9010 ORAL

18F-FDG-PET 12 Weeks After Stereotactic Body Radiotherapy for Stage I Non-Small-Cell Lung Cancer Predicts Outcome

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Background: To investigate the prognostic value of post-treatment ^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET) 12 weeks after stereotactic body radiotherapy (SBRT) for stage I non-small-cell-lung cancer (NSCLC).
Materials and Methods: From November 2006 to February 2010, 132 medically inoperable patients with proven stage I NSCLC or FDG-PET-positive lung tumours were analyzed retrospectively. SBRT consisted of 60 Gy delivered at the 80% isodose, in 3−8 fractions. The maximum Standardized Uptake Value (SUV_{max}) of the treated lesion was assessed 12 weeks after SBRT using FDG-PET. Patients were subsequently followed at regular intervals using serial CT-scans. The association of post-SBRT SUV_{max} with local control (LC), mediastinal failure (MF), distant failure (DF), overall survival (OS), and disease specific survival (DSS) was examined.
Results: The median follow-up time was 17 months (range: 2−40 months). The post-SBRT median SUV_{max} was 3.0 (range: 0.55–14.50). The median lesion size was 25 mm (range: 9−70 mm). There were 6 local failures, 15 mediastinal failures, 15 distant failures, 13 disease-related deaths, and 16 intercurrent deaths (in total: 29 deaths). Using SUV_{max} 5.0 as a cut-off, the 2-year LC, MF and DF rates for the high and low SUV_{max} groups were 78.8% versus 97.1% ($P = 0.001$), 20.3% versus 13.0% ($P = 0.333$), and 28.8% versus 11.8% ($P = 0.078$), respectively. In the multivariate analysis, SUV_{max} >5.0 was a better predictor for LC than lesion size ($p = 0.025$). The 2-year OS and DSS rates for high and low SUV_{max} were 62.3% versus 80.7% ($P = 0.087$), and 73.6% versus 90.4% ($P = 0.037$) respectively.
Conclusion(s): Residual FDG uptake (SUV_{max} >5.0) predicts LC and DSS. A trend was found towards better OS for $SUV_{max} \leqslant 5.0$. A single FDG-PET scan at 12 weeks could be used to tailor further follow-up, according to the risk of failure.

9011 ORAL

Multicenter Analysis of High-resolution Computed Tomography and Fluorodeoxyglucose-positron Emission Tomography/Computed Tomography to Predict Malignant Grade of Clinical Stage IA Lung Adenocarcinoma

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Background: To understand malignant aggressiveness preoperatively is critical to choose suitable therapeutic strategies, such as sublobar resection, for patients with small lung cancers. The aim of this study was to examine the malignant biological behavior of clinical stage IA adenocarcinoma using HRCT, fluorodeoxyglucose-positron emission tomography/computed tomography (FDG-PET/CT), and a pathologic analysis in the setting of a multicenter study.
Methods: We performed HRCT and FDG-PET/CT on 502 patients with clinical T1N0M0 adenocarcinoma before they underwent curative surgery. We evaluated the relationships between clinicopathological characteristics and maximum standardized uptake values (maxSUV) on FDG-PET/CT, ground-glass opacity (GGO) ratio and tumour disappearance rate (TDR) on HRCT and component of bronchioloalveolar carcinoma (BAC) on surgical specimens, as well as between these and surgical outcomes. We used a phantom study to correct the serious limitation of any multi-institution study using PET/CT, namely a discrepancy in maxSUV values among institutions.
Results: Lymph node metastasis, lymphatic invasion, blood vessel invasion and pleural invasion was evident in 38 (8%), 76 (15%), 92 (18%) and 56 (11%) patients, respectively. Analyses of receiver operating characteristics curves identified an optimal cut-off value to predict pathologic high-grade malignancy (lymph node metastasis, lymphatic invasion, blood vessel invasion, or pleural invasion) of 2.5 for revised maxSUV, 20% for GGO ratio, 30% for TDR and 30% for BAC ratio. A significant difference in disease-free survival (DFS) was identified between patients whose adenocarcinoma had maxSUV $\leqslant$ 2.5 (n = 343; 3-year DFS rate, 96%) and >2.5 (n = 159, 3-year DFS rate, 77%; $p < 0.001$). Among patients with solid tumours showing GGO $\leqslant$50% and TDR $\leqslant$50% (n = 259), 19% (n = 27) and 15% (n = 22) of those with a maxSUV >2.5 (n = 143) had nodal metastasis and tumour recurrence, respectively, whereas those with tumours showing maxSUV $\leqslant$1.5 (n = 48) had neither nodal metastasis nor recurrence.
Conclusions: MaxSUV is a significant preoperative predictor for surgical outcomes. The findings of FDG-PET/CT in addition to HRCT are important to select therapeutic strategies for clinical stage IA adenocarcinoma of the lung.

