obtained pre- and postinfusion for all subsequent AUY922 infusions. Ophthalmologic examinations (pretreatment and after cycles one and three) included assessments of visual acuity, intraocular pressure, slit-lamp test, dilated fundus, color-vision test, and electroretinography where indicated.

Pharmacokinetics

Whole-blood samples for plasma were collected at prescheduled time points for pharmacokinetic (PK) evaluation of patients treated in the phase I portion (at 30 minutes during 1-hour infusion, at end of 1-hour infusion, and post-AUY922 infusion on C1D1 at 5 minutes, 30 minutes, 1 hour, 2 hours, 4 hours, 5 hours, 24 hours, 48 hours, and 168 hours). AUY922 and its phenolic glucuronide metabolite BJP762 were analyzed for concentration in plasma using a validated liquid chromatography and tandem mass-spectrometry method. PK parameters were determined from the concentration-time data by noncompartmental analysis, including area under the plasma concentration time curve (AUC), maximum (peak) plasma drug concentration (C_{max}), and elimination half-life ($t_{1/2}$) for AUY922 and BJP762. Because blood concentrations of AUY922 and BJP762 were measured for PK assessment in the first-in-man phase I study for AUY922, the single-agent PK parameters in plasma were estimated based on PK modeling for comparison with those observed in our combination study.[22]

Response Assessments

All patients treated at MTD were evaluable for response assessment (using RECIST [version 1.1]) after 4 weeks, after 8 weeks, and then after every 8 weeks of study. The primary end point for the phase II trial was complete plus partial response rate. Secondary end points for the phase II trial included progression-free and overall survival for all patients and specifically for patients with *EGFR* T790M.

Statistical Analysis

Descriptive data are reported as frequencies, proportions, means, medians, and ranges. Survival analyses for progression-free and overall survival were performed using Kaplan-Meier methodology. Survival curves were compared between mutation status subgroups using the log-rank test. Response rates were calculated using exact binomial proportions and CIs. A Simon minimax design was used to test the response rate of 10% versus 30%, using 10% type I and II error rates, and determine the sample size (stage I, 16 patients [$\geq$ two responses needed to proceed to stage II]; stage II, nine patients). Five or more responses were required among the 25

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Table 2. Baseline Patient and Tumor Molecular Characteristics

Characteristic	All Patients (N = 37)		AUY922 (25 to 55 mg/m^2; n = 12)		AUY922 (70 mg/m^2; n = 25)*	
	No.	%	No.	%	No.	%
Female sex	27	73	9	75	18	72
Age, years						
Median	59		62		58	
Range	30-76		30-76		42-76	
Never-smoker	26	70	8	67	18	72
ECOG performance status						
0	14		5		9	
1	20		5		15	
2	3		2		1	
Race/ethnicity						
White	20		5		15	
Asian	13		5		8	
Black	4		2		2	
Primary *EGFR* mutation						
Exon 19 deletion	25		10		15	
Exon 21 L858R	11		2		9	
Exon 21 L861Q	1		0		1	
EGFR T790 mutation on repeat tumor biopsy	16	43	6	50	10	40
Prior lines of therapy, months						
Median	2		2		2	
Range	1-7		1-4		1-7	
Duration of EGFR TKI before developing AR, months						
Median	12		13		11	
Range	2-42		8-32		2-42	
Receiving any EGFR-directed therapy immediately before trial†	36		12†		24	
Receiving erlotinib monotherapy immediately before trial	22		10		11	
Newly diagnosed AR at enrollment	8		2		6	
T790 mutation in patients with newly diagnosed AR	5		2		3	
Patients with previously diagnosed AR	29		10		19	
T790 mutation in patients with previously diagnosed AR	12		5		7	

Abbreviations: AR, acquired resistance; ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor.
*Including six patients from phase I treated at maximum-tolerated dose.
†Erlotinib containing in every case except one patient treated with afatinib plus cetuximab.

evaluable patients (ie, objective response rate, 20%) to demonstrate the combination was worthy of further study.

RESULTS

Patients

Thirty-seven patients were enrolled. Eighteen patients received escalating doses of AUY922 IV once per week and erlotinib orally once per day in the phase I study. Twenty-five patients were treated at the MTD. The clinical characteristics of patients enrolled are listed in Table 2. All patients had advanced lung adenocarcinoma with known *EGFR* mutations (25 exon 19 deletions [68%], 11 exon 21 L858R [30%], and one L861Q [3%]). Patients had developed acquired resistance after treatment with EGFR TKIs for a median of 12 months (range, 2 to 42 months). The median number of prior therapies was two (range, one to seven; Fig 1). At trial enrollment, 43% of patients (16 of 37) harbored *EGFR* T790M.

