Impact of afatinib dosing on safety and effectiveness in real-world patients with *EGFR* mutation-positive advanced NSCLC (RealGiDo)

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Background

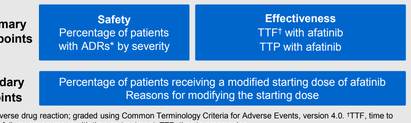
- Randomized controlled trials (RCTs) are a trusted standard for assessing safety and efficacy, but may not always reflect real-world experience
  - RCTs generally involve select groups of patients and are set in well-defined, controlled clinical conditions
- In the real-world, patients may be less compliant, and have poorer prognostic factors and/or more co-morbidities
- Further, routine medical practice may differ from that specified in clinical trial protocols
- In the LUX-Lung clinical trials involving patients with *EGFR* mutation-positive (*EGFR*m+) non-small-cell lung cancer (NSCLC), the incidence and severity of adverse events was reduced by the use of tolerability-guided dose adjustments, without compromising efficacy[1,2]
- We report findings from the RealGiDo study, which evaluated the impact of afatinib dose adjustment on efficacy and safety in a real-world setting

Methods

Study design and patients

- Non-interventional, observational study
- Conducted at 29 sites across 13 countries worldwide (Austria, Canada, France, Germany, Italy, Japan, South Korea, Mexico, Poland, Singapore, Spain, Taiwan and United States; NCT02751879)
  - A maximum of 15 patients were enrolled per site
- Retrospective review of medical records from consecutive patients with *EGFR*m+ (Del19/L858R) tyrosine kinase inhibitor (TKI)-naïve advanced NSCLC who were treated first-line with afatinib within the approved label
  - Patients provided written informed consent where required
  - Patients were excluded if they had been treated in a clinical trial
  - To avoid early censoring and enable collection of mature data, inclusion was restricted to patients with treatment initiation ≥6 months prior to enrollment
  - However, patients who discontinued afatinib before completing 6 months of treatment (e.g. due to toxicity or progressive disease) were included to prevent selection bias

Methods



*ADR, adverse drug reaction; graded using Common Terminology Criteria for Adverse Events, version 4.0. †TTF, time to treatment failure; synonymous with time on treatment. TTP, time to progression

Results

- 228 patients were included
- Baseline characteristics were consistent with the pivotal, global, phase III LUX-Lung 3 trial,[3] with the exception of:
  - More Del19 patients (78% vs 49%)
  - Fewer Asian patients (44% vs 72%)
  - 12% had Eastern Cooperative Oncology Group (ECOG) Performance Status 2–3 (vs none in LUX-Lung 3)

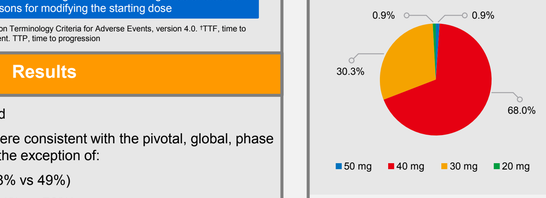
Patient demographics and disease characteristics

	RealGiDo			LUX-Lung 3
N (%)	Any starting dose (n=228)	Starting dose ≤30 mg (n=71)	Starting dose 40 mg (n=155)	Starting dose 40 mg (n=230)
Female	138 (60.5)	48 (67.6)	89 (57.4)	147 (63.9)
Median age, yr (range)	67.0 (32–90)	69.0 (35–85)	67.0 (32–90)	62.0 (28–86)
Race				
White	96 (42.1)	37 (52.1)	57 (36.8)	61 (26.5)
Asian	100 (43.9)	26 (36.6)	74 (47.7)	166 (72.2)
Stage IV disease	216 (94.7)	66 (93.0)	149 (96.1)	210 (91.3)
ECOG PS				
0	90 (39.5)	25 (35.2)	63 (40.7)	92 (40.0)
1	102 (44.7)	31 (43.7)	71 (45.8)	138 (60.0)
2/3	**27 (11.9)**	**8 (11.3)**	**19 (13.2)**	**0**
EGFR mutation				
Del19	178 (78.1)	59 (83.1)	117 (75.5)	112 (48.7)
L858R	49 (21.5)	12 (16.9)	37 (23.9)	91 (39.6)

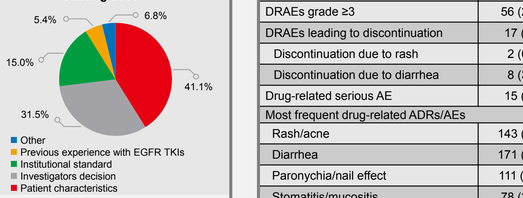
Results

- 31% of patients received an afatinib starting dose of <40 mg; 20% of these patients had dose increases during the study
- The main reason for dose modification was ADRs

Afatinib starting dose in RealGiDo

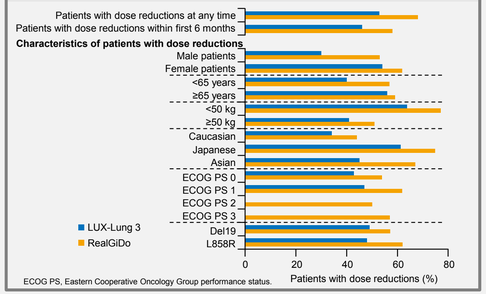


Reasons given for a modified starting dose



- 78% of patients in RealGiDo had a dose modification.
- Among patients who received a starting dose of afatinib 40 mg/day and had a dose modification within the first 6 months (n=91), data were consistent with LUX-Lung 3:
  - Most dose reductions occurred within the first 6 months of treatment (86% in RealGiDo and LUX-Lung 3)
  - The rate of dose reductions was numerically higher in RealGiDo (67% RealGiDo vs 53% LUX-Lung 3).

