Phase II activity of the HSP90 inhibitor AUY922 in patients with ALK-rearranged (ALK+) or EGFR-mutated advanced non-small cell lung cancer (NSCLC)

E. Felip,[1] E. Carcereny,[2] F. Barlesi,[3] L. Gandhi,[4] L. Sequist,[5] S-W. Kim,[6] H. J. M. Groen,[7] B. Besse,[8] D-W. Kim,[9] E. Smit,[10] M. Akimov,[11] E. Avsar,[12] S. Pain,[11] W. Ofosu-Appiah[12] and E. B. Garon[13]

1. Vall d'Hebron University Hospital, Barcelona, Spain; 2 Catalan Institute of Oncology, Badalona, Spain; 3. Aix Marseille University, Marseille, France; 4. Dana-Farber Cancer Institute, Boston, MA; 5. Massachusetts General Hospital, Boston, MA; 6. Asan Medical Center, Seoul, South Korea; 7. University Medical Center Groningen, Groningen, Netherlands; 8. Institut Gustav Rossy, Villejuif, France; 9. Seoul National University Hospital, Seoul, South Korea; 10. Vrije Universiteit Medical Centre, Amsterdam, Netherlands; 11. Novartis Pharma AG, Basel; 12. Novartis Pharmaceuticals Corporation, East Hanover, NJ; 13. David Geffen School of Medicine at UCLA, Los Angeles, CA.

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Disclosures

- B Besse, E Carcereny, E Felip, L Gandhi, D-W Kim, S-W Kim, and E Smit have no disclosures to declare
- L Sequist is a paid consultant for Celgene, Clovis, and GSK, and an unpaid consultant for Daiichi Sankyo and Merrimack
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Background

- HSP90 is a chaperone of client proteins relevant in NSCLC pathogenesis, including ALK and EGFR
- Oncogenic fusion genes giving constitutive ALK activity occur in 5–7% of unselected NSCLCs,[1] and *EGFR* gene mutation occurs in 10–17% of cases[1]
- AUY922 is a highly potent, non-geldanamycin HSP90 inhibitor, which competitively inhibits the ATPase activity of HSP90
- AUY922 is effective against most NSCLC cell lines *in vitro*,[2,3] and against NSCLC xenograft models with either *T790M* mutation or *EML4-ALK* translocation[4]

ALK, anaplastic lymphoma kinase; EGFR, epidermal growth factor receptor; HSP90, heat-shock protein 90; NSCLC, non-small cell lung cancer.

1. Janku F, *et al. Nat Rev Clin Oncol* 2010;7:401–414; 2. Ueno T, *et al. Lung Cancer* 2011;76:26–31; 3. Eccles SA, *et al. Cancer Res* 2008;68:2850–2860; 4. Novartis data on file.

Study Design

NCT01124864

Phase II Study Population

- ► Previously treated stage IIIb or IV NSCLC
- ► ≥2 lines of chemotherapy
- ► Prior EGFR TKI therapy if *EGFR* is mutated
- ► WHO PS ≤2

AUY922 70 mg/m^2	AUY922 70 mg/m^2	AUY922 70 mg/m^2	AUY922 70 mg/m^2
KRAS-activating mutation	**EGFR-activating mutation**	**EGFR/KRAS/ALK wild type**	**ALK+**
n=28	**n=35**	**n=33**	**n=22**

Bayesian design:
Primary endpoint – efficacy classified as 3 categories (mutually exclusive):
1. Response (CR or PR) or 2. SD at 18 weeks or 3. No clinical benefit (NCB)
Secondary endpoints – efficacy (OS, or PFS) and PK, safety/tolerability

Null hypothesis (no efficacy): response ≤5%, and NCB ≥85%
Alternative hypothesis (efficacious): response ≥10% (≥20% for ALK+ arm), or NCB ≤60% (≤40% for ALK+ arm)

CR, complete response; OS, overall survival; PFS, progression-free survival; PK, pharmacokinetics; PR, partial response; SD, stable disease; TKI, tyrosine kinase inhibitor; WHO PS, World Health Organization performance status.

