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WCLC 2016 Late Publication Abstracts | Tuesday, December 6, 2016

PRESIDENTIAL SYMPOSIUM

SESSION PL03: PRESIDENTIAL SYMPOSIUM
TUESDAY, DECEMBER 6, 2016 – 08:35-10:25

PL03.03 RANDOMISED PHASE III STUDY OF OSIMERTINIB VS PLATINUM-PEMETREXED FOR EGFR T790M-POSITIVE ADVANCED NSCLC (AURA3)

Vassiliki Papadimitrakopoulou[1], Yi Long Wu[2], Myung-Ju Ahn[3], Suresh Ramalingam[4], Marina Garassino[5], Hye Ryun Kim[6], Frances Shepherd[7], Hiroaki Akamatsu[8], Willemijn Theelen[9], Chee Khoon Lee[10], Martin Sebastian[11], Alison Templeton[12], Marcelo Marotti[12], Serban Ghiorghiu[12], Tony Mok[13]

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Background: Osimertinib is a potent, irreversible, CNS active, epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) selective for sensitising (EGFRm) and T790M resistance mutations. Osimertinib is indicated for the treatment of patients with locally advanced or metastatic EGFR T790M-positive NSCLC. AURA3 (NCT02151981) is a Phase III, open-label, randomised study assessing the efficacy and safety of osimertinib versus platinum-based chemotherapy plus pemetrexed in patients with EGFR T790M-positive advanced NSCLC, whose tumours progressed on first-line EGFR-TKI therapy. **Methods:** Eligible patients were ≥18 years with documented EGFRm, radiological disease progression following first-line EGFR-TKI and centrally confirmed T790M-positive (by cobas® EGFR Mutation Test) from a tissue biopsy after disease progression. Asymptomatic, stable CNS metastases were allowed. Patients were randomised 2:1 to osimertinib 80 mg orally, once daily or platinum-pemetrexed (pemetrexed 500 mg/m^2 plus either cisplatin 75 mg/m^2 or carboplatin AUC5) every three weeks for up to six cycles; pemetrexed could be continued as maintenance treatment. Primary endpoint was progression-free survival (PFS) by investigator assessment according to RECIST v1.1; sensitivity analysis was by blinded independent central review (BICR). **Results:** A total of 419 patients were randomised to treatment (osimertinib, n=279; platinum-pemetrexed, n=140). Baseline characteristics were generally balanced across treatment groups: female 64%, Asian 65%, never smoker 68%, CNS metastases 34%, EGFR exon 19 deletion 66%. Osimertinib significantly improved PFS compared with platinum-pemetrexed: hazard ratio [HR] 0.30; 95% CI: 0.23, 0.41; p<0.001 (median 10.1 months vs 4.4 months). The result was consistent with PFS analysis by BICR: HR 0.28; 95% CI: 0.20, 0.38; p<0.001 (11.0 months vs 4.2 months). Objective response rate was significantly improved with osimertinib (71%) vs platinum-pemetrexed (31%); odds ratio 5.39 (95% CI: 3.47, 8.48; p<0.001). Median duration of response was 9.7 months (95% CI 8.3, 11.6) with osimertinib and 4.1 months (95% CI 3.0, 5.6) with platinum-pemetrexed. Grade ≥3 causally-related adverse events (AEs) as assessed by the investigator were reported in 6% of patients (n=16) treated with osimertinib and 34% (n=46) treated with platinum-pemetrexed. Most common causally-related AEs in the osimertinib group: diarrhoea (29% [grade ≥3, 1%]), rash (28% [<1%]); in the platinum-pemetrexed group: nausea (47% [3%]), decreased appetite (32% [3%]). **Conclusion:** In patients with EGFR T790M-positive advanced NSCLC following progression on EGFR-TKI treatment, osimertinib demonstrated a superior clinically-meaningful efficacy over platinum-pemetrexed, with a 70% reduction in the risk of disease progression, and well-characterised safety profile, establishing the new standard of care for these patients.
Keywords: T790M, EGFRm, AZD9291, osimertinib

