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| Additional Table 1 Characteristics of RCTs on NSCLC drugs |
| Studies  |  | Treatment | Route of Placebo Administration | Number of patients | Registered studies |
| Cancer type | Stage of cancer | Drug group | Placebo group | Drug group | Placebo group |
| Reck et al., 2014[1] | NSCLC(Adenocarcinoma 50.1%, Combination 0.7%, Large-cell carcinoma 3.1%, Squamous-cell carcinoma 42.2%, Other 3.9%) | IIIB/IV | 75mg/m² docetaxel + 200mg nintedanib | 75mg/m² docetaxel + 200mg placebo | Oral | 655 | 659 | LUME-Lung 1 |
| Shepherd et al., 2005[2] | NSCLC (Adenocarcinoma 50%, Squamous-cell carcinoma 30%, Other 20%） | IIIB/IV | 150mg erlotinib | 150mg placebo | Oral | 427 | 211 | BR.21 |
| Garon et al., 2014[3] | NSCLC (non-squamous 73%, squamous 26%, Other 1%) | IV | 75mg/m² docetaxel + 10 mg/kg ramucirumab | 75mg/m² docetaxel + 10mg/kg placebo | intravenous | 627 | 618 | REVEL |
| Nakagawa et al., 2019[4] | NSCLC (Adenocarcinoma 96.4%, Other 3.6%) | IV | 150mg/day erlotinib + 10mg/kg ramucirumab | 150mg/day erlotinib + 10mg/kg placebo | intravenous | 224 | 225 | RELAY |
| Reck et al., 2017[5] | NSCLC (Non-squamous 72% (Adenocarcinoma 59%), Squamous 27%, Other 1%) | IV | 75mg/m² docetaxel + 10mg/kg IV ramucirumab | 75mg/m² docetaxel + 10mg/kg placebo | intravenous | 178 | 182 | REVEL |
| Ciuleanu et al., 2009[6] | NSCLC (Non-squamous 73% (Adenocarcinoma 49%, Large cell 3%, Other 20%), Squamous 27%） | IIIB/IV | 500mg/m² pemetrexed + best supportive care | placebo + best supportive care | intravenous | 441 | 222 | H3E-MC-JMEN |
| Garon et al., 2017[7] | NSCLC | IV | 150mg/d erlotinib + 10mg/kg ramucirumab | 150mg/d erlotinib + placebo | intravenous | 225 | 225 | REVEL |
| Hanna et al., 2016[8] | NSCLC (Adenocarcinoma 94%, Combination 0.4%, Large-cell carcinoma 3%, Squamous cell carcinoma 0.7%, Other 1.9%） | IIIB/IV | 500mg/m² pemetrexed + 200mg nintedanib | 500mg/m² Pemetrexed + matching placebo | oral | 353 | 360 | LUME-Lung 2 |
| Wu et al., 2013[9] | NSCLC (Adenocarcinoma 76%, Other 24%） | IIIB/IV | 1250mg/m² gemcitabine +carboplatin / 75mg/m²cisplatin + on day 1, intravenously) platinum with intercalated (150mg/day on days 15–28, orally; chemotherapy plus erlotinib) erlotinib | 1250mg/m²gemcitabine + placebo | oral | 226 | 225 | FASTACT-2 |