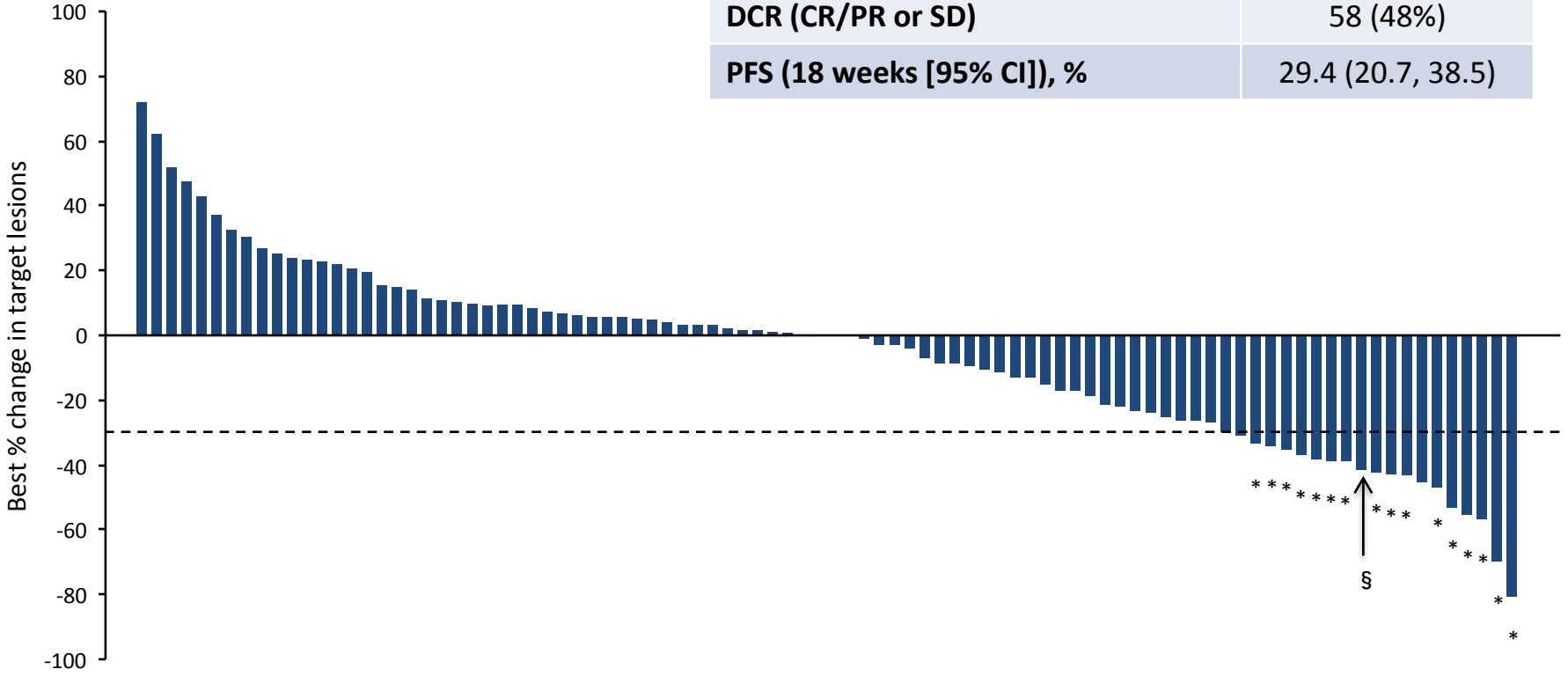
Results: Patient Demographics and Disease Characteristics