SESSION PL03: PRESIDENTIAL SYMPOSIUM
TUESDAY, DECEMBER 6, 2016 – 08:35-10:25

PL03.05 BRAIN: A PHASE III TRIAL COMPARING WBI AND CHEMOTHERAPY WITH ICOTINIB IN NSCLC WITH BRAIN METASTASES HARBORING EGFR MUTATIONS (CTONG 1201)

Yi Long Wu[1], Jin -Ji Yang[2], Caicun Zhou[3], Jifeng Feng[4], Shun Lu[5], Yong Song[6], Cheng Huang[7], Gang Wu[8], Ying Cheng[9], Li Zhang[10], Chengping Hu[11], Gongyan Chen[12], Li Zhang[13], Xiaoqing Liu[14], Hong-Hong Yan[1], Fenlai Tan[15], Yi-Sheng Huang[16]

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Background: Non-small cell lung cancer (NSCLC) with brain metastases (M) had a poor prognosis. Whole brain irradiation (WBI) is a standard of care for this critical medical condition. The median survival is only 4-6 months. Small molecule inhibitors of epidermal growth factor receptor (EGFR) including icotinib achieved very successful results in advanced NSCLC with *EGFR* mutations. There were no prospective randomized clinical trials to explore the efficacy of EGFR tyrosine kinase inhibitors (TKIs) on brain M. **Methods:** Advanced NSCLC with *EGFR* sensitive mutations and brain M were randomized to WBI plus chemotherapy (chemo) or icotinib. Patients in WBI arm received radiotherapy with 30Gy/3Gy/10 fractions plus concurrent

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or sequential doublet chemo of 4-6 cycles. Patients in EGFR TKI arm received icotinib 125mg orally tid until disease progression. Icotinib could be continued beyond progression if clinical benefit was observed by the investigator. Crossover to icotinib from WBI could be permitted. Key inclusion criteria were *EGFR* mutations and radiologically confirmed brain M with at least 3 lesions. The primary endpoint was intracranial progression-free survival (iPFS) by investigator assessments according to RECIST v1.1. The secondary endpoints included objective response rate (ORR), PFS and overall survival (OS). Safety and tolerability were assessed by measuring adverse events (AEs) (CTCAE v4). **Results:** From Dec. 2012 to June 2015, 176 patients from 17 sites were randomized to WBI+Chemo arm (N=91) or icotinib arm (N=85). The baseline clinicopathologic factors were balanced between the two groups. Median age was 58, PS 1 was 87.2%, non-smoker 70.9%, adenocarcinoma 96.8%, symptomatic brain M were 16.5%. Icotinib significantly improved median iPFS compared with WBI+chemo: hazard ratio [HR] 0.56; 95% CI: 0.36-0.90; *p*=0.014 (10.0 vs 4.8 months). Median PFS was 6.8 vs 3.4 months, (HR 0.44, 95% CI 0.31-0.63, *P*<0.001). Median OS had no significant difference between the arms (18.0 vs 20.5 months, HR 0.93, 95%CI 0.60-1.44, *P*=0.734). Intracranial ORR was significantly improved with icotinib than WBI+Chemo (67.1% vs 40.9%; p<0.001); Overall ORR was 55.0% vs 11.1% (*P*<0.001). Grade ≥3 AEs assessed by the investigators were reported in 8.2% (N=7) of patients treated with icotinib and 26.2% (N=28) treated with WBI+Chemo. Most common causally related AEs in the icotinib arm were increased liver transaminase & rash; in the WBI+Chemo arm were hematologic toxicity. **Conclusion:** Icotinib demonstrated superior iPFS, PFS and ORR over WBI+Chemo in EGFR mutant advanced NSCLC with brain M, and well-tolerated safety profile. Icotinib would be a treatment option for *EGFR* mutant patients with brain M (NCT01724801).
Keywords: phase 3 trial, WBI, Brain metastasis, EGFR TKI

SESSION PL03: PRESIDENTIAL SYMPOSIUM
TUESDAY, DECEMBER 6, 2016 – 08:35-10:25

PL03.07 FIRST-LINE CERITINIB VERSUS CHEMOTHERAPY IN PATIENTS WITH ALK-REARRANGED (ALK+) NSCLC: A RANDOMIZED, PHASE 3 STUDY (ASCEND-4)