Determining MTD

There were no DLTs among patients treated in cohorts one to four of the phase I study. At the highest dose level (cohort five), there was one DLT (grade 3 junctional rhythm secondary to prolongation of QTc), and three additional patients were enrolled onto this cohort to confirm MTD. All patients in the phase II expansion were treated with AUY922 70 mg/m^2 IV once per week and erlotinib 150 mg orally once per day.

PKs

Samples were collected from the 18 patients in the dose-escalation phase I portion of the study for PK analysis. The exposure (AUC and C_{max}) of AUY922 and metabolite BJP 762 increased with increasing doses of AUY922 and erlotinib. In general, with coadministration of erlotinib, the total exposure to AUY922 and BJP762 was comparable to that observed when AUY922 was administered as a single agent[22] (Table 3).

Patient Disposition

In the phase I portion of the study, patients received a median of two cycles of treatment (range, one to 11). Twelve patients (66%) discontinued AUY922 and erlotinib because of progressive disease, and four others (22%) for adverse events, discussed under Toxicity. Two patients withdrew consent: one after 11 cycles of treatment with

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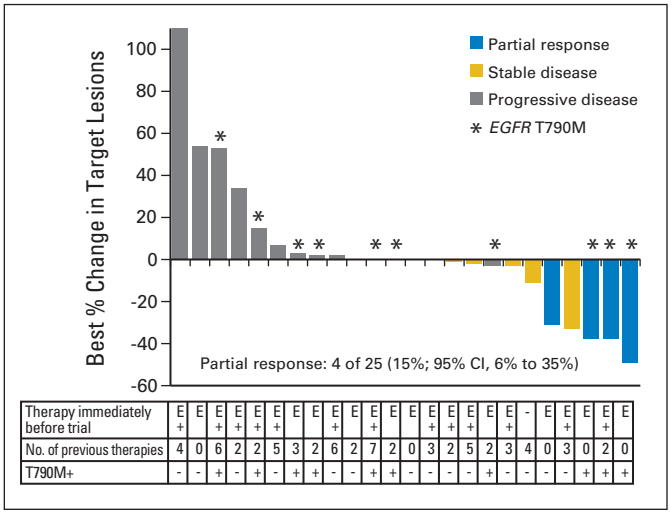

Fig 1. Best response to AUY922 and erlotinib. Maximum percentage change in measurable tumor target lesions using RECIST (version 1.1) at baseline and time of best response for patients treated with AUY922 and erlotinib at maximum-tolerated doses. One patient was removed for clinical progression during cycle one and was not included. Legend below waterfall plot notes number of lines of therapy each patient received, whether treatment immediately before trial was erlotinib (E), erlotinib in combination with chemotherapy (E+), or no therapy (−). (*) Patients with *EGFR* T790M.

minimal toxicity for personal reasons, and the other because of generalized drug intolerance.

In the phase II expansion, patients received a median of one cycle of AUY922 and erlotinib, although one patient remained on study for 18 months. Twelve patients (63%) discontinued therapy because of progressive disease, and four patients (21%) for adverse events, also discussed under Toxicity. Two patients withdrew consent: one after thromboembolic strokes, and the other with declining performance status (both disease related).

Toxicity

All 37 patients were evaluable for toxicity. All patients experienced at least one adverse event (Table 4). The most common drug-related adverse events that occurred among phase I patients were diarrhea, rash, nausea, and fatigue. Other than one patient who experienced a DLT, no other patients experienced cardiac adverse events. Three phase I patients discontinued therapy for grade 2 night blindness, reversible once AUY922 was suspended. Although common, diarrhea was tolerable (grades 1 and 2 only) and managed with loperamide.

The drug-related adverse events most frequently reported by patients in the phase II study were diarrhea, night blindness, and skin rash. Night blindness was reported in 72% of patients in the phase II study, mostly grade 1. Asymptomatic elevations in glucose (92%), AST/ALT (84%), and bilirubin (64%), as well as hypoalbuminemia (84%) and hyponatremia (68%), were frequently observed. Five patients experienced asymptomatic grade 3 lymphopenia. Four phase II patients discontinued study drugs because of toxicity: two patients with grade 3 AST/ALT abnormalities, one with grade 2 night blindness, and one with grade 3 diarrhea/colitis. There were no grade 4 or 5 toxicities.