Demographic or characteristic	*KRAS*-mut (n=28)	*EGFR*-mut (n=35)	*EGFR*/*KRAS*/ *ALK* wt (n=33)	ALK+ (n=22)	All* (N=121)
Age (median), years	60	63	63	53	60
Sex (male), %	17 (61)	10 (29)	15 (45)	7 (32)	52 (43)
WHO PS					
0	10 (36)	13 (37)	10 (30)	9 (41)	43 (36)
1	18 (64)	19 (54)	20 (61)	11 (50)	70 (58)
2	0 (0)	3 (9)	3 (9)	2 (9)	8 (7)
Histology					
Adenocarcinoma	23 (82)	32 (91)	27 (82)	20 (91)	105 (87)
Squamous cell carcinoma	1 (4)	0 (0)	2 (6)	0 (0)	3 (2)
Other	4 (14)	3 (9)	4 (12)	2 (9)	13 (11)
Prior regimens					
1	1 (4)	3 (9)	0 (0)	1 (5)	5 (4)
2	8 (29)	13 (37)	16 (48)	5 (23)	42 (35)
3	14 (50)	11 (31)	4 (12)	7 (32)	38 (31)
≥4	5 (18)	8 (23)	13 (39)	9 (41)	36 (30)
Prior ALK inhibitor (crizotinib)	NA	NA	NA	14 (64)	NA
Prior EGFR TKI	NA	34 (97)	NA	NA	NA
Erlotinib		30 (86)			
Gefitinib		4 (11)			
None		1 (3)			

*Includes unknown genotype patients (n=3; stratum not listed); NA, not applicable; wt, wild type.

Best CT Response: All Patients (n=92†/121)

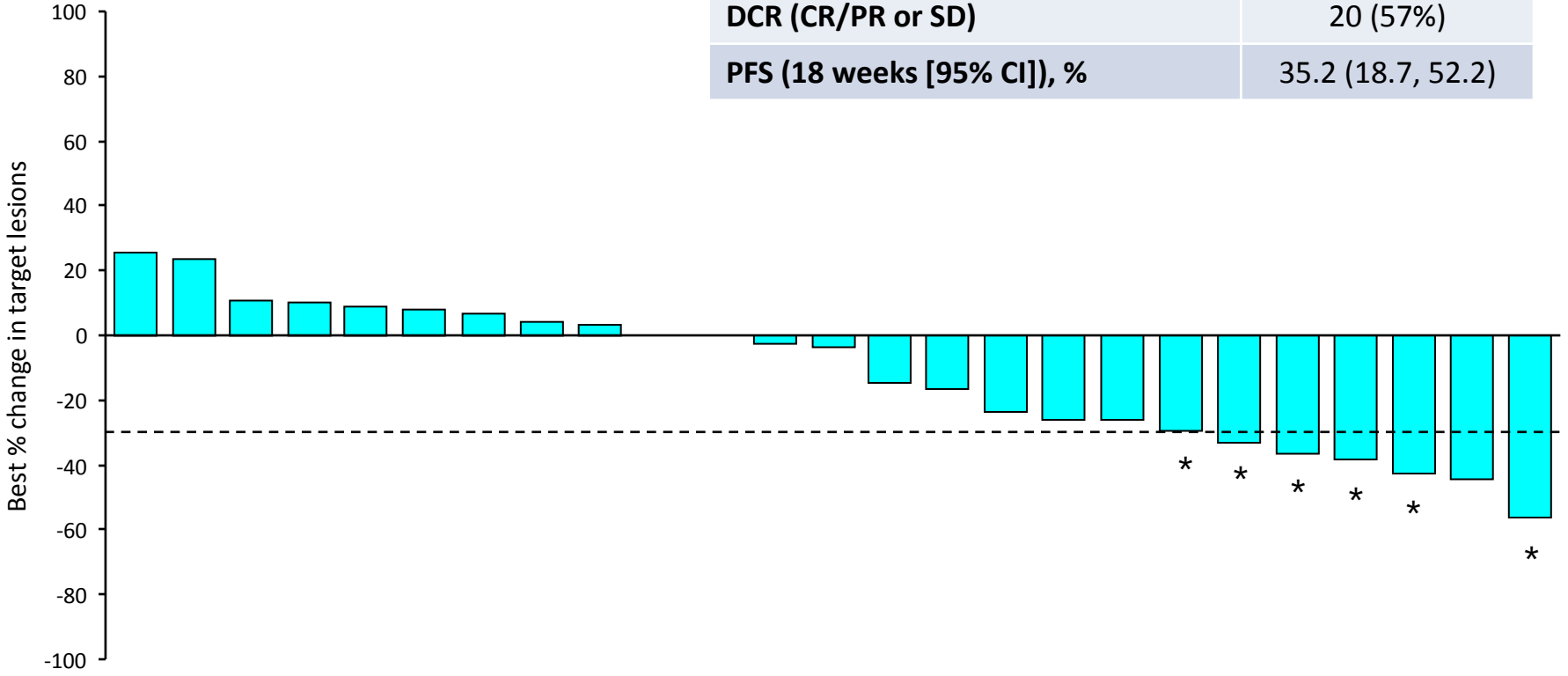
All patients (N=121)	
ORR (any PR)	19 (16%)‡
DCR (CR/PR or SD)	58 (48%)
PFS (18 weeks [95% CI]), %	29.4 (20.7, 38.5)