Gilberto De Castro Jr[1], Daniel Shao-Weng Tan[2], Lucio Crinò[3], Yi Long Wu[4], Luis Paz-Ares[5], Jürgen Wolf[6], Sarayut Geater[7], Sergey Orlov[8], Diego Cortinovis[9], Chong-Jen Yu[10], Maximilian Hochmair[11], Alexis Cortot[12], Chun-Ming Tsai[13], Denis Moro-Sibilot[14], Rosario García Campelo[15], Fabrice Branle[16], Paramita Sen[17], Tracey Mcculloch[17], Jean-Charles Soria[18]

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Background: Here, we report results of ceritinib versus chemotherapy as first-line treatment for advanced ALK+ NSCLC. **Methods:** Untreated ALK+ (IHC confirmed), advanced, nonsquamous NSCLC patients (N=376; median age, 54 years) were randomized (1:1) to ceritinib 750 mg/day (n=189 [59 with brain metastases (BM)]) or chemotherapy (n=187 [62 with BM]; [pemetrexed 500 mg/m^2 plus cisplatin 75 mg/m^2 or carboplatin AUC 5-6] for 4 cycles followed by maintenance pemetrexed), stratified by WHO PS (0 vs 1-2), BM at screening, and prior neo-/adjuvant chemotherapy. Crossover from chemotherapy to ceritinib was allowed at progression (n=80 crossed-over). **Results:** Median treatment exposure was 66.4 weeks for ceritinib and 26.9 weeks for chemotherapy. Median follow-up duration was 19.7 months (randomization to cut-off date). The study met its primary objective, with ceritinib demonstrating statistically significant improvement in BIRC PFS (RECIST 1.1; median, 16.6 [12.6, 27.2] vs 8.1 months [5.8, 11.1], HR=0.55, P<0.001) versus chemotherapy. OS was immature (HR, 0.73 [0.50, 1.08]; P=0.056) with 42.3% of required events at interim analysis. ORR (BIRC, 72.5% vs 26.7%) and DOR (BIRC, median, 23.9 vs 11.1 months) were also higher with ceritinib versus chemotherapy. Among patients with measurable baseline BM and ≥1 postbaseline assessment, intracranial ORR (BIRC neuroradiologist; modified RECIST v1.1) was higher with ceritinib (72.7% [49.8, 89.3] vs 27.3% [10.7, 50.2]) versus chemotherapy (Table). Most common AEs (>50%) with ceritinib were diarrhea (84.7%), nausea (68.8%), vomiting (66.1%), ALT increase (60.3%), and AST increase (52.9%). Overall, 5.3% ceritinib- and 11.4% chemotherapy-treated patients discontinued due to AEs suspected to be drug-related. **Conclusion:** First-line ceritinib achieved statistically significant and clinically meaningful improvement in median PFS with an estimated 45% risk reduction in advanced ALK+ NSCLC versus chemotherapy including maintenance. Moreover, ceritinib achieved high and durable systemic responses and high OIRR in patients with measurable BM. Safety profile of ceritinib is consistent with previously reported.
Keywords: Ceritinib, ASCEND-4, ALK, NSCLC

	Ceritinib (n=189)	Chemotherapy (n=187)
By BIRC		
Median PFS, months (95% CI)	16.6 (12.6, 27.2)*	8.1 (5.8, 11.1)
ORR (CR+PR), % (95% CI)	72.5 (65.5, 78.7)	26.7 (20.5, 33.7)
DCR (CR+PR+SD), % (95% CI)	84.7 (78.7, 89.5)	73.8 (66.9, 79.9)
Median DOR, months (95% CI)	23.9 (16.6, NE)	11.1 (7.8, 16.4)
Estimated 21-month DOR rate, % (95% CI)	59.0 (49.3, 67.4)	NE^
Median OS, months (95% CI)†	NE (29.3, NE)	26.2 (22.8, NE)
Estimated 27-month OS rate, % (95% CI)	67.8% (57.7%, 76.0%)	48.9% (33.2%, 62.8%)

Intracranial response in patients with measurable baseline brain metastases and ≥1 postbaseline assessment (BIRC neuroradiologist)				
	All patients		Patients with no prior RT	
	Ceritinib (n=22)	Chemotherapy (n=22)	Ceritinib (n=13)	Chemotherapy (n=18)
OIRR, % (95% CI)	72.7 (49.8, 89.3)	27.3 (10.7, 50.2)	69.2 (38.6, 90.9)	27.8 (9.7, 53.5)