| Ramalingam et al., 2018[10] | NSCLC (Nonsquamous 72.8%, Squamous26.2%） | IV | 75mg/m² docetaxel + 10mg/kg ramucirumab | 75mg/m²docetaxel + 10mg/kg placebo | intravenous | 628 | 625 | ARCHER 1009 |
| Pérol et al., 2019[11] | NSCLC (Nonsquamous 73%, Squamous 26%, Unknown 1%） | IIIB/IV | 75mg/m² docetaxel + 10mg/kg ramucirumab | 75mg/m² docetaxel + 10mg/kg placebo | intravenous | 493 | 501 | REVEL |
| Lee et al., 2012[12] | NSCLC (Adenocarcinoma 79%, Squamous 11%, Other 10%） | IIIB/IV | 300 mg/d vandetanib | 300mg/d placebo | oral | 617 | 307 | ZEPHYR |
| Cappuzzo et al., 2010[13] | NSCLC (Adenocarcinoma/bronchoalveolar carcinoma 45%, Squamous cell carcinoma 40%, Other 15% | IIIB/IV | 150mg/d erlotinib | 150mg/d placebo | oral | 438 | 451 | SATURN; BO18192 |
| Scagliotti et al., 2012[14] | NSCLC (Adenocarcinoma 52.7%, Bronchioloalveolar carcinoma 2.7%, Large-cell carcinoma 3.8%, Squamous cell carcinoma 28.1%, Other/NOS 12.7%） | IIIB/IV | 37.5mg/d sunitinib + 150mg/d erlotinib | 150mg/d erlotinib + 150mg/d placebo | oral | 473 | 477 | MONET1 |
| Paz-Ares et al., 2012[15] | NSCLC (Adenocarcinoma 79.4%, Bronchoalveolar 1.6%, Large-cell carcinoma 11.5%, Undifferentiated carcinoma 5.4%, Other 2.1%） | IIIB/IV | 1250mg/m² gemcitabine + 75mg/m² cisplatin + 400mg\*2/d sorafenib | 1250mg/m² gemcitabine + 75mg/m² cisplatin + 400mg\*2/d placebo | oral | 385 | 384 | PARAMOUNT |
| Goss et al., 2010[16] | NSCLC (Adenocarcinoma 42.6%, Squamous 17.9%, Other 39.5%） | IIIB/IV | 200mg/m² Paclitaxel and carboplatin + 30mg cediranib | 200mg/m²Paclitaxel and carboplatin + 30mg placebo | oral | 126 | 123 | BR24 |
| Cicenas et al., 2016[17] | NSCLC (Nonsquamous 64%, Squamous 36%） | IIIB/IV | 150mg/d erlotinib | Placebo | oral | 322 | 319 | IUNO study |
| Herbst et al., 2004[18] | NSCLC (Adenocarcinoma 55.2%, Adenosquamous 2.3%, Bronchoalveolar 3%, Large cell 9%, Squamous 18.8%, Other 11.7%） | IIIA/IIIB/IV | 225mg/m² paclitaxel + carboplatin + 250mg/d gefitinib | 225mg/m² paclitaxel + carboplatin + 250mg/d placebo | oral | 345 | 345 | INTACT 2 |

