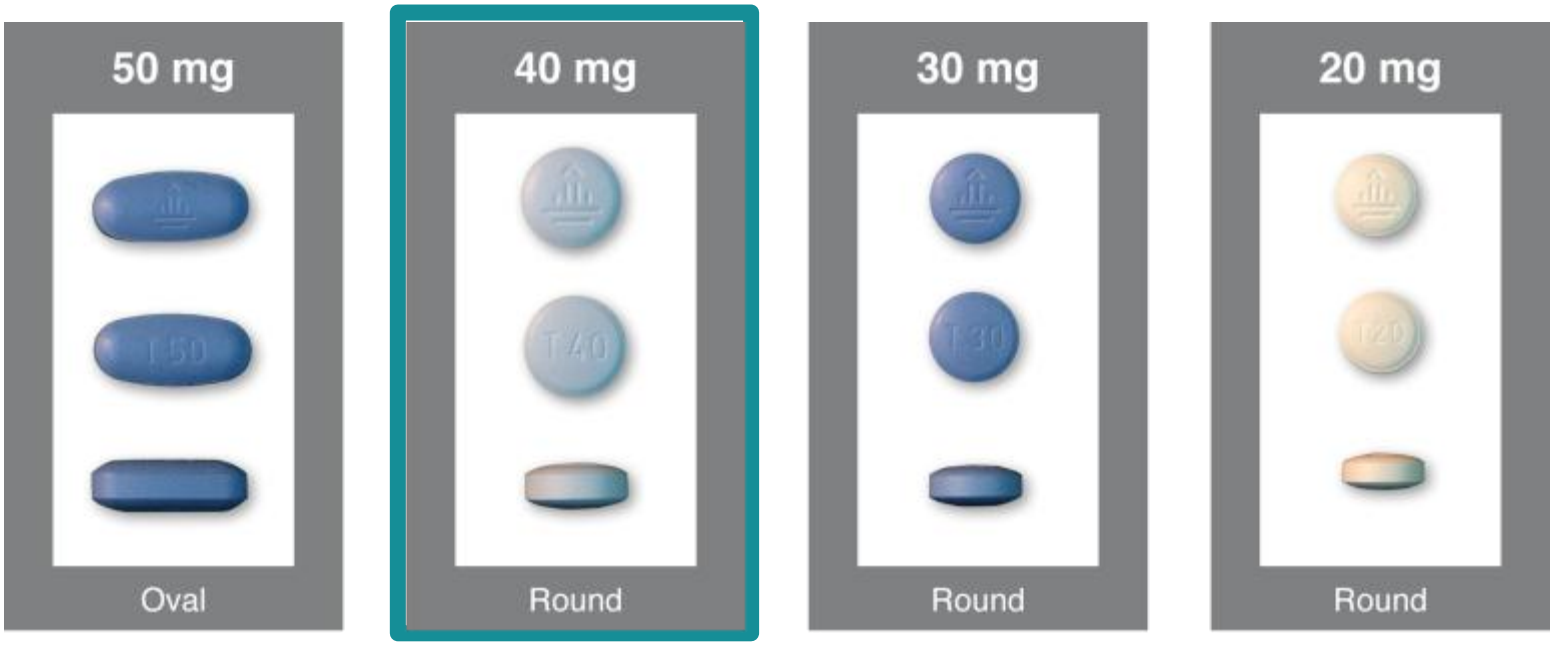
Influence of Dose Adjustment on Afatinib Safety and Efficacy in Patients with Advanced *EGFR* Mutation-positive NSCLC

Afatinib Dosing and Administration

- Standard dosing: 40 mg once daily
- Administration: orally (film-coated tablets)



Dose Modification Scheme for Afatinib in the Protocol

Continue with 50 mg/d Dose

- **Absence of** drug-related events >CTCAE grade 1 within first 3 weeks of treatment

Standard Dose of 40 mg/d

- Grade ≥3 adverse events
- Prolonged grade 2 (≥7 consecutive days)
- **Diarrhoea** grade 2 >48 hours despite optimal care
- Worsening of **renal function** grade 2

