

despite not having been exposed to all drugs used to treat the patient. A prospective clinical trial is planned to validate these results.

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Meta-Analysis Examining Impact of Age on Pemetrexed (pem) Efficacy for the Treatment of Advanced Nonsquamous (NS) Non-Small Cell Lung Cancer (NSCLC)

Metastatic Non-Small Cell Lung Cancer

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Purpose/Objective(s): Elderly patients are often undertreated relative to younger patients in clinical practice. Pem is efficacious as a first-line, second-line, and maintenance treatment for advanced NS NSCLC. Analysis of individual trials in first-line (JMDB) and maintenance (JMEN, PARAMOUNT) settings showed comparable survival (favoring pem over comparators) and toxicity profiles of pem in elderly and nonelderly subgroups. Now, a meta-analysis is presented to give an integrated review of the impact of age on pem efficacy.

Materials/Methods: Data from NS NSCLC patients participating in four pem phase 3 studies underwent meta-analysis using a random-effects model that includes a statistical parameter representing inter-study variation including population size and event number. The method of DerSimonian and Laird was used to estimate the inter-study treatment effect variance. Studies included in the meta-analysis were: JMEI (second-line pem, N=399); JMDB (first-line pem/cisplatin, N=1252); JMEN (pem maintenance after non-pem/platinum doublet, N=481); and PARAMOUNT (pem maintenance after first-line pem/cisplatin, N=539). Patients in all studies were ECOG performance status (PS) 0/1, except JMEI had 11%-12% PS 2 patients. Due to differences in treatment regimens across studies, the ratio of the overall survival (OS) hazard ratio (HR) (pem vs control) for younger patients over the OS HR for older patients within each study was used as the measure of the differential effect of pem. Data were examined using age cutoffs of 65 and 70.

Results: Among the 4 studies, 32% of the patients were age ≥65, and 14% were age ≥70. The test of heterogeneity among studies was non-significant for subgroups defined by age 65 ($P=.083$) and age 70 ($P=.848$). The pooled ratio of the OS HR (pem vs control) in patients <65 to that in patients ≥65 was estimated as 0.92 (95% CI 0.67-1.25). Similar results were seen for the analysis using the age 70 cutoff, with a pooled ratio of 0.80 (95% CI 0.62-1.04).

Conclusions: In an analysis including 2671 good PS NS NSCLC patients, the effect of pem on OS was similar in younger and older patients as evidenced by the pooled HR ratio close to one. Pem is an efficacious treatment for advanced NS NSCLC regardless of patient age.

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Analysis of Predictive Factors in a Phase 3 Trial of Nab-Paclitaxel (nab-P) Plus Carboplatin (C) as First-Line Therapy for Patients (Pts) With Advanced Non-Small Cell Lung Cancer (NSCLC)

Metastatic Non-Small Cell Lung Cancer

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Purpose/Objective(s): Identification of predictive factors is critical for appropriate selection of pts and treatment regimens. In a phase 3 trial, nab-P/C vs solvent-based paclitaxel (sb-P) + C significantly improved ORR (primary endpoint; 33% vs 25%, $P=.005$), with a trend toward improved OS and PFS. Nab-P/C vs sb-P/C was associated with less severe peripheral neuropathy, arthralgia, and myalgia, but more anemia and thrombocytopenia in pts with advanced NSCLC. This analysis evaluated the correlation between pt and clinical factors and outcomes with nab-P/C vs sb-P/C.

Materials/Methods: Pts with untreated stage IIIB/IV NSCLC were randomized 1:1 to nab-P 100 mg/m² on d 1, 8, 15 or sb-P 200 mg/m² d 1 q21d; both arms received C AUC 6 d 1 q21d. ORR and PFS were assessed by blinded, centralized review. P values were based on χ^2 for ORR and log-rank for OS and PFS. Factors, including sex, age (< 70 and ≥ 70 y), histology (squamous and nonsquamous), stage (IIIB/IV), and geographic region (North America, Eastern Europe, and Asia/Pacific), baseline ECOG score, smoking status, diabetes, body mass index, number and location of metastatic sites, were analyzed for association with outcomes.

