Treating Lung Cancer in the Real World

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Outline

- Real-World Studies and Randomised Controlled Trials Defined
- Gap and Consistency Between RWS and RCT: Insights From Afatinib and Osimertinib

RCT = randomised controlled trials; RWS = real-world studies.

Real-World Studies and Randomized Controlled Trials Defined

Real-World Evidence, Real-World Studies and Randomised Controlled Trials

- Real-World Evidence[1]
  - Clinical evidence regarding the usage, and potential benefits or risks, of a medical product derived from analysis of real-world data
  - RWE is generated through the conduct of real-world studies
- Relationship between RWS and Randomized Controlled Trial[2]
  - RWS are complementary and not antithetical to RCT

1. US Food and Drug Administration. https://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm513027.pdf. Accessed October 30, 2018; 2. Wu et al. Real World Study Guidelines 2018.

Real-World Studies and Randomized Controlled Trials

Based on Real World Study Guidelines 2018 by Wu et al.

Characteristics	Randomized Controlled Trial	Real-World Study
Study Objective	Primarily **efficacy**	Diverse study objectives, including **effectiveness**
Study Population	**Ideal** world population, strict inclusion and exclusion criteria	**Real-world** population, relatively broader inclusion and exclusion criteria
Sample Size	Obtained from **calculation based on statistical formula**, typically smaller sample size	Obtained from calculation based on real data environment or statistical formula, **flexible sample size**
Study Duration	Short (**mostly assessing outcome index** as the endpoint)	Short-term or long-term (obtaining all treatment and **long-term clinical outcomes** as the endpoint)
Study Design	Randomized controlled; prospective study	Random or non-random sample, or observational; prospective or retrospective
Study Scenario	**Ideal world**: a highly standardized environment	**Real world**: medical institutions, communities, families
Data	**Standardized**, strictly normalized collection process	**Diverse sources, high heterogeneity**

Wu et al. Real World Study Guidelines 2018.

Gap and Consistency Between RWS and RCT: Insights From Afatinib and Osimertinib

Some Questions Addressed Within RCT and RWS: Differences and Similarities

- Dose modification of afatinib
  - Frequency of dose modification and characteristics of patients who have dose modification
  - Safety in patients with dose modification
  - Impact of dose modification on effectiveness
- Outcomes in patients with brain metastases treated with afatinib
- Sequential treatment with afatinib followed by osimertinib in EGFR M+ patients
- Effectiveness of osimertinib as second-line therapy in T790M-positive lung cancer patients

EGFR M+ = epidermal growth factor receptor mutation positive.

Frequency of Dose Reduction and Characteristics of Patients Who have Dose Modification

	Study	Frequency of Dose Reduction	More Frequently Occurred Patients
RCT	LUX-Lung 3[1]	53%	• Females • Low body weight (<50 kg) • Low body surface area • Older patients (≥65 years) • Japanese site
	LUX-Lung 6[1]	28%	• Females • Lower body weight (<50 kg) • Low body surface area
RWS	1200.66[2a]	24.8%	Not available
	RealGiDo[3b]	67%[c]	• Females • Lower body weight (<50 kg) • Eastern Asian

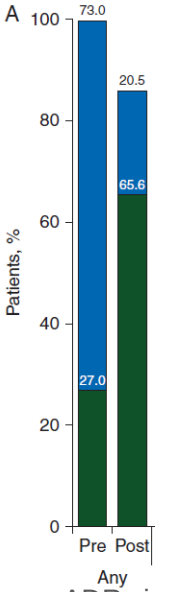
Gap: Frequency of dose reduction is different in RCT and RWS

[a]Phase 3b study in a setting similar to real-world practice. [b]Starting dose of 40 mg/day in RealGiDo study.
[C] Previously published clinical data from LUX-Lung 3 and 6, where afatinib dose reduction did not impact efficacy, may have influenced the willingness of physicians to dose reduce more frequently, which was captured in the RealGiDo study

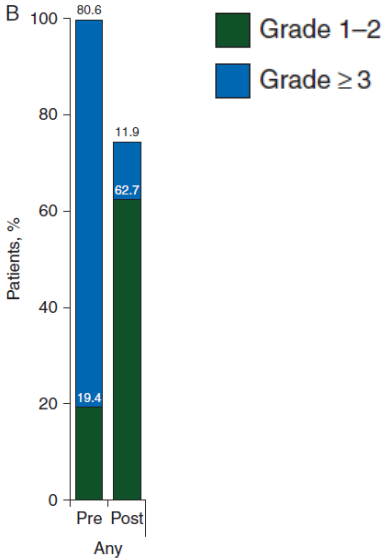
1. Yang et al. *Ann Oncol*. 2016;27:2103; 2. Wu et al. WCLC 2017. Poster P3.01-036; 3. Halmos et al. WCLC 2018. Poster P1.01-28.

