Sequencing to Prolong the Chemotherapy-Free Period

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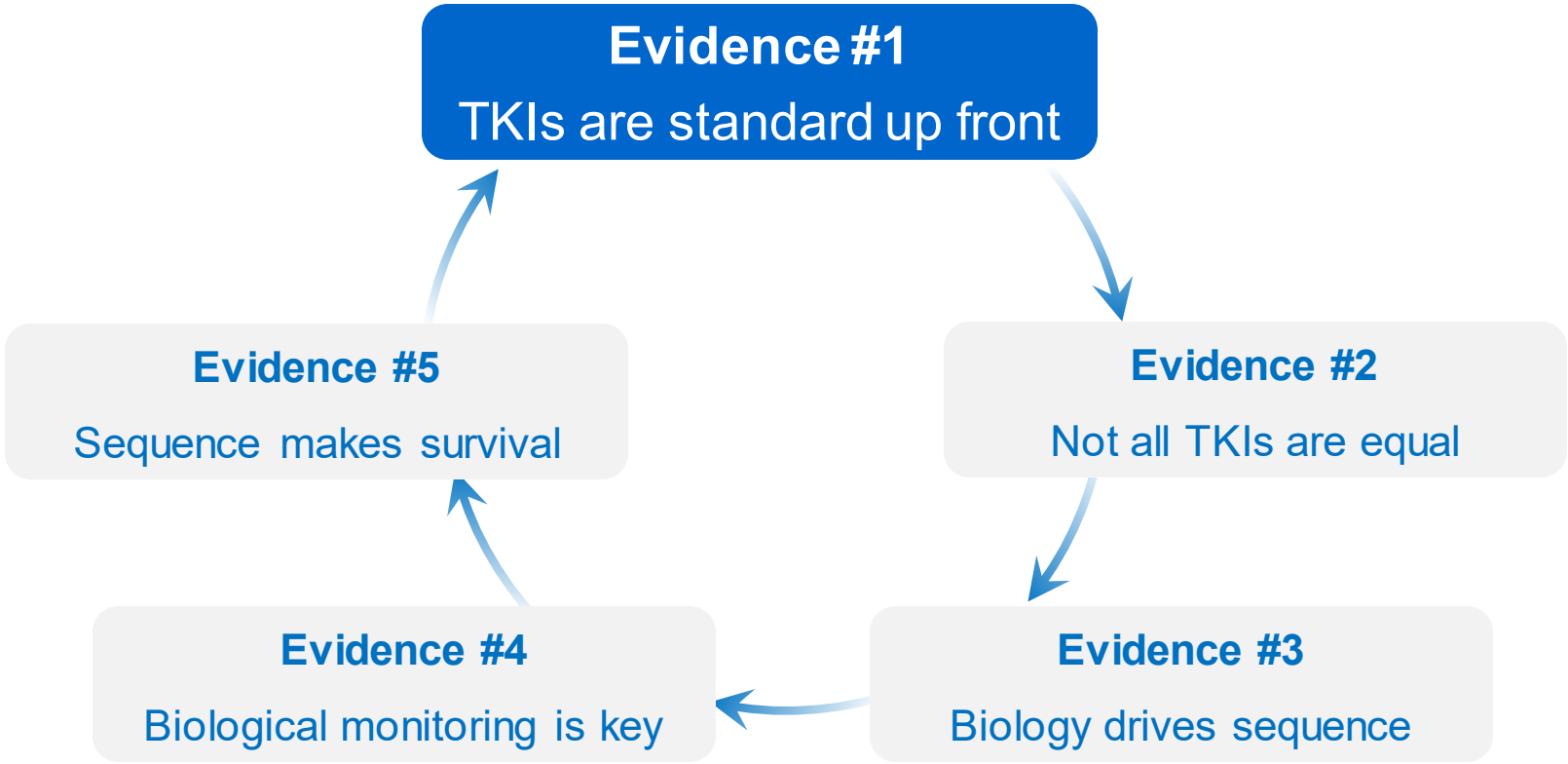
Disclosures

- Honoraria: AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Eli Lilly, Merck, Novartis, Pfizer

Evidence to Select and Sequence Therapies in *EGFR* M+ NSCLC



Girard. *Future Oncol*. 2018;14:1117.

First- and Second-Generation EGFR TKIs Are Standard in the 1L Treatment of NSCLC Harbouring Common EGFR Mutations

First- and second-generation TKIs demonstrate a longer PFS vs platinum-based chemotherapy across multiple phase III clinical trials

Erlotinib

- EURTAC: 9.7 vs 5.2 mo (HR 0.37; 95% CI, 0.25-0.54; *P*<0.0001)[1]
- ENSURE: 11.0 vs 5.5 mo (HR 0.34; 95% CI, 0.22-0.51; *P*<0.0001)[2]
- OPTIMAL: 13.1 vs 4.6 mo (HR 0.16; 95% CI, 0.10-0.26; *P*<0.0001)[3]

Gefitinib

- WJTOG3405: 9.2 vs 6.3 mo (HR 0.489; 95% CI, 0.336-0.710; *P*<0.0001)[4]
- NEJ0002: 10.8 vs 5.4 mo (HR 0.30; 95% CI, 0.22-0.41; *P*<0.001)[5]
- IPASS: 9.5 vs 6.3 mo (HR 0.48; 95% CI, 0.36-0.64; *P*<0.001)[6,a]