Antitumor Activity

Twenty-five patients treated at the MTD were evaluable for complete plus partial response rate, the primary end point of the phase II trial. Four patients had a confirmed partial response (16% [four of 25]; 95% CI, 5% to 36%). Another 10 patients had stable disease (lasting ≥ 6 months in four patients). Responders remained on therapy for a median duration of 14 weeks (range, 8 to 77 weeks). The maximum

Table 3. Summary of PK Parameters for Plasma AUY922 and Metabolite BJP762 When Combined With Erlotinib Compared With Parameters AUY922 Alone by Dose Cohort

	Dose (mg/m^2)															
	25				40				55				70			
	A Plus E (n = 3)		A (n = 8)*		A Plus E (n = 3)		A (n = 16)*		A Plus E (n = 3)		A (n = 18)*		A Plus E (n = 6)		A (n = 28)*	
Parameter	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
AUY922																
AUC_{last}, h × ng/mL	849	342	888	488	1,359	437	1,027	248	2,498	1,258	1,726	702	2,354	644	1,947	211
AUC_{inf}, h × ng/mL	885	346	973	483	1,426	439	1,146	312	2,589	1,271	1,808	706	2,453	694	2,041	224
C_{max}, ng/mL	577	352	547	160	824	323	672	45	1,093	276	1,047	484	1,531	568	1,128	248
$T_{1/2}$, h	58	21	23	5	52	20	57	35	63	38	43	20	64	32	42	27
Cl, L/h/m^2	36	13	30	10	31	9	37	11	25	11	35	17	31	11	35	4
VZ, L/m^2	3,053	1,524	998	451	2,254	1,012	2,703	1,346	2,357	1,475	1,857	189	2,743	1,301	2,036	1,277
BJP762																
AUC_{last}, h × ng/mL	5,390	7,145	2,654	1,108	11,494	8,917	7,276	7,151	12,093	8,368	4,968	2,943	14,533	15,433	10,411	5,520
AUC_{inf}, h × ng/mL	5,525	7,177	2,716	1,112	12,008	9,161	7,488	7,292	12,552	8,648	5,067	2,938	15,349	15,897	10,597	5,626
C_{max}, ng/mL	1,051	702	627	249	1,893	1,238	1,617	993	2,616	1,469	1,227	654	2,934	2,001	2,454	1,551
$T_{1/2}$, h	23	9	28	8	38	17	33	15	46	21	31	7	40	33	33	5

Abbreviations: A, AUY922; AUC, area under the plasma concentration time curve; C_{max}, maximum (peak) plasma drug concentration; E, erlotinib; PK, pharmacokinetic; SD, standard deviation; t1/2, half-life; VZ, volume of distribution.
*Single-agent PKs measured at 28, 40, 54, and 70 mg/m^2.[22]

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Table 4. Most Frequent Drug-Related Adverse Events by Dose of AUY922

Adverse Event	25 to 55 mg/m^2 (n = 12)			70 mg/m^2 (n = 25)*			Total Incidence (N = 37)
	Grade 1	Grade 2	Grade 3†	Grade 1	Grade 2	Grade 3†	
Diarrhea	8	3	0	14	6	4	35
Skin rash	9	0	0	16	0	0	25
Hyperglycemia	0	0	0	18	5	0	23
Night blindness	3	0	0	14	4	0	21
Hypoalbuminemia	0	0	0	18	3	0	21
Fatigue	6	1	1	4	7	0	19
Elevated AST	1	0	0	14	1	2	18
Nausea	7	1	0	9	0	0	17
Hyponatremia	0	0	0	16	0	1	17
Elevated bilirubin	0	0	0	12	3	1	16
Elevated ALT	0	0	0	9	3	2	14
Myalgias/arthralgias	4	1	0	5	4	0	14
Visual complaints‡	4	0	0	10	0	0	14
Vomiting	3	1	0	8	0	0	12
Elevated ALP	0	0	0	6	4	0	10
Decreased leukocytes	0	0	0	4	5	1	10
Hypokalemia	0	0	0	9	1	0	10
Pruritis/dry skin	4	0	0	5	0	0	9
Hypocalcemia	0	0	0	6	2	0	8
Anemia	2	0	0	3	0	1	6
Mucositis	0	0	0	5	1	0	6
Decreased lymphocytes	0	0	0	1	0	5	6
Decreased platelets	0	0	0	6	0	0	6
Hypomagnesemia	0	0	0	6	0	0	6
Decreased neutrophils	0	0	0	0	5	0	5

*Including six patients from phase I treated at maximum-tolerated dose.
†No grade 4 toxicities.
‡Flashing lights, floaters, or dry eyes.

percent change in radiographic assessment of tumor target lesions is shown in Figure 1.