*Confirmed responses; †Patients with at least one post-baseline scan;
‡Including two PRs not confirmed; § PD due to new lesion (brain metastases).
CT, computed tomography; DCR, disease control rate;
ORR, overall response rate.

Best CT Response: *EGFR*-mutant Patients (n=25†/35)

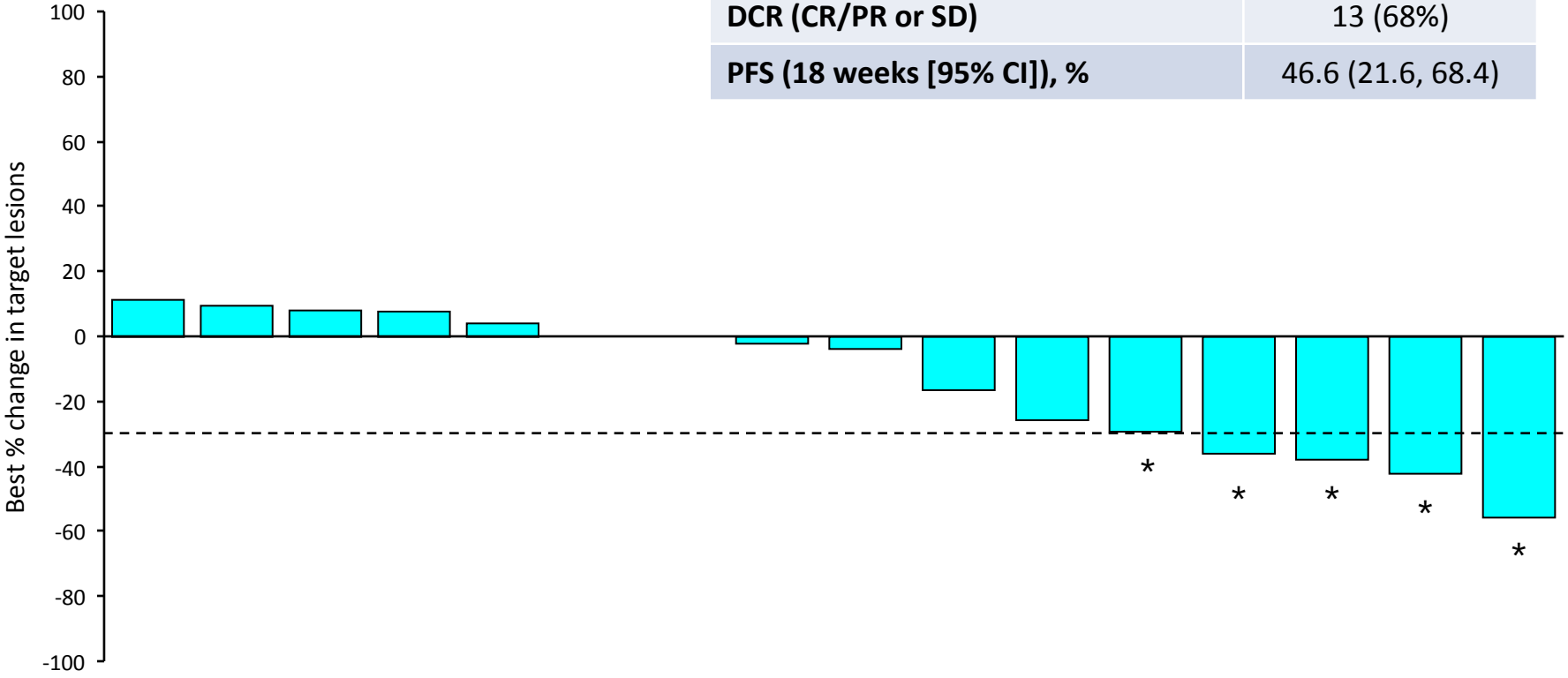
EGFR-mutant (n=35)	
ORR (any PR)	7 (20%)‡
DCR (CR/PR or SD)	20 (57%)
PFS (18 weeks [95% CI]), %	35.2 (18.7, 52.2)