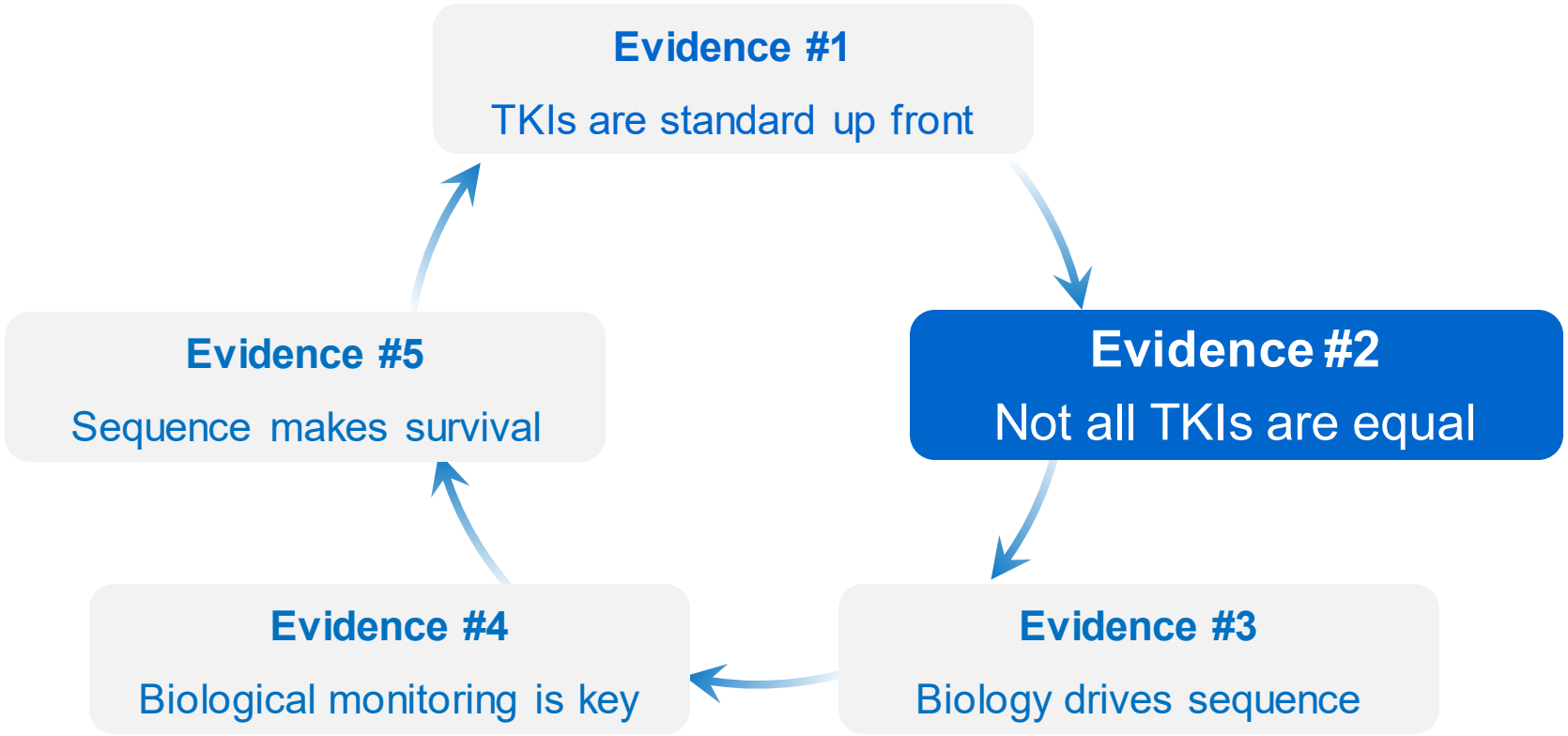
Afatinib

- LUX-Lung 3: 13.6 vs 6.9 mo (HR 0.47; 95% CI, 0.34-0.65; *P*=0.001)[7]
- LUX-Lung 6: 11.0 vs 5.6 mo (HR 0.28; 95% CI, 0.20-0.39; *P*<0.001)[8]

[a]PFS not reported for common mutations only.
PFS = progression-free survival.

1. Rosell et al. *Lancet Oncol.* 2012;13:239; 2. Wu et al. *Ann Oncol.* 2015;26:1883; 3. Zhou et al. *Lancet Oncol.* 2011;12:735; 4. Mitsudomi et al. *Lancet Oncol.* 2010;11:121;
5. Maemondo et al. *N Engl J Med.* 2010;362:2380; 6. Fukuoka et al. *J Clin Oncol.* 2011;29:2866; 7. Sequist et al. *J Clin Oncol.* 2013;31:3327; 8. Wu et al. *Lancet Oncol.* 2014;15:213.

Evidence to Select and Sequence Therapies in *EGFR* M+ NSCLC



Girard. *Future Oncol*. 2018;14:1117.

First-, Second-, and Third-Generation EGFR TKIs Are Not Equal: Efficacy

- Afatinib vs. gefitinib (LUX-Lung 7[a]):
  - Significantly **longer PFS** [HR, 0.74 (0.57-0.95); *P*=0.0178], **TTF** [HR, 0.75; 95% CI, 0.60-0.94; *P*=.00136], and higher **ORR** [*P*=0.002][1]
- Dacomitinib vs gefitinib (ARCHER 1050[b], excluding brain mets)
  - Significantly **longer PFS** [0.59 (95% CI, 0.47-0.74); *P*<0.0001]. No significant difference in ORR [*P*=0.3883][2,3]
- Osimertinib vs erlotinib/gefitinib (FLAURA[c])
  - Significantly **longer OS** [HR, 0.80 (95.05% CI, 0.641-0.997); *P*=0.0462] **and PFS** [HR, 0.46 (95% CI, 0.37-0.57); *P*<0.001] with no significant difference in ORR [*P*=0.24][4,5]

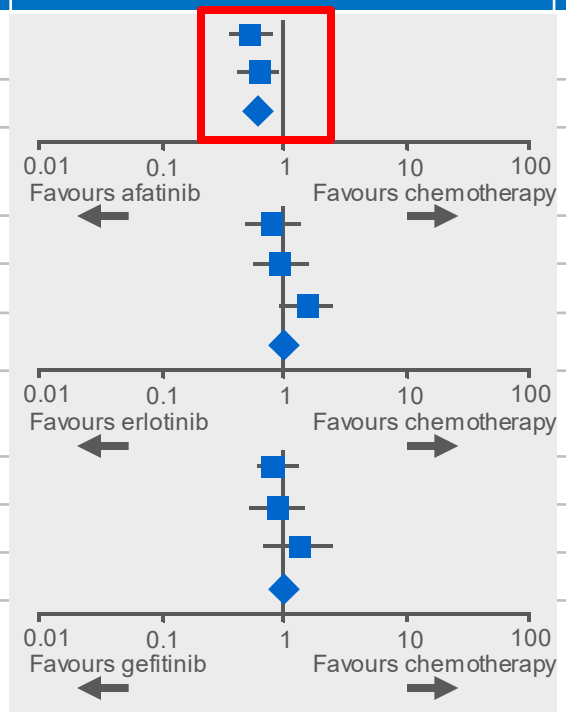
[a]LUX-Lung 7 is a randomised, phase IIb trial evaluating afatinib vs. gefitinib for the 1L treatment of patients with EGFR M+ advanced adenocarcinoma of the lung.
[b]ARCHER 1050 is a randomised, phase III trial evaluating dacomitinib vs. gefitinib for the 1L treatment of patients with EGFR M+ advanced NSCLC, excluding patients with CNS metastases.
[c]FLAURA is a randomised, phase III trial evaluating osimertinib vs. erlotinib or gefitinib for the 1L treatment of patients with EGFR M+ advanced NSCLC.

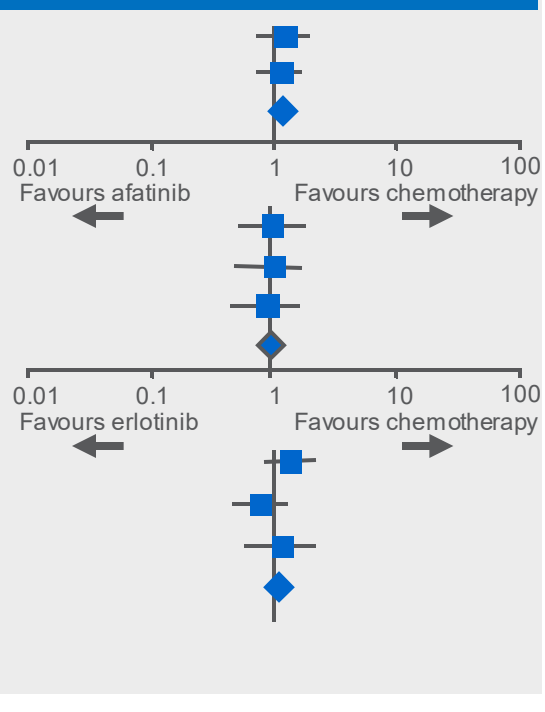
1. Corral et al. *Ann Oncol*. 2017;28(suppl 2):ii28 (poster presentation; abstract 93PD); 2. Mok et al. *J Clin Oncol*. 2017;35(suppl 18):LBA9007 (oral presentation); 3. Wu et al. *Lancet Oncol*. 2017;18:1454; 4. Soria et al. *N Engl J Med*. 2018;378:113; 5. Ramalingham et al. Presented at ESMO 2019. Abstract LBA5_PR (oral presentation).