DISCUSSION

In this combination-drug trial, we established the MTD of AUY922 and erlotinib for patients with *EGFR*-mutant lung cancer with acquired resistance and report a partial response rate of 16%, one patient short of meeting the primary end point of the trial. Preliminary results from a large trial evaluating single-agent AUY922 in patients with advanced lung cancer, including a cohort with *EGFR* mutations, reported a similar objective response rate of 12 of 66 patients (18%; 95% CI, 11 to 29).[25,26] Contrary to our hypothesis, the addition of erlotinib did not improve response rates for patients with *EGFR*-driven tumors.

Patient responses were observed regardless of *EGFR* T790M status (Fig 1). Whether the primary *EGFR* mutation was exon 19 deletion or L858R likewise did not correlate with response. Three patients with partial responses had primary *EGFR* exon 19 and T790M. However, the patient who received 18 months of AUY922 and erlotinib had a tumor harboring *EGFR* L858R, without a T790M resistance mutation. Whether this patient's response can be attributed to inhibition of EGFR specifically, or whether it was the result of HSP90 inhibition of other client proteins (eg, MET, human epidermal growth factor receptor 2, or AKT[20]) is uncertain.

Two other HSP 90 inhibitors (retaspimycin and ganetespib) have been evaluated in patients with advanced lung cancer, including patients with *EGFR* mutations previously treated with EGFR TKIs. Sequist et al[31] reported that patients with *EGFR* mutations treated with single-agent retaspimycin had a response rate of 4% (one of 28 patients). No objective responses (zero of 15 patients) were observed among those with *EGFR*-mutant lung cancer treated with single-agent ganetespib.[32] Patients in both trials had discontinued EGFR TKIs before starting investigational HSP90 inhibitors. Despite combining erlotinib with AUY922 in this trial, the majority of patients (15 of 25) still developed progressive disease, many within one or two cycles.

In the single-agent phase I AUY922 trial, DLTs included diarrhea, asthenia/fatigue, anorexia, atrial flutter, and visual symptoms.[22] QTc prolongation was noted in 23% of patients, but it was never dose limiting.[22] Limited single-agent phase II data have been reported; diarrhea, nausea, decreased appetite, and eye disorders were most common, largely grades 1 and 2.[25,26] Notably absent from the single-agent AUY922 data are reports of hepatotoxicity or AST/ALT abnormalities, which derailed the development of earlier geldanamycin-based analogs.[22] Although the PK parameters (C_{max} and AUC) of patients treated with erlotinib and AUY922 showed similar drug exposure compared with single-agent pharmacokinetic data, we observed that the adverse effects of AUY922 were intensified with the addition of erlotinib. Seven patients were removed from the study with AUY922-related toxicities. Three patients treated at the MTD withdrew from the study for ophthalmologic toxicities (night blindness or visual disturbances). Two other patients discontinued therapy with AST/ALT elevations, and one did so with a junctional

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cardiac rhythm. One patient withdrew after developing bloody diarrhea with colonic ulcerations. Ophthalmologic toxicities of any sort (blurred vision, flashing lights, floaters, night blindness, or nonspecific visual changes) were reported in 60% of patients. Although eye disorders were reported in a similar frequency of patients (77% [93 of 121]) in the single-agent AUY922 trial, our study represents the first report to our knowledge of night blindness at a dose lower than AUY922 40 mg/m^2.[22,25,26] By contrast, AST/ALT abnormalities were reported in 65% of patients in our combination study but were not reported in the single-agent AUY922 experience.[22,25,26]

Ophthalmologic toxicities have been associated with many different HSP90 inhibitors.[22] Ophthalmologic symptoms (eg, blurry vision, night blindness or nyctalopia, and flashing lights) are caused by HSP90 inhibitor–mediated damage of the retinal pigment epithelial cells and adjacent photoreceptors.[33] Although ophthalmologic toxicity has been deemed a class effect, further investigation across HSP90 compounds has suggested that hydrophilic agents (including AUY922) result in more sustained retinal exposure, slower elimination, and therefore more pronounced retinal/photoreceptor toxicity,[34] whereas hydrophobic HSP90 compounds result in far less retinal exposure or toxicity.[35] Ongoing trials evaluating single-agent AUY922 and increased experience with newer HSP90 inhibitors may therefore circumvent the ophthalmologic effects, which were so apparent in our trial.[36]