PAUSE until recovery to grade ≤1 or baseline

Resume treatment at dose **REDUCED** by 10 mg

Giotrif SmPC

Influence of Dose Adjustment on Afatinib Safety and Efficacy - Post-hoc Analyses of LUX-Lung 3

- All patients treated with afatinib in LUX-Lung 3 were included in the analyses
- For patients who had afatinib dose reductions, frequency and severity of the most common AEs pre- and post-dose reduction from 40 mg were analyzed
- PK data collected at Day 22 and as part of the final standard visit schedule (Day 43) were used to compare plasma afatinib concentrations in patients who reduced to 30 mg versus those remaining at 40 mg
- PFS (at time of primary PFS analysis) was compared between patients who dose reduced within the first 6 months of treatment and those who remained on afatinib 40 mg once daily A cut-off of 6 months was used as most dose reductions occur during this time

Yang J et al. J Clin Oncol 33, 2015 (suppl; abstr 8073)

Patient Characteristics at Baseline

- 53% patients treated with afatinib reduced dose
- 86% dose reductions occurred within the first 6 months of treatment
- Dose reductions tended to be more common in:
  - female patients,
  - older patients,
  - patients of Eastern Asian ethnicity and
  - patients with lower body weight

Characteristic	Dose reduced to <40 mg at any time (n=122)	Dose at ≥40 mg throughout (n=107)
Gender		
Male	31 (25.4)	51 (47.7)
Female	91 (74.6)	56 (52.3)
Age		
<65 years	65 (53.3)	74 (69.2)
≥65 years	57 (46.7)	33 (30.8)
Race		
Caucasian	23 (18.9)	38 (35.5)
Eastern Asian	98 (80.3)	66 (61.7)
Other	1 (0.8)	2 (1.9)
Other Asian	0 (0.0)	1 (0.9)
Smoking status		
Never smoked	87 (71.3)	67 (62.6)
Ex-smoker	34 (27.9)	36 (33.6)
Currently smokes	1 (0.8)	4 (3.7)
Weight category		
<50 kg	31 (25.4)	14 (13.1)
≥50 kg	91 (74.6)	93 (86.9)
ECOG PS		
0	48 (39.3)	44 (41.1)
1	74 (60.7)	63 (58.9)