OS Efficacy of First-Generation and Second-Generation TKIs Is Different in Del19 Mutations

- Data from patients with Del19 (n=1037) and L858R (n=816) mutations were analysed in a pair-wise meta-analysis including studies of afatinib, erlotinib, or gefitinib vs chemotherapy

Agent	Study	Hazard Ratio (95% CI)	Hazard Ratio (95% CI)
Afatinib	LUX-Lung 3	0.53 (0.36-0.79)	1.30 (0.80-2.11)
	LUX-Lung 6	0.64 (0.44-0.94)	1.22 (0.81-1.83)
	Total	**0.59 (0.45-0.77)**	**1.25 (0.91-1.71)**
Erlotinib	ENSURE	0.79 (0.48-1.30)	1.05 (0.60-1.84)
	EURTAC	0.94 (0.57-1.54)	1.00 (0.56-1.79)
	OPTIMAL	1.52 (0.9-2.52)	0.92 (0.55-1.54)
	Total	**1.04 (0.71-1.51)**	**0.98 (0.72-1.35)**
Gefitinib	IPASS	0.86 (0.61-1.22)	1.40 (0.91-2.15)
	NEJ002	0.83 (0.52-1.34)	0.82 (0.49-1.38)
	WJTOG3405	1.19 (0.65-2.18)	1.11 (0.60-2.05)
	Total	**0.90 (0.70-1.17)**	**1.11 (0.81-1.54)**





CI = confidence interval; HR = hazard ratio; TKI = tyrosine kinase inhibitor.
Kato T et al. *Value Health*. 2015;18:A436 (poster presentation; abstract PCN40).

SPECIAL PATIENT POPULATIONS

Tolerability

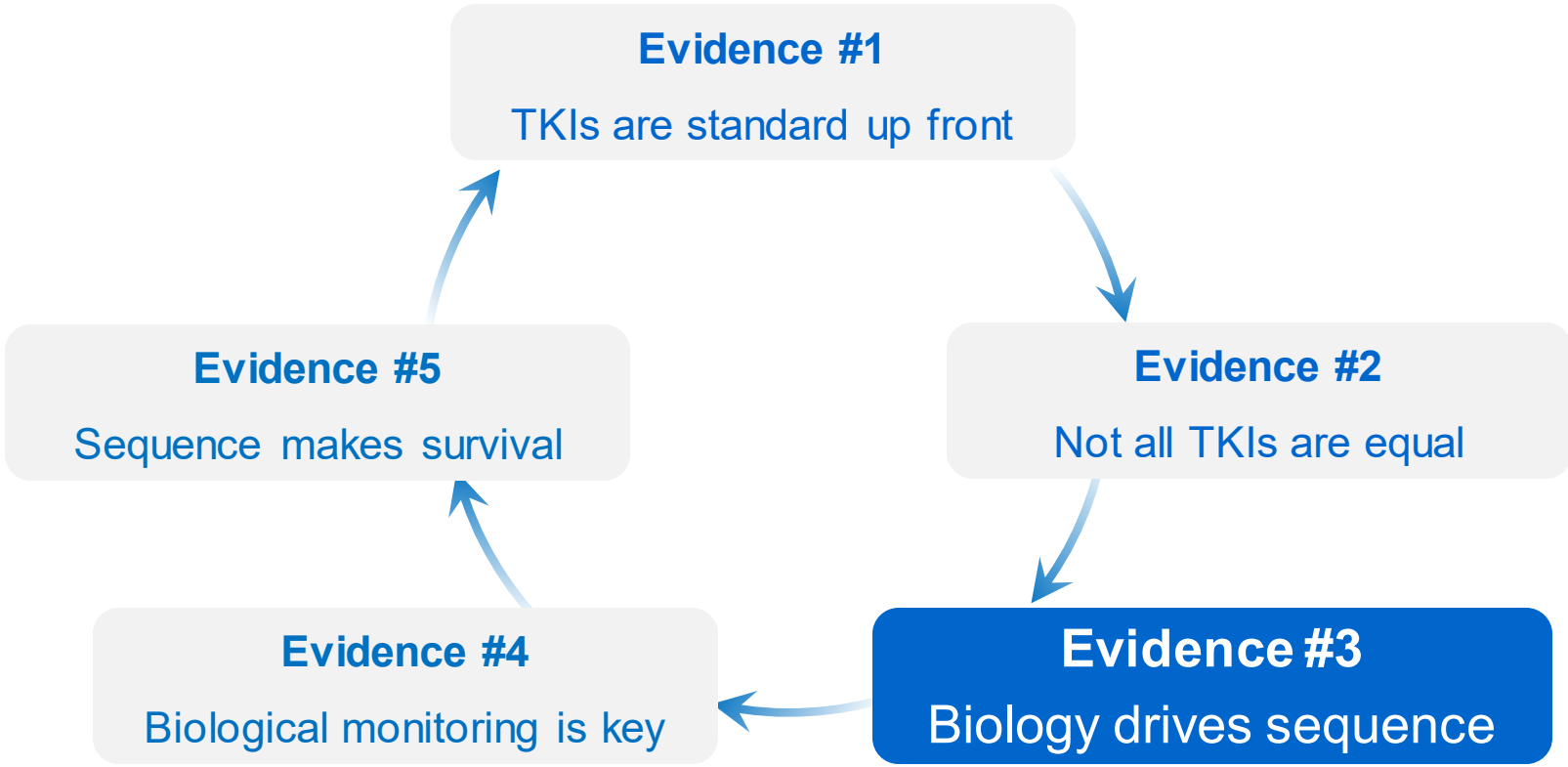
First-, Second-, and Third-Generation EGFR TKIs Are Not Equal: Safety

Treatment discontinuation rates and common grade ≥3 AEs for second- or third generation TKIs vs First-Generation TKIs[a]

- LUX-Lung 7: **Treatment discontinuation rates** were **6%** for both afatinib and gefitinib[1,2]
  - Most common grade ≥3 AEs for afatinib were diarrhoea (13%) and rash/acne (9%); most common for gefitinib were liver enzyme elevation (9%) and rash/acne (3%)
  - Dose reduction of afatinib in LUX-Lung 7 reduced drug-related AEs without compromising efficacy[3]
- ARCHER 1050: **Treatment discontinuation rate** was **10%** and **7%** for dacomitinib and gefitinib, respectively[4]
  - Most common grade ≥3 AEs for dacomitinib were acne (14%), diarrhoea (8%), and paronychia (7%); most common for gefitinib were liver enzyme elevation (12%) and dyspnoea (3%)
- FLAURA: **Treatment discontinuation rates** were **10%** and **14%** for osimertinib and 1st-gen TKI, respectively[5]
  - Most common grade ≥3 AEs for osimertinib were diarrhoea (2%) and decreased appetite (2%); most common for 1st-gen TKI were rash/acne (7%) and liver enzyme elevation (13%)

[a]Comparison of studies should be interpreted with caution due to differences in study design, populations and methodology.
AE = adverse event.
1. Park et al. *Lancet Oncol*. 2016;17:577; 2. Paz-Ares et al. *Ann Oncol*. 2017;28:270; 3. Hirsh et al. *J Clin Oncol*. 2016;34(suppl 15):9046 (poster presentation); 4. Wu et al. *Lancet Oncol*. 2017;18:1454; 5. Soria et al. *N Engl J Med*. 2018;378:113.