Poster Discussion Presentations (Mon, 26 Sep, 11:00−12:00)

Lung Cancer

9012 POSTER DISCUSSION

A Phase Ib Study to Evaluate the PI3-Kinase Inhibitor GDC-0941 With Paclitaxel (P) and Carboplatin (C), With and Without Bevacizumab (BEV), in Patients With Advanced Non-small Cell Lung Cancer (NSCLC)

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Background: PI3K may be an important target in NSCLC as evidenced by genetic alterations in the pathway such as PIK3CA amplification and PTEN loss. The pathway has also been implicated as a mechanism for cell survival and resistance to chemotherapy. Preclinical NSCLC models show that concurrent dosing of GDC-0941 improved activity of taxanes, platins, and anti-VEGF therapy. This Phase 1b study aims to establish the safety and tolerability of GDC-0941 + C + P +/- BEV.
Methods: This 2-arm study is being conducted in 1L and 2L pts with advanced NSCLC. Arm A (GDC-0941+C+P) includes squamous (Sq) and non-squamous (NSq) pts who were ineligible for BEV. Arm B (G+C+P+BEV) includes NSq BEV-eligible pts. Pts received increasing doses of GDC-0941 (3 + 3 design) with P (200 mg/m^2) and C (AUC 6 mg/mL·min) (Arm A) and BEV (15 mg/kg, Arm B) every 3 weeks. In both arms, GDC-0941 was given PO qd on Days 1−14 of a 21-day cycle. While P+C were given for 4−6 cycles, GDC-0941 $\pm$ BEV were given until progression or toxicity. Study objectives were to evaluate safety and pharmacokinetics (PK), and to determine the maximum tolerated dose of GDC-0941 in both arms.
Results: As of 7 April 2011, 23 pts were enrolled into cohorts of 60, 100, 165, 250 and 330 mg GDC-0941 (Arm A) and cohorts of 100, 165, 250 and 330 mg GDC-0941 (Arm B). Treatment-related adverse events (TAEs) seen in $\geqslant$20% of pts (n = 20, safety cutoff 25 Feb 2011) were alopecia, asthenia, nausea, stomatitis, neutropenia, rash, decreased appetite (anorexia), leukopenia, peripheral neuropathy, paresthesia, epistaxis and arthralgia. All TAEs were Grade 1 (G1) and 2 except for neutropenia. G3 (15%) and 4 (10%) neutropenia AEs were not dose-limiting. GDC-0941 has shown dose-proportional exposures through 250 mg, similar to single-agent GDC-0941. PK characteristics of P and 6-OH-P were similar to historical profiles. Based on preclinical efficacy, an exposure consistent with a combination effect has been achieved at the 250 mg dose. A 330-mg dose cohort is currently under evaluation in Arms A and B with no DLTs thus far. Confirmed partial responses (PRs) were seen in 3 of 4 Sq pts, including 1 pt with a pathologic complete response (Arm A, 165 mg). Six of 9 (66%) NSq patients also had PRs (Arm B, 100–250 mg).
Conclusions: The combination of GDC-0941, P and C ($\pm$BEV) has been well tolerated at doses consistent with preclinical activity. Evaluation of 330 mg GDC-0941 + C + P$\pm$BEV is ongoing. Randomized studies are planned.