Safety of Dose Modification

Lux-Lung 3 [1]



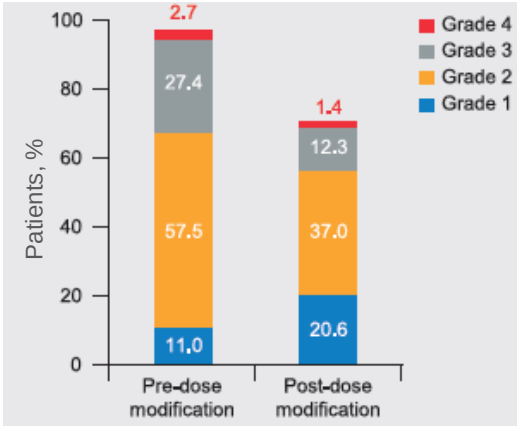
Lux-Lung 6 [1]



ADRs in Patients Starting With 40 mg and Dose Reduction Within the First 6 Months

RealGiDo [2]

ADRs in Patients Receiving Afatinib 40 mg/day Who Had a Dose Reduction Within 6 Months (n=91)



Consistency: Frequency and grade of ADRs were reduced after dose modification

ADR = adverse drug reaction.

1. Yang et al. *Ann Oncol*. 2016;27:2103; 2. Halmos et al. WCLC 2018. Poster P1.01-28.

Impact of Dose Modification on Effectiveness

	Study	Efficacy (<40 mg vs >40 mg in first 6 months)
RCT	LUX-Lung 3[1]	PFS: 11. 3 m vs 11.0 m. HR:1.25(0.91-1.72), *P*=0.175
	LUX-Lung 6[1]	PFS: 12.3 m vs 11.0 m. HR:1.00(0.69-1.46), *P*=0.982
RWS	1200.66[2a]	PFS: 14.1 m vs 11.3 m. HR:1.37(1.01-1.85), *P*=0.041 TTSP: 17.7 m vs 14.7 m. HR:1.26(0.92-1.72), *P*=0.150
	RealGiDo[3b]	TTF: 19.5 m vs 17.7 m. *P*=0.540 TTP: 29.0 m vs 20.0 m. *P*=0.390

Consistency: Dose modification didn't have an impact on effectiveness

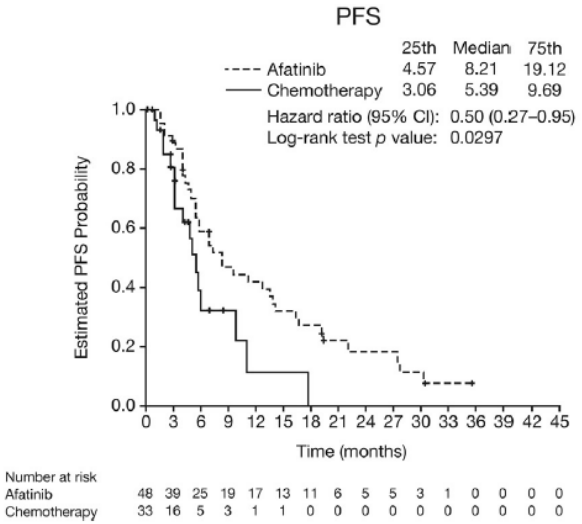
[a]Phase 3b study in a setting similar to real-world practice. [b]Starting dose 40 mg/day in RealGiDo study.

HR = heart rate; PFS = progression-free survival; TTF = time to treatment failure; TTP = time to progression; TTSP = time to symptomatic progression.

1. Yang et al. *Ann Oncol*. 2016;27:2103; 2. Wu et al. WCLC 2018. Poster P1.01-98; 3. Halmos et al. WCLC 2018. Poster P1.01-28.