Evidence to Select and Sequence Therapies in *EGFR* M+ NSCLC

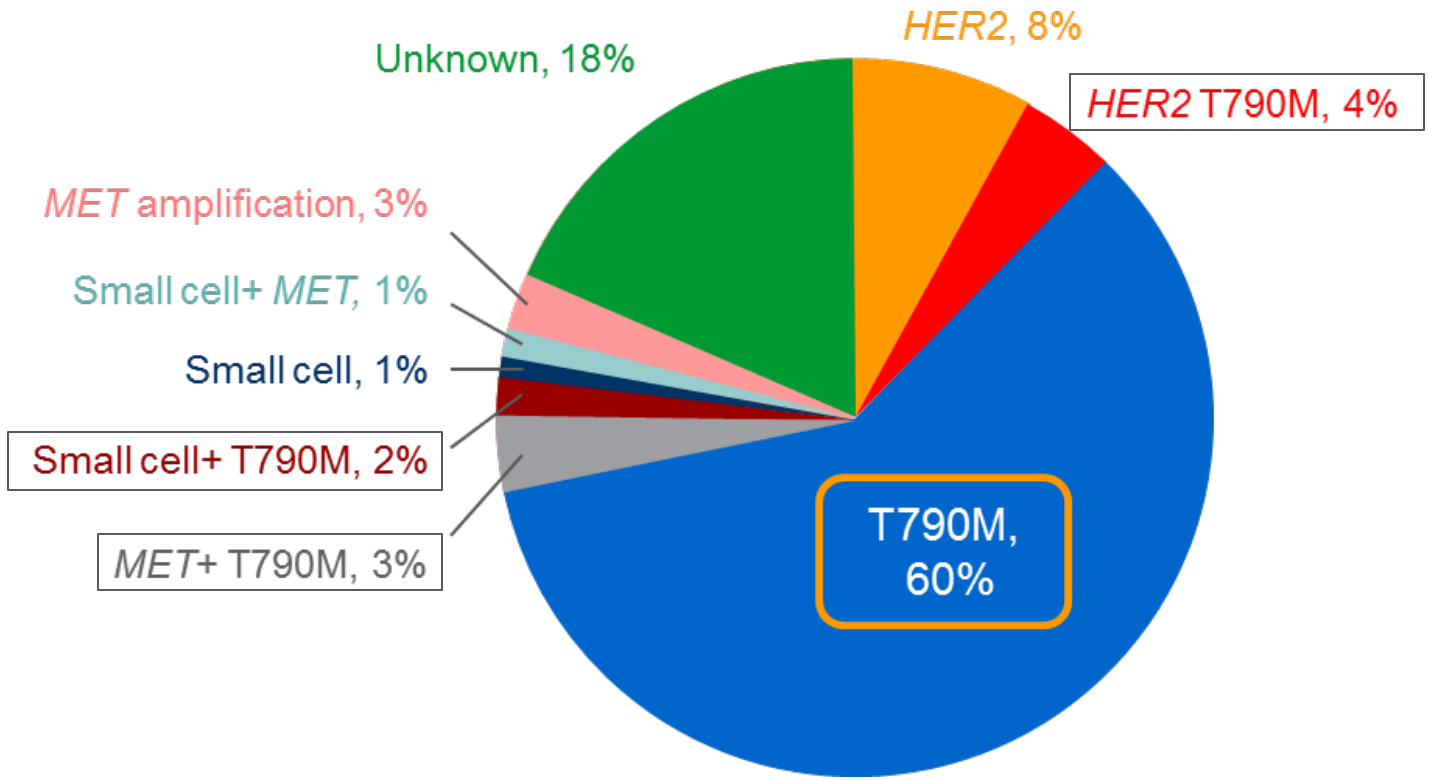


Girard. *Future Oncol*. 2018;14:1117.

Molecular Mechanisms of Acquired Resistance to First- and Second-Generation EGFR TKIs

- ≈50%-70% develop a T790M mutation on first- or second-generation TKI[1-7,a]
- Likelihood to acquire T790M is 1.5 fold higher in Del19 compared to L858R[8-11]
- **Patients with a Del19 disease have a likelihood to acquire T790M ≈75%**[12,13]
- Osimertinib is the SOC for T790M+ acquired resistance to first- and second-generation EGFR TKIs: AURA3[14]
  - mPFS: 10.1 vs 4.4 months for osimertinib and platinum/pem, respectively [HR, 0.30 (0.23-0.41) P<0.001]

Mechanisms of Acquired Resistance After First-generation TKI in EGFR-mutant NSCLC (n=155)[1]

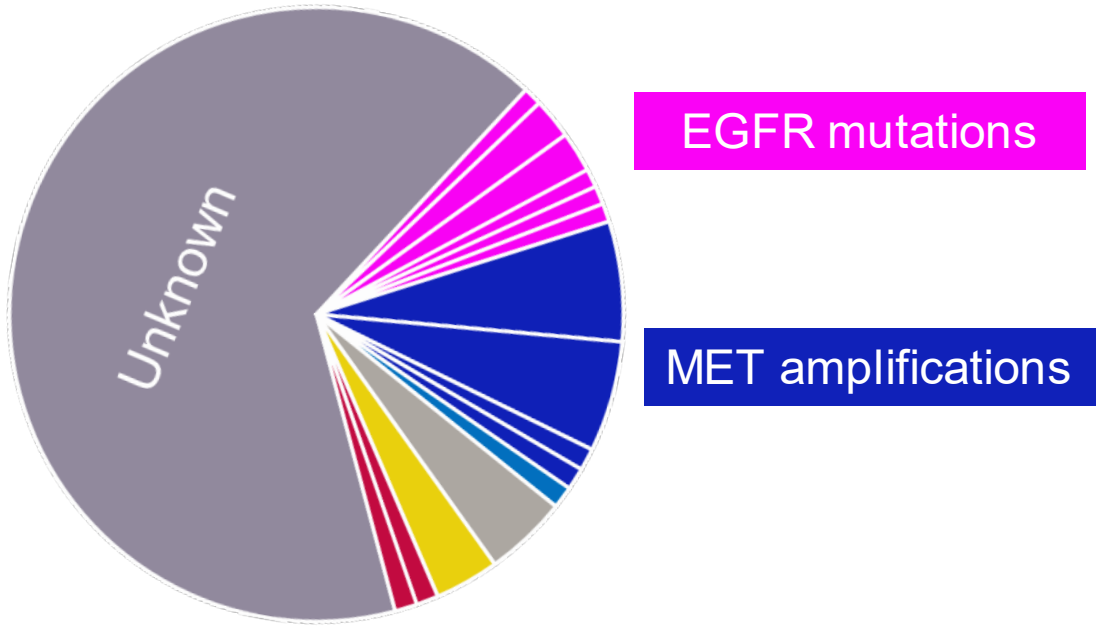


[a]Molecular analyses on rebiopsy specimen.
MET = mesenchymal-epithelial transition.