*Log-rank *P*<0.001 vs chemotherapy; and HR=0.55.
†Log-rank *P*=0.056 vs chemotherapy; HR=0.73; OS data is immature at the 2nd interim analysis with 42.3% of the required events for the final OS analysis, at the time of primary PFS analysis.
^No patients were at risk at the specified timepoint.
Abbreviations: BIRC, blinded independent review committee; CI, confidence interval; DCR, disease control rate; DOR, duration of response; NE, not evaluable; OIRR, overall intracranial response rate; ORR, overall response rate; PFS, progression-free survival; RT, radiotherapy.

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SESSION PL03: PRESIDENTIAL SYMPOSIUM
TUESDAY, DECEMBER 6, 2016 – 08:35-10:25

PL03.09 PHASE 3 STUDY OF GANETESPIB, A HEAT SHOCK PROTEIN 90 INHIBITOR, WITH DOCETAXEL VERSUS DOCETAXEL IN ADVANCED NON-SMALL CELL LUNG CANCER (GALAXY-2)

Rathi Pillai[1], Dean Fennell[2], Vladimir Kovcin[3], Tudor Ciuleanu[4], Rodryg Ramlau[5], Dariusz Kowalski[6], Michael Schenker[7], Branislav Perin[8], Ilker Yalcin[9], Florentina Teofilovici[9], Vojo Vukovic[9], Suresh Ramalingam[10]

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Background: Heat shock protein 90 functions as a chaperone to stabilize oncoproteins. Ganetespib (G), a highly potent Hsp90 inhibitor, has demonstrated efficacy in combination with docetaxel (D) over D alone in the second-line therapy of patients with advanced adenocarcinoma of the lung in a phase 2 study. **Methods:** GALAXY-2 is a randomized (1:1), international, open-label study of D with or without G. Patients with advanced (stage IIIB/IV) non-small cell lung cancer (NSCLC) of adenocarcinoma histology, EGFR and ALK wild-type, diagnosed ≥ 6 months prior to study entry, one prior systemic therapy and ECOG PS 0-1 were eligible. D was given at 75 mg/m^2 on day 1 of three-week cycle; D was given on day 1 with G at 150 mg/m^2 on Days 1 and 15 of each cycle. Patients were stratified by performance status (PS), LDH, and geographic region. Primary endpoint was overall survival (OS). Secondary endpoints included progression free survival (PFS) and OS in elevated LDH (eLDH) patients. We report the results of a planned interim analysis at 336 events, which occurred on October 5, 2015, with type I error level set at 0.01 (2 sided stratified log-rank test). **Results:** 677 patients were randomized with 335 patients in G+D arm and 337 patients in D arm. Baseline characteristics: females 60%, age < 65 68%; never-smoker 18%; PS 0 36%; eLDH 29%; North America/Western Europe 39%. The median number of cycles delivered was 5 in G+D and 4 in D arm. There was no difference in median OS (mOS) for the two arms: 10.9 months with G+D versus 10.5 months with D alone. The hazard ratio for OS was 1.111 (95% CI 0.899-1.372), which met the early stopping criteria for futility. Median PFS was similar in the two arms: 4.2 versus 4.3 months, G+D and D, respectively (HR 1.161, 95% CI 0.961-1.403). There was no improvement with the addition of G for any secondary endpoint, including survival in the eLDH and EGFR and ALK negative populations, response rate, or progression due to new metastatic lesions. The most common grade 3/4 treatment-emergent adverse event in both arms was neutropenia (31.1% versus 24.3%, G+D and D, respectively). **Conclusion:** The addition of ganetespib to docetaxel did not result in improved efficacy for salvage therapy of patients with advanced stage lung adenocarcinoma.
Keywords: NSCLC, lung adenocarcinoma, docetaxel, HSP90 inhibitor

ORAL ABSTRACT SESSIONS

SESSION OA09: LOCALLY ADVANCED NSCLC: INNOVATIVE TREATMENT STRATEGIES
TUESDAY, DECEMBER 6, 2016 – 11:00-12:30

OA09.06 METFORMIN USE DURING CONCURRENT CHEMORADIOTHERAPY FOR LOCALLY ADVANCED NON-SMALL CELL LUNG CANCER (NSCLC)