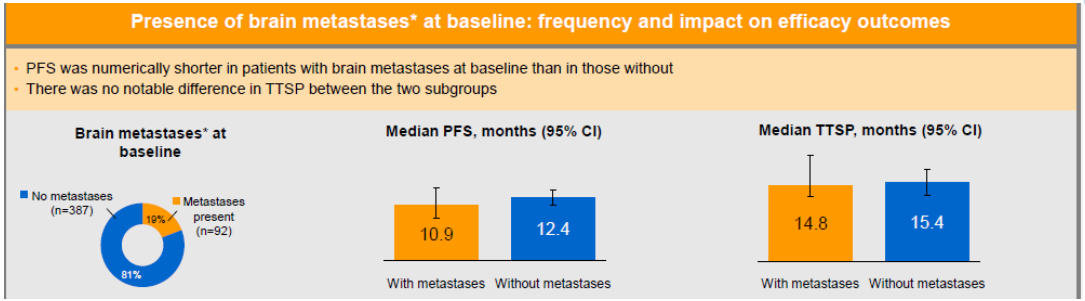
Patients With Brain Metastases Treated With Afatinib

Lux-Lung 3 & Lux-Lung 6[1]



PFS with baseline brain metastases and common EGFR mutations on the basis of an exploratory combined analysis of LUX-Lung 3 and LUX-Lung 6

1200.66[2]



Consistency: Afatinib is an effective treatment for brain metastases

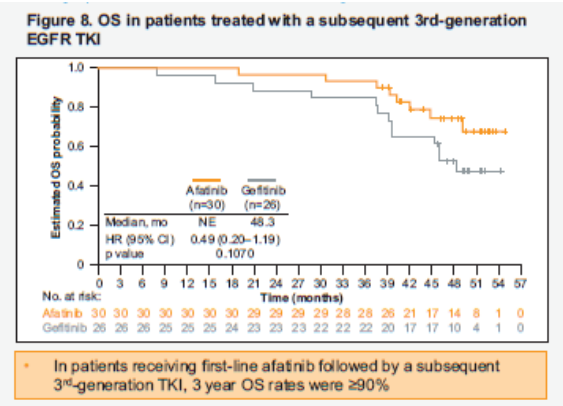
*Asymptomatic

CI = confidence interval; HR = hazard ratio; PFS = progression-free survival; TTSP = time to symptomatic progression.

1. Schuler et al. *J Thorac Oncol*. 2016;11:380; 2. Wu et al. WCLC 2018. Poster P1.01-98.

Sequential Treatment With Afatinib Followed by Osimertinib in EGFR M+ NSCLC Patients

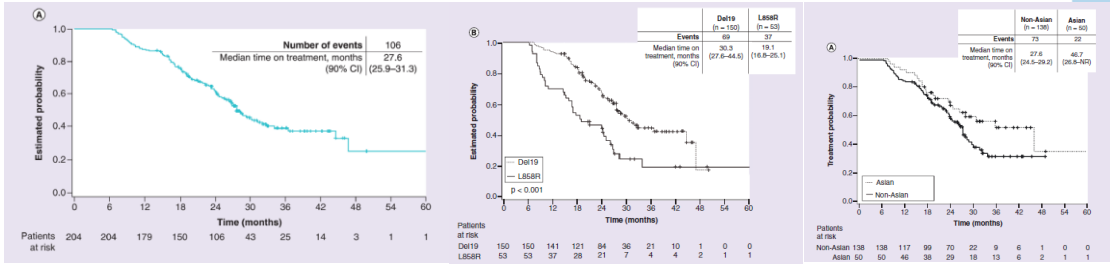
LUX-Lung 7[1a]: OS in Patients Treated With a Subsequent 3rd-generation EGFR-TKI



- In patients receiving first-line afatinib followed by a subsequent 3rd-generation TKI, 3 year OS rates were ≥90%

	Afatinib N=30	Gefitinib N=26
Median OS (months)	NE	48.3
HR (95% CI) P-value	0.49 (0.20-1.19) 0.107	

GioTag[2]: Time on Treatment With Sequential Afatinib Followed by Osimertinib



	Total (n=204)	Del19 (n=150)	L858R (n=53)	Non-Asian (n=138)	Asian (n=50)
Number of events	106	69	37	73	22
Median time on treatment (months) 90% CI	27.6 (25.9-31.3)	30.3 (27.6-44.5)	19.1 (16.8-25.1)	27.6 (24.5-29.2)	46.7 (26.8-NR)

Consistency: Afatinib followed by osimertinib is a potentially attractive strategy for EGFR M+ patients