*Confirmed responses; †Patients with at least one post-baseline scan;
‡Including one PR not confirmed.

Best CT Response: *EGFR*-mutant Patients with EGFR TKI as Part of Their Last Regimen (n= 16†/19)

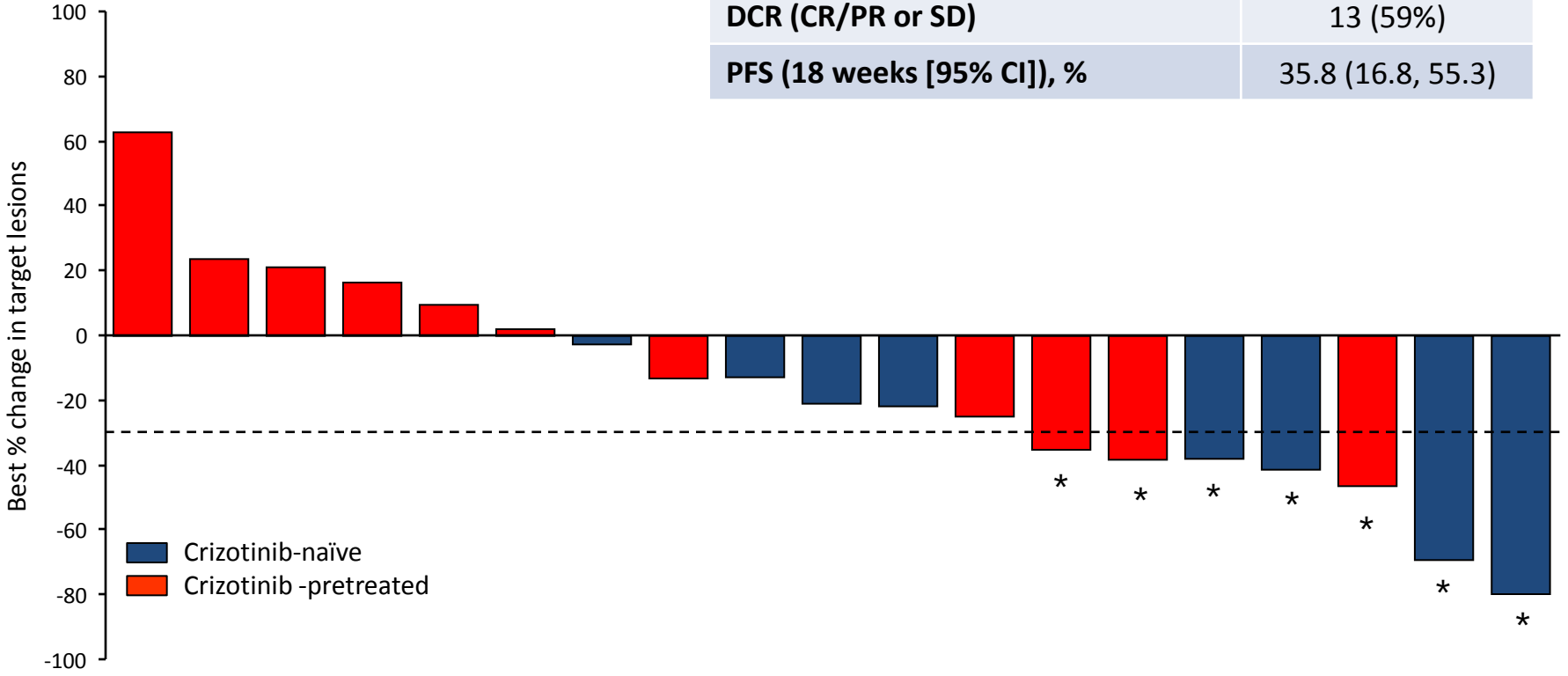
EGFR-mutant with TKI as part of last regimen (n=19)	
ORR (any PR)	5 (26%)
DCR (CR/PR or SD)	13 (68%)
PFS (18 weeks [95% CI]), %	46.6 (21.6, 68.4)



