9016 POSTER DISCUSSION

Erlotinib Vs Chemotherapy (CT) in Advanced Non-Small-Cell Lung Cancer (NSCLC) Patients (p) With Epidermal Growth Factor Receptor (EGFR) Activating Mutations − the EURTAC Phase II Randomized Trial Interim Results

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Background: EGFR tyrosine kinase activating mutations are present in 10−26% of NSCLC tumours and are associated with increased response to gefitinib and erlotinib. However, little is known about how the efficacy and safety profile of erlotinib compares with CT in EGFR-mutant Caucasian p. The Spanish Lung Cancer Group has performed the European Tarceva® vs Chemotherapy (EURTAC) phase III randomized trial comparing erlotinib with platinum-based CT in chemonaive advanced NSCLC p with EGFR mutations (clinicaltrials.gov NCT00446225).
Material and Methods: From February 2007 to January 2011, we screened 1275 p from 42 centers in Spain, France and Italy for EGFR mutations, and 154 patients were randomly assigned to receive erlotinib or platinum-based CT. The primary endpoint was progression-free survival (PFS). Secondary endpoints included response, overall survival and toxicity profiles. Investigator-assessed PFS and response were reviewed by an independent review committee.
Results: Accrual is now complete. 55 patients have died, 2 patients were lost to follow-up and 97 patients remain on study. 153 p (76 CT, 77 erlotinib) are evaluable for the interim analysis. p characteristics CT arm: 16 males; median age, 64; never smokers, 56; PS 0, 26; PS 1, 41; adenocarcinoma, 67. p characteristics erlotinib arm: 25 males; median age, 65; never smokers, 54; PS 0, 23; PS 1, 44; adenocarcinoma, 73. Preliminary results of the interim analysis are now available. Response rate was 10.5% to CT vs 54.5% to erlotinib (P < 0.0001). PFS in the CT arm was 5.2 months (m) (95% CI, 4.4−5.8 m) compared to 9.4 m (95% CI, 7.9–12.3) in the erlotinib arm (HR, 0.42; P < 0.0001). Median survival was 18.8 m in the CT arm and 22.9 m in the erlotinib arm (HR, 0.80; P = 0.42). Most common toxicities were asthenia (68.9%), anemia (45.9%), nausea (40.5%) and neutropenia (36.5%) in the CT arm, and diarrhea (57.3%), asthenia (53.3%), and rash (49.3%) in the erlotinib arm. Final results of the interim analysis will be presented.
Conclusions: The EURTAC study met its primary endpoint at the interim analysis. Erlotinib as first-line treatment for advanced NSCLC p with EGFR mutations improves PFS, with acceptable toxicity, compared to platinum-based chemotherapy.

9017 POSTER DISCUSSION

Initial Detection of the Double Epidermal Growth Factor Receptor (EGFR) Mutation (L858R or Deletion in Exon 19 [del 19] Plus T790M) in Non-Small-Cell Lung Cancer (NSCLC) Patients (p) With Brain Metastases (mets) and the Influence of First-Line Chemotherapy on Outcome to Erlotinib

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Background: Progression-free survival (PFS) in EGFR-mutant NSCLC p treated with erlotinib is unpredictable at the individual level. The initial presence of double mutations (EGFR L858R or del 19 plus T790M) is associated with shorter PFS. We hypothesized that the site of mets and/or prior chemotherapy could also influence outcome in these p with double EGFR mutations.
Material and Methods: The T790M mutation was assessed in 129 advanced NSCLC p by TaqMan assay in the presence of a peptide-nucleic acid designed to inhibit the amplification of the wild-type allele.
Results: De novo T790M mutations were identified in 35% (45 of 129) of EGFR-mutant p before receiving erlotinib. PFS was 12 months (m) for p with double mutations and 18 for p with only L858R or del 19 (P = 0.02). The T790M mutation was detected more frequently in p with bone mets (35.6% vs 16.7%; P = 0.03). No effect on PFS or MS was observed in p with the T790M mutation according to bone, lung, liver or pleura mets. However, when p with T790M were divided according to the presence of brain mets, PFS was 1 m for 4 p with brain mets vs 13 m for 41 p without brain mets (P = 0.002), and MS was 6 m for p with brain mets vs 36 m for those without (P = 0.009). Overall, in the multivariate analysis, the presence of the double mutation did not affect the risk of shorter MS (HR, 1.3; P = 0.49), but p who had received prior chemotherapy had significantly longer MS (HR, 0.48; P = 0.02).
Conclusions: The initial double EGFR mutation (EGFR L858R or del 19 plus T790M) is a marker for poor prognosis in p with brain mets. In addition, initial chemotherapy can play a role in the management of NSCLC p with the double EGFR mutation.

