

#### 2019台灣胸腔暨重症加護醫學會

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Clinical outcomes and secondary epidermal growth factor receptor (EGFR) T790M mutation among first-line gefitinib, erlotinib and afatinib-treated non-small cell lung cancer patients with activating EGFR mutations

Lin YT et al. Int J Cancer. 2019 Jun 1;144(11):2887-2896.

台大醫院內科部 林彥廷 Dec 07, 2019



# FDA APPROVED EGFR TKIS

- First generation
  - Gefitinib
  - Erlotinib
- Second generation
  - Afatinib
  - Dacomitinib
- Third generation
  - Osimertinib



Hsu K-H et al. PLoS ONE. 2015, 10(3):e0120852.



# DIRECT COMPARISON BETWEEN FIRST-LINE EGFR TKIS IN RCTS

#### **CTONG 0901**

- Erlotinib vs Gefitinib RCT
- A single center trial
- N=128/128
- Trial start: 2009/06
- Sponsor: nil

#### LUX-Lung 7

- Afatinib vs GefitinibRCT
- A global trial
- N=160/159
- Trial start: 2011/12
- Sponsor: Boehringer Ingelheim



## CTONG 0901

#### • Erlotinib

- Median PFS
  - 13.4 months
- Median OS
   22.9 months

#### • Gefitinib

- Median PFS
   o 10.4 months
- Median OS20.1 months

П

Group

Gefitinib

Erlotinib

20

6

73

30

50

49

Time (months)





P

0.250

Median (m)

20.1

22.9

Event

92

92

Hazard ratio (95% Cl) = 0.84 (0.63~1.13)

128

128

Yang JJ et al. Br J Cancer. 2017 Feb 28;116(5):568-574.

40

38

41

50

38

39

60

70



# LUX-LUNG 7

#### • Afatinib

- Median PFS
  - 11.0 months
- Median OS
  - 27.9 months



- Median PFS
   0 10.9 months (p=0.017)
- Median OS

   24.5 months (p=0.258)





Park K et al. *Lancet Oncol.* 2016; 17: 577–89 Paz-Ares L et al. *Ann Oncol.* 2017 Feb 1;28(2):270-277.



# LUX-LUNG 7 PFS

В

|   | Events (n)/patients (n)   |                                      | Median progression<br>months (95% CI)                 | n-free survival,                                     | HR (95% CI)  | p <sub>interaction</sub> |  |
|---|---------------------------|--------------------------------------|---|--|--|--------------------------|--|
|   |                           |                                      | Afatinib  | Gefitinib  |  |                          |  |
| EGFR mutation   |                           |                                      |   |  |  |                          |  |
| Leu858Arg<br>Del19  | 102/133<br>144/186        | <br>                                 | 10·9 (8·1–12·9)<br>12·7 (10·6–14·7)                   | 10·8 (7·2–12·8)<br>11·0 (9·1–12·7)                   | 0·71 (0·48–1·06)<br>0·76 (0·55–1·06)                     | 0.809                    |  |
| Brain metastases<br>Absent<br>Present                           | 204/268<br>42/51          | _ <b>+</b>                           | 12·7 (10·9–13·3)<br>7·2 (3·7–17·0)                    | 10·9 (9·1–12·7)<br>7·4 (5·4–12·8)                    | 0·74 (0·56–0·98)<br>0·76 (0·41–1·44)                     | 0.93                     |  |
| Baseline ECOG PS  |                           |                                      |   |  |  |                          |  |
| 0<br>1  | 63/98<br>183/221          | <br>                                 | 11·0 (10·6–17·4)<br>11·0 (9·0–13·2)                   | 12·8 (10·8–14·7)<br>10·5 (8·0–11·0)                  | 0·89 (0·54–1·47)<br>0·71 (0·52–0·95)                     | 0.43                     |  |
| Sex   |                           |                                      |   |  |  |                          |  |
| Men<br>Women  | 99/122<br>147/197         | <br>                                 | 10·9 (7·3–12·9)<br>12·8 (10·8–14·7)                   | 10·8 (7·3–12·8)<br>10·9 (9·0–12·2)                   | 0·88 (0·59–1·31)<br>0·65 (0·47–0·91)                     | 0.39                     |  |
| Age (years)   |                           |                                      |   |  |  |                          |  |
| <65<br>≥65  | 131/177<br>115/142        | <b>+_</b> _                          | 11·0 (9·2–17·0)<br>11·0 (9·2–12·9)                    | 9·2 (7·3–11·0)<br>11·4 (10·8–12·9)                   | 0·68 (0·48–0·97)<br>0·85 (0·59–1·22)                     | 0.309                    |  |
| Ethnic origin   |                           |                                      |   |  |  |                          |  |
| Non-Asian<br>Asian  | 105/137<br>141/182        | <br>                                 | 12·7 (10·8–14·7)<br>11·0 (9·1–12·9)                   | 10·6 (7·4–12·7)<br>11·0 (9·1–12·8)                   | 0·72 (0·49–1·06)<br>0·76 (0·54–1·06)                     | 0.88                     |  |
| Smoking history   |                           |                                      |   |  |  |                          |  |
| Never smoked<br>Light ex-smoker*<br>Other current or ex-smokers | 161/212<br>35/40<br>50/67 |                                      | 11·0 (9·2–12·9)<br>9·2 (7·2–10·9)<br>17·0 (10·7–20·1) | 11·0 (9·1–12·8)<br>10·9 (7·2–13·3)<br>9·1 (3·5–12·7) | 0·80 (0·58–1·10)<br>1·09 (0·56–2·14)<br>0·48 (0·27–0·85) | 0.083                    |  |
| Total   | 246/319                   | -                                    | 11.0 (10.6–12.9)                                      | 10·9 (9·1–11·5)                                      | 0.73 (0.57-0.95)   |                          |  |
|   | 1/16<br>Fav               | 1/4 1 4<br>vours afatinib Favours ge | 16<br>£fitinib<br>▶                                   |  |  |                          |  |