NSCLC=non-small cell lung cancer, RCT=randomized controlled trial.

**References**

1. Reck M, Kaiser R, Mellemgaard A, et al. Docetaxel plus nintedanib versus docetaxel plus placebo in patients with previously treated non-small-cell lung cancer (LUME-Lung 1): a phase 3, double-blind, randomised controlled trial. Lancet Oncol 2014;15:143-155.

2. Shepherd FA, Rodrigues Pereira J, Ciuleanu T, et al. Erlotinib in previously treated non-small-cell lung cancer. N Engl J Med 2005;353:123-132.

3. Garon EB, Ciuleanu TE, Arrieta O, et al. Ramucirumab plus docetaxel versus placebo plus docetaxel for second-line treatment of stage IV non-small-cell lung cancer after disease progression on platinum-based therapy (REVEL): a multicentre, double-blind, randomised phase 3 trial. Lancet 2014;384:665-673.

4. Nakagawa K, Garon EB, Seto T, et al. Ramucirumab plus erlotinib in patients with untreated, EGFR-mutated, advanced non-small-cell lung cancer (RELAY): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol 2019;20:1655-1669.

5. Reck M, Paz-Ares L, Bidoli P, et al. Outcomes in patients with aggressive or refractory disease from REVEL: A randomized phase III study of docetaxel with ramucirumab or placebo for second-line treatment of stage IV non-small-cell lung cancer. Lung Cancer 2017;112:181-187.

6. Ciuleanu T, Brodowicz T, Zielinski C, et al. Maintenance pemetrexed plus best supportive care versus placebo plus best supportive care for non-small-cell lung cancer: a randomised, double-blind, phase 3 study. Lancet 2009;374:1432-1440.

7. Garon EB, Reck M, Paz-Ares L, et al. Treatment rationale and study design for the RELAY study: a multicenter, randomized, double-blind study of erlotinib with ramucirumab or placebo in patients with epidermal growth factor receptor mutation-positive metastatic non-small-cell lung cancer. Clin Lung Cancer 2017;18:96-99.

8. Hanna NH, Kaiser R, Sullivan RN, et al. Nintedanib plus pemetrexed versus placebo plus pemetrexed in patients with relapsed or refractory, advanced non-small cell lung cancer (LUME-Lung 2): A randomized, double-blind, phase III trial. Lung Cancer 2016;102:65-73.

9. Wu YL, Lee JS, Thongprasert S, et al. Intercalated combination of chemotherapy and erlotinib for patients with advanced stage non-small-cell lung cancer (FASTACT-2): a randomised, double-blind trial. Lancet Oncol 2013;14:777-786.

10. Ramalingam SS, Perol M, Reck M, et al. Efficacy and safety of ramucirumab with docetaxel versus placebo with docetaxel as second-line treatment of advanced non-small-cell lung cancer: a subgroup analysis according to patient age in the REVEL trial. Clin Lung Cancer 2018;19:270-279 e273.

11. Perol M, Winfree KB, Cuyun Carter G, et al. Association of baseline symptom burden with efficacy outcomes: Exploratory analysis from the randomized phase III REVEL study in advanced non-small-cell lung cancer. Lung Cancer 2019;131:6-13.

12. Lee JS, Hirsh V, Park K, et al. Vandetanib Versus placebo in patients with advanced non-small-cell lung cancer after prior therapy with an epidermal growth factor receptor tyrosine kinase inhibitor: a randomized, double-blind phase III trial (ZEPHYR). J Clin Oncol 2012;30:1114-1121.

13. Cappuzzo F, Ciuleanu T, Stelmakh L, et al. Erlotinib as maintenance treatment in advanced non-small-cell lung cancer: a multicentre, randomised, placebo-controlled phase 3 study. Lancet Oncol 2010;11:521-529.

14. Scagliotti GV, Krzakowski M, Szczesna A, et al. Sunitinib plus erlotinib versus placebo plus erlotinib in patients with previously treated advanced non-small-cell lung cancer: a phase III trial. J Clin Oncol 2012;30:2070-2078.

15. Paz-Ares LG, Biesma B, Heigener D, et al. Phase III, randomized, double-blind, placebo-controlled trial of gemcitabine/cisplatin alone or with sorafenib for the first-line treatment of advanced, nonsquamous non-small-cell lung cancer. J Clin Oncol 2012;30:3084-3092.

16. Goss GD AA, Shepherd FA, Dediu M, et al. Randomized, double-blind trial of carboplatin and paclitaxel with either daily oral cediranib or placebo in advanced non-small-cell lung cancer: NCIC clinical trials group BR24 study. J Clin Oncol 2010;28:49-55.

17. Cicènas S, Geater SL, Petrov P, et al. Maintenance erlotinib versus erlotinib at disease progression in patients with advanced non-small-cell lung cancer who have not progressed following platinum-based chemotherapy (IUNO study). Lung Cancer 2016;102:30-37.

18. Herbst RS, Giaccone G, Schiller JH, et al. Gefitinib in combination with paclitaxel and carboplatin in advanced non-small-cell lung cancer: a phase III trial--INTACT 2. J Clin Oncol 2004;22:785-794.