Krista Wink[1], José Belderbos[2], Edith Dieleman[3], Maddalena Rossi[2], Coen Rasch[3], Ronald Damhuis[4], Ruud Houben[1], Esther Troost[5]

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Background: An increasing body of (pre)clinical evidence has suggested that metformin has an anticancer effect. The aim of this study was to investigate whether the use of metformin during concurrent chemoradiotherapy (cCRT) for locally advanced non-small cell lung cancer (NSCLC) improved treatment outcome. **Methods:** A total of 682 patients were included in this retrospective cohort study (59 metformin users, 623 control patients). All received cCRT in one of three participating radiation oncology departments in the Netherlands between January 2008 and January 2013. Primary endpoint was locoregional recurrence free survival (LRFS), secondary endpoints were overall survival (OS), progression-free survival (PFS) and distant metastasis free survival (DMFS) **Results:** No significant differences in LRFS or OS were found. Metformin use was associated with an improved DMFS (74% versus 53% at 2 years; p = 0.01) and PFS (58% versus 37% at 2 years and a median PFS of 41 months versus 15 months; p = 0.01). In a multivariate cox-regression analysis, the use of metformin was a statistically significant independent variable for DMFS and PFS (p = 0.02 and 0.03). **Conclusion:** Metformin use during cCRT is associated with an improved DMFS and PFS for locally advanced NSCLC patients, suggesting that metformin may be a valuable treatment addition in these patients. Evidently, our results merit to be verified in a prospective trial.
Keywords: NSCLC, metformin, Radiotherapy, Diabetes

SESSION OA13: IMMUNOTHERAPY IN MALIGNANT PLEURAL MESOTHELIOMA: CURRENT STATUS OF TRIALS AND NEW APPROACHES
TUESDAY, DECEMBER 6, 2016 – 14:20-15:50

OA13.01 A PHASE II STUDY OF NIVOLUMAB IN MALIGNANT PLEURAL MESOTHELIOMA (NIVOMES): WITH TRANSLATIONAL RESEARCH (TR) BIOPIES

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Background: No studies have reported any survival benefit in recurrent MPM. We examined the effect of nivolumab, in patients who presented with progressive disease and agreed to have biopsies taken before and during treatment. **Methods:** In this single center, phase II study, patients received nivolumab (3mg/kg q2w) until progression or toxicity. The primary endpoint was an improvement of disease control rate at 12 weeks of 20 to >40% compared to historic control according to a Simon two-stage design. A total of 33 patients were planned with paired biopsies at week -1 and 6 according to treatment start. PD-L1 status and other biomarkers were analyzed. **Results:** From 09-2015 until 06-2016, 38 patients were included with 33 having paired biopsies; 4 were not evaluable. There were no treatment related death and DCR at 12 weeks was 50%. Five patients had a confirmed PR; 12 had SD and 17 PD. Three patients showed pseudo-progression. Grade 3 toxicity occurred in 8 patients leading to discontinuation of the treatment in 4. The table shows the patients/tumor details. PD-L1 ≥1% was expressed in 9/32 evaluable patients with 2/9 having a confirmed PR at 12 weeks. **Conclusion:** Nivolumab in 2nd or later lines in recurrent MPM met the primary endpoint. The toxicity was mild and long lasting results were observed. A clear correlation between PD-L1 expression and response was observed.

	Outcome
Age	mean 66 yrs (51-81)
M/F	28 / 6
Epithelial/mixed/non epithelial	28 / 4 / 2
PR/SD/PD	5 / 12 / 17
PD-L1 + (1-10; 10-25; 25-50; >50%)	2 / 1 / 3 / 3
Correlation PR/SD/PD according to PD-L1 expression	<1% : 3/8/12 1 - 10% : 0/1/1 10-25% : 0/0/1 25-50% : 1/1/1 > 50% : 1/1/1
Correlation PR/SD/PD with histology	Epithelioid : 4/9/15 Mixed : 1/2/1 Non-epithelial : 0/1/1

Keywords: Mesothelioma, Nivolumab, Immunotherapy, translational research

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