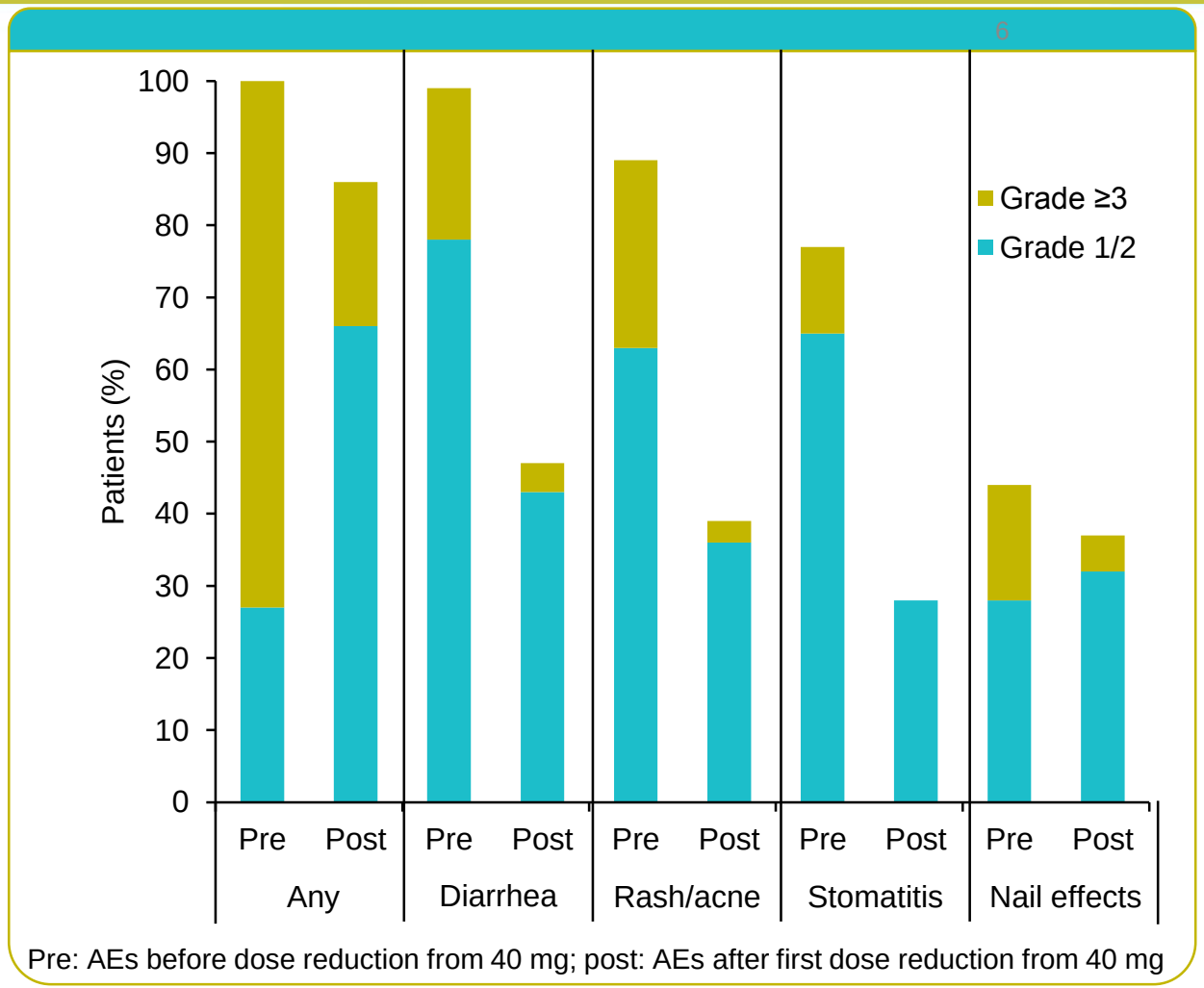
Data are n (%)

Yang J et al. J Clin Oncol 33, 2015 (suppl; abstr 8073)

Key Treatment-related AEs in Patients Requiring Tolerability-guided Dose Modification

Median treatment exposure for dose-reduced patients:

- 48.5 days on 40 mg (n=122),
- 140 days on 30 mg (n=120),
- 276.5 days on 20 mg (n=40)