Park K et al. Lancet Oncol. 2016; 17: 577-89

#### LUX-LUNG 7 ADVERSE EFFECTS

|                             | Afatinib (n=160) |          |         |         | Gefitinib (n=159) |          |         |         |
|-----------------------------|------------------|----------|---------|---------|-------------------|----------|---------|---------|
|                             | Grades 1-2       | Grade 3  | Grade 4 | Grade 5 | Grades 1–2        | Grade 3  | Grade 4 | Grade 5 |
| Total                       | 106 (66%)        | 47 (29%) | 3 (2%)  | 0       | 124 (78%)         | 26 (16%) | 2 (1%)  | 1 (1%)  |
| Diarrhoea                   | 124 (78%)        | 19 (12%) | 1(1%)   | 0       | 95 (60%)          | 2 (1%)   | 0       | 0       |
| Rash or acne*               | 127 (79%)        | 15 (9%)  | 0       | 0       | 124 (78%)         | 5 (3%)   | 0       | 0       |
| Stomatitis†                 | 96 (60%)         | 7 (4%)   | 0       | 0       | 38 (24%)          | 0        | 0       | 0       |
| Paronychia‡                 | 86 (54%)         | 3 (2%)   | 0       | 0       | 26 (16%)          | 1(1%)    | 0       | 0       |
| Dry skin                    | 52 (33%)         | 0        | 0       | 0       | 59 (37%)          | 0        | 0       | 0       |
| Pruritus                    | 37 (23%)         | 0        | 0       | 0       | 36 (23%)          | 0        | 0       | 0       |
| Fatigue§                    | 24 <b>(</b> 15%) | 9 (6%)   | 0       | 0       | 23 (14%)          | 0        | 0       | 0       |
| Decreased appetite          | 25 (16%)         | 1(1%)    | 0       | 0       | 19 (12%)          | 0        | 0       | 0       |
| Nausea                      | 24 (15%)         | 2 (1%)   | 0       | 0       | 22 (14%)          | 0        | 0       | 0       |
| Alopecia                    | 17 (11%)         | 0        | 0       | 0       | 24 (15%)          | 0        | 0       | 0       |
| Vomiting                    | 17 (11%)         | 0        | 0       | 0       | 5 (3%)            | 1(1%)    | 0       | 0       |
| Increased ALT/AST           | 16 (10%)         | 0        | 0       | 0       | 25 (16%)          | 13 (8%)  | 1 (1%)  | 0       |
| Nasal dryness               | 10 (6%)          | 1(1%)    | 0       | 0       | 0                 | 0        | 0       | 0       |
| Conjunctivitis¶             | 7 (4%)           | 0        | 0       | 0       | 9 (6%)            | 1(1%)    | 0       | 0       |
| Hand-foot syndrome          | 5 (3%)           | 1(1%)    | 0       | 0       | 3 (2%)            | 0        | 0       | 0       |
| Weight decreased            | 5 (3%)           | 1(1%)    | 0       | 0       | 0                 | 0        | 0       | 0       |
| Hypokalaemia                | 4 (3%)           | 3 (2%)   | 0       | 0       | 1(1%)             | 0        | 0       | 0       |
| Neutropenia                 | 2 (1%)           | 0        | 1 (1%)  | 0       | 1 (1%)            | 0        | 0       | 0       |
| Increased aminotransferases | 2 (1%)           | 0        | 0       | 0       | 0                 | 1(1%)    | 0       | 0       |
| Toxic skin eruption         | 2 (1%)           | 1(1%)    | 0       | 0       | 0                 | 0        | 0       | 0       |
| Dehydration                 | 1 (1%)           | 3 (2%)   | 0       | 0       | 0                 | 0        | 0       | 0       |
| Pneumonia                   | 1 (1%)           | 1 (1%)   | 0       | 0       | 0                 | 0        | 0       | 0       |
| Confusional state           | 1(1%)            | 1(1%)    | 0       | 0       | 0                 | 0        | 0       | 0       |