Results: The HR/risk ratio favored nab-P/C for ORR, PFS, and OS for most factors analyzed. Significant quantitative treatment-by-predictive factor interactions were noted for several key factors, including number of metastatic sites, diabetes, histology, and age, with respect to outcomes, and the comparative treatment effect was maintained in all other subgroups. In pts with ≥ 4 metastatic sites, significant treatment differences favoring nab-P/C were noted for ORR (response rate ratio [RRR] 3.40; $P=.003$) and OS (HR 0.562; $P=.009$) and trended in favor of nab-P/C for PFS (HR 0.735; $P=NS$). In pts with diabetes, significant treatment differences favoring nab-P/C were noted for ORR (RRR 1.935; $P=.046$) and PFS (HR 0.416; $P=.016$) and trended in favor of nab-P/C for OS (HR 0.553; $P=NS$). In pts with squamous NSCLC, significant treatment differences favoring nab-P/C were noted for ORR (RRR 1.68; $P<.001$) and trended in favor of nab-P/C for OS (HR 0.890; $P=NS$). In pts ≥ 70 y, significant treatment differences favoring nab-P/C were noted for OS (HR 0.583; $P=.009$) and trended in favor of nab-P/C for ORR (RRR 1.385; $P=.196$) and PFS (HR 0.687; $P=NS$). No treatment differences significantly favoring sb-P/C were observed.

Conclusions: A trend toward improved outcomes was noted with nab-P/C vs sb-P/C in most factors analyzed. Squamous NSCLC, diabetes, age ≥ 70 y, and ≥ 4 metastatic sites were predictive of improved outcomes with nab-P/C vs sb-P/C. These factors should be taken into consideration during treatment selection for pts with advanced NSCLC.

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Acquired Resistance to Afatinib in EGFR-Mutant Lung Cancer Metastatic Non-small Cell Lung Cancer

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Purpose/Objective(s): Afatinib is a second gen irreversible ErbB family tyrosine kinase inhibitor (TKI) approved for EGFR mutant lung cancer. Mechanisms of acquired resistance (AR) to afatinib are not well described. In vitro, afatinib overcomes the T790M mutation associated with AR to first gen EGFR TKIs, though single agent activity in pts with clinically-acquired AR is minimal. We performed this prospective clinical trial to determine if the prevalence of T790M is less common in pts who develop AR on afatinib as their first TKI compared to those with AR arising on 1st gen EGFR TKIs (null hypothesis = no different and 50% prevalence).

Materials/Methods: Eligible pts had advanced EGFR mutant lung cancer, were EGFR TKI-naïve, and had RECIST measurable disease. Treated brain mets and 1 prior line of chemo were allowed. Pts had to agree upfront to undergo a biopsy at the time of AR to be analyzed centrally for T790M and other AR mechanisms. Pts received afatinib 40 mg QD. Restaging was every 8 wks; treatment beyond progression was allowed. The study was amended to exclude exon 20 insertion mutations. Statistical assumptions: up to 6 pts would not be able to have an AR biopsy; hence with 18 biopsies and a significance level of 0.05, we would have 86% power to determine if afatinib yielded a lower rate (<20%) of T790M at AR than 1st gen TKIs. Financial support provided by Boehringer Ingelheim.