1. Yu et al. *Clin Cancer Res*. 2013;19:2240; 2. Yang et al. *J Clin Oncol*. 2017;35:1288; 3. Wu et al. *Oncotarget*. 2016;7:10684; 4. Hochmair et al. *Target Oncol*. 2019;14:75; 5. Tanaka et al. *J Clin Oncol*. 2018;36(suppl 15):e21173 (eposter); 6. Li et al. *J Clin Oncol*. 2019;37(suppl):e20518 (eposter); 7. Lau et al. *Clin Lung Cancer*. 2019. [Epub ahead of print]; 8. Ke et al. *J Thorac Oncol*. 2017;12:1368; 9. Matsuo et al. *Sci Rep*. 2016;6:36458; 10. Nosaki et al. *Lung Cancer*. 2016;101:1; 11. Lau et al. *Ann Oncol*, 2016;27(Suppl_6):1243P; 12. Jenkins et al. *J Thorac Oncol*. 2017;12:1247; 13. Pignataro et al. Poster presented at WCLC 2019. Abstract 2442; 14. Mok et al. *N Engl J Med*. 2017;376:629.

Molecular Mechanisms of Acquired Resistance to 1L Osimertinib

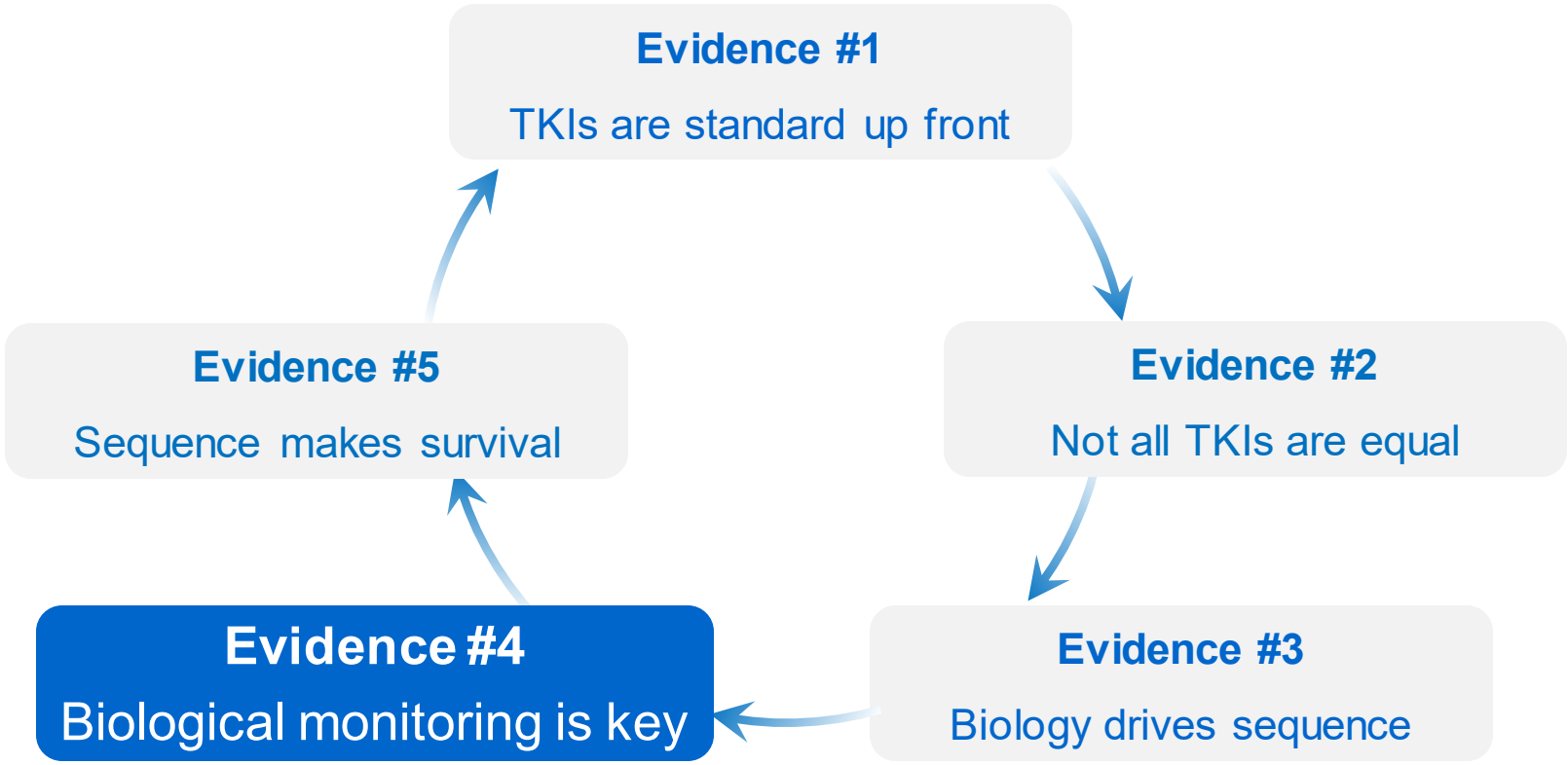
FLAURA (liquid biopsy)[1,2]



- In FLAURA, the most frequent resistance mechanisms for osimertinib were **MET amplification (15%)** and EGFR C797S mutation (7%)[1,2]
- Additional studies have shown that the frequency of **histologic transformation** after resistance to osimertinib was about **14%**[3,4]

1. Ramalingam et al. *Ann Oncol*. 2018;29(suppl 8) (oral presentation; abstract LBA50); 2. Rudin. ESMO 2018. Discussant of Abstract LBA50 (oral presentation); 3. Schoenfeld et al. *J Clin Oncol*. 2019;37 (suppl); abstract 9028 (poster presentation); 4. Kang et al. *J Clin Oncol*. 2019;37 (suppl); abstract e20615 (eposter).