# EFFICACY OF FIRST-LINE EGFR TKIS IN THE RCTS

- The efficacy among first-line gefitinib, erlotinib and afatinib TKI is still controversial.
  - Afatinib has better PFS but more adverse effects.
  - The OS were similar among the 3 EGFR TKIs.



| Variable                                     | Gefitinib (n = 134) | Erlotinib (n = 68)     | Afatinib ( $n = 99$ ) | p              |
|--|---------------------|------------------------|-----------------------|----------------|
| Median age (years old) (IQR)                 | 71 (60–80)          | 67 (61–73)             | 60 (53–71)            | <0.001 (ANOVA) |
| Male   | 36 (27%)            | 22 (32%)               | 38 (38%)              | 0.18           |
| Never smoker                                 | 110 (82%)           | 57 (84%)               | 66 (67%)              | 0.007          |
| Adenocarcinoma                               | 130 (97%)           | 65 <mark>(</mark> 96%) | 95 (96%)              | 0.85           |
| EGFR mutation                                |                     |                        |                       | <0.001         |
| Del 19                                       | 48 (36%)            | 27 (40%)               | 59 (60%)              |                |
| L858R  | 76 (57%)            | 37 (53%)               | 23 (23%)              |                |
| G719X, L861X, S768X                          | 3 (2%)              | 2 (3%)                 | 13 (13%)              |                |
| Single T790M                                 | 0 (0%)              | 0 (0%)                 | 0 (0%)                |                |
| Del 19 or L858R or G719X AND T790M           | 4 (3%)              | 1 (2%)                 | 2 (2%)                |                |
| Other complex                                | 3 (2%)              | 0 (0%)                 | 2 (2%)                |                |
| Others                                       | 0 (0%)              | 1 (2%)                 | 0 (0%)                |                |
| Cancer status before EGFR TKI                |                     |                        |                       | 0.21           |
| Post-operative or post-CCRT recurrence       | 25 (19%)            | 17 (25%)               | 14 (14%)              |                |
| Stage IV                                     | 109 (81%)           | 51 (75%)               | 85 (86%)              |                |
| ECOG 0–1 before EGFR TKI                     | 128 (89%)           | 64 (94%)               | 92 (93%)              | 0.26           |
| M1a disease or intrathoracic recurrence only | 62 (46%)            | 16 (24%)               | 29 (29%)              | 0.002          |
| Brain metastasis                             | 11 (8%)             | 38 <b>(</b> 56%)       | 31 (31%)              | <0.001         |
| Bone metastasis                              | 45 (34%)            | 27 (40%)               | 44 (44%)              | 0.24           |
| Liver metastasis                             | 13 (10%)            | 10 (15%)               | 9 (9%)                | 0.46           |
| Median follow-up time (month) (IQR)          | 21.1 (17.4–27.4)    | 19.5 (12.6–26.6)       | 20.3 (14.1–25.0)      | 0.72           |