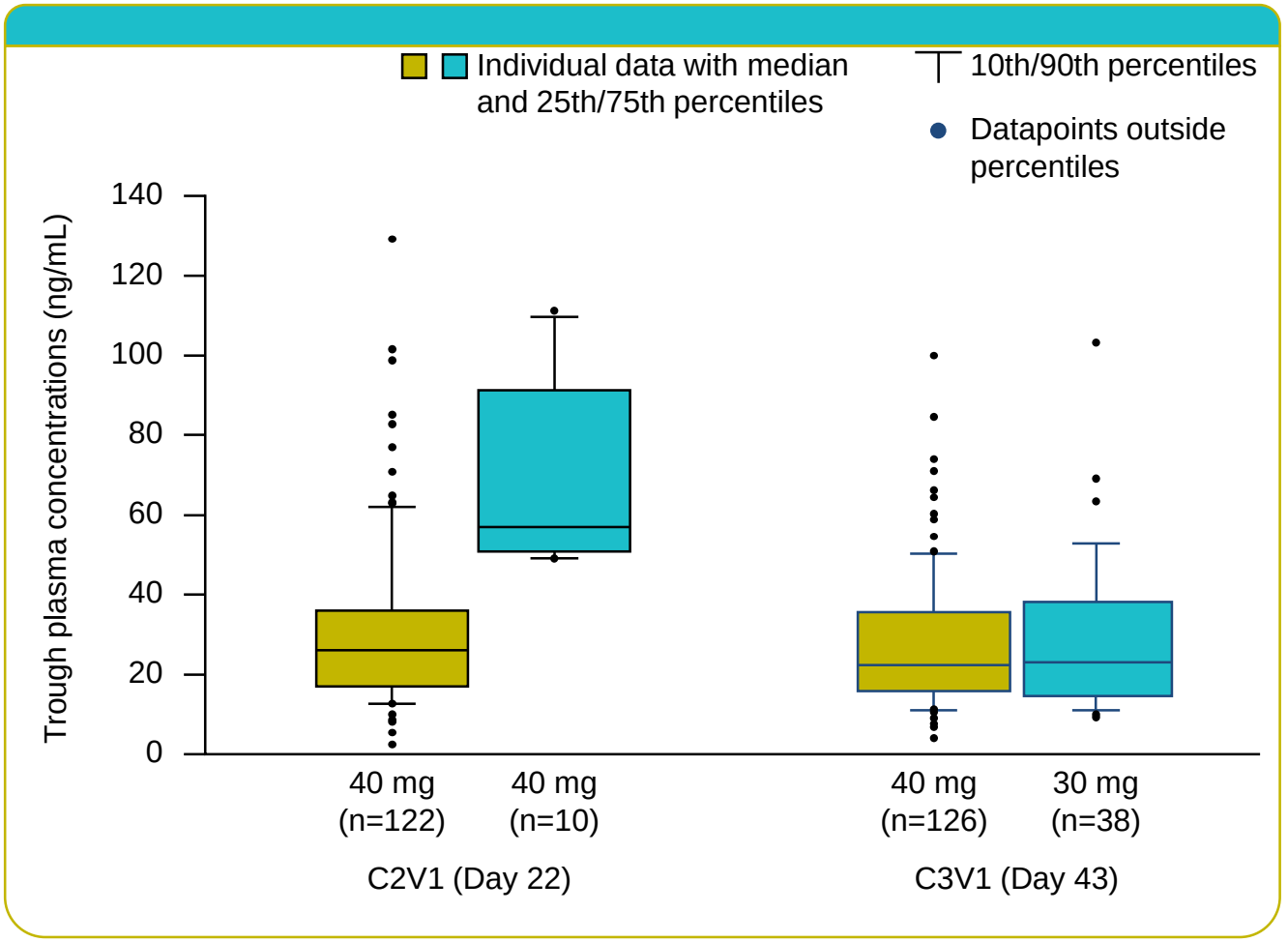
Pre: AEs before dose reduction from 40 mg; post: AEs after first dose reduction from 40 mg

Despite longer treatment exposure at lower doses, tolerability-guided dose reduction led to decreases in the incidence and severity of treatment-related AEs.

Yang J et al. J Clin Oncol 33, 2015 (suppl; abstr 8073)

Afatinib Plasma Levels in Patients Who Dose Reduced and Those Who Remained on Afatinib 40 mg