Proportion of patients who started on afatinib 40 mg and had a dose reduction within the first 6 months of treatment (overall and by patient subgroup): RealGiDo compared with LUX-Lung 3



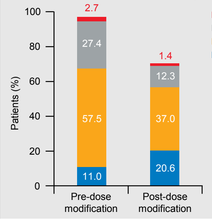
ECOG PS, Eastern Cooperative Oncology Group performance status.

Safety: comparison to LUX-Lung 3

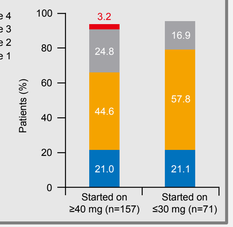
N (%)	RealGiDo		LUX-Lung 3
	Any starting dose	Starting dose 40mg	Starting dose 40mg
Total number of patients	228 (100)	155 (100)	229 (100)
Drug-related adverse event (DRAE)	215 (94.3)	146 (94.2)	229 (100)
DRAEs grade ≥3	56 (24.6)	44 (28.4)	112 (48.9)
DRAEs leading to discontinuation	17 (7.5)	13 (8.4)	18 (7.9)
Discontinuation due to rash	2 (0.9)	2 (1.3)	0 (0.0)
Discontinuation due to diarrhea	8 (3.5)	5 (3.2)	3 (1.3)
Drug-related serious AE	15 (6.6)	8 (5.2)	32 (14.0)
Most frequent drug-related ADRs/AEs			
Rash/acne	143 (62.7)	95 (61.3)	204 (89.1)
Diarrhea	171 (75.0)	120 (77.4)	219 (95.2)
Paronychia/nail effect	111 (48.7)	73 (47.1)	130 (56.8)
Stomatitis/mucositis	78 (34.2)	58 (37.4)	165 (72.1)
Vomiting	2 (0.9)	1 (0.7)	39 (17.0)
Fatigue	7 (3.1)	6 (3.9)	40 (17.5)
Nausea	8 (3.5)	3 (1.9)	41 (17.9)
Dry skin/pruritus	60 (26.3)	32 (20.7)	67 (29.3)

- No new safety signals were identified in RealGiDo
- Among the 91 patients who received a starting dose of afatinib 40 mg/day and had a dose modification within the first 6 months:
  - 72 (98.6%) experienced an ADR of any grade prior to dose modification, compared with 52 (71.2%) after dose modification
  - Dose reductions also led to decreases in severity of ADRs

ADRs in patients receiving afatinib 40 mg/day who had a dose reduction within 6 months (n=91)

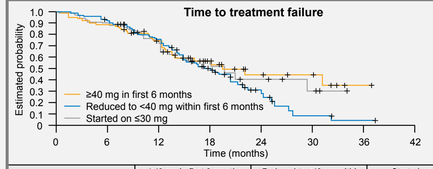


ADRs by starting dose



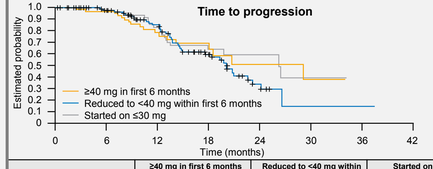
Effectiveness

Time to treatment failure



	≥40 mg in first 6 months (n=66)	Reduced to <40 mg within first 6 months (n=91)	Started on ≤30 mg (n=71)
Median TTF (months), 95% CI	19.5 (13.4–NR)	17.7 (14.5–21.5)	19.4 (12.9–NR)
Total population		18.7 (15.1–21.5)	
Estimated 12 / 18 month rate	70% / 53%	74% / 50%	66% / 53%

Time to progression



	≥40 mg in first 6 months (n=66)	Reduced to <40 mg within first 6 months (n=91)	Started on ≤30 mg (n=71)
Median TTP (months), 95% CI	29.0 (17.9–NR)	20.0 (14.7–23.0)	25.9 (17.3–NR)
Total population		20.8 (19.1–25.9)	
Estimated 12 / 18 month rate	79% / 65%	84% / 60%	86% / 64%

Key findings and conclusions

- Dose adjustments with afatinib in real-world practice reduced the frequency and intensity of ADRs without impacting effectiveness
- As seen in the LUX-Lung trials, the effectiveness of afatinib (as shown by overall median TTF and TTP of 18.7 and 20.8 months, respectively) was consistent regardless of whether patients had a dose reduction or a modified starting dose
- These results show that outcomes can be optimized by tailoring afatinib dose based on individual patient characteristics and ADRs

References

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2. Hirsh V, et al. J Clin Oncol 2016;34:9046–9046.
3. Sequist LV, et al. J Clin Oncol 2013;31:3327–3334.

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