Evidence to Select and Sequence Therapies in EGFR M+ NSCLC



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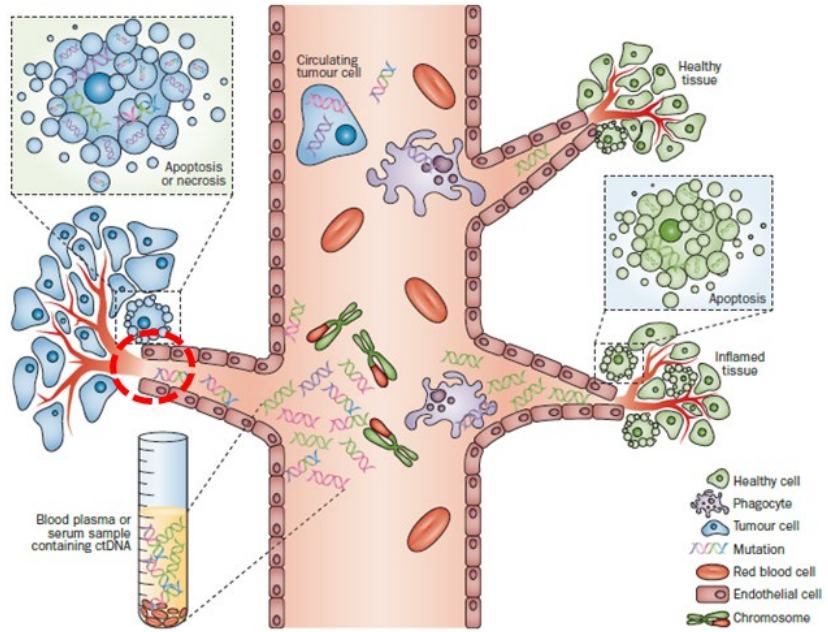
Biopsy or Plasma May Be Used to Determine EGFR T790M Status

Methodologies for ctDNA Detection[1]

Sanger sequencing[1]	>10% sensitivity; optimal for tumour tissue
Pyrosequencing[1]	10% sensitivity; optimal for tumour tissue
Therascreen T790M[6]	>7% sensitivity; optimal for tumour tissue
NGS[1]	2% sensitivity; optimal for tumour tissue
Quantitative-PCR[1]	1% sensitivity; optimal for tumour tissue
COLD-PCR[2]	0.10% sensitivity; optimal for ctDNA
ARMS[1]	0.10% sensitivity; optimal for tumour tissue
COBAS, Therascreen[3,4] (adapted for ctDNA)	0.10% sensitivity; optimal for ctDNA
ddPCR[5]	0.01% sensitivity; optimal for ctDNA

ctDNA will be detected in this range

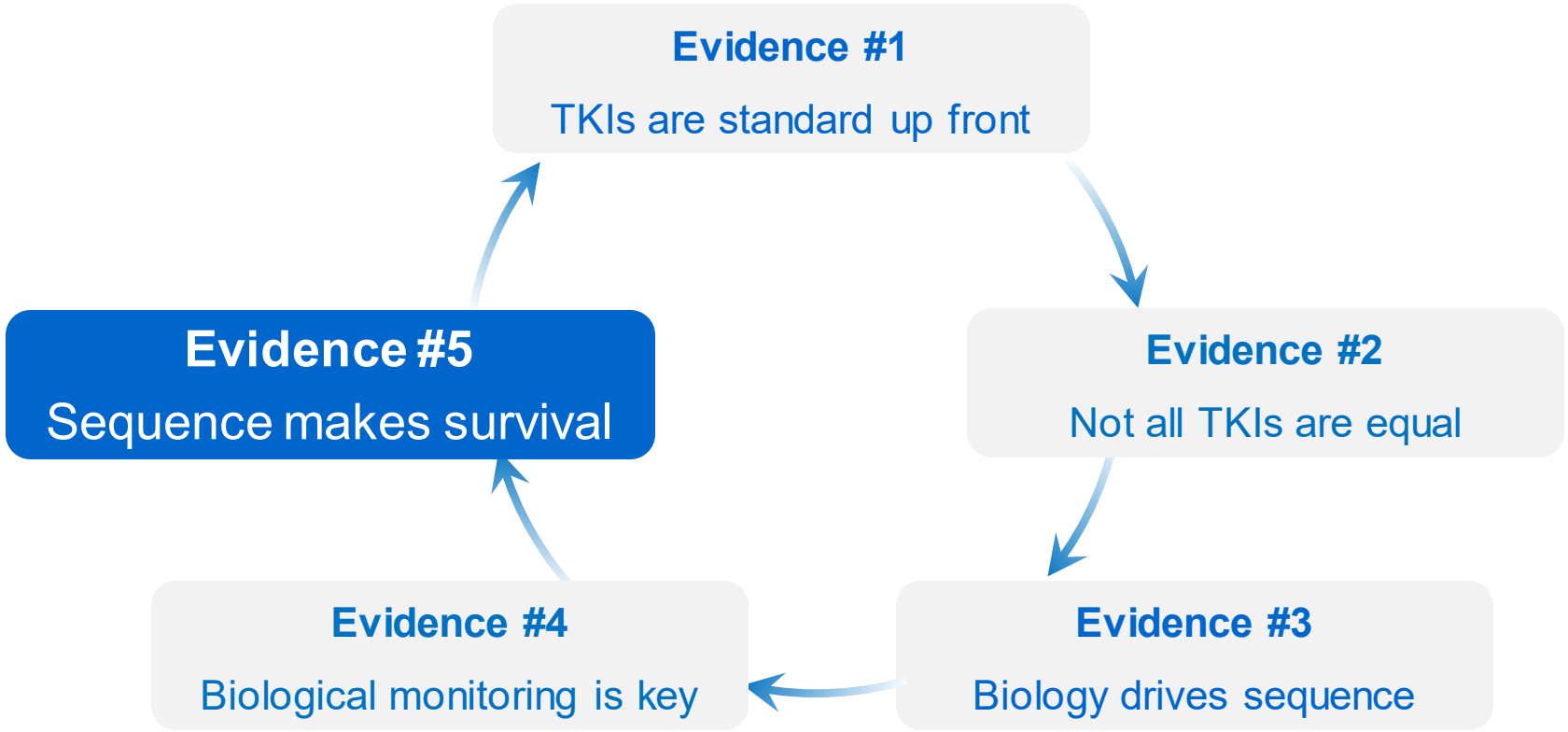
Tumour DNA Is Shed Into the Circulation (ctDNA)[6]



ARMS = amplification-refractory mutation system; cDNA = complementary DNA; COLD-PCR = coamplification at lower denaturation temperature-polymerase chain reaction; ctDNA = circulating tumour DNA; ddPCR = Droplet Digital™ PCR; NGS = next-generation sequencing.