#### **Table 1.** Patents' Demographic Data (n = 301)



### FIRST LINE EGFR TKI PFS

n = 301 p = 0.67 by log-rank test





### FIRST LINE EGFR TKI TTF

n = 301 p = 0.19 by log-rank test





#### PROGRESSION-FREE SURVIVAL

#### **Table 2.** Progression-free Survival: Univariate and Multivariate Analysis (n = 301)

|                                 | Univariate analysis |           |         | Mu                 | Multivariate analysis |                |  |  |
|---------------------------------|---------------------|-----------|---------|--------------------|-----------------------|----------------|--|--|
| Variable                        | Hazard ratio        | 95% CI    | p Value | Adjusted hazard ra | tio 95% Cl            | <i>p</i> Value |  |  |
| Age (≥70)                       | 1.06                | 0.80-1.41 | 0.67    |                    |                       |                |  |  |
| Male sex                        | 1.06                | 0.79-1.41 | 0.72    |                    |                       |                |  |  |
| Never-smoker                    | 0.79                | 0.58-1.09 | 0.15    |                    |                       |                |  |  |
| ECOG ≥2                         | 2.13                | 1.38-3.30 | 0.001   | 1.73               | 1.09-2.75             | 0.02           |  |  |
| Post-operative recurrence       | 0.62                | 0.42-0.91 | 0.02    | 0.69               | 0.46-1.03             | 0.07           |  |  |
| EGFR mutation                   |                     |           |         |                    |                       |                |  |  |
| Exon 19 deletion                | 1.00 <sup>2</sup>   |           | 0.004   | 1.00 <sup>2</sup>  |                       | 0.01           |  |  |
| L858R                           | 1.20                | 0.89-1.62 | 0.23    | 1.13               | 0.82-1.56             | 0.44           |  |  |
| Uncommon mutation <sup>1</sup>  | 2.14                | 1.37-3.33 | 0.001   | 2.02               | 1.27-3.21             | 0.003          |  |  |
| EGFR TKI                        |                     |           |         |                    |                       |                |  |  |
| Gefitinib                       | 1.00 <sup>3</sup>   |           | 0.67    | 1.00 <sup>3</sup>  |                       | 0.46           |  |  |
| Erlotinib                       | 0.85                | 0.59-1.22 | 0.38    | 0.78               | 0.52-1.18             | 0.25           |  |  |
| Afatinib                        | 0.94                | 0.68-1.29 | 0.68    | 0.84               | 0.59-1.21             | 0.84           |  |  |
| M1a or intrathoracic recurrence | 0.66                | 0.48-0.89 | 0.007   | 0.82               | 0.58-1.16             | 0.27           |  |  |
| Initial brain metastasis        | 1.39                | 1.02-1.88 | 0.04    | 1.27               | 0.87-1.84             | 0.21           |  |  |
| Initial liver metastasis        | 1.55                | 1.03-2.35 | 0.04    | 1.45               | 0.94-2.25             | 0.09           |  |  |