Results: Twenty-four pts were enrolled: 18 female, median age 57 years (range 27-83), 10 (42%) with brain mets and 5 (21%) with 1 prior chemo. EGFR mutations were del 19 (n=10, 42%), L858R (n=8, 33%), exon 20 insertions (n=3), G719X (n=2), S768I (n=1). Adverse events were typical; mainly rash, diarrhea, mucositis, paronychia and fatigue. Fifteen (62%) pts had a dose reduction. Two pts withdrew prior to developing AR, 5 remain on afatinib without AR. Best response distribution: any partial response (n=14, 58%), confirmed partial response (n=12, 50%), stable disease (n=6, 25%), progression (n=4, 17%). Median follow-up=8.2 mo; median PFS = 11.8 mo. Among 17 pts who developed AR, 12 (71%) have had a biopsy; the others had progression in CNS only (n=2) or were too ill (n=3). Three biopsies were insufficient for molecular analyses. Therefore, 9 pts had evaluable biopsies (4 L858R and 5 del19). All maintained the original EGFR mutation and 3 (33%) were T790M positive, 6 (66%) were T790M negative, which was not statistically different from the null hypothesis ($P=0.25$).

Conclusions: This prospective trial of afatinib in TKI-naïve EGFR mutants with a primary endpoint of molecular analysis at AR demonstrated that even among a group of pts motivated to sign consent for a future biopsy <50% ultimately had a successful, evaluable biopsy. In this small cohort, T790M appears to be less common (33%) than is expected with AR to first gen EGFR TKIs. Further analyses on biopsy specimens will be presented.

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Survival Benefit of Asian Females in the Era of Targeted Therapy for Advanced Lung Cancer

Metastatic Non-Small Cell Lung Cancer

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Purpose/Objective(s): Development of the EGFR tyrosine kinase inhibitors (TKIs) and FDA approval of erlotinib in 2004 began a decade of advances in targeted therapy for advanced lung cancer. Lung adenocarcinomas in Asian females are highly enriched for EGFR mutations. Despite randomized studies with improvements in progression free survival, TKIs have not yet proven to extend survival for patients harboring EGFR mutations. We sought to examine the survival advantage attributable to the use of TKIs, by comparing outcomes before and after the implementation of TKI therapy.

Materials/Methods: We examined the SEER database for cases of stage IV adenocarcinoma of the lung diagnosed 1998-2010. We divided our cohort into those diagnosed 1998-2004 (no TKI), and diagnosed 2005-2010 (TKI); and further by race/gender into Asian females (AF) and non-Asian males (NAM). We constructed Kaplan-Meier curves and compared curves by log-rank test. We used Cox Proportional Hazards models to evaluate lung cancer specific survival differences between recently and remotely diagnosed cases, controlling for known predictive variables.

Results: We included 2381 AF with stage IV adenocarcinoma diagnosed 1998-2010: 964 (40.5%) diagnosed 1998-2004, and 1417 (59.5%) diagnosed 2005-2010; and 28862 NAM: 13322 (46.2%) diagnosed 1998-2004, and 15540 (53.8%) diagnosed 2005-2010. Median age (67 for AF and 66 for NAM) and grade were comparable between groups. There were 1734 (72.8%) lung cancer related deaths in AF, and 24872 (85.9%) in NAM. Asian females diagnosed 2005-2010 had a survival advantage (mortality HR 0.76 [95% CI 0.69-0.83]) relative to AF diagnosed 1998-2004, controlling for age and tumor grade. Non-Asian males diagnosed 2005-2010 had a survival advantage (mortality HR 0.85 [95%CI 0.83-0.87]) relative to NAM diagnosed 1998-2004, controlling for age, grade, race (black/white), and Hispanic ethnicity.

Conclusions: Patients diagnosed with stage IV adenocarcinoma of the lung 2005-2010, regardless of ethnicity, had a survival benefit relative to those diagnosed 1998-2004. The benefit for Asian females was significantly larger than the benefit for non-Asian males. The additional survival benefit is likely attributable in part to the effects of TKIs.

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Economic Burden and Treatments of Progression to Metastatic Disease in ALK+ NSCLC Patients

Metastatic Non-Small Cell Lung Cancer

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Purpose/Objective(s): To investigate treatments (tx), healthcare resource utilization (HRU), and costs in patients (pts) with anaplastic lymphoma