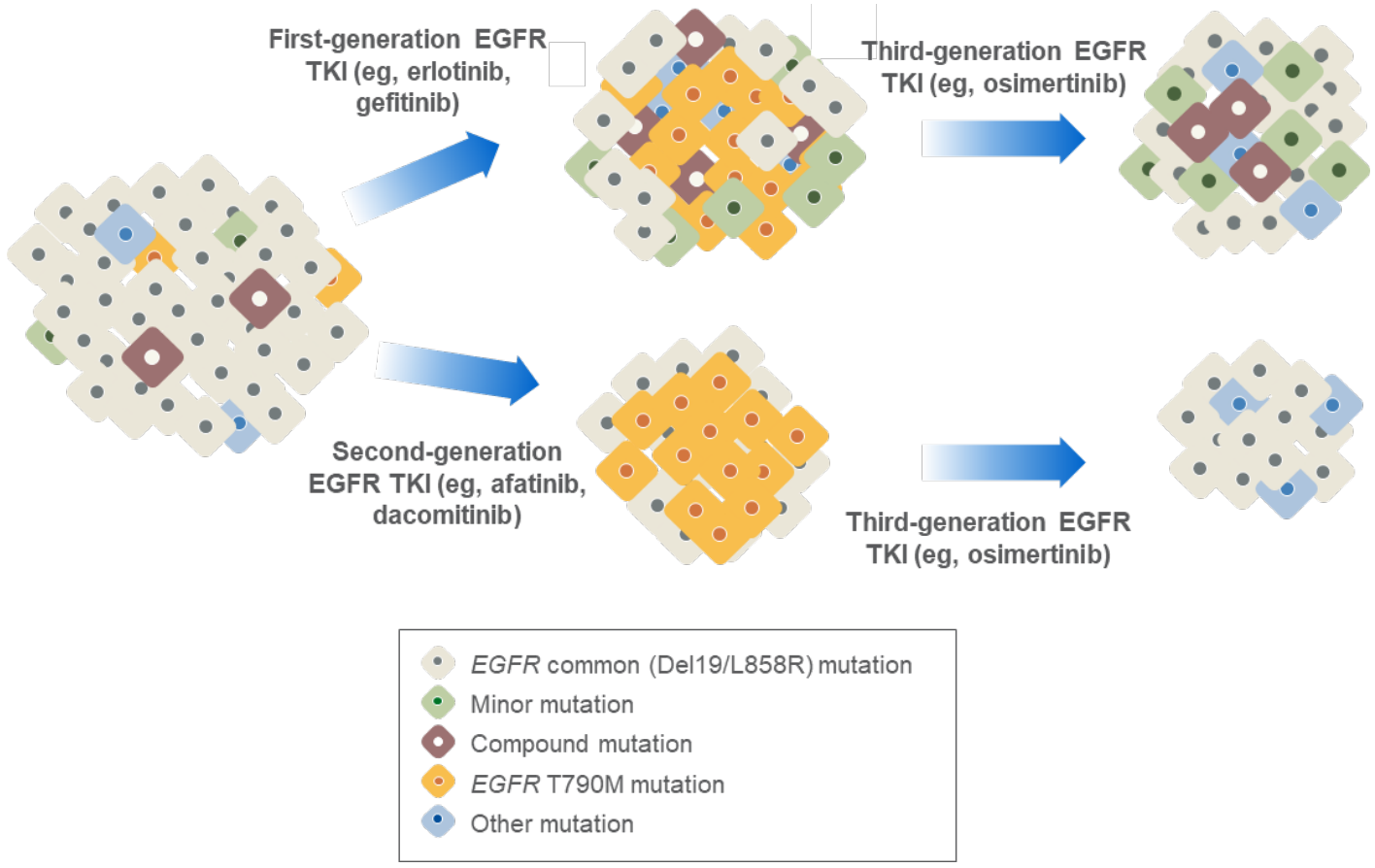
1. Diaz and Bardelli. *J Clin Oncol*. 2014;32:579; 2. Milbury et al. *Expert Rev Mol Diagn*. 2011;11:159; 3. Kim et al. *BioMed Res Int*. 2018;2018:7392419; 4. How et al. *Hum Mutat*. 2013;34:1568; 5. Oxnard et al. *Clin Cancer Res*. 2014;20:169; 6. Crowley et al. *Nat Rev Clin Oncol*. 2013;10(8):472.

Evidence to Select and Sequence Therapies in EGFR M+ NSCLC



Girard. *Future Oncol*. 2018;14:1117.

Hypothetical Changes in Clonal Composition Over Time Following Treatment With Sequential EGFR TKIs

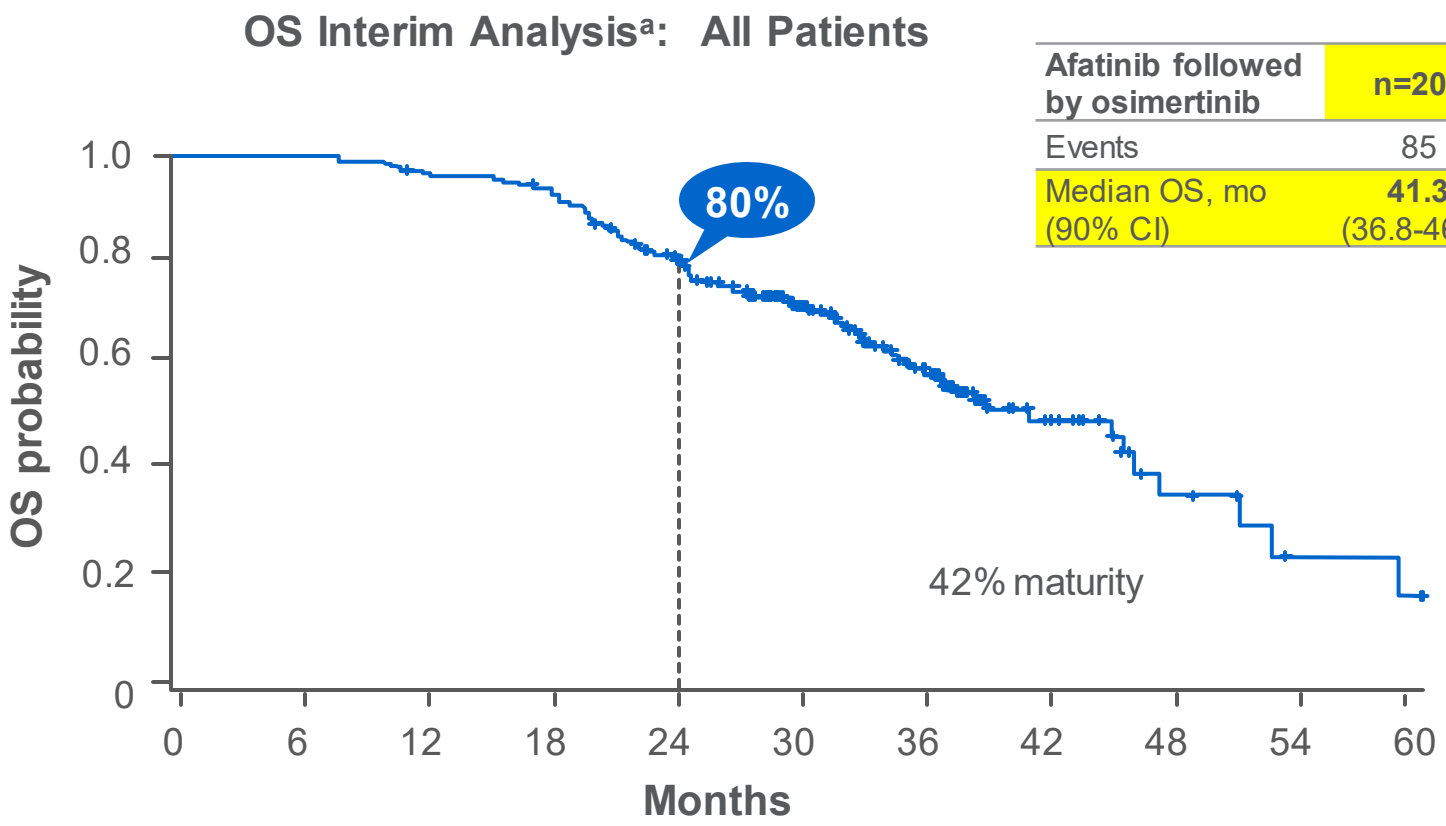


- After 1st-gen. TKI, tumour clones are **heterogenous**.
- Broad inhibitory profile of 2nd-gen TKIs could delay onset of clonal expansion, resulting in a more **homogenous** subclone, and delay acquired resistance as with 1st-gen. TKIs
- This might be the reason for observed improvements in PFS
- After 3rd-gen. TKI, tumour clones are very **heterogenous**, decreasing availability of targeted therapies

Kohsaka et al. *Future Oncol*. 2019;15(6):637.