*Confirmed responses; †Patients with at least one post-baseline scan.

Best CT Response: ALK+ Stratum Patients (n=19†/22)

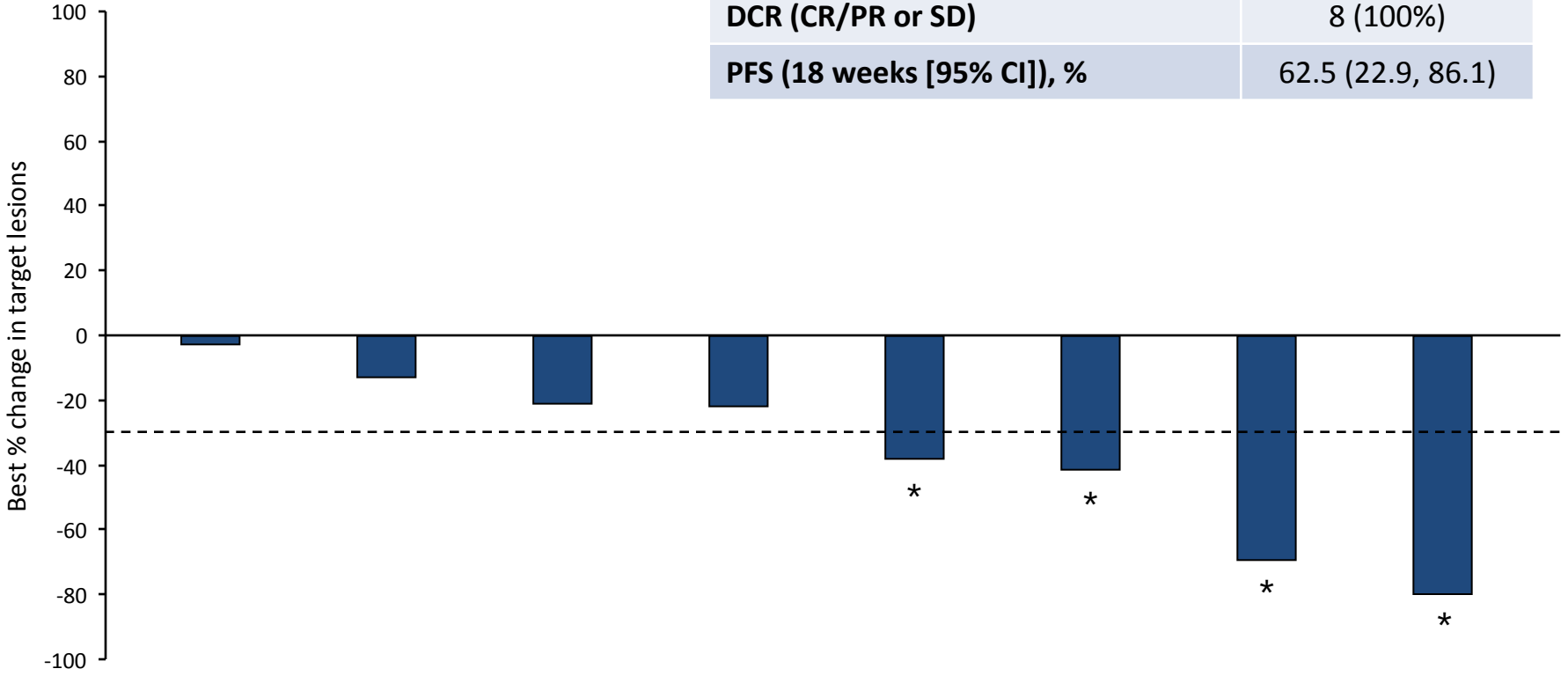
ALK+ (n=22)	
ORR (any PR)	7 (32%)
DCR (CR/PR or SD)	13 (59%)
PFS (18 weeks [95% CI]), %	35.8 (16.8, 55.3)