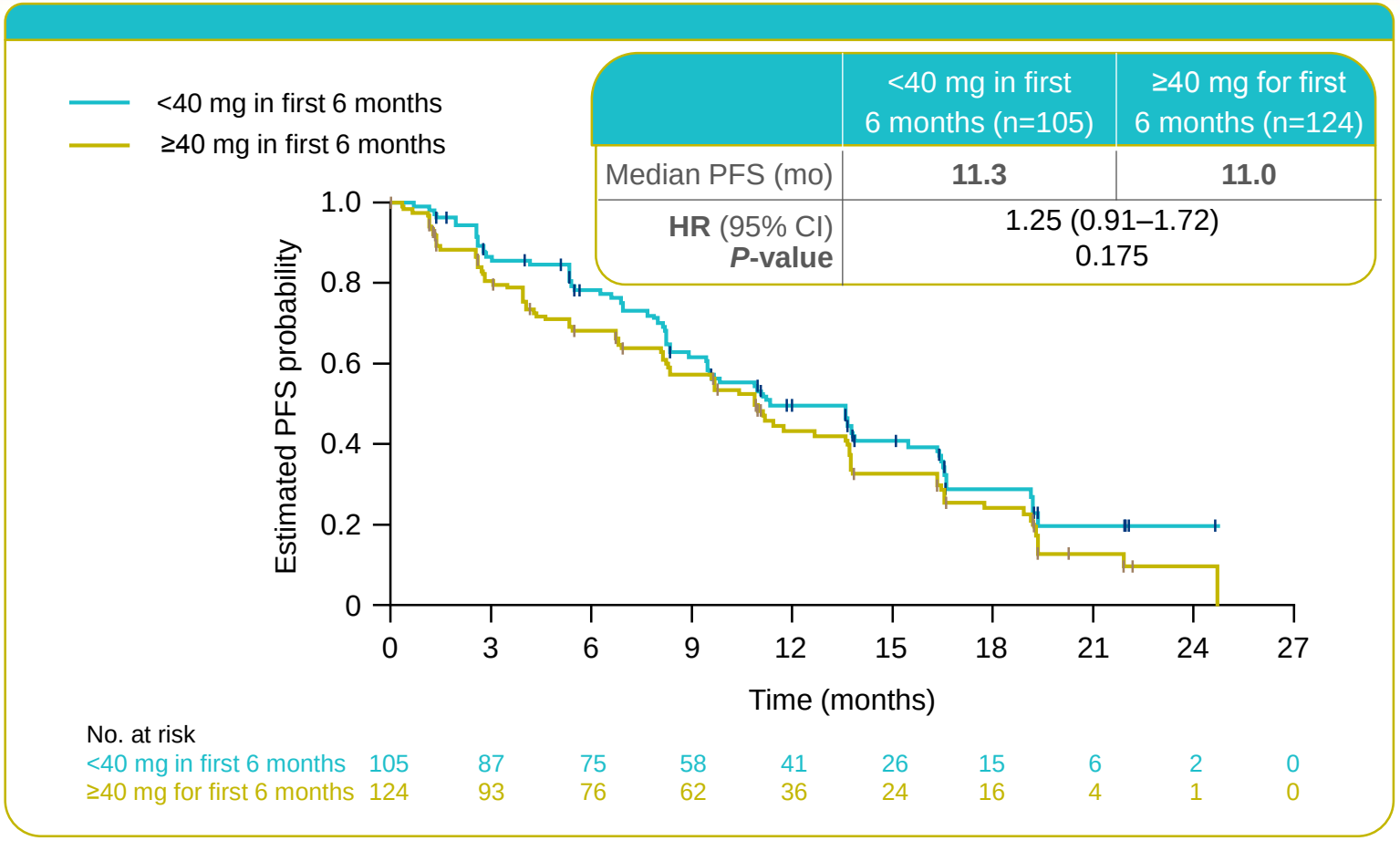
- Dose reduction was more likely in patients with higher plasma concentrations
- Geometric mean plasma concentrations
  - 24.4 ng/mL after dose reduction to 30 mg ≥4 days previously (n=38)
  - 23.7 ng/mL in patients who remained on 40 mg (n=126)



: patients who remained on 40 mg until C3V1 (n=126); , patients who dose reduced to 30 mg before C3V1 (n=38; only 10 of these patients had valid trough concentrations on 40 mg afatinib at C2V1 [the rest had either no PK sampling due to dose interruption, were already on 30 mg afatinib or were excluded due to invalid sampling])

Yang J et al. J Clin Oncol 33, 2015 (suppl; abstr 8073)