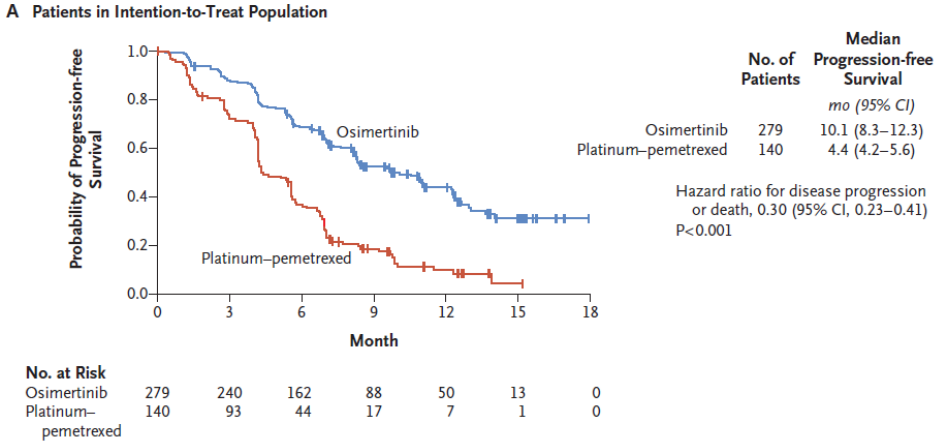
[a]LUX-Lung 7 was a phase IIb, prospective, global, randomised trial comparing afatinib (n=160) with gefitinib (n=159) in treatment-naïve patients with advanced EGFR M+ NSCLC. The trial met its primary endpoints of progression-free survival (independent review) and time to treatment failure. The OS data presented here comes from a post-hoc analysis that only includes patients in the trial who received 3rd-generation TKI after discontinuing afatinib (n=30) or gefitinib (n=26).

NE = not evaluable; NR = not reached; NSCLC = non-small cell lung cáncer; OS = overall survival; TKI = tyrosine kinase inhibitor.

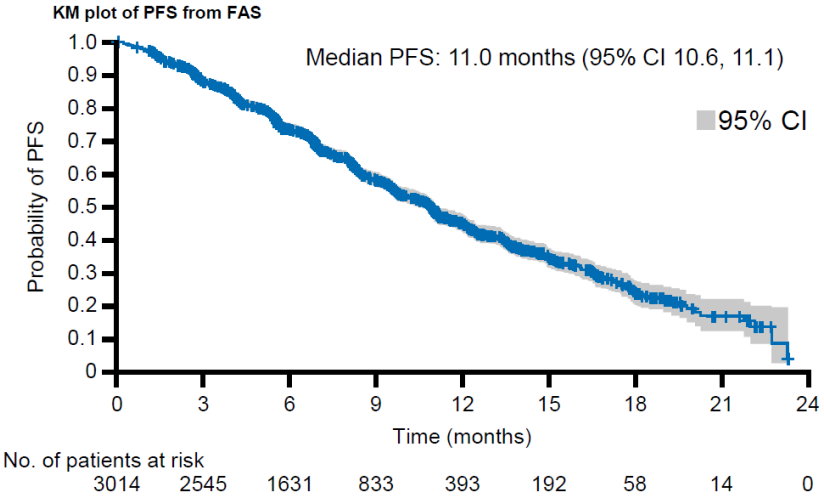
1. Corral et al. ELCC 2017; #93PD; 2. Hochmair et al. *Future Oncol*. 2018 October 19. [Epub published ahead of print].

Effectiveness of Osimertinib in EGFR T790M-Positive NSCLC

AURA 3[1]



ASTRIS[2]



Consistency: Osimertinib is effective for EGFR T790M NSCLC

FAS = full analysis set; NSCLC = non-small cell lung cancer.

1. Mok et al. *N Engl J Med*. 2017;376:629; 2. Wu et al. WCLC 2018. MA02.03.

Summary

- RWS are complementary and not antithetical to RCT
- RWS are needed as these include patients with conditions that usually exclude them from an RCT (eg, patients with poor ECOG PS and comorbidities)
- Consistency between RCT and RWS can help clinical doctors make a decision in clinical practice
- Gaps between RCTs and RWS also exist (eg, frequency of dose modification); personalized treatment is the trend

ECOG PS = Eastern Cooperative Oncology Group performance status.