9013 POSTER DISCUSSION

Phase I Dose-escalation Study of AXL1717: a Novel Targeted Oral Insulin-like Growth Factor-1 Receptor (IGF-1R) Inhibitor and Its Implications for Patients With Non-small Cell Lung Carcinoma

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Background: The IGF-1R signaling pathway has been shown to be important for the growth and survival of many types of cancer cells. AXL1717 is a small molecule oral compound that has been optimized to

inhibit IGF-1R without inhibiting closely related receptors such as the insulin receptor. AXL1717 is presently studied in phase II setting.
Materials and Methods: Advanced-stage cancer patients with progressive solid tumours and no remaining treatment options were included in the Phase I/II clinical trial. The primary objective of the study was to identify and confirm a recommended Phase II dose (RP2D). AXL1717 has been administered every third week as a single-day BID oral treatment in consecutively increasing doses as the only treatment with anti-tumour efficacy. Doses have been increased both within and between patients. In the recently completed phase I multidose part of the study, consecutive cohorts of advanced-stage cancer patients were given 7−28 days of increasing BID doses of AXL1717. A total of 35 patients (median age 63) were included in phase I and they were given approximately 1192 doses of AXL1717. A total of 178 of full-day pharmacokinetic assessments were performed. An additional 7 patients have been treated as confirmation of RP2D.
Results: The single-day dosing part of the study was successfully concluded. The results showed that AXL1717 could be administered as a single-day BID treatment in very high doses with excellent tolerability. Dose-limiting toxicity was not been reported in single day dosing. 390 mg BID were identified as recommended phase II dose (RP2D) following 28 days of dosing. Reversible, dose-related and probably mechanism-driven neutropenia was identified as the only dose-limiting adverse event in multidosing. No neutropenias have been reported within the study in connection to 28 days dosing of RP2D. 12 out of 42 patients had non-small cell lung cancer (NSCLC) and were treated with single agent AXL1717 longer than 7 days in the study resulting in a median survival of 45 weeks and of the 7 patients with RECIST confirmed progression, the median time to progression was 37 weeks as of 2011−04−05.
Conclusion: Phase I/II study of AXL1717 has shown that the agent can be administrated safely orally to advanced-stage cancer patients resulting in good bioavailability and tolerability. Even though the study was not designed to assess anti-tumour effects, encouraging signs suggesting clinical activity were seen in patients with NSCLC.

9014 POSTER DISCUSSION

Randomized Phase II Trial of NGR-hTNF and Chemotherapy in Chemo-naive Patients With Non-small Cell Lung Cancer (NSCLC) − Preliminary Results

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Background: NGR-hTNF is a vascular targeting agent obtained by fusing the NGR peptide, that binds to CD13 overexpressed on tumour blood vessels, to the tumour necrosis factor (hTNF). By selective damaging tumour vasculature and decreasing interstitial pressure, NGR-hTNF improves the intratumoral penetration of cytotoxic agents.
Methods: Chemo-naive, stage IIIb-IV NSCLC patients, including patients with brain metastasis, stratified by histology (nonsquamous vs squamous) and PS (0 vs 1), were randomly assigned to receive cisplatin 80 mg/m^2 day 1 plus either gemcitabine 1,250 mg/m^2 days 1, 8 for squamous histology or pemetrexed 500 mg/m^2 day 1 for nonsquamous histology for up to 6 cycles plus NGR-hTNF 0.8 μg/m^2 day 1 until progression (arm A) or chemotherapy alone (arm B). Primary study objective was progression-free survival (PFS). Assuming a 15% absolute increase in PFS rate ($\beta = 20\%$ and 1-sided $\alpha = 10\%$), a sample size of 102 patients was calculated.
Results: Of the 98 patients recruited so far, 64 patients (32 in each arm) were presently assessed for safety and preliminary activity. Baseline characteristics were (arm A/B): median age: 63/62 years; PS of 1: 11/9; squamous histology: 8/8. A total of 180 cycles (range 1−17) were administered in arm A and 133 cycles (range 1−6) in arm B. Treatment-related grade 3−4 toxicities for arm A vs B were 23% vs 34% for all adverse events and included: neutropenia 13% vs 15%; thrombocytopenia 3% vs 6%; fatigue 3% vs 12%; renal or respiratory failures 0% vs 6%; thromboembolism 6% vs 0%. Grade 1−2 hypertension was 3% in arm A and 11% in arm B. No grade 3 or 4 toxicities related to NGR-hTNF were observed, while 31% of patients experienced NGR-hTNF-infusion related grade 1 transient chills. Neither pulmonary hemorrhage nor bleeding were reported in both arms. Median follow-up time was 8.6 months in arm A and 5.5 in arm B. In patients with nonsquamous histology (n = 48), PFS rates at eight months were 38% in arm A and 18% in arm B. In nonsquamous patients who achieved disease control (partial response plus stable disease; n = 36), PFS rates at eight months were 51% in arm A and 21% in arm B. Among patients with squamous histology (n = 16), 2 partial responses, 5 stable diseases and 1 progressive disease in arm A and 1 partial response, 4 stable diseases and 3 progressive diseases in arm B were observed.
Conclusion: NGR-hTNF and chemotherapy can be safely combined in NSCLC, regardless of histology, showing promising antitumour activity.