PFS in Patients Who Had or Had Not Dose Reductions Within the First 6 Months



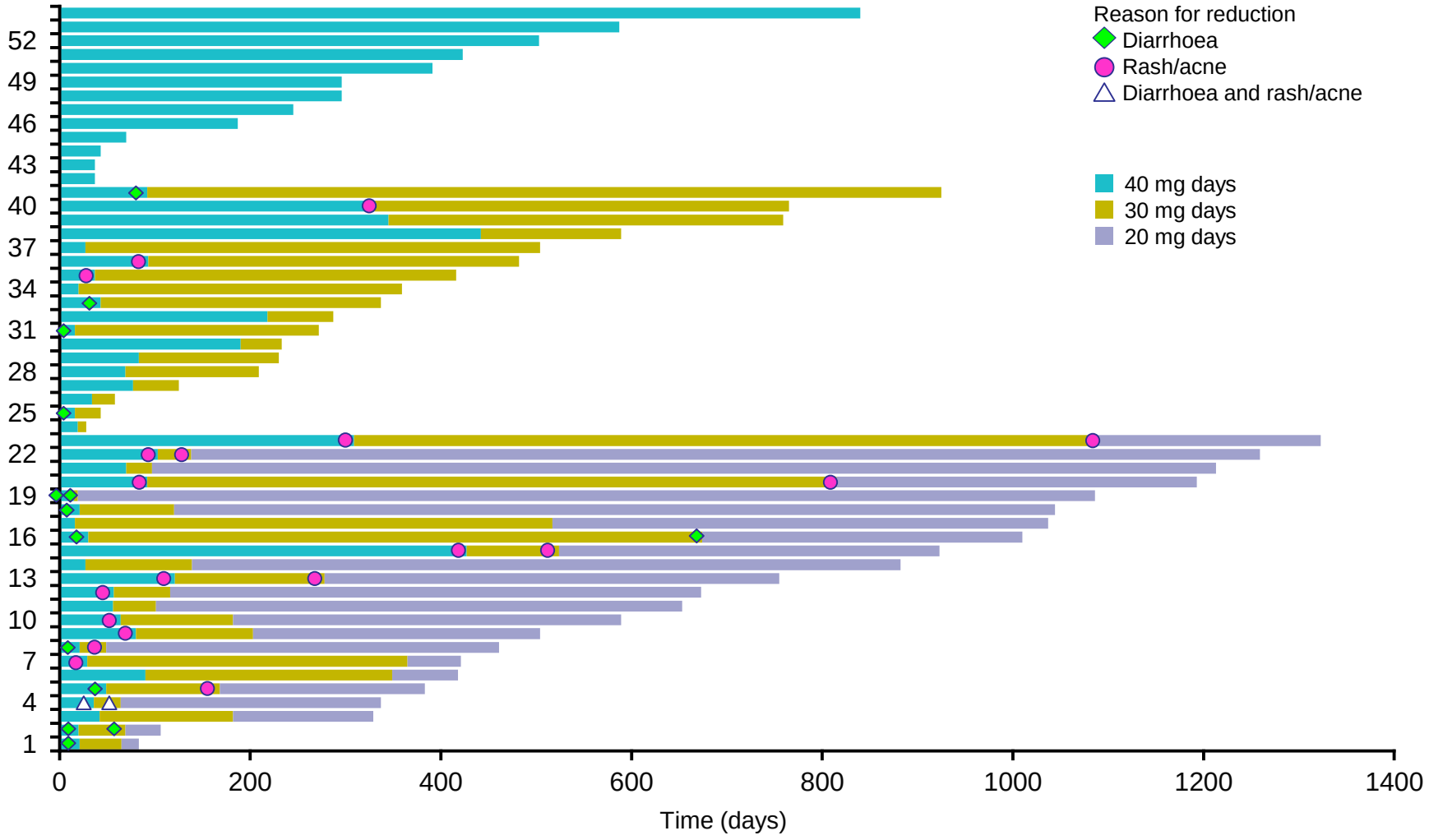
	<40 mg in first 6 months (n=105)	≥40 mg for first 6 months (n=124)
Median PFS (mo)	**11.3**	**11.0**
HR (95% CI) ***P*-value**	1.25 (0.91–1.72) 0.175	

Median PFS was similar in patients who had afatinib dose reductions in the first 6 months and those who remained on afatinib 40 mg once daily

CI, confidence interval; HR, hazard ratio

Yang J et al. J Clin Oncol 33, 2015 (suppl; abstr 8073)

Subgroup Analyses of Treatment Duration and Afatinib Dose Level in Japanese Patients



Kato et al. Cancer Sci. 2015;106(9):1202-11.

Conclusions

- Tolerability-guided dose adjustment of afatinib seems to be an effective measure to reduce treatment-related AEs without affecting therapeutic efficacy
- Incidence and severity of treatment-related AEs was lower following dose reduction
- Tolerability-guided dose modification reduced the interpatient variability of afatinib exposure, while maintaining efficacious plasma levels
- Efficacy outcomes were similar in patients who dose reduced due to AEs versus those who did not. Similar was observed in Japanese patients