## FIRST LINE EGFR TKI OS





## OVERALL SURVIVAL

**Table 3.** Overall survival: univariate and multivariate analysis (n = 301)

|                                 | Univariate analysis |           |         |        | Multivariate analysis |           |                |  |  |
|---------------------------------|---------------------|-----------|---------|--------|-----------------------|-----------|----------------|--|--|
| Variable                        | Hazard ratio        | 95% CI    | p Value | Adjust | ed hazard ratio       | 95% CI    | <i>p</i> Value |  |  |
| Age (≥ 70)                      | 1.31                | 0.90-1.92 | 0.16    |        |                       |           |                |  |  |
| Male sex                        | 0.96                | 0.64-1.43 | 0.83    |        |                       |           |                |  |  |
| Never-smoker                    | 0.84                | 0.55-1.30 | 0.43    |        |                       |           |                |  |  |
| ECOG ≥2                         | 3.11                | 1.82-5.31 | <0.001  |        | 2.67                  | 1.52-4.72 | 0.001          |  |  |
| Post-operative recurrence       | 0.47                | 0.26-0.84 | 0.01    |        | 0.56                  | 0.31-1.01 | 0.06           |  |  |
| EGFR mutation                   |                     |           |         |        |                       |           |                |  |  |
| Exon 19 deletion                | 1.00 <sup>2</sup>   |           | 0.14    |        | 1.00 <sup>2</sup>     |           | 0.18           |  |  |
| L858R                           | 1.10                | 0.73-1.66 | 0.65    |        | 0.92                  | 0.59-1.42 | 0.70           |  |  |
| Uncommon mutation <sup>1</sup>  | 1.78                | 1.00-3.17 | 0.049   |        | 1.61                  | 0.89-2.94 | 0.12           |  |  |
| EGFR TKI                        |                     |           |         |        |                       |           |                |  |  |
| Gefitinib                       | 1.00 <sup>3</sup>   |           | 0.81    |        | 1.00 <sup>3</sup>     |           | 0.80           |  |  |
| Erlotinib                       | 1.17                | 0.73-1.90 | 0.51    |        | 0.93                  | 0.54-1.61 | 0.81           |  |  |
| Afatinib                        | 1.07                | 0.69-1.66 | 0.77    |        | 0.84                  | 0.51-1.39 | 0.51           |  |  |
| M1a or intrathoracic recurrence | 0.60                | 0.39-0.91 | 0.02    |        | 1.00                  | 0.60-1.67 | 0.99           |  |  |
| Initial brain metastasis        | 2.27                | 1.54-3.35 | <0.001  |        | 2.11                  | 1.28-3.46 | 0.003          |  |  |
| Initial liver metastasis        | 1.63                | 0.94-2.81 | 0.08    |        | 1.69                  | 0.94-3.03 | 0.08           |  |  |



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#### SECONDARY T790M

- Accounting for around 50% EGFR TKI resistance
  - Gefitinib Kobayash
    - Kobayashi S et al. N Engl J Med. 2005 Feb 24;352(8):786-92.

• Erlotinib

Pao W et al. *PLoS Med*. 2005 Mar;2(3):e73.

• Afatinib

Wu SG et al. Oncotarget. 2016 Mar 15;7(11):12404-13.

- Tumors with T790M tends to grow slower.
- Patients with T790M have better TKI PFS and



Yoon BW et al. Transl Oncol. 2019 Jun;12(6):852-858.



#### OSIMERTINIB IS EFFECTIVE TO CONTROL LUNG CANCER WITH ACQUIRED EGFR T790M MUTATION.







#### Patients with Adequate Tissue for Rebiopsy\* (n=92)

| Variable                                      | Secondary       | No secondary    | Total Rebiopsied | p value (between                    |
|---|-----------------|-----------------|------------------|-------------------------------------|
|   | T790M           | T790M           | patients         | with/without 2 <sup>nd</sup> T790M) |
|   | (n=40)          | (n=52)          | (n=92)           | _                                   |
| Median age (year-old) (IQR)                   | 65 (58-71)      | 66 (55-73)      | 66 (57-73)       | 0.96                                |
| Male  | 19 (48%)        | 18 (35%)        | 37 (40%)         | 0.21                                |
| Never smoker                                  | 36 (90%)        | 37 (71%)        | 67 (73%)         | 0.68                                |
| Adenocarcinoma                                | 40 (100%)       | 50 (96%)        | 90 (98%)         | 0.46                                |
| Initial EGFR mutation                         |                 |                 |                  | 0.06                                |
| Del 19  | 22 (55%)        | 20 (39%)        | 42 (46%)         |                                     |
| L858R   | 16 (40%)        | 22 (42%)        | 38 (41%)         |                                     |
| G719X, L861X, S768                            | 0 (0%)          | 8 (15%)         | 8 (9%)           |                                     |
| T790M   | 0 (0%)          | 0 (0%)          | 0 (0%)           |                                     |
| Del 19 or L858R or G719X AND T790M            | 0 (0%)          | 0 (0%)          | 0 (0%)           |                                     |
| Other Complex                                 | 2 (5%)          | 2 (4%)          | 4 (4%)           |                                     |
| Others  | 0 (0%)          | 0 (0%)          | 0 (0%)           |                                     |
| First line EGFR TKI                           |                 |                 |                  | 0.14                                |
| Gefitinib                                     | 22 (55%)        | 18 (35%)        | 40 (44%)         |                                     |
| Erlotinib                                     | 6 (15%)         | 10 (19%)        | 16 (17%)         |                                     |
| Afatinib                                      | 12 (30%)        | 24 (46%)        | 36 (39%)         |                                     |
| Cancer status before EGFR TKI                 |                 |                 |                  | 0.43                                |
| Post-operative or post-CCRT recurrence        | 6 (15%)         | 5 (10%)         | 11 (12%)         |                                     |
| Stage IV                                      | 34 (85%)        | 47 (90%)        | 81 (88%)         |                                     |
| ECOG 0-1 before 1 <sup>st</sup> line EGFR TKI | 39 (98%)        | 48 (92%)        | 87 (95%)         | 0.28                                |
| Initial M1a disease or intrathoracic          | 13 (33%)        | 16 (31%)        | 29 (32%)         | 0.86                                |
| recurrence only                               |                 |                 |                  |                                     |
| Initial brain metastasis                      | 5 (13%)         | 15 (29%)        | 20 (22%)         | 0.06                                |
| Initial bone metastasis                       | 15 (38%)        | 20 (39%)        | 35 (38%)         | 0.93                                |
| Initial liver metastasis                      | 9 (23%)         | 4 (8%)          | 13 (14%)         | 0.04                                |
| First line EGFR TKI Duration (month) (IQR)    | 15.1 (8.3-17.2) | 10.7 (6.4-15.2) | 11.8 (6.9-16.6)  | 0.02                                |