9015 POSTER DISCUSSION

EGFR Mutation Status in NSCLC Patients Stage IIIB/IV in Germany − Initial Results From a German Registry

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Background: Lung cancer is the leading cause of cancer deaths worldwide. In Germany, each year approximately 47,000 patients are newly diagnosed with lung cancer and 41,000 die of the disease. Mutations in the EGFR gene are known to predict for sensitivity to EGFR tyrosine kinase inhibitors (TKI) in patients with advanced non-small-cell lung cancer (NSCLC). Clinico-pathological characteristics associated with a higher prevalence of EGFR mutations are adenocarcinoma histology, Asian origin, non-smoking history, and female gender; however, most of this information comes from Asian studies. REASON was set up to investigate the prevalence of EGFR mutations in German patients with advanced NSCLC and the association between mutations and clinico-pathological parameters, thus generating data from a predominantly Caucasian population.
Methods: REASON is an AstraZeneca sponsored registry (ClinTrials ID: NCT00997230). Patients with stage IIIB/IV NSCLC for whom EGFR mutation testing was planned were enrolled at approximately 150 participating sites The primary objective was to collect incidence data on the EGFR mutation status in the German patient population and correlate the EGFR mutation status with patient characteristics. Secondary objectives include clinical outcome of EGFR mutation positive patients, clinical management and pharmaco-economic data associated with diagnosis and first-line treatment options of EGFR mutation positive patients.
Results: To date, information covering the period up to the first-line treatment is available on 3155 patients. The majority of patients (89%) were newly diagnosed with NSCLC and presented with symptomatic (89%) stage IV disease (86%). Baseline data is displayed in Table 1.

Table 1. Baseline data

		n	%
Gender	Male	1967	62.3
	Female	1188	37.7
Smoking status	Ever-smoker	2571	81.5
	Non-smoker	584	18.5
Histology	Adenocarcinoma	2146	68.0
	Squamous cell carcinoma	616	19.5
	Others	393	12.4
EGFR mutation all histologies	Negative	2716	86.1
	Positive	310	9.8
	Positive, but not TKI sensitive	14	0.4
	Not evaluable for mutation	115	3.6
	Positive	310	9.8
	Positive, but not TKI sensitive	14	0.4
	Not evaluable for mutation	115	3.6
EGFR mutation adenocarcinoma	Positive	274	12.8
Total number		3155	100

The study is currently ongoing and follow up data will be available soon.
Conclusion: REASON aims to provide the largest data base yet on baseline epide-mio-logical and clinico-pathological characteristics of patients with newly diagnosed stage IIIB/IV NSCLC in a predominantly Caucasian population. Additionally, information on treatment decisions for patients with stage IIIB/IV EGFR mutation positive NSCLC, clinical outcomes and their pharmaco-economic impact, will help to build an enhanced knowledge base for improved patient care.