*Confirmed responses; †Patients with at least one post-baseline scan.

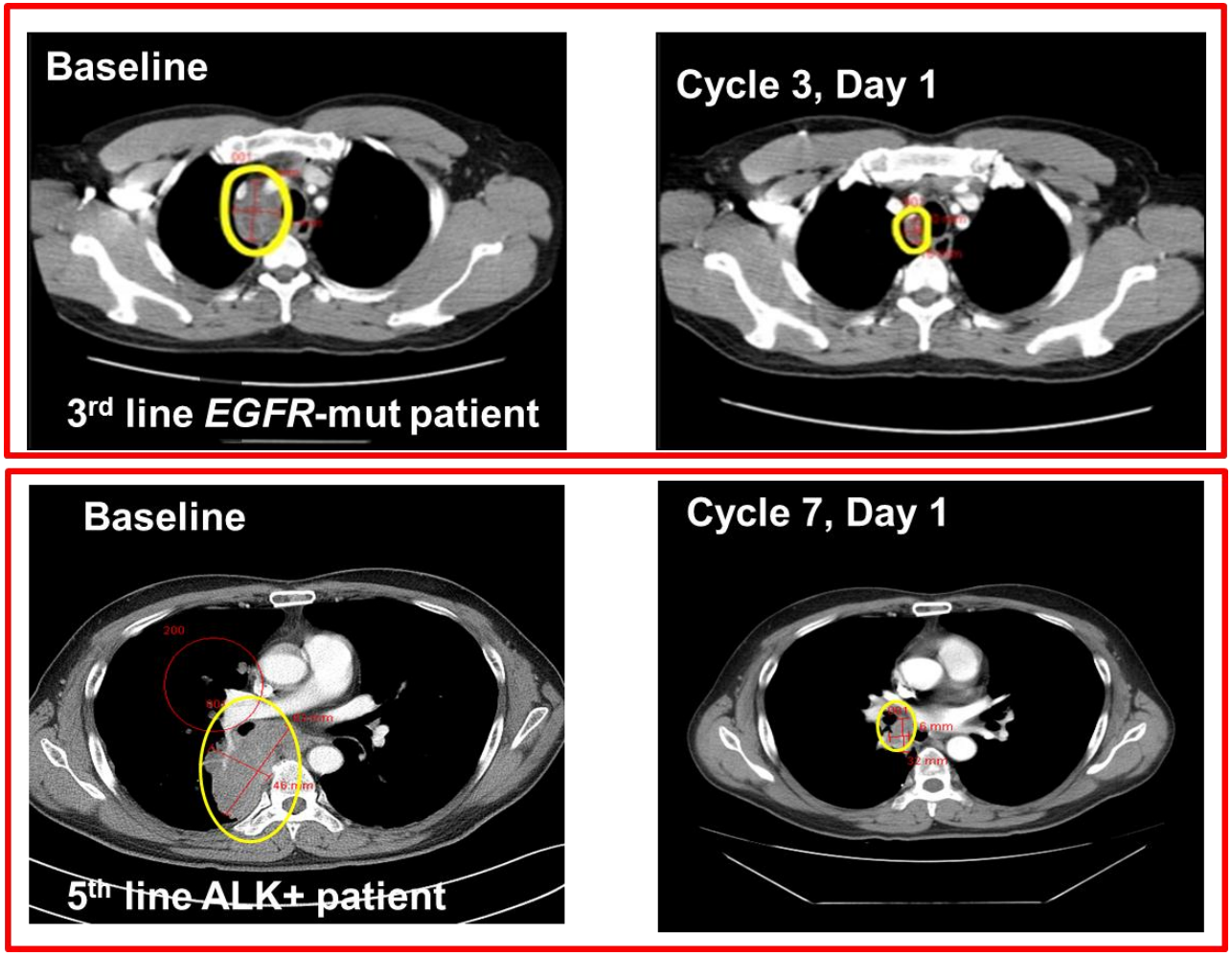
Best CT Response: ALK+ Patients Crizotinib-naïve n=8†/8