\*Patients with initial EGFR T790M mutation before TKI treatment were excluded.



# FACTORS ASSOCIATED WITH SECONDARY T790M

|                                       | Univariate analysis |            |         |        | Multivariate Backward LR model |            |                |  |
|---------------------------------------|---------------------|------------|---------|--------|--------------------------------|------------|----------------|--|
| Variable                              | Odds ratio          | 95% CI     | p Value | Adjust | ed odds ratio                  | 95% CI     | <i>p</i> Value |  |
| Age (≥ 70)                            | 1.11                | 0.46-2.65  | 0.82    |        |                                |            |                |  |
| Male                                  | 1.71                | 0.74-3.97  | 0.21    |        | 3.25                           | 1.10-9.66  | 0.034          |  |
| Never-smoker                          | 1.22                | 0.48-3.09  | 0.68    |        |                                |            |                |  |
| EGFR mutation                         |                     |            |         |        |                                |            |                |  |
| Exon 19 deletion                      | 1.00 <sup>1</sup>   |            | 0.11    |        | 1.00 <sup>1</sup>              |            | 0.10           |  |
| L858R                                 | 0.66                | 0.27-1.60  | 0.36    |        | 0.47                           | 0.16-1.36  | 0.16           |  |
| Uncommon mutation <sup>2</sup>        | 0.18                | 0.04-0.93  | 0.04    |        | 0.14                           | 0.02-0.97  | 0.047          |  |
| Gefitinib <sup>3</sup>                | 2.31                | 0.99-5.38  | 0.05    |        | 3.29                           | 1.15-9.46  | 0.027          |  |
| 1st-line EGFR TKI duration ≥13 months | 3.34                | 1.40-7.95  | 0.006   |        | 3.16                           | 1.20-8.33  | 0.020          |  |
| Initial brain metastasis              | 0.35                | 0.12-1.07  | 0.07    |        |                                |            |                |  |
| Initial liver metastasis              | 3.48                | 0.99-12.30 | 0.052   |        | 4.97                           | 1.18-20.96 | 0.029          |  |

**Table 4.** Logistic Regression for Secondary T790M: Univariate and Multivariate analysis (n = 92)

Independent factors from the study: Male, uncommon EGFR mutation, first-line gefitinib, EGFR TKI duration and initial liver metastasis



#### FINDINGS FROM THE STUDY

- Choosing first-line EGFR TKI according to patients' clinical characteristics yielded good clinical outcome.
  - Median OS 37.0 months
  - <u>Neither PFS nor OS difference was seen</u> among gefitinib, erlotinib and afatinib groups.
  - <u>Uncommon</u> EGFR mutation was associated with <u>shorter</u> PFS.
- We reported factors associated with secondary T790M mutation.
  - EGFR TKI treatment duration
  - EGFR mutation type
  - EGFR TKI
  - Gender
  - Initial metastasis site

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