9018 POSTER DISCUSSION

Identification of Driver Mutations in Tumour Specimens From 1000 Patients With Lung Adenocarcinoma for the Lung Cancer Mutation Consortium (LCMC)

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Background: The ability to detect driver mutations including *EGFR* and *EML4-ALK* in tumour specimens from patients with ACL and administer agents targeting the molecular alterations is revolutionizing the management of patients with ACL. Multiplexed assays are available to detect these different driver mutations in adenocarcinoma specimens at diagnosis and are enlarging the numbers of candidates who can be effectively treated with targeted agents. Therefore, we created the LCMC to determine the frequency of 10 different genetic alterations from at least 1000 advanced stage ACL patients, to compare the presence of the alterations with clinical features, with other alterations, and with clinical outcome, and to give the information to clinicians for their ongoing care and future research.
Materials and Methods: The 14 member LCMC have recruited patients with ACL and tested the DNA from their ACL in CLIA laboratories for *KRAS, EGFR, HER2, BRAF, PIK3CA, AKT1*, *MEK1,* and *NRAS* variants using standard multiplexed assays and for *ALK* rearrangements and *MET* amplifications using fluorescence in situ hybridization (FISH). All had advanced stage (IIIB/IV) and performance status 0−2 with available tissue.
Results: To date, 1,104 patients have been registered with about 80 enrolling per month. Each of the institutions has enrolled a median of 54 patients (range 11 to 275) from 02/10 to 04/11. Multiplexed assays have been performed for 713 patients thus far, with a 92% assay success rate. Among the 656 patients with assays completed successfully, one or more mutations has been detected in 51.1% (335/656, 95% CI 47.3 to 54.9%; see below for breakdown of patients with mutations in multiple genes). The mutation proportion as follows: *KRAS* in 164 (25%), *EGFR* in 137 (21%), *PIK3CA* in 15 (2%), *BRAF* in 16 (2%), *HER2* in 6 (1%), *AKT1* in 1 (<1%), *NRAS* in 2 (<1%) and MEK1 in 3 (<1%). In addition to the mutations, FISH has been performed and reported for 464 patients, with *ALK* rearrangements found in 36 (8%) and *MET* amplification in 7 (2%). Among the total set of patients thus far evaluated by FISH and/or multiplex assay, 16 had alterations in more than one gene: PIK3CA + EGFR (3 patients), BRAF (2), MEK1 (1), and KRAS (1); MET + KRAS (2), EGFR (1), MEK1 (1), and ALK (1); ALK + KRAS (1) and BRAF (1); AKT1 + EGFR (1); and BRAF + KRAS (1).
Conclusions: We detected a driver mutation in more than 50% of the evaluable DNA from ACL. The results of *EGFR* mutation testing are now used by treating physicians to select erlotinib as initial treatment according to NCCN, ASCO, and ESMO guidelines. Patients with other driver mutations are being offered participation in LCMC-linked clinical trials testing agents targeting the mutation identified (e.g. crizotinib with *EML4-ALK*). At half of LCMC sites, multiplexed testing for all mutations is now routine practice of pathology departments for patients with ACL.
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