Limitations to our study include the heterogeneity of patients with acquired resistance enrolled. Any number of past therapies was allowed, and the treatments patients received immediately before trial enrollment varied. Only eight patients had developed acquired resistance just before trial enrollment, including three of the patients with partial responses to treatment, which suggests that AUY922 may be more effective for patients earlier in their disease course whose tumors are still largely dependent on EGFR signaling. However, because the majority of patients (n = 29) had instead received multiple prior therapies (including EGFR-targeted and cytotoxic chemotherapies), our study may have included a disproportionate number of patients with indolent disease, in whom many sequential treatments are possible, as well as patients whose tumors had developed resistance pathways independent of *EGFR*. We believe this explains the large number of patients with stable disease, as shown in Figure 1, along with the fact that patients' first imaging assessment was at 4 weeks, which may have been too early to capture patients destined to progress by 8 or 16 weeks.

Finally, the proportions of patients with *EGFR* exon 19 deletions (68%; 95% CI, 53% to 83%) and L858R substitutions (30%; 95% CI, 15% to 45%) varied slightly from the frequencies expected in a newly diagnosed cohort of patients with *EGFR*-mutant disease (exon 19 deletion, 50%; L858R, 45%).[37] The frequencies we report are similar to those reported for another single-arm phase II trial also enrolling only patients with acquired resistance, treated with afatinib and cetuximab (exon 19 deletion, 62%; 95% CI, 53% to 69%; L858R, 33%; 95% CI, 25% to 41%).[38] Because patients with tumors harboring *EGFR* exon 19 deletions may have improved outcomes compared with patients with L858R substitutions,[39-42] one final caveat to our results is that they may be mildly inflated because of the slight overrepresentation of patients with tumors with exon 19 deletions.

In summary, despite a promising preclinical rationale, patients tolerated the combination with more toxicities than expected and with a limited efficacy similar to that in studies evaluating single-agent AUY922. No additional studies testing this combination are planned.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at www.jco.org.

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Data analysis and interpretation: All authors
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Final approval of manuscript: All authors

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GLOSSARY TERMS

BRAF: an isoform of *RAF*. See *Raf*.

epidermal growth factor receptor (EGFR): a member of a family of receptors (HER2, HER3, HER4 are other members of the family) that binds to the EGF, TGF-α, and other related proteins, leading to the generation of proliferative and survival signals within the cell. EGFR (also known as HER1) also belongs to the larger family of tyrosine kinase receptors and is generally overexpressed in several solid tumors of epithelial origin.

epithelial to mesenchymal transition (EMT): cellular changes that occur in epithelial cells to loss epithelial cell junction proteins and to gain mesenchymal phenotypes by expressing proteins such as vimentin and fibronectin.

erlotinib: also known as Tarceva (Genentech, South San Francisco, CA). Erlotinib is a small molecule that inhibits the tyrosine kinase activity of epidermal growth factor receptor/HER1 and has been evaluated extensively in clinical trials in patients with non–small-cell lung cancer, pancreatic cancer, and glioblastoma multiforme.

HSP90: a member of the family of heat shock proteins. HSP90 is important for cellular viability and acts as a molecular chaperone for other proteins by forming multimolecular complexes. These complexes are important regulatory elements in the fate of proteins, which include refolding of denatured proteins, intracellular transport of proteins, and preventing protein unfolding and aggregation. Although heat shock proteins are usually produced in response to stress (eg, heat, nutrient deprivation), HSP90 is typically expressed at high levels even under nonstress conditions.

MET: the receptor for hepatocyte growth factor. MET is a transmembrane receptor tyrosine kinase. The primary single chain precursor protein is post-translationally cleaved to produce the alpha and beta subunits; the mature receptor is composed of these subunits linked via disulfide bonds. Various mutations in the *MET* gene have been associated with papillary renal carcinoma.

PIK3CA: the catalytic subunit of phosphatidylinositol 3-kinase involved in the generation of PIP3 which, in turn, leads to the activation of AKT and other oncogenic kinases. Mutations in the *PIK3CA* gene have been found in several cancers, including ovarian, breast, colon, and lung carcinomas. See *PI3K* and *AKT/PKB*.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Phase I/II Study of HSP90 Inhibitor AUY922 and Erlotinib for *EGFR*-Mutant Lung Cancer With Acquired Resistance to Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitors

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