**Table 2. Number of biopsy and detection on T790M**

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **1st** | **2nd** | **3rd** | **4th** |  |  |  |  |  |  | **Total** |
| **Tissue biopsy (Individual test)** |  |  |  |  |  |  |  |
| **T790M positive** | **21** | **2** | **0** | **1** |  |  |  |  |  |  | **24** |
| With original mutation | 26 | 5 | 3 | 3 |  |  |  |  |  |  | 37 |
| **Total** | **31** | **6** | **3** | **3** |  |  |  |  |  |  | **43** |
| **Tissue biopsy (Cumulative test)** |  |  |  |  |  |  |  |
| **T790M positive** | **21** | **23** | **23** | **24** |  |  |  |  |  |  | **24** |
| Cumulative sensitivity | 0.81 | 0.79 | 0.77 | 0.77 |  |  |  |  |  |  | 0.77 |
| **Total** | **31** | **37** | **40** | **43** |  |  |  |  |  |  | **43** |
|  | **1st** | **2nd** | **3rd** | **4th** | **5th** | **6th** | **7th** | **8th** | **9th** | **10th** | **Total** |
| **Liquid biopsy (Individual test)** |  |
| **T790M positive** | **3** | **4** | **1** | **0** | **0** | **1** | **1** | **1** | **0** | **0** | **11** |
| With original mutation | 13 | 5 | 4 | 1 | 1 | 2 | 1 | 1 | 0 | 0 | 28 |
| **Total** | **37** | **17** | **11** | **7** | **7** | **7** | **5** | **4** | **2** | **1** | **98** |
| **Liquid biopsy (Cumulative test)** |  |
| **T790M positive** | **3** | **7** | **8** | **8** | **8** | **9** | **10** | **11** | **11** | **11** | **11** |
| Cumulative sensitivity | 0.13 | 0.21 | 0.2 | 0.18 | 0.17 | 0.17 | 0.18 | 0.19 | 0.19 | 0.19 | 0.19 |
| **Total** | **37** | **54** | **65** | **72** | **79** | **86** | **91** | **95** | **97** | **98** | **98** |

**Table 3. Rebiopsy outcomes**

|  |  |  |
| --- | --- | --- |
| Variable | T790M mutation |  |
| Positive patients (*n* = 29) | Negative patients (n = 17) | Total patients (n = 46) |
| Tissue biopsy (included cytology) count | **31** | **12** | **43** |
|  | T790M positive count | **24 (77.4)** | **-** | **24 (55.8)** |
|  | With Original mutation | 22 | - | 22 |
|  | Without Original mutation | 2 | - | 2 |
|  | T790M negative count | **7 (22.6)** | **12** | **19 (44.2)** |
|  | With Original mutation | 5 | 10 | 15 |
|  | Without Original mutation | 2 | 2 | 4 |
| Liquid biopsy count | **58** | **40** | **98** |
|  | T790M positive count | **11 (19.0)** | **-** | **11 (11.2)** |
|  | With Original mutation | 10 | - | 10 |
|  | Without Original mutation | 1 | - | 1 |
|  | T790M negative count | **47 (81.0)** | **40** | **87 (88.8)** |
|  | With Original mutation | 9 | 11 | 20 |
|  | Without Original mutation | 38 | 29 | 67 |
| Total rebiopsy count | **89** | **52** | **141** |

Data are number of patients (%) unless specified otherwise.

**Table 4. Logistic regression analysis to identify patients harboring the T790M substitution among those with EGFR-mutated lung cancer (n = 53)**

|  |  |  |
| --- | --- | --- |
| Variables | Univariate Analyses | Multivariate Analysis |
| OR | 95%CI | *P-value* | OR | 95%CI | *P-value* |
| **Mutation site at initial diagnosis; Exon 19 Deletion vs. L858R** | **0.17** | **0.05 - 0.51** | **0.002** | **0.04** | **0.004 - 0.34** | **0.003** |
| **Reason for termination of TKIs;**  | **2.26** | **1.25 - 4.11** | **0.007** | **3.65** | **1.39 - 9.59** | **0.008** |
| **Ongoing** | **Reference** | **Reference** |
| **AEs** | **1** | **-** | **-** | **1** | **-** | **-** |
| **Tumor** **growth** | **37.3** | **3.30 – 421.6** | **0.003** | **33.8** | **1.60 – 713.3** | **0.024** |
| **New lesions** | **12.4** | **1.32 – 117.0** | **0.027** | **44.9** | **2.13 – 950.9** | **0.014** |
| **Medical Drugs at TKI-naïve line** | **0.24** | **0.08 - 0.72** | **0.01** | **0.09** | **0.01 - 0.62** | **0.014** |
| **Gefitinib** | **Reference** | **Reference** |
| **Erlotinib** | **0.18** | **0.035 - 0.95** | **0.044** | **0.49** | **0.02 – 0.99** | **0.049** |
| **Afatinib** | **0.06** | **0.007 – 0.55** | **0.012** | **0.01** | **0.0002 – 0.53** | **0.02** |
| Chemotherapy; absent vs. present | 2.63 | 0.84 - 8.22 | 0.09 | NI |
| “Serum level of CEA at progression” divided by “Serum nadir level of CEA” | 1.16 | 0.97 - 1.39 | 0.11 | 1.22 | 0.77 - 1.93 | 0.4 |
| Serum nadir level of CEA (ng/mL) | 0.97 | 0.95 - 1.01 | 0.14 | NI |

Abbreviations: OR, Odds ratio; CI, confidence interval; TKI, tyrosine kinase inhibitor; AEs, adverse effects; CEA, carcinoembryonic antigen; Variables with a p-value < 0.15 on univariate analysis were entered into multivariate logistical analysis by a simultaneous method. NI, not included in the best multivariate logistic regression model.