Overall Survival in Patients Receiving Afatinib Followed by Osimertinib in Acquired T790M+ NSCLC

GioTag: Global, retrospective, observational, real-world study on sequential therapy in patients with EGFR M+ advanced NSCLC



Primary outcome; median TTF[b] with sequential afatinib and osimertinib was **28.1 months** (90% CI, 26.8-30.3), with 15.6 months (90% CI, 13.8-17.1) time on osimertinib.

[a]Data cutoff April 2019.
[b]Time on treatment defined as the time from the first dose of afatinib to that of the last dose of osimertinib or death.
OS = overall survival; TTF = time to treatment failure.
Hochmair et al. *Future Oncol*. 2019;15:2905.

Overall Survival in Patients Receiving Afatinib Followed by Osimertinib in Acquired T790M+ NSCLC

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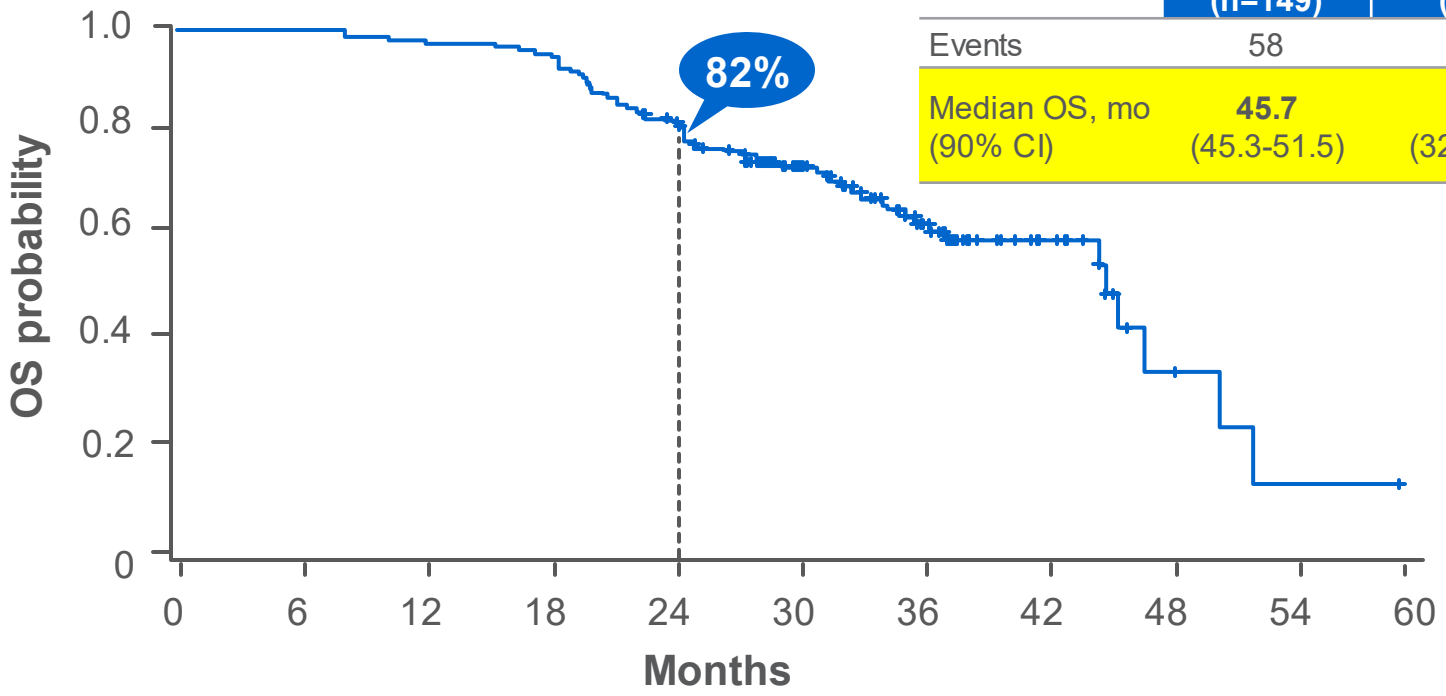
OS Interim Analysis[a]: Del19 Subgroup



	Del19 (n=149)	L858R (n=53)
Events	58	27
Median OS, mo (90% CI)	**45.7** (45.3-51.5)	**35.2** (32.0-39.1)

No. at risk											
Afa-Osi	149	149	145	141	119	82	50	18	4	1	1

[a]Data cutoff April 2019.
[b]Time on treatment defined as the time from the first dose of afatinib to that of the last dose of osimertinib or death.
OS = overall survival; TTF = time to treatment failure.
Hochmair et al. *Future Oncol*. 2019;15:2905.

FLAURA Final Analysis: Overall Survival

	Osimertinib	Comparator EGFR-TKI
Median OS, mo (95% CI)	38.6 (34.5, 41.8)	31.8 (26.6, 36.0)
HR (95.05% CI)	**0.799 (0.641, 0.997); *P*=0.0462**	

Data cut-off 25 June 2019.
For statistical significance, a p-value of less than 0.0495, determined by O'Brien-Fleming approach, was required.
Ramalingham et al. Presented at ESMO 2019. Abstract LBA5_PR (oral presentation).

EGFR TKI 1L Combination Strategies

- Combination strategies may help overcome resistance mechanisms and enhance the anticancer effect of individual strategies[1]
- Combination strategies with antiangiogenics or chemotherapy have shown encouraging results[2-7]
  - **Antiangiogenics**
    - **Bevacizumab + erlotinib[2-4]**
    - **Ramucirumab + erlotinib[5]**
  - **Chemotherapy**
    - **Gefitinib + carboplatin/pemetrexed[6,7]**
- After combination therapy, appropriate subsequent therapy options may need further investigation

1. Yang Z et al. Int *J Biol Sci*. 2018;14:204; 2. Seto et al. *Lancet Oncol*. 2014;15:1236; 3. Furuya et al. *J Clin Oncol*. 2018;36(suppl_abstract 9006) (oral presentation); 4. Saito et al. *Lancet Oncol*. 2019;20:625; 5. Nakagawa et al. *J Clin Oncol*. 2019;37(suppl):9000 (oral presentation); 6. Nakamura et al. *J Clin Oncol*. 2018;36(suppl):9005 (oral presentation); 7. Noronha et al. *J Clin Oncol*. 2019. [Epub ahead of print].