ALK+ (crizotinib-naïve, n=8)	
ORR (any PR)	4 (50%)
DCR (CR/PR or SD)	8 (100%)
PFS (18 weeks [95% CI]), %	62.5 (22.9, 86.1)



*Confirmed responses; †Patients with at least one post-baseline scan.

Responses in *EGFR*-mutant and ALK+ NSCLC



Images presented at ASCO 2012 (Garon EB, *et al. J Clin Oncol* 2012;30(suppl):abstr 7543)

Adverse Events (All Grades, >10% and Grade 3/4) Suspected as Study Drug-Related

Adverse event (AE, all grades)	All grades (N=121)	Grade 3 and 4 (N=121)
Eye disorders*	89 (74)	8 (7)
Diarrhea	82 (68)	7 (6)
Nausea	47 (39)	0 (0)
Asthenia	35 (29)	4 (3)
Vomiting	31 (26)	2 (2)
Fatigue	25 (21)	5 (4)

AEs by preferred term unless otherwise indicated
*System organ class

- Most AEs were Grade 1 or 2
  - Reversible mainly Grade 1 and 2 eye disorders were most commonly photopsia and visual impairment (both 20%)

Conclusions

- AUY922 70 mg/m^2 IV once weekly exhibited an acceptable safety profile
  - No new safety signals were observed
- AUY922 showed strong clinical activity as a single-agent therapy in patients with *EGFR*-mutated NSCLC who progressed following treatment with EGFR TKIs
- AUY922 also showed strong clinical activity as a single-agent therapy in patients with ALK+ NSCLC, both in crizotinib-treated and crizotinib-naïve patients
- Data support further AUY922 development in NSCLC
  - Expansion *EGFR* mutation stratum is ongoing and further studies are planned to confirm these efficacy signals

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Back-Up Slides

Patients and Methods: Trial Design

- The trial followed a Phase II Bayesian, partially exchangeable, multinomial model for the statistical analysis of the study, allowing sharing of information between strata based on assessing similarity in observed response data
- Observed outcomes for each strata are assumed to be derived from multinomial distributions whose parameters are dependent on a regression structure with additional random effects
- The regression structure exploits the fact that a number of study strata are considered a priori to be exchangeable
- Primary endpoint comprises 3 categories (complete and mutually exclusive)
  1. Response versus non-response
  2. Non-response: prolonged stable disease (18 weeks)
  3. Non-response: no clinical benefit
- Secondary endpoints include overall survival (OS), progression-free survival (PFS), PK, and safety/tolerability

Summary of Responses in Other Strata

	KRAS-mut (n=28)	*KRAS*/*EGFR*/*ALK* wt (n=33)
ORR (any PR)	0 (0)	4 (12)
DCR	10 (36)	14 (42)
PFS (18 weeks [95% CI]), %	8.2 (0.7, 28.4)	30.7 (15.1, 47.8)