**Table 6. Logistic regression analysis to identify patients harboring the T790M substitution upon rebiopsy (n = 89)**

|  |  |  |
| --- | --- | --- |
| Variables | Univariate Analyses | Multivariate Analysis |
| OR | 95%CI | *P-value* | OR | 95%CI | *P-value* |
| **Original mutation; absent vs. present** | **30.5** | **8.05 - 115.3** | **< 0.001** | **41.5** | **6.53 - 264.3** | **< 0.001** |
| Type of Biopsy; Liquid vs. Tissue | 14.6 | 5.04 - 42.6 | < 0.001 | NI |
| Detection of New tumor lesion; < 4 vs 4 ≤ | 5.67 | 2.24 - 14.4 | < 0.001 | NI |
| Number of Tissue biopsy | 5.72 | 2.30 - 14.2 | < 0.001 | NI |
| Detection of New metastatic organ; 0 → 4 | 2.35 | 1.39 - 3.97 | 0.001 | NI |
| Number of tumor lesion; < 6 vs 6 ≤ | 5.61 | 2.0 - 15.7 | 0.001 | NI |
| **Brain metastases; absent vs. present**　 | **4.40** | **1.71 - 11.3** | **0.002** | **27.8** | **3.13 - 247.8** | **0.003** |
| Bone metastases; absent vs. present　 | 3.94 | 1.55 - 9.98 | 0.004 | NI |
| Number of Liquid biopsy | 0.69 | 0.52 - 0.90 | 0.006 | NI |
| **Enlargement of Tumor size; < 12mm vs 12mm** ≤ | **3.47** | **1.42 - 8.49** | **0.007** | **24.5** | **2.65 - 226.7** | **0.005** |
| New brain metastases; absent vs. present | 4.5 | 1.26 - 16.1 | 0.02 | NI |
| Mutation site at initial diagnosis; Exon19 Deletion vs. L858R | **3.08** | **1.06 - 8.95** | **0.04** | 3.90 | 0.63 - 24.3 | 0.145 |
| **Minor site metastases; absent vs. present** | **4.20** | **1.07 - 16.5** | **0.04** | **21.3** | **1.40 - 325.6** | **0.03** |
| New hepatic metastases; absent vs. present | 3.64 | 0.85 - 15.7 | 0.08 | NI |
| New minor site metastases; absent vs. present | 4.48 | 0.82 - 24.6 | 0.08 | NI |
| Hepatic metastases; absent vs. present | 2.54 | 0.99 - 1.09 | 0.141 | NI |

 Abbreviations: OR, Odds ratio; CI, confidence interval; Variables with a p-value < 0.15 on univariate analysis were entered into multivariate logistical analysis by a simultaneous method. NI, not included in the best multivariate logistic regression model.

**Table 8. Logistic regression analysis to identify patients harboring the T790M substitution through liquid biopsy
(n = 58)**

|  |  |  |
| --- | --- | --- |
| Variables | Univariate Analyses | Multivariate Analysis |
| OR | 95%CI | *P-value* | OR | 95%CI | *P-value* |
| Original mutation; absent vs. present | 42.2 | 4.77 - 373.6 | 0.001 | NI |
| **Bone metastases; absent vs. present** | **48.8** | **5.45 - 436.4** | **0.001** | **77.9** | **5.32 - 1140** | **0.001** |
| Enlargement of Tumor size; < 12mm vs 12mm ≤ | 0.10 | 0.02 - 0.43 | 0.002 | NI |
| Brain metastases; absent vs. present | 7.39 | 1.77 - 30.8 | 0.006 | NI |
| **Detection of New tumor lesion; < 4 vs 4** ≤ | **7.39** | **1.77 - 30.8** | **0.006** | **14.5** | **1.38 - 151.2** | **0.026** |
| Detection of New metastatic organ; 0 → 4 | 1.98 | 1.09 - 3.59 | 0.024 | NI |
| New minor site metastases; absent vs. present | 8.44 | 1.21 - 58.8 | 0.031 | NI |
| Hepatic metastases; absent vs. present | 5.50 | 0.94 - 32.2 | 0.059 | NI |
| Minor site metastases; absent vs. present | 5.50 | 0.94 - 32.2 | 0.059 | NI |
| Mutation site at initial diagnosis; Exon19 Deletion vs. L858R | 3.91 | 0.87 - 17.5 | 0.075 | 1.15 | 0.13 - 10.1 | 0.897 |
| New hepatic metastases; absent vs. present | 5.00 | 0.62 - 40.3 | 0.131 | NI |

Abbreviations: OR, Odds ratio; CI, confidence interval; Variables with a p-value < 0.15 on univariate analysis were entered into multivariate logistical analysis by a simultaneous method. NI, not included in the best